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

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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).

Keywords: IDH, high-grade gliomas, Nivolumab, immunotherapy, clinical trial

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[4–8], 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%[10–13]. Recent trials of molecularly targeted therapies were collectively negative[14–16]. 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.

Methods

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 (ANSM).

Patients

The eligible patients were adults (aged 18-85 years) with WHO 2016 grade 3-4 gliomas bearing an IDH1/2 mutation (as detected by IDH1R132H immunohistochemistry or targeted IDH1/2 gene sequencing) and recurring after radiotherapy and at least one line of alkylating chemotherapy.

Other key inclusion criteria were: i) tumor recurrence occurring >12 weeks from the end of the radiotherapy or outside the irradiated volume; ii) Karnofsky performance status (KPS) >50; iii) radiologically measurable disease[28]; iv) glucocorticoids dose at inclusion ≤10 mg prednisone equivalent. Patients previously treated with any drug targeting T-cell co-stimulation or immune checkpoint pathways were excluded.

Treatment

Patients received intravenous Nivolumab 240 mg every two weeks for eight cycles, followed by 480 mg every four weeks for eight cycles. Treatment was administered until the end of the study scheme, tumor progression, unacceptable toxicity, or death.

Response assessment

Tumor response was assessed on brain Magnetic Resonance Imaging (MRI, **Supplementary Methods**) performed at baseline (no more than 35 days before the start of the treatment) and then every eight weeks. In case of end of treatment, a brain MRI was performed four weeks after last infusion. Tumor response was assessed by local investigators according to the Response Assessment in Neuro-Oncology (RANO)[28] and immunotherapy Response Assessment for Neuro-Oncology (iRANO)[29] criteria.

Endpoints

The primary endpoint was the 24-week PFS rate (24w-PFS), defined as the percentage of patients alive without progression according to RANO criteria at 24 weeks (+/- 2 weeks) after treatment initiation.

Secondary endpoints were the 24w-PFS according to iRANO criteria, the median PFS according to RANO and iRANO criteria, the overall survival (OS) defined as the time from treatment initiation to death from any cause, the overall response rate (ORR) according to RANO and iRANO criteria, the duration of response according to RANO and iRANO criteria, the longitudinal changes in health-related quality of life according to the EORTC quality of life questionnaire core-30 (QLQ-C30, version 3) and the EORTC quality of life questionnaire – brain cancer module (QLQ-BN20), and the type, frequency, and severity of adverse events and serious adverse events graded according to the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) V4.03.

Sample size

The sample size was based on a single-stage A'Hern's design[30]. Assuming a minimum 24w-PFS of 30% based on previous studies[10–13], 39 patients were needed to detect an improvement of 20% with a type I error rate of 5% and a power of 80% with a binomial confidence interval. Based on A'Hern's design, the following decision rule was established: if at least 17 patients were alive without progression at 24 weeks, Nivolumab would be tested in phase III.

Statistical analyses

Analyses were performed on patients receiving at least one dose of treatment. The 24w-PFS was given with its 95% Clopper-Pearson confidence interval. The analysis of the prognostic factors on the primary endpoint was carried out with Wilcoxon test for quantitative variables and the exact Fisher test for qualitative ones. Comparisons were made for subgroups containing at least five patients.

Median PFS was estimated with its 95% confidence interval by the Brookmeyer and Crowley method. PFS and OS were estimated using Kaplan-Meier method, and their 95% confidence interval was calculated using Greenwood variance. Patients without event were censored to their last known contact. The ORR was calculated as the percentage of patients who had at least one partial or complete response documented during the treatment, according to RANO and iRANO criteria, and given with its Clopper-Pearson 95% confidence interval. The duration of response was calculated as the time from confirmation of stable, partial, or complete response using RANO and iRANO criteria until tumor progression. Longitudinal changes in quality of life were analysed with a mixed linear model for repeated measures, with random intercept and slope. The estimation was performed with the Restricted Maximum Likelihood method, and the convergence algorithm was the Newton-Raphson algorithm. No adjustment was made for multiple testing.

Analyses were performed using Rv4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Data availability

The data are available upon reasonable request and in compliance with the applicable regulations.

Results

Between July 2019 and June 2020, forty-two patients were enrolled, and thirty-nine received at least one dose of Nivolumab (**Figure 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 anaplastic transformation (presence of clear contrast-enhancing lesions). The chromosomes 1p/19q were codeleted in 39%of cases with available information (13/33). The median time from diagnosis was 5.7 years and the median time from the end of radiotherapy was 4.5 years. The median number of previous systemic therapy lines was two. All but three patients previously received temozolomide (median number of cycles = 14).

Treatment exposure

The median study follow-up was 17.6 months (range 14.2-21.3). The median number of doses received was six (range 1-16). The median treatment duration was twelve weeks (range 2-55). Eight patients (21%) reached the end of treatment period, while 30 (77%) discontinued Nivolumab due to tumor progression. One patient (3%) discontinued the treatment due to a serious adverse event not attributed to the investigational drug (intracranial haemorrhage under anticoagulant treatment). No patient discontinued Nivolumab due to treatment toxicity.

Efficacy analysis

According to local investigator assessment, eleven patients were considered alive without progression according to RANO criteria at 24 weeks +/- 2 weeks (24w-PFS = 28.2%, 95%CI 15.0-44.9%, **Figure 2**), which was below the predefined threshold of seventeen patients.

Thirty-five patients (90%) progressed during the follow-up period. The median PFS was 1.84 months (95%CI 1.81-5.89 months, **Figure 3a**). The PFS rates at 12 and 18 months were 18.0% (95%CI 9.2-35.1%) and 12.8% (95%CI 5.7-29.1%), respectively.

The PFS was also assessed according to investigator-assessed iRANO criteria. The iRANO 24w-PFS was 33.3% (95%CI 19.1-50.2%). The median PFS based on iRANO was 3.06 months (95%CI 1.84-6.22, **Supplementary Figure 1**). The iRANO PFS rates at 12 and 18 months were 18.0% (95%CI 9.2-35.1%) and 12.8% (95%CI 5.7-29.1%), respectively.

Twenty-five patients (64%) died during the follow-up period. The median OS was 14.7 months (95%CI 9.18-not reached) (**Figure 3b**). The OS rates at 6, 12, and 18 months were 69.2% (95%CI 56.2-85.3%), 56.4% (95%CI 42.8-74.3%), and 41.8% (95%CI 28.5-61.3%), respectively.

