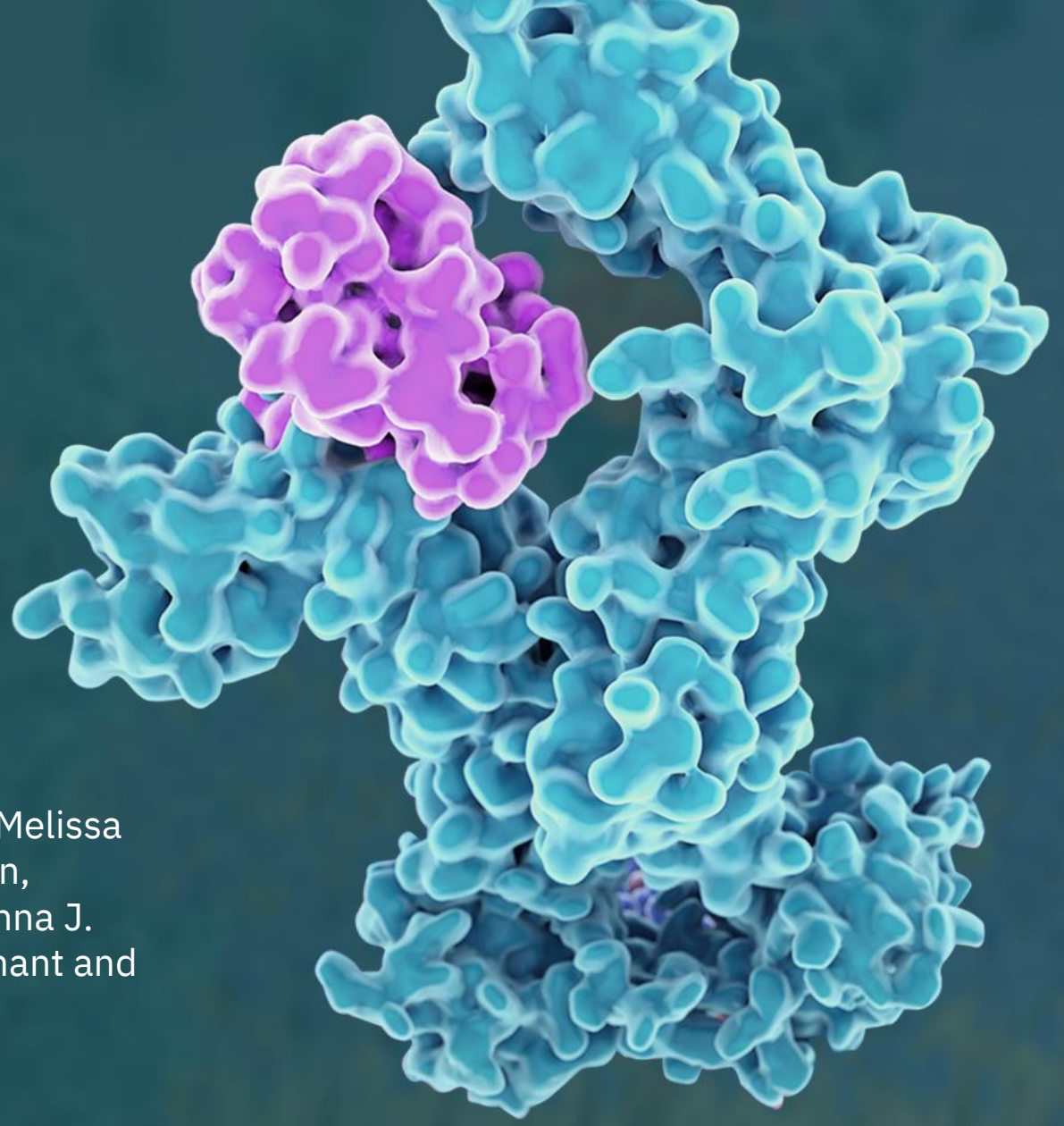
Phase 2b Study of Bizaxofusp, an IL-4R Targeted Toxin Payload, in nonresectable recurrent GBM; Comparison of Overall Survival with Contemporaneous Eligibility-Matched and Propensity Score Balanced External Control Arm



John H. Sampson, Martin Bexon, Steven Brem, Andrew J. Brenner, Melissa Coello, Sunit Das, Ruthie Davi, Annick Desjardins, Seunggu Jude Han, Santosh Kesari, Sudhir Madduri Karanam, Rosemina Merchant, Joanna J. Phillips, Minh D. To, Michael Vogelbaum, Frank Vrionis, Fahar Merchant and Nicholas A. Butowski

MEDICENNA

ASCO Annual Meeting 2024 | May 31st – June 3rd, 2024 | Chicago, IN

Background: Bizaxofusp and the Unmet Need in rGBM

- **Unmet need:** Median overall survival (mOS) in recurrent glioblastoma (rGBM) is 6-9 months with limited treatment options and no approved standard of care.
- **Selectivity:** IL-4 receptor (IL-4R) is overexpressed in > 70% of GBM but not in normal brain, therefore it is an important therapeutic target.
- **Reversing immune suppression:** GBM tumor micro-environment (TME) comprises of MDSCs and TAMs that are also known to express IL-4R and suppress effector T cells.
- **Bypasses blood-brain barrier (BBB):** Local administration using convection enhanced delivery (CED) maximizes drug exposure at tumor site and minimizes systemic exposure

