Journée scientifique SNOB
Société de
Neuro-Oncologie Bretonne

Actualités en Neuro-Oncologie

Docteur Elodie VAULEON

Brest, le 06/10/2023

Actualités en Neuro-Oncologie

- **Présentations lors congrès 2022- 2023**
- **Publications de 2022-2023**
- GLIOBLASTOME
- GLIOME DE BAS GRADE
- GLIOME DE LA LIGNE MEDIANE et du TRONC
- ASTROBLASTOME
- XANTHOASTROCYTOME
- EPENDYMOME
- Tumeur des PLEXUS CHOROIDES
- Tumeur GLIONEURONALE
- Tumeur de REGION PINEALE
- MEDULLOBLASTOME
- MENINGIOME
- HEMANGIOPERICYTOME
- ADENOME HYPOPHYSAIRE
- METASTASES CEREBRALES
- SCHWANNOME VESTIBULAIRE

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INDIGO: Phase 3 randomisée en double aveugle du VORASIDENIB versus placebo chez patient avec un gliome IDH1 ou IDH2 muté de grade 2 résiduel ou récidivant

The NEW ENGLAND JOURNAL of MEDICINE

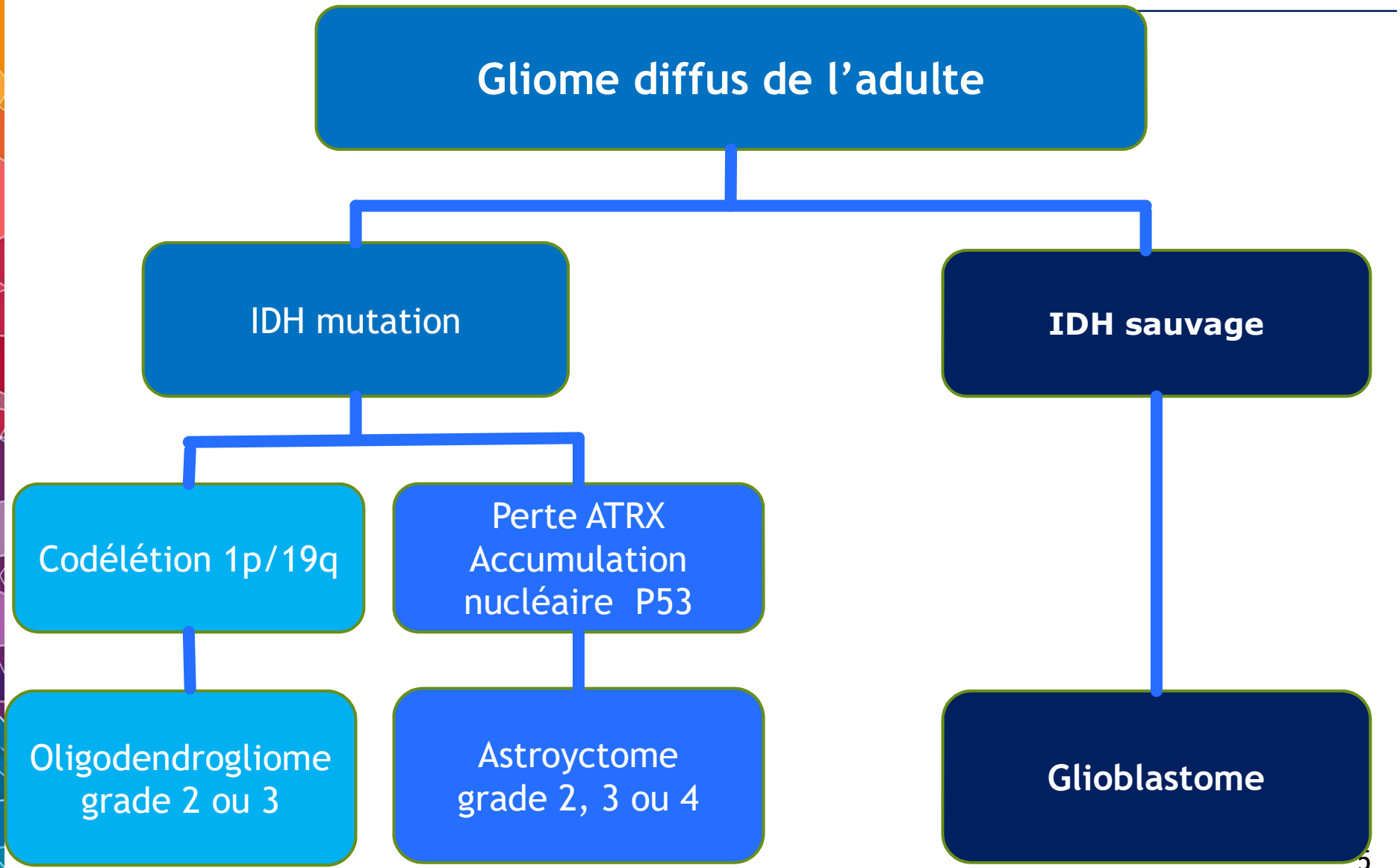
ORIGINAL ARTICLE

Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma

I.K. Mellinghoff, M.J. van den Bent, D.T. Blumenthal, M. Touat, K.B. Peters, J. Clarke, J. Mendez, S. Yust-Katz, L. Welsh, W.P. Mason, F. Ducray, Y. Umemura, B. Nabors, M. Holdhoff, A.F. Hottinger, Y. Arakawa, J.M. Sepulveda, W. Wick, R. Soffietti, J.R. Perry, P. Giglio, M. de la Fuente, E.A. Maher, S. Schoenfeld, D. Zhao, S.S. Pandya, L. Steelman, I. Hassan, P.Y. Wen, and T.F. Cloughesy*

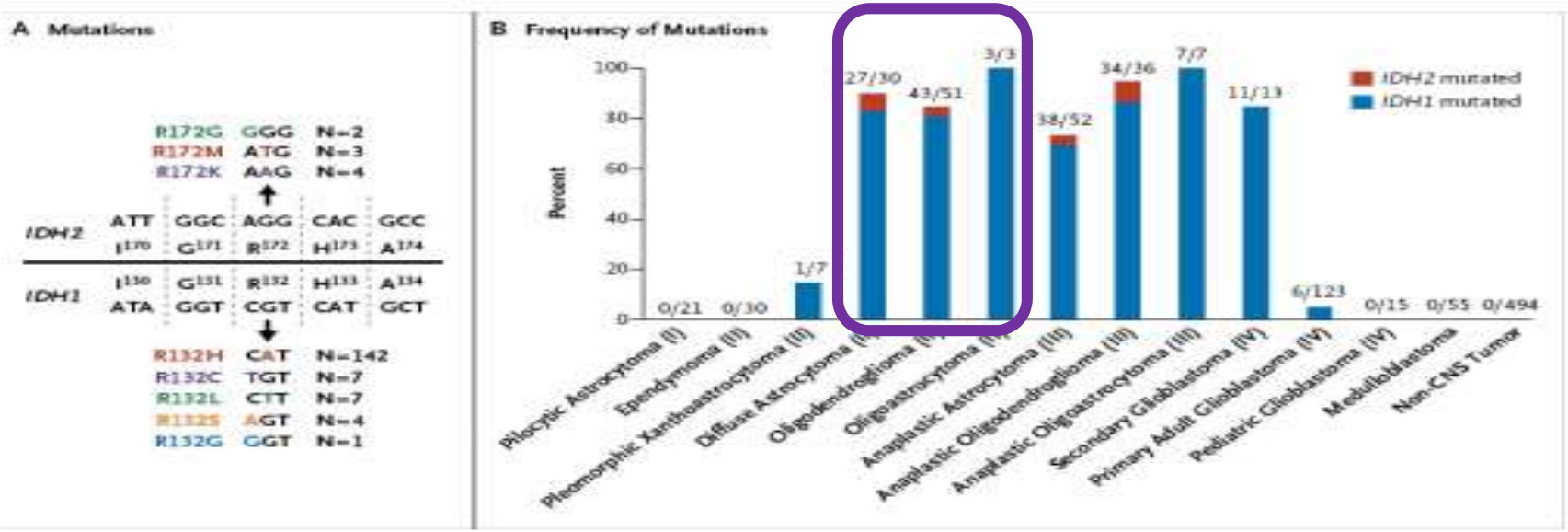
ASCO 2023

Classification OMS 2021 des gliomes



Mutation IDH1 et IDH2

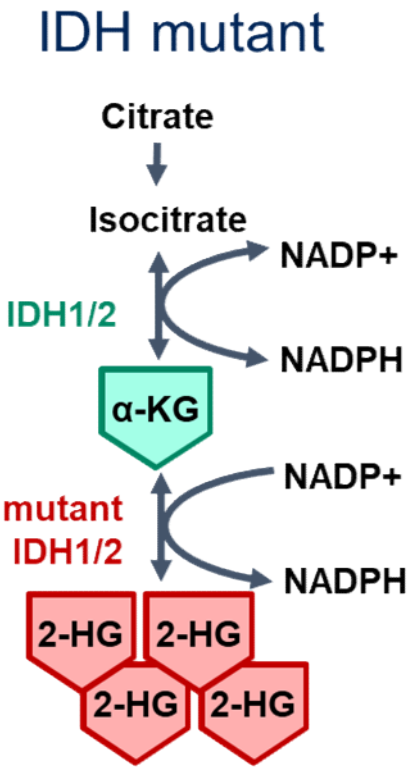
- **Évènement le plus précoce dans la gliomagenèse**



Yan *et al.*, 2009

- **méthodes de détection :**
  - **IHC : protéine mutée IDH1 R132H dans 95 % des cas**
  - **NGS**
  - **Séquençage Sanger IDH1/2**

IDH isocyanate deshydrogénase



Competitive inhibition of α-KG-dependent enzymes

- Mutation IDH1/2 est connue pour induire :
  - Augmentation de production du 2-HG 2-hydroxyglutarate
  - Dysrégulation épigenetique
  - Défaut de différenciation cellulaire
  - Microenvironment immnosuppresseur

Lu and al, 2020

Traitement des gliomes de grade 2

- **CHIRURGIE :** résection maximale possible

- **Si bas risque** : surveillance possible

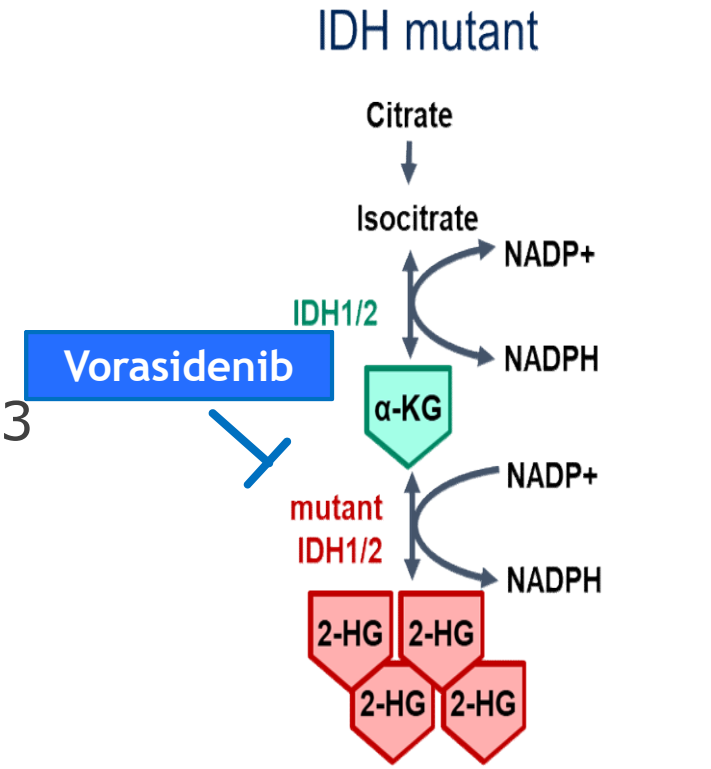
- **SI HAUT RISQUE** : quelle définition ? Différentes selon essais….
  - **Plus de 40 ans**
  - **Résection subtotale**
  - …
  - Astrocytome, bihémisphérique, ≥ 6 cm, déficit neurologique ?

  - **Oligodendrogliome codélété 1p/19q muté IDH de grade 2 :**
    - **Radiothérapie puis PCV**
  - **Astrocytome IDH muté de grade 2** :
    - **Radiothérapie puis TEMOZOLOMIDE**

… long terme ?…

VORASIDENIB

- Inhibiteur oral des mutants IDH1 and IDH2
- Conçu pour meilleure prénétrance **BHE**
- Réduit concentration tumorale de 2 HG de plus 90% dans gliome de grade 2 et 3 sans prise de contraste
- Réduction de 2-HG est associée à :
  - Prolifération cellulaire plus faible
  - Augmentation de lymphocytes infiltrants la tumeur
  - …



Competitive inhibition of α-KG-dependent enzymes

Mellinghoff I *et al. Nat Med* 2023;29:615–22

Essai INDIGO

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

n=331

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

*Centrally confirmed using an investigational clinical trial assay, based on the Oncomine Dx Target Test and developed in partnership with Thermo Fisher Scientific Inc.
†Real-time single BIRC reader
IDMC, independent data monitoring committee.

Critère principal de jugement

Endpoints and planned analyses

1 Primary endpoint

PFS: time from randomization to the first imaging-based disease progression as assessed by BIRC or death because of any cause

- MRI every 3 months for 3 years, then every 6 months

2 Key secondary endpoint

TTNI: time from randomization to the initiation of first subsequent anticancer therapy or death because of any cause

Three prespecified analyses*

IA1: futility
(~55 PFS events) – Jan 2022

↓

IA2: futility/superiority
(~123 PFS events) – Sep 2022

Final analysis (~164 events) → no longer needed after IA2 superiority outcome

Other secondary/exploratory endpoints include: safety, tumor growth rate by volume, objective response rate, overall survival, HRQoL, seizure activity and neuro-cognitive function.
*With multiplicity adjustment and alpha spending.
HRQoL, health-related quality of life; IA, interim analysis; MRI, magnetic resonance imaging.

Caractéristiques des patients

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.

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Données des patients

Patient disposition

As of Sep 2022 data cutoff (IA2):

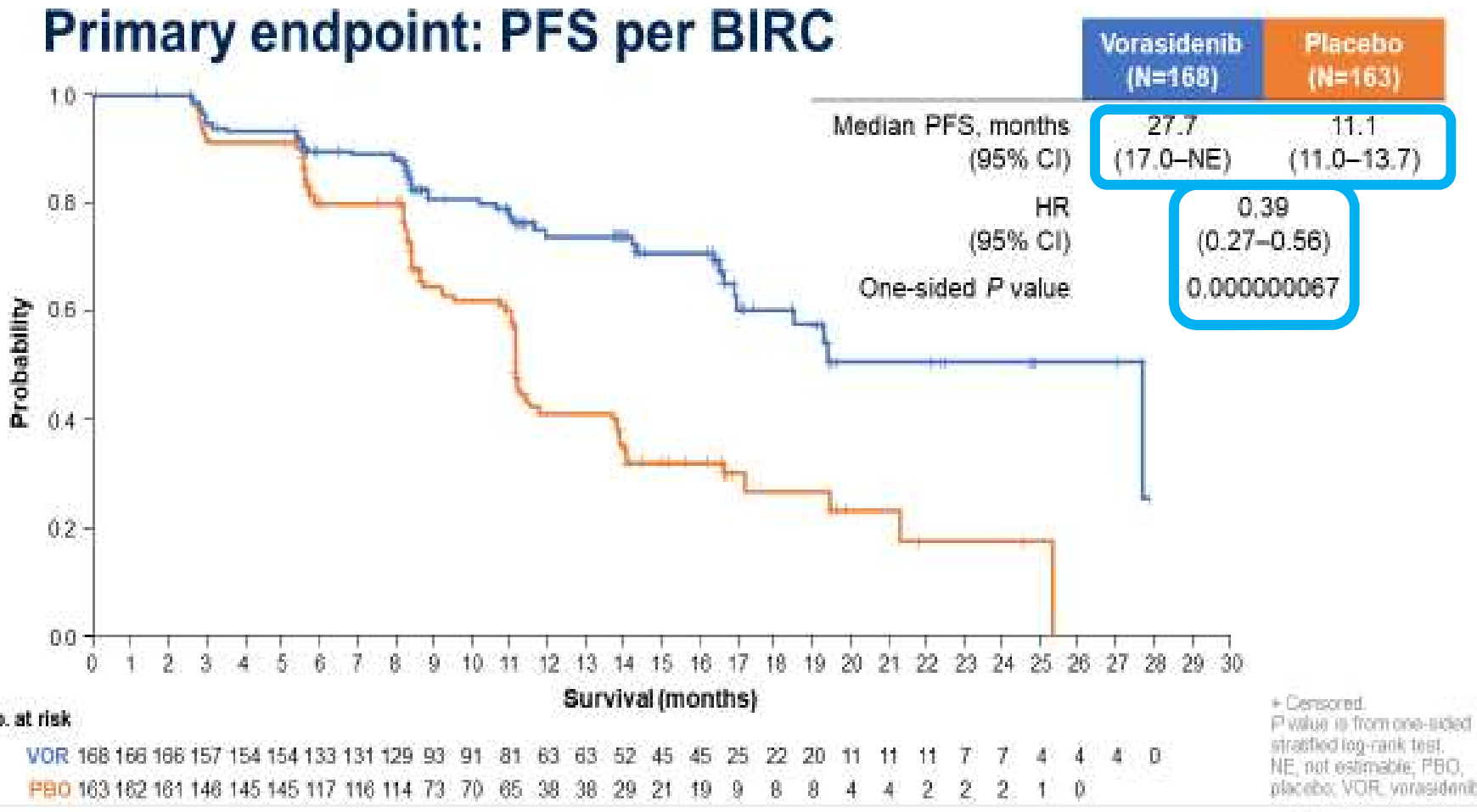
- Enrollment:
  - Jan 2020 to Feb 2022
- 77 centers across 10 countries
- Median follow-up:
  - 14.0 months with vorasidenib
  - 14.3 months with placebo
- No deaths
- No patients lost to follow-up for the primary outcome

	Vorasidenib	Placebo
Randomized to treatment – n (%)	168 (100)	163 (100)
Received treatment (safety set)	167 (99.4)*	163 (100)
Discontinued treatment – n (%)	36 (21.4)	68 (41.7)
Centrally confirmed disease progression†	24 (14.3)	59 (36.2)
Patient decision	5 (3.0)	5 (3.1)
Adverse event	6 (3.6)	2 (1.2)
Investigator decision	1 (0.6)	1 (0.6)
Clinical disease progression‡	0	1 (0.6)
Crossed over to vorasidenib – n (%)	–	52 (31.9)

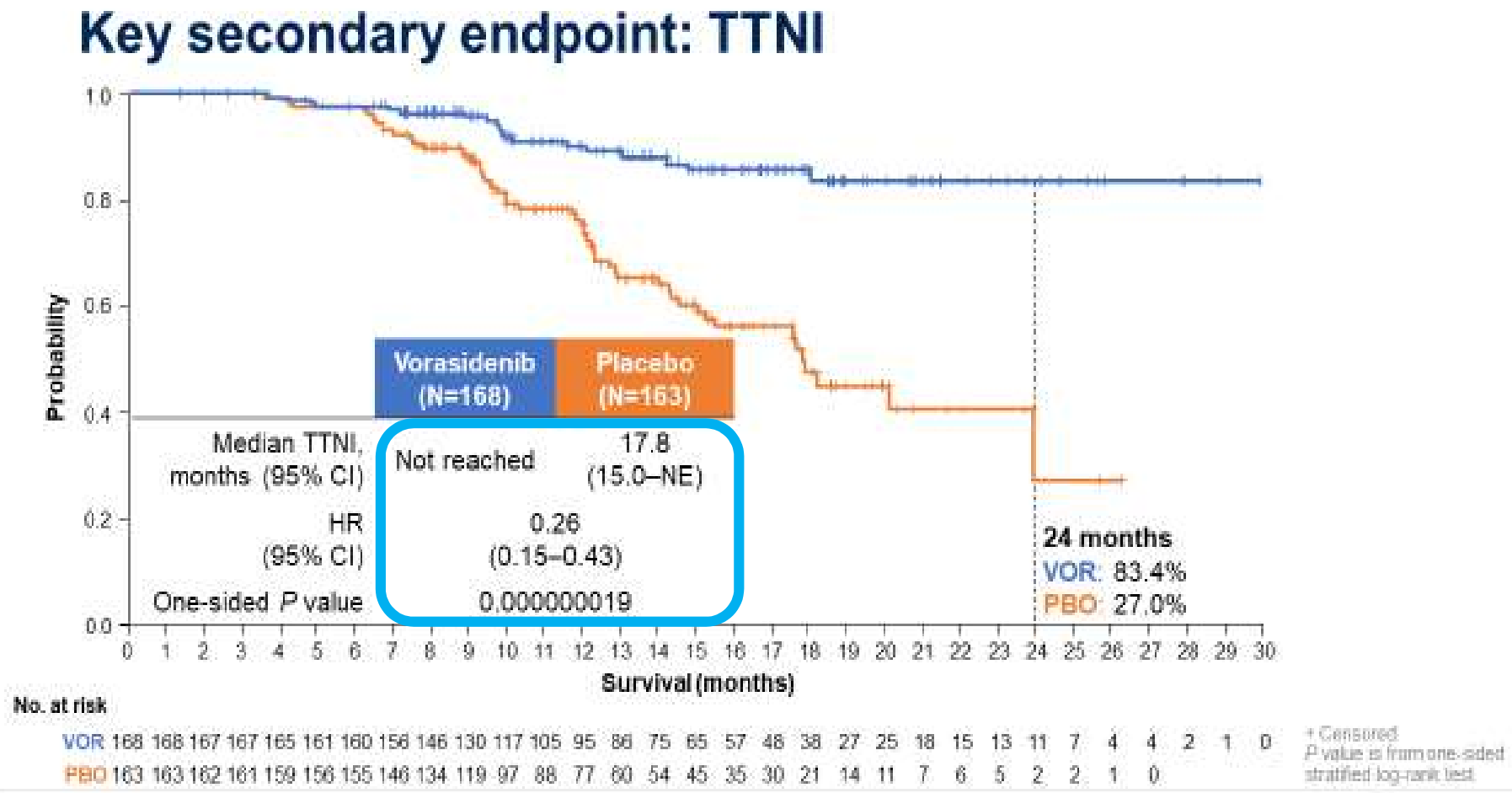
Study unblinded in Mar 2023 following IDMC recommendation based on early demonstration of efficacy, after which the majority of patients randomized to placebo crossed over to vorasidenib

*One patient withdrew consent from study treatment and later withdrew consent from the study overall. †Real-time single BIRC reader. ‡In absence of imaging-based progression.

Résultats : critère principal de jugement
PFS / revue radiologique centralisée



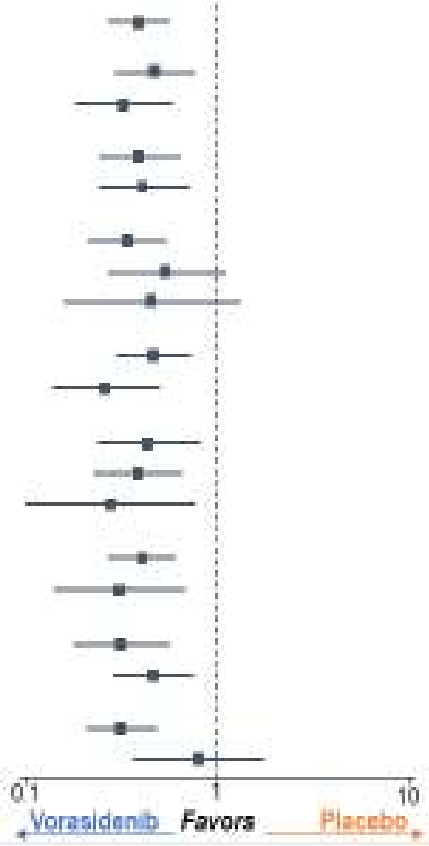
Critère secondaire : Temps de randomisation et traitement ou décès



Analyse de sous-groupes

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 1p/19q*	59/172 (34.3)	0.32 (0.18–0.57)
Non-codeleted chromosome 1p/19q	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.

