Novel Targets And Strategies in Glioblastomas

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DISCLOSURES

• **Research Support**
  - Amgen
  - Astra Zeneca
  - Boehringer Ingelheim
  - Esai
  - Exelixis
  - Genentech/Roche
  - Geron
  - Medimmune
  - Merck
  - Novartis
  - Sanofi-Aventis
  - Vascular Biogenics

• **Advisory Board**
  - Merck
  - Novartis
  - Vascular Biogenic
  - NeOnc Inc

• **Speaker**
  - Merck
  - Genentech/Roche
Treatment of High-Grade Gliomas
Milestones in Neuro-Oncology

Approvals

Radiotherapy
- Lomustine
- Carmustine

1970
- First US commercial CT

1980
- Levin criteria: CT scans
- First US commercial MRI

1990
- Macdonald criteria: MRI + steroids; WHO Pathology Criteria
- Gliadel wafer
- TMZ up front for GBM

2000
- TMZ for relapsed AA accelerated approval
- Brain Tumor Clinical Trial Endpoints Workshop

2010
- Avastin for recurrent GBM
- RANO Criteria
- ASCO Workshop

Technology Advances

AA=anaplastic astrocytoma; CT=computed tomography; GBM=glioblastoma multiforme; MRI=magnetic resonance imaging; RANO=Response Assessment in Neuro-Oncology.
 THERE IS NEW AMMUNITION
IN THE WAR AGAINST
CANCER.
 THESE ARE THE BULLETS.

Revolutionary new pills like GLEEVEC
combat cancer by targeting only the
diseased cells. Is this the breakthrough
we've been waiting for?
Outline

• Issues
• New therapies and targets
• New approaches to trial design
Reasons for Lack of Progress in Targeted Molecular Therapies in Glioblastomas

- Poor models
- Blood-brain barrier
- Co-activation of tyrosine kinases
- Redundant signaling pathways
- Spatial and temporal heterogeneity
- Failure to genetically enrich patient population
- Stem cells
Bypassing The Blood Brain Barrier

Endothelial cells forming the BBB:
- Express tight junctions
- Lack fenestra
- Lack transendothelial channels
- Lack pinocytic vesicles
- High levels of active efflux proteins, Pgp
Figure 2  Transport mechanisms at the blood-brain barrier (BBB)
Connolly et al, SNO 2012

Slide courtesy of May Han, Aveo
Current Design

- Recurrent Tumor
  - PK
  - PET
  - MRI
  - Blood biomarkers

- Surgery

- Therapy
  - PK
  - PET
  - MRI
  - Blood biomarkers

- Therapy
Convection-Enhanced Delivery
Low density Lipoprotein Receptor Related Protein (LRP-1)

- Transports small and large molecules (> 40 ligands)
- One of the most expressed receptor at the surface of the BBB
- Expressed on cancer cells
- Expressed also in liver, lung and ovarian tissues

**LRP-1:** ~600kDa

\( \alpha: 515, \beta: 85 \)
Figure 3.1-1 Schematic Representation of ANG1005 Composed of Three Molecules of Paclitaxel (in Blue) with its Succinyl Linker (in Green) Conjugated to Angiopep2 (in Black)
Low density lipoprotein receptor related protein (LRP1)
Accumulation of $[^3\text{H}]$Taxol and $[^{125}\text{I}]$ANG1005

Accumulation in mouse brain with NCI-H460 tumours (lung tumour cell line)

- $[^3\text{H}]$Taxol 5 mg/kg in DMSO
- $[^{125}\text{I}]$ANG1005 10 mg/kg in Solutol HS15

Tissue distribution (μg/g of tissue)

- Normal Brain
- Tumoral Brain

10 minutes post-IV injection
# Phase I Study of GRN1005 in Recurrent Malignant Glioma

Jan Drappatz\(^1\), Andrew Brenner\(^7\), Eric T. Wong\(^3\), April Eichler\(^4\), David Schiff\(^9\), Morris D. Groves\(^8\), Tom Mikkelsen\(^10\), Steve Rosenfeld\(^11\), John Sarantopoulos\(^7\), Christina A. Meyers\(^8\), Robert M. Fielding\(^12\), Kelly Elian\(^13\), Xiaolin Wang\(^14\), Betty Lawrence\(^13\), Mona Shing\(^14\), Stephen Kelsey\(^14\), Jean Paul Castaigne\(^13\), and Patrick Y. Wen\(^1\)

