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

evaluation of MAPK signaling inhibitors, VEGF signaling inhibitors, survival kinase inhibitors, and cyclin-dependent kinase inhibitors in melanoma. An overview of melanoma biology and established targets, followed by a summary of completed and ongoing early phase clinical trials will highlight the failure of the first generation of targeted therapies to improve outcomes as single agents. In contrast, early hints of improved outcomes have been generated by clinical trials testing the combination of sorafenib and chemotherapy. The potential of targeted therapies in combination with chemotherapy or regimens consisting of multiple targeted therapies will be explored as increasing evidence suggests that combination therapeutics could finally impact the outcome of metastatic melanoma.

175 INVITED

Target discovery in melanoma

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Tumor metastasis to regional (sentinel) lymph nodes represents the first step of tumor dissemination in most melanomas and serves as a major prognostic indicator for disease progression. However, little is known about the mechanisms how tumor cells gain entry into the lymphatic system. In this respect, we have previously shown that tumors can actively induce the formation of lymphatic vessels (leading to the new concept of tumor lymphangiogenesis) and that tumor lymphangiogenesis was correlated with lymph node metastasis in an orthotopic breast cancer model. Our studies in human cutaneous malignant melanomas demonstrated the presence of both intratumoral and peritumoral lymphangiogenesis in cutaneous melanoma. They also showed that primary melanomas that later metastasized were characterized by increased lymphangiogenesis – as compared to non-metastatic tumors – and that the degree of tumor lymphangiogenesis can serve as a novel predictor of lymph node metastasis and overall patient survival, independently of tumor thickness. Moreover, we found that the extent of lymphatic vessel growth in primary human cutaneous melanomas was the most sensitive parameter for predicting whether these tumors had already metastasized to the sentinel (draining) lymph node at the time of surgery. Importantly, we have recently found - for the first time - that metastastic tumor cells can induce lymphatic vessel growth within lymph nodes, furthering their metastatic spread. This has led to the new concept of lymph node lymphangiogenesis. Surprisingly, we found that tumor cells can induce lymph node lymphangiogenesis already before they metastasize, giving a new twist to the seed-and-soil hypothesis and suggesting that tumors can prepare lymph nodes for their future arrival. We have characterized the transcriptional profile of normal and of tumor-associated lymphatic and blood vessels by laser capture microdissection. This has enabled us to identify a number of new targets for anti-(lymph)angiogenic cancer therapy. Taken together, tumor lymphangiogenesis has emerged as a novel prognostic parameter for the metastatic risk of human melanomas, and inhibition of tumor-associated lymphangiogenesis appears to represent an exciting new strategy to inhibit cancer progression.

Symposium (Wed, 26 Sep, 14:45−16:45)
New drugs and new tools in the treatment of patients with myeloma

