Efficacy results

	XELOX	FOLFOX4	HR [95% CI]
PFS (PPP), months	5.1	5.5	1.03 [0.87–1.24]
PFS (ITT), months	4.7	4.8	0.97 [0.83–1.14]
OS (PPP), months	12.7	13.2	1.07 [0.88–1.31]
OS (ITT), months	11.9	12.6	1.03 [0.87–1.23]

Conclusions: Second-line treatment of MCRC with XELOX is non-inferior to FOLFOX4 in terms of PFS, OS and ORR. This study supports the results of another large phase III study in first-line MCRC reported recently [Cassidy et al. ASCO GI 2007], which compared XELOX +/− bevacizumab vs. FOLFOX4 +/− bevacizumab and also showed similar efficacy in PFS and OS. The safety profile was similar to previous studies, with no unexpected toxicities.

3013 ORAL

Tissue biomarkers in colon cancer (COC): Early results of the translational study on a phase III trial comparing infused irinotecan/ 5-fluorouracil (5-FU)/folinic acid (FA) to 5-FU/FA in stage II−III COC patients (PETACC 3–EORTC 40993–SAKK 60/00)

A. Roth[1], S. Tejpar[2], P. Yan[3], R. Fiocca[4], S. Hsu Schmitz[5], G. Bodoky[6], R. Labianca[7], D. Cunningham[8], E. Van Cutsem[2], F. Bosman[3].
[1]University Hospital of Geneva, Oncosurgery, Geneva 14, Switzerland; [2]Universaty Hospital Gasthuisberg, Digestive Oncology Unit, Leuven, Belgium; [3]Lausanne University, Dpt of Pathology, Lausanne, Switzerland; [4]University of Genova, Dpt of Surgical and Morphological Sciences, Genova, Italy; [5]Swiss Group of Clinical Cancer Reasearch, Sakk, Bern, Switzerland; [6]St Lazlo Hospital, Oncology, Budapest, Hungary; [7]Ospedali Riuniti, Unit of Medical Oncology, Bergamo, Italy; [8]The Royal Marsden Hospital, Medical Oncology, Sutton, United Kingdom

Background and Aims: PETACC 3 is a large adjuvant trial with 3005 COC pts. The value of biomarkers (BIOM) in COC in adjuvant setting is still a matter of debate because of lack of large data sets. We took advantage of PETACC 3 to assess P53, SMAD4, thymidylate synthetase (TS), telomerase (HTERT) expressions, UGT1A1 genotype, KRAS and BRAF mutations, microsatellite instability (MSI), 18q and 8p LOH with regard to their prognostic and predictive values and their interactions on a very large homogeneous cohort of COC pts.
Methods: 1564 formalin fixed paraffin embedded (FFPE) tissue blocks of PETACC 3 pts were prospectively collected and 5−20μ sections cut. DNA from normal (Nor) and tumoral (Tu) tissues was extracted after section microdissection. P53, SMAD4, TS and HTERT were assessed by immunohistochemistry (IHC); MSI was typed with 10 markers, KRAS exon 2 and BRAF exon 15 mutations by allele specific real time PCR on Tu DNA; 18q and 8p LOH by typing multiple SNPs by pyrosequencing on Nor/Tu DNA; UGT1A1 genotypes by PCR and fragment sizing on Nor DNA. Prognostic/predictive value of each BIOM is analysed by Cox regression for disease free survival and by logistic regression for specific toxicity. Associations between any 2 categorized BIOM and between each BIOM and each known prognostic variable are tested by chi-square tests.
Results: DNA of 1405 pts was extracted and successfully analysed in 97.1% for KRAS, 98.6% for BRAF, 94% for 18q LOH, 93.6% for MSI, 95% for UGT1A1, 8p LOH is still ongoing. Of 1530 pts slides IHC analysis was successful in 94.5% for P53, 94.2% for SMAD4, 82.9% for TS, 53.9% for HTERT. Early results show significant improvement of prognosis with high SMAD4 expression ($p < 0.001$), lack of p53 overexpression ($p = 0.04$), high MSI ($p = 0.04$) and a trend for better prognosis with high TS expression ($p = 0.07$) and lack of BRAF mutation ($p = 0.11$). None of the 4 KRAS mutations tested had any impact on prognosis.
Conclusion: This is the largest multicenter centrally coordinated tissue BIOM study performed in COC to date. The high success rate of analysis shows that large prospective BIOM studies can be performed on routine decentrally processed FFPE material. These early data obtained on a large patient population confirm (MSI, SMAD4, KRAS) or challenge (p53, TS) published results coming from smaller patient cohorts.Further analysis of these data is ongoing.

