

ESMO 2008 late-breaking abstracts

LBA1 **BO17704 (AVAIL): A PHASE III RANDOMISED STUDY OF FIRST-LINE BEVACIZUMAB COMBINED WITH CISPLATIN/GEMCITABINE (CG) IN PATIENTS (PTS) WITH ADVANCED OR RECURRENT NON-SQUAMOUS, NON-SMALL CELL LUNG CANCER (NSCLC)**

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Background: The E4599 study showed that addition of bevacizumab (Bev) to carboplatin/paclitaxel improved overall (OS) and progression-free survival (PFS) in pts with advanced NSCLC [Sandler et al. NEJM 2006]. Study BO17704 evaluated the efficacy and safety of Bev plus CG in pts with advanced NSCLC.

Methods: BO17704 was a double-blind trial that randomised 1,043 pts to C 80mg/m² (d1) and G 1,250mg/m² (d1 and d8) q3w for up to 6 cycles plus either Bev 7.5mg/kg q3w (n=345), Bev 15mg/kg q3w (n=351) or placebo (n=347). Bev/placebo was administered until disease progression (PD). Primary endpoint was PFS; secondary endpoints included OS, response rates, duration of response and safety. Key eligibility criteria: histologically or cytologically documented untreated locally advanced, metastatic or recurrent non-squamous NSCLC; ECOG PS 0/1; no CNS metastases and no tumours abutting or invading major vessels.

Results: The significant prolongation of the primary endpoint PFS in pts receiving Bev + CG previously reported [Manegold et al. ASCO 2007] was maintained with longer follow-up. The risk of progression or death was reduced by 25% with Bev 7.5mg/kg, and 15% with Bev 15mg/kg vs placebo (hazard ratio (HR) 0.75 (p=0.003) and 0.85 (p=0.046), respectively). Median OS was 13.1 months (mo) for CG alone, 13.6 mo for Bev 7.5mg/kg + CG (HR vs placebo 0.92, 95% CI 0.77–1.10) and 13.4 mo for Bev 15mg/kg + CG (HR 1.02, 95% CI 0.85–1.22). The majority of pts received subsequent therapy following PD, which was not pre-specified in the protocol and thus introduced an uncontrolled element to the OS analysis. No new safety signals were identified.

Conclusions: Longer follow-up confirms the significant improvement in PFS, the primary endpoint, with Bev combined with CG. The overall survival benefit did not reach statistical significance; however, administration of heterogeneous subsequent therapy may have hampered the detection of a significant difference. Together with E4599, BO17704 demonstrates that first-line Bev-based therapy provides important clinical benefits for pts with advanced or recurrent non-squamous NSCLC.

LBA2 **PHASE III, RANDOMISED, OPEN-LABEL, FIRST-LINE STUDY OF GEFITINIB (G) VS CARBOPLATIN/PACLITAXEL (C/P) IN CLINICALLY SELECTED PATIENTS (PTS) WITH ADVANCED NON-SMALL-CELL LUNG CANCER (NSCLC) (IPASS)**

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Introduction: This Phase III study compared efficacy, safety and tolerability of oral G vs C/P in clinically selected chemo-naïve pts in Asia with advanced NSCLC (IRESSA™ Pan Asia Study – IPASS).

Methods: Between Mar 06 and Oct 07, chemo-naïve, never or light ex-smokers with WHO PS 0-2, adenocarcinoma histology and stage IIIB/IV NSCLC were randomised to G 250 mg/day (n=609) or C (AUC 5 or 6)/P (200 mg/m²) (n=608). Primary objective was to assess non-inferiority of G vs C/P for PFS in ITT population.

Secondary endpoints were overall survival (OS), objective response rate (ORR, RECIST), QoL (FACT-L, TOI), symptom improvement (LCS subscale of FACT-L) and tolerability. Exploratory endpoints included association of efficacy with EGFR biomarkers.

