



Scientific Highlights

Travel Award Winners

A limited number of abstract travel awards for participants from developing nations have been awarded. A ceremony will be held on **Thursday, 1 July at 15:50** in the General Session to present these awards. We would like to congratulate the following winners:

- Kun Guo, PhD, China
- Shaleen Kumar, MD, India
- Nazar Lukavetsky, MD, Ukraine
- Mahdi Montazer Haghighi, PhD, Iran
- Ali Motlagh, MD, MPH, Iran
- Nanuli Ninashvili, Georgia
- Pongsanat Pongcharoen, Thailand
- D.S. Pramod, MD, CCH, India
- Lucia Maria Procopciuc, MD, Romania
- Subrata Saha, MD, India
- Angela Salvana, MD, Phillipines
- Ben Selvan, MS, India
- Vaishali Shankhpal, DPH, India
- Vijay Sharma, MD, DM, India
- Alexander Shtanko, MD, Ukraine
- Markiyana Soloviy, MD, PhD, Ukraine

Featured Abstracts

(Note: All abstract details are embargoed until 30 June 2010 at 15:00)

The following abstracts have been selected as featured abstracts for the ESMO 12th World Congress on Gastrointestinal Cancer®.

❖ New data on Neuroendocrine tumors

•O-0028 Everolimus versus placebo in patients with advanced pancreatic neuroendocrine tumors (pNET) (RADIANT-3).

Authors: James C. Yao¹, Manisha H. Shah², Tetsuhide Ito³, Catherine Lombard-Bohas⁴, Edward M. Wolin⁵, Eric Van Cutsem⁶, Timothy Hobday⁷, Carolin Sachs⁸, Sakina Hoosen⁸, Jeremie Lincy⁸, David Lebwohl⁸, and Kjell Oberg⁹

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Background: Treatment options for patients with advanced pNET are limited. Everolimus (RAD001), an oral inhibitor of mTOR, demonstrated promising antitumor activity in two phase II studies (both as a single agent and in combination with octreotide LAR) in patients with advanced NET (J Clin Oncol 2010;28:69-76; J Clin Oncol 2008;26:4311-18).

Methods: This phase III randomized placebo controlled trial evaluated the efficacy and safety of everolimus 10mg/d orally plus best supportive care (BSC) compared to matching placebo plus BSC in patients with advanced low- or intermediate-grade pNET with disease progression within the prior 12 months. The primary endpoint was progression-free survival (PFS).

Results: The trial randomized 410 patients (n=207 everolimus arm and n= 203 placebo arm). Everolimus is associated with a 65% reduction in the risk of progression (HR 0.35; 95% CI: 0.27, 0.45; p<0.0001). Treatment with everolimus resulted in a clinically meaningful 2.4-fold prolongation in median PFS, 11.04 months for everolimus compared with 4.60 months for placebo. Eighteen-month PFS estimates of 34.2% for everolimus compared with 8.9% for placebo indicate that a sizeable portion of patients derive more prolonged benefit with everolimus. The most common AE was stomatitis (53.9% everolimus vs. 12.3% placebo). Grade 3/4 adverse events occurred in 59.8% of the everolimus arm and 38.9% of the placebo arm and amongst the most frequent included (% in Everolimus vs. % in Placebo): anemia (8.3% vs. 2.0%); hyperglycemia (7.8% vs. 3.4%); diarrhea (5.4% vs. 2.5%); abdominal pain (2.9% vs. 5.9%); stomatitis (4.9% vs. 0%); thrombocytopenia (3.9% vs. 0%); and asthenia (2.9% vs. 3.4%). The remainder of grade 3/4 adverse events were less than 3%. Median duration of exposure to everolimus was 38 weeks vs. 16 weeks on placebo. Treatment discontinuation for adverse events was 17.4% in the everolimus arm vs 3.4% in the placebo arm.

Conclusions: In this large phase III clinical trial, everolimus demonstrates a statistically and clinically significant improvement in PFS over placebo. Treatment was well tolerated and is consistent with the known safety profile of everolimus in patients with cancer. These results represent an important advance for the treatment of patients with advanced pNET.

Acknowledgment: This study is sponsored by Novartis Pharmaceuticals Corporation.

•O-0009. **Evidence of activity and clinical benefit with sunitinib in patients with pancreatic neuroendocrine tumors (NET)**

Authors: Raymond E1, Niccoli P2, Raoul J3, Bang Y4, Borbath I5, Lombard-Bohas C6, Valle J7, Hörsch D8, Patyna S9, Lu D9, Korytowsky B9, Mundayat R9, Chao R9, Vinik A10

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Background: In a randomized, double-blind phase III trial, sunitinib was associated with superior progression-free survival (PFS; primary endpoint) over placebo in patients with progressive pancreatic NET (11.4 vs. 5.5 mo, respectively; P=0.0001). We report further assessment of clinical benefit in this trial, including patient reported outcome and exploratory analyses of prognostic factors for PFS.

Methods: Patients with advanced well-differentiated pancreatic NET, and disease progression in the past 12 mo, were randomized 1:1 to receive sunitinib 37.5 mg orally once-daily (n=86) or placebo (n=85), each with best supportive care. Patients completed the 15-domain EORTC Quality-of-Life (QoL)

Questionnaire—Core 30 (QLQ-C30) version 3.0, on Day 1, every 4 wks (cycle) thereafter, and at end of treatment/withdrawal. Repeated-measures mixed-effects models were used to assess statistical (2-sided P value; 0.05 level) and clinical (≥ 10 point minimally important difference) mean between-treatment

differences in QLQ-C30 changes from baseline. The influences of baseline characteristics on treatment effect were assessed using a Cox proportional hazards model.

Results: At baseline, all 15 QLQ-C30 domain scores had a ≤ 7 -point mean difference between treatment arms. Post-baseline QLQ-C30 data were available for 73/86 and 71/85 patients in the sunitinib and placebo arms, respectively, through up to 10 cycles (during which each arm had ≥ 10 patients). Overall, compared with the placebo arm, patients on sunitinib had a clinically and statistically significant worsening of diarrhea (diff.=21.38; $P < 0.001$) and a significant trend toward worsening of insomnia (diff.=7.753, $P = 0.0372$). However, within the QLQ-C30, there were no clinically or statistically significant between-treatment differences in the following domains: cognitive, emotional, physical, role, social functioning nor other symptoms and scales; in addition, there were no significant between-treatment differences in mean change from baseline in the global QoL domain nor most other domains, when compared using a 2-sample T-test. The treatment effect significantly favored sunitinib regardless of age (< 65 vs. ≥ 65 yrs), race (white vs. non-white), gender, ECOG status (0 vs. 1/2), number of metastatic sites (≤ 2 vs. ≥ 3), or time from diagnosis to study enrolment (< 3 vs. ≥ 3 yrs). Sunitinib showed benefit over placebo in non-functioning tumors, with a trend for benefit in functioning tumors. The hazard ratio (HR) for PFS favored sunitinib patients, regardless of treatment with or without somatostatin analogs, which were allowed before and/or during the study. Similarly, sunitinib improved PFS relative to placebo regardless of prior chemotherapy use. By multivariate analysis, only time from diagnosis to enrolment (≥ 3 vs. < 3 yr) was a potential independent predictor of PFS (HR 0.603; 95% CI 0.382, 0.952; $P = 0.0299$). The PFS advantage with sunitinib was greater when adjusting for time from diagnosis (HR 0.374; 95% CI 0.234, 0.599; $P < 0.0001$).

