Extended Abstract

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Final Efficacy Results of a Randomized Phase II Study of Recombinant Interleukin-21 Compared to Decarbonize in Patients with Recurrent or Metastatic Melanoma

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Abstract:

Interleukin-21(IL-21) is a T-cell derived cytokine with antitumour activity dependent on NK cells or CD8+ T cells. A previous phase II study demonstrated an overall response rate (ORR) of 22.5% in previously untreated patients with metastatic melanoma. We conducted a multi-centre randomized phase II study in metastatic melanoma patients to evaluate the efficacy, toxicity, immunogenicity and biomarkers associated with response to IL-21 versus dacarbazine (DTIC).

Keywords: Randomized; Phase II; Melanoma; Immunotherapy; Interleukin-21; Dacarbazine; Efficacy; Toxicity

INTRODUCTION:

Many immunotherapeutic strategies have been developed in recent decades for the treatment of melanoma. Interleukin-21 (IL-21) is a T-cell cytokine that has been described to play a role in the proliferation, survival and function of T cells. It is secreted by CD4 + progression-free survival (PFS)) and the profile of biomarkers in patients with metastatic melanoma. Forty patients without prior systemic treatment, good performance status, without brain metastases and low tumor load (defined as the largest measurable lesion must be 50 mm in diameter maximum), were treated with IL-21 using 3 different dosage regimens . Of the 39 patients evaluable for the response: 9 had a partial response (PR) (ORR = 22.5%; median duration of response of 5.3 months) 16 had a stable disease (SE) (median PFS 5.3 months) and 14 had progressive T helper cells and promotes the function of CD8 + effector T cells. Several studies have shown that its activity involves NK cells and CD8 + T cells by the induction of central and effector memory cells. These observations led to an evaluation of the activity of IL-21 in patients with metastatic melanoma. To date, two phase II single arm studies have evaluated the efficacy of IL-21 in metastatic melanoma. Davis and colleagues showed a confirmed complete response and a partial response in 24 patients (ORR = 8.3% 95% confidence intervals, 2.7% to 27%). The Canadian Cancer Trials Group (CCTG formerly NCIC CTG) conducted an open-arm phase II study of IL-21 by assessing the objective response rate (ORR defined by the criteria for assessing tumor response solids (RECIST) 1.1), toxicity, disease (PD) with a median PFS of 4.3 months. These promising results from the CCTG trial led to the development of this randomized phase II study comparing IL-21 with dacarbazine (DTIC).

METHOD:

Eligible patients had histologically confirmed metastatic skin melanoma. The other inclusion criteria were as follows: no prior treatment except for BRAF inhibitors, a disease measurable by RECIST 1.1, patients must have had a maximum tumor lesion size of 50 mm or if the tumor lesion was> 50 mm, lactate dehydrogenase (LDH) must be 2.5 x upper limit of normal (ULN), life expectancy of 3 months, age 18 years, performance status (PS) of the Eastern Cooperative Oncology Group (ECOG) 0 or 1, adequate function of the bone marrow (absolute granulocytes 1.5, 109 / L, platelets 100109 / L), serum creatinine 1.5 x LSN, bilirubin LSN and AST and ALT 2.5 x LSN. The main exclusion criteria included patients with known HIV infection, hepatitis B or C, uncontrolled intestinal disease and known brain metastases. Written consent was obtained from each patient in accordance with the requirements of the local institutional and / or university human experimentation committee of the participating centers. The primary endpoint of this study was PFS, defined as the time from randomization to the time of documented progression or death from any cause (RECIST 1.1). For subjects who were alive with no progression event at the time of cutting the data for the final analysis, PFS was censored on the date of the last follow-up. The PFS of the subjects in the two treatment arms was described by the Kaplan-Meier method. A unilateral stratified log-rank test adjusting the stratification factors was the primary method for comparing PFS between the IL-21 and the DTIC arms. As an exploratory analysis, a Cox proportional hazards model was used to identify and adjust the factors significantly related to PFS.

The study sample size was calculated to compare PFS between subjects randomized and treated in arm 1 compared to arm 2. The historical PFS expected with dacarbazine in the general population of metastatic melanomas is 1 ,7 months.

RESULT:

Soluble IL2 receptor alpha (sCD25) has been shown to increasewith treatment of IL-21. Patients receiving IL-21 had low sCD25 values at day 1 of each cycle and sCD25 increased at day 5 in cycles 1, 2, 3, 4,5, 7 and 8 (Figure 4). There were no data for cycle 6, 9, and 10 (Figure 4). Exploratory analysis of PFS with sCD25 as a continuous covariate showed that baseline sCD25 was not associated with PFS outcome (p=0.44). There was a trending association between maximum change sCD25 and PFS outcome.

CONCLUSION:

In conclusion, this trial has shown that IL-21 is comparable to DTIC in this patient population with possibly more toxicity. Treatment of metastatic melanoma has improved over the last several years with the advent of better therapies. Given the low response rates and higher toxicity that were seen in this trial, as well as evidence for synergy of IL- 21 with checkpoint inhibitors in murine models, IL-21 may be better studied in combination with other therapies, specifically checkpoint inhibitors.

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