Results: G demonstrated superior PFS compared with C/P (HR 0.74; 95% CI 0.65-0.85; p<.0001), exceeding the primary objective. Treatment effect was not constant over time, favouring C/P for first 6 mths and G for remaining 16 mths, potentially driven by differences in PFS outcomes for pts with EGFR mutation (M) + and M-tumours. ORR was significantly higher with G than C/P (43.0 vs 32.2%; odds ratio [OR] 1.59; 95% CI 1.25-2.01; p=.0001). Preliminary OS (37% maturity) was similar for G and C/P (HR 0.91; 95% CI 0.76-1.10; median OS 18.6 vs 17.3 mths); follow-up is ongoing. QoL improvement rates were significantly higher with G than C/P (FACT-L 48 vs 41%, OR 1.34, 95%, CI 1.06-1.69, p=.0148; TOI 46 vs 33%, OR 1.78, 95% CI 1.40-2.26, p<.0001); symptom improvement rates were similar (LCS 52 vs 49%; OR 1.13; 95% CI 0.90-1.42; p=.3037). Tolerability profile was more favourable with G. PFS was longer for G than C/P in M+ pts (HR 0.48; 95% CI 0.36-0.64; p<.0001) and longer with C/P than G in M- pts (HR 2.85; 95% CI 2.05-3.98; p<.0001).

Conclusions: This study demonstrated superior efficacy, higher QoL and similar symptom improvement rates and a more favourable tolerability profile for G in chemo-naïve, never or light ex-smokers in Asia with advanced NSCLC and adenocarcinoma histology compared with C/P. PFS favoured C/P initially and then G, potentially driven by different outcomes according to EGFR mutation status.

LBA3 **VICTOR: A PHASE III PLACEBO-CONTROLLED TRIAL OF ROFECOXIB IN COLORECTAL CANCER PATIENTS FOLLOWING SURGICAL RESECTION**

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Background: Laboratory and case-control studies suggest a pivotal role for the COX-2 pathway in colorectal carcinogenesis. The cyclo-oxygenase-2 inhibitor, rofecoxib (R) was hypothesised to improve survival in colorectal cancer (CRC) patients in the adjuvant setting.

Methods: This was a phase III randomised, placebo-controlled double-blind trial of R in patients after potentially-curative surgery and completion of adjuvant therapy for stage II/III CRC. 7000 patients were planned to receive 25mg R daily or an identical placebo (P) for 2 or 5 years, however the trial was terminated early after the worldwide withdrawal of R. A revised protocol and statistical analysis plan permitted detection of a reduction (HR=0.75) in risk of death with 87% power, with one pre-planned event-driven interim analysis. Genomic DNA was extracted from 939 VICTOR patients. Following characterization of linkage disequilibrium across the PTGS2 (COX-2) gene, sixteen variant SNPs were found, distributed across an extended genetic region with nine SNPs 5' to the start codon, one synonymous SNP in exon 3 (Val102Val), two intronic SNPs (introns 1 and 5) and four SNPs in the 3' untranslated region.

Results: 1167 patients received R and 1160 received P for median treatment durations of 7.4 months and 8.2 months respectively. Median follow-up was 3.0 and 3.1 years (R vs P), with 177 vs 191 deaths and 291 vs 316 recurrences. The pre-planned analyses demonstrated no difference in overall survival (OS), HR 0.94 (95% CI 0.77-1.16; p=0.57), or DFS, HR 0.91 (95% CI 0.78-1.07; p=0.25), comparing the two groups. Three SNPs, all 5' to the start codon of the gene, were associated with a positive treatment interaction (p=0.04) in favour of R.

Conclusions: In this study of truncated treatment duration, therapy with R is unlikely to have resulted in a substantial improvement in OS or in protection from recurrence of CRC. However, COX-2 genotyping might identify a subgroup of responsive patients. Kaplan Meier curves will be presented that demonstrate that patients harbouring these variant sequences benefit from treatment with rofecoxib in terms of disease-free survival whereas those with wild type at these loci do not.

LBA4 A RANDOMIZED PHASE III STUDY OF TRABECTEDIN WITH PEGYLATED LIPOSOMAL DOXORUBICIN (PLD) VERSUS PLD IN RELAPSED, RECURRENT OVARIAN CANCER (OC)

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Background: Phase II studies have demonstrated activity of Trabectedin (T) in OC. This is one of the largest studies designed to establish clinical activity of a non-platinum doublet in second-line OC.

