Abstract LB255

A Phase 1b Trial of Cirmtuzumab and Paclitaxel in Locally Advanced/Unresectable or Metastatic Her2 Negative Breast Cancer

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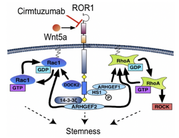
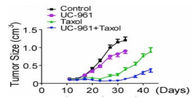
BACKGROUND

- Cirmtuzumab is a humanized monoclonal antibody (mAb) targeting the tyrosine kinase-like receptor 1, ROR1, expressed by tumor cells with stem-like properties of self-renewal, migration and metastasis.
- ROR1 is expressed in neoplastic disease including breast cancer.
- Preclinical studies showed cirmtuzumab had at least additive activity when combined with paclitaxel in treating mice bearing patient-derived xenografts.
- Cirmtuzumab was safe and effective in targeting ROR1+ leukemia cells in a Phase I trial.



Choi M et al, Cell Stem Cell 2018

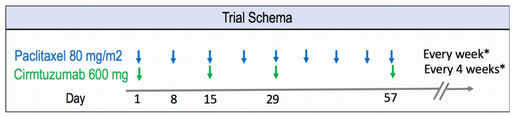


Zhang S et al PNAS 2019

METHODS

Study Endpoints	Eligibility
Primary: Safety **Secondary**: Clinical effects **Exploratory:** Biologic effects ***Duration of therapy until progression***	•Metastatic or locally advanced Her2 negative •No prior Taxane for mets •Any line of prior therapy

Trial Schema



*Paclitaxel or cirmtuzumab may continue as monotherapy if the other agent stopped due to toxicity

- Primary objective was to determine safety of cirmtuzumab and weekly paclitaxel in advanced Her2 negative breast cancer based upon dose limiting toxicities (DLTs) in the first cycle.
- Secondary/exploratory objectives were clinical activity, pharmacokinetics and correlative biomarkers on tumor specimens.
- Eligible patients had no paclitaxel in the metastatic setting, ECOG performance status 0-2, adequate laboratory parameters and any number of prior therapies.
- Study treatment included fixed dose 600 mg cirmtuzumab on days 1 and 15 of cycle 1 and then day 1 of each 28-day cycle along with paclitaxel weekly at 80mg/m^2 IV.
- 3 cohorts of 5 patients were planned for accrual for DLT assessment (15 total).

Figure 1: Baseline ROR1 Immunohistochemistry

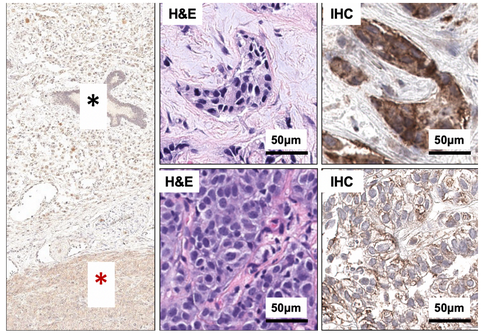


Figure 1: Left panel: Negative ROR1 staining in non-neoplastic mammary gland (black star) and in tumor area (red star). Top right panel ROR1 high expressor with 99% of the cells highly positive (3+= 5%; 2+ =67%; 1+ =27%; 0+ =1%). Bottom right panel ROR1 low expressor; 48% of the cells weakly positive (3+= 0%; 2+ =0.2%; 1+ =48%; 0+ =52% The stained FFPE sections were scanned and quantified using a Leica-Aperio T2 scanner

Figure 2: Pharmacokinetic Data in Plasma

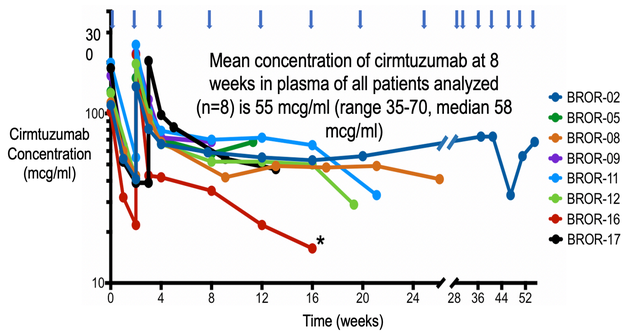


Figure 2. Cirmtuzumab concentration in plasma of eight patients. Cirmtuzumab concentration (mcg/mL) is indicated on the y axis, and time (weeks) is indicated on the x axis. Arrows indicate days of infusion of cirmtuzumab. Values indicated were determined by interpolation using a four-parameter logistic nonlinear regression model compared to a standard curve generated by serial dilutions of a known concentration of cirmtuzumab mAb. Cirmtuzumab half life was ≥28 days except for BROR-16.
* BROR-16 had frequent removal of ascitic fluid with a mean concentration of 7.6 ug/ml.

Figure 3: Pharmacokinetic Data in Pleural Fluid and Ascites

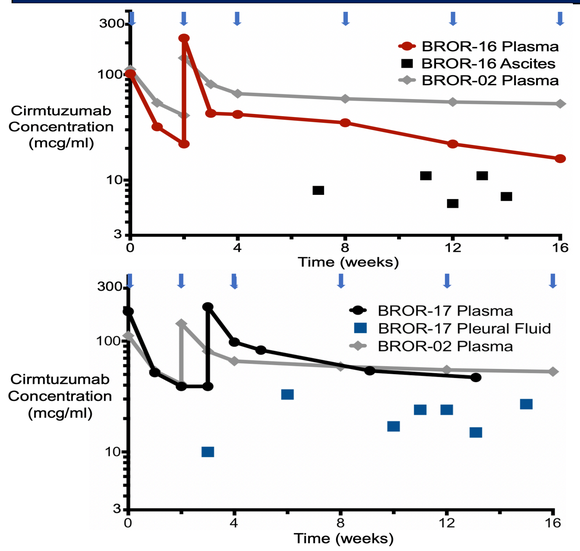


Figure 3 Cirmtuzumab concentration in plasma vs. ascites in BROR-16 and plasma vs. pleural fluid in BROR-17. Cirmtuzumab concentration (mcg/mL) is indicated on the y axis, and time (weeks) is indicated on the x axis. Arrows indicate days of infusion of cirmtuzumab. Decreases in antibody concentration in plasma seen in BROR-16 (Figure 2) may be due to accumulation of antibody in body fluid and frequent removal of ascites by paracentesis.

