

Preliminary Report of A Phase 1b/2a Trial, An Oral Inhibitor of Phosphorylated P68 (P-p68), Which Mediates β -catenin Nuclear Translocation in Advanced Triple-Negative Breast Cancer (TNBC)

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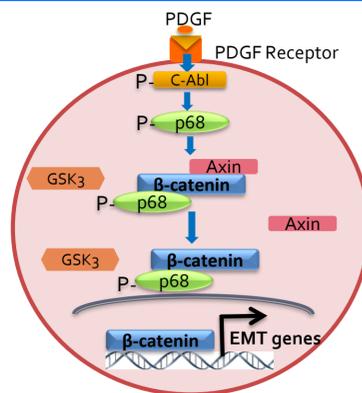
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Background: RX-5902 is a novel oral anti-cancer compound targeting phosphorylated p68 (P-p68) (RNA helicase DDX5, a member of the DEAD box family of RNA helicases) affecting the Wnt canonical pathway. P-p68 may play a role in cell proliferation and cancer progression by blocking the nuclear translocation of β -catenin. RX-5902 inhibits tumor growth and enhances survival in numerous xenograft animal models, including breast, melanoma and ovarian. Methods: This is a Phase 1b/2a trial in patients with previously treated advanced triple-negative breast cancer. Eligible subjects received 250 mg of RX-5902 orally for 5 consecutive days followed by 2 days off and continued until unacceptable toxicity or disease progression. Primary objectives include efficacy and safety of the recommended phase 2 dose and schedule, as was previously determined in the phase 1 study. A pre-planned interim analysis will be performed when 10 response evaluable subjects have been enrolled and have completed 4 cycles of therapy or have discontinued therapy due to progressive disease. Tumor imaging is performed every 2 cycles. If at least 2 objective responses are seen in the first 10 evaluable patients, enrollment will continue to stage 2 of the Phase 2a portion of the study. Results: As of Feb 2018, 11 subjects with TNBC were enrolled and treated in Stage 1 of the Phase 2a component. These subjects had received a median of 3 prior therapies (range 2 to 6). Preliminary evidence after 2 cycles of therapy showed 5 subjects with stable disease as the best overall response; 3 subjects had progressive disease, 2 subjects stopped therapy early and 1 subject just started treatment. One subject had a tumor reduction of 18.2% and 1 subject remains on study with stable disease for 5 cycles. The most common related adverse events, were Grade (G)1/2 nausea (2.8%), G1 vomiting (1.8%), G1/G2 diarrhea (1.8%) and G1/G2/G3 fatigue (4.6%). Conclusions: Preliminary evidence suggests that oral administration of RX-5902 at 250 mg/day appears safe and well tolerated. Early anti-tumor activity was observed in 1 patient. Recruitment to Phase 2 is ongoing.

RX-5902 Validated Mechanism of Action

- RX-5902 binds with high affinity to Phosphorylated p68 and decreases β -catenin translocation into the nucleus of a cancer cell
 - Downregulation of β -catenin/Wnt pathway
 - Decrease in oncogene expression
 - Decrease in cancer cell proliferation and growth
 - Increase in tumor T-cell infiltration



Study Design

This is a Phase 1/2a, 2-stage study (NCT02003092) designed (to evaluate safety, tolerability and pharmacokinetics (PK) following treatment with RX-5902 in subjects with metastatic triple negative breast cancer. Primary objectives include safety, tolerability and tumor response. Secondary objectives include evaluation of PK and antitumor activity. Eligible subjects (aged ≥ 18 years) with relapsed/refractory triple negative breast cancer received oral treatment with 250 mg of RX-5902 for 5 times, followed by 2 days off, per week for 4 weeks. The interim analysis in Stage 1 of the Phase 2 study was performed after the first 10 subjects were treated at the recommended Phase 2 dose and schedule, were evaluable for response, completed up to 4 cycles of therapy or have discontinued therapy before 4 cycles. Since 5 protocol defined responders (those who completed up to 2 cycles of therapy) were observed out of the initial 10 evaluable subjects with triple negative breast cancer, subject enrollment is continuing. Preliminary data has been updated and is presented for 12 subjects.

