ESMO 2012

胶质母细胞瘤

417PD 关于多靶点酪氨酸激酶抑制剂 LENVATINIB（E7080）用于既往贝伐珠单抗治疗后疾病进展的复发性胶质母细胞瘤（GBM）患者的 II 期临床试验

417PD A PHASE 2 TRIAL OF THE MULTITARGETED KINASE INHIBITOR LENVATINIB (E7080) IN PATIENTS (PTS) WITH RECURRENT GLIOBLASTOMA (GBM) AND DISEASE PROGRESSION FOLLOWING PRIOR BEVACIZUMAB TREATMENT

D.A. Reardon, E. Pan, J. Fan, et al.

背景：目前对于血管内皮生长因子（VEGF）靶向药物——贝伐珠单抗治疗后疾病进展的复发 GBM，尚无有效的治疗，历史数据报告的 6 个月无进展生存率（PFS-6）仅为 2%。一些关于抗 VEGF 治疗后的肿瘤适应机制，包括备选血管生成细胞因子水平上调等理论被提出。因此，我们进行了一项单组 II 期临床研究，旨在对一种以 FGFR1-4、PDGFRβ、VEGFR1-3、RET 和 KIT 为靶点的口服酪氨酸激酶抑制剂，lenvatinib（L）用于贝伐珠单抗治疗后疾病进展的复发性 GBM 患者进行评价。

方法：32 例贝伐珠单抗治疗后疾病进展的复发性 GBM（既往≤2 次进展）患者接受 L 24mg/日治疗，28 天为一个周期，持续至疾病进展或发生不可接受的毒性。在 L 治疗 1 天前后，对一个队列患者（n=16）进行动态对比增强 MRI 检查。根据 RANO 标准对肿瘤缓解进行评估。主要终点为 PFS-6。该队列已完成入选；1 例患者仍在进行研究。

结果：中位年龄为 52 岁，56%的患者为男性，19%的患者的 KPS 小于 80；16%的患者因毒性而需要降低剂量，25%的患者因治疗相关的毒性停止治疗。最常见的不良事件为高血压 47%（3 级：18.8%）、疲劳 44%（3 级：15.6%）、头痛 41%、蛋白尿 31%（3 级：6.3%）和腹泻 31%；2 例患者（6.3%）分别出现 4 级 疲劳和高血压。1 例患者死于肺栓塞；28%的患者达到疾病稳定。未观察到疾病客观缓解。PFS-6 率为 8.3%；中位无进展生存期为 1.9 个月（95%可信区间：0.95-2.73）；6 个月总生存率（OS）为 28%；中位总生存期为 4.11 个月（95%可信区间：3.02-5.88）。10 例患者（63%）的平均 Ktrans 下降≥33%，并且在治疗后 1 天，病变体积显著降低（平均降幅：33%，P=0.00287），表明 L 可影响肿瘤血管和血管渗透性。

结论：与其他酪氨酸激酶抑制剂相比，Lenvatinib 具有中度活性并且毒性特征相似。将来需要对 VEGF 治疗失败机制以及结局生物标记物作进一步研究。

Background: There is no effective therapy for recurrent GBM pts following progression on the vascular endothelial growth factor (VEGF)-targeting agent bevacizumab (BV), with historical series reporting progression-free survival at 6 months (PFS-6) of only 2%. Several mechanisms of tumor adaptation following anti-VEGF therapy have been proposed, including upregulation of alternative angiogenic cytokines. We therefore performed a single-arm phase 2 study to evaluate lenvatinib (L), an oral tyrosine kinase inhibitor targeting FGFR1-4, PDGFRβ, VEGFR1-3, RET, and KIT, in pts with recurrent GBM progressing on BV.

Methods:32 pts with recurrent GBM (≤2 prior progressions) and progression on BV received L 24mg once daily in 28-day cycles until PD or unacceptable toxicity. Dynamic contrast-enhanced MRI was performed before and after 1 day of L on a subset of pts (n=16). Response was assessed using Response Assessment in Neuro-Oncology criteria. Primary endpoint was PFS-6. This cohort has completed enrollment; 1 pt is still ongoing.

Results: Median age was 52 y, 56% were male, and 19% had a KPS<80; 16% required dose reduction for toxicity and 25% withdrew from therapy due to treatment-related toxicity. Most common AEs were hypertension 47% (Gr 3:18.8%), fatigue 44% (Gr 3:15.6%), headache 41%, proteinuria 31% (Gr 3:6.3%), and diarrhea 31%; 2 pts (6.3%) experienced Gr 4 fatigue and hypertension, respectively. One patient died due to pulmonary embolism; 28% of pts achieved stable disease. No objective responses were observed. PFS-6 rate was 8.3%; median PFS was 1.9 months (95% CI:0.95-2.73); 6-month overall survival (OS) rate was 28%; median OS was 4.11 months (95% CI:3.02-5.88). A≥33% reduction in mean Ktrans was observed in 10 pts (63%) and a significant decrease in lesion volume (mean reduction:33%, P=0.00287) was found 1 day after therapy, indicating L affected tumor vascularity and vascular permeability.

Conclusions: Lenvatinib has modest activity and a similar toxicity profile when compared with other tyrosine kinase inhibitors. Further study of VEGF therapy failure mechanisms as well as biomarkers of outcome is needed.

435TiP 关于TH-302 和贝伐珠单抗用于贝伐珠单抗治疗失败的可切除复发性胶质母细胞瘤的I/II期临床研究

435TiP A DUAL PHASE I/II STUDY OF TH-302 AND BEVACIZUMAB IN RESECTABLE RECURRENT GLIOBLASTOMA FOLLOWING BEVACIZUMAB FAILURE

R.M. Zuniga, J. Sun, J.R. Floyd, et al.

引言：贝伐珠单抗是一种重组人单克隆抗 VEGF 抗体，在复发性胶质母细胞瘤中具有抗肿瘤活性；然而，在贝伐珠单抗治疗期间疾病进展，且后续治疗不含贝伐珠单抗的患者中位无进展生存期（PFS）仅为 1.6 个月。临床前研究表明，抗血管生成治疗可导致肿瘤微环境缺氧增加，从而导致侵袭性增加。缺氧可上调生存机制、抑制凋亡和刺激侵袭性。TH-302 是一类缺氧活化的药物前体，一旦被活化，可释放出烷化剂 Br-IPM。这类药物在体内可增强其他抗血管生成药物的抗肿瘤疗效。这项二联治疗 I/II 期临床研究入选了贝伐珠单抗治疗失败后计划再次开颅术的复发性胶质母细胞瘤患者。

方法：这是一项单中心、剂量递增、前瞻性研究，患者术前接受TH-302 单次给药 575mg/m^{2}或安慰剂，术后给予贝伐珠单抗 10mg/kg，每 2 周一次与TH-302 剂量递增 240–480 mg/m^2，每 2 周一次（4 周为一周期）的联合治疗，直至疾病进展。在切除的肿瘤组织中，通过γ-H2AX和MGMT表达对缺氧诱导的哌莫硝唑加成物、内源性CAIX染色、双链DNA损伤进行评估。

结果：5 例患者接受开颅术，并开始TH-302 加贝伐珠单抗治疗。未报告剂量限制性毒性。在 240 mg/m^{2}剂量组，未观察到 3 级或 4 级不良事件（AE），在 340 mg/m^{2}的第 2 队列中，观察到 1 例 3 级不良事件（皮肤溃疡），未观察到 4 级不良事件。在最初接受治疗的 5 例患者中，根据RANO标准，1 例患者部分缓解（PR），3 例患者疾病稳定（SD）。对切除后肿瘤的组织学评估显示，根据哌莫硝唑测量法，存在广泛缺氧区，且γ-H2AX 染色分布不均。

结论：TH-302 与贝伐珠单抗合用的耐受性良好。尚未达到 MTD，仅观察到 1 例 3 /4 级毒性。剂量递增仍在进行中，计划增至 MTD。

Introduction: Bevacizumab, a recombinant human monoclonal anti-VEGF antibody, exhibits anti-tumor activity in recurrent glioblastoma; however, the median progression free survival (PFS) of patients who progress on bevacizumab and are subsequently started on a non-bevacizumab containing regimen is only 1.6 months. Pre-clinical studies have shown that anti-angiogenic treatment leads to an increase in hypoxia in the tumor microenvironment leading to increased invasiveness. Hypoxia upregulates survival mechanisms, inhibits apoptosis, and stimulates invasiveness. TH-302 is a hypoxia-activated prodrug that once activated releases the alkylating agent Br-IPM. This drug has shown to potentiate, in vivo, the anti-tumor efficacy of other anti-angiogenic agents. This dual phase I/II study enrolled subjects with recurrent glioblastoma following bevacizumab failure that were planned for repeat craniotomy.

Methods: Single center, dose-escalation, prospective study with TH-302 single dose at 575mg/m^2 or placebo administered pre-operatively, followed by postoperative combination therapy of bevacizumab at 10mg/kg every 2 weeks and TH-302 dose escalated 240–480mg/m^2 every 2 weeks (4 week cycle) until disease progression. Resected tumor tissue was evaluated for hypoxia induced pimonidazole adducts, endogenous CAIX staining, double-strand DNA damage by gamma-H2AX and MGMT expression.

Results: Five patients underwent craniotomy and initiated TH-302 plus bevacizumab. No dose limiting toxicity was reported. There were no grade 3 or 4 adverse events (AEs) observed at 240mg/m^2, and one grade 3 (skin ulceration) and no grade 4 AEs observed thus far in the second cohort at 340mg/m^2. Of the initial 5 patients treated, one patient had a partial response (PR) and 3 patients had stable disease (SD) per RANO criteria. Histological assessment of resected tumors demonstrated extensive areas of hypoxia as measured by pimonidazole and a heterogeneous distribution of gamma-H2AX staining.

Conclusions:TH-302 demonstrates good tolerability when combined with bevacizumab. The MTD has not been reached and only one grade 3/4 toxicity was observed. Dose escalation is ongoing, with planned expansion at the MTD.

437TiP 卡铂和贝伐珠单抗用于复发性多形性胶质母细胞瘤的随机、II期临床研究（CABARET 研究）神经肿瘤学协作试验组（COGNO）

437TiP A RANDOMISED PHASE II STUDY OF CARBOPLATIN AND BEVACIZUMAB IN RECURRENT GLIOBLASTOMA MULTIFORME (CABARET STUDY). COOPERATIVE TRIALS GROUP FOR NEURO-ONCOLOGY (COGNO)

K. Field, M.A. Rosenthal, H. Wheeler, et al.

背景：胶质母细胞瘤（GBM）是侵袭性最强的恶性神经胶质瘤。在疾病进展后，尚无公认的标准疗法。关于贝伐珠单抗（bev）的最佳用法，包括疾病进展后继续治疗的作用和使用期间与使用后放射学进展特征的许多信息尚且未知。此外，尚未对新的神经肿瘤学疗效评估（RANO）标准进行前瞻性验证。

方法：这项研究是一项多中心、分层、随机、II 期临床试验。入组患者为放疗联合替莫唑胺治疗后复发的 GBM，未接受其他针对 GBM 的化疗，ECOG 体力状态评分为 0–2。放疗后至少经过 3 个月。在第 1 部分，患者按 1：1 的比例随机接受贝伐珠单抗 10mg/kg2 周 1 次静脉输注和卡铂 AUC5 4 周一次或贝伐珠单抗单药治疗。疾病进展的合格患者随机继续或停止贝伐珠单抗治疗（第 2 部分）。主要目的是根据改良 RANO 标准，确定贝伐珠单抗加卡铂与贝伐珠单抗单药对无进展生存期的影响。次要终点为缓解率、认知功能、生活质量、类固醇剂量、毒性和总生存期。在该人群中，首次前瞻性使用了 CogState，这是一套经过验证的神经认知测验系统，并与简明精神状态检查进行比较。探索性终点包括生物标记物分析、改良 RANO 和改良 MacDonald 标准的比较、2 次贝伐珠单抗治疗后早期 MRI 的预测价值、类固醇给药方案和治疗期间与治疗后放射学进展的部位与类型。

结果：2010 年 11 月开始入组，2012 年 3 月完成第 1 部分入组，来自 17 个澳大利亚研究中心的 122 例患者接受随机分组。继续第 2 部分的随机化分组。将列出可行性和安全性数据；预计在 2013 年获得有效性结果。

结论：该研究可显著增加关于贝伐珠单抗治疗复发性 GBM 的认识并首次对 CogState 神经认知测验用于脑瘤患者进行前瞻性分析。

Background: Glioblastoma (GBM) is the most aggressive malignant glial tumor. There is no accepted standard management after disease progression. Much remains unknown about the optimal use of bevacizumab (bev), including the role of continuing beyond progression, and patterns of radiological progression during and after use. In addition, the new Response Assessment in Neuro-Oncology (RANO) criteria have yet to be validated prospectively.

Methods: This study is a multi-centre, stratified randomised phase II trial. Patients have recurrent GBM after radiotherapy and temozolomide, have had no other chemotherapy for GBM, and have ECOG performance status 0–2. At least three months have elapsed since radiotherapy. In Part 1, patients are randomised 1:1 to intravenous bev 10mg/kg 2-weekly and carboplatin AUC5 4-weekly or bev monotherapy. On progression, eligible patients are randomised to continue or cease bev (Part 2). The primary objective is to determine the effect of bev plus carboplatin versus bev alone on progression-free survival according to modified RANO criteria. Secondary endpoints are response rates, cognitive function, quality of life, steroid dose, toxicity, and overall survival. CogState, a validated neurocognitive testing system, is being used prospectively for the first time in this population and compared with mini-mental state examination. Exploratory endpoints include biomarker analyses, comparison of modified RANO and modified MacDonald criteria, predictive value of early MRI after 2 doses of bev, steroid dosing, and location and type of radiological progression during and after therapy.

Results: Enrolment commenced in Nov 2010, completing Part 1 accrual in Mar 2012 with 122 patients randomised from 17 Australian sites. Randomisation to Part 2 continues. Feasibility and safety data will be presented; efficacy outcome results are not expected until 2013.

Conclusions: The study results will significantly improve knowledge regarding the use of bevacizumab in the setting of recurrent GBM, as well as providing for the first time a prospective analysis of CogState neurocognitive testing for patients with brain tumours.

LBA15　伊立替康和贝伐珠单抗作为新辅助和辅助治疗联合含替莫唑胺的放化疗对比放化疗治疗不可切除的胶质母细胞瘤的随机多中心II期试验（TEMAVIR ANOCEF研究的确定性结果）

LBA15　RANDOMIZED MULTICENTER PHASE II TRIAL OF IRINOTECAN AND BEVACIZUMAB AS NEO-ADJUVANT AND ADJUVANT TO TEMOZOLOMIDE-BASED CHEMORADIATION VERSUS CHEMORADIATION FOR UNRESECTABLE GLIOBLASTOMA (DEFINITIVE RESULTS OF THE TEMAVIR ANOCEF STUDY)

B. Chauffert, L. Feuvret, F. Bonnetain, et al.

背景：不可切除的胶质母细胞瘤（GBM）即使使用替莫唑胺（TMZ）为基础的放化疗方案，其预后仍然较差。已经报告了贝伐珠单抗/伊立替康治疗复发性 GBM 的活性（Vredenburgh, 2007）。我们对伊立替康（IRI）和贝伐珠单抗（BVZ）作为新辅助和辅助疗法治疗不可切除胶质母细胞瘤的含替莫唑胺（TMZ）放化疗进行了评估。

方法：不可切除的原发性GBM、18-70 岁、KPS>50、RPA 5 级的患者可以合格地参与本研究。试验组（A组）包含新辅助疗法BVZ 10 mg/kg和IRI 125 mg/m^2，每 2 周一个疗程，共 4 个疗程，然后进行放疗（60Gy，30 次）并同时使用TMZ 75 mg/m^2/天和BVZ，每 2 周一次。每 2 周给予一次辅助治疗BVZ和IRI，共 6 个月。对照组（B组）为TMZ同步治疗组，放疗期间伴随使用TMZ 75 mg/m^2/天，随后使用TMZ 150-200 mg/m^2，每 28 天中前 5 天用药，共 6 个月。在进展时允许交叉用药。计划每组入选 60 例患者，使用Fleming 2 步设计，目标是 6 个月时的PFS（PFS6）从 50%增加到 66%，而且单侧α为 5%，效能为 80%。在入组结束后 16 个月时进行最终分析，包括总生存期（OS）分析。

结果：在 2009 年 4 月和 2011 年 1 月期间进行了患者入组（120 例）。两组间的临床特征分布均衡。在 A 组中，与治疗有关的严重不良事件是脑出血（3 例；3 例致死性事件）、胆道或消化道穿孔/感染（3 例，1 例致死性事件）、血栓栓塞（4 例，0 例致死性事件）。B 组中与治疗有关的严重不良事件是胆道或消化道穿孔/感染（2 例，0 例致死性事件）、肺部感染（1 例，无致死性事件）、血栓栓塞（2 例，0 例致死性事件）、血栓和/或中性粒细胞减少症（4 例，0 例致死性事件）。A 组的 6 个月和 12 个月时 PFS 较长，但两组中的 OS 相似（见下表）。

结论：尽管试验组 6 个月和 12 个月时的 PFS 表现出优于对照组的趋势，但两个组的总生存期没有差异。

Background: The prognosis of unresectable glioblastoma (GBM) remains poor despite temozolomide (TMZ)- based chemoradiation. Activity of bevacizumab/irinotecan has been reported in recurrent GBM (Vredenburgh,2007). We evaluate irinotecan (IRI) and bevacizumab (BVZ) as neo-adjuvant and adjuvant to TMZ-based chemoradiation for unresectable glioblastoma.

Method: Pts with de novo unresectable GBM, aged 18-70, and KPS>50, and RPA class 5 were eligible. Experimental arm (A) consisted of neo-adjuvant BVZ 10 mg/kg and IRI 125 mg/m^2, every 2 wk for 4 cycles before radiotherapy (60 Gy in 30 fractions) with concurrent TMZ 7 mg/m^2/day and BVZ every 2wk. Adjuvant BVZ and IRI were given every 2wk for 6 months. The control arm (B) consisted of concomitant TMZ, 75 mg/m^2/d during radiotherapy and 150-200 mg/m^2 for 5 d every 28 d for 6 months. Cross over were allowed at progression. The inclusion of 60 pts/arm was planned using Fleming's 2 steps design aiming at an increase of PFS at 6 month (PFS6) from 50% to 66%, with unilateral alpha 5% and 80% power. Final analysis, including overall survival (OS), was performed 16 months after the end of inclusion.

Results: Patients (120) were included from April 2009 to January 2011. Clinical factors were well balanced between arms. Treatment-related serious adverse events were brain haemorrhages (3; 3fatal), biliary or digestive perforation/infection (3, 1 fatal), thrombo-embolism (4, 0 fatal) in Arm A, and biliary or digestive perforation/infection (2, 0 fatal), pulmonary infection (1, no fatal), thrombo-embolism (2, 0 fatal), thrombo- and/or neutrepenia (4, 0 fatal) in arm B. PFS at 6 and 12 months appears to be longer in arm A, but OS was similar in both arms (table).

Conclusion: Despite a trend to a better PFS at 6 and 12 month in the experimental arm, overall survival was not different between arms.

分组/ARM （患者）/(patients)	PFS 6 % [IC95,%]	PFS 12 % [IC95,%]	OS 6 % [IC95,%]	OS 12 % [IC95,%]
A (60)	65 [51-75]	31 [20-43]	75 [62-84]	48 [34-60]
B (60)	41 [29 -53]	18 [9-28]	72 [59-82]	50 [36-62]

LBA16　接受贝伐珠单抗治疗的复发性高级别神经胶质瘤患者中基质金属蛋白酶 2（MMP2）血浆水平与疗效和患者生存的相关性

LBA16　ASSOCIATION OF MATRIX METALLOPROTEINASE 2 (MMP2) PLASMA LEVEL WITH RESPONSE AND SURVIVAL IN PATIENTS TREATED WITH BEVACIZUMAB FOR RECURRENT HIGH GRADE GLIOMA

E. Tabouret, F. Boudouresque, M. Barrié, et al.

背景：贝伐珠单抗活性的预测指标是一个未满足的医学需求，而且据报告，这种抗-VEGF 单抗的活性具有异质性，尤其是对于胶质母细胞瘤。

目的：明确可预测贝伐珠单抗疗效和复发性高级别胶质瘤（HGG）预后的循环生物标志物。

方法：在由我们单位 26 例 HGG 患者组成的第一个队列（队列 1）中，基线时和贝伐珠单抗治疗开始后 1 个月时，通过 ELISA 法对 11 种血管生成标志物进行了分析；评估了血浆标志物剂量与客观缓解（RANO 标准）、无进展生存期（PFS）和总生存期（OS）之间的相关性。在另一个 50 例患者组成的队列（队列 2）中对相关性进行了验证。在放疗之前（队列 3，n=20）或伴随放疗（队列 4，n=24）接受细胞毒性药物治疗的另外 2 个队列中进行了标志物分析。

结果：在队列 1 中，基线高水平 MMP2 对应 83.3%的缓解率，而低水平 MMP2 的缓解率为 15.4%（p=0.001）。通过单变量分析表明，并经多变量分析的确认，MMP2 与 PFS（p=0.007）和 OS（p=0.001）存在相关性，血浆 VEGF 水平降低（对于 PFS，p=0.038，对于 OS，p=0.013）和 MMP9 水平（PFS p=0.016，OS p=0.025）降低也是如此。在队列 2 中，仅确认了 MMP2 有相似的结果（缓解 p<0.0001，PFS p=0.009，OS p=0.009）。在队列 3 和队列 4 中，未发现 MMP2 与缓解、PFS 或 OS 之间存在相关性。

结论：在接受贝伐珠单抗治疗但未接受细胞毒性药物治疗的复发性 HGG 患者中，较高的血浆 MMP2 水平与客观缓解、肿瘤控制时间延长和生存期有关。需要进一步研究来验证这些/这个生物标志物对胶质瘤和其他癌症的预测价值。

Background: Predictive marker of bevacizumab activity is an unmet medical need, while activity of this anti-VEGF Mab is reported to be heterogeneous, particularly in glioblastoma.

Objective: To identify circulating biomarker that predicts response to bevacizumab and outcome in recurrent high grade glioma (HGG).

Methods: Eleven angiogenic makers were analyzed, using ELISA, at baseline and one month apart from bevacizumab initiation in a first cohort of 26 HGG patients of our institution (cohort 1); Plasma marker dosages were correlated to objective response (RANO criterias), Progression-free survival (PFS), and overall survival (OS). Correlations were validated in a separate cohort of 50 patients (Cohort 2). Markers analyses were performed in two other cohorts treated with cytotoxic agents up front (cohort 3 n=20) or concomitant to radiotherapy (cohort 4 n=24).

Results: In cohort 1, high MMP2 baseline level was associated to a probability of response of 83.3% versus 15.4% in case of low MMP2 level (p=0.001). By univariate analyses, confirmed by multivariate analysis, MMP2 correlated with PFS (p=0.007) and OS (p=0.001), as decrease of plasmatic VEGF level (p=0.038 for PFS and p=0.013 for OS) and MMP9 level (PFS p=0.016, OS p=0.025). These results were confirmed with a similar magnitude in cohort 2 for MMP2 only (p<0.0001 for response, p=0.009 for PFS and p=0.009 for OS). In cohort 3 and 4, no association was found between MMP2 and response, PFS, or OS.

Conclusions: Among patients with recurrent HGG treated with bevacizumab, but apparently not with cytotoxic agent, higher plasma MMP2 levels were associated with objective response, prolonged tumor control and survival. Further studies are needed to validate the predictive value of these/this biomarker(s) both with glioma and other cancers.

410O 接受替莫唑胺治疗的多形性胶质母细胞瘤患者的条件生存概率

410O CONDITIONAL PROBABILITY OF SURVIVAL IN PATIENTS WITH GLIOBLASTOMA MULTIFORME IN THE TEMOZOLOMIDE TREATMENT ERA

M. McNamara, Z. Lwin, H. Jiang, et al.

引言：多形性胶质母细胞瘤（GBM）是侵袭性最强的神经胶质瘤。采用标准治疗，即手术后放疗（RT）同步及辅助替莫唑胺（TMZ）治疗，中位生存期约为 14.6 个月。这些估计值不适用于诊断后生存一段时间的患者。目的：回顾性分析就诊于三级转诊中心，多伦多 Princess Margaret 医院的多学科团队，且诊断为 GBM 的患者，报告条件概率估计值。

方法：从 01/04 至 08/10 期间共分析了 892 例患者。对完整人口统计学、体力状态（PS）、GBM 部位、手术范围、接受 RT +/− TMZ 的百分比、总生存期（OS）和条件概率数据进行分析。

结果：队列包括 548（61%）例男性，中位年龄为 62 岁（5-93）。600（67%）例患者基线期 PS 为 0-1，有 251（28%）例患者为 2-3。205（23%）例患者存在额叶肿瘤。手术范围；26%组织活检、68%部分切除术/次全切、6%未知。516（58%）例患者接受 RT/TMZ 联合治疗+/− TMZ 辅助治疗。患额叶肿瘤与其他部位肿瘤的患者生存期相似（10.2 与 9.7 个月，时序检验 p=0.28）。组织活检患者的总生存期为 4.5 个月（3.5-6.2），部分切除术/次全切患者；11.6 个月（10.3-12.5）（p<0.001）。在接受标准 RT/TMZ +/− TMZ 治疗的患者中，总生存期为 14.2 个月（13.3-15.1）。年龄和 PS 为总生存期的显著预后因素（p<0.001）。在这 892 例患者中，总生存期和条件生存概率详见表格。43（5%）例患者仍然生存，727（81%）例患者死亡，122（14%）例患者生存状态未知。

结论：诊断后生存 2 年后，再生存 1 年的条件概率超过 1 年生存率，表明生存 2 年的患者的预后与近期诊断患者相似。在这个接受 TMZ 治疗的一般疾病人群中，条件生存概率可更准确地预测 GBM 存活者的预期寿命。

Introduction: Glioblastoma multiforme (GBM) is the most aggressive of gliomas. With standard treatment consisting of surgery followed by radiotherapy (RT) with concurrent and adjuvant temozolomide (TMZ), median survival is approximately 14.6 mo. These estimates are not as informative to patients (pts) who have survived for some time after diagnosis. Aim:To retrospectively review outcomes and report conditional probability estimates in the TMZ treatment era of pts who presented to a multidisciplinary team at the tertiary referral center PrincessMargaretHospital, Toronto, with a diagnosis of GBM.

Methods:892 pts were followed from 01/04-08/10. Complete demographics, performance status (PS), GBM localization, extent of surgery, percent receiving RT +/− TMZ, overall survival (OS) and conditional probability were analyzed.

Results: The cohort includes 548 (61%) males with median age 62 (5-93). Baseline PS was 0-1 in 600 (67%), 2-3 in 251 (28%) pts. 205 (23%) had frontal lobe tumors. Extent of surgery; 26% biopsy, 68% partial/subtotal resection, 6% unknown. 516 (58%) received concurrent RT/TMZ +/− adjuvant TMZ. Survival was similar for those with frontal lobe tumors vs other locations (10.2 vs 9.7 mo, Logrank test p=0.28). OS for biopsy pts was 4.5 mo (3.5-6.2), and partial/subtotal resection pts; 11.6 mo (10.3-12.5) (p<0.001). OS for pts receiving standard RT/TMZ +/− TMZ was 14.2 mo (13.3-15.1). Age and PS were significant prognostic factors for OS (p<0.001). The OS and conditional probability of survival for entire cohort of 892 pts is detailed in Table.43 (5%) are still alive, 727 (81%) deceased, status unknown in 122 (14%).

Conclusion: The conditional probability of surviving an additional yr after survival to 2 yrs post diagnosis exceeds the 1 yr survival rate, indicating that the future prognosis of a pt who has survived for 2 yrs may be as good as those recently diagnosed. Conditional probabilities of survival in this general disease population in the era of TMZ therapy may provide more accurate life expectancy predictions for survivors of GBM.

时间/ Time	总生存率(%)/Overall Survival(%)	95% CI	生存条件概率(%)/Conditional Probability of Survival (%)	95% CI
1 年/1 Year	43.1	39.8-46.4	41.4	35.9-47.0
2 年/2 Year	17.9	15.2-20.7	57.4	47.5-67.4
3 年/3 Year	10.3	8.0-12.8	80.6	68.4-92.8
4 年/4 Year	8.3	6.1-10.9	85.6	71.1-100
5 年/5 Year	7.1	5.0-9.7	81.5	60.9-100

胃癌

667PD 表柔比星、奥沙利铂和卡培他滨（EOC）+帕尼单抗治疗胃食管癌的随机、多中心试验（REAL3）：更新结果

667PD A RANDOMISED MULTICENTRE TRIAL OF EPIRUBICIN, OXALIPLATIN AND CAPECITABINE (EOC)+PANITUMUMAB IN ADVANCED OESOPHAGO-GASTRIC CANCER (REAL3):UPDATED RESULTS

T.S. Waddell, J. Reis-Filho, D. Gonzalez-De-Castro, et al.

背景：30%-90%的胃食管腺癌（OGA）会发生 EGFR 过度表达，并且与预后不良相关。REAL-3 试验对表柔比星、奥沙利铂和卡培他滨（EOC）方案中添加抗 EGFR 抗体帕尼单抗（P）用于晚期 OGA 进行了评价。

方法：将未经治疗的、转移性或局部晚期OGA患者随机分入EOC组（E 50mg/m^2，O 130mg/m^2，C 1250mg/m^2/天）或mEOC+P 组（E 50mg/m^2，O 100mg/m^2，C 1000mg/m^2/天，P 9mg/kg）。主要终点是总生存期（OS），次要终点为无进展生存期（PFS）、缓解率（RR）、毒性和生物标记物的评价。在 4 个和 8 个疗程后，根据RECIST对缓解情况进行评估。

结果：553 例患者入组（EOC 组 275 例，mEOC+P 组 278 例）。EOC 组的中位 OS 为 11.3 个月，mEOC+P 组为 8.8 个月（HR 1.37，95%CI 1.07-1.76，P=0.013）。两组的中位 PFS 分别为 7.4 个月和 6.0 个月（HR 1.22 95%CI 0.98-1.52，P=0.068），RR 分别为 42%与 46%（优势比为 1.16；95%CI 0.81-1.57，P=0.467）。在 mEOC+P 组中，G1-3 皮疹患者（77%，n=209）的 OS 较没有 G1-3 皮疹的患者（23%，n=63）显著延长；中位 OS 分别为 10.2 个月与 4.3 个月（P<0.001），RR 和 PFS 也有相似的显著提高。多变量分析证实，KRAS 突变（HR 2.1，95%CI 为 1.10-4.05，P=0.025）和 PIK3CA 突变（HR 3.2：95%CI 1.01-10.40，P=0.048）对预后有负面影响。上述信息已经在 2012 ASCO 大会中公布。更新的转化结果将在 ESMO 大会中公布。这些新结果将包括该人群中皮疹与 EGFR 和 KRAS 基因扩增相关毒性终点和数据的相关性。

Background:EGFR overexpression occurs in 30-90% of oesophago-gastric adenocarcinomas (OGA), and correlates with poor prognosis. The REAL-3 trial evaluated the addition of the anti-EGFR antibody panitumumab (P) to epirubicin, oxaliplatin and capecitabine (EOC) in advanced OGA.

Methods: Patients with untreated, metastatic or locally advanced OGA were randomised to EOC (E 50mg/m^2, O 130mg/m^2, C 1250mg/m^2/day) or mEOC+P (E 50mg/m^2, O 100mg/m^2, C 1000mg/m^2/day, P 9mg/kg). Primary endpoint was overall survival (OS); secondary endpoints were progression-free survival (PFS), response rate (RR), toxicity, and biomarker evaluation. Response was evaluated by RECIST after 4 and 8 cycles.

Results:553 patients were recruited (EOC 275, mEOC+P 278). Median OS was 11.3 months with EOC compared to 8.8 months with mEOC+P (HR 1.37:95% CI 1.07-1.76, p=0.013). Median PFS was 7.4 and 6.0 months respectively (HR 1.22:95% CI 0.98-1.52, p=0.068), with RR being 42% compared to 46% (odds ratio 1.16:95% CI 0.81-1.57, p=0.467). In the mEOC+P arm, OS was significantly improved in patients with G1-3 rash (77%, n=209) on treatment compared to those without (23%, n=63); median OS 10.2 vs 4.3 months (p<0.001), with similar significant improvements seen in RR and PFS. Multivariate analysis demonstrated a negatively prognostic role for KRAS mutation (HR 2.1:95% CI 1.10-4.05, p=0.025) and PIK3CA mutation (HR 3.2:95% CI 1.01-10.40, p=0.048). The above information is being presented at ASCO 2012. Updated translational results will be available for presentation at ESMO Congress. This will include correlation of rash with toxicity endpoints and data relating to EGFR and KRAS amplification in this population.

683P 卡培他滨用于胃腺癌术后放化疗的疗效
683P POSTOPERATIVE RADIOCHEMOTHERAPY WITH CAPECITABINE FOR GASTRIC ADENOCARCINOMA

M. Skoblar Vidmar Ljubljana/SI

背景：彻底切除恶性肿瘤是非转移性胃癌的首选治疗。INT-0116的组间研究报告显示辅助放化疗可显著提高生存率。
2001 年，斯洛文尼亚将 5-氟尿嘧啶和甲酰四氢叶酸的辅助放化疗方案应用于临床实践中。卡培他滨是一种口服 5-FU 的前体药物，我们假设它可以作为标准化疗方案的替代治疗。
患者和方法：在 2006-2010 年间，101 例接受胃腺癌术后放化疗的患者使用了卡培他滨，这些患者平均年龄为 59 岁，疾病分期为IB-IIIC。分别有 97 例患者和 4 例患者接受了根治性（R0）与非根治性（R1）肿瘤切除术。治疗开始的第一个疗程，给予口服卡培他滨（在第 1-14 天，1250 mg/m^2，每日 2 次）化疗，3 周后接受总剂量为 45 Gy的放射治疗。患者接受 15MV电子直线加速器照射，每周 5 天，每天剂量为 1.8 Gy。放疗期间患者接受低剂量卡培他滨（825 mg/m^2，每日 2 次，每周 7 天）治疗，1 次在照射前 1 小时给药和 1 次在照射后 12 小时后给药。放疗结束后，患者再接受 3 三个疗程的化疗，每个疗程间隔 3 周。
结果：术后 2.6-11.3 周开始接受术后 ChT（中位值为 6 周）。59 例患者按照方案完成了治疗。没有患者因治疗死亡。分别有 1、0、5、2、9、4 和 3 例患者发生三级口腔炎、吞咽困难、恶心呕吐、腹泻、手足综合征、心绞痛和脱发。就治疗开始时体重而言，约 56 例患者出现体重减轻。最大体重减轻程度为 18.9%（平均 6.2%）。66 例生存患者的中位随访时间为 4 年（范围为 2.5-5.7 年）。在第 5 年时，局部区域控制率（LRC）、无疾病生存率（DFS）、疾病相关生存率（DSS）和总生存率（OS）分别为 95%、69%、74%和 63%。
结论：在可切除胃癌患者中，术后放化疗使用卡培他滨是可行的，且毒性较低。

Background: Complete removal of malignancy represents the treatment of choice in nonmetastatic gastric cancer. The Intergroup Study INT-0116 reported a significant improvment in survival with adjuvant radiochemotherapy. In Slovenia, the program of adjuvant radiochemotherapy with 5-fluorouracil and leucovorin was introduced into clinical practice in 2001. Capecitabine is an oral 5-FU prodrug and we assume that it can replace standard chemotherapy.
Patients and methods: During 2006-2010, 101 patients with the mean age of 59 years, were treated for gastric adenocarcinoma, stage Ib-IIIC, with post-operative radiochemotherapy with capecitabine. Radical (R0) and non-radical (R1) resection of the tumor was performed in 97 and 4 patients, respectively. Treatment was started with the first cycle of chemotherapy with oral capecitabine (1250 mg m^2 twice daily on day 1-14), radiotherapy with the total dose of 45 Gy was added after 3 weeks. Patients were irradiated on linear accelerator with 15MV photon beams for five days per week, at a daily dose of 1.8 Gy. During radiotherapy patients received capecitabine in lower dose (825 mg/m^2 twice daily, 7 days per week), but one dose was taken 1 hour before irradiation and the second twelve hours after. Three cycles of chemotherapy were added after the end of radiotherapy in 3-week intervals.
Results: Postoperative ChT started 2.6–11.3 weeks after surgery (median 6 weeks). The treatment was completed according to the protocol in 59 patients. No death occurred due to the therapy. Stomatitis, dysphagia, nausea and vomiting, diarrhea, hand foot syndrome, stenocardia and alopecia of grade three occurred in 1, 0, 5, 2, 9, 4 and 3 patients, respectively. Some 56 patients lost weight as measured with respect to the weight they had at the beginning of treatment. The maximum body weight loss was 18.9% (mean 6.2%). The median follow-up time of 66 survivors was 4 years (range 2.5-5.7 years). At 5 years, locoregional control (LRC), disease-free survival (DFS), disease-specific survival (DSS) and overall survival (OS) rates were 95%, 69%, 74%, and 63%, respectively.
Conclusion: In operable gastric carcinoma, postoperative radiochemotherapy with capecitabine is feasible and its toxicity is low.

687P 利妥木单抗（R）联合表柔比星、顺铂、卡培他滨（ECX）治疗胃癌（G）或食管胃交界（EGJ）癌的II期研究的疗效、生物标记物及暴露-应答更新数据

687P UPDATED EFFICACY, BIOMARKER, AND EXPOSURE-RESPONSE DATA FROM A PHASE 2 STUDY OF RILOTUMUMAB (R) PLUS EPIRUBICIN, CISPLATIN, AND CAPECITABINE (ECX) IN GASTRIC (G) OR ESOPHAGOGASTRIC JUNCTION (EGJ) CANCER

I. Davidenko, T. Iveson, R.C. Donehower, et al.

背景：R（AMG 102）是一种研究性人源化肝细胞生长因子/分散因子单克隆抗体，是 MET 受体的配体。之前我们曾开展了一项 R+ECX 治疗 G / EGJ 癌的安慰剂对照、双盲、随机 II 期研究，并报告了 12.5 个月(mo)随访获得的安全性和疗效数据(Iveson et al, Eur J Cancer. 2011; 47(suppl 1):S443. abstract 6.504)。在此我们报告了 21.7 个月的随访数据。

方法：入组标准包括不可切除局部晚期或转移性G / EGJ腺癌；ECOG PS≤1；且入组前未针对该疾病进行全身性治疗。按照 1:1:1 的比例将患者(pts)随机分为 3 组，ECX（剂量分别为 50 mg/m^2 IV第 1 天，60 mg/m^2 IV第 1 天，625 mg/m^2 BID口服第 1-21 天）+R 15 mg/kg（ A组）；R 7.5mg/kg（B组）或安慰剂（C组）IV第 1 天，每 3 周一次。我们对总生存期（OS）和无进展生存期（PFS）进行了评价。采用IHC对存档肿瘤样本进行了MET蛋白测定。对所有患者的R血清浓度进行了测量。通过人群PK模型对个体的R稳态Cminss进行了估计。

结果：在 2009 年 10 月至 2010 年 6 月间，将 121 例患者（A / B / C 组：40/42/39 例）随机分入 3 个治疗组。数据见表格（截止到 2012 年 1 月 16 日）。

结论：在本项小型、随机、II 期研究中，R+ECX 方案可以改善 G / EGJ 癌患者的结局。高 MET 肿瘤和高 R 暴露组的治疗效果最好。这一结果与以往报告的数据一致，结果显示，16 个月后，A 组+B 组与 C 组数据的持续分离。计划开展一项 III 期研究，将对 R+ECX 治疗 MET 阳性 G / EGJ 癌的安全性和有效性进行评估。

Background:R (AMG 102) is an investigational, fully human monoclonal antibody to hepatocyte growth factor/scatter factor, the MET receptor ligand. Safety and efficacy of a placebo-controlled, double-blind, randomized phase 2 study of R+ECX in G/EGJ cancer from a 12.5-month (mo) follow up were previously reported (Iveson et al, Eur J Cancer. 2011; 47(suppl 1):S443. abstract 6.504). Updated data from a 21.7-mo follow up are presented.

Methods: Eligibility included unresectable, locally advanced or metastatic G/EGJ adenocarcinoma; ECOG PS ≤1; and no prior systemic therapy for this disease. Patients (pts) were randomized 1:1:1 to ECX (50 mg/m^2 IV day 1, 60 mg/m^2 IV day 1, 625 mg/m^2 BID orally days 1–21, respectively)+R 15 mg/kg (Arm A); R 7.5 mg/kg (Arm B); or placebo (Arm C) IV day 1 every 3 weeks. Overall survival (OS) and progression-free survival (PFS) were evaluated. MET protein was measured in archival tumor samples by IHC. R serum concentrations for all pts were measured. Individual R steady-state Cminss were estimated with a population PK model.

Results:121 pts (Arms A/B/C:40/42/39) were randomized Oct 2009 to June 2010. See table for data (Jan 16, 2012 cutoff).

Conclusions: Within the context of a small, randomized phase 2 study, R+ECX improved outcomes in G/EGJ cancer pts. The treatment effect was strongest in pts with high MET tumors and high R exposure. Consistent with previously reported data, these results show continued separation of Arm A+B vs C beyond 16 mo. A planned phase 3 study will test the safety and efficacy of R+ECX in MET-positive G/EGJ cancer.

表：687P
Table:687P

	中位OS (80% CI), mo / Median OS (80% CI), mo	OS HR (95% CI)	中位 PFS (80% CI), mo / Median PFS (80% CI), mo	PFS HR (95% CI)	
所有 pts / All pts	A+B 组 n=82 / Arm A+B n=82	10.6 (9.5–12.0)		5.7 (5.1–6.9)	
	C 组 n=39 / Arm A+B n=82	8.9(5.7–10.6)		4.2 (3.7–4.6)	
	A+B 组 vs C 组 / Arm A+B n=27		0.70 (0.45–1.09)		0.60(0.39–0.91)
METH*	A+B 组 n=27 / Arm A+B n=27	11.5 (9.2–12.1)		6.9 (5.5–7.5)	
	C 组 n=11 / Arm C n=11	5.7(4.5–10.4)		4.6 (3.7–5.2)	
	A+B 组 vs C 组 / Arm A+B vs C		0.34 (0.15–0.78)		0.44(0.20–0.96)
METH*, RH†	A+B 组 n=13 / Arm A+B n=13	17.6(13.3–21.0)		10.7(6.9–15.3)	
	C 组 n=11 / Arm C n=11	5.7(4.5–10.4)		4.6(3.7–5.2)	
	A+B 组 vs C 组 / Arm A+B vs C		0.18(0.06–0.52)		0.19(0.06–0.57)

* 肿瘤细胞 MET 阳性的患者超过 50%，† R 中位 Cminss ≥ 94 μg/mL 的患者.
*Pts with >50% tumor cells MET positive, †Pts with R median Cminss ≥ 94 μg/mL.

700P 伏立诺他（V）联合卡培他滨（X）和顺铂（P）作为晚期胃癌患者的一线治疗方案的 I 期剂量探索性研究

700P A PHASE I DOSE-FINDING STUDY OF VORINOSTAT (V) COMBINED WITH CAPECITABINE (X) AND CISPLATIN (P) AS FIRST-LINE THERAPY IN PATIENTS WITH ADVANCED GASTRIC CANCER

C. Yoo, M.H. Ryu, B.-Y. Ryoo, et al.

背景：本试验的目的是确定一种组蛋白去乙酰化酶抑制剂，伏立诺他（V）与卡培他滨（X）和顺铂（P）联合用于晚期胃癌治疗的推荐剂量（RD），并且探讨 RD 的 V-XP 方案的可行性。

患者和方法：本研究使用了标准的 3+3 方法，以确定在第一个疗程每 3 周一次V-XP治疗的RD。X（第 1-14 天，p.o.）、P（第 1 天，i.v.）和V（第 1-14 天，p.o.）的剂量按照以下方案逐渐增加：在第 1 个剂量水平，X 1600 mg/m^2/天，P 60 mg/m^2，V 300mg/天；在第 2A剂量水平，X 1600 mg/m^2/天，P 60 mg/m^2, V 400 mg/天；在第 2B剂量水平，X 2000 mg/m^2/天, P 60 mg/m^2，V 300 mg/天；在第 3 个剂量水平，X 2000 mg/m^2/天，P 60 mg/m^2，V 400 mg/天；在第 4 个剂量水平，X 2000 mg/m^2/天，P 80 mg/m^2，V 400 mg/天。

结果：共有 24 例患者入组。中位年龄为 50 岁（范围 25-66 岁），11 例患者（46%）为男性。试验记录到剂量限制性毒性（DLT），第 1 个剂量水平的 6 例患者中有 1 例发生 DLT（4 级血小板减少症），第 2A 剂量水平的 3 例患者中 0 例发生 DLT，2B 剂量水平的 6 例患者中有 1 例发生 DLT（3 级疲劳），第 3 个剂量水平的 6 例患者中有 1 例发生 DLT（3 级口腔炎），第 4 个剂量水平的 3 例患者中有 2 例发生 DLT（4 级血小板减少，以及因 3 级厌食和 3 级疲劳而停用超过 25%处方剂量的 X 或 V）。第 4 个剂量水平为最大耐受剂量，将第 3 个剂量水平确定为 RD。另外有 6 例患者入组第 3 个剂量水平以确认 RD 的可行性，在这些患者中没有发生 DLT。在接受第 3 个剂量水平的 12 例患者中，中位化疗疗程数量为 6 个疗程（范围 3-10 个疗程），最常见的 3/4 级的毒性反应为中性粒细胞减少症（n=5，42%），厌食（n=3，25% ）。总体而言，研究证实 19 例病灶可测量患者中，9 例患者（47%）实现客观缓解。在 9 个月的中位随访期，中位无进展生存期为 7 个月（95%可信区间，4-10 个月），没有达到中位总生存期。

结论：V-XP方案主要的DLT为血小板减少、乏力、厌食、口腔炎。在晚期胃癌患者中推荐进一步研究的化疗方案是X（2000 mg/m^2/天 第 1-14 天），P（60 mg/m^2，第 1 天），和V（400 mg/天 第 1-14 天），每 3 周一次。

Background: The purpose of this trial is to determine the recommended dose (RD) of vorinostat (V), a histone deacetylase inhibitor, in combination with capecitabine (X) and cisplatin (P) and to explore feasibility of V-XP at the RD in advanced gastric cancer.

Patients and methods: The standard 3+3 method was used to determine the RD of 3-weekly V-XP during the first cycle. The doses of X (days 1-14, p.o.), P (day 1, i.v.), and V (days 1-14, p.o.) were escalated as following scheme; X 1,600 mg/m^2/ day, P 60 mg/m^2, V 300 mg/day in level 1; X 1,600 mg/m^2/ day, P 60 mg/m^2, V 400 mg/ day in level 2A; X 2,000 mg/m^2/ day, P 60 mg/m^2, V 300 mg/ day in level 2B; X 2,000 mg/m^2/ day, P 60 mg/m2, V 400 mg/ day in level 3; X 2,000 mg/m^2/ day, P 80 mg/m^2, V 400 mg/ day in level 4.

Results:A total of 24 patients were enrolled. Median age was 50 years (range, 25-66), and 11 (46%) were male. Dose limiting toxicity (DLT) was noted in 1 of 6 in level 1 (Grade 4 thrombocytopenia), 0 of 3 in level 2A, 1 of 6 in level 2B (Grade 3 fatigue), 1 of 6 in level 3 (Grade 3 stomatitis) and 2 of 3 in level 4 (Grade 4 thrombocytopenia, and discontinuation of X or V more than 25% of prescribed dosage due to Grade 3 anorexia and Grade 3 fatigue). Level 4 was maximal tolerated dose, and RD was determined as level 3. Six additional patients were enrolled at level 3 to confirm the feasibility, and DLT was not occurred. In 12 patients who received dose level 3, median 6 cycles (range, 3-10) of chemotherapy were given and most frequent Gr 3/4 toxicities were neutropenia (n=5, 42%) and anorexia (n=3, 25%). In overall, the objective responses were confirmed in 9 (47%) out of 19 patients with measurable lesions. With a median follow-up of 9 months, median progression-free survival was 7 months (95% confidence interval, 4 to 10 months), and median overall survival was not reached.

Conclusion: Major DLTs of V-XP were thrombocytopenia, fatigue, anorexia and stomatitis. The 3-weekly schedule of X (2,000 mg/m^2/ day on day 1-14), P (60 mg/m^2 on day 1), and V (400 mg/day on day 1-14) is recommended for further development of this regimen in patients with advanced gastric cancer.

698P 紫杉醇静脉注射和腹腔注射联合 S-1 治疗远端腹膜转移胃癌患者的 II 期临床研究

698P PHASE II STUDY OF INTRAVENOUS AND INTRAPERITONEAL PACLITAXEL COMBINED WITH S-1 FOR GASTRIC CANCER WITH METASTASES TO THE DISTANT PERITONEUM

H. Ishigami, J. Kitayama, H. Yamaguchi, et al.

背景：腹腔（i.p.）化疗对胃癌腹膜转移是一种有前景的治疗方案。我们之前曾开展紫杉醇（PTX）静脉注射（i.v.）和 i.p.联合 S-1 治疗的 I 期和 II 期临床研究，并在肉眼可见腹膜转移和/或腹腔细胞学检查发现癌细胞的胃癌患者中验证了该方案的安全性和有效性（Oncology 2009, Ann Oncol 2010）。日本卫生劳动及福利部已经批准了这一先进的医疗方案，日本医疗保险系统通过这一批准尚需要进一步的临床研究。因此，我们在肉眼可见腹膜转移的胃癌患者中开展了 II 期研究。

患者和方法：将通过分期腹腔镜检查证实的肉眼可见腹膜转移的胃癌患者纳入研究。在第 1 天和第 8 天，PTX i.v. 50 mg/m^{2}和i.p. 20 mg/m^{2}治疗，每天两次。S-1 80 mg/m^2/天口服用药，每天 2 次连续给药 14 天，之后停药 7 天。主要终点是 1 年总生存率。次要终点为缓解率、对恶性腹水的有效性和安全性。

结果：35 例患者入组。所有患者都有数处至多处腹膜远端转移灶。中位疗程数为 11 个（范围 2-29 个）。1 年总生存率为 77%（95%CI，63%-91%）。7 例靶病变患者的总有效率为 71%。9 例（67%）大量腹水患者中，6 例患者的恶性腹水消退或减少。29 例患者中，有 28 例患者（97%）腹腔细胞学检查没有再检测到肿瘤细胞。3/4 级血液学和非血液学毒性的发生率分别为 34%和 9%，所有这些毒性反应都是可控制和可逆的。常见 3/4 级毒性包括中性白血球减少（34%）、白细胞减少（23%）和贫血（10%）。没有与治疗相关的死亡发生。

结论：PTX i.v. 和 i.p.（每周一次）与 S-1 联合化疗方案对肉眼可见腹膜转移的胃癌患者有效且耐受性良好。

Background: Intraperitoneal (i.p.) chemotherapy is a promising treatment option for gastric cancer with peritoneal metastasis. We previously carried out phase I and phase II studies of intravenous (i.v.) and i.p. paclitaxel (PTX) combined with S-1, and verified the safety and efficacy in gastric cancer with macroscopic peritoneal metastasis and/or cancer cells on peritoneal cytology (Oncology 2009, Ann Oncol 2010). This regimen was approved as an advanced medical treatment by the Ministry of Health, Labour and Welfare of Japan, and further clinical studies were required for approval of coverage by the Japanese Health Insurance System. Therefore, we carried out another phase II study in gastric cancer patients with macroscopic peritoneal metastasis.

Patients and methods: Gastric cancer patients with macroscopic peritoneal metastasis confirmed by staging laparoscopy were enrolled. PTX was administered i.v. at 50 mg/m^2 and i.p. at 20 mg/m^2 on days 1 and 8. S-1 was administered orally twice daily at 80 mg/m^2/day for 14 consecutive days followed by 7 days rest. The primary endpoint was the 1-year overall survival rate. Secondary endpoints were the response rate, efficacy against malignant ascites and safety.

Results: Thirty-five patients were enrolled. All patients had several to numerous metastases to the distant peritoneum. The median number of courses was 11 (range 2-29). The 1-year overall survival rate was 77% (95% CI, 63-91%). The overall response rate was 71% in 7 patients with target lesions. Malignant ascites disappeared or decreased in 6 of 9 (67%) patients with massive ascites. Cancer cells ceased to be detected by peritoneal cytology in 28 of 29 (97%) patients. The incidences of grade 3/4 hematological and non-hematological toxicities were 34% and 9%, respectively, all of which were manageable and reversible. The frequent grade 3/4 toxicities included neutropenia (34%), leukopenia (23%) and anemia (9%). There were no treatment-related deaths.

Conclusion: Combination chemotherapy of weekly i.v. and i.p. PTX combined with S-1 is well tolerated and active in gastric cancer patients with macroscopic peritoneal metastasis.

779TiP　S-1 每 2 周方案加紫杉醇（SPA）或奥沙利铂（SOX）作为晚期胃癌患者的一线化疗方案的随机 II 期试验：初步结果

779TiP　A RANDOMIZED PHASE II TRIAL OF BIWEEKLY S-1 WITH PACLITAXEL (SPA) OR OXALIPLATIN (SOX) AS FIRST-LINE CHEMOTHERAPY IN ADVANCED GASTRIC CANCER PATIENTS:PRELIMINARY RESULTS

M. Haibo, W. Fang, Y. Zheng, et al.

背景：接受含 S-1 化疗方案的胃癌患者常需要 3 周或更长时间治疗，以确保暴露于治疗剂量 2 周。在第 2 周治疗期间，往往会发生 S-1 的重度副作用，如黏膜炎、腹泻和中性粒细胞减少症等。我们在晚期胃癌患者中，评价了每隔一周 S-1 方案联合紫杉醇或奥沙利铂一线化疗的有效性和安全性。

患者和方法：将病理学确证晚期胃癌的合格患者随机分为两组。S-1（80 mg/m^2/天）口服给药，连续 7 天，在第 1 天联合紫杉醇 120 mg/m^2（SPA）或奥沙利铂 85 mg/m^2 (SOX)治疗，随后停药 7 天。以每两周一疗程的方式持续给药，直至疾病进展、发生不可接受的毒性或患者拒绝继续治疗。主要终点是总缓解率（ORR）。次要终点为无进展生存期（PFS）、总生存期（OS）和安全性。

结果：2010 年 6 月至 2012 年 3 月间，81 例胃癌患者入组。患者随机接受 SPA（43 例）或 SOX（38 例）治疗。76 例患者的结果如下： A 组的 ORR 为 43.6%，B 组为 33.3%，组间无显著差异（P=0.35）。A 组的中位 PFS 为 6.2 个月，B 组为 5.1 个月（P=0.80），A 组的中位 OS 为 10.8 个月，B 组为 10.0 个月（P=0.17）。研究期间没有发生与治疗相关的死亡。最常见的毒性为中性粒细胞减少症（A 和 B 组 3/4 级中性粒细胞减少症的发生率分别为 30.8% 和 17.4%）。最常见的非血液学毒性是粘膜炎，腹泻、外周神经病，发生所有上述毒性的患者都不足 5%。

结论：这些初步研究结果表明，晚期胃癌患者接受含每两周方案 S-1 治疗，ORR 可以接受且副作用可以耐受。本研究计划入组 100 例患者。

Background: Gastric cancer patients are commonly treated with S-1-based chemotherapy for three weeks or more to ensure two weeks of exposure at therapeutic doses. Severe side effects of S-1 such as mucositis, diarrhea and neutropenia often occur in the second week of treatment. We evaluated the activity and safety of every other week S-1 regimens with paclitaxel or oxaliplatin combinations as first-line chemotherapy in advanced gastric cancer patients. Patients and methods:Eligible patients with pathologically confirmed advanced gastric cancer patients were randomized into two arms. S-1 was administered orally (80 mg/m^2/day) for 7 consecutive days in combination with paclitaxel 120 mg/m^2 (SPA) or oxaliplatin 85 mg/m^2 (SOX) on day 1 followed by a 7-day rest. Treatment continued in a biweekly manner until disease progressed, unacceptable toxicity was observed or the patient refused to continue. The primary endpoint was overall response rate (ORR). The secondary endpoints were progression-free survival (PFS), overall survival (OS) and safety.

Results: Eighty-one gastric cancer patients were enrolled from June 2010 to March 2012. Patients were randomized to receive SPA (43) or SOX (38). Results are presented for 76 patients. The ORR for arm A was 43.6%, and that for arm B was 33.3% with no significant difference between the two arms (p=0.35). The median PFS was 6.2 months for arm A vs. 5.1 months for arm B (p=0.80); the median OS was 10.8 months for arm A and 10.0 months for arm B (p=0.17). No treatment-related deaths occurred during the study. The most frequent toxicity was neutropenia (30.8% and 17.4% of grade 3/4 in arms A and B, respectively). The most common non-hematological toxicities were mucositis, diarrhea, and peripheral neuropathy, all in less than 5% of patients.

Conclusions: These preliminary findings suggest that biweekly S-1-based regimens have an acceptable ORR with tolerable side effects in advanced gastric cancer patients. The study will continue until 100 patients have been enrolled.

690P　多西他赛、顺铂和氟尿嘧啶（DCF）对比顺铂+氟尿嘧啶（CF）作为中国晚期胃癌患者一线治疗的随机、对照III期试验

690P　A RANDOMIZED, CONTROLLED PHASE III TRIAL OF DOCETAXEL, CISPLATIN AND FLUOROURACIL (DCF) VERSUS CISPLATIN PLUS FLUOROURACIL (CF) AS FIRST-LINE THERAPY IN CHINESE ADVANCED GASTRIC CANCER

L. Shen, R. Xu, J. Wang, et al.

背景：在中国,胃癌是第 2 大常见癌症，每年因其死亡的人数超过 20 万。因此对胃癌患者而言，需要有效的治疗方案以改善治疗结局。TAX 325 研究证实，在西方人群中，DCF 方案较 CF 具有 OS 获益和较高毒性。因此，在这项前瞻性、多中心、开放性、随机、平行对照、III 期临床研究中，我们对改良的 DCF（mDCF）方案治疗中国晚期胃癌患者的疗效进行了研究。

方法：将既往没有接受过姑息性化疗的晚期胃癌患者随机分为两组，一组接受mDCF治疗（多西他赛 60mg/m^{2}静脉滴注（IV）1 小时，第 1 天顺铂 60mg/m^2 IV 1-3 小时，随后氟尿嘧啶IV 600mg/m^2 / d，连续用药 5 天，每 3 周为 1 疗程），一组接受改良的CF（mCF）治疗（第 1 天，顺铂 75mg/m^2 IV 1-3 小时，随后氟脲嘧啶IV 600mg/m^2/d，连续用药 5 天，每 3 周为 1 疗程）。持续治疗至疾病进展、发生不可接受的毒性、死亡或主动退出。研究的主要终点是无进展生存期（PFS）。

结果：在 2008 年 11 月至 2010 年 12 月间，共 241 例患者接受了随机化，234 例患者接受了治疗和数据分析（MDCF=119，MCF=115）。mDCF 组较 mCF 组的 PFS 显著延长（HR 0.63，95%CI，0.48-0.85 ;P=0.0018，中位 PFS 分别为 7.2 个月比 4.9 个月），并观察到 OS 延长的趋势（HR，0.78; 95%CI，0.58-1.05，P=0.099，中位 OS 分别为 10.2 个月比 8.5 个月）。mDCF 组较 mCF 组的总有效率（ORR）显著提高（58%比 39%，P=0.0244）。与治疗相关的 3/4 级不良事件（AE）发生率分别为 75.6%（DCF）和 33.0%（CF），P <0.0001。最常见的 3/4 AE 包括中性粒细胞减少（60.5%比 8.7%）、腹泻（12.6%比 0）、呕吐（7.6%比 11.3%）和发热性中性粒细胞减少（12.6%比 0）。

结论：mDCF 方案的 PFS 和 ORR 有显著改善。本研究的安全性数据与既往报告一致。mDCF 可以作为未经治疗的中国晚期胃癌患者的一种治疗选择。

Background: Gastric cancer is the second prevalent cancer in China accounting for more than 200,000 deaths per year. Effective regimens are needed to improve the outcome for gastric cancer patients. TAX 325 study has demonstrated OS benefit and high toxicity of DCF regimen compared with CF in western population. Thus we investigated the effect of modified DCF (mDCF) regimen in Chinese patients with advanced gastric cancer in this prospective, multicenter, open-label, randomized and parallel-controlled phase III study.

Methods: Eligible no prior palliative chemotherapy, advanced gastric cancer patients were randomized to either mDCF (Docetaxel 60mg/m^2 1-hour intravenous infusion (IV) and cisplatin 60mg/m^2 1-3-hour IV on day 1, followed by fluorouracil 600mg/m^2/d continuous IV for 5 days, every 3 weeks) or modified CF (mCF) (cisplatin 75mg/m^2 1-3-hour IV on day 1, followed by fluorouracil 600mg/m^2/d continuous IV for 5 days, every 3 weeks). Treatment continued until disease progression, unacceptable toxicity, death, or consent withdrawal. The primary end point was progression-free survival (PFS).

Results: Between Nov 2008 and Dec 2010, a total of 241 patients were randomized, 234 patients were treated and analyzed (mDCF=119, mCF=115) PFS was prolonged with mDCF vs mCF significantly (HR, 0.63; 95% CI, 0.48 to 0.85; P=0.0018; median PFS, 7.2 months vs.4.9 months), the trend of OS improvement was seen (HR, 0.78; 95% CI, 0.58 to 1.05; P=0.099; median OS 10.2 months vs. 8.5 months), Overall best response rate (ORR) was improved significantly with mDCF vs mCF (58% vs 39%, P=0.0244). Treatment related grade 3/4 AEs occurred in 75.6% (DCF) vs 33.0% (CF), P<0.0001. The most frequent 3/4 AEs included neutropenia (60.5% vs 8.7%), diarrhea (12.6% vs 0), vomiting (7.6% vs 11.3%) and febrile neutropenia (12.6% vs 0).

Conclusion:mDCF regimen significantly improved PFS and ORR. The safety profile was consistent with previous report. mDCF should be considered as an option for untreated Chinese advanced gastric cancer patients.

701P　高剂量亚叶酸钙、静脉 5-氟尿嘧啶、多西他赛和顺铂（改良的 DCF方案）每 2 周方案用于晚期胃腺癌患者

701P　BIMONTHLY REGIMEN OF HIGH DOSE LEUCOVORIN, INFUSIONAL 5-FLUOROURACIL, DOCETAXEL AND CISPLATIN (MODIFIED DCF) IN ADVANCED GASTRIC ADENOCARCINOMA

I.T. Unek, T. Akman, I. Oztop, et al.

多西他赛、顺铂和 5-氟尿嘧啶（DCF）联合化疗是一种有效但毒性很高的晚期胃癌治疗方案。在肿瘤姑息性化疗中，确保疗效的同时必须改善药物安全性。我们开发了一种改良的DCF方案，其目标是最大限度地减轻毒性且不影响其疗效。在研究中，70 例晚期胃癌患者接受了治疗。每 2 周为一个疗程，方案包括多西他赛（60 mg/m^2）、顺铂（50 mg/m^2）、5-氟尿嘧啶（400 mg/m^2）静脉推注和 5-氟尿嘧啶（2400 mg/m^2）IV 46 小时以上，加亚叶酸钙（400mg/m^2）IV 2 小时以上。中位无进展生存期和总生存期分别为 9.0 个月（95%CI，7.1-10.9）和 10.8 个月（95%CI，7.4-14.2）；1 年和 2 年生存率分别为 46.3%和 18.4%。研究发现 29 例患者（41.4%）部分缓解，19 例患者（27.1%）疾病稳定，22 例患者（31.4%）疾病进展。3-4 级毒性包括中性粒细胞减少（37.1%）、发热性中性粒细胞减少（15.7%）、血小板减少（10.0%）、贫血（8.6%）、恶心和呕吐（10.0%）、口腔炎（5.7%）、感染（8.6%）、腹泻（2.9%）。总之，我们的研究结果表明，改良的DCF方案的不良反应可以耐受，该方案是一种有效且便利的晚期胃癌姑息性疗法。

The combination of docetaxel, cisplatin and 5-fluorouracil (DCF) is an effective but highly toxic regimen for the treatment of advanced gastric cancer. In the palliative chemotherapy of tumors, it is necessary to improve the drug safety while ensuring efficacy. We developed a modified DCF regimen with goal to minimize toxicity without compromising efficacy. In our study, seventy patients with advanced gastric cancer were treated. Each 2-week cycle consisted of docetaxel (60 mg/m^2), cisplatin (50 mg/m^2), 5-fluorouracil (400 mg/m^2) IV bolus and 5-fluorouracil (2400 mg/m^2) IV over 46 hours plus leucovorin (400 mg/m^2) IV over 2 hours. The median progression-free survival and overall survival were 9.0 months (95% CI, 7.1-10.9) and 10.8 months (95% CI, 7.4-14.2), respectively; the 1-year and 2-year survival rates were 46.3% and 18.4%, respectively. Twenty-nine (41.4%) partial responses, 19 (27.1%) stable disease, and 22 (31.4%) progression of disease were observed. Grade 3-4 toxicities included neutropenia (37.1%), febrile neutropenia (15.7%), thrombocytopenia (10.0%), anemia (8.6%), nausea and vomiting (10.0%), stomatitis (5.7%), infection (8.6%), diarrhea (2.9%). In summary, our results show that a modified DCF regimen may have tolerable toxicities and be an effective and convenient palliative treatment of advanced gastric cancer.

LBA3　西妥昔单抗联合卡培他滨和顺铂作为晚期胃癌的一线治疗：随机对照 III 期扩展研究

LBA3　CETUXIMAB IN COMBINATION WITH CAPECITABINE AND CISPLATIN AS FIRST-LINE TREATMENT IN ADVANCED GASTRIC CANCER:RANDOMIZED CONTROLLED PHASE Ⅲ EXPAND STUDY

F. Lordick, G. Bodoky, H. Chung et al.

背景：晚期胃癌的预后较差，对更有效的晚期胃癌治疗方法仍有很大的临床需求未满足。在 II 期研究中，西妥昔单抗（一种 EGFR 抗体）+一线氟嘧啶联合伊立替康或铂类药物表现出显著的活性。这项开放性、随机、对照 III 期研究（EudraCT 编号：2007-004219-75）对卡培他滨和顺铂+/-西妥昔单抗治疗胃癌和食管胃交界处癌进行了评估。

方法：将患者随机（1:1）分配接受卡培他滨（X，Xeloda®）1000 mg/m^{2}每日两次给药（第 1-15 天，每 3 周一个疗程）和静脉顺铂（P）80 mg/m^2（第 1 天）+每周一次西妥昔单抗（第 1 天）400 mg /m^{2}初始输注，然后是 250 mg/m^2/周，每 3 周一个疗程；或接受卡培他滨+顺铂（XP）治疗。主要终点是由设盲的独立审查委员会（IRC）评估的无进展生存期（PFS）。次要终点包括总生存期（OS）、最佳总体缓解率（ORR）和安全性。

结果：在 2008 年 6 月和 2010 年 12 月之间，25 个国家的 904 例患者接受了随机分配；455 例患者随机分配到 XP +西妥昔单抗组，449 例随机分配到 XP 组。大部分患者为男性（74%），患有胃癌（83%）和转移性疾病（97%）。两个治疗组间的基线特征分布均衡。西妥昔单抗治疗的中位持续时间为 14.9 周，88%患者接受的相对剂量强度≥80%。两个治疗组间 X 和 P 的暴露量相似。两个治疗组间的 PFS、OS 和最佳总体缓解相似（见下表），而且各亚组间的 PFS 和 OS 结果相似。XP +西妥昔单抗组中 3/4 级和严重不良事件多于 XP 组（见下表）。安全性特征与这些药物的已知特征一致。

结论：对于晚期胃癌的一线治疗，XP+西妥昔单抗联合治疗与 XP 治疗相比并未表现出益处。可能需要对这种异质性疾病进行进一步分类以改善患者治疗。

Background: There is a high unmet clinical need for more efficacious treatment in advanced gastric cancer, which has a poor prognosis. In phase II studies, cetuximab, an EGFR antibody,+first-line fluoropyrimidine with irinotecan or platinum compounds showed promising activity. This open-label, randomized, controlled phase III study (EudraCT No:2007-004219-75) investigated capecitabine and cisplatin +/- cetuximab in gastric and gastroesophageal junction cancer.

Methods: Patients (pts) were randomized (1:1) to 3-week cycles of twice daily (days1-15) capecitabine (X, Xeloda®) 1000 mg/m^2 and iv cisplatin (P) 80 mg/m^2(day 1)+weekly cetuximab (day 1) 400 mg /m^2 initial infusion followed by 250 mg/m^2/week thereafter, or XP alone. The primary endpoint was progression-free survival (PFS) assessed by blinded independent review committee (IRC). Secondary endpoints included overall survival (OS), best overall response (IRC) and safety.

Results: Between June 2008 and December 2010, 904 pts from 25 countries were randomized; 455 to XP+cetuximab and 449 to XP alone. Most were male (74%), had stomach cancer (83%) and metastatic disease (97%). Baseline characteristics were balanced between treatment arms. Median duration of cetuximab treatment was 14.9 weeks with relative dose intensity ≥80% received by 88% of pts. Exposure to X and P was similar between treatment arms. PFS, OS and best overall response were similar between the treatment arms (Table) with comparable results for PFS and OS across subgroups. More grade 3/4 and serious adverse events were found in the XP+cetuximab vs XP arm (Table). Safety profiles were consistent with those known for these agents.

Conclusions:XP+cetuximab showed no benefit compared with XP alone in the first-line treatment of advanced gastric cancer. Further classification of this heterogeneous disease may be required before advances in patient treatment are to be made.

	XP+西妥昔单抗/ XP+cetuximab	XP
有效性分析[a]/ Efficacy analysis[a]		
患者数量/ Number of patients	455	449
PFS（IRC）		
中位值，月[95% CI]/ Median, months [95% CI]	4.4 [4.2–5.5]	5.6 [5.1–5.7]
分层 HR [95% CI]/ Stratified HR [95% CI]	1.091 [0.9 20 – 1.292]	
分层时序检验 p 值 / Stratified log-rank p value	0.3158	
OS		
中位值，月[95% CI]/ Median, months [95% CI]	9.4 [8.3–10.6]	10.7 [9.4 –11.3]
分层 HR [95% CI]/ Stratified HR [95% CI]	1.004 [0.8 66 – 1.165]	
分层时序检验 p 值/ Stratified log-rank p value	0.9547	
最佳总体缓解 (IRC)/ Best overall response (IRC)		
ORR[b]，% [95% CI]	30 [26 –34]	29 [25 –34]
安全性分析摘要/ Summary of safety analysis		
患者数量/ Number of patients	446	436
任何 AE，%/Any AEs, %	100	99
3-4 级 AE，%/ Grade 3-4 AEs, %	83	77
任何严重 AE，%/ Any serious AEs, %	54	45

[a]分层因素为疾病状态、既往食管胃切除术、既往新辅助治疗/放化疗。

[a] Stratification factors were disease status, prior esophago-/gastrectomy, prior neo adjuvant/radiochemotherapy.

[b]ORR=完全缓解+部分缓解。

[b] ORR=complete response+partial response.

AE，不良事件；CI，置信区间；HR，风险比；IRC，独立审查委员会；ORR，最佳总体缓解率；OS，总生存期；PFS，无进展生存期。

AE, adverse event; CI, confidence interval; HR, hazard ratio; IRC, independent review committee; ORR, best overall response rate; OS, overall survival; PFS, progression-free survival.

680P 将卡妥索单抗用于原发性可切除胃癌的多元疗法的II期研究的 2 年随访结果

680P 2-YEAR FOLLOW-UP OF A PHASE II STUDY ON CATUMAXOMAB AS PART OF A MULTIMODAL APPROACH IN PRIMARILY RESECTABLE GASTRIC CANCER

C. Bokemeyer, K. Ridwelski, D. Atanackovic, et al.

背景：在随机试验中已经证明了围手术期化疗（CT）用于局部晚期胃癌（GC）患者的生存获益。然而，总治愈率仅为 30%-40%，并且很多患者不能够接受 CT 方案术后部分的治疗。在欧洲，基于一项纳入 GC 患者的关键性试验，批准将三功能抗体卡妥索单抗用于治疗恶性腹水。我们开展了一项单组、多中心、II 期临床研究，对一种新多元疗法进行了评估，该方法为新辅助 CT，然后行胃切除术，并且腹腔注射（i.p.）卡妥索单抗免疫治疗。在此我们报告了 2 年的随访数据。

方法：GC 患者（T2/T3/T4，N+/-，M0）接受 3 个疗程的新辅助含氟嘧啶/铂 CT，然后行′en-bloć R0-胃切除术。在术中腹腔推注卡妥索单抗（10 μg），然后连续 4 次输液，每次 3 小时，剂量为 10-150μg。主要安全终点是术后 30 天内的特定术后并发症的发生率。主要疗效终点包括无疾病生存期（DFS）和总生存期（OS）。

结果：初步研究数据在 2011 年 WCGC（Schuhmacher 等人，Ann Oncol (2011) 22(suppl. 5)）中进行了陈述，数据显示符合主要终点，并且描述治疗方案安全。在手术时，根据 pTNM 分期对患者进行评估，27.8%的患者为 I 期，27.8%的患者为 II 期，22.3%的患者为 III 期，14.8%的患者为 IV 期。在 24 个月时，54 例患者（安全性分析集）中，39 例患者仍然生存，14 例患者死亡，（一例患者失访），37 例患者中，24 例患者疾病没有进展，仅 13 例患者疾病复发（2 例患者的疾病状态没有记录）。在 2 年截止日期时，DFS 为 56.4%（95%CI：41-69%），OS 为 75%（95%CI：60-85%）。

结论：卡妥索单抗作为多元疗法中的一部分，用于原发性可切除 GC 是可行的。2 年随访的疗效结果显示了一个局部晚期胃癌患者队列中有可期待的 DFS 和 OS 数据。

Background: Perioperative chemotherapy (CT) has demonstrated as survival benefit in locally advanced gastric cancer (GC) in randomized trials. However, the overall cure rate is 30-40% and a significant number of patients are not able to receive the postoperative part of their CT regimen. In Europe, the trifunctional antibody catumaxomab is approved for the treatment of malignant ascites based on a pivotal trial which also included GC patients. A new multimodal approach combining neoadjuvant CT, followed by gastrectomy and intraperitoneal (i.p.) immunotherapy with catumaxomab was assessed in a single-arm multicenter phase II study. We here report 2-year follow-up data.

Methods:GC pts (T2/T3/T4, N+/–, M0) received 3 cycles of neoadjuvant fluoropyrimidin/platinum-based CT followed by ′en-bloć R0-gastrectomy. Catumaxomab was administered i.p. as intraoperative bolus (10 μg) followed by 4 consecutive 3-hour infusions of 10-150 μg. Primary safety endpoint was the rate of predefined postoperative complications observed during 30 days after surgery. Key efficacy endpoints included disease-free (DFS) and overall survival (OS).

Results: The original study data presented at the WCGC in 2011 (Schuhmacher et al., Ann Oncol (2011) 22(suppl. 5)) showed that the primary endpoint was met and the described application regimen is safe. At time of surgery, 27.8% of patients were stage I, 27,8% of patients were stage II, 22,3% of patients were stage III and 14,8% of patients were stage IV as assessed according to pTNM measures. At 24 months 39/54 (safety analysis set) patients were still alife,14/54 were dead, (one patient lost to follow-up), 24/37 had no progression, only 13/37 patients relapsed (for 2 patients disease status was not recorded). At the 2 year cut off DFS was 56.4% (95% CI:41–69%), OS was 75% (95% CI:60–85%).

Conclusions: Catumaxomab as part of a multimodal therapy in primarily resectable GC is a feasible option. The 2-year follow up efficacy results show promising data for DFS and OS in a cohort of locally advanced gastric cancer pts.

691P 依维莫司（EVE）治疗既往接受过治疗的晚期胃癌（AGC）患者
691P EVEROLIMUS (EVE) EXPOSURE IN PATIENTS (PTS) WITH PREVIOUSLY TREATED ADVANCED GASTRIC CANCER (AGC)

S.-E. Al-Batran, N. Tebbutt, J. Xu, et al.

背景：在 GRANITE 1 研究中，EVE 治疗与最佳支持治疗（BSC）相比，并不能显著延长既往接受过治疗的 AGC 患者的总生存期（OS）（EVE 组中位 OS 为 5.4 个月，BSC 组为 4.3 个月； HR，0.90；P=0.1244）。EVE 组与 BSC 组的中位无进展生存期（PFS）分别为 1.7 个月与 1.4 个月（HR，0.66；P <.0001）。本分析对 EVE 暴露量及其与有效性和安全性的关系进行了观察。

方法：将确诊 AGC 且在 1 线或 2 线化疗后疾病进展的患者以 2:1 的比例随机分入 EVE 10 mg/d+BSC 组或安慰剂+BSC 组。主要终点为 OS。在给药前、给药后第 5 周第 1 天的 1 小时和 2 小时采集全血血样，使用液相色谱/质谱法（定量下限为 0.3 ng/mL）对 EVE 的 Cmin 和 Cmax 进行测定。按照地区（亚洲/世界其他国家 [ROW]）和胃切除术（是/否）对 Cox 模型进行调整，并且用于探索 PFS 与时间标准化（TN）的 EVE Cmin 之间的关系。采用线性混合效应模型探索基线目标病灶的大小和 TN Cmin 变化之间的关系。绘制特定不良事件（AE）比 TN Cmin 类型的 Kaplan-Meier 曲线。

结果：从 2009 年 7 月至 2010 年 12 月，656 例患者入组研究，并且接受 EVE（n= 439）或安慰剂（n=217）治疗。患者的中位年龄为 62 岁，74%为男性，55%来自亚洲，50%之前接受了胃切除术。在接受 EVE 10 mg/d 给药的患者中，采样时 Cmin 和 Cmax 的平均值±SD 分别为 16.1±10.8 ng / mL 和 72.8±36.5 ng / mL。来自亚洲和 ROW 的患者无论是否接受胃切除术，EVE 的 Cmin 和 Cmax 均相似。研究观察到的 TN Cmin 和 PFS（HR，0.83; 95%CI，0.65-1.06）之间没有显著关联。TN Cmin 增加 2.72 倍，目标病灶体积与基线值相比相应地显著缩小 7.6%。对于 TN Cmin <10 ng/mL 与 TN Cmin 10-25 ng/mL 的患者，发生非感染性肺炎、口炎/口腔粘膜炎、传染/感染的风险没有显著差异。Cmin 10-25 ng/mL 组发生的肾脏事件更多（与 TN Cmin <10 ng/mL 组相比为 4 例比 1 例）。

结论：研究观察到的 EVE 暴露量与之前 EVE 10 mg/d 的研究一致。地区和既往胃切除术不会对暴露量产生影响。EVE Cmin 增加可使肿瘤体积产生相应更大程度的缩小。除了肾脏事件（较高 Cmin 水平时更常见）外，EVE 暴露量不会对特定临床显著不良事件的发生风险产生影响。

Background: In GRANITE 1, EVE did not significantly improve overall survival (OS) over best supportive care (BSC) in previously treated AGC (median OS 5.4 mo with EVE vs 4.3 mo with BSC; HR, 0.90; P=.1244). Median progression-free survival (PFS) was 1.7 mo with EVE vs 1.4 mo with BSC (HR, 0.66; P<.0001). This analysis examined EVE exposure and its relationship with efficacy and safety.

Methods: Pts with confirmed AGC who progressed after 1 or 2 chemotherapy lines were randomized 2:1 to EVE 10 mg/d+BSC or placebo+BSC. Primary endpoint was OS. EVE Cmin and Cmax were determined in whole blood from samples collected predose and 1 and 2 h postdose on day 1 of wk 5 using liquid chromatography/mass spectrometry (lower limit of quantification 0.3 ng/mL). Cox models adjusted for region (Asia/rest of world [ROW]) and gastrectomy (yes/no) were used to explore relationships between PFS and time-normalized (TN) EVE Cmin. A linear mixed-effects model was used to explore the relationship between change from baseline in target lesion size and TN Cmin. Kaplan-Meier curves for select adverse events (AEs) by TN Cmin categories were prepared.

Results:656 pts were enrolled from Jul 2009 to Dec 2010 and received EVE (n=439) or placebo (n=217). Median age was 62 y, 74% were men, 55% were from Asia, and 50% had previous gastrectomy. Mean ± SD Cmin and Cmax were 16.1 ± 10.8 ng/mL and 72.8 ± 36.5 ng/mL in pts receiving EVE 10 mg/d at sampling. EVE Cmin and Cmax were similar in pts from Asia and ROW and in pts with and without gastrectomy. No significant relationship between TN Cmin and PFS was observed (HR, 0.83; 95% CI, 0.65-1.06). A 2.72-fold increase in TN Cmin corresponded to a significant 7.6% reduction from baseline in target lesion volume. No differences in noninfectious pneumonitis, stomatitis/oral mucositis, or infection/infestation risk in pts with TN Cmin <10 ng/mL vs 10-25 ng/mL were observed. More renal events occurred in the TN Cmin 10-25 ng/mL group (4 vs 1 in TN Cmin <10 ng/mL group).

Conclusion:EVE exposure was consistent with that previously observed for EVE 10 mg/d. Region and prior gastrectomy did not impact exposure. Increased EVE Cmin corresponded to a greater reduction in tumor volume. EVE exposure did not affect the risk of selected clinically notable AEs except for renal events (more common with higher Cmin).

696P 西妥昔单抗联合改良FOLFIRI作为转移性胃癌患者二线治疗多中心、II期研究和预测性生物标记物分析

696P A MULTI-CENTER PHASE II STUDY AND PREDICTIVE BIOMARKER ANALYSIS OF COMBINED CETUXIMAB AND MODIFIED FOLFIRI AS SECOND-LINE TREATMENT IN PATIENTS WITH METASTATIC GASTRIC CANCER

L. Jin Shanghai/CN

背景：本研究旨在探索可以预测西妥昔单抗联合改良 FOLFIRI（mFOLFIRI）治疗临床结局的潜在生物标记物，并且分析本方案用作转移性胃癌患者二线治疗的安全性。

方法：共 61 例患者接受西妥昔单抗起始静脉（IV）治疗（400 mg/m^2），此后每周治疗一次（250 mg/m^2）。在每 14 天周期的第 2 天，患者接受IV伊立替康（180 mg/m^2）、亚叶酸钙（200 g/m^2）和 5-FU静脉推注（400 mg/m^2），随后持续静脉输注 5-FU（2400 mg/m^2）46 小时。主要研究终点为至疾病进展时间（TTP）。

发现：在 54 例可评价患者中，缓解率（RR）为 33.3%。在意向性治疗（ITT）分析中，中位 TTP 为 4.6 个月（95%可信区间[CI]：3.6-5.6 个月），中位总生存期（OS）为 8.6 个月（95%CI：7.3-9.9 个月）。研究表明，血管内皮生长因子（VEGF）血浆水平可能是治疗预后的预测因子。在低基线 VEGF 血浆水平（≤12.6 pg/ml）患者和高基线 VEGF 血浆水平（>12.6 pg/ml）患者中，RR 分别为 55.0%和 5.3%（P=0.001）；中位 TTP 分别为 6.9 个月和 2.8 个月（P=0.0005）；且中位 OS 分别为 12 个月和 5 个月（P <0.0001）。没有患者显示 KRAS、BRAF 或 PIK3CA 突变。

说明：将基线血浆 VEGF 低水平确定为一种可预测治疗预后的生物标记物。西妥昔单抗和 mFOLFIRI 联合治疗的耐受性良好，有用作晚期胃癌患者二线治疗的潜能。

Background: This study was conducted to explore potential biomarkers for predicting clinical outcome of cetuximab in combination with modified FOLFIRI (mFOLFIRI) and to analyze safety of this regimen as a second-line treatment in metastatic gastric cancer patients.

Methods:A total of 61 patients received an initial intravenous (IV) dose of cetuximab (400 mg/m^2) and weekly doses (250 mg/m^2) thereafter. On day 2 of each 14-day period, patients received IV irinotecan (180 mg/m^2), leucovorin (200 mg/m^2), and an IV bolus dose of 5-FU (400 mg/m^2) followed by a continuous infusion of 5-FU (2400 mg/m^2) for 46 hours. The primary endpoint was time-to-progression (TTP).

Findings: The response rate (RR) was 33.3% among 54 evaluable patients. In the intention-to-treat (ITT) analysis, median TTP was 4.6 months (95% confidential interval [CI]:3.6-5.6 months) and median overall survival (OS) was 8.6 months (95% CI:7.3-9.9 months). It was demonstrated that plasma vascular endothelial growth factor (VEGF) levels could be a predictive factor for the treatment prognosis. In patients with low (≤12.6 pg/ml) and high (>12.6 pg/ml) baseline ^{plasma} VEGF levels, RR values were 55.0% and 5.3%, respectively (P=0.001); median TTP values were 6.9 months and 2.8 months, respectively (P=0.0005); and median OS values were 12 months and 5 months, respectively (P<0.0001). None of these patients exhibited KRAS, BRAF, or PIK3CA mutations.

Interpretation: Low baseline plasma VEGF levels were identified as a potential predictive biomarker of prognosis. Combination therapy comprising cetuximab and mFOLFIRI was well tolerated, which would be potentially used as a second-line treatment for patients with advanced gastric cancer.

492P　一种口服酪氨酸激酶抑制剂，MGCD265 与埃罗替尼或多西他赛联合治疗晚期胃癌和非小细胞肺癌的临床疗效

492P　CLINICAL EFFECTS OF MGCD265, AN ORAL TYROSINE KINASE INHIBITOR, IN COMBINATION WITH ERLOTINIB OR DOCETAXEL FOR TREATMENT OF ADVANCED GASTROESOPHAGEAL AND NSCLC TUMORS

A. Patnaik, K. Papadopoulos, A.W. Tolcher, et al.

背景：MGCD265 是一种具有对抗 Met、VEGFR 1、2 和 3、 Tie-2 和 Ron 的 nM IC50 的多激酶抑制剂，在临床前模型中证实，本品具有广谱抗肿瘤作用。开展了一项 I 期研究，对 MGCD265 加多西他赛或厄洛替尼治疗实体瘤进行了评估。

方法：采用标准 3+3 设计方案，将晚期实体瘤患者纳入一项开放性、剂量递增研究。根据研究者制定的标准治疗，所有患者接受 MGCD265（p.o. QD 或 BID）加多西他赛或厄洛替尼治疗，每 3 周 1 个疗程。终点为联合治疗的安全性、药效学、药代动力学和抗肿瘤活性。

结果：在入组研究的 89 例患者中，12 例患非小细胞肺癌（NSCLC）（多西他赛组）和 9 例患胃食管癌（GE）（厄洛替尼组）。在 10 例疗效可评价 NSCLC 患者中，所有患者都符合疾病稳定（SD）标准持续≥2 个疗程（包括 2 例部分缓解）。5 例患者实现 SD 持续 5-16 个月，4 例患者的 SD 时间超过之前的治疗。2 例患者在第 1 次评价前死亡。3 例患者继续治疗。

9 例 GE 患者中，4 例患者实现 SD。3 例患者保持 SD10-18 个月，超出了既往治疗的时间。1 例患者仍在继续治疗。一项血浆 Met 磷酸化检测结果显示，在至今给予的剂量下，Met 磷酸化抑制达到 30%。PK 分析尚未进行。剂量递增研究仍在继续进行。毒性多为轻至中度。在每个治疗组中，20%的患者报告了≥3 级的非血液学不良事件（AE），这些 AE 主要与 GI 相关。同时也观察到预期的多西他赛相关血液学 AE。

结论：I 期研究的初步结果表明，MGCD265 加多西他赛或厄洛替尼有望用于 NSCLC 和 GE 肿瘤的治疗。在大多数 NSCLC 患者中观察到了临床疗效，近 50%的患者实现 SD≥5 个月。所选 GE 患者实现 SD 超过 10 个月。联合治疗的 AE 发生率在预期的范围内。

Background:MGCD265, a multikinase inhibitor with nM IC50 against Met, VEGFR 1, 2 and 3, Tie-2 and Ron, has been shown in preclinical models to possess broad antitumor effects. A phase I study was undertaken to assess therapy with MGCD265 and docetaxel or erlotinib for treatment of solid tumors.

