

RX-5902, a Phosphorylated p68 Targeting Agent, to Treat Subjects with Advanced Solid Tumors

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Abstract TPS#778

Background: Phosphorylated p68 may play a vital role in cell proliferation and tumor/cancer progression. RX-5902 is a novel compound that targets phosphorylated p68 RNA helicase (also known as DDX5), a member of the DEAD box family of RNA helicases. As a single agent, RX-5902 inhibits tumor growth and enhances survival in a variety of xenograft tumor models (e.g., pancreatic, renal, ovarian, melanoma).

Methods: This Phase 1, open-label, multicenter study evaluates the efficacy and safety of RX-5902 in subjects with solid tumors. RX-5902 is administered orally 1, 3 or 5 times per week for 3 weeks with 1 week of rest in each 4 week cycle. Dose escalation starts with an accelerated design treating 1 subject per dose followed by a standard 3 + 3 design using a modified Fibonacci sequence after the occurrence of a single Grade 2 or greater adverse event that is considered at related to RX-5902. The primary endpoint is the overall safety profile characterized by the type, frequency, severity, timing of onset, duration and relationship to study therapy of any adverse events, or abnormalities of laboratory tests or electrocardiograms as well as the description of any dose limiting toxicities that occur during Cycle 1, serious adverse events, or adverse events leading to discontinuation of study treatment. Secondary endpoints include pharmacokinetic parameters (e.g., time to maximum observed concentration [T_{max}], maximum observed plasma concentration [C_{max}], trough concentration [C_{trough}], area under the concentration-time curve [AUC]) and indices of anti-tumor activity (e.g., overall response rate, time to response, duration of response, and progression-free survival during treatment). Exploratory endpoints are biochemical levels of drug targets in blood and tumor samples. Eligible subjects must have confirmed histologic or cytologic evidence of metastatic or locally advanced solid neoplasm that has failed to respond to standard therapy, progressed despite standard therapy or for which standard therapy does not exist. There is no limit on the number of prior treatment regimens. NCT02003092

Study Design

Methodology: This is a Phase 1 multicenter, dose finding, open-label, single agent study of RX-5902 administered orally to subjects with advanced or metastatic solid tumors. One subject will be treated per dose group until the appearance of a related grade 2 or greater adverse event, after which 3 subjects will be treated using the modified Fibonacci schedule.

Treatment: Subjects will be treated for up to 6 cycles of therapy. RX-5902 will be taken 5 consecutive days per week for 3 weeks with 1 week of rest in each 28-day cycle. All subjects will be followed for at least 30 days after the last dose of RX-5902. Additional cycles allowed for subjects receiving benefit.

Key Exclusion Criteria

- Primary brain tumor or active brain metastases
- Persistent toxicities >Grade 1 (except Grade 2 alopecia or neuropathy) associated with previous cancer therapies
- Any other cancer treatment within 2 weeks of planned study treatment
- History of clinically significant GI bleed, intestinal obstruction, or GI perforation within 6 months of study dosing
- History of long QT syndrome or clinically significant cardiac arrhythmias (except stable atrial fibrillation)
- Myocardial infarction within 6 months of study dosing
- Active infection requiring IV antibiotics within 2 weeks of dosing
- History of Hepatitis B, C, or HIV
- Use of potent inhibitor or inducer of CYP3A4/3A5 within 14 days of planned study treatment or expected requirement for use of such a drug during study
- Use of a potent inhibitor or inducer of drug transporters or conjugating enzymes within 14 days prior to planned study treatment or expected requirement for use of such a drug during study

Study Objectives

Primary objectives:

- Evaluate safety and tolerability of escalating doses of RX-5902 in subjects

Secondary objectives:

- Characterize the safety and tolerability of multiple doses of RX-5902
- Characterize the PK profile of RX-5902
- Characterize the antitumor activity of RX-5902

