Results: According to the two depression and anxiety scales used, a mild degree of anxiety and depression was diagnosed but with unimportant statistical difference (p = ns) between patients and healthy controls. Self-perceived HRQOL of patients appeared to be affected, with vitality ($p \leqslant 0.002$), physical ($p \leqslant 0.001$) and social functioning ($p \leqslant 0.003$) as the most impaired subscales of the SF-36. The deterioration in their HRQOL was mainly related to the post-diagnosis alteration of their socioeconomic status. As accessed by the multiple regression analyses, none of the disease history and medication-related variables were found to have any influence on the results of the SF-36 subtests.
Conclusion: Despite the fact that we studied a relatively small sample of patients with NHL, our results showed that their HRQOL was obviously affected, while their psychological health remained nearly unaffected.

Oral Presentations (Sat, 24 Sep, 11:15−13:00)
Melanoma and Skin Cancer

9300 ORAL

Dramatic Efficacy of Neoadjuvant Therapy by the Association Cisplatin, Fluorouracil and Cetuximab in Locally Advanced Non Resectable Epidermoid Skin Carcinoma

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Background: No standard therapy is known for locally advanced non resectable cutaneous squamous cell carcinoma. Chemotherapy (platin ± fluorouracil) and radiotherapy are commonly used separately or in association mostly as palliative treatment. We report 7 patients with locally advanced unresectable skin carcinomas in whom the association of cisplatin, fluorouracil and cetuximab induced a tumour reduction allowing secondary complete surgical resection.
Materials and Methods: We have treated prospectively 7 patients from july 2008 to february 2009 adressed to our center for skin carcinomas no accessible to a surgery. The treatment had included a neoadjuvant chemotherapy (cisplatin, fluorouracil and cetuximab) followed by surgery if a regression tumoral was obtained. An adjuvant radiotherapy was proposed depending on histological results (positive surgical margins, angio or neurotropism). We present the results after a follow up of 3 years.
Results: All 7 patients had voluminous tumours located on the face (nose, ear, cheek). For 5 patients, tumours were recurring after one or several surgical resections. Two patient had a rapidly progressing non respectable inflammatory tumour when he was first diagnosed. All patients received 2 or 3 cycles of chemotherapy associating cisplatin 100 mg/m^2 J1, fluorouracil 1000 mg/m^2 J1−4, cetuximab J1-J8-J15 (J1=J21). Tolerance was manageable. All patients had a dramatic tumour response with rapid tumour regression allowing subsequent surgical resection. Histology showed a complete sterilisation without any active tumoral residue in 2 patients and complete resection (R0) in the remaining 5 patients. An adjuvant radiotherapy was proposed for 3 patients because histological signs of aggressiveness were observed at histology. A distant recurrence (pulmonary metastasis) was seen in a patient after 18 months. No local recurrence was seen after a median follow up of 31 months.
Conclusions: The association of cisplatin, fluorouracil and cetuximab is approved for treatment of metastatic head and neck carcinoma and but has not been yet evaluated in cutaneous squamous cell carcinoma. The dramatic tumour responses and the long term local control observed in our 7 patients, warrant evaluation of this association both in the neoadjuvant and in the metastatic settings for patients with non resectable skin squamous cell carcinomas.

9301 ORAL

Ultrasound (US) Guided Fine Needle Aspiration Cytology (FNAC) Predicts Sentinel Node (SN) Metastases and Improves the Nomogram for Melanoma Patients

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Background: Ultrasound (US) guided fine needle aspiration cytology (FNAC) prior to the surgical sentinel node (SN) procedure has recently been proven to have an increased accuracy due to the introduction of new US morphology criteria This study reports on a larger dataset, increased follow-up and analyzed US-FNAC versus the validated Memorial Sloan Kettering Cancer Center (MSKCC) Nomogram (Wong et al., 2005).
Material and Methods: Prior to SN-biopsy patients (pts) underwent lymphoscintigraphy followed by US-exam. US images were prospectively scored for predetermined morphologic criteria. FNAC was performed in all suspicious US. All pts underwent a SN biopsy. Sensitivity (sens), specificity (spec) and negative/positive predictive value (NPV and PPV) and Hazard Ratios (HR) were calculated for prognostic factors and correlated with survival. Multivariate analyses were performed and compared to the nomogram.
Results: Since 2001 over 1000 consecutive pts have been included into a prospective database. Median Breslow thickness was 1.6 mm, 56% were male, mean follow-up 33 months for all pts, 56 months for the first 400 pts., ulceration present in 24%. SN positivity rate was 20%(n = 202). Sens and spec. of US-FNAC was 106/196(54%) and 768/779(99%). PPV and NPV were 91% and 90%. Peripheral perfusion showed a sens of 69% and PPV of 56%. Balloon shaped lymph nodes had a sens of 25% and PPV of 94%. 5-ys overall survival (OS) was 55% for US-FNAC positive vs. 92% for US-FNAC neg compared to 65% vs. 93% for SN histological pos and neg pts. There was no increase in late relapses for the first 400 pts (194 at risk at 5 yrs). The MSKCC nomogram accurately predicted SN involvement in this external dataset. Multivariate analysis for OS demonstrated that both the MSKCC Nomogram (HR 3.2, (1.5−6.8) P = 0.002) and US-FNAC (HR 4.6 (2.6−8.2) P < 0.001) were independent prognostic factors for OS.
Conclusions: This large dataset has validated previous results on the accuracy of US-FNAC performed with new morphology criteria and the MSKCC- nomogram. US-FNAC and MSKCC are independent prognostic factors for OS. US-FNAC might be able to improve the accuracy of the nomogram, a follow-up study will address this.

9302 ORAL

Prognostic Significance of the Size, Site and Penetrative Depth of Sentinel Node Metastases in Melanoma Patients − an International Multicenter Study

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Background: Immediate additional completion lymph node dissection (CLND) is standard management for sentinel node (SN) positive melanoma patients. Approximately 80% of SN positive patients have no additional non SN (NSN) metastases in the CLND specimen. Prognosis of the group of SN positive patients is highly heterogeneous. Different parameters of sentinel node (SN) tumour burden are able to predict the heterogeneous outcome in SN positive melanoma patients. The aim of this study was to evaluate the predictive value of SN tumour burden parameters for NSN status and for melanoma specific survival (MSS).
Material and Methods: Size, site and the penetrative depth of SN tumour burden have been measured and classified according to the Rotterdam criteria (<0.1 mm, 0.1−1.0 mm, >1.0 mm largest diameter), the modified Dewar criteria (subcapsular, non-subcapsular located), the S-classification ($\leqslant$0.3 mm, >0.3−1.0 mm, >1.0 mm penetrative depth) and the Rotterdam and Dewar combined (RDC) criteria in 1189 SN positive patients diagnosed between 1993 and 2008 at ten centers of the European Organisation for Research and Treatment of Cancer (EORTC) Melanoma Group (MG). CLND has been performed in 1117 (94%) patients. Mean and median Breslow thickness was 3.94 and 3.00 (interquartile range (IQR) 1.85–4.70) mm. Median follow-up was 35 (IQR 21−61) months.
Results: All four parameters for SN tumour burden were significant predictors for melanoma specific survival and for NSN status. When correcting for Breslow thickness, ulceration, age, gender and NSN status in multivariate analysis, the Cox hazard regression models for MSS with the S-classification and the Rotterdam criteria contained the greatest power. Patients with micrometastases <0.1 mm located subcapsularly had NSN positivity of 7% and a five-year MSS rate of 93%.

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.