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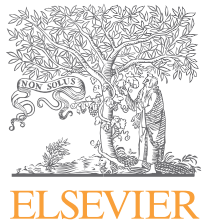

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EORTC Melanoma Group achievements

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ABSTRACT

Since its inception in 1969, the EORTC Melanoma Group has employed a multidisciplinary approach in the fight against melanoma and has registered significant achievements in many areas of melanoma treatment and research. The group showed that sentinel node (SN) tumor burden according to the Rotterdam Criteria and the microanatomic location were the most important prognostic factors for melanoma-specific survival and non-SN positivity in the completion lymph node dissection specimen. They demonstrated that extended schedule escalated dose temozolomide is feasible and has an acceptable safety profile. They also showed that the interferon-α targeted therapy should occur in a targeted patient population, and should probably not be offered to 70% of the patients that are currently being given this treatment. Through EORTC trial 18991, Sylatron™, pegylated interferon α-2b, for the treatment of melanoma patients with microscopic or gross nodal involvement within 84 days of definitive surgical resection including complete lymphadenectomy, was approved by the US FDA. The present article describes the achievements and future strategies of the Melanoma Group.

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1. Introduction

The worldwide incidence of malignant melanoma has been increasing over the past 30 years with an annual increase above 2%.[1–3] The disease stage of melanoma at diagnosis is the major determinant of prognosis and survival, and though early-stage disease is often cured by surgical excision of the primary tumor, melanoma with distant spread is often fatal.[4]

The European Organisation for Research and Treatment of Cancer (EORTC) has been at the forefront of oncology practice-changing trials throughout the world. In 1969, the EORTC Melanoma Group (EORTC MG) was one of the first EORTC groups. Founded by a small group of like-minded colleagues from all over Europe, the EORTC MG has been and still remains a unique group within the EORTC as manifested by its multidisciplinary approach in harnessing all disciplines of the medical community in the fight against melanoma. Over the past 40 years successive Chairs of the EORTC MG have enthusiastically fostered the collaboration of immunologists, pathologists, and clinicians, and the young investigators platform of the EORTC MG offers a unique forum for development of budding melanoma researchers.

The EORTC MG has always pursued an unwavering interest in tumor biology with a special focus on the immunological aspects of melanoma. The group has successfully performed many clinical, epidemiological, histopathological, and surgical studies that have defined standards and guidelines in the management of melanoma. There has been a great emphasis on translational research with respect to the prognostic factors and various metastatic and immunological aspects of melanoma. This led to the development of quality assurance programs for immunological and molecular biological assays in laboratory networks.

The EORTC MG currently has subcommittees concerned with the management of cutaneous and ocular melanoma which focus on the development of new treatment strategies and conducting epidemiological, genetic, and pathological research on melanoma. These comprise adjuvant therapy, systemic therapy for advanced disease, epidemiology, genetics, ocular melanoma, pathology, surgery, translational research in melanoma (an 'umbrella' subcommittee), and Young Investigator subcommittees.

2. Major advances

2.1. Status of the sentinel node in melanoma

The sentinel node (SN) procedure was introduced in penile cancer by Cabanas in the late 1970's.[5] With the introduction of lymphatic mapping, it was adapted by Donald Morton and colleagues in the 1990's to the situation in melanoma.[6,7] Since then, the SN procedure has become standard of care for the staging of melanoma patients in many countries. However, many controversies still remain, which have led to an enormous amount of research on the subject of the SN in melanoma and in which the EORTC MG has played a prominent role.

One of the groundbreaking achievements was the analysis and implementation of an optimal pathology protocol for the work-up of SNs in melanoma. A study by Cook et al. on behalf of the EORTC MG analyzed a number of different protocols with respect to the type and extent of the pathology work-up of SNs.[8] This study demonstrated a massive 42% increase in SN positivity rate and thus also led to a significant reduction in false negative rates.[4] Since 2003, this protocol has been implemented by the entire EORTC MG network and in all EORTC MG protocols.