Four patients achieved a RANO partial response (10.3%, 95%CI 2.9-24.2%). Their characteristics are reported in **Supplementary Table 1**. The median duration of response for them was 8.1 months (2.6-14.7 months). Thirteen patients (33.3%, 95%CI 19.1-50.2%) achieved stable disease, and 22 (56.4%, 95%CI 39.6-72.2%) disease progression as their best response (**Figure 2**).

Subgroup analysis of the primary endpoint

The 24w-PFS did not differ significantly when comparing for age, sex, 1p19q codeletion status, number of previous chemotherapies, time since the end of the previous treatment, previous bevacizumab, or size of the enhancing lesion at baseline (**Table 2**). There was a trend for increased 24w-PFS in patients with a histological grade 2-3 gliomas compared to histological grade 4 (38% versus 8% respectively, p=0.06; **Supplementary Figure 2**).

Safety and quality of life analysis

Fourteen (36%) patients had at least one grade ≥3 AE. (**Supplementary Table 2**). Adverse events attributed to Nivolumab are reported in **Supplementary Table 2**: only two were grade ≥3 (one grade 3 fatigue and one grade 4 neutropenia). No unexpected toxicities were seen under Nivolumab.

Quality of life

Regarding the longitudinal evaluation of quality of life, we were not able to detect significant changes in most of the evaluated domains (**Supplementary Tables 4-5**). The score of the "motor dysfunction" item in BN20 questionnaire significantly increased with time (p=0.023), but this was likely due to tumor progression. "Skin itching" score also significantly increased overtime (p=0.047).

Ancillary biomarkers analysis

We performed an ancillary analysis to identify potential histomolecular predictors of response. We were able to retrieve a recent specimen from six patients (**Supplementary Methods**). Overall, most tumors showed scant lymphocytic infiltration, intratumoral myeloid cells expressing CD163 (a marker of M2 immunosuppressive phenotype), and PD1 positivity (**Supplementary Data**). None of the evaluated markers of myeloid populations (CD163), lymphoid populations (CD3, CD8, CD20), or immune checkpoint (PD1, PD-L1) expression appeared clearly associated with an increased 24w-PFS (**Supplementary Table 6**).

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 immunotherapy trials, in nonresponding patients, tumor progression occurred early. A subset of cases, however, achieved prolonged disease stabilization, and, in 10% of the patients, partial responses were observed, lasting for 3-15 months.

We were not able to clearly identify clinical or histomolecular biomarkers of response. A higher rate of grade 2-3 gliomas was free from progression at 24 weeks compared to grade 4 patients; indeed, we cannot exclude that this reflects the intrinsic growth rates of these tumors rather than response to Nivolumab. The 2021 WHO Classification recognises grade 4 IDHm astrocytoma as a separate entity from glioblastomas[1]. This will result in their exclusion from future glioblastoma trials. Nonetheless, we caution against assimilating them to WHO grade 3 IDHm astrocytoma, as their aggressiveness may differ substantially.

No unexpected safety signals were detected. Nivolumab was well tolerated, with no treatment discontinuation due to adverse effects or a detrimental impact on the quality of life. A recurrent concern in patients undergoing immunotherapy for brain tumors is the risk of clinically relevant pseudoprogression. We did not see clinically or radiologically manifest pseudoprogression in our cohort. Pseudoprogression under immunotherapy has been linked to an emerging antitumor immune response[32], and its absence in this study is in line with the absence of immunotherapy efficacy in the majority of the patients.

Recent studies on the immune landscape of IDHm gliomas could shed insight into the reasons for these negative results. IDHm gliomas appear as “immune desert” tumors, with reduced immune cell infiltrates compared to other tumors[33], including IDHwt gliomas[34,35]. They show *PDL1* gene promoter hypermethylation and reduced PD-L1 expression[36]. The oncometabolite D-2-hydroxyglutarate act in a paracrine manner by reducing T lymphocytes recruitment[37,38] and activation[39]. Combining IDH inhibitors with checkpoint inhibition might improve responses. Indeed, IDH inhibitor treatment results in the upregulation of proinflammatory pathways and increases T-lymphocytes infiltration[40,41]. Synergistic effects of IDH inhibition and immune checkpoint inhibitors (ICIs) have been seen in murine models of IDHm astrocytoma[42] and cholangiocarcinoma[43]. Phase I-

II clinical trials associating IDH inhibitors and ICIs are ongoing in IDHm gliomas (NCT04056910, NCT05484622).

All the patients in the study underwent at least one line of alkylating chemotherapy, in most cases Temozolomide, which is known to induce a specific hypermutated phenotype[24,25]. The fact that hypermutation could increase the response to ICIs[26] was part of the rationale behind this trial. Nonetheless, demonstration of hypermutation and/or MMR deficiency was not a prerequisite for entering the trial, as resurgery was not mandatory. Exploratory histopathological analysis on a small subset of patients did not identify MMR deficiency at inclusion, hampering us from drawing any conclusion. Retrospective data suggest that post-Temozolomide hypermutation is not a predictor of benefit from ICIs[25]. Results from prospective trials are awaited (NCT02658279).

We acknowledge that our work has several limitations. It involved a heterogeneous patient population at various stages of the disease. The absence of a central pathological and MRI reviews are potential limits in the interpretation of the results. We were unable to retrieve the CDKN2A/B homozygous deletion status, which is an unfavorable prognostic marker in IDHm astrocytomas. The absence of re-surgery severely hampers us from understanding the exact disease biology of these tumors at the time of inclusion; furthermore, five patients were included based on radiological-only evidence of anaplastic transformation (without a histological confirmation), deviating from the original protocol.

Even though it did not meet its primary outcome, this trial, as the companion OLAGLI study (NCT03561870), shows the feasibility of clinical trials dedicated to IDHm HGGs. REVOLUMAB completed accrual in less than twelve months, highlighting the added value of national networks dedicated to rare tumors such as the French POLA network.

In conclusion, phase II trials evaluating novel agents are feasible in IDHm HGGs. REVOLUMAB did not meet its prespecified primary endpoint; however, Nivolumab was well tolerated, and long-lasting responses were observed in a subset of this population. We support further evaluation in IDHm gliomas, alone or in combination with other agents such as IDH inhibitors.

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

Conflict of Interest

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.

Authorship

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, writing–review and editing. D.S.A.L.: patients inclusion, writing–review and editing. I.L.: methodology, data curation, analysis and visualization. J.L.: translational analyses. C.C.: data curation, translational analyses. B.F.: study conceptualization, translational analyses, data analysis, writing–original draft and editing. D.F.: study conceptualization, methodology, patients inclusion, data analysis, writing–review and editing. D.C.: study conceptualization, methodology, patients inclusion, data analysis, writing– original draft and editing.

