Novel Therapy in Treatment of Brain Cancers

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Glioblastoma[1,2]

Age, y	5-Year Relative Survival Rate, %
20-44	22
45-54	9
55-64	6

Treatment

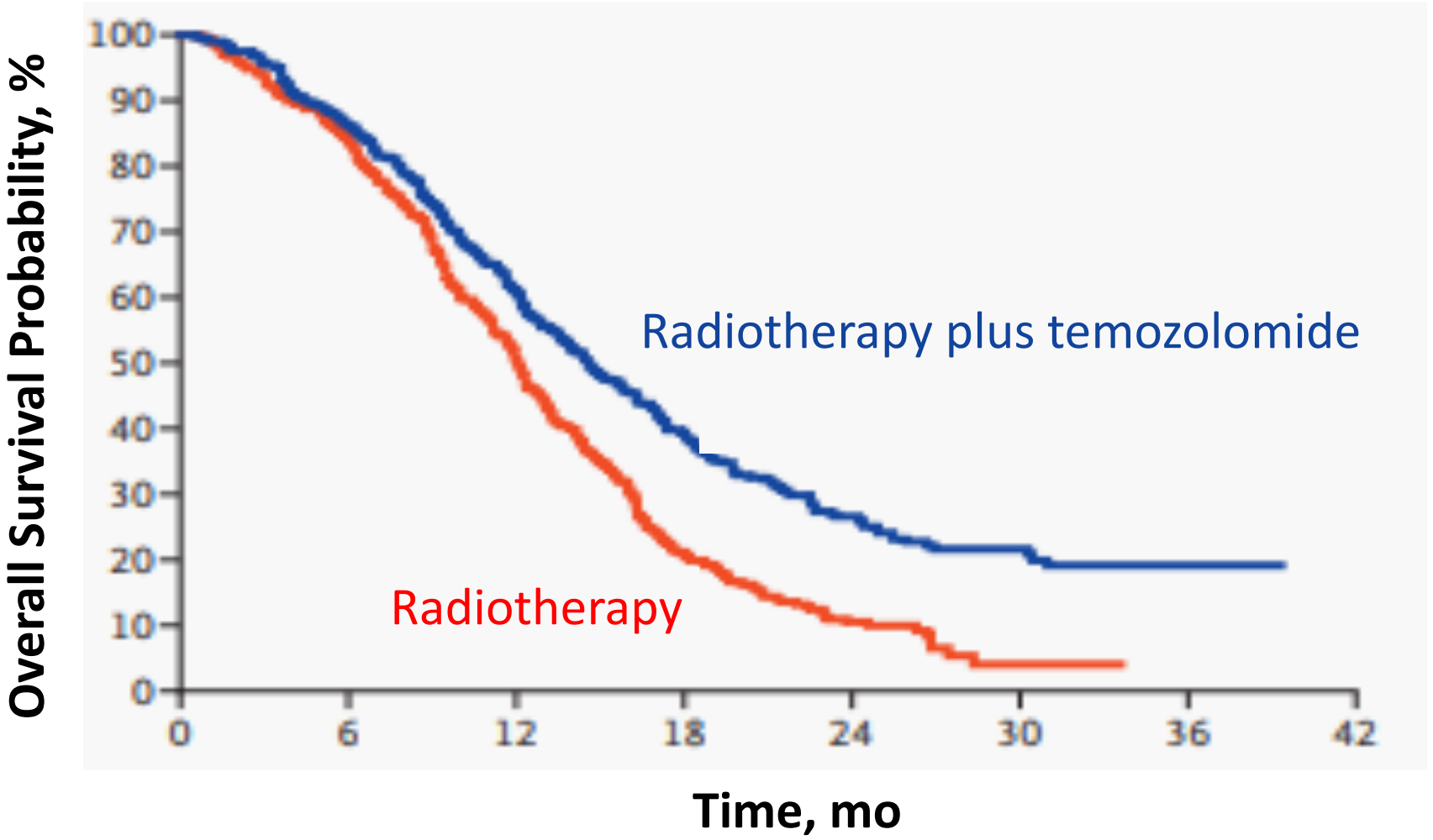
Local/Regional	Systemic
• Surgery • Radiation • TTFields	• Chemotherapy • Biologic therapy • Immunotherapy • Targeted therapy

Glioblastoma presents unique treatment challenges due to:

- Localization of tumors in the brain
- Inherent resistance to conventional therapy
- Limited capacity of the brain to repair itself
- Migration of malignant cells into adjacent brain tissue
- The variably disrupted tumor blood supply, which inhibits effective drug delivery
- Tumor capillary leakage

1. https://www.cancer.org/cancer/brain-spinal-cord-tumors-adults/detection-diagnosis-staging/survival-rates.html.
2. https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Glioblastoma-Multiforme.

The Challenge With Glioblastoma[1]



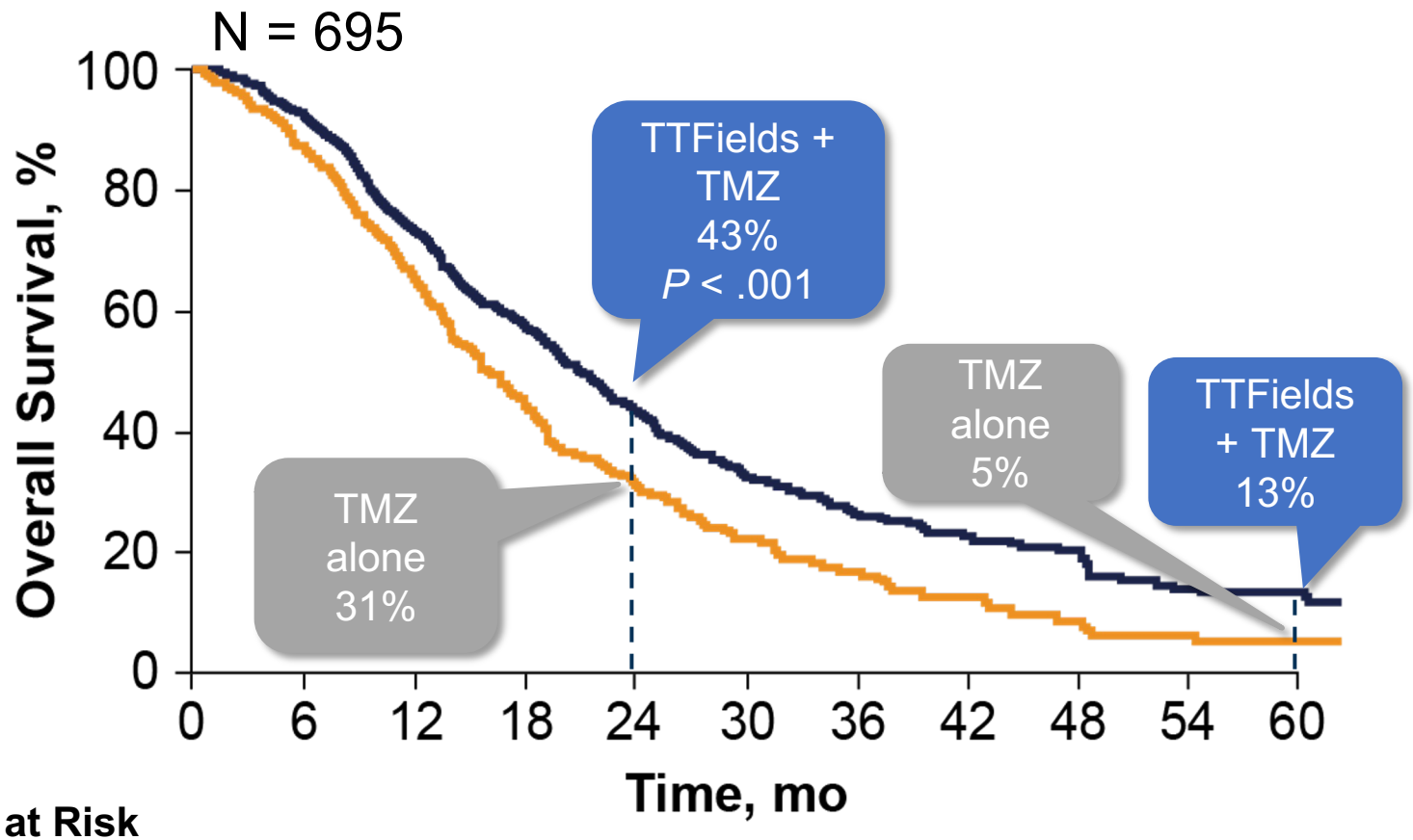
1. Stupp R et al. *N Engl J Med*. 2005;352:987-996.

Delivery of TTFields in Glioblastoma[1-3]

- A portable, noninvasive device that provides localized treatment with TTFields
- TTFields are low-intensity (1-3 V/cm), intermediate-frequency (200 kHz), alternating electric fields delivered in two directions
- Single-use transducer arrays are applied to the scalp to deliver TTFields
- Positioning of transducer arrays is individualized for every patient

1. https://www.accessdata.fda.gov/cdrh_docs/pdf18/H180002B.pdf. 2. https://www.mskcc.org/sites/default/files/node/105264/document/novocure_piom.pdf.
3. Lacouture ME et al. *Semin Oncol*. 2014;41(suppl 4):s1-s14.

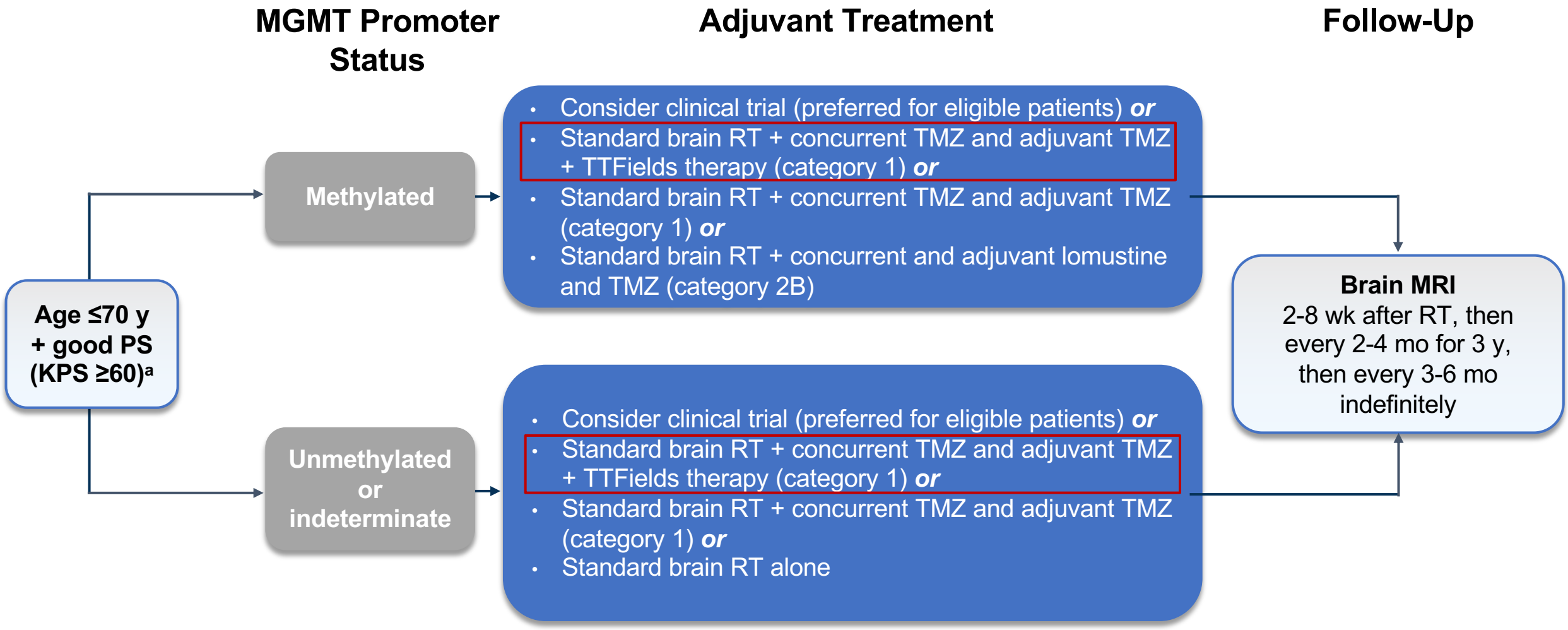
EF-14: Addition of TTFields Improved OS vs Temozolomide Alone (ITT Population)[1-3]



Outcomes	TTFields + TMZ	TMZ
Survival from randomization		
Median, mo (95% CI)	20.9 (19.3-22.7)	16.0 (14.0-18.4)
2 y, % (95% CI)	43.1 (38.7-48.0)	30.7 (25.1-37.5)
HR (95% CI)	0.63 (0.53-0.76)	
P	.00006	
Survival from diagnosis		
Median, mo (95% CI)	24.5 (22.8-26.3)	19.8 (17.6-22.1)

1. Stupp R et al. *JAMA*. 2017;318:2306-2316. 2. Stupp R et al. SNO 2016. Presentation. 3. Stupp R et al. AACR 2017. Abstract CT007.

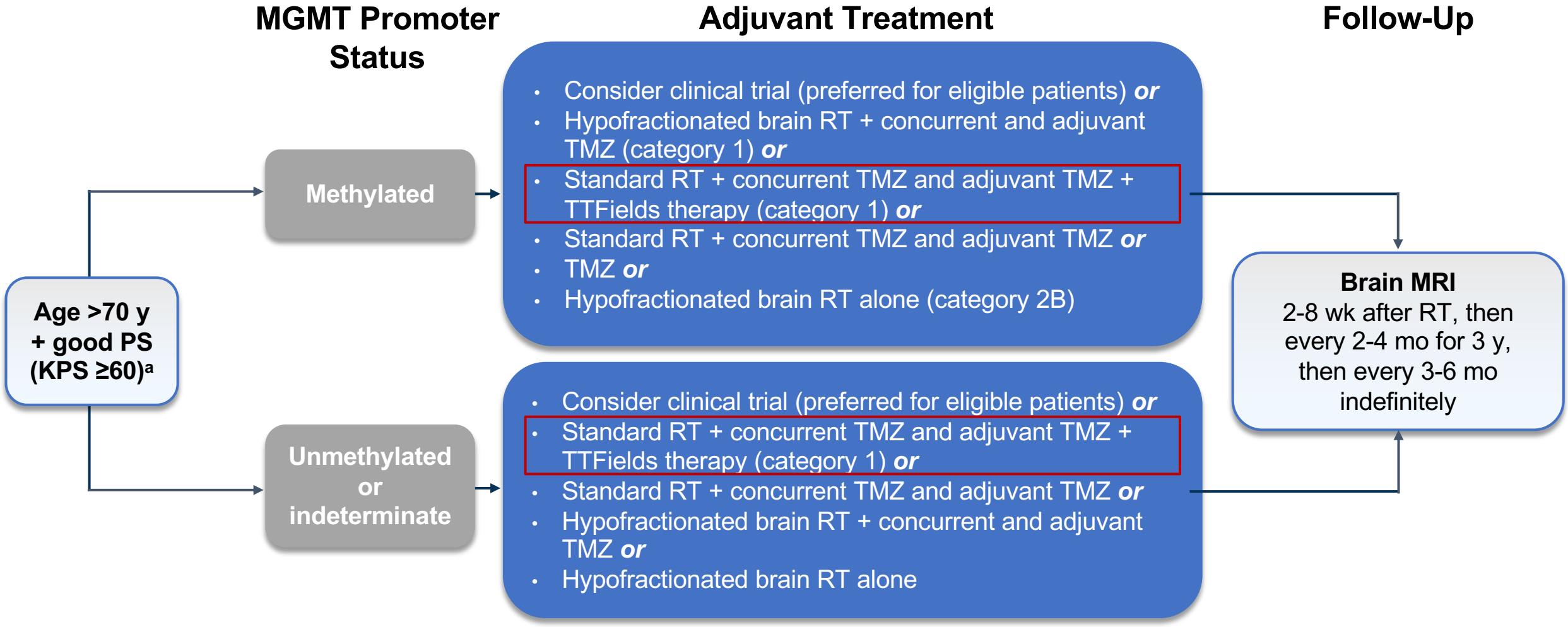
NCCN Recommended Treatment Approaches: Newly Diagnosed Glioblastoma[1]



[a] For patients with poor PS (KPS <60), adjuvant treatment consists of hypofractionated brain RT (preferred) ± concurrent or adjuvant TMZ, TMZ, or palliative/best supportive care, and follow-up consists of brain MRI 2-8 wk after RT, then every 2-4 mo for 3 y, then every 3-6 mo indefinitely.

