The Arizona Clinical Oncology Society Fall Conference
Saturday November 11th, 2023. Paradise Valley, AZ

Advancing Brain Tumor Treatment: Collaborating Through Clinical Research

Yoshie Umemura, MD

Chief of Neuro-oncology
William and Joan Shapiro Chair of Neuro-Oncology Research
Chief Medical Officer, Ivy Brain Tumor Center
Barrow Neurological Institute, Phoenix AZ

Ivy Brain Tumor Center
AT THE BARROW NEUROLOGICAL INSTITUTE

Barrow Neurological Institute

Disclosures

- I have no stocks, patent rights or employment with any company.
- I serve on the advisory board for Servier Pharmaceuticals.
- I have clinical trial support from Gateway for Cancer Research.

Topics

- Clinical challenges in neuro-oncology
- New advancements in neuro-oncology
- Clinical collaborations

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- New advancements in neuro-oncology
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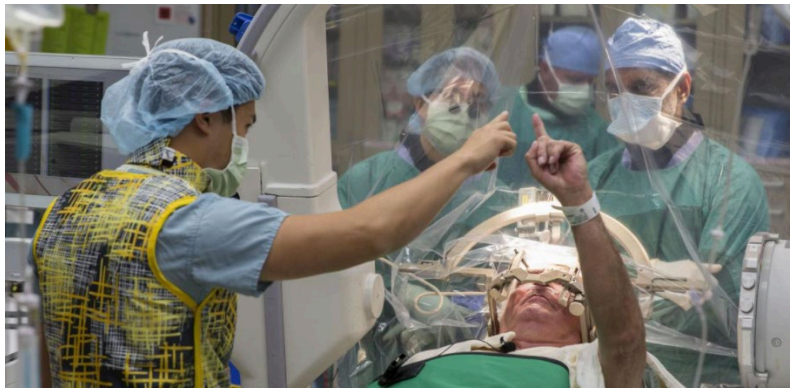
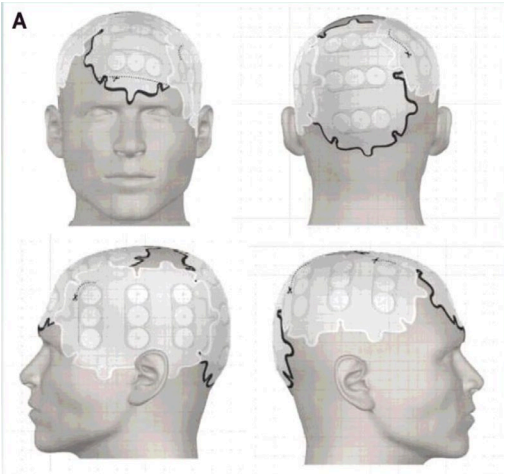
Glioblastoma

- Most common primary brain tumor in adults
- Approx. 20,000-30,000 cases yearly in the US
- Median OS 14-16 months with standard of care

EJ Mun et al. CCR. Jan 2018. DOI: 10.1158/1078-0432.CCR-17-1117





Advancement in Oncology

~~Molecular characterization~~

~~Personalized approach~~

100s of failed GBM trials

~~Vaccines~~

~~Targeted therapies~~

~~Immune checkpoint inhibitors~~

Stumbling Blocks in Neuro-Oncology

Blood brain barrier

Intra-tumoral heterogeneity

100s of failed GBM trials

Blood CSF barrier

Unique CNS microenvironment

Compensatory signaling

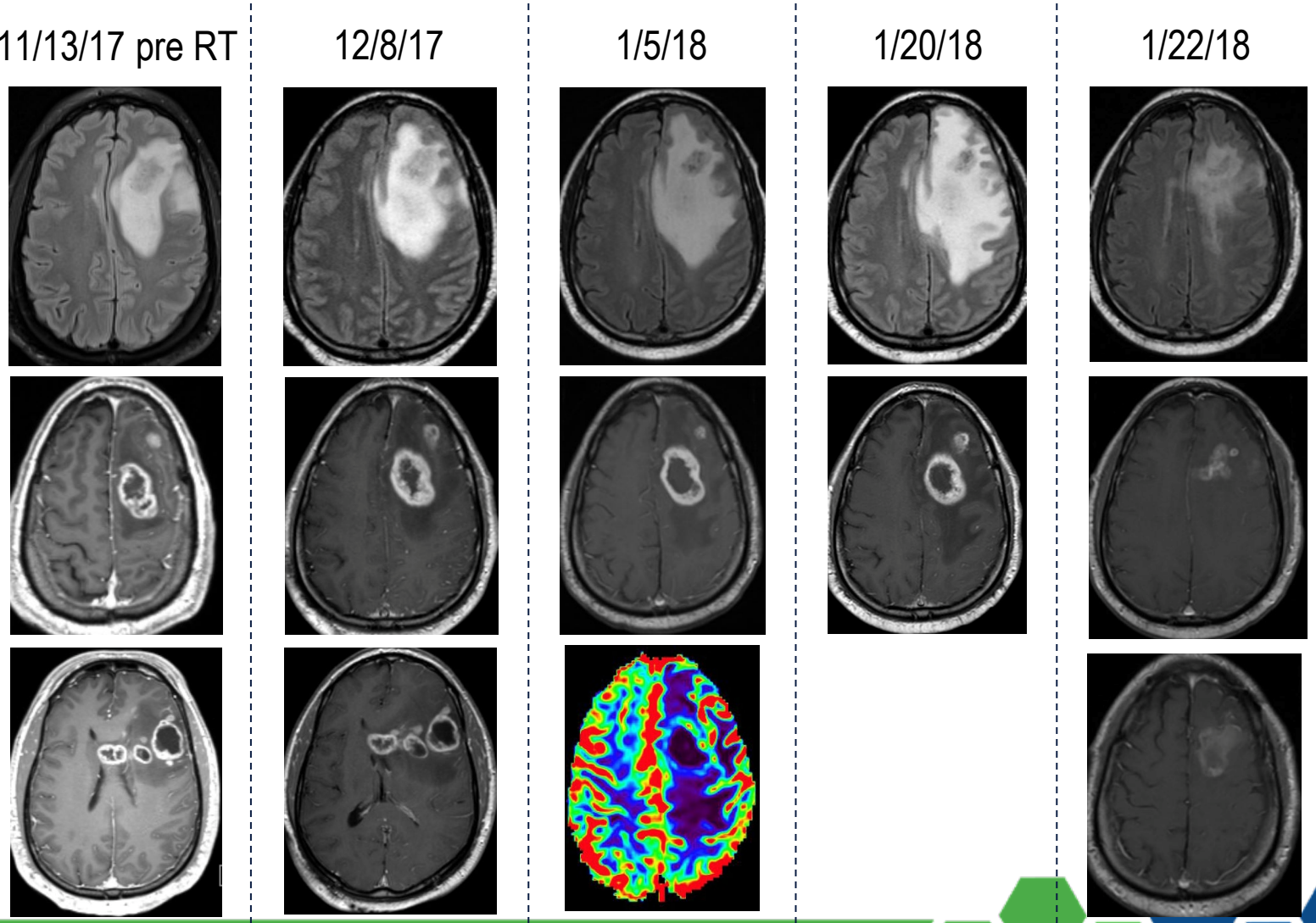
54 yo man with MGMT methylated GBM

- Biopsy
- IMRT

- Treatment effect
  - Stopped RT early
  - Stopped TMZ a few days early

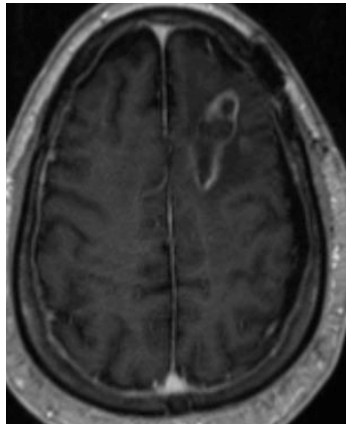
- Severe ”pressure waves”