Methods: Patients (pts) progressing after response to first line therapy and measurable disease were randomized to PLD 30 mg/m² over 60 min plus T 1.1mg/m² over 3 hrs q 3 wks or PLD 50 mg/m² q 4 wks. Approximately 650 patients were targeted to be enrolled to achieve the required 415 progression-free survival (PFS) events. The primary endpoint was PFS based on independent radiology review (IR) by RECIST. Pts were evaluated every 8 wks. PFS was analyzed using Kaplan-Meier curves and the log rank test.

Results: From April 2005 to May 2007 672 pts were enrolled. The clinical cut-off for final PFS analysis was 15 May 2008. Demographic characteristics were comparable between arms; median age: 57 yrs, platinum-free interval (PFI) >6 m: 64%. Median number of cycles: 5 for PLD and 6 for PLD + T. A total of 389 pts progressed by IR. Median PFS for PLD+T was 7.3m (95% CI 5.9-7.9) and for PLD 5.8m (95% CI 5.5-7.1), HR=0.79, p=0.019. For pts with a PFI > 6 m the median PFS was 9.2 m (95% CI 7.4-11.1) for PLD+T vs. 7.5m (95% CI 7.0-9.2) for PLD HR 0.73, p= 0.017. Response rate (RR) for all pts: 28% vs. 19% (p=0.008) and if PFI >6m: 35% vs. 23% p= 0.0042 by IR and 47% vs. 33% p=0.0022 by investigator, for PLD+T vs. PLD respectively. Interim survival (OS) at 300 deaths revealed: 20.5 m for PLD + T vs. 19.4 m for PLD, HR 0.85, p=0.15. There were 16 % of pts discontinued from PLD+T vs. 10% PLD, due to treatment related adverse events. Grade 3/4 adverse events included neutropenia: 63 vs. 22%, ALT: 31 vs. 1% and hand-foot syndrome: 4 vs. 20% for PLD + T vs. PLD respectively.

Conclusions: PLD+T is superior to PLD in both the primary endpoint PFS, and secondary endpoint of RR. Adverse events were managed with appropriate monitoring, dose adjustments and delays. This non-platinum doublet also demonstrates competitive efficacy compared to previously described platinum based doublets in platinum sensitive pts.

LBA5 A RANDOMISED TRIAL OF PROCARBAZINE, CCNU AND VINCRISTINE (PCV) VS TEMOZOLOMIDE (5-DAY OR 21-DAY SCHEDULE) FOR RECURRENT HIGH GRADE GLIOMA (MRC BR12, ISRCTN83176944)

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Background: Although temozolomide (TMZ) is frequently used in patients (pts) with recurrent high grade glioma (HGG), it has never been directly compared with PCV chemotherapy. Prolonged TMZ dosing and dose intensification have also been postulated to improve efficacy. We report the first randomised comparison of PCV vs TMZ sub-randomised between 5 vs 21 day schedule in chemo-naïve pts with recurrent HGG.

Methods: Patients with radiologically confirmed, recurrent HGG were randomised 2:1:1 to PCV, TMZ-5, and TMZ-21. The TMZ schedules were 200mg/m² for 5 days (TMZ-5) or 100mg/m² for 21 days (TMZ-21), both schedules repeated every 28 days for up to 9 cycles or until progression. PCV comprised procarbazine 100mg/m² po days 1-10, CCNU 100mg/m² po day 1 and vincristine 1.5mg/m² (max 2mg) iv day 1; cycles repeated every 6 weeks for up to 6 cycles or until progression. With an anticipated 500 pts (380 deaths) the trial was powered to detect a 2-3 month increase in median survival with TMZ, corresponding to hazard ratios (HR) of 0.75-0.67. In this intention-to-treat analysis HRs are presented with 95% confidence intervals and compared by the logrank test.

