Gastro-intestinal malignancies − Colorectal II
Tuesday 22 September 2009, 09:00−11:15

14LBA LATE BREAKING ABSTRACT

Randomized phase 3 study of panitumumab with FOLFIRI vs FOLFIRI alone as second-line treatment (tx) in patients (pts) with metastatic colorectal cancer (mCRC)

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Background: Panitumumab (pmab) is a fully human anti-epidermal growth factor receptor (EGFR) monoclonal antibody (mAb) approved as monotherapy for pts with mCRC. The 181 study was designed to evaluate the efficacy and safety of pmab with FOLFIRI vs FOLFIRI alone as 2nd-line tx for mCRC (clinicaltrials.gov identifier: NCT00339183; sponsor: Amgen Inc).
Methods: This was a randomized, multicenter, phase 3 study. Pts were randomized 1:1 to receive pmab 6.0 mg/kg Q2W+FOLFIRI (Arm 1) vs FOLFIRI alone (Arm 2). Pts had metastatic adenocarcinoma of the colon or rectum; only 1 prior chemotherapy regimen for mCRC; ECOG 0−2; and available tumor tissue for biomarker testing. Randomization was stratified by ECOG 0−1 vs 2, prior oxaliplatin, and prior bevacizumab exposure. The co-primary endpoints were progression-free survival (PFS) and overall survival (OS) and were independently tested. Originally designed to compare the tx effect in the all randomized population, the study was amended to focus on hypothesis testing in the wild-type (WT) KRAS subset. KRAS status was determined by a blinded central laboratory using allele-specific PCR prior to the first efficacy analysis.
Results: From June 2006 to March 2008, a total of 1186 pts were randomized, signed informed consent, and received tx. 591 Arm 1, 595 Arm 2. Overall demographics included 61% men, median (range) age 61 (28−86) years, ECOG 0 or 1 94%. 1083/1186 pts (91%) had KRAS results: 597 (55%) WT, 486 (45%) mutant (MT). For pts with WT KRAS, median PFS was 5.9 months for Arm 1, and 3.9 months for Arm 2; HR (95% CI) = 0.73 (0.593, 0.903), p = 0.004; median OS was 14.5 months for Arm 1, and 12.5 months for Arm 2; HR (95% CI) = 0.85 (0.702, 1.039); p = 0.115, and response rate (by blinded central review) was 35% (Arm 1) and 10% (Arm 2). There was no difference in PFS, OS, or response rate among patients with MT KRAS who received pmab. In general, adverse event rates were comparable across arms with the exception of known toxicities associated with anti-EGFR therapy such as rash, diarrhea, and hypomagnesemia. Pmab-related grade 3/4 infusion reactions were reported for 2 patients in Arm 1 (<1%).
Conclusions: Pmab significantly improves PFS and is well tolerated when added to FOLFIRI for 2nd-line tx in pts with WT KRAS mCRC. This study confirms the importance of KRAS as a predictive biomarker in the setting of 2nd-line mCRC tx with a mAb against EGFR in combination with standard chemotherapy.

15LBA LATE BREAKING ABSTRACT

Intermittent versus continuous oxaliplatin-based combination chemotherapy in patients with advanced colorectal cancer: a randomised non-inferiority trial (MRC COIN)