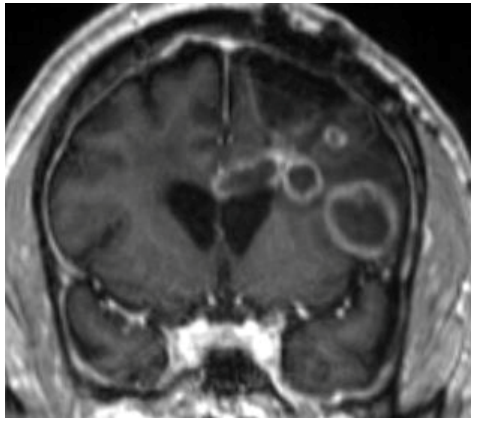
- 01/21/18 debulking



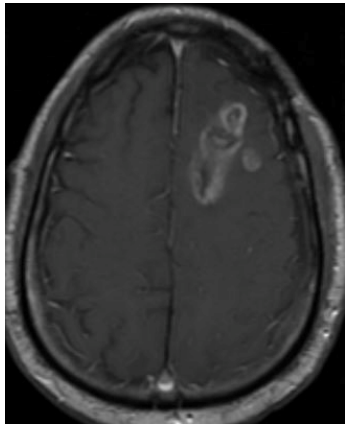
54 yo man with MGMT methylated GBM

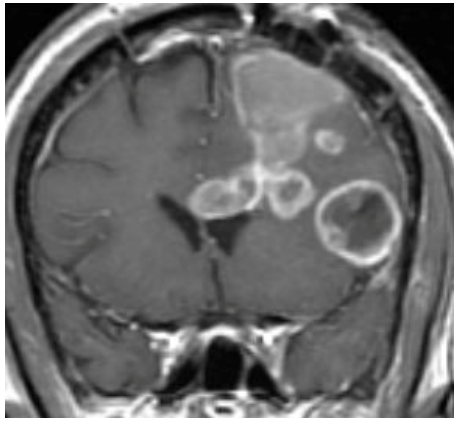
2/12/18





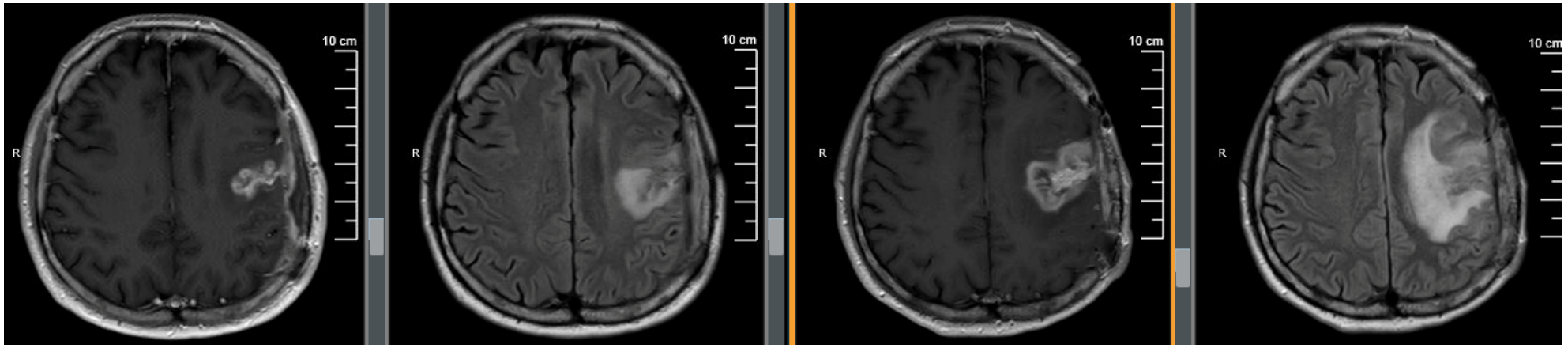
12/22/18



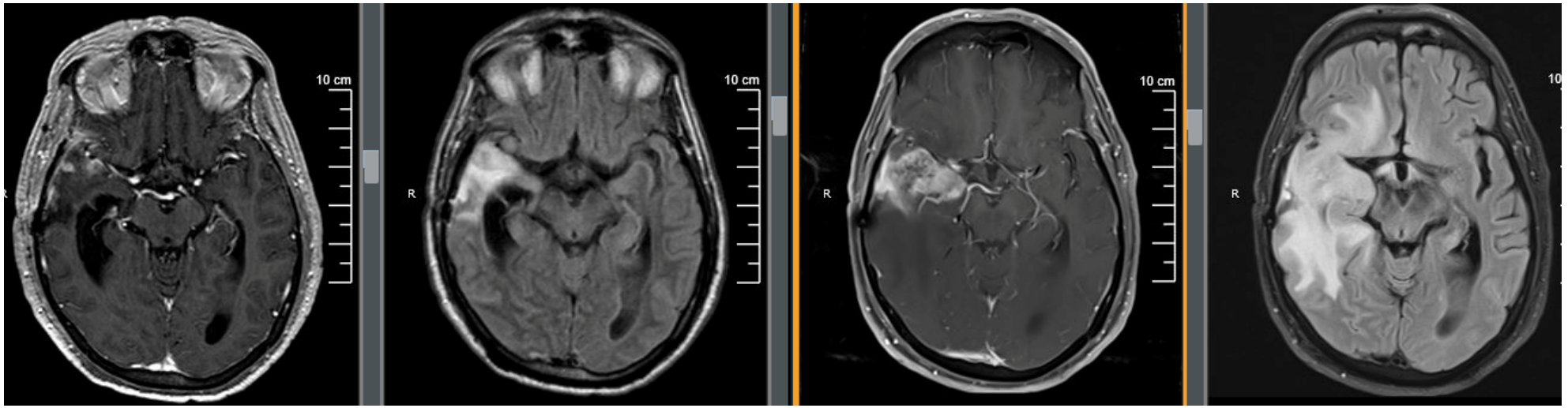


GBM with increased perfusion

- Patient 1

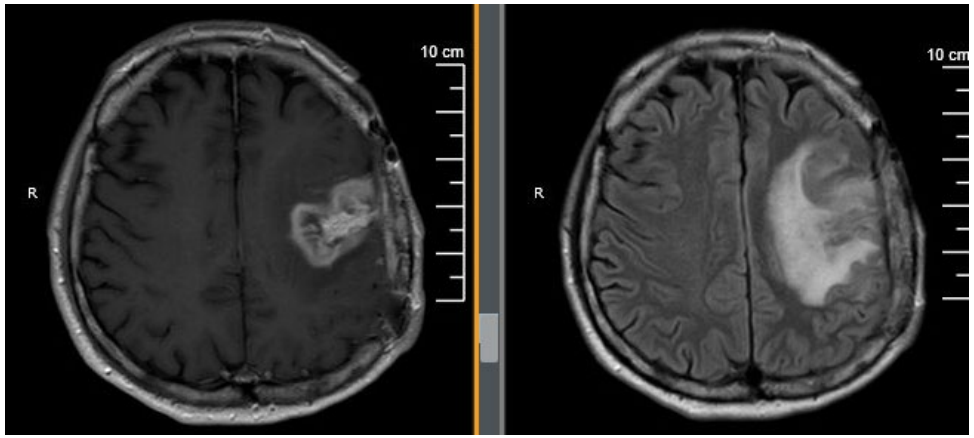


- Patient 2



- **Both GBM s/p GTR, RT+TMZ, adj TMZ, increased perfusion**

- Patient 1: MGMT promotor umethylated



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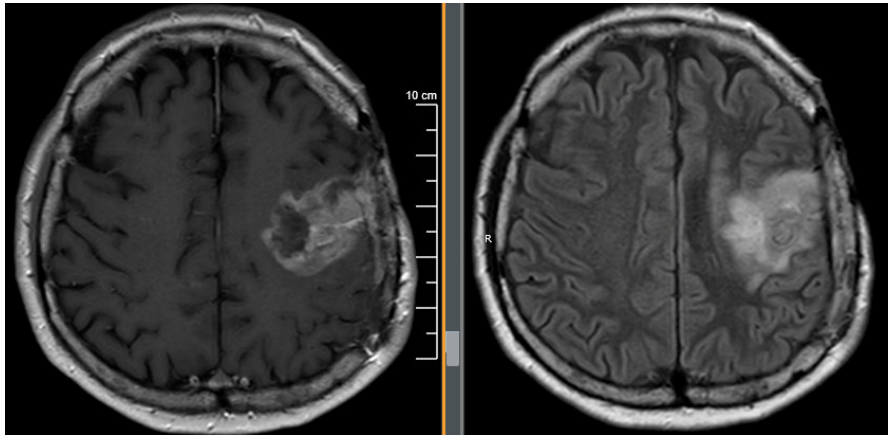
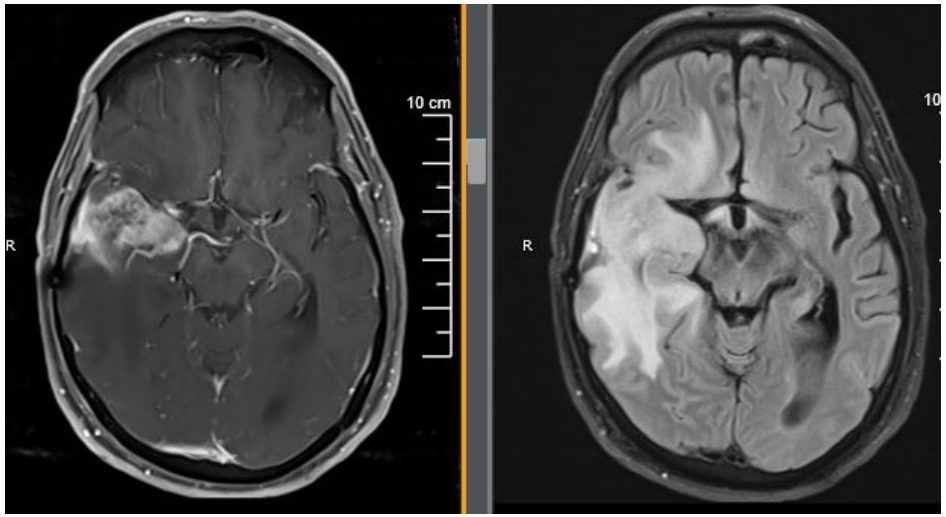
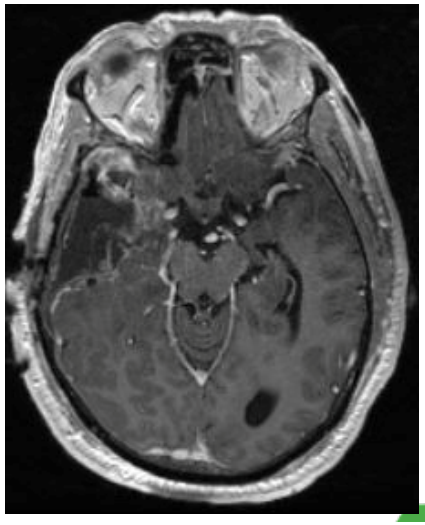


- Patient 2: MGMT promotor methylated



OR #2

PsP



- DIFFUSE GLIOSIS, MACROPHAGE INFILTRATION, HYALINIZED VESSELS, AND NECROSIS, CONSISTENT WITH RADIATION INJURY.

RANO 2.0

Neurotherapeutics. 2017 Apr; 14(2): 307–320. Published online 2017 Jan 20.
doi: 10.1007/s13311-016-0507-6

PMCID: PMC5398984 | PMID: 28108885

Modified Criteria for Radiographic Response Assessment in Glioblastoma Clinical Trials

Benjamin M. Ellingson,[1,2,3,5] Patrick Y. Wen,[4] and Timothy F. Cloughesy[5,6]

ORIGINAL REPORTS | Neurooncology

Evaluation of Standard Response Assessment in Neuro-Oncology, Modified Response Assessment in Neuro-Oncology, and Immunotherapy Response Assessment in Neuro-Oncology in Newly Diagnosed and Recurrent Glioblastoma

Check for updates

Gilbert Youssef, MD[1]; Rifaquat Rahman, MD[2]; Camden Bay, PhD[3]; Wei Wang, PhD[4,5,6]; Mary Jane Lim-Fat, MD, MSc, FRCPC[7]; Omar Arnaout, MD[8]; ...

PURPOSE

The Response Assessment in Neuro-Oncology (RANO) criteria are widely used in high-grade glioma clinical trials. We compared the RANO criteria with updated modifications (modified RANO [mRANO] and immunotherapy RANO [iRANO] criteria) in patients with newly diagnosed glioblastoma (nGBM) and recurrent GBM (rGBM) to evaluate the performance of each set of criteria and inform the development of the planned RANO 2.0 update.

CONCLUSION

RANO and mRANO demonstrated similar correlations between PFS and OS. Confirmation scans were only beneficial in nGBM within 12 weeks of completion of radiotherapy, and there was a trend in favor of the use of postradiation MRI as the baseline scan in nGBM. Evaluation of FLAIR can be omitted. The iRANO criteria did not add significant benefit in patients who received immune checkpoint inhibitors.

Topics

- Clinical challenges in neuro-oncology
- New advancements in neuro-oncology
- Clinical collaborations

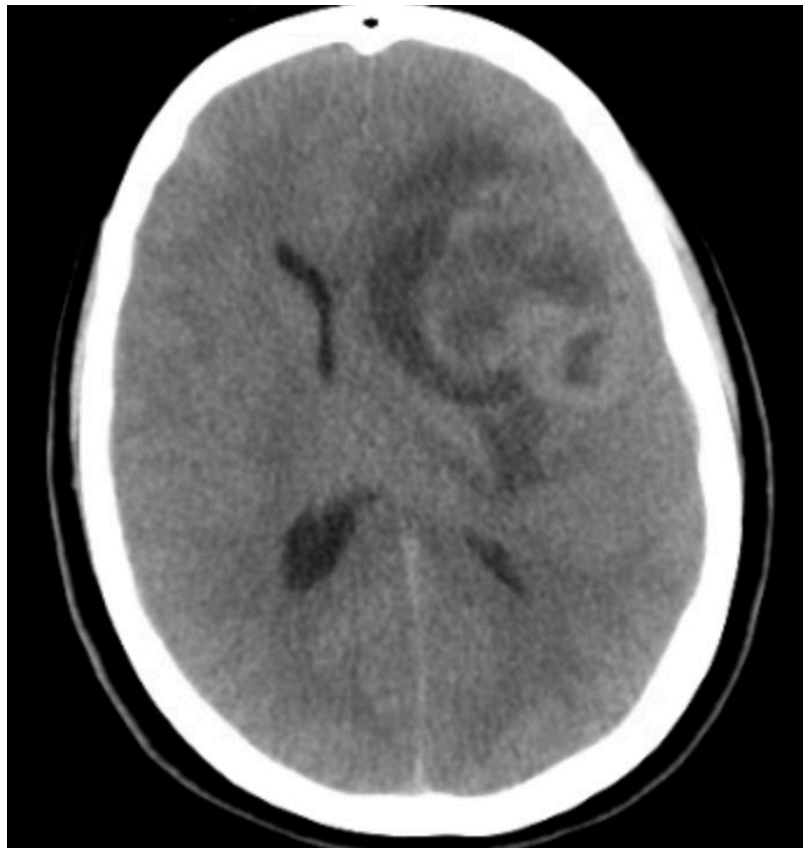
Case: Patient KC

September 2018

- Elbowed in the head → Progressive headache
- Headache worse with position change

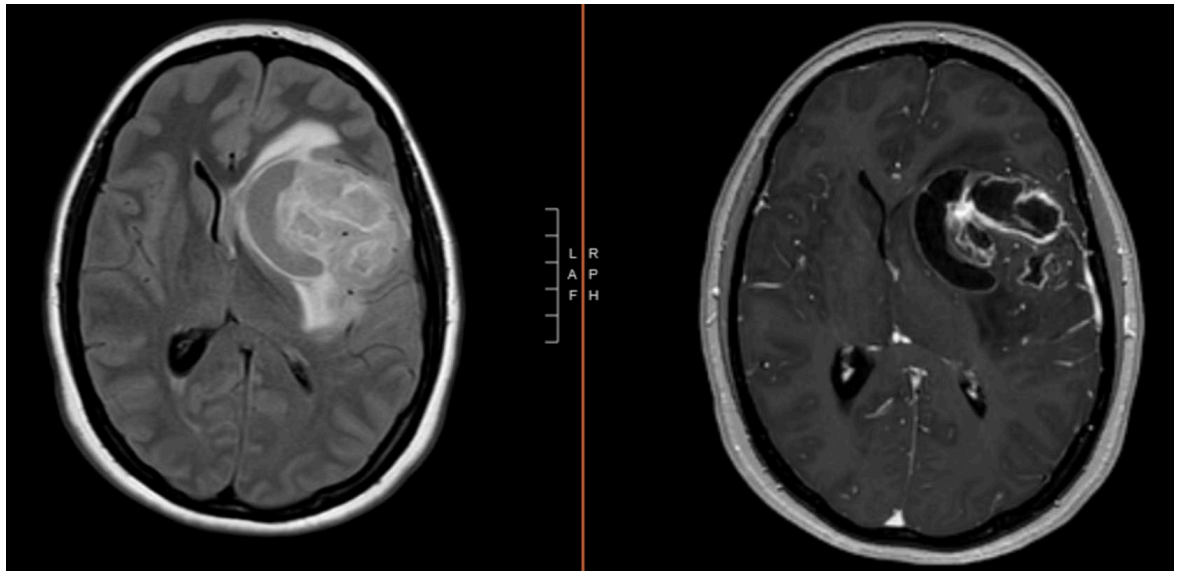
\+ Dizziness, nausea & vomiting, blurry vision, photophobia, phonophobia, weakness & paresthesia of UEs

CT head

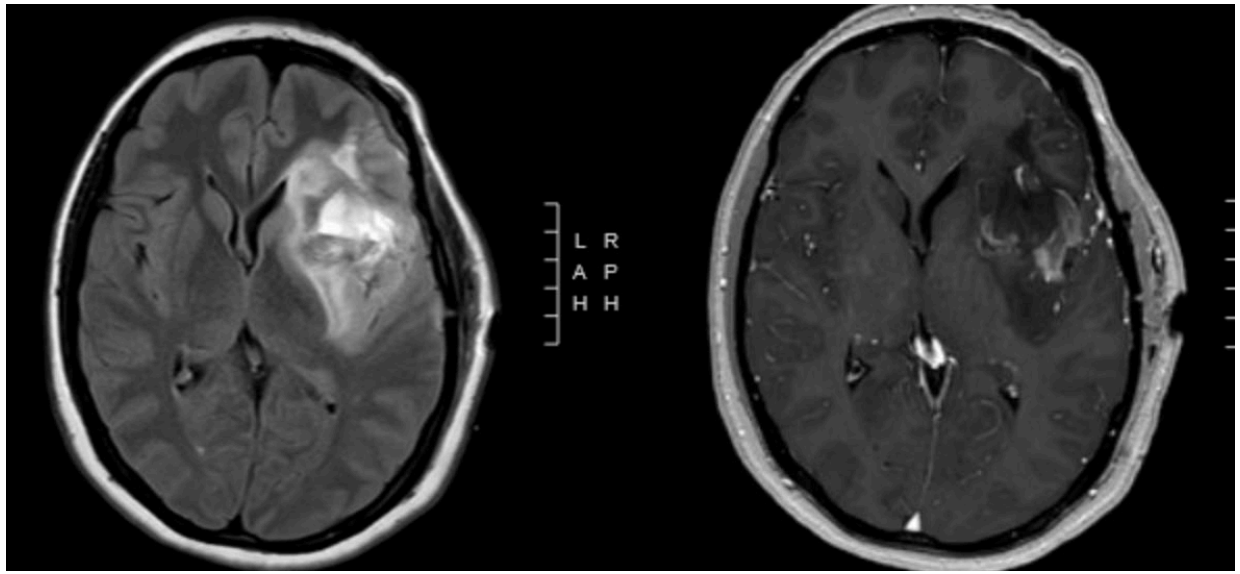


40 yo woman with L frontal lesion

Pre-operative MRI



Post-operative MRI



Initial Diagnosis: Oligodendroglioma

FINAL REPORT AFTER MOLECULAR RESULTS

I. BRAIN TUMOR: The specimen is received fresh for frozen section and consists of soft pale pink and red tissue aggregating 0.6 x 0.6 x 0.3 cm. One touch prep and one frozen section are submitted and the diagnosis by Dr. Wang and Dr. Kim is "high-grade

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examination findings.

DIAGNOSIS:

I. Brain tumor, craniotomy:

1. Malignant glioma.
2. Pending IHC and molecular studies. See comment.

II. Brain tumor, craniotomy:

1. Malignant glioma.
2. Pending IHC and molecular studies. See comment.

COMMENT: Differential diagnosis includes small cell glioblastoma versus anaplastic oligodendroglioma. Anaplastic oligodendroglioma is favored.

IGH 1/2, 1p/19q, TP53, MGMT are ordered and will be reported in an addendum

Anaplastic oligodendroglioma (1p/19q deleted, IDH wild type) is favored based on the histology and molecular studies.

