6106 POSTER

Immune-boost Treatment With Gemcitabine, Oxaliplatin, Levofolinate, 5-flurouracil, Granulocyte/macrophage Colony-stimulating-factor (GM-CSF) and Aldesleukine Enhances Progression-free and Overall-survival Over FOLFOX Chemotherapy in Metastatic Colorectal Cancer Patients − Early Results From the GOLFIG-2 Phase III Trial

P. Correale[1], M.S. Rotundo[2], C. Botta[1], A. Guglielmo[1], A. Licchetta[1], R. Conca[1], P. Tassone[2], R. Ridolfi[3], E. Mini[4], P. Tagliaferri[2]. [1]*"S. Maria alle Scotte" Siena University Hospital, Department of Oncology, Siena, Italy;* [2]*Magna Græcia University and Tommaso Campanella Cancer Center Catanzaro, Medical Oncology, Catanzaro, Italy;* [3]*"Morgagni-Pieranton" Hospital of Forlì, Oncology Unit, Forlì, Italy;* [4]*"Careggi" University Hospital of Florence, Department of Preclinical and Clinical Pharmacology, Florence, Italy*

Background: Previous translational studies demonstrated the safety, the immunological and anti-tumour activity of a newest chemo-immunotherapy boost with gemcitabine + FOLFOX followed by sc. GM-CSF and low dose aldesleukine (GOLFIG regimen) in largely pretreated metastatic colorectal cancer (mCRC) patients. We designed a phase III trial to compare the efficacy of this regimen with standard FOLFOX-4 chemotherapy in frontline treatment of mCRC.
Material and Methods: GOLFIG/2 is a multicenter open label/randomized phase III trial (EUDRACT#457/05) designed test the hypothesis of a two months advantage of GOLFIG over FOLFOX-4 regimen in term of progression-free-survival (PFS). Patients were randomized in a 1:1 ratio in the two arms to receive FOLFOX-4 or GOLFIG regimen [gem-citabine (1000 mg/m^2, day-1); oxaliplatin (85 mg/m^2, day-2); levofolinate (100 mg/m^2, days 1−2), 5-FU (400 mg/m^2 in bolus followed by 24 h infusion at 800 mg/m^2, days 1−2), sc. GM-CSF (100 μg, days 3−7); sc. aldesleukine (0.5 MIU bi-daily, days 8−14)]. Kaplan–Meier, Log-rank test and cox analysis were used for statistical comparisons.
Results. The study was prematurely terminated on January 2010 for outcome imbalance in favor of the experimental arm at the first preplanned interim analysis at 130 patients. No differences were observed in term of frequency of adverse events, with the exception of a higher frequency of fever, and self-limiting signs of autoimmunity in experimental arm. The GOLFIG regimen showed significant superiority over FOLFOX in term of response-rate [63.1 vs. 33.8%, P = 0.001], PFS [16.5 (95% CI;11.18–21.81) vs. 7.43 (95% CI;5.72–9.15) months, P = 0.001; HR = 0.372, P < 0.001] and overall-survival (OS) [30.51 (95% CI 22.86–38.16) vs. 21.51 (95% CI 16.17–26.84) months, P = 0.049; HR = 0.37, P = 0.001]. Several treatment-related changes in different lymphocyte subsets and myeloid-lineage cells were observed in patients enrolled in the GOLFIG arm, however, none of these was predictive of positive outcome with exception of a baseline neutrophil-count ⩽5,500 cell/μl (HR = 3.693 in term of OS, P = 0.001). In this group of patients, sex, age, primary tumour and metastatic sites, histotype, grading and k-ras-status did not achieve statistical predictive value.
Conclusion: The results of this trial provide the first proof of efficacy for a chemo-immunological regimen as first line treatment of mCRC.

