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RESEARCH

Using *EGFR* amplification to stratify recurrent glioblastoma treated with immune checkpoint inhibitors

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Abstract

Purpose While immune checkpoint inhibitors (ICI) have had success with various malignancies, their efficacy in brain cancer is still unclear. Retrospective and prospective studies using PD-1 inhibitors for recurrent glioblastoma (GBM) have not established survival benefit. This study evaluated if ICI may be effective for select patients with recurrent GBM.

Methods This was a single-center retrospective study of adult patients diagnosed with first recurrence GBM and received pembrolizumab or nivolumab with or without concurrent bevacizumab. Archival tissue was used for immunohistochemistry (IHC) and targeted DNA next-generation sequencing (NGS) analysis.

Results Median overall survival (mOS) from initial diagnosis was 24.5 months (range 10–42). mOS from onset of ICI was 10 months (range 1–31) with 75% surviving > 6 months and 46% > 12 months. Additional IHC analysis on tumors from eight patients demonstrated a trend of longer survival after ICI for those with elevated PD-L1 expression. NGS of samples from 15 patients identified *EGFR* amplification at initial diagnosis and at any time point to be associated with worse survival after ICI (HR 12.2, 95% CI 1.37–108, $p = 0.025$ and HR 3.92, 95% CI 1.03–14.9, $p = 0.045$, respectively). This significance was corroborated with previously tested *EGFR* amplification via in situ hybridization.

Conclusion ICI did not extend overall survival for recurrent GBM. However, molecular sequencing identified *EGFR* amplification as associated with worse survival. Prospective studies can validate if *EGFR* amplification is a biomarker of ICI resistance and determine if its use can stratify responders from non-responders.

Keywords *EGFR* amplification · Next-generation sequencing · Nivolumab · Pembrolizumab · Recurrent glioblastoma

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Introduction

Despite standard of care treatment, the survival of patients with glioblastoma (GBM) remains poor with limited therapeutic options in the recurrent setting. A current benchmark for recurrent GBM mOS is 9.2 months for patients treated with bevacizumab monotherapy [1]. ICI, such as PD-1 inhibitors, have seen clinical efficacy in various cancers including advanced melanoma [2]. Based on results with other malignancies, ICI might be a therapeutic option for GBM. Initial trials of ICI in GBM patients have shown good tolerability [3]. However, studies examining PD-1 inhibitor treatment of recurrent high-grade gliomas and GBMs have demonstrated no survival benefit or similar survival results to bevacizumab monotherapy [4–8]. A phase 3 clinical trial for recurrent GBM, Checkmate 143, treated patients with either nivolumab or bevacizumab, and found no significant difference in overall survival between the nivolumab group (9.8 mOS) and bevacizumab group (10.0 mOS) [7]. Similarly, a recent randomized phase 2 trial comparing pembrolizumab + / − bevacizumab for recurrent GBM concluded no survival benefit of pembrolizumab monotherapy or in combination with bevacizumab compared to historical monotherapy bevacizumab treatment [8]. Nonetheless, there is still thought that ICI may be an effective therapeutic option for select patients, as evidenced by a small study examining neoadjuvant ICI for recurrent GBM [9]. Due to the lack of efficacious treatment options and well-tolerated nature of ICI, we treated a group of patients with recurrent GBM with either pembrolizumab or nivolumab with or without bevacizumab. This retrospective review evaluates this subset of patients, determining survival and analyzing pathological and molecular markers that could influence survival and treatment outcomes.

Methods

Study population

This study is an Icahn School of Medicine at Mount Sinai Institutional Review Board approved single-center observation retrospective study conducted with a waiver of consent at Mount Sinai Hospital, New York. We retrospectively evaluated patients with recurrent GBM treated with ICI of pembrolizumab or nivolumab with the addition of bevacizumab. These were consecutive patients with no apparent risks of treating with ICI for whom the treating physicians thought ICI was a reasonable option. To comply with the WHO 2021 classification of GBM, we excluded two patients with IDH mutant GBM. We included in our analysis patients who had pathology of IDH wildtype GBM, were treated with initial standard of care therapy as per Stupp protocol, had the first recurrence with radiographic progression of their GBM, at least 18 years of age, and who received at least 2 cycles of either pembrolizumab or nivolumab between July 2014 and February 2019, after diagnosis of recurrent GBM. Patients were treated with nivolumab 240 mg every 2 weeks or pembrolizumab 200 mg every 3 weeks. Bevacizumab was dosed at either 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks. Toxicity was assessed retrospectively according to the Common Terminology Criteria for Adverse Events 4.03.

