IMMU-39 - Efficacy of immune checkpoint inhibitors in glioblastoma from real-world data analysis

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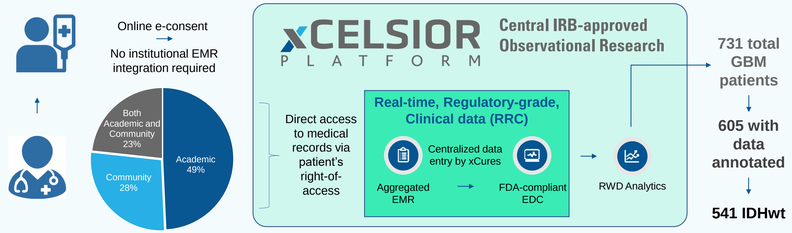
Abstract



Immune checkpoint inhibitors (ICIs) failed to show efficacy in a randomized trial in glioblastoma (GBM). We utilized the patient-led XCELSIOR platform (NCT03793088) to evaluate ICIs in real-world GBM treatment. XCELSIOR centralizes EMR data from all care sites, creating longitudinal, source-verified data. Identity verification permits accurate overall survival (OS) calculations. As of 10/1/2023, 731 GBM patients were enrolled in XCELSIOR with 605 patients with longitudinal data annotated of which 113 (19%) received ICIs: 77 received pembrolizumab (66%) and 33 received nivolumab (29%) including 11 with ipilimumab (10%). Three patients (3%) received atezolizumab. Key features in the ICI cohort were 37% methylated *MGMT* and 47% gross total resection. Median days from diagnosis to ICI initiation was 297 days with 17 patients treated at adjuvant setting, 19 at maintenance, and 54 at recurrence, and 23 at second recurrence or later. Notably, 79% of patients were treated with ICIs off-label, outside of clinical trials. A diversity of combination partners was observed, most commonly bevacizumab (58 patients), temozolomide (17), Optune (14), neoantigen peptide vaccines (10), lomustine (6), and lenvatinib (5). Across 113 patients, 52 unique combination regimens were employed. Among 541 patients with *IDH* wild-type disease used for survival analysis, 101 patients were treated with ICIs (19%) and 440 patients not treated with ICIs (No ICI). Median OS (mOS) from diagnosis for all ICI patients vs. No ICI with inverse propensity weighting was 26.7 months (95% CI 21.0 to 31.4) vs. 21.0 months (19.4 to 23.4, p = 0.02*). Analysis of patients treated at first recurrence with ICIs alone +/- bevacizumab vs. inverse propensity weighted patients without treatment with ICIs found mOS from start of ICI vs. start of lomustine to be non-significant (8.0 months vs. 8.5 months). However, comparison of patients treated at recurrence with ICIs alone (+/- bevacizumab) vs. patients with other combinations showed a numerical increase in mOS from start of ICI (14.8 months vs. 7.2 months, p=0.4). Next steps will focus on discrete combination regimens in this evolving data.

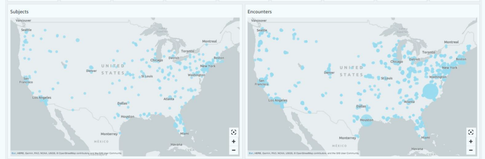
Summary of Real-World Dataset

As of October 1st, 2023:

605 GBM patients in XCELSIOR registry with longitudinal data available

113 (19%) Treated with immune checkpoint inhibitors (ICIs)

Subjects	Subjects with Records	Median Records per Patient	Conditions	Medications	Procedures	Observations	Encounters	Unique Locations
605	605	2,041	20,569	137,383	135,974	1,007,726	358,816	8,917



For Analysis

541 **IDH wild-type** GBM patients used for survival analysis

Features	All patients (n=605)	ICI (n=113)	no ICI (n=492)
	100%	19%	81%
Age at diagnosis			
Median [IQR]	54 [45-62]	52 [44-59]	55 [45-62]
Sex			
Male	65%	66%	65%
Female	35%	34%	35%
***IDH* status**			
Wild-type	89%	89%	89%
Mutant	11%	11%	11%
***MGMT* status**			
Methylated	28%	37%	26%
Unmethylated	54%	48%	56%
Unknown	18%	15%	18%
Extent of resection			
Total	42%	47%	41%
Partial	41%	39%	41%
None	17%	14%	18%
Care Sites			
Academic	49%	47%	50%
Community	28%	24%	29%
Both	23%	30%	21%

