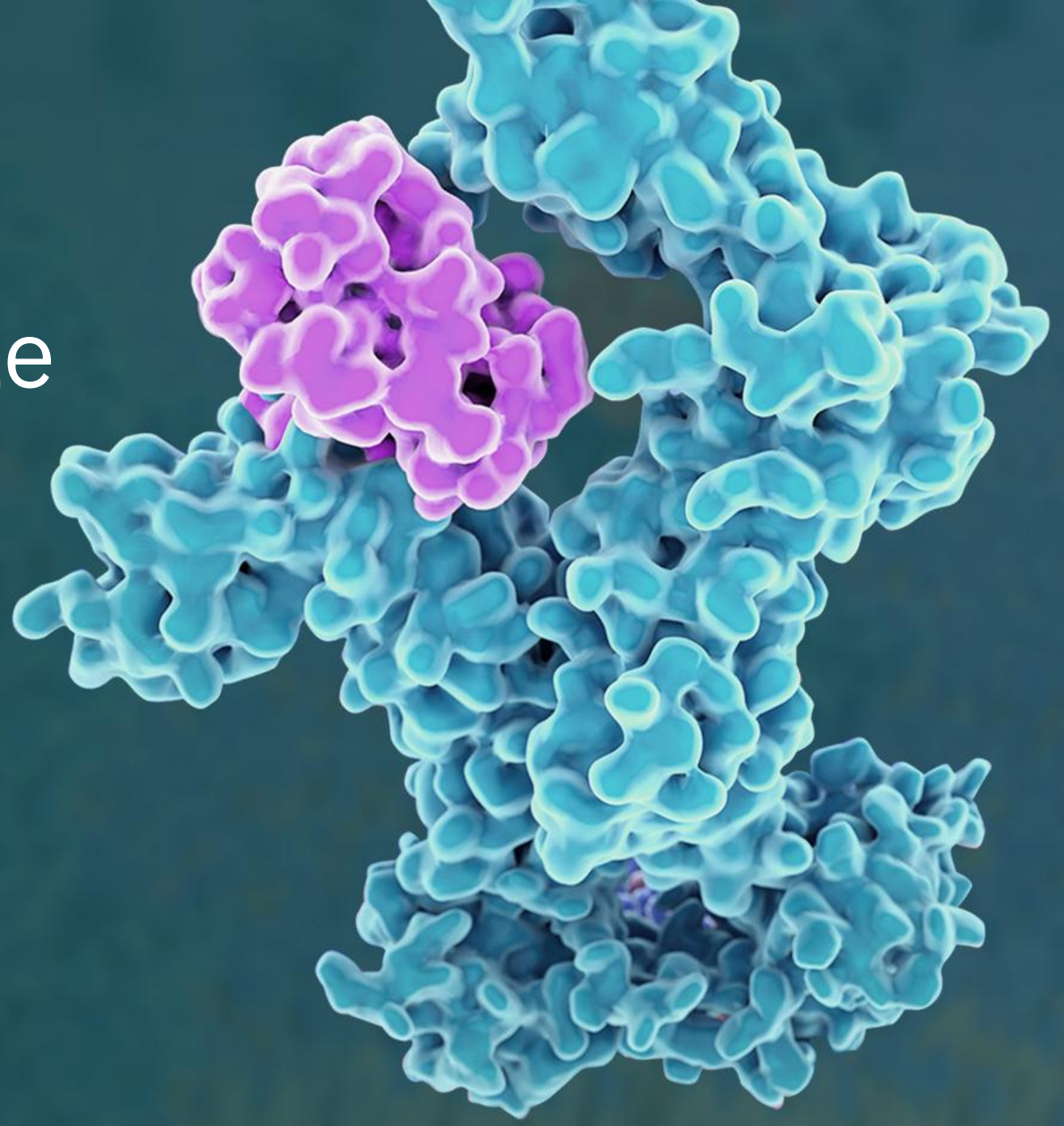
THURSDAY JULY 20, 2023

NBTS Research Roundtable

Washington, D.C.



Planning of a Phase 3 Randomized Controlled Trial Incorporating an External Control Arm

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President and CEO

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Bizaxofusp (aka MDNA55) : A Multi- Pronged Targeted Immunotherapy for rGBM

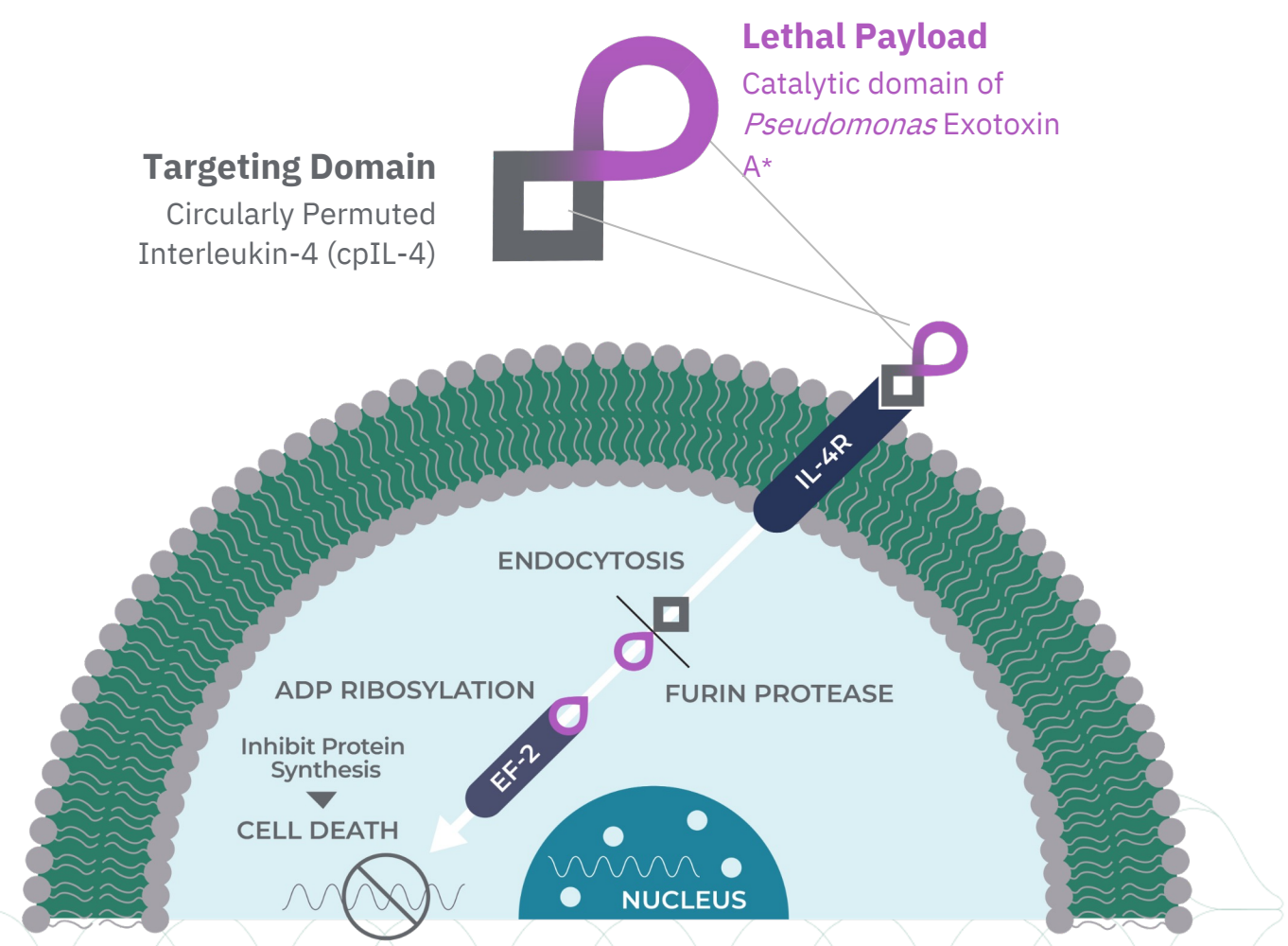
By Passes BBB
Single intra-tumoral CED infusion avoids systemic toxicity and achieves tumor control