Pathology

Tumor characteristics, including basic histology and immunohistochemical (IHC) markers, were collected through chart review. Additional IHC testing was performed on archival tissue from both initial and recurrent samples assessing the percentage and distribution of CD3, CD8, CD20, CD163, PD-L1 expressing cells, and Ki-67 to determine cell proliferation. EGFR and chromosome 7 were routinely evaluated using the FDA-approved Ventana UltraView silver-enhanced in situ hybridization (SISH) and red ISH DNP Detection kits with EGFR and CEP7 ISH DNA probes. Molecular sequencing was performed internally at Icahn School of Medicine at Mount Sinai on the Ion Torrent platform using DNA from archival tissue from both initial and recurrent samples with a validated commercially available Oncomine™ Comprehensive Assay v3M panel. The cohort of Samstein et al. was utilized as a comparative data source for molecular sequencing on glioma patients treated with immunotherapy [10]. Briefly, this was a multi-cancer cohort of immunotherapy-treated patients, including 82 with GBM who also had next-generation sequencing of their tumors.

Statistical analysis

Kaplan–Meier survival curves accessible in the supplementary section were created using GraphPad Prism version 9.4.0. The date of death was obtained through either chart review of medical records, family notification to treating physician, or search of available public records. Genomic correlates of overall survival after PD-1 blockade were analyzed by univariable Cox proportional hazards models. Since there were some differences in genomic findings between initial biopsy and biopsy at recurrence, we conducted the regression analysis three ways: using genomic alterations found at any time, at initial biopsy (only among those with sequencing at initial biopsy), and at recurrence (only among those with sequencing at

recurrence). Genomic correlates of overall survival after immunotherapy in the Samstein et al. cohort were analyzed using univariable and multivariable Cox proportional hazards models [10]. Multivariable models were adjusted for age, sex, tumor mutation burden, and immune checkpoint inhibitor class. A two-sided *p* value of less than 0.05 was considered statistically significant. All analyses were conducted in R 4.0.0.

Results

Twenty-four patients with a diagnosis of IDH wildtype GBM who received either pembrolizumab or nivolumab were reviewed through electronic medical records. Full patient characteristics are noted in Table 1.

The median age was 62 years (range 36–78) with 14 men (58%) and 10 women (42%). The median initial Karnofsky Performance Status prior to initiation of ICI was 70 (range 60–100). For initial surgical treatment of the 24 patients, 10 (42%) had gross total resections and 10 (42%) had subtotal resections. Eight patients (33%) had tumors with MGMT promoter methylated, 15 (63%) unmethylated and one (4%) was indeterminate. The indeterminate tumor on subsequent resection after initiation of ICI was determined to be MGMT methylated. Five patients (21%) did not receive adjuvant temozolomide after concurrent radiation and chemotherapy due to either severe side effect of temozolomide or progression of disease. Eight patients (33%) had a second surgical resection due to recurrence prior to initiation of PD-1 inhibitor. Nine patients (38%) received a second radiation treatment within two months of starting ICI with six of those patients receiving re-irradiation within one month of ICI. Seventeen patients (71%) were treated with nivolumab and seven patients (29%) with pembrolizumab. The entire cohort received a median of 10 cycles (range 4–31) of ICI. Twenty-two patients (92%) were treated concurrently with a median number of six cycles (range 1–26) of bevacizumab. Six patients (25%) received corticosteroids prior to initiation of ICI and 10 (42%) during ICI treatment either for increased cerebral edema or ICI adverse effects.

