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Brain Tumors: Is it Time for Personalized Medicine?

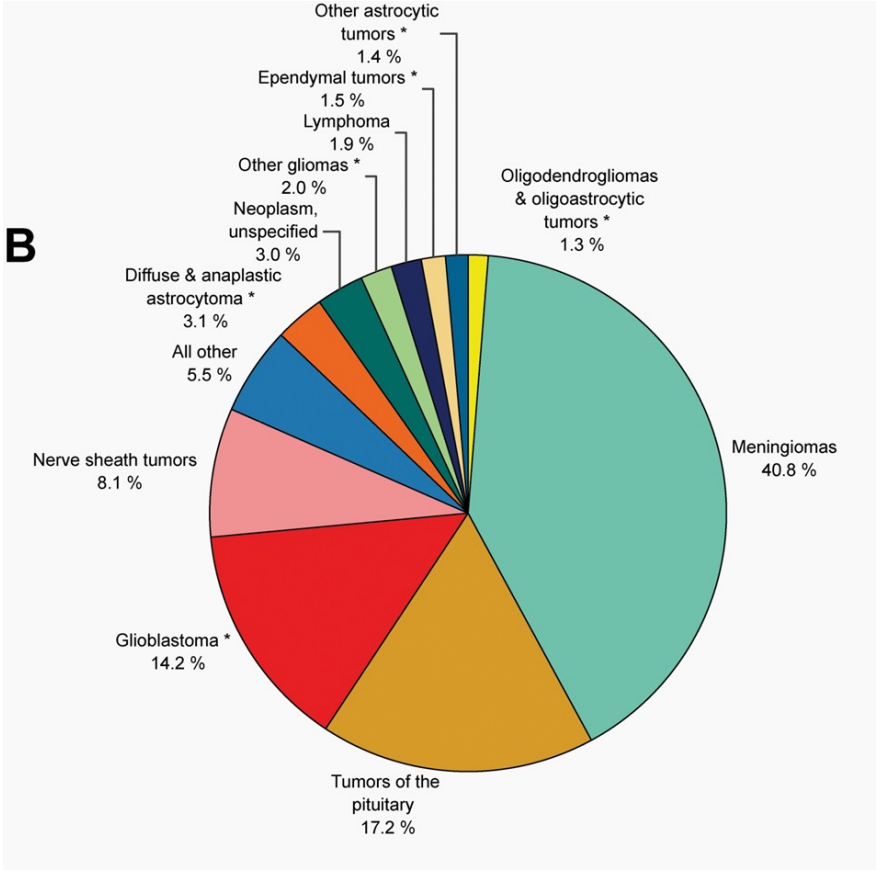
Rimas V. Lukas, MD
Malnati Brain Tumor Institute
Northwestern University

WCS 2024

OVERVIEW

Precision Medicine in Neuro-Oncology

- Failures of Precision Medicine
  - GBM IDHwt
- Promising New Directions
  - IDH mutant gliomas
  - Craniopharyngioma
  - CNS Hemangioblastoma
  - BRAF mutant tumors
  - NTRK fused tumors
- Conclusions



Ostrom QT, et al. Neuro Oncol. 2023;25(4):iv1-iv99

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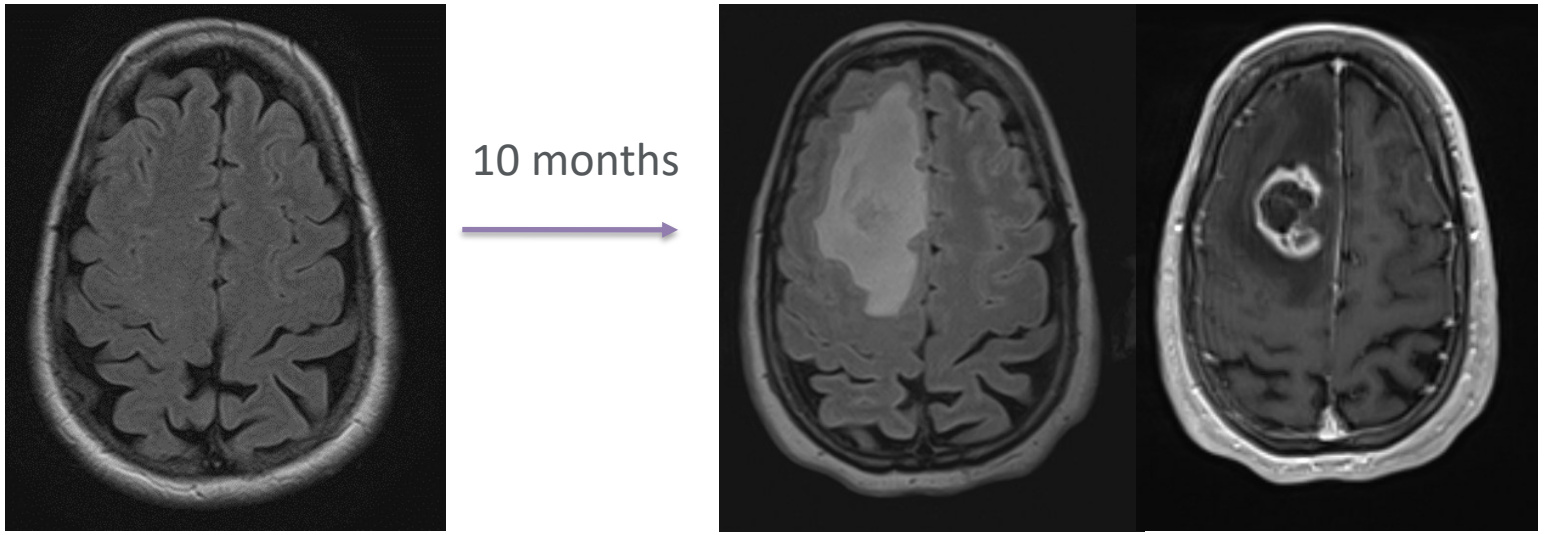
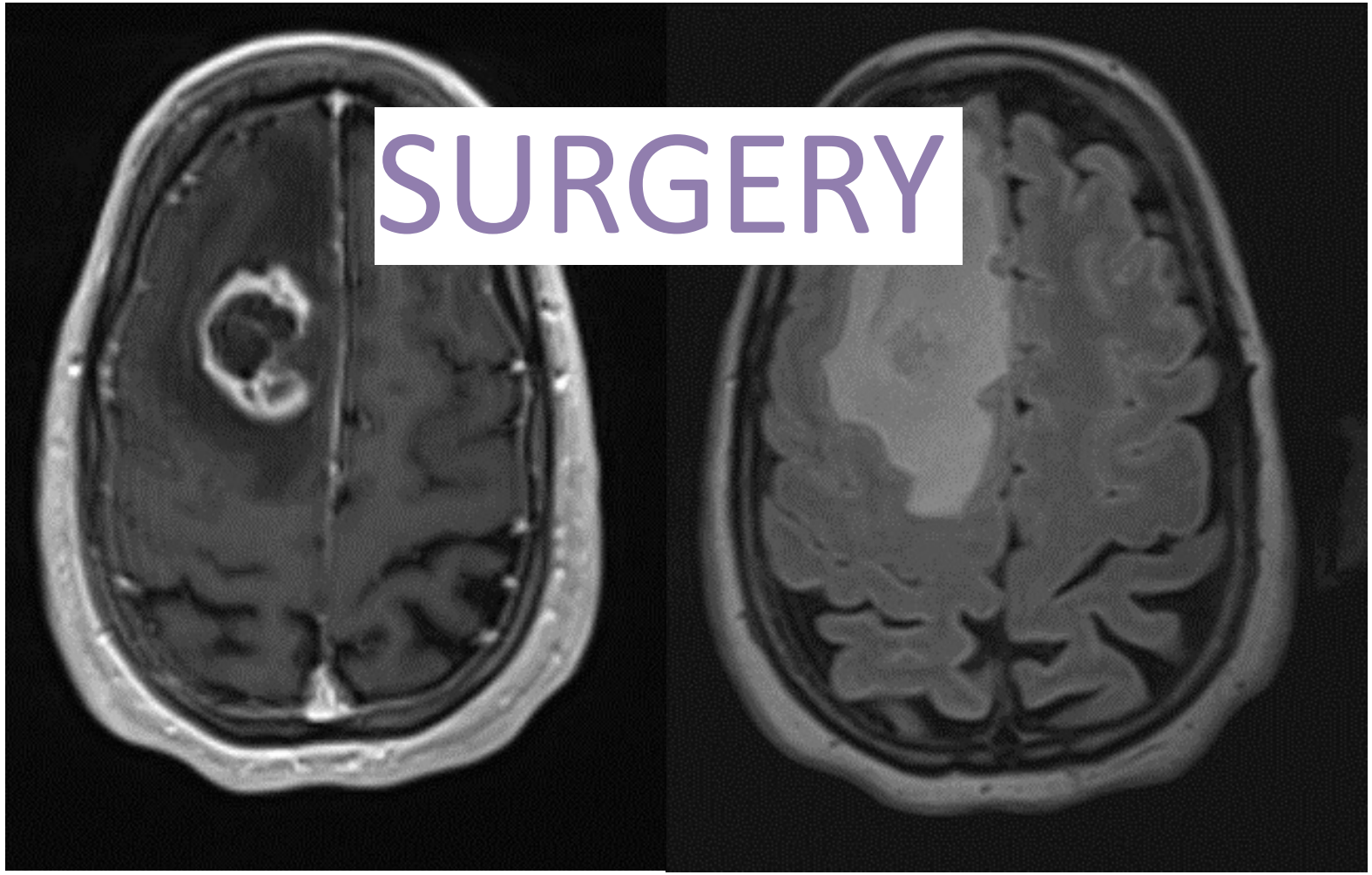
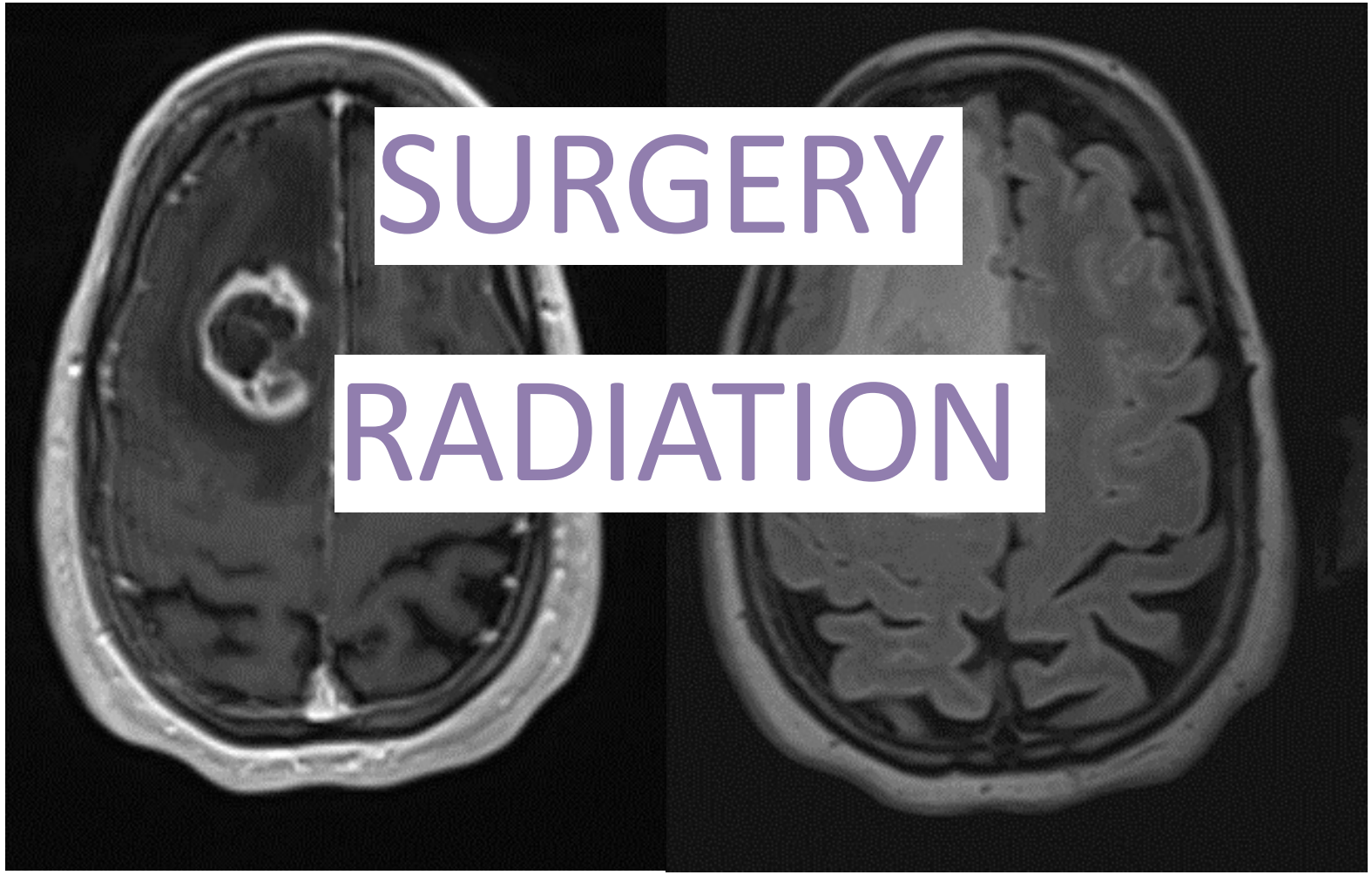
GBM IDHwt



