CCC MÜNCHEN
COMPREHENSIVE
CANCER CENTER

17. Juni 2023

„Highlights 2023 vom Amerikanischen Krebskongress“

Neuroonkologische Tumoren

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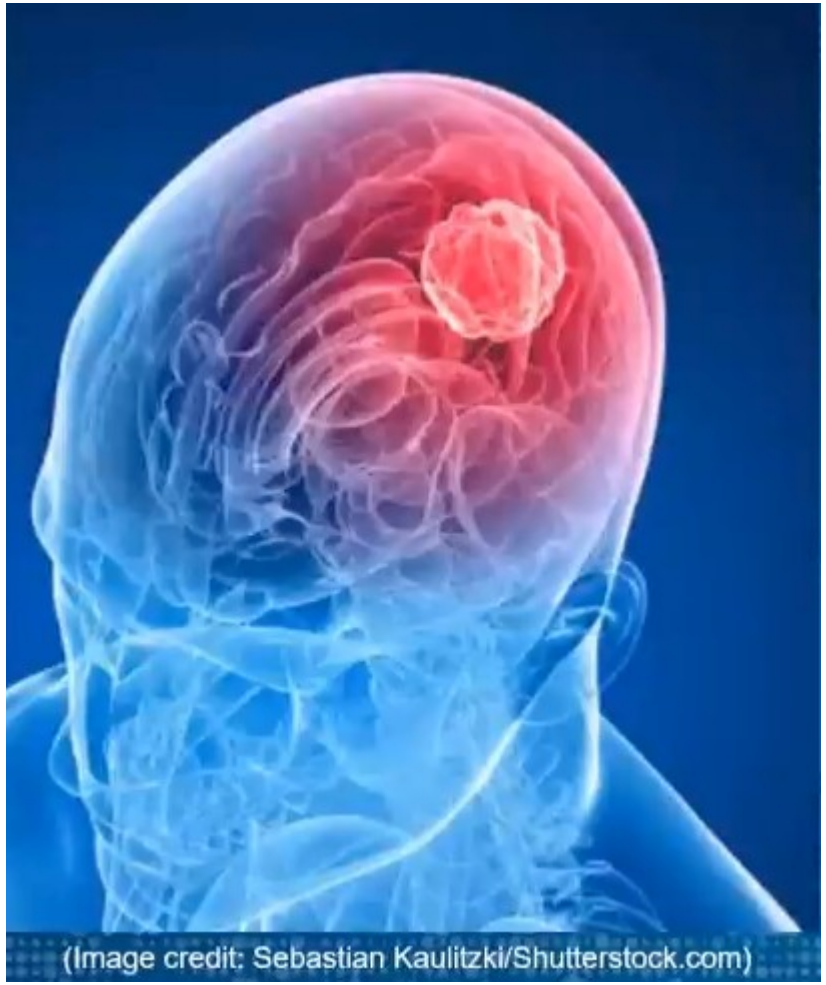
Es bestehen keine

Interessenskonflikte



Studienauswahl:

- **Grad 2 Gliom: - Vorasidenib vs. Placebo beim IDH mutierten Gliom (INDIGO Phase 3 Studie)**

- **Grad 4 Gliom: - MRT/PET Imaging-basierte hypofraktionierte Protonentherapie beim alten Patienten**
  - **Anti-TERT Vakzinierung in neu diagnostizierten MGMT-neg. GBM**
  - **Stellenwert der Re-Resektion (RANO Resect)**
  - **Bortezomid und TMZ beim MGMT neg. GBM-Rezidiv**

- **Hämangioblastom: - Effekt der Belzutifan (HIF2a-Inhibitor) Therapie**

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INDIGO: a Phase 3 global, randomized, double-blinded study of vorasidenib versus placebo in patients with residual or recurrent grade 2 glioma with an IDH1/2 mutation

Ingo K. Mellinghoff,[1] Martin J. van den Bent,[2] Deborah T. Blumenthal,[3] Mehdi Touat,[4] Katherine B. Peters,[5] Jennifer Clarke,[6] Joe Mendez,[7] Liam Welsh,[8] Warren P. Mason,[9] Andreas F. Hottinger,[10] Juan M. Sepulveda,[11] Wolfgang Wick,[12] Riccardo Soffietti,[13] Steven Schoenfeld,[14] Dan Zhao,[14] Susan Pandya,[14] Lori Steelman,[14] Islam Hassan,[14] Patrick Y. Wen,[15*] Timothy F. Cloughesy[16*]

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ClinicalTrials.gov identifier: NCT04164901. This study was sponsored by Servier

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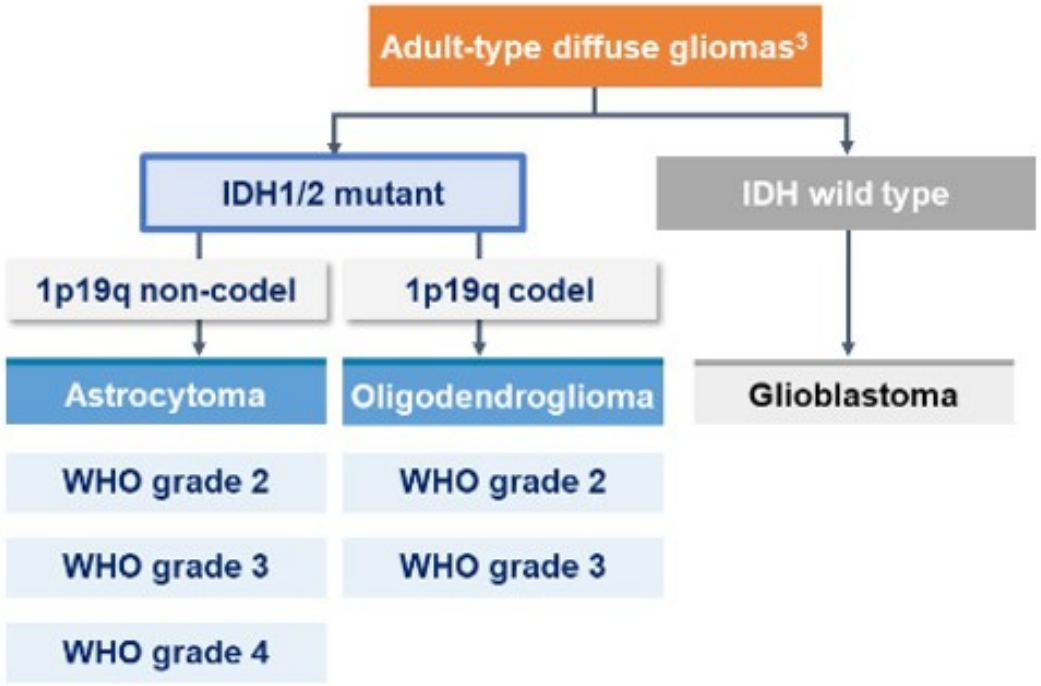
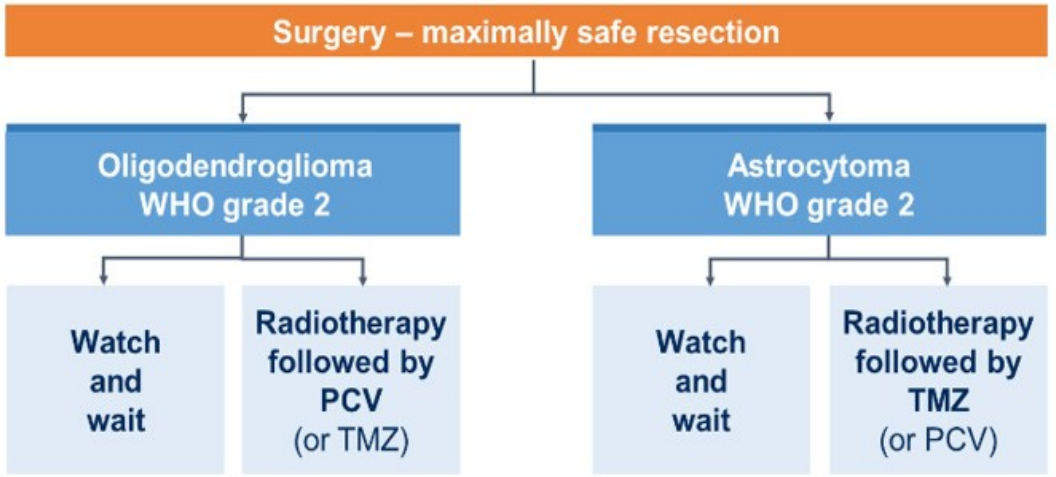
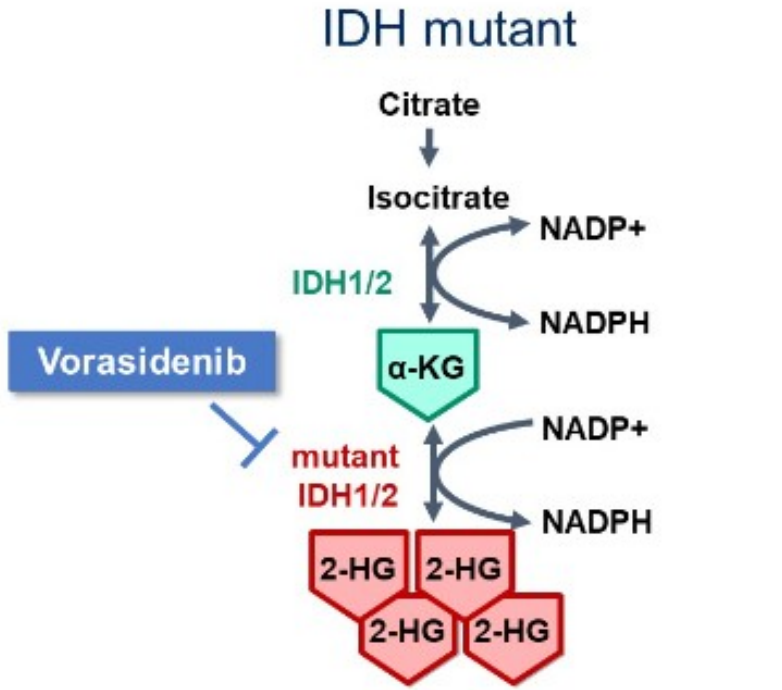
IDH1/2-mutant diffuse gliomas







Competitive inhibition of α-KG-dependent enzymes

Vorasidenib

- Oral inhibitor of mutant IDH1 and IDH2[1]
- Specifically designed for brain penetrance[1]
- Reduced tumor 2-HG by >90% in resected grade 2/3 non-enhancing diffuse glioma[1]
- 2-HG reduction associated with:[2]
  - Lower tumor cell proliferation
  - Reversal of IDH1/2 mutation-associated gene expression programs
  - Increased DNA 5-hydroxy-methylcytosine
  - Increased tumor infiltrating lymphocytes

INvestigating vorasiDenIb in GliOma (NCT04164901)

Key eligibility criteria

- ≥12 years of age
- IDH1/2-mutated* grade 2 oligodendroglioma or astrocytoma per WHO 2016 guidelines
- Prior surgery only
- Measurable non-enhancing disease (≥1 target lesion measuring ≥1 cm × ≥1 cm), confirmed by blinded review
- Not in need of immediate chemotherapy or radiotherapy per investigator assessment

1:1
double-blind randomization
(N=331)

Stratified by 1p19q status and baseline tumor size

Vorasidenib 40 mg (N=168)

Placebo (N=163)