Tolérance

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.

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Conclusion

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

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2023 ASCO ANNUAL MEETING

Anti-Telomerase vaccine in patients with newly diagnosed, unmethylated MGMT glioblastoma: a phase II study

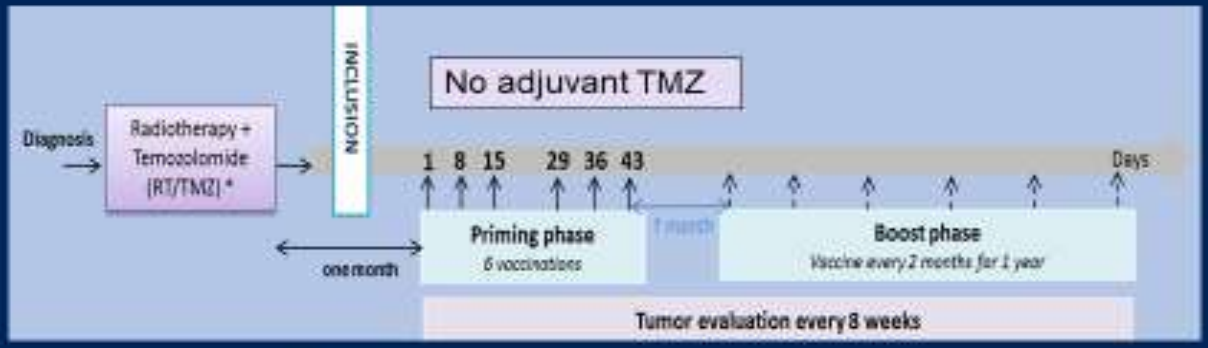
Antoine F Carpentier, Clotilde Verlut, François Ghiringhelli, Charlotte Bronnimann, Renata Ursu, Jean David Fumet, Elisabeta Gherga, Felix Lefort, Catherine Belin, Dewi Vernerey, Alice Hervieu, Caroline Laheurte, Aurelia Meurisse, Marion Jacquin, Marine Malfroy, Christine Fagnoni-Legat, Jacqueline Lehmann-Che, Laura Boullerot, Stefania Cuzzubbo, Olivier Adotevi

Investigating Centers : University hospitals of Paris, Besançon, Dijon and Bordeaux; France

UCPvax clinical trial

Design and objectives

Multi-center, prospective, non-controlled, phase II trial. (NCT04280848)



Primary endpoint:
TERT-specific CD4 T-cell response in peripheral blood (IFN-gamma ELISPOT)

Secondary endpoints:
- safety (CTCAE v 4.03)
- OS & PFS

s.c. injections : UCP2 and UCP4 (0,5mg each) + Montanide ISA-51

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%

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%)

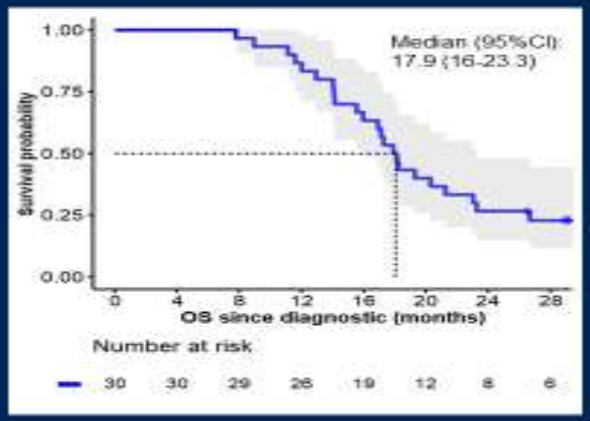
number of Adverse Event with relatedness	Grade 1	Grade 2	Grade 3	Grade 4	Overall	
Injection site reaction/induration	99	20	0	0	119	66%
General disoders (Asthenia, pyrexia)	14	4	1	0	19	11%
Nervous system disorders (Epilpsy, headaches, aphasia)	4	6	1	0	11	6%
Skin and subcutaneous tissue disorders (Pruritus, Urticaria, Rash)	9	2	0	0	11	6%
Musculoskeletal and connective tissue disorders (Myalgia, Arthralgia)	6	2	0	0	8	4%
Blood and lymphatic system disorders	5	0	0	0	5	3%
Investigations	2	1	0	0	3	2%
Infections and infestations	1	1	0	0	2	1%
Gastrointestinal disorders	1	0	0	0	1	1%
Endocrine disorders	1	0	0	0	1	1%
Total	142	36	2	0	180	100%

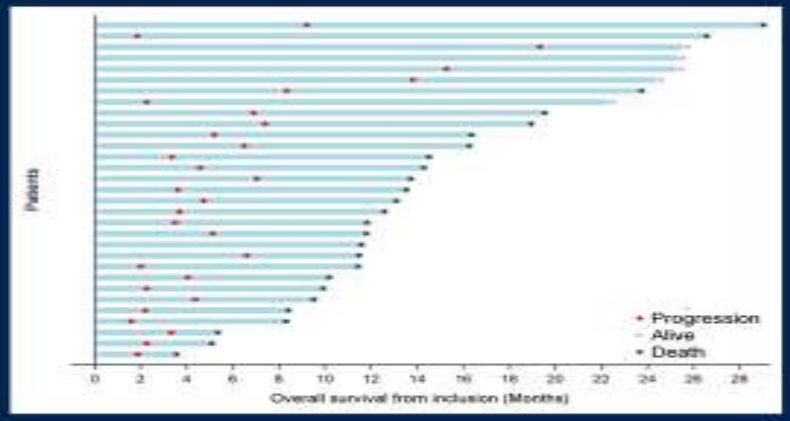
UCPvax clinical trial

Outcome

In the intent-to-treat population (n = 31):

Median PFS= 8.9 months , median OS: 17.9 months (No patients lost for follow-up)





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

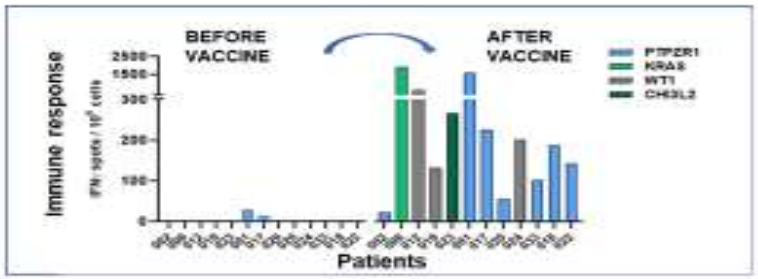
Presented by: Antoine Carpentier, MD, PhD

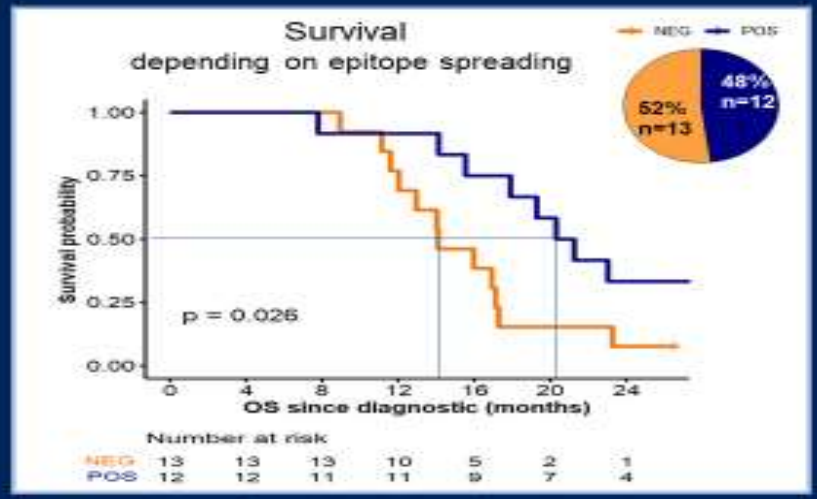
UCPvax clinical trial

Epitope spread responses

Epitope spread response against other glioma Ags

PTPRZ1, WT1, CHI3L2, KRAS, BCAN, ELOVL2
(IFN-g response ELISpot assay after IVS)





UCPvax clinical trial

Conclusions

UCPVax is:

- highly immunogenic
- provides an interesting survival in unmethylated MGMT GBM patients

This supports further clinical studies in newly-diagnosed GBM patients:

- UCPVax + TMZ (on-going)
- UCPVax + TMZ + anti-PD1 (MATVAC: Q1 2024)

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

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

CNS, central nervous system; FDA, US Food and Drug Administration; HIF-2α, hypoxia-inducible factor-2 alpha; pNET, pancreatic neuroendocrine tumor; RCC, renal cell carcinoma; VHL, von Hippel-Lindau. 1. Kanno H et al. J Kidney Cancer VHL. 2014;1:46-55. 2. Lonser RR et al. J Neurosurg. 2014;120:1055-1062. 3. WELIREG™ (belzutifan) tablets, for oral use, in. 05/2022. Rahway, NJ: Merck Sharp & Dohme LLC. 4. Jonasch E et al. N Engl J Med. 2021;385:2036-2046. 5. Srinivasan R et al. Ann Oncol. 2022;33(suppl_7):S808-S869.

LITESPARK-004 (NCT03401788) Study Design

Key Eligibility Criteria

- Diagnosis of VHL disease, based on germline alteration
- ≥1 measurable RCC tumor
- No RCC tumor >3 cm or other VHL tumor requiring immediate surgery
- No prior systemic anticancer therapy
- No metastatic disease
- ECOG PS 0 or 1

N = 61

Belzutifan
120 mg orally once daily[a]

Tumor Assessments
- At screening and every 12 weeks for a minimum of 3 years, then every 24 weeks thereafter

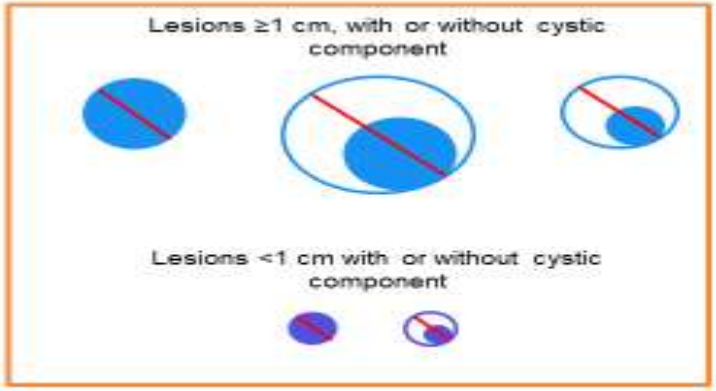
End points evaluated in patients with CNS hemangioblastomas
- ORR, DOR, PFS per RECIST v1.1 by (IRC); TTR, and safety

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.

Assessment of CNS Hemangioblastomas

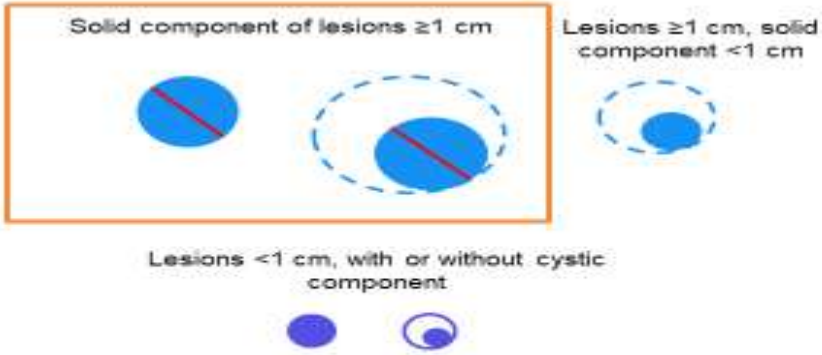
Approach 1
Lesion definition: **SOLID and associated CYSTIC (if present)** components **(S + C)**

Patient population: 50 patients with **measurable** (≥1 cm) and/or **non-measurable** lesions only at baseline



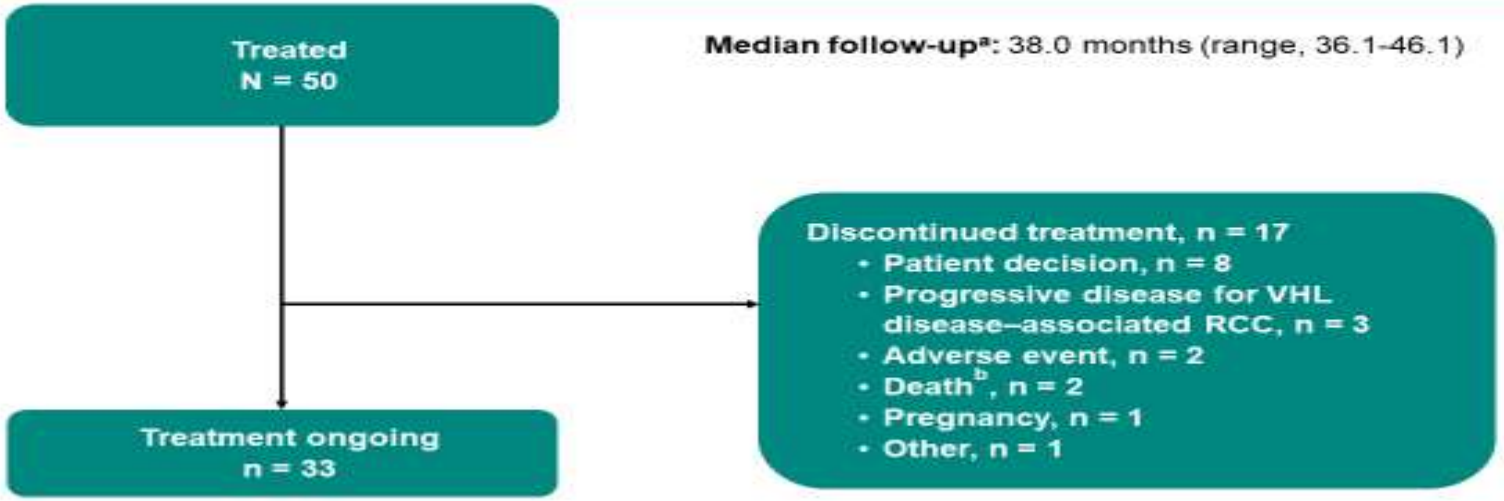
Approach 2
Lesion definition: **SOLID (S)** component only

Patient population: 25 patients with at least 1 **measurable** lesion (≥1 cm)



Essai LITESPARK 004

Disposition of Patients With CNS Hemangioblastomas

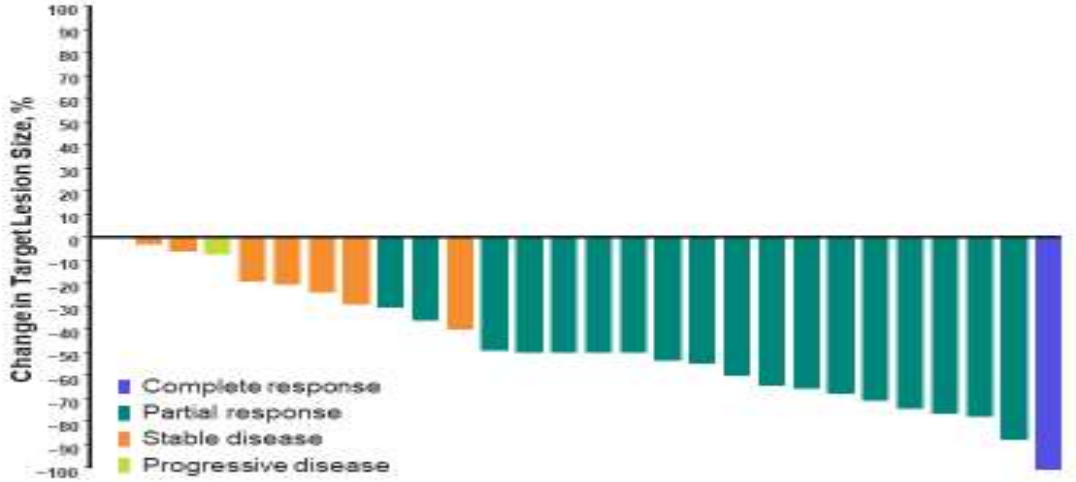


Baseline Characteristics

	S + C N = 50	S only N = 25
Age, median (range), years	40.5 (19-65)	34.0 (22-65)
Sex		
Male	30 (60)	19 (76)
Female	20 (40)	6 (24)
ECOG PS		
0	39 (78)	18 (72)
1	10 (20)	7 (28)
2	1 (2)	0
≥1 prior surgery for CNS hemangioblastomas	46 (92)	23 (92)

Best Overall Response and Best Percentage Change From Baseline: S + C (N = 50)

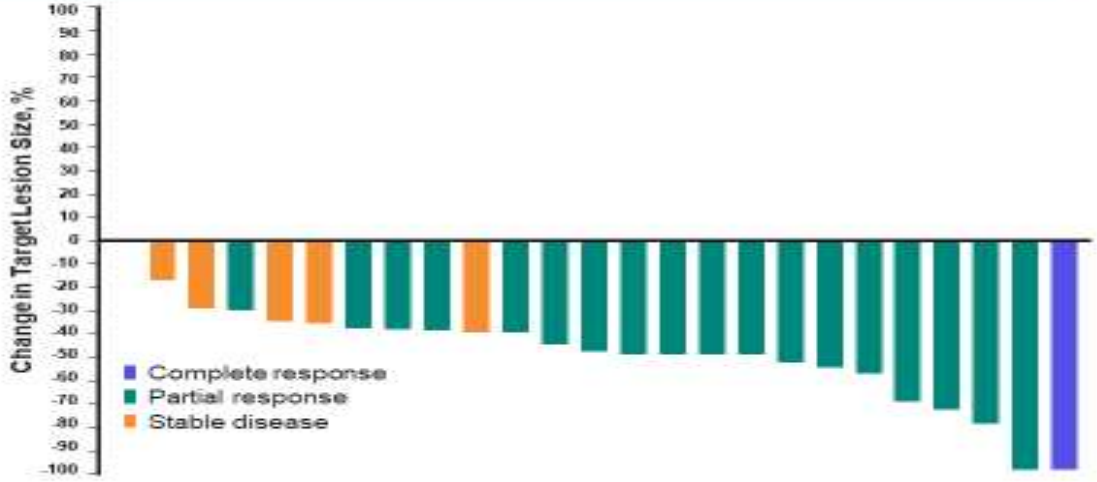
	S + C N = 50
ORR, n (%) [95% CI]	22 (44) [30-59]
DCR, n (%) [95% CI]	45 (90) [78-97]
Best overall response, n (%)	
Complete response	4 (8)
Partial response	18 (36)
Stable disease	23 (46)
Progressive disease	3 (6)
Nonevaluable	2 (4)



28 of 50 patients had evaluable postbaseline measurable disease data; 4 patients achieved complete response, including 3 patients who had nonmeasurable disease at baseline; 2 patients had progressive disease, including 1 who had only nonmeasurable disease at baseline (not shown on the waterfall plot). Data cutoff date: April 1, 2022.

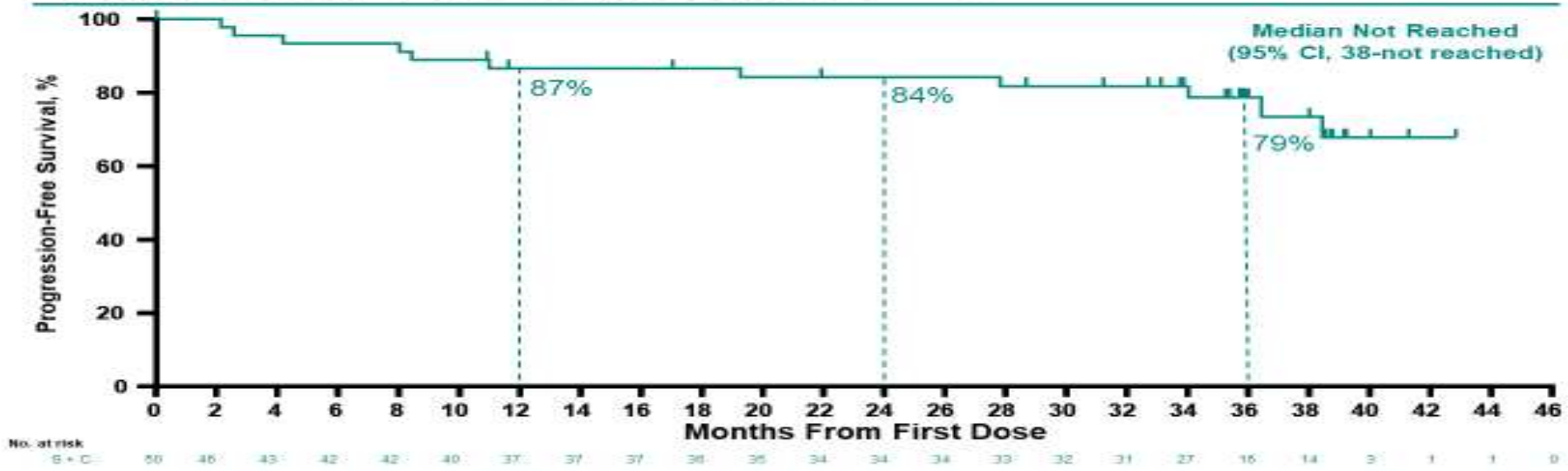
Best Overall Response and Best Percentage Change From Baseline: S only (N = 25)

	S only n = 25
ORR, n (%) [95% CI]	19 (76) [55-91]
DCR, n (%) [95% CI]	24 (96) [80-100]
Best overall response, n (%)	
Complete response	1 (4)
Partial response	18 (72)
Stable disease	5 (20)
Progressive disease	0
Nonevaluable	1 (4)



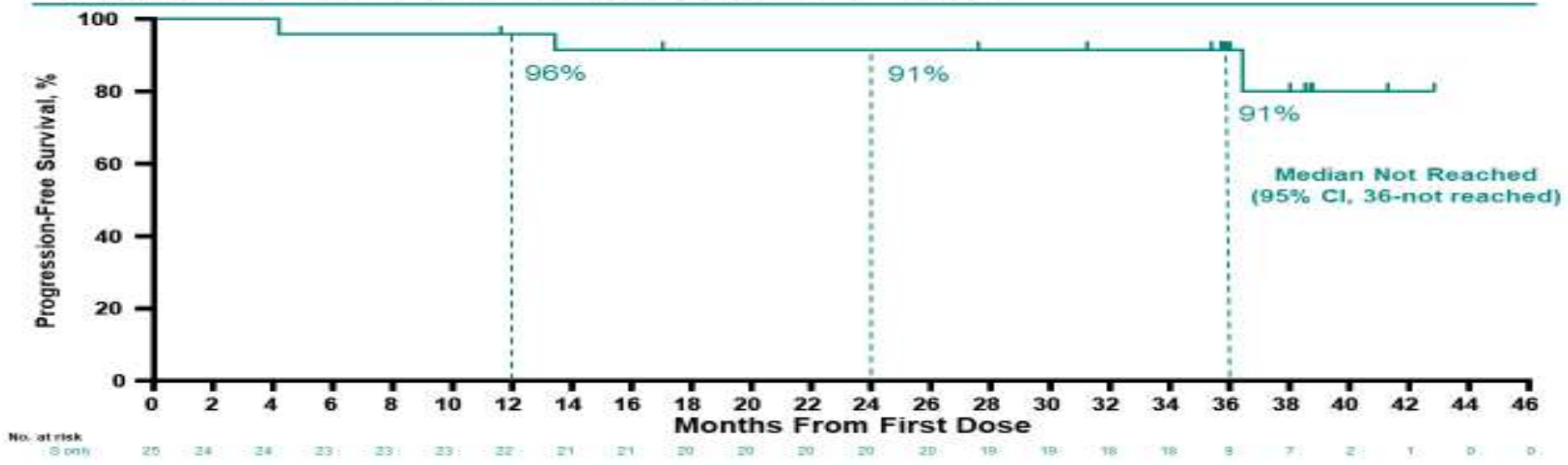
Data cutoff date: April 1, 2022.