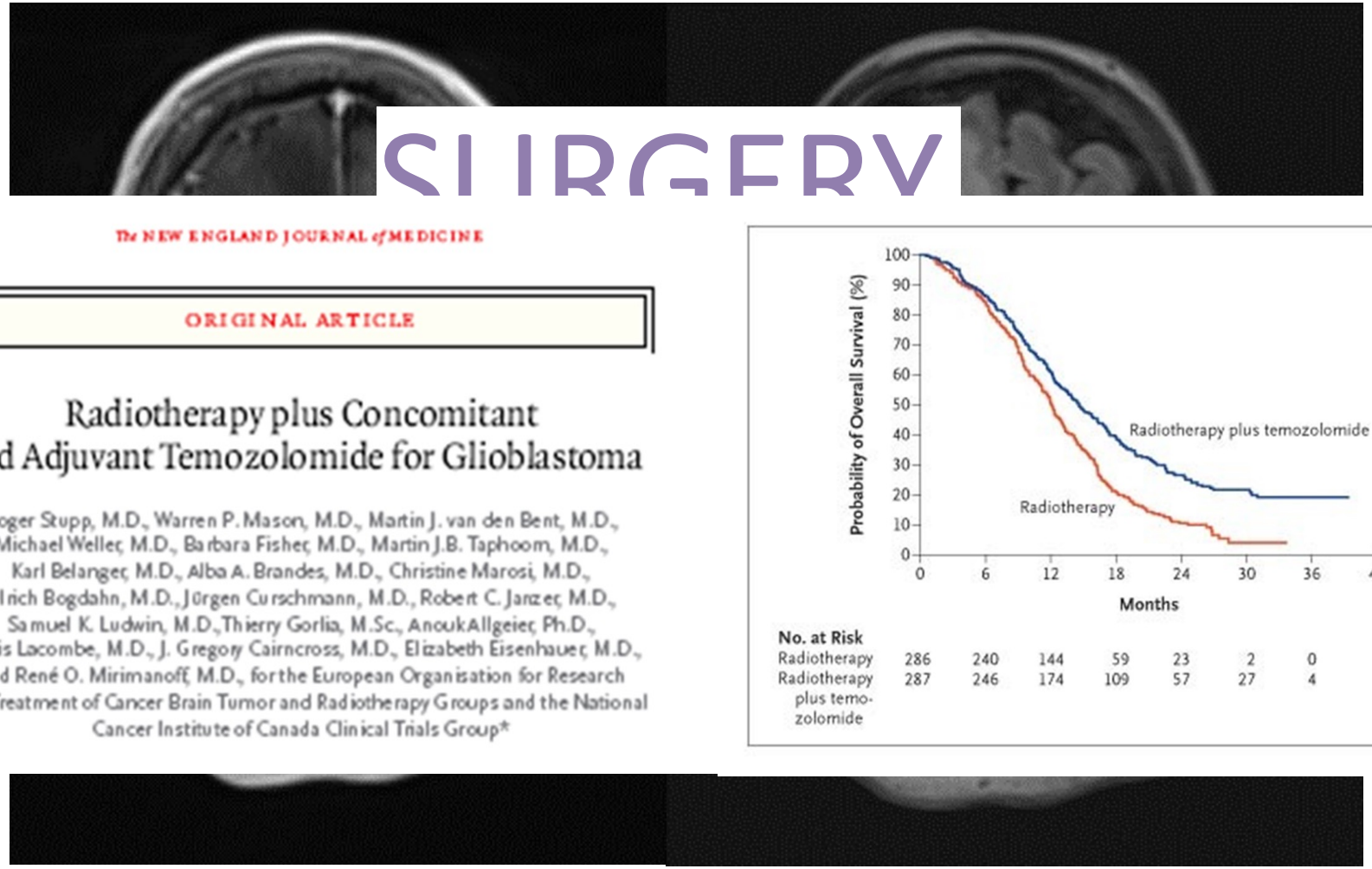
GBM IDHwt: Era of Non-Precision Medicine



GBM IDHwt: Era of Non-Precision Medicine



GBM IDHwt: Era of Non-Precision Medicine



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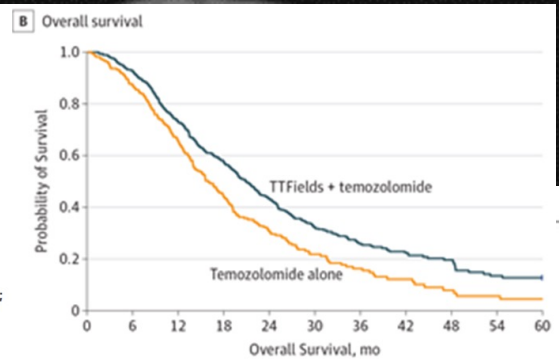
GBM IDHwt: Era of Non-Precision Medicine

JAMA | Original Investigation

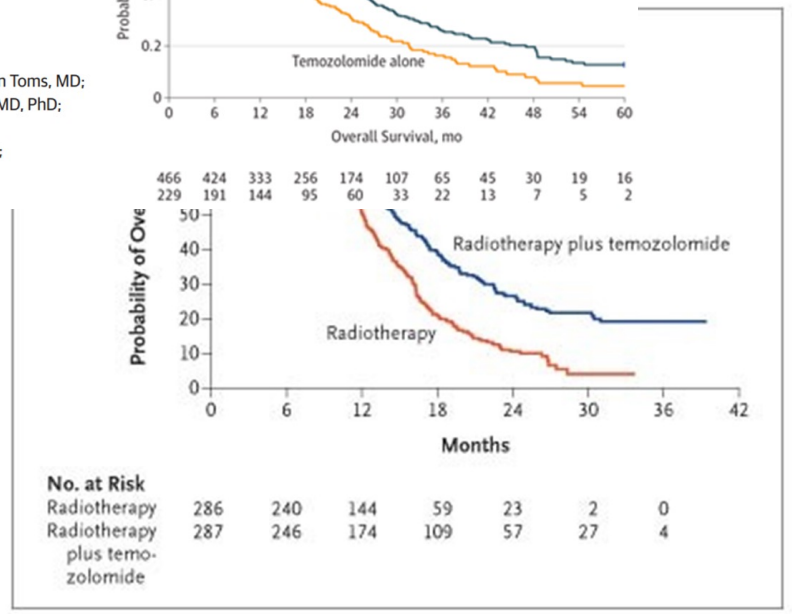
Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma
A Randomized Clinical Trial

Roger Stupp, MD; Sophie Taillibert, MD; Andrew Kanner, MD; William Read, MD; David M. Steinberg, PhD; Benoit Lhermitte, MD; Steven Toms, MD; Ahmed Idbaih, MD; Manmeet S. Ahluwalia, MD; Karen Fink, MD, PhD; Francesco Di Meco, MD; Frank Lieberman, MD; Jay-Jiguang Zhu, MD, PhD; Giuseppe Stragliotto, MD, PhD; David D. Tran, MD, PhD; Steven Brem, MD; Andreas F. Hottinger, MD, PhD; Eilon D. Kirson, MD, PhD; Gitit Lavy-Shahaf, PhD; Uri Weinberg, MD, PhD; Chae-Yong Kim, MD, PhD; Sun-Ha Paek, MD, PhD; Garth Nicholas, MD; Jordi Bruna, MD; Hal Hirte, MD; Michael Weller, MD; Yoram Palti, MD, PhD; Monika E. Hegi, PhD; Zvi Ram, MD



Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*



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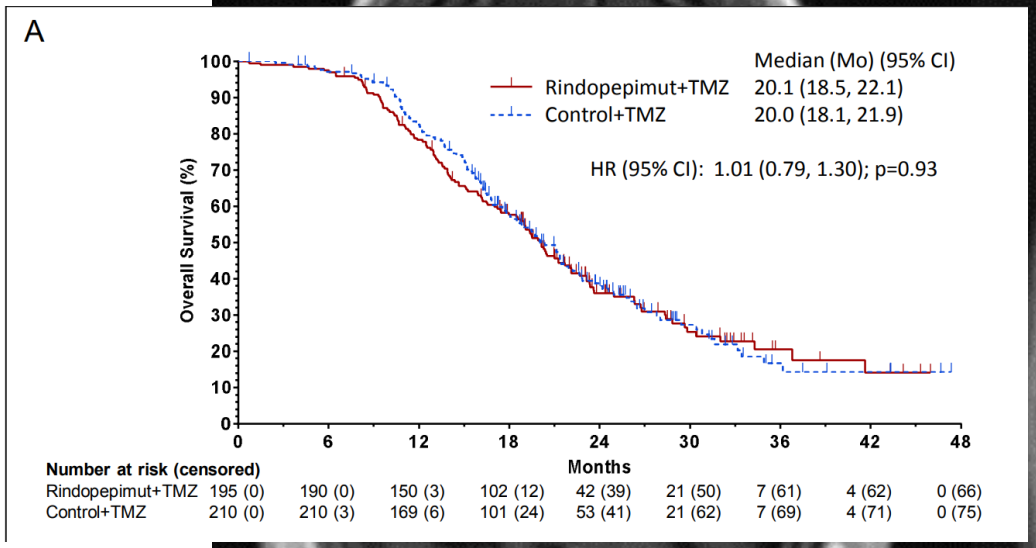
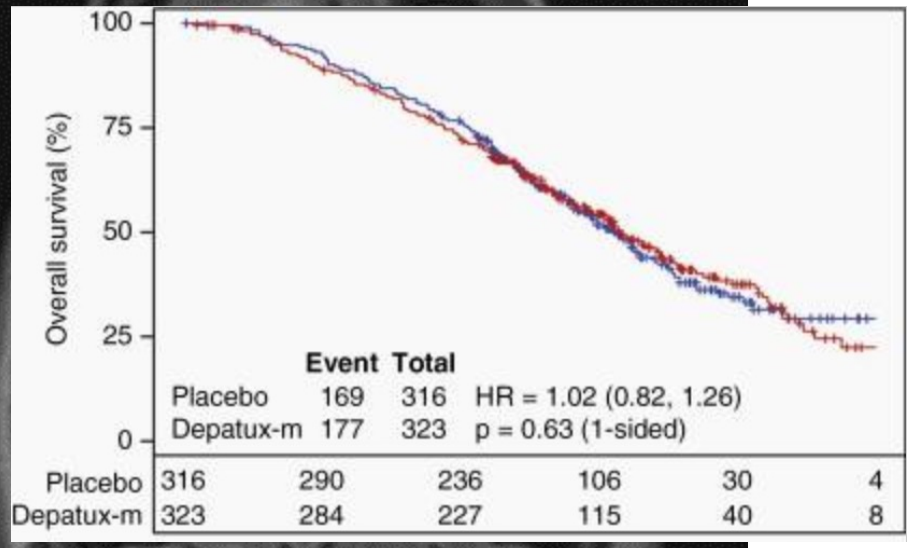
GBM IDHwt: Era of Non-Precision Medicine

EGFR targeting therapies: vaccine and ADC





Weller, et al. Lancet Oncol. 2017;18(10):1373-1385

Lassman, et al. Neuro Oncol. 2023;25(2):339-350

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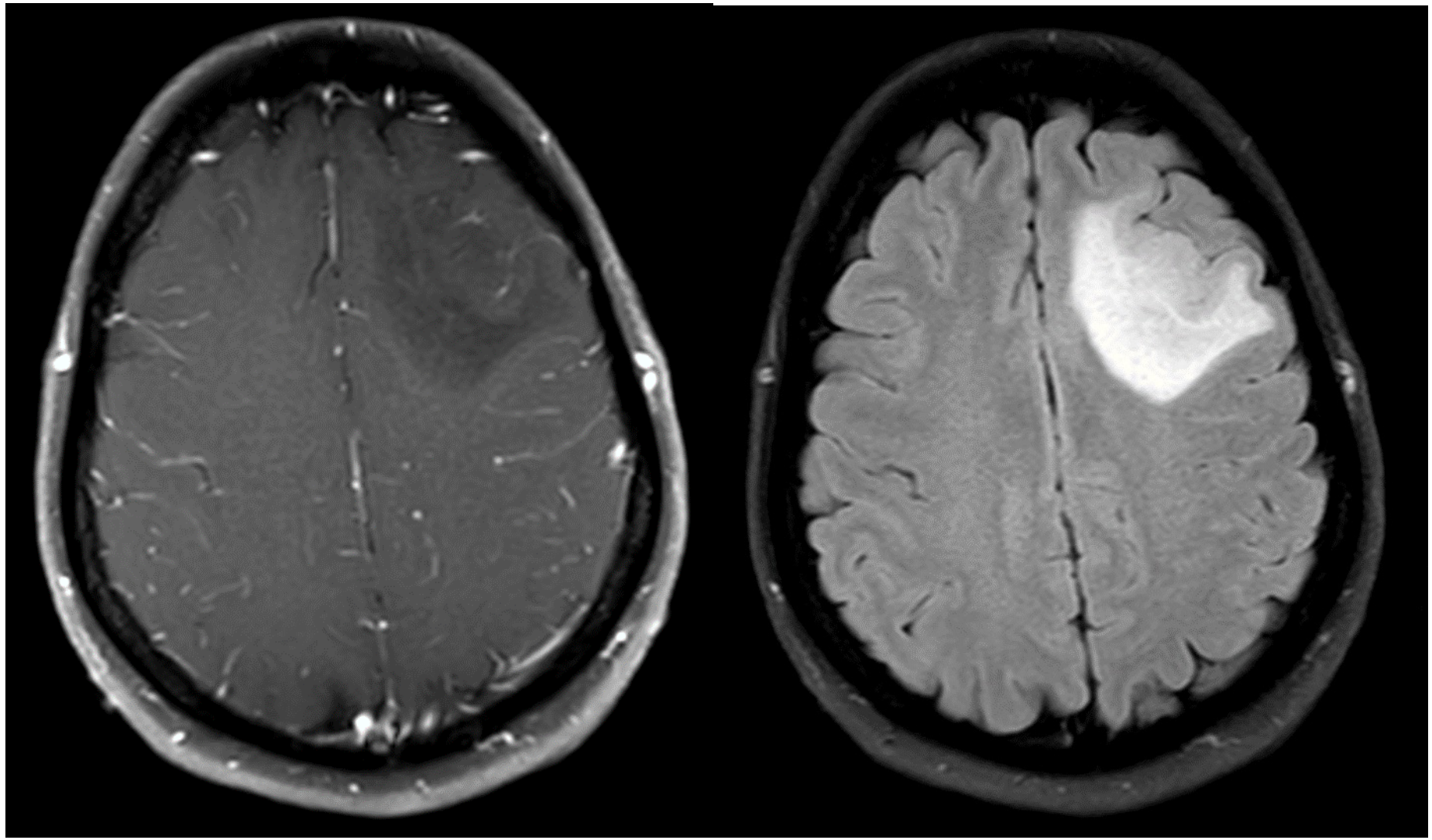
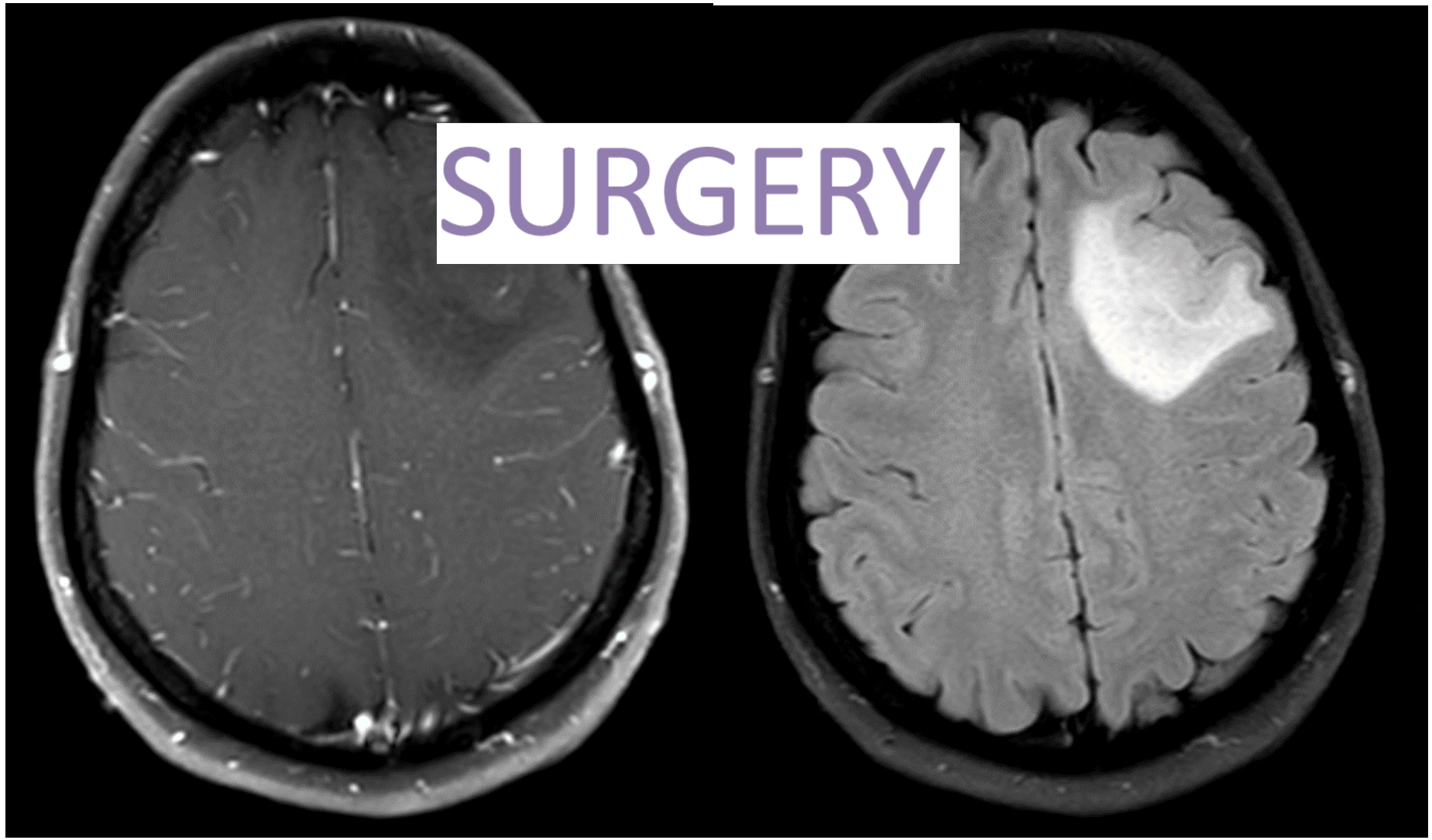
IDH mutant gliomas