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Legends

Figure 1. **Inclusion flowchart**.

Figure 2. Swimmer plot showing time on therapy, time to events (progression according to RANO criteria, death) and best response (per local investigator) for each patient. The vertical bar indicates the primary endpoint (24 weeks). ORR = overall response rate; PD = progressive disease.

Figure 3. Progression-free survival (a) and overall survival (b) curves and corresponding risk tables, estimated with the Kaplan-Meier method. The grey area indicates the corresponding 95% confidence interval.

Table 1. **Demographic and clinical features of patients at baseline**. *less than 10 mg/day of prednisone equivalents, §with radiological evidence of anaplastic transformation. N = number, M = male, F = female, IQR = interquartile range, KPS = Karnofsky performance status, NA = not available, RT = radiation therapy, CHT = chemotherapy, TMZ = temozolomide

Table 2. Subgroup analysis of primary endpoint. 24-w PFS = 24-weeks progression-free survival rate; CI95% = 95% confidence interval; CHT = chemotherapy. * Measure of the longest perpendicular diameters of enhancing tumour.

Individuals, n	39
Sex, n (%) - M - F	 - 30 (77%) - 9 (23%)
Age (years) - Median - Range - IQR	 - 44 - 27-71 - 39-53
KPS at baseline, n (%) - 90-100 - 70-80 - <70	 - 17 (43%) - 19 (48%) - 3 (8%)
Glucocorticoids at baseline, n (%) - No - Yes*	 - 36 (92%) - 3 (8%)
Time since histological diagnosis (years) - Median - Range - IQR	 - 5.7 - 0.8-22.8 - 2.8-10.7
Histological grading at inclusion, n (%) - Grade 2§ - Grade 3 - Grade 4	 - 5 (13%) - 21 (54%) - 13 (33%)
1p/19q codeletion, n (%) - No - Yes - NA	 - 20 (61%) - 13 (39%) - 6
Time since the end of RT (months) - Median - Range - IQR	 - 53.6 - 6.6-151.9 - 20.2-75.8
Number of previous CHT lines, n (%) - 1 - 2 - 3 - 4	 - 10 (26%) - 10 (49%) - 3 (8%) - 7 (18%)
Number of TMZ cycles received, n - Median - Range - IQR	 - 13 - 0-37 - 6-22
Prior bevacizumab, n (%)	

- No - Yes	- 29 (74%) - 10 (26%)
Time since the end of the previous treatment (months) - Median - Range - IQR	 - 5.0 - 1.0-91.2 - 1.7-20.2
Measure of the longest perpendicular diameters of enhancing tumour (mm) - Median - Range - IQR	 - 47 - 18-124 - 30-81

Table 1.

Variable	Groups	24w-PFS (CI95%)	p value
Age	*<44 years*	22.2% (6.4 – 47.6)	0.44
	>44 years	33.3% (14.6 – 57.0)	
Sex	*Male*	30.0% (14.7 – 49.4)	1.00
	Female	22.2% (2.8 – 60.0)	
1p19q codeletion	*Yes*	46.2% (19.2 – 74.9)	0.27
	No	25.0% (8.7 – 49.1)	
Histological grade at diagnosis	*Grade 2-3*	38.5% (20.2 – 59.4)	0.06
	Grade 4	7.7% (0.2 – 36.0)	
Number of previous CHT lines	*1-2*	34.5% (17.9 – 54.3)	0.23
	3-4	10.0% (0.3 – 44.5)	
Time since the end of the previous treatment	*<3 months*	21.1% (6.1 – 45.6)	0.33
	≥3 months	35.0% (15.4 – 59.2)	
Previous bevacizumab	*Yes*	10.0% (0.3 – 44.5)	0.23
	No	34.5% (17.9 – 54.3)	
*Size of the enhancing lesion at baseline**	*<47 mm*	33.3% (11.8 – 61.6)	0.22
	≥47 mm	12.5% (1.6 – 38.3)	

Table 2. Subgroup analysis of primary endpoint. 24-w PFS = 24-weeks progression-free survival rate; CI95% = 95% confidence interval; CHT = chemotherapy. * Measure of the longest perpendicular diameters of enhancing tumour

