Contemporary Pharmacotherapy Management of High-grade Gliomas

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December 1, 2022

Rosetta Stone

	Shorthand
α-thalassemia mental retardation syndrome X-linked	ATRX
lomustine	CCNU
copy number alteration	CNA
central nervous system	CNS
glioblastoma	GBM
isocitrate dehydrogenase	IDH
Karnofsky performance scale	KPS
O^6-methylguanine DNA methyltransferase	MGMT
Response Assessment in Neuro-Oncology	RANO
telomerase reverse transcriptase	TERT
temozolomide	TMZ
World Health Organization	WHO

Objectives

1. Understand the role of molecular markers in the diagnosis and management of high-grade gliomas

2. Develop a treatment/monitoring plan based on the assessment of patient information, available evidence, and current guidelines for the management of primary gliomas

3. Discuss future direction for precision oncology and immunotherapy approaches in the treatment of high-grade gliomas

Incidence, Survival, and Mortality

Malignant CNS tumors account for ~1% of all invasive cancer cases in the United States

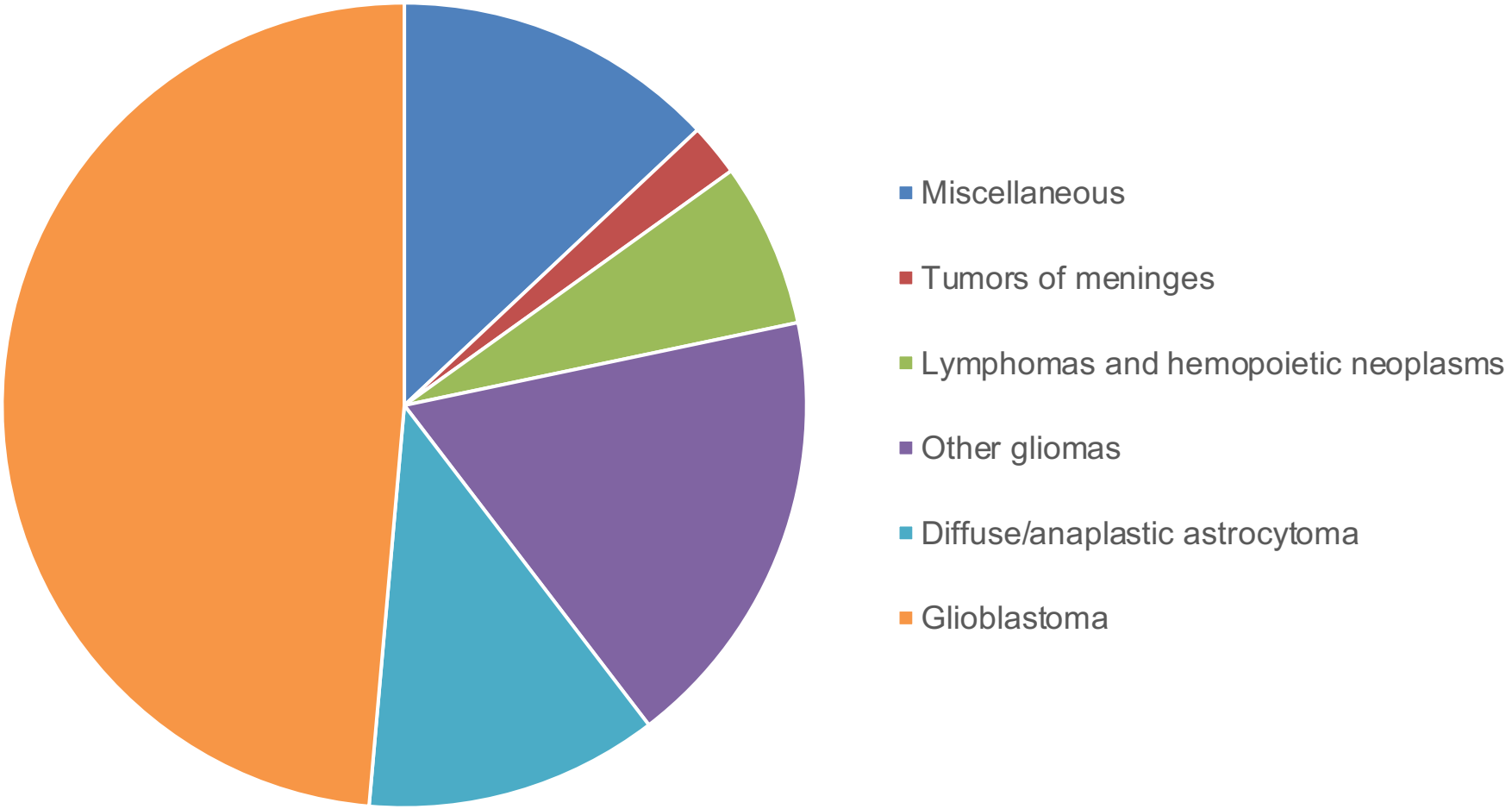
- Most commonly diagnosed solid tumor in children/adolescents
- Leading cause of cancer death
  - Males <40 years
  - Females <20 years

Less than one-third of all CNS tumors are malignant

- Majority of deaths from disease

Siegel RL. CA Cancer J Clin. 2021;71:7-33

Incidence, Survival, and Mortality



Siegel RL. CA Cancer J Clin. 2021;71:7-33

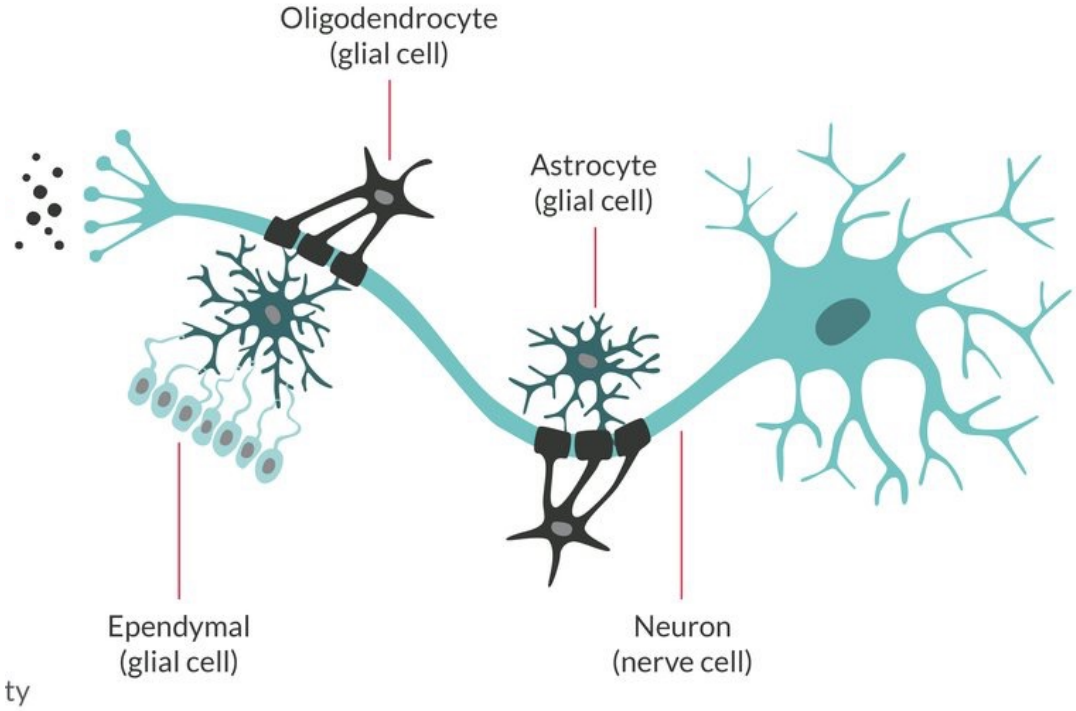
What's In a Name?

