Results: Data are available on 30 patients (12 female, 18 male; median age 28 years; range 17−48 years) treated and followed between January 1989 and February 2007. Three patients referred from outside institutions solely for the treatment of relapses were excluded from the survival analysis. Headache was the most common presenting symptom (76%) followed by nausea, vomiting, ataxia and gait disturbances (48%). Median symptom duration was 2 months. Seventy-four percent of lesions arose from the cerebellar hemispheres. Twenty-six patients were assigned to poor (46%) or standard (54%) risk categories. Of the twenty-seven patients treated and followed exclusively at McGill, twenty-five (93%) underwent surgical resection followed by craniospinal radiotherapy. The median time delay between surgery and initiation of radiotherapy was 35 days (range 11−75 days). Twelve (44%) patients were prescribed adjuvant chemotherapy using the CCG 921, POG 9031 or MOPP protocols. Five patients received vincristine concurrent with radiotherapy. The most frequently reported treatment-related adverse effects were myelotoxicity, ototoxicity and neuropathy. Twelve patients relapsed, most frequently in the posterior fossa (58%). Median time to relapse was 3.3 years (range 0.3−7.9 years). Median survival was 7.5 years. By February 2007, 10 patients were deceased. No treatment related deaths were reported.
Conclusion: Adult medulloblastoma is a rare disease for which the optimal management has yet to be defined. At McGill, pediatric chemotherapy protocols have been used to treat these patients and our overall survival data are comparable with pediatric data. By comparing our experience with that of other institutions we hope to improve the care provided to patients presenting with adult medulloblastoma.

2523 POSTER

Concomitant chemo radiation (CRT) in high-risk primitive CNS embryonal tumours (PCET): a prospective pilot study at Tata Memorial Hospital (TMH)

P. Kurkure[1], B. Arora[1], R. Sarin[2], R. Jalali[2], T. Gupta[2], D. Mazumdar[3], S. Kane[4], H. Menon[1], T. Vora[1], P. Parikh[1]. *[1]Tata Memorial Hospital, Medical Oncology, Mumbai, India; [2]Tata Memorial Hospital, Radiation Oncology, Mumbai, India; [3]K.E.M Hospital, Neuro Surgery, Mumbai, India; [4]Tata Memorial Hospital, Pathology, Mumbai, India*

Objective: The outcome of high risk PCET is dismal and novel approaches are urgently required. We present our preliminary observation of safety and feasibility of concomitant CRT in these patients.
Methods: Treatment naive patients with confirmed diagnoses of high risk PCET, >3 yrs & <22 yrs were prospectively accrued on this phase II study at TMH since July 2004. All patients underwent surgery followed by CRT within 6 wks of surgery The CRT includes craniospinal radiation (35 Gy/21#) with local tumour bed boost 19.8 Gy/11# along with carboplatin 35 mg/m^2/day given 5 days a week for 15 doses (during first 3 wks.). This was followed by 6 cycles of maintenance chemotherapy at 4 weekly interval beginning 4 to 6 wks post CRT using Vincristine, Carboplatin and Cyclophosphamide.
Results: A total of 17 patients have completed the CRT. Median age was 9 years (range 3−19 years), M:F ratio of 2:1 Medulloblastoma was seen in 59% and supratentorial PNET in 41%; M Stage M0 (53%), M1 (6%), M2 (6%), M3 (35%). All patients completed CRT as per schedule except interruption for 1 week in one patient due to facial cellulitis and another due to Malaria. In hematological toxicity 82% developed anemia, 94% developed neutropenia & 82% developed thrombocytopenia. Severe (Grade III/IV) anemia was observed in 19%, neutropenia in 62% and thrombocytopenia in 25% patients. In non hematological toxicity 94% patients had anorexia, 100% had nausea/ vomiting, 75% developed mucositis, 88% had radiation dermatitis and 94% had alopecia. Severe nonhematological toxicity included anorexia in 6%. A total of 62% patients required GCSF for > grade II neutropenia. Only 3 (20%) patients required RBC transfusion and one needed platelet support. None of the patients died of treatment related toxicity. At the end of CRT, 67% have achieved complete remission, 20% have good partial remission and remaining 13% have stable disease.
Conclusion: Concomitant CRT in PCET is feasible, safe, with manageable toxicities and can be given on out patient basis. We need to evaluate whether the promising early response translates in to long term benefit.