Methods: Patients (pts) with advanced solid tumors were enrolled in an open-label, dose-escalation study using the standard 3+3 design. All pts received 3-wk cycles of MGCD265 (p.o. QD or BID) with docetaxel or erlotinib per standard of care, as defined by investigators. Endpoints were safety, pharmacodynamics, pharmacokinetics and antitumor activity of the combination therapy.

Results: Of 89 pts enrolled, there were 12 cases of NSCLC (docetaxel group) and 9 cases of gastroesophageal (GE) cancer (erlotinib group). Of 10 response-evaluable NSCLC pts, all met criteria for stable disease (SD) for ≥2 cycles (including 2 pts with partial response). Five pts achieved SD for 5-16 mos, with four exceeding time on prior therapy. Two pts have not reached first evaluation. Treatment continues in 3 pts.

Four of nine GE pts achieved SD. Three remained stable for 10-18 mos, exceeding time on prior therapy. Treatment continues in 1 pt. A plasma-based assay of Met phosphorylation showed up to 30% inhibition at doses to date. PK analysis is pending. Dose escalation continues. Toxicities were mostly mild to moderate. Nonhematologic adverse event (AEs) ≥ grade 3 were reported in 20% of pts in each treatment arm, and were primarily GI-related. Expected docetaxel–associated hematologic AEs were also observed.

Conclusions: Preliminary findings from a phase I study suggest that MGCD265 and docetaxel or erlotinib may hold promise for treatment of NSCLC and GE tumors. Clinical response was seen in the majority of NSCLC pts, with almost 50% achieving SD for ≥5 mos. Select GE pts achieved SD for more than 10 mos. AE rates with combination therapy were in the expected range.

677P　HER2 状态对胃癌患者生存的影响：在日本开展的一项多中心大规模研究

677P　SURVIVAL IMPACT OF HER2 STATUS IN PATIENTS WITH GASTRIC CANCER:A MULTICENTER LARGE-SCALE STUDY IN JAPAN

Y. Kurokawa, N. Matsuura, Y. Kimura, et al.

背景：尽管在 ToGA 研究中已经证明，HER2 表达是曲妥珠单抗治疗的预测因子，但是在胃癌患者中 HER2 状态与预后之间的关系尚未明确。我们开展了一项多中心大规模研究，评价胃癌中 HER2 状态的预后价值。

方法：将 2000 年到 2006 年间已行手术切除的 1152 例胃癌患者登记至本研究中。研究排除新辅助治疗病例。将肿瘤集中检测，采用免疫组织化学（IHC）和荧光原位杂交（FISH）进行 HER2 状态的检测。依据与 ToGA 研究相同的标准，对切除组织中 HER2 表达进行评价。采用 Fisher 精确检验法对 HER2 表达与临床病理学因素之间的关系进行了分析。对 HER2 阳性病例的死亡风险比（HR）进行了检验，采用时序检验法将 HER-2 阳性和 HER2 阴性病例的总生存期（OS）进行了比较。

结果：IHC 0 / 1+/ 2+/ 3+的病例数分别为 662 / 208 / 120 / 162 例，18 例 IHC 2 +病例表现为 FISH 阳性。总体而言，HER2 阳性比例为 15.6%（180/1152）。分化型肿瘤（P <0.001）、上半身肿瘤（P=0.065）和 T3-4b 肿瘤（P=0.074）更常见 HER-2 阳性病例。HER2 阳性病例的 OS 较 HER2 阴性患者显著缩短（HR 1.55（95%CI，1.21-1.97），P <0.001）。根据肿瘤分期，HER2 阳性病例的 HR（95%CI）和 P 值如下，I 期：2.05（1.14-3.68），P=0.015；II 期：1.87（1.001-3.47）， P=0.046；III 期：1.46（0.95-2.27），P=0.085；IV 期：1.41（0.93-2.14），P=0.101。各亚组均未显示 HER2 状态与任何背景因素之间具有相互作用。9 个背景因素的 Cox 多因素分析显示，HER2 表达是一种独立的预测因子[HR 1.55（95%CI，1.19-2.02），P=0.001]。

结论：HER2 表达是已切除胃癌的一个独立预后不良因素，提示较早期胃癌的 HR 更高。

Background: Although it has been proven in the ToGA study that HER2 expression is a predictive factor of trastuzumab treatment, the relation between HER2 status and prognosis in gastric cancer patients was still unknown. A multicenter large-scale study was conducted to evaluate the prognostic value of HER2 status in gastric cancer.

Methods:A total of 1152 cases with gastric cancer which was surgically resected between 2000 and 2006 were registered to this study. The neoadjuvant treatment cases were excluded. Tumors were centrally tested for HER2 status with immunohistochemistry (IHC) and fluorescence in-situ hybridization (FISH). HER2 expressions of resected tissues were evaluated according to the same criteria with the ToGA study. The relation between HER2 expression and clinicopathological factors was examined by Fisher's exact test. The hazard ratio (HR) for death in HER2-positive cases was estimated, and overall survivals (OS) were compared between HER2-positive and HER2-negative cases using log-rank test.

Results: The number of cases with IHC 0 / 1+/ 2+/ 3+was 662 / 208 / 120 / 162, and eighteen of IHC 2+cases showed FISH-positive. In total, the proportion of HER2-positive was 15.6% (180/1152). HER2-positive cases were more frequent in differentiated type tumors (P<0.001), in upper body tumors (P=0.065), and in T3-4b tumors (P=0.074). OS in HER2-positive cases was clearly worse than in HER2-negative cases (HR 1.55 (95%CI, 1.21-1.97); P<0.001). According to the tumor stage classification, the HR (95%CI) in HER2-positive cases and P values were as follows; Stage I:2.05 (1.14-3.68), P=0.015; Stage II:1.87 (1.001-3.47), P=0.046; Stage III:1.46 (0.95-2.27), P=0.085; Stage IV:1.41 (0.93-2.14), P=0.101. There was no subgroup which showed interaction between HER2 status and any background factors. The Cox multivariate analysis with nine background factors revealed that HER2 expression was an independent prognostic factor (HR 1.55 (95%CI, 1.19-2.02); P=0.001).

Conclusions:HER2 expression is an independent factor of poor prognosis in resected gastric cancer, showing trends of higher HR in earlier stage.

699P 曲妥珠单抗治疗的晚期胃癌患者的 HER2 状态

699P HER2 STATUS IN ADVANCED GASTRIC CARCINOMA PATIENTS TREATED WITH TRASTUZUMAB

C. Gomez-Martin, J.C. Plaza1, E. Del Valle, et al.

背景：标准化疗方案中添加曲妥珠单抗（T）可延长 HER2 阳性晚期胃癌（AGC）患者的总生存期。EMA 对 T 用于 AGC 的批准基于免疫组化法（IHC）确定的 HER2 状态，仅允许在 2+亚群中进行杂交。考虑到先前在乳腺癌 HER2 检测中的高限和低限，我们对采用双色银染原位杂交（dc-SISH）选择抗 HER2 治疗的 AGC 候选患者进行评估。

材料和方法：将 69 例符合原特定入组标准的 AGC 患者纳入本研究，包括：接受过含曲妥珠单抗既往化疗、充足的随访时间、获得病理学资料，并且有适用于分子分析的样本。IHC 结果采用抗 HER2/neu 蛋白抗体（4B5）方法通过全自动化平台 BenchMark ULTRA®（Ventana Medical Systems, Inc, Tucson, AZ）测定。对 Ventana Benchmark XT (Ventana Medical Systems, Tucson, AZ)进行自动化 DC-SISH。按照制造商的方案，INFORM HER2 DNA 探针和 INFORM 17 号探针染色体可在同一张片子上看到。采用扩增 HER2/CEN-17 比值≥2 截断值计算 HER2/CEN-17 比值。按照发布的指导原则进行 IHC 评估。

结果：所有病例均进行了基因扩增。在 4 例中表现出低多倍体。24 例病例（34.78%）中观察到异质性。研究发现 IHC 和 dc-SISH 的结果之间的关系具有统计学显著性差异（P <0.0001），94%的 IHC 3 +表达 dc-SISH 的比值>4。所有患者的中位 OS 为 19.8 个月（95%可信区间：13.4-23.9 个月）。扩增率>4 的患者组的平均 OS 显著延长（21.4 个月比 8.0 个月，HR 0.41，P=0.0087； 可信区间 95%0.2126-0.8180）。按照 IHC 结果分层为两组（3 +与 0/1+2 +）时，2 组的 OS 没有显著差异（21.0 个月比 10.9 个月，HR 0.5288，95%可信区间 0.2469-1.1325，P=0.0955）。

结论：在本研究中，曲妥珠单抗治疗的 AGC 患者 dc-SISH 扩增率>4 可预测 OS 获益。一项更大患者队列研究正在进行中。

Background: Trastuzumab (T) added to standard chemotherapy increases overall survival for HER2 positive advanced gastric carcinoma (AGC) patients. The approval of T by the EMA in AGC was linked to the determination of the HER2-status by immunohistochemistry (IHC), and hybridization was only permitted in the 2+subgroup. Taking into consideration the previous highs and lows in breast carcinoma HER2 testing, we sought to evaluate the use of Dual Colour Silver-staining in situ Hybridization (dc-SISH) for selecting patients with AGC as candidates to anti-HER2 therapies.

Material and methods: Sixty-nine AGC patients meeting a previously set of specific inclusion criteria were included:previous treatment with Trastuzumab-based chemotherapy, adequate follow-up, available pathology data and suitable sample for molecular analyses. IHC results were determined by the Pathway anti HER2/neu (4B5) antibody in the fully automated platform BenchMark ULTRA® (Ventana Medical Systems, Inc, Tucson, AZ). Automated dc-SISH was performed on Ventana Benchmark XT (Ventana Medical Systems, Tucson, AZ). INFORM HER2 DNA Probe and INFORM Chromosome 17 Probe was visualized on the same slide following the manufacturer's protocols. Gene to CEN-17 ratio was calculated using the cut-off value of HER2/CEN-17 ratio ≥2 as amplified. IHC evaluation was performed according to published guidelines.

Results: All cases were amplified. Low polisomy was present in 4 cases. Heterogeneity was observed in 24 (34.78%) cases. A statistically significant relationship was found between IHC and dc-SISH results (p<0.0001), with 94% of IHC 3+expressing dc-SISH ratio >4. Median OS was 19.8 months (95% CI:13.4 – 23.9 months) for the entire population. Mean OS was significantly longer in the group of patients with amplification ratio >4 (21.4 vs. 8.0 months, HR 0.41; p=0.0087; CI95% 0.2126 – 0.8180). No differences were observed in OS according to IHC results when stratified in two groups (3+vs 0/1+2+) (21.0 vs 10.9 months, HR 0.5288, CI95% 0.2469 – 1.1325, p=0.0955).

Conclusions: Dc-SISH amplification ratio >4 predicts OS benefit in AGC patients treated with trastuzumab in this study. Characterization in a larger cohort of patients is ongoing.

750　胃食管交界癌和胃癌的HER2 状态-爱尔兰观察报告

750　HER2 STATUS IN OESOPHAGOGASTRIC JUNCTION AND GASTRIC CANCER – THE IRISH LANDSCAPE

A. Jayaram, J.E. Battley, M.Y. Teo, et al.

大约 7-34%的胃腺癌（GE）存在 HER2 过度表达。ToGA 研究证实了曲妥珠单抗联合化疗对 HER2（+）转移性 GE 肿瘤的益处。在本研究中，22%的患者为 HER2（+）；免疫组织化学（IHC）3+或荧光原位杂交（FISH）(+)。我们通过 IHC 和 FISH 检测 GE 肿瘤的 HER2 状态，报告了一项多中心爱尔兰研究经验。

方法：对三个地方癌症中心的数据库进行检索，以确定胃食管交界癌或胃腺癌患者。对 2008 年至 2011 年之间诊断为早期和转移性 GE 肿瘤患者的活检或切除标本进行 HER2 检测。我们规定 HER2 阳性为 IHC3 +或 FISH（+）； HER2：17ch≥2。此外，我们还对年龄、性别、组织学、疾病分期进行了记录。我们对临床病理学特征进行了采集，并采用 t 检验或 Fisher 精确检验法对临床病理学特征进行比较。

结果：从 2008 年到 2011 年间，确定了 177 例患者。中位年龄为 68 岁（范围：25-96 岁），36%的患者为男性。51%的患者确诊胃肿瘤，而 53%在确诊时已经发生转移。中位转移部位数量为 1（0-4）。对 170 例患者（96%）和 131 例患者（74%）分别进行了 IHC 和 FISH 检测。IHC 评分 0、1、2 和 3 所占比例分别为 38%、32%、19%和 11%。关于 HER2 扩增的肿瘤异质性，在 IHC3+时，50%为 FISH（+）；在 IHC2 +时，21.1%为 FISH（+）；在 IHC1 +时，3.7%为 FISH（+）。队列总 HER2（+）率为 16.4%（n=29）。将 HER2（+）和 HER2（-）的患者进行比较，两组在性别（男性，38%比 38%，P=0.84）、年龄（69 比 68，P=0.79）和胃病变部位的分布（45%比 52% P=0.54）方面均相同。确诊时的转移率相似，分别为 54%和 53%。在两个患者队列中，肝脏转移（69 对 48%，P=0.22）、腹膜转移（38 对 49%，P=0.55）、脑转移（8 比 3%，P=0.44）相似。

结论：分析队列中的 HER2（+）GE 腺癌显示 IHC 染色和 FISH 阳性的异质性相似，但 HER2 扩增的发生率比 ToGA 研究报告的发生率低（16.4%）。深入分析没有发现 HER2（+）和 HER2（-）患者的临床病理学特征存在差异。

HER2 is overexpressed in ~ 7-34% of gastroesophageal (GE) adenocarcinomas. The ToGA study, established the benefit of trastuzumab in combination with chemotherapy in HER2(+) metastatic GE tumours. In this study, 22% of patients were HER2(+);immunohistochemistry (IHC)3+or fluorescence insitu hybridization (FISH)(+);. We report a multi-center Irish experience by examining HER2 status by IHC and FISH in GE tumours.

Methods: Database from three regional cancer centres were examined to identify pts with junctional or gastric adenocarcinoma. HER2 testing was performed on biopsy or resection specimens of patients with early stage and metastatic GE tumors between 2008–2011. We defined HER2 positive as IHC3+or FISH(+);HER2:17ch ≥ 2;. In addition, age, gender, histology, stage of disease, were recorded. Clinicopathologic characteristics were extracted and compared with t-test or Fisher's exact as appropriate.

Results: Between 2008 and 2011, 177 pts were identified. Median age was 68 years (range:25 – 96), 36% were male. Gastric tumours were identified in 51%, while 53% were metastatic at diagnosis. Median number of metastatic sites was 1 (0 – 4). IHC and FISH were performed on 170 pts (96%) and 131 (74%) of patients. Distribution of IHC score of 0, 1, 2 and 3 were 38%, 32%, 19% and 11%, respectively. With respect to tumour heterogeneity of HER2 amplification, in IHC3+, 50% were FISH(+), IHC2+, 21.1% were FISH(+) and IHC1+, 3.7% were FISH(+). Overall HER2(+) rate for the cohort was 16.4% (n=29). Comparing patients with HER2(+) and HER2(-)disease, gender (males, 38 vs 38%, p=.84), age(69 vs 68, p=.79) and site distribution gastric, (45 vs 52%, p=.54) were identical .The rate of metastasis at diagnosis were similar, at 54 vs 53%. Presence of metastases in the liver (69 vs 48%, p=.22), peritoneum (38 vs 49%, p=.55), brain (8 vs 3%, p=.44) were comparable in both patient cohorts.

Conclusions:HER2(+) GE adenocarcinomas in the analyzed cohort displays similar pattern of heterogeneity in IHC staining and FISH positivity but with lower incidence (16.4%) of HER2 amplification than was reported in the ToGA study. Further analysis did not identify differences in clincopathologic characteristics in HER2+ve patients.

756 按照肿瘤的组织学和部位接受一线化疗的晚期胃癌（GC）患者的临床结局

756 CLINICAL OUTCOME OF ADVANCED GASTRIC CANCER (GC) PATIENTS RECEIVING FIRST-LINE CHEMOTHERAPY ACCORDING TO TUMOUR HISTOLOGY AND LOCATION

A. Bittoni, M. Scartozzi, R. Giampieri, et al.

背景：在日常临床实践中，GC 被认为是一种单一疾病。然而，初步数据确定了不同的亚型，可以根据流行病学、致癌性和基因表达谱的相关差异进行描述。最近，已经提出了一种新分类方法，根据 Lauren 的组织学和解剖学肿瘤位置，将 GC 分为三个亚型：1 型（近端非弥漫型 GC），2 型（弥漫型 GC）和 3 型（远端非弥漫型 GC）。我们分析的目的是根据不同的 GC 亚型（1、2、3），对接受一线化疗患者的临床结局（有效率[RR]、无进展生存期[PFS]和总生存期[OS]）进行比较。

患者和方法：将接受一线联合化疗的晚期 GC 患者纳入我们的分析。根据先前的分型将患者分为 3 个亚组（1 型、2 型和 3 型）。

结果：共纳入 202 例晚期 GC 患者：大多数患者属于 2 型（50.5%）和 3 型（40.6%）；1 型包括 18 例患者（8.9%）。大多数患者（62%）接受了三种药物联合化疗方案，包括铂衍生物、氟嘧啶加蒽环类抗生素、紫杉烷类或丝裂霉素 C；其余患者接受了铂类和氟嘧啶的联合化疗。三个亚组的相关临床因素相似，如 ECOG PS、肿瘤分期、转移部位数、既往手术切除、一线联合化疗和使用二线治疗；如预期所料，腹腔癌在 2 型患者中更为常见。分析发现 3 型患者的 RR（RR=45.1%）高于 1 型患者（27.8%）和 2 型患者（25.5%）（P=0.017）。与 1 型（中位 PFS=6.9 个月）和 3 型（中位 PFS 为 7.8 个月）患者相比，2 型患者的 PFS（中位 PFS 5.7 个月）较短（P=0.0069）。这些差异并没有转变为 OS 的统计学显著差异。

结论：我们的研究结果表明，GC 亚型可能是晚期胃癌患者化疗获益的重要预测因素。为了更好的对患者进行分层，未来的临床试验应考虑到这些差异。

Background: In the daily clinical practice GC is considered as a single disease. However, preliminary data identified distinct subtypes characterized by relevant differences in epidemiology, carcinogenesis and gene expression profiles. Recently, a new classification has been proposed, based on Lauren's histology and on anatomic tumour location, identifying three subtypes:type 1 (proximal non diffuse GC), type 2 (diffuse GC) and type 3 (distal non diffuse GC). Aim of our analysis was to compare clinical outcome (in terms of response rate, RR, progression-free survival, PFS, and overall survival, OS) according to different GC subtypes (1,2,3) in patients (pts) receiving first-line chemotherapy.

Patients and methods: Advanced GC pts treated with a first-line combination chemotherapy were included in our analysis. Pts were divided in three subgroups (type 1, type 2 and type 3) as previously defined.

Results:A total of 202 advanced GC pts were included:most of pts belonged to type 2 (50.5%) and type 3 (40.6%); type 1 included 18 pts (8.9%). The majority of pts (62%) received a three-drugs chemotherapy combinations including a platinum derivate, a fluoropyrimidine with the addition of an anthracycline, a taxane or mytomicin C; the remaining patients received a platinum and fluoropyrimidine combination. The three pts subgroups resulted comparable for relevant clinical factors such as ECOG PS, tumour stage, number of metastatic sites, previous surgical resection, first-line combination and use of second-line treatments; as expected peritoneal carcinosis was more common in type 2 pts. RR was found to be higher in type 3 pts (RR=45.1%) than in type 1 (27.8%) and type 2 (25.5%) (p=0.017). Type 2 pts presented a shorter PFS (median PFS 5.7 months) compared to type 1, median PFS=6.9 months, and type 3, median PFS=7.8 months (p=0.0069). These differences did not translate in statistically significant differences in OS.

Conclusions: Our results suggest that GC subtypes may be important predictors of benefit from chemotherapy in advanced GC patients. Future clinical trials should take in account these differences for a better stratification of patients.

678P 在胃癌和胃食管交界癌中 HER2 过度表达的临床意义

678P CLINICAL SIGNIFICANCE OF HER2 OVEREXPRESSION IN GASTRIC AND GASTROESOPHAGEAL JUNCTION CANCERS

M. Baykara, M. Benekli, O. Ekinci, et al.

目的：在本研究中，我们对胃癌和胃食管交界癌（GC，GEJC）中 HER2 的过度表达率，以及 HER2 表达与临床、病理学参数和预后之间的关系进行了观察。

材料和方法：采用免疫组织化学（IHC）和银原位杂交法（SISH），对 285 例（202 例男性，83 例女性）GC 或 GEJC 患者手术或活检标本中的 HER2 过度表达进行了评价。研究对 HER2 阳性与肿瘤大小（TS）、病理组织学（H）、分级（G）、浆膜浸润（SI）、淋巴管浸润（LVI）、神经周围浸润（PNI）、Lauren 和 Borrmann 分型、肿瘤部位（TL）、TNM 分期、局部复发（LR）和转移（M）以及生存期（OS）之间的关系进行了观察。

结果：HER2 IHC 评分为：194 例（68.1%）IHC 0，34 例（11.9%）IHC +1，30 例（10.5%）IHC +2，27 例（9.5%）IHC +3。30 例 IHC +2 患者，12 例为 SISH 阳性（4.2%），18 例为 SISH 阴性。评价 IHC +3 或 IHC +2 和 SISH 阳性患者例数，HER2 阳性率为 13.7%。HER2 阳性与年龄、性别、TNM 分期、TS、TL、LR、M、LVI、PNI 和 Borrmann 分型之间没有相关性。与弥漫型肿瘤相比，肠型肿瘤的 HER2 阳性率较高（16.7%与 6.9%，P=0.075）。高度-中度分化肿瘤的 HER2 阳性率明显高于低分化肿瘤（24.3%，23.4%和 7.3%，P=0.001）。腺癌的 HER2 阳性率高于其他组织学亚型，HER2 阳性腺癌为 19.4%，印戒细胞癌为 4.2%（P=0.013）。HER2 阳性对中位 OS（22.7vs 18.4 个月，P=0.81）没有显著影响。但在肿瘤早期中，HER2 阳性患者的中位 OS 较 HER2 阴性的患者短（54.9 个月 vs 未达到，P=0.022）。然而，晚期肿瘤 HER2 阳性和阴性患者之间的中位 OS 率没有显著差异。

结论：在 GC 和 GEJC 中，HER2 阳性与肿瘤的分化程度和组织病理学相关。对于肿瘤早期患者，HER2 阳性与预后不良相关。

Objectives: In this study, we investigated the rate of HER2 overexpression in gastric and gastroesophageal junction cancers (GC, GEJC), and the relationship with HER2 expression and clinical, pathological parameters and prognosis.

Materials and methods: Surgery or biopsy specimen of 285 (202 male, 83 female) patients with GC or GEJC, the presence of HER2 overexpression by immunohistochemistry (IHC) and silver insitu hybridization (SISH) were evaluated. The relationship between HER2 positivity and tumor size (TS), histopathology (H), grade (G), serosal invasion (SI), lenfovascular invasion (LVI), perineural invasion (PNI), Lauren and Borrmann type, tumor location (TL), TNM stage, local recurrence (LR) and metastasis (M) and survival (OS) were investigated.

Results:HER2 IHC scores were; 194 (68.1%) IHC 0, 34 (11.9%) IHC +1, 30 (10.5%) IHC +2, 27 (9.5%) IHC +3. Twelve of 30 (4.2%) patients with IHC +2, SISH positive, and 18 patients SISH negative. The number of patients evaluated with IHC +3 or IHC +2 and SISH positive, HER2 positivity was 13.7%. There was no relationship between HER2 positivity and the age, gender, TNM stage, TS, TL, LR, M, LVI, PNI, and Borrmann type. HER2 positivity was higher in intestinal type tumors than in diffuse type (16.7% vs 6.9%, p=0.075). HER2 positivity was significantly higher in well-moderately diferantiated tumors than poorly diferantiated tumors (24.3% and 23.4% vs 7.3%, p=0.001). HER2 positivity was higher in adenocarcinomas than the other histologic subtypes; 19.4% of adenocarcinomas, 4.2% of signet-ring cell carcinomas were HER2-positive (p=0.013). HER2 pozitivity was no significant effect on median OS (22.7 vs 18.4 months, p=0.81). But in the early stage median OS of HER2-positive patients was shorter than HER2-negative patients (54.9 months vs not reach, p=0.022). However patients with advaced stage HER2-positive and –negative there was no significant difference between the median OS rates.

Conclusion:HER2 positivity is associated with the degree of tumor differantiation and histopathology in GC and GEJC. Patients with early-stage, HER2 positivity is related to poor prognosis.

结直肠肿瘤

559P 对既往接受贝伐珠单抗+化疗的转移性结直肠癌（MCRC）患者在首次疾病进展后给予贝伐珠单抗（BEV）+化疗（CT）的有效性和安全性：一项随机 III 期组间研究(ML18147)的年龄亚组分析

559P EFFICACY AND SAFETY OF TREATMENT WITH BEVACIZUMAB （BEV）+CHEMOTHERAPY（CT）BEYOND FIRST PROGRESSION IN PATIENTS WITH METASTATIC COLORECTAL CANCER（MCRC）PREVIOUSLY TREATED WITH BEV+CT:AGE SUBGROUP ANALYSIS FROM A RANDOMISED PHASE III INTERGROUP STUDY (ML18147)

O. Bouché, C.-C. Steffens, T. André, et al.

背景：ML18147 研究表明，贝伐珠单抗+标准 CT 作为二线治疗，在含贝伐珠单抗的一线化疗后疾病进展的 mCRC 患者中可显著改善生存期，且毒性可接受。然而，需要更多证据证明该治疗选择在老年患者中可以耐受且具有疗效。在此，我们根据 ML18147 研究中的患者年龄对有效性和安全性进行了评估。

方法：停止一线贝伐珠单抗治疗后 3 个月内疾病进展的患不可切除、组织学证实 mCRC 的患者随机接受含氟嘧啶的二线化疗±贝伐珠单抗治疗（2.5mg/kg/wk 等量）。根据一线治疗方案选择二线奥沙利铂或伊立替康治疗（交叉设计）。我们对<65 岁与≥65 岁患者的总生存期（OS）、无进展生存期（PFS）和耐受性进行了事后分析。

结果：820 例患者接受随机分组，409 例患者随机分入贝伐珠单抗+化疗组，411 例患者随机分入单纯化疗组。458 例患者<65 岁，361 例患者≥65 岁。在<65 岁（中位值 5.9 个月与 3.9 个月；风险比=0.66；95%可信区间 0.55–0.80；p<0.0001）和≥65 岁（5.5 个月与 4.3 个月；风险比=0.71；95%可信区间 0.57–0.87；p=0.0011）的患者中，贝伐珠单抗+化疗组中无进展生存期长于单纯化疗组，具有统计学意义。在< 65 岁的患者中，贝伐珠单抗+化疗组的总生存期长于单纯化疗组，具有统计学意义（中位值 11.6 与 9.9 个月；风险比=0.79；95%可信区间 0.65–0.98；p=0.0274），而在≥65 岁的患者中，贝伐珠单抗+化疗组的总生存期长于单纯化疗组，但差异没有显著性（10.7 个月与 9.8 个月；风险比=0.83；95%可信区间 0.66–1.04；p=0.1056）。2 个年龄组接受贝伐珠单抗+化疗或单纯化疗的患者的 3 级–5 级不良事件发生率参见表格。

结论：对 ML18147 进行的这项亚组分析表明，在< 65 岁和≥65 岁的患者中，疾病进展后在化疗基础上添加贝伐珠单抗可改善无进展生存期和总生存期。在各年龄组中，3 级–5 级不良事件的发生率相似。

Background: The ML18147 study showed that BEV+standard CT as second-line treatment for pts with mCRC who progressed after first-line BEV-containing CT significantly improved survival with an acceptable toxicity profile. However, more evidence is needed that current treatment options are tolerable and efficacious in older pts. Here, we assessed efficacy and safety according to age in the ML18147 study.

Methods: Pts with unresectable, histologically confirmed mCRC who progressed <3 months from discontinuing first-line BEV were andomized to second-line fluoropyrimidine-based CT ± BEV (2.5mg/kg/wk equivalent). Choice of second-line oxaliplatin or irinotecan depended on first-line regimen (crossover). We present a post-hoc analysis of overall survival (OS), progression-free survival (PFS) and tolerability in pts <65 years vs≥65 years of age.

Results:820 pts were andomized, 409 to BEV+CT and 411 to CT alone. 458 pts were <65 years and 361 pts were≥65 years of age. PFS was statistically significantly longer with BEV+CT vs CT alone in pts <65 years (median 5.9 vs 3.9 months; HR=0.66; 95% CI 0.55–0.80; p<0.0001) and≥65 years (5.5 vs 4.3 months; HR=0.71; 95% CI 0.57–0.87; p=0.0011). OS was statistically significantly longer with BEV+CT in pts <65 years (median 11.6 vs 9.9 months; HR=0.79; 95% CI 0.65–0.98; p=0.0274) and numerically but not significantly longer in pts≥65 years (10.7 vs 9.8 months; HR=0.83; 95% CI 0.66–1.04; p=0.1056). The incidence of grade 3–5 Aes in pts receiving BEV+CT or CT alone in both age groups is shown in the Table.

Conclusions: This subgroup analysis of ML18147 suggests that the addition of BEV to CT after disease progression improves PFS and OS in pts <65 years and ≥65 years of age. The incidence of grade 3–5 Aes was similar within age groups.

	< 65 岁/< 65 years		≥65 岁/≥65 years	
	单纯化疗/CT alone	贝伐珠单抗+化疗/BEV+CT	单纯化疗/CT alone	贝伐珠单抗+化疗/BEV+CT
患者百分比/% of Patients	（n=230）	（n=222）	（n=179）	（n=179）
3–5 级不良事件/Grade 3–5 Aes	54	64	62	63
贝伐珠单抗组中特别关注的 3–5 级不良事件/Grade 3–5 Aes of special interest for BEV				
高血压/Hypertension	<1	2	2	1
蛋白尿/Proteinuria	0	<1	0	<1
出血/Bleeding/haemorrhage	<1	2	0	2
脓肿/瘘/Abscess/fistula	0	<1	0	1
胃肠道穿孔/GI perforation	<1	2	<1	2
充血性心力衰竭/Congestive heart failure	<1	0	<1	0
静脉血栓栓塞事件/Venous thromboembolic event	3	5	3	5
动脉血栓栓塞事件/Arterial thromboembolic event	0	<1	1	<1
创口愈合并发症/Wound-healing complications	0	<1	<1	0
非疾病进展导致的死亡/Deaths not due to progression	4.3	5.0	6.7	6.7

565P 对既往接受含贝伐珠单抗治疗的转移性结直肠癌（MCRC）患者在首次疾病进展后给予贝伐珠单抗（BEV）+化疗（CT）：ML18147 的总生存期亚组分析结果

565P BEVACIZUMAB (BEV)+CHEMOTHERAPY (CT) BEYOND FIRST PROGRESSION IN PATIENTS (PTS) WITH METASTATIC COLORECTAL CANCER (MCRC) PREVIOUSLY TREATED WITH BEV-BASED THERAPY:OVERALL SURVIVAL SUBGROUP FINDINGS FROM ML18147

J.M. Vieitez de Prado, C. Borg, D. Arnold, et al.

背景：ML18147 评估了继续给予贝伐珠单抗+标准 CT 作为二线治疗（2L）在含贝伐珠单抗的一线（1L）化疗后疾病进展的 mCRC 患者中的获益。我们报告了预定亚组和探索性 KRAS 突变分析的结果。

方法：停用一线贝伐珠单抗治疗后 3 个月内疾病进展的患不可切除、组织学证实 mCRC 的患者随机接受氟嘧啶+奥沙利铂或伊立替康（从一线治疗交叉）±贝伐珠单抗（2.5mg/kg/wk 等量）二线治疗。主要终点为总生存期（OS）。采用与主要分析相同的统计方法对总生存期进行亚组分析。

结果：409 例患者随机分入贝伐珠单抗+化疗组，411 例患者随机分入化疗组（1 例患者未接受治疗）。贝伐珠单抗+化疗组的中位总生存期为 11.2 个月，化疗组为 9.8 个月（未分层风险比=0.81；95%可信区间 0.69–0.94；p=0.0062）。总生存期的亚组分析基本符合总人群结果（见表格）。尽管女性患者中治疗效果较差，但治疗-性别相互作用检验没有统计学意义。对 616 例患者（75%）进行探索性分析获得了 KRAS 突变数据；在 KRAS 野生型（WT）患者中，贝伐珠单抗+化疗组与化疗组的中位总生存期分别为 15.4 个月与 11.1 个月（风险比=0.69，95%可信区间 0.53–0.90；p=0.0052）；在 KRAS 突变（MT）患者中，中位总生存期分别为 10.4 个月与 10.0 个月（风险比=0.92；95%可信区间 0.71–1.18；p=0.4969）。在 KRAS 野生型患者中，贝伐珠单抗+化疗组与化疗组的中位无进展生存期分别为 6.4 个月与 4.5 个月（风险比=0.61；95%可信区间 0.49–0.77；p<0.0001）；在 KRAS 突变患者中，中位无进展生存期分别为 5.5 个月与 4.1 个月（风险比=0.70；95%可信区间 0.56–0.89；p=0.0027）。对于总生存期（p=0.1266）或无进展生存期（p=0.4436），未见治疗与 KRAS 状态的相互作用。

结论：ML18147 表明，与单纯化疗相比，疾病进展后继续给予贝伐珠单抗+化疗可显著改善患者的生存期。总生存期的亚组分析结果与总人群基本一致。

Background:ML18147 evaluated the benefit of continuing BEV+standard CT as second-line (2L) treatment for pts with mCRC progressing after first-line (1L) BEV-containing therapy. Here we report results of pre-specified subgroup and exploratory KRAS mutation analyses.

Methods: Pts with unresectable, histologically confirmed mCRC progressing within 3 mo after discontinuing 1L BEV were randomised to 2L fluoropyrimidine+oxaliplatin or irinotecan (crossed over from 1L) ± BEV (2.5mg/kg/wk equivalent). The primary endpoint was overall survival (OS). Subgroup analyses for OS were performed using the same statistical method as for the primary analysis.

Results:409 pts were randomised to BEV+CT and 411 to CT (1 pt not treated). Median OS was 11.2 mo for BEV+CT vs 9.8 mo for CT (unstratified HR=0.81; 95% CI 0.69–0.94; p=0.0062). Subgroup analyses for OS were generally consistent with the overall population (Table). While the treatment effect in female pts appeared to be lower, the treatment-gender interaction test was not statistically significant.

KRAS mutation data were available from an exploratory analysis in 616 pts (75%); median OS for KRAS wild-type (WT) pts was 15.4 mo for BEV+CT vs 11.1 mo for CT (HR=0.69, 95% CI 0.53–0.90; p=0.0052); in KRAS mutant (MT) pts median OS was 10.4 vs 10.0 mo, respectively (HR=0.92; 95% CI 0.71–1.18; p=0.4969). Median PFS for KRAS WT pts was 6.4 mo for BEV+CT vs 4.5 mo for CT (HR=0.61; 95% CI 0.49–0.77; p<0.0001); in KRAS MT pts median PFS was 5.5 vs 4.1 mo, respectively (HR=0.70; 95% CI 0.56–0.89; p=0.0027). No treatment interaction by KRAS status was seen for OS (p=0.1266) or PFS (p=0.4436).

Conclusions:ML18147 showed that BEV+CT continued beyond progression significantly improves survival vs CT alone. Findings from the subgroup analyses for OS were generally consistent with the overall population.

分类/Category	亚组/Subgroup	N	总生存期的风险比/HR for OS	95%可信区间/95% CI
所有/All	所有/ All	819	0.81	0.69–0.94
性别/Gender	女性/ Female 男性/Male	294 525	0.99 0.73	0.77–1.28 0.60–0.88
年龄/Age	<65 岁/<65 y ≥65 岁/⩾65 y	458 361	0.79 0.83	0.65–0.98 0.66–1.04
ECOG PS/ECOG PS	0 ≥1	357 458	0.74 0.87	0.59–0.94 0.71–1.06
一线 PFS /First-line PFS	≤9 个月/⩽9 mo >9 个月/>9 mo	449 369	0.89 0.73	0.73–1.09 0.58–0.92
一线化疗/First-line chemotherapy	含奥沙利铂 /Oxaliplatin-based 含伊立替康 /Irinotecan-based	343 476	0.79 0.82	0.62–1.00 0.67–1.00
距末次贝伐珠单抗治疗的时间/Time from last BEV dose	≤42 天/⩽42 d >42 天/>42 d	630 189	0.82 0.76	0.69–0.97 0.55–1.06
仅肝转移/Liver metastases only	否/ No 是/ Yes	592 226	0.81 0.79	0.67–0.97 0.59–1.05
出现转移的器官数/No. of organs with metastasis	1 >1	307 511	0.83 0.77	0.64–1.08 0.64–0.94

571P 对既往接受一线贝伐珠单抗+化疗的转移性结直肠癌（MCRC）患者在首次疾病进展后给予贝伐珠单抗（BEV）+化疗（CT）（ML18147）：奥沙利铂与伊立替康的有效性和安全性分析

571P BEVACIZUMAB (BEV)+CHEMOTHERAPY (CT) BEYOND FIRST PROGRESSION IN PATIENTS (PTS) WITH METASTATIC COLORECTAL CANCER (MCRC) PREVIOUSLY TREATED WITH FIRST-LINE BEV+CT (ML18147):EFFICACY AND SAFETY ANALYSES BY OXALIPLATIN VS I

P. Österlund, V. Alonso-Orduna, C. Schlichting, et al.

背景：ML18147 是一项随机临床研究，首次证明标准一线（1L）贝伐珠单抗治疗后出现进展的 mCRC 患者中继续给予贝伐珠单抗+标准 CT 作为二线治疗（2L）可显著改善总生存期（OS）和无进展生存期（PFS）。在此，我们采用奥沙利铂与伊立替康一线化疗作为分层因子，对二线治疗结局进行了评价。

方法：停止贝伐珠单抗一线治疗后 3 个月内疾病进展的患不可切除、组织学证实的 mCR 患者随机接受含氟嘧啶的二线化疗±贝伐珠单抗（2.5mg/kg/wk 等量）治疗。根据一线方案选择奥沙利铂或伊立替康二线治疗（交叉设计）。采用奥沙利铂与伊立替康一线化疗作为分层因子，对二线治疗背景下的总生存期、无进展生存期、总缓解率（ORR）和不良事件（AE）进行分析。

结果：820 例患者在 2006 年 2 月至 2010 年 6 月间接受了随机分组。其中 343 例患者接受含奥沙利铂一线化疗，476 例患者接受含伊立替康一线化疗，之后按交叉设计接受含奥沙利铂或伊立替康的二线化疗。无论一线化疗中使用奥沙利铂还是伊立替康，疾病进展后给予贝伐珠单抗+化疗都可以延长总生存期和无进展生存期（见表）。在接受化疗和贝伐珠单抗+化疗的 2 组患者中，总缓解率较低。在接受奥沙利铂或伊立替康化疗的患者中，与贝伐珠单抗相关的不良事件基本相似。

结论：这项事后亚组分析表明，无论一线化疗中使用奥沙利铂还是伊立替康，继续接受贝伐珠单抗+含奥沙利铂或伊立替康的二线化疗（交叉设计）可以延长总生存期和无进展生存期。

Background:ML18147 is the first randomised study to show that continuing BEV+standard CT as second-line (2L) treatment significantly improves overall survival (OS) and progression-free survival (PFS) in pts with mCRC who progressed after receiving a standard first-line (1L) BEV-containing regimen. Here we evaluate outcome in the 2L setting using, as a stratification factor, 1L oxaliplatin vs irinotecan-based CT.

Methods: Pts with unresectable, histologically confirmed mCRC who progressed within 3 months of discontinuing 1L BEV were randomised to 2L fluoropyrimidine-based CT±BEV (2.5mg/kg/wk equivalent). Choice of 2L oxaliplatin or irinotecan was dependent on the 1L regimen (crossover). OS, PFS, overall response rate (ORR) and adverse events (AEs) were analysed in the 2L setting using the 1L oxaliplatin or irinotecan-based CT as a stratification factor.

Results:820 pts were randomised from Feb 2006 to Jun 2010. Of these, 343 received 1L oxaliplatin-based CT and 476 received 1L irinotecan-based CT, after which they crossed over to receive either oxaliplatin or irinotecan-based CT in 2L. BEV+CT beyond progression prolonged OS and PFS, regardless of whether oxaliplatin or irinotecan-based CT was used in 1L (Table). ORR was low in CT and BEV+CT-treated pts in both groups. AEs associated with BEV were generally similar in pts treated with either oxaliplatin or irinotecan-based CT.

Conclusions: This post-hoc subgroup analysis suggests that continuing BEV+2L oxaliplatin or irinotecan-based CT (following crossover) leads to prolonged OS and PFS, regardless of the type of oxaliplatin or irinotecan-based CT used 1L.

二线治疗结局/Outcome in 2L	含奥沙利铂的一线化疗/1L oxaliplatin-based CT		含伊立替康的一线化疗/1L irinotecan-based CT	
	化疗/CT（n=174）	贝伐珠单抗+化疗/BEV+CT（n=169）	化疗/CT（n=236）	贝伐珠单抗+化疗/BEV+CT（n=240）
中位总生存期，月/Median OS, months	10.0	12.0	9.3	10.9
p 值/p-value	0.0524		0.0454	
风险比 （95%可信区间）/HR (95% CI)	0.79 （0.62–1.00）		0.82 （0.67–1.00）	
中位无进展生存期，月/Median PFS, months	4.2	6.2	3.8	5.4
p 值/p-value	0.0005		<0.0001	
风险比（95%可信区间）/HR (95% CI)	0.68 （0.55–0.85）		0.67 （0.56–0.81）	
ORR,%	2.9	5.5	4.7	5.4
p 值/p-value	0.2414		0.7145	
有>1%的患者发生的 3–5 级不良事件，%/Grade 3–5 AEs in >1% of pts, %				
任何/Any	52	66	60	61
高血压/Hypertension	0	1	2	2
出血 Bleeding/haemorrhage	<1	3	0	1
胃肠穿孔/GI perforation	<1	2	<1	1
静脉血栓栓塞事件/Venous thromboembolic event	5	7	1	3

555P 贝伐珠单抗治疗转移性结直肠癌（MCRC）的有效性和安全性：一线随机对照试验（RCTS）合并数据分析

555P EFFICACY AND SAFETY OF BEVACIZUMAB IN METASTATIC COLORECTAL CANCER (MCRC):FIRST-LINE ANALYSIS OF POOLED DATA FROM RANDOMIZED CONTROLLED TRIALS (RCTS)

F.F. Kabbinavar, H. Hurwitz, N.C. Tebbutt, et al.

背景：贝伐珠单抗（BV）加化疗（CT）是 mCRC 的标准治疗。本分析合并了 6 项贝伐珠单抗 RCT（II 期或 III 期）的临床数据库中的个例患者数据，目的是进一步明确一线治疗的临床结局，包括亚组内结果。

方法：将贝伐珠单抗一线治疗 mCRC 临床试验（AVF2107、NO16966、ARTIST、AVF2192、AVF0780、AGITG MAX）的患者数据合并。所有分析基于意向性治疗人群进行。采用 Kaplan-Meier 法估算总生存期和无进展生存期（OS、PFS）。为评估治疗组（化疗与贝伐珠单抗+化疗）间缓解时间的差异，采用分层随机模型（总人群）和固定模型（亚组比较）估算合并风险比（HR）和 95%可信区间（CI），以每项研究为一层。

结果：在 3178 例合并一线治疗组患者（化疗[n=1481]；贝伐珠单抗+化疗 [n=1697]）中，58.5%的患者为男性，40.1%的患者≥65 岁，44.9%的患者 ECOG 体力状态≥1 分。与对照组患者相比，贝伐珠单抗治疗组患者的总生存期和无进展生存期延长，具有统计学意义。本项合并分析的贝伐珠单抗相关不良事件中，没有发现任何新的安全性信号。

结论：对于纳入总体分析的 mCRC 患者，一线化疗基础上添加贝伐珠单抗可延长总生存期和无进展生存期，具有统计学意义，在化疗强度、肿瘤转移部位和 KRAS 状态亚组中，无进展生存期也有延长。

Background: Bevacizumab (BV) with chemotherapy (CT) is a standard treatment for mCRC. This analysis pooled individual patient data from the clinical databases of six RCTs (phase 2 or 3) of BV to further define clinical outcomes with first-line treatment, including within subgroups.

Methods: Patient data were pooled from first-line (AVF2107, NO16966, ARTIST, AVF2192, AVF0780, AGITG MAX) mCRC trials of BV. All analyses were based on the intent-to-treat population. Overall and progression-free survival estimates (OS, PFS) were calculated by Kaplan-Meier methods. To assess differences in time to response variables by treatment arm (CT vs BV+CT), stratified random (overall) and fixed (subgroup comparisons) models were used to estimate pooled hazard ratios (HRs) and 95% confidence intervals (CIs), with each study included as a stratum.

Results: Of the 3178 pooled first-line patients (CT [n=1481]; BV+CT [n=1697]), 58.5% were male, 40.1% were≥65 years, and 44.9% had an ECOG performance status≥1. OS and PFS were statistically significantly increased in BV-treated patients vs control patients. The BV-associated adverse event profile from this pooled analysis identified no new safety signals.

Conclusions: The addition of bevacizumab to first-line CT resulted in statistically significant improvements in OS and PFS for mCRC patients in the overall analysis, with PFS benefit extending across subgroups defined by CT intensity, site of metastatic disease, and KRAS status.

总人群：贝伐珠单抗+化疗与化疗相比/Overall:BV+CT vs CT	风险比（95%可信区间）/HR (95% CI)	P 值/P value
总生存期/OS	0.81 （0.70 − 0.93）	.0034
无进展生存期/PFS	0.58 （0.46 − 0.73）	<.0001
亚组比较：贝伐珠单抗+化疗与化疗/Subgroup comparisons:BV+CT vs CT		
	总生存期的风险比 （95%可信区间）/ HR (95% CI) for OS	无进展生存期的风险比（95%可信区间）/ HR (95% CI) for PFS
单药治疗/Monotherapy（n=751）	0.86 （0.72–1.02）	0.56 （0.48–0.67）
双药联合治疗/Doublet therapy（n=2427）	0.84 （0.77–0.92）	0.73 （0.67–0.80）
仅出现肝转移的患者/Patients with liver metastases only（n=1095）	0.87 （0.76–1.00）	0.67 （0.59–0.77）
出现广泛性疾病的患者/Patients with extensive disease（n=1049）	0.79 （0.69–0.90）	0.67 （0.59–0.77）
KRAS 野生型患者/ KRAS wildtype patients（n=364）	0.70 （0.54–0.91）	0.57 （0.45–0.72）
KRAS 突变患者/ KRAS mutant patients（n=166）	0.85 （0.60–1.22）	0.54 （0.38–0.76）

567P 早期贝伐珠单抗加放化疗治疗直肠癌的多学科新辅助治疗的 II 期临床研究（BRANCH）：有效性、安全性和生物标记物

567P NEOADJUVANT MULTIDISCIPLINARY PHASE II STUDY (BRANCH) OF AN EARLY BEVACIZUMAB SCHEDULE PLUS CHEMO-RADIATION THERAPY IN RECTAL CANCER:EFFICACY, SAFETY, AND BIOMARKERS

A. Avallone, E. Di Gennaro, L. Aloj, et al.

背景：在 BRANCH 研究中，我们评估了早期（提前 4 天）贝伐珠单抗（BEV）加新辅助化疗（CT）和放疗（RT）试验性治疗方案在高危局部晚期直肠癌（pLARC）患者中的安全性和有效性，并探索了循环内皮细胞（CECs）和肿瘤病变糖酵解（TLG）作为病理缓解（PR）的替代标记物的可能性。

患者和方法：46 例患者（cT4，cN +，cT3 距肛外缘≤ 5cm和/或环切边缘阳性，M1 可切除）在盆腔放疗（45 Gy）期间，第 1 天接受奥沙利铂（100mg/m^2）/雷替曲塞（2.5mg/m^2）治疗，每 2 周一次，连续治疗 3 个疗程，并且在第 2 天接受 5-氟尿嘧啶（800mg/m^2）/亚叶酸（250mg/m^2）治疗。开始放化疗前 4 天给予贝伐珠单抗（5mg/kg），两周一次，共 2 个疗程。使用NCI-CTC v.3 对毒性进行分级。使用Mandard 肿瘤消退分级（TRG）定义 PR。根据Simon 2 阶段设计，假设 50% TRG1（完全肿瘤消退）（一类错误率=0.05，二类错误率=0.20），则必须获得至少 6/16 例TRG1，才可继续招募至获得 46 例患者。在基线时（BL）、第 10天和术前，分别通过流式细胞计量术和FDG-PET对CEC和TLG进行评估。采用Mann-Whitney检验法进行统计分析。

结果：我们共获得了 23 例 TRG（肿瘤退缩分级）1（50%）、14 例 TRG2（30%）和 8 例 TRG3-4（17%）。最常见的不良事件为¾ 级中性粒细胞减少症（13/46 例患者，28%）。在应答者 TRG1-2 中，第 10 天 TLG 相对基线时降幅显著大于未应答者 TRG3-4（中位值 -72%，范围-90%+31%与中位值-38%，范围-45%+25%；p<0.05）。在 TRG1-2 患者中，基线时中位 CEC 大于 TRG3-4 患者（中位值 0.22/μl，范围 0-3.98 与中位值 0/μl，范围 0-0.174；p=0.009）。此外，在 TRG1-2 患者中，第 10 天的 CEC 与基线时相比显著下降（中位值 0.014/μl，范围 0-2.29；p=0.002）。在 TRG3-4 患者中未见这一特征，其 CEC 水平趋于增加（中位值 0.316/μl，范围 0-2.64；p=0.097）。在 TRG 1-2 和 TRG 3-4 患者中，术前 CEC 和 PET-CT 检查不能预测 PR。

结论：本研究中贝伐珠单抗加化疗和放疗方案是安全和有效的，在 pLARC 患者中产生的 TRG1 和 TRG2 应答率较高。早期 FDG-PET 和 CEC 评估可以作为治疗选择的潜在生物标记物，需要纳入该治疗方案的未来研究设计中。将在会议上提供 CEP 和 citochine 数据。

Background: In BRANCH study we assess the safety and efficacy of an experimental schedule of early (4 days before) bevacizumab (BEV) added to neoadjuvant chemotherapy (CT) and radiotherapy (RT) in poor-risk locally advanced rectal cancer (pLARC) patients (pts) and explore the potential of circulating endothelial cells (CECs) and tumor lesion glycolysis (TLG) as surrogate markers of pathological response(PR).

Patients and methods:46 pts (cT4, cN+, cT3≤ 5cm from the anal verge and/or positive circumferential margin, M1 resectable) received 3 biweekly courses of oxaliplatin (100mg/m^2)/raltitrexed (2.5mg/m^2) on day 1, and 5-FU (800mg/m2)/folinic acid (250mg/m^2) on day 2 during pelvic RT (45 Gy). BEV (5mg/kg) was given biweekly 4 days before beginning of CT/RT for 2 courses. Toxicity was graded with NCI-CTC v.3. PR was defined using Mandard tumor regression grade (TRG). According to the Simon's two-stage design, assuming an hypothesis of a 50% TRG1 (complete tumor regression) (α error=0.05, β error=0.20), at least 6/16 TRG1 should be obtained to continue accrual to 46 pts. CECs and TLG were evaluated at baseline (BL) on day 10 and before surgery, by flow cytometry and FDG-PET, respectively. Statistical analysis was by Mann-Whitney test.

Results: We obtained 23 TRG1 (50%), 14 TRG2 (30%) and 8 TRG3-4 (17%). Grade ¾ neutropenia was the most common adverse event (13/46 pts, 28%). TLG reduction on day 10 vs BL was significantly higher in responders TRG1-2 compared to non-responders TRG3-4 pts (median -72%, range -90%+31% vs -38%, range -45%+25%; p<0.05). Median CECs at BL were higher in TRG1-2 vs TRG3-4 pts (median 0.22/μl, range 0-3.98 vs 0/μl, range 0-0.174; p=0.009). Moreover, in TRG1-2 pts CECs were significantly reduced on day 10 vs BL (median 0.014/μl, range 0-2.29; p=0.002). This pattern was not seen in TRG3-4 pts with a tendency toward increased levels (median 0.316/μl, range 0-2.64; p=0.097). In both TRG 1-2 and TRG 3-4 preoperative CECs and PET-CT studies were not predictive of PR.

Conclusions: Current scheme of BEV plus CT and RT appears safe and active, yielding high rate of TRG1 and TRG2 responses in pLARC. Early FDG-PET and CECs evaluation emerged as potential biomarkers for treatment selection to be incorporated in design of future studies with this regimen. CEP and citochine data will be provided at the meeting.

600P 2 次给药 CPT-11 与 LV5FU2 输液（FOLFIRI-3）联合贝伐珠单抗治疗，随后卡培他滨和贝伐珠单抗维持治疗：转移性结直肠癌一线治疗的 II 期临床研究

600P BIFRACTIONATED CPT-11 WITH LV5FU2 INFUSION (FOLFIRI-3) IN COMBINATION WITH BEVACIZUMAB FOLLOWED BY A CAPECITABINE AND BEVACIZUMAB MAINTENANCE THERAPY:A PHASE II STUDY IN FIRST-LINE METASTATIC COLORECTAL CANCERS

C.H.S. Kim, E. Curti, T. Nguyen, et al.

背景：贝伐珠单抗（Bev）加 FOLFIRI 或 FOLFOX 治疗方案是转移性结直肠癌（mCRC）的一线标准疗法。作为 FOLFOX 治疗后的二线方案，FOLFIRI-3 与其他含伊立替康方案相比可显著改善无进展生存期。因此，我们对 FOLFIRI-3 联合贝伐珠单抗作为 mCRC 初始治疗的安全性、有效性以及可能的预后因素进行了评估。由于尚缺乏 mCRC 中经过充分验证的生物标记物，我们决定评估血管生成素-2（Ang-2）的预后价值。

患者和方法：我们开展了一项研究FOLFIRI-3 治疗方案作为 mCRC一线治疗的 3 中心II期临床研究（氟尿嘧啶连续输液 46 小时（2400mg/m^2）加贝伐珠单抗（5mg/kg，第 1 天）治疗前后给予伊立替康 100mg/m^2，每 2 周一次）。给予为期 6 个月的诱导治疗（FOLFIRI-3 和贝伐珠单抗），之后给予维持治疗，包括贝伐珠单抗（7.5mg/kg，第 1 天）和卡培他滨（1000mg/m^2，第 1 至 14 天），每 3 周一次。在基线时测定血浆 VEGF和血清 Ang-2 水平。主要终点为总缓解率。次要终点为无进展生存期、总生存期和对治疗缓解预后因素的生物分析。

结果：61 例患者入组。总缓解率为 66.7%（95%可信区间，55-79）。25%的患者疾病稳定（DCR 为 91.7%）。无进展生存期为 12 个月（95%可信区间，9-16 个月），总生存期为 33 个月（95%可信区间，19-44 个月）。共有 41 例患者入组研究的维持期。贝伐珠单抗/卡培他滨维持治疗是适当且耐受性良好的治疗选择。在该队列中，治疗前血清 Ang-2 水平升高被视为结局较差的潜在生物标记物（中位无进展生存期分别为 14.7 个月 与 7.3 个月，p<0.01）。在多变量分析中，转移灶手术和 Ang-2 水平是无进展生存期和总生存期仅有的独立预后因素。

结论：作为 mCRC 的一线治疗方案，FOLFIRI-3/贝伐珠单抗，然后给予含卡培他滨的维持治疗是有效的，可能在未来开发中考虑，尤其是针对接受奥沙利铂辅助治疗的患者。血清血管生成素 2 是接受化疗和贝伐珠单抗治疗的 mCRC 患者中预测无进展生存期和总生存期的良好生物标记物。正在进行外部验证。

Background: Bevacizumab (Bev) with FOLFIRI or FOLFOX regimen is a standard of care in first-line metastatic colorectal cancers (mCRC). As second-line regimen after FOLFOX, FOLFIRI-3 has shown a significantly better PFS in comparison with other irinotecan-based regimen. We therefore evaluated the safety, efficacy and possible predictive factors for FOLFIRI-3 in combination with Bev as initial treatment for mCRC. Since fully validated biomarkers in mCRC are still lacking, we decided to assess the prognostic value of Angiopoietin-2 (Ang-2).

Patients and methods: We conducted a three-institution phase II trial of FOLFIRI-3 regimen (irinotecan 100mg/m2 before and after a 46-hour continuous infusion of fluorouracil (2400mg/m^2) with Bev (5mg/kg day 1) repeated every 2 weeks, as first-line treatment in mCRC. Induction treatment (FOLFIRI-3 and Bev) was administrated for 6 months, followed by a maintenance treatment including Bev (7.5mg/kg day 1) and capecitabine (1000mg/m^2 day 1 to 14), repeated every 3 weeks. Plasma VEGF and serum Ang-2 were measured at baseline. The primary endpoint was ORR. Secondary endpoints were PFS, OS, and biologic analysis of potential predictive factors of response to treatment.

Results:61 patients were enrolled for treatment. The ORR was 66.7% (95% CI, 55-79). SD in 25% of patients (DCR of 91.7%). PFS was 12 months (95% CI, 9-16) and OS was 33 months (95% CI, 19-44). A total of 41 patients entered the maintenance phase of the study. Bev/capecitabine maintenance therapy appeared as an appropriate and well-tolerated option. High pre-therapeutic serum Ang-2 level was identified as a potential biomarker correlated to worse outcomes in this cohort (median progression free survival of 14.7 months vs. 7.3 months, p<0.01). In multivariate analysis, metastasis surgery and Ang-2 levels were the only independent prognostic factors for PFS and OS.

Conclusions: As front-line regimen in mCRC, FOLFIRI-3/Bev regimen, followed by a capecitabine-based maintenance therapy, is effective and might be considered for future development particularly in patients treated by oxaliplatin in the adjuvant setting. Serum angiopoietin 2 is a promising biomarker to predict PFS and OS in mCRC patients treated with chemotherapy and bevacizumab. External validation is in course.

607P　2 种含贝伐珠单抗的新辅助治疗用于局部晚期可切除直肠癌的有效性和安全性：随机、非对照、II 期临床研究的中期结果

607P　EFFICACY AND SAFETY OF TWO NEOADJUVANT STRATEGIES WITH BEVACIZUMAB IN LOCALLY ADVANCED RESECTABLE RECTAL CANCER:INTERIM RESULTS OF A RANDOMIZED, NON-COMPARATIVE PHASE II STUDY

J.-F. Bosset, G. Mantion, T. André, et al.

背景：目前对局部晚期可切除直肠癌（LARC）的治疗包括联合化疗（CT）、放疗（RT）和全直肠系膜切除术（TME）。在一项随机、开放性、多中心、II 期临床研究中对 2 种含贝伐珠单抗（Bv）的新辅助治疗进行评估。

方法：患者接受序贯治疗，包括贝伐珠单抗诱导治疗/6 个周期（5**mg**/2 周）+Folfox4，之后接受放化疗（贝伐珠单抗/6 个周期+5-FU/5 个周期）+RT（45Gy），然后为 TME（A 组）和相同放化疗后 TME（B 组）。主要终点为肿瘤消退率（pCR）- 每组至少 10%。由独立委员会对有效性和安全性进行审查。显示术后 8 周的结果。

结果：A 组（n=46）和 B 组（n=45）的患者特征为：男性占 67%，年龄 60 ± 9 岁，ECOG 评分 0(85%)，直肠中位(60%)，直肠低位(40%)，MRI 分期：T3N0M0/T3N1M0/T3N2M0（20%/65%/15%）。在 A 组中，94%的患者完成诱导治疗，91%的患者接受 CT-RT 和手术；在 B 组中，100%的患者接受 CT-RT，98%的患者接受手术。在 91%的患者中，肉眼可见完全切除肿瘤。中位术后住院期为 15[0-84]天。在意向性治疗人群中，A 组与 B 组的 pCR（ypT0-N0）率分别为 23.8% [12.1%- 39.5%]（p=0.015）和 11.4% [3.8%- 24.6%]（p=0.91），而初始假设为 10% pCR。集中审查得到的 pCR 结果相似。在术中和术后 4 周，2 组均有 10 例患者（22%）报告 3 级/4 级不良事件（AE）。在术后 8 周，A 组有 59%的患者和 B 组有 36%的患者报告 3 级/4 级不良事件（AE）。在贝伐珠单抗治疗组中，A 组有 20%的患者和 B 组有 22%的患者报告 3 级/4 级特别关注的不良事件。在术后 8 周随访时，没有报告死亡病例。

结论：接受 2 种新辅助治疗的 LARC 患者的中期结果表明，在 B 组中，贝伐珠单抗联合 CT-RT 新辅助治疗未显著增加 pCR。A 组中，新辅助治疗评估结果较好，值得做进一步研究。在术后 8 周，A 组和 B 组的安全性相似。

Background: Current therapy of locally advanced resectable rectal cancer (LARC) involves a combination of chemotherapy (CT), radiation therapy, (RT) and total mesorectal excision (TME) surgery. Two neoadjuvant strategies with bevacizumab (Bv) were assessed in a randomized, open-label, multicentre, phase II study.

Method: Patients (pts) were treated with a sequential strategy including induction Bv/6 cycles (5mg/2weeks)+Folfox4, followed by CT-RT (Bv/6 cycles+5-FU/5 cycles)+RT(45Gy) then TME in Arm A and the same CT-RT, then TME in Arm B. Primary end-point was tumor sterilization rate (pCR)-at least 10% in each arm. Efficacy and safety were reviewed by an independent committee. Results at 8 weeks post-surgery are presented.

Results: Pts characteristics in Arm A (n=46) and in Arm B (n=45) were:men 67%, age 60 ± 9 years, ECOG score 0 (85%), mid-rectum (60%), low-rectum (40%), MRI stage:T3N0M0/T3N1M0/T3N2M0 (20%/65%/15%). In Arm A, 94% pts completed induction and 91% had CT-RT and surgery; in Arm B 100% had CT-RT and 98% surgery. Resection was macroscopically complete in 91% pts. Median post-surgery hospitalization duration was 15 [0-84] days. In the ITT population, pCR (ypT0-N0) rate was 23.8% [12.1%-39.5%] in Arm A (p=0.015) and 11.4% [3.8%-24.6%] in Arm B (p=0.91), both compared to the 10% pCR initial hypothesis. Central review found similar results for pCR. At surgery and 4 weeks post-surgery grade 3/4 adverse events (AE) were reported in 10 (22%) of pts in both arms. At 8 weeks post-surgery, grade 3/4 adverse events (AE) were reported in 59% of pts in Arm A and 36% in Arm B. Grade 3/4 AEs of special interest for bevacizumab were reported in 20% of pts in Arm A and 22% in Arm B. No death was reported at 8 weeks post-surgery follow-up.

Conclusions: Interim results in patients with LARC treated with 2 neoadjuvant strategies showed that bevacizumab combination to neoadjuvant CT-RT did not significantly increase pCR in Arm B. The neoadjuvant strategy assessed in Arm A seems promising and deserves further investigation. Safety was comparable in Arms A and B at 8 weeks post-surgery.

663TIP　AXE BEAM：贝伐珠单抗、卡培他滨+/-奥沙利铂新辅助治疗加放疗治疗局部晚期直肠癌取得令人鼓舞的早期结果

663TIP　AXE BEAM:ENCOURAGING EARLY RESULTS OF A NEO-ADJUVANT BEVACIZUMAB, CAPECITABINE +/- OXALIPLATIN AND RADIATION MULTIMODALITY REGIMEN FOR LOCALLY ADVANCED RECTAL CANCER

G. Chiritescu, K. Dumon, P. Vergauwe, et al.

在一项学术性多中心II期临床研究中，局部晚期直肠癌患者随机接受贝伐珠单抗（5mg/kg）、卡培他滨（1650mg/m^2/d）和放疗（1.8 Gy/d）与（A组）或不与（B组）奥沙利铂（50mg/m^2）联合治疗。在首次贝伐珠单抗输液后 2 周开始放化疗（CRT），并持续 5 周。计划在放化疗后 6-8 周行全直肠系膜切除术。在签署知情同意书的患者中，对组织和血样进行免疫组化染色，研究血管功能以及进行Luminex 分析，评估循环VEGF配基水平的变化。将病理完全缓解（pCR）率、安全性特征和识别早期缓解预测生物标记物作为主要终点。

结果：目前共 65 例患者入组研究，中位年龄为 60 岁。57 例患者完成了完整治疗方案，贝伐珠单抗的相对剂量强度为 97%，卡培他滨为 95%，奥沙利铂为 93%。

60 例可评估患者的初步安全性数据表明，该方案基本上具有良好的耐受性。大多数重度不良事件发生在术后（创口感染、渗漏），见于 9 例患者，在各组间均匀分布。在 CRT 期间，A 组中 3 级毒性更为常见：疲劳（1）、腹泻（2）、感染（2）、发热性中性粒细胞减少症（1）、感觉神经病（1）。2 例患者死于疾病进展，1 例患者死于术后肺栓塞。

52 例患者可评估缓解情况。11 例患者实现 pCR，A 组为 30%（8/26），B 组中为 12%（3/26）（p=0.08）。A 组（18/26）中良好缓解者（Dworak TRG 3、4）比例大于 B 组（10/26）（p=0.05）。观察到血管周细胞覆盖、肿瘤细胞增殖和 PDGF-AA、PDGF-BB 和 VEGF 血浆浓度发生变化，并将作进一步评估。

结论：放化疗与贝伐珠单抗联合治疗在该患者人群中的安全性特征可以接受。添加奥沙利铂会导致毒性略有增加，但可能增加缓解者比例。

在该背景下，PDGF 是缓解预后因素。正在作进一步分析。

In an academic multicentric phase II study, patients (pts) with locally advanced rectal cancer are randomized to receive bevacizumab (5mg/kg), capecitabine (1650mg/m^2/day) and radiotherapy (1.8Gy/day) with (Arm A) or without (Arm B) oxaliplatin (50mg/m^2). Chemoradiotherapy (CRT) starts at 2 weeks after 1st infusion of bevacizumab and continues for 5 weeks. Total mesorectal excision is planned at 6-8 weeks post CRT. Immunohistochemical staining to study the functionality of blood vessels and Luminex analyses to assess the changes in circulating VEGF ligands are performed on tissues and blood samples from consenting pts. Pathological complete response (pCR) rate, safety profile and identification of biomarkers for early response prediction are the main endpoints.

Results: Sixty five pts with median age 60 have been enrolled to date. Fifty seven pts completed the full protocol scheme, with a relative dose intensity of 97% for bevacizumab, 95% for capecitabine and 93% for oxaliplatin.

Preliminary safety data from 60 evaluable pts show that the regimen is generally well tolerated. Most severe adverse events were post-operative (wound infections, leaks) in 9 pts, equally distributed between arms. During CRT, grade 3 toxicities were more frequent in Arm A:fatigue (1), diarrhea (2), infection (2), febrile neutropenia (1), sensory neuropathy (1). Two pts deceased due to disease progression and one due to lung embolism post-surgery.

Fifty two pts are evaluable for response. pCR was seen in 11 pts, 30% (8/26) in Arm A and 12% (3/26) in Arm B (p=0.08). The rate of good responders (Dworak TRG 3,4) was higher in Arm A 18/26 versus Arm B 10/26 (p=0.05).

Changes in the pericyt coverage of the blood vessels, proliferation of the tumour cells and plasma concentrations of PDGF-AA, PDGF-BB and VEGF were observed and will be further assessed.

Conclusions: Chemoradiotherapy in combination with bevacizumab showed an acceptable safety profile in this patient population. Adding oxaliplatin determined a slight increase of toxicity but might enhance the percentage of responders.

PDGF may be a predictor of response in this setting. Further analyses are ongoing.

LBA17　评价在接受贝伐珠单抗作为部分一线治疗的转移性结直肠癌（mCRC）患者疾病进展后继续给予贝伐珠单抗（BV）的随机 III 期临床研究：GRUPPO ONCOLOGICO NORD OVEST（GONO）进行的 BEBYP 试验结果

LBA17　A RANDOMIZED PHASE III STUDY EVALUATING THE CONTINUATION OF BEVACIZUMAB (BV) BEYOND PROGRESSION IN METASTATIC COLORECTAL CANCER (MCRC) PATIENTS (PTS) WHO RECEIVED BV AS PART OF FIRST-LINE TREATMENT:RESULTS OF THE BEBYP TRIAL BY THE GRUPPO ONCOLOGICO NORD OVEST (GONO)

G. Masi, F. Loupakis, L. Salvatore, et al.

引言：回顾性数据表明在 BV 一线治疗进展后继续使用 BV+二线化疗（CT）可以改善生存期。

方法：这项 III 期研究将 BV+一线 CT（氟嘧啶、FOLFIRI FOLFOX 或 FOLFOXIRI）治疗的不可切除 mCRC 患者随机分配接受二线 CT+FOLFOX 或 FOLFIRI（取决于一线化疗）单药（A 组）或联合 BV（5mg/Kg i.v.，每 2 周一次）（B 组）。按照研究中心、PS（0 vs 1-2）、一线 CT 最后一次治疗后的无病生存期（≤3 个月 vs >3 个月）、二线方案对患者进行了分层。主要终点是无进展生存期（PFS）。为了检测到 PFS 的 HR 为 0.70，在试验设计中计划对 262 名患者进行随机分配。考虑到研究设计相似的 AIO/AMG ML18147 试验证明了进展后使用 BV 治疗使总生存期（OS）改善，在 2012 年 5 月 11 日终止了入选工作。

结果：对 185 例患者进行了随机分配，而且将 184 例患者纳入到 ITT 分析中（1 例患者被错误地随机分配）。患者特征（A 组/B 组）：数量：92/92；性别：男性 75%-女性 25%/男性 57%-女性 43%；中位年龄：66（38-75）岁/62（38-75）岁；PS=0 82%/82%；多个病变部位：76%/77%；仅肝脏病变：15%/13%。本研究达到了其主要终点。在经过中位期为 18 个月的随访后，PFS 事件的数量为 172 例（93%）；A 组和 B 组的中位 PFS 分别为 4.97 个月和 6.77 个月（HR=0.65; 95% CI 0.48–0.89; 未分层的时序检验，p=0.0062）。PFS 的调整后分析考虑到了分层因素、年龄和性别，该分析确认了 B 组的 PFS 增加（HR=0.70; 95% CI 0.50–0.97; p=0.032）。CT 的缓解率为 18%，而 BEV+CT 的缓解率为 21%（p=0.71）。OS 数据尚不完善，A 组发生 52 例事件，B 组发生 46 例事件。不良事件特征与之前报告的 BEV+CT 数据一致。

结论：本研究证明了继续使用 BV 二线治疗使 PFS 增加。将会列出更新的结果。

Introduction: Retrospective data suggested that the continuation of BV with second line chemotherapy (CT) beyond the progression to a first line treatment with BV was associated with improved survival.

Methods: This phase III study randomized pts with unresectable mCRC treated with BV plus first line CT (fluoropyrimidine, FOLFIRI, FOLFOX or FOLFOXIRI) to receive a second line CT with FOLFOX or FOLFIRI (depending on first-line chemotherapy) alone (arm A) or in combination with BV at 5mg/Kg i.v. every 2 weeks (arm B). Pts were stratified according to center, PS (0 vs 1-2), disease free interval from the last administration of first line CT (≤3 months vs >3 months), second line regimen. The primary endpoint was progression-free survival (PFS). To detect a HR for PFS of 0.70 the trial was designed to randomize 262 pts. Considering that the AIO/AMG ML18147 trial with a similar design demonstrated an improved overall survival (OS) with BV beyond progression, the accrual was stopped on May 11th 2012.

Results:A total of 185 pts were randomized and 184 pts were included in the ITT analysis (1 pt randomized in error). Pts characteristics (arm A/arm B):number 92/ 92, gender M75%-F25%/M57%-F43%, median age 66 (38-75) years/62 (38-75) years, PS=0 82%/82%, multiple site of disease 76%/77%, liver-only disease 15%/13%. The study met its primary endpoint. After a median follow up of 18 months the number of events for PFS was 172 (93%); median PFS was 4.97 months for arm A and 6.77 months for arm B (HR=0.65; 95% CI 0.48–0.89; unstratified log-rank test, p=0.0062). Adjusted analysis for PFS taking into account stratification factors, age and sex confirmed the increased PFS for arm B (HR=0.70; 95% CI 0.50–0.97; p=0.032). The response rate was 18% for CT and 21% for BEV+CT (p=0.71). The OS data are still immature with a number of events of 52 in arm A and 46 in arm B. The adverse event profile was consistent with previously reported data for BEV+CT.

Conclusions: This study demonstrates an increased PFS by continuing BV in second-line. Updated results will be presented.

594P 贝伐珠单抗、西妥昔单抗和帕尼单抗一线治疗 KRAS 野生型转移性结直肠癌（MCRC）的加拿大药物经济学分析

594P CANADIAN ECONOMIC ANALYSIS OF BEVACIZUMAB, CETUXIMAB, AND PANITUMUMAB IN THE FIRST LINE TREATMENT OF KRAS WILD-TYPE METASTATIC COLORECTAL CANCER (MCRC)

D. Lawrence, M. Maschio, S. Yunger, et al.

背景：在加拿大，CRC 是第二大常见致死癌症。重组人化单克隆抗体贝伐珠单抗可选择性结合人类血管内皮生长因子，已在加拿大获得批准，并作为 mCRC 的一线治疗。一项子研究也证实了贝伐珠单抗在 KRAS 野生型患者中的有效性。最新证据还证明了抗表皮生长因子治疗，帕尼单抗和西妥昔单抗在这些患者中的临床获益。目的：我们评估了单纯含氟嘧啶化疗（FBC）以及化疗与贝伐珠单抗、帕尼单抗或西妥昔单抗合用作为 KRAS 野生型 mCRC 患者一线治疗时的成本效益。

方法：使用单独报告的试验生存数据和每种对照药的不良事件结果对加拿大医疗保健系统进行成本效益估算。我们采用了按无进展生存期/总生存期标准化的 Markov 模型，并计算质量调整寿命年（QALY）。通过已发表数据和加拿大肿瘤科医师的信息获得健康状态资源利用情况。通过已发表的文献和标准加拿大数据来源获得健康状态效益和单位价格。

结果：每例患者最长 10 年的结果如下，折扣 5%。按总成本对对照药物进行排序，并且对比既往非主导治疗确定每种药物的增量成本效益比（ICER）。

结论：作为加拿大 KRAS 野生型 mCRC 的一线治疗，贝伐珠单抗+FBC 的用药相关成本显著低于帕尼单抗+FBC 或西妥昔单抗+FBC。3 种生物制剂产生的 QALY 相似，但得出该结论的理论基础有所局限，即根据各项单独试验对预期寿命建模。鉴于这些结果，贝伐珠单抗在该患者人群中可能产生最佳的经济价值。

Background:CRC is the second leading cause of cancer death in Canada. Bevacizumab, a recombinant humanised monoclonal antibody that selectively binds to human vascular endothelial growth factor, is approved and funded for first line mCRC use in Canada. A substudy has also confirmed its effectiveness in KRAS wild-type patients. Recent evidence has also shown clinical benefit from anti-epidermal growth factor treatments panitumumab and cetuximab in these patients. Objective:We assessed cost-effectiveness of fluoropyrimidine-based chemotherapy (FBC) alone and in combination with bevacizumab, panitumumab or cetuximab for first line treatment of KRAS wild-type mCRC patients.

Methods: Cost-effectiveness to the Canadian health care system was estimated using separately reported trial survival and adverse event results for each comparator. We used a Markov model calibrated to progression-free/overall survival, and calculated quality-adjusted life years (QALYs). Health-state resource utilization was derived from published data and Canadian oncologist input. Health state utilities and unit prices were obtained from published literature and standard Canadian sources.

Results: Results per patient over a lifetime horizon, to a maximum 10 years with 5% discounting are presented below. Comparators are ordered by total cost, and the incremental cost-effectiveness ratio (ICER) of each is determined against the previous non-dominated therapy.

Conclusion: For first line treatment of KRAS wild-type mCRC in Canada, bevacizumab+FBC is associated with substantially lower costs than panitumumab+FBC or cetuximab+FBC. All three biologics may be associated with similar QALYs, although; this conclusion was based on the limitation of modelling life expectancy from separate trials. Given these findings, bevacizumab seems likely to offer the best value for money for this patient population.

对照/ Comparator	总成本/ Total Cost	总 QALYs/Total QALYs	Δ 成本/ Δ Cost	ΔQALYs/ Δ QALYs	ICER/ ICER
FBC	39,061 美元/dollar	1.354	-	-	-
贝伐珠单抗+FBC/ Bevacizumab+FBC	104,054 美元/dollar	1.848	64,993 美元/dollar	0.494	131,631 美元/dollar
帕尼单抗+FBC/ Panitumumab+FBC	151,776 美元/dollar	1.806	47,722 美元/dollar	-0.041	主导/ Dominated
西妥昔单抗+FBC/ Cetuximab+FBC	161,596 美元/dollar	1.865	57,542 美元/dollar	0.017	3,327,501 美元/dollar

629 根据 KRAS 基因型和疾病扩散程度，接受强化三药化疗加贝伐珠单抗（FIR-B/FOX）治疗的转移性结直肠癌（MCRC）患者的不同临床结局

629 DIFFERENT CLINICAL OUTCOME OF METASTATIC COLORECTAL CANCER (MCRC) PATIENTS TREATED WITH INTENSIVE TRIPLET CHEMOTHERAPY PLUS BEVACIZUMAB (FIR-B/FOX) ACCORDING TO KRAS GENOTYPE AND DISEASE EXTENSION

G. Bruera, K. Cannita, D. Di Giacomo, et al.

背景：在局限性肝转移（L-L）患者中，贝伐珠单抗（BEV）加三联化疗可以增加 MCRC 一线治疗的有效性（Bruera G 等人，BMC Cancer 2010，10:567），尤其是与二次肝脏手术合用时（Bruera G 等人，Clin Colorectal Cancer 2012）。在 L-L 和其他 MCRC 患者中根据 KRAS 基因型对 FIr-B/FOx 方案的临床结局进行评估。

方法：通过 SNaPshot 和/或直接测序法，对肿瘤和转移瘤样本中 KRAS 密码子 12 和 13 和 BRAF 突变进行筛查。MCRC 患者被分为 L-L 和其他或多处转移（O/MM）。使用时序检验法对活性和有效性进行评价和比较。

结果：共有 59 例患者接受评价：31 例为 KRAS 野生型，53%；28 例为 KRAS 突变体，47%。在 21.5 个月的中位随访期，客观缓解率（ORR）、无进展生存期（PFS）和总生存期（OS）分别为：KRAS 野生型：90%、14 个月、38 个月；KRAS 突变体：67%、11 个月、20 个月。在总计 25 例 L-L 与 32 例 O/MM 可评估患者中，无进展生存期和总生存期分别为：17 个月和 12 个月，与 47 个月和 21 个月，存在显著差异；在 L-L 组 12 例与 O/MMKRAS 组 18 例野生型患者中，分别为 21 个月和 12 个月，与 47 个月和 28 个月，存在显著差异；在 L-L 组 13 例与 O/MMKRAS 组 14 例 KRAS 突变体患者中，分别为 11 个月和 11 个月，与 39 个月和 19 个月，没有显著差异。

结论：Fir-B/Fox 一线治疗可以改善 KRAS 野生型和突变体 MCRC 患者中的活性和有效性；结合二次肝脏手术可显著区别 KRAS 野生型 L-L 与 O/MM 患者之间的临床结局改善，但在 KRAS 突变患者中则没有这一效果。

Background: Bevacizumab (BEV) plus triplet chemotherapy can increase efficacy of first-line treatment of MCRC (Bruera G et al, BMC Cancer 2010, 10:567), particularly if integrated with secondary liver surgery in liver-limited (L-L) patients (pts) (Bruera G et al, Clin Colorectal Cancer 2012). Clinical outcome of Fir-B/Fox regimen was evaluated according to KRAS genotype in L-L and other MCRC pts.

Methods: Tumoral and metastatic samples were screened for KRAS codon 12 and 13, and BRAF mutations by SnaPshot and/or direct sequencing. MCRC pts were classified as L-L and other or multiple metastatic (O/MM). Activity and efficacy were evaluated and compared using log-rank test.

Results: Fifty-nine pts were evaluated:31 KRAS wild-type, 53%; 28 KRAS mutant, 47%. At 21.5 months median follow-up, objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) were, respectively:KRAS wild-type 90%, 14 months, 38 months; KRAS mutant 67%, 11 months, 20 months. PFS and OS were, respectively:overall in 25 L-L compared to 32 O/MM evaluable pts, 17 and 12 months, 47 and 21 months, significantly different; in KRAS wild-type, 12 L-L compared to 18 O/MM, 21 and 12 months, 47 and 28 months, significantly different; in KRAS mutant, 13 L-L compared to 14 O/MMS, 11 months equivalently, 39 and 19 months, not significantly different.

Conclusion: First line Fir-B/Fox regimen can increase activity and efficacy of KRAS wild-type and mutant MCRC pts; integration with secondary liver surgery significantly discriminates increased clinical outcome in KRAS wild-type L-L compared to O/MM pts while not in KRAS mutant pts.

651 贝伐珠单抗治疗后结直肠癌肝转移的病理缓解的回顾性分析：结果更新

651 RETROSPECTIVE ANALYSIS OF PATHOLOGICAL RESPONSE IN COLORECTAL CANCER LIVER METASTASES FOLLOWING TREATMENT WITH BEVACIZUMAB:UPDATED FINDINGS

R. Vera, J. Figueras, M. Gomez Dorronsoro, et al.

背景：最近的报告表明，病理缓解可以预测术前化疗和手术切除结直肠癌（CRC）肝转移瘤后的结局（总生存期）较好。这项回顾性分析的目的是在CRC 肝转移患者中评价在标准化疗基础上添加贝伐珠单抗（BEV）治疗对病理缓解的影响。

方法：对于在 2 个西班牙研究中心接受新辅助化疗（奥沙利铂或伊立替康）的 IV 期 CRC 肝转移瘤患者进行了回顾性分析。对病理缓解进行评价，如下所示：病理完全缓解（cPR）、PR1（< 25% 的残留活肿瘤细胞）、PR2（25%-50%的残留肿瘤）、PR3（>50% 的残留肿瘤）。cPR 或 PR1 被视为应答良好，PR2 或 PR3 为应答不良。根据瘤块确定 KRAS 状态。

结果：95 例患者接受评估。其中 44 例患者接受化疗，51 例患者接受化疗 +贝伐珠单抗治疗。基线特征如下所示：中位年龄为 61.0 岁（范围 43.0–80.0 岁）；男性/女性（68%/32%）；肿瘤部位 –结肠（72%）/直肠（28%）；肝转移-同时（74%）/异时（26%）；肝外疾病– 是（26%）/否（74%）；KRAS 状态-突变体（37%）/野生型（29%）/未获得（34%）。根据 RECIST，总缓解率（ORR）为 51%（1 例 CR 和 47 例 PR），48%的患者实现疾病稳定。在接受或未接受贝伐珠单抗治疗的患者中，总缓解率未发生变化。在病理缓解方面，49%接受贝伐珠单抗治疗的患者与 27%仅接受化疗的患者获得良好缓解（cPR+PR1）（p=0.0302）。KRAS 状态为突变的患者（31%）中良好病理缓解率（cPR+PR1）略低于野生型（43%）患者（无显著差异）。在分析结束时，45%的患者出现复发，67%的患者仍生存。

结论：在新辅助治疗中，标准化疗基础上添加贝伐珠单抗可在 IV 期 CRC 患者中改善肝转移的病理缓解。需要作进一步的研究检验 CRC 和肝转移患者中病理缓解和生存结局之间的潜在关系。

Background: Recent reports have shown that pathological response predicts for better outcome (overall survival) following preoperative chemotherapy and surgical resection of colorectal cancer (CRC) liver metastases. The aim of this retrospective analysis was to evaluate the effect of adding bevacizumab (BEV) to standard chemotherapy on pathological response in patients (pts) with CRC liver metastases.

Methods: Pts with stage IV CRC with liver metastases who received neoadjuvant chemotherapy (oxaliplatin-or irinotecan-based) at two Spanish centres were analysed retrospectively. Pathological response was evaluated as follows:complete pathological response (cPR), PR1 (<25% of residual viable tumour cells), PR2 (25–50% of residual tumour), PR3 (>50% of residual tumour). cPR or PR1 was considered to be a good response, and PR2 or PR3 a poor response. KRAS status was determined from tumour blocks.

Results:95 pts were evaluated. Of these, 44 received chemotherapy alone and 51 received chemotherapy+BEV. Baseline characteristics were as follows:median age 61.0 years (range 43.0–80.0 years); male/female (68%/32%); tumour location – colon (72%) / rectum (28%); hepatic metastases – synchronous (74%) / metachronous (26%); extrahepatic disease – yes (26%) / no (74%); KRAS status – mutated (37%) / wild type (29%) / not available (34%). The overall response rate (ORR) by RECIST was 51% (1 CR and 47 PRs) and 48% of pts had stable disease. ORR did not appear to vary in pts who did or did not receive BEV. In terms of pathological response, 49% of pts receiving BEV had a good response (cPR+PR1) compared with 27% of those receiving chemotherapy alone (p=0.0302). Good pathological response (cPR+PR1) was slightly lower in pts with mutant (31%) vs wild type (43%) KRAS status (difference not significant). At the end of the analysis, 45% of pts had relapsed and 67% were alive.

Conclusion: Adding BEV to standard chemotherapy in the neoadjuvant setting improves pathological response of liver metastases in pts with stage IV CRC. Further studies are required to examine the potential relationship between pathological response and survival outcomes in pts with CRC and liver metastases.

596P 老年转移性结直肠癌（MCRC）患者中与贝伐珠单抗（BV）相关的不良事件（AES）

596P ADVERSE EVENTS (AES) ASSOCIATED WITH BEVACIZUMAB (BV) IN OLDER PATIENTS (PTS) WITH METASTATIC COLORECTAL CANCER (MCRC)

V. Shankaran, D. Mummy, L. Koepl, et al.

背景：有关贝伐珠单抗在老年 mCRC 患者中的相对安全性研究不足。这项分析的目的是在老年 mCRC 患者人群样本中研究与治疗相关的不良事件发生率以及确定不良事件的相关因素。

方法：从 SEER-Medicare 中确认 2001-2007 年期间，年龄≥65 岁，诊断（Dx）为 mCRC 的患者。根据诊断后 3 个月内的保险理赔数据确认一线（1L）化疗（CTx）；患者分为未接受一线化疗、单独一线化疗或一线化疗+贝伐珠单抗。还根据诊断期（2001-3 与 2005-7）对患者进行了分类；排除 2004 年诊断的患者，原因是无法可靠确认该年的贝伐珠单抗使用情况。诊断前 1 年的已有状况（PC）可分为 5 类（心血管（CV）、脑血管（CNS）、胃肠道（GI）、组织完整性（TI）和肺部（Pulm）。在开始一线化疗至随访结束期间，针对这些疾病的理赔确认为不良事件。按诊断年份和一线化疗队列确定不良事件的发生率。我们采用竞争性风险回归模型比较 2005-2007 年期间接受一线化疗+贝伐珠单抗治疗的患者与 2001-2007 年期间单独接受一线化疗的患者的首次不良事件发生时间。构建类似的模型，用于分析特定的严重不良事件（中风、深静脉血栓形成/肺栓塞、胃肠出血、胃肠穿孔）。

结果：共确认 6,899 例患者（中位年龄为 77 岁）。在 2001-2003 年期间，37%的患者接受了一线化疗；在 2005-2007 年，分别有 21%和 19%的患者仅接受一线化疗和一线化疗+贝伐珠单抗治疗。在 2001-2003 年期间单独接受一线化疗（135 例不良事件/ 100,000 人-天（PD））和 2005-2007 年期间接受一线化疗+贝伐珠单抗治疗（140 例不良事件/ 100,000 PD）的患者间，不良事件发生率相似。2005-2007 年期间接受一线化疗+贝伐珠单抗治疗的患者与 2001-2007 年期间单独接受一线化疗的患者相比，首次不良事件发生时间未见缩短（风险比 0.99，p=0.90）。类似的，一线化疗 +贝伐珠单抗不会缩短特定不良事件的发生时间。（见表）

结论：接受一线化疗+贝伐珠单抗治疗的老年患者与单独接受一线化疗的患者相比，不良事件发生率没有增加，首次不良事件发生时间也未缩短。在老年 mCRC 患者中，使用贝伐珠单抗不会增加不良事件的风险。

首次不良事件发生时间：贝伐珠单抗与单独一线化疗

Background: The relative safety of BV in older mCRC pts is understudied. The objectives of this analysis are to investigate treatment-related AE incidence and to determine factors associated with Aes in a population-based sample of older mCRC pts.