3014 (Presidential session, Tue 25 Sep 12.30–14.30) ORAL

Association of somatic KRAS gene mutations and clinical outcome in patients (pts) with metastatic colorectal cancer (mCRC) receiving panitumumab monotherapy

D. Freeman[1], T. Juan[1], N.J. Meropol[2], J.R. Hecht[3], J. Berlin[4], E. Van Cutsem[5], M. Reiner[6], R. Radinsky[1], R.G. Amado[7], M. Peeters[8]. *[1]Amgen Inc., Oncology Research, Thousand Oaks CA, USA; [2]Fox Chase Cancer Center, Medical Oncology, Philadelphia PA, USA; [3]University of California Los Angeles Medical School, Medical Oncology, Los Angeles CA, USA; [4]Vanderbilt University Medical Center, Medical Oncology, Nashville TN, USA; [5]University Hospital Gathuisburg, Digestive Oncology, Leuven, Belgium; [6]Amgen Inc., Biostastitics, Thousand Oaks CA, USA; [7]Amgen Inc., Clinical Development, Thousand Oaks CA, USA; [8]Ghent University Hospital, Digestive Oncology, Ghent, Belgium*

Background: Panitumumab, a fully human monoclonal antibody directed against the epidermal growth factor receptor has demonstrated efficacy as monotherapy in pts with mCRC. Identifying markers of responsiveness would allow physicians to target therapy to those pts most likely to benefit. In this analysis, pt samples from 4 mCRC monotherapy studies of safety and efficacy with panitumumab were used to test the hypothesis that KRAS mutations are associated with resistance to panitumumab.
Methods: Tumor sections from 59/709 treated pts (57/533 pts from three phase 2 studies, and 2/176 pts from a phase 3 extension study) were consented, had response data, and were available for analysis of KRAS gene mutations. Genomic DNA was isolated from FFPE tumor sections (pretreatment). PCR was performed on KRAS (exons 2 & 3) to determine the prevalence of activating mutations. More than 30 colonies per exon were sequenced and resolved on a Genetic Analyzer. Subsequent PCR and genomic DNA sequencing confirmed the existence of mutations. In all 4 studies, best objective response (OR) was assessed using RECIST criteria at prespecified weeks; the phase 2 studies were assessed by blinded central review; the extension study was assessed by local review.
Results: Of the 59 pts, 6 (10%) had a partial response (PR), 22 (37%) had stable disease (SD), and 31 (53%) had progressive disease (PD) as their best OR. 21 of the 59 pts harbored a KRAS mutation: 5 pts had SD (24%) and 16 pts had PD (76%) as their best OR. All of these mutations were located in exon 2 (amino acids 12 and 13). No responders had a KRAS mutation. In the wild-type KRAS population, the PR rate was 16% (95% CI: 4, 27), the SD rate was 45% (95% CI: 29, 61), and the PD rate was 39% (95% CI: 24, 55). There was a statistically significant association between KRAS mutation status and response to panitumumab (Fisher's exact test, $p = 0.013$). From a Cox PH model for KRAS mutation as a predictor of PFS, the HR was 1.7 (95% CI: 1.0−2.9); for OS the HR was 1.73 (95% CI: 1.0−3.1).
Conclusion: Although the sample size is limited, these data suggest that CRC pts with activating KRAS mutations may be less likely to respond to treatment with panitumumab monotherapy. These findings warrant further investigation, including sequencing a larger set of samples to correlate KRAS mutations with pt responsiveness to panitumumab. A prospective trial to evaluate KRAS as a predictive biomarker of response is currently ongoing.