Results

Statistics of Immune Checkpoint Inhibitor (ICI) use among all 605 GBM patients:

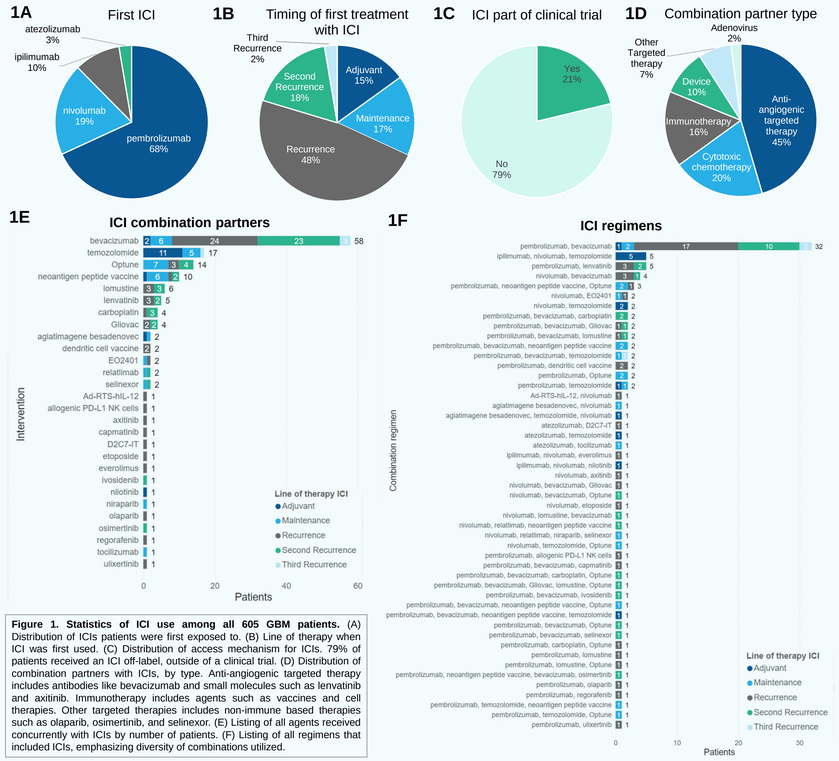
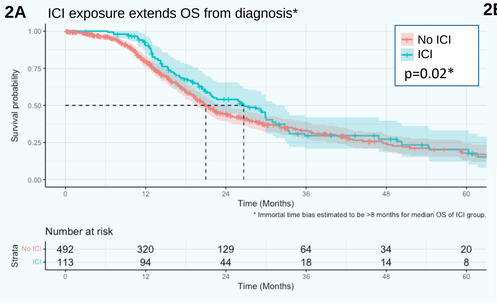


Figure 1. Statistics of ICI use among all 605 GBM patients. (A) Distribution of ICIs patients were first exposed to. (B) Line of therapy when ICI was first used. (C) Distribution of access mechanism for ICIs. 79% of patients received an ICI off-label, outside of a clinical trial. (D) Distribution of combination partners with ICIs, by type. Anti-angiogenic targeted therapy includes antibodies like bevacizumab and small molecules such as lenvatinib and axitinib. Immunotherapy includes agents such as vaccines and cell therapies. Other targeted therapies includes non-immune based therapies such as olaparib, osimertinib, and selinexor. (E) Listing of all agents received concurrently with ICIs by number of patients. (F) Listing of all regimens that included ICIs, emphasizing diversity of combinations utilized.

