Therapeutic resistance to temozolomide and temozolomide sensitizing strategies

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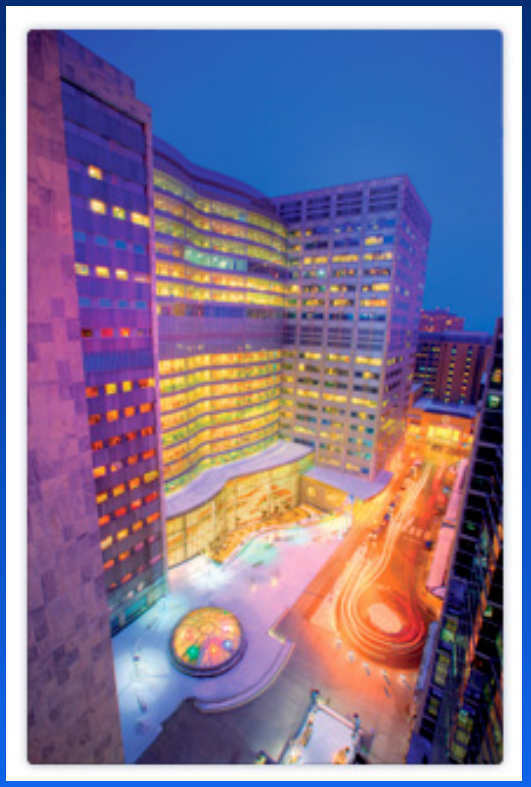
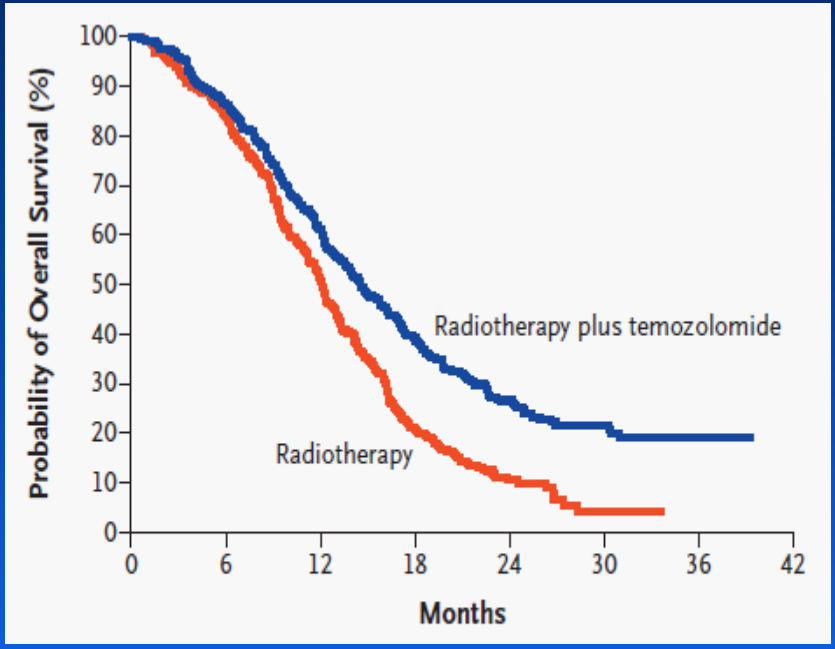