Progression-Free Survival in S + C[a]



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

Progression-Free Survival in S Only[a]



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

Adverse Event Summary: All Enrolled Patients

	All patients in LITESPARK-004 N = 61
Any-grade AE	61 (100)
Grade 3-5 AE	27 (44)
Treatment-related AE	61 (100)
Grade 3 treatment-related AE	11 (18)
Serious AE	18 (29)
Serious treatment-related AE	4 (7)
Treatment discontinuation because of a treatment-related AE	2 (3)[a]
Treatment interruption because of a treatment-related AE	13 (21)
Dose reduction because of a treatment-related AE	8 (13)
Death	2 (3)
Death because of a treatment-related AE	0

AE, adverse event. [a]Grade 1 dizziness and grade 2 intracranial hemorrhage. AEs were assessed in all 61 patients. Data cutoff date: April 1, 2022.

Conclusions

- With a median follow-up of 38.0 months, belzutifan continues to demonstrate clinically meaningful antitumor activity and durable responses in treatment-naive patients with VHL disease–associated CNS hemangioblastomas
- Robust responses were seen regardless of methodology used to assess CNS hemangioblastomas
  - ORR was 44%, with 4 CRs in solid + associated cystic lesions, if present (previously[a] 38%, with 3 CRs)
  - ORR was 76%, with 1 CR in solid lesions only
  - Median DOR was not yet reached and 33 (66%) patients with CNS hemangioblastomas remain on treatment
- 1 of 50 patients (2%) with CNS hemangioblastomas underwent 2 CNS-related surgeries on the same lesion after starting belzutifan
- Results from the LITESPARK-004 study support the use of belzutifan as a treatment option for patients with VHL disease–associated CNS hemangioblastomas not requiring immediate surgery

[a]Previous data cutoff date: July 15, 2021.

Actualités en Neuro-Oncologie

- **Présentations lors congrès 2022- 2023**
- **Publications de 2022-2023**
- **GLIOBLASTOME**
- GLIOME DE BAS GRADE
- GLIOME DE LA LIGNE MEDIANE et du TRONC
- ASTROBLASTOME
- XANTHOASTROCYTOME
- EPENDYMOME
- Tumeur des PLEXUS CHOROIDES
- Tumeur GLIONEURONALE
- Tumeur de REGION PINEALE
- MEDULLOBLASTOME
- MENINGIOME
- HEMANGIOPERICYTOME
- ADENOME HYPOPHYSAIRE
- METASTASES CEREBRALES
- SCHWANNOME VESTIBULAIRE

Neuro-Oncology

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Phase III trial of chemoradiotherapy with temozolomide plus nivolumab or placebo for newly diagnosed glioblastoma with methylated *MGMT* promoter

Michael Lim[†], Michael Weller[†], Ahmed Idbaih, Joachim Steinbach, Gaetano Finocchiaro, Raju R. Raval, George Ansstas, Joachim Baehring, Jennie W. Taylor, Jerome Honnorat, Kevin Petrecca, Filip De Vos, Antje Wick, Ashley Sumrall, Solmaz Sahebjam, Ingo K. Mellinghoff, Masashi Kinoshita, Mustimbo Roberts, Ruta Slepetis, Deepti Warad, David Leung, Michelle Lee, David A. Reardon[‡], and Antonio Omuro[‡]

Abstract

Background. Nearly all patients with newly diagnosed glioblastoma experience recurrence following standard-of-care radiotherapy (RT) + temozolomide (TMZ). The purpose of the phase III randomized CheckMate 548 study was to evaluate RT +TMZ combined with the immune checkpoint inhibitor nivolumab (NIVO) or placebo (PBO) in patients with newly diagnosed glioblastoma with methylated *MGMT* promoter (NCT02667587).

Methods. Patients (N = 716) were randomized 1:1 to NIVO [(240 mg every 2 weeks × 8, then 480 mg every 4 weeks) + RT (60 Gy over 6 weeks) +TMZ (75 mg/m^2 once daily during RT, then 150-200 mg/m^2 once daily on days 1-5 of every 28-day cycle × 6)] or PBO + RT +TMZ following the same regimen. The primary endpoints were progression-free survival (PFS) and overall survival (OS) in patients without baseline corticosteroids and in all randomized patients.

Results. As of December 22, 2020, median (m)PFS (blinded independent central review) was 10.6 months (95% CI, 8.9-11.8) with NIVO + RT +TMZ vs 10.3 months (95% CI, 9.7-12.5) with PBO + RT +TMZ (HR, 1.1; 95% CI, 0.9-1.3) and mOS was 28.9 months (95% CI, 24.4-31.6) vs 32.1 months (95% CI, 29.4-33.8), respectively (HR, 1.1; 95% CI, 0.9-1.3). In patients without baseline corticosteroids, mOS was 31.3 months (95% CI, 28.6-34.8) with NIVO + RT +TMZ vs 33.0 months (95% CI, 31.0-35.1) with PBO + RT +TMZ (HR, 1.1; 95% CI, 0.9-1.4). Grade 3/4 treatment-related adverse event rates were 52.4% vs 33.6%, respectively.

Conclusions. NIVO added to RT +TMZ did not improve survival in patients with newly diagnosed glioblastoma with methylated or indeterminate *MGMT* promoter. No new safety signals were observed.

Key Points

- NIVO did not improve survival in newly diagnosed glioblastoma with methylated *MGMT* promoter.
- No new safety signals were detected with NIVO + standard of care in this study.
- Nivolumab could be considered within future combination strategies.

Neuro-Oncology

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Radiotherapy combined with nivolumab or temozolomide for newly diagnosed glioblastoma with unmethylated *MGMT* promoter: An international randomized phase III trial

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Background. Addition of temozolomide (TMZ) to radiotherapy (RT) improves overall survival (OS) in patients with glioblastoma (GBM), but previous studies suggest that patients with tumors harboring an unmethylated *MGMT* promoter derive minimal benefit. The aim of this open-label, phase III CheckMate 498 study was to evaluate the efficacy of nivolumab (NIVO) + RT compared with TMZ + RT in newly diagnosed GBM with unmethylated *MGMT* promoter.

Methods. Patients were randomized 1:1 to standard RT (60 Gy) + NIVO (240 mg every 2 weeks for eight cycles, then 480 mg every 4 weeks) or RT + TMZ (75 mg/m^2 daily during RT and 150–200 mg/m^2/day 5/28 days during maintenance). The primary endpoint was OS.

Results. A total of 560 patients were randomized, 280 to each arm. Median OS (mOS) was 13.4 months (95% CI, 12.6 to 14.3) with NIVO + RT and 14.9 months (95% CI, 13.3 to 16.1) with TMZ + RT (hazard ratio [HR], 1.31; 95% CI, 1.09 to 1.58; $P = .0037$). Median progression-free survival was 6.0 months (95% CI, 5.7 to 6.2) with NIVO + RT and 6.2 months (95% CI, 5.9 to 6.7) with TMZ + RT (HR, 1.38; 95% CI, 1.15 to 1.65). Response rates were 7.8% (9/116) with NIVO + RT and 7.2% (8/111) with TMZ + RT; grade 3/4 treatment-related adverse event (TRAE) rates were 21.9% and 25.1%, and any-grade serious TRAE rates were 17.3% and 7.6%, respectively.

Conclusions. The study did not meet the primary endpoint of improved OS; TMZ + RT demonstrated a longer mOS than NIVO + RT. No new safety signals were detected with NIVO in this study. The difference between the study treatment arms is consistent with the use of TMZ + RT as the standard of care for GBM.

ClinicalTrials.gov NCT02617589

Key Points

- NIVO did not improve survival in newly diagnosed GBM with unmethylated *MGMT* promoter.
- No new safety signals were detected with NIVO + standard of care in this study.
- Immunotherapy with NIVO is not a suitable replacement for chemotherapy with TMZ.

Vaccin GBM de novo ou récidivant

JAMA Oncology

View Article

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PMID: 36394838

Association of Autologous Tumor Lysate-Loaded Dendritic Cell Vaccination With Extension of Survival Among Patients With Newly Diagnosed and Recurrent Glioblastoma

A Phase 3 Prospective Externally Controlled Cohort Trial

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Importance

Glioblastoma is the most lethal primary brain cancer. Clinical outcomes for glioblastoma remain poor, and new treatments are needed.

Objective

To investigate whether adding autologous tumor lysate-loaded dendritic cell vaccine (DCVax-L) to standard of care (SOC) extends survival among patients with glioblastoma.

Design, Setting, and Participants

This phase 3, prospective, externally controlled nonrandomized trial compared overall survival (OS) in patients with newly diagnosed glioblastoma (nGBM) and recurrent glioblastoma (rGBM) treated with DCVax-L plus SOC vs contemporaneous matched external control patients treated with SOC. This international, multicenter trial was conducted at 94 sites in 4 countries from August 2007 to November 2015. Data analysis was conducted from October 2020 to September 2021.

Interventions

The active treatment was DCVax-L plus SOC temozolomide. The nGBM external control patients received SOC temozolomide and placebo; the rGBM external controls received approved rGBM therapies.

Main Outcomes and Measures

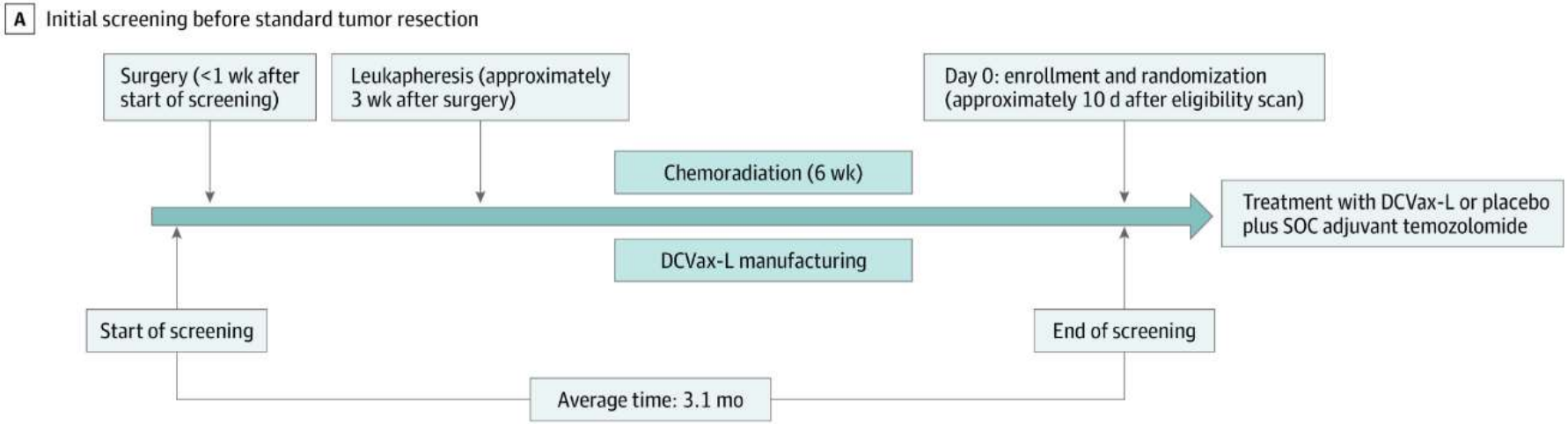
The primary and secondary end points compared overall survival (OS) in nGBM and rGBM, respectively, with contemporaneous matched external control populations from the control groups of other formal randomized clinical trials.

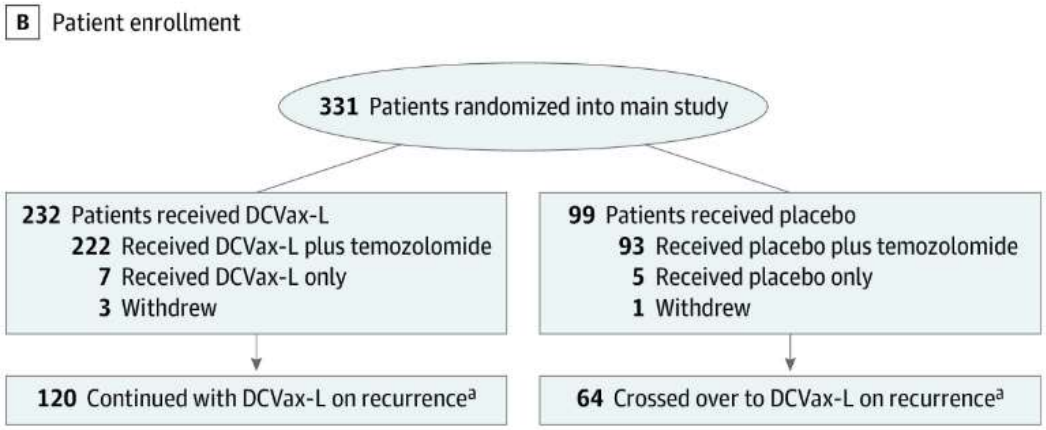
Results

A total of 331 patients were enrolled in the trial, with 232 randomized to the DCVax-L group and 99 to the placebo group. Median OS (mOS) for the 232 patients with nGBM receiving DCVax-L was 19.3 (95% CI, 17.5-21.3) months from randomization (22.4 months from surgery) vs 16.5 (95% CI, 16.0-17.5) months from randomization in control patients (HR = 0.80; 98% CI, 0.00-0.94; $P = .002$). Survival at 48 months from randomization was 15.7% vs 9.9%, and at 60 months, it was 13.0% vs 5.7%. For 64 patients with rGBM receiving DCVax-L, mOS was 13.2 (95% CI, 9.7-16.8) months from relapse vs 7.8 (95% CI, 7.2-8.2) months among control patients (HR, 0.58; 98% CI, 0.00-0.76; $P < .001$). Survival at 24 and 30 months after recurrence was 20.7% vs 9.6% and 11.1% vs 5.1%, respectively. Survival was improved in patients with nGBM with methylated MGMT receiving DCVax-L compared with external control patients (HR, 0.74; 98% CI, 0.55-1.00; $P = .03$).

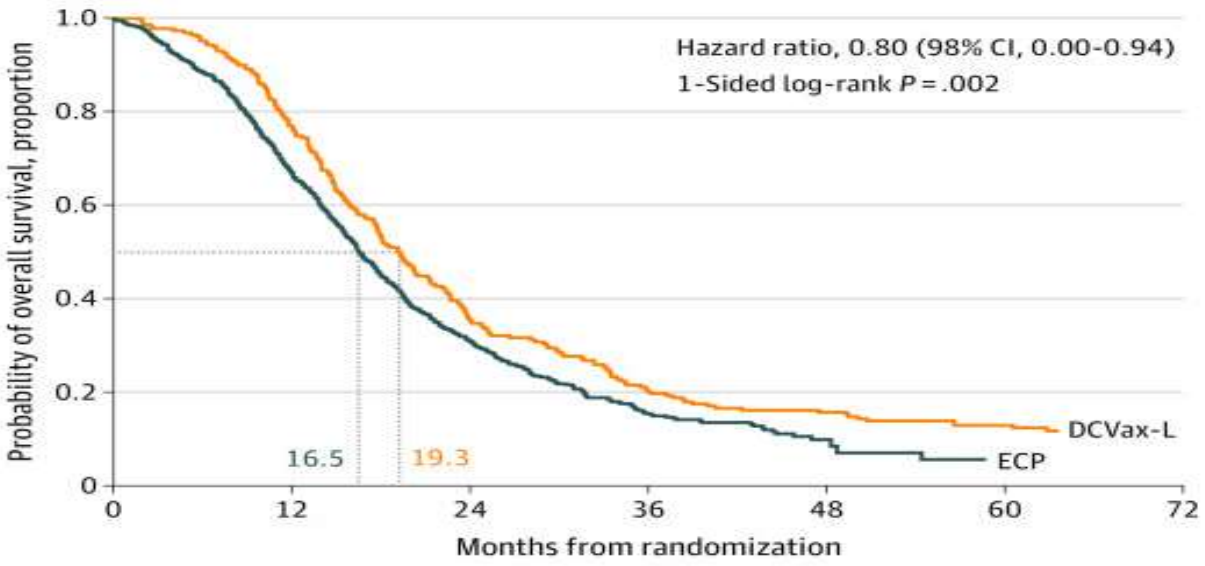
Conclusions and Relevance

In this study, adding DCVax-L to SOC resulted in clinically meaningful and statistically significant extension of survival for patients with both nGBM and rGBM compared with contemporaneous, matched external controls who received SOC alone.


A Initial screening before standard tumor resection
Surgery (<1 wk after start of screening)
Leukapheresis (approximately 3 wk after surgery)
Day 0: enrollment and randomization (approximately 10 d after eligibility scan)
Chemoradiation (6 wk)
DCVax-L manufacturing
Treatment with DCVax-L or placebo plus SOC adjuvant temozolomide
Start of screening
End of screening
Average time: 3.1 mo


B Patient enrollment
331 Patients randomized into main study
232 Patients received DCVax-L
222 Received DCVax-L plus temozolomide
7 Received DCVax-L only
3 Withdrew
99 Patients received placebo
93 Received placebo plus temozolomide
5 Received placebo only
1 Withdrew
120 Continued with DCVax-L on recurrence[a]
64 Crossed over to DCVax-L on recurrence[a]

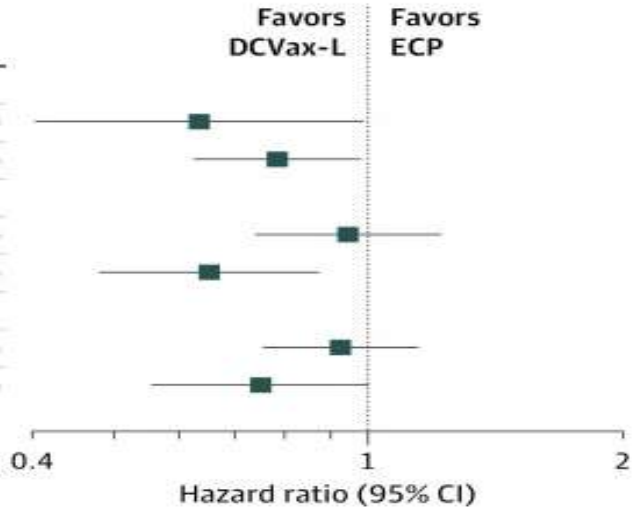
A Overall survival



No. at risk						
DCVax-L	232	178	81	45	35	25
ECP	1366	888	306	62	7	0

B Subgroup analyses

	Hazard ratio (95% CI)
Age, y	
≥65	0.63 (0.40-0.99)
<65	0.78 (0.62-0.98)
Residual disease	
Minimal	0.95 (0.73-1.22)
Significant	0.65 (0.48-0.87)
MGMT	
Unmethylated	0.93 (0.75-1.14)
Methylated	0.74 (0.55-1.00)



GBM moléculaire selon OMS 2021 CATNON

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Temozolomide and radiotherapy versus radiotherapy alone in patients with glioblastoma, IDH-wildtype: post-hoc analysis of the EORTC randomized phase 3 CATNON trial

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Purpose—In a post-hoc analysis of the CATNON trial (NCT00626990), we explored whether adding temozolomide to radiotherapy improves outcome in patients with *IDH1/2*wt anaplastic astrocytomas with molecular features of glioblastoma (redesignated as glioblastoma, IDH-wildtype in the 2021 WHO classification of CNS tumors).

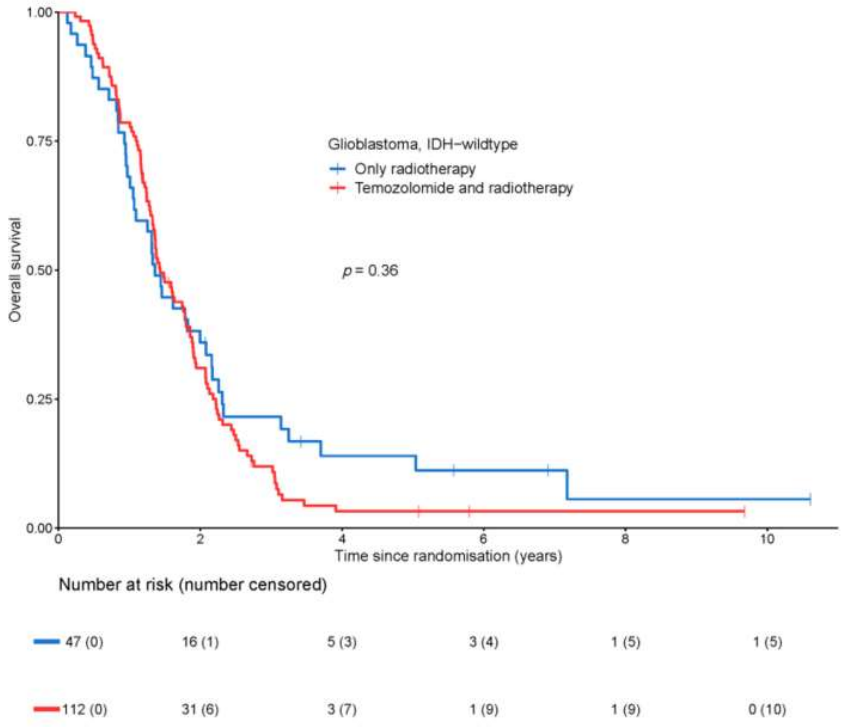
Experimental Design—From the randomized phase 3 CATNON study examining the addition of adjuvant and concurrent temozolomide to radiotherapy in anaplastic astrocytomas, we selected a subgroup of *IDH1/2*wt and *H3F3A*wt tumors with presence of *TERT* promoter mutations and/or *EGFR* amplifications and/or combined gain of chromosome 7 and loss of chromosome 10. Molecular abnormalities including *MGMT* promoter methylation status were determined by next-generation sequencing, DNA methylation profiling, and SNaPshot analysis.

Results—Of the 751 patients entered in the CATNON study, 670 had fully molecularly characterized tumors. 159 of these tumors met the WHO 2021 molecular criteria for glioblastoma, IDH-wildtype. Of these patients, 47 received radiotherapy only and 112 received a combination of radiotherapy and temozolomide. There was no added effect of temozolomide on either overall survival (HR 1.19, 95% CI 0.82–1.71) or progression-free survival (HR 0.87, 95% CI 0.61–1.24). *MGMT* promoter methylation was prognostic for overall survival, but was not predictive for outcome to temozolomide treatment either with respect to overall survival or progression-free survival.