Over 120 subtypes of CNS tumors in existence

- Cell type, histology, molecular characterization

Nervous tissue cell types

- **Messaging**
  - Neurons
- **Structural/glial cells**
  - Ependymal
  - Oligodendrocyte
  - Astrocyte
  - Microglia



Morest DK. Glia. 2003;43(1):6-18

Brain Tumor Pathology

Tumor classification using histopathology and molecular data

- Methods: IHC, sequencing (CNA-seq, pyro-seq, etc.)
- Performed at time of initial resection/biopsy

Molecular characterization to discern histologically similar neoplasms for prognosis and potential response to therapies

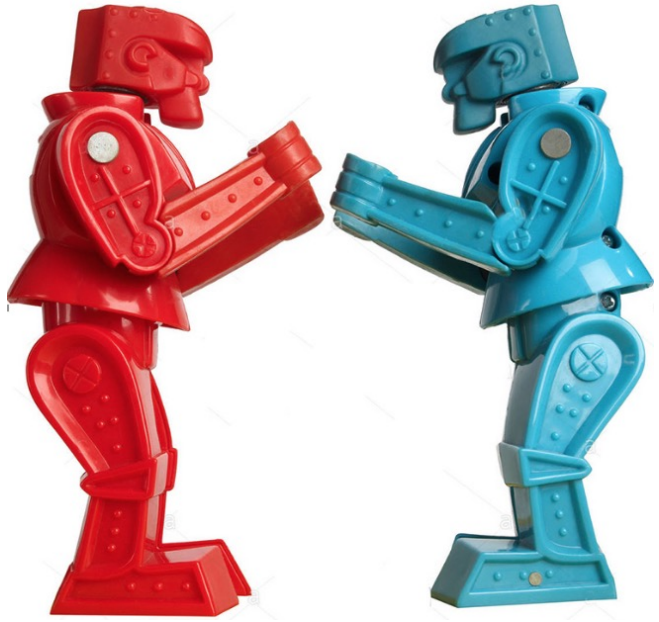
- MGMT promoter methylation
- IDH mutation
- ATRX mutation
- TERT mutation
- Co-deletion of 1p and 19q

NCCN: CNS Malignancies. Version1.2019. | Louis DN. Acta Neuropath. 2016;131:803-20

MGMT? IDK

Temozolomide

Alkylates DNA at the O^6 and N^7 positions of guanine



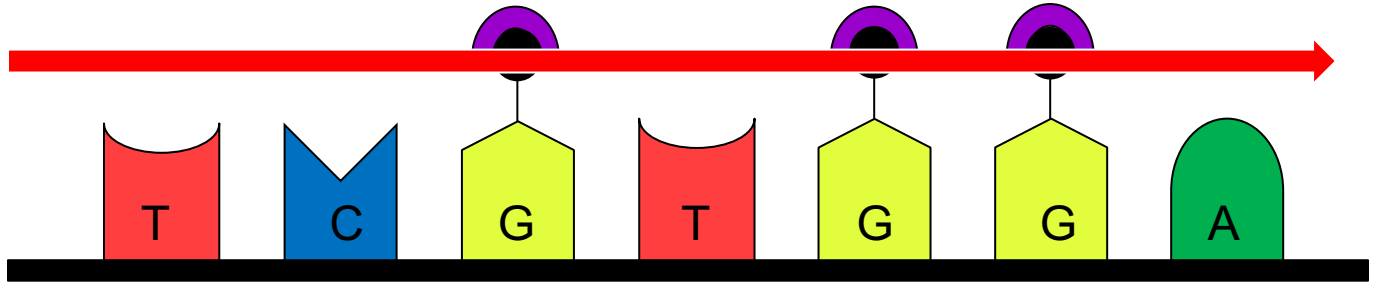
MGMT

Removes alkyl groups from the O^6 position of guanine

Methylation silences gene expression

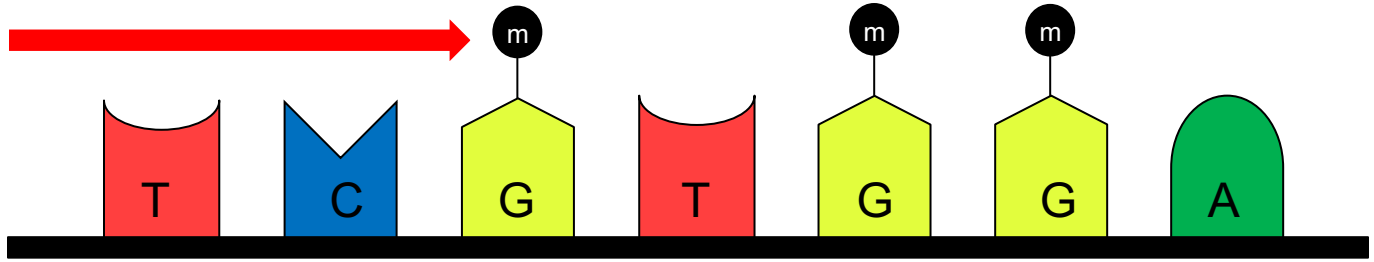
MGMT MECHANISM

Undesired effect: Accurate replication of malignant DNA



MGMT METHYLATION

Desired effect: Halt of malignant DNA replication



Molecular Characterization

MGMT promoter methylation

- Recommendation: *essential* for all high-grade gliomas (Grade 3 and 4)
- Prognostic value:
  - Confers survival advantage in GBM
  - Less benefit from TMZ if not MGMT promoter methylated

IDH1 and *IDH2* mutation

- Recommendation: testing *required* for the workup of all gliomas
- Diagnostic value: distinguishes lower-grade gliomas from GBM (WT)
- Prognostic value: associated with relatively favorable prognosis
  - Survival benefit for patients treated with radiation or alkylating systemic therapy

NCCN: CNS Malignancies. Version2.2022. | Louis DN. Acta Neuropath. 2016;131:803-20

Molecular Characterization Continued

ATRX mutation

- Recommendation: testing *required* for the workup of glioma
- Diagnostic value:
  - Strongly associated with *IDH* mutations, nearly always mutually exclusive with 1p/19q co-deletion

TERT (promoter mutation)

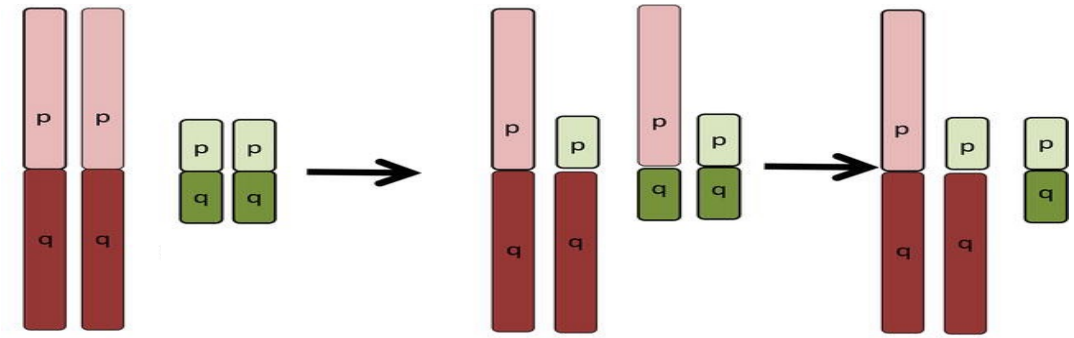
- Recommendation: testing *required* for the workup of glioma
- Diagnostic value: found in most GBM
  - *TERT* absence in the presence of mutant *IDH* designates astrocytoma
- Prognostic value:
  - *TERT* presence in absence of *IDH* mutation in diffusely infiltrative gliomas associated with reduced overall survival