Temozolomide (TMZ) combined with RT is the standard of care

Conventional TMZ Rx

TMZ 75 mg/m2 daily during RT

TMZ 150-200 mg/m2 days 1-5 x 6 cycles

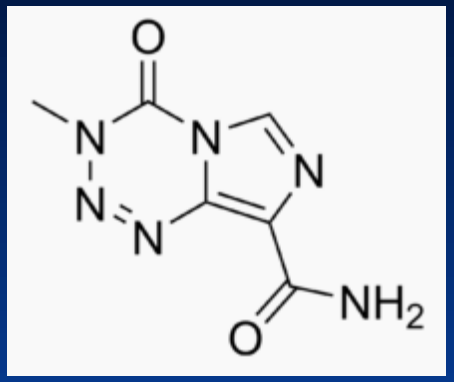


Stupp et al, NEJM 2005

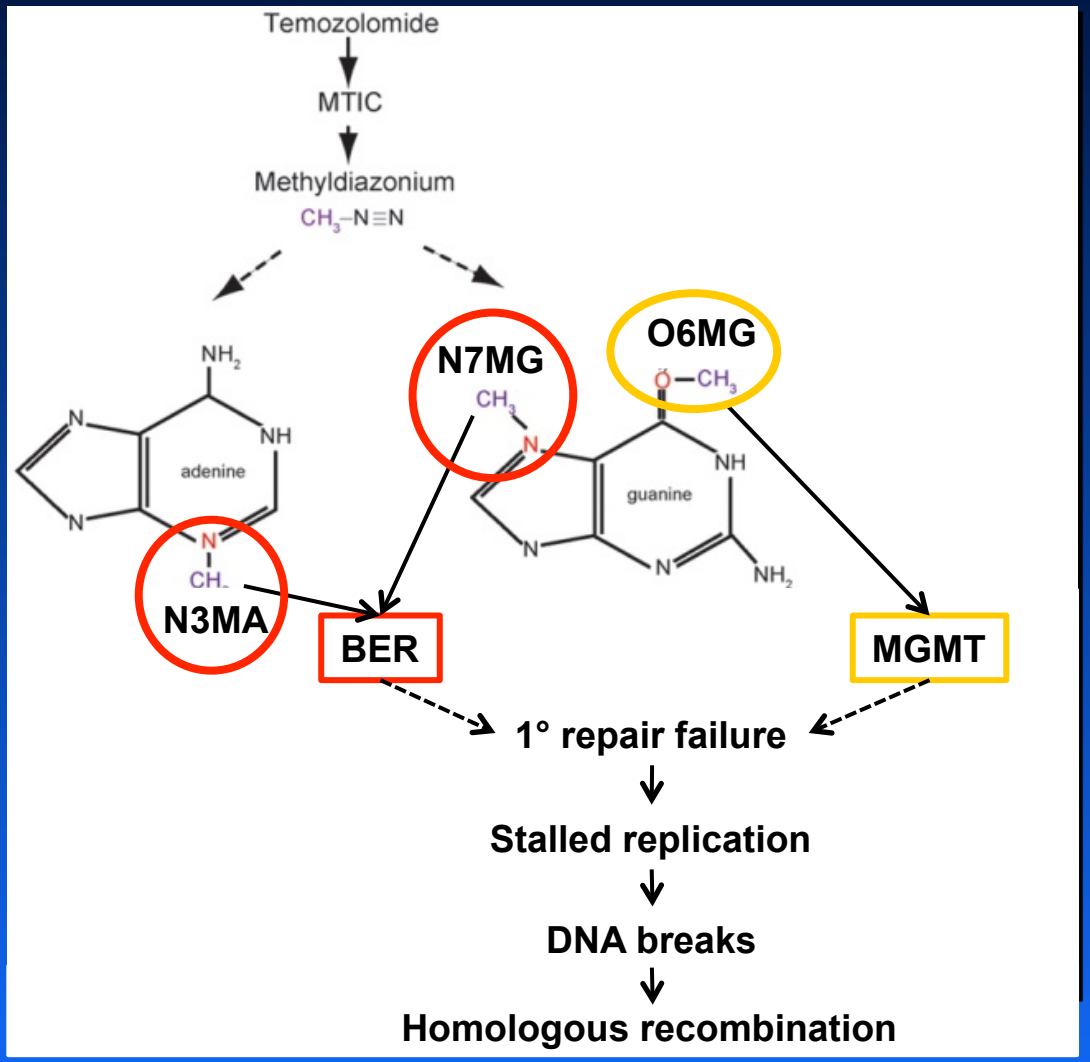
- Biochemistry of TMZ lesions
  - O6-methyl-guanine
  - N7-methyl-guanine
  - N3-methyl-adenine
- Mechanisms of resistance
  - MGMT
  - Mismatch repair
- Sensitizing strategies
  - O6-benzyl guanine
  - PARP inhibitors
  - ATR/ATM inhibitors

