<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

enrolled in a Belgian academic multi-centre phase II trial, following a Simon's two-stage design. Patients received treatment with sunitinib in 6 weekly cycles comprising of a 50 mg once daily dosing for 4 consecutive weeks, followed by a 2-week off-treatment period. The primary end point of the study was RECIST-defined objective response. Angiogenic biomarkers were collected to study their potential predictive value for response. Peripheral blood was drawn every 2 weeks during the first treatment cycle and serum VEGF, VEGFR-1, VEGFR-2 and PlGF levels were determined by ELISA. The number of circulating endothelial cells was enumerated weekly by FACS during the 1st cycle and at day 1 of following cycles.
Results: At present, 21 patients (18 evaluable) with metastatic melanoma have been enrolled in the first stage of the study. Three patients were not evaluable for response because of early discontinuation of sunitinib, due to adverse events (1 cardiac insufficiency, 1 cerebral haemorraghia) and inability to swallow medication (1). Two patients (11.1% of evaluable) demonstrated partial response as best response with a mean duration of 5.4 months, 5 had stable disease (27.8%) with a mean duration of 4.4 months and 11 had progressive disease (61.1%). The most frequent toxicities were asthenia (61.9%), anorexia (33.3%) and nausea (42.9%). No grade 4 toxicity was observed. The correlative data with response analysis of the angiogenic biomarkers is ongoing and will be reported.
Conclusion: In the present phase II trial, early antitumor activity of sunitinib was detected in advanced melanoma patients, with an overall clinical benefit rate of 33%. The recruitment into the second stage of the study is ongoing. Angiogenic biomarkers are being correlated with clinical activity.

9306 ORAL

Phase II multi-institution trial of ipilimumab for patients with melanoma and brain metastasis

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Background: Ipilimumab (ipi) is a fully-human antibody (Ab) that blocks the engagement of CTLA4 on activated T lymphocytes with ligands on antigen-presenting cells. As a single agent, ipi has activity in advanced melanoma (mel), induces antigen-specific immune responses, and has been reported effective in patients with brain metastasis (met). We performed this phase II trial (CA-184−042) to better assess the activity of ipi against mel with brain met.
Patients and Methods: Patients (pts) had measurable brain met(s) with at least one lesion >0.5 cm or 2 lesions >0.3 cm and none >3 cm in diameter. Any size and site of extracranial met was also permitted. Prior-therapy (Rx) exclusions included investigational Ab and focused radiotherapy (RT) to the index lesion(s). Prior whole brain (WB) RT was allowed. Steroid Rx was prohibited except for Rx of immune-related adverse events (irAE), which, if severe, could be treated with glucocorticosteroid and additional immunosuppressants according to established algorithms. Ipi, 10 mg/kg, was administered intravenously over 90 minutes every 3 weeks for 4 doses, and stable or responding pts could continue to receive ipi on a q 12 week maintenance schedule. A 2-stage accrual design required >2 objective responses among the first 21 pts in order to proceed to stage 2 (21 additional pts)[Arm A]. A separate cohort of 21 pts on glucocorticoid Rx (Arm B) was then treated at the same time that Arm A was re-opened for second-stage accrual to the total of 41 patients.
Results: All patients have been accrued to both Arm A (41 pts) and Arm B (21 pts), and data will be complete for both cohorts by August, 2009. Complete data are provided for the 21 pts in first-stage accrual of arm A: Eight had prior WBRT with or without additional SRT to lesions not used for response assessment in this study. All pts had one or more prior systemic Rx. The World Health Organization response criteria were modified to take immune-related changes into account. Three pts had confirmed partial responses by World Health Organization criteria, all of which were continuing at the time of reporting, with durations of 7+, 6+ and 2+ months. One pt had an extracranial partial response but progressed in the brain. The frequency, grade and nature of irAE was similar to those reported in large trials of ipi for mel with colitis as the major toxicity requiring Rx discontinuation.
Conclusions: Ipi appears to have activity in mel met to the brain at a level consistent with reports of its activity in pts without brain met. For pts with recurrent brain met following surgery, focused RT and/or WBRT, ipi is an appropriate Rx alternative.
Support: Bristol-Myers Squibb

Poster presentations (Tue, 22 Sep, 14:00−17:00)
Melanoma and skin cancer

9307 POSTER

Long-term survival in advanced melanoma patients treated with ipilimumab at 10 mg/kg: ongoing analyses from completed Phase II trials

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Background: The monoclonal antibody ipilimumab blocks cytotoxic T lymphocyte antigen-4, thereby activating an antitumor immune response. Updated survival data from ipilimumab studies in previously treated (⩾1 prior anti-cancer therapy) and treatment-naïve patients (pts) with advanced melanoma are reported.
Methods: Follow-up of pts treated with ipilimumab at 10 mg/kg in three completed Phase II trials is ongoing (CA184008 was an open-label, single-arm study of ipilimumab at 10 mg/kg; CA184022 was a dose-ranging study of pts randomized to ipilimumab at 0.3, 3, or 10 mg/kg; CA184007 was a randomized study in which pts were treated with ipilimumab at 10 mg/kg with or without prophylactic budesonide). Ipilimumab was given every 3 weeks (Q3W) ×4 (induction); eligible pts could receive maintenance ipilimumab Q12W from Week 24.
Results: Median overall survival and 18-month survival rates after a median follow-up ranging from 10.1 to 16.3 months for pts receiving ipilimumab at 10 mg/kg are presented (Table). Across the three studies, the number of prior therapies was not associated with response to ipilimumab. Long-term survivors included pts with progressive disease (PD) [per modified World Health Organization (mWHO) criteria] at the first tumor assessment (Week 12).

Study	Median overall survival, months [95% CI]	12-month survival rate, % [95% CI]	18-month survival rate, % [95% CI]	Longest survival time, months*
CA184008 (N = 155)				
(previously treated)	10.2 [7.6, 16.3]	47.2 [39.5, 55.1]	39.4 [31.7, 47.2]	28.6
CA184022 (N = 214)				
10 mg/kg (n = 71) (previously treated)	11.4 [6.9, 16.1]	48.6 [36.8, 60.4]	34.5 [23.6, 46.2]	26.9
CA184007 (N = 115)				
Ipilimumab+placebo (n = 57)	19.3 [12.0, NR]	62.4 [49.4, 75.1]	50.9 [37.5, 64.1]	29.2
Treatment-naive (N = 32)	NR [13.9, NR]	71.4 [55.2, 87.2]	61.0 [43.4, 77.7]	28.7
Previously treated (N = 25)	14.7 [6.6, 20.5]	50.8 [31.5, 71.1]	38.1 [20.0, 57.6]	29.2
Ipilimumab+budesonide (n = 58)	17.7 [6.8, NR]	55.9 [42.7, 68.8]	47.9 [34.7, 61.2]	32.5
Treatment-naive (N = 21)	22.5 [11.7, NR]	65.9 [45.0, 85.7]	65.9 [45.0, 85.7]	29.9
Previously treated (N = 37)	8.4 [6.0, 22.6]	49.9 [33.3, 66.6]	37.9 [22.2, 54.3]	32.5

NR, not reached; *follow-up ongoing

Conclusions: Ipilimumab therapy resulted in long-term survival in a sizeable proportion of previously treated and treatment-naïve pts, including some pts characterized as PD by mWHO criteria at Week 12. Follow-up of pts from the three studies is ongoing and 24-month survival data will be presented at the meeting.