Methods: Pts age ≥65 diagnosed (Dx) with mCRC in 2001-7 were identified from SEER-Medicare. First-line (1L) chemotherapy (CTx) was identified by claims within 3 months of Dx; pts were categorized as receiving no 1L CTx, 1L CTx alone, or 1L CTx+BV. Pts were also categorized by Dx period (2001-3 vs. 2005-7); pts Dx in 2004 were excluded as BV use could not be reliably identified in that year. Preexisting conditions (PCs) identified in the year prior to Dx were grouped into 5 categories (cardiovascular (CV), cerebrovascular (CNS), gastrointestinal (GI), tissue integrity (TI), and pulmonary (Pulm). Claims for these conditions between start of 1L CTx and end of follow-up were identified as Aes. AE incidence rates were determined by Dx year and 1L CTx cohort. We used a competing risks regression model to compare time to 1st AE for pts who received 1L CTx+BV in 2005-7 to pts who received 1L CTx alone in 2001-7. Similar models were constructed for specific serious Aes (stroke, DVT/PE, GI bleed, GI perforation).

Results:6,899 pts (median age 77) were identified. In 2001-3, 37% of pts received 1L CTx alone; in 2005-7, 21% and 19% of pts received 1L CTx alone and 1L CTx+BV. AE incidence was similar between pts receiving 1L CTx alone in 2001-3 (135 Aes / 100,000 person-days (PD)) and 1L CTx+BV in 2005-7 (140 Aes / 100,000 PD). Time to 1st AE was not shorter in pts receiving 1L CTx+BV in 2005-7 compared with 1L CTx alone in 2001-7 (HR 0.99, p=0.90). Similarly, receipt of 1L CTx+BV was not associated with a shorter time to specific AE. (Table)

Conclusions: Older pts who received 1L CTx+BV had neither increased AE incidence nor decreased time to 1st AE compared with pts who received 1L CTx alone. BV utilization may not increase AE risk among elderly mCRC pts.

Time to 1st AE:BV vs. 1L CTx alone

不良事件类型/AE Type	风险比/HR	95%可信区间 /95% CI
任何不良事件/Any AE	0.99	0.90-1.10
中风/Stroke	1.04	0.95-1.15
深静脉血栓形成/肺栓塞/DVT/PE	1.03	0.94-1.14
胃肠出血/GI bleed	1.03	0.94-1.14
胃肠穿孔/GI perforation	1.05	0.95-1.15

根据以下因子对模型进行调整：年龄、并存疾病、人种、性别、CTx 主药、PC

Models adjusted for:age, comorbidity, race, gender, CTx backbone, PC

557P 西妥昔单抗加化疗用于 KRAS 野生型不可切除的结直肠癌局限性肝转移患者的随机、对照试验

557P A RANDOMIZED, CONTROLLED TRIAL OF CETUXIMAB PLUS CHEMOTHERAPY FOR PATIENTS WITH KRAS WILD-TYPE UNRESECTABLE COLORECTAL LIVER-LIMITED METASTASES

J. Xu, L. Ye, L. Ren, Y. Wei

背景：评估西妥昔单抗联合一线化疗治疗不可切除的结直肠癌肝转移（CLM）的效果。

方法：切除原发病灶后，同时有不可切除的局限性肝转移的野生型 KRAS 结直肠癌患者随机接受化疗（FOLFIRI 或 mFOLFOX6）加西妥昔单抗（A 组）或单独化疗（B 组）。主要终点为肝转移二次切除率。次要终点包括肿瘤缓解和生存状况。

结果：从 2008 年 6 月至 2011 年 12 月，116 例患者合格入组研究（A 组 59 例患者和 B 组 57 例患者）。在所有患者中，3 年总生存(OS)率和中位生存期(MST)分别为 32%和 27.5 个月(mo)。在 A 组和 B 组中，肝转移瘤 R0 切除率分别为 30.5%（18/59）和 8.8%（5/57），并存在显著差异（优势比=4.57，p< .01）。在 A 组中接受 R0 切除的 18 例患者中，中位无瘤生存期和中位生存期分别为 11.4 个月和 46.6 个月。与 B 组相比，A 组患者的客观缓解率有所改善（OR，66.1%与 33.3%，优势比=3.90，p< .01）、3 年总生存率增加（43%与 21%，p=.01）且中位生存期延长（32.8 个月与 22.8 个月，风险比=0.49，p=.01）。此外，在未接受肝脏手术的患者中，A 组患者得到的生存获益大于 B 组，包括 3 年总生存率（25%与 17%，p=.047）、MST（28.2 个月与 21.2 个月，风险比=0.55，p=.047）和无进展生存期（8.3 个月与 5.2 个月，风险比=0.64，p=.03）。此外，在 A 组中，肝转移切除患者的 3 年总生存率（74%与 25%，p=.02）和 MST（46.6 个月与 28.2 个月，风险比=0.29，p=.02）与未接受肝脏手术的患者相比显著改善，而携带 BRAF 野生型肿瘤的患者中，MST 的获益大于（35.8 个月与 23.4 个月，风险比=0.39，p=.045）突变 BRAF 肿瘤患者，但对于 OR（70.0%与 44.4%，优势比=2.92，p>.05）无获益。

结论：在 KRAS 野生型不可切除 CLM 患者人群中，西妥昔单抗联合化疗与单独化疗相比可改善肝转移瘤可切除性、缓解率和生存状况（ClinicalTrials.gov 编号 NCT01564810）。

Background: To assess the effect of cetuximab combined with chemotherapy in first-line treatment for unresectable colorectal liver metastases (CLM).

Methods: After resection of the primary focus, patients (pts) with non-resectable synchronous liver-limited metastases from wild-type KRAS colorectal cancer were randomly assigned to received chemotherapy (FOLFIRI or mFOLFOX6) plus cetuximab (arm A) or chemotherapy alone (arm B). The primary end point was the rate of secondary resection for liver metastases. Secondary end points included tumor response and survival.

Results: From June 2008 to December 2011, 116 pts were eligible (59 in arm A and 57 in arm B). The 3-year overall survival (OS) rate and median survival time (MST) of the total pts was 32% and 27.5 months (mo), respectively. R0 resection rate for liver metastases was 30.5% (18/59) in arm A and 8.8% (5/57) in arm B, with significant difference (Odds ratio=4.57, p< .01). In R0 resected 18 pts from arm A, the median disease free survival and MST was 11.4 and 46.6 mo. The pts in arm A had improved objective response (OR, 66.1% v 33.3%, Odds ratio=3.90, p< .01), increased 3-year OS rate (43% v 21%, p=.01) and prolonged MST (32.8 v 22.8 mo, HR =0.49, p=.01) compared with those in arm B. Furthermore, for the pts without liver surgery, people from arm A also got more survival benefit than those from arm B on 3-year OS rate (25% v 17%, p=.047), MST (28.2 v 21.2 mo, HR =0.55, p=.047) and progressives free survival (8.3 v 5.2 mo, HR =0.64, p=.03). In addition, in arm A, pts who experienced resection of liver metastases were significantly improved 3-year OS rate (74% v 25%, p=.02) and MST (46.6 v 28.2 mo, HR=0.29, p=.02) than those without liver surgery, and the pts harboring BRAF wild-type tumors gained more benefit on MST (35.8 v 23.4 mo, HR =0.39, p=.045) rather than on OR (70.0% v 44.4%, Odds ratio=2.92, p>.05), when compared to those with mutated BRAF tumors.

Conclusion: For initially unresectable CLM population with KRAS wild-type, cetuximab combined with chemotherapy could improve resectability of liver metastases, response rates and survival compared with chemotherapy alone (ClinicalTrials.gov number NCT01564810).

561P 接受一线 FOLFIRI 加西妥昔单抗的 KRAS 野生型转移性结直肠癌患者的生活质量分析

561P QUALITY OF LIFE ANALYSIS IN PATIENTS WITH KRAS WILD-TYPE METASTATIC COLORECTAL CANCER TREATED WITH FIRST-LINE FOLFIRI PLUS CETUXIMAB

Láng, C.H. Köhne, G. Folprecht, et al.

背景：在 CRYSTAL 研究中，一线 FOLFIRI 的基础上添加西妥昔单抗在 KRAS 野生型转移性结直肠癌（mCRC）患者中可显著改善临床结局。对生活质量（QoL）进行评估，并对肿瘤应答和生存之间的相关性进行研究。

材料和方法：使用了欧洲癌症研究和治疗组织 QoL 调查问卷 core-30。主要分析是对整体健康评分（GHS）/QoL 和社会功能量表的 模式-混合分析。探索性分析包括根据皮肤反应严重程度的 QoL 评分相对基线时的变化、根据肿瘤应答和治疗的报告症状相对基线时的变化和基线时症状对应答和生存的影响。

结果：在 627/666 例 KRAS 野生型肿瘤患者（94%）中，生活质量可评估，52%的患者接受 FOLFIRI，48%的患者接受 FOLFIRI 加西妥昔单抗治疗。在 2 个治疗组之间，GHS/QoL（p=0.12）和社会功能评分（p=0.43）无显著差异。在接受西妥昔单抗治疗的患者中，无皮肤反应者的 GHS/QoL 与基线值相比的平均变化为 3.00，出现 I 级和 II-IV 级早期皮肤反应的患者分别为-1.09 和 -0.51。无皮肤反应的患者社会功能评分降低（平均值-6.41），而出现 I 级（平均值 1.64）和 II-IV 级（平均值 1.48）早期皮肤反应的患者略有改善。基线时无症状与有症状患者相比，肿瘤缓解率较高（58%vs 40%，p=0.0002）且生存期较长（风险比 1.68，p<0.0001）。在基线时有症状（65%vs 52%，p=0.0388）和无症状的患者（52%vs 31%，p=0.0034）以及肿瘤应答、相对基线时的最大程度的症状缓解发生较早（855566616 周）的患者中，FOLFIRI 加西妥昔单抗与单独 FOLFIRI 相比可增加肿瘤应答。

结论：在肿瘤缓解的患者中，FOLFIRI 的基础上添加西妥昔单抗可改善临床结局，不会对生活质量产生不良影响，可在有基线症状的情况下改善应答状况，并可较早地缓解症状。在 mCRC 患者中，基线时症状是有效的预后因素。

Background: In the CRYSTAL study adding cetuximab to first-line FOLFIRI significantly improved clinical outcome in patients (pts) with KRAS wild-type metastatic colorectal cancer (mCRC). Quality of life (QoL) was assessed and associations with tumor response and survival were studied.

Material and methods: The European Organization for Research and Treatment of Cancer QoL questionnaire core-30 was used. The primary analysis was a pattern-mixture analysis for the global health score (GHS)/QoL and social functioning scales. Exploratory analyses included the change from baseline QoL scores by severity of skin reactions, the change in reported symptoms from baseline according to tumor response and treatment, and the effect of symptomatic status at baseline on response and survival.

Results: QoL was evaluable in 627/666 pts (94%) with KRAS wild-type tumors, 52% received FOLFIRI, and 48% FOLFIRI plus cetuximab. No significant differences for GHS/QoL (p=0.12) and social functioning scores (p=0.43) were found between the treatment arms. In pts receiving cetuximab, the mean change from baseline in GHS/QoL was 3.00 in pts without skin reactions compared with -1.09 and -0.51 in those with grade I and grade II-IV early skin reactions, respectively. Social functioning score worsened in pts with no skin reactions (mean -6.41) compared with a slight improvement in those with grade I (mean 1.64) and grade II-IV (mean 1.48) early skin reactions, respectively. Tumor response was higher (58% vs 40%, p=0.0002) and survival longer (hazard ratio 1.68, p<0.0001) in asymptomatic versus symptomatic pts at baseline. FOLFIRI plus cetuximab increased tumor response in symptomatic (65% vs 52%, p=0.0388) and asymptomatic pts at baseline (52% vs 31%, p=0.0034), and in pts whose tumors had responded, maximum symptom relief from baseline occurred earlier (8 vs 16 weeks) compared with FOLFIRI alone.

Conclusions: Adding cetuximab to FOLFIRI improved clinical outcome without negatively impacting on QoL, improving response despite baseline symptoms and leading to earlier symptom relief in pts whose tumors had responded. Symptom status at baseline was demonstrated to be a useful prognostic factor in mCRC.

558P 了解早期肿瘤退缩（ETS）在接受帕尼单抗（P）加 FOLFOX（F）治疗的野生型 KRAS MCRC 患者中的价值

558P UNDERSTANDING THE VALUE OF RESPONSE AND EARLY TUMOUR SHRINKAGE (ETS) IN PTS WITH WT KRAS MCRC TREATED WITH PANITUMUMAB (P) PLUS FOLFOX (F)

J.-Y. Douillard, S. Siena, J. Tabernero, et al.

引言：在临床试验中，根据 RECIST（ORR），如病变缩小≥30%，认为肿瘤应答有临床意义。据报道，在接受抗 EGFR mAb 治疗的野生型 KRAS mCRC 患者中，总缓解率和早期肿瘤缩小（第 8 周 [W8]；≥20%）可预测与标准治疗相比的总生存率改善。我们试图探索这些假设的可靠性。

方法：根据 PRIME 的最终分析数据，我们计算了 WT KRAS mCRC 患者的中位总生存期和无进展生存期，这些患者在第 8 周达到或未达到：RECIST 应答（≥/< 30%）或早期肿瘤缩小（≥/< 20%）。我们计算了第 8 周满足缩小标准（是/否）和 2 年中总生存率相关性的二元相关系数（Phi）。

结果：与既往发表的结果相符，即 P+F 治疗组总缓解率大于 F，在第 8 周，接受 P+F 治疗的患者中出现 RECIST 应答的人数较多（与 F 相比）（见表）。无论在哪个治疗组，实现早期肿瘤缩小或 RECIST 应答的患者中，中位总生存期和无进展生存期显著延长（与未实现这些应答的患者相比；见表）。在每个肿瘤缩小组，接受 P+F（与 F 相比）治疗的患者的中位总生存期和无进展生存期较长。在实现早期肿瘤缩小的患者中，P 治疗组的总生存率较好（与 F 相比；见表）。然而，在第 8 周实现 RECIST 应答的患者中，治疗组间的结局相似。满足≥30%或≥20% 标准和 2 年总生存率之间的相关系数分别为 0.21 和 0.27。

结论：无论在哪个治疗组，第 8 周实现 RECIST 应答（≥30%）或早期肿瘤缩小（≥20%）的患者与未实现这些应答的患者相比，无进展生存期和总生存期改善。在接受 P+F 治疗且达到早期肿瘤缩小的患者中，总生存期长于接受 F 单药治疗的患者。试验后抗 EGFR mAb 的使用和切除率的潜在失衡对总缓解率预测总生存率的结果解释产生限制。第 8 周肿瘤缩小度和 2 年总生存率之间 PRIME 的 Phi 值较差表明，在 mCRC 一线治疗中，总缓解率和早期肿瘤缩小不适合预测总生存率。

Introduction: In clinical trials, tumour response is considered clinically meaningful when a lesion shrinks by≥30%, according to RECIST (ORR). It has been purported that in pts with WT KRAS mCRC treated with an anti-EGFR mAb, both ORR and ETS (week 8 [W8];≥20%) predict improved OS compared with standard treatment. We explore the validity of these hypotheses.

Methods: Using final analysis data from PRIME, we calculated median OS and PFS in pts with WT KRAS mCRC who did or did not achieve:a RECIST response (≥/<30%); or ETS (≥/<20%) at W8. We calculated the binary correlation coefficients (Phi) for the association between meeting the above shrinkage criteria at W8 (yes/no) and OS at 2 years.

Results: Consistent with the previously published finding that ORR is higher with P+F vs F, at W8 more pts treated with P+F (vs F) had a RECIST response (Table). Irrespective of treatment arm, median OS and PFS were significantly longer in pts who achieved either ETS or a RECIST response (vs pts who did not; Table). Pts receiving P+F (vs F) showed longer median OS and PFS in each shrinkage group. OS trends favoured the P arm for pts achieving ETS (vs F alone; Table). However, outcomes were similar between arms in pts that achieved a RECIST response at W8. The correlation coefficients between meeting the≥30% or≥20% criterion and OS at 2 years were 0.21 and 0.27, respectively.

Conclusions: Regardless of treatment arm, pts achieving a RECIST response (≥30%) or ETS (≥20%) at W8 demonstrated improved PFS and OS compared with those who did not. Trends toward longer OS were observed in pts treated with P+F achieving ETS compared with F alone. Potential imbalances in post-protocol anti-EGFR mAb use and resection rate limit the interpretation of ORR in predicting OS. The poor Phi values found in PRIME between W8 tumour shrinkage and 2-year OS suggest that ORR and ETS alone in the first-line treatment of mCRC are inappropriate surrogates for predicting OS.

	FOLFOX		帕尼单抗+FOLFOX/ Panitumumab+FOLFOX	
	<30%	≥30%	<30%	≥30%
ITT (N=584)	N=186 (62%)	N=112 (38%)	N=141 (49%)	N=145 (51%)
中位 PFS，月/Median PFS, mo	17.6	29.5	18.0	30.3
[95% CI]	[15.4-20.2]	[22.5-34.5]	[14.2-21.7]	[26.6-36.8]
HR	0.543		0.540	
[95% CI]	[0.404-0.730]		[0.404-0.722]	
p-值/ P value	<0.0001		<0.0001	
中位 PFS，月/Median PFS, mo	7.3	9.6	7.4	11.1
[95% CI]	[5.8-8.7]	[7.7-10.8]	[6.2-9.2]	[9.6-13.0]
HR	0.648		0.617	
[95% CI]	[0.500-0.839]		[0.478-0.796]	
p-值/ P value	0.0010		0.0002	
	<20%	≥20%	<20%	≥20%
ITT (N=584)	N=130 (44%)	N=168 (56%)	N=87 (30%)	N=199 (70%)
中位 OS，月/Median OS, mo	16.6	25.1	10.7	30.2
[95% CI]	[12.4-18.8]	[22.1-32.8]	[9.4-16.1]	[27.4-33.1]
HR	0.519		0.431	
[95% CI]	[0.394-0.683]		[0.320-0.582]	
p-值/ P value	<0.0001		<0.0001	
中位 PFS，月/Median PFS, mo	5.7	9.3	5.7	11.0
[95% CI]	[5.3-7.6]	[7.7-9.9]	[4.0-7.1]	[9.6-12.8]
HR	0.624		0.462	
[95% CI]	[0.487-0.799]		[0.350-0.609]	
p-值/ P value	0.0002		<0.0001	

581P 对阿柏西普-FOLFIRI 与安慰剂-FOLFIRI 治疗转移性结直肠癌（MCRC）后无进展生存期（PFS）的敏感性分析：VELOUR 研究的结果

581P SENSITIVITY ANALYSES OF PROGRESSION-FREE SURVIVAL (PFS) OF AFLIBERCEPT-FOLFIRI VERSUS PLACEBO-FOLFIRI IN METASTATIC COLORECTAL CANCER (MCRC):RESULTS FROM THE VELOUR STUDY

E.J.D. van Cutsem, J. Tabernero, R. Lakomy, et al.

背景：在既往接受治疗的 mCRC 患者中进行的 VELOUR 研究[NCT00561470]表明，阿柏西普-FOLFIRI 与安慰剂-FOLFIRI 相比可显著改善总生存期（13.5vs12.06 个月；P=0.0032）和无进展生存期（6.9vs4.67 个月；P=0.00007）。进行了 2 项敏感性分析（SAs），旨在评估主要分析中无进展生存期的稳健性。

方法：在主要无进展生存期分析中，独立审查委员会（IRC）根据放射学肿瘤进展评估了疾病进展。主要无进展生存期分析中使用保守 α 水平 0.0001。在 SA #1 中，对末次有效肿瘤评估未见进展后大于 9 周出现放射学进展或死亡的患者和接受进一步抗癌治疗且未出现进展的患者在末次有效肿瘤评估当日进行截尾。在 SA #2 中，根据研究者的病变评估确定无进展生存期；临床进展被视为一个事件。

结果：SA #1（见表）显示阿柏西普-FOLFIRI 与安慰剂-FOLFIRI 相比可显著改善无进展生存期（P<0.00001），从而证实了主要无进展生存期分析结果。SA #2 也证明阿柏西普与安慰剂相比可改善无进展生存期；在 0.0001 α 水平下，差异不显著（P=0.0017）。在安慰剂（n=273，45.8%）和阿柏西普（n=231，39.3%）治疗组中，IRC 和研究者评估之间存在偏差。比较 2 组主要无进展生存期的非分层时序检验与分层分析相符，表明阿柏西普的无进展生存期有显著差异（P=0.00005）。阿柏西普可产生典型的抗 VEGF 副作用。

结论：这些无进展生存期敏感性分析（Sas）的数据与 VELOUR 中无进展生存期主要分析相符，进一步支持主要分析中无进展生存期的统计学显著和有临床意义的改善。

Background: The VELOUR study [NCT00561470] in previously treated mCRC showed significant improvement in overall survival (13.5 vs 12.06 months; P=0.0032) and PFS (6.9 vs 4.67 months; P=0.00007) with aflibercept-FOLFIRI vs placebo-FOLFIRI. Two sensitivity analyses (SAs) were performed to assess robustness of PFS observed in the primary analysis.

Methods: In the primary PFS analysis, an Independent Review Committee (IRC) assessed disease progression per radiological tumor progression. The primary PFS analysis was performed at a conservative α level of 0.0001. In SA#1, patients with documented radiological progression or death occurring >9 weeks after the last valid tumor assessment without progression and patients who received further anti-cancer therapy without documented progression were censored at the last valid tumor assessment date. In SA#2, PFS was per the investigators' assessment of lesions; clinical progression was considered as an event.

Results: SA #1 (Table) showed significant improvement in PFS with aflibercept-FOLFIRI compared to placebo-FOLFIRI (P<0.00001), thus confirming primary PFS analysis. SA #2 also showed an improvement in PFS with aflibercept vs placebo; difference was not significant (P=0.0017) at the 0.0001 α level. Discrepancies between IRC and investigators' assessments were noted in placebo (n=273, 45.8%) and aflibercept (n=231, 39.3%) arms. An unstratified log-rank test comparing primary PFS in the two arms was consistent with the stratified analysis, showing a significant difference in PFS with aflibercept (P=0.00005). Aflibercept showed typical anti-VEGF side effects.

Conclusion: The data from these PFS sensitivity analyses (Sas) are consistent with the primary analysis of PFS in VELOUR, further supporting the statistically significant and clinically meaningful improvement in PFS seen in the primary analysis.

分析：PFS（月）/Analysis:PFS (months)	安慰剂/Placebo N=614	阿柏西普/Aflibercept N=612	风险比 [99.99% 可信区间]/HR [99.99% CI]
主要：/Primary:	4.67 4.07 – 5.55	6.90 5.88 – 7.85	0.758 [0.578 – 0.995]
SA#1：	4.53 4.07 – 5.68	6.97 6.05 – 8.51	0.654 [0.477 – 0.895]
SA#2：	4.50 4.04 – 5.55	6.24 5.49 – 7.19	0.814 [0.630 – 1.052]

LBA18　Regorafenib 治疗转移性结直肠癌（MCRC）的 III 期 CORRECT 试验：总生存期数据更新
LBA18　PHASE 3 CORRECT TRIAL OF REGORAFENIB IN METASTATIC COLORECTAL CANCER (MCRC):OVERALL SURVIVAL UPDATE

E.J.D. van Cutsem, A. Grothey, A. Sobrero, et al.

背景：CORRECT 试验的目的是在所有已批准标准疗法治疗后疾病进展的 mCRC 患者中对口服多激酶抑制剂 regorafenib（REG）进行评估。在预先计划的中期分析时，该试验达到了其主要终点，而且之前已经公布了中期分析的结果（(J Clin Oncol 30, 2012 [suppl; abstr 3502])。此处报告了更新的总生存期（OS）数据。

方法：入组标准包括确诊为 mCRC 而且在接受最后一次标准疗法期间或之后 3 个月内出现进展。患者按 2:1 的比例随机接受最佳支持治疗+REG(160mg，od，po)或安慰剂（PL）治疗，治疗 3 周/停药 1 周。主要终点是总生存期（OS）。次要终点包括无进展生存期（PFS）、总缓解率和疾病控制率。还对安全性和生活质量进行了评估。

结果：从 2010 年 5 月到 2011 年 3 月，对 760 例患者进行了随机分配（REG：505 例；PL：255 例）。两组间的基线特征分布均衡。根据截止到 2011 年 11 月 13 日的数据库，进行了一项 OS 的描述性更新分析，共包括 566 例事件（原来要求 97%的事件）。在该项分析中，OS 的风险比（HR, REG/PL）为 0.79（95% CI，0.66-0.94，单侧 p=0.0038）。REG 组和 PL 组的中位 OS 分别为 6.4 个月（95% CI, 5.8-7.0）和 5.0 个月（95% CI, 4.4-5.9）。REG 组的 6 个月和 12 个月时 OS 率分别为 52.2%和 24.1%，而 PL 组分别为 43.1%和 17%。这些数据是对之前报告的中期分析（基于 432 例事件，74%）OS 数据的更新，在之前的中期分析中，OS 的 HR 为 0.77（95% CI, 0.64-0.94，单侧 p 值=0.0052）。REG 组的患者平均接受了计划剂量的 78.9%，而 PL 组的患者平均接受了计划剂量的 90.2%。平均治疗持续时间分别为 12.1 ± 9.7 周（REG）和 7.8 ± 5.2 周（PL）。在年龄、性别、肾功能和肝功能亚组中，REG 相关不良事件的发生率相似，而亚洲患者的不良事件发生率（98.6%）高于高加索人患者（92.3%），而且基线 ECOG 评分为 0 的患者中不良事件的发生率（97.0%）高于 ECOG 评分为 1 的患者（88.6%）。

结论：这项更新的 OS 分析证明：在之前治疗的 mCRC 患者中，REG 治疗相比与安慰剂的 OS 获益具有稳定性和一致性。

Background: The CORRECT trial was conducted to evaluate the oral multikinase inhibitor regorafenib (REG) in patients (pts) with mCRC whose disease had progressed after all approved standard therapies. This trial met its primary endpoint at a pre-planned interim analysis, the results of which were presented previously (J Clin Oncol 30, 2012 [suppl; abstr 3502]). The updated overall survival (OS) data are reported here.

Methods: Enrollment criteria included documented mCRC and progression during or ≤3 months after last standard therapy. Pts were randomized 2:1 to receive best supportive care plus either REG (160mg od po) or placebo (PL) on a 3 weeks on/1 week off schedule. The primary endpoint was overall survival (OS). Secondary endpoints included progression-free survival (PFS), overall response rate, and disease control rate. Safety and quality of life were also evaluated.

Results: From May 2010 to March 2011, 760 pts were randomized (REG:505; PL:255). Baseline characteristics were balanced between the two arms. A descriptive updated analysis of OS was performed, based on a database cutoff of Nov 13, 2011 with 566 total events (97% of events originally required). In this analysis, the hazard ratio (HR, REG/PL) for OS was 0.79 (95% CI, 0.66-0.94, 1-sided p=0.0038). Median OS was 6.4 months (95% CI, 5.8-7.0) in the REG arm vs 5.0 months (95% CI, 4.4-5.9) in the PL arm. OS rate at 6 and 12 months was 52.2% and 24.1% in the REG arm vs 43.1% and 17% in the PL arm, respectively. These data serve as an update to previously reported OS data from the earlier interim analysis based on 432 (74%) events, which showed a HR for OS of 0.77 (95% CI, 0.64-0.94, 1-sided p=0.0052). Pts in the REG arm received an average of 78.9% of the planned dose, and pts in PL arm 90.2% of the planned dose. The mean treatment duration was 12.1 ± 9.7 wks (REG) and 7.8 ± 5.2 wks (PL), respectively. Incidence of treatment-emergent, REG-related adverse events was similar in subgroups by age, sex, renal function and hepatic function, whereas the incidence was higher in Asian pts (98.6%) compared with Caucasian pts (92.3%), and higher in pts with a baseline ECOG score of 0 (97.0%) compared with pts with ECOG score of 1 (88.6%).

Conclusions: This updated OS analysis demonstrated the robustness and consistency of the OS benefit of REG treatment over PL in pts with previously treated mCRC.

518O 标准一线诱导治疗后免疫调节剂 mgN1703 维持治疗可以延长转移性结直肠癌（MCRC）患者的无进展生存期：II 期/III 期 IMPACT 试验结果

518O MAINTENANCE TREATMENT WITH IMMUNOMODULATORmgN1703 FOLLOWING INDUCTION WITH STANDARD 1ST LINE THERAPY PROLONGS PROGRESSION-FREE SURVIVAL IN PATIENTS WITH METASTATIC COLORECTAL (MCRC):RESULTS OF THE PHASE II/III IMPACT TRIAL

D. Arnold, H.J. Schmoll, J. Riera-Knorrenschild, et al.

引言：在接受一线治疗的 mCRC 患者中，成功“诱导”后越来越多患者停止标准化疗。MGN1703 是一类人工合成基于 DNA 的免疫调节剂，作为 TLR-9 激动剂，在 mCRC 中具有临床前活性。这项研究旨在评估 MGN1703 维持治疗与安慰剂相比的临床有效性、免疫原性和安全性。

方法：IMPACT 研究是一项国际性、多中心、随机、双盲、安慰剂对照 II 期/III 期临床研究。4.5 至 6 个月的 FOLFOX/XELOX 或 FOLFIRI +/-贝伐珠单抗一线标准治疗（研究者选择）后实现疾病控制（CR、PR 或 SD）的 mCRC 患者入选研究。

结果：对揭盲数据的中期分析表明，与预期无进展生存期相比，治疗效应较强。因此，根据指导委员会的决定，停止了对患者的进一步随机分组。在意向性治疗人群（N=55 例患者）中，风险比（HR）为 0.53，结果有利于 MGN1703（p=0.062）。在符合方案人群（排除筛选失败者；N=50）中，风险比为 0.43（p=0.015）。在预先定义的目标人群（3 个因素中满足 2 个：CEA<30 x ULN、GGT<2 x ULN、AP<2 x ULN；N=46 例患者）中，MGN1703 和安慰剂治疗组的中位无进展生存期分别为 5. 8 个月和 2.7 个月，风险比为 0.39，p=0.013。3 个月的 MGN1703 治疗后，无进展生存率分别为 43% 与 8%（p<0.001）； 6 个月和 9 个月后，MGN 1703 组与安慰剂治疗组的无进展生存率分别为 34%与 8%（p=0.011）和 22%与 0%（p=0.010）。与药物相关的不良事件包括 3 例患者报告的发热、各 1 例患者报告的非典型肺炎、肌肉疼痛、关节痛、疲劳、感觉异常、皮疹、注射部位瘙痒和 ANA 水平升高。

结论：与安慰剂相比，含或不含贝伐珠单抗的标准化疗后给予 MGN1703 维持治疗可显著改善无进展生存期，并且毒性较低。目前正计划在转移性 CRC 患者中进行一项确定性临床研究。

Introduction: Standard chemotherapy is increasingly discontinued after successful “induction” in patients (pts) undergoing 1st line treatment for mCRC.MGN1703 is a synthetic DNA-based immunomodulator acting as an agonist of TLR-9 that has shown preclinical activity in mCRC. This study has been conducted to assess clinical efficacy, immunogenicity, and safety of MGNN1703 as maintenance vs. placebo.

Methods: The IMPACT study is an international, multicenter, randomized double-blind placebo-controlled phase II/III study. Pts with mCRC showing disease control (CR, PR or SD) after 4.5 to 6 months of 1st-line standard therapy with FOLFOX/XELOX or FOLFIRI +/- bevacizumab (investigatoŕs choice) were included.

Results: Interim analysis of the unblinded data revealed a strong therapeutic effect compared to anticipated PFS. Therefore, patients were withheld from further randomization, according to a decision of the steering committee. In the ITT population (N=55 pts), hazard ratio (HR) was 0.53 in favor ofmgN1703 (p=0.062). In the per-protocol population (excluding screening failures; N=50), HR was 0.43 (p=0.015). In the pre-defined target population (2 out of 3 factors:CEA <30 x ULN, GGT <2 x ULN, AP <2 x ULN; N=46 pts), median PFS were 5.8 and 2.7 months formgN1703 and placebo, respectively, with a HR at 0.39 and p=0.013. The PFS rates after three months of treatment withmgN1703 were 43% vs. 8% (p<0.001); after six and nine months 34% vs. 8% (p=0.011) and 22% vs. 0% (p=0.010) formgN 1703 vs. placebo, respectively. Drug-related Aes included fever reported in 3 pts, atypical pneumonia, muscle aching, arthralgia, fatigue, paresthesia, rash, pruritus on injection sites, and increased ANA reported in one patient, each.

Conclusions: Maintenance therapy with MGN 1703 after standard chemotherapy with or without bevacizumab, is associated with significantly improved progression-free survival compared to placebo and is accompanied by low toxicity. A confirmatory clinical study in patients with metastatic CRC is currently being planned.

608P EXCITE：术前西妥昔单抗、伊立替康和卡培他滨加放疗（RT）治疗 MRI 确诊的局部晚期直肠癌（LARC）的 II 期临床试验

608P EXCITE:A PHASE II TRIAL OF PREOPERATIVE CETUXIMAB, IRINOTECAN AND CAPECITABINE PLUS RADIOTHERAPY (RT) IN MRI-DEFINED LOCALLY ADVANCED RECTAL CANCER (LARC)

S. Gollins, A.S. Myint, M.P. Saunders, et al.

引言：这项 II 期临床试验评估了联合西妥昔单抗、伊立替康和卡培他滨以及放疗在术前对 LARC 实施降期。

方法：患者在MRI检查中出现局部晚期/临界性不可切除直肠腺癌。治疗前未对KRAS/BRAF进行评估。患者接受盆腔放疗，剂量 45 Gy，分 25 次，为期 5 周，同时口服卡培他滨 650mg/m^2，每日两次，每周 5 天。患者在放疗前 1 周还接受西妥昔单抗 400mg/m^{2}静脉输液（IV），之后在放疗第 1-5 周，每周输液一次，剂量为 250mg/m^2，并且在疗第 1-4 周，伊立替康静脉输液，每周一次，剂量 60mg/m^2，放。在放化疗（CRT）后 8 周安排手术切除，主要终点为组织学切缘（CRM）阴性率。

结果：从 2009 年 4 月- 2011 年 10 月，共招募 82 例患者。基线情况：男性/女性 61/21，中位年龄为 62 岁，WHO PS 0/1/缺失 60/19/3。在 MRI 检查中，6/67/9 例患者的肿瘤为 T2/3/4，14/41/27 例患者为 N0/1/2，45 例患者（55%）的直肠系膜筋膜或提肛肌-括约肌复合体先兆受累（距离≤1mm），21（26%）例患者明确受累，16 例患者（20%）出现肿瘤破坏。2 例患者未接受放疗，并且停止研究治疗。显著急性毒性数量（%）分别为 3 级（Gr）腹泻：20 例（25%）、3 级痤疮样皮疹：7 例（9%）、3 级疲劳：6 例（8%），3 级和 4 级血栓形成事件分别为 1 例（1%）和 5 例（6%）以及 3 级和 4 级发热性中性粒细胞减少症分别为 1 例（1%）和 1 例（1%）。75 例患者接受手术（36 例前位切除术、37 例经腹腹膜切除术、2 例 Hartmans 术）。切除术后组织学检查显示 67 例患者（89%）的 CRM 阴性（>1 mm），14 例患者（19%）出现完全病理缓解（pCR）（T0N0），15/2/16/40/2 例患者为 T0/1/2/3/4，51/15/9 例患者为 N0/1/2。38/75 例接受切除术的患者（51%）的 T 降期，49/63（78%）例患者的 N1-2 降期。5 例 CRT 后实现临床 CR（cCR）的患者未接受手术，并且在 8、12、14、24 和 26 个月生存，没有疾病证据。

结论：EXCITE 是有关三联放化疗，包括 EGFR 靶向治疗用于 LARC 的最大规模的 II 期临床试验，其毒性和依从性可以接受。在 MRI 确诊的局部晚期/临界性不可切除肿瘤患者中，pCR+cCR 率为 19/80（24%），结果较好。在 2012 年 8 月可获得对 KRAS 和 BRAF 影响的数据。

Introduction: This phase II trial examined combining cetuximab, irinotecan and capecitabine concurrently with RT in the preoperative downstaging of LARC.

Methods: Patients (pts) had rectal adenocarcinoma with locally advanced/borderline unresectable disease on MRI. KRAS/BRAF was not assessed before treatment. Pts had pelvic RT to 45 Gy in 25 daily fractions over 5 weeks with concurrent oral capecitabine at 650mg/m^2 twice daily 5 days/week. They also received intravenous (IV) cetuximab at 400mg/m^2 one week before RT then weekly at 250mg/m^2 weeks 1-5 of RT plus IV irinotecan weekly at 60mg/m^2 weeks 1-4 of RT. Surgical resection was stipulated at 8 weeks after chemoradiation (CRT) with primary end point histological circumferential resection margin (CRM) negative rate.

Results: From Apr 2009-Oct 2011 82 pts were recruited. At baseline:male/female 61/21, median age 62, WHO PS 0/1/missing 60/19/3. On MRI tumour was T2/3/4 in 6/67/9 and N0/1/2 in 14/41/27 pts, mesorectal fascia or levator-sphincter complex was threatened (≤ 1mm gap) in 45 (55%), definitely involved in 21 (26%) and breached in 16 pts (20%). 2 pts did not commence RT and were withdrawn from trial treatment. The no. (%) of significant acute toxicities were diarrhoea grade (Gr)3 20 (25%), acneiform rash Gr3 7 (9%), fatigue Gr3 6 (8%), thrombotic event Gr3 1 (1%) and Gr4 5 (6%) and febrile neutropenia Gr3 1 (1%) and Gr4 1 (1%). 75 pts had surgery (36 anterior resection, 37 abdominoperineal, 2 Hartmans). Post-resection histology showed a negative CRM (>1mm) in 67 (89%), a pathological complete response (pCR) (T0N0) in 14 (19%), T0/1/2/3/4 in 15/2/16/40/2 and N0/1/2 in 51/15/9 pts. 38 of the 75 resected pts (51%) had their T and 49 of 63 (78%) their N1-2 stage downstaged. 5 pts with a clinical CR (cCR) post CRT did not have surgery and were alive with no evidence of disease at 8, 12, 14, 24 and 26 m.

Conclusion:EXCITE is the largest reported phase II trial of a triplet CRT regime including EGFR targeted therapy in LARC, showing acceptable toxicity and compliance. In MRI-defined locally advanced/borderline unresectable disease a combined pCR+cCR rate of 19/80 (24%) is promising. Data on KRAS and BRAF influence will be available by Aug 2012.

580P 奥沙利铂肝动脉输注（HAI）加氟尿嘧啶（FU）、亚叶酸钙（LV）和西妥昔单抗静脉输注（IV）用于不可切除的结直肠癌肝转移（CRLM）的一线治疗：多中心 II 期临床研究（CHOICE）的最终结果

580P HEPATIC ARTERIAL INFUSION (HAI) OF OXALIPLATIN PLUS INTRAVENOUS (IV) FLUOROURACIL (FU), LEUCOVORIN (LV) AND CETUXIMAB FOR FIRST-LINE TREATMENT OF UNRESECTABLE COLORECTAL LIVER METASTASES (CRLM):FINAL RESULTS OF A MULTICENTER PHASE 2 STUDY (CHOICE)

D. Malka, V. Boige, M. Faron, et al.

背景：确定奥沙利铂 HAI 加 FU/LV 和西妥昔单抗静脉输注在不可切除的 CRLM 患者中的疗效和耐受性。

方法：主要合格性标准：组织学证实的结直肠腺癌；肿瘤KRAS状态为野生型（wt）（2008 年 9 月版试验方案修订版）；不可切除的CRLM；无肝外疾病（除了原发性疾病，无症状/轻度症状并且直径≤ 5 mm的非特异性肺部结节≤ 3 个）；既往未因转移性肿瘤接受化疗；WHO体力状态 0-1。手术或经皮植入可植入HAI导管后，患者接受HAI 奥沙利铂（100mg/m^2，2 小时）加静脉输注改良LV5FU2 方案（LV，400mg/m^2，2 小时；FU，400mg/m^2 推注，之后 2400mg/m^2，46 小时），每 2 周加静脉输液西妥昔单抗（400mg/m^2，之后 250mg/m^2/周或 500mg/m^2，每 2 周），直至疾病进展、限制性毒性或CRLM切除。主要终点为客观缓解率（ORR）（RECIST 1.0）。次要终点包括毒性（NCI CTC-AE v3.0）、疾病控制率（DCR）、切除率、无进展生存期（PFS）和总生存期（OS）。

结果：从 2006 年 11 月至 2009 年 12 月，共有 36 例患者入选 8 个研究中心。在 35 例合格患者（男性，63%；中位年龄为 54 岁[范围，33-75]）中，多数出现多发性肿瘤（≥4 CRLM，88%；双叶 CRLM，91%）。患者接受的治疗周期数中位值为 10（范围，1-41）。主要的重度毒性为腹痛（40%）、中性粒细胞减少症（37%）、周围神经病变（34%）和皮疹（29%）。在 32 例可评估患者中，总缓解率为 87%，DCR 为 97%。在肿瘤状态为野生型 KRAS（n=27）或野生型 KRAS/BRAF（n=24）的可评估患者中，总缓解率分别为 89%和 96%，DCR 分别为 96%和 100%。总体而言，23/35 例患者（66%）接受根治性切除术和/或射频消融（野生型 KRAS 患者，21 例[70%]；野生型 KRAS/BRAF 患者，20 例[74%]）。48 个月的中位随访期后，中位无进展生存期为 29 个月（中位总生存期，未达到）。

结论：一线 HAI 奥沙利铂加 LV5FU2 和西妥昔单抗静脉输注在不可切除的 CRLM 患者中是可行和高效的。

Background: To determine the efficacy and tolerance of HAI oxaliplatin plus iv FU/LV and cetuximab in patients (pts) with unresectable CRLM.

Methods: Main eligibility criteria for this phase 2 study were:histologically proven colorectal adenocarcinoma; tumor wild-type (wt) KRAS status (protocol amendment in 09/2008); unresectable CRLM; no extrahepatic disease (except primary with absent/mild symptoms, and≤3 nonspecific lung nodules≤5 mm in diameter); no prior chemotherapy for metastatic disease; WHO performance status 0-1. After surgical or percutaneous insertion of an implantable HAI catheter, pts were treated with HAI oxaliplatin (100mg/m^2 in 2 hrs) plus iv modified LV5FU2 regimen (LV, 400mg/m^2 in 2 hrs; FU, 400mg/m2 bolus then 2400mg/m^2 in 46 hrs) every two weeks plus iv cetuximab (400mg/m^2 then 250mg/m^2/week, or 500mg/m^2 every two weeks) until disease progression, limiting toxicity, or CRLM resection. Primary endpoint was objective response rate (ORR) (RECIST 1.0). Secondary endpoints included toxicity (NCI CTC-AE v3.0), disease control rate (DCR), resection rate, progression-free survival (PFS), and overall survival (OS).

Results:A total of 36 pts were included in 8 centers from 11/2006 to 12/2009. Most of the 35 eligible pts (male, 63%; median age, 54 yrs [range, 33-75]) had extensive disease (≥4 CRLM, 88%; bilobar CRLM, 91%). Pts received a median of 10 cycles (range, 1-41). Main severe toxicity was abdominal pain (40%), neutropenia (37%), peripheral neuropathy (34%) and rash (29%). Among 32 evaluable pts, ORR was 87% and DCR was 97%. Among the evaluable pts with wt KRAS (n=27) or wt KRAS/BRAF (n=24) tumor status, ORR were 89% and 96% and DCR 96% and 100%, respectively. Overall, 23 of the 35 pts (66%) underwent curative-intent resection and/or radiofrequency ablation (wt KRAS pts, 21 [70%]; wt KRAS/BRAF pts, 20 [74%]). After a median follow-up of 48 months, median PFS was 29 months (median OS, not reached).

Conclusions: First-line HAI oxaliplatin plus iv LV5FU2 and cetuximab seems feasible and highly effective in pts with unresectable CRLM.

568P 西妥昔单抗（CET）静脉输注和伊立替康、5-氟尿嘧啶和奥沙利铂肝动脉输注在不可切除的野生型 KRAS 结直肠癌（CRC）肝转移患者中的安全性和有效性：OPTILIV 欧洲 II 期临床试验的结果

568P SAFETY AND EFFICACY OF INTRAVENOUS CETUXIMAB (CET) AND HEPATIC ARTERY INFUSION OF IRINOTECAN, 5-FLUOROURACIL AND OXALIPLATIN IN PATIENTS WITH UNRESECTABLE LIVER METASTASES FROM WT KRAS COLORECTAL CANCER (CRC):RESULTS FROM OPTILIV EUROPEAN PHASE II TRIAL

F. Levi, V. Boige, P. Rougier, et al.

背景：在既往静脉化疗失败的CRC 肝转移患者中，时辰（Chrono）肝动脉输注（HAI）伊立替康（I）、5-氟尿嘧啶（F）和奥沙利铂（O）或 flat O 合用静脉输液（iv）F-亚叶酸钙可以对转移灶进行二次切除并延长生存期（Bouchahda，Cancer 2009；Goere，Ann Surg 2010）。

目的：前瞻性评估合用静脉输液 Cet 与 HAI IFO 在 CRC 肝转移患者中的安全性和有效性。

方法：这项II期临床试验入选了既往接受治疗的不可切除的 CRC 肝转移患者，患者接受Cet（500mg/m^2）和时辰（Chrono）或普通（Conv）HAI I（180mg/m2）、F（2800mg/m^2）和O（85mg/m^2）静脉输注，每 2 周一次。实现充分降期后切除肝转移灶。

结果：2012 年 3 月 13 日，在 9 个研究中心（4 个国家）招募了 64 例患者（42 例男性，22 例女性；年龄，33-76 岁；4 例患者仍在参加研究）。在 62 例受监测的患者中：PS 0/1/2（61/36/3%），双叶肝脏病变（84%），转移灶中位数量 9（1-50；最大直径，54 mm；范围，15-172），受累肝段中位数量为 6（1-8）。患者既往接受 1 种（44%）、2 种（30%）或 3 种（26%）静脉化疗。59 例患者接受中位 5 个疗程（1-13）（Chrono，18；Conv，41；3 例未接受治疗），其中动脉闭塞为退出研究的主要原因（53%）。患者发生的主要 3-4 级毒性为中性粒细胞减少症（39%）、腹痛（25%）、疲劳（17%）、腹泻（15%）和恶心（10%）。3%的患者发生 3 级感觉神经病变。意向性治疗人群的客观肿瘤缓解率为 45%[95% 可信区间，31-59]，包括 2 例放射学完全缓解。疾病控制率为 83%。符合方案人群中二次肝脏手术率为 33.3% [20.4-46.2]。1 例患者的所有肝段的 24/25 处转移灶（1-6cm）出现完全病理学应答，无疾病期大于 25 个月，生存期大于 38 个月。中位无进展生存期（41 例事件）为 9.1 个月 [6.5-11.6]。初步中位生存期（19 例事件）为 28.6 个月 [16.3-40.9]。

结论：联合使用静脉输液西妥昔单抗与三联 HAI 化疗可以安全和高效地治疗化疗难治性 CRC 肝转移患者。

Background: Hepatic artery infusion (HAI) of chronomodulated (Chrono) irinotecan (I), 5-Fluorouracil (F) and oxaliplatin (O), or flat O combined with intravenous (iv) F-Leucovorin allowed secondary metastases resections and prolonged survival in patients (pts) with CRC liver metastases despite prior failure of iv chemotherapy (Bouchahda, Cancer 2009; Goere, Ann Surg 2010).

Purpose: To prospectively evaluate safety and efficacy of combining iv Cet with HAI of IFO in pts with CRC liver metastases.

Methods

This Phase II trial involved pretreated pts with unresectable CRC liver metastases receiving iv Cet (500mg/m^2) and Chrono or Conventional (Conv) HAI of I (180mg/m^2), F (2800mg/m^2), and O (85mg/m^2) q2 weeks. Liver metastases were resected whenever adequately downstaged.

Results: Accrual of 64 pts (42 M, 22F; age, 33-76 years; 4 ongoing) was complete at 9 centers (4 countries) on 13/03/2012. In 62 monitored pts:PS 0/1/2 (61/36/3%), bilobar liver lesions (84%), a median of 9 metastases (1-50; largest diameter, 54 mm; range, 15-172) involving a median of 6 segments (1-8). Pts received one (44%), two (30%) or three (26%) prior iv chemotherapy lines. A median of 5 courses (1-13) was given to 59 pts (Chrono, 18; Conv, 41; 3 never treated), with artery occlusion as main cause of withdrawal (53%). Main grade 3-4 toxicities per pt were neutropenia (39%), abdominal pain (25%), fatigue (17%), diarrhea (15%), and nausea (10%). Grade 3 sensory neuropathy occurred in 3% of the pts. Intent-to-treat objective tumor response rate was 45% [95% CL,31-59], including 2 radiological complete responses. Disease control rate was 83%. Per-protocol secondary liver surgery rate was 33.3% [20.4-46.2]. One pt had pathologic complete response in 24/25 metastases in all liver segments (1-6cm) and has been disease-free for 25+months and alive at 38+months. Median progression-free survival (41 events) was 9.1 months [6.5-11.6]. Preliminary median survival (19 events) is 28.6 months [16.3-40.9].

Conclusions: The combination of intravenous cetuximab with triplet HAI chemotherapy offers a safe and highly effective treatment option for patients with chemotherapy- refractory CRC liver metastases.

LBA4　FOLFOX4 辅助治疗联合或不联合西妥昔单抗（CTX）治疗行切除术的 III 期结肠癌（CC）患者：PETACC8 组间对比 III 期试验的 DFS 和 OS 结果及亚组分析

LBA4　ADJUVANT FOLFOX4 WITH OR WITHOUT CETUXIMAB (CTX) IN PATIENTS (PTS) WITH RESECTED STAGE III COLON CANCER (CC):DFS AND OS RESULTS AND SUBGROUP ANALYSES OF THE PETACC8 INTERGROUP PHASE III TRIAL

J. Taieb, J. Tabernero, E. Mini, et al.

背景：评估 III 期结肠癌的当前标准治疗中加用 CTX 的潜在益处。人口统计学、肿瘤学和分子学数据的亚组分析可以提高我们对该患者人群的认识。

方法：在行切除术后 28-56 天，对结肠癌患者进行了随机分配。患者接受了 12 个疗程（每 2 周为一个疗程）的奥沙利铂 85mg/m^2（第 1 天），及醛氢叶酸 200mg/m^2，5-FU 400mg/m^2 静脉推注，然后是 5-FU 600mg/m^2 22-hr 静脉给药（第 1-2 天）（FOLFOX4），不联合CTX（A组），或联合CTX（B组）250mg/m^2（初始剂量 400mg/m^2，第 1 个疗程）。主要终点是无疾病生存时间（DFS）。次要终点包括总生存期（OS）、治疗依从性和安全性。在双侧 α=0.05 水平下，1407 例KRAS野生型（wt）患者的计划样本量检出 0.75 风险比（HR）的效能可以达到 90%，而且在出现 65%的计划事件后，进行中期分析。进行了预先计划的亚组分析。

结果：对 1602 例 KRAS wt 患者（A 组 811 例，B 组 791 例）进行了随机分配。测定了 1134 例（71%）KRAS wt 患者的 BRAF 状态；中位随访期为 40 个月。中期分析表明在 KRAS wt 患者中两组间的 DFS（HR 1.047, 95% CI 0.85, 1.29; p=0.66）或 OS（HR 1.09, 95% CI 0.81, 1.46；p=0.55）没有差异，或在 KRAS/BRAF 患者中（n=984），两组间的 DFS（HR 0.985, 95% CI 0.75, 1.28; p=0.91）或 OS（HR 0.98, 95% CI 0.67, 1.44; p=0.92）没有差异。在年龄>70 岁的患者（n=149, DFS:HR 1.97, 95% CI 0.99, 3.93; p=0.051）、女性患者（n=666, HR 1.45, 95% CI 1.03, 2.02; p=0.03）和右侧 CC 患者（n=570, HR 1.40, 95% CI 1.01, 1.94; p=0.04）中，观察到 CTX 治疗后的结果恶化。相反地，在有预后不良肿瘤的患者中（高级别，T4，N2，穿孔/梗阻，VELI+），观察到结果好转的趋势，而且在 pT4N2 患者中这种趋势是显著的（n=146, HR 0.55, 95% CI 0.35-0.88; p=0.01）。

结论：在本试验中，FOLFOX4 加 CTX 对于行切除术的 III 期 KRAS wt 和 KRAS/BRAF wt CC 没有益处。这个大型人群中的各亚组分析表明在本研究的条件下 pT4N2 肿瘤患者可能从 CTX 获得一定益处。正在进行 MSI 状态测定，探索 MSI 状态与女性患者和右侧肿瘤患者不良结果之间的相互作用。

Background: The potential benefit of adding CTX to the current standard treatment for stage III CC, was assessed. Subgroup analyses of demographic, oncologic and molecular data may improve our understanding of this patient population.

Methods:CC pts were randomized 28-56 days following resection. They received 12 biweekly cycles of oxaliplatin 85mg/m^2 day (d) 1, with leucovorin 200mg/m^2, 5-FU 400mg/m^2 bolus IV, followed by 5-FU 600mg/m^2 22-hr IV on d1-2 (FOLFOX4), without (arm A) or with weekly CTX (arm B) 250mg/m^2 (initial dose 400mg/m^2, cycle 1). Primary endpoint was disease free survival time (DFS). Secondary endpoints included overall survival (OS), treatment compliance and safety. Planned accrual of 1,407 KRAS wild-type (wt) pts provided 90% power to detect a hazard ratio (HR) of 0.75 with 2-sided α=0.05, with interim analyses after 65% of planned events. Preplanned subgroup analyses were performed.

Results:1,602 KRAS wt pts (811 arm A, 791 arm B), were randomized. BRAF status was determined in 1134 (71%) KRAS wt pts; median follow-up 40 months. This interim analysis showed no difference between arms for DFS (HR 1.047, 95% CI 0.85, 1.29; p=0.66) or OS (HR 1.09, 95% CI 0.81, 1.46; p=0.55) in KRAS wt pts or for DFS (HR 0.985, 95% CI 0.75, 1.28; p=0.91) or OS (HR 0.98, 95% CI 0.67, 1.44; p =0.92) in KRAS/BRAF wt pts (n =984). Worse outcomes were seen with CTX in pts >70 years (n=149, DFS:HR 1.97, 95% CI 0.99, 3.93; p=0.051), in females (n=666, HR 1.45, 95% CI 1.03, 2.02; p=0.03) and pts with right-sided CC (n=570, HR 1.40, 95% CI 1.01, 1.94; p=0.04). Conversely, a trend towards a better outcome was seen in pts with poor prognosis tumors (high grade, T4, N2, perforation/ obstruction, VELI+) and was significant in pts with pT4N2 at diagnosis (n=146, HR 0.55, 95% CI 0.35-0.88; p=0.01).

Conclusions: In this trial adding CTX to FOLFOX4 offered no benefit to pts with resected stage III KRAS wt and KRAS/BRAF wt CC. Subgroup analyses in this large population suggest that pts with pT4N2 tumors may receive some benefit from CTX in this setting. MSI status determination is ongoing to explore its interaction with poor outcome in female pts and those with right-sided tumors.

601P　III 期结肠癌（CC）老年患者（EPS）开始和提前停止辅助化疗（AC）

601P　ADJUVANT CHEMOTHERAPY (AC) INITIATION AND EARLY DISCONTINUATION IN ELDERLY PATIENTS (EPS) WITH STAGE III COLON CANCER (CC)

W. Cheung, D. Renouf, H. Lim, et al.

背景：研究表明，老年癌症患者接受的治疗常常不充分，但确切原因尚未明确。我们的研究目的是 1）评估老龄对采用辅助化疗（未使用与卡培他滨与 FOLFOX）治疗 III 期 CC 的影响，2）确定选择和停用某一治疗方案的特定原因，3）考察年龄是否可改变辅助化疗对结局的影响。

方法：确认 2006 至 2008 年期间诊断为 III 期结肠癌，并转诊至加拿大英属哥伦比亚省的 5 个癌症中心之一的患者。采用用描述性统计学指标总结< 70 岁的年轻患者（YPs）与>/=70 岁的老年患者的治疗模式。采用 Logistic 回归分析法评估年轻与老年患者中辅助化疗和癌症相关生存（CSS）之间的关系。

结果：我们确认了 810 例患者：51%的患者为男性，52%为年轻患者，48%为老年患者，在整个队列中，74%的患者接受了辅助化疗。与年轻患者相比，老年患者的 ECOG 较差，且并存疾病较多（p<0.01）。老年患者接受辅助化疗的可能性小于年轻患者（57%vs 91%，p<0.01）。未接受治疗的常见原因包括年龄、并存疾病和认为辅助化疗的获益较小。在接受辅助化疗的患者中，老年患者接受 FOLFOX 的可能性较小（32%vs 74%，p<0.01），而是更偏好卡培他滨，原因与患者选择、年龄和并存疾病相关。一旦开始辅助化疗，老年患者的提前停药率与年轻患者相似（70%与 62%，p=0.08）。在老年患者和年轻患者之间，提前停药的原因相似。与单独手术相比，接受 FOLFOX 或卡培他滨治疗可以改善 CSS。无论选择何种辅助化疗，年龄都不会影响 CSS（卡培他滨和年龄的相互作用 p=0.26；FOLFOX 和年龄的相互作用 p=0.40）。

结论：由于年龄较大和并存疾病，III 期结肠癌老年患者常常不接受辅助治疗或接受卡培他滨单药治疗。在各年龄组之间，辅助化疗对 CSS 的治疗效应相似，且老年和年轻患者中副作用和停药率相似。在结肠癌患者中，不应当单纯根据老龄而停用辅助化疗。

Background: Research suggests that Eps with cancer are commonly undertreated, but the precise reasons for this observation are unclear. Our aims were to 1) evaluate the impact of advanced age on AC use (none vs capecitabine vs FOLFOX) for stage III CC, 2) determine the specific reasons for selecting and discontinuing a particular regimen, and 3) examine if the effect of AC on outcomes is modified by age.

Methods: Patients diagnosed with stage III CC from 2006 to 2008 and referred to any 1 of 5 cancer centers in British Columbia, Canada were identified. Descriptive statistics were used to summarize treatment patterns in young patients (Yps) aged <70 vs Eps aged >/=70 years. Logistic regression was used to evaluate the association between AC and cancer-specific survival (CSS) in Yps and Eps.

Results: We identified 810 patients:51% men, 52% Yps and 48% Eps, and 74% received AC in the entire cohort. When compared to Yps, Eps had worse ECOG and more comorbidities (both p<0.01). Eps were less likely than Yps to receive AC (57 vs 91%, p<0.01). Frequent reasons for no treatment included age, comorbidities and perceived minimal benefit from AC. Among those treated with AC, Eps were less likely to receive FOLFOX (32 vs 74%, p<0.01) in favor of capecitabine due to patient preference, age and comorbidities. Once started on AC, Eps had similar rates of early treatment discontinuation as Yps (70 vs 62%, p=0.08). Reasons for early discontinuation were comparable between Eps and YPs. Receipt of either FOLFOX or capecitabine was correlated with improved CSS, compared to surgery alone. Age did not modify CSS, irrespective of AC choice (interaction p for capecitabine and age=0.26; interaction p for FOLFOX and age=0.40).

Conclusions:EPs with stage III CC frequently received either no adjuvant treatment or capecitabine monotherapy due to advanced age and comorbidities. The treatment effect of AC on CSS is similar across age groups, with comparable side effects and rates of discontinuation between EPs and YPs. AC should not be withheld from CC patients based on advanced age alone.

551P 存在与不存在预后不良特征的 II 期结肠癌（CC）患者中的辅助化疗（AC）使用情况和结局

551P ADJUVANT CHEMOTHERAPY (AC) USE AND OUTCOMES IN STAGE II COLON CANCER (CC) WITH VS. WITHOUT POOR PROGNOSTIC FEATURES

A. Kumar, H. Kennecke, H. Lim,, et al.

背景：在“高危”II 期结肠癌患者中，常考虑给予辅助化疗，“高危”定义为存在>/=1 个预后不良特征：梗阻或穿孔、T4 分期、切除<12 个淋巴结、切缘阳性和淋巴血管或神经周围侵犯。在高危患者中，辅助化疗相关的生存获益尚未得到证实。我们的目的是检验 II 期结肠癌患者中的辅助化疗使用情况和辅助化疗在高危与低危患者中对生存的影响。

方法：对 1999 至 2008 年期间所有在英属哥伦比亚省 1/5 个地区中心接受评估的 II 期结肠癌患者进行回顾。采用 Kaplan-Meier 和 Cox 回归法确定高危与低危状态和接受辅助化疗与无复发生存期（RFS）、疾病相关生存期（DSS）和总生存期（OS）之间的相关性。

结果：我们共确认了 1,697 例患者：1,236 例（73%）高危患者和 461 例（27%）低危患者，其中 363 例（29%）和 61 例（13%）患者分别接受辅助化疗。接受辅助化疗的高危疾病患者年龄较轻（中位年龄为 62 与 72 岁，p<0.001），且体力状态较好（ECOG 0/1 47%与 34%，p=0.02）。在高危患者中，辅助化疗可改善 5 年总生存率（表 1）。根据混杂因素进行调整后，接受辅助化疗的高危患者中总生存期存在优势（风险比 0.67，95%可信区间 0.52-0.86，p=0.002），但无复发生存期或疾病相关生存期无显著获益。亚组分析表明，T4 病变患者的无复发生存期（风险比 0.63，95%可信区间 0.42-0.95，p=0.03）、疾病相关生存期（风险比 0.59，95%可信区间 0.37-0.93，p=0.02）和总生存期（风险比 0.50，95%可信区间 0.33-0.77，p=0.001）显著改善。在低危患者中，辅助化疗可以缩短无复发生存期（风险比 2.27，95%可信区间 1.03-4.97，p=0.04）和疾病相关生存期（风险比 2.97，95%可信区间 1.10-8.02，p=0.03）。

结论：在这项基于人群的队列研究中，辅助化疗在高危患者中对总生存期有益，原因很可能与患者选择有关。无复发生存期和疾病相关生存期的获益主要见于 T4 病变患者，表明辅助化疗在高危患者中的作用有限。在接受辅助化疗的低危患者中，可能出现有害趋势。必须对根据分子检测的风险分层作进一步探索。

Background:AC is frequently considered in patients (pts) with “high risk” stage II CC, defined by the presence of >/=1 poor prognostic features:obstruction or perforation, T4 stage, <12 lymph nodes removed, positive margins, and lymphovascular or perineural invasion. Survival benefits associated with AC use in high risk pts remain largely unproven. Our aims were to examine patterns of AC use in stage II CC and the impact on survival in high vs low risk pts.

Methods: All pts with stage II CC in British Columbia from 1999 to 2008 and evaluated at 1/5 regional centers were reviewed. Kaplan-Meier and Cox regression methods were used to correlate high vs low risk status and receipt of AC with relapse-free (RFS), disease specific (DSS) and overall survival (OS).

Results: We identified 1,697 pts:1,236 (73%) high risk and 461 (27%) low risk among whom 363 (29%) and 61 (13%) received AC, respectively. Individuals with high risk disease who received AC were younger (median 62 vs 72 yrs p<0.001) and had better performance status (ECOG 0/1 47% vs 34%, p=0.02). For high risk pts, AC was associated with improved 5-year OS (Table 1). Adjusting for confounders, an OS advantage from AC persisted for high risk pts (HR 0.67, 95CI 0.52-0.86, p=0.002), with no significant RFS or DSS benefits. Subgroup analyses revealed individuals with T4 lesions had significantly improved RFS (HR 0.63, 95CI 0.42-0.95, p=0.03), DSS (HR 0.59, 95CI 0.37-0.93, p=0.02), and OS (HR 0.50, 95CI 0.33-0.77, p=0.001). For low risk pts, AC was associated with decreased RFS (HR 2.27, 95CI 1.03-4.97, p=0.04) and DSS (HR 2.97, 95CI 1.10-8.02, p=0.03).

Conclusions: In this population-based cohort study, AC was associated with an OS advantage in high risk pts, likely due to pt selection. RFS and DSS benefits were mainly seen in T4 lesions, suggesting a limited role for AC in pts deemed high risk. A possible trend towards harm was seen in the low risk group receiving AC. Risk stratification based on molecular testing should be further explored.

表 1：
Table1:

	3 年 RFS %/3yr RFS %	p 值/ p value	5 年 DSS %/5yr DSS %	p 值/ p value	5 年 OS %/5yr OS %	p 值/ p value
高危/High risk						
辅助化疗/AC	78	0.98	80	0.83	75	< 0.01
无辅助化疗/No AC	80		79		68	
低危/Low risk						
辅助化疗/ AC	87	0.18	93	0.78	87	0.26
无辅助化疗/No AC	93		93		85	

657 MFOLFOX6 辅助治疗用于老年结肠癌患者
657 ADJUVANT MFOLFOX6 IN THE TREATMENT OF ELDERLY COLON CANCER PATIENTS

J. Godinho Bexiga, F. Carneiro, D.S. Marques, et al.

背景：在欧洲，60%以上的新发癌症病例和 70%以上的癌症致死病例都发生于老年患者。大约有 50%的结直肠癌病例见于≥70 岁的患者。尽管如此，较少的老年患者入组临床试验。在 III 期结肠癌临床试验中，氟嘧啶和奥沙利铂辅助化疗为推荐治疗方案。我们的目的是确定 mFOLFOX6 辅助治疗在老年结肠癌患者中的疗效。

材料和方法：对 2004 年 9 月至 2009 年 11 月期间在葡萄牙癌症中心接受 mFOLFOX6 辅助治疗的结肠癌（CC）患者进行了回顾性队列研究。老年患者定义为年龄≥70 岁。采用通用不良事件术语标准 （CTCAE），v 3 对毒性进行评估。通过 Charlson 指数对并存疾病进行评估。主要有效性变量为无瘤生存期（DFS）。次要终点为癌症相关生存期（CSS）、总生存期（OS）和≥3 级的毒性。使用 Cox 比例风险模型计算风险比和 95%可信区间。

结果：在研究期，277 例患者接受 mFOLFOX6 辅助治疗。53 例患者（19.1%）≥70 岁，其中 76.8%为男性，80%出现 III 期结肠癌。与年轻患者相比，老年患者更可能为男性，且并存疾病指数更高（p<0.05）。大于 70 岁的患者更容易出现 ≥3 级毒性，且平均相对剂量强度较低（奥沙利铂：66%vs 72%，p=0.062；5-氟尿嘧啶：70%与 76%，p=0.01）。在 45 个月的中位随访期，老年患者的 3 年无瘤生存率、癌症相关生存率和总生存率分别为 82%、92%和 84%。生存率未显著低于< 70 岁的患者（DFS：风险比 0.612，p=0.243；CSS：风险比 0.533，p=0.166；OS：风险比 1.226，p=0.674）。

结论：mFOLFOX6 辅助治疗适用于老年患者，并且获益与年轻患者相似。选择偏倚可以解释这项研究的良好结果，并限制了我们结论的外部效度。

Background: In Europe, more than 60% of new cancer cases and more than 70% of cancer deaths occur in elderly patients. Approximately 50% of colorectal cancer cases occur in patients ≥70 years. Despite this, elderly patients are under-represented in clinical trials. Adjuvant chemotherapy with Fluoropyrimidines and Oxaliplatin is the recommended treatment for stage III colon cancer. Our aim was to determine the effectiveness of mFOLFOX6 in the adjuvant treatment of elderly colon cancer patients.

Material and methods: Retrospective cohort study of colon cancer (CC) patients treated with adjuvant mFOLFOX6, in a Portuguese cancer centre, from September 2004 till November 2009. Elderly patients were defined as having≥70 years old. Toxicity was evaluated using Common terminology criteria for adverse events (CTCAE), v 3. Comorbidity was assessed by Charlson's Index. The primary efficacy variable was disease-free survival (DFS). Secondary endpoints were cancer-specific survival (CSS), overall survival (OS) and toxicity grade≥3. Hazard ratios and 95% confidence intervals were calculated with the use of the Cox proportional hazards model.

Results: In the study period, 277 patients were treated with adjuvant mFOLFOX6. Fifty three patients (19.1%) were≥70 years and of these, 76.8% were male and 80% had stage III CC. Elderly patients were more likely to be male and have a higher comorbidity index than younger patients (p< 0.05). Patients older than 70 were more prone to grade≥3 toxicity and a lower mean relative dose-intensity (Oxaliplatin:66% vs 72%, p=0.062; 5-Fluorouracil:70% vs 76%, p=0.01). With a median follow-up time of 45 months, elderly patients had 3 year DFS, CSS and OS of 82%, 92% and 84%, respectively. Survival wasn't significantly lower than that of patients aged<70 (DFS:HR 0.612, p=0.243; CSS:HR 0.533, p=0.166; OS:HR 1.226, p=0.674).

Conclusions: Adjuvant mFOLFOX6 is feasible in elderly patients and its benefit is similar to that of younger patients. Selection bias might explain the good results of this study and limit the external validity of our conclusions.

576P 接受 UFT/LV 或 S-1 辅助治疗的 III 期结肠癌老年患者发生的不良事件：ACTS-CC 试验[TRICC0706]

576P ADVERSE EVENTS IN ELDERLY PATIENTS ON ADJUVANT THERAPY WITH UFT/LV OR S-1 FOR STAGE III COLON CANCER:ACTS-CC TRIAL [TRICC0706]

M. Ishiguro, H. Uetake, T. Ishikawa, et al.

背景：ACTS-CC 试验是一项 III 期临床试验，旨在验证 S-1 非劣于 UFT/ LV，后者是日本 III 期结肠癌的标准辅助治疗。我们报告了这项临床试验的安全性特征（Brit J Cancer 2012）。为了阐明老年患者中的不良事件（AEs）特征，进行了亚组分析。

方法：20-80 岁的 III 期结肠癌患者随机接受 UFT/LV（UFT：300-600mg/天和 LV：75mg/天，第 1-28 天用药，之后为 7 天休疗期，连续 5 个疗程）或 S-1（80-120mg/天，第 1-28 天用药，之后为 14 天休疗期，连续 4 个疗程）治疗。我们对比了 A 组（年龄≤ 70 岁）、B 组（年龄 71-75 岁）和 C 组（年龄 76-80 岁）的治疗状态和安全性。

结果：共对 1,504 例患者（S-1 治疗组 756 例、UFT/LV 治疗组 748 例）进行分析。A、B 和 C 组中的患者数量分别为 506 例（69%）、160 例（20%）和 90 例（11%），每组 PS 1 患者比例分别为 2.6%、4.3%和 16.8%。

B 组和 C 组患者的治疗前血红蛋白水平低于 A 组，而中性粒细胞、血小板和肌酐水平没有任何差异。

在 S-1 治疗组中，C 组中贫血（A 组：29%、B 组：37%、C 组：47%）、厌食（30%、34%、46%）和疲劳（25%、29%、39%）发生率（任何分级）较高。在≥3 级不良事件中，C 组中厌食（3%、7%、13%）、腹泻（4%、3%、7%）和疲劳（2%、3%、7%）发生率较高。

在 UFT/LV 治疗组中，B 组和 C 组中（任何分级）厌食（22%、33%、30%）和贫血（24%、32%、35%）发生率较高，而在 A 组中，AST（23%、15%、12%）和 ALT（25%、15%、12%）水平升高的发生率较高。

在 S-1 治疗组中，C 组的治疗完成率较低（A 组：78%、B 组：77%、C 组：69%），但在 UFT/LV 治疗组中，各组的治疗完成率没有差异。在各组之间，因停药标准上所列不良事件导致的停药率没有差异，而 C 组中，因未列于标准的不良事件（医师判断或患者要求）导致的停药率较高。

结论：在老年患者中，主观不良事件，例如厌食和疲劳较常见，而三分之一≥71 岁的患者出现轻度贫血。

Background: The ACTS-CC trial is a phase III trial designed to validate non-inferiority of S-1 to UFT/ LV, a standard adjuvant therapy for stage III colon cancer in Japan. We reported the safety profile of this trial (Brit J Cancer 2012). To clarify the characteristics of adverse events (Aes) in elderly patients, subgroup analysis was performed.

Methods:20-80 aged patients with stage III colon cancer were randomly assigned to receive UFT/LV (UFT:300 to 600mg/day and, LV:75mg/day on days 1-28, followed by 7 days rest, 5 courses) or S-1 (80 to 120mg/day on days 1-28, followed by 14 days rest, 4 courses). We compared treatment status and safety among group A (age≤70), group B (age 71-75) and group C (age 76-80).

Results:A total of 1,504 patients (756 in S-1 group, 748 in UFT/LV group,) were analyzed. The numbers of patients of group A, B and C were 506 (69%), 160 (20%) and 90 (11%), and the rates of patients with PS 1 in each group were 2.6%, 4.3% and 16.8%, respectively.

Pre-treatment value of Hemoglobin of group B and C was lower than that of group A, while there were no differences in that of neutrophils, platelets and creatinine.

In S-1 treatment, incidences (any grades) of anemia (group A:29%, B:37%, C:47%), anorexia (30%, 34%, 46%) and fatigue (25%, 29%, 39%) were higher in group C. In ≥grade 3 Aes, incidences of anorexia (3%, 7%, 13%), diarrhea (4%, 3%, 7%) and fatigue (2%, 3%, 7%) were higher in group C.

In UFT/LV treatment, incidence (any grades) of anorexia (22%, 33%, 30%) and anemia (24%, 32%, 35%) were higher in group B and C, while incidence of elevation of AST (23%, 15%, 12%) and ALT (25%, 15%, 12%) were higher in group A.

The completion rates of S-1 treatment was lower in group C (group A:78%, B:77%, C:69%), although those of UFT/LV did not differ among the groups. There was no difference in the rate of discontinuation due to Aes listed on the discontinuation criteria among the groups, while that due to Aes not listed on the criteria (i.e. physician's judgment or patient's request) was higher in group C.

Conclusions: In elderly patients, subjective Aes such as anorexia and fatigue were common, and mild anemia was observed in one-third of≥71 aged patients.

553P 斯堪的纳维亚 29 628 例转移性结直肠癌（MCRC）患者在过去二十年内的中位和长期生存率出现年龄依赖性增加

553P AGE DEPENDENT INCREASE IN MEDIAN AND LONG-TERM SURVIVAL IN 29 628 METASTATIC COLORECTAL CANCER (MCRC) SCANDINAVIAN PATIENTS DURING THE PAST TWO DECADES

C. Qvortrup, M. Cvancarova, B. Glimelius, et al.

背景：在最近几十年的 mCRC 研究中，中位生存期从 6-8 个月增至 20 个月以上。但尚不能明确生存率改善是否也可见于 mCRC 一般人群或所选的特定亚组。

方法：从挪威（1980-2008）、瑞典（1996-2008，乌普萨拉/厄勒布鲁和斯德哥尔摩）和丹麦（2001-2009）癌症登记处收集同时性 mCRC 患者的生存数据。采用 Kaplan-Meier 法对生存期进行建模，采用时序检验对差异进行评估。

结果：共确认 18114 例挪威患者、6477 例丹麦患者和 5037 例瑞典患者。在初始诊断时，IV 期挪威 CRC 患者百分比为 22%，并且在研究期间没有变化。在 1980-1985 年至 2006-2008 年见，挪威患者的中位生存期 从 5 个月（95%可信区间 4.7-5.3）延长至 10 个月（95%可信区间 9.1-10.9）。同期 3 年生存率从 7%增至 21%（p<0.001），5 年生存率从 4%增至 9%（p<0.001）。年轻患者的中位和长期生存率显著较大，而在年轻患者中，最近几年生存率增幅较大。在< 60 岁年龄组中，中位生存期从 8 个月增至 16 个月，而最近的生存率估值分别为 14%（5 年）和 28%（3 年）。在瑞典（8 至 11 个月和 11%至 21%（p<0.001），1996-2001 至 2006-2008）和丹麦（7 至 10 个月和 12 至 18%（p<0.001），2001-2005 至 2006-09），中位生存期和 3 年生存率出现类似改善。在年龄大于 80 岁的患者中，未观察到生存率增加。

结论：研究表明，从 1980 至 2008 年，未经选择的同时性 mCRC 患者人群的中位和长期生存率显著改善。我们认为，该生存获益主要体现了更有效的全身治疗的使用率增加。中位和长期生存率高度依赖于诊断时的年龄，表现为在年轻患者中，近期生存率改善最为显著。

Background: In mCRC studies, median survival has increased from 6-8 months to above 20 months during the last decades. Uncertainty exists whether this improvement in survival is also seen in a general mCRC population or in selected subgroups.

Methods: Survival data from patients with synchronous mCRC were collected from Norwegian (1980-2008), Swedish (1996-2008, Uppsala/ Orebro and Stockholm) and Danish (2001-2009) cancer registries. Survival was modeled using Kaplan-Meier method and the differences assessed with log-rank test.

Results:A total of 18114 Norwegian, 6477 Danish and 5037 Swedish patients were identified. The percentage of stage IV, Norwegian CRC patients at initial diagnosis was 22% and unchanged during the study period. From 1980-85 to 2006-08, median survival increased from 5 months (95% CI 4.7-5.3) to 10 months (95% CI 9.1-10.9) for Norwegian patients. Three-year survival increased from 7% to 21% (p<0.001) and five-year survival from 4% to 9% (p<0.001) in the same period. Younger patients had significantly higher median and long-term survival, and the increase in survival in recent years was much higher for younger patients. For age groups <60 years, median survival has doubled from 8 to 16 months and the most recent survival estimates were 14% (5-year) and 28% (3-year). A similar improvement in median survival and 3-year survival was seen in Sweden (8 to 11 months and 11% to 21% (p<0.001) from 1996-2001 to 2006-2008 and in Denmark (7 to 10 months and 12 to 18% (p<0.001) from 2001-2005 to 2006-09). No increase in survival was observed in patients above 80 years.

Conclusions: The study shows a marked improvement in median and long-term survival from 1980 to 2008 in an unselected population of patients with synchronous mCRC. We believe this survival benefit mainly reflects increased use of more effective systemic therapy. Median and long-term survival were highly dependent on age at diagnosis, as the recent improvement in survival was most pronounced for younger patients.

612P 可切除直肠癌患者的境况在多学科治疗时代是否会更好?
612P ARE PATIENTS WITH RESECTABLE RECTAL CANCER BETTER OFF IN THE ERA OF MULTIDISCIPLINARY CARE?

V.T. Broadbridge, J. Hardingham, K. Pittman, et al.

引言：全直肠系膜切除术（TME）、磁共振成像（MRI）分期、化疗和放疗的改变和多学科会诊（MDTs）使直肠癌（RC）的治疗取得了进步。随着新辅助放化疗（CRT）成为标准疗法，根据较低的局部复发率，T3/4 和/或淋巴结阳性直肠癌的治疗时机也发生变化。考虑到直肠癌治疗的这些变化，我们对 1992 至 2006 年期间在 Queen Elizabeth 医院（TQEH）接受治疗的患者的无瘤生存率（DFS）、总生存期（OS）以及局部和远端复发率进行了评估。

方法：对 2 个不同时间队列 1992-99（A）和 2000-06（B）年间来自 TQEH 癌症登记处且诊断为早期直肠癌的患者的人口统计学和结局数据进行分析。采用 Kaplan-Meier 法进行生存分析，并采用 cox 比例风险回归法对预后因素进行分析。

结果：共确认 423 例患者；A 组 235 例患者，B 组 188 例患者。患者特征基本相似。A 组中位年龄为 68.1 岁（范围 32-94），B 组为 67.4 岁（范围 25-92）。在队列 A（47%），发生 B 期肿瘤的患者多于队列 B（39%）。队列 A 的 56%的患者和队列 B 的 47%的患者仅接受手术治疗。任何“辅助”治疗的比例相似（A=41%与 B=46%），但在队列 B 中，接受新辅助放化疗的患者比例翻倍（A=7.2%与 B=16%）。5 年局部/远端复发率出现显著改善；A 87%/71%与 B 95%/81%，p<0.0001。5 年无瘤生存率随时间改善；A 65.2%与 B 73.3%，p=0.03。5 年总生存率分别为 A=66.1%与 B=78.4%，队列 A 的中位总生存期为 14.62 年，队列 B 尚未达到（p=0.007）。肿瘤分期和队列 B 为总生存期的预后因素，而年龄、性别、术前放疗和任何化疗则不是预后因素。

结论：在诊断为早期直肠癌的患者中，无瘤生存率、总生存期和局部和远端复发率显著改善。队列 B 新辅助放化疗的使用率增加符合实际变化，这是局部控制改善中的一个因素，但对生存状况没有影响。其他可能改善总体结局的因素包括：TME 率增加、术前分期改善，包括使用 MRI 和使用 MDT。

Introduction: The management of rectal cancer (RC) has evolved with the introduction of Total Mesorectal Excision Surgery (TME), use of Magnetic Resonance Imaging (MRI) for staging, changes in chemotherapy and radiotherapy and multidisciplinary meetings (MDTs). The timing of therapy for T3/4 and/or node positive RC has also changed with neoadjuvant chemoradiotherapy (CRT) becoming standard based on lower local recurrence rates. Given these changes in management over time, we assessed disease free survival (DFS), overall survival (OS) and rates of local and distant recurrences of patients treated at The Queen Elizabeth Hospital (TQEH) between 1992 to 2006.

Method: Demographic and outcome data of patients diagnosed with early stage RC from TQEH Cancer Registry from 2 different time cohorts 1992-99 (A) and 2000-06 (B) were analysed. Survival analysis was by Kaplan-Meier method and prognostic factors were analysed using cox proportional hazards regression.

Results:423 patients were identified; 235 in A, 188 in B. Patient characteristics were generally similar. Median age A 68.1 yrs (range 32-94), B was 67.4 yrs (range 25-92). More patients had stage B in cohort A (47%) v B (39%). 56% of patients had surgery alone in cohort A compared to 47% in cohort B. Rates of any “adjuvant” therapy was similar (A=41% v B=46%), although there was a doubling in proportion of patients who received neoadjuvant CRT in the latter cohort (A=7.2% v B=16%). There was a significant improvement in rate of 5 year local/distal recurrence; A 87%/71% v B 95%/81%, p<0.0001. 5 year DFS improved over time; A 65.2% v B 73.3%, p=0. 03. 5 year OS was A 66.1% v B=78.4% and median OS for A was 14.62 years and not reached for cohort B (p=0.007). Stage and cohort B were prognostic for OS while age, sex, preoperative RT and any chemotherapy were not.

Conclusion: There has been significant improvement in DFS, OS and local and distant recurrence rates in patients diagnosed with early stage RC. The trend to greater use of neoadjuvant CRT in the latter cohort is consistent with changes in practice, and this may be a factor in improved local control, but does not appear to impact on survival. Other factors likely to have improved overall outcomes include:increased TME rates, improved preoperative staging including use of MRI and potentially the introduction of MDTs.

530PD 卡培他滨（CAPE）+/-贝伐珠单抗（BEV）辅助治疗用于结直肠癌（CRC）-国际性 III 期 QUASAR2 试验的首要和最终毒性结果

530PD CAPECITABINE (CAPE) +/- BEVACIZUMAB (BEV) IN THE ADJUVANT TREATMENT OF COLORECTAL CANCER (CRC) – FIRST AND FINAL TOXICITY RESULTS FROM THE INTERNATIONAL PHASE III QUASAR2 TRIAL

R.S. Midgley, S. Love, V. Potter, et al.

背景：贝伐珠单抗是一类抗 VEGF 抗体，批准用于转移性结直肠癌（CRC）。然而，2 项临床试验表明，贝伐珠单抗联合二联辅助化疗缺乏疗效，并且某些证据表明毒性谱不同于晚期肿瘤患者。

方法：国际性III期临床试验，QUASAR2 对接受根治性切除术的III期和高危II期CRC患者进行了随机分组，卡培他滨（1250mg/m^2 bd，第 1-14 天，q 21d）单药口服治疗，为期 6/12 或卡培他滨（6/12）加贝伐珠单抗静脉输液（7.5mg/kg q 21d），为期 12/12。本摘要概述了来自Q2 试验的最终毒性数据（患者的最短随访期 15/12）。

结果：1952 例患者签署了知情同意书，并接受随机分组，排除没有接受至少 1 个治疗周期的患者后，对 963 例接受卡培他滨单药治疗的患者和 959 例接受卡培他滨加贝伐珠单抗联合治疗的患者进行了分析。2 个治疗组的基线特征（性别/年龄/疾病分期）相似。特定毒性频率参见下表，按患者百分比显示。

讨论：如预期所料，在接受贝伐珠单抗治疗的患者中，高血压（所有级别或高级）以及蛋白尿和创口愈合不良（所有级别）的发生率显著较高。尽管添加贝伐珠单抗不会增加腹泻发生率，但 HFS 的发生率和严重程度增加。这一点尚未得到充分认识。尽管添加贝伐珠单抗不会增加心源性胸痛，但动脉和静脉血栓栓塞（ATE/VTE）发生率增加，但在这项研究中，仅有关 VTE 的差异存在显著性。这与晚期肿瘤患者中的大部分结果不同，并且可能时术后 VTE 风险和贝伐珠单抗的促血栓形成作用之间的相互作用所致。需要注意的是，在接受贝伐珠单抗治疗的患者中，“可能与治疗相关的”死亡增加（1.9%与 0.8%：RR2.3：可信区间 1.0-5.2），并且刚好具有显著性差异（p=0.05）。所有结果将在报告/海报中详细描述。

Background: Bevacizumab is an anti-VEGF antibody approved for use in metastatic colorectal cancer (CRC). However 2 trials have suggested lack of efficacy in combination with dual agent chemotherapy in the adjuvant setting and there has been some indication that the spectrum of toxicity may be different compared to that observed in patients with advanced disease.

Methods: The international phase III trial, QUASAR2, randomised stage III and high risk stage II CRC patients who had undergone potentially curative resection to receive oral Cape (1250mg/m^2 bd, days 1-14 q 21d) alone for 6/12 or Cape (6/12) plus intravenous Bev(7.5mg/kg q 21d) for 12/12. This abstract overviews the final toxicity data (15/12 minimum follow up per patient) from the Q2 trial.

Results:1952 patients were consented and randomised and, after excluding patients who did not receive at least one cycle of treatment, 963 patients receiving Cape alone and 959 patients receiving Cape plus Bev were analysed. Baseline characteristics (gender /age /stage of disease) were balanced across the 2 arms. See frequency of selected toxicities, as % patients, in table below.

Discussion: As expected, the rates of hypertension (all grade or high grade) and proteinuria and wound healing (all grade) were significantly higher among patients receiving Bev. Although the addition of Bev did not increase diarrhoea rates, the frequency and severity of HFS was increased. This is not well recognised. Although cardiac chest pain was not increased by the addition of Bev, both arterial and venous thrombo-embolism (ATE/VTE) rates were increased although the difference only reached significance for VTE in this study. This is in contrast to most results in the advanced disease setting and may be a result of an interaction between post-operative risk of VTE and pro-thrombotic potential of Bev. Of note, an excess of ‘possibly treatment-related’ deaths was found in patients receiving Bev (1.9% vs 0.8%:RR2.3:CI 1.0-5.2) and this just reached significance (p=0.05). All results will be expanded in detail in the presentation / poster.