Biochemistry of TMZ

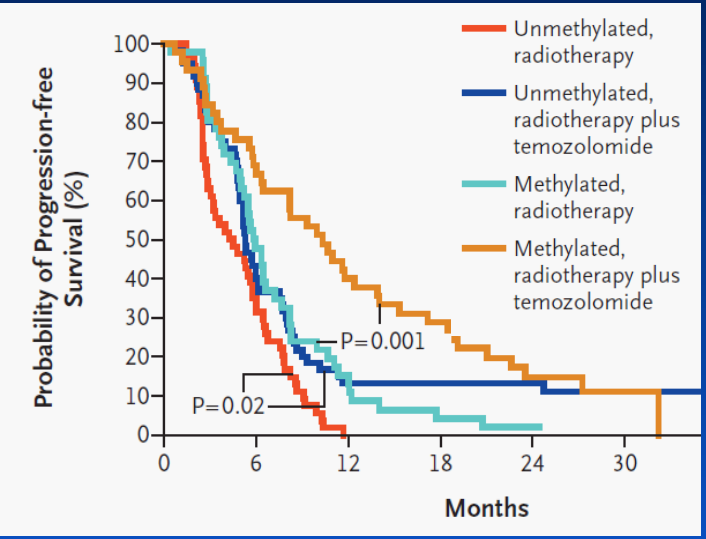
Methylation lesions



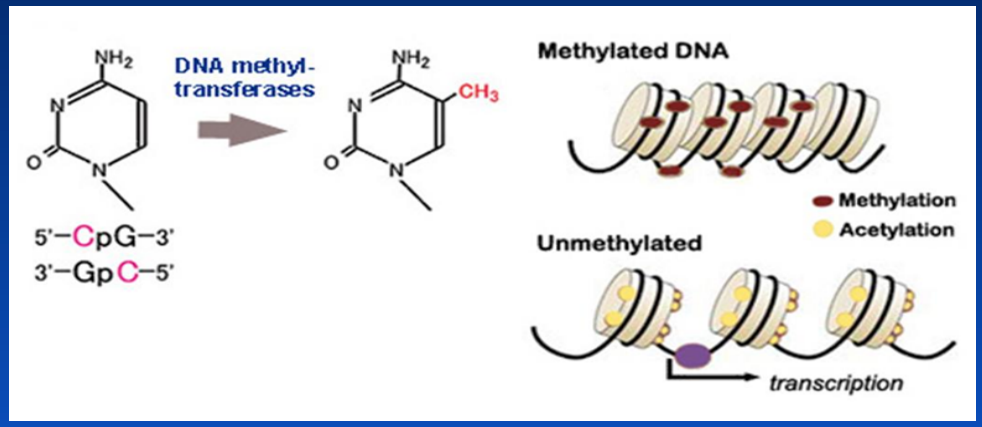
- 3 main lesions induced:
- O6-methylguanine (O6MG)
  - 10%
- N7-methylguanine (N7MG)
  - 60-80%
- N3-methyladenine (N3MA)
  - 10-20%



