

Surmounting Barriers
in **Non-resectable Recurrent
Glioblastoma** with a Single Treatment
of **Bizaxofusp**, an Engineered IL-4R
Directed Fusion Protein

7th Annual Glioblastoma Drug Development Summit
Fahar Merchant, PhD



MEDICENNA

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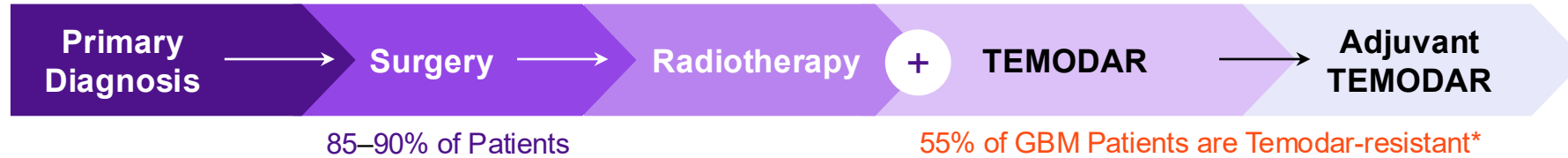
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Innovative Mechanism to Address Urgent Unmet Need in rGBM

- IL-4R-Targeted Immunotoxin: a Molecular Trojan Horse
- Phase 3-Ready Asset with Orphan & Fast Track Designations
- FDA-Endorsed Phase 3 Hybrid Trial Design

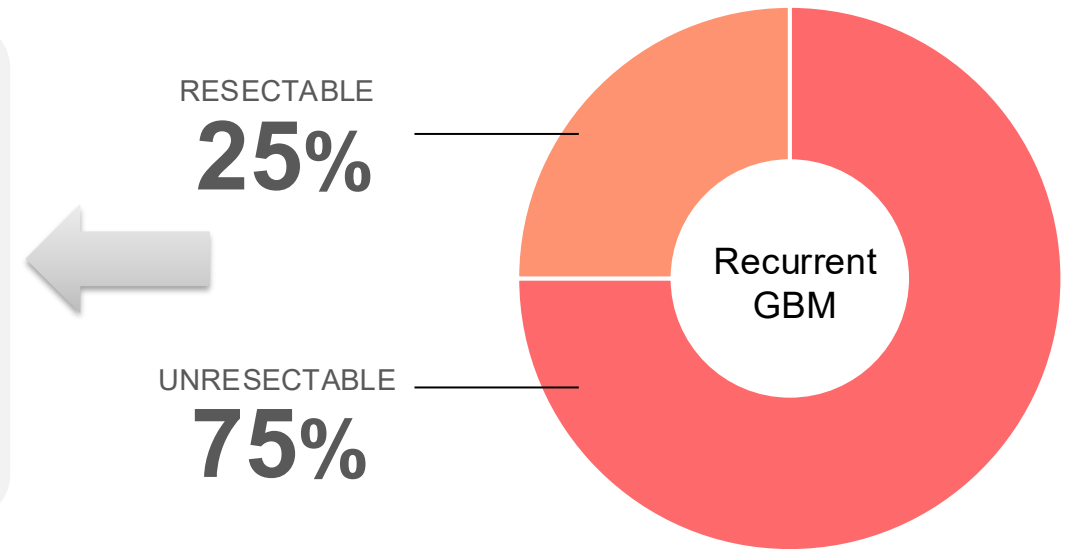
GBM Treatment Paradigm Has Not Changed in Decades and GBM Remains Uniformly Fatal

Patient Journey



100%
of Patients
RELAPSE

- 1 rGBMs are less surgically accessible
- 2 No defined standard of care for rGBM
- 3 Median overall survival (mOS) with approved therapies[†] is 7 months in unresectable IDH^{WT} rGBM (WHO definition)
- 4 2-year survival in rGBM is 5–10%

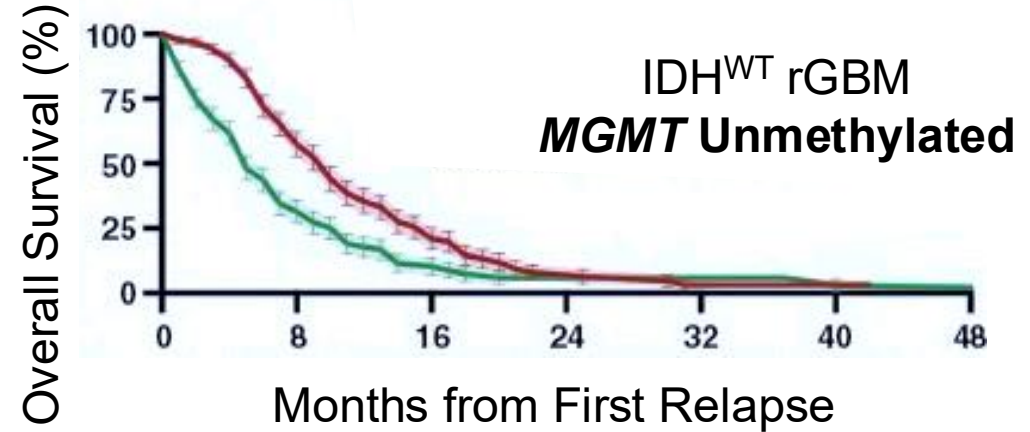
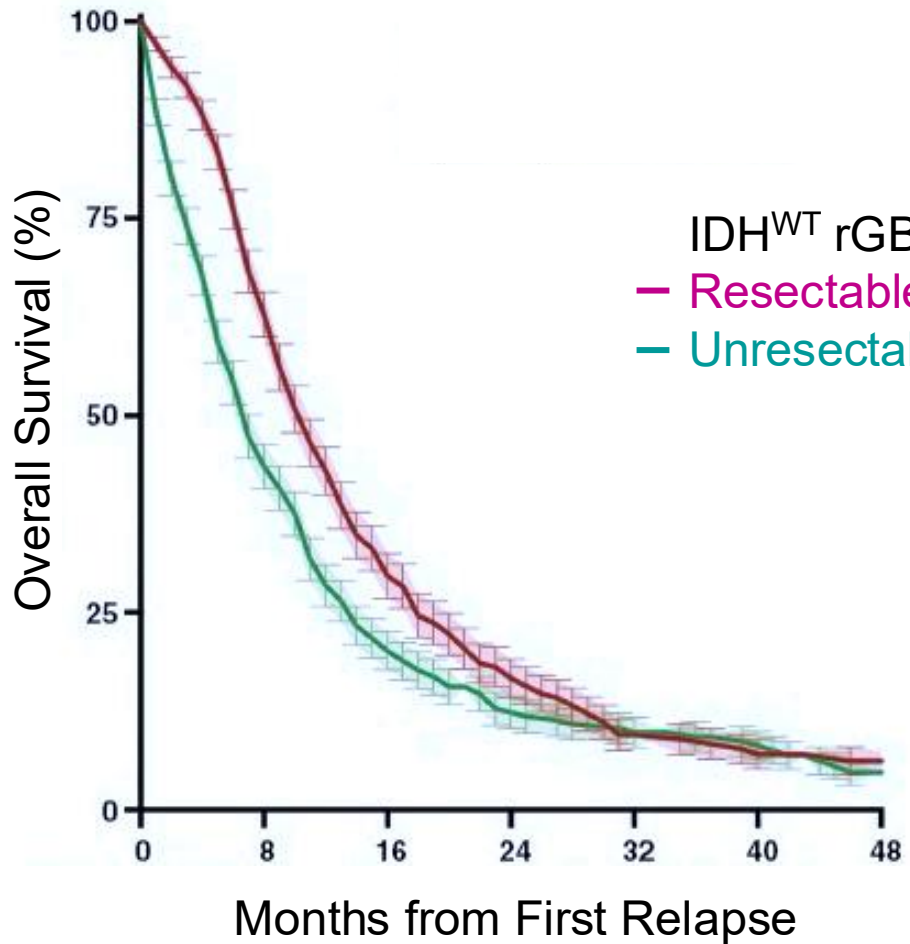


*Expression of the DNA repair protein O⁶-methylguanine-DNA methyltransferase (MGMT) is a key driver of Temodar resistance

[†]Avastin®, Lomustine, Gliadel®, Optune®, Temodar®, Radiotherapy

Unresectable rGBM has a Dismal Prognosis

Unresectable IDH^{WT} rGBM mOS is 7 months¹



	All IDH ^{WT} rGBM (n = 681)		MGMT Unmethylated (n = 257)	
	Resectable (n = 310)	Unresectable (n = 371)	Resectable (n = 122)	Unresectable (n = 135)
mOS (months)	11 ± 0.7	7 ± 0.5	10 ± 0.7	5 ± 0.5
	**p = 0.001		**p = 0.001	

Bizaxofusp: A Molecular Trojan Horse

Multi-action Targeted Immunotoxin

Bypasses BBB

Single intratumoral CED infusion **avoids systemic toxicity** while achieving tumor control

Targets IL-4R

Receptor is expressed in brain tumors and immunosuppressive, non-malignant TME, but not in healthy brain cells