176 INVITED

New insights in the biology of multiple myeloma: basis for novel therapies

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Multiple myeloma (MM) remains as an incurable disease; therefore, new treatment strategies are needed in order to improve the outcome of these MM patients. The increase knowledge in MM biology is already contributing to a more specific drug design, and we have recently learned that in the pathogenesis of MM, as important as the malignant cells themselves, is their interaction with the microenvironment.
Multiple myeloma requires a multistep transformation process that implies the sequential generation of primary Ig translocations, chromosomal instability (including mutations – RAS s– and deletions − RB), as well as secondary translocations. Most Primary immunoglobulin gene translocations occur early in the pathogenesis of MM. These translocations, which are mediated by errors in immunoglobulin heavy-chain switch recombination, result in the juxtaposing of an oncogene and an immunoglobulin enhancer. On the basis of Ig H translocations MM patients can be divided into 5 subgroups: (1) D-type cyclins: Cyclin D1 on 11q23, Cyclin D3 on 6p21 and Cyclin D2 on 12p13 (25% of cases); (2) MMSET/FGFR3 proteins (4p16.3) (15% of cases); (3) B-zip transcription factors: c-maf on 16q23 and maf B on 20q11 (15% of cases); (4) other Ig H translocations (20% of cases); and (5) No Ig H translocations (25% of cases). Secondary oncogenic events may involve both genes different from Ig locus, as well as the 14q32 region, as occur in the c-myc translocations.
Some of these molecular events represent potential therapeutic targets. Thus t(4;14) translocation generate a constitutive activation of the oncogenic receptor tyrosine kinase FGFR3 with subsequent phosphorylation of the antiapoptotic STAT3 signaling pathway. Therefore, the use of Kinase inhibitors of FGFR3 tyrosine kinase as well as Kinase inhibitors of cyclin dependent kinases would be attractive therapeutic targets. Similarly C-maf, that is over expressed in MM patients with t(14;16) as well as in some MM cases lacking this translocation, also represent a potential target.
The second area of MM pathogenesis that may have important implications for treatment intervention is the interaction between the malignant cell and the bone marrow microenvironment. MM cells adhere to the extra cellular matrix (ECM) proteins and bone marrow stromal cells (BMSC) through a series of adhesion molecules, such as the β1-integrin family (VLA-4, VLA-5 and VLA-6 or CD49d, e and f, respectively) as well as ICAM-1 and VCAM-1. Adhesion of myeloma cells to BM microenvironment induces a CAM-DR phenotype (cell-adhesion-mediated drug resistance). Interruption by downregulating the interactions between the tumor cell and its microenvironment can potentially halt cell growth and proliferation, and be of benefit to patients with MM. The binding of MM cell to BM microenvironment it also induces the transcription and secretion of cytokines (TNFa, IL-6, IGF-1, IL-21, SDF1a, VEGF), by both the PC and BMSC, which triggers signalling pathways (such as the RAF/MEK/MAPK, PI3K/AKT, and JAK/STAT pathways), that promote cell proliferation and prevent apoptosis. These pathways are also potential targets for therapeutic intervention.

177 INVITED

New drugs

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Abstract not received.

178 INVITED

Autologous and allogeneic transplantation in multiple myeloma

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In patients with multiple myeloma (MM) high-dose therapy/stem cell transplant (HDT/SCT) can be applied in different clinical settings and by using different approaches. In patients with relapsed/refractory disease, HDT/SCT is of no benefit. In contrast, patients with sensitive relapse are the most likely to benefit. Concerning newly diagnosed patients, two randomized trials showed that autologous transplant resulted in higher response rate as well as in longer progression-free and overall survival when compared with standard chemotherapy; however, other three randomized trials failed to show a significant survival advantage in favour of high-dose therapy. In any event, autologous transplantation in currently considered as part of the up-front therapy in younger myeloma patients. Double autologous (tandem) seems to be of benefit for patients not achieving complete remission or very good partial response with a single procedure. Allogeneic transplant with conventional conditioning results in a high response rate and cure in about 20% of patients. However, the transplant-related mortality (TRM) is between 30 and 50%. For this reason, the so-called “mini-allogeneic” or reduced-intensity conditioning allogeneic transplant (allo-RIC) is currently used in most institutions. The TRM with allo-RIC is about 20%; however, the relapse rate is higher than with conventional conditioning, this resulting in a similar long-term outcome with the two allogeneic approaches. In patients with advanced disease the allo-RIC seems to be of no benefit. In MM, HDT/SCT constitutes an important tool for tumour mass decrease. In the current era of novel agents and more effective treatment combinations, the additional tumour mass reduction achieved with HDT/SCT will hopefully result in an improved long-term outcome for patients with multiple myeloma.

179 INVITED

Waldenström macroglobulinaemia

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Waldenström’s macroglobulinemia (WM) results from the clonal proliferation of lymphocytes that produce monoclonal immunoglobulin M (IgM) and always involves the bone marrow. The normal counterpart of WM malignant cell is believed to be a post-germinal center B cell. WM cells do not bare