Targets IL4R
Receptor is expressed in brain tumors and immunosuppressive, non-malignant tumor microenvironment (TME), but not in healthy brain cells

Highly Selective
Avoids off-target toxicity

Disrupts the TME
Targets IL4R positive MDSCs in GBM unblinds the immunosuppressive TME

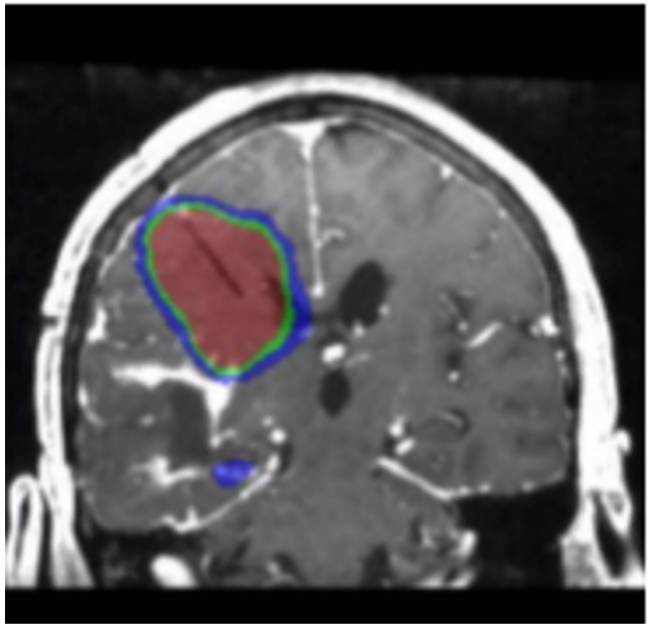
Causes Immunogenic Cell Death
Sustained anti-tumor immunity remains after clearance of Bizaxofusp



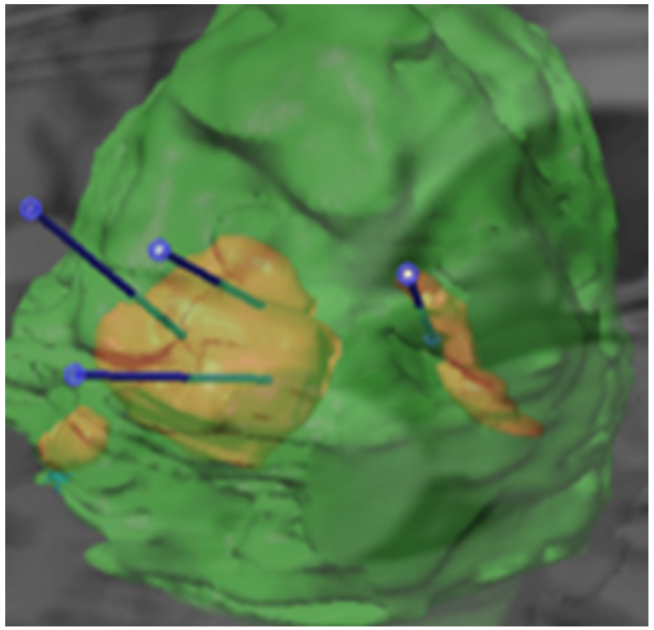
Bizaxofusp: Localized “One And Done” Tumor Delivery

- **High –flow Convection - Enhanced Delivery (CED) Achieves Uniform Distribution to Tumoral & Peritumoral Areas**

Next-Gen High Flow CED



Unique catheter stepped design to **prevent backflow**



Novel delivery improves tumor coverage

MDNA55-05 Phase 2b Study Design

➢ **Open-Label Single Arm Study in Recurrent GBM Patients (n=47) (NCT02858895)**

ELIGIBILITY

- Adults ≥ 18 yrs
- De novo GBM
- 1st or 2nd relapse
- No resection
- KPS ≥ 70
- IDH wild-type only
- Retrospective IL4R analysis from initial Dx

PLANNING

- MRI - tumor size and location
- Optimal catheter trajectory

TREATMENT

- Image-guided catheter placement
- Monitor real-time drug distribution with co-infusion of Magnevist ®
- Single infusion (median 26.5 hrs.)
- Conc. range: 1.5-9.0 µg/mL
- Volume range: 12-66 mL
- Total Dose range: 18-240µg
- Transient low-dose BEV allowed for symptom control and/or steroid sparing (6 and 9 µg/mL cohorts only)

ENDPOINTS

1º Endpoint

- OS

2º Endpoint

- ORR
- PFS
- OS vs. IL4R expression
- Safety

Efficacy Analysis – Primary Endpoint

➢ Statical Design and Sample Size

PRIMARY ENDPOINT

- OS, defined as the time from treatment until death

TEST HYPOTHESIS

- Null hypothesis that survival is 8.0 months (kill) versus the alternative hypothesis (pursue) that survival is 11.5 months following treatment with MDNA55. Hypothesis based on aggregated mOS data from previous clinical trials[1-3]