At the same time the analysis of SN metastases with regard to their extent and intranodal site has become equally important. A paper by the EORTC MG analyzed practical issues with respect to difficulties in the analyses of SN tumor burden and the SN microanatomic location of metastases.[5] These analyses led to recommendations and guidelines for the analysis of these factors and have been implemented by the EORTC MG network.[9]

A multicenter EORTC MG study by van der Ploeg et al.[10] has reviewed the largest dataset of SNs worldwide. In 1080 SN-positive melanoma patients (1993–2008), SN tumor burden defined by the Rotterdam Criteria according to van Akkooi et al.[11] and the microanatomic location according to Dewar et al.[12] were the most important prognostic factors for melanoma-specific survival and non-SN positivity in the completion lymph node dissection (CLND) specimen. Patients with minimal SN tumor burden might therefore safely be spared a routine CLND.

The EORTC MG has launched a prospective registration study, the MINITUB. Patients with minimal SN tumor burden will be managed without routine CLND. Simultaneously, SN tumor burden has become an important issue in the adjuvant interferon (IFN) studies. SN tumor burden has become an important stratification tool for all new adjuvant studies in melanoma and we look to integrating this in future studies of EORTC MG.

2.2. IFN in melanoma

The EORTC MG has been at the forefront of evaluating interferon in melanoma patients. Two landmark studies were published, and they are described briefly below.

2.2.1. EORTC trial 18952 – Post-surgery adjuvant therapy with intermediate doses of interferon alfa-2b versus observation in patients with stage IIb/III melanoma[13]

Background: Treatment with high-dose and low-dose interferon alfa had been evaluated, with the former having

substantial toxicity and a consistent effect on relapse-free survival (RFS) but not on overall survival (OS), and the latter having no consistent effect on either. Hence, the objective of this trial was to assess the efficacy and toxicity of two regimens of interferon of intermediate dose *versus* observation.

Methods: EORTC trial 18952 was a randomized controlled trial involving 1388 patients with thick primary tumors (thickness $\geqslant$4 mm) resected (stage IIb) or regional lymph node metastases dissected (stage III). Patients were randomly allocated to a 13-month (n = 553) or 25-month (n = 556) treatment arm with subcutaneous interferon alfa-2b, or observation (n = 279). Treatment consisted of 4 weeks of 10 million units (MU) of interferon alfa (5 days per week) followed by either 10 MU 3 times a week for 1 year or 5 MU 3 times a week for 2 years, for a total dose of 1760 MU. The primary endpoint was distant metastasis-free interval (DMFI) and OS was secondary endpoint. Data were analyzed following the intent to treat principle.

Findings: The 25-month interferon group presented an increase of 7.2% in the DMFI rate at 4.5 years (hazard ratio [HR] = 0.83, 97.5% confidence interval [CI] 0.66–1.03) as well as a 5.4% improvement in OS. In comparison, the 13-month interferon treatment arm showed a 3.2% increase in rate of DMFI at 4.5 years (HR = 0.93, 97.5% CI 0.75–1.16) while no significant impact on the OS was found. Toxicity was acceptable with 18% (195 of 1076) of patients going off study because of toxicity or as a result of refusal of treatment because of side-effects.

Interpretation: The interferon alfa regimens tested in the study did not improve outcome for patients with stage IIb/III melanomas, and therefore cannot be recommended. Notably, the duration of treatment seemed more important than dose, and should be assessed in future study proposals.

2.2.2. EORTC 18991 – Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma [14]

Background: Any benefit of adjuvant interferon alfa-2b for melanoma could depend on dose and duration of treatment. Our aim was to determine whether pegylated interferon alfa-2b can facilitate prolonged exposure while maintaining tolerability.

Methods: A total number of 1256 patients with resected stage III melanoma were randomly assigned to observation (n = 629) or pegylated interferon alfa-2b (n = 627) 6 μg/kg per week for 8 weeks (induction) then 3 μg/kg per week (maintenance) for an intended duration of 5 years. Randomization was stratified for microscopic (N1) *versus* macroscopic (N2) nodal involvement, number of positive nodes, ulceration and tumor thickness, sex, and center. The primary endpoint was recurrence-free survival (RFS). Analyses were done by intention to treat.