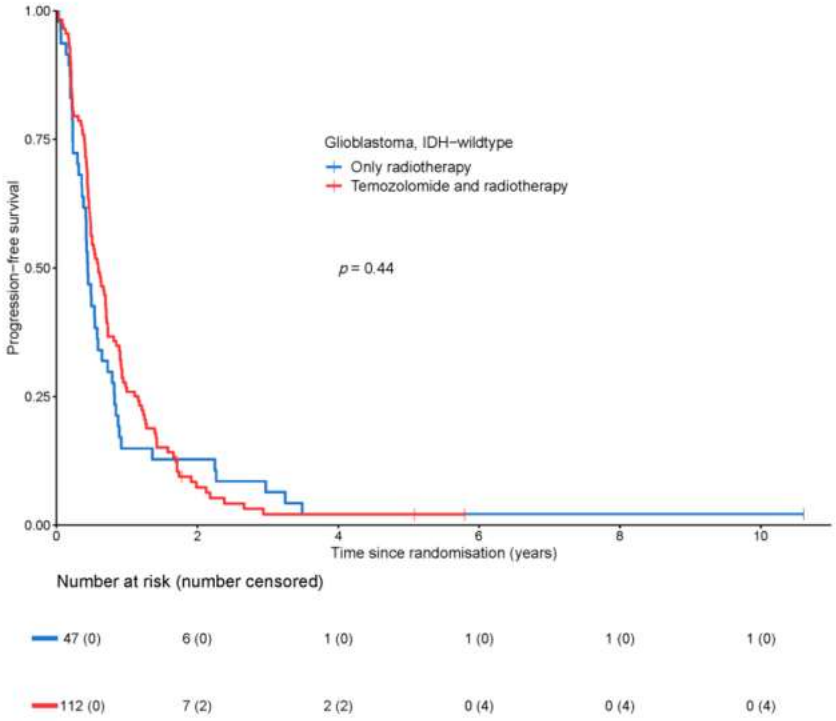
Conclusions—In this cohort of patients with glioblastoma, IDH-wildtype temozolomide treatment did not add benefit beyond that observed from radiotherapy, regardless of *MGMT* promoter status. These findings require a new well-powered prospective clinical study to explore the efficacy of temozolomide treatment in this patient population.

pas impact TMZ + RT

A: Overall survival.

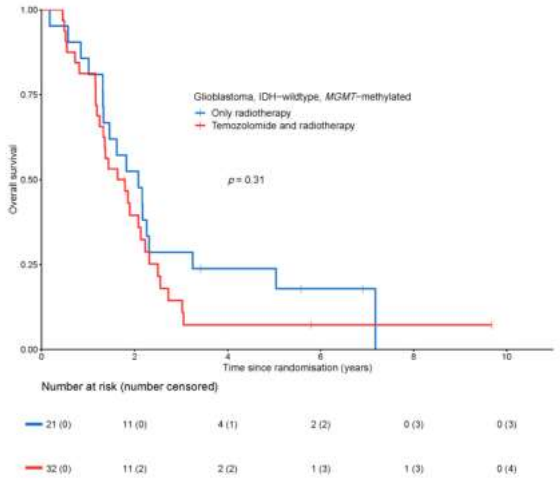


B: Progression-free survival.

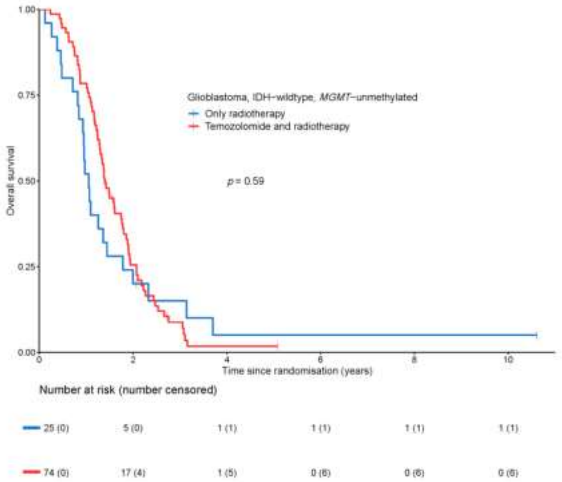


Pas impact TMZ en fonction MGMT

B: Patients with glioblastoma, IDH-wildtype, *MGMT*-methylated: temozolomide and radiotherapy vs. only radiotherapy.



C: Patients with glioblastoma, IDH-wildtype, *MGMT*-unmethylated: temozolomide and radiotherapy vs. only radiotherapy.



GBM récidivant Bévacizumab +/- réirradiation

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NRG Oncology/RTOG1205: A Randomized Phase II Trial of Concurrent Bevacizumab and Reirradiation Versus Bevacizumab Alone as Treatment for Recurrent Glioblastoma

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PURPOSE To assess whether reirradiation (re-RT) and concurrent bevacizumab (BEV) improve overall survival (OS) and/or progression-free survival (PFS), compared with BEV alone in recurrent glioblastoma (GBM). The primary objective was OS, and secondary objectives included PFS, response rate, and treatment adverse events (AEs) including delayed CNS toxicities.

METHODS NRG Oncology/RTOG1205 is a prospective, phase II, randomized trial of re-RT and BEV versus BEV alone. Stratification factors included age, resection, and Karnofsky performance status (KPS). Patients with recurrent GBM with imaging evidence of tumor progression ≥ 6 months from completion of prior chemo-RT were eligible. Patients were randomly assigned 1:1 to re-RT, 35 Gy in 10 fractions, with concurrent BEV IV 10 mg/kg once in every 2 weeks or BEV alone until progression.

RESULTS From December 2012 to April 2016, 182 patients were randomly assigned, of whom 170 were eligible. Patient characteristics were well balanced between arms. The median follow-up for censored patients was 12.8 months. There was no improvement in OS for BEV + RT (hazard ratio, 0.98; 80% CI, 0.79 to 1.23; $P = .46$; the median survival time was 10.1 versus 9.7 months for BEV + RT versus BEV alone. The median PFS for BEV + RT was 7.1 versus 3.8 months for BEV, hazard ratio, 0.73; 95% CI, 0.53 to 1.0; $P = .05$). The 6-month PFS rate improved from 29.1% (95% CI, 19.1 to 39.1) for BEV to 54.3% (95% CI, 43.5 to 65.1) for BEV + RT, $P = .001$. Treatment was well tolerated. There were a 5% rate of acute grade 3+ treatment-related AEs and no delayed high-grade AEs. Most patients died of recurrent GBM.

CONCLUSION To our knowledge, NRG Oncology/RTOG1205 is the first prospective, randomized multi-institutional study to evaluate the safety and efficacy of re-RT in recurrent GBM using modern RT techniques. Overall, re-RT was shown to be safe and well tolerated. BEV + RT demonstrated a clinically meaningful improvement in PFS, specifically the 6-month PFS rate but no difference in OS.

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GBM récidivant et FGFR

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

Infigratinib in Patients with Recurrent Gliomas and *FGFR* Alterations: A Multicenter Phase II Study

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Purpose: *FGFR* genomic alterations (amplification, mutations, and/or fusions) occur in ~8% of gliomas particularly *FGFR1* and *FGFR3*. We conducted a multicenter open-label, single-arm, phase II study of a selective FGFR1–3 inhibitor, infigratinib (BGJ398), in patients with *FGFR*-altered recurrent gliomas.

Patients and Methods: Adults with recurrent/progressive gliomas harboring *FGFR* alterations received oral infigratinib 125 mg on days 1 to 21 of 28-day cycles. The primary endpoint was investigator-assessed 6-month progression-free survival (PFS) rate by Response Assessment in Neuro-Oncology criteria. Comprehensive genomic profiling was performed on available pretreatment archival tissue to explore additional molecular correlations with efficacy.

Results: Among 26 patients, the 6-month PFS rate was 16.0% [95% confidence interval (CI), 5.0–32.5], median PFS was 1.7 months (95% CI, 1.1–2.8), and objective response rate was 3.8%. However 4 patients had durable disease control lasting longer than 1 year. Among these, 3 had tumors harboring activating point mutations at analogous positions of *FGFR1* (K656E; $n = 2$) or *FGFR3* (K650E; $n = 1$) in pretreatment tissue; an *FGFR3-TACC3* fusion was detected in the other. Hyperphosphatemia was the most frequently reported treatment-related adverse event (all-grade, 76.9%; grade 3, 3.8%) and is a known on-target toxicity of FGFR inhibitors.

Conclusions: FGFR inhibitor monotherapy with infigratinib had limited efficacy in a population of patients with recurrent gliomas and different *FGFR* genetic alterations, but durable disease control lasting more than 1 year was observed in patients with tumors harboring *FGFR1* or *FGFR3* point mutations or *FGFR3-TACC3* fusions. A follow-up study with refined biomarker inclusion criteria and centralized *FGFR* testing is warranted.

unicancer

Vaccin GBM

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

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PURPOSE Despite intensive treatment with surgery, radiation therapy, temozolomide (TMZ) chemotherapy, and tumor-treating fields, mortality of newly diagnosed glioblastoma (nGBM) remains very high. SurVaxM is a peptide vaccine conjugate that has been shown to activate the immune system against its target molecule survivin, which is highly expressed by glioblastoma cells. We conducted a phase IIa, open-label, multicenter trial evaluating the safety, immunologic effects, and survival of patients with nGBM receiving SurVaxM plus adjuvant TMZ following surgery and chemoradiation (ClinicalTrials.gov identifier: NCT02455557).

METHODS Sixty-four patients with resected nGBM were enrolled including 38 men and 26 women, in the age range of 20-82 years. Following craniotomy and fractionated radiation therapy with concurrent TMZ, patients received four doses of SurVaxM (500 μg once every 2 weeks) in Montanide ISA-51 plus sargramostim (granulocyte macrophage colony-stimulating factor) subcutaneously. Patients subsequently received adjuvant TMZ and maintenance SurVaxM concurrently until progression. Progression-free survival (PFS) and overall survival (OS) were reported. Immunologic responses to SurVaxM were assessed.

RESULTS SurVaxM plus TMZ was well tolerated with no serious adverse events attributable to SurVaxM. Of the 63 patients who were evaluable for outcome, 60 (95.2%) remained progression-free 6 months after diagnosis (prespecified primary end point). Median PFS was 11.4 months and median OS was 25.9 months measured from first dose of SurVaxM. SurVaxM produced survivin-specific CD8+ T cells and antibody/immunoglobulin G titers. Apparent clinical benefit of SurVaxM was observed in both methylated and unmethylated patients.

CONCLUSION SurVaxM appeared to be safe and well tolerated. The combination represents a promising therapy for nGBM. For patients with nGBM treated in this manner, PFS may be an acceptable surrogate for OS. A large randomized clinical trial of SurVaxM for nGBM is in progress.

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Méta-analyse

The efficacy of targeted therapy combined with radiotherapy and temozolomide-based chemotherapy in the treatment of glioma: A systemic review and meta-analysis of phase II/III randomized controlled trials

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TYPE Systematic Review
PUBLISHED 26 January 2023
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Background: Glioma is the most common intracranial tumor, accounting for about half of the primary intracranial tumors, with the characteristics of hidden onset and high mortality. Even after surgery, radiotherapy and chemotherapy, the prognosis of glioma is not ideal. Targeted therapy has developed rapidly in the treatment of other malignant tumors, which is also an important direction in the research and development of new therapies for glioma. So far, targeting combined with radiotherapy and chemotherapy have been used as the treatment of glioma in many clinical trials, but the role of targeted combined radiotherapy and chemotherapy in the treatment of glioma is still controversial. The purpose of this study was to evaluate the efficacy of targeted therapy combined with radiotherapy and temozolomide (TMZ)-based chemotherapy in the treatment of glioma.

Methods: Phase II or phase III clinical trials involving targeted therapy combined with radiotherapy and chemotherapy and temozolomide-based radiotherapy and chemotherapy for gliomas were searched using PubMed, Embase and Web of Science databases, and a comprehensive meta-analysis was conducted. The primary outcome was overall survival time (OS) and progression-free survival time (PFS), and the secondary outcome was adverse reaction. The time-to-event data is summarized as hazard ratio (HR), and the binary results are summarized as odds ratio (OR). Two researchers conducted literature screening, data extraction and quality evaluation according to inclusion and exclusion criteria. Stata16.0 software was used for analysis, random effect model was used for data merging, and forest map was used for display.

Results: A total of 11 eligible literatures and 12 prospective randomized controlled clinical trials of 1284 cases were included in the meta-analysis. The results showed that compared with radiotherapy and chemotherapy alone, targeted drugs combined with temozolomide-based radiotherapy and chemotherapy could significantly improve OS in phase II trial, but there was no improvement in Phase III trial, and PFS of newly diagnosed glioma patients was improved (HR=0.82(0.71-0.94) 95%CI, p =0.005). The PFS of the third phase of the experiment also improved. Compared with radiotherapy and chemotherapy alone, there was no statistically significant increase in adverse events in targeted combined radiotherapy and chemotherapy group.

Systematic review registration: https://www.crd.york.ac.uk/prospero, identifier CRD42022326012.

Depatuxizumab

Neuro-Oncology

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Depatuxizumab mafodotin in EGFR-amplified newly diagnosed glioblastoma: A phase III randomized clinical trial

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Abstract

Background. Approximately 50% of newly diagnosed glioblastomas (GBMs) harbor *epidermal growth factor receptor* gene amplification (*EGFR*-amp). Preclinical and early-phase clinical data suggested efficacy of depatuxizumab mafodotin (depatux-m), an antibody–drug conjugate comprised of a monoclonal antibody that binds activated EGFR (overexpressed wild-type and EGFRvIII-mutant) linked to a microtubule-inhibitor toxin in *EGFR*-amp GBMs.

Methods. In this phase III trial, adults with centrally confirmed, *EGFR*-amp newly diagnosed GBM were randomized 1:1 to radiotherapy, temozolomide, and depatux-m/placebo. Corneal epitheliopathy was treated with a combination of protocol-specified prophylactic and supportive measures. There was 85% power to detect a hazard ratio (HR) ≤0.75 for overall survival (OS) at a 2.5% 1-sided significance level (ie traditional two-sided $p \leq 0.05$) by log-rank testing.

Results. There were 639 randomized patients (median age 60, range 22–84; 62% men). Prespecified interim analysis found no improvement in OS for depatux-m over placebo (median 18.9 vs. 18.7 months, HR 1.02, 95% CI 0.82–1.26, 1-sided $p = 0.63$). Progression-free survival was longer for depatux-m than placebo (median 8.0 vs. 6.3 months; HR 0.84, 95% confidence interval [CI] 0.70–1.01, $p = 0.029$), particularly among those with *EGFRvIII*-mutant (median 8.3 vs. 5.9 months, HR 0.72, 95% CI 0.56–0.93, 1-sided $p = 0.002$) or *MGMT* unmethylated (HR 0.77, 95% CI 0.61–0.97; 1-sided $p = 0.012$) tumors but without an OS improvement. Corneal epitheliopathy occurred in 94% of depatux-m-treated patients (61% grade 3–4), causing 12% to discontinue.

Conclusions. Interim analysis demonstrated no OS benefit for depatux-m in treating *EGFR*-amp newly diagnosed GBM. No new important safety risks were identified.

Key Points

- Approximately 50% of newly diagnosed glioblastomas (GBMs) harbor *EGFR*-amplification (EGFR-amp).
- The antibody–drug conjugate depatuxizumab mafodotin binds activated EGFR.
- Depatuxizumab mafodotin did not improve overall survival in *EGFR*-amp newly diagnosed GBM.

Dabrafenib plus trametinib in patients with *BRAF*^{V600E}-mutant low-grade and high-grade glioma (ROAR): a multicentre, open-label, single-arm, phase 2, basket trial

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Background Effective treatments are needed to improve outcomes for high-grade glioma and low-grade glioma. The activity and safety of dabrafenib plus trametinib were evaluated in adult patients with recurrent or progressive *BRAF*^{V600E} mutation-positive high-grade glioma and low-grade glioma.

Methods This study is part of an ongoing open-label, single-arm, phase 2 Rare Oncology Agnostic Research (ROAR) basket trial at 27 community and academic cancer centres in 13 countries (Austria, Belgium, Canada, France, Germany, Italy, Japan, the Netherlands, Norway, South Korea, Spain, Sweden, and the USA). The study enrolled patients aged 18 years or older with an Eastern Cooperative Oncology Group performance status of 0, 1, or 2. Patients with *BRAF*^{V600E} mutation-positive high-grade glioma and low-grade glioma received dabrafenib 150 mg twice daily plus trametinib 2 mg once daily orally until unacceptable toxicity, disease progression, or death. In the high-grade glioma cohort, patients were required to have measurable disease at baseline using the Response Assessment in Neuro-Oncology high-grade glioma response criteria and have been treated previously with radiotherapy and first-line chemotherapy or concurrent chemoradiotherapy. Patients with low-grade glioma were required to have measurable non-enhancing disease (except pilocytic astrocytoma) at baseline using the Response Assessment in Neuro-Oncology low-grade glioma criteria. The primary endpoint, in the evaluable intention-to-treat population, was investigator-assessed objective response rate (complete response plus partial response for high-grade glioma and complete response plus partial response plus minor response for low-grade glioma). This trial is ongoing, but is closed for enrolment, NCT02034110.

Findings Between April 17, 2014, and July 25, 2018, 45 patients (31 with glioblastoma) were enrolled into the high-grade glioma cohort and 13 patients were enrolled into the low-grade glioma cohort. The results presented here are based on interim analysis 16 (data cutoff Sept 14, 2020). In the high-grade glioma cohort, median follow-up was 12·7 months (IQR 5·4–32·3) and 15 (33%; 95% CI 20–49) of 45 patients had an objective response by investigator assessment, including three complete responses and 12 partial responses. In the low-grade glioma cohort, median follow-up was 32·2 months (IQR 25·1–47·8). Nine (69%; 95% CI 39–91) of 13 patients had an objective response by investigator assessment, including one complete response, six partial responses, and two minor responses. Grade 3 or worse adverse events were reported in 31 (53%) patients, the most common being fatigue (five [9%]), decreased neutrophil count (five [9%]), headache (three [5%]), and neutropenia (three [5%]).

Interpretation Dabrafenib plus trametinib showed clinically meaningful activity in patients with *BRAF*^{V600E} mutation-positive recurrent or refractory high-grade glioma and low-grade glioma, with a safety profile consistent with that in other indications. *BRAF*^{V600E} testing could potentially be adopted in clinical practice for patients with glioma.

Management gliome haut grade

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Managing cancer and living meaningfully (CALM) in adults with malignant glioma: a proof-of-concept phase IIa trial

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Background—Managing Cancer and Living Meaningfully (CALM) is an evidence-based, brief, semi-structured psychotherapy designed to help patients with advanced cancer cope with the practical and profound challenges of their illness. However, no study to date has investigated its feasibility, acceptability, and preliminary effectiveness in adults with malignant glioma, despite the well-documented incidence of psychological distress in this vulnerable and underserved population.

Methods—Fourteen patients with glioma and elevated symptoms of depression and/or death anxiety enrolled in the trial: 83% glioblastoma, 75% female, M_{age} = 56 years (SD = 15.1; range = 27–81). Feasibility was assessed based on established metrics. Acceptability was measured by post-session surveys and post-intervention interviews. Preliminary intervention effects were explored using paired t-tests, comparing psychological distress at baseline and post-intervention.

Results—Of the 14 enrolled patients, 12 were evaluable. Nine completed the study (75% retention rate). Three patients withdrew due to substantial disease progression which affected their ability to participate. Participants reported high perceived benefit, and all recommended the program to others. Baseline to post-intervention assessments indicated reductions in death anxiety, generalized anxiety, and depression, and increases in spirituality. Quality of life and fear of cancer recurrence remained stable throughout the study period.

Conclusions—CALM appears feasible for use with adults with malignant glioma. Enrollment and retention rates were high and comparable to psychotherapy trials for patients with advanced cancer. High perceived benefit and reductions in symptoms of death anxiety, generalized anxiety, and depression were reported by participants. These findings are extremely encouraging and support further study of CALM in neuro-oncology.

Soins palliatifs

Neuro-Oncology

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Palliative care and end-of-life care in adults with malignant brain tumors

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Abstract

Background. This systematic review provides updated insights, from the published literature in the past 5 years, based on the 2017 European Association of Neuro-Oncology (EANO) guidelines for palliative care in adults with malignant brain tumors. It provides an overview of palliative care options, including during the end-of-life phase for patients with malignant brain tumors.

Methods. A systematic literature search was conducted from 2016 to 2021 focusing on four main topics: (1) symptom management, (2) caregiver needs, (3) early palliative care, and (4) care in the end-of-life phase. An international panel of palliative care experts in neuro-oncology synthesized the literature and reported the most relevant updates. A total of 140 articles were included.

Results. New insights include that: Hippocampal avoidance and stereotactic radiosurgery results in a lower risk of neurocognitive decline in patients with brain metastases; levetiracetam is more efficacious in reducing seizures than valproic acid as first-line monotherapy antiseizure drug (ASD) in glioma patients; lacosamide and perampanel seem well-tolerated and efficacious add-on ASDs; and a comprehensive framework of palliative and supportive care for high-grade glioma patients and their caregivers was proposed. No pharmacological agents have been shown in randomized controlled trials to significantly improve fatigue or neurocognition.

Conclusions. Since the 2017 EANO palliative care guidelines, new insights have been reported regarding symptom management and end-of-life care, however, most recommendations remain unchanged. Early palliative care interventions are essential to define goals of care and minimize symptom burden in a timely fashion. Interventional studies that address pain, fatigue, and psychiatric symptoms as well as (the timing of) early palliative care are urgently needed.

Keywords

brain metastases | brain tumor | end of life | glioma | palliative care

Fatigue

JAMA Oncology

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Efficacy of Treatment With Armodafinil for Cancer-Related Fatigue in Patients With High-grade Glioma

A Phase 3 Randomized Clinical Trial

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Importance

Nearly 96% of patients with high-grade glioma (HGG) report moderate-to-severe fatigue. Armodafinil is a psychostimulant that might help cancer-related fatigue in patients with HGG.

Objective

To determine whether armodafinil reduces fatigue in patients with HGG and moderate-to-severe fatigue.

Design, Setting, and Participants

In this randomized multicenter, phase 3, double-blinded, placebo-controlled clinical trial, adults with HGG and moderate-to-severe fatigue who were clinically stable at least 4 weeks after completing radiation therapy were randomized to receive armodafinil daily (150 mg or 250 mg) or placebo over 8 weeks. A score of at least 6 out of 10 on severity scale for the brief fatigue inventory scale, with 10 being the worst, was required to suggest moderate-to-severe fatigue. Patients were allowed stable doses of corticosteroids but were excluded if they required increasing amounts of corticosteroids, were receiving some other treatment for fatigue, or had an uncontrolled seizure disorder. The study was conducted from June 2013 to December 15, 2019.

Interventions

Patients were randomized to 150 mg of armodafinil, 250 mg of armodafinil, or placebo for a total of 8 weeks with assessments at weeks 4 and 8.

Main Outcomes and Measures

The primary outcome was efficacy in treating cancer-related fatigue. Secondary outcomes included safety, neurocognitive function, and quality of life. Patients were evaluated at baseline and at weeks 4 and 8. Efficacy between the placebo and the 2 doses of study drug was determined by an improvement by 2 points on the 0 to 10 brief fatigue inventory scale. Kruskal-Wallis and χ^2 tests were used and followed by confirmatory analyses.

Results

A total of 328 patients were enrolled, of whom 297 had evaluable end point data. Of these, 103 received 150 mg of armodafinil (mean [SD] age, 58.5 [11.9] years; 42 women [40.8%]), 97 250 mg of armodafinil (mean [SD] age, 56.6 [12.5] years; 37 women [38.1%]), and 97 placebo (mean [SD] age, 57.1 [12.5] years; 39 women [40.2%]). There was no difference in the proportion of patients who achieved clinically meaningful fatigue reduction between arms (28% [95% CI 20%-30%] for 150 mg of armodafinil, 28% [95% CI 19%-38%] for 250 mg of armodafinil, and 30% [95% CI 21%-40%] for placebo). There was a statistically significant reduction in global fatigue for corticosteroid users compared with nonusers (−0.7 [95% CI, −1.5 to −0.3] vs −1.7 [95% CI, −2.1 to −1.3]; $P < .001$). More patients (2 vs 7) reported insomnia with treatment with 250 mg of armodafinil.