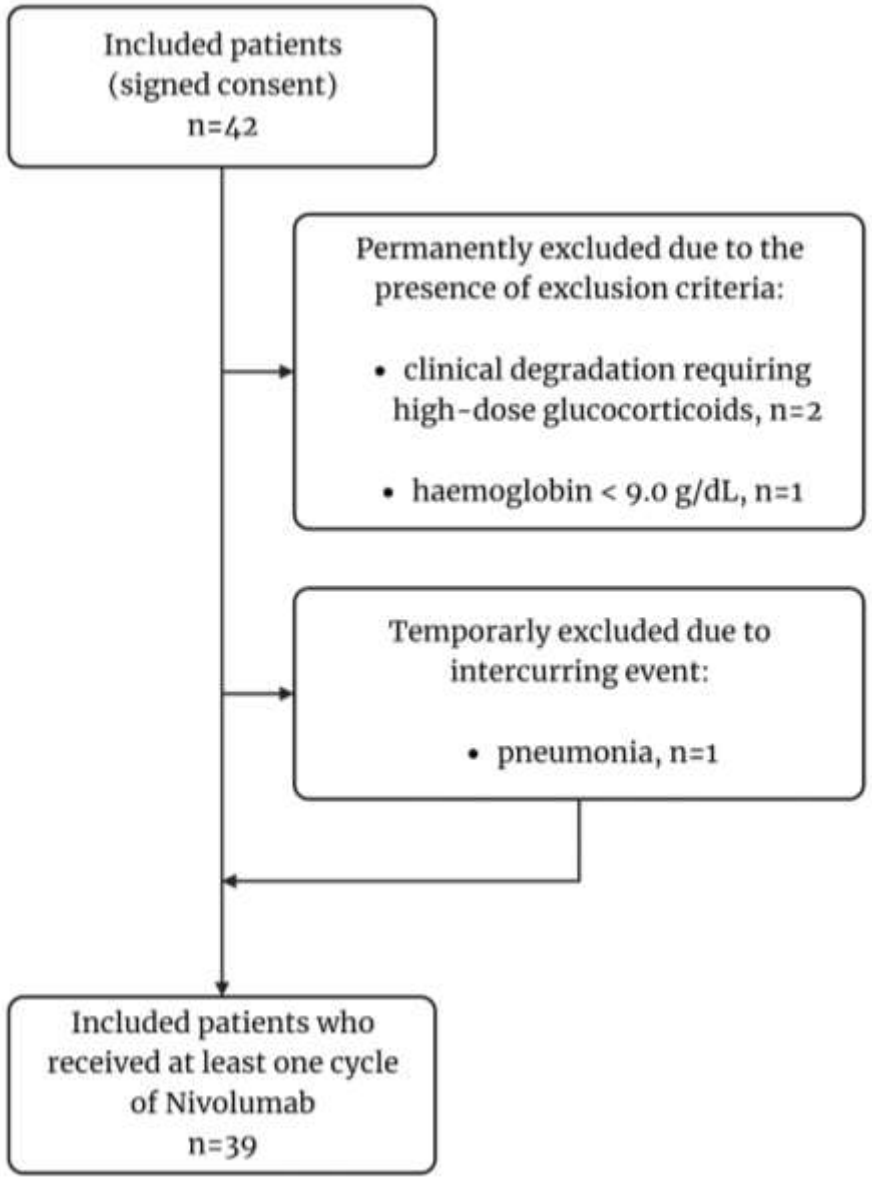

Included patients
(signed consent)
n=42
Permanently excluded due to the presence of exclusion criteria:
• clinical degradation requiring high-dose glucocorticoids, n=2
• haemoglobin < 9.0 g/dL, n=1
Temporarly excluded due to intercurring event:
• pneumonia, n=1
Included patients who received at least one cycle of Nivolumab
n=39

Figure 1

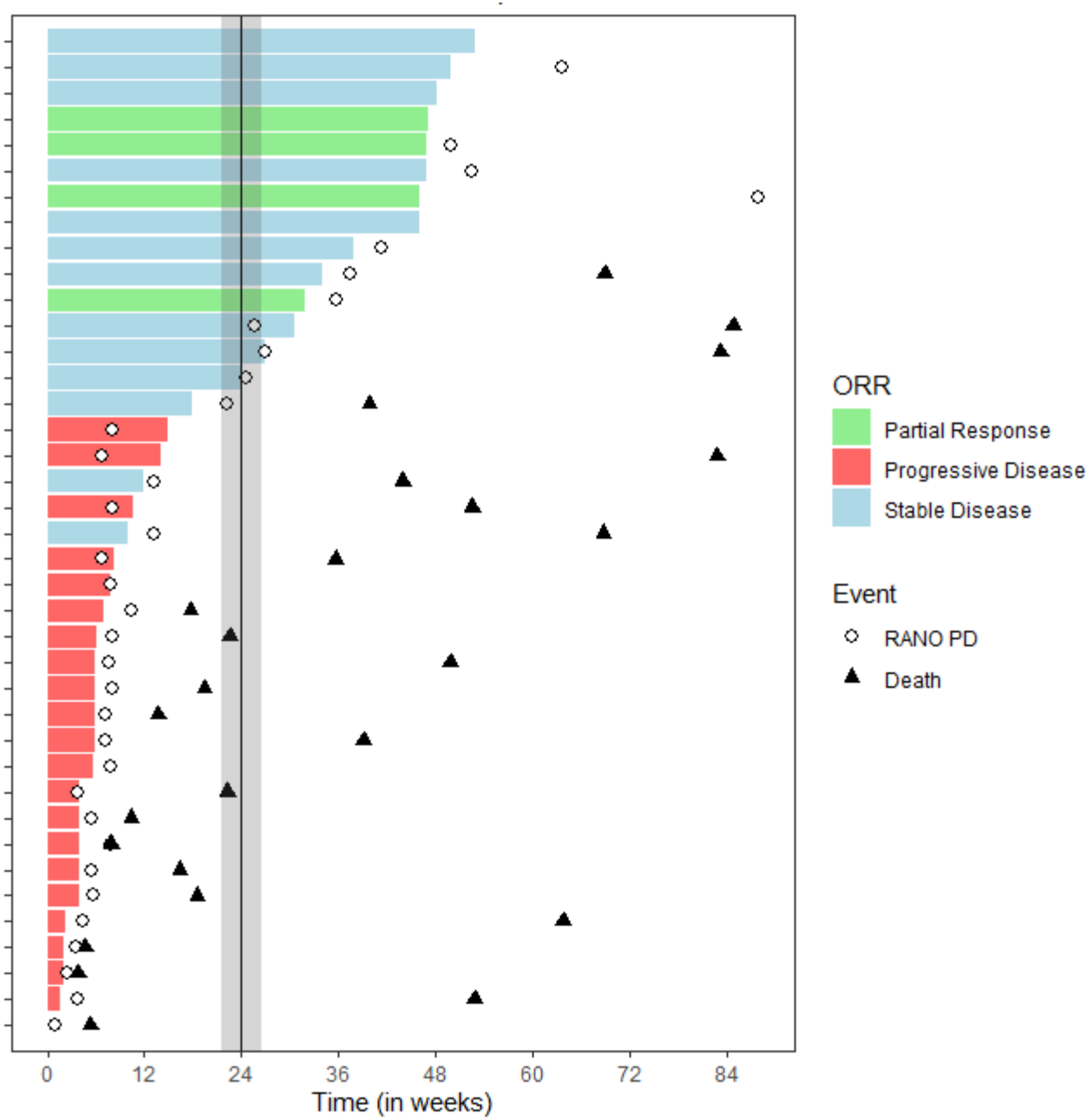
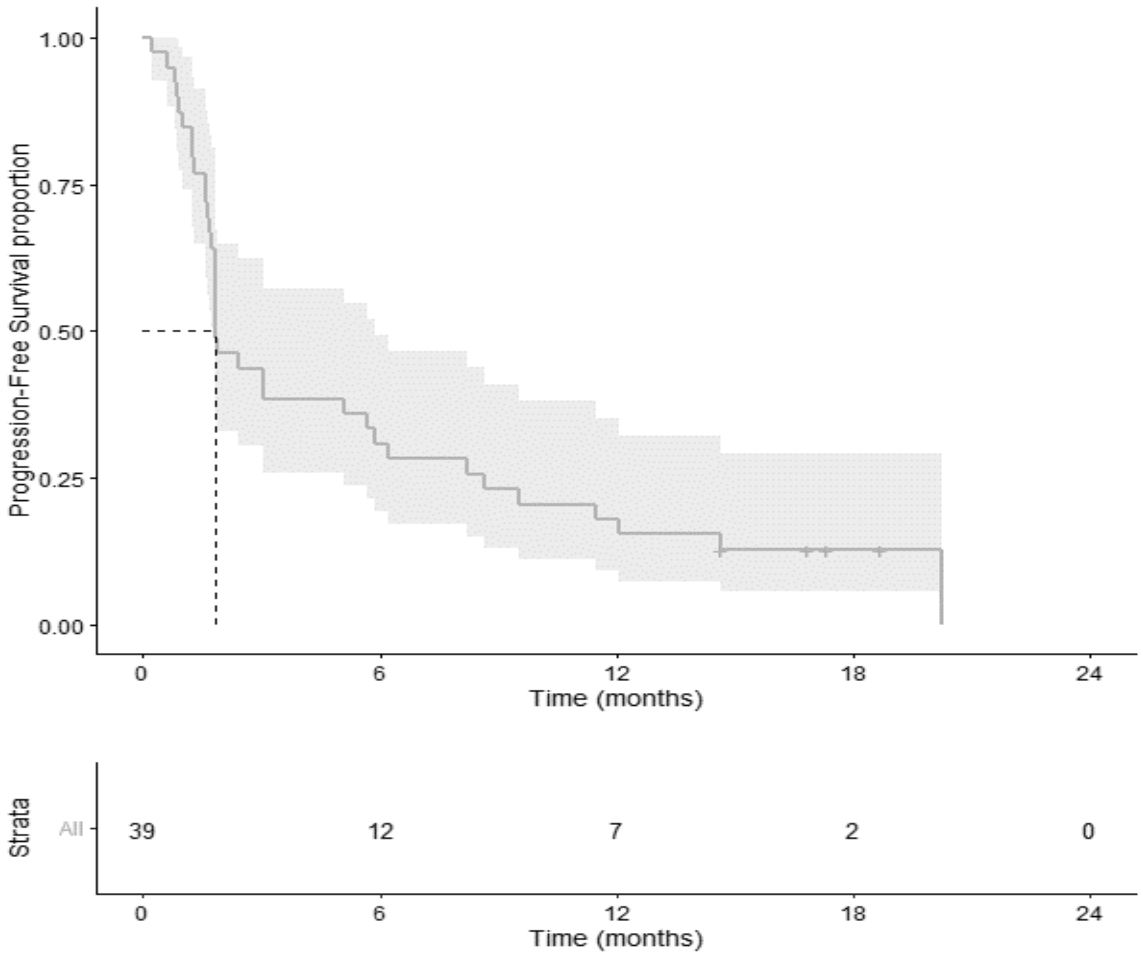

