Gliomi di alto grado: dalla caratterizzazione molecolare al trattamento

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DEL SACRO CUORE

Disclosures of Veronica Biassoni

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
ONCOSCIENCE						X	
ELI LILLY			X				Concluded

pHGG: Epidemiology

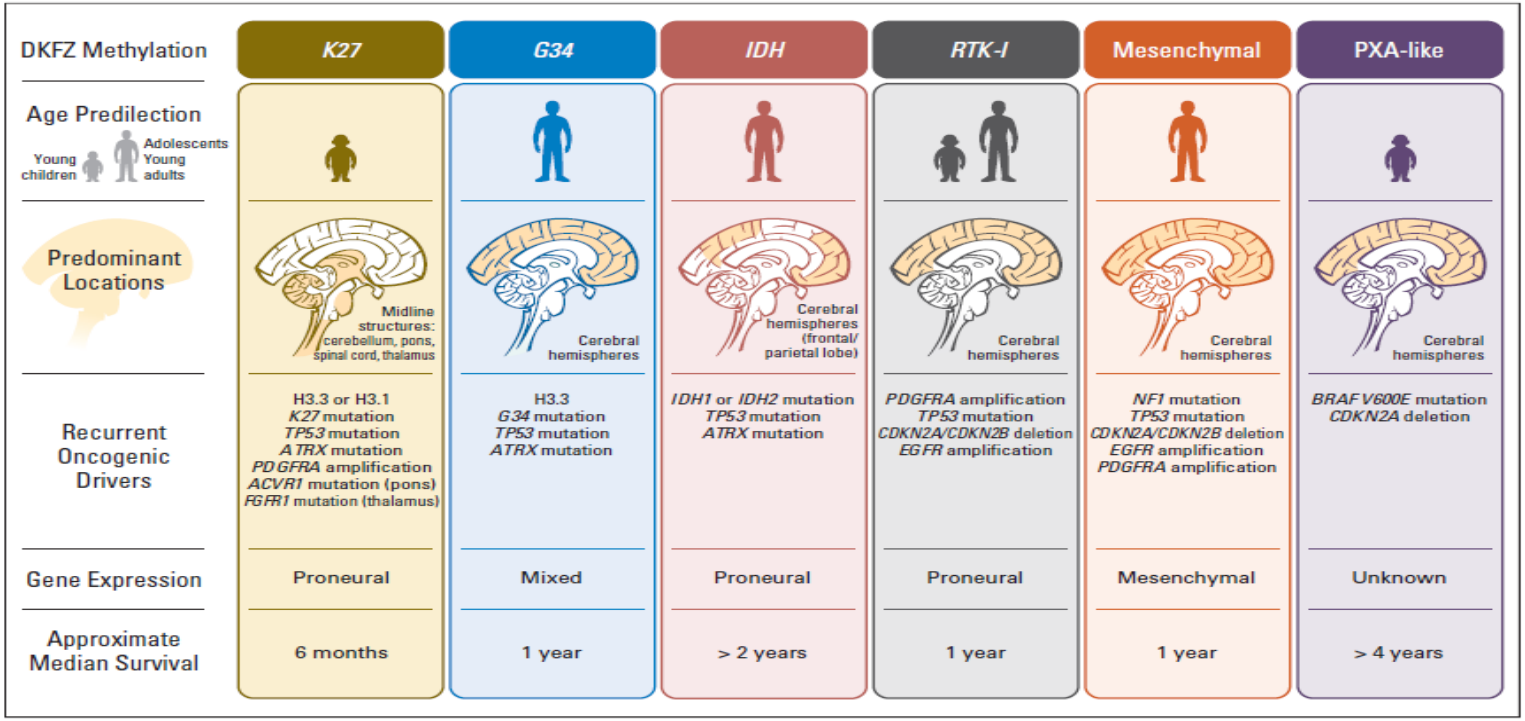
- Global incidence rate: 1.1 -1.78 cases per 100,000 children
- pHGGs account for 15% of CNS tumours in children and adolescents
- Reported OS ranges from 10 to 73 months
- pHGGs have a five-year survival rate of less than 10%, even with aggressive treatment regimens
- Survival varies according to their anatomical location: for tumors located in the supratentorial region, the 5-year overall survival rate is less than 20%, with most patients succumbing to the disease within 2 years of diagnosis. Tumors located in the brain stem, also carry a dismal median survival of less than 1 year
- Although clinical presentation and tumor histology of adult HGG and pHGG are often very similar, these two entities are **distinct in the genetic and epigenetic alterations**

Abigail Y et al, Emerging and biological concepts in pediatric high-grade gliomas, Cells 2024

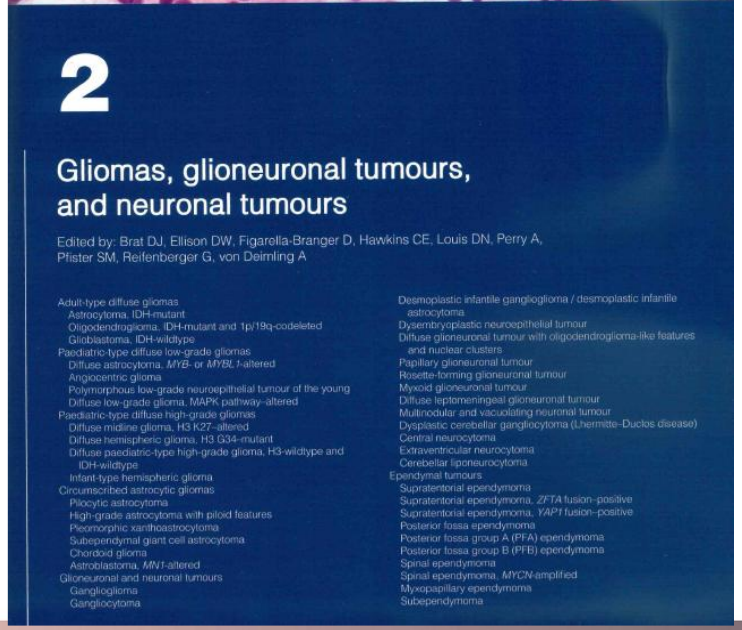
Paediatric and adult malignant glioma: close relatives or distant cousins?