Highly Selective

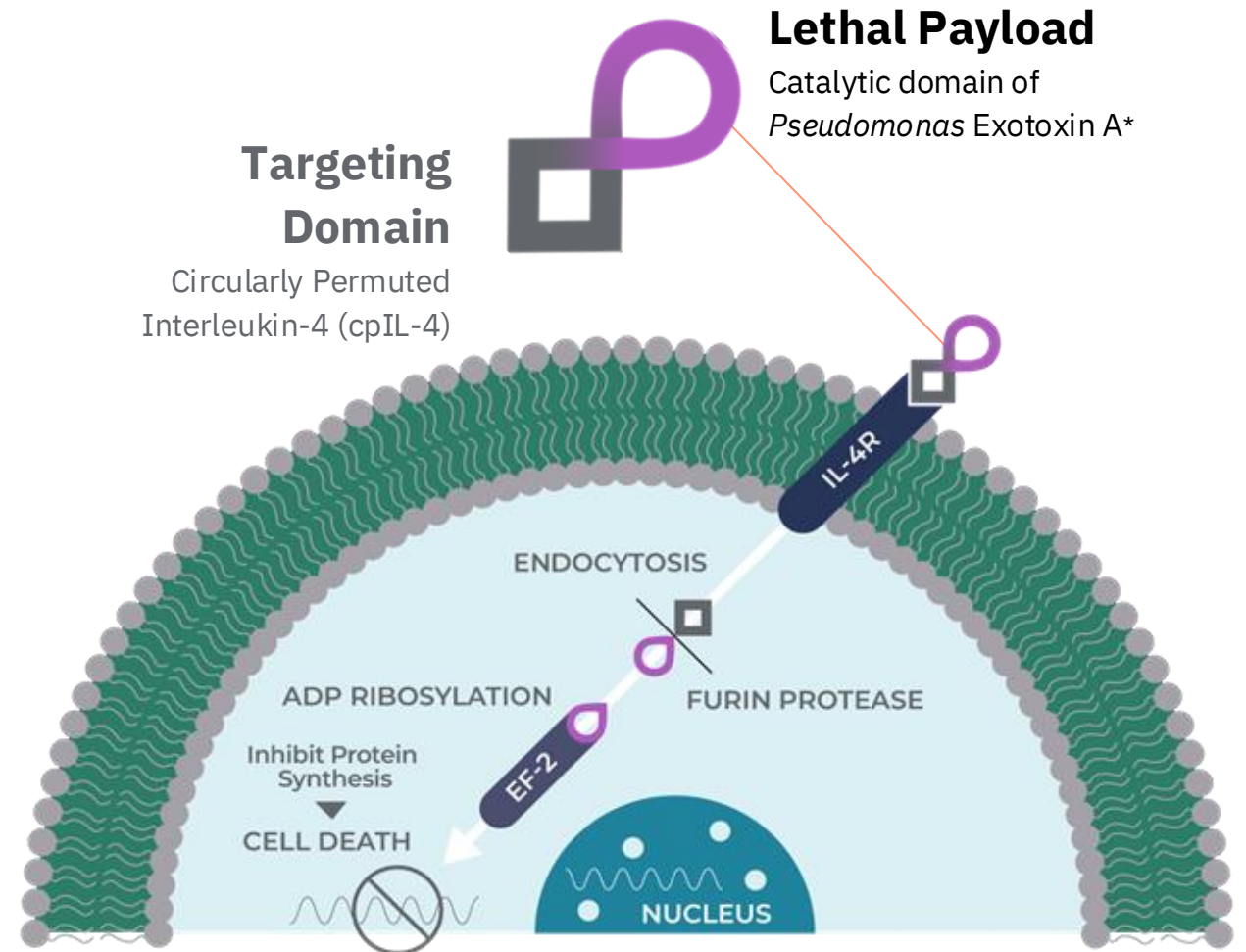
Avoids off-target toxicity

Disrupts the TME

Targets IL-4R positive MDSCs in GBM and unblinds the immunosuppressive TME

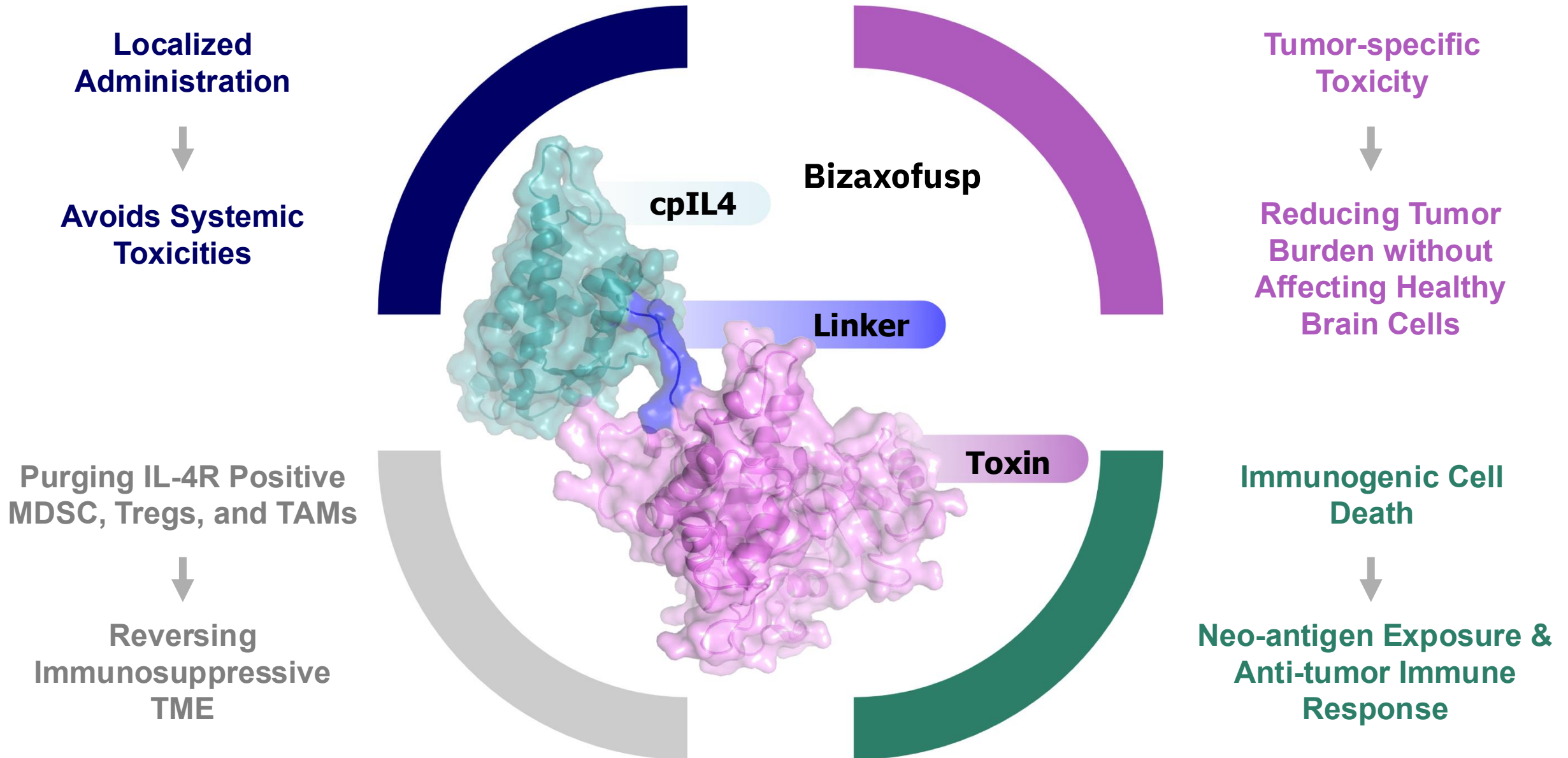
Causes Immunogenic Cell Death

Sustained anti-tumor immunity after clearance of bizaxofusp



***Bizaxofusp was designed to be only active intracellularly**

Bizaxofusp: Multi-Pronged Anti-Cancer Therapy

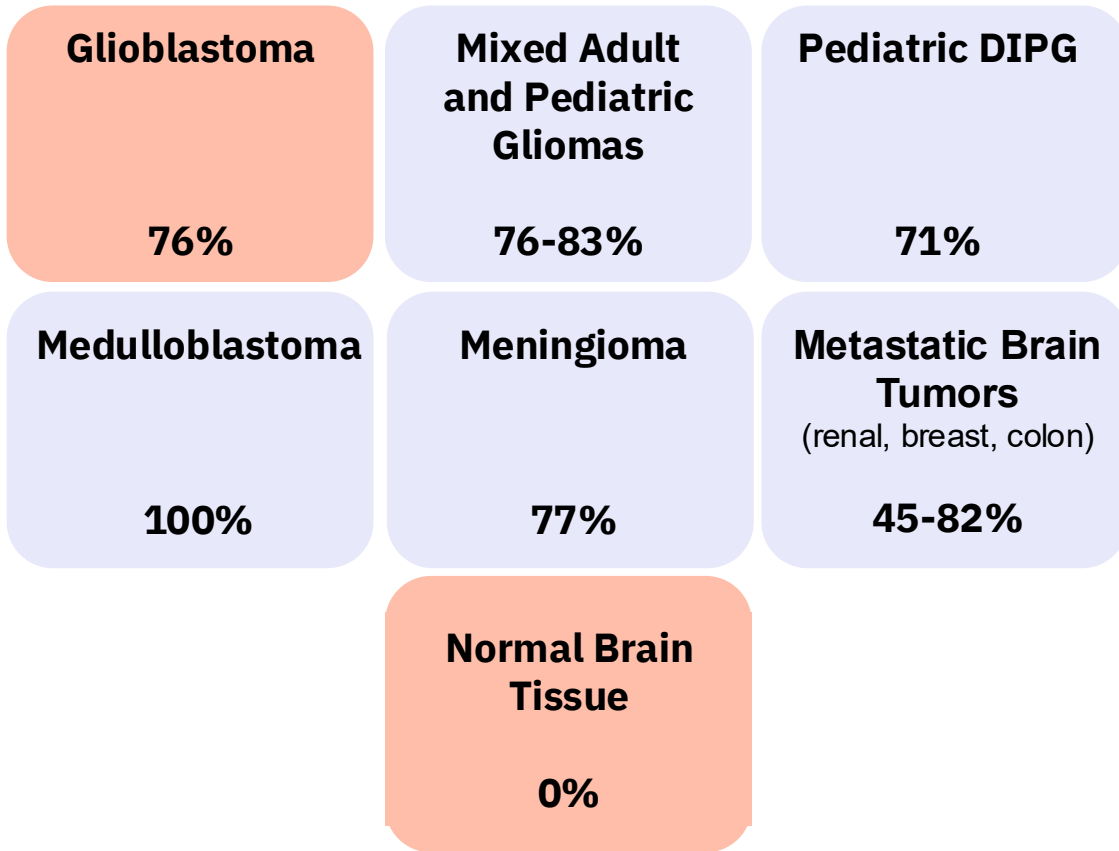


Bizaxofusp Selectively Kills Cancer Cells

CELL LINE	DESCRIPTION	IC ₅₀ (ng/mL)	SOURCE
Normal Cell Lines			
NT-2	Human Neuronal cell line	>1000	Joshi et al., 2001
NHA	Normal Brain astrocyte cell line	350	Joshi et al., 2001
HUAEC	Normal Human Umbilical Artery Endothelial Cells	>1000	Husain et al., 1997
HUVEC	Normal human umbilical vein endothelial cells	>1000	Joshi et al., 2015
U937	Promonocytic cells	>1000	Puri et al., 1996
H9	T cells, resting	>1000	Puri et al., 1996
Tumor Cell Lines			
(N/A)	Primary explant patient with GBM	4.5	Joshi et al., 2001
U251	GBM	6.5	Puri et al., 1996
T98G*	GBM	1.2	Puri et al., 1996
UW-228-3	Medulloblastoma	0.9	Joshi et al., 2002
HN12	Head and Neck Cancer	0.4	Kawakami et al., 2000
H322	NSCLC	2	Kawakami et al., 2002
MCF-7	Breast Cancer	0.6	Kreitman et al., 1995
HT-29*	Colon Cancer	0.4	Kreitman et al., 1995
RC2	Renal Cell	1.7	Kreitman et al., 1995
MIA-PaCa-2*	Pancreatic cancer	0.065	Shimamura et al., 2007
Cal62	Anaplastic thyroid carcinoma	10	Joshi et al., 2015

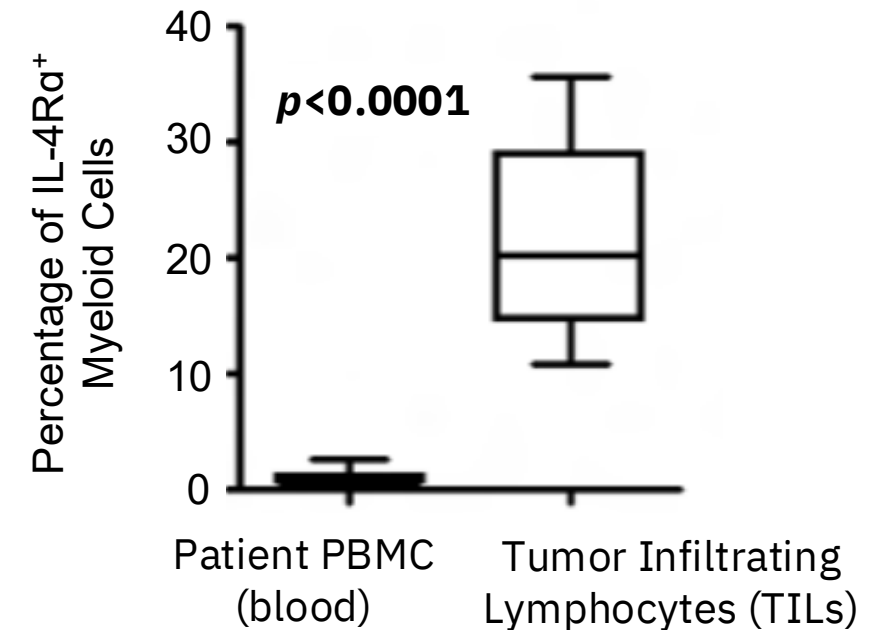
IL-4R is Selectively Overexpressed on GBM tumor cells and MDSCs within the TME, with Broad Relevance Across CNS Malignancies