Demographics

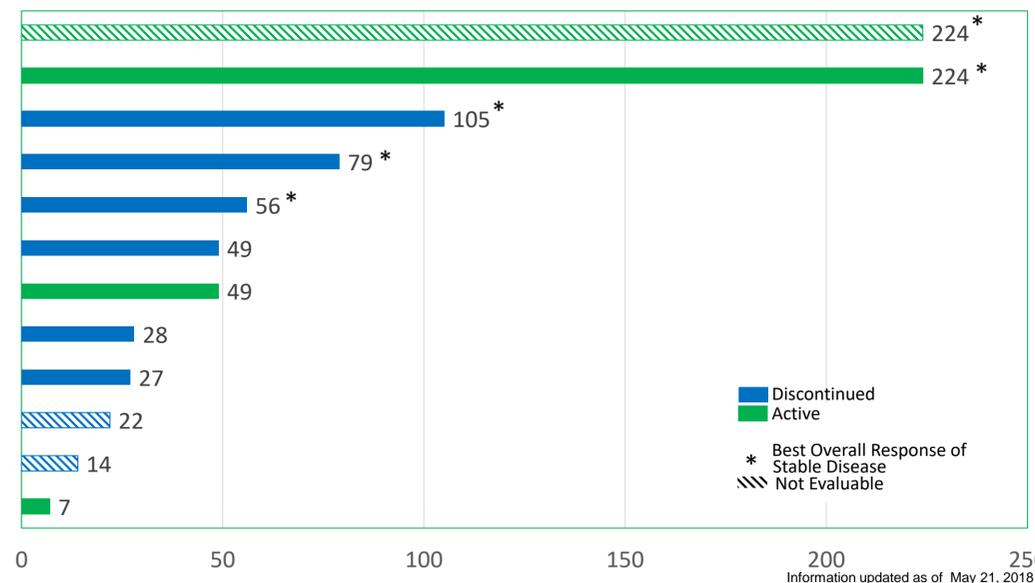
Parameter	Overall
Gender, n (%)	12
Female	12 (100%)
ECOG performance status, n (%)	
0	4 (33.3%)
1	8 (66.7%)
Prior anticancer treatments, n (%)	
1	0 (0.0%)
2	5 (41.7%)
3	2 (16.6%)
4+	5 (41.7%)

Safety Profile

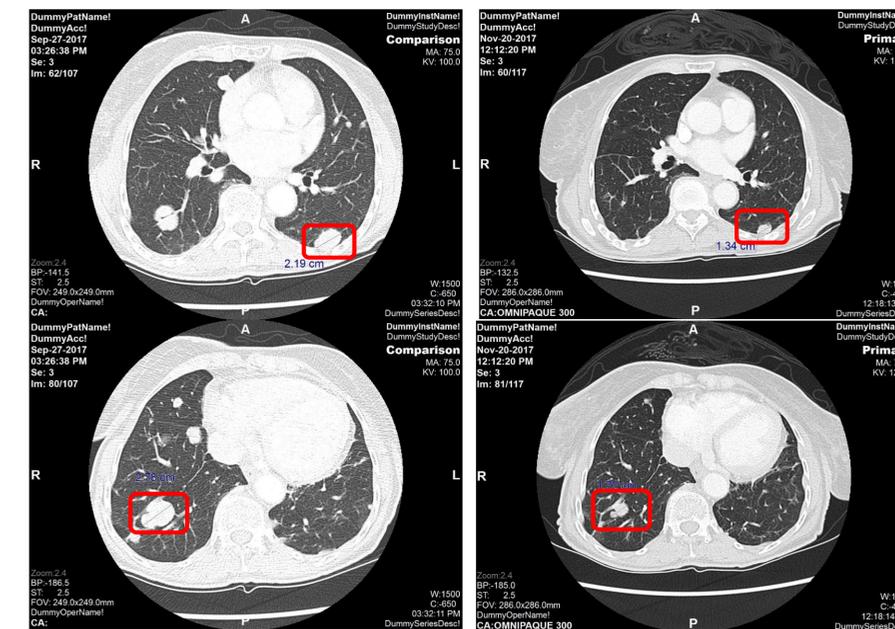
Most Frequent Adverse Events	Related Events n (%)	Highest Severity Grade Per Related AE (n)			
		Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	7 (20.6%)	3	2	2	0
Nausea	3 (8.8%)	1	2	0	0
Vomiting	3 (8.8%)	3	0	0	0
Constipation	2 (5.9%)	2	0	0	0
Diarrhoea	2 (5.9%)	1	1	0	0
Gait disturbances	2 (5.9%)	2	0	0	0
Stomach pain	2 (5.9%)	2	0	0	0
Rash skin	2 (5.9%)	1	1	0	0
Anorexia	1 (2.9%)	0	2	0	0
Blurred vision	1 (2.9%)	1	0	0	0
Hand tremor	1 (2.9%)	1	0	0	0
Headache	1 (2.9%)	1	0	0	0
Lack of appetite	1 (2.9%)	1	0	0	0
Muscle weakness	1 (2.9%)	1	0	0	0
Pain joint	1 (2.9%)	1	0	0	0
Pain muscle	1 (2.9%)	1	0	0	0
Thrombocytopenia	1 (2.9%)	0	1	0	0
Weakness	1 (2.9%)	1	0	0	0
Weight loss	1 (2.9%)	1	0	0	0

Most related adverse events were Grade 1 or Grade 2.

Days on Study



Patient Response



A 78 year old woman of Haitian descent presented with malignant neoplasm of the right breast. The subject previously received treatment with capecitabine (3 months), nab-paclitaxel and pembrolizumab (5 months) and erubulin (5 months) for the indicated time periods but progressed on all prior therapies. The panels on the left show the pre-treatment scans and those on the right were after 2 cycles of therapy with RX-5902. The subject showed a overall tumor reduction of 18.2%.

Conclusions

- RX-5902 appears safe and well tolerated when administered at the recommended Phase 2 Dose
- Preliminary data show encouraging responses in heavily pretreated patients
 - One patient had a 18.2% tumor reduction after two cycles of treatment
 - Two patients had progression free survival of >200 days
- Additional subjects are enrolling in Stage 2 of the Phase 1b/2a

Investigator Disclosures

- Christine Peterson, PhD, Ely Benaim, MD – Rexahn Pharmaceuticals