3015 ORAL

Sequential vs. combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (ACC). A Dutch Colorectal Cancer Group (DCCG) phase III study

M. Koopman[1], N.F. Antonini[2], J. Douma[3], J. Wals[4], A.H. Honkoop[5], F.L.G. Erdkamp[6], R.S. de Jong[7], C.J. Rodenburg[8], L. Mol[9], C.J.A. Punt[1]. *[1]University Medical Centre St Radboud, medical oncology, Nijmegen, The Netherlands; [2]Netherlands Cancer Institute (NKI), Biometrics Department, Amsterdam, The Netherlands; [3]Rijnstate Hospital, medical oncology, Arnhem, The Netherlands; [4]Atrium Medical Centre, medical oncology, Heerlen, The Netherlands; [5]Isala Hospital, medical oncology, Zwolle, The Netherlands; [6]Maasland Hospital, medical oncology, Sittard, The Netherlands; [7]Martini Hospital, medical oncology, Groningen, The Netherlands; [8]Meander Hospital, medical oncology, Amersfoort, The Netherlands; [9]University Medical Centre St Radboud, Comprehensive Cancer Centre East (IKO), Nijmegen, The Netherlands*

Background: Imbalances in salvage treatments may affect overall survival (OS) in phase III studies with 1st line combination therapy in ACC. This is the first trial that prospectively evaluates the sequential versus the combined use of all available effective cytotoxic drugs.
Methods: Previously untreated patients (pts) with ACC, WHO PS 0−2 were randomized between 1st line capecitabine (Cap), 2nd line irinotecan (Iri), and 3rd line Cap + oxaliplatin (CapOx) (Arm A, sequential) vs 1st

line CapIri and 2nd line CapOx (Arm B, combination). The dose of Cap was 1250 mg/m^2 (mono) or 1000 mg/m^2 (combination) b.i.d. day 1−14, Iri 350 mg/m^2 (mono) or 250 mg/m^2 (combination), and Ox 130 mg/m^2. All cycles were q 3 weeks with Iri/Ox given i.v. on day 1. Response was assessed every 3 cycles. Primary endpoint was OS. The study was designed to detect a 20% reduction in the hazard of death (HR = 0.80) for an increase in median OS from 14 to 17.5 months (alpha=0.05, 2-tailed test).
Results: 820 pts were randomized between Jan 2003 and Dec 2004 in 74 Dutch hospitals. Of 803 eligible pts, 795 received $\geqslant$1 cycle. Median age was 63 (27−84) yrs, median WHO PS 0 (0−2), median follow-up 32 m. Pts in arm A: 397 (1st line), 246 (2nd line), 142 (3rd line); arm B: 398 (1st line), 211 (2nd line). Median OS in arm A was 16.2 m (95% CI 14.2−18.0) and in arm B 18.0 m (15.3−19.4), logrank p = 0.19. Overall toxicity over all lines did not differ significantly except for grade 3 hand–foot syndrome (HFS) (13% in A vs 6.5% in B, p = 0.004), and incidence of cholinergic syndrome (18% in A vs 24% in B, p = 0.03). Death was probably related to treatment in 11 pts (neutropenic sepsis and/or diarrhea, 8 arm A, 3 arm B). In 1st line significant differences in grade 3−4 toxicity in arm A vs arm B were diarrhea (11% vs 26%, p < 0.0001), febrile neutropenia (1% vs 7%, p < 0.0001), HFS (12% vs 6%, p = 0.002), incidence of cholinergic syndrome (p < 0.0001), nausea (4% vs 8%, p = 0.004) and vomiting (3% vs 9% p = 0.0002). All-cause 60-day mortality was 3.0% (n = 12) in arm A and 4.5% (n = 18) in arm B.
Conclusions: Combination therapy does not significantly improve OS compared with sequential therapy. Both treatment strategies are valid options for pts with ACC. Updated results will be presented at the meeting, including data on progression free survival and response rate.