Conclusions and Relevance

The results of this randomized clinical trial found no meaningful benefit of using treatment with armodafinil to reduce cancer-related fatigue in patients with HGG.

Qualité de vie TAVAREC

Clinical Trial > Eur J Cancer. 2023 Sep;190:112946. doi: 10.1016/j.ejca.2023.112946.
Epub 2023 Jun 19.

Health-related quality-of-life results from the randomised phase II TAVAREC trial on temozolomide with or without bevacizumab in 1p/19q intact first-recurrence World Health Organization grade 2 and 3 glioma (European Organization for Research and Treatment of Cancer 26091)

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Background: In an international randomised controlled phase II study of temozolomide (TMZ) versus TMZ in combination with bevacizumab (BEV) in locally diagnosed non-1p/19q co-deleted World Health Organization grade 2 or 3 gliomas with a first and contrast-enhancing recurrence after initial radiotherapy, and overall survival at 12 months was not significantly different (61% in the TMZ arm and 55% in the TMZ + BEV arm).

Objectives: Health-related quality of life (HRQoL) was a key secondary end-point in this trial, and the main objective of this study was to determine the impact of the addition of BEV to TMZ on HRQoL.

Methods: HRQoL was assessed using the European Organization for Research and Treatment of Cancer QLQ-C30 (version 3) and QLQ-BN20 at baseline, and then every 12 weeks until disease progression. The pre-selected primary HRQoL end-point was the QLQ-C30 global health scale, with self-perceived cognitive functioning and pain selected as secondary HRQoL issues. Analysis was undertaken using linear mixed modelling and complemented with sensitivity analyses using summary statistics. A difference was considered clinically relevant with ≥10 points difference on a 100-point scale.

Results: Baseline compliance was high at 94% and remained above 60% until 72 weeks limiting the analysis to 60 weeks. Compliance was similar in both arms. We found no statistically significant or clinically significant differences between the primary HRQoL end-point in both treatment arms ($p = 0.2642$). The sensitivity analyses confirmed this finding. The overall test for post-baseline differences between the two treatment arms also showed no statistically or clinically significant differences regarding the selected secondary end-point scales.

Interpretation: The addition of BEV to TMZ in this patient group neither improves nor negatively impacts HRQoL.

F-DOPA dans réirradiation

Clinical Trial > J Neurooncol. 2022 Jul;158(3):323-330. doi: 10.1007/s11060-022-04011-w. Epub 2022 May 18.

Initial results of a phase II trial of ^{18}F-DOPA PET-guided re-irradiation for recurrent high-grade glioma

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Purpose: In-field high-grade glioma (HGG) recurrence is a common challenge with limited treatment options, including re-irradiation. The radiotracer 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine (^{18}F-DOPA) crosses the blood brain barrier and demonstrates high uptake in tumor, but low uptake in normal tissue. This study investigated whether ^{18}F-DOPA positron emission tomography (PET) and MRI guided re-irradiation for recurrent HGG may improve progression free survival (PFS).

Methods: Adults with recurrent or progressive HGG previously treated with radiation were eligible. The primary endpoint was a 20% improvement from the historical control PFS at 3 months (PFS3) of 20% with systemic therapy alone. Re-RT dose was 35 Gy in 10 fractions. The target volume was MRI T1 contrast-enhancement defined tumor plus ^{18}F-DOPA PET defined tumor.

Results: Twenty patients completed treatment per protocol. Diagnosis was most commonly glioblastoma, IDH-wildtype (60%). MRI-defined volumes were expanded by a median 43% (0-436%) by utilizing ^{18}F-DOPA PET. PFS3 was 85% (95% CI 63.2-95.8%), meeting the primary endpoint of PFS3 ≥ 40%. With 9.7 months median follow-up, 17 (85%) had progressed and 15 (75%) had died. Median OS from re-RT was 8.8 months. Failure following re-RT was within both the MRI and PET tumor volumes in 75%, MRI only in 13%, PET only in 0%, and neither in 13%. Four (20%) patients experienced grade 3 toxicity, including CNS necrosis (n = 2, both asymptomatic with bevacizumab initiation for radiographic findings), seizures (n = 1), fatigue (n = 1), and nausea (n = 1). No grade 4-5 toxicities were observed.

Conclusion: ^{18}F-DOPA PET-guided re-irradiation for progressive high-grade glioma appears safe and promising for further investigation.

F-DOPA boost + radiochimiothérapie

> Neuro Oncol. 2023 Jul 7;noad119. doi: 10.1093/neuonc/noad119. Online ahead of print.

Randomized phase III trial of metabolic imaging–guided dose escalation of radio–chemotherapy in patients with newly diagnosed glioblastoma (SPECTRO GLIO trial)

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Purpose: Glioblastoma (GBM) systematically recurs after a standard 60 Gy radio-chemotherapy regimen. Since Magnetic Resonance Spectroscopic Imaging (MRSI) has been shown to predict the site of relapse, we analyzed the effect of MRSI-guided dose escalation on overall survival (OS) of patients with newly diagnosed GBM.

Patients and methods: In this multicentric prospective phase III trial, patients who had undergone biopsy or surgery for a GBM were randomly assigned to a standard dose (SD) of 60 Gy or a high dose (HD) of 60 Gy with an additional simultaneous integrated boost totaling 72 Gy to MRSI metabolic abnormalities, the tumor bed and residual contrast enhancements. Temozolomide was administered concomitantly and maintained for 6 months thereafter.

Results: One hundred and eighty patients were included in the study between March 2011 and March 2018. After a median follow-up of 43.9 months (95% IC [42.5; 45.5]), median OS was 22.6 months (95% IC [18.9;25.4]) versus 22.2 months (95% IC [18.3;27.8]) for HD, and median progression-free survival was 8.6 (95% IC [6.8;10.8]) versus 7.8 months (95% IC [6.3;8.6]), in SD versus HD, respectively. No increase in toxicity rate was observed in the study arm. The pseudoprogression rate was similar across the SD (14.4%) and HD (16.7%) groups.For O(6)-methylguanine-DNA methyltransferase (MGMT) methylated patients, the median OS was 38 months (95% IC [23.2; NR]) for HD patients versus 28.5 months (95% IC [21.1; 35.7]) for SD patients.

Conclusion: The additional MRSI-guided irradiation dose totaling 72 Gy was well-tolerated but did not improve OS in newly diagnosed GBM.

Telmisartan

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Telmisartan attenuates human glioblastoma cells proliferation and oncogenicity by inducing the lipid oxidation

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Background: Glioblastoma (GBM) is one of the most common primary brain tumors, which accounts up to 80% of malignant brain tumors and the 5-year relative survival rate is below 5%. Recent studies showed that the lipid metabolism played an essential role in GBM development. As a peroxisome proliferators-activated receptors γ (PPAR-γ) agonist, telmisartan improves the lipid metabolism and has been used to treat hypertension for long time. It has also been shown to have anticancer function, such as in lung cancer and melanoma.

Methods: Incucyte real-time live cell imaging system was used to assess the effect of telmisartan on glioma cell lines U87 and U251 proliferation. Transwell assay and colony formation assay were conducted to detect the effect of telmisartan on oncogenicity of GBM cell lines. Western blot and immunofluorescence analysis were used to detect the effect of telmisartan on the expression of PPAR-γ and hydroxyacyl-coenzyme A dehydrogenase alpha subunit (HADHA).

Results: We demonstrate that telmisartan inhibits two glioma cell lines U87 and U251 proliferation in a time- and dose-dependent manner, and arrests the cell cycle at S phase. We further show that telmisartan decreases the oncogenicity of GBM cell lines. Our data show that telmisartan treatment significantly increases the PPAR-γ expression level, enhances the lipid oxidation, and upregulates the level of fatty acid oxidation key enzyme HADHA.

Conclusions: Telmisartan inhibits the proliferation and oncogenicity while it also increases the lipid oxidation of human GBM cells.

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- SCHWANNOME VESTIBULAIRE

Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma

I.K. Mellinghoff, M.J. van den Bent, D.T. Blumenthal, M. Touat, K.B. Peters, J. Clarke, J. Mendez, S. Yust-Katz, L. Welsh, W.P. Mason, F. Ducray, Y. Umemura, B. Nabors, M. Holdhoff, A.F. Hottinger, Y. Arakawa, J.M. Sepulveda, W. Wick, R. Soffietti, J.R. Perry, P. Giglio, M. de la Fuente, E.A. Maher, S. Schoenfeld, D. Zhao, S.S. Pandya, L. Steelman, I. Hassan, P.Y. Wen, and T.F. Cloughesy

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Neuro-Oncology

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Olutasidenib (FT-2102) in patients with relapsed or refractory *IDH1*-mutant glioma: A multicenter, open-label, phase Ib/II trial

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Abstract

Background: Olutasidenib (FT-2102) is a highly potent, orally bioavailable, brain-penetrant and selective inhibitor of mutant isocitrate dehydrogenase 1 (IDH1). The aim of the study was to determine the safety and clinical activity of olutasidenib in patients with relapsed/refractory gliomas harboring an *IDH1*^{R132X} mutation.

Methods: This was an open-label, multicenter, nonrandomized, phase Ib/II clinical trial. Eligible patients (≥18 years) had histologically confirmed *IDH1*^{R132X}-mutated glioma that relapsed or progressed on or following standard therapy and had measurable disease. Patients received olutasidenib, 150 mg orally twice daily (BID) in continuous 28-day cycles. The primary endpoints were dose-limiting toxicities (DLTs) (cycle 1) and safety in phase I and objective response rate using the Modified Response Assessment in Neuro-Oncology criteria in phase II.

Results: Twenty-six patients were enrolled and followed for a median 15.1 months (7.3–19.4). No DLTs were observed in the single-agent glioma cohort and the pharmacokinetic relationship supported olutasidenib 150 mg BID as the recommended phase II dose. In the response-evaluable population, disease control rate (objective response plus stable disease) was 48%. Two (8%) patients demonstrated a best response of partial response and eight (32%) had stable disease for at least 4 months. Grade 3–4 adverse events (≥10%) included alanine aminotransferase increased and aspartate aminotransferase increased (three [12%], each).

Conclusions: Olutasidenib 150 mg BID was well tolerated in patients with relapsed/refractory gliomas harboring an *IDH1*^{R132X} mutation and demonstrated preliminary evidence of clinical activity in this heavily pretreated population.

Key Points

- Olutasidenib is a potent, brain-penetrant, selective inhibitor of mutant IDH1
- Olutasidenib was well tolerated in patients with relapsed/refractory gliomas
- The disease control rate (objective response plus stable disease) was 48%

CANCER RESEARCH COMMUNICATIONS

AACR American Association for Cancer Research

RESEARCH ARTICLE https://doi.org/10.1158/2767-9764.CRC-22-0436

OPEN ACCESS

Multicenter Phase II Trial of the PARP Inhibitor Olaparib in Recurrent *IDH1*- and *IDH2*-mutant Glioma

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ABSTRACT

Purpose: Isocitrate dehydrogenase (*IDH*) *1* and *IDH2* mutations (*IDH1*/2mt) are frequent in glioma. Preclinical studies suggest *IDH1*/2mts confer "BRCAness" phenotype, a vulnerability that can be targeted through PARP inhibition. To test this hypothesis, we conducted a multicenter study of olaparib monotherapy in patients with *IDH1*/2mt gliomas.

Methods: Patients with recurrent, contrast-enhancing *IDH1*/2mt gliomas were enrolled in a two-step phase II trial; the primary endpoint was overall response rate per Response Assessment in Neuro-Oncology (RANO) criteria. Olaparib 300 mg orally twice daily was given.

Results: A total of 15 evaluable patients were enrolled. Histology was astrocytoma ($N = 12$) and oligodendroglioma ($N = 3$). Most toxicities were grade 1 or 2. Best response was stable disease (SD) in 9 (60%) patients. Median progression-free survival (PFS) was 3.63 months and median overall survival was 20.7 months. For patients with SD, median PFS was 5.53 months; 4 patients had SD for >6 months. Among patients with best response progressive disease ($N = 6$), 5 had grade 4 tumor and 4 had known *CDKN2A* alteration. PFS was 5.23 months for grades 2 or 3 tumors ($N = 10$) versus 1.8 months for grade 4 ($N = 5$; $P = 0.0013$).

Conclusion: The study did not meet the prespecified response-based activity threshold for moving to step 2. However, prolonged SD was observed in patients with grades 2 and 3 histologies, suggesting olaparib monotherapy could be of clinical benefit in select populations. Grade 4 tumors per 2021 World Health Organization classification defined by histology or *CDKN2A* alteration derived no benefit from this drug, highlighting the usefulness of this classification for future patient stratification and trial design.

Significance: A single-arm phase II trial of olaparib in *IDH*-mutant glioma demonstrated clinically significant prolonged SD for select patients with grade 2/3 disease, suggesting potential benefit of olaparib in *IDH*-mutant gliomas.

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- ADENOME HYPOPHYSAIRE
- METASTASES CEREBRALES
- SCHWANNOME VESTIBULAIRE

Centre Eugène Marquis RENNES

Clinical Trial > J Clin Oncol. 2023 Jun 20;41(18):3374-3383. doi: 10.1200/JCO.22.01777.
Epub 2023 May 1.

Phase II Randomized Trial of Lenalidomide in Children With Pilocytic Astrocytomas and Optic Pathway Gliomas: A Report From the Children's Oncology Group

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unicancer

Purpose: Children with low-grade glioma often require long-term therapy and suffer from treatment morbidity. Although targeted agents are promising, tumor targets often encompass normal developmental pathways and long-term effects of inhibition are unknown. Lenalidomide is an immunomodulatory agent with wide-ranging properties. Phase I studies indicated greater tolerability of lenalidomide in children compared with adults and a potential dose-response effect.

Patients and methods: We performed a phase II trial of lenalidomide in children with pilocytic astrocytomas and optic pathway gliomas who failed initial therapy. Primary objectives included determination of objective response rate of children randomly assigned to regimen A, low-dose (20 mg/m^2/dose), or regimen B, high-dose (115 mg/m^2/dose) lenalidomide, and assessment for early progression. Secondary objectives included estimation of event-free survival, overall survival, incidence of toxic events, and assessment of plasma lenalidomide concentrations. Lenalidomide was administered once daily × 21 days of each 28-day cycle for each regimen.

Results: Seventy-four eligible patients were enrolled (n = 37, each arm). The predefined activity level of interest was achieved for both arms. Four objective responses were observed in each arm, and the number of early progressors was low. Eighteen patients completed 26 cycles of therapy (regimen A, n = 12; regimen B, n = 6). The median number of cycles was 14 (range, 2-26) for regimen A and 11 for regimen B (range, 1-26). Of 74 eligible patients who received study drug, 30 required dose reduction for toxicity (regimen A, n = 6; regimen B, n = 24) and 16 discontinued because of toxicity (regimen A, n = 2; regimen B, n = 14).

Conclusion: Lenalidomide demonstrates a sufficient level of activity in children with low-grade glioma to warrant further exploration. Low-dose (20 mg/m^2/dose administered once daily × 21 days of each 28-day cycle) lenalidomide appears to have better tolerability with comparable activity.

Gliome des voies optiques

cancers

MDPI

Article

Bevacizumab as Single Agent in Children and Teenagers with Optic Pathway Glioma

Pierluigi Calò [1,*], Nicolas Pianton [2], Alexandre Basle [3], Alexandre Vasiljevic [4], Marc Barritault [4], Pierre Aurélien Beuriat [5], Cécile Faure-Conter [1] and Pierre Leblond [1]

Simple Summary: Nowadays, there is no univocal therapeutical care for children with optic pathway gliomas (OPG) different chemotherapy regimens are proposed, but no one has clearly proved its superiority over the others on the PFS (Progression free survival). The efficacy of bevacizumab, an anti-VEGF monoclonal antibody, used in combination with Irinotecan, has been raised by several recent publications. However, Irinotecan has demonstrated side effects, especially digestive. Our main goal is to understand if bevacizumab could be efficacious used as a single agent against OPG.

Abstract: This is a retrospective study conducted on patients with OPG, aged less than 19 years, treated with bevacizumab as a single agent, since 2010 at IHOPe (Institute of Pediatric Hematology and Oncology). Efficacy of the treatment was evaluated on the tumor response rate on MRI with a centralized review basing upon RAPNO criteria and with visual assessment basing upon a 0.2 log change in the logMAR scale. Thirty-one patients with OPG have been included. From a radiological point of view, best anytime responses were: 1 major response, 6 partial responses, 7 minor responses and 14 stable diseases achieving disease control in 28 (96%) out of 29 patients. Ophthalmological response was evaluated in 25 patients and disease control was achieved in 22 (88%) out of 25, with 14 steady states and 8 significant improvements. Among patients treated with chemotherapy after the bevacizumab course, nine relapsed and have been retreated with objective responses. Bevacizumab used as single agent seems effective in children and adolescents with OPG. Our work paves the way for a phase II study in which bevacizumab alone could be used as frontline therapy.

Keywords: bevacizumab; optic pathway glioma; pediatric low-grade glioma

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- SCHWANNOME VESTIBULAIRE

Vaccin gliome du tronc pédiatrique

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oncolytic DNX-2401 Virus for Pediatric Diffuse Intrinsic Pontine Glioma

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BACKGROUND

Pediatric patients with diffuse intrinsic pontine glioma (DIPG) have a poor prognosis, with a median survival of less than 1 year. Oncolytic viral therapy has been evaluated in patients with pediatric gliomas elsewhere in the brain, but data regarding oncolytic viral therapy in patients with DIPG are lacking.

METHODS

We conducted a single-center, dose-escalation study of DNX-2401, an oncolytic adenovirus that selectively replicates in tumor cells, in patients with newly diagnosed DIPG. The patients received a single virus infusion through a catheter placed in the cerebellar peduncle, followed by radiotherapy. The primary objective was to assess the safety and adverse-event profile of DNX-2401. The secondary objectives were to evaluate the effect of DNX-2401 on overall survival and quality of life, to determine the percentage of patients who have an objective response, and to collect tumor-biopsy and peripheral-blood samples for correlative studies of the molecular features of DIPG and antitumor immune responses.

RESULTS

A total of 12 patients, 3 to 18 years of age, with newly diagnosed DIPG received 1×10^{10} (the first 4 patients) or 5×10^{10} (the subsequent 8 patients) viral particles of DNX-2401, and 11 received subsequent radiotherapy. Adverse events among the patients included headache, nausea, vomiting, and fatigue. Hemiparesis and tetraparesis developed in 1 patient each. Over a median follow-up of 17.8 months (range, 5.9 to 33.5), a reduction in tumor size, as assessed on magnetic resonance imaging, was reported in 9 patients, a partial response in 3 patients, and stable disease in 8 patients. The median survival was 17.8 months. Two patients were alive at the time of preparation of the current report, 1 of whom was free of tumor progression at 38 months. Examination of a tumor sample obtained during autopsy from 1 patient and peripheral-blood studies revealed alteration of the tumor microenvironment and T-cell repertoire.

CONCLUSIONS

Intratumoral infusion of oncolytic virus DNX-2401 followed by radiotherapy in pediatric patients with DIPG resulted in changes in T-cell activity and a reduction in or stabilization of tumor size in some patients but was associated with adverse events. (Funded by the European Research Council under the European Union's Horizon 2020 Research and Innovation Program and others; EudraCT number, 2016-001577-33; ClinicalTrials.gov number, NCT03178032.)

Ribociclib et Evérolimus DIPG

Neuro-Oncology Advances

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Phase I study of ribociclib and everolimus in children with newly diagnosed DIPG and high-grade glioma: A CONNECT pediatric neuro-oncology consortium report

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Background. Genomic aberrations in the cell cycle and PI3K/Akt/mTOR pathways have been reported in diffuse intrinsic pontine glioma (DIPG) and high-grade glioma (HGG). Dual inhibition of *CDK4/6* and mTOR has biologic rationale and minimal overlapping toxicities. This study determined the recommended phase 2 dose (RP2D) of ribociclib and everolimus following radiotherapy in children with DIPG and HGG.

Methods. Patients were enrolled according to a Rolling-6 design and received ribociclib and everolimus once daily for 21 and 28 days, respectively. All patients with HGG and biopsied DIPG were screened for retinoblastoma protein presence by immunohistochemistry. Pharmacokinetics were analyzed.

Results. Nineteen patients enrolled (median age: 8 years [range: 2-18]). Three patients enrolled at each dose level 1 and 2 without dose-limiting toxicities (DLT). Thirteen patients were enrolled at dose level 3, with one patient experiencing a DLT (grade 3 infection). One patient came off therapy before cycle 9 due to cardiac toxicity. The most common grade 3/4 toxicities were neutropenia (33%), leucopenia (17%), and lymphopenia (11%). Steady-state everolimus exposures in combination were 1.9 ± 0.9-fold higher than single-agent administration. Median overall survival for 15 patients with DIPG was 13.9 months; median event-free survival for four patients with HGG was 10.5 months. Two longer survivors had tumor molecular profiling identifying *CDKN2A/B* deletion and *CDK4* overexpression.

Conclusion. The combination of ribociclib and everolimus following radiotherapy in children with newly diagnosed DIPG and HGG was well tolerated, with a RP2D of ribociclib 170 mg/m^2 and everolimus 1.5 mg/m^2. Results will inform a molecularly guided phase II study underway to evaluate efficacy.

Key Points

- This study defined the RP2D of ribociclib and everolimus in children with DIPG/HGG.
- Therapy was well tolerated, with the potential impact of ribociclib on everolimus pharmacokinetics.
- Results will inform a phase II study, under development, to evaluate efficacy.

IRM DIPG

Review > Tomography. 2023 Aug 18;9(4):1526-1537. doi: 10.3390/tomography9040122.

The Role of Advanced MRI Sequences in the Diagnosis and Follow-Up of Adult Brainstem Gliomas: A Neuroradiological Review

Alessia Guarnera [1 2], Andrea Romano [1], Giulia Moltoni [1 2], Tamara Ius [3], Serena Palizzi [1], Allegra Romano [1], Daniele Bagatto [4], Giuseppe Minniti [5 6], Alessandro Bozzao [1]

The 2021 WHO (World Health Organization) classification of brain tumors incorporated the rapid advances in the molecular, genetic, and pathogenesis understanding of brain tumor pathogenesis, behavior, and treatment response. It revolutionized brain tumor classification by placing great emphasis on molecular types and completely splitting adult-type and pediatric-type diffuse gliomas. Brainstem gliomas (BSGs) are the leading primary tumors of the brainstem, although they are quite uncommon in adults compared with the pediatric population, representing less than 2% of adult gliomas. Surgery is not always the treatment of choice since resection is rarely feasible and does not improve overall survival, and biopsies are not generally performed since the location is treacherous. Therefore, MRI (Magnetic Resonance Imaging) without and with gadolinium administration represents the optimal noninvasive radiological technique to suggest brainstem gliomas diagnosis, plan a multidisciplinary treatment and for follow-up evaluations. The MRI protocol encompasses morphological sequences as well as functional and advanced sequences, such as DWI/ADC (Diffusion-Weighted Imaging/Apparent Diffusion Coefficient), DTI (Diffusion Tensor Imaging), PWI (Perfusion-Weighted Imaging), and MRS (Magnetic Resonance Spectroscopy), which improve the accuracy of the diagnosis of BSGs by adding substantial information regarding the cellularity, the infiltrative behavior toward the v fiber tracts, the vascularity, and the molecular changes. Brainstem gliomas have been divided into four categories on the basis of their MRI radiological appearance, including diffuse intrinsic low-grade gliomas, enhancing malignant gliomas, localized tectal gliomas, and other forms. The aim of our review is to provide insight into the role of advanced MRI sequences in the diagnosis and follow-up of adult brainstem gliomas.

