Phase II Study of Selumetinib vs Temozolomide in Patients with Advanced Uveal Melanoma (CTEP #8443)

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Disclosures

• No relevant relationships to disclose
Background

• Uveal melanoma is an orphan disease that is biologically distinct its cutaneous counterpart

• There is **no effective systemic therapy** for metatastic uveal melanoma

• The standard of care for patients with advanced disease is clinical trial participation

• Thus far, no trial of systemic therapy has been positive in this disease
The Gα Pathway

- Gnaq/Gna11 mutations are frequent early oncogenic events in uveal melanoma
- Gnaq/Gna11 encode for members of the q class of G-protein alpha subunits
- Mutations in Gnaq/Gna11 result in activation of the MAPK pathway

Tumor growth and proliferation

Selumetinib (AZD6244; ARRY-142886) Results in Decreased Viability of Uveal Melanoma in a Mutation Dependent Fashion


Subset Analysis of 20 Uveal Melanoma Patients Treated on a Completed Study of Selumetinib vs Temozolomide (NCT00338130)

<table>
<thead>
<tr>
<th>Genotype</th>
<th>IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>&gt; 1 μmol/L</td>
</tr>
<tr>
<td>GNAQ mut</td>
<td>&lt; 0.1 μmol/L</td>
</tr>
</tbody>
</table>

- PFS HR = 0.76, 80% CI (0.38, 1.53)
  - Comparing 7 and 13 pts init randomized to selumetinib and TMZ, respectively
We therefore systematically assessed the efficacy of selumetinib, a non-ATP competitive inhibitor of MEK1/2, in patients with metastatic uveal melanoma
Study Design

**TMZ/DTIC Naïve Metastatic Uveal Melanoma**

*Stratified by:* 1. Mutation Status; 2. Stage (M1a/b vs M1c); 3. Prior therapy (0 vs >1)

- **Temozolomide 150 mg/m2 QD (or DTIC)**
  - (n = up to 60; at least 40 mutant)

- **Selumetinib 75 mg BID**
  - (n = up to 60; at least 40 mutant)

**Primary Endpoint:** PFS

**Secondary Endpoints:** Overall Survival, Response, Safety

- Radiographic assessments using RECIST 1.1 performed at week 4, week 8, and every 8 weeks subsequently
- Patients treated until progression, intolerable toxicity, or withdrawal of consent

Probability is 80% that this design will detect a treatment difference at a one-sided 10% significance level if the true PFS hazard ratio is 0.68 in the overall population AND 0.6 in the Gnaq/11 mutant population.

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Key Eligibility Criteria

• Advanced uveal melanoma with measurable disease

• Disease must be progressive in the opinion of the treating investigator

• Determination of exon 5 Gnaq/11 mutation status on a CLIA certified assay

• No prior therapy with a MEK inhibitor, temozolomide or DTIC

• Adequate performance status and hematologic/organ function
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CONSORT Diagram
(as of 4/22/13)

Randomized (n = 98)

Temozolomide/DTIC (n = 50)
- Treated: 49 (4 DTIC; 45 TMZ)
- Not Treated: 1 (Clinical POD)
  - On Treatment: 2
  - Off Treatment: 47
    - 44 Radiographic Progression
    - 3 Clinical Progression
    - 0 Toxicity

Selumetinib (n = 48)
- Treated: 47
- Not Treated: 1 (Clinical POD)
  - On Treatment: 7
  - Off Treatment: 40
    - 34 Radiographic Progression
    - 2 Clinical Progression
    - 4 Toxicity

Cross-Over to Selumetinib (n = 40)
- On Treatment: 5
- Off Treatment: 35
  - 32 Radiographic Progression
  - 2 Clinical Progression
  - 1 Toxicity
### Patient Characteristics
(as of 4/22/13)

<table>
<thead>
<tr>
<th></th>
<th>Selumetinib (n = 48)</th>
<th>TMZ/DTIC (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age, Years (Range)</strong></td>
<td>62 (32-86)</td>
<td>61 (34-86)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>25 (52%)</td>
<td>31 (62%)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>23 (48%)</td>
<td>19 (38%)</td>
</tr>
<tr>
<td><strong>Median ECOG PS (Range)</strong></td>
<td>0 (0-1)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td><strong>AJCC Cutaneous Stage M1c (%)</strong></td>
<td>46 (96%)</td>
<td>47 (94%)</td>
</tr>
<tr>
<td>Elevated LDH (%)</td>
<td>24 (50%)</td>
<td>29 (58%)</td>
</tr>
<tr>
<td><strong>Median Prior Tx (Range)</strong></td>
<td>0 (0-3)</td>
<td>0 (0-2)</td>
</tr>
<tr>
<td>Prior Ipilimumab (%)</td>
<td>8 (17%)</td>
<td>11 (22%)</td>
</tr>
</tbody>
</table>

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**Tumor Mutational Screening**

- Tumor samples from all patients (97 metastatic; 1 primary) prospectively tested for codon 209 (exon 5) mutations in Gnaq/Gna11