Orally, once daily, 28-day cycles

Centrally confirmed progressive disease permitted unblinding and crossover†

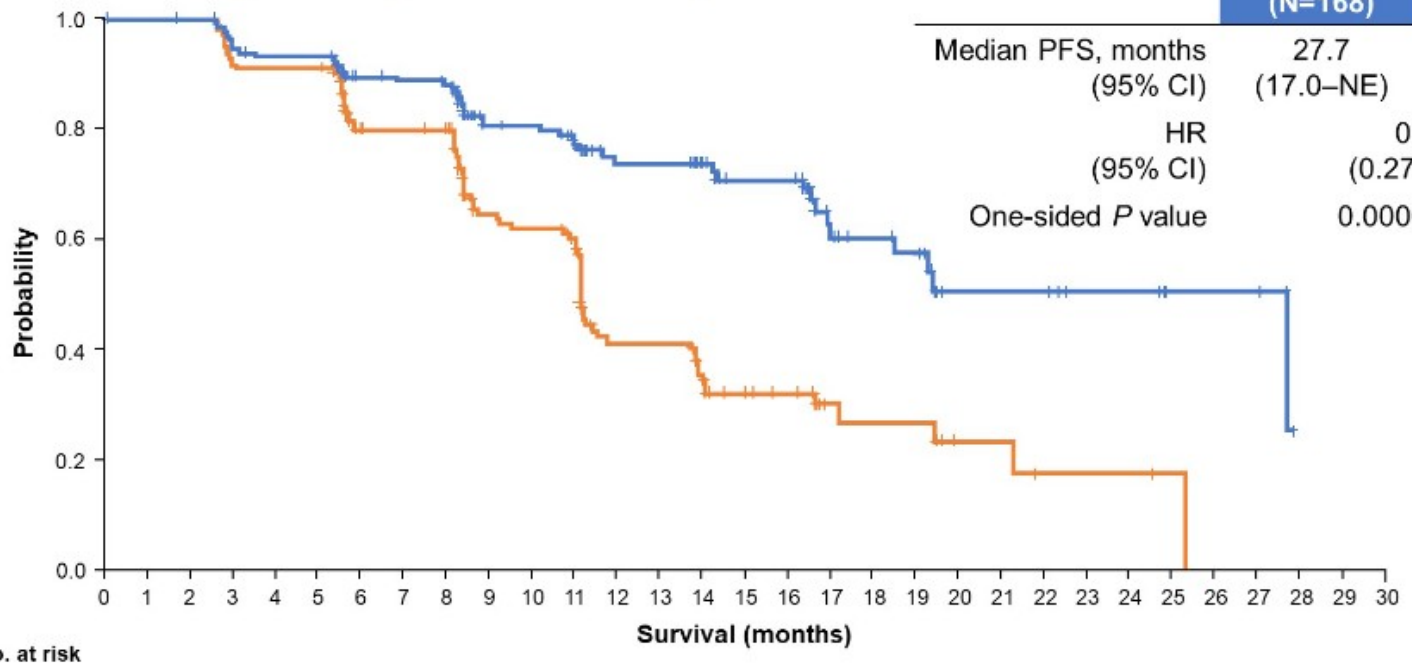
IDMC regularly reviewed safety and other clinical data, as well as the efficacy data following prespecified interim analyses

Baseline patient characteristics

	Vorasidenib (N=168)	Placebo (N=163)
Median age (range) – year	40.5 (21–71)	39.0 (16–65)
Sex – n (%)		
Male/female	101/67 (60.1/39.9)	86/77 (52.8/47.2)
Karnofsky performance score – n (%)		
100	90 (53.6)	87 (53.4)
90–80*	77 (45.8)	76 (46.6)
Time from last surgery for glioma to randomization – year		
Median (range)	2.5 (0.2–5.2)†	2.2 (0.9–5.0)
Chromosome 1p19q codeletion status – n (%)‡		
Codeleted/non-codeleted	88/80 (52.4/47.6)	84/79 (51.5/48.5)
Tumor size at baseline – n (%)‡		
Longest diameter of ≥2 cm/<2 cm	139/29 (82.7/17.3)	137/26 (84.0/16.0)

*One additional patient (0.6%) met eligibility criteria during screening, but then had score of 70 on Day 1 of the first cycle; †One patient had a biopsy during prescreening to obtain tumor tissue for IDH mutation status testing, which was allowed per protocol; ‡Data are reported as collected by electronic case report forms.

Primary endpoint: PFS per BIRC



	Vorasidenib (N=168)	Placebo (N=163)
Median PFS, months (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	0.000000067	

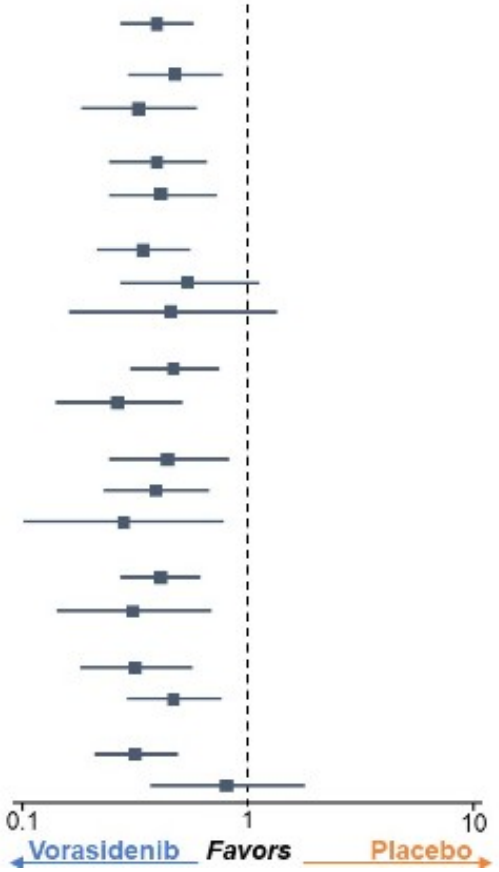
No. at risk

VOR	168	166	166	157	154	154	133	131	129	93	91	81	63	63	52	45	45	25	22	20	11	11	11	7	7	4	4	4	0
PBO	163	162	161	146	145	145	117	116	114	73	70	65	38	38	29	21	19	9	8	8	4	4	2	2	2	1	0		

+ Censored.
P value is from one-sided stratified log-rank test.
NE, not estimable; PBO, placebo; VOR, vorasidenib.

Subgroup analysis for PFS by BIRC

Subgroup	Events/N (%)	HR (95% CI)
Overall	135/331 (40.8)	0.39 (0.27–0.56)
18–<40 years	80/163 (49.1)	0.47 (0.29–0.75)
40–<65 years	53/164 (32.3)	0.32 (0.18–0.58)
Male	72/187 (38.5)	0.39 (0.24–0.64)
Female	63/144 (43.8)	0.41 (0.24–0.70)
North America	89/193 (46.1)	0.34 (0.21–0.54)
Western Europe	31/97 (32.0)	0.54 (0.27–1.10)
Rest of the World	15/41 (36.6)	0.45 (0.16–1.31)
Frontal tumor at initial diagnosis	92/222 (41.4)	0.47 (0.30–0.73)
Non-frontal tumor at initial diagnosis	43/109 (39.4)	0.26 (0.14–0.50)
<2 years from last surgery to randomization	51/130 (39.2)	0.44 (0.24–0.82)
2–<4 years from last surgery to randomization	59/145 (40.7)	0.39 (0.23–0.66)
≥4 years from last surgery to randomization	25/56 (44.6)	0.28 (0.10–0.76)
1 prior surgery	106/260 (40.8)	0.41 (0.27–0.61)
≥2 prior surgeries	29/71 (40.8)	0.31 (0.14–0.68)
Codeleted chromosome 1p19q*	59/172 (34.3)	0.32 (0.18–0.57)
Non-codeleted chromosome 1p19q	76/159 (47.8)	0.47 (0.29–0.75)
Longest tumor diameter of ≥2 cm at baseline*	109/269 (40.5)	0.32 (0.21–0.48)
Longest diameter of <2 cm at baseline	26/62 (41.9)	0.81 (0.37–1.77)



*Data are reported as collected by the interactive web response system.

Safety: TEAEs

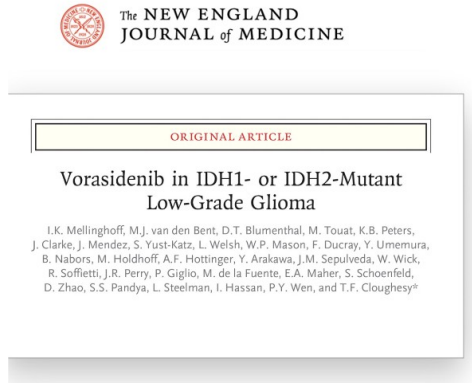
	Vorasidenib (N=167)	Placebo (N=163)
Any grade ≥3 AE – n (%)	38 (22.8)	22 (13.5)
Increased alanine aminotransferase	16 (9.6)	0
Increased aspartate aminotransferase	7 (4.2)	0
Seizure	7 (4.2)	4 (2.5)
Increased gamma-glutamyltransferase	5 (3.0)	2 (1.2)
Syncope	3 (1.8)	1 (0.6)
Hypertension	2 (1.2)	3 (1.8)
Decreased neutrophil count	2 (1.2)	0

- Treatment interruption due to TEAE
  - **Vorasidenib** 29.9% (n=50)
  - **Placebo** 22.7% (n=37)
- Dose reduction due to TEAE
  - **Vorasidenib** 10.8% (n=18)
  - **Placebo** 3.1% (n=5)
- Discontinuation due to TEAE
  - **Vorasidenib** 3.6% (n=6)
  - **Placebo** 1.2% (n=2)
- No fatal TEAE

The safety set included all the patients who received at least one dose of study treatment.
Preferred terms listed are those that occurred at Grade ≥3 in two or more patients in the vorasidenib group.
AE, adverse event; TEAE, treatment-emergent adverse event.

Summary

- Diffuse gliomas with IDH1/2 mutations are not curable with current therapies and infiltrate the brain in the absence of treatment
- Vorasidenib is an oral inhibitor of the mutant IDH1/2 enzymes with proven brain penetrance
- Treatment with vorasidenib significantly improved imaging-based PFS and TTNI with a manageable safety profile in patients who were not in need of immediate chemotherapy or radiotherapy



Offene Fragen:

- Stellenwert von Vorasidenib in Kombination/ nach RCT

- Stellenwert von Vorasidenib beim Grad 3 und 4 IDH-mut Tumor

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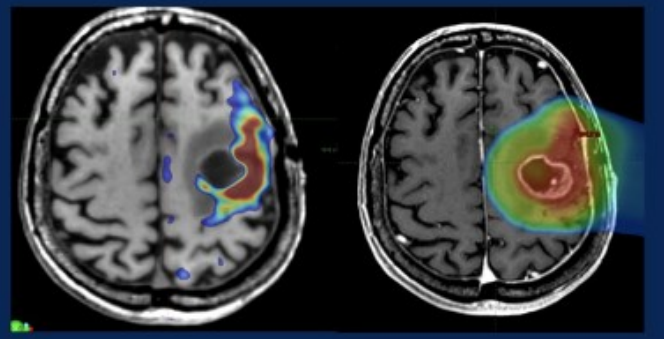

Phase II Study of Short Course Hypofractionated Proton Beam Therapy Incorporating 18F-DOPA PET/MRI for Elderly Patients with Newly Diagnosed Glioblastoma

Department of Radiation Oncology, Nuclear Medicine, Radiology, Neurology, Neurosurgery, Medical Statistics. Mayo Clinic

Sujay A. Vora, MD Associate Professor, Dept of Radiation Oncology, Mayo Clinic Arizona