Table 1 Patients and tumor characteristics

Median age	62 (range 36–78)
Sex	
Male	14 (58%)
Female	10 (42%)
Ethnicity	
White	13 (54%)
African-American	3 (13%)
Hispanic	3 (13%)
Asian	1 (4%)
Other	4 (17%)
Median KPS prior to ICI	70 (range 60–100)
Initial Resection Type	
Gross Total	10 (42%)
Subtotal	10 (42%)
None	2 (8%)
Unknown	2 (8%)
MGMT Promotor Methylation	
Methylated	8 (33%)
Unmethylated	15 (63%)
Indeterminate	1 (4%)
Initial Radiotherapy/TMZ regimen	
6 weeks RT/TMZ	22* (88%)
3 weeks RT/TMZ	2 (8%)
Treated with adjuvant TMZ	
Adjuvant TMZ	19 (79%)
No adjuvant TMZ	5 (21%)
Median adjuvant cycles TMZ	3 (range 1–14)
Patients with second resection prior to ICI	8 (33%)
Patients with re-RT	
Less than 2 months prior to ICI	9 (38%)
During ICI	5 (21%)
Type of ICI Treatment	
Nivolumab	17 (71%)
Pembrolizumab	7 (29%)
Median Cycles ICI	10 (range 4–31)
Corticosteroid use	
At onset of ICI	6 (25%)
Started during ICI	10 (42%)
None prior to or during ICI	8 (33%)
Patients receiving concurrent bevacizumab	22 (92%)
Median concurrent bevacizumab cycles	6 (1–26)

ICI Immune checkpoint inhibitor, *KPS* Karnofsky Performance Status, *RT* radiation therapy, *TMZ* temozolomide

*One patient treatment was interrupted at 4 weeks due to severe thrombocytopenia and subsequently developed myelodysplastic syndrome

Toxicity

Overall, treatment was well tolerated. A total of nine patients (38%) had ten documented immune-related adverse events (IRAE) ranging from Grade I to Grade III as listed in supplementary section table: three grade I, four grade II and three grade III. A patient with pneumonitis required cessation of ICI.

Survival analysis

The mOS for the total cohort from initial diagnosis was 24.5 months (range 10–42). The eight patients with MGMT

methylated tumors had a mOS of 26.5 months (range 19–42) compared to a mOS of 22 months (range 10–34) for the 15 patients with MGMT unmethylated. The patient that had undetermined MGMT methylation status at initial resection with MGMT methylated at subsequent resection had an overall survival of 34 months. The mOS for all patients from onset of ICI was 10 months (range 1–31), with 18 patients (75%) surviving > 6 months and 11 patients (46%) surviving > 12 months.

Molecular analysis

IHC testing to assess proliferation index and the percentage and distribution of immunological markers from initial and recurrent tumor tissue was done on samples from eight of the 24 patients (Table 2).

NGS assessment using targeted DNA sequencing of the initial diagnostic and recurrent tumor tissue was performed on archival samples of 15 patients (Table 3).

In eleven patients with NGS on an initial biopsy, *EGFR* amplification was observed in five samples and associated with worse overall survival (HR 12.2, 95% CI 1.37–108, $p = 0.025$) (Fig. 1).

Among patients with sequencing at any time ($N = 15$), *EGFR* amplification was also associated with worse outcomes ($N = 5$, HR 3.92, 95% CI 1.03–14.9, $p = 0.045$). There were no other statistically significant genomic correlates of immunotherapy outcomes. However, some other notable but nonsignificant findings included *TERT* mutations at recurrence ($N = 6$, 3.91, 95% CI 0.76–20.1, $p = 0.1$) and TP53 mutations at initial biopsy/resection ($N = 3$, HR 0.182, 95% CI 0.0219–1.52, $p = 0.12$). We compared our data with the publicly available 82 immunotherapy-treated GBM patients in the dataset of Samstein et al. [10]. In univariable analyses, *EGFR*vIII mutations were significantly associated with worse OS (HR 1.81, 95% CI 1.13–2.89, $p = 0.01$), though this was no longer significant after adjusting for age, sex, tumor mutation burden, and immunotherapy class (HR 1.47, 95% CI 0.92–2.35, $p = 0.11$). In additional multivariable analyses, *IDH1* ($N = 6$) and *FAT1* ($N = 4$) mutations were associated with better (HR 0.15, 05% CI 0.03–0.80, $p = 0.03$) and worse outcomes (HR 12.0, 95% CI 1.66–85.8, $p = 0.013$), respectively.