Results: 447 pts were randomised between 06/03 and 01/08; 382 died by 09/07/08; median follow-up of survivors is 12 months. The % of pts completing 9 months of treatment was 17% (PCV) 26% (TMZ-5) and 13% (TMZ-21). The % of pts with grade 3 or 4 toxicities was similar across all 3 groups. Primary comparisons: (1) Overall survival (OS): (PCV vs TMZ) median survival 6.7 months vs 7.2 months, HR=0.91 (0.74-1.11) p=0.350, (2) Progression-free survival (PFS) at 12 weeks: (TMZ-5 vs TMZ-21) 63.6% vs. 65.7%, p=0.745. Secondary outcome comparisons: (3) OS: (TMZ-5 vs TMZ-21) HR=1.32 (0.99, 1.75) p=0.056, (4) PFS: (TMZ-5 vs TMZ-21) HR=1.38 (1.04, 1.82) p=0.023, (5) PFS: (PCV vs TMZ) HR= 0.89 (0.73-1.08) p=0.229.

Conclusion: While TMZ did not show a clear benefit compared to PCV in patients with recurrent HGG, the comparison of the two TMZ schedules demonstrated that the apparently more intensive TMZ-21 regimen was inferior to TMZ-5. This challenges the current understanding of increasing TMZ dose intensity by prolonged scheduling.

LBA6 KRAS MUTATION STATUS IS A PREDICTIVE BIOMARKER FOR CETUXIMAB BENEFIT IN THE TREATMENT OF ADVANCED COLORECTAL CANCER - RESULTS FROM NCIC CTG CO.17: A PHASE III TRIAL OF CETUXIMAB VERSUS BEST SUPPORTIVE CARE

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Background: Cetuximab, a monoclonal antibody that targets the epidermal growth factor receptor (EGFR), improves overall survival (OS) and progression free survival (PFS) and preserves quality of life in patients with chemotherapy refractory advanced colorectal cancer (CRC). The K-ras mutation status of the tumour may predict which patients will optimally benefit from cetuximab in this setting. In addition, the prognostic significance of K-Ras mutation status is unclear.

Methods: CRC tumour samples were collected and analysed as part of a phase III clinical trial of cetuximab plus best supportive care (BSC) versus BSC alone (NEJM 2007; 357(20): 2040-8). Activating mutations in exon 2 of the K-Ras gene were detected in tumour-derived genomic DNA by direct gene sequencing without knowledge of clinical outcome. The predictive effect of K-Ras mutation status on OS and PFS was examined using a Cox model with tests for treatment-biomarker interaction.

Results: K-Ras mutation status was ascertained in 394 (69%) of the total study population (198 cetuximab, 196 BSC). Mutant K-Ras was detected in 164 (42%) patients. Within the mutant K-Ras group the median PFS was the same (1.8 months) for both groups (HR, 0.99; 95% CI, 0.73 to 1.35; p=0.96), while median OS was 4.6 months with cetuximab and 4.5 months with BSC (HR, 0.98; 95% CI, 0.70 to 1.37; p=0.89). In the 230 (58%) WT patients, median PFS was 3.8 months for the cetuximab treated group and 1.9 months with BSC (HR, 0.40; 95% CI, 0.30 to 0.54; p < 0.0001). The survival of patients with WT K-Ras was longer when they were treated with cetuximab, with a median OS of 9.5 months with cetuximab vs. 4.8 months with BSC (HR, 0.55; 95% CI, 0.41 to 0.74; p<0.0001). The test for interaction between K-Ras mutation status and cetuximab treatment demonstrates that the effect of cetuximab on OS (p=0.01) and PFS (p=0.0001) is significantly greater in the K-Ras WT group than mutant group. The difference in the OS of patients with either WT or mutant K-Ras in the BSC arm was not significant (HR, 1.01; 95% CI, 0.74 to 1.37; p=0.97).

Conclusions: In the setting of pre-treated advanced CRC, there is an almost doubling of median overall and progression free survival in patients with WT K-Ras tumours while no significant benefit is observed in patients with mutant K-Ras. K-Ras mutation status did not demonstrate a prognostic effect within a 'no treatment' group. Determination of K-Ras mutation status should now be considered a new standard of care in the selection of patients for EGFR targeted therapy.