1. NCCN Clinical Practice Guidelines in Oncology. Central Nervous System Cancers. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf.

NCCN Recommended Treatment Approaches: Newly Diagnosed Glioblastoma[1] (Cont'd)



[a] For patients with poor PS (KPS <60), adjuvant treatment consists of hypofractionated brain RT alone, TMZ, or palliative/best supportive care, and follow-up consists of brain MRI 2-8 wk after RT, then every 2-4 mo for 3 y, then every 3-6 mo indefinitely.

1. NCCN Clinical Practice Guidelines in Oncology. Central Nervous System Cancers. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf.

Treatment Approaches for Recurrent Glioblastoma[1,a]

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Bevacizumab • TMZ • Lomustine or carmustine • PCV • Regorafenib	• Systemic therapy + bevacizumab – Carmustine or lomustine + bevacizumab – TMZ + bevacizumab	• If failure or intolerance to the preferred or other recommended regimens – Etoposide (category 2B) – Platinum-based regimens (category 3) • *NTRK* gene fusion tumors – Larotrectinib – Entrectinib • *BRAF* V600E activation mutation – BRAF/MEK inhibitors ➢ Dabrafenib/trametinib ➢ Vemurafenib/cobimetinib

[a] All recommendations are category 2A unless otherwise indicated.

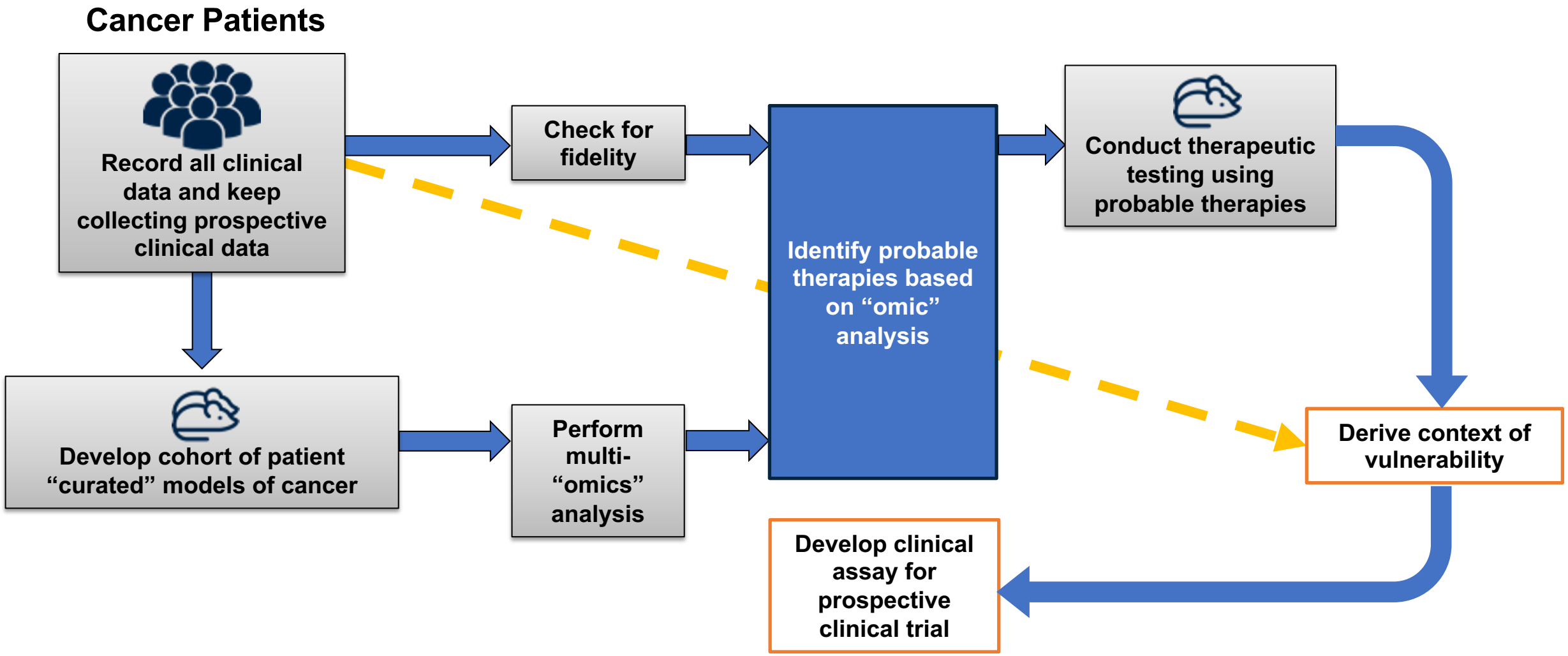
1. NCCN Clinical Practice Guidelines in Oncology. Central Nervous System Cancers. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/cns_blocks.pdf.

Studying Glioblastoma: A New Paradigm[1,2]

- Fewer than 11% of patients with glioblastoma enroll in clinical trials
- Clinical need: changing the clinical trial paradigm
  - Improving patient access
  - Making criteria less restrictive
  - New agents tend to fail in the recurrent setting and are then abandoned

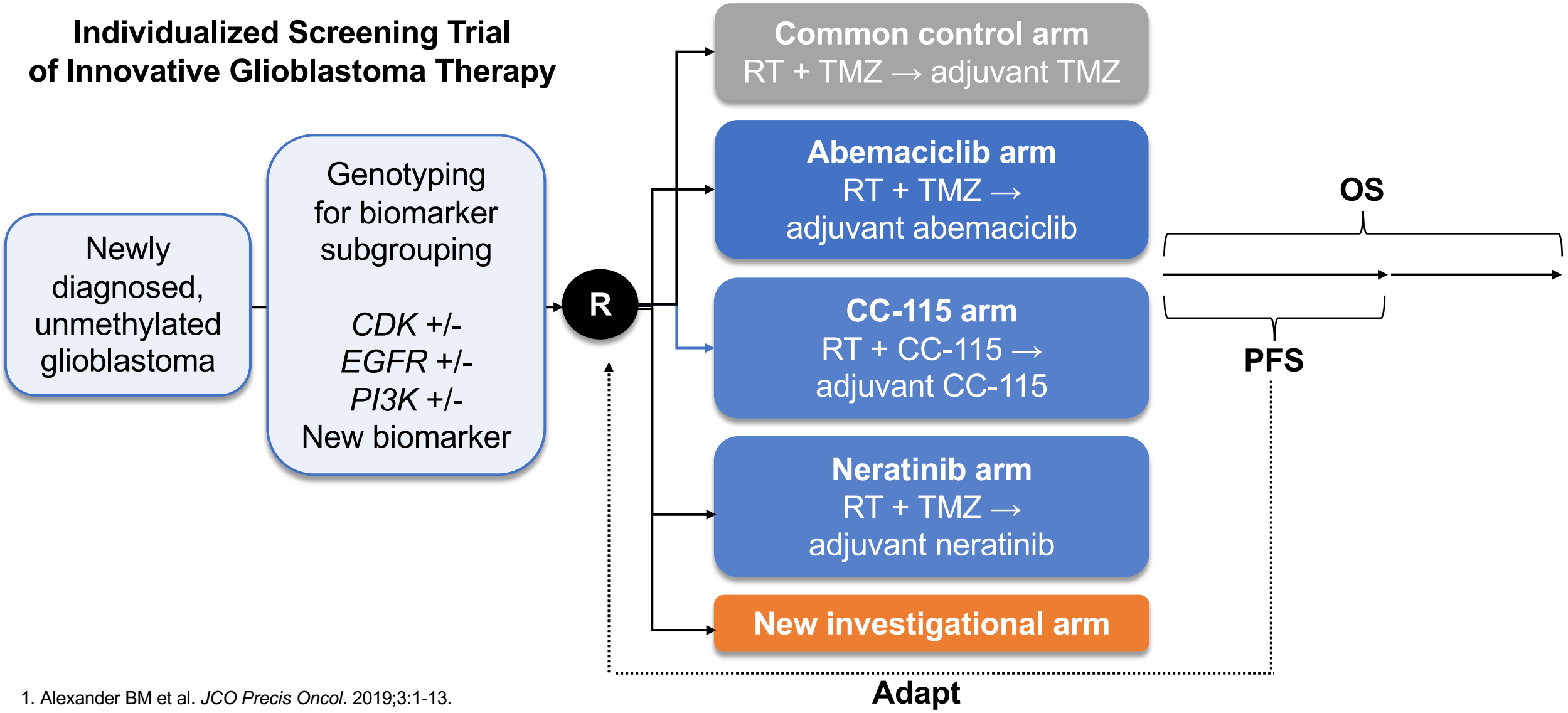
1. Bates AJ et al. *Neuro Oncol*. 2017;19(suppl 6):vi109. 2. Vanderbeek AM et al. *Neuro Oncol*. 2018;20:1034-1043.

Precision Medicine in Cancer: A Top-Down Approach[1]



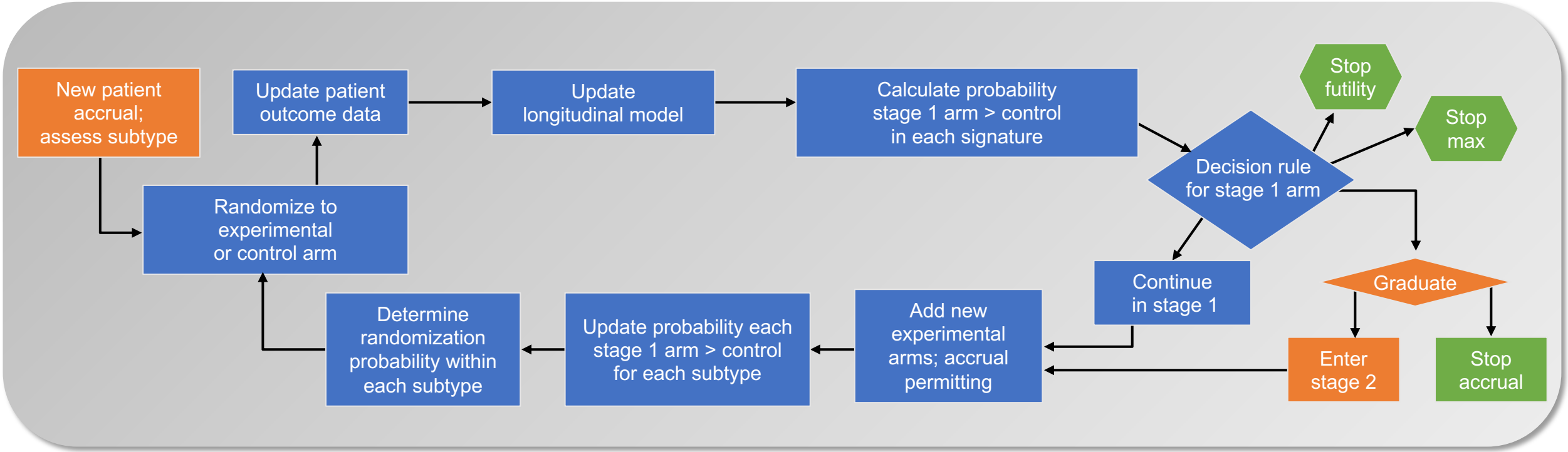
1. Quant Lee E et al. *J Clin Oncol*. 2022;40(suppl 16):2012.

INSIGhT: Study Design[1]



1. Alexander BM et al. *JCO Precis Oncol*. 2019;3:1-13.

GBM AGILE[1,2]

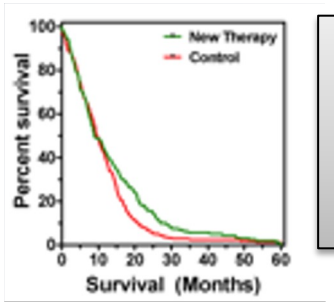


- An adaptive phase 2/3 trial enrolling patients with newly diagnosed and recurrent glioblastoma
- Regorafenib was the first experimental drug in this trial
- Paxalisib and VAL-083 are also being tested in this trial

1. https://clinicaltrials.gov/ct2/show/NCT03970447. 2. Buxton M et al. SNO 2020. Abstract RTID-11.

