2X-121- a novel, dual inhibitor of PARP and tankyrase- shows promising clinical benefit in a phase 2 trial in advanced, recurrent ovarian cancer patients (NCT#03878849)

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Abstract

2X-121 (stenoparib/ E7499) inhibits PARP1/2 (1nM ~IC50) and Tankyrase 1/2 (IC50 ~50nM). As such, 2X-121 impairs DNA repair while simultaneously inhibiting the WNT/ß-catenin oncogenic signaling pathway. A Drug Response Predictor (DRP®) specific for 2X-121 has been developed from the *in vitro* sensitivity of cell lines in monolayer culture and highlights the gene expression profiles correlated with sensitivity to 2X-121. This DRP® signature is comprised of 414 genes, many of which reflect WNT/ ß-catenin pathway activity.

In a phase 1 dose escalation clinical study, 2X-121 showed clinical responses, especially in ovarian cancer patients. The 2X-121 DRP® retrospectively was able to identify patients who were most likely to benefit from 2X-121. A follow-on, open label phase 2 trial in 3L+ ovarian cancer patients with a DRP score > 50 started May 2023 with 2X-121 dosed BID for the first time. A total of fifteen (15) patients were enrolled independent of BRCA or Homologous DNA Repair status. Most patients were heavily pre-treated. Prior treatment included PARP inhibitors, mirvetuximab soravtansine and immunotherapy. Fourteen patients had platinum resistant disease, one had primary platinum refractory disease. The data show durable clinical benefit in patients with varied genetic and treatment backgrounds. 8 of 15 patients remained on study drug at least 16 weeks. 4 of these continued for more than 20 weeks and two patients remain on therapy now for more than 22 months – one being BRCA mutated, one BRCAwt/ HRP. The patient with primary platinum refractory ovarian cancer remained on study drug for nearly 50 weeks. In addition, one patient showed a complete, confirmed RECIST-based response and stayed on study drug for more than 30 weeks. Importantly, 2X-121 was well tolerated and did not show the myelotoxicity typical of earlier PARP inhibitors.

These data prompted the development of a refined clinical trial protocol that has recently opened to enrollment. In this new protocol, eligible patients are either platinum resistant or ineligible and have had no more than 1 additional line of chemotherapy after the designation of platinum resistance, other than ADCs. Patients will be randomized to receive 600mg or 800 mg total daily dose given BID. DRP will be assessed retrospectively. In addition to safety, this study will assess Clinical Benefit Rate, RECIST v1.1 based response, and PFS. Collectively, the safety profile and clinical benefit coupled to the unique dual mechanism of action suggest that 2X-121 may be a promising new therapy for advanced ovarian cancer patients.

NCT03878849 Trial Specifics

PhII Open Label Clinical Study to Evaluate Stenoparib 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 of ≥3 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 PO BID (200mg + 400 mg) until progression

Primary Objective:
- Objective Response rate by RECIST v1.1

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

New Protocol Now Enrolling PROC pts

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

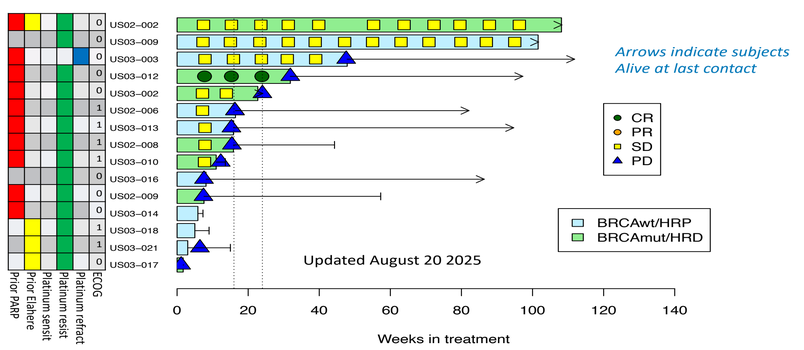
Patients with Platinum resistant or Platinum ineligible disease
- No more than 1L of chemo beyond declaration of Platinum Resistance, except ADCs
- No Platinum Refractory Pts or Pts with Ascites
- BRCA mutant and BRCA wt patients accepted

