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Preliminary safety and antitumor activity of RP-1664, a first-in-class PLK4 inhibitor, as monotherapy in advanced solid tumors with and without TRIM37 amplification

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Background: *TRIM37* encodes an E3 ubiquitin ligase that is amplified (TM37amp) in 15% of breast cancers, 90% of neuroblastomas, and in 5-20% of other solid tumors. Excess TRIM37 depletes pericentriolar mitotic material and confers synthetic lethal dependence on the serine/threonine kinase PLK4, which regulates centrosome duplication. Here we report the first-in-human safety and preliminary anti-tumor activity of RP-1664, a first-in-class, highly-selective PLK4 inhibitor, in patients with and without TRIM37 amplification.

Methods: In this Phase I study (NCT06232408), adults and children (≥12yo) with previously treated solid tumors with and without TM37amp were treated with escalating doses of RP-1664 (10-90mg) in 3 or 4-week cycles (2 weeks on/1 week off or 1 on/1 off). Patients were eligible for enrollment based on either: (1) known TM37amp or amplification of colocalized surrogate genomic markers *RAD51C, PPM1D, BRIP1,* or *RNF43*; or (2) genomically unaltered *TP53*, which enriched for responses in preclinical models. Antitumor efficacy was assessed with RECIST and ctDNA fold changes between baseline (C1D1) and on-treatment (C2D8).

Results: As of the August 26, 2025 data cutoff, 29 patients received RP-1664, including 6 patients with neuroblastoma and 23 with other solid tumors such as breast (n = 7), cholangiocarcinoma (n = 3), pancreatic (n = 2), and others (n = 11). Fifteen patients were enrolled based on TM37amp; the remainder based on unaltered TP53. Patients received a median of 5 (range: 2-18) prior therapy lines. Doses ranged from 10mg QD 2w on/1w off to 90mg 1w on/1w off; the recommended phase 2 dose (RP2D) was determined to be 60mg QD 1w on/1w off. Common Grade 3+ (G3+) treatment-related adverse events (TRAEs) included anemia (38%), neutropenia (24%) and thrombocytopenia (7%); 59% of patients had a G3+ TRAE. Three patients developed pneumonitis (2 G2; 1 G3; 10%). At the RP2D, the most common G3 TRAEs were anemia (4/16, 25%), neutropenia (1/16, 6%), and

pancreatitis (1/16, 6%). PK data showed in general linear dose increases with normal variability and achievement of predicted therapeutic concentrations.

At data cutoff, in the adult solid tumor cohort, the overall response (OR) was 16% (2 confirmed responses, 1 unconfirmed; all at doses ≥ RP2D) and CBR (OR or SD ≥ 16w) was 37%. Three additional patients had SD > 18 weeks. In patients with neuroblastoma, 1/6 (17%) had an unconfirmed complete response. Among patients at the RP2D with detectable ctDNA at baseline and on-treatment, 8/12 (67%) had a relative ctDNA decline ≥ 50%, including 6/6 patients with breast cancer. 6/8 molecular responders had NGS evidence of TRIM37 amplification. 4 of these patients had FISH confirmation of TRIM37 amp.

Conclusions: RP-1664 is a first-in-class PLK4 inhibitor which demonstrated tolerability and preliminary anti-tumor efficacy, most notably among heavily pretreated patients with breast cancer. The most common toxicities were hematologic, and cases of pneumonitis were observed. These data support further investigation.