22LBA LATE BREAKING ABSTRACT

Overall survival analyses from the SATURN phase III placebo-controlled study of erlotinib as first-line maintenance therapy in advanced non-small-cell lung cancer (NSCLC)

F. Cappuzzo[1], B. Coudert[2], R. Wierzbicki[3], K. Park[4], F. Custers[5], G.A. Curbera[6], G. Giaccone[7], W. Hilbe[8], G. Klingelschmitt[9], T.E. Ciuleanu[10]. [1]*Istituto Clinico Humanitas, Oncology, Rozzano Milano, Italy;* [2]*Centre George-François Leclerc, Medical oncology, Dijon, France;* [3]*RS McLaughlin Durham Regional Cancer Centre, Oncology, Oshawa, Canada;* [4]*Samsung Medical Centre, Oncology, Seoul, South Korea;* [5]*Atrium Medisch Centrum, Oncology, Heerlen, The Netherlands;* [6]*Medical Oncology Service Hospital Juan Canalejo, Oncology, La Coruña, Spain;* [7]*National Institutes of Health, Oncology, Bethesda, USA;* [8]*University Hospital, Oncology, Innsbruck, Austria;* [9]*F. Hoffmann-La Roche Ltd, Statistics, Basel, Switzerland;* [10]*Institute of Oncology Ion Chiricuta, Oncology, Cluj-Napoca, Romania*

Background: Erlotinib is an established option for 2nd-line treatment of patients (pts) with advanced NSCLC. A substantial proportion of pts do not, however, receive 2nd-line therapy, possibly because of worsening overall condition. In the phase III, randomised, placebo-controlled SATURN study (BO18192; Roche), erlotinib was evaluated as 1st-line maintenance therapy in pts whose disease had not progressed after 1st-line chemotherapy.
Materials and Methods: Pts without progressive disease or residual toxicity following 4 cycles of 1st-line platinum-doublet chemotherapy were randomised to erlotinib 150 mg/day or placebo until progression or unacceptable toxicity. Co-primary endpoints were PFS in all pts and in pts with EGFR IHC+ tumours. OS was a secondary endpoint, and was measured from the time of randomisation. Tumour sampling was mandatory, with pre-planned biomarker analyses performed.
Results: 889 pts were randomised to maintenance therapy (erlotinib n = 438; placebo n = 451). Baseline characteristics were well balanced between arms. A diverse range of post-study therapies was received by 71% pts in the erlotinib group and 72% in the placebo group; the use of specific therapies was similar between arms, except for subsequent EGFR TKIs (11% and 21% pts in the erlotinib and placebo groups, respectively). The co-primary endpoints were met: HR for PFS: 0.71 in all pts, 0.69 in EGFR IHC+ (both $p < 0.0001$). Erlotinib produced a significant OS benefit (HR 0.81; $p = 0.0088$) in the ITT population, with a larger benefit obtained in the adenocarcinoma subgroup (HR 0.77). As observed for PFS, an OS benefit was obtained in both *EGFR* wild-type and *EGFR* mutation+ groups (see table); median OS has not been reached in the mutation+ group, and there was a high-degree of cross-over to 2nd-line EGFR TKI in the placebo arm of this group.
Conclusions: Erlotinib significantly prolongs both PFS and OS in the overall population when used as 1st-line maintenance therapy. The OS benefit was obtained against a background of high use of diverse subsequent therapies, and was particularly large in patients with adenocarcinoma histology. Furthermore, the OS benefit was not driven by the *EGFR* mutation-positive subgroup, with a significant improvement in OS observed in the *EFGR* wild-type group.

Group	n	HR for OS
All patients	889	0.81
Adenocarcinoma	403	0.77
Squamous-cell carcinoma	360	0.86
EGFR mutation+	49	0.83
EGFR wild-type	388	0.77

Melanoma and skin cancer
Wednesday 22 September 2009, 14:45–17:00

23LBA LATE BREAKING ABSTRACT

BEAM: A randomized phase II study evaluating the activity of BEvacizumab in combination with carboplatin plus paclitaxel in patients with previously untreated Advanced Melanoma