Chris Jones, Lara Perryman and Darren Hargrave

Nat Rev Clin Oncol 9,400-413(2012)



WHO 2021 CLASSIFICATION OF PEDIATRIC HGG



World Health Organization Classification of Tumors of the Central Nervous System, fifth edition
Gliomas, glioneuronal tumors, and neuronal tumors
- **Adult-type diffuse gliomas**
Astrocytoma, IDH-mutant
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted
Glioblastoma, IDH-wildtype
- **Pediatric-type diffuse low-grade gliomas**
Diffuse astrocytoma, MYB- or MYBL1-altered
Angiocentric glioma
Polymorphous low-grade neuroepithelial tumor of the young
Diffuse low-grade glioma, MAPK pathway-altered
- **Pediatric-type diffuse high-grade gliomas**
Diffuse midline glioma, H3 K27-altered
Diffuse hemispheric glioma, H3 G34-mutant
Diffuse pediatric-type high-grade glioma, H3-wildtype and IDH-wildtype
Infant-type hemispheric glioma
- **Circumscribed astrocytic gliomas**
Pilocytic astrocytoma
High-grade astrocytoma with piloid features
Pleomorphic xanthoastrocytoma
Subependymal giant cell astrocytoma
Chordoid glioma
Astroblastoma, MN1-altered

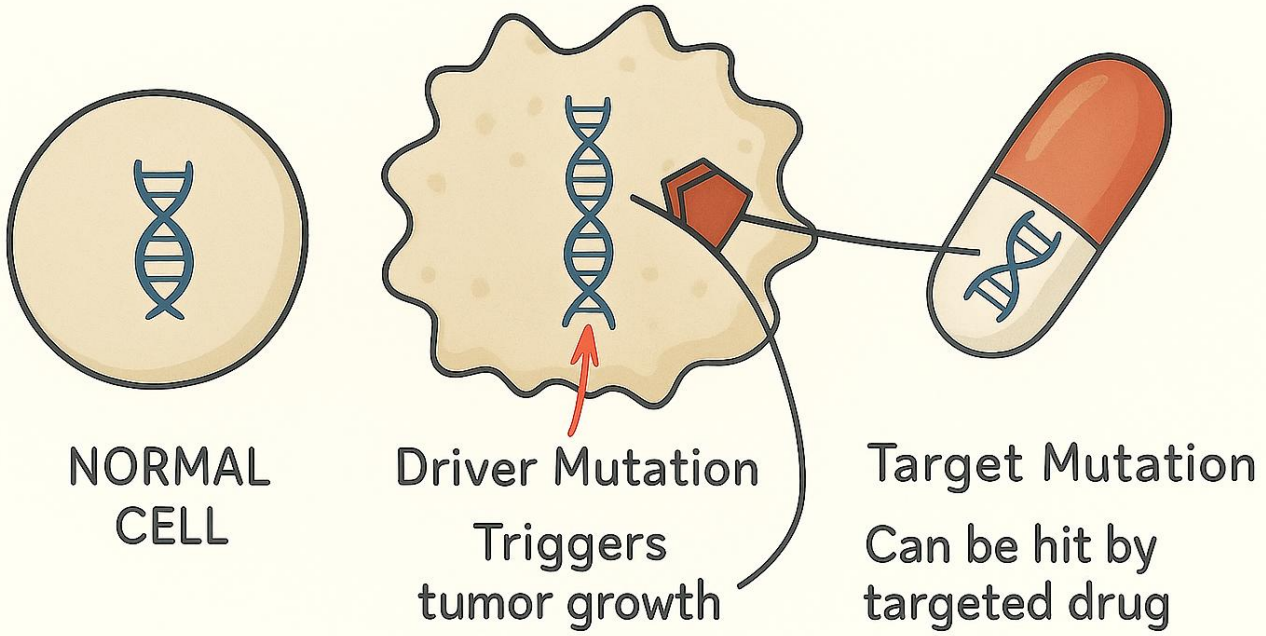
WHO 2021 CLASSIFICATION: WHAT'S NEW

The WHO CNS5

- Introduces changes mainly related to pediatric CNS tumors
- Integration of histologic diagnosis with molecular pofile («integrated diagnosis»)
- Introduction of novel molecular techniques such as DNA methylation, NGS
- Differentiation between «adult-type» and «pediatric-type» tumors
- The association with CPS is clearly reported
- The introduction of novel tumor entities (i.e. High-grade astrocytoma with piloid features)
- CNS tumor grading are written in arabic numbers
- Switch to «within tumor type» grading
- Simplified tumor nomenclature for better clinical utility

*Its implementation on a routine clinical basis presents some challenges that require real-world interaction in **multidisciplinary molecular tumor board** (MTB) in order to identify the appropriate treatment according to the histopathological features and the genetic alterations*

D'Amati et al, Frontiers in Molecular Neuroscience, 2024


NORMAL CELL
Driver Mutation
Triggers tumor growth
Target Mutation
Can be hit by targeted drug

Pediatric-type diffuse high-grade gliomas (pHGG)

Within the pHGG tumor there are distinct sub-types defined by epigenetic and characteristic somatic mutations:

1. Diffuse Midline Gliomas, H3 K27-altered

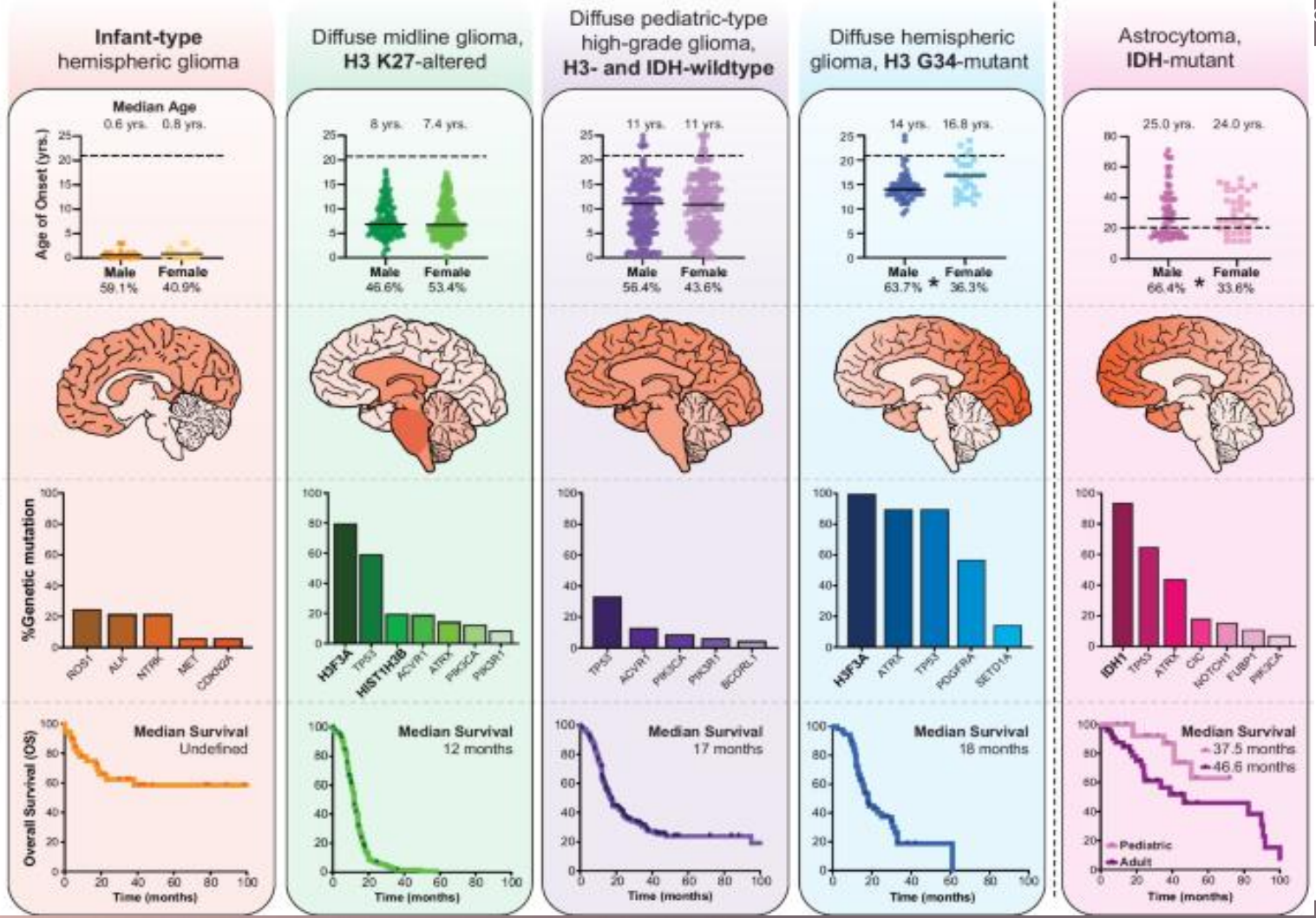
2. Diffuse Hemispheric Glioma, H3 G34-mutant

