Conclusions: The present study demonstrated that histological parameters for SN tumour burden provide prognostic and predictive information for survival and NSN status. SN positive patients with micrometastases smaller than 0.1 mm in largest diameter might be indicated for observation instead of CLND, especially when located subcapsularly. Evidence based conclusions of currently running prospective trials such as the Multicenter Selective Lymphadenectomy Trial (MSLT) − II and the EORTC MG MINITUB study might conclude if and/or which SN positive patients might benefit from undergoing immediate CLND.

9303 ORAL

131I Targeted Radionuclide Therapy by Melanin Linked Molecules for Melanoma Treatment

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Background: Cutaneous melanoma is characterized by a poor prognosis when disseminated, with a very low efficacy of current chemotherapy, only 15% of patients treated with dacarbazine are alive after a 5 years follow-up. In this context, different targeted therapies including those supported by melanin presence in melanoma are still a crucial topic. We developed arylcarboxamides, that are small molecules with strong melanin affinity, for melanoma targeted radionuclide therapy. We tested the ability of I^{131} labelled arylcarboxamides to reduce melanoma growth in syngenic B16 models and human xenografts. We also characterized uveal toxicity as mechanisms linked with melanin targeting.
Materials and Methods: Long lasting B16 tumoural uptake structures were selected and labelled with I^{131} for internal targeted melanoma cell irradiation. B16/C57Bl6 syngenic model as human cell lines xenografts were used for preclinical evaluations.
Results: Systemic administration of I^{131}−ICF01012 (2 × 18.5 Mbq) led to a significant growth inhibition of B16F0 and B16Bl6 syngenic tumours although an uveal damage could be observed in this highly pejorative C57Bl6 pigmented mouse model. However, one 18.5 Mbq injection was still effective on B16Bl6 tumoural growth and decreased I^{131}−ICF01012 uveal toxicity (30% of the mice did not present any histological ocular insult). Mechanistic studies on B16Bl6 model demonstrated that this targeted irradiation induced characteristic cellular responses to radiations: $P53_{S15}$ phosphorylation, increase of cells in G2/M, decrease of proliferation estimated by PCNA, pAKT and pERK expressions. [I^{131}]-ICF01012 treatment was also effective in reducing growth of human cell lines pigmented xenografts (M4Beu and SkMel3) while no modification of tumoural growth could be pointed out in M3Dau achromic tumours.
Conclusions: Targeted radionuclide therapy using ^{131}I labelled arylcarboxamides represents a new potential treatment strategy for melanoma. Experimental preclinical studies showed obviously a specific internal irradiation of pigmented melanoma tumours. Further studies including dosimetry are ongoing to allow a rapid clinical transfert.

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9304 ORAL

Percutaneous Hepatic Perfusion (PHP) Vs. Best Alternative Care (BAC) for Patients (pts) With Melanoma Liver Metastases − Efficacy Update of the Phase 3 Trial (NCT00324727)

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Background: There is no standard of care for liver-dominant metastatic melanoma. Meta-analyses have reported median overall survival of 2−4 months. One-year survival is around 10%. PHP was designed to saturate the liver with high doses of chemotherapy, via a minimally invasive approach. We report updated efficacy results of the first-ever phase 3 multi-center randomized trial for pts with unresectable liver melanoma metastases, comparing PHP with melphalan to BAC.
Materials & Methods: Pts were prospectively randomized 1:1. On the PHP arm, melphalan (3 mg/kg ideal body weight) was infused via the hepatic artery over 30 minutes. Hepatic venous return was captured from the intrahepatic IVC using a specially-designed double-balloon catheter, and directed through extra-corporeal filters to extract melphalan before return of filtered blood. The procedure was repeated every 4−8 weeks on recovery from hematological toxicity. The control arm was the investigators' pre-specified choice of therapy. The primary endpoint was hepatic progression-free survival (hPFS) using RECIST at pre-defined 6-week intervals on both study arms. Secondary endpoints included safety, ORR, PFS, OS. Cross-over to PHP on hepatic progression was permitted. All analyses were ITT. The NCI-led study with 9 additional US centers was sponsored by Delcath Systems, Inc., NY.
Results: From 2/2006 to 7/2009, 93 patients were randomized to PHP (n = 44) or BAC (n = 49). Mean age was 54.8 yrs with no significant imbalances in baseline characteristics. AEs were primarily hematological (grade 3/4), as expected. As of 4/2011, investigator-assessed hPFS was significantly better in the PHP group, median 8.1 vs. 1.6 months, HR 0.34, $p < 0.0001$, with a 6.5 month difference at the median. Overall PFS showed similar benefit (HR 0.41, $p < 0.0001$, median 6.1 vs. 1.6 months). 1-year OS was 29% on PHP vs. 26% on BAC. OS was not significantly different (median PHP 11.4 vs. BAC 9.9 months, $p = 0.982$) due to 51% crossover. Crossover pts had a median hPFS from crossover date of 9.2 months and overall PFS 6.5 months.
Conclusions: This first phase 3 study in pts with liver-dominant metastatic melanoma met its primary endpoint. hPFS, ORR and overall PFS were significantly improved with PHP vs. BAC. PHP with melphalan should provide a new treatment option for unresectable metastatic melanoma in the liver.

