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Current Perspective

Adjuvant ipilimumab in stage III melanoma: New landscape, new questions



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Abstract The recently reported significant prolongation of overall survival with ipilimumab as adjuvant in high-risk stage III melanoma patients represents an important event in the adjuvant treatment landscape. The European Organisation for Research and Treatment of Cancer 18071 trial demonstrated a 28% reduction in risk of death in patients treated with ipilimumab at 10 mg/kg (hazard ratio for death, 0.72; 95.1% CI, 0.58–0.88; $P = 0.001$) compared with placebo. All end-points—recurrence-free survival (RFS), distant-metastasis-free survival (DMFS) and overall survival (OS)—showed similar benefits. Survival rates at 5 years in ipilimumab-treated patients were OS 11%, DMFS 9% and RFS 11% higher than in placebo-treated patients. Global Health quality-of-life scores were not significantly different between treatment arms, in spite of significant adverse event rates that resulted in only 42% of patients receiving more than four doses of ipilimumab and only 28.9% of patients going beyond 1 year of treatment. Grades 3–4 immune-related adverse events occurred in 41.6% of ipilimumab-treated patients and in 2.7% of placebo-treated patients. One can speculate on dose and duration of treatment, as well as on the requirement for complete lymph-node dissection in sentinel-node-positive patients. The remaining role of interferons will be discussed regarding differences in sensitivity profiles—such as in ulcerated melanoma versus non-ulcerated melanoma—and access to new drugs. Ongoing trials with targeted agents and with anti programmed cell death protein 1 (anti-PD-1) agents may bring significant additional results in the next few years that will redefine how we treat stage III patients. Overall, pricing of new treatments will determine access and whether patients will actually benefit from new treatment options.

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1. Background

The incidence of cutaneous melanoma continues to rise steeply, and so does the number of patients with stage III melanoma (i.e. patients with regional nodal involvement) which is associated with high death rates in the absence of adjuvant therapies with a clear impact on survival [1]. The stage III patient population is quite heterogeneous with disease-specific survival rates of 78%, 59% and 40% for stage IIIA, IIIB and IIIC melanoma, respectively [2,3]. As a result risk-benefit ratios considered acceptable per substage may differ for adjuvant therapies. Even within sentinel-node-positive (SN-positive) patients, prognosis varies significantly depending on tumour load, and for the stage IIIA population with metastasis/metastases <0.1 mm in diameter prognosis may be indistinguishable from that in SN-negative patients [4–7]. In the European Organisation for Research and Treatment of Cancer (EORTC) 18071 trial comparing adjuvant therapy with ipilimumab to placebo, these observations led to the decision to require that in stage IIIA patients a metastasis should be > 1 mm in diameter.

Approved drugs for adjuvant therapy for stage III melanoma are interferon- α 2b (United States of America [USA] and European Union [EU]), based on trial Eastern Cooperative Oncology Group (ECOG) 1684 [8] and pegylated interferon- α 2b (USA), based on trial EORTC 18991 [9]. In meta-analyses of adjuvant interferon trials, no dose effect or duration of treatment effect could be demonstrated, and only a marginal impact on survival of about 3% was observed [10–12]. Adjuvant therapy with interferon is not widely accepted or used as standard of care [1,13].

The checkpoint inhibitor ipilimumab was approved for advanced melanoma in 2011, based on improved survival observed in phase III trials [14,15]. The EORTC 18071 trial was designed prior to the approval of ipilimumab at a dose of 3 mg/kg. The dose chosen for the adjuvant trial was 10 mg/kg, which was based on a randomised phase II trial comparing 0.3-, 3- and 10-mg/kg doses of ipilimumab [16]. The dose of 10 mg/kg was recently reported to provide a survival benefit in advanced melanoma patients compared to a dose of 3 mg/kg in a phase III trial [17]. Now we have mature data demonstrating prolonged survival with adjuvant ipilimumab in stage III melanoma. The data need a closer look, and raise a number of questions.

2. Prolonged survival with adjuvant ipilimumab

In the EORTC 18071 trial 951 stage III melanoma patients, after full regional lymph-node dissection, were randomised to receive either an intravenous infusion of ipilimumab 10 mg/kg or placebo every 3 weeks for 4 doses (induction), then every 3 months for up to 3 years

(maintenance), or until disease recurrence or unacceptable toxicity occur. The primary end-point was recurrence-free survival (RFS). A significant improvement of RFS by adjuvant ipilimumab (hazard ratio 0.75, $P = 0.0013$) had already been reported in 2015, leading to the US Food and Drug Administration approval [18]. Now, in 2016, at a median follow up of 5.3 years, ipilimumab (compared with placebo) significantly improved overall survival (OS; hazard ratio for death, 0.72; 95.1% CI, 0.58–0.88; $P = 0.001$) and distant-metastasis-free survival (DMFS; hazard ratio for death or distant metastasis, 0.76; 95.8% CI, 0.64–0.92; $P = 0.002$). Five-year OS rates were 65.4% in the ipilimumab arm and 54.4% in the placebo arm. The 5-year DMFS rates were 48.3% in the ipilimumab arm and 38.9% in the placebo arm [19]. The RFS benefit observed previously was maintained (hazard ratio for death or recurrence, 0.76; 95% CI, 0.64–0.89; $P < 0.001$). Treatment benefits were by and large consistent across subgroups, with stage III apparently deriving more benefit than stage IIIB and more than stage IIIA, which was the only subgroup that did not seem to benefit (HR 0.98). In general, patients with only microscopic nodal involvement seemed to derive a greater benefit than patients with palpable nodes, as did patients with an ulcerated primary compared with patients with a non-ulcerated primary.

