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Adjuvant therapy with pegylated interferon alfa-2b (36 months) versus low-dose interferon alfa-2b (18 months) in melanoma patients without macrometastatic nodes: An open-label, randomised, phase 3 European Association for Dermato-Oncology (EADO) study

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Abstract ***Aim:*** Both low-dose interferon (IFN) alfa-2b and pegylated interferon (Peg-IFN) alfa-2b have been shown to be superior to observation in the adjuvant treatment of melanoma without macrometastatic nodes, but have never been directly compared. Peg-IFN facilitates prolongation of treatment, which could provide additional benefit. This multicentre, open-label, randomised, phase 3 trial compared standard low-dose interferon IFN and prolonged treatment with Peg-IFN.

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Patients and methods: Patients with resected melanoma ⩾1.5 mm thick and without clinically detectable node metastases were randomised 1:1 to treatment with IFN 3 MU subcutaneously (SC) three times weekly for 18 months or Peg-IFN 100 μg SC once weekly for 36 months. Sentinel lymph node dissection (SLND) was optional. The primary endpoint was disease-free survival (DFS). Secondary endpoints included distant metastasis-free survival (DMFS), overall survival (OS) and adverse events (AEs) grade 3–4.

Results: Of 898 patients enrolled, 896 (443 Peg-IFN, 453 IFN) were eligible for evaluation (median follow-up 4.7 years). SLND was performed in 68.2% of patients. There were no statistical differences between the two arms for the primary outcome of DFS (hazard ratio [HR] 0.91, 95% confidence interval [CI] 0.73–1.15) or the secondary outcomes of DMFS (HR 1.02, 95% CI 0.80–1.32) and OS (HR 1.09, 95% CI 0.82–1.45). Peg-IFN was associated with higher rates of grade 3–4 AEs (47.3% versus 25.2%; $p < 0.0001$) and discontinuations (54.3% versus 30.4%) compared with IFN.

Conclusion: This trial did not show superiority for adjuvant Peg-IFN over conventional low-dose IFN in melanoma patients without clinically detectable nodes. ClinicalTrials.gov identifier: NCT00221702.

1. Introduction

Clinical trials and meta-analyses have shown a consistent, significant improvement in relapse-free survival (RFS) with high- and low-dose interferon alfa (IFN) therapy versus observation as adjuvant treatment of melanoma.[1–9] A recent meta-analysis of 14 randomised clinical trials ($n = 8122$) of high- and low-dose IFN confirmed statistically significant improvements in RFS and overall survival (OS), with relative risk reductions of 28% and 11%, respectively, compared with observation.[9] In most European countries, a standard low-dose adjuvant IFN regimen of 3 MU three times weekly for 18 months is used for melanoma with tumour thickness ⩾1.5 mm and no clinically detectable node metastases, since this dose has shown disease-free survival (DFS) benefits versus observation.[2,3,10] High-dose IFN for 12 months is approved in the United States (US) and proposed in European countries for adjuvant therapy of resected melanoma at high risk of recurrence.

It has been hypothesised that prolonged treatment is critical for increasing the benefit of adjuvant IFN for resected melanoma, and this hypothesis has been tested in clinical trials.[5,11] Pegylation prolongs the half-life of IFN without affecting its biological activity, allowing for more convenient once-weekly administration and potentially longer treatment.[12] In the european organisation for research and treatment of cancer (EORTC) 18991 study, pegylated IFN alfa-2b (Peg-IFN) was tested versus observation in patients with resected stage III melanoma at a dose of 6 μg/kg/week for 8 weeks followed by 3 μg/kg/week for up to 5 years.[13] The improved 4-year RFS with Peg-IFN (18% risk reduction versus observation), which was most pronounced in the microscopic nodal disease subgroup (27% risk reduction versus observation), demonstrated that adjuvant Peg-IFN has a beneficial effect in melanoma.

Peg-IFN and IFN have never been compared head to head in a melanoma clinical trial. In the present study, we compare the efficacy and safety of prolonged adjuvant low-dose Peg-IFN therapy (36 months) and standard European low-dose IFN therapy (18 months) in an intermediate-risk melanoma population (Breslow tumour thickness ⩾1.5 mm without clinically detectable nodes).

2. Methods

2.1. Study design

For this multicentre, open-label, randomised phase 3 study, patients were recruited at 70 centres in France, Germany and Austria. Patients were randomised 1:1 to open-label, low-dose treatment with Peg-IFN 100 μg once-weekly subcutaneously (SC) for 36 months or IFN 3 MU SC three times weekly for 18 months. The primary endpoint was DFS, defined as time from randomisation to any recurrence or death. Secondary endpoints were distant metastasis-free survival (DMFS), defined as time from randomisation to any distant metastasis or death; OS, defined as time from randomisation to death; first occurrence of adverse events (AEs) grade 3–4; and quality of life (QoL).

The protocol was approved by the ethics committee of Bordeaux for all French centres, by all ethics committees of participating centres in Germany and Austria, and by institutional review boards where present. The study was conducted in accordance with all applicable regulations and the ethical principles laid out in the Declaration of Helsinki. All patients provided written informed consent before randomisation.

2.2. Patients

Eligible patients were 18–75 years old, had histologically proven primary cutaneous melanoma with a Breslow tumour thickness of ⩾1.5 mm that had been completely resected with surgical margins of at least