0
12
24
36
48
60
72
84
Time (in weeks)
ORR
Partial Response
Progressive Disease
Stable Disease
Event
RANO PD
Death

Figure 2


1.00
0.75
0.50
0.25
0.00
Progression-Free Survival proportion
0
6
12
18
24
Time (months)
Strata
All
39
12
7
2
0
0
6
12
18
24
Time (months)

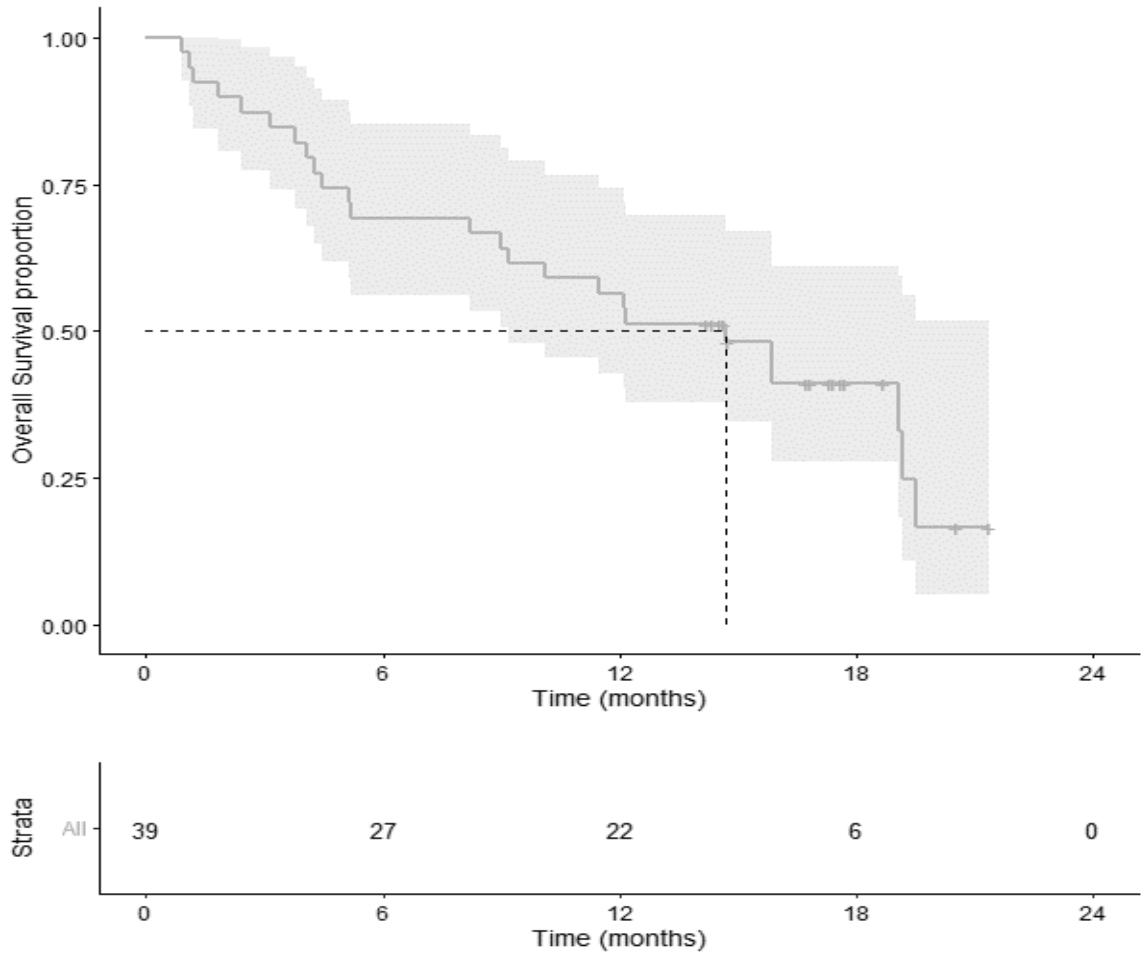

1.00
0.75
0.50
0.25
0.00
Overall Survival proportion
0
6
12
18
24
Time (months)
Strata
All
39
27
22
6
0
0
6
12
18
24
Time (months)

Figure 3a-b

Supplementary Methods

MRI assessment protocol

Tumor response was assessed on brain Magnetic Resonance Imaging performed according to the standard practices of every centre, and including at least: axial T1-weighted, 3D T1-weighted post-gadolinium injection, 3D T2-weighted or fluid-attenuated inversion recovery (FLAIR), and diffusion sequences, and a regional cerebral blood volume (rCBV) map.