IL-4R is Commonly Overexpressed in GBM & CNS Tumors



Human GBMs Contain Abundant IL-4R α^+ MDSCs

Immune suppressive MDSC constitutes ~50% of GBM tumor mass



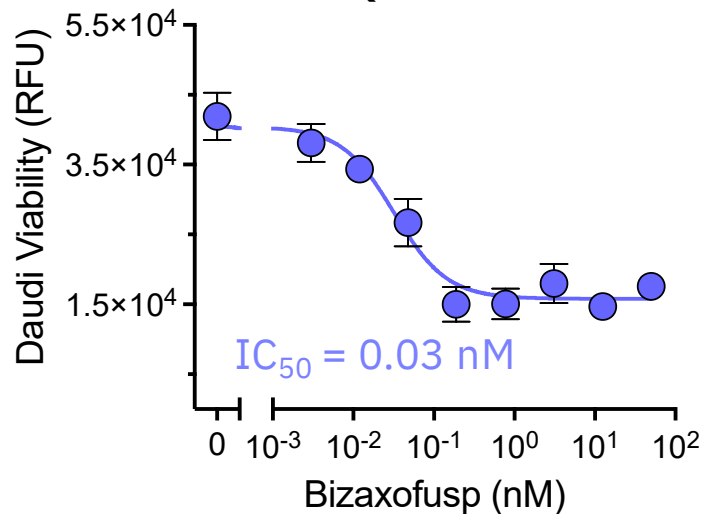
Analysis by flow cytometry based on CD14⁺HLA-DR⁻ cells

Kohanbash G et al. Cancer Res (2013)

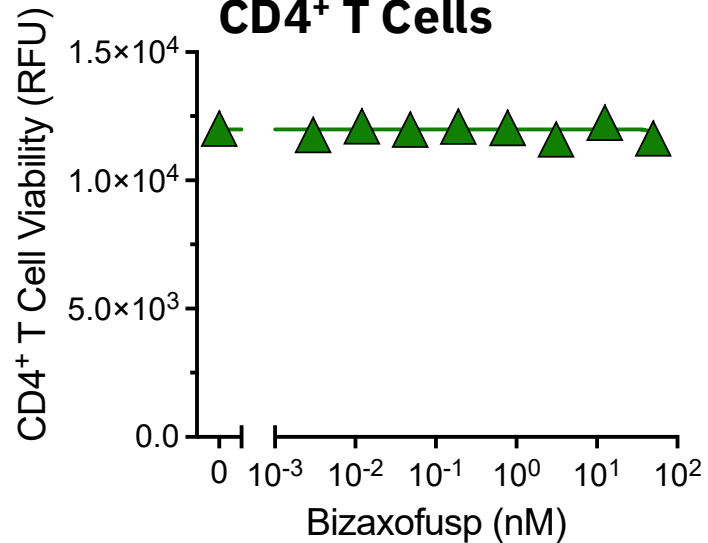
Joshi BH et al., Cancer Res (2001); Puri RK et al., Cancer Res (1996); Kawakami M et al., Cancer (2004); Berlow NE et al., PLoS One (2018); Joshi BH et al., British J of Cancer (2002); Chen L et al., Neurosci Lett. (2007); Puri S et al., Cancer (2005); Kang et al., Cancers (2019); Koller et al., Carcinogenesis (2010); Venmar et al., Mol Cellular Pathobiology (2014).

Bizaxofusp Selectively Kills Immunosuppressive Tregs

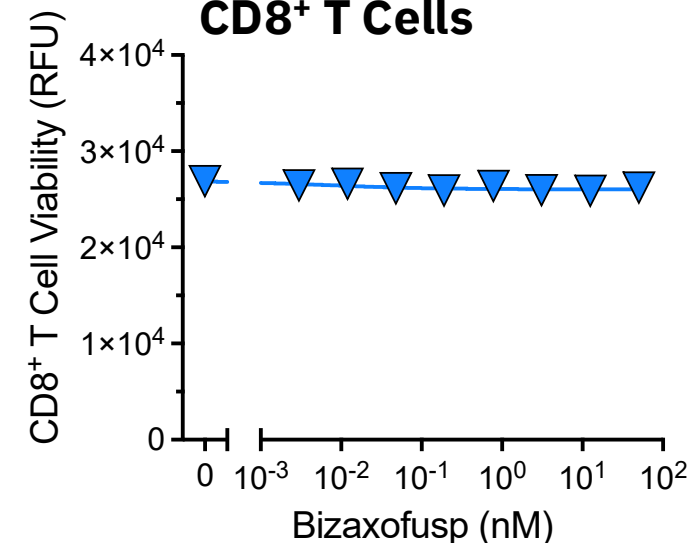
Daudi Cells (IL-4R α Positive Control)



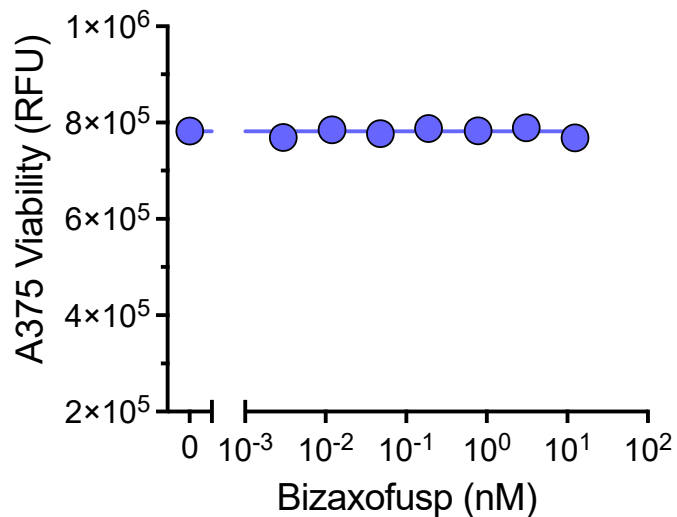
CD4⁺ T Cells



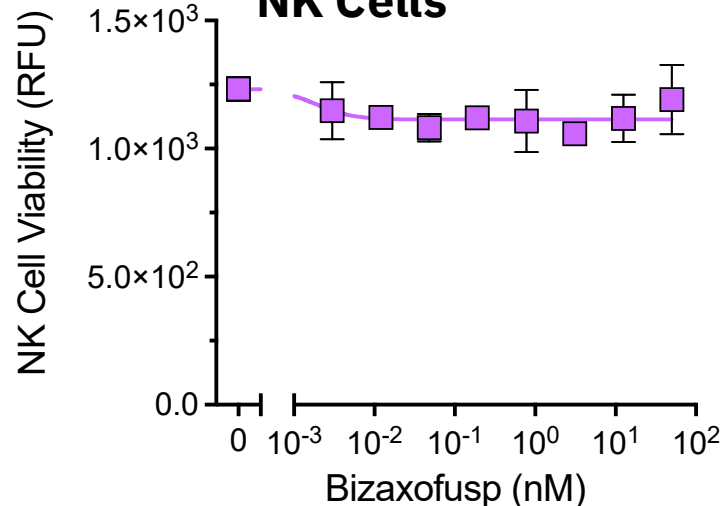
CD8⁺ T Cells



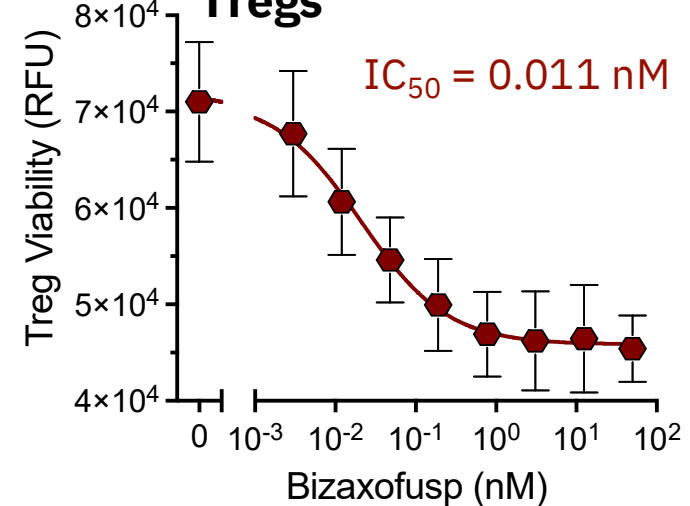
A375 Cells (IL-4R α Negative Control)



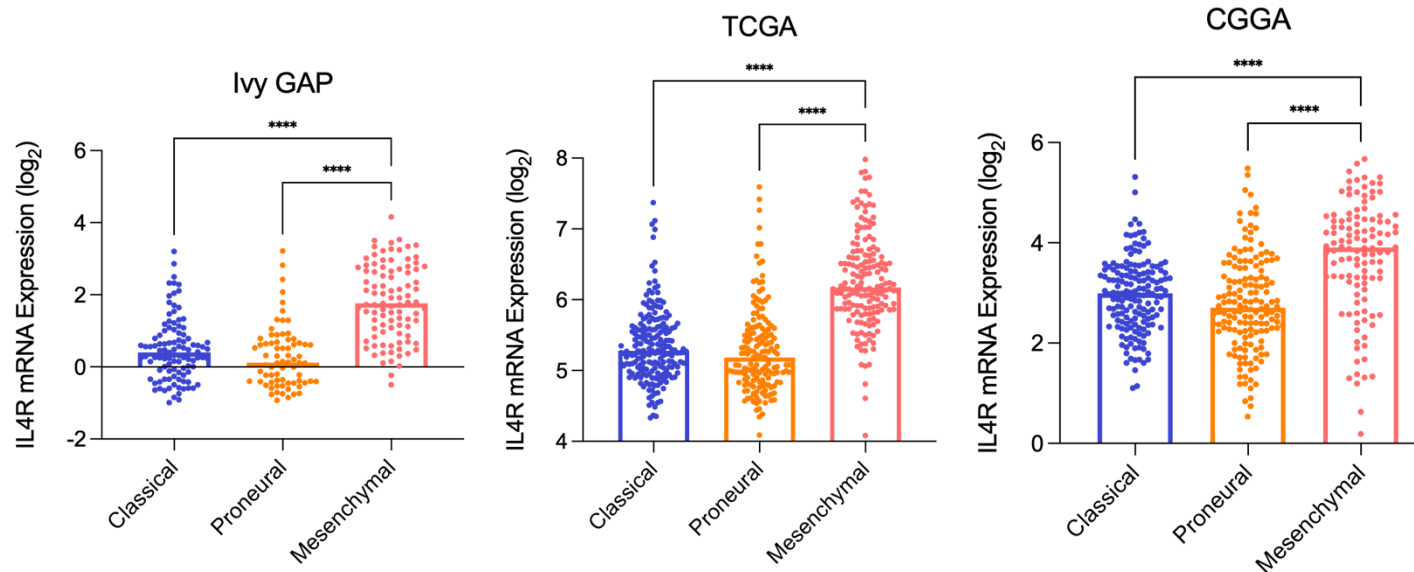
NK Cells



Tregs



rGBM is Enriched for Mesenchymal Transcriptional Programs, which are Associated with Increased IL-4R Expression



