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Ulceration and stage are predictive of interferon efficacy in melanoma: Results of the phase III adjuvant trials EORTC 18952 and EORTC 18991 ☆

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ABSTRACT

Summary: Adjuvant interferon has modest activity in melanoma patients at high risk for relapse. Patient selection is important; stage and ulceration of the primary tumour are key prognostic factors.

Methods: In this *post hoc* meta-analysis of European Organisation for Research and Treatment of Cancer (EORTC) trials 18952 (intermediate doses of interferon α-2b [IFN] versus observation in stage IIb-III patients) and 18991 (pegylated [PEG]-IFN versus observation in stage III patients), the predictive value of ulceration on the efficacy of IFN/PEG-IFN with regard to relapse-free survival (RFS), distant metastasis-free survival (DMFS), and overall survival (OS) was assessed in the overall population and in subgroups stratified by stage (IIb and III-N1 [microscopic nodal disease] and III-N2 [macroscopic nodal disease]).

Findings: In the overall population, the comparison of IFN/PEG-IFN versus observation for RFS, DMFS and OS yielded estimated hazard ratios (HR) of 0.85 ($p = 0.004$), 0.89 ($p = 0.04$) and 0.94 ($p = 0.36$), respectively. The impact of treatment was greater in the ulceration

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group (n = 849) compared with the non-ulceration group (n = 1336) for RFS (test for interaction: $p = 0.02$), DMFS ($p < 0.001$) and OS ($p < 0.001$). The greatest risk reductions were observed in patients with ulceration and stage IIb/III-N1, with estimated HR for RFS, DMFS, and OS of 0.69 ($p = 0.003$), 0.59 ($p < 0.0001$) and 0.58 ($p < 0.0001$), respectively. The efficacy of IFN/PEG-IFN was lower in stage III-N2 patients with ulceration and uniformly absent in patients without ulceration. There was consistency between the data of both trials.

Interpretation: This meta-analysis of the EORTC 18952 and 18991 trials indicated that both tumour stage and ulceration were predictive factors for the efficacy of adjuvant IFN/PEG-IFN therapy.

1. Introduction

Based on the European Organisation for Research and Treatment of Cancer (EORTC) 18991 trial, the United States (US) Food and Drug Administration (FDA) approved pegylated interferon α-2b (PEG-IFN; Sylatron™) in March 2011 for the treatment of melanoma patients with microscopic or gross nodal involvement within 84 days of definitive surgical resection, including complete lymphadenectomy.[1] The EORTC 18991 trial comparing adjuvant PEG-IFN treatment with observation in stage III cutaneous melanoma patients[1] is the largest randomised controlled trial (RCT) in this patient population. The EORTC 18952 trial, which is the largest RCT in stage IIB/III melanoma patients, compared intermediate doses of interferon α-2b (IFN) with observation.[2] Importantly, these are the only trials in which patients were stratified by sentinel node staging (microscopic involvement only: stage III-N1, or gross macroscopic relapse: stage III-N2). Patients in both trials were also stratified by the ulceration status of the primary tumour. Thus, these trials permit analysis of the potential interaction between tumour load and treatment as well as ulceration and treatment, which is crucial given that stage and ulceration are key prognostic factors.[3,4] Patients with only microscopic involvement of the regional lymph node basin have a better prognosis than patients with palpable regional node metastases.[5] Palpable nodal disease may represent more aggressive disease from the onset or by acquisition of additional mutations over time. For the same Breslow thickness, patients with an ulcerated primary have a 10–25% lower survival probability at 10 years, indicating a distinct biologic entity.[4] This hypothesis is strengthened by a number of additional observations: (a) ulcerated primaries have a distinct gene profile[6]; (b) sentinel nodes of ulcerated primaries demonstrate a severely immune-suppressed status even in the absence of tumour cells[7]; and (c) the stromal response of ulcerated primaries is distinctly different from that of non-ulcerated primaries.[8]

Twenty-five years of RCTs in melanoma are a testimony to the fact that efficacy of adjuvant therapy with IFN is modest. Meta-analyses of phase III trials demonstrated that IFN has a consistent effect on relapse-free survival (RFS) but no (or only marginal) effect on overall survival (OS).[9–11] These findings suggest that only a minority of patients are sensitive to IFN and mandate that we identify these patients. Interestingly, the meta-analysis by Wheatley et al.[10] which reported on individual patient data, is the only study to date that has investigated the role of ulceration of the primary tumour on efficacy outcomes. Their analysis, which did not include data from the EORTC 18991 trial, demonstrated a correlation between ulceration and IFN efficacy.

