How Do Research Ideas Make It In To The Clinic?

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Global PI GBM AGILE
Disclosures
I have the following financial relationships to disclose:

**Consultant for:** Trizel, Medscape, Bayer, Amgen, Odonate Therapeutics, Pascal Biosciences, Bayer, Del Mar Pharmaceuticals, Tocagen, Karyopharm, GW Pharma, Kiyatec, Abbvie, Boehinger Ingelheim, VBI, Deciphera, VBL, Agios, Merck, Roche, Genocea, Celgene, Puma, Lilly, BMS, Cortice, Wellcome Trust, Novocure, Novogen, Boston Biomedical, Sunovion, Human Longevity, Insys, ProNai, Pfizer, Notable labs, Medqia

**Stockholder in:** Stock options for Notable Labs

**Board Member for:** Global Coalition for Adaptive Research

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**Patents:** U.S. Provisional Application No.: 62/819,322

**Title:** COMPOSITIONS AND METHODS FOR TREATING CANCER
UCLA Neuro-oncology therapeutic development pipeline

Preclinical Translational Labs

Target & Drug Discovery
- Target Identification
  - Genomics, cell culture, functional assays
  - Medicinal chemistry (Pharma Drugs, UCLA development)
- Proof-of-Concept
  - Patient-derived GliomaPDX Models
  - Molecular Imaging (PET)

Efficacy in GBM in vivo models
- IND enabling and Phase I Studies
  - Create safe drug for humans
  - Dose escalation studies in humans

Drug is safe

Drug does something of value to a patient

Drug has improved value over standard

Clinical

Phase II
- Single Arm randomized trial

Phase III

300 million US$: 6 - 8 years

1.5 to 3 Billion US$: 10-17 years

Phase Ib/early Phase II
- Repurposed drug
- Drug Brain PK/PD
Somatic mutation at R132(tumor not germline)  
- R132H most common  
- Hemizygous  
- Common in secondary glioblastoma  
- Associated with younger age at diagnosis  
- Associated with improved outcome

Mutant IDH1/2 produces D-2-HG (R(-)-2-HG) indicating ‘Gain-of-Function’


Ward et al, Cancer Cell (2010) 17(3), 225-34

Elevated 2-HG may have many roles in promoting tumors

- 2-HG inhibits α-KG dependent dioxgenases

IDH Mutation is Common in Low Grade (II and III) Glioma

• IDH1m+ highly prevalent:
  • 5% primary GBM
  • 83% secondary GBM
  • 60-80% of low grade diffuse glioma
• IDH2m+ are uncommon

Molecular Classification Improves Low Grade Glioma Classification

- Molecular understanding of LGG and prognostic implications have recently been described
- 3 molecular classes of LGG: More concordant with IDH, 1p/19q, and TP53 status than with histologic class
- LGG with an IDH mutation either had 1p/19q codeletion or a TP53 mutation

![Graph showing survival by histologic class and molecular subtype]

- A: Gliomas Classified According to Histologic Class and Grade
- B: Gliomas Classified According to Molecular Subtype

P<0.001 by log-rank test
IDH/1p19q is predictive for addition of chemotherapy in AG: RTOG 94-02

Potential therapeutic target in IDH-mutant Gliomas

- Mutant IDH enzyme: IDHmt inhibitors (AG120, AG881 and DS-1001b)
- DNA Hypermethylation: Histone deacetylase inhibitors/DNA demethylating agents
- Depletion of NAD: inhibitors of NAMPT
- Genome instability: DNA damaging agents or agents interfering with DNA repair
- Oxidative mitochondrial metabolism dependence:
  - Glutaminase inhibition:
  - HIF-1α:
  - mTOR signaling:
  - 2HG immune suppression
UCLA Neuro-oncology therapeutic development pipeline

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Phase Ib/early Phase II
- Repurposed drug
- Drug Brain PK/PD

300 million US$: 6 - 8 years

- Drug does something

1.5 to 3 Billion US$: 10-17 years
Clinical Development: Standard Early Phase Development

**Early Stage**

- **Dose escalation phase**
  - Cohort 5: N = 7
  - Cohort 4: N = 6
  - Cohort 3: N = 3
  - Cohort 2: N = 6
  - Cohort 1 qd: N = 3