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

Randomization to one of two BID dose cohorts to address FDA's Project Optimus Edict
- 200mg + 400mg (n =20)
- 400mg + 400mg (n=20)

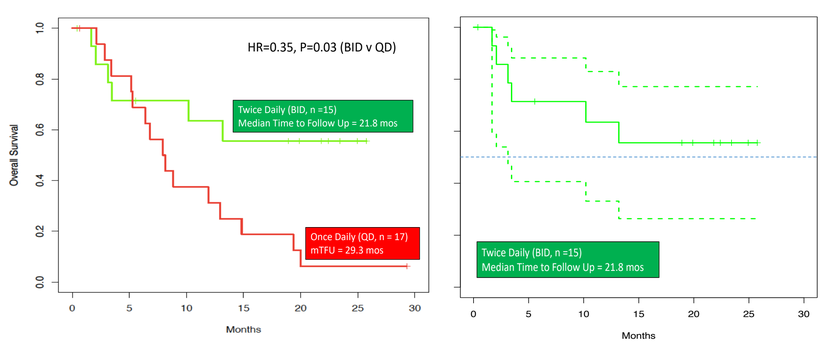
Safety and Efficacy
- Response Rate, Clinical Benefit Rate, Progression Free Survival, Overall Survival

Extended Clinical Benefit in BRCAwt and BRCAmut



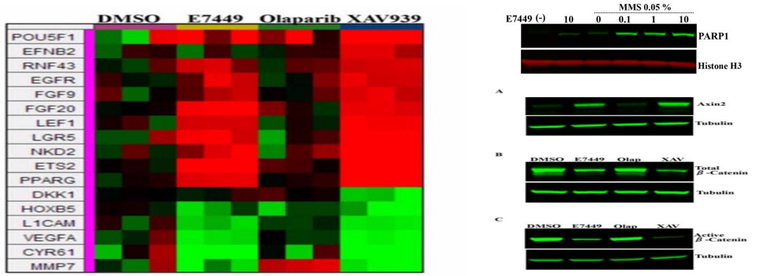
Swimmer's Plot for the BID Cohort of NCT03878849. Each bar represents a single patient across time from first dose. Patient platinum status, key prior therapies are shown on the grid to the left. Note: 14 of the 15 enrolled patients were platinum resistant. The remaining patient was Primary platinum refractory. Arrows represent survival of patients. Data are preliminary as the study continues with 2 patients – 1 BRCAmut and 1 BRCAwt- still on therapy now beyond 24 months.

mOS has not been reached (K-M Estimate >25 Months)



Kaplan-Meier Survival Analyses. Median Overall Survival (mOS) has not yet been reached for patients in the BID cohort of NCT03878849. Median Time to Follow-up is more than 22 months. Left panel includes the original QD cohort patients in red for context. Right panel shows the K-M plots with the confidence intervals represented by the dotted lines.

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 McConigle et al., 2016

2X-121/ E7449 Shows a Favorable Safety Profile

Stenoparib BID (N=15)

	Grade 1-4	Grade 3-4
Neutropenia	7%	0%
Anemia	21%	21%
Thrombocytopenia	0%	0%

Approved PARPi ex. Niraparib QD (N=463)[FDA Label]

	Grade 1-4	Grade 3-4
Neutropenia	20%	13%
Anemia	51%	27%
Thrombocytopenia	52%	28%

Conclusions

1. **2X-121 shows extended clinical benefit with 2 patients on therapy > 24 mos**
2. **Median Overall Survival has not yet been reached (K-M estimate >25 mos)**
3. **2X-121 shows a favorable safety profile**
4. **2X-121 has a unique, dual mechanism of therapeutic action (PARP/ WNT)**
5. **A new protocol in PROC is now enrolling to explore 2X-121 more deeply**

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