diarrhoea (5% vs 5%), dyspnoea (4% vs 5%), neutropaenia (3% vs 5%), mucositis (4% vs 1%), and others less frequently. The no. of pts discontinuing treatment due to adverse events in the CAP+PL arm was 9 (8%) and in the CAP+SOR arm was 15 (13.4%). The most common reasons for discontinuation (CAP+PL vs CAP+SOR) include HFSR (2 vs 8) and diarrhoea (3 vs 1).
Conclusions: In this randomised double-blind phase 2 trial, the oral combination of CAP+SOR demonstrated significant improvement in PFS in pts with locally adv or met BC. The regimen was tolerable and exhibited a clinically manageable toxicity profile. No new or unexpected side effects were observed with this combination. These results represent the first randomised study to demonstrate the efficacy of SOR in the treatment of adv BC.

4LBA LATE BREAKING ABSTRACT

Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated vs conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC)

M. Baumann[1], T. Herrmann[1], R. Koch[2], B. Wahlers[3], L. Kepka[4], G. Marschke[5], D. Feltl[6], R. Fietkau[7], V. Budach[8], J. Dunst[9], on behalf of the CHARTWEL-bronchus group. *[1]Universitätsklinikum Carl Gustav Carus, Klinik und Poliklinik Strahlentherapie, Dresden, Germany; [2]Universitätsklinikum Carl Gustav Carus, Institut für Informatik und Biometrie, Dresden, Germany; [3]Lungenklinik Hemer, Strahlentherapie, Hemer, Germany; [4]Cancer Center Marie Sklodowska-Curie, Radiation Oncology, Warsaw, Poland; [5]Städtisches Klinikum Görlitz, Strahlentherapie, Görlitz, Germany; [6]University Hospital Kralovkse Vinohrady, Radiation Oncology, Praha, Czech Republic; [7]Universität Rostock, Strahlentherapie, Rostock, Germany; [8]Humbold Universität Berlin – Charité, Strahlentherapie, Berlin, Germany; [9]Martin Luther Universität Halle, Strahlentherapie, Halle, Germany*

Background: Accelerated radiotherapy counteracts repopulation of tumor cells during treatment and may significantly improve local control and survival in patients with locally advanced NSCLC (CHART-trial, Saunders 1997). Nevertheless local failure rates $\geqslant$80% call for radiation dose escalation, using conformal techniques. We report here the final results of the CHARTWEL trial (CHART weekend less).
Patients and Methods: Between 1997 and 2005 406 pts. with NSCLC were randomized by 15 centres in Germany, Poland and Czech Republic. Inclusion criteria: UICC stage (I: 10%, II: 6%, IIIA:38% IIIB:46%), WHO performance 0−1. Randomization was stratified according to stage, histology, neoadjuvant chemotherapy (CTx; no = 300/yes = 106) and center. All patients were treated with 3D RT using a linear accelerator to 60 Gy/40 f/2.5 w (CHARTWEL) or 66 Gy/33 f/6.5 w (CF). The trial was carried out within the Arbeitsgemeinschaft Radioonkologie (trial # ARO 97-1) of the Deutschen Krebsgesellschaft and sponsored by the Deutsche Krebshilfe.
Results: Intent-to-treat analysis did not reveal significant differences of overall survival (primary endpoint) at 2, 3 and 5 yrs after CHARTWEL (31%, 22% and 11%) vs CF (32%, 18% and 7%; HR 0.92, 95% CI 0.75–1.13, p = 0.43). Also local tumor control rates (LC; HR 0.86; 0.68–1.09; p = 0.22) and distant metastasis rates (HR 1.06; 0.78–1.44; p = 0.71) did not significantly differ between the arms. Acute dysphagia was more pronounced after CHARTWEL. Pneumonitis determined by imaging was increased after CHARTWEL, without clinical differences. Exploratory analysis revealed a significant trend for improved LC after CHARTWEL vs CF with increasing UICC, T or N stage (p = 0.006–0.025) and after CTx (HR 0.48, 0.26–0.89, p = 0.019).
Conclusions: OS and LC were not significantly different after CHARTWEL and CF in the overall trial population. The impact of higher total dose in CF on LC was compensated by the shorter overall treatment time in CHARTWEL. This confirms a time factor of fractionated radiotherapy in NSCLC, and cautions treatment prolongation. The efficacy of CHARTWEL vs CF was higher in advanced stages and after CTx. From this we hypothesize that CHARTWEL after neoadjuvant CTx is a promising avenue to intensify treatment of locally advanced NSCLC which may overcome current limitations by toxicity of simultaneous radiochemotherapy.