NCCN: CNS Malignancies. Version2.2022. | Louis DN. Acta Neuropath. 2016;131:803-20

Molecular Characterization Continued

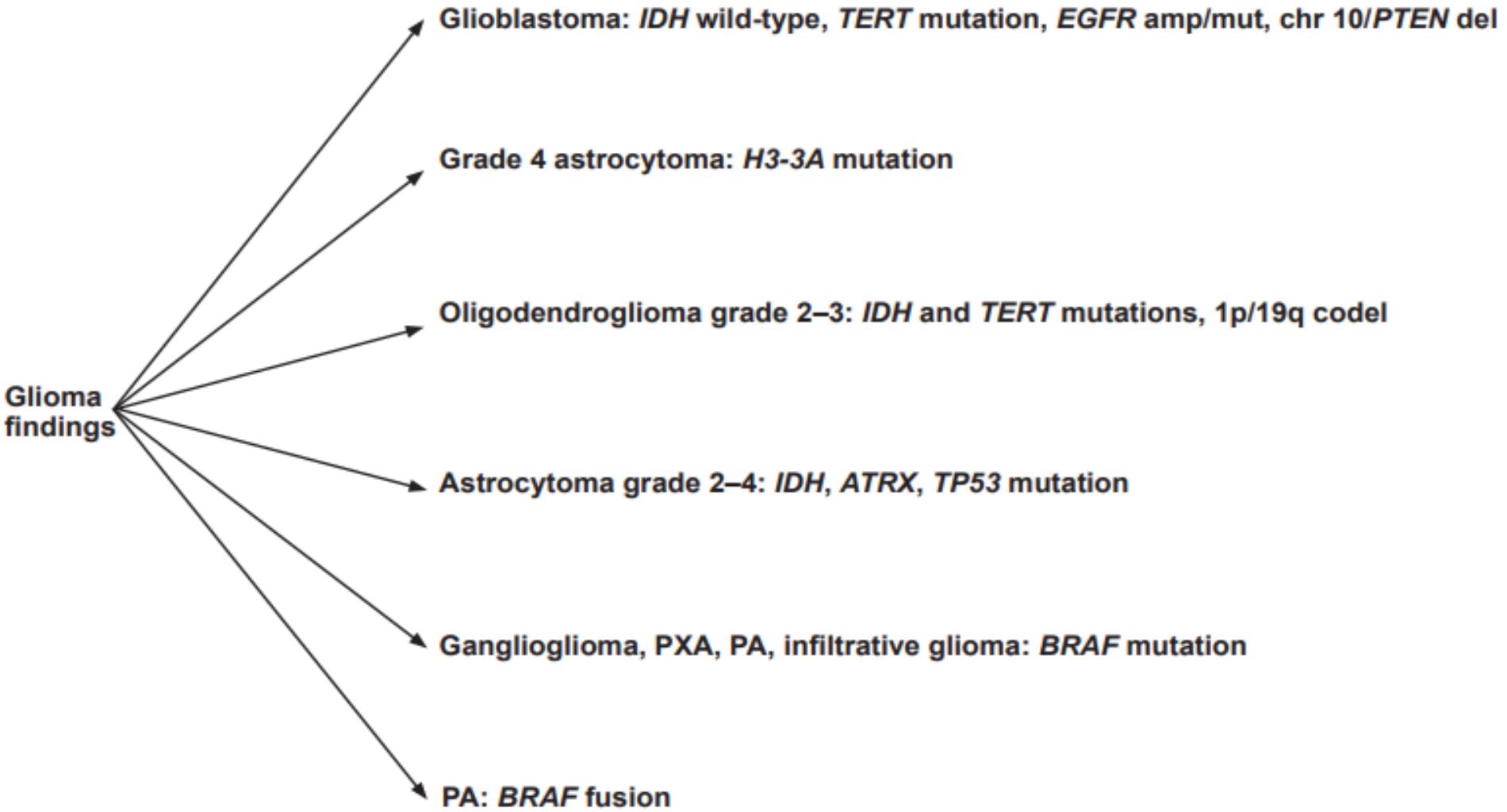
Co-deletion of 1p and 19q

- Recommendation: testing *essential* part of diagnostics for oligodendroglioma
- Diagnostic value:
  - must contain both *IDH* mutation and 1p/19q co-deletion for diagnosis of oligodendroglioma
- Prognostic value: confers favorable prognosis
  - Predictive of response to alkylating systemic therapy +/- radiation



NCCN: CNS Malignancies. Version2.2022. | Louis DN. Acta Neuropath. 2016;131:803-20

WHO CNS5 Classification (2021)



NCCN: CNS Malignancies. Version2.2022

Treatment Strategies

Pharmacologic Challenges

Blood brain barrier (BBB)

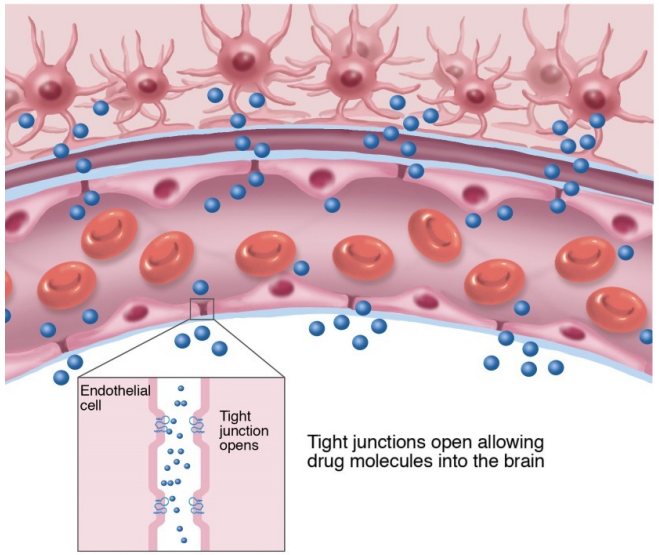
- Selectively restricts blood to brain paracellular diffusion

Favorable characteristics for BBB penetrance

- Molecular weight <500 daltons
- Lipophilic: high Log P values

Dose modification

- Ex: methotrexate
  - Non-Hodgkin lymphoma: 1,000 mg/m^2
  - CNS lymphoma: 8,000 mg/m^2



Luissint AC. Flu Barriers CNS. 2012; doi: 10.1186/2045-8118-9-23

General Treatment Approach

Surgery

* *Overall survival benefit*

- Stereotactic biopsy or open biopsy
- Gross total resection*
- Subtotal resection

Radiation therapy (RT)

- Standard: 60 Gy/30 fx, *6 week duration*
- Hypofractionated: 34 Gy/10 fx or 40.05 Gy/15 fx, *2-3 week duration*