3. Diffuse pediatric-type high-grade glioma, H3-wildtype IDH-wildtype

4. Infant-type hemispheric glioma

Diagnostic Criteria According to the 5° CNS WHO Classification

	Essential	Desirable
K27 M-altered	• Diffuse glioma with loss of K27me3 by immunohistochemistry, midline location **AND** • K27M mutation for H3 K27–mutant subtype, **OR** • Pathogenic mutation or amplification of EGFR for the EGFR-mutant subtype, **OR** • Overexpression of EZHIP for the H3-wildtype with EZHIP overexpression subtype, **OR** • Methylation profile of one of the subtypes of diffuse midline glioma	• Molecular results discriminating the H3.1 or H3.2 subtype from the H3.3 subtype
H3 G34-mutant	• Cellular, infiltrative glioma with mitotic activity **AND** • H3.3 G34R or G34V mutation **AND** • Hemispheric location **AND** • Methylation profile of diffuse hemispheric glioma, H3 G34–mutant (for unresolved lesions)	• OLIG2 immunonegativity • Loss of ATRX expression • Diffuse p53 immunopositivity
pHGG H3/IDH WT	• A diffuse glioma in a child or young adult with high mitotic activity **AND** • Lack of IDH1/IDH2 mutations **AND** • Lack of H3 mutations **AND** • Methylation profile: pHGG RTK1, RTK2 or MYCN **OR** • PDGFRA alteration, EGFR alteration, or MYCN amplification	• Microvascular proliferation • Necrosis, typically palisading • K27me3 retained
Infant-type hemispheric glioma	• Cellular astrocytoma **AND** • Presentation in early childhood **AND** • Hemispheric location **AND** • Receptor tyrosine kinase alterations (e.g. fusion in NTRK family gene or ROS1, MET1, or ALK) **OR** • Methylation profile: infant-type hemispheric glioma	



Ocasio JK et al. Oncohistones and disrupted development in pediatric-type diffuse high-grade glioma. Cancer Metastasis Rev. 2023 Jun;42(2):367-388

MOLECULAR LANDSCAPE OF pHGG

Genetic mutations/pathways	Characteristics	Available therapies
Receptor Tirosine Kinase (RTK): PDGFR, EGFR, FGFR	- 60% DMG amplification/mutation within the RTK-RAS-PI3K - EGFR amplification/overexpression in 4%	- AIFA (2025) Inclusion of Nimo + Vino in combination (concomitant with and subsequent to RT) in the list established, pursuant to Law No. 648/1996, for the treatment of DIPG. (Determination No. 832/2025) - Ph1/2 Study with avapritinib in ped pts with mutations in KIT or PDGFRA just closed.
TP53	Mutations (including deletions of CDKN2A/ARF and/or amplif MDM2 and MDM4) in up to 80% of DMG but also in H3WT (associated with more aggressiveness)	
ACVR1	Mutations in up to 20% of DMG	
ATRX	17% of pHGG have inactivating mutations	
BRAFV600E	6-15% pHGG, more favourable prognosis	AIFA (2024) Dabra+Trame indicated for pediatric patients aged 1 year and older with HGG with a BRAFV600E mutation who have received at least one prior RT and/or CT.
NF1	Uncommon association (occurrence of HGG in NF1 in 0.28-5%)	
RTK FUSIONS (IHG)	In a recent meta-analysis on 156 pts: 131 (**84%) had fusions in RTK**, of which ALK was most prevalent (62/131), followed by NTRK1/2/3 (30/131), ROS1 (30/131), and MET (9/131) (*Chavaz L et al, Infant -type hemispheric glioma (IHG): An individual patient data meta-analysis; in publication)*	- AIFA (2021): Entrectinib indicated in adult/pediatric >12yrs with solid tumors NTRK fused, • with locally advanced, m+ disease, or where surgical resection has severe morbidity, not previously treated with an NTRK inhibitor • w/o satisfactory treatment options - Alectinib under evaluation in a phase I/II, open-label, multicenter study in pediatric patients with ALK fusion-positive solid or CNS tumors with uneffective prior treatment/without satisfactory treatment available **- RTK-fusions** in 60-80% of cases (20-40% no «targetable» disease): “old drugs” still play a role → CCG-945 study, Baby POG I (1986-1996), BBSFOP protocol, UKCCSG/SIOP CNS 9204 trial

STANDARD OF CARE

SURGERY

- ✓ Diagnosis
- ✓ Alleviate ICP
- ✓ Cytoreductive: for supratentorial/hemispheric/infratentorial tumors GTR gives a survival benefit, for midline tumors no survival advantage (*Yang T et al, World Neurosurg 2013; Han Q et al, Front Oncol 2020; Hatoum R et al, JAMA Netw. Open 2022)*

RT

- ✓ SOC for children after surgery (Skliarenko J et al, Medicine 2020)
- ✓ 54 Gy in 30 1.8 Gy daily fractions over 6 weeks
- ✓ avoided < 3yrs