Ancillary biomarker analysis

We performed an ancillary histological analysis to identify potential predictors of response. We analysed tumor specimens from surgeries performed no more than 12 months before the trial inclusion, and without oncological treatments between these two.

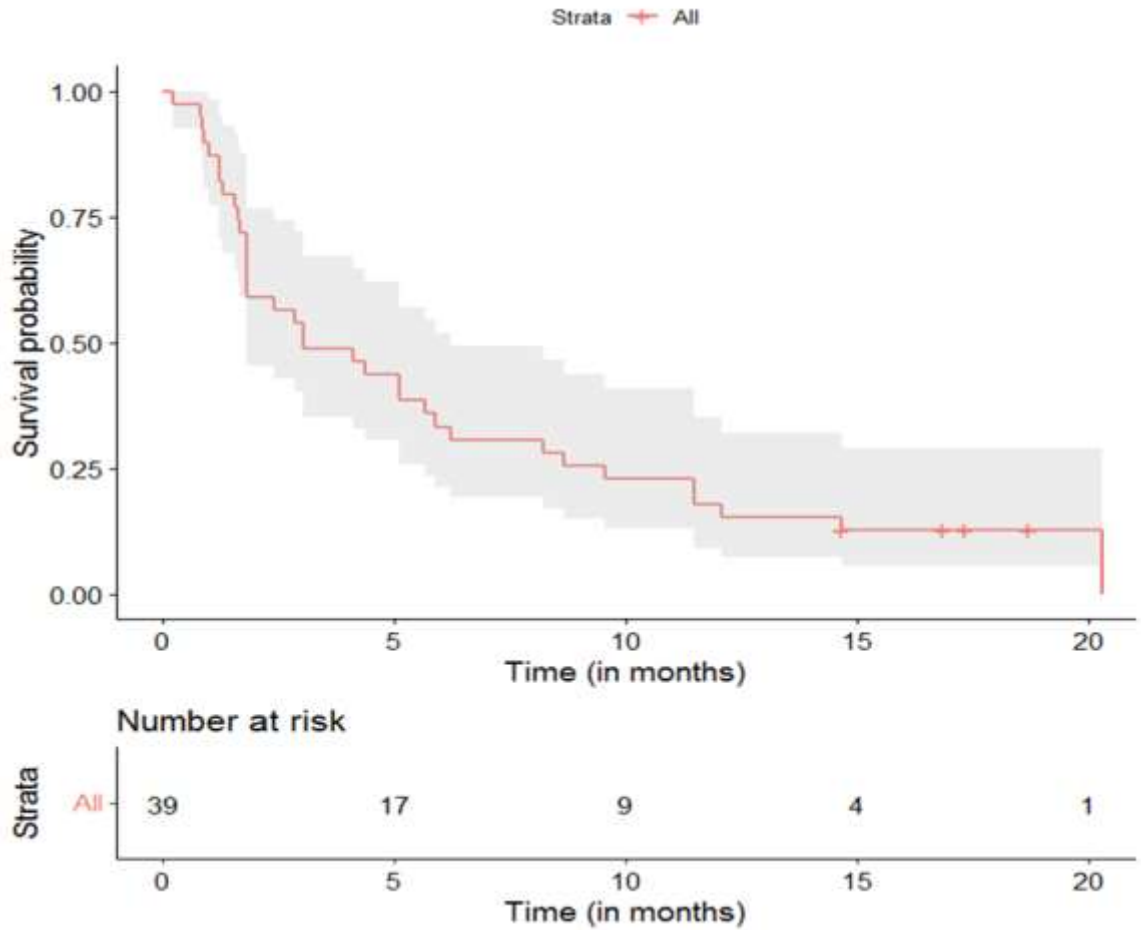
Immunostaining

Four micrometer-thick tissue sections were cut from formalin-fixed formalin-embedded tumor samples and were processed using a fully automated immunohistochemistry system Ventana benchmark ULTRA system (Roche, Basel, Switzerland) using streptavidin-peroxidase complex with diaminobenzidine as chromogen (Roche). Primary antibodies were as follows: mouse monoclonal antibody (mAb) against the B cell marker CD20 [clone L26, 1:100, Agilent technologies, Santa Clara, CA], rabbit mAb against the T lymphocyte marker CD3 [prediluted clone 2GV6, Roche], mouse mAb against cytotoxic T lymphocyte marker CD8 [prediluted clone C8/144B, Agilent technologies, Santa Clara, CA], mouse mAb against the macrophage marker CD163 [prediluted clone MRQ-26, Roche], rabbit polyclonal antibody against the microglia and macrophage marker IBA1 [1:500, Wako, Japan], mouse mAb against MLH1 [prediluted clone M1, Roche Ventana], mouse mAb against MSH2 [prediluted clone G219-1129, Roche Ventana], rabbit mAb against MSH6 [prediluted clone SP93, Roche Ventana], rabbit mAb against the immune checkpoint PD-L1 [prediluted clone QR001, Quartett, Germany], mouse mAb against the receptor of immune checkpoint PD1 [prediluted clone NAT105, Roche], and mouse mAb againts PMS2 (prediluted clone A16-4, RocheVentana). A senior neuropathologist (FB) evaluated the CD163, CD20, IBA1, MLH1, MSH2, MSH6, PD-L1, PD1 and PMS2 immunostainings. PD1 and PD-L1 immunostaining were interpreted as the presence of positive cells versus negativity. CD20 was interpreted as the presence of rare isolated positive cells (low) versus clusters of positive cells (high). About CD163 and IBA1, samples were classified as "CD163 positive" if myeloid cells infiltrating the tumor tissue were IBA1+ and CD163+ or as "CD163 negative" if myeloid cells infiltrating the tumor tissue were IBA1+ and CD163-. The tumor was annotated as "MMR proficient" if the expression of MLH1, MSH2, MSH6 and PMS2 was maintained. A loss of expression of one or two of the MMR proteins by the tumor cells was annotated