PRIMARY ANALYSIS

- Assessed according to a single-arm, single-stage binomial design at 1-sided alpha =0.1. A total of 46 Subjects will provide >80% power

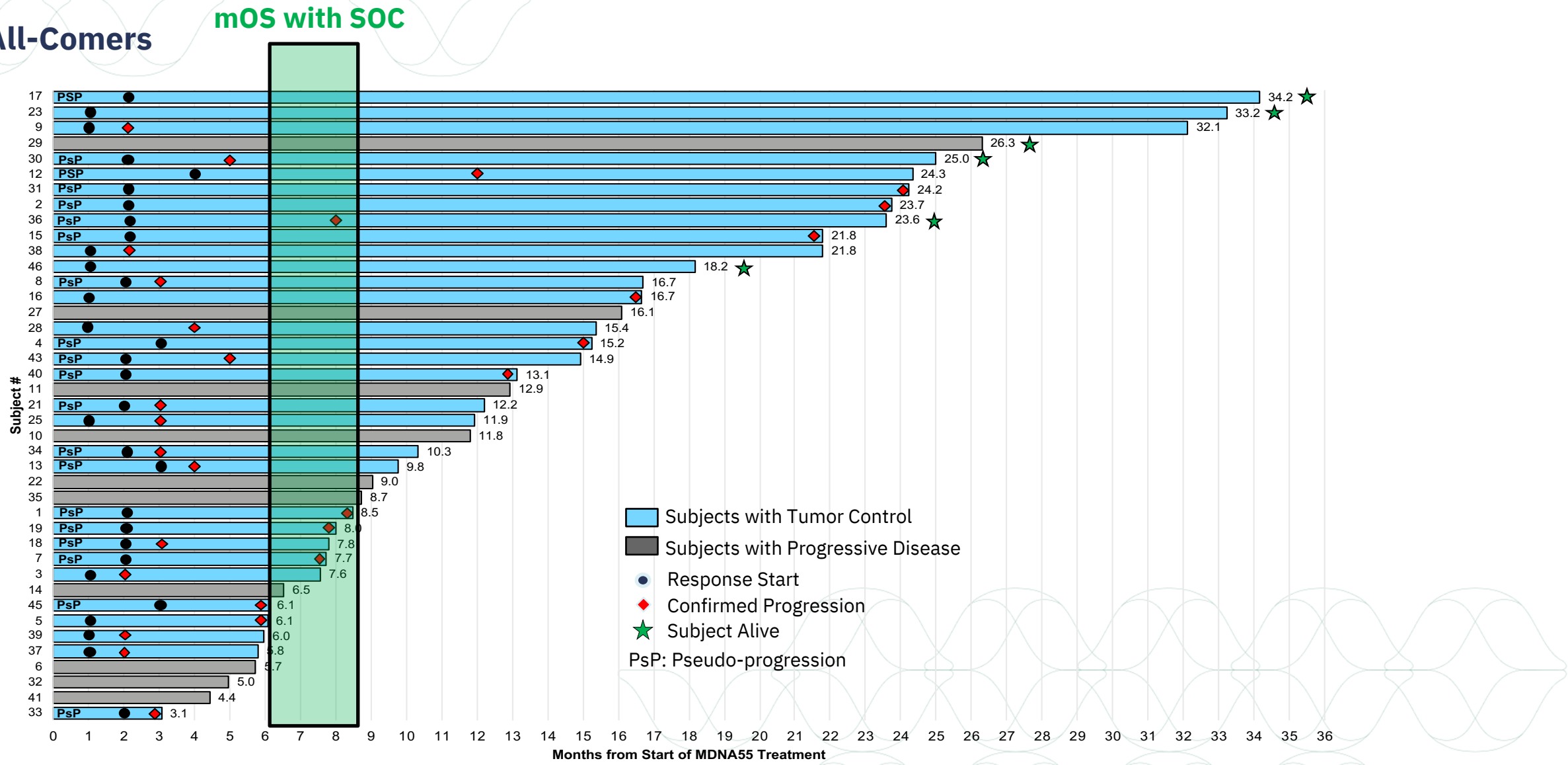
1 Friedman et al., Bevacizumab Alone and in Combination With Irinotecan in Recurrent Glioblastoma. J Clin Oncol. 2009 Oct 1;27(28):4733-40.
2 Taal et al, Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomized controlled phase 2 trial. Lancet Oncol 2014 Aug;15(9):943-53
3 Kim et al., Outcome of salvage treatment for recurrent glioblastoma. J Clin Neuroscience 22 (2015) 468–473, 2015.

MDNA55-05 Phase 2b Trial Patient Demographics

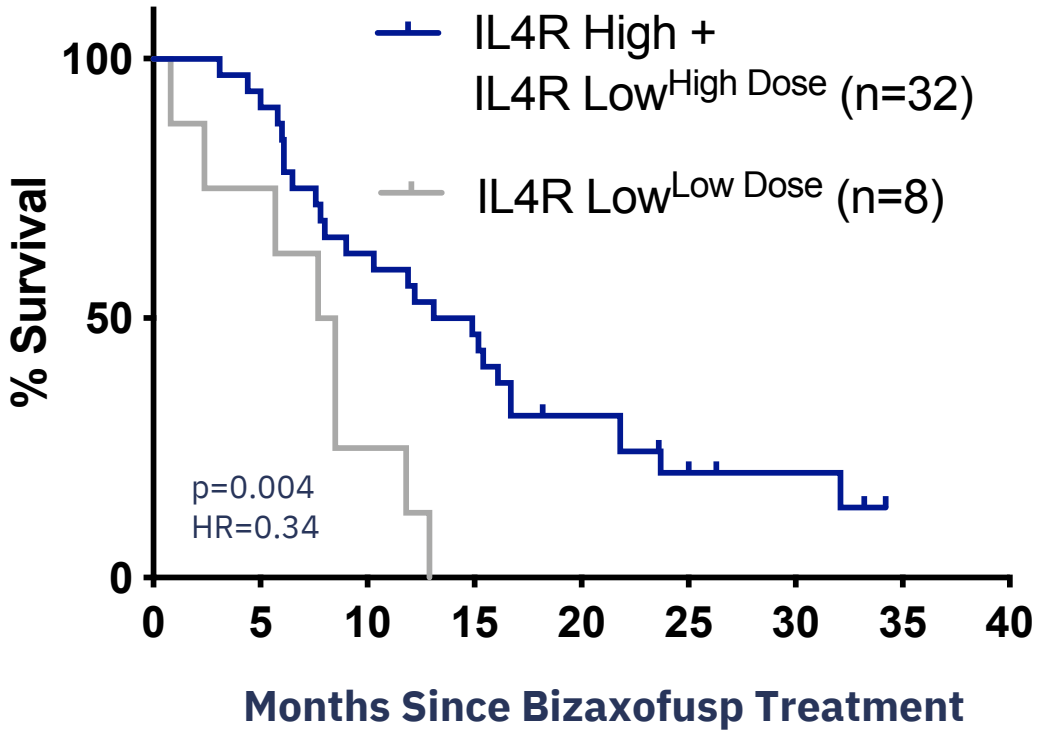
Patient Demographics	N=44
Age (median, range)	55 years (34 – 77)
Sex (Male)	27 / 44 (61%)
KPS at Enrolment: 70, 80 90, 100	22 / 44 (50%) 22 / 44 (50%)
De novo GBM	44 / 44 (100%)
Poor candidates for repeat surgery	44 / 44 (100%)
IDH Wild-type	37 / 37 (100%)
Unmethylated *MGMT*	23 / 40 (58%)
IL4R over-expression	21 / 40 (53%)
Steroid use > 4mg/day	23 / 44 (52%)
Max Tumor Diameter*	29.6 mm (8 – 59)
# Prior Relapse: 1 , 2	35 (80%) , 9 (20%)