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Background

- 50% of newly diagnosed glioblastoma are 65 and older with median survival of 6-9 months
- The care of elderly patients can be challenging and lead to undertreatment
  - Declining performance status
  - Medical comorbidities
  - Poor survival rates
- Reducing burden led to shorter course hypofractionated radiation therapy compared to standard 6 weeks of treatment with similar phase III outcomes

Phase III Trial	Arm 1	Arm 2	Arm 3	Survival
Canada (Roa)	60 Gy/30 fx	40 Gy/15 fx		5.1 vs. 5.6 months (p=ns)
International (Roa)	25 Gy/5 fx	40 Gy/15 fx		7.9 vs. 6.4 months (p=ns)
Intergroup(Perry)	40 Gy	40 Gy+TMZ		7.6 vs 9.3 months (p=ss)
Nordic (Malmstrom)	60 Gy/30 fx	34 Gy/10 fx	TMZ	6.3 vs 7.5 vs. 8.3 months (p=ns)

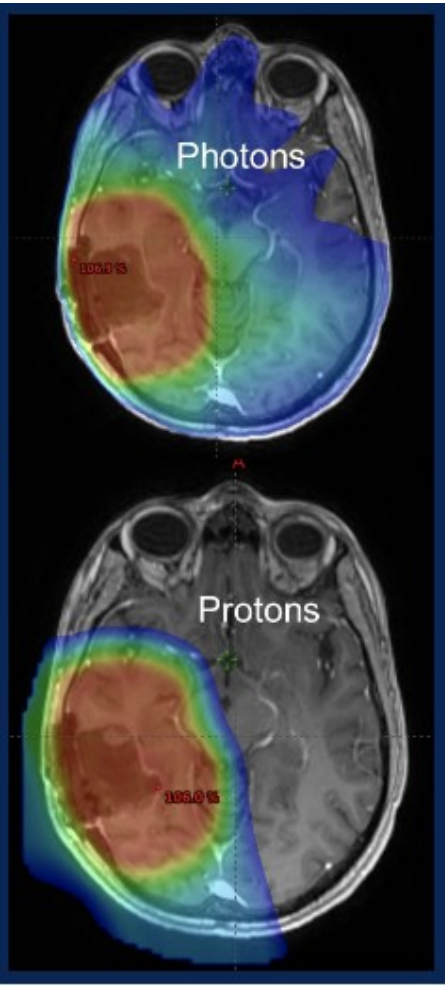
Strategies to improve outcomes

- Reduce local failures
  - Local recurrence is still dominant cause of death
  - Enhance target delineation and identify the highest risk disease
    - Opportunities for dose escalation

- Reduce Toxicity
  - Effects of radiation on aging brain
  - Improve quality of life

Potential advantages of using protons

- Preserve quality of life/neurocognition
  - Reducing dose to normal structures (ex. hippocampus)
    - Brown et al. JCO 38:1019-1029, 2020
- Reduce toxicity
  - Proton patients reported less fatigue and grade 2+ toxicity in phase IIR study
    - Brown et al. Neuro-Oncology 23(8), 1337-1347, 2021
- Aging effect of radiation
  - Cortical volume loss
    - Gui et al. J Neurooncol 9/2019 144(2): 351-8
  - Accelerated aging
    - Rammohan et al. Neuro-Oncology 2/3/2023



Scientific Question

With improved targeting of disease with 18F-DOPA along with dosimetric advantages of proton beam therapy, can this combination offer both improved survival and quality of life?

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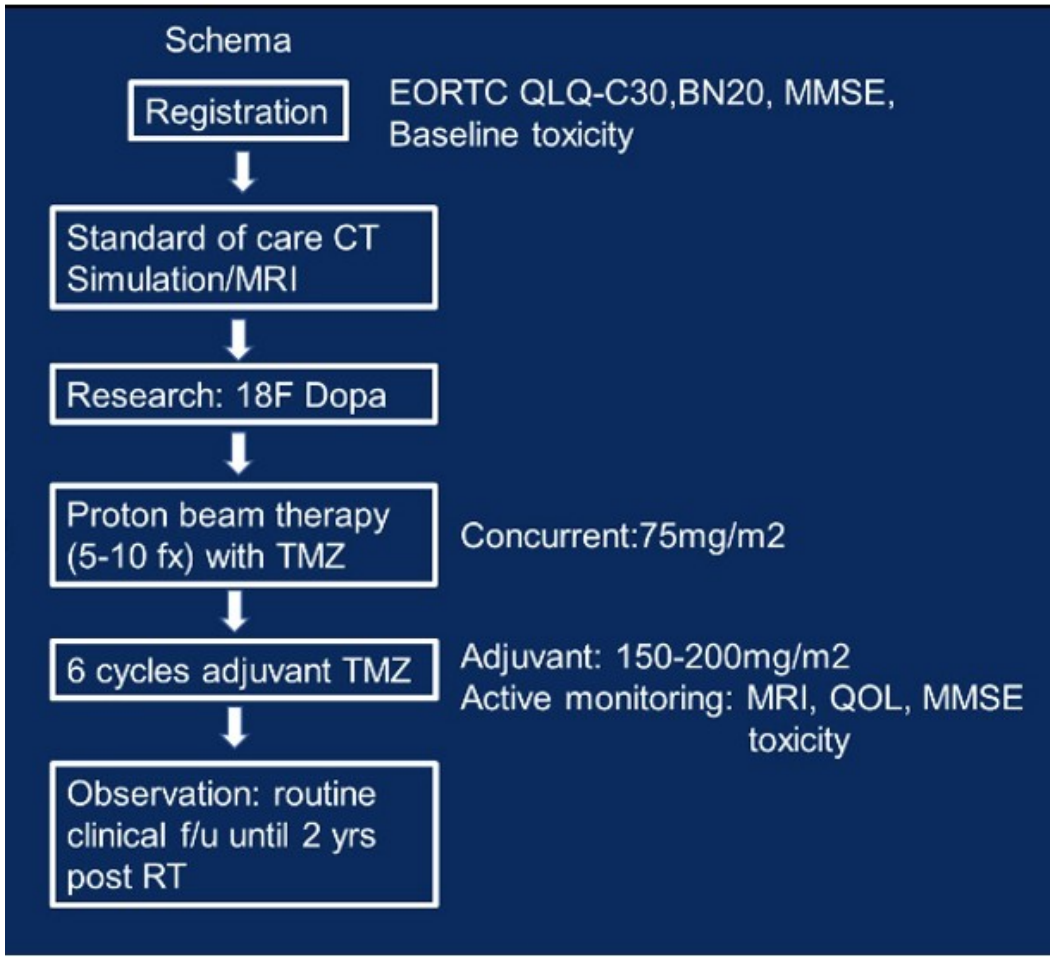
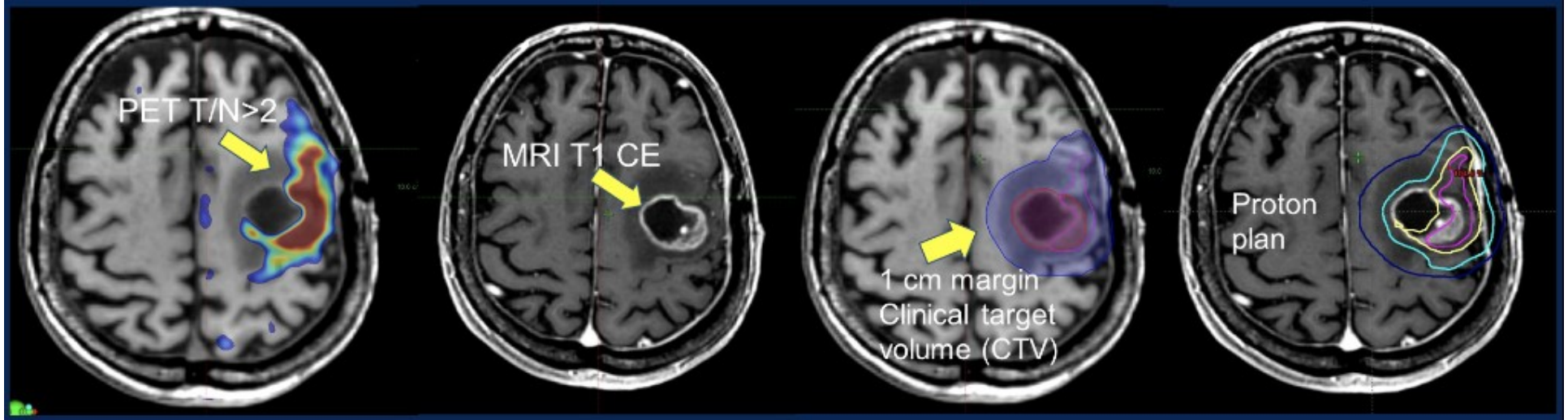
Inclusion:

- Age ≥65 years.
- Histologically confirmed newly diagnosed Grade IV malignant glioma.
- Provide informed written consent.
- Patients with eGFR ≥ 60 mg/min/1.72m2
- Ability to complete questionnaire(s) by themselves or with assistance.
- ECOG performance status 0, 1, 2



Treatment technique

The dose/fractionation was dependent on the gross tumor volume (GTV): PET(T/N>2.0) + MRI T1 CE



≤65 cc: 35 GyE to PET, 30 GyE to MRI, 25 GyE to 1 cm margin(CTV) – 5 fractions
>65 cc: 40 GyE to PET, 35 GyE to MRI, 30 GyE to 1 cm margin(CTV) – 10 fractions

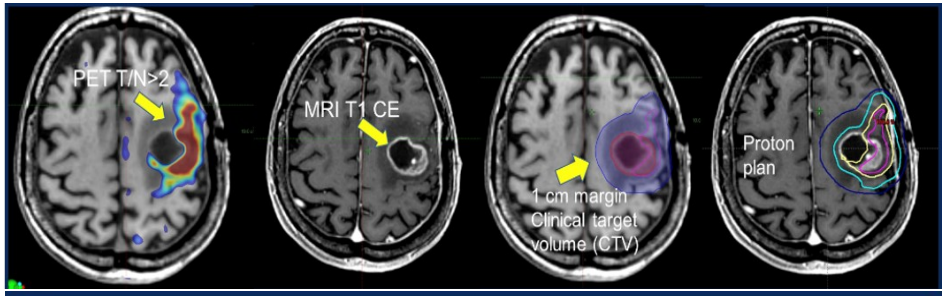
Results

Patient demographics

43 patients enrolled between 5/2019-6/2021

4 patients never treated
- 1 insurance denial
- 3 rapid progression (hospice)

Age	
Median	70.2
Range	65.4 - 83.2
Gender	
Male	28 (71.8%)
Female	11 (28.2%)
Unifocal or Multifocal	
Unifocal	29 (74.4%)
Multifocal	10 (25.6%)
ECOG PS	
0	13 (33%)
1	19 (48.7%)
2	7 (17.9%)
Extent of Surgery	
Gross Total Resection	16 (41%)
Subtotal resection	8 (20.5%)
Biopsy	15 (38.5%)
IDH status	
wildtype	39(100%)
mutant	0 (0%)
MGMT	
Methylated	13 (33.3%)
Unmethylated	24 (61.5%)
Not available	2 (5.1%)
Use of alternating electrical therapy	
Yes	1 (2.5%)
No	38 (97.5%)
Follow-up Months	
Median	12.5
Range	2.3 - 31.8



High risk PET(T/N>2.0) contained within:

