Phase 1B Study of Vemurafenib in Combination with the MEK inhibitor, GDC-0973, in Patients with Unresectable or Metastatic $BRAF^{V600}$-Mutated Melanoma (BRIM7)

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Disclosures

- Consulting, advisory boards for Roche/Genentech and GSK
- Corporate sponsored research for Roche/Genentech and GSK
Acquired resistance to BRAF inhibition

**MEK-dependent resistance**

- NRAS mutations
- \(BRAF^{V600}\) mutation truncation/amplification
- COT overexpression
- MEK mutations

**MEK-independent resistance**

- RTK ligand overexpression
- RTK overexpression

**Diagram**

- \(BRAF^{V600}\) mutation
- MEK
- ERK
- Cell survival
- vemurafenib
- GDC-0973
- RTK
- PI3K
- AKT
- Cell survival

References:

Combined BRAF & MEK inhibition: Preclinical data & PET scan response

- Preclinical data support combined inhibition of BRAF and MEK:
  - Prevents the emergence of resistance
  - Overcomes acquired resistance

In vivo combination of vemurafenib and MEK inhibition in the vemurafenib-resistant A375 melanoma xenograft model overcomes acquired resistance (KRAS$^{K117N}$ mutation)

PET scan response in a patient after progression on vemurafenib and after treatment with vemurafenib + GDC-0973

GDC-0973 & BRIM7 study objectives

**GDC-0973**:  
- Orally available, potent and highly selective small-molecule inhibitor of both MEK 1 and MEK 2  
- GDC-0973 monotherapy Phase I study:  
  - 14 day on/14 day off schedule MTD = 100mg  
  - 21 day on/7 day off schedule MTD = 60mg  
  - Common AEs: diarrhea, rash, edema, fatigue, nausea  
  - Encouraging single-agent activity in $BRAF^{V600}$ melanoma  
    - 7 responders out of 12 melanoma patients  
    - 6 responders were $BRAF^{V600E}$ mutation-positive (1 pt unknown mutation status)  
    - Median time on GDC-0973 treatment: 9.3 months (range 1.4 - 23 + months).

**BRIM7 Objectives**:  
- To evaluate the safety and tolerability of vemurafenib + GDC-0973  
- To identify the dose-limiting toxicities (DLTs) that determine the maximum tolerated dose (MTD) of vemurafenib + GDC-0973  
- To identify a Phase II/III dose and schedule for vemurafenib + GDC-0973

*GDC-0973 is being developed by Genentech, a member of the Roche Group, under a collaboration agreement with Exelixis.*
BRIM7 study design: Dose-escalation and expansion stages

- **Dose escalation stage:** 10 cohorts, 3–6 patients/cohort
- **Expansion stage:** up to 20 BRAFi-naïve and vemurafenib-progressing patients, respectively
**Key inclusion and exclusion criteria**

- Patients with either unresectable Stage IIIc or Stage IV metastatic melanoma
- Measurable disease (RECIST version 1.1)
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤1
- Adequate hematologic, liver and renal function
- Patients had either:
  - no prior exposure to BRAF inhibitor therapy, OR
  - progressed on vemurafenib immediately prior to enrollment in this study
- Patients were excluded if they had:
  - Ocular pathology or risk factors that predispose to retinal vein occlusion
  - QTc > 450ms
  - Active CNS metastasis. Patients treated with stereotactic RT or surgery are eligible if stable for ≥ 3 weeks
### BRIM7 Study: Patient characteristics

(6 July 2012)

<table>
<thead>
<tr>
<th>Treated patients (n=70)</th>
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<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>57.5 years (19–76)</td>
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<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>49 (70.0)</td>
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<tr>
<td>Female</td>
<td>21 (30.0)</td>
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<tr>
<td><strong>ECOG performance status, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>PS 0</td>
<td>35 (50.0)</td>
</tr>
<tr>
<td>PS 1</td>
<td>35 (50.0)</td>
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<tr>
<td><strong>Elevated LDH at baseline, n (%)</strong></td>
<td>44 (63.0)</td>
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<tr>
<td><strong>Melanoma stage at enrollment, n (%)</strong></td>
<td></td>
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<tr>
<td>Unresectable stage IIIc</td>
<td>6 (8.6)</td>
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<tr>
<td>Stage IV, M1a</td>
<td>2 (2.9)</td>
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<tr>
<td>Stage IV, M1b</td>
<td>10 (14.3)</td>
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<tr>
<td>Stage IV, M1c</td>
<td>52 (74.3)</td>
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<tr>
<td><strong>Vemurafenib progressors, n (%)</strong></td>
<td>38 (54.3)</td>
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<tr>
<td><strong>Median treatment cycles</strong></td>
<td>3 cycles (1 – 13)</td>
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BRIM7 Results: Cohort Assignment and Dose-limiting toxicity (6 July 2012)

