Phase I Study of Two Dosing Schedules of the Investigational Oral Pan-RAF Kinase Inhibitor TAK-580 (MLN2480) in Patients with Advanced Solid Tumors or Melanoma

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- **Speakers bureau:** TL (BMS, GSK, Novartis, Pfizer, Prometheus, Wyeth)

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- **Stock ownership:** VB (Millennium)

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- **None:** PC, AP, MG, CH, SSA, SNK, SS
TAK-580 is an Investigational, Oral Pan-RAF Kinase Inhibitor$^{1-4}$

Figure adapted from Zhou X, et al. EORTC-NCI-AACR 2014;(abstr 324)

1. Galvin K. AACR 2012 (Special Session: New Drugs on the Horizon 1);
2. Elenbaas B, et al. Eur J Cancer Suppl 2010;8:40–1 (abstr 105);
C28001 Study Design

POC in Melanoma Q2D Expansion:
- BRAF+ Naïve to MAPK inhibitor
- NRAS+ Naïve to MAPK inhibitor
- PK: solid tumors*

Additional Melanoma Q2D Expansion:
- BRAF+ Prior MAPK Inhibitors
- NRAS+ Prior MAPK Inhibitor
- BRAF/ NRAS WT Naïve to Chemotx
- BRAF/ NRAS WT Prior Chemotx

Endpoints:
- Safety: AEs/SAEs
- PK/PD: Tumor biopsy pre- and post-treatment
- Preliminary Activity: ORR, PFS

*Patients with any advanced solid tumor (excluding lymphoma, including melanoma)
AE, adverse event; MAPK, mitogen-activated protein kinase; MTD, maximum tolerated dose; ORR, objective response rate; Q2D, every other day; PD, pharmacodynamic; PFS, progression-free survival; PK, pharmacokinetic; POC, proof of concept; SAE, serious adverse event; WT, wild type.
## Q2D Expansion Phase: Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=78*)</th>
<th>Melanoma (n=58*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>65.5 (31–94)</td>
<td>66.0 (31–83)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>42 (54)</td>
<td>30 (52)</td>
</tr>
<tr>
<td>ECOG PS 0 / 1, n</td>
<td>38 / 39</td>
<td>27 / 30</td>
</tr>
<tr>
<td>Disease stage at entry III / IV / missing, n</td>
<td>4 / 61 / 12</td>
<td>3 / 44 / 11</td>
</tr>
<tr>
<td>Prior regimens 0 / 1 / 2 / 3 / 4+</td>
<td>26 / 15 / 18 / 9 / 8</td>
<td>22 / 9 / 15 / 7 / 3</td>
</tr>
</tbody>
</table>

*Includes an additional 2 patients with unknown BRAF/NRAS mutation status
ECOG PS, Eastern Cooperative Oncology Group performance status.
Safety Profile of TAK-580*: 200 mg Q2D (N=78)

<table>
<thead>
<tr>
<th>AEs</th>
<th>All grades n (%)</th>
<th>Grade ≥3 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash (combined)</td>
<td>37 (47)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>↑ Creatine phosphokinase</td>
<td>21 (27)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>16 (21)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>33 (42)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32 (41)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Nausea</td>
<td>27 (35)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>31 (40)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Headache</td>
<td>8 (16)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>24 (31)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>16 (21)</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>18 (23)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>10 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Back pain</td>
<td>11 (14)</td>
<td>0</td>
</tr>
<tr>
<td>Periorbital edema</td>
<td>14 (18)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

53 SAEs, n=38

13 drug-related events, n=10

- Rash (combined) 3
- Cardiac 2
  - Heart failure 1
  - Atrial fibrillation 1
- Hepatic 2
  - ↑ Bilirubin 1
  - ↑ ALT 1
- GI (constipation) 1
- Respiratory (ARF) 1
- Blood (anemia) 1
- Renal (ARI) 1
- General (pyrexia) 1

*As of 09 July 2015
ALT, alanine aminotransferase; ARF, acute respiratory failure; ARI, acute renal insufficiency; GI, gastrointestinal; SAE, serious adverse event.
Initial TAK-580 AE Profile: Consistent with pan-RAF Inhibitory Activity

- Skin AEs attributed to paradoxical MAP kinase pathway activation with BRAF inhibitors are rarely observed with TAK-580 200 mg Q2D:¹,²
  - Melanocytic nevi: 1% (1/78) patients dosed ≥200 mg Q2D TAK-580
  - Squamous cell carcinoma: 3% (2/78) patients dosed ≥200 mg Q2D
- Selected AEs consistent with MEK inhibition or BRAF+ MEK inhibition have been commonly observed with TAK-580 200 mg Q2D:³-⁵
  - Asymptomatic blood creatine phosphokinase (CPK) elevation (27%)
  - Hair depigmentation (17%)
- The frequency and type of AEs observed with TAK-580 in the clinic suggests:
  - Inhibitory activity of all 3 RAF isoforms with 200 mg Q2D
    - Biologically active exposure overcomes paradoxical MAP kinase activation
- A unique mechanistic entity in the field of MAPK pathway inhibitors

TAK-580 at 200 mg Q2D*:
Target Inhibition Confirmed By Changes in pERK and BIM Expression

Matched tumor biopsies from a *BRAF* mut Melanoma patient receiving 200 mg Q2D

Decreased pERK expression and increased BIM expression were observed in *BRAF*-mut and *NRAS*-mut melanoma expansion arms with TAK-580 200 mg Q2D