MGMT promoter methylation

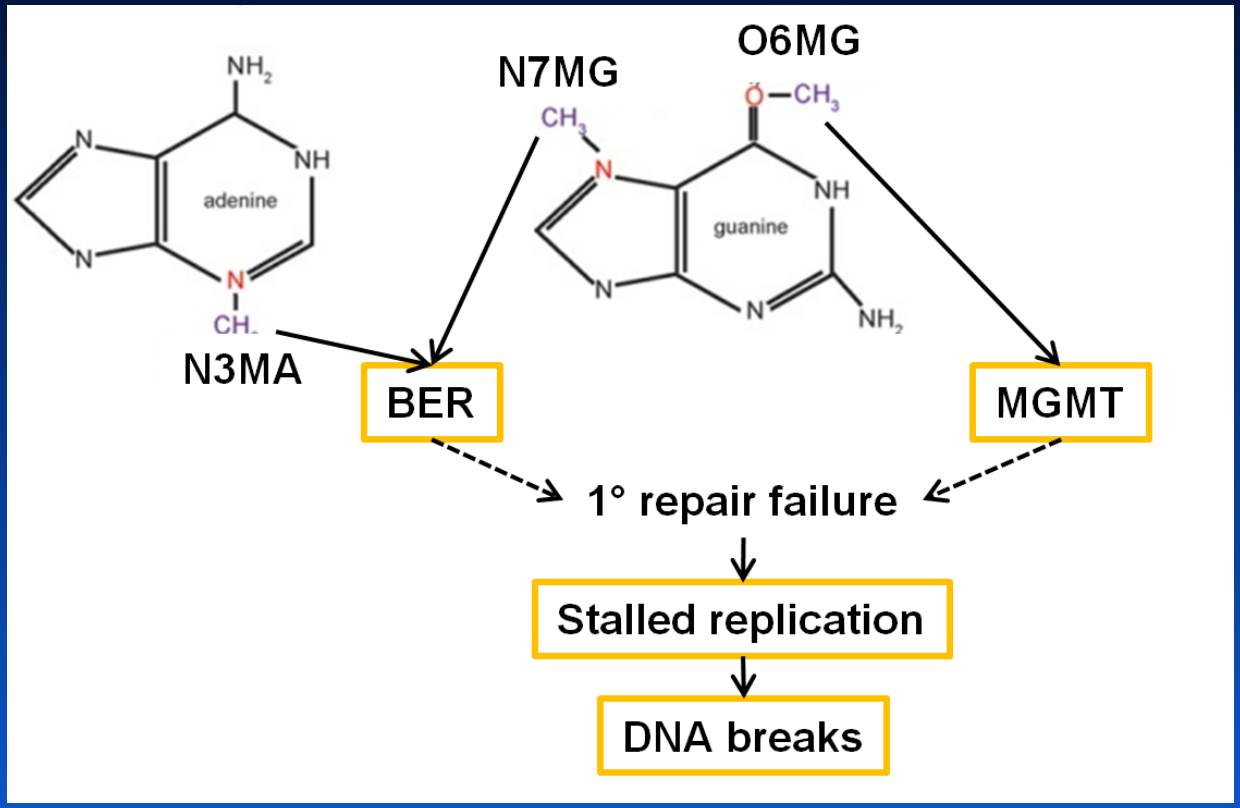


Hegi et al, NEJM 2005



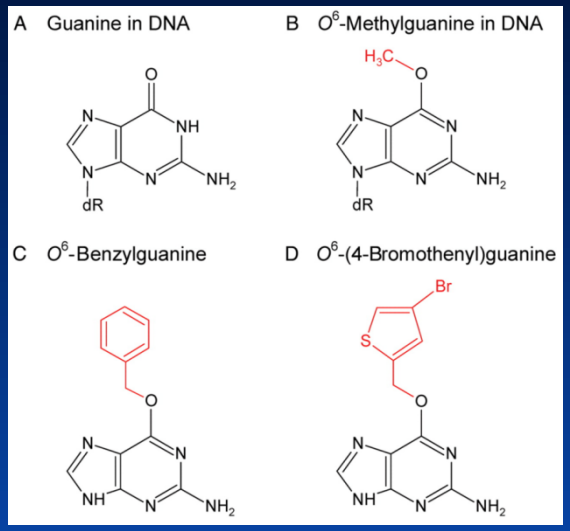
http://helicase.pbworks.com/w/page/17605615/DNA%20Methylation

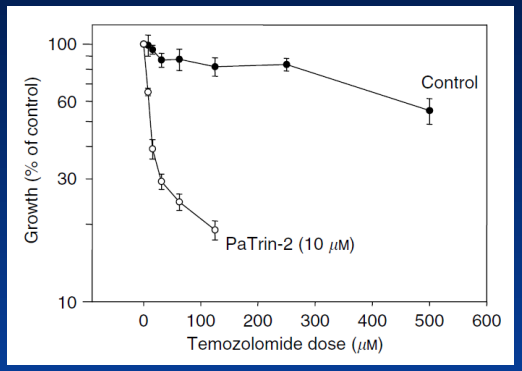
TMZ sensitizing strategies

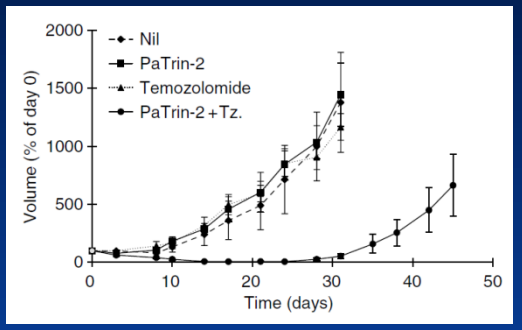


- **Directly inhibit MGMT** or BER
- Interfere with replication recovery
- Disrupt DNA DSB repair