Herein we present a meta-analysis of the two largest adjuvant IFN/PEG-IFN randomised trials in a combined total of 2644 patients with high-risk melanoma (stage IIb/III) who were uniquely stratified to evaluate the importance of tumour load in the regional lymph nodes and ulceration of the primary tumour.

2. Methods

2.1. The EORTC trials

Details on the EORTC 18991 and 18952 trials have been published[1,2]; the trial characteristics are briefly summarised below.

2.1.1. EORTC 18991

The 18991 was a phase III RCT in 1256 patients with resected stage III melanoma. Patients were randomised to PEG-IFN or observation in a 1:1 ratio, with stratification by disease substage (microscopic non-palpable nodes [N1] versus palpable nodes [N2]), number of positive lymph nodes, Breslow thickness, ulceration of primary tumour, gender and centre. Treatment with PEG-IFN consisted of an induction phase of subcutaneous administration of 6 μg/kg/week for 8 weeks, followed by a maintenance phase of subcutaneous administration of 3 μg/kg/week for a maximum of 5 years. The initial primary end-point was distant metastasis-free survival (DMFS), which was revised to RFS at the request of the FDA; the secondary efficacy end-point was OS (ClinicalTrials.gov, number NCT00006249).

2.1.2. EORTC 18952

The 18952 was a phase III RCT in 1388 patients with stage IIb or resected stage III melanoma. Patients were randomised to 13 or 25 months of IFN or observation in a 2:2:1 ratio, with stratification by tumour staging (T4N0, $T_{any}N1$, $T_{any}N2$), number of positive lymph nodes, Breslow thickness, ulceration of primary tumour site, gender and centre. Treatment with IFN consisted of an induction phase with intravenous administration of 10 million units (MU) 5 days per week for 4 weeks, followed by a maintenance phase of either subcutaneous administration of 10 MU three times per week for 1 year or 5 MU three times a week for 2 years. The primary end-point

was distant metastases-free interval (defined as time from randomisation to appearance of distant metastases); secondary efficacy end-points included RFS, DMFS and OS from randomisation (ClinicalTrials.gov, number NCT00002763).

In both studies, all patients provided written informed consent and the EORTC protocol review committee and local institutional ethics committees approved the study protocol. Both trials had a quality-of-life assessment.[12]

2.2. End-points

Relapse-free survival: RFS was the time from randomisation until first relapse (local, regional lymph node or distant metastasis) or death due to any cause.

Distant metastasis-free survival: DMFS was the time from randomisation until the occurrence of first distant metastasis or death due to any cause.

Overall survival: OS was defined as the time between randomisation and death regardless of the cause.

2.3. Statistical methods

Kaplan–Meier curves were used to estimate the survival distribution of time-to-event analyses (RFS, DMFS and OS). The Cox model stratified for study was used to assess the treatment effect for these end-points by estimation of the hazard ratio (HR) of the event intensity per time unit in the IFN/PEG-IFN versus the observation arms and its confidence intervals (CI); 95% CI was used for overall patient population and 99% CI was used for subgroups (i.e. ulceration status and tumour stage). The Wald test was used to determine the statistical significance of the treatment effect. Similar methods were used for assessing the prognostic value of other variables in univariate or multivariate setting: ulceration status (presence versus absence), stage of disease (III-N2 versus IIb or III-N1) and number of lymph nodes involved (see Supplemental Table 1 for details). The predictive value of a variable regarding treatment effect was assessed by including interaction terms in the Cox model stratified for study: stage (1 = stage III-N2, 0 = stage III-N1 or T4N0 = IIb) × treatment (1 = IFN/PEG-IFN, 0 = observation) and/or ulceration (1 = present, 0 = absent) × treatment (1 = IFN/PEG-IFN, 0 = observation).

2.4. Role of funding source

This publication was supported by Fonds Cancer (FOCA) in Belgium. These EORTC trials were performed with the financial support of Schering Plough Research International that also provided the study drugs at no cost.