IDH2 mutation: Not detected.
TP 53 mutation: Not detected.
MGMT Gene Promoter Methylation: Detected.
-Percent of MGMT methylation: 12.54%.

COMMENT: Anaplastic oligodendroglioma (1p/19q deleted, IDH wild type) is favored based on the histology and molecular studies.

Oligodendroglioma: Basics

- Infiltrating diffuse glioma
- Approx. 1000 oligodendrogliomas diagnosed per year in US
- 5% of adult gliomas, 0.5% of all primary CNS tumors
- Most has seizure at the time of presentation
- Most are diagnosed between age 25-45

- Anaplastic = WHO grade 3, Median survival 15 years

Oligodendroglioma: PCV vs Temozolomide

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Radiation Therapy With Concomitant and Adjuvant Temozolomide Versus Radiation Therapy With Adjuvant PCV Chemotherapy in Patients With Anaplastic Glioma or Low Grade Glioma

Sponsor:

Alliance for Clinical Trials in Oncology

Collaborators:

National Cancer Institute (NCI)

European Organisation for Research and Treatment Center (EORTC)

Canadian Cancer Trials Group

Information provided by (Responsible Party):

Alliance for Clinical Trials in Oncology

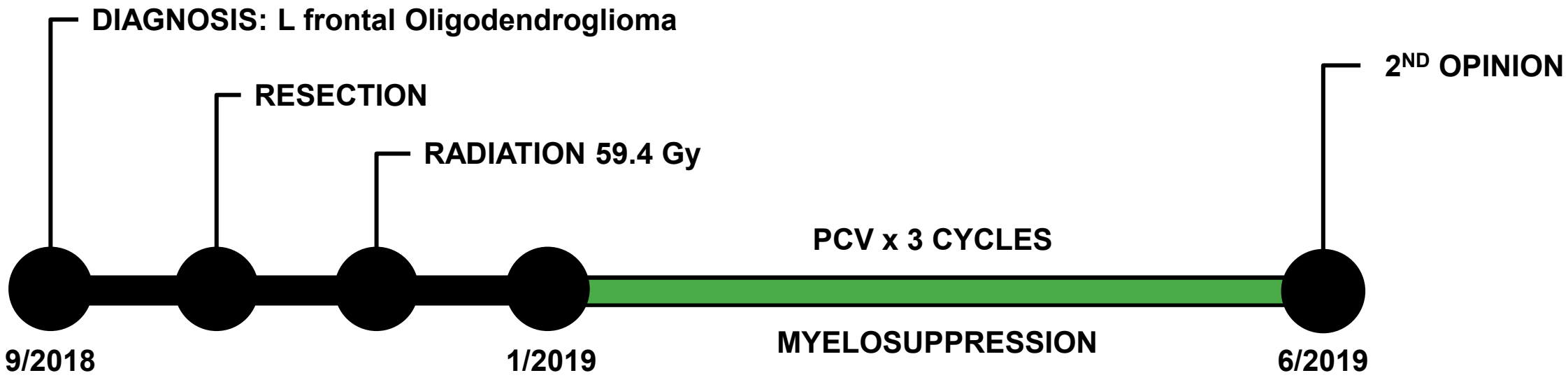
ClinicalTrials.gov Identifier: NCT00887146

Recruitment Status : Recruiting

First Posted : April 23, 2009

Last Update Posted : March 24, 2022

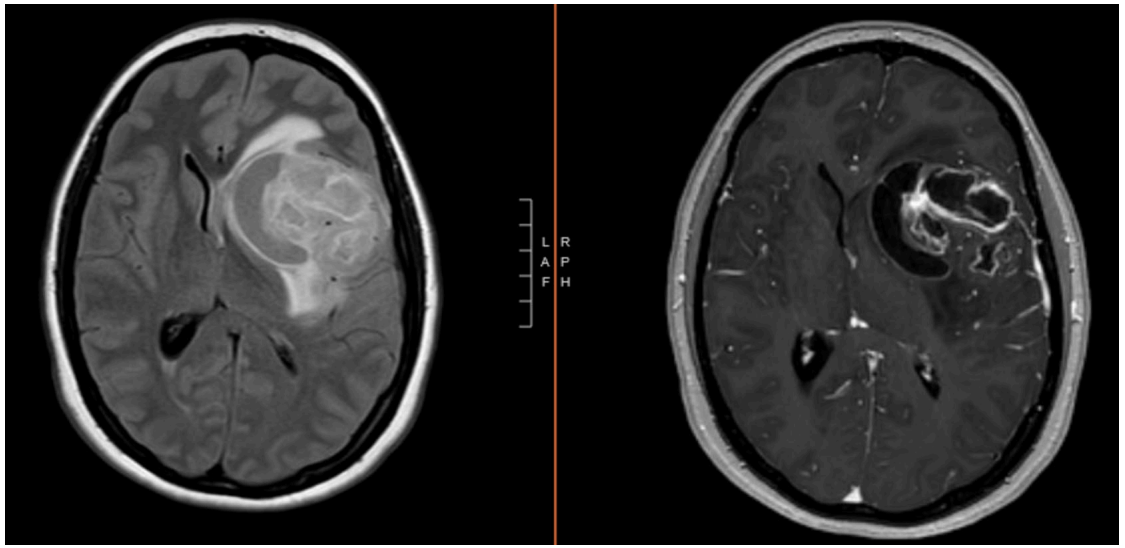
L Frontal Oligodendroglioma Treatment



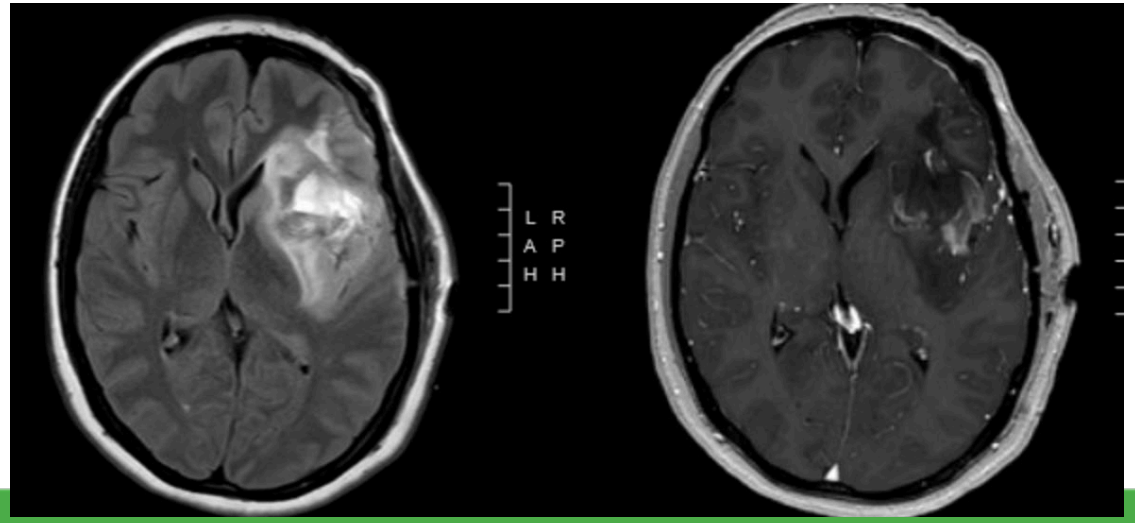
	4/26/19	5/10/19	5/14/19	5/18/19	5/24/19	6/7/19	6/20/19	7/5//19	8/9/19	8/26/19
WBC	3.2	3.5	1.2	1.9	1.2	1.2	3.1	2.5	1.5	1.2
HB	9.1	9.4	8.9	8.3	9.0	9.9	11.1	10.8	10.3	11.0
PLT	92	18	15	39	46	148	169	154	47	116
	NC					0.6	2.1	1.4	0.8	0.6

Second Opinion: History & Imaging

Pre-op MRI

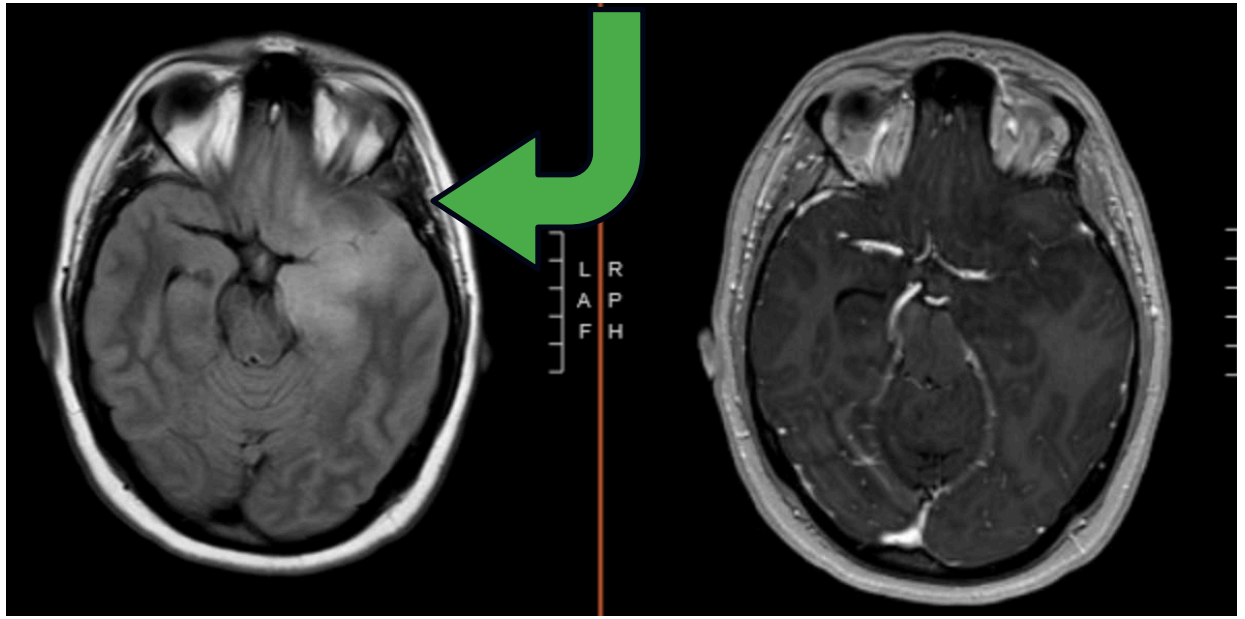


Post-op MRI



Additional non-enhancing lesion

Not included in the RT treatment field

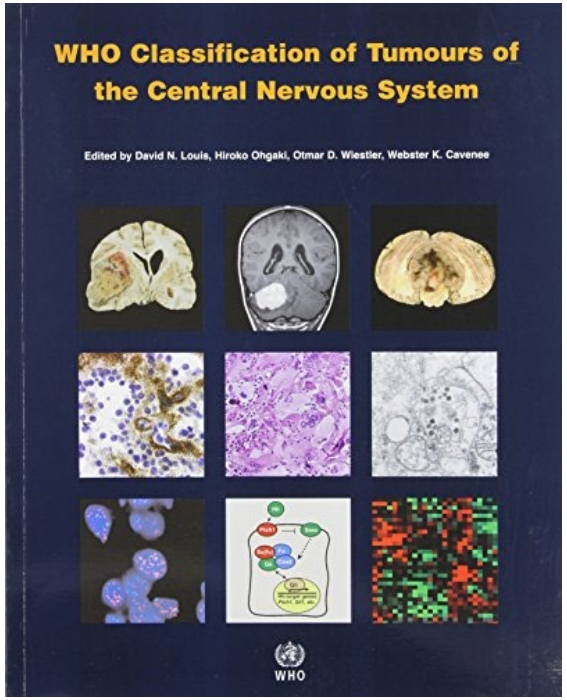


Weekly episodes of inability to speak x 5-10 minutes x 6 months **SEIZURES**

Molecular Focus in WHO Classifications

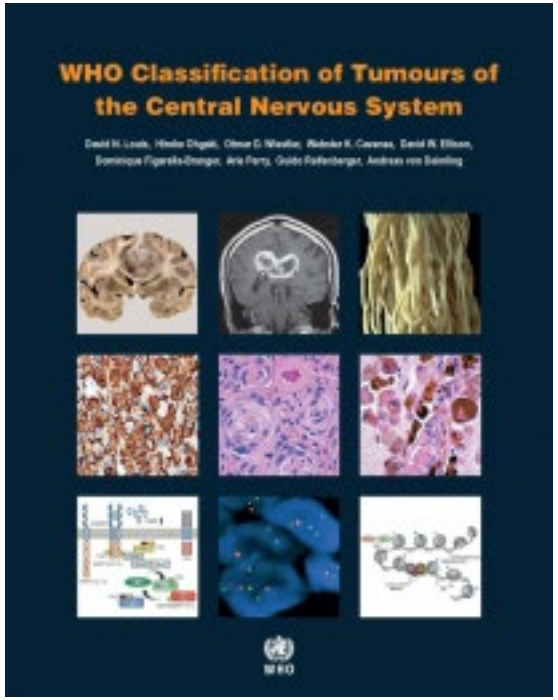
1979: 1st edition, 1993: 2nd edition, 2000: 3rd edition

2007: 4th Edition

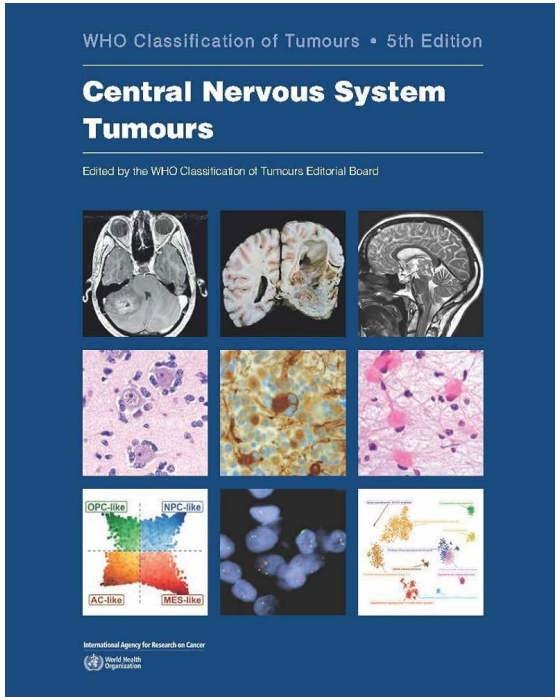


Histopathology
vs
Molecular Diagnoses

2016: Revised 4th Edition



2021: 5th Edition



WHO 2016 Update: Oligodendroglioma

Review > Acta Neuropathol. 2016 Jun;131(6):803-20.
doi: 10.1007/s00401-016-1545-1. Epub 2016 May 9.