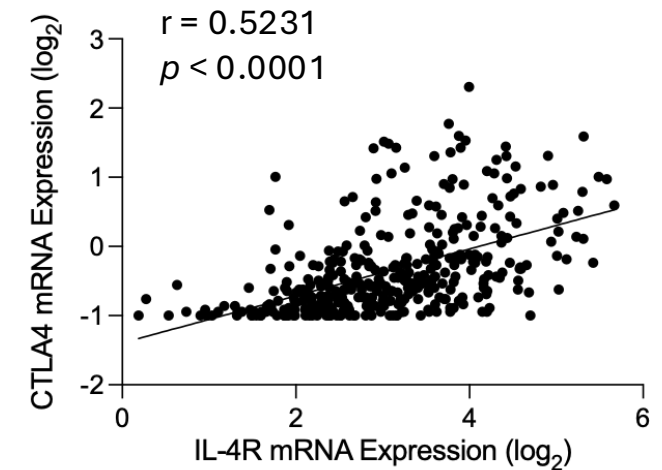
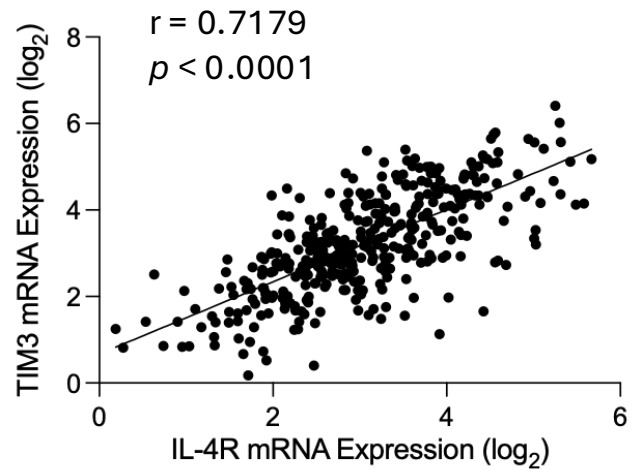
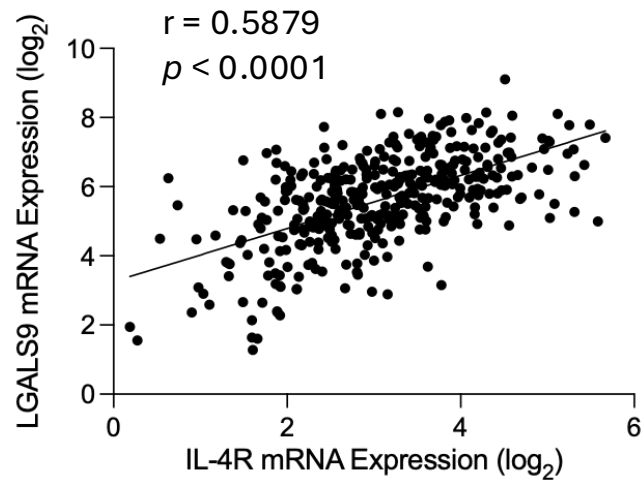
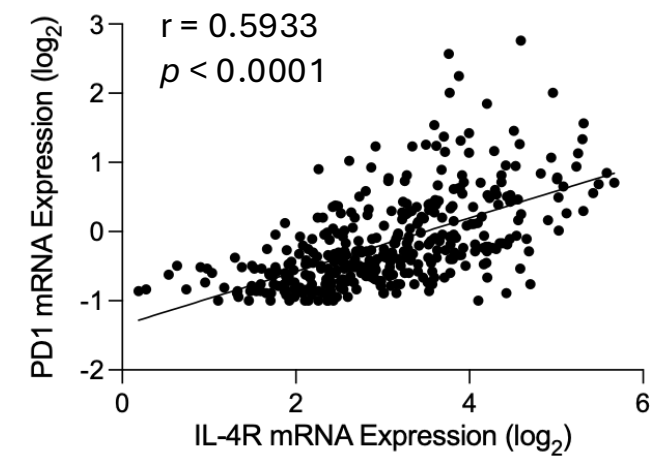
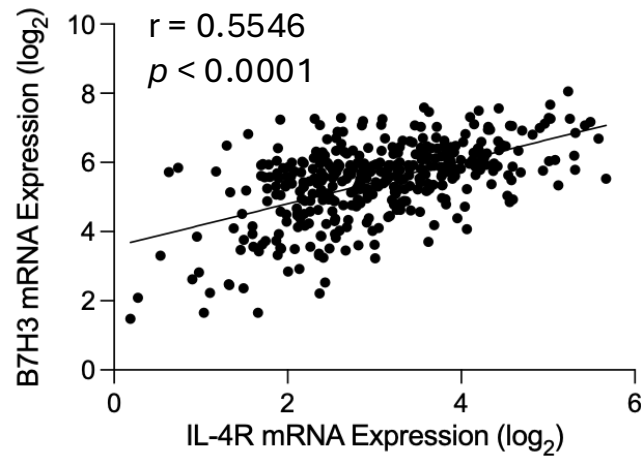
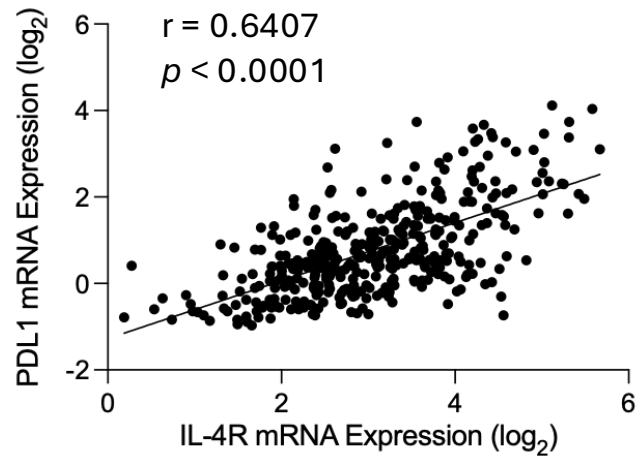
- Analyses of **matched primary-recurrent** GBM demonstrate that rGBM is characterized by a **mesenchymal** cell-state shift¹
- Mesenchymal-enriched GBM has an **immunosuppressive, myeloid-dominated** microenvironment
- **IL-4R mRNA expression** is higher in mesenchymal-enriched GBM compared with other subtypes across multiple independent datasets

Analysis of RNA-seq data obtained from 2017, *Neuro-Oncology*, 19 (1)
The Cancer Genome Atlas: 2008, *Nature*, 455 (7216)
The Chinese Glioma Genome Atlas: 2021, *Genomics, Proteomics & Bioinformatics*, 19 (1)
Ivy GAP: 2018, *Science*, 360 (6389)

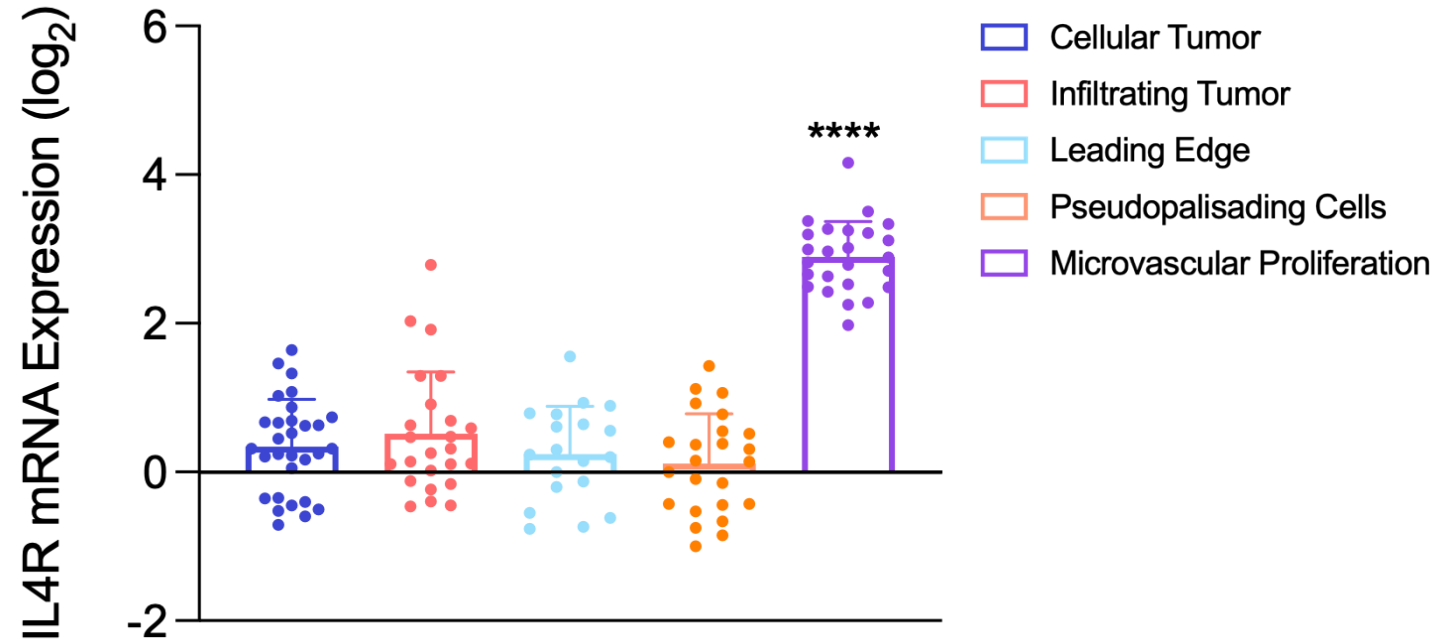
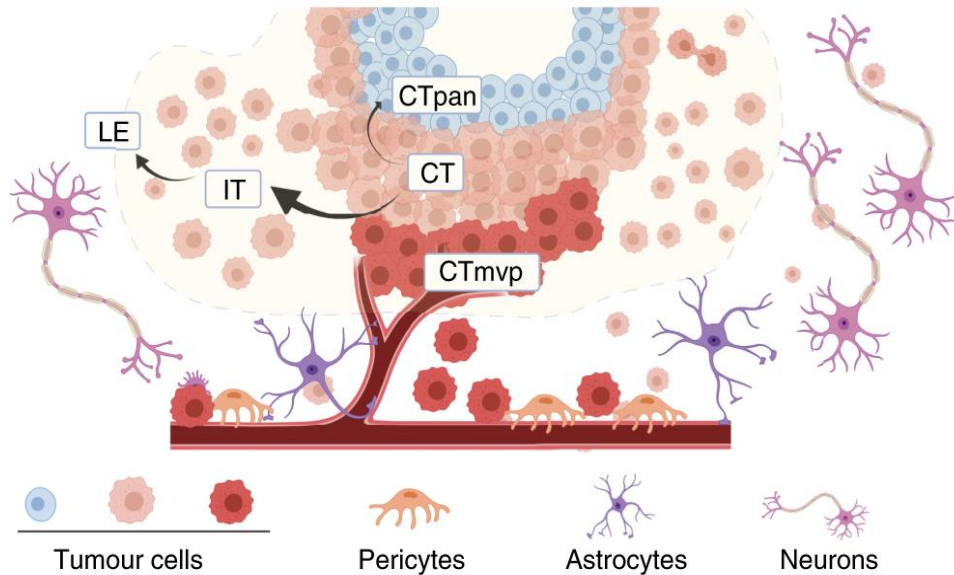
Subtype classifications are based on bulk RNA expression using TCGA GBM classifiers
**** $p < 0.0001$ One-way ANOVA and post-hoc Tukey's pairwise comparisons
** $p = 0.0059$ Welch's t-test