Conclusions: Complementing prior reports of efficacy from this trial in which sunitinib demonstrated improved PFS in patients with pancreatic NET, these results indicate that sunitinib maintains global QoL with overall clinical benefit observed across all patient subgroups studied.

❖ New Phase 3 studies

Pancreatic

•O-0006. **Double-blind, placebo-controlled randomized phase III trial of aflibercept (A) plus gemcitabine (G) versus placebo (P) plus gemcitabine (G) in patients with metastatic pancreatic cancer: Final results**

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Background: Aflibercept, a recombinant fusion protein, is a potent inhibitor of vascular endothelial growth factor (VEGF) that also binds to placental growth factor. The primary objective of this multicenter randomized study (EFC10547) was to determine whether AG prolongs overall survival (OS) compared to PG, in patients (pts) with metastatic pancreatic cancer (MPC).

Methods: Main eligibility criteria were: metastatic disease, no prior therapy for advanced disease, PS 0-2 and no bleeding risk. Pts were stratified on PS (0 vs 1 vs 2), primary pancreas tumor resection (yes/no) and geographical region. This trial had 90% power to detect a median OS improvement from 5.5 to 6.3 months (mo). The trial was stopped according to recommendation of the independent Data Monitoring Committee after first interim analysis (IA) as pre-specified futility criteria was met. Results of final analysis including the period from data cutoff (May 09) for IA to the unblinding of pts (Sep 09) are presented.

Results: Between December 2007 and September 2009, 546 patients were randomized to receive either placebo or aflibercept 4mg/kg administered every 2 weeks (q2w) in combination with weekly intravenous gemcitabine 1000 mg/m², 7 weeks on/1 week off, then day 1, 8, 15 q4w. Pts characteristics (275PG/271AG): male (57%/59%), age>65year (35%/41%), PS1-2 (64%/63%), pancreas tumor resection (11%/10%), >1 organ involved (58%/60%). Median duration of follow-up was 7.9mo. As of 11 Sep 09, 284 (142/142) pts have died. Median OS (PG/AG) 7.8/6.5mo (HR 1.16; 95%CI: 0.92, 1.47). Median progression free survival (PFS) (PG/AG) 3.7/3.7mo (HR 1.02; 95%CI: 0.83, 1.25). 541 pts were treated and evaluable for safety. Median infusions P5/G10, A4/G7. Main grade (Gr) 3/4 adverse events (AE) related to VEGF blockade (%pts PG/AG): hypertension 3.0/14.1, venous thromboembolic events 10.0/7.0, proteinuria 1.2/5.3, bleeding 1.5/3.7, arterial thromboembolic events 1.8/2.2, cardiac dysfunction 0.4/1.5. Other Gr 3/4 AE >10%pts (%PG/AG): neutropenia 24.5/30.8, asthenia 10.3/14.8, alkaline phosphates increase 11.1/11.9, thrombocytopenia 6.4/11.2, hyperbilirubinemia 10.5/8.0. 26 fatal AEs: 12 pts in PG arm (main reasons: 4pts unknown cause, 3 pts sepsis), 14 pts in AG arm (3 pts cerebrovascular accident, 3 pts sepsis, 2 pts gastrointestinal hemorrhage).

Conclusions: The addition of A to G did not result in an OS benefit in patients with MPC. The median survival time in PG arm was longer than expected for this disease setting. The safety profile of AG was in accordance with what was expected in this disease setting and with such combination treatment including a VEGF pathway inhibitor.

•O-0007. A phase III study comparing larotaxel to 5-FU (continuous intravenous 5-FU or capecitabine) in patients with advanced pancreatic cancer (APC) previously treated with a gemcitabine containing regimen

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Background: Larotaxel (LARO) is a microtubule interacting agent with reduced recognition to P-glycoprotein that showed preclinical efficacy in tumors resistant to or refractory to docetaxel, another taxane that had shown clinical activity in patients (pts) with APC. The primary objective of this international randomized study was to determine whether LARO prolongs overall survival (OS) compared to 5-FU (5-FU continuous intravenous (CIV) or capecitabine according to the choice of the investigator for whole study duration) in pts with APC.

Methods: Main eligibility criteria were: advanced disease, previous treatment with a gemcitabine-based regimen for advanced disease or in adjuvant setting with disease free interval less than 6 months, performance status (PS) 0-1, no prior locoregional radiotherapy and adequate biological functions. Pts were stratified on disease stage locally advanced (LA) vs. metastatic (M) and prior adjuvant therapy yes vs. no. A total of 400 pts had to be randomized to detect 30% reduction in hazard ratio (HR) in LARO group with 90% power. Starting dose of LARO was reduced from 90 to 75 mg/m² following safety issues (Amendment 2) – patients randomized prior to amendment 2 were excluded from Intent To Treat population.

Results: Between July 2007 and July 2009, 408 patients (204 patients by arm) were randomized to receive either LARO 75 mg/m² on day 1 every 3 weeks (q3w) or 5-FU q3w (5-FU 1000 mg/m²/day CIV over 4 days or capecitabine 2000 mg/m²/day over 14 days and 1 week rest). In 5-FU arm, 71 pts (34.8%) were treated with 5-FU CIV. Results are presented LARO/5-FU. Pts characteristics were well balanced: male 55.4%/59.3%, age≥65year 40.2%/34.8%, PS 0 37.7%/37.7%, PS 1 60.8%/60.8%, metastatic 93.1%/92.6%, pancreatectomy 36.8%/36.3%, >2 organs involved 50.5%/45.1%. Efficacy results: median OS 4.8/5.1 months (mos) (HR 1.05; 95%CI: 0.842, 1.30, p= 0.69); median progression free survival 2.0/2.0 mos (HR 1.02; 95%CI: 0.83, 1.26). In both arms, pts with PS 0 had a better prognostic compared to pts with PS1: median OS PS0/PS1 in LARO arm was 6.2/4.0 mos; in 5-FU arm was 7.3/3.7 mos. A total of 395 pts were treated and evaluable for safety (198/197). Median (min-max) number of cycles were

2 (1-25) and 2 (1-22). Incidence per pts of clinical adverse events of any NCI grade with $\geq 10\%$ difference between both arms were diarrhea 47.0%/29.9% (including colitis 2.0%/1.0%, enteritis 1.5%/0%), nausea 39.4%/28.9%, alopecia 35.4%/3.0%, constipation 24.7%/13.7%, sensory neuropathy 19.2%/6.6%, myalgia 13.1%/1.0%, stomatitis/mucositis 15.7%/27.9%, and hand foot syndrome 0.5%/22.3%. Main hematological toxicities were grade 3-4 neutropenia 42.1%/6.3%, and complicated neutropenia (febrile neutropenia and/or neutropenic infection) 15.7%/0.5%.

