

Oral presentation
Breast cancer
Monday, 21 September 2009, 11:00-13:00

Abstract: 5001

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CIRG/TORI 010: first analysis of a randomized phase II trial of motesanib plus weekly paclitaxel (P) as first line therapy in HER2-negative metastatic breast cancer (MBC)

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Background: Motesanib (M) is an oral tyrosine kinase inhibitor of VEGF, PDGF and Kit receptors. We assessed, in an ongoing double-blinded placebo-controlled trial, the effect of adding M to P as first line treatment of patients (pts) with MBC. A P plus bevacizumab (B) arm was included. The CIRG/TORI 010 study was supported by Amgen.

Methods: 282 pts with HER2-negative and measurable MBC were randomly assigned treatment with P 90 mg/m² on days 1, 8 and 15 in combination with blinded placebo (P: arm A), blinded M 125 mg once daily (PM: arm B) or open label B 10 mg/kg on days 1 and 15 (PB: arm C). Treatment was administered in 28-day cycles until disease progression, toxicity or consent withdrawal. The primary objective was to determine the difference in response rate (RR) between P and PM. Treatment efficacy was assessed every 8 weeks according to RECIST and scans were independently centrally reviewed.

Results: 277 pts received the assigned treatment. Pts characteristics at entry were balanced: median age was 55, 80% had hormone receptor positive tumors and 66% had received prior chemotherapy with curative intent. At the first planned analysis, 16 weeks after last patient enrolment, the median treatment duration was 6 cycles. The median cumulative dose of P was similar across the arms: 1328, 1282 and 1438 mg/m² in arm A, B and C, respectively. Pts received a median cumulative dose of B=133 mg/kg (arm C) and an averaged daily dose of M = 111 mg (arm B). The table displays the efficacy results and relevant differences in toxicities incidences (all grade).

	Arm A (P)	Arm B (PM)	Arm C (PB)
Efficacy (all pts)	n = 94	n = 91	n = 97
RR (95% CI)	35% (26-46)	48% (38-59)	45% (35-56)
Progression-Free Survival (95% CI)	8.0 mo (6.6-9.6)	9.1 mo (8.1-11.6)	10.1 mo (9.0-15.3)
Toxicity Incidence (% treated pts)	n = 90	n = 91	n = 96
Nausea	44	60	48
Diarrhea	33	69	42
Vomiting	24	40	23
Abdominal Pain	21	44	16
Stomatitis	11	15	29
Alopecia	63	59	71
Infections	54	55	66
Hypertension	13	57	30
Anorexia	16	35	25
Left Ventricular dysfunction	1	8	3
Hepatobiliary disorders	6	17	3
Back Pain	1415	23	
Peripheral Neuropathy	42	48	54

The RR favored PM and PB as compared with P but the differences were not statistically significant ($p = 0.09$, adjusting for stratification factors). The distributions of times to progression or death did not significantly differ between the three arms.

Conclusion: The administration of M in combination with weekly P is feasible with no unexpected toxicities. This regimen is efficacious in the treatment of pts with Her2-negative MBC.

Abstract 15LBA: **Intermittent versus continuous oxaliplatin-based combination chemotherapy in patients with advanced colorectal cancer: a randomised non-inferiority trial (MRC COIN)**

Citation: *European Journal of Cancer Supplements*, Vol. 7, No 3, September 2009, Page 10

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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.

Abstract 6LBA:

Addition of cetuximab to oxaliplatin-based combination chemotherapy (CT) in patients with KRAS wild-type advanced colorectal cancer (ACRC): a randomised superiority trial (MRC COIN)

Citation: European Journal of Cancer Supplements, Vol. 7, No 3, September 2009, Page 4

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Background: Cetuximab (C) has proven efficacy in KRAS wild-type (wt) advanced colorectal cancer (ACRC). One of the two questions posed by the COIN trial (ISRCTN27286448) was whether the addition of cetuximab to continuous oxaliplatin-based chemotherapy (CT) improves overall survival (OS) when given as first-line therapy. The relevance of KRAS mutations as a predictor of resistance to anti-EGFR antibody therapy became clear after completion of COIN accrual but before outcome analysis was undertaken; therefore the primary analysis of the \pm C comparison will be in the cohort of KRASwt pts.

Materials and Methods: Pts had measurable, inoperable ACRC; no prior CT for metastases; WHO Performance Status (PS) 0–2 and good organ function. The treatment arms are: A: OxFp (Ox + 5Fluorouracil + Folinic acid (OxFU) q2w or Ox + Capecitabine (Cap) q3w); B: OxFp + weekly C. Pts/clinicians chose OxFU or Ox+cap before randomisation. With at least 511 OS events in the KRASwt population the trial will have at least 82% power ($\alpha = 0.05$) to detect an OS hazard ratio (HR) of 0.78. An unstratified log-rank test will be used to compare treatment groups.

Results: 1630 pts were randomised to this comparison between 03/05 and 05/08 from 109 hospitals in the UK and Ireland. Efficacy analyses by KRAS status have not yet been performed. Pt characteristics in all pts at baseline are as follows: median age was 63 years, 92% pts had PS 0–1, 66% pts received Ox+cap and 34% received OxFU, 41% of pts had unresected or unresectable primary tumours while 23% of pts had liver-only metastases. Tumour samples from 1305 (80%) pts were available for KRAS analysis. 724 (56%) pts were KRASwt while 561 (43%) had a KRAS mutation. 20 pts failed analysis (<1%). Arm B pts experienced significantly greater G3/4 diarrhoea (25% vs 14%, $p < 0.001$), skin rash (21% vs <1%, $p < 0.001$), lethargy (26% vs 19%, $p < 0.001$), hand-foot syndrome (11% vs 4%, $p < 0.001$) and hypomagnesaemia (5% vs 0%, $p < 0.001$) but significantly less G3/4 peripheral neuropathy (14% vs 19%, $p < 0.012$). No evidence of differences in treatment-related or 60-day all cause mortality were observed between the two arms (1.1% vs 1.2%, $p = 0.817$ and 5.3% vs 4.4%, $p = 0.419$). Results from the analyses of primary (OS) and secondary endpoints and toxicity will be reported by KRAS status at the symposium.

Presidential session IV Thursday 24 September 2009, 09.30–11.15