IDH MUTANT GLIOMAS



IDH MUTANT GLIOMAS



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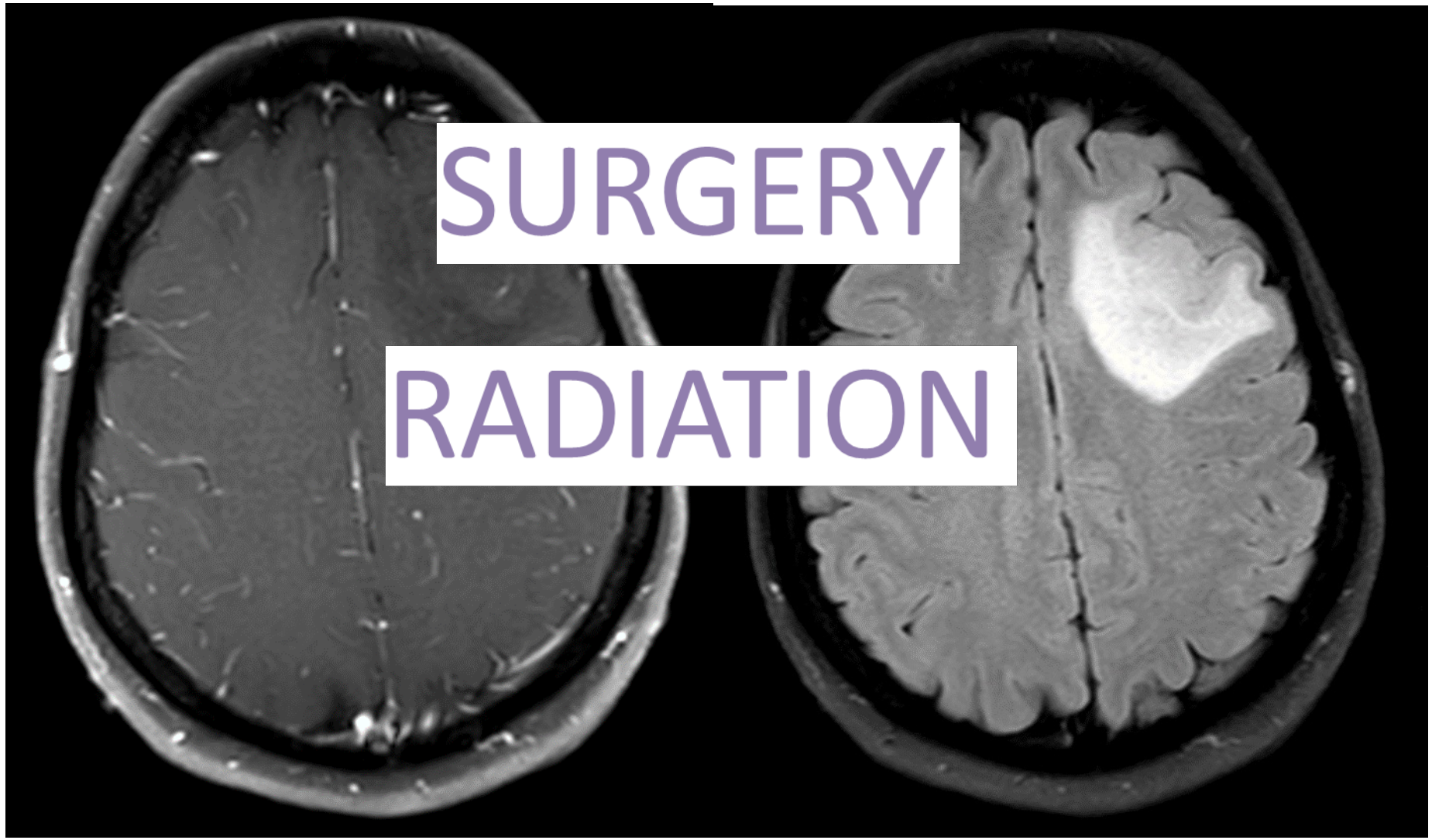
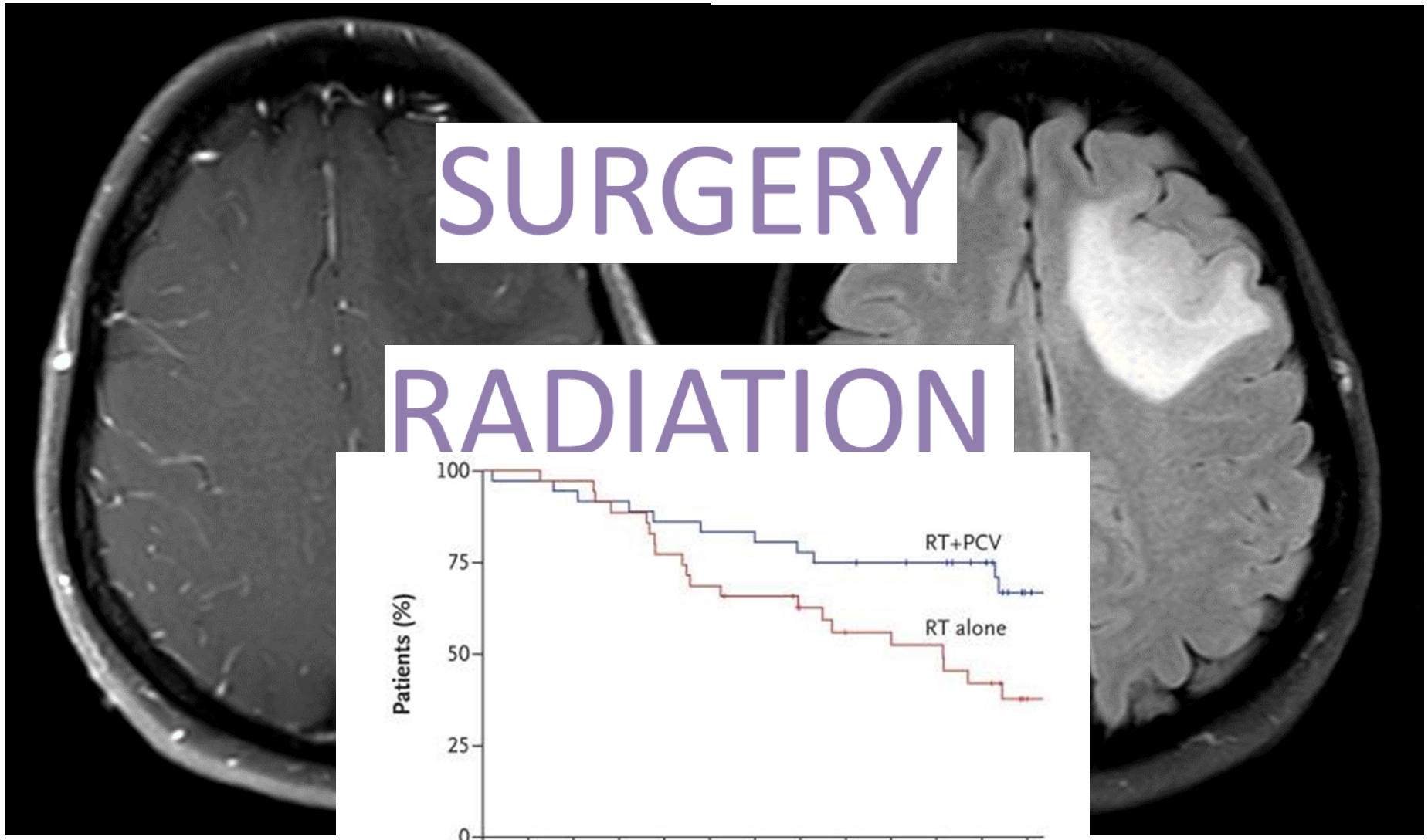


IDH MUTANT GLIOMAS



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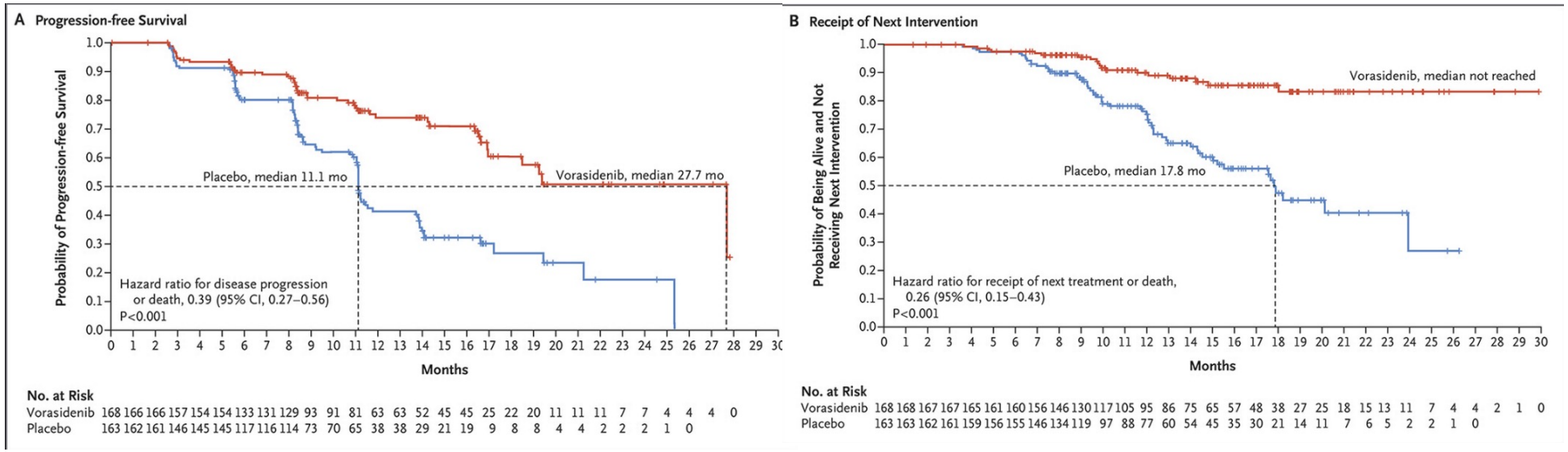
IDH inhibition in IDH mutated gliomas

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., for the INDIGO Trial Investigators*