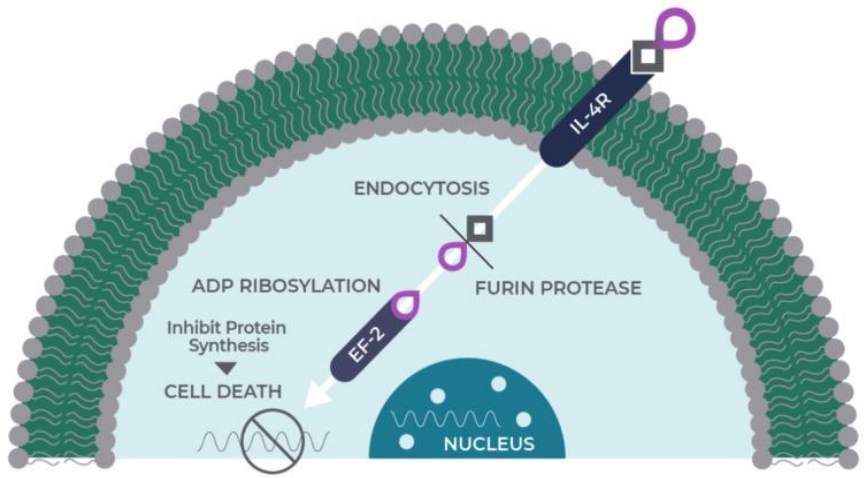
Bizaxofusp (*aka* MDNA55) is a Potent IL-4R Targeted Toxin Payload

Targeting Domain
Circularly Permuted Interleukin-4 (cpIL-4)

Lethal Payload
Catalytic domain of *Pseudomonas* Exotoxin A

(**FDA approved in 2018, Moxetumomab pasudotox**)

- **Multipronged Mechanism:**
  - Direct tumor cell killing by inhibiting protein synthesis with the catalytic domain of Pseudomonas toxin
  - Immunogenic cell death triggers anti-tumor immune response within the TME



MEDICENNA

Phase 2b Study Design: Bizaxofusp Treatment Arm

1. Key Eligibility Criteria

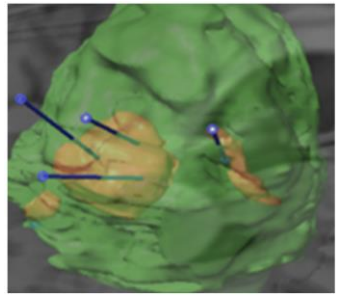
- Adults ≥ 18 yrs
- *De novo* GBM at initial diagnosis
- 1st or 2nd relapse
- No resection
- KPS ≥ 70
- IDH wild-type
- Retrospective IL-4R analysis from initial Dx

2. Characteristics	N (%)
Total # of Patients	**44**
Age (median, range)	56 years (34 – 77)
Sex (Male)	27 / 44 (61%)
KPS at Enrolment: 70, 80 90, 100	18 / 44 (41%) 26 / 44 (59%)
De novo GBM	44 / 44 (100%)
Poor candidates for repeat surgery	44 / 44 (100%)
Confirmed IDH Wild-type*	37 / 37 (100%)
Unmethylated MGMT*	23 / 40 (58%)
IL-4R High*	21 / 40 (53%)
Steroid use during study > 4 mg/day	23 / 44 (52%)
Max. Tumor Diameter	29.6 mm (8 – 59)
# Prior Relapse: 1 , 2	35 (80%) , 9 (20%)

3. Bizaxofusp Administration

Single infusion of 6-240 µg by CED

- Bypasses blood-brain barrier
- Maximizes drug exposure at tumor
- Avoids systemic toxicities.
- Uniform drug distribution



Blue: Catheters
Orange: Tumor
Green: Bizaxofusp

4. Study Objectives

- **Primary Endpoint:**
  - Overall Survival (OS)
- **Secondary Endpoints:**
  - Safety
  - ORR (mRANO)
  - PFS (mRANO)
  - mOS vs. IL4R expression