Findings: The median length of treatment with pegylated interferon alfa-2b was 12 months (IQR 3.8–33.4). At 3.8 years (3.2–4.2) median follow-up, 328 recurrence events had occurred in the interferon group compared with 368 in the observation group (HR = 0.82, 95% CI 0.71–0.96; p = 0.01); the 4-year rate of RFS was 45.6% (SE 2.2%) in the interferon group and 38.9% (2.2%) in the observation group. There was no difference in OS between the groups. A total of 608 patients in the interferon group and 613 patients in the observation group were included in safety analyses. Grade 3/4 adverse events occurred in 246 (40%)/32 (5%) patients in the interferon group and 60 (10%)/14 (2%) in the observation group. In the interferon group, the most common grade 3 or 4 adverse events were fatigue (97 patients, 16%), hepatotoxicity (66, 11%), and depression (39, 6%). Treatment with pegylated interferon alfa-2b was discontinued because of toxicity in 191 (31%) patients.

Interpretations: The final conclusion was that adjuvant pegylated interferon alfa-2b for stage III melanoma has a significant, sustained effect on RFS. FDA has approved this drug based on this trial for this indication.

2.2.3. Meta-analysis

Background: As ulcerated (Ulc) melanomas have a worse prognosis than non-ulcerated (N-Ulc) melanomas, resulting from a difference in biology, the outcome after adjuvant IFN therapy in the two above mentioned phase III trials (EORTC 18952 and 18991) was analyzed. [15]

Methods: Using meta-analytical methods, predictive value for Ulc on the value of IFN on relapse-free survival (RFS), DMFS, and OS was evaluated among a total of 2644 patients.

Findings: In the Ulc group, representing a total of 849 patients, the treatment effect was much greater than in the N-Ulc group for RFS (Test For Interaction: p = 0.02), DMFS (p < 0.001), and OS (p < 0.001). The greatest impact occurred in patients with Ulc and stages IIb/III–N1.

Interpretations: The *post hoc* analyses of EORTC trials 1892 and 18991 and the consistency in the treatment impact seen in both indicate strongly that patients with an Ulc primary are far more sensitive to IFN than patients with N-Ulc primaries. This hypothesis will now be tested in the EORTC 18081 trial which compares PEG-IFNα-2b *versus* observation in patients with Ulc primaries >1 mm.

2.3. Immunotherapy in melanoma

The EORTC MG has been a leading network for the testing of new immunotherapies, including vaccines, cytokines and now new antibodies. Vaccines have been tested in a variety of cancers with varying success.

2.3.1. EORTC trial 18961 – Adjuvant phase III study assessing the efficacy and toxicity of ganglioside GM2-KLH/QS-21 vaccination versus observation in stage II melanoma. [16]

Background: Preliminary studies showed that vaccination with ganglioside GM2-KLH/QS-21 led to responses in advanced melanoma.

Methods: Patients were randomized between observation and ganglioside GM2-KLH/QS-21 sc vaccinations once weekly weeks 1–4, every 3 months from week 12 for the first 2 years and every 6 months during the third year (total of 14 vaccinations). The primary endpoint was RFS, and DMFS and OS were secondary endpoints. An intent-to-treat analysis was performed.

Results: Over a 3-year recruitment period, 1,314 patients were enrolled in the trial. An interim analysis performed when 267 RFS events were reached showed that the criteria for stopping for futility were for the primary endpoint, RFS. In addition, for DMFS and OS, a trend favoring the observation arm was observed. Consequently, the EORTC IDMC recommended that GM2-KLH/QS-21 vaccine be stopped in the patients still under treatment while patients continued to be followed for the trial's endpoints.

Conclusions: Adjuvant GM2-KLH/QS-21 vaccination is ineffective and could even be detrimental in stage II melanoma patients.

2.3.2. EORTC trial 18951 – Randomized phase III trial. Treatment of metastatic melanoma with DTIC, CDDP and IFN-alpha with or without IL-2. [17]

Background: This landmark study is one of few carried out in melanoma that specifically examined the role of systemic interleukin-2 in patients with stage IV melanoma.

