Antibody Drug Conjugates in Glioblastoma?

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Trends in Central Nervous System Malignancies
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Boston, MA USA
# ADC in Clinical Development

<table>
<thead>
<tr>
<th>Name</th>
<th>mAb Target</th>
<th>Toxin</th>
<th>Status</th>
<th>Indication</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab-emtansine (T-DM1)</td>
<td>HER2/neu (herceptin)</td>
<td>Maytansine</td>
<td>EMA/FDA approved</td>
<td>Breast CA</td>
<td>Genentech/Roche/Immunogen</td>
</tr>
<tr>
<td>Brentuximab vedotin</td>
<td>CD30</td>
<td>Auristatin</td>
<td>EMA/FDA approved</td>
<td>Hodgkin’s; Anaplastic large cell lymphoma</td>
<td>Seattle Genetics/Millenium/Takeda</td>
</tr>
<tr>
<td>Inotuzumab ozogamicin</td>
<td>CD22</td>
<td>Calicheamycin</td>
<td>FDA approval withdrawn</td>
<td>NHL</td>
<td>Pfizer</td>
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<tr>
<td>AMG595</td>
<td>EGFRvIII</td>
<td>Maytansine</td>
<td>Ph I discontinued</td>
<td>GBM</td>
<td>Amgen</td>
</tr>
<tr>
<td>ABT-414</td>
<td>EGFR/EGFRvIII</td>
<td>Monomethylauristatin-F (MMMF)</td>
<td>Ph I/II</td>
<td>GBM</td>
<td>Abbvie</td>
</tr>
</tbody>
</table>
ABT-414 (ABT-806 vC MMAF)
Exploits Tumor-Specific EGFR Binding With a Potent Toxin Payload

ABT-414 targets a unique epitope exposed upon EGFR activation
- Selective binding confirmed in FIH and imaging studies
  - Minimal EGFR-mechanism related side effects
  - Binding to tumors confirmed with ABT-806i imaging

mcMMAF Toxin
- Non-cleavable maleimide caproyl (mc) linker
- Monomethylauristatin F (MMAF) toxin
  - Microtubule toxin
  - Not membrane permeable
  - Low potential for bystander effect
  - Potential to bypass MDR/PGP mediated resistance
  - About 1,000 X more potent than other microtubule inhibitors

Antibody + mcMMAF > either alone
- Selective toxin delivery increases efficacy at tumor cell and minimizes normal tissue damage
- Can circumvents EGFR-signaling resistance mechanisms
ABT-414: Antibody-Drug Conjugate (ABT-806 + MMMF)

- ABT-414 exploits tumor-specific binding properties of ABT-806
  - Binds EGFR domain II

- Unique epitope exposed *only* when EGFR is in the activated, or extended, conformation
  - EGFR overexp, activation, or de2-7

- Normal tissues have low levels of activated EGFR

- **Efficacy ABT-414 >>> ABT-806 (preclinical)**
• **ABT-806 binds a unique EGFR epitope**
  – High affinity for EGFRΔ2-7 mutant – not a target for approved agents
  – Epitope also available for binding on *activated* wild-type (wt) EGFR

• **Advantages**
  – Tumor-specific binding, reduces side effects
  – Niche indications not addressed with current inhibitors
  – Conjugated antibody products (imaging, ADCs, etc.)
Potent ABT-414 In Vivo Activity against GBM Tumors with EGFRvIII Overexpression (SC model)

U-87 MG EGFRde2-7 (Glioblastoma); EGFRvIII (+++)

[Graph showing tumor growth over time with different treatments indicated by various markers.]
Potent Activity of ABT-414 in Both EGFRvIII and WT EGFR GBM Patient-Derived Xenograft (PDX) Models (SQ)

SN-0199 Glioblastoma with EGFRvIII

SN-0207 Glioblastoma with WT EGFR

![Graphs showing the effect of ABT-414 on tumor growth in PDX models.](image)

(Day 1 = treatment initiation)