Table 1: Safety Data

Table 1: Most Common Adverse Events

Adverse Event	# of Events	# of Patients	Grade 1	Grade 2	Grade 3	Grade 4
Fatigue	14	13	12	1	0	0
Nausea	11	10	10	0	0	0
Peripheral motor neuropathy	7	6	5	2	0	0
Peripheral sensory neuropathy	7	6	5	2	0	0
Neutrophil Count decrease	7	4	0	1	4	1
Constipation	6	6	6	0	0	0
Alopecia	6	6	5	1	0	0

*All AEs were related to paclitaxel except for one Grade 3 neutropenia that was categorized as possibly related to cirmtuzumab.

Figure 4: BROR-2 Response Scans at Start of Therapy and Cycle 6

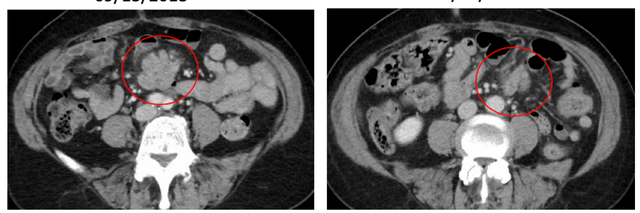


Figure 5: Best Tumor Response by Patient and % Tumor Volume Reduction

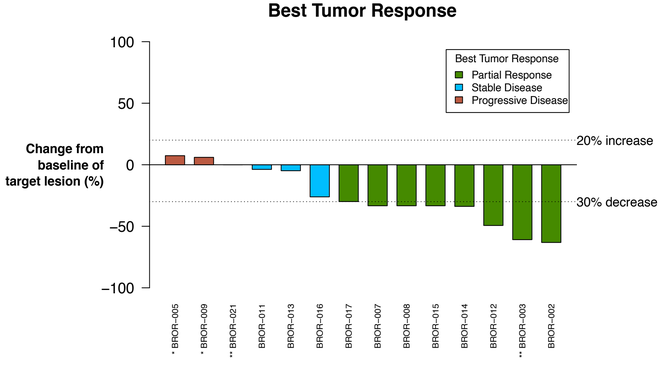


Figure 5: * BROR-05 and BROR-09 had stable disease with targeted lesion response, overall response was PD due to new or worsening non-targeted lesions.
** BROR-03 and BROR-21 were still on treatment as of 2/26/2021.
BROR-01 was not included in the graph due to progressive disease symptoms 3 weeks after treatment initiation requiring study discontinuation before first imaging assessment.

RESULTS

- To date, 15 patients were treated, ranging in age from 30-72. All 15 were evaluable for efficacy and 14 were evaluable for DLT's.
- Patients had received a median of 6 prior therapies for metastatic disease (endocrine + chemotherapy) prior to enrollment. 4/15 patients had triple negative breast cancer.
- No patient stopped cirmtuzumab due to toxicity, no dose reductions of cirmtuzumab were required and no DLTs were observed.
- Adverse events (AEs) were consistent with known safety profile of paclitaxel, with grade 3/4 neutropenia in 4 patients, grade 3 flu-like symptoms in 1 patient and grade 3 hyperglycemia in 1 patient.
- Only 8 of 15 patients had fresh or archival tissue at study enrollment; all 8 had ROR1+ tumor cells by IHC.
- At a dose of 600 mg every 4 weeks cirmtuzumab reached a median plasma concentration of 58 µg/mL.
- Analysis of pleural or ascitic fluid showed cirmtuzumab levels that were ≈30% those in plasma.
- On PK analyses cirmtuzumab was found to have a half-life of ≥28 days, except in one patient who had malignant ascites.
- Of 15 intent-to-treat patients to date, 8 (53%) had a partial response (PR), one durable for 52 weeks, and 4/15 patients had stable disease.
- Per protocol efficacy analysis of patients completing the first 2 cycles of study therapy 8/14 (57%) had a partial response (PR), one durable for 52 weeks, and 4/14 patients had stable disease.
- Patient derived xenografts (PDXs) have been generated from some tumor specimens to explore the mechanism(s) of activity of cirmtuzumab combination therapy.

CONCLUSIONS

- Cirmtuzumab given with paclitaxel was well-tolerated and demonstrated no added toxicity over that expected with paclitaxel alone in heavily pre-treated patients with metastatic breast cancer.
- All pre-treatment breast cancer samples available for analysis expressed ROR1 by immunohistochemistry.
- Pharmacokinetic analysis showed that cirmtuzumab had a half-life of ≥ 28 days and reached steady-state therapeutic levels with a dose of 600 mg, given every 4 weeks
- By RECIST criteria, 53% (8/15) achieved a partial response and another 27% (4/15) had stable disease; this is encouraging given that these patients had advanced breast cancer and had failed a median of 6 prior therapies.
- Further clinical evaluation of cirmtuzumab is warranted in patients with breast cancer.