	卡培他滨/贝伐珠单抗/Cape/ Bev	卡培他滨/Cape	RR/CI/p
高血压（所有级别）/Hypertension (all grades)	33.4	7.8	4.3/3.4-5.4/p<0.001
高血压（3/4 级）/Hypertension (3/4 级)	3.8	0.6	6.0/2.6-14.2/p<0.001
蛋白尿（所有级别）/Proteinuria (all grades)	20.5	5.1	4.0/3.0-5.4/p<0.001
创口愈合不良（所有级别）/Poor wound healing (all grades)	3.1	1.8	1.8/1.0-3.2/p=0.05
腹泻（3/4 级）/Diarrhoea (g3/4)	10.8	10.6	1.0/0.8-1.3/p=0.9
手足综合征（3/4 级）/Hand-foot syndrome (g3/4)	26.8	20.9	1.3/1.1-1.5/p=0.002
心源性胸痛 SAE/Cardiac chest pain SAE	2.7	2.6	1.0/0.6-1.8/p=0.9
动脉血栓栓塞 SAE/Arterial Thromboembolism SAE	1.1	0.6	1.8/0.7-5.0/p=0.2
静脉血栓栓塞 SAE/Venous Thromboembolism SAE	4.3	2.3	1.9/1.1-3.1/p=0.01

591P MFOLFOX-6 辅助治疗用于结肠癌–降低奥沙利铂剂量强度对生存的影响
591P COLON CANCER ADJUVANT MFOLFOX-6 – SURVIVAL IMPACT OF OXALIPLATIN REDUCED DOSE-INTENSITY

A.F. Carneiro, J. Godinho Bexiga, D.S. Marques, et al.

背景：结肠癌的辅助治疗包括奥沙利铂/氟嘧啶联合治疗。在这些患者中，联合治疗与氟嘧啶单药治疗相比有益于无进展生存期（PFS）和总生存期（OS）。不良事件较为常见，并可导致治疗延迟或药物减量。降低奥沙利铂剂量强度（RDI）对生存的影响尚不明确。

目的：在接受 mFOLFOX-6 辅助治疗的结肠癌患者中评估奥沙利铂 RDI 对生存的影响。材料和方法：2004 年 9 月至 2009 年 11 月期间，一组结肠癌患者在我们中心接受 mFOLFOX-6 辅助治疗。采用 Cox 比例风险模型估算奥沙利铂<75%（A 组）和≥75%（B 组）对无进展生存期和总生存期的影响。

结果：在治疗组之间，年龄、性别、ECOG、并存疾病、组织学分级和疾病分期的分布没有差异。确认了 277 例患者（A 组为 53%）。59%的患者完成了 12 个 mFOLFOX-6 周期，中位辅助化疗疗程为 6.5 个月。奥沙利铂平均剂量强度为 71%（中位值 74%）。分别有 53%和 40%的患者因为不良事件而导致降低剂量和中断给药。治疗期间发生 3 例死亡。RDI 的主要原因为≥3 级血液系统毒性（47%）和神经病（12%）–首次神经系统重度不良事件时的奥沙利铂中位累积剂量为 1024mg。在 RDI 组间，无进展生存期和总生存期没有差异，按分期分层后，也没有差异。

结论：在我们的队列中，患者特征和毒性与已发表的临床试验相似。FOLFOX 完成率低于 MOSAIC 试验（59%与 74.7%）。尽管完成率较低，但奥沙利铂 RDI<75%组中无进展生存期和总生存期未受影响。

Background: Adjuvant colon cancer treatment may include the oxaliplatin/fluoropirimidine combination. This association has shown benefit on progression free survival (PFS) and overall survival (OS) compared to fluoropirimidine monotherapy in these patients. Adverse events are frequent and may cause delay on treatment delivery or drug dose reduction. The survival impact of oxaliplatin reduced dose intensity (RDI) is unknown.

Objective: Evaluation of survival impact of oxaliplatin RDI in colon cancer patients treated with adjuvant mFOLFOX-6. Material and methods:A consecutive series of colon cancer patients treated with adjuvant mFOLFOX-6 at our institution between 09/2004 and 11/2009. The impact of Oxaliplatin<75% (group A) and ≥75% (group B) on PFS and OS was estimated with a Cox Proportional Hazards model.

Results: There were no differences in age, sex, ECOG, comorbidity, histologic grade and stage distribution between groups. Two hundred and seventy seven (277) patients were identified (53% in group A). Fifty nine percent (59%) of patients completed the 12 mFOLFOX-6 cycles and the median duration of adjuvant chemotherapy was 6,5 months. The mean oxaliplatin dose-intensity was 71% (median 74%). Adverse events led to dose reduction and drug suspension in 53% and 40% of patients, respectively. There were 3 deaths during treatment. The main causes to RDI were grade ≥3 hematologic toxicity (47%) and neuropathy (12%)–median cumulative oxaliplatin dose at first neurologic severe event was 1024mg. There were no differences in PFS and OS between RDI groups, neither after stage stratification.

Conclusion: In our cohort patient's characteristics and toxicity profile were similar to published trials. FOLFOX conclusion rate was inferior than the described in MOSAIC trial (59% vs 74,7%). Despite the inferior accomplishment rate, there was no impact in PFS and OS in oxaliplatin RDI<75% group.

526PD 在接受西妥昔单抗治疗的 MCRC 患者中使用双调蛋白（AREG）、表皮调节素（EREG）和 EGFR-FISH 表达水平建立疗效预测评分：德国 AIO CRC-0104 试验的分析

526PD DEVELOPMENT OF A PREDICTIVE SCORE USING AMPHIREGULIN (AREG), EPIREGULIN (EREG) AND EGFR-FISH EXPRESSION LEVELS TO DETERMINE TREATMENT EFFICACY IN MCRC PATIENTS RECEIVING CETUXIMAB-BASED THERAPY. ANALYSIS OF THE GERMAN AIO CRC-0104 TRIAL

V. Heinemann, R. Laubender, D.P. Modest,et al.

背景：我们在接受一线抗 EGFR 靶向西妥昔单抗加 CAPOX 或 CAPIRI 治疗的 mCRC 患者的肿瘤标本中研究了 EGFR 配基双调蛋白（AREG）和表皮调节素（EREG）的表达水平以及 EGFR 基因扩增。这 3 种因素可区分不同预后的患者组。在这里，我们使用综合评分计算缓解率。

方法：共有 185 例 mCRC 患者随机接受西妥昔单抗加 CAPIRI 或加 CAPOX 治疗。主要研究终点为总缓解率。年龄、性别、研究组、KRAS 突变状态、BRAF 突变状态、AREG、EREG 和 EGFR-FISH 表达水平用于多变量 Logistic 回归分析。

结果：AREG 和 EGFR-FISH 与总缓解率显著相关。通过 Logistic 回归模型，使用这些因子建立总缓解率的预测模型。该模型的线性预测因子表示为 LP=-7.63+（0.35*log[AREG]）+（6.58*[EGFR-FISH]），可用于计算总缓解率，公式为 exp（LP）/ [1+exp（LP）]。通过 ROC 分析评估该模型的区分能力，它是区分缓解者与非缓解者（根据总缓解率）的线性预测因子的最佳断点，采用 Youden 指数确认，并表示为-0.095。ROC 曲线下面积（AUC）为 0.79（95%可信区间：0.63，0.90）。使用这个公式，计算缓解和生存时间，总缓解率断点值为 50%。阳性队列中总缓解率显著大于阴性队列，分别为 81%与 42%（p=0.009）。这导致阳性队列中无进展生存期（8.6 个月与 4.6 个月；风险比 0.44；p=0.003）和总生存期（38.4 个月与 17.2 个月；风险比 0.37；p=0.001）显著延长。

结论：在这项回顾性和探索性分析中，在分子标记物的帮助下才可以预测总缓解率。AREG 和 EGFR-FISH 预测总缓解率的区分能力（根据 AUC）可接受。因此，这 2 种分子标记物可以作为预测西妥昔单抗方案的总缓解率的良好候选标记物，同时需要对这些标记物进行前瞻性评估，以重现并且验证我们的结果。

Background: We investigated the expression of the EGFR ligands amphiregulin (AREG) and epiregulin (EREG) as well as the amplification of the EGFR-gene in tumor specimens of mCRC patients (pts) treated first-line with anti-EGFR targeted cetuximab together with CAPOX or CAPIRI. All three factors have shown the capability to separate patient groups of different prognosis. Here we used a composite score to calculate response probability.

Methods:A total of 185 mCRC pts were randomized to cetuximab plus CAPIRI or plus CAPOX. The primary study endpoint was ORR. Age, gender, study arm, KRAS mutational status, BRAF mutational status, AREG, EREG and EGFR-FISH expression levels were used for multivariate logistic regression analysis.

Results:AREG and EGFR-FISH significantly correlated with ORR. These factors were used to create a prediction model for ORR by using logistic regression model. The linear predictor of this model is given by LP=-7.63+(0.35*log[AREG])+(6.58*[EGFR-FISH]) which can be used to calculate the probability of ORR by exp(LP) / [1+exp(LP)]. The discriminatory ability of this model was assessed by ROC analyses were the optimal cut-off of the linear predictor discriminating best between responders and non-responders with respect to ORR was identified by using the Youden index and is given by -0.095. The area under the ROC curve (AUC) is 0.79 (95% confidence interval:0.63, 0.90). Using this formula, response and survival times with a cut-off of 50% of ORR probability were calculated. ORR was significantly higher in the positive cohort and reached 81% vs. 42% in the negative cohort (p=0.009). This led to significantly longer survival times in the positive cohort, with regard to PFS (8.6 mo vs 4.6 mo; HR 0.44; p=0.003) and OS (38.4 mo vs 17.2 mo; HR 0.37; p=0.001).

Conclusion: In this retrospective and exploratory analysis it was possible to predict ORR probability with the help of molecular markers. There is an acceptable discriminatory performance as measured by the AUC for predicting ORR by AREG and EGFR-FISH Hence, both molecular markers might be promising candidates for predicting ORR under cetuximab-based treatment regimens and prospective evaluation of these markers is needed for replicating and validating our findings.

599P 早期肿瘤缩小（ETS）预测转移性结直肠癌（MCRC）的治疗有效性：伊立替康一线治疗随机试验的事后分析

599P EARLY TUMOR SHRINKAGE (ETS) FOR THE PREDICTION OF EFFICACY IN METASTATIC COLORECTAL CANCER (MCRC):POST-HOC ANALYSIS FROM AN IRINOTECAN-BASED RANDOMIZED FIRST-LINE TRIAL

C. Giessen, R. Laubender, S. Stintzing, et al.

背景：在含或不含西妥昔单抗的细胞毒性化疗中，早期肿瘤缩小（ETS）是无进展生存期（PFS）和总生存期（OS）相关的良好预后因素。我们在含伊立替康的一线治疗转移性结直肠癌随机III期临床试验中对早期肿瘤缩小≥20%和< 20%的患者进行了评估。

材料和方法：对 479 例患者中比较 FUFIRI 与 mIROX 的随机 III 期临床研究的数据进行评估。根据 Piessevaux 等人的观点，早期肿瘤缩小定义为基线时直径总和（RECIST）和首次缓解对照影像学检查之间至少缩小 20%。由于在我们的研究中，1 个周期为 50 天治疗，时间间隔为 7.2 周。201 例患者可以进行早期肿瘤缩小评估。计算早期肿瘤缩小≥20%和< 20%患者中的无进展生存期和总生存期。此外，对绝对肿瘤缩小度进行线性回归分析，并对总生存期进行 Cox 回归。

结果：在早期肿瘤缩小≥20%和< 20%的患者中，基线特征相似，但中位肿瘤直径除外（基线时 ETS≥20%，81.5mm 和第 50 天 47.0 mm，与基线时 ETS<20%，68.0 mm 和第 50 天 72.0 mm）。与早期肿瘤缩小< 20%的患者（n=107）相比，早期肿瘤缩小 ≥20%的患者（n=94）的无进展生存期（9.9 个月与 6.1 个月，p=0.001）和总生存期（27.5 个月与 17.8 mo，p=0.001）结果较好。尽管早期肿瘤缩小通常表示为百分比，但基线时肿瘤直径与绝对肿瘤缩小度相关。早期肿瘤缩小< 20%的患者细分为“轻微缩小”患者（19–0%；n=65）（无进展生存期 8.4 个月，总生存期 21.6 个月）、第 7 周出现“肿瘤进展”的患者（任何增幅）（n=36；无进展生存期 4.0 个月，总生存期 15.3 个月）和出现“新发靶病变”的患者（n=6；无进展生存期 2.2 个月，总生存期 7.6 个月）。对基线时肿瘤直径的绝对缩小度的线性回归表明，基线时肿瘤直径每增加 1cm，则平均绝对缩小度增加 0.354cm（p<0.001）。采用绝对肿瘤缩小度对总生存期的 Cox 回归分析表明风险比为 0.923（95%可信区间 0.878-0.971；p=0.002）

结论：在这项伊立替康研究中，早期肿瘤缩小≥20%对于无进展生存期和总生存期可产生显著获益。早期肿瘤缩小< 20%的患者特征各异，包括轻微缩小、疾病进展和新发病变的患者。基线时肿瘤直径对缩小程度具有显著影响。

Background: Early tumor shrinkage (ETS) has been highlighted as a favorable prognostic factor related to progression-free survival (PFS) and overall survival (OS) in cytotoxic chemotherapy with or without cetuximab. We investigated ETS≥20% and <20% in an irinotecan-based randomized phase III trial for first-line treatment for metastatic colorectal cancer.

Material and methods: Data from a randomized phase III study comparing FUFIRI vs. mIROX in 479 pts were evaluated. ETS has been defined as at least 20% shrinkage between the sum of baseline diameters (RECIST) and the first remission control imaging according to Piessevaux et al. As in our study one cycle consisted in 50 days of treatment our time interval was 7.2 weeks. ETS assessment was possible in 201 pts. PFS and OS for ETS ≥20% and <20% pts were calculated. Additionally, linear regression for modeling of the absolute tumor shrinkage and Cox regression for OS were estimated.

Results: Baseline characteristics between ETS≥20% and <20% were comparable, except for median tumor diameter (ETS≥20% 81.5mm at baseline and 47.0 mm at day 50 vs. ETS <20% 68.0 mm at baseline and 72.0mm at day 50). When compared to pts with ETS <20% (n=107), patients with ETS≥20% (n=94) had a favorable PFS (9.9 vs. 6.1 mo, p=0.001) and OS (27.5 vs. 17.8 mo, p=0.001). While ETS is usually indicated as a percentage, measurement of baseline tumor diameters relates to the absolute magnitude of tumor shrinkage. Pts with ETS <20% were subclassified in pts with “minor shrinkage”, (19–0%; n=65) (PFS 8.4 mo, OS 21.6 mo), pts with “numerical tumor progression” (any increase) at 7 wks (n=36; PFS 4.0 mo, OS 15.3 mo), and pts with “new target-lesions” (n=6; PFS 2.2, OS 7.6). Linear regression of the absolute shrinkage on the baseline tumor diameter revealed that with each 1cm increase in baseline tumor diameter, mean absolute shrinkage increases, namely by 0.354cm (p<0.001). Cox regression for OS using absolute tumor shrinkage indicated a hazard ratio of 0.923 (95%C.I. 0.878-0.971; p=0.002)

Conclusion: In this irinotecan-based study the presence of ETS≥20% was associated with a significant benefit in PFS and OS. Pts with ETS <20% were found to be a heterogeneous group consisting of pts with minor shrinkage, progressive disease, and new lesions. Baseline tumor diameters had a significant impact on the magnitude of shrinkage.

625 关于结直肠癌肝转移切除后 UFT/LV 辅助治疗的随机、多中心、对照、III 期临床试验的可行性报告

625 FEASIBILITY REPORT OF A RANDOMIZED MULTICENTER CONTROLLED PHASE III TRIAL OF ADJUVANT UFT/LV THERAPY AFTER RESECTION FOR LIVER METASTASIS FROM COLORECTAL CARCINOMA

J. Yamamoto, K. Hatsuse, N. Kokudo, et al.

目前尚无明确证据支持结直肠癌肝转移切除后的辅助化疗。开展了一项随机、多中心、对照、III期临床试验，从 20 家医院招募患者，目的是在结直肠癌肝转移患者中比较术后UFT/LV辅助治疗（UTF：300mg/m^2/d和LV：75mg/d，第 1-28 天，每 5 周一次，5 个周期）与单独手术的有效性。2004 年 1 月至 2010 年 12 月期间入组研究的 180 例患者目前正在接受随访。主要终点为无复发生存期，次要终点为总生存期，正在等待结果。预计在这项研究中，接受肝切除术的患者不同于对原发灶进行手术治疗的II期或III期结肠癌患者。我们报告了 175 例患者的依从性和安全性的中期分析结果，收集了这些患者与本研究相关的病例报告表。88 例患者接受手术治疗，87 例患者接受手术加UFT/LV治疗。2 组间的人口统计学或临床病理学因素没有显著差异。在UFT/LV治疗组中，治疗完成率（5 个疗程）为 53.8%（43/80），截至 3 个月和 6 个月，治疗完成率分别为 71.3%（57/80）和 53.8%（43/80）。平均剂量强度为 70.1%。在 37 例停止治疗的患者中，停药原因为 26 例患者中的不良事件 （7 例患者与停药标准冲突，19 例患者未冲突）和 8 例患者中的复发。在UFT/LV治疗组中，CTCAE 3 级或 3 级以上的不良事件包括血红蛋白水平下降（3.8%）、AST/ATL水平升高（2.6%）、发热性中性粒细胞减少症（1.3%）、高胆红素血症（1.3%）、腹泻（5.0%）、食欲不振（2.5%）和恶心（2.5%）。未出现与治疗相关的死亡。这些症状的发生率与 ACTS-CC 研究中III期结肠癌术后安全性相关的结果无较大差异，这表明即使在接受肝切除术的IV期结直肠癌患者中，UFT/LV治疗的耐受性仍可维持。

There is no established evidence yet to support the of postoperative adjuvant chemotherapy after resection of colorectal liver metastasis. A randomized multicenter controlled phase III trial was conducted and patients were recruited from 20 hospitals to compare the efficacy of postoperative adjuvant UFT/LV therapy (UTF:300mg/m^2/day and LV:75mg/day, Day 1-28, once every 5 weeks, 5 cycles) with that of surgical monotherapy in patients with colorectal liver metastasis. A total of 180 patients enrolled from January 2004 to December 2010 are currently under follow-up. The primary endpoint is recurrence-free survival time and the secondary endpoint is overall survival time, the results of which are awaited. It is expected that the patients who underwent liver resection in this study are different from the stage II or III colon cancer patients treated by surgery for primary diseases. We shall report the results of the interim analysis of compliance and safety in the 175 patients for whom the CRFs relevant to this study could be collected. Eighty-eight patients received surgical monotherapy and 87 received surgery plus UFT/LV therapy. There were no significant differences in the demographic or clinicopathological factors between the two groups. The rate of completion of UFT/LV therapy (5 courses) was 53.8% (43/80), and the rates of completion up to 3 and 6 months were 71.3% (57/80) and 53.8% (43/80), respectively. The mean rate of dose intensity was 70.1%. Of the 37 patients in whom the treatment was discontinued, the reason for the discontinuation was adverse events in 26 patients (in conflict with discontinuation criteria in 7 patients and no conflict in 19) and appearance of recurrence in 8 patients. Adverse events of CTCAE grade 3 or higher observed in the UFT/LV Group included decrease in hemoglobin (3.8%), increase in AST/ATL (2.6%), febrile neutropenia (1.3%), hyperbilirubinemia (1.3%), diarrhea (5.0%), loss of appetite (2.5%), and nausea (2.5%). There were no treatment-related deaths. The incidence rates of these symptoms are not greatly different from those reported in relation to the safety profile after surgery for stage III colon cancer from the ACTS-CC study, which suggested that the tolerability of UFT/LV therapy was maintained even in stage IV colorectal cancer patients treated by hepatectomy.

588P 结肠癌手术后接受卡培他滨辅助化疗的患者的 HRQOL：JFMC37-0801 的附加研究

588P HRQOL DURING ADJUVANT CHEMOTHERAPY WITH CAPECITABINE IN PATIENTS AFTER SURGERY FOR COLON CANCER:ADDITIONAL STU DY OF JFMC37-0801

Y. Kinugasa, T. Shiroiwa, M. Nakamura, et al.

目的：JFMC37-0801 试验是一项 III 期临床试验，旨在验证为期 1 年的卡培他滨治疗作为 III 期结肠癌的辅助化疗时优于 6 个月治疗。在研究中附加对健康相关生活质量（HRQOL）和成本效益进行评估。我们分析了延长卡培他滨治疗期对患者 HRQOL 的影响。

方法：患者在第 1-14 天口服卡培他滨（每日 2500mg/m^2），之后是 7 天休疗期。入组患者随机分入A组（接受 8 疗程的卡培他滨）或B组（16 疗程）。对于同意参加附加研究的患者，在开始研究治疗时、3、6、9、12、15 和 18 个月通过患者自行填写的调查问卷对HRQOL进行评估。调查问卷包括抗癌治疗功能评估-C（FACT-C）和 5 维度EuroQol （EQ-5D）。

结果：在 1306 例入组 JFMC37-0801 试验的患者中，对 171 例受试者的 HRQOL 进行评估（A 组 81 例、B 组 90 例）。在 A 组和 B 组中，患者的平均年龄分别为 63.3 和 64.5 岁。在 1197 个调查点，回收 959 份调查问卷（80.1%）。完成治疗后，调查问卷的回收率逐渐下降。在整个调查期内，FACT-C（96.9-103）和 EQ-5D（0.85-0.93）的平均评分令人满意。在评分相对基线时变化的纵向分析中，A 组和 B 组完成治疗期后评分趋于增加。在每个调查时间点，A 组和 B 组的评分都没有显著差异。在不同年龄和肿瘤分期之间，未观察到差异。

结论：在调查期，接受术后卡培他滨辅助化疗的患者的 HRQOL 满意。在 8 个和 16 个疗程的卡培他滨之间，HRQOL 无显著差异。

Objectives: The JFMC37-0801 trial is a phase III trial designed to validate superiority of 1-year treatment with capecitabine to 6 months treatment as adjuvant chemotherapy for stage III colon cancer. Health related quality of life (HRQOL) and cost-effectiveness have been evaluated as an additional study. We analyzed impact of prolonged treatment with capecitabine on patients' HRQOL.

Methods: Capecitabine (2500mg/m^2/day) was orally given on days 1-14, followed by a 7-day rest. Enrolled patients were randomly assigned to group A (received 8 courses of capecitabine) or group B (16 courses). In patients agreed to participate to the additional study, HRQOL was evaluated by self-administered questionnaire at the start of the protocol treatment, 3, 6, 9, 12, 15 and 18 months. The questionnaire includes Functional Assessment of Cancer therapy-C (FACT-C) and EuroQol 5 Dimension (EQ-5D).

Results: In 1306 patients enrolled to the JFMC37-0801 trial, HRQOL of 171 participants (81 in group A, 90 in group B) were evaluated. Mean age of the patients in group A and B was 63.3 and 64.5 years-old, respectively. Among a total of 1197 points of survey, 959 questionnaires (80.1%) were retrieved. Recovery rates of questionnaires tended to decrease with time after finishing treatment. Through the entire survey period, mean score of FACT-C (96.9-103) and EQ-5D (0.85-0.93) were satisfactory. In longitudinal analysis of the change from baseline score, the scores tended to increase after finishing the treatment period in both group A and group B. Significant difference between the score of group A and group B was not observed in each survey point. No difference by age and tumor stage was also observed.

Conclusions:HRQOL of the patients received postoperative adjuvant chemotherapy with capecitabine was satisfactory through the survey period. There was no significant difference of HRQOL between 8 and 16 courses of capecitabine treatment.

647 CAPOX 用于转移性结直肠癌二线化疗的总生存期和无进展生存期的预测标记物

647 PREDICTIVE MARKERS FOR OVERALL AND PROGRESSION-FREE SURVIVAL WITH CAPOX IN SECOND-LINE CHEMOTHERAPY OF METASTATIC COLORECTAL CANCER

M.D.P. Solís Hernández, P. Jimenez Fonseca, Q. Perez, et al.

背景：年龄、性别、卡式评分（KPS）、转移灶数目（NMS）、原发性肿瘤部位、基线 CEA、CEA 应答、影像学应答和 k-RAS 状态是转移性结直肠癌（mCRC）化疗后无进展生存期（PFS）和总生存期（OS）的预测因素。本研究的目的是探索哪些因素可能影响二线治疗后的无进展生存期和总生存期。

患者和方法：对 138 例在 2002 至 2010 年期间接受了卡培他滨和奥沙利铂二线治疗（CAPOX）的患者进行了分析。采用 Cox 风险模型构建单变量和多变量分析。

结果：无进展生存期和总生存期分别为 3.5 个月和 7.85 个月。在单变量分析的所有评估因素中，只有 KPS ≥70、CEA 应答和影像学应答与无进展生存期和总生存期改善相关，且具有统计学显著意义。年龄< 65 岁和< 2 处转移灶只能预测总生存期。（参见表 1）多变量分析表明，影像学应答（风险比=0.34，p=0.0003）和 KPS ≥70%（风险比=0.96，p=0.0002）可以预测无进展生存期和总生存期的改善（影像学应答：风险比=0.36，p=0.0001 和 KPS>70%：风险比=0.97，p=0.0007），而 PTL（直肠，风险比=1.50，p=0.032）和 NMS（>2 个部位，风险比=1.25，p=0.0043）可预测最差无进展生存期和总生存期。（参见表 2）

结论：这些结果表明，在 mCRC 患者中，影像学应答和 KPS 良好可预测无进展生存期和总生存期的改善，而原发性肿瘤部位、CEA 应答和 NMS 应作进一步验证。

Background: Age, sex, Karnofsky (KPS), number of metastatic sites (NMS), primary tumour localization, baseline CEA, CEA response, scan response and k-RAS status are focused on progression free survival (PFS) and overall survival (OS) as predictive factors in chemotherapy metastatic colorectal cancer (mCRC). This study aims to find which might generate impact on PFS and OS for a second line therapy.

Patients and methods: 138 patients treated with capecitabine and oxaliplatin (CAPOX) in second-line from 2002 to 2010 were analyzed. Cox hazard model was employed to build univariante and multivariate analysis.

Results: PFS and OS were 3.5 and 7.85 months, respectively. Among all evaluated factors, only KPS≥70, CEA response and scan response were associated with better PFS and OS on univariate analysis with statistical significance. Age <65 years and <2 metastatic sites were predictive only for OS. (See table 1) Multivariable analysis showed that scan response (HR=0.34, p=0.0003) and KPS≥70% (HR=0.96, p=0.0002) were predictive for better PFS and OS (scan response:HR=0.36, p=0.0001 and KPS>70%:HR=0.97, p=0.0007), while PTL (rectum, HR=1.50, p=0.032) and NMS (>2 sites, HR=1.25, p=0.0043) were predictive for worst PFS and OS, respectively. (See table 2)

Conclusion: These findings suggest that scan response and good KPS may predict better PFS and OS in mCRC while primary tumour localization, CEA response and NMS should be further validated.

表 1 – 无进展生存期和总生存期的单变量分析/Table1 – PFS and OS univariate analyses

		N	中位值/ Median	P 值/P-value
PFS	KPS			<0.001
	<70%	43	2.3	
	≥70%	95	4.8	
	应答/Response			
	是/Yes	23	6.8	
	否/No	115	2.9	
	CEA 应答/ CEA response			
	是/Yes	34	6.9	
	否/No	104	2.9	
OS	KPS			<0.01
	<70%	43	4.7	
	≥70%	95	11.9	
	应答/Response			
	是/Yes	23	23.4	
	否/No	115	7.2	
	CEA 应答/ CEA response			
	是/Yes	34	13.6	
	否/No	104	7.8	
	年龄/Age			
	< 65	68	11.7	
	≥65	70	6.7	
	NMS			
	≤ 2	78	9.9	
	>2	60	6.8	

表 2 – 无进展生存期和总生存期多变量分析/Table 2 – PFS and OS multivariate analyses

		P 值/P-value	HR	IC 95%	
				LIC	HIC
PFS	RECIST 应答/RECIST Response				
		< 0.001	0.34	0.20	0.56
	KPS ≥70				
		< 0.001	0.96	0.95	0.98
	原发性肿瘤部位直肠/Primary tumor localization Rectum				
		0.03	1.49	1.03	2.16
OS	RECIST 应答/RECIST Response				
		<0.001	0.36	0.21	0.61
	KPS≥70	<0.001	0.97	0.96	0.98
	转移灶 >2/ Metastatic sites >2				
		0.004	1.25	1.07	1.46

1704P　评价新辅助-同步 S-1+放疗治疗局部晚期直肠癌的前瞻性可行性研究：一项多中心 II 期临床试验（UMIN ID03396）

1704P　PROSPECTIVE FEASIBLE STUDY TO EVALUATE NEOADJUVANT-SYNCHRONUS S-1+RT FOR LOCALLY ADVANCED RECTAL CANCER:A MULTICENTER PHASE-II TRIAL (UMIN ID03396)

M. Inomata Yufu/JP

背景：含氟尿嘧啶的放化疗（CRT）被视为局部晚期直肠癌的标准围手术期治疗。我们研究了用口服前体药物 TS-1 代替氟尿嘧啶的有效性和安全性。

方法：在 2009 年 4 月至 2011 年 8 月期间，开展了一项多中心（17 个专科中心）、干预性、II期临床试验。这项研究在UMIN-CTR登记，编号为C003396。入组研究的患者在新辅助放化疗前必须满足以下要求：（i）组织学证实的直肠癌；（ii）肿瘤位于直肠（上位、下位）；（iii）癌症被归类为T3-4、N0–3 和M0；给予 2 个周期的 TS-1 新辅助放化疗（100mg/m^2，第 1-5 天、第 8-12 天、第 22-26 天和第 29-33 天），并进行放疗（总剂量 45 Gy/25 fr，1.8 Gy/天第 1-5 天、第 8-12 天、第 22-26 天和第 29-33 天）。在新辅助放化疗结束后第 4 周和第 8 周进行全直肠系膜切除术与D3 淋巴结切除术。主要终点为新辅助放化疗的完成率。次要终点为新辅助放化疗的有效率、短期临床结局、根治性切除率和病理应答（2/3 度）。

结果：这项临床试验入组了 37 例患者。83.3%的患者（95%可信区间；71.2%至 95.5%）完成了新辅助放化疗，4 例患者（11.1%）发生不良事件（3 级/4 级）。总降期率（PR/CR；RECIST 1.0）为 83.3%（95%可信区间；71.2%至 95.5%），病理缓解率为 50.0%（95%可信区间；33.7%至 66.3%）。

结论：我们这项前瞻性 II 期临床研究证明，根据病理缓解和不良事件，新辅助-同时性 TS-1 +放疗适用于治疗局部晚期直肠癌。

Background: Fluorouracil-based chemoradiotherapy (CRT) is regarded as a standard perioperative treatment in locally advanced rectal cancer. We investigated the efficacy and safety of substituting fluorouracil with the oral prodrug TS-1.

Methods:A multi-institutional (17 specialized centers), interventional phase II trial, was conducted from April 2009 to August 2011.This study is registered with UMIN-CTR, number C003396. For inclusion, patients must fulfill the following requirements before neoadjuvant CRT:(i) histologically proven rectal carcinoma; (ii) tumor located in the rectum (upper,lower); (iii) cancer classified as T3-4, N0–3 and M0; Two cycles of neoadjuvant CRT with TS-1 (100mg/m^2 on days 1-5, 8-12, 22-26, and 29-33) is administered, and irradiation (total 45Gy/25fr, 1.8Gy/day, on days 1-5, 8-12, 15-19, 22-26, and 29-33) is performed. Total mesorectal excision with D3 lymphadenectomy is performed during the 4th and 8th week after the end of the neoadjuvant CRT. The primary end-point is rate of complete treatment of neoadjuvant CRT. Secondary endpoints are response rate of neoadjuvant CRT, short-term clinical outcomes, rate of curative resection, and pathological response (grade2/3).

Results: This trial included 37 patients. A complete treatment of neoadjuvant CRT was found in 83.3% of patients (95%CI;71.2-95.5%), and an adverse event (grade 3/4) occurred in 4 patients(11.1%). A rate of an overall downstaging (PR/CR;RECIST 1.0) was 83.3% (95%CI; 71.2- 95.5%), and a pathologic response rate was 50.0% (95%CI; 33.7-66.3%).

Conclusion: Our prospective phase-II study demonstrated that a neoadjuvant-synchronus TS-1+RT for locally advanced rectal cancer was feasible in terms of pathological response and adverse events.

566P 奥沙利铂加 S-1（OS）与奥沙利铂加卡培他滨（XELOX）治疗转移性或复发性结直肠癌患者的随机 II 期临床研究

566P RANDOMIZED PHASE II STUDY OF OXALIPLATIN AND S-1 (OS) VERSUS OXALIPLATIN AND CAPECITABINE (XELOX) IN PATIENTS WITH METASTATIC OR RECURRENT COLORECTAL CANCER

D.Y. Zang, I.J. Chung, H.-S. Oh, et al.

背景：奥沙利铂加 S-1（OS）或奥沙利铂加卡培他滨（XELOX）联合化疗在晚期结直肠癌中具有显著疗效。为了评价这些药物的有效性和安全性，我们在转移性或复发性结直肠癌患者中进行了一项随机 II 期临床研究。

方法：合格患者为病变可测量并且除辅助化疗外无化疗史的患者。88 例患者随机接受奥沙利铂 130mg/m^{2}静脉输液（第 1 天）加S-1 80mg/m^2（OS，A组）或卡培他滨 2,000mg/m^2（XELOX，B组）口服用药（第 1-14 天）。每 21 天为一个周期。患者接受治疗至证实疾病进展或发生不可接受的毒性。研究的主要终点为总缓解率（ORR）。

结果：除原发性肿瘤部位及转移器官数量，两治疗组患者特征相似，其中原发性肿瘤部结肠、直肠乙状结肠和直肠的百分比分别为 42%、16%和 42%（A 组）以及 58%、22%和 20%（B 组），转移器官数量小于 1 处和大于 2 处的百分比分别为 53%和 47%（A 组）以及 67%和 33%（B 组）。A 组共计接受了 284 个周期的治疗（中位值 6，范围 1-39）；B 组接受了 298 个周期的治疗（中位值 5，范围 1-19）。83 例患者（A 组为 41 例，B 组为 42 例）接受了毒性和缓解评估。主要毒性为血小板减少症 [1 /2/3/4 级=8/10/7/1 例患者（A）；10/10/7/5（B）]、中性粒细胞减少症 [1 /2/3/4 级=9/8/1/0（A）；8/12/5/2（B）]、贫血 [1/2/3/4 级=21/13/3/1（A）；20/11/4/0（B）]、周围神经病 [1/2/3 级=11/10/0（A）；11/8/3（B）]和手足综合征 [1/2/3 级=2/0/0（A）；7/1/2（B）]。共有 3 例 CR、11 例 PR、25 例 SD 和 2 例 PD（A 组）；5 例 CR、13 例 PR、16 例 SD 和 7 例 PD（B 组）。在意向性治疗人群中，A 组和 B 组经证实的总缓解率分别为 32.6%（95%可信区间：18.6-47.4%）和 40.0%（95%可信区间，25.0-55.0%）。中位至疾病进展时间分别为 6.7 个月（95%可信区间，4.8-8.7 个月）（A）和 8.0 个月（95%可信区间，6.3-9.6 个月）（B）。中位生存期分别为 19.0 个月（95%可信区间，7.6-30.5 个月）（A）和 22.1 个月（95%可信区间，17.9-26.3 个月）（B）。

结论：这些数据表明，在转移性或复发性结直肠癌患者中，OS 和 XELOX 治疗方案有效且耐受性良好。

Background: Combination oxaliplatin and S-1 (OS) or oxaliplatin and capecitabine (XELOX) chemotherapy have shown significant efficacy in advanced colorectal cancer. To evaluate those efficacy and safety, we performed a randomized phase II study in patients with metastatic or recurrent colorectal cancer.

Methods: Eligible patients were those who had measurable lesions and had no previous history of chemotherapy except adjuvant chemotherapy. Eight-eight patients were randomly assigned to receive oxaliplatin 130mg/m^2 was administered intravenously on day 1 and S-1 80mg/m^2 (OS, arm A) or capecitabine 2,000mg/m^2 (XELOX, arm B) was administered orally on days 1-14. Cycles were repeated every 21 days. Patients were treated until proved to have disease progression or unacceptable toxicity. The primary endpoint of the study was to assess the overall response rate (ORR).

Results: Characteristics of the patients were well-balanced between arms, except for primary disease site, where the percentage of colon, rectosigmoid, and rectum were 42%, 16%, and 42% (arm A) and 58%, 22%, and 20% (arm B), and number of metastatic organs, where the percentage of less than 1 and more than 2 were 53% and 47% (arm A) and 67% and 33% (arm B). A total of 284 cycles (median 6, range 1-39) in Arm A; 298 cycles (median 5, range 1-19) in arm B were administered. Eighty-three (41 for arm A and 42 for arm B) patients were evaluated for toxicity and response. The main toxicities were thrombocytopenia [grade 1/2/3/4=8/10/7/1 patients (A); 10/10/7/5 (B)], neutropenia [grade 1/2/3/4=9/8/1/0 (A); 8/12/5/2 (B)], anemia [grade 1/2/3/4=21/13/3/1 (A); 20/11/4/0 (B)], peripheral neuropathy [grade 1/2/3=11/10/0 (A); 11/8/3 (B)], and hand-foot syndrome [grade 1/2/3=2/0/0 (A); 7/1/2 (B)]. There were 3 CR, 11 PR, 25 SD and 2 PD (A); 5 CR, 13 PR, 16 SD and 7 PD (B). The confirmed ORR in the intention-to-treat population was 32.6% (95% CI:18.6-47.4%) in arm A and 40.0% (95% CI, 25.0-55.0%) in arm B. The median time to progression was 6.7 (95% CI, 4.8-8.7) months (A) and 8.0 (95% CI, 6.3-9.6) months (B). The median survival time was 19.0 (95% CI, 7.6-30.5) months (A) and 22.1 (95% CI, 17.9-26.3) months (B).

Conclusion: These data suggest that both OS and XELOX regimens are active and are well tolerated regimens in patients with metastatic or recurrent colorectal cancer.

528PD 化疗间期对晚期结直肠癌患者总生存期的影响：随机试验的荟萃分析

528PD THE EFFECT OF CHEMOTHERAPY HOLIDAY ON THE OVERALL SURVIVAL OF PATIENTS WITH ADVANCED COLORECTAL CANCER:A META-ANALYSIS OF RANDOMIZED TRIALS

A.A.L. Pereira, J.F.M. Rego, P.M. Hoff, et al.

背景：化疗持续时间对晚期结直肠癌患者治疗结局的影响尚存有争议。我们的目的是对在转移性结直肠癌患者中比较持续化疗至疾病进展与暂停化疗的随机对照试验（RCT）进行系统性回顾和荟萃分析。

方法：我们系统性检索了转移性结直肠癌患者随机继续治疗至疾病进展或实现最大缓解后化疗中断或接受固定周期数的所有RCT。在 PubMed、Cochrane Library 和 2012 年 2 月前的 ASCO/ESMO 摘要中进行检索。由 2 名作者各自单独提取数据，如出现分歧，需要达成共识。采用随机效应模型进行荟萃分析。在荟萃分析中使用风险比（HR），并与 95%可信区间（CI）一起表示。使用卡方检验对数据的统计异质性进行评估，并使用 I2 指数进行表达。

结果：我们检索到 42 项 RCT，其中 5 项适合纳入分析，共包含 1815 例患者。由于各项试验的无进展生存期定义不同，因此无法对无进展生存期（PFS）进行分析。在停药组中，中位无化疗期为 3.9 个月。总生存期的汇总分析包含 1776 例患者（由于未显示可提取的数据，未纳入 1 项临床试验）。荟萃分析表明，持续化疗与化疗休疗策略相比可产生统计学显著的生存收益（风险比=0.90，95%可信区间=0.82 至 0.99；p=0.03；I2 0%）。1 项临床试验报告了生活质量，并且未发现差异。

结论：在晚期结直肠癌患者中，持续化疗至肿瘤进展与化疗中断疗效比，患者生存略好，但差异具有显著性。在肿瘤侵袭性较强的特定患者中，应考虑持续化疗。

Background: The impact of the duration of chemotherapy on the outcomes of patients with advanced colorectal cancer is controversial. Our objective was to perform a systematic review and meta-analysis of randomized controlled trials (RCT) that compared chemotherapy continuously administered until disease progression versus chemotherapy interruption in patients with metastatic colorectal cancer.

Methods: We systematically searched for all RCT in which metastatic colorectal cancer patients were randomized to continuous therapy until progression or chemotherapy discontinuation after maximal response or fixed number of cycles. Trials were located through searches of PubMed, Cochrane Library and of ASCO/ESMO abstracts up to February 2012. Two authors independently extracted the data, and consensus was achieved when there was disagreement. Meta-analyses were performed using random-effects model. Hazard ratios (HR) were used for the meta-analysis and were expressed with 95% confidence intervals (CI). Statistical heterogeneity of data was evaluated with the chi-square test, and expressed using the I2 index.

Results: Our search retrieved 42 RCT, of which five were eligible, with 1815 patients included. The analysis of progression-free survival (PFS) was not possible due to the different definitions of PFS across trials. The median chemotherapy free interval in the discontinuation group was 3.9 months. The pooled analysis of overall survival included 1776 patients (one trial was not included because it did not present extractable data). The metanalysis showed a statistically significant survival benefit with continuously given chemotherapy (HR=0.90, 95% CI=0.82 to 0.99; p=0.03; I2 0%) in comparison to chemotherapy holiday strategy. Quality of life was reported in one trial and no difference was found in it.

Conclusions: Chemotherapy delivered continuously until tumor progression appears to be associated with a modest but significantly better survival in patients with advanced colorectal cancer over chemotherapy interruption. Continued therapy may be available for selected patients with more aggressive disease.

550P　TP、TS 和 DPD 作为卡培他滨加奥沙利铂（XELOX）对比 5-氟尿嘧啶/亚叶酸钙（5-FU/LV）推注辅助治疗用于 III 期结肠癌后的治疗结局的潜在预测因素：研究 NO16968（XELOXA）的生物标记物结果更新

550P　TP, TS AND DPD AS POTENTIAL PREDICTORS OF OUTCOME FOLLOWING CAPECITABINE PLUS OXALIPLATIN (XELOX) VS. BOLUS 5-FLUOROURACIL/LEUCOVORIN (5-FU/LV) AS ADJUVANT THERAPY FOR STAGE III COLON CANCER:UPDATED BIOMARKER FINDINGS FROM STUDY NO16968 (XELOXA)

H.-J. Schmoll, J. Tabernero, J.A. Maroun, et al.

背景：在试验 NO16968 中，XELOX 用于 III 期结肠癌辅助治疗的无瘤生存期（DFS）和总生存期（OS）优于 5-FU/LV 推注[Schmoll 等人，ASCO GI 2012]。3 种关键酶：胸苷磷酸化酶（TP）、胸苷酸合酶（TS）和二氢嘧啶脱氢酶（DPD），具有预测含氟嘧啶治疗的有效性和/或安全性的潜质。我们评估了基线 TP、TS 和 DPD 值与治疗结局（DFS 和 OS）之间的相关性。

方法：III 期结肠癌患者接受 XELOX 治疗（8 个周期，24 周）或 5-FU/LV 推注（梅奥诊所，6 个周期，24 周；Roswell Park，4 个周期，32 周）治疗。主要研究终点为 DFS；次要终点包括总生存期。在福尔马林固定、石蜡包埋的组织中，通过 RT-PCR 测定 TP、TS 和 DPD 表达水平，以中位值作为断点：高（大于中位值）与低（小于中位值）。

结果：生物标记物人群包括 498（26%）/1886 例入组患者（XELOX，n=242；5-FU/LV，n=256）。基线人口统计学特征、肿瘤特征、癌症史和有效性（DFS 和 OS）与主研究人群相似。DFS 的 Cox 回归分析可参见表格。在 XELOX 治疗组中，肿瘤 DPD 和 TP 水平较低和 TP/DPD 比值较高患者的 DFS 显著改善；在 5-FU/LV 治疗组没有观察到这一效果。

结论：这些探索性结果表明，肿瘤 DPD 低水平可能对 XELOX 辅助治疗用于已切除 III 期结肠癌患者中的有效性具有预测性。在 5-FU/LV 治疗组中，DPD 水平和结局之间无相关性。这些数据提示这些酶可能作为 XELOX 治疗的预测标记物，但目前对于治疗决策尚无作用，需要进行前瞻性验证。

Background: In NO16968, XELOX was superior in terms of disease-free survival (DFS) and overall survival (OS) to bolus 5-FU/LV as adjuvant therapy for stage III colon cancer [Schmoll et al. ASCO GI 2012]. Three key enzymes appear to have the potential to predict efficacy and/or safety of fluoropyrimidine-based treatment:thymidine phosphorylase (TP), thymidylate synthase (TS), and dihydropyrimidine dehydrogenase (DPD). We evaluated the association between baseline TP, TS and DPD and outcome (DFS and OS).

Methods: Patients (pts) with stage III colon cancer received either XELOX (8 cycles, 24w) or bolus 5-FU/LV (Mayo Clinic, 6 cycles, 24w; Roswell Park, 4 cycles, 32w). The primary study endpoint was DFS; secondary endpoints included OS. TP, TS and DPD expression levels were determined in formalin-fixed, paraffin-embedded tissues by RT-PCR, and the median used as a cut-off point:high (above median) vs. low (below median).

Results: The biomarker population included 498 (26%) of 1886 pts entered (XELOX, n=242; 5-FU/LV, n=256). Baseline demographics, tumour characteristics, cancer history and efficacy (DFS and OS) were similar to those in the main study population. Cox regression analysis for DFS is shown in the table. In the XELOX group pts with low tumour DPD and TP levels and a high TP/DPD ratio appeared to have significantly better DFS; this effect was not observed with 5-FU/LV. XELOX 5-FU/LV Covariate (high vs. low) HR 95% CI p value HR 95% CI p value DPD 2.45 1.55–3.86 0.0001 0.69 0.47–1.00 NS TP 1.73 1.10–2.72 0.0186 0.81 0.55–1.18 NS TS 0.90 0.58–1.40 NS 0.91 0.62–1.33 NS TP/DPD ratio 0.54 0.34–0.86 0.0091 0.76 0.51–1.13 NS

Conclusions: These exploratory findings suggest that low tumour levels of DPD may be predictive for XELOX efficacy when given as adjuvant therapy in pts with resected stage III colon cancer. There was no correlation between DPD levels and outcome in the 5-FU/LV group. These data raise the possibility of predictive markers for XELOX but, until validated prospectively, would currently not have a role in treatment decisions

	XELOX			5-FU/LV		
协变量（高比低）/ Covariate (high vs. low)	HR	95% CI	p 值/ p value	HR	95% CI	p 值/ p value
DPD	2.45	1.55–3.86	0.0001	0.69	0.47–1.00	NS
TP	1.73	1.10–2.72	0.0186	0.81	0.55–1.18	NS
TS	0.90	0.58–1.40	NS	0.91	0.62–1.33	NS
TP/DPD 比	0.54	0.34–0.86	0.0091	0.76	0.51–1.13	NS

553P 斯堪的纳维亚 29 628 例转移性结直肠癌（MCRC）患者在过去二十年内的中位和长期生存率出现年龄依赖性增加

553P AGE DEPENDENT INCREASE IN MEDIAN AND LONG-TERM SURVIVAL IN 29 628 METASTATIC COLORECTAL CANCER (MCRC) SCANDINAVIAN PATIENTS DURING THE PAST TWO DECADES

C. Qvortrup, M. Cvancarova, B. Glimelius,et al.

背景：在最近几十年的 mCRC 研究中，中位生存期从 6-8 个月增至 20 个月以上。但尚不能明确生存率改善是否也可见于 mCRC 一般人群或所选的特定亚组。

方法：从挪威（1980-2008）、瑞典（1996-2008，乌普萨拉/厄勒布鲁和斯德哥尔摩）和丹麦（2001-2009）癌症登记处收集同时的 mCRC 患者的生存数据。采用 Kaplan-Meier 法对生存期进行建模，采用时序检验对差异进行评估。

结果：共确认 18114 例挪威患者、6477 例丹麦患者和 5037 例瑞典患者。在初始诊断时，IV 期挪威 CRC 患者百分比为 22%，并且在研究期间没有变化。在 1980-1985 年至 2006-2008 年见，挪威患者的中位生存期 从 5 个月（95%可信区间 4.7-5.3）延长至 10 个月（95%可信区间 9.1-10.9）。同期 3 年生存率从 7%增至 21%（p<0.001），5 年生存率从 4%增至 9%（p<0.001）。年轻患者的中位和长期生存率显著较大，而在年轻患者中，最近几年生存率增幅较大。在< 60 岁年龄组中，中位生存期从 8 个月增至 16 个月，而最近的生存率估值分别为 14%（5 年）和 28%（3 年）。在瑞典（8 至 11 个月和 11%至 21%（p<0.001），1996-2001 至 2006-2008）和丹麦（7 至 10 个月和 12 至 18%（p<0.001），2001-2005 至 2006-09），中位生存期和 3 年生存率出现类似改善。在年龄大于 80 岁的患者中，未观察到生存率增加。

结论：研究表明，从 1980 至 2008 年，未经选择的同时性 mCRC 患者人群的中位和长期生存率显著改善。我们认为，该生存收益主要体现了更有效的全身治疗的使用率增加。中位和长期生存率高度依赖于诊断时的年龄，表现为在年轻患者中，近期生存率改善最为显著。

Background: In mCRC studies, median survival has increased from 6-8 months to above 20 months during the last decades. Uncertainty exists whether this improvement in survival is also seen in a general mCRC population or in selected subgroups.

Methods: Survival data from patients with synchronous mCRC were collected from Norwegian (1980-2008), Swedish (1996-2008, Uppsala/ Orebro and Stockholm) and Danish (2001-2009) cancer registries. Survival was modeled using Kaplan-Meier method and the differences assessed with log-rank test.

Results

A total of 18114 Norwegian, 6477 Danish and 5037 Swedish patients were identified. The percentage of stage IV, Norwegian CRC patients at initial diagnosis was 22% and unchanged during the study period. From 1980-85 to 2006-08, median survival increased from 5 months (95% CI 4.7-5.3) to 10 months (95% CI 9.1-10.9) for Norwegian patients. Three-year survival increased from 7% to 21% (p<0.001) and five-year survival from 4% to 9% (p<0.001) in the same period. Younger patients had significantly higher median and long-term survival, and the increase in survival in recent years was much higher for younger patients. For age groups <60 years, median survival has doubled from 8 to 16 months and the most recent survival estimates were 14% (5-year) and 28% (3-year). A similar improvement in median survival and 3-year survival was seen in Sweden (8 to 11 months and 11% to 21% (p<0.001) from 1996-2001 to 2006-2008 and in Denmark (7 to 10 months and 12 to 18% (p<0.001) from 2001-2005 to 2006-09). No increase in survival was observed in patients above 80 years.

Conclusions: The study shows a marked improvement in median and long-term survival from 1980 to 2008 in an unselected population of patients with synchronous mCRC. We believe this survival benefit mainly reflects increased use of more effective systemic therapy. Median and long-term survival were highly dependent on age at diagnosis, as the recent improvement in survival was most pronounced for younger patients.

597P 接受二线治疗的转移性结直肠癌（MCRC）患者的总生存期：系统性回顾

597P OVERALL SURVIVAL IN METASTATIC COLORECTAL CANCER (MCRC) PATIENTS RECEIVING 2ND-LINE THERAPY:A SYSTEMATIC REVIEW

A.L. Martin, Y. Xu, K. Knopf, et al.

背景：目前，含奥沙利铂或伊立替康的治疗方案是 mCRC 一线和二线治疗中的标准疗法（SOC），常与贝伐珠单抗或 EGFR 抑制剂联合使用。进行了一项系统性文献回顾，以补充目前证据的不足并且了解二线化疗在 mCRC 患者中的临床有效性。

方法：在 EMBASE、PubMed、CENTRAL 和关键会议中，使用关键词 CRC 和化疗进行检索，以确认 1992 年至 2012 年 4 月期间发表，旨在评估二线治疗的临床有效性的相关随机临床试验。

结果：纳入 23 项旨在评估 mCRC 二线治疗的主要试验。评估的化疗药物包括伊立替康单药治疗（k=11）、FOLFOX4（k=6）、FOLFIRI（k=4）、IROX（k=3）、伊立替康/5-FU/FA（k=3）和 IRIS（k=1）。含氟尿嘧啶方案是最常见的既往治疗，其中 13 项研究报告称 100%的转移瘤患者接受氟尿嘧啶作为一线治疗。8 项研究未入组既往接受伊立替康治疗的患者。在纳入分析的研究中，旨在比较阿柏西普+FOLFIRI 与 FOLFIRI 的 VELOUR 试验是唯一一项在接受奥沙利铂一线化疗的患者中评估当前标准疗法（含 FOLFIRI 的方案）的临床试验。在各项研究中，总生存期（OS）范围为 6.4 个月至 18 个月。在化疗方案中添加特定靶向药物可以显著延长生存期。在 FOLFOX4 二线疗法中添加贝伐珠单抗使中位总生存期达到 12.9 个月，而单用 FOLFOX4 时为 10.8 个月。类似的，在 KRAS 野生型患者中，在 FOLFIRI 中添加帕尼单抗可使中位总生存期从 12.5 个月延长至 14.5 个月，而添加阿柏西普可使中位总生存期从 12.1 个月延长至 13.5 个月。

结论：在二线治疗临床试验中，化疗中添加靶向药物后，总生存期显著改善。然而，治疗选择的可变性、既往化疗方案、患者选择和研究方法，在对结局开展可靠的汇总分析以检验比较疗效的结果时会产生阻碍。VELOUR 是为数不多的评估接受当前一线 SOC 的患者的临床试验之一。

Background: Currently, oxaliplatin or irinotecan-based regimens are the standard of care (SOC) in 1st– and 2nd-line therapy of mCRC, often combined with bevacizumab or an EGFR inhibitor. A systematic literature review was conducted to address gaps in the current evidence and gain an understanding of the clinical efficacy of 2nd-line chemotherapy in patients with mCRC.

Methods: Searches were conducted in EMBASE, PubMed, CENTRAL, and key congresses using keywords for CRC and chemotherapy to identify relevant randomized trials assessing 2nd-line clinical efficacy, published between 1992 and April 2012.

Results: Twenty-three primary trials evaluating 2nd-line treatment of mCRC were identified for inclusion. Chemotherapeutic agents investigated included irinotecan monotherapy (k=11), FOLFOX4 (k=6), FOLFIRI (k=4), IROX (k=3), irinotecan/5-FU/FA (k=3) and IRIS (k=1). FU-based regimens were the most common prior therapy, with 13 studies reporting that 100% of patients received FU as 1st-line therapy for metastatic disease. Eight studies excluded patients who previously received irinotecan. Of the included studies, the VELOUR trial, comparing aflibercept+FOLFIRI versus FOLFIRI, was the only trial evaluating the current SOC (FOLFIRI based regimens) in patients who received oxaliplatin-based chemotherapy as a 1st-line agent. Overall survival (OS) ranged from 6.4 to 18 mos across studies. The addition of specific targeted agents to chemotherapy regimens demonstrated significant incremental survival gains. Addition of bevacizumab to FOLFOX4 in the 2nd-line setting was associated with a median OS of 12.9 mos, compared with 10.8 mos for FOLFOX4 alone. Similarly, the addition of panitumumab to FOLFIRI improved median OS from 12.5 mos to 14.5 mos in KRAS wild type patients and addition of aflibercept improved median OS from 12.1 mos to 13.5 mos.

Conclusions:OS in 2nd-line trials showed significant survival gains when targeted agents were added to chemotherapy regimens. However, variability in treatment choices, prior chemotherapy regimen, patient selection and study approaches may hamper efforts to conduct reliable pooled analyses on outcomes to examine comparative effectiveness. VELOUR was one of the few trials that investigated patients who had received the current SOC in their 1st-line therapy.

589P 对 1,061 例同时性结直肠癌肝转移患者的生存分析

589P SURVIVAL ANALYSIS OF 1,061 PATIENTS WITH SYNCHRONOUS COLORECTAL HEPATIC METASTASES

J. Xu, Y. Zhong, D. Zhu, et al.

目的：考察同时性结直肠癌肝转移患者的生存状况并且确定预后因素。

方法：在 1,061 例于 2000-2010 年间在中山医院接受治疗的同时性结直肠癌肝转移患者中，回顾性收集了临床、病理学和随访数据。通过单变量和多变量分析研究不同因子的预后价值。

结果：在可切除性肝转移患者中，同时切除组的每位患者的总费用低于分期切除组（25,693 RMB 与 34,129 RMB，P<0.050），并且在同时切除组和分期切除组之间，并发症率（24.5% 与 20.5%）或中位总生存期（48.5 与 47.0 个月）没有显著差异。在不可切除的肝转移患者中，切除原发性肿瘤可以改善中位总生存期（19.0 个月与 9.3 个月，P<0.001）。根据多变量分析，6 个因子是生存结局不良的独立预测因子：原发性肿瘤低分化、肝转移灶≥4 处、肝转移灶最大直径≥5cm、肝外转移、未切除原发性肿瘤和未对肝转移进行手术治疗。如果对上述每个因素进行给分，则所有患者可分为低危组（0-1 分）、中危组（2-3 分）和高危组（4-6 分），5 年生存率分别为 51%、16%和 0%（P<0.001）。

结论：在可切除的同时性结直肠癌肝转移患者中，同时切除原发性肿瘤和肝转移灶被视为预后因素。在无症状性不可切除的肝转移患者中，建议在正确时机切除原发性肿瘤。可使用含上述 6 个因素的预测模型指导对同时性结直肠癌肝转移患者的临床处理。

Objectives: To investigate survival and to identify prognostic factors in patients with synchronous colorectal hepatic metastasis.

Methods: Clinical, pathologic and follow-up data were retrospectively collected from 1,061 consecutive patients treated for synchronous colorectal hepatic metastases at Zhongshan Hospital between 2000 and 2010. The prognostic values of different factors were studied through univariate and multivariate analyses.

Results: For patients with resectable hepatic metastases, the total expense per patient in the simultaneous resection group was lower than that in the staged resection group (25,693 RMB vs. 34,129 RMB, P<0.050), and there were no significant differences in the complication rates (24.5% vs. 20.5%) or median overall survival (48.5 vs. 47.0 months) between the simultaneous and staged resection groups. For patients with unresectable hepatic metastases, resection of the primary tumor was associated with improved median overall survival (19.0 vs. 9.3 months, P<0.001). Six factors were found to be independent predictors of poor survival by multivariate analysis:a poorly differentiated primary tumor, number of hepatic metastases≥4, maximum hepatic metastasis size≥5cm, extra-hepatic metastases, no resection of the primary tumor and no surgical treatment of hepatic metastases. Giving one point to each of the above factors, all of the patients were divided into low-risk (0-1 points), medium-risk (2-3 points) and high-risk (4-6 points) groups with 5-year survival rates of 51%, 16% and 0%, respectively (P<0.001).

Conclusions: Simultaneous resection of the primary tumor and hepatic metastases were accepted as prognostic factors in patients with resectable synchronous colorectal hepatic metastases. Resection of the primary tumor was recommended at the right time for asymptomatic patients with unresectable hepatic metastases. A prediction model using the above six factors can be used to guide the clinical management of patients with synchronous colorectal hepatic metastases.

626 对结直肠癌肺转移的根治性局部治疗应选择什么方式：手术、射频消融或立体定向放疗？
626 WHAT TO CHOOSE AS RADICAL LOCAL TREATMENT FOR LUNG METASTASES FROM COLO-RECTAL CANCER:SURGERY, RADIOFREQUENCY ABLATION OR STEREOTACTIC RADIOTHERAPY?

R. Schlijper, D. De Ruysscher, J.P. Grutters, et al.

背景：在对结直肠癌肺转移给予局部治疗后可以实现长期生存。然而，尚未明确最佳局部治疗方式：手术、射频消融（RFA）或立体定向放疗（SBRT）。

方法：经过系统性回顾后，纳入满足选择标准的 27 项研究，最重要的标准是至少 50 例患者和随访期≥24 个月。然而，尚没有合格的 SBRT 研究。因此对 4 项 RFA 研究和 23 项手术研究进行了回顾。

结果：4 项手术研究为前瞻性研究，其他所有研究都是回顾性研究。未发现随机临床试验。研究之间报告的数据不同，因此难以进行分析。在 RFA 和手术组中，治疗相关死亡率分别为 0%和 1.4%-2.4%，而报告发病率各不相同，不过手术组的发病率最低。在RFA和手术组中，加权2年和5年生存率分别为69.6%和40.7%与 76.5%和 44.9%。

结论：尽管大多数证据支持手术治疗，但由于缺少 III 期临床试验，无法得出确切的结论。尚需要高质量临床试验来比较目前使用的治疗类型，例如 SBRT、RFA 和手术。

Background: Long-term survival can be obtained with local treatment of lung metastases from colorectal cancer. However, it is unclear as to what the optimal local therapy is:surgery, radiofrequency ablation (RFA) or stereotactic radiotherapy (SBRT).

Methods: After a systematic review, 27 studies were included matching with the a priori selection criteria, the most important being at least 50 patients and a follow-up period of≥24 months. However, no SBRT studies were eligible. The review was therefore conducted on 4 RFA and 23 surgical series.

Results: Four of the surgical studies were prospective, all others were retrospective. No randomized trial was found. The reported data differed between the studies, which led to difficulties in the analyses. Treatment-related mortality rates for RFA and surgery were 0% and 1.4-2.4%, respectively, whereas morbidity rates were reported inconsequently but seemed the lowest for surgery. Weighted 2- and 5-year survival were 69.6% and 40.7% for RFA and 76.5% and 44.9% for surgery.

Conclusion: Due to the lack of phase III trials, no firm conclusions can be drawn, although most evidence supports surgery. High-quality trials comparing currently used treatment modalities such as SBRT, RFA and surgery are needed.

519O 大洋洲胃肠试验组（AGITG）ARCTIC 研究的最终结果：雷替曲塞用于氟嘧啶（FP）所致心脏毒性患者的国际性稽查研究

519O FINAL RESULTS OF AUSTRALASIAN GASTRO-INTESTINAL TRIALS GROUP (AGITG) ARCTIC STUDY:AN INTERNATIONAL AUDIT OF RALTITREXED FOR PATIENTS WITH CARDIAC TOXICITY INDUCED BY FLUOROPYRIMIDINES (FP)

T. Price, K. Wilson, R.J. Simes, et al.

背景：心脏毒性（CT）是氟嘧啶的一种不罕见但有致命风险的副作用。如果继续相同的化疗，进一步化疗后该毒性的发生率报告为 20%*。对于这些患者的处理尚不明确，可以选择继续相同剂量/方案的氟嘧啶化疗、添加硝酸盐和钙拮抗剂、更换氟嘧啶给药方案，或者用雷替曲塞代替，后一方法主要基于病例报告。

方法：AGITG 和 OCTO（肿瘤临床试验学会-牛津）成员确定了发生氟嘧啶所致心脏毒性并换用雷替曲塞的患者。心脏毒性包括心绞痛、心肌梗死（MI）或心律失常。不是必须进行冠状动脉造影检查。

结果：42 例患者纳入本次临床稽查。癌症诊断包括结直肠癌（39 例患者）、食管癌（2）和壶腹癌（1）。患者的中位年龄为 62 岁（范围 36-81 岁）。27 例患者（64%）为男性。换用雷替曲塞前的中位化疗周期数量为 2 个周期（范围 1 -11 个）。氟嘧啶方案包括 FOLFOX、CAPOX、5FU 连续输注、ECF、卡培他滨单药治疗。40 例患者发生心绞痛，5 例心肌梗死，2 例心律失常，一些患者同时发生不止 1 例事件。在换用雷替曲塞前，8 例患者发生 2 例单独的心脏毒性事件，2 例患者发生 3 例事件。发生心脏毒性后，9 例患者接受雷替曲塞单药治疗，32 例患者接受雷替曲塞与其他药物或放疗合用，1 例患者接受雷替曲塞单药治疗，然后接受联合治疗。中位雷替曲塞化疗周期数量为 6 个周期（范围：1-21 个周期）。1 例患者（CT 发生率为 2.4%，95% CI：0.1-12.3）在换用雷替曲塞后发生可能相关的心脏事件（治疗 5 个月发生急性心律失常），该 CT 发生率显著低于继续氟嘧啶化疗时报告的 20%（精确二项式检验，p=0.004）。

结论：由氟嘧啶换用雷替曲塞后，心脏毒性的复发率较低。对于希望从含氟嘧啶化疗中获益而又担忧心脏毒性的患者而言，换用雷替曲塞的治疗策略可能是一个合适的选择。（* Jensen SA et al. Cancer Chemotherapy & Pharm. 58:487-93, 2006）

Background: Cardiac toxicity (CT) is an uncommon but potentially fatal side effect of FP. The incidence of further CT if the same chemotherapy is continued is
reported to be 20%*. Management of these patients remains poorly defined and options include continuing same dose/schedule of FP, adding a nitrate and calcium antagonist, switching administration schedule of FP, or substituting with raltitrexed, the later based primarily on case reports.

Methods:AGITG and OCTO (Oncology Clinical Trials Office – Oxford) members identified patients who had CT from FP, and were subsequently switched to raltitrexed. CT included angina, myocardial infarct (MI) or arrhythmia. A coronary angiogram was not mandatory.

Results:42 patients were included in this clinical audit. Cancer diagnoses included colorectal (39pts), oesophageal (2) and ampullary carcinoma (1). Median age-62 years (range 36-81). 27 patients (64%) were male. Median number of cycles prior to switching to raltitrexed was 2 (range 1-11). FP regimens included FOLFOX, CAPOX, continuous infusion 5FU, ECF, capecitabine alone. 40 patients had angina, 5 MI, and 2 arrhythmia with some patients experiencing >1 event at that time. 8 patients experienced two separate CT events, and 2 had 3 events prior to switching to raltitrexed. Following CT, 9 patients received raltitrexed alone, 32 received raltitrexed in combination with other agents or radiotherapy and one received raltitrexed alone followed by combination. Median number of raltitrexed cycles was 6 (range 1-21). One patient (CT rate 2.4%, 95% CI:0.1-12.3) experienced a potentially related cardiac event (acute arrhythmia 5 mths into therapy) after switching to raltitrexed, a CT rate significantly lower than the 20% reported when continuing FP (exact binomial test p=0.004).

Conclusion: The rate of recurrent CT after switching from FP to raltitrexed was low. The strategy of switching to raltitrexed may represent an acceptable option for patients that are deriving a benefit from FP based chemotherapy but in whom cardiac toxicity is a concern. (* Jensen SA et al. Cancer Chemotherapy & Pharm. 58:487-93, 2006).

521O 转移性结直肠癌（MCRC）患者的错配修复缺陷（DMMR）和 BRAF 基因突变（MT）状态：CAIRO、CAIRO2、COIN 和 FOCUS 研究的荟萃分析

521O DEFICIENT MISMATCH REPAIR (DMMR) AND BRAF MUTATION (MT) STATUS IN PATIENTS (PTS) WITH METASTATIC COLORECTAL CANCER (MCRC):A META-ANALYSIS OF THE CAIRO, CAIRO2, COIN AND FOCUS STUDIES

S. Venderbosch, T. De Haan, D.A.M. Heideman, et al.

引言：在 II-III 期结直肠癌中，BRAF 基因突变和错配修复缺陷的总发生率分别为 8%和 10%-20%。在散发性错配修复缺陷中，BRAF 基因突变的发生率高（24%，Roth et al.，JCO 2010），并且 BRAF 基因突变与错配修复缺陷不同，其并无预后价值。在转移性结直肠癌患者中，错配修复缺陷和 BRAF 基因突变的发生率大约分别为 4%和 8%。关于 BRAF 基因突变联合错配修复缺陷的预后价值，尚未获得大规模转移性结直肠癌患者的数据。

方法：我们对 4 项转移性结直肠癌临床试验进行了一项荟萃分析：CAIRO、CAIRO2、COIN 和 FOCUS。主要结局指标是与 BRAF 和 MMR 状态相关的无进展生存期（PFS）和总生存期（OS）的风险比（HR）。关于荟萃分析，对个体患者数据进行了 Cox 回归分析。

结果：共对 3064 例患者进行了分析，其中 151 例患者（4.9%）显示错配修复缺陷，263 例患者（8.6%）发生 BRAF 基因突变。分别有 211 例错配修复正常（ pMMR）患者（7.2%）和 52 例错配修复缺陷患者（34.4%）发生 BRAF 基因突变。错配修复缺陷患者与错配修复正常患者相比，无进展生存期显著缩短（HR 1.22；95% CI，1.03-1.46），但总生存期没有这一变化（HR 1.13；95% CI，0.94-1.36）。BRAF 基因突变患者与 BRAF 野生型（wt）患者相比，无进展生存期和总生存期均显著缩短（HR 1.28；95% CI，1.12-1.46 和 HR 1.81；95% CI，1.57-2.09）。在错配修复正常组，BRAF 基因突变患者的无进展生存期和总生存期较 BRAF 野生型患者显著缩短（HR 1.32；95% CI 1.09-1.61 和 HR 1.88；95% CI 1.53-2.30）。在错配修复缺陷组，BRAF 基因突变患者与 BRAF 野生型患者的无进展生存期和总生存期没有显著差异(HR 1.05；95% CI 0.65-1.68 和 HR 1.49；95% CI 0.91-2.43）。在 BRAF 基因突变组，错配修复正常患者和错配修复缺陷患者的无进展生存期和总生存期没有显著差异（HR 0.96；95% CI 0.63-1.47 和 HR 1.03；95% CI 0.67-1.59）。在 BRAF 野生型组，错配修复正常患者和错配修复缺陷患者的无进展生存期和总生存期没有显著差异（HR 1.32；95% CI 0.99-1.75 和 HR 1.22；95% CI 0.90-1.65）。

结论：在本项对转移性结直肠癌患者进行的荟萃分析中，我们发现，与早期结直肠癌患者报告数值相比，错配修复缺陷患者中的 BRAF 基因突变发生率更高。在转移性结直肠癌患者中，与错配修复正常患者相比，错配修复缺陷患者的无进展生存期缩短。BRAF 基因突变在转移性结直肠癌中的预后作用仅限于错配修复正常患者。我们的数据证实了 BRAF 基因突变相比 BRAF 野生型的预后价值较差。

Introduction: In stage II-III CRC the overall incidence of BRAF mt and dMMR is 8% and 10-20%, resp. The incidence of BRAF mt in sporadic dMMR is high (24%, Roth et al., JCO 2010), and BRAF mt, in contrast to dMMR, has a negative prognostic value. The incidence of dMMR and BRAF mt in mCRC is approx. 4% and 8%, resp. No data from large series of mCRC pts are available on the prognostic value of BRAF mt in combination with dMMR.

Methods: We performed a meta-analysis of 4 mCRC trials:CAIRO, CAIRO2, COIN and FOCUS. The primary outcome measure was the hazard ratio (HR) for progression free survival (PFS) and overall survival (OS) in relation to BRAF and MMR status. For the meta-analysis a cox regression analysis was performed on individual pt data.

Results: In total 3064 pts were analysed, of whom 151 (4.9%) exhibited dMMR, and 263 (8.6%) BRAF mt. A BRAF mt was observed in 211 (7.2%), and 52 (34.4%) of the pts with a proficient mismatch repair system (pMMR) and dMMR, resp. PFS was significantly worse for dMMR vs. pMMR pts (HR 1.22; 95% CI, 1.03-1.46), but not OS (HR 1.13; 95% CI, 0.94-1.36). PFS and OS were significantly worse for BRAF mt vs. BRAF wildtype (wt) pts (HR 1.28; 95% CI, 1.12-1.46 and HR 1.81; 95% CI, 1.57-2.09, resp.). Within the pMMR group, BRAF mt pts had a significantly worse PFS and OS compared to BRAF wt pts (HR 1.32; 95% CI 1.09-1.61, and HR 1.88; 95% CI 1.53-2.30, resp.). Within the dMMR group no significant differences were found for PFS and OS in BRAF mt pts vs. BRAF wt pts (HR 1.05; 95% CI 0.65-1.68, and HR 1.49; 95% CI 0.91-2.43, resp.). Within the BRAF mt group PFS and OS were not significantly different between pMMR and dMMR pts (HR 0.96; 95% CI 0.63-1.47, and HR 1.03; 95% CI 0.67-1.59, resp.). Within the BRAF wt group, PFS and OS were not significantly different for pMMR vs. dMMR pts (HR 1.32; 95% CI 0.99-1.75, and HR 1.22; 95% CI 0.90-1.65, resp.).

Conclusion: In this meta-analysis of mCRC pts we observed a higher incidence of BRAF mt in dMMR than reported for early-stage CRC pts. In mCRC pts, dMMR is associated with a worse PFS compared to pMMR. The prognostic role of BRAF mt in mCRC is restricted to pMMR pts. Our data confirm the worse prognostic value of BRAF mt vs BRAF wt.

肺部肿瘤

1254P EGFR 突变的非小细胞肺癌患者临床结局的汇总分析：一项更新

1254P POOLED ANALYSIS OF CLINICAL OUTCOMES FOR PATIENTS WITH EGFR MUTATIONS IN NON-SMALL-CELL LUNG CANCER:AN UPDATE

L.Paz-Ares D.Soulières B.Klughammer, et al.

背景：在 2010 年，报告了一项研究EGFR突变与临床结局之间相关性的汇总分析[1]；EGFR TKI似乎是EGFR突变阳性的非小细胞肺癌（NSCLC）的最有效治疗药物。在这项报告之后，又发布了许多试验（包括大型对照III期临床研究），合格患者的数量增加了一倍。所以进行了一项更新性分析，旨在为评估EGFR突变阳性NSCLC的治疗提供一个更全面的数据集。

方法：通过文献检索查找了报告有关接受化疗、厄洛替尼或吉非替尼治疗的 EGFR 突变阳性 NSCLC 患者无进展生存期（PFS）的会议报告和论文（II/III 期研究/回顾性分析），并且对这些文献进行重复检索。大部分论文报告了高水平的结果，如中位 PFS。计算是基于简化假设，对结果进行汇总，并获取准确估计值（代替可信区间）。通过研究样本量 N (i)加权平均值对汇总中位 PFS、MPFS（全部）进行了估算：MPFS（全部）=1/N（全部）∑N(i)MPFS(i)。采用漏斗图对发表偏倚的可能性进行了评估。计划进行排列检验。所有方法描述见[1]。

结果：数据来源于 20 项化疗研究（n=984；之前 n=375[1]）、27 项厄洛替尼研究（n=735；之前 n=365[1]）和 56 项吉非替尼研究（n=1843；之前 n=1069[1]）。对于所有治疗线，与化疗相比，2 种 EGFR TKI 治疗后的 PFS 都较长（见表格）。

结论：在过去 3 年内，多项重要的研究已经在 EGFR 突变阳性的 NSCLC 患者中对 EGFR TKI 疗法进行了评估。此次更新的数据集提供了该患者亚组治疗结果的全面描述，确认了该患者亚组从 EGFR TKI 疗法获得的益处大于传统化疗，尤其是作为一线治疗给药时。[1] Paz-Ares J Cell Mol Med 2010

Background: In 2010, the results of a pooled analysis examining the correlation of EGFR mutations with clinical outcome were reported [1]; EGFR TKIs appeared to be the most effective treatment for EGFR mutation-positive NSCLC. Since this report, more trials (including large controlled phase III studies) have been published, doubling the number of eligible patients. An updated analysis was carried out to provide a comprehensive dataset assessing the treatment of EGFR mutation-positive NSCLC.

Methods: Congress reports and papers reporting progression-free survival (PFS) for EGFR mutation-positive NSCLC treated with chemotherapy, erlotinib or gefitinib (phase II/III studies/retrospective analyses) were identified in a literature search and checked for duplication. Most papers report high level results e.g. median PFS. Calculations were based on simplifying assumptions to allow for pooling of results and to obtain an accuracy estimate (surrogate for confidence intervals). The pooled median PFS, MPFS(all), was estimated by a study-size N (i) weighted average**:**MPFS(all)=1/N(all)∑N(i)MPFS(i). The potential for publication bias was assessed using funnel plots. Permutation testing will be carried out. For full methodology see [1].

Results: Data were included from 20 chemotherapy studies (n=984; updated from n=375 [1]), 27 erlotinib studies (n=735; from n=365 [1]), and 56 gefitinib studies (n=1843; from n=1069 [1]). Longer PFS was seen with both EGFR TKIs compared with chemotherapy across treatment lines (Table).

Conclusion: In the past three years, several important studies have examined EGFR TKI therapy in patients with EGFR mutation-positive NSCLC. This updated dataset provides a comprehensive picture of treatment outcomes in this patient subset, confirming that this subgroup derives a greater benefit from EGFR TKIs than from conventional chemotherapy, especially when administered as first line. [1] Paz-Ares J Cell Mol Med 2010

EGFR 突变阳性肿瘤患者的中位 PFS 汇总（95%准确性区间）
Pooled median PFS (95% accuracy interval) for patients with EGFR mutation-positive tumours

厄洛替尼单药治疗/Single-agent erlotinib	
所有治疗线/All lines of therapy (n=735)	12.4 个月/12.4 months (11.6–13.4)
*主要是一线治疗/*Predominantly first-line (n=354)	12.0 个月/12.0 months (10.8–13.3)
吉非替尼单药治疗/Single-agent gefitinib	
所有治疗线/All lines of therapy (n=1843)	9.3 个月/9.3 months (8.9–9.8)
*主要是一线治疗/*Predominantly first-line (n=716)	9.3 个月/9.3 months (9.0–10.5)
化疗（可能是单药或多药治疗）/Chemotherapy (may be single- or multiple-agent treatment)	
所有治疗线/All lines of therapy (n=984)	5.6 个月/5.6 months (5.3–6.0)
*主要是一线治疗/*Predominantly first-line (n=868)	5.6 个月/5.6months (5.5–6.2)

*主要是一线治疗指的是有≥ 90%的患者接受一线治疗
*Predominantly first-line is ≥90% of patients treated in first-line setting

1226O 厄洛替尼交替联合一线化疗治疗晚期非小细胞肺癌（NSCLC）的随机、安慰剂对照、III 期 FASTACT-2 研究中的生物标记物分析和总生存期（OS）

1226O BIOMARKER ANALYSES AND OVERALL SURVIVAL (OS) FROM THE RANDOMIZED, PLACEBO-CONTROLLED, PHASE 3, FASTACT-2 STUDY OF INTERCALATED ERLOTINIB WITH FIRST-LINE CHEMOTHERAPY IN ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC)

T.S.K. Mok, J.S. Lee, L. Zhang, et al.

背景：FASTACT-2 是一项晚期 NSCLC 一线治疗的随机、安慰剂对照、III 期研究，本研究达到了其主要终点，即化疗交替联合厄洛替尼与单独化疗相比可以显著延长 PFS：中位值分别为 7.6 个月与 6.0 个月；HR=0.57；p<0.0001（Mok et al. ASCO 2012）。我们报告本研究的 OS 结果及生物标记物与 PFS 的相关性。

方法：未治疗的IIIB/IV期NSCLC且ECOG PS评分为 0/1 分的患者接受了最多 6 个疗程的吉西他滨（1,250 mg/m^2，第 1 天和第 8 天）+铂类药物（卡铂AUC=5 或顺铂 75 mg/m^2，第 1 天），q4w，并且交替使用厄洛替尼（150 mg/天，第 15–28 天；GC-E；n=226）或安慰剂（GC-P；n=225）治疗。无进展的患者接受厄洛替尼或安慰剂维持治疗，持续至疾病进展、发生不可接受的毒性或死亡。鼓励提供肿瘤样本；在中心实验室进行生物标记物检验，且优先次序如下：EGFR突变；KRAS突变[都使用基于PCR的检验方法（COBAS）]；使用免疫组织化学法测定ERCC1 表达（IHC；中位阈值）；使用荧光原位杂交法（FISH）测定EGFR基因拷贝数；EGFR IHC。

结果：OS 数据尚不完善（截止到 2011 年 10 月，GC-E 组和 GC-P 组分别有 45.1%和 52.4%的患者发生事件），但观察到 GC-E 组的 OS 与 GC-P 组相比有延长的趋势：HR=0.78（95%CI 0.60–1.02）；p=0.0686；中位值分别为 18.3 个月与 14.9 个月。将会提供截止到 2012 年 6 月的 OS 更新数据。在 451 例患者中，共 283 例患者（62.7%）提供了用于生物标记物分析的样本。下表列出了总生物标记物人群和 EGFR 野生型（WT）亚组的生物标记物与 PFS 的相关性。

结论：与预期结果一样，EGFR 突变阳性（Mut+）亚组在厄洛替尼交替联合一线化疗后，获得了最大的 PFS 益处。ERCC1 IHC+状态也与 GC-E 组的 PFS 长于 GC-P 组有关联，即使是在 EGFR WT 状态已知的患者中。

Background:FASTACT-2 is a randomized, placebo-controlled, phase 3 study in first-line advanced NSCLC, which met its primary endpoint of significantly prolonged PFS with intercalated erlotinib and chemotherapy**:**median 7.6 vs 6.0 months; HR=0.57; p<0.0001 (Mok et al. ASCO 2012). We report OS results and correlations of biomarkers with PFS for this study.

Methods: Patients (pts) with untreated stage IIIB/IV NSCLC and ECOG PS 0/1 received up to 6 cycles of gemcitabine (1,250mg/m^2 on d1 & 8) plus platinum (carboplatin AUC=5 or cisplatin 75mg/m^2 on d1) q4w, with either intercalated erlotinib (150mg/day on d15–28; GC-E; n=226) or placebo (GC-P; n=225). Pts without progression received maintenance erlotinib or placebo until progression, unacceptable toxicity or death. Provision of tumour samples was encouraged; tests were conducted at a central laboratory and prioritized as follows**:**EGFR mutation; KRAS mutation (both by PCR-based test [COBAS]); ERCC1 expression by immunohistochemistry (IHC; median cut-off); EGFR gene copy number by fluorescence in-situ hybridization (FISH); and EGFR IHC.

Results:OS data are not fully mature yet (45.1% and 52.4% of pts in GC-E and GC-P arms with event, respectively, in Oct 2011), but a trend towards prolonged OS with GC-E vs GC-P was observed**:**HR=0.78 (95%CI 0.60–1.02); p=0.0686; median 18.3 vs 14.9 months. Updated OS data with June 2012 cut-off will be presented. A total of 283/451 pts (62.7%) provided samples for biomarker analyses. The table shows correlations with PFS for the overall biomarker populations and the EGFR wild-type (WT) subgroup.

Conclusions: As expected, the EGFR mutation-positive (Mut+) subgroup had the strongest PFS benefit with intercalated erlotinib and first-line chemotherapy. ERCC1 IHC+status was also associated with longer PFS with GC-E vs GC-P, even in pts with known EGFR WT status

生物标记物亚组/Biomarker subgroup	PFS 的 HR(95%CI)/HR for PFS(95%CI)	GC-E vs GC-P 的中位 PFS，月/Median PFS with GC-E vs GC-P,	p-值 /p-value
EGFR Mut+(n=97)	0.21 (0.12–0.35)	15.6 vs 6.9	<0.0001
EGFR WT (n=136)	0.95 (0.67–1.34)	7.1 vs 5.9	0.7511
KRAS Mut+(n=21)	0.63 (0.25–1.58)	6.0 vs 4.5	0.3169
KRAS WT (n=202)	0.51 (0.37–0.70)	8.0 vs 6.8	<0.0001
EGFR WT 和 KRAS Mut+(n=21) /EGFR WT and KRAS Mut+(n=21)	0.63 (0.25–1.58)	6.0 vs 4.5	0.3169
EGFR WT 和 KRAS WT (n=109)/ EGFR WT and KRAS WT (n=109)/	1.01 (0.68–1.49)	6.6 vs 6.5	0.9609
ERCC1 IHC+(n=70)	0.51 (0.30–0.85)	9.0 vs 5.4	0.0091
ERCC1 IHC– (n=71)	0.65 (0.39–1.08)	7.6 vs 7.2	0.0931
EGFR WT 和 ERCC1 IHC+(n=37)/ EGFR WT and ERCC1 IHC+(n=37)	0.55 (0.27–1.12)	7.6 vs 4.6	0.0941
EGFR WT 和 ERCC1 IHC– (n=38)/ EGFR WT and ERCC1 IHC– (n=38)	1.10 (0.56–2.18)	7.3 vs 7.2	0.7751
EGFR FISH+(n=34)	0.26 (0.11–0.64)	12.9 vs 5.9	0.0017
EGFR FISH– (n=48)	0.67 (0.37–1.22)	7.5 vs 6.0	0.1880
EGFR WT 和 EGFR FISH+(n=11)/ EGFR WT and EGFR FISH+(n=11)	0.69 (0.18–2.68)	7.8 vs 7.6	0.5865
EGFR WT 和 EGFR FISH– (n=31) /EGFR WT and EGFR FISH– (n=31)	0.90 (0.42–1.92)	7.0 vs 5.7	0.7795
EGFR IHC+(n=76)	0.51 (0.31–0.86)	8.1 vs 6.0	0.0091
EGFR IHC– (n=37)	0.40 (0.18–0.88)	10.2 vs 6.7	0.0179
EGFR WT 和 EGFR IHC+(n=38) /EGFR WT and EGFR IHC+(n=38)	0.83 (0.42–1.63)	7.4 vs 5.8	0.5842
EGFR WT 和 EGFR IHC– (n=22) / EGFR WTand EGFR IHC– (n=22)	0.48 (0.18–1.29)	7.8 vs 7.2	0.1305

LBA31 入组 EURTAC 试验的 EGFR 突变非小细胞肺癌（NSCLC）患者的伴随可作用突变和总生存期（OS）：EGFR L858R、EGFR T790M、TP53 R273H 和 EML4-ALK (V3)

LBA31 CONCOMITANT ACTIONABLE MUTATIONS AND OVERALL SURVIVAL (OS) IN EGFR-MUTANT NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS (P) INCLUDED IN THE EURTAC TRIAL:EGFR L858R, EGFR T790M, TP53 R273H AND EML4-ALK (V3)

R.Rosell1, B.Massuti Sureda, C.Costa,et al.

背景：在 2012 年 4 月最终截止日期时，在随机 III 期 EURTAC 试验中，作为 EGFR 突变阳性 NSCLC 欧洲患者的一线治疗，厄洛替尼与化疗相比可以延长无进展生存期（PFS）（HR, 0.34; P < 0.0001）。总生存期（OS）方面未见差异[22.9 个月与 20.8 个月（m）]。

方法：使用 EURTAC 试验中 95 例患者的治疗前肿瘤样本评估了 EGFR T790M 和 TP53 突变、EML4-ALK 易位和 BIM mRNA 表达，及其与临床结果之间的相关性。

结果：分别有 37.89%、24.21%和 15.8%的患者伴有 T790M、TP53 和 EML4-ALK 突变。55.8%患者的 BIM 表达为低水平或中等水平，31.6%患者的 BIM 表达为高水平。在接受化疗的 45 例患者中，86.7%的患者在进展时交叉接受了 EGFR TKI 治疗。在接受厄洛替尼治疗的患者中，高水平 BIM 表达患者的总缓解率（ORR）为 87.5%，而低中等水平 BIM 表达患者的 ORR 为 34.6%；化疗组的 ORR 分别为 11.1%和 14.2%（P=0.0002）。在无 T790M 突变的厄洛替尼组患者中，高水平 BIM 表达患者的 ORR 为 100%，低中等水平 BIM 表达患者的 ORR 为 35.2%（P=0.01）。多变量分析显示，仅厄洛替尼（HR, 0.36; P < 0.0001）和高水平 BIM 表达（HR, 0.55; P=0.03）是 PFS 延长的标记物。在高水平 BIM 表达的患者中，T790M 突变患者的 OS 为 40.1 个月，在低中等水平 BIM 表达的患者中，T790M 突变患者的 OS 为 15.4 个月（P=0.04）。在包括 T790M、TP53 和 EML4-ALK 的多变量分析中，仅高水平 BIM 表达是 OS 延长的标记物（HR, 0.47; P=0.02）。

结论：我们的研究结果可以促使以是否存在 EGFR T790M 突变和 BIM 表达水平为基础的研究设计。目前，我们正在设计一项基于这些研究结果的临床试验。

Background: At the final cutoff of April 2012, in the randomized phase III EURTAC trial, erlotinib improved progression-free survival (PFS) in comparison with chemotherapy as first-line treatment in European p with EGFR-mutation-positive NSCLC (HR, 0.34; P < 0.0001). No differences were observed in overall survival (OS) (22.9 vs 20.8 months [m]).