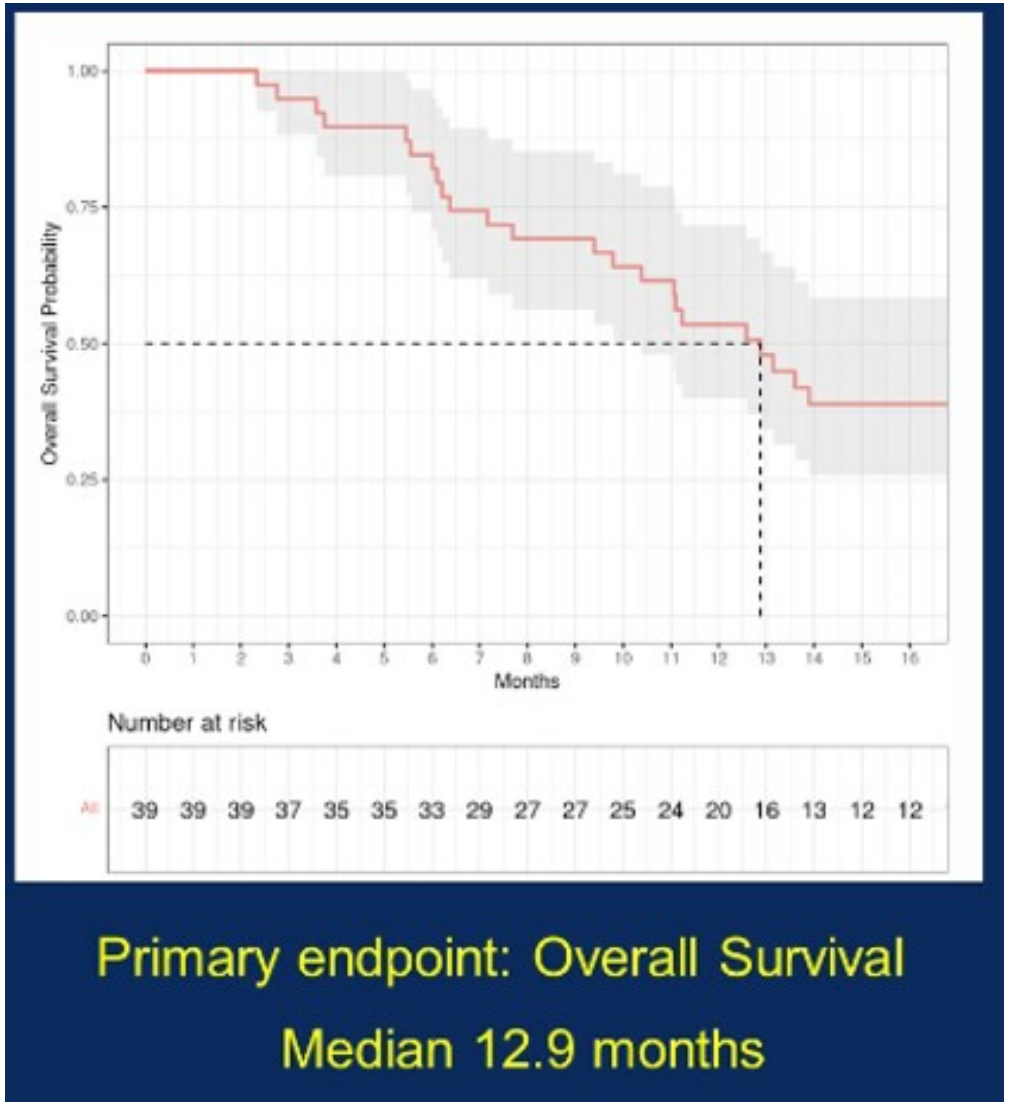
- MRI T1CE 18/39 (46%)
- MRI T1CE +T2W(Flair) 13/39 (33%)
- MRI T1CE +T2W(Flair) +Remote 4/39 (10%)
- Remote only 2/39 (5%)
- No uptake 2/39 (5%)

The addition of PET imaging allowed inclusion of disease that would have been missed with traditional CTV in 9/39 cases (23%)

Results

Treatment Received

- All patients completed entire course of prescribed RT
  - 35 GyE in 5 fractions (18/39)
  - 40 GyE in 10 fractions (21/39)
- TMZ concurrent (39/39)
- TMZ adjuvant: median 5 cycles (range 0-12)
- 1 patient received adjuvant alternating electric field therapy (TTF)
- Salvage therapies at progression included bevacizumab (22 pts), re-resection (5), re-RT (5), lomustine (10), TTF (2), other chemo (3)



Primary endpoint: Overall Survival

Median 12.9 months

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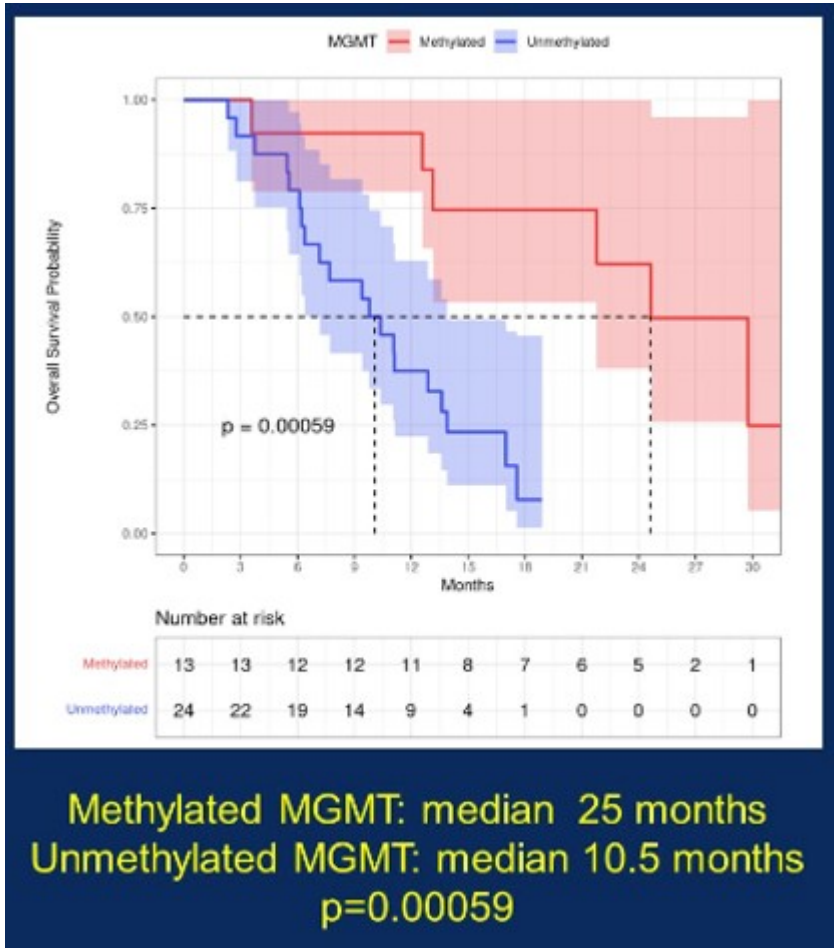


Methylated MGMT: median 25 months
Unmethylated MGMT: median 10.5 months
p=0.00059

Variable	Hazard Ratio	95% CI	P-value
ECOG 1 vs 0	0.87	(0.32,2.34)	0.78
ECOG 2 vs 0	2.09	(0.61,7.12)	0.24
STR vs GTR	1.76	(0.47, 6.62)	0.41
Biopsy vs GTR	2.11	(0.62,7.26)	0.23
MGMT:Unmeth	9.46	(2.33,38.41)	0.002
MGMT:Unknown	16.35	(1.84,145.15)	0.012
Tumor cross midline	0.42	(0.12,1.48)	0.18
MRI volume	1.01	(0.99,1.03)	0.43
PET volume	1.01	(0.98,1.04)	0.55

Results - Toxicity

There were no grade 4 or 5 treatment related events

Grade 2+ treatment-related toxicities (N=39 pts)

- CNS necrosis 15 (38%)
- Confusion 3 (8%)
- Dysphasia 1 (3%)
- Fatigue 9 (23%)
- Headache 2 (5%)
- Seizure 5 (13%)
- Alopecia 4 (10%)

Grade 3 treatment-related toxicities (N=39 pts)

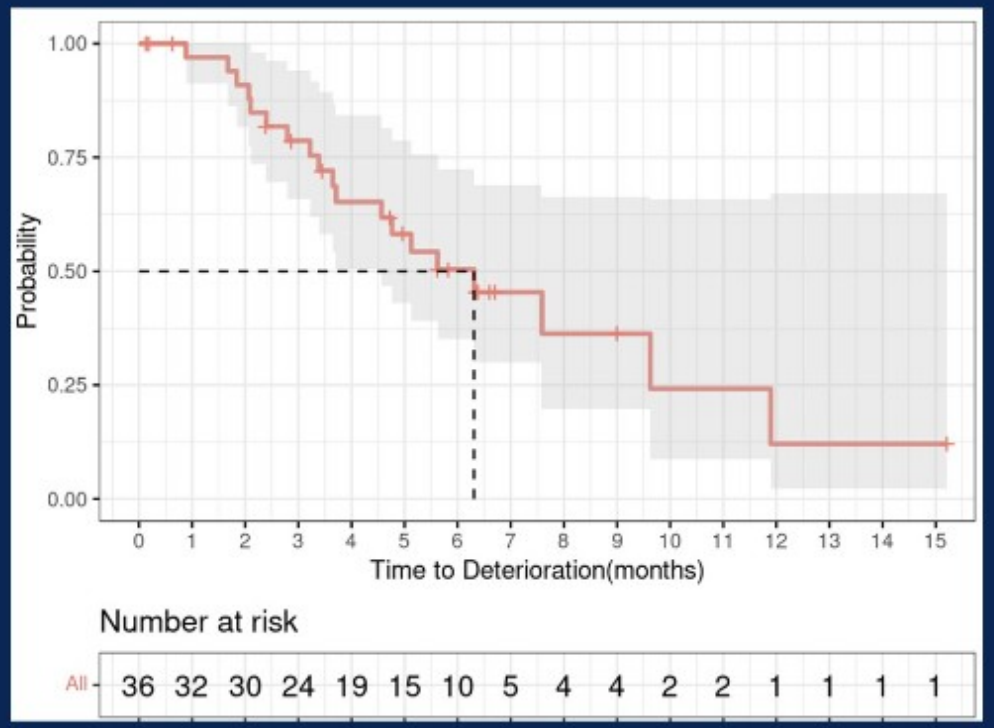
- Confusion 1 (3%)
- Fatigue 2 (5%)
- Seizure 1 (3%)
- CNS necrosis 5 (13%)
  - 2 cases of pseudoprogression vs. progression
    - 1 case tx with bevacizumab
    - 1 case tx with surgery (minimal viable tumor + extensive treatment effect)
  - 2 cases of necrosis tx with bevacizumab
  - 1 case of edema tx with bevacizumab

Quality of Life (QLQ-C30)

Global time to deterioration, defined as a 10-point decrease in the score of the function domain or 10-point increase in score of symptom domain, was evaluated

Median time to deterioration: 6.3 months

Compares favorably to Intergroup elderly trial 40 Gy +/- TMZ: median 1.3 months (Perry et al. NEJM 2017;376:1027-37)



Conclusions / Take Away

This is the first prospective study to utilize hypofractionated proton beam therapy to provide elderly patients and caregivers a convenient yet effective treatment option