2524 POSTER

A treatment results comparison of: whole brain radiation therapy (WBRT), radiosurgery (SRS) and combination both method WBRT + SRS used for patients suffering from brain metastases

E. Wolny, B. Jochymek, L. Miszczyk. *Institute of Oncology, Department of Radiotherapy, Gliwice, Poland*

Purpose: An evaluation of overall survival time (OST) of patients with brain metastases after 3 modalities treatment: whole brain radiotherapy – WBRT, radiosurgery – SRS and combination of both – WBRT + SRS and an assessment of some prognostic factors.
Materials and Methods: 200 patients (132 men and 68 women, age 31−74) suffering from brain metastases, treated with WBRT, SRS or WBRT + SRS between April 1998 and April 2004. 82 patients had solitary cerebral metastasis (subgroup 1), 70 patients – 2 to 3 metastases (subgroup 2) and 48 patients – 3 or more metastases (subgroup 3). In subgroup 1, 28 patients underwent WBRT, 41 patients SRS and 13 – WBRT + SRS. In subgroup 2, 28 – WBRT, 29 – SRS and 13 – WBRT + SRS. In subgroup 3, 48 patients had only WBRT.
The volume of solitary lesion was within the range from 0.5 cm^3 to 90 cm^3. SRS was performed using linear accelelator (dose ranged from 12 to 20 Gy) and WBRT was performed delivering five 4 Gy fractions. Median survivals were estimated using Weibull regression and Cox model.
Results: With the combination of the two methods – WBRT and SRS for subgroups 1 and 2 doubled OST was obtained in comparison to application one of these methods alone ($p = 0.003$). The influence of number metastases (1 vs more) on overall survival was confirmed ($p = 0.03$). The increase of tumor volume about 1 cm^3 enhanced failure risk of 1.2% (SD 0.54%). For solitary brain metastasis in capacity of $\leqslant$1 cm^3 and $\geqslant$10 cm^3 the statistically significant difference was obtained ($p = 0.05$). Survival of patients in subgroups 1 and 3 (aged <60 and $\geqslant$60) was statistically significant ($p = 0.02$).
Conclusion: The combination of both methods, WBRT + SRS, gives better results (survival) than these methods applied individually. The most important prognostic factors influence on OST of patients with brain metastases are: number and volume of metastases and age of patients.

Gastrointestinal Malignancies

Oral presentations (Tue, 25 Sep, 09.00−11.15)

Gastrointestinal malignancies – colorectal cancer (1)

3000 ORAL

Randomised phase III study of capecitabine, oxaliplatin and bevacizumab (CAPOX-B) with or without cetuximab in advanced colorectal cancer (ACC), the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). An interim safety analysis

J. Tol[1], M. Koopman[1], C.J. Rodenburg[2], A. Cats[3], G.J. Creemers[4], C.A.M. de Swart[5], F.L.G. Erdkamp[6], L. Mol[7], N.F. Antonini[8], C.J.A. Punt[1]. *[1]University Medical Centre St Radboud, medical oncology, Nijmegen, The Netherlands; [2]Meander Medical Centre, internal medicine, Amersfoort, The Netherlands; [3]The Netherlands Cancer Institute, Gastroenterology and Hepatology, Amsterdam, The Netherlands; [4]Catharina Hospital, internal medicine, Eindhoven, The Netherlands; [5]Spaarne Hospital, internal medicine, Hoofddorp, The Netherlands; [6]Maasland Hospital, internal medicine, Sittard, The Netherlands; [7]Comprehensive Cancer Centre East, (IKO), Nijmegen, The Netherlands; [8]The Netherlands Cancer Institute, biometrics, Amsterdam, The Netherlands*