Methods: We have assessed EGFR T790M and TP53 mutations, the EML4-ALK translocation and BIM mRNA expression in pretreatment tumor samples of 95 p from the EURTAC trial and correlated our findings with outcome.

Results: Concomitant T790M was found in 37.89%, TP53 in 24.21% and EML4-ALK in 15.8% of p. BIM expression was low or intermediate in 55.8% of p and high in 31.6%. 86.7% of the 45 p receiving chemotherapy had crossed over to receive EGFR TKIs at the time of progression. In p treated with erlotinib, overall response rates (ORR) were 87.5% in p with high BIM expression and 34.6% in p with low/intermediate BIM; ORR in the chemotherapy group were 11.1 and 14.2, respectively (P=0.0002). Among p in the erlotinib group without T790M mutations, ORR was 100% for p high BIM expression vs 35.2% for p low/intermediate BIM levels (P=0.01). In the multivariate analysis, only erlotinib (HR, 0.36; P < 0.0001) and high BIM expression (HR, 0.55; P=0.03) were markers of longer PFS. OS for p with T790M mutations was 40.1 m in p with high BIM levels and 15.4 m in p with low/intermediate BIM levels (P=0.04). In the multivariate analysis, including T790M, TP53 and EML4-ALK, only high BIM expression emerged as a marker of longer OS (HR, 0.47; P=0.02).

Conclusions: Our results can lead to the design of studies of treatment based on the presence of the EGFR T790M mutation and BIM expression levels. We are currently designing a clinical trial based on our findings.

1225O 一项厄洛替尼加培美曲塞联合疗法对比厄洛替尼或培美曲塞单药疗法作为不吸烟晚期非鳞非小细胞肺癌（NSCLC）患者的二线治疗的随机 II 期研究

1225O A RANDOMIZED PHASE 2 STUDY OF ERLOTINIB PLUS PEMETREXED VS ERLOTINIB OR PEMETREXED ALONE AS SECOND-LINE TREATMENT FOR NEVER-SMOKER PATIENTS WITH NON-SQUAMOUS ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

D.H. Lee, J.S.Lee, S.-W.Kim, et al.

背景：厄洛替尼（E）和培美曲塞（P）已经被批准用于复发性 NSCLC 患者的二线治疗，并且联合治疗可能有效。本随机 II 期研究对比了 E+P 疗法与两种药物单药治疗作为不吸烟晚期非鳞 NSCLC 患者的二线治疗的有效性和安全性。

方法：2007 年 11 月至 2010 年 7 月，本研究入组了不吸烟、ECOG 体力状态（PS）评分≤2 分且 1 次既往化疗失败的NSCLC患者，并将这些患者随机分配接受：E 150 mg（每日 1 次）或P 500mg/m^2（第 1 天），或P 500 mg/m^2（第 1 天）+E 150 mg（每日 1 次，第 2-14 天；每 21 天为一个疗程），持续治疗至符合停药标准。使用序列分析评估主要研究终点即无进展生存期（PFS）。多元 Cox模型被用来进行总体比较分析，3 个治疗组间两两通过在模型内设定对照进行比较。如果在双侧 0.2 显著性水平（SL）下总体无效假设被否定，则进行 2 组配对检验E+P与E或P。在双侧 0.05 显著性水平下，如果配对比较和总体无效假设都被否定，则可认为具有统计学显著性

结果：共入组了 240 例非鳞 NSCLC 患者（男性，34.6%；东亚裔，55.4%；ECOG PS 评分 0-1，92.9%）。观察到 3 个治疗组间的 PFS 存在统计学显著差异（总体 p=0.003），E+P 组显著优于 2 个单药治疗组[E+P vs E 的 HR（95% CI）为 0.57（0.40, 0.81），p=0.002；E+P vs P 的 HR（95%CI）为 0.58（0.39, 0.85），p=0.005）。E+P 组的中位 PFS（95%CI）为 7.4 个月（4.4, 12.9），E 组为 3.8（2.7, 6.3），P 组为 4.4（3.0, 6.0）。安全性分析表明 E+P 组中发生≥1 例 CTCAE 3/4 级毒性 TEAE 的患者数量（n=45；60.0%）高于 P 组（n=10；28.9%）或 E 组（n=22；12.0%），大部分是中性粒细胞减少症、贫血、皮疹和腹泻。

结论：在临床上选择的人群中，厄洛替尼+培美曲塞联合治疗与 2 种药物的单药治疗相比，显著延长了 PFS。E+P 联合治疗的毒性较高，但都是临床上可控制的。EGFR 突变状态的进一步分析将有助于了解和预测哪类患者从这种联合疗法中获益最多。

Background: Erlotinib (E) and Pemetrexed (P) are approved second-line treatments in patients (pts) with relapsed NSCLC and may be effective in combination. This randomized phase 2 study compared the efficacy and safety of E+P vs either agent alone, as second-line treatment in never-smoker pts with advanced non-squamous NSCLC.

Methods: From Nov 2007 to Jul 2010, never-smoker NSCLC, ECOG Performance Status (PS) ≤2 pts who had failed 1 prior chemotherapy regimen were enrolled and randomized to either**:**E 150mg daily, P 500 mg/m2 day 1, or P 500 mg/m2 day 1 plus E 150mg daily on days 2 to 14 of a 21-day cycle, continued until discontinuation criteria were met. The primary endpoint of progression-free survival (PFS) was analyzed using a sequential approach. A multivariate Cox model was used to perform a global comparison across the 3 arms with pairwise comparisons between treatments using contrasts within the model. If the global null hypothesis was rejected at a 2-sided 0.2 significance level (SL), then 2 pairwise comparisons of E+P vs E or P were conducted. Statistical significance was claimed if both pairwise and global null hypotheses were rejected at a 2-sided 0.05 SL.

Results:A total of 240 non-squamous pts (Male, 34.6%; East Asian, 55.4%; ECOG PS 0-1, 92.9%) were included. A statistically significant difference in PFS was found across the 3 arms (global p=0.003), with E+P significantly better than both single agents (HR (95% CI) for E+P vs E was 0.57 (0.40, 0.81), p=0.002; for E+P vs P was 0.58 (0.39, 0.85), p=0.005). Median PFS (95% CI) was 7.4 months (4.4, 12.9) in E+P, 3.8 (2.7, 6.3) in E and 4.4 (3.0, 6.0) in P. Safety analyses showed a higher number of pts with ≥1 TEAE with CTCAE grade 3/4 toxicity in E+P (n=45; 60.0%) than in P (n=10; 28.9%) or E (n=22; 12.0%), the majority being neutropenia, anemia, rash and diarrhea.

Conclusions: Erlotinib+Pemetrexed significantly improved PFS compared to either agent alone in this clinically selected population. E+P had more toxicity, but was clinically manageable. Further analysis of the EGFR mutational status will help to understand and predict which pts will benefit most from this approach

LBA29　一项对比厄洛替尼（E）与 E 和化疗交替疗法治疗复发性非小细胞肺癌（NSCLC）患者的随机 II 期研究—NVALT10 研究

LBA29　A RANDOMIZED PHASE II STUDY COMPARING ERLOTINIB (E) VERSUS E ALTERNATING WITH CHEMOTHERAPY IN RELAPSED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS. THE NVALT10 STUDY

J.G.Aerts, H.Codrington, S.Burgers, et al.

引言：表皮生长因子受体酪氨酸激酶抑制剂（TKI）与化疗同时用药不能改善临床结果。但是，在临床前模型和早期非对比性研究中，化疗和 TKI 的药效学分离表现出协同效果。

方法：在一线含铂化疗过程中或化疗后发生进展的晚期 NSCLC 患者中进行了一项随机开放性 II 期研究。患者接受了厄洛替尼单药治疗，每日 150 mg（A 组），或者在多西他赛治疗鳞状（SQ）NSCLC 或培美曲塞治疗非鳞状（NSQ）NSCLC 的 4 个疗程（每 21 天为一个疗程）中，在第 2-16 天使用厄洛替尼 150 mg（B 组）。在化疗完成后，继续使用厄洛替尼每日给药方案，直至出现疾病进展。主要终点是无进展生存期（PFS）。次要终点包括毒性和总生存期（OS）。预先计划对 SQ 和 NSQ 进行亚组分析。本研究设计检测进展风险下降 33%的效能为 80%（α=0.05，双侧时序检验）。

结果： 2009 年 3 月至 2011 年 12 月，随机分组 231 例患者，A 组 115 例（42 例 SQ 患者，73 例 NSQ 患者），B 组 116 例（35 例 SQ 患者，81 例 NSQ 患者）。所有患者 PFS 的校正 HR 为 0.80（95%CI 0.60-1.06），p=0.12，OS 的校正 HR 为 0.68（95% CI 0.50-0.94），p=0.02。A 组和 B 组分别有 19%和 55%的患者发生了 3 级以上毒性反应，最常见的毒性反应是皮疹（分别为 7%和 15%）。A 组和 B 组中发热性中性粒细胞减少症的发生率分别为 0%和 6%。

结论：组间的主要终点 PFS 无显著差异。联合用药组的 OS 得到显著改善，而且仅限于非鳞状 NSCLC 患者。

Introduction: Epidermal growth factor receptor tyrosine kinase inhibitors (TKIs) administered concurrently with chemotherapy did not improve outcome. However, in preclinical models and early phase non-comparative studies pharmacodynamic separation of chemotherapy and TKIs did show a synergistic effect.

Methods:A randomized open label phase II study was performed in pts with advanced NSCLC who had progressed on or following first-line platinum containing chemotherapy. Pts received E monotherapy 150 mg daily (Arm A) or E 150 mg from day 2 to 16 of the 21 day cycle during 4 cycles of docetaxel for squamous (SQ) or pemetrexed for non-squamous (NSQ) pts (Arm B). After completion of chemotherapy E was continued as a daily regimen until PD. Primary endpoint is progression-free survival (PFS). Secondary endpoints include toxicity and overall survival (OS). Subgroup analysis for the SQ and NSQ was preplanned. The study was designed with 80% power to detect a 33% decrease in the hazard of progression (alpha=0.05 two sided log rank test).

Results: Between March 2009 and December 2011, 231 patients were randomized, 115 in arm A (42 SQ, 73 NSQ) and 116 in arm B (35 SQ, 81 NSQ). The adjusted HR for PFS for all patients is 0.80 (95% CI 0.60-1.06), p=0.12, for OS 0.68 (95% CI 0.50-0.94), p=0.02. Toxicity gr 3+occurred in 19% (arm A) and 55% (arm B), most frequent rash (7 vs 15%, resp). Febrile neutropenia was 0 vs 6%, resp.

Conclusion:PFS as primary endpoint was not significantly different between arms. OS was significantly improved in the combination arm and was restricted to non squamous histology.

1662P MCPH1 (BRIT1)与厄洛替尼治疗 EGFR 突变的非小细胞肺癌（NSCLC）患者的结局之间的相关性
1662P MCPH1 (BRIT1) AND OUTCOME TO ERLOTINIB IN NON-SMALL-CELL LUNG CANCER (NSCLC) PATIENTS (P) HARBORING EGFR MUTATIONS

M.R.Garcia-Campelo, J.J. Sánchez, C.Costa, et al.

背景：接受厄洛替尼治疗的 EGFR 突变 NSCLC 患者的无进展生存期（PFS）短的达数月，长的可达到 2 年以上，但遗传学对缓解持续时间的影响仍然不清楚。已经证明厄洛替尼的细胞毒性作用与一些调控 DNA 损伤应答的蛋白质（如 BRCA1、BRCA2）有关。MCPH1 包含 3 个 BRCT 结构域，它们存在于参与 DNA 损伤信号传递的重要分子中，包括 BRCA1、MDC1 和 53BP1。MCPH1 与 BRCA2 结合，并且调控 BRCA2 和 Rad51 在 DNA 损伤位点上的定位。MCPH1 在 DNA 修复过程中还可以调控 ATP-依赖性 SWI-SNF 染色质重构复合物。

方法：我们采用 NanoString nCounter 基因表达系统，该系统可捕获单个 mRNA 转录并对其进行计数，对 55 例厄洛替尼治疗的 NSCLC 患者中选择的 44 种基因的表达进行分析，这些基因中许多都参与 DNA 损伤应答。我们观察了 MCPH1 及相关表达水平与临床结果之间的相关性。

结果：患者特征：16 例男性，39 例女性（70.9%）；39 例从未吸烟者（70.9%），12 例曾吸烟者，4 例当前吸烟者；34 例患者 EGFR 基因外显子 19 缺失（61.8%），21 例患者 L858R 突变（38.2%）。高水平 MCPH1 的患者未达到，而中等水平 MCPH1 患者的 PFS 为 19 个月，低水平 MCPH1 患者的 PFS 为 9 个月（P=0.01）。高水平患者的中位生存期为 31 个月，中等水平患者的中位生存期尚未达到，而低水平患者的中位生存期为 17 个月（P=0.004）。

结论：厄洛替尼在高水平 MCPH1 条件下效果增强可能是由于 MCPH1 可干扰 MDC1 和 53BP1 的功能。MCPH1 的这一作用使其可以作为厄洛替尼疗效的预测标记物。

Background: Progression-free survival (PFS) in EGFR-mutant NSCLC p treated with erlotinib can range from a few months (m) to more than two years, but genetic influences on the duration of response remain unclear. The cytotoxic effect of erlotinib has been related to several proteins that regulate DNA damage response (eg, BRCA1, BRCA2). MCPH1 contains 3 BRCT domains which are conserved in important molecules involved in DNA damage signaling, including BRCA1, MDC1 and 53BP1. MCPH1 binds to BRCA2 and regulates the localization of BRCA2 and Rad51 at sites of DNA damage. MCPH1 also regulates the ATP-dependent SWI-SNF chromatin remodeling complex during DNA repair.

Methods: We used the NanoString nCounter gene expression system, which captures and counts individual mRNA transcripts, to analyze the expression of 44 selected genes, many of which are involved in DNA damage response, in 55 erlotinib-treated NSCLC p. We identified MCPH1 and correlated expression levels with clinical outcomes.

Results:p characteristics**:**16 males, 39 females (70.9%); 39 never-smokers (70.9%), 12 former smokers, 4 current smokers; 34 with EGFR deletion in exon 19 (61.8%), 21 with L858R mutation (38.2%). PFS was not reached for patients with high MCPH1, while it was 19m for those with intermediate levels and 9m for those with low levels (P=0.01). Median survival was 31m for p with high levels, not reached for p with intermediate levels and 17 m for p with low levels (P=0.004).

Conclusions: The enhanced effect of erlotinib in the presence of elevated MCPH1 could be due to the fact that MCPH1 can interfere with the function of MDC1 and 53BP1. The role of MCPH1 merits validation as a predictive marker of erlotinib response.

1282P　TOPICAL：厄洛替尼与安慰剂相比治疗不适合一线化疗的晚期非小细胞肺癌（NSCLC）患者的随机 III 期试验：更新分析

1282P　TOPICAL:RANDOMIZED PHASE III TRIAL OF ERLOTINIB COMPARED WITH PLACEBO IN PATIENTS WITH ADVANCED NON–SMALL CELL LUNG CANCER (NSCLC) UNSUITABLE FOR FIRST-LINE CHEMOTHERAPY:UPDATED ANALYSIS

S.-M.Lee1, S.Upadhyay, C.Lewanski1,et al.

背景：尽管推荐使用含铂化疗方案治疗晚期 NSCLC，但是大部分这类患者由于体力状态较差或患有多种并发症，只能接受积极的支持性疗法（ASC）。我们之前已经证明了厄洛替尼可显著改善这类患者的 PFS，但对于女性患者而言，OS 和 PFS 效果更强。在此，我们报告了完善的 OS 数据，包括与第一治疗周期出现皮疹（FCR）的相关性。

方法：670 例 IIIB/IV 期 NSCLC 患者（ECOG PS 评分 2/3 或 0/1，伴有多种并发症、不适合化疗）随机接受安慰剂（n=320）或厄洛替尼 150 mg/天（n=350）和 ASC，持续到出现疾病进展/毒性。评估 OS、PFS、不良事件和 OoL。预先设定的亚组分析包括开始治疗 28 天内发生的厄洛替尼相关性皮疹（FCR）和 EGFR（如果可行）。

结果：在主要是老年 NSCLC 患者的人群中，基线特征分布均衡（中位年龄=77 岁，范围：42-91 岁）。在所有患者中，OS 的风险比（HR）为 0.94（95% CI 0.81-1.10, P=0.46）。接受厄洛替尼治疗患者的 PFS 较佳，HR=0.83（95% CI 0.71-0.97, P=0.02）。厄洛替尼治疗组中 59%的患者出现了 FCR。在一项包含皮疹、年龄、性别、组织学、ECOG 评分和疾病分期的多变量分析中，FCR 是唯一可预测 OS 的独立因子（HR=0.17; P=0.02）。与安慰剂相比，厄洛替尼治疗在 OS（HR=0.76, 95% CI 0.63-0.92, P=0.01）和 PFS（HR=0.66, CI 0.54-0.80, P < 0.01）方面都有收益。在所有亚组中都观察到这些益处，包括 PS 评分最差（ECOG 3）的患者亚组，OS HR=0.58 和 PFS HR=0.41；以及 IV 期患者，OS HR=0.66 和 PFS=0.56。OS 中位值分别为 6.2 个月（厄洛替尼组出现皮疹患者）、2.9 个月（无皮疹）和 4.1 个月（安慰剂）。连续厄洛替尼治疗但未发生皮疹可能与一些亚组（如男性、ECOG 3）中 OS 恶化有关。390 例患者可获得 EGFR 和 KRAS 突变的结果。7%（27/390）的患者发生 EGFR 活化突变；不论 EGFR 状态如何，都观察到厄洛替尼的益处。KRAS 突变（19%，73/390）不能表示预后和预测厄洛替尼的益处。厄洛替尼组中 3/4 级腹泻更为常见（8.4% vs. 1.3%, p < 0.001）；治疗组间其他不良事件的发生率相似。

结论：厄洛替尼延长了不适合化疗的晚期 NSCLC 患者的 PFS 和 OS，但仅在出现 FCR 的患者中。

Background: Despite the recommendation to treat advanced NSCLC with platinum-based chemotherapy, the majority of these pts receive only active supportive care (ASC) because of poor performance or multiple co-morbidities. We previously showed that erlotinib significantly improved PFS in such patients, but with an enhanced OS and PFS effect in female pts. Here, we report mature OS data including the association of first-cycle rash (FCR).

Methods:670 pts with stage IIIB/IV NSCLC (ECOG PS 2/3 or PS 0/1 with multiple co-morbidities unsuitable for chemotherapy) were randomized to receive placebo (n=20) or erlotinib 150mg/day (n=350) and ASC until disease progression/toxicity. OS, PFS, adverse events, and QoL were examined. Pre-specified subgroup analyses included erlotinib-rash ≤28 days of starting treatment (FCR), and EGFR where available.

Results: Baseline characteristics were well balanced in these predominantly elderly NSCLC pts (median=77 yrs, range 42-91). Among all pts, the hazard ratios (HRs) were 0.94 (95% CI 0.81-1.10, P=0.46) for OS. Pts receiving erlotinib had a better PFS, HR=0.83 (95% CI 0.71-0.97, P=0.02). 59% of pts on erlotinib developed FCR. FCR was the only independent factor predictive of OS (HR=0.17; P=0.02) in a multivariate analysis containing rash, age, gender, histology, ECOG score and stage. There was a benefit for both OS (HR=0.76, 95% CI 0.63-0.92, P=0.01) and PFS (HR=0.66, CI 0.54-0.80, P<0.01), compared to placebo. The benefits were seen in all the subgps including those with the worst PS score (ECOG 3); OS HR=0.58 and PFS HR=0.41 & stage IV; OS HR=0.66 and PFS=0.56. The OS medians (months) were 6.2 (erlotinib-rash), 2.9 (no rash) and 4.1 (placebo). Continuous erlotinib, without rash, appeared to be associated with worse OS in some subgroups (e.g. males, ECOG 3). Results for EGFR and KRAS mutations are available on 390 pts. 7% (27/390) of pts had activating EGFR mutation; the benefits of erlotinib were seen regardless of EGFR status. KRAS mutations (19%, 73/390) were neither prognostic nor predictive of erlotinib benefit. Grade 3/4 diarrhea was more common with erlotinib (8.4% vs. 1.3%, p<0.001); other adverse events were similar between groups.

Conclusions: Erlotinib prolongs PFS and OS in patients with advanced NSCLC considered unsuitable for chemotherapy, but only if they develop FCR.

1265P 酪氨酸激酶抑制剂与化疗一线治疗相比对 EGFR 突变的晚期非小细胞肺癌（NSCLC）患者的生存是否有益？一项荟萃分析

1265P IS THERE A BENEFIT ON SURVIVAL OF TYROSINE-KINASE INHIBITORS VERSUS CHEMOTHERAPY IN FIRST LINE IN MUTATED EGFR PATIENTS WITH ADVANCED NON-SMALL CELL CANCER (NSCLC)? A META-ANALYSIS

G.Des Guetz1, B.Uzzan1, K.Chouahnia1, et al.

背景：酪氨酸激酶抑制剂（TKI）显著改善了表皮生长因子受体（EGFR）突变的晚期 NSCLC 患者的无进展生存期（PFS）。关于总生存期（OS）的结果尚存有疑问。因此，我们进行了一项基于文献的荟萃分析，进一步对该问题进行评估。

方法：我们同时使用了多个关键词（肺癌、TKI、EGFR 突变、生存期）在 PubMed 中进行检索。我们还在 ASCO、ESMO、WCLC 年会的会议录中检索了相关的摘要。我们反复核对了来源于所有论文的参考文献。仅纳入了对比 TKI 和化疗的 III 期随机对照试验。我们使用了 EasyMA 软件。

结果：6 项合格研究共入组 2223 例患者（516 例男性，1688 例女性，大部分是亚洲患者，中位年龄 60 岁，2155 例腺癌患者（97%），996 例突变肿瘤，389 例 IIIB 期患者，1572 例 IV 期患者（71%），1989 例从未吸烟者（89.5%））。4 项研究评估了吉非替尼，2 项研究评估了厄洛替尼。化疗是包含铂盐的双药标准化疗。4 项研究仅入组了突变的患者。与化疗相比，EGFR TKI 显著改善了 PFS（HR=0.39，95 % CI 0.28-0.53，随机效应模型）。相反地，一线治疗首选 TKI 或化疗的患者的 OS 相似（HR=1.00，CI 0.83-1.22，固定效应模型）。在 2 项入组突变和野生型 EGFR 患者的研究中，未突变患者的 PFS 显著缩短，而 OS 未发生变化。在副作用方面，TKI 治疗后皮疹、腹泻和间质性肺病的发生率显著较高（RR 分别为 5.00、2.40 和 6.07）。与预期结果一样，化疗后疲劳（RR=0.41）、恶心/呕吐（RR=0.19）和血液学病症的发生率（中性粒细胞减少症、血小板减少症和贫血的 RR 分别为 0.08、0.18 和 0.26）都显著较高。

结论：TKI 治疗与化疗相比显著改善的 PFS，但 OS 结果无明显差别的原因可能与 2 组间后续治疗的交叉有关。我们发现在野生型患者中，TKI 对 OS 没有不利影响。

Background: Tyrosine-Kinase Inhibitors (TKIs) markedly improve Progression Free Survival (PFS) of advanced NSCLC patients mutated for Epidermal Growth Factor Receptor (EGFR). Results on Overall Survival (OS) are more questionable. Therefore, we performed a publication-based meta-analysis to further assess this issue.

Methods: We did a PubMed query using keywords simultaneously (lung neoplasm, TKI, EGFR mutation, survival). We also searched for relevant abstracts in proceedings of ASCO, ESMO, WCLC annual meetings. We cross-checked all references from all articles. Only phase III randomized controlled trials comparing TKI and chemotherapy were included. We used EasyMA software.

Results: The 6 eligible studies included 2223 patients (516 males, 1688 females, mostly Asian, median age 60 years, 2155 adenocarcinomas (97 %), 996 mutated tumors, 389 stage IIIB, 1572 Stage IV (71 %), 1989 never smokers (89.5 %). Four studies assessed gefitinib, 2 erlotinib. Chemotherapies were doublets including a platinum salt. Four studies included only mutated patients. Compared to chemotherapy, EGFR TKIs significantly improved PFS (HR=0.39, 95 % CI 0.28-0.53, random effect model). Conversely, OS was similar among patients who first received TKI or chemotherapy (HR=1.00, CI 0.83-1.22, fixed effect model). PFS was significantly worse among non mutated patients in the 2 studies including both mutated and wild-type EGFR patients, whereas OS was unchanged. Concerning side-effects, rash, diarrhoea and interstitial lung disease were significantly more frequent after TKI (RRs 5.00; 2.40 and 6.07). As expected, fatigue (RR 0.41), nausea/vomiting (0.19) and haematological disorders were all significantly more frequent after chemotherapy (RRs for neutropenia, thrombocytopenia and anaemia 0.08; 0.18 and 0.26).

Conclusions: The major discrepancy between a markedly improved PFS and a similar OS after TKI compared with chemotherapy could be related to the high level of crossing-over between the 2 groups. We found no detrimental effect on OS of TKIs among wild-type patients.

1307P 厄洛替尼治疗对 K-RAS 野生型肺腺癌的有效性—— 一项匈牙利观察性队列研究的结果（激发）

1307P EFFECTIVENESS OF ERLOTINIB TREATMENT IN K-RAS WILD TYPE LUNG ADENOCARCINOMAS –RESULTS OF A HUNGARIAN OBSERVATIONAL COHORT STUDY (MOTIVATE)

G.Ostoros1, V.Sárosi, G.Losonczy1, et al.

背景：作为靶向治疗的厄洛替尼是一种表皮生长因子受体酪氨酸激酶活性的强效抑制剂。K-RAS 突变见于 25%-35%的肺腺癌，而且这些突变可能预示着对厄洛替尼治疗的耐药性。我们分析的目的是前瞻性地研究厄洛替尼二线和三线治疗对除外 K-RAS 突变阳性的晚期肺腺癌患者的有效性和安全性。

材料和方法：这项观察性研究在 27 个匈牙利研究中心进行。入组患者都接受了厄洛替尼治疗。接受分析的患者都患有组织学上或细胞学确诊的晚期（IIIB/IV 期）、K-RAS（密码子-12，密码子-13）突变阴性且既往至少一种化疗难治的肺腺癌。主要终点是无进展生存期。次要终点是基于 RECIST 标准的最佳肿瘤缓解率、总生存期和安全性。

结果：对 2008 年 2 月至 2010 年 12 月入组的 327 例患者进行分析。本研究的结束日期为 2011 年 12 月 31 日。患者基线特征为：中位年龄：60.3 岁；男性：50.2%；疾病分期：IIIB 期：31.1%，IV 期：68.9%；吸烟状态：曾吸烟者/当前吸烟者/从未吸烟者：39.1%/28.8%/31.9% 。 ECOG PS 评分：0/1/2/3：35.9%/51.8%/11%/1.2%。最佳肿瘤缓解：达到 CR/PR/SD/PD 分别占所有患者的 0.9%/16.2%/41.9%/24.5%。在获得最佳缓解数据的患者中，疾病控制率为 70.48%。中位无进展生存期（PFS）为 3.27 个月。中位总生存期为 14.1 个月。ECOG PS 评分 0-1 的患者，中位 OS 为 16.1 个月，中位 PFS 为 3.47 个月，而 ECOG PS 评分 2-3 的患者，中位 OS 为 2.5 个月，中位 PFS 为 1.9 个月。

结论：我们的结果确认了厄洛替尼对 K-RAS 突变阴性肺腺癌的的疗效，而且是在真实临床实践条件下，OS 为 14.1 个月。在接受厄洛替尼治疗的 ECOG PS 评分 0-1 的患者中，观察到显著的中位 OS 为 16.1 个月。

Background: Erlotinib as a targeted therapy is a highly potent inhibitor of epidermal growth factor receptor tyrosine-kinase activity. K-RAS mutations are found in 25-35% of lung adenocarcinomas, and these mutations may be predictive of resistance to treatment with erlotinib. The aim of our analysis was to investigate prospectively the efficacy and safety of second and third line erlotinib treatment in advanced lung adenocarcinoma excluding the K-RAS mutation positive cases.

Materials and methods: This observational study was conducted in 27 Hungarian sites. Enrolled patients were treated with erlotinib. Analyzed patients have histologically or cytologically verified, advanced (IIIB/IV), K-RAS (codon-12, codon-13) mutation negative lung adenocarcinoma, refractory to at least one prior chemotherapy. Primary endpoint was progression-free survival. Secondary endpoints were best tumor response rate according to RECIST, overall survival and safety.

Results:327 patients' data were analyzed, who were enrolled between February 2008 and December 2010. The study closure date was 31. December 2011. Baseline patients' characteristics**:**median age**:**60,3 years; male**:**50,2%; stage**:**III/B**:**31,1%, IV**:**68,9%; smoking status**:**former/current/never smoker**:**39,1/28,8/31,9%. ECOG PS**:**0/1/2/3**:**35,9/51,8/11/1,2%. Best tumor response**:**CR/PR/SD/PD were achieved**:**0,9/16,2/41,9/24,5 % of all patients. The disease control rate was 70,48% in patients for whom the best response data were available . The median progression-free survival (PFS) was 3.27 months. The median overall survival was 14,1 months. For ECOG PS 0-1 patients, the median OS was 16,1 months and the median PFS was 3,47 months, while median OS of 2.5 and median PFS of 1,9 months were detected for ECOG PS 2-3 patients.

Conclusions: Our results confirm the favorable efficacy of erlotinib in K-RAS mutation negative lung adenocarcinoma with an OS of 14,1 months in this real-life setting. A remarkable, 16.1 months median OS was identified in patients with ECOG PS 0-1 receiving erlotinib.

1277P　III 期临床研究 BR.21 和 SATURN 中，厄洛替尼治疗鳞状非小细胞肺癌（NSCLC）与非小细胞肺腺癌的有效性和安全性的比较

1277P　COMPARATIVE EFFICACY AND SAFETY OF ERLOTINIB IN NON-SMALL CELL LUNG CANCER (NSCLC) OF SQUAMOUS CELL AND ADENOCARCINOMA HISTOLOGY IN THE PHASE III NCIC CTG BR.21 AND SATURN (BO18192) TRIALS

S.Wojtowicz-Praga, L.Leon South San Francisco, CA/US

背景：鳞状细胞癌（SC）占肺癌患者的 25%–30%，在有吸烟史的患者中更为多见。厄洛替尼是一种口服 EGFR TKI，已经证实在 NSCLC 一线（1L）维持治疗（SATURN; Cappuzzo, Lancet Oncol 2010）和二线或三线治疗（2L/3L）（BR-21; Shepherd, NEJM 2005）中，厄洛替尼与安慰剂相比可以延长无进展生存期（PFS）。在此回顾性分析这些关键性研究的数据，对比鳞状细胞癌患者与非小细胞肺腺癌（AD）患者的生存结果。

方法：BR.21 研究按照 2:1 比例将 1L 或 2L 化疗后进展的 ECOG PS 评分 0–3 的晚期 NSCLC 患者随机分组接受厄洛替尼（每日 150mg）或安慰剂治疗。SATURN 研究按照 1:1 比例将 1L 化疗后未进展的 ECOG PS 评分 0–1 的晚期 NSCLC 患者随机分组接受厄洛替尼（每日 150mg）或安慰剂维持治疗。使用 Kaplan-Meier 方法评估 PFS 和总生存期（OS），使用 Cox 回归分析计算风险比（HR）。

结果：在 BR.21 和 SATURN 研究中，分别有 587 例和 763 例患者可用于评估。在两项研究中，SC 患者中吸烟者（当前吸烟者或曾吸烟者）和男性的比例高于 AD 患者，SC 组和 AD 组间的其他大部分基线特征都相似。有效性和安全性结果见下表。在一个根据 SC 和 AD 组织学分类分析不同治疗方法对生存期影响的相互作用模型中，BR.21 研究中 PFS 和 OS 的 P 值分别>0.65 和>0.45，在 SATURN 研究中 PFS 的 P 值>0.2，表明治疗效果无统计学显著性差异。

结论：两项大型关键性研究数据的分析表明，在 SC 和 AD 组织学亚组中，都观察到厄洛替尼的显著生存获益，支持了在一线维持治疗及二线和三线治疗中，厄洛替尼对 SC NSCLC 患者的有效性。

Background: Tumors of squamous cell (SC) histology are present in 25–30% of lung cancer patients (pts), and are more frequent in pts with a history of smoking. Erlotinib is an oral EGFR TKI shown to prolong progression-free survival (PFS) compared with placebo in first-line (1L) maintenance (SATURN; Cappuzzo, Lancet Oncol 2010) and second- or third-line (2L/3L) NSCLC settings (BR-21; Shepherd, NEJM 2005). Data from these pivotal studies were retrospectively analyzed to compare outcomes for pts with tumors of SC histology with those of pts diagnosed with adenocarcinomas (AD).

Methods:BR.21 randomized ECOG PS 0–3 pts with advanced NSCLC who progressed after 1L or 2L chemotherapy 2:1 to erlotinib (150 mg daily) or placebo. SATURN randomized ECOG PS 0–1 pts with advanced NSCLC who did not progress after 1L chemotherapy 1:1 to maintenance therapy with erlotinib (150 mg daily) or placebo. PFS and overall survival (OS) were estimated using Kaplan-Meier methods. Hazard ratios (HRs) were calculated using Cox regression analysis.

Results:587 and 763 pts were evaluable in BR.21 and SATURN, respectively. A higher percentage of SC pts were smokers (current or ex-) and males versus AD pts in both studies. Most other baseline characteristics were similar between histology groups within each study. Efficacy and safety outcomes are shown (Table). In an interaction model analyzing for differential treatment effects on survival by SC and AD histology, P-values were >0.65 and >0.45 for PFS and OS in BR.21, respectively, and >0.2 for PFS in SATURN, providing no evidence for a statistically significant differential effect.

Conclusions: Analyses of data from two large pivotal trials associated erlotinib treatment with significant survival benefit in both SC and AD histology subgroups, supporting its efficacy in pts with SC NSCLC in the 1L maintenance, 2L, and 3L settings.

评估/Measure	安慰剂组/Placebo arm	厄洛替尼组/Erlotinib arm	HR (95% CI)
BR.21 (N=587)			
3-5 级不良事件，n (%)/Grade 3–5 adverse events, n (%)			
AD (n=365)	75 (63)	148 (60)	–
SCC	56 (72)	109 (76)	–
中位 PFS，月/Median PFS, mo			
AD	1.84	2.37	0.62 (0.49–0.79)
SCC	1.81	2.27	0.48 (0.35–0.67)
中位 OS，月/Median OS, mo			
AD	5.36	7.75	0.76 (0.58–0.98)
SCC	3.58	5.57	0.60 (0.44–0.82)
SATURN (N=763)			
3-5 级不良事件，n (%)/Grade 3–5 adverse events, n (%)			
AD (n=403)	27 (14)	59 (29)	–
SCC (n=360)	23 (12)	41 (25)	–
中位 PFS，月/Median PFS, mo			
AD	2.60	2.83	0.63 (0.51–0.78)
SCC	2.60	3.02	0.77 (0.61–0.96)

1236PD　贝伐珠单抗联合化疗作为晚期非鳞非小细胞肺癌（NS-NSCLC）一线治疗的 II 期研究（ABIGAIL）中，肿瘤生物标记物与血浆时相数据

1236PD　TUMOUR BIOMARKER AND PLASMA TIME COURSE DATA FROM ABIGAIL, A PHASE II STUDY OF 1ST-LINE BEVACIZUMAB+CHEMOTHERAPY IN ADVANCED NON-SQUAMOUS NON-SMALL-CELL LUNG CANCER (NS-NSCLC)

M. Reck, V.A.Gorbunova, E.Juhasz, et al.

背景：BO21015 (NCT00700180)是一项在未接受过化疗的晚期/复发性NSCLC患者中探索生物标记物（BM）与贝伐珠单抗+卡铂/吉西他滨（CG）或卡铂/紫杉醇（CP）治疗后的最佳总缓解率（BOR）之间相关性的II期、随机、多中心研究。之前已经报告了有效性、安全性及 7 种血浆BM（bFGF、E-选择素、ICAM、PLGF、VEGFA、VEGFR-1 和VEGFR-2）基线值（BL）与BOR和无进展生存期（PFS）之间的相关性[1]。本摘要报告肿瘤组织、血浆时相和临床结果的BM分析。

方法：按照 1:1 的比例将 303 例合格患者随机分组接受贝伐珠单抗 7.5 mg/kg或 15 mg/kg治疗，直至疾病进展（PD）或出现不可耐受的毒性（根据研究者的选择，同时接受 6 个周期CG或CP）。签署知情同意书的患者提供用于BM分析的血样[1]和肿瘤标本。预先设定的探索性分析评估了血浆BM基线值与总生存期（OS）之间的相关性，及血浆BM水平从基线期至PD、第 2 个周期、第 4 个周期和第 6 个周期的变化。用ELISA法测定血浆BM水平；对 5 种肿瘤BM（VEGFR-1、MVD、VEGFA、VEGFR-2 和NRP1）的IHC分析结果与BOR、PFS和OS及血浆BM基线水平之间的相关性进行评估。

结果：根据基线期预后因子调整且包含多重检验的进一步探索性分析表明，高水平的 VEGFA 基线值（中位值为 3）与较短的 OS（n=280; 19.8 个月 vs 11.1 个月; p=0.0042）存在相关性。其他血浆 BM 基线值与 OS 没有相关性。对于所有 BM，未观察到基线与 PD、和/或第 2 个周期、第 4 个周期或第 6 个周期的血浆 BM 水平之间有显著的变化。唯一的肿瘤和血浆标记物之间的相关性是肿瘤 VEGFR1 表达和 VEGFA 血浆 BL 的相关性（p=0.025, 0.26）。未观察到肿瘤 BM 水平与 BOR、PFS 或 OS 之间的显著相关性。

结论：探索性分析表明，高水平的血浆 VEGFA 基线值与较短的 OS 之间存在显著的相关性，与之前报告的 PFS 数据一致。其他血浆 BM 基线值与 OS 之间都没有相关性。血浆 VEGFA 基线水平与肿瘤 VEGFR1 表达之间存在相关性。所有研究的肿瘤 BM 与临床结果之间都没有显著的相关性。

Background:BO21015 (NCT00700180) is a phase II, randomized, multicentre study exploring correlation between biomarkers (BMs) and best overall response (BOR) to bevacizumab with carboplatin/gemcitabine (CG) or carboplatin/paclitaxel (CP) in chemonaïve patients with advanced/recurrent NSCLC. Efficacy, safety and correlation of 7 baseline (BL) plasma BM (bFGF, E-selectin, ICAM, PLGF, VEGFA, VEGFR-1 and VEGFR-2) with BOR and progression-free survival (PFS) have been reported.[1] This abstract presents BM analysis for tumour tissue, plasma time course and clinical outcome.

Methods:303 eligible patients were randomized 1:1 to receive bevacizumab 7.5mg/kg or 15mg/kg until disease progression (PD) or unacceptable toxicity (with 6 cycles of CG or CP, at investigators' discretion). Consented patients provided blood[1] and tumour samples for BM analysis. Pre-specified exploratory analyses examined correlation between BL plasma BM and overall survival (OS) and changes in plasma BM levels from BL to PD, cycles 2, 4 and 6. Plasma BM levels were measured by ELISA. IHC analyses of 5 tumour BMs (VEGFR-1, MVD, VEGFA, VEGFR-2 and NRP1) were assessed for correlation with BOR, PFS and OS, and with BL plasma BM levels.

Results: Further exploratory analyses adjusting for BL prognostic factors and accounting for multiple testing showed a correlation of high BL VEGFA levels (3median) with shorter OS (n=280; 19.8 vs 11.1 mos; p=0.0042). No other BL plasma BMs correlated with OS. No significant changes in plasma BM levels were seen between baseline and PD, and/or cycles 2, 4 or 6 for any of the BMs. The only correlation between tumour and plasma markers was for tumour VEGFR1 expression and VEGFA plasma BL (p=0.025, 0.26). No significant correlation was seen between tumour BM level and BOR, PFS or OS.

Conclusions: Exploratory analysis showed high plasma BL VEGFA significantly correlated with shorter OS, consistent with previously reported data on PFS. No other BL plasma BMs correlated with OS. BL plasma VEGFA levels correlated with tumour VEGFR1 expression. None of the investigated tumour BMs significantly correlated with clinical outcome.

1235PD PARAMOUNT：晚期非鳞（NS）非小细胞肺癌患者在培美曲塞（PEM）+顺铂（CIS）诱导治疗后接受 PEM 维持治疗或安慰剂（PLB）治疗的 III 期研究的最终总生存期结果（OS）的描述性亚组分析

1235PD PARAMOUNT:DESCRIPTIVE SUBGROUP ANALYSES OF FINAL OVERALL SURVIVAL (OS) FOR THE PHASE III STUDY OF MAINTENANCE PEMETREXED (PEM) VERSUS PLACEBO (PLB) FOLLOWING INDUCTION TREATMENT WITH PEM PLUS CISPLATIN (CIS) FOR ADVANCED NONSQUAMOUS (NS) NON-SMALL CELL LUNG CANCER

M.Reck, L.Paz-Ares, F.De Marinis, et al.

背景：PARAMOUNT 证实了在晚期 NS NSCLC 患者中培美曲塞继续维持治疗与安慰剂相比显著降低了疾病进展（HR=0.62）和死亡（HR=0.78）的风险。预先计划的根据基线特征的亚组分析表明 OS 结果是一致的，在所有亚组中都观察到获益。在此报告最终 OS 数据的描述性亚组分析。

方法：939 例患者接受了诱导治疗（4 个周期的PEM 500 mg/m^{2}和 CIS 75 mg/m^2，第 1 天给药，每 21 天为一个周期）；之后，未出现进展且ECOG体力状态（PS）评分为 0/1 分的 539 例患者被随机分组（2:1）接受PEM维持治疗（500 mg/m^2，第 1 天给药，每 21 天为一个周期）或安慰剂治疗，持续至疾病进展。所有患者都接受了维生素B12、叶酸和地塞米松治疗。

结果：各组之间的患者特征分布均衡。下表概述了随机分组后生存 6-24 个月的 PEM 组患者的基线特征。生存时间较长的患者与生存时间较短的患者特征相似，表明接受维持治疗的所有亚组患者都有 OS 获益。PS 是已知的预后因子，是唯一与 OS 改善相关的基线特征。在 PEM 组中，诱导治疗后实现完全/部分（CR/PR）缓解与疾病稳定（SD）的患者比例随时间变化而保持稳定。另一项分析显示，肿瘤缩小的百分比与最终 OS 之间没有相关性（rho <0.1），表明诱导治疗阶段的的肿瘤缓解不是 OS 的指标。

结论：在 PARAMOUNT 研究中，所有亚组中都观察到 OS 获益。除 PS 之外，没有其他基线值或临床参数明确表明某一亚组更有可能获益。应该根据个体患者的具体情况决定是否给予维持治疗。

Background:PARAMOUNT demonstrated that pem continuation maintenance significantly reduced the risk of disease progression (HR=0.62) and death (HR=0.78) versus plb in patients (pts) with advanced NS NSCLC. Preplanned subgroup analyses by baseline characteristics revealed the OS results were consistent, with benefit seen across all subgroups. Here we present descriptive subgroup analyses of the final OS data.

Methods:939 pts received induction therapy (4 cycles pem 500mg/m^2 and cis 75mg/m^2 on day 1 of 21-day cycles), after which 539 pts who had not progressed and had an ECOG performance status (PS) of 0/1 were randomized (2:1) to maintenance pem (500 mg/m2, on day 1 of 21-day cycles) or plb until disease progression. All pts received vitamin B12, folic acid, and dexamethasone.

Results: Pt characteristics were well balanced between arms. The table summarizes baseline characteristics for pts on the pem arm surviving 6-24 months after randomization. Characteristics of pts surviving for longer periods were comparable to those of pts surviving shorter periods, suggesting OS benefit for all subgroups of pts on maintenance therapy. PS, a known prognostic factor, was the only baseline characteristic associated with improved OS. On the pem arm, the percentage of pts with an induction response of complete/partial (CR/PR) versus stable disease (SD) was consistent over time. An additional analysis showed no correlation between the percent of tumor shrinkage with final OS (rho <0.1), showing that tumor response to induction is not an indicator of OS.

Conclusions: In PARAMOUNT, the OS benefit was seen across all subgroups. Other than PS, no baseline or clinical parameter clearly identifies a subgroup more likely to benefit. Maintenance treatment decisions should be made on an individual basis

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	基线/baseline	生存期超过以下时间患者的基线特征/ Baseline characteristics for pts surviving at least			
		6 个月/6 mos	12 个月/ 12 mos	18 个月/ 18 mos	24 个月/ 24 mos
培美曲塞组患者/Pemetrexed Arm Pts					
中位年龄，岁/Median age, yrs	61	61	62	62	63
年龄<65 岁，%患者/Age <65, % pts	66	65	62	62	61
男性，%患者/Male, % pts	56	55	54	47	49
高加索人，%患者/Caucasian, % pts	94	95	96	96	96
吸烟者，%患者/Smoker, % pts					
曾吸烟者/Ever smoker	76	72	69	66	68
从未吸烟者/Never smoker	23	27	30	33	30
ECOG PS 评分，% 患者/ECOG PS, % pts					
0	32	39	42	46	53
1	68	61	59	54	47
IV 期，%患者/Stage IV, % pts	91	92	92	92	90
组织学，%患者/Histology, % pts					
腺癌/Adenocarcinoma	86	89	89	88	89
大细胞/Large cell	7	6	7	7	6
诱导治疗后缓解，%患者/Induction response, % pts					
CR/PR	44	44	45	48	47
SD	53	55	54	50	51
PD/未知 / PD/Unknown	3	1	2	2	3
安慰剂组患者/Placebo Arm Pts					
诱导治疗后缓解，%患者/Induction response, % pts					
CR/PR	42	40	42	49	52
SD	53	55	54	47	44
PD/未知 / PD/Unknown	6	5	4	4	4

1194P 非小细胞肺癌（NSCLC）II 期研究 INNOVATIONS 中，组织和血清生物标记物结果

1194P TISSUE AND SERUM BIOMARKER RESULTS FROM THE PHASE II INNOVATIONS STUDY IN NON-SMALL CELL LUNG CANCER (NSCLC)

N.Reinmuth, S.J.Schere, R.Penzel,et al.

背景：II期研究INNOVATIONS是一项入组了 224 例晚期非鳞NSCLC患者的随机试验，这些患者接受了厄洛替尼（E）+贝伐珠单抗（B）或顺铂（P）+吉西他滨（G）+B一线治疗。在无进展生存期（PFS）方面，PGB优于EB。EGFR突变阳性的NSCLC患者最有可能从EB治疗中获益[1]。本摘要报告了可选性生物标记物（BM）亚组研究中的探索性分析，这些候选BM在之前贝伐珠单抗治疗NSCLC的试验中经常被研究。

方法：通过免疫组织化学 H 评分测定组织（t）标记物；在第 0 天和第 43 天，使用一种新型蛋白质芯片法/ELISA 法对血清（s）标记物进行分析。以中位基线值将患者分为两个组（低水平与高水平 BM），并且确定 BM 与 PFS/总生存期（OS）的相关性（Cox 模型）。未针对多重检验对分析进行校正。

结果：BM 人群代表 88%的意向性治疗人群；基线特征分布均衡。提供组织样本（n=198）和血清样本（第 0 天，n=184；第 43 天，n=151）进行 BM 分析；未对可溶性 VEGFA 进行评估；仅收集血清样本。血清分析显示：基线 IL8（HR=0.55，$p < 0.05$）和 FLT4（HR=0.50，$p < 0.05$）低水平的 BM 人群的 PFS 较长；EB 治疗组和 PGB 治疗组的趋势一致。第 43 天分析的结果（PFS/OS）相似。基线 FLT1 低水平与 PGB 患者较长的 PFS 有关（HR=0.53，$p < 0.05$）。ICAM 低水平与较好的临床结果（PGB 组）有关。组织分析显示：所检验的 3 个肿瘤标记物都未表现出与 PFS/OS 的显著相关性（$p>0.05$）。观察到以下肿瘤或血清标记物之间存在显著的相关性（$p < 0.05$）：tVEGFR1 和 tVEGFR2/tVEGF；tVEGFR2 和 tVEGF；sFLT1 和 sTie2；sKDR 和 sICAM；sFLT4 和 sICAM。

结论：一些血清基线候选 BM 表现出与 OS/PFS 具有统计学意义的相关性，尤其是 FLT4/IL8。贝伐珠单抗联合药物（E/PG）的选择可能会影响 BM 值。对本研究和其他贝伐珠单抗研究数据的进一步评估可提供进一步的认识。

Background: The phase II INNOVATIONS study was a randomised trial of 224 patients (pts) with advanced non-squamous NSCLC who received 1st-line treatment with either erlotinib (E) plus bevacizumab (B) or cisplatin (P) plus gemcitabine (G) plus B. PGB was superior to EB for progression-free survival (PFS). Pts with EGFR mutation-positive NSCLC were most likely to benefit from EB [1]. This abstract reports exploratory analyses from the optional biomarker (BM) sub-study for a number of candidate BMs commonly examined in previous NSCLC bevacizumab trials.

Methods: Tissue (t) markers were determined by immunohistochemistry H-score. Serum (s) markers were analysed on day 0 and 43 using a novel protein array/ELISA. Median baseline values were used to dichotomise pts (low vs high BM) and to correlate BMs with PFS/overall survival (OS) (Cox model). Analyses were not adjusted for multiple testing.

Results:BM population represented 88% of the intent-to-treat population; baseline characteristics were well balanced. Tissue (n=198) and serum samples (day 0, n=184; day 43, n=151) were provided for BM analysis. Soluble VEGFA was not assessed; only serum samples were available. Serum analyses**:**PFS was longer for the BM population with low baseline IL8 and FLT4 (HR=0.55, $p<0.05$ and HR=0.50, $p<0.05$, respectively); the trend was consistent in EB and PGB treatment arms. Similar results were seen for day 43 analyses (PFS/OS). Low baseline FLT1 was associated with longer PFS in PGB pts (HR=0.53, $p<0.05$). Low ICAM levels were associated with better clinical outcomes (PGB arm). Tissue analyses**:**None of the three tumour markers tested showed significant association with PFS/OS ($p>0.05$). Significant correlations ($p<0.05$) were observed between tumour and serum markers**:**tVEGFR1 and tVEGFR2/tVEGF; tVEGFR2 and tVEGF; sFLT1 and sTie2; sKDR and sICAM; sFLT4 and sICAM.

Conclusion: Several serum baseline candidate BMs showed a statistically significant correlation with OS/PFS, in particular FLT4/IL8. The choice of treatment partner (E/PG) for bevacizumab may influence the value of BMs. Further examination of the data from this and other bevacizumab trials may provide greater insight.

1299P 贝伐珠单抗联合一线化疗或二线厄洛替尼治疗伴未经治疗的无症状脑转移的非鳞 NSCLC（NS-NSCLC）患者的 II 期研究(ML21823)

1299P PHASE II STUDY OF BEVACIZUMAB IN COMBINATION WITH 1ST-LINE CHEMOTHERAPY OR 2ND-LINE ERLOTINIB IN NON-SQUAMOUS NSCLC (NS-NSCLC) PATIENTS WITH ASYMPTOMATIC UNTREATED BRAIN METASTASES (ML21823)

B. Besse, S.Le Moulec, H.Senellart, et al.

背景：56%的晚期癌症患者发生脑转移（BM），安全性数据表明 BM 并非贝伐珠单抗治疗的禁忌症。非对照 II 期 BRAIN 研究（NCT00800202）是第一项评估贝伐珠单抗联合全身疗法治疗伴未经治疗 BM 的 ns-NSCLC 患者的有效性和安全性研究。

方法：合格患者（IV期ns-NSCLC；PS评分 0-1；未经治疗；无症状BM；不适宜手术/放射外科手术）接受了：A组（n=67），贝伐珠单抗（15 mg/kg q3w，直至疾病进展/发生不可耐受的毒性）联合卡铂（AUC 6 q3w，≤6 个周期）+紫杉醇（200 mg/m^2 q3w，≤6 个周期）（B+CP）一线治疗；或B组（n=24），贝伐珠单抗（同上）联合厄洛替尼（150 mg/天，直至疾病进展/发生不可耐受的毒性）（B+E）二线治疗。主要终点：各治疗组的 6 个月无进展生存（PFS）率；次要终点：有效率（RR; RECIST v1.1）、总生存期（OS）和安全性。如果在B+CP组中脑出血（ICH）的发生>3 例或B+E组中发生>2 例，则可能会终止本研究。每 6 周对所有病变部位进行一次评估，包括强制性MRI。

结果：下表列出了患者的基线特征和生存结果。有效性：6 个月 PFS 率分别为 56.5%（B+CP）和 58.0%（B+E）。安全性：ICH 频率与之前公布的相似患者人群的数据相当（B+CP，1 级 n=1；B+E，n=0）。分别有 19.4% (B+CP)和 20.8% (B+E)的患者发生了 3-5 级值得特别关注的不良事件（AESI）。未观察到与厄洛替尼有关的 3-5 级 AESI。发生了 3 例导致死亡的不良事件（B+CP 组 1 例癫痫；B+E 组 1 例高血压性脑病和 1 例缺血性卒中）。

结论：与既往对照值相比，本研究证实了贝伐珠单抗联合一线化疗或二线厄洛替尼治疗伴未经治疗的无症状脑转移的 ns-NSCLC 患者的有效性及可耐受的安全性。

Background: Brain metastases (BM) occur in up to 56% of pts with advanced cancer and are no longer a contraindication to bevacizumab treatment based on safety data. The non-comparative phase II BRAIN trial (NCT00800202) is the first study to assess the efficacy/safety of bevacizumab in combination with systemic treatments in ns-NSCLC pts with untreated BM.

Methods: Eligible pts (stage IV ns-NSCLC; PS 0–1; untreated, asymptomatic BM; ineligible for surgery/radiosurgery) received**:**arm A (n=67),1st-line bevacizumab (15mg/kg q3w until progression/unacceptable toxicity) plus carboplatin (AUC 6 q3w, ≤6 cycles) and paclitaxel (200mg/m^2 q3w, ≤6 cycles) (B+CP); or arm B (n=24), bevacizumab (as above) plus erlotinib (150mg/day until progression/unacceptable toxicity) (B+E) in 2nd line. Primary endpoint**:**6-month progression-free survival (PFS) by treatment arm. Secondary endpoints**:**response rate (RR; RECIST v1.1), overall survival (OS) and safety. The trial could be halted if the incidence of brain haemorrhage (ICH) was >3 in B+CP or >2 in B+E. All sites of disease were assessed every 6 weeks including mandatory MRI for BM assessment.

Results: Pt baseline characteristics and outcomes are shown (Table). Efficacy**:**the observed 6-month PFS was 56.5% (B+CP) and 58.0% (B+E). Safety**:**ICH frequency comparable to previously published data in a similar pt population (B+CP, n=1 grade 1; B+E, n=0). Grade 3–5 adverse events of special interest (AESI) were seen in 19.4% (B+CP) and 20.8% (B+E) of pts. No erlotinib-related grade 3–5 AESIs were seen. There were 3 AEs leading to death (1 epilepsy, B+CP; 1 hypertensive encephalopathy, 1 ischaemic stroke, B+E).

Conclusion: Bevacizumab with 1st-line chemotherapy or 2nd-line erlotinib demonstrated efficacy and acceptable safety in pts with ns-NSCLC with asymptomatic untreated brain metastases when compared to historical controls.

BRAIN 研究中患者的基线特征和临床结果

Baseline characteristics and clinical outcomes for patients in the BRAIN study.

		B+CP	B+E
		n=67	n=24
基线特征/Baseline characteristics			
性别/Gender, n (%)	男性/Male	46 (68.7)	11 (45.8)
	女性/Female	21 (31.3)	13 (54.2)
中位年龄，岁（范围）/Median age, years (range)		61.0 (40–79)	54.0 (34–70)
ECOG 体力状态评分，n (%) ECOG performance status, n (%)	0	37 (55.2)	13 (54.2)
	1	30 (44.8)	11 (45.8)
WHO 组织学，n (%)/WHO histology, n (%)	腺癌/Adenocarcinoma	59 (88.1)	23 (95.8)
	大细胞癌/Large-cell carcinoma	8 (11.9)	1 (4.2)
复发/Recurrence, n (%)	否/No	61 (91.0)	13 (54.2
	是/Yes	6 (9.0)	11 (45.8)
临床结果/Clinical outcomes (95% CI)			
6 个月 PFS/6-month PFS, %		56.5 (43.8–67.4)	58.0 (36.0–74.8)
中位 PFS，月/Median PFS, months		6.7 (5.7–7.1)	6.3 (2.5–8.4)
中位 OS，月/Median OS, months		15.1 (11.8–NR)	13.6 (7.5–26.3)
12 个月 OS/12-month OS, %		62.8 (49.7–73.4)	50.7 (28.7–69.0)
18 个月 OS/18-month OS %		41.1 (27.4–54.3)	40.5 (20.2–60.0)
总 RR/Overall RR, %		62.7 (50.0, 74.2)	12.5 (2.7, 32.4)
RR, %	颅内转移/Intracranial metastases	61.2 (48.5–72.9)	20.8 (7.1–42.2)
	颅外转移/Extracranial metastases	64.2 (51.5–75.5)	12.5 (2.7–32.4)

NR=未达到

NR=not reached

1245P Ramucirumab（IMC 1121B; RAM）联合含铂化疗治疗复发性或晚期非小细胞肺癌（NSCLC）患者的 II 期随机开放性研究：非鳞（NSQ）NSCLC 患者的结果（NCT01160744）

1245P A PHASE 2 RANDOMIZED OPEN-LABEL STUDY OF RAMUCIRUMAB (IMC 1121B; RAM) IN COMBINATION WITH PLATINUM-BASED CHEMOTHERAPY IN PATIENTS (PTS) WITH RECURRENT OR ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC):RESULTS FROM NON-SQUAMOUS (NSQ) PTS (NCT01160744)

R. Doebele, D.R.Spigel, M.Tehfe, et al.

背景：血管内皮生长因子（VEGF）介导的血管发生在 NSCLC 的发病机制中起着重要作用。RAM 是一种完全人源性的 IgG1 单克隆抗体，可抑制 VEGF 受体-2（VEGFR-2）的结合和信号传递。本研究评估了 RAM 联合一线含铂化疗治疗晚期 NSCLC 的效果。

方法：患有 IV 期 NSCLC、ECOG PS 评分≤ 2 分且有足够的血液学、肝脏和肾脏功能的 NSQ 患者被随机分配到 A 组（培美曲塞+卡铂/顺铂），或 B 组（RAM+培美曲塞+卡铂/顺铂），每 3 周一次治疗。计划在 NSQ 患者中观察到 103 例无进展生存（PFS）事件时，进行主要分析。在观察到 61 例 NSQ PFS 事件时，进行了这项预先计划的中期分析。其他中期终点包括客观缓解率、疾病控制率（DCR）和安全性。

结果：A 组（n=71）患者的中位年龄为 64 岁，63%男性（M），37%女性（F），ECOG PS 评分 0-1/2（91.6% / 5.6%）。B 组（n=69）患者的中位年龄为 64 岁，52%M，48%F，ECOG PS 评分 0-1/2（89.9% / 7.2%）。

A 组的非血液学不良事件（AE）包括疲劳[61%; 17% 3 级（G3）]、恶心（55%; 7% G3）、呕吐（36%; 4% G3）、便秘（30%; 1% G3）、高血压（HTN）（6%; 1% G3）、蛋白尿（4%; 0 G3）；B 组的非血液学不良事件包括疲劳（63%; 12% G3）、恶心（51%; 10% G3）、呕吐（33%; 8% G3）、便秘（27%; 0 G3）、HTN（19%; 10% G3）、蛋白尿（5%; 0 G3）。A 组的血液学不良事件包括贫血（A）（55%; 16% G3）、中性粒细胞减少症（N）（23%; 16% G3）、血小板减少症（T）（23%; 12% G3）；B 组的血液学不良事件包括 A（39%; 8% G3）、N（33%; 13% G3）、T（31%; 15% G3）。

结论：基于 PFS 的中期分析及可接受的耐受性和安全性，NSQ NSCLC 患者可从 RAM 与一线含铂化疗联合治疗中获得临床益处。C 组和 D 组的鳞状 NSCLC 患者的入组工作正在进行中。

Background: Vascular endothelial growth factor (VEGF)-mediated angiogenesis plays an important role in NSCLC pathogenesis. RAM is a fully human IgG1 monoclonal antibody that inhibits VEGF receptor-2 (VEGFR-2) binding and signaling. This study investigates RAM in combination with first-line platinum-based chemotherapy in advanced NSCLC.

Methods:NSQ pts with Stage IV NSCLC, ECOG PS≤2, adequate hematologic, hepatic and renal function were randomized to either Arm A**:**pemetrexed+carboplatin/cisplatin or Arm B**:**RAM+pemetrexed+carboplatin/cisplatin, once every 3 weeks. The primary analysis will be when 103 progression-free survival (PFS) events are observed in NSQ pts. This pre-planned interim analysis was performed when 61 NSQ PFS events were observed. Other interim endpoints**:**objective response rate, disease control rate (DCR), and safety.

Results: Arm A (n=71) median (medn) age 64, 63% male (M), 37% female (F), ECOG PS 0-1 / 2 (91.6% / 5.6%). Arm B (n=69) medn age 64, 52% M, 48% F, ECOG PS 0-1 / 2 (89.9% / 7.2%).

Nonhematologic adverse events (AEs) were fatigue (61%; 17% Grade[G]3), nausea (55%; 7% G3), vomiting (36%; 4% G3), constipation (30%; 1% G3), hypertension (HTN) (6%; 1% G3), proteinuria (4%; 0 G3), on Arm A; fatigue (63%; 12% G3), nausea (51%; 10% G3), vomiting (33%; 8% G3), constipation (27%; 0 G3), HTN (19%; 10% G3), proteinuria (5%; 0 G3) on Arm B. Hematologic AEs were anemia (A) (55%; 16% G3), neutropenia (N) (23%; 16% G3), thrombocytopenia (T) (23%; 12% G3) on Arm A; A (39%; 8% G3), N (33%; 13% G3), T (31%; 15% G3) on Arm B.

Conclusions: Based on interim analyses of PFS and acceptable tolerability and safety, RAM may provide clinical benefit in combination with first-line platinum-based chemotherapy in NSQ NSCLC. Enrollment of pts in squamous Arms C and D is ongoing.

中期有效性分析/ Interim efficacy analyses	A 组 (N=71) n (%)/Arm A (N=71) n (%)	B 组(N=69) n (%)/Arm B (N=69) n (%)
PFS 事件，截尾值，中位值（月） 90%CI/PFS Events Censored Median (months) 90% CI	37 (52)，34 (48)，4.3 (3.8, 5.7)	24 (35)，45 (65)，6.3 (5.7, -)
最佳缓解 PR SD DCR (SD+PR)/ Best Response PR SD DCR (SD+PR)	26 (37)，25 (35)，51 (72)	30 (44)，30 (44)，60 (88)

239P 临床基因分型和有效性结局：一线贝伐珠单抗+化疗治疗非鳞非小细胞肺癌（NS-NSCLC）的 II 期 ABIGAIL 研究的探索性生物标记物数据

239P CLINICAL GENOTYPING AND EFFICACY OUTCOMES:EXPLORATORY BIOMARKER DATA FROM THE PHASE II ABIGAIL STUDY OF 1ST-LINE BEVACIZUMAB+CHEMOTHERAPY IN NON-SQUAMOUS NON-SMALL-CELL LUNG CANCER (NS-NSCLC)

C.Pallaud, M.Reck, E.Juhasz, et al.

背景：ABIGAIL (BO21015; NCT00700180)是一项在未接受过化疗的晚期/复发性 ns-NSCLC 患者中探索生物标记物（BM）与贝伐珠单抗+卡铂/吉西他滨（CG）或卡铂/紫杉醇（CP）治疗后的最佳总疗效（BOR）之间相关性的 II 期、随机、多中心研究。已经报告了 ABIGAIL 的有效性、安全性和血浆基线结果。本摘要列出了本研究中的探索性临床基因分型数据。

方法：按照 1:1 的比例将 303 例未经治疗的晚期/复发性 ns-NSCLC 患者随机分配接受贝伐珠单抗 7.5 mg/kg 或 15 mg/kg 治疗，持续至疾病进展或发生不可耐受的毒性（6 个疗程的 CG 或 CP）。签署知情同意书的患者提供了用于 BM 分析的血样和肿瘤样本。进行多项探索性分析，评估 VEGFA 通道的遗传性变型是否可以作为有效性和安全性的生物标记物。此处我们报告了 3 种基因的 12 种单核苷酸多态现象（SNP）：VEGFA (5 SNPs)、VEGFR-1 (3 SNPs) 和 VEGFR-2 (4 SNPs)。使用各种特异性基因分型检测法对 SNP 进行鉴定。

结果：VEGFA：c.+405/c.-634 (CG)，VEGFA:c.-460T>C; c.-1498T>C (CT)和 VEGFA:c.-2578 C>A (AC)都与治疗缓解的可能性升高>50%有关。VEGFR-1 rs9554316 (GT)与进展风险升高>30%和死亡风险升高>40%有关。VEGF：c.+936 C>T (CT) 与高血压的发生率升高有关。当根据治疗和预后因子对 p 值进行校正时，所有 SNP 都与高血压风险的显著升高有关。

结论：1 种 SNP 与进展/死亡的风险升高有关，而另外 3 种 SNP 与 BOR 风险升高有关。但是，针对多重检验校正后，p 值不再有统计学显著性。其他研究之前已经报告了本研究中分析的 SNP 可能有预测价值：乳腺癌研究（E2100）和 NSCLC 研究（E4599）中的 VEGFA SNP；胰腺癌研究（AVITA）中的 VEGFR1 SNP。基于本试验和其他贝伐珠单抗试验的更多探索性分析可提供进一步的认识。

Background:ABIGAIL (BO21015; NCT00700180) is a phase II, randomized, multicentre study exploring correlation between biomarkers (BMs) and best overall response (BOR) to bevacizumab with carboplatin/gemcitabine (CG) or carboplatin/paclitaxel (CP) in chemonaïve patients with advanced/recurrent ns-NSCLC. ABIGAIL efficacy, safety and plasma baseline results have been reported. This abstract presents exploratory clinical genotyping data from this study.

Methods:303 patients with untreated advanced/recurrent ns-NSCLC were randomized 1:1 to receive bevacizumab 7.5 mg/kg or 15 mg/kg until progression or unacceptable toxicity (with 6 cycles of CG or CP). Patients who consented provided blood and tumour samples for BM analysis. Exploratory analyses were conducted to assess whether genetic variants in the VEGFA pathway may act as biomarkers for efficacy and safety. Here we report data from DNA analysis for 12 single-nucleotide polymorphisms (SNPs) across 3 genes:VEGFA (5 SNPs), VEGFR-1 (3 SNPs) and VEGFR-2 (4 SNPs). SNPs were identified using specific individual genotyping assays.

Results:VEGFA:c.+405/c.-634 (CG), VEGFA:c.-460T>C; c.-1498T>C (CT) and VEGFA:c.-2578 C>A (AC) were all associated with >50% higher odds of responding to treatment. VEGFR-1 rs9554316 (GT) was associated with >30% higher risk of progression and >40% higher risk of death. VEGF:c.+936 C>T (CT) was associated with higher incidence of hypertension. When p-values were adjusted for treatment and prognostic factors, no SNPs were associated with significantly higher risk of hypertension.

Conclusions: One SNP was associated with increased risk of progression/death, while 3 others were associated with increased BOR. However, adjustment for multiple testing would no longer result in statistically significant p-values. SNPs analysed in this study have been previously reported as showing potential predictive value in other studies:VEGFA SNPs in breast cancer (E2100) and NSCLC (E4599); VEGFR1 SNP in pancreatic cancer (AVITA). More exploratory analyses from this and other trials of bevacizumab may provide further insight.

1278P 晚期非小细胞肺癌（NSCLC）患者诱导治疗后贝伐珠单抗（BV）维持治疗的累积暴露量（EXP）和生存期：一项基于 SAiL（MO19390）研究的时间依赖性分析

1278P CUMULATIVE EXPOSURE (EXP) TO BEVACIZUMAB (BV) MAINTENANCE AFTER INDUCTION THERAPY AND SURVIVAL IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC):A TIME-DEPENDENT ANALYSIS FROM THE SAIL (MO19390) STUDY

N.Thatcher,P.Garrido Lopez, N.Pavlakis, et al.

背景：多项随机观察性研究的探索性分析已经证明了连续使用 BV 至疾病进展（PD）与晚期 NSCLC 患者的总生存期（OS）延长有关。我们评估了诱导期后（IP 后）BV 的累积暴露量（exp）和 NSCLC 患者 OS 之间的相关性。

方法：跨国性Ⅳ期 SAiL 研究入组了接受 BV 和一线化疗（CT）的晚期NSCLC患者。将同时开始使用BV和CT并且在完成12-18周（4-6 个疗程）CT 后疾病没有进展的患者纳入分析。从每例患者的 BV+CT IP 结束时开始测量 OS。随访期内的 BV 暴露量定义为 IP 后 BV 治疗（tx）的累积天数。对时间依赖性 Cox 回归模型进行拟合，评估累积的 IP 后 BV 暴露量对 OS 的影响，而且对潜在的时间依赖性混淆因子和时间固定性混淆因子进行匹配。一项界标敏感性分析对比了 IP 后继续和未继续 BV 的分析人群中患者的 OS。

结果：在 SAiL 研究的 2212 例患者中，1625 例 NSCLC 患者在 IP 治疗过程中生存且没有 PD。基线特征（n=1625）为：58%男性，13%≥70 岁，32%从未吸烟者，和 4% ECOG PS 评分 ≥2。1047 例患者(64%)接受了 IP 后 BV。在界标期内，接受 IP 后 BV 的患者和未接受 IP 后 BV 的患者之间的基线特征及 IP 结束时的特征基本相似。在随访期间，累积暴露的每 21 天间期内 OS 的风险比（HR）减少 7%（范围，5%-9%；见下表）。标志性敏感性分析还支持了 IP 后 BV 与 OS 延长有关（IP 后 BV vs. 非 IP 后 BV；HR，0.74；95% CI, 0.64–0.85）。

结论：SAiL 研究的这些数据与之前提供的 ARIES 研究数据表明，IP 后 BV 的累积暴露量与 NSCLC 患者的 OS 逐步延长有关。

Background: Exploratory analyses from randomized and observational studies have shown that continuation BV until progressive disease (PD) is associated with prolonged overall survival (OS) in advanced NSCLC. We evaluated the correlation between cumulative exp to post-induction phase (post-IP) BV and OS in patients (pts) with NSCLC.

Methods: The multinational phase 4 SAiL study enrolled advanced NSCLC pts receiving BV with 1st-line chemotherapy (CT). Pts who began BV and CT simultaneously and did not have PD after completing 12–18 weeks (4–6 cycles) of CT were included for analysis. OS was measured from the end of each pt's BV+CT IP. BV exp, over follow-up, was defined as the cumulative days of post-IP BV treatment (tx). A time-dependent Cox regression model was fitted to assess the effect of cumulative post-IP BV exp on OS, while controlling for potential time-dependent and -fixed confounders. A landmark sensitivity analysis compared OS in pts in the analysis population who did and did not continue BV after IP.

Results: Of 2212 pts in SAiL, 1625 NSCLC pts were alive and without PD through IP tx. Baseline characteristics (n=1625) were**:**58% male, 13% ≥70 y, 32% never smokers, and 4% ECOG PS ≥2. 1047 (64%) pts received post-IP BV. Baseline and end-of-IP characteristics were generally similar between pts receiving post-IP BV or no post-IP BV within the landmark period. Across follow-up, the hazard ratios (HRs) for OS decreased by 7% (range, 5%–9%) with each additional 21-day interval of cumulative exp (Table). Landmark sensitivity analyses also support that post-IP BV was associated with longer OS (post-IP BV vs no post-IP BV; HR, 0.74; 95% CI, 0.64–0.85).

Conclusions: These data from SAiL along with previously presented data from ARIES suggest that cumulative exp to post-IP BV is associated with incremental increases in OS for NSCLC pts.

IP后BV的累积疗程[a] /Cumulative post-IP BV cycles[a]	继续接受累积疗程的IP后BV的患者数量[b]/No. of pts who received cumulative cycles of post-IP BV continuously[b]	OS 的 HR（95%可信区间）/HR (95% confidence interval) for OS
1	1006	0.91 (0.89–0.93)
2	884	0.82 (0.79–0.86)
3	758	0.75 (0.70–0.80)
4	643	0.68 (0.62–0.74)
5	530	0.62 (0.55–0.69)
6	447	0.56 (0.49–0.64)
7	370	0.51 (0.44–0.59)
8	315	0.46 (0.39–0.55)

[a]一个疗程大约为IP后累积暴露 21 天。

[a] A cycle is approximately 21 days of post-IP cumulative exp.

[b] 如，n=530 例患者继续接受治疗至IP后第 105 天（第 5 个疗程）。

[b] Eg, n=530 pts were continuously dosed through day 105 (cycle 5) after IP.

1279P 疾病进展（PD）后贝伐珠单抗（BV）的累积暴露量与非小细胞肺癌（NSCLC）患者生存期之间的相关性：基于 ARIES 观察性队列研究的时间依赖性分析

1279P CUMULATIVE EXPOSURE TO BEVACIZUMAB (BV) AFTER DISEASE PROGRESSION (PD) CORRELATES WITH SURVIVAL IN NON-SMALL CELL LUNG CANCER (NSCLC):A TIME-DEPENDENT ANALYSIS OF THE ARIES OBSERVATIONAL COHORT STUDY

T.J.Lynch, M.Jahanzeb, D.R.Spigel,et al.

背景：对于一些癌症（如 CRC、卵巢癌），BV 使用的持续时间可能与疗效有关。在一项 III 期 mCRC 试验中，在二线治疗时继续使用 BV 和化疗（CT）达到了该试验的 1 个终点，即进展后总生存期（ppOS）改善。一项 II 期研究表明，在未使用过 BV 的二线 NSCLC 的化疗中加用 BV 时，表现出 OS 获益的趋势（(HR 0.71; 95% CI 0.41–1.21；Herbst JCO 2007）。此分析评估了 PD 后的 BV 暴露量是否与 NSCLC 患者的 ppOS 存在相关性。

方法：此分析纳入了 ARIES 研究中接受一线（1L）BV 治疗而且首次 PD 后生存的 NSCLC 患者。ppOS 等于首次 PD 到任何原因导致死亡的时间。随访期内 BV 暴露量等于从首次 PD 起 BV 的累积暴露天数。对时间依赖性 Cox 回归模型进行拟合，评估累积 BV 暴露量对 ppOS 的效果，并对潜在的时间依赖性混淆因子和时间固定性混淆因子进行匹配。一项界标敏感性分析（也针对混淆因子进行校正）对比了 PD 后接受 BV 治疗的患者（BBP）和 PD 后 30 天内接受其他治疗的患者（非 BBP）的 ppOS。

结果：截止至 2011 年 9 月，在入组的 1967 例一线治疗患者中，1461 例患者（74%）发生了首次 PD。特征（n=1461）为：48% 在 6 个月内发生首次 PD，52%男性，31% ≥70 岁，13%从未吸烟者，及 13% ECOG 体力状态评分≥2。发生首次 PD 的所有患者的中位 ppOS 为 6 个月（95% CI 5.6–6.7）。在接受任何 BV 治疗的患者中，平均累积 BV 暴露量为 116 天（范围，2–1140 天）。在随访期间，累积暴露的每 21 天间期内 ppOS 的风险比（HR）减少 4%（见下表）。累积 BV 持续时间与 ppOS 改善有关（P <0.0001）。标志性分析还证明了 BBP 与 ppOS 延长独立相关（BBP vs 非 BBP；HR, 0.75; 95% CI, 0.65–0.86）。

结论：此分析表明首次 PD 后 BV 的累积暴露量可能与 NSCLC 患者的 ppOS 逐步延长有关，而且支持 III 期 AvaALL 试验的开展。

Background: Duration of BV use appears to contribute to treatment (tx) efficacy in some cancers (eg, CRC, ovarian). A phase 3 mCRC trial met its 1 endpoint of improved postprogression overall survival (ppOS) when continuing BV with chemotherapy (CT) into 2nd-line (2L) tx. A phase 2 study showed a trend for OS benefit when adding BV to CT in BV-naive 2L NSCLC (HR 0.71; 95% CI 0.41–1.21) (Herbst JCO 2007). This analysis evaluated whether BV exposure (exp) after PD correlates with ppOS in NSCLC.

Methods:ARIES 1st-line (1L) BV-treated NSCLC patients (pts) who survived 1st PD were included. ppOS equaled the time from 1st PD to any-cause death. BV exp, over follow-up, equaled the cumulative days of BV from 1st PD. A time-dependent Cox regression model was fitted to assess the effect of cumulative BV exp on ppOS, while controlling for potential time-dependent and -fixed confounders. A landmark sensitivity analysis, also adjusting for confounders, compared ppOS in pts treated with BV beyond PD (BBP) and pts treated otherwise (No BBP) ≤30 days after PD.

Results :As of 09/2011, of 1967 enrolled 1L pts, 1461 (74%) had 1st PD. Characteristics (n=1461) were**:**48% had 1st PD within 6 mos, 52% male, 31% ≥70 y, 13% never smokers, and 13% ECOG status ≥2. The median ppOS for all pts with 1st PD was 6 mos (95% CI 5.6–6.7). Among pts with any BV tx, the mean cumulative BV exp was 116 days (range, 2–1140). Across follow-up, the HRs for ppOS decreased by 4% for each additional 21-day interval of cumulative exp (Table). Cumulative BV duration was associated with improved ppOS (P<.0001). The landmark analysis also showed that BBP was independently associated with higher ppOS (BBP vs No BBP; HR, 0.75; 95% CI, 0.65–0.86).

Conclusions: This analysis suggests that cumulative exp to BV after 1st PD may correspond with incremental increases in ppOS for NSCLC pts, and supports the conduct of the phase 3 AvaALL trial.

疗程[a]/Cycle[a]	继续接受累积疗程BV治疗的患者数量[b]/No. of pts who received cumulative cycles of BV continuously[b]	ppOS 的风险比（HR）/Hazard ratio (HR) for ppOS	95%可信区间（CI）/95% confidence interval (CI)
1	229	0.959	0.941–0.978
2	159	0.920	0.885–0.956
3	118	0.883	0.833–0.935
4	84	0.847	0.784–0.914
5	72	0.812	0.738–0.894
6	55	0.779	0.694–0.874
7	41	0.747	0.653–0.855
8	32	0.717	0.614–0.836

[a].一个疗程计算为PD后累积暴露 21 天。

[a] A cycle is calculated as 21 days of cumulative exposure after PD.

[b]如，n=55 例患者连续接受治疗至PD后第 126 天（第 6 个疗程）左右。

[b] Eg, n=55 patients were continuously dosed through approximately day 126 (cycle 6) after PD.

1255P 表皮生长因子受体（EGFR）突变阳性晚期非小细胞肺癌（NSCLC）一线吉非替尼治疗后使用化疗的基于人群的评估

1255P POPULATION BASED EVALUATION OF CHEMOTHERAPY USE AFTER FIRST LINE GEFITINIB IN EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

C.Mariano, I.Bosdet, D.Ionescu, et al.

引言：IPASS 试验证明了与卡铂/紫杉醇相比，吉非替尼一线治疗较少/从未吸烟的亚洲晚期肺腺癌患者无进展生存期较长，其中，59%的试验患者为 EGFR 突变阳性（MUT+）患者。在 IPASS 研究中，39%的吉非替尼治疗患者转为继续接受含铂治疗。我们假设在基于人群的背景下，较少的患者接受了二线含铂化疗。

方法：Iressa 联盟项目向英属哥伦比亚省的所有晚期非鳞 NSCLC 患者（450 万人群）提供标准 EGFR 突变检测和合适的吉非替尼获取通道。EGFR 突变检测限于最常见的突变：外显子 19 和 21。我们回顾性地分析了 2010 年 3 月至 2011 年 6 月间本项目中检测的所有患者的临床、病理情况和结果。

结果：共 548 例患者接受了检测，其中 107 例患者（19%）为 MUT+。MUT-和 MUT+患者的基线特征为：中位年龄 67/65 岁，男性 41%/31%，亚裔 15%/51%，从未吸烟者 21%/58%，IV 期 80%/91%。总生存期为 10.9 个月 vs. 14.9 个月（$p < 0.0001$）。在接受吉非替尼一线治疗的 MUT+患者中，治疗的平均持续时间为 312 天。5%的患者出现 CR，43% PR，34% SD，5% PD，12%无法评估。23%的患者在放射影像学评估为进展后继续使用吉非替尼治疗。在分析时，有 51 例吉非替尼治疗的患者疾病进展；15%的患者仅接受吉非替尼治疗，33%接受含铂双联疗法，10%接受其他化疗，42%未接受进一步治疗。5 例患者接受了三线治疗。

结论：这项基于北美人群的研究中 MUT+患者使用吉非替尼治疗的有效性与 IPASS 试验相似。临床医师一般在疾病进展后继续给予患者吉非替尼治疗，这可能是由于持续的临床获益。与我们的假设相反，在大部分吉非替尼治疗的患者中，二线化疗给药是可行的，与临床试验中观察到的结果相似。MUT+患者的预后较好，而这可能有助于他们接受进一步的治疗。

Introduction: The IPASS trial demonstrated superior progression free survival for Asian, light/never smoking, advanced, adenocarcinoma patients treated with first line Gefitinib compared to carboplatin/paclitaxel, of which 59% of those tested were EGFR mutation positive (MUT+). In IPASS 39% of Gefitinib treated patients went on to receive platin based therapy. We hypothesize that in a population-based setting fewer patients receive second line platin based chemotherapy.

Methods: The Iressa Alliance Program provided standardized EGFR mutation testing and appropriate access to Gefitinib to all patients in British Columbia (population 4.5 million) with advanced, non squamous NSCLC. EGFR mutation testing was limited to the most common mutations; exon 19 and 21. We retrospectively analyzed clinical, pathologic and outcomes for all patients tested in this program between March 2010 and June 2011.

Results:A total of 548 patients were referred for testing and 107 (19%) patients were MUT+. Baseline characteristics of MUT- and MUT+; median age 67/65, male 41%/31%, Asian 15%/51%, never smoker 21%/58%, stage IV 80%/91%. Overall survival was 10.9 versus 14.9 months ($p<0.0001$). In MUT+patients treated with first line Gefitinib average duration of therapy was 312 days. 5% of patients had a CR, 43% PR, 34% SD, 5% PD with 12% not evaluable. 23% of patients continued on Gefitinib after radiographic progression. 51 Gefitinib treated patients progressed at the time of analysis; 15% of patients received Gefitinib only, 33% platin based doublet, 10% other chemotherapy and 42% no further treatment. Five patients received 3rd line therapy.

Conclusions: This North American population based study shows similar efficacy of Gefitinib in MUT+patients compared to the IPASS trial. Clinicians often continued Gefitinib past progression, likely due to ongoing clinical benefit. Contrary to our hypothesis, delivery of second line chemotherapy was feasible in a significant proportion of Gefitinib treated patients, similar to results seen in clinical trials. MUT+patients have a better prognosis and this may contribute to their ability to receive further therapy.

1234PD 对比 S-1+顺铂与多西他赛+顺铂治疗晚期非小细胞肺癌的随机 III 期试验（TCOG0701）

1234PD RANDOMIZED PHASE III TRIAL OF S-1 PLUS CISPLATIN VERSUS DOCETAXEL PLUS CISPLATIN FOR ADVANCED NON-SMALL-CELL LUNG CANCER (TCOG0701)

H.Sakai,A. Gemma, K.Kubota, et al.

背景：在晚期非小细胞肺癌（NSCLC）患者的治疗过程中，生活质量（QOL）无疑是优先考虑事项。多西他赛+顺铂（DP）是唯一的第三代治疗方案，被证实与第二代治疗方案（长春地辛+顺铂）相比，对晚期 NSCLC 患者有总生存期获益以及 QOL 改善出现统计学差异。在 II 期临床试验中已经证明了 S-1+顺铂（SP）的有效性和良好的耐受性。

方法：患有既往未经治疗的IIIB期或IV期NSCLC、ECOG PS评分0-1 并且器官功能充分的患者被随机分配接受口服S-1 80 mg/m^2/天（40 mg/m^2 b.i.d.）（第 1-21 天）+顺铂 60 mg/m^2（第 8 天，每 5 周一次），或接受多西他赛 60 mg/m^2（第 1 天）+顺铂 80 mg/m^2（第 1 天，每 3 周一次）治疗，两种方案都持续 6 个疗程。主要终点是总生存期（OS）。采用非劣效性研究设计；风险比（HR）的可信区间（CI）上限< 1.322。次要终点包括无进展生存期（PFS）、缓解率、安全性和QOL。

结果：2007 年 4 月至 2008 年 12 月，日本 66 个研究中心的 608 例患者被随机分配到 SP（n=303）或 DP（n=305）组。两组患者人口统计学特征分布均衡。预先计划了 2 项中期分析。在最终分析时，共发生 480 例死亡事件。本研究达到了主要终点。SP 组的 OS 非劣于 DP 组（中位生存期分别为 16.1 个月和 17.1 个月；HR=1.013；96.4%可信区间：0.837-1.227）。SP 组的 PFS 为 4.9 个月，DP 组的 PFS 为 5.2 个月。SP 组中发热性中性粒细胞减少症（7.4%比 1.0%）、3/4 级中性粒细胞减少症（73.4%比 22.9%）、3/4 级感染（14.5%比 5.3%）和 1/2 级脱发（59.3%比 12.3%）的发生率都显著低于 DP 组。根据 EORTC QLQ-C30 上的身体功能和总体功能评分及肺癌测量模块（LC-13），DP 组的生活质量恶化（重复测量 ANOVA：$p < 0.01$）。

结论：S-1+顺铂是晚期 NSCLC 的标准一线化疗方案。

Background: Quality of life (QOL) should be an explicit priority throughout the course of care for patients with advanced non-small-cell lung cancer (NSCLC). Docetaxel plus cisplatin (DP) is the only third-generation regimen that has demonstrated statistically significant improvements in overall survival and QOL by a head-to-head comparison with a second-generation regimen (vindesine plus cisplatin) in patients with advanced NSCLC. S-1 plus cisplatin (SP) has shown activity and good tolerability in phase II settings.

Method: Patients with previously untreated stage IIIB or IV NSCLC, an ECOG PS of 0-1 and adequate organ functions were randomly assigned to receive either oral S-1 80 mg/m2/day (40 mg/m2 b.i.d.) on days 1 to 21 plus cisplatin 60 mg/m2 on day 8 every 5 weeks or docetaxel 60 mg/m2 on day 1 plus cisplatin 80 mg/m2 on day 1 every 3 weeks, both up to 6 cycles. The primary endpoint was overall survival (OS). A non-inferiority study design was employed; the upper confidence interval (CI) limit of the hazard ratio (HR) was <1.322. Secondary endpoints included progression-free survival (PFS), response, safety, and QOL.