9305 ORAL

A Phase II Study Combining Ipilimumab and Fotemustine in Patients With Metastatic Melanoma − the NIBIT-M1 Trial

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Background: The anti-CTLA-4 mAb ipilimumab prolongs survival in pre-treated metastatic melanoma (MM) patients (pts). MM pts with brain metastases have been excluded from trials with ipilimumab; however, initial evidences indicate its potential effectiveness as single-agent in this clinical setting. Fotemustine, a cytotoxic alkylating drug that efficiently crosses the blood-brain barrier, is active as single-agent in MM. The Italian Network for Tumour Biotherapy (NIBIT) trial NIBIT-M1 was designed to investigate the clinical and immunologic efficacy of ipilimumab in combination with fotemustine in MM pts with or w/o brain metastases.

Material and Methods: From July 2010 to April 2011 the NIBIT-M1 enrolled the 86 cutaneous MM pts, stage III (2) or IV (84) pts (60 males, 26 females), median age 54 (24−78) years, ECOG performance status 0−1, planned in the study. Twenty-one pts had evidence (19) or history (2) of brain metastases. Forty-three pts were treatment naive and the remaining had received one line of systemic treatment for metastatic disease. Ipilimumab was administered i.v. at 10 mg/kg q3 weeks (wk) for 4 doses in the induction phase (IP) and once q12 wk from wk 24 in the maintenance phase (MP); fotemustine was administered i.v. at 100 mg/m^2 weekly for 3 wk (IP), and q3 wk from wk 9 (MP). Tumour assessment (TA) *per* immune-related response criteria (irRC), was performed at screening and wk 12, then every 8 wk until W36, and every 12 wk from W36 onwards. A pre-spe-specified safety analysis was planned at wk 6 of treatment for the initial 18 pts. Adverse Events (AE) and immune related AE (irAE) were collected according to Common Terminology Criteria for Adverse Events version 4.0.
Results: On November 2010, the safety analysis was successfully met, and no additive toxicities were observed; thus, the Safety Committee allowed resuming the accrual. As of April 2011, 28 pts have terminated the IP and 13 of them have already entered the MP. Of the remaining pts, 43 are completing the IP and 15 have been withdrawn for AE severity (1) or disease progression (14). Of the 17 pts for which TA at wk 12 is available, 14 achieved a disease control (CR, PR or SD), including brain metastases in 5 out of 6 pts, while 3 had PD.
Conclusions: Though very initial, the available data suggest for the safety and efficacy of ipilimumab in combination with fotemustine in MM pts with or w/o brain metastases. The six months results from the study closure will be presented.

9306 ORAL

Safety and Efficacy of Ipilimumab-treated Patients With Melanoma and Brain Metastases

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Background: Ipilimumab (Yervoy™), an anti-CTLA-4 monoclonal antibody that augments T-cell-mediated antitumour responses, is indicated in the US for patients (pts) with unresectable or metastatic melanoma. At diagnosis of metastatic disease, 30% of pts have brain metastasis and an additional 30% will develop these within 1−2 years. Herein, we describe overall survival and safety of ipilimumab in pts with melanoma and brain metastases in clinical trials CA184–042 (NCT00623766) and CA184–045 (NCT00495066).
Patients and Methods: The prospective trial CA184–042 included pts with active, measurable brain metastasis ($\geqslant$1 lesion >0.5 cm and/or $\geqslant$2 lesions >0.3 cm with none >3 cm). At baseline, pts were either stable without steroid therapy (Arm A) or required steroids for central nervous system symptoms (Arm B). Ipilimumab 10 mg/kg was given Q3W for four doses with potential maintenance dosing Q12W. The expanded access program CA184–045, a multicenter, open-label study of ipilimumab 3 or 10 mg/kg Q3W for four doses, included pts with stable and asymptomatic brain metastases at baseline. Among pts who received 10 mg/kg, overall survival (OS) at 1 year was retrospectively collected via database; pts lost to follow up were assumed dead. Safety was monitored prospectively in both trials.
Results: In CA184–042, 51 pts in Arm A and 21 in Arm B were treated with ipilimumab 10 mg/kg. Patients in Arms A & B were all Caucasian with ECOG-PS of 0 or 1, 65% and 52% male, and of mean age 58 and 55, respectively. The 12- and 18-month OS in pts not requiring steroids was 30% at both time points (CIs 0.2−0.5; 0.2−0.4, respectively). The 12-month OS rate in pts with symptomatic brain metastases was 10% (CI 0.0−0.3). There were no unexpected toxicities − grade 3−4 central nervous system adverse events (AEs) occurred in 31% of patients in Arm A and 29% in Arm B. In CA184–045, of 874 pts treated with ipilimumab 10 mg/kg, 165 were identified with brain metastasis. The 1 year OS for these pts was 20%. Drug-related AEs of any grade and grade 3/4 occurred in 41% and 22% of all pts, respectively.
Conclusions: Safety and efficacy of ipilimumab in pts with melanoma and brain metastases are consistent between the prospective and open label trials and ipilimumab also shows similar antitumour activity in the brain as reported overall for extracranial metastases. Two-year survival results and safety observations from fully mature CA184–042 data will be presented.