3. Results

A total of 2644 patients were randomised in the two trials (n = 1256 in EORTC 18991 and n = 1388 in EORTC 18952). Patient characteristics are reported in Supplemental Table 2. The number of patients with an ulcerated melanoma was 849 (32%) and those with non-ulcerated melanoma totalled 1336 (51%); 459 (17%) patients had an unknown ulceration status, of whom 121 (5%) had an unknown primary tumour.

3.1. Efficacy of IFN/PEG-IFN: overall population

Comparison of IFN/PEG-IFN versus observation in the overall patient population of EORTC 18952 and 18991 yielded HRs that were significant for RFS (HR 0.85 [95% CI 0.76–0.95]; p = 0.004) and DMFS (HR 0.89 [95% CI 0.79–1.00]; p = 0.04), but not for OS (HR 0.94 [95% CI 0.80–1.11]; p = 0.36). Stage and ulceration were strong prognostic factors for RFS (Supplemental Figs. 1 and 2).

3.2. Analyses in 2185 patients with known ulceration status

To investigate the prognostic importance of stage and ulceration as well as their potential predictive value with regard to IFN/PEG-IFN efficacy, all subsequent analyses were performed on the 2185 patients for whom the ulceration status of the primary tumour was known. In this subgroup, the treatment effect was similar to that observed in the entire patient population, with estimated HRs for RFS, DMFS, and OS of.0.85, 0.88 and 0.92, respectively.

Using the Cox multivariate model stratified for study, the estimated HR for treatment effect, adjusted for stage, presence of ulceration, and gender was significant for RFS (HR 0.85) and DMFS (HR 0.88), but not for OS (HR 0.93) (Table 1).

Table 1 – Cox multivariate model stratified for EORTC studies 18952 and 18991: treatment effect on relapse-free, distant metastasis-free and overall survivals.

End-point	RFS				DMFS				OS			
Variable	HR	95% (CI)		p Value	HR	95% CI		p Value	HR	95% CI		p Value
Treatment adjusted for stage, presence of ulceration and sex: IFN/PEG-IFN versus observation	0.85	0.76	0.96	0.009	0.88	0.78	1.00	0.05	0.93	0.81	1.07	0.31
Sex: male versus female	1.27	1.13	1.42	<0.0001	1.36	1.21	1.54	<0.0001	1.43	1.26	1.63	<0.0001
Stage: III-N2 versus IIb/III-N1/	2.04	1.83	2.28	<0.0001	2.27	2.02	2.56	<0.0001	2.33	2.05	2.65	<0.0001
Ulceration: yes versus no	1.48	1.32	1.65	<0.0001	1.47	1.31	1.65	<0.0001	1.45	1.27	1.64	<0.0001
Stage × treatment	1.24	0.98	1.55	0.07	1.35	1.06	1.73	0.02	1.25	0.95	1.63	0.11
Ulceration × treatment	0.86	0.68	1.08	0.19	0.73	0.57	0.93	0.01	0.71	0.54	0.92	0.01

EORTC = European Organisation for Research and Treatment of Cancer. RFS = relapse-free survival. DMFS = distant metastasis-free survival. OS = overall survival. HR = hazard ratio. CI = confidence interval.

