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

toxicities (H-tox and NH-tox) at 4 months and grade 2−4 neurological at 6 months were the endpoints of the study. Thirteen genetic variants in 10 candidate genes were selected for pharmacogenetic analysis: ERCC1_04 (rs3212961), ERCC1_05 (rs11615), ERCC1_06 (rs3212948), ERCC1_24 (rs3212955), ERCC2_02 (rs1799793), ERCC2_03 (rs13181), ERCC2_06 (rs238406), ERCC2_09 (rs1799787), GSTM1 (null/present), GSTT1 (null/present), TS (TSER, Ins/del6bp) and UGT1A1 (rs8175347). Genotyping was performed using Taqman probes, QMPSF and fragment analysis.
Results: 327 pts (156/171) out of 410 were included (61 had no blood samples, 16 had less than 2 cycles, 3 had incomplete data on toxicity, 3 had insufficient DNA). No difference was found between included and excluded pts in the analysis for gender, age, OMS, number of metastatic organs and adjuvant chemotherapy. Pts received similar 5FU doses in both arms. Number of patients with at least one toxicity in arms 1/2 were as follows: 5/54 grade 3−4 H-tox, 28/47 grade 3−4 NH-tox, and 0/103 grade 2−4 neurological. The genotype CC of ERCC2_02 correlated with higher NH-tox at 4 months in arm 2 ($p = 0.0008$, OR = 0.31, 95% CI=[0.15−0.62] versus $p = 0.87$, OR = 0.93, CI=[0.39−2.21] in arm 1) compared to genotypes CT and TT, with borderline interaction ($p = 0.05$).
Conclusions: These preliminary results on early toxicity in first-line are in favour of an effect of ERCC2_02 on NH-tox of FOLFOX6 and a predictive effect on NH-tox of oxaliplatin.

3019 POSTER

Association of gene copy number (GCN) of the epidermal growth factor receptor (EGFr) and clinical outcome in patients (pts) with metastatic colorectal cancer (mCRC) treated with panitumumab monotherapy

J. Berlin[1], J.R. Hecht[2], M. Reiner[3], M. Mullenix[4], S. Suggs[5], R. Radinsky[6], D. Freeman[6], R.G. Amado[7], N.J. Meropol[8]. *[1]Vanderbilt University Medical Center, 777 Preston Research Building, Nashville TN, USA; [2]University of California Los Angeles Medical School, Hematology/Oncology, Los Angeles CA, USA; [3]Amgen Inc., Biostatistics, Thousand Oaks CA, USA; [4]Amgen Inc., Clinical Immunology, Thousand Oaks CA, USA; [5]Amgen Inc., Molecular Sciences, Thousand Oaks CA, USA; [6]Amgen Inc., Oncology Research, Thousand Oaks CA, USA; [7]Amgen Inc., Clinical Development, Thousand Oaks CA, USA; [8]Fox Chase Cancer Center, Medical Oncology, Philadelphia PA, USA*

Background: Panitumumab, a fully human monoclonal antibody directed against EGFr, has demonstrated efficacy as monotherapy in pts with mCRC. Recently, differences with regards to the predictive value of EGFr GCN with response to anti-EGFr therapy have been published. In this analysis, we associate clinical outcome with EGFr GCN from pt samples from a large, phase 2 panitumumab monotherapy study of mCRC.
Methods: Tumor sections from 39/148 treated pts who were consented, had response data, and were available for testing were included in this analysis. EGFr GCN was analyzed by FISH using the Vysis® kit (per the kit protocol; Des Plaines, IL). Increased GCN (# EGFr signals per nucleus) was defined as >2.5, and amplification (EGFr signals/CEP7 signals) was defined as >1.1. Best objective response (OR) was assessed using modified RECIST criteria at prespecified weeks by blinded central review. Association of EGFR GCN with clinical outcomes was tested using a Fisher's Exact Test for best OR, and a Cox Proportional Hazards model for progression-free survival (PFS) and overall survival (OS).

	PR	SD	PD
GCN > 2.5	0/5	4/13	5/18
Rate[a]	0%	31%	28%
p-value		0.51	
Amplification >1.1	0/5	6/13	2/18
Rate[a]	0%	46%	11%
p-value	0.05		
GCN (continuous)	**PFS**	**OS**	
HR[b]	1.00	1.00	
95% CI	0.83−1.21	0.82−1.21	
Amplification (continuous)			
HR[b]	0.87	0.93	
95% CI	0.37−2.04	0.42−2.08	

[a]Fisher's exact test; [b]CoxPH model.

Results: 36/39 pt samples were evaluable by FISH and were included in this analysis. Five (14%) pts had a partial response (PR), 13 (36%) pts had stable disease (SD), and 18 (50%) had progressive disease (PD). Analyses by clinical efficacy outcomes are shown (table). Additional analyses on FISH using ROC curves for parameters of response, survival and PFS were negative. Similar results were obtained with gene amplification. Based on these results, we would be unable to ascribe any value to GCN or gene amplification as an indicator of outcome.
Conclusion: In this data set, EGFr GCN and gene amplification do not predict response (PR, SD, or PD), OS or PFS with panitumumab. These findings warrant further investigation in a larger set of samples.

