Therapeutic resistance to temozolomide and temozolomide sensitizing strategies

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Temozolomide (TMZ) combined with RT is the standard of care

Conventional TMZ Rx
- TMZ 75 mg/m² daily during RT
- TMZ 150-200 mg/m² days 1-5 x 6 cycles

- Biochemistry of TMZ lesions
  - O6-methyl-guanine
  - N7-methyl-guanine
  - N3-methyl-adenine

- Mechanisms of resistance
  - MGMT
  - Mismatch repair

- Sensitizing strategies
  - O6-benzyl guanine
  - PARP inhibitors
  - ATR/ATM inhibitors

Stupp et al, NEJM 2005
Biochemistry of TMZ
Methylation lesions

- 3 main lesions induced:
  - O6-methylguanine (O6MG)
    - 10%
  - N7-methylguanine (N7MG)
    - 60-80%
  - N3-methyladenine (N3MA)
    - 10-20%

Stalled replication
DNA breaks
Homologous recombination

1° repair failure
Stalled replication
DNA breaks
Homologous recombination
MGMT promoter methylation

Hegi et al, NEJM 2005

http://helicase.pbworks.com/w/page/17605615/DNA%20Methylation
TMZ sensitizing strategies

- Directly inhibit MGMT or BER
- Interfere with replication recovery
- Disrupt DNA DSB repair
Inhibition of MGMT
O6-benzylguanine and lomeguatrib

Robust pre-clinical data
Multiple clinical trials of MGMT inhibitors + alkylating agents
Combinations require dose reduction of cytotoxic agent or unconventional dosing
Hematologic toxicities predominate
TMZ sensitizing strategies

- Directly inhibit MGMT or BER
- Interfere with replication recovery
- Disrupt DNA DSB repair
ABT888 combinations with TMZ

**GBM6**

- Placebo
- TMZ
- ABT-888 + TMZ

* p<0.001

**GBM39**

- Placebo
- ABT-888
- TMZ
- ABT-888 + TMZ

* p=0.02

### Table: MGMT unmethylated

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<thead>
<tr>
<th></th>
<th>placebo</th>
<th>ABT-888</th>
<th>TMZ*</th>
<th>TMZ+ABT*</th>
<th>p-value</th>
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### Table: MGMT methylated

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MGMT expression abrogates ABT-888 efficacy

**GBM12**
- Placebo
- TMZ
- TMZ + ABT-888

* p<0.001

**GBM12 + MGMT**
- Placebo
- ABT-888
- TMZ
- ABT-888 + TMZ

* p=0.87
Planned phase II/III clinical trial

- Complete RT/TMZ with recovery from toxicity
- Register for central path & MGMT testing
  - MGMT +
  - MGMT – Not eligible
- Register for therapeutic trial
- Randomization 1:1
  - TMZ 150-200 mg/m² Days 1-5 every 28 and ABT-888 40 mg bid Days 1-7
  - Placebo bid Days 1-7
- Overall Survival endpoint
- 1° endpoint - PS
- 2° - PFS, response, AE
- Correlative - DNA repair mutations
• Pre-reg. consent for Central path and Central MGMT review
• Anytime after surgery
• MRI prior to RT/TMZ – specific technique not required
• RT/TMZ not part of protocol treatment
  • Does not need to be done at registering site
  • 60 or 59.4 Gy + 75 mg/m2 TMZ daily
Registration

- Complete RT/TMZ – register 21 to 42 days later
- Recover from toxicities to Gr 2
- Baseline MRI after RT/TMZ – protocol specific technique
- Optune currently not allowed – modification will allow
- Key exclusion criteria
  - Gliadel wafer or therapy other than RT/TMZ
  - Platelets < 75K during RT/TMZ
  - ECOG PS ≤ 2
  - True tumor progression
  - Prior cancer requiring brain radiation exposure
  - Active malignancy or < 3 yr. disease-free interval *
Pseudo-progression

- Progression T1+C or T2/FLAIR lesions limited to radiation volume
- Clinically stable or improved
- Very common in MGMT methylated tumors

Pre-RT/TMZ  4 wk post-RT/TMZ  3 mo post-RT/TMZ