#TPS1117
Poster Session: Breast Cancer–Metastatic 6/4/2017 8:00 AM-11:30 AM

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

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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 (eg, *PALB2, RAD51C*) implicated in homologous recombination repair (HRR) pathways lead to genomic loss of heterozygosity (LOH) that is also associated with PARPi sensitivity.
- Rucaparib is a potent, oral small molecule inhibitor of poly (ADP-ribose) polymerase (PARP)-1, -2, and -3 being developed for treatment of tumors associated with homologous recombination repair deficiency (HRD).
- 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 (MBC) associated with a somatic *BRCA* mutation and/or high tumor genomic LOH.

Genomic LOH

- **Loss of Heterozygosity:** 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 loss of heterozygosity across the tumor genome (tumor genomic 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 mechanisms (Wang, Clin Cancer Res 2012).
- ARIEL2 (NCT01891344) was the first study to assess the utility of genomic LOH quantified by use of a next-generation sequencing (NGS) assay to predict response to the PARP inhibitor rucaparib (Swisher *et al*, Lancet Oncol 2017).
- 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).

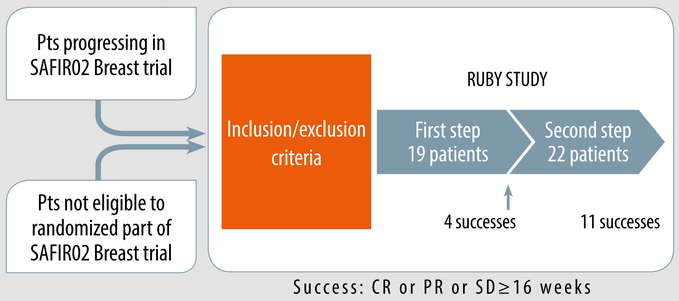
PARP Inhibitors

- **Inhibition of Poly (ADP-ribose) polymerase (PARP)-1, -2, and -3**, which has a major role in the repair of DNA single-strand breaks, results in accumulation of double-strand DNA breaks that are repaired through HRR. Defects in HRR or HRD (eg, mutations in *BRCA1*, *BRCA2*, or other HRR pathway genes) can sensitize tumors to PARP inhibition through synthetic lethality.
- **Rucaparib** is a potent small molecule inhibitor of PARP-1, -2, and -3. 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. 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).

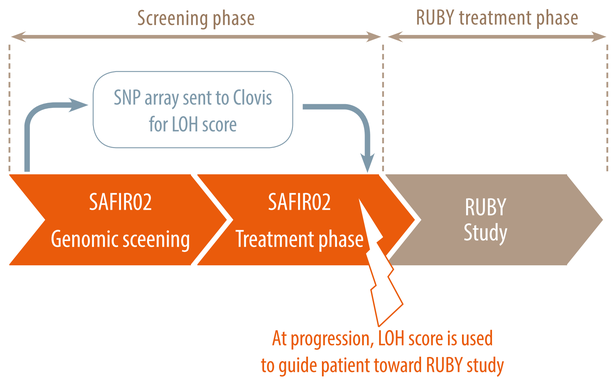
Methods

- Pts with HER2- MBC exhibiting a high tumor genomic LOH phenotype, or a somatic