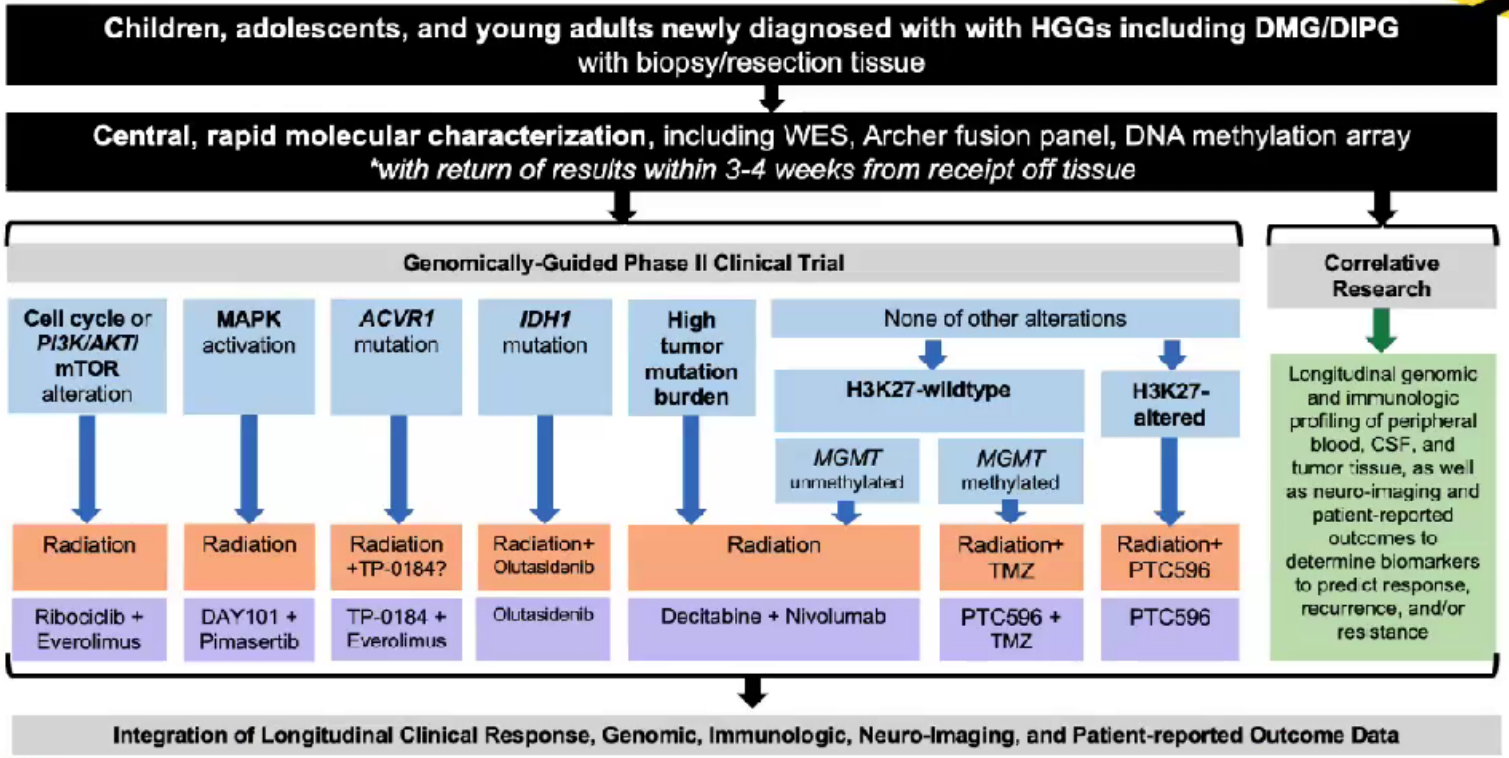
STANDARD OF CARE (II): CHEMOTHERAPY

Stupp regimen comes from adult **randomized Ph 3 study** comparing RT +/- concomitant and adjuvant TMZ therapy in newly diagnosed HGG (*Stupp R et al,. N Engl J Med. 2005)*. **Experimental arm** had a median OS of 14.6 months in the TMZ plus RT arm vs. 12.1 months in the RT alone arm. In the **follow-up** the 5-year OS of the exp group was 9.8% vs. 1.9% in the control group *(Stupp R et al. The Lancet Oncology. 2009).*

- ✓ **COG phase II ACNS0126** trial, RT+TMZ failed to demonstrate significant improvement compared with previous RTCT regimens in pHGG, in contrast, **HIT-HGG-2007** trial was launched by the GPOH to investigate the non-inferiority of a less toxic TMZ radiochemotherapy for pHGG (including DIPG in comparison to the previous protocols HIT-GBM-C and D). Results did not only confirm non-inferiority and less toxicity for the analyzed **438 HIT-HGG-2007 patients**, but demonstrated even increased OS in non-pontine HGG (median OS: 19.3 months) and improved EFS rates for patients with both non-pontine and pontine HGG (median EFS +3.3 /+2 months) compared with the historical cohort. The significance of MGMT overexpression in predicting response to alkylating agents remains a matter of debate in pediatric HGG. In the HIT-HGG 2007 trial, TMZ response was independent from MGMT status: patients with unmethylated MGMT promoter did not experience an inferior response to TMZ radio-chemotherapy compared to patients with methylated MGMT promotor *(Karreman M et al, EJC Pediatric Oncology, 2025).*
- ✓ With its comparatively favorable toxicity profile and the possibility of an oral outpatient treatment, TMZ radiochemotherapy is nowadays widely considered as the treatment of choice in pediatric patients with (non-DIPG/non-DMG) hemispheric HGG *(Cohen JK et al, Neuro-Oncology 2011).*
- ✓ The **addition of CCNU** as adjuvant treatment to TMZ radiotherapy was associated with superior OS and EFS rates compared to TMZ alone, especially in pHGG without resection, GBM patients and in tumors showing MGMT overexpression but with increased toxicity *(Jakacki RI et al, Neuro-Oncology 2016; Gupta T et al Neuro-Oncol Pract 2022).*
- ✓ **Phase II HERBY trial** explore the role of Bevacizumab (anti VEGFR) added to TMZ radiochemotherapy. No improvement in survival, but considerable treatment toxicity was reported. 12 TMZ cycles feasible *(Grill J et al, Journal of Clin Oncology 2018).*

TREATMENT STRATEGIES FOR PEDIATRIC HGG:
AN OVERVIEW

Schema



connect

COllaborative Network for NEuro-oncology Clinical Trials

Open /Enrolling/Approved PNOC Studies

DMG/DIPG

- **PNOC018** (KIND T cell trial H3.3K27M DMG)
- **PNOC022** (DMG platform trial)
- **PNOC023** (Phase 1 ONC206 which includes one stratum for all malignant brain tumors)
- *PNOC034* (ADI-PEG; non DIPG)
- *PNOC036* (B-SYNC) in 2025
- *PNOC040* (FUS platform) in 2025
- *PNOC043* (NEO100 DMG) in