S.J. O'Day[1], K.B. Kim[2], J.A. Sosman[3], A.C. Peterson[4], S. Feng[5], D.R. Minor[6], J.P. Fruehauf[7], G.P. Linette[8], S.N. Markovic[9], W.E. Carson[10]. [1]*The Angeles Clinic and Research Institute, Medicine, Santa Monica, USA;* [2]*The University of Texas M.D. Anderson Cancer Center, Medicine, Houston, USA;* [3]*Vanderbilt-Ingram Cancer Center, Medicine, Nashville, USA;* [4]*Genentech, BioOncology, S. San Francisco, USA;* [5]*Genentech, BioStatistics, S. San Francisco, USA;* [6]*California Pacific Medical Center, Medicine, San Francisco, USA;* [7]*Chao Family Comprehensive Cancer Center, Medicine, Irvine, USA;* [8]*Washington University, Medicine, St. Louis, USA;* [9]*Mayo Clinic, Medicine, Rochester, USA;* [10]*The Ohio State University Comprehensive Cancer Center, Surgery, Columbus, USA*

Background: Malignant melanoma (MM) is a highly vascular tumor and expression of VEGF has been associated with a worse overall prognosis. Bevacizumab (B) prevents the interaction of VEGF with its receptors and neutralizes its biological activity. The combination of carboplatin (C) and paclitaxel (P) has demonstrated activity in MM. As in other cancers, B may enhance the efficacy of this chemotherapy in MM.
Materials and Methods: AVF4096g is a phase II randomized, placebo-controlled Genentech sponsored study designed to estimate the clinical benefit and characterize the safety of B when added to CP in subjects with stage IV, treatment naïve MM. Randomization was 2:1 (CPB:CP) and stratified on ECOG PS (0,1) and disease stage (M1a/b, M1c). C (AUC = 5, maximum of 10 cycles), P (175 mg/m^2) and B (15 mg/kg) were administered IV on Day 1 every 3 weeks. Evaluations for RECIST response were performed every 2 cycles. Progression free survival (PFS) was the primary endpoint, secondary endpoints included overall survival (OS), response rates (RR) and safety.
Results: 214 subjects were randomized from 2/07–8/08. Baseline characteristics were well balanced between treatment groups, 73% of subjects had M1c disease, 54% of M1c subjects had abnormal LDH levels. Median follow up at the time of analysis was approximately 13mos for each arm. There was a trending benefit in PFS with the addition of B (median 5.6 vs 4.2 mos, HR 0.78 with 95% CI 0.56–1.09, $p = 0.14$). A statistically significant improvement in OS was observed with CPB vs CP, with median of 12.3 vs 8.6 months, HR 0.67 (95% CI 0.46, 0.98), and $p = 0.04$. RR were also higher in the CBP arm (25.5% vs 16.4%, $p = 0.16$). Grade 3–5 AEs occurring with 2% or more increase incidence over CP included febrile neutropenia, neutropenia, peripheral neuropathy, pulmonary embolism, hypertension, anorexia and musculoskeletal pain.
Conclusions: This is the first randomized placebo controlled trial in metastatic melanoma to demonstrate a statistically significant and clinically meaningful improvement in OS. Similar trending benefits were seen in PFS and RR. The majority of subjects had M1c disease. The combination of CPB was well tolerated; no new safety events were observed and B-related safety events were in line with observations from other disease-based clinical studies using similar chemotherapy.

24LBA LATE BREAKING ABSTRACT

Temozolomide combined with bevacizumab in metastatic melanoma. A multicenter phase II trial (SAKK 50/07)

R. Von Moos[1], B. Seifert[2], A. Ochsenbein[3], R. Cathomas[1], M. Schläppi[4], S. Gillessen[4], J.C. Schuller[5], O. Michielin[6], S. Goldinger[7], R. Dummer[7]. [1]*Kantonsspital Graubuenden, Medical Oncology, Chur, Switzerland;* [2]*University Hospital Basel, Medical Oncology, Basel, Switzerland;* [3]*University Hospital Bern, Medical Oncology, Bern, Switzerland;* [4]*Kantonsspital St. Gallen, Medical Oncology/Hematology, St. Gallen, Switzerland;* [5]*Swiss Group for clinical cancer research (SAKK), Headquarter, Bern, Switzerland;* [6]*Centre Hospitalier Universitaire Vaudois (CHUV), Medical Oncology, Lausanne, Switzerland;* [7]*University Hospital Zürich, Department of Dermatology, Zürich, Switzerland*

Background: Single agent DTIC is the standard therapy for metastatic melanoma (MM) with response rates of 5–20%. Temozolomide (Tem) as an oral drug has shown equal efficacy in phase III trials. Preclinical models have shown an inhibitory effect for bevacizumab (Bev) on the proliferation of melanoma cells as well as on sprouting endothelial cells. Therefore, a therapeutic approach that combines angiogenesis inhibitors with cytotoxic agents may provide clinical benefit in MM.