MEDICENNA

*based on available data

Study Design: ECA for Comparison with Bizaxofusp in Phase 2b Study

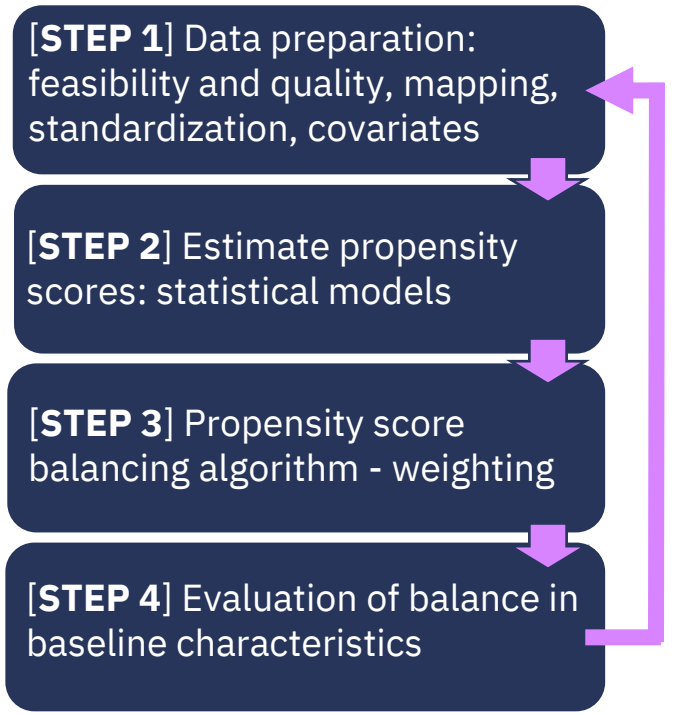
1. Key Eligibility Criteria for ECA

Same as bizaxofusp arm

2. Baseline Parameters for Propensity Score Modeling

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

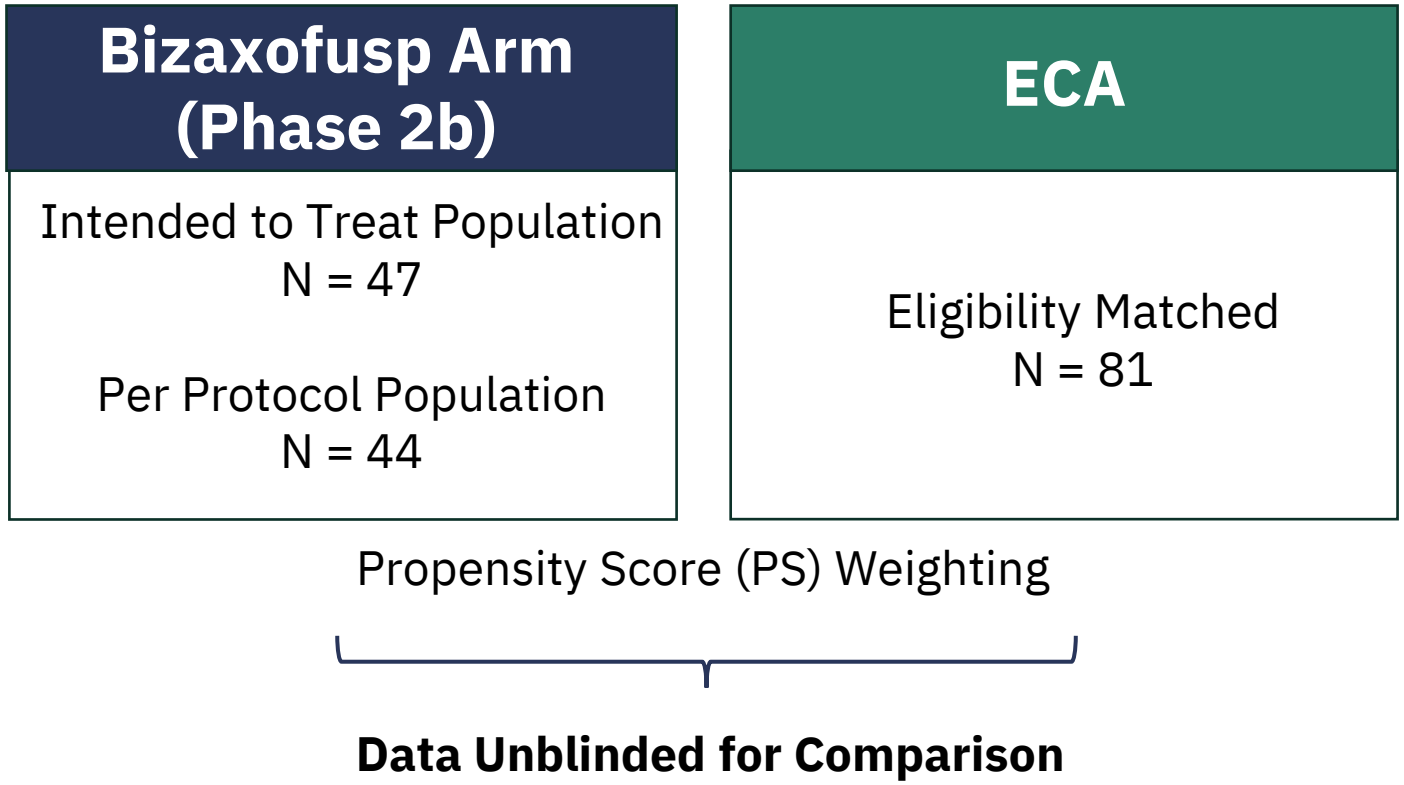
3. Construction of ECA



4. Unblinding of Outcome Data

Bizaxofusp arm and ECA

Study Design: Comparison of Overall Survival Between Bizaxofusp Arm in the Phase 2b Study and the External Control Arm (ECA)



Safety Profile of Bizaxofusp in Phase 2b Study

RELATED AEs ≥ GRADE 3 OCCURRING IN ≥ 5% SUBJECTS (SOC / PREFERRED TERM)	TOTAL N = 47 [n (%)]
# of Subjects	10 (21.3)
Nervous system disorders	**10 (21.3)**
Brain Edema / Hydrocephalus	4 (8.5)
Hemiparesis	3 (6.4)
Seizure	3 (6.4)

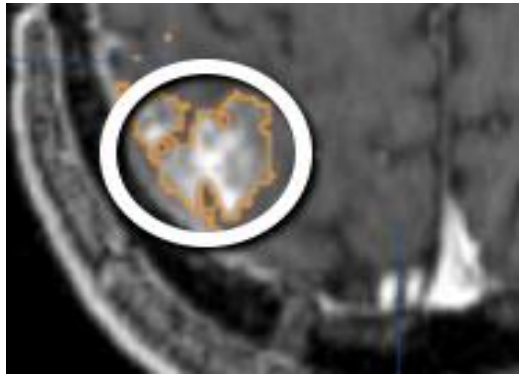
RELATED SAEs OCCURRING IN ≥ 5% SUBJECTS (SOC / PREFERRED TERM)	TOTAL N = 47 [n (%)]
# of Subjects	9 (19.1)
Nervous system disorders	**4 (8.5)**
Seizure	4 (8.5)

Treatment-related adverse events were primarily neurological or aggravation of pre-existing neurological deficits consistent with rGBM and no laboratory abnormalities nor systemtic toxicities were reported across all doses.