*Based on central tumor assessments

Compelling Survival Seen with Bizaxofusp Treatment



High Dose Bizaxofusp Improves Overall Survival Irrespective of IL4R Expression



mOS	OS-12	OS-24
14.0	56%	20%
8.1	13%	0%

IL4R High (irrespective of dose) and IL4R Low patients receiving high dose were identified to benefit most from single treatment of Bizaxofusp

Retrospective Study of an Eligibility Matched External Control Arm (ECA)

Comparison of Survival Outcome with Subjects Enrolled in the MDNA55-05 Clinical Study

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Challenges Associated with a Traditional Randomized Controlled Trial (RCT) in rGBM

- Current NCCN guidelines specify "efficacy of **SOC for rGBM is suboptimal** and consideration of **clinical trials is highly encouraged**"
- Very high unmet need and dismal prognosis result in **patients seeking experimental therapy** in a trial where there is **no risk of randomization to a control SOC arm**
- Blinding may be unfeasible (i.e. due to method of administration) – **inability to blind undermines the purpose of randomization**
- **Withdrawal prior to study therapy initiation** of a significant percentage of participants randomized to the control arm may jeopardize the validity of the control arm and **undermine the value of a randomized trial design.**
- **Disproportionate discontinuation from SOC** arm has been reported as a **cause of study failure** in GBM studies

Retrospective Eligibility Matched External Control Arm Study

➢ **For Comparison of Survival Versus MDNA55-05 Study**

ELIGIBILITY

- Adults ≥ 18 yrs
- De novo GBM
- 1st or 2nd relapse
- Not candidates for resection
- KPS ≥ 70
- IDH wild-type only
- Tumor size ≥1cm x ≤ 4cm
- Archive tissue from initial Dx if available

SOURCE

- Patient registries at:
  - University of California, San Francisco (UCSF)
  - St. Michael's Hospital (Toronto, Canada)
- Study conducted under IRB-approved protocols
- Investigators and Medicenna blinded to survival outcome
- IL4R analysis used same IHC assay as MDNA55-05 study

TREATMENT

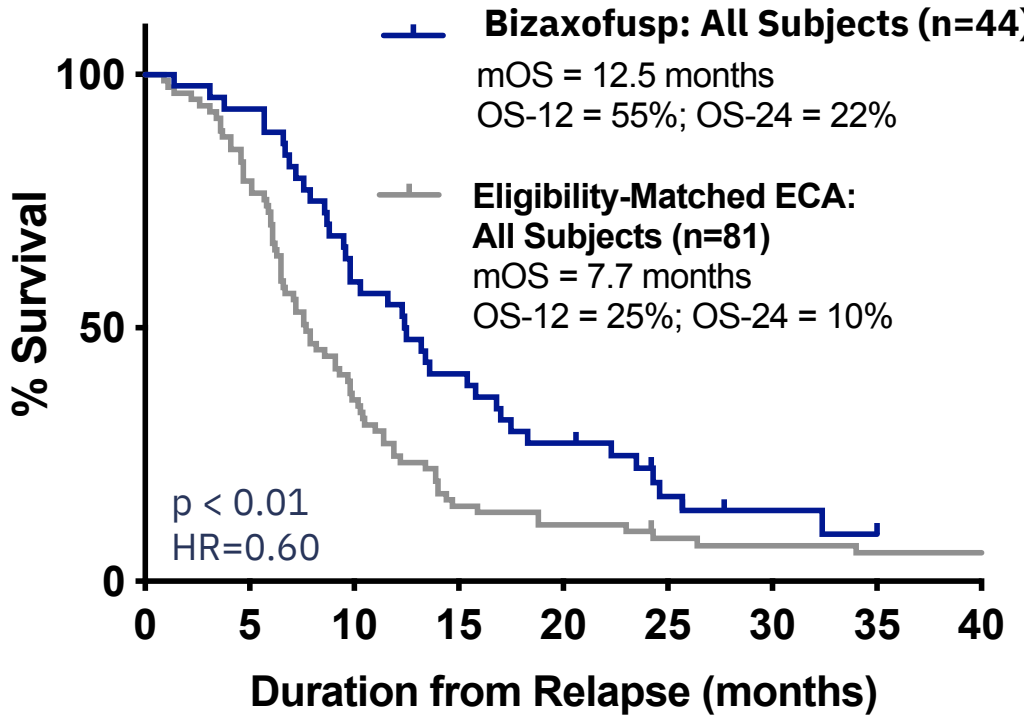
Types of therapies received in the ECA (n=81):

- Avastin (26%)
- Lomustine (25%)
- Temozolomide (14%)
- Experimental Therapy (20%)
- Irinotecan (7%)
- Avastin + Lomustine (5%)
- Radiotherapy (2%)
- Avastin + Radiotherapy (1%)