Conclusions: In patients with APC previously treated with a gemcitabine-based regimen the median survival times were longer than expected and no difference was observed between LARO and 5-FU. The safety profile of LARO was as expected for a taxane in this setting.

Colorectal

•O-0026. **Final results from a randomized, double-blind, phase III study of sunitinib plus FOLFIRI vs. placebo plus FOLFIRI in first-line treatment of patients (pts) with metastatic colorectal cancer (mCRC)**

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Background: Sunitinib is an oral, multitargeted inhibitor of VEGFRs, PDGFRs and other tyrosine kinase receptors in clinical development for gastrointestinal cancers. In non-clinical models of CRC, sunitinib has shown single-agent antitumor activity, inhibiting the growth of established tumor xenografts at well-tolerated doses. Combining sunitinib with chemotherapy in these models blocked tumor growth to a greater extent than either agent alone, suggesting that it may enhance the activity of cytotoxic chemotherapies in patients with CRC. The objective of this double-blind, randomized, phase III study was to demonstrate that sunitinib plus FOLFIRI has superior efficacy to placebo plus FOLFIRI in patients with treatment-naïve mCRC.

Methods: Eligible patients had previously untreated mCRC clinically indicated for therapy with FOLFIRI, ECOG performance status (PS) 0/1 and no prior therapy with a VEGF or tyrosine kinase inhibitor. Patients were randomized 1:1 to receive FOLFIRI (irinotecan 180 mg/m², leucovorin 200 mg/m², and 5-fluorouracil [5-FU] 400 mg/m² bolus, followed by 2400 mg/m² 46-hour infusion) every 2 weeks, combined with either oral sunitinib 37.5 mg/day for 4 weeks on, 2 weeks off (Schedule 4/2) or placebo. Progression-free survival (PFS) was the primary endpoint. Secondary endpoints included overall survival (OS), RECIST-defined objective response rate (ORR), and safety. Tumor assessments were performed every 6 weeks and evaluated by an independent third-party imaging laboratory. The study was designed to detect a statistically significant difference in PFS at the 0.025 level with a power of 0.85. Patients were stratified by ECOG PS, number of metastatic organ sites, primary tumor site (rectal vs colon), and prior adjuvant treatment.

Results: Overall, 768 patients were enrolled from July 2007 to September 2008 and randomized to receive FOLFIRI plus sunitinib (n=386) or placebo (n=382). Following a pre-specified interim analysis, the Independent Data Monitoring Committee determined that the futility boundary had been crossed in June 2009, and the study would be unable to meet the primary endpoint. Patients on treatment were notified, treatment was unblinded, and discontinuation of sunitinib was recommended or left to investigator discretion in cases of clinical benefit. No unexpected adverse events were reported, although the

frequency of common grade ≥ 3 toxicities was higher with sunitinib plus FOLFIRI, compared with placebo plus FOLFIRI.

Conclusions: The addition of sunitinib to FOLFIRI did not demonstrate a significant improvement in PFS in patients with treatment-naïve mCRC. Further analyses of efficacy and safety are ongoing, and final results will be presented.

❖ Updated information on new treatment in Colorectal cancer

•O-0013 Phase IB study of the Src inhibitor dasatinib with FOLFOX and cetuximab in refractory metastatic colorectal cancer

Authors: Kopetz S, Wolff R, Eng C, Overman M, Henry L, Coulson R, Garrett C, Abbruzzese J, Gallick G

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Background: The nonreceptor tyrosine kinase Src is activated in metastatic colorectal cancer (mCRC) and has been implicated as a mechanism of acquired oxaliplatin resistance. Oxaliplatin exposure results in chronic Src activation preclinically and in patients. Inhibition of Src with the tyrosine kinase inhibitor dasatinib is synergistic with oxaliplatin and cetuximab in preclinical studies. Based on these results, a combination study of dasatinib was investigated in combination with FOLFOX and cetuximab.

Methods: Previously-treated mCRC patients (pts) were enrolled in this phase IB study, with a requirement for biopsiable liver metastases in the expansion cohort. Primary objectives were to determine the maximum tolerated dose and pharmacodynamics of this regimen. Using a 3+3 design, cohorts of 3-6 pts received standard dosing of mFOLFOX6 with weekly cetuximab and escalating daily PO doses of dasatinib (100, 150, 200 mg), followed by a 12 pt expansion cohort. Surrogate blood biomarkers of Src inhibition and paired liver biopsies were obtained in all pts in the expansion cohort.

Results: Thirty pts were enrolled with a median age of 54 [37-78]; 63% were female with a PS 0/1 in 13/17 pts. These pts were heavily pretreated including other experimental therapies, with a median of 3 prior regimens [2-6]. Each of the 3 escalation cohorts were expanded to 6 patients, with 25 pts evaluable for response. The dose-limiting toxicity in both the 100mg and 150mg cohorts was gr 4 and 3 fatigue, respectively. Grade 3-4 toxicities in all cycles included neutropenia (23%), fatigue (20%), pleural effusions (3%), and thrombocytopenia (3%); delayed myelosuppression was associated with the 200mg and 150mg dose in these heavily pretreated pts. Median PFS was 4.6 months with a 6 month PFS of 23%. Partial response (PR) rate was 24% with a 17% PR rate in pts previously reported to be refractory to FOLFOX and cetuximab. Pharmacodynamic data demonstrated paradoxically increased Src activity in peripheral blood mononuclear cells (PBMCs) on treatment, while this effect was not noted in the paired liver biopsies.

Conclusions: The recommended phase II dose of dasatinib in combination with mFOLFOX6 and cetuximab is 150mg daily; however due to delayed myelosuppression in heavily pretreated patients, a dose of 100mg daily is recommended for further study in this population. There is evidence of clinical activity of this regimen in patients previously treated with oxaliplatin and cetuximab. Pharmacodynamic data suggest a mixed modulation of Src in the liver and PBMC surrogate tissue, likely reflecting the confounding effects of oxaliplatin-induced Src activation with concurrent pharmacologic Src inhibition. A two-arm phase II study is being conducted in refractory patients, with and without cetuximab in patients with KRAS wild-type and mutant tumors respectively, to better define the profile of activity,

•O-0016 Updated safety data from a randomized phase 2 trial of hedgehog pathway inhibitor GDC-0449 vs. placebo with FOLFOX or FOLFIRI and bevacizumab in patients with previously untreated metastatic colorectal cancer (mCRC)

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Background: GDC-0449 is an HPI which has clinical activity in advanced basal cell carcinoma and preclinical activity in CRC. The most common single agent toxicities seen in phase I trials of GDC-0449 include mild-to-moderate fatigue, anorexia, muscle spasms, alopecia and dysgeusia. The primary objective of this trial was to compare the PFS of FOLFOX-bev or FOLFIRI-bev plus either GDC-0449 or placebo in previously untreated mCRC pts. Safety data from this trial are presented here as efficacy data mature.