Poster presentations (Mon, 24 Sep, 09:00−12:00)
Gastrointestinal malignancies – colorectal cancer

3016 POSTER

Trends in chemotherapy (CT) utilization for colorectal cancer: A provincial population-based analysis

D. Renouf, H. Kennecke, S. Gill. *BC Cancer Agency, Medical Oncology, Vancouver BC, Canada*

Background: Significant advances have been made in the treatment of colorectal cancer in both the adjuvant and metastatic setting. The purpose of this study is to examine chemotherapy (CT) prescribing patterns for adjuvant therapy of colon cancer and metastatic colorectal cancer over the last 15 years in British Columbia, Canada.
Methods: All patients (pts) with stage 2 or 3 colon cancer, or stage 4 colorectal cancer at presentation referred to the BC Cancer Agency during a one year period for three time cohorts: 1990, 2000 and 2004, were reviewed. A pt was considered to be treated with CT if they received a cycle of CT within 6 months of referral.
Results: A total of 1421 patients were included: stage 2/3 n = 915, stage 4 n = 506. Chemotherapy utilization increased significantly from 1990 to 2004 for adjuvant CT [1990: 49 (29%), 2000: 129 (45%), 2004: 235 (52%), p < 0.001] and for palliative CT [1990: 41(35%), 2000: 100 (51%), 2004 120 (63%), p < 0.001]. The proportion of pts with stage 2 disease treated with adjuvant CT increased dramatically [1990: 3(4%), 2000: 38 (26%), 2004: 50 (30%), p < 0.001]. CT utilization was directly associated with later time cohort and younger age of presentation. The use of palliative CT was significantly associated with male gender (p = 0.025). This gender bias was not observed in the adjuvant setting. Among pts >70y, only 25% (99/394) received adjuvant CT [1990: 5(8%), 2000:38 (28%), 2004: 57 (28%)] and 31% (50/162) received palliative CT [1990:4 (15%), 2000:17 (24%), 2004:30 (45%)].
Conclusions: In this population-based cohort, adjuvant and palliative CT utilization has increased since 1990 however there is room for improvement. Despite the lack of conclusive evidence, the use adjuvant CT for stage II disease has increased significantly. Female pts appear less likely to receive palliative CT. Despite evidence that the elderly can accrue similar proportional benefits, the majority of referred pts >70y still do not receive adjuvant or palliative CT. Such discrepancies in CT utilization require further investigation.

3017 POSTER

Cetuximab dose-escalation in patients (pts) with metastatic colorectal cancer (mCRC) with no or slight skin reactions on standard treatment: pharmacokinetic (PK), pharmacodynamic (PD) and efficacy data from the EVEREST study

Y. Humblet[1], M. Peeters[2], H. Gelderblom[3], J.B. Vermorken[4], F. Viret[5], B. Glimelius[6], F. Ciardiello[7], E. Gallerani[8], O. Kisker[9], E. Van Cutsem[10]. *[1]University St-Luc, Medical Oncology, Brussels, Belgium; [2]University Hospital Gent, Medical Oncology, Gent, Belgium; [3]University Medical Center, Oncology, Leiden, The Netherlands; [4]University Hospital Antwerp, Department of Medical Oncology, Antwerp, Belgium; [5]Institut Paoli Calmettes, Oncology, Marseille, France; [6]Akademiska University Hospital, Oncology, Uppsala, Sweden; [7]Second University of Naples, Dipartimento Medico-Chirurgico di Internistica Clinica e Sperimentale, Naples, Italy; [8]Institute of Oncology of Southern Switzerland, Oncolgy, Bellinzona, Switzerland; [9]Merck KGaA, R& D Medical Sciences Oncology, Darmstadt, Germany; [10]University Hospital Gasthuisberg, Department of Gastroenterology, Leuven, Belgium*