The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary

David N Louis [1], Arie Perry [2], Guido Reifenberger [3 4], Andreas von Deimling [4 5], Dominique Figarella-Branger [6], Webster K Cavenee [7], Hiroko Ohgaki [8], Otmar D Wiestler [9], Paul Kleihues [10], David W Ellison [11]

Affiliations + expand

PMID: 27157931
DOI: 10.1007/s00401-016-1545-1

Oligodendrogliomas

The diagnosis of oligodendroglioma and anaplastic oligodendroglioma requires the demonstration of both an IDH gene family mutation and combined whole-arm losses of 1p and 19q (1p/19q codeletion). In the absence of positive mutant R132H IDH1 immunohistochemistry, sequencing of *IDH1* codon 132 and *IDH2* codon 172 is recommended. In the absence of testing capabilities or in the setting of inconclusive genetic results, a histologically typical oligodendroglioma should be diagnosed as NOS. In the setting of an anaplastic oligodendroglioma with non-diagnostic genetic results, careful evaluation for genetic features of glioblastoma may be undertaken [6]. It is also recognized that tumors of childhood that histologically resemble oligodendroglioma often do not demonstrate IDH gene family mutation and 1p/19q codeletion; until such tumors are better understood at a molecular level, they should be included in the oligodendroglioma, NOS category. However, care should be taken to exclude histological mimics like pilocytic astrocytoma, dysembryoplastic neuroepithelial tumor and clear cell ependymoma.

Initial Diagnosis: Oligodendroglioma??

FINAL REPORT AFTER MOLECULAR RESULTS

I. BRAIN TUMOR: The specimen is received fresh for frozen section and consists of soft pale pink and red tissue aggregating 0.6 x 0.6 x 0.3 cm. One touch prep and one frozen section are submitted and the diagnosis by Dr. Wang and Dr. Kim is "high-grade glioma, favor GBM".

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2. Pending IHC and molecular studies. See comment.

COMMENT: Differential diagnosis includes small cell glioblastoma versus anaplastic oligodendroglioma. Anaplastic oligodendroglioma is favored.

IGH 1/2, 1p/19q, TP53, MGMT are ordered and will be reported in an addendum.

SUPPLEMENTAL A:

-Percent of MGMT methylation: 12.54%.

ioma (1p/19q deleted, IDH
logy and molecular studies.

Anaplastic oligodendroglioma (1p/19q deleted, IDH wild type) is favored based on the histology and molecular studies.

CHROMOSOMAL MICROARRAY: NO EVIDENCE OF 1p19q CODELETION

Second Opinion: Diagnosis Review

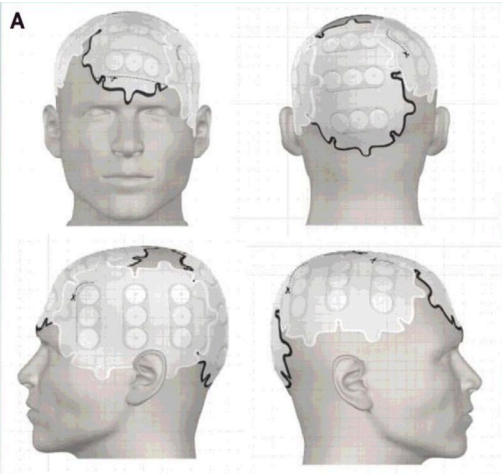
GLIOBLASTOMA, IDH-WILD TYPE, WHO GRADE 4

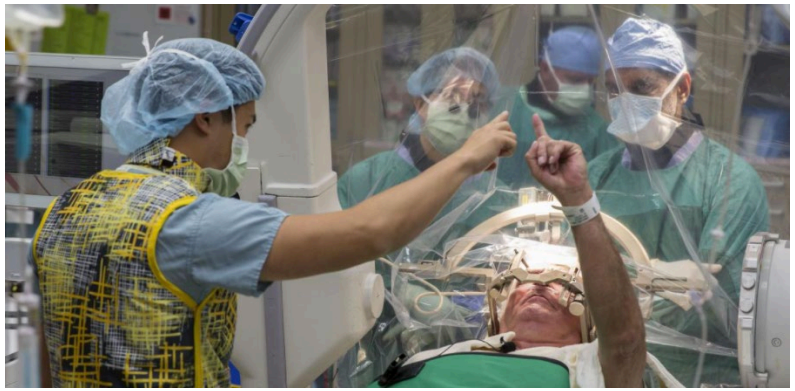
- IDH1 and IDH2 wildtype
- ATRX retained
- **MGMT promoter methylated**

Glioblastoma, WHO grade 4

- More common in older adults age > 45
- 10 times more common than Grade 2 & 3 oligo combined
- MEDIAN survival 24 months for MGMT methylated

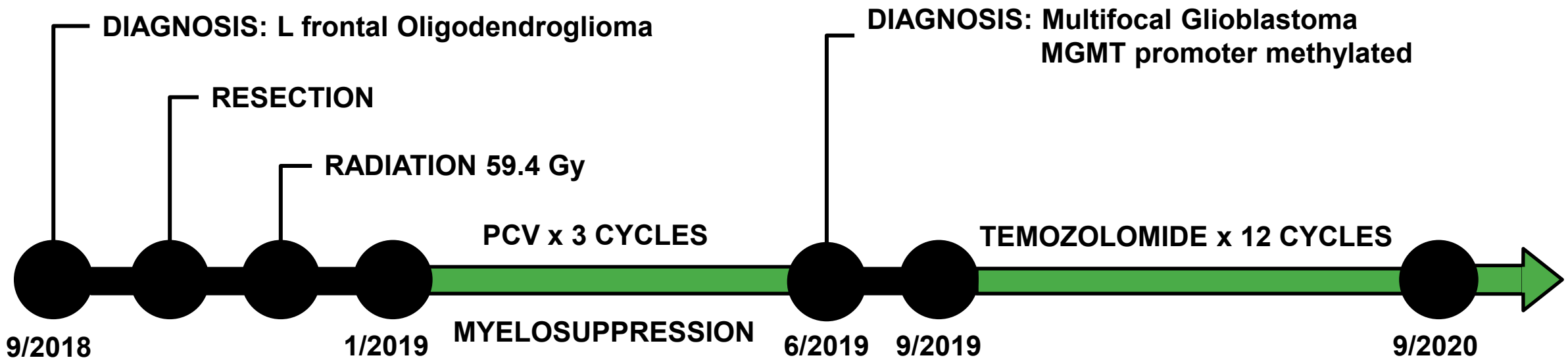
EJ Mun et al. CCR. Jan 2018. DOI: 10.1158/1078-0432.CCR-17-1117





60 Gy

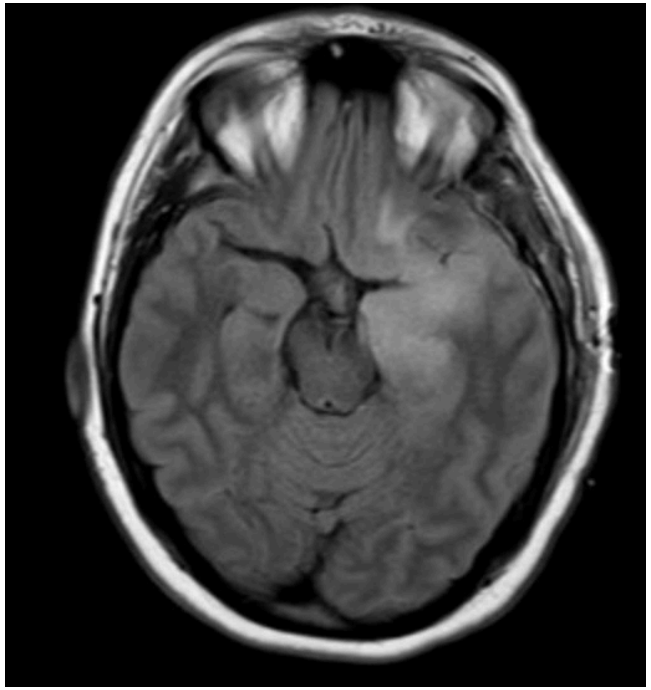
Multifocal Glioblastoma Treatment



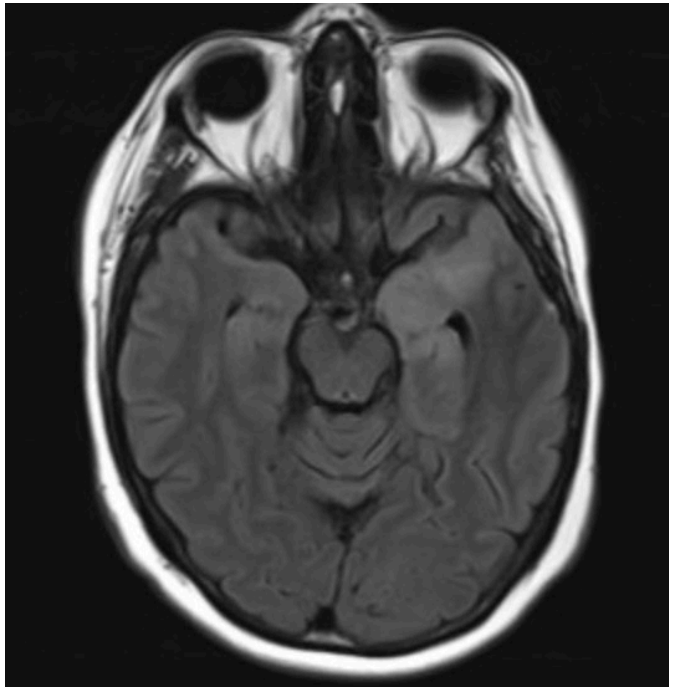
10/2023 Stable MRI brain (5+ years from diagnosis)

Radiographic response

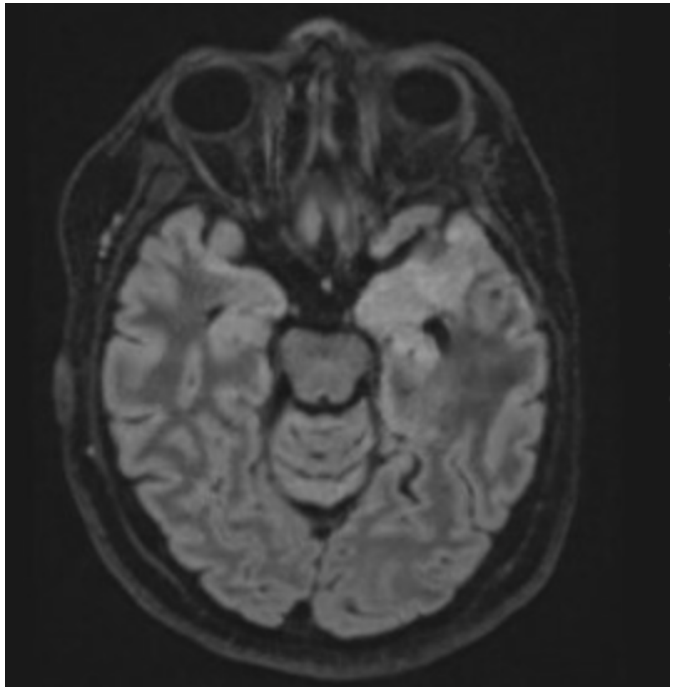
9/2020



9/2021



9/2022



Topics

- Clinical challenges in neuro-oncology
- New advancements in neuro-oncology
  - Diagnoses
  - Treatments

Target: IDH mutation

THE WALL STREET JOURNAL.

HEALTH

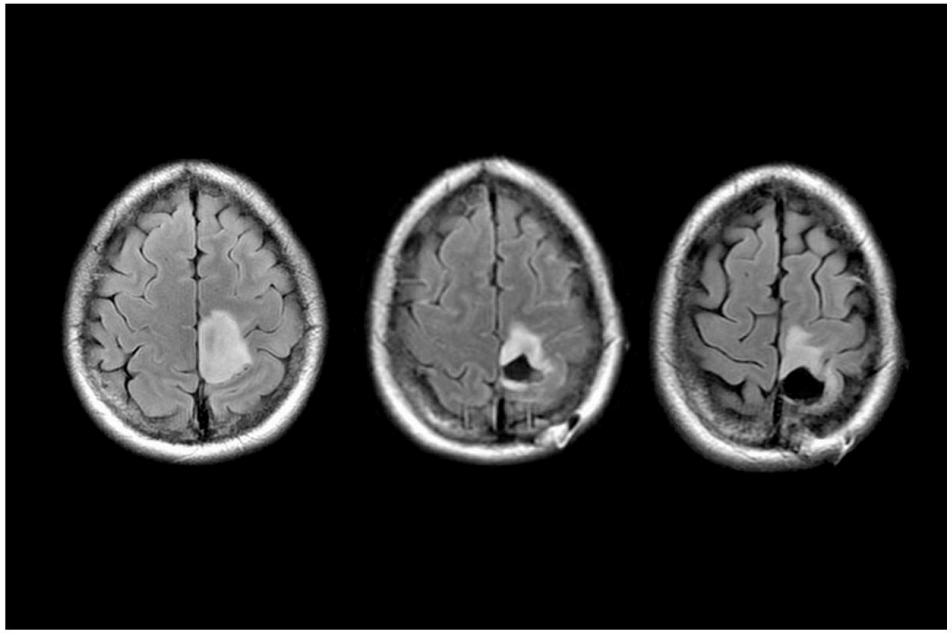
Treatment Breakthrough for an Intractable Brain Cancer

Servier's drug vorasidenib helped glioma patients stave off cancer growth

By Brianna Abbott Follow

Updated June 4, 2023 3:34 pm ET

Save 54



A brain MRI shows a slow-moving glioma, a type of tumor. PHOTO: DANA-FARBER CANCER