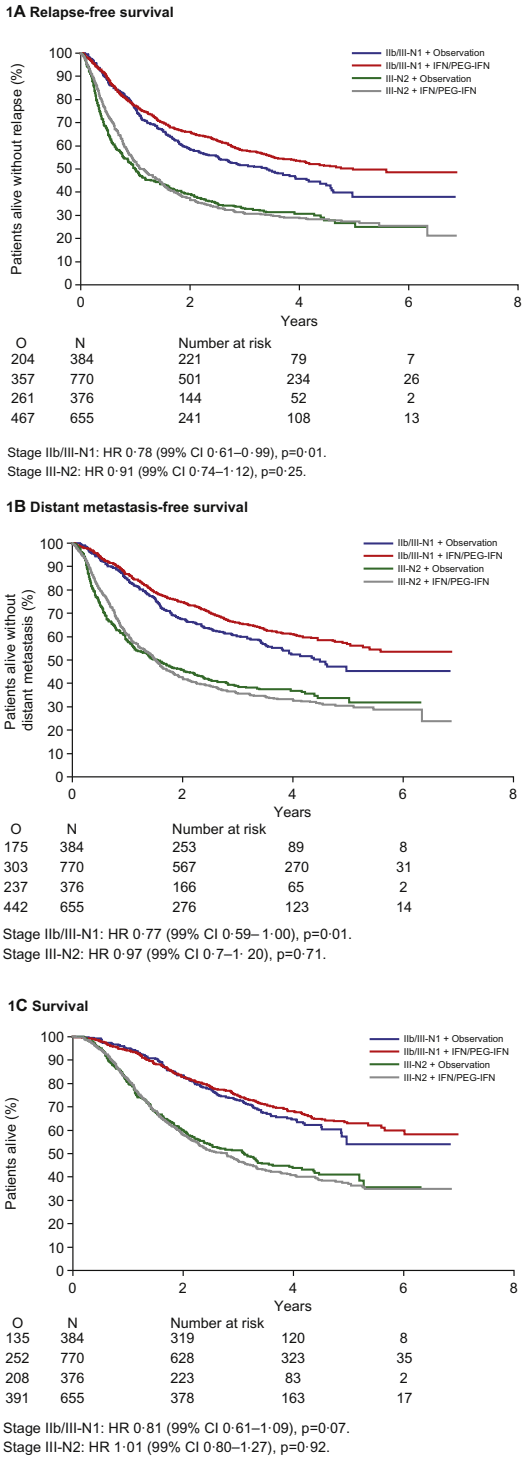

Fig. 1 – Kaplan–Meier curves obtained by meta-analysis of data from the EORTC 18952 and 18991 studies according to stage and treatment regarding three end-points: (A) relapse-free survival, (B) distant metastasis-free survival, and (C) overall survival. EORTC = European Organisation for Research and Treatment of Cancer. IFN/PEG-IFN = interferon α-2b/pegylated interferon α-2b. O = observed events. N = total number of patients. HR = hazard ratio. CI = confidence interval.

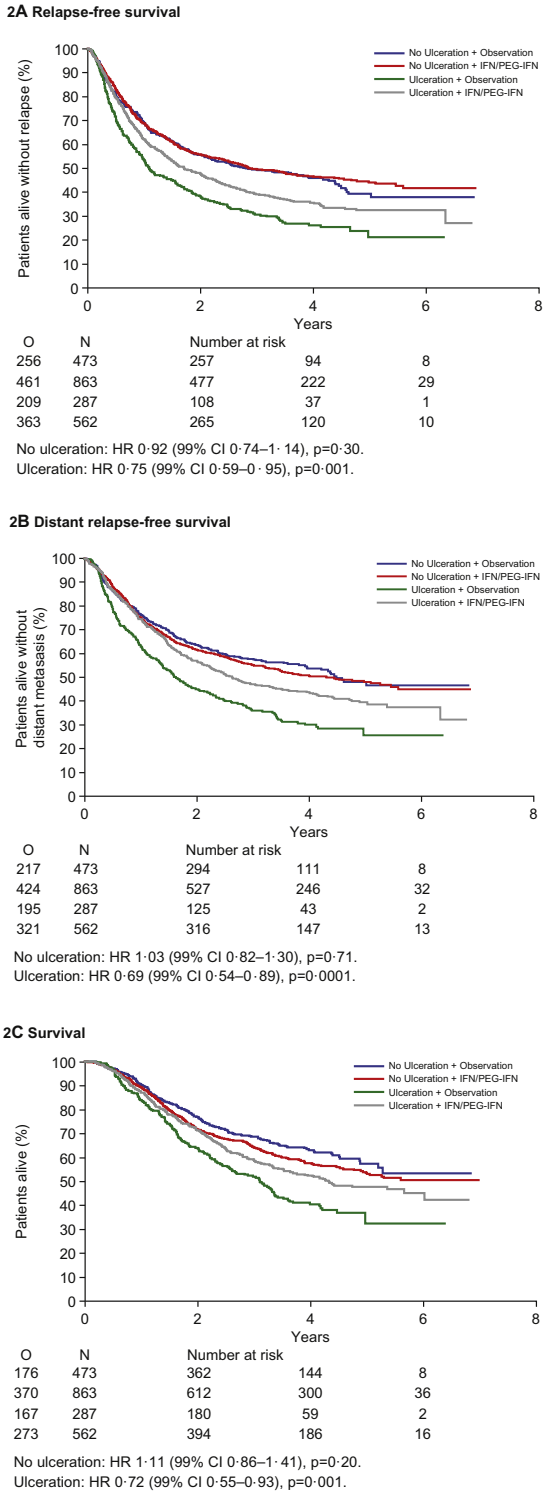

Fig. 2 – Kaplan–Meier curves obtained by meta-analysis of data from the EORTC 18952 and 18991 studies according to ulceration status and treatment regarding three end-points: (A) relapse-free survival, (B) distant metastasis-free survival, and (C) overall survival. EORTC = European Organisation for Research and Treatment of Cancer; IFN/PEG-IFN = interferon α-2b/pegylated interferon α-2b. O = observed events. N = total number of patients. HR = hazard ratio. CI = confidence interval.

