INNV-37 - XCELSIOR: A real-time, real-world learning platform for patients with advanced cancer

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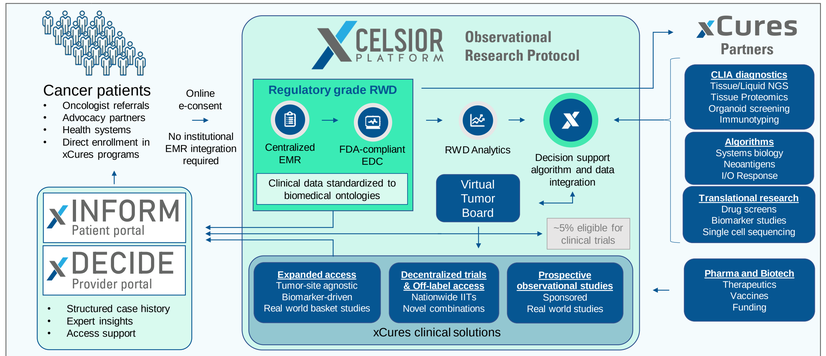
Abstract



xCures operates a direct-to-patient, real-world evidence platform for decentralized clinical research. The platform leverages a nationwide observational research protocol (XCELSIOR, NCT03793088) to aggregate, normalize, and analyze N-of-1 clinical outcomes to continuously learn from and inform treatment decisions. Individual data elements are extracted directly from medical documents such as clinic notes, and radiology, genomics, and pathology reports. The data elements are standardized to established biomedical ontologies and stored in a validated and part 11 compliant electronic database, suitable for statistical analyses and regulatory filings. This permits comparison of patient outcomes across institutions and removes the burden of data entry from oncologists and their staff. As an extremely efficient real-world data solution, we have utilized this platform to accelerate both academic- and commercial-sponsored clinical research, prospectively integrating diagnostics and algorithms with interventional treatments. For each patient that participates in XCELSIOR, artificial intelligence-powered clinical decision support algorithms suggest testing and treatment options. These options and supporting treatment rationales are sourced from key opinion leaders, tumor boards, clinical researchers, practicing oncologists, and published literature, and ranked using the real-world outcomes data from the registry. At the conference, we will present an overview of this real-time learning infrastructure and report on clinical case studies for pharma and non-profit groups including over 75 virtual tumor boards and real-world evidence generated from over 150 patients with CNS cancers that we have helped in partnership with Cancer Commons and The Musella Foundation for Brain Tumor Research and Education. Outcomes analyses stratified by therapeutic interventions and biomarkers will be reported, including frequency of adverse events, time to treatment failure, time to disease progression, and overall survival. Interventions include standard-of-care chemotherapies as well as therapies accessed by clinical trial, expanded access, and off-label prescription.

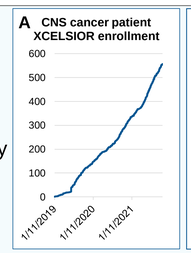
Summary of Real World Dataset

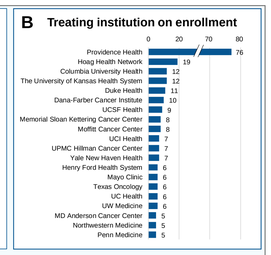
As of November 1st, 2021:

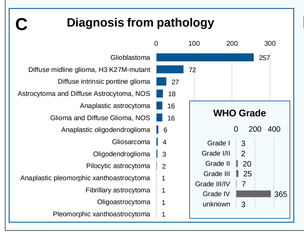
556 patients with CNS cancer within XCELSIOR registry

425 patients with primary CNS tumors with longitudinal history

1.1 years median follow up time from diagnosis
IQR = [0.57, 1.84]







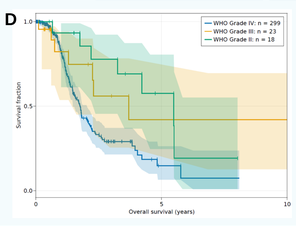
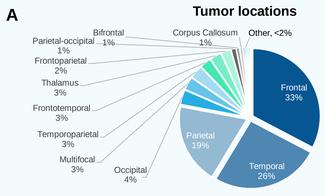


Figure 1. Summary of CNS real world dataset from XCELSIOR. As of 11/1/2021, a total of 556 patients with self-identified brain cancer have enrolled. Of 425 patients with primary CNS cancers, we have a median follow-up of 1.1 years from diagnosis. (A) CNS enrollment since study launch in 2019. (B) Treating institution where patients were receiving care at the time of enrollment. (C) Total counts of each diagnosis according to pathology for 425 primary CNS cancer patients. Inset, number of patients with the shown grades according to pathology or imaging or clinic notes if pathology is unavailable. (D) Survival plots across a subset of CNS patients with confirmed WHO grade II, III, or IV.