Methods: Patients were randomized 1:1 to receive GDC-0449 150 mg/day or placebo in combination with FOLFOX-bev (oxaliplatin 85 mg/m², LV 400 mg/m², 5-FU bolus 400 mg/m², 5-FU infusion 2400 mg/m² over 46 hours, bev 5 mg/kg) or FOLFIRI-bev (irinotecan 180 mg/m², LV 400 mg/m², 5-FU bolus 400 mg/m², 5-FU infusion 2400 mg/m² over 46 hours, bev 5 mg/kg) every 2 weeks. The study is currently blinded pending completion of the primary analysis of PFS, but will be unblinded by presentation. For this abstract a blinded analysis of adverse events is reported with GDC-0449 and placebo-treated cohorts designated as groups X or Y.

Results: Between May 2008 and July 2009, 199 patients were randomized. As of Oct 1, 2009, 191 were safety evaluable; 121 FOLFOX-bev; 70 FOLFIRI-bev. 57% male; 26% received prior adjuvant chemotherapy. FOLFOX and FOLFIRI pts have so far received a median of 7 (range 1-29) and 9 (range 1-53) 2 week cycles containing oxaliplatin or irinotecan, respectively. Grade 3-5 AEs occurring in more than 5% of patients in any treatment arm are listed in the table:

Grade 3-5 AE	FOLFOX (%)		FOLFIRI (%)		TOTAL (%)	
	X, n=61	Y, n=60	X, n=35	Y, n=35	X, n= 96	Y, n=95
Neutropenia	16.4	10.0	31.4	22.9	21.9	14.7
Anemia	8.2*	0	5.7	0	7.3*	0
Fatigue/asthenia	4.9	13.3	8.6	28.6*	6.3	18.9*
Diarrhea	9.8	5.0	11.4	20.0	10.4	10.5
Nausea	3.3	3.3	5.7	8.6	4.2	5.3
Decreased appetite	0	5.0	2.9	5.7	1.0	5.3
Dehydration	1.6	11.7*	0	5.7	1.0	9.5*
Pulmonary embolism/Deep vein thrombosis	1.6	10.0	14.3	2.9	6.3	7.4
Peripheral neuropathy	3.3	10.0	2.9	2.9	3.1	7.4
Infection (all sites)	4.9	6.7	8.6	5.7	6.3	6.3
Hypertension	4.9	0	5.7	2.9	5.2	1.1

*p<0.05

Plasma concentrations of GDC-0449 were similar to those in phase 1 patients receiving GDC-0449 alone.

Conclusions: These safety results show that GDC-0449 in combination with FOLFOX-bev or FOLFIRI-bev chemotherapy is feasible, and concurrent chemotherapy does not seem to alter plasma concentration of GDC-0449 compared to single agent data. Unblinded and updated safety data will be presented including results pertaining to the time of onset of AEs as a function of treatment arm.

O-0017 Subset analysis of 5-FU refractory patients from a randomized ph II study of perifosine + capecitabine (P-CAP) vs. placebo + capecitabine (CAP) in patients with 2nd or 3rd line metastatic CRC

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Background: Perifosine (P) is a synthetic alkylphospholipid that inhibits or modifies signal transduction pathways including AKT, MAPK and JNK. A randomized phase II study of P-CAP vs. placebo + capecitabine (CAP) included 38 pts with 2nd or 3rd line mCRC, randomized 1:1 to receive P-CAP (P 50 mg PO QD + CAP 825 mg/m² PO BID d1-14) or CAP (placebo + CAP 825 mg/m² PO BID d 1-14). Cycles were 21 days. Final results showed an improvement in ORR (20% vs. 7%), median TTP (28 vs. 11 wks (p=0.012), HR 0.284 [0.127,0.636]), and median OS (18 vs. 11 mos (p=0.0136), HR 0.375 [0.167,0.840]). This subset analysis looks only at the population of patients with known 5-FU refractory disease.

Methods: Patients with previous progressive disease on 5-FU therapy were selected for analysis. Results: 27 pts were identified (14 P-CAP/13 CAP). Median age 65 (44-83); 74% male. Median prior Rx = 2 (2-4). Prior Rx of P-CAP arm vs. CAP arm: FOLFIRI (93% vs. 92%); FOLFOX (93% vs. 85%); bevacizumab (86% vs. 85%); EGFR antibody (64% vs. 62%). All 27 pts were evaluable for toxicity. Most frequent AE's (P-CAP vs. CAP): G3 /4: hand/foot syndrome (HFS) (28% vs. 0%), anemia (14% vs. 0%), abdominal pain (0% vs. 15%); G1/2: diarrhea (57% vs. 15%), nausea (28% vs. 23%), fatigue (50% vs. 23%), HFS (14% vs. 15%). 25/27 5-FU refractory pts evaluable for efficacy (2 CAP not evaluable; 1 AE, 1 with new malignancy):

Group	5-FU ref n (%)	PR / SD	Median TTP months	Median OS months
P-CAP	14 (70%)	1 / 8	4.1 [95% CI (2.8-8.3)]	15.3 [95% CI (8.4-26)]
CAP	11 (73%)	0 / 3	2.3 [95% CI (1.5-2.5)]	6.8 [95% CI (4.8-11.7)]
p-value			p = 0.0004	p = 0.0088
Hazard ratio			0.186 (0.066, 0.521)	0.294 (0.112, 0.773)

Conclusions: P-CAP is a well-tolerated regimen that has promising activity as a 2nd or 3rd line therapy for pts with 5-FU refractory metastatic colorectal cancer. A randomized phase III trial of P-CAP vs. CAP is underway for refractory advanced colorectal cancer patients.

❖ Updates on molecular profiling of Colon cancer

•O-0018 Molecular and clinical determinants of survival following relapse after treatment of stage II-III colon cancer (CC). Results of the translational study on the PETACC 3 - EORTC 40993 -SAKK 60-00 trial

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Background: We presented the prognostic (prog) impact of molecular markers (MM) on relapse free survival (RFS) of stage II-III CC (ASCO proc 2009, 27, abstr. #4002). We analyse now the impact of the 8 same MM on the overall survival (OS) after relapse of stage II-III CC in PETACC 3, an adjuvant trial with 3278 patients (pts).

Methods: 1564 blocks were prospectively collected, tumor (Tu) DNA extracted and 8 MM assessed as described previously. Markers prog value was analysed by Cox regression for OS, multivariate analysis (MA) and Kaplan-Meier estimates of median survival (MS). Time to recurrence (TTR) of ≤ 18 m defined early relapse (ER), >18 m late relapse (LR).

Results: 392 out 990 relapsing pts were assayed for the 8 MM, 221 ER, 171 LR. The MA investigating prog factors impacting on OS after relapse is presented in the Table.