6107 POSTER

Improved Overall Survival in the Patients With Metastatic Colorectal Cancer Associated With Ant-VEGF Antibody Drug and Anti-EGFR Antibody Drug Administration

T. Denda[1], N. Nakamura[1], K. Sudo[1], K. Nakamura[1], K. Minashi[2], S. Hironaka[2], T. Hara[3], H. Soda[4], N. Takiguchi[4], T. Yamaguchi[1]. [1]*Chiba Cancer Center Hospital, Division of Gastroenterology, Chiba, Japan;* [2]*Chiba Cancer Center Hospital, Department of Cllinical Trial Promotion, Chiba, Japan;* [3]*Chiba Cancer Center Hospital, Division of Endoscopy, Chiba, Japan;* [4]*Chiba Cancer Center Hospital, Division of Gastroenterological Surgery, Chiba, Japan*

Background: In Japan, new anti-cancer drug oxaliplatin was approved for the treatment of metastatic colorectal cancer (CRC) in 2005. Subsequently, anti-vascular endothelial growth factor (VEGF) antibody bevacizumab was approved in 2007, anti-Epidermal growth factor receptor (EGFR) antibody cetuximab in 2008, and anti-EGFR antibody panitumumab in 2010. Indirect evidence suggests that the introduction of anti-VEGF antibody drug and anti-EGFR antibody drugs is improving patient-outcomes; however, the gain has not yet been quantified.
Material and Methods: We performed a retrospective review of patients newly diagnosed with metastatic CRC treated at our institution from 2005 to 2010. Landmark analysis evaluated the association between diagnosis year and administration of molecular-targeted drugs with overall survival.
Results: Three hundred eighty patients who were diagnosed with metastatic CRC received primary treatment at our institution during this period. The median overall survival for patients diagnosed from 2005 to 2011 was 27.9 months that appeared to increase over time and was 25.7 and 28.8 months for patients diagnosed from 2005 to 2006 and 2007 to 2008, respectively. The median survival had not yet been reached for those diagnosed from 2009 to 2011. There were significant differences ($p < 0.05$) between each time period. The rate of bevacizumab use among patients diagnosed from 2005 to 2011 was 51%; it was 39%, 67%, and 78% among patients diagnosed from 2005 to 2006, 2007 to 2008, and 2009 to 2011, respectively, showing a gradual increase. The rate of anti-EGFR antibody use among patients diagnosed from 2005 to 2011 was 24%; it was 20%, 36%, and 17% among patients diagnosed from 2005 to 2006, 2007 to 2008, and 2009 to 2011, respectively, not showing a gradual increase. Thus, the improved outcomes from 2005 to 2011 appeared to be as a result of increased bevacizumab administration.
Conclusions: Profound improvements in outcomes in metastatic CRC appear to be associated with increased bevacizumab administration at present. If more patients with K-ras wild type CRC will be administered with anti-EGFR antibody drugs, there is a possibility of improvement of overall survival of patients with CRC.

6108 POSTER

Adjuvant Chemotherapy for Colon Cancer in the Netherlands: Who Are We Treating Actually?

N. van Leersum[1], K. van der Hoeven[2], R. Tollenaar[3], M. Wouters[4]. [1]*Leiden University Medical Center, Surgery K6−50, Leiden, The Netherlands;* [2]*Medisch Centrum Alkmaar, Surgery, Alkmaar, The Netherlands;* [3]*Leiden University Medical Center, Surgery, Leiden, The Netherlands;* [4]*Antonie van Leeuwenhoek, Surgery, Amsterdam, The Netherlands*