With our NGS data indicating *EGFR* amplification was associated with worse survival for patients treated with ICI, we further evaluated the EGFR status in our cohort by reviewing previous pathology results from in situ hybridization of EGFR and chromosome 7. Using in situ hybridization, 19 tumors were tested for *EGFR* amplification at initial diagnosis: 11 (58%) were *EGFR* amplified

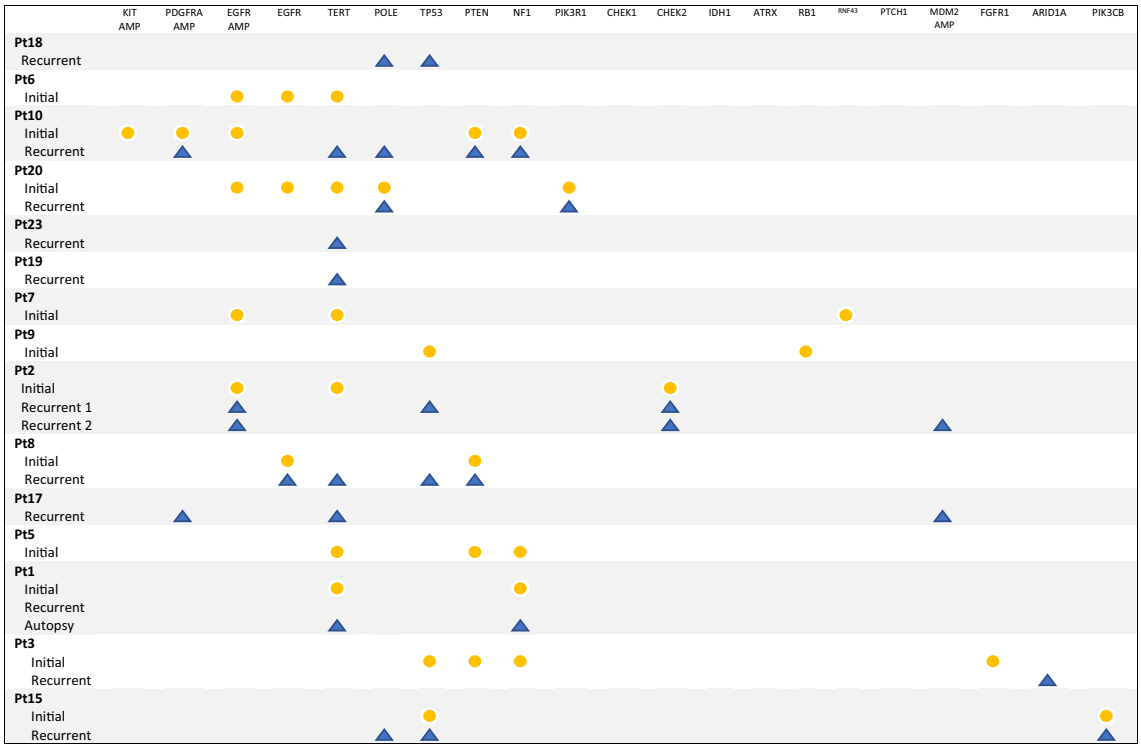
Table 2 Immunohistochemical analysis of tumors from patients treated with immune checkpoint inhibitor

	Survival Post PD1 (months)	CD3%	Dist	CD8%	Dist	CD20%	Dist	CD163%	Dist	PDL1%	Dist	MIB-1%	Dist
Pt20	5	1	PV	1	PV	0	NA	40	F	4–5	F	50	NA
Initial		10–20	TB	5–10	NA	2–3	NA	20	MAC	30–40	F	NA	NA
Recurrent													
Pt10	5	2–3	TB	1	TB	0	NA	60	F	1	TB	40–50	F
Initial		2–3	TB	2–3	TB	0	NA	40–50	NA	1	TB	15–20	NA
Recurrent													
Pt23	9	2–3	PV	2–3	PV	0	NA	40	MAC	1	PV		
Initial													
Pt2	16	3–5	TB	4	TB	3–4	PV	60–70	F, P	< 1	F		
Recurrent													
Pt8	17	4–5	PV	2	PV	6–7	PV	10–15	MAC	2–3	S	40–50	NA
Initial												40	NA
Recurrent													
Pt17	18	5	PV	5	PV	0	NA	20	MAC	5	F, P	10	F
Initial												30–40	F
Recurrent													
Pt1	19	2–3	PV	2	PV	< 1	PV	20	P	20	NA	40	NA
Initial		2–3	S	2–3	S	0	NA	10–20	NA	5–10	F	10	NA
Recurrent													
Pt15	31	5–10	PV	3	PV	1–2	PV	50–60	TB	20	D	60–70	F
Initial		3–5	PV	3	PV	0	NA	50–60	NA	40	NA	10–20	F
Recurrent													