The NEW ENGLAND JOURNAL of MEDICINE

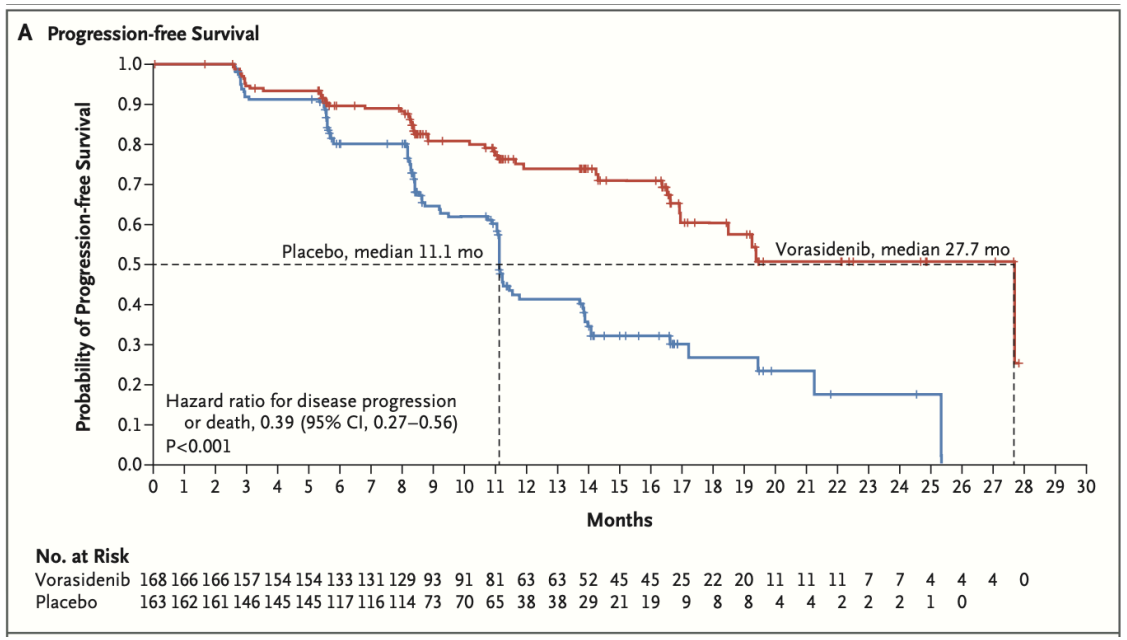
ORIGINAL ARTICLE

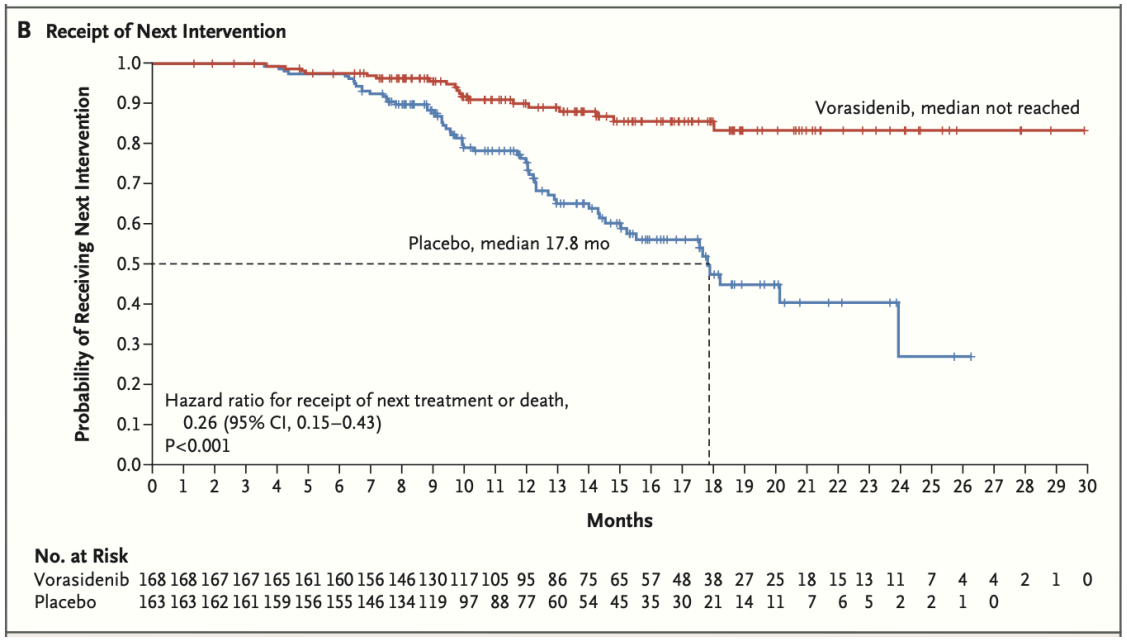
Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma

Ingo K. Mellinghoff, M.D., Martin J. van den Bent, M.D., Deborah T. Blumenthal, M.D., Mehdi Touat, M.D., Katherine B. Peters, M.D., Jennifer Clarke, M.D., M.P.H., Joe Mendez, M.D., Shlomit Yust-Katz, M.D., Liam Welsh, M.D., Ph.D., Warren P. Mason, M.D., François Ducray, M.D., Yoshie Umemura, M.D., et al.

- Low grade IDH mutated glioma
- > 1 year, < 5 year from surgery
- No prior tumor directed therapy

Voracidenib vs Placebo





- N=331 (vorasidenib N=168, placebo N=163)
- PFS 27.7 months vs 11.1 months (HR 0.39, p<0.001)
- Time to next intervention NR vs 17.8 months (HR 0.26, p<0.001)

Expanded Access Program: Voracidenib

Vorasidenib Expanded Access Program

ClinicalTrials.gov ID NCT05592743

Sponsor Servier

Information provided by Servier (Responsible Party)

Eligibility Criteria

Description

Inclusion Criteria:

- Age ≥ 12 years old and weighing at least 40 kg.
- Have IDH-mutant oligodendroglioma or astrocytoma per WHO 2021 criteria, with the IDH1 or IDH2 gene mutation confirmed by tissue-based diagnosis.
- Have at least 1 prior surgery for glioma (including biopsy).
- Is not in immediate need of chemotherapy and/or radiotherapy based on the clinical judgement of the treating oncologist.
- Have adequate bone marrow function.
- Have adequate hepatic function.
- Have adequate renal function.
- Have adequate cardiac function.

Ages Eligible for Study

12 Years and older (Child, Adult, Older Adult)

Sexes Eligible for Study

All

Exclusion Criteria:

- Patient has IDH1-mutant glioma that is predominantly contrast-enhancing and the patient is eligible for ivosidenib Patient Assistance Program or able to access ivosidenib through a third-party payer.
    - Patients whose disease progresses after treatment with ivosidenib or who are unable to tolerate ivosidenib may be eligible
- Patient is eligible for a clinical trial with vorasidenib. (Note that patients who are enrolled in a Servier-sponsored clinical trial and have completed all requirements of the trial may be eligible if the patient continues to benefit from vorasidenib and does not meet criteria for discontinuation of treatment)
- Patient has a grade 4 tumor and has not received appropriate standard of care or been approved for an exception by a Servier-designated panel of independent experts.
- Patient has a heart-rate corrected QT interval using Fridericia's formula (QTcF) ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome). Subjects with bundle branch block and prolonged QTcF may be eligible at the discretion of Servier Pharmaceuticals and the investigator.
- Patient is pregnant or breastfeeding.

IDH Inhibitor: Safusidenib Phase 2 Trial

SAFUSIDENIB (AB-218) FOR IDH1 MUTANT GLIOMA

A Phase 2 randomized open-label trial to evaluate safety and efficafy of Safusidenib (AB-218) in patients with recurrent or progressive IDH1 mutant Glioma.

LEARN MORE

Trial Eligibility

Status: Recruiting

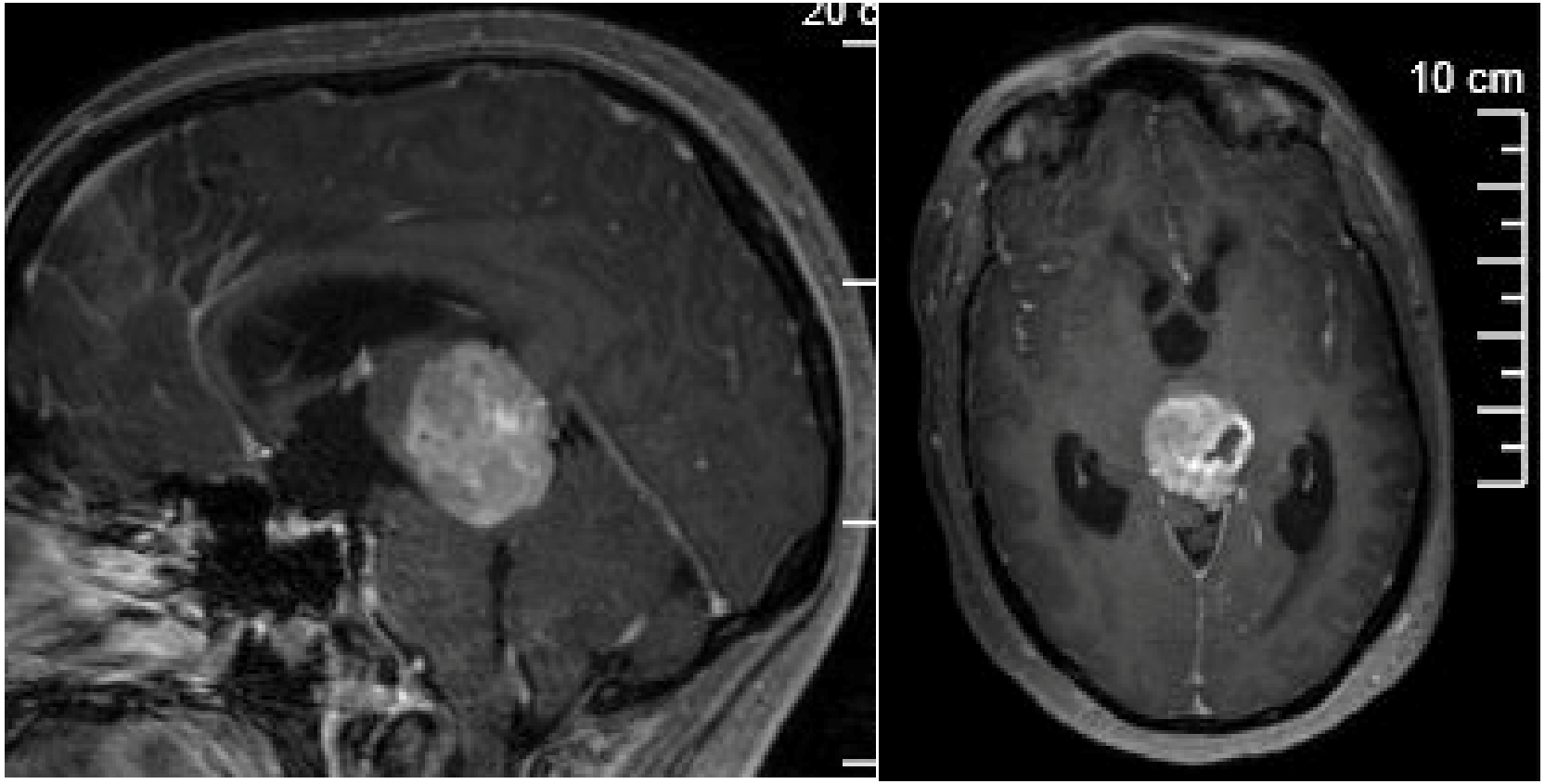
Visit ClinicalTrials.gov or use NCT identifier NCT05303519 to view inclusion criteria and additional study details.