	HR (95% CI)	P-value
TTR (ER/LR)	1.60 (1.23-2.09)	0.0005
age	1.00 (0.99-1.01)	0.98
sex	1.24 (0.95-1.62)	0.11
Tu grade	1.52 (1.02-2.25)	0.04
stage	1.53 (1.00-2.36)	0.051
Tu site (right/left)	1.69 (1.29-2.21)	0.0002
Treatment group	1.09 (0.84-1.39)	0.52
Microsat. Instabil.	0.51 (0.28-0.95)	0.034
Thymidilate synth.	0.99 (0.68-1.44)	0.95
SMAD4	1.21 (0.91-1.60)	0.18
p53	0.96 (0.73-1.26)	0.76
hTERT	1.37 (0.96-1.96)	0.09
18qLOH	0.86 (0.60-1.24)	0.43
BRAF mutation +/-	3.61 (2.24-5.81)	1.24e-07
KRAS	1.13 (0.85-1.51)	0.40

BRAF, Tu site and TTR were found to be major predictors of OS after relapse. MS (95%CI) according to BRAF was 7.5m (4.8-11.2) vs 25.2m (21.1-29.5) $p=1.9e-11$, according to Tu site 16.1m (12.6-19.0) vs 27.6m (22.9-33.6) $p=2.71e-06$, according to TTR 17.9m (15.5-20.3) vs 30.0m (24.7-38.4) $p=0.00032$. Similar MS according to Tu site (16.2m vs 28.6m, $p=4.52e-14$) and TTR (18.4m vs 30.5m, $p=2.18e-08$) were observed in the full relapsing pts set ($n=990$)

Conclusions: Whereas BRAF and Tu site had no prog value on RFS of stage II-III CC (Roth AD, doi: 10.1200/JCO.2009.23.3452), BRAF, Tu site and TTR are strong determinants of CC OS after relapse and should imperatively be used to stratify studies in metastatic CC. The independent effects of Tu site and TTR might be indicative of additional non-yet identified MM

•O-0019 Mutant KRAS and BRAF gene expression profiles in colorectal cancer: Results of the translational study on the PETACC 3 - EORTC 40993 -SAKK 60-00 trial

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Background: KRAS and BRAF activating mutations (mut) are frequent in colorectal cancer (CRC). Both genes act in the ERK pathway, but they occur in different CRC subtypes and have different prognostic implications, suggesting they might entail disruptions in different signaling pathways.

Methods: RNA extracted from 1378 formalin-fixed tissues was used for expression profiling on the Affymetrix-based ALMAC platform "Colorectal Cancer DSA™". KRAS G12S, G13V, G13C, G13D, G12R, G13A, G12V, G12D, G12G, G12C, G12A, G12G mut and BRAF V600 were assessed. BRAF mut vs KRAS mut and BRAF or KRAS mut versus double wildtype (wt) were compared. Statistical analysis of differential expression was performed with standard methods in R. Classifiers were constructed using AdaBoost and DLDA algorithms and performance estimated by cross-validation.

Results: KRAS mut were found in 37%, BRAF mut in 8%. Outcome correlations were reported (Roth A, JCO 2010). To date, 244 hybridized samples were analyzed (25 BRAF mut, 91 KRAS mut), additional samples are ongoing.

(a) Gene expression downstream of KRAS and BRAF mut is highly different (common 6 genes, different 166). Supervised classification using 42 genes achieved an AUC of 0.98 [95% CI: 0.97-0.99] in separating KRAS from BRAF mut.

(b) BRAF mut induce highly consistent gene expression changes (in 725 genes, <1% FDR) in comparison to wt, allowing trained classifiers to discriminate BRAF mut from wt with an AUC of 0.94 [95% CI: 0.92-0.96], using 30 selected genes. The differential gene expression downstream of BRAF indicates unique activation of key developmental pathways, including Wnt, TGF- β and MAPK.

(c) KRAS mut tumors are heterogeneous in their gene expression signatures. The AUC of trained classifier (KRAS mut vs. wt) was 0.73 [95% CI: 0.69-0.76], using 148 selected genes, indicating that the signatures explain a large part of the variance, but there is additional heterogeneity within the KRAS mut and wt subgroups.

Conclusion: KRAS and BRAF mutations induce very different downstream gene activation in CRC. The strikingly uniform and novel BRAF mut downstream gene signature, might lead to novel therapeutic avenues for these aggressive tumors.

•O-0020 **Additional validation of a genomic signature (ColoPrint) for the risk stratification of stage II colon cancer patients**

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Background: Between 25 - 35% of stage II colon cancer (CC) patients will experience a recurrence of their disease and may benefit from adjuvant chemotherapy. In this study, we show the validation of a robust genomic signature that predicts disease relapse and can be used for risk stratification of stage II patients.

Methods: We recently described the development of an 18- gene prognostic signature developed by an unbiased analysis of the entire human genome using Agilent 44K oligonucleotide arrays. The signature was validated in an independent clinical study of 208 stage I-III patients from the ICO Hospital (validation 1). In addition, the signature was validated on three publicly available datasets generated on different platforms (GSE5206, GSE10402 and MEXP-1245) consisting of 322 CC tumors. This 18-gene signature was translated into a diagnostic test using the Agilent 8-pack format that supports high throughput, high quality and robustness. The ColoPrint test was further validated in a second clinical study blinded from the clinical data (validation 2) with patients from Hospital rechts der Isar Munich (n=232) and is currently tested in patients (n=80) treated at the Vall d'Hebron Hospital from 2002 -2004 (validation 3). All studies

have a minimal median follow-up of 5 years and most patients (83%) had more than 12 lymph nodes assessed, giving an indirect measure of the quality of surgery in all validation sets.

Results: In the clinical validation study 1, the ColoPrint signature classified 61% of the patients as low-risk and 39% as high-risk and showed a significant performance within stage II ($P=0.0058$) and III ($P=0.036$) only samples. Focusing on stage II patients only ($n=115$), the HR was 3.61 ($p=0.01$) with a 5-year distant-metastasis disease-free survival (DMFS) rates of 91% (95CI, 84 -98%) for low-risk and 71.8% (95CI, 57-87%) for high-risk patients. The signature was the most significant predictor in univariate and multivariate analysis. The results were fully confirmed in the validation study 2. Here ColoPrint identified 74% of the stage II patients ($n=137$) as low risk. The 5-year DMFS was 95% for low risk patients and 79.9% for high risk patients. In the univariate analysis, ColoPrint was the only significant parameter to predict the development of distant metastasis with a HR of 4.3 (95% CI 1.36-13.56, $p=0.007$). The ASCO recommended risk assessment using T4, high grade, perforation, emergency presentation and less than 12 assessed lymph nodes as high risk criteria was not significant in identifying high risk patients in our datasets. A combined analysis of all stage II patients is underway and will be presented.

A prospective clinical study is currently recruiting patients to prospectively analyze the risk assessment by ColoPrint in combination with clinical parameters.

Conclusion: The gene expression signature is able to predict the prognosis of stage II patients and facilitates the identification of patients who are most likely to benefit from adjuvant chemotherapy.

❖ Updates on new targeted agents in gastric cancer

•O-0012. **AVAGAST: Randomized, double-blind, placebo-controlled, multicentre phase III study of capecitabine / cisplatin + bevacizumab or placebo as 1st-line therapy in patients with advanced gastric cancer**

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Background: Patients with advanced gastric cancer have a life expectancy of approximately 1 year with best treatment options. More effective and less toxic treatments are needed. Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor, has shown favourable treatment outcomes when combined with chemotherapy in phase II studies in patients with advanced gastric cancer. The phase III AVAGAST trial is the first randomized study to compare the efficacy and safety of bevacizumab plus chemotherapy (capecitabine [or 5-FU] and cisplatin) vs placebo plus chemotherapy.