Background: According to Dutch guidelines, chemotherapy should be considered in all patients with stage III and high-risk stage II colon carcinoma. The definition of high-risk stage II and the benefit of chemotherapy for these patients is subject of debate in literature. In an ageing population with a large number of patients with comorbid conditions, weighing of the risks and benefits of adjuvant chemotherapy may therefore lead to less use of chemotherapy. We evaluated the use of adjuvant chemotherapy in the Netherlands.
Materials and Methods: Analysis was based on data of 11.000 patients with primary colon cancer enrolled in the Dutch Surgical Colorectal Audit between 2009–2010. Multivariate logistic regression was performed on the risk of not applying adjuvant chemotherapy in patients in who treatment is indicated.
Results: 3391 patients had stage III (31%) and 1507 patients had high risk stage II colon carcinoma (14%). Mean age was 71 years and 19% had substantial concomitant disease (Charlson >1). Chemotherapy was administered in 59% of patients with stage III and 18% of patients with high risk stage II. In patients aged over 80 years with high risk stage II, only 2% received chemotherapy. The most recognized risk factor in stage II patients was T4 tumour, treated with chemotherapy in 30% of patients. Only a quarter of patients with stage III disease who did not receive chemotherapy had substantial comorbidity. In multivariate analysis, age was most frequently associated with lower probability of receiving chemotherapy (OR 25.1). The correlation with both ASA score IV-V and Charlson score >1 was less robust (resp. OR 3.8 and OR 1.6). Severe complications after surgery had a substantial contribution (OR 2.2) to the risk of not receiving chemotherapy as well.
For patients younger than 75 years with stage III, a large variation in administration of chemotherapy between individual hospitals was observed, ranging from 18 to 89% in the whole group and from 18 to 100% in patients with only minor comorbidities (ASA I-II or Charlson 0−1).
Conclusions: In the Netherlands, high-risk stage II colon cancer is not always recognized as an indication for adjuvant chemotherapy. Age seems a more important factor than comorbidity when considering chemotherapy. This may imply undertreatment of a large group of healthy old patients, who might benefit from chemotherapy. There is large variation in the use of chemotherapy between hospitals, even in patients with a favourable casemix.

6109 POSTER

Difference in Overall Survival in Colorectal Cancer Patients With the KRas P.G13D and Other KRas Mutations After the Failure of 5-fluorouracil, Oxaliplatin, and Irinotecan

K. Suyama[1], T. Yoshino[2], Y. Kawamoto[2], H. Bando[2], T. Doi[2], H. Baba[3], A. Ohtsu[2]. [1]*National Cancer Center Hospital East, Medical Oncology, Kashiwa Chiba, Japan;* [2]*National Cancer Center Hospital East, GI Oncology, Kashiwa Chiba, Japan;* [3]*Kumamoto University, Gastroenterological Surgery, Kumamoto, Japan*

Background: Metastatic colorectal cancer (mCRC) patients with *KRAS* codon 12 or 13 mutations are currently not treated with cetuximab (Cmab).

Recent studies have shown that patients with *KRAS* p.G13D mutations treated with Cmab have longer overall survival (OS) and progression-free survival (PFS) than patients with other *KRAS* mutations. Cmab might also have therapeutic benefits in CRC patients with the *KRAS* p.G13D mutation (Bando H, Gastrointestinal Cancers Symposium, 2011). Survival estimates in patients with the p.G13D mutation not treated with anti-epidermal growth factor receptor (EGFR) antibodies from another cohort were necessary, because only the National Cancer Institute of Canada (NCIC) CO.17 study, which suggested that CRC patients with the *KRAS* p.G13D mutation have a worse prognosis than those with other *KRAS* mutations, provides survival data as reference.

Methods: From 2008 to 2010, we selected 47 consecutive patients with the *KRAS* mutant mCRC that had been refractory to 5-fluorouracil (5-FU), oxaliplatin, and irinotecan; these patients had never received anti-EGFR antibodies. We retrospectively assessed the OS according to the *KRAS* mutational status (p.G13D versus other mutations). The relationship between the *KRAS* mutational status and OS were evaluated using the log-rank test.

Results: Among these patients, 12 and 35 had the *KRAS* p.G13D and other *KRAS* mutations, respectively. The baseline characteristics of each subset were not remarkably different. OS was not remarkably different between the p.G13D and other mutations (hazard ratio, 1.10; p = 0.79). In addition, OS curves divided by the major genotypes were not different in G12D (n = 15), G12S (n = 8), G12V (n = 7), and G13D.

Conclusions: It suggested there was no remarkable difference of survival between CRC patients with the p.G13D and other *KRAS* mutations after the failure of 5-FU, oxaliplatin, and irinotecan. These results were different from those of the NCIC CO.17 study. Our results may serve as reference data for further clinical trials on the therapeutic effect of Cmab in CRC patients with the *KRAS* p.G13D mutation.

