

GLIOBLASTOMA MULTIFORME

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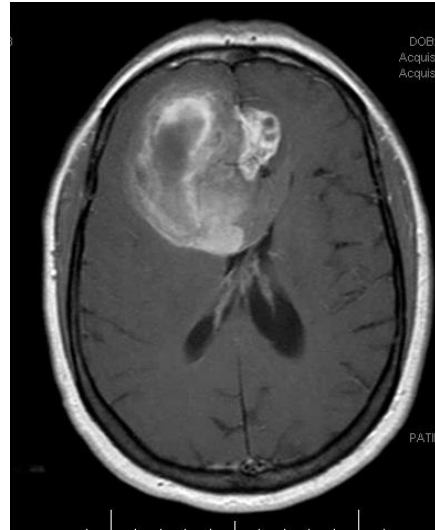
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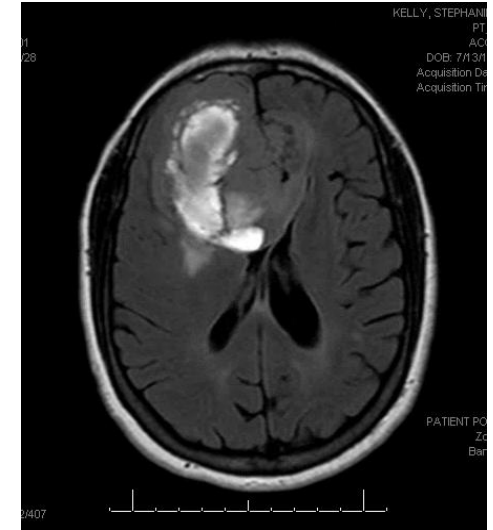
Rochester, NY

Case

- 68 year old woman presented with 2 weeks of headache (worse in the AM), vomiting, and then a fall with loss of consciousness
- MRI brain demonstrated:
7.5 x 5.7 x 5.7 cm heterogeneously enhancing hemorrhagic mass



T1+C



T2 FLAIR

What is your differential for this mass?

MAGLA

Metastasis

Anaplastic Astrocytoma

GBM

Lymphoma

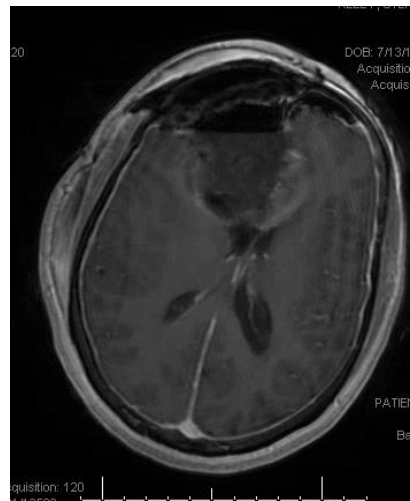
Abscess

Evaluation and Initial Management

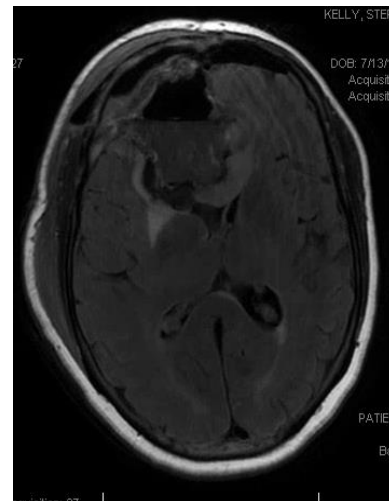
- History:
 - Symptoms and symptom duration
 - Past medical history
 - Are they immunocompromised?
 - History of seizure like events
- Physical:
 - Full neurologic exam
- Dexamethasone + GI prophylaxis
- Neurosurgery consult

Next steps

- Neurosurgery performs surgical resection
- How do you assess extent of resection?
 - Post-op MRI within 72 hours



T1 post contrast



T2 FLAIR

No residual
mass

Pathology

- Glioblastoma, WHO grade IV
 - IDH1 mutated
 - TP53 wild type
 - ATRX wild type
 - no EGFR gene amplification
 - MGMT methylated

