

(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 *KRAS*wt 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 *KRAS*wt 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 *KRAS*wt 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

5BA

BEST ABSTRACT

Identification of gene expression profiles that predict response to HER2-targeted therapy

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Background: Lapatinib (L), an oral small molecular inhibitor of EGFR and HER2, has a mechanism of action distinct from that of trastuzumab (T). L was shown to be effective alone or in combination with T in a randomized study of 296 heavily pretreated patients (pts) (198 pts per arm) with HER2-positive metastatic breast cancer (MBC) that progressed on prior T-based therapy. L in combination with T improved PFS (HR: 0.73; $p = 0.008$) and doubled clinical benefit rate (CBR, 24.7% vs. 12.4%). Gene expression analysis in tumor samples from this study was used to identify pts with HER2-positive MBC who are more likely to derive benefit from HER2 targeted therapies.

Methods: Tumor tissue was obtained from 135 pts in the form of formalin-fixed, paraffin-embedded (FFPE) material from primary or MBC. Tumor tissue was isolated from 10 μ m sections using manual microdissection. RNA was extracted using the High Pure RNA Paraffin kit (Roche). cDNA-mediated annealing, selection, and ligation (DASL) assay (Illumina Corp) was performed to determine the expression of 502 known cancer genes using 200 ng of total RNA. PFS was analyzed using proportional hazards regression and CBR was analyzed using Wilcoxon and logistic regression tests. Tests were considered significant if $p \leq 0.05$.

Results: The 135 tumor tissue samples were representative of the entire study population, providing similar PFS and CBR. Increased expression of HER2, GRB7, FLI1 and PNUTL1 were among the genes associated with improved PFS following L; similarly expression of COL4A3, PTCH, ESR1, PGR and TGFBR2 correlated with improved PFS following L+T.

Conclusions: Gene expression analyses revealed differences in HER2-positive tumors and response to L or L+T therapies. The relevance of these genes to HER2 tumor biology, including the pathways they regulate, will be discussed. Prospective patient selection for L or L+T therapies based on intratumoral gene expression patterns may be feasible.

6BA

BEST ABSTRACT

Early efficacy signal demonstrated in advanced melanoma in a phase I trial of the oncogenic BRAF-selective inhibitor PLX4032

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Background: PLX4032 is an oral, selective inhibitor of the oncogenic V600E mutant BRAF kinase, observed in a variety of cancers, including approx. 60% of melanomas (MEL) and 10% of colorectal carcinomas. We conducted a phase I trial with PLX4032 (RO5185426) to determine maximum tolerated dose (MTD), safety, and pharmacokinetics (PK). We also evaluated anti-tumor responses and, in select patients (pts), tumor biopsies for pharmacodynamics.

Materials and Methods: Pts took PLX4032 by mouth twice daily. Doses were escalated in cohorts of 3 to 6 pts. PK was measured on days 1 and 15. Once the MTD was determined, an extension cohort of MEL patients with BRAF mutations was treated at the MTD. Anti-tumor effects were evaluated by RECIST criteria every 8 weeks.

Results: 55 pts were enrolled in the dose escalation phase. Of these, 30 pts were treated at doses from 160 mg to 1120 mg bid using an optimized formulation with much greater bioavailability. With the optimized formulation, minimum target exposure ($\geq 400 \mu\text{M}\cdot\text{h}$) was achieved at 240 mg bid, and systemic exposure increased in a dose-proportional manner up to 960 mg bid (1700 $\mu\text{M}\cdot\text{h}$). At 1120 mg bid, 4/6 pts developed dose-limiting toxicity (DLT; Grade 3 rash with pruritus, fatigue, or arthralgia), which resolved with temporary drug interruption. In all cases, pts resumed treatment at lower doses. The MTD was determined to be 960 mg bid. Of the 26 pts treated at doses ≥ 240 mg bid, 16 had MEL with an activating BRAF mutation. Of these 16 MEL pts, 11 had a partial response (PR) that has been confirmed in 9 pts to date. 30 additional MEL pts with activating BRAF mutations have been treated at the MTD of 960 mg bid. Most patients had been previously treated for systemic disease (median # prior therapies = 2, range 0–7). Of the 22 pts evaluable for response to date, there have been 14 PRs (64%); 6 other pts have had regression but do not fulfill criteria for PR. Responses have been seen in subcutaneous sites, liver, lung, GI, and bone, and have been associated with resolution of symptoms. DLTs (all grade 3) at the MTD reported to date were: fatigue, arthralgias, photosensitivity, rash, and elevated alkaline phosphatase. Squamous cell cancer of the skin as been seen in 4 pts.