LBA7 12-MONTH SURVIVAL DATA OF A PHASE II TRIAL: FIRST LINE TREATMENT OF INOPERABLE PANCREATIC ADENOCARCINOMA WITH CATIONIC LIPID COMPLEXED PACLITAXEL NANOPARTICLES (ENDOTAG-1®) PLUS GEMCITABINE COMPARED WITH GEMCITABINE MONOTHERAPY

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Background: Cationic Lipid Complexed Paclitaxel (EndoTAG-1®) represents a novel anti-neovascular therapy designed to destroy newly formed tumorous blood vessels. EndoTAG-1® targets activated negatively charged endothelial cells of tumor blood vessels due to its cationic carrier liposomes.

Methods: CT4001 is a controlled, randomized, open-label phase II trial to evaluate safety and efficacy of a first line combination treatment with weekly infusions of gemcitabine (G: 1000 mg/m²) and twice weekly administration of EndoTAG-1® (E) at 3 different dose levels (E_{low}: 11 mg/m², E_{med}: 22 mg/m², E_{high}: 44 mg/m²) compared to G monotherapy in locally advanced or metastatic pancreatic adenocarcinoma (PC). Patients received treatment for 7 weeks and were followed up for overall survival (OS). From Jan 2007 the amended protocol allowed repeated treatment cycles of combination therapy in case of at least stable disease (RECIST) until disease progression.

Results: 200 patients received treatment. 102 patients were included under the amended protocol, 28 continued with up to 6 cycles of combination therapy. Patients continuing treatment in arm G received any kind of treatment. Patients were evenly distributed to the 4 treatment groups. 80 % of patients proved to have metastatic and 20 % locally advanced PC. Results (cut-off 24 July 2008) show a prolongation of median OS for the E + G combination therapy compared to G monotherapy (G: 7.2 months, G+E_{low}: 8.4 months, G+E_{med}: 8.7 months, G+E_{high}: 9.4 months). 12-months survival rates were 17% (G), 22% (G+E_{low}), 36% (G+E_{med}) and 33% (G+E_{high}). Data of patients included under the amended protocol indicate an even more pronounced increase in median OS (G: 6.8 months, G+E_{low}: 9.1 months, G+E_{med}: 13.6 months, G+E_{high}: 10.8 months). 34 possibly or probably related serious adverse events were reported, mostly pyrexia and chills.

Conclusion: Treatment with E + G led to a substantially extended survival time compared to standard therapy in this controlled trial and was well tolerated. Further studies with the most effective dose of E in combination with G are needed in this patient population.

LBA8 EXTENDED SCHEDULE, ESCALATED DOSE TEMOZLOMIDE VERSUS DACARBAZINE IN STAGE IV MALIGNANT MELANOMA: FINAL RESULTS OF THE RANDOMISED PHASE III STUDY(EORTC 18032)

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Background: Temozolomide (TMZ) is an imidazotetrazine oral alkylating agent with activity in advanced melanoma. Administration on an extended schedule may prolong depletion of the DNA repair enzyme MGMT, a known mediator of chemotherapy resistance, and allows a 2.1 fold higher cumulative administered dose than the daily x5/28 regimen. We therefore compared the efficacy of an extended schedule of temozolomide with standard dose single agent dacarbazine (DTIC) in stage IV melanoma.

Methods: This is a phase III open label randomised trial. Chemotherapy naive patients with stage IV melanoma, ECOG PS 0-1 and serum LDH <=2xULN were eligible. Patients were randomised to receive Arm A: Temozolomide 150mg/m²/day orally days 1-7 repeated every 14 days ('week on-week off') or Arm B: Dacarbazine 1000mg/m² IV every 21 days. The primary endpoint was overall survival (OS) with progression free survival (PFS), overall response rate (OR), duration of response and toxicity as secondary endpoints. The study, with planned recruitment of 850 patients with follow up of 616 patients until death, was designed to detect a hazard ratio of 0.77 with 90% power at the 0.05 significance level.