Inhibition of MGMT
O6-benzylguanine and lomeguatrib



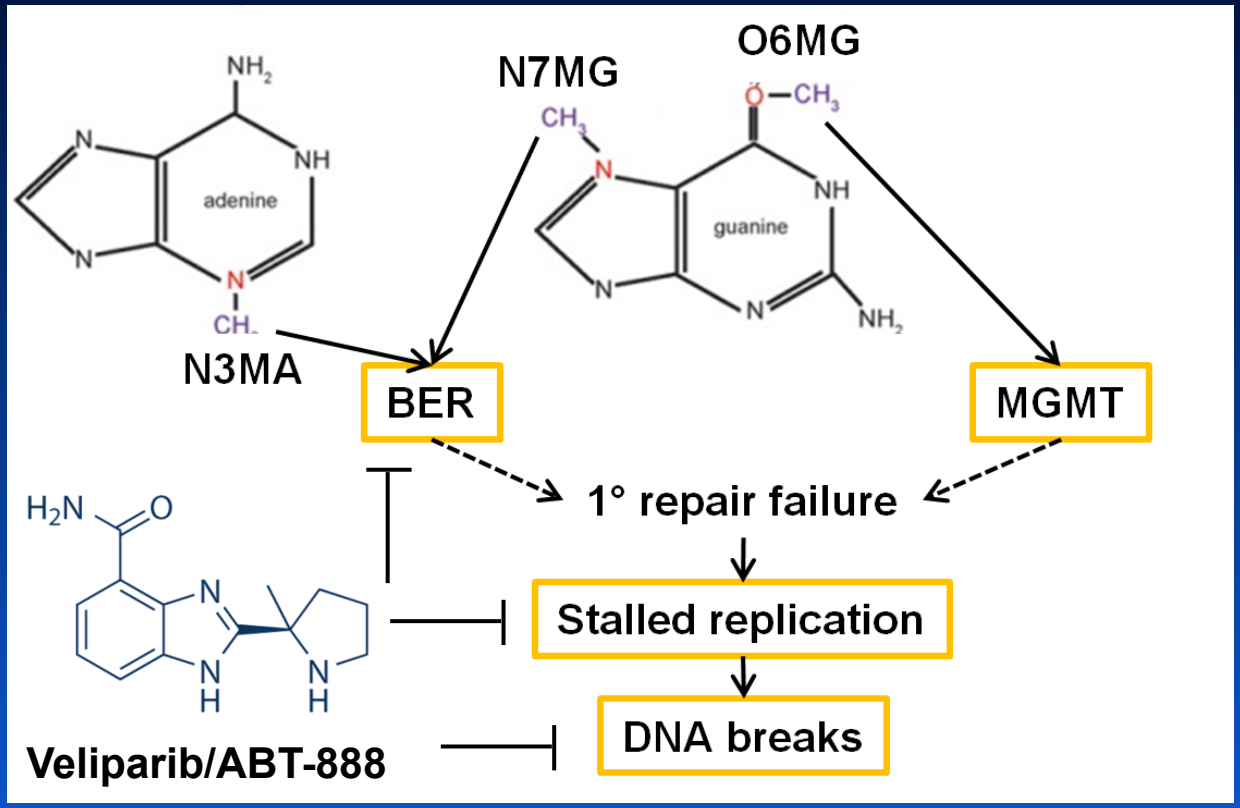




Clemons et al., Br J Cancer 2005

- 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



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- Interfere