Development of a brain-penetrant EGFR inhibitor and non-invasive predictive biomarker of response for glioblastoma

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David Geffen School of Medicine at UCLA
Disclosures

- Co-Founder and Shareholder
  - Katmai Pharmaceuticals, Trethera Corporation

- Shareholder
  - Sofie Biosciences

- Contracted Research/MTA/Consulting Agreements
  - Abbvie
  - Roche
  - Sanofi
  - Astra Zeneca
  - Erasca
Glioblastoma (GBM): A universally fatal malignancy

Median survival: ~15 months

Standard of Care
Surgery/Chemo/Radiation

Targeted Therapy
Checkpoint blockade
CARs
Vaccine (e.g., EGFRvIII)

Immunotherapy
No improvement over SoC
Too early, yet ‘signal’ only in minority of patients

Steka B, *Scientific American*, March 2019
The epidermal growth factor receptor (EGFR) is frequently altered in GBM.
EGFR tyrosine kinase inhibitors (TKIs) have failed for GBM patients

<table>
<thead>
<tr>
<th>NSCLC or Breast Cancer</th>
<th>Glioblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapy</strong></td>
<td><strong>Clinical Trial</strong></td>
</tr>
</tbody>
</table>


EGFR TKIs – designed for non-CNS cancer - have low brain penetration

<table>
<thead>
<tr>
<th>Compound (Brand Name)</th>
<th>Company</th>
<th>Penetration Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afatinib (Gilotrif)</td>
<td>Boehringer Ingelheim</td>
<td>0.7</td>
</tr>
<tr>
<td>Erlotinib (Tarceva)</td>
<td>Genentech</td>
<td>8</td>
</tr>
<tr>
<td>Gefitinib (Iressa)</td>
<td>AstraZeneca</td>
<td>1.1</td>
</tr>
<tr>
<td>Lapatinib (Tykerb/Tyberb)</td>
<td>GlaxoSmithKline</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Vivanco et. al., Can Discov, 2012.
Intracranial GBM fail to recapitulate responses to EGFR TKIs in subcutaneous models.
The type of EGFR alteration impacts EGFR TKI affinity

Vivanco et. al. *Cancer Discovery* 2012
Graphic adapted from Gomez et. al., *Cancer Biology & Medicine* 2013
In patients with ECD mutations (e.g., EGFRvIII), both amplified Wild-Type EGFR and EGFRvIII are highly expressed.
Need for BBB penetrant EGFR TKI to target both EGFRvIII and amplified wild-type EGFR

An ideal EGFR TKI for GBM:

<table>
<thead>
<tr>
<th>Property</th>
<th>Available EGFR TKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target EGFRvIII</td>
<td>Lapatinib, Neratinib</td>
</tr>
<tr>
<td>Target Amplified EGFR</td>
<td>Erlotinib, Gefitinib</td>
</tr>
<tr>
<td>Brain Penetrant</td>
<td>Tagrisso (30%)</td>
</tr>
</tbody>
</table>

- Lapatinib, Neratinib: Target EGFRvIII
- Erlotinib, Gefitinib: Target Amplified EGFR
- Tagrisso (30%): Brain Penetrant

Tim Cloughesy, MD  
Professor (Neurology/Pharm)

- Led ~100 clinical trials in brain tumors, 10 EGFR-directed
- Involved in development of multiple drugs of various classes (e.g., small molecules, antibody

Michael Jung, PhD  
Distinguished Professor (Chemistry, Pharm)

- Co-Inventor of 2 FDA approved cancer therapies (Xtandi, Erleada)
- Founder, Trethera
Improved BBB penetrating properties of ERAS-801

<table>
<thead>
<tr>
<th>Property</th>
<th>Optimal for BBB penetration</th>
<th>FDA Approved EGFR TKI</th>
<th>ERAS-801</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotatable Bonds</td>
<td>≤5</td>
<td>✗</td>
<td>✔</td>
</tr>
<tr>
<td>Lipophilicity (clogP)</td>
<td>≤4</td>
<td>✗</td>
<td>✔</td>
</tr>
<tr>
<td>H-Bond Donors</td>
<td>≤4</td>
<td>✗</td>
<td>✔</td>
</tr>
<tr>
<td>H-Bond Acceptors</td>
<td>≤5</td>
<td>✗</td>
<td>✔</td>
</tr>
<tr>
<td>Polar Surface Area (Å$^2$)</td>
<td>≤80</td>
<td>✗</td>
<td>✔</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>≤400</td>
<td>✗</td>
<td>✔ ($\leq$500)</td>
</tr>
</tbody>
</table>
ERAS-801 shows high unbound brain exposures
ERAS-801 has potent activity against activated WTEGFR
ERAS-801 is potent against EGFRvIII

