<0.1 metastases, 58% for 0.1−1.0 metastases and 40% for metastases > 1.0 mm. 5-year DMFS rate was 91% for metastases <0.1 mm. NSN positivity occurred in 6% of <0.1 mm, 13% of > 0.2 mm metastases, 16% of 0.1−1.0 and 28% of metastases > 1.0 mm ($p < 0.001$).
Conclusion: This large multicenter experience (n = 663) has demonstrated that long-term follow-up of melanoma patients with minimal SN tumor burden (<0.1 mm) indicates very low relapse rates and excellent MSS, seemingly identical to SN negative patients. With prolonged follow-up, an increase in the occurrence of relapses of any kind between 5 and 10 years follow up has not been identified, and excellent 10-year survival rates are expected.

9303 ORAL

New ultrasound morphology criteria can predict melanoma metastases in the sentinel lymph node (SN) and correlate with tumour burden and survival

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Background: We demonstrated that US guided FNAC (fine needle aspiration cytology) prior to SN biopsy can identify up to 65% of SN-positive patients (EJC, 2007; 5(6):11: abstract 3BA). We presented for the first time US patterns of SN-involvement at ASCO 2008 (JCO 26: 2008 (suppl; abstr 9014). The aim of the present study is to show in how far these patterns correlate with progression of disease, tumor burden, survival and prognosis.
Methods: Prior to SN-biopsy patients (pts) underwent lymphoscintigraphy followed by US-exam. US images were prospectively scored for 6 morphologic criteria: presence of peripheral perfusion, loss of central echoes, balloon shaped lymph node, moreover for hump structure, echo-poor islands, cap structure. FNAC was performed in suspicious US. All pts underwent a SN biopsy. Final SN pathology was the gold standard. Sensitivity, specificity and negative/positive predictive value (NPV and PPV) of combinations of US patterns were calculated and correlated with tumor burden and survival. Hazard ratios (HR) were calculated for the patterns by multivariate analysis.
Results: Since 2001 850 consecutive pts have been included into a prospective database. Median Breslow thickness of the first 400 stage I/II melanoma pts was 1.8mm, median follow-up 42 months. Balloon Shape (BS) & Loss of Central Echoes (LCE) are often linked (up to 83%) and are *late* signs correlating with high tumor load. In contrast the presence of Peripheral Perfusion (PP) is an *early* sign, correlating with small tumor load. PP and/or BS and/or LCE together raise the sensitivity of US alone to > 80%, spec.80%, PPV 52%, NPV of 94% ($p < 0.001$). Overall Survival of neither vs. Peripheral Perfusion (PP) only vs. BS/LCE (with or without PP) was 93% vs. 87% vs. 56% and Distant Metastasis-Free Survival was 74% vs. 60% vs. 26%. BS/LCE was a late sign correlating with high tumor load, fast progression and a high HR (5.50). PP alone was an early sign correlating with small tumor load, slow progression and a low HR (2.19).
Conclusions: We have identified 2 ultrasound morphology signs of lymph node metastasis in melanoma patients: Peripheral perfusion as early and Balloon Shaped Lymph Node and / or Loss of Central Echoes as late signs. BS and/or LCE indicate high tumor load, PP alone indicates small tumor load in the SN. With these criteria we can identify any amount of SN tumor burden correctly prior to the surgical SN procedure in 75% - 90% of cases. Balloon Shaped Lymph Node and/or Loss of Central Echoes and Peripheral Perfusion are independent prognostic factors for Survival.

9304 ORAL

Identification of tumor biopsy markers as potential predictors of ipilimumab clinical activity in patients with advanced melanoma

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Background: Ipilimumab, a monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4, has demonstrated activity in advanced melanoma patients (pts). As part of a completed Phase II study (CA184−004), we sought to identify tumor biomarkers of early ipilimumab effects that can be used to predict clinical activity.
Methods: Pts received ipilimumab at 3 mg/kg (n = 40) or 10 mg/kg (n = 42), given every 3 weeks (Q3W) ×4; eligible pts could receive ipilimumab Q12W starting at Wk24. Ninety-one fresh tumor biopsy samples (50 pre-treatment and 41 post-treatment at Wk4) from 57 pts were evaluable by immunohistochemistry (IHC) and hematoxylin and eosin (H&E) staining. The expression of 8 proteins, including FoxP3 and indoleamine 2,3-dioxygenase (IDO), was assessed by IHC. Six tumor characteristics, including tumor-infiltrating lymphocytes (TILs), were assessed by H&E; mRNA expression levels were quantified in biopsy sub-samples by Affymetrix microarray analysis (54 pts with both pre- and post-treatment data). Response was evaluated using modified World Health Organization criteria.
Results: Clinical activity (complete response, partial response, or stable disease ⩾24 wks from first dose) was associated with increased baseline expression of FoxP3 (n = 33) and IDO (n = 35), and with an increase in TILs at Wk4 relative to baseline (n = 27) [Table]. In tumor biopsies, expression of 466 mRNA probe sets had a significant change from baseline (after multiplicity correction, q-value <0.05). Genes with significant increased expression included various immune-response genes, e.g., immunoglobulins, granzyme B, and T cell receptor alpha and beta subunits. Genes with significant decreased expression included known melanoma antigens, e.g., tyrosinase-related protein 2, gp100, and melan-A.

Biomarker[a]	Clinical activity	No clinical activity	P value[b]	Dose response
TILs at Wk4, change from baseline	4/7 had increase 0/7 had decrease 3/7 had no change	2/20 had increase 3/20 had decrease 15/20 had no change	P = 0.005	No
FoxP3 expression at baseline	6/8 were positive	9/25 were positive	P = 0.014	N/A
IDO expression at baseline	3/8 were positive	3/27 were positive	P = 0.012	N/A

[a]Using 3-point scale for TILs (absent, ⩽50%, >50%) and a 9-point scale for IHC (0−4, in 0.5 increments); [b]P-values were not corrected for multiple testing.

Conclusions: Increased baseline expression of tumor FoxP3 and IDO, and increase from baseline of TILs at Wk4, may be used to identify pts who will experience clinical activity with ipilimumab.

9305 ORAL

Activity of sunitinib in advanced malignant melanoma and its correlation with potential predictive biomarkers

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Background: Sunitinib is approved for the treatment of renal cell carcinoma and GIST tumours. It is a small molecule that inhibits members of the split-kinase domain family of tyrosine kinase receptors, including VEGFR, PDGFR, c-KIT and RET kinases. These kinases are important for neoangiogenesis, tumor cell proliferation and survival. Treatment options for advanced melanoma after dacarbazine-based chemotherapy are limited. We report here our initial observations with sunitinib in advanced melanoma patients, whose disease failed at least one line chemotherapy.
Methods: Patients with locally advanced or metastatic melanoma, whose disease failed at least one line of dacarbazine-based chemotherapy were