TRIAL SCREENING ›

Patient CB

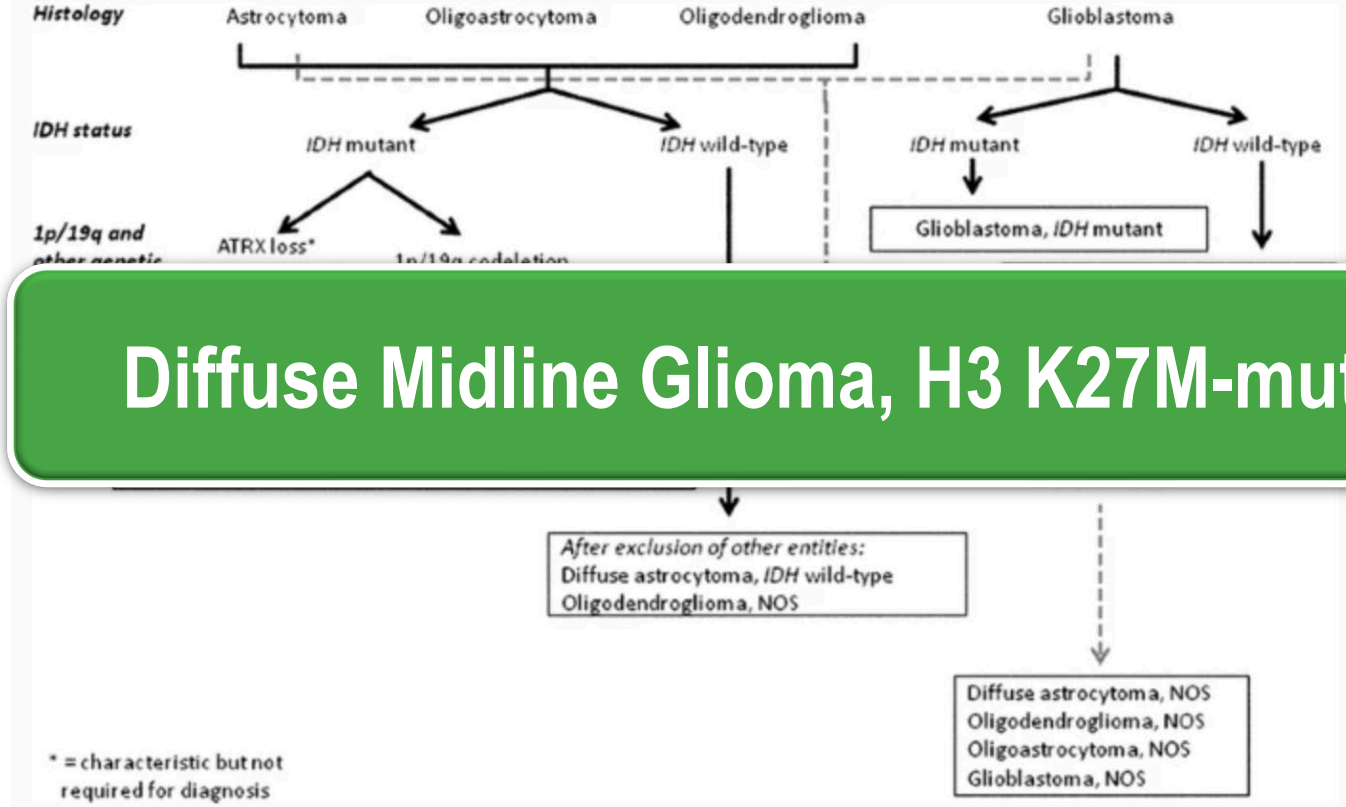
26 yo woman

- Headache
- Nausea
- Vomiting
- Diplopia



WHO Criteria Change

Fig. 1



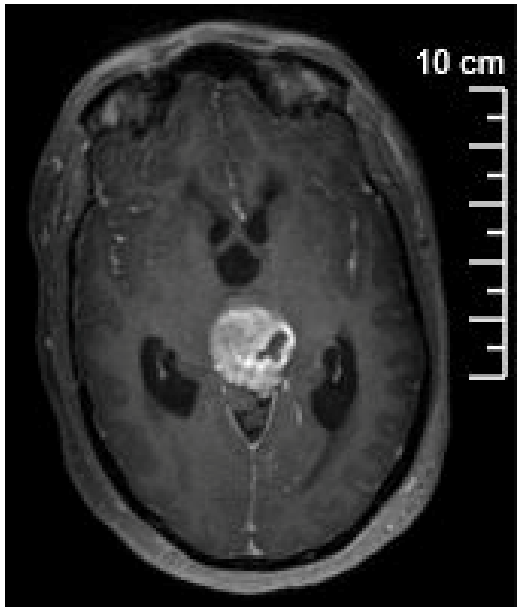
Diffuse Midline Glioma, H3 K27M-mutant

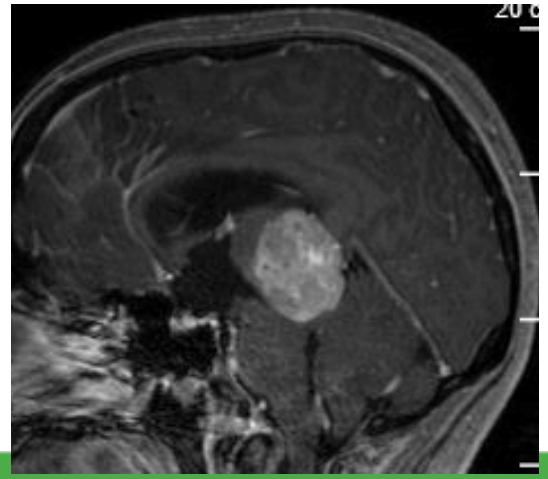
Louis, D.N., Perry, A., Reifenberger, G. *et al.* The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* **131**, 803–820 (2016). https://doi.org/10.1007/s00401-016-1545-1

WHO classification of tumours of the central nervous system

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	9400/3
Gemistocytic astrocytoma, IDH-mutant	9411/3
Diffuse astrocytoma, IDH-wildtype	*9400/3*
Diffuse astrocytoma, NOS	9400/3
Anaplastic astrocytoma, IDH-mutant	9401/3
Anaplastic astrocytoma, IDH-wildtype	*9401/3*
Anaplastic astrocytoma, NOS	9401/3
Glioblastoma, IDH-wildtype	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Epithelioid glioblastoma	*9440/3*
Glioblastoma, IDH-mutant	9445/3*
Glioblastoma, NOS	9440/3
Diffuse midline glioma, H3 K27M–mutant	9385/3*
Oligodendroglioma, IDH-mutant and 1p/19q-codeleted	9450/3
Oligodendroglioma, NOS	9450/3
oglioma, IDH-mutant	
ted	9451/3
oglioma, NOS	*9451/3*
S	*9382/3*
ytoma, NOS	*9382/3*
urs	
	9421/1
Pilomyxoid astrocytoma	9425/3
Subependymal giant cell astrocytoma	9384/1
Pleomorphic xanthoastrocytoma	9424/3
Anaplastic pleomorphic xanthoastrocytoma	9424/3
Ependymal tumours	
Subependymoma	9383/1
Myxopapillary ependymoma	9394/1
Ependymoma	9391/3
Papillary ependymoma	9393/3
Clear cell ependymoma	9391/3
Tanycytic ependymoma	9391/3
Ependymoma, *RELA* fusion–positive	9396/3*
Anaplastic ependymoma	9392/3
Other gliomas	
Chordoid glioma of the third ventricle	9444/1
Angiocentric glioma	9431/1
Astroblastoma	9430/3
Choroid plexus tumours	
Choroid plexus papilloma	9390/0
Atypical choroid plexus papilloma	9390/1
Choroid plexus carcinoma	9390/3
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	9413/0
Gangliocytoma	9492/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Dysplastic cerebellar gangliocytoma (Lhermitte–Duclos disease)	9493/0
Desmoplastic infantile astrocytoma and ganglioglioma	9412/1
Papillary glioneuronal tumour	9509/1
Rosette-forming glioneuronal tumour	9509/1
Diffuse leptomeningeal glioneuronal tumour	
Central neurocytoma	9506/1
Extraventricular neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma	8693/1
Tumours of the pineal region	
Pineocytoma	9361/1
Pineal parenchymal tumour of intermediate differentiation	9362/3
Pineoblastoma	9362/3
Papillary tumour of the pineal region	9395/3
Embryonal tumours	
Medulloblastomas, genetically defined	
Medulloblastoma, WNT-activated	9475/3*
Medulloblastoma, SHH-activated and *TP53*-mutant	9476/3*
Medulloblastoma, SHH-activated and *TP53*-wildtype	9471/3
Medulloblastoma, non-WNT/non-SHH	9477/3*
Medulloblastoma, group 3	
Medulloblastoma, group 4	
Medulloblastomas, histologically defined	
Medulloblastoma, classic	9470/3
Medulloblastoma, desmoplastic/nodular	9471/3
Medulloblastoma with extensive nodularity	9471/3
Medulloblastoma, large cell / anaplastic	9474/3
Medulloblastoma, NOS	9470/3
Embryonal tumour with multilayered rosettes, C19MC-altered	9478/3*
Embryonal tumour with multilayered rosettes, NOS	*9478/3*
Medulloepithelioma	9501/3
CNS neuroblastoma	9500/3
CNS ganglioneuroblastoma	9490/3
CNS embryonal tumour, NOS	9473/3
Atypical teratoid/rhabdoid tumour	9508/3
CNS embryonal tumour with rhabdoid features	*9508/3*
Tumours of the cranial and paraspinal nerves	
Schwannoma	9560/0
Cellular schwannoma	9560/0
Plexiform schwannoma	9560/0

Patient CB





Diagnosis:
A-B. Brain, pineal region tumor, biopsy:

- Diffuse midline glioma, H3K27M-mutant, WHO grade IV

SEQUENCING QC REPORT

Libraries:	Tumor and normal OncoSeq exome capture libraries and tumor whole transcriptome capture libraries were analyzed.		
Sample Quality	Sequencing Quality	Library Quality	Sample Identity (SNP Fingerprinting)
Pass	Pass	Pass	Pass

POTENTIALLY ACTIONABLE/INFORMATIVE RESULTS

Mutation class	Gene/Aberration	Potential Therapies/*Clinical Trials (*Contingent on meeting study eligibility criteria)
Somatic Point Mutations (Total: 7) 2 Mutations/Mb	**FGFR1: p.N546K, activating** **H3F3A: p.K28M (K27M), hotspot** **ATRX: Splice acceptor of exon 14** Mutations of uncertain significance: BAZ2A (p.R691H), CDX2 (p.W77R), PAX1 (p.S148R), PRPF6 (p.R590W)	FGFR1: NCT03352427, NCT02465060 H3F3A: NCT03134131, NCT03295396
Somatic Indels (Total: 1)	**NF1: Frameshift deletion, p.S340fs, copy neutral LOH**	NF1: NCT02465060
Copy Number Aberrations	**Low level of aneuploidy** **Co-deletion of regions on chromosomes 1p and 19q:** copy loss of 1(p12-p22.3) and 19(q13.12-q13.43) (see copy number plot below)	
Gene Fusions	No driver fusion detected	
Outlier Gene Expression	**Outliers: *FGF1, ALK, CCND2, GAP43, CHL1*** ***MGMT* is expressed at a low level** (see expression plots below)	
Germline Variants for Disclosure	No pathogenic variants detected	

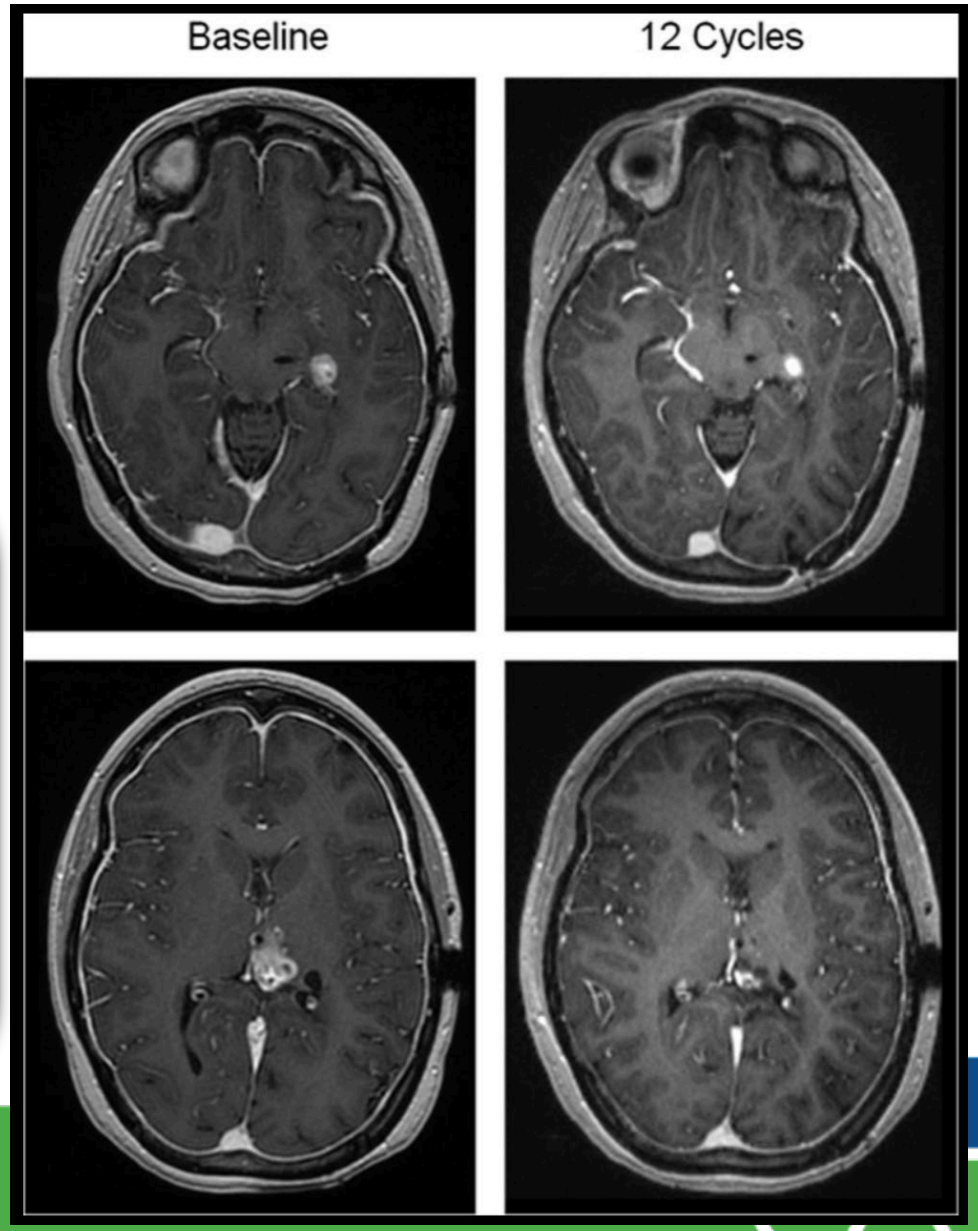
Tumors with H3K27M mutation

› Oncotarget. 2017 May 12;8(45):79298-79304. doi: 10.18632/oncotarget.17837.
eCollection 2017 Oct 3.

A phase 2 study of the first imipridone ONC201, a selective DRD2 antagonist for oncology, administered every three weeks in recurrent glioblastoma

Isabel Arrillaga-Romany [1], Andrew S Chi [2], Joshua E Allen [3], Wolfgang Oster [3], Patrick Y Wen [4], Tracy T Batchelor [1]

"One of these patient had a durable response with a secondary glioblastoma possessing a H3.3 K27M mutation, exhibiting regression by 85% in one lesion and 76% in the second lesion"



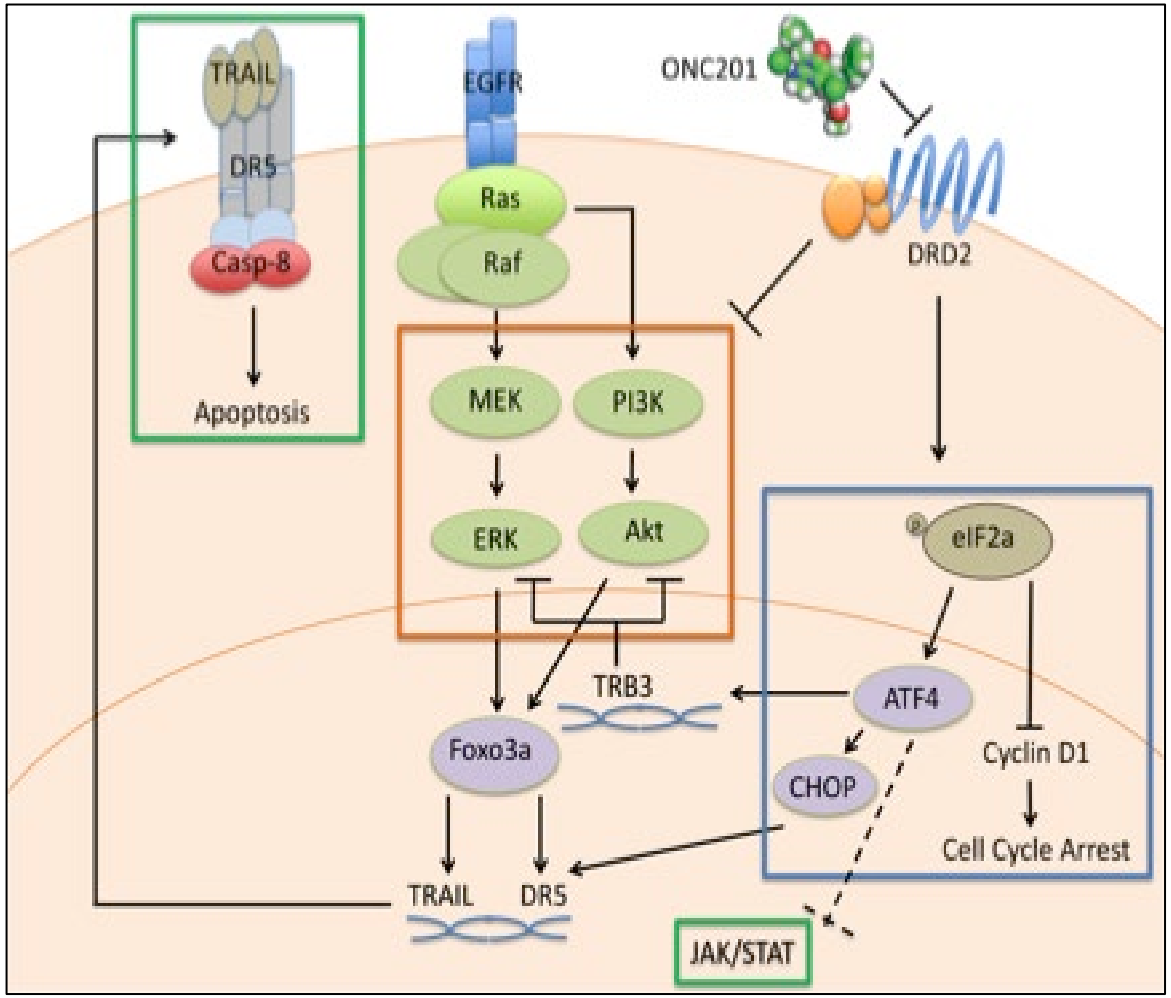
was observed as a surrogate marker of target engagement, and DRD2 was expressed in all evaluated archival tumor specimens. In summary, ONC201 is well tolerated and may have single agent activity in recurrent glioblastoma patients.