The primary endpoint was met with median overall survival of 12.9 months

18F DOPA PET guided dose escalation utilizing proton beam therapy appears safe

Quality of life via QLQ-C30 compared favorably to prior trials

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2023 ASCO
ANNUAL MEETING
Anti-Telomerase vaccine
in patients with newly diagnosed,
unmethylated MGMT glioblastoma:
a phase II study
Antoine F Carpentier, Clotilde Verlut, François Ghiringhelli, Charlotte Bronnimann, Renata Ursu, Jean David Fumet, Elisabeta Gherga, Felix Lefort, Catherine Belin, Dewi Vernerey, Alice Hervieu, Caroline Laheurte, Aurelia Meurisse, Marion Jacquin, Marine Malfroy, Christine Fagnoni-Legat, Jacqueline Lehmann-Che, Laura Boullerot, Stefania Cuzzubbo, Olivier Adotevi
Investigating Centers : University hospitals of Paris, Besançon, Dijon and Bordeaux; France
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#ASCO23
PRESENTED BY: Antoine Carpentier, MD, PhD
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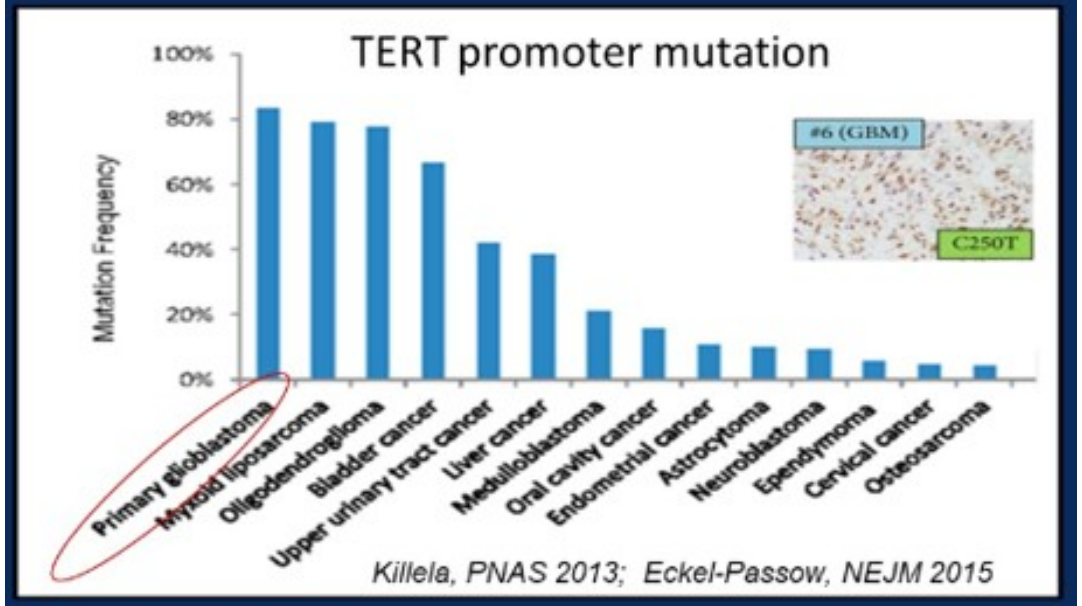
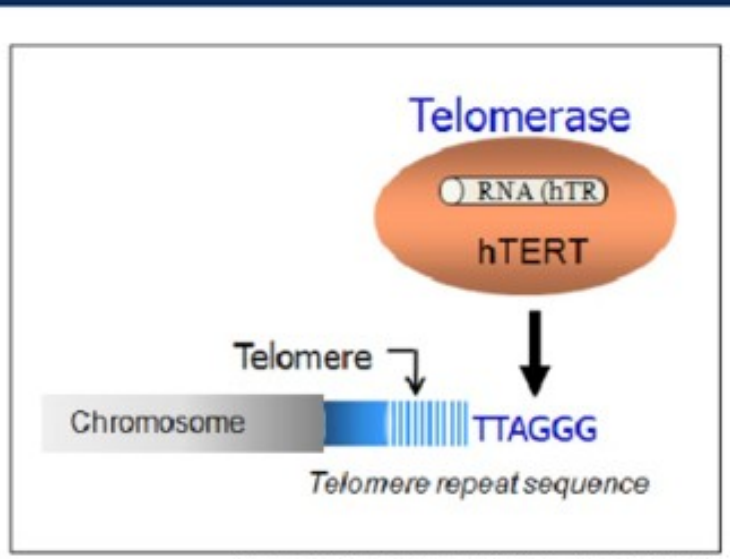
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY
KNOWLEDGE CONQUERS CANCER

High incidence of activating TERT promoter mutation in glioblastomas (GBM)



Killela, PNAS 2013; Eckel-Passow, NEJM 2015

TERT is strongly expressed in GBM, but not in normal brain



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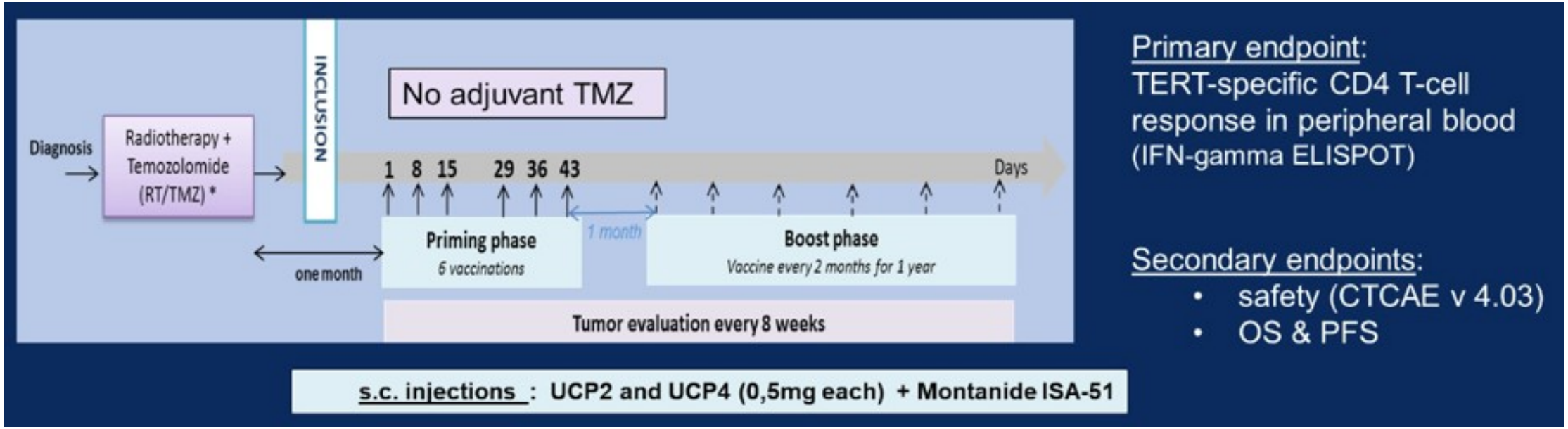
Diagnosis
Radiotherapy + Temozolomide (RT/TMZ) *
INCLUSION
No adjuvant TMZ
1 8 15 29 36 43
Days
one month
Priming phase
6 vaccinations
1 month
Boost phase
Vaccine every 2 months for 1 year
Tumor evaluation every 8 weeks
s.c. injections : UCP2 and UCP4 (0,5mg each) + Montanide ISA-51
Primary endpoint:
TERT-specific CD4 T-cell response in peripheral blood (IFN-gamma ELISPOT)
Secondary endpoints:
• safety (CTCAE v 4.03)
• OS & PFS

UCPvax clinical trial

Baseline characteristics

	Number of patients	% of patients
Glioblastoma, IDH1 wild-type	31	100%
Age, median (range), years	60.2 (37.5-85.5)	
Gender, female/male	12 / 19	39% / 61%
KPS 70-80 % **KPS 90-100 %**	6 25	19% 81%
***MGMT* promoter methylation (Yes/No)**	0 / 31	0% / 100%
Initial surgical procedure **biopsy** **partial resection** **complete resection**	 3 13 15	 10% 46% 54%
Baseline steroid use (at inclusion) **No** **Yes (dexamethasone ≤ 1.5 mg/d)**	 26 5	 84% 16%

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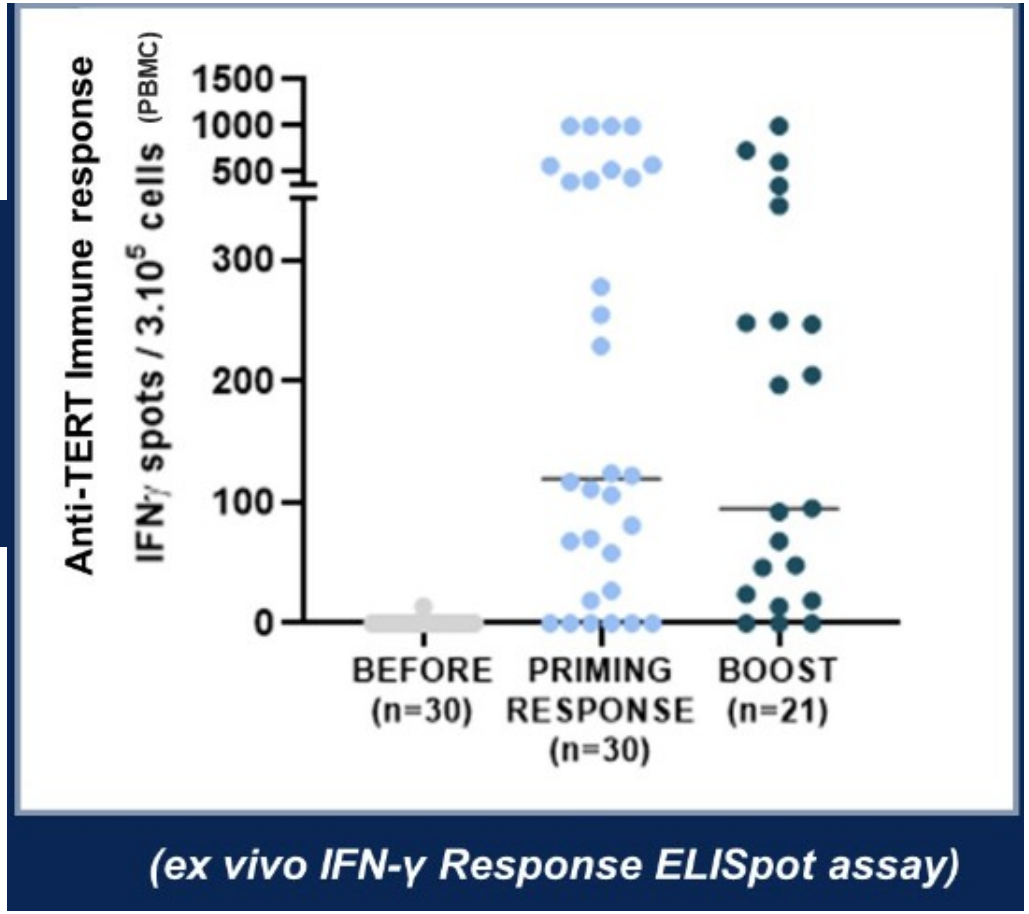
UCPvax clinical trial

Safety

Good compliance : vaccinations were given for 4.5 months on average (min 2– max 14)

- No Dose limiting toxicity (DLT)
- Grade 1-2 local skin reactions in 29/31 pts (93.5%)



(ex vivo IFN-γ Response ELISpot assay)

UCPvax clinical trial

Outcome

	UCPvax (n=31 pts)		Historical data *	
OS since diagnosis:	**17.9 months**	⟷	**14.6 months** **14.9 months**	*Gilbert, NEJM, 2014* *Omuro, Neuro Oncol, 2023*
OS since end of radiotherapy				
• All patients	**15.0 months**	⟷	*No relevant historical data*	
• Pts without progression / pseudo-progression after RT	**18.1 months** (n=16 pts)	⟷	**14.7 months** **14.6 months**	*Stupp, JAMA, 2017* *Liau JAMA Oncol, 2023*

* unmethylated MGMT population, control groups

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2023 ASCO Annual Meeting

2023 ASCO ANNUAL MEETING

Prognostic evaluation of surgical re-resection for recurrent glioblastoma using the novel RANO classification for extent of resection