Mean Tumor Volume (mm$^3$ ± SE)

Control
ABT-414 10 mg/kg

Days
In vivo Potency of ABT-414 in Combination with TMZ and Radiation

**U87MGde2-7 (GBM)**

- Rituximab (1 mkd)
- TMZ (1.5) + XRT (2 Gy)
- ABT-414 (1 mkd)
- ABT-414 + TMZ
- ABT-414 + Radiation
- ABT-414 + TMZ + XRT

ABT-414 combination with suboptimal dose of TMZ and fractionated radiation therapy results in significant increase in tumor growth inhibition.
ABT-806i SPECT Images: ABT-806 Binds to Intracranial Tumors

Whole-body Posterior Scan

Magnified Images of H & N Region

1 h | 48 h | 120 h

Anterior nasal sinus blood pool radioactivity

Posterior fossa GBM on Gd-T1 MRI
Study M12-356

Ongoing phase Ib study to evaluate the safety and PK of ABT414 in subjects with glioblastoma
Phase Ib: Safety and Pharmacokinetics of ABT-414 for subjects with GBM

Arm A: Newly diagnosed GBM
  Tx: RT/TMZ + ABT-414
  expanded cohort @ RPTD (15 – 20 subjects)

Arm B: 1. newly diagnosed GBM after RT/TMZ. 2. recurrent GBM
  Tx: TMZ + ABT-414
  expanded cohort @ RPTD (50 EGFR amp + subjects)

Arm C: recurrent GBM
  Tx: ABT-414 monotherapy
  expanded cohort @ RPTD (50 EGFR amp + subjects)
M12-356: Arm A and Arm A Expanded Cohort Schematic

TMZ
Daily (including weekends)

RT
Daily excluding weekends for 6 weeks (total of 30 +/- 3 fractions)

ABT-414
Week 1
W1
Informed Consent

W2
W3
W4
W5
W6
W7
W9

Screening (<21 Days)

Weekly Study Visits

4 week TMZ Dosing Holiday

Arm A Only:
DLT Assessment Period Ends

Cycles 2, 3, 4...

C1
D1
D8
D15
D22

Maintenance Phase:
Resume ABT-414 and TMZ Dosing
ABT-414: D1 q2 weeks (Days 1 and 15 of q28 days)
TMZ: D1-DS q28 days per local prescribing information

35 Day PUI

Final Visit

RT = Radiation therapy; C = Cycle; D = Day; W = Week

▲ = Tumor Assessment; Screening, every 8 weeks during treatment and Final Visit (if not within 3 weeks)
M12-356 Study Design (Arm B)
TMZ/ABT-414 for recently completed RT patients and those with recurrent disease

Arm B and Expanded Cohort B Schematic

- **Temozolomide**
  - D1-D5
  - Q28 day cycle per local prescribing information

- **ABT-414**
  - Dosing C1D2, C1D15 then D1 and D15 of q28 day cycle

- **Weekly visits**

- **Screening (≤28 Days)**

- **Informed Consent**

- **DLT Assessment Period Ends**

- **Cycles 3, 4, 5, etc. Visits D1, 15, 22**

- **35 Day F/U**

- **Final Visit**

**Legend**
- ▲ = Tumor Assessment: Screening, every other cycle during treatment and Final Visit (if not within 3 weeks)
- ● = ABT 806i SPECT Imaging

**Abbreviations**
- C = Cycle
- D = Day
M12-356 Study Design (Arm C)
ABT-414 monotherapy: for recurrent disease patients

Arm C and Expanded Cohort C Schematic

ABT-414
Dosing D1 and D15 of q28 day cycle

DLT Assessment Period Ends

Cycles 3, 4, 5,... Visits D1 and D15

C1
D1

C1
D15

C2
D1

C2
D15

C3
D1

Screening (≤28 Days)

