Journée scientifique SNOB
Société de
Neuro-Oncologie Bretonne

Actualités en Neuro-Oncologie

Docteur Elodie VAULEON

Saint-Malo, le 04/10/2024

Actualités en Neuro-Oncologie

- **Présentations lors congrès 2024**
- **Publications de 2023-2024**
- GLIOBLASTOME
- GLIOME DE BAS GRADE
- GLIOME DE LA LIGNE MEDIANE et du TRONC
- ASTROBLASTOME
- XANTHOASTROCYTOME
- EPENDYMOME
- Tumeur des PLEXUS CHOROIDES
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Meeting Abstract: 2024 ASCO Annual Meeting I
FREE ACCESS | Central Nervous System Tumors | May 29, 2024

The TAC-GReD trial: The combination of talazoparib and carboplatin in DNA damage repair deficient recurrent high-grade glioma.

Authors: Marc Lecoultre, Peter Yat Ming Woo, Gilberto Leung, Shuk Wan Joyce Chow, Jason Ho, Ji Hyung Hong, Chi Leung Chiang, Dennis Kwok Chuen Leung, Tai-Chung Lam, and Aya EL Helali | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 42, Number 16_suppl • https://doi.org/10.1200/JCO.2024.42.16_suppl.2047

- **Background:** Recurrent high-grade glioma (rHGG) has a dismal prognosis with limited treatment options. Given that a high proportion of these gliomas harbor deficiencies in the DNA damage repair (**DDRd) pathway**, this genomic occurrence may confer synergistic lethality and sensitivity to poly (ADP-ribose) polymerase **(PARP) inhibitors**. Therefore, we hypothesize that DDRd rHGG may be sensitive to the combination of a PARP inhibitor, talazoparib, and carboplatin.
- **Methods:** This is a prospective phase II, single-arm open-label biomarker stratified single-institution trial conducted in Hong Kong (NCT04740190). Tumor tissue was sent for comprehensive next-generation sequencing (C-NGS) to screen for genomic aberrations associated with the DDRd pathway. Patients with rHGG (WHO grade III-IV) and at least one pathogenic mutation in the DDR pathway were deemed eligible. Patients were initially treated with whole-brain radiotherapy (2 Gy/1 Fr) on C1D1. Starting at dose level 0, talazoparib (0.75mg on Days 1-4) and carboplatin (AUC 1.5 on Day 1), were administered weekly for a total of 18 cycles, followed by maintenance talazoparib. The primary endpoint was the 6-month progression-free survival (PFS-6).
- **Results:** 61 patients were screened and 33 patients with DDRd rHGG were enrolled, 23 males, 10 females, and a median age of 55 years (range: 29-70 years). 73% (n=24) had a baseline ECOG PS of 0-1. Among the recruited patients, 12% (n=4) were classified as WHO grade III, while the remaining 88% (n=29) were WHO grade IV. Dose level escalation was achieved in 27% (n=9) of the cohort. The 6-PFS was 29% (95% CI 16.2-51.9%) and the median PFS was 3.5 months (95% CI: 2.4-6.3 months). The OS at 3 and 12 months were 90.4% (95% CI 80.7-100%) and 30% (95% CI 17-53%), respectively. The most common grade 3-4 toxicities were neutropenia (21.2%, n=7), thrombocytopenia (18.2%, n=6) and anemia (9.1%, n=3). One patient developed a grade 4 thromboembolic event. Dose level reduction was implemented in 54% (n=18) of patients and treatment was terminated in 6.1% (n=2) due to toxicity.
- **Conclusions: Talazoparib and carboplatin in a DDRd-enriched rHGG is feasible and tolerable.** Additional analysis including correlation of biomarkers with long-term outcomes is underway.

Meeting Abstract: 2024 ASCO Annual Meeting I
FREE ACCESS | Central Nervous System Tumors | May 29, 2024

Niraparib efficacy in patients with newly-diagnosed glioblastoma: Clinical readout of a phase 0/2 "trigger" trial.

Authors: Nader Sanai, Yoshie Umemura, Tigran Margaryan, Jennifer Molloy, Hualin Zhang, William Knight, Jocelyn Harmon, ... SHOW ALL ..., and Shwetal Mehta | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 42, Number 16_suppl • https://doi.org/10.1200/JCO.2024.42.16_suppl.2002

Background: Poly (ADP-ribose) polymerase (PARP) mediates DNA damage response; niraparib is an investigational PARP1/2-selective inhibitor. This Phase 0 study evaluates newly-diagnosed glioblastoma (GBM) tumor pharmacokinetics (PK) and pharmacodynamics (PD), graduating patients with O6-methylguanine methyltransferase (MGMT) unmethylated tumors into a therapeutic regimen of niraparib plus fractionated radiotherapy when PK threshold is met.

Methods: Presumed newly-diagnosed GBM patients received 4 days of **niraparib (300/200 mg QD) prior to planned resection 3-5 (cohort 1)** or 8-10 hours (cohort2) following the last dose. Tumor tissue (Gadolinium enhancing and non-enhancing regions), cerebrospinal fluid (CSF), and plasma were collected. Total and unbound niraparib concentrations were measured using validated LC-MS/MS methods. PARP inhibition was assessed by quantification of PAR induction after *ex vivo* irradiation of surgical vs non-irradiated tissue. A PK 'trigger' determined eligibility for the Phase 2 component of the study and was defined as unbound [niraparib] > 5-fold biochemical IC50 (i.e., 19 nM) in non-enhancing tumor. Patients with MGMT unmethylated tumors in excess of the PK threshold were eligible for Phase 2 dosing of niraparib plus radiotherapy followed by a maintenance phase of niraparib monotherapy.

Results: All Phase 0 patients (n=46) met the PK threshold. In non-enhancing tumor regions, the mean unbound concentration of niraparib was 335.1 nM (n=43) for cohort 1 and 331.9 nM (n=3) for cohort 2. PAR suppression after ex vivo radiation was observed in 73% of the patients (24/33). Nineteen of 27 (70.3%) patients with unmethylated tumors were enrolled into Phase 2. Five patients in Phase 2 experienced Grade 4 thrombocytopenia related to niraparib. All adverse events resolved without sequelae. At time of data cutoff, median progression-free survival was 11.7 months. Mature overall survival (OS) data will be reported for the first time.

Conclusions: Niraparib achieves pharmacologically relevant concentrations in non-enhancing, newly-diagnosed GBM tissue in excess of any other studied PARP inhibitor. Accompanying PD effects were observed in patient tumor tissue. For the first time, we report on the clinical efficacy of the study.

A global phase 3, open-label, randomized 2-arm study comparing niraparib versus temozolomide in adult patients with newly diagnosed, MGMT unmethylated glioblastoma is being planned.

Meeting Abstract: 2024 ASCO Annual Meeting I
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A phase I trial on the intra- and post-operative intracranial administration of ipilimumab and nivolumab in patients with recurrent high-grade glioma.

Authors: Bart Neyns, Iris Dirven, Louise Lescrauwaet, Jacomi Del'haye, Wietse Geens, Xenia Geeraerts, Latoya Stevens, ... SHOW ALL ..., and Johnny Duerinck | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 42, Number 16_suppl • https://doi.org/10.1200/JCO.2024.42.16_suppl.2037

Background: Intracerebral (iCer) administration (admin) of ipilimumab (IPI) and nivolumab (NIVO) plus IV NIVO following resection of recurrent high-grade glioma (rHGG) was well tolerated and showed encouraging overall survival (OS) (J. Duerinck et al. JITC 2021). The safety of additional postoperative (postop) bi-weekly intracavitary (iCav) admin of NIVO or NIVO + IPI (: first in human intracranial CTLA-4 blockade) was investigated in a phase I trial (3+3 design with cohort expansion).

Methods: Within 24h prior to surgery, 10 mg NIVO IV was admin, followed by a maximal safe resection and injection of the brain tissue lining the resection cavity with 5 mg IPI + 10 mg NIVO, and positioning of a catheter in the resection cavity connected to an Ommaya reservoir.
Only in patients (pts) receiving postop iCav IPI, 10 mg NIVO and 5 mg IPI were admin via the Ommaya at the end of surgery.
Postop 1, 5, or 10 mg NIVO was admin iCav as a single agent. In subsequent pts, postop 10 mg iCav NIVO was combined with 1, 5 or 10 mg iCav IPI. All postop iCav admin were combined with NIVO 10 mg IV, and repeated Q2w (< 24w). On-treatment CSF samples were used for cytology, chemical analysis, and measurements of NIVO/IPI concentrations.

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A phase I trial on the intra- and post-operative intracranial administration of ipilimumab and nivolumab in patients with recurrent high-grade glioma.

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Publication: Journal of Clinical Oncology • Volume 42, Number 16_suppl • https://doi.org/10.1200/JCO.2024.42.16_suppl.2037

Results: 43 pts (32 male) initiated treatment, all receiving the predefined pre- and intraop doses of IV and iCer IPI/NIVO. No unexpected AE related to the intraop treatment occurred. Postop treatment was initiated in 39 pts, all receiving 10 mg NIVO IV Q2w. Postop NIVO IV was combined with iCav NIVO 1, 5 or 10 mg in 3, 4, and 9 pts. The median number of postop IV/iCav NIVO admin was 7 (3-7), 4.5 (0-11), and 2 (1-11), resp. Next, postop iCav NIVO 10 mg was combined with iCav IPI 1, 5 or 10 mg in 10, 6, and 11 pts. The median number of postop IV/iCav NIVO + IPI admin was 3 (0-12), 4 (1-11), and 4 (0-12), resp. Dose limiting toxicity consisted of transient grade 3 aseptic neutrophilic pleocytosis with pyrexia and neurological deterioration in 1 and 3 pts treated with 5 and 10 mg IPI iCav, resp. Most frequent TRAEs were fatigue (n=24), headache (n=19), fever (n=17), and bacterial Ommaya colonization (n=11). No grade 5 AE occurred. At database lock, all pts were off study treatment, 1 pt stayed progression-free, and 5 were alive (mFU 80w (31-140)).
OS compared favorably against a Belgian historical control cohort (469 pts; log rank p: 0.010) with an improved 1 and 2y OS rate (33 vs. 18.6% and 11.7 vs. 5.7%, resp.). Adding iCav IPI postop did not significantly alter PFS or OS. There was an elevated protein level and lymphocytic pleocytosis in >90% of CSF samples and no evidence for NIVO accumulation in the CSF (IPI under evaluation).

Conclusions: In this first in human phase I trial on intracranial CTLA-4/PD-1 blockade in pts with rHGG amenable for resection, intraop iCer and postop iCav admin of NIVO+/- IPI was found to be feasible and safe up to a bi-weekly postop iCav dose of 1 mg IPI + 10 mg NIVO; with encouraging OS results.

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Meeting Abstract: 2024 ASCO Annual Meeting I
FREE ACCESS | Central Nervous System Tumors | May 29, 2024

INB-200: Fully enrolled phase 1 study of gene-modified autologous gamma-delta (γδ) T cells in patients with newly diagnosed glioblastoma multiforme (GBM) receiving maintenance temozolomide (TMZ).

Authors: Mina Lobbous, Trishna Goswami, Lawrence S. Lamb Jr., Kate Rochlin, Thriumaine Pillay, Mariska ter Haak, and Louis B. Nabors | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 42, Number 16_suppl • https://doi.org/10.1200/JCO.2024.42.16_suppl.2042

Background: γδ T cells can target NKG2D ligands that are upregulated on tumor cells after alkylating chemotherapy exposure. IN8bio's DeltEx drug resistant immunotherapy (DRI) are **genetically engineered γδ T cells expressing methylguanine-DNA methyltransferase (MGMT),** which conveys TMZ resistance to enable concomitant therapy and continued surveillance against tumor cells. Updated results from the Phase 1 trial which fully enrolled adult newly diagnosed **GBM** patients with adequate organ function, KPS ≥ 70% follow.

Methods: Cohorts (C) 1, 2 and 3 received 1, 3 or 6 doses (1 x 10^7 DRI cells/dose) into the resection cavity with 150 mg/m^2 of IV TMZ on Day (D) 1 of each Stupp maintenance cycle. The primary endpoint is **safety** and secondary endpoints include survival; immunologic correlative analyses are included. Dose limiting toxicities (DLTs) are defined as treatment related ≥ grade (G) 3 cardiopulmonary or hepatic toxicity, G4 toxicity exceeding 72 hours or neurologic deterioration that exceeds 2 weeks.

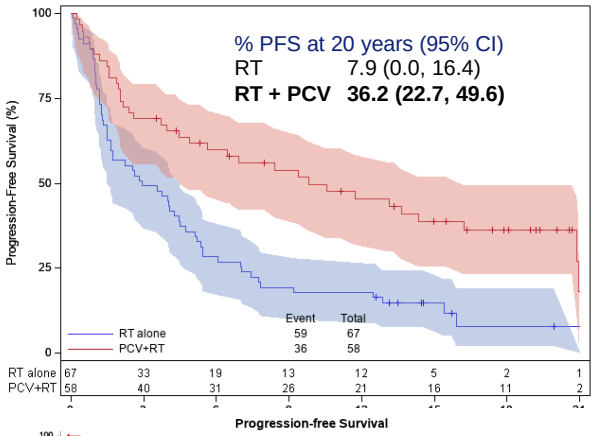
Results: **23** patients were enrolled, with 11 dosed and 2 awaiting dosing (61% male; median age 68 (range: 21-74); 92% IDH-WT, **54% MGMT unmethylated**). No DLTs, cytokine release syndrome (CRS) or neurotoxicity (ICANS) are reported. Most common adverse events were **decreased WBC/platelet count**, asthenia, fatigue, hydrocephalus, headache, decreased appetite, urinary tract infection, thrombosis and balance disorder.

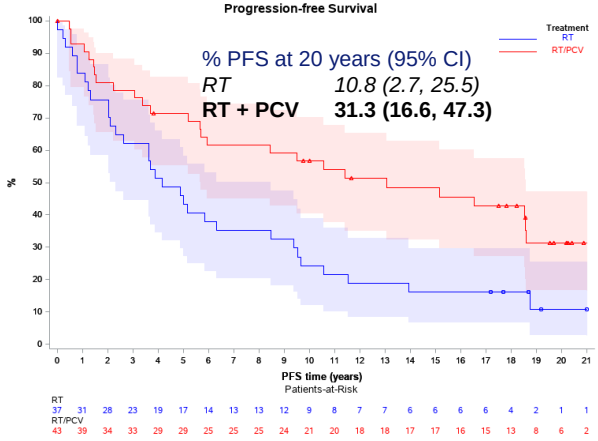
Conclusions: γδ T cells successfully infused with peripheral TMZ-based lymphodepletion evidenced with near or below normal range T, B, and NK subsets for up to 1 year. The majority of dosed patients who received DRI exceeded the expected median PFS of 7 months (5.8-8.2 months) with Stupp alone and **had manageable toxicity with a continued encouraging trend in PFS**. Long-term follow-up for durability of PFS and OS continue.

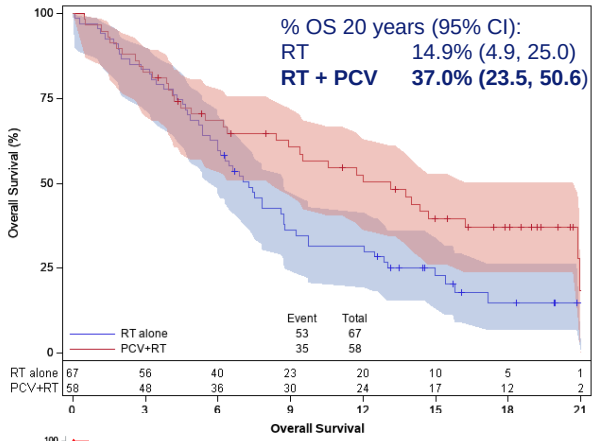
15 ans du réseau

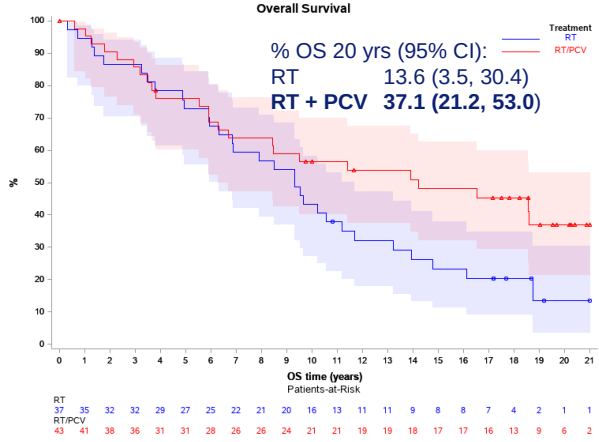
pola

RTOG 9402 + EORTC 26951: RT and PCV in 1p/19q codel oligodendroglioma : very long term follow-up









RTOG 9402:
RT vs PCVi + RT

EORTC 26951:
RT vs RT+ PCV

Lassman, van den Bent et al,
J Clin Oncol 2022;40:2539-45

Survival outcomes associated with first-line PCV or temozolomide in combination with radiotherapy in IDH-mutant 1p/19q-codeleted grade 3 oligodendroglioma