Prolonged Survival Observed After Bizaxofusp Treatment

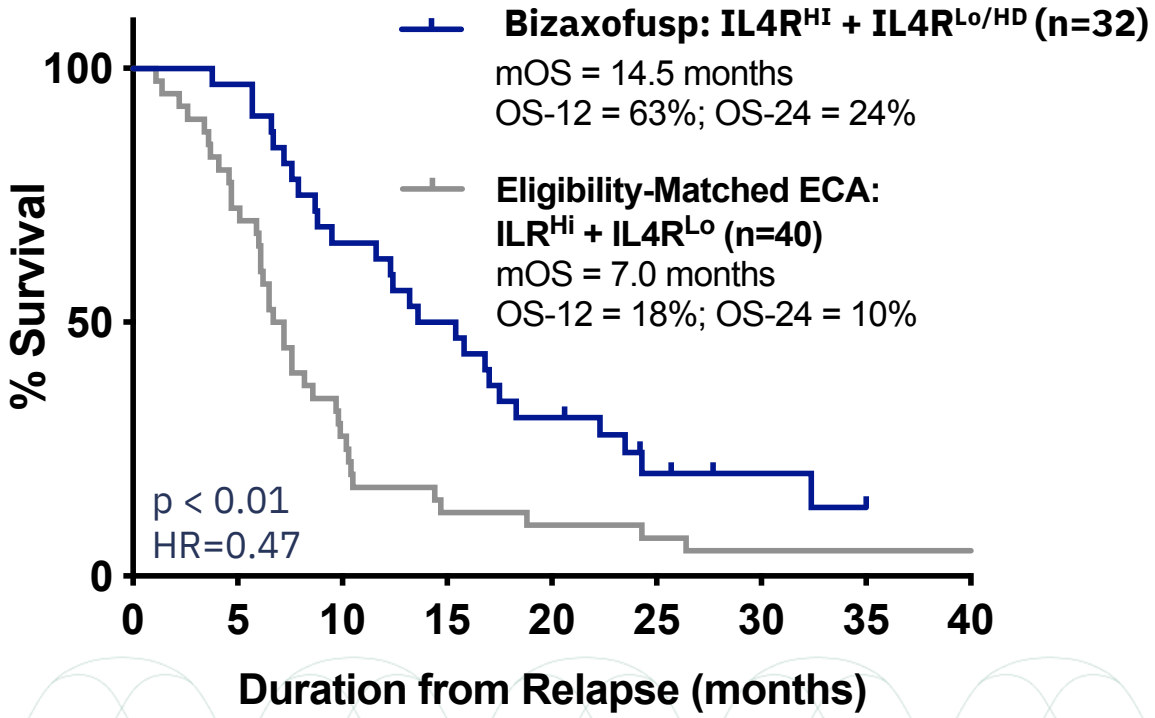
➢ **2 – Year Survival Rate > 20% in Bizaxofusp Subjects**

All-Comers



*Survival calculated from date of relapse.
Median OS from time of Bizaxofusp treatment is 11.9 months; OS-12 = 48%; OS-24 = 20%

IL4R^{Hi} + IL4R$^{Lo/HD}$



*Survival calculated from date of relapse.
Median OS from time of Bizaxofusp treatment is 14.0 months;
OS-12 = 56%; OS-24 = 20%

Retrospective Study of a Propensity Matched External Control Arm (ECA)

Comparison of Survival Outcome with Subjects Enrolled in the MDNA 55-05 Clinical Study

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Retrospective Propensity Matched External Control Arm Study

➢ **For Comparison of Survival Versus MDNA55-05 Study**

ELIGIBILITY

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- Avastin + Radiotherapy (1%)

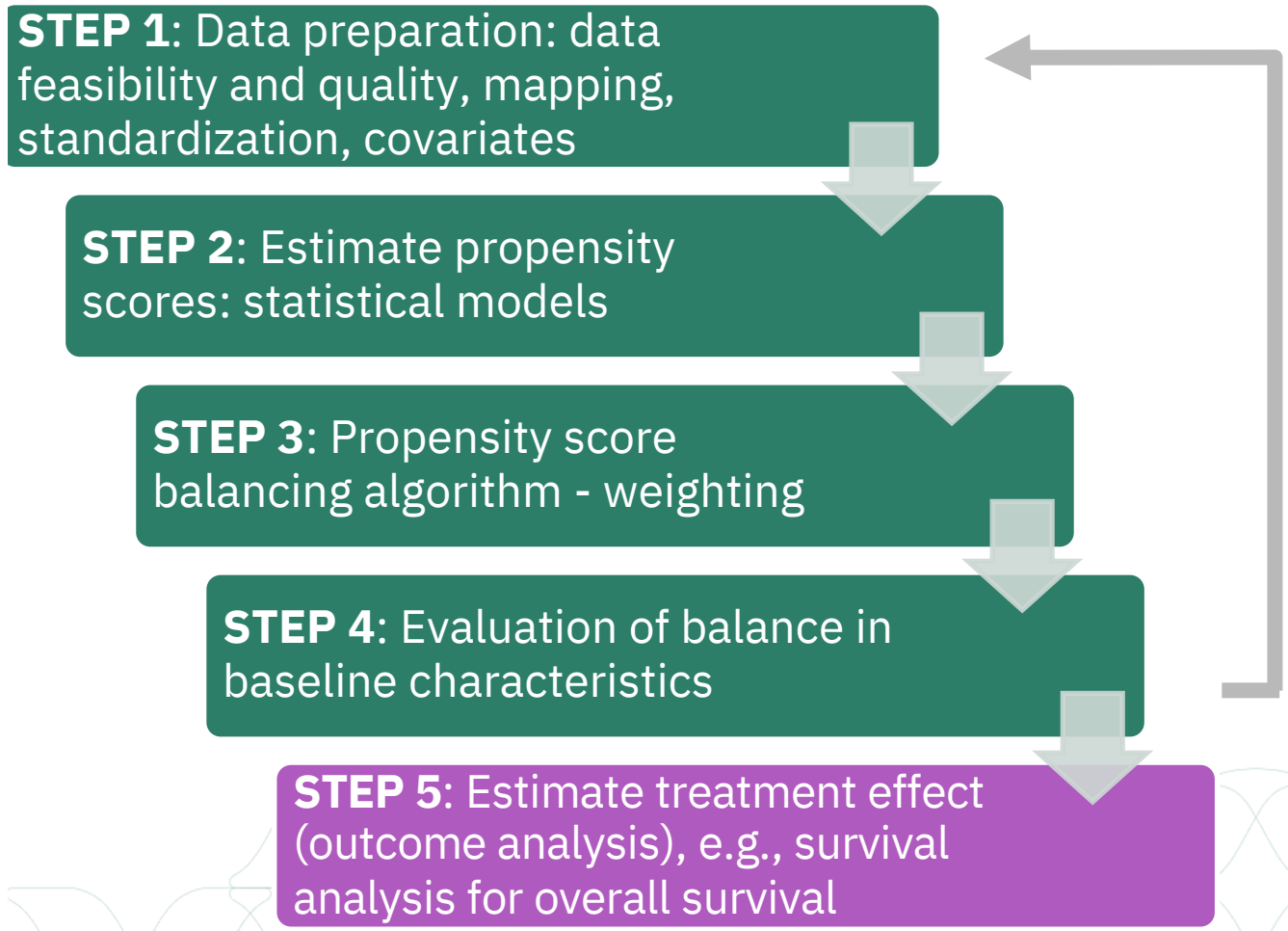
ANALYSIS

- Propensity score methodology was used to balance groups on key prognostic factors; performed prior to unblinding survival data
- Survival time was computed using a common index date (i.e., date of relapse)
- KM curves and HRs were calculated accounting for propensity score weights