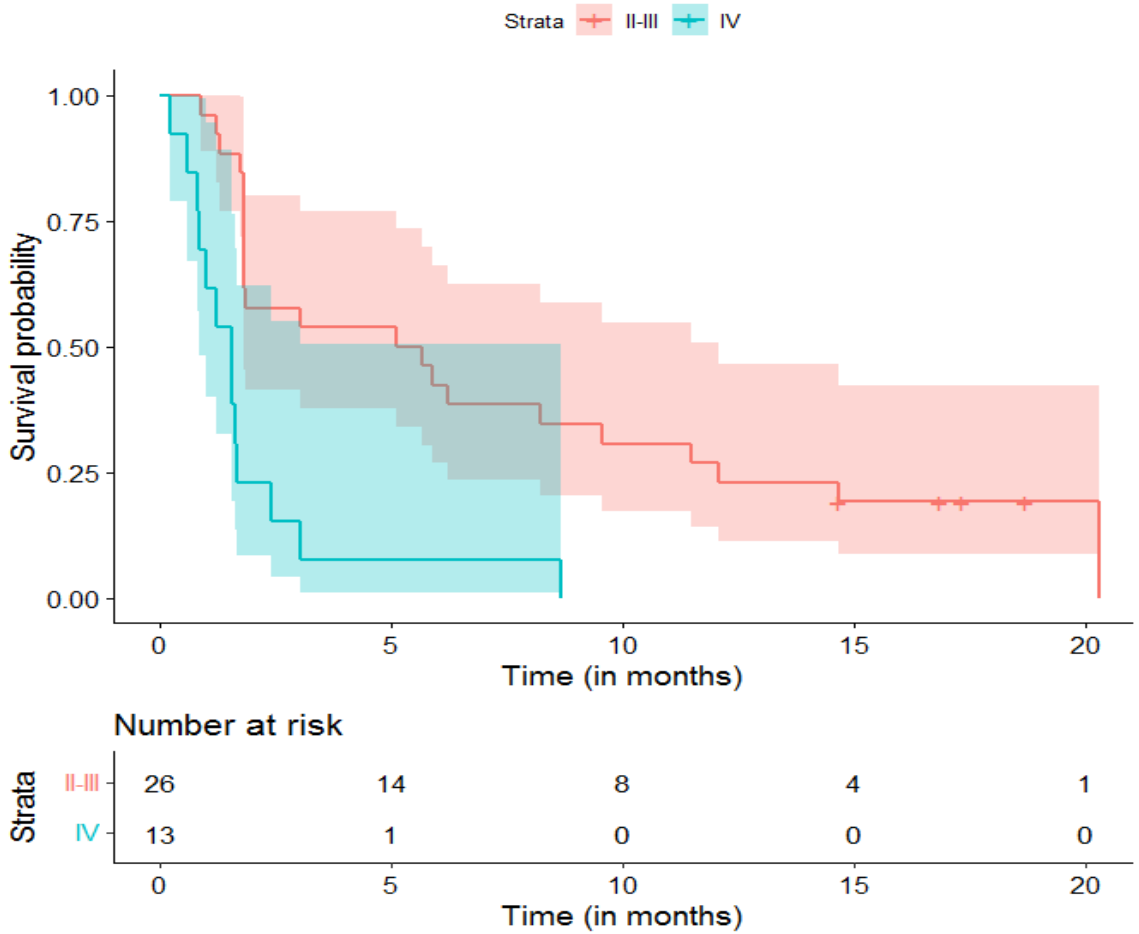
as "MMR deficient" and validated by detection by targeted NGS of an inactivating mutation in an MMR gene and of the mutational signature 11.

Digital pathology

Slides immunostained for CD3 and CD8 were scanned at magnification 20X on a Zeiss Axioscan Z1 (Zeiss, Oberkochen, Germany). For the quantification of CD3 and CD8 positive cells, the images were imported into the Visiopharm Image Analysis software (Visiopharm, Hørsholm, Denmark). Regions of interest (ROIs) were drawn to delineate quantification for tumor areas. A Visiopharm application based on the staining threshold and designed by the Histomics Platform of Paris Brain Institute (ICM) enabled quantification of the positive cells for CD3 on the one hand and for CD8 on the other hand and the negative cells through the detection of nuclear counterstaining. The proportion of positive cells over the number of negative nuclei and the cell density ("relative number") in relation to the quantified ROI surface were calculated.



Supplementary Figure 1. Progression-free survival curve according to iRANO criteria (per local investigator).



Supplementary Figure 2. Progression-free survival curves according to 2016 WHO grading.

		RANO response	
		PR	**SD/PD**
Individuals, n		4	35
Age, years	Median	44	44
	Range	35-56	27-71
	IQR	39-50	39-53
Sex, n (%)	Male	3 (75%)	27 (77%)
	Female	1 (25%)	8 (23%)
1p/19 codeletion, n (%)	No	3 (75%)	17 (59%)
	Yes	1 (25%)	12 (41%)
	NA	0	6
Histological grading at inclusion, n (%)	2§	0 (0%)	5 (14%)
	3	4 (100%)	17 (49%)
	4	0 (0%)	13 (37%)
Number of previous CHT lines, n (%)	1	1 (25%)	9 (26%)
	2	2 (50%)	17 (49%)
	3	1 (25%)	2 (6%)
	4	0 (0%)	7 (20%)
Number of TMZ cycles received, n	Median	12.5	13
	Range	5-20	0-37
	IQR	9.5-15.5	6-24
Previous bevacizumab, n (%)	No	3 (75%)	26 (74 %)
	Yes	1 (25%)	9 (25%)
Time since the end of the previous treatment (months)	Median	16	5
	Range	3-79	1-91
	IQR	4-40	2-17
Measure of the longest perpendicular diameters of enhancing tumour (mm)	Median	52	47
	Range	28-96	18-124
	IQR	40-68	30-81
	NA	0	8

Supplementary Table 1. Characteristics of responding versus non-responding patients (according to RANO). §with radiological evidence of anaplastic transformation. PR = partial response, SD = stable disease, PD = progression disease, n = number, IQR = interquartile range, NA = not available, CHT = chemotherapy, TMZ = temozolomide