Results

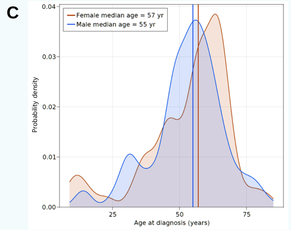
257 glioblastoma cases
248 primary
9 secondary



B

Predictor	LogHR	LogHR Std Error	HR	P-value
Received ICI	-0.31	0.13	0.73	0.016
Sex: male	-0.23	0.13	0.8	0.078
Age	0.55	0.14	1.74	<0.001
MGMT methylated	-0.35	0.15	0.7	0.018
ATRX loss[1]	0.39	0.13	1.48	0.003
EGFR alteration[2]	-0.1	0.13	0.91	0.448
IDH1 variant[3]	-0.17	0.14	0.84	0.209
H3F3A variant[4]	0.0	0.11	1.0	0.992

ICI, Immune Checkpoint Inhibitor (1) ATRX Loss includes negative detection of protein by IHC or presence of point mutations, frameshift mutations, or genomic deletion (2) EGFR alteration includes amplification, or point mutation (3) IDH1 variant is limited to point mutations at the R132 position (4) H3F3A variant includes point mutations only.



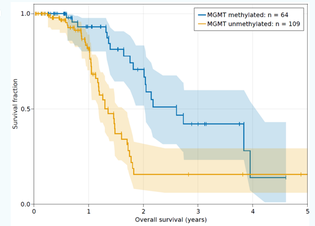
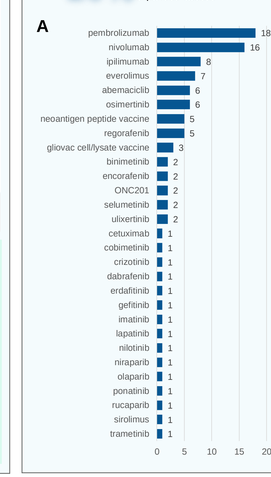
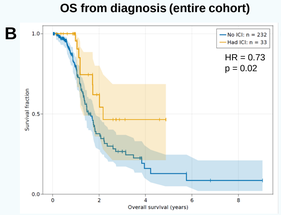


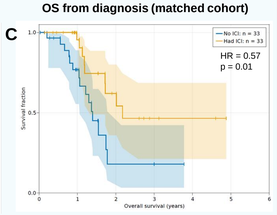
Figure 2. Topline analysis of glioblastoma cohort. (A) Tumor location breakdown of 257 patients diagnosed with glioblastoma. (B) Cox Proportional Hazards Regression analysis confirms increased hazard with age and decreased hazard with MGMT methylation. Treatment with an immune checkpoint inhibitor (ICI) is associated with a favorable OS - reduced hazard (see Figure 4B) – and ATRX loss is associated with increased hazard. (C) Median age of diagnosis is 55-57 years. (D) Kaplan-Meyer survival curve confirms MGMT methylation is associated with favorable overall survival. Censoring was done based on the date of last medical record entered in XCELSIOR.

~20% of glioblastoma patients received at least one therapy off-label or via expanded access



Immune Checkpoint Inhibitor (ICI; anti-PD1) cohort analysis



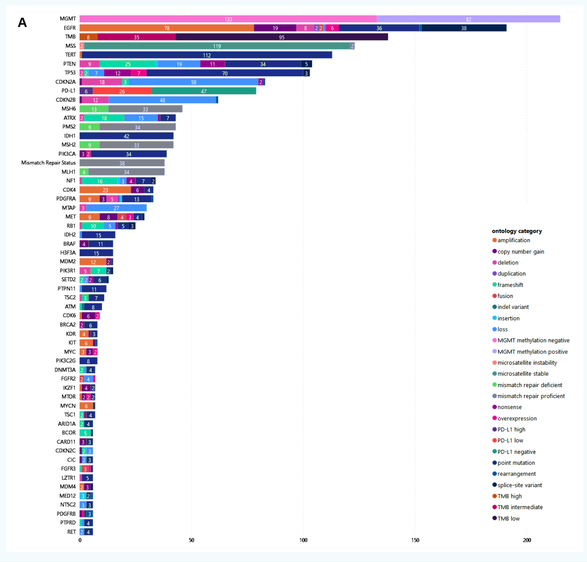


D

Matched cohorts	Received ICI (n=33)	No ICI (n=33)
2 year OS	61%	21%
Median age at diagnosis [range]	55 [10 to 77]	55 [28 to 76]
MGMT methylated	50%	52%
ATRX loss	24%	24%
Sex: male	68%	74%
Median days from diagnosis to start of ICI [range]	142 [-25 to 1708]	n/a
Median days on ICI [range]	58 [1 to 768]	n/a
PD-L1 positive	50% (8/16)	33% (3/9)
TMB high	9% (2/22)	6% (1/18)
TMB low	59% (13/22)	56% (10/18)
GTR on diagnosis	21%	12%
Treatment with other unapproved agents	55%	12%