IDH inhibition in IDH mutated gliomas

INDIGO phase 3 trial: vorasidenib vs placebo



Mellinghoff, et al. NEJM. 2023;389(7):589-601

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RARE TUMORS WITH TARGETABLE ABNORMALITIES

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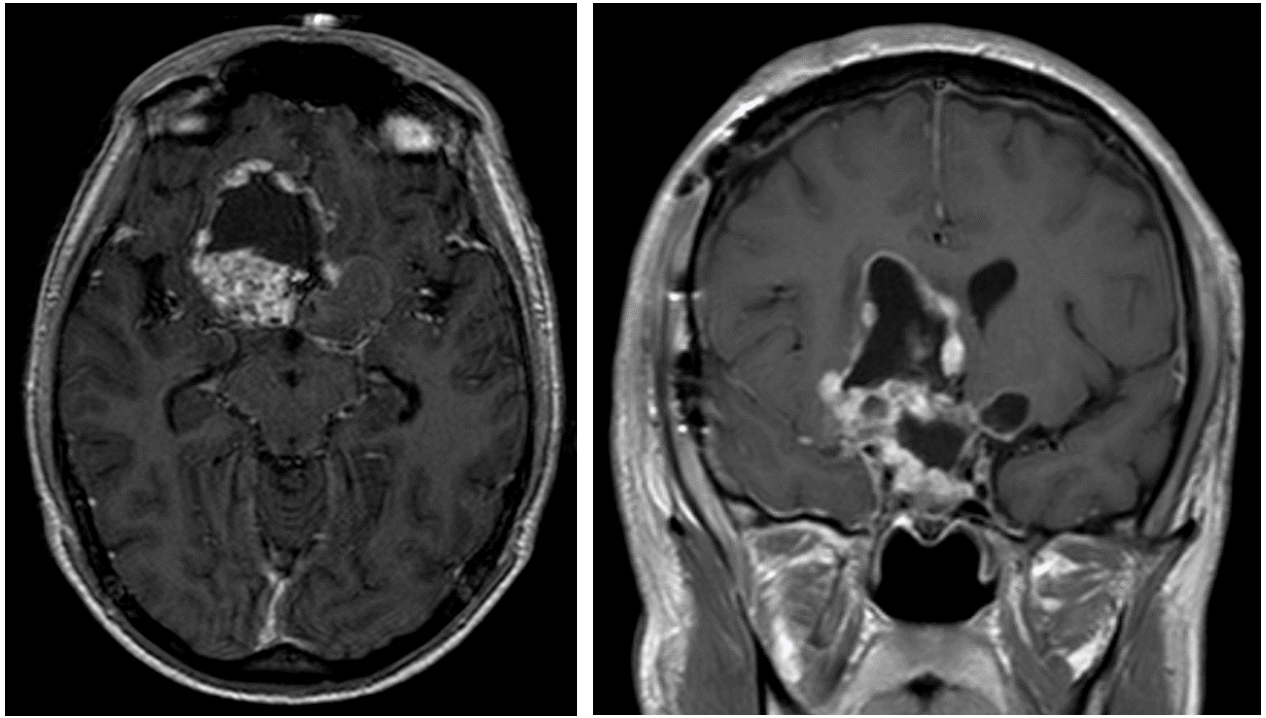
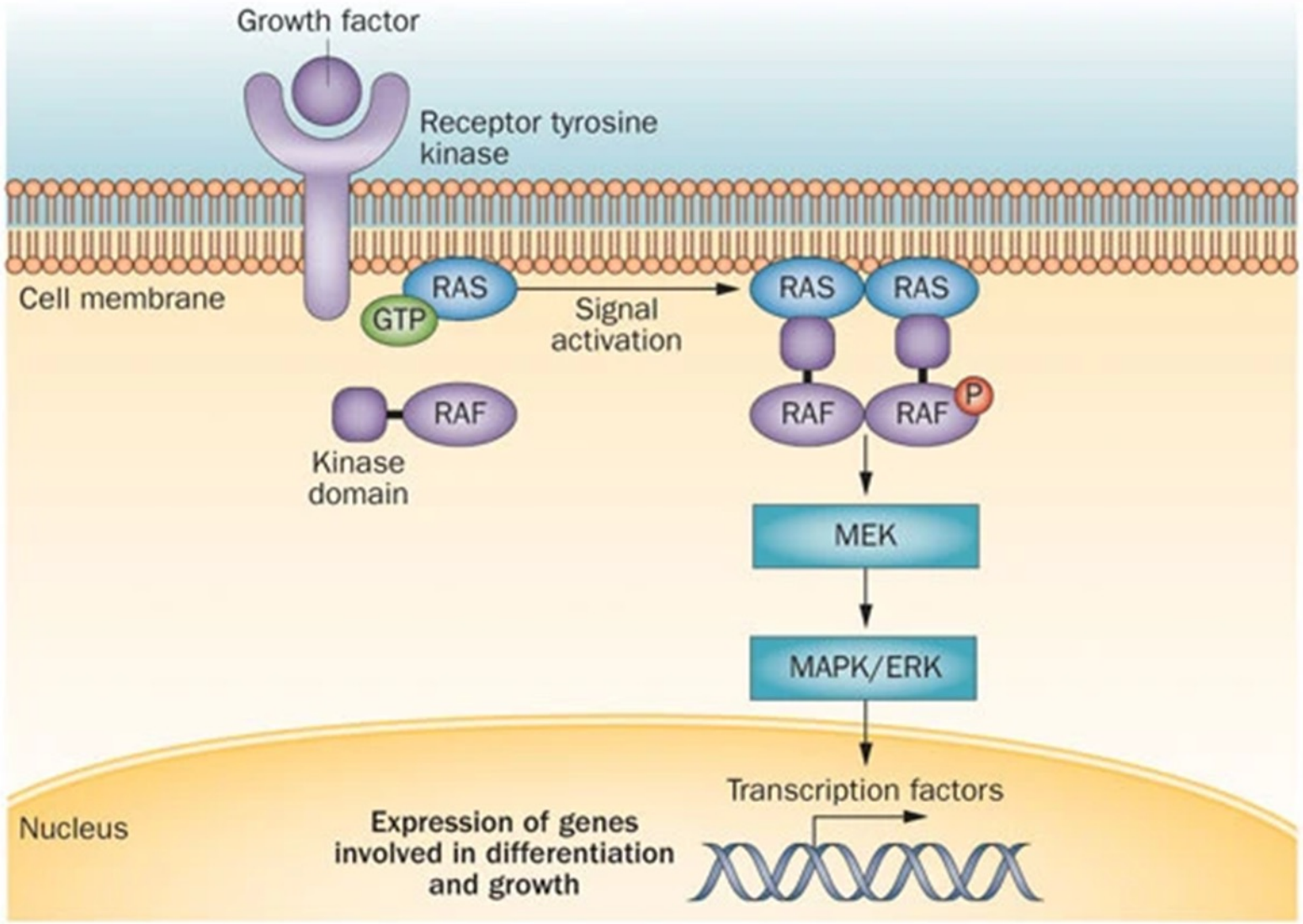
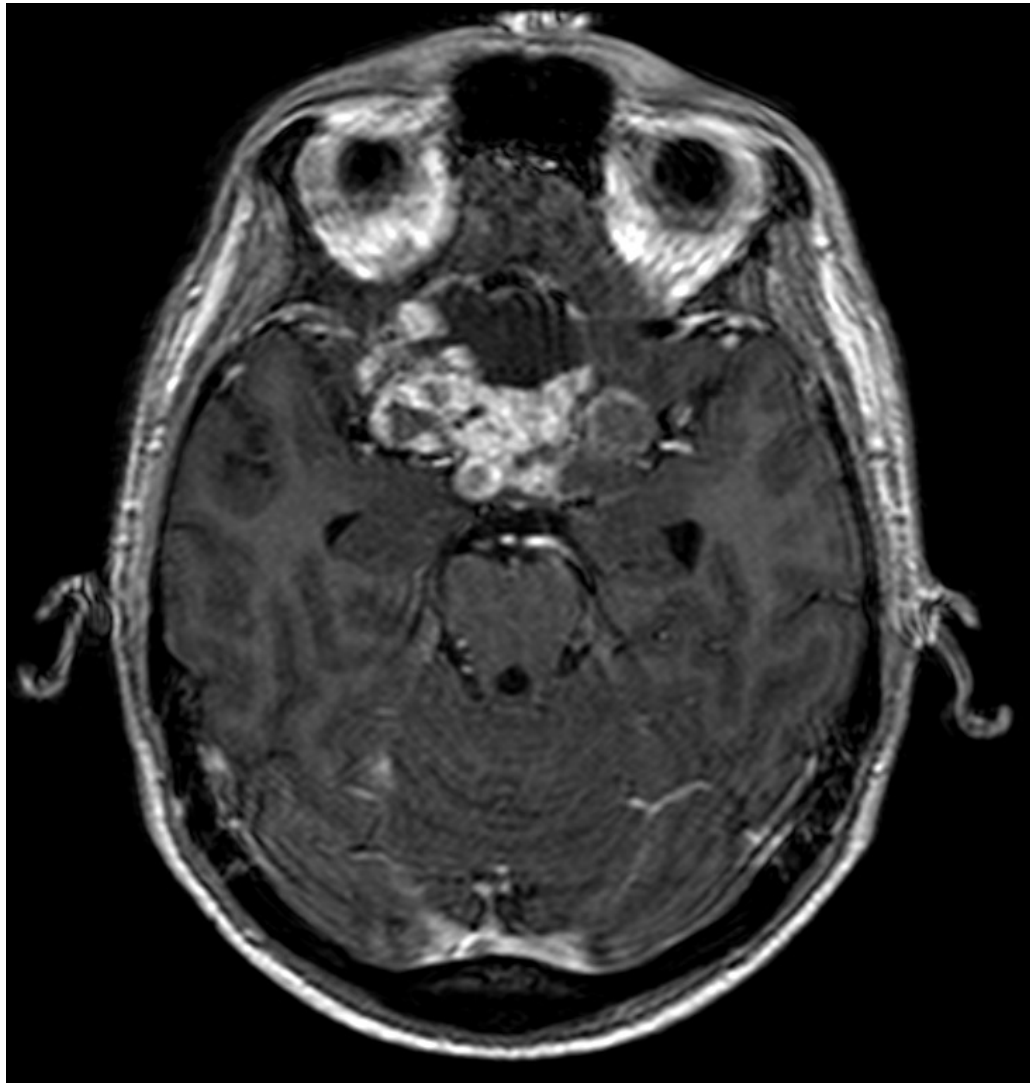
CRANIOPHARYNGIOMA





Gibney, et al. Nat Rev Clin Oncol. 2013;10:390-399

CRANIOPHARYNGIOMA



WHO Grade 1

BRAF mutated

papillary subtype

V600E

**adamantinous subtype*

CTNNB1 mutated

**adamantinous subtype*

**pediatric*

CRANIOPHARYNGIOMA

- **Surgery**
- **RT**
  - Photon vs **proton**
- **Systemic therapy**
  - BRAF/MEK inhibition
  - Alliance **A071601**
  - **Vemurafenib+cobimetinib**
  - RT-naïve pts
  - N=16, 15/16 responded (volumetric)
  - Median reduction= -83%

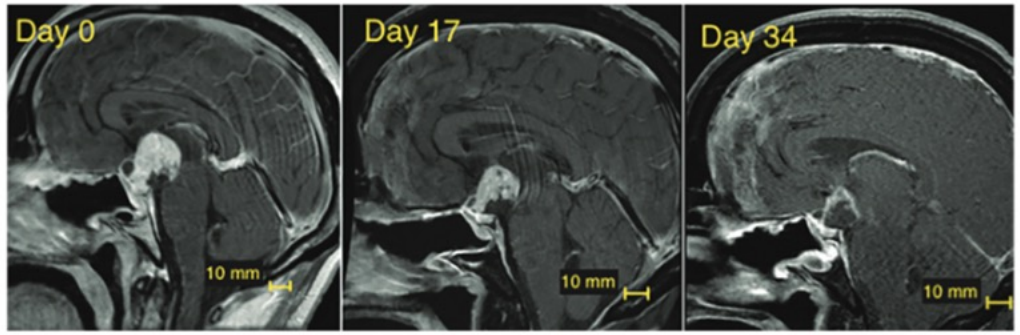


FIGURE 3-4
Craniopharyngioma with *BRAF* V600E mutation. Sagittal postcontrast T1-weighted MRIs demonstrate a partial response to dabrafenib and trametinib resulting in an 85% reduction of the tumor volume within approximately 1 month.
Reprinted with permission from Brastianos PK, et al, J Natl Cancer Inst.[64] © 2015 Oxford University Press.