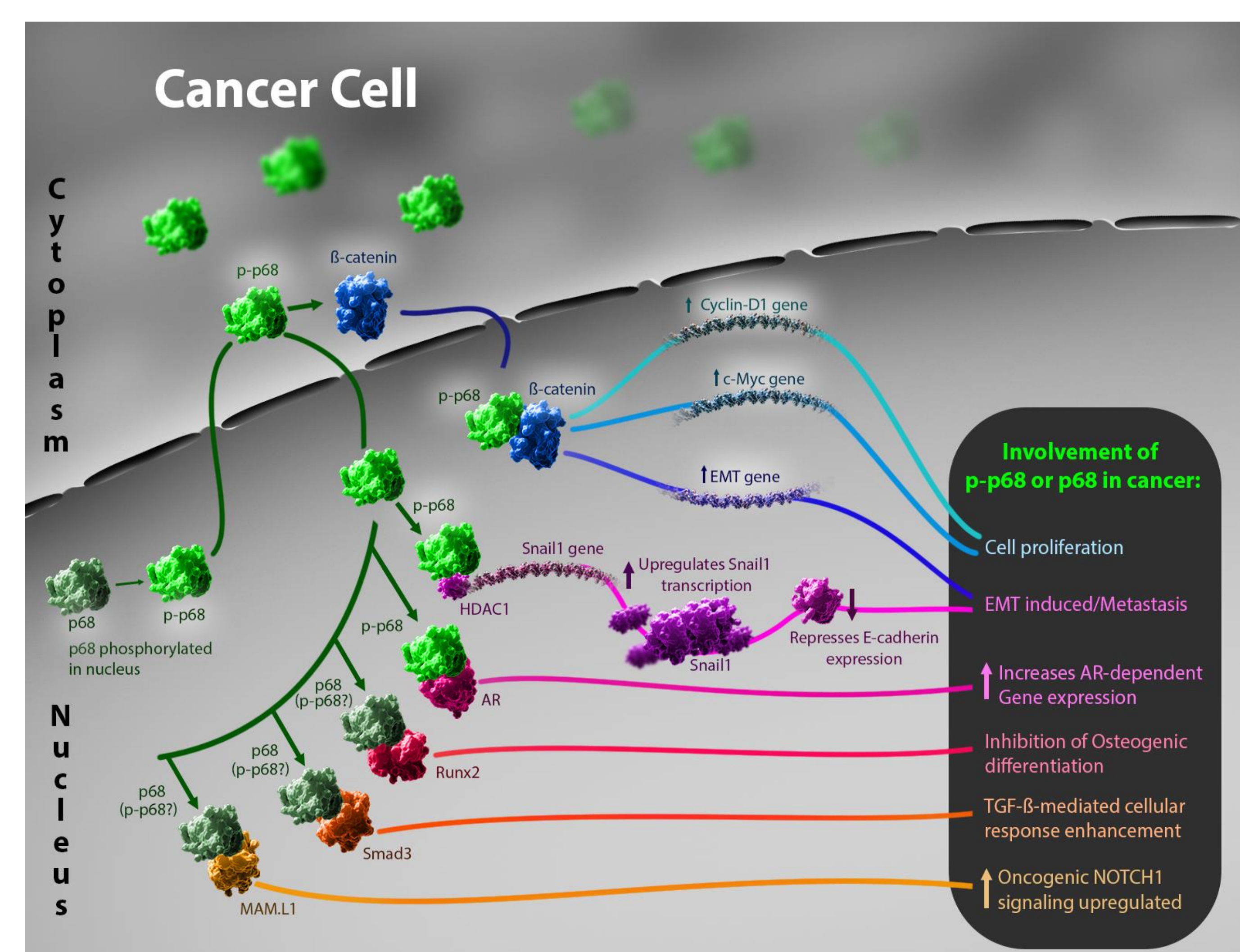
Exploratory objective:

- Investigate the effect of RX-5902 on potential biomarkers (e.g., Phosphorylated-p68, c-myc, c-jun) in blood or tumor samples

References

- Kost et al. (2015) J. Cell. Biochem. 10:1002.
- Lee et al. AACR; Cancer Res 2011;71(8 Suppl):Abstract # 1371
- Yang et al. (2006) Cell, 127: 139-155.

Proposed Mechanism of Action



Key Inclusion Criteria

- Male and female patients who are 18 yrs or older
- Histologically confirmed solid tumor malignancy that is refractory, intolerant, or ineligible to receive approved standard therapy
- Measurable or evaluable disease per Response Evaluation Criteria in Solid Tumors (RECIST)
- ECOG performance score ≤ 1
- Able to swallow capsules
- Hemoglobin ≥ 9.0 g/dL
- Absolute neutrophil count $\geq 1500/uL$
- Platelet count $\geq 100,000/uL$

Investigator Disclosures

- Dr. Martin Gutierrez– nothing to disclose
- Dr. S. Gail Eckhardt– nothing to disclose
- Dr. W. Larry Gluck – nothing to disclose
- Dr. Ely Benaim – Rexahn Pharmaceuticals

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