Figure 4. Immune checkpoint inhibition is associated with increased overall survival. (A) Bar chart of glioblastoma patients treated with therapies accessed off-label or via expanded access indicates immune checkpoint inhibitors (ICIs) are the most commonly utilized off-label therapies. Cohorts of patients treated with targeted therapies continue to emerge. (B-C) Kaplan-Meyer survival curves for patients treated with anti-PD1 ICIs pembrolizumab or nivolumab vs. the overall population (B) or a matched control cohort (C) showing statistical significance in Cox Proportional Hazard regressions of real world data aggregated from across the country in XCELSIOR. (D) Table comparing key features of patients treated with ICIs and the matched control cohort utilized for analysis (panel C). As additional patients are enrolled, more complete patient feature matching can be done to better identify patients that could benefit from ICIs.

Biomarker counts across patients with glioblastoma



63% of glioblastoma patients had received NGS testing on enrollment

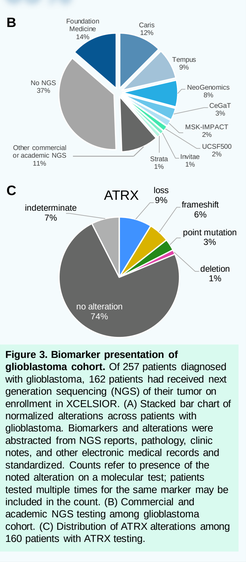


Figure 3. Biomarker presentation of glioblastoma cohort. Of 257 patients diagnosed with glioblastoma, 162 patients had received next generation sequencing (NGS) of their tumor on enrollment in XCELSIOR. (A) Stacked bar chart of normalized alterations across patients with glioblastoma. Biomarkers and alterations were abstracted from NGS reports, pathology, clinic notes, and other electronic medical records and standardized. Counts refer to presence of the noted alteration on a molecular test; patients tested multiple times for the same marker may be included in the count. (B) Commercial and academic NGS testing among glioblastoma cohort. (C) Distribution of ATRX alterations among 160 patients with ATRX testing.

114 Virtual tumor boards (VTBs)

182 Distinct options

1259 Unique rationales

1.4 months median follow up from date of tumor board

Of 27 patients with confirmed treatment, **44%** chose a VTB-supported option

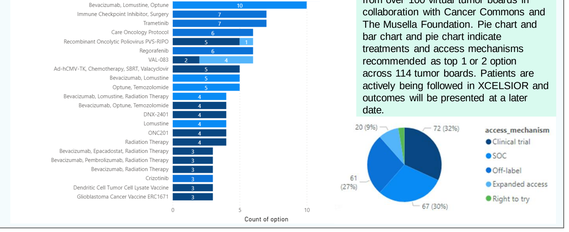


Figure 5. Summary of virtual tumor board (VTB) data. We aggregated data from over 100 virtual tumor boards in collaboration with Cancer Commons and The Musella Foundation. Pie chart and bar chart and pie chart indicate treatments and access mechanisms recommended as top 1 or 2 option across 114 tumor boards. Patients are actively being followed in XCELSIOR and outcomes will be presented at a later date.

Conclusions

XCELSIOR

- XCELSIOR is a master observational research protocol focused on aggregating real world data (RWD) on patients with advanced cancer.
- Clinical data elements are abstracted into an FDA-compliant EDC from EMR generated in standard practice of medicine – each data element is source-verified by electronic documents.
- XCELSIOR is a platform to be leveraged for patient/oncologist decision support and N-of-1 research.

xINFORM / xDECIDE

- Patients and their physicians access online portals (xINFORM, xDECIDE) to view a structured summary of their cancer history and a list of personalized treatment options.
- Treatment options are sourced from experts via virtual tumor boards run by xCures and partner advocacy groups and matched to patient characteristics and tumor features derived from structured real world data.
- Oncologists and their staff can create and account in xDECIDE to easily refer patients to XCELSIOR.

Real World Research

- XCELSIOR is a pan-cancer real-world registry and platform for N-of-1 research.
- Access to entire longitudinal EMR including clinic notes, lab reports, imaging reports, raw DICOMS, raw NGS data, and other diagnostic testing offers potential to answer multiple real-world research questions.
- Interventional protocols such as expanded access protocols, investigator-initiated trials, and diagnostic research protocols can also be supported by the XCELSIOR data collection framework.