Poster Presentations (Sun, 25 Sep, 14:00−16:30)
Melanoma and Skin Cancer

9307 POSTER

Oncogenic Mutation Dependent Response to Growth Factors in Melanoma Cells

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Background: Malignant melanoma has one of the worst prognosis among solid tumours. The high mortality of melanoma is due to the metastatic potential of tumour cells that requires increased cell motility. Epidermal and basic fibroblast growth factors (EGF and FGF2) are major autocrin and paracrin signaling molecules in human melanoma. Since two of the most common oncogenic mutations, namely BRAF and NRAS are critical components of this signaling network, in this study we compared the oncogenic mutation dependent effect of growth factors on the proliferation and migration of melanoma cells.
Materials and Methods: Growth factor receptor expression had been measured by Western blot and NRAS and BRAF mutations had been determined by direct sequencing and restriction fragment length polymorphism, respectively. Cell motility and proliferation were determined by the analysis of three-days-long time-lapse videomicroscopic recordings. Both the baseline and induced activation of the growth factor receptor pathway had been quantified by the immunoblot analysis of the phosphorylation of two major downstream effectors, including Erk1/2 and S6.
Results: Both BRAF and NRAS mutations resulted in a higher baseline activation of Erk1/2 and S6 when compared to double wild-type cells under control conditions. Both mutations attenuated the activation of the two downstream targets in response to EGF and FGF2 treatment. Interestingly we found a more profound response in cell motility as compared to cell proliferation. Of note, double wild-type cells responded to both EGF and FGF2 treatment. In contrast BRAF and NRAS mutated melanoma cells displayed varying degree of sensitivity to these growth factors.
Conclusions: In summary our findings demonstrate that the different oncogenic mutations in melanoma cells have an impact on the motogenic effect of the activation of growth factor receptor signaling networks. Since a large number of the emerging molecularly targeted therapies aim at the growth factor receptor signaling, the appropriate mutational analysis of melanoma cases are essential in both preclinical studies and in the clinical trials and practice.

9308 POSTER

The XPC A2920C, the XPF T30028C and the P53 Arg72Pro Polymorphisms, Involved in DNA Repair, Alter the Risk for the Malignant Melanoma

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Background: The *XPC*, the *XPF* and the *P53* genes act on the nucleotide excision repair of the UV induced DNA damage and seem to be involved in origin of malignant melanoma (MM). The variant C allele of the *XPC* A2920C and the wild Arg allele of the *P53* Arg72Pro polymorphisms encode proteins with lower activities in DNA repair than those coded by others alleles. To the best of our knowledge, there are no functional studies of the proteins encoded by the wild and variant alleles of the *XPF* gene. The roles of these polymorphisms for the risk of MM are unclear and therefore this was the aim of the present study.
Material and Methods: Genomic DNA from peripheral blood of 137 consecutive MM patients and 137 age and race-matched controls were analyzed by the PCR-RFLP.
Results: The frequency of the *XPC* CC variant genotype (13.9% vs 6.6%, $P = 0.03$) and the *P53* Arg/Arg wild-type genotype (60.6% vs 47.5%, $P = 0.02$) were higher in patients than in controls. Carriers of the genotypes had a 2.47 (95% CI: 1.05–5.84) and a 1.73 (95% CI: 1.05–2.84) fold increased risks for disease than others, respectively. The frequency of the *XPC* CC and *P53* Arg/Arg combined genotype was higher in patients than