Results: 859 patients were randomised between Oct 04 and May 07 from 92 institutions. Median follow-up is 18 months and 645 deaths were reported. The 2 arms were well matched for age, sex, ECOG PS and LDH. There was no significant difference in overall survival [hazard ratio =0.99, median 9.13 (TMZ) vs 9.36 (DTIC) months], PFS [hazard ratio = 0.92, median 2.30 (TMZ) vs 2.17 (DTIC) months] and OR (CR/PR)(14% TMZ vs 10 % DTIC). The main toxicities were haematological, more pronounced in the TMZ dose intense arm and there were no treatment related deaths in either arm.

Conclusion: This extended schedule Temozolomide regimen gives no survival advantage over Dacarbazine in stage IV melanoma.

LBA9 DARBEPOETIN ALFA (DA) 500MCG OR 300MCG ONCE EVERY THREE WEEKS (Q3W) WITH OR WITHOUT IRON IN PATIENTS (PTS) WITH CHEMOTHERAPY-INDUCED ANEMIA (CIA)

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Background: DA is an erythropoiesis-stimulating agent (ESA) approved for CIA at 500mcg Q3W (with reduction to 300mcg Q3W). Absolute or functional iron deficiency may account for those CIA pts (20%-30%) who don't respond to ESAs. This phase 2 study examined DA Q3W (fixed dose of 500mcg or 300mcg with no dose increase) with and without IV iron for optimizing ESA response in CIA.

Methods: This 15-week factorial study was blinded to DA dose but open-label for IV iron use (400mg Q3W low molecular weight iron-dextran). Pts were randomized 1:1:1:1 to DA 500mcg Q3W ± IV iron and DA 300mcg Q3W ± IV iron. DA was withheld at hemoglobin [Hb] > 13g/dL. Eligible pts were ≥ 18 years old and had nonmyeloid cancer, CIA (Hb ≤ 10g/dL), and no iron deficiency. The primary endpoint was incidence of pts achieving Hb ≥ 11g/dL. Secondary endpoints included transfusion rate, incidence of hematopoietic response, and health-related quality of life parameters from baseline to end of treatment. Safety endpoints included incidence of adverse events and percentage of pts with Hb > 13g/dL or > 1.5g/dL Hb rise in 21 days.

Results: 238 pts were randomized and treated. In each treatment group, most pts were female, white, with stage III/IV disease. Mean baseline Hb ranged from 9.2 to 9.4 g/dL and mean age from 61 to 67 years. Most common tumor types were lung, gastrointestinal, and breast. Since there was no significant interaction between DA dose and IV iron use, efficacy and safety data are presented by DA dose and IV iron use (238 pts per analysis) (Table).

Conclusions: In this study, IV iron added to DA Q3W was well tolerated and improved hematological response. An initiation dose of 500mcg DA Q3W may correct anemia faster and improve hematopoietic response compared to 300mcg DA Q3W; safety results were similar for both DA doses. Future studies should examine the need for dose increase when initiating with 300mcg DA Q3W and should further validate IV iron use with DA in CIA pts.

Table LBA9

	Darbepoetin alfa		IV iron usage	
	500mcg N = 120	300mcg N = 118	Without IV Iron N = 122	With IV Iron N = 116
K-M percent who achieved the target Hb (95% CL) [N]	78 (70, 87) [115]	75 (65, 85) [112]	72 (62, 82) [117]	82 (73, 90) [110]
K-M median weeks to achieve target Hb (95% CL) [N]	8 (6, 10) [115]	10 (7, 11) [112]	9 (7, 11) [117]	8 (5, 10) [110]
K-M percent with hematopoietic response (95% CL)	76 (67, 85)	69 (59, 78)	63 (53, 73)	82 (74, 90)
K-M median weeks to achieve hematopoietic response (95% CL)	9 (8, 10)	11 (8, 12)	12 (10, 15)	8 (7, 9)
K-M percent with transfusions week 1 to end of study (95% CL)	36 (27, 45)	40 (30, 49)	40 (31, 49)	36 (27, 44)
Crude percent with 3-point rise in FACT-F score from baseline during the study (95% CL) [N]	61 (52, 70) [114]	69 (61, 78) [114]	62 (53, 71) [115]	69 (61, 78) [113]
Any adverse event, n (%) [N]	109 (91) [120]	105 (89) [118]	110 (91) [121]	104 (89) [117]
Embolism/Thrombosis, n (%) [N]	10 (8) [120]	8 (7) [118]	10 (8) [121]	8 (7) [117]
Deaths, n (%) [N]	10 (8) [120]	11 (9) [118]	13 (11) [121]	8 (7) [117]
Hb > 13g/dL without transfusions, n (%) [N]	33 (28) [120]	25 (21) [118]	21 (17) [121]	37 (32) [117]
> 1.5g/dL Hb rise in 21-days without transfusions, n (%) [N]	76 (63) [120]	64 (54) [118]	57 (47) [121]	83 (71) [117]