## Tumor samples

<table>
<thead>
<tr>
<th>Patient</th>
<th>09-001-122(^a)</th>
<th>09-006-129(^a)</th>
<th>09-008-134(^a)</th>
<th>09-009-135(^a)</th>
<th>09-100-144(^a)</th>
<th>09-1011-146(^a)</th>
<th>09-1013-156(^a)</th>
<th>09-1028-162(^a)</th>
<th>09-1078-162(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose level</td>
<td>200 mg/m²</td>
<td>300 mg/m²</td>
<td>450 mg/m²</td>
<td>550 mg/m²</td>
<td>550 mg/m²</td>
<td>550 mg/m²</td>
<td>650 mg/m²</td>
<td>550 mg/m²</td>
<td></td>
</tr>
<tr>
<td>Extraction time</td>
<td>- 4.0 h</td>
<td>- 5.0 h</td>
<td>- 4.0 h</td>
<td>- 4.5 h</td>
<td>- 6.0 h</td>
<td>- 4.5 h</td>
<td>- 6.0 h</td>
<td>- 3.5 h</td>
<td>- 5.5 h</td>
</tr>
</tbody>
</table>

## Plasma

<table>
<thead>
<tr>
<th>GRN1005(^a)</th>
<th>Free paclitaxel</th>
<th>% Free paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>33.6 μmol/L</td>
<td>0.70 μmol/L</td>
<td>2.0%</td>
</tr>
<tr>
<td>34.1 μmol/L</td>
<td>0.34 μmol/L</td>
<td>1.0%</td>
</tr>
<tr>
<td>52.6 μmol/L</td>
<td>0.67 μmol/L</td>
<td>1.6%</td>
</tr>
<tr>
<td>59.2 μmol/L</td>
<td>1.13 μmol/L</td>
<td>1.8%</td>
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<tr>
<td>55.0 μmol/L</td>
<td>1.52 μmol/L</td>
<td>1.8%</td>
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<tr>
<td>62.5 μmol/L</td>
<td>0.44 μmol/L</td>
<td>0.7%</td>
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<tr>
<td>69.7 μmol/L</td>
<td>1.57 μmol/L</td>
<td>2.3%</td>
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<tr>
<td>120.4 μmol/L</td>
<td>2.30 μmol/L</td>
<td>1.5%</td>
</tr>
<tr>
<td>79.5 μmol/L</td>
<td>1.52 μmol/L</td>
<td>1.9%</td>
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</tbody>
</table>

## Tumor

<table>
<thead>
<tr>
<th>GRN1005(^a)</th>
<th>Free paclitaxel</th>
<th>% Free paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0 μmol/L</td>
<td>0.81 μmol/L</td>
<td>28.7%</td>
</tr>
<tr>
<td>8.5 μmol/L</td>
<td>0.90 μmol/L</td>
<td>9.6%</td>
</tr>
<tr>
<td>5.6 μmol/L</td>
<td>1.22 μmol/L</td>
<td>17.3%</td>
</tr>
<tr>
<td>22.4 μmol/L</td>
<td>0.57 μmol/L</td>
<td>2.5%</td>
</tr>
<tr>
<td>95.2 μmol/L</td>
<td>2.77 μmol/L</td>
<td>2.8%</td>
</tr>
<tr>
<td>237.6 μmol/L</td>
<td>0.60 μmol/L</td>
<td>0.3%</td>
</tr>
<tr>
<td>19.6 μmol/L</td>
<td>8.61 μmol/L</td>
<td>30.6%</td>
</tr>
<tr>
<td>18.4 μmol/L</td>
<td>0.93 μmol/L</td>
<td>4.6%</td>
</tr>
<tr>
<td>28.4 μmol/L</td>
<td>3.16 μmol/L</td>
<td>10.0%</td>
</tr>
</tbody>
</table>

