Phase 1 Safety, Pharmacokinetics & Efficacy of ABT-414 in Subjects With Glioblastoma

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ABT-414 is an investigational drug that is not approved by the FDA. Safety and efficacy have not been established.
ABT-414: ADC Comprised of EGFR-Targeting Ab, ABT-806

Rationale for ABT-414

- EGFR is a validated oncology target
- Normal tissue expression prevents the use of most EGFR Abs for payload delivery
- ABT-806 enables selective toxin delivery
  - Tumor-specific binding demonstrated preclinically and clinically
  - Expected to minimize normal tissue damage
- MMAF payload may circumvent resistance to EGFR inhibitors
Properties of ABT-806

- Distinct epitope from cetuximab
- Binds activated wild-type EGFR when the receptor has undergone a conformational change
  - Epitope minimally exposed on normal tissue
  - Takes advantage of increased surface expression of EGFR in specific tumors
- Also has high affinity for EGFRvIII (EGFRde2-7) truncated mutant
- No EGFR skin rash observed with ABT-806 doses up to 24 mg/kg, but insufficient tumor activity
**ABT-414 Combines Potent Cytotoxin with Selectivity of ABT-806**

**ABT-414** =

**ABT-806**

+ mcMMAF Toxin

- Maleimide caproyl (mc) linker
  - Stable, non-cleavable
- Monomethylauristatin F (MMAF) toxin
  - Microtubule toxin \( \rightarrow \) bypasses EGFR signaling pathway
  - Not membrane permeable \( \rightarrow \) Low potential for bystander effect
Glioblastoma (GBM)

• Primary brain tumors account for ~2% of adult tumors in US and EU
  — Most common primary brain tumor in adults (peak age 55-65 yr)

• GBM classified as grade IV (most malignant) brain cancer

• Characterized by:
  — Rapid tumor growth
  — Heterogeneity and molecular complexity
  — Debilitating neurological symptoms
  — Poor survival rates:
    1L OS ~14 month
    2L OS ~ 7 month

• SOC: Surgery, then RT/temozolomide (TMZ) (6 weeks) + adjuvant TMZ (6 – 12 months)

• GBM has highest rate of EGFR overexpression, amplification
ABT-414 Data in Mouse Models of Glioblastoma

Patient-derived (PDX) glioblastoma cells

Wild-Type EGFR

EGFRvIII

![Graphs showing tumor volume over days for Wild-Type EGFR and EGFRvIII with ABT-414 treatment compared to control.](image)
ABT-414 Synergizes with TMZ and Radiation Therapy in EGFRvIII GBM Tumor Model

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

Graph showing the mean tumor volume ± S.E.M. (mm³) over days post cell inoculation with different treatments.
Backbone Ab of ABT-414 (ABT-806) Binds to Intracranial Tumors

Phase 1 Trial Results Evaluating $[^{111}\text{In}]$ ABT-806 (ABT-806i) as an Imaging Agent

Demonstration of specific uptake of ABT-806i into active GBM tumor

6 days post-ABT-806i infusion
ABT-806z Intracranial Binding with PET
ABT-414 Patient Selection/ Companion Diagnostic Strategy in GBM

Genetic Biomarkers

- ~60% overexpress EGFR
- ~40-50% harbor EGFR gene amplification
- 25-35% express EGFRvIII
  - EGFRvIII mRNA is detected almost exclusively in patients with EGFR amplification

Strategy

- Assays developed to detect EGFR amplification and EGFRvIII
**Objectives:**

**Primary:** safety and PK profile, MTD, RPTD

**Secondary:** preliminary efficacy (ORR, PFS), assessment of tumor biomarkers

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**Arm A: RT/TMZ + ABT-414**

- Newly diagnosed GBM

RPTD = 2 mg/kg with RT/TMZ

= 1.25 mg/kg with adjuvant TMZ

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**Arm B: TMZ + ABT-414**

1. Recurrent GBM
2. Newly diagnosed GBM after initial RT/TMZ

RPTD = 1.25 mg/kg with TMZ

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**Arm C: ABT-414**

Recurrent GBM

RPTD = 1.25 mg/kg as monotherapy

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**Arm A: expanded cohort @ RPTD**

(15 – 20 patients)

**Arm B: expanded cohort @ RPTD**

(50 EGFR-amplified patients)

**Arm C: expanded cohort @ RPTD**

(50 EGFR-amplified patients)

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GBM, glioblastoma; MTD, maximum tolerated dose; ORR, objective response rate; PK, pharmacokinetics; RPTD, recommended phase 2 dose; RT, radiation therapy; TMZ, temozolomide; Tx, treatment
M12-356: ABT-414 Pharmacokinetic Profiles

- ABT-414 demonstrated dose-proportional PK over 0.5 to 3.2 mg/kg dose range
- Low PK variability (CV < 25%)
- Majority of circulating total ABT-806 antibody in blood was ABT-414
- Circulating cys-mcMMAF level was > 500-folder lower than ABT-414 on a molar concentration basis
- The half-lives of ABT-414, total ABT-806 and cys-mcMMAF are 7, 9 and 4 days, respectively
# Phase 1 ABT-414 Safety Data – Treatment-Emergent Adverse Event in ≥ 15% of Subjects