Dist. distribution, *PV* perivascular, *MAC* macrophage, *F* focal, *P* periphery, *TB* tumor bed, *D* diffuse, *S* scattered, *NA* not applicable

Each column represents a specific immunological marker and the adjacent column represents the specific distribution (if any) of that particular marker. Patients are listed in ascending order of survival from start of PD-1 inhibitor

Table 3 Genomic profile of tumors from diagnosis and recurrence



Yellow circles—a mutation or amplification found in tissue from initial diagnosis. Blue triangles—a mutation or amplification found in tissue from recurrent disease

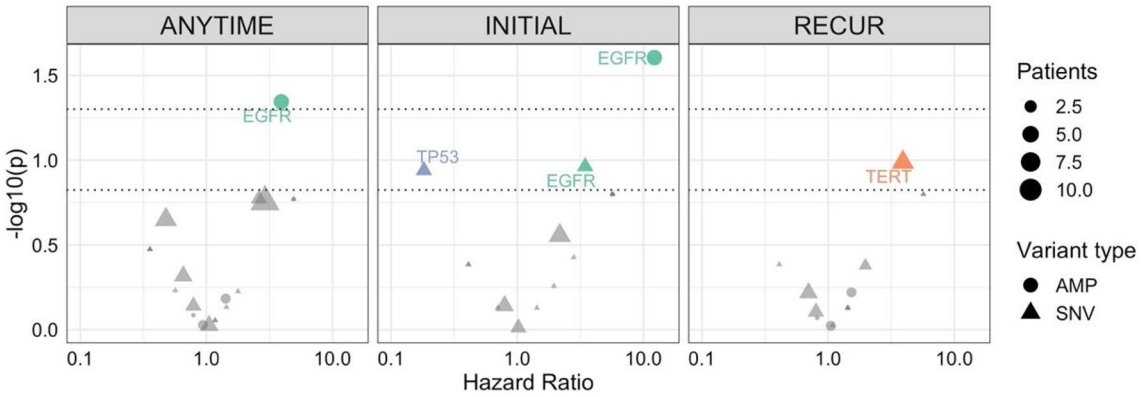


Fig. 1 Cox regression analysis of molecular mutations or amplifications found in tumor samples from 15 patients in the cohort. Three analyses were performed for mutations or amplifications found at any time point, at initial diagnosis only, or at recurrence only. Dotted lines represent $p < 0.05$ and $p < 0.15$ significance thresholds. Shapes correspond to amplifications (circles) or single nucleotide variants (triangles), with size corresponding to number of patients with the alteration. Hazard ratios greater than 1 represent an increased risk of death. AMP amplification, SNV single nucleotide variant

compared to 8 (42%) that were not. Median overall survival from initial diagnosis for patients with tumors with *EGFR* amplified was 24 months (range 11–42) and for those with tumors not amplified was 23.5 months (range 10–34). However, mOS after initiation of PD-1 therapy was 8 months (range 1–26) for patients with tumors with *EGFR* amplification compared to 14.5 months (range 6–31) for those without. Nine recurrent tumors were tested for *EGFR* amplification via in situ hybridization: 4 tumors (44%) were *EGFR* amplified, and 5 (56%) were not. After initiation of PD-1 inhibitor for recurrent disease tissue with *EGFR* amplification, the mOS was 7 months (range 5–16) compared to 18 months (range 9–25) for those without *EGFR* amplification.

Discussion

Here, we report a single-center retrospective study evaluating the clinical course, survival, and correlative tissue biomarkers of patients with recurrent GBM treated with ICI. Pembrolizumab and nivolumab were generally well tolerated and there was no ICI treatment-related fatality in any of our patients. Previous retrospective studies focused on ICI in GBM have included either a mixture of high-grade gliomas or a heavily pre-treated GBM population with multiple recurrences for a range of mOS from 4 to 6.5 months [4, 6, 11]. With a mOS of 10 months for all patients from onset of ICI, our cohort had similar survival to patients with recurrent GBM treated with bevacizumab monotherapy [1], prospective studies using ICI with or without bevacizumab [8, 12] and nivolumab combined with bevacizumab [7].