Conclusions: Dose escalation of PLX4032 reached DLT at 1120 mg bid; 960 mg bid is the MTD. In heavily pre-treated MEL patients with tumors that harbor an activating mutation in BRAF, we have observed anti-melanoma activity in the majority of patients treated at doses >240 mg bid and in almost all patients treated at the MTD. Phase II and phase III trials are planned.

8LBA

LATE BREAKING ABSTRACT

Biomarker evaluation in the randomized, double-blind, placebo-controlled, Phase IIb ATLAS Trial, comparing bevacizumab (B) therapy with or without erlotinib (E), after completion of chemotherapy with B for the treatment of locally-advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC)

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Background: The ATLAS (AVF 3671g) study investigated whether E 1st line maintenance therapy improved the progression-free survival (PFS) of advanced NSCLC patients (pts) when added to B following chemotherapy with B.

The trial met its primary endpoint of improved PFS for the B+E cohort (hazard ratio [HR] 0.722, $p = 0.0012$), compared to the B + placebo (P) cohort. The ATLAS study included a prospective analysis of the

prognostic/predictive value of several biomarkers (BM): epidermal growth factor receptor (EGFR) immunohistochemistry (IHC), EGFR fluorescence in situ hybridization (FISH), and EGFR and Kras mutation status.

Methods: 743 pts with advanced NSCLC whose disease had not progressed following 4 cycles of 1st-line chemotherapy with B were randomized by the interim analysis data cut-off to receive B+E or B+P. B dosing was 15 mg/kg every 3 weeks; E dosing was 150 mg daily. Maintenance therapy continued until unacceptable toxicity or disease progression.

Archival tumor tissue was collected for BM analysis. EGFR FISH and IHC analyses were performed using the PathVysion[®] and PharmDx kits[™] from Abbott-Vysis and DAKO. Analyses of EGFR tyrosine kinase mutations in exons 18–21 and Kras mutations in exons 2 and 3 were performed using DHPLC (denaturing high-performance liquid chromatography) and mutations were validated by sequencing.

Results: Biomarker assay results were available for 49.4% of randomized patients. Their demographics were similar to the overall trial population. The PFS HRs for the BM defined subgroups are presented in the table.

Overall survival data for the ATLAS trial remains immature.

BM status	n = 367 (49.4%) ^a	HR ^b (95% CI) for PFS
EGFR IHC+	191 (25.7%)	0.92 (0.64, 1.32)
EGFR IHC-	67 (9.0%)	1.00 (0.55, 1.82)
EGFR FISH+	87 (11.7%)	0.66 (0.39, 1.13)
EGFR FISH-	109 (14.7%)	1.40 (0.86, 2.28)
EGFR mut+	52 (7.0%)	0.44 (0.22, 0.86)
EGFR wt	295 (39.7%)	0.85 (0.64, 1.13)
KRAS mut+	93 (12.5%)	0.93 (0.55, 1.56)
KRAS wt	239 (32.2%)	0.67 (0.49, 0.91)

^aDenominator for % is number of patients in ITT population (n = 743).

^bHR for B+E, compared with B+P.

Conclusions: Pts with assay results for BM analysis were representative of the overall population. The PFS results of the BM defined subgroups were consistent with the overall PFS benefit seen in the trial. These results suggest that EGFR FISH+, EGFR mutated, and Kras wildtype pts could derive the greatest improvement in PFS with B+E.

9LBA LATE BREAKING ABSTRACT A randomized phase III study comparing gefitinib with carboplatin (CBDCA) plus paclitaxel (TXL) for the first-line treatment of non-small cell lung cancer (NSCLC) with sensitive EGFR mutations: NEJ002 study

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Background: Based on our promising results of phase II studies estimating gefitinib for NSCLC with sensitive EGFR mutations, this multicenter phase III study comparing gefitinib with standard chemotherapy, i.e. CBDCA plus TXL, for the first-line treatment of advanced NSCLC with EGFR mutations was conducted.

