(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 ±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

S. Badve[1], C. Shen[2], M. Thorat[1], L. Li[2], R. Gagnon[3], M. Koehler[3], C. Ellis[3], J. O'Shaughnessy[4], J. Baselga[5], G. Sledge[6]. [1]*I.U. Simon Cancer Center, Department of Pathology, Indianapolis, USA;* [2]*I.U. Simon Cancer Center, Department of Medicine, Indianapolis, USA;* [3]*GlaxoSmithKline, Oncology Medicine Development Center, Collegeville, USA;* [4]*Baylor Sammons Cancer Center Texas Oncology PA US Oncology, Medical Oncology, Dallas, USA;* [5]*Vall d'Hebron University Hospital, Medical Oncology, Barcelona, Spain;* [6]*I.U. Simon Cancer Center, Department of Hematology and Oncology, Indianapolis, USA*

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 μm 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 $p \leqslant 0.05$.
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

P. Chapman[1], I. Puzanov[2], J. Sosman[3], K. Kim[4], A. Ribas[5], G. McArthur[6], R. Lee[7], J. Grippo[8], K. Nolop[9], K. Flaherty[10]. [1]*Memorial Sloan-Kettering Cancer Center, Department of Medicine, New York, USA;* [2]*Vanderbilt Ingram Cancer Center, Department of Medical Oncology, Nashville, USA;* [3]*Vanderbilt University Medical Center, Department of Medical Oncology, Nashville, USA;* [4]*MD Anderson Cancer Center, Department of Melanoma Medical Oncology, Houston, USA;* [5]*UCLA, Division of Hematology and Oncology, Los Angeles, USA;* [6]*Peter MacCallum Cancer Center, Division of Hematology and Oncology, East Melbourne, Australia;* [7]*Hoffmann-La Roche Inc., Department of Oncology, Nutley, USA;* [8]*Hoffmann-La Roche Inc., Clinical Research and Exploratory Development – Pharmacology, Nutley, USA;* [9]*Plexxikon Inc., Development, Berkeley, USA;* [10]*University of Pennsylvania, Department of Hematology/Oncology, Philadelphia, USA*

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 ($\geqslant$400 μM·h) was achieved at 240 mg bid, and systemic exposure increased in a dose-proportional manner up to 960 mg bid (1700 μM·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 $\geqslant$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 IIIb 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)

B. Johnson[1], V. Miller[2], L. Amler[3], H. Stern[3], C. Soh[4], P. O'Connor[5], F. Kabbinavar[6]. [1]*Dana Farber Cancer Institute, Medical Oncology, Boston, USA;* [2]*Memorial Sloan Kettering Cancer Institute, Medical Oncology, New York, USA;* [3]*Genentech Inc, Research, South San Francisco, USA;* [4]*Genentech Inc, Biostatistics, South San Francisco, USA;* [5]*Genentech Inc, Oncology, South San Francisco, USA;* [6]*University of California Los Angeles, Translational Oncology Research International, Los Angeles, USA*

Background: The ATLAS (AVF 3671 g) 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