Methods: Design: Multicenter phase II trial. Primary endpoint: Clinical benefit (CR, PR and SD) at 12 weeks; secondary endpoints: best overall response by RECIST, response duration, progression free survival, adverse events, survival after 6 months and overall survival. Sample size was calculated according to Simon's two stage optimal design (5% significance level and 80% power) with an overall sample size of 62 patients (pts) to test H0: 20% versus H1: 35% rate of clinical benefit. Response assessment was done every 6 weeks (3 cycles). Eligibility: Stage IV MM, ECOG PS 0−2, no prior treatment for metastatic disease. Treatment regimen: One cycle consisted of Tem at 150 mg/m^2 days 1−7 po and Bev at 10 mg/kg day 1 over 30 min iv and was repeated every 2 weeks until progression or unacceptable toxicity.
Results: Between January 2008 and April 2009, 62 pts (40 male/22 female) at a median age of 61 years (range 30−86) with stage IV (M1a:4, M1b:12, M1c:46) melanoma were enrolled in 9 centers. The first 50 pts, who received 415 cycles are included in this interim report. The overall response rate was 26% (CR: 1 pt, PR: 12 pts; PR not confirmed yet in 3 pts), and 44% (22 pts) had stable disease over 1.5−7.5 months (median: 3). Only 30% (15 pts) had disease progression at the first evaluation at week 6. The hematological grade 3/4 toxicities according to NCI CTAE 3.0 were thrombocytopenia 10% (5 pts), neutropenia 8% (4 pts), lymphopenia and leucocytopenia each 2% (1 pt). Cumulative non-hematological toxicities grade 3/4 were nausea and fatigue each 6% (3 pts), hypertension, vomiting and hemorrhage, each 4% (2 pts), thrombosis/embolism, infection, constipation, anorexia, elevation of alkaline phosphatase, bilirubin, GGT, ALT and AST each 2% (1 pt).
Conclusion: In metastatic melanoma the combination of Tem/Bev is a safe regimen with a promising efficacy and few grade 3/4 toxicities. Updated results of all 62 pts will be presented.

25LBA LATE BREAKING ABSTRACT

A novel highly prognostic nine gene signature can change the algorithm of adjuvant alfa-interferon in malignant melanoma at 1st diagnosis

G. Brunner[1], M. Reitz[2], A. Heinecke[3], A. Lippold[4], C. Berking[5], L. Suter[1], J. Atzpodien[6]. *[1]Fachklinik Hornheide, Department of Cancer Research, Münster, Germany; [2]European Institute for Tumor Immunology and Prevention, Department of Research, Sassenberg, Germany; [3]University of Münster, Department of Medical Informatics and Bioinformatics, Münster, Germany; [4]Fachklinik Hornheide, Department of Documentation, Münster, Germany; [5]Ludwig-Maximilians-University of Munich, Department of Dermatology and Allergology, Munich, Germany; [6]Fachklinik Hornheide, at the University of Münster, Münster, Germany*

Background: Classical staging criteria, such as Breslow tumor thickness, lymph node status, and ulceration, are used to define the need for adjuvant Alfa Interferon in cutaneous malignant melanoma at 1st diagnosis. Since these criteria remain largely inadequate for precisely predicting clinical outcome, here, we release the first gene signature of high prognostic power in melanoma.
Materials and Methods: To identify prognostic genes we correlated whole genome expression profiles of 136 primary melanomas with overall survival. A comparative analysis of high-risk vs. low-risk primary melanomas with a clinical follow-up of more than 20 years yielded 95 candidate genes, which were further analyzed by RT-PCR using 91 primary melanomas as training cohort. The resulting prognostic nine-gene signature was validated by RT-PCR using an independent set of 45 primary melanomas.
Results: Expression scoring of these nine genes (SPINK7/ECG2, KBTBD10, KRT9, HES6, DCD, COL6A6, PIP, SCGB1D2, SCGB2A2) or subgroups of these genes predicted overall survival independently of AJCC staging ($p = 0.0004$, hazard ratio 3.83). When combining gene expression scores and AJCC staging, approximately two thirds (29/45, 64%) of patients with AJCC intermediate prognosis (i.e., stages IIA, IIB, and IIIA) were reclassified into good prognosis, exhibiting a long term overall survival probability of 95%. Misclassification rate of all patients classified into good prognosis (low risk gene score combined with AJCC stages I, IIA/B, or IIIA) was extremely low at 4.6% and 6.25% in the training and validation cohorts, respectively.
Conclusion: Reclassification of AJCC intermediate prognosis patients using this novel gene signature is the basis for a more specific and effective use of Alfa Interferon as an adjuvant therapy of cutaneous malignant melanoma; it may allow patients at low risk to stay treatment free while experiencing excellent long term survival.