Table 2 – Hazard ratios (HR) for treatment effect (IFN/PEG-IFN versus observation) stratified for EORTC studies (18952, 18991) regarding relapse-free, distant metastasis-free and overall survivals.

End-point	Stage IIb/III-N1				Stage III-N2			
	Non-ulcerated melanoma		Ulcerated melanoma		Non-ulcerated melanoma		Ulcerated melanoma	
	HR (99% CI)	*p* Value	HR (99% CI)	*p* Value	HR (99% CI)	*p* Value	HR (99% CI)	*p* Value
Relapse-free survival								
Univariate	0.83 (0.59–1.18)	0.18	0.69 (0.50–0.96)	0.003	0.96 (0.74–1.25)	0.70	0.83 (0.59–1.16)	0.15
Multivariate	0.80 (0.56–1.13)	0.10	0.68 (0.49–0.94)	0.002	0.90 (0.69–1.17)	0.30	0.87 (0.62–1.22)	0.28
Distant metastasis-free survival								
Univariate	0.96 (0.65–1.42)	0.80	0.59 (0.42–0.83)	<0.0001	1.07 (0.81–1.41)	0.55	0.83 (0.59–1.17)	0.16
Multivariate	0.91 (0.64–1.35)	0.54	0.57 (0.40–0.81)	<0.0001	1.01 (0.76–1.33)	0.96	0.91 (0.64–1.29)	0.47
Overall survival								
Univariate	1.11 (0.72–1.73)	0.53	0.58 (0.40–0.86)	0.0003	1.10 (0.81–1.49)	0.42	0.89 (0.62–1.28)	0.41
Multivariate	1.03 (0.66–1.61)	0.86	0.56 (0.38–0.82)	0.0001	1.04 (0.77–1.41)	0.75	0.99 (0.69–1.42)	0.92

Multivariate analysis: treatment effect adjusted for gender (male versus female), number of lymph nodes involved in stage IIb/III-N1 patients (1 versus 0, 2–4 versus 0, 5+ versus 0) and stage III-N2 patients (2–4 versus 1, 5+ versus 1, presence of in-transit metastasis versus 1). IFN/PEG-IFN interferon α-2b/pegylated interferon α-2b. EORTC = European Organisation for Research and Treatment of Cancer. HR = hazard ratio. CI = confidence interval.

In addition, stage and ulceration were independent strong prognostic factors for RFS, DMFS and OS, followed by gender (male patients had a worse outcome than female patients).

In the Cox multivariate model (Table 1), the stage × treatment interaction appeared to be borderline significant or significant for RFS ($p = 0.07$), DMFS ($p = 0.02$) and OS ($p = 0.11$), indicating that treatment effect was lower in stage III-N2 patients than in stage IIb or III-N1 patients (Fig. 1). Additionally, in the Cox multivariate model (Table 1), the ulceration × treatment appeared to be borderline significant or significant for RFS ($p = 0.19$), DMFS ($p = 0.01$), and OS ($p = 0.01$), indicating a greater treatment effect in patients with ulcerated melanoma than with non-ulcerated melanoma (Fig. 2). Based on the above results, four subgroup analyses, according to these dual two-categorical variables, were performed.

3.3. *Subgroup analyses according to stage and ulceration status*

The four subgroups included stage IIb/III-N1/with either non-ulcerated melanoma ($n = 670$; 32.6%) or ulcerated melanoma ($n = 484$; 23.6%) and stage III-N2 with either non-ulcerated melanoma ($n = 666$; 32.4%) or ulcerated melanoma ($n = 235$; 11.4%).