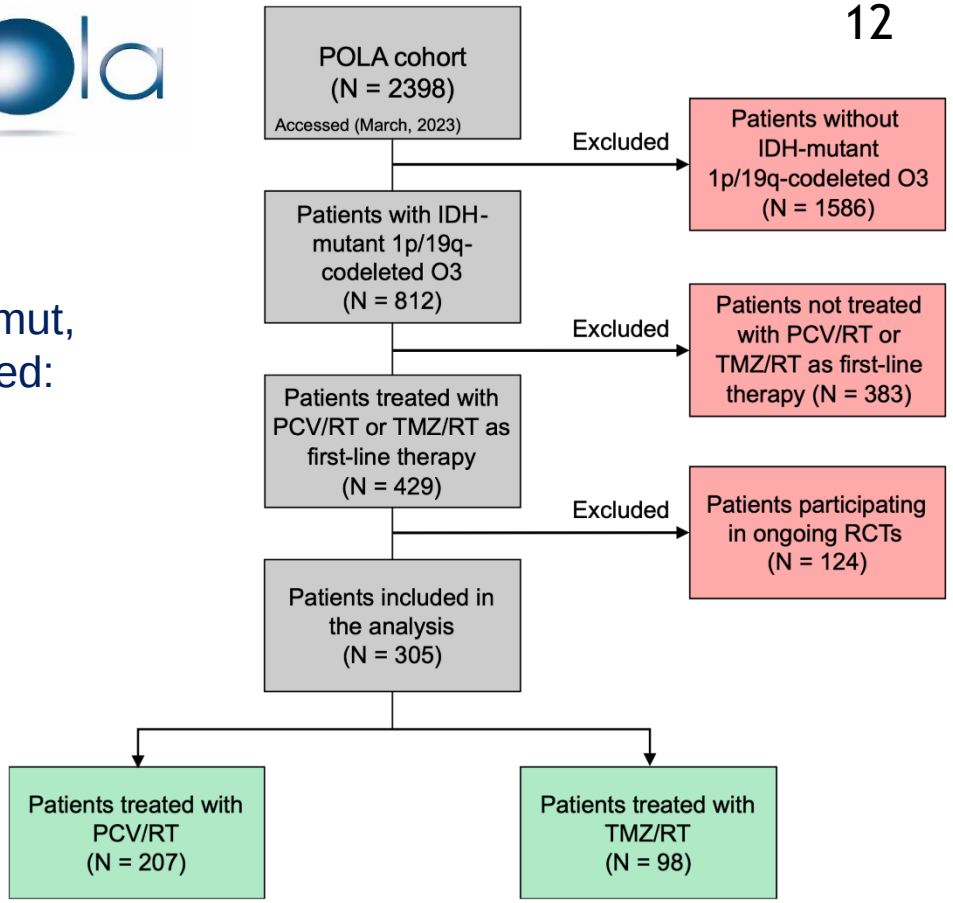
Salah Eddine O. Kacimi, Caroline Dehais, Loïc Feuvret, Olivier Chinot, Catherine Carpentier, Charlotte Bronnimann, Elodie Vauleon, Apolline Djelad, Elizabeth Cohen-Jonathan Moyal, Olivier Langlois, Mario Campone, Mathilde Ducloie, Georges Noel, Stefania Cuzzubbo, Luc Taillandier, Carole Ramirez, Nadia Younan, Philippe Menei, Frédéric Dhermain, Christine Desenclos, François Ghiringhelli, Veronique Bourg, Damien Ricard, Thierry Faillot, Romain Appay, Emeline Tabouret, Lucia Nichelli, Bertrand Mathon, Alice Thomas, Suzanne Tran, Franck Bielle, Agusti Alentorn, J Bryan Iorgulescu, Pierre-Yves Boëlle, Karim Labreche, Khê Hoang-Xuan, Marc Sanson, Ahmed Idbaih, Dominique Figarella-Branger, François Ducray, Mehdi Touat, ***POLA Network***

Presented by: Salah Eddine O. Kacimi, MD
Paris Brain Institute (ICM), Paris
Supervision: Mehdi Touat, MD, PhD

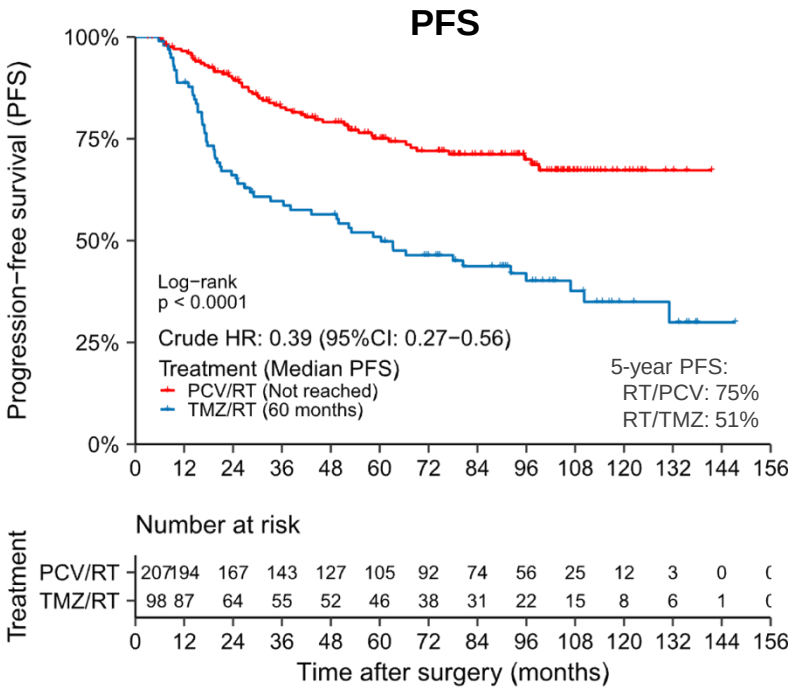
Results

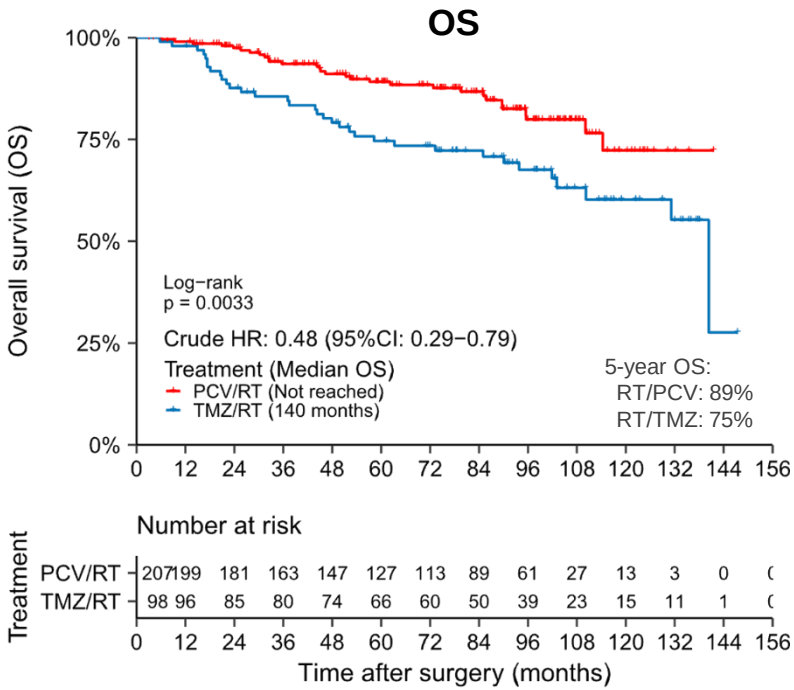
305 pts with newly-diagnosed grade 3, IDH-mut, 1p/19q codel oligodendroglioma were included:

- 207 treated with RT/PCV
- 98 treatd with RT/TMZ

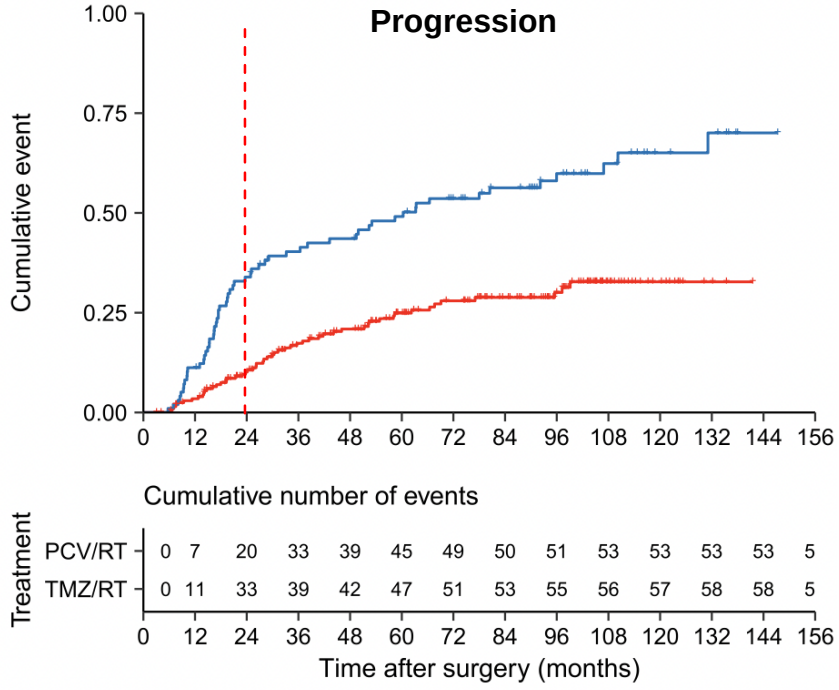


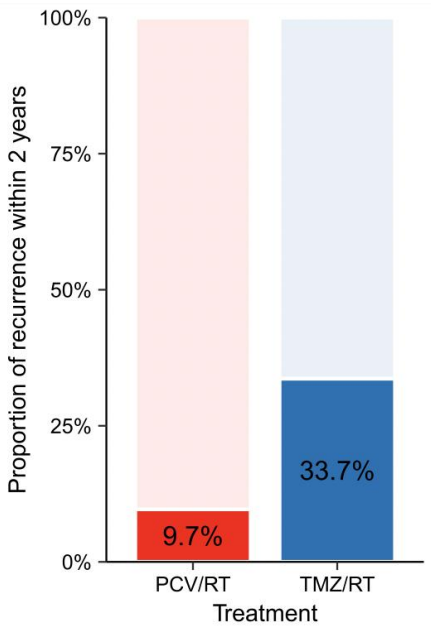
RT/PCV was associated with better survival outcomes compared to RT/TMZ





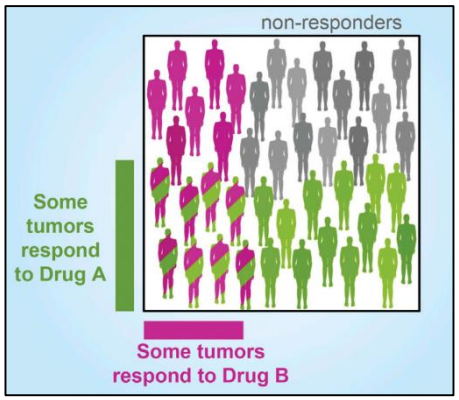
Increased proportion of early progression with RT/TMZ





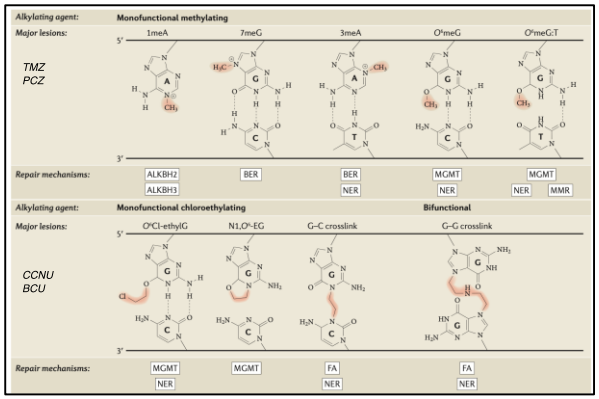
Discussion

Multiagent more beneficial than single-agent chemotherapy in chemosensitive cancers



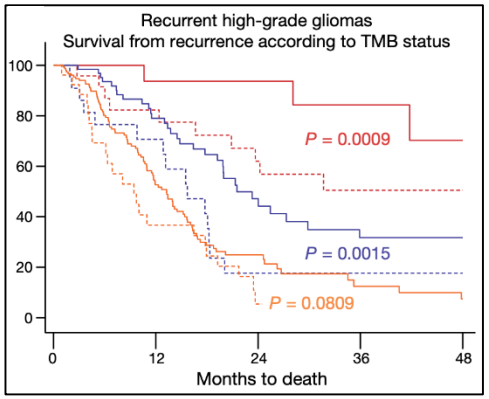
Palmer AC et al. Cell 2017
Carrick S et al. Coch Syst Rev 2009

CCNU causes additional toxic lesions (DNA crosslinks, protein carbamylation)



Fu D et al. Nat Rev Cancer 2012
Lamba N et al. Neurooncol Pract 2022

TMZ-induced hypermutation is associated with worse survival at relapse



Touat M et al. Nature 2020
Yu Y et al. Neuro-oncol 2021

Limitations:

- Study design (observational study)

- Small sample size (especially in TMZ group)

- Lack of detailed annotation of quality of life and toxicity in the cohort

CONCLUSION

In patients with newly-diagnosed grade 3 IDH-mut, 1p/19q codel oligodendroglioma from the POLA cohort, first line RT/PCV was associated with better outcomes compared to RT/TMZ:

aHR for PFS: 0.38 (95%CI: 0.25-0.58), P<0.001

aHR for OS: 0.53 (95%CI: 0.30-0.92), P=0.025

This data from a national prospective dataset suggest that the improved safety profile associated with TMZ comes at the cost of inferior efficacy in this population

Further investigation using prospective randomized studies is warranted

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Clinical Trial > J Neurosurg. 2023 Oct 13;140(4):987-1000. doi: 10.3171/2023.7.JNS231170.
Print 2024 Apr 1.

Use of 5-ALA fluorescence-guided surgery versus white-light conventional microsurgery for the resection of newly diagnosed glioblastomas (RESECT study): a French multicenter randomized phase III study

Thiébaud Picart [1 2], Johan Pallud [3 4], Julien Berthiller [5], Chloé Dumot [1 2], Moncef Berhouma [1 2], Francois Ducray [2 6], Xavier Armoiry [2 7], Jennifer Margier [8], Pascale Guerre [2 8], Pascale Varlet [4 9], David Meyronet [2 10], Philippe Metellus [11], Jacques Guyotat [1 2]; Members of RESECT study group:

- **Objective:** Only one phase III prospective randomized study, published in 2006, has assessed the performance of 5-aminolevulinic acid (5-ALA) fluorescence-guided surgery (FGS) for glioblastoma resection. The aim of the RESECT study was to compare the onco-functional results associated with 5-ALA fluorescence and with white-light conventional microsurgery in patients with glioblastoma managed according to the current standards of care.
- **Methods:** This was a **phase III prospective randomized single-blinded study**, involving **21** French neurosurgical centers, comparing 5-ALA FGS with white-light conventional microsurgery in patients with glioblastoma managed according to the current standards of care, including neuronavigation use and postoperative radiochemotherapy. Randomization was performed in a 1:1 ratio stratified by institution. 5-ALA (20 mg/kg) or placebo (ascorbic acid) was administered orally 3-5 hours before the incision. The primary endpoint was the rate of gross-total resection (GTR) blindly assessed by an independent committee. Patients without a confirmed pathological diagnosis of glioblastoma or with unavailable postoperative MRI studies were excluded from the per-protocol analysis.
- **Results:** Between March 2013 and August 2016, a total of **171** patients were assigned to the 5-ALA fluorescence group (n = 88) or to the placebo group (n = 83). Twenty-four cases were excluded because the WHO histological criteria of grade 4 glioma were not met. The proportion of **GTR** was significantly **higher in the 5-ALA fluorescence group (53/67, 79.1%)** than in the placebo group (**33/69, 47.8%; p = 0.0002**). After adjustment for age, preoperative Karnofsky Performance Scale score, and tumor location, GTR was still associated with 5-ALA fluorescence (OR 4.13 [95% CI 1.94-8.79]). The mean 7-day postoperative Karnofsky Performance Scale score (≥ 80% in 49/71, 69.0% [5-ALA group]; 50/71, 70.4% [placebo group], p = 0.86) and the proportion of patients with a worsened neurological status 3 months postoperatively (9/68, 13.2% [5-ALA group]; 9/70, 12.9% [placebo group], p = 0.95) were similar between groups. **Adverse events related to 5-ALA intake were rare** and consisted of photosensitization in 4/87 (4.6%) patients and hepatic cytolysis in 1/87 (1.1%) patients. The 6-month PFS (70.2% [95% CI 57.7%-79.6%] and 68.4% [95% CI 55.7%-78.1%]; p = 0.39) and 24-month OS (30.1% [95% CI 18.9%-42.0%] and 37.7% [95% CI 25.8%-49.5%]; p = 0.89) did not significantly differ. In multivariate analysis, GTR was an independent predictor of PFS (hazard ratio 0.56 [95% CI 0.36-0.86], p = 0.008) and OS (hazard ratio 0.65 [95% CI 0.42-1.01], p = 0.05). The use of 5-ALA FGS generates a significant extra cost of 2732.36€ (95% CI 1658.40€-3794.11€).
- **Conclusions:** The authors found that **5-ALA FGS is an easy-to-use**, **cost-effective, and minimally time-consuming technique** that safely optimizes the extent of resection in patients harboring glioblastoma amenable to a large resection.

unicancer

Clinical Trial > Neuro Oncol. 2024 Sep 5;26(9):1670-1682. doi: 10.1093/neuonc/noae053.

