normal melanocytes, leading to NF-κB activation which in turn regulates the expression of anti-apoptotic proteins such as the inhibitor of apoptosis (IAP) proteins, survivin as well as Bcl-2 like proteins. These events are major molecular mechanisms for melanocytes transformation [1]. It has been found that a short cell-permeable peptide spanning the IKKβ NEMO binding domain (NBD), named NBD peptide, disrupted the association of NEMO with IKKs *in vitro* and blocked TNFα-induced NF-κB activation *in vivo* [2]. In the present study we investigated the effect of the NBD peptide on IKK/NF-κB signalling pathway and survival of several human melanoma cell lines (A375, WM115, SK-Mel-5).

Materials and Methods: viability was determined by vital-dye exclusion assay. For the electrophoretic mobility shift assay, aliquots of whole-cell extracts were incubated ^{32}P-labeled κB DNA probe and were analyzed by non-denaturing 4% polyacrylamide gel electrophoresis. A375 cells were stained with 7-AAD and incubated at 4°C until analysis on the flow cytometer. The active form of caspase-3 was measured by FACScalibur cytometer using the PE-conjugated anti-human-active caspase-3 monoclonal antibody. Proteins electrophoretic analyses was performed via immunoblotting.

Results: we report that NBD peptide is able to inhibit the proliferation of all human melanoma cell lines used as compared to normal human melanocytes. Inhibition of cell growth was associated with direct inhibition of i) constitutive IKK activity; ii) NF-κB DNA-binding activation, iii) induction of apoptosis in all cell lines tested. Using as a model the A375 melanoma cell line, we show that inhibition of IKK/NF-κB signalling pathway by NBD peptide leads to down-regulation of the expression of several NF-κB-dependent antiapoptotic gene products and to the activation of caspase-3 as confirmed by the cleavage and consequently inactivation of poly (ADPribose) polymerase (PARP-1) known as the best marker of this process.

Conclusions: our studies indicate that selective inhibition of IKK/NF-κB activation can be an effective strategy for challenging melanoma.

References

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9314 POSTER

Impact of ipilimumab on the health-related quality of life (HRQL) of patients with previously treated unresectable stage III or IV melanoma

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Objective: The anti-CTLA-4 monoclonal antibody, ipilimumab, induces anti-tumor activity that has resulted in significant survival benefit in many patients with advanced melanoma. We evaluated the impact of ipilimumab treatment on patient-reported functioning and symptoms in patients with unresectable stage III or IV melanoma.

	022			008
	0.3 mg/kg (n = 44)	3 mg/kg (n = 44)	10 mg/kg (n = 46)	10 mg/kg (n = 102)
Score				
Physical function	−8.0	−10.2	−7.4	−8.1
Role function	−17.1	−19.7	−9.1	−11.9
Emotional function	1.7	−0.6	−1.2	−3.5
Cognitive function	−1.5	−4.9	−7.6	−7.6
Social function	−10.2	−7.6	−9.4	−7.6
Global health	−9.7	−11.5	−10.0	−7.0
Fatigue	10.9	15.2	5.6	9.5
Nausea/vomiting	8.3	6.1	3.3	3.8
Pain	8.3	14.8	2.5	−0.8
Dyspnea	9.1	7.6	6.5	4.3
Insomnia	−6.1	3.8	4.4	2.0
Appetite loss	10.6	12.4	8.2	4.6
Constipation	−1.5	2.3	−4.4	8.7
Diarrhea	12.9	2.3	4.4	11.3

For the function and global health scales, improvements are indicated by positive scores. For symptom scales, improvements are indicated by negative scores.

Methods: Data from a randomized, double-blind, fixed dose phase II trial (022) and a single-dose, open label phase II clinical study (008) were used for these analyses. In study 022, pts were randomly assigned to treatment with 0.3 mg/kg (n = 73), 3 mg/kg (n = 72) or 10 mg/kg (n = 72) at weeks 1, 4, 7 and 10. In study 008 all pts (n = 155) were treated with 10 mg/kg at weeks 1, 4, 7, and 10. HRQL was assessed using the EORTC Quality of Life Questionnaire C30 which measures physical, role, emotional, social and cognitive functioning, global health status, and 8 symptoms (pain, nausea/vomiting, fatigue, dyspnea, appetite loss, insomnia, diarrhea, constipation). HRQL data were collected at weeks 1, 4, 7, and 12. Baseline to endpoint changes were interpreted through mean change in scores as "no change" (0), "a little" (5−10 points), "moderate" (10−20 points) and "very much" (>20).

Results: HRQL completion rates were 77% and 80% at week 12. Most observed changes were in the "no change" to "a little" range across the treatment groups. Mean baseline to 12-week changes in HRQL scores for studies 022 and 008 are reported (Table). The best overall response profile of HRQL outcomes was demonstrated with 10 mg/kg.

Conclusions: These findings show that ipilimumab 10.0 mg/kg has a little impact on functional and symptom domains suggesting that relevant aspects of HRQL are maintained in this advanced stage melanoma population.

9315 POSTER

Ipilimumab in pretreated metastatic uveal melanoma patients: safety and clinical efficacy

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Background: The anti-CTLA-4 monoclonal antibody ipilimumab induces anti-tumor responses in cutaneous metastatic melanoma (MM) patients (pts). However, no data are available on the clinical effectiveness of ipilimumab treatment in uveal MM pts. We report the European (7 Institutions) experience utilizing ipilimumab in uveal MM pts.

Materials and Methods: Fourteen stage IV pts (8 male, 6 female), median age 57 (30−76) years, ECOG performance status 0−1, with uveal MM progressing to 2 median (1−4) previous therapies for metastatic disease received ipilimumab within a compassionate use program. Thirteen pts had history (1) or evidence (12) of liver metastases, 2 of brain metastases and 3 of elevated (>1× upper limit of normal [ULN]) LDH values. In the induction phase (IF) pts received ipilimumab (10 mg/Kg i.v.) q3 weeks (wks) ×4 cycles; after a 12 wks rest, treatment was repeated q12 wks in the maintainance phase (MF). Tumor assessment (TA) *per* modified World Health Organization criteria was evaluated at baseline, at week (wk) 12 and wk 24, than every 12 wks. Adverse Events (AE) and immune related AE (irAE) were collected according to Common Terminology Criteria for Adverse events version 3.0.

Results: All pts received at least one ipilimumab dose, and 10/14 completed the IF. The remaining 4 pts were withdrawn for early disease progression, while 4 pts entered the MF and are still on treatment. TA at wk 12 showed partial response (PR) in 1/10 or stable disease (SD) in 3/10 pts; TA at wk 24 showed PR and SD in 1/4 and 3/4 pts, respectively, with a clinical benefit (SD+PR) of 29%. As previously reported for cutaneous MM, slow, steady decline in tumor volume and appearance of new lesions with subsequent shrinking has been observed. No grade 3/4 AE and irAE were reported. Median overall survival is 32 (2−52) wks.

Conclusions: Ipilimumab administration in pretreated uveal MM pts is feasible and safe. A sizeable proportion of treated pts experienced clinical benefit with extended survival. These data, thought preliminary and in a limited number of pts, suggest that uveal MM might represent a promising indication for ipilimumab treatment to be further investigated.