Bi-weekly Visits

35 Day F/U

Final Visit

C = Cycle, D = Day

▲ = Tumor Assessment: Screening, every other cycle during treatment and Final Visit (if not within 3 weeks)
● = ABT 806i SPECT Imaging
ABT-414 demonstrated dose-proportional PK with low inter-subject variability. Majority of circulating total ABT-806 antibody in blood was ABT-414. Circulating cys-mcMMAF level was about 400-folder lower than ABT-414 on the molar basis. The half-lives of ABT-414, total ABT-806 and cys-mcMMAF are 9, 12 and 4 days, respectively.
# M12-356 INTERIM SAFETY AND DOSE ESCALATION RESULTS

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Doses</th>
<th>MTD</th>
<th>RPTD</th>
<th>DLTs</th>
<th>Efficacy</th>
</tr>
</thead>
</table>
| A   | 45 | 0.5 – 3.2 mg/kg | 2.4 mg/kg | 2.0 mg/kg | • LFTs  
  • Eye Tox  
  • Radiation Skin Reaction | • Too early to read for efficacy |
| B   | 35 | 0.5 – 1.5 mg/kg | 1.5 mg/kg | 1.25 mg/kg | • Eye Tox | • One PR at 0.5 mg/kg  
  • One CR and one PR at 1.0 mg/kg  
  • Two PR at 1.25 mg/kg  
  • One PR at 1.5 mg/kg |
| C   | 29 | 1.25 mg/kg | n/a | 1.25 mg/kg | • n/a | • One CR and two PR 1.25 mg/kg |
Patient Population

1. Measurable progressive or recurrent GBM by MRI.
2. Progression ≥ 3 months after completion of concomitant RT/TMZ.
3. Arm B only: last TMZ dose < 3 months prior to progression
4. Tumor tissue tested + centrally for EGFR amplification.
5. Age > 18
6. KPS ≥ 70.
7. No prior Bevacizumab.
8. No more than 1 line of chemotherapy.
9. No prior EGFR therapies

Endpoints

Primary endpoint: Objective response rate (ORR)

Secondary endpoints: PFS-6, PFS, OS, Safety and tolerability

Arm B: ABT-414 + TMZ (N = 50)

Arm C: ABT-414 monotherapy (N = 50)

US sites: 12
Ex-US sites: 2

M12-356 Amendment
Increase Arm B and C Expansion Cohorts & Require EGFR Amplification
### M12-356: Primary Toxicity is Ocular (MMMF)

<table>
<thead>
<tr>
<th>Arm (N)</th>
<th>Dose (mg/kg)</th>
<th>Any Grade N (%)</th>
<th>Grade 3 / 4 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B (35)</td>
<td>0.5 - 1.5</td>
<td>33 (94%)</td>
<td>8 (22.9%)</td>
</tr>
<tr>
<td>C (25)</td>
<td>1.25</td>
<td>17 (68%)</td>
<td>5 (20%)</td>
</tr>
</tbody>
</table>

Data reported as of 12 Dec 2014

corticosteroid eye drops (before and after ABT414 dosing) help in alleviating eye symptoms
Number and Percentage of Subjects with Treatment-Emergent Adverse Events > 5% of Subjects Receiving ABT-414 Thru 12 December 2014

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>ABT-414 Monotherapy</th>
<th>ABT-414 + TMZ + Radiation (N=45)</th>
<th>Total ABT-414 (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>M13-379 (N=53) n (%)</td>
<td>M12-356 Arm C (N=25) n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td>Arm A ABT-414</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td></td>
<td>M12-356</td>
<td>1 (2.2)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td></td>
<td>M12-356</td>
<td>5 (11.1)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td>M12-356</td>
<td>3 (6.7)</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>M12-356</td>
<td>15 (33.3)</td>
<td>5 (14.3)</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td></td>
<td>M12-356</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal cyst</td>
<td></td>
<td>M12-356</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Corneal deposit</td>
<td></td>
<td>M12-356</td>
<td>0</td>
<td>2 (4.4)</td>
</tr>
<tr>
<td>Diplopia</td>
<td></td>
<td>M12-356</td>
<td>1 (1.9)</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>Dry eye</td>
<td></td>
<td>M12-356</td>
<td>19 (35.8)</td>
<td>5 (20.0)</td>
</tr>
<tr>
<td>Eye irritation</td>
<td></td>
<td>M12-356</td>
<td>3 (5.7)</td>
<td>2 (8.0)</td>
</tr>
</tbody>
</table>
### Number and Percentage of Subjects with Treatment-Emergent Adverse Events

