



## Travel Award Winners

Based on the scientific merit of their abstract submissions, grants for participants from developing nations have been awarded. A ceremony will be held on Thursday, 28 June 2007 at 10:50 in the General Session to present these awards. We would like to congratulate the following winners:

Hesham Abdeldayem, Egypt  
Aloke Ghosh Dastidar, India  
Shaleen Kumar, India  
Yan Li, China  
Viktor Malkevich, Belarus  
Mahsa Molaei, Iran  
Aleksandra Nikolic, Serbia  
Subrata Saha, India  
Nitin Saini, India  
Ben Selvan, India  
Pramod Shankhpal, India  
Shantanu Sharma, India  
Chilukuri Srinivas, India  
Zheng Wang, China  
Wei Wu, China

## Top Abstracts

*(Note: All abstract details are embargoed until 27 June 2007 at 15:00)*

The following abstracts have been selected by the Scientific Committee and the Congress Chairs as the Top Abstracts for the 9<sup>th</sup> World Congress on Gastrointestinal cancer<sup>®</sup>.

### **1. PACCE An interim analysis of efficacy and safety from a randomized controlled trial of panitumumab with chemotherapy plus bevacizumab (bev) in metastatic colorectal cancer (mCRC)**

**J Hecht, et al.**

**Introduction:** Panitumumab (Vectibix<sup>®</sup>) is a fully human monoclonal antibody targeting the epidermal growth factor receptor (EGFr) and is indicated for the treatment of patients with mCRC after disease progression on standard therapy. Current standard treatment for first-line therapy for mCRC includes the combination of chemotherapy (oxaliplatin [Ox] - or irinotecan [Iri]- based) and bev, an anti-VEGF agent. The activity of 2 targeted agents in this setting has not yet been established. We conducted a phase 3, randomized controlled trial to evaluate panitumumab plus bev plus chemotherapy vs bev plus chemotherapy alone as first-line treatment for mCRC.

**Methods:** Eligible patients had mCRC, ECOG score of 0 or 1, no prior chemotherapy or biologic agent for metastatic disease, no radiotherapy within 14 days of randomization, and no adjuvant therapy within 6 months of randomization. Per physician's choice, patients were entered into one of two separate cohorts to receive Q2W 5-FU/Ox (F/Ox, eg, FOLFOX; planned n=800 patients) or Q2W 5-FU/Iri (F/Iri, eg, FOLFIRI; planned n=200 patients). Patients received bev at a dose in accordance with the prescribing information. Within each cohort, patients were randomized 1:1 (using a dynamic allocation process) to receive concomitant panitumumab 6 mg/kg Q2W or no additional treatment until disease progression or drug intolerance. Randomization was stratified by a number of factors: chemotherapy dose, prior adjuvant therapy, ECOG score, disease site, and number of organs with metastases. Tumor

assessments per modified RECIST were taken at week 12 and every 12 weeks thereafter until disease progression. The primary objective is to assess whether treatment with panitumumab plus F/Ox/bev improves progression-free survival (PFS) vs F/Ox/bev alone evaluated by central review. The primary analysis is based on PFS in patients receiving F/Ox; 462 PFS events are required to yield at least 80% power at an alpha of 0.05 and to detect a 30% improvement in median PFS in the panitumumab plus F/Ox/bev group vs the F/Ox/bev group. A preplanned interim analysis of PFS is to be conducted at ~231 events (50% of the required events for the study). The treatment effect on PFS will be tested using the Wald Chi-square test based on the Cox-model analysis. The hazard ratio and CI will be reported. To control for the overall type 1 error rate at 0.05, a group sequential analysis approach with the Lan-DeMets alpha spending function and the O'Brien-Fleming type boundaries will be used. Secondary endpoints include response and stable disease rates at week 12 as well as safety. The study data monitoring committee will review data from this interim analysis.

Results: Enrollment is complete with 1054 patients. Median (range) follow-up time is 6.85 (0.04-19.09) months. Data from this interim analysis on PFS will be reported.