Global Health quality-of-life scores were not significantly different between treatment arms [20], despite significant adverse event rates that resulted in only 42% of patients receiving more than 4 doses of ipilimumab and only 28.9% of patients going beyond 1 year of treatment. Grades 3–4 immune-related adverse events (irAEs) occurred in 41.6% of ipilimumab-treated and 2.7% of placebo-treated patients. The most important grades 3–4 irAEs were: diarrhoea/colitis in 17.2%, hepatitis in 15.2% and endocrinopathies in 7.8% with hypophysitis in 4.4%, and neurological events in 1.1%. Five patients died from drug-related causes: three with colitis, one with myocarditis, and one with a Guillain–Barre syndrome leading eventually to multiple organ failure. The great majority of grade 3–4 irAEs occurred during the induction phase. Median time to resolution after stopping ipilimumab and corticosteroid medication was 6 weeks, with the exception of endocrinopathies (31 weeks). In conclusion, one can state that adjuvant ipilimumab therapy provides consistent improvements in terms of RFS, DMFS and OS, but that it comes at a price in terms of irAEs that need expertise and experience for early recognition and handling with established treatment algorithms. This treatment should be handled by centres with sufficient experience.

3. New questions

- 1) Is the dose of 10 mg/kg necessary in the adjuvant setting? Obviously EORTC 18071 cannot answer that question, but

valuable answers may be provided in the near future by the ECOG 1609 trial, which is comparing 1 year of treatment with ipilimumab at 3 mg/kg versus ipilimumab at 10 mg/kg versus high-dose interferon- α 2b.

- 2) One may also question the need for maintenance treatment up to 3 years, as scheduled in the EORTC 18071. Given the facts that only 42% of patients received one or more doses beyond induction, and that only 28.9% went beyond 1 year of treatment, this question seems quite valid. The EORTC 18071 trial results cannot prove or refute the value of maintenance therapy.
- 3) Should adjuvant ipilimumab therapy be proposed to all stage III patients? The lack of impact in patients with stage IIIA disease in the EORTC 18071 trial merits further discussion. This patient population by definition does not include any patients with an ulcerated primary; this may have contributed to the lack of impact in light of the fact that overall, in the trial, patients with an ulcerated primary seemed to derive greater benefit. Moreover, the event rate in stage IIIA is low, and this result may lack discriminatory power. The risk-benefit ratio seems better for stage IIIB–C and thus a treatment with significant toxicities may help in decision-making.
- 4) Should all SN-positive patients have a complete lymph-node dissection (CLND) to qualify for adjuvant therapy? In the EORTC 18071 trial all patients underwent full lymph-node dissection. For patients with a positive SN we observe a current trend that a rapidly increasing percentage of patients do not want CLND and prefer follow up by ultrasound exams. The Deutsche Cooperative Oncology Group (DeCOG) trial results reported by Leiter *et al.* [21] demonstrated that patients randomised between CLND versus ultrasound follow up fared equally well and do not support CLND as a mandatory procedure for all SN-positive patients. For adjuvant trials in the future we will need to adapt to these findings and find a solution by stratification of patients by surgical treatment.

4. Is there still a role for interferon- α ?

Interferon- α will still play a role for various reasons. First of all, at this point in time ipilimumab is approved for adjuvant use only in the USA. Even if ipilimumab, on the basis of improved OS, were to be approved in the EU in the future, it will take time for access to be established pending pricing issues. Even within the EU this access may be highly variable, and undoubtedly even more so outside the EU.

Second, we should not forget that interferon (IFN) sensitivity is greatest in microscopic stage III, and is mostly driven by the presence of ulceration of the primary. In this population the impact on RFS, DMFS and OS has been demonstrated in the EORTC 18952 (intermediate doses of IFN versus observation) and EORTC 18991 (high-dose pegylated IFN versus observation) [9,22–25]. Also in an individual patient meta-analysis of 15 adjuvant versus observation phase III trials, ulceration of the primary was the most important predictive factor for IFN sensitivity [12]. Therefore,

during the prolonged time that it may take in different parts of the world for ipilimumab use to settle in, IFN therapy in patients with an ulcerated primary and only microscopic stage III remains a clear option.

5. What is next?

A phase III trial evaluating the impact of dabrafenib + trametinib in BRAF mutant stage III melanoma patients has been fully accrued and may provide new options for these patients. Regarding checkpoint inhibitors, there are two trials evaluating the potential value of anti-PD-1 agents. Both trials have reached full accrual. One trial is comparing nivolumab versus ipilimumab and the other trial is comparing pembrolizumab versus placebo. By the end of 2018 we may see new data that may further define the adjuvant therapy landscape of stage III melanoma patients.

Conflict of interest

Honoraria for scientific advisory board participation: Actelion, Agenus, BMS, GSK, Incyte, MSD, Pfizer, Sanofi.

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