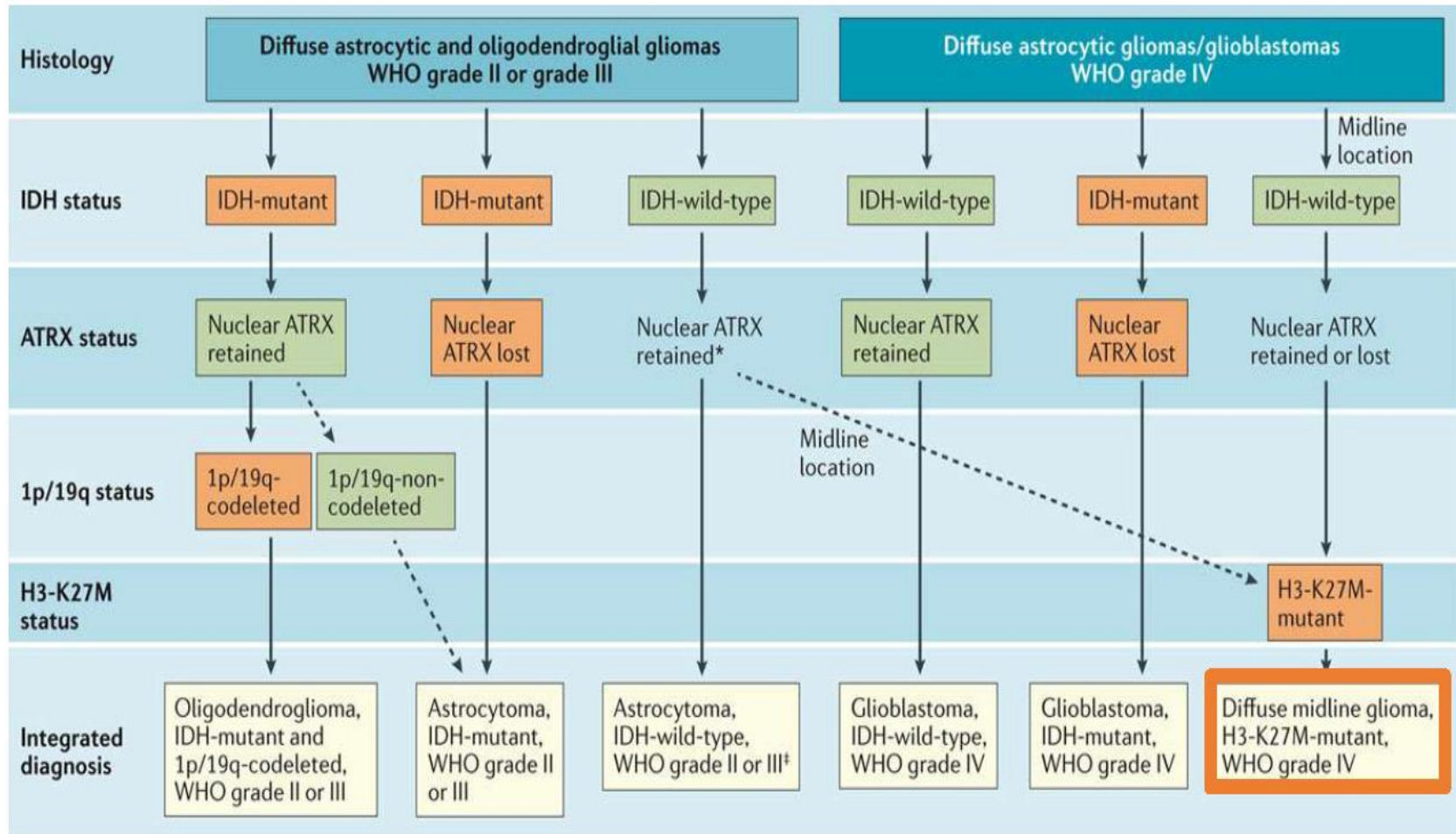
High Grade Glioma

- Most common primary malignant CNS tumor in adults
- Multicentric in <5% of cases
- Incidence increases with age and peaks at 45-55 years
- Most common presentation: headache (50%), seizure (20%)

Pathologic classification

- CNS tumor classification is based on the World Health Organization Classification of CNS tumors
 - First published in 1979, last revised in 2016
- 2016 version incorporated a combination of molecular and histologic parameters

WHO 2016 CNS Tumor Classification



Nature Reviews | Clinical Oncology

Glioma molecular factors

- Favorable prognostic factors:
 - IDH1/2 mutation
 - 1p/19q co-deletion
 - ATRX loss (ATRX and 1p19q are mutually exclusive)
 - TP53 WT
 - TERT promotor WT
 - MGMT methylation
- Primary GBM: IDH WT
- Secondary GBM: IDH mutant

Extent of resection

- 1993 meta-analysis of 3 RTOG trials, n=645, surgery + RT +/- chemo
 - Biopsy only (17%) vs partial resection (64%), total resection (19%)
- Median survival
 - Total resection 11.3 months
 - Partial resection 10.4 months
 - Biopsy 6.6 months
- No difference in survival for different tumor sizes

J.R Simpson et al. IJROBP, 1993

Early studies show that HGG post-op RT improved OS

- 1978 BTSG 69-01: 4 arms BCNU (carmustine) vs. WBRT (50-60 Gy) vs WBRT+BCNU vs. observation
 - Median OS: obs 3.2 m, BCNU 4.2m, RT 8.1m, RT+BCNU 8.0m
 - Established role of RT
- 1980 BTCG 72-01: 4 arms MeCCNU (semustine) vs. RT vs. BCNU+RT vs. MeCCNU+RT
 - RT alone comparable to RT+chemo but RT+chemo does give “long survivors”

WBRT to 60 Gy is not necessary

- BTCG 80-01
 - 571 patients with histologically confirmed supratentorial malignant glioma
 - **Randomized** to WBRT 60 Gy + chemotherapy vs WBRT 43 Gy + cone down boost (CDB) 17Gy + chemotherapy (chemotherapy = BCNU vs BCNU alternated with procarbazine for 8 wks vs BCNU + HU alternating with procarbazine + VM-26 (epipodophyllotoxin))
 - Results: MS from chemotherapy randomization ranged 11-14 months with OS at 18 months ranging from 29-37%.
 - Conclusions: **CDB + reduced-dose WBRT equivalent to higher-dose WBRT in survival benefit** and that single-agent chemotherapy equivalent to multi-agent regimen.
- Other centers (MDACC 1991, Jefferson 2007) have reported similar results for retrospective studies, including multi-focal disease.

Shapiro WR, *J Neurosurgery* 1989 Jul;71(1):1-9

Why not dose escalate?

- WBRT: BTSG 6901, 7201, 7501 median survival times
 - <45 Gy: 13 weeks
 - <50 Gy: 28 weeks
 - 55 Gy: 36 weeks
 - 60 Gy: 42 weeks
- MRB BR2, 1991: 45 Gy/20 vs. 60 Gy/30
 - Median OS: 9m vs. 12m (SS)
 - No additional acute toxicity
- Greater than 60 Gy?
 - 70 Gy: no. RTOG 7401 60 Gy WBRT + 10 Gy boost.
 - 90 Gy: no. Michigan 2002 78% central, 13% in field, 9% marginal, 0% distal recurrence.
 - SRS boost: no. RTOG 9305 SRS 15-24Gy x1 + EBRT 60 Gy no better than EBRT alone. Chemo for both arms.

Variations in RT target volume delineation

Table 8. Target volume definitions utilized by cooperative groups in the United States and Europe

Cooperative Group	One or Two Phase	CTV (initial)	CTV(boost)	PTV
ABTC	Two-phase: 46 + 14 = 60 Gy	T2 + T1E + cavity + 5 mm	Cavity + T1E + 5 mm	Institution specific but generally 3-5 mm
EORTC	One-phase	Cavity + T1E + 2-3 cm	-	Institution specific but generally 5-7 mm
NCCTG/Alliance	Two-phase: 50 + 10 = 60 Gy	T2 + T1E + cavity + 20 mm to block edge	Cavity + T1E + 20 mm to block edge	PTV addressed in CTV expansions
RTOG/NRG	Two-phase: 46 + 14 = 60 Gy	T2 + T1E + cavity + 20 mm	Cavity + T1E + 20 mm	3-5 mm

T1E=residual T1-enhancing abnormality. RTOG (Radiation Therapy Oncology Group) is now part of NRG. The listed RTOG margins from RTOG derive from RTOG 0825. New Approaches to Brain Tumor Therapy (NABTT) and the North American Brain Tumor Consortium (NABTC) were combined to form the American Brain Tumor Consortium (ABTC). Mayo/North Central Cancer Treatment Group (NCCTG) is now part of the Alliance for Oncology Trials consortium (described in table as Alliance). In most cases, editing of the CTV along anatomic barriers (e.g. bone) is allowed. The panel emphasizes that these cooperative group target volume definitions continue to evolve as data on outcomes and patterns of failure accrue.