Adverse event class	CTCAE grade					
	1	**2**	**3**	**4**	**5**	**Total**
Nervous system disorders	13 (33%)	5 (13%)	6 (15%)	2 (5%)	4 (10%)	30 (77%)
General disorders and administration site conditions	16 (41%)	7 (18%)	1 (3%)	0 (0%)	0 (0%)	24 (62%)
Blood and lymphatic system disorders	9 (23%)	6 (15%)	2 (5%)	1 (3%)	0 (0%)	18 (46%)
Gastrointestinal disorders	14 (36%)	2 (5%)	0 (0%)	0 (0%)	0 (0%)	16 (41%)
Skin and subcutaneous tissue disorders	11 (28%)	2 (5%)	0 (0%)	0 (0%)	0 (0%)	13 (33%)
Hepatobiliary disorders	3 (8%)	4 (10 %)	1 (3%)	1 (3%)	0 (0%)	9 (23 %)
Respiratory, thoracic, and mediastinal disorders	8 (21%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	8 (21%)
Infections and infestations	4 (10%)	2 (5%)	1 (3%)	0 (0%)	0 (0%)	7 (18%)
Endocrine disorders	4 (10%)	2 (5%)	0 (0%)	0 (0%)	0 (0%)	6 (15%)
Metabolism and nutrition disorders	5 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (13%)
Renal and urinary disorders	5 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (13%)
Vascular disorders	1 (3%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	2 (5%)
Musculoskeletal and connective tissue disorders	2 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (5%)
Cardiac disorders	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	1 (3%)
Eye disorders	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Immune system disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Supplementary Table 2. Categories and frequency of adverse events, ordered by all-grade occurrence. For each category, each patient is represented once, with the highest reported toxicity.

Adverse event class	CTCAE Grade				
	1-2	**3**	**4**	**5**	**Total**
General disorders and administration site conditions	17 (44%)	**1 (3%)***	0 (0%)	0 (0%)	18 (47%)
Gastrointestinal disorders	9 (23%)	0 (0%)	0 (0%)	0 (0%)	9 (23%)
Skin and subcutaneous tissue disorders	8 (21%)	0 (0%)	0 (0%)	0 (0%)	8 (21%)
Hepatobiliary disorders	6 (15%)	0 (0%)	0 (0%)	0 (0%)	6 (15%)
Nervous system disorders	6 (15%)	0 (0%)	0 (0%)	0 (0%)	6 (15%)
Blood and lymphatic system disorders	2 (5%)	0 (0%)	**1 (3%)****	0 (0%)	3 (8%)
Endocrine disorders	3 (8%)	0 (0%)	0 (0%)	0 (0%)	3 (8%)
Respiratory, thoracic, and mediastinal disorders	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Renal and urinary disorders	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Eye disorders	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Infections and infestations	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cardiac disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Vascular disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Musculoskeletal and connective tissue disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Neoplasms benign, malignant, and unspecified	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Immune system disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Metabolism and nutrition disorders	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Supplementary Table 3. **Categories and frequency of adverse events attributed to the investigational drug, ordered by all-grade frequency.** For each category, each patient is represented once, with the highest reported toxicity. * grade 3 fatigue; ** grade 4 neutropenia.

Dimension		β estimate (standard error)	p-value
Global health	Intercept	62.02 (3.18)	0.000
	Time	0.05 (0.15)	0.737
Role functioning	Intercept	68.43 (4.70)	0.000
	Time	0.01 (0.19)	0.953
Emotional functioning	Intercept	74.07 (3.48)	0.000
	Time	-0.21 (0.29)	0.463
Cognitive functioning	Intercept	71.72 (3.59)	0.000
	Time	0.09 (0.14)	0.520
Social functioning	Intercept	76.01 (3.94)	0.000
	Time	0.01 (0.16)	0.946
Fatigue	Intercept	44.53 (4.60)	0.000
	Time	-0.18 (0.23)	0.441
Nausea and vomiting	Intercept	7.62 (2.38)	0.002
	Time	0.01 (0.09)	0.906
Pain	Intercept	14.56 (3.12)	0.000
	Time	-0.07 (0.19)	0.717
Dyspnea	Intercept	10.55 (3.51)	0.004
	Time	-0.13 (0.14)	0.358
Insomnia	Intercept	26.11 (4.63)	0.000
	Time	0.17 (0.22)	0.446
Diarrhea	Intercept	3.66 (2.10)	0.086
	Time	0.05 (0.12)	0.680
Financial difficulties	Intercept	13.45 (3.73)	0.001
	Time	-0.22 (0.14)	0.138

Supplementary Table 4. Results for linear mixed model for each dimension of the questionnaire QLQ-C30. For each dimension, the Time p-value indicates whether ($p<0.05$) or not this aspect significantly differed over time for patients.

Dimension	Fixed effects	β estimate (standard error)	p-value
Uncertainty about the future	Intercept	32.94 (3.72)	0.000
	Time	0.02 (0.23)	0.936
Visual disturbances	Intercept	8.73 (1.85)	0.000
	Time	-0.02 (0.09)	0.857
Motor dysfunction	Intercept	21.75 (4.18)	0.000
	Time	0.43 (0.18)	**0.023**
Communication deficit	Intercept	30.45 (4.80)	0.000
	Time	-0.03 (0.12)	0.815
Headaches	Intercept	22.46 (3.96)	0.000
	Time	-0.26 (0.20)	0.215
Skin itching	Intercept	4.10 (2.49)	0.104
	Time	0.38 (0.19)	**0.047**
Leg weakness	Intercept	11.22 (3.69)	0.003
	Time	0.11 (0.25)	0.653

Supplementary Table 5. Results for linear mixed model for each dimension of the questionnaire BN20. For each dimension, the Time p-value indicates whether ($p<0.05$) or not this aspect significantly differed over time for patients.

Variable	Groups	N	24w-PFS (CI95%)
CD20	High	1	100% (2.5 – 100)
	Low	5	40% (5.3 – 85.3)
PD1	Positive	5	40% (5.3 – 85.3)
	Negative	1	100% (2.5 – 100)
PD-L1	Positive	1	0% (0 – 97.5)
	Negative	5	60% (14.7 – 94.7)
CD163	Positive	3	33% (0.8 – 90.6)
	Negative	3	67% (9.4 – 99.2)
Relative CD8 number	High	3	33% (0.8 – 90.6)
	Low	3	67% (9.4 – 99.2)
CD3 proportion	High	3	33% (0.8 – 90.6)
	Low	3	67% (9.4 – 99.2)
Relative CD3 number	High	3	33% (0.8 – 90.6)
	Low	3	67% (9.4 – 99.2)

Supplementary Table 6. Survival analysis according to immunohistochemical characterization of the tumor immune microenvironment. N = number; CI95% = 95% confidence interval; ND = not done (subgroups with <5 patients).