Systemic treatment

- Age, performance status, MGMT methylation

NCCN: CNS Malignancies. Version2.2022

High-grade Glioma: Initial Treatment

Age >70 years

** Category 1 Recommendation*

- KPS ≥60
  - MGMT Methylated
    - Clinical trial
    - Hypofractionated RT ± concurrent/adjuvant temozolomide*
    - RT + concurrent/adjuvant temozolomide ± alternating electric field therapy*
    - Temozolomide
  - MGMT Unmethylated/Indeterminate
    - Clinical trial
    - Hypofractionated RT ± concurrent/adjuvant temozolomide
    - RT + concurrent/adjuvant temozolomide ± alternating electric field therapy*
    - Hypofractionated RT
- KPS <60
    - Hypofractionated RT
    - Temozolomide
    - Palliative/best supportive care

NCCN: CNS Malignancies. Version2.2022

High-grade Glioma: Initial Treatment

Age ≤70 years

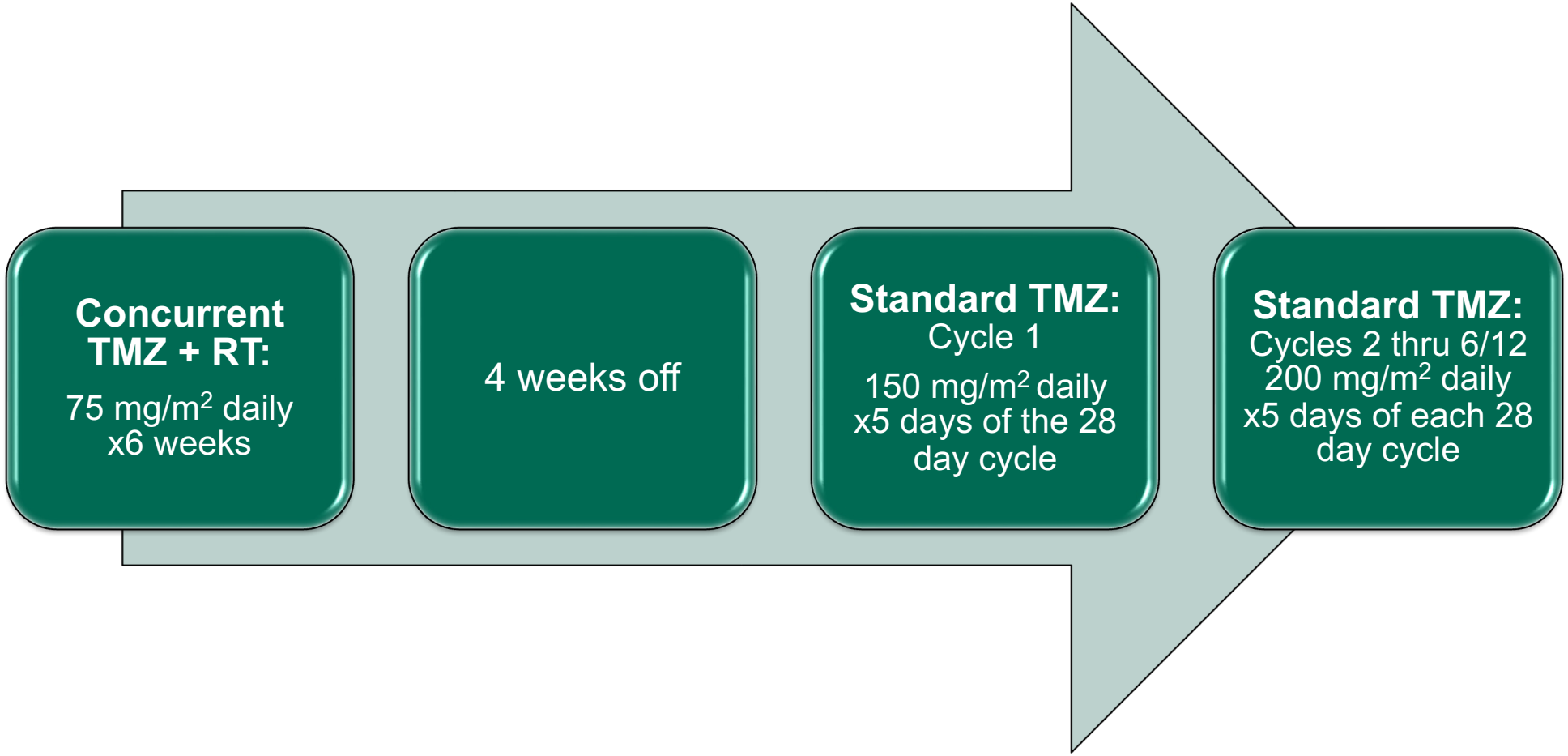
** Category 1 Recommendation*

- KPS ≥60
  - MGMT Methylated
    - Clinical trial
    - RT + concurrent/adjuvant temozolomide ± alternating electric field therapy*
    - RT + concurrent/adjuvant temozolomide + CCNU
  - MGMT Unmethylated/Indeterminate
    - Clinical trial
    - RT + concurrent/adjuvant temozolomide + alternating electric field therapy*
    - RT ± concurrent/adjuvant temozolomide
- KPS <60
    - Hypofractionated RT ± concurrent or adjuvant temozolomide
    - Temozolomide
    - Palliative/best supportive care

"You can't really know where you are going until you know where you've been."

-Maya Angelou

Standard of Care Timeline



Stupp R. NEJM. 2005;352(10):987-96

Stupp, et al. NEJM 2005

Compared the efficacy and safety of RT alone with RT + TMZ given concurrently and after RT in high-grade glioma patients

– Randomized, multicenter, phase 3 trial

	RT (n=286)	**RT + TMZ** (n=287)
Age – no. (%)		
<50 years	81 (28)	90 (31)
≥50 years	205 (72)	197 (69)
Findings on pathological review – no. (%)		
Glioblastoma	229 (93)	221 (92)
Anaplastic astrocytoma	9 (4)	7 (3)
Inconclusive material/other	8 (3)	11 (5)

Stupp R. NEJM. 2005;352(10):987-96

Stupp, et al. NEJM 2005: Outcomes

Median survival 14.6 months vs 12.1 months

- Overall survival benefit of 2.5 months with RT + TMZ

Hazard ratio for death in RT + TMZ group

- 0.63 (95% CI, 0.52 to 0.75; P<0.001)

Median PFS: 6.9 (5.8-8.2) vs 5.0 (4.2-5.5) in favor of RT + TMZ

Grade 3/4 hematologic toxicity

- Concurrent RT + TMZ: 19/284 (7%) / Adjuvant TMZ: 32/223 (14%)
- Study duration: 46/284 (16%)

Stupp R. NEJM. 2005;352(10):987-96

Stupp, et al. Lancet 2009

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Median Overall Survival	RT	RT + TMZ
2 Years	10.9%	27.2%
3 Years	4.4 %	16.0%
4 Years	3.0%	12.1%
5 Years	1.9%	9.8%

Stupp R. NEJM. 2009;10:459-66

Alternating Electric Field Therapy

Portable medical device that generates low-intensity alternating electric fields to stop mitosis/cell division

- FDA approved in 2015 for newly diagnosed glioblastoma

Open-label, Phase 3 EF-14 Trial (N=695)