- As of 6 July 2012, **6 out of 10 dose cohorts** have met the protocol-specified criteria to be declared safe (cohorts shown in green in figures below)
- **One DLT observed in Cohort 1B**: Gr 3 QT interval prolongation, related to vemurafenib
BRIM-7 Results: AEs attributed to either vemurafenib or GDC-0973 in all patients* (6 July 2012)

<table>
<thead>
<tr>
<th>Most common AEs attributed to either vemurafenib or GDC-0973</th>
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<tbody>
<tr>
<td>n=70</td>
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<tr>
<td></td>
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<tr>
<td>n</td>
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<tr>
<td>Total number of patients with AEs</td>
</tr>
<tr>
<td>Non-acneiform rash(^a)</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Photosensitivity / Sunburn</td>
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<tr>
<td>Fatigue</td>
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<tr>
<td>Nausea</td>
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<table>
<thead>
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<th>Selected AEs attributed to either vemurafenib or GDC-0973</th>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>n</td>
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</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Creatine phosphokinase elevation</td>
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<tr>
<td>Liver function test elevation(^b)</td>
</tr>
<tr>
<td>Arthralgia</td>
</tr>
<tr>
<td>Serous chorioretinopathy(^c)</td>
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<tr>
<td>Cutaneous squamous cell carcinoma, KA</td>
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*Includes all patients reporting each of AE general terms, even for zero incidence.
\(^a\)Non-acneiform rash includes MedDRA terms rash, rash generalised, rash maculo-papular, rash macular, rash papular, rash erythematous, erythema, rash pruritic, dermatitis, skin exfoliation, dermatitis exfoliative, lividity
\(^b\)LFT elevation includes MedDRA terms alkaline phosphatase increased, bilirubin increased, hyperbilirubinaemia, AST & ALT increased, transaminases increased, and gamma-glutamyltransferase increased.
\(^c\)Serous chorioretinopathy includes MedDRA terms chorioretinal disorder, chorioretinopathy, 1 pt with blurred vision later diagnosed as serous choreoretinopathy.
BRIM-7: AEs leading to dose interruptions, reductions and permanent discontinuations (6 July 2012)

<table>
<thead>
<tr>
<th></th>
<th>All pts (n=70)</th>
<th>Vemurafenib</th>
<th>GDC-0973</th>
<th>Vem and GDC-0973</th>
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<tbody>
<tr>
<td><strong>Temporary interruption</strong></td>
<td></td>
<td>17 (24.3%)</td>
<td>15 (21.4%)</td>
<td>13 (18.6%)</td>
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<td><strong>Dose reduction</strong></td>
<td></td>
<td>3 (4.3%)</td>
<td>2 (2.9%)</td>
<td>2 (2.9%)</td>
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<tr>
<td><strong>Permanent discontinuation due to AE</strong></td>
<td>1 (1.4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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Most common reasons for temporary interruption of vem: Rash 8pts, LFT abnormalities 3pts and arthralgia 3pts
Most common reasons for temporary interruption of GDC-0973: Rash 5pts and diarrhea 3pts

Reasons for primary dose reduction interruption of vem: LFT abnormality 1pt, central serous retinopathy 1pt and rash 1pt
Reasons for primary dose reduction interruption of GDC-0973: Central serous retinopathy 1pt and rash 1pt

Reason for discontinuation of vemurafenib: QT interval prolongation 1pt
BRIM7 Results: Change in tumor size from baseline to best response in patients who progressed on prior vemurafenib

Best Tumor Response for Each Patient (Vemurafenib Progressors)

n=32 evaluable patients
BRIM7 Results: Change in tumor size from baseline to best response in BRAFi-naïve patients

Best Tumor Response for Each Patient (BRAFi-naïve)

Individual Patients Treated with Vemurafenib and GDC-0973

n=25 evaluable patients

SLD, sum of longest diameters
BRIM7: Conclusions

- GDC-0973 in combination with vemurafenib can be delivered safely at the respective single-agent MTDs:
  - vemurafenib 960 mg BID, and
  - GDC-0973 60 mg QD 21 days on / 7 days off

- Adverse events were tolerable and manageable

- Preliminary anti-tumor activity in vemurafenib-naïve patients is encouraging

- Phase 3 study of vemurafenib + GDC-0973 is being initiated
We thank the patients and their families who participated in this trial.

The following investigators and sponsor members have contributed to the study:

- Karl Lewis, MD
- Omid Hamid, MD
- Theodore Logan, MD
- Lawrence Flaherty, MD
- Study co-ordinators and research nurses
- Genentech/Roche:
  - Hina Maniar (Clinical science);
  - Scott Chandler, Erica Park and Jacob Zeffren (Safety);
  - Luna Musib and WeiJiang Zhang (Pharmacology)