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Background: Intervals off palliative chemotherapy (CT) may be a welcome respite for patients (pts). One of the two questions posed by the COIN trial (ISRCTN27286448) was whether intermittent CT with oxaliplatin + fluoropyrimidine (iOxFp) was non-inferior to standard continuous OxFp (cOxFp) in terms of overall survival (OS).
Materials and Methods: Pts had measurable, inoperable aCRC; no prior CT for metastases; WHO Performance Status (PS) 0−2; and good organ function. The arms were: **A**: cOxFp (Ox + fluorouracil/leucovorin (OxFU) q2w or Ox + Capecitabine (Cap) q3w), continued until treatment failure; **C**: iOxFp, same regimen for 3 months initially, with further 3-month courses upon progression. Pts/clinicians chose OxFU or OxCap before randomisation. The trial was powered to exclude a HR >1.162, equivalent to an absolute difference in 2 yr survival greater than 4.6% assuming 20% 2 year survival on cOxFp, with a one-sided alpha of 0.1 and 90% power.
Results: 1630 pts were randomised between 03/05 and 05/08 from 109 hospitals in the UK and Ireland. Median age was 63 yrs; 92% of pts had PS 0−1. 66% pts received OxCap and 34% received OxFU. Over the entire treatment period, pts on iOxFp had significantly less G3/4 hand-foot syndrome and peripheral neuropathy (2% vs 4%, p = 0.044 and 5% vs 19%, p < 0.001). No evidence of differences in treatment-related (1.2% vs 1.2%, p = 0.999) or 60-day all cause mortality (4.2% vs 4.4%, p = 0.810) were observed. Overall, 1231 pts (76%) have died. The intention-to-treat (ITT) analysis shows a 9% increase in the hazard of death in pts on iOxFp (HR 1.09, with a one-sided upper 90% CI of 1.17; this just exceeds the pre-specified boundary). Median OS on cOxFp is 15.6 months (mo) vs 14.3 mo on iOxFp. The estimated 2-yr survival is 28.3% with cOxFp and 26.1% with iOxFp. In the per-protocol analysis (PPA, n = 1103) the HR is 1.10 with an upper 90% CI of 1.21; median OS on cOxFp is 19.1 mo vs 17.6 mo on iOxFp. The estimated 2-yr survivals are 34.8% and 31.1% in the cOxFp and iOxFp groups respectively.
Conclusions: In this large trial an estimated difference in favour of cOxFp of 1.3 mo in median survival was observed. The survival data indicate that a priori specified non-inferiority cannot be confirmed, but we can reliably exclude a detriment of larger than 2.3 mo in median survival with iOxFp in the ITT population (3.3 mo in the PPA). These small differences in survival need to be balanced against the reduced toxicity observed with iOxFp.

Gastro-intestinal malignancies − Non-colorectal cancer
Wednesday 23 September 2009, 09:00−11:00

16LBA LATE BREAKING ABSTRACT

VEGFR-1 polymorphisms as potential predictors of clinical outcome in bevacizumab-treated patients with metastatic pancreatic cancer

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Background: Based on evidence that genetic determination may influence sensitivity of the endothelium to VEGF, we explored genetic variability in underlying signaling pathways as a promising approach to discover predictive patterns for anti-angiogenic treatment. In a retrospective analysis, the correlation of genetic variability in the VEGF signaling pathway with clinical outcome of patients with metastatic pancreatic cancer treated with gemcitabine-erlotinib (GE) plus bevacizumab (bev) or placebo in a phase III trial (AVITA) was evaluated.
Materials and Methods: Germline DNA was available from 154 out of 607 patients, of which 77 received GE plus bev and 77 GE alone (median OS = 7.5 and 6.8 months). Common single nucleotide polymorphisms (SNPs) located in the hypoxia-inducible factor-1α and -2α, VEGF, its receptors (VEGFR-1 and -2) and other relevant genes were selected using a SNP tagging approach ($f \geqslant 0.1$ and $r^2 \leqslant 0.8$). 157 SNPs were successfully genotyped using MALDI-TOF mass spectrometry. Risk and survival estimates were calculated using Cox regression analyses.
Results: Four SNPs in the VEGFR-1 gene correlated with OS in the bev-treated group. The most significant SNP, rs9582036, had a p-value $\leqslant 3 \times 10^{-4}$ according to an allelic risk effect model. Relative to AA carriers, the hazard ratio was 2.0 (CI = 1.2−3.4; p = 0.009) and 4.7 (CI = 2.1–10.7; p = 0.0002) for AC and CC carriers, respectively. Median OS increased from 4.8 months in CC (n = 9) carriers to 6.0 and 10.3 months in AC (n = 28) and AA (n = 40) carriers. A similar association was observed with the PFS end-point. After adjustment for baseline prognostic factors (neutrophil counts, CRP and tumor location) the effect was attenuated but not suppressed. No effect was detected in the control group. A test for interaction between rs9582036 genotype and treatment resulted in a p-value of 0.02. All 4 SNPs were located in the same chromosomal region encompassing exon 25 to 28 of the VEGFR-1 gene coding for the essential receptor tyrosine-kinase (TK) domain. No association with the previously reported VEGF-2578C/A polymorphism could be detected in this data set.
Conclusions: These retrospective subgroup data describe a genetic locus in the TK domain of VEGFR-1 that may correlate with clinical outcome in pancreatic cancer patients treated with bevacizumab. Further prospective evaluation is warranted to review and further validate the potential predictive value of the described parameters for anti-angiogenic treatment.