HGG

- **PNOC017** (IDH mutant)
- **PNOC020** (RNA vaccine for newly diagnosed HGG)
- **PNOC021** (combination of everolimus and trametinib)
- **PNOC025** (Phase 1of CD47 inhibitor magrolimab)
- *PNOC034* (ADI-PEG; G34 and WT HGG) in 2025
- *PNOC038* (LAG-3; recurrent HGG) in 2025

LGG

- **PNOC017** (IDH LGG)
- **PNOC021** (everolimus and trametinib)
- *PNOC037* (de-escalation trial) in 2025

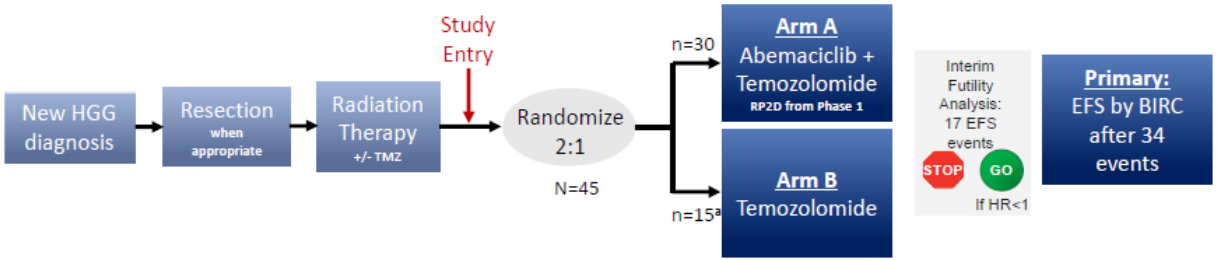
Medullo

- **PNOC025** (Phase 1 magrolimab)
- **PNOC027** (real time drug testing)
- PNOC044 (T3 in 2025)

Other

- **PNOC023**
- **PNOC028** (NK cells)
- **PNOC029** (cranio)
- *PNOC033* (CPC)
- *PNOC038* (LAG-3; ependymoma)
- *PNOC041* (LITT)
- *PNOC042*

ABEMACICLIB (Ph 2 Randomized study)



[a]Bayesian augmented control arm (in addition to the 15 participants enrolled)

Stratification

CDK4/6 pathway alterations (Yes *vs* No *vs* Unknown)

Secondary endpoints

EFS by inv. assessment, OS, response, safety, PK, acceptability and palatability of abemaciclib

Centri aperti:
- Napoli-Santobono (10/2024)
- Genova-Gaslini (9/2024)
- INT (1/2025)
- Roma OPBG e Gemelli
- Padova-IOV
- Torino-Ospedale Regina Margherita

Study and Enrollment Status

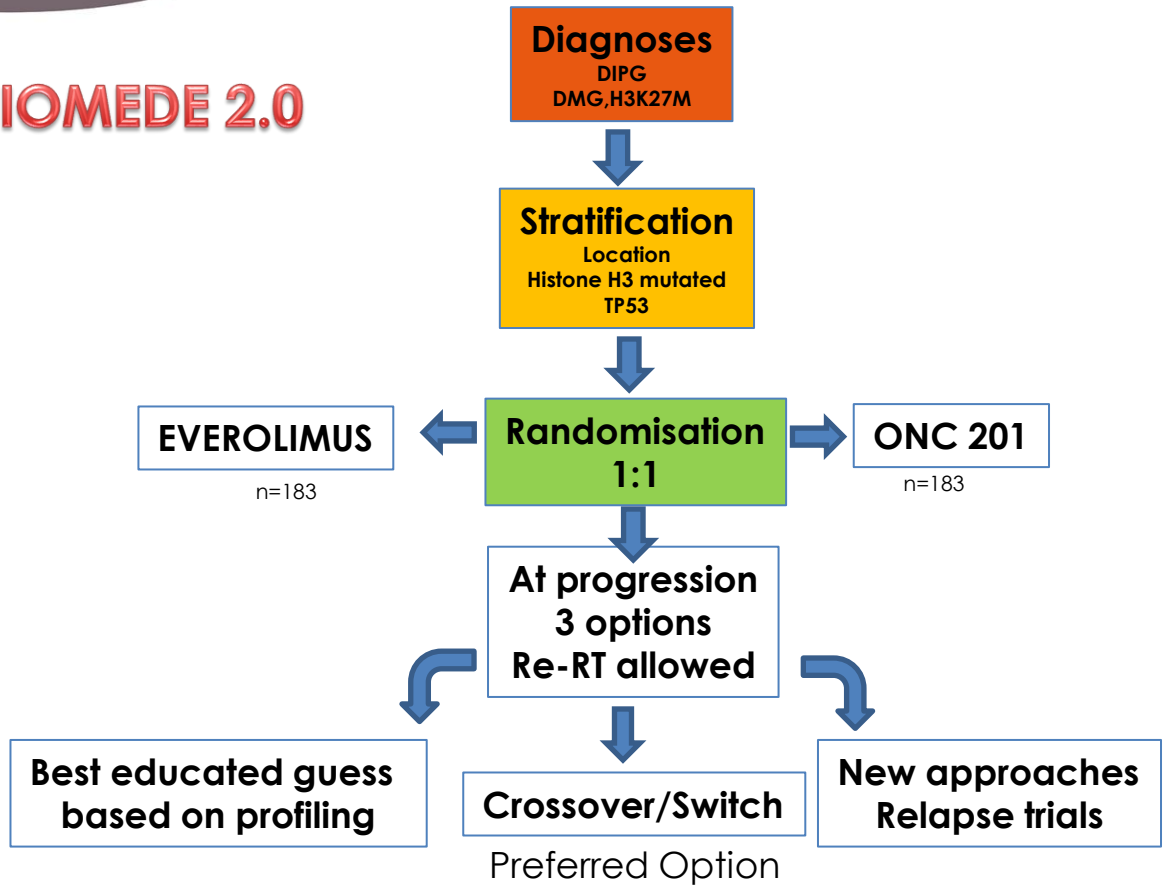
Screenings = 42
In Screening = 5
Enrollments = 28
Sites Activated = 55

Enrollment completion (n=46), originally projected for 31-Oct-2025, has been updated to the first quarter of 2026.