Precision Medicine in Cancer: A Bottom-Up Approach[1]

Cancer patients clinical trial



Select patient "curated" models of cancer from cohort

Retrospective molecular analysis

Derive context of vulnerability for exceptional responders

Predicted

Responder

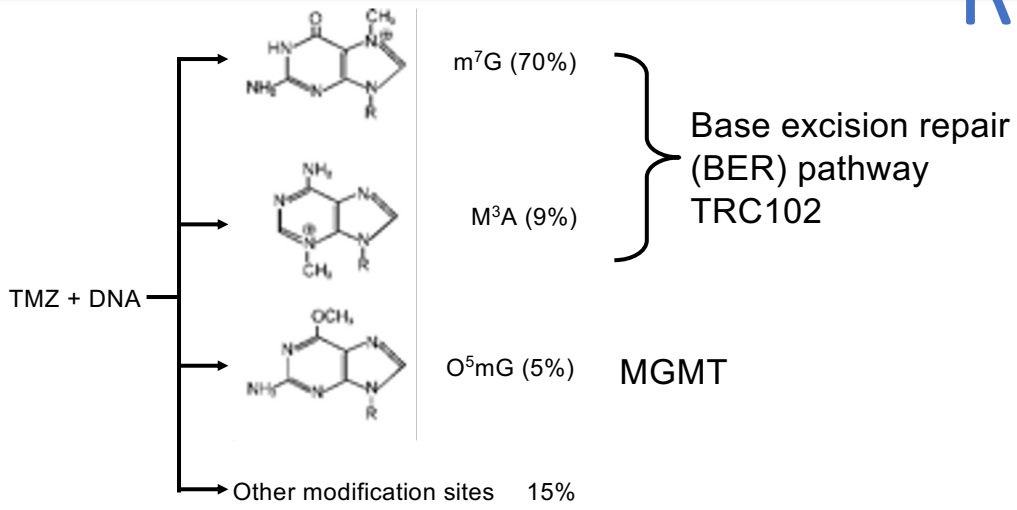
Nonresponder

Develop clinical assay for prospective clinical trial

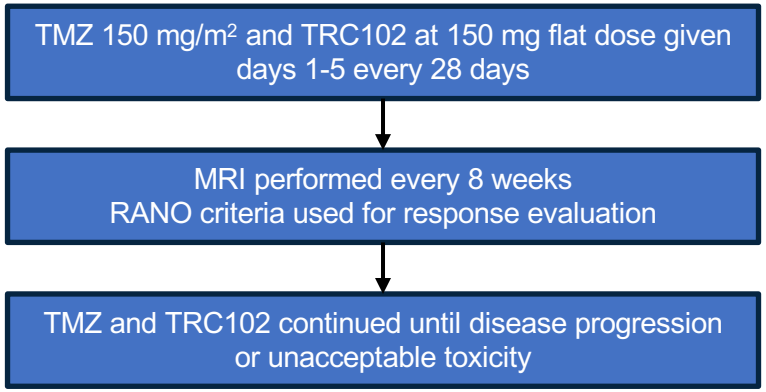
Validate predicted response to new therapy

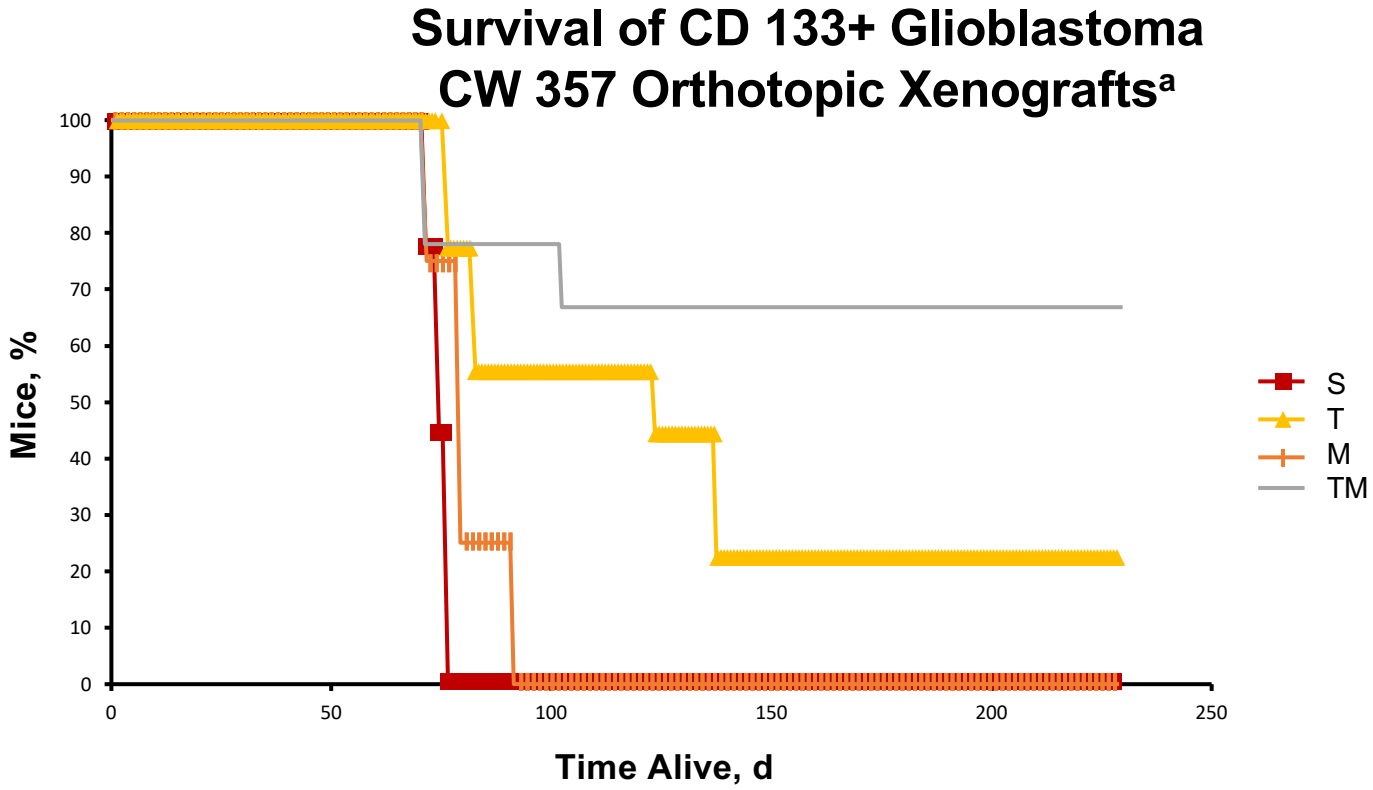
1. Unpublished data.

ABTC 1402: A Phase 2 Trial of Temozolomide and TRC102, in Bevacizumab-Naïve Glioblastoma at First Recurrence[1]



Schema





OS: 11.04 months (95% CI, 8-18 months)

PFS: 1.99 months (95% CI, 1.8-3.6 months)

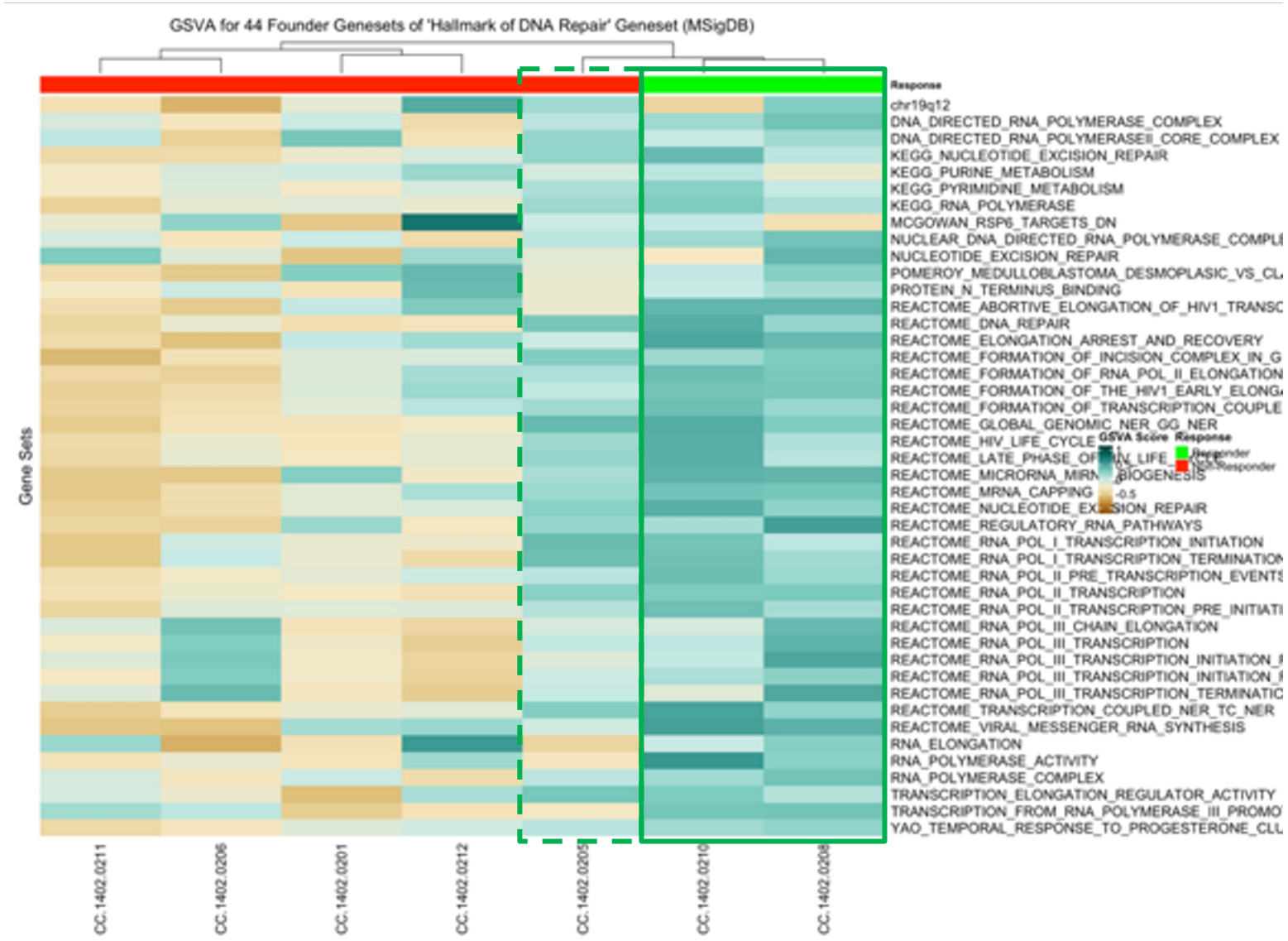
PFS6 rate: 10.5% (2/19)

PFS of 18-30 months in two patients + MPG expression

[a] S = saline (control), T = TMZ 75 mg/kg, M = TRC102 alone, TM = TMZ + TRC102. Unpublished data: courtesy of Andy Sloan, UH-Case Medical Center.

1. Ahluwalia M et al. *Neuro Oncol*. 2018;20(suppl 6):vi15.

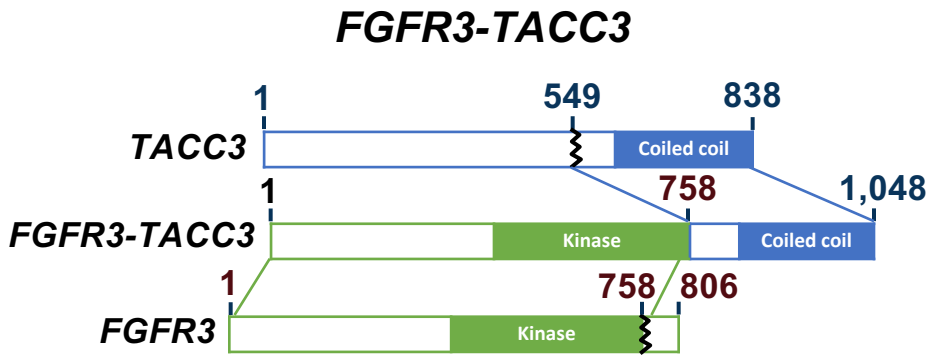
Responder Patients Show Overactivation of DNA Damage Response Pathways[1]

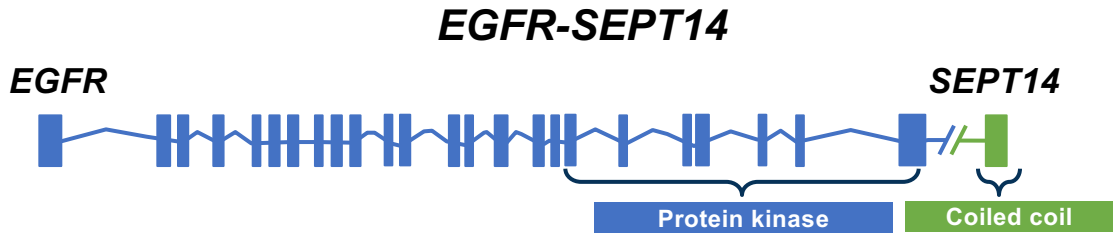


1. Unpublished data.

Gene Fusions as Potential Therapeutic Targets in Glioblastoma[1-3]

- Recurrent fusions thought to be likely drivers
  - Recurrent TCGA analysis estimated that fusions drive development of 16.5% of cancer cases and are the sole driver in more than 1%
- Many fusions result in activation of receptor kinases
- Several examples of successful therapeutic targeting in other cancer types
  - *BCR-ABL*, *PML-RARA*, and *EML4-ALK*
- Multiple fusions identified in small percentage of glioblastoma tumors from multiple studies
  - *FGFR3-TACC3*
  - *EGFR-SEPT14*
  - *NTRK*, *ROS*, and *MET* fusions





1. Gao Q et al. *Cell Rep*. 2018;23:227-238. 2. Singh D et al. *Science*. 2012;337:1231-1235. 3. Frattini V et al. *Nat Genet*. 2013;45:1141-1149.

Investigator-Assessed Efficacy of Larotrectinib in *NTRK* Fusion–Positive Primary CNS Tumors[1,2,a]

	Evaluable Patients (N = 14)
ORR, % (95% CI)	36 (13-65)
Best overall response,[b] n (%)	
CR[c]	2 (14)[d]
PR	3 (21)[d]
SD	9 (64)
PD	0
DCR ≥16 wk,[e] n (%)	11 (79)
DCR ≥24 wk,[e] n (%)	10 (71)
mPFS,[f] mo (95% CI)	11.0 (2.8-NE)

[a] Data cutoff date: February 19, 2019. [b] Investigator assessment based on RANO and RECIST v1.1. [c] Pending confirmation.
[d] All responses were seen in pediatric cases (ORR = 45%; n = 5/11). [e] DCR = CR + PR + SD. [f] In 18 patients with median follow-up of 4.4 months.
1. Drilon AE et al. 2019 American Society of Clinical Oncology Annual Meeting (ASCO 2019). Abstract 2006. 2. Doz F et al. *Neuro Oncol.* 2019;21(suppl 6):vi231.

BRAF/MEK Inhibition in Glioblastoma[1-3]

- Phase 2 VE-BASKET trial of vemurafenib
  - ORR: 42.9% (n = 7)
  - PFS: 5.7 mo
  - OS: not reached
- Phase 2 trial of dabrafenib/trametinib
  - ORR: 56%

Vemurafenib/cobimetinib is associated with improved outcomes and safety compared with vemurafenib monotherapy

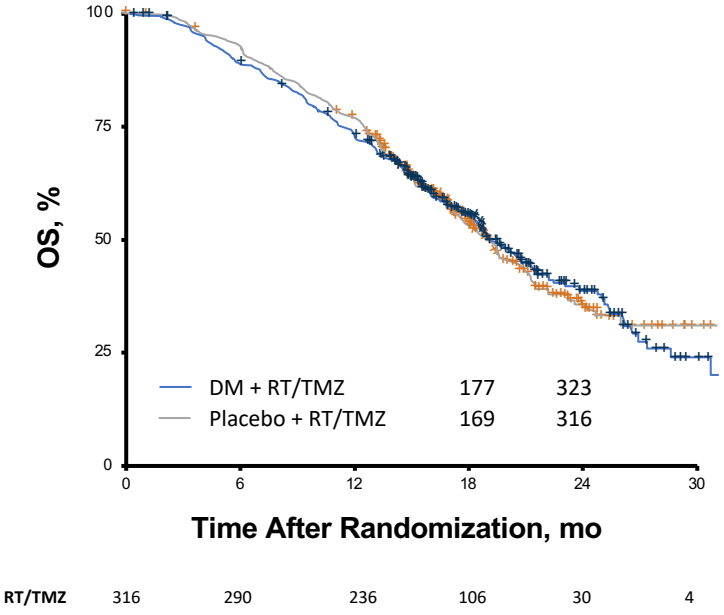
1. Wen P et al. *Neuro Oncol.* 2019;21(suppl 6):vi19-vi20. 2. Brown NF et al. *CNS Oncol.* 2017;6:291-296. 3. Kaley T et al. *J Clin Oncol.* 2018;36:3477-3484.