Background: Cetuximab, a chimaeric Moab against the EGFR, has shown efficacy in ACC. However, no data are available on its combination with chemotherapy and bevacizumab (B) in 1st line. Recently a study with panitumumab, a human anti-EGFR, in combination with chemotherapy plus B was discontinued due to toxicity and decreased survival. We here present an interim safety analysis on a phase III study evaluating the efficacy of adding cetuximab to CAPOX-B.
Methods: 755 previously untreated ACC patients (pts) were randomised between CAPOX-B (arm A) and CAPOX-B plus cetuximab (arm B) between June 2005 and Dec 2006. Toxicity during the first 9 treatment cycles in the first 400 pts was evaluated.
Results: 381 pts were eligible and evaluable for toxicity (195 pts in arm A and 186 pts in arm B). The overall incidence of grade 3−4 toxicity in arms A and B was 66% and 76%, respectively ($p = 0.12$). Toxicity as the main reason for treatment discontinuation occurred in 65 pts (18%), 30 pts (15%) in arm A and 35 pts (19%) in arm B ($p = 0.70$). Grade 3−4 toxicities in arm A versus B were: hand–foot syndrome 12% vs 13% (grade 2: 14% vs 20%), diarrhoea 16% vs 23%, vomiting 7% vs 6%, febrile neutropenia 1% vs 0%, hypertension 4% vs 2%, cardiovascular events 4% vs 3% (myocardial ischemia 1% vs 2% and cerebrovascular ischemia 1% vs 0%), thromboembolic events 5% vs 7%, allergic reactions 3% vs 6%, and gastrointestinal perforations 2% vs 1%, with none of these differences

being statistically significant. When toxicity of all grades was considered, hypertension occurred in 25% vs 17% (p = 0.06), hypomagnesemia 10% vs 32% (p < 0.001), infections 32% vs 28% (p = 0.36) and hypersensitivity reactions 11% vs 19% (p = 0.03). Grade 2 or higher proteinuria was observed in 5% vs 3% (p = 0.86). In arm B, the incidence of all grade and grade 3−4 acneiform skin reactions was 80% and 20%, and all grade and grade 3−4 nail changes 27% and 4%, respectively. These toxicities did not occur in arm A (p < 0.001). The overall 60-day all-cause mortality was 3% (10 pts), 5 pts in each arm. A total of 17 patients died within 30 days after the last administration of study drugs (8 arm A and 9 arm B), of which a drug-related cause was evident in 3 pts in arm A.
Conclusions: Toxicity was acceptable in both treatment arms. Except for skin toxicity due to cetuximab no difference in the incidence of other grade 3−4 toxicities was observed between the two treatment arms. Updated results will be presented at the meeting.

3001 ORAL

CRYSTAL, a randomized phase III trial of cetuximab plus FOLFIRI vs. FOLFIRI in first-line metastatic colorectal cancer (mCRC)

E. Van Cutsem[1], G. Bodoky[2], J. Kyung Roh[3], G. Folprecht[4], Y.S. Park[5], J.L. Van Laethem[6], J.L. Raoul[7], F. Ciardiello[8], P. Lebrun[9], P. Rougier[10].
[1]University Hospital Gasthuisberg, Department of Gastroenterology, Leuven, Belgium; [2]Fovarosi Onkormanyzat Szent Laszlo Korhaza, Oncology Department, Budapest, Hungary; [3]Yonsei Medical Center, Oncology, Seoul, South Korea; [4]Universitaetsklinikum Carl Gustav Carus, Medizinische Klinik I, Dresden, Germany; [5]Samsung Medical Center, Oncology, Seoul, South Korea; [6]Erasme Hospital, Gastroenterology, Brussels, Belgium; [7]Centre Eugene Marquis, Gastrointestinal Oncology, Rennes, France; [8]Second University of Naples, Medical Oncology, Naples, Italy; [9]Merck Sante, Clinical R&D, Paris, France; [10]Hopital Ambroise Pare, Oncology, Boulogne, France