- Erlotinib (15.24nM)
- Lapatinib (4.14nM)
- Tagrisso (17.65nM)
- ERAS-801 (2.50nM)
ERAS-801 is specific for EGFR

Primary Screen of ~490 WT and mutant kinases @ 10µM ERAS-801

15 "hits" (>50% inhibition at 10µM)

Full IC50 of "hits"

EGFR
HER2
LYN B
LYN A
HER4
RIPK3
GAK
EPHB2
RIPK2
DRAK1
FGR
YES1
EPHA6
LCK
EPHB4

0
1
2
2000
4000
Kinases
IC50 (nM)

0
1
2
0.454nM
200nM

UCLA Health
Brain Tumor Center
ERAS-801 is potent against EGFR altered patient derived GBM cells with negligible activity against normal brain cells.
ERAS-801 significantly extends EGFRvIII PDX survival at **clinically relevant exposures**
# A Preclinical Trial of ERAS-801

## GBM patient derived models

<table>
<thead>
<tr>
<th>Tumor Recurrence</th>
<th>Patient Sex</th>
<th>MGMT Methylation</th>
<th>Molecular Subtype</th>
<th>EGFRvIII</th>
<th>Copy Number</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prima</td>
<td>Male</td>
<td>No</td>
<td>Classical</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Recurrent</td>
<td>Female</td>
<td>Yes</td>
<td>Protonal</td>
<td>NA</td>
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## Short-Term Goals (n=40-50 unique models)

1) **To define the breadth of response across molecularly heterogeneous models**

2) **To define the molecular determinants of response**

### Vehicle/ERAS-801

n=6-8 mice/treatment
ERAS-801 improves outcome of >90% of EGFR mutant and/or amplified GBM PDXs.
Challenge for Clinical Translation in GBM – How do we know drug is reaching the tumor and having a meaningful biological effect

1. Does the drug reach the target?

2. Is target sufficiently inhibited to modify downstream signaling?

3. Is downstream signaling adequately modulated to elicit a clinical effect?
GBM tumor metabolism is regulated by aberrant EGFR signaling

Mai et al., *Nature Medicine* 2017
Babic et al., *Cell Metabolism* 2013
Rapid dynamics in FDG PET may serve as a non-invasive biomarker for biologically meaningful inhibition of EGFR signaling.
ERAS-801 can robustly inhibit intracranial EGFR signaling at predicted clinically relevant doses.
Dose dependent changes in FDG is associated with dose dependent change in EGFR signaling with ERAS-801

**Vehicle**

- Coronal
- Sagittal

**3 mg/kg**

- Coronal
- Sagittal

**25 mg/kg**

- Coronal
- Sagittal

72 hour $^{18}$FDG-PET

![Graph showing mean ROI change (%) for different doses.](image-url)
ERAS-801 induced changes in FDG uptake predict outcome in an orthotopic EGFR altered GBM PDX
Same PDX model: FDG PET delineates ineffective EGFR TKIs compared to ERAS-801 all administered at equivalent dose.
Summary

• EGFR is genetically altered in ~60% of GBM patients, yet available EGFR TKI have failed in GBM clinical trials
  - Failure due to 1) insufficient BBB penetration and 2) inability to potently inhibit all oncogenic forms of EGFR found in GBM, including amp WT EGFR and ECD mutants

• ERAS-801 has high BBB penetration (Kpuu: 1.2) and potently inhibits both ECD mutant EGFR (e.g., EGFRvIII) and amplified WT EGFR

• In GBM PDX preclinical trial, ERAS-801 extends survival of >90% of EGFR-altered patient derived orthotopic GBM xenografts with negligible side effects

• FDG PET may serve as a robust, non-invasive biomarker of meaningful target inhibition with ERAS-801

ERAS-801
370% Brain Penetrant (Kpuu:1.2)
EGFRvIII IC50: 2.5nM
EGFR IC50: 1.2nM
Acknowledgment

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- R01 CA227089 (PI: NATHANSON)
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- National Brain Tumor Society (NBTS)
- Uncle Kory Foundation
- Erasca