with replication recovery
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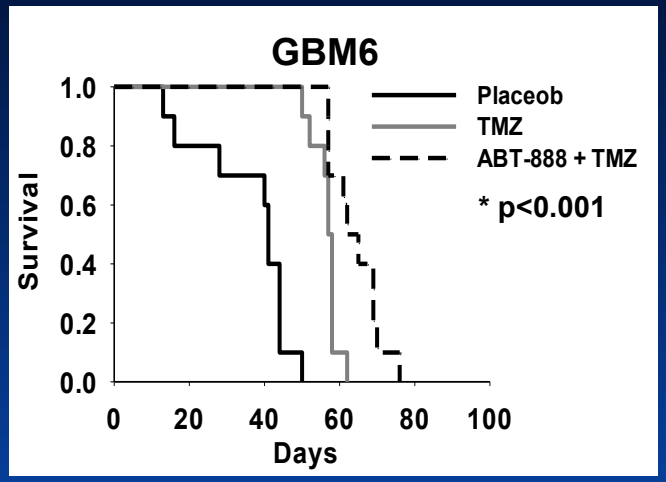
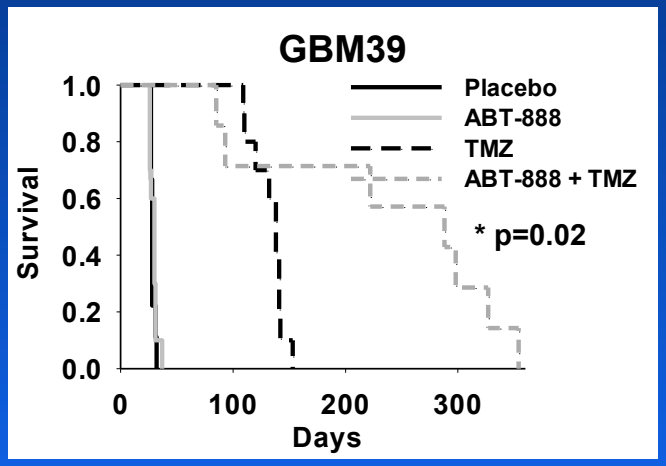
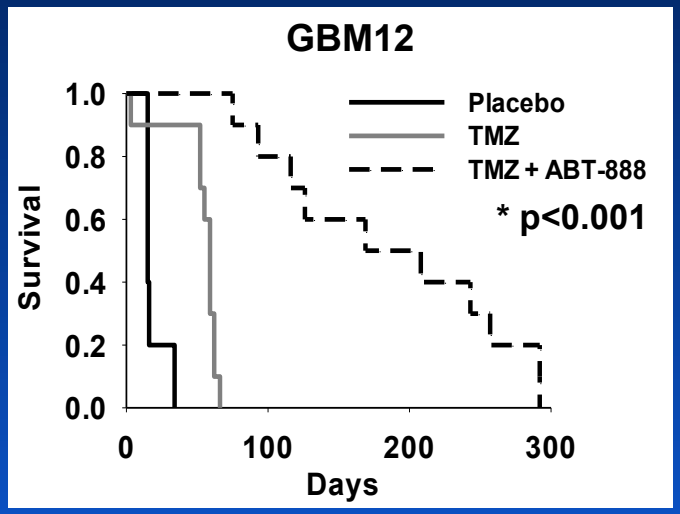
ABT888 combinations with TMZ