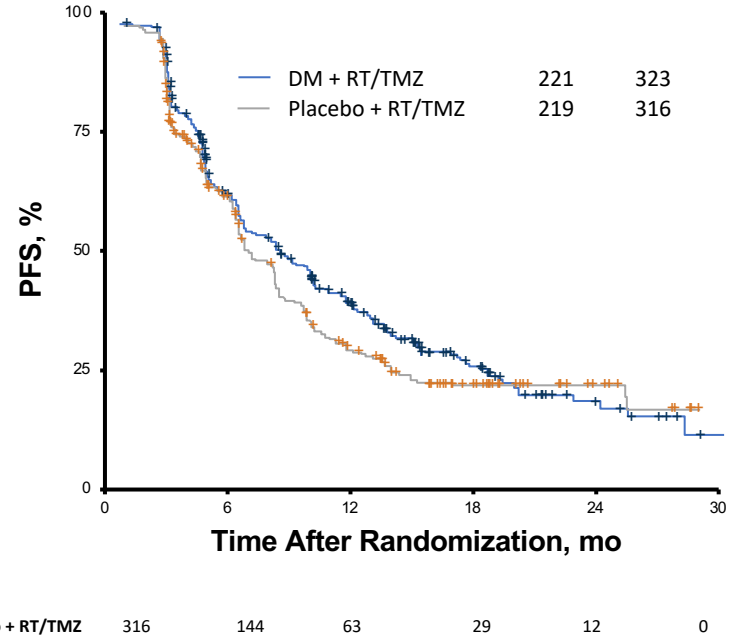
Challenges in Glioblastoma

1. Targeting EGFR
2. Immunotherapy

EGFR-Targeted Therapies in Glioblastoma: Depatuxizumab Mafodotin[1,2]

- 50% of patients with glioblastoma have some form of genetic alteration in the EGFR pathway
- Antibody–drug conjugate: a monoclonal antibody that binds activated EGFR (WT and EGFRvIII mutant) linked to a microtubule-inhibitor toxin



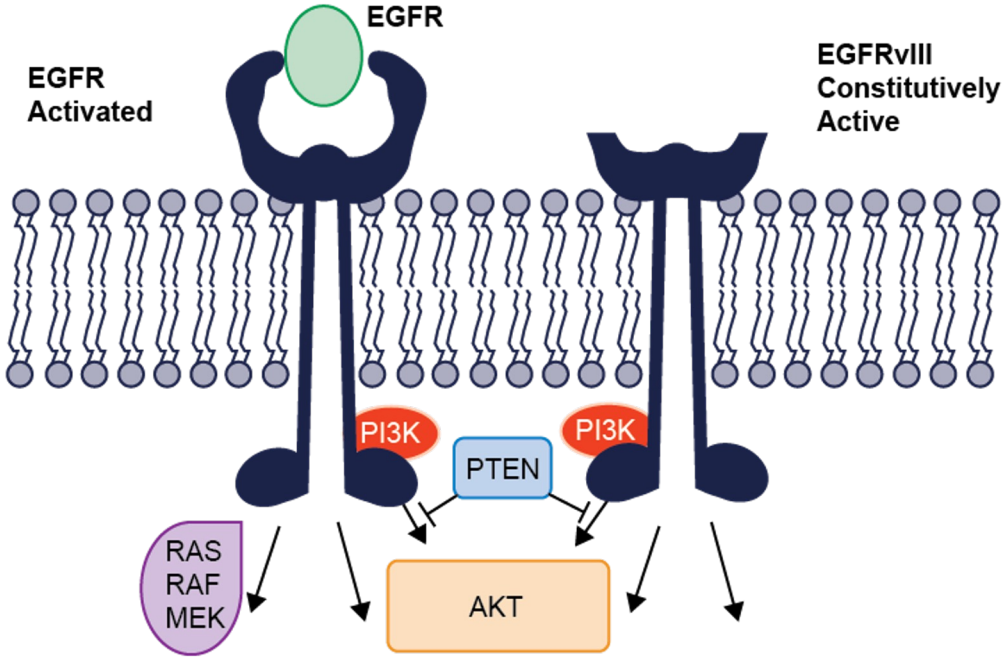


1. Lassman A et al. SNO 2020. Abstract ACTR-21. 2. Lassman AB et al. *Neuro Oncol*. 2022 Jul 15 [Epub ahead of print].

EGFR-Targeted Therapies in Glioblastoma

Ongoing Trials Targeting EGFR

- D2C7-CED: single-chain, monoclonal antibody–fragment immunotoxin (also targets EGFRvIII)
- EGFR (V)-EDV-Dox: nanotechnology + panitumumab
- CAR-T cells that are anti-EGFRvIII
- BiTE: bispecific T-cell engagers
- BATs: bi-armed activated T cells
- ABBV-321: ADC for EGFR
- Cetuximab: intra-arterial infusion



Downstream signaling leads to invasion, survival, proliferation, and angiogenesis

Continued preclinical and clinical research is needed to understand the effect of targeting EGFR in newly diagnosed and recurrent glioblastoma

Immunotherapy Advances in Glioblastoma: Immune Checkpoint Inhibitors and Combination Therapies

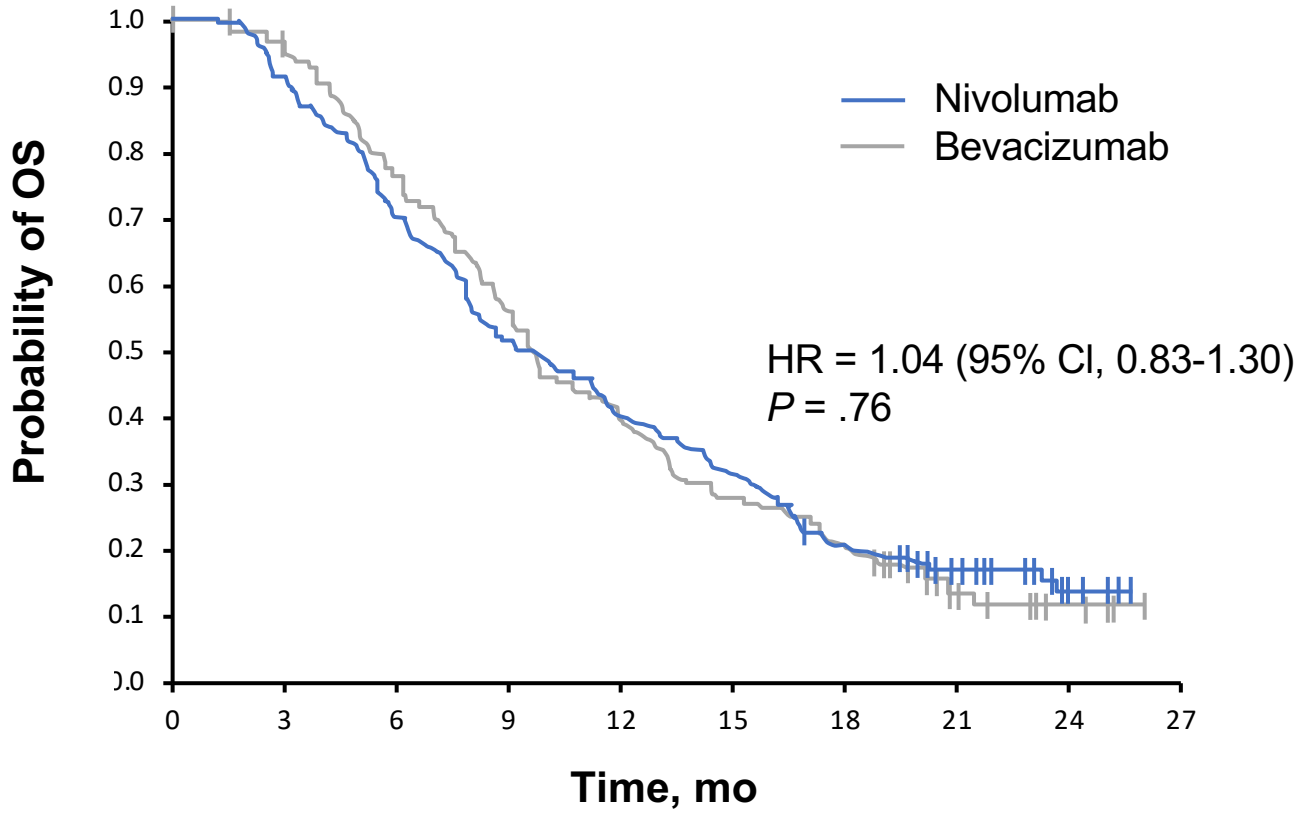
In general, the neuro-oncology community has not enjoyed the groundbreaking studies and observations in glioblastoma that have been seen in other cancers with single-agent use of immune checkpoint inhibitors

In a rare subset of patients with glioblastoma whose tumors have a signature hypermutation burden because of germline biallelic mismatch repair deficiency, there can be a benefit from immune checkpoint inhibition[1]

1. Bouffet E et al. *J Clin Oncol*. 2016;34:2206-2211.

CheckMate -143: Effect of Nivolumab vs Bevacizumab in Patients With Recurrent Glioblastoma[1]

Intervention	Events, n	Median OS, mo (95% CI)	OS Rate, % (95% CI)		
			6 mo	12 mo	18 mo
Nivolumab	154	9.8 (8.2-11.8)	72.3 (65.2-78.2)	41.8 (34.7-48.8)	21.7 (16.1-27.9)
Bevacizumab	147	10.0 (9.0-11.8)	78.2 (71.2-83.6)	42.0 (34.6-49.3)	21.6 (15.8-28.0)

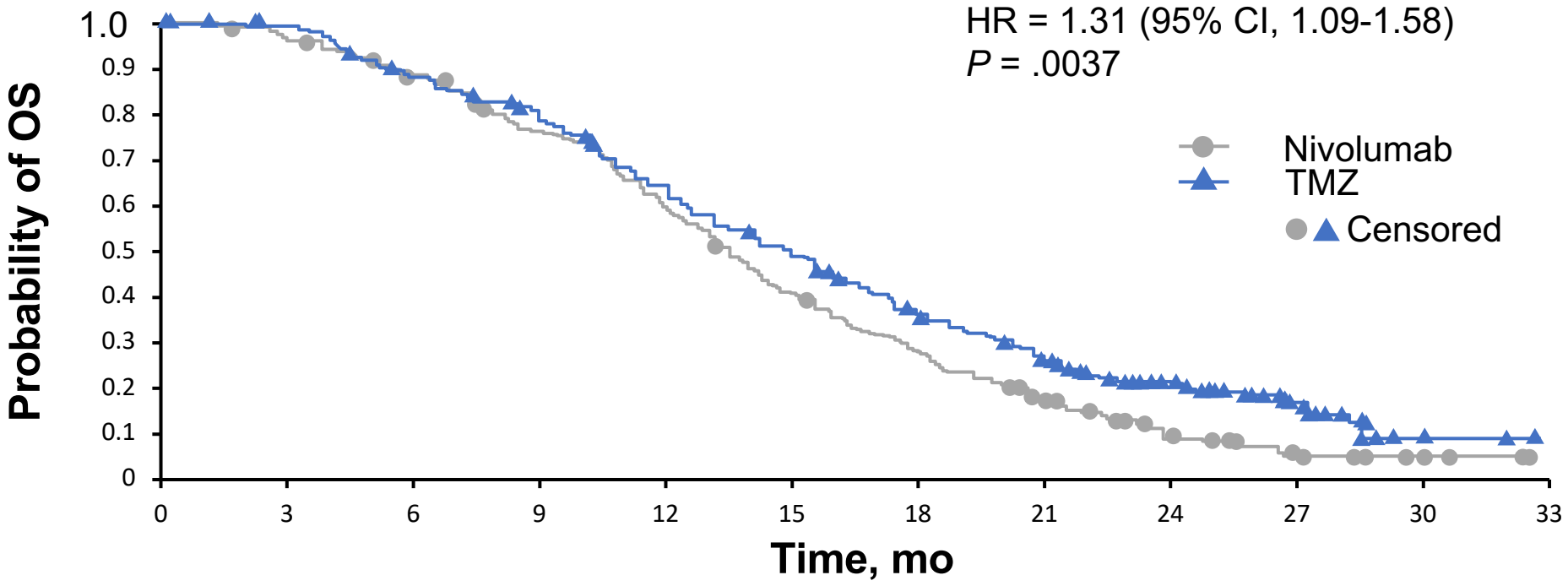


Although the primary endpoint was not met in this randomized clinical trial, mOS was comparable between nivolumab and bevacizumab in the overall patient population with recurrent glioblastoma

1. Reardon DA et al. *JAMA Oncology*. 2020;6:1003-1010.

CheckMate -498: RT + Nivolumab vs RT + TMZ for Newly Diagnosed Glioblastoma With Unmethylated MGMT[1]

Intervention	Events, n	Median OS, mo (95% CI)	OS Rate, % (95% CI)			
			6 mo	12 mo	18 mo	24 mo
Nivolumab + RT	244	13.4 (12.6-14.3)	88.5 (84.1-91.7)	58.3 (52.2-63.9)	28.5 (23.3-34.0)	10.3 (6.8-14.6)
TMZ + RT	218	14.9 (13.3-16.1)	88.7 (84.4-91.9)	62.3 (65.3-67.8)	36.4 (30.7-42.2)	21.1 (16.4-26.5)