<table>
<thead>
<tr>
<th>Exon 5 Mutation Status</th>
<th>All Patients (n = 98)</th>
<th>Selumetinib (n = 48)</th>
<th>Temozolomide (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gnaq mut (Exon 5)</td>
<td>36 (37%)</td>
<td>18 (37%)</td>
<td>18 (36%)</td>
</tr>
<tr>
<td>Gna11 mut (Exon 5)</td>
<td>46 (47%)</td>
<td>21 (44%)</td>
<td>25 (50%)</td>
</tr>
<tr>
<td>Gnaq/11 wt (Exon 5)</td>
<td>16 (16%)</td>
<td>9 (19%)</td>
<td>7 (14%)</td>
</tr>
</tbody>
</table>

- Codon 183 mutations (exon 4) currently being tested retrospectively in exon 5 wild-type cases

<table>
<thead>
<tr>
<th>Exon 4 Mutation Status</th>
<th>All Patients (n = 5)</th>
<th>Selumetinib (n = 3)</th>
<th>Temozolomide (n = 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gnaq mut (Exon 4)</td>
<td>2 (40%)</td>
<td>2 (66%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Gna11 mut (Exon 4)</td>
<td>1 (20%)</td>
<td>1 (33%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Gnaq/11 wt (Exon 4)</td>
<td>2 (40%)</td>
<td>0 (0%)</td>
<td>2 (100%)</td>
</tr>
</tbody>
</table>
## Hematologic Toxicities Possibly, Probably or Definitely Related to Therapy

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>TMZ/DTIC (n = 49)</th>
<th>Selumetinib (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gr 1/2</td>
<td>Gr 3</td>
</tr>
<tr>
<td>Anemia</td>
<td>7 (14%)</td>
<td>-</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>8 (16%)</td>
<td>-</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>4 (8%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (8%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8 (16%)</td>
<td>-</td>
</tr>
</tbody>
</table>
Select Non-Hematologic Toxicities Possibly, Probably or Definitely Related to Therapy Observed in > 5% of Cases

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>TMZ/DTIC (n = 49)</th>
<th></th>
<th></th>
<th>Selumetinib (n = 47)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gr 1/2</td>
<td>Gr 3</td>
<td>Gr 4</td>
<td>Gr 1/2</td>
<td>Gr 3</td>
<td>Gr 4</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (6%)</td>
<td>-</td>
<td>-</td>
<td>40 (85%)</td>
<td>1 (2%)</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24 (49%)</td>
<td>-</td>
<td>-</td>
<td>28 (60%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CPK Elevation</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>17 (36%)</td>
<td>6 (13%)</td>
<td>-</td>
</tr>
<tr>
<td>AST/ALT</td>
<td>6 (12%)</td>
<td>-</td>
<td>-</td>
<td>16 (34%)</td>
<td>7 (15%)</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (8%)</td>
<td>-</td>
<td>-</td>
<td>19 (40%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Edema</td>
<td>1 (2%)</td>
<td>-</td>
<td>-</td>
<td>18 (38%)</td>
<td>1 (2%)</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (39%)</td>
<td>-</td>
<td>-</td>
<td>18 (38%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11 (22%)</td>
<td>-</td>
<td>-</td>
<td>11 (23%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pain</td>
<td>5 (10%)</td>
<td>-</td>
<td>-</td>
<td>10 (21%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mucositis</td>
<td>1 (2%)</td>
<td>-</td>
<td>-</td>
<td>6 (13%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7 (8%)</td>
<td>1 (2%)</td>
<td>-</td>
</tr>
<tr>
<td>Muscle Weakness</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7 (8%)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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Response Pattern Differs Between Treatment Arms

**Temozolomide/DTIC**
(n = 46 evaluable for response)

- Gnaq mutant
- Gna11 mutant
- Gnaq/11 WT

* Exon 4 mutation assessed and absent

**Tumor Regression:** 11%
**RECIST Response:** 0%

**Selumetinib**
(n = 46 evaluable for response)

* Exon 4 mutation assessed and present

**Tumor Regression:** 50%
**RECIST Response:** 15%

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RECIST Responses to Selumetinib

- 35/46 (76%) patients achieved stable disease
- Another 7/46 (15%) patients achieved a RECIST response
- Median duration of response is 23 weeks (range, 7.9 – 40.3)

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Exon 5 Mutation Status</th>
<th>Tumor Response</th>
<th>Progression-Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTS-46</td>
<td>Gnaq mut</td>
<td>-30%</td>
<td>40.3</td>
</tr>
<tr>
<td>CTS-17</td>
<td>Gna11 mut</td>
<td>-30%</td>
<td>7.9</td>
</tr>
<tr>
<td>CTS-26</td>
<td>Gna11 mut</td>
<td>-31%</td>
<td>15.7</td>
</tr>
<tr>
<td>CTS-134</td>
<td>Gnaq mut</td>
<td>-49%</td>
<td>18.6+</td>
</tr>
<tr>
<td>CTS-79</td>
<td>Gnaq mut</td>
<td>-50%</td>
<td>23.0</td>
</tr>
<tr>
<td>CTS-5</td>
<td>Wt</td>
<td>-54%</td>
<td>23.4</td>
</tr>
<tr>
<td>CTS-24</td>
<td>Gna11 mut</td>
<td>-79%</td>
<td>25.3</td>
</tr>
</tbody>
</table>
Tumor Regression with Selumetinib Occurred Less Frequently After Cross-Over