Construction of a Propensity Matched External Control Arm

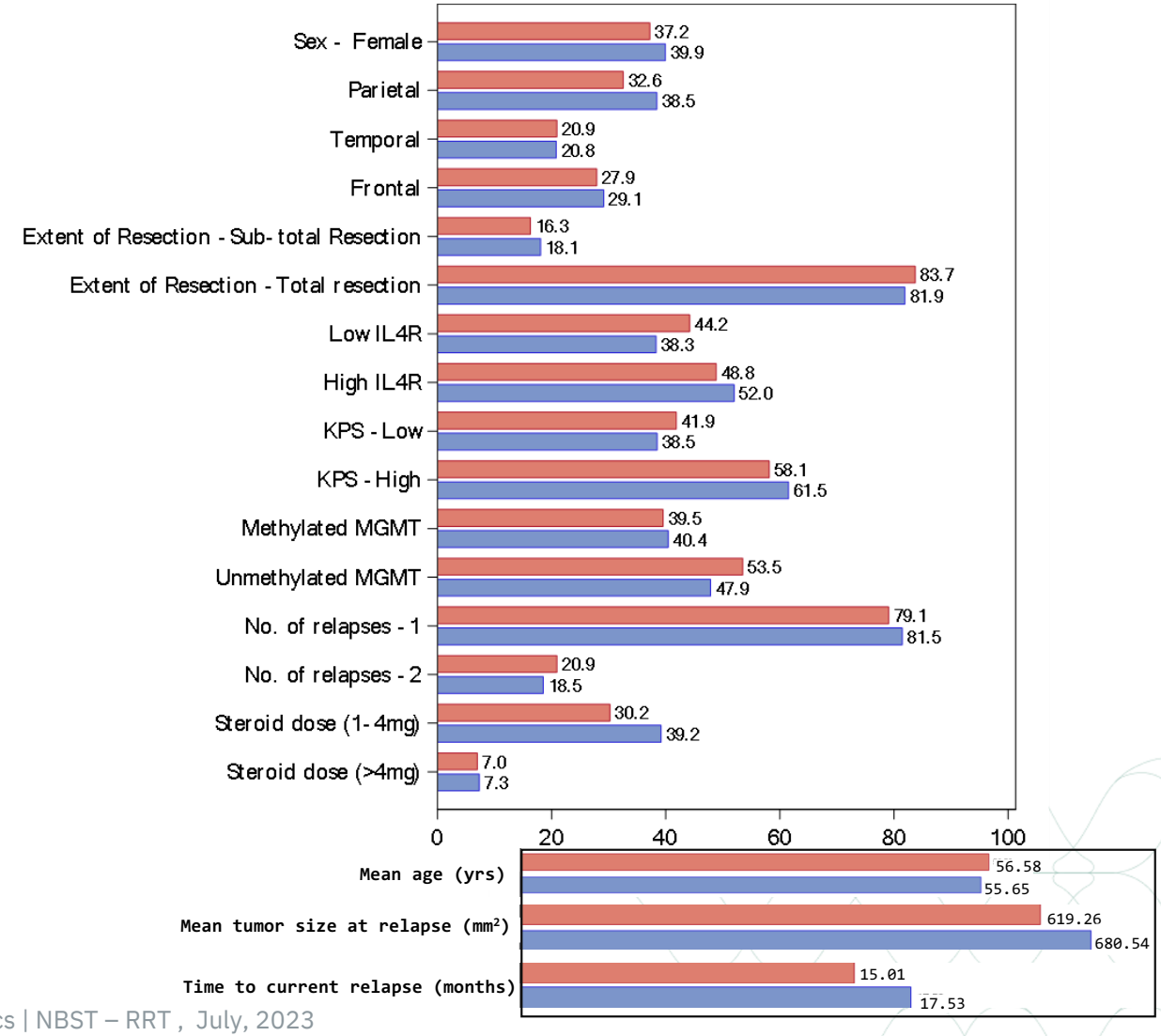
Baseline Characteristics used for Propensity Matching

- Age
- Sex
- KPS
- MGMT methylation status
- IL4R expression level
- 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



Weighted Baseline Characteristics are Well Matched in Both Arms

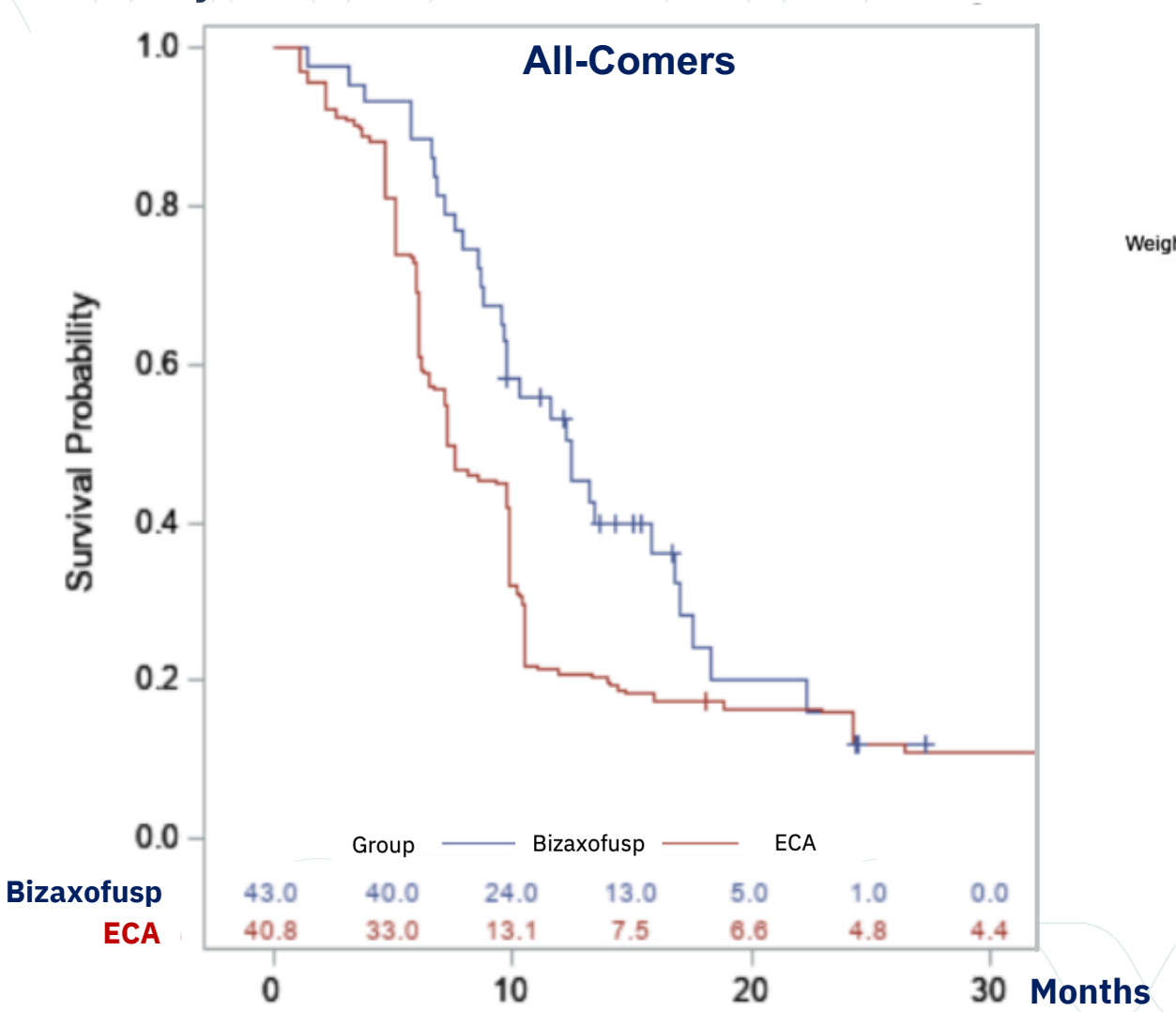
➢ Baseline Demographic and Disease Characteristics