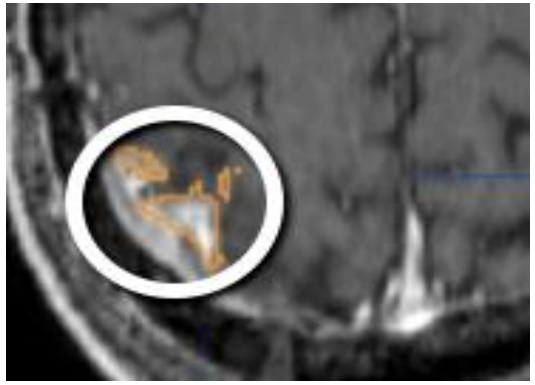
Efficacy: Tumor Response Following a Single Dose of Bizaxofusp

Direct tumor response (i.e., no pseudo-progression)

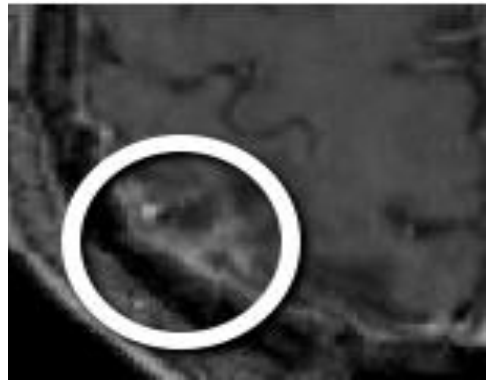
Baseline



Day 60

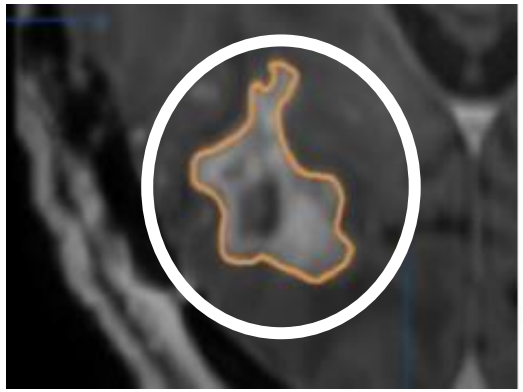


Day 120

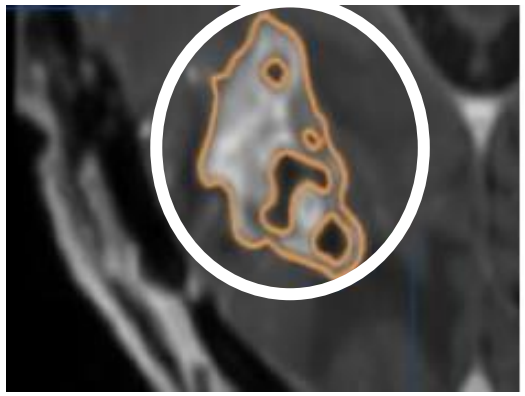


Tumor response following pseudo-progression

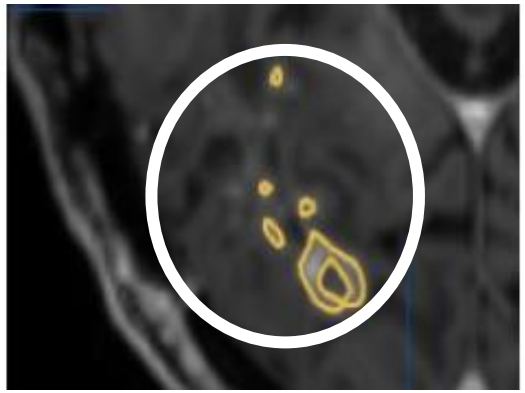
Baseline



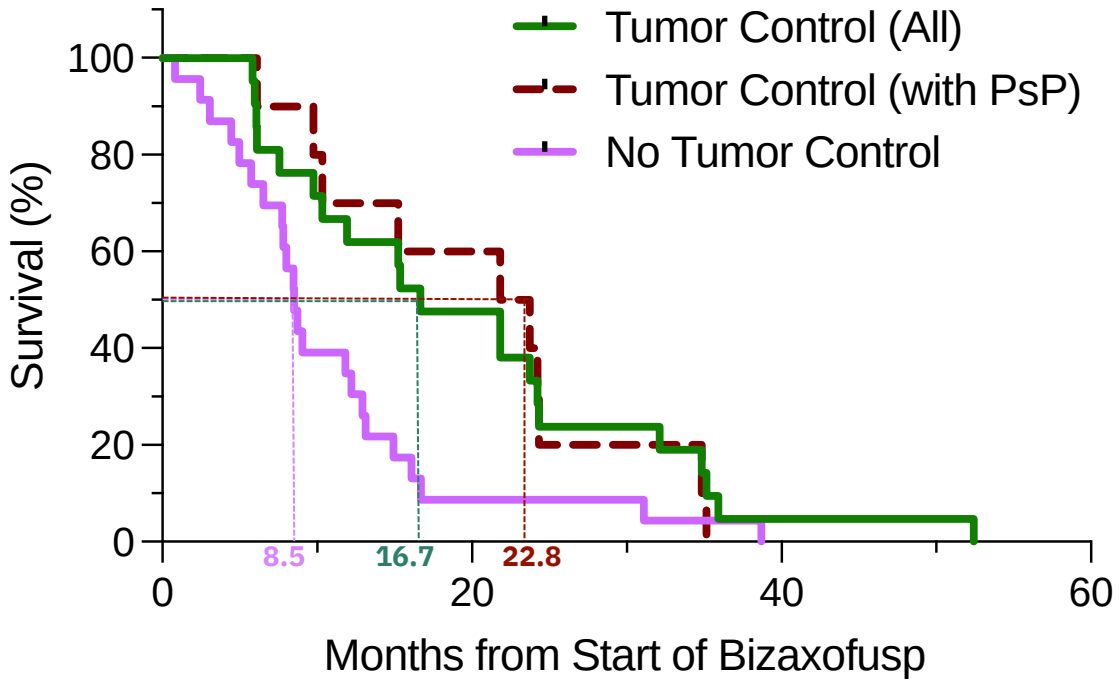
Day 60



Day 120



Tumor Control and Pseudo-progression Following Bizaxofusp Treatment Resulted in Significant Increase in mOS