Brastianos, et al. J Clin Oncol. 2021;39(15_Suppl):2000.

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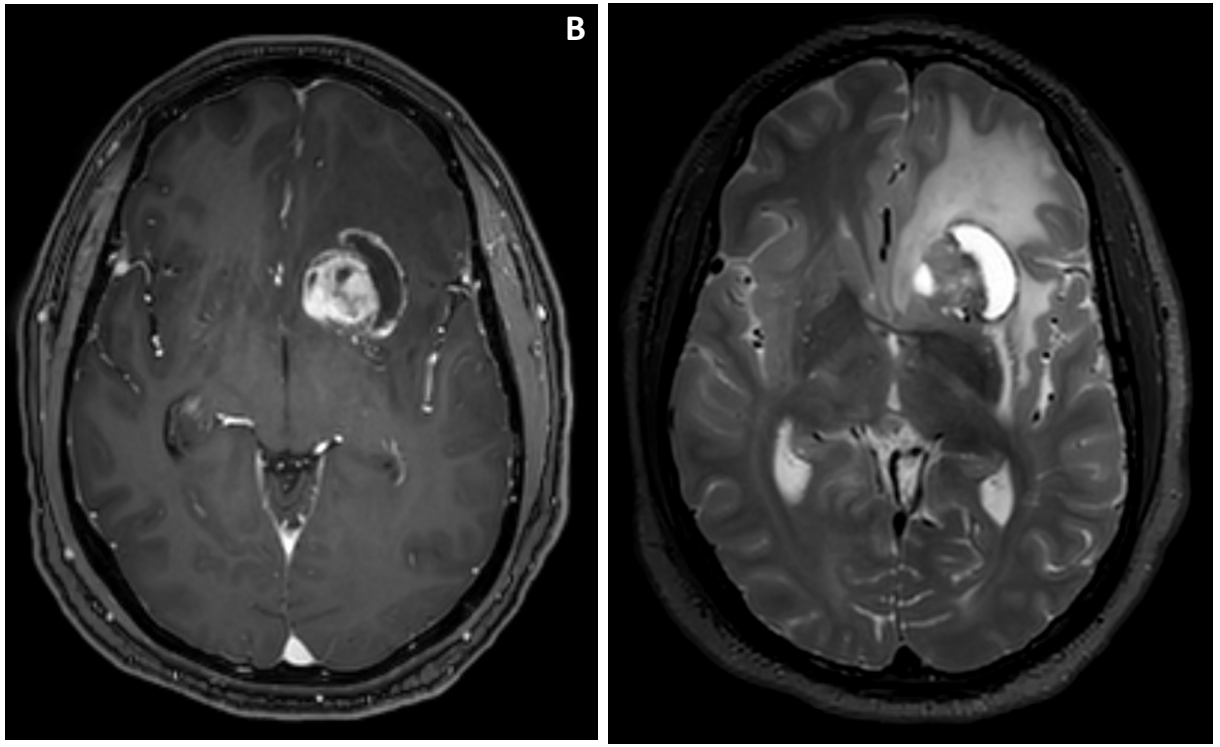
PXA & OTHER BRAF MUTATED TUMORS

PLEOMORPHIC XANTHOASTROCYTOMA (PXA)



- A circumscribed Astrocytic Glioma (WHO 2021)
- Managed by surgery
- +/-RT for residual/progressive disease
- BRAF+MEK inhibition (for BRAF V600E mutated)

VE-BASKET

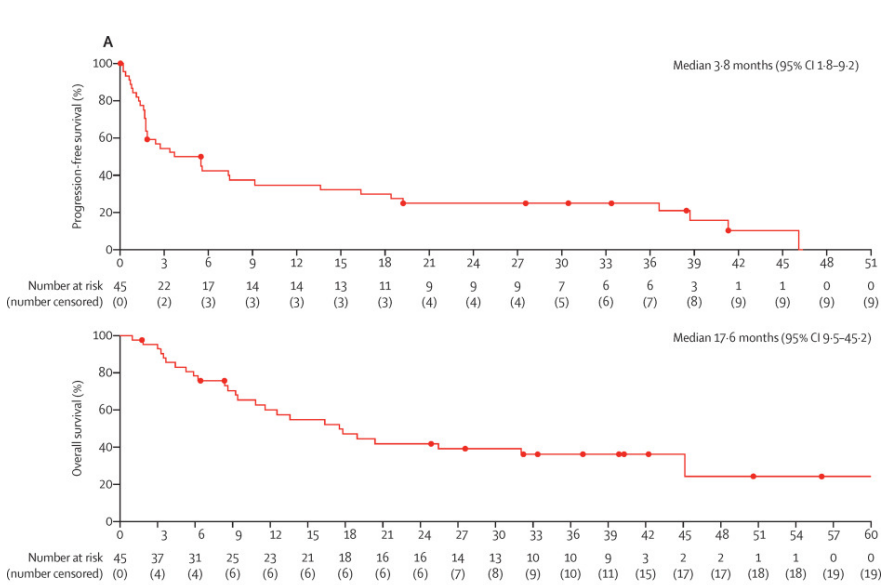
- N=24, GBM=6, AA=5, PXA=7, HGG NOS=1
- **BRAF V600 mutation**
- **Vemurafenib** 960mg po BID
- **RR**=25%,
  - 44% in PXA,
  - 9% in malignant diffuse glioma,
  - 0% in GBM
- **PFS**=5.5mo,
  - 5.3mo in malignant diffuse glioma

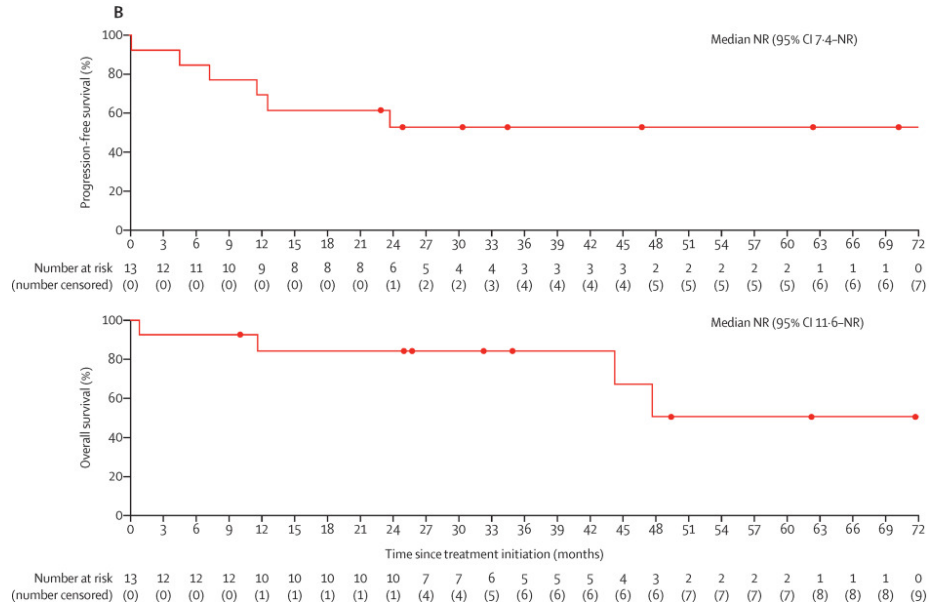
ROAR

- N=45 High grade glioma (GBM=31), N=13 Low grade glioma
- **BRAF V600E**
- **Dabrafenib** 150 mg po BID **+ trametinib** 2 mg po Qday
- RR=33% in HGG, 69% in LGG (investigator assessment**)
- **HGG mOS** 17.6 mo (9.5-45.2mo)
- **LGG mOS** NR (11.6mo-NR)
- **HGG mPFS** 3.8 mo (1.8-9.2m0)
- **LGG mPFS** NR (7.4mo-NR)

Kaley T, et al. J Clin Oncol. 2018;36(35):3477-3484 Wen PY, et al. Lancet Oncol. 2022;23(1):53-64.

ROAR





Kaley, et al. JCO. 2018;36(35):3477-3484

Wen, et al. Lancet Oncol. 2022;23(1):53-64

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ROAR

Dabrafenib+Trametinib

Histology agnostic FDA approval on 6/22/2022

Unresectable or metastatic solid tumors w/ BRAF V600E mut

Progressed following prior Tx and satisfactory alternative Txs available

Kaley, et al. JCO. 2018;36(35):3477-3484

Wen, et al. Lancet Oncol. 2022;23(1):53-64

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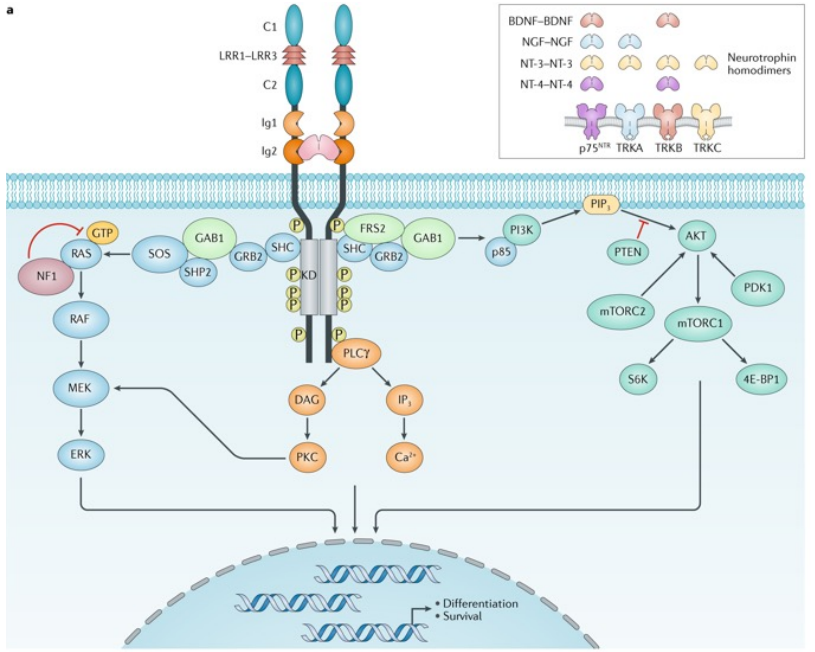
NTRK FUSION TUMORS