Methods: In this study, 363 patients were randomized to receive dacarbazine 250 mg/m^2 and cisplatin 30 mg/m^2 on days 1–3 combined with interferon-alfa-2b 10 MU/m^2 subcutaneously on days 1 through 5 without (arm A) or with (arm B) a high-dose intravenous decrescendo regimen of IL-2 on days 5 through 10 (18 MU/m^2/6 hours, 18 MU/m^2/12 hours, 18 MU/m^2/24 hours, and 4.5 MU/m^2 for 3×24 hours). Treatment was given every 28 days to a maximum of 4 cycles or until disease progression.

Results: This study recruited 363 patients with advanced metastatic disease. The median survival was 9 months in both arms, with a 2-year OS rate of 12.9% and 17.6% in arms A and B, respectively (HR = 0.90, 95% CI 0.72–1.11; P = 0.32). In addition, there was no statistically significant difference regarding PFS (median, 3.0 *versus* 3.9 months) and response rate (22.8% *versus* 20.8%).

Conclusion: Despite its activity in melanoma as a single agent or in combination with interferon-alfa-2b, the chosen schedule of IL-2 added to the chemoimmunotherapy combination had no clinically relevant efficacy.

2.3.3. Translational research project linked to EORTC trial 18951

Background: As elevated count of blood neutrophils and monocytes had been shown to independently predict short survival in patients with stage IV melanoma undergoing interleukin-2-based immunotherapy, neutrophil and leukocyte counts were analyzed together with other known prognostic factors like serum lactate dehydrogenase, performance status, metastatic site, and sex in the EORTC 18951 study population. Two multivariate prognostic factor analyses were performed in the model: one with leukocyte counts and one with neutrophil counts.

Results: Counts of baseline blood neutrophil and leukocyte were available from 316 and 350 patients, respectively. A high neutrophil count (>7.5×10^9/L) was an independent prognostic factor for short OS (HR = 1.5, 95% CI 1.1–2.1; P = 0.02), and a high leukocyte count (>10×10^9/L) was an independent prognostic factor of both short OS (HR = 1.7, 95% CI 1.3–2.4; P = 0.0005) and short PFS (HR = 1.5, 95% CI 1.1–2.1; P = 0.008). [18]

Conclusion: This retrospective prognostic study has confirmed that a high pretreatment count of neutrophils in blood is indeed an independent prognostic factor for short OS in stage IV melanoma patients undergoing interleukin-2-based immunotherapy. Moreover, a high count of leukocytes was found to be an independent prognostic factor for short OS and PFS.

2.3.4. EORTC 16032-18031 – Immunization with the recombinant MAGE-3 protein combined with adjuvant AS02B or AS15 in patients with unresectable and progressive metastatic cutaneous melanoma. [19]

Background: Earlier studies showed that active immunization against the tumor-specific MAGE-A3 antigen was followed by a few but definite clinical responses. In a bid to increase this anti-tumor activity, this randomized Phase II trial in stage IV melanoma was performed to evaluate immunization with the recombinant MAGE-A3 protein combined with two different immunostimulants.

Methods: Patients with MAGE-A3-positive in-transit or unresectable stage III or stage IV M1a melanoma were randomly assigned to receive as first-line treatment the recombinant MAGE-A3 protein combined either with AS02B or with AS15 immunostimulant. Clinical endpoints were toxicity and rates of objective clinical responses (OR), PFS and OS.

Results: Thirty-six patients were accrued to both arms. Both treatments were equally well tolerated. In the AS15 arm, four OR were observed (three CR and one PR) and only one PR in the AS02B arm. The PFS at six months was 25% *versus* 14% and the median OS 33.0 months *versus* 19.9 months with a median follow-up of 48 months. Antibodies against MAGE-A3 were found in all patients,

with a three-fold higher titer in the AS15 arm. The anti-MAGE-A3 cellular response was also more pronounced in the AS15 arm.

