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

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

phosphoproteomics upon sorafenib treatment was conducted in four biological replicate experiments leading to the identification of more than 20,000 phosphorylation sites. About 700 phosphorylation sites were significantly regulated at a false discovery rate of 5%. Mapping of the regulated phosphorylation sites to signal transduction pathways revealed severe down-regulation of the MAP kinase pathway thus confirming the expected cellular inhibition of various members of the MAP kinase family. In addition, several other pathways were deregulated. In particular the mTOR pathway was significantly affected by sorafenib.
Conclusions: Systems-wide analysis of sorafenib effects in a prostate cancer cell line revealed important, yet unknown modes of action, such as a significant influence on the mTor-signalling pathway. We demonstrated that global phosphoproteome analysis provides a better understanding on how this kinase inhibitor works on a molecular level in the treatment of cancer.

28LBA LATE BREAKING ABSTRACT

Conceptual change in oncology: Progression-Free-Survival (PFS) is a more appropriate surrogate for Overall Survival (OS) than Time-To-Progression (TTP)

F. Porzsolt[1], A.S. Weber[1], R. Muche[2]. *[1]Clinical Economics, Medical Faculty, Ulm, Germany; [2]Department Biostatistics and Medical Information, Medical Faculty, Ulm, Germany*

Background: Time-To-Progression (TTP) and Progression-Free-Survival (PFS) are often used to approve new treatments and to support guidelines. This study describes the relationship between TTP, PFS and OS and provides a model which explains differences and important consequences for research and practice in oncology.
Methods: Data on TTP or PFS as well as on OS were extracted from randomized clinical trials published in 2007 and 2008. Linear regression of TTP and OS, PFS and OS were computed, OS being the dependent variable. Their correlation was expressed with Pearson's correlation coefficients. The frequencies of significant differences of TTP, PFS and OS were compared.
Results: 56% of the studies used TTP, 25% used PFS and 19% used other measures in addition to OS to describe the results. In some studies TTP/PFS was measured from the time of randomization and in others from begin of therapy. In some studies only tumor specific deaths were included but in others deaths of any cause. About 10% of studies claimed to measure PFS (according to the definitions of the US Dept. Health and Human Services 2000) but in fact measured TTP or vice versa. In two studies TTP was longer than survival. The correlation coefficient of TTP and OS was 0.54 (n = 163) and of PFS and OS was 0.89 (n = 75). In 26% of studies which reported TTP significant differences in OS and in 40% of cases significant differences in TTP were reported. In studies which reported PFS significant differences in PFS were reported in 45% and in OS in 17% of cases.
Discussion: PFS is defined as time to progression or death whatever comes first and considers both, structural and functional aspects. TTP is defined as time to progression where cases are censored if death occurs before progression. This means that TTP excludes the functional aspect which is included in PFS. The model predicted that the correlation of PFS and OS will be better than the correlation of TTP and OS and that the effects of most treatments which do not extend OS will be overestimated. Researchers may preferably report TTP in cancers with favourable prognosis but report PFS when the prognosis is poor. In conclusion, our model predicts and our data confirm the findings of several other studies which suggested that PFS is a better surrogate for survival then TTP. Authorized organisations should supplement the missing criteria for assessment of PFS. TTP overestimates the effects of treatment and may be used only together with PFS.

29LBA LATE BREAKING ABSTRACT

Efficacy, safety and patient acceptability of fentanyl pectin nasal spray compared with immediate-release morphine sulphate tablets in the treatment of breakthrough cancer pain: a multicentre, double-blind, double-dummy, multiple-crossover study

M. Fallon[1], A. Gatti[2], A. Davies[3], E.A. Lux[4], K. Kumar[5], R. Galvez[6], on behalf of the Fentanyl Nasal Spray Study 044 Investigators Group. *[1]Western General Hospital, Palliative Care Team, Edinburgh, United Kingdom; [2]Azienda Policlinico Tor Vergata, AFA Emergenza Urgenza Terapia Intensiva e Terapia del Dolore, Rome, Italy; [3]The Royal Marsden NHS Foundation Trust, Palliative Care, Surrey, United Kingdom; [4]St. Marien-Hospital, Abt. Schmerztherapie, Lunen, Germany; [5]Meenakshi Mission Hospital, Department of Radiation & Clinical Oncology, Madurai, India; [6]Unidad del Dolor/Hospital Virgen de las Nieves, Unidad de Pain and Palliative Care, Granada, Spain*