> 5% of Subjects Receiving ABT-414 Thru 12 December 2014

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term</th>
<th>ABT-414 Monotherapy</th>
<th>ABT-414 +TMZ +Radiation (N=45) n (%)</th>
<th>ABT-414 +TMZ (N=35) n (%)</th>
<th>Total ABT-414 (N=158) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M13-379 (N=53) n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M12-356 Arm C (N=25) n (%)</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>M12-356 Arm A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye disorders (con’t)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye pain</td>
<td>8 (15.1)</td>
<td>0</td>
<td>10 (22.2)</td>
<td>9 (25.7)</td>
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<tr>
<td>Eye pruritus</td>
<td>7 (13.2)</td>
<td>0</td>
<td>0</td>
<td>4 (11.4)</td>
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<tr>
<td>Eye swelling</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>0</td>
<td>5 (20.0)</td>
<td>6 (13.3)</td>
<td>10 (28.6)</td>
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<tr>
<td>Glaucoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Keratitis</td>
<td>13 (24.5)</td>
<td>5 (20.0)</td>
<td>15 (33.3)</td>
<td>8 (22.9)</td>
</tr>
<tr>
<td>Lacrimation increased</td>
<td>7 (13.2)</td>
<td>0</td>
<td>10 (22.2)</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Ocular hyperaemia</td>
<td>2 (3.8)</td>
<td>1 (4.0)</td>
<td>3 (6.7)</td>
<td>5 (14.3)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>13 (24.5)</td>
<td>7 (28.0)</td>
<td>14 (31.1)</td>
<td>14 (40.0)</td>
</tr>
<tr>
<td>Vision blurred</td>
<td>26 (49.1)</td>
<td>14 (56.0)</td>
<td>28 (62.2)</td>
<td>18 (51.4)</td>
</tr>
<tr>
<td>Visual acuity reduced</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (5.7)</td>
</tr>
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</table>
Number and Percentage of Subjects with Treatment-Emergent Adverse Events Meeting NCI CTCAE Grade 3 or 4 Criteria Receiving ABT-414 Thru 12 December 2014

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term</th>
<th>ABT-414 Monotherapy</th>
<th></th>
<th></th>
<th></th>
<th>Total ABT-414 (N=158)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ABT-414 Arm C (N=25) n (%)</td>
<td>ABT-414 Arm A ABT-414 +TMZ + Radiation (N=45) n (%)</td>
<td>ABT-414 Arm B ABT-414 + TMZ (N=35) n (%)</td>
<td>ABT-414 (N=158) n (%)</td>
<td></td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corneal deposits</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2.9)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>1 (1.9)</td>
<td>0</td>
<td>0</td>
<td>1 (2.9)</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Eye pain</td>
<td>1 (1.9)</td>
<td>0</td>
<td>1 (2.2)</td>
<td>0</td>
<td>2 (1.3)</td>
</tr>
<tr>
<td>Foreign body sensation in eyes</td>
<td>0</td>
<td>1(4.0)</td>
<td>0</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Keratitis</td>
<td>4 (7.5)</td>
<td>3 (12.0)</td>
<td>5 (11.1)</td>
<td>4 (11.4)</td>
<td>16 (10.1)</td>
</tr>
<tr>
<td>Lacrimation decreased</td>
<td>0</td>
<td>0</td>
<td>1 (2.2)</td>
<td>0</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Optic nerve disorder</td>
<td>0</td>
<td>1 (4.0)</td>
<td>0</td>
<td>0</td>
<td>1 (0.6)</td>
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<tr>
<td>Punctate Keratitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2.9)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Photophobia</td>
<td>1 (1.9)</td>
<td>1 (4.0)</td>
<td>1 (2.2)</td>
<td>0</td>
<td>3 (1.9)</td>
</tr>
<tr>
<td>Vision Blurred</td>
<td>3 (5.7)</td>
<td>1 (4.0)</td>
<td>3 (6.7)</td>
<td>1 (2.9)</td>
<td>8 (8.9)</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (2.9)</td>
<td>1 (0.6)</td>
</tr>
</tbody>
</table>
M12-356 Arms B and C: All EGFR Amplified Patients with Measurable Disease
Data cutoff: 25 Feb 2015

