An open-label, phase II study of rucaparib, a PARP inhibitor, in HER2- metastatic breast cancer patients with high genomic loss of heterozygosity

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Background

• **BRCA1** and/or **BRCA2** mutations confer sensitivity to poly(ADP-ribose) polymerase (PARP) inhibitors (PARPI).

• In addition to **BRCA1/2**, alterations in other genes (e.g., **PALB2, RAD51C**) implicated in homologous recombination repair (HRR) pathways lead to genomic loss of heterozygosity (LOH) that is also associated with PARPI sensitivity.

• **Inhibition of PARP-1, -2, and -3**, results in accumulation of double-strand DNA breaks that are repaired through HRR. Defects in HRR can sensitize tumors to PARP inhibition through synthetic lethality.

• **Rucaparib** is a potent, oral small molecule inhibitor of PARP-1, -2, and -3 being developed for treatment of tumors associated with HRR deficiency (HRD). It was approved in the US in December 2016 for the treatment of patients with deleterious **BRCA** mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies. Since April 2018, marketing approval has been extended to the management of advanced ovarian cancer who are in a complete or partial response to platinum-based chemotherapy.

• Rucaparib has shown activity in a previous phase I study in breast cancer patients with a germline **BRCA1/2** mutation (Kristeleit et al, Clin Can Res 2017).

**Genomic Loss of Heterozygosity (LOH)**

• Additional data indicates that the tumor activity of rucaparib extends beyond tumors with a **BRCA1/2** mutation to a broader group of tumors with HRD.

• Clovis Oncology, in collaboration with Foundation Medicine, has developed an integrative method to assess HRD by determining LOH, which increases due to the use of error-prone DNA repair pathways when HR repair is compromised (Tutt et al, EMBO 2001; Venkitaraman, NEJM 2003). One of the main advantages of detecting tumor genomic LOH is that it can identify HRD tumors regardless of the underlying mechanisms, which include both known (i.e., **BRCA1/2** mutations, **BRCA1** methylation) and unknown genetic/epigenetic changes (Wang, Clin Cancer Res 2012).

• **ARIEL3** (NCT01968213) demonstrated a statistically significant improvement in median progression-free survival (PFS) for advanced ovarian cancer patients randomized to rucaparib compared with placebo in the HRD population (LOH high) (Coleman, Lancet 2017).

**RUBY STUDY**

This single arm, open-label, multicenter phase II study (NCT02505048) is evaluating the efficacy and safety of rucaparib in patients (pts) with HER2- metastatic breast cancer associated with a high tumor genomic LOH and/or **BRCA** mutation (excluding germline mutation).

**Study methods and design**

• The primary endpoint is clinical benefit rate (CBR), defined by complete (CR) and partial response (PR) and stable disease (SD) ≥16 weeks. If CBR is significant, the objective response rate will be assessed according to a hierarchic procedure.

• Secondary endpoints:
  - Progression Free Survival
  - Overall Survival
  - Safety
  - To evaluate the predictive value of high genomic LOH
  - To evaluate the prognostic value of high genomic LOH

• Targeted enrollment is 41 pts using a Simon two-stage design.

**Study assessments and procedures**

• **Trial duration:**
  - Inclusion period initially planned: 1 year
  - Post-treatment follow-up period: 24 months
  - Overall trial duration: 3.5 years

**Genomic LOH screening**

• **RUBY screening phase** is covered by the SAFIR patient informed consent form.

• LOH is determined by Clovis Oncology on Affymetrix (CytoScan HD or OncoScan) array available from the SAFIR protocol.

• For patients to be eligible for RUBY, a prespecified cutoff of ≥18% was used to define high genomic LOH based on platinum-based chemotherapy outcome data for both primary breast tumors in The Cancer Genome Atlas (TCGA) and metastatic breast tumors in the SAFIR01 (NCT01414933) and SAFIR02 (NCT02299999) studies (André et al, Lancet Oncol 2014).

• If LOH high, or somatic **BRCA** mutation, and baseline assessments fulfill inclusion criteria, patient can be included in RUBY.

**Eligibility**

**INCLUSION CRITERIA:**

• Women age ≥18 years

• Histologically proven breast cancer, Her2 negative

• WHO Performance Status 0/1

• At least one line of chemotherapy in the metastatic setting

• High genomic LOH as defined by the Clovis genomic signature or inactivating **BRCA1/2** somatic mutation (without known germline **BRCA2** mutation)

• Measurable target lesion (RECIST criteria v1.1)

**EXCLUSION CRITERIA:**

• **BRCA1 or BRCA2** germline known mutation

• Life expectancy <3 months

• Patients previously treated with a PARP inhibitor

• Toxicities of grade ≥2 from any previous anti-cancer therapy, with the exception of alopecia

• Altered haematopoietic, liver and renal function

**Study progress**

• Study initiated in August 2016

• To date
  - 582 SNP array data have been screened by Clovis Oncology
  - 19 pts have been enrolled in the 1st step and 7 pts in the 2nd step, with enrollment ongoing

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