Glioblastoma: Emerging Approaches

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Confluence of Interests

• **Consultant:** Cavion, Novocure, Varian
• **Stock Options:** Pharmacyclics
• **Board of Directors:** Pharmacyclics
• **DMSB:** Monteris
• **Research Funding:** Novocure, Cellectar

Current as of May 2016
Background

- Overall survival for the vast majority of GBM remains dismal, even in the modern era.
- Molecular profiling yields numerous subcategories, based on the toolkit utilized.
- Future small incremental gains may be made by combining current approaches.
- Radical transformation will only occur when profiling is married to actionable therapies, or radical new therapeutic strategies are defined.
- This will likely mean creating multiple GBM subsets for future therapeutic selection.
Combining Current Approaches: NRG BN001

Randomized Phase II Trial Hypofractionated Dose-Escalated IMRT or Proton Therapy vs. Conventional Photon RT with TMZ in Newly Diagnosed Glioblastoma

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Neuro-Oncology: Mark Gilbert, MD (MDACC), Antonio Omuro, MD (MSKCC)
QOL: Terri Armstrong, PhD (MDACC)  Neurocog: Jeffrey Wefel, PhD (MDACC)
Imaging: Christina Tsien, MD (WashU)   TRP: Erik Sulman, MD (MDACC)
Local Failure with RT-TMZ

- Majority of relapses occur in high-dose RT field
  - N=54, analysis of newly dxed GBM txed with TMZ-RT to 60 Gy
  - Central recurrence: arising from surgical cavity
  - In-field recurrence: new lesion in 95% isodose line
  - Marginal recurrence: new lesion crossing 95% isodose line
  - Distant recurrence: new lesion entirely outside 95% isodose line
    - If relative to 90% IDL, 4 of 8 distant recurrences would be reclassified as marginal

92% of 1st recurrences were in-field (95% IDL)

Milano MT et al. IJROBP 2010
Dose Escalation with TMZ

- University of Michigan phase I/II trial
  - RT dose escalation (66 Gy to 81 Gy/6 weeks) with TMZ
  - N=38, late CNS grd 3+ toxicity at 78 Gy (2/7 pts) and 81 Gy (1/9 pts)
  - MTD: 75 Gy in 30 fractions
    → Zero of 22 pts had RT necrosis
  - Median OS: 20.1 mos (14.0-32.5 mos); Median PFS: 9.0 mos (6.0-11.7 mos)
  - Probability of 95% IDL failure decreased with increased RT dose ($p=0.05$)

Hypothesis: Local Therapy Intensification Alters Patterns of Failure

NRG BN001 Schema

NRG-BN001: Phase IIR Trial HypoFx Dose-Esc IMRT or proton therapy vs. conventional photon RT with TMZ in newly diagnosed glioblastoma

Basic Eligibility: Newly dxed GBM; Residual tumor/postop cavity ≤ 5cm; KPS ≥ 70

- Newly-dx GBM
- RPA
- MGMT
- IMRT or PBT Dose-Painting 75 Gy/50 Gy in 30 fx + TMZ
- Standard Photon RT 60 Gy/30 + TMZ

Sample Size: 576 patients
Primary endpoint: Overall survival

Basic Statistical Design: Median survival 16 months with standard photon RT vs. 22.2 months with dose-esc IMRT or PBT
Isodose comparison of simultaneous integrated boost (SIB) and dose escalation using IMXT and IMPT. The proton approach allows better tumor tissue coverage while sparing more uninvolved structures, and possibly causing less lymphopenia.

