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

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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

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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