### % Total Concentration in Tumor relative to Plasma

<table>
<thead>
<tr>
<th>U87 control</th>
<th>LRP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.2%</td>
<td>27.3%</td>
</tr>
<tr>
<td>13.3%</td>
<td>23.0%</td>
</tr>
<tr>
<td>17.3%</td>
<td>17.3%</td>
</tr>
<tr>
<td>37.9%</td>
<td>39.6%</td>
</tr>
<tr>
<td>15.4%</td>
<td>38.9%</td>
</tr>
</tbody>
</table>
The Hedgehog Pathway Promotes Blood-Brain Barrier Integrity and CNS Immune Quiescence

Jorge Ivan Alvarez,1* Aurore Dodelet-Devillers,1* Hania Kebir,1 Igal Ifergan,1 Pierre J. Fabre,2 Simone Terouz,1 Mike Sabbagh,1 Karolina Wosik,1 Lyne Bourbonnière,1 Monique Bernard,1 Jack van Horssen,3 Helga E. de Vries,3 Frédéric Charron,2 Alexandre Prat1†
Pulse Dosing
Differential Sensitivity of Glioma- versus Lung Cancer-Specific EGFR Mutations to EGFR Kinase Inhibitors

GBM

Lung Cancer

Vivanco et al. Cancer Discovery 2012;2:458-71
### Table

<table>
<thead>
<tr>
<th>EGFR TKI</th>
<th>KINASE BINDING</th>
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</thead>
<tbody>
<tr>
<td>Lapatinib</td>
<td>Type II (inactive conformation)</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Type I (active conformation)</td>
</tr>
</tbody>
</table>

### Diagram

The diagram shows Western blots for different EGFR mutants treated with either Erlotinib or Lapatinib at various concentrations. The blots are labeled with "WT" for wild type, and several mutants: A289D, A289V, G599V, T283P, and vIII. The blots are stained for pEGFR (Y1068) and EGFR.
Are we delivering the drugs appropriately?

- Continuous dosing versus pulse dosing
- Administer targeted drug before or after chemotherapy
- NSCLC
  - Solit et al CCR 2005;11:1983
  - Riely JCO 2009:27;264
Targeted Molecular Therapies

### Epigenetic and Biological Subgroups of Glioblastoma

<table>
<thead>
<tr>
<th>Mutations / Cytogenetics</th>
<th>DNA Methylation</th>
<th>Gene Expression</th>
<th>IHC Protein Marker</th>
<th>Age Distribution (years)</th>
<th>Tumor Location</th>
<th>Patient Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDH $^{1mut}$</td>
<td>H3F3A$^{K27}$</td>
<td>H3F3A$^{G34}$</td>
<td>PDGFRA ampl.</td>
<td>CDKN2A del.</td>
<td>CNV$^{CD}$</td>
<td>CIMP+</td>
</tr>
<tr>
<td>TP53$^{mut}$</td>
<td>TP53$^{mut}$</td>
<td>TP53$^{mut}$</td>
<td>CDKN2A del.</td>
<td>CDKN2A del.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIMP+</td>
<td>CHOP+</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proneural</td>
<td>Proneural</td>
<td>Mixed</td>
<td>Proneural</td>
<td>Mesenchymal</td>
<td>Classical</td>
<td></td>
</tr>
<tr>
<td>IDH1R153H</td>
<td>OLIG1+ / OLIG2+ / FOXG1+</td>
<td>OLIG1+ / OLIG2+ / FOXG1+</td>
<td>OLIG1+ / OLIG2+ / FOXG1+</td>
<td>OLIG1+ / OLIG2+ / FOXG1+</td>
<td>OLIG1+ / OLIG2+ / FOXG1+</td>
<td></td>
</tr>
<tr>
<td>0 30 60 90</td>
<td>0 30 60 90</td>
<td>0 30 60 90</td>
<td>0 30 60 90</td>
<td>0 30 60 90</td>
<td>0 30 60 90</td>
<td>0 60 120</td>
</tr>
</tbody>
</table>

Stum et al.  
Cancer Cell  
2012;22:425-437
Failure To Genotype Patients
Sequencing

Epigenetic Analysis

Set of activated kinases and pathways

Combinations of appropriate drugs

Ivy Foundation Early Phase Clinical Trials Consortium
DF/HCC
MSKCC
UCLA
UCSF
MDACC
U Utah
New Targets