Marizomib for patients with newly diagnosed glioblastoma: A randomized phase 3 trial

Patrick Roth [1 2], Thierry Gorlia [3], Jaap C Reijneveld [4], Filip de Vos [5], Ahmed Idbaih [6], Jean-Sébastien Frenel [7], Emilie Le Rhun [8 9 10], Juan Manuel Sepulveda [11], James Perry [12], G Laura Masucci [13], Pierre Freres [14], Hal Hirte [15], Clemens Seidel [16], Annemiek Walenkamp [17], Slavka Lukacova [18], Paul Meijnders [19], Andre Blais [20], Francois Ducray [21 22], Vincent Verschaeve [23], Garth Nicholas [24], Carmen Balana [25], Daniela A Bota [26], Matthias Preusser [27], Sarah Nuyens [3], Fréderic Dhermain [28], Martin van den Bent [29], Chris J O'Callaghan [30], Maureen Vanlancker [3 31], Warren Mason [32], Michael Weller [1 2]

- **Background:** Standard treatment for patients with newly diagnosed glioblastoma includes surgery, radiotherapy (RT), and temozolomide (TMZ) chemotherapy (TMZ/RT→TMZ). The proteasome has long been considered a promising therapeutic target because of its role as a central biological hub in tumor cells. **Marizomib is a novel pan-proteasome inhibitor that crosses the blood-brain barrier.**
- **Methods:** European Organisation for Research and Treatment of Cancer 1709/Canadian Cancer Trials Group CE.8 was a multicenter, randomized, controlled, open-label **phase 3** superiority trial. Key eligibility criteria included newly diagnosed glioblastoma, age > 18 years and Karnofsky performance status > 70. Patients were randomized in a 1:1 ratio. The primary objective was to compare overall survival (OS) in patients receiving marizomib in addition to TMZ/RT→TMZ with patients receiving the only standard treatment in the whole population and in the subgroup of patients with MGMT promoter-unmethylated tumors.
- **Results:** The trial was opened at 82 institutions in Europe, Canada, and the U.S. A total of **749** patients (99.9% of the planned 750) were randomized. **OS was not different** between the standard and the marizomib arm (median 17 vs. 16.5 months; HR = 1.04; P = .64). PFS was not statistically different either (median 6.0 vs. 6.3 months; HR = 0.97; P = .67). In patients with MGMT promoter-unmethylated tumors, OS was also not different between standard therapy and marizomib (median 14.5 vs. 15.1 months, HR = 1.13; P = .27). More **CTCAE grade 3/4** treatment-emergent adverse events were observed in the marizomib arm than in the standard arm.
- **Conclusions:** **Adding marizomib to standard temozolomide-based radiochemotherapy resulted in more toxicity, but did not improve OS or PFS in patients with newly diagnosed glioblastoma.**

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Clinical Trial > Neuro Oncol. 2024 Jan 5;26(1):153-163. doi: 10.1093/neuonc/noad119.

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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- **Background:** 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.
- **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% CI [42.5; 45.5]), **median OS** was **22.6 months** (95% CI [18.9; 25.4]) versus 22.2 months (95% CI [18.3; 27.8]) for HD, and median progression-free survival was 8.6 (95% CI [6.8; 10.8]) versus 7.8 months (95% CI [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% CI [23.2; NR]) for HD patients versus 28.5 months (95% CI [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.**

Review > J Neurooncol. 2024 Sep;169(3):469-487. doi: 10.1007/s11060-024-04752-w.
Epub 2024 Jul 11.

Prognostic value of surgical resection over biopsy in elderly patients with glioblastoma: a meta-analysis

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- **Purpose:** Maximal-safe resection has been shown to improve overall survival in elderly patients with glioblastoma in observational studies, however, the only clinical trial comparing resection versus biopsy in elderly patients with surgically-accessible glioblastoma showed no improvements in overall survival. A meta-analysis is needed to assess whether surgical resection of glioblastoma in older patients improves surgical outcomes when compared to biopsy alone.
- **Methods:** A search was conducted until October 9th, 2023, to identify published studies reporting the clinical outcomes of glioblastoma patients > 65 years undergoing resection or biopsy (PubMed, MEDLINE, EMBASE, and COCHRANE). Primary outcomes were overall survival (OS), progression-free survival (PFS), and complications. We analyzed mean difference (MD) and hazard ratio (HR) for survival outcomes. Postoperative complications were analyzed as a dichotomic categorical variable with risk ratio (RR).
- **Results:** From 784 articles, **20 cohort studies and 1 randomized controlled trial** met our inclusion criteria, considering 20,523 patients for analysis. Patients undergoing surgical resection had an overall survival MD of 6.13 months (CI 95%=2.43-9.82, p = < 0.001) with a HR of 0.43 (95% CI = 0.35-0.52, p = < 0.00001). The progression-free survival MD was 2.34 months (95%CI = 0.79-3.89, p = 0.003) with a 0.50 h favoring resection (95%CI = 0.37-0.68, p = < 0.00001). The complication RR was higher in the resection group favoring biopsy (1.49, 95%CI = 1.06-2.10).
- **Conclusions:** **Our meta-analysis suggests that upfront resection is associated with improved overall survival and progression-free survival in elderly patients with newly diagnosed glioblastoma over biopsy**. However, postoperative complications are more common with resection. Future clinical trials are essential to provide more robust evaluation in this challenging patient population.

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Clinical Trial > Cancer Biol Med. 2024 Mar 4;21(5):433-444.
doi: 10.20892/j.issn.2095-3941.2023.0373.

Efficacy and safety of anlotinib combined with the STUPP regimen in patients with newly diagnosed glioblastoma: a multicenter, single-arm, phase II trial

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- **Objective:** Glioblastomas are highly vascularized malignant tumors. We determined the efficacy and safety of the anti-angiogenic multi-kinase inhibitor, anlotinib, for a newly diagnosed glioblastoma.
- **Methods:** This multicenter, single-arm trial (NCT04119674) enrolled **33** treatment-naïve patients with histologically proven **glioblastomas** between March 2019 and November 2020. Patients underwent treatment with the standard **STUPP regimen** [fractionated focal irradiation in daily fractions of 1.8-2 Gy given 5 d/w × 6 w (total = 54-60 Gy)] or radiotherapy plus continuous daily temozolomide (TMZ) (75 mg/m^2 of body surface area/d, 7 d/w from the first to the last day of radiotherapy), followed by 6 cycles of adjuvant TMZ (150-200 mg/m^2 × 5 d during each 28-d cycle) plus **anlotinib** (8 mg/d on d 1-14 of each 3-w cycle for 2 cycles during concomitant chemoradiotherapy, 8 maximal cycles as adjuvant therapy, followed by maintenance at 8 mg/d. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS) and adverse events (AEs).
- **Results:** Thirty-three patients received the planned treatment. The **median PFS** was **10.9 months** (95% CI, 9.9-18.7 months) and the 12-month PFS rate was 48.5%. The median OS was 17.4 months (95% CI, 14.5-21.1 months) and the 12-month OS rate was 81.8%. The most common AEs included hypertriglyceridemia [58% (*n* = 19)], hypoalbuminemia [46% (*n* = 15)], and hypercholesterolemia [46% (*n* = 15)] during concurrent chemoradiotherapy and leukopenia [73% (*n* = 24)], hypertriglyceridemia [67% (*n* = 22)], and neutropenia [52% (*n* = 17)] during adjuvant therapy. Five patients discontinued treatment due to AEs. *HEG1* (HR, 5.6; 95% CI, 1.3-23.7; *P* = 0.021) and *RP1L1* alterations (HR, 11.1; 95% CI, 2.2-57.2; *P* = 0.004) were associated with a significantly shorter PFS.
- **Conclusions:** Anlotinib plus the STUPP regimen has promising anti-tumor activity against glioblastoma and manageable toxicity. ***HEG1* and *RP1L1* alterations might be novel predictive biomarkers of the response to anlotinib.**

Clinical Trial > J Clin Oncol. 2023 Feb 20;41(6):1285-1295. doi: 10.1200/JCO.22.00164. Epub 2022 Oct 19.

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**.

Clinical Trial > J Clin Oncol. 2023 Dec 20;41(36):5524-5535. doi: 10.1200/JCO.23.00493. Epub 2023 Sep 18.

Inaugural Results of the Individualized Screening Trial of Innovative Glioblastoma Therapy: A Phase II Platform Trial for Newly Diagnosed Glioblastoma Using Bayesian Adaptive Randomization

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- **Purpose:** The Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT) is a **phase II** platform trial that uses response adaptive randomization and genomic profiling to efficiently **identify novel therapies for phase III testing**. Three initial experimental arms (**abemaciclib** [a cyclin-dependent kinase [**CDK]4/6 inhibitor**], **neratinib** [an epidermal growth factor receptor [**EGFR**]/human epidermal growth factor receptor **2 inhibitor**], and **CC-115** [a deoxyribonucleic acid-dependent protein kinase/mammalian target of **rapamycin inhibitor]**) were simultaneously evaluated against a common control arm. We report the results for each arm and examine the feasibility and conduct of the adaptive platform design.
- **Patients and methods:** Patients with newly diagnosed O^6-methylguanine-DNA methyltransferase-**unmethylated glioblastoma** were eligible if they had tumor genotyping to identify prespecified biomarker subpopulations of dominant glioblastoma signaling pathways (EGFR, phosphatidylinositol 3-kinase, and CDK). Initial random assignment was 1:1:1:1 between control (radiation therapy and temozolomide) and the experimental arms. Subsequent Bayesian adaptive randomization was incorporated on the basis of biomarker-specific progression-free survival (PFS) data. The primary end point was overall survival (OS), and one-sided *P* values are reported.
- **Results:** Two hundred thirty-seven patients were treated **(71 control; 73 abemaciclib; 81 neratinib; 12 CC-115**) in years 2017-2021. **Abemaciclib and neratinib** were **well tolerated**, but CC-115 was associated with ≥ grade 3 treatment-related toxicity in 58% of patients. **PFS was significantly longer** with abemaciclib (hazard ratio [HR], 0.72; 95% CI, 0.49 to 1.06; one-sided $P = .046$) and neratinib (HR, 0.72; 95% CI, 0.50 to 1.02; one-sided $P = .033$) relative to the control arm but there was no PFS benefit with CC-115 (one-sided $P = .523$). None of the experimental therapies demonstrated a significant OS benefit ($P > .05$).
- **Conclusion:** The INSIGhT design enabled efficient simultaneous testing of three experimental agents using a shared control arm and adaptive randomization. **Two investigational arms had superior PFS compared with the control arm, but none demonstrated an OS benefit.** The INSIGhT design may promote improved and more efficient therapeutic discovery in glioblastoma. New arms have been added to the trial.

Clinical Trial > Nat Med. 2024 May;30(5):1320-1329. doi: 10.1038/s41591-024-02893-z. Epub 2024 Mar 13.

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

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- **Recurrent glioblastoma** (rGBM) remains a major unmet medical need, with a median overall survival of less than 1 year. Here we report the first six patients with rGBM treated in a **phase 1** trial of intrathecally delivered bivalent chimeric antigen receptor **(CAR) T cells** targeting epidermal growth factor receptor (**EGFR**) and interleukin-13 receptor alpha 2 (**IL13Rα2**). The study's primary endpoints were **safety** and determination of the maximum tolerated dose. Secondary endpoints reported in this interim analysis include the frequency of manufacturing failures and objective radiographic response (ORR) according to modified Response Assessment in Neuro-Oncology criteria. All six patients had progressive, multifocal disease at the time of treatment. In both dose level 1 (1×10^7 cells; n = 3) and dose level 2 (2.5×10^7 cells; n = 3), administration of CART-EGFR-IL13Rα2 cells was associated with early-onset neurotoxicity, most consistent with immune effector cell-associated neurotoxicity syndrome (**ICANS**), and **managed with high-dose dexamethasone and anakinra (anti-IL1R**). One patient in dose level 2 experienced a dose-limiting toxicity (grade 3 anorexia, generalized muscle weakness and fatigue). **Reductions in enhancement and tumor size at early magnetic resonance imaging timepoints were observed in all six patients; however, none met criteria for ORR**. In exploratory endpoint analyses, substantial CAR T cell abundance and cytokine release in the cerebrospinal fluid were detected in all six patients. Taken together, these first-in-human data demonstrate the preliminary safety and bioactivity of CART-EGFR-IL13Rα2 cells in rGBM. An encouraging early efficacy signal was also detected and requires confirmation with additional patients and longer follow-up time.

Clinical Trial > Nat Med. 2023 Jun;29(6):1370-1378. doi: 10.1038/s41591-023-02347-y. Epub 2023 May 15.

Oncolytic DNX-2401 virotherapy plus pembrolizumab in recurrent glioblastoma: a phase 1/2 trial

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- Immune-mediated anti-tumoral responses, elicited by oncolytic viruses and augmented with checkpoint inhibition, may be an effective treatment approach for glioblastoma. Here in this multicenter **phase 1/2 study** we evaluated the combination of intratumoral delivery of **oncolytic virus DNX-2401** followed by intravenous anti-PD-1 antibody **pembrolizumab** in **recurrent glioblastoma**, first in a dose-escalation and then in a dose-expansion phase, in **49** patients.
- The **primary endpoints** were overall safety and objective response rate. The primary **safety** endpoint was **met**, whereas the primary **efficacy endpoint was not met**. There were no dose-limiting toxicities, and full dose combined treatment was well tolerated. The objective response rate was 10.4% (90% confidence interval (CI) 4.2-20.7%), which was not statistically greater than the prespecified control rate of 5%.
- The secondary endpoint of overall survival at 12 months was 52.7% (95% CI 40.1-69.2%), which was statistically greater than the prespecified control rate of 20%. Median overall survival was 12.5 months (10.7-13.5 months). Objective responses led to longer survival (hazard ratio 0.20, 95% CI 0.05-0.87). A total of 56.2% (95% CI 41.1-70.5%) of patients had a clinical benefit defined as stable disease or better. **Three patients** completed treatment **with durable responses and remain alive at 45, 48 and 60 months**. Exploratory mutational, gene-expression and immunophenotypic analyses revealed that the balance between immune cell infiltration and expression of checkpoint inhibitors may potentially inform on response to treatment and mechanisms of resistance.
- Overall, the combination of intratumoral DNX-2401 followed by pembrolizumab was safe with notable survival benefit in select patients

Review > J Neurosurg. 2023 Feb 10;139(3):748-759. doi: 10.3171/2022.12.JNS222173.
Print 2023 Sep 1.

Pseudoprogression versus true progression in glioblastoma: what neurosurgeons need to know

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- Management of patients with glioblastoma (GBM) is complex and involves implementing standard therapies including resection, radiation therapy, and chemotherapy, as well as novel immunotherapies and targeted small-molecule inhibitors through clinical trials and precision medicine approaches. As treatments have advanced, the radiological and clinical assessment of patients with GBM has become even more challenging and nuanced. Advances in spatial resolution and both anatomical and physiological information that can be derived from MRI have greatly improved the noninvasive assessment of GBM before, during, and after therapy. Identification of **pseudoprogression (PsP),** defined as changes concerning for tumor progression that are, in fact, transient and related to treatment response, is critical for successful patient management. **These temporary changes can produce new clinical symptoms due to mass effect and edema**. Differentiating this entity from true tumor progression is a major decision point in the patient's management and prognosis. Providers may choose to start an alternative therapy, transition to a clinical trial, consider repeat resection, or continue with the current therapy in hopes of resolution.
- **In this review, the authors describe the invasive and noninvasive techniques neurosurgeons need to be aware of to identify PsP and facilitate surgical decision-making**.

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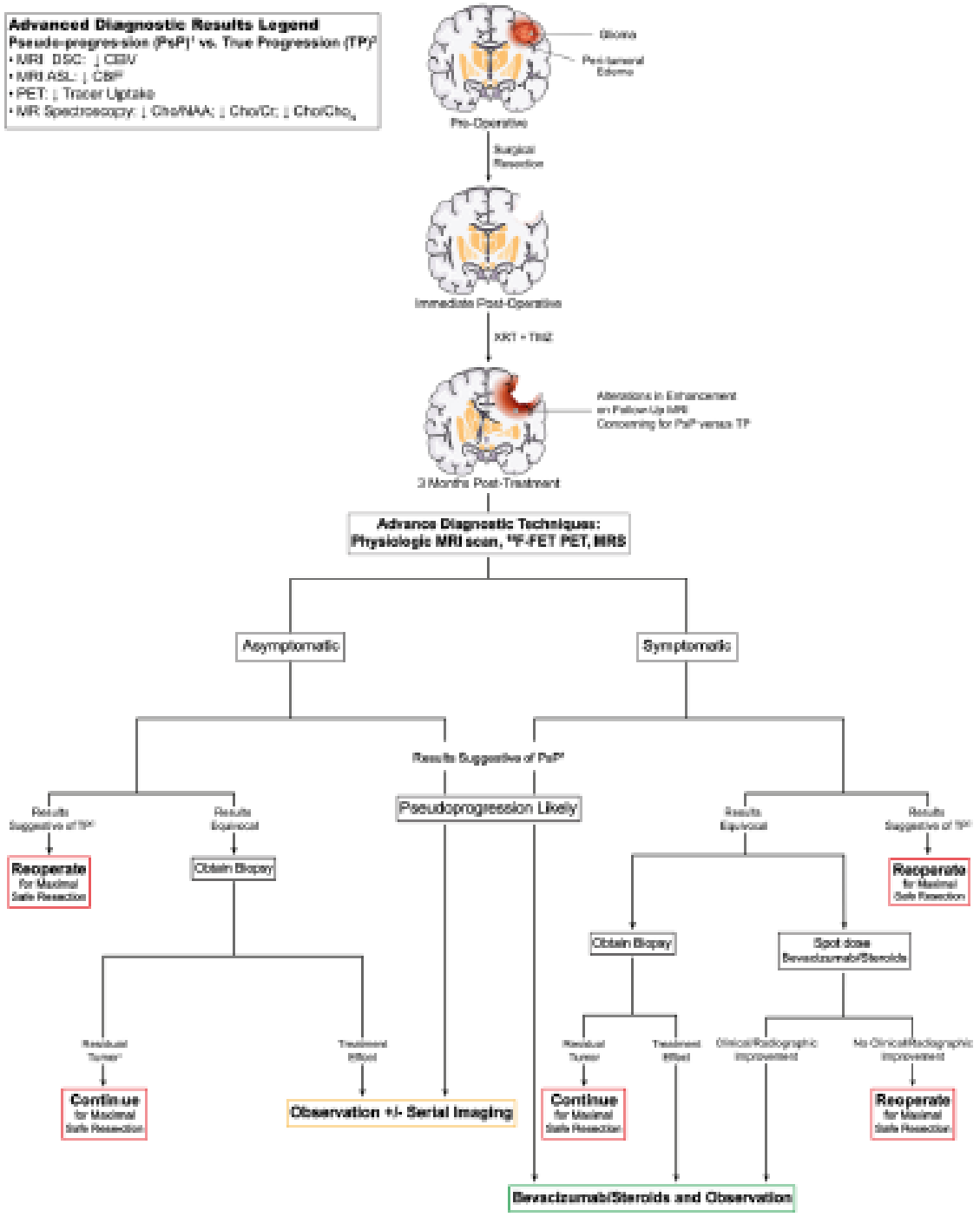
Advanced Diagnostic Results Legend
Pseudo-progression (PsP)[1] vs. True Progression (TP)[2]
- MRI DSC: ↓ CBV
- MRI ASL: ↓ CBF
- PET: ↓ Tracer Uptake
- MR Spectroscopy: ↓ Cho/NAA; ↓ Cho/Cr; ↓ Cho/Cho$_N$



Multicenter Study > Eur J Nucl Med Mol Imaging. 2023 Nov;50(13):3970-3981.
doi: 10.1007/s00259-023-06371-5. Epub 2023 Aug 11.