Background: Breakthrough cancer pain (BTCP) affects most cancer patients; the analgesic time course of current oral therapies does not match the typical time course of BTCP. Fentanyl pectin nasal spray (FPNS) has kinetics that enable a rapid onset of pain relief (PR). The aim of this study was to assess efficacy of FPNS compared with immediate-release morphine sulphate (IRMS) in the treatment of BTCP.
Material and Methods: Patients (N = 110) experiencing 1−4 BTCP episodes/day whilst taking $\geqslant$60 mg/day of oral morphine (or equivalent) for background cancer pain entered a double-blind, double-dummy (DB/DD), multiple-crossover study. Those who completed an open-label titration phase (N = 84) continued to a DB/DD phase; 10 episodes of BTCP were randomly treated with FPNS and oral capsule placebo (5) or IRMS and nasal spray placebo (5). Pain intensity (PI; 11-point numerical scale) and PR (5-point scale) were measured at 5, 10, 15, 30, 45 and 60 min post dose. The primary endpoint was pain intensity difference from baseline at 15 min (PID_{15}) vs IRMS. Secondary endpoints included time to meaningful PR ($\geqslant$2-point PI decrease), onset of pain improvement ($\geqslant$1-point PI decrease), patient acceptability/satisfaction, safety and tolerability. By-patient and by-episode analyses were completed. Safety was evaluated by adverse events (AEs) and objective and subjective nasal assessments.
Results: FPNS significantly improved mean PID_{15} scores compared with IRMS ($P = 0.0396$; modified intent-to-treat analysis N = 79). 740 BTCP episodes were analysed (FPNS N = 372; IRMS N =D 368): 57.5% of FPNS-treated episodes showed onset of PI improvement by 5 min and 95.7% at 30 min (both $P < 0.05$ vs IRMS). Clinically meaningful PR was seen in 52.4% of episodes by 10 min ($P < 0.05$ vs IRMS). More episodes treated with FPNS vs IRMS showed a $\geqslant$1-point PR score at 5 min ($P < 0.05$) and at all points through to 30 min. Patients were 'satisfied' or 'very satisfied' with the convenience (79.8%) and ease of use (77.2%) of FPNS. Overall treatment satisfaction was high; patients were 'satisfied' or 'very satisfied' with FPNS for 81.5% of episodes compared with 71.2% treated with IRMS ($P < 0.01$). Only 4.7% of patients withdrew from titration (2.4% in DB/DD phase) due to AEs; no significant nasal effects were reported.
Conclusions: FPNS provides clinically meaningful PR and a more rapid onset of analgesia than IRMS that better matches the typical time course of a BTCP episode.

30LBA LATE BREAKING ABSTRACT

Design of 1,4-dihydropyridine derivatives for overcoming ABC-mediated transporter multidrug resistance

A. Nematollahi[1], A. Nabbi[2]. *[1]Islamic Azad University-Pharmaceutical Sciences Branch, Medicinal Chemistry, Tehran, Iran; [2]Islamic Azad University-Pharmaceutical Sciences Branch, Pharmacology, Tehran, Iran*

Introduction: Multidrug resistance (MDR) is one of the main reasons of failure in tumor chemotherapy, as tumor cells, by increasing drug efflux, acquire resistance to many anticancer agents, which never achieve effective concentrations. Drug resistant cell lines have shown increased levels of membrane glycoprotein, named P-glycoprotein (P-gp). It is an ATP-dependent extrusion pump for drugs and physiological substrates. Studies have shown the ability of neutralizing Pgp-related MDR by some reversing agents. 1,4-Dihydropyridine (DHP) is one of the MDR reversing agents. Docking is frequently used to predict the binding orientation of drug candidates to their protein targets to predict the affinity of the molecule. Hence, docking plays an important role in the rational design of drugs. In this study, therefore, we investigate the effects of DHP derivatives on MDR.
Material and Method: The structure of reversing agents was drawn by HYPERCHEM program. Conformations of the designed compounds were optimized through semi-empirical method followed by PM3 calculation by the program HYPERCHEM. Among all energy minimal conformers, the global minimum was selected. Then the crystal of Human ABCB2 was obtained from the Protein Data Bank (PDB) server. Finally Docking calculations were carried out using AutoDock program. The DHP