- a report of the RANO resect group -

Philipp Karschnia, Antonio Dono, Jacob S. Young, Stefanie T. Jünger, Nico Teske, Levin Häni, Tommaso Sciortino, Christine Y. Mau, Francesco Bruno, Michael Weller, Roberta Rudà, Michael A. Vogelbaum, Lorenzo Bello, Oliver Schnell, Stefan J. Grau, Susan M. Chang, Mitchel S. Berger, Yoshua Esquenazi, & Joerg-Christian Tonn

on behalf of the RANO resect investigators

DKTK German Cancer Consortium

LMU KLINIKUM DER UNIVERSITÄT MÜNCHEN

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Neuro-Oncology
XX(XX), 1–15, 2022 | https://doi.org/10.1093/neuonc/noac193 | Advance Access date 12 August 2022

Prognostic validation of a new classification system for extent of resection in glioblastoma: A report of the RANO *resect* group

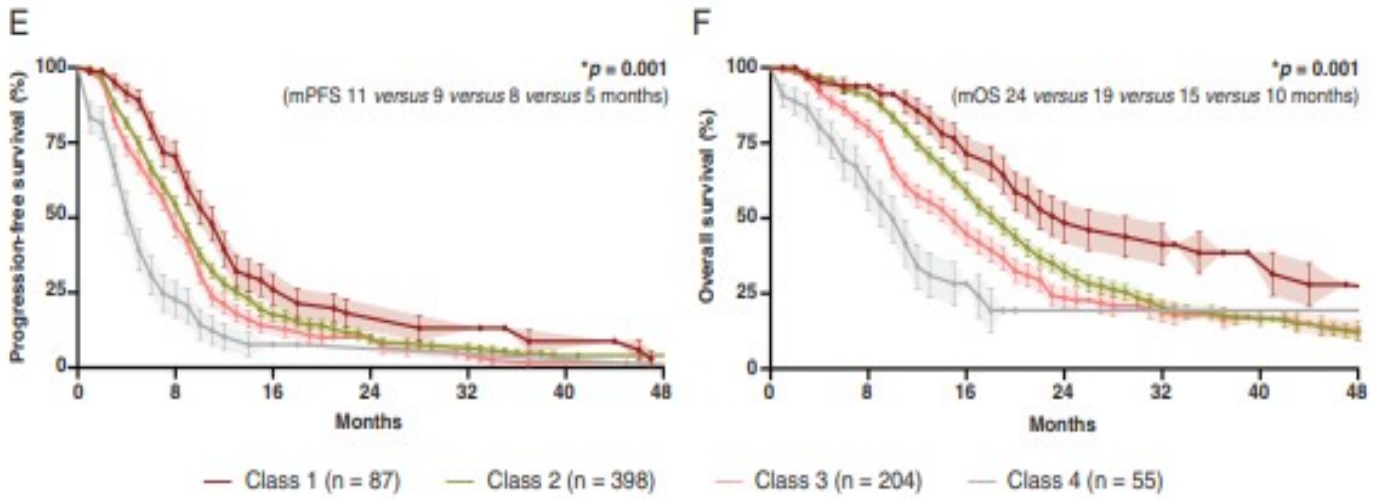
Karschnia et al., 2022

Role of EOR in newly diagnosed GBM

What about recurrent GBM?

D

RANO categories for extent of resection in glioblastoma					
Class 1: supramaximal CE resection	Class 2: maximal CE resection		Class 3: submaximal CE resection		Class 4: biopsy
	Class 2A: complete CE resection	*Class 2B: near total CE resection*	*Class 3A: subtotal CE resection*	*Class 3B: partial CE resection*	
0 cm^3 CE + ≤5 cm^3 nCE	0 cm^3 CE + >5 cm^3 nCE	≤1 cm^3 CE	≤5 cm^3 CE	>5 cm^3 CE	No reduction of tumor volume



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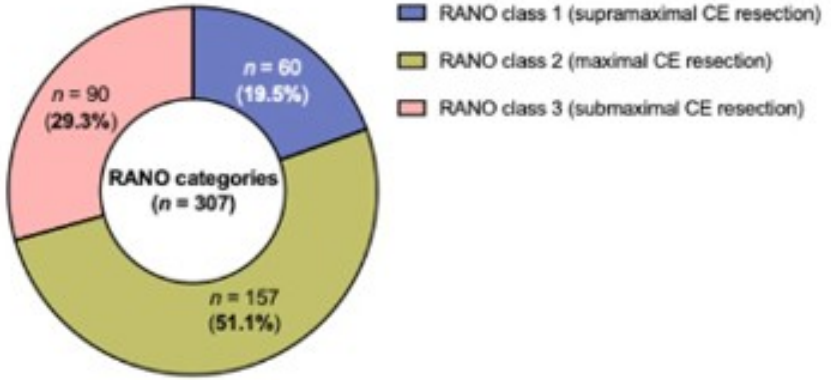

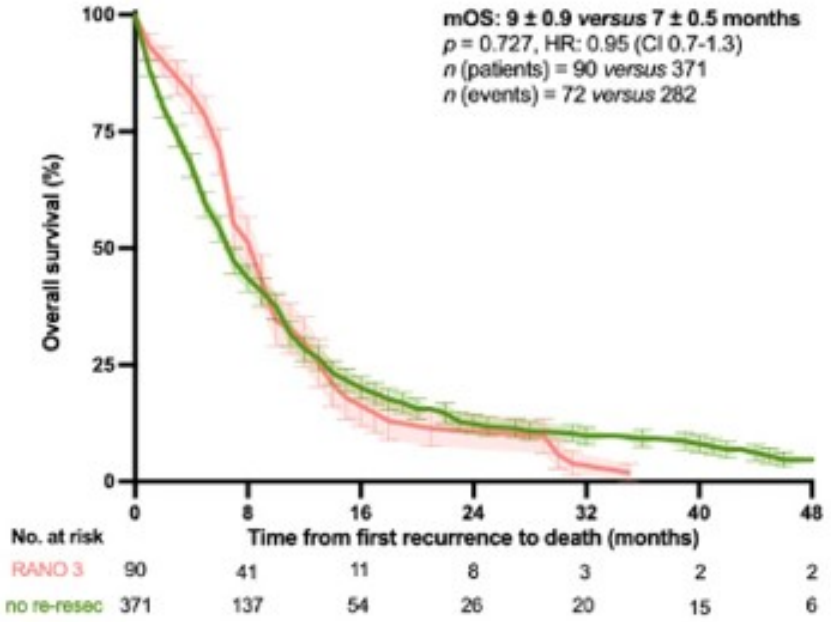

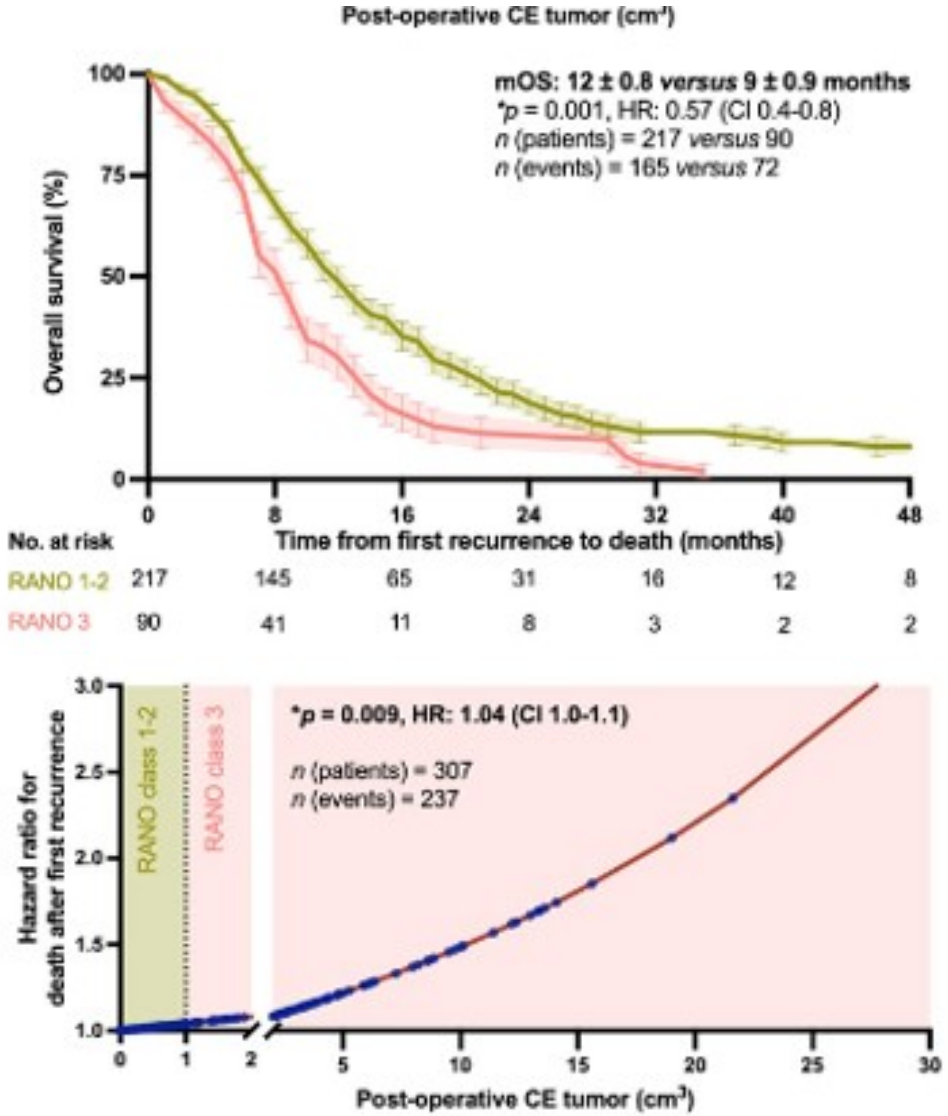

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BORTEM-17 - Phase IB/II single arm, a multicenter study investigating the efficacy of sequential Bortezomib and Temozolomide in recurrent GBM with unmethylated MGMT promoter

The results of an interim analysis

Dorota Goplen, MD, PhD, Haukeland University Hospital, Bergen, Norway

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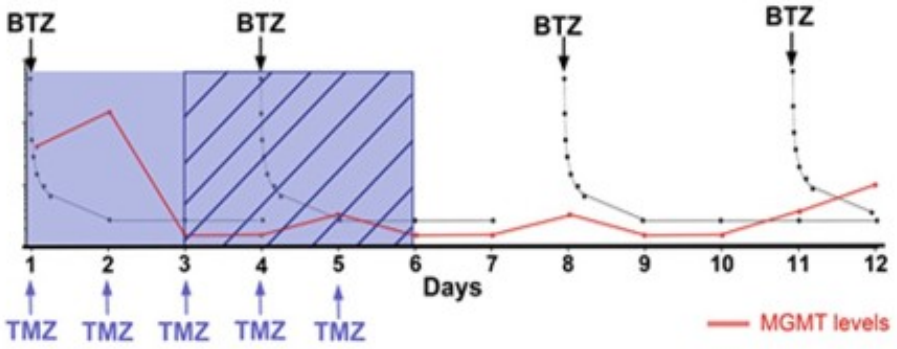
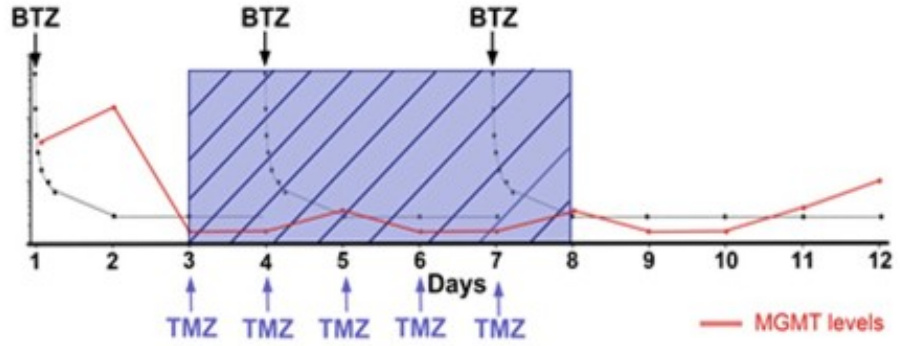
Background