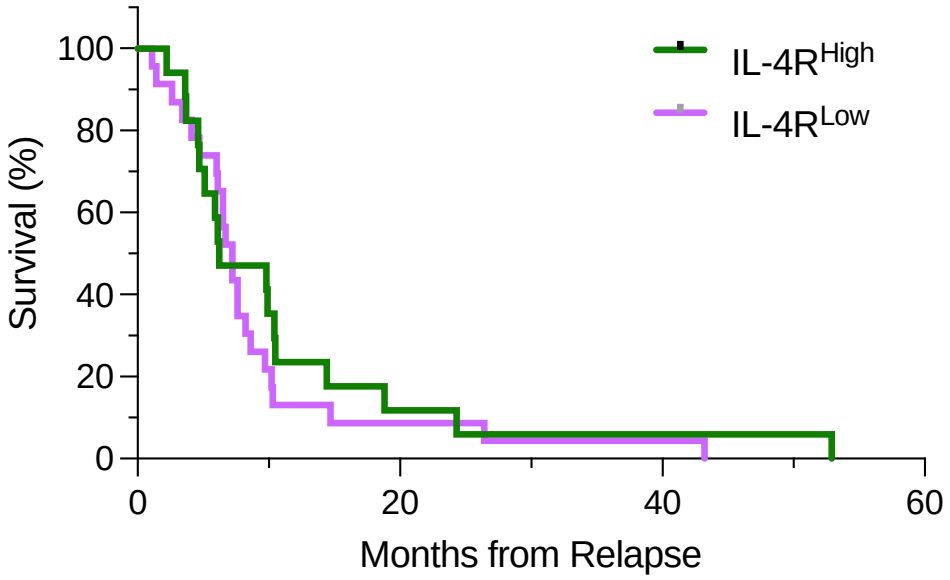
	No Tumor Control (N = 23)	Tumor Control (N = 21)	
		All (N =21)	PsP# (N = 10)
OS-12	34.8%	61.9%	70%
OS-18	8.7%	47.6%	60%
OS-24	8.7%	33.3%	40%
OS-30	8.7%	23.8%	20%
mOS	8.5 months	16.7 months	22.8 months
p-value*	-	**0.0168**	**0.0493**
HR* (95% CI)	-	**0.51 (0.273, 0.937)**	**0.498 (0.252, 0.988)**

Tumor assessment by mRANO/RANO 2.0
Tumor control: SD, PR or CR

*Log-rank test, compared to No Tumor Control
PSP: pseudo-progression

IL-4R Expression Had No Effect on mOS in Bizaxofusp Arm or ECA

ECA

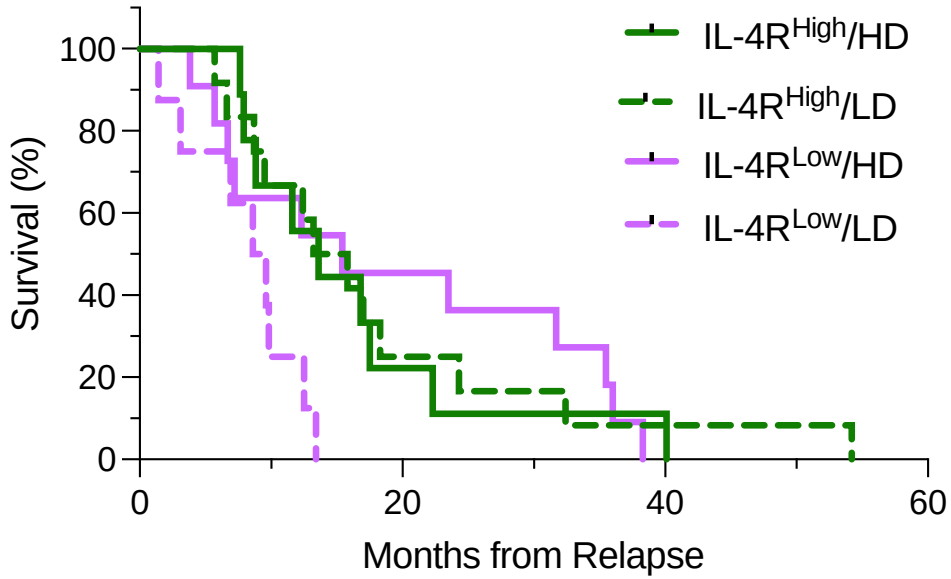


	N	OS-12	OS-24	mOS (months)
IL-4R^{High}	17	23.5%	11.8%	6.2
IL-4R^{Low}	23	13.0%	8.7%	7.2

$p = 0.49$

p-values determined using the log-rank test

Bizaxofusp



	N	OS-12	OS-24	mOS (months)
IL-4R^{High}/HD*	9	55.6%	11.1%	13.6
IL-4R^{High}/LD*	12	66.7%	25%	14.5
IL-4R^{Low}/HD*	11	63.6%	36.4%	15.4
IL-4R^{Low}/LD	8	25%	0%	9.1