Stupp Regimen

- EORTC/NCIC Phase III, n=573, 18-70yo, PS 0-2
- PBI 60 Gy vs. 60 Gy + cc/adj TMZ
- Results: +TMZ better
 - Median OS: 12 vs 15m
 - 2y OS: 11 vs. 27%
 - 5y OS: 2% vs. 10%
 - PFS 7m vs. 5m
- Minimal toxicity: TMZ 7% Gr3-4 heme tox vs. 0% but no QOL impact

2yr outcomes in NEJM 2005, 5 year outcomes in Lancet Oncol 2009

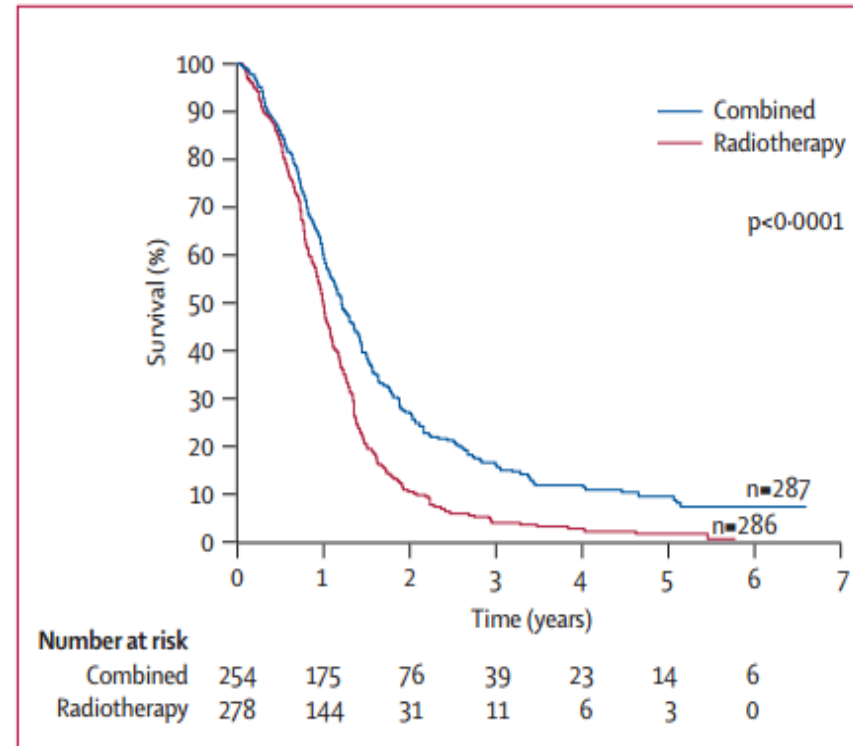
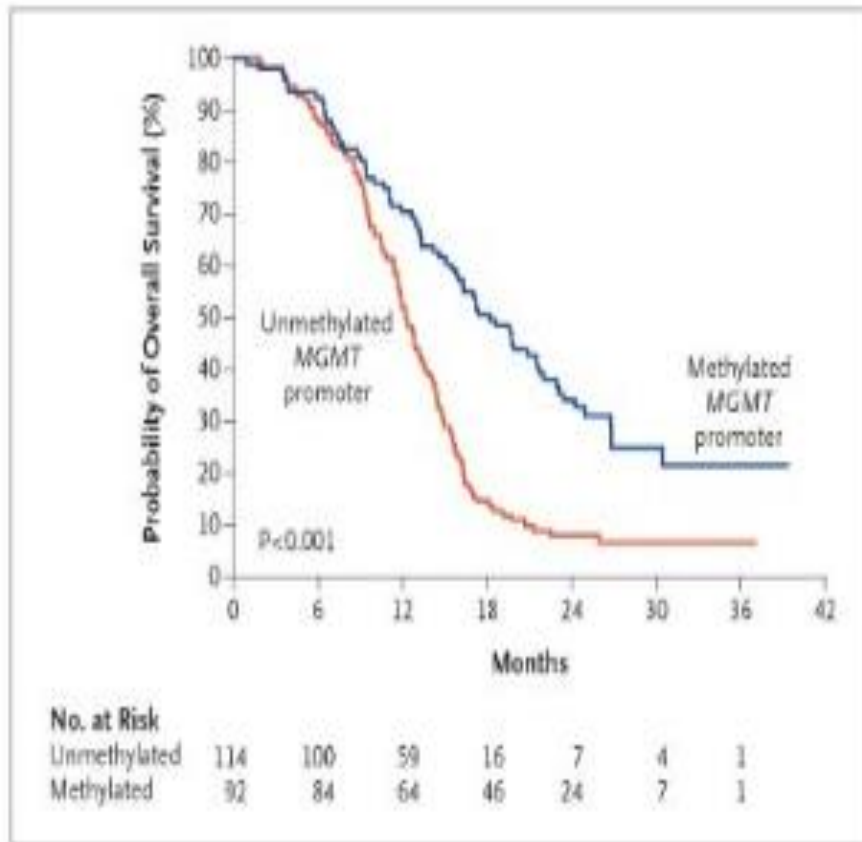