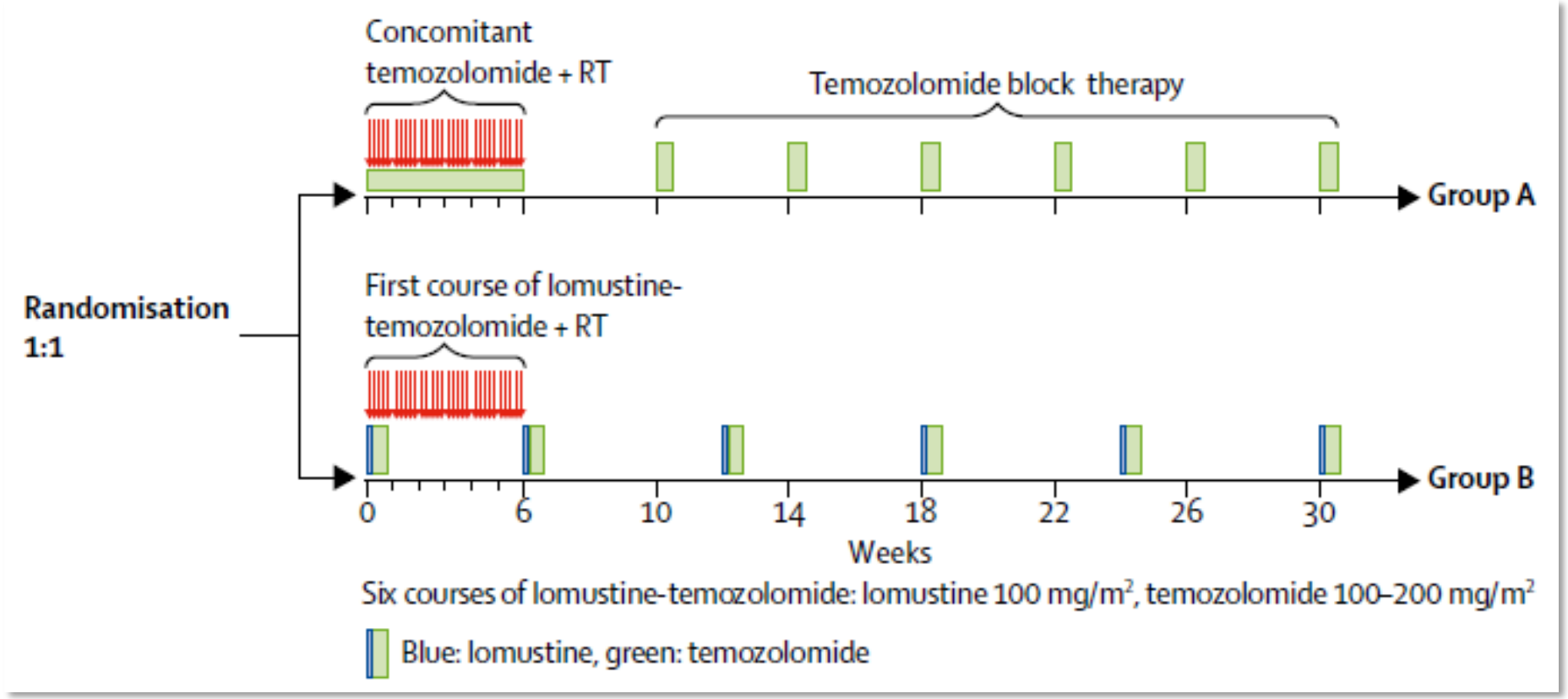
- Treatment Arms
  - Adjuvant temozolomide + alternating electric field therapy
  - Adjuvant temozolomide
- mPFS: (6.7 vs. 4.0 months; HR, 0.63; 95% CI, 0.52–0.76; $P < .001$)
- OS (20.9 vs. 16.0 months; HR, 0.63; 95% CI, 0.53–0.76; $P < .001$)

Stupp R. JAMA. 2015;314:2535-2543. | Stupp R. JAMA. 2017;318:2306-2316.

Herrlinger et al. Lancet 2019

Randomized, multicenter, open-label, phase 3 trial

- Combination CCNU + TMZ vs standard of care in nGBM

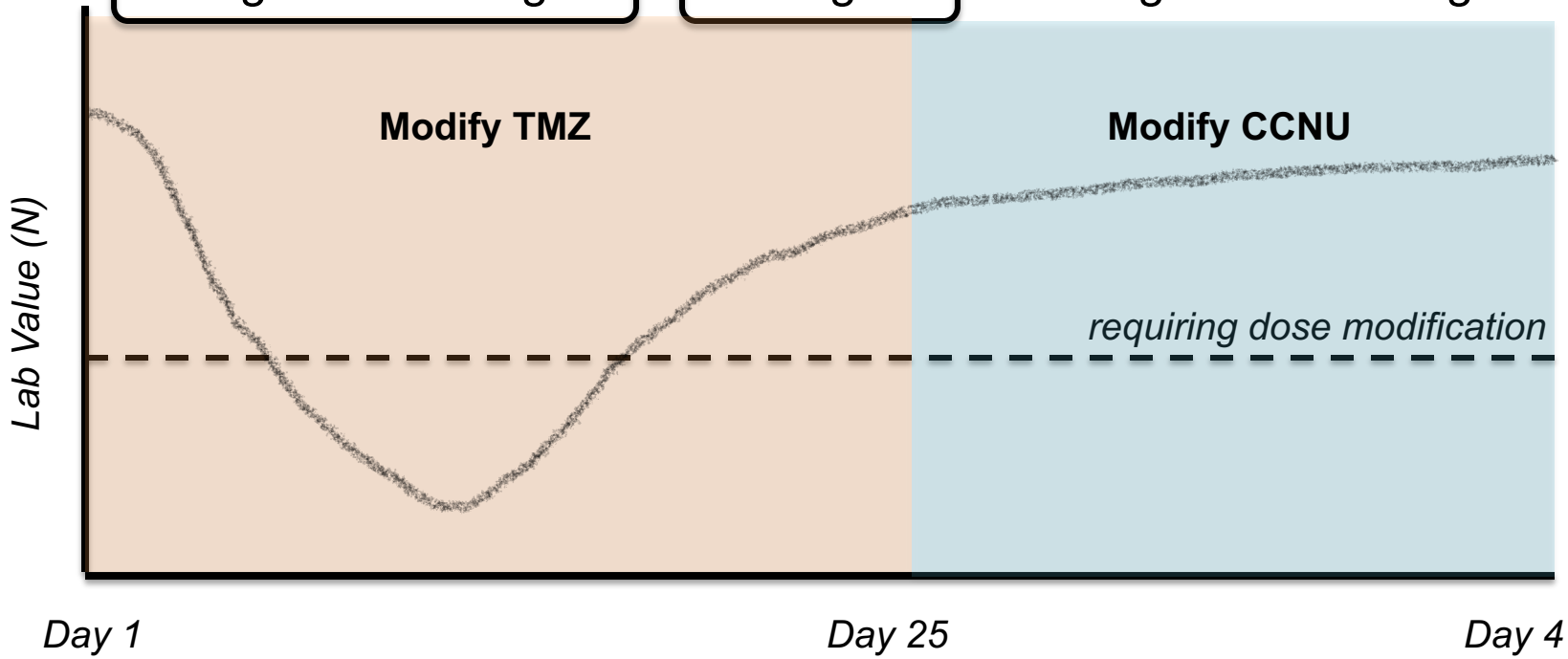


Herrlinger U. Lancet 2019;393:678-88

Herrlinger Protocol Dosing/Modifications

Treatment Regimen

- **Lomustine 100 mg/m^2, Day 1 of 42 each 42 day cycle**
  - 25% reduction → 50% reduction
- **Temozolomide 100-200 mg/m^2, Days 2 thru 6 of each 42 day cycle**
  - 50 mg/m^2 ← 75 mg/m^2 ← 100 mg/m^2 → 120 mg/m^2 → 150 mg/m^2 → 200 mg/m^2