Delineation and agreement of FET PET biological volumes in glioblastoma: results of the nuclear medicine credentialing program from the prospective, multi–centre trial evaluating FET PET In Glioblastoma (FIG) study–TROG 18.06

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- **Purpose:** The O-(2-[^{18}F]-fluoroethyl)-L-tyrosine **(FET) PET** in Glioblastoma (FIG) trial is an Australian prospective, multi-centre study evaluating FET PET for glioblastoma patient management. FET PET imaging timepoints are **pre-chemoradiotherapy** (FET1), **1-month post-chemoradiotherapy** (FET2), and at **suspected progression** (FET3). Before participant recruitment, site nuclear medicine physicians (NMPs) underwent credentialing of FET PET delineation and image interpretation.
- **Methods:** Sites were required to **complete contouring and dynamic analysis by ≥ 2 NMPs** on benchmarking cases (n = 6) assessing biological tumour volume (BTV) delineation (3 × FET1) and image interpretation (3 × FET3). Data was reviewed by experts and violations noted. BTV definition includes tumour-to-background ratio (TBR) threshold of 1.6 with crescent-shaped background contour in the contralateral normal brain. **Recurrence/pseudoprogression interpretation (FET3) required assessment of maximum TBR (TBR_{max}), dynamic analysis** (time activity curve [TAC] type, time to peak), and qualitative assessment. Intraclass correlation coefficient (ICC) assessed volume agreement, coefficient of variation (CoV) compared maximum/mean TBR (TBR_{max}/TBR_{mean}) across cases, and pairwise analysis assessed spatial (Dice similarity coefficient [DSC]) and boundary agreement (Hausdorff distance [HD], mean absolute surface distance [MASD]).
- **Results:** Data was accrued from 21 NMPs (10 centres, n ≥ 2 each) and 20 underwent review. The initial **pass rate** was 93/119 (**78.2%**) and 27/30 requested resubmissions were completed. Violations were found in 25/72 (34.7%; 13/12 minor/major) of FET1 and 22/74 (29.7%; 14/8 minor/major) of FET3 reports. The primary reasons for resubmission were as follows: BTV over-contour (15/30, 50.0%), background placement (8/30, 26.7%), TAC classification (9/30, 30.0%), and image interpretation (7/30, 23.3%). CoV median and range for BTV, TBR_{max}, and TBR_{mean} were 21.53% (12.00-30.10%), 5.89% (5.01-6.68%), and 5.01% (3.37-6.34%), respectively. BTV agreement was moderate to excellent (ICC = 0.82; 95% CI, 0.63-0.97) with good spatial (DSC = 0.84 ± 0.09) and boundary (HD = 15.78 ± 8.30 mm; MASD = 1.47 ± 1.36 mm) agreement.
- **Conclusion:** The FIG study credentialing program has increased expertise across study sites.

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TBR_{max} and TBR_{mean} were robust, with considerable variability in BTV delineation and image interpretation observed.

> BMJ Open. 2024 Mar 8;14(3):e078926. doi: 10.1136/bmjopen-2023-078926.

Brain Re-Irradiation Or Chemotherapy: a phase II randomised trial of re-irradiation and chemotherapy in patients with recurrent glioblastoma (BRIOChe) – protocol for a multi-centre open-label randomised trial

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Introduction: Glioblastoma (GBM) is the most common adult primary malignant brain tumour. The condition is incurable and, despite aggressive treatment at first presentation, almost all tumours recur after a median of 7 months. The aim of treatment at recurrence is to prolong survival and maintain health-related quality of life (HRQoL). Chemotherapy is typically employed for recurrent GBM, often using nitrosourea-based regimens. However, efficacy is limited, with reported median survivals between 5 and 9 months from recurrence. Although less commonly used in the UK, there is growing evidence that re-irradiation may produce survival outcomes at least similar to nitrosourea-based chemotherapy. However, there remains uncertainty as to the optimum approach and there is a paucity of available data, especially with regards to HRQoL. **Brain Re-Irradiation Or Chemotherapy (BRIOChe)** aims to assess re-irradiation, as an acceptable treatment option for recurrent IDH-wild-type GBM.

Methods and analysis: BRIOChe is a **phase II**, multi-centre, open-label, randomised trial in patients with recurrent GBM. The trial uses Sargent's three-outcome design and will recruit approximately **55** participants from 10 to 15 UK radiotherapy sites, allocated (2:1) to receive **re-irradiation (35 Gy in 10 daily fractions) or nitrosourea-based chemotherapy (up to six, 6-weekly cycles).** The primary endpoint is **overall survival rate for re-irradiation patients at 9 months**. There will be no formal statistical comparison between treatment arms for the decision-making primary analysis. The chemotherapy arm will be used for calibration purposes, to collect concurrent data to aid interpretation of results. Secondary outcomes include HRQoL, dexamethasone requirement, anti-epileptic drug requirement, radiological response, treatment compliance, acute and late toxicities, progression-free survival.

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Repeated peripheral infusions of anti–EGFRvIII CAR T cells in combination with pembrolizumab show no efficacy in glioblastoma: a phase 1 trial

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- We previously showed that chimeric antigen receptor (**CAR) T-cell** therapy targeting epidermal growth factor receptor variant III (**EGFRvIII**) produces upregulation of programmed death-ligand 1 (PD-L1) in the tumor microenvironment (TME). Here we conducted a phase 1 trial (NCT03726515) of CAR T-EGFRvIII cells administered concomitantly with the anti-PD1 (aPD1) monoclonal antibody **pembrolizumab** in patients with newly diagnosed, **EGFRvIII^{+} glioblastoma** (GBM) (n = 7).
- The primary outcome was **safety**, and no dose-limiting toxicity was observed.
- Secondary outcomes included median progression-free survival (5.2 months; 90% confidence interval (CI), 2.9-6.0 months) and median overall survival (11.8 months; 90% CI, 9.2-14.2 months).
- In exploratory analyses, comparison of the TME in tumors harvested before versus after CAR + aPD1 administration demonstrated substantial evolution of the infiltrating myeloid and T cells, with more exhausted, regulatory, and interferon (IFN)-stimulated T cells at relapse.
- Our study suggests that the combination of CAR T cells and PD-1 inhibition in GBM is safe and biologically active but, given the lack of efficacy, also indicates a need to consider alternative strategies.

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Dosimetric feasibility analysis and presentation of an isotoxic dose-escalated radiation therapy concept for glioblastoma used in the PRIDE trial (NOA-28; ARO-2022-12)

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- **Background and purpose:** The PRIDE trial (NOA-28; ARO-2022-12; NCT05871021) is scheduled to start recruitment in October 2023. Its primary objective is to enhance median overall survival (OS), compared to historical median OS rates, in patients with methylguanine methlyltransferase (MGMT) promotor unmethylated glioblastoma by incorporating **isotoxic dose escalation to 75 Gy in 30 fractions**. To achieve isotoxicity and counteract the elevated risk of **radiation necrosis (RN)** associated with dose-escalated regimens, the addition of protective concurrent **bevacizumab (BEV)** serves as an innovative approach. The current study aims to assess the dosimetric feasibility of the proposed concept.
- **Materials and methods:** A total of **ten** patients diagnosed with glioblastoma were included in this dosimetric analysis. Delineation of target volumes for the reference plans adhered to the ESTRO-EANO 2023 guideline. The experimental plans included an additional volume for the integrated boost. Additionally, the **60 Gy-volume was reduced by using a margin of 1.0 cm instead of 1.5 cm**. To assess the risk of symptomatic RN, the Normal Tissue Complication Probability (NTCP) was calculated and compared between the reference and experimental plans.
- **Results:** Median NTCP of the reference plan ($NTCP_{ref}$) and of the experimental plan ($NTCP_{ex}$) were 0.24 (range 0.11-0.29) and 0.42 (range 0.18-0.54), respectively. $NTCP_{ex}$ was a median of 1.77 (range 1.60-1.99) times as high as the $NTXP_{ref}$. In a logarithmic comparison, the risk of RN is enhanced by a factor of median 2.00 (range 1.66-2.35). The defined constraints for the organs at risk were feasible.
- **Conclusion:** When considering the potential protective effect of BEV, which we hypothesized might reduce the risk of RN by approximately two-fold, achieving isotoxicity with the proposed dose-escalated experimental plan for the PRIDE trial seems feasible.

Clinical Trial > Nat Med. 2024 Apr;30(4):1001-1012. doi: 10.1038/s41591-024-02875-1. Epub 2024 Mar 7.

Locoregional delivery of IL-13Rα2-targeting CAR-T cells in recurrent high-grade glioma: a phase 1 trial

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- Chimeric antigen receptor T cell (**CAR-T**) therapy is an emerging strategy to improve treatment outcomes for recurrent high-grade glioma, a cancer that responds poorly to current therapies. Here we report a completed **phase I trial evaluating IL-13Rα2-targeted CAR-T cells** in **65** patients **with recurrent high-grade glioma**, the majority being recurrent glioblastoma (rGBM). Primary objectives were safety and feasibility, maximum tolerated dose/maximum feasible dose and a recommended phase 2 dose plan. Secondary objectives included overall survival, disease response, cytokine dynamics and tumor immune contexture biomarkers. This trial evolved to evaluate three routes of locoregional T cell administration (intratumoral (ICT), intraventricular (ICV) and dual ICT/ICV) and two manufacturing platforms, culminating in arm 5, which utilized dual ICT/ICV delivery and an optimized manufacturing process.
- **Locoregional** CAR-T cell administration was **feasible and well tolerated**, and as there were no dose-limiting toxicities across all arms, a maximum tolerated dose was not determined. Probable treatment-related grade 3+ toxicities were one grade 3 encephalopathy and one grade 3 ataxia. A clinical maximum feasible dose of 200 × 10^6 CAR-T cells per infusion cycle was achieved for arm 5; however, other arms either did not test or achieve this dose due to manufacturing feasibility. A recommended phase 2 dose will be refined in future studies based on data from this trial. **Stable disease or better was achieved in 50% (29/58) of patients, with two partial responses, one complete response and a second complete response after additional CAR-T cycles off protocol.** For rGBM, median overall survival for all patients was 7.7 months and for arm 5 was 10.2 months. Central nervous system increases in inflammatory cytokines, including IFNγ, CXCL9 and CXCL10, were associated with CAR-T cell administration and bioactivity. Pretreatment intratumoral CD3 T cell levels were positively associated with survival. These findings demonstrate that locoregional IL-13Rα2-targeted CAR-T therapy is safe with promising clinical activity in a subset of patients.

Clinical Trial > Clin Cancer Res. 2024 Aug 1;30(15):3167-3178.
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Evaluating the Base Excision Repair Inhibitor TRC102 and Temozolomide for Patients with Recurrent Glioblastoma in the Phase 2 Adult Brain Tumor Consortium Trial BERT

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- **Purpose:** Patients with glioblastoma (GBM) have a dismal prognosis. Although the DNA alkylating agent temozolomide (TMZ) is the mainstay of chemotherapy, therapeutic resistance rapidly develops in patients. Base excision repair inhibitor TRC102 (methoxyamine) reverses TMZ resistance in preclinical glioma models. We aimed to investigate the efficacy and safety of **oral TRC102+TMZ in recurrent GBM** (rGBM).
- **Patients and methods:** A preregistered (NCT02395692), nonrandomized, multicenter, **phase 2** clinical trial (BERT) was planned and conducted through the Adult Brain Tumor Consortium (ABTC-1402). Arm 1 included patients with bevacizumab-naïve GBM at the first recurrence, with the primary endpoint of response rates. If sufficient activity was identified, a second arm was planned for the bevacizumab-refractory patients. The secondary endpoints were overall survival (OS), progression-free survival (PFS), PFS at 6 months (PFS6), and toxicity.
- **Results:** Arm 1 enrolled **19** patients with a median of two treatment cycles**. Objective responses were not observed; hence, arm 2 did not open**. The median OS was 11.1 months [95% confidence interval (CI), 8.2-17.9]. The median PFS was 1.9 months (95% CI, 1.8-3.7). The PFS6 was 10.5% (95% CI, 1.3%-33.1%). Most toxicities were grades 1 and 2, with two grade 3 lymphopenias and one grade 4 thrombocytopenia. Two patients with PFS ≥ 17 months and OS > 32 months were deemed "**extended survivors**." RNA sequencing of tumor tissue, obtained at diagnosis, demonstrated significantly enriched **signatures of DNA damage response (DDR), chromosomal instability (CIN70, CIN25), and cellular proliferation (PCNA25)** in "extended survivors."
- **Conclusions:** These findings confirm the safety and feasibility of TRC102+TMZ in patients with rGBM. They also warrant further evaluation of combination therapy in biomarker-enriched trials enrolling GBM patients with baseline hyperactivated DDR pathways.

Clinical Trial > Int J Radiat Oncol Biol Phys. 2024 Apr 1;118(5):1371-1378.
doi: 10.1016/j.ijrobp.2024.01.011. Epub 2024 Jan 9.

Concurrent Olaparib and Radiation Therapy in Older Patients With Newly Diagnosed Glioblastoma: The Phase 1 Dose–Escalation PARADIGM Trial

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- **Purpose:** Patients with glioblastoma who are older or have poor performance status (PS) experience particularly poor clinical outcomes. At the time of study initiation, these patients were treated with short-course radiation therapy (**40 Gy in 15 fractions**). **Olaparib** is an oral inhibitor of the DNA repair enzyme poly (ADP-ribose) polymerase (PARP) that is well tolerated as a single agent but exacerbates acute radiation toxicity in extracranial sites. Preclinical data predicted that PARP inhibitors would enhance radiosensitivity in glioblastoma without exacerbating adverse effects on the normal brain.
- **Methods and materials:** **Phase 1** of the **PARADIGM trial** was a 3+3 dose-escalation study testing olaparib in combination with radiation therapy (40 Gy 15 fractions) in patients with newly diagnosed glioblastoma who were unsuitable for radical treatment either because they were aged **70 years** or older (World Health Organization PS 0-1) or aged **18 to 69 years with PS 2**. The primary outcome was the recommended phase 2 dose of olaparib. Secondary endpoints included safety and tolerability, overall survival, and progression-free survival. Effects on cognitive function were assessed via the Mini Mental State Examination.
- **Results:** Of **16** eligible patients (56.25% male; median age, 71.5 years [range, 44-78]; 75% PS 0-1), 1 dose-limiting toxicity was reported (grade 3 agitation). Maximum tolerated dose was not reached and the recommended **phase 2 dose** was determined as **200 mg twice daily**. **Median overall survival** and progression-free survival were **10.8 months** (80% CI, 7.3-11.4) and 5.5 months (80% CI, 3.9-5.9), respectively. Mini Mental State Examination plots indicated that cognitive function was not adversely affected by the olaparib-radiation therapy combination.
- **Conclusions:** Olaparib can be safely combined with hypofractionated brain radiation therapy and is well tolerated in patients unsuitable for radical chemoradiation. These results enabled initiation of a randomized phase 2 study and support future trials of PARP inhibitors in combination with radiation therapy for patients with brain tumors.

Nat Commun. 2024 Aug 7;15(1):6707. doi: 10.1038/s41467-024-50558-9.

Sacituzumab Govitecan in patients with breast cancer brain metastases and recurrent glioblastoma: a phase 0 window-of-opportunity trial

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- Sacituzumab Govitecan (SG) is an antibody-drug conjugate that has demonstrated efficacy in patients with TROP-2 expressing epithelial cancers. In a xenograft model of intracranial breast cancer, SG inhibited tumor growth and increased mouse survival. We conducted a prospective window-of-opportunity trial (NCT03995706) at the University of Texas Health Science Center at San Antonio to examine the intra-tumoral concentrations and intracranial activity of SG in patients undergoing craniotomy for breast cancer with **brain metastases (BCBM) or recurrent glioblastoma (rGBM)**. We enrolled **25** patients aged ≥18 years diagnosed with BCBM and rGBM to receive a single intravenous dose of SG **at 10 mg/kg given one day before resection** and continued on **days 1 and 8 of 21-day cycles following recovery**.
- The PFS was 8 months and 2 months for BCBM and rGBM cohorts, respectively. The **OS** was **35.2** months and **9.5 months**, respectively. Grade≥3 AE included neutropenia (28%), hypokalemia (8%), seizure (8%), thromboembolic event (8%), urinary tract infection (8%) and muscle weakness of the lower limb (8%). In post-surgical tissue, the median total SN-38 was 249.8 ng/g for BCBM and 104.5 ng/g for rGBM, thus fulfilling the primary endpoint. Biomarker analysis suggests delivery of payload by direct release at target site and that hypoxic changes do not drive indirect release. Secondary endpoint of OS was 35.2 months for the BCBM cohort and 9.5 months for rGBM. Non-planned exploratory endpoint of ORR was 38% for BCBM and 29%, respectively.
- Exploratory endpoint of **Trop-2 expression** was observed **in 100% of BCBM and 78% of rGBM tumors**. In conclusion, SG was found to be well tolerated with adequate penetration into intracranial tumors and promising preliminary activity within the CNS.

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Causal relationship between gut microbiota and glioblastoma: a two-sample Mendelian randomization study

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- **Background:** Observational research and medical trials have suggested a connection between gut microbiota and glioblastoma, but it remains unclear if the relationship is causal.
- **Method:** A two-sample Mendelian randomization (MR) study was conducted by employing data from the MiBioGen consortium's largest genome-wide association study (**n=18340**) and the FinnGen consortium R8 release information (**162 cases and 256,583 controls**). Inverse variance weighted (IVW), weighted median estimator (WME), weighted model, MR-Egger, simple mode, and MR-PRESSO were used to determine the causal relationship between gut microbiota and glioblastoma. Reverse MR analysis was also performed on bacteria identified as causally related to glioblastoma.
- **Results:** **Seven causal relationships** were identified between **genetic liability** in the **gut microbiota and glioblastoma**, involving various bacterial families and genera. No significant causal effect was found on gut microbiota from glioblastoma, and no significant heterogeneity of instrumental variables (IVs) or horizontal pleiotropy was observed.
- **Conclusion:** A two-sample MR analysis reveals a causal association between the gut microbiota and glioblastoma, highlighting the need for more investigation to comprehend the processes behind this association.