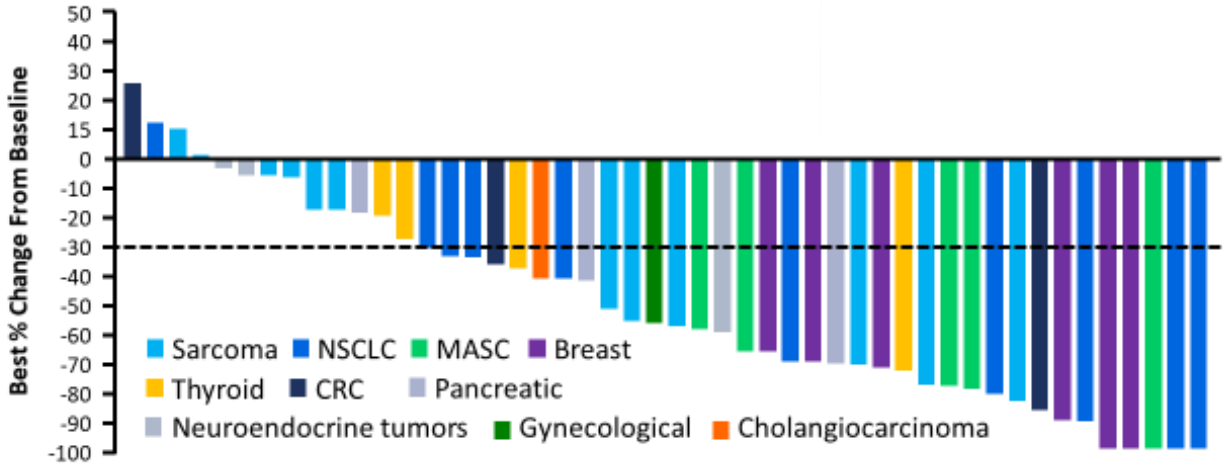
NTRK INHIBITION

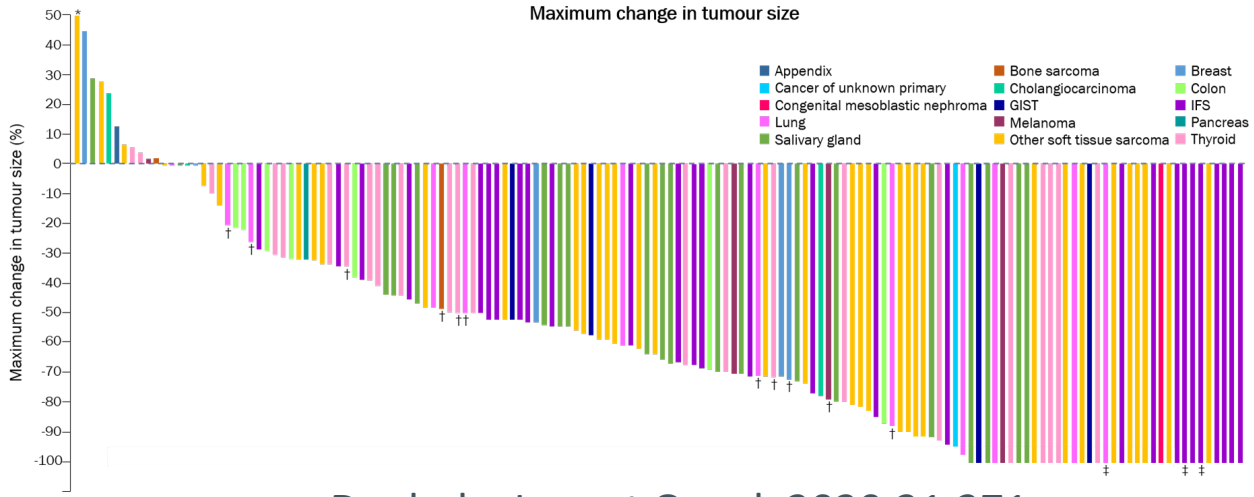
NT Receptor	Gene	Neutrophin Ligands
TRKA	*NTRK1*	NGF, NT-3
TRKB	*NTRK2*	BDNF, NT-4, NT-3
TRKC	*NTRK3*	NT-3

- Different isoforms present in different tissues
- Adult nervous system
- Embryonal development
- High freq incidence in some rare tumors
- Low freq incidence in common tumors
- <5% in gliomas (higher in pontine)



Cocco. Nat Rev Clin Oncol. 2018;15:731. Jones. Nat Genet. 2013;45:927. Stransky. Nat Commun. 2014;5:4846. Kim. PLoS One. 2014;9:e91940. Wu. Nat Genet. 2014;46:444.





Doebele. Lancet Oncol. 2020;21:271

Hong. Lancet Oncol. 2020;21:531

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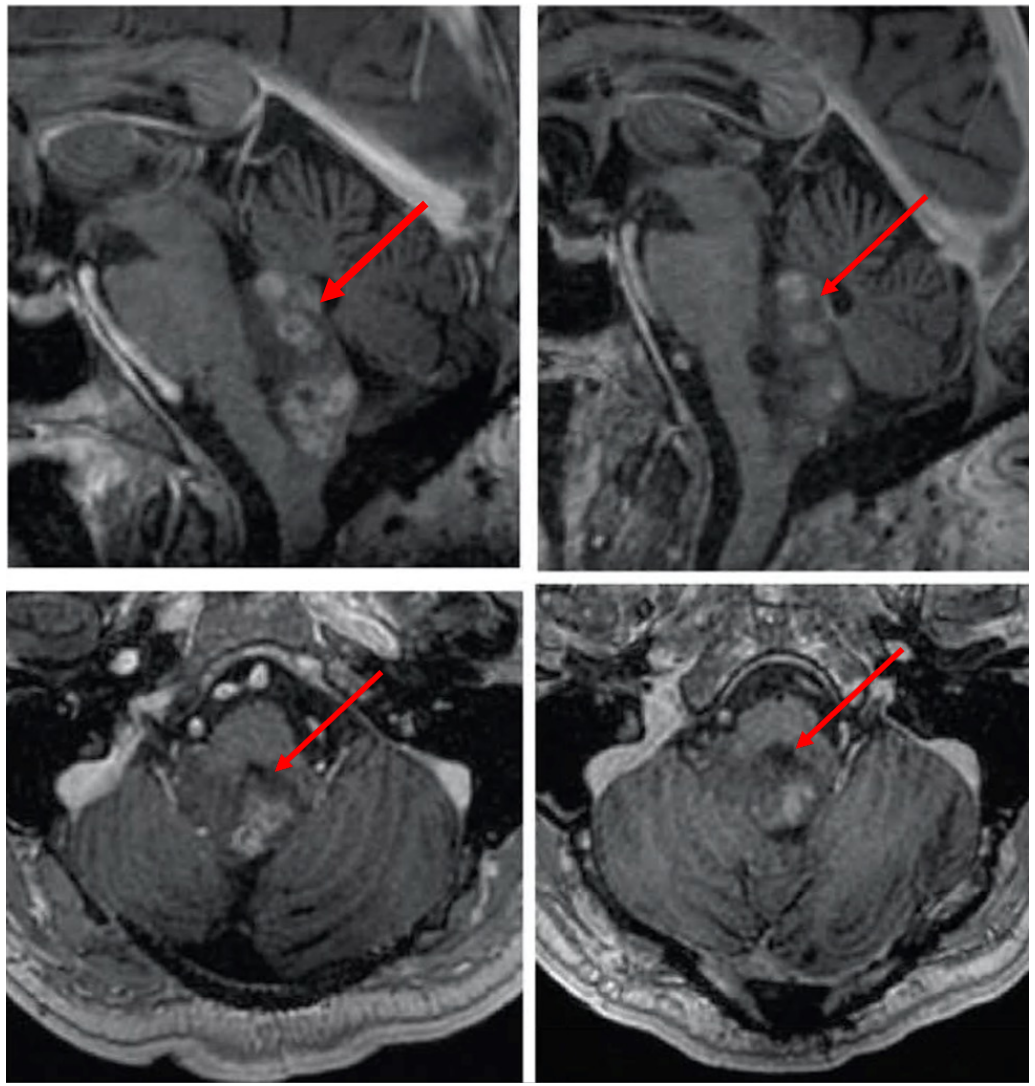
NTRK Inhibitors: First-generation, FDA approved

- **Larotrectinib** (approved 2018)
  - indicated for adult and pediatric patients with solid tumors that:
    - have a *NTRK* gene fusion without a known acquired resistance mutation and
    - have metastatic disease or where surgical resection is likely to result in severe morbidity and
    - have no satisfactory alternative treatments or that have progressed following treatment

- **Entrectinib** (approved 2019)
  - Indicated for adult patients with NSCLC that is *ROS1*-positive
  - Indicated for adult and pediatric patients ≥ 12 years of age with solid tumors that:
    - have a *NTRK* gene fusion without a known acquired resistance mutation,
    - have metastatic disease or where surgical resection is likely to result in severe morbidity, and
    - have progressed following treatment or have no satisfactory alternative therapy

Larotrectinib PI. Entrectinib PI.

NTRK inhibition



Highlights importance of obtaining tissue for Dx and molecular studies and incorporating extensive molecular interrogation (mutation + fusion)

Lukas & Mrugala. Continuum.2020;26(6):1495-1522

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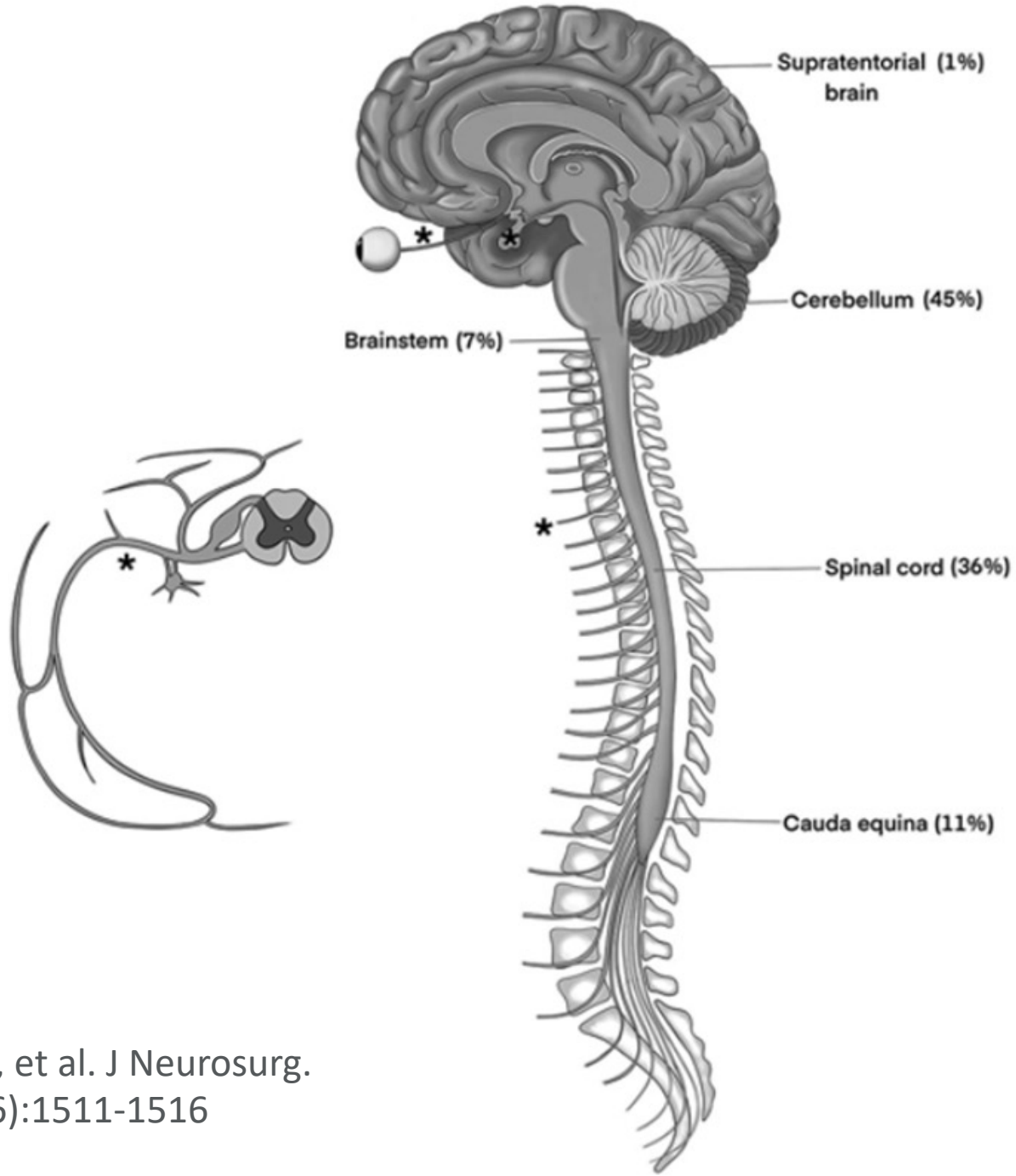
CNS HEMANGIOBLASTOMA