Keywords: 2021 WHO classification; DTI; DWI; MRI; MRS; PWI; brainstem glioma; diffuse intrinsic low-grade gliomas; enhancing malignant gliomas; localized tectal gliomas.

Biopsie DIPG

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Biopsies of Caudal Brainstem Tumors in Pediatric Patients-A Single-Center Retrospective Case Series

Anton Früh [1], Andreas Schaumann [2], Gesa Cohrs [2], Valentina Pennacchietti [2], Matthias Schulz [2], Pablo Hernáiz Driever [3], Arend Koch [4], Ulrich-Wilhelm Thomale [5]

Objective: The indication for performing biopsies in patients with diffuse lesions in the brain stem is controversial. The possible risks associated with the technically challenging interventions must be balanced against clarifying the diagnosis and the possible therapeutic options. We reviewed the feasibility, risk profile, and diagnostic yield of different biopsy techniques in a pediatric cohort.

Methods: We retrospectively included all patients aged <18 years who had undergone biopsy of the caudal brainstem region (pons, medulla oblongata) at our pediatric neurosurgical center from 2009 to 2022.

Results: We identified 27 children. Biopsies were performed using frameless stereotactic (Varioguide; n = 12), robotic-assisted (Autoguide; n = 4), endoscopic (n = 3), and open biopsy (n = 8) techniques. Intervention-related mortality was not observed. Three patients experienced a transient postoperative neurological deficit. No patient experienced intervention-related permanent morbidity. Biopsy yielded the histopathological diagnosis in all 27 cases. Molecular analysis was feasible for 97% of the cases. The most common diagnosis was H3K27M-mutated diffuse midline glioma (60%). Low-grade gliomas were identified in 14% of patients. Overall survival was 62.5% after 24 months of follow-up.

Conclusions: Biopsies of the caudal brainstem in children were feasible and safe in the presented setup. The amount of tumor material acquired allowing for an integrated diagnosis and was obtained at reasonable risk. The selection of the surgical technique depends on the tumor location and growth pattern. We recommend the performance of brainstem tumor biopsies in children at specialized centers to better understand the biology and enable possible novel therapeutic options.

Keywords: Brain stem; DIPG; Frameless biopsy.

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- SCHWANNOME VESTIBULAIRE

Astroblastoma

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https://doi.org/10.1007/s00401-021-02388-y

CORRESPONDENCE

Check for updates

EWSR1-BEND2 fusion defines an epigenetically distinct subtype of astroblastoma

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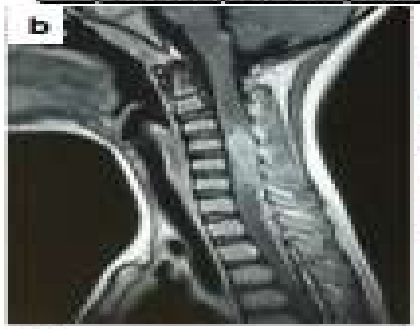
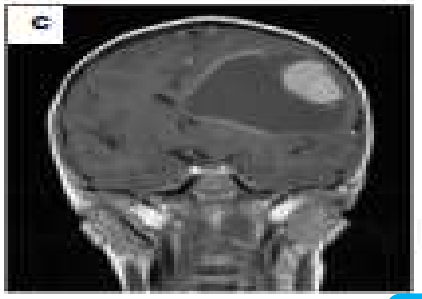
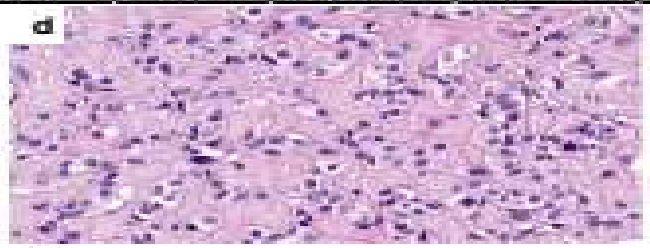
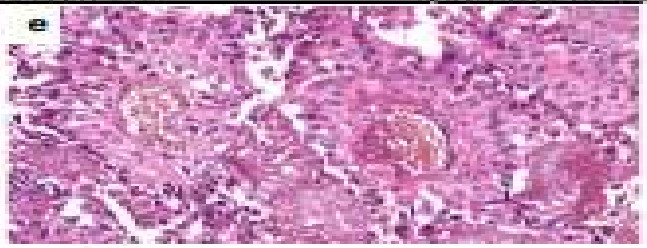
a

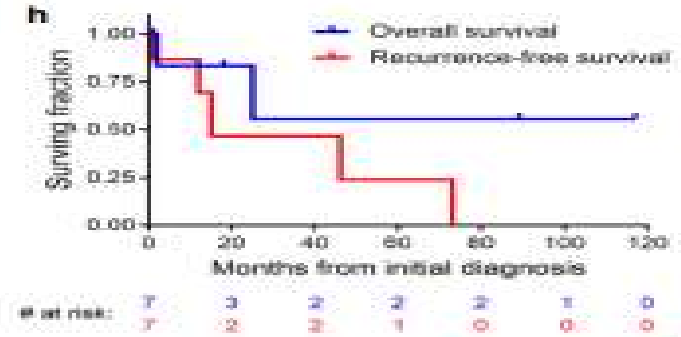
Pt #	Age at dx (yrs)	Sex	Clinical presentation	Location	Histologic features	Fusion	Methylation class	Source
1	20	M	Arm weakness	Brainstem	Astroblastoma	*EWSR1-BEND2*	Astroblastoma, *EWSR1-BEND2* fused	current study
2	6	F	Arm weakness	Spinal cord	Astroblastoma	*EWSR1-BEND2*	Astroblastoma, *EWSR1-BEND2* fused	current study
3	26	F	Seizure	Right frontal	Astroblastoma	*EWSR1-BEND2*	Astroblastoma, *EWSR1-BEND2* fused	current study
4	6	F	Seizure	Left frontal	Astroblastoma	*EWSR1-BEND2*	Astroblastoma, *EWSR1-BEND2* fused	current study
-	38	M	Leg numbness	Spinal cord	Astroblastoma	*EWSR1-BEND2*	reported as "HGNET, MN1"	Smith-Cohn et al
-	0	M	Unknown	Spinal cord	Astroblastoma	*EWSR1-BEND2*	reported as "HGNET, MN1"	Yamasaki et al
-	36	M	Leg numbness	Spinal cord	Astroblastoma	*EWSR1-BEND2*	reported as "HGNET, MN1"	Tsutsui et al
-	Unknown	Unknown	Unknown	Unknown	Astroblastoma	*EWSR1-BEND2*	Not performed	Ramkissoon et al

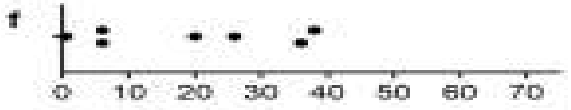


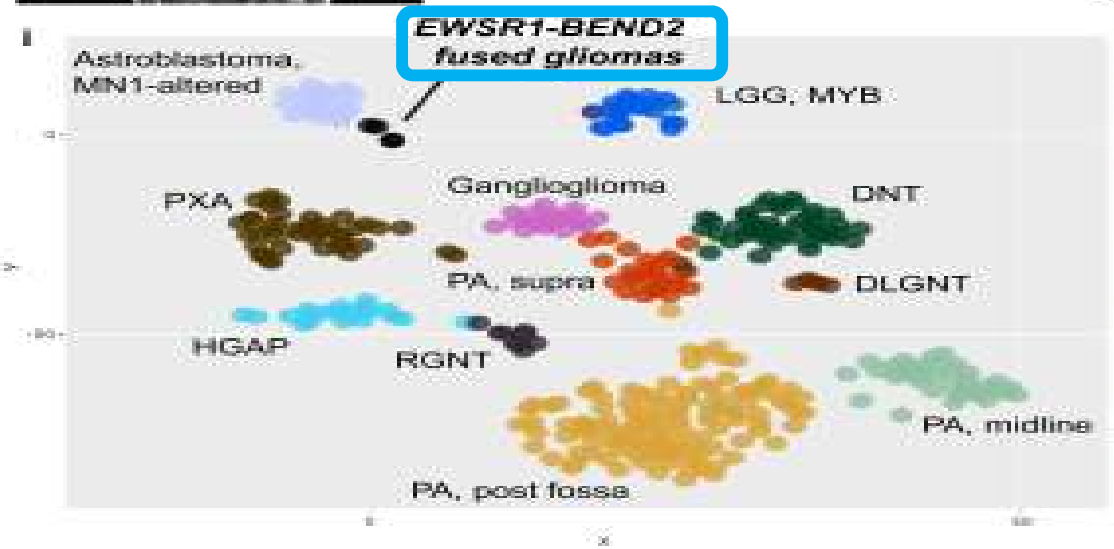


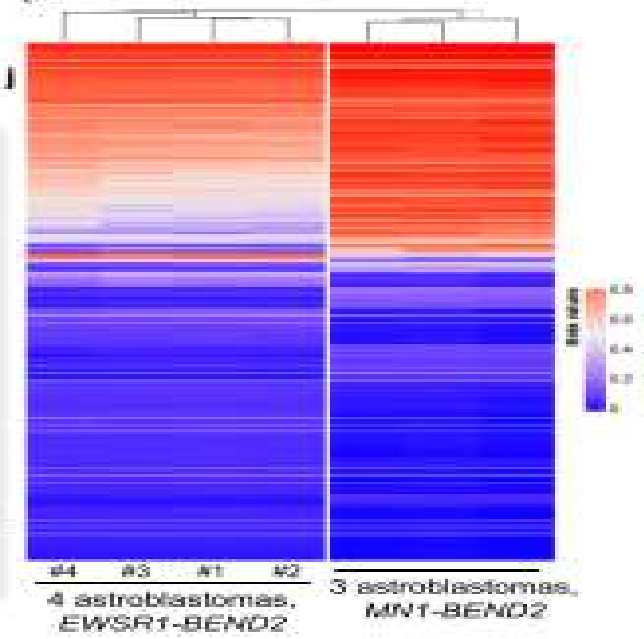












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Xanthoastrocytoma

Original Article | Published: 22 December 2022

Correlation of MTAP immunohistochemical deficiency with *CDKN2A* homozygous deletion and clinicopathological features in pleomorphic xanthoastrocytoma

Lei Lou, Jiajun Li, Manman Qin, Xiaoxi Tian, Wenli Guo & Yuehong Li

Brain Tumor Pathology **40**, 15–25 (2023) | Cite this article

Pleomorphic xanthoastrocytoma (PXA) is a rare tumor ranging from World Health Organization (WHO) grades 2–3 and can potentially recur and metastasize throughout the central nervous system (CNS). *Cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B)* deletion is a frequent genomic alteration of PXA. Methylthioadenosine phosphorylase (MTAP) immunohistochemistry is a promising surrogate marker for *CDKN2A* homozygous deletion in different cancers but has not been examined in PXA. Therefore, we performed *CDKN2A* fluorescence in situ hybridization and MTAP immunohistochemistry on specimens from 23 patients with CNS WHO grades 2 (n = 10) and 3 (n = 13) PXAs, including specimens from primary and recurrent tumors, and determined whether MTAP immunohistochemistry correlated with *CDKN2A* homozygous deletion and clinicopathological features. *CDKN2A* homozygous deletion was detected in 30% (3/10) and 76.9% (10/13) of CNS WHO grades 2 and 3 PXAs, respectively. In addition, MTAP loss was inconsistent with *CDKN2A* homozygous deletion (sensitivity = 86.7%, specificity = 100%). Furthermore, *CDKN2A* homozygous deletion was correlated with WHO grade (p = 0.026) and the Ki-67 labeling index (p = 0.037). Therefore, MTAP immunostaining can be a suitable surrogate marker for *CDKN2A* homozygous deletions in PXAs, and *CDKN2A* homozygous deletions may be an important prognostic factor for PXAs.

> Zh Vopr Neirokhir Im N N Burdenko. 2022;86(2):45-54. doi: 10.17116/neiro20228602145.

[Anaplastic pleomorphic xanthoastrocytoma – single-center analysis of 42 patients]

[Article in Russian]
A Yu Belyaev [1], S V Shugai [1], G L Kobyakov [1], Yu V Strunina [1], A I Batalov [1], I N Pronin [1], D Yu Usachev [1]

- Anaplastic pleomorphic xanthoastrocytoma is a rare tumor. There are still no objective data on the incidence of its diagnosis.
- **Objective:** To study neuroimaging, morphological features of tumors, as well as factors affecting treatment and prognosis.
- **Material and methods:** A retrospective study enrolled 42 patients operated on at the Burdenko Neurosurgery Center between 2003 and 2020. MR characteristics of anaplastic pleomorphic xanthoastrocytoma were analyzed. All patients underwent resection of tumor (total resection in 83.3% of cases). Redo surgeries were performed in 1/3 of patients. Mutational status of BRAF V600E was assessed in all patients. Adjuvant radio- and chemotherapy was performed in more than 80% of cases. Tyrosine kinase inhibitors were administered in 19% of cases. The follow-up period was 152 months (median 34 months).
- **Results:** We found no pathognomonic MR signs of this disease. Indeed, anaplastic pleomorphic xanthoastrocytoma have the same signal characteristics as other malignant gliomas. The BRAF V600E mutation status was positive in 54.8% of cases. None patient had IDH-1 mutation. Mean Ki-67 index was 12.5%. The overall survival was 79 months (range 4-152). Seven (17%) patients are alive for more than 90 months. Only Ki-67 index and BRAF mutation significantly influenced the treatment prognosis and overall survival regardless the use of tyrosine kinase inhibitors.
- **Conclusion:** Such well-known factors for malignant glioma as patient age, total resection and adjuvant therapy did not significantly affect overall survival. Perhaps, searching for new molecular genetic features will reveal additional significant factors of prognosis in patients with anaplastic pleomorphic xanthoastrocytoma.

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Ependymome

Eur Spine J. 2023 Jul;32(7):2459-2467. doi: 10.1007/s00586-023-07690-9. Epub 2023 Apr 7.

Clinical management and prognosis of spinal myxopapillary ependymoma: a single-institution cohort of 72 patients

Yao-Wu Zhang [1], Bo Wang [1], Song-Yuan An [1], Wei-Hao Liu [1], Chong Wang [1], Hao Yan [1], Yu-Lun Xu [1], Yong-Zhi Wang [# 2], Wen-Qing Jia [# 3]

Purpose: Myxopapillary ependymoma (MPE) was classified as grade 2 tumor in the 2021 World Health Organization central nervous system classification because of its high recurrence probability. This study aimed to investigate predictive factors and management of tumor recurrence.

Methods: Seventy-two patients with spinal MPE underwent initial surgical treatment at our hospital between 2011 and 2021. Kaplan-Meier curves and Cox regression were used to analyze the correlation between clinical variables and progression-free survival (PFS).

Results: The median age at diagnosis was 33.5 years (range 8-60 years). Twenty-one patients (29.2%) had preoperative spinal drop metastases. Gross total resection (GTR) was performed in 37 patients (51.4%). The median follow-up was 7.2 years, and the follow-up rate was 88.9% (64 of 72 cases). Twelve of the 64 patients (18.9%) relapsed, and preoperative drop metastasis occurred in 7 patients (58.3%). The estimated 5-year and 10-year PFS rates were 82% and 77%, respectively. Univariate analysis showed that GTR was associated with improved PFS (hazard ratio [HR] 0.149, p = 0.014), while preoperative drop metastasis (HR 3.648, p = 0.027) and tumor involvement sacrococcygeal region (HR 7.563, p = 0.003) were associated with tumor recurrence. Adjuvant radiotherapy (RT) was significantly associated with mproved PFS in patients with preoperative drop metastasis (p = 0.039).

Conclusion: Complete surgical resection under the premise of protecting neurological function is an important factor in reducing spinal MPE recurrence. Adjuvant RT is recommended when the tumor invades the capsule with preoperative drop metastasis or adhesion to the nerve and cannot reach GTR.

Evérolimus épendymome pédiatrique

Neuro-Oncology Advances

5(1), 1–7, 2023 | https://doi.org/10.1093/noajnl/vdad011 | Advance Access date 10 February 2023

1

Phase II study of everolimus for recurrent or progressive pediatric ependymoma

Daniel C. Bowers, Veena Rajaram, Matthias A. Karajannis, Sharon L. Gardner, Jack Meng-Fen Su, Patricia Baxter, Sonia Partap, and Laura J. Klesse

Background. Preclinical studies have suggested that mTOR pathway signaling may be a potential therapeutic target for childhood ependymoma.

Methods. A phase II clinical trial (ClinicalTrials.gov identifier: NCT02155920) of single-agent everolimus was performed to test the hypothesis that mTOR pathway inhibition would result in tumor responses for children with recurrent and/or progressive ependymomas.

Results. Eleven subjects [sex: 4 females (36.4%); median age: 8 years (range: 2-15 years); race: 9 white; prior therapies: median 6 (range: 3-9)] were enrolled on the study. Ten primary tumors were located in the posterior fossa and one primary tumor was located in the spinal cord. Eight of 9 tumors were PF-A subtype epenydmomas. All subjects were treated with oral everolimus 4.5 mg/m^2/day (each cycle = 28 days) that was titrated to achieve serum trough levels of 5-15 ng/ml. Overall, everolimus was well tolerated; except for a single event of grade 3 pneumonia, all adverse events were grade 1-2. No objective tumor responses were observed. Participating subjects experienced tumor progression and discontinued therapy after a median of 2 cycles of therapy (1 cycle = 2; 2 cycles = 6; 3, 4, and 8 cycles = 1 each).

Conclusions. Everolimus does not appear to have activity for children with recurrent or progressive PF-A ependymoma.

Key Points

- Pediatric ependymoma often has immunohistochemical evidence of mTOR pathway activation.
- Everolimus does not appear to have activity for recurrent or progressive PF-A ependymoma.

Etoposide IV épendymome récidivant

Neuro-Oncology Advances

4(1), 1–11, 2022 | https://doi.org/10.1093/noajnl/vdac053 | Advance Access date 13 April 2022

1

Phase II study of intravenous etoposide in patients with relapsed ependymoma (CNS 2001 04)

John R. Apps, Shanna Maycock, David W. Ellison, Timothy Jaspan, Timothy A. Ritzmann, Donald Macarthur, Conor Mallucci, Keith Wheatley, Gareth J. Veal, Richard G. Grundy, and Susan Picton

Abstract

Background. Relapsed ependymoma has a dismal prognosis, and the role of chemotherapy at relapse remains unclear. This study prospectively evaluated the efficacy of intensive intravenous (IV) etoposide in patients less than 21 years of age with relapsed intracranial ependymoma (NCT00278252).

Methods. This was a single-arm, open-label, phase II trial using Gehan's two-stage design. Patients received IV etoposide 100 mg/m^2 on days 1-3, 8-10, and 15-17 of each 28-day cycle, up to maximum of 6 cycles. Primary outcome was radiological response after 3 cycles. Pharmacokinetic analysis was performed in 10 patients.

Results Twenty-five patients were enrolled and included in the intention-to-treat (ITT) analysis. Three patients were excluded in per-protocol (PP) analysis. After 3 cycles of etoposide, 5 patients (ITT 20%/PP 23%) had a complete response (CR), partial response (PR), or objective response (OR). Nine patients (ITT 36%/PP 41%,) had a best overall response of CR, PR, or OR. 1-year PFS was 24% in ITT and 23% in PP populations. 1-year OS was 56% and 59%, 5-year OS was 20% and 18%, respectively, in ITT and PP populations. Toxicity was predominantly hematological, with 20/25 patients experiencing a grade 3 or higher hematological adverse event.

Conclusions. This study confirms the activity of IV etoposide against relapsed ependymoma, however, this is modest, not sustained, and similar to that with oral etoposide, albeit with increased toxicity. These results confirm the dismal prognosis of this disease, provide a rationale to include etoposide within drug combinations, and highlight the need to develop novel treatments for recurrent ependymoma.

Key Points

- Intravenous etoposide has activity in relapsed ependymoma.
- Toxicity is greater than oral etoposide.
- Relapsed ependymoma has poor outcomes.

CDDP Endoxan Bévacizumab
mOS :19.96 mo
mPFS :12.36 mo

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Tumeur du plexus choroïde

Original Article | Published: 20 September 2023

The composition of choroid plexus tumor research: a bibliometric analysis of the 100 most impactful studies to date

Julian S. Rechberger, Leo F. Nonnenbroich, Erica A. Power & David J. Daniels

Child's Nervous System (2023) | Cite this article

Purpose

Choroid plexus tumors (CPT) are relatively rare CNS tumors that primarily occur in children. They are classified as low-grade choroid plexus papilloma, including atypical ones, and high-grade choroid plexus carcinoma based on histological characteristics. There has been extensive academic research regarding these complex tumors. The goal of this work was to identify the 100 most-cited articles pertaining to CPTs in order to better understand the most impactful studies to date.

Methods

In August 2023, Elsevier's Scopus database was searched for the 100 most-cited articles about CPT. To look for trends, articles were classified as either basic science or clinical, and the earliest 50 articles were separated from the latest 50 articles and then were compared. Various bibliometric parameters were summarized and compared using Pearson's chi-square exact test and Wilcoxon rank sum test/Mann–Whitney *U* test.

Results

The 100 most-cited articles were published between 1955 and 2016 in 53 different scientific journals, originating from 16 distinct countries. Over 75% of the articles were clinical in nature, and overall mean (range) values were as follows: citation count 78.5 (42–371), citation rate per year 3.4 (0.9–12), number of authors 6.2 (1–28). Newer articles had statistically higher citation rate ($P < 0.01$) and number of authors ($P < 0.01$) compared to their older counterparts. Additionally, while there was no significant difference in article focus ($P = 0.64$), there was a difference in study design ($P < 0.01$).

Conclusion

This study used citation number as a surrogate for article impact and identified the 100 most-cited CPT articles. New mutational analyses have allowed for further subgrouping and positive trends in collaboration shine hope for improvement in treatment outcomes and long-term survival.

Tumeur du plexus choroïde CPT-SIOP-2000

Journal of Neuro-Oncology (2022) 156:599–613
https://doi.org/10.1007/s11060-021-03942-0

CLINICAL STUDY

Final results of the Choroid Plexus Tumor study CPT-SIOP-2000

Johannes E. Wolff[1,2] · Stefaan W. Van Gool[3] · Tezer Kutluk[4] · Blanca Diez[5] · Rejin Kebudi[6] · Beate Timmermann[7] · Miklos Garami[8] · Jaroslav Sterba[9,10] · Gregory N. Fuller[11] · Brigitte Bison[12] · Uwe R. Kordes[13]

Introduction: Standards for chemotherapy against choroid plexus tumors (CPT) have not yet been established.

Methods: CPT-SIOP-2000 (NCT00500890) was an international registry for all CPT nesting a chemotherapy randomization for high-risk CPT with Carboplatin/Etoposide/Vincristine (CarbEV) versus Cyclophosphamide/Etoposide/Vincristine (CycEV). Patients older than three years were recommended to receive irradiation: focal fields for non-metastatic CPC, incompletely resected atypical choroid plexus papilloma (APP) or metastatic choroid plexus papilloma (CPP); craniospinal fields for metastatic CPC/APP and non-responsive CPC. High risk was defined as choroid plexus carcinoma (CPC), incompletely resected APP, and all metastatic CPT. From 2000 until 2010, 158 CPT patients from 23 countries were enrolled.