Herrlinger U. Lancet 2019;393:678-88

Herrlinger et al. Lancet 2019: Outcomes

Efficacy Outcomes

- Median OS
  - 48.1 months (32.6 – not assessable) vs 31.4 months (95% CI, 27.7-47.1)
  - p=0.0492
- Median PFS
  - 16.7 months (95% CI, 12.0-32.0) vs 16.7 months (95% CI, 11.4-24.2)
  - p=0.4735

Safety Outcomes

- Grade 3/4 adverse effects: 59% vs 51%
- High grade hematologic events: 36% vs 29%
- Percent of patients with cycle delays >2 weeks: 40% vs 17%

Herrlinger U. Lancet 2019;393:678-88

Recurrence Treatment Options

Preferred Regimens	Dosing Schedule*
Bevacizumab	10 mg/kg q14d OR 15 mg/kg q21d
Temozolomide	150-200 mg/m^2, daily, days 1-5 of each 28 day cycle
Lomustine	80-110 mg/m^2, oral, day 1 of each 42 day cycle
Carmustine	200 mg/m^2, IV, day 1 of each 42 day cycle
Procarbazine/Lomustine/ Vincristine (PCV)	Procarbazine: 60 mg/m^2, oral, days 8-21 Lomustine: 110 mg/m^2, oral, day 1 Vincristine: 1.4 mg/m^2 [max 4 mg], IV, day 8 & 29 of each 42 day cycle
Regorafenib	160 mg, oral, days 1-21 of each 28 day cycle

**multiple dosing schemes exist*

NCCN: CNS Malignancies. Version2.2022

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**multiple dosing schemes exist*

NCCN: CNS Malignancies. Version2.2022

Lombardi, et al. Lancet 2018 (REGOMA)

Randomized, multicenter, open-label, phase 2 trial

- Regorafenib vs lomustine in treatment of recurrent glioblastoma

Inclusion criteria

- Patients with first progression following surgery and chemoradiation
- Age ≥18 years, KPS ≥70, known MGMT status

Exclusion criteria

- Previous treatment with VEGF targeting kinase inhibitor
- Uncontrolled hypertension, use of strong CYP3A4 inhibitors/inducers

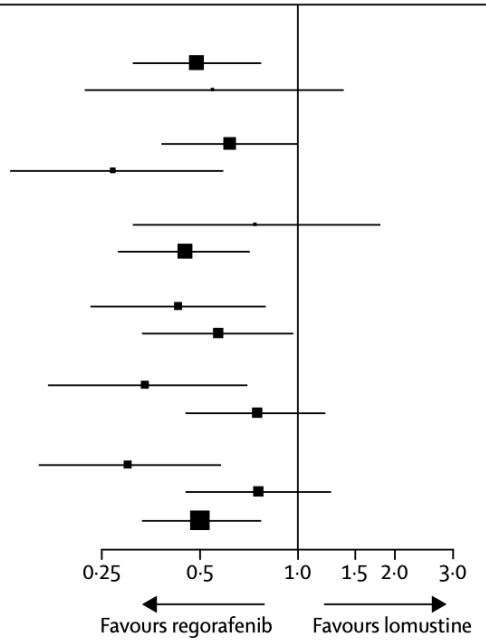
Lombardi G. Lancet 2018;18(1):30675-82

Lombardi, et al. Lancet 2018: Outcomes

Median overall survival

- 7.4 months (95% CI, 5.8-12.0) vs 5.6 months (95% CI, 4.7-7.3)
- HR 0.50 (95% CI, 0.33-0.75; log rank p=0.0009)

	Regorafenib Events/N (%)	Lomustine Events/N (%)	HR (95% CI)	p value for interaction*
Age (years)				
<65	35/50 (70%)	43/45 (96%)	0·49 (0·31–0·77)	0·81
≥65	7/9 (78%)	14/15 (93%)	0·55 (0·22–1·39)	
Sex				
Male	30/41 (73%)	40/43 (93%)	0·62 (0·38–1·00)	0·07
Female	12/18 (67%)	17/17 (100%)	0·27 (0·13–0·59)	
Surgery at relapse				
Yes	9/13 (69%)	11/14 (79%)	0·74 (0·31–1·79)	0·32
No	33/46 (72%)	46/46 (100%)	0·45 (0·28–0·71)	
MGMT				
Methylated	17/29 (59%)	25/27 (93%)	0·43 (0·23–0·80)	0·50
Unmethylated	25/30 (83%)	31/32 (97%)	0·57 (0·33–0·97)	
Dexamethasone use				
No	14/27 (52%)	19/21 (90%)	0·34 (0·17–0·70)	0·08
Yes	28/32 (88%)	38/39 (97%)	0·75 (0·45–1·22)	
ECOG PS				
0	14/27 (52%)	27/28 (96%)	0·30 (0·16–0·58)	0·03
1	28/32 (88%)	30/32 (94%)	0·76 (0·45–1·27)	
Overall	**42/59 (71%)**	**57/60 (95%)**	**0·50 (0·33–0·77)**	**0·0009**



Lombardi G. Lancet 2018;18(1):30675-82 | Bekaii-Saab TS. Lancet Oncol. 2019;20(8):1070-1082

Old Drugs, New Tricks?