Methods: Patients with inoperable, locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction with no prior treatment for advanced gastric cancer were randomized in a 1:1 ratio to receive capecitabine with cisplatin and either bevacizumab (7.5 mg/kg iv) or iv placebo every 3 weeks. 5-FU could replace capecitabine if needed. Cisplatin was given for 6 cycles; bevacizumab/placebo and capecitabine/5-FU were given until disease progression or unmanageable toxicity. The primary objective was to compare overall survival; secondary objectives were to compare progression-free survival, time to progression, overall response rate, duration of response, disease control rate, and safety in both treatment arms. Safety was overseen by an independent data and safety monitoring board. A sample size of 760 patients was planned in order to observe 509 events, which would have 80% power to detect a hazard ratio of 0.78 using a two-sided log-rank test at the alpha level

of 5% (based on an assumed overall survival of 10 months in the control arm and 12.8 months in the experimental arm).

Results: Between September 2007 and December 2008, 774 patients have been enrolled. Database cut-off was November 30th, 2009. Final efficacy and safety data will be presented.

•O-0011. **Quality of life results from a phase III study of trastuzumab plus chemotherapy as first-line therapy in patients with HER2-positive advanced gastric and gastro-esophageal junction cancer**

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Background: Trastuzumab in combination with capecitabine or 5-fluorouracil and cisplatin (XP/FP) improves overall survival (OS) versus XP/FP alone for patients with HER2-positive advanced gastric or gastro-oesophageal (GE) junction cancer, without significant impact on the overall safety profile¹ or quality of life (QoL)², as shown by the international, randomised, Phase III ToGA (Trastuzumab for GAstric Cancer) study.

Methods: Patients were asked to complete standard EORTC QoL questionnaires QLQ-C30 (version 3) and QLQ-STO22 every 3 weeks (on Day 1) until disease progression (scoring range: 0–100). Summary and descriptive statistics for all scales from both treatment groups are presented. In addition, pain intensity was assessed using the visual analog scale (VAS). To minimize bias on QoL due to selection of patients with better prognosis in both treatment arms, an analysis was performed excluding patients who had progressed prior to Week 37 (median time-to-progression).

Results: QLQ C30: Global Health Status and functioning scores improved from baseline to the end of chemotherapy (Week 19) in both arms and showed a sustained effect beyond chemotherapy. Symptom scores (pain, appetite loss, nausea/vomiting and constipation) showed improvement of QoL in both arms for patients who had not progressed at Week 37.

QLQ-STO22: In both treatment arms, improvements over time were seen for dysphagia, pain (in stomach or during eating), anxiety and reflux symptoms. Additionally, there were significant average monthly decreases observed for eating restrictions, dry mouth and body image scores. Around the end of chemotherapy, scores for dry mouth, taste, body image and hair loss had also improved in this patient population.

An improvement in pain intensity scores over time was observed in both treatment arms and no difference was observed between the two arms.

Conclusions: In the ToGA study, the addition of trastuzumab to XP/FP improved OS without compromising QoL.^{1,2} This result was further confirmed in a separate QoL analysis in patients who had not progressed at Week 37. Overall scores suggest an improved QoL over time in both study arms with an apparent sustained effect beyond the administration of chemotherapy.

References:

1. Van Cutsem E et al, ASCO 2009; Abstract No. LBA4509
2. Satoh T et al, ASCO GI 2010; Abstract No. 7

❖ **Updates on large trials on colorectal cancer**

•O-0021 Macro/TTD phase III study of first-line XELOX plus BEV for 6 cycles followed by XELOX plus BEV or single agent (s/a) BEV as maintenance therapy in patients (pts) with metastatic colorectal cancer

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Background: The optimal length and content of first-line therapy in pts with metastatic colorectal cancer (mCRC) once they have achieved the maximal response remains controversial. This multicenter, randomized, phase III study was aimed to evaluate the efficacy and tolerability of 6 cycles of XELOX (capecitabine + oxaliplatin) + bevacizumab (BEV) followed by maintenance XELOX-BEV or s/a BEV. Methods: Pts with previously untreated mCRC were randomized to receive XELOX (capecitabine 1000 mg/m² bid d1–14 + oxaliplatin 130 mg/m² d1) + BEV (7.5 mg/kg d1) q3w x6 cycles continued by maintenance therapy with XELOX-BEV (Arm A) or s/a BEV (Arm B) until progression. The primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival (OS), objective response rate (ORR) and safety. The statistical design was based on a non-inferiority hypothesis; a mPFS of 10 months in Arm A; unilateral α of 0.025 and β of 0.8; and a sample size of 470 pts for a hazard ratio (HR) of 1,2.

Results: Patient disposition: 480 pts (median age 64 years, range 30–82) were randomized (239 Arm A, 241 Arm B, well balanced). Median follow-up was 16 months (range: 0.7–35.7). There were not statistically significant differences in ORR, PFS and OS between the 2 arms. Preliminary analysis of safety shows that tolerability was acceptable in the 2 arms, with grade 3/4 diarrhoea in 11% and 13%, HFS in 12% and 6%, and neuropathy in 24% and 7% in Arms A and B, respectively.

Conclusions: BEV as a maintenance therapy following induction XELOX-BEV was not inferior to continuation XELOX-BEV. This study suggests that maintenance therapy with s/a BEV may be an appropriate option following induction XELOX-BEV in pts with mCRC. Further studies evaluating s/a BEV after standard chemotherapy in mCRC are warranted

Efficacy	Arm A	Arm B	p-value	HR/OR [95% CI]
mPFS, months	11.0	10.3	0.59	HR: 1.07 (0.84-1.36)
mOS, months	25.3	20.7	0.63	HR: 1.07 (0.81-1.41)
ORR, %	60	57	0.51	OR: 1.13 (0.79-1.63)
M1 resection, %	10	8.3	0.51	OR:1.23(0,66-2,32)

•O-0022 The addition of cetuximab to oxaliplatin-fluoropyrimidine chemotherapy in first-line advanced colorectal cancer in the MRC COIN trial: Identification of potentially responsive subsets of patients

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Background: In the COIN trial one randomization was between continuous oxaliplatin (Ox) and fluoropyrimidine (Fp) chemotherapy and the same chemotherapy plus cetuximab. The choice of Fp, capecitabine (Cap) or infusional 5-fluorouracil plus leucovorin (FU), was decided by the patient/clinician prior to randomization. The primary outcome was overall survival (OS) in KRAS wild-type (wt) patients. Further analysis of NRAS, BRAF, MSI and EGFR status has been performed.

Methods: Patients had measurable, inoperable advanced colorectal cancer (aCRC); no prior chemotherapy for metastases; WHO performance status 0-2 and good organ function. Patients were randomized between (A) continuous OxFp (OxFU q2w or OxCap q3w) and (B) OxFp + weekly cetuximab.