¹2022, *Nature Cancer*, 3, (1534–1552)

IL-4R Expression in GBM is Correlated with the Expression of Immune Checkpoint Proteins



IL-4R is Highly Expressed in GBM Microvascular Proliferating Cells



- Increased IL-4R expression is found in **proliferating microvascular regions**, which support **tumor survival and growth**
- Potential to target the **vascular infrastructure** with **bizaxofusp**

Bizaxofusp: Localized “One and Done” Tumor Treatment

High-flow CED Achieves Uniform Distribution to Tumoral & Peritumoral Areas

- Minimally invasive and safe procedure akin to routine brain tumor biopsy
- Thousands of procedures conducted for Deep Brain Stimulation annually
- **FDA approved** for the delivery of gene therapy (KEBILIDI™) to the brain

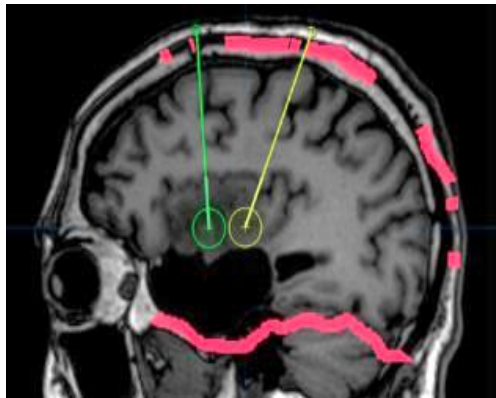
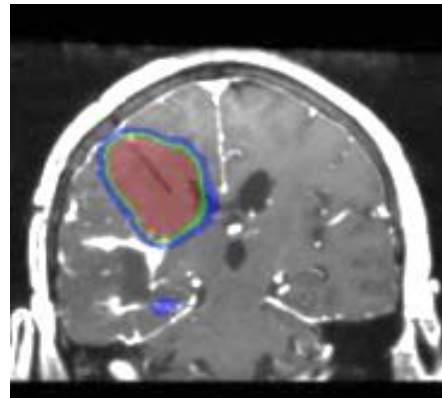
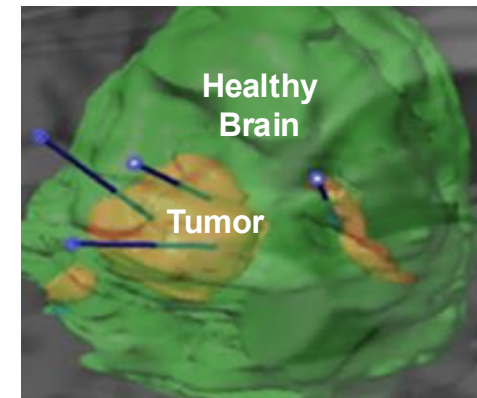


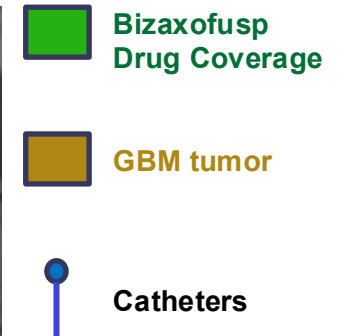
Image guided catheter placement pinpoints **ideal catheter trajectories**



Unique catheter stepped design **prevents backflow**



Novel delivery improves tumor coverage



“I like that this product has a local application because you get less side effects than with a systemic therapy. I also often see recurrences at the same site as the primary tumor, which tells me this is mainly a local disease and thus an efficacious local technology is preferable.” – German Neurosurgeon



Bizaxofusp Demonstrates Significant Survival Benefit in rGBM

- Promising Phase 2b Efficacy & Safety in Unresectable rGBM

Neuro-Oncology

25(6), 1085–1097, 2023 | <https://doi.org/10.1093/neuonc/noac285> | Advance Access date 14 January 2023

1085

Targeting the IL4 receptor with MDNA55 in patients with recurrent glioblastoma: Results of a phase IIb trial

John H. Sampson, Achal Singh Achrol, Manish K. Aghi, Krystof Bankiewicz, Martin Bexon, Steven Brem*, Andrew Brenner, Chandtip Chandhasin, Sajeel Chowdhary, Melissa Coello, Benjamin M. Ellingson*, John R. Floyd, Seunggu Han, Santosh Kesari, Yael Mardor, Fahar Merchant, Nina Merchant, Dina Randazzo, Michael Vogelbaum, Frank Vrionis, Eva Wembacher-Schroeder, Miroslaw Zabek, and Nicholas Butowski

Phase 2b Study Design

Open-label single arm study of Bizaxofusp in rGBM patients (n=47) (NCT02858895)

ELIGIBILITY

- Adults \geq 18 yrs
- ***de novo* GBM**
- **1st or 2nd relapse**
- **No resection**
- **KPS \geq 70**
- **IDH wild-type only**
- Failed 1L surgery, radiation, and/or chemotherapy (Stupp Protocol)
- Retrospective IL-4R analysis from initial Dx

TREATMENT

- Image-guided catheter placement
- Monitor real-time drug distribution with co-infusion of Magnevist [®]
- Single infusion (median 26.5 hrs.)
- Total Dose range: 18-240 μ g
- Transient low-dose bevacizumab allowed for symptom control and/or steroid sparing

ENDPOINTS

1^o Endpoint

- OS

2^o Endpoint

- ORR
- PFS
- OS vs. IL-4R expression
- Safety

The Phase 2b trial intentionally enrolled patients with baseline characteristics associated with poorer clinical outcomes.

Increases Confidence in Phase 2b Data and Reduces Phase 3 Risk

MDNA55-05 Phase 2b Trial Patient Demographics (PPP)

Patient Demographics	ITT Population N=47	PP Population N=44 *
Age (median, range)	56 (34-78)	56 years (34 – 77)
Sex (Male)	30 / 47 (64%)	27 / 44 (61%)
KPS at Enrolment:		
70, 80	23 / 47 (49%)	22 / 44 (50%)
90, 100	24 / 47 (51%)	22 / 44 (50%)
de novo GBM	47 / 47 (100%)	44 / 44 (100%)
Poor candidates for repeat surgery	47 / 47 (100%)	44 / 44 (100%)
IDH Wild-type**	38 / 47 (81%) (9 / 47, unknown)	37 / 44 (84%) (7 / 44, unknown)
Unmethylated MGMT**	24 / 47 (51%) (5 / 47, unknown)	23 / 44 (52%) (4 / 47, unknown)
IL-4R over-expression**	23 / 47 (49%)	21 / 44 (48%)
Max Tumor Diameter, median (range)	29.6 mm (7.8-58.5)	29.6 mm (8 – 59)
# Prior Relapse: 1, 2	37 (79%), 10 (21%)	35 (80%) , 9 (20%)

* Reflects all patients completing the study without major protocol deviations

** Based on actual testing with available tissues.

Bizaxofusp: Favorable Safety Profile in 118 Patients

No signs of systemic toxicity at any dose in Phase 1, Phase 2, or Phase 2b trials

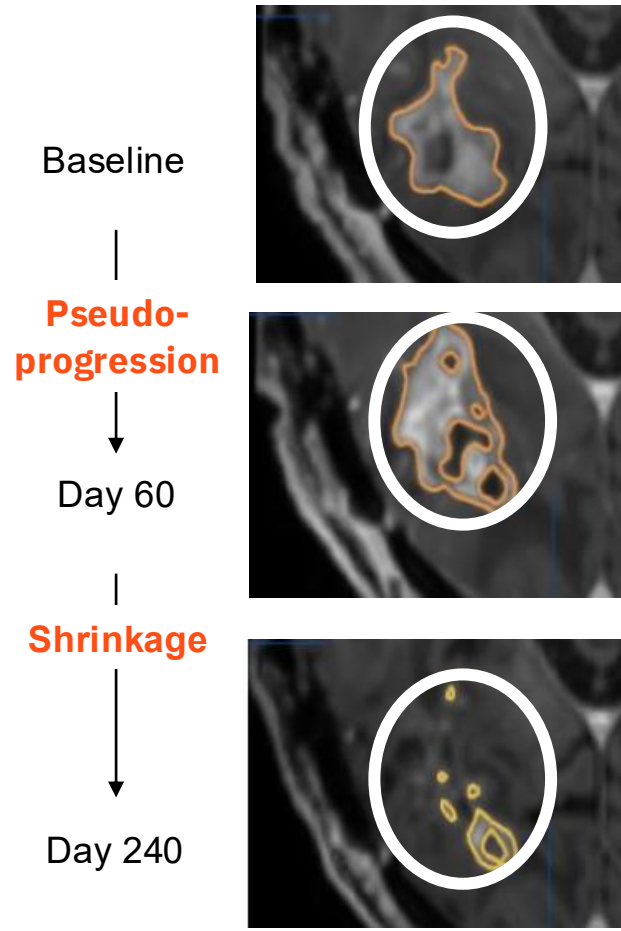
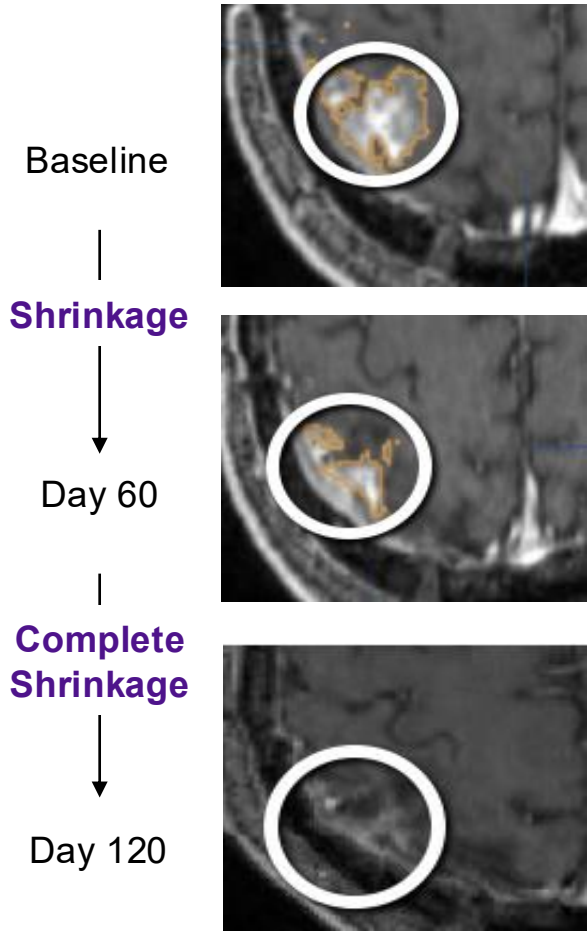
STUDY	PATIENT	DOSE (µg)
NIH-sponsored Investigator Initiated (U.S.)	Recurrent GBM (n = 9)	6 – 720
Multi-Center (U.S./Germany) Phase 1 “Non-resected Trial”	Recurrent HGG No Resection (n = 31; 25 rGBM+6 AA)	240 – 900
Multi-Center (U.S./Germany) Phase 2 “Resected Trial”	Recurrent GBM + Resection (n = 32)	90 – 300
Medicenna-sponsored Multi-Center (U.S./Poland) Phase 2b	Recurrent <i>de novo</i> GBM No Resection (n = 47)	18 – 240

