gynaecological cancers

**PHASE 1/2 STUDY OF ORAL RUCAPARIB: UPDATED PHASE 1 AND PRELIMINARY PHASE 2 RESULTS**


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**Aim:** Rucaparib is a potent, oral PARP inhibitor that induces synthetic lethality in homologous recombination deficient (HRD) tumors. Multiple mechanisms lead to HRD, which in turn leads to extensive genomic loss of heterozygosity (LOH). Patients (pts) with a BRCA mutation and/or high LOH may benefit from rucaparib treatment.

**Methods:** Phase 1 employed a 3 + 3 dose escalation design in patients with advanced solid tumors to identify the RP2D. Phase 2 is enrolling platinum-sensitive gBRCA OC pts (n = 41; 2-4 prior regimens required) with relapsed disease at the RP2D.

**Results:** Phase 1 enrolled 56 pts with advanced solid tumors (BRCA mutation and measurable disease not required) and established 600 mg BID as the RP2D. RECIST and/or CA-125 responses (2 CRs, 7 PRs, 3 CA-125) occurred in pts with ovarian, breast, or pancreatic cancer and a gBRCA mutation. At doses ≥360 mg BID, disease control (CR + PR + SD > 24 wks) in gBRCAmut OC pts was 82% (9/11), with 100% (3/3) of platinum-sensitive pts and 75% (6/8) of platinum-resistant pts deriving benefit. At the RP2D, 80% of gBRCAmut OC (3/4) and BC (1/1) pts had a RECIST or CA125 response. In addition, an OC pt, BRCAwt with high LOH in tumor, derived durable benefit (PFS = 36 wks). Overall, the most common AEs were mild to moderate GI effects and fatigue. At rucaparib doses ≥360 mg BID, treatment-related AEs in ≥20% of pts (%G1/G2/G3) included nausea (33/15/4), fatigue (19/22/0), vomiting (26/11/0). Grade 3 lab abnormalities included low Hgb (n = 5, 17%), low platelets (n = 2, 7%), low ANC (n = 1, 3%), and increased ALT (n = 1, 3%). No G4 AEs occurred and no pt discontinued rucaparib due to an AE. Phase 2 is ongoing, with early signs of clinical activity; updated efficacy and safety data will be presented at the meeting.

**Conclusions:** Overall, rucaparib is well tolerated with clinical benefit in pts with evidence of HRD in tumor. Durable benefit in a BRCAmut OC pt with high LOH highlights the treatment opportunity for rucaparib in this pt population. A pivotal program which prospectively tests an HRD molecular signature associated with rucaparib benefit in OC pts is ongoing.

**Disclosure:** R. Kristeleit: Membership on Clovis advisory boards; A.M. Oza: Clinical Trial Funding from sponsor to Princess Margaret Cancer Centre; J. Balmaña: Participated in a CLOVIS advisory board; L. Chen: Moderated a Genentech advisory board; R. Plummer: research funding from Clovis to run clinical trials and laboratory research, and honoraria for advisory boards; L. Maloney and E. Dominy: Employment and stock ownership; G. Shapiro: Research Funding is provided to Dana-Farber Cancer Institute for the conduct of the study. All other authors have declared no conflicts of interest.