Background: Cetuximab (Erbitux®), an IgG1 monoclonal antibody targeting the epidermal growth factor receptor (EGFR), is active in combination with irinotecan in previously-treated mCRC patients (pts). FOLFIRI is a standard first-line treatment for mCRC. The CRYSTAL trial investigated the effectiveness of cetuximab in combination with FOLFIRI as compared to FOLFIRI alone in first-line treatment of pts with EGFR-expressing mCRC.
Material and Methods: Pts were randomized 1:1 to Group A: cetuximab (400 mg/m^2 initial dose then 250 mg/m^2/week [w]) plus FOLFIRI q 2 w (irinotecan 180 mg/m^2, FA 400 mg/m^2, 5-FU bolus 400 mg/m^2, 5-FU infusion 2400 mg/m^2 over 46 hours) or Group B: FOLFIRI alone. The primary endpoint was progression-free survival (PFS). Secondary endpoints included: overall survival, response rate (RR), disease control rate and safety. PFS and RR were assessed by an Independent Review Committee. 633 events were required to statistically differentiate PFS between groups with 80% power.
Results: 1217 pts were randomized from August 2004 to October 2005: 608 to Group A and 609 to Group B. In the Intent to treat population: 60% were male, median age 61 [19−84], ECOG performance status <2 = 96.5%. The addition of cetuximab significantly prolonged progression free survival HR = 0.85, 95% CI [0.726, 0.998], p < 0.05). In a subgroup analysis of Group A pts, PFS was correlated to the grade of acne-like rash. RR was significantly increased by cetuximab (46.9% vs. 38.7%, p < 0.005). Significantly more pts underwent complete (R0) resection of metastases in Group A (4.3%) than in Group B (1.5%) p = 0.0034. Treatment was generally well tolerated with neutropenia (26.7% Group A, 23.3% Group B), diarrhea (15.2% and 10.5% respectively) and skin reactions (18.7% and 0.2% respectively) as the most common grade 3/4 adverse events.
Conclusions: Cetuximab in combination with FOLFIRI significantly prolongs PFS in previously untreated patients with mCRC, reducing the relative risk of progression by approximately 15%, and significantly increases response and resection rates. Treatment-related side effects of cetuximab in combination with FOLFIRI were as expected, with diarrhea moderately, and skin reactions significantly, more frequent as compared to FOLFIRI alone.

3002 ORAL

Comprehensive assessment of molecular markers predicting response to cetuximab therapy in colorectal cancer

F. Cappuzzo[1], G. Finocchiaro[1], P.A. Janne[2], W.A. Franklin[3], K. Bencardino[4], L. Crinò[5], M. Roncalli[1], C. Carnaghi[1], A. Santoro[1], M. Varella-Garcia[3]. *[1]Istituto Clinico Humanitas-IRCCS, Oncology, Rozzano Milano, Italy; [2]Dana Farber Cancer Institute, Oncology, Boston, USA; [3]Colorado Cancer Center, Oncology, Aurora, USA; [4]Policlinico S. Matteo, Oncology, Pavia, Italy; [5]Policlinico Monteluce, Oncology, Perugia, Italy*