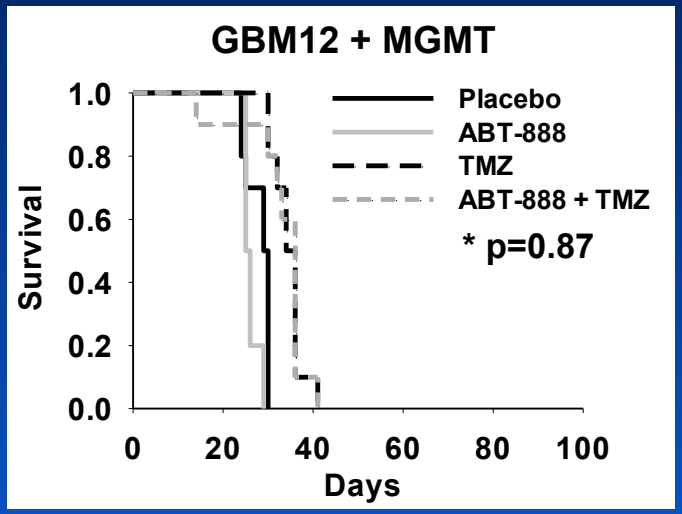




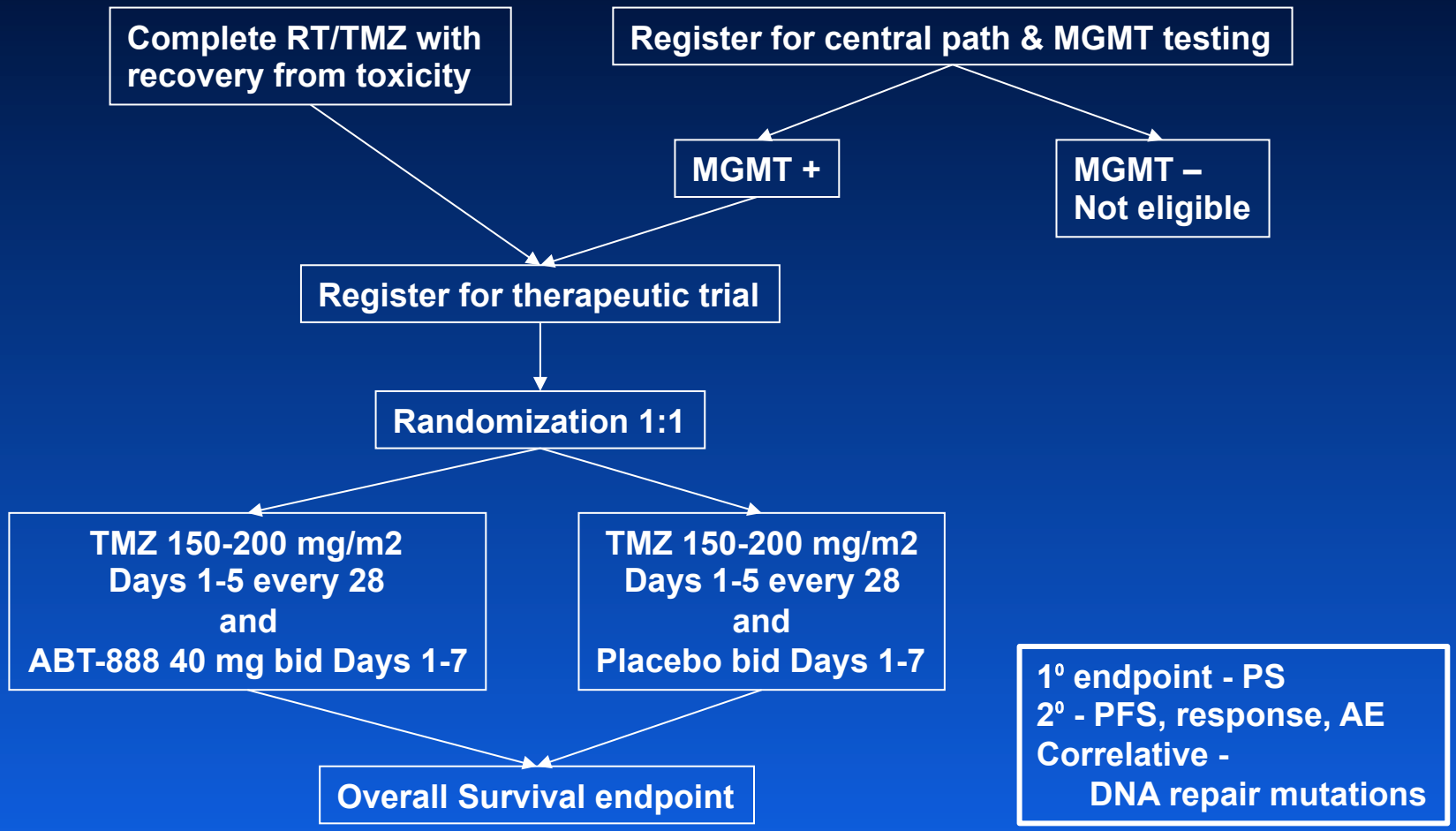
	MGMT unmethylated				
	placebo	ABT-888	TMZ*	TMZ+ABT*	*p-value
GBM6	41	NA	58	65	<0.001
GBM28A	26	NA	33	34	0.24
GBM43	14	NA	62	39	0.43
GBM79	31	NA	32	31	0.02
	MGMT methylated				
	placebo	ABT-888	TMZ*	TMZ+ABT*	*p-value
GBM5	103	106	237	286	0.27
GBM12	31	28	79	154	0.01
GBM22	20	19	58	94	0.03
GBM28B	34	37	98	188	0.04
GBM39	28	30	138	288	0.02
GBM46R	34	38	36	48	0.78
GBM59	48	52	96	174	0.13
GBM63	82	95	262	276	0.18