Huntoon K, et al. J Neurosurg. 2021;136(6):1511-1516

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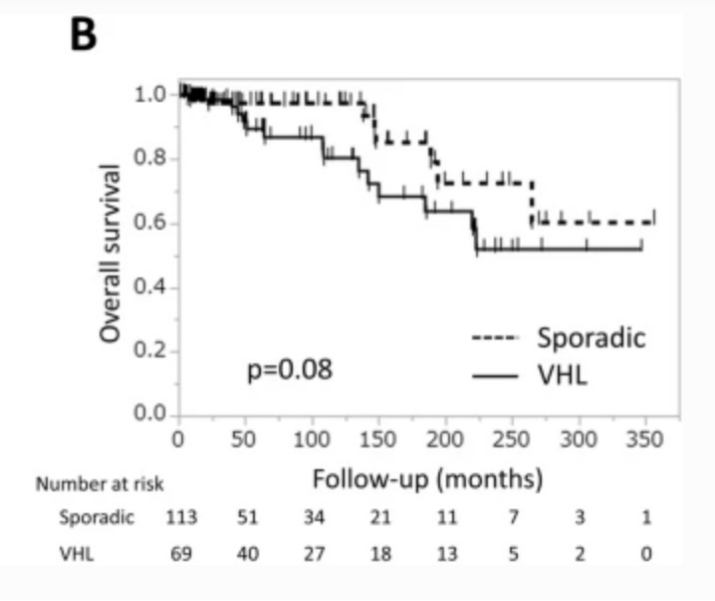
CNS HEMANGIOBLASTOMAS

Natural History Study

- Mean age of Dx in ~30s (younger than sporadic hemangioblastomas)
- Often multiple (60-79%)
- Symptoms related to **tumor+cyst** size/location
- Growth pattern
  - Saltatory = 72%
  - Exponential = 22%
  - Linear = 6%
- Synchronous and Non-synchronous phase changes
- ?Effect of pregnancy on growth patterns?



Wanebo, et al. J Neurosurg. 2003;98:82-94

Lonser, et al. J Neurosurg. 2014;120:1055-1062.

Takami, et al. J Neurooncol. 2022;159:221-231.

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Table 1.
Pan-VHL and Hemangioblastoma Clinical Trials

Principal Investigator	Clinical Trial ID	Year	Patients	Phase	Agent	Target	PFS (Mos.)	RR (PR+CR) (%)
Emily Chew	NCT00056199	2003–2005	5	1	Pegaptanib	VEGF	N/A	20% (rHBL*)
Novartis	NCT00052013	2003–2006	11	2	Vatalanib	RTK	N/A	0%
Adrian L. Harris	N/A	2004	6	1,2	Semaxanib	VEGF	N/A	0%
Emily Chew	NCT00089765	2004–2007	5	1	Ranibizumab	VEGF	N/A	20% (rHBL*)
William M. Linehan	NCT00088374	2004–2009	9	2	Tanespimycin	HSP-90	N/A	0%
Eric Jonasch	NCT00330564	2006–2011	15	2	Sunitinib	RTK	N/A	33% (RCC), 0% (HBL)
Catherine Meyerle	NCT00673816	2008–2011	3	1,2	Sunitinib	RTK	N/A	0%
William M. Linehan	NCT00566995	2008–2015	37	2	Vandetanib	RTK	(11.0 to 22.1)	8% (RCC)
J. Marc Pipas	NCT01015300	2009–2012	1	1	Bevacizumab	VEGF	N/A	0%
Stephane Richard	NCT01168440	2010–2011	5	2	Sunitinib	RTK	N/A	0%
Eric Jonasch	NCT01266070	2012–2015	6	2	Dovitinib	RTK	N/A	0%
Eric Jonasch	NCT01436227	2012–2021	31	2	Pazopanib	RTK	N/A	42% (ORR), 52% (RCC), 53% (pNETs), 4% (HBL)
Kevin D. Courtney	NCT03108066	2014–2016	51	1	PT2385	HIF-2α	53% at 52 Weeks	14% (RCC)
Prashant Chittiboina	NCT02108002	2014–2018	7	0	Vorinostat	HDAC	N/A	0%
Henry E. Wiley	NCT02859441	2016–2020	3	1,2	E10030 and Ranibizumab	PDGF, VEGF	N/A	0%
Eric Jonasch	NCT03401788	2016–2020	95	1	Belzutifan	HIF-2α	14.5 Months	25% (RCC)
Kevin D. Courtney	NCT03108066	2017–2022	4	2	PT2385	HIF-2α	N/A	N/A
Eric Jonasch	NCT03401788	2018–2026	61	2	Belzutifan	HIF-2α	98% at 52 Weeks	47% (ORR), 80% (pNETs), 32% (HBL), 69% (rHBL*)

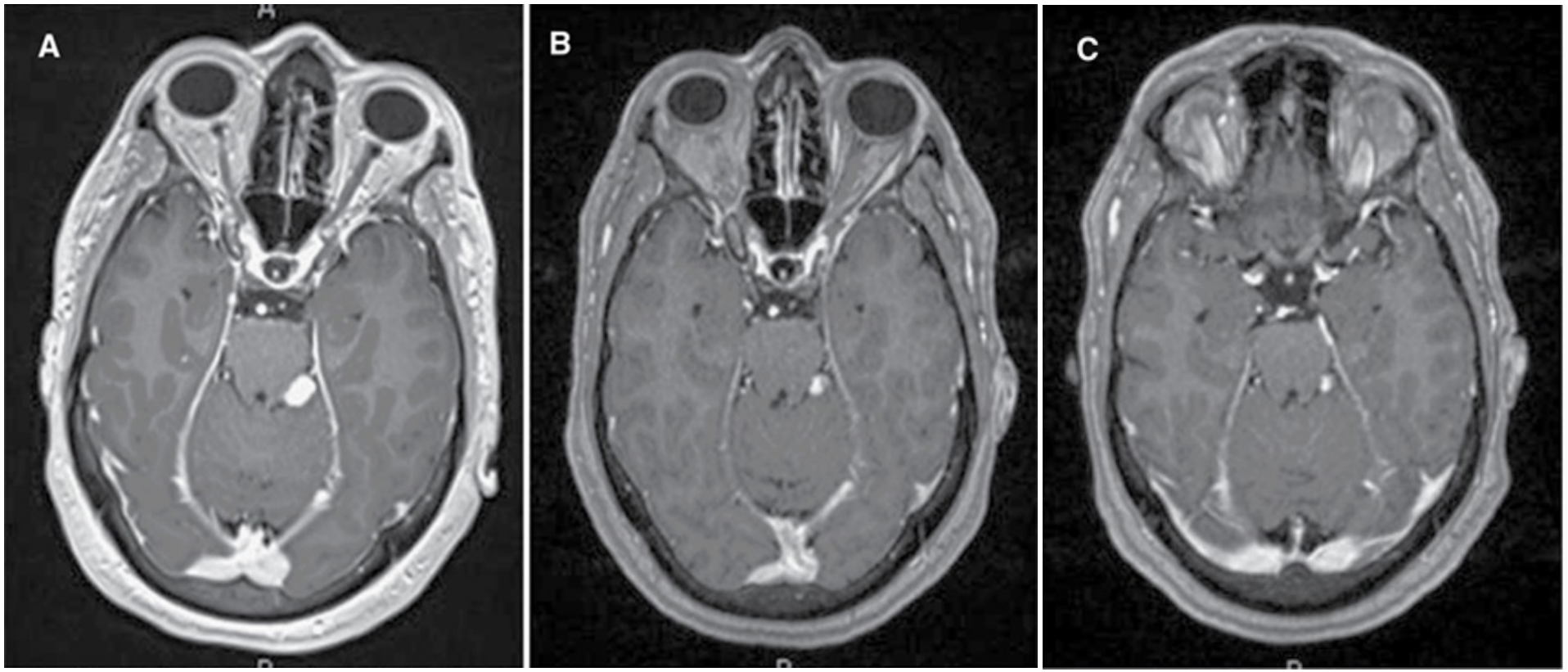
HEMANGIOBLASTOMA

Belzutifan (MK6482)

- HIF2α inhibitor
- 120mg daily
- **Non-randomized phase 2** (n=61)
- SEs: anemia, SOB, DOE
- ORR (RECIST): **30-44%** (6% CR)
- Time to response: 3.2 mo
- Duration of response: ???
- Optimal dosing schedule: ???
- Optimal patient selection: ???

Jonasch, et al. NEJM. 2021;385(22):2036-2046
Srinivasan, et al. ESMO. 9/2022

BELZUTIFAN RESPONSE IN CNS HEMANGIOBLASTOMA



Zhang, et al. Neuro Oncol. 2023;25(5):827-838

CONCLUSIONS

- Targeted therapies *lack* benefit in vast majority of brain tumor patients
- Targeted therapies *can* demonstrate benefit in appropriately selected patient populations
- Necessity of extensive molecular testing as SOC
- Anticipate further successes in near-medium term

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ACKNOWLEDMENTS

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  - Matthew Tate
  - Adam Sonabend
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  - Atique Ahmed
  - Irena Balyasnikova
  - Catalina Lee Chang
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  - Tarita Thomas
  - Sean Sachdev
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  - Eric Nesbit
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  - Jared Ahrensen
  - Rudolph Castellini
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