166TiP - NCT03878849: A phase 2 trial of stenoparib/2X-121, a novel dual inhibitor of PARP and the WNT pathway, in platinum resistant/ ineligible Ovarian Cancer patients

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Abstract

Background:

2X-121 is an inhibitor of PARP1/2 and Tankyrase, a key enzyme activating the WNT/Beta-catenin oncogenic pathway. In a prior phase 2 study enrolling only advanced, recurrent ovarian cancer patients (pts) (14 platinum resistant, 1 primary platinum refractory) with a 2X-121-specific Drug Response Predictor (DRP) score of 50+, 2X-121 dosed BID (600mg total daily dose) showed evidence for durable clinical benefit. Benefit was evident in pts previously treated with PARP inhibitors and regardless of BRCA status. One BRCAmut and one BRCAwt pt stayed on drug nearly 30 months. Another showed complete, confirmed response by RECIST v1.1 (> 30 weeks of treatment). The pt with primary platinum refractory disease stayed on drug more than 10 months. Kaplan-Meier analysis showed a median OS of ~22 months with median time to follow-up of 29 months.

Methods:

Ph 2, randomized dose optimization study of 2X-121 investigating safety, tolerability, anti-tumor effects, and PK/PD in pts assessing two dose regimens (600 or 800 mg 2X-121 BID) in up to 40 pts randomized 1:1. Eligible pts must have histologically/ cytologically documented epithelial ovarian, fallopian tube, or primary peritoneal tumors with high-grade serious or endometroid, or predominantly serious/ endometroid histology (independent of BRCA1, HRD status), have platinum-resistant disease (progression less than 6 mo after last dose of platinum-based chemotherapy or are platinum ineligible), and 1 or fewer prior line of therapy (excluding ADCs) in the platinum resistant/ ineligible setting. Pts will be treated in 28-day cycles with tumor assessment via RECISTv1.1 every 8 weeks, dosed until progression or discontinuation for other reason. Primary endpoint is safety. Secondary endpoints include ORR, CBR, DCR, and PFS and OS, QOL and PK. Exploratory PD endpoints are planned (PARP and Wnt pathway activity). The use of the 2X-121-DRP and the establishment of a score cut-point for identifying patients most likely to benefit from 2X-121 will be assessed retrospectively from pre-treatment tumor biopsies. The optimal dose will be selected based on an integrated analysis of PK/PD, safety, and efficacy data. Enrollment is ongoing in the US and UK.

Clinical Trial identification: NCT03878849

Prior Trial in 3L+ Advanced Ovarian Cancer Patients

PhII Open-Label Clinical Study to Evaluate Stenoparib/2X-121 Monotherapy BID in Advanced, Recurrent Ovarian Cancer (NCT03878849)

Key Inclusion Criteria:

- Histologically or cytologically documented epithelial ovarian carcinoma
  - High grade serous, endometrioid, clear cell, carcinosarcoma, undifferentiated, and mixed histological subtypes
- Independent of platinum response, Platinum- free interval ≥ months
- Independent of BRCA/HRD status
- 2 or more previous chemotherapies/antibody therapies including treatment with other PARPi
- DRP > 50 on patient tumor biopsy for enrollment

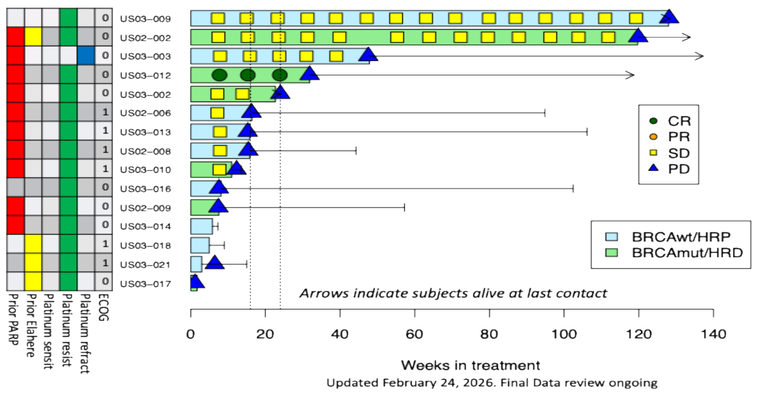
Dosing: Stenoparib/2X-121 PO BID (200mg + 400 mg) until progression

Primary Objective:

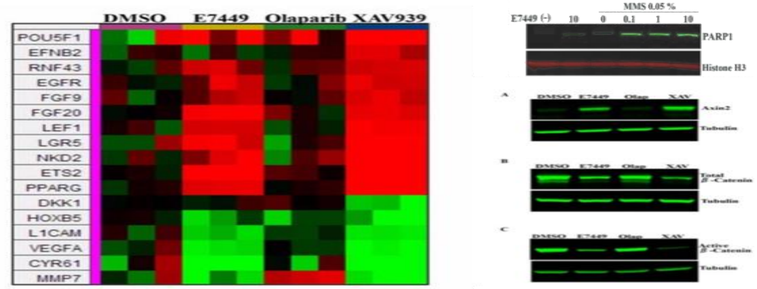
- Objective Response Rate by RECIST v 1.1

Secondary Objectives:

- Clinical Benefit Rate at 16 weeks (CR+PR+SD)
- PFS, DoR, OS, Clinical benefit correlation with DRP score, QoL



2X-121: a Dual PARP and Wnt Pathway Inhibitor



Left Panel shows gene expression profiles for 2X-121/ E7449 compared to DMSO control, the PARP inhibitor Olaparib and the Tankyrase inhibitor XAV939. The Right Panel Top shows PARP trapping by 2X-121/ E7499. The remaining three panels on the right show western blots for WNT pathway components – Axin and Beta catenin. Data from McGonigle et al., 2016

Trial In Progress: NCT03878849 *Now Enrolling*

Stenoparib Monotherapy in Platinum Resistant or Ineligible Ovarian Cancer

Objective: Solidify Dose for Pivotal Trial, Establish Cut-point for DRP Pre-selection in Pivotal Trial

Patients with Platinum Resistant or Platinum Ineligible Disease

- No more than 1L of chemo beyond declaration of Platinum Resistance, except ADCs
- No Platinum Refractory Pts or Pts with Ascites
- BRCA mutant and BRCAwt patients accepted

No DRP pre-selection- DRP will be assessed retrospectively in newer biopsy tissues

Randomization to one of two BID dose cohorts to address FDA's Project Optimus

- 200mg + 400mg (n=20) or 400mg + 400mg (n=20)

Safety and Efficacy

- Response Rate by RECIST v1.1, Clinical Benefit Rate, Progression Free Survival, Overall Survival

Study Sponsored by Allarity Therapeutics, Inc.
For Correspondence, please email Jeremy R Graff, PhD (President and Chief Development Officer, Allarity Therapeutics): jgraff@allarity.com)
COI- Dr Graff is an employee and officer of Allarity Therapeutics Inc

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