## 2. FOLFOX4 in adjuvant treatment of colon cancer: Survival results from the MOSAIC trial A de Gramont, et al.

Background: The MOSAIC study was designed to evaluate the effects of the FOLFOX4 regimen (5-FU/LV + oxaliplatin) on 3-year disease free survival (DFS) probability in patients with stage II and III colon cancer.

Methods: Patients (n=2246) with completely resected stage II (40%) or III (60%) colon cancer were randomly assigned to receive 5-FU/LV (LV5FU2) or FOLFOX4 every 2 weeks for 12 cycles.

Results: Results for the primary endpoint of the study (for the overall population, with a median follow-up [FU] of 3 years), showed a significant benefit in DFS for the FOLFOX4-treated patients (78.2% vs 72.9%; HR: 0.77, p=0.002) (André et al, NEJM, 2004). Patients were followed beyond the 3-year cut-off for DFS and overall survival (OS) updates. Final DFS, at 5 years FU, are consistent with earlier results (HR: 0.80, p = 0.003). At a median FU of 6 years, no survival benefit was shown for stage II patients. For stage III patients, a 4.6% absolute difference in the probability of surviving at 6 years was observed. It translated in a significant survival advantage, with a reduction in the risk of death of 20%.

	Probability of surviving at 6 years		HR
	LV5FU2	FOLFOX4	
Overall population	75.8%	78.5%	0.85 [0.71, 1.01]
Stage III	68.3%	72.9%	0.80 [0.66, 0.98]
Stage II	86.8%	86.8%	1.00 [0.70, 1.43]

Long-term safety update shows no increase in the rate of secondary cancer (5.0% in both treatment arms).

Conclusions: Longer follow-up confirms the benefit of FOLFOX4, showing that the benefit of prevention of relapse already seen now actually translates into a survival advantage for patients with stage III colon cancer.

## 3. KRAS mutations in colorectal cancer is a predictive factor of response and survival in patients treated with cetuximab P. Laurent-Puig, et al.

Background: The Cetuximab anti-EGFR (epidermal growth factor receptor) antibody has been shown to be efficient in metastatic colorectal cancer (CRC). We previously showed in 30 CRC patients that *KRAS* mutations were associated with the absence of response to Cetuximab (1). The aim of this retrospective study was to confirm, in a larger series of pts treated with Cetuximab, the predictive value of *KRAS* mutations in comparison with that of skin toxicity and its impact on progression free survival (PFS).

Methods: A series of 76 EGFR+ metastatic CRC patients treated with Cetuximab in 7 centers were analyzed for *KRAS* mutation (exon 2). The mutational analysis was performed by direct sequencing on DNA extracted from fresh frozen or paraffin-embedded tissues. The association between tumor

response (RECIST criteria) and *KRAS* mutations and skin toxicity was analyzed, as PFS of the patients according to the presence or absence of *KRAS* mutation.

Results: Among the 76 patients analyzed (M/F: 39/37; mean age: 60.1 years), 24 (31.5%) had an objective response to Cetuximab (CR: 2, PR : 22), administered in monotherapy (n=2) or in combination with irinotecan (alone, n=66 ; FOLFIRI regimen, n=8). A *KRAS* mutation was present in 35.5% of the cases (n=27) and was significantly associated with the absence of response to Cetuximab (0 responder among the 27 mutated patients vs 24 (49%) among the 49 non-mutated patients;  $p=10^{-5}$ ). A severe skin toxicity was more frequent in responder compared to non responder patients (grade 2-3 toxicity in CR/PR/SD/PD groups: 100%/64%/52%/35%;  $p=0.02$  trend test). Median PFS was 19.2 weeks. In univariate analysis, PFS was longer when tumor was not mutated (median: 32 vs 8.6 weeks, Log-rank  $p<5.10^{-6}$ ). The prognostic value of *KRAS* mutations remained significant in multivariate Cox model including age, sex and skin toxicity (progression in the presence of *KRAS* mutation, HR = 3.50 (IC95%: 1.88-6.51),  $p<0.0001$ ).