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Paclitaxel and Carboplatin in Combination with Low-intensity Pulsed Ultrasound for Glioblastoma

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- **Purpose:** We recently reported on clinical trials for patients with **recurrent glioblastoma** where **low-intensity pulsed ultrasound and microbubbles** (LIPU/MB) improved paclitaxel or carboplatin delivery into the brain. Here, we report variable local tumor control with paclitaxel at the maximal/target dose in our phase I trial (NCT04528680). To address this, we investigated the combination of paclitaxel with carboplatin in preclinical glioma models.
- **Experimental design:** We performed MRI-based analysis to evaluate disease control in patients from our trial. We studied the cytotoxicity of paclitaxel and carboplatin against 11 human glioma lines as monotherapy and in combination at concentrations derived from human intraoperative studies. Synergy was assessed with the Loewe model and the survival benefit evaluated in two xenografts. We examined the effects on cell cycle progression, DNA damage, and apoptosis.
- **Results:** Patients treated with **paclitaxel and LIPU/MB** exhibited variable local tumor control, which correlated with overall survival. We observed limited cross-resistance to paclitaxel and carboplatin in glioma lines, with almost a third of them being exclusively susceptible to one drug. This combination led to susceptibility of 81% of lines and synergy in 55% of them. The combination proved more efficacious in two intracranial xenografts when administered with LIPU/MB, leading to complementary effects on cell cycle arrest.
- **Conclusions:** Combining paclitaxel and carboplatin in gliomas may be more efficacious than monotherapy, as in other cancers, due to synergy and independent susceptibility to each drug. These results form the basis for an ongoing **phase II trial** (NCT04528680) where we investigate this combination with LIPU/MB.

Clinical Trial > BMC Cancer. 2024 Jan 26;24(1):135. doi: 10.1186/s12885-024-11846-1.

PerSurge (NOA-30) phase II trial of perampanel treatment around surgery in patients with progressive glioblastoma

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- **Background:** Glioblastoma is the most frequent and a particularly malignant primary brain tumor with no efficacy-proven standard therapy for recurrence. It has recently been discovered that excitatory synapses of the AMPA-receptor subtype form between non-malignant brain neurons and tumor cells. This neuron-tumor network connectivity contributed to glioma progression and could be efficiently targeted with the EMA/FDA approved **antiepileptic AMPA receptor inhibitor perampanel** in preclinical studies. The PerSurge trial was designed to test the clinical potential of perampanel to reduce tumor cell network connectivity and tumor growth with an extended window-of-opportunity concept.
- **Methods:** **PerSurge** is a **phase IIa** clinical and translational treatment study around surgical resection of progressive or recurrent glioblastoma. In this multicenter, 2-arm parallel-group, double-blind superiority trial, patients are 1:1 randomized to either receive **placebo or perampanel (n = 66** in total). It consists of a treatment and observation period of 60 days per patient, starting **30 days before a planned surgical resection**, which itself is not part of the study interventions. Only patients with an expected safe waiting interval are included, and a safety MRI is performed. Tumor cell network connectivity from resected tumor tissue on single cell transcriptome level as well as AI-based assessment of tumor growth dynamics in T2/FLAIR MRI scans before resection will be analyzed as the co-primary endpoints. Secondary endpoints will include further imaging parameters such as pre- and postsurgical contrast enhanced MRI scans, postsurgical T2/FLAIR MRI scans, quality of life, cognitive testing, overall and progression-free survival as well as frequency of epileptic seizures. Further translational research will focus on additional biological aspects of neuron-tumor connectivity.
- **Discussion:** This trial is set up to assess **first indications of clinical efficacy and tolerability of perampanel in recurrent glioblastoma**, a repurposed drug which inhibits neuron-glioma synapses and thereby glioblastoma growth in preclinical models. If perampanel proved to be successful in the clinical setting, it would provide the first evidence that interference with neuron-cancer interactions may indeed lead to a benefit for patients, which would lay the foundation for a larger confirmatory trial in the future.

BMC Cancer. 2024 Jan 15;24(1):83. doi: 10.1186/s12885-023-11792-4.

A randomised phase II trial of temozolomide with or without cannabinoids in patients with recurrent glioblastoma (ARISTOCRAT): protocol for a multi-centre, double-blind, placebo-controlled trial

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- **Background:** Glioblastoma (GBM) is the most common adult malignant brain tumour, with an incidence of 5 per 100,000 per year in England. Patients with tumours showing O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation represent around 40% of newly diagnosed GBM. Relapse/tumour recurrence is inevitable. There is no agreed standard treatment for patients with GBM, therefore, it is aimed at delaying further tumour progression and maintaining health-related quality of life (HRQoL). Limited clinical trial data exist using **cannabinoids in combination with temozolomide** (TMZ) in this setting, but early phase data demonstrate prolonged overall survival compared to TMZ alone, with few additional side effects. Jazz Pharmaceuticals (previously GW Pharma Ltd.) have developed **nabiximols (trade name Sativex®)**, an oromucosal spray containing a blend of cannabis plant extracts, that we aim to assess for preliminary efficacy in patients with recurrent GBM.
- **Methods:** ARISTOCRAT is a **phase II**, multi-centre, double-blind, placebo-controlled, randomised trial to assess cannabinoids in patients with recurrent MGMT methylated GBM who are suitable for treatment with TMZ. Patients who have **relapsed ≥ 3 months after completion of initial first-line treatment** will be randomised 2:1 to receive either nabiximols or placebo in combination with TMZ. The primary outcome is **overall survival** time defined as the time in whole days from the date of randomisation to the date of death from any cause. Secondary outcomes include **overall survival at 12 months**, progression-free survival time, HRQoL (using patient reported outcomes from QLQ-C30, QLQ-BN20 and EQ-5D-5L questionnaires), and adverse events.
- **Discussion:** Patients with recurrent MGMT promoter methylated GBM represent a relatively good prognosis sub-group of patients with GBM. However, their median survival remains poor and, therefore, more effective treatments are needed. The phase II design of this trial was chosen, rather than phase III, due to the lack of data currently available on cannabinoid efficacy in this setting. A randomised, double-blind, placebo-controlled trial will ensure an unbiased robust evaluation of the treatment and will allow potential expansion of recruitment into a phase III trial should the emerging phase II results warrant this development.

Clinical Trial > Int J Radiat Oncol Biol Phys. 2024 Jul 15;119(4):1122-1132.
doi: 10.1016/j.ijrobp.2024.01.013. Epub 2024 Jan 15.

Prospective Randomized Phase 2 Trial of Hypofractionated Stereotactic Radiation Therapy of 25 Gy in 5 Fractions Compared With 35 Gy in 5 Fractions in the Reirradiation of Recurrent Glioblastoma

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- **Purpose:** The aim of this work was to investigate whether **reirradiation of recurrent glioblastoma** with **hypofractionated stereotactic radiation therapy (HSRT) consisting of 35 Gy in 5 fractions** (35 Gy/5 fx) compared with (25 Gy/5 fx) improves outcomes while maintaining acceptable toxicity.
- **Methods and materials:** We**25 Gy in 5 fractions** conducted a prospective **randomized phase 2** trial involving patients with recurrent glioblastoma (per the 2007 and 2016 World Health Organization classification). A minimum interval from first radiation therapy of 5 months and gross tumor volume of 150 cc were required. Patients were randomized 1:1 to receive HSRT alone in 25 Gy/5 fx or 35 Gy/5 fx. The primary endpoint was progression-free survival (PFS). We used a randomized phase 2 screening design with a 2-sided α of 0.15 for the primary endpoint.
- **Results:** From 2011 to 2019, **40** patients were randomized and received HSRT, with 20 patients in each group. The median age was 50 years (range, 27-71); a new resection before HSRT was performed in 75% of patients. The median PFS was 4.9 months in the 25 Gy/5 fx group and 5.2 months in the 35 Gy/5 fx group (P = .23). Six-month PFS was similar at 40% (85% CI, 24%-55%) for both groups. The median overall survival (**OS**) was **9.2** months in the 25 Gy/5 fx group and **10 months** in the 35 Gy/5 fx group (P = .201). Grade ≥3 **necrosis** was numerically higher in the **35 Gy/5 fx** group (3 [16%] vs 1 [5%]), but the difference was not statistically significant (P = .267). In an exploratory analysis, median OS of patients who developed treatment-related necrosis was 14.1 months, and that of patients who did not was 8.7 months (P = .003).
- **Conclusions:** **HSRT alone with 35 Gy/5 fx was not superior to 25 Gy/5 fx in terms of PFS or OS**. Due to a potential increase in the rate of clinically meaningful treatment-related necrosis, we suggest 25 Gy/5 fx as the standard dose in HSRT alone. During follow-up, attention should be given to differentiating tumor progression from potentially manageable complications.

Clinical Trial > Brain Commun. 2024 Jul 30;6(4):fcae241. doi: 10.1093/braincomms/fcae241. eCollection 2024.

The STELLAR trial: a phase II/III randomized trial of high-dose, intermittent sunitinib in patients with recurrent glioblastoma

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- Previously, the **tyrosine kinase inhibitor sunitinib** failed to show clinical benefit in patients with recurrent glioblastoma. **Low intratumoural sunitinib** accumulation in glioblastoma patients was reported as a possible explanation for the lack of therapeutic benefit. We designed a randomized **phase II/III** trial to evaluate whether a high-dose intermittent sunitinib schedule, aimed to increase intratumoural drug concentrations, would result in improved clinical benefit compared to standard treatment with lomustine. Patients with recurrent glioblastoma were randomized 1:1 to high-dose intermittent **sunitinib 300 mg once weekly** (Q1W, part 1) or 700 mg once every two weeks (Q2W, part 2) or lomustine. The primary end-point was progression-free survival. Based on the pre-planned interim analysis, the trial was terminated for **futility after including 26 and 29 patients** in parts 1 and 2. **Median progression-free survival** of sunitinib 300 mg Q1W was **1.5 months** (95% CI 1.4-1.7) compared to **1.5 months** (95% CI 1.4-1.6) in the lomustine arm (P = 0.59). Median progression-free survival of sunitinib 700 mg Q2W was 1.4 months (95% CI 1.2-1.6) versus 1.6 months (95% CI 1.3-1.8) for lomustine (P = 0.70). Adverse events (≥grade 3) were observed in 25%, 21% and 31% of patients treated with sunitinib 300 mg Q1W, sunitinib 700 mg Q2W and lomustine, respectively (P = 0.92). T
- o conclude, high-dose intermittent sunitinib treatment failed to improve the outcome of patients with recurrent glioblastoma when compared to standard lomustine therapy. Since lomustine remains a poor standard treatment strategy for glioblastoma, innovative treatment strategies are urgently needed.

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Long term follow-up of patients with newly diagnosed glioblastoma treated by intraoperative photodynamic therapy: an update from the INDYGO trial (NCT03048240)

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- **Purpose:** Glioblastoma remains incurable despite optimal multimodal management. The interim analysis of open label, single arm **INDYGO pilot trial** showed actuarial 12-months progression-free survival (PFS) of 60% (median 17.1 months), actuarial 12-months overall survival (OS) of 80% (median 23.1 months). We report updated, exploratory analyses of OS, PFS, and health-related quality of life (HRQOL) for patients receiving intraoperative photodynamic therapy (PDT) with 5-aminolevulinic acid hydrochloride (5-ALA HCl).
- **Methods:** Ten patients were included (May 2017 - April 2021) for standardized therapeutic approach including **5-ALA** HCl fluorescence-guided surgery (FGS), followed by intraoperative PDT with a single **200 J/cm² dose of light.** Postoperatively, patients received adjuvant therapy (Stupp protocol) then followed every 3 months (clinical and cerebral MRI) and until disease progression and/or death. Procedure safety and toxicity occurring during the first four weeks after PDT were assessed. Data concerning relapse, HRQOL and survival were prospectively collected and analyzed.
- **Results:** At the cut-off date (i.e., November 1st 2023), median follow-up was 23 months (9,7-71,4). No unacceptable or unexpected toxicities and no treatment-related deaths occurred during the study. Kaplan-Meier estimated **23.4 months median OS, actuarial 12-month PFS rate 60%**, actuarial 12-month, 24-month, and 5-year OS rates 80%, 50% and 40%, respectively. Four patients were still alive (1 patient free of recurrence).
- **Conclusion:** **At 5 years-follow-up**, intraoperative PDT with surgical maximal excision as initial therapy and standard adjuvant treatment suggests an increase of time to recurrence and overall survival in a high proportion of patients. Quality of life was maintained without any severe side effects.

Clinical Trial > JCO Precis Oncol. 2024 Apr:8:e2300407. doi: 10.1200/PO.23.00407.

Phase II Study of Erdafitinib in Patients With Tumors With Fibroblast Growth Factor Receptor Mutations or Fusions: Results From the NCI–MATCH ECOG–ACRIN Trial (EAY131) Subprotocol K2

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- **Purpose:** Subprotocol K2 (EAY131-K2) of the NCI-MATCH platform trial was an open-label, single-arm, phase II study designed to evaluate the antitumor efficacy of the **oral FGFR1-4 inhibitor**, **erdafitinib**, in patients with tumors harboring **FGFR1-4 mutations or fusions**.
- **Methods:** Central confirmation of tumor FGFR1-4 mutations or fusions was required for outcome analysis. Patients with urothelial carcinoma were excluded. Enrolled subjects received oral erdafitinib at a starting dose of **8 mg daily continuously** until intolerable toxicity or disease progression. The primary end point was objective response rate (ORR) with key secondary end points of safety, progression-free survival (PFS), and overall survival (OS).
- **Results:** **Thirty-five** patients were enrolled, and **25** patients were included in the **primary efficacy analysis** as prespecified in the protocol. The median age was 61 years, and 52% of subjects had received ≥3 previous lines of therapy. The confirmed **ORR was 16%** (4 of 25 [90% CI, 5.7 to 33.0], *P* = .034 against the null rate of 5%). An additional seven patients experienced **stable disease** as best-confirmed response. Four patients had a prolonged PFS including two with recurrent WHO grade IV, IDH1-/2-wildtype glioblastoma. The median PFS and OS were 3.6 months and 11.0 months, respectively. Erdafitinib was manageable with **no new safety signals**.
- **Conclusion:** This study met its primary end point in patients with several pretreated solid tumor types harboring FGFR1-3 mutations or fusions. These findings support **advancement of erdafitinib for patients with fibroblast growth factor receptor-altered tumors outside of currently approved indications in a potentially tumor-agnostic manner**

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Temozolomide based treatment in glioblastoma: 6 vs. 12 months

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- The Stupp regimen remains the standard treatment for newly diagnosed glioblastomas, although the prognosis remains poor. Several temozolomide alternative schedules have been studied, with extended adjuvant treatment (>6 cycles of temozolomide) frequently used, although different trials have indicated contrasting results. Survival data of **87** patients who received **6 ('6C' group) or 12 ('12C' group)** cycles of temozolomide were collected between **2012 and 2022**. A total of 45 patients were included in the 6C group and 42 patients were included in the 12C group. Data on isocitrate dehydrogenase mutation and methylguanine-DNA-methyltransferase (MGMT) promoter methylation status were also collected. **The 12C group exhibited statistically significantly improved overall survival [OS; 22.8 vs. 17.5 months; hazard ratio (HR), 0.47; 95% CI, 0.30-0.73; P=0.001] and progression-free survival (15.3 vs. 9 months; HR, 0.39; 95% CI, 0.25-0.62; P=0.001).** However, in the subgroup analysis according to MGMT status, OS in the 12C group was significantly superior to OS in the 6C group only in the **MGMT unmethylated tumors**. The present data suggested that extended adjuvant temozolomide appeared to be more effective than the conventional six cycles.

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TARGET: A phase I/II open-label multicenter study to assess safety and efficacy of fexagratinib in patients with relapsed/refractory FGFR fusion-positive glioma

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- **Background:** Oncogenic **FGFR-TACC fusions** are present in 3-5% of high-grade gliomas (HGGs). **Fexagratinib** (AZD4547) is an **oral FGFR1-3 inhibitor** with preclinical activity in FGFR-TACC+ gliomas. We tested its safety and efficacy in patients with recurrent FGFR-TACC + HGGs.
- **Patients and methods:** TARGET (NCT02824133) is a **phase I/II open-label multicenter** study that included adult patients with FGFR-TACC + HGGs relapsing after ≥1 line of standard chemoradiation. Patients received fexagratinib **80 mg bd on a continuous** schedule until disease progression or unacceptable toxicity. The primary endpoint was the 6-month progression-free survival rate (PFS6).
- **Results:** **Twelve** patients with recurrent IDH wildtype FGFR-TACC + HGGs (all FGFR3-TACC3+) were included in the efficacy cohort (male/female ratio = 1.4, median age = 61.5 years). Most patients (67%) were included at the **first relapse**. The PFS6 was 25% (95% confidence interval 5-57%), with a median PFS of 1.4 months. All patients without progression at 6 months (n = 3) were treated at first recurrence (versus 56% of those in progression) and remained progression-free for 14-23 months. The best response was RANO **partial response** in 1 patient **(8%), stable disease in 5 (42%),** and progressive disease in 6 (50%). Median survival was 17.5 months from inclusion. Grade 3 toxicities included **lymphopenia, hyperglycaemia, stomatitis, nail changes, and alanine aminotransferase increase** (n = 1 each). No grade 4-5 toxicities were seen. A 32-gene signature was associated with the benefit of FGFR inhibition in FGFR3-TACC3 + HGGs.
- **Conclusions:** **Fexagratinib exhibited acceptable toxicity but limited efficacy in recurrent FGFR3-TACC3 + HGGs**. Patients treated at first recurrence appeared more likely to benefit, yet additional evidence is required.

medRxiv [Preprint]. 2024 Apr 24:2024.04.23.24304634. doi: 10.1101/2024.04.23.24304634.