Background: In colorectal cancer, biological mechanisms underlying response or resistance to cetuximab, a monoclonal antibody against the extracellular domain of the Epidermal Growth Factor Receptor (EGFR) are not defined. Small retrospective studies suggested that EGFR increased gene copy number measured by fluorescence in situ hybridization (FISH) or presence of KRAS mutations were associated with cetuximab response or resistance, respectively. This study aimed to identify biological predictors for sensitivity/resistance to cetuximab treatment in colorectal cancer. We also compared biomarker results in primary tumors and corresponding metastases.
Methods: We analyzed EGFR (IHC, FISH), HER2 (FISH), and KRAS (mutation) in paraffin embedded tumor blocks from 85 colorectal cancer patients treated with cetuximab.
Results: EGFR FISH positive patients (48.2%), defined as ratio EGFR/nucleus $\geqslant$3, had a significantly higher RR (p = 0.007) and TTP (p = 0.056) than EGFR FISH negative (51.8%). EGFR expression assessed by IHC was no associated with any clinical end-point. HER2 amplification (4.9%) and high polysomy (14.6%) were not associated with response but were significantly associated with a shorter time to progression (p = 0.01) and survival (p = 0.03). KRAS mutation carriers (39.5%) had a significantly lower response rate (p = 0.02) and shorter time to progression (p = 0.07) compared to patients with wild type KRAS. Combination of EGFR FISH and KRAS identified the group of patients deriving respectively the highest response rate (40.0%: EGFR FISH+/KRAS wild type) and the lowest response rate (0%: EGFR FISH-/KRAS mutated) from the treatment.
In 22 patients with available primary and metastatic tumor tissue, there was no difference between these sites for EGFR FISH, HER2 FISH and KRAS results.
Conclusions: Combination of EGFR FISH and KRAS mutation should improve the detection of responder and refractory patients candidate for cetuximab therapy. HER2 genomic gain predicts early escape from cetuximab therapy. Prospective validation of these results is warranted.

3003 ORAL

Cetuximab plus irinotecan in patients (pts) with metastatic colorectal cancer (mCRC) failing prior oxaliplatin-based therapy: the EPIC trial

W. Scheithauer[1], A. Sobrero[2], H.J. Lenz[3], J. Maurel[4], M. Lutz[5], G. Middleton[6], M. Saleh[7], A. Zubel[8], K. Williams[9], H.A. Burris III[10].
[1]Vienna University Medical School, Department of Internal Medicine, Vienna, Austria; [2]Ospedale San Martino, Medical Oncology, Genova, Italy; [3]USC Norris Cancer Center, Oncology, Los Angeles CA, USA; [4]Hospital Clinic i Provincial de Barcelona, Oncology, Barcelona, Spain; [5]Caritasklinik St Resia, Oncology, Saarbruecken, Germany; [6]Royal Surrey Hospital, St Lukes Cancer Centre, Guildford, United Kingdom; [7]Georgia Cancer Specialists, Oncology, Tucker GA, USA; [8]Merck KGaA, Medical Sciences Oncology, Darmstadt, Germany; [9]Bristol-Myers-Squibb, Oncology, Wallingford CT, USA; [10]The Sarah Cannon Research Institute, Oncology, Madison TN, USA

Background: Cetuximab, an IgG1 MAb targeting the EGFR, is active in irinotecan-refractory mCRC in combination with irinotecan. The multinational, randomized, phase III trial, EPIC, was designed to demonstrate the impact of cetuximab on survival in pts with EGFR-expressing mCRC failing prior oxaliplatin and fluoropyrimidine therapy. The primary objective was overall survival (OS). Secondary objectives included progression-free survival (PFS), overall response rate (RR), safety and quality of life (QoL).
Methods: Pts with ECOG PS $\leqslant$ 2, were randomized to Arm A (cetuximab 400 mg/m^2 initial dose, then 250 mg/m^2 weekly and irinotecan 350 mg/m^{2}q 3 weeks) or Arm B (irinotecan 350 mg/m^2 q 3 weeks). Health Related Quality of Life (HRQoL) was assessed using the EORTC QLQ-C30 questionnaire.
Results: 1298 pts were randomized (648 to Arm A and 650 to Arm B): 62.9% pts male, median age 62 years, and 94% had an ECOG PS of 0−1. Efficacy (OS, PFS, RR) is shown in the table. 47% pts in Arm B received post-study cetuximab (87% of these in combination with irinotecan). Median OS in Arm A was found to be correlated to the presence of acne-like rash: gr 0: 5.8 mo, gr 1/2: 11.7 mo, gr 3/4: 15.6 mo. The most common grade 3/4 adverse events (AEs) were neutropenia (31.8% Arm A, 25.4% Arm B) and