Interpretation: These results confirm the high predictive value of *KRAS* mutations for the response to Cetuximab in CRC and show their association with a shorter PFS, which could be relevant in clinical practice by allowing the identification of patients that could benefit from Cetuximab and those (with *KRAS* mutation) for whom Cetuximab is likely to be inefficient, and potentially toxic.

#### **4. Survival after peri-operative chemotherapy with Folfox 4 and surgery for resectable colorectal cancer liver metastases. Final results of the EORTC Intergroup randomized phase III study 40983** **B Nordlinger, et al.**

Background: The 5y survival after resection of colorectal cancer liver metastases is 30% but recurrence is common. This study evaluates the benefit of combining peri-operative chemotherapy and surgery for patients with potentially resectable liver metastases from colorectal cancer (LM).

Methods: Between September 2000 and July 2004, 364 patients with up to 4 LM were randomized between peri-operative FOLFOX4 (oxaliplatin 85mg/m<sup>2</sup> and LV5FU2), 6 cycles before and 6 cycles after surgery (CT arm: 182 patients), and surgery alone (S arm: 182 patients). The primary endpoint was progression free survival (PFS). Safety issues were a secondary endpoint, and were reported at ASCO 2005. The final results for PFS will be reported at the 2-sided 0.0434 significance level, owing to one interim look.

Results: Baseline characteristics were similar in both arms. In the CT arm, a median of 6 preoperative cycles were delivered. Post-operative CT was initiated in 114 patients for a median of 6 cycles. There was no CT-related death. Surgery was performed within the timelines foreseen (median 115 days in the CT arm and 14 days in the S arm). 85.2% and 92.9% of evaluated patients underwent surgery and complete resection was achieved in 95.5% and 89.4% of operated patients in CT and S arm, respectively. Surgical complications required re-operation in 2.6% and 1.2% patients, and resulted in post-operative deaths in 1.3% and 0.6% patients in the CT and control arm, respectively.

Currently, the median follow-up amounts to 37 months and 235 events of PFS have been reported (of 281 required). After an interim look at the data, the Independent Data Monitoring Committee authorized the presentation of final results updated and in full detail at the ASCO 2007 meeting.

Conclusions: The final results available in April 2007 will determine whether or not peri-operative chemotherapy with FOLFOX4 and surgery can become the new standard treatment for patients with colo-rectal cancer liver metastases.

#### **5. A randomised phase 2 study of axitinib (AG-013736) and gemcitabine vs gemcitabine in advanced pancreatic cancer** **J Spano, et al.**

Background: The current standard of care for patients with advanced pancreatic cancer (APC) is gemcitabine-based chemotherapy. Axitinib is a potent inhibitor of vascular endothelial growth factor

receptors (VEGFR). A phase I study of axitinib in solid tumours identified 5 mg BID as the therapeutic starting dose. The lead-in phase 1 portion of current study indicated that gemcitabine doses of 1000 mg/m<sup>2</sup> administered over 30 minutes on days 1, 8, 15 every 28 days in combination with axitinib at a starting dose of 5 mg po BID were well tolerated. The pharmacokinetics of gemcitabine and axitinib appeared to be unchanged in combination. The main objective of this randomised phase 2 trial is to determine whether the overall survival of the patients receiving combination of axitinib and gemcitabine is superior to that of patients receiving gemcitabine alone as first-line therapy in patients with APC.

Methods: For the randomised phase 2 portion of the trial, 103 patients with locally advanced or metastatic disease, no prior gemcitabine or VEGF/VEGFR inhibitors, ECOG PS 0–2 were randomised (2:1) to gemcitabine 1000 mg/m<sup>2</sup> over 30 minutes on days 1, 8, 15 every 28 days with (Arm A) or without axitinib (Arm B) at a starting dose of 5 mg po BID between January 06 and August 06. CT scans were performed every 2 cycles.