What's ONC201?

- Selective DRD2 antagonist
- Akt/ERK inhibitor
- Inactivates prosurvival signaling
- Activates apoptosis pathway

- Water soluble, penetrates BBB
- PO route
- Preclinical efficacy in aggressive malignancy

Figure 1.3 Proposed model of ONC201 in tumor cells.



ONC201 for H3K27M mutated gliomas

J Neurooncol. 2019 Oct;145(1):97-105. doi: 10.1007/s11060-019-03271-3. Epub 2019 Aug 27.

Pediatric and adult H3 K27M-mutant diffuse midline glioma treated with the selective DRD2 antagonist ONC201

Andrew S Chi [1], Rohinton S Tarapore [2], Matthew D Hall [3 4], Nicole Shonka [5], Sharon Gardner [1], Yoshie Umemura [6], Ashley Sumrall [7], Ziad Khatib [4], Sabine Mueller [8], Cassie Kline [8], Wafik Zaky [9], Soumen Khatua [9], Shiao-Pei Weathers [9], Yazmin Odia [3], Toba N Niazi [4], Doured Daghistani [4], Irene Cherrick [10], David Korones [11], Matthias A Karajannis [12], Xiao-Tang Kong [13], Jane Minturn [14], Angela Waanders [14], Isabel Arillaga-Romany [15], Tracy Batchelor [15], Patrick Y Wen [16], Krystal Merdinger [2], Lee Schalop [2], Martin Stogniew [2], Joshua E Allen [2], Wolfgang Oster [2], Minesh P Mehta [17 18]

Affiliations + expand

PMID: 31456142 PMCID: PMC7241441 DOI: 10.1007/s11060-019-03271-3

Free PMC article

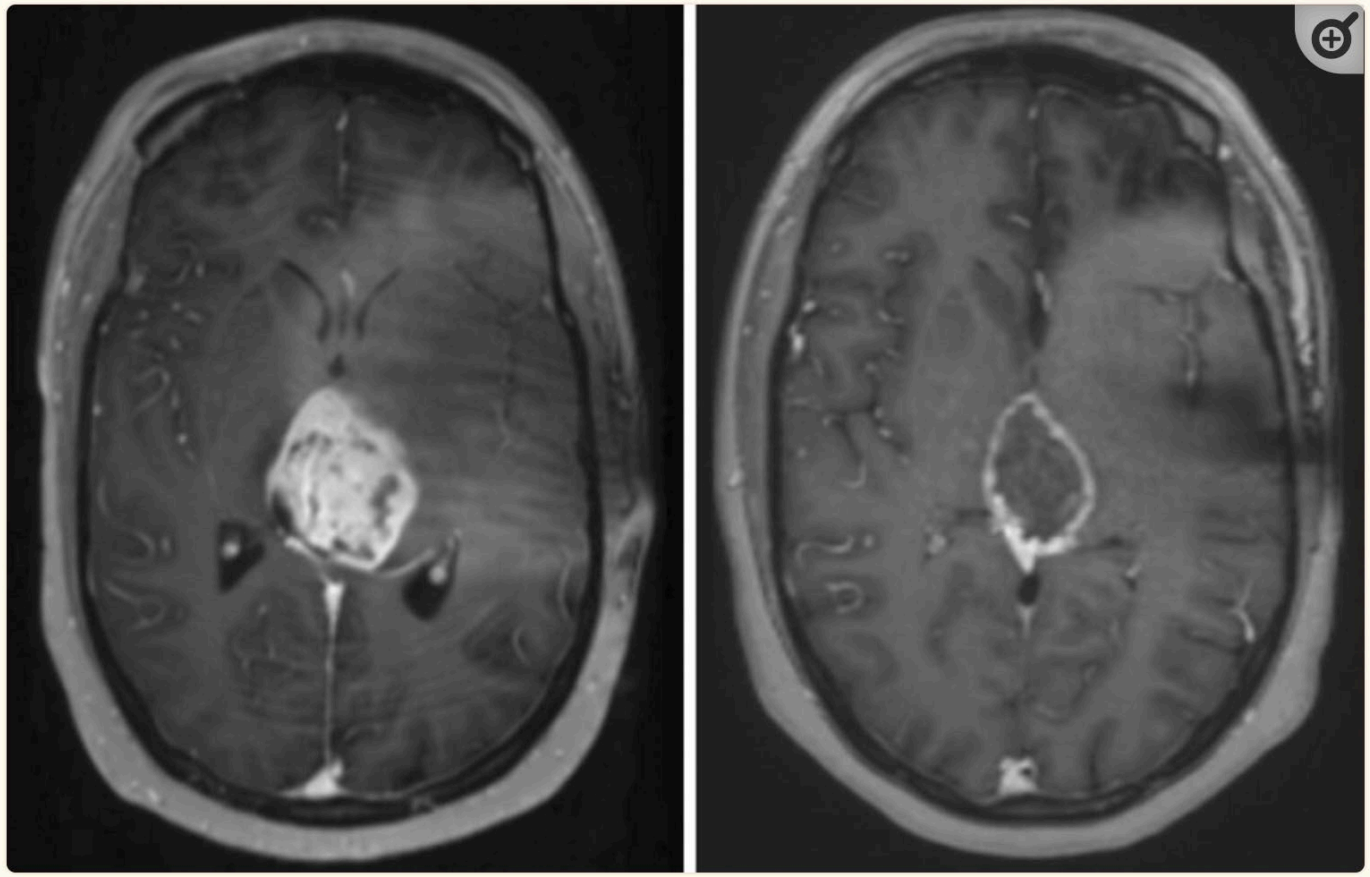


Figure 3.

Gadolinium-enhanced MRI of adult recurrent H3 K27M-mutant glioma patient at baseline (left) and one year (right) after initiating ONC201 (625mg PO, weekly). The on-treatment scan was taken 50 weeks after initiation of ONC201 and 22.5 weeks since the last dose of bevacizumab.

Tumors with H3K27M mutation

ONC201 in H3 K27M-mutant Diffuse Glioma Following Radiotherapy (the ACTION Study)

STATUS: ACTIVE

Open all Close all

Description

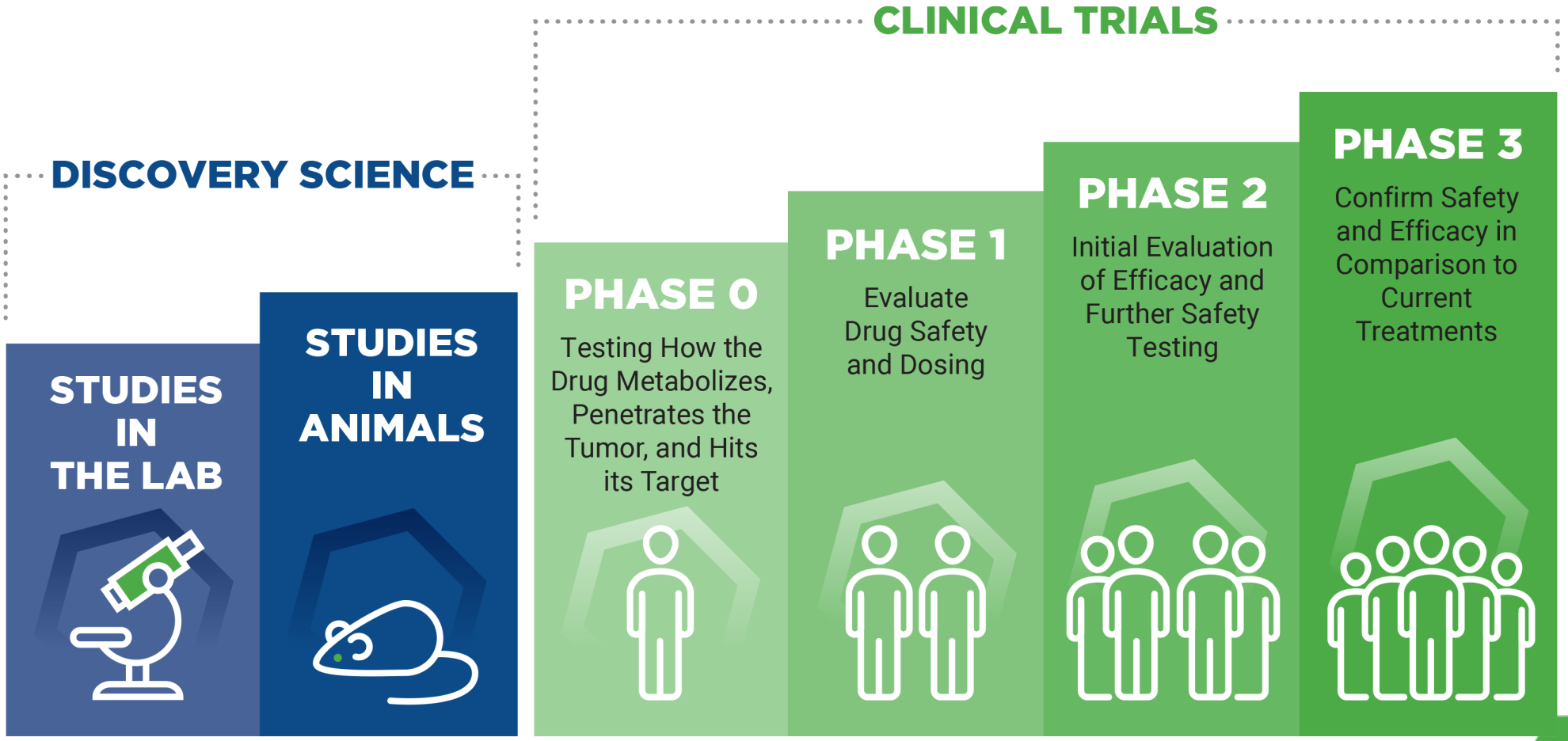
This is a randomized, double-blind, placebo-controlled, parallel-group, international, Phase 3 study in patients with newly diagnosed H3 K27M-mutant diffuse glioma to assess whether treatment with ONC201 following frontline radiotherapy will extend overall survival and progression-free survival in this population. Eligible participants will have histologically diagnosed H3 K27M-mutant diffuse glioma and have completed standard frontline radiotherapy.

Topics

- Clinical challenges in neuro-oncology
- New advancements in neuro-oncology
  - Diagnoses
  - Treatments
  - Clinical trials

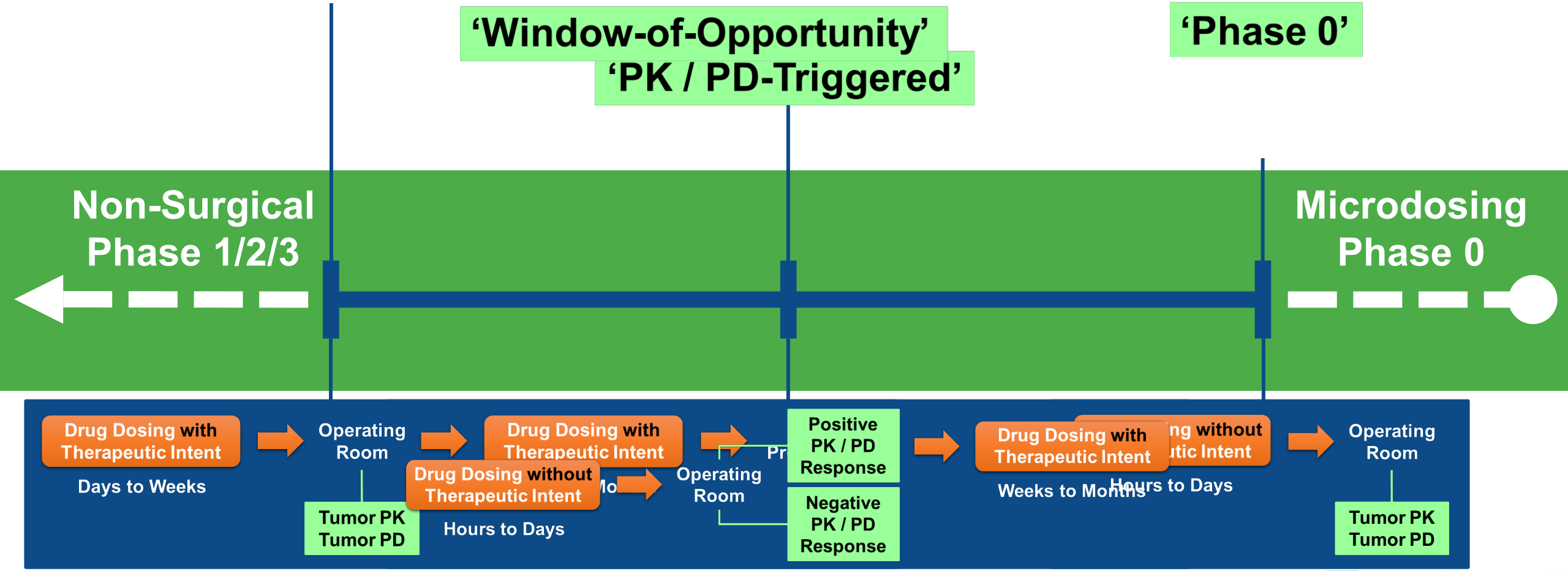
Setting the Goals

Preclinical vs. Clinical Research



‘Humanizing’ the Animal Model

Tissue-Based Trialing Often Precedes or Coincides with Phase 1/2



Phase 0/Expansion Trial Design

Niraparib plus Radiotherapy in Newly-Diagnosed Glioblastoma (NCT05076513)