6110 POSTER

Combination Chemotherapy With Capecitabine (C), Irinotecan (I) Oxaliplatin (O) and Bevacizumab (B) (XELOXIRIA) as First Line Treatment of Metastatic Colorectal Cancer (MCRC) − Preliminary Results of a Phase I-II Trial

S. Bazarbashi[1], A. Aljubran[1], H. Soudy[1], A. Alzahrani[1], A. Darwish[1], A. Eltaigani[1], M. Nabil-Ahmed[1], W. Edesa[1], M. Shoukri[2]. [1]*King Faisal Specialist Hospital and Research Centre, Oncology Center, Riyadh, Saudi Arabia;* [2]*King Faisal Specialist Hospital and Research Centre, Biostatistics Epidemiology and Scientfic Computing, Riyadh, Saudi Arabia*

Background: FOLFOXIRI has been shown to be superior to FOLFIRI with respect to response rate and survival in patients (pts) with metastatic colorectal cancer (mCRC). Capecitabine has the advantage over 5-Flourouracil of the convenience of oral administration and possibly lower toxicity.

Materials and Methods: We conducted a prospective phase I-II study in pts with mCRC to determine the Maximum Tolerable Dose (MTD) and the efficacy of fixed dosed of Capecitabine (C), Oxaliplatin (O) and Bevacizumab (B) in combination of escalating doses of Irinotecan (I). The planned treatment in the first 3 pts was: I 150 mg/sqm over 90 min on day 1, O 130 mg/sqm over 2-h on day 1, C 2,000 mg/sqm/day from day 1 to 14, and Bevacizumab 7.5 mg/kg over 30 min on day 1. Cycles repeated every 3 weeks. I dose was increased to 200 mg/sqm or C dose was decrease to 1300 mg/sqm/day in subsequent groups of 3 pts on the basis of the observed dose limiting toxicities (DLT). We report here the result of the first 30 patients.

Results: Pts characteristic are: sex (M/F) = 18/12, PS (0/1/2) = 3/22/5, age (median/range) = 51/24−73 years, sites of disease (single/multiple) = 10/20. The DLT was G3−4 diarrhea that was observed in 2 out of 3 pts receiving I at 200 mg/sqm, The I recommended dose was 150 mg/sqm which continued as phase II trial. Grade 3−4 toxicities were: nausea and vomiting 21.4%, diarrhea 41.4%, neutropenia 20.6%, thrombocytopenia 3.4%, febrile neutropenia 14.3%, fatigue 17.9%, acute hypersensitivity reaction 3.4%. Response evaluation was done according to ITT analysis. 6 Pts were not assessable for response because of 2 or less cycles of chemotherapy (3 consent withdrawal, 2 grade 4 toxicity, one toxic death). One CR, and 12 PR were observed for an overall response rate of 43% (95% CI: 26−60%). Nine had SD and 2 progressed. Relative dose intensity for C was 0.78; for O was 0.91 and for I was 0.91. At a median follow-up of 12 months median progression free survival (PFS) was 18.3 months and median overall survival was not reached.

Conclusion: These results demonstrate that this combination is toxic at the recommended dose, with diarrhea being the dose limiting toxicity. Recruitment continues with reduction in C dose to 800 mg. This combination has significant antitumour activity in advanced CRC and encouraging PFS.

6111 POSTER

Combining Capecitabine, Oxaliplatin and Gemcitabine (XELOXGEM) for Colorectal Carcinoma Patients Pretreated With Irinotecan − a Multicenter Phase I/II Trial

S.H. Kim[1], S.J. Shin[1], S.Y. Kim[2], S.H. Lee[3], Y.S. Park[3], K.H. Lee[4], T.W. Kim[5], Y.S. Hong[5], J.B. Ahn[1]. [1]*Yonsei Cancer Center Yonsei University College of Medicine, Department of Internal Medicine, Seoul, South Korea;* [2]*Research Institute and HospitalHospital National Cancer Center, Center for Colorectal Cancer, Gyeonggi-do, South Korea;* [3]*Samsung Medical Center, Division of Hematology-oncology Department of Medicine, Seoul, South Korea;* [4]*College of Medicine Yeungnam university, Department of Hematology-Oncology, Daegu, South Korea;* [5]*Asan Medical Center, Department of Oncology, Seoul, South Korea*

Background: Capecitabine plus oxaliplatin (XELOX) is an effective second-line regimen for advanced colorectal carcinoma (CRC) patients pretreated with irinotecan. Previous studies have shown supra-additive anti-tumour activity of gemcitabine (GEM) when administered with oxaliplatin. We investigated the dose, toxicity, and efficacy of a second-line XELOXGEM regimen in CRC patients pretreated with irinotecan.