Phase 2 Study of Sorafenib, Valproic Acid, and Sildenafil in the Treatment of Recurrent High-Grade Glioma

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- Here we report the results of a single-center **phase 2** clinical trial combining **sorafenib tosylate, valproic acid, and sildenafil** for the treatment of patients with **recurrent high-grade glioma** (NCT01817751). Clinical toxicities were grade 1 and grade 2, with one grade 3 toxicity for maculopapular rash (6.4%). For all evaluable patients, the **median progression-free survival was 3.65 months and overall survival (OS) 10.0 months**. There was promising evidence showing clinical activity and benefit.
- In the 33 evaluable patients, low protein levels of the chaperone GRP78 (HSPA5) was significantly associated with a better OS ($p < 0.0026$). A correlation between the expression of PDGFRα and OS approached significance ($p < 0.0728$).
- Five patients presently have a mean OS of 73.6 months and remain alive. This is the first therapeutic intervention glioblastoma trial to significantly associate GRP78 expression to OS.

- Our data suggest that the combination of **sorafenib tosylate, valproic acid, and sildenafil requires additional clinical development in the recurrent glioma** population.

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Olaparib in recurrent isocitrate dehydrogenase mutant high-grade glioma: A phase 2 multicenter study of the POLA Network

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- **Background:** Based on preclinical studies showing that IDH-mutant (IDHm) gliomas could be vulnerable to PARP inhibition we launched a **multicenter phase 2 study** to test the efficacy of olaparib monotherapy in this population.
- **Methods:** Adults with **recurrent IDHm high-grade gliomas** (HGGs) after radiotherapy and at least one line of alkylating chemotherapy were enrolled. The primary endpoint was a 6-month progression-free survival rate (PFS-6) according to response assessment in neuro-oncology criteria. Pre-defined threshold for study success was a PFS-6 of at least 50%.
- **Results:** **Thirty-five** patients with recurrent IDHm HGGs were enrolled, 77% at ≥ 2nd recurrence. Median time since diagnosis and radiotherapy were 7.5 years and 33 months, respectively. **PFS-6 was 31.4%** (95% CI [16.9; 49.3%]). Two patients (6%) had an objective response and 14 patients (40%) had a stable disease as their best response. Median PFS and median overall survival were 2.05 and 15.9 months, respectively. Oligodendrogliomas (1p/19q codeleted) had a higher PFS-6 (53.4% vs. 15.7%, $P = .05$) than astrocytomas while an initial diagnosis of grade 4 astrocytoma tended to be associated with a lower PFS-6 compared to grade 2/3 gliomas (0% vs 31.4%, $P = .16$). A grade 2 or 3 treatment-related adverse event was observed in 15 patients (43%) and 5 patients (14%), respectively. No patient definitively discontinued treatment due to side effects.
- **Conclusions:** Although it did not meet its primary endpoint, the present study shows that in this heavily pretreated population, **olaparib monotherapy was well tolerated and resulted in some activity**, supporting further PARP inhibitors evaluation in IDHm HGGs, especially in oligodendrogliomas.

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REVOLUMAB: A phase II trial of nivolumab in recurrent IDH mutant high-grade gliomas

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- **Background:** Novel effective treatments are needed for recurrent IDH mutant high-grade gliomas (**IDHm HGGs**). The aim of the **multicentric, single-arm, phase II REVOLUMAB** trial (NCT03925246) was to assess the efficacy and safety of the **anti-PD1 Nivolumab** in patients with recurrent IDHm HGGs.
- **Patients and methods:** Adult patients with IDHm WHO grade 3-4 gliomas recurring after radiotherapy and ≥ 1 line of alkylating chemotherapy were treated with intravenous **Nivolumab until end of treatment (12 months), progression**, unacceptable toxicity, or death. The primary endpoint was the 24-week progression-free survival rate (24w-PFS) according to RANO criteria.
- **Results:** From July 2019 to June 2020, **39** patients with recurrent IDHm HGGs (twenty-one grade 3, thirteen grade 4, five grade 2 with radiological evidence of anaplastic transformation; 39% 1p/19q codeleted) were enrolled. Median time since diagnosis was 5.7 years, and the median number of previous systemic treatments was two. The 24w-PFS was 28.2% (11/39, CI95% 15-44.9%). Median PFS and OS were 1.84 (CI95% 1.81-5.89) and 14.7 months (CI95% 9.18-NR), respectively. **Four patients (10.3%) achieved partial response according to RANO criteria**. There were no significant differences in clinical or histomolecular features between responders and non-responders. The safety profile of Nivolumab was consistent with prior studies.
- **Conclusions:** We report the results of the first trial of immune checkpoint inhibitors in IDHm gliomas. Nivolumab failed to achieve its primary endpoint. However, treatment was well tolerated, and long-lasting responses were observed in a subset of patients, supporting further evaluation in combination with other agents (e.g. IDH inhibitors).

BMJ Open. 2024 Mar 12;14(3):e081783. doi: 10.1136/bmjopen-2023-081783.

What do spouse primary caregivers of patients with glioblastoma want medical providers to know? A qualitative thematic reflexive analysis of letters written by primary caregivers from a secret Facebook support group

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- **Objectives:** To analyse the content of letters written by female spouse primary caregivers of patients with glioblastoma multiforme (GBM), a devastating and terminal primary brain cancer, and give voice to their experiences for medical providers of patients with GBM.
- **Design:** A **qualitative study** using **reflexive thematic analysis of letters written by female spouses/life partners and primary caregivers of patients with GBM.**
- **Participants:** **101** current or former female spouse primary caregivers of patients with GBM wrote letters to share with the medical community **between July 2019 and August 2019**.
- **Inclusion criteria:** (1) the primary caregiver who is a spouse of a patient with glioblastoma, (2) be a member of the secret Facebook group, **'We are the wives of GBM and this is our story'** and (3) completed informed consent for the contents of their letter to be included for primary and secondary data analysis. Participants who wrote letters but did not complete the informed consent were excluded from the study.
- **Results:** Themes from the letters included the **patient experiences**: (1) medical details of the disease trajectory, (2) interactions of the patient/caregiver dyads with healthcare and (3) the changing patient condition over time. Themes focused on the **caregiver experiences: (1) caregiver challenges, (2) caregiver responses and (3) caregiver coping strategies, and description of tangible needs that would help other caregivers in the future.** Caregiver needs were highest during the living with disease progression phase. Caregivers wanted more education and to be valued as members of the care team.
- **Conclusion:** Shared decision-making through family-centred care would be beneficial for primary caregivers of patients with GBM. **These findings provide opportunities to guide more timely and tailored interventions to provide support and improve care for patient/caregiver dyads to help mitigate the burden of this progressive disease and improve quality of life for caregivers.**

Clinical Trial > Pediatr Blood Cancer. 2024 Apr;71(4):e30874. doi: 10.1002/pbc.30874. Epub 2024 Jan 17.

A phase 1 study of mebendazole with bevacizumab and irinotecan in high-grade gliomas

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- **Background:** High-grade gliomas (**HGG**) have a dismal prognosis despite multimodal therapy. **Mebendazole is an anti-helminthic benzimidazole** that has demonstrated efficacy in numerous in vitro cancer models, and is able to cross the blood-brain barrier. We conducted a **phase 1** trial (NCT01837862) to evaluate the safety of mebendazole in combination with bevacizumab and irinotecan in children and young adults with HGG.
- **Objective:** To determine the maximally tolerated dose of mebendazole when given in combination with bevacizumab and irinotecan in children with HGG; to describe the progression-free survival (PFS) and overall survival (OS) for this group.
- **Design/method:** Patients between 1 and 21 years of age with HGG were enrolled in a 3 + 3 design to escalating doses of **mebendazole in combination with bevacizumab (10 mg/kg/dose) and irinotecan (150 mg/m^2 /dose**). Subjects were eligible upfront after completion of radiation or at the time of progression. Mebendazole was taken **orally twice per day continuously, and bevacizumab and irinotecan were given intravenously on Days 1 and 15 of 28-day cycles**.
- **Results:** Between 2015 and 2020, **10** subjects were enrolled at mebendazole doses of 50 mg/kg/day (n = 3), 100 mg/kg/day (n = 4), and 200 mg/kg/day (n = 3). One subject assigned to 100 mg/kg/day was not evaluable. Seven subjects had a diagnosis of diffuse midline glioma, one subject had anaplastic astrocytoma, and one subject had a spinal HGG. All subjects received radiation. There were no dose-limiting toxicities. **The most frequent G3/4 adverse events were neutropenia (n = 3) and lymphopenia (n = 4). The overall response rate was 33%, with two subjects achieving a partial response and one subject achieving a complete response sustained for 10 months.** The mean PFS and OS from the start of study treatment were 4.7 and 11.4 months, respectively.
- **Conclusion:** Mebendazole was safe and well tolerated when administered with bevacizumab and irinotecan at doses up to 200 mg/kg/day. Further studies are needed to determine the efficacy of this treatment.

Actualités en Neuro-Oncologie

- **Présentations lors congrès 2024**
- **Publications de 2023-2024**
- 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

Childs Nerv Syst. 2024 Jun 15. doi: 10.1007/s00381-024-06486-6. Online ahead of print.

Molecular-targeted therapy for childhood low-grade glial and glioneuronal tumors

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- Since the discovery of the association between BRAF mutations and fusions in the development of childhood low-grade gliomas and the subsequent recognition that most childhood low-grade glial and glioneuronal tumors have aberrant signaling through the **RAS/RAF/MAP kinase pathway**, there has been a dramatic change in how these tumors are conceptualized. Many of the fusions and mutations present in these tumors are associated with molecular targets, which have agents in development or already in clinical use.
- Various agents, **including MEK inhibitors, BRAF inhibitors, MTOR inhibitors and, in small subsets of patients NTRK inhibitors**, have been used successfully to treat children with recurrent disease, after failure of conventional approaches such as surgery or chemotherapy. The relative benefits of chemotherapy as compared to molecular-targeted therapy for children with newly diagnosed gliomas and neuroglial tumors are under study. Already the **combination of an MEK inhibitor and a BRAF inhibitor has been shown superior to conventional chemotherapy (carboplatin and vincristine) in newly diagnosed children with BRAF-V600E mutated low-grade gliomas and neuroglial tumors**. However, the long-term effects of such molecular-targeted treatment are unknown. The potential use of molecular-targeted therapy in early treatment has made it mandatory that the molecular make-up of the majority of low-grade glial and glioneuronal tumors is known before initiation of therapy. The primary exception to this rule is in children with neurofibromatosis type 1 who, by definition, have NF1 loss; however, even in this population, gliomas arising in late childhood and adolescence or those not responding to conventional treatment may be candidates for biopsy, especially before entry on molecular-targeted therapy trials.

Clinical Trial > BMC Cancer. 2024 Jan 30;24(1):147. doi: 10.1186/s12885-024-11820-x.

LOGGIC/FIREFLY-2: a phase 3, randomized trial of tovorafenib vs. chemotherapy in pediatric and young adult patients with newly diagnosed low-grade glioma harboring an activating RAF alteration

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- **Background:** Pediatric low-grade glioma (pLGG) is essentially a single pathway disease, with most tumors driven by genomic alterations affecting the mitogen-activated protein kinase/ERK (MAPK) pathway, predominantly KIAA1549::BRAF fusions and BRAF V600E mutations. This makes pLGG an ideal candidate for MAPK pathway-targeted treatments. The type I **BRAF inhibitor**, **dabrafenib**, in combination with the **MEK inhibitor, trametinib**, has been approved by the United States Food and Drug Administration for the systemic treatment of **BRAF V600E-mutated pLGG**. However, this combination is not approved for the treatment of patients with tumors harboring BRAF fusions as type I RAF inhibitors are ineffective in this setting and may paradoxically enhance tumor growth. **The type II RAF inhibitor, tovorafenib** (formerly DAY101, TAK-580, MLN2480), has shown promising activity and good tolerability in patients with **BRAF-altered pLGG in the phase 2 FIREFLY-1 study**, with an objective response rate (ORR) per Response Assessment in Neuro-Oncology high-grade glioma (RANO-HGG) criteria of 67%. Tumor response was independent of histologic subtype, BRAF alteration type (fusion vs. mutation), number of prior lines of therapy, and prior MAPK-pathway inhibitor use.
- **Methods:** LOGGIC/FIREFLY-2 is a two-arm, randomized, open-label, multicenter, global, **phase 3** trial to evaluate the efficacy, safety, and tolerability of tovorafenib monotherapy vs. current standard of care (SoC) chemotherapy in patients < 25 years of age with pLGG harboring an activating RAF alteration who require first-line systemic therapy. Patients are randomized 1:1 to either **tovorafenib, administered once weekly at 420 mg/m^2 (not to exceed 600 mg),** or investigator's choice of prespecified SoC chemotherapy regimens. The primary objective is to compare ORR between the two treatment arms, as assessed by independent review per RANO-LGG criteria. Secondary objectives include comparisons of progression-free survival, duration of response, safety, neurologic function, and clinical benefit rate.
- **Discussion:** The promising tovorafenib activity data, CNS-penetration properties, strong scientific rationale combined with the manageable tolerability and safety profile seen in patients with pLGG led to the SIOPe-BTG-LGG working group to nominate tovorafenib for comparison with SoC chemotherapy in this first-line phase 3 trial. The efficacy, safety, and functional response data generated from the trial may define a new SoC treatment for newly diagnosed pLGG.

Clinical Trial > Nat Med. 2024 Jan;30(1):207-217. doi: 10.1038/s41591-023-02668-y. Epub 2023 Nov 17.

The type II RAF inhibitor tovorafenib in relapsed/refractory pediatric low-grade glioma: the phase 2 FIREFLY-1 trial

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- BRAF genomic alterations are the most common oncogenic drivers in pediatric low-grade glioma (pLGG). Arm 1 (n = 77) of the ongoing **phase 2 FIREFLY-1** (PNOC026) trial investigated the efficacy of the oral, selective, central nervous system-penetrant, **type II RAF inhibitor tovorafenib (420 mg m^{-2} once weekly; 600 mg maximum)** in patients with **BRAF-altered, relapsed/refractory pLGG**. Arm 2 (n = 60) is an extension cohort, which provided treatment access for patients with RAF-altered pLGG after arm 1 closure. Based on independent review, according to Response Assessment in Neuro-Oncology High-Grade Glioma (RANO-HGG) criteria, the overall response rate (ORR) of 67% met the arm 1 prespecified primary endpoint; median duration of response (DOR) was 16.6 months; and median time to response (TTR) was 3.0 months (secondary endpoints). Other select arm 1 secondary endpoints included ORR, DOR and TTR as assessed by Response Assessment in Pediatric Neuro-Oncology Low-Grade Glioma (RAPNO) criteria and safety (assessed in all treated patients and the primary endpoint for arm 2, n = 137). The **ORR** according to RAPNO criteria (including minor responses) was **51%**; median DOR was 13.8 months; and median TTR was 5.3 months. The most common treatment-related adverse events (TRAEs) were **hair color changes (76%), elevated creatine phosphokinase (56%) and anemia (49%)**. Grade ≥3 TRAEs occurred in 42% of patients. Nine (7%) patients had TRAEs leading to discontinuation of tovorafenib. These data indicate that tovorafenib could be an effective therapy for BRAF-altered, relapsed/refractory pLGG.

Clinical Trial > J Clin Oncol. 2024 Feb 1;42(4):441-451. doi: 10.1200/JCO.23.01838. Epub 2023 Nov 17.

Everolimus for Children With Recurrent or Progressive Low-Grade Glioma: Results From the Phase II PNOC001 Trial

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- **Purpose:** The PNOC001 **phase II single-arm trial** sought to estimate progression-free survival (PFS) associated with everolimus therapy for progressive/recurrent pediatric low-grade glioma (pLGG) on the basis of phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway activation as measured by phosphorylated-ribosomal protein S6 and to identify prognostic and predictive biomarkers.
- **Patients and methods:** Patients, age 3-21 years, with **progressive/recurrent pLGG** received **everolimus orally, 5 mg/m^2 once daily**. Frequency of driver gene alterations was compared among independent pLGG cohorts of newly diagnosed and progressive/recurrent patients. PFS at 6 months (primary end point) and median PFS (secondary end point) were estimated for association with everolimus therapy.
- **Results:** Between 2012 and 2019, 65 subjects with progressive/recurrent pLGG (median age, 9.6 years; range, 3.0-19.9; 46% female) were enrolled, with a median follow-up of 57.5 months. The 6-month PFS was 67.4% (95% CI, 60.0 to 80.0) and median PFS was 11.1 months (95% CI, 7.6 to 19.8). Hypertriglyceridemia was the most common grade ≥3 adverse event. PI3K/AKT/mTOR pathway activation did not correlate with clinical outcomes (6-month PFS, active 68.4% *v* nonactive 63.3%; median PFS, active 11.2 months *v* nonactive 11.1 months; $P = .80$). Rare/novel ***KIAA1549::BRAF* fusion breakpoints were most frequent in supratentorial midline pilocytic astrocytomas**, in patients with progressive/recurrent disease, and correlated with **poor** clinical outcomes (median PFS, rare/novel *KIAA1549::BRAF* fusion breakpoints 6.1 months *v* **common *KIAA1549::BRAF* fusion** breakpoints 16.7 months; $P < .05$). Multivariate analysis confirmed their independent risk factor status for disease progression in PNOC001 and other, independent cohorts. Additionally, rare pathogenic germline variants in homologous recombination genes were identified in 6.8% of PNOC001 patients.
- **Conclusion:** Everolimus is a well-tolerated therapy for progressive/recurrent pLGGs. rare/novel *KIAA1549::BRAF* fusion breakpoints may define biomarkers for progressive disease and should be assessed in future clinical trials.

Actualités en Neuro-Oncologie

- **Présentations lors congrès 2024**
- **Publications de 2023-2024**
- 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

Clinical Trial > Neuro Oncol. 2024 May 3;26(Supplement_2):S173-S181.
doi: 10.1093/neuonc/noae031.