Response rate: $\frac{7}{22} \times 100 = 32\%$

*522 and 531 are EGFR amplified by site data, and are not yet confirmed by AbbVie*
Subject #405: Partial Response

- Clinical history: 43 y/o man with a diagnosis of GBM in July 2012. S/p gross total resection in July 2012, RT Aug 2012 and TMZ from Aug 2012 to Mar 2013. This subject also received rindopepimut vs. placebo Oct 2012 to Jun 2013. MGMT methylation unknown. EGFRvIII+. Treated at 1.0 mg/kg, dose reduced to 0.5.

Baseline Scan 25Jul2013
Sum: 792 mm²

Week 16 Scan 19Sep2013
Sum: 12 mm²
Subject #406: Partial Response


Baseline Scan 26Aug2013
Sum: 1125 mm²

Week 8 Scan 21Oct2013
Sum: 510 mm²
Subject #531: Durable Partial Response

11/12/2014

10/2/2015
ABT414: Next Steps

1. M14-483: Randomized phase II study for recurrent GBM (EORTC)

2. M13-813: Randomized phase II/III study for newly diagnosed GBM (EORTC)
M14-483: Study Schema

Stratification Factors:
- Region of World
- WHO PS
- Recurrence > or < 3 months after last TMZ dose

Endpoints
- Primary Objective: Overall Survival
- Secondary Objectives:
  - PFS
  - RANO Response
  - OS in the EGFRvIII Population
  - QOL
  - WHO PS
  - Steroid Use
  - Safety

Patient Population
- Histologically confirmed de novo GBM (primary) with unequivocal first progression after RT concurrent/adjuvant chemotherapy
- Tumor demonstrates EGFR amplification by central testing.
- No more than one line of chemotherapy
- ECOG score 0 – 2
- Age > 18
- No prior EGFR or EGFRVIII directed therapy

Endpoints
- N = 80
- Arm A: ABT-414
- N = 80
- Arm B: ABT-414 + TMZ
- N = 80
- Arm C: TMZ or Lomustine*

*< 3 mos to recurrence = Lomustine
> 3 mos to recurrence = TMZ
M14-483 (EORTC-1410-BTG)

Stratification: Time since last TMZ dose

Stratification
- Recurrence ≥ 3 months since last TMZ (30 – 40%)
  - Arm A: ABT-414 (Experimental)
  - Arm B: ABT-414 + TMZ (Experimental)
  - Arm C: TMZ re-challenge (Control)
  - N=24-32

Stratification
- Recurrence < 3 months since last TMZ (60-70%)
  - Arm A: ABT-414 (Experimental)
  - Arm B: ABT-414 + TMZ (Experimental)
  - Arm C: Lomustine (Control)
  - N=48-56
M14-483 (EORTC-1410-BTG): Eligibility

• Major Inclusion Criteria
  • Histologically confirmed \textit{de novo} glioblastoma (primary) with unequivocal first progression after RT concurrent/adjuvant temozolomide chemotherapy
  • EGFR amplification required
  • Age $\geq$ 18 years
  • WHO Performance status 0 – 2
  • No current or recent (within 4 weeks before randomization) treatment with another investigational drug
  • No prior treatment with nitrosoureas
  • No prior treatment with bevacizumab
  • No previous exposure to EGFR targeted agents, including EGFRvIII targeting agents
M14-483: Statistical Considerations