Results: For randomized CPC, the 5/10 year progression free survival (PFS) of patients on CarbEV (n = 20) were 62%/47%, respectively, compared to 27%/18%, on CycEV (n = 15), (intention-to-treat, HR 2.6, p = 0.032). Within the registry, histological grading was the most influential prognostic factor: for CPP (n = 55) the 5/10 year overall survival (OS) and the event free survival (EFS) probabilities were 100%/97% and 92%/92%, respectively; for APP (n = 49) 96%/96% and 76%/76%, respectively; and for CPC (n = 54) 65%/51% and 41%/39%, respectively. Without irradiation, 12 out of 33 patients with CPC younger than three years were alive for a median of 8.52 years. Extent of surgery and metastases were not independent prognosticators.

Conclusions: Chemotherapy for Choroid Plexus Carcinoma is feasible and effective. CarbEV is superior to CycEV. A subset of CPC can be cured without irradiation.

Keywords: Chemotherapy; Choroid plexus tumors; Irradiation; Li–Fraumeni syndrome.

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Tumeur glioneuronale

NEUROPATHOLOGY

Review Article

The landscape of common genetic drivers and DNA methylation in low-grade (epilepsy-associated) neuroepithelial tumors: A review

Joana Jesus-Ribeiro ✉, Olinda Rebelo, Ilda Patrícia Ribeiro, Luís Miguel Pires, João Daniel Melo, Francisco Sales, Isabel Santana, António Freire, Joana Barbosa Melo

Low-grade neuroepithelial tumors (LNETs) represent an important group of central nervous system neoplasms, some of which may be associated to epilepsy. The concept of long-term epilepsy-associated tumors (LEATs) includes a heterogenous group of low-grade, cortically based tumors, associated to drug-resistant epilepsy, often requiring surgical treatment. LEATs entities can sometimes be poorly discriminated by histological features, precluding a confident classification in the absence of additional diagnostic tools. This study aimed to provide an updated review on the genomic findings and DNA methylation profiling advances in LNETs, including histological entities of LEATs. A comprehensive search strategy was conducted on PubMed, Embase, and Web of Science Core Collection. High-quality peer-reviewed original manuscripts and review articles with full-text in English, published between 2003 and 2022, were included. Results were screened based on titles and abstracts to determine suitability for inclusion, and when addressed the topic of the review was screened by full-text reading. Data extraction was performed through a qualitative content analysis approach. Most LNETs appear to be driven mainly by a single genomic abnormality and respective affected signaling pathway, including BRAF p.V600E mutations in ganglioglioma, FGFR1 abnormalities in dysembryoplastic neuroepithelial tumor, MYB alterations in angiocentric glioma, BRAF fusions in pilocytic astrocytoma, PRKCA fusions in papillary glioneuronal tumor, between others. However, these molecular alterations are not exclusive, with some overlap amongst different tumor histologies. Also, clustering analysis of DNA methylation profiles allowed the identification of biologically similar molecular groups that sometimes transcend conventional histopathological classification. The exciting developments on the molecular basis of these tumors reinforce the importance of an integrative histopathological and (epi)genetic classification, which can be translated into precision medicine approaches.

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Tumeur de glande pinéale et gamma knife

Review > J Pineal Res. 2023 Sep 13;e12910. doi: 10.1111/jpi.12910. Online ahead of print.

Primary Gamma Knife Radiosurgery for pineal region tumors: A systematic review and pooled analysis of available literature with histological stratification

Filippo Gagliardi [1], Pierfrancesco De Domenico [1], Enrico Garbin [1], Silvia Snider [1], Pietro Mortini [1]

Pineal region tumors (PTs) represent extremely rare pathologies, characterized by highly heterogeneous histological patterns. Most of the available evidence for Gamma Knife radiosurgical (GKSR) treatment of PTs arises from multimodal regimens, including GKSR as an adjuvant modality or as a salvage treatment at recurrence. We aimed to gather existing evidence on the topic and analyze single-patient-level data to address the efficacy and safety of primary GKSR. This is a systematic review of the literature (PubMed, Embase, Cochrane, Science Direct) and pooled analysis of single-patient-level data. A total of 1054 original works were retrieved. After excluding duplicates and irrelevant works, we included 13 papers (n = 64 patients). An additional 12 patients were included from the authors' original series. A total of 76 patients reached the final analysis; 56.5% (n = 43) received a histological diagnosis. Confirmed lesions included pineocytoma WHO grade I (60.5%), pineocytoma WHO grade II (14%), pineoblastoma WHO IV (7%), pineal tumor with intermediate differentiation WHO II/III (4.7%), papillary tumor of pineal region WHO II/III (4.7%), germ cell tumor (2.3%), neurocytoma WHO I (2.3%), astrocytoma WHO II (2.3%) and WHO III (2.3%). Presumptive diagnoses were achieved in the remaining 43.5% (n = 33) of cases and comprised of pineocytoma (9%), germ cell tumor (6%), low-grade glioma (6%), high-grade glioma (3%), meningioma (3%) and undefined in 73%. The mean age at the time of GKSR was 38.7 years and the mean lesional volume was 4.2 ± 4 cc. All patients received GKSR with a mean marginal dose of 14.7 ± 2.1 Gy (50% isodose). At a median 36-month follow-up, local control was achieved in 80.3% of cases. Thirteen patients showed progression after a median time of 14 months. Overall mortality was 13.2%. The median OS was not reached for all included lesions, except high-grade gliomas (8mo). The 3-year OS was 100% for LGG and pineal tumors with intermediate differentiation, 91% for low-grade pineal lesions, 66% for high-grade pineal lesions, 60% for germ cell tumors (GCTs), 50% for HGG, and 82% for undetermined tumors. The 3-year progression-free survival (PFS) was 100% for LGG and pineal intermediate tumors, 86% for low-grade pineal, 66% for high-grade pineal, 33.3% for GCTs, and 0% for HGG. Median PFS was 5 months for HGG and 34 months for GCTs. The radionecrosis rate was 6%, and cystic degeneration was observed in 2%. Ataxia as a presenting symptom strongly predicted mortality (odds ratio [OR] 104, p = .02), while GCTs and HGG histology well predicted PD (OR: 13, p = .04). These results support the efficacy and safety of primary GKSR treatment of PTs. Further studies are needed to validate these results, which highlight the importance of the initial presumptive diagnosis for choosing the best therapeutic strategy.

Tumeur de glande pinéale et chirurgie

J Neurosurg Pediatr. 2023 May 5;32(2):184-193. doi: 10.3171/2023.3.PEDS22468. Print 2023 Aug 1.

Outcomes and surgical approaches for pineal region tumors in children: 30 years' experience

Sergio Cavalheiro [1 2], Linoel Curado Valsechi [1], Patricia Alessandra Dastoli [1 2], Jardel Mendonça Nicácio [1 2], Andrea Maria Cappellano [3], Nasjla Saba da Silva [3], Marcos Devanir Silva da Costa [1 2]

Objective: Pineal region tumors account for 2.7%-11% of all CNS tumors in children. In this series, the authors present their surgical results and long-term outcomes from a pediatric pineal region tumor cohort.

Methods: A total of 151 children aged 0-18 years were treated from 1991 to 2020. Tumor markers were collected in all patients; if positive, chemotherapy was performed, and if negative, biopsy was performed, preferably endoscopically. Resection was performed when there was a residual germ cell tumor (GCT) lesion after chemotherapy.

Results: The distribution based on histological type, as verified by markers, biopsy, or surgery, was germinoma (33.1%), nongerminomatous GCT (NGGCT) (27.2%), pineoblastoma (22.5%), glioma (12.6%), and embryonal tumor (atypical teratoid rhabdoid tumor) (3.3%). A total of 97 patients underwent resection, and gross-total resection (GTR) was achieved in 64%; the highest GTR rate (76.6%) was found in patients with GCTs, and the lowest (30.8%) was found in those with gliomas. The supracerebellar infratentorial approach (SCITA) was the most common, performed in 53.6% of patients, followed by the occipital transtentorial approach (OTA), performed in 24.7% of patients. Lesions were biopsied in 70 patients, and the diagnostic accuracy was 91.4. The overall survival (OS) rates at 12, 24, and 60 months as stratified by histological type were 93.7%, 93.7%, and 88% for patients with germinomas; 84.5%, 63.5%, and 40.7% for patients with pineoblastomas; 89.4%, 80.8%, and 67.2% for patients with NGGCTs; 89.4%, 78.2%, and 72.6% for patients with gliomas; and 40%, 20%, and 0% for patients with embryonal tumors, respectively ($p < 0001$). The OS at 60 months was significantly higher in the group with GTR (69.7%) than in the group with subtotal resection (40.8%) ($p = 0.04$). The 5-year progression-free survival was 77% for patients with germinomas, 72.6% for patients with gliomas, 50.8% for patients with NGGCTs, and 38.9% for patients with pineoblastomas.

Conclusions: The efficacy of resection varies by histological type, and complete resection is associated with higher OS rates. Endoscopic biopsy is the method of choice for patients presenting with negative tumor markers and hydrocephalus. For tumors restricted to the midline and with extension to the third ventricle, a SCITA is preferred, whereas for lesions with extension toward the fourth ventricle, an OTA is preferred.

Keywords: germ cell tumor; occipital transtentorial approach; oncology; pineal biopsy; pineal tumor; supracerebellar approach.

Tumeur de glande pinéale et chirurgie

Review > Childs Nerv Syst. 2023 Sep;39(9):2341-2348. doi: 10.1007/s00381-023-06071-3. Epub 2023 Jul 12.

The surgical intervention for pineal region tumors

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Histological and molecular characterization is essential for the diagnosis of pediatric brain tumors. In the pineal region tumors, it is necessary to remove a sufficient tumor volume to make a diagnosis. However, surgery in this region is challenging due to its deep anatomical location and surrounded by critical structures and complex venous system. Knowledge of the anatomy and function of the pineal region and tumor histological types is imperative for the successful management of pineal region tumors. This article describes surgical approaches to pineal tumors, focusing on the occipital transtentorial approach and adding the author's experience to what has been known in the literature. Recent innovations have made this approach more popular and can be applied to occipital fossa lesions.

Keywords: Germ cell tumors; Gliomas; Pediatric brain tumors; Pineal parenchymal tumors; Pineal region tumors; Pineoblastoma.

Tumeur de glande pinéale

Multicenter Study > J Neurooncol. 2023 Apr;162(2):425-433. doi: 10.1007/s11060-023-04310-w. Epub 2023 Apr 13.

Clinicopathologic analysis of pineal parenchymal tumors of intermediate differentiation: a multi-institutional cohort study by the Kyushu Neuro-Oncology Study Group

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Purpose: Pineal parenchymal tumors of intermediate differentiation (PPTIDs) which were recognized in the 2007 World Health Organization (WHO) classification, are rare, accounting for less than 1% of all central nervous system tumors. This rarity and novelty complicate the diagnosis and treatments of PPTID. We therefore aimed to evaluate the clinicopathological significance of this tumor.

Methods: At 11 institutions participating in the Kyushu Neuro-Oncology Study Group, data for patients diagnosed with PPTID were collected. Central pathology review and KBTBD4 mutation analysis were applied to attain the diagnostically accurate cohort.

Results: PPTID was officially diagnosed in 28 patients: 11 (39%) with WHO grade 2 and 17 (61%) with WHO grade 3 tumors. Median age was 49 years, and the male:female ratio was 1:2.1. Surgery was attempted in all 28 patients, and gross total resection (GTR) was achieved in 46% (13/28). Adjuvant radiotherapy and chemotherapy were administered to, respectively, 82% (23/28) and 46% (13/28). The 5-year progression-free survival (PFS) and overall survival rates were 64.9% and 70.4% respectively. Female sex ($p = 0.018$) and GTR ($p < 0.01$) were found to be independent prognostic factors for PFS and female sex ($p = 0.019$) was that for OS. Initial and second recurrences were most often leptomeningeal (67% and 100% respectively). 80% (20/25) of patients harbored a KBTBD4 mutation.

Conclusions: Female sex and GTR were independent prognostic factors in our patients with PPTID. Leptomeningeal recurrence was observed to be particularly characteristic of this tumor. The rate of KBTBD4 mutation observed in our cohort was acceptable and this could prove the accuracy of our PPTID cohort.

Keywords: Cohort study; KBTBD4 mutation; Leptomeningeal recurrence; PPTID.

Tumeur de glande pinéale

Review > Cancers (Basel). 2022 Jul 27;14(15):3646. doi: 10.3390/cancers14153646.

Diagnosis and Treatment of Pineal Region Tumors in Adults: A EURACAN Overview

Giuseppe Lombardi [1], Pietro Luigi Poliani [2], Renzo Manara [3], Moncef Berhouma [4], Giuseppe Minniti [5 6], Emeline Tabouret [7], Evangelia Razis [8], Giulia Cerretti [1], Vittorina Zagonel [1], Michael Weller [9], Ahmed Idbaih [10]

Pineal region tumors are rare intracranial tumors, accounting for less than 1% of all adult intracranial tumor lesions. These lesions represent a histologically heterogeneous group of tumors. Among these tumors, pineal parenchymal tumors and germ cell tumors (GCT) represent the most frequent types of lesions. According to the new WHO 2021 classification, pineal parenchymal tumors include five distinct histotypes: pineocytoma (PC), pineal parenchymal tumors of intermediate differentiation (PPTID), papillary tumor of the pineal region (PTPR), pinealoblastoma (PB), and desmoplastic myxoid tumor of the pineal region, SMARCB1-mutant; GCTs include germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, teratoma, mixed GCTs. Neuroradiological assessment has a pivotal role in the diagnostic work-up, surgical planning, and follow-up of patients with pineal masses. Surgery can represent the mainstay of treatment, ranging from biopsy to gross total resection, yet pineal region tumors associated with obstructive hydrocephalus may be surgically managed via ventricular internal shunt or endoscopic third ventriculostomy. Radiotherapy remains an essential component of the multidisciplinary treatment approach for most pineal region tumors; however, treatment volumes depend on the histological subtypes, grading, extent of disease, and the combination with chemotherapy. For localized germinoma, the current standard of care is chemotherapy followed by reduced-dose whole ventricular irradiation plus a boost to the primary tumor. For pinealoblastoma patients, postoperative radiation has been associated with higher overall survival. For the other pineal tumors, the role of radiotherapy remains poorly studied and it is usually reserved for aggressive (grade 3) or recurrent tumors. The use of systemic treatments mainly depends on histology and prognostic factors such as residual disease and metastases. For pinealoblastoma patients, chemotherapy protocols are based on various alkylating or platinum-based agents, vincristine, etoposide, cyclophosphamide and are used in association with radiotherapy. About GCTs, their chemosensitivity is well known and is based on cisplatin or carboplatin and may include etoposide, cyclophosphamide, or ifosfamide prior to irradiation. Similar regimens containing platinum derivatives are also used for non-germinomatous GCTs with very encouraging results. However, due to a greater understanding of the biology of the disease's various molecular subtypes, new agents based on targeted therapy are expected in the future. On behalf of the EURACAN domain 10 group, we reviewed the most important and recent developments in histopathological characteristics, neuro-radiological assessments, and treatments for pineal region tumors.

Keywords: EURACAN; pineal region tumors; pinealoblastoma; rare tumors.

Tumeur pinéale

› Brain Tumor Pathol. 2022 Jul;39(3):130-138. doi: 10.1007/s10014-021-00421-2. Epub 2022 Jan 9.

Role of proliferative marker index and KBTBD4 mutation in the pathological diagnosis of pineal parenchymal tumors

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Germinome pinéal

Cancers (Basel). 2022 Jul 21;14(14):3555. doi: 10.3390/cancers14143555.

Evaluation of the Perioperative and Postoperative Course of Surgery for Pineal Germinoma in the SIOP CNS GCT 96 Trial

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Background: CNS germinoma, being marker-negative, are mainly diagnosed by histological examination. These tumors predominantly appear in the suprasellar and/or pineal region. In contrast to the suprasellar region, where biopsy is the standard procedure in case of a suspected germ-cell tumor to avoid mutilation to the endocrine structures, pineal tumors are more accessible to primary resection. We evaluated the perioperative course of patients with pineal germinoma who were diagnosed by primary biopsy or resection in the SIOP CNS GCT 96 trial. Methods: Overall, 235 patients had germinoma, with pineal localization in 113. The relationship between initial symptoms, tumor size, and postoperative complications was analyzed. Results: Of 111 evaluable patients, initial symptoms were headache (n = 98), hydrocephalus (n = 93), double vision (n = 62), Parinaud syndrome (n = 57), and papilledema (n = 44). There was no significant relationship between tumor size and primary symptoms. A total of 57 patients underwent primary resection and 54 underwent biopsy. Postoperative complications were reported in 43.2% of patients after resection and in 11.4% after biopsy ($p < 0.008$). Biopsy was significantly more commonly performed on larger tumors ($p = 0.002$). Conclusions: These results support the practice of biopsy over resection for histological confirmation of pineal germinoma.

Keywords: SIOP CNS GCT 96 trial; biopsy; perioperative course; pineal germinoma; resection.

Pineal parenchymal tumors (PPTs) are clinically rare and a biopsy is often required for a definitive diagnosis. To improve the accuracy of histological assessment of PPTs, we examined the proliferative capacity of PPT cells and investigated DICER1 expression and KBTBD4 mutations. This study included 19 cases of PPTs [3 pineocytomas (PCs), 10 PPTs of intermediate differentiation (PPTID), and 6 pineoblastomas (PBs)]. Immunohistochemistry for Ki-67, PHH3, and DICER1, as well as Sanger sequencing analysis for KBTBD4 mutations, was performed using formalin-fixed paraffin-embedded tissue specimens that were resected during surgery. Tumor cell proliferation was quantified using an image analysis software. For the PHH3 and MIB-1 indices, a significant difference was observed between the PPTIDs and PBs ($P < 0.05$). Loss of DICER1 was not specific for PB; 0/3 PCs (0.0%), 2/9 PPTIDs (22.2%), and 2/4 PBs (50.0%). KBTBD4 mutations were detected in 1/3 PCs (33.3%), 6/9 PPTIDs (66.7%), and 0/4 PBs (0.0%). Thus, combined application of the proliferative marker index and KBTBD4 mutation analysis may be useful for the differential diagnosis of PPTs. Furthermore, detection of KBTBD4 mutations using Sanger sequencing analysis may support the diagnosis of PPTID.

Keywords: Differential diagnosis; KBTBD4 mutation; MIB-1; PHH3; Pineal parenchymal tumor.

Germinome

Clinical Trial > Neuro Oncol. 2022 Jun 1;24(6):974-983. doi: 10.1093/neuonc/noab270.

Phase II trial of response-based radiation therapy for patients with localized germinoma: a Children's Oncology Group study

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Background: The study aimed to evaluate whether simplified chemotherapy followed by dose-reduced irradiation was effective for treating patients (ages 3-21 years) with localized germinoma. The primary endpoint was 3-year progression-free survival (PFS) rate.

Methods: Patients with a complete response to chemotherapy with carboplatin and etoposide received 18 Gy WVI + 12 Gy boost to the tumor bed. Patients with partial response proceeded to 24 Gy WVI + 12 Gy. Longitudinal cognitive functioning was evaluated prospectively on ALTE07C1 and was a primary study aim.

Results: One hundred and fifty-one patients were enrolled; 137 were eligible. Among 90 evaluable patients, 74 were treated with 18 Gy and 16 with 24 Gy WVI. The study failed to demonstrate noninferiority of the 18 Gy WVI regimen compared to the design threshold of 95% 3-year PFS rate, where, per design, patients who could not be assessed for progression at 3 years were counted as failures. The Kaplan-Meier (KM)-based 3-year PFS estimates were 94.5 ± 2.7% and 93.75 ± 6.1% for the 18 Gy and 24 Gy WVI cohorts, respectively. Collectively, estimated mean IQ and attention/concentration were within normal range. A lower mean attention score was observed at 9 months for patients treated with 24 Gy. Acute effects in processing speed were observed in the 18 Gy cohort at 9 months which improved at 30-month assessment.

Conclusions: While a failure according to the prospective statistical noninferiority design, this study demonstrated high rates of chemotherapy responses, favorable KM-based PFS and OS estimates in the context of reduced irradiation doses and holds promise for lower long-term morbidities for patients with germinoma.

Keywords: braintumor; germinoma; response-based radiation.

Germinome

J Neurooncol. 2023 Apr;162(2):443-448. doi: 10.1007/s11060-023-04307-5. Epub 2023 Apr 11.

Time to dismiss boost? Outcomes of children with localized and metastatic germinoma

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Purpose: To determine long-term outcomes of a cohort of children with germinoma treated with chemotherapy and radiation therapy without primary tumor boost even in the absence of complete response to chemotherapy METHODS: This retrospective study analyzed the outcome of patients with germinoma consecutively diagnosed and treated at a tertiary care center from January 2000 to December 2021. MRIs were reviewed by two radiologists, blinded to patient data. Tumor location at diagnosis, tumor response to chemotherapy and at completion of radiation therapy and site of relapse were assessed. Tumor response was assessed radiologically by determining the tumor size and response on diffusion-weighted imaging, in addition to biochemical, cytological parameters and neurological status.

Results: Of 46 pediatric germinoma patients, 29 children (14 male; median age 12.8 years) received no primary tumor boost. Median follow-up was 63 months (range 9-187 months). Twenty-five children had localized disease and tumor location was suprasellar (n = 11), pineal (n = 10), bifocal (n = 3) and basal ganglia (n = 1) while 4 children had metastatic disease at presentation. All patients completed multi-agent chemotherapy followed by either ventricular irradiation (VI) (23.4 Gy) (n = 23), whole brain (WBI) (23.4 Gy) (n = 5) or craniospinal radiation (CSI) (23.4 Gy) (n = 1). Two children, who had localized disease at presentation and received VI after chemotherapy, relapsed 9 months and 32 months after completion of treatment respectively. No patient had a local relapse. Location of relapse was distant, outside (n = 1) and out- and inside (n = 1) the irradiation field. Five-year progression free survival (PFS) was 91% and overall survival (OS) was 100%.

Conclusions: In this case series, excellent 5-year PFS and OS rates were achieved with chemotherapy followed by radiation therapy of 23.4 Gy delivered without primary tumor boost. No local relapse was observed despite omitting primary tumor boost in patients with localized and metastatic germinoma.

Keywords: Germinoma; Primary tumor boost; Radiotherapy; Residual disease.

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- **MEDULLOBLASTOME**
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- ADENOME HYPOPHYSAIRE
- METASTASES CEREBRALES
- SCHWANNOME VESTIBULAIRE

Médulloblastome

Clinical Trial > Int J Cancer. 2023 Sep 1;153(5):1026-1034. doi: 10.1002/ijc.34569. Epub 2023 May 29.