Images: Anita Mahajan
Lymphopenia Decreases OS in GBM

- Severe lymphopenia occurs in 40% of GBM patients
- This lymphopenia is associated with decreased survival in GBM
- The Hopkins group (ASCO 2012, Yovino et al) modeled the effect of cranial RT on lymphopenia
  - Conventional photons irradiate the entire circulating lymphocyte population to a mean dose of 2.2 Gy over 30 fractions (0.5 Gy is lymphotoxic)
  - Marked reduction in treated volume was the only factor associated with lowering the lymphocytopenic dose
- Protons with steep dose gradients and almost no exit dose represent a unique modality to reduce treated volume

CD4 Counts vs. Survival in GBM

Data from Johns Hopkins: Survival in GBM patients by CD4 count
Anti-tumor activity of triple therapy is CD4+ dependent

http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0101764
Creating Radical New Therapeutic Strategies: NRG BN002

Phase I Study of Ipilimumab, Nivolumab, and the Combination in Patients with Newly Diagnosed Glioblastoma

Mark Gilbert, MD
PDL-1 Expression in GBM

- 9/10 in vitro GBM cell lines express PDL-1 mRNA and PDL-1 protein
- 50% of in vivo GBM cell lines express PDL-1 mRNA
- GBM tumors express PDL-1 mRNA at higher rates than non-neoplastic brain tissue

Multi-Cohort Phase 1 Trial

- Cohort 1: Concurrent TMZ and Ipilimumab: Closed
- Cohort 2: Concurrent TMZ and Nivolumab: Closed
- Cohort 3: Concurrent TMZ with Ipi and Nivo: To open next
Radiation Therapy and Immune Response

• RT counteracts immunosuppressive tumor microenvironment by:
  – \( \uparrow \) MHC Class 1 expression by tumor cells
  – \( \uparrow \) Expression of pro-inflammatory cytokines
  – Promotes dendritic cell maturation
  – \( \downarrow \) Fas-ligand expression leading to \( \downarrow \) T-cell apoptosis
  – Eradicates \( T_{\text{regulatory}} \) cells
  – Unleashes neoantigens promoting neoantigenic response

• However, prolonged RT leads to immunosuppression via leucopenia

Preclinical Testing of Anti-PD-1 (with XRT) in Intracranial Glioblastoma

- Mice treated with stereotactic radiation followed by an anti-PD-1 antibody had significantly longer survival than mice treated with no treatment, anti-PD-1 antibody alone, or radiation alone, respectively (53 days vs 25 days vs 27 days vs 28 days, all p values <0.05)
Proposed recGBM Trial

- Phase I multiinstitutional trial
  - Recurrent, high-grade glioma
    - Radiation: 5 fractions once daily (days 1-5) followed by anti-PD1 antibody to be given in two doses (days 7 and 10)
    - Primary endpoint: re-operation due to toxicity within 45 days of treatment
    - Continuous re-assessment model phase I trial

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RTOG Foundation-Abbvie Trial

Randomized phase II-III trial of radiotherapy and temozolomide with or without ABT-414 for newly diagnosed glioblastoma (GBM)

Andrew B. Lassman, MD
Department of Neurology & Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center
Introduction To ABT-414

• ~40% of GBM patients have EGFR abnormalities
• Prior trials targeting EGFR activity have failed
• ABT-414 uses EGFR as a Trojan Horse
  – Antibody (ABT-806)
    • Binds to activated wild-type EGFR and EGFRvIII
  – Conjugated Toxin (MMMF)
    • Highly potent, microtubule inhibitor impermeable to cell membrane
    • Must be internalized to be effective
ABT-414 as a Trojan Horse

ABT-806 (Naked EGFR Ab) + MMAF = ABT-414 (Ab Conjugate)
Preliminary Data

• Phase I (Sponsored) trial, presented at ASCO, 2014
• 3 arms (newly diagnosed, recurrent + TMZ, recurrent monotherapy)
• MTD established, main toxicities:
  – Keratitis, dose dependent, reversible
M12-356 Waterfall Plot

Percent Change from Baseline

- Cohort 1 (0.5 mg/kg)
- Cohort 2 (1.0 mg/kg)
- Cohort 3 (1.5 mg/kg)

Shading denotes newly diagnosed patients

ABT414 (16 weeks)
RTOG 3508: nGBM, Ph II R → III

Strat:
RPA, MGMT

Major Elig
• GBM
• Tissue available
• *EGFR Amp or EGFRvIII*
Conclusions

• Conventional combinations in GBM have likely reached a plateau.
• More complex, large trials, with innovative combinations, targeted approaches, and novel therapeutics currently dominate the landscape.
• Molecular subsetting of patients and utilizing more specific agents...will lead to more trials with fewer patients in each.