$p = 0.71$

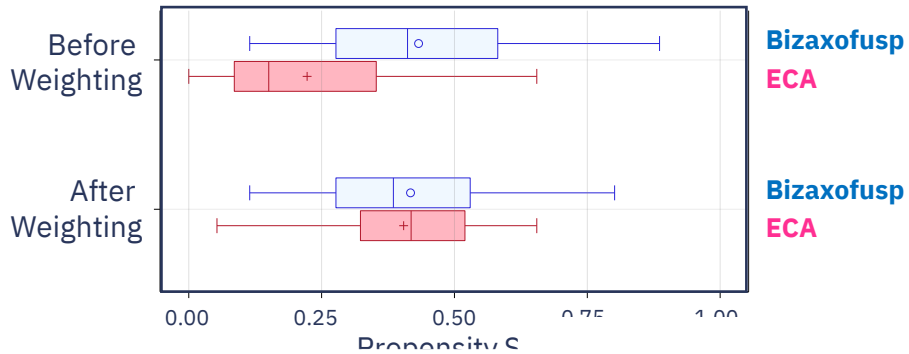
$p = 0.94$

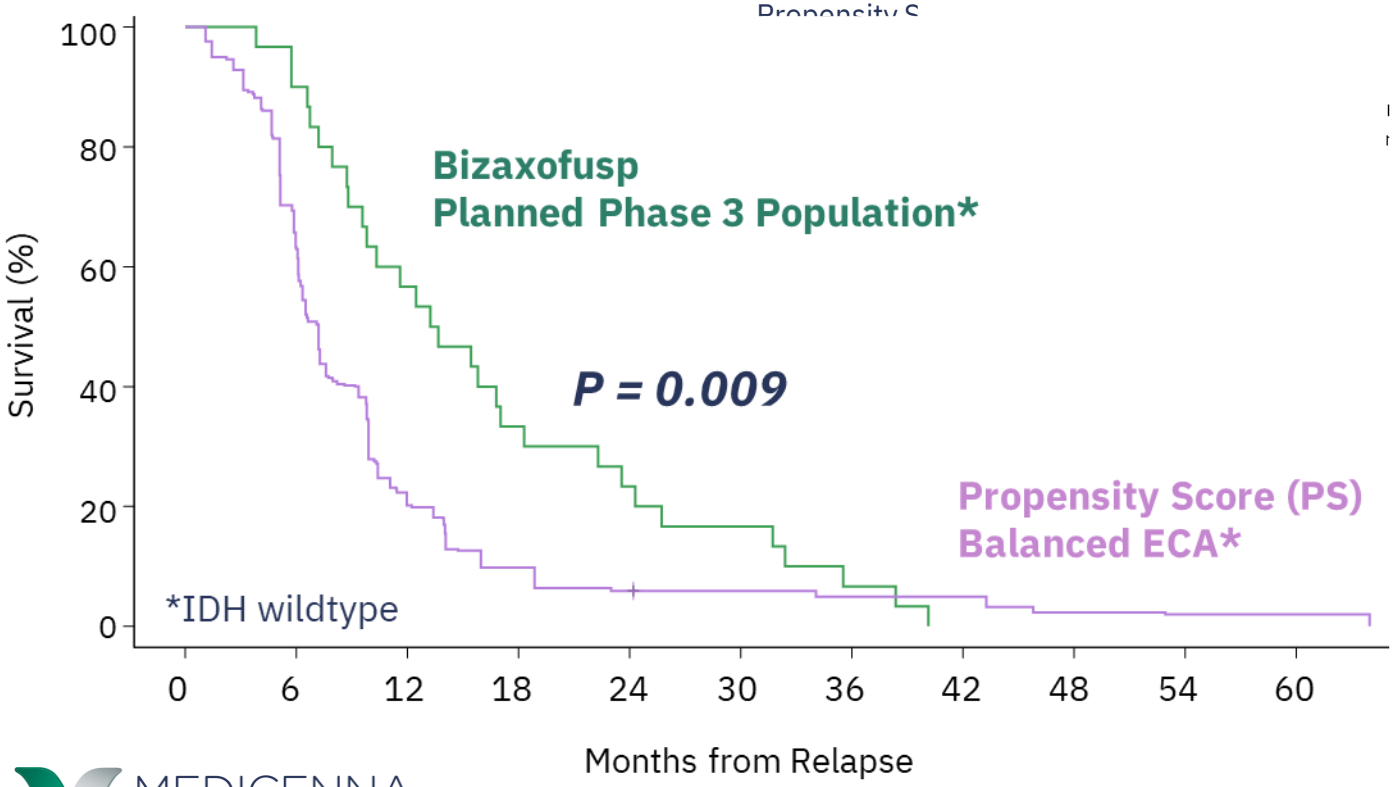
$p = 0.035$

*Planned phase 3 population.
HD: high dose (≥180 ug); LD: low dose (<180 ug)

MEDICENNA

Significant Survival Benefit Observed in Planned Phase 3 Population in Unresectable rGBM