Phase 2b study was the most recently completed study

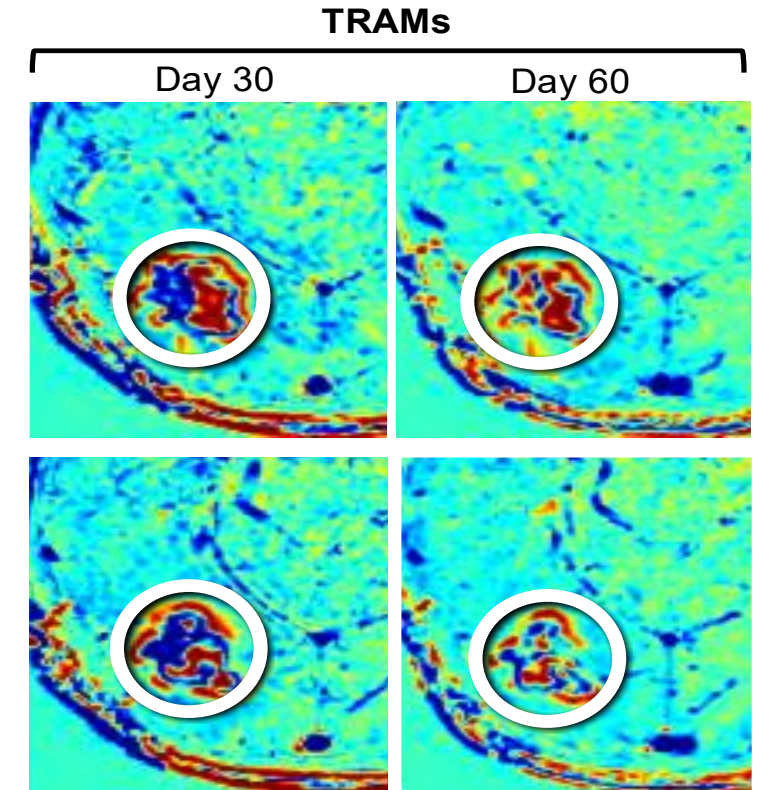
Consolidated Safety Profile

- No systemic toxicity at any dose
- No clinically significant laboratory abnormalities
- Most adverse events were due to local effects and similar to those typically seen in this patient population
- Manageable inflammation and edema associated with tumor necrosis
- 2 grade 5 events unrelated to study drug
- MTD established at >240 µg

Tumor Shrinkage Following Single Treatment with Bizaxofusp



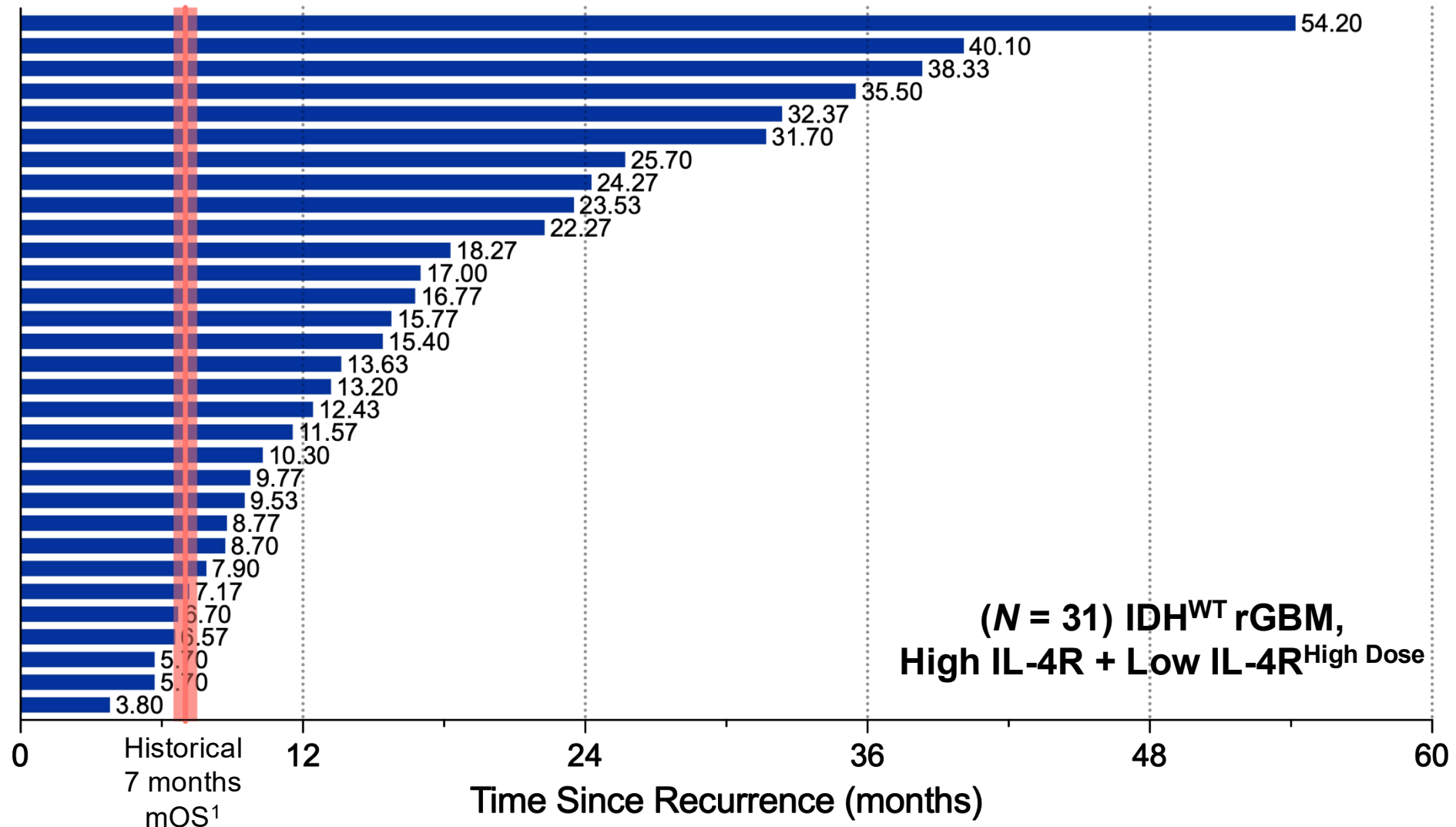
Increasing Tumor Necrosis Detection by MRI TRAMs



● Active tumor ● Necrotic tumor

TRAMs: Treatment Response Assessment Maps

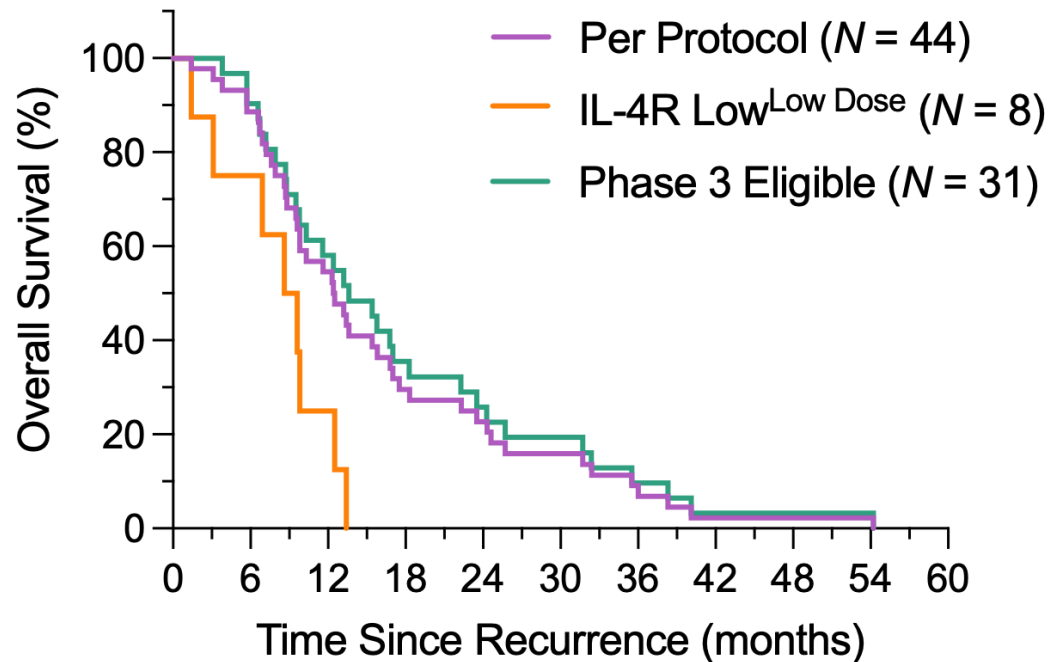
High Dose Bizaxofusp Improves Overall Survival vs. Historical Benchmark in **Unresectable IDH^{WT} rGBM**



Long Term Survival Following Single Dose of Bizaxofusp

OS results exceeded pre-specified primary endpoint of 8.0 months (No-Go) vs 11 months (Go)

High dose bizaxofusp meaningfully improves OS and represents the planned phase 3 dose



	Per Protocol Population (N = 44)	IL-4R Low Low Dose (N = 8)	Planned Phase 3 (N = 31)
mOS (months)	12.5	9.1	13.6
OS-12 (%)	54.5	25.0	58.1
OS-24 (%)	22.7	0	25.8