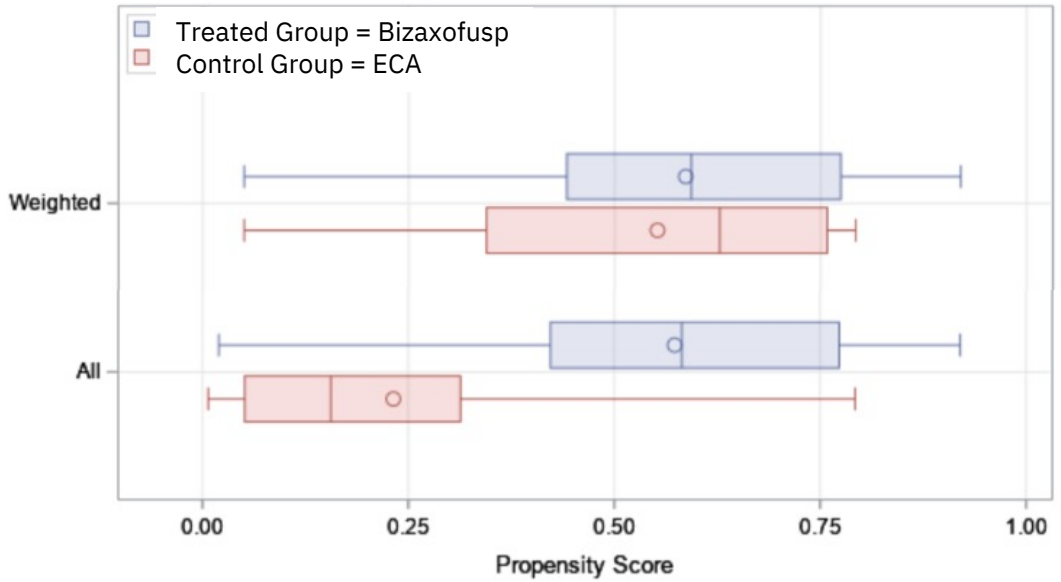
Blue = Bizaxofusp treated
Red = External Control Arm

Weighted Survival For All- Comers

- **Adjusted Product – Limit Survival Estimates**



Distribution of PS



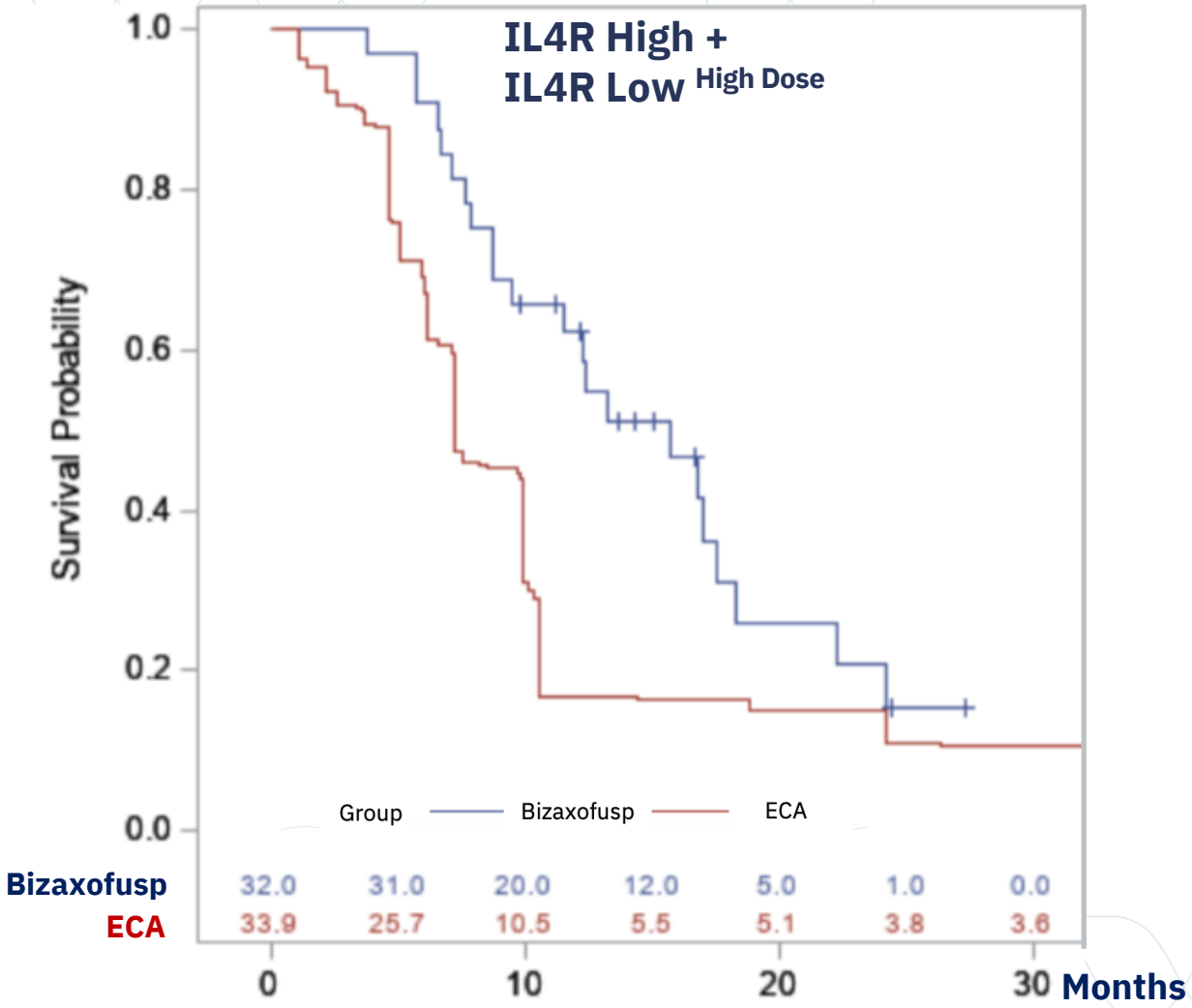
Propensity Score Weighted Estimates:

