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Follow-up study in high-risk uveal melanoma patients

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Uveal melanomas have a significant predilection for metastasis to the liver: up to 50% of patients will develop metastases, the liver is the sole or dominant site in more than 80% of them. Microscopic complete (R0) surgical resection of liver metastases improves survival to 22 months in very high selected patients. Despite aggressive therapy, survival is poor, the 1-year survival rate is 10%. Prognostic factors from the primary include tumor diameter and thickness, anterior location, extraocular extension, epithelioid cell type, monosomy 3 and gene expression profile. Early identification of a high-risk group of patients might allow early detection of metastases, and increase R0 liver surgery.

We began in October 2006 an intensive follow-up prospective study to detect early minimal lesions with liver MRI in asymptomatic high risk patients. High-risk was defined by thickness >8 mm or diameter >15 mm, or extrascleral extension, or monosomy 3. Primary objective was to increase R0 liver resection rate from 10 to 30% (α risk = 0.04 and β risk = 0.05); secondary objectives were overall survival, metastasis-free survival, predictive value of MRI and liver functional tests (LFT's). After treatment of the primary, patients undergo liver MRI and serum samples/6 months, LFTs/3 months. MRI screening consists in T1, T2, T1 dynamic series with gadolinium injection and LFT's in total bilirubin, ALAT/ASAT, Alkaline phosphatase, GGT, LDH. MRI suspect abnormalities lead to surgical procedure. Information document is sent to radiologists, MRI central review is conducted by Institut Curie radiologists.

From Oct 2006 to March 2009, 85 patients were enrolled, median age 60 (32−83), sex ratio M39/F46. The median uveal tumor diameter was 19 mm (11−26), median thickness 11.6 mm (2.7−17), with retinal detachment in 65 patients, and extraocular spread in 7. Local primary treatment consisted in proton beam therapy in 9 patients, enucleation in 76. Secondary enucleation was performed in 5 cases (2 for local relapse). The histological cell type was epithelioid in 18 cases, fusiform in 17, mixed in 41. Monosomy 3 (FISH) was present in 41/58 analysed enucleations. With a median follow up of 15 months, the metastasis-free survival is 72%. 2 Patients underwent enucleation for local relapse. 24 patients developed metastasis, 2/11 operated patients had R0 liver surgery (18%). To date, 6 patients died (5 from metastasis, 1 myocardial infarction) and 17 patients are alive with metastasis.

MRI and LFT's screening analysis will be presented with an updated follow up in the 85 available patients.

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Ipilimumab re-induction after progression in patients with advanced melanoma enrolled in Phase II clinical trials

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Background: Ipilimumab is a monoclonal antibody that activates an antitumor immune response by blocking cytotoxic T-lymphocyte antigen-4. The safety and efficacy of ipilimumab at 10 mg/kg given in an induction/maintenance regimen to patients (pts) with advanced melanoma have been evaluated in completed Phase II clinical trials. In the ongoing rollover study presented here, pts with disease control (DC) were offered re-induction with ipilimumab at 10 mg/kg upon progressive disease (PD). The safety and efficacy of re-induction was assessed as one objective of this rollover study.

Methods: In the Phase II clinical program (CA184−007, 008, -004, and MDX010−15), ipilimumab was administered every 3 weeks (Q3W) x 4 (induction) and pts treated with ipilimumab at 10 mg/kg who achieved DC [complete response, partial response, or stable disease] could be re-induced with ipilimumab at 10 mg/kg in the rollover study, CA184−025, after PD. The exception was study 022 (based on the use of lower doses in 2 arms of the study), where any pt with PD was eligible for re-induction in study 025. The pts rolled over to study 025 were re-induced with ipilimumab at 10 mg/kg immediately upon enrollment. Pts who achieved DC and entered the maintenance phase of a parent trial continued maintenance therapy with ipilimumab at 10 mg/kg (Q12W) in study 025, and received re-induction with ipilimumab at 10 mg/kg upon PD. Any pt who did not achieve DC following re-induction, withdrew, or had unacceptable toxicity requiring discontinuation of ipilimumab, entered a follow-up phase.

Results: We present 49 pts treated with ipilimumab at 10 mg/kg in a parent study who were re-induced with ipilimumab at 10 mg/kg in study 025 following initial DC and subsequent PD; 35 of 49 pts were re-induced with ipilimumab at 10 mg/kg immediately upon enrollment in study 025. Of pts that entered the maintenance phase in study 025, 14 have been re-induced with ipilimumab at 10 mg/kg following PD. Objective response and/or disease stabilization after re-induction were observed. Preliminary data showed safety and efficacy of retreatment is comparable to what was observed at first induction. Data collection is ongoing.

Conclusions: Data on the activity and safety of ipilimumab during re-induction will be of special interest for the long-term management of advanced melanoma pts. Details of the final analyses will be presented at the meeting.

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Clinical and histopathological risk factors to predict sentinel lymph node positivity, disease free and overall survival in clinical stage I-II AJCC skin melanoma – a prospective study

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Background: The aim of the study was to investigate clinical and pathological risk factors to predict the sentinel node positivity (SLN), the disease free (DFS) and overall survival (OS) in clinical stage I-II AJCC primary cutaneous melanoma (PCM) through a prospective mono-institutional data base.

Materials and Methods: The study included consecutive patients with PCM, all diagnosed, treated and followed up prospectively by a multidisciplinary team. Logistic regression was used to investigate the association between DFS, OS, SLN positivity and Breslow thickness, Clark level, tumor infiltrating lymphocytes (TIL), ulceration, lesion site, gender, regression and age.

Results: From November 1998 to December October 2008, 1251 patients with PCM were referred to the Bergamo Riuniti Hospital. The median age was 51.7±16.6 years; 32.2% (N = 393) with > 60 years, male: 45%. Among those 394 patients with primary vertical growth phase (VGP) melanoma and no clinical evidence of metastatic disease who underwent SLN biopsy. In all, 74 of the 394 patients had 1 positive SLN (18.8%). In the multivariate analysis, no extremity primary (extremity vs axial = truncal and headh/neck) OR 0.44, 95% CI 0.22−0.89, $p < 0.023$), TIL (TIL vs no TIL 0.46, 95% CI 0.24−0.88, $p < 0.02$), and thickness (>4 mm vs 1.1−2 mm OR 25, 95% CI 4.95−126.32) predicted SLN positivity. A multivariate stepwise analysis confirmed these results. The histologic status of the SLN was the most significant predictor of DFS and OS. Patients with a negative SLN had a 5-year DFS of 75.9%, compared with 35.2% in patients with a positive SLN ($p < 0.0001$) and a 5-years OS of 88.7% versus 42.9% respectively ($p < 0.0001$).

Conclusions: Our study demonstrate that the absence of TILs predicts SLN metastasis, at multivariate analysis only the SLN positivity predicts DFS and OS.

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Alterations in the expression patterns of micro-RNAs during the transformation process of normal human melanocytes into malignant melanoma

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Background: Malignant melanoma is a devastating disease with a constantly increasing incidence worldwide. Metastatic melanoma is almost inevitably fatal, with current treatment options being highly disappointing. Although this disease has been extensively studied, little is known about the molecular mechanisms underlying melanocyte transformation. Recently, a novel regulatory mechanism of gene expression has been discovered, based on the cellular generation of short RNA sequences termed micro-RNAs (miRNAs). miRNAs can silence or decrease the expression of genes within cells. Many lines of evidence indicate that miRNAs have an important role in cancerous transformation. Our work is aimed at studying the role of miRNAs in the pathogenesis of melanoma.