Conclusions: This very important study with a very large translational research component demonstrated that clinical activity appeared to be higher in the MAGE-A3+AS15 arm, together with a more robust cellular and humoral immune response and without relevant toxicity. Therefore the AS15 immunostimulant has been selected for combination with the recombinant MAGE-A3 protein in phase III trials.

2.4. Chemotherapy

2.4.1. EORTC trial 18032 – Extended schedule, escalated dose temozolomide versus dacarbazine in stage IV metastatic melanoma: a randomized phase III study of the EORTC Melanoma Group [20]

Background: With the imminent development of new small molecule targeted therapies, it was important to define the standard chemotherapy regimen against which new agents should be compared or with which they should be combined.

Purpose: EORTC trial 18032, the largest trial in stage IV melanoma to have been carried out at the time, compared the efficacy of an extended schedule, escalated-dose of temozolomide, that delivered a higher dose of temozolomide than previous regimens, *versus* standard-dose dacarbazine in stage IV melanoma.

Patients and Methods: A total of 859 patients were randomized to receive oral temozolomide at 150 mg/m^2/day for 7 consecutive days every 2 weeks or dacarbazine, administered as an intravenous infusion at 1000 mg/m^2/day on day 1 every 3 weeks. The primary endpoint was OS using an intent-to-treat principle.

Results: There was no difference in OS or PFS. The median OS was 9.1 months in the temozolomide arm and 9.4 months in the dacarbazine arm with a HR of 1.00 (95% CI 0.86–1.17; P = 0.99). Median PFS was 2.3 months in the temozolomide arm and 2.2 months in the dacarbazine arm, with a HR of 0.92 (95% CI 0.80–1.06; P = 0.27). The most common non-hematologic treatment-emergent adverse events reported in both treatment arms were nausea, fatigue, and vomiting and constipation.

Conclusion: Extended schedule escalated-dose temozolomide (7 days on, 7 days off) is feasible and has an acceptable safety profile but does not improve OS and PFS in metastatic melanoma when compared to standard-dose dacarbazine.

2.5. Rare tumor initiative

Ocular melanoma is a rare disease, and the EORTC network is ideally placed to address the therapeutic challenges in this area. Initially through collaboration with the EORTC Ophthalmic Oncology Task Force and more recently by incorporating an Ocular Melanoma subcommittee in its structure, the EORTC MG is working on trials in this difficult area. EORTC trial 18021 of intrahepatic *versus* intravenous fotemustine has recruited more than any other randomized trial in this area and will report its findings shortly. This resulted in the creation of a specific network of more than 30 institutions in 10 European countries which was able to conduct high-quality trials in this rare disease. A study exploring the combination of bleomycin, vincristine, lomustine, and dacarbazine (BOLD) in combination with recombinant interferon alpha-2b for metastatic uveal melanoma was conducted. [21] EORTC trial 18021 of intrahepatic *versus* intravenous fotemustine for stage IV metastatic ocular melanoma has recruited more than any other randomized trials in this area and will report its findings shortly.

2.6. Translational research

The EORTC MG has a long and distinguished track record of translation research both within its trials and within the network's multi-disciplinary expertise. Good prognostic markers have been identified for cutaneous melanoma, yet little is known about their biological significance. Therefore, understanding the correlations between the prognostic factors and the biology of the disease is a major objective of melanoma translational research. [22]

In 2004, the EORTC MG conducted the first genomics study on a large cohort of primary melanomas using more than 105 validated frozen primary tumor samples. The correlation of gene-expression profiles with clinical outcome led to a signature based on 60 genes discriminating between primary melanomas associated with good and poor prognosis. Key pathways associated with melanoma progression have been identified. [23]

The EORTC MG has played an important role in systematically evaluating prognostic and predicative markers including serum markers, immunological markers and RT-PCR for circulating tumor cells. In the process it has developed quality assurance programs for immunological assays and molecular biological assays such as RT-PCR, S100B as a soluble marker of melanoma, TNFalpha and Melphalan combination in isolated limb perfusions, [24] as well as in patients' sera in EORTC trial 18952. [25,26] The findings highlighted the origin, half-life, and the value of serial S100B blood measurements in the follow-up and management of the disease.