5LBA LATE BREAKING ABSTRACT

First efficacy findings from a randomized phase III trial of capecitabine + oxaliplatin vs. bolus 5-FU/LV for stage III colon cancer (NO16968/XELOXA study)

D. Haller[1], J. Tabernero[2], J. Maroun[3], F. de Braud[4], T. Price[5], E. Van Cutsem[6], M. Hill[7], F. Gilberg[8], K. Rittweger[9], H. Schmoll[10]. *[1]University of Pennsylvania, Hematology/Oncology, Philadelphia, USA; [2]Vall d'Hebron University Hospital, Medical Oncology, Barcelona, Spain; [3]Ottawa Regional Cancer Centre, Medical Oncology, Ottawa, Canada; [4]Istituto Europeo di Oncologia, Clinical Pharmacology and New Drugs, Milano, Italy; [5]The Queen Elizabeth Hospital, Medical Oncology, Adelaide, Australia; [6]University Hospital Gasthuisberg, Digestive Oncology Unit, Leuven, Belgium; [7]Maidstone Hospital, Mid Kent Oncology Centre, Maidstone, United Kingdom; [8]F. Hoffmann-La Roche Ltd., Biostatistics, Basel, Switzerland; [9]F. Hoffmann-La Roche Ltd., Clinical Development Oncology, Nutley, USA; [10]Martin Luther University Innere Med. IV, Haematology/Oncology, Halle, Germany*

Background: Adjuvant capecitabine is at least equivalent to bolus i.v. 5-FU/LV in disease-free survival (DFS) and overall survival (OS) in stage III colon cancer [Twelves et al. NEJM 2005; ASCO GI 2008]. Phase III clinical trials in 1st- and 2nd-line metastatic colorectal cancer have shown that capecitabine + oxaliplatin (XELOX) is as effective and safe as oxaliplatin + infusional 5-FU/LV [Cassidy et al. JCO 2008; Rothenberg et al, Ann Oncol 2008; Ducreux et al. ASCO 2007; Diaz-Rubio et al. JCO 2007; Porschen et al. JCO 2007]. NO16968 was designed to compare the efficacy and safety of XELOX with bolus i.v. 5-FU/LV (the standard regimen at study start) for stage III colon cancer. In a planned safety analysis, XELOX had an acceptable safety profile in this setting [Schmoll et al. JCO 2007].
Materials and Methods: Patients were randomized to receive either XELOX (capecitabine 1000 mg/m^2 orally bid d1−14 + oxaliplatin 130 mg/m^2 i.v. d1, q3w for 8 cycles) or bolus i.v. 5-FU/LV according to the Mayo Clinic (LV 20 mg/m^2 + 5-FU 425 mg/m^2 d1−5, q4w for 6 cycles) or Roswell Park (LV 500 mg/m^2 + 5-FU 500 mg/m^2 d1, w1−6 in 8w cycles $\times$4) regimens, as both had shown nearly identical efficacy in a prior trial [Haller et al. JCO 2005]. Each participating center's preferred 5-FU/LV regimen was selected at study start and used in all patients treated at that center.
Results: 1886 patients were recruited and randomized between April 2003 and October 2004. Of these, 1864 were evaluable in the previously reported safety analysis. After a median follow-up of 57 months, 1886 patients are evaluable for the primary study endpoint, DFS, which was significantly superior for XELOX at 3 and 4 years.

	3-year DFS	4-year DFS
XELOX	71.0%	68.4%
5-FU/LV	67.0%	62.3%
	HR 0.80, p = 0.0045	

Conclusions: XELOX is superior to i.v. bolus 5-FU/LV in DFS as adjuvant treatment for stage III colon cancer. The results with XELOX in the adjuvant setting confirm the benefits shown with oxaliplatin plus 5-FU combinations in stage III patients enrolled in the MOSAIC (FOLFOX vs. LV5FU2) and NSABP C-07 (5-FU/LV vs. FLOX) trials, and may provide a potential additional option for patients with stage III disease. OS data are currently immature; follow-up is ongoing, and updates will be reported when available.

6LBA LATE BREAKING ABSTRACT

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)

T. Maughan[1], R.A. Adams[1], C.G. Smith[2], M.T. Seymour[3], R. Wilson[4], A.M. Meade[5], D. Fisher[5], A. Madi[1], J. Cheadle[2], R. Kaplan[5]. *[1]Cardiff University, Section of Clinical Oncology and Palliative Medicine, Cardiff, United Kingdom; [2]Cardiff University, Institute of Medical Genetics, Cardiff, United Kingdom; [3]University of Leeds, St. James's Institute of Oncology, Leeds, United Kingdom; [4]Queen's University Belfast, Oncology, Belfast, United Kingdom; [5]Medical Research Council, Clinical Trials Unit, London, United Kingdom*

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 ±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