- PI3K
- FGFR/TACC
- BRAF
- CDK4
- Wee1
PI3 Kinase Inhibitors

Growth Factors, etc

PI3K inhibitor
- XL765
- XL147
- BKM120
- PX866
- GDC0084

Proliferation
BKM120

- Oral pan-class I phosphatidylinositol-3-kinase (PI3K) inhibitor belonging to the 2,6-dimorpholino pyrimidine derivative family
- Inhibits p110α, p110β, p110δ and p110γ
- Cross the blood-brain barrier (brain/blood ratio 2)
- Taken orally once daily
- Inhibits the growth of U87MG and GBM explants in vivo
Ivy Foundation Early Phase Clinical Trials Consortium
A Phase II study of BKM120 for patients with recurrent glioblastoma and activated PI3K pathway

Cohort 1

Recruit
15 participants with recurrent GBM, PI3K pathway activation, and pAkt positive by IHC

Pre-Surgical Treatment
BKM120 100mg daily x 8 to 12 days

Surgery
Special samples and tissue processing

Post-Surgical Treatment
BKM120 100mg daily

Assess Response
CR
PR
SD
PD

Treatment
BKM 120 100mg daily until progression or unacceptable toxicity
Off Study Drug

MRI every 8 weeks

Cohort 2

Recruit
50 participants with recurrent GBM and PI3K pathway activation

Treatment
BKM 120 100mg daily

Assess Response
CR
PR
SD
PD

Treatment
BKM 120 100mg daily until progression or unacceptable toxicity
Off Study Drug

MRI every 8 weeks
BKM 120 Trial

Patient Eligibility

• Activation of PI3K pathway:
  – PIK3CA/PIK3R1 mutation or
  – PTEN mutation, loss of PET by FISH, or PTEN IHC negative

Goal

• 30 PTEN loss
• 20 PIK3CA/PIK3R1 mutants
Next Steps

• Isoform specific Inhibitors
  – ? Beta specific isoforms better for PTEN loss
  – ? Alpha specific isoforms for PI3Ca mutants
• Combinations
  – BKM120 +RT+TMZ
  – BKM120 + LDE225 (SMO inhibitor)
  – BKM120 + INC 280 (MET inhibitor)
Transforming Fusions of FGFR and TACC Genes in Human Glioblastoma


Science 2012
Phase II Trial of BGJ398 (FGFR inhibitor)

GROUP 1 (non-surgical) unresectable disease N ~24
BGJ398 125 mg p.o., q.d., 28 d cycle, 3 weeks on 1 week off

GROUP 2 (surgical), resectable disease N ~10
Pre-Surgery
BGJ398 125 mg p.o., q.d. x 5 to 10 d

SURGERY

BGJ398 125 mg p.o. q.d., 28 d cycle, 3 weeks on 1 week off
PD-0332991 (CDK 4/6 inhibitor)
Michaud et al: Cancer Res 2010;70:3228
Michaud et al: Cancer Res 2010;70:3228
LY2835219 (CDK4/6 Inhibitor)
Sanchez Martinez et al

Dose-dependent efficacy of LY2835219-MsOH in a rat orthotopic glioma model

Surviving
Survival Time in Days
Rx days 4-25

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Survival (days)</th>
<th>SE</th>
<th>P value Log-rank</th>
<th>P value Wilcoxon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>25.14</td>
<td>2.82</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>20mg/kg</td>
<td>29.83</td>
<td>0.70</td>
<td>0.5</td>
<td>0.146</td>
</tr>
<tr>
<td>40mg/kg</td>
<td>33.5</td>
<td>1.32</td>
<td>0.0316</td>
<td>0.0333</td>
</tr>
<tr>
<td>80mg/kg</td>
<td>36.86</td>
<td>1.28</td>
<td>0.0005</td>
<td>0.0010</td>
</tr>
</tbody>
</table>

Exposure Summary U87MG Orthotopic Glioma Model

Day of Dosing (24 hrs post dose n=2/dose group)
Combinations of LY2835219-MsOH and temozolomide are additive in a rat orthotopic glioma model
BRAF and/or MEK inhibitors for BRAFV600E mutated gliomas?
Flaherty et al. Combined BRAF and MEK Inhibition in Melanoma with BRAF V600E Mutations
NEJM 2012; 2012 Nov;367(18):1694-703
A Phase II, Open-label Study in Patients with BRAF \textsuperscript{V600E} Mutated Rare Cancers with Several Histologies to Investigate the Clinical Efficacy and Safety of the Combination Therapy of Dabrafenib and Trametinib
Histologies