Supplemental Table 1 shows the patient characteristics according to stage and ulceration status. Male and female patients were well balanced by treatment arm in all but one of four subgroups: in stage III-N2 ulcerated patients, the observation group comprised more males than the IFN/PEG-IFN group (67.6% versus 54.6%, respectively). The number of patients with five+ nodes was slightly higher in the IFN/PEG-IFN group compared with the observation group, respectively, in stage IIb/III-N1 non-ulcerated patients (3.2% versus 1.7%). and in stage III-N2 non-ulcerated patients (17.8% versus 15.4%). In stage IIb/III-N1 patients with ulcerated melanoma, an increased percentage of males in the IFN/PEG-IFN group compared with observation was compensated by an increased percentage of patients with involvement of two to four lymph nodes in the observation group.

Table 2 presents treatment effect on RFS, DMFS and OS in the four subgroups. No significant differences were observed between the IFN/PEG-IFN and observation arms in the non-ulcerated patients, either in stage IIb/III-N1 or stage III-N2 (Supplemental Fig. 3). Multivariate analyses confirmed the findings of univariate analyses even though HRs for the multivariate analysis were slightly lower, as they took into consideration the imbalance in patient characteristics that disfavoured the observation arm.

In stage III-N2 patients with ulcerated melanoma, the estimated HRs of treatment effect adjusted for gender and number of lymph nodes were not significantly different from 1. The lack of treatment effect on RFS is also indicated in Fig. 3A. In contrast, in stage IIb/III-N1 patients with ulcerated tumours, all estimated HRs were <0.7: RFS, HR 0.69 ($p = 0.003$; Fig. 3A); DMFS, HR 0.59 ($p < 0.0001$; Fig. 3B); and OS, HR 0.58 ($p = 0.0003$; Fig. 3C). The results of multivariate analyses confirmed these findings (Table 2).

In stage IIb/III-N1 patients, the ulceration status adjusted for gender, number of lymph nodes, and treatment was not only of prognostic importance but also of predictive value for treatment effect on RFS ($p = 0.25$), DMFS ($p = 0.008$), and OS ($p = 0.002$), indicating that treatment effect was greater in patients with ulcerated melanoma than in non-ulcerated melanoma. Conversely, in patients with ulcerated tumours,

