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.