ACTION: a randomized phase 3 study of ONC201 (dordaviprone) in patients with newly diagnosed H3 K27M–mutant diffuse glioma

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- **Background:** **H3 K27M-mutant diffuse glioma** primarily affects children and young adults, is associated with a poor prognosis, and no effective systemic therapy is currently available. ONC201 (dordaviprone) has previously demonstrated efficacy in patients with recurrent disease. This phase 3 trial evaluates ONC201 in patients with newly diagnosed H3 K27M-mutant glioma.
- **Methods:** **ACTION** (NCT05580562) is a randomized, double-blind, placebo-controlled, parallel-group, international phase 3 study of ONC201 in newly diagnosed H3 K27M-mutant diffuse glioma. Patients who have **completed standard frontline radiotherapy are randomized 1:1:1 to receive placebo, once-weekly dordaviprone, or twice-weekly dordaviprone on 2 consecutive days.** Primary efficacy endpoints are overall survival (OS) and progression-free survival (PFS); PFS is assessed by response assessment in neuro-oncology high-grade glioma criteria (RANO-HGG) by blind independent central review. Secondary objectives include safety, additional efficacy endpoints, clinical benefit, and quality of life. Eligible patients have histologically confirmed H3 K27M-mutant diffuse glioma, a Karnofsky/Lansky performance status ≥70, and completed first-line radiotherapy. Eligibility is not restricted by age; however, patients must be ≥10 kg at time of randomization. **Patients with a primary spinal tumor, diffuse intrinsic pontine glioma, leptomeningeal disease, or cerebrospinal fluid dissemination are not eligible.**
- ACTION is currently enrolling in multiple international sites.

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Actualités en Neuro-Oncologie

- **Présentations lors congrès 2024**
- **Publications de 2023-2024**
- 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

Actualités en Neuro-Oncologie

- **Présentations lors congrès 2024**
- **Publications de 2023-2024**
- 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

> Acta Neuropathol. 2024 Jan 24;147(1):24. doi: 10.1007/s00401-023-02674-x.

Molecular characteristics and improved survival prediction in a cohort of 2023 ependymomas

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- The diagnosis of **ependymoma** has moved from a purely histopathological review with limited prognostic value to an integrated diagnosis, relying heavily on molecular information. However, as the integrated approach is still novel and some molecular ependymoma subtypes are quite rare, few studies have correlated integrated pathology and clinical outcome, often focusing on small series of single molecular types. We collected data from 2023 ependymomas as classified by DNA methylation profiling, consisting of **1736 previously published and 287 unpublished methylation profiles**. Methylation data and clinical information were correlated, and an integrated model was developed to predict progression-free survival. **Patients with EPN-PFA, EPN-ZFTA, and EPN-MYCN tumors showed the worst outcome with 10-year overall survival rates of 56%, 62%, and 32%, respectively**.
- **EPN-PFA harbored chromosome 1q gains and/or 6q losses** as markers for worse survival.
- In supratentorial **EPN-ZFTA, a combined loss of CDKN2A and B** indicated worse survival, whereas a single loss did not. Twelve out of 200 EPN-ZFTA (6%) were located in the posterior fossa, and these tumors relapsed or progressed even earlier than supratentorial tumors with a combined loss of CDKN2A/B. Patients with MPE and PF-SE, generally regarded as non-aggressive tumors, only had a 10-year progression-free survival of 59% and 65%, respectively. For the prediction of the 5-year progression-free survival, Kaplan-Meier estimators based on the molecular subtype, a Support Vector Machine based on methylation, and an integrated model based on clinical factors, CNV data, and predicted methylation scores achieved balanced accuracies of 66%, 68%, and 73%, respectively. Excluding samples with low prediction scores resulted in balanced accuracies of over 80%.
- In sum, our large-scale analysis of ependymomas provides robust information about molecular features and their clinical meaning. Our data are particularly relevant for rare and hardly explored tumor subtypes and seemingly benign variants that display higher recurrence rates than previously believed.

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Actualités en Neuro-Oncologie

- **Présentations lors congrès 2024**
- **Publications de 2023-2024**
- 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

Neurooncol Adv. 2024 Jul 4;6(1):vdae101. doi: 10.1093/noajnl/vdae101. eCollection 2024 Jan-Dec.

Molecular genetics and diversity of choroid plexus tumors

Christian Thomas [1], Martin Hasselblatt [1]

- Choroid plexus tumors are rare intraventricular brain tumors predominantly arising in children but also affecting adults.
- **Chromosome-wide copy-number alterations and *TP53* mutations** do occur, but in most choroid plexus tumors, driver mutations have not been identified.
- Here we give a brief overview of the histopathological and clinical diversity of choroid plexus tumors and their genetic and epigenetic heterogeneity. Preliminary data indicate that choroid plexus carcinomas comprise at least 2 epigenetic subgroups, one of which is associated with *TP53* mutation status.
- These findings strongly encourage us to further investigate the genetic and epigenetic heterogeneity in a larger cohort and to align molecular subgroup status with clinical annotations, in order to identify prognostic markers that may also aid stratification within future international trials.

Actualités en Neuro-Oncologie

- **Présentations lors congrès 2024**
- **Publications de 2023-2024**
- 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

Review > CNS Oncol. 2024 Dec 31;13(1):2357532. doi: 10.1080/20450907.2024.2357532. Epub 2024 Jun 14.

Novel insights toward diagnosis and treatment of glioneuronal and neuronal tumors in young adults

Vincenzo Di Nunno [1], Marta Aprile [2], Lidia Gatto [1], Alicia Tosoni [1], Lucia Ranieri [1], Stefania Bartolini [1], Enrico Franceschi [1]

- **Aim:** **Glioneuronal and neuronal tumors are rare** primary central nervous system malignancies with heterogeneous features. Due to the rarity of these malignancies diagnosis and treatment remains a clinical challenge.
- **Methods:** Here we performed a narrative review aimed to investigate the principal issues concerning the diagnosis, pathology, and clinical management of glioneuronal tumors.
- **Results:** Diagnostic criteria have been recently overturned thanks to a better characterization on a histological and molecular biology level. The study of genomic alterations occurring within these tumors has allowed us to identify **potential therapeutic targets including BRAF, FGFR, and PDGFRA.**
- **Conclusion:** Techniques allowing molecular sequencing DNA methylation assessment of the disease are essential diagnostic tools. Targeting agents should be included in the therapeutic armamentarium after loco-regional treatment failure.

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Actualités en Neuro-Oncologie

- **Présentations lors congrès 2024**
- **Publications de 2023-2024**
- 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 Oncol. 2024 Jun 5:noae092. doi: 10.1093/neuonc/noae092. Online ahead of print.

Risk factors for domain-specific neurocognitive outcome in pediatric survivors of a brain tumor in the posterior fossa – Results of the HIT 2000 trial

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- **Background:** Neurocognition can be severely affected in pediatric brain tumor survivors. We analyzed the association of cognitive functioning with radiotherapy dose, postoperative cerebellar mutism syndrome (pCMS), hydrocephalus, intraventricular methotrexate (MTX) application, tumor localization and biology in pediatric survivors of a posterior fossa tumor.
- **Methods:** Subdomain-specific neurocognitive outcome data from **279 relapse-free survivors of the HIT-2000 trial (241 medulloblastoma and 38 infratentorial ependymoma)** using the Neuropsychological Basic Diagnostic (NBD) tool based on Cattell-Horn-Carroll's model for intelligence were analyzed.
- **Results:** **Cognitive performance 5.14 years** (mean; range=1.52-13.02) after diagnosis was significantly **below normal** for all subtests. Processing speed and psychomotor abilities were most affected. Influencing factors were domain-specific: CSI-dose had strong impact on most subtests. pCMS was associated with psychomotor abilities (β=-0.25 to -0.16) and processing speed (β=-0.32). Postoperative hydrocephalus correlated with crystallized intelligence (β=-0.20) and short-term memory (β=-0.15), age with crystallized intelligence (β=0.15) and psychomotor abilities (β=-0.16 and β=-0.17). Scores for fluid intelligence (β=-0.23), short-term memory (β=-0.17) and visual processing (β=-0.25) declined, and scores for selective attention improved (β=0.29) with time after diagnosis.
- **Conclusion:** **Dose of CSI was strongly associated with neurocognitive outcome.**
- Low **psychomotor abilities and processing speed** both in patients treated with and without CSI suggest a strong contribution of the tumor and its surgery on these functions. Future research therefore should analyze strategies to both reduce CSI-dose and toxicity caused by other treatment modalities.

> Clin Cancer Res. 2024 Jun 3;30(11):2545-2557. doi: 10.1158/1078-0432.CCR-23-1880.

GD2–Targeting CAR T–cell Therapy for Patients with GD2+ Medulloblastoma

Roselia Ciccone [# 1], Concetta Quintarelli [# 1 2], Antonio Camera [# 1], Michele Pezzella [1], Simona Caruso [1], Simona Manni [1], Alessio Ottaviani [1], Marika Guercio [1], Francesca Del Bufalo [1], Maria Cecilia Quadraccia [1], Domenico Orlando [1], Stefano Di Cecca [1], Matilde Sinibaldi [1], Mariasole Aurigemma [1], Laura Iaffaldano [1], Andrea Sarcinelli [1], Maria Luisa D'Amore [1], Manuela Ceccarelli [1], Francesca Nazio [1], Veronica Marabitti [1], Ezio Giorda [3], Marco Pezzullo [3], Cristiano De Stefanis [3], Andrea Carai [4], Sabrina Rossi [5], Rita Alaggio [5], Giada Del Baldo [1], Marco Becilli [1], Angela Mastronuzzi [1], Biagio De Angelis [# 1], Franco Locatelli [# 1 6]

- **Purpose:** **Medulloblastoma** (MB), the most common childhood malignant brain tumor, has a poor prognosis in about 30% of patients. The current standard of care, which includes surgery, radiation, and chemotherapy, is often responsible for cognitive, neurologic, and endocrine side effects. We investigated whether **chimeric antigen receptor (CAR) T cells directed toward the disialoganglioside GD2** can represent a potentially more effective treatment with reduced long-term side effects.
- **Experimental design:** GD2 expression was evaluated on primary tumor biopsies of MB children by flow cytometry. GD2 expression in MB cells was also evaluated in response to an EZH2 inhibitor (tazemetostat). In in vitro and in vivo models, GD2+ MB cells were targeted by a CAR-GD2.CD28.4-1BBζ (CAR.GD2)-T construct, including the suicide gene inducible caspase-9.
- **Results:** **GD2 was expressed in 82.68% of MB tumors**. The **SHH and G3-G4 subtypes** expressed the highest levels of GD2, whereas the WNT subtype expressed the lowest. In in vitro coculture assays, **CAR.GD2 T cells were able to kill GD2+ MB cells**. Pretreatment with tazemetostat upregulated GD2 expression, sensitizing GD2dimMB cells to CAR.GD2 T cells cytotoxic activity. In orthotopic mouse models of MB, intravenously injected CAR.GD2 T cells significantly controlled tumor growth, prolonging the overall survival of treated mice. Moreover, the dimerizing drug AP1903 was able to cross the murine blood-brain barrier and to eliminate both blood-circulating and tumor-infiltrating CAR.GD2 T cells.
- **Conclusions:** Our experimental data indicate the potential efficacy of CAR.GD2 T-cell therapy. **A phase I/II clinical trial is ongoing** in our center (NCT05298995) to evaluate the safety and therapeutic efficacy of CAR.GD2 therapy in high-risk MB patients.

Clinical Trial > Clin Cancer Res. 2024 Feb 16;30(4):741-753. doi: 10.1158/1078-0432.CCR-23-2959.

Phase I/II Study of the WEE1 Inhibitor Adavosertib (AZD1775) in Combination with Carboplatin in Children with Advanced Malignancies: Arm C of the AcSé–ESMART Trial

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- **Purpose:** **AcSé-ESMART Arm C** aimed to define the recommended dose and activity of the **WEE1 inhibitor adavosertib in combination with carboplatin** in children and young adults with molecularly enriched recurrent/refractory malignancies.
- **Patients and methods:** **Adavosertib** was administered **orally, twice every day on Days 1 to 3 and carboplatin intravenously on Day 1 of a 21-day cycle, starting at 100 mg/m2/dose and AUC 5, respectively**. Patients were enriched for molecular alterations in cell cycle and/or homologous recombination (HR).
- **Results:** **Twenty** patients (median age: 14.0 years; range: 3.4-23.5) were included; 18 received 69 treatment cycles. Dose-limiting toxicities were prolonged grade 4 neutropenia and grade 3/4 thrombocytopenia requiring transfusions, leading to **two de-escalations to adavosertib 75 mg/m2/dose and carboplatin AUC 4**; no recommended phase II dose was defined. Main treatment-related toxicities were hematologic and gastrointestinal. Adavosertib exposure in children was equivalent to that in adults; both doses achieved the cell kill target. Overall response rate was 11% (95% confidence interval, 0.0-25.6) with **partial responses in 2 patients with neuroblastoma. One patient with medulloblastoma** experienced unconfirmed partial response and 5 patients had stable disease beyond four cycles. Seven of these eight patients with clinical benefit had alterations in HR, replication stress, and/or RAS pathway genes with or without TP53 alterations, whereas TP53 pathway alterations alone (8/10) or no relevant alterations (2/10) were present in the 10 patients without benefit.
- **Conclusions:** **Adavosertib-carboplatin combination exhibited significant hematologic toxicity. Activity signals** and identified potential biomarkers suggest further studies with less hematotoxic DNA-damaging therapy in molecularly enriched pediatric cancers.

Actualités en Neuro-Oncologie

- **Présentations lors congrès 2024**
- **Publications de 2023-2024**
- 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

Clinical Trial > Neuro Oncol. 2024 Jul 5;26(7):1302-1309. doi: 10.1093/neuonc/noae037.

3D volume growth rate evaluation in the EORTC-BTG-1320 clinical trial for recurrent WHO grade 2 and 3 meningiomas

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- **Background:** We previously reported that tumor **3D volume growth rate (3DVGR)** classification could help in the assessment of drug activity in patients with meningioma using 3 main classes and a total of 5 subclasses: class 1: decrease; 2: stabilization or severe slowdown; 3: progression.
- The **EORTC-BTG-1320** clinical trial was a randomized phase II trial evaluating the efficacy of trabectedin for recurrent WHO 2 or 3 meningioma. Our objective was to evaluate the discriminative value of 3DVGR classification in the EORTC-BTG-1320.
- **Methods:** All patients with at least 1 available MRI before trial inclusion were included. 3D volume was evaluated on consecutive MRI until progression. 2D imaging response was centrally assessed by MRI modified Macdonald criteria. Clinical benefit was defined as neurological or functional status improvement or steroid decrease or discontinuation.
- **Results:** **Sixteen** patients with a median age of 58.5 years were included. Best 3DVGR classes were: 1, 2A, 3A, and 3B in 2 (16.7%), 4 (33.3%), 2 (16.7%), and 4 (33.3%) patients, respectively. All patients with progression-free survival longer than 6 months had best 3DVGR class 1 or 2. **3DVGR classes 1 and 2 (combined) had a median overall survival of 34.7 months versus 7.2 months for class 3 (P = .061). All class 1 patients (2/2), 75% of class 2 patients (3/4), and only 10% of class 3 patients (1/10) had clinical benefit.**
- **Conclusions:** **Tumor 3DVGR classification may be helpful to identify early signals of treatment activity in meningioma clinical trials.**

Actualités en Neuro-Oncologie

- **Présentations lors congrès 2024**
- **Publications de 2023-2024**
- 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

> Cureus. 2024 May 7;16(5):e59798. doi: 10.7759/cureus.59798. eCollection 2024 May.

Intracranial Solitary Fibrous Tumor/Hemangiopericytoma: A Series of 14 Cases and Review of the Literature

Corneliu Toader [1], Dorel Arsene [2], Andrei Adrian Popa [1], Razvan-Adrian Covache-Busuioc [1], Bogdan-Gabriel Bratu [1], Luca-Andrei Glavan [1], David-Ioan Dumitrascu [1], Alexandru Vladimir Ciurea [1]

- **Solitary fibrous tumor (SFT)** is a rare type of tumor characterized by spindle-shaped cells originating from mesenchymal tissue.
- This case series presents a collection of **14 intracranial** solitary fibrous tumors treated between 2014 and 2022 in our institute in Bucharest, Romania. Through a systematic investigation, key aspects spanning the preoperative, intraoperative, and postoperative phases of patient care were highlighted.
- Our study examines various factors including tumor location (which was very heterogeneous), size (median of 49 mm, ranging between 22 mm and 70 mm), surgical techniques employed, and recurrence rates. The data was analyzed using Python version 3.10 (Python Software Foundation, Wilmington, Delaware, United States). Gender disparities in SFT were noted, particularly the **male-to-female ratio which was 5:9**. The use of the Medical Research Council (MRC) Scale for Muscle Strength aided in evaluating severity and postoperative outcomes.
- **GTR was achieved in nine out of 14 cases (64.28%), prolonging the period of recurrence-free survival.**

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> Acta Neurochir (Wien). 2024 Aug 2;166(1):320. doi: 10.1007/s00701-024-06191-y.