Figure 2: Kaplan-Meier estimates of overall survival by treatment group

MGMT methylation status: EORTC/NCIC phase III

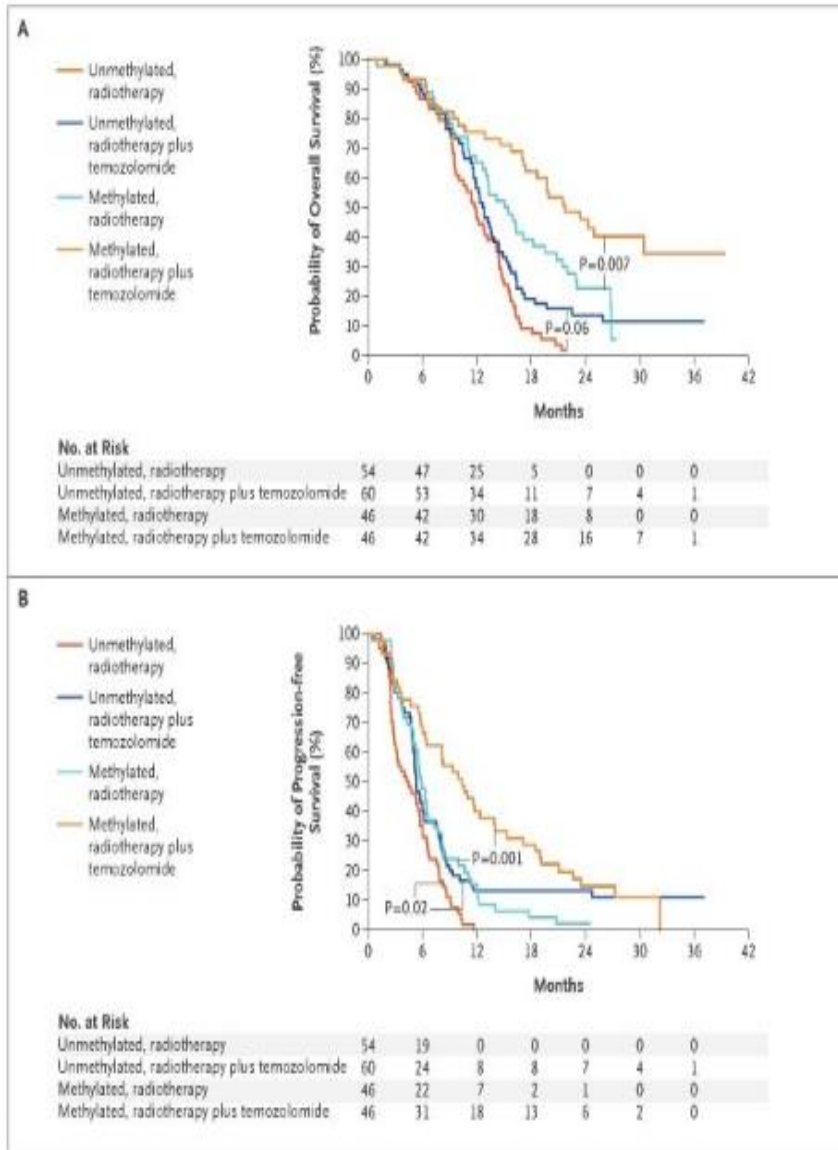


Regardless of treatment, MGMT methylation was a favorable prognostic factor (HR 0.45, $p < 0.0001$)

MGMT methylation: strongest predictor of outcome (secondary retrospective analysis): 23 mo vs 13 mo

Impact of MGMT methylation

Kaplan–Meier Estimates of Overall (A) and Progression-free Survival (B) according to *MGMT* Promoter Methylation Status and treatment group



MGMT methylated cases

- MS was 21.7 vs 15.3 mo for chemoRT vs RT alone
- 2-year survival rate of 46.0 percent vs 22.7 percent

MGMT un-methylated cases:

- Difference in overall survival favoring the temozolomide-plus-radiotherapy group was only marginally significant (P=0.06 by the log-rank test)
- MS was 12.7 vs 11.8 mo for chemoRT vs RT alone
- 2-year survival rates of 13.8 percent and less than 2 percent

Temozolomide TMZ (Temodar) dosing

- Based on Stupp et al. *NEJM* 2005
- Oral pill
- Concurrent 75 mg/m² daily with RT
- 1 month break
- 6-12 cycles of adjuvant TMZ at 150-200mg/m² given days 1-5 of 28 day cycle
- Side effects: nausea, constipation, 7% thrombocytopenia and lymphocytopenia

6 vs 12 cycles of TMZ

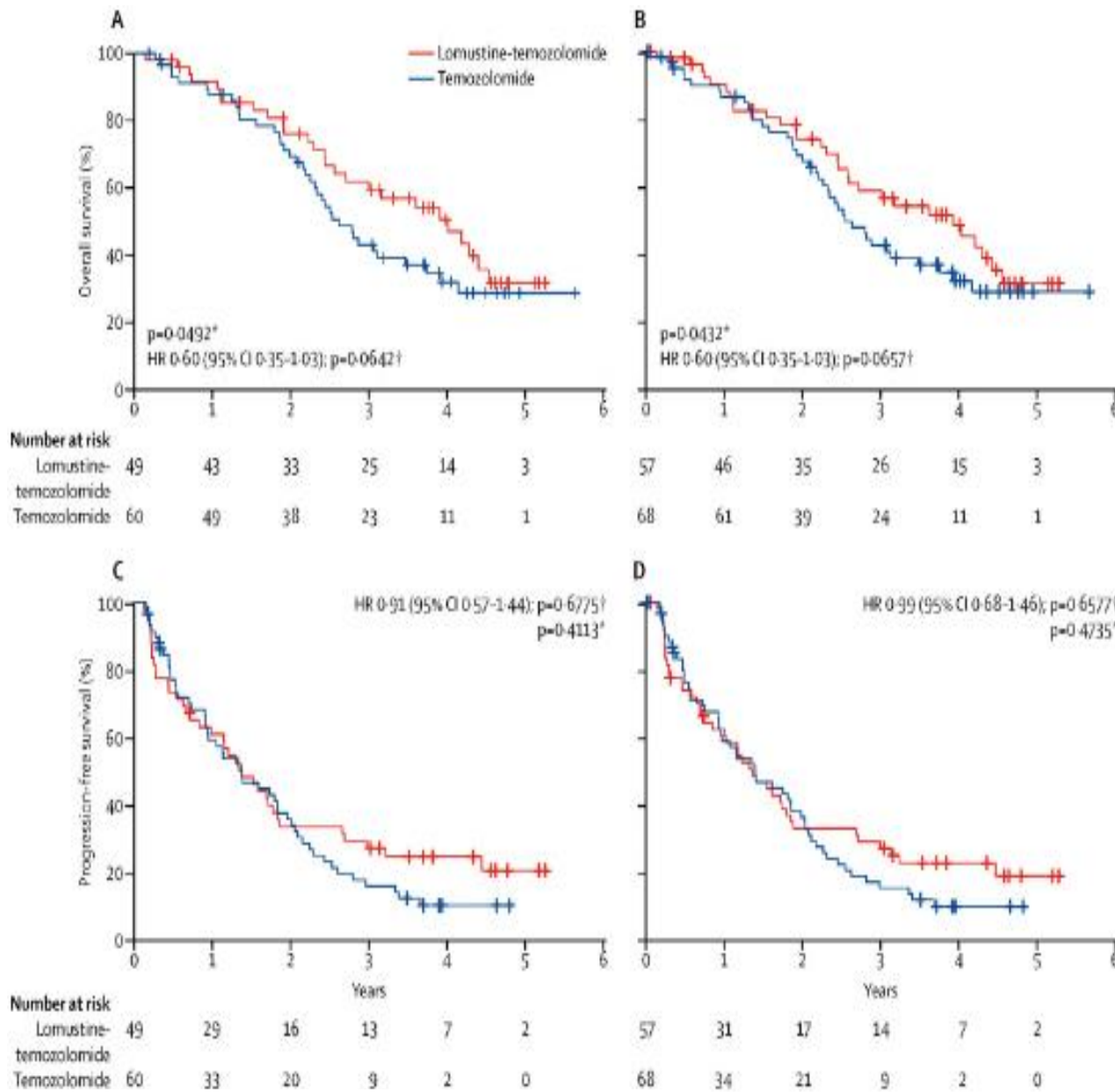
- Pooled analysis of individual patient data from 4 randomized trials
 - 2214 patients evaluated, 624 patients who were progression free 28 days after cycle 6 of TMZ were analyzed
 - Decision to continue TMZ at physician discretion
 - 291 continued maintenance TMZ until progression or up to 12 cycles
 - 333 discontinued maintenance TMZ after 6 cycles
- Treatment with 6+ cycles of TMZ was associated with improved PFS (hazard ratio [HR] 0.80 [0.65–0.98], $P = .03$)
 - Better in patients with methylated *MGMT* ($n = 342$, HR 0.65 [0.50–0.85], $P < .01$)
- Overall survival was not impacted by the number of TMZ cycles (HR = 0.92 [0.71–1.19], $P = .52$)