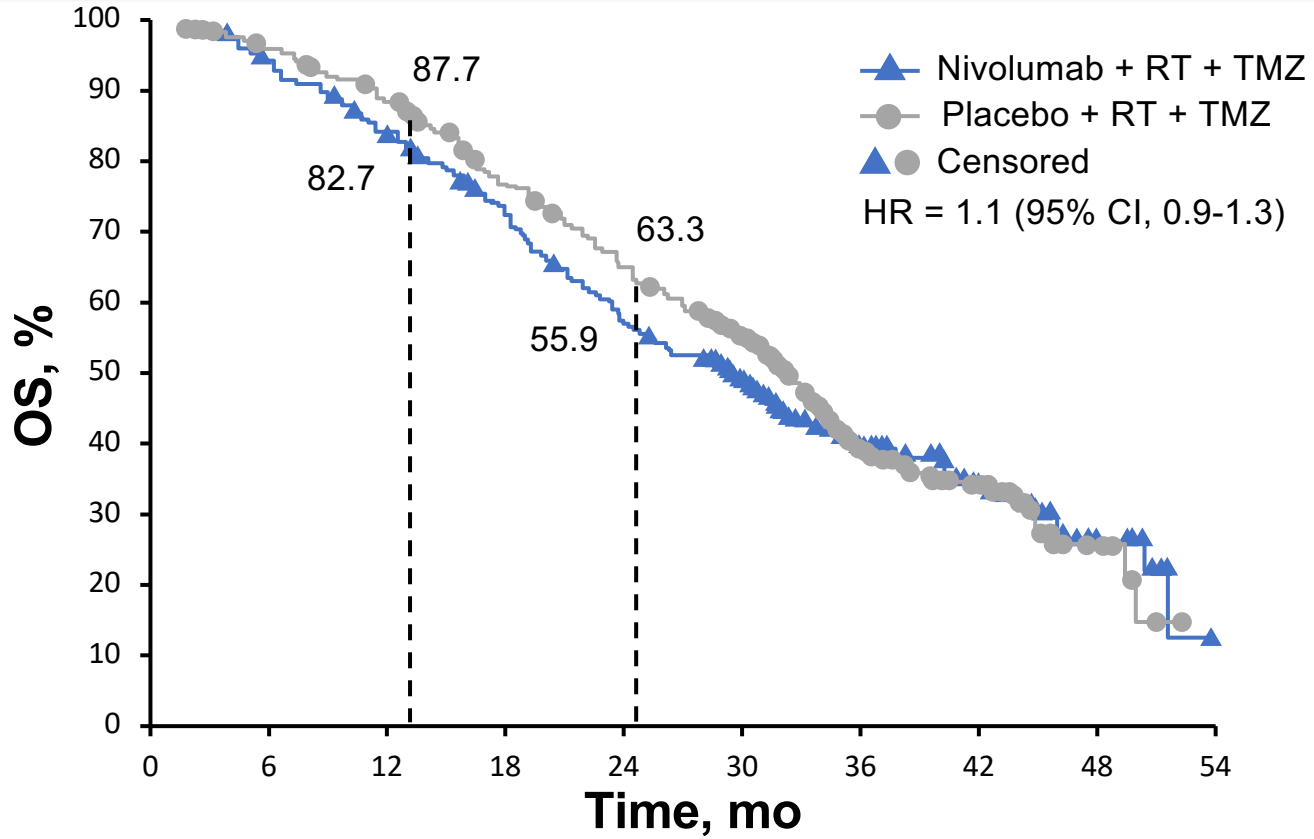


No. at Risk												
Nivolumab	280	270	243	209	158	110	76	44	19	9	2	0
TMZ	280	272	242	212	166	131	92	67	37	19	2	0

1. Omuro A et al. *Neuro Oncol*. 2022 Apr 14 [Epub ahead of print].

CheckMate -548: RT + Temozolomide + Nivolumab for Newly Diagnosed Glioblastoma With Methylated MGMT[1,2]

- Patients (N = 716) aged ≥18 y were randomized 1:1 regardless of tumor PD-L1 expression
- mPFS: 10.6 mo with nivolumab + RT + TMZ vs 10.3 mo with placebo + RT + TMZ (HR = 1.06 [95% CI, 0.90-1.25])
- mOS: 28.9 mo with nivolumab + RT + TMZ vs 32.1 mo with placebo + RT + TMZ (HR = 1.10 [95% CI, 0.91-1.33])

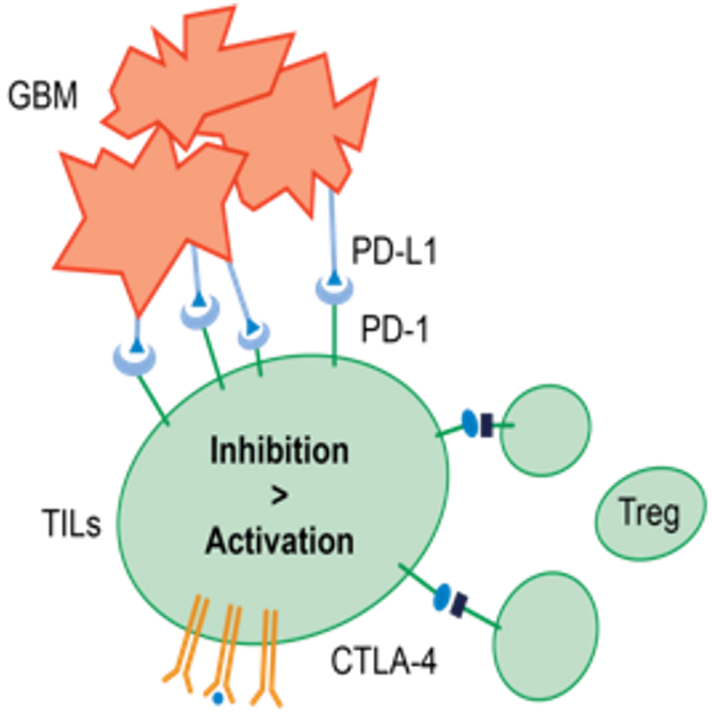


Intervention	All Patients		No Baseline Steroids				PD-L1 <1%	
	Events, n	Median OS, mo (95% CI)	Events, n	Median OS, mo (95% CI)	Events, n	Median OS, mo (95% CI)	Events, n	Median OS, mo (95% CI)
Nivolumab + RT + TMZ	222	28.9 (24.4-31.6)	146	31.3 (28.6-34.8)	74	29.8 (23.3-34.6)	147	28.7 (23.2-32.2)
Placebo + RT + TMZ	216	32.1 (29.4-33.8)	150	33.0 (31.0-35.1)	71	31.0 (26.5-34.5)	145	32.1 (28.9-34.2)

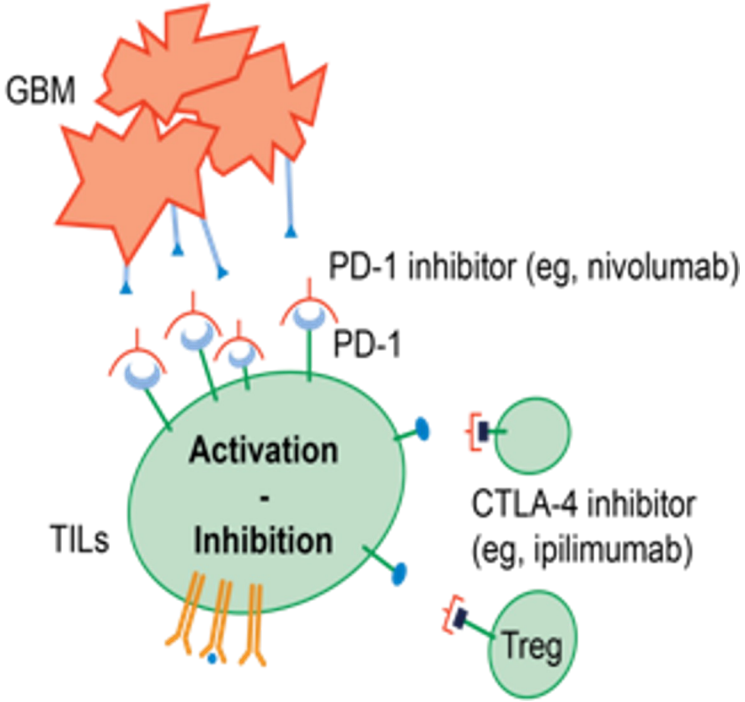
1. Weller M et al. SNO 2021. Abstract CNTI-25. 2. Lim M et al. *Neuro Oncol*. 2022;24:1935-1949.

Challenges With Utilization of Immune Checkpoint Inhibition in Glioblastoma[1-3]

- Immunosuppression via CTLA-4 is upregulated in patients with glioblastoma because the total fraction of Tregs is much higher, even though total CD4 counts are lower
- T cells that should be involved in tumor response are sequestered in the bone marrow



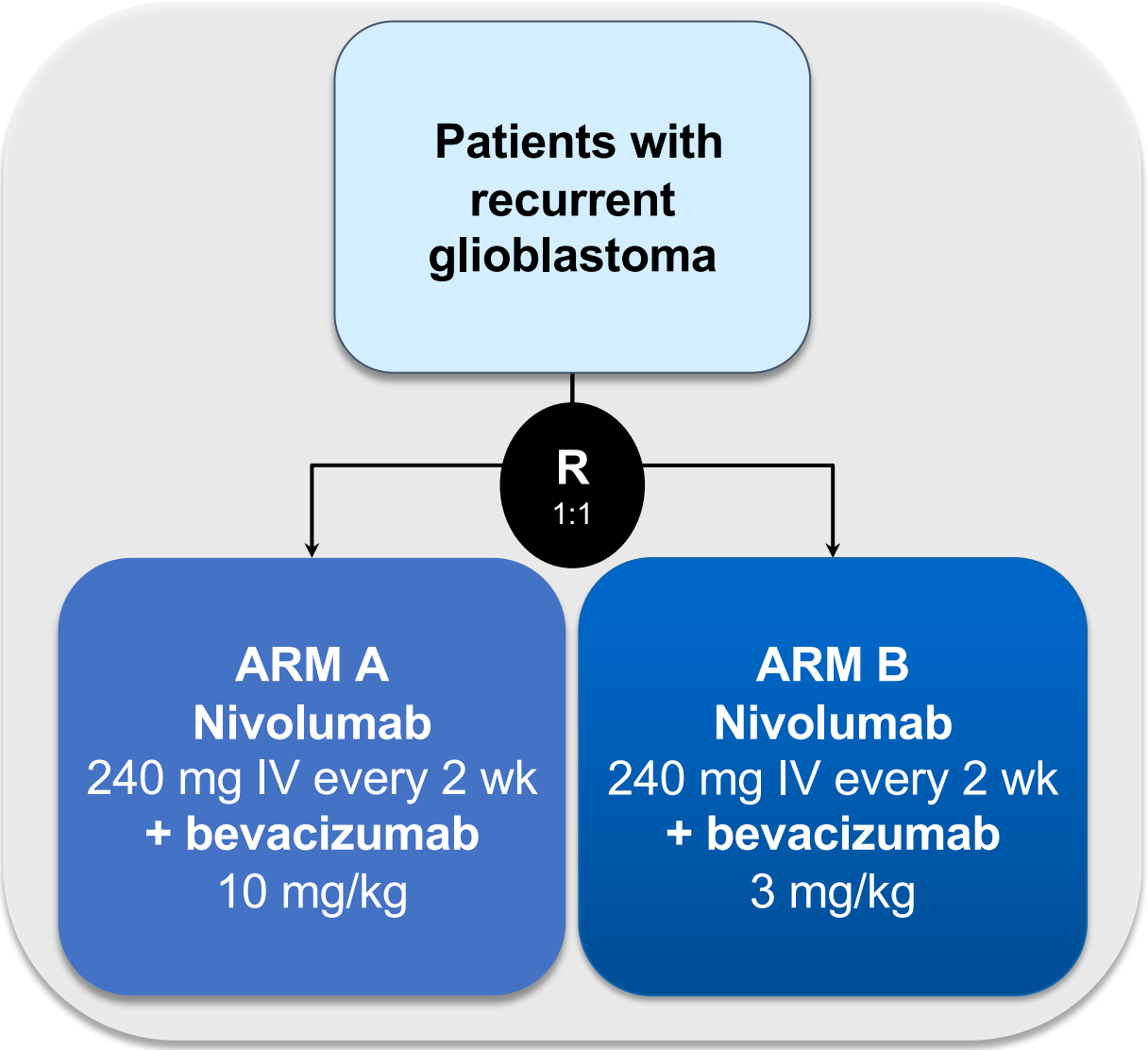
Inhibition of TILs because of PD-1/PD-L1 interactions and CTLA-4 interactions via Tregs



Checkpoint inhibition of CTLA-4 and PD-1 reduces TIL suppression and increases TIL activity

1. Fecci PE et al. *Cancer Res*. 2006;66:3294-3302. 2. Chongsathidkiet P et al. *Nat Med*. 2018;24:1459-1468. 3. Lakin N et al. *Front Oncol*. 2017;7:141.

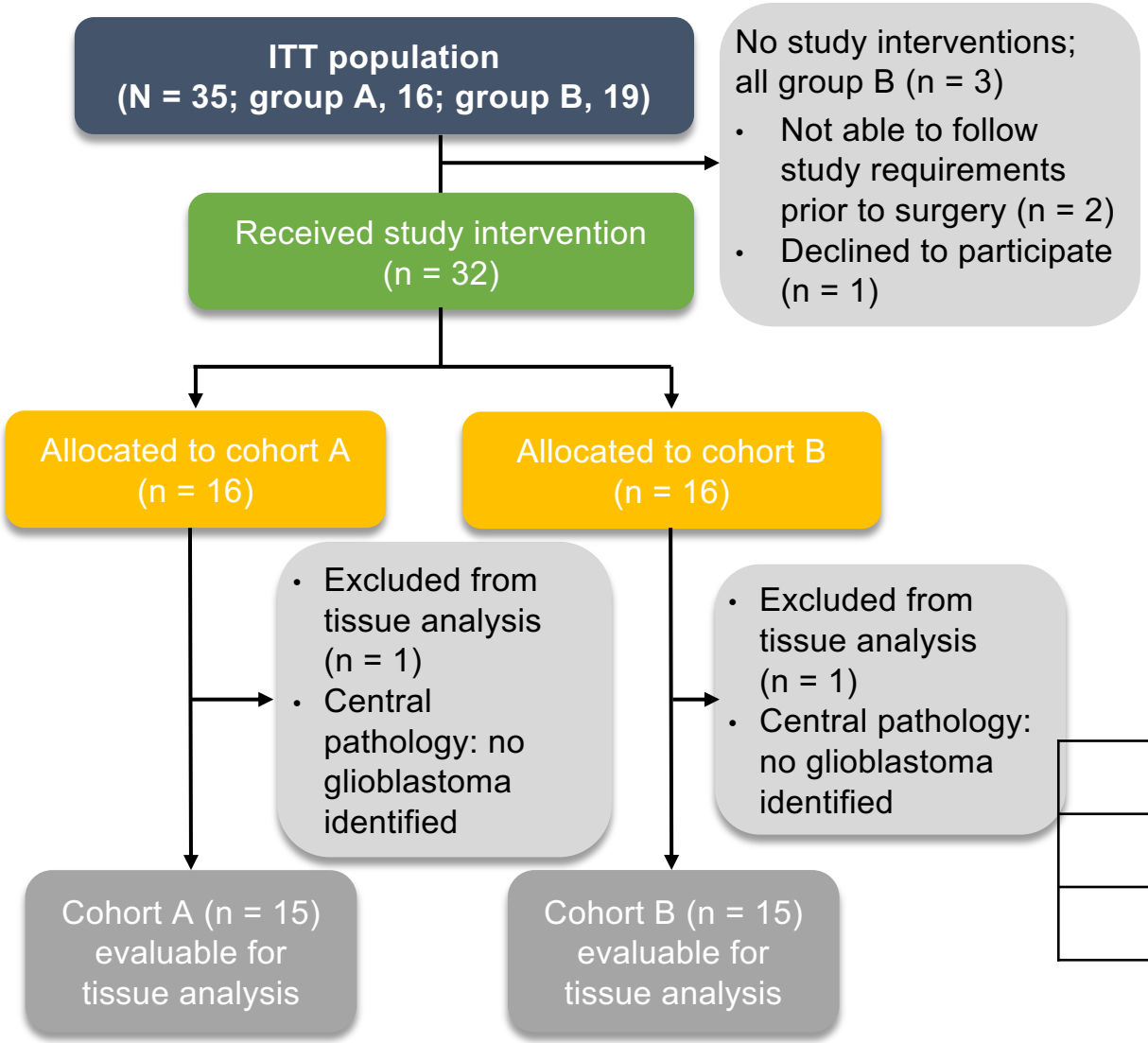
Phase 2 Trial: Nivolumab + Bevacizumab in Recurrent Glioblastoma[1]

