

# **Adjuvant Therapy with Pegylated Interferon $\alpha$ -2b Versus Observation in Resected Stage III Melanoma: A Phase Three Randomized Controlled Trial of Health-Related Quality of Life and Symptoms by the EORTC Melanoma Group**

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- The **incidence** of melanoma is rising more rapidly in the western world than the incidence of any other cancer site.
- Melanoma patients with **stage IIB and III** are at high risk of recurrence after definitive surgery.
- The **therapy** most investigated for these patients is **Interferon (IFN) $\alpha$ -2b**, which was associated in previous trials with:
  - ◆ Improvement of Recurrence-Free Survival (RFS)
  - ◆ Significant toxic side-effects

- Up to date there is no proof of the clinical benefit of this therapy on **overall survival (OS)**.
- The **proximal benefits** of pegylated interferon  $\alpha$ -2b (PEG-IFN $\alpha$ -2b) are considered:
  - **recurrence-free survival (RFS)**
  - **distant-metastatic free survival (DMFS)**



**HRQOL**, influenced by significant toxicity, must be carefully weighed against RFS and DMFS improvement.

## Aim of the study

The primary aim of the **EORTC 18991 study** was investigating RFS and combining **HRQOL** and **symptoms** as one of the **secondary outcomes** in stage III melanoma patients, undergoing  $\alpha$ -2b (PEG-IFN $\alpha$ -2b) versus observation.

- **International multi-centered study** with
  - Primary outcome = RFS
  - Secondary outcomes = DMFS, OS, HRQOL
- Patients with stage III melanoma (N = 1256) were **randomized**, after full lymphadenectomy, to receive:
  - Observation (N = 629)
  - PEG-IFN $\alpha$ -2b (N = 627) for a duration of 5 years
- **HRQOL** was assessed by using the **EORTC QLQ-C30**
  - Primary scale: global Health / HRQOL scale
  - Time points: baseline, months 3, 12, 24, 36, 48, 60
  - **Clinically meaningful** change:  $\geq 10$  points
  - **Statistical** significance:  $p \leq 0.01$

- It was hypothesized that there would be a difference in global HRQOL scale between both arms, showing worse HRQOL in the PEG-IFN $\alpha$ -2b arm.
- The remaining HRQOL variables were to be examined on an exploratory basis.

- Oct 2000 - Aug 2003: **1256 patients** were randomized from **99 institutions** in **17 countries**.
- **Baseline characteristics** between patients with (1183) and without (73) valid HRQOL forms were not significantly different.
  - ◆ Mean age = 50
  - ◆ Male (58%); Female (42%)
  - ◆ N1 stage (41%); N2 stage (59%)
- **Clinical results** are reported in Eggermont et al. '08:
  - Overall adjuvant **PEG-IFN $\alpha$ -2b** had a significant sustained **impact on RFS**.

	<b>Observation</b>	<b>Peg-intron</b>
<b>Baseline</b>	<b>83 %</b>	<b>83 %</b>
<b>3 months</b>	<b>70 %</b>	<b>67 %</b>
<b>12 months</b>	<b>58 %</b>	<b>51 %</b>
<b>24 months</b>	<b>50 %</b>	<b>50 %</b>
<b>36 months</b>	<b>45 %</b>	<b>50 %</b>
<b>48 months</b>	<b>30 %</b>	<b>23 %</b>
<b>60 months</b>	<b>39 %</b>	<b>30 %</b>

- Compliance was not significantly different between the treatment and observation arm at any time point (  $p = 0.10$ ).
- Given limited data at years four and five, these data were excluded from analysis.

- Baseline scores in the study sample were comparable with scores from a **normative population**, with the exception of role functioning (lower in study sample).
- Baseline scores between the two treatment arms were not significantly different ( $p > 0.01$ ; less than 10-point difference).



**Comparability of treatment arms** in baseline HRQOL

## Results: primary HRQOL outcome

- Patients receiving adjuvant PEG-IFN $\alpha$ -2b had a **statistically significant lowering of global HRQOL** levels, compared to patients under observation ( $p \leq 0.001$ ) at each post-baseline time point.
- This difference was **clinically significant** at 3 months and 2 years after baseline.

- The **PEG-IFN $\alpha$ -2b arm** was (statistically and clinically) significantly more **impaired in functioning**:
  - ◆ **Social functioning** (at all time points)
  - ◆ **Role functioning** (at 3 months)
  - ◆ No clinically meaningful difference on physical, emotional and cognitive functioning between treatment arms.
- The **PEG-IFN $\alpha$ -2b arm** was (statistically and clinically) significantly more **impaired in symptoms**:
  - ◆ **Appetite loss** (at all time points)
  - ◆ **Fatigue** (at most time points)
  - ◆ **Dyspnea** (at 3 months and 3 years)
  - ◆ No clinically meaningful difference on diarrhea, nausea/vomiting, insomnia and pain between treatment arms.

- **Exploratory analysis of 5 interferon-specific symptoms** showed statistically significant increases in PEG-IFN:
  - **Fever, chills, stiff or sore muscles, and headaches** ( $p < 0.01$ )
  - No statistically difference for sweating
- **Sensitivity analysis**
  - **Grade 4 toxicity and progression status** was related to drop out in both treatment groups.
  - Higher levels of **HRQOL missingness** were related to factors such as later time points – higher disease stage – PEG-IFN $\alpha$ -2b.
  - A **prediction model** and **imputation methods** still showed HRQOL results to be in favor of the observation arm – at least during 1st year.

Adjuvant **PEG-IFN $\alpha$ -2b** had a significant sustained impact on recurrence-free survival, but **deteriorated patients' global HRQOL, functioning and symptoms** significantly compared to the observation arm.

- ❖ Patients treated with PEG-IFN $\alpha$ -2b were impaired in their **social functioning** for an extensive period during treatment.
- ❖ Patients' **role functioning** was impaired as well, though they were able to perform their roles to the same degree as those in the observation arm did, after one year.
- ❖ PEG-IFN $\alpha$ -2b was related to higher suffering from **fatigue** and **appetite loss** for up to three years after baseline.

## **Limitations** concerned:

- **Drop out over time, hindering a long-term analysis on HRQOL outcomes.**
- **Absence of a placebo arm which would allow investigating the impact of patients' treatment knowledge on their HRQOL reporting.**

**PEG-IFN $\alpha$ -2b may be a treatment option for stage III melanoma patients, but patients should be educated on the HRQOL impairment and, when choosing this treatment, should be supported by offering them interventions to improve HRQOL, such as symptom management.**