**Interim Futility Analysis: PFS**
- Based on data available at month 9
- ~90 patients enrolled, 30 per arm
- ~42 PFS events in 3 arms (18:13:13)
- Futility boundary HR = 0.9
- Assumes a true PFS HR = 0.54, mPFS = 2.6 months

<table>
<thead>
<tr>
<th>Futility cutoff (stop the arm if PFS HR is higher than the threshold)</th>
<th>True PFS hazard ratio</th>
<th>Probability of continuing at futility interim (%)</th>
<th>Power for the final analyses of OS (%)</th>
<th>Overall study power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>0.54</td>
<td>93</td>
<td>83</td>
<td>77</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>39</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Primary Endpoint: Overall Survival Analysis**

- Total N=240 (assume a 5% drop out rate)
- 10/pts/month enrollment in first 12 months, 20/pts/months after
- 7 months mOS for the control
- Hochberg procedure to test OS endpoint in the final analyses for the comparisons 2 vs 1 and 3 vs 1
  (Note the power calculation is based on the bonferroni adjustment to be conservative)

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>Total duration</th>
<th>HR</th>
<th>N/Ne (for 2 arms)</th>
<th>Power</th>
<th>Alpha (1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>31</td>
<td>0.54</td>
<td>160/107</td>
<td>0.83</td>
<td>0.0125</td>
</tr>
</tbody>
</table>
M13-813 Study Design: Phase II/III Newly Diagnosed GBM

Phase II study scheme

**Patient Population**
- Histologically confirmed de novo glioblastoma (primary) or gliosarcoma
- Tumor demonstrates EGFR amplification by central testing
- ECOG Score 0 – 2
- Initiation of chemoradiation within 5 weeks of diagnosis
- Baseline MRI within 72 hours post-op.

**Endpoints**

- **Primary Objective**
  - PFS
- **Secondary Objectives**
  - OS
  - RANO Response
  - PFS and OS in the EGFRvIII Population
  - QOL, WHO PS
  - Neurocognitive function
  - Steroid Use
  - Safety

**Arm A: RT/TMZ**
- N = ~120

**Arm B: RT/TMZ + ABT-414**
- N = ~120

**Stratification Factors:**
- RPA class
- Region of the world
- MGMT methylation
- EGFRvIII

1:1 Randomization
Placebo controlled
M13-813 Study Design: Phase III Study Schema

Patient Population
- Histologically confirmed de novo glioblastoma (primary) or gliosarcoma
- Tumor demonstrates EGFR amplification by central testing
- ECOG Score 0 – 2
- Initiation of chemoradiation within 5 weeks of diagnosis
- Baseline MRI within 72 hours post-op.

Endpoints
- Primary Objective
  OS
- Secondary Objectives
  PFS
  RANO Response
  PFS and OS in the EGFRvIII Population
  QOL, WHO PS
  Neurocognitive function
  Steroid Use
  Safety

Stratification Factors:
- RPA class
- Region of the world
- MGMT methylation
- EGFRvIII

Arm A: RT/TMZ
- 1:1 Randomization
- Placebo controlled
- N = ~360 (total including phase II)

Arm B: RT/TMZ + ABT-414
- N = ~360 (total including phase II)

# of sites: ~175 worldwide for a target recruitment of 30 subjects/mo.
Conclusions

• Antibody drug conjugates are a novel class of oncology compounds

• Key attributes
  – Tumor specific delivery
  – Diminish systemic/non-specific toxicities
  – May enhance outcome when used in combinatorial regimens

• Key concerns
  – Delivery (large molecules)
    • Despite this concern, efficacy established in solid and hematologic malignancies and encouraging radiographic responses noted in GBM
  – Acquired resistance

• Further clinical trials are warranted