Anything other than Temodar?

CeTeG/NOA-09 Trial

- Investigated TMZ vs TMZ + CCNU (lomustine)
 - TMZ is primarily alkylator, lomustine is an alkylator, but also causes crosslinking and carbamylation of amino acids
- 129 patients (age 18-70, KPS at least 70, MGMT methylated) randomized to:
 - 60 Gy + TMZ → 6 cycles TMZ
 - 60 Gy + 6 cycles TMZ and CCNU
- Results:
 - Improved median survival 31.4 → 48.1 months ($p = 0.0492$)
 - Log-rank test, not significant on Cox regression
 - No impact on PFS
- Toxicity increased with TMZ-lomustine
 - Increased late and prolonged pseudoprogressions in the lomustine-TMZ group
 - Grade 3 or 4 events:
 - Lomustine-TMZ 59%
 - TMZ 51%
 - Grade 3 hematologic events:
 - Lomustine-TMZ 36%
 - TMZ 29%

Herrlinger U, Tzaridis T, et al. Lancet 2019; 393: 678-88.



Kaplan-Meier plots of patients in both groups matched by respective center and RPA class strata. Overall survival: (A) in the modified intention-to-treat population (n=109; stratified log-rank test) and (B) in the intention-to-treat population (n=125; stratified log-rank test). Progression-free survival: (C) in the modified intention-to-treat population (D) intention-to-treat population

HR=hazard ratio. *Stratified log-rank test (primary analysis). †Multivariate [Cox regression](#) analysis.

Herrlinger U, Tzaridis T, et al. Lancet 2019; 393: 678-88.

TTF EF-11: recurrent GBM

- Prospective, randomized phase III
- Compared TTFields monotherapy (n=117) with investigator's choice of systemic therapy (n=120) in patients with recurrent GBM
- Primary endpoint: OS
- Secondary endpoints: PFS, PFS at 6 months, overall response rate, 1-year survival, safety, and quality of life (QoL)
- MS 6.6 mo in TTF arm, 6 mo in chemo arm
- PFS 2.2 mo for TTF arm, 2.1 mo for chemo arm
- Patients in TTF arm had higher QOL self-report and fewer serious adverse events
- Post-hoc analyses:
 - OS was significantly longer in patients whose time on therapy was 18 hours/day or greater (>75% compliance rate) than in those with a <75% compliance rate (7.7 vs. 4.5 mo, $P=0.042$)

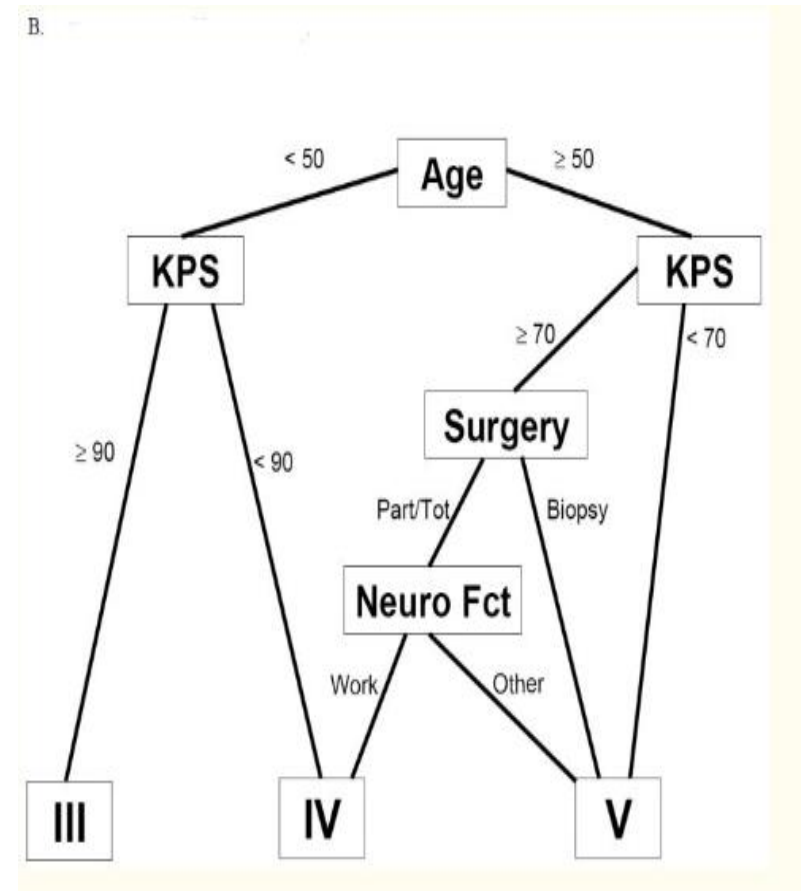
Led to FDA approval for use for recurrent GBM