Results: 1,630 patients were accrued between 03/05 and 05/08 from hospitals in the UK and Ireland. Patient characteristics: median age 63; 92% had PS 0-1; 66% received OxCap and 34% received OxFU. Tumor samples from 1,316 (81%) patients were available for KRAS analysis. 729 (55%) were KRAS wt. 102 (8%) had BRAF and 50 (4%) had NRAS mutations. 4% had MSI. In the primary analysis cohort there was no evidence of a difference in either OS or progression-free survival (PFS) from addition of cetuximab to Ox-Fp chemotherapy (OS: HR=1.04, 95% CI 0.87-1.23, p=0.67; PFS: HR = 0.96, 95%CI 0.82-1.12, p=0.60). A small difference in best overall response (CR/PR at any time on treatment) was observed (57% with OxFp, 64% with OxFp + C, p = 0.049). From pre-specified exploratory analyses of 15 potential predictive covariates, we observed a suggestion of an interaction between the choice of chemotherapy (OxFU vs. OxCap) and the effect of adding cetuximab on PFS (p=0.07), suggesting a benefit from cetuximab in OxFU treated patients, but no evidence of a benefit in OxCap treated patients. Among patients with no KRAS, BRAF or NRAS mutation (N=581; a subset of the primary cohort) we also observed an interaction between the number of metastatic sites at baseline (0/1 vs >1) and randomised treatment on OS (p=0.01) and PFS (p=0.04), suggesting a benefit from cetuximab in patients with 0/1 metastatic sites at baseline.

Conclusions: The addition of cetuximab to Ox-Fp chemotherapy did not improve OS or PFS in KRASwt patients. However, we have identified at least two possible predictive covariates. These relationships require further analysis which will be presented at the congress.

•O-0023 Randomized phase III study of panitumumab (pmab) with FOLFOX4 compared to FOLFOX4 alone as first line treatment (tx) for metastatic colorectal cancer (mCRC):PRIME trial

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Background: Pmab is a fully human anti epidermal growth factor receptor (EGFR) monoclonal antibody. PRIME was designed to evaluate the efficacy and safety of FOLFOX4 ± pmab as first line tx for mCRC. Methods: Patients (pts) were randomized 1:1 in this phase 3 multicenter study to receive pmab 6.0 mg/kg Q2W + FOLFOX4 (Arm 1) vs FOLFOX4 (Arm 2). Pts had mCRC, no prior chemotherapy for metastatic disease, no prior oxaliplatin, ECOG 0-2, and available tumor tissue for biomarker testing. Randomization was stratified by ECOG 0-1 vs 2 and region. The primary endpoint was progression-free survival (PFS). Overall survival (OS) was a key secondary endpoint. Additional endpoints included time to progression (TTP), time to response (TTR), and duration of response (DOR). The primary analysis of OS was performed when at least 50% of pts with wild-type (WT) KRAS tumor status in each arm had an event. KRAS status was determined by a blinded central laboratory prior to the primary analysis of PFS.

Results: From 8/06 to 2/08, 1183 pts were randomized: 593 Arm 1, 590 Arm 2. Demographics were well-balanced. 1096/1183 pts (93%) had KRAS results: as previously presented (Douillard et al ECCO/ESMO

2009), pts with WT KRAS tumors had a median PFS of 9.6 months (mo) for Arm 1 and 8.0 mo for Arm 2 (HR=0.80; 95% CI: 0.66-0.97; p=0.02). For pts with MT KRAS tumors, median PFS was 7.3 mo for Arm 1 and 8.8 mo for Arm 2 (HR=1.29; 95% CI: 1.04–1.62; p=0.02). Median OS was 23.9 mo for Arm 1 and 19.7 mo for Arm 2 in the WT KRAS subset (HR=0.83; 95% CI: 0.67 1.02; p=0.07) and 15.5 mo for Arm 1 and 19.3 mo for Arm 2 in the MT KRAS subset (HR=1.24; 95% CI: 0.98 1.57; p=0.07). Median TTP was 10.8 mo for Arm 1 and 9.2 mo for Arm 2 in the WT KRAS subset (HR=0.77; 95% CI: 0.62 0.97; p=0.02), and 7.5 mo for Arm 1 and 9.0 mo for Arm 2 in the MT KRAS subset (HR=1.20; 95% CI: 0.94 1.55; p=0.14). Median (95% CI) TTR was 1.8 (1.8 1.9) mo for Arm 1 and 1.9 (1.9 2.1) mo for Arm 2 in the WT KRAS subset, and 1.9 (1.8 2.1) mo for Arm 1 and 2.5 (1.9 3.5) mo for Arm 2 in the MT KRAS subset. Median (95% CI) DOR was 11.1 (9.5 13.0) mo for Arm 1 and 8.8 (7.8 9.7) mo for Arm 2 in the WT KRAS subset, and 7.4 (5.9 8.3) mo for Arm 1 and 8.0 (6.5 9.5) mo for Arm 2 in the MT KRAS subset. Adverse event rates were comparable across arms with the exception of known toxicities associated with anti-EGFR therapy.

Conclusions: Pmab significantly improves PFS and is well tolerated when added to FOLFOX4 for first line tx of pts with WT KRAS mCRC; TTP and DOR were also longer for pmab-treated pts. PFS was inferior in pts with MT KRAS tumors who received pmab. Outcomes according to grade of skin toxicity will also be presented.

•O-0024 **The influence of KRAS and BRAF tumor mutation status on treatment outcome with cetuximab plus FOLFIRI: Final data from the CRYSTAL study**

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Background: The phase III CRYSTAL study showed that patients with KRAS wild-type (wt) tumors benefit from the addition of cetuximab to FOLFIRI as 1st-line treatment for metastatic colorectal cancer (mCRC). The serine-threonine kinase BRAF is a direct downstream effector of KRAS. BRAF mutation status has been suggested to be predictive of cetuximab efficacy in pretreated patients with mCRC. Here we report an updated analysis of the CRYSTAL study with increased follow-up time and an enhancement from the published study in the number of samples for which tumor KRAS mutation status has been determined. The impact of BRAF tumor mutations in patients with KRAS wt tumors on cetuximab efficacy was investigated.

Methods: Tumor KRAS and BRAF mutation status (wt or mutant [mt]) was determined for an expanded patient population using a polymerase chain reaction clamping and melting curve assay. Treatment arms were compared according to mutation status (log-rank and Cochran-Mantel-Haenszel tests).

Results: Of 1198 patients in the primary analysis population, 1063 (89%) were evaluable for KRAS mutation status; double the previous ascertainment rate. In patients with KRAS wt tumors, all efficacy endpoints were significantly improved in patients receiving cetuximab + FOLFIRI compared with FOLFIRI alone. Tumor BRAF status was evaluable in 625/666 patients with KRAS wt tumors. BRAF mutation was a marker of poor prognosis in both treatment arms (see Table).