**Initial Tx with Selumetinib**  
(n = 46 evaluable for response)

- **Tumor Regression:** 50%
- **RECIST Response:** 15%

**TMZ/DTIC → Selumetinib**  
(n = 35 evaluable for response)

- **Tumor Regression:** 23%
- **RECIST Response:** 0%

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# Responses in Liver and Orbital Tumors
(GNA11 Q209L Mutant)

<table>
<thead>
<tr>
<th></th>
<th>Orbital Tumor</th>
<th>CT Scan</th>
<th>PET/CT Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td><img src="image1" alt="Orbital Tumor Image" /></td>
<td><img src="image2" alt="CT Scan Image" /></td>
<td><img src="image3" alt="PET/CT Scan Image" /></td>
</tr>
<tr>
<td>(1/5/11)</td>
<td></td>
<td>(1/5/11)</td>
<td>(1/21/11)</td>
</tr>
<tr>
<td>On Study</td>
<td><img src="image4" alt="Orbital Tumor Image" /></td>
<td><img src="image5" alt="CT Scan Image" /></td>
<td><img src="image6" alt="PET/CT Scan Image" /></td>
</tr>
<tr>
<td>(2/8/11)</td>
<td></td>
<td>(2/21/11)</td>
<td>(3/21/11)</td>
</tr>
</tbody>
</table>

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Progression-Free Survival is Improved with Selumetinib in Both the Overall and Mutant Only Populations

**Overall Population**

Selumetinib (n = 38) vs Temozolomide (n = 42)

Selumetinib (n = 47) vs Temozolomide (n = 49)

15.9 weeks (95% CI, 8.4 – 23.1) vs 7.0 weeks (95% CI, 4.3 – 8.4)

HR 0.46 (95% CI, .30 - .71)  
*p = 0.0005*

**Exon 5 Gq/11 Mutation Positive**

Selumetinib (n = 38) vs Temozolomide (n = 42)

15.4 weeks (95% CI, 8.1 – 16.9) vs 7.0 weeks (95% CI, 4.3 – 11.9)

HR 0.55 (95% CI, .34 - .87)  
*p = 0.011*

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## Progression-Free Survival Rates

### Overall Population

<table>
<thead>
<tr>
<th></th>
<th>Selumetinib (n = 47)</th>
<th>Temozolomide (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Month</td>
<td>43.1%</td>
<td>8.5%</td>
</tr>
<tr>
<td>6 Month</td>
<td>22.9%</td>
<td>5.7%</td>
</tr>
</tbody>
</table>

### Exon 5 Gq/11 Mutant

<table>
<thead>
<tr>
<th></th>
<th>Selumetinib (n = 38)</th>
<th>Temozolomide (n= 42)</th>
<th>Selumetinib (n = 9)</th>
<th>Temozolomide (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Month</td>
<td>34.2%</td>
<td>9.5%</td>
<td>88.9%</td>
<td>0%</td>
</tr>
<tr>
<td>6 Month</td>
<td>19.9%</td>
<td>6.4%</td>
<td>37.0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

### Exon 5 Gq/11 Wild-Type

<table>
<thead>
<tr>
<th></th>
<th>Selumetinib (n = 9)</th>
<th>Temozolomide (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Month</td>
<td>88.9%</td>
<td>0%</td>
</tr>
<tr>
<td>6 Month</td>
<td>37.0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

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No Significant Effect Upon Survival is Observed

Overall Population

Selumetinib (n = 47) vs Temozolomide (n = 49)

10.8 months (95% CI, 7.5 – 12.9) vs 9.4 months (95% CI, 6.0 – 11.4)

Exon 5 Gq/11 Mutation Positive

Selumetinib (n = 38) vs Temozolomide (n = 42)

10.2 months (95% CI, 7.0 – 12.6) vs 9.5 months (95% CI, 6.1 – 13.9)

HR 0.79 (95% CI, 0.46 – 1.37) p = 0.4

HR 1.05 (95% CI, 0.59 – 1.88) p = 0.88

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Conclusions

• This study is the first to demonstrate improved clinical outcome with any systemic therapy in patients with metastatic uveal melanoma

• MEK inhibition with selumetinib results in a median progression-free survival double that achieved with chemotherapy in uveal melanoma (15.9 vs 7 weeks)

• Tumor shrinkage is achieved in 50% patients treated with selumetinib, with 15% achieving a RECIST response

• Patients previously treated with chemotherapy may be less likely to respond to selumetinib

• Selumetinib is a promising therapy for patients with advanced uveal melanoma and provides a platform for the development of new combinatorial therapeutic approaches
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