TTF EF-14: newly diagnosed GBM

- 695 patients s/p chemoRT → TTF + TMZ or TMZ alone
- No placebo or sham device was utilized
- Interim analysis performed after the first 315 patients reached a minimum follow-up of 18 months demonstrated efficacy with acceptable tolerability and safety and led to early mandatory stoppage of the trial
- Primary endpoint: PFS in intent to treat
- Secondary endpoint: OS
- Results: PFS 7.1 vs 4.0 mo favoring TTF arm, OS 20.5 vs 15.6 mo favoring TTF arm
- Some criticisms:
 - **no placebo/“sham” control**
 - patients in TMZ only arm received 4 cycles vs. 6 cycles in TTF/TMZ cohort
 - bulky device

RPA score based prognosis

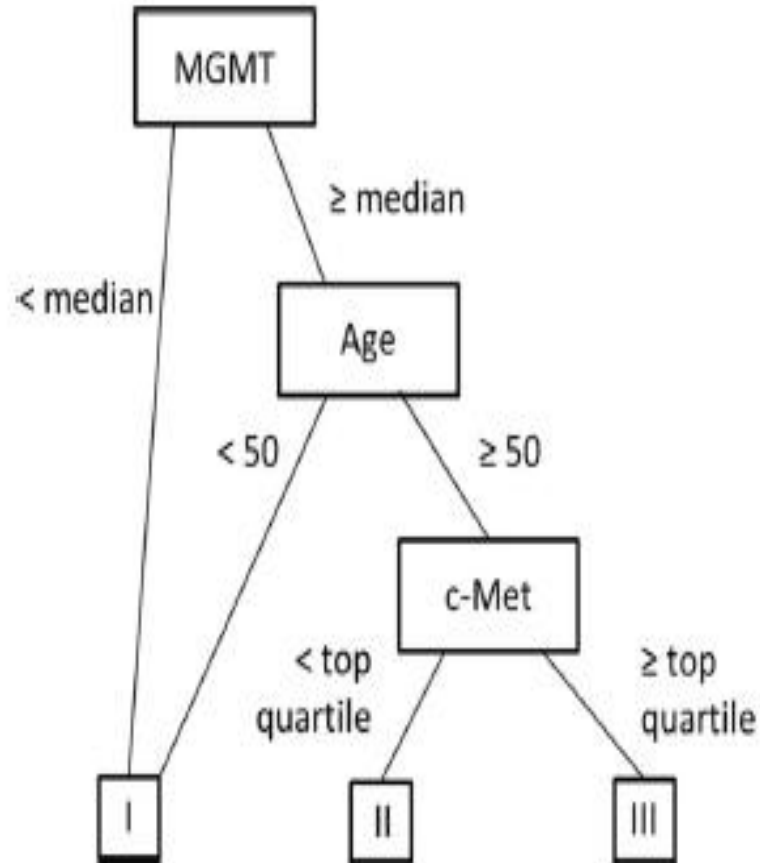
- In 1993, a score was used to stratify GBM patients
 - Analysis identified 6 prognostic groups with distinct survival outcomes
- A follow-up study with only GBM patients revised the original RPA model into three classes (III, IV, and V/VI)



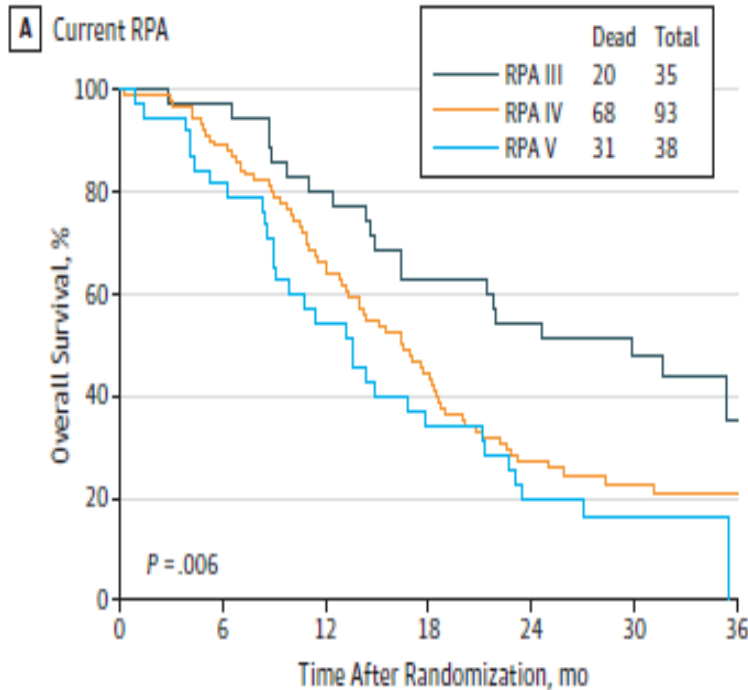
New molecular-based RPA classification system: NRG-GBM-RPA

- NRG-GBM-RPA published in 2017 refined RPA classification using molecular markers
- Evaluated protein biomarkers + clinical variables (age, KPS, extent of resection, neurologic function)
- Ki-67, c-Met (tyrosine-kinase protein Met), and MGMT found to be significant prognostic markers
 - Higher MGMT protein was significantly associated with decreased MGMT promoter methylation
 - Protein MGMT expression was found to have greater prognostic significance than MGMT methylation
 - IDH status was unavailable for 0525
- NRG-GBM-RPA achieved better separation compared to clinically based RPA in RTOG 0525
 - KPS and extent of resection did not add any prognostic information