Results: The demographics were well balanced in the two arms (Arms A:B): males (51%: 48%), mean age (63.6: 60.2), performance status 0/1 (91%:91%), and locally advanced disease (40%: 38%). Gr. 3+ haematologic adverse events were anaemia (14%: 22%), leucopenia (18%: 15%), neutropenia (28%: 30%), thrombocytopenia (17%: 15%), and lymphopenia (14%: 22%). The most common non-haematologic adverse events were fatigue (45%: 32%), diarrhoea (41%: 26%), nausea (37%: 42%), vomiting (33%: 39%), anorexia (28%: 19%), asthenia (27%: 13%), hypertension (20%: 3%), constipation (20%: 23%), dyspnea (20%: 13%), pyrexia (16%: 26%), dysphonia (16%: 0%), mucositis (15%: 3%), stomatitis (15%: 7%), abdominal pain (13%: 26%), decreased weight (13%: 13%), pruritus (13%: 3%), alopecia (11%: 0%), dizziness (11%: 10%), decreased performance status (11%: 0%) and pain (11%: 7%). An interim analysis performed at 55 events showed a pooled median overall survival of 204 days with a 95% CI of (159, not estimable). The median follow-up time is currently 224 days. Final overall survival results by treatment arm will be presented.

Conclusions: Axitinib can be safely administered at a starting dose of 5 mg BID in combination with standard dose gemcitabine in patients with APC. Final overall survival results by treatment arm will be presented.

## **6. Comparative evaluation in tolerance of neoadjuvant versus adjuvant docetaxel based chemotherapy in resectable gastric cancer in a randomized trial of the Swiss Group for Clinical Cancer Research (SAKK) and the European Institute of Oncology (EIO) A Roth, et al.**

Background: Adjuvant chemotherapy has been reported as minimally effective in the curative treatment of gastric cancer and is often difficult to administer after gastrectomy. Moreover, there is no established reference regimen in this setting. We investigated the value of neoadjuvant chemotherapy compared to adjuvant chemotherapy using a docetaxel based regimen in a randomized phase III trial in locally advanced resectable gastric cancer (LARGC).

Methods: Patients with newly diagnosed LARGC, PS ≤2, normal blood counts, and normal hepatic and renal functions, staged by gastroscopy CT-scan, echoendoscopy, peritoneal lavage and/or laparoscopy, were randomized to receive 4 cycles of TCF q3w (docetaxel 75mg/m<sup>2</sup>, cisplatin 75mg/m<sup>2</sup>, 5-FU continuous infusion 300mg/m<sup>2</sup>/d for 2w) before or after gastrectomy. The trial was planned for 240 patients to have 80% power detecting median event-free survival of 1.29 (adjuvant) vs 1.98 (neoadjuvant) years, but, due to slow enrollement, the trial was prematurely closed after including 69 patients. Tolerance and toxicity results are compared between the 2 arms. Analysis are exploratory, p-values are two-sided and not adjusted for multiple testing.

Results: 69 patients, median age 58 years (range 24 – 75 years) and baseline characteristics well balanced, were enrolled. 34 and 35 were treated with neoadjuvant (arm A) and adjuvant (arm B) chemotherapy, respectively. Disease stages at entry were stage 1b: 1%, stage 2: 7%, stage 3a: 65%, stage 3b: 24%, stage 4: 3%. In arm A, of 33 pts starting neoadjuvant chemotherapy, 25 (75%) completed 4 cycles and 32 patients (96%) underwent surgery. A pCR was achieved in 4 patients (12.9%). In arm B, of 35 pts undergoing surgery, 23 (66%) started adjuvant chemotherapy and 12 (34%) completed 4 cycles. No perioperative death was recorded in either arm. The dose intensity of chemotherapy per administered cycle (% of planned dose) was 93.2% in arm A and 81.8% in arm B (p <0.0003). A mean of 1.5 and 1.94 grade 3-4 toxicity per cycle was observed in arm A and B, respectively (p =0.23).

Conclusions: These results constitute the first objective data to date coming from a head to head comparison between a neoadjuvant and an adjuvant treatment strategy in gastric cancer. Neoadjuvant chemotherapy could be delivered with a higher dose-intensity without decreasing the chances for radical surgery and no increase in perioperative mortality. These results provide the rationale to investigate further the role of novel chemotherapy regimens as neoadjuvant chemotherapy in the curative management of LARGC in randomized phase III studies.