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Clinical Trial

REVOLUMAB: A phase II trial of nivolumab in recurrent IDH mutant high-grade gliomas

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Highlights

- REVOLUMAB is the first phase II trial of checkpoint inhibitors in r/r IDHmut gliomas.
- The trial did not meet its primary endpoint on the 24-week progression-free survival.
- Nivolumab was well tolerated in patients with r/r IDHmut gliomas.
- Long-lasting partial responses were observed in a subset of patients.

Abstract

Background

Novel effective treatments are needed for recurrent IDH mutant high-grade gliomas (IDHm HGGs). The aim of the multicentric, single-arm, phase II REVOLUMAB trial (NCT03925246) was to assess the efficacy and safety of the anti-PD1 Nivolumab in patients with recurrent IDHm HGGs.

Patients and methods

Adult patients with IDHm WHO grade 3–4 gliomas recurring after radiotherapy and ≥1 line of alkylating chemotherapy were treated with intravenous Nivolumab until end of treatment (12 months), progression, unacceptable toxicity, or death. The primary endpoint was the 24-week progression-free survival rate (24w-

PFS) according to RANO criteria.

Results

From July 2019 to June 2020, 39 patients with recurrent IDHm HGGs (twenty-one grade 3, thirteen grade 4, five grade 2 with radiological evidence of anaplastic transformation; 39% 1p/19q codeleted) were enrolled. Median time since diagnosis was 5.7 years, and the median number of previous systemic treatments was two. The 24w-PFS was 28.2% (11/39, CI95% 15–44.9%). Median PFS and OS were 1.84 (CI95% 1.81–5.89) and 14.7 months (CI95% 9.18-NR), respectively. Four patients (10.3%) achieved partial response according to RANO criteria. There were no significant differences in clinical or histomolecular features between responders and non-responders. The safety profile of Nivolumab was consistent with prior studies.

Conclusions

We report the results of the first trial of immune checkpoint inhibitors in IDHm gliomas. Nivolumab failed to achieve its primary endpoint. However, treatment was well tolerated, and long-lasting responses were observed in a subset of patients, supporting further evaluation in combination with other agents (e.g. IDH inhibitors).

Introduction

Isocitrate dehydrogenase 1/2 mutant high-grade (WHO grade 3–4) gliomas, thereafter IDHm HGGs, account for 10–15% of glial tumors [1], [2]. They represent a distinct subgroup of HGGs with a better prognosis compared to their IDH wildtype (IDHwt) counterpart [3]. Despite a good sensitivity to first-line treatments consisting of maximal safe surgical resection followed by adjuvant radiotherapy and chemotherapy with alkylating agents [4], [5], [6], [7], [8], most IDHm HGGs recur. At recurrence, there is no standard of care. Because of the paucity of dedicated clinical trials, most patients receive alkylating chemotherapy (nitrosourea- or temozolomide-containing regimens) [9]. However, these treatments have modest efficacy, with response rates of 17–44% and 6-month progression-free survival (PFS) of 29–51% [10], [11], [12], [13]. Recent trials of molecularly targeted therapies were collectively negative [14], [15], [16]. Better solutions for recurrent IDHm HGGs are thus urgently needed [17].

Immune-checkpoint inhibitors (ICIs), such as the anti-programmed cell death protein 1 (PD-1) Nivolumab, enable the reactivation of an efficient immune response against tumor cells [18]. Their utilisation led to impressive results in several advanced, otherwise refractory cancers [19]. In gliomas, clinical benefit with ICIs is mainly limited to rare patients [20], and no benefit was observed in both primary [21], [22] and recurrent [23] glioblastoma. However, these studies focused on IDHwt HGGs. In recurrent IDHm HGGs, the use of alkylating agents (particularly temozolomide) can lead to the inactivation of mismatch repair (MMR) proteins and the acquisition of a hypermutated phenotype at recurrence [24], [25]. Hypermutation can result in the accumulation of immunogenic neoantigens and therefore enhance response to ICIs [20], [26], [27], suggesting that at least a subset of IDHm HGGs might benefit from ICI.

In this multicentric phase II trial, we evaluated the efficacy and safety of Nivolumab in patients with IDHm HGGs recurring after radiotherapy and at least one line of alkylating chemotherapy.

Section snippets

Study design

REVOLUMAB (NCT03925246) was a phase II, open-label, single-arm multicentric trial aiming to assess the efficacy and safety of Nivolumab in patients with recurrent IDHm HGGs. Patients were recruited from seven centers in the French POLA Network.

The trial was performed according to the Declaration of Helsinki. The final trial protocol and the informed consent forms were approved by the Institutional Review Board/Ethics Committee (CPP Ile de France 8) and authorized by the competent authority…

Results

Between July 2019 and June 2020, forty-two patients were enrolled, and thirty-nine received at least one dose of Nivolumab (Fig. 1). Their baseline characteristics are summarized in Table 1. There were thirty men and nine women, with a median age of 44 years. KPS was ≥70 in 36 patients (92%). WHO 2016 histological grading [31] at inclusion was grade 3 in 21 (54%) and 4 in 13 (33%). Five patients (13%) with a previous diagnosis of grade 2 glioma were included based on radiological evidence of…

Discussion

We report here the outcomes of our phase II trial of Nivolumab in recurrent IDHm HGGs. Overall, the study did not meet its prespecified endpoint. The median PFS was disappointing, not reaching two months. Nonetheless, this could be biased by the choice of the timing of response evaluation, with the median PFS corresponding at the time of first MRI. Furthermore, a subset of patients seemed to benefit, and when looking at curves in detail, a biphasic trend was observed. As often seen in…

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CRediT authorship contribution statement

P.A.: data analysis, writing–original draft and editing. T.M.: study conceptualization, methodology, patients inclusion, data analysis, writing–original draft and editing. B.L.: methodology, data analysis, writing–original draft and editing. G.C.: patients inclusion, writing–review and editing. H.V.: patients inclusion, writing–review and editing. C.S.: patients inclusion, writing–review and editing. C-J.M. E.: patients inclusion, writing–review and editing. C.B.: patients inclusion,…

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The following authors have disclosed financial relationships with commercial entities that may be impacted by this work: CD (BMS, travel support). The other authors have declared no conflict of interest.…

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REVOLUMAB results have been previously presented at the 2022 ASCO Annual Meeting in poster form (abstract ID 2048)....

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