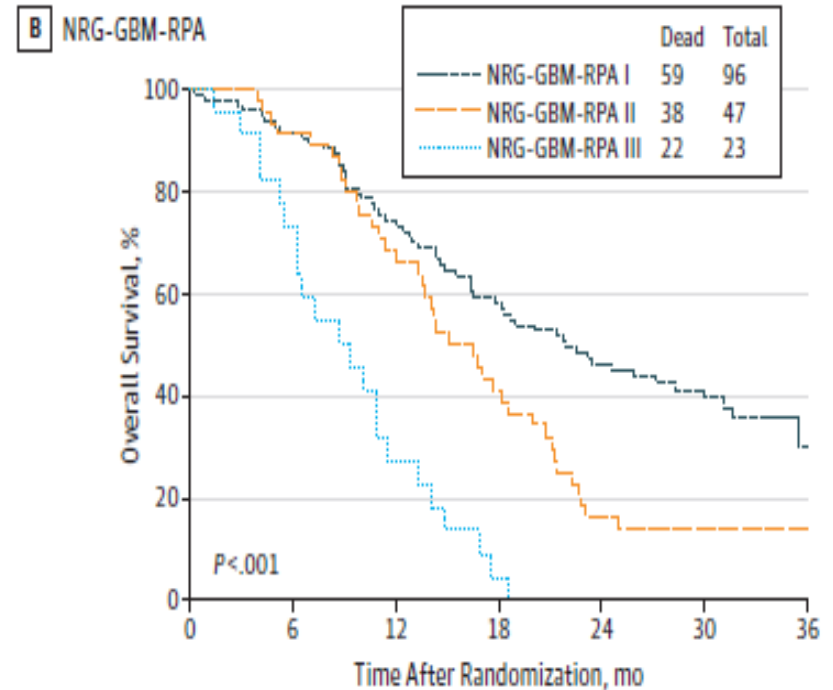
NRG-GBM-RPA



RPA vs NRG-GBM-RPA



No. at risk	0	6	12	18	24	30	36
RPA III	35	34	28	22	19	13	4
RPA IV	93	78	57	39	23	11	7
RPA V	38	31	19	12	7	4	0



No. at risk	0	6	12	18	24	30	36
NRG-GBM-RPA I	96	85	69	54	42	24	9
NRG-GBM-RPA II	47	42	29	18	7	4	2
NRG-GBM-RPA III	23	16	6	1	0		

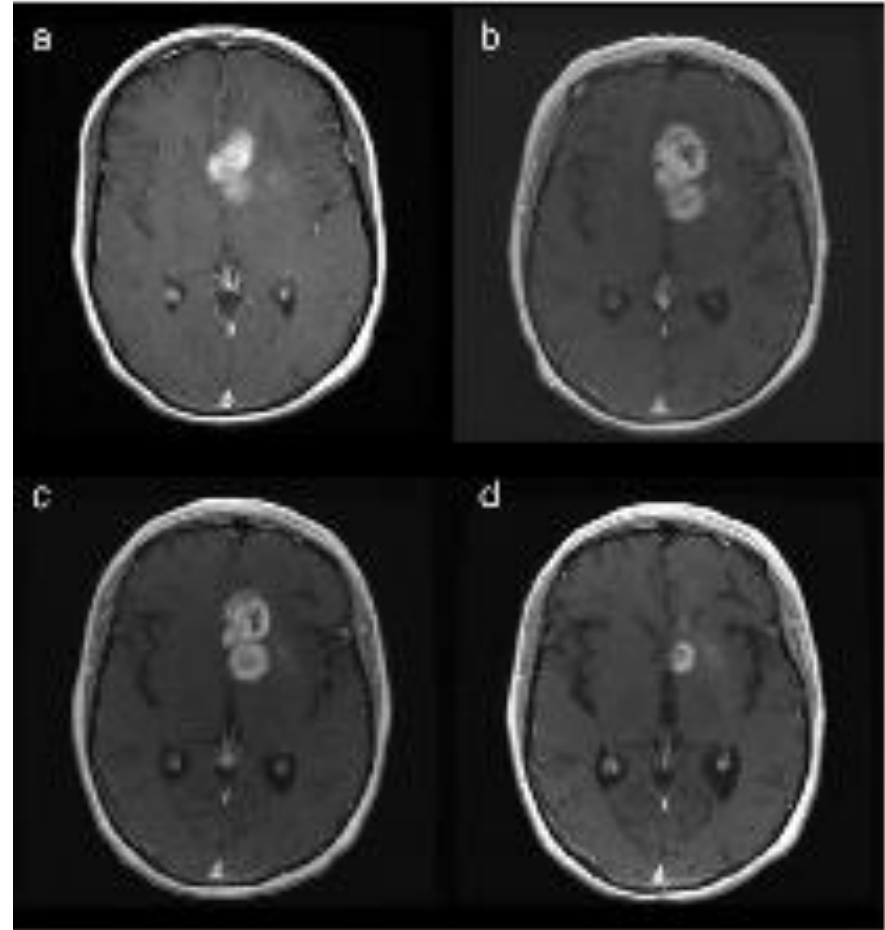
Median OS 21.9, 16.6, and 9.4 months

Elderly/Frail patients

Study	Design	Results
NCIC (Roa JCO 2004)	phase III trial, 100 pts age ≥ 60 years, KPS ≥ 50 randomized to 60 Gy/30 fx vs 40 Gy/15 fx	No difference in MS (5.1 vs 5.6 mo). Fewer patients in short course arm required increased steroids (23 vs 49%)
Nordic (Malmstrom Lancet Onc 2012)	291 pts age >60 , randomized to TMZ alone, RT with 34 Gy/10 fx, RT with 60 Gy/30 fx	MS better with TMZ than standard RT; for pts age >70 , survival better with TMZ or hypofractionated RT
IAEA (Roa JCO 2015)	Phase III non-inferiority, 98 patients ≥ 65 years, KPS 50-70, or both, randomized to 25 Gy/5 fx vs 40 Gy/15 fx	No difference in OS (7.9 vs 6.4 mo), PFS (4.2 mo for both), or QOL
NCIC CTG CE.6 (Perry, NEJM 2017)	Phase III, 562 pts, 65 years or older, randomized to short course RT (40 Gy/15 fx) +/- TMZ (adjuvant + concurrent)	TMZ improved MS (9.3 vs 7.6 mo) and PFS (5.3 vs 3.9 mo); for MGMT unmethylated, MS 10 vs 7.9 mo (p = 0.055)

Pseudoprogression

- What is pseudoprogression?
 - 20-30% of patients undergoing their first postradiation MRI show increased contrast enhancement that eventually subsides without any change in therapy
 - Mechanism: transiently increased permeability of the tumor vasculature from irradiation, which may be enhanced by temozolomide
 - More frequent in patients with a methylated *MGMT* gene promoter



Grading tumor response: McDonald Criteria (historical)

Table 1. Current Response Criteria for Malignant Gliomas (Macdonald Criteria)⁵

Response	Criteria
Complete response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; no corticosteroids; and stable or improved clinically
Partial response	Requires all of the following: $\geq 50\%$ decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no new lesions; stable or reduced corticosteroid dose; and stable or improved clinically
Stable disease	Requires all of the following: does not qualify for complete response, partial response, or progression; and stable clinically
Progression	Defined by any of the following: $\geq 25\%$ increase in sum of the products of perpendicular diameters of enhancing lesions; any new lesion; or clinical deterioration