Hypothesis: Recurrent GBM patients with unmethylated MGMT promoter may obtain clinical benefit from sequential combination of BTZ and TMZ treatment



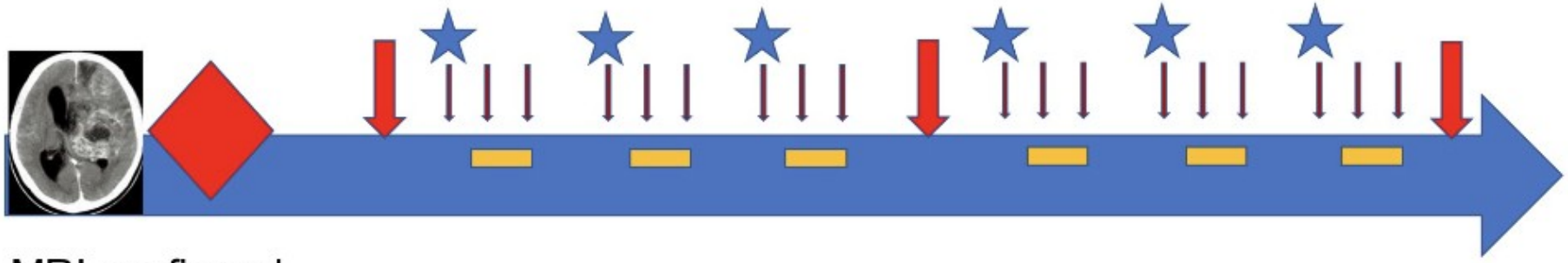
Previous studies



BORTEM-17

- Previous clinical trails failed to show efficacy of BTZ in treatment of glioblastoma
- The pre-clinical trials have shown that BTZ administered 48 hrs before TMZ abrogates the MGMT function and sensitizes the tumor to TMZ therapy

Treatment schedule of BORTEM-17



MRI confirmed relapse.
Trial inclusion

Trial MRI at baseline and as response assessment

Bortezomib, day 1,4, 7, q4w

Temozolomid, day 3-7, q4w

Clinical status, NANO assessment, blood sampling

The treatment continues for up to 6 cycles if no PD is confirmed by RANO criteria

Methods

- Sample size: 63 patients, of whom 10 included in phase IB.
- Cycle duration: 4 weeks:
  - Bortezomib: 1.3mg/m^2 IV days 1, 4, and 7
  - Temozolomide 200mg/m^2 PO days 3-7
- The control group: a retrospective cohort of age matched patients with MGMT unmethylated glioblastoma (n=116).
- The clinical benefit is is defined as CR, PR or SD at the scheduled control MRI

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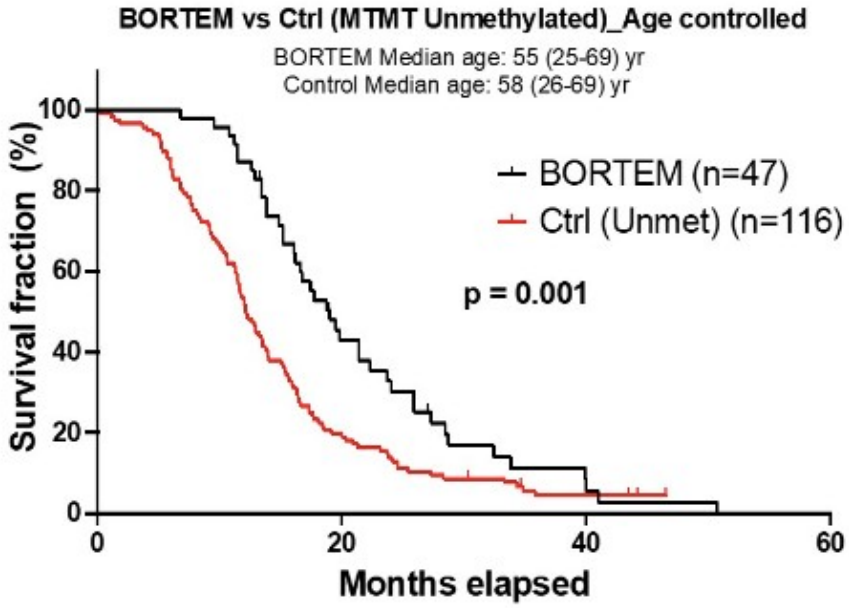
Results

- Median survival for BORTEM-17 patients was 19 months vs. 12.2 months for the control MGMT unmethylated age matched patients
- Median survival after recruitment was 5.5 months (1.0-23.8)



	BORTEM	Ctrl (Unmet)
Median survival	19	12.15

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Conclusions

- The sequential BTZ+TMZ therapy is safe, feasible and effective as indicated by preliminary data when almost 70% of planned MGMT unmethylated patients have been included.
- Preliminary data indicate that the combination of BTZ and TMZ may offer an additional line of treatment with limited toxicity to the group of patients with particularly dismal prognosis

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Belzutifan Treatment for von Hippel-Lindau Disease–Associated Central Nervous System Hemangioblastomas in the Phase 2 LITESPARK-004 Study

Othon Iliopoulos[1]; Ane B. Iversen[2]; Kathryn E. Beckermann[3]; Vivek Narayan[4]; Benjamin L. Maughan[5]; Stephane Oudard[6]; Tobias Else[7]; Jodi K. Maranchie[8]; Wei Fu[9]; Rodolfo. F. Perini[9]; Yanfang Liu[9]; W. Marston Linehan[10]; Ramaprasad Srinivasan[10]; Eric Jonasch[11]

[1]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [2]Aarhus University Hospital, Aarhus, Denmark; [3]Vanderbilt University Medical Center, Nashville, TN, USA; [4]University of Pennsylvania, Philadelphia, PA, USA; [5]University of Utah, Salt Lake City, UT, USA; [6]Hôpital Européen Georges Pompidou, Paris, France; [7]University of Michigan, Ann Arbor, MI, USA; [8]University of Pittsburgh, Pittsburgh, PA, USA; [9]Merck & Co., Inc., Rahway, NJ, USA; [10]Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA; [11]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

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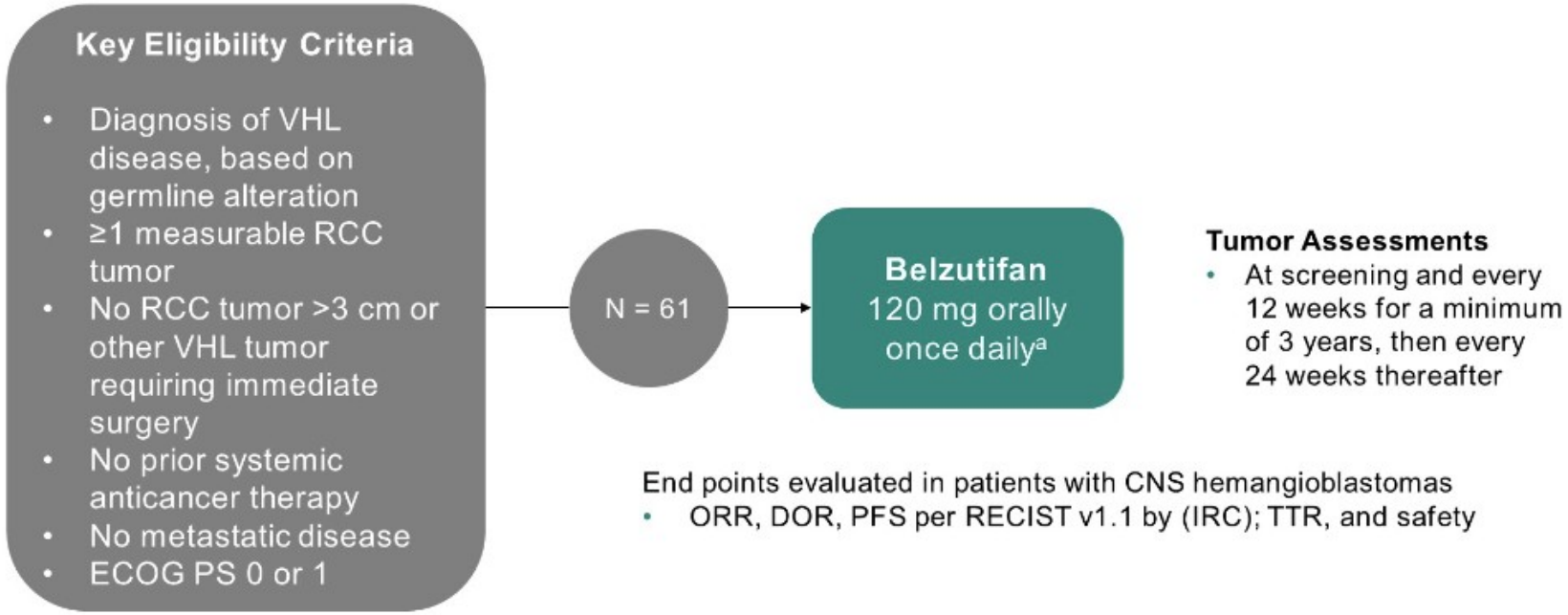
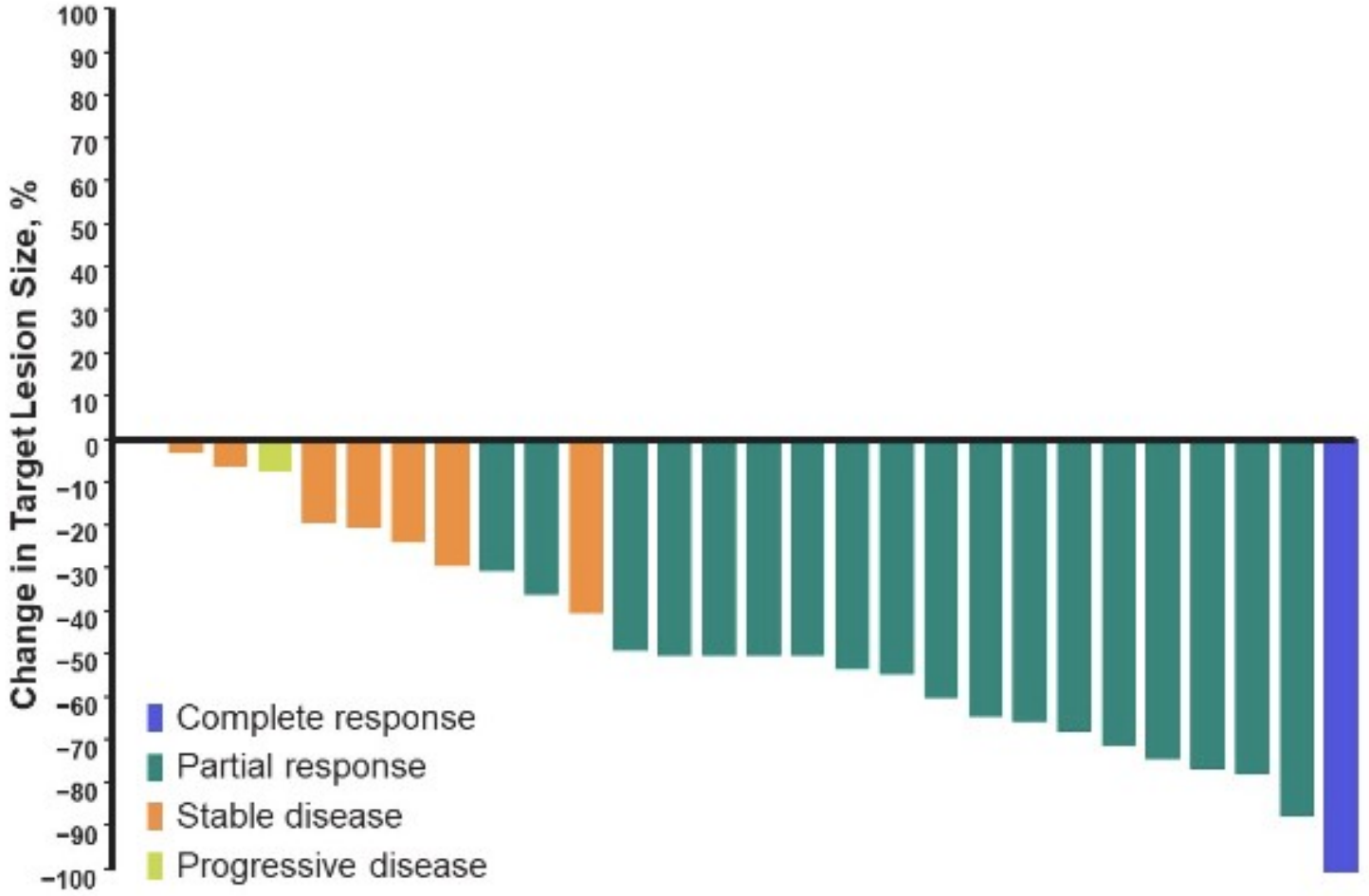
Background