K-M, Kaplan-Meier; FACT-F, Functional Assessment of Cancer Therapy-Fatigue.

Update to 710

KRAS STATUS AND EFFICACY IN THE CRYSTAL STUDY: 1ST-LINE TREATMENT OF PATIENTS WITH METASTATIC COLORECTAL CANCER (MCRC) RECEIVING FOLFIRI WITH OR WITHOUT CETUXIMAB

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Objective: The efficacy of cetuximab alone or in combination with chemotherapy (CT) has been shown to be associated with KRAS mutation status in patients (pts) with mCRC. In the phase III CRYSTAL study, addition of cetuximab to FOLFIRI significantly improved overall response rate (ORR) and progression-free survival (PFS). The objective of this evaluation was to assess the influence of KRAS mutation status on treatment outcomes and giving an update with mature overall survival data.

Methods: Of 1198 randomized pts, 578 provided archived tumor material. Genomic DNA was isolated and KRAS mutation status determined on codons 12/13 using a mutation-specific, quantitative PCR-based assay. The relationship between KRAS mutation status (wild-type [wt] or mutant [mt]) and outcome was assessed in 540 KRAS-evaluable pts for best ORR using the stratified CMH test and for PFS (primary endpoint; Independent Review Committee evaluation) using the stratified log-rank test.

Results: The KRAS-evaluable population was generally representative of the ITT population. Of the 540 pts with evaluable samples, KRAS mt was detected in 192 (35.6%) pts. A statistically significant difference in favor of cetuximab was seen in KRAS wt pts for best ORR (p=0.0025) and PFS (p=0.0167). The improvement in OS from 21.0 to 24.9 months showed a strong trend in favor of cetuximab.

73.1% of patients in the FOLFIRI arm and 68.6% in the cetuximab plus FOLFIRI arm received at least one line of follow up treatment, 25.4% and 6.2% respectively received EGFR-antibody treatment as follow up therapy.

Conclusions: Cetuximab added to CT in pts with KRAS wt tumors demonstrated an even more pronounced benefit than that seen in unselected pts who themselves saw a significant enhancement in efficacy. Pts with KRAS mt appeared not to benefit from cetuximab treatment. KRAS mutation status can be considered a predictive marker for clinical outcome in terms of all relevant clinical endpoints in pts with mCRC receiving 1st line treatment with cetuximab plus FOLFIRI.

	ITT Cetuximab+ FOLFIRI (n = 599)	FOLFIRI (n = 599)	KRAS wt Cetuximab+ FOLFIRI (n = 172)	FOLFIRI (n = 176)	KRAS mt Cetuximab+ FOLFIRI (n = 105)	FOLFIRI (n = 87)
ORR (%)	47	39	59	43	36	40
Odds ratio [95% CI]	1.40 [1.115, 1.766]		1.91 [1.245, 2.929]		0.80 [0.440, 1.443]	
p value	0.0038		0.0025		0.46	
PFS (months)	8.9	8.0	9.9	8.7	7.6	8.1
Hazard ratio [95% CI]	0.85 [0.726, 0.998]		0.68 [0.501, 0.934]		1.07 [0.710, 1.610]	
p value	0.0479		0.0167		0.75	
OS (months)	19.9	18.6	24.9	21.0	17.5	17.7
Hazard ratio [95% CI]	0.93 [0.812, 1.067]		0.84 [0.644, 1.105]		1.031 [0.741, 1.436]	
p value	0.30		0.22		0.85	