Patients and Methods: Patients with metastatic or recurrent CRC who failed after a first-line irinotecan-containing regimen received escalating doses of gemcitabine (600, 800, 1000 mg/m^2 d1, d8) followed by capecitabine (1000 mg/m^2 b.i.d d1−14) and oxaliplatin (100 mg/m^2 d1) on a 21-day cycle.

Results: A total of 38 patients were treated. At 800 mg/m^2, two of six patients experienced dose-limiting toxicities (diarrhea and thrombocytopenia). Therefore, the clinically recommended dose was defined as 600 mg/m^2 gemcitabine (d1, d8) followed by 1000 mg/m^2 capecitabine (b.i.d d1−14) and 100 mg/m^2 oxaliplatin (d1). The most common grade 3/4 toxicities were neutropenia (32%), thrombocytopenia (13%), anemia (11%) and peripheral neuropathy (11%). Ten (26.3%) and 23 (60.5%) patients experienced partial response and stable disease, respectively. The median progression-free survival and overall survival were 5.4 months (95% CI 3.8–6.9 months) and 17.7 months (95% CI 8.4–26.9 months), respectively.

Conclusions: The XELOXGEM triplet combination is an active and safe second-line regimen for advanced CRC patients pretreated with irinotecan.

6112 POSTER

Health-related Quality of Life at 12 Months in Patients With Metastatic Colorectal Cancer (mCRC) Initiating a Treatment With Bevacizumab (Bv) Plus Chemotherapy (CT) − Results From the CONCERT French Non Interventional Study

M. Ducreux[1], J.M. Phelip[2], T. André[3], B. Asselain[4], H. Senellart[5], W. Younes[6], S. Kraemer[7], J. Bennouna[5]. [1]*Institut Gustave Roussy, Digestive Oncology, Villejuif, France;* [2]*CHU de Saint Etienne, Medical Oncology, Saint Etienne, France;* [3]*Hôpital Pitié Salpêtrière, Medical Oncology, Paris, France;* [4]*Institut Curie, Biostatistics, Paris, France;* [5]*Centre René Gauducheau, Medical Oncology, Saint Herblain, France;* [6]*Laboratoires Roche, Oncology, Paris, France;* [7]*Laboratoires Roche, Biostatistics, Paris, France*

Background: Chemotherapy and targeted treatments can impact Health-Related Quality of Life (HRQoL) in cancer patients (pts). HRQoL is an increasingly important endpoint measured in clinical trials in mCRC pts who are now living longer, to assess treatment outcomes and improve mCRC care.

Patients and Methods: This prospective, multicenter, non-interventional cohort study assessed pts with mCRC initiating a treatment with Bv plus CT (all lines) in daily medical practice in France and followed-up for 36 months. Changes in HRQoL, a secondary efficacy endpoint of CONCERT, were assessed using the QLQ-C30 questionnaire at baseline, 6 and 12 months of follow-up.

Results: Of the 765 evaluable patients included in the cohort, 435 (60%) were men, median age 66 years (25−88), ECOG score of 0 or 1 (90%). HRQoL was assessed in 133 pts (17%) who completed the questionnaire at M1 and M12 (100 in 1st line, 23 in 2nd line and 10 in 3rd line), their profile was comparable to the whole population. Mean Global health QoL at 12-months from baseline was −1.6 points. Mean score differences for functional and symptom scale scores between baseline and 12 months are shown in the table.

Conclusion: Compliance to HRQoL questionnaires was low in a real life setting. Use of bevacizumab and chemotherapy treatments in clinical practice routine seems to be associated with no clinically significant changes and no deterioration in HRQoL scores in patients with mCRC.