MGMT expression abrogates ABT-888 efficacy

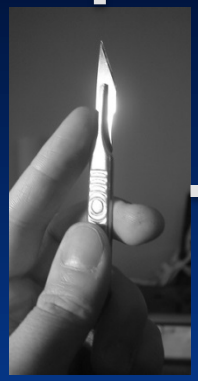




Planned phase II/III clinical trial

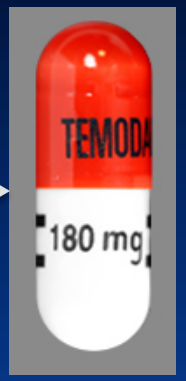


Pre-registration



2-4 weeks

4-6 weeks

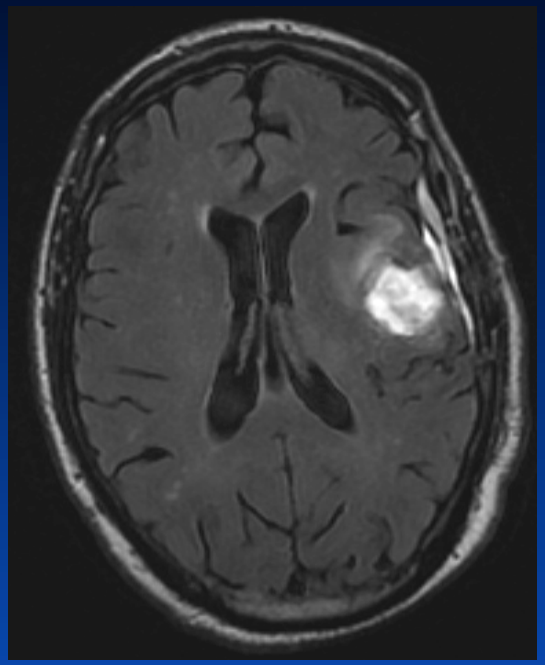


- Pre-reg. consent for Central path and Central MGMT review
- Anytime after surgery
- MRI prior to RT/TMZ – specific technique not required
- RT/TMZ not part of protocol treatment
  - Does not need to be done at registering site
  - 60 or 59.4 Gy + 75 mg/m2 TMZ daily

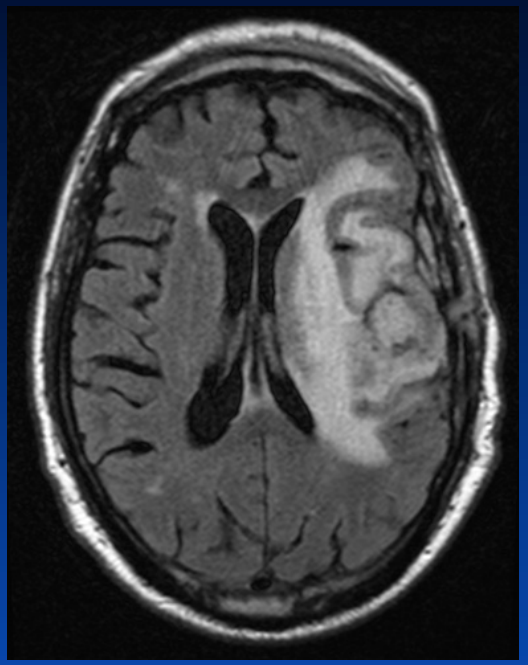
Registration

- 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 *

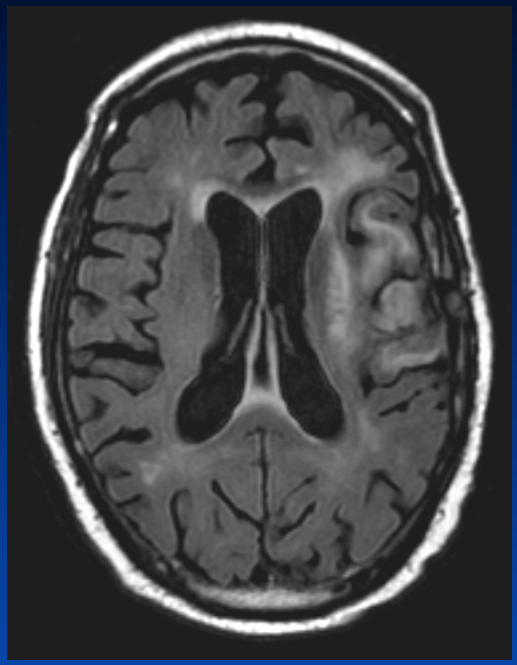
Pseudo-progression



Pre-RT/TMZ



4 wk post-RT/TMZ



3 mo post-RT/TMZ

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