Group	Median (months)	Log-rank test p-value
Bizaxofusp (n=43)	12.4	0.1426
ECA (n=40.8)	7.2	

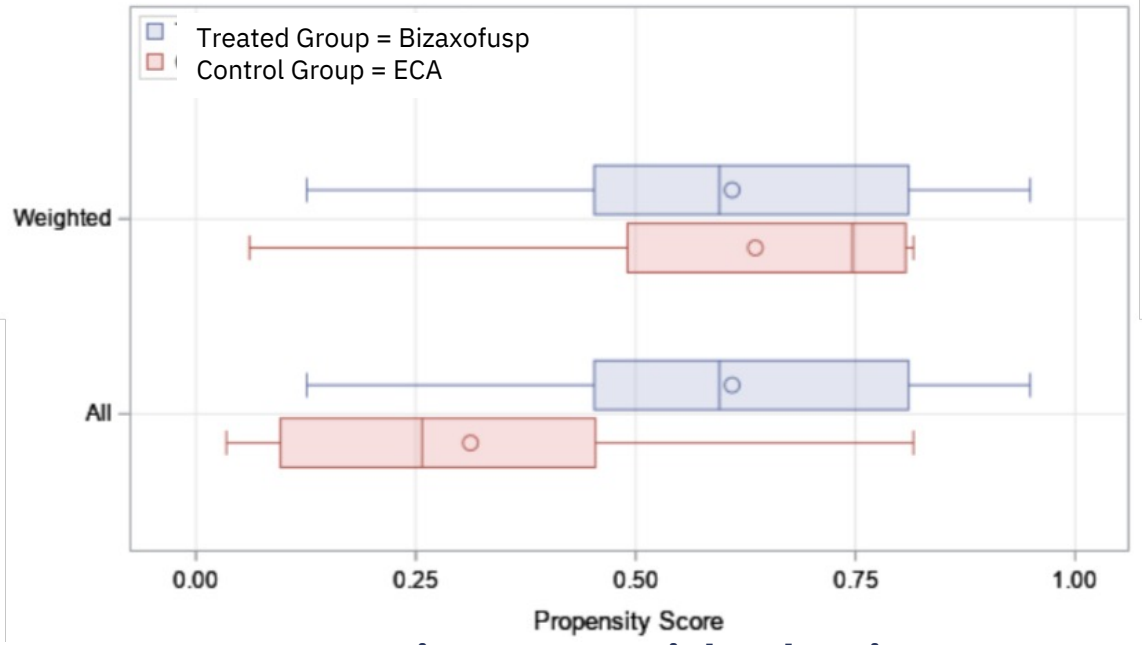
Comparison	Hazard Ratio	95% Confidence Limits	
Bizaxofusp vs ECA	0.634	0.392	1.026

Weighted Survival For IL4R High + IL4R Low^{HD} Group (Phase 3 Population)

➢ **Adjusted Product – Limit Survival Estimates**



Distribution of PS



Propensity Score Weighted Estimates:

Group	Median (months)	Log-rank test p-value
Bizaxofusp (n=32)	15.7	0.1177
ECA (n=33.86)	7.2	

Comparison	Hazard Ratio	95% Confidence Limits	
Bizaxofusp vs ECA	0.523	0.300	0.913

Planned Phase 3 Trial

ECA Arm Details

- Subjects for ECA will be identified at same sites enrolling in bizaxofusp treatment arm to reduce variability.
- ECA subjects will be required to have been treated for recurrence within 5 yrs to ensure contemporaneity.
- Subject will not be eligible for ECA unless all data capture requirements are met to mitigate risk of missing data.
- All efficacy endpoints including survival for the ECA will remain blinded until all data standardization and propensity score balancing has been completed.

Study Assumptions

- 90% power
- HR of bizaxofusp vs. pooled control = 0.65
- 2-sided alpha = 0.05
- Effect size = 4.6 months in mOS time
- Drop-out rate = approximately 5%

Phase 3 Trial – Hybrid Design with ECA

Eligibility:

- Age ≥ 18 yrs
- *De novo* rGBM
- *IDH1/IDH2* WT
- KPS ≥70
- 1st or 2nd relapse
- Re-resection not indicated
- Tumor size <16 cm^2 (SPD)

Protocol enrollment into RCT

Protocol enrollment from ECA

Randomization 3:1

Propensity Score balancing

Bizaxofusp (N~150)
Dose 240 µg

SOC (N~50)

SOC / Matched ECA (N~100)

Primary Endpoint

- Overall survival (OS)

Secondary Endpoint

- OS within IL4R subgroups
- OS within *MGMT* methylation subgroups
- OS-12

SOC therapies allowed:

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

Summary

- First randomized hybrid control arm with an ECA component for a registration trial in oncology
- Trial design retains many elements preferred by FDA for a registration trial
  - Large proportion of patients randomized
  - OS endpoint
  - All data elements required for ECA
- Keys to FDA's acceptance of trial design
  - Large effect size demonstrated in Phase 2b study
  - Significant unmet medical need
  - No substantive change in SOC for rGBM over the time period covered in the ECA
  - Near-contemporaneous ECA by limiting to last 5 years
  - **Buy-in and, in fact, encouragement from FDA statistical review group**

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