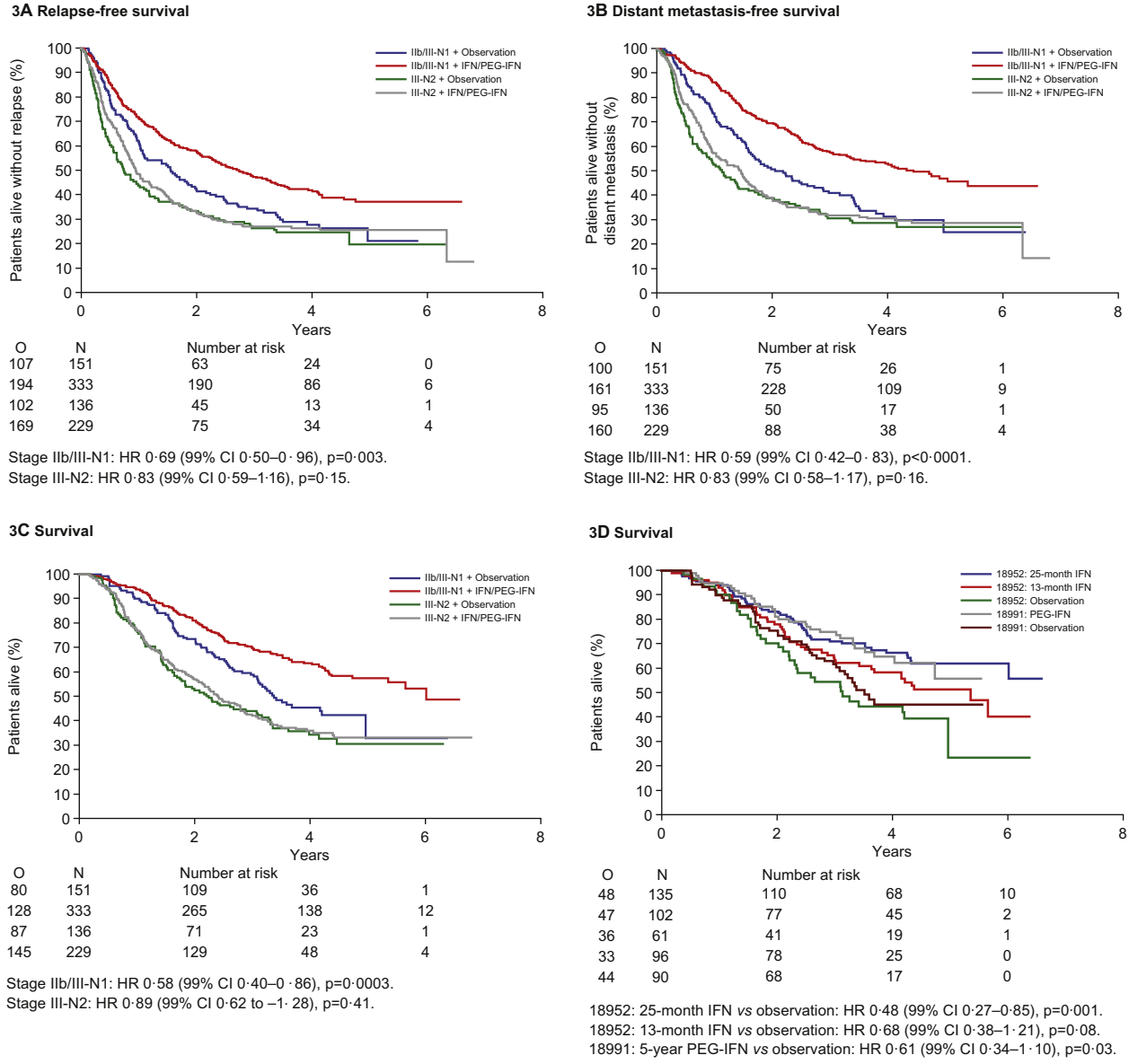

Fig. 3 – Kaplan–Meier curves obtained by meta-analysis of data from the EORTC 18952 and 18991 studies in patients with ulcerated melanoma, according to stage and treatment, regarding three end-points: (A) relapse-free survival, (B) distant metastasis-free survival, (C) overall survival and (D) overall survival by EORTC trial. EORTC = European Organisation for Research and Treatment of Cancer. IFN/PEG-IFN = interferon α-2b/pegylated interferon α-2b. O = observed events. N = total number of patients. HR = hazard ratio. CI = confidence interval.

stage (III-N2 versus IIb/III-N1) adjusted for gender, number of lymph nodes, and treatment was of prognostic importance and also of predictive value for treatment effect on RFS ($p = 0.13$), DMFS ($p = 0.01$) and OS ($p = 0.01$), indicating that the treatment effect was more pronounced in stage IIb/III-N1 than in stage III-N2.

3.4. *Consistency between EORTC 18991 and 18952 data*

Impact of treatment was consistent between the EORTC 18952 and 18991 trials. In each trial, no advantage of IFN/PEG-IFN over observation was demonstrated in patients without ulceration or in patients with stage III-N2 and ulcerated melanoma (Supplemental Fig. 4). In contrast, treatment effect was observed in stage IIb/III-N1 on RFS and DMFS (Supplemental Fig. 5) as well as OS (Fig. 3D) in each trial.

4. Discussion

This *post hoc* meta-analysis of the two largest adjuvant IFN/PEG-IFN trials in high-risk patients with melanoma demonstrated that stage and ulceration are not only strong prognostic factors but are also predictive for efficacy of adjuvant IFN/

PEG-IFN. Both trials were stratified for stage (microscopic non-palpable nodal involvement versus palpable nodal relapse) as well as for the presence of ulceration in the primary melanoma. The results are limited by the *post hoc* nature of the analysis; although stage and ulceration were stratification factors, they were not defined as primary or secondary end-points of either trial; therefore, the conclusions of this analysis are hypothesis-generating. Nonetheless, the findings are compelling due to the striking consistency between the two trials.

The results of the meta-analysis showed that patients with stages IIb/III-N1 melanoma benefited significantly from IFN/PEG-IFN treatment, whereas patients with stage III-N2 disease did not. Also, patients with an ulcerated primary tumour benefited significantly from adjuvant IFN/PEG-IFN therapy, whereas patients with a non-ulcerated primary tumour did not. Patients with both favourable stage (IIb and III-N1) and ulcerated primary tumour benefited greatly (HRs 0.56–0.69) with regard to RFS, DMFS and OS (Table 2). Patients with stage III-N2 disease did not derive significant benefit for any end-point, even when they had an ulcerated primary tumour, although, in these patients, a small beneficial trend was present.