Screening and Enrollments To-Date

	AUS	BE	DK	FR	IT	JP	NL	RO	ES	US	Total
Screened	3	1	1	5	6	5	1	1	11	8	42
Enrolled	2	0	1	4	4	4	1	1	7	4	28

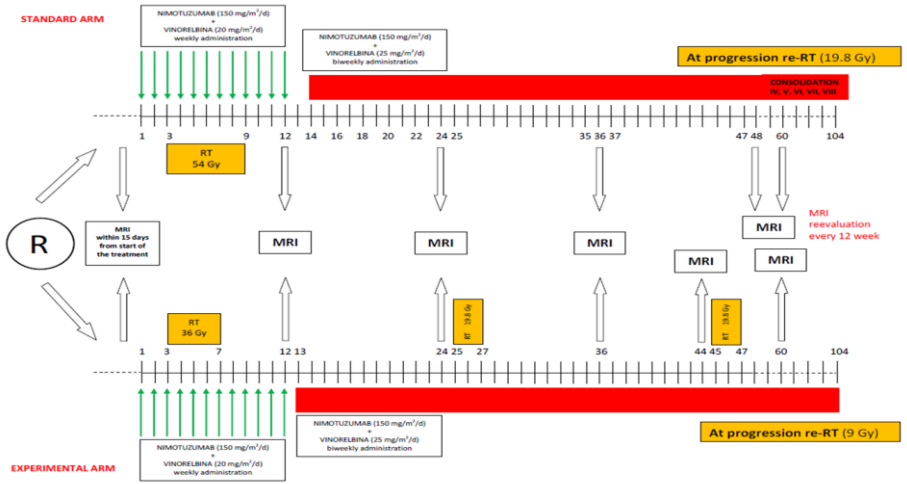
BIOMEDE 2.0



Phase III multicentric, randomized, open-label, controlled trial evaluating the efficacy of ONC201 in comparison with everolimus in children and adults with **pontine and nonpontine DMG**.

- FPI 29/09/2022
- Duration of the study 9 years (4 inclusion + 5 follow-up)
- LPLV October 2031

DIPG-INT2015



End of enrolment: 14 april 2022
5 italian centers
55 pts enrolled (27 in ST,28 exp)
Median age 7.1 years (range 3.1-17.6)
23 pts biopsied, 21 according to local protocols
54 relapsed (35 locally, 19 with a component of dissemination)
Sperimental irradiation was feasible and never produced significant radionecrosis.
.

- Median EFS/OS were 8.4/14.0 months, respectively. EFS/OS at 1 year were 20.0%/60.0%, OS was 9.1% at 2 years
- Patients submitted to biopsies had more dissemination (P=0.058)
- Median EFS/OS for standard and experimental arms were 8.4/8.4 and 14.0/13.9 months, respectively
- EFS/OS for 24/54 patients with RECIST 20% reduction were 9.9/18 months(P=0.02), respectively

Conclusions

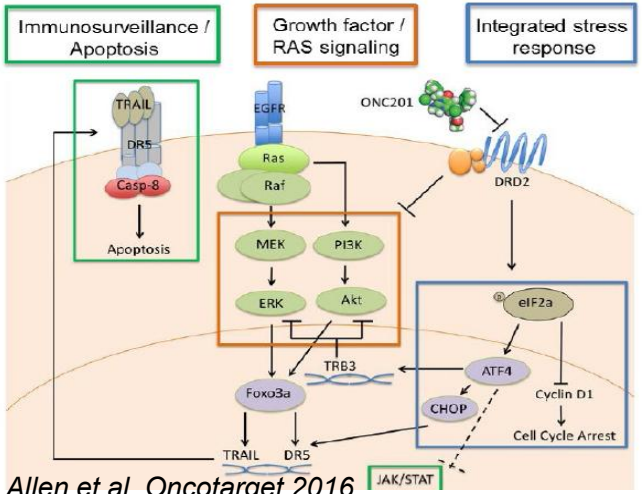
- SP arm with metronomic radiotherapy, never applied before, demonstrated feasible.
- Treatment responses were determinant for survival.

ONC201

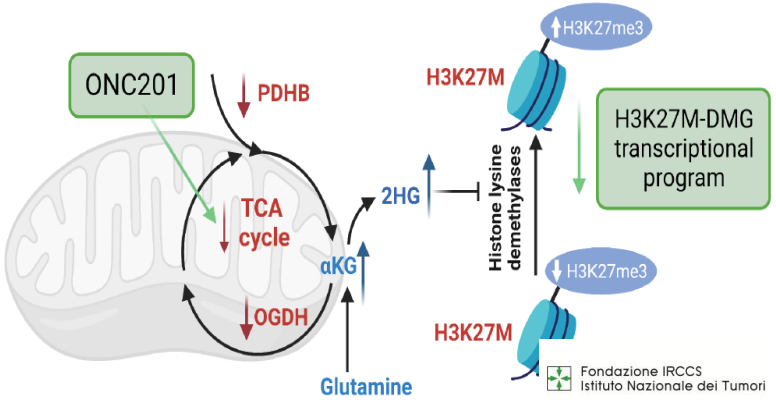
DRD2 antagonist and **mithocondrial ClpP agonist**→ it suppresses the producing-metabolism pathways + reverses the pathognomonic loss of H3K27me3.

2 cohorts of recurrent DMG:
-ONC201-018 11 pts
-ONC201-014 24 pts
Median OS 21 mos
Median PFS 11.2 mos
BUT: selected, lack uniform enrolment criteria, treated before PD, 42% thalamic, not clear the role of re-RT.

AND: they allowed to discover
- High EGFR+ClpP mutations: poor response to ONC201
- RAS/MAPK activation: better response→ combination with PI3K inhibitor (paxalisib) evaluated preclinically and now ongoing



Allen et al, Oncotarget 2016



Jacson et al, Neuro-Oncology 2023
Venneti et al, Cancer Discov. 2023
Yang Z et al, Helion 2024

Arillaga-Romany et al, Neurooncology 2024
Hansford et al, JCO 2024

Ongoing trials that will help:

- **PNOC022** (Phase II trial with ONC201 combined with different drugs, panobinostat or paxalisib, for DMG)
- **BIOMEDE 2.0** (Phase III multicenter, randomized, open-label, controlled trial evaluating the efficacy of ONC201 in comparison with everolimus in children and adults with pontine and nonpontine DMG)
- **ACTION** (Phase III, ONC201 for the Treatment of Newly Diagnosed H3 K27M-mutant Diffuse Glioma Following Completion of Radiotherapy: A Randomized, Double-Blind, **Placebo-Controlled**, Multicenter Study)

Possible role of combination therapies is advocated.

