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Original Research

Phase II trial of ipilimumab in melanoma patients with preexisting humoural immune response to NY-ESO-1☆

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Abstract ***Background:*** Immune checkpoint therapy has dramatically changed treatment options in patients with metastatic melanoma. However, a relevant part of patients still does not respond to treatment. Data regarding the prognostic or predictive significance of preexisting immune responses against tumour antigens are conflicting. Retrospective data suggested a higher clinical benefit of ipilimumab in melanoma patients with preexisting NY-ESO-1–specific immunity.

Patients and methods: Twenty-five patients with previously untreated or treated metastatic melanoma and preexisting humoural immune response against NY-ESO-1 received ipilimumab at a dose of 10 mg/kg in week 1, 4, 7, 10 followed by 3-month maintenance treatment for a maximum of 48 weeks. Primary endpoint was the disease control rate (irCR, irPR or irSD) according to immune-related response criteria (irRC). Secondary endpoints included the disease control rate according to RECIST criteria, progression-free survival and overall survival (OS). Humoural and cellular immune responses against NY-ESO-1 were analysed from blood samples.

☆ Previous presentations: An interim analysis of this study has been published at the ASCO 2015 Annual Meeting. (DOI: 10.1200/jco.2015.33.15_suppl.e20061. J Clin Oncol 33, no. 15s).

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Results: Disease control rate according to irRC was 52%, irPR was observed in 36% of patients. Progression-free survival according to irRC was 7.8 months, according to RECIST criteria it was 2.9 months. Median OS was 22.7 months; the corresponding 1-year survival rate was 66.8%. Treatment-related grade 3 AEs occurred in 36% with no grade 4–5 AEs. No clear association was found between the presence of NY-ESO-1–specific cellular or humoural immune responses and clinical activity.

Conclusion: Ipilimumab demonstrated clinically relevant activity within this biomarker-defined population. NY-ESO-1 positivity, as a surrogate for a preexisting immune response against tumour antigens, might help identifying patients with a superior outcome from immune checkpoint blockade.

Clinical trial information: NCT01216696

1. Introduction

Historically, survival of patients with metastatic melanoma has been poor with a median survival of about 8–9 months and a 5-year overall survival (OS) rate of about 5% [1]. During the last few years, immunotherapy, specifically immune checkpoint blockade, has dramatically changed treatment options in metastatic melanoma.

Leading to an increased T-cell response to tumour antigens and enhanced immune-mediated antitumour activity, CTLA-4 blockade has shown to improve immunological response to melanoma [2].

The anti-CTLA-4 monoclonal antibody (mAb) ipilimumab has shown to improve survival in patients with metastatic melanoma as monotherapy or in combination with a glycopeptide vaccination [3]. Similarly an increased OS was observed with the combination of ipilimumab (at a dosage of 10 mg/kg) and dacarbazine in a phase III trial in previously untreated patients [4].

More recently, mAbs targeting the PD-1 or PD-L1 axis have shown increased clinical efficacy in patients with metastatic melanoma with responses seen in about 30–40% of patients in monotherapy and a 1-year survival rate of about 65–75% [5,6]. With ipilimumab and nivolumab given as a combination therapy, responses are seen in about 55–60% of patients [7]; in terms of OS, the combination exhibits numerical superiority in comparison to anti PD-1 monotherapy, however toxicity is increased.

The cancer/testis antigen NY-ESO-1 is expressed in about 20% of melanoma patients [8,9] with a higher frequency in advanced disease stages. NY-ESO-1 elicits spontaneous humoural and cellular responses in many patients with cancer [10].

Data regarding the prognostic effect of cancer/testis antigen expression in melanoma patients are conflicting: an inferior outcome in early-stage patients with cancer/testis antigen expressing tumours or with antibody responses against cancer/testis antigens has been reported [11,12], whereas the presence of functional NY-ESO-1–specific T-cells correlated with a superior survival in patients with metastatic melanoma [13].

In patients receiving ipilimumab, the predictive role of NY-ESO-1 preexisting immune responses is unclear: Yuan et al. [14,15] observed a higher response rate and a superior survival in patients being seropositive for NY-ESO-1, whereas Goff et al.[16] could not confirm the higher efficacy of ipilimumab in NY-ESO-1 seropositive patients.

Based on these data, we initiated a phase II trial using ipilimumab in patients with metastatic melanoma that have preexisting humoural immunity to NY-ESO-1.

2. Patients and methods

Patient eligibility: the study population consisted of patients with previously treated or untreated metastatic (stage IV) or unresectable stage III malignant melanoma with preexisting humoural immune response to NY-ESO-1 (see 'ELISA' section below). Further inclusion criteria included an age $\geq$18 years, an ECOG-score of 0 or 1, measurable disease according to RECIST criteria (Version 1.1) [17], a white blood count $\geq$ 2000/μL, an absolute neutrophil count of $\geq$1000/μL, thrombocytes $\geq 100 \times 10^3$/μL, haemoglobin $\geq$9 g/dL, creatinine$\leq$ 2 × ULN, AST/ALT $\leq$ 2.5 × ULN for subjects without liver metastasis, $\leq$ 5 × ULN for subjects with liver metastasis and a bilirubin $\leq$2.0 × ULN ($\leq$3.0 × ULN for subjects with Gilbert's Syndrome).

Exclusion criteria excluded patients with ocular or mucosal melanoma, patients with untreated or progressive brain metastasis as well as patients with a secondary malignancy within the previous 5 years except for locally curable cancers that have been adequately treated. Furthermore, patients with autoimmune diseases, patients on chronic steroid or immunosuppressive medication or patients having previously participated in NY-ESO-1–derived vaccination studies were excluded.

Treatment and tumour assessment: ipilimumab was administered at a dose of 10 mg/kg intravenously over 90 min in week 1, 4, 7, 10 (induction period). The