EORTC 18991 Trial: Long Term Adjuvant Pegylated Interferon-alpha2b (PEG-IFN) vs Observation in Resected Stage III Melanoma: Final Results of a Randomized Phase 3 Trial by the EORTC Melanoma Group.
Background: EORTC 18991 is the largest adjuvant trial ever conducted in stage III melanoma. It assessed the efficacy and toxicity of long term PEG-IFN vs Observation (Obs.).
Methods and Patients: PEG-IFN (Induction at 6μg/Kg/wk, sc, 8 weeks; followed by Maintenance at 3μg/Kg/wk, sc) for a total treatment duration of 5 years was compared to Obs. in 1256 patients (pts) with stage III melanoma (anyTN1−2M0 without in-transit metastases). Randomization was stratified for nodal involvement N1 (microscopic) vs N2 (palpable nodes), number of nodes, Breslow andulceration of primary, sex and center. Distant Metastasis-Free Survival (DMFS) was the primary endpoint. Relapse-Free Survival (RFS) was the pre-specified regulatory primary endpoint. Overall survival (OS) was the secondary endpoint. Intent-to-treat analysis was performed.

	RFS		DMFS		OS	
	Obs.	PEG-IFN	Obs.	PEG-IFN	Obs.	PEG-IFN
Nb. events	368	328	325	304	263	262
4-year rates	39%	46%	45%	48%	56%	57%
Median (yrs)	2.1	2.9	3.0	3.8	NR	NR
HR (95% CI)	0.82 (0.71−0.96)		0.88 (0.75−1.03)		0.98 (0.82−1.16)	
p-value	0.01		0.11		0.78	

HR = Hazard Ratio; NR = Not Reached.

Results: See the table. Median follow-up was 3.8 yrs. Important is much better outcome in Stage III-N1 disease (sentinel node positive patients). In N1-pts (n = 543) the benefit of PEG-IFN seemed more pronounced than in N2-pts (n = 713): RFS (HR 0.73 p = 0.02 and HR 0.86 p = 0.12 for N1 and N2, respectively), DMFS (HR 0.75 p = 0.03 and HR 0.94 p = 0.53) and OS (HR 0.88 p = 0.43 and HR 1.01 p = 0.91).
PEG-IFN treatment relative dose intensity (actual/planned dose while treated) reached median 88% (induction) and 83% (maintenance). 251 pts (31%) stopped PEG-IFN because of toxicity, 9% because of other reasons. Grade 4 toxicities occurred in 9 and 7% in the PEG-IIFN and observation group respectively and were disease related rather than treatment related. Grade 3 toxicity(ies) were reported in 21% of PEG-IFN treated patient more frequently than in observation patients and were mostly treatement related including most frequently fatigue (14%), hepatotoxicity (10%) and depression (6%) with ECOG 0−1 Performance Status maintained in 83% of pts during maintenance.
Conclusions: Long term PEG-IFN therapy in stage III melanoma had a significant and sustained impact on RFS, but not on DMFS and OS. Pts with only microscopic nodal involvement (Sentinel Node positive) seemed to have greater benefit in terms of both RFS and DMFS. Similar better effects of adjuvant IFN therapy in pts with lower disease burden are observed in 2 consecutive EORTC trials (18952 and 18991) involving 2644 pts.
Hellenic Melanoma Group trial: Dr H. Gogas and collegues of the Hellenic melanoma group reported at ASCO on a randomized phase III trial comparing 1 month iv HDI versus the traditional ECOG1684 HDI 1 year schedule: The rationale for this trial was that the ECOG 1684 high dose IFNα regimen was unique for the incorporation of an induction phase of maximally-tolerated dosages of IV therapy for the initial 4 weeks. This is the only trial that has shown prolongation of overall survival and disease-free survival in comparison to observation. Analysis of the hazard curves for DFS and OS in E1684 reveal early and durable separation of the high-dose and observation arms suggesting that the induction phase may represent a critical component of the high-dose regimen. The Hellenic trial consisted of a prospective randomized study of IV induction therapy vs a full year of high-dose IFN with primary endpoints of DFS and OS for stage IIB, IIC and III melanoma patients within 56 days of curative surgery. Patients were randomized to receive IFN alfa-2b 15×10^6 U/m^2 IV × 5/7 days weekly × 4 weeks (arm A) versus the same regimen followed by 10×10^6 U (flat dose) SC 3 times a week for 48 weeks (arm B). The proposed treatment would be considered at least as good as the conventional treatment, if the relapse rate at 3 years from study entry is at most 15% higher in the former arm (power 85%, one-sided test a = 0.05, required sample size: 340).
Results: Between 1998 and 2004, 364 patients were enrolled (355 eligible: 178 arm A and 177 arm B). Patients' and tumor characteristics were well balanced between the two arms. At a median follow up of 51 months (95% CI 46−55), the median DFS is 32 months vs 31 months (p = 0.836) and the median OS is 61 months vs 63 months (p = 0.444). Eleven patients discontinued treatment in arm A and 54 in arm B. The discontinuation rate is significantly higher in group B (p <0.001), possibly due to the longer duration. Reasons for discontinuation were disease progression (69%) and toxicity (19%). Patients in arm B had more grade 3−4 hematologic, constitutional and neurologic toxicity.
Conclusions: There are no significant differences in OS and DFS between the regimen of 1 month and 1 year treatment tested.
Translational Research projects regarding the prognostic value of the presence/emergence of auto-antibodies during IFN therapy were evaluated in ECOG adjuvant trials and in the EROTC 18952 trials and revealed only a trend or borderline significance for the presence/emergence of auto-antibodies in contrast to the orginal observation as published in the NEJM by Gogas et al.
Regarding the prognostic value of S-100 determinations in the serum of patients in adjuvant trials of ECOG and in EORTC 18952, a strong ion-dependent prognostic valure for S-100 determinations was demonstrated.
Conclusions: PEG-IFN therapy has significant and consistent impact in Stage III-N1 (positive sentinel nodes) disease and only marginal effects in Stage III-N2 (palpable nodes) disease. This outcome is fully consistent with the outcome in EORTC 18952 and thus in 2644 randomized patients. This is an important obseervation that shows that the biology of N1 disease differs from N2 disease and that IFN-sensitivity differs accordingly. Moreover 4 wks of iv HDI induction therapy was demonstrated in the Hellenic trial as non-inferior (at least as good) as a full year of HDI according to the ECOG1684 regimen, Both trials have therefore important outcomes. Auto-antibodies are of only borderline significance as a prognostic factor, whereas serial S-100 determinations were demonstrated to be of strongly independent significant prognostic value in stage III disease. All these findings will be discussed in the setting of defining new questions and new adjuvant therapy trials in melanoma, such as the EORTC 18071 trial in Stage III-N2 disease comparing adjuvant therapy with anti-CTLA4 vs Observation.