IHC analysis showed no correlation of survival from ICI onset with T or B cell infiltration, macrophage presence, or cell proliferation index. However, there was an observational trend with longer survival from start of PD-1 inhibitor and increased expression of PD-L1 in tumor samples; the three longest survivors post-ICI each had PD-L1 expression ≥ 5% (Table 2). Nonetheless, these observations are from a small collection of patients and should not be interpreted as significant. Previous research showed no correlation between PD-L1 expression and survival from ICI in GBM patients [8, 13]. Studies in other cancers such as melanoma have suggested that a more comprehensive immune profiling may be required to differentiate responders from non-responders [14]. In addition, a few case reports of GBM tumors responding to ICI harbor mismatch repair deficiency [15, 16].

Utilizing a commercially available targeted NGS panel, we found that *EGFR* amplification at initial diagnosis and at any time was significantly associated with worse survival for patients treated with ICI. As a comparative data set for GBMs treated with ICI, Samstein et al.'s cohort did not share any molecular alterations with our data set associated with significantly worse survival [10]. However, their study focused on mutational load and did not include *EGFR* amplification status. For significant associations found in regression analysis in our cohort and Samstein et al.'s, high hazard ratios are most likely due to small sample sizes. Supporting our NGS findings, our in situ hybridization of EGFR and chromosome 7 also identified *EGFR* amplification at either initial diagnosis or recurrent disease associated with worse survival after ICI treatment. *EGFR* alterations such as amplifications and mutations are common in GBM and potentially associated with a worse prognosis [17–19]. Therefore, our findings could result from tumors with *EGFR* amplification having worse survival regardless of specific treatment, including ICI. The role of *EGFR* mutations in resistance to ICI has been studied in other malignancies, particularly non-small cell lung cancer (NSCLC) [20]. Subgroup analysis of clinical trials investigating the utility of ICI in NSCLC demonstrated that tumors harboring *EGFR* mutations had significantly worse outcomes to ICI than tumors with *EGFR* wildtype genotypes [21–23]. Multiple studies have identified that *EGFR* mutations in NSCLC are associated with tumoral *T*-lymphocyte depletion and an immunosuppressive tumor microenvironment (TME) that may hinder ICI's therapeutic benefit [21, 24, 25]. While the precise mechanism of how EGFR overexpression results in ICI resistance is unknown, it has been proposed that EGFR upregulation leads to TGFβ activation and subsequent local immune suppression [24]. TGFβ is a well-known cytokine contributing to immunosuppression of the TME in GBM [26]. Therefore, we can hypothesize that in GBM, EGFR upregulation may lead to TGFβ activation. For lung adenocarcinoma, different *KRAS* mutations have been identified to confer ICI resistance by affecting the expression of tumor-infiltrating lymphocytes and promoting tumor evasion with induction of Tregs, secretion of TGFβ and IL-10, and upregulation of PD-L1 potentially via MEK/ERK signaling [27–29]. MYC-KRAS axis was identified in a group of GBM patients via mass spectrometry, and those tumors exhibited a more invasive, proliferative phenotype and increased resistance of cell lines with KRAS signature to therapy [30]. More common, however, in GBM are PI3K/AKT/mTOR pathway alterations occurring in approximately 89% of GBMs as reported in the Cancer Genome Atlas (TCGA) project and hyperactivity of the Ras/Raf/MAPK pathway from upregulation of upstream signals such as EGFR [31, 32]. Although a relative increase in MAPK pathway mutations (*PTPN11* and *BRAF*) has been found in responders, and *PTEN* mutations have also been associated with immunosuppression in non-responders [33]. Recently in patients with colon adenocarcinoma and multiple other cancers treated with ICI, mutations in the PI3K/AKT/mTOR pathway, another downstream signaling cascade triggered by EGFR activation, were associated with better survival and the concurrent presence of immune effector cells in the TME [34, 35]. Less is known regarding the crosstalk of upregulation of the PI3K/AKT/mTOR pathway and the immune cell composition of the TME in GBM. Nevertheless, preclinical work showed that GBM initiating-cells activate mTOR pathways in microglia, the tissue-resident macrophages of the brain, generating an immunosuppressive microglial phenotype that leads to negative regulation of T cells and subsequent immune escape and proliferation of tumor cells [17, 36]. It is important to note that *EGFR* mutations and amplifications have different biological characteristics, as