	KRAS wt n=666		KRAS wt/BRAF wt n= 566		KRAS wt/BRAF mt n=59	
	FOLFIRI n=350	Cetuximab + FOLFIRI n= 316	FOLFIRI n=289	Cetuximab + FOLFIRI n=277	FOLFIRI n=33	Cetuximab + FOLFIRI n= 26
Median OS months [95% CI]	20.0 [17.4–21.7]	23.5 [21.2–26.3]	21.6 [20.0–24.9]	25.1 [22.5–28.7]	10.3 [8.4–14.9]	14.1 [8.5–18.5]
Hazard ratio [95% CI] p	0.796 [0.670–0.946] 0.0093		0.830 [0.687–1.004] 0.0549		0.908 [0.507–1.624] 0.7440	
Median PFS months [95% CI]	8.4 [7.4–9.2]	9.9 [9.0–11.3]	8.8 [7.6–9.4]	10.9 [9.4–11.8]	5.6 [3.5–8.1]	8.0 [3.6–9.1]
Hazard ratio [95% CI] p	0.696 [0.558–0.867] 0.0012		0.679 [0.533–0.864] 0.0016		0.934 [0.425–2.056] 0.8656	
OR rate (%) [95% CI]	39.7 [34.6–45.1]	57.3 [51.6–62.8]	42.6 [36.8–48.5]	61.0 [55.0–66.8]	15.2 [5.1–31.9]	19.2 [6.6–39.4]
Odds ratio [95% CI] p	2.0693 [1.5154–2.8258] <0.0001		2.1750 [1.5505–3.0511] <0.0001		1.0842 [0.2644–4.4456] 0.9136	

Conclusions: For all efficacy endpoints, including survival, this analysis confirms the value of KRAS mutational status as a predictor of treatment outcome in patients with mCRC receiving cetuximab plus FOLFIRI 1st-line. BRAF mutation status does not appear to be a predictive biomarker for cetuximab when added to FOLFIRI in 1st-line mCRC, but the sample size may be too small to be conclusive. However BRAF mutation status is a strong prognostic factor, and should be considered as a possible stratification factor in future clinical trials involving patients with mCRC treated with EGFR-targeted agents or chemotherapy alone

•O-0025 **Intermittent vs. continuous oxaliplatin-fluoropyrimidine chemotherapy in the MRC COIN trial in advanced colorectal cancer: Updated efficacy results, quality of life and potential predictive factors**

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Background: Intervals off chemotherapy may be a welcome respite for patients with advanced colorectal cancer (aCRC). The COIN randomized controlled trial (RCT) compared intermittent and continuous chemotherapy strategies.

Methods: Patients had measurable, inoperable aCRC; no prior CT for metastases; WHO performance status 0-2 and were randomized to A: cOxFlu - continuous oxaliplatin (Ox) + fluorouracil/leucovorin q2w or Ox + capecitabine q3w until treatment failure or C: iOxFlu - same regimen for 12 wks, with further 12 wk courses upon progressive disease (PD). The trial was powered to exclude an HR >1.162, equivalent to an absolute difference in 2-year survival greater than 4.6%. The EORTC QLQ-C30 was the QL tool used pre-randomization, at 6 and 12 weeks, and 12-weekly thereafter. Clinical and biochemical parameters at baseline and 12 weeks were analyzed to identify factors predicting benefit from cOxFlu or iOxFlu. Individual clinicians were classified into those above or below average in complying with the protocol goal of restarting iOxFlu on PD.

Results: 1,630 patients were accrued between 2005 and 2008. Patients on iOxFp had significantly less toxicity, and spent a median of 15 weeks on treatment compared to 25 weeks on cOxFp. The intention-to-treat (ITT) OS analysis showed a 9% relative increase in the hazard of death in patients on iOxFp (HR 1.084, 80% CI 1.008-1.165). Median OS was 15.6 months on cOxFp and 14.3 months on iOxFp. QL at 24 weeks suggested improved role functioning, less fatigue, anorexia and diarrhoea on iOxFp. In the Per Protocol Analysis, after exploring 16 factors, there was a suggestion of treatment interactions with: presence of liver-only metastases (p=0.07), platelet count at baseline (p=0.003) and KRAS status (p=0.07). Non-compliance in recommencing iOxFp (< 60%) also led to a modest early survival disadvantage for Arm C, but this was not statistically significant (HR 1.14, p=0.2 compared with HR 1.05, p=0.7 for compliant clinicians).

Conclusions: Intermittent therapy is a reasonable strategy for the treatment of aCRC. It results in minimal detriment in OS, but improved QL, less time on chemotherapy and less toxicity. We have identified several potential predictive variables which could, if validated, aid selection of patients for this innovative approach.

•O-0026 Final results from a randomized, double-blind, phase III study of sunitinib plus FOLFIRI vs. placebo plus FOLFIRI in first-line treatment of patients (pts) with metastatic colorectal cancer (mCRC)

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Background: Sunitinib is an oral, multitargeted inhibitor of VEGFRs, PDGFRs and other tyrosine kinase receptors in clinical development for gastrointestinal cancers. In non-clinical models of CRC, sunitinib has shown single-agent antitumor activity, inhibiting the growth of established tumor xenografts at well-tolerated doses. Combining sunitinib with chemotherapy in these models blocked tumor growth to a greater extent than either agent alone, suggesting that it may enhance the activity of cytotoxic chemotherapies in patients with CRC. The objective of this double-blind, randomized, phase III study was to demonstrate that sunitinib plus FOLFIRI has superior efficacy to placebo plus FOLFIRI in patients with treatment-naïve mCRC.

Methods: Eligible patients had previously untreated mCRC clinically indicated for therapy with FOLFIRI, ECOG performance status (PS) 0/1 and no prior therapy with a VEGF or tyrosine kinase inhibitor. Patients were randomized 1:1 to receive FOLFIRI (irinotecan 180 mg/m², leucovorin 200 mg/m², and 5-fluorouracil [5-FU] 400 mg/m² bolus, followed by 2400 mg/m² 46-hour infusion) every 2 weeks, combined with either oral sunitinib 37.5 mg/day for 4 weeks on, 2 weeks off (Schedule 4/2) or placebo. Progression-free survival (PFS) was the primary endpoint. Secondary endpoints included overall survival (OS), RECIST-defined objective response rate (ORR), and safety. Tumor assessments were performed every 6 weeks and evaluated by an independent third-party imaging laboratory. The study was designed to detect a statistically significant difference in PFS at the 0.025 level with a power of 0.85. Patients were stratified by ECOG PS, number of metastatic organ sites, primary tumor site (rectal vs colon), and prior adjuvant treatment.

Results: Overall, 768 patients were enrolled from July 2007 to September 2008 and randomized to receive FOLFIRI plus sunitinib (n=386) or placebo (n=382). Following a pre-specified interim analysis, the

Independent Data Monitoring Committee determined that the futility boundary had been crossed in June 2009, and the study would be unable to meet the primary endpoint. Patients on treatment were notified, treatment was unblinded, and discontinuation of sunitinib was recommended or left to investigator discretion in cases of clinical benefit. No unexpected adverse events were reported, although the frequency of common grade ≥ 3 toxicities was higher with sunitinib plus FOLFIRI, compared with placebo plus FOLFIRI.

Conclusions: The addition of sunitinib to FOLFIRI did not demonstrate a significant improvement in PFS in patients with treatment-naïve mCRC. Further analyses of efficacy and safety are ongoing, and final results will be presented.

•O-0029 **Final results of the EORTC intergroup randomized study 40004 (CLOCC) evaluating the benefit of radiofrequency ablation combined with chemotherapy for unresectable colorectal liver metastases**

Authors: T. Ruers et al.

Late breaking abstract