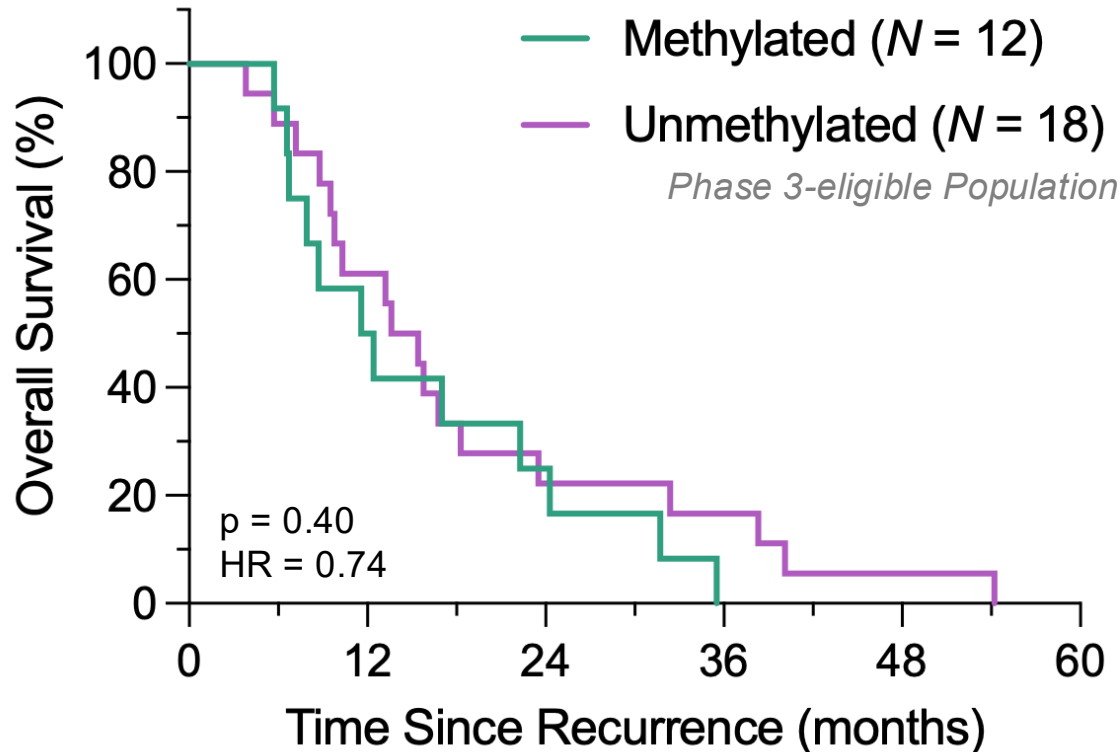
$p = 0.017$ (Log-rank)

IL-4R High: H-score > 60
 High Dose Bizaxofusp: $\geq 180 \mu\text{g}$
 Planned Phase 3: IDH^{WT} unresectable rGBM; High IL-4R + Low IL4R^{High Dose}

Bizaxofusp is Effective Irrespective of MGMT Methylation Status

“MGMT status is a real limitation for patients using Temodar, but it is still used as first- and second-line treatment. Bizaxofusp gives another option for unmethylated patients.”

– US Neurosurgeon



MGMT Status	mOS (months)	OS-12 (%)	OS-24 (%)
Methylated	12.0	50	25
Unmethylated	14.5	61	22

MGMT unmethylated, unresectable IDH^{WT} rGBM has a historical mOS of 5 months¹

Contextualizing OS Benefit: Retrospective Matched ECA Study

For Comparison of Survival Against MDNA55-05 Phase 2b Study

POPULATION

- Patient registries at:
 - University of California, San Francisco (UCSF)
 - St. Michael's Hospital (Toronto, Canada)
- Study conducted under IRB-approved protocols
- **Investigators (Medidata, AcornAI) and Medicenna blinded to survival outcome**
- Subjects in the ECA and Phase 2b study were treated during the same time period.

ELIGIBILITY

- Adults \geq 18 yrs
- **de novo GBM at initial diagnosis**
- **1st or 2nd relapse (rGBM)**
- **No resection**
- **KPS \geq 70**
- **IDH wild-type only**

10 ECA BALANCING CRITERIA

- Age
- Sex
- KPS
- MGMT methylation status
- Time from initial diagnosis to relapse
- Number of prior relapses
- Extent of resection at initial diagnosis
- Tumor size/location at relapse
- Steroid use prior to treatment

ECA PROPENSITY SCORE BALANCING

- **STEP 1**
Data preparation: feasibility and quality, mapping, standardization, covariates
- **STEP 2**
Estimate propensity scores: statistical models
- **STEP 3**
Propensity score balancing algorithm - weighting
- **STEP 4**
Evaluation of balance in baseline characteristics

Propensity score methodology was used to balance bizaxofusp and control groups on key prognostic factors;
performed prior to unblinding survival data

Contextualizing OS Benefit: Retrospective Matched ECA Study

For Comparison of Survival Against MDNA55-05 Phase 2b Study

ECA PROPENSITY SCORE BALANCING

STEP 1

Data preparation: feasibility and quality, mapping, standardization, covariates

STEP 2

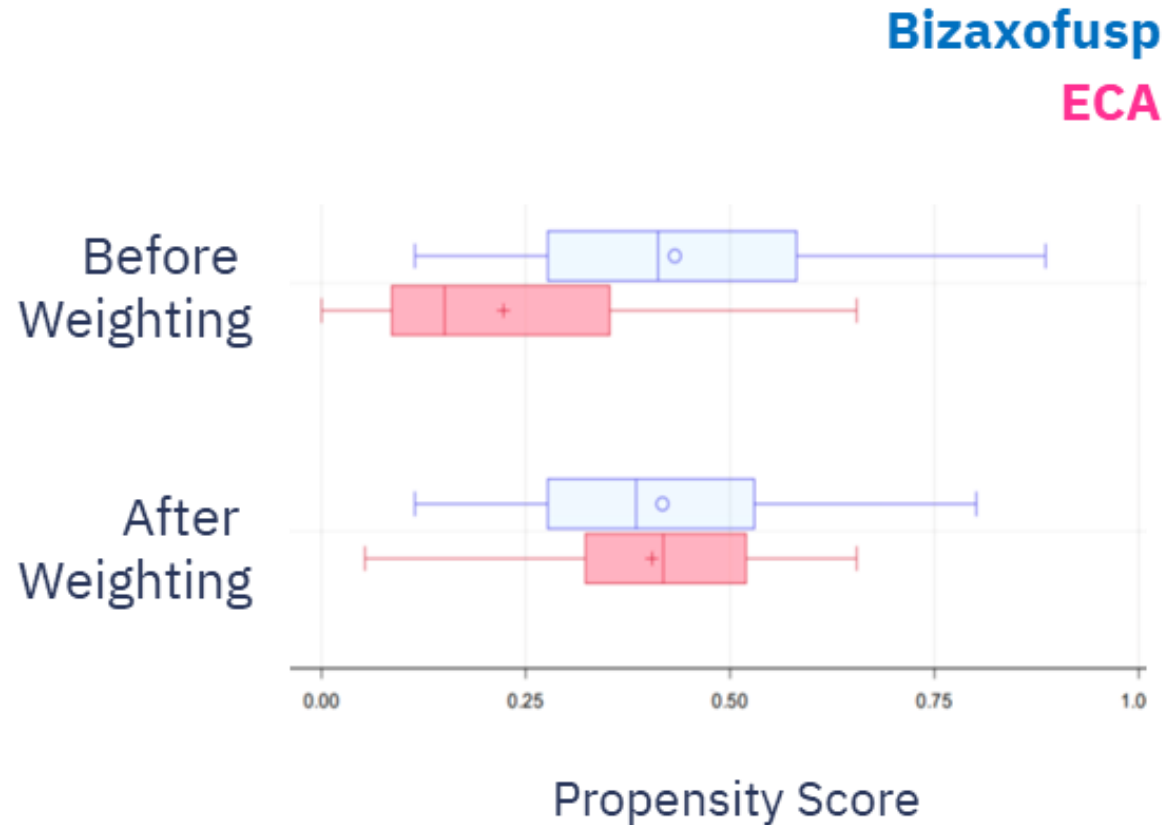
Estimate propensity scores: statistical models

STEP 3

Propensity score balancing algorithm - weighting

STEP 4

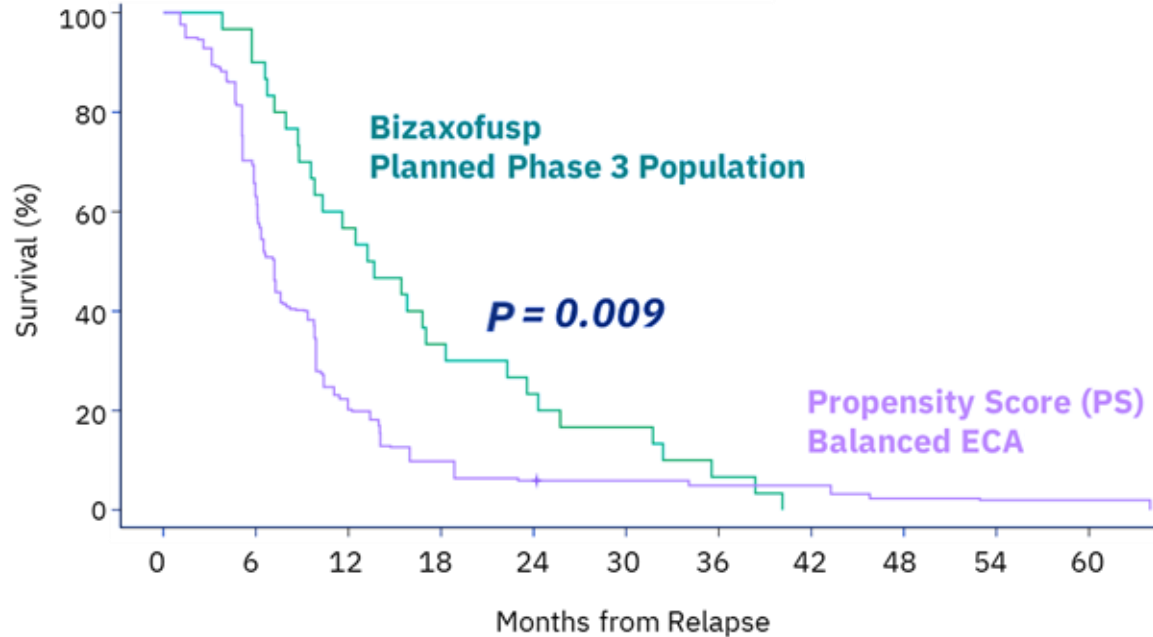
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Propensity score methodology was used to balance bizaxofusp and control groups on key prognostic factors;
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Median Overall Survival (OS) Doubled with Single Treatment

OS increased by 180% at 12 months and 290% at 24 months when compared with ECA



	PS-balanced ECA (n = 29.5)	Bizaxofusp (n = 30)
OS-12	20.2%	56.7%
OS-18	9.8%	33.3%
OS-24	5.9%	23.3%
OS-30	5.9%	16.7%
mOS (months)	7.2	13.5
p-value*	0.009	
HR* (95 % CI)	0.536 (0.344, 0.834)	