- **Dose confirmation phase**
  - MTD
  - Pt enrollment: N = 20

- **Disease specific expansion cohort**
  - Pt enrollment: N = 40
Efficacy not recognized in Patients with CE tumor
7/25/13 – Historic #1
8/7/14 – Historic #2
10/26/15 - Screening
12/29/15 – Cycle #3
2/25/16 – Cycle #5
4/21/16 – Cycle #7
6/16/16 – Cycle #9
8/11/16 – Cycle #11
10/6/16 – Cycle #13
12/1/16 – Cycle #15
1/26/17 – Cycle #17
3/23/17 – Cycle #19
5/18/17 – Cycle #21
7/12/17 – Cycle #23
9/7/17 – Cycle #25
11/2/17 – Cycle #27
12/21/17 – Cycle #29
7/25/13 – Historic #1
8/7/14 – Historic #2
10/26/15 - Screening
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3/23/17 – Cycle #19
5/18/17 – Cycle #21
7/12/17 – Cycle #23
9/7/17 – Cycle #25
11/2/17 – Cycle #27
12/21/17 – Cycle #29
XRT and chemotherapy provide durable tumor control in IDHmt/codeleted AO with long term cognitive consequences

Patient with a IDHmt codeleted Right Frontal Lobe AO

Health-related quality of life and cognitive functioning in long-term anaplastic oligodendroglioma and oligoastrocytoma survivors

Esther J. J. Habets · Martin J. B. Taphorn · Sylvie Nederend · Martin Klein · Daniel Delgalillo · Khé Hoang-Su · Andrew Bottomley · Anouk Allgeier · Tatjana Seute · Anja M. M. Gijtenbeek · Jean de Cans · Roelien H. Ewling · Crees C. Tijsen · Martin J. van den Bent · Jaap C. Reijneveld

Patient progression free:
81% live independently
41% employed
30% severely cognitively impaired
Clinical Development: Standard Early to Late Stage Development in Neuro-Oncology

**Early Stage**
- Dose escalation phase
  - Cohort 5: N = 7
  - Cohort 4: N = 6
  - Cohort 3: N = 3
  - Cohort 2: N = 6
  - Cohort 1 qd: N = 3

**MTD** → **Pt enrollment** N = 20

**Late Stage**
- Disease specific expansion cohort
  - Single arm Phase II
    - N = 40-60
- Phase II/III evaluations
  - Randomized Phase II
  - Randomized Phase II/III
  - Randomized Phase III

**Endpoints**
- ORR
- PFS
- OS
Clinical Development: Standard Early to Late Stage Development in Neuro-Oncology

- Non enhancing grade II IDH mutated glioma
- Randomize
  - IDH inhibitor → PFS
  - Placebo → PFS
  - IDH inhibitor → ORR
  - PFS
Clinical Development: Standard Early Phase Development

Early Stage

Dose escalation phase

Cohort 1 qd
N = 3

Cohort 2
N = 6

Cohort 3
N = 3

Cohort 4
N = 6

Cohort 5
N = 7

MTD

Dose confirmation phase

Pt enrollment
N = 20

Disease specific expansion cohort

Pt enrollment
N = 40
Clinical Development: Standard Early to Late Stage Development in Neuro-Oncology

- **Early Stage**
  - Dose escalation phase
    - Cohort 1 qd N = 3
    - Cohort 2 N = 6
    - Cohort 3 N = 3
    - Cohort 4 N = 6
    - Cohort 5 N = 7
  - MTD
  - Pt enrollment N = 20

- **Late Stage**
  - Disease specific expansion cohort
    - Single arm Phase II N = 40-60
  - Phase II/III evaluations
    - ORR
    - PFS
    - OS
    - Randomized Phase II
    - Randomized Phase II/III
    - Randomized Phase III
GBM Development has many lengthy, costly (knowable?) failures

<table>
<thead>
<tr>
<th>Experimental</th>
<th>Indication</th>
<th>Phase II-phase III time</th>
<th>Phase III N</th>
<th>Phase II N</th>
<th>Phase II endpoint</th>
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<td>Cilengitide</td>
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<tr>
<td>Bevacizumab</td>
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Courtesy of Brian Alexander
## Reasons for single arm trial variability when using continuous endpoint (PFS, OS)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Description</th>
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<tr>
<td>TUMOR SIZE</td>
<td>Over-estimate of OS, mOS = 9.8 vs 10.0, HR = 1.04 [95% CI: 0.83, 1.30], P = 0.76</td>
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<td>IDH WT</td>
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<td>IDH MUTATION</td>
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<tr>
<td>METHYLATED MGMT</td>
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<td>IMMUNE TX</td>
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<td>PSEUDOPROGRESSION</td>
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<td>SINGLE CENTER</td>
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<td>SURGICAL RESECTION</td>
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<tr>
<td>UNICENTRIC</td>
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</tr>
</tbody>
</table>