These findings illustrate that the effects of adjuvant IFN/PEG-IFN therapy benefit a subpopulation that represents a minority in all the adjuvant trials conducted with IFN over the last 25 years. This explains why, in general, adjuvant IFN trials have only shown marginal effects. In contrast, in this analysis, when patients with ulcerated primary tumours and limited tumour burden were analysed, we observed reductions in risk of relapse or death of approximately 30%–45% for RFS, DMFS and OS. We found consistency not only among the end-points but also between the trials. This consistency and the size of the trials strengthen the reliability of these findings.

The meta-analysis of the EORTC 18952 and 18991 trials stratified for stage and ulceration confirmed the observation by Wheatley et al. regarding ulceration and IFN sensitivity in their meta-analysis of individual patient data from a variety of trials that did not include EORTC 18991.[10] The results of their study showed that in 1393 patients with ulcerated melanomas, the HR of adjuvant IFN therapy for OS was 0.77 (99% CI 0.63–0.93); however, there was no impact of adjuvant IFN therapy in the 2118 patients without ulceration (HR 0.98 [99% CI 0.87–1.17]).

Since our report on the treatment interaction between ulceration and PEG-IFN,[1] it has been investigated in both the Sunbelt and the Nordic trials.[13,14] In the Sunbelt trial, which enrolled sentinel node–staged patients with microscopic nodal involvement only, no impact of adjuvant IFN was observed in the non-ulcerated patient population and significant treatment benefit occurred in patients with ulcerated primary tumours.[13] In the Nordic trial, almost all patients had palpable nodal involvement and, consistent with the results of our analysis, no significant benefit was conferred by the presence of ulceration.[14]

Because IFN treatment is associated with significant side-effects, it is important to identify IFN-sensitive patients. We believe that optimisation of treatment schedules can only be done in an IFN-sensitive patient population, not in the overall high-risk patient population. In this context, it is interesting to observe that in the EORTC 18952 trial, the three survival curves in the best-responding patient population (IIb/III-N1 with ulceration) were distinctly different and improved with prolonged IFN exposure (Fig. 3D).

Research on tissue samples to identify gene profiles and cytokine profiles potentially predictive for IFN-sensitivity is ongoing.[15] Based on the promising initial findings by Gogas et al.[16] we evaluated the prognostic and potentially predictive value of the presence or emergence of autoimmune antibodies in the EORTC 18952, EORTC 18991, and the Nordic trials. However, our analyses indicated that the presence of autoimmune antibodies was not a strong prognostic factor and did not have predictive value.[17,18]

For patients with advanced stage III melanoma, a large (estimated enrolment, 950) randomised, double-blind, controlled trial comparing adjuvant therapy with ipilimumab versus placebo for 3 years recently completed accrual (EORTC 18071; ClinicalTrials.gov, number NCT00636168).[19] Preliminary data suggest ipilimumab activity in the adjuvant setting in advanced stage III and resected stage IV disease.[20]

For adjuvant interferon therapy, it is clear that the hypotheses generated by the meta-analysis of the EORTC 18952 and 18991 trials need prospective evaluation. The importance of ulceration as a potential and plausible distinct biologic entity led to the decision to activate the EORTC 18081 adjuvant trial with PEG-IFN in sentinel node negative stage II patients with ulcerated primary tumours. It could be considered the first adjuvant trial targeted for IFN-sensitive patients.

Conflict of interest statement

Alexander M.M. Eggermont: Consultant in advisory boards for melanoma for Merck, BMS, Roche, GSK. Poulam Patel: *Ad hoc* advisory boards for Schering-Plough Research Institute – honoraria paid. Reinhard Dummer: Advisory board relationship with Roche and MSD. Antoine Yver: Was employed full time by Schering-Plough. Currently employed by AstraZeneca LP, Wilmington DE, USA as VP, Global Head Clinical Development Oncology, with no conflict on the subject matter of this manuscript. Stefan Suciu, Alessandro Testori, Wim H. Kruit, Jeremy Marsden, Cornelius J. Punt, Mario Santinami, François Salès, Dirk Schadendorf, Caroline Robert, Ulrich Keilholz, Alan Spatz: No conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2011.09.028.

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