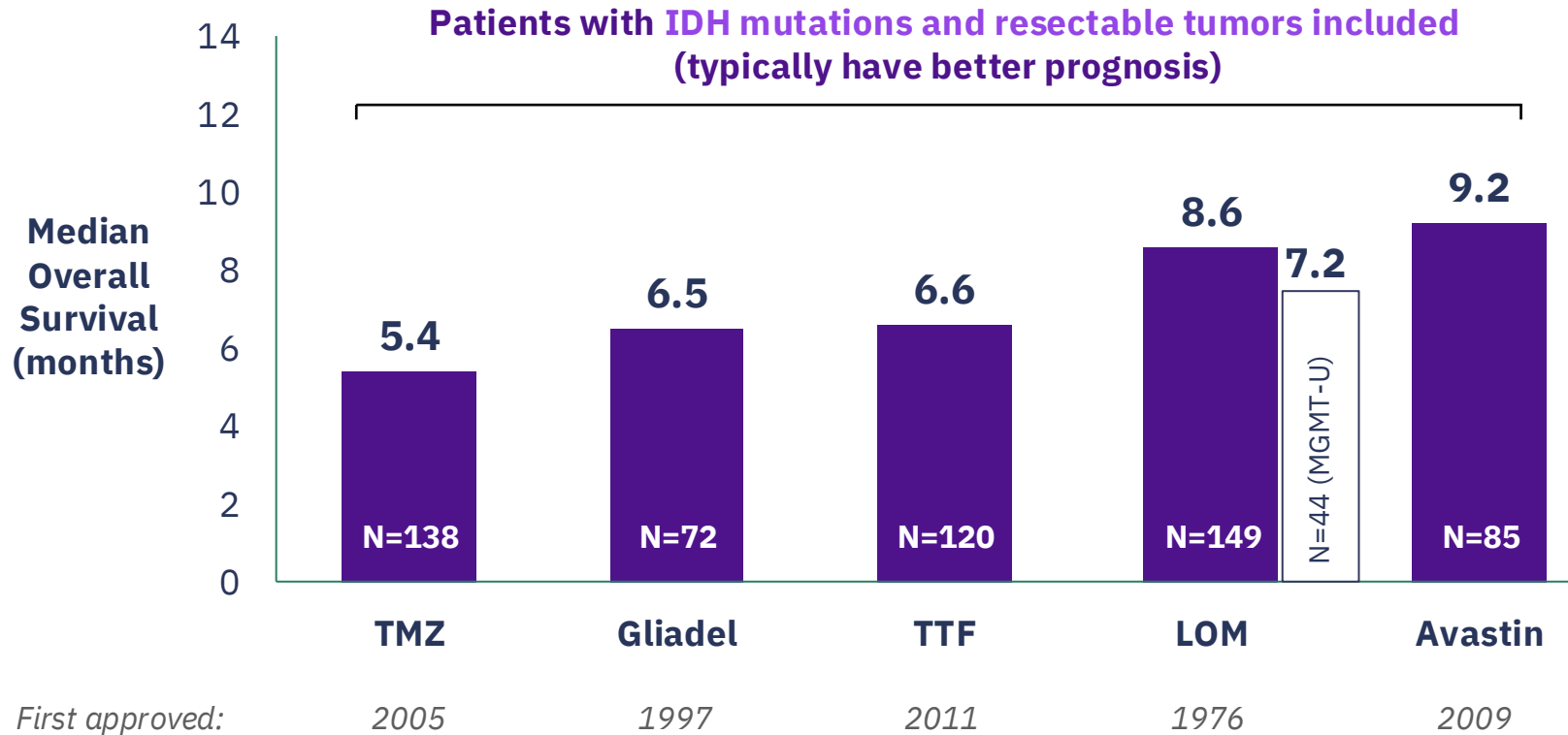
*Log-rank test

Patients enrolled in the ECA met the same eligibility criteria as the Phase 2b study and were subsequently matched using propensity score balancing.

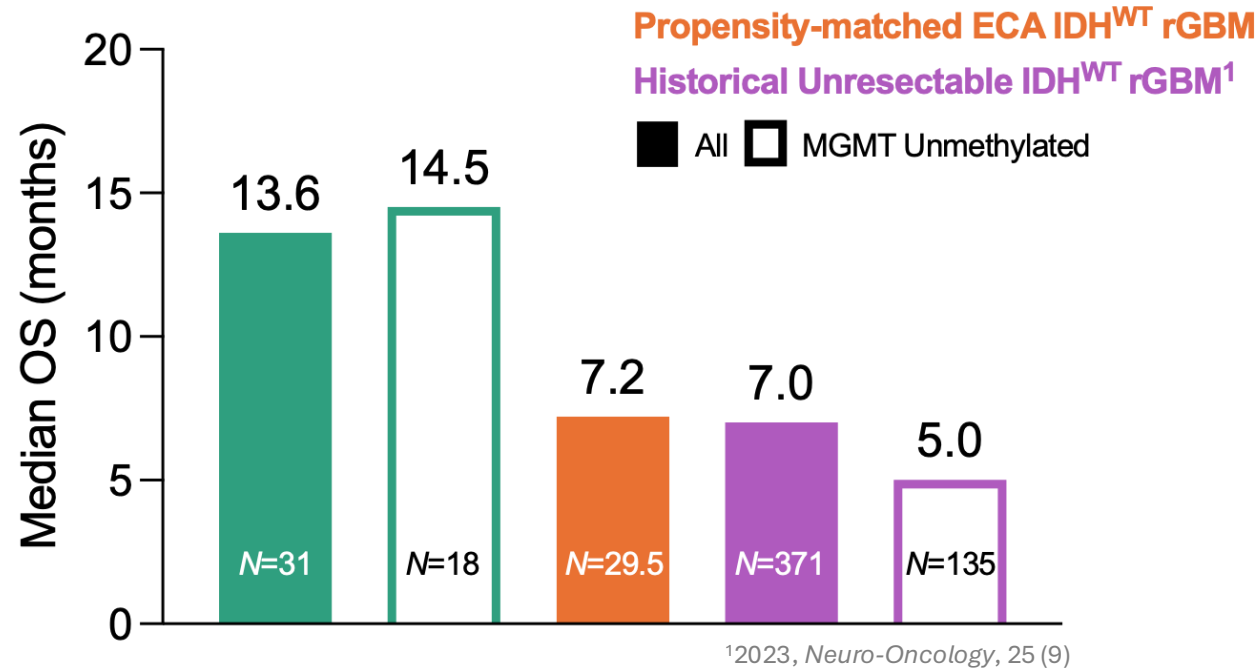
Bizaxofusp Demonstrates a Substantial Improvement in Overall Survival in Unresectable rGBM

“MGMT status is a real limitation for patients using temodar, but it is still used as first- and second-line treatment. Bizaxofusp gives another option for unmethylated patients.”

– US Neurosurgeon

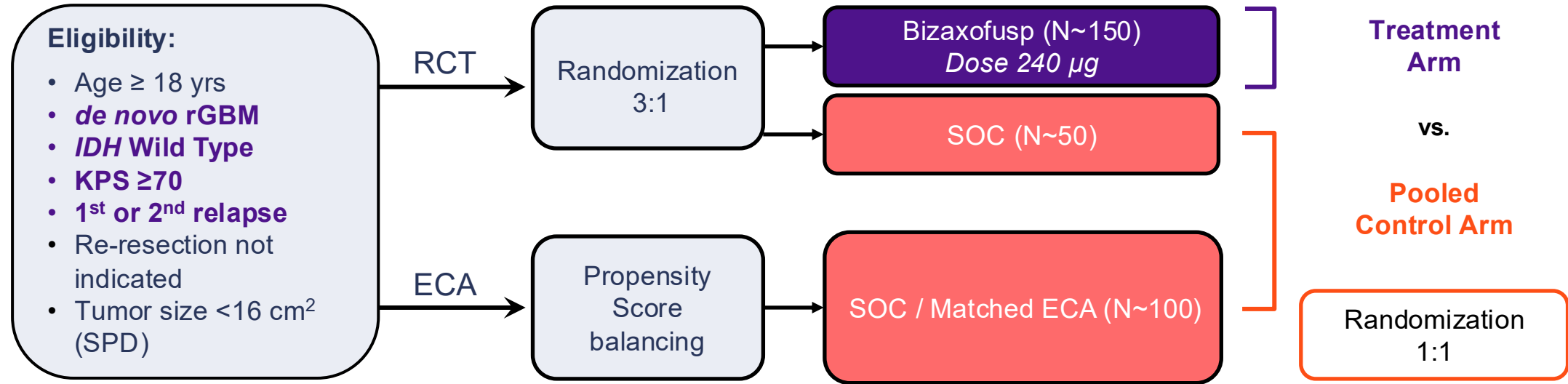


Bizaxofusp Demonstrates a Substantial Improvement in Overall Survival in Unresectable rGBM



Bizaxofusp's improvement in survival (mOS 13.6 months vs. ~7.0 months) is supported by both ECA and a retrospective analysis of 681 patients with unresectable IDH^{WT} rGBM.

Pivotal Hybrid Trial Design Supported by FDA



SOC therapies allowed:

- Bevacizumab (Avastin®)
- Lomustine (CCNU, CeeNU®, Gleostine™)
- Temozolomide (Temodar®)
- Tumor Treating Fields (Optune®)
- Radiation Therapy

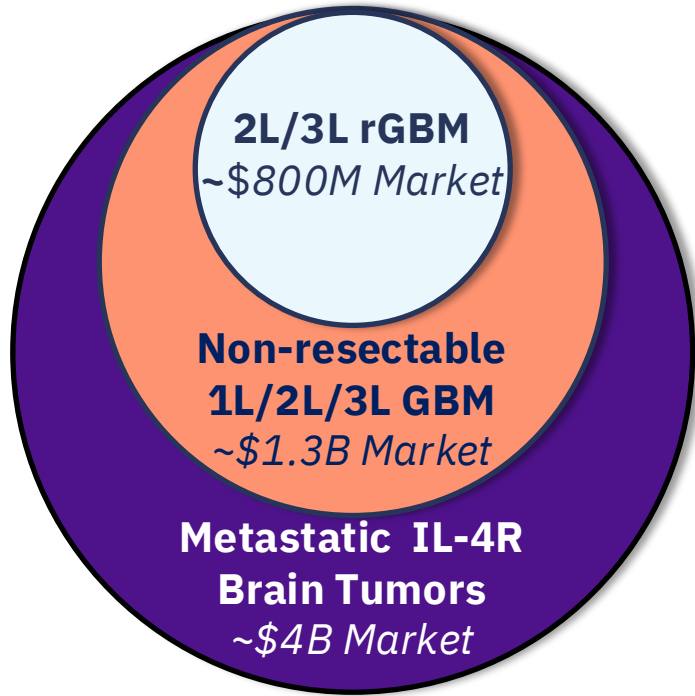
Primary Endpoint:

- OS

Assumptions:

- Effect size = 4.6 months in mOS (vs. 6.4 months achieved in Phase 2b)
- 90% power
- HR of Bizaxofusp vs. pooled control = 0.65
- 2-sided alpha = 0.05

Bizaxofusp has Potential Beyond rGBM



Near-term

**2L/3L
rGBM**

Total market

~19,000 annually (US/EU)

Medium-term

**Non-resectable
newly diagnosed
GBM**

Total market

~22,000 annually (US/EU)

Longer-term

**Metastatic
IL-4R Brain
Tumors**

Renal | Breast | Colon

Total market:

~76,000 annually (US/EU)

Beyond GBM

IL-4R Overexpressing
Metastatic Brain Tumors



Renal Cancer
~6,000



Breast Cancer
~47,000



Colon Cancer
~23,000

IL-4R Positive Cancers
Amenable to
Local/Regional
Administration



60% Ovarian
~21,500



73% Bladder
~85,000



96% Mesothelioma
~3,000

“There’s a group of first line patients that are not candidates for surgery. This product would be very impactful for them.”

– UK Neuro-Oncologist

One Target: Infinite Hope

1

TARGET

13.5

Months of Median Overall
Survival in IL-4R High + IL-4R
Low^{High Dose} Subjects

~100%

Improvement in Median
Survival compared to
Standard of Care

4,000

Brain Tumor Patients that
can be treated with 1
Gram of Bizaxofusp

19,000

Number of Patients
Annually Diagnosed with
rGBM in US and EU4+UK

250,000

Global Annual Incidence of
Primary and Metastatic
Brain Cancers

20

Number of Cancers
Known to Over-Express
the IL-4R

1 Million

Global Annual Incidence
of IL-4R Positive Cancers

∞

HOPE

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**.....And most of all, to
the patients & their
families**

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CANCER PREVENTION & RESEARCH
INSTITUTE OF TEXAS