173 INVITED

Immunotherapy approaches to stage IV melanoma

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Melanoma has always been considered to be a partially immunogenic tumor, and because of the lack of chemotherapy efficacy, a variety of immunoitherapies have been tested in this disease. This presentation will review the experience with non-specific immunostimulation (IL2-based therapies) and more novel approaches including specific modulation of immune responses, e.g. targeting of CTLA4.
Immunotherapy with IL2 has shown principle efficacy in metastatic melanoma, albeit the objective response rate did not exceed 30% in randomized clinical trials, regardless of the treatment combination used. A constant observation, however, wasre long-term complete remissions in a small subgroup of patients in all clinical trials with intravenous IL2 schedules. A variety of doses and schedules of IL2 alone have been tested as well as combinations of IL2 with interferons, chemotherapies and histamine dihidrochloride. Unfortunately, none of the combinations used prooved to be superior over IL2 alone, and none of the combinations prooved to be superior over chemotherapy regimens without IL2. More recently, the dual effect of IL2 on cytotoxic as well as regulatory T cell subsets was partially elucidated providing a potential explanation for the limited clinical efficay.
Currently, various strategies of modulating regulatory T cell responses are being investigated within early and advanced clinical trials. Most mature are the experiences using antibodies to CTLA4, a molecule expressed on T cells after activation physiologically in order to dampen immune responses and prevent autoimmunity. According to the physiologic role of CTLA4, a variety of very specific autoimmune reactions have been observed in patients receiving anti-CTLA4 antibody treatments, resembling to some extent the clinical picture of chronic graft-versus-host disease. In addition, in all trials with CTLA4 targeting, objective melanoma regression was observed in a subset of patients, often long-lasting. Current strategies investigate the combination of CTLA4 antibodies with vaccines. Furthermore, targeting of a similar immunoregulatory molecule, PD1 is under way in early clinical trials.
The fascination of long lasting remissions in subsets of patients with metastatic melanoma continues to support clinical testing of a variety of immunologic approaches in this disease, which continues to be difficult to treat.

174 INVITED

B-Raf mutations – old and new drugs

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Metastatic melanoma remains one of the most treatment-refractory malignancies. Despite decades of clinical trials testing chemotherapy and immunotherapy, a standard first-line treatment for metastatic melanoma has not yet been established. Recent advances in our understanding of the pathophysiology of melanoma have given rise to systemic