Top-line analysis of 541 IDH wild-type GBM patients:

2A ICI exposure extends OS from diagnosis*



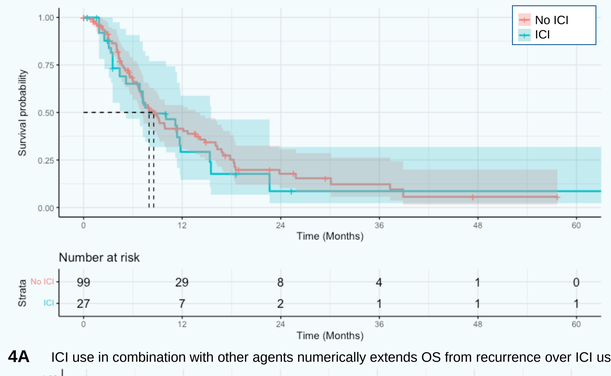
2B

	mOS	95% CI
No ICI	21.0 mo	[19.4 to 23.4]
ICI	26.7 mo	[21.0 to 31.4]

Figure 2. Analysis of ICI-treated patients. (A) Unstratified K-M curve of patients exposed to an ICI at any point in diagnosis vs. patients never exposed to an ICI. Overall survival (OS) is reported from diagnosis with inverse propensity score weighting. Importantly, this does not account for immortal time bias (patients must have lived long enough to be able to receive and ICI) or effects at recurrence (patients must have survived long enough to be treated with ICIs at recurrence (since close to ¾ of patients were treated with an ICI first at recurrence or later, see Figure 1B). (B) Table of results. mOS: median overall survival; 95% CI: 95% confidence interval; mo: months.

Sub-population analysis of 541 IDH wild-type GBM patients

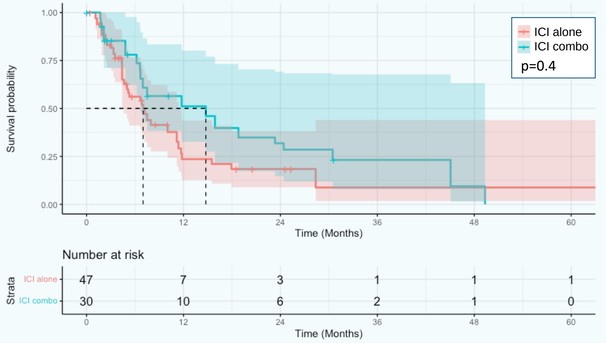
3A ICI use alone (+/- bevacizumab) at recurrence does not extend survival over lomustine



	mOS	95% CI
No ICI	8.5 mo	[7.1 to 14.2]
ICI	8.0 mo	[5.2 to 15.5]

Figure 3. Treatment with ICIs at recurrence as single agents does not extend OS. (A) K-M curve of OS from recurrence for patients exposed to an ICI as a single agent or in combination with bevacizumab at first recurrence (ICI) vs. inverse propensity weighted patients treated with lomustine at first recurrence (No ICI). Overall survival (OS) is reported from start of ICI or start of lomustine. mOS: median overall survival; 95% CI: 95% confidence interval; mo: months.

4A ICI use in combination with other agents numerically extends OS from recurrence over ICI use alone (+/- bevacizumab)



	mOS	95% CI
ICI alone	7.2 mo	[4.6 to 11.4]
ICI combo	14.8 mo	[6.7 to NR]

Figure 4. Treatment with ICIs at recurrence in combination regimens numerically extends survival vs. ICIs as single agents. (A) K-M curve for patients treated with an ICI in combinations other than solely bevacizumab at first, second, or third recurrence (ICI combo) vs. patients treated with an ICI alone or in combination with bevacizumab, but no other agents (ICI alone +/- bevacizumab). Overall survival (OS) is reported from start of ICI and is inverse propensity weighted. mOS: median overall survival; 95% CI: 95% confidence interval; mo: months; NR: Not reached.

Conclusions

- **xCures clinical research platform:** The master observational research protocol XCELSIOR permits generation of ***Real-time, Regulatory-grade, Clinical data (RRC)***. Electronic medical records (EMR) are automatically aggregated and structured from all sites of care for any patient in the US. Complete longitudinal clinical data is annotated from EMR, source-verified, and normalized to a standard data model. Data is available to academic and government researchers for no charge via partnership with xCures. Contact medical-affairs@xcures.com
- **Immune Checkpoint inhibitors (ICIs):**
  - ICIs are employed broadly by oncologists outside of clinical trials in the US in diverse combination regimens and at multiple lines of therapy during GBM treatment
  - Exposure to ICIs is associated with extended OS compared to patients not exposed to ICIs.
  - Treatment of patients at recurrence with ICIs alone or in combination with bevacizumab does not extend survival vs. an inverse-propensity-weighted control group
  - Treatment of patients at recurrence or beyond with ICIs in complex combination regimens beyond just bevacizumab may extend OS