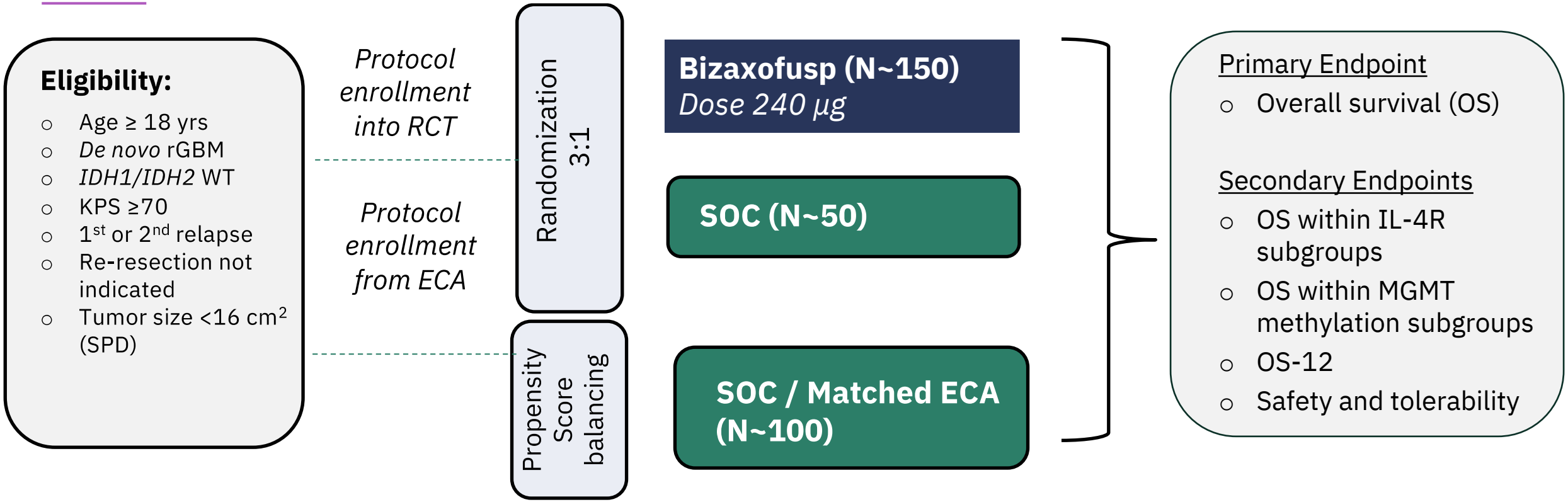


	PS Balanced ECA (N = 29.5)	Bizaxofusp (N = 30)
OS-12	20.2%	56.7%
OS-18	9.8%	33.3%
OS-24	5.9%	23.3%
OS-30	5.9%	16.7%
mOS (months)	7.2	13.5
p-value*	**0.009**	
HR* (95 % CI)	**0.536 (0.344, 0.834)**	

*Log-rank test

MEDICENNA

Planned Phase 3 Study with Bizaxofusp vs. Hybrid Control Arm



Key Advantages of an ECA:

- Provides alternative double arm clinical trial design, when blinded randomization is not feasible or ethical.
- Data are readily available within validated electronic medical records and/or patient registries.
- Achieves study objectives within a shorter time frame.
- Reduces study cost.

Conclusions and Implications

1. A single treatment with bizaxofusp achieved significant survival benefit vs. propensity score balanced ECA (p = 0.009; HR: 0.536; 95% CI: 0.344, 0.834) in the phase 2b study, irrespective of IL-4R expression

   Negates the need for a companion diagnostic, expanding patient eligibility for bizaxofusp treatment, and broadening data availability for ECA in Phase 3 study

2. Patients who showed tumor control had significantly longer mOS when compared with patients with no tumor control (p = 0.0168; HR: 0.51; 95% CI: 0.273, 0.937)

   Tumor control may act as a potential surrogate endpoint of survival outcome in Phase 3 study

3. TRAEs were primarily neurological or aggravation of pre-existing neurological deficits consistent with indication with no laboratory abnormalities nor any systemic toxicities at all doses

   Acceptable Safety Profile

4. Based on results of the phase 2 b study, a Phase 3 registrational trial in unresectable rGBM will comprise of a **high dose bizaxofusp** arm and a control arm with 1/3 randomized subjects to SOC and 2/3 propensity matched ECA receiving SOC (**hybrid control arm**)

Author Affiliations

Duke University Medical Center, Durham, NC; Hospital of the University of Pennsylvania, Philadelphia, PA; University of Texas Health Antonio Cancer Center, San Antonio, TX; St. Michael's Hospital, University of Toronto, Toronto, ON; Medidata Solutions, Medidata AI, a Dassault Systemes Company, Frederick, MD; Stanford University, Stanford, CA; Pacific Neuroscience Institute, Providence Saint John's Health Center, Santa Monica, CA; University of California San Francisco, San Francisco, CA; H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; Boca Raton Regional Hospital, Boca Raton, FL; Medicenna Therapeutics Inc., Toronto, ON.

Acknowledgements

John Sampson, MD, PhD
Dina Randazzo, DO
Annick Desjardins, MD
Duke University School of Medicine

Nicholas Butowski, MD
Krystof Bankiewicz, MD, PhD,
Manish K. Aghi, MD, PhD
Joanna Phillips, MD, PhD
John Bringas
University of California San Francisco

Achal Achrol, MD
Santosh Kesari, MD, PhD
Pacific Neuroscience Institute and John Wayne Cancer Institute

Michael Vogelbaum, MD, PhD
Cleveland Clinic

Steven Brem, MD
Hospital of the University of Pennsylvania

Seunggu Han, MD
Oregon Health & Science University

.....and most of all, to the patients & their families

Andrew Brenner, MD, PhD
John R. Floyd, MD
Cancer Therapy and Research Center at University of Texas at San Antonio

Frank Vrionis, MD, PhD
Sajeel Chowdhary, MD
Boca Raton Regional Hospital

Miroslaw Zabek, MD
Mazovian Brodnowski Hospital

David Reardon, MD
Dana-Farber Cancer Institute

Ben Ellingson, PhD
University of California Los Angeles

Puneet Plaha, MD
University of Oxford

Eva Wembacher-Schroder, PhD
BrainLab, Munich, Germany

Ruthie Davi, PhD
Antara Majumdar, PhD
Acorn AI, a Medidata company

Amy McKee, MD
Martin Roessner, MS
Parexel

Sunit Das, MD, PhD
Sorcha Kellett
Labeeba Nusrat
St. Michael's Hospital, Toronto

Yael Mardor, PhD
Sheba Medical Center

Fahar Merchant, PhD
Martin Bexon, MBBS
Nina Merchant, MSc
Melissa Coello, BSc
Minh D. To, PhD
Sudhir Madduri Karanam, MBSS
Medicenna Therapeutics Inc.