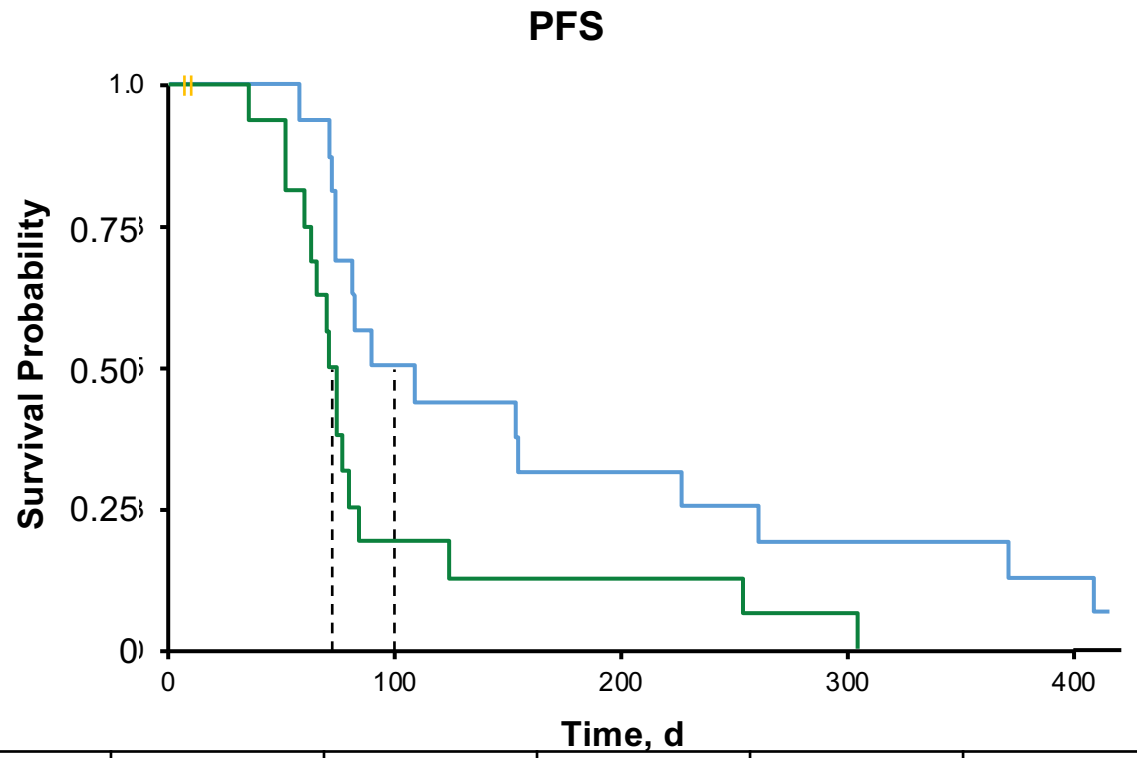


Outcomes	Arm A	Arm B
PFS, mo	6.13	10.85
OS, mo	4.59	9.61
OS12, mo	49	38

1. Ahluwalia M et al. SNO 2020. Abstract CTIM-12.

Neoadjuvant Anti–PD-1 Immunotherapy in Recurrent Glioblastoma[1]

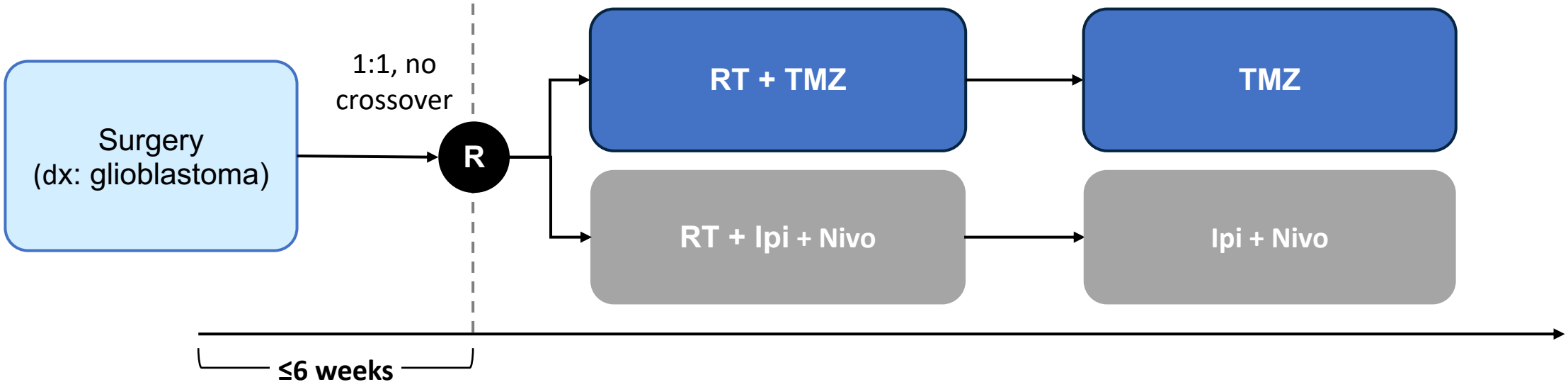




No. at Risk					
Neoadjuvant	16	8	5	3	2
Adjuvant	19	3	2	1	0

1. Cloughesy TF et al. *Nat Med*. 2019;25:477-486.

NRG-BN007: A Randomized Phase 2/3 Trial of Ipi+Nivo vs Temozolomide in MGMT Unmethylated Newly Diagnosed Glioblastoma[1]



Stratify

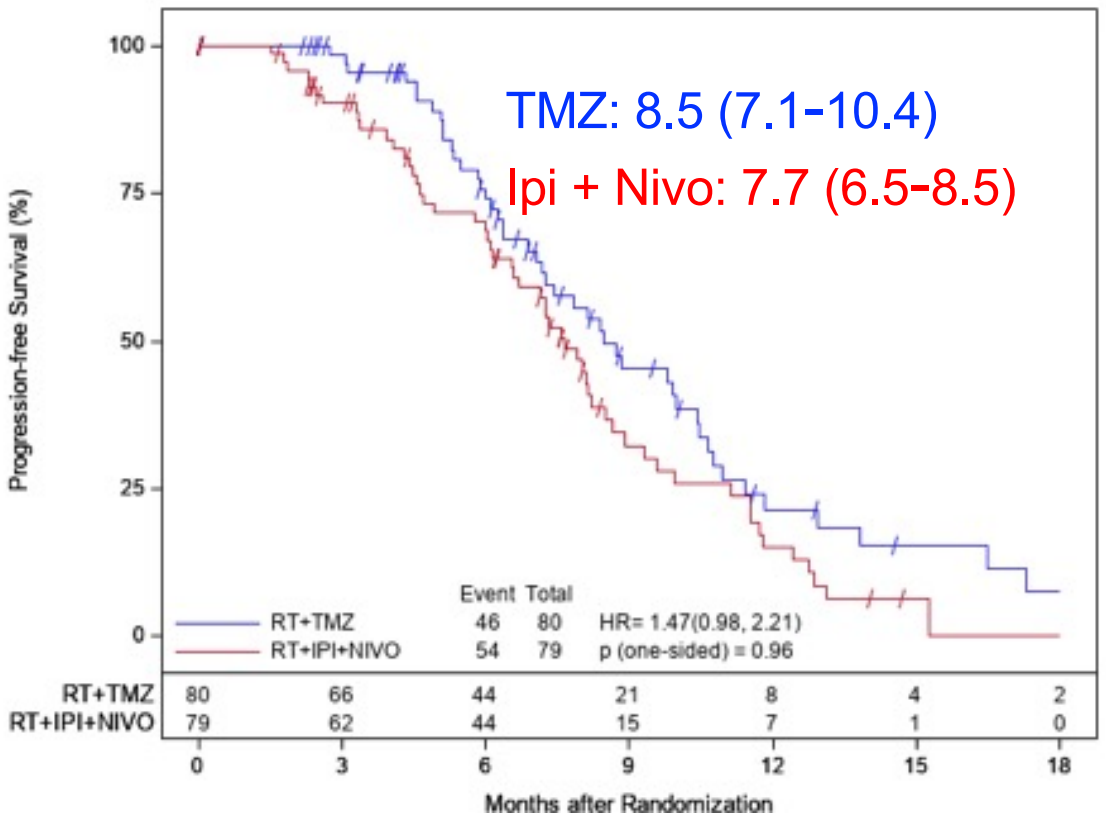
- RTOG glioblastoma RPA, III vs. IV vs. V
- Intent to use TTFields
  - FDA approved therapy: concerns about disallowing TTFields for patients on control arm
  - Disallowed on treatment arm, concern regarding scalp tox/rash

1. Lassman et al. Neuro-Oncology. 2023;25:iii2.

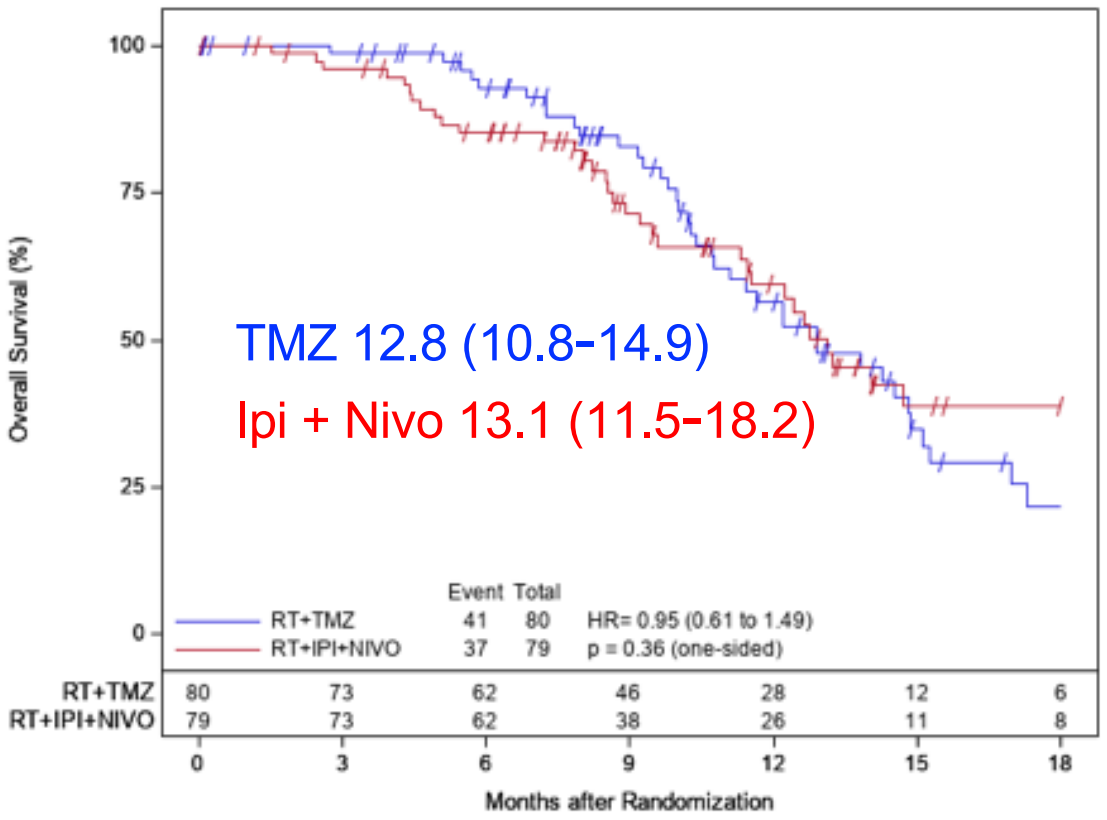
NRG-BN007: A Randomized Phase 2/3 Trial of Ipi+Nivo vs Temozolomide in MGMT Unmethylated Newly Diagnosed Glioblastoma[1] (Cont'd)

Ipi+Nivo did not prolong survival vs. temozolomide (+-/TTFields)

PFS (Central Review)



OS



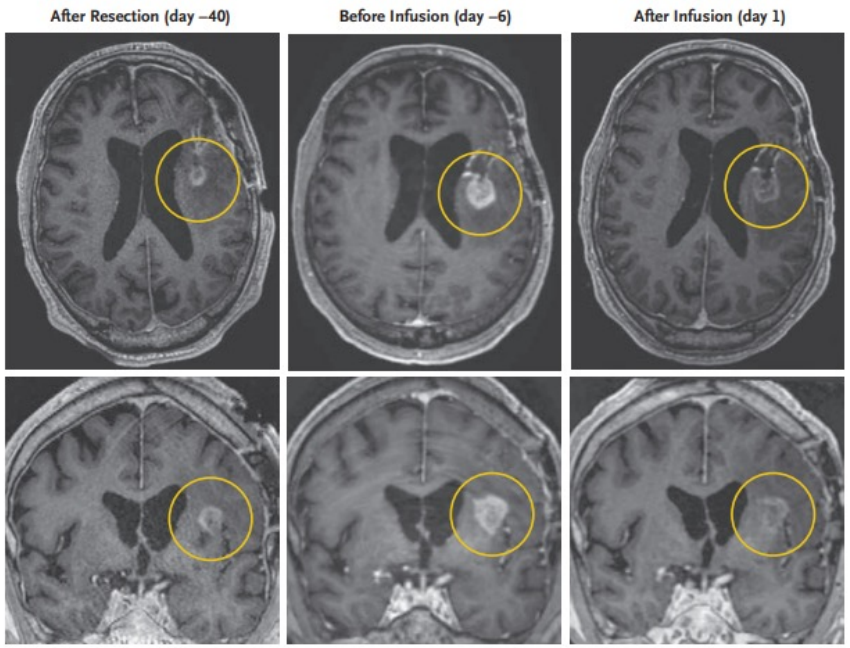
mPFS: 8.5mo (8.8,14.7); mOS 13.7mo (11.9, 14.9)

