gynaecological cancers

PRELIMINARY RESULTS OF ARIEL2, A PHASE 2 OPEN-LABEL STUDY TO IDENTIFY OVARIAN CANCER PATIENTS LIKELY TO RESPOND TO RUCAPARIB


1Wolton Wohl Cancer Research Centre, University of Glasgow, Glasgow, UK
2Department of Gynecologic Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA
3Dept. of Medicine, Princess Margaret Hospital, Toronto, ON, CANADA
4Gynecologic Oncology, Hematology & Oncology, UCLA Westwood Oncology Hematology, Los Angeles, CA, USA
5Department of Obstetrics and Gynecology, The Ohio State University Wexner Medical Center, Columbus, OH, USA
6Medical Oncology, Flinders Centre for Innovation in Cancer-FCIC, Bedford Park, AUSTRALIA
7Royal Melbourne Hospital, Parkville, AUSTRALIA
8Medical Oncology, Vall d’Hebron University Hospital Institut d’Oncologia, Barcelona, SPAIN
9Oncologie, Institut Bergonìe, Bordeaux, FRANCE
10St. Jude Heritage Medical Group, St Jude Heritage Medical Center, Fullerton, CA, USA
11Medical Oncology, Cancer Research UK, Cambridge Research InstituteAddenbrooke’s Hospital, Cambridge, UK
12Clovis Oncology, Clovis Oncology, San Francisco, CA, USA
13Clinical Science, Clovis Oncology, San Francisco, CA, USA
14Translational Medicine, Clovis Oncology, San Francisco, CA, USA
15Sheraton House, Clovis Oncology UK Ltd, Cambridge, UK
16Department of Obstetrics and Gynecology, University of Washington School of Medicine, Seattle, WA, USA

Aim: PARP inhibitors (PARPi) such as oral rucaparib are thought to be effective in cancers with homologous recombination deficiency (HRD), best shown to date in patients (pts) with a germline BRCA1/2 mutation (gBRCAmut). The Cancer Genome Atlas (TCGA) estimated ~50% of pts with high-grade serous ovarian carcinoma (OC) have HRD tumors. Multiple mechanisms can lead to HRD, which in turn can lead to genomic loss of heterozygosity (LOH). Currently, the best molecular predictors of PARPi response (other than BRCA mutation) are not known and platinum-sensitivity, a surrogate predictive indicator for PARPi response, is inadequate. Molecular analysis of tumor tissue to assess BRCA mutations as well as genomic LOH, a phenotypic endpoint of HRD, could be a more inclusive method for selection of pts for PARPi therapy.

Methods: The primary objective of Phase 2 study ARIEL2 is to identify a molecular HRD signature associated with clinical benefit from rucaparib treatment. This signature will be prospectively applied to the final analysis of the “all-comer” Phase 3 randomized pivotal trial (ARIEL3). ARIEL2 is an ongoing single-arm, open-label biomarker study designed to refine the molecular HRD signature associated with rucaparib response. Eligible pts (n = 180) have relapsed, platinum-sensitive, high-grade OC and measurable disease. Tumor HRD status is assessed using Foundation Medicine’s next generation sequencing platform with the current HRD algorithm, based on BRCA status and genomic LOH, developed using in vitro/in vivo and TCGA (and similar) bioinformatic data. PFS and response by RECIST will be correlated with tumor HRD status. Enrollment of gBRCAmut pts is limited to maximize non-gBRCAmut response predictors.

Results: Preliminary efficacy data from ARIEL2 indicate RECIST responses in patients who are BRCA wild-type and have high tumor genomic LOH as well as BRCAmut pts. Data for approximately 75 pts is anticipated to be available in late September.

Conclusions: Preliminary data indicate tumor genomic LOH as well as BRCA mutation analysis may predict OC pts likely to respond to rucaparib.

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