Jacson et al, Neuro-Oncology 2023
Venneti et al, Cancer Discov. 2023
Yang Z et al, Helion 2024
Arillaga-Romany et al, Neurooncology 2024
Hansford et al, JCO 2024

SIOPE-HGG-01

International cooperative randomized trial of the SIOPE HGG/DIPG Working Group for the treatment of newly diagnosed and recurrent high-grade gliomas in children, adolescents, and young adults

Responsible Pediatric Oncologists: Veronica Biassoni, Michael Karremann, Christof Kramm, and Maura Massimino

Overview

HGG/DIPG Working Group

Patient with High Grade Glioma
Diffuse HGG, non-diffuse HGG, DIPG and Gliomatosis cerebri

Primary diagnosis and age 3 to 21 years

Screening: central review process (2-3 weeks)
(neuropathology and/or neuroradiology)

DIPG or **DMG**, **non-metastatic**	**Other HGG** incl. metastatic DMG/DIPG
⇩	⇩
Stratum 1	**Stratum 2**
⇩	⇩
Randomization: CSI vs. focal radiotherapy 158 patients Estimated recruitment 4.08 years	**Randomization:** Perampanel vs. Metformin 141 patients Estimated recruitment 3,85 years
Treatment: 13 months	**Treatment:** 13 months

Minimum follow up: 24 months from time of diagnosis

Relapse/Progression and age 3 to 24 years

Screening: central review process (2-3 weeks)
(neuroradiology ± neuropathology)

DIPG or **DMG**	**Other HGG** non-DMG/non-DIPG
⇩	⇩
Stratum 3	**Stratum 4**
⇩	⇩
Randomization: Nimo/Vino vs. Vino 129 patients Estimated recruitment 3.30 years	**Observational trial:** Re-irradiation + mebendazole 100 patients Estimated recruitment 4.00 years
Treatment: 12 months	**Treatment:** 12 months

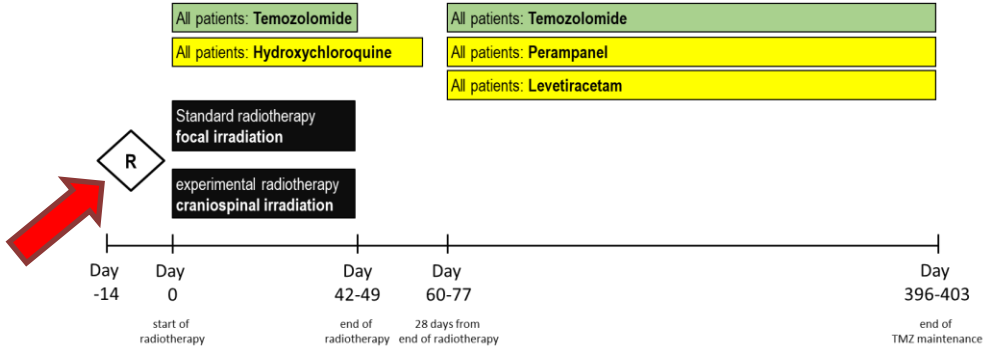
Minimum follow up: 24 months from time of preceeding progression

First-line treatment

Stratum 1: DMG/DIPG, non-metastatic

Primary Objective: CSI vs. Focal

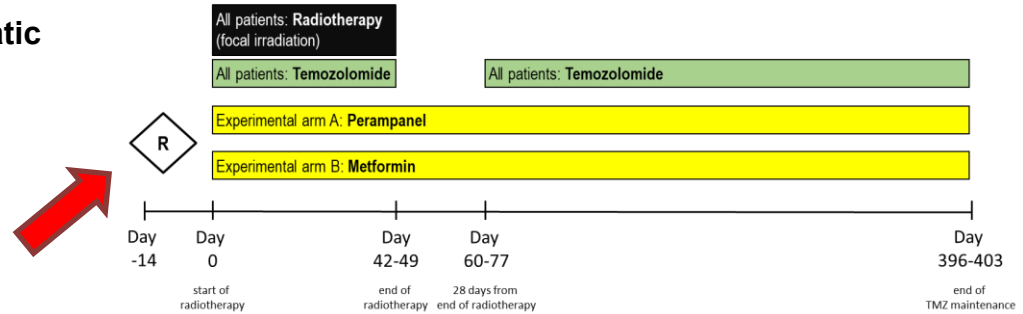
Recruitment: n= 158; 4.08 years



Stratum 2: hemispheric and/or metastatic HGG

Primary Objective: Perampanel vs. Metformin

Recruitment: n= 141; 3.85 years

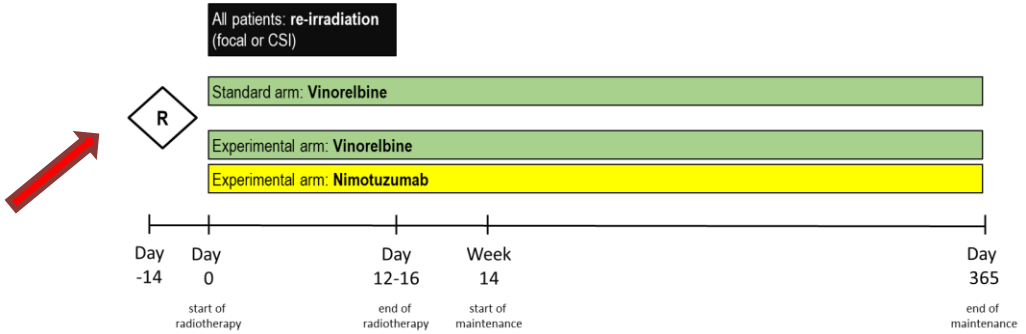


Treatment at Progression

Stratum 3: DMG/DIPG

Primary Objective: Nimotuzumab

Recruitment: n= 129; 3.30 years



Stratum 4: hemispheric HGG

Major Objectives: Toxicity and Survival

Recruitment: n= 100; 4.0 years

Funding

By March 2024, the protocol has been submitted for funding to the

German Childhood Cancer Foundation

Financial volume requested

4.141.069 € (7.842,93€ per patient)

Sponsor will be

German Pediatric Oncology Group, GPOH gGmbH

Countries involved

Austria
Germany
Italy
Switzerland
The Netherlands
Spain

Recruiting: 4 years

METABOLIC	IMMUNOLOGICAL (DMG «cold» immunological environment)		EPIGENETIC	CANCER NEUROSCIENCE	DELIVERY
	CAR-T	ONCOLYTIC VIRUSES			
Polyamines are upregulated in DMG→ targeting polyamine metabolism is a potential terapeutic approach. Preclinical data present but clinically limited by cardiotoxicity	4 potential targets: -GD2 } Clinical data available -B7-H3 } - IL13RA2 } No available data in DMG - HER2 } **How is chosen the target:** - High expression in DMG - Tumor expression >healthy tissue - Homogeneous expression **Further challenges**: - Overcome the «antigen negative» escape - Optimal route of administration - Optimal tumor access, durable engraftement and minimum toxicicty	- tumor selectivity - low probability of resistance - high oncolitic capacity - genetic manipulation **TRIALS**: - ph1 DNX-2401 for DIPG (median OS/PFS 17.8/10.7) - Ph2 in developement	**- SMARCA4** inhibition - **EZH2** inhibition - **HDAC** inhibition Under evaluation/early phase clinical trials (ph 1 panobinostat PBTC). Need for BBB penetrant epigenetic modifiers with high potency and selectivity	Neuronal activity increases ped glioma growth through paracrine factors such as: - neurologin 3 - GABAergic synapsis - AMPAR signalling →Potential targets, compounds in developement	CED FUS Need for combination with other systemic treatment to avoid dissemination