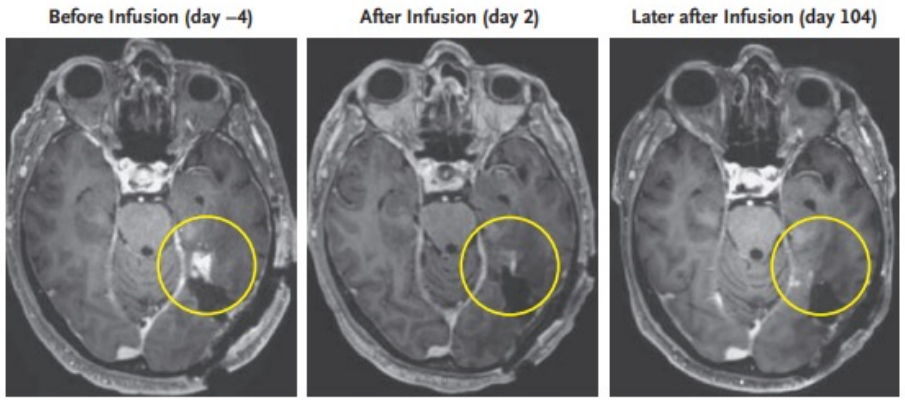
Trial discontinued after phase 2 for futility

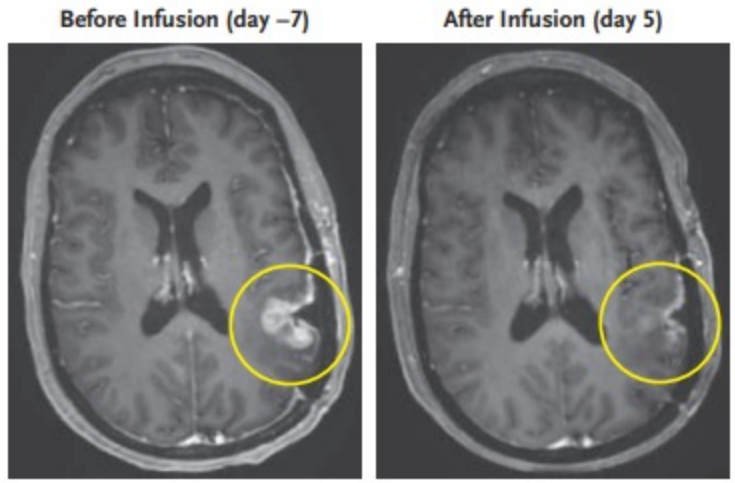
1. Lassman et al. *Neuro-Oncology*. 2023;25:iii2.

Intraventricular CARv3-TEAM-E T Cells in Recurrent Glioblastoma

March 13, 2024, NEJM

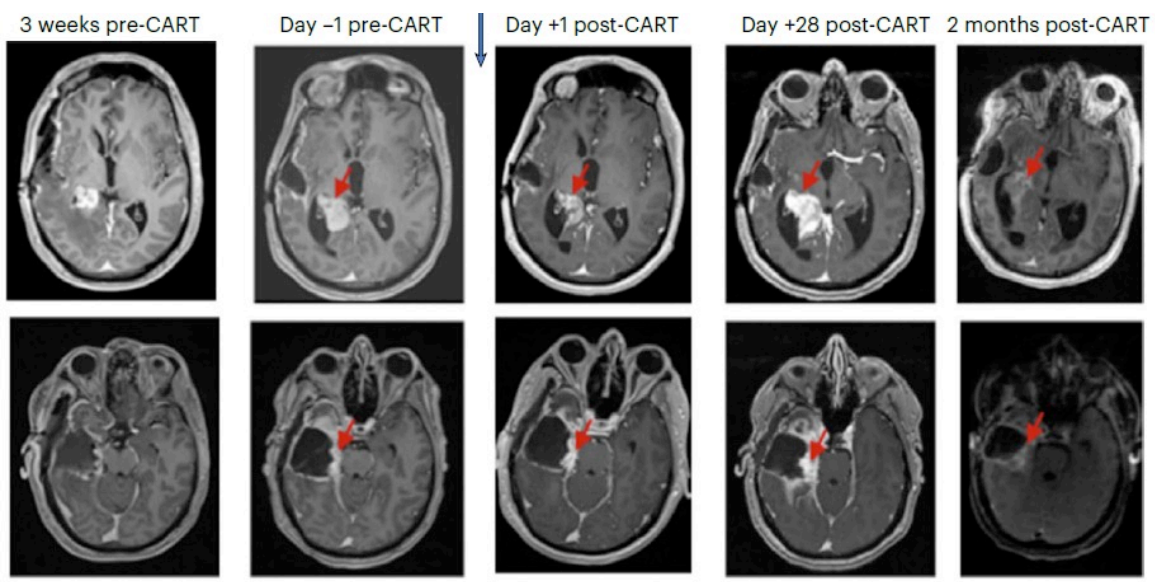


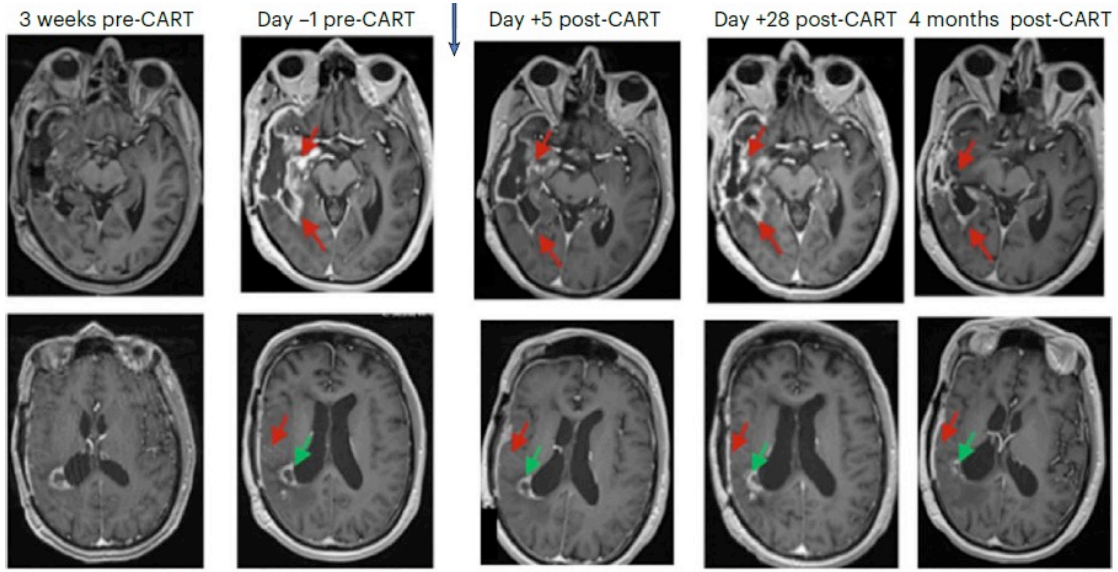




- 3 participants with recurrent glioblastoma were treated with CARv3-TEAM-E T cells
- CAR T cells engineered to target the EGFR vIII tumor-specific antigen, as well as the wild-type EGFR protein, through secretion of a T-cell–engaging antibody molecule (TEAM)
- Radiographic tumor regression was dramatic and rapid, occurring within days after receipt of a single intraventricular infusion, but the responses were transient in two of the three participants

Intrathecal bivalent CAR T cells targeting EGFR and IL13Rα2 in recurrent glioblastoma: phase 1 trial interim results





- In both dose level 1 (1 ×107 cells; *n* = 3) and dose level 2 (2.5 × 107 cells; *n* = 3), administration of CART-EGFR-IL13Rα2 cells was associated with early-onset neurotoxicity, most consistent with immune effector cell-associated neurotoxicity syndrome (ICANS) and managed with high-dose dexamethasone and anakinra (anti-IL1R)
- Reductions in enhancement and tumor size at early MRI timepoints were observed in all six patients; however, none met criteria for ORR

https://doi.org/10.1038/s41591-024-02893-z

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nature medicine

Phase IIa Study of SurVaxM Plus Adjuvant Temozolomide for Newly Diagnosed Glioblastoma

Journal of Clinical Oncology®

Volume 41, Issue 7 **1453**

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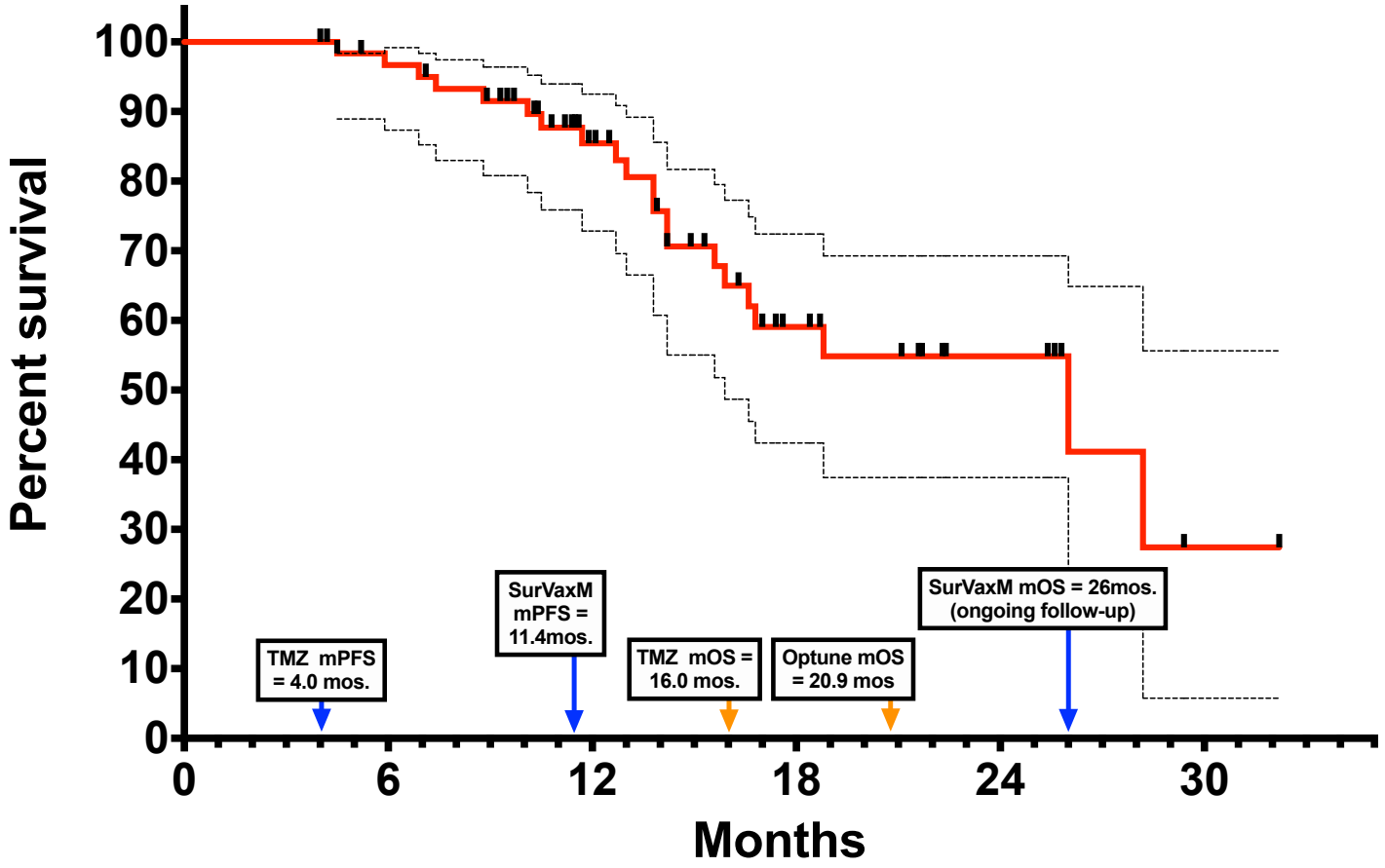


- Temozolomide mPFS of 4 mos. and mOS of 16.0 mos. obtained from 2017 Stupp Phase 3 data
- Optune was approved as a medical device with mOS of 20.9 mos.
- SurVaxM mPFS is 11.4 months
- SurVaxM mOS at 26 months is still immature with ongoing follow-up

Methylation	mPFS (months)	95% CI	mOS (months)	95% CI
All patients	11.4	9.9 to 12.7	25.9	22.5 to 29.0
unMGMT	7.0	5.7 to 8.2	16.5	13.4 to 19.3
meMGMT	17.9	14.7 to 20.7	41.4	32.1 to 49.4
Methylation/IDH	**mPFS (months)**	95% CI	**mOS (months)**	95% CI
All patients/IDHwt	10.3	8.9 to 11.6	23.0	19.8 to 25.9
unMGMT/IDHwt	6.9	5.6 to 8.0	15.6	12.6 to 18.3
meMGMT/IDHwt	19.3	15.4 to 22.6	NR (> 41.4)	37.1 to 59.4 (at 41.4)
Survival	**PFS (%)**	95% CI	**OS (%)**	95% CI
All patients				
6 months	69.80	56.8 to 79.5	—	—
12 months	47.60	34.9 to 59.3	87.20	76.1 to 93.4
24 months	26.60	16.4 to 37.9	51	38.3 to 63.0
36 months	22.60	12.9 to 33.9	41.40	27.8 to 54.5

Phase 2b Study of SurVaxM in nGBM (SURVIVE)

"Prospective Randomized Placebo-Controlled Trial of SurVaxM for Newly Diagnosed Glioblastoma"

NCT05163080

PHASE 2b RCT DESIGN:

NEWLY DIAGANOSED GLIOBLASTOMA (*n*=270)

Gross total resection (≤ 1cm^3)
& completed initial Standard of Care therapy
(Same as Phase 2a)

Stratified for MGMT methylation & IDH1 status

RANDOMIZED 3:2

SurVaxM (Arm A)
SurVaxM in emulsion with Montanide
Sargramostim (local injection)
Standard-of-care TMZ

Placebo (Arm B)
Saline in emulsion with Montanide
Saline (local injection)
Standard-of-care TMZ

- Dosing q2w x 4 doses and then q2m until tumor progression or unacceptable toxicity occurs.