- CNS hemangioblastomas affect up to 80% of patients with VHL disease[1] and are among the leading causes of morbidity and mortality in patients with VHL disease[2]
- Belzutifan is a first-in-class HIF-2α inhibitor approved in the US and several other countries for the treatment of adult patients with VHL disease who require therapy for associated RCC, CNS hemangioblastomas, or pNETs not requiring immediate surgery[3]
  - Durable responses were observed with belzutifan in patients with VHL disease-associated CNS hemangioblastomas in previous analyses of the phase 2 LITESPARK-004 study[4,5]
- We present efficacy results based on more than 3 years of follow-up for the subgroup of patients with CNS hemangioblastomas enrolled in LITESPARK-004

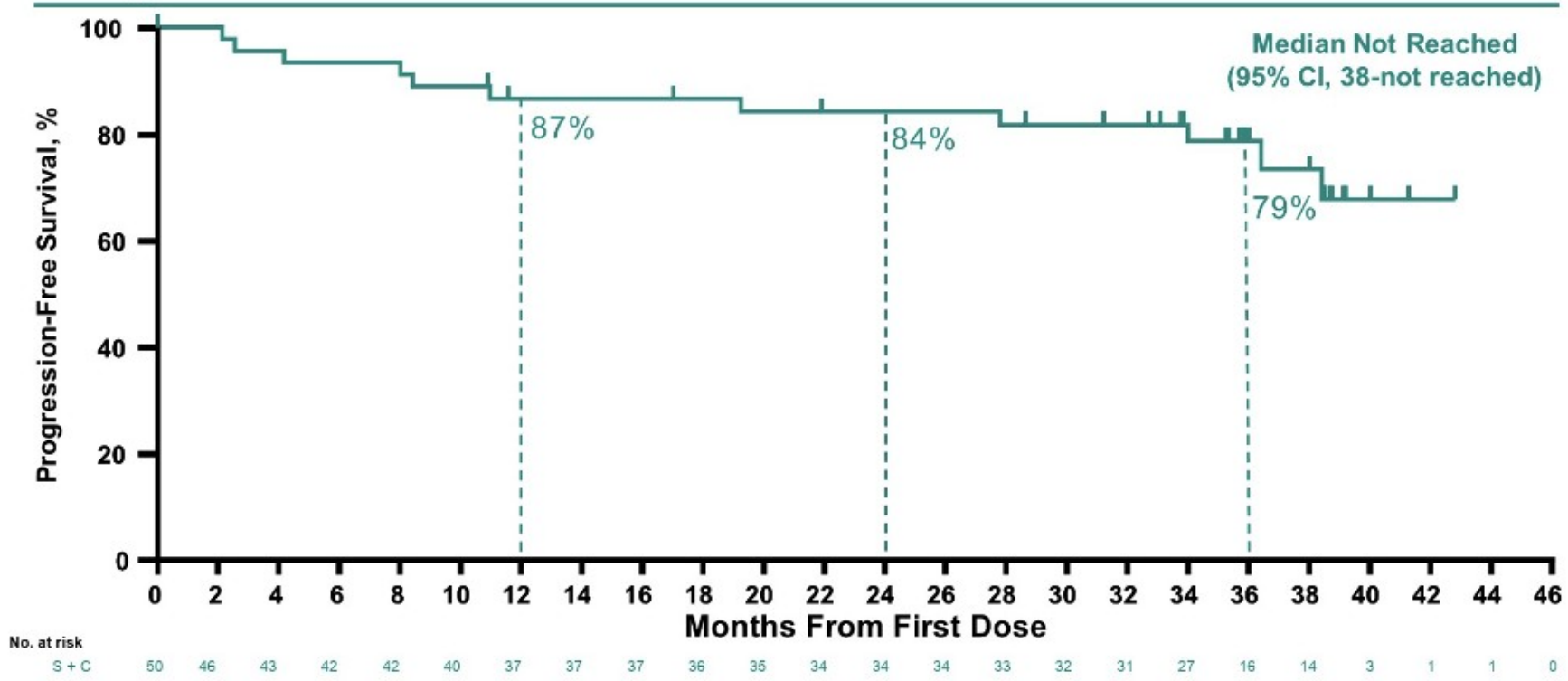
LITESPARK-004 (NCT03401788) Study Design



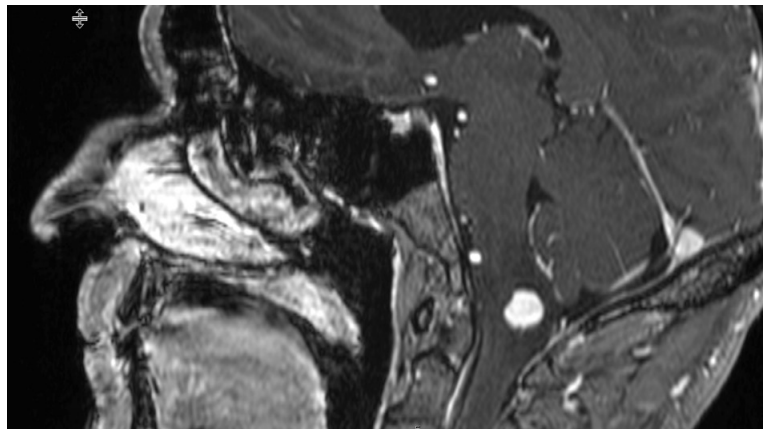
DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; ORR, overall response rate; PFS, progression-free survival; TTR, time to response.
[a]Study treatment continued until unacceptable toxicity, disease progression, or patient withdrawal. In an event of a mixed response (ie, continuing radiographic response in RCC lesions but progression or surgical requirement for a non-RCC lesion), study treatment may be continued if patient is tolerating the study drug and no alternative treatments are available for patient's progressive VHL associated non-RCC lesions.

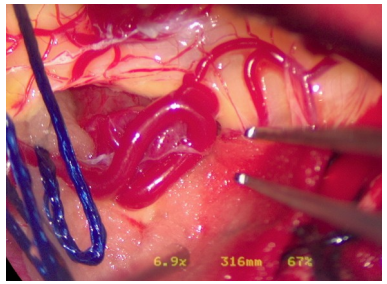

Change in Target Lesion Size, %
100
90
80
70
60
50
40
30
20
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
Complete response
Partial response
Stable disease
Progressive disease

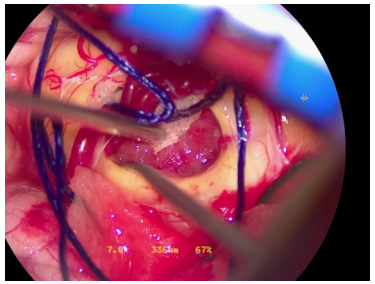
Progression-Free Survival in S + C[a]

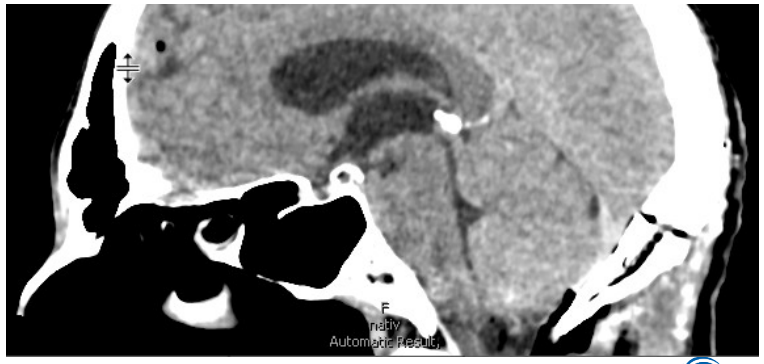


[a]By IRC assessment. Data cutoff date: April 1, 2022.









Distribution of CNS-Related Surgeries

- 46 patients (92%) had at least 1 CNS-related surgery before starting belzutifan
- 1 patient (2%) underwent 2 CNS-related surgeries to the same lesion after starting belzutifan treatment

CNS-related surgery
Treatment ongoing
Patient had ≥1 CNS-related surgery beyond 4 years

−4 −3 −2 −1 0 1 2 3 4
Years From Starting Belzutifan Treatment

Data cutoff date: April 1, 2022

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Take-Home-Message ASCO 2023: Primäre Hirntumore

- **INDIGO Phase 3 Studie** (präsentiert von Dr. Ingo Mellinghoff/ Plenary Session):
  - Der frühe Einsatz des oralen IDH1/2-Inhibitors Vorasidenib führt zu einer 61% Risikoreduktion (bildmorphologisch) für eine Tumorprogression bei guter Verträglichkeit
  - Practise-Changing: Vorasidenib rechtfertigt einen Aufschub der Strahlen-/ Chemotherapie beim teiloperierten/ rezidivierten niedergradigen Gliom IDH-mutiert, ZNS Grad 2

- Weitere (in der Regel nicht RCT, Baskettrials, monozentrisch) Studien deuten auf eine Wirksamkeit von zielgerichteten Therapien (z. B. EGFR) beim rezidivierten malignen Gliom

- Phase II Studie zur 18F-DOPA-Pet/MRI geführten **hypofraktionierten Protonentherapie beim alten Patienten** (>65 Jahre) mit **neu diagnostiziertem Glioblastom** zeigt verbessertes OS im Vergleich zu historischen Kontrollen bei tolerabler Verträglichkeit *(Vora et al., J Clin Oncol 41, Abstract 2002)*

- **BORTEM-17**: Der Einsatz von Bortezomid in Kombination mit Temozolomid verbessert die Kontrolle des wiederkehrenden Glioblastoms in einer einarmigen Phase IB/II Studie bei guter Verträglichkeit *(Goplen et al., J Clin Oncol 41, Abstract 2019)*

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Herzlichen Dank für Ihre Aufmerksamkeit.

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