DMG OTHER INVOLVED PATHWAYS/STRATEGIES

Gállego Pérez-Larraya J et al, NEJM 2022
Zarychta J et alTher Adv Med Oncol. 2024
Drexler R, bioRxiv 2024

OTHER ISSUES

HGG IN CPS

HGG IN CMMRD

HGG AT RELAPSE

Cancer	Associated syndrome and genes involved	Surveillance recommendation
Low-grade glioma, including optic pathway gliomas	Neurofibromatosis type 1: *NF1*	As per current AACR–CPWG guidelines
Subependymal giant cell astrocytoma	Tuberous sclerosis: *TSC1, TSC2*	As per current AACR–CPWG guidelines
Dysplastic gangliocytoma of the cerebellum	*PTEN* tumor hamartoma syndrome: *PTEN*	As per current AACR–CPWG guidelines
High-grade glioma	Li–Fraumeni: *TP53*	As per current AACR–CPWG guidelines
	Replication-repair deficiency: *PMS2, MSH6, MSH2, MLH1, POLE*	As per current AACR–CPWG guidelines
	Ollier and Maffucci: post-zygotic *IDH1, IDH2, PTHR1*	As per current AACR–CPWG guidelines
	POT1-tumor predisposition syndrome: *POT1*	Follow published guidelines for adults (88)
Spinal ependymoma	Neurofibromatosis type 2: *NF2*	As per current AACR–CPWG guidelines

Note: Once an abnormality is identified on imaging, follow-up intervals should be more frequent and adjusted at the clinician's discretion. Surveillance MRI when screening for brain ± spine tumors should use gadolinium-based contrast agents for the first brain and/or spine MRI, with noncontrast imaging thereafter, unless an abnormality is suspected on noncontrast imaging, when the addition of contrast-enhanced imaging and additional sequences may be indicated.

Hansford JR et al. Update on Cancer Predisposition Syndromes and Surveillance Guidelines for Childhood Brain Tumors. Clin Cancer Res. 2024

OTHER ISSUES

HGG IN CPS | **HGG IN CMMRD** | HGG AT RELAPSE

ICI plays a role in: cancers with high TMB, high MSI and a proimmune microenvironment (high PD-L1 expression and high CD8 T-cell infiltration).

ICI has failed to reveal therapeutic benefit in non-RRD pediatric cancers possibly because of their significantly lower TMB as compared with their adult counterparts

NCT02992964 investigator-initiated, multicenter, open label, single-arm pilot study that represents the first prospective assessment of the utility of immune checkpoint blockade in pediatric cancers with increased mutation burden (>=5 mutations/megabase) and/or mismatch repair deficiency. The best overall response rate of 50% and remarkable prolonged overall survival particularly in patients with relapsed HGG demonstrates a clear role for ICI in this rare pediatric population and lays a foundation for incorporating ICI in the upfront treatment of these patients. In children, hypermutation driven by germline MMRD is essential for ICI response.

Larkin T et al. JCO Precis Oncol. 2021
Das A et al. Clin Canc Res 2023

OTHER ISSUES

HGG IN CPS

HGG IN CMMRD

HGG AT RELAPSE

Few **reported series** in literature about re-RT in pHGG:

- Muller K et al, 2014 (german) 8 pts re-irradiated median PFS 11.4 mos, median OS 26.6 mos
- Lucas JT Jr et al,2017 (St Jude): focused on patterns of failure in relapsed pHGG
- Tsang DS et al, 2019 (Canadian): retrospective cohort study of 40 children with recurrent pHGG. 14/40 re-irradiated had improved median survival from the time of first disease progression→ 9.4 VS 3.8 mos of the 26 pts not re-irradiated (P=0.005)

-Massimino et al, 2022: retrspective study on **21 relapsed pHGG**, patterns of failure are described together with the role of re-irradiation in 21 pts. 3/21 had 3° RT course.
Median time to progression/survival after re-RT were 3.7 mos/6.9 mos improved for:

- Longer interval between 1st RT and re-RT (P = 0.017)
- for non-PD after reRT (P < 0.001).

First marginal relapse showed potential association with dissemination after re-RT (P = 0.081).
This is the biggest series of re-RT in paediatric HGG.
Considering the dissemination observed at relapse (9/21), the results could prompt the investigation of different first RT fields in a randomized trial.

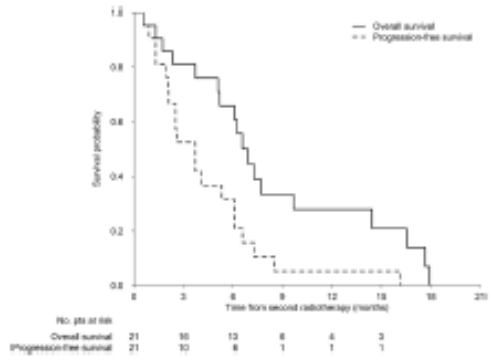


Fig. 3 Kaplan
from re-irradi

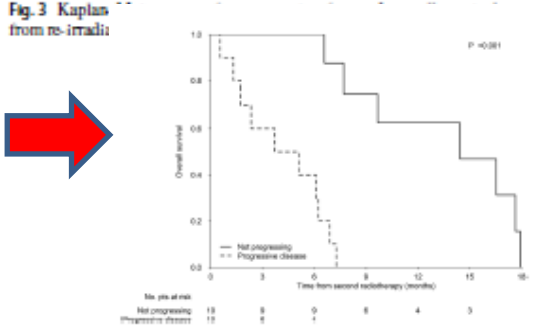
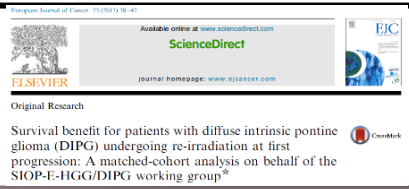


Fig. 4 Kaplan-Meier curves for overall survival from re-irradiation according to response to re-irradiation



CONCLUSIONS

What we would like for our patients at best ?

A treatment like a perfect tailor-made dress sewed by expert hands of an artist

Giovanni Battista Moroni ca 1522 - 1578/1579

- Dismal prognosis
- Heterogeneity of entities and treatments
- Role of new drugs/repurposing of drugs
- Clinical trials

Grazie per l'attenzione!

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