**Overall Survival**

- mOS = 9.8 vs 10.0
- HR = 1.04 [95% CI: 0.83, 1.30]
- P = 0.76

**Median Survival in Months**

- 0 1 2 3 4 5 6 7 8 9 10 11 12
Reasons for single arm trial variability when using continuous endpoint (PFS, OS)

**Under-estimate**
- > TUMOR SIZE
- < KPS
- > STEROIDS
- > PROGRESSION #
- > AGE
- IDH WT
- MGMT U
- ANTIANGIOGENESIS TX
- MULTIPLE CENTERS
- MULTICENTRIC TUMOR

**Over-estimate**
- < TUMOR SIZE
- > KPS
- < STEROIDS
- < PROGRESSION #
- < AGE
- IDH MUTATION
- METHYLATED MGMT
- IMMUNE TX
- PSEUPOPREGRESSION
- SINGLE CENTER
- SURGICAL RESECTION
- UNICENTRIC

mOS= 7.4 vs 5.6 months
HR= 0.50, p = 0.0007
Standard protocol would allow for trials to be run in parallel: faster results.

- CONTROL
- DRUG A
- VS
- CONTROL
- DRUG B
- CONTROL
- DRUG C
- CONTROL
- DRUG D
- CONTROL
- DRUG E
Master protocol: provides additional efficiencies (especially if harmonization of endpoints)
SUBTYPES
SUBTYPES
STAGE 1
Fixed Randomization

STAGE 2
Fixed Randomization

NDA
Fixed Randomization

Adaptive Randomization

STAGE 1

Control

Drug A

Drug B

Drug C

Drug D

Drug E

STAGE 2

Fixed Randomization

NDA

Drug A

Drug B

Drug C

Drug D

Drug E

.20

.16

.00

.36

.08

.20
Fixed Randomization

Adaptive Randomization

STAGE 1

STAGE 2

Fixed Randomization

NDA FOR PATIENT POPULATION WITH DRUG C

NDA
GBM AGILE: Value to Drug Makers

• De-Risk (faster, cheaper)
  • Create a Master protocol with shared control and shared infrastructure
  • Infrastructure designed to shorten timelines
  • Use Bayesian statistics to right size trial (Fail early, Win Early)
  • Used for variety of development opportunities (1st to market, expanding indications)
  • Cost savings encourages involvement in orphan disease

• Innovate
  • Regulatory interest in these endeavors: seen as the future of clinical trials
  • Borrow across multiple signatures (possible indications) to increase power
  • Empower ability to ask biomarker questions (CDx)
  • For significant effect size allow for NDA with regulators
GBM AGILE: Value to Drug Makers (Cont.)

- Capitalize on a Win
  - Evaluate Multiple possible indications
  - Evaluate in multiple countries simultaneously
  - Establishing New controls
  - Opportunity for Rational Combinations
- International regulatory alignment
GBM AGILE: Value to Patients and Advocates

• Access
  • Multiple therapies available
  • Offered at many sites, potentially reducing travel distance

• Opportunity for continuous improvement
  • Trial becomes Standard of Care

• Precision Medicine
  • More likely to get most beneficial treatment for patient subtype today

• Design informed by patients and advocates
  • Disease centric not drug centric
  • Patient-centric trial design informed by patient and caregiver input
  • Shared control group
  • Faster to fail and faster to market
GBM AGILE: Value to Academics and Physicians

- Provides Late Stage Clinical Trial Portfolio
  - Less bias toward what is thought to be better drug
- Leadership Opportunities
  - Lead late stage development of therapy
  - Broader international community interactions/engagement
- Opportunities for Continuous learning
  - Massive, longitudinal, highly annotated data set (imaging, outcomes, biomarkers) available to community of investigators
STANDARD TRIAL: 3 populations (1stLM, 1stLU, R), frequentist statistics, half of the patients are controls, multiple countries, 1500 patients = $250 Million dollars

FASTER: 5 trials run in parallel; data available faster but 7500 patients (half controls) = $1.25 Billion dollars

GBM AGILE: Master protocol; Many arms; common control (20% of pop) Bayesian adaptive randomization; Multiple countries 1200 (Max) patients = $125 Million dollars With 5 experimental arms

Faster, cheaper, less patients, lower development cost = lower consumer costs
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  - Disease specific expansion cohort
  - Pt enrollment: N = 40
  - ORR
  - PFS
  - OS
  - Phase II/III evaluations

- **ORR**
- **PFS**
- **OS**