- Anaplastic Thyroid Carcinoma
- Biliary Tract Cancer
- Diffuse Large B Cell Lymphoma
- GIST
- Hairy Cell Leukemia
- High Grade Glioma (GBM, Anaplastic PXA, Anaplastic ganglioglioma)
- Low-Grade Gliomas (PXA, Ganglioglioma, Pilocytic Astrocytoma)
- Multiple Myeloma
- NSGCT/NGGCT
- Small Intestine Adenocarcinoma
Plummer: Clin Cancer Res 2010;16(18); 4527–31

Double strand break

Single strand break

Homologous Recombination

Non-homologous end joining (NHEJ)

Error prone NHEJ in G1

Error free H2 Active in dividing cells
Plummer: Clin Cancer Res 2010;16(18); 4527–31
Increasing Cytotoxicity of TMZ and RT

- **PARP Inhibitors**
  - ABT 888 (ABTC; RTOG)

- **Wee1 Inhibitor**
  - MK1775
Wee1

G2 Arrest

MK1775

G2 progression and mitotic catastrophe
Glioma Initiating Cells

BKM120+LDE225 In vivo data: orthotopic xenograft

LDE225+BKM120
Many choices; limited resources
Challenges

• Phase II trials often not predictive of positive outcome in phase III studies
  – Imatinib mesylate and hydroxyurea
  – Enzastaurin
  – Cediranib
  – Cintredekin Besudotox (*IL13-PE38QQR*)
  – Cilengitide
• More drugs and more combinations
• Limited resources
• Need more efficient trial designs
• Need better response criteria, endpoints and more efficient trials and design
"I want you to find a bold and innovative way to do everything exactly the same way it’s been done for 25 years."
New Clinical Trial Designs

- **Improve efficiency**
  - Rapid elimination of ineffective regimens
  - Test multiple combinations simultaneously
  - Shorter path to definitive testing
- **Designs**
  - “Pick the Winner”
  - Seamless integration of phase II/III trials
  - Sequential Accrual Design for Phase I/II studies
  - Factorial Design
  - Adaptive Randomization
Adaptive Randomization Strategies

- Multiple arm study
- Allocation of patients based on Bayesian probability of treatment efficacy
- Treatment arms with success are more likely to accrue patients
- Treatment arms with poor results are dropped, alternative arms added, and accrual continues until clear evidence of superior treatment(s) emerge

Adaptive Randomized “Bayesian” Design
Trippa et al (JCO 2012; 30:3258-3263)
Trippa et al (JCO 2012;30:3258-3263)
Trippa et al (JCO 2012;30:3258-3263)
Ideally we can have trials that evaluate multiple drugs efficiently and identify predictive biomarkers.
The BATTLE Trial: Personalizing Therapy for Lung Cancer

I-SPY 2: An Adaptive Breast Cancer Trial Design in the Setting of Neoadjuvant Chemotherapy

Patient Enrolled

Tissue biopsy; Blood specimen

MRI

MRI Biopsy

MRI Blood

HER2 (+)

Randomize

AC (4 cycles)

Paclitaxel + trastuzumab ± new drug A, B, or C

HER2 (-)

Randomize

AC (4 cycles)

Paclitaxel ± New Drug C, D, or E (12 weekly cycles)

Surgery

ADAPT

Translational Medicine, Clinical Pharmacology & Therapeutics, 99, 1, 97–100, 2009.
What Molecular Subgroups?

- **EGFR amplification** (45%) or mutation (20%)
- **PTEN loss** (40%) / **PIK3Ca** or **PIK3R1** mutations (15%)
- **CDK4/6 amp** (18%); **P16/15 loss** (50%)
- **MDM2 amplification** (15%) (with intact p53)
- **PDGFRα amplification** (13%)
- Other less common subgroups
Predictive or Prognostic Biomarkers

![Graphs showing survival curves for predictive and prognostic biomarkers.]