Biomarkers

Final Report

Biomarker
IDH1
IDH2
MSI
NTRK1/2/3
Tumor Mutational Burden
ATRX
BRAF
CDKN2A

Biomarker
CDKN2B
CIC
EGFR
EGFRvIII
FGFR1
FGFR2
FGFR3

Biomarker
FUBP1
H3F3A
HIST1H3B
NF1
NOTCH1
PDGFRA
PIK3CA
POT1

Biomarker
PTEN
TERT promoter
TP53
TSC1
TSC2

NTRK 1/2/3 Inhibitors

0.56-1.69% adult GBM patients

Larotrectinib 100 mg oral BID

Entrectinib 600 mg oral once daily

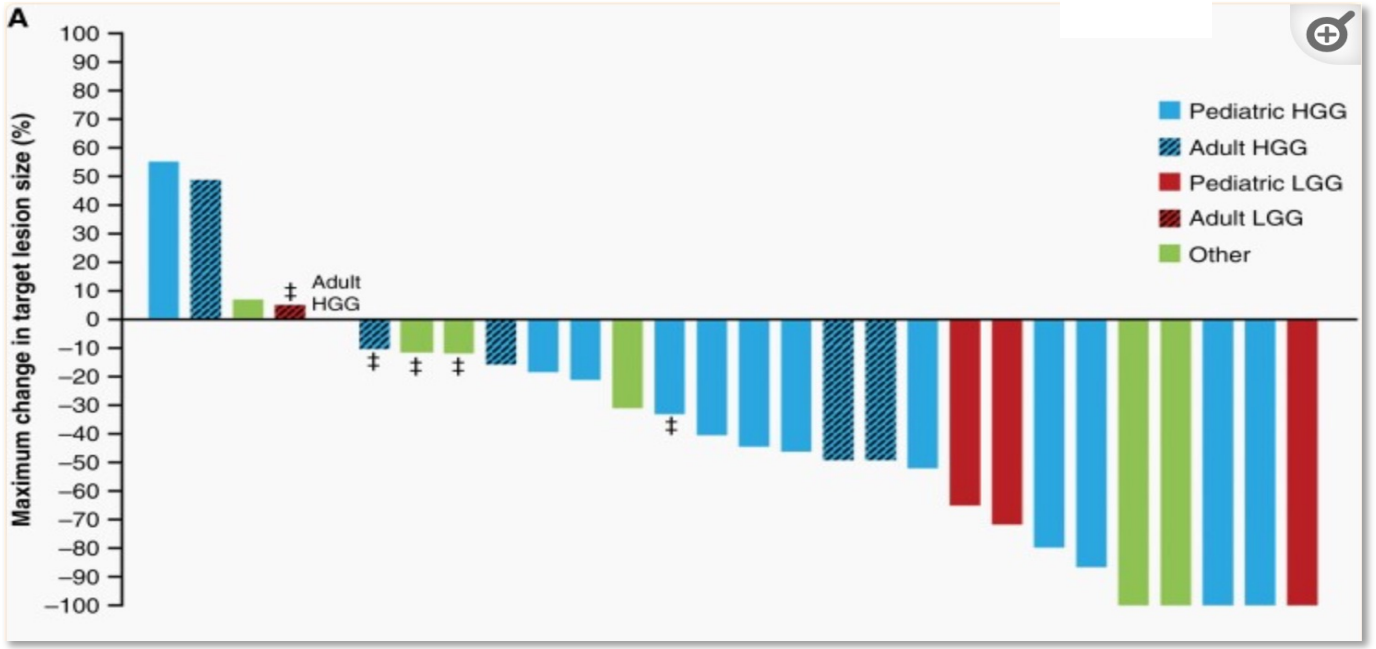
Relative Adverse Event Profiles	
Larotrectinib	**Entrectinib**
Anemia 42% (grade 3/4: 10%)	Anemia 67% (grade 3/4: 9%)
Neutropenia 36% (grade 3/4: 14%)	Neutropenia 28% (grade 3/4: 7%)
Nausea/vomiting 25%	Nausea/vomiting 34%
Increased ALT 45% / AST 52%	Increased ALT 38% / AST 44%
Cognitive dysfunction 11%	Cognitive dysfunction 27%
Fever 24%	Fever 21%
MISC: musculoskeletal pain 42%, rash 19%, cough 32%, edema 19%	MISC: visual disturbances 21%, ↑ SCr 73%, edema 40%, peripheral neuropathy 18%

Entrectinib. South San Francisco, CA: Genentech Inc; July 2022 | Larotrectinib. Whippany, NJ: Bayer Inc; March 2021

Doz et al. Neuro-Oncology 2022

Efficacy Outcomes

- ORR: 30% (95% CI, 16-49) for all patients
- PFS & OS: 56% (95% CI, 38-74) 85% (95% CI, 71-99) respectively
- Twenty-three of 28 patients (82%) experienced tumor shrinkage



Doz F. Neuro-Onc 2022. 24(6):997-1007

BRAF/MEK Inhibitors

Medication	Number of Tablets	Frequency	Total Pill Burden
Dabrafenib	2 caps	BID	5
Trametinib	1 tab	Daily	
Encorafenib	4 caps	Daily	10
Binimetinib	3 tabs	BID	
Vemurafenib	4 tabs	BID	11
Cobimetinib	3 tabs	Daily	

Hudson (OH):Lexicomp Inc.: Accessed November 1, 2022

Wen et al. Lancet 2022

Dabrafenib plus trametinib in patients with recurrent/refractory *BRAF*^{V600E} mutant low-grade and high-grade glioma

- Multicenter, open-label, single arm, phase 2, basket trial

High-grade cohort inclusion criteria

- ECOG ≤2, measure baseline disease, previously treated with SOC

Outcomes

- Objective response rate 33% (95% CI, 20-49)
  - 3 complete responses, 12 partial responses
- Grade 3 or worse adverse events reported in 53% patients
  - Fatigue (9%), decreased neutrophil count (9%), headache (5%), neutropenia (5%)

Wen PY. Lancet 2022;23(1)53-64

BRAF/MEK Inhibitors

Dabrafenib 150 mg oral BID

- Dosage form: capsules

Administration:

- At least 1 hour before or 2 hours after meal

Adverse Effects:

- Hand/foot syndrome, hyponatremia, arthralgias, constipation, cough, VTE

Warnings/Precautions:

- Cardiomyopathy, febrile reactions, hyperglycemia, ocular toxicity

Monitoring:

- Confirm BRAF V600 mutation status, CBC w/ diff, CMP, ECHO, derm evaluation

Trametinib 2 mg oral daily

- Dosage form: tablets

Administration:

- At least 1 hour before or 2 hours after meal

Adverse Effects:

- Edema, hypertension, hypoalbuminemia, diarrhea, increased AST/ALT, anemia

Warnings/Precautions:

- Cardiomyopathy, hemorrhage, hypertension, pulmonary toxicity

Monitoring:

- CBC w/ diff, CMP, ECHO, BP

Hudson (OH):Lexicomp Inc.: Accessed November 1, 2022

Biomarkers

Final Report

Biomarker
IDH1
IDH2
MSI
NTRK1/2/3
Tumor Mutational Burden
ATRX
BRAF
CDKN2A

Biomarker
CDKN2B
CIC
EGFR
EGFRvIII
FGFR1
FGFR2
FGFR3

Biomarker
FUBP1
H3F3A
HIST1H3B
NF1
NOTCH1
PDGFRA
PIK3CA
POT1

Biomarker
PTEN
TERT promoter
TP53
TSC1
TSC2

** Many multi-targeted TKIs*

Drug-Target Pairs

IDH 1
ivosidenib

IDH 2
enasidenib

NTRK 1/2/3
larotrectinib
entrectenib

PIK3CA
alpelisib

PDGFR*
avapritinib

BRAF
dabrafenib/trametinib
encorafenib/binimetinib
vemurafenib/cobimetinib

CDKN 2A/B
abemaciclib
palbociclib
ribociclib

FGFR 1/2/3
erdaftinib
pemigatinib
futibatinib

EGFR
osimertinib
afatinib
erlotinib
getitinib
lapatinib
vandetanib

PIK3CA
alpelisib
duvelisib
umbralisib
idelalisib
copanlisib

IDH1 Inhibitor

NCT02073994

Ivosidenib 500 mg oral daily

- Do not administer with high fat meal
- Dosage forms: tablets

Adverse effects

- Endocrine/metabolic disturbances, stomatitis, arthralgia, dyspnea, edema

Monitoring

- *IDH1* mutation status, CBC w/ diff, CMP, CPK, EKG

Warnings/Precautions

- QT prolongation (patients with baseline QTc $\geq$ 450 or $\geq$ 470 msec excluded)
- ~~Differentiation syndrome~~

Ivosidenib. Boston, MA:Servier Pharmaceuticals;May 2022

IDH2 Inhibitor

~~***NCT02273739***~~

Enasidenib 100 mg oral daily

- Dose adjustments: moderate hepatic impairment (-50%), if severe do not use
- Dosage forms: tablets

Adverse effects

- Endocrine/metabolic disturbances, diarrhea, increased serum bilirubin
- Emetic potential: moderate/high