ENDPOINTS:

1º Overall Survival:
- OS12 (surrogate)
- mOS (confirmatory)

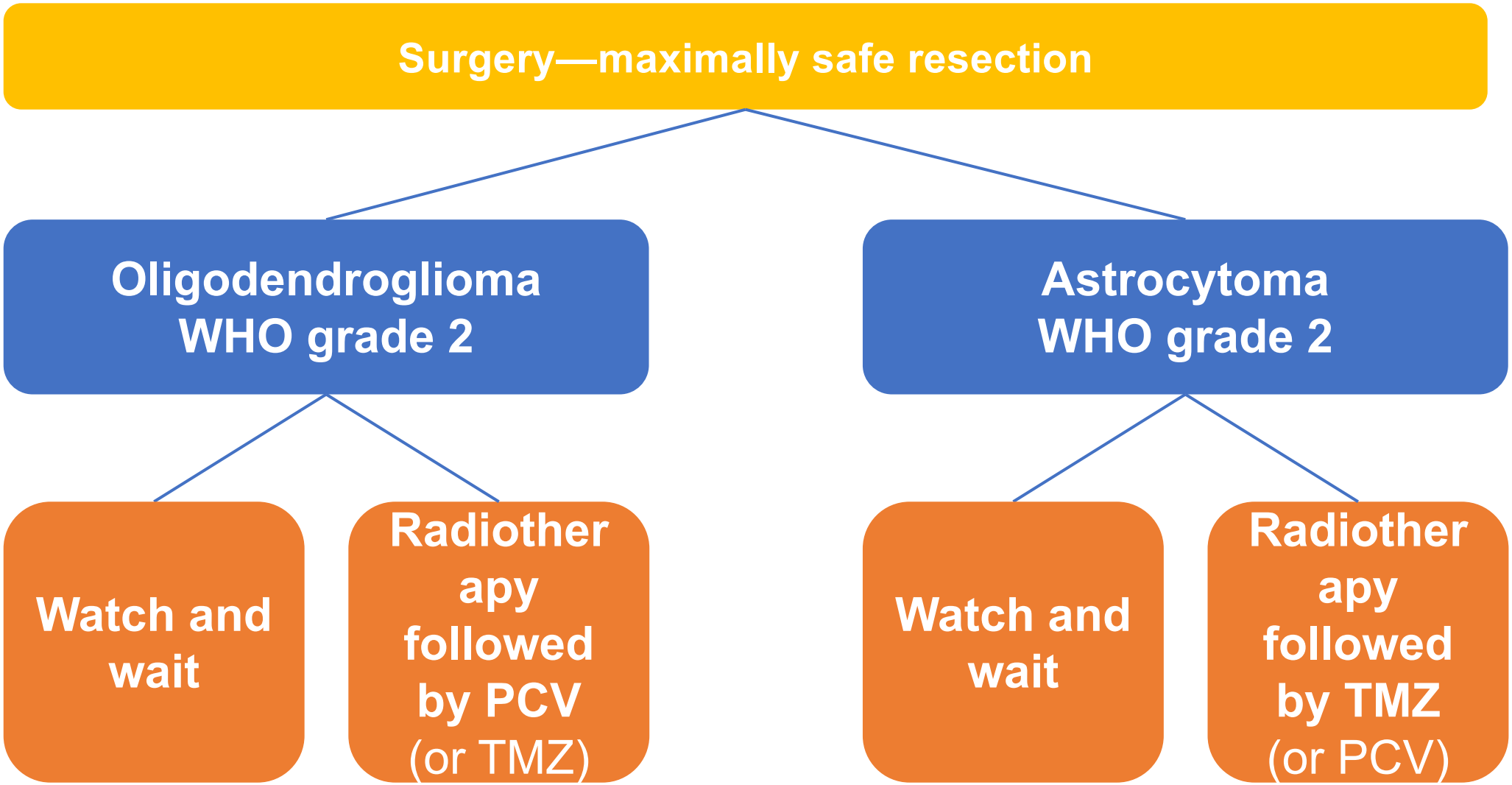
2º Progression Free Survival:
- mPFS
- 1^{rst} per Central Imaging (RANO)
- 2nd per PI

3º Immune Response & Biomarker Analysis (DNA/RNA)

Now Enrolling at:

Roswell Park Comprehensive Cancer Center
Dana-Farber Cancer Institute
Norton Cancer Institute
Fred Hutch Cures Start Here
Overlook Medical Center, Atlantic Health System
Cleveland Clinic
UCSF Brain Tumor Center
Texas Oncology – More breakthroughs. More victories.
NYU Langone Health
Miami Cancer Institute, Baptist Health South Florida
Northwell Lenox Hill Hospital

Targeting IDH Mutations: Current Treatment Approach to Newly Diagnosed IDH1/2-Mutant Glioma

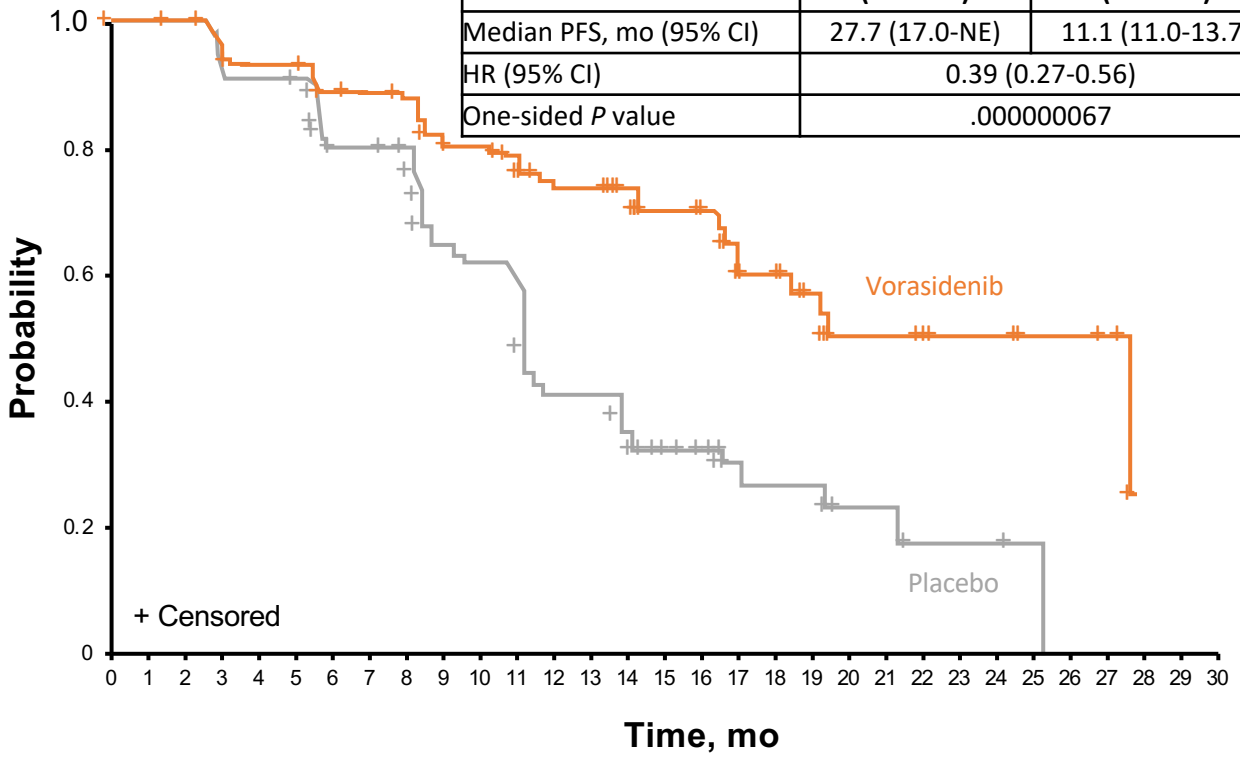


1. Weller M et al. *Nat Rev Clin Oncol.* 2021;18:170-86.

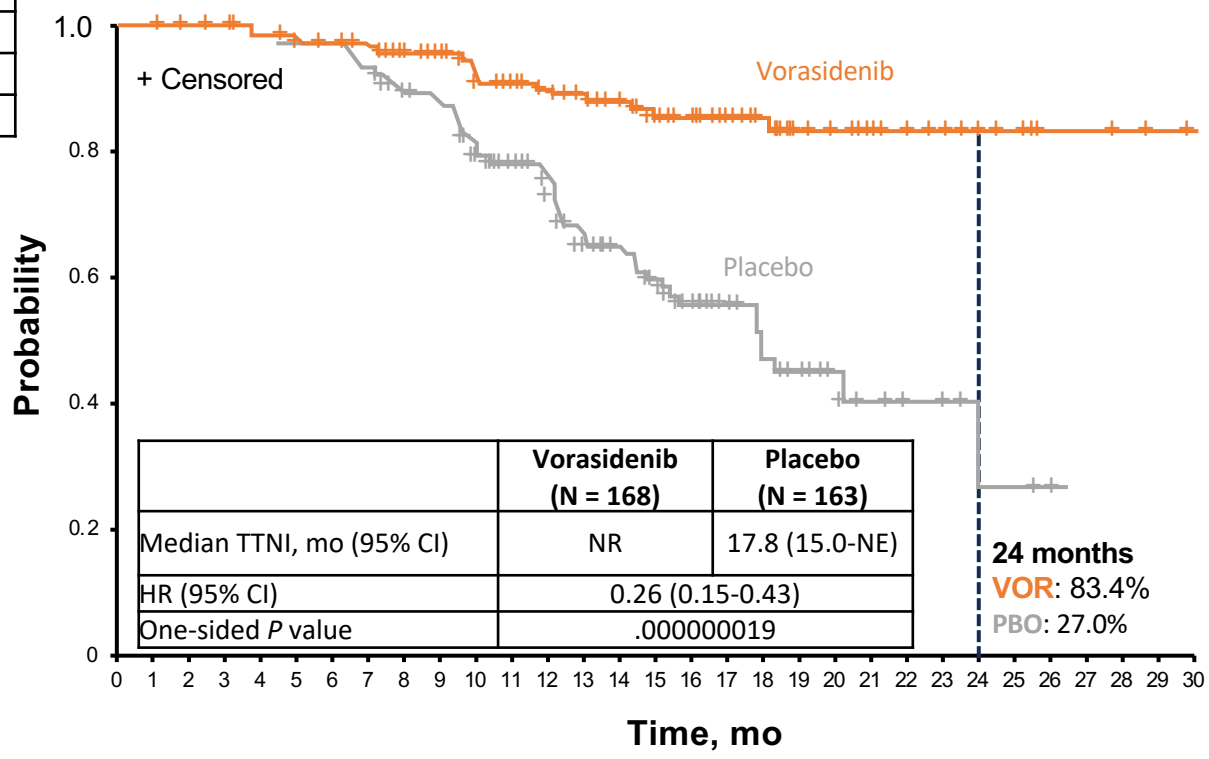
INDIGO: A Phase 3 Study of Vorasidenib Versus Placebo in Patients with Residual or Recurrent IDH1/2-Mutant Glioblastoma[1]

Primary Endpoint: PFS per BIRC

	Vorasidenib (N = 168)	Placebo (N = 163)
Median PFS, mo (95% CI)	27.7 (17.0-NE)	11.1 (11.0-13.7)
HR (95% CI)	0.39 (0.27-0.56)	
One-sided *P* value	.000000067	



Key Secondary Endpoint: TTNI

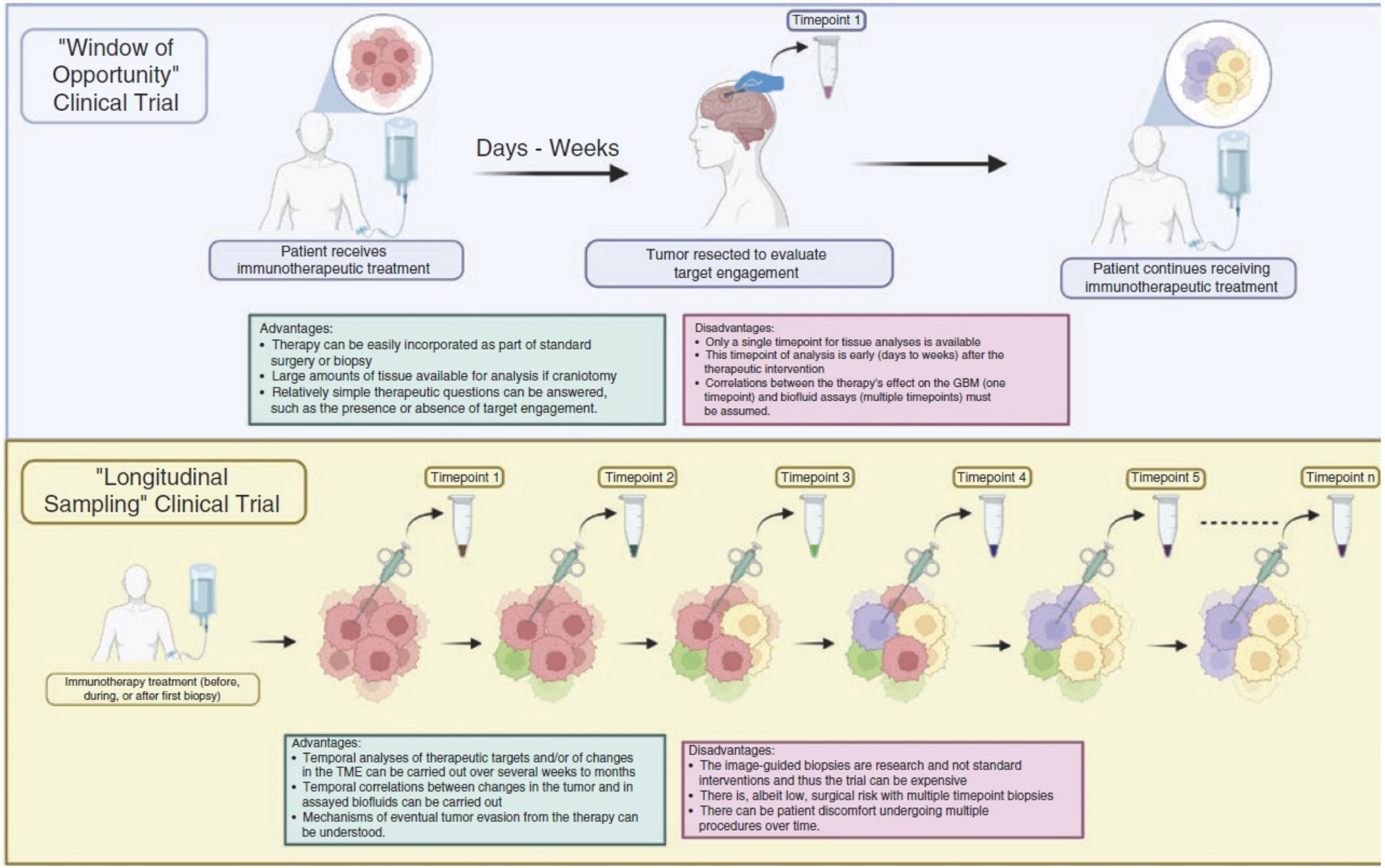


	Vorasidenib (N = 168)	Placebo (N = 163)
Median TTNI, mo (95% CI)	NR	17.8 (15.0-NE)
HR (95% CI)	0.26 (0.15-0.43)	
One-sided *P* value	.000000019	

1. Mellinghoff et al. ASCO 2023. Abstract LBA1

Future Directions

Neuro-Oncology
XX(XX), 1–15, 2023 | https://doi.org/10.1093/neuonc/noad211 | Advance Access date 23 November 2023



Conclusions

- GBM Oncology Clinical trials = Soccer Match
- More shots on goal = more chances of success
- Not successful for GBM
- Bold Approach = Apollo Space Program
- First human landing on the moon in 1969 (Apollo -11)
- No multiple shots on goal- rather one space mission after other to test each component needed for success