- **Predictive Biomarkers**: These biomarkers are used to predict the likelihood of a treatment response or outcome. The graph on the left shows survival curves for different biomarker statuses and treatment groups, indicating which biomarkers are predictive of survival benefit or worse outcomes.

- **Prognostic Biomarkers**: These biomarkers are used to predict the natural history of a disease or the likelihood of a particular outcome. The graph on the right shows survival curves for different biomarker statuses, illustrating how biomarkers can influence survival outcomes in the absence of treatment differences.
<table>
<thead>
<tr>
<th>EGFR</th>
<th>PI3K</th>
<th>MDM2</th>
<th>CDK4/6</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>+</td>
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<td>3 (3%)</td>
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<td>+</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>+</td>
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<td>1 (1%)</td>
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<td>+</td>
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<td>18 (20%)</td>
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<td>-</td>
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<td>4 (4%)</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>24 (26%)</td>
</tr>
</tbody>
</table>

**TCGA (all)**

Courtesy of Brian Alexander

|        | 41 (18) | 38 (17) | 13 (1) | 16 (4) | 91     |
How to prioritize overlapping classification

- Adaptive design with equal or weighted randomization will allow each subgroup to be evaluated
# Biomarkers

<table>
<thead>
<tr>
<th>EGFR amplification/mutation</th>
<th>Pik3Ca/PIK3R1 mutations/ PTEN loss</th>
<th>CDK4/6 amplification/P16 loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
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Recurrent GBM
Mosaic Amplification of Multiple Receptor Tyrosine Kinase Genes in Glioblastoma

Red: EGFR Amplification
Green: PDGFRA Amplification
PNAS 2013;110:4013

Intratumor heterogeneity in human glioblastoma reflects cancer evolutionary dynamics

Andrea Sottoriva, Inmaculada Spiteri, Sara G. M. Piccirillo, Anestis Touloumis, V. Peter Collins, John C. Marioni, Christina Curtis, Colin Watts, and Simon Tavare
Recurrent GBM

Reoperation and Genotype

3-5 weeks

RANDOMIZE

- EGFR Amplified 40%; mutations 20%
  - Drug A or A+B

- MDM2 Amplified 14%
  - Drug C or C+D

- PIK3Ca/R1 mutations 15% or loss of PTEN 40%
  - Drug E or E+F

- CDK4 amplification 16%; P16 and 15 deletion 50%
  - Drug G or G+H

Survival
Surgical Study
Possible Studies

- PI3K + MEK
- EGFR/mTOR inhibitor + Arsenic Trioxide
- etc
PML mediates glioblastoma resistance to mammalian target of rapamycin (mTOR)-targeted therapies

Akio Iwanami\textsuperscript{a}, Beatrice Gini\textsuperscript{b,c,1}, Ciro Zanca\textsuperscript{b,1}, Tomoo Matsutani\textsuperscript{b}, Alvaro Assuncao\textsuperscript{d}, Ali Nael\textsuperscript{e}, Julie Dang\textsuperscript{f}, Huijun Yang\textsuperscript{b}, Shaojun Zhu\textsuperscript{g}, Jun Kohyama\textsuperscript{g}, Issay Kitabayashi\textsuperscript{h}, Webster K. Cavenee\textsuperscript{b,l}, Timothy F. Cloughesy\textsuperscript{j}, Frank B. Furnari\textsuperscript{b,l,k}, Masaya Nakamura\textsuperscript{a}, Yoshiaki Toyama\textsuperscript{a}, Hideyuki Okano\textsuperscript{l}, and Paul S. Mischel\textsuperscript{b,l,k,2}

PNAS 2013; 110:4339-4344
Figure 1. PML mediates resistance to mTOR targeted therapies in GBM, which is reversed by ATO. (A) Schematic diagram showing that persistent mTOR signaling promotes tumor cell proliferation, while PML opposes it. (B) In GBMs treated with mTOR inhibitors or EGFR inhibitors such as erlotinib that also block mTOR signaling, PML is upregulated, promoting tumor cell arrest. (C) ATO, which leads to degradation of PML protein, synergizes with mTOR inhibitors, potently causing tumor cell death.
We are slowly making progress!

“We’re making progress—he set off the motion detector this morning.”
Thank You!