Monitoring

- *IDH2* mutation status, CBC w/ diff, CMP

Warnings/Precautions

- Electrolyte imbalances, hepatotoxicity
- ~~Differentiation syndrome~~

Enasidenib. Summit, NJ: Celgene Corporation; November 2020

CDK4/6 Inhibitor

BEST CNS PENETRANCE IN CLASS
LEAST MYELOSUPPRESION

Abemaciclib 150 mg oral BID

- Dose adjustments: Child-Pugh C reduce frequency to once daily
- Dosage form: tablets

Adverse Effects

- Hepatotoxicity, diarrhea, VTE, bone marrow suppression, pulmonary toxicity, nausea/vomiting (mod/high), increased SCr, increased AST/ALT

Supportive Care

- Scheduled anti-emetic, loperamide

~~NCT02977780~~
NCT02981940

Monitoring

- CBC w/ diff, CMP, s/sx of pneumonitis and PE/DVT

Abemaciclib. Indianapolis, IN: Lilly USA; October 2021

EGFR Inhibitor

SIGNIFICANT BLOOD BRAIN BARRIER PENETRATION

Osimertinib 160 mg oral daily

- Dose adjustments: Child-Pugh B/C reduce initial dose 50%
- Dosage form: tablets

Administration: can be dispersed in 60 mL water for oral administration, 15 mL water for nasogastric

Adverse Effects

- Nail disease, stomatitis, myelosuppression, increased AST/ALT, hypermagnesemia, constipation/diarrhea

Warnings/Precautions

- QTc prolongation (withhold until <481 msec), interstitial lung disease, bone marrow suppression

Monitoring

- CBC w/ diff, CMP, EKG, ECHO

Osimertinib. Wilmington, DE: AstraZeneca Pharmaceuticals; October 2022

New Drugs, New Tricks

Vorasidenib

Dual inhibitor of mutant *IDH1/2*

- Oral, daily until unacceptable toxicity or progression

Objective response rate per RANO criteria

- Non-enhancing glioma: 18% (1 partial, 3 minor responses)

Median PFS

- Non-enhancing glioma: 36.8 months (95% CI, 11.2-40.8)
- Enhancing glioma: 3.6 months (95% CI, 1.8-6.5)

Preliminary antitumor activity in patient with recurrent or progressive *IDH* mutated low-grade gliomas

Mellinghoff IK. Clin Cancer Res. 2021;27(16):4491-4499

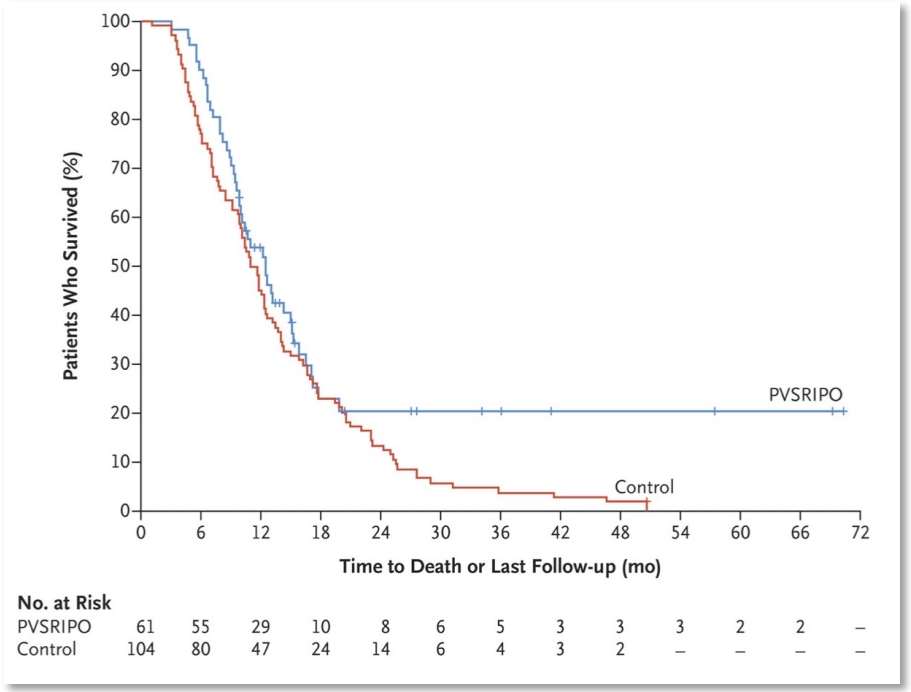
Recombinant Polio Virus

Polio-rhinovirus chimera (PVSRIPO)

- Targets poliovirus receptor CD155 expressed on neoplastic cells
- PVSRIPO $5.0*10^7$ $TCID_{50}$ administered over 6.5 hours

Adult patients with supratentorial recurrent WHO Grade 4 gliomas

- OS reached plateau of 21% (95% CI, 11-33) at 24 months
- 19% of patients experienced a Grade 3 or higher adverse event



Desjardina A N Engl J Med 2018; 379:150-161

Autologous Tumor Lysate-Loaded Dendritic Cell Vaccination (DCVax-L)

Phase 3, prospective, externally controlled, nonrandomized trial

Compared OS in newly diagnosed and recurrent GBM

- Standard of care adjuvant TMZ + placebo
- Standard of care adjuvant TMZ + DCVax-L

Inclusion criteria

- Age 18-70 years, KPS ≥70, life expectancy of ≥8 weeks

Excluded if radiographic evidence of progression following chemoradiation

Liau LM. JAMA Oncology. 2022; doi: 10.1001/jamaoncol.2022.5370

Autologous Tumor Lysate-Loaded Dendritic Cell Vaccination (DCVax-L)

Newly diagnosed GBM (nGBM) results

- From randomization
  - Median OS: 19.3 (95% CI, 17.5-21.3) months vs 16.5 (95% CI, 16.0-17.5) months
  - HR=0.80; 98% CI, 0.00-0.94; *P* = .002

B Subgroup analyses

Table 2. Landmark Survival Rates in Patients With nGBM and rGBM

Time	Patients, %		Relative rate, DCVax-L vs ECP, %
	ECP	DCVax-L group	
nGBM			
No.	1366	232	NA
Landmark survival rate			
36 mo	15.5	20.2	130
48 mo	9.9	15.7	159
60 mo	5.7	13.0	228

0.4 1 2

Hazard ratio (95% CI)

Liau LM. JAMA Oncology. 2022; doi: 10.1001/jamaoncol.2022.5370

Autologous Tumor Lysate-Loaded Dendritic Cell Vaccination (DCVax-L)

Recurrent GBM results (rGBM)

- From relapse
  - Median OS: 13.2 (95% CI, 9.7-16.8) months vs 7.8 (95% CI, 7.2-8.2) months
  - HR=0.58; 98% CI, 0.00-0.76; *P* < .001

Table 2. Landmark Survival Rates in Patients With nGBM and rGBM

rGBM			
No.	640	64	
Landmark survival rate measured from date of progression			
6 mo	64.0	90.6	142
12 mo	30.8	54.1	175
18 mo	15.9	31.8	200
24 mo	9.6	20.7	215
30 mo	5.1	11.1	217

Liau LM. JAMA Oncology. 2022; doi: 10.1001/jamaoncol.2022.5370

The Takeaways

Multimodal approach remains essential for best patient outcomes

Advanced role of molecular diagnostics in tumor classification

Despite >400 clinical trials since 2005, minimal meaningful benefit in patient outcomes particularly overall survival

- Distinct pharmacologic challenges
- Substantial efforts in exploring precision medicine and immunotherapy

Contemporary Pharmacotherapy Management of High-grade Gliomas

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