(through April 29, 2015)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>ABT-414 Monotherapy</th>
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<tr>
<td></td>
<td>M13-379 (N=54)</td>
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<td>n (%)</td>
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<td>M12-356 Arm C (N=42)</td>
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<td></td>
<td>M12-356 ABT-414 + TMZ + Radiation (N=45)</td>
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<tr>
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<td>Total ABT-414 (N=181)</td>
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<td>Vision blurred</td>
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<td></td>
<td>25 (59.5)</td>
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<td>29 (64.4)</td>
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<td>11 (26.2)</td>
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<td>53 (29.3)</td>
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<td>28 (15.5)</td>
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*TMZ = temozolomide*
Dose-related eye toxicity was the dose-limiting toxicity for all groups in Ph1.
Hypothesized mechanism: Transient Amplifying Cell death -> corneal epithelial microcysts -> symptoms.
Other ADC programs are reporting similar findings as ABT-414 studies.
Microcystic Keratopathy – Clinical Presentation

• Both eyes typically affected

• Symptoms develop 7 – 28 days from 1st ABT-414 infusion
  – Blurred vision
  – Photophobia
  – Foreign body sensation
  – Dry Eye
  – Eye Pain

• Symptoms are reversible, generally resolving by 4 – 6 weeks

• Dose interruption, dose reductions generally enable subjects to continue treatment
## Attempts to Improve Therapeutic Index for ABT-414

<table>
<thead>
<tr>
<th>Dose schedule</th>
<th>• Different dosing schedules (q3wk, q2wk, or 2 wks on/1 wk off) do not clearly alter ocular AE incidence or severity (at equivalent avg. weekly doses)</th>
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</thead>
<tbody>
<tr>
<td>Drug-antibody ratio</td>
<td>• Decreasing the <em>average</em> DAR from ~4 to ~3 by removing DAR8, DAR6 species. No significant impact</td>
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</tbody>
</table>
| Ocular Steroid Prophylaxis | • Based on experience with high-dose cytarabine  
• Prophylactic steroid eye drops mitigate but do not prevent |
| Supportive Care | • Lubricant eye drops decrease shearing force on eye  
• Sunglasses improve photophobia  
• Bandage contact lenses have been very helpful for improving symptoms (eye discomfort, blurred vision, photophobia)  
• Punctal plugs used in some cases to decrease outflow of tears |
Best percentage change in tumor size for evaluable patients – EGFR-amplified, recurrent GBM

9/62 patients (15%) displayed confirmed response

GBM, glioblastoma; EGFR, epidermal growth factor receptor; TMZ, temozolomide
Best overall response and study duration – EGFR-amplified, recurrent GBM

Best objective responses (as determined by the investigator)

• Arm B: 3 PR
• Arm C: 1 CR, 3 PR

Duration of overall response (50th percentile)

• Arm B: 7.6 months
• Arm C: 6 months
FISH assay for EGFR amplification chosen for patient selection

FISH assay was best predictor of tumor response:

- All confirmed responses (PR/CR) were in EGFR-amplified subjects
  - Responses seen in both wt EGFR and EGFRvIII mutant
- Regulators have agreed with use of EGFR FISH for subject selection

*Patients with a response (PR or CR)
2L GBM Phase 2 Study (Intellance 2)

Patient Population

- Histologically confirmed *de novo* glioblastoma (primary) with unequivocal first progression after RT concurrent/adjuvant chemotherapy
- Tumor demonstrates EGFR amplification
- No more than one line of chemotherapy (adjuvant temozolomide chemotherapy is considered one line of chemotherapy)

Endpoints

1:1:1 Randomization
Open Label

- Arm 1: ABT-414 + TMZ
  - N = 80
- Arm 2: ABT-414
  - N = 80
- Arm 3: TMZ or Lomustine*
  - N = 80

*If < 3 months to recur = lomustine
If > 3 months to recur = TMZ

Primary Objective
Overall Survival

Secondary Objectives
- PFS
- RANO Response Rate
- OS / PFS / Response in the EGFRvIII Population
- QoL, KPS
- Safety
- Steroid Use

Stratification Factors:
- WHO PS
- Region of the World (US vs. EU vs. Asia/others)
- Time at Recurrence (< 4 months vs. ≥ 4 months after last TMZ cycle)
**1L GBM Phase 2/3 Study (Intellance 1)**

**Patient Population**
- Histologically confirmed *de novo* GBM
- EGFR amplification
- Chemoradiation therapy start within 6 weeks of surgery
- Baseline MRI within 72 hours post-op
- Karnofsky Performance Score ≥ 70

**Endpoints**
- **Primary Objective**
  - Overall Survival (OS)
- **Secondary Objectives**
  - Progression-Free Survival (PFS)
  - OS / PFS in EGFRvIII subgroup
  - Time to deterioration in:
    - Cognitive performance (CTB-comp)
    - Symptoms severity (MDASI-BT)
    - Symptom interference (MDASI-BT)

**1:1 Randomization Placebo-controlled**

**Stratification Factors**
- EGFRvIII status
- MGMT methylation status
- RPA (recursive partitioning analysis) score
- Region of World (NA vs. ROW)

**RT/TMZ + PBO**

**RT/TMZ + ABT-414**

**Ph2 Interim analysis by IDMC at 129 PFS events**

N = 360