Results: From April 2007 through December 2008, 608 patients were randomly assigned to SP (n=303) or DP (n=305) at 66 sites in Japan. Patient demographics were well balanced between the two groups. Two interim analyses were preplanned. At the final analysis, a total of 480 deaths had occurred. The primary endpoint was met. OS in the SP arm was non-inferior to that in the DP arm (median survival, 16.1 vs. 17.1 months, respectively; HR=1.013; 96.4% confidence interval, 0.837-1.227). PFS was 4.9 months in the SP arm and 5.2 months in the DP arm. The rates of febrile neutropenia (7.4% vs. 1.0%), grade 3/4 neutropenia (73.4% vs. 22.9%), grade 3/4 infection (14.5% vs. 5.3%), and grade 1/2 alopecia (59.3% vs. 12.3%) were significantly lower in the SP arm than in the DP arm. In terms of physical functioning and global functioning on the EORTC QLQ-C30 and lung cancer module (LC-13), QOL was worse in the DP arm (repeated measures ANOVA:$p<0.01$).

Conclusion:S-1 plus cisplatin is a standard first-line chemotherapeutic regimen for advanced NSCLC

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LBA1_PR　对比 crizotinib 与培美曲塞或多西他赛化疗治疗晚期 ALK-阳性非小细胞肺癌（NSCLC）患者的 III 期研究（PROFILE 1007）

LBA1_PR　PHASE III STUDY OF CRIZOTINIB VERSUS PEMETREXED OR DOCETAXEL CHEMOTHERAPY IN PATIENTS WITH ADVANCED ALK-POSITIVE NON-SMALL CELL LUNG CANCER (NSCLC) (PROFILE 1007)

A.T. Shaw, D.W. Kim, K. Nakagawa, et al.

背景：间变性淋巴瘤激酶（ALK）的染色体重排与 crizotinib 的显著临床疗效有关，crizotinib 是一种以 ALK 为靶点的口服酪氨酸激酶抑制剂。本项全球性随机 III 期研究对比了 crizotinib (C) 与标准化疗（培美曲塞或多西他赛 [P/D]）作为晚期 ALK+NSCLC 患者二线治疗的有效性和安全性。

方法：2010 年 2 月至 2012 年 2 月，347 例接受了 1 种既往含铂方案治疗的IIIB/IV期ALK+NSCLC患者随机接受C 250 mg po BID (n=173)，或者P 500 mg/m^{2}或D 75 mg/m^2 IV q3w (n=174; 58% P, 42% D)。在中心实验室采用FISH法对ALK进行检测。在 PROFILE 1005 中，向接受P/D治疗后疾病进展的患者提供了 crizotinib。主要终点是基于独立放射学审查的无进展生存期（PFS）；次要终点包括客观缓解率（ORR）、总生存期（OS）、安全性和患者报告结局。

结果：本研究达到了其主要终点，证明了 crizotinib 在延长 PFS 方面优于 P/D（中位值 7.7 个月比 3.0 个月；HR 0.49；95% CI 0.37-0.64; P < 0.0001）。接受 crizotinib 治疗患者的 ORR 显著较高（65%比 20%; P < 0.0001）。OS 的中期分析（28%的事件）表明 crizotinib 和 P/D 之间没有统计学显著差异（初步中位估计值 20.3 个月比 22.8 个月；HR 1.02; 95% CI 0.68-1.5; P=0.5394），但未针对后续交叉治疗进行校正（108 名患者[62%]交叉接受 crizotinib 治疗）。Crizotinib 组中最常见的与治疗相关的不良事件（TRAE）是视觉障碍（59%）、腹泻（53%）、恶心（52%）、呕吐（44%）和转氨酶水平升高（36%），而 P/D 组中最常见的与治疗相关的不良事件（TRAE）包括恶心（35%）、疲乏（29%）、中性粒细胞减少症（22%）、食欲减退（21%）和脱发（20%）。Crizotinib 组和 P/D 组中 3/4 级 TRAE 的发生率相同（31%）。Crizotinib 组和 P/D 组中导致退出的 TRAE 发生率分别为 6%和 10%。Crizotinib 组的治疗持续时间长于 P/D 组（开始的中位疗程 11 比 4）。

结论：与 P/D 组相比，crizotinib 组的 PFS 和 ORR 都有显著改善，而且安全性特征是可接受的。这些结果证实 crizotinib 可以作为之前接受过治疗的晚期 ALK+NSCLC 患者的标准疗法。

Background: Chromosomal rearrangements of anaplastic lymphoma kinase (ALK) are associated with marked clinical responses to crizotinib, an orally available tyrosine kinase inhibitor targeting ALK. This global randomized phase III study compared the efficacy and safety of crizotinib (C) with standard chemotherapy (pemetrexed or docetaxel [P/D]) as 2nd-line therapy for patients (pts) with advanced ALK+NSCLC.

Methods: Between Feb 2010 and Feb 2012, 347 pts with stage IIIB/IV ALK+NSCLC previously treated with 1 prior platinum-based regimen were randomized to receive C 250 mg PO BID (n=173) or either P 500 mg/m^2 or D 75 mg/m^2 IV q3w (n=174; 58% P, 42% D). ALK was detected by FISH in a central lab. Pts with progressive disease on P/D were offered C on PROFILE 1005. The primary endpoint was progression-free survival (PFS) per independent radiologic review; secondary endpoints included objective response rate (ORR), overall survival (OS), safety, and patient-reported outcomes.

Results: The study met its primary objective by demonstrating the superiority of C over P/D in prolonging PFS (median 7.7 vs 3.0 mo; HR 0.49; 95% CI 0.37-0.64; P < 0.0001). ORR was significantly higher in pts treated with C (65% vs 20%; P < 0.0001). Interim analysis of OS (28% events) showed no statistically significant difference between C and P/D (preliminary median estimate 20.3 vs 22.8 mo; HR 1.02; 95% CI 0.68-1.5; P=0.5394), but was not adjusted for crossover (108 pts [62%] crossed over to C). The most common treatment-related adverse events (TRAE) with C were visual disturbance (59%), diarrhea (53%), nausea (52%), vomiting (44%), and elevated transaminases (36%), and with P/D, nausea (35%), fatigue (29%), neutropenia (22%), decreased appetite (21%), and alopecia (20%). The incidence of grade 3/4 TRAE was the same for C vs P/D (31%). The incidence of TRAE leading to discontinuation was 6% for C vs 10% for P/D. Duration of treatment was longer for C vs P/D (median cycles started 11 vs 4).

Conclusions:C showed significant improvement in PFS and ORR compared with P/D and had an acceptable safety profile. These findings establish C as the standard of care for pts with previously treated advanced ALK+NSCLC.

1233PD　司美替尼（AZD6244, ARRY-142866；SEL）+多西他赛（DOC）治疗 KRAS-突变的晚期非小细胞肺癌（NSCLC）的有效性和患者（PT）报告结局（PRO）：一项随机 II 期试验

1233PD　EFFICACY AND PATIENT (PT)-REPORTED OUTCOMES (PROS) WITH SELUMETINIB (AZD6244, ARRY-142866; SEL)+DOCETAXEL (DOC) IN KRAS-MUTANT ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC):A RANDOMIZED, PHASE II TRIAL

P.A.Janne, A.T. Shaw, J.Rodrigues Pereira, et al.

目的：本项随机、双盲、安慰剂（PBO）对照 II 期试验评估了 SEL+DOC 作为 KRAS-突变晚期 NSCLC 患者二线治疗的有效性和安全性。探索性目的是肺癌症状的发生率、严重程度和随时间变化的评估。

方法：IIIB-IV期的KRAS-突变晚期NSCLC患者接受了多西他赛（DOC）75 mg/m^{2}静脉给药和司美替尼（SEL）75 mg口服给药或安慰剂（PBO）BD二线治疗。使用肺癌特异性症状调查问卷（LSSQ）对患者报告结局（PRO）进行评估，LSSQ包括肺癌子量表（LCS）+症状相关项目和FACT-L上的功能活动。患者在第 1 天完成调查问卷，每 3 周一次，直到终止研究治疗，并且在终止时完成调查问卷。

结果：在 12 个国家的 67 个中心对 442 例患者进行了筛选；87 例患者接受随机分组（SEL+DOC，44； PBO+DOC，43）。基线特征的分布均衡。SEL+DOC 组的 OS 长于 PBO+DOC（9.4 个月比 5.2 个月），但是差异没有统计学意义（HR 0.80；80% CI 0.56–1.14），而且风险不成比例。与 PBO+DOC 组相比，SEL+DOC 组的所有次要终点都得到了显著改善，包括缓解率（37% vs 0%；p < 0.0001）和 PFS（5.3 vs 2.1 个月；HR 0.58; 80% CI 0.42–0.79）。最常见的 3/4 级不良事件是中性粒细胞减少症和发热性中性粒细胞减少症。在基线及至少 1 次随访访视时完成 LSSQ 的依从性达到 85.5%。在整个评估期内，与 PBO+DOC 组相比，SEL+DOC 组的 LSSQ 评分与基线相比的变化出现数值上的改善。在一项事后分析中，SEL+DOC 组中 LCS 评分出现有临床意义改善的患者百分比（44%）高于 PBO+DOC 组（24%；OR 2.50；80% CI 1.34–4.77；单侧 p 值=0.029）。LCS 评分恶化时间也表明 SEL+DOC 优于 PBO+DOC 组（HR 0.33；80% CI 0.22–0.49；单侧 p 值= 0.0002）。

结论：这是第一项证明靶向治疗（SEL+DOC）在任何类型的 KRAS-突变癌症患者中的临床益处的前瞻性研究。在一项事后分析中，SEL+DOC 组中肺癌症状出现有临床意义改善的患者数量高于 PBO+DOC 组。

Objectives: This randomized, double-blind, placebo (PBO)-controlled, phase II trial evaluated the efficacy and safety of SEL+DOC as second-line treatment for pts with KRAS-mutant advanced NSCLC. Assessment of the prevalence, severity, and change over time of lung cancer symptoms was an exploratory objective.

Methods: Pts with stage IIIB-IV, second-line KRAS-mutant advanced NSCLC, received iv DOC 75mg/m2, and po SEL 75mg or PBO BD. PROs were assessed using the Lung Cancer-Specific Symptom Questionnaire (LSSQ), which includes the Lung Cancer Subscale (LCS) plus items relating to symptoms and functional activities from the FACT-L. Pts completed the questionnaire on Day 1, and every 3 weeks until discontinuation from study treatment, and at discontinuation.

Results:422 pts were screened across 67 centers in 12 countries; 87 were randomized (SEL+DOC, 44; PBO+DOC, 43). Baseline characteristics were reasonably balanced. OS was longer for SEL+DOC vs PBO+DOC (9.4 vs 5.2 mo), but not statistically significant (HR 0.80; 80% CI 0.56–1.14) and hazards were non-proportional. All secondary endpoints, including response rate (37% vs 0%; p<0.0001) and PFS (5.3 vs 2.1 mo; HR 0.58; 80% CI 0.42–0.79), were significantly improved for SEL+DOC vs PBO+DOC. Most frequent grade 3/4 AEs were neutropenia and febrile neutropenia. Compliance for completion of the LSSQ at baseline and at least 1 follow-up visit was 85.5%. There was a numerical improvement in the change from baseline in the LSSQ scores with SEL+DOC compared with PBO+DOC, throughout the assessment period. In a post-hoc analysis, the % pts with a clinically meaningful improvement in LCS score was greater for SEL+DOC (44%) than PBO+DOC (24%; OR 2.50; 80% CI 1.34–4.77; 1-sided p=0.029). The time to deterioration of LCS score was also in favor of SEL+DOC (HR 0.33; 80% CI 0.22–0.49; 1-sided p=0.0002).

Conclusions: This is the first prospective study to demonstrate a clinical benefit of targeted therapy (SEL+DOC) for pts with KRAS-mutant cancer of any type. In a post-hoc analysis, more pts experienced clinically meaningful improvements in lung cancer symptoms with SEL+DOC than PBO+DOC.

1237PD　抗程序性死亡-1（PD-1）类药物（BMS-936558/MDX-1106/ONO-4538）在晚期非小细胞肺癌（NSCLC）患者中的临床作用和安全性

1237PD　CLINICAL ACTIVITY AND SAFETY OF ANTI-PROGRAMMED DEATH-1 (PD-1) (BMS-936558/MDX-1106/ONO-4538) IN PATIENTS (PTS) WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

S.Gettinger, L.Horn, S.J. Antoni, et al.

目的：BMS-936558 是一种完全人源化单克隆抗体，可阻断活化 T 细胞表达的 PD-1 共抑制受体。在此我们报告了 BMS-936558 在曾接受治疗的晚期 NSCLC 患者中的作用和安全性，之前认为免疫疗法对该类肿瘤无效。

方法：在剂量递增期和/或队列扩展期内，各种实体瘤患者接受 BMS-936558 静脉给药，剂量为 1-10mg/kg（q2wk）。接受过至少 1 次既往治疗的晚期 NSCLC 患者可入组。患者接受最多 12 个疗程（4 剂/疗程）的治疗，或持续至出现不可接受的毒性、确认疾病进展或完全缓解。采用 RECIST v1.0 对临床作用进行评估。

结果：截止至 2012 年 2 月 24 日，122 例 NSCLC 患者接受了 BMS-936558 治疗，剂量为 1 mg/kg（n=31）、3 mg/kg（n=33）或 10 mg/kg（n=58）。122 例患者中，117 例患者的 ECOG 体力状态评分≤1 分；67 例患者接受过≥3 次既往治疗。中位治疗持续时间为 12 周（范围：2-101.3 周）。NSCLC 患者中常见的与药物相关的不良事件包括疲劳（18%）、食欲减退（10%）、贫血（8%）和恶心（7%）。与药物相关的 3-4 级不良事件的发生率为 8%。发生 2 例与药物相关的肺炎导致的死亡病例。在 76 例可评估的患者中，14 例患者实现部分缓解（PR）（见下表）；所有 14 例患者的治疗持续时间都≥ 24 周，而且 8 例患者的缓解持续时间≥ 24 周。5 例患者的疾病稳定（SD）时间≥24 周。此外，3 例患者的靶病灶肿瘤负荷在新病灶存在的条件下持续下降，但不能归类为缓解者。

结论：在既往治疗的晚期 NSCLC 患者中，BMS-936558 的风险是可以接受的。对鳞状 NSCLC 的作用尤其明显。将会报告其他长期随访数据。

Purpose:BMS-936558 is a fully human monoclonal antibody that blocks the PD-1 co-inhibitory receptor expressed by activated T cells. We report here the activity and safety of BMS-936558 in pretreated pts with advanced NSCLC, a tumor not previously considered responsive to immunotherapy.

Methods:BMS-936558 was administered IV q2wk to pts with various solid tumors at 1 − 10 mg/kg during dose escalation and/or cohort expansion. Pts with advanced NSCLC previously treated with at least 1 prior line of therapy were eligible. Pts received up to 12 cycles (4 doses/cycle) of treatment or until unacceptable toxicity, confirmed progressive disease, or complete response. Clinical activity was assessed by RECIST v1.0.

Results: As of Feb 24, 2012, 122 NSCLC pts had received BMS-936558 at 1 (n=31), 3 (n=33), or 10mg/kg (n=58). ECOG performance status was ≤1 for 117/122 pts; 67/122 pts had received ≥3 prior therapies. Median duration of therapy was 12 weeks (range 2−101.3 wks). Common drug-related AEs in NSCLC pts were fatigue (18%), decreased appetite (10%), anemia (8%), and nausea (7%). The incidence of grade 3–4 related AEs was 8%. There were 2 drug-related deaths from pneumonitis. Of 76 evaluable pts, 14 had a partial response (PR) (Table); all 14 were treated ≥24 wk, and 8 had responses of ≥24 wk. 5 Five pts had stable disease (SD) lasting ≥24 wk. Additionally, 3 pts had a persistent decrease in target lesion tumor burden in the presence of new lesions and were not categorized as responders.

Conclusions:BMS-936558 had an acceptable risk**:**benefit profile in previously treated, advanced NSCLC. Activity in squamous NSCLC was particularly intriguing. Additional long-term follow-up data will be reported.

剂量/Dose, mg/kg	患者数量[a]/ No. pts[a]	ORR,患者数量/No. pts (%)[95% CI]	24 周时的 PFSR/ PFSR at24 wks, %[95% CI]
1	18	1 (6) [0.1−27]	16 [0−34]
3	19	6 (32) [13−57]	41 [18−64]
10	39	7 (18) [8−34]	24 [11−38]
所有 NSCLC/All NSCLC	76[b]	14 (18) [11−29]	26 [16−36]
所有非鳞 NSCLC/ All–Nonsquamous NSCLC	56	7 (13) [5−24]	22 [11−34]
所有鳞状 NSCLC/ All–Squamous NSCLC	18	6 (33) [13−59]	33 [12−55]

a 截止到 2011 年 7 月 1 日接受治疗的缓解-可评估的患者

a Response-evaluable pts dosed by 07/01/2011

b 包括 2 例组织学特征未知的患者，1 例 PR 的患者 ORR=客观有效率（[{CR+PR} ÷ n] × 100)）；PFSR=无进展生存率

b Includes 2 pts with unknown histology, 1 with PR ORR=objective response rate ([{CR+PR}÷n]×100); PFSR=progression-free survival rate

1227O 阿法替尼/西妥昔单抗在对 EGFR 抑制剂获得性耐药（AR）的 EGFR 突变非小细胞肺癌（NSCLC）患者中的作用

1227O ACTIVITY OF AFATINIB/CETUXIMAB IN PATIENTS (PTS) WITH EGFR MUTANT NON-SMALL CELL LUNG CANCER (NSCLC) AND ACQUIRED RESISTANCE (AR) TO EGFR INHIBITORS

Y.Y.Janjigian, E.F. Smit,L.Horn, et al.

背景：在 50%的表皮生长因子受体（EGFR）突变 NSCLC 病例中，对可逆 EGFR 特异性酪氨酸激酶抑制剂（TKI）的获得性耐药（AR）与外显子 20 EGFR T790M 的突变有关。在 T790M 转基因鼠模型中，阿法替尼（A）（一种强效 ErbB 类阻滞剂）和西妥昔单抗（C）的靶向联合治疗几乎诱导完全缓解。在测定最大耐受剂量后，早期临床数据表明 A/C 的推荐剂量联合治疗是可以接受的，在 AR 病例中表现出明显的作用（Janjigian Y. J Clin Oncol 2011; 29 (suppl); abstr 7525）。在此我们报告了一个 AR NSCLC 扩展队列的安全性和有效性数据。

方法：接受厄洛替尼或吉非替尼治疗过程中出现疾病进展的 EGFR突变晚期NSCLC患者直接换为（间隔至少 3 天）阿法替尼（A）40 mg/天口服用药和西妥昔单抗（C）500 mg/m^{2}静脉给药，每周 2 次。根据方案，要求在AR后和研究治疗前，进行肿瘤活检。有效性终点包括客观缓解（OR）和无进展生存期（PFS），并且在第 4、8、12 周进行影像学检查，之后每 8 周进行一次影像学检查。

结果：迄今为止，100 例合格患者已经接受了治疗（中位持续时间 4.1 个月，范围 1–14+个月）。分别有 63%和 31%的患者出现了 EGFR del 19 和 L858R 突变，53%的患者出现了 EGFR T790M 突变。不良事件包括皮疹（1/2 级：65%；3 级：12%）和腹泻（1/2 级：63%；3 级：6%）。90 例患者可纳入有效性评估；疾病控制率为 94%，在 3、6 和 9 个月时 PFS 概率分别为 70%、42%和 18%。在数据截止日期前至少 6 个月时入组的前 60 例可评估的患者中，确认的 OR 率为 40%（95% CI:27.6–53.5），T790M+(38%)和 T790M- (47%)肿瘤的 OR 率相似；中位 PFS 为 4.7 个月，中位缓解持续时间为 7.7 个月。

结论：阿法替尼/西妥昔单抗在对厄洛替尼或吉非替尼产生 AR 的患者中表现出良好的临床疗效，证明了许多 EGFR 突变 NSCLC 患者的生存仍然取决于 ErbB 信号传递。正在努力尝试解释潜在的机制，并且将列出更新的临床数据。计划进行进一步的研究，以确定这种靶向联合疗法在 EGFR 突变 NSCLC 治疗中的潜在作用。

Background:AR to reversible epidermal growth factor receptor (EGFR)-specific tyrosine kinase inhibitors (TKIs) in EGFR mutant (mt) NSCLC is associated with an exon 20 EGFR T790M mutation in □50% of cases. The targeted combination of afatinib (A), a potent ErbB Family Blocker, and cetuximab (C), induced nearly complete regression in T790M transgenic murine models. Following determination of the maximum tolerated dose, early clinical data suggest that the recommended dose combination of A/C is tolerable, with encouraging activity in AR cases (Janjigian Y. J Clin Oncol 2011; 29 (suppl); abstr 7525). Here, we report safety and efficacy data from an expanded cohort in AR NSCLC.

Methods: Pts with EGFR mt advanced NSCLC – progressive on erlotinib or gefitinib – transitioned directly (interval minimum 3 days) to oral, daily A 40 mg and intravenous, bi-weekly C 500 mg/m2. Tumour biopsy after AR, prior to study therapy, was mandated by protocol. Efficacy endpoints included objective response (OR) and progression-free survival (PFS) with imaging at week 4, 8, 12 and every 8 weeks thereafter.

Results: To date, 100 eligible pts have been treated (median duration 4.1 months, range 1–14+months). EGFR del 19 and L858R mt were present in 63% and 31% of pts, and EGFR T790M mt in 53% of pts. Adverse events included rash (Grade 1/2:65%; Grade 3:12%) and diarrhoea (Grade 1/2:63%; Grade 3:6%). Ninety pts were evaluable for efficacy; rate of disease control was 94% and probability of PFS at 3, 6 and 9 months was 70, 42 and 18%, respectively. In the first 60 evaluable pts enrolled at least 6 months before data cut-off, the confirmed OR rate was 40% (95% CI:27.6–53.5), similar in both T790M+(38%) and T790M- (47%) tumours; the median PFS was 4.7 months and the median duration of response was 7.7 months.

Conclusions: Afatinib/cetuximab shows encouraging clinical efficacy in pts with AR to erlotinib or gefitinib, demonstrating that many EGFR mt NSCLCs continue to depend on ErbB signalling for survival. Efforts to elucidate the underlying mechanisms are ongoing, and updated clinical data will be presented. Further studies are planned to establish the potential role of this targeted combination in the treatment of EGFR mt NSCLC.

1228O Dacomitinib（PF-00299804），一种不可逆的泛-HER 酪氨酸激酶抑制剂（TKI），用于 EGFR-突变或 HER2-突变或扩增肺癌的一线治疗

1228O DACOMITINIB (PF-00299804), AN IRREVERSIBLE PAN-HER TYROSINE KINASE INHIBITOR (TKI), FOR FIRST-LINE TREATMENT OF EGFR-MUTANT OR HER2-MUTANT OR -AMPLIFIED LUNG CANCERS

M.Kris,Z.Goldberg, P.A.Janne, et al.

背景：Dacomitinib 可抑制 EGFR、HER2 和 HER4，具有不可逆性，而且在 EGFR-突变肺癌模型中（包括耐药模型）表现出优于可逆性 EGFR TKI 的活性。本项开放性 II 期研究在 EGFR-突变，或 HER2-扩增或突变的晚期 NSCLC 患者中对 dacomitinib 进行了评估。

方法：患者有 IIIB/IV 期腺癌，没有既往全身性治疗（EGFR 队列），吸烟少于 10 包-年（在入组前 15 年内未吸烟）或已知 EGFR 突变。HER2 扩增或突变的患者之前可以接受任何治疗。患者接受 dacomitinib 连续口服用药，每日一次，剂量为 45 mg 或 30 mg，可以选择增加到 45 mg；每 28 天进行一次评估。终点包括 4 个月时的无进展生存率（PFS@4M，主要终点）；PFS，部分缓解（PR）率；安全性。

结果：89 例患者入组 EGFR 队列，并且接受了治疗；46 例患者发生 EGFR 外显子 19（n=25）或 21（n=21）突变，32 例（70%）是女性患者。在 46 例 EGFR 外显子 19 或 21 发生突变的可评估患者中，34 例患者实现了 PR（PR 率=74%；95% CI：59–86；外显子 19 组为 72%；外显子 21 为 76%）。外显子 19 和 21 的初步 PFS 相似。在 4 个月时的初步 PFS 为 96%（95% CI:84–99），12 个月时的初步 PFS 率为 74% (95% CI:59–85)，而且初步中位 PFS 为 17 个月（95% CI:13–24）。中位治疗持续时间为 14 个月。迄今为止，HER2 队列中有 17 例患者接受了治疗（3 例出现扩增）。对于获得缓解数据的 16 例患者，出现 2 例 PR（1 例经确认），2 例都有 HER2 突变。5 例患者的最佳缓解为疾病稳定。常见的副作用包括痤疮样皮炎（3/4 级=16.9%/0）和腹泻（13.5%/0）。共 5 例患者因为与药物有关的毒性而停止治疗。

结论：74%的 EGFR 外显子 19 或 21 突变肺癌患者在一线 dacomitinib 治疗后实现 PR；在 1 年时的初步 PFS 率为 74%；初步中位 PFS 为 17 个月；EGFR 外显子 19 和 21 突变患者的 PR 率和初步 PFS 相似；计划在这些患者人群中进行进一步的研究。早期证据表明 dacomtinib 对晚期 NSCLC 的 HER2 有作用，而且招募工作仍在继续。

Background: Dacomitinib irreversibly inhibits EGFR, HER2 and HER4, and showed superior activity vs. reversible EGFR TKI in EGFR-mutant lung cancer models, including resistant forms. This open-label Phase II study evaluates dacomitinib in patients with EGFR-mutant or HER2-amplified or -mutant advanced NSCLCs.

Methods: Patients had stage IIIB/IV adenocarcinoma, no prior systemic treatment (EGFR cohort), had smoked <10 pack years (none within 15 years of enrolment) or had known EGFR mutation. Patients with HER2 amplifications or mutations, could have had any number of prior lines of therapy. Patients received dacomitinib orally once daily continuously at 45 mg, or 30 mg with the option to escalate to 45 mg; evaluation was every 28 days. Endpoints included progression-free survival rate at 4 months (PFS@4M, primary); PFS, partial response (PR) rate; and safety.

Results:89 patients were enrolled and dosed in the EGFR cohort; 46 had EGFR mutation in exons 19 (n=25) or 21 (n=21) and 32 (70%) were female. 34/46 evaluable patients with EGFR exon 19 or 21 mutations had a PR (PR rate=74%; 95% CI:59–86; exon 19=72%; exon 21=76%). Preliminary PFS were similar for exons 19 and 21. Preliminary PFS@4M was 96% (95% CI:84–99), preliminary PFS rate at 12 months was 74% (95% CI:59–85) and preliminary median PFS was 17 months (95% CI:13–24). Median duration of tx was 14 months. To date, 17 patients have been dosed in the HER2 cohort (3 with amplification). For 16 patients with response data, there are 2 PR (1 confirmed), both with HER2 mutation. 5 patients had SD as their best response. Common side effects included dermatitis acneiform (grade 3/4=16.9%/0) and diarrhea (13.5%/0). 5 patients in total discontinued treatment due to drug-related toxicity.

Conclusions:74% of patients with EGFR exon 19 or 21 mutant lung cancers experienced PRs with 1st-line dacomitinib; preliminary PFS rate was 74% at 1 year; preliminary median PFS was 17 months; PR rates and preliminary PFS were similar for patients with EGFR exon 19 and 21 mutations; further research is planned in these patient populations. There are early signs of activity of dacomtinib in targeting HER2 in advanced NSCLCs and recruitment continues.

1191PD　Crizotinib 在 ROS1 基因重排的晚期非小细胞肺癌（NSCLC）患者中的临床作用

1191PD　CLINICAL ACTIVITY OF CRIZOTINIB IN PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) HARBORING ROS1 GENE REARRANGEMENT

S.-H.I.Ou,R.Camidge, J.Engelman, et al.

背景：受体酪氨酸激酶（RTK）ROS1 中染色体重排产生一种 NSCLC 的新分子亚型。ALK 抑制剂可以抑制细胞系中 ROS1 激酶活性。Crizotinib 是其他两种 RTK（MET 和 ALK）的小分子抑制剂，我们在 ROS1-重排的晚期 NSCLC 患者中研究了 crizotinib 的有效性和安全性。

方法：将使用 Break-apart FISH 检测方法测定的 ROS1 重排的晚期 NSCLC 患者纳入到 crizotinib 原始Ⅰ期研究的扩展队列中。患者接受 crizotinib 治疗，方案为标准口服剂量 250 mg BID。根据 RECIST v1.0 测定客观有效率（ORR）。在第 8 周和第 16 周时评估疾病控制率（DCR；疾病稳定[SD]+部分缓解[PR]+完全缓解[CR]）。

结果：在 2012 年 4 月 19 日数据截止时，15 例 ROS1 NSCLC 患者接受 crizotinib 治疗，其中 14 例可进行缓解评估。中位年龄为 54 岁（范围：31-72 岁）。14 例患者是从未吸烟者，而且所有患者组织学检查都为腺癌。所有患者都确认为 ALK 重排阴性。中位既往治疗次数为 1 次（范围：0-6 次）。第一例 ROS1 患者在 2010 年 10 月 19 日接受 crizotinib 治疗。迄今为止，ORR 为 57%（8/14; 95% CI 28.9–82.3），7 例 PR 和 1 例 CR。4 例 SD，在数据截止时，其中 1 例为未确认的 PR。在 8 周 DCR 为 79% (11/14)。中位治疗持续时间为 25.7 周（范围：0.1+至 65.3 +），12 例患者仍继续参与研究。在该组患者中，crizotinib 的药代动力学、抗肿瘤活性和安全性特征与 ALK-阳性 NSCLC 患者中观察到的结果相似。

结论：Crizotinib 与 ROS1 NSCLC 患者出现的临床上显著抗肿瘤活性有关。与 ALK 相似，ROS1 重排产生了另一种独特的分子亚型 NSCLC 患者，而对于这些患者，crizotinib 治疗可能有很高的疗效。重要的是，本研究代表了第一项以 ROS1 为驱动突变和癌症治疗靶点的临床研究。

Background: Chromosomal rearrangements in the receptor tyrosine kinase (RTK) ROS1 define a new molecular subset of NSCLC. ALK inhibitors can inhibit ROS1 kinase activity in cell lines. We examined the efficacy and safety of crizotinib, a small molecule inhibitor of two other RTKs, MET and ALK, in patients with advanced, ROS1-rearranged NSCLC.

Methods: Patients with advanced NSCLC harboring ROS1 rearrangement, as determined using a break-apart FISH assay, were recruited into an expansion cohort of the original phase 1 study of crizotinib. Patients were treated with crizotinib at the standard oral dose of 250 mg BID. The objective response rate (ORR) was determined based on RECIST v1.0. The disease control rate (DCR; stable disease [SD]+partial response [PR]+complete response [CR]) was evaluated at weeks 8 and 16.

Results: At the time of data cut-off on April 19, 2012, 15 patients with ROS1 NSCLC had received crizotinib and 14 were evaluable for response. The median age was 54 years (range 31–72). Fourteen patients were never-smokers and all had adenocarcinoma histology. All patients were confirmed negative for ALK rearrangement. The median number of prior treatments was 1 (range 0–6). The first ROS1 patient received crizotinib on October 19, 2010. To date, the ORR is 57% (8/14; 95% CI 28.9–82.3), with 7 PR and 1 CR. There were 4 SD, one of which was unconfirmed as PR at the time of data cut-off. The DCR at 8 weeks was 79% (11/14). Median duration of treatment was 25.7 weeks (range 0.1+to 65.3+), and 12 patients continue on study. The pharmacokinetics, antitumor activity and safety profile of crizotinib in this group of patients were similar to those observed in patients with ALK-positive NSCLC.

Conclusions: Crizotinib is associated with clinically significant antitumor activity in patients with ROS1 NSCLC. Similar to ALK, ROS1 rearrangement defines another unique molecular subset of NSCLC patients for whom crizotinib therapy may be highly effective. Importantly, this study represents the first clinical investigation of ROS1 as a driver mutation and therapeutic target in cancer.

1329 V（长春瑞滨）/C（顺铂）/B（贝伐珠单抗）治疗后使用 D（多西他赛）/G（吉西他滨）/B 与 D/C/B 相比作为晚期或转移性非鳞非小细胞肺癌（NSCLC）的一线治疗的多中心、随机 II 期研究

1329 A MULTICENTER, RANDOMIZED PHASE II STUDY OF V (VINORELBINE)/C (CISPLATIN)/B (BEVACIZUMAB) FOLLOWED BY D (DOCETAXEL)/G(GEMCITABINE)/B VERSUS D/ C /B AS A FIRST-LINE THERAPY FOR ADVANCED OR METASTATIC NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSCLC)

A.Kotsakis, E.Kontopodis, N.Vardakis, et al.

背景：含铂双联疗法被认为是 NSCLC 治疗的基石，多西他赛（D）/吉西他滨（G）联合疗法已经表现出与含铂双联疗法相同的活性，而且表现出更有利的毒性特征。近期对使用 4 种活性药物的序贯治疗（包括顺铂）进行了研究，认为这种疗法可以实现良好的缓解率（Pallis A, et al; Lung Cancer 2006 52(2)**:**165-71）。在标准含铂治疗方案中加用贝伐珠单抗（B）可以改善临床结果。对比了 4 种药物序贯治疗+贝伐珠单抗与标准不含铂治疗方案+贝伐珠单抗的有效性。

方法：77 例患有不可切除的IIIB期和IV期非鳞NSCLC且未接受过治疗的患者被随机分配接受长春瑞滨（V） 60 mg/m^2 PO（第 1 天和第 8 天）、顺铂（C）80 mg/m^2 IV（第 1 天）和贝伐珠单抗（B）15 mg/kg IV，共 3 个疗程，然后接受多西他赛（D）75 mg/m^2 IV、/吉西他滨（G）1100 mg/m^2 IV 和贝伐珠单抗（B）15 mg/kg IV（都在第 1 天给药）（A组），或多西他赛（D）75 mg/m^2 IV、顺铂（C）80mg/m^2 IV和贝伐珠单抗（B）15 mg/kg IV。每 3 周为一个疗程，共 6 个疗程。主要终点是有效率（RR），次要终点是总生存期（OS）和无进展生存期（PFS）。

结果：39 例患者被随机分配到 B 组（对照组），38 例患者被分配到序贯治疗组。A 组和 B 组中的总 RR 分别为 36.8%和 46.2%（p= 0.49）。出现 3 例完全缓解，A 组 1 例。A 组和 B 组的中位 PFS 分别为 5.77 和 5.53 个月（p= 0.368）。中位 OS 分别为 16.9 和 10.9 个月（p= 0.39）。A 组和 B 组的 1 年和 2 年生存率估计值分别为 64.1% 和 35%及 48.4% 和 24%。2 组间的毒性特征没有差异，虽然试验组中观察到更多的疗程延迟（29.5 vs. 12.2; p< 0.001）。

结论：使用 4 种活性药物的序贯治疗是可行且安全的。与标准含铂治疗方案相比，联合治疗表现出良好的结果。

Background: The combination of D/G has shown equal activity compared to the platinum-based doublets, which is considered the cornerstone for the treatment of NSCLC, with a more favorable toxicity profile. Sequential therapy with four active drugs, including C, was recently investigated and attributed a favorable response rate (Pallis A, et al; Lung Cancer 2006 52(2)**:**165-71). Incorporation of B to the standard platinum-based regimen improved its clinical outcome. The efficacy of sequential four drug treatment in combination with B was compared to the standard non platinum-based regimen combined with B.

Methods: Seventy-seven treatment-naïve patients with unresectable stage IIIB and IV non-squamous NSCLC were randomized to receive V 60 mg/m2 PO on day 1 and 8, C 80mg/m2 IV on day 1 and B 15 mg/kg IV on day 1, for 3 cycles followed by D 75 mg/m2 IV, G 1100 mg/m2 IV and B 15 mg/kg IV, all on day 1 (Arm A) or D 75 mg/m2 IV, C 80mg/m2 IV and B 15 mg/kg IV on day. The cycles were repeated every 3 weeks for a total of 6 cycles. The primary endpoint was response rate (RR) and the secondary end points overall survival (OS) and progression free survival (PFS).

Results: Thirty-nine patients were randomized to arm B (control) and 38 patients to the sequential arm. The overall RR was 36.8% and 46.2% in arm A and B, respectively (p= 0.49). There were 3 complete responses, one in arm A. Median PFS was 5.77 and 5.53 months in arm A and B, respectively (p= 0.368). Median OS was 16.9 and 10.9, respectively (p= 0.39). The estimated 1 and 2-year survival for arm A versus B were 64.1% and 35% versus 48.4% and 24%, respectively. No difference in the toxicity profile was observed between the 2 arms, although more cycle-delays were observed in the experimental arm (29.5 versus 12.2; p< 0.001).

Conclusion: Sequential treatment with four active drugs is feasible and safe. The combination attributes encouraging results compared to the standard platinum-based regimen.

1327 一项对非鳞状细胞肺癌患者给予顺铂-多西他赛-贝伐珠单抗诱导化疗后使用贝伐珠单抗和培美曲塞维持治疗的 II 期试验：日本冈山肺癌研究组试验 0903

1327 A PHASE II TRIAL OF CISPLATIN-DOCETAXEL-BEVACIZMAB INDUCTION CHEMOTHERAPY FOLLOWED BY BEVACIZMAB AND PEMETREXED MAINTENANCE THERAPY IN PATIENTS WITH NONSQUAMOUS CELL LUNG CARCINOMA:OKAYAMA LUNG CANCER STUDY GROUP TRIAL 0903

A. Nishiyama, H. Yoshioka, K. Kunimasa, et al.

背景：在含铂双联疗法中加用贝伐珠单抗（BEV）产生了显著但程度不大的生存优势。最近，在 PARAMOUNT 试验中，培美曲塞（PEM）维持治疗实现了很高程度的 PFS 改善。OLCSG 0903 II 期试验在晚期非鳞非小细胞肺癌患者中研究了顺铂（CDDP）-多西他赛（DOC）-BEV 诱导治疗后使用 BEV-PEM 维持治疗的有效性和安全性。

方法：在本试验中，40 例PS评分良好（0 或 1 分）的患者进入诱导期，具体为 4 个疗程的诱导CDDP（80mg/m^2）、DOC（60mg/m^2）和 BEV （15mg/kg）治疗，在第 1 天给药，每 21 天为一个疗程。在CDDP-DOC-BEV诱导期内未进展的患者在第 1 天接受了BEV (15mg/kg)和PEM (500mg/m^2)维持治疗，直到疾病进展（每 21 天为一个疗程）。主要终点是PFS，而次要终点包括毒性、OS和有效率。

结果：患者特征如下：中位年龄：62 岁；78%男性；100%日本人；30%PS 评分为 0 分；73% IV 期；70%腺癌。在此项分析时，23 例患者（58%）停止了治疗，由于不良事件而停止治疗的患者比例为 35%（8/23）。主要毒性是骨髓抑制（4 级血液学毒性：20 例患者[50%]），而且观察到 10 例患者（25%）发生了 3/4 级发热性中性粒细胞减少症，未出现与治疗有关的死亡。客观缓解率和疾病控制率（% CR/PR/SD 患者）分别为 82.5%和 97.5%。中位 PFS 时间为 10.2 个月，而 6 个月 PFS 率为 63.2%（95%可信区间：44.9-76.9 %）。

结论：对于晚期非鳞非小细胞肺癌患者，CDDP-DOC-BEV 后使用 BEV-PEM 维持治疗是一种有效且可适当耐受的治疗方案。

Background: Addition of bevacizmab (BEV) to platinum-based doublet yields a significant but only modest survival advantage. Recently, in the PARAMOUNT trial pemetrexed (PEM) maintenance therapy produced a high magnitude of PFS improvement. The OLCSG 0903 phase 2 trial investigated efficacy and safety of cisplatin (CDDP)-docetaxel (DOC)-BEV induction therapy followed by BEV-PEM maintenance therapy in patients with advanced nonsquamous non-small cell lung carcinoma.

Methods: In this trial, 40 patients with good PS (0 or 1) participated in the induction phase, specified as four cycles of induction CDDP (80mg/m^2), DOC (60mg/m^2) and BEV (15mg/kg) on day 1 of a 21-day cycle. Patients who had not progressed during CDDP-DOC-BEV induction received maintenance BEV (15 mg/kg) and PEM (500mg/m2) on day 1 of a 21-day cycle until disease progression. The primary endpoint was PFS, and the secondary endpoints included toxicity, OS and response rate.

Results: Patient characteristics were as follows**:**median age**:**62 years; 78% male; 100% Japanese; 30% PS 0; 73% stage IV; and 70% adenocarcinoma. At the time of this analysis, 23pts (58%) discontinued the treatment, and the proportion of discontinuations to AEs was 35% (8/23). The principal toxicity was myelosuppression (grade 4 hematological**:**20 patients [50%]), and grade 3/4 febrile neutropenia was observed in 10 (25%) despite no treatment-related deaths. The objective response rate and disease control rate (% patients with CR/PR/SD) was 82.5% and 97.5%, respectively. The median PFS time was 10.2 months, and the 6-month PFS rate was 63.2% (95% confidence interval**:**44.9-76.9 %).

Conclusions:CDDP-DOC-BEV followed by BEV-PEM maintenance seems an effective and moderately tolerated treatment for patients with advanced nonsquamous non-small cell lung carcinoma.

1336 EGFR 酪氨酸激酶抑制剂治疗晚期非小细胞肺癌失败的临床模式和后续处理
1336 CLINICAL MODES OF EGFR TYROSINE KINASE INHIBITOR FAILURE AND SUBSEQUENT MANAGEMENT IN ADVANCED NON-SMALL CELL LUNG CANCER

H.Chen, J.Yang, H.Yan, et al

背景：虽然偶有表皮生长因子受体（EGFR）酪氨酸激酶抑制剂（TKI）治疗晚期非小细胞肺癌（NSCLC）失败的多样性报告，但没有发表 EGFR-TKI 失败模式的综述，这可能妨碍了对不同失败模式患者的适当处理。

目的：本研究的主要目的是对 TKI 治疗失败的多样性进行分类，并且研究失败临床模式对后续管理和预后的有用性。

患者和方法：这项回顾性研究入组了 227 例 EGFR-TKI 治疗失败的中国晚期 NSCLC 患者。将 120 例连续参与临床试验的患者纳入到培训集，以根据临床因素确定临床模式。按照 Bayes 判别分析，将另外 107 例常规患者纳入验证集。对 EGFR 突变和 c-MET 扩增进行分析。采用 Kaplan–Meier 生存分析检验不同临床模式下预后和后续处理的差异。

结果：疾病控制的持续时间、症状改善和肿瘤负荷的进展确定为可行的分组变量。正确分组率达到 84.1%。将队列分类为 3 个组，如下：130 例患者出现显著进展、42 例患者出现逐步进展，55 例患者出现局部进展。显著进展组、逐步进展组和局部进展组的无进展生存期（PFS）分别为 9.3 个月、12.9 个月和 9.2 个月（P=0.007）。3 个组的总生存期分别为 17.1 个月、39.4 个月和 23.1 个月（P <0.001）。在对逐步进展组患者的后续管理中，TKI 继续治疗优于转换化疗（39.4 个月比 17.8 个月，P =0.02）。这 3 个组中 EGFR 突变或 c-MET 扩增的差异不显著。

结论：EGFR-TKI 治疗失败的临床模式可能有助于制定后续治疗策略及预测晚期 NSCLC 的生存益处。

Context: The diversity of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) failure in advanced non-small cell lung cancer (NSCLC) has been reported sporadically, but there is no published overview of EGFR-TKI failure modes, which could hinder the appropriate management for patients with distinct failure modes.

Objectives: This study mainly aimed to classify the diversity of TKI failure, and to investigate the usefulness of clinical modes in subsequent management and prognosis.

Patients and methods: The retrospective study accrued 227 Chinese advanced NSCLC patients with EGFR-TKI failure. One-hundred and twenty consecutive clinical trial patients were enrolled as the training set to establish a clinical model based on clinical factors. Another 107 routine patients were enrolled as the validating set according to a Bayes discriminant analysis. EGFR mutations and c-MET amplification were analyzed. Kaplan–Meier survival analysis was used to test the differences of prognosis and subsequent management in clinical modes.

Results: The duration of disease control, symptom improvement, and evolution of tumor burden were verified as feasible grouping variables. A correct grouping rate achieved 84.1%. The cohort was classified into three groups, as follows**:**130 patients with dramatic progression, 42 with gradual progression, and 55 with local progression. Progression-free survivals (PFSs) for the dramatic progression, gradual progression, and local progression groups were 9.3, 12.9, and 9.2 months, respectively (P =0.007). Overall survivals for the groups (OSs) were 17.1, 39.4, and 23.1 months, respectively (P <0.001). TKI continuation was superior to switching chemotherapy in a subsequent setting for gradual progression (39.4 vs. 17.8 months, P =0.02). The difference of EGFR mutations or c-MET amplification among the three groups was not significant.

Conclusions: Clinical modes of EGFR-TKI failure could favor strategies for subsequent treatment and predicting a survival benefit in advanced NSCLC.

1352 接受一线贝伐珠单抗（B）治疗的晚期非鳞非小细胞肺癌（NSNSCLC）患者疾病进展（PD）的临床特征和模式：AVVA 研究

1352 CLINICAL PROFILE AND PATTERNS OF PROGRESSION (PD) OF PATIENTS (PTS) WITH ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER (NSNSCLC) TREATED WITH FIRST LINE BEVACIZUMAB (B):AVVA STUDY

J.De Castro, J.M.Garcia-Bueno, M.Domine, et al.

背景：对于未接受过化疗的晚期非鳞 NSCLC 患者，贝伐珠单抗与含铂双联疗法联合治疗可延长生存期并延迟 PD，而且多项临床试验已经对贝伐珠单抗的安全性特征进行了广泛的描述。研究的目的是评估在 44 个西班牙研究中心接受贝伐珠单抗治疗的真实条件下 nsNSCLC 患者的行为表现、临床特征和 PD 模式。

方法：AVVA 是一项评估临床特征（性别、年龄、PS、组织学、疾病分期、并发症、肿瘤负荷、治疗、缓解和耐受性）和描述 PD 模式的多中心、流行病学研究。入组了确诊为晚期 nsNSCLC 而且在标准化疗（CT）+贝伐珠单抗治疗 6 个疗程后序贯贝伐珠单抗维持治疗后出现 PD 证据的患者。

结果：列出了 158 例患者的数据。临床特征包括：中位年龄 58 岁（范围：34-79）；男性 65%；IV 期 91%；腺癌 77%；ECOG PS 评分 0/1/≥2(%)：35/56/9；从未吸烟者/当前吸烟者/曾吸烟者（%）：23/40/37。64%的患者在基线时有相关的伴随疾病（27%心血管疾病，24%肺病）。接受的治疗：贝伐珠单抗+卡铂双联疗法/顺铂双联疗法/其他：70%/25%/5%。CT/B 的中位疗程数：6/9。PD 的模式：44%出现高肿瘤负荷（肿瘤直径≥55mm，而且≥5 个病灶）；97%的患者出现胸内病变，53%的患者出现胸外病变，13%的患者仅出现肺部病变。高肿瘤负荷与胸外病变有关（p<0.05）。ORR 为 53% (95% CI:45%-61%)，而疾病控制率为 85%。在中位 4 个疗程（范围：1-16 个疗程）后实现最佳缓解。在 PD 时 ECOG 评分 0/1：15%/50%。中位 PFS 为 7.7 个月（95% CI:7.3-8.1）。根据肿瘤负荷和胸内/外病变，ORR 或 PFS 没有差异。3/4 级毒性包括：静脉血栓形成（3.2%/0）、蛋白尿（0.6%/0）、咯血（0.6%/0）、肺栓塞（0/0.6%）和粘膜炎（0.6%/0）。

结论：在真实患者人群中，不论肿瘤负荷和病变的部位如何贝伐珠单抗均有效。这些结果确认了贝伐珠单抗作为 nsNSCLC 一线治疗的良好安全性和有效性。

Background:B in combination with platinum doublets prolongs survival and delays PD in chemo-naïve pts with advanced nsNSCLC and its safety profile has been widely described in clinical trials. In this study we aim to evaluate the behavior, clinical profile and patterns of PD of real-life nsNSCLC pts treated with B in 44 Spanish institutions.

Methods:AVVA is a multicenter, epidemiological study to define the clinical profile (gender, age, PS, histology, stage, comorbidities, tumor load, Tx, response and tolerability) and describe the patterns of PD. Pts diagnosed with advanced nsNSCLC and evidence of PD after treatment (Tx) with standard chemotherapy (CT) plus B up to 6 cycles followed by maintenance B were included.

Results: Data of 158 pts are presented. Clinical profile was:median age 58 years (range 34-79); male 65%; stage IV 91%; adenocarcinoma 77%; ECOG PS 0/1/≥2 (%):35/56/9; never/current/former smokers (%):23/40/37. 64% of pts presented relevant concomitant disease at baseline (27% cardiovascular disease, 24% pulmonary disease). Tx received:B plus carboplatin-doublet/cisplatin-doublet/other (%) 70/25/5. Median no. of cycles for CT/B:6/9. Patterns of PD:44% presented high tumor load (tumor diameter ≥55mm and ≥5 lesions); 97% of pts presented intra-thoracic disease, 53% presented extra-thoracic disease and 13% only pulmonary disease. High tumor load was associated with extra-thoracic disease (p<0.05). ORR was 53% (95% CI:45-61) and disease control rate was 85%. Best response was achieved after a median of 4 cycles (range 1-16). ECOG 0/1 at PD (%):15/50. Median PFS was 7.7 months (95% CI:7.3-8.1). No differences were found in ORR or PFS according to tumor load and intra/extra-thoracic disease. Grade 3/4 toxicities were:venous thrombosis (3.2%/0), proteinuria (0.6%/0), hemoptysis (0.6%/0), pulmonary embolism (0/0.6%) and mucositis (0.6%/0).

Conclusions:B was effective in this real-life patients' population, irrespective of tumor load and location of the disease. These results confirm the well-established safety profile and the efficacy of B as frontline Tx in nsNSCLC.

1351 贝伐珠单抗（BV）的入组标准是否会导致选择偏倚？
1351 DOES ELIGIBILITY FOR BEVACIZUMAB (BV) LEAD TO SELECTION BIAS?

Y.Takagi, A.Toriihara, Y.Hosomi, et al.

背景：在靶向药物的临床试验中，由于特殊的副作用，所以入组标准一般都很窄。修改入组标准可能会影响治疗终点，如总生存期不依赖于研究药物的实际效果。

方法：对 2005 年-2009 年间开始化疗的 IIIB/IV 期非鳞非小细胞肺癌（NSCLC）患者进行了回顾分析。我们单位在 2010 年首次使用贝伐珠单抗（BV）治疗肺癌。将患者分为 BV 符合入组标准（A）组和 BV-不符合入组标准（B）组。计算 Kaplan-Meier 曲线，并使用时序检验进行组间对比用于估计生存期。使用 Cox 比例风险模型评估年龄、性别、M 因子、体力状态（PS）、一线化疗中使用铂类药物、咯血史、肿瘤的主要血管浸润（MVI）和临床显著心血管疾病对总生存期的预后影响。由对临床结果保持盲态的放射科医师评估了 MVI。所有检验都是双侧检验，显著性水平为 0.05。

结果：在接受化疗的 576 例肺癌患者中，283 例患有 IIIB/IV 期非鳞 NSCLC。在排除 15 例适合接受化放疗的患者和 22 例 PS 评分 3/4 的患者后，对 246 例患者的 BV 合格性进行了最终评估。基于咯血史（N=32）、MVI（N=64）和心血管疾病（N=13）中的一种或多种因素，认为 89 例患者不符合 BV 治疗的入组标准（队列 B）。10 例患者无法判定是否符合入组标准，将其余 147 例患者归类到队列 A。队列 A 中的总生存期（中位值，14.9 个月）显著优于队列 B（中位值，8.6 个月；风险比，0.55; 95%CI, 0.42-0.74; P<0.0001）。多变量分析表明性别、PS、咯血史和 MVI 是重要预后因子。

结论：BV 符合入组标准本身也是非鳞 NSCLC 患者的一个有力的预后因子。

Background: Eligibility is often narrowed in clinical trials of targeted drugs because of specific adverse effects. Modified eligibility criteria can affect endpoints such as overall survival independently of the actual effect of an investigational drug.

Methods: Patients with stage IIIB/IV, non-squamous non-small cell lung cancer (NSCLC) who started chemotherapy from 2005 to 2009 were reviewed. Bevacizumab (BV) was first used to treat lung cancer at our institution in 2010. We divided patients into BV-eligible (A) and -ineligible (B) groups. To estimate survival, Kaplan-Meier curves were calculated and compared between the groups using the log-rank test. We also examined the prognostic impact of age, gender, M factor, performance status (PS), use of platinum in first-line chemotherapy, history of hemoptysis, major blood vessel invasion (MVI) by the tumor and clinically significant cardiovascular disease upon overall survival using the Cox proportional hazards model. A radiologist who was blinded to the clinical outcomes evaluated MVI. All tests were two sided with a significance level of 0.05.

Results: Among 576 patients with lung cancer who undergone chemotherapy at our department, 283 of them had stage IIIB/IV non-squamous NSCLC. After excluding 15 patients with indications for combined chemoradiotherapy and 22 with PS 3/4, the eligibility of 246 patients for BV was finally evaluated. Eighty-nine patients were considered ineligible for BV (cohort B), based on one or more of a history of hemoptysis (N=32), MVI (N=64) and cardiovascular disease (N=13). Eligibility could not be determined in ten patients and the remaining 147 patients were classified into cohort A. Overall survival was significantly better in cohort A (median, 14.9 months) than in cohort B (median, 8.6 months; hazard ratio, 0.55; 95%CI, 0.42-0.74; P<0.0001). Multivariate analysis indicated that gender, PS, a history of hemoptysis and MVI are significant prognostic factors.

Conclusion: Eligibility for BV itself is a powerful prognostic factor for patients with non-squamous NSCLC.

1348 未经过表皮生长因子受体（EGFR）突变选择的晚期非小细胞肺癌（NSCLC）患者在酪氨酸激酶抑制剂（TKI）治疗后接受化疗的有效性

1348 EFFICACY OF CHEMOTHERAPY (CHT) BEYOND TYROSINE KINASES INHIBITORS (TKI) IN ADVANCED NON SMALL CELL LUNG CANCER (NSCLC) PATIENTS (PTS) UNSELECTED FOR EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATION

P.Trenta, R.Iacovelli, A.Palazzo, et al.

背景：在二线或三线 TKI 治疗失败后，尽管还没有临床试验支持，许多临床医师为他们的晚期 NSCLC 患者提供了新的化疗方案，。我们目的是分享在EGFR突变状态未知或EGFR野生型患者中使用厄洛替尼或吉非替尼靶向治疗后给予细胞毒性治疗方面的经验。

患者和方法：2003 年 1 月至 2011 年 12 月，84 例患者接受了 TKI 二线或三线治疗，在疾病进展后，其中 34 例患者接受了至少一种后续化疗。我们收集了缓解数据，使用 Kaplan-Meier 法分析了 TKI 之外化疗的总生存期（OS）和无进展生存期（PFS），并且使用时序检验分析它们与疾病控制率（DC）及一线化疗和 TKI 的 PFS 之间的相关性。

结果：34 例患者中，29 例患者接受三线化疗，5 例患者接受四线化疗。67.6%的患者接受单药治疗，32.4%的患者接受联合治疗，7 例病例接受了含铂治疗方案。缓解率（RR）为 20.5%，DC 率为 52.9%。TKI 治疗后的中位 OS 和 PFS 分别为 13 个月（95% CI. 6.36-19.63）和 3 个月（95% CI 0.5-5.5）。在 TKI 治疗期间实现疾病控制患者的 OS 为 18.2 个月，靶向治疗无效患者的 OS 为 5.7 个月（p=0.019）。在单变量分析时，TKI 治疗后良好的 PS（≤1）（p=0.022）、DC（p=0.025）和一线化疗后 PFS>6 个月（p=0.002）是 TKI 后化疗 PFS 较长的唯一预测因子。在多变量分析时，只有一线化疗后 PFS>6 个月被确认为 TKI 治疗后 PFS 较长的独立预测因子（p=0.05）。年龄在 65 岁以上或以下（p=0.7）、联合疗法的使用（p=0.84）和含铂疗法（p=0.75）似乎不会改善 TKI 之外化疗的生存结果和疾病控制率。

结论：TKI 的疾病控制率是一个良好的患者预后指标。一线化疗后的良好缓解和缓解时间延长（>6 个月）及 PS ≤1 是选择靶向药物治疗失败后可能从细胞毒性治疗中获益患者的有用预后因子。在这种情况下，高强度化疗似乎没有真正的优势。

Background: After failure of a second or third line therapy with TKI, many clinicians offer to their advanced NSCLC pts a new line of cht, even if there are no perspective trials that support this choice. We report our experience about cytotoxic treatment administered after a target therapy with Erlotinb or Gefitinib in pts with unknown EGFR mutational status or EGFR wild type.

Patients and methods: Since January 2003 to December 2011, 84 pts received TKI in second or third line and after progression 34 of them were treated with at least one subsequent line of cht. We collected response data, analyzed overall survival (OS) and progression free survival (PFS) of cht beyond TKI with Kaplan-Meier method and correlated them with Disease Control (DC) and PFS of first line cht and TKI using log-rank test.

Results:29 out of 34 pts received cht as third and 5 pts as forth line treatment. 67,6 % of pts received a monotherapy, while 32,4% a combination treatment, platinum based in 7 cases. A response rate (RR) of 20,5% and a DC rate of 52,9% were registered. Median OS post-TKI and PFS were 13 (95% CI. 6,36-19,63) and 3 months (mos) (95% CI 0,5-5,5) respectively. OS of pts who obtained DC during TKI was 18,2 mos compared to 5,7 mos of pts not responder to target treatment (p=0,019). At univariate analysis good PS(≤1) after TKI (p=0,022), DC (p=0,025) and PFS>6 mos with first line cht(p=0,002) were found to be the only predictive factors of a better PFS with post-TKI cht. At multivariate analysis only the PFS>6 mos with first line cht was confirmed as an independent predictive factor of better PFS in post-TKI setting (p=0,05). Age more or less than 65 years (p=0,7) use of combination (p=0,84) and platinum-based therapy (p=0,75) seems not to improve survival outcome and DC of cht beyond TKI.

Conclusions:DC with TKI identify a good prognostic group of pts. Good and prolonged response (>6 mos) to the first line cht and a PS ≤1 are useful predictive factors to select pts who could benefit from receiving a cytotoxic treatment after target agents failure. Aggressive cht strategies do not seem to produce a real advantage in this setting.

1335 多西他赛、顺铂和贝伐珠单抗作为晚期/转移性非小细胞肺癌患者的一线治疗：希腊肿瘤研究组（HORG）的一项多中心 II 期研究

1335 FRONT-LINE TREATMENT WITH DOCETAXEL, CISPLATIN AND BEVACIZUMAB FOR PATIENTS WITH ADVANCED/METASTATIC NON-SMALL CELL LUNG CANCER:A MULTICENTER PHASE II STUDY OF THE HELLENIC ONCOLOGY RESEARCH GROUP (HORG)

N.Kentepozidis, M.Agelidou, C.Christophylakis,et al.

背景：在一项多中心 II 期研究中，评估多西他赛/顺铂联合贝伐珠单抗（DCV 方案）治疗转移性非小细胞肺癌（NSCLC）患者的有效性和耐受性。

方法：48 例有可测量的、经组织学确认、非鳞状IIIB（湿性）/IV期NSCLC患者符合治疗标准，患者的PS评分 0-2 且未接受过化疗，患者接受多西他赛（75 mg/m^2 IV）、顺铂（80 mg/m^2 IV）和贝伐珠单抗（15 mg/kg IV），每 21 天为一个疗程。患者没有接受贝伐珠单抗维持治疗。

结果：所有患者均达到缓解标准。2 例患者实现完全缓解（4.2%），14 例患者实现部分缓解（29.2%）[总有效率：33,3%; 95% CI=(20.0%-46.7%)]，而 14 例患者达到疾病稳定。中位 PFS 为 4.4 个月（95% CI:1.32-7.48），中位 OS 为 13.27 个月(95% CI:9.72-16.81)。与治疗有关的 3 级或 4 级血液学不良事件包括白细胞减少症、中性粒细胞减少症和贫血，发生率分别为 8.4%、18.7%和 2.1%。3 例患者（6.3%）发生了 2-4 级发热性中性粒细胞减少症，1 例患者（2.1%）由于肠穿孔引发的脓毒症导致死亡。

结论：DCV 方案作为晚期非鳞 NSCLC 患者的一线治疗是一种有效的治疗方案，而且毒性可以控制，相关益处需要进一步考察。

Background: To evaluate in a multicenter phase II study the efficacy and tolerance of the docetaxel/cispaltin combination in association with bevacizumab (DCV regimen) in metastatic nom-small cell lung cancer (NSCLC) patients.

Methods:48 chemotherapy-naïve patients with measurable, histologically confirmed, non-squamous, IIIB (wet)/IV NSCLC and PS 0-2 were eligible for treatment and received docetaxel (75mg/m2 IV), cisplatin (80 mg/m2 IV) and bevacizumab (15 mg/kg IV) in cycles of 21 days. Patients did not receive maintenance bevacizumab.

Results: All patients were eligible for response. Complete and partial responses were achieved in two (4,2%) and 14 (29.2%) patients, respectively [overall response rate:33,3%; 95% CI=(20.0%-46.7%)] whereas stable disease was documented in 14 patients. The median PFS was 4. 4 months (95% CI:1.32-7.48) and the median OS 13.27 (95% CI:9.72-16.81). Treatment-related grade 3 or 4 hematologic adverse events were leucopenia, neutropenia, and anemia in 8.4%, 18.7% and 2.1% of the patients, respectively. Three (6.3%) patients developed grade 2-4 febrile neutropenia and one (2.1%) patient (2,1%) died because of sepsis due to bowel perforation.

Conclusions: The DCV regimen is an active regimen with manageable toxicity when administered as front line treatment in patients with advanced non-squamous NSCLC and merits to be further investigated.

1337 对比 NP 化疗联合治疗与单独 NP 化疗作为 IIIB/IV 期非小细胞肺癌一线治疗的回顾性研究

1337 NP CHEMOTHERAPY PLUS ENDOSTAR COMPARED WITH NP ALONE AS FIRST-LINE THERAPY IN STAGE IIIB/IV NON-SMALL CELL LUNG CANCER:A RETROSPECTIVE STUDY

M.Zhao, H.Deng, B.Jin, et al.

目的：重组人内皮抑制素是一种新型的肿瘤血管生成抑制剂。既往研究表明重组人内皮抑制素（恩度）联合长春瑞滨-顺铂化疗可以提高晚期非小细胞肺癌（NSCLC）患者的客观缓解率（ORR）并延长至疾病进展时间（TTP），减少毒性。本研究的目的是回顾性对比 NP 化疗联合治疗与单独 NP 化疗作为 IIIB/IV 期非小细胞肺癌一线治疗的有效性和安全性。

方法：我们回顾性分析了 2005 年 1 月至 2010 年 12 月期间在中国医科大学附属第一医院接受了NP化疗联合治疗或单独NP化疗的 65 例既往未接受过治疗的IIIB/IV期NSCLC的中国患者。在治疗的第 1 天和第 8 天给予了长春瑞滨（25 mg/m^2），第 1 天给予了顺铂（75 mg/m^2），在第 1-14 天给予了恩度（7.5 mg/m^2）。每 3 周一个疗程，最多 6 个疗程。根据实体瘤疗效评价标准（RECIST 1.1）对最佳肿瘤缓解率进行了评估。按照NCI-CTC 3.0 标准对不良事件进行定义。采用SPSS 20.0 软件进行了单变量和多变量分析。

结果：患者的中位年龄为 58 岁（范围：34–77 岁）。主要结果如下：标准 NP 化疗加用恩度可以显著降低疾病进展和死亡的风险。NP+恩度组和 NP 组的中位无进展生存期分别为 7.4 个月和 5.5 个月（P= 0.042）。NP+恩度组和 NP 组的中位总生存期分别为 17.6 个月和 12.6 个月（P=0.046）。两组间的客观有效率和疾病控制率没有统计学差异。NP+恩度组中 3/4 级血液学不良事件的发生率较高（48.5%比 21.9%, P=0.025），但可以耐受。

结论：本研究证明了 NP 联合恩度治疗方案对于既往未接受过治疗的 IIIB/IV 期非小细胞肺癌患者是一种有效的治疗方法，而血液学毒性的增加是可以耐受的。

Purpose: Recombinant human endostatin is a novel inhibitor of tumor angiogenesis. Previous studies have indicated that Recombinant human endostatin (endostar) plus vinorelbine-cisplatin chemotherapy could improve objective response rates (ORR) and time to progression (TTP) of advanced non-small cell lung cancer (NSCLC) patients with decreased toxicity. The purpose of this study was to retrospectively compare the efficacy and safety of NP chemotherapy plus endostar with NP alone as first-line therapy in stage IIIB/IV non-small cell lung cancer.

Methods: We reviewed the records of 65 previously untreated Chinese patients with stage IIIB/IV NSCLC who were treated with NP chemotherapy plus endostar or NP alone between January 2005 and December 2010 at The First Hospital of China Medical University. Vinorelbine (25mg/m^2) was administered on days 1 and 8, cisplatin(75mg/m^2) was administered on day 1, and endostar (7.5mg/m^2) was administered on days 1-14. Treatments were repeated every 3 weeks for a maximum of 6 cycles. The best tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The adverse events were defined by NCI-CTC 3.0 criteria. Univariate and multivariate analyses were performed using the SPSS 20.0 software.

Results: The median age of patients was 58 years (range, 34–77 years). Our main results are as follows**:**Addition of endostar to standard NP chemotherapy significantly reduced the risks of disease progression and death. The median progression-free survival of the NP plus endostar group and NP group were 7.4 months and 5.5 months (P= 0.042). The median overall survival of the NP plus endostar group and NP group were 17.6 months and 12.6 months (P=0.046). There was no statistical difference in objective response rates and disease control rates between the two groups. The incidence of grade 3/4 hematologic adverse events was higher in NP plus endostar group (48.5% vs 21.9%, P=0.025) but tolerable.

Conclusion: This study demonstrated that the addition of endostar to the NP regimen is an effective treatment option with an acceptable increase in hematologic toxicity in previously untreated patients with stage IIIB/IV non-small cell lung cancer.

1353 贝伐珠单抗联合多西他赛治疗既往接受过治疗的非鳞非小细胞肺癌患者的 II 期试验
1353 PHASE II TRIAL OF BEVACIZUMAB PLUS DOCETAXEL IN PATIENTS WITH PREVIOUSLY TREATED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

F.Ohyanagi, K.Kudo, N.Yanagitani, et al.

背景：贝伐珠单抗（B）添加到非鳞（Nsq）非小细胞肺癌（NSCLC）一线化疗中的效果已经被证实。但是，尚未对其添加到二线及以上化疗中的有效性进行充分研究。多西他赛（D）是 NSCLC 二线治疗的一种标准疗法，而且在临床前模型中已经证明多西他赛和贝伐珠单抗（B）联合治疗（D+B）的协同效应。因此，本项 II 期研究评估了 D+B 方案在既往接受过治疗的 Nsq NSCLC 患者中的有效性和安全性。

方法：经过组织学或细胞学确认的Nsq NSCLC（20-74 岁）、ECOG 评分（PS）0-2 分而且至少接受过一次既往化疗的患者入组本研究。患者在第 1 天接受D（60 mg/m^2）和B（15 mg/kg）治疗，每 3 周重复一次，直到疾病进展（PD）或出现不可接受的毒性。主要终点是有效率（RR）。

结果： 2010 年 5 月至 2011 年 7 月，本研究入组了 28 例患者（16 例男性/12 例女性；中位年龄，65 岁；PS，0/1/2：19/9/0；腺癌/其他：22/6；既往化疗方案的数量，1/2/3/4/5：16/5/2/1/4）。在这些患者中，28 例患者被纳入毒性分析，而且对 27 例患者进行了缓解率评估。18 例患者实现了客观缓解（部分缓解，18 例；疾病稳定，8 例；疾病进展，1 例）。缓解率和疾病控制率分别为 66.7%和 96%。在中位随访 15.7 个月后，中位无进展生存期为 7.2 个月，中位总生存期为 16.7 个月。观察到的主要毒性反应为骨髓抑制（3/4 级中性粒细胞减少症，85.7%：发热性中性粒细胞减少症，21%）。另外轻度的非血液学毒性轻微出血也有观察到。

结论：在既往接受过治疗的 Nsq NSCLC 患者中，D+B 联合疗法高度有效，有必要进行进一步的研究。

Background: The additional effects of bevacizumab (B) as a first line chemotherapy for non-squamous (Nsq) non-small cell lung cancer (NSCLC) have been established. However, its efficacy as a second line or higher chemotherapeutic agent is not sufficiently investigated. Docetaxel (D) is a standard second line therapy for NSCLC, and the synergistic effects of a combination of D and B (D+B) have been demonstrated in preclinical models. Therefore, this phase II study evaluated the efficacy and safety of D+B in patients with previously treated Nsq NSCLC.

Methods: Patients with histologically or cytologically confirmed Nsq NSCLC (20–74 years) with an Eastern Cooperative Oncology Group performance status (PS) of 0-2 and at least one prior course of chemotherapy were eligible for the study. Patients were treated with D (60mg/m^2) and B (15mg/kg) on day 1, which was repeated every 3 weeks until progressive disease (PD) or unacceptable toxicity occurred. The primary endpoint was the response rate (RR).

Results: Between May 2010 and July 2011, 28 patients were enrolled in the study (16 males/12 females; median age, 65 years; PS, 0/1/2**:**19/9/0; adeno/other**:**22/6; number of prior chemotherapy regimens, 1/2/3/4/5**:**16/5/2/1/4). Of these, 28 patients were included in the analysis of toxicities and 27 were evaluated for their response. An objective response was observed in 18 patients (partial response, 18; stable disease, 8; PD, 1). RR and disease control rate were 66.7% and 96%, respectively. After a median follow-up of 15.7 months, the median progression-free survival was 7.2 months and median overall survival was 16.7 months. The main toxicity observed was myelosuppression (grade 3/4 neutropenia, 85.7%; febrile neutropenia, 21%). Mild nonhematological toxicity with minimal bleeding was also observed.

Conclusions:A combination of D and B was highly active in patients with previously treated Nsq NSCLC; further study is warrented.

1313 转移性非小细胞肺癌（MNSCLC）患者体内循环肿瘤细胞（CTC）中 EGFR、HER-2、CEA 的预后意义

1313 PROGNOSTIC SIGNIFICANCE OF EGFR, HER-2, CEA ON CIRCULATING TUMOUR CELLS (CTCS) IN PATIENTS WITH METASTATIC NON-SMALL-CELL LUNG CANCER (MNSCLC)

C.Loretelli, E. Galizia, M.Scartozzi, et al.

目的：我们的目的是评估 CTC 在提供接受化疗的 mNSCLC 患者的预后方面的作用。

患者和方法：在这项单中心前瞻性研究中，从既往未接受过治疗的 mNSCLC 患者获得了 CTC 分析的血样。使用上皮细胞粘附分子的免疫磁性技术对 CTC 进行了评估。对表达上皮细胞粘附分子（EpCAM）的细胞进行了免疫磁珠富集，然后对一系列标记基因（EGFR、HER-2、CEA）进行实时定量 PCR。

结果：我们对 45 例 mNSCLC 患者进行了分析：24 例腺癌患者、8 例鳞癌患者和 13 例低分化患者。分别在 12 例、5 例和 11 例患者的 CTC 中发现了 EGFR、HER-2 和 CEA 表达。总体上，在治疗过程中有 31 例患者（68.9%）发生疾病进展，而 14 例患者（31.1%）实现了疾病控制（即部分/完全缓解或疾病稳定的患者）。在疾病进展的 31 例患者中，检测到 11 例患者（35.5%）有 EGFR 表达，在实现疾病控制的 14 例患者中，仅检测到 1 例患者（7.1%）有 EGFR 表达（p 0.07）。在疾病进展的 31 例患者中，检测到 3 例患者（35.5%）有 HER-2 表达，在实现疾病控制的 14 例患者中，仅检测到 2 例患者（14.3%）有 HER-2 表达（p 0.64）。在疾病进展的 31 例患者中，检测到 10 例患者（32.3%）有 CEA 表达，在实现疾病控制的 14 例患者中，仅检测到 1 例患者（7.1%）有 CEA 表达（p 0.13）。仅 CTC 中的 EGFR 表达与临床预后（表现为无进展生存期）存在相关性。CTC 中有和无 EGFR 表达的患者临床特征分布均衡。无和有 EGFR 表达的患者的 PFS 分别为 2.8 个月和 2.3 个月（p 0.03）。

结论：在 mNSCLC 患者体内可检测到 CTC，而且其可能作为该疾病的新型预后因子。在进入常规临床应用前，还需要进一步的验证。

Purpose: We aimed to assess the role of CTCs in providing prognostic information of mNSCLC patients receiving chemotherapy.

Patients and methods: In this single-center prospective study, blood samples for CTCs analysis were obtained from patients with previously untreated mNSCLC. CTCs were measured using an epithelial cell adhesion molecule-based immunomagnetic technique. Immunomagnetic bead enrichment for cells expressing epithelial cell adhesion molecule (EpCAM) was performed, followed by multi-marker quantitative real-time PCR of a panel of marker genes**:**EGFR, HER-2, CEA.

Results: We analysed 45 patients with mNSCLC**:**24 adenocarcinoma, 8 squamous cell carcinoma and 13 poorly differentiated. EGFR, HER-2 and CEA expression were found in CTCs of respectively 12, 5 and 11 patients. Globally, 31 patients (68.9%) progressed during treatment, whereas disease control (i.e. patients with partial/complete response or stable disease) was achieved in 14 patients (31.1%). EGFR expression was detected in 11/31 patients with disease progression (35.5%) and in only 1 out of 14 patients with disease controlled (7.1%) (p 0.07). HER-2 expression was detected in 3/31 patients with disease progression (9.7%) and in 2/14 patients with disease controlled (14.3%) (p 0.64). CEA expression was detected in 10/31 patients with disease progression (32.3%) and in 1/14 patients with disease controlled (7.1%) (p 0.13). Only EGFR expression in CTCs showed a correlation with clinical outcome, expressed by progression free survival (PFS). Patients with and without EGFR expression in CTCs were homogeneous for clinical characteristics. PFS was 2.8 v 2.3 months (p 0.03) respectively for patients without and with EGFR expression.

Conclusion:CTCs are detectable in patients with mNSCLC and could show novel prognostic factor for this disease. Further validation is warranted before routine clinical application.

78IN 靶向药物或生物制品对 I–III 期 NSCLC 有效果吗？
78IN IS THERE A ROLE FOR TARGETED AGENTS OR BIOLOGICALS IN STAGE I–III NSCLC?

演讲者：O.Gautschi Luzern/CH

50%以上的非小细胞肺癌（NSCLC）患者（包括不同肿瘤分期和组织学亚型的患者）存在有活性的驱动基因突变。在晚期 NSCLC 伴有 EGFR 突变的患者中进行的多项随机 III 期试验证明，EGFR 抑制剂（吉非替尼、厄洛替尼和阿法替尼）的有效率和无进展生存期优于化疗。II 期试验证明了克唑替尼治疗 ALK-易位的晚期 NSCLC 有着很高的有效率，并且有 2 项随机 III 期试验在期待结果。肿瘤特异性治疗的其他靶点在 I-II 期试验和回顾性系列分析中被初步验证，包括 MET、ROS1、HER2、BRAF、KRAS、PI3K 和其他。此外，在基于组织学和 EGFR 表达选择的晚期 NSCLC 患者中进行的多项 III 期试验显示了贝伐珠单抗和西妥昔单抗联合化疗具有临床疗效。目前，许多机构都可进行快速分子检测，而且已经开始了将这些新型疗法从用于 IV 期疾病提前至用于更早期疾病的转化。用药应该谨慎，因为治疗的最终目标是治愈，而不仅仅肿瘤缓解，并且对 I-III 期 NSCLC 患者给予尚未经临床研究验证的新药具有危险性。应该注意的是，S0023 和 BR.19 研究表明，在根治治疗中加用吉非替尼对局灶性 NSCLC 患者并没有益处，不论 EGFR 突变状态如何。而且，III 期试验表明在 IV 期 NSCLC 患者中，EGFR-TKI 联合化疗可能会产生拮抗效应。更多的近期研究表明药效学分离（或“交替”）可以避免这种负面相互作用，而且 EGFR-TKI 单药治疗作为细致筛选的 I-III 期 NSCLC 患者的术前诱导治疗是安全且有效的。本次会议中将对这些数据进行审查，并且就该领域内正在进行中的试验进行讨论，包括 RADIANT（厄洛替尼）、ADJUVANT（吉非替尼）和 ECOG 1505（贝伐珠单抗）。将会提供临床病例以便更好地体现在对照临床研究之外治疗患者所存在的问题和缺陷，并将会说明临床和转化研究的新途径。

More than half of the patients with non-small cell lung cancer (NSCLC), including different tumor stages and histology subtypes, have actionable driver mutations. In patients with advanced NSCLC and activating EGFR mutations, randomized phase III trials with EGFR inhibitors (gefitinib, erlotinib and afatinib) demonstrated superior response rates and progression free survival compared with chemotherapy. Phase II trials showed high response rates for crizotinib in advanced NSCLC with ALK-translocation and the results of two randomized phase III trials are awaited. Preliminary data from phase I-II trials and retrospective series suggest further targets for tumor-specific therapies, including MET, ROS1, HER2, BRAF, KRAS, PI3K and others. Moreover, bevacizumab and cetuximab have shown clinical activity in phase III trials in combination with chemotherapy in patients with advanced NSCLC selected by histology and EGFR expression, respectively. Rapid molecular testing is now available at many institutions, and the translation of these novel therapies from stage IV to earlier stages has begun. Caution is warranted, because cure – not tumor response – is the ultimate goal of therapy, and the use of new drugs outside of a clinical trial in patients with stage I-III NSCLC may be risky. Of note, S0023 and BR.19 showed no benefit with the addition of gefitinib to a radical treatment in patients with localized NSCLC, irrespective of EGFR mutation status. Furthermore, phase III trials suggested a possible antagonism when EGFR-TKIs were combined with chemotherapy in patients with stage IV NSCLC. More recent studies indicate that such negative interaction may be avoided by pharmacodynamic separation (or "intercalation"), and that EGFR-TKIs as single agents could be used safely and effectively as induction therapy before surgery in carefully selected patients with stage I-III NSCLC. At the meeting, these data will be reviewed, and ongoing trials in this field will be discussed, including RADIANT (erlotinib), ADJUVANT (gefitinib), and ECOG 1505 (bevacizumab). Clinical cases will be presented to highlight problems and pitfalls of treating patients outside of controlled trials, and new avenues for clinical and translational research will be elucidated.

妇科肿瘤

967O OCEANS 的总生存期分析更新：吉西他滨（G）+卡铂（C）和贝伐珠单抗（BV）或安慰剂（PL），之后给予 BV 或 PL 用于铂敏感性复发性卵巢上皮癌（ROC，腹膜原发灶）患者的随机、III 期临床试验

967O UPDATED OVERALL SURVIVAL ANALYSIS IN OCEANS, A RANDOMIZED PHASE 3 TRIAL OF GEMCITABINE (G)+CARBOPLATIN (C) AND BEVACIZUMAB (BV) OR PLACEBO (PL) FOLLOWED BY BV OR PL IN PLATINUM-SENSITIVE RECURRENT EPITHELIAL OVARIAN (ROC), PRIMARY PERITON

C. Aghajanian, L.R. Nycum, B. Goff, et al.

背景：在 OCEANS 试验中，贝伐珠单抗联合 GC 治疗铂敏感（Plat-S）ROC 患者，可以使无进展生存期产生有统计学意义和有临床意义的改善（中位无进展生存期，12.4 与 8.4 个月；风险比= 0.484；P<.0001）。这些结果得到了总缓解率（ORR）、应答持续时间（DOR）和独立审查委员会（IRC）分析的支持。在最终无进展生存期分析时，总生存期数据尚不完整。已经对其他总生存期数据进行了更新；在此我们介绍第 3 次中期总生存期分析。

方法：入组标准包括Plat-S OC、PPC或FTC，ECOG PS为 0 或 1 分，没有针对ROC的既往贝伐珠单抗治疗或化疗，以及肿瘤可测量。按 1:1 比例将患者随机分入A组：GC（G [1000mg/m^2，第 1 天和第 8 天]和C [AUC 4，第 1 天]，q3w，6–10 个周期）+联合PL（q3w），之后给予PL，直至疾病进展（PD）或发生不可接受的毒性；或分入B组：GC +同步BV（15 mg/kg q3w），之后给予BV，直至疾病进展或发生不可接受的毒性。主要终点为根据RECIST，研究者评估的无进展生存期。次要终点包括总缓解率、总生存期、应答持续时间和安全性。第 3 次中期总生存期分析的数据截止日期为 2012 年 3 月 30 日。

结果：至截止日期，共发生了 286 例事件（59%的患者）。 治疗组间的总生存期没有差异，风险比为 0.960（95%可信区间，0.760–1.214；时序检验 P=0.736）。在 42 个月的中位随访期，GC+PL 和 GC+BV 治疗组的中位总生存期分别为 33.7 个月和 33.4 个月。在 2 个治疗组间，治疗中出现的 5 级不良事件数量没有差异（每组各 1 例），治疗组间的死亡病例数相似且 2 组大多病例的死因为疾病进展。在 PL 和 BV 治疗组中，89%和 86%的患者接受了后续治疗（包括贝伐珠单抗，分别用于 39%和 22%的患者）。

结论：这些数据可确保在该疗法基础上添加贝伐珠单抗不会有损总生存期，并证明 GC+BV 方案良好的收益，可以显著延长铂敏感性 ROC 患者无进展生存期的风险比。

Background: In OCEANS, BV in combination with GC resulted in a statistically significant and clinically meaningful improvement in PFS in patients (pts) with platinum-sensitive (Plat-S) ROC (median PFS, 12.4 vs 8.4 months; HR=0.484; P<.0001). These results were supported by the overall response rate (ORR), duration of response (DOR), and independent review committee (IRC) analyses. At the time of the final PFS analysis, the OS data were still not mature. Additional OS updates have been performed; here we present the 3rd interim OS analysis.

Methods: Eligibility criteria included first recurrence of Plat-S OC, PPC, or FTC with an ECOG PS of 0 or 1, no prior BV or chemotherapy for ROC, and measurable disease. Pts were randomized 1:1 to arm A**:**GC (G [1000mg/m^2, days 1 and 8] and C [AUC 4, day 1], q3w for 6–10 cycles)+concurrent PL (q3w), followed by PL until disease progression (PD) or unacceptable toxicity; or arm B**:**GC+concurrent BV (15 mg/kg q3w), followed by BV until PD or unacceptable toxicity. The primary end point was investigator-assessed PFS by RECIST. Secondary end points included ORR, OS, DOR, and safety. The 3rd interim OS analysis was conducted with a data cutoff date of March 30, 2012.

Results: As of the data cutoff date, 286 events (59% of pts) had occurred. There was no difference in OS between the arms, with an HR of 0.960 (95% CI, 0.760–1.214; log-rank P=0.736). With a median follow-up of 42 months, median OS was 33.7 months in the GC+PL arm and 33.4 months in the GC+BV arm. There was no difference in the number of grade 5 treatment-emergent adverse events between arms (1 in each), the number of deaths was balanced between arms, and the cause of death in the majority of cases was PD in both arms. 89% and 86% of pts received subsequent therapy (including BV in 39% and 22%) in the PL and BV arms, respectively.

Conclusions: These data provide assurance that there is no detriment to OS with the addition of BV in this setting, and supports the positive benefit:risk ratio of the GC+BV regimen in significantly improving PFS in patients with platinum-sensitive ROC.

978P ROSIA:超过 1000 例卵巢癌（OC）患者接受一线贝伐珠单抗（BEV）+化疗（CT）的单组研究

978P ROSIA:A SINGLE-ARM STUDY IN MORE THAN 1000 PATIENTS (PTS) RECEIVING FRONT-LINE BEVACIZUMAB (BEV)+CHEMOTHERAPY (CT) FOR OVARIAN CANCER (OC)

C. Mendiola, I.Davidenko, N.Colombo, et al.

背景：在 ICON7 和 GOG-0218 III 期试验中，贝伐珠单抗可显著增加卵巢癌一线化疗的有效性。全球单组 ROSiA 研究旨在常规肿瘤学实践基础上，评估贝伐珠单抗治疗至疾病进展或最长 36 个周期的安全性。

方法：患有FIGO IIb–IV期或 3 级I–IIa期卵巢上皮癌、输卵管癌或原发性腹膜癌，没有接受过既往卵巢癌术后治疗，年龄≥ 18 岁且ECOG PS 0–2 的患者合格。允许既往接受新辅助化疗。如患者在过去 6 个月内发生不受控制的高血压、有胃肠梗阻的临床体征/症状，或有腹壁瘘、胃肠穿孔或腹腔内脓肿病史，则不适合入选研究。根治性手术后，患者接受贝伐珠单抗 15mg/kg q3w（或 7.5mg/kg，由研究者判断）加 4–8 个周期的化疗（紫杉醇 [175mg/m^2 d1 q3w或 80mg/m^2 qw）+q3w卡铂 [AUC 5 或 6]）联合治疗。继续按相同剂量给予贝伐珠单抗单药治疗，直至疾病进展（PD）、发生不可接受的毒性或最长 36 个周期。主要目标是评估安全性（CTCAE v4.03）。次要终点包括无进展生存期、总缓解率（根据RECIST）和/或 CA-125 缓解标准、缓解持续时间和总生存期。研究探索了血浆、肿瘤和遗传生物标记物与贝伐珠单抗有效性和毒性的潜在相关性。

结果：2010 年 12 月至 2012 年 4 月期间，35 个国家大约 1000 例患者入组研究，患者主要来自西班牙（n=180）、意大利（n=110）和法国（n=101）。截至 2012 年 1 月 30 日，获得 677 例患者的基线特征。大多数患者患有 III/IV 期卵巢癌（I/II/III/IV 期：7%/11%/60%/18%）。大多数患者（93%）接受了紫杉醇 q3w 治疗，94%的患者接受贝伐珠单抗 15mg/kg 治疗；14%的患者既往接受过新辅助化疗。将报告大约 1000 例患者的基线特征，以及化疗和贝伐珠单抗详细方案。

结论：ROSiA 可以提供有关贝伐珠单抗在接受新辅助化疗患者中最长治疗 36 周期安全性的有价值新信息，以及可以进行广泛的转化研究。

Background:BEV significantly improved the efficacy of front-line CT for OC in the ICON7 and GOG-0218 phase III trials. The global single-arm ROSiA study was designed to assess the safety of BEV-containing therapy, given until progression or for up to 36 cycles, in the context of routine oncology practice.

Methods: Eligible pts have FIGO stage IIb–IV or grade 3 stage I–IIa epithelial ovarian, fallopian tube or primary peritoneal carcinoma, have received no prior post-surgical therapy for OC, are aged ≥18 years and have ECOG PS 0–2. Prior neoadjuvant CT is permitted. Pts with uncontrolled hypertension, clinical signs/symptoms of GI obstruction, or a history of abdominal fistula, GI perforation or intra-abdominal abscess within the preceding 6 months are ineligible. After definitive surgery, pts receive BEV 15mg/kg q3w (or 7.5mg/kg at the investigator's discretion) in combination with 4–8cycles of CT (paclitaxel [175mg/m^2 d1 q3w or 80mg/m^2 qw)+q3w carboplatin [AUC 5 or 6]). BEV is continued at the same dose as a single agent until disease progression (PD), unacceptable toxicity or for up to 36 cycles. The primary objective is to assess safety (CTCAE v4.03). Secondary endpoints include progression-free survival, overall response rate by RECIST and/or CA-125 response criteria, duration of response and overall survival. The study includes exploration of potential correlations of plasma, tumour and genetic biomarkers with BEV efficacy and toxicity.