Materials and Methods: Peptide nucleic acid-locked nucleic acid PCR clamp test (Cancer Res 2005) was employed to detect EGFR mutations from cytological or histological samples. NSCLC patients (pts) having sensitive EGFR mutations, measurable lesion, ECOG PS 0–1, age of 20–75 years, and no prior chemotherapy were randomized (balanced for institution, sex, and clinical stage) to receive arm A: gefitinib (250 mg/day) daily, or arms B: CBDCA AUC 6 and TXL 200 mg/m² in 21-day cycles. The primary endpoint was progression-free survival (PFS) and secondary endpoints were overall survival, response rate, quality of life, time to PS 3, and toxicity profiles. The sample size was calculated to be 320 in total (alpha = 5%, power = 80%) to confirm the PFS superiority of arm A (hazard ratio = 0.69). Per protocol, an interim analysis was performed 4 months after 200 pts entered.

Results: From April 2006 to December 2008, 200 pts were enrolled, and according to the study protocol, the interim analysis was performed

at the end of May 2009 on 198 pts except for 2 ineligible pts (arm A, 98; arm B, 100). Patients' characteristics were well balanced between arms: median age = 63/63 years; 63%/64% female; 79%/75% stage IV; 90%/96% adenocarcinoma, respectively. Significantly higher response rate was obtained in arm A (74.5% vs. 29.0%, p < 0.001). There were several differences in toxicities between arms: grade 4 neutropenia 1% vs. 33%, grade 3–4 liver dysfunction 25% vs. 1%, and grade 3 neuropathy 0% vs. 5%, respectively, p < 0.01. An interim analysis clearly showed a significantly longer PFS in arm A than arm B (10.4 months vs. 5.5 months, hazard ratio = 0.357, p < 0.001). Therefore, the independent safety committee recommended terminating accumulation of pts at the end of May 2009. Preliminary results of median survival time were 28.0 months in arm A and 23.6 months in arm B (p = 0.353).

Conclusions: The NEJ002 study met its primary endpoint with high statistical significance. Gefitinib as the first-line treatment for advanced NSCLC harboring EGFR mutations significantly improves PFS with favorable toxicity profiles against CBDCA plus TXL, thus should be considered as the new standard treatment for sensitive EGFR mutation-positive NSCLC pts.

10LBA LATE BREAKING ABSTRACT Randomized phase 3 study of panitumumab with FOLFOX4 compared to FOLFOX4 alone as 1st-line treatment (tx) for metastatic colorectal cancer (mCRC): the PRIME trial

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Background: Panitumumab (pmab) is a fully human anti-epidermal growth factor receptor (EGFR) monoclonal antibody (mAb) approved as monotherapy for patients (pts) with mCRC. The PRIME trial was designed to evaluate the efficacy and safety of pmab with FOLFOX4 vs FOLFOX4 alone as 1st-line tx for mCRC (clinicaltrials.gov identifier: NCT00364013; 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 + FOLFOX4 (Arm 1) vs FOLFOX4 (Arm 2). Pts had metastatic adenocarcinoma of the colon or rectum; no prior chemotherapy for mCRC; no prior oxaliplatin; ECOG 0–2; and available tumor tissue for biomarker testing. Randomization was stratified by ECOG 0–1 vs 2 and region. The primary endpoint was progression-free survival (PFS). Originally designed to compare the tx effect in the all randomized population, the study was amended to focus 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 primary analysis.

Results: From Aug 2006 to Feb 2008, a total of 1,183 pts were randomized after signing an informed consent, and received tx: 593 Arm 1, 590 Arm 2. Demographics were generally well-balanced and included 63% men, median age 62 years [range: 24–85]; ECOG 0 or 1; 95%. 1096/1183 pts (93%) had KRAS results: 656 (60%) WT, 440 (40%) mutant (MT). For pts with WT KRAS, median PFS was 9.6 months for Arm 1 and 8.0 months for Arm 2; HR (95% CI) = 0.80 (0.66, 0.97); p = 0.0234 and response rate (by blinded central review) was 55% (Arm 1) and 48% (Arm 2). For pts with MT KRAS, median PFS was 7.3 months for Arm 1 and 8.8 months for Arm 2; HR (95% CI) = 1.29 (1.04, 1.62); p = 0.0227. 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 infusion reactions were reported for 2 patients in Arm 1 (<1%).

Conclusions: Pmab significantly improves PFS and is well tolerated when added to FOLFOX4 for 1st-line tx of pts with WT KRAS mCRC. PFS was inferior in the pts with MT KRAS tumors who received pmab. This study confirms the importance of KRAS as a predictive biomarker in the setting of 1st-line mCRC tx with an anti-EGFR mAb in combination with chemotherapy.