our study highlights amplification events. Interestingly, our report of a recurrent GBM ICI-responder with regional immunological heterogeneity uniformly lost focal amplifications and developed a new subclonal *EGFR* mutation at recurrence, accounting for the complexity and impact of tumor evolution on immunological and molecular heterogeneity [15]. EGFR variations, including focal amplification of *EGFR* and *EGFR*vIII mutation, have been identified in 57% of GBMs, and expression level of receptor tyrosine kinases such as EGFR can fluctuate over their disease course [37]. ICI trials in GBM may not have been successful partly due to the high frequency of EGFR alterations that may play a critical role in immune dysregulation and suppression. Future trials may benefit from a further subgroup analysis of molecular markers such as EGFR, especially with the 2021 WHO classification of CNS tumors integrating molecular markers to a greater extent into tumor characterization and grading [38]. Our study underscores the potential importance of molecularly profiling GBMs, as this heterogenous tumor may respond differently to therapies based on genetic makeup.

Our study has multiple limitations. First, it is a retrospective analysis, which resulted in omitting some standard metrics in treating patients with GBM and lacks a control group of patients not treated with ICI + / − bevacizumab. We did not include progression-free survival (PFS) analysis because standard radiographic criteria, such as Response Assessment in Neuro-Oncology, were not readily available for all patients. Of note, in a separate radiology retrospective study that evaluated some of these same patients, we demonstrated that an increase in the relative apparent diffusion coefficient may correlate with early treatment response of GBM patients to ICI and may represent a future biomarker [39]. Five patients did not start adjuvant temozolomide during the initial Stupp regimen, creating variability in the upfront treatment of the cohort; GBM is a very aggressive tumor, and it is not uncommon to find early progression shortly after first-line therapy requiring a change of the regimen. However, 4/5 (80%) underwent surgical biopsies confirming viable tumors to corroborate the clinical and radiographic progression. The remaining patient developed temozolomide-related myelodysplastic syndrome, a rare complication of temozolomide treatment, and could not undergo further tissue biopsy. However, she had a clear progression of disease based on clinical and radiographic features and disease course. We used bevacizumab to limit steroid use, with 75% of the patients not receiving steroids at the onset of ICI and 33% receiving them only when ICI was discontinued. There have been conflicting reports on the activity of bevacizumab in GBM [1, 40], and it is conceivable that it may affect outcomes in combination with ICI [41]. NGS and tissue biomarker analysis were only available for testing in a subset of the cohort due to patient's lack of available archival tissue. Moreover, we utilized a targeted NGS panel, limiting the scope of alterations able to be identified. Whole exome sequencing or whole genome sequencing would allow a more comprehensive analysis of potential significant amplifications and variants. In addition, this study is underpowered, and multivariate analysis cannot be performed with our small sample size.

The finding of EGFR amplification's potential impact on GBM survival with ICI is hypothesis-generating. A prospective analysis with stratification of EGFR with larger cohorts in multi-institutional trial settings should help clarify the subsets of tumors that do not profit from ICI and direct the therapy to the subset that will benefit. In conclusion, GBM immunotherapy responses may need systematic molecular analysis, which may uncover the tail of patients that appear to benefit from ICI.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00262-023-03381-y.

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Author contributions First author J.F. perform data acquisition, analysis, drafting of the paper. Lead author A.H., provide conception, design, analysis, interpretation and drafting, O.R. and N.T. immunohistochemical and molecular data acquisition and analysis; E.E., and R.S. next-generation sequencing acquisition, analysis and drafting of results; K.L.H. and T.J. genomic and statistical analysis and drafting of results; P.K., K.N. and P.B. radiological data acquisition and analysis.

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Data availability The data have been deposited to SRA under the accession PRJNA922203 in the NCBI BioProject database (https://www.ncbi.nlm.nih.gov/bioproject/).

Declarations

Conflict of interest JSF, OR, HKL, EE, PK, PB, KN, NT have nothing to disclose. TJ is employed by Sema4. RS is VP of Technology Development at Sema4. AH is on the advisory board of TargTex and is the recipient of grants from Novocure, EMD Serono (Merck KGaA), National Brain Tumor Society and Cancer Research Institute.

Ethical approval This study was approved by the Mount Sinai Hospital Institutional Review Board as a retrospective observational study that confirmed no ethical approval is required.

Consent for publication This study is not publishing any identifiable individual details such as images or videos which would require consent to publish.

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