Screening
- ❑ Planned resection of newly-diagnosed GBM

Phase 0
- ❑ Niraparib 300mg PO Daily x 3 days

Consent

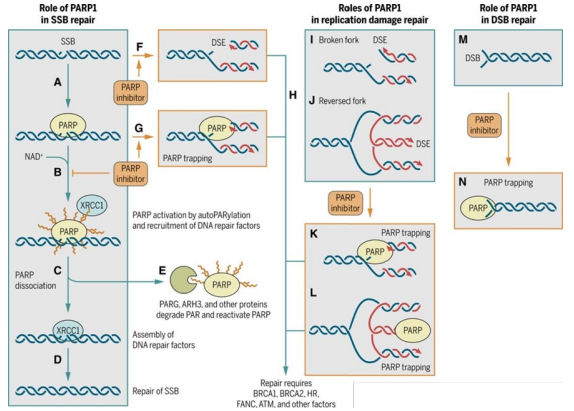
Days 1-3 → BLOOD

Arm A (2-4 hours post-dose)
Arm B (8-12 hours post-dose)
→ Resection → TUMOR | BLOOD | CSF

Pharmacokinetic Trigger
- ❑ Unbound [Niraparib] in Nonenhancing Tumor > 5xIC_{50}

✓ NET Unbound [Niraparib 1] > 5x IC_{50}

Expansion Phase
- ❑ Niraparib 300mg PO QD + 6 weeks IMRT
  - ✓ Must have MGMT-unmethylated tumor
- ❑ Maintenance Dosing: Niraparib 300mg PO QD until progression



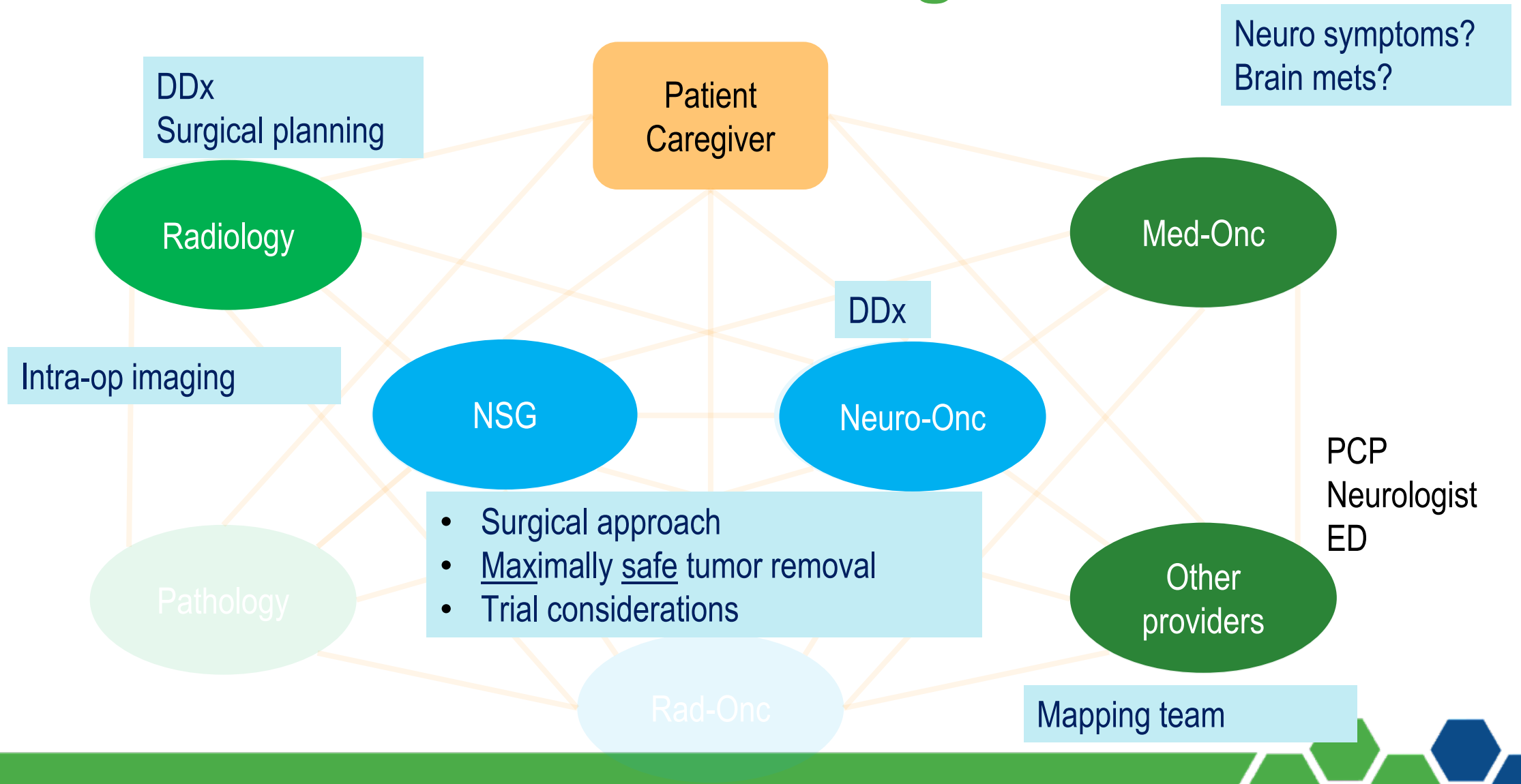
SCREENING & ACCRUAL → RESECTION → CAP/CLIA PK-TRIGGER → EXPANSION PHASE → THERAPY

EXPOSURE

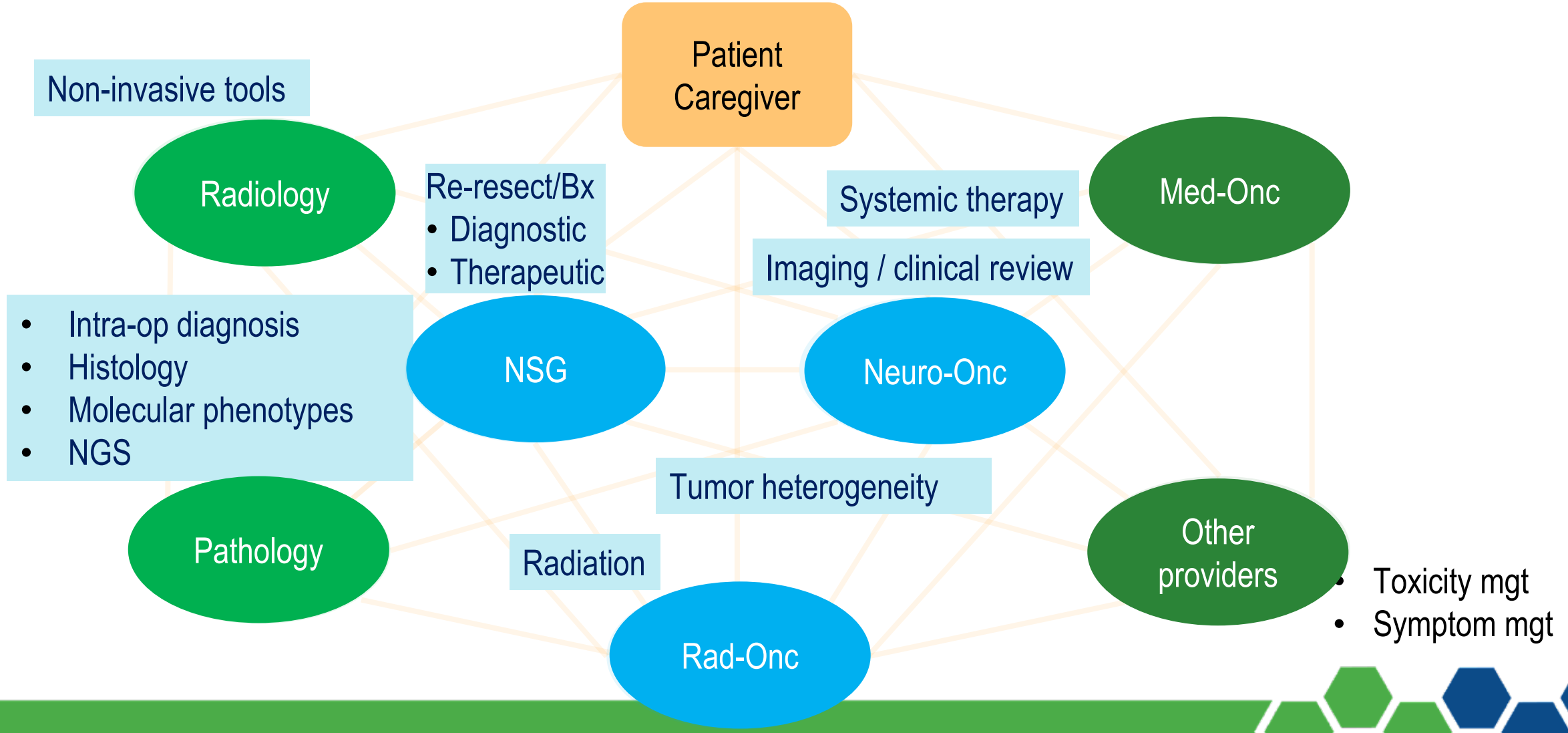
Topics

- Clinical challenges in neuro-oncology
- New advancements in neuro-oncology
- Clinical collaborations

The web of brain tumor diagnosis



The web of brain tumor treatment

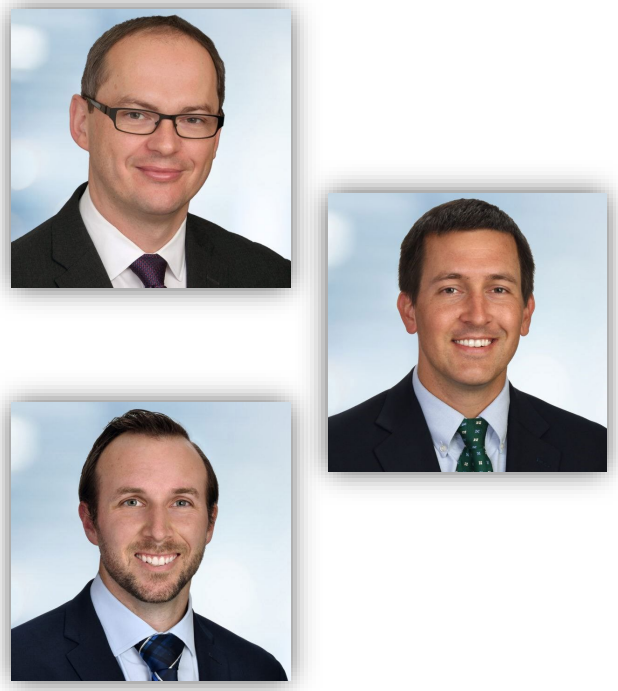


Ivy Brain Tumor Clinical Team

Neurosurgery

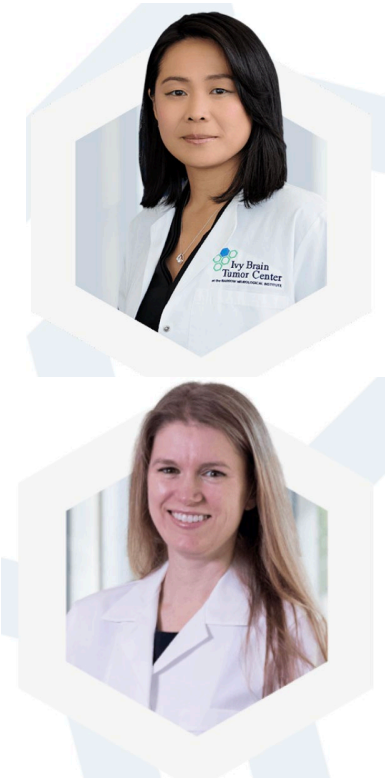
- Biopsy, Resection
- Post-operative matters

Radiation Oncology



- Radiation
- Post-radiation matters

Neuro-Oncology



- Chemotherapy
- MRI follow ups
- Seizures
- Goals of Care

Clinical Trials at Ivy Brain Tumor Center

Clinical Trial:	Phase	Gliomas					Meningioma	BM
		GBM	G4	G3	G2	H3K27M		
Radiotherapy planning using fluciclovine PET	2	N						
Pamiparib in newly diagnosed and recurrent GBM	0/2	N/R						
AZD1390 in recurrent and newly diagnosed grade 4 glioma	0/1b	N/R	N/R					
Niraparib in newly diagnosed and recurrent grade 2-4 glioma	0	N/R	N/R	N/R	N/R			
Sonodynamic therapy in recurrent GBM	1/2	R						
Abemaciclib plus LY3214996 in recurrent GBM	0	R						
DSC-MRI for recurrent GBM	3	R						
Sonodynamic therapy in recurrent HGG	0	R	R	R				
BDTX-1535 in recurrent HGG with EGFR alterations or fusions	0/1	R	R	R				
Superselective intra-arterial cerebral infusion of temsirolimus in recurrent HGG	0	R	R	R				
Safusidenib (AB-218) in recurrent or progressive IDH1 mutant glioma	2				R			
ONC201 in newly diagnosed H3 K27M-mutant diffuse glioma	3					N		
Abemaciclib in newly diagnosed grade 3 meningioma	2						N (G3)	
Radiation therapy vs. observation for newly diagnosed meningioma	3						N (G2)	
SMO/AKT/NF2/CDK inhibitors in progressive meningioma	2						R	
Stereotactic radiosurgery in brain metastases	3							N/R

N=new, R=recurrent / progressive, G=Grade

Thank you

Ivy Brain Tumor Center:

602-406-8605

Info@ivybraintumorcenter.org
www.ivybraintumorcenter.org

Barrow Neuro-Oncology Clinic

602-406-2800

Questions: Yoshie.Umemura@IvyBrainTumorCenter.Org