3020 POSTER

Preliminary efficacy of Bevacizumab with first-line Folfox, Xelox, Folfiri and fluoropyrimidines for mCRC: First BEAT trial

S. Berry[1], D. Cunningham[2], M. Michael[3], A. Kretzschmar[4], F. Rivera[5], M. DiBartolomeo[6], M. Mazier[7], B. Lutiger[8], E. Van Cutsem[9], On behalf of the First BEAT investigators. *[1]Sunnybrook Regional Cancer Centre, Medical Oncology, Toronto, Canada; [2]Royal Marsden Hospital, Department of Medicine, Sutton, United Kingdom; [3]Peter MacCallum Cancer Institute, Haematology and Medical Oncology, Melbourne, Australia; [4]HELIOS-Klinikum Berlin, Robert Rossle Klinik der Charite, Berlin, Germany; [5]Hospital Marques de Valdecilla, SV Oncologia Medica, Santander, Spain; [6]Istituto Nazionale Tumori, Division of Medical Oncology Unit 2, Milan, Italy; [7]Paraxel, Statistics Department, Paris, France; [8]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [9]University Hospital Gasthuisberg, Digestive Oncology Unit, Leuven, Belgium*

Background: In a phase III pivotal trial in patients (pts) with metastatic colorectal cancer (mCRC), BEV (BEV, Avastin®) increased overall survival (OS) by 30% when added to first-line IFL chemotherapy (CT). Recently, a second trial reported a significant improvement in progression free survival (PFS) when BEV was added to FOLFOX/XELOX in a similar patient population. Although, First BEAT was opened to evaluate the safety profile of BEV in a broader pt population using a variety of CT regimens, efficacy endpoints were investigated.
Material and Methods: First BEAT screened 1,965 mCRC patients in 41 countries between June 2004 and February 2006. 1,914 eligible pts were treated with first-line CT (physician's choice) in combination with BEV (5 mg/kg q2w [5-FU-based CT] or 7.5 mg/kg q3w [capecitabine [cap, Xeloda®]-based CT]) until disease progression. Secondary endpoints included OS, time to progression (TTP) and PFS. Disease progression was assessed by investigators. A confirmatory analysis censored pts who discontinued Bev before progression.
Results: All eligible pts were evaluable by 16 March 2007 (male 58%; median age 59 years, 33% ⩾65 years; ECOG PS 0/1 65%/34%). Median follow-up was 18 months; 60-day mortality was 2.5%. First-line CT regimens used with BEV included FOLFOX (28%), FOLFIRI (26%), XELOX (18%) and 5-FU /cap monotherapy (15%). 55% of pts were treated until progression. Pts receiving 5 FU/cap CT appeared to have poorer prognosis with respect to age ⩾65 years (41%), ECOG PS 0/1 (58%/42%) and 60-day mortality rate (6.6%), compared with those receiving doublet CT regimens plus BEV. Median overall PFS was 10.7 (95% CI: 10.3−11.2 months, based on 1,110 events), 10.6 (9.8−12.0) in FOLFOX, 10.7 (10.1−11.6) in XELOX, 11.3 (10.7−12.4) in FOLFIRI and 9.1 (8.1−10.3) in pts receiving 5-FU or cap CT with BEV, respectively. Median overall TTP was 11.1 (95% CI: 10.6−11.6) months (based on 1,026 events). On treatment median PFS was 11.2 (95% CI: 10.7−11.7 months) and TTP was 11.5 (95% CI: 11.0−12.3 months). Metastasectomy was performed in 143 (7.5%) pts, of which 85% were done with curative intent. 614 pts have died, but OS data are immature. Updated analyses will be presented.
Conclusions: In this ongoing, large community-based study, the preliminary efficacy of first line BEV in mCRC pts receiving a variety of CT regimens appears consistent with that observed in large phase III randomised trials.

3021 POSTER

Association between exposure to bevacizumab (BV) beyond first progression (BBP) and overall survival (OS) in patients (pts) with metastatic colorectal cancer (mCRC): results from a large observational study (BRiTE)

A. Grothey[1], M. Sugrue[2], E. Hedrick[2], D. Purdie[2], P. Chiruvolu[2], W. Dong[2], D. Sargent[1], M. Kozloff[3]. *[1]Mayo Clinic, Rochester, USA; [2]Genentech Inc., South San Francisco, USA; [3]Ingalls Hospital and the University of Chicago, Harvey, USA*

Background: While BV (Avastin®) prolongs OS when used with standard 1st- or 2nd-line chemotherapy (CT) in mCRC, no data exist on the effects of BBP. A previous report from BRiTE showed favorable median OS (27.1 mo, 95% CI 24.8-NE), with 1st line PFS (median 10.1 mo, 95% CI:9.7−10.4)