Descriptive epidemiology of 399 histologically confirmed newly diagnosed meningeal solitary fibrous tumours and haemangiopericytomas in France: 2006–2015

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French Brain Tumour DataBase (FBTDB) Participants and Investigators with the participation of the Société française de neurochirurgie (SFNC), Club de neuro-oncologie de la société française de neurochirurgie, Société française de neuropathologie (SFNP), Association des neuro-oncologues d'expression française (ANOCEF)

- **Purpose:** Meningeal solitary fibrous tumour (SFT) and haemangiopericytoma (HPC) are uncommon tumours that have been merged into a single entity in the last 2021 WHO Classification of Tumors of the Central Nervous System. To describe the epidemiology of SFT/HPC operated in France and, to assess their incidence.
- **Methods:** We processed the **French Brain Tumour Database (FBTDB)** to conduct a nationwide population-based study of all histopathologically confirmed SFT/HPC between 2006 and 2015.
- **Results:** Our study included **399 SFT/HPC** patients, operated in France between **2006 and 2015**, in one of the 46 participating neurosurgical centres. The incidence reached 0.062, $_{95\%}$CI[0.056-0.068] for 100,000 person-years. SFT accounted for 35.8% and, HPC for 64.2%. The ratio of SFT/HPC over meningioma operated during the same period was 0.013. SFT/HPC are about equally distributed in women and men (55.9% vs. 44.1%). For the whole population, mean age at surgery was 53.9 (SD ± 15.8) years. The incidence of SFT/HPC surgery increases with the age and, is maximal for the 50-55 years category. Benign SFT/HPC accounted for 65.16%, SFT/HPC of uncertain behaviour for 11.53% and malignant ones for 23.31%. The number of resection progresses as the histopathological behaviour became more aggressive. 6.7% of the patients with a benign SFT/HPC had a second surgery vs.16.6% in case of uncertain behaviour and, 28.4% for malignant SFT/HPC patients.
- **Conclusion:** Meningeal SFT and HPC are rare CNS mesenchymal tumours which both share common epidemiological characteristics, asserting their merging under a common entity. SFT/HPC incidence is less that one case for 1 billion per year and, for around 100 meningiomas-like tumours removed, one SFT/HPC may be diagnosed. **SFT/HPC are equally distributed in women and men and, are mainly diagnosed around 50-55 years. The more aggressive the tumour, the higher the probability of recurrence.**

Actualités en Neuro-Oncologie

- **Présentations lors congrès 2024**
- **Publications de 2023-2024**
- GLIOBLASTOME
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- 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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Lanreotide versus placebo for tumour reduction in patients with a ^{68}Ga–DOTATATE PET–positive, clinically non–functioning pituitary macroadenoma (GALANT study): a randomised, multicentre, phase 3 trial with blinded outcome assessment

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- **Background:** No established medical treatment options currently exist for patients with non-functioning pituitary macroadenoma (NFPMA). Somatostatin analogues may prevent tumour growth, but randomised controlled trials are lacking. *In vivo* somatostatin receptor assessment with ^{68}Ga-DOTATATE PET could help in selecting patients for treatment. **We aimed to determine the effect of the somatostatin analogue lanreotide on tumour size in patients with a ^{68}Ga-DOTATATE PET-positive NFPMA**.
- **Methods:** The **GALANT** study was an investigator-initiated, **multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 3** trial with recruitment at three academic hospitals in the Netherlands. Adult patients with a suprasellar extending NFPMA, either surgery-naïve or postoperative remnant ≥10 mm, were eligible for inclusion. Important exclusion criteria were previous sellar radiotherapy and use of dopamine receptor agonists. Somatostatin receptor expression in the NFPMA was determined through **^{68}Ga-DOTATATE PET/CT**, co-registered with MRI. A predefined sample of **44** patients with **PET-positive NFPMA were randomly assigned (1:1) to lanreotide acetate 120 mg or placebo, both administered as deep subcutaneous injections every 28 days for 72 weeks** Primary outcome was the change in cranio-caudal tumour diameter measured on pituitary MRI from baseline to end-of-treatment in the intention-to-treat population. Participants, investigators and outcome assessors were masked to treatment allocation. The trial is registered with the Netherlands Trial Registry, NL5136, and EudraCT, 2015-001234-22.
- **Findings:** Between Nov 3, 2015, and Dec 10, 2019, **49** patients were included in the study. Forty-four patients with a ^{68}Ga-DOTATATE PET-positive NFPMA were randomly assigned to lanreotide (22 [50%]) or placebo (22 [50%]). Study treatment was completed in 13 (59%) lanreotide and 19 (86%) placebo participants. The mean (SD) change from baseline in cranio-caudal tumour diameter after treatment was +1·2 (2·5) mm with lanreotide and +1·3 (1·5) mm with placebo; adjusted mean difference versus placebo -0·1 mm (95% CI -1·3 to 1·2, p = 0·93). Adverse events occurred in 22 (100%, 147 events) lanreotide and 21 (95%, 94 events) placebo participants. **Gastrointestinal complaints were most common, reported by 18 (82%) lanreotide and 8 (36%) placebo participants**. There were no treatment-related serious adverse events.
- **Interpretation:** **Compared with placebo, lanreotide treatment did not reduce tumour size or growth in patients with ^{68}Ga-DOTATATE PET-positive NFPMA.**

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- SCHWANNOME VESTIBULAIRE

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Encorafenib and binimetinib followed by radiotherapy for patients with BRAFV600–mutant melanoma and brain metastases (E–BRAIN/GEM1802 phase II study)

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- **Background:** **Encorafenib plus binimetinib (EB)** is a standard of care treatment for advanced **BRAFV600-mutant melanoma**. We assessed efficacy and safety of encorafenib plus binimetinib in patients with BRAFV600-mutant melanoma and brain metastasis (BM) and explored if radiotherapy improves the duration of response.
- **Methods:** E-BRAIN/GEM1802 was a **prospective, multicenter, single arm, phase II** trial that enrolled patients with melanoma BRAFV600-mutant and BM. Patients received **encorafenib 450 mg once daily plus binimetinib 45 mg BID**, and those who achieved partial response or stable disease at first tumor assessment were offered radiotherapy. Treatment continued until progression.Primary endpoint was intracranial response rate (icRR) after 2 months of EB, establishing a futility threshold of 60%.
- **Results:** The study included **25** patients with no BM symptoms and **23** patients with **BM symptoms** regardless of using corticosteroids. Among them, 31 patients (64.6%) received sequential radiotherapy. After two months, **icRR was 70.8%** (95% CI: 55.9-83.1); 10.4% complete response. Median intracranial PFS and OS were 8.5 (95% CI: 6.4-11.8) and 15.9 (95% CI: 10.7-21.4) months, respectively (8.3 months for icPFS and 13.9 months OS for patients receiving RDT). Most common grade 3-4 treatment-related adverse event was **alanine aminotransferase (ALT) increased (10.4%).**
- **Conclusion:** **Encorafenib plus binimetinib showed promising clinical benefit in terms of icRR, and tolerable** safety profile with low frequency of high grade TRAEs, in patients with BRAFV600-mutant melanoma and BM, **including those with symptoms and need for steroids. Sequential radiotherapy is feasible but it does not seem to prolong response.**

Clinical Trial > Signal Transduct Target Ther. 2024 Aug 13;9(1):215.
doi: 10.1038/s41392-024-01927-9.

Gefitinib (an EGFR tyrosine kinase inhibitor) plus anlotinib (an multikinase inhibitor) for untreated, EGFR-mutated, advanced non-small cell lung cancer (FL-ALTER): a multicenter phase III trial

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- Dual inhibition of vascular endothelial growth factor and epidermal growth factor receptor (EGFR) signaling pathways offers the prospect of improving the effectiveness of EFGR-targeted therapy. In this **phase 3** study (ClinicalTrial.gov: NCT04028778), **315** patients with treatment-naïve**, EGFR-mutated, advanced non-small cell lung cancer (NSCLC)** were randomized (1:1) to receive **anlotinib or placebo plus gefitinib once daily on days 1-14 per a 3-week cycle**. At the prespecified final analysis of progression-free survival (**PFS**), a significant improvement in PFS was observed for the **anlotinib arm over the placebo arm (hazards ratio [HR] = 0.64, 95% CI, 0.48-0.80, P = 0.003**).
- **Particularly, patients with brain metastasis** and those harboring **EGFR amplification or high tumor mutation** load gained significant more **benefits in PFS from gefitinib plus anlotinib**.
- The incidence of grade 3 or higher treatment-emergent adverse events was 49.7% of the patients receiving gefitinib plus anlotinib versus 31.0% of the patients receiving gefitinib plus placebo.
- **Anlotinib plus gefitinib significantly improves PFS in patients with treatment-Naïve , EGFR-mutated, advanced NSCLC,** with a manageable safety profile.

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Efficacy and Safety of KRASG12C Inhibitor IBI351 Monotherapy in Patients With Advanced NSCLC: Results From a Phase 2 Pivotal Study

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- **Introduction:** KRAS glycine-to-cysteine substitution at codon 12 (**G12C**) **mutation** is a well-recognized and increasingly promising therapeutic target with huge unmet clinical needs in NSCLC patients. IBI351 is a potent covalent and irreversible inhibitor of KRAS G12C. Here, we present the efficacy and safety of IBI351 from an open-label, single-arm, phase 2 pivotal study.
- **Methods:** Eligible patients with **NSCLC with KRAS G12C** who failed standard therapy were enrolled. IBI351 was orally administered at a dose of 600 mg twice daily. The primary endpoint was confirmed objective response rate assessed by an independent radiological review committee (IRRC) as per Response Evaluation Criteria in Solid Tumors v1.1. Other endpoints were safety, IRRC-confirmed disease control rate, duration of response, progression-free survival (PFS), and overall survival.
- **Results:** As of December 13, 2023, **116** patients were enrolled (Eastern Cooperative Oncology Group Performance Status 1: 91.4%; brain metastasis: 30.2%; prior treatments with both anti-PD-1 or anti-PD-L1 inhibitors and platinum-based chemotherapy: 84.5%). As per the IRRC assessment, the **confirmed objective response rate was 49.1% (95% confidence interval [CI]: 39.7-58.6), and the disease control rate was 90.5%** (95% CI: 83.7-95.2). The median duration of response was not reached whereas disease progression or death events occurred in 22 patients (38.6%), and the median PFS was 9.7 months (95% CI: 5.6-11.0). overall survival data was immature. Treatment-related adverse events (TRAEs) occurred in 107 patients (92.2%) whereas 48 patients (41.4%) had equal to or higher than grade three TRAEs. **Common TRAEs were anemia (44.8%), increased alanine aminotransferase (28.4%), increased aspartate aminotransferase (27.6%), asthenia (26.7%) and presence of protein in urine (25.0%). TRAEs leading to treatment discontinuation occurred in nine patients (7.8%)**. In biomarker evaluable patients (n = 95), all patients had positive KRAS G12C in tissue whereas 72 patients were blood-positive and 23 were blood-negative for KRAS G12C. Patients with KRAS G12C in both blood and tissue had higher tumor burden at baseline ($p < 0.05$) and worse PFS ($p < 0.05$). Tumor mutation profiling identified tumor protein p53 (45.3%), serine/threonine kinase 11 (STK11) (30.5%), and kelch-like ECH-associated protein 1 (21.1%) as the most common genes co-mutated with KRAS G12C. Among 13 genes with mutation frequency equal to or higher than 5%, mutations of six genes (STK11, kelch-like ECH-associated protein 1, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma, DNA polymerase epsilon, SMAD family member 4, and BMP/retinoic acid-inducible neural-specific protein 3) were significantly associated with worse PFS ($p < 0.05$). Mutation in STK11 was also found to have a significant association with higher tumor burden at baseline and lower response rate ($p < 0.05$).
- **Conclusions:** **IBI351 monotherapy demonstrated promising and sustained efficacy with manageable safety, supporting its potential as a new treatment option for KRAS G12C-mutant NSCLC.**

> Cancer Commun (Lond). 2024 Jul 17. doi: 10.1002/cac2.12594. Online ahead of print.

Central nervous system efficacy of aumolertinib versus gefitinib in patients with untreated, EGFR-mutated, advanced non-small cell lung cancer: data from a randomized phase III trial (AENEAS)

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- **Background:** The initial randomized, double-blinded, actively controlled, **phase III ANEAS** study (NCT03849768) demonstrated that **aumolertinib showed superior efficacy relative to gefitinib** as first-line therapy in epidermal growth factor receptor **(EGFR)-mutated advanced non-small cell lung cancer (NSCLC)**. Metastatic disease in the central nervous system (CNS) remains a challenge in the management of NSCLC. This study aimed to compare the efficacy of aumolertinib versus gefitinib among patients with baseline CNS metastases in the ANEAS study.
- **Methods:** Eligible patients were enrolled and randomly assigned in a 1:1 ratio to orally receive either aumolertinib or gefitinib in a double-blinded fashion. Patients with asymptomatic, stable CNS metastases were included. Follow-up imaging of the same modality as the initial CNS imaging was performed every 6 weeks for 15 months, then every 12 weeks. CNS response was assessed by a neuroradiological blinded, independent central review (neuroradiological-BICR). The primary endpoint for this subgroup analysis was CNS progression-free survival (PFS).
- **Results:** Of the **429** patients enrolled and randomized in the ANEAS study, **106 patients were found to have CNS metastases** (CNS Full Analysis Set, cFAS) at baseline by neuroradiological-BICR, and 60 of them had CNS target lesions (CNS Evaluable for Response, cEFR). **Treatment with aumolertinib significantly prolonged median CNS PFS compared with gefitinib** in both cFAS (29.0 vs. 8.3 months; hazard ratio [HR] = 0.31; 95% confidence interval [CI], 0.17-0.56; P < 0.001) and cEFR (29.0 vs. 8.3 months; HR = 0.26; 95% CI, 0.11-0.57; P < 0.001). The confirmed CNS overall response rate in cEFR was 85.7% and 75.0% in patients treated with aumolertinib and gefitinib, respectively. Competing risk analysis showed that the estimated **probability of CNS progression without prior non-CNS progression or death was consistently lower with aumolertinib than with gefitinib** in patients with and without CNS metastases at baseline. No new safety findings were observed.
- **Conclusions:** These results indicate a **potential advantage of aumolertinib over gefitinib in terms of CNS PFS and the risk of CNS progression in patients with EGFR-mutated advanced NSCLC** with baseline CNS metastases.

Actualités en Neuro-Oncologie

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- METASTASES CEREBRALES
- **SCHWANNOME VESTIBULAIRE**

Meta-Analysis > Neurosurg Rev. 2024 Jul 9;47(1):307. doi: 10.1007/s10143-024-02552-4.

Comparative analysis of upfront stereotactic radiosurgery and watchful waiting in the management of newly diagnosed vestibular schwannomas: a systematic review and meta-analysis

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- Vestibular schwannomas (VS) are benign intracranial tumors posing significant management challenges. This study aims to compare the outcomes of stereotactic radiosurgery (SRS) and watchful waiting (WW) in the management of newly diagnosed VS, integrating findings from both retrospective and the pioneering V-REX prospective trial.
- Adhering to PRISMA guidelines, a systematic review was conducted using MEDLINE, Embase, and Cochrane databases. Studies directly comparing SRS with WW for newly diagnosed VS were included. Primary outcomes focused on hearing preservation assessed through the AAO-HNS or Gardner-Robertson hearing classification scales and tumor progression, with secondary outcomes focusing on neurological symptoms, and the need for further treatment.
- **Thirteen studies** encompassing **1,635 patients** (WW: 891; SRS: 744) were included.While no significant difference was found in serviceable hearing loss at last follow-up (RR = 1.51, [95%CI: 0.98, 2.32], p = 0.06), significant differences favoring WW were observed in pure tone audiometry (PTA) (MD = -13.51 [95%CI: -22.66, -4.37], p = 0.004) and word recognition score (WRS) (MD = 20.48 [95%CI: 9.72, 31.25], p = 0.0002). Analysis of tumor progression indicated no overall significant difference in risk between SRS and WW (RR = 0.40, [95%CI 0.07, 2.40], p = 0.32), but subgroup analysis suggested a lower risk with SRS in certain contexts. The need for further treatments favored SRS (RR = 0.24, [95%CI: 0.07, 0.74], p = 0.007). **No significant differences were found in tinnitus and imbalance between the two groups.** This comprehensive analysis suggests **no marked difference in functional hearing preservation between SRS and WW in managing VS**. However, untreated tumors commonly necessitate additional interventions. These findings highlight the need for individualized treatment decisions and underscore the importance of continued monitoring.
- The study advocates for further prospective trials to refine management strategies for VS.

Clinical Trial > N Engl J Med. 2024 Jun 27;390(24):2284-2294. doi: 10.1056/NEJMoa2400985. Epub 2024 Jun 21.

Brigatinib in *NF2*–Related Schwannomatosis with Progressive Tumors

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- **Background:** ***NF2*-related schwannomatosis** (*NF2*-SWN, formerly called neurofibromatosis type 2) is a tumor predisposition syndrome that is manifested by multiple vestibular schwannomas, nonvestibular schwannomas, meningiomas, and ependymomas. The condition is relentlessly progressive with no approved therapies. On the basis of preclinical activity of **brigatinib** (an **inhibitor of multiple tyrosine kinases**) in *NF2*-driven nonvestibular schwannoma and meningioma, data were needed on the use of brigatinib in patients with multiple types of progressive *NF2*-SWN tumors.
- **Methods:** In this **phase 2** platform trial with a basket design, patients who were 12 years of age or older with *NF2*-SWN and progressive tumors were treated with oral brigatinib at a dose of 180 mg daily. A central review committee evaluated one target tumor and up to five nontarget tumors in each patient. The primary outcome was radiographic response in target tumors. Key secondary outcomes were safety, response rate in all tumors, hearing response, and patient-reported outcomes.
- **Results:** A total of **40** patients (median age, 26 years) with progressive target tumors **(10 vestibular schwannomas, 8 nonvestibular schwannomas, 20 meningiomas, and 2 ependymomas)** received treatment with brigatinib. After a median follow-up of 10.4 months, the percentage of tumors with a radiographic **response was 10%** (95% confidence interval [CI], 3 to 24) for target tumors and 23% (95% CI, 16 to 30) for all tumors; **meningiomas and nonvestibular schwannomas had the greatest benefit**. Annualized growth rates decreased for all tumor types during treatment. **Hearing improvement occurred in 35%** (95% CI, 20 to 53) of eligible ears. Exploratory analyses suggested a decrease in self-reported pain severity during treatment (-0.013 units per month; 95% CI, -0.002 to -0.029) on a scale from 0 (no pain) to 3 (severe pain). No grade 4 or 5 treatment-related adverse events were reported.
- **Conclusions:** Brigatinib treatment resulted in radiographic responses in multiple tumor types and clinical benefit in a heavily pretreated cohort of patients with *NF2*-SWN. (Funded by the Children's Tumor Foundation and others; INTUITT-NF2 ClinicalTrials.

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