**BACKGROUND**

RXDX-105 is a VEGFR-sparring, potent RET inhibitor.  
- RXDX-105 exhibits high potency against wild-type RET (biochemical IC₅₀ 0.3 nM), RET fusions (IC₅₀ 0.3-0.8 nM) and RET mutations (IC₅₀ 0.5-1.5 nM).  
- RXDX-105 has demonstrated potent antitumor activity in multiple patient-derived xenograft (PDX) models of RET fusion–positive cancers.  
- The Phase 1 dose escalation portion of the study has been completed with 55 patients enrolled across 8 dose cohorts, doses up to 350 mg, po, QD were tested; an MTD based on DLT was not determined.  
- Target efficacious exposures for RET inhibition based on animal models have been achieved in the clinical setting at doses of at or above 150 mg, po, QD.

**RESULTS: Safety**

As of November 3, 2016, the majority of treatment-related AEs were Grades 1-2 and were reversible with dose modifications.  
- Toxicties commonly associated with VEGFR inhibition, such as hypertension, hypothyroidism, proteinuria, and neutotoxicity, were rarely observed (<5%).  
- Nine patients (18%) experienced 14 treatment-related serious adverse events  
  - Two of these patients experienced drug rashes, including 1 case reported as Grade 3 drug reaction with eosinophilia and systemic symptoms, in the patient recovered with drug discontinuation; 1 case of Grade 3 rash complicated by fatal alveolar hemorrhage.  
  - The most common treatment-related AEs are presented below.

**RXDX-105 Preclinical Profile**

- Sub-nanomolar to nanomolar biochemical potency against RET fusions and activating mutations  
- Differentiated from broad multi kinase inhibitors with >50x higher potency against RET than VEGFR in vitro  
- Clinical exposures achieved for complete RET inhibition, while remaining significantly below those required for VEGFR inhibition  
- RXDX-105’s high RET potency translated into strong antitumor activity in vivo, including tumor regression at clinically achievable exposures in several PDX models harboring clinically relevant RET fusions.

**RESULTS: Response in RET Inhibitor–Naïve Patients with RET Fusion–Positive Cancer**

RXDX-105 has demonstrated clinical activity in patients with RET fusion–positive cancer.  
- 9 RET inhibitor-naïve patients with RET fusion–positive tumors have been treated in Phase 1/1b and are evaluable for response.  
- 8 patients from Phase 1b  
  - 1 additional patient from Phase 1 with NCCDA4 RET mCRC  
  - 5 out of 6 had a RECIST response, 1 confirmed (3, 1 PR) and 1 unconfirmed (1 PR) for a preliminary ORR of 56%  
  - All responding patients continue on treatment with RXDX-105.

**CONCLUSIONS**

- RXDX-105 has an acceptable safety profile in patients with advanced or metastatic solid tumors  
- 5 out of 9 RET inhibitor-naïve patients with RET fusion–positive tumors have a RECIST response, 4 confirmed (1, 3 PR) and 1 unconfirmed (1 PR) unconfirmed (1 PR) for a preliminary ORR of 56%  
- Additionally, a previously disclosed Phase 1 patient with RET M918T mutated medullary thyroid cancer had a confirmed PR and is ongoing in Cycle 10  
- Enrollment in Phase 1b basket study is ongoing to further explore safety and efficacy at several doses  
- Compelling early clinical data from this Phase 1/1b study justify further development of RXDX-105 in patients with RET fusion–positive solid tumors.