The group has shown the importance of neutrophil count in predicting outcome in advanced melanoma [18] and evaluated RT-PCR-detected circulating tumor cells. [27] Importantly the group has examined the utility of autoantibodies in predicting response to interferon and demonstrated the absence of predictive value. [27,28]

The pathology committee has played an important role in setting standards for central pathology review and quality assurance for the EORTC MG trials and has published a number of important papers on criteria and guidelines in the field of dysplastic naevi, melanoma in childhood and melanoma staging systems. [29–31] The diagnosis of melanoma in childhood is marred with pitfalls and the diagnosis is often incorrect. In a review/reassessment of >100 cases by the EORTC MG pathologist-panel it was concluded that in almost half the cases the diagnosis melanoma was incorrect. [32] At present, the EORTC MG is a full partner in the EU telematics project that aims to improve exchange of diagnostic images through a European network.

Another focus of studies performed by the pathology committee has been the expression of various classes of antigen in primary, regionally metastatic and distant metastatic melanoma. The EORTC MG carried out the most extensive inventory study on the use of monoclonal antibodies in the early 1990's and documented changes of expression under cytokine treatments. [33,34] The differential expression of antigens in relation to the progression of the disease was shown to have important implications for both diagnosis as well as immunotherapeutic treatment strategies. [35] In yet another study on the EORTC MG primary melanoma material it was demonstrated that high tPA expression in primary melanoma of the limb correlates with good prognosis. [36] The pathology group led the research into identifying pathological markers in sentinel lymph node biopsies (section 2.1).

2.7. Collaboration with other groups

The EORTC MG has a productive cooperation with European Society for Pigment Cell Research (ESPCR) with the aim of increasing the collaboration between basic and clinical research in melanoma. On the clinical side, cooperative studies were launched with the WHO Melanoma Program, the Scandinavian Melanoma Group and the North American Perfusion Group.

3. Future strategy

The EORTC MG is committed to further execute and expand a comprehensive melanoma program through the fully integrated and collaborative approach by its member scientists and clinicians. Molecular therapeutics and immunotherapy will be an important focus for the next decade as is the ever challenging task of identifying a systemic adjuvant therapy regimen for high-risk melanoma that is effective enough to be accepted as standard of care and a stepping stone for further developments.

Recent developments in immune and targeted therapy have opened new therapeutic perspectives for metastatic melanoma patients. Both modalities act *via* distinct mechanisms; targeting MAPK pathway induces rapid responses at high rate, however, drug resistance develops in the vast majority of patients. On the other hand, response rates to immunotherapy are rather low, but remarkably, responding patients in general have long-lasting clinical benefit. We now face the challenge to exploit these novel approaches selectively and effectively in order to achieve long-term tumor control.

In the field of genetic and epidemiology studies, the time for a molecular genetic and epidemiological program has arrived and innovative studies will be launched in that field. The membership of the group will grow further and incorporate especially scientists from fields of research such as genetics and genomics. The EORTC MG is thus headed for even more exciting times in its existence.

4. Conflict of interest statement

Alessandro Testori, Stefan Suciu, Alexander C.J. van Akkooi, Ghanem Ghanem, Ravi Karra Gurunath, Ulrich Keilholz, Martin Mihm, Gaetan de Schaetzen, Alan Spatz, Leon van Kempen, Caroline Robert, Serge Leyvraz and Esther de Vries declare no conflicts of interest. Dirk Schadendorf consulted for and received honoraria and research funds from Merck, consulted for and received honoraria from GSK, Roche, BMS, AstraZeneca, and Amgen, and consulted for Morphotek. Alexander M.M. Eggermont consulted in advisory boards for melanoma for Merck, BMS, Roche, and GSK. Julia Newton-Bishop advised for Roche. Martin Cook advised for GSK. Poulam Patel advised for, and received honoraria from, BMS, GSK, and Roche, and advised for SPRI.

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