A phase II trial of nifurtimox combined with topotecan and cyclophosphamide for refractory or relapsed neuroblastoma and medulloblastoma

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Children with relapsed/refractory (R/R) neuroblastoma (NB) and medulloblastoma (MB) have poor outcomes. We evaluated the efficacy of nifurtimox (Nfx) in a clinical trial for children with R/R NB and MB. Subjects were divided into three strata: first relapse NB, multiply R/R NB, and R/R MB. All patients received Nfx (30 mg/kg/day divided TID daily), Topotecan (0.75 mg/m^2 /dose, days 1-5) and Cyclophosphamide (250 mg/m^2 /dose, days 1-5) every 3 weeks. Response was assessed after every two courses using International Neuroblastoma Response Criteria and Response Evaluation Criteria in Solid Tumors (RECIST) criteria. One hundred and twelve eligible patients were enrolled with 110 evaluable for safety and 76 evaluable for response. In stratum 1, there was a 53.9% response rate (CR + PR), and a 69.3% total benefit rate (CR + PR + SD), with an average time on therapy of 165.2 days. In stratum 2, there was a 16.3% response rate, and a 72.1% total benefit rate, and an average time on study of 158.4 days. In stratum 3, there was a 20% response rate and a 65% total benefit rate, an average time on therapy of 105.0 days. The most common side effects included bone marrow suppression and reversible neurologic complications. The combination of Nfx, topotecan and cyclophosphamide was tolerated, and the objective response rate plus SD of 69.8% in these heavily pretreated populations suggests that this combination is an effective option for patients with R/R NB and MB. Although few objective responses were observed, the high percentage of stabilization of disease and prolonged response rate in patients with multiply relapsed disease shows this combination therapy warrants further testing.

Keywords: medulloblastoma; neuroblastoma; nifurtimox.

Médulloblastome et RT

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Research Letter

An Analysis of Major Target Deviations in Craniospinal Irradiation Treatment Plans for Patients With Intermediate-Risk Medulloblastoma Within a Phase 3 Clinical Trial (Children's Oncology Group Study ACNS0331)

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Purpose: Craniospinal irradiation remains an essential and yet difficult part of the treatment of patients with medulloblastoma. Whereas technological advances offer promise of increased conformity, realiance on advanced technology is not without risk, and it remains critical to carefully delineate targets. We describe examples of target deviations (TDs) in craniospinal irradiation treatment plans for postoperative patients with medulloblastoma in a phase 3 clinical trial (ACNS 0331).

Methods and materials: The principal investigator independently performed a review of the treatment plans and portal films of enrolled patients and evaluated the plans for TDs. TDs of dose, dose uniformity, and volume were defined as major or minor deviations. Major TDs scored as protocol violations. The effect of major TDs on event-free survival (EFS) and overall survival (OS) was evaluated using the stratified Cox proportional hazards model.

Results: Of the 549 patients enrolled, 461 were available for this analysis. Thirty-two (7%) plans did not have data sufficient for TD evaluation. Major TDs were found in 32 of the 461 plans (7%). Of those, 21 were deviations of target volume alone, 7 were deviations of target dose alone, and 4 were deviations of both target volume and dose. The 25 patients with TDs of volume involved 29 sites. The most common major TDs of volume involved the brain (9 of 29) and the posterior fossa (9 of 29). On Cox proportional hazards modeling, the presence of a major TD did not statistically significantly affect EFS (hazard ratio, 0.98; 95% confidence interval, 0.45-2.11; P = .9541) or OS (hazard ratio, 1.10; 95% confidence interval, 0.51-2.38; P = .8113).

Conclusions: Although intensity modulated radiation therapy and proton therapy are promising in improving conformity and sparing organs at risk, technology does not substitute for careful anatomic definition of target volumes. The study was not powered to evaluate the effect of TDs on EFS and OS; therefore, the statistical analysis presented in this study must be interpreted with caution.

Médulloblastome et risque moléculaire

Multicenter Study > Neuro Oncol. 2022 Jul 1;24(7):1166-1175. doi: 10.1093/neuonc/noab284.

Revised clinical and molecular risk strata define the incidence and pattern of failure in medulloblastoma following risk-adapted radiotherapy and dose-intensive chemotherapy: results from a phase III multi-institutional study

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Background: We characterize the patterns of progression across medulloblastoma (MB) clinical risk and molecular subgroups from SJMB03, a Phase III clinical trial.

Methods: One hundred and fifty-five pediatric patients with newly diagnosed MB were treated on a prospective, multi-center phase III trial of adjuvant radiotherapy (RT) and dose-intense chemotherapy with autologous stem cell transplant. Craniospinal radiotherapy to 23.4 Gy (average risk, AR) or 36-39.6 Gy (high risk, HR) was followed by conformal RT with a 1 cm clinical target volume to a cumulative dose of 55.8 Gy. Subgroup was determined using 450K DNA methylation. Progression was classified anatomically (primary site failure (PSF) +/- distant failure (DF), or isolated DF), and dosimetrically.

Results: Thirty-two patients have progressed (median follow-up 11.0 years (range, 0.3-16.5 y) for patients without progression). Anatomic failure pattern differed by clinical risk (P = .0054) and methylation subgroup (P = .0034). The 5-year cumulative incidence (CI) of PSF was 5.1% and 5.6% in AR and HR patients, respectively (P = .92), and did not differ across subgroups (P = .15). 5-year CI of DF was 7.1% vs. 28.1% for AR vs. HR (P = .0003); and 0% for WNT, 15.3% for SHH, 32.9% for G3, and 9.7% for G4 (P = .0024). Of 9 patients with PSF, 8 were within the primary site RT field and 4 represented SHH tumors.

Conclusions: The low incidence of PSF following conformal primary site RT is comparable to prior studies using larger primary site or posterior fossa boost volumes. Distinct anatomic failure patterns across MB subgroups suggest subgroup-specific treatment strategies should be considered.

Keywords: Group 3; Group 4; SHH; WNT; medulloblastoma.

Médulloblastome RT / cognition

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Association Between Brain Substructure Dose and Cognitive Outcomes in Children With Medulloblastoma Treated on SJMB03: A Step Toward Substructure–Informed Planning

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Purpose: To characterize the association between neurocognitive outcomes (memory and processing speed) and radiation (RT) dose to the hippocampus, corpus callosum (CC), and frontal white matter (WM) in children with medulloblastoma treated on a prospective study, SJMB03.

Patients and methods: Patients age 3-21 years with medulloblastoma were treated at a single institution on a phase III study. The craniospinal RT dose was 23.4 Gy for average-risk patients and 36-39.6 Gy for high-risk patients. The boost dose was 55.8 Gy to the tumor bed. Patients underwent cognitive testing at baseline and once yearly for 5 years. Performance on tests of memory (associative memory and working memory) and processing speed (composite processing speed and perceptual speed) was analyzed. Mixed-effects models were used to estimate longitudinal trends in neurocognitive outcomes. Reliable change index and logistic regression were used to define clinically meaningful neurocognitive decline and identify variables associated with decline.

Results: One hundred and twenty-four patients were eligible for inclusion, with a median neurocognitive follow-up of 5 years. Mean right and left hippocampal doses were significantly associated with decline in associative memory in patients without posterior fossa syndrome (all $P <$ .05). Mean CC and frontal WM doses were significantly associated with decline in both measures of processing speed (all $P <$ .05). Median brain substructure dose-volume histograms were shifted to the right for patients with a decline in associative memory or processing speed. The odds of decline in associative memory and composite processing speed increased by 23%-26% and by 10%-15% for every 1-Gy increase in mean hippocampal dose and mean CC or frontal WM dose, respectively.

Conclusion: Increasing RT dose to the CC or frontal WM and hippocampus is associated with worse performance on tests of processing speed and associative memory, respectively. Brain substructure-informed RT planning may mitigate neurocognitive impairment.

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Méningiome et évaluation réponse

Clinical Trial › Ther Innov Regul Sci. 2023 May;57(3):603-610. doi: 10.1007/s43441-022-00494-x.
Epub 2023 Jan 5.

Efficacy Endpoints in Phase II Clinical Trials for Meningioma: An Analysis of Recent Clinical Trials

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Background: Response Evaluation Criteria in Solid Tumors (RECIST)-based response rates are commonly used as efficacy endpoints in phase II clinical trials for solid tumors. However, no consensus has been reached concerning adequate efficacy endpoints for phase II clinical trials targeting meningioma. Irregularity of lesions after resection, and varying degrees of dysplasia and histologic subtypes make establishing an appropriate efficacy evaluation difficult.

Methods: We analyzed primary efficacy endpoints (PEEs) and background factors from 48 trials retrieved from ClinicalTrials.gov (https://clinicaltrials.gov/) using the search criteria "meningioma," "interventional," "phase II," and "study start 4/1/2001 to 3/31/2021." Primary purpose of the study was efficacy endpoint setting in overall population and three subgroups.

Results: Among 45 PEEs set in the 39 trials included 33 trials with single PEE, and six trials with double PEEs, 17/45 (38%) trials adopted progression-free survival (PFS) rate, 15/45 (33%) trials response rate (seven Macdonald criteria or modified, three RECIST, three volumetric estimation, one RANO criteria, one unknown), 10/45 (22%) PFS, 1/45 (2%) OS, and 2/45 (4%) other endpoints. Although 26 PEEs were time-to-event endpoints, 19 of the 26 PEEs were single-arm studies.

Conclusions: Time-to-event efficacy endpoints were often compared to historical data, and two-dimensional evaluation is more suitable than one-dimensional one. Accumulation of prognostic data is essential to standardize time-to-event efficacy endpoints. Considering the difficulty of setting design for phase II clinical studies targeting meningioma, evaluation might be done with multiple efficacy endpoints.

Keywords: Brain tumor; Efficacy endpoint; Meningioma; Phase II clinical trial; Regulatory science.

Méningiome et Bévacizumab

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A multi-institutional phase II trial of bevacizumab for recurrent and refractory meningioma

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Background: Systemic therapies for refractory meningiomas are limited with no FDA-approved therapeutics. Vascular endothelial growth factor (VEGF) is a signaling protein associated with neovascularization, peritumoral edema, and meningioma tumorigenesis.

Methods: This phase II study investigates the efficacy of bevacizumab (BEV), a VEGF binding monoclonal antibody, in patients with progressive Grade I (G1M), Grade II (G2M), Grade III (G3M) meningioma, and other non-parenchymal tumors including vestibular schwannoma (*n* = 4) and hemangiopericytoma (*n* = 4) with the primary endpoint of progression-free survival rate at 6-months (PFS-6). Non-meningiomas were included with the respective meningioma grade in the analysis. Secondary endpoints include median overall survival (mOS) and response rate.

Results: Fifty Patients (26 women; median age 54 years; range 23-81), 42 with progressive meningioma were treated: 10 G1M, 20 G2M, and 12 G3M. Prior treatments include surgical resection (41 patients), radiosurgery (24 patients), external beam radiotherapy (28 patients), and chemotherapy (14 patients). Median infusions administered were 16 (range, 2-68). Response was graded using the Macdonald's criteria. PFS-6, median PFS, and mOS were 87%, 22 months, 35 months for G1M; 77%, 23 months, 41 months for G2M; and 46%, 8 months, 12 months for G3M. Best radiographic responses include stable disease (G1M: 100%; G2M: 85%; G3M: 82%); partial response (G1M: 0%; G2M: 5%; G3M: 0%) and progressive disease (G1M: 0%; G2M: 10%; G3M:18%). The most common toxicities were hypertension (*n* = 19, 42.2%), proteinuria (*n* = 16, 35.6%), and fatigue (*n* = 14, 31.1%).

Conclusion: This study showed BEV is well tolerated and appears to be a promising systemic treatment option for patients with recurrent and refractory meningiomas.

Keywords: anti-angiogenic; bevacizumab; dural tumors; hemangiopericytoma; high-grade meningioma; meningioma; solitary fibrous tumor.

Méningiome et radiochirurgie

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Hypofractionated Radiosurgery for Large or in Critical-Site Intracranial Meningioma: Results of a Phase 2 Prospective Study

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Purpose: Radiosurgery is a well-known, safe, and effective technique used in the treatment of intracranial meningiomas. However, single-fraction radiosurgery can lead to high toxicity rates when large-volume or critically located lesions are targeted. Multisession-also called hypofractionated-radiosurgery (hypo-RS) might overcome these limitations. Accordingly, we carried out a prospective phase 2 trial, aiming to establish whether a fractionated RS schedule of 25 Gy in 5 fractions would be safe and effective in treating large (≥ 3 cm) and/or critically located (<3 mm from critical structures) grade 1 intracranial meningiomas. The main aim was to evaluate the safety of hypo-RS in terms of absence of adverse events. The secondary aim was to evaluate tumor response in terms of local control, defined as stability or reduction of lesion volume.

Methods and materials: We prospectively enrolled patients with diagnoses of grade 1 meningiomas, large size and/or critically located lesions, either histologically diagnosed or imaging defined. Additional inclusion criteria were signed informed consent, an age of ≥18 years, and Karnofsky Performance Status ≥70.

Results: Between 2011 and 2016, 178 patients were consecutively enrolled. The median follow-up was 53 months (range, 4-101 months). Overall, the toxicity rate was 12.7% (21 of 166 patients). At a 5-year minimum follow-up, the patients' toxicity rates were 11.7 % (9 of 77 patients). Symptom evaluation at both 3-year and last follow-up showed an improvement in most of the patients. Five-year local tumor control was 97% (95% confidence interval, 92%-99%).

Conclusions: Hypo-RS schedule of 25 Gy in 5 fractions is a well-tolerated option in the treatment of large-volume and/or critically located benign meningiomas. Early results suggest favorable local control, although longer-term follow-up is needed.

Méningiome de bas risque

Clinical Trial > Neuro Oncol. 2023 Jan 5;25(1):137-145. doi: 10.1093/neuonc/noac137.

Low-risk meningioma: Initial outcomes from NRG Oncology/RTOG 0539

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Background: Three- and five-year progression-free survival (PFS) for low-risk meningioma managed with surgery and observation reportedly exceeds 90%. Herewith we summarize outcomes for low-risk meningioma patients enrolled on NRG/RTOG 0539.

Methods: This phase II trial allocated patients to one of three groups per World Health Organization grade, recurrence status, and resection extent. Low-risk patients had either gross total (GTR) or subtotal resection (STR) for a newly diagnosed grade 1 meningioma and were observed after surgery. The primary endpoint was 3-year PFS. Adverse events (AEs) were scored using Common Terminology Criteria for Adverse Events (CTCAE) version 3.

Results: Among 60 evaluable patients, the median follow-up was 9.1 years. The 3-, 5-, and 10-year rates were 91.4% (95% CI, 84.2 to 98.6), 89.4% (95% CI, 81.3 to 97.5), 85.0% (95% CI, 75.3 to 94.7) for PFS and 98.3% (95% CI, 94.9 to 100), 98.3%, (95% CI, 94.9 to 100), 93.8% (95% CI, 87.0 to 100) for overall survival (OS), respectively. With centrally confirmed GTR, 3/5/10y PFS and OS rates were 94.3/94.3/87.6% and 97.1/97.1/90.4%. With STR, 3/5/10y PFS rates were 83.1/72.7/72.7% and 10y OS 100%. Five patients reported one grade 3, four grade 2, and five grade 1 AEs. There were no grade 4 or 5 AEs.

Conclusions: These results prospectively validate high PFS and OS for low-risk meningioma managed surgically but raise questions regarding optimal management following STR, a subcohort that could potentially benefit from adjuvant therapy.

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Hémangiopéricytome

Case Reports > J Investig Med High Impact Case Rep. 2022 Jan-Dec:10:23247096221132244.
doi: 10.1177/23247096221132244.

Liver Metastasis From Intracranial Hemangiopericytoma 8 Years After Initial Resection: Case Report

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Solitary fibrous tumor/hemangiopericytoma (SFT/HPC) is a rare intracranial tumor that arises from pericytes surrounding the blood vessels. Solitary fibrous tumor/hemangiopericytoma accounts for less than 1% of primary brain tumors and is classified as grades I, II, or III based on mitotic count. These tumors often masquerade as meningiomas. Histologically, SFT/HPC is vascular with high cellularity and often surrounded by connective tissue. Immunohistochemistry is positive for stat 6, vimentin, and CD34. Although aggressive surgical resection is the mainstay of treatment, close long-term follow-up is necessary as recurrence or extra cranial metastasis can present several years after resection.

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Adénome hypophysaire

Review > Best Pract Res Clin Endocrinol Metab. 2022 Dec;36(6):101712.
doi: 10.1016/j.beem.2022.101712. Epub 2022 Oct 12.

Immunotherapy in pituitary carcinomas and aggressive pituitary tumors

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After temozolomide failure, no evidence-based treatment option is currently available for aggressive pituitary tumors (APTs) and pituitary carcinomas (PCs). Moreover, once temozolomide has failed, the survival of these patients is very poor. The use of immune-checkpoint inhibitors (ICIs) has been so far reported in a large cohort, a small phase 2 clinical trial and in another five isolated cases (24 cases in total). Here, we review the available evidence on the efficacy and potential predictors of response to ICIs in PCs and APTs, namely the histological type (corticotroph versus lactotroph), the tumor type (PC versus APT), the presence of uncontrolled endogenous hypercortisolism, the type of protocol (combined ICIs versus monotherapy), programmed death-ligand 1 (PD-L1) expression, CD8+ cell infiltration, tumor mutational burden (TMB), microsatellite instability (MSI), and mismatch repair (MMR) status. We also discuss key clinical aspects that can already be implemented in the everyday practice and identify future research needs.

Keywords: CD8+ cell infiltration; corticotroph; immune-checkpoint inhibitors; lactotroph; programmed death-ligand 1 (PD-L1) expression; tumor mutational burden (TMB).

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Métastases cérébrales

Clinical Trial > JAMA Oncol. 2022 Dec 1;8(12):1809-1815. doi: 10.1001/jamaoncol.2022.5049.

Association of Long-term Outcomes With Stereotactic Radiosurgery vs Whole-Brain Radiotherapy for Resected Brain Metastasis: A Secondary Analysis of The N107C/CEC.3 (Alliance for Clinical Trials in Oncology/Canadian Cancer Trials Group) Randomized Clinical Trial

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Importance: Long-term outcomes of radiotherapy are important in understanding the risks and benefits of therapies for patients with brain metastases.

Objective: To determine how the use of postoperative whole-brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS) is associated with quality of life (QOL), cognitive function, and intracranial tumor control in long-term survivors with 1 to 4 brain metastases.

Design, setting, and participants: This secondary analysis of a randomized phase 3 clinical trial included 48 institutions in the US and Canada. Adult patients with 1 resected brain metastases but limited to those with 1 to 4 brain metastasis were eligible. Unresected metastases were treated with SRS. Long-term survivors were defined as evaluable patients who lived longer than 1 year from randomization. Patients were recruited between July 2011 and December 2015, and data were first analyzed in February 2017. For the present study, intracranial tumor control, cognitive deterioration, QOL, and cognitive outcomes were measured in evaluable patients who were alive at 12 months from randomization and reanalyzed in June 2017.

Interventions: Stereotactic radiosurgery or WBRT.

Main outcomes and measures: Intracranial tumor control, toxic effects, cognitive deterioration, and QOL.

Results Fifty-four patients (27 SRS arm, 27 WBRT arm; female to male ratio, 65% vs 35%) were included for analysis with a median follow-up of 23.8 months. Cognitive deterioration was less frequent with SRS (37%-60%) compared with WBRT (75%-91%) at all time points. More patients declined by 2 or more standard deviations (SDs) in 1 or more cognitive tests for WBRT compared with SRS at 3, 6, and 9 months (70% vs 22%, 46% vs 19%, and 50% vs 20%, respectively). A 2 SD decline in at least 2 cognitive tests was associated with worse 12-month QOL in emotional well-being, functional well-being, general, additional concerns, and total scores. Overall QOL and functional independence favored SRS alone for categorical change at all time points. Total intracranial control for SRS alone vs WBRT at 12 months was 40.7% vs 81.5% (difference, -40.7; 95% CI, -68.1% to -13.4%), respectively. Data were first analyzed in February 2017.

Conclusions and relevance: The use o SRS alone compared with WBRT resulted in less cognitive deterioration among long-term survivors. The association of late cognitive deterioration with WBRT was clinically meaningful. A significant decline in cognition (2 SD) was associated with overall QOL. However, intracranial tumor control was improved with WBRT. This study provides detailed insight into cognitive function over time in this patient population.

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Schwannome NF2 et Bévacizumab

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Multicenter, prospective, phase II study of maintenance bevacizumab for children and adults with NF2–related schwannomatosis and progressive vestibular schwannoma

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Background: Prospective data on maintenance therapy with bevacizumab for persons with NF2-related schwannomatosis (NF2-SWN) is lacking. In this prospective multicenter phase II study, we evaluated the efficacy, safety, and tolerability of bevacizumab for maintenance therapy in children and adults with NF2-SWN and hearing loss due to vestibular schwannomas (VS).

Methods: Following induction therapy, participants received bevacizumab 5 mg/kg every 3 weeks for 18 months. Participants were monitored for changes in hearing, tumor size, and quality of life (QOL), and for adverse events. Hearing loss was defined as a statistically significant decline in word recognition score (WRS) or pure-tone average compared to the study baseline; tumor growth was defined as >20% increase in volume compared to baseline.

Results: Twenty participants with NF2-SWN (median age 23.5 years; range, 12.5-62.5 years) with hearing loss in the target ear (median WRS 70%, range 2%-94%) received maintenance bevacizumab. Freedom from hearing loss in the target ear was 95% after 48 weeks, 89% after 72 weeks, and 70% after 98 weeks. Freedom from tumor growth in the target VS was 94% after 48 weeks, 89% after 72 weeks, and 89% after 98 weeks. NF2-related QOL remained stable for 98 weeks whereas tinnitus-related distress decreased. Maintenance bevacizumab was well tolerated, with 3 participants (15%) discontinuing treatment due to adverse events.

Conclusions: Maintenance bevacizumab (5 mg/kg every 3 weeks) is associated with high rates of hearing and tumor stability during 18 months of follow-up. No new unexpected adverse events related to bevacizumab were identified in this population.

Keywords: NF2; bevacizumab; maintenance; neurofibromatosis 2; vestibular schwannoma.

Schwannome

Clinical Trial > Neurosurgery. 2022 May 1;90(5):506-514. doi: 10.1227/neu.0000000000001869.

Fractionated Proton Radiation Therapy and Hearing Preservation for Vestibular Schwannoma: Preliminary Analysis of a Prospective Phase 2 Clinical Trial

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Background: Local management for vestibular schwannoma (VS) is associated with excellent local control with focus on preserving long-term serviceable hearing. Fractionated proton radiation therapy (FPRT) may be associated with greater hearing preservation because of unique dosimetric properties of proton radiotherapy.

Objective: To investigate hearing preservation rates of FPRT in adults with VS and secondarily assess local control and treatment-related toxicity.

Methods: A prospective, single-arm, phase 2 clinical trial was conducted of patients with VS from 2010 to 2019. All patients had serviceable hearing at baseline and received FPRT to a total dose of 50.4 to 54 Gy relative biological effectiveness (RBE) over 28 to 30 fractions. Serviceable hearing preservation was defined as a Gardner-Robertson score of 1 to 2, measured by a pure tone average (PTA) of ≤50 dB and a word recognition score (WRS) of ≥50%.

Results: Twenty patients had a median follow-up of 4.0 years (range 1.0-5.0 years). Local control at 4 years was 100%. Serviceable hearing preservation at 1 year was 53% (95% CI 29%-76%), and primary end point was not yet reached. Median PTA and median WRS both worsened 1 year after FPRT ($P < .0001$). WRS plateaued after 6 months, whereas PTA continued to worsen up to 1 year after FPRT. Median cochlea D90 was lower in patients with serviceable hearing at 1 year (40.6 Gy [RBE] vs 46.9 Gy [RBE]), trending toward Wilcoxon rank-sum test statistical significance ($P = .0863$). Treatment was well tolerated, with one grade 1 cranial nerve V dysfunction and no grade 2+ cranial nerve dysfunction.

Conclusion: FPRT for VS did not meet the goal of serviceable hearing preservation. Higher cochlea doses trended to worsening hearing preservation, suggesting that dose to cochlea correlates with hearing preservation independent of treatment modality.