Background: Response to cetuximab treatment appears to correlate with the intensity of the associated skin reaction. This phase I/II randomized study investigated cetuximab dose-escalation in pts with EGFR-expressing mCRC failing prior irinotecan-containing therapy.
Methods: The primary objective was to investigate the effects of dose-escalation on EGFR and downstream signaling in skin and tumor biopsies compared to standard cetuximab regimen. Secondary objectives included PK, efficacy, safety, tolerability, tumor and plasma biomarker analysis in relation to treatment, side effects and response. Pts received cetuximab (400 mg/m^2 initial dose, then 250 mg/m^2/week [w]) with irinotecan (180 mg/m^2 q2w) until randomization at day 22. Pts were randomized if they had not experienced > Grade (Gr) 1 skin reaction or any other >Gr2 cetuximab-related AE and were tolerant to irinotecan. Randomization was to Arm A (cetuximab standard dose, 250 mg/m^2/w) or Arm B (cetuximab dose increased by 50 mg/m^2 q2w, until >Gr2 toxicity, tumor response or dose=500 mg/m^2/w). Pts not randomized (Arm C) continued on cetuximab 250 mg/m^2/w. All pts continued to receive irinotecan.
Results: 284 pts were screened, 221 (78%) EGFR-expressing, 166 enrolled: 45 randomized to Arm A; 44 to Arm B; 77 non-randomized to Arm C. 106 pts (64%) were male, median age 60 years [25−79], and median KPS 90 [70–100]. In Arm B, 24 pts reached the maximum cetuximab dose. Response rate (RR) in Arm B was 30% vs 16% in Arm A (22% in Arm C). Progression-free survival in Arm B was 4.8 months vs 3.9 months in Arm A (3.9 months in Arm C). Gr3/4 skin reactions occurred in 11% of pts in Arm B, 0% in Arm A (14% in Arm C). Dose-related increases in C_{max} and AUC were observed. $T_{1/2}$ values were dose-independent. IHC analysis in skin biopsies showed no significant association of baseline levels or on-treatment changes of candidate EGFR-signalling markers with dose-escalation or response, whereas in tumor some markers show a trend for association with response. Gene candidate expression in tumor (microarray analysis) and some plasma proteins (Luminex proteomics) appear to be associated with response.
Conclusions: Pts with no or slight skin reactions on standard dose cetuximab may demonstrate improved RRs and PFS with dose-escalation up to 500 mg/m^2/w. Overall cetuximab PK behavior is in good agreement with previous experience. Treatment was generally well tolerated. Detailed PD data will be presented at the meeting.

3018 POSTER

Pharmacogenetic analysis of toxicity after 5-fluorouracil (5FU) or 5FU/Oxaliplatin therapy for metastatic colorectal cancer: Preliminary results in FFCD 2000−05 trial

V. Boige[1], M. Castaing[2], M.A. Loriot[3], M. Barrois[4], I. Miran[4], C. Mulot[3], J.P. Pignon[2], M. Ducreux[1], P. Laurent-Puig[3]. *[1]Institut Gustave Roussy, Medicine, Villejuif, France; [2]Institut Gustave Roussy, Biostatistics, Villejuif, France; [3]INSERM, U775, Paris, France; [4]Institut Gustave Roussy, Oncogenetics, Villejuif, France*

Background: The FFCD 2000−05 randomized trial compared simplified LV5FU2 followed by FOLFOX6 (arm 1) to FOLFOX6 followed by FOLFIRI (arm 2) in the treatment of metastatic colorectal cancer. The aim was predicting the toxicity profile of oxaliplatin after the first line treatment using pharmacogenetic data.
Materials and Methods: Patients (pts) with available blood samples were compared to the other pts for clinical prognostic factors (chi2 test). A logistic model was computed to test the association between polymorphisms and toxicity in each arm. An interaction test was used to assess a differential effect according to treatment (predictive effect), in order to identify a predictive effect of oxaliplatin. Grade 3−4 hematological and non-hematological