A phase 1 dose escalation study of RXDX-105, an oral RET and BRAF inhibitor, in patients with advanced solid tumors

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Background

RXDX-105 is a small molecule multikinase inhibitor (MKI) with potent activity against targets such as RET and BRAF. RXDX-105 is being developed as an oral therapy for patients with solid tumors, including those that harbor RET or BRAF alterations.

• The potential for RET and BRAF inhibition to result in durable cytoreductive responses in lung cancer patients has been demonstrated in phase 2 trials of the multikinase RET inhibitor cabozantinib (Drilon et al., 2015) and the BRAF inhibitor dabrafenib (Planchard et al., 2015).

• RXDX-105 is a potent RET and BRAF inhibitor with biochemical IC50 values of 0.3 and 0.8 nM against wild-type RET and wild-type BRAF, respectively. In addition, RXDX-105 potently inhibits RET mutants identified in RET-M918T (IC50 = 3-8 nM), RET-M918E (IC50 = 4 nM) and BRAF V600E (IC50 = 54 nM).

• RXDX-105 has demonstrated potent antitumor activity in multiple preclinical models of RET mutant and RET-rearrangement driven cancers.

• Hence, solid tumors with RET or BRAF rearrangements or mutations may respond to treatment with RXDX-105.

• Due to the MKI properties of RXDX-105, it may also be active in patients with unselected tumors.

Phase 1 Trial Overview

Patient Population: Patients not selected based upon molecular, histological or cytologic characteristics of advanced solid tumor; any number of systemic therapies allowed, including RET or BRAF inhibitors. ECOG performance status 0 or 1.

• 55 patients were treated across 8 dose levels and 4 DLTs were observed.

• An MTD based on DLTs was not reached; the RP2D was set at 350 mg after the overall safety and PK data and was determined to be 350 mg administered once daily under Fed condition.

• 36 patients across 7 dose levels were treated (31 patients evaluable) in a phase 1 dose escalation study.

• The primary objective of the study was to determine the RP2D in patients with advanced solid tumors who have RET or BRAF mutations or rearrangements.

• Patients were enrolled based on NSCLC drivers.

• The toxicity data were analyzed using the standard 3+3 design.

• The study was conducted at 3 dose levels: 350 mg, 275 mg, and 200 mg under Fed condition.

• Of these, 11 patients had an actionable alteration.

• There were no DLTs at 350 mg Fed condition.

• The most common treatment-emergent AEs in Phase 1 patients are presented below.

Safety

Phase 1 Patients with an Actionable RET or BRAF Alteration Treated at ≥275 mg (Fed)

<table>
<thead>
<tr>
<th>Best</th>
<th>Response</th>
<th>BRAF V600E Papillary Thyroid</th>
<th>BRAF V600E Papillary Thyroid</th>
<th>BRAF V600E Ovarian</th>
<th>BRAF V600E Ovarian</th>
<th>BRAF D594G CRC</th>
<th>BRAF D594G NSCLC</th>
<th>BRAF D594G NSCLC</th>
<th>BRAF D594G NSCLC</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>SD (-14%)</td>
<td>SD (-28%)</td>
<td>SD (-28%)</td>
<td>SD (-28%)</td>
<td>PD</td>
<td>PD</td>
<td>PD</td>
<td>PD</td>
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<tr>
<td>BRAF D594G CRC</td>
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<td>BRAF D594G NSCLC</td>
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<tr>
<td>BRAF V600E Ovarian</td>
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<tr>
<td>BRAF V600E Papillary Thyroid</td>
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</table>

Preliminary Results

Phase 1 was an all-comers dose escalation study. Fifty-five patients were treated in the Phase 1 portion of the study; 20 were treated at the clinically relevant doses of 275 mg and 350 mg. Fed condition. Of those, 11 patients had an actionable RET or BRAF alteration.

Data as of May 3, 2016, for tumor response and duration of therapy in these patients are displayed below.

Conclusions

RXDX-105 has been generally well-tolerated. All AEs that have occurred to date are reversible with dose reduction or holiday. The safety data are current as of May 3, 2016.

• Four DLTs have occurred: G3 maculopapular rash (200 mg), G3 fatigue (275 mg), G3 ophthalmia (275 mg Fed) and G3 hypothyroidism (350 mg Fed). All DLTs resolved upon study drug discontinuation. Two patients resumed treatment at a reduced dose; one patient discontinued treatment due to progression prior to resuming treatment and the patient with hypothyroidism continues to treat.

• Ten Grade ≥3 AEs were observed (intestinal obstruction and abnormality, neither of which were considered drug-related). There have been no Grade 5 treatment-related events.

• Three SAEs were considered treatment-related: G2 headache, G3 hypothyroidism and G3 drug reaction with eosinophilia and systemic symptoms (DRESS syndrome).

• The most common treatment-emergent AEs in Phase 1 patients are presented below.

• Median Maximum Plasma Concentration (ng/mL)

<table>
<thead>
<tr>
<th>Time on Treatment (months)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
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</thead>
<tbody>
<tr>
<td>BSA Normalized Day 15 Linear Plot</td>
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</table>

As previously reported at ENA (Wang, 2015), one confirmed RECIST PR was noted in a patient treated with 235 mg, Fed condition. This patient was an 17 y/o female with metastatic NSCLC. Molecular analysis of her baseline tumor (2007) revealed KRAS G12C mutation. At Cycle 2, the patient had 40% reduction in target lesion. She continues on study after 10 cycles. The 17 y/o female with metastatic NSCLC. Molecular analysis of her baseline tumor (2007) revealed KRAS G12C mutation. At Cycle 2, the patient had 40% reduction in target lesion. She continues on study after 10 cycles.

MPatel@flcancer.com. Thank you to all the patients and their families who participated in this study.