- **Using these criteria, a significant increase (at least 25%) in the contrast-enhancing lesion is used as a reliable surrogate marker for tumor progression, and its presence mandates a change in therapy**

Revision to McDonald: RANO criteria

- RANO criteria:
 - 12 weeks post-RT: progression can only be determined if the majority of the new enhancement is outside 80% IDL or with pathologic confirmation

RANO Criteria	CR	PR	SD	PD
T1 enhancing disease	None	≥ 50%	< 50% if ↓ but < 25% if ↑	≥ 25% ↑
T2/FLAIR	Stable/ improved	Stable/ improved	Stable/ improved	Stable/ improved
New lesion	None	None	None	Present
Corticosteroid use	None	Stable or ↓	Stable or ↓	NA
Clinical status	Stable/ improved	Stable/ improved	Stable/ improved	Declined

Management of Recurrent Disease

- Surgical resection
- Bevacizumab
- Immunotherapy
- TMZ
- Reirradiation- SRS vs hypofractionated
- Clinical Trial

Negative trials: bevacizumab (Avastin)

- Bevacizumab: VEGF inhibitor
- Two large phase 3 trials RTOG 0825 and AVAglio did not find improved OS with addition of Avastin to standard CRT + TMZ
- Both trials suggested improved PFS with Avastin, but RTOG 0825 did not meet specified target
- RTOG 0825 Avastin patients had “modest increases” in hypertension, thromboembolic events, intestinal perforation and neutropenia
 - Bev arm had increased symptom burden, worse QOL, and decline in neurocognitive function
- AVAglio Avastin patients had longer maintenance QOL and PS but more grade 3+ toxicities

Negative Trials: RTOG 3508/INTELLANCE-1 (abstract, SNO 2019)

- Depatux-m: monoclonal antibody (depatuxizumab) that binds to both wild type epidermal growth factor receptor (EGFR) and the mutant “variant III (vIII)” form of the receptor, conjugated to a microtubule-inhibitor toxin (mafodotin)
- Patients (639 trial participants) with *EGFR*-amplified GBM were randomly assigned to receive either depatux-m or placebo
- Interim analysis following 346 events on the trial found no OS improvement for patients who received study treatment over placebo (median 18.9 vs. 18.7 months, HR 1.01, 95% CI 0.82-1.26, one-sided p= 0.63)
- EGFRvIII mutant subgroup
 - PFS trend favoring group that received deptux-m (median 8.3 vs. 5.9 months, HR 0.72, 95% CI 0.56-0.93)
 - No OS benefit
 - Trial stopped for futility

Negative trials: ACTR-32/NRG 1205

- Compared re-irradiation + bevacizumab to bevacizumab alone
- Primary outcome: OS
- 182 pts randomized to re-irradiation (35 Gy/10 fx) + Bev or Bev alone
- BEV+ReRT did not improve OS vs BEV alone, with median OS of 10.1 vs 9.7 mos, (HR=0.98, 95% CI=0.70–1.38, p=0.46)
- Median PFS for BEV+RT and BEV was 7.1 vs. 3.8 mos, respectively (HR=0.73, 95% CI=0.53–1.0, p=0.051)
- BEV+ReRT improved 6-mo PFS rate (PFS6): 54 vs. 29%, (HR=0.42, 95% CI=0.34–0.5, p=0.001)
- 5% acute and 0% delayed grade 3+ treatment-related AE
- Notes: accepted multifocal disease; per presentation, many plans were not able to give the full dose due to dose constraints

Tsien, et al. Presentation. SNO 2019

What is the role of immunotherapy for GBM?

- Challenges for immunotherapy and GBM:
 - Immunologically quiet tumor, low tumor mutational burden (TMB), few tumor infiltrating T cells (TILS), and low PD-1/PD-L1 expression
- Phase I: Checkmate 143: nivo better tolerated than nivo + ipilimumab
- Phase III: OS 10.3 Nivo vs Bev in recurrent GBM
 - At interim analysis of 369 patients, no OS benefit (9.8 v 10 month)
 - Responses more durable in nivo arm (11.1 mo nivo vs 5.3 mo bev)
- Checkpoint 498 and 548 (use of nivo for newly diagnosed GBM) ongoing
- At this time, phase 3 clinical trials have not demonstrated efficacy for immunotherapy in GBM and no FDA-approved immunotherapy for GBM exists

Omuro, Neuro-onc 2018; Reardon, SNO presentation 2017

Immunotherapy and GBM: vaccines

- Cancer vaccine therapy is designed to elicit immune response against the tumor
- Best studied tumor-specific antigen is a constitutively activated mutation of epidermal growth factor (EGFR), EGFRvIII (in 25-30% of GBM)
 - ACT IV, newly diagnosed GBM: Rindopepimut vs control showed similar OS in vaccine and control arm
 - Phase 2 of Rindopepimut in recurrent GBM favored vaccine (12 mo vs 8.8 mo OS)
 - Ongoing CAR-T cell studies targeting EGFRvIII
- Other promising vaccines include SurVaxM
- Customized vaccines using patient's tumor

McGranahan, Current Treatment Options
Oncology, 2019.

Other ongoing studies

- NRG BN001: RT dose escalation to 75 Gy/30 fx vs 60 Gy/30 fx with TMZ
- NOA-20: Phase I/II trial of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed non-MGMT hypermethylated glioblastoma

NOA-20: Phase I/II trial of molecularly matched targeted therapies plus radiotherapy in patients with newly diagnosed non-MGMT hypermethylated glioblastoma

- Open-label, multicenter, phase I/IIa umbrella trial for patients with newly diagnosed isocitrate dehydrogenase (IDH) wildtype glioblastoma without MGMT promoter hypermethylation to show safety, feasibility, and preliminary efficacy of treatment with targeted compounds in addition to standard radiotherapy based on molecular characterization
 - 5 subtrials:
 - Alectinib, idasanutlin, palbociclib, vismodegib, and temsirolimus as targeted therapies, according to the best matching molecular alteration
 - Patients without matching alterations are randomized between subtrials without strong biomarkers using atezolizumab and asinercept (APG101) and the standard of care, TMZ

Case:

- Patient was treated with post-operative radiation with concurrent temozolamide
- RT per RTOG guidelines using a simultaneous integrated boost
 - CTV 60: resection cavity + 2 cm margin
 - CTV containing critical structures (chiasm) limited to 54 Gy
 - CTV 52: edema (FLAIR) + 2 cm margin
 - PTV: CTV + 0.3 cm margin

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