Radiotherapy and radiobiology
Thursday 24 September 2009, 09:00−11:15

26LBA LATE BREAKING ABSTRACT

Tumor blood supply evaluation for NSCLC radiotherapy planning

K. Szluha[1], K. Lazányi[1], M. Simon[1], A. Abramyuk[2], S. Tokalov[2], G. Wolf[2], S. Appold[3], T. Herrmann[3], N. Abolmaali[2]. *[1]University of Debrecen – Radiation Oncology Department of University Medical School and Health Science Center, Radiation Oncology, Debrecen, Hungary; [2]Oncoray – Center for Radiation Research in Oncology, Radiation Oncology, Dresden, Germany; [3]Radiotherapy TU Dresden, Radiation Oncology, Dresden, Germany*

Background: The aim of this study was to investigate the local tumor blood supply parameters relative tumor blood volume (rTBV) and transfer coefficient (Ktrans) measurable with dynamic contrast enhanced computed tomography (DCE-CT) in patients with nonsmall-cell lung cancer (NSCLC) scheduled for radiation therapy (RT).
Materials and Methods: rTBV and Ktrans were assessed in 31 patients with inoperable NSCLC (stage I−IV), which received or did not receive induction chemotherapy (IChT) and were assigned to RT. To evaluate DCE-CT in the management of NSCLC patients, possible links between rTBV and Ktrans and time-to-progression (TTP), overall survival (OS) and maximal standardized uptake value (SUVmax) from fluorodeoxyglucose positron emission tomography (FDG-PET) as well as histological findings were analyzed.
Results: NSCLC showed a wide range of rTBV and Ktrans values depending on stage and IChT. A significant difference in rTBV values was found in patients with and without IChT. A negative correlation between rTBV and TTP was revealed only in RT patients with curative therapeutic intent who manifested progression in developing distant metastases ($n = 7$, $r = -0.96$, $p = 0.0006$). An inverse correlation was shown between Ktrans and TTP ($n = 24$, $r = -0.53$, $p = 0.008$) in all RT patients. In patients with curative therapeutic intention, an inverse correlation between Ktrans and TTP was found ($n = 20$, $r = -0.53$, $2p = 0.016$). No relevant correlation was found between rTBV, Ktrans and SUVmax or histological subtypes and grading.
Conclusions: Tumor blood supply parameters derived from DCE-CT may be useful to characterize tumor vascularity before radiotherapy in patients with NSCLC and outcome prediction may be supplemented.

Late breaking poster session
Tuesday 22 September 2009, 09:00−17:00
(Viewing: 11:00−13:00)

27LBA LATE BREAKING ABSTRACT

Mode of action analysis of sorafenib by integrating chemical proteomics and phosphoproteomics

A. Tebbe[1], M. Klammer[2], M. Kaminski[1], S. Wandinger[3], C. Eckert[3], S. Müller[3], M. Gorray[4], E. Enghofer[4], C. Schaab[2], K. Godl[3]. *[1]KINAXO Biotechnologies, Mass Spectrometry, Munich, Germany; [2]KINAXO Biotechnologies, Bioinformatics, Munich, Germany; [3]KINAXO Biotechnologies, Chemical Biology, Munich, Germany; [4]Bayer Vital GmbH, Oncology, Leverkusen, Germany*

Background: Multi-targeted kinase inhibitors such as sorafenib (Nexavar®, Bayer HealthCare AG) have emerged as promising anti-cancer drugs. However, due to their broad selectivity, it is particularly challenging to understand their modes of action in a cellular context. Systems-wide approaches integrating comprehensive target identification and global phosphoproteome analysis are now available to gain valuable insights into the inhibitor's mode of action.
Material and Methods: The cellular target profile of sorafenib was analyzed applying a quantitative chemical proteomics workflow. PC3 cell lysates were incubated with immobilized sorafenib and competed with free compound. Bound proteins were analyzed by quantitative LC-MS allowing identification and quantification of the cellular target proteins. For global phosphoproteome analysis triply SILAC-labeled PC3 cells were incubated with sorafenib for 0, 30, and 90 min. Proteins were digested, phosphopeptides were specifically enriched and analyzed by LC-MS. Identified phosphorylation sites were further statistically analyzed and mapped to signal transduction pathways and protein-protein interaction networks.
Results: We integrated advanced chemical proteomics and global phosphoproteomics to reveal new modes of action of sorafenib. We confirmed previously known kinase targets such as B-Raf and p38α. In addition, previously unknown targets Mekk1, Taok3, and Mylk were identified with reasonable affinities (up to 30 nM). In parallel, quantitative