This study is partly supported by a grant from Cancer Prevention and Research Institute of Texas (CPRIT)

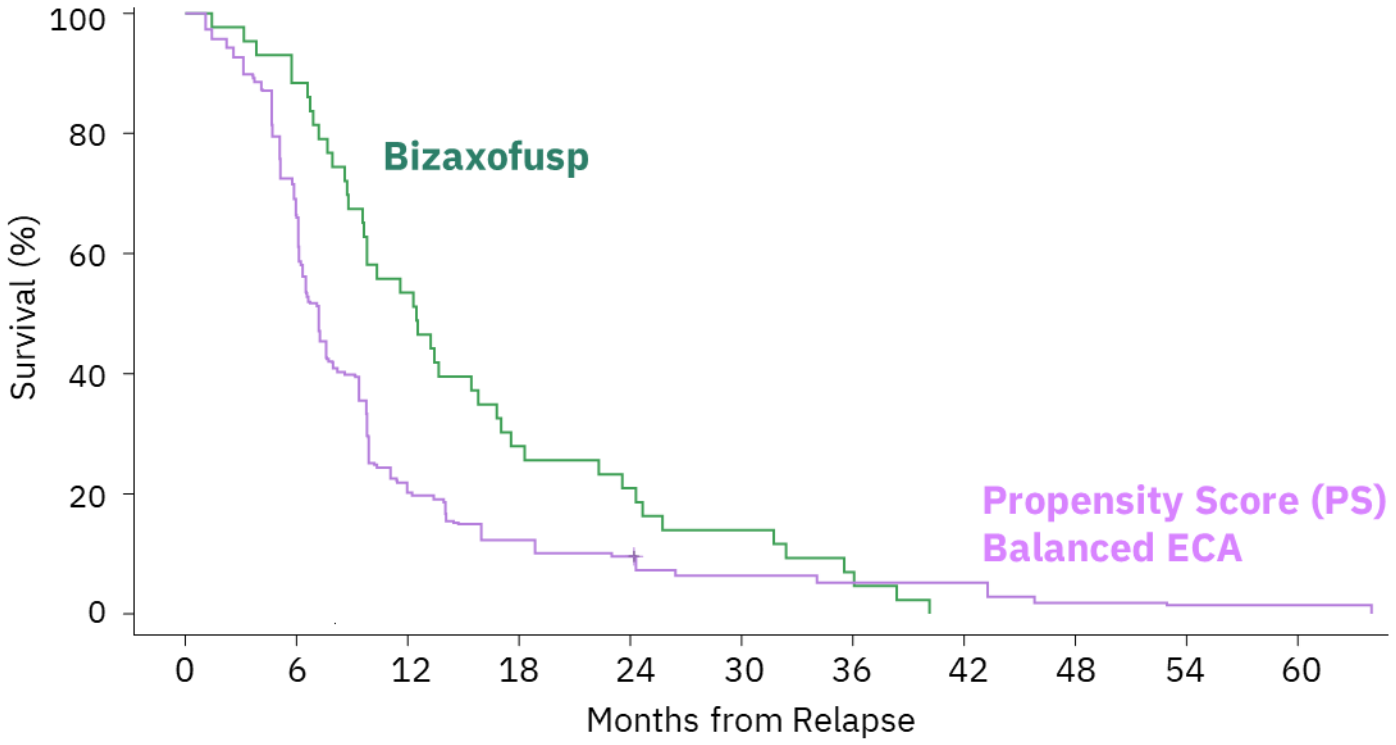
MEDICENNA

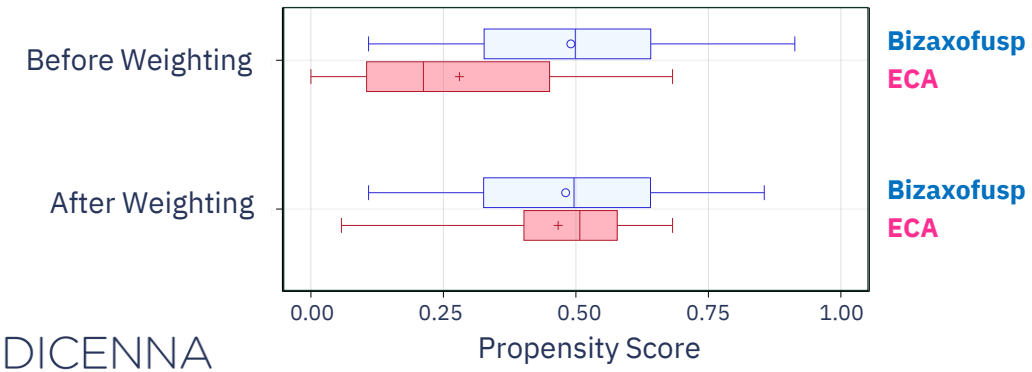
CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Supplement

MEDICENNA

Single Dose of Bizaxofusp Significantly Increased Survival in Phase 2b Study





	PS Balanced ECA (N = 42)	Bizaxofusp (N = 43)
OS-12	20.2%	53.5%
OS-18	12.3%	27.9%
OS-24	9.6%	20.9%
OS-30	6.4%	14.0%
mOS (months)	7.2	12.5
p-value*	**0.0227**	
HR* (95 % CI)	**0.621 (0.413, 0.934)**	

*Log-rank test

MEDICENNA