*Data presented are preliminary*
## 200 mg Q2D Expansion Phase: Preliminary Activity

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Treatment naïve</th>
<th>n</th>
<th>ORR</th>
<th>Median PFS, mo (range)</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF+ mutant melanoma</td>
<td>Treatment naïve</td>
<td>13</td>
<td>54%</td>
<td>7.2 (3.6–24.3)*</td>
<td>Single-agent activity in BRAF mutant disease on Q2D schedule</td>
</tr>
<tr>
<td></td>
<td>Prior BRAFi</td>
<td>6</td>
<td>17%</td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td>NRAS+ mutant melanoma</td>
<td>Treatment naïve</td>
<td>14</td>
<td>7%</td>
<td>3.2</td>
<td>Modest single-agent activity in RAS mutant disease on Q2D schedule</td>
</tr>
<tr>
<td></td>
<td>Prior MEKi</td>
<td>1</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>WT</td>
<td>Treatment naïve</td>
<td>5</td>
<td>0</td>
<td>NA</td>
<td>Insufficient single-agent activity in WT disease on Q2D</td>
</tr>
<tr>
<td></td>
<td>Prior therapy</td>
<td>8</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

*3 patients ongoing

BRAFi, BRAF inhibitor; MEKi, MEK inhibitor; ORR, overall response rate; PFS, progression-free survival; Q2D, every other day; WT, wild-type.
TAK-580 Pharmacologic Modeling: QW Dosing May Increase Efficacy

PK profiles of TAK-580

- Total exposure of 700 mg QW equivalent to 200 mg Q2D
- Higher $C_{\text{max}}$ with continuous (72 h) exposure $>$ Css at which observed MEKi AEs could provide greater inhibition of Ras mutation signaling

AE, adverse event; BRAFi, BRAF inhibitor;Css, concentration of drug in plasma at steady state; MEKi, MEK inhibitor.
C28001 Study: Updated Design

POC in Melanoma Q2D Expansion:
- BRAF+ Naïve to MAPK inhibitor
- NRAS+ Naïve to MAPK inhibitor
- PK: solid tumors*

MTD = 200 mg

Additional Melanoma Q2D Expansion:
- BRAF+ Prior MAPK inhibitor
- NRAS+ Prior MAPK inhibitor

MTD = 600 mg

Additional QW Expansion:
- BRAF/ NRAS WT Naïve to chemotx
- BRAF/ NRAS WT Prior chemotx
- NRAS+ Naïve to MAPK inhibitor

MTD = 800 mg

QW escalation: 400–800 mg

*Patients with any advanced solid tumor (excluding lymphoma, including melanoma)

MTD, maximum tolerated dose; QW, once-weekly; Q2D, every other day; PK, pharmacokinetic; POC, proof of concept; WT, wild type.
### QW Dose-escalation Phase: Patient Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=19)</th>
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<tbody>
<tr>
<td>Median age, years (range)</td>
<td>62.0 (39–74)</td>
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<td>Male, n (%)</td>
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<td>Prior regimens 0 / 1 / 2 / 3 / 4+, n</td>
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ECOG PS, Eastern Cooperative Oncology Group performance status.
High-dose Pulsatilie QW Schedule Demonstrates a Predicted PK Profile

Mean Day 22

- QW schedule demonstrates a dose-proportional increase in C_{max} and AUC following dose escalation from 400 to 800 mg
- 600 mg QW dosing
  - >48 h continuous exposure above Css for MEKi AEs
  - Exposure > Css for BRAFi AEs throughout QW dosing interval

AE, adverse event; AUC, area under the curve; C_{max}, time to peak plasma concentration; Css, concentration of drug in plasma at steady state; PK, pharmacokinetics.
### Safety: Treatment Emergent AEs

<table>
<thead>
<tr>
<th>AEs*, n (%)</th>
<th>TAK-580 MTDs</th>
<th>200 mg Q2D N=78</th>
<th>600 mg QW N=12</th>
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*AEs occurring in either >20% of patients at 200 mg Q2D or ≥2 patients at 600 mg QW DLT, dose-limiting toxicity

- 2 patients at 800 mg QW experienced cycle 1 DLTs:
  - 1 grade 3 rash
  - 1 grade 3 hyperbilirubinemia
- QW dosing may reduce DLTs observed with Q2D dosing
- No cases of nevi observed to date in the QW cohorts
- Early evidence of clinical benefit in BRAF mutant disease with QW dosing
  - Thyroid carcinoma (n=3)
Summary & Next Steps

**TAK-580**
- Investigational, oral pan-RAF kinase inhibitor

**Safety**
- Safety profile consistent with pan-RAF inhibition
  - AEs similar to other therapies targeting MAPK pathway
  - 200 mg Q2D demonstrates a low rate of AEs associated with paradoxical MAPK pathway activation
  - 600 mg QW has an initial safety profile that is different from the QOD schedule

**Antitumor activity**
- Early signs of antitumor activity observed at 200 mg Q2D
- QW dosing under study

**Next steps**
- QW expansion phase: NRAS melanoma expansion cohort for direct comparison with Q2D dosing
- Initial safety profile of QW dosing suggest this schedule may be optimal for novel combination strategies; C28002 study (ongoing):
  - TAK-580 + TORC1/2i (TAK-228 [MLN0128])
  - TAK-580 + alisertib
  - TAK-580 + paclitaxel
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