Results: Between Dec 2010 and Apr 2012, 1000 pts were enrolled from 35 countries, predominantly Spain (n=180), Italy (n=110) and France (n=101). Baseline characteristics were available from 677 pts as of 30 Jan 2012. Most pts had stage III/IV OC (stage I/II/III/IV**:**7%/11%/60%/18%). The majority (93%) received paclitaxel q3w and 94% received BEV at a dose of 15 mg/kg; 14% had received prior neoadjuvant CT. Baseline characteristics from the entire population of 1000 pts will be reported, together with details of CT and BEV schedules selected.

Conclusions:ROSiA should provide valuable new information on the safety of BEV for up to 36 cycles and in pts who have received neoadjuvant CT, as well as enabling extensive translational research.

973PD　每周一次剂量密集紫杉醇联合卡铂作为晚期卵巢癌的初步治疗比每三周一次紫杉醇联合卡铂治疗更具成本效益

973PD　DOSE-DENSE WEEKLY PACLITAXEL AND CARBOPLATIN IS MORE COST-EFFECTIVE THAN BEVACIZUMAB PLUS TRIWEEKLY PACLITAXEL AND CARBOPLATIN FOR THE PRIMARY TREATMENT OF ADVANCED OVARIAN CANCER

K. Harano, T. Shiroiwa, M. Watanabe, et al.

目的：确定与贝伐珠单抗加每三周一次紫杉醇联合卡铂（PCB）相比，每周一次剂量密集紫杉醇联合卡铂（ddPC）作为晚期卵巢癌的初步治疗是否具有较好的成本效益。

方法：对 3 种治疗方案进行了成本效益分析比较：6 个周期的紫杉醇和卡铂（PC）、6 个周期的 PC 加贝伐珠单抗序贯 12 个周期的贝伐珠单抗（PCB）维持治疗、6 个周期的每周一次剂量密集紫杉醇联合卡铂（ddPC）治疗。从 ICON7（PC 和 PCB）和 JGOG3016（ddPC）报告的结果中采集数据。确定每种方案的治疗成本加并发症成本的实际值和估计值。根据临床试验结果估算无进展生存期和并发症发生率。估算成本效益增量比（ICER）/无进展寿命年（PFLYS）。

结果： ddPC 与 PC 相比 ICER 为 5,000 美元/PFLYS。PCB 与 PC 相比，ICER 为 285,000 美元/PFLYS。PCB 的成本大于 ddPC 且有效性更低。

结论：在这一模型中，每周一次剂量密集紫杉醇联合卡铂治疗晚期卵巢癌的成本效益大于 PCB。

Purpose: To determine whether dose-dense weekly paclitaxel and carboplatin (ddPC) is cost effective compared to bevacizumab plus triweekly paclitaxel and carboplatin (PCB) for the primary treatment of advanced ovarian cancer.

Methods:A cost-effectiveness analysis compared three treatments**:**6 cycles of paclitaxel and carboplatin (PC), 6 cycles of PC plus bevacizumab followed by 12 cycles of maintenance bevacizumab (PCB), and 6 cycles of dose-dense weekly paclitaxel and carboplatin (ddPC). Data were taken from reported results of ICON7 (PC and PCB) and JGOG3016 (ddPC). Actual and estimated costs of treatment plus costs of complications were established for each regimen. Progression-free survival and rates of complications were estimated based on the results of clinical trials. Incremental cost-effective ratios (ICER) per progression-free life-year saved (PFLYS) were estimated.

Results: The ICER for ddPC was $5,000 per PFLYS compared to PC. For PCB compared to PC, the ICER was $285,000 per PFLYS. When compared simultaneously, PCB was more costly and less effective than ddPC.

Conclusions: In this model, dose-dense weekly paclitaxel and carboplatin is more cost effective than PCB for the treatment of advanced ovarian cancer.

198P GOG-0218，一线贝伐珠单抗（BV）+化疗（CT）治疗卵巢癌（OC）的 III 期临床试验的生物标记物（BM）结果

198P BIOMARKER (BM) RESULTS FROM GOG-0218, A PHASE 3 TRIAL OF FRONT-LINE BEVACIZUMAB (BV)+CHEMOTHERAPY (CT) FOR OVARIAN CANCER (OC)

M.J. Birrer, H. Lankes, R.A. Burger, et al.

背景：GOG-0218 结果显示，在接受贝伐珠单抗 15 mg/kg q3w 联合化疗序贯贝伐珠单抗单药治疗至疾病进展或最长 15 个月的患者中，无进展生存期（PFS）显著延长。GOG-0218 进行了广泛的 BM 评估，以确认贝伐珠单抗治疗后获益最大的患者。根据几类肿瘤的贝伐珠单抗临床试验的良好结果，优先分析血浆 VEGF-A 和 VEGFR-2 水平。表：198P

方法：新诊断为 IV 期或肉眼最佳分期为 III 期的卵巢癌患者随机接受 6 个周期（c）的化疗联合：安慰剂（PL）c2−22（A 组）；或 BV c2−6→PL c7−22（B 组）；或 BV c2−22（C 组）。使用多重 ELISA 对术后化疗前血浆样本进行分析。根据基线（BL）BM 水平对患者进行分层。采用时序检验和 Cox 回归分析法对 BM 水平与无进展生存期（主要终点）和总生存期（OS；次要终点）的潜在相互作用进行检验。

结果：采集 A 组和 C 组 1248 例患者中 582 例患者的术后样本。VEGF-A 和 VEGFR-2 的中位基线水平分别为 144.3 pg/mL 和 14.7 ng/mL。在 α=0.05 水平下，未观察到显著的相互作用。为计算潜在预测（VEGF-A 和 VEGFR-2）或预后（VEGF-A：OS）价值假设其他阈值进行探索性分析。探索性分析表明，血浆 VEGF-A 与术后时间之间无相关性。

结论：使用中位阈值，乳腺癌、胰腺癌和胃癌中潜在预后（VEGF-A）和预测（VEGF-A、VEGFR-2）价值未见于 GOG-0218 的术后样本。基于其他阈值的结果可进一步研究潜在预后和预测价值。结果体现了各类肿瘤中 VEGF-A 异构体之间不同的生物学性质和相互作用。还对术前和术后样本的可能影响进行了研究。

Background:GOG-0218 showed significantly improved progression-free survival (PFS) in patients (pts) receiving BV 15 mg/kg q3w concurrently with CT and continued alone until progression or for up to 15 mo. GOG-0218 includes extensive BM evaluation to identify pts benefitting most from BV. Analysis of plasma VEGF-A and VEGFR-2 was prioritised based on encouraging findings in BV trials in several tumour types. Table**:**198P

Methods: Pts with newly diagnosed stage IV or macroscopic optimal stage III OC were randomised to 6 cycles (c) of CT with**:**placebo (PL) c2−22 (arm A); BV c2−6→PL c7−22 (arm B); or BV c2−22 (arm C). Post-surgery pre-CT plasma samples were analysed using a multiplex ELISA. Baseline (BL) BM levels were used to dichotomise pts. Potential interactions between BM levels and PFS (1° endpoint) and overall survival (OS; 2 endpoint) were tested using log-rank testing and Cox regression approaches.

Results: Post-surgery samples were available from 582 of 1248 pts in arms A and C. Median BL VEGF-A and VEGFR-2 levels were 144.3 pg/mL and 14.7ng/mL, respectively. No significant interaction was seen at α=0.05. Exploratory analyses with other cut-offs are hypothesis generating for potential predictive (VEGF-A and VEGFR-2) or prognostic (VEGF-A**:**OS) value. Exploratory analyses revealed no correlation between plasma VEGF-A and time since surgery.

Conclusions: The potential prognostic (VEGF-A) and predictive (VEGF-A, VEGFR-2) value seen in breast, pancreatic and gastric cancers was not apparent in post-surgery samples from GOG-0218 using a median cut-off. Results with other cut-offs provide a rationale for further investigation of potential prognostic and predictive value. Findings may reflect differing biology and interplay between VEGF-A isoforms across tumour types. The possible impact of pre- vs post-surgery samples is also being investigated.

	无进展生存期/ PFS			总生存期/ OS		
	中位值，月/ Median, mo		HR	中位值，月/ Median, mo		HR
亚组/Subgroup	PL	BV		PL	BV	
VEGF-A						
≤中位值/≤median	12.3	18.6	0.52	43.0	48.5	0.87
>中位值>median	11.0	17.5	0.70	33.9	41.8	0.78
≤ Q3	12.3	18.6	0.59	45.1	48.5	0.89
>Q3	9.7	13.8	0.67	28.6	37.7	0.72
VEGFR-2						
≤中位值/≤ median	12.0	18.0	0.68	35.1	40.6	0.90
>中位值/>median	10.4	18.2	0.53	38.4	48.5	0.69
≤ Q3	11.0	17.3	0.63	38.2	41.8	0.87
>Q3	12.5	22.1	0.46	38.6	−	0.59

Q =四分位数
Q=quartile

LBA26 每周一次紫杉醇（PAC）、聚乙二醇多柔比星脂质体（PLD）或托泊替康（TOP）±贝伐珠单抗（BEV）治疗铂类（PT）耐药的复发性卵巢癌（OC）：GCIG AURELIA 随机 III 期试验中按照化疗（CT）队列进行的分析

LBA26 WEEKLY PACLITAXEL (PAC), PEGYLATED LIPOSOMAL DOXORUBICIN (PLD) OR TOPOTECAN (TOP) ± BEVACIZUMAB (BEV) IN PLATINUM (PT)-RESISTANT RECURRENT OVARIAN CANCER (OC):ANALYSIS BY CHEMOTHERAPY (CT) COHORT IN THE GCIG AURELIA RANDOMISED PHASE III TRIAL

A.M. Poveda, F. Selle, F. Hilpert, et al.

背景：AURELIA 试验是第一项对 BEV+CT 与 CT 治疗 PT 耐药复发性 OC 进行比较的试验。在总人群中，基于 RECIST 的无进展生存期（PFS）（主要终点）的风险比（HR）为 0.48（95% CI 0.38–0.60; p<0.001）。我们按照选择的 CT 对探索性分析进行了报告。

方法：符合入组标准的患者为：卵巢癌在≥4 个疗程的含铂化疗后进展<6 个月。有难治性卵巢癌、肠梗阻史或>2 种既往抗癌治疗方案治疗的患者均不符合入组标准。研究者为每例患者选择单药化疗（PAC 80 mg/ m^2，第 1、8、15 和 22 天，q4w；PLD 40 mg/m^2，第 1 天q4w；或TOP 4 mg/m^2，第 1、8 和 15 天，q4w 或 1.25 mg/m^2，第 1–5 天，q3w），然后将患者随机分配至单独CT组，或与BEV（10 mg/kg q2w或 15 mg/kg q3w ，取决于CT）联合治疗组，持续治疗至疾病进展，发生不可接受的毒性或患者同意停药。

结果：在 2009 年 10 月至 2011 年 4 月间，对 361 例患者进行了随机分配。在下文中对基线特征、CT 暴露量和有效性进行了总结。

结论：在 PT 耐药的 OC 患者中，观察到所有 CT 队列中单药 CT 加用 BEV 都实现了 PFS 和 ORR 的改善。伴随 PFS 延长的 CT 暴露量增加可以解释某些累积 CT 毒性的增加。

Background:AURELIA is the first trial to compare BEV+CT vs CT in PT-resistant recurrent OC. The hazard ratio (HR) for progression-free survival (PFS) by RECIST (primary endpoint) in the overall population was 0.48 (95% CI 0.38–0.60; p<0.001). We report exploratory analyses according to selected CT.

Methods: Eligible patients (pts) had OC that had progressed <6 mo after ≥4 cycles of PT-based therapy. Pts with refractory OC, history of bowel obstruction or >2 prior anticancer regimens were ineligible. Investigators chose single-agent CT (PAC 80 mg/ m^2 d1, 8, 15 & 22 q4w; PLD 40 mg/m2 d1 q4w; or TOP 4 mg/m^2 d1, 8 & 15 q4w or 1.25 mg/m^2 d1–5 q3w) for each pt before randomisation to CT either alone or with BEV (10 mg/kg q2w or 15 mg/kg q3w depending on CT) until progression, unacceptable toxicity or withdrawal of consent.

Results: Between Oct 2009 and Apr 2011, 361 pts were randomised. Baseline characteristics, CT exposure and efficacy are summarised below.

Conclusion: In PT-resistant OC, the improvement in PFS and ORR gained by adding BEV to single-agent CT was observed across all CT cohorts. Increased CT exposure associated with prolonged PFS accounts for some increase in cumulative CT toxicity.

986P 贝伐珠单抗加环磷酰胺节拍疗法治疗既往多次治疗的卵巢癌患者：单中心经验

986P BEVACIZUMAB PLUS METRONOMIC CYCLOPHOSPHAMIDE FOR HEAVILY PRETREATED OVARIAN CANCER:A SINGLE INSTITUTION EXPERIENCE

I. Ghanem, C. Mendiola, A. Diaz, et al.

背景：贝伐珠单抗联合化疗作为一线和二线治疗化疗已经证实对卵巢癌具有活性。本研究的目的是评估贝伐珠单抗加环磷酰胺节拍疗法治疗既往多次治疗的卵巢癌患者中的有效性和安全性。

方法：我们对 29 例复发性卵巢癌患者（p）进行了回顾性审查，患者于 2007 年 1 月至 2012 年 1 月间在 1 所研究中心接受了贝伐珠单抗 10 mg/Kg IV 治疗，每 14 天加口服环磷酰胺 50 mg/天治疗。收集了患者特征、肿瘤特征、生存数据和不良事件（AE）。

结果：对 29 例患者进行了分析，中位年龄为 59 岁（31-79）且 ECOG 1（0-2）。在接受贝伐珠单抗-环磷酰胺治疗前，分别有 15 例患者为 IV 期卵巢癌（52%）和 14 例 I 患者为 IIIC 期卵巢癌（48%）。最常见的病理学亚型为 22 例患者（76%）的浆液性。中位既往治疗次数为 4 次（2-9），药物包括卡铂 29p（100%）、紫杉醇 29p（100%）、聚乙二醇化脂质体多柔比星 26p（90%）、吉西他滨 20p（69%）、六甲蜜胺 10p（34%）、托泊替康 9p（31%）或 trabectedine 1p（3%）。23 例患者（79%）为铂耐药（上一次铂治疗后无进展期小于 6 个月）。中位治疗周期数量为 9 个周期（3-67）。26 例患者可以进行 CA 125 标记物评价：4 例患者（15%）的 CA125 正常，7 例患者（27%）部分应答（PR），8 例患者（31%）疾病稳定（SD），7 例患者（27%）疾病进展（PD）。在 23 例患者中进行了放射学评估：6 例患者（26%）出现 PR，9 例患者（39%）出现 SD，8 例患者（35%）出现 PD。中位无进展生存期（PFS）和总生存期（OS）分别为 3.7 个月和 12.1 个月。铂耐药性肿瘤患者的无进展生存期（3.2 个月与 36.0 个月，p=0.001）和总生存期（12 个月与未达到，p=0.009）显著较差。ECOG>1 分的患者的无进展生存期（2.8 个月与 4.7 个月，p=0.047）和总生存期（5.4 个月与 34.5 个月，p=0.011）较差。重度不良事件为 G3 动脉性高血压（1p）、G3 粘膜炎（1p）、G3 贫血和 G4 消化道出血（1p）。未观察到脱发和神经毒性恶化。

结论：在既往接受多次治疗的卵巢癌患者中，包含贝伐珠单抗加环磷酰胺节拍治疗的疗法有效，且具有良好的耐受性。

Background: Bevacizumab in combination with chemotherapy has demonstrated activity for ovarian cancer in first and second lines. The purpose of this study is to evaluate the efficacy and safety of bevacizumab plus metronomic cyclophosphamide in heavily pretreated ovarian cancer patients

Methods: We reviewed retrospectively 29 patients (p) with recurrent ovarian cancer treated with bevacizumab 10 mg/Kg IV every 14 days plus oral cyclophosphamide 50 mg daily between January 2007 and January 2012 at a single institution. P characteristics, tumour features, survival data and adverse events (AE) were collected.

Results: Twenty-nine p with a median age of 59 years old (31-79) and ECOG 1 (0-2) were analyzed. Fifteen (52%) and 14 (48%) p had stage IV and IIIC respectively before receiving bevacizumab-cyclophosphamide. The most frequent pathologic subtype was serous in 22 p (76%). The median of previous lines was 4 (2-9), including drugs as carboplatin 29p(100%), paclitaxel 29p (100%), pegylated liposomal doxorubicin 26p(90%), gemcitabine 20p(69%), altretamine 10p(34%), topotecan 9p(31%) or trabectedine 1p(3%). Twenty-three cases(79%) were platinum-resistant (progression free interval less than 6 months from last platinum treatment). The median of cycles administered was 9(3-67). Twenty-six p were assessable for CA 125 marker evaluation**:**4p (15%) had CA125 normalization, 7p (27%) partial response (PR), 8p (31%) stable disease (SD) and 7p(27%) progression disease (PD). The radiologic evaluation was performed in 23 patients**:**There were 6p (26%) with PR, 9p(39%) with SD and 8p (35%) with PD. Median progression free survival (PFS) and overall survival (OS) were 3.7 months and 12.1 months respectively. P with platinum-resistant disease had significantly worse PFS (3.2m vs 36.0m) p=0.001 and OS (12m vs not reached) p=0.009. P with ECOG >1 also had worse PFS (2.8m vs 4.7m) p=0.047 and OS (5.4m vs 34.5m) p=0.011). Severe AE were G3 arterial hypertension (1p), G3 mucositis (1p), G3 anaemia and G4 digestive bleeding (1p). No alopecia and neurotoxicity deterioration were observed.

Conclusions: This schedule consisting on bevacizumab plus metronomic cyclophosphamide shows activity in heavily pre-treated ovarian cancer with a well toxicity profile

淋巴瘤

641N　后利妥昔单抗时代中的新抗体：又一个突破？
641N　NEW ANTIBODIES IN THE POST-RITUXIMAB-ERA:ANOTHER BREAKTHROUGH?

主讲人：P. Johnson Southampton/UK

随着利妥昔单抗首个广泛应用于临床，单药治疗疗效显著且与其他药物联合治疗多种类型的 CD20+淋巴瘤时也获得良好的效果，单克隆抗体（mAb）成为一种非常有效的现代癌症治疗药物，在开展广泛临床研究的同时，我们也在继续发掘淋巴细胞表面生物学的新知识。几十年前，研究已经确定了 mAb 的靶向分子，而最近又出现了一些新的靶向分子，但现在人们对靶向 T-或 NK-细胞的效应机制、放射性核素或毒素的选择性传递，和双特异性分子的兴趣越来越大。人们曾经将 CD20 视为相对惰性的细胞膜组分，但实际上它是一种动态分子。CD20 可以进行快速再分布，并且不同的 mAb 可对它造成不同的影响：那些与妥昔单抗相似（“I 型”）的 mAb 可导致 CD20 再分布到富含脂质筏，介导补体结合和抗体靶向细胞介导的细胞毒性（ADCC）。与之相反，那些与第一抗 B 细胞 mAb 表现出的特征相似的 mAb，B1（“II 型”）不会造成 CD20 再分布到脂质筏，但可介导同型细胞的粘附和细胞程序性死亡。这些差异的存在对治疗结果有重要的影响，我们还发现，在表达 CD32 抗原（Fcgamma-R2B）的淋巴瘤中，I 型 mAb 可通过溶酶体消耗介导 CD20 快速再分布，而 II 型 mAb 却没有这种作用。正如具有不同糖基的 mAb 与各种 Fc 受体所表现的亲和力，这种差异可对疗效产生潜在后果。除了放射性结合物之外，我们也重新使用过去废弃的方法，如免疫毒素，连接子化学的进步提高了它们的治疗率。毒素的游离和全身毒性的问题已在很大程度上得到解决，且新一代的轭合物正应用于淋巴瘤的治疗中。最后，产生双特异性结构的能力可使 T-细胞靶向作用于恶性细胞表面，并保证其除了体液免疫外还具有细胞免疫功能。抗体治疗淋巴瘤的最初目的已经实现，新一代的化合物激发了我们的挑战性并具有巨大的潜力。

Monoclonal antibodies (mAb) are one of the successes of modern cancer medicine, with rituximab the first to enter widespread clinical application following the demonstration of significant activity as a single agent, and superior results when combined with chemotherapy for a variety of CD20+lymphoma types. In parallel to extensive clinical studies, we continue to uncover novel aspects of biology of the lymphoid cell surface. The molecules to which mAb have been targeted were identified several decades ago and few new ones have emerged recently, but there is now increasing interest in effector mechanisms, selective delivery of radionuclides or toxins, and bispecific molecules to target T- or NK- cells. Once thought of as a comparatively inert component of the cell membrane, CD20 is in fact a dynamic molecule. It can undergo rapid redistribution, and different mAb cause different effects:those like Rituximab (“type I”) elicit redistribution into lipid-rich rafts, mediate complement fixation and antibody-directed cell-mediated cytotoxicity (ADCC). In contrast, those like the first anti-B-cell mAb characterised, B1 (“type II”) do not cause redistribution into rafts but mediate homotypic cell adhesion and programmed cell death. These differences have important therapeutic results, and we have found that in lymphomas expressing the CD32 antigen (Fcgamma-R2b), type ImAb mediate rapid internalization of CD20 with lysosomal consumption, while type II do not. This has potential consequences for the therapeutic effect, as does the avidity with which mAb with different sugar groups bind to various Fc receptors. As well as radioconjugates, we are also returning to previously discarded approaches such as immunotxins, which have benefitted from advances in linker chemistry to improve their therapeutic ratio. Problems of toxin liberation and systemic toxicity have been largely overcome, and a new generation of conjugates is finding application in lymphoma therapy. Finally, the capacity to generate bispecific constructs that allow targeting of T-cells to the malignant cell surface holds the promise of harnessing cellular as well as humoral immunity. The initial promise of antibody therapy for lymphoma is already being fulfilled, and the next generation of compounds holds exciting challenges and great potential.

651N　MTOR 抑制剂与超越：以临床途径为靶向
651N　MTOR INHIBITORS AND BEYOND:TARGETING A CRITICAL PATHWAY

主讲人：M.H. Dreyling Munich/DE

在众多淋巴瘤亚型，包括套细胞淋巴瘤（MCL）中发现了 PI3K/Akt/mTOR 信号转导通路的上调。根据 162 例复发 MCL 患者中开展的一项前瞻性随机研究，mTOR 抑制剂坦西莫司已经在欧盟注册上市。与单一化疗相比较，接受坦西莫司治疗患者的可获得明显高于前者的缓解率（22%比 2%）和更长的无进展生存期（4.8 比 1.9 个月）。此外，mTOR 抑制剂的疗效不仅在 MCL 中得到证实，而且在滤泡和弥漫性大 B 细胞淋巴瘤的许多 II 期临床研究也得到证实。目前在体外研究的基础上开展对 mTOR 抑制剂联合化疗疗效的研究。因此，所有 12 例初治复发 MCL 患者均对苯达莫司汀-利妥昔单抗-坦西莫司（BeRT）的联合化疗方案产生应答。近期的研究已经证实，在恶性淋巴瘤的分子发病机制中，B-细胞受体途径 mTOR 的上游传导信号起着关键的作用。这条途径代表着生发中心内逐渐成熟淋巴细胞的生理学生存信号。因此，在各种亚型淋巴瘤中，小分子攻击这条信号途径可显示出很好的疗效，即使是采用单药治疗。

因此，研究已证明 SYK 抑制剂对治疗复发性弥漫性大细胞淋巴瘤的患者是有效的。

尤其是两种抑制剂，一种只在淋巴样细胞中表达的 PI3Kδ 异构体抑制剂（GS-1101，形式上是 Cal-101），和 BTK 抑制剂 ibrutinib，均对治疗复发性套细胞淋巴瘤（缓解率约 70%）以及 CLL（在复发性或以前未治疾病中缓解率为 70-90%）显示出很好的疗效。相反，在滤泡性淋巴瘤中缓解率较低，假定这个淋巴瘤亚型中表示不同生存信号的 BCL-2 结构性过度表达。这些数据也证实，在淋巴疾病中通过抑制 B 细胞受体途径而受到阻碍的微环境的关键作用。最后，最近的体外研究数据表明，在使用 mTOR 抑制剂联合方案的治疗中，B 细胞受体途径的不同抑制剂之间存在一些协同作用。因此，这种分子靶向策略有可能成为众多类型淋巴瘤的治疗新策略中的一部分。

Upregulation of the PI3K/AKT/mTOR signal pathway has been detected in numerous lymphoma subtypes including mantle cell lymphoma (MCL). Accordingly, the mTOR inhibitor Temsirolimus has been registered in EU based on a prospective randomized trial in 162 patients with relapsed MCL. In comparison to monochemotherapy, Temsirolimus achieved significantly higher response rates (22% vs 2%) and longer progression-free survival (4.8 vs. 1.9 months). Moreover, the efficacy of the mTOR inhibitor was confirmed not only in MCL, but also follicular and diffuse large B-cell lymphoma in numerous phase II studies. Based on in vitro studies current trials investigate the combination with chemotherapy. Thus, all 12 initial patients with relapsed MCL responded to a Bendamustin-Rituximab-Temsirolimus combination (BeRT). Recent research has confirmed the critical role of the B-cell receptor pathway upstream of mTOR in the molecular pathogenesis of malignant lymphoma. This pathway represents the physiological survival signal for maturating lymphocytes in the germinal center. Accordingly, small molecules attacking this pathway displayed high efficacy in various lymphoma subtypes even in monotherapy. Thus, a SYK inhibitor has been shown to be effective in patients with relapsed diffuse large cell lymphoma. Especially both, an inhibitor of the PI3K delta isoform (GS-1101, formally Cal-101) only expressed in lymphoid cells and the BTK inhibitor ibrutinib showed high efficacy in relapsed mantle cell lymphoma (response rate about 70%) as well as CLL (response rate between 70–90% in relapsed or previously untreated disease). In contrast, response rates were lower in follicular lymphoma presumely indicating the different survival signal of the constitutive BCL-2 overexpression in this lymphoma subtype. These data also confirm the crucial role of the micromilieu in lymphoid diseases which are hampered by the inhibition of the B-cell receptor pathway. Finally, recent in vitro data suggest some synergism of different members of the B-cell receptor pathway in combination with mTOR inhibition. Such molecular targeted strategies have therefore the potential to become part of the new treatment strategies in a broad spectrum of lymphoid neoplasias.

1073P 滤泡淋巴瘤（FL）（GOTEL-FL1LC）的高危患者经 R-CHOP 方案诱导后接受 Y90-替伊莫单抗联合治疗：一项多中心、前瞻性研究

1073P CONSOLIDATION TREATMENT WITH Y90-IBRITUMOMAB TIUXETAN AFTER R-CHOP INDUCTION IN HIGH-RISK PATIENTS WITH FOLLICULAR LYMPHOMA (FL) (GOTEL-FL1LC):A MULTICENTRIC, PROSPECTIVE STUDY

M. Provencio Pulla, M.A. Cruz Mora, J. Gomez Codina, et al.

复发是 FL 治疗失败的主要原因，这使得我们有必要对旨在消除微小残留病灶的治疗策略进行研究。为此，我们在高风险的 FL 患者中对使用 Y90-替伊莫单抗（RIT）巩固治疗的作用进行了评估。我们根据已有数据推测，先前使用利妥昔单抗治疗可能会降低 RIT 的疗效，因此我们设计了一项 RIT 的研究，在 4 个疗程的 CHOP-R 和 2 个疗程不含 R 的 CHOP 治疗后给予 RIT。

材料和患者：在 2008 年 4 月至 2010 年 4 月期间，本试验共纳入 30 例患者：男性 17 例（56.7%），女性 13 例（43.3%）。他们的平均年龄为 54.8 岁（范围 34-76 岁）。 20 例（69%）为 ECOG 0。RIT 给药剂量没有延迟或减少。

结果：客观临床缓解率为 92.1%（CR+CRI+PR），[95%CI：83-100%]。18 例患者经诱导治疗达到部分缓解，有 11 例患者（61.1%）在巩固治疗后获得完全 CR 或缓解。只有一例患者因甲型 H1N1 流感病毒性肺炎死亡。最重要的 G 3/4 毒性为血液学毒性，46%发生血小板减少和 56%发生中性粒细胞减少。在试验中没因淋巴瘤死亡的患者。因中位随访期为 26 个月（12-37），无病生存期或总生存期的平均值还没有达到。

结论：在 RIT 巩固治疗之前给予 4 个疗程 CHOP-R+2 个疗程 CHOP 诱导过程可获得良好的缓解率，且 RIT 可提高 CR。此联合化疗方案是安全的，在诱导和巩固过程中均显示出较高的活性。

Relapse is the main cause of therapeutic failure in FL, which makes it necessary to investigate strategies that aim to eradicate minimal residual disease. This is why we set out to evaluate the role of consolidation with Y90-Ibritumomab Tiuxetan (RIT) in high-risk FL patients. As we possessed data making us suspect that prior treatment with Rituximab could reduce the efficacy of RIT, we designed a study with RIT after 4 cycles of CHOP-R and 2 CHOP, but without R.

Material and Patients: Between April 2008 and April 2010, 30 patients were included in this trial:17 male (56.7%) and 13 female (43.3%).Their median age was 54.8 (range, 34-76). 20 (69%) patients had ECOG 0. There were no delays or reductions in RIT doses.

Results: The objective rate of clinical response was 92.1% (CR+CRi+PR), [CI 95%:83-100%]. Of the 18 patients who presented with partial remission to the induction treatment, 11 (61.1%) had complete CR or remission after the consolidation treatment. There was only one exitus, due to H1N1 viral pneumonia. The most important G 3/4 toxicity was hematological, with 46% thrombopenia and 56% neutropenia. None of the patients in the trial died because of Lymphoma. With median follow-up of 26 months (12-37), the means for disease-free survival or overall survival were not reached.

Conclusion: The induction procedure with 4 CHOP-R+2 CHOP prior to consolidation with RIT gives good response rates and RIT improves CR. This combination is safe and shows a high activity in both, induction and consolidation procedures.

1076P　利妥昔单抗+克拉屈滨皮下注射用于黏膜相关组织的结外边缘区 B 细胞淋巴瘤（MALT 淋巴瘤）患者的治疗：一项由 AGMT 开展的 II 期研究

1076P　RITUXIMAB PLUS SUBCUTANEOUS CLADRIBINE IN PATIENTS WITH EXTRANODAL MARGINAL ZONE B-CELL LYMPHOMA OF THE MUCOSA ASSOCIATED TISSUE (MALT-LYMPHOMA):A PHASE II STUDY BY THE AGMT (ARBEITSGEMEINSCHAFT MEDIKAMENTöSE TUMORTHERAPIE)

M.Troch, B.Kiesewetter, W.Willenbacher, et al.

背景：目前，黏膜相关淋巴组织的结外边缘区 B 细胞淋巴瘤（MALT 淋巴瘤)还没有标准化的系统治疗方案。利妥昔单抗(R)和 2 -氯脱氧腺苷（2CdA）这两种要去均在一定程度上对这种疾病有效，但到目前为止尚未对两者的联合化疗方案进行试验。鉴于此，我们已开始了一项 II 期研究，以评估 MALT 淋巴瘤患者中 R/2CdA 的有效性和安全性。

患者和方法：经病理证实的MALT淋巴瘤患者纳入本研究。治疗包括R 375mg/m^2 i.v. 第 1 天和 2CdA 0.1mg/kg s.c. 第 1–4，每 21 天给药一次。在两个疗程化疗后获得完全缓解（CR）的情况下，需接受另外两个疗程的治疗，而达到部分缓解（PR）或疾病稳定（SD）的患者将安排接受 6 个疗程的治疗。

结果：在可评价数据的 40 例患者（14 例女性，26 例男性）中，39 例患者按计划接受了治疗，而 1 例病人在治疗开始前死亡，在意向治疗分析中评估为 PD。21 例患者患胃淋巴瘤，19 例患者患胃外 MALT 淋巴瘤（分别为 6 例肺淋巴瘤、2 例唾液腺淋巴瘤、5 例眼眶淋巴瘤、4 例肠道淋巴瘤、1 例乳腺淋巴瘤和 1 例皮肤淋巴瘤）。副作用是可控制的，主要为由血液毒性，包括白细胞减少、淋巴细胞减少、贫血和血小板减少。23 例患者获得 CR（58%），9 例患者获得 PR（23%），整体应答率为 81%，而 5 例患者为 SD（13%）和 2 例患者在治疗过程中发生疾病进展。在中位随访 16.7 个月（四分位数间距：15.9-18.7 个月）后，35 例患者（88%）仍然存活，而 4 例患者死亡（1 例患者在随访期间因后狭窄性肺炎导致死亡，1 例患者在治疗开始前因尿脓毒症死亡，1 例患者因心梗死亡和 1 例患者因淋巴瘤恶化死亡），1 例撤销知情同意，并拒绝进一步随访。

结论：

我们的数据表明，R 加 2CdA 联合化疗方案治疗 MALT 淋巴瘤患者是有效的和安全的。

Background: Currently, there is no standard systemic treatment for extranodal marginal zone B-cell lymphoma of the mucosa associated lymphoid tissue (MALT-lymphoma). Both rituximab (R) and 2-chlorodeoxyadenosine (2CdA) have shown activity to some extent in this disease, but the combination has not been tested so far. In view of this, we have initiated a phase II study to assess the activity and safety of R/2CdA in patients with MALT-lymphoma.

Patients and methods: Patients with histologically verified MALT-lymphoma were included in this study. Treatment consisted of R 375mg/m^2 i.v. day 1 and 2CdA 0.1mg/kg s.c. days 1 – 4 every 21 days. In case of complete remission (CR) after two courses, another two cycles of therapy were administered, while patients achieving partial response (PR) or stable disease (SD) were scheduled to receive 6 cycles of treatment.

Results: Out of 40 evaluable patients (14 female, 26 male), 39 received treatment as scheduled while one patient died before initiation of therapy and was rated as PD in the intent to treat analysis. Twenty-one patients had gastric lymphoma, while 19 suffered from extragastric MALT-lymphoma (6 lung, 2 salivary gland, 5 ocular adnexae, 4 intestinal, one breast and one cutaneous lymphoma, respectively). Side effects were manageable and consisted mainly of hematotoxicity including leukopenia, lymphopenia, anemia and thrombocytopenia. Twenty-three patients had a CR (58 %), 9 PR (23%) for an overall reponse rate of 81%, while 5 had SD (13%) and two progressed during therapy. After a median follow-up of 16.7 months (Inter Quartile Range; 15.9–18.7months), 35 patients are alive (88 %) while four patients have died (one patient of post-stenotic pneumonia during the follow-up period, one of urosepsis before initiation of therapy, one due to myocardial infarction and one patient due to lymphoma progression) and one patient withdrew consent and did not allow further follow up.

Conclusion: Our data demonstrate that R plus 2CdA is active and safe in patients with MALT-lymphoma.

1079P 接受抗癌治疗加利妥昔单抗治疗伴感染丙型肝炎病毒的淋巴瘤患者的结局

1079P THE OUTCOME OF LYMPHOMA PATIENTS WITH HEPATITIS C VIRUS UNDERGOING ANTICANCER THERAPY PLUS RITUXIMAB

L. Ezz Elarab, M.M.A.M. Wahab, M. Swellam, et al.

原理：丙型肝炎病毒（HCV）是埃及的一种地方性疾病，是由于埃及血吸虫病患者接受注射治疗导致的。近期的研究已经得出结论，联合化疗中使用利妥昔单抗与乙型肝炎复发相关，但是其与丙型肝炎病毒感染的关系仍无定论。本研究的目的是在感染丙肝病毒的淋巴瘤患者中评估利妥昔单抗加 CHOP 方案的安全性和有效性。

患者和方法：2008 年 1 月至 2009 年 6 月期间，43 例大 B 细胞淋巴瘤的化疗初治患者纳入研究。所有病例均有 CD 20 的过度表达。要求使用聚合酶链反应（PCR）检测抗原或用酶联免疫吸附试验（ELISA）检测抗体，从而检测基线 HCV 血清学结果。对所有患者进行肝脏毒性和丙型肝炎病毒复发的观察。

结果：对所有患者均进行了缓解率和安全性的评估。所纳入患者的特征：年龄中位数为 47 岁，28 例淋巴结受累，60%LDH 水平升高，所有患者均没有肝硬化病史，18 例患者因 HCV 接受治疗和 29 例（67%）患者在入组时转氨酶（AST 和 ALT）水平正常，14 例患者有 I 级转氨酶水平异常（33%），32 例患者 PCR 阴性，25%存在低病毒血症。根据国际预后指数（IPI）25 例患者为低危淋巴瘤，其余的患者为高危或中高危淋巴瘤。28 例（65%）患者报告了 R-CHOP 的总肝脏毒性，其中 71%为 GI 和 II（20 例患者）（疗程中位数= 4。范围 2-8）。通过 PCR 检测 4 例患者 HCV 复发，2 例在 6 个疗程治疗后和 2 例在治疗 6 个月内。

预后：完全缓解患者为 29/43（67%）。中位随访期 32 个月，2 年总生存率为 70%（95%CI 59-81%）和无病生存率为 59%（95%CI 48-70%），未记录到治疗相关死亡事件。25%的患者因毒性需要减量。

结论：利妥昔单抗+CHOP 是 HCV+淋巴瘤患者中有效且可耐受的治疗方案。预防性抗病毒治疗对这些患者的作用仍有待评估。

Rationale:Hepatitis C Virus (HCV) is an endemic disease in Egypt due to parenteral treatment of Egyptian patients with bilharziasis. Recently, it was concluded that the introduction of rituximab in combination with chemotherapy has been associated with hepatitis B reactivation but with HCV infection it is still a matter od debate. The objectives of the current study were to evaluate the safety profile and efficacy of rituximab plus CHOP in patients with lymphoma plus virus C.

Patients and methods: Between January 2008 and June 2009, forty three chemo-naïve patients with large B cell lymphoma were enrolled. All cases were strongly expressed CD 20 .Baseline HCV serology results were requested “detection of antigens by polymerase chain reaction (PCR) or antibodies by Enzyme Linked Immuno- sorbent Assay (ELISA)”. All patients were observed for hepatic toxicity and HCV reactivation.

Results: All patients were assessable for response and safety. The included patients characterized by median age was 47, nodal presentation in 28 cases, LDH level was elevated in 60%, no patients had history of cirrhosis, 18 had been treated for HCV & Transaminase (AST & ALT) levels at inclusion were normal in 29 patients (67%) and grade I in 14 (33 %), PCR was negative in 32 patients & low viremia in the 25 % of cases. 25 patients had low risk lymphoma according to the International Prognostic Index (IPI) and the remainder had high & high- intermediate risk. The overall hepatic toxicity of R-CHOP was reported in 28 patients (65%) and from those 71% were GI and II (20 patients) (median no. of cycles=4, Range 2-8). 4 patients developed HCV reactivation by PCR, 2 cases after cycle 6 and 2 within 6 months of therapy.

Outcome: Complete Remission for uncertain CR was 29/43 (67%). With the median follow up of 32 months, The 2 year overall survival was 70% (95%CI 59-81%) and disease free survival was 59% (95% CI 48-70%) with no recorded treatment related mortality. Dose reduction was required for toxicity in 25% of all patients.

Conclusion: Rituximab plus CHOP is an effective and marginally tolerable regimen in therapy of HCV +ve lymphoma patients. Role of prophylactic antiviral therapy has to be evaluated for those patients.

1083P 间变性大细胞淋巴瘤（ALCL）患者接受 BRENTUXIMAB VEDOTIN 治疗后的外周血干细胞（PBSC）的动员和移植

1083P PERIPHERAL BLOOD STEM CELL (PBSC) MOBILIZATION AND ENGRAFTMENT AFTER BRENTUXIMAB VEDOTIN TREATMENT IN ANAPLASTIC LARGE CELL LYMPHOMA (ALCL) PATIENTS

A.R. Shustov, J.D. Rosenblatt, D.A. Kennedy, et al.

背景：Brentuximab vedotin 是一种 CD30-靶向抗体，可通过蛋白酶可裂解连接子与微管破坏剂一甲基 auristatin E（MMAE）结合。在一项 II 期关键研究中（ClinicalTrials.gov NCT00866047），58 例接受 brentuximab vedotin 治疗的复发/难治性 ALCL 患者中，有 50 例（86%）获得客观反应。超过一半的患者达到完全缓解（CR）（59%），使一些患者接受后续的干细胞移植（SCT）作为巩固治疗成为可能。一项研究对 brentuximab vedotin 治疗（tx）后 PBSC 动员和干细胞移植的特征进行了回顾性评价。

方法：患者在门诊接受 1.8mg/kg brentuximab vedotin 每 3 周一次，每次 30 分钟 IV 共 16 个疗程。一招 2007 年 Cheson 的标准通过独立评价的方式，在应答评估的基础上对药物的抗肿瘤疗效进行评价。

结果：8 例疾病缓解患者在停止brentuximab vedotin治疗后，接受自体SCT作为第一治疗。2 例患者在brentuximab vedotin 治疗开始之前完成PBSC采集，6 例患者在brentuximab vedotin治疗之后。这 6 例患者接受brentuximab vedotin 治疗获得了最佳的临床反应-CR。在brentuximab vedotin治疗之后，使用化疗动员、Plerixafor（n=1）和粒细胞集落刺激因子（G-CSF）（n=2）对PBSC进行动员（n=3）。采集CD34 +细胞/kg的数量和采集的天数见表。每例患者的 CD34 +/kg的产量均大于≥2.5×10^6的标准目标，中位数为 7.0×10^6。所有接受移植的患者中，动员至移植的中位时间，中性粒细胞为 10.5 天（范围 9-14），血小板为 11.5 天（范围 9-13）。SCT后 100 天的死亡率为 0%。

结论：在接受大剂量化疗和自体 SCT 的患者中，Brentuximab vedotin 不会对 PBSC 动员或移植产生不利影响。

Background: Brentuximab vedotin is a CD30-targeted antibody conjugated to the microtubule-disrupting agent, monomethyl auristatin E (MMAE), by a protease-cleavable linker. In a pivotal phase 2 study (ClinicalTrials.gov NCT00866047), an objective response was achieved in 50 of 58 (86%) relapsed/refractory ALCL patients (pts) treated with brentuximab vedotin. More than half of the pts achieved a complete remission (CR) (59%), enabling some pts to subsequently receive a stem cell transplant (SCT) as consolidation. A retrospective evaluation was performed to characterize PBSC mobilization and engraftment following brentuximab vedotin treatment (tx).

Methods: Pts received 1.8 mg/kg brentuximab vedotin every 3 weeks as a 30-minute outpatient IV infusion for up to 16 cycles. Antitumor efficacy was based on response assessments by independent review according to Cheson 2007.

Results: Eight pts received autologous SCT as the first therapy after discontinuing tx with brentuximab vedotin in remission. PBSC collection was completed prior to initiation of brentuximab vedotin tx in 2 pts, and following brentuximab vedotin tx in 6 pts. These 6 pts achieved a best clinical response of CR with brentuximab vedotin tx. After brentuximab vedotin tx, PBSCs were mobilized using chemomobilization (n=3 pts), plerixafor (n=1), and granulocyte colony-stimulating factor alone (G-CSF) (n=2). The number of CD34+cells/kg obtained and the days of collection are shown in the table. The CD34+/kg yield for each pt was greater than the standard target of ≥2.5 x 106, with a median of 7.0 x 106. All pts engrafted, and the median time to engraftment was 10.5 days (range 9–14) for neutrophils and 11.5 days (range 9–13) for platelets. The 100-day mortality rate post SCT was 0%.

Conclusions: Brentuximab vedotin does not appear to have a negative impact on the outcome of PBSC mobilization or engraftment in pts receiving high-dose therapy and auto SCT.

年龄/Age	性别/Sex	B-V 疗程/ Cycles of B-V	动员方案/ Mobilization Regimen	采集天数/ Days Collected	CD34+Cells/kg (x 106)
46	M	4	IE/GCSF	1	46.9
57	F	8	IE/GCSF	2	7.1
61	M	7	plerixafor	4	4.1
41	F	8	GCSF	2	6.9
50	F	8	CED/GCSF	1	28.1
45	F	4	GCSF	2	4.0

IE=异环磷酰胺、足叶乙甙

IE=ifosfamide, etoposide

CED=环磷酰胺、足叶乙甙、地塞米松

CED=cyclophosphamide, etoposide, dexamethasone

乳腺肿瘤

LBA5-PR PHARE 研究结果：早期乳腺癌患者辅助治疗中应用曲妥珠单抗 6 个月和 12 个月的比较
LBA5-PR PHARE TRIAL RESULTS COMPARING 6 TO 12 MONTHS OF TRASTUZUMAB IN ADJUVANT EARLY BREAST CANCER

X. Pivot, G. Romieu, H. Bonnefoi, et al.

背景：自 2005 年以来，曲妥珠单抗(T)治疗 1 年对HER2 过度表达的早期乳腺癌患者已经显示出生存益处。然而，基于对曲妥珠单抗的心脏毒性的关注，以及FinHer研究显示应用曲妥珠单抗 9 周与 1 年的治疗疗效相似的结果，曲妥珠单抗最适宜的应用持续时间一直存在争议。法国国立癌症研究所(INCa)发起了一项随机、非劣效试验，旨在对更短的 6 个月曲妥珠单抗治疗与标准的 12 个月治疗进行比较。这项名为PHARE的研究[NCT00381901]将减少赫赛汀®作为辅助治疗方案的应用时间，已经通过了一个独立的伦理委员会的IDMC（独立数据监测委员会）审查。

患者和方法：入组标准为：接受过至少 4 个周期的（新）辅助化疗的 HER2+早期乳腺癌患者。使用最小化算法按 1:1 随机分组，并基于曲妥珠单抗与化疗同时或序贯、雌激素受体(ER)状态和所在中心进行分层。主要终点是比较无病生存期(DFS)。次要终点是调查总生存期(OS)和心脏毒性。试验组中 DFS 绝对丢失 2%被定义为非劣效界值（相对而言为 1.15）且需要样本量 3400 名患者，同时 α =0.05 和统计效能 80%。

结果：从 2006 年 5 月到 2010 年 7 月，3382 名患者随机分为 6 个月或 12 个月曲妥珠单抗组，按照 IDMC 的意见中断或长期随访。两组的疾病特点和治疗特性得到了很好的平衡：中位年龄 55 岁（21-86），中位肿瘤大小 20mm（0-270），淋巴结转移 45%，三级 SBR 56%，ER 阳性 58%，接受放疗 88%，放疗同时接受曲妥珠单抗 58%，含蒽环类和紫杉类的化疗 73%。数据库在 2012 年 7 月 30 日关闭。从开始使用曲妥珠单抗起计的中位随访时间为 47.2 个月。无病生存期的风险比（HR）为 1.28(95% CI:1.05-1.56)。由于 95%CI 的下限越过了预先设定的 1.15 的非劣效界值，6 个月的曲妥珠单抗治疗相对于 12 个月的曲妥珠单抗治疗并未显示出非劣效性。

Background: Since 2005, One year trastuzumab (T) treatment has been providing survival benefit to patients with early breast cancer and HER2 overexpression. However, the optimal duration of T has been debatable due to concerns forcardiac toxicity and results from the FinHer trial which showed that 9 weeks of T provided a similar magnitude of benefit than the 1-year treatment. The French National Cancer Institute (INCa) initiated an academic randomised non-inferiority trial aiming to compare a shorter T exposure of 6 months versus the standard 12 months. This trial, named PHARE for 'Protocol for Herceptin® as Adjuvant therapy with Reduced Exposure' [NCT00381901] was approved by an independent ethics committee with regularly planned IDMC meetings.

Patients and methods: Patients with HER2+early breast cancer who received at least 4 cycles of (neo)-adjuvant chemotherapy were eligible. Randomization 1:1 using a minimisation algorithm was stratified on concomitant or sequential T administration with chemotherapy, oestrogen receptors (ER) status and center. The primary objective was to compare disease free survival (DFS). Overall survival (OS) and cardiac toxicity were investigated as secondary aims. An absolute loss of 2% in DFS in the experimental arm was defined as the non-inferiority margin (1.15 in relative terms) and required 3400 patients with alpha=0.05 and 80% power.

Results: Between 5/2006 and 7/2010, 3382 patients were randomized to 6 or 12 months of T following the IDMC recommendation for accrual interruption and extended follow-up. Disease and treatment characteristics were well balanced betweenthe 2 arms:median age 55 years (range 21–86), median tumour size 20 mm (0–270), node involvement 45%, SBR grade III 56%, ER positive 58%, radiotherapy 88%; concomitant T administration 58%, anthracyclin and taxane containing chemotherapy 73%. The data-base was locked on July 30th, 2012. Median follow-up is 47.2 months since the start of T treatment. The DFS HR is 1.28 (95% CI:1.05-1.56). The non inferiority of 6 months of trastuzumab compared to 12 months could not be demonstrated as the lower bound of the 95% CI crosses the prespecified non inferiority margin of 1.15.

LBA6-PR　HERA 试验：对辅助化疗后应用 2 年或 1 年曲妥珠单抗的 HER2 阳性早期乳腺癌女性中位随访 8 年的结果

LBA6-PR　HERA TRIAL:2 YEARS VERSUS 1 YEAR OF TRASTUZUMAB AFTER ADJUVANT CHEMOTHERAPY IN WOMEN WITH HER2-POSITIVE EARLY BREAST CANCER AT 8 YEARS OF MEDIAN FOLLOW UP

R.D. Gelber, A. Goldhirsch, M. Piccart, et al.

背景：1 年曲妥珠单抗治疗显著改善 HER2 阳性早期乳腺癌患者（EBC）的无病生存期（DFS）和总生存期（OS），因此被作为标准治疗方案。HERA 试验是唯一一个探究更长时间的曲妥珠单抗的应用是否能够进一步提高疗效的研究。

材料和方法：HERA(BIG01-01)是一项国际、多中心、随机对照的 III 期临床研究，纳入了 5102 名 HER2 阳性的早期乳腺癌妇女。患者在完成其主要治疗（手术、化疗、指定的放疗）后被随机分为每 3 周使用曲妥珠单抗 1 年组或 2 年组或观察组。这项里程碑式的疗效分析比较了 2 年组或 1 年组曲妥珠单抗在随机分组 1 年后仍然无病生存患者的结果。（2 年组 N=1553，1 年组 N=1552）。主要终点为无病生存期，次要终点为总生存期和远处复发时间（TTDR）。在平均为期 8 年的随访（FU）中，也会对曲妥珠单抗组与观察组的疗效进行对比。

结果：2012 年 4 月 12 日，HERA 研究达到了为比较曲妥珠单抗给药 2 年或 1 年组而设定的 725 例无病生存事件数量。（真实风险比 HR 为 0.8，统计效能为 80%）。未校正时，2 年组 vs 1 年组的事件发生风险 HR 为 0.99 (95% CI 0.85-1.14; P=0.8588)。两组总生存类似[HR=1.05 (95% CI 0.86-1.28; P=0.6333)]。TTDR 结果也类似。主要心脏终点*也相似(2 年组 0.96% vs 1 年组 0.83%)，但次要心脏终点**在 2 年组更高(7.17% vs. 4.10%)。重要的是，中位随访 8 年时，1 年组/2 年组曲妥珠单抗组与观察组比较，DFS 和 OS 的持续受益保持稳定。

结论：这些结果更肯定了 1 年的曲妥珠单抗辅助治疗仍然是 HER2 阳性早期乳腺癌患者的标准治疗方案。令人欣慰的是，在中位随访 8 年时，DFS 和 OS 的长期保持显著改善，并且心脏终点事件的发生率很低。

注：*心源性死亡或严重的慢性心力衰竭（NYHAⅢ级或Ⅳ级，经心脏专科医生确诊，及显著的左室射血分数下降）

**左室射血分数相对基线下降的绝对值≥10%且绝对值<50%。

Background: One year (yr) of trastuzumab (T) significantly improves disease-free (DFS) and overall survival (OS) in patients with HER2-positive early breast cancer (EBC) and is considered the standard of care. HERA is the only randomized trial investigating whether longer duration of T can further improve efficacy outcome.

Materials and methods:HERA (BIG 01-01) is an international, multicenter, phase III randomized trial involving 5102 women with HER2-positive EBC. Pts were randomized, after completion of primary therapy [surgery, chemotherapy and radiotherapy as indicated], to T every 3 weeks for 1 yr, 2 years (yrs), or observation.This landmark efficacy analysis compares the outcome of pts randomized to either2 yrs or 1 yr of T who were disease-free at 1 yr after randomization (N=1553 for 2 yrs, and N=1552 for 1 yr). The primary endpoint is DFS and secondary endpoints are OS and time to distant recurrence (TTDR). Updated efficacy analyses of the T arms vs. observation at 8-yrs of median follow-up (FU) are also presented.

Results: On 12 April 2012 HERA reached the target number of 725 DFS events needed for 80% power to detect a true hazard ratio (HR) of 0.80 for the comparison of 2 yrs vs. 1 yr of T. The unadjusted HR for an event in the 2-yr vs. 1-yr T arms was 0.99 (95% CI 0.85-1.14; P=0.8588). OS in the two arms was comparable [HR=1.05 (95% CI 0.86-1.28; P=0.6333)]. TTDR results were similar. The primary cardiac endpoint* was comparable (0.96% vs. 0.83% for 2-yr and 1-yr arms, respectively), but the secondary cardiac endpoint** was higher in the 2-yr arm (7.17% vs. 4.10%). Importantly, the durable benefit in DFS and OS for both 1 yr and 2 yrs of T compared with observation remains stable at 8 yrs of median FU.

Conclusions: These results confirm that 1 yr of adjuvant T remains the standard of care for HER2-positive EBC pts. It is also reassuring that the significant improvement in DFS and OS persists over time and that the incidence of cardiac endpoints remains low at a median FU of 8 yrs.

Note:*Cardiac death or severe CHF (NYHA class III or IV, confirmed by a cardiologist, and a significant LVEF decrease)

**An absolute decline≥10% points from baseline LVEF and to <50%

346P LORHA 研究中期分析：曲妥珠单抗一线治疗 HER2 阳性转移性乳腺癌(MBC)或局部晚期乳腺癌(ABC)获得无进展期至少 3 年的患者特征

346P CHARACTERISTICS OF PATIENTS WITH HER2-POSITIVE METASTATIC (MBC) OR LOCALLY ADVANCED BREAST CANCER (ABC), TREATED WITH TRASTUZUMAB (T) AS 1ST LINE-THERAPY AND PROGRESSION-FREE FOR AT LEAST 3 YEARS:INTERIM ANALYSIS OF THE LORHA STUDY

O.Tredan, B.You, P.Beuzeboc, et al.

背景：近 10 年以来，HER2+的转移性乳腺癌患者的一线治疗都是基于曲妥珠单抗+紫杉醇的治疗方案。迄今为止，在大量的研究中，观察到接受曲妥珠单抗为基础的一线治疗的患者（长期缓解者）只有极少数在数年后不出现疾病进展。本研究在于从临床和生物学角度观察这些患者的特征。

材料和方法：法国的一项双向、多中心、非干预性研究。入选人群为年龄≥18 岁的 HER2+晚期/转移性乳腺癌患者，都接受过含曲妥珠单抗的一线治疗方案，并且从起始应用曲妥珠单抗开始至少 3 年无疾病进展。主要终点在于描述这些患者临床和肿瘤特征。收集这些患者的 PFS，OS，治疗方式和安全方面的数据。并分析了肿瘤组织样本的生物标志物。在此展示基于中期分析的初步结果。

结果：2011 年招募的 159 名患者中，110 名患者的资料可用于数据分析。中位年龄为 59 岁[34-95]。肿瘤的特征为：96 名浸润性导管癌患者（88%），63 名受体阳性患者（58%）。初诊时的疾病阶段：52 名患者为 I-II 期（50%），36 名患者为晚期/转移性乳腺癌。主要的转移部位为骨（51 名，47%)、肝脏（35 名，32%）和肺（22 名，20%）。曲妥珠单抗一线治疗的持续时间的中位值为 4.1 年[0.8-11.0]。86 名（78%）患者采用曲妥珠单抗与紫杉醇为基础的化疗方案联用。PFS 的中位值为 6.4 年[4.9;-]。OS 的中位值未得到。13 例与曲妥珠单抗相关的回顾性不良事件（心脏毒性或停药），均非严重不良事件。

结论：在这部分应用曲妥珠单抗一线治疗的晚期/转移性乳腺癌的患者中，临床和组织学特征方面均未观察特别之处。因此，生物标记物分析对区分这种情况将会非常有用。

Background: For more than ten years, treatment of HER2-positive mBC patients (Pts) is based on T plus taxane in 1st line therapy. So far, in numerous studies, we have observed few subsets of Pts (long-term responders) who have not experienced disease progression for several years after T-based regimen in 1st line treatment. This study aims to characterise these Pts in the daily practice from a clinical and biological perspective.

Material and methods: This is an ambispective French multicentre non-interventional study. Eligible Pts were women aged≥18 years with HER2-positive mBC or aBC treated with T as 1st line and who were progression-free for at least 3 years after starting T. The primary objective was to describe the clinical and tumor characteristics of these Pts. Progression Free Survival (PFS), Overall Survival (OS), data on treatment administration and safety were also collected. An exploratory biomarkers analysis is planned on tumor tissue samples. Here we present some preliminary results based on the interim analysis performed at the end of inclusions.

Results:159 Pts were enrolled in 2011 and 110 Pts were eligible for data analysis. Median age was 59 years [34-95]. Tumor characteristics were:invasive ductal carcinoma for 96 Pts (88%), positive hormonal receptors in 63 Pts (58%). At initial diagnosis, presenting stages were I-II for 52 Pts (50%). 36 Pts (33%) had a mBC de novo or an aBC. The main metastatic localisations were bone, liver and lung in 51 (47%), 35 (32%) and 22 (20%) Pts respectively. Median T treatment duration was 4.1 years [0.8-11.0] in 1st line. T was associated with a taxane-based chemotherapy in 86 Pts (78%). Median PFS was 6.4 years [4.9;-]. Median OS was not reached. 13 retrospective adverse events related to T (cardiac or leading to discontinuation) were reported. None of these was serious.

Conclusions: In this long PFS population treated with a T-based treatment in first line for aBC or mBC Pts, no specific profile in terms of clinical or histological characteristics have been observed. Thus, the exploratory biomarkers analysis will be useful to identify such a profile.

271P HANNAH 研究的附加安全性结果：一项关于 HER2 阳性早期乳腺癌患者的皮下注射曲妥珠单抗的随机对照、开放性、国际性、临床 III 期研究

271P ADDITIONAL SAFETY RESULTS OF HANNAH:A PHASE III RANDOMISED, OPEN-LABEL, INTERNATIONAL STUDY OF THE SUBCUTANEOUS FORMULATION OF TRASTUZUMAB (H) IN HER2-POSITIVE EARLY BREAST CANCER PATIENTS

C. Jackisch, M. Dank, G. Frasci, et al.

背景：HannaH 研究根据药代动力学（血清谷浓度）和疗效（病理学完全缓解），证实了固定剂量皮下注射(SC)曲妥珠单抗不劣于静脉滴注给药(IV)。(Jackisch，EBCC 2012)。

方法：HER2 阳性、可手术的局部晚期乳腺癌或炎性乳腺癌患者随机接受 8 个周期的化疗（4 周期多西他赛 75mg/m^2 序贯 4 周期 FEC方案 600/75/600mg/m^2）同时给与 3 周一次曲妥珠单抗的新辅助治疗，曲妥珠给药方式为皮下注射(600mg/5mL)或静滴(6~8mg/kg)。术后，患者继续皮下注射或静滴曲妥珠单抗 1 年。包括心脏监测的安全性监测持续到最后一剂曲妥珠单抗后 24 个月。

结果：分析了来自 HannaH 研究的 298 名静滴患者和 297 名皮下注射患者的安全性数据。在中位随访 12.3 个月时，116 名患者完成了辅助治疗并接受了 17.5 个周期（静滴组）或 17.0 个周期（皮下注射组）的曲妥珠单抗治疗。患者情况在基线时平行。总体上，两组的安全性相似。最常见的不良事件（两组均>25%）是脱发、恶心、中心粒细胞减少、腹泻、乏力和疲劳，且两组的发生率类似。严重不良事件（等级≥3）的发生率在两组也类似（均为 52%），其中最常见的是出血(静滴组 36.9%；皮下注射组 35.4%)、胃肠不良反应(6.4%；5.7%)和感染(5.0%；6.7%)。12.4%的静滴组患者和 20.9%的皮下注射组患者报告有严重不良反应(SAEs)。两者间的失衡主要是由严重不良事件中的“感染”疾病差异导致（静滴组 35.1%；皮下注射组 38.7%）。多元 Logistic 回归分析未显示曲妥珠单抗给药途径、体重、暴露程度（AUC）对严重不良事件或 3-5 级不良反应的影响。不良事件导致了 2.3%静滴组患者和 5.7%皮下注射组患者的撤药，其中心脏不良反应事件的比例在静滴组为 1.3%，在皮下注射组为 3.0%。患者撤药原因中，1/2 级的不良事件分别占静滴组的 43%和皮下注射组 61%。1/2 级的心脏性不良事件分别导致了 1.0%的静滴患者和 2.0%皮下注射患者的撤药。心脏不良事件的发生率在两组类似：12.1% (静滴)和 11.4% (皮下注射)。

结论：曲妥珠单抗皮下注射给药与静脉滴注给药的安全性相似。对于观察到的严重不良事件和撤药失衡的详细分析将在之后公布。

Background: HannaH demonstrated non-inferiority of the fixed-dose subcutaneous (SC) formulation of H compared with the intravenous (IV) formulation, based on co-primary endpoints of pharmacokinetics (Ctrough) and efficacy (pCR) (Jackisch et al, EBCC 2012).

Methods: Pts with HER2-positive, operable, locally advanced or inflammatory BC were randomised to receive 8 cycles of chemotherapy (4x docetaxel 75mg/m2 followed by 4x FEC 600/75/600mg/m2) concurrently with 3-wkly H, either SC (600mg/5 mL) or IV (8mg/kg to 6mg/kg). After surgery, pts continued H-SC or IV to complete 1 year of treatment. Safety has been monitored until 24 mths after last dose of H, including cardiac monitoring.

Results: Safety data from 298 (IV) /297 (SC) HannaH pts were analysed. At a median F/U of 12.3 months, 116 pts had completed adjuvant treatment and received a median of 17.5 (IV) and 17.0 (SC) H cycles. Pt characteristics were balanced at baseline. Overall, safety was comparable between arms. Most common AEs (>25% in either arm) were alopecia, nausea, neutropenia, diarrhoea, asthenia, and fatigue, with similar incidence in the two arms. Incidence of severe AEs (≥ grade 3) was comparable between arms (both 52%); the most common of which were haematologic (36.9 [IV] v 35.4% [SC]), GI (6.4 v 5.7%) and infections (5.0 v 6.7%). Serious AEs (SAEs) were reported in 12.4% (IV) v 20.9% (SC) of pts. The imbalance was largely driven by increased reporting of SAEs in the “infections” disease category in the SC v the IV arm (38.7 v 35.1%). Multiple logistic regression analyses did not reveal interactions between route of H treatment, body weight, and exposure (AUC) for SAEs or grade 3–5 AEs. AEs led to the withdrawal of 2.3% (IV) and 5.7% (SC) pts, with a contribution from cardiac AEs (3.0% [SC] v 1.3% [(IV]). Grade 1/2 AEs were reasons for withdrawal in 43% (IV) v 61% (SC) of pts. Grade 1/2 cardiac AEs led to withdrawal in 1.0% (IV) v 2.0% (SC) of pts. Incidence of cardiac AEs was similar in both arms:12.1% % (IV) v 11.4% (SC).

Conclusions: The safety profile of H-SC was comparable to that of H-IV. Detailed analyses of observed imbalances in SAEs and withdrawals will be provided.

315TiP　SAFEHER 试验：早期 HER2 阳性乳腺癌（EBC）患者辅助治疗方案中采用曲妥珠单抗皮下注射（H-SC）方式给药的研究

315TiP　SAFEHER:A STUDY OF ASSISTED- AND SELF-ADMINISTERED SUBCUTANEOUS TRASTUZUMAB (H-SC) AS ADJUVANT THERAPY IN PATIENTS WITH EARLY HER2-POSITIVE BREAST CANCER (EBC)

J. Gligorov, H.A. Azim, B. Ataseven, et al.

目的：赫赛汀（H）为基础的治疗方案治疗 1 年（18 个 q3w 疗程）是 HER2 阳性早期乳腺癌标准的辅助治疗方案。目前 H 需要超过 30-90 分钟的静脉注射（IV）给药。给药更迅速（最多 5 分钟）的 H 的皮下注射（H-SC）已经开发，并有可能为患者和临床工作人员带来更多的便利性，并降低了给药成本。临床 III 期的 HannaH 研究（NCT00950300）显示，H-SC 的药代动力学和药效不逊于 H-IV，联合治疗终点相似。H-SC 的安全性和已知的 H-IV 安全性具有可比性和一致性。SafeHer 研究旨在进一步评价在更广泛的患者群中 H-SC 的安全性和耐受性；允许更深入的了解范围内的安全数据。H-SC 将通过两种不同的途径给药（手持[配方]注射器或一次性使用注射装置，两者均可以自我给药）。收集一次性使用注射装置（SID）的安全性和病人对自我给药的满意度的支持性数据。

方法：SafeHer 是一个多中心、国际、临床 III 期开放性研究（NCT01566721）。主要终点是 H-SC 的安全性和耐受性。次要终点包括无病生存、总生存和患者对 SID 给药的满意度。在选定站点对使用 SID 患者的亚组人群进行赫赛汀和重组人透明质酸酶的免疫原性分析是一个探索性的目标。

研究计划入组 2500 例，根据研究者的意愿分为两个队列并±同步/序贯化疗。所有患者不考虑体重都将接受 600mg 的固定剂量，最多 5 分钟注射到大腿的 H-SC，共 18 个周期（q3w）。队列 A 的患者（n =1800）将采用手持式注射器。队列 B 的患者（n= 700）将使用 SID，先辅助给药再过度到自我给药（在选定的患者中）。招募患者从 2012 年 5 月开始，在选定的中心将并行亚组研究来评估医疗资源的利用度（时间-动作研究）。

Purpose: One year of H-based therapy, consisting of 18 q3w cycles, is standard of care for the adjuvant treatment of HER2-positive EBC. H is administered intravenously (IV) over 30–90 mins. An SC formulation of H has been developed, which is rapidly administered (up to 5 mins), potentially improving convenience for patients and clinical staff, and reducing administration costs. The Phase III HannaH study (NCT00950300) demonstrated that the pharmacokinetics and efficacy of H-SC were non-inferior to that of H-IV, meeting the co-primary endpoints. The safety profile of H-SC was comparable and consistent with the known safety profile of H-IV. SafeHer is designed to further evaluate the safety and tolerability of H-SC in a broader patient population; to allow greater understanding of a range of safety data. H-SC will be administered via one of two different routes (handheld syringe [vial formulation] or single-use injection device [SID]; which allows self-administration). Supportive data on SID safety and patient satisfaction with self-administration will be collected.

Methods: SafeHer is a multicentre, international, Phase III open-label trial (NCT01566721). The primary objective is the safety and tolerability of H-SC. Secondary objectives include disease-free survival, overall survival and patient satisfaction with SID administration. Immunogenicity of H and recombinant human hyaluronidase in a subset of patients using the SID at select sites is an exploratory objective. Planned enrolment is 2500 patients, assigned to one of two cohorts at the investigators' discretion ± concurrent/sequential chemotherapy. All patients will receive H-SC at a fixed dose of 600mg regardless of body weight, for a total of 18 cycles (q3w) via injection into the thigh over a period of up to 5 minutes. Patients in cohort A (n=1800) will receive H-SC using handheld syringes. Patients in cohort B (n=700) will receive H-SC using an SID, first via assisted administration and then self-administered (in select patients).

Enrolment began in May 2012 and parallel substudies may be performed at selected centres to evaluate medical resource utilisation ("time and motion study").

406Tip　临床 II 期研究：多西他赛序贯 EC 方案（高剂量表柔比星联合环磷酰胺）同时加用曲妥珠单抗用于 II-III 期 HER-2 阳性乳腺癌患者的初始全身性治疗

406Tip　PHASE II TRIAL OF PRIMARY SYSTEMIC THERAPY (PST) WITH DOCETAXEL (D) FOLLOWED BY HIGH-DOSE EPIRUBICIN IN COMBINATION WITH CYCLOPHOSPHAMIDE (EC) PLUS CONCURRENT TRASTUZUMAB (T) FOR STAGE II-III HER-2 POSITIVE BREAST CANCER PATIENTS (PTS)

P. Vici, L. Pizzuti, M. Mottolese, et al.

背景：初始全身性治疗的患者，应用紫杉类、含蒽环类方案和曲妥珠单抗的方案显示较高的病理完全缓解率(pCR)；化疗与曲妥珠单抗联用则更有效，但曲妥珠单抗与蒽环类的联合可能会导致心脏毒性风险增加。本研究评估了在新辅助治疗中多西他赛序贯 EC 方案（表柔比星联合环磷酰胺）同时给予曲妥单抗的疗效和毒性。

材料和方法：II期单组研究纳入患者的标准为：cT2-T4, N0-2, M0, HER2 阳性(IHC扩增 2+或 3+)的乳腺癌患者。治疗前必须进行核心切片的组织学活检，评估激素受体、Ki67、拓扑异构酶II、HER2；如果可能，在手术时再次进行活检并测定这些参数。在治疗前和治疗中进行评估左室射血分数。基线时采血并评估与心脏毒性发展高风险相关的遗传多态性基因。使用多重探针扩增技术（MLPA）定量分析基因拷贝数目，检测PTEN、p-Akt,、p-MAPK及PIK3CA 突变。患者接受 4 个周期的多西他赛（100mg/m^2）联合曲妥珠单抗（初剂量 8mg/kg，维持剂量 6mg/kg）；后续 4 个周期的EC方案（120/600mg/m^2）联合曲妥珠单抗，三周为 1 个周期。计划在初始全身性治疗结束后进行手术，辅助治疗为标准放疗，如激素受体阳性则同时给予激素治疗，同时给予曲妥珠单抗治疗 6 个月。本研究的主要终点是病理学完全缓解（乳房和腋窝无侵袭性肿瘤细胞），次要终点包括心脏安全性、毒性、无病生存率。计划样本量为 42 例。

结果：已纳入 29 名患者，中位年龄 45 岁，绝经前/后分别为 22/7 例，16 名患者雌激素受体和（或）孕激素受体阳性。结果显示共 27 名患者评估为病理学缓解；20 名患者观察到病理学完全缓解（74%, 95%CI, 57.5-90.6）。最常见的毒性为 3-4 级中性粒细胞减少症，在患者中发生率达到了 75%，其他毒性为轻到中度。临床未发现心脏毒性事件。

结论：经初步分析，在 II-III 期乳腺癌患者中，多西他赛序贯 EC 方案同时联用曲妥珠单抗的初始系统治疗是非常有效和安全的。

Background:PST with taxanes, anthracycline-containing regimens and T showed a high percentage of pathologic complete response (pCR); T administered concurrently with chemotherapy is more effective, but the combination with anthracyclines may be at risk of cardiotoxicity. The present study evaluates efficacy and toxicity of T administered concurrently with a sequential regimen of D followed by EC in neoadjuvant setting.

Materials and methods: This phase II single stage trial is enrolling pts with cT2-T4, N0-2, M0, Her-2 positive (IHC 3+or 2+amplified) breast cancer. A core biopsy is required prior treatment start to evaluate hormonal receptors, Ki67, topoisomerase II, Her-2, with re-evaluation of these parameters, whenever possible, at definite surgery. LVEF is evaluated before and during treatment. Blood samples are collected at baseline for evaluation of 9 genetic polymorphisms related to higher risk of developing cardiac toxicity. We are quantitatively evaluating gene copy number by multiple ligand probe amplification (MLPA), PTEN, p-Akt, p-MAPK, and PIK3CA mutations. Pts receive 4 cycles of D (100mg/m2) plus T (loading dose 8mg/kg followed by 6mg/kg), followed by 4 cycles of EC (120/600mg/m2) plus T, every 3 weeks. Definite surgery is planned at the end of PST, and standard radiotherapy and hormonal adjuvant treatment in case of positive hormonal receptors are given; adjuvant T is given for 6 months. The primary objective of the trial is pCR (absence of invasive tumor cells in the breast and axilla); secondary objectives are cardiac safety, toxicity, disease-free survival. The planned sample size is 42 pts.

Results: To date, 29 pts have been enrolled; median age is 45 years, pre/postmenopausal 22/7, ER and/or PgR positive in 16 pts. 27 pts are evaluable for pathological response:we observed 20 pCR (74%, 95%C.I, 57.5-90.6). Grade 3-4 neutropenia was the most frequent toxicity, encountered in 75% of the pts, other toxicities were mild to moderate. No clinical cardiotoxicity was observed.

Conclusions: At preliminary analysis, PST with sequential administration of D followed by EC, given concurrently with T, appears to be very active and safe in stage II-III breast cancer pts.

246O 早期乳腺癌患者剂量密集序贯辅助方案（表柔比星+紫杉醇+CMF vs 表柔比星+CMF+多西他赛周疗 vs 表柔比星+CMF+紫杉醇周疗）后续使用曲妥珠单抗治疗 1 年

246O DOSE-DENSE SEQUENTIAL ADJUVANT CHEMOTHERAPY WITH EPIRUBICIN, PACLITAXEL AND CMF VERSUS EPIRUBICIN, CMF AND WEEKLY DOCETAXEL OR PACLITAXEL FOLLOWED BY TRASTUZUMAB FOR ONE YEAR IN PATIENTS WITH EARLY BREAST CANCER

G. Fountzilas, H. Gogas, N. Pavlidis, et al.

背景：蒽环类和紫杉类剂量密集化疗已被证实在辅助治疗高风险可手术乳腺癌中的作用。然而目前更合适的紫杉类药物和优化给药计划仍未能确定。

患者和方法：自 2005 年 7 月到 2008 年 11 月共纳入 1001 例患者（990 名符合标准），随机分组为：A组（n=333）接受 3 个周期表柔比星 110mg/m^2，后续 3 个周期紫杉醇 200mg/m^2，后续 3 个周期CMF方案（环磷酰胺 840mg/m^2、甲氨蝶呤 57mg/m^2、氟尿嘧啶 840mg/m^2）和G-CSF支持治疗。B组（n=331）接受 3 个周期表柔比星，后续 3 个周期CMF（具体剂量同A组），间断 3 周后给予 9 个多西他赛 35mg/m^{2}周疗周期的治疗。C组（n=328）和B组的差别是多西他赛改为紫杉醇 80mg/m^2。在化疗结束后给予放疗和激素治疗。曲妥珠单抗在所有HER2 阳性乳腺癌患者放疗后给药 1 年。

结果：中位随访 60 个月时，共记录到 123 名患者疾病复发（A 组 51 例、B 组 37 例，C 组 35 例）；并观察到 81 名患者死亡（A 组 30 例、B 组 22 例、C 组 29 例）。各组的 3 年无疾病生存（DFS）分别为 86%、91%、89%。总生存率（OS）分别为 96%、97%、96%。三组的 DFS 和 OS 无统计学差异（log-rank,p=0.38；p=0.48）。报道的最常见严重不良反应事件为中心粒细胞减少（29%、27%、24%，p=0.31）和白细胞减少（12%、13%、10%，p=0.66）。50 例患者出现中心粒细胞减少性发热（6%、5%、5%，p=0.81）。严重的口腔黏膜炎在 B 组的发生率更高（3%、6%、1%，p=0.001）；严重神经病变在 A 组的发生率更高（4%、0%、1%，p＜0.001）。

讨论：三组之间的 DFS 和 OS 无显著差异。紫杉类药物方案和给药计划更多的影响了严重药物毒性反应的类型。本研究中 HER2 阳性患者的 3 年 DFS 和 OS 率和其他研究报道相似。

Background: Dose-dense sequential chemotherapy including anthracyclines and taxanes has been well established in the adjuvant setting of high-risk operable breast cancer. However, the preferable taxane and optimal schedule of administration have not been defined, as yet.

Patients and methods: From July 2005 until November 2008, 1,001 patients (990 eligible) were randomized to receive 3 cycles of epirubicin 110mg/m2 followed by 3 cycles of paclitaxel 200mg/m2 followed by 3 cycles of CMF (cyclophosphamide 840mg/m2; methotrexate 57mg/m2; fluorouracil 840mg/m2) with G-CSF support (Group A; 333 patients) or to 3 cycles of epirubicin followed by 3 cycles of CMF, as in Group A, followed 3 weeks later by 9 weekly cycles of docetaxel 35mg/m2 (Group B; 331 patients) or 9 weekly cycles of paclitaxel 80mg/m2 (Group C; 328 patients). Radiation and hormonal therapy were given after the completion of chemotherapy. Trastuzumab was administered for 1 year to all HER2-positive patients post radiation.

Results: At a median follow-up of 60 months, 123 patients had documented disease relapse (51 in Group A, 37 in Group B and 35 in Group C) and 81 deaths (30 in group A, 22 in group B and 29 in group C) had been observed. The 3-year disease-free survival (DFS) rate was 86%, 91% and 89%, with overall survival (OS) rates of 96%, 97% and 96%, respectively. No differences were found in DFS or OS between the three treatment groups (log-rank, p=0.38 and p=0.48, respectively). The most frequently reported severe adverse events were neutropenia (29% vs 27% vs 24%, p=0.31) and leucopenia (12% vs 13% vs 10%, p=0.66). Febrile neutropenia occurred in fifty patients (6%, vs 5% vs 5%, p=0.81). Severe mucositis was more frequent in Group B (3% vs 6% vs 1%, p=0.001), while severe neuropathy was more frequent in Group A (4% vs 0% vs 1%, p<0.001).

Conclusions: No significant differences in DFS and OS between the three regimens were identified. Taxane regimen and schedule of administration preferentially influenced the type of severe toxicities. HER2-positive patients demonstrated comparable 3-year DFS and OS rates with those reported in other similar studies.

LBA12　EMILIA 研究总生存期结果更新：曲妥珠单抗-emtansine(T-DM1)对比卡培他滨(X)联合拉帕替尼(L)治疗 HER2 阳性晚期或转移性乳腺癌的 III 期临床研究

LBA12　UPDATED OVERALL SURVIVAL RESULTS FROM EMILIA, A PHASE 3 STUDY OF TRASTUZUMAB EMTANSINE (T-DM1) VS CAPECITABINE (X) AND LAPATINIB (L) IN HER2-POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER (MBC)

S. Verma, D. Miles, L. Gianni, et al.

背景：T-DM1 是一个抗体药物偶联物，通过一个稳定的连接偶联结合了曲妥珠单抗的靶向抗肿瘤特性和微管抑制剂 DM1 的细胞毒作用。

方法：确诊 HER2 阳性(IHC 3+和/或 FISH+)且之前接受过曲妥珠单抗和一种紫杉类治疗的转移性乳腺癌患者被随机分入 T-DM1 组（3.6mg/kg IV q3w）或 XL 组 (X：1000mg/m2 bid, d1–14, q3w；L：1250 m g PO qd, d1-21)。主要终点是独立评估的无进展生存期(PFS)、总生存期(OS)和安全性。在最后 PFS 评估的同时会进行一次 OS 的中期分析。

结果：招募了 991 名患者，978 名患者接受治疗。平均随访时间：T-DM1 组为 12.9 个月，XL 组为 12.4 个月。两组的基线人口统计、之前的治疗和疾病特征均相似。T-DM1 组的 PFS 显著提高。OS 中期分析 T-DM1 组更优。中期的疗效界限也未交叉（见下图）。尽管>75 岁的亚组患者不能确定获益，PFS 获益可见于多数亚组，包括 MBC 的治疗方案（1 线、2 线、3 线或之后的几线治疗），之前接受的治疗类型，绝经情况，雌激素受体状态，发病部位数目，种族和年龄等。次要终点的结果，包括客观缓解率、临床获益率和至治疗失败的时间，均对 T-DM1 有利。T-DM1 的耐受性良好且 3 级不良事件更少(不良事件; 40.8% vs 57.0%)。两组的心源性不良事件和左心室功能失常发生率相似且都较低。

结论：与 XL 相比，T-DM1 获得了显著的、具有临床意义的 PFS 改善。而且 T-DM1 在其他终点的结果，包括 OS、安全性和关键性的次要终点方面也更有利。这证实了该方案对之前使用曲妥珠单抗和紫杉类治疗的 HER2+转移性乳腺癌患者可作为一个有效的新选择。

Background:T-DM1 is an antibody–drug conjugate incorporating the HER2–targeted antitumor properties of trastuzumab (T) with the cytotoxic activity of the microtubule inhibitor DM1, conjugated by a stable linker.

Methods: Patients (pts) with confirmed HER2+MBC (IHC3+and/or FISH+) and prior treatment with T and a taxane were randomized to T-DM1 (3.6mg/kg IV q3w) or X (1000mg/m2 bid, days 1–14 q3w)+L (1250mg PO qd, days 1-21). Primary end points were progression-free survival (PFS) by independent review, overall survival (OS), and safety. An interim OS analysis occurred at the time of the final PFS analysis.

Results:991 pts were enrolled; 978 received treatment. Median durations of follow-up were 12.9 (T-DM1) and 12.4 (XL) mos. Baseline demographics, prior therapy, and disease characteristics were balanced. PFS was significantly improved with T-DM1; the interim OS analysis favored T-DM1, but the interim efficacy boundary was not crossed (see Table). PFS benefit was observed in most subgroups, including line of MBC therapy (1st, 2nd, 3rd, or later), type of prior treatment received, menopausal status, hormone receptor status, number of disease sites, race, and age, although the subgroup of pts >75 yrs old was too small to confirm benefit. Results for secondary end points, including objective response rate, clinical benefit rate, and time to treatment failure, favored T-DM1. T-DM1 was well tolerated and was associated with fewer grade =3 adverse events (AEs; 40.8% vs 57.0%). The incidence rates of cardiac AEs and left ventricular dysfunction were low and similar in both arms.

Conclusions:T-DM1 conferred a significant and clinically meaningful improvement in PFS compared with XL. Results of other study end points, including interim OS, safety, and key secondary end points, favor T-DM1 and establish its role as a potential new therapy for HER2+MBC pts previously treated with T and a taxane.

	T-DM1（n=495）	XL（n=496）
中位 PFS（月）/PFS, median mos	9.6	6.4
风险比(95% CI)/ HR (95% CI)	0.650 (0.549~0.771)	
P 值/ P value	<0.0001	
中位 OS（中期分析）（月）/ Interim OS, median mos	30.9	25.1
风险比 (95% CI)/ HR (95% CI)	0.682 (0.55~0.85)	
P 值/ P value	0.0006	
	疗效边界:HR=0.727 P=0.0037/ Efficacy boundary:HR=0.727 or P=0.0037	

226P HER2+转移性乳腺癌患者的随机、II 期研究：对曲妥珠单抗-EMTANSINE (T-DM1)和曲妥珠单抗+多西他赛（HT）作为一线治疗的疗效与 HER2 表达（QRT-PCR）之间关系的探索性分析

226P EXPLORATORY ANALYSIS OF THE RELATIONSHIP BETWEEN HER2 EXPRESSION (BY QRT-PCR) AND EFFICACY WITH FIRST-LINE TRASTUZUMAB EMTANSINE (T-DM1) VS TRASTUZUMAB PLUS DOCETAXEL (HT) IN A RANDOMIZED PHASE 2 STUDY OF PATIENTS (PTS) WITH HER2-POSITIVE MBC

E.A. Perez, S. Hurvitz, L.C. Amler, et al.

背景：在 TDM4450g (NCT00679341)中，137 名先前未经治疗的 HER2+转移性乳腺癌患者随机接受 T-DM1 或 HT 治疗。中位无进展生存分别为 14.2 和 9.2 个月（HR=0.594）。客观缓解率（ORR）分别为 64.2%和 58.0%(Hurvitz 2011)。在 T-DM1 的 II 期转移性乳腺癌患者的单组分析中，HER2mRNA（通过 qRT-PCR）表达越高，ORR 也越高，PFS 越长(Burris 2011; Krop 2012, in press)。在此报告 TDM4450g 研究中，回顾性分析 qRT-PCR HER2 表达和接受 T-DM1 或 HT 治疗的疗效之间的关系。

方法：患者按 1:1 随机分为 T-DM1 3.6mg/kg q3w 或 H 6mg/kg q3w（周期 1 中 8 kg/mg）+T75 或 100mg/m2 q3w 治疗直至疾病进展。所有随机分配的患者中提取的组织标本通过 qRT-PCR 检测 HER2 表达，疗效结果包括研究者评估的 PFS 和 ORR。基于每组中位随访 14 个月的临床数据得出的分析结果。

结果：137 名参与随机分组的患者中所提取的 122 个存档肿瘤标本通过 qRT-PCR 检测了未经治疗的 HER2，共有 116 患者的标本有效（6 个标本低于可测量值的下限）。疗效结果根据 HER2 表达水平的低（<中位值）和高（≥中位值）分类在表中进行了小结。

结论：分析结果表明 T-DM1 vs HT 疗效的扩大与 HER2 表达水平相关（qRT-PCR）。这种影响在 PFS 中尤为显著。计划对这些发现与基线特征的关系进一步分析，同样也计划在正在进行的 T-DM1 的一项 III 期研究中作类似的分析。

Background: In TDM4450g (NCT00679341), 137 pts with HER2-positive MBC and no prior treatment for metastatic disease were randomized to T-DM1 or HT. Median progression-free survival (PFS) was 14.2 vs 9.2 mo, respectively (HR=0.594); objective response rates (ORR) were 64.2% and 58.0%, respectively (Hurvitz 2011). In exploratory analyses of single-arm phase 2 MBC studies of T-DM1, greater expression of HER2 mRNA (assessed by qRT-PCR) was associated with greater ORR and longer PFS (Burris 2011; Krop 2012, in press). We now report a retrospective exploratory analysis of the relationship between qRT-PCR HER2 expression and efficacy outcomes in pts receiving T-DM1 or HT in TDM4450g.

Methods: Pts were randomized 1:1 to T-DM1 3.6mg/kg q3w or H 6mg/kg q3w (8 kg/mg in cycle 1)+T 75 or 100mg/m2 q3w and treated until disease progression. HER2 expression was measured by qRT-PCR in archival tissue samples from all randomized pts. Efficacy outcomes included investigator-assessed PFS and ORR. The analysis results presented here are based on the clinical data with a median follow-up of 14 mo in each arm. Table:226P

Results: In total, 122 tumor samples from 137 randomized pts were available for analysis of pre-treatment HER2 by qRT-PCR, resulting in a valid result for 116 pts (6 samples were below the limit of quantification). Efficacy outcomes by low (<median) and high (≥median) HER2 expression are summarized in the table.

Conclusions: These results from an exploratory analysis suggest that the magnitude of efficacy from T-DM1 vs HT may correlate with HER2 expression levels (by qRT-PCR); this effect appears to be most pronounced for PFS. Analyses exploring the relationship between these findings and baseline characteristics are planned. Similar analyses are planned for ongoing phase 3 studies of T-DM1.

	治疗前 HER2 的中位值,浓度比单位 (范围)/ Median pre-treatment HER2 levels, concentration ratio units (range)		
	HT	T-DM1	
	(n=61) 8.7 (0.5-105.0)	(n=55) 10.3 (0.4-103.0)	
中位 PFS, 月/ Median PFS, months			
HER2 表达/ HER2 expression	HT	T-DM1	与 HT 相关的 HR 值(95% CI)/ Hazard ratio relative to HT (95% CI)
低/Low	(n=32) 9.8	(n=26) 10.6	0.85 (0.44-1.67)
高/High	(n=29) 8.8	(n=29) Not reached	0.39 (0.18-0.85)
ORR, %			
HER2 表达/ HER2 expression	HT	T-DM1	与 HT 相关的 OR 值(95% CI)/ Odds ratio relative to HT (95% CI)
低/Low	(n=31) 58.1	(n=26) 53.8	0.84 (0.30-2.41)
高/High	(n=29) 65.5	(n=29) 72.4	1.58 (0.50-4.98)

329P 临床 III 期 EMILIA 研究的患者报告结果：曲妥珠单抗-EMTANSINE (T-DM1)和卡培他滨联合拉帕替尼 (XL)治疗 HER2 阳性局部晚期或转移性乳腺癌的比较

329P PATIENT-REPORTED OUTCOMES (PROS) FROM EMILIA, A PHASE 3 STUDY OF TRASTUZUMAB EMTANSINE (T-DM1) VS CAPECITABINE AND LAPATINIB (XL) IN HER2-POSITIVE LOCALLY ADVANCED OR MBC

M. Welslau, V. Diéras, J.-H. Sohn, et al.

背景：抗体药物偶联物 T-DM1 结合了曲妥珠单抗 (T)的抗肿瘤活性和细胞毒药物 DM1 的胞内传递作用。EMILIA 研究比较了 T-DM1 与 XL 的功效及安全性。患者报告结局（PRO）结果展示如下。

方法：已确诊 HER2 阳性转移性乳腺癌、且之前接受过曲妥珠单抗和紫杉类治疗的患者，随机分入 T-DM1 组或 XL 组，接受 21 天一个周期的治疗。患者在基线、在疾病进展(PD)前每 2 个周期的第 1 天、出现疾病进展(PD)、疾病进展 6 周后及自此以后每 3 个月均须完成由 37 个项目、5 个分量表组成的 FACT-B（乳腺癌患者生存质量量表）量表。FACT-B 量表中的 24 个分项，TOI（试验结果指数）反映整体的身体健康和功能状况及乳腺癌的特别症状。在基线和基线后 TOI 评分≥1 的女性患者中，至出现 FACT-B TOI 恶化（如，TOI 评分降低≥5）的时间，主要 PRO 分析将通过 Kaplan-Meier 法和 Cox 模型进行评估。一个 24 个项目的 FACT-B 子集，试验结局指数(TOI)能够概况体质和功能的健康状况及特定的乳腺癌症状。在基线和基线后 TOI 评分≥1 的女性患者中，至出现 FACT-B TOI 恶化（如，TOI 评分降低≥5）的时间，主要 PRO 分析将通过 Kaplan-Meier 法和 Cox 模型进行评估。探索性 PRO 终点定义为根据腹泻评分量表（DAS）测得的症状发生率，该量表从 4 个方面（腹泻频率、急迫感、不适感、便稠度）评估患者的腹泻症状，分值为 4 分，在基线水平及每个周期的第一天测量，直至出现 PD。

结果：相对于使用 XL 的患者，使用 T-DM1 的患者具有更长的 PFS (9.6 vs 6.4 个月; HR=0.650; P<0.0001)和更少的 3/4 级不良事件 (41% vs 57%)。在疗效与安全性有获益的同时，450 名 T-DM1 组和 445 名 XL 组患者的 PRO 评估健康状况有改善。T-DM1 组患者较 XL 组患者具有更高、更稳定的 FACT-B TOI 得分(出现 TOI 恶化的时间 7.1 个月 vs 4.6 个月;HR=0.796)。两治疗组 FACT-B 亚量表的比较将会在未来发表。从第 2-第 8 个周期，XL 组患者较 T-DM1 组患者出现了更多的腹泻症状，如大便＞1 次/日（57% vs 30%）；稀便或水样便(70% vs 37%)；强烈的急迫感(54% vs 26%)及中度到非常严重的腹部不适感并伴有排便(45% vs 25%)。

结论：在疗效及安全性改善的同时，T-DM1 组较 XL 组在健康相关的生活质量方面有显著的临床获益。

Background: The antibody-drug conjugate T-DM1 combines the antitumor activities of trastuzumab (T) with intracellular delivery of the cytotoxic agent DM1. In the EMILIA study, the efficacy and safety of T-DM1 was compared to XL. Here we report the PRO results.

Methods: Pts with centrally confirmed HER2-positive MBC and prior therapy with T and a taxane were randomized to T-DM1 or XL administered in 21-day cycles. Pts completed the FACT-B, a 37-item questionnaire composed of 5 subscales at baseline and on day 1 every 2 cycles until disease progression (PD), 6 wks after PD and every 3 mos thereafter. A 24-item subset of FACT-B, the Trial Outcome Index (TOI) provides a summary of physical and functional well-being and breast cancer-specific symptoms. Time to FACT-B TOI worsening (ie,≥5 point decrease in TOI), the main PRO analysis, was assessed by Kaplan-Meier methods and a Cox model in female pts with baseline and≥1 post-baseline TOI score. An exploratory PRO end point was the incidence of symptoms measured by the Diarrhea Assessment Scale (DAS), in which pts rated diarrhea symptoms in 4 domains (frequency, urgency, discomfort, stool consistency) on a 4-point scale at baseline and on day 1 of each cycle until PD.

Results: Pts treated with T-DM1 had longer PFS (9.6 vs 6.4 months; HR=0.650; P<0.0001) and fewer grade 3/4 AEs (41% vs 57%) than those treated with XL. These gains in efficacy and safety were accompanied by improvements in patient-reported health status in the 450 T-DM1 and 445 XL PRO-evaluable pts. T-DM1 pts maintained stable FACT-B TOI scores longer than XL pts (time to TOI worsening 7.1 vs 4.6 months; HR=0.796). A comparison in FACT-B subscales between treatment arms will be presented. From cycle 2 through 8, more pts in the XL arm than in the T-DM1 arm reported diarrhea symptoms such as having >1 stool per day (57% vs 30%); loose or watery stools (70% vs 37%); somewhat to very urgent stools (54% vs 26%) and mild-moderate to very severe abdominal discomfort with bowel movements (45% vs 25%).

Conclusions: Improvements in efficacy and safety were accompanied by, clinically significant benefits in health-related quality of life in pts treated with T-DM1 vs XL.

408TiP　单组、双队列、临床 II 期研究(VELVET)：帕妥珠单抗和曲妥珠单抗联合长春瑞滨用于 HER2 阳性局部晚期或转移性乳腺癌(LABC/MBC)的一线治疗

408TiP　PERTUZUMAB AND TRASTUZUMAB IN COMBINATION WITH VINORELBINE FOR FIRST-LINE TREATMENT OF PATIENTS WITH HER2-POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER (LABC/MBC):A SINGLE-ARM, TWO-COHORT, PHASE II STUDY (VELVET)

M. Andersson, J.M. Lopez-Vega, L. Del Mastro, et al.

背景：人源单克隆抗体-帕妥珠单抗可抑制 HER2 的二聚体，阻断其异聚和下游信号传导。因为帕妥珠单抗所针对的位点与曲妥珠单抗不同，所以两药联用能够产生更全面的 HER2 阻断作用。CLEOPATRA 研究显示帕妥珠单抗联合曲妥珠单抗加多西他赛可显著提高疗效，但在转移性乳腺癌中上没有帕妥珠单抗加曲妥珠单抗与其它化疗药物联合使用的试验。曲妥珠单抗联合长春瑞滨与曲妥珠单抗联合多西他赛具有相似的疗效，并且不良事件更少。VELVET 研究将评估帕妥珠单抗和曲妥珠单抗联合长春瑞滨用于 HER2 阳性转移性乳腺癌一线治疗的总缓解率（ORR）。同时还将评估在同一输液袋中应用帕妥珠单抗和曲妥珠单抗的影响。

方法：VELVET是一个多中心、开放性、双队列、HER2 阳性局部晚期/转移性乳腺癌患者的临床II期研究，其中转移性患者之前没有使用过非激素类抗肿瘤药物治疗。患者必须达到左室射血分数≥55%且ECOG-PS评分 0 或 1。本研究在 2012 年 4 月开始注册，计划招募 210 名患者。队列 1（前 105 名注册患者）将接受帕妥珠单抗和曲妥珠单抗的序贯治疗；队列 2（后 105 名注册患者）如果在第一个疗程周期中能够耐受，则将在第 2 个周期中接受帕妥珠单抗和曲妥珠单抗在同一输液袋中给药。两个队列中都会加入长春瑞滨。治疗将持续到出现疾病进展或者发生不可耐受的毒性。本研究的药物剂量（均为静滴给药）为:帕妥珠单抗初始剂量 840mg，维持剂量 420mg，三周一个周期；曲妥珠单抗：起始剂量 8mg/kg，维持剂量 6mg/kg，三周一个周期；长春瑞滨：第 1 个周期的第 1 天和第 8 天给予 25mg/m^2，之后的周期为第 1 天和第 8 天给予 30~35mg/m^2，三周一个周期（随调查者意愿调整剂量）。预计最佳总缓解率为 70–80%，目标可信区间限制和评估比例之间的差异在 8-11%。每个队列中需要有 95 名患者可评估（假定撤药率约为 10%）。主要终点为独立评估的总缓解率。次要终点包括调查者的总缓解率率评估、至缓解时间、缓解持续时间、无进展生存、至肿瘤进展时间、总生存、安全性/耐受性和生活质量。

Background: The humanised monoclonal antibody pertuzumab binds to the dimerisation domain of HER2, preventing heterodimerisation and downstream signalling. As pertuzumab is directed against a different epitope to trastuzumab, a more comprehensive HER2 blockade is achieved by combining the agents. The CLEOPATRA study showed significantly improved efficacy for pertuzumab and trastuzumab plus docetaxel, but pertuzumab with trastuzumab has not been tested with other chemotherapies in MBC. Trastuzumab plus vinorelbine (V) has comparable efficacy to trastuzumab plus docetaxel but with fewer adverse events. VELVET will assess the overall response rate (ORR) of pertuzumab with trastuzumab+V in first-line treatment of HER2-positive MBC. Administration of pertuzumab and trastuzumab in the same infusion bag will also be assessed.

Methods:VELVET is a multicentre, open-label, two-cohort, Phase II trial in patients (pts) with HER2-positive LABC/MBC not previously treated in the metastatic setting with non-hormonal anticancer therapy. Pts must have LVEF≥55% and ECOG PS of 0/1. Enrolment began in April 2012 and 210 pts will be recruited. Cohort 1 (first 105 pts enrolled) will receive pertuzumab and trastuzumab sequentially, and Cohort 2 (next 105 pts) will receive pertuzumab and trastuzumab in the same infusion bag at Cycle 2 onwards assuming Cycle 1 was tolerated. V will be given in both cohorts. Treatment will continue until disease progression/unacceptable toxicity. Study doses (all iv):pertuzumab:840mg initial dose, 420mg q3w; trastuzumab:8mg/kg initial dose, 6mg/kg q3w, and V:25mg/m2 Day 1 and 8 (first cycle) then 30 − 35mg/m2 Days 1 and 8 q3w (dose escalation at investigator discretion). Assuming best overall response of 70–80% and aiming at a distance from the estimated proportion to the CI limits of 8–11%, a total of 95 pts need to be evaluable per cohort (assuming withdrawal rate □10%). Primary endpoint is ORR by independent assessment. Secondary endpoints include investigator ORR assessment, time to response, duration of response, PFS, TTP, OS, safety/ tolerability and QoL.

409TiP　单组 IIIB 期研究(PERUSE)：帕妥珠单抗和曲妥珠单抗联合紫杉类药物用于 HER2 阳性晚期乳腺癌的一线治疗

409TiP　PERTUZUMAB IN COMBINATION WITH TRASTUZUMAB AND A TAXANE FOR THE FIRST-LINE TREATMENT OF PATIENTS WITH HER2-POSITIVE ADVANCED BREAST CANCER:A SINGLE ARM PHASE IIIB STUDY (PERUSE)

D. Miles, T. Peretz-Yablonski, E. Ciruelos, et al.

背景：帕妥珠单抗（P）通过阻滞 HER2 与其它 HER 家族成员的异聚来阻断下游信号传导。帕妥珠单抗与曲妥珠单抗识别的表面抗原不同，所以当二者联合应用时，两者间相互补充的机制导致了更为全面的 HER2 抑制。临床 III 期 CLEOPATRA 研究的数据显示：在 HER2 阳性的转移性乳腺癌患者中接受帕妥珠单抗和曲妥珠单抗联合多西他赛作为一线治疗方案的患者显著提高了无进展生存期。由于曲妥珠单抗在 CLEOPATRA 研究招募之前没有得到广泛应用，故该研究之前使用过曲妥珠单抗的患者比例相对较低。PERUSE 研究将评估 HER2 阳性转移性乳腺癌或局部晚期癌乳腺癌患者接受帕妥珠单抗和曲妥珠单抗联合一种紫杉类药物的治疗方案的安全性和耐受性，PERUSE 研究的患者群有更多人之前接受过曲妥珠单抗治疗。

方法：PERUSE 是一个 IIIb 期、多中心、开放性、单组研究，研究人群为未接受非激素抗肿瘤系统治疗的 HER2 阳性转移性乳腺癌患者。计划样本量为 1500 例。患者的治疗方案如下：帕妥珠单抗：起始剂量 840mg，维持剂量 420mg，三周为一个周期，静滴；曲妥珠单抗：起始剂量 8mg/kg，维持剂量 6mg/kg，三周为一个周期，静滴。依据当地指南选择使用多西他赛、紫杉醇或白蛋白结合紫杉醇。预定的修正方案与临床实践保持一致，将允许激素受体阳性患者在完成紫杉类治疗后接受与帕妥珠单抗和曲妥珠单抗联用的激素治疗。治疗将持续至疾病进展或出现不能耐受的毒性。患者在基线水平必须达到左室射血分数≥50%，且 ECOG-PS 评分 0~2，同时之前不能接受过抗 HER2 药物治疗转移性乳腺癌。若之前的（新）辅助治疗中使用过曲妥珠单抗和（或）拉帕替尼，但治疗期间无疾病进展也可纳入。要求患者治疗期间有≥6 个月的无病间期。主要终点为安全性和耐受性；次要终点包括无进展生存期、总生存期、整体缓解率、临床受益缓解、缓解持续时间、至缓解时间和生活质量。最终的分析结果将在患者随访 12 个月后得出。计划在患者注册量达到 350、700 和 1000 时进行中期分析。定期的中期安全评估将通过 DSMB（独立数据安全检测委员会）完成。

Background: Pertuzumab (P) inhibits downstream signaling of HER2 by preventing its heterodimerization with other HER family members. The epitope recognized by P is distinct from that bound by trastuzumab (H) and their complementary mechanisms of action lead to a more comprehensive HER2 blockade when combined. Data from the phase III trial CLEOPATRA showed significantly improved PFS in pts with HER2-positive 1L MBC given P+H+docetaxel (D). As H was not widely available in the (neo)adjuvant setting prior to CLEOPATRA recruitment, a relatively low proportion of pts in CLEOPATRA had previously received H. PERUSE will assess the safety and tolerability of P+H+one of a choice of taxanes (T) as 1L therapy for pts with HER2-positive metastatic or locally advanced BC. Efficacy endpoints will also be recorded in PERUSE, in a pt population likely to have experienced wider exposure to prior H therapy.

Methods:PERUSE is a phase IIIb, multicenter, open-label, single-arm study in pts with HER2-positive BC who have not been treated with systemic non-hormonal anticancer therapy for MBC. The planned sample size is 1500. Pts will receive, P:840mg initial dose, 420mg q3w IV; H:8mg/kg initial dose, 6mg/kg q3w IV, T:D, paclitaxel or nab-paclitaxel according to local guidelines. A planned protocol amendment will allow HR-positive pts to receive endocrine therapy in conjunction with P+H following completion of T in line with clinical practice. Treatment will be administered until disease progression or unacceptable toxicity. At baseline, pts must have an LVEF of≥50%, ECOG PS of 0, 1 or 2 and must not have received prior anti-HER2 agents for MBC. Prior H and/or lapatinib in the (neo)adjuvant setting is allowed, provided there was no disease progression on-treatment. A disease-free interval of≥6 months is required. The primary endpoint is safety and tolerability. Secondary endpoints include PFS, OS, ORR, CBR, duration of response, time to response and QoL. The final analysis will be carried out when pts have been followed up for≥12 months. Interim analyses are planned after enrollment of □350, 700 and 1000 pts. Regular interim safety assessments by a DSMB will take place.

202P　II 期 TRYPHAENA 研究：帕妥珠单抗和曲妥珠单抗伴或不伴蒽环为基础化疗的新辅助治疗方案用于 HER2 阳性的早期乳腺癌患者

202P　BIOMARKER (BM) ANALYSES OF A PHASE II STUDY OF NEOADJUVANT PERTUZUMAB AND TRASTUZUMAB WITH AND WITHOUT ANTHRACYCLINE (ATC)-CONTAINING CHEMOTHERAPY FOR TREATMENT OF HER2-POSITIVE EARLY BREAST CANCER (BC) (TRYPHAENA)

A. Schneeweiss, S. Chia, R. Hegg, et al.

背景：TRYPHAENA 研究表明，曲妥珠单抗（H）+帕妥珠单抗（P）给药的同时给予蒽环类药物或序贯使用蒽环类，或不使用蒽环类药物，三种辅助治疗的心脏耐受性相似。此外，对于 HER2 阳性的乳腺癌患者，P+H 与 ATC 联用或与以卡铂为基础的化疗方案 CT 联用，不管是那种 CT 药物，均可得到较高的病理学完全缓解率(pCR, [ypT0/is])，达到病理学完全缓解的患者与那些未达到的患者进行了分子学比较。

方法：参与 TRYPHAENA 研究的 225 名患者中超过 90%的基线核心切片和血清样本可用于生物标志物分析。生物标志物的评估包括：通过 IHC 检测 HER1/2/3, PTEN, IGF1R 蛋白表达（FISH 检测 HER2）。qRT-PCR 方法检测 HER1/2/3 的 mRNA 表达。通过 FISH 检测 c-myc 和 TOP2A，PCR 为基础的 PIK3CA 分析检测 8 个突变。生物标志物与 pCR 的关系通过分类分析方法进行测定。（chi-平方检测相关性，Cochran–Mantel–Haenszel 进行统计学分析），除 TOP2A 和 PTEN 外，其余均取中位值作为标准，根据生物学理由给出 TOP21 和 PTEN 的参考值。

结果：对每个治疗组患者的生物标志物样本各自分析，除了 HER2 蛋白水平外，没有其他的可测量的生物标志物与 pCR 具有相关性。32%的患者有 TOP2A 扩增（≥2.0 倍），与 ATC 药物的环节无相关性。经不同 CT 药物治疗后，生物标志物和 pCR 结果之间的相关性从生物学上很难解释。因此，抽取了所有患者的资料。在联合分析中，HER2 蛋白水平仍与 pCR 显著相关。HER2 mRNA 的高水平是 pCR 率改善的指标。24%的患者发生了 PIK3CA 突变，与 pCR 无相关性。

结论：该分析表明：对于 HER2 阳性的乳腺癌患者，在用 H+P+CT 新辅助治疗后，HER2 过表达与临床相关密切，是一个良好的可预测病理学完全缓解的生物标志物。

Background:TRYPHAENA showed that concurrent administration of trastuzumab (H) plus pertuzumab (P) with ATC in the neoadjuvant setting resulted in similar cardiac tolerability to sequential administration of ATC or to an ATC-free regimen. In addition, neoadjuvant P with H administered in combination with ATC- or carboplatin-based standard chemotherapy (CT) resulted in high pathological complete response (pCR, [ypT0/is]) rates, regardless of the CT regimen, in patients (pts) with HER2-positive BC. The molecular profile of pts who achieved a pCR was compared with those who did not.

Methods: Baseline core biopsies and sera from over 90% of the 225 pts enrolled in TRYPHAENA were available for BM analyses. The BMs and methods of assessment included:HER1/2/3, PTEN, and IGF1R protein expression by IHC (and FISH for HER2); HER1/2/3 mRNA expression by qRT-PCR; c-myc and TOP2A by FISH and PCR-based PIK3CA analyses detecting 8 mutations. Potential relationships between BMs and pCR were measured primarily using categorical analysis methods (chi-square test of association and Cochran–Mantel–Haenszel statistic). Median values were used as cut-offs except for TOP2A and PTEN where cut-offs were applied following a biologic rationale.

Results: Besides HER2 protein levels, no other measured BM was associated with pCR when BM samples from pts in each treatment arm were considered separately. TOP2A amplification (≥2.0 ratio) was observed in 32% of pts and was not associated with response to ATC regimen. There is no strong biologic rationale for correlation between BMs and pCR outcomes after treatment with different CT regimens; therefore, data from all pts were pooled. In the combined analysis, HER2 protein levels remained significantly correlated with pCR and high levels of HER2 mRNA were also indicative of improved pCR rates. PIK3CA mutations were seen in 24% of pts and were not associated with pCR.

Conclusion: This analysis supports the use of HER2 overexpression as the strongest predictive and clinically relevant BM for pCR after treatment with H+P+CT neoadjuvant regimen for pts with HER2-positive BC.

344P　III 期 CLEOPATRA 试验：帕妥珠单抗（P）与曲妥珠单抗（T）、多西他赛（D）联合用于一线治疗 HER2+转移性乳腺癌（MBC）的药代动力学

344P　PHARMACOKINETICS (PK) OF PERTUZUMAB (P) WITH TRASTUZUMAB (T) AND DOCETAXEL (D) IN HER2-POSITIVE FIRST-LINE METASTATIC BREAST CANCER (MBC):RESULTS FROM THE PHASE III TRIAL CLEOPATRA

J. Cortes, S. Swain, I. Kudaba, et al.

介绍：帕妥珠单抗是一个抑制 HER2 异二聚体的人源化单克隆抗体。帕妥珠单抗和曲妥珠单抗直接与 HER2 的表面抗原结合，由于两者作用机制的互补性，对 HER2 信号的阻断更为全面。基于有效的临床前实验模型，选定 20μg/ml 作为帕妥珠单抗稳定血清谷浓度的目标值。CLEOPATRA 是一项比较 HER2+晚期乳腺癌患者 P+T+D 和安慰剂+T+D 两种方案的 III 期研究。亚组分析的目的在于确定与 T 和 D 联用时帕妥珠的药代动力学特征，研究潜在的药物相互作用。

方法：每个周期第一天使用帕妥珠单抗或安慰剂（初剂量为 840mg，420mg维持）；在第 1 个周期的第 2 天及之后每个周期的第 1 天使用曲妥珠单抗（初剂量为 8mg/kg,6mg/kg维持）；在第 1 个周期的第2天及之后每个周期的第1天使用多西他赛（75mg/m^2, 如能耐受渐增至 100mg/m^2）。所有的药物均静脉注射q3w iv。检测帕妥珠的血液样本在第 1、3、6、9、12、15、18 个周期注射前及注射后及治疗中断时收集。曲妥珠的样本在第 1、3 个周期注射前和注射后收集，多西他赛的样本在第 1 个周期注射时及注射后超过 24 小时的 8 个不同的时间点收集，以计算出Cmax（血药峰值），CL（清除率），Vss（稳态表观分布容积），t1/2（半衰期），浓度-时间曲线下面积（AUC_{0-t}，AUC_{0-inf}）。

结果：37 名患者（17 名安慰剂组，20 名帕妥珠单抗组）的资料可用于PK分析。血清帕妥珠谷浓度超高目标值 20 ug/ml的患者比例>90%，与之前研究的数据比较，曲妥珠单抗和多西他赛对帕妥珠单抗的药代动力学无影响。两组第 1 周期和第 3 周期的曲妥珠单抗血清浓度Cmax 和 Cmin均相似。两组曲妥珠单抗血清浓度的最小二乘几何平均值比值P+T+D/Pla+T+D x100 为：第 1 周期Cmax90.3；第 3 周期Cmax 81.0，Cmin 95.9。两组的多西他赛药代动力学参数值相似。两组多西他赛的参数值为最小二乘几何平均值比值P+T+D/Pla+T+D x100 为：AUC_{0-t} 104.9, AUC_{0-inf} 101.4, Cmax 92.5。

结论：帕妥珠单抗的药代动力学与之前的研究一致，在 HER2 阳性转移性乳腺癌患者中与曲妥珠单抗及多西他赛同时联用对其药动学无影响。帕妥珠单抗与曲妥珠单抗或帕妥珠单抗与多西他赛间不存在药物相互作用，彼此具有不同的清除途径。

Introduction:P is a humanized mAb that inhibits heterodimerization of HER2. P and T bind distinct HER2 epitopes, and due to their complementary mechanisms of action they provide a more comprehensive blockade of HER2 signaling. Based on preclinical efficacy models, a steady-state trough P concentration (Ctrough) of 20 ug/ml was selected as target in pts. CLEOPATRA is a Phase III study comparing P+T+D vs placebo (Pla)+T+D in HER2-positive 1L MBC (Baselga NEJM 2012). The objectives of the substudy reported here are to characterize the P PK in the presence of T and D, and to explore potential drug − drug interactions.

Methods:P/Pla (840mg loading, 420mg maintenance) was administered on Day 1 of each cycle; T (8mg/kg loading, 6mg/kg maintenance) was administered on Day 2 of Cycle 1 and on Day 1 of each cycle onward following P; D (75mg/m^2, escalation to 100mg/m^2 if tolerated) was administered on Day 2 of Cycle 1 following T and on Day 1 of each cycle onward following T. All drugs were given q3w iv. Blood samples for P were collected before and after infusion at Cycles 1, 3, 6, 9, 12, 15, 18, and at treatment discontinuation. Samples for T were collected before and after infusion at Cycles 1 and 3. Samples for D were collected at Cycle 1 at 8 serial time points during and following the infusion over a 24 h period to allow calculation of Cmax, CL, Vss, t1/2, AUC0–t, and AUC0-inf.

Results:37 pts (17 Pla arm, 20 P arm) were available for PK evaluation. Serum P Ctrough exceeded the target of 20 ug/ml in >90% of pts and there was no impact of T and D on P PK, compared with historical data. Mean serum T Cmax and Cmin at Cycles 1 and 3 were similar in both arms. Ratios of geometric LS means of P+T+D/Pla+T+D x100 for serum T were:Cycle 1 Cmax 90.3; Cycle 3 Cmin 95.9; Cycle 3 Cmax 81.0. D PK parameters were similar in both arms. Ratios of geometric LS means of P+T+D/Pla+T+D x100 for plasma D were:AUC_{0-t} 104.9, AUC_{0-inf} 101.4, Cmax 92.5.

Conclusion:P PK parameters were consistent with previous studies, and co-administration of T and D appears not to influence P PK in HER2-positive MBC. There was no evidence of drug − drug interactions between P and T, or between P and D, which have different clearance pathways.

407TiP 开放性随机对照临床 II 期研究（PERTAIN）：对激素受体（HR）阳性和 HER2 阳性的局部晚期或转移性乳腺癌患者应用帕妥珠单抗和曲妥珠单抗联合芳香化酶抑制剂（AI）的治疗

407TiP TREATMENT OF PATIENTS WITH HORMONE RECEPTOR (HR)-POSITIVE AND HER2-POSITIVE LOCALLY ADVANCED OR METASTATIC BC WITH A COMBINATION OF PERTUZUMAB AND TRASTUZUMAB PLUS AN AROMATASE INHIBITOR (AI):AN OPEN-LABEL RANDOMISED PHASE II STUDY (PERTAIN)

G. Arpino , C. Poole , J.-M. Ferrero, et al.

背景：乳腺癌患者内分泌治疗抵抗一直是临床主要关注的问题。临床前研究认为阻滞 HR 同时使用 HER2 抑制剂可能是克服激素抵抗并改善临床疗效的关键。帕妥珠单抗、曲妥珠单抗和多西他赛联用通过联合阻止 HER2 信号通路显著改善了疗效。然而初步结果显示对于激素受体阳性患者这种收益可能较不明显。

PERTAIN 是首个评估帕妥珠单抗及曲妥珠单抗联用芳香化酶抑制剂能否使 HER2 阳性肿瘤对内分泌治疗恢复敏感的研究（该方案更全面的阻断 HER 信号），同时评估该方案能否成为激素受体阳性和 HER2 阳性晚期乳腺癌的一线治疗方案。

方法：PERTAIN 是一个多中心，开放性的临床 II 期研究，评估绝经后 HER2 阳性和激素受体阳性的局部晚期/转移性乳腺癌妇女患者接受帕妥珠单抗+曲妥珠单抗+芳香化酶抑制剂作为一线治疗的疗效。患者按 1：1 随机分为组 1(帕妥珠单抗：初始剂量 840mg，维持剂量 420mg，q3w iv; 曲妥珠单抗：初始剂量 8mg/kg，维持剂量 6mg/kg，q3w iv; 芳香化酶抑制剂【阿那曲唑 1mg 或来曲唑 2.5mg qdpo】)；组 2（相同剂量的曲妥珠单抗和芳香化酶抑制剂）。诱导化疗（多西他赛或紫杉醇）可随受试者的意愿持续至 18 周。研究药物方案会持续给予直到出现疾病进展或不能耐受的毒性。患者必须在之前未曾接受过抗 HER2 药物治疗，（新）辅助治疗中用过曲妥珠单抗和（或）拉帕替尼除外；也未曾有中枢神经系统事件或临床显著的心血管疾病。主要终点是无进展生存（PFS）；次要终点包括总生存、总缓解率、临床获益率、缓解持续时间、至缓解时间、安全性、耐受性和生活质量。本研究在 2012 年 4 月开放，并将招募 250 名患者。对主要终点的主要分析（在 165 例 PFS 事件之后）包括治疗组变量，并且按是否选择诱导化疗和接受辅助激素治疗的时间（<12 个月,≥12 个月，未接受激素治疗）进行分层。

Background: Development of resistance to endocrine therapy in patients (pts) with breast cancer (BC) is a major clinical concern. Preclinical studies suggest that blockade of HR with HER2 inhibition may be key to overcoming resistance and improving clinical outcomes. The combination of pertuzumab (P) and trastuzumab (H) with docetaxel significantly improves outcomes by a comprehensive blockade of HER2 signalling. However, initial results suggest that this benefit may be less apparent in HR-positive pts. PERTAIN is the first study to assess whether a fuller blockade of HER signalling with P and H in conjunction with an AI may resensitise HER2-positive tumours to endocrine therapy and provide an effective first-line treatment option in pts with HR-positive and HER2-positive advanced BC.

Methods:PERTAIN is a multicentre, open-label, Phase II trial for postmenopausal women with HER2-positive and HR-positive locally advanced/metastatic BC to assess the efficacy of P plus H with an AI as first-line therapy. Pts will be randomised 1:1 to Arm 1 (P:840mg initial dose, 420mg q3w iv; H:8mg/kg initial dose, 6mg/kg q3w iv; AI [anastrozole 1mg or letrozole 2.5mg qd po]) or Arm 2 (H+AI at same dose as Arm 1). Induction chemotherapy (CT) (docetaxel or paclitaxel) may be given to pts for up to 18 weeks at the investigator's discretion. Administration of study medications will continue until disease progression or unacceptable toxicity. Pts must not have been treated with anti-HER2 agents, except H and/or lapatinib in the (neo)adjuvant setting, and must have no CNS involvement or clinically significant cardiovascular disease. The primary endpoint is progression free survival (PFS); secondary endpoints include overall survival, overall response rate, clinical benefit rate, duration of response, time to response, safety and tolerability, and QoL. The study opened in April 2012 and will recruit 250 pts. The main analysis for the primary endpoint (after 165 PFS events) will include a treatment group variable and be stratified by whether pts were chosen to receive induction CT (Yes/No) and time since adjuvant hormone therapy (<12 months,≥12 months, and no prior hormone therapy).

255PD NEOALTTO 试验的亚组研究：原发性 HER2 阳性乳腺癌患者中循环肿瘤细胞（CTCS）与 PET/CT 反应和病理完全缓解(PCR)的关系

255PD CORRELATION BETWEEN CIRCULATING TUMOR CELLS (CTCS), PET/CT RESPONSE AND PATHOLOGICAL COMPLETE RESPONSE (PCR) IN PRIMARY HER2-POSITIVE (HER2+) BREAST CANCER PATIENTS:A SUB-STUDY FROM THE NEOALTTO TRIAL

H.A. Azim Jr, F. Rothe, C.M. Aura, et al.

背景：尽管在术前化疗患者中研究过循环肿瘤细胞的检测，但很少有术前化疗与抗 HER2 药物病人联用的相关数据。NeoALTTO 试验的亚组研究报告了有关肿瘤循环细胞的检测。

方法：NeoALTTO 试验是一个随机的 III 期研究，原发性 HER2+乳腺癌患者在术前被随机给予曲妥珠单抗、拉帕替尼或二者联用，治疗持续 6 周后，接着加入紫杉醇继续治疗 12 周。患者可自由决定是否加入 CTC 亚组研究。在基线时、单独使用抗 HER2 治疗 2 周后和术前收集血液样本。经过 2 周的术前单独抗 HER2 治疗后，在基线水平收集血样。经过水溶性聚蔗糖工艺处理，22.5mL 的血样减少至 7.5mL，然后使用 CellSearch®处理。由 CellSearch® 程序概要分析组件评估循环肿瘤细胞的 HER2 表达。HER2 染色强度为 2+/3+的 CTC 定义为 HER2+。使用 Chi 平方检验评估检测到 CTC 与原发性肿瘤特征、病理学完全缓解和 PET/CT 反应（2 周和 6 周时）之间的关系。

结果：参与随机分组的 455 名患者中，16 个中心的 51 名（11%）患者的样本可用于 CTC 分析。其中 11 名（21%）在至少 1 个时间点上有≥ 1 CTC/22.5ml。（见表 1）在基线时，第 2 周和手术时，分别在 5/46 (11%), 4/41 (10%), 和 5/31 (16%)患者的样本中检测到≥ 1 CTC/22.5ml。使用抗 HER2+紫杉醇进行术前治疗 18 周后，3/31 (10%)的患者检测到 HER2+CTCs。检测到 CTC（无论是在基线、2 周或手术时）与临床病理学特征 pCR (p=0.36)，2 周或 6 周时的 PET/CT 缓解率(2 周 p=0.34，6 周 p=0.90)之间无显著相关性。

结论：对于接受术前抗 HER2+紫杉醇治疗的患者，检测到 CTC 与 pCR 之间不存在相关性，本研究认为缺少这种证据。

Background: Although CTC detection has been studied in patients receiving preoperative chemotherapy, fewer data exist for preoperative chemotherapy combined with anti-HER2 agents. Here, we report a sub-study of CTC detection within the NeoALTTO trial.

Methods: NeoALTTO is a randomized phase III trial in which patients with primary HER2+breast cancer were randomized to trastuzumab, lapatinib or their combination for 6 weeks followed by the addition of paclitaxel for 12 weeks prior to surgery. Participation in the CTC sub-study was optional. Blood samples were prospectively collected at baseline, after 2 weeks of anti-HER2 treatment alone and prior to surgery. A total of 22.5mL of blood was reduced to 7.5mL using a modified ficoll procedure that was then processed using CellSearch®. Evaluation of HER2 expression in CTCs was performed using the CellSearch® HER2 profiling kit. CTCs with HER2 staining intensity of 2+/3+were considered as HER2+. Associations between CTC detection and primary tumor characteristics, pCR and PET/CT response (at week 2 & 6) were assessed using the chi-square test.

Results: Out of 455 patients randomized, samples for CTC analysis were available for 51 (11%) patients from 16 sites, of whom 11 (21%) had≥ 1 CTC/22.5ml in at least one time point (Table 1). At baseline, week 2 and surgery, we detected≥1 CTC/22.5ml in 5/46 (11%), 4/41 (10%), and 5/31 (16%) patients with evaluable samples respectively. HER2+CTCs were still detectable after 18 weeks of preoperative treatment with anti-HER2 agents plus paclitaxel in 3/31 (10%) patients. No significant association was observed between CTC detection (either at baseline or week 2 or surgery), and clinicopathologic characteristics, pCR (p=0.36) or PET/CT response at week 2 (p=0.34) or week 6 (p=0.90).

Conclusion:CTC detection does not appear to be associated with pCR in patients receiving preoperative anti-HER2 agents plus paclitaxel, acknowledging the lack of power within our study.

患者/ Patient	治疗方案/ Treatment arm	CTC / HER2+CTC (每 22.5mL 的数量)/ CTC / HER2+CTC (number per 22.5mL)			病理学完全缓解/ pCR
		基线/ Baseline	两周/ Week 2	术前/ Prior to Surgery	
1	L	0	0	2 /2	否/NO
2	L	NA	2 /2	2 /2	否/NO
3	L	1 /1	0	0	否/NO
4	L	NA	4 /3	NA	否/NO
5	T	0	1 /0	0	否/NO
6	T	65 /52	0	2 /1	否/NO
7	L+T	0	0	1 /0	否/NO
8	L+T	1 /0	0	NA	否/NO
9	L+T	1 /0	0	0	是/YES
10	L+T	1 /0	0	NA	是/YES
11	L+T	0	1 /0	1 /0	是/YES

L：拉帕替尼；t：曲妥珠单抗；NA：不适用
L:lapatinib; T:trastuzumab; NA:not applicable.

267P CHER-LOB 研究：对于 HER2+可手术乳腺癌患者，选择新辅助化疗与曲妥珠单抗、拉帕替尼、或曲妥珠单抗+拉帕替尼联用治疗时，是否根据病理学缓解和 P95-HER2 预测无疾病生存期

267P DISEASE-FREE SURVIVAL ACCORDING TO PATHOLOGIC RESPONSE AND P95-HER2 IN THE CHER-LOB NEOADJUVANT STUDY OF CHEMOTHERAPY PLUS TRASTUZUMAB, LAPATINIB OR COMBINED TRASTUZUMAB AND LAPATINIB IN HER2+OPERABLE BREAST CANCER

V. Guarneri, G. Bisagni, A. Bottini, et al.

介绍：这是一项随机对照的临床 II 期研究，对于 HER2+可手术乳腺癌患者，术前序贯给予紫杉烷类-蒽环类药物并与曲妥珠单抗、拉帕替尼、或曲妥珠单抗+拉帕替尼联用。我们此前曾报道曲妥珠单抗和拉帕替尼双重阻滞 HER2 可显着提高病理完全缓解（pCR）率。事后分析的目的在于评估无病生存率（DFS）与 pCR，p95-HER2 表达和不同治疗方案之间的关系。

方法：121 例患者被随机分配到紫杉醇周疗序贯 FE75C 联用曲妥珠单抗（A 组，n =36），或拉帕替尼（B 组，n =39），或曲妥珠单抗+拉帕替尼（C 组，n= 46）的治疗组。P95-HER2 表达由 IHC 测定（bioTheranostics, Inc. San Diego, CA）。存在强免疫染色细胞≥80%的被归类为 p95-HER2 阳性肿瘤。病理学完全缓解（pCR）定义为乳房和腋窝淋巴结浸润性疾病消失。无病生存（DFS）为自手术之日起到复发（局部或远端）或死亡之日。

结果：总体而言，32%的患者获得病理学完全缓解。各组的 pCR 率分别为 A：25%，B：26.3%，C：46.7%（C 组对比 A+B 组：p=0.018）。35 例患者（29%）为 p95-HER2 阳性。在本次分析时间，报道了 17 例 DFS 事件。p95-HER2 的表达与各治疗组和总体人群的复发没有显著相关性。获得 pCR 的患者复发风险显著降低（HR 0.09，p=0.019）。3 年 DFS 在 C 组为 88%，A+B 组为 72%。

讨论：在接受新辅助治疗的 HER2 阳性乳腺癌患者中，乳房和腋窝淋巴结获得病理学完全缓解是可预期的，这与其他新辅助化疗的研究结果一致。p95-HER2 在这个患者人群中不能预测疾病转归。曲妥珠单抗+拉帕替尼联用组有更好的 DFS 趋势，反映为较高的 pCR 率。

Introduction: This is a randomized phase II trial of preoperative sequential taxanes-anthracyclines in combination with trastuzumab, lapatinib, or combined trastuzumab and lapatinib in HER2 positve operable breast cancer. We previously reported that dual HER2 blockade with trastuzumab and lapatinib significantly increased the pathologic complete response (pCR) rate. The aim of the present post-hoc analysis is the evaluation of disease free survival (DFS) according to pCR, p95-HER2 expression, and treatment arm.

Methods:121 patients were randomly assigned to weekly paclitaxel followed by FE75C combined with trastuzumab (arm A, n= 36), lapatinib (arm B, n= 39), or trastuzumab and lapatinib (arm C, n= 46). P95-HER2 expression was measured by IHC (bioTheranostics, Inc. San Diego, CA). Patients were classified as having a p95-HER2 positive tumor in case of strong immunostaining in≥80% of cells. pCR was defined as disappearance of infiltrating disease in breast and axillary nodes. DFS was calculated from the date of surgery to the date of recurrence (local or distant) or death.

Results: Overall, pCR was observed in 32% of patients. The pCR rates per treatment arm were 25% in arm A, 26.3% in arm B, and 46.7% in arm C (Arm C vs combined Arms A+B:p=0.018). Thirty-five patients (29%) resulted p95-HER2 positive. At the time of the present analysis, 17 DFS events have been reported. The expression of p95-HER2 was not significantly correlated with the probability of relapse, overall and per treatment arm. The risk of relapse was significantly lower for patients achieving a pCR (hazard ratio 0.09, p=0.019). The 3-yr DFS rate was 88% in arm C vs 72% in arms A+B.

Conclusions: The achievement of a pCR in breast and axillary nodes is predictive of outcome in HER2 positive breast cancer patients treated with neoadjuvant therapy. This is consistent with other neoadjuvant studies. p95-HER2 appears to be neither predictive nor prognostic in this patient population. The combination arm resulted in a trend for a better DFS, probably reflecting the higher pCR rate observed. Sponsored by GlaxoSmithKline.

345P 观察性横断面研究 ONCOSUR-AVALOX：在常规临床实践中影响选择贝伐珠单抗联合化疗治疗的 HER2 阴性转移性乳腺癌患者预后的因素

345P PROGNOSTIC FACTORS INFLUENCING THE SELECTION OF BEVACIZUMAB COMBINED WITH CHEMOTHERAPY IN PATIENTS WITH HER2-NEGATIVE METASTATIC BREAST CANCER IN ROUTINE CLINICAL PRACTICE. ONCOSUR-AVALOX:OBSERVATIONAL CROSS-SECTIONAL STUDY

L. Manso, R. Perez-Carrion, J..I. Chacon Lopez-Muniz, et al.

背景：HER2 阴性的转移性乳腺癌（MBC）患者联合贝伐珠单抗（BEV）与化疗（CT）治疗改善了生存期。我们在 BEV 联合 CT 治疗的 MBC 患者中调查了年龄、ECOG、激素状态、转移部位和数量等因素的影响。

方法：对于接受 BEV 联合 CT 进行一线治疗的 HER2 阴性的 MBC 患者的观察性横断面多中心研究

结果：自 2010 年 11 月至 2011 年 11 月共收入 124 例患者：平均年龄 51 岁（45-64）岁；50%的患者 ECOG 评分 0 分；60%患者是绝经前女性；23%患者为三阴性（TN）乳腺癌；77%患者激素受体阳性（HR+）；转移状况：≥3 个转移灶为 42%（其中 TN 32%; HR+45%）；转移部位：骨骼 44%，肺部 35%，肝脏 30%。最常见的 BEV 为基础的联合方案为紫杉醇/BEV（53%）和多西他赛/BEV（14.5%）；中位化疗周期数：6（5-8）。无病生存期（DFS）≥12 个月的患者比例达到 73%（TN 68%; HR+76%）。总缓解率（ORR）为 58%：部分缓解（PR）51%；完全缓解（CR）7%；疾病稳定（SD）28%；疾病进展 10%。TN 患者：ORR 为 44%（40%为 PR）；临床获益率 80%（36%为 SD）。HR+患者：ORR 为 62%（54%为 PR），临床获益率 87%（25%为 SD）。58%患者出现至少一种毒性，主要为 1-2 级；其中 26%与 BEV 相关：仅 3 例（2.4%）为 3 级毒性反应，未有患者出现 4 级毒性反应。接受辅助激素治疗与 DFS≥12 个月具有相关性（P<0.05）。在所有患者中(TN 或 HR+)，ER+肿瘤（OR:0.215; 95%CI:0.08-0.56, P=0.002）和 1 个转移灶（与≥3 个转移灶比较，OR:0.309; 95% CI:0.12-0.83; p=0.020）是选择紫杉醇-BEV 治疗的独立相关因素。肝脏转移与紫杉醇-BEV 给药方案显著相关（P <0.01）。

结论：我们的研究结果表明，对三阴和激素受体阳性转移性乳腺癌患者， CT 联合 BEV 做为一线治疗是积极且可耐受的。ER+肿瘤和单一转移部位被确定为选择紫杉醇+BEV 治疗的独立相关因素。存在肝脏转移和紫杉醇+BEV 给药方案显著相关。

Background: Combining bevacizumab (BEV) with chemotherapy (CT) improves survival in HER2-negative metastatic breast cancer (MBC). We investigated the influence of age, ECOG, hormonal status, number of sites and location of metastases and patient decision on the selection of BEV combined with CT in MBC.

Methods: Observational cross-sectional multicenter study in pts with HER2- negative MBC who have received first-line CT with BEV.

Results: From November 2010 to November 2011, 124 pts were included:median age 51 (45-64) yr; ECOG:0=50%; 60% pre-menopausic; 23% triple-negative (TN);77% hormone receptorpositive (HR+). Metastatic disease:≥3 sites=42% (TN:32%; HR+:45%); location:44% bone, 35% lung, 30% liver. Most frequent BEV-based combinations were paclitaxel/BEV (53%) and docetaxel/BEV (14.5%); median no. of CT cycles:6 (5-8). A disease-free survival (DFS)≥12 months was achieved by 73%; TN:68%; HR+:76%. Overall response rate (ORR) was 58%:51% partial response (PR), 7% complete response (CR); 28% stable disease (SD) and 10% disease progression. TN:ORR 44% (40% PR), clinical benefit 80% (36% SD); HR+:ORR 62% (54% PR), clinical benefit 87% (25% SD). 58% presented at least one toxicity, mainly grade 1-2; 26% BEV-related:only 3 (2.4%) grade 3 toxicities; no grade 4. Receiving adjuvant hormonal therapy was associated to DFS≥12 months (p<0.05). ER+tumors (OR:0.215; 95% CI:0.08-0.56; p=0.002) and one metastatic site, vs.≥3 sites (OR:0.309; 95% CI:0.12-0.83; p=0.020) were independent factors associated with the selection of paclitaxel-BEV therapy in the overall population (TN or HR+). Metastases in the liver were significantly related to paclitaxel-BEV administration (p<0.01).

Conclusions: Our findings suggest that first-line CT with BEV is an active and tolerable treatment option for pts with TN and HR+MBC. ER+tumors and a single metastatic site were identified as independent factors for the selection of a paclitaxel-BEV therapy. The presence of metastases in the liver was significantly associated to the administration of a paclitaxel-BEV regimen.

1657P 临床 III 期 AVEREL 研究：贝伐珠单抗（BV），曲妥珠单抗（H）+多西紫杉醇（T）一线治疗 HER2 阳性的局部复发/转移性乳腺癌（LR/ MBC）患者的生物标志物（BM）结果

1657P BIOMARKER (BM) RESULTS FROM THE PHASE III AVEREL TRIAL OF 1ST-LINE BEVACIZUMAB (BV), TRASTUZUMAB (H)+DOCETAXEL (T) FOR HER2-POSITIVE LOCALLY RECURRENT/METASTATIC BREAST CANCER (LR/MBC)

L. Gianni, A. Chan, M. Mansutti, et al.

背景：AVEREL 的疗效和安全性结果已经被报道。在可选的生物标记物的亚研究中，我们进行了探索性分析

方法：HER2 阳性的LR / MBC患者接受T（100mg/m^2 Q3W）+H（8→6mg/kg Q3W）±BV（15mg/kg Q3W）作为一线治疗。主要终点为研究者评估的PFS。基线时从许可的患者中收集血液和组织样本。在基线时收集的血清样本中，通过一种新型ELISA（酶联免疫吸附反应）方法测定选定的生物标志物水平。根据每种生物标记物的基线中位值分为高值（＞中位值，H）和低值（≤中位值，L）组，并依此进行生物标记物与PFS的预后因素的Cox回归分析。

结果：血清样本来自 424 名患者中的 162 位(38%)。其中 ICAM-1 与 PFS 存在显著的统计学相关性 α =0.05.

结论：使用 BV 治疗时，ICAM-1 基线高水平与更大的 PFS 获益显著相关，α = 0.05，该结果和肺癌的数据相一致。VEGF-A，VEGFR-2/-3，E-selectin 显示出潜在的预测作用。VEGF-A 和 VEGFR-2 的结果与 HER2 阴性转移性乳腺癌和胰腺癌的数据一致。

Background:AVEREL efficacy and safety results have been reported. We present exploratory analyses from the optional BM substudy.

Methods: Patients (pts) with HER2-positive LR/mBC received 1st-line T (100mg/m^2 q3w)+H (8→6mg/kg q3w)±BV (15mg/kg q3w). The primary endpoint was investigator-assessed PFS. Baseline (BL) blood and tissue samples were collected from consenting pts. BL plasma levels of candidate BMs were measured using a novel ELISA. Median BL values for each BM were used to define high (>median; H) vs low (≤ median; L) BM cohorts and to correlate BMs with PFS using Cox regression corrected for prognostic factors.

Results: Plasma samples were available from 162/424 pts (38%). ICAM-1 correlated statistically significantly with PFS at α=0.05. Table:1657P

Conclusions: High BL ICAM-1 correlated significantly with greater PFS benefit from BV at α=0.05, consistent with data in lung cancer. VEGF-A, VEGFR-2 and -3 and E-selectin showed potential predictive value. VEGF-A and VEGFR-2 results are in line with data in HER2-negative mBC and pancreatic cancer.

亚组/ Subgroup		TH		BV+TH		风险比 (95% CI)/ HR (95% CI)	P 值/p value
		事件/患者, n/ Events/pts, n	中位，月/ Median, mo	事件/患者, n/ Events/pts, n	中位，月/ Median, mo		
整体/ All		64/82	11.2	66/80	16.5	0.78 (0.56–1.11)	
E-selectin	L	31/44	16.4	30/36	16.5	1.01 (0.61–1.68)	0.241
	H	32/37	8.2	35/43	16.6	0.57 (0.35–0.92)	
IL-8	L	35/45	13.6	28/35	16.4	0.84 (0.51–1.40)	0.506
	H	28/36	8.4	37/44	17.8	0.74 (0.45–1.22)	
ICAM-1	L	30/45	16.4	29/35	16.5	1.13 (0.68–1.89)	0.017
	H	33/36	10.3	36/44	16.2	0.49 (0.30–0.80)	
bFGF	L	32/41	13.3	33/39	16.4	0.80 (0.49–1.30)	0.837
	H	31/40	11.1	32/40	19.1	0.80 (0.49–1.32)	
PDGF-C	L	29/40	17.1	32/41	16.5	0.87 (0.52–1.44)	0.342
	H	35/42	8.5	34/39	16.6	0.72 (0.45–1.16)	
VEGF-A	L	33/45	13.6	30/36	16.5	0.83 (0.50–1.36)	0.795
	H	31/37	8.5	35/43	16.6	0.70 (0.43–1.14)	
VEGF-C	L	35/42	13.5	32/39	14.8	0.70 (0.43–1.15)	0.649
	H	29/40	9.6	34/41	19.1	0.92 (0.56–1.51)	
VEGFR-1	L	30/40	11.1	33/40	16.2	0.76 (0.46–1.25)	0.982
	H	33/41	13.3	32/39	16.6	0.84 (0.52–1.37)	
VEGFR-2	L	35/44	11.2	30/36	13.7	0.95 (0.58–1.55)	0.174
	H	28/37	11.0	35/43	19.2	0.67 (0.40–1.10)	
VEGFR-3	L	35/48	12.2	25/32	15.3	0.88 (0.52–1.47)	0.051
	H	28/33	11.0	40/47	16.6	0.65 (0.40–1.06)	

A 模型包含了预后因子

A Model includes prognostic factors.

200P 用于预测贝伐珠单抗为基础新辅助治疗乳腺癌病理缓解的影像及分子生物标记物

200P NEW IMAGING AND MOLECULAR BIOMARKERS TO PREDICT PATHOLOGICAL RESPONSE TO BEVACIZUMAB-BASED TREATMENT IN NEOADJUVANT BREAST CANCER

J. Garcia Foncillas, A. Plazaola, B. Hernando, et al.

背景：对于乳腺癌新辅助治疗早期可靠的预测病理学缓解可帮助筛选出哪些患者接受贝伐珠单抗为基础的治疗方案可受益。本项多中心临床研究对于不同的影像方法和分子生物学方法进行了评价。

方法：73 位未接受过化疗的II/III期乳腺癌患者入选了该项单组、多中心、开放性的前瞻性临床II期研究。患者在开始新辅助化疗的 3 周前接受了单次输注贝伐珠单抗（15mg/kg）（C1）；新辅助化疗方案为 4 个周期的多西紫杉醇（60mg/m2），阿霉素（50mg/m^2）和贝伐珠单抗（15mg/kg），21 天一周期（C2-C5）；之后是手术治疗。分别使用 18F-氟（FLT）和 18F-米索硝唑（FMISO）正电子发射断层扫描（PET/ CT）和动态对比增强磁共振（DCE-MR）对肿瘤细胞增殖，缺氧和灌注进行了评估。这一系列的影像学研究分别在下述时间点进行，包括：基线（BL），单剂贝伐珠单抗（C1）后的 14-21 天。在贝伐珠单抗输注（C1）前后，采用免疫组化方法对分子标记物（Ki67、CD31、CD31/Ki67、VEGFR2、pVEGFR2[Y951]）的表达进行了评估。采用Affimetrix人类基因ST1.0 对基因表达进行分析。

结果：FMISO 摄取减少>10%的患者 ROC（受试者工作特性曲线）曲线下面积 0.7（95%CI：0.56~0.85），具有较高的特异性（94%）。磷酸化状态 VEGFR2（Y951）的减少>70%的患者 ROC 曲线下面积 0.681（95%CI：0.536~0.825），灵敏度 84%，特异度 95%。在多因素分析中，校正临床病理学特征后，VEGFR2p 磷酸化状态的变化是预测缓解率的一个重要的生物标志物（OR= 0.9%95，IC0.96-0.99，P=0.04）。

结论：我们的研究结果表明，单用 1 个周期的贝伐珠单抗后，FMISO pVEGFR 这两种标记物的早期变化预测了贝伐珠单抗为基础的新辅助治疗乳腺癌患者的病理缓解率。

Background: Early and robust prediction of pathological response in neoadjuvant breast cancer may help to identify which patients may benefit from bevacizumab-based therapy. Different imaging and molecular approaches have been 0evaluated in a multicenter clinical trial.

Methods:73 chemotherapy naïve, stage II and III breast cancer (BC) patients (pts) were enrolled in a phase II, single-arm, multicenter, open-label and prospective clinical trial. Pts received single infusion of bevacizumab (15mg/ kg) (C1) 3 weeks prior to the beginning of neoadjuvant chemotherapy (NAC) consisting of 4 cycles of docetaxel (60mg/mq), doxorubicin (50mg/mq) and bevacizumab (15mg/ kg) every 21 days (C2-C5), followed by surgery. Tumor proliferation, hypoxia and perfusion were evaluated respectively using 18F-Fluorothymidine (FLT) and 18F-Misonidazole (FMISO) positron emission tomography (PET/CT) and dynamic contrast enhancement magnetic resonance (DCE-MR). Serial imaging studies were performed in parallel at several time points including baseline (BL) and 14-21 days after bevacizumab alone (C1). Biomarker expression was assessed by immunohistochemistry (Ki67, CD31, CD31/Ki67, VEGFR2, pVEGFR2 [Y951]) before and after bevacizumab infusion (C1). Gene expression was analyzed using Affimetrix Human Gene ST 1.0.

Results: Decrease in FMISO uptake >10% yielded a ROC curve area of 0.7 (95% CI:0.56-0.85) with high specificity (94%). Decrease in the phosphorilation status of VEGFR2 (Y951) >70% yielded a receiver operating characteristic (ROC) curve area of 0.681 (95% CI:0.536-0.825) with 84% sensitivity and 95% specificity. The change in phosphorilation status of VEGFR2p remains a significant predictor biomarker of response in multivariate analysis (OR=0.9, IC%95 0.96-0.99, p=0.04) after adjusting for clinical-pathological characteristics.

Conclusion: Our findings suggest that early changes on both biomarkers, FMISO and pVEGFR, with one cycle of bevacizumab alone predict pathological response in bevacizumab-based neoadjuvant therapy in breast cancer.

323PD GEICAM/GBG LEA 研究的安全性分析：评估内分泌治疗中加入贝伐珠单抗作为晚期乳腺癌一线治疗方案的临床 III 期研究

323PD PHASE III TRIAL EVALUATING THE ADDITION OF BEVACIZUMAB TO ENDOCRINE THERAPY AS FIRST-LINE TREATMENT FOR ADVANCED BREAST CANCER:THE GEICAM/GBG LEA STUDY. SAFETY ANALYSIS

S. Loibl, J.R. De La Haba, G. von Minckwitz, et al.

背景：我们设计了这个贝伐珠单抗联合内分泌治疗作为一线治疗方案的随机对照临床 III 期 LEA 研究，目的在于确认一个假设：对内分泌治疗敏感的晚期乳腺癌的患者，抗 VEGF 治疗可以防止内分泌治疗耐药性的产生。

方法：本研究为在两个国家进行的临床 III 期、多中心、随机对照、开放性研究，研究来曲唑或氟维司群（250mg/ 4 周）的内分泌治疗（ET）中增加贝伐珠单抗（B，15mg/kg，每 3 周）作为一线方案治疗转移性乳腺癌的作用。患者纳入标准为 HER2 阴性和激素受体阳性的绝经后乳腺癌。主要终点是比较治疗组间的无进展生存（PFS）。次要终点是总生存、至治疗失败时间、总缓解率、缓解持续时间、临床受益率和安全性。患者纳入在 2011 年 9 月完成。疗效分析将在发生 270 例事件后开展。

结果：从 2007 年 11 月到 2011 年 11 月，380 例 ER/PgR 阳性的 HER2 阳性肿瘤患者被随机分为 ET±B 组。其中 38 例患者接受了氟维司群。两组的患者基线特征得到了很好的平衡。患者中位年龄为 65 岁（38-85）；27%的患者存在脏器转移；36%的患者之前接受过芳香化酶抑制剂的治疗；110 例患者仍然在接受治疗。到目前为止，共有 335/380 例合格的安全性数据。总共在 46 例患者中报告了 58 起严重不良事件，44 起发生在 ET+B 组中，其中 7 个是致命的（血栓栓塞事件×2，高血压，心脏衰竭，猝死，肝功能衰竭，小脑梗死），但只有 2 例由研究者确认与贝伐珠单抗相关。另外 14 起严重不良事件在 ET 组。ET+B 组和 ET 组中，任何级别的主要副作用发生率对比如下：贫血 76% vs 44%，P<0.001；疲劳 50% vs 31%，P=0.001；出血 19% vs 2%，P <0.001；高血压 55% vs 12%，P<0.001；蛋白尿 21% vs 3%，P <0.001；3-4 级血栓形成 2.3% vs 0%，P=0.057。

结论：LEA 是第一个探讨内分泌治疗和抗血管生成药物联合使用的研究。安全性分析显示主要的副作用为 1-2 级。

Background: We designed the randomized phase III LEA study of first-line bevacizumab in combination with endocrine therapy, to address the hypothesis that anti-VEGF treatment can prevent resistance to endocrine therapy in patients (pts) with advanced breast cancer sensitive to such treatment.

Methods:A multicentre, binational, randomised, open label, phase III study investigated the addition of Bevacizumab (B) 15mg/kg every 3 weeks to an endocrine therapy (ET) with letrozole or fulvestrant (250mg/4 weeks) as first-line therapy in metastatic breast cancer.Postmenopausal pts with HER2-negative and hormone-receptor-positive breast cancer were eligible. The primary objective was to compare progression-free survival (PFS) in the treatment arms. Secondary objectives were overall survival, time to treatment failure, overall response rate, response duration, clinical benefit rate and safety. The recruitment was completed in September 2011. Efficacy analysis will be triggered after 270 events.

Results: From 11/2007 to 11/2011, 380 pts with ER/PgR+and HER2-tumours were randomised to ET±B. 38 patients received fulvestrant. Baseline characteristics were well balanced. Median age was 65 years (38-85). 27% had visceral metastases. 36% patients had a prior AI. 110 pts are still on treatment. So far safety data from 335/380 patients are available. Overall 58 serious adverse events in 46 patients were reported 44 in ET-B of which seven were fatal (thromboembolic event x2, hypertension, heart failure, sudden death, liver failure, cerebellum infarction) but only 2 drug related to bevacizumab by the investigator and 14 in ET arm. The main side effects any grade per patient ET-B vs ET were as follows anemia 76% vs 44%,p<0.001; fatigue 50%vs 31%, p=0.001; hemorrhage 19% vs 2%,p<0.001; hypertension 55% vs 12%, p<0.001; proteinuria 21%vs 3%, p<0.001; thrombosis grade 3-4, 2.3%vs 0%, p=0.057.

Conclusions:LEA is the first study to explore the use of an anti-angiogenic drug in combination with an endocrine treatment. The main side effects are of grade 1-2. Final safety data will be presented at the meeting.

317O 临床 III 期 TURANDOT 研究的第一次疗效结果：用于 HER2 阴性的转移性乳腺癌（MBC）的两个含贝伐珠单抗（BEV）的一线治疗方案的比较

317O FIRST EFFICACY RESULTS FROM THE TURANDOT PHASE III TRIAL COMPARING TWO BEVACIZUMAB (BEV)-CONTAINING REGIMENS AS FIRST-LINE THERAPY FOR HER2-NEGATIVE METASTATIC BREAST CANCER (MBC)

C. Zielinski, I. Láng, M.J. Inbar, et al.

背景：TURANDOT 是第一个比较 BEV 结合紫杉醇（PAC）或卡培他滨（CAP）的前瞻性研究。按照计划，我们报告将疗效中期分析（IA）结果。

方法：之前未接受针对 MBC 化疗方案的 HER2 阴性 MBC 患者随机分别接受 BEV-PAC 方案（BEV 10mg/kg d1d15+PAC 90mg/m2 d1,8,15 q4w）或 BEV-CAP 方案（BEV 15mg/kg d1+CAP 1000mg/m2 bid d1-14 q3w）治疗，直至疾病进展或出现不可耐受的毒性。研究的主要目的是证明 BEV-CAP 对照 BEV-PAC 非劣性改善总生存期（OS）。计划在符合方案数据分析人群（PP 人群）中出现 175 例和 389 例死亡后分别进行中期及最终的 OS 分析，用以排除劣性的零假设，统计效能为 80%的 HR≥1.33，整体 α = 0.025。次要终点包括缓解率（RR）、无进展生存期（PFS）、安全性和生活质量。

结果：到中期分析截止时间（2011/9/1），中位随访时间为 19 个月。两个治疗组的患者基线特征相似。

结论：在这个中期分析中，BEV-CAP 对照 BEV-PAC 未满足非劣效性标准，但两者的 OS 的结果没有显著差异。最终结果预计在 2014 年公布。BEV-PAC 的 PFS 和 RR 更优的结果和来自以前的 BEV-PAC（E2100）和 BEV-CAP（RIBBON-1）数据的非常相似。

Background:TURANDOT is the first prospective trial to compare BEV combined with either paclitaxel (PAC) or capecitabine (CAP). We report the planned interim analysis (IA) of efficacy.

Methods: Patients with HER2-negative mBC who had received no prior chemotherapy for mBC were randomised to receive either BEV–PAC (BEV 10mg/kg d1 & 15+PAC 90mg/m d1, 8 & 15 q4w) or BEV–CAP (BEV 15mg/kg d1+CAP 1000mg/m bid d1–14 q3w) until disease progression or unacceptable toxicity. The primary objective is to demonstrate non-inferior overall survival (OS) with BEV–CAP vs BEV–PAC. Interim and final OS analyses were planned after 175 and 389 deaths, respectively, in the per-protocol (PP) population to reject the null hypothesis of inferiority (hazard ratio [HR]≥1.33) with 80% power and overall α=0.025. Secondary endpoints include response rate (RR), progression-free survival (PFS), safety and quality of life.

Results: Median follow-up was 19 months at data cut-off for this IA (1 Sep 2011). Baseline characteristics were generally similar in the 2 treatment arms.

Conclusion: In this planned IA, the non-inferiority criterion has not been met but OS results do not indicate relevant differences. Final results are expected in 2014. PFS and RR were better with BEV–PAC and very similar to previous data for BEV–PAC (E2100) and BEV–CAP (RIBBON-1).

	BEV-PAC (n=285)	BEV–CAP (n=279)
中位年龄（岁）/ Median age, years	59	59
脏器转移, %/ Visceral metastases, %	65	73
之前接受紫杉类（新）辅助治疗（%）/ Prior (neo)adjuvant taxane, %	20	18
OS [a]		
事件（%）/ Events, %	33	35
1 年OS率（%）[b]/ 1-year OS rate, %b	81	79
非劣效性HR (97.5% RCI [c])/ HR (97.5% RCIc)for non-inferiority	1.04 (−∞ to 1.69) p=0.0593 [d]	
治疗缓解率/ RR		
总生存率, %/ Overall, %	44	27
CMH 测试（优效性)/ CMH test (superiority)	p<0.0001	
PFS		
事件（%）/ Events, %	62	77
中位值（月）/ Median, months	11.0	8.1
HR (95% CI)	1.36 (1.09 to 1.68)	
对数秩(优效性)/ Log-rank (superiority)	p=0.0052	

RCI=重复置信区间

RCI=repeated confidence interval

a：符合方案数据分析人群（n=533）

a:PP population (n=533)

b：Kaplan–Meier 评估

b:Kaplan–Meier estimate

c：使用 O'Brien-Fleming 界值

c:Using O'Brien–Fleming boundaries

d：基于不良事件的 p>0.00105（中期分析 α），BEV-CAP 对照 BEV-PAC 未达到非劣效性，这和已知的 BEV、PAC 和 CAP 的安全特性一致。最常见的≥3 级不良事件为：BEV-PAC 组中为嗜中性白血球减少症（18%）；周围神经病变（14%）；和白细胞减少（7%）；BEV-CAP 组中为手足综合征（16%）；高血压（6%）和腹泻（5%）。

d:Non-inferiority not shown as p>0.00105 (α at IA) AEs were consistent with the known safety profiles of BEV, PAC and CAP. The most common grade≥3 AEs were neutropenia (18%), peripheral neuropathy (14%) and leucopenia (7%) with BEV–PAC and hand-foot syndrome (16%), hypertension (6%) and diarrhoea (5%) with BEV–CAP.

343P 一项单中心研究：新的免疫组化标志物可预测 HER2 阳性局部晚期乳腺癌对新辅助化疗+曲妥珠单抗的疗效

343P NEW IMMUNOHISTOCHEMICAL MARKERS PREDICTIVE OF RESPONSE TO NEOADJUVANT CHEMOTHERAPY PLUS TRASTUZUMAB IN HER2-POSITIVE LOCALLY ADVANCED BREAST CANCER:A SINGLE CENTER EXPERIENCE

G. Faggioni, C. Ghiotto, E. Orvieto, et al.

这项研究旨在评估新免疫组化标志物在局部晚期 HER2 乳腺癌患者中的的预测价值。在晚期乳腺癌患者中，pTEN 丢失，pAKT 和 HER-3 的过表达引起 PI3K 激活，无论在体内还是体外均诱导出曲妥珠耐药，从而导致较差的临床疗效。在 31 名接受新辅助化疗+曲妥珠单抗的局部晚期 HER2+乳腺癌患者中，研究了 EGFR, HER-3, pTEN 和 pAKT 的表达。患者的平均年龄为 55.7 岁（中位值为 55 岁，95%CI 为 44.2-63.5 岁）。

患者在诊断时、接受蒽环类-紫杉醇和曲妥珠为基础的新辅助治疗时的瘤负荷水平一致。31 名患者中的 14 位获得了病理学完全缓解。在得到完全缓解的患者中，Ki-67 和 HER3 H 的值均显著升高（中位值 45.5% vs 25%, p=0.022; 100% vs 50%, p=0.045）. EGFR H 分数和 HER3 H 分数之间存在相关性(p=0.02)。年龄和 EGFR H 分数呈负相关（p=0.05），PgR 和 AKT 加强之间也存在负相关(p=0.03)。多因素分析显示获得完全病理学缓解的患者与不完全应答者比较，Ki-67 和 HER3 H 分数的中位值存在显著差异(p<0.01)。

下表显示免疫组化染色结果：

We present the results of a prospective pilot study aimed to investigate the value of new immunohistochemichal predictive markers of response to chemotherapy in locally advanced HER-2 breast cancer. pTEN loss, pAKT and HER-3 overexpression cause PI3K activation and induce resistance to trastuzumab in vitro and in vivo, with poorer clinical responses in patients with advanced disease. We studied the espression of EGFR, HER-3, pTEN and pAKT in 31 patients with locally advanced HER-2 positive breast cancer who received neoadjuvant chemotherapy plus trastuzumab. Mean age of patients was 55.7 years (median 55, 95% CI 44,2-63,5 years).

Patients were homogeneous for tumor burden at diagnosis and received anthraciclin-taxane and trastuzumab-based neoadjuvant treatment. 14 out of 31patients achieved pathological complete remission. Ki-67 and HER3 H score were significatively higher in patients who achieved complete remission (medians were 45.5% versus 25%, p=0.022; 100% versus 50%, p=0.045 respectively. We found a correlation between EGFR H score and HER3 Hscore (p=0.02), and an inverse correlation between age and EGFR H score (p=0.05) and between PgR and AKT intensity (p=0.03). Ki-67 and HER3 H score maintained significatively different medians in the group of patients who experienced pathological complete response versus the group on incomplete responders with multivariate analysis (p<0.01).

Results of immunohistochemistral staining are reassumed in the table:

	平均值/ Mean	中位值/ Median	25% C.I.	75% C.I.
ER%	40,6	40,0	0,0	77,5
PgR%	23,1	10,0	0,0	40,0
Ki-67%	38,2	40,0	25,0	50,0
EGFR 组化评分/ EGFR Hscore	6,1	0,0	0,0	1,0
HER3 (% 阳性细胞)/ HER3 (% positive cells)	50,0	50,0	32,5	70,0
HER3 强度/ HER3 intensity	1,5	1,0	1,0	2,0
HER3 组化评分/ HER3 H score	82,6	70,0	32,5	115,0
PTEN (% 阳性细胞)/ PTEN (% positive cells)	48,9	70,0	2,5	70,0
PTEN 强度/ PTEN intensity	1,5	1,0	1,0	2,0
AKT 组化评分/ AKT Hscore	56,7	20,0	0,0	70,0
AKT IRS	2,5	2,0	0,0	3,0

ER-雌激素受体 PgR-孕激素受体 Ki-67-细胞增殖活性标记物 IRS-胰岛素受体底物

322PD 对可手术/局部晚期乳腺癌（O/LABC）患者，单个/双重 HER2 抑制剂和新辅助化疗联用的治疗方案分析，平衡病理学完全缓解率和心脏毒性

322PD A TREATMENT-INTERACTION ANALYSIS BALANCING PATHOLOGICAL COMPLETE RESPONSES (PCR) AND CARDIOTOXICITY OF SINGLE-(S)/DUAL-(D) HER2 INHIBITION AND NEOADJUVANT CHEMOTHERAPY (CT) BACKBONE IN OPERABLE/LOCALLY ADVANCED BREAST CANCER (O/LABC) PATIENTS

E. Bria, M. Bonomi, J. Furlanetto, et al.

目的：由于蒽环类药物与 1 个双重 HER2 抑制剂联用存在潜在的毒性，因此本项随机研究完成了治疗方案相互作用的分析。

方法：从文献中收集病理学完全缓解率（乳房+腋窝），保乳手术（BCS），3-4 级中性粒细胞减少/心脏毒性和中粒减少性发热（FN），不良事件等数据，并根据一个随机效应模型计算，导出 95%可信区间（CI）。根据单个/双重 HER2 抑制剂、激素受体和化疗方案（蒽环-紫杉醇或单用紫杉醇）的不同进行相互作用的分析。计算出绝对差（AD）及 95%CI,NNT/NNT 数目来推算受益或伤害的似然比（LHH）。

结果：8 个研究（2092 例患者）中的 1955 名患者接受了抗 HER2 治疗（曲妥珠单抗、拉帕替尼、帕妥珠单抗），不同 HER2 抑制剂的 pCR 率见下表。

激素受体阴性人群的 pCR 率显著增高，且与 HER2 抑制剂和化疗方案无关（Neg. vs. Pos. 蒽环类/紫杉类[S] AD 9.4%, p=0.002; TAX [S] AD 15.3% p<0.0001; TAX [D] AD 28%, p<0.0001)。关于化疗，在双重-HER2 抑制剂亚组中，pCR （AD 15.4%）、BCS（AD 10.8%）和蒽环类使用之间有显著相关性（p＜0.0001），支持在紫杉类中添加蒽环类；且在 D-HER2 抑制剂亚组无相互作用。不同的 HER2 和化疗方案，FN 和心脏毒性无显著差异。在蒽环类-紫杉类+S-HER2 抑制剂治疗人群中评估心脏毒性，LHH 值为 77。

结论：基于可用的数据，对可手术/局部晚期乳腺癌患者，紫杉类基础化疗与 HER2 抑制剂联用时应考虑给予蒽环类药物，因为获得完全病理学缓解的可能性比受到临床意义的心脏毒性的性高出 70 倍。

Purpose: Given the toxicity drawbacks potentially related to the combination of anthracylines and a D-HER2 inhibition, a treatment interaction analysis of the available randomized trials was accomplished.

Methods:pCR (breast+axilla), breast conserving surgery (BCS), grade 3-4 neutropenia/cardiotoxicity, and febrile neutropenia (FN), events were extracted from papers/presentation and cumulated according to a random-effect model; 95% confidence intervals (CI) were derived. A sensitivity analysis according to S/D HER2 inhibition, hormonal receptors (HRs) and CT (anthracyclines-taxanes:anthra-TAX; TAX alone) was accomplished to test for interaction. Absolute differences (AD) with 95% CIs, and the number of pts needed to treat/harm (NNT/NNH) for 1 to benefit were calculated to derive the Likelihood of being Helped or Harmed (LHH).

Results:8 trials (2092 pts) with 1955 pts treated with anti-HER2 therapy (Trastuzumab, Lapatinib and Pertuzumab), were gathered; pCR rates according to HER2 inhibition follow:

pCR rates were significantly higher in the HRs negative population, regardless of the HER2 inhibition and CT backbone (Neg. vs. Pos. Anhtra-TAX [S] AD 9.4%, p=0.002; TAX [S] AD 15.3% p<0.0001; TAX [D] AD 28%, p<0.0001). With regard to CT, a significant interaction (p<0.0001) in favour of adding Anthra to TAX was found in the context of S-HER2 inhibition subgroup with regard to pCR (AD 15.4%) and BCS (AD 10.8%) with no interaction in the D-subgroup. No significant differences in FN and cardiotoxicity were found according to HER2 inhibition and CT. In the Anhtra-TAX [S] population weighted for cardiotoxity, LHH was 77.

Conclusions: On the basis of the available data, anthracyclines should be considered for O/LABC patients receiving TAX-based CT plus HER2 inhibition, given the likelyhood 70-times greater to achieve pCR than to be harmed by clinically meaningful cardiotoxicity.

化疗/ CT	HER2 抑制剂/ HER2-Inhibition	pCR (95% CI)/ Rates (95% CI)	相关性 (p)/ Interaction (p)	NNT
蒽环类-紫杉类/ Anthra-TAX	单/ S	37.0 [34.0, 40.0]	0.22	2.7
	双/ D	44.3 [33.3, 55.2]		2.2
紫杉类/ TAX	单/ S	21.7 [18.1, 25.3]	<0.0001	4.6
	双/ D	42.4 [36.4, 48.5]		2.3

172O ER+/HER2+及 ER-/HER2+乳腺癌在分子水平上存在差异，但二者的免疫基因特征对疾病转归有预测意义

172O ER+/HER2+AND ER-/HER2+BREAST CANCERS ARE MOLECULARLY DISTINCT BUT IMMUNE GENE SIGNATURES ARE PROGNOSTIC AND PREDICTIVE IN BOTH GROUPS

T. Iwamoto, L. Pusztai, J. Matsuoka, et al.

目的：检测 HER2（人类表皮生长因子受体Ⅱ）阳性乳腺癌患者不同 ER（雌激素受体）状态的基因表达模式是否不同。评估 ER 亚组分超过 3000 个基因集对疾病预后和化疗结果的预测作用。

方法：研究了公开发布的 537 名 HER2+(ER-/HER2+n=278, ER+/HER2+n=259)和 2985 名 HER2- (ER thinsp;+/HER2- n=1923, ER-/HER2- n=1062)乳腺癌患者的临床注释 Affymetrix 基因表达数据，其中包括 121 名淋巴结阴性(ER+n=61, ER- n=60)、未经系统性辅助治疗的患者与 86 名给予紫杉醇类新辅助治疗或蒽环类环化疗的 HER2+患者 (ER+n=27 and ER- n=59)。

结果：HER2+的患者不同ER状态的基因差异更小（不同ER状态的差异表达基因，分别为n=194, n=6750, p<1.0E10-6，共同基因84%）。根据ER状态分层，HER2+和HER2-之间表现出显著的差异（HER2-相关差异表达基因在ER+n=242,ER- n=1200, p<1.0E10-6,共同基因为 20%）。在ER+/HER2+肿瘤中，67 个基因集与良好的预后相关。（如B,T和NK细胞和INF-ɣ的生成），2 个基因集与较差的预后相关（PTEN依赖的细胞周期停滞和凋亡）(p≤.001)。这些基因集对ER-/HER2+型肿瘤也具有同样的预测作用。在新辅助治疗方面，在ER+和ER-/HER2+组，有病理学完全缓解相关的基因集为 11 个（如：T-细胞活化和分化），与残留疾病（RD）相关的基因集为 2 个（如：细胞-细胞间的连接）（联合p≤.001）。ER与pCR或RD具有特殊相关性。在ER-/HER2+类型中，18 个基因集与pCR相关(p≤.001)，但在ER+/HER2+型肿瘤中却无相关性。（如趋化性细胞因子C-C连接、活化和磷脂代谢过程）。

结论：在 HER2+肿瘤，ER- 和 ER+表现出不同的分子亚型。在HER2+癌症中，不管 ER 状态如何，免疫学特征均预示着良好的预后及更高的化疗敏感性。

Objectives: We examined if gene expression patterns differ among HER2 positive breast cancers by estrogen receptor (ER) status. We also assessed the prognostic and chemotherapy response predictive values of over 3000 gene sets separately in the ER subsets.

Methods: Publically available, clinically annotated Affymetrix gene expression data of 537 HER+(ER-/HER2+n=278, ER+/HER2+n=259) and 2985 HER2- (ER thinsp;+/HER2- n=1923, ER-/HER2- n=1062) patients were studied including 121 node-negative, HER2+cases with no systemic adjuvant therapy (ER+n=61, ER- n=60) and 86 HER2+patients treated with neoadjuvant taxane or anthracycicline chemotherapy (ER+n=27 and ER- n=59).

Results: Genes that distinguished ER+from ER- cases differed for HER2+and HER2- cancers. HER2+cancers showed less difference by ER status compared to HER2- cancers (differentially expressed genes by ER status:n=194 and n=6750, p<1.0E10-6, shared genes 84%). Significant differences were also observed when HER2+and HER2- cancers were compared stratified by ER status (HER2-related differentially expressed genes in ER+n=242, in ER- n=1200, p<1.0E10-6, shared genes 20%). In ER+/HER2+tumors, 67 gene sets (GSs) were associated with good prognosis (e.g. B, T and NK cells and interferon-gamma production) and 2 GS with poor prognosis (PTEN dependent cell cycle arrest and apoptosis) (p≤.001). The same GSs were also prognostic in ER-/HER2+cancers. In the neoadjuvant series, 11 and 2 GSs were associated in both ER+and ER-/HER2+groups with pathologic complete response (pCR) (e.g. T-cell activation and differentiation) and residual disease (RD) (e.g. Cell-cell junction) respectively (combined p≤.001). We also noted ER specific associations with pCR or RD. For instance, 18 GSs were associated with pCR in ER-/HER2+(p≤.001) but not in ER+/HER2+tumors (e.g. chemochine C-C binding and activity, phospholipid catabolic process).

Conclusions: Among HER2+tumors, ER- and ER+cancers represent distinct molecular subtypes. Immune signatures predict for good prognosis and higher chemotherapy sensitivity in HER2+cancers regardless of ER status.

228P 一种新型定量测试方法用于 HER2+乳腺癌患者新辅助化疗中预测 ADCC（抗体依赖性细胞介导的细胞毒）和病理学完全缓解

228P DEVELOPMENT OF A NOVEL QUANTITATIVE ASSAY FOR PREDICTING ADCC, ANTIBODY DEPENDENT CELL MEDIATED CYTOTOXICITY, AND PREDICTION OF PATHOLOGICAL COMPLETE RESPONSE IN NEOADJUVANT CHEMOTHERAPY FOR HER-2 POSITIVE BREAST CANCER

K. Tamura, M. Yunokawa, H. Yamamoto, et al.

背景：抗体依赖性细胞介导的细胞毒性（ADCC）是曲妥珠单抗作用机制的一种。我们之前曾报道 FcγRIIIa-158V/V 和 Fc γ RIIa-131 H/H 基因型可以预测曲妥珠单抗用于 HER2 阳性乳腺癌患者新辅助和转移性治疗的临床结果。本研究的目的是直接测量个体 ADCC 的差异，并开发一个用于预测曲妥珠单抗临床效果的新系统。

材料和方法：分析 11 名健康志愿者（HVs）的外周血单核细胞（PBMCs）证实了个体间差异的稳定性。之后我们采用了一种体外基因表达分析用以确定与 ADCC 活性相关的分子。我们研究了来自 8 个 HVs，在体外使用 Hem A（+）系统，暴露于热凝集 IgG1 4 小时后的 14 个候选基因的表达变化。在鉴定 ADCC 的预测分子后，前瞻性评估了这些分子的倍增值（FIs）是否与 18 例接受曲妥珠单抗为基础的新辅助化疗的 HER2 阳性乳腺癌患者的病理完全缓解（pCR）相关。

结果：TNFSF15, IL-6, CxCL-3 表达的倍增与 ADCC 活性显著相关（R 值分别为：0.74，0.85，0.87）。患者的入选标准包括 HER2 阳性乳腺癌，之前未接受化疗，可测得的疾病，PS 评分 0-2 分和器官功能耐受。患者接受标准 FEC 方案（5FU/表柔比星/环磷酰胺）q3w 共 4 周期，后续每周紫杉醇/曲妥珠单抗 12 周。获得 pCR 的患者较没有获得 pCR 的患者具有更高的 CXCL-1、CXCL-3、TNFSF-2、TNFSF-15 倍增值（p 值分别为 0.004, 0.015, 0.0495, 0.014）。

讨论：这些结果提示新 ADCC 定量测定具有预测曲妥珠单抗新辅助化疗 pCR 的作用。

Background: Antibody-dependent cell-mediated cytotoxicity (ADCC) has been shown to be one of the modes of action for trastuzumab. We have previously reported that Fc γ RIIIa-158 V/V and Fc γ RIIa-131 H/H genotypes predicted clinical outcome of trastuzumab in both neoadjuvant and metastatic setting in patients with HER-2 positive breast cancer. The purpose of this study is to directly measure an inter-individual ADCC and to develop a new system for predicting to a clinical effectiveness of trastuzumab.

Materials and methods: The stability of the inter-individual differences has been confirmed using peripheral blood mononuclear cells (PBMCs) of 11 healthy volunteers (HVs). Next, we adopted an ex vivo gene expression analysis to identify the molecules which correlate with ADCC activity. We examined the expression change of 14 candidate genes in the 8 HVs after ex vivo exposure to heat-aggregated IgG1 for 4 hr using Hem A (+) system. After identification of the molecules predicting ADCC, we evaluated prospectively whether values of fold increase (FIs) of these the molecules are associated with a pathological complete response (pCR) in 18 patients with HER2 positive breast cancer, who received trastuzumab-based neoadjuvant chemotherapy.

Results:FI in expressions of TNFSF15, IL-6, and CxCL3 are significantly correlated with ADCC activity (R=0.74, R=0.85, R=0.87, respectively). Eligible criteria of the prospective comfort include HER2 positive breast cancer, chemotherapy-naïve, measurable disease, PS 0-2 and adequate organ functions. Patients received standard FEC (5-fluorouracil/epirubicin/cyclophosphamide) q3w for 4cycles followed by weekly paclitaxel/trastuzumab for 12 weeks. Patients who achieved a pCR had a higher FI of CXCL-1, CXCL-3, TNFSF-2, and TNFSF-15 than those who did not (p=0.004, 0.015, =0.0495, and =0.014, respectively).

Conclusions: These results suggest the novel quantitative ADCC assay have a potential to predict pCR to trastuzumab-based neoadjuvant chemotherapy.

206P 乳腺癌患者的 HER-2 受体表达和二聚体的定量测量预测疾病转归

206P PREDICTION OF DISEASE OUTCOME WITH QUANTITATIVE MEASUREMENT OF HER-2 RECEPTOR EXPRESSION AND DIMERIZATION IN PATIENTS WITH BREAST CANCER

H. Bazin, F. Andre, M.-C. Mathieu, et al.

介绍：HER2 的表达通常使用免疫组化学（IHC）方法评估，IHC-HER2 阳性的乳腺癌患者被招募过来进行抗 HER2 治疗。然后 IHC 不可定量，不能发现 HER2 表达的轻微改变，也不能评估对它的激活至关重要的 HER2 的二聚体状况。该研究的目的是确定乳腺癌患者的 HER2 表达和二聚体状况，并将此结果与疾病转归进行相关性分析。

方法：使用微量滴定板时间分辨荧光分析（TR-FRET）技术确定 100 名乳腺癌患者冰冻肿瘤标本HER2 受体表达和二聚体的数量。归一化荧光信号可都所有受体和二聚体表达进行定量测量。每名患者的无疾病生存（DFS）和总生存（OS）进行了评估。

结果：100 名患者中，82 名 IHC-HER2 为阴性，包括 60 名 ER+接受激素治疗的患者。使用 COX 比例风险模型分析表明在 IHC-HER2 阴性、ER+的患者中，HER2 二聚体的出现与 DFS (p=0.0001)和 OS(p=0.00237)的降低显著相关。HER2 表达的量与 DFS (p=0.0005)和 OS (p=0.03)呈相关性。

结论：对 IHC-HER2 阴性，ER+的乳腺癌患者，通过 TR-FRET 分析定量测定 HER2 的表达和二聚体状况可预测疾病转归。这些新的生物标志物可用于分辨出激素治疗失败的患者是否可以从抗 HER2 的辅助治疗中获益。未来将提交在 200 个 FFPE-样本中进行的验证结果。

Introduction: Expression of HER2 is commonly assessed by immunohistochemistry (IHC) and IHC-HER2 positive patients with breast cancer are candidate for anti-HER2 therapy. However IHC is not quantitative, does not allow to detect subtle changes in HER2 expression and cannot assess HER2 dimerization which is critical for its activation. The aim of this study was to quantify the expression and dimerization of HER2 in patients with breast cancer and to relate these measurements to disease outcome.

Methods: Using a novel microtiter plate based Time Resolved Fluorescence (TR-FRET) assay we quantify HER2 receptor expression and dimerization on frozen tumor samples from 100 patients with breast cancer. Normalized fluorescence signals allowed a quantitative measure of the overall receptors/dimers expression. Disease free (DFS) and overall survival (OS) was assessed in each subject.

Results: Among the 100 patients, 82 were IHC-HER2 negative, including 60 subjects who were ER+and treated with hormonal therapy. Using Cox proportional hazard analyses we showed that in IHC-HER2 negative, ER+subjects, the presence of HER2 dimer was significantly associated with both reduced DFS (p=0.0001) and OS (p=0.00237). Quantitative measure of HER2 expression was also associated with DFS (p=0.0005) and OS (p=0.03).

Conclusion: Quantitative measurement of expression and dimerization of HER2 by the novel TR-FRET assay predicts disease outcome in IHC-HER2 negative, ER+breast cancer patients. These new biomarkers may be useful to identify failure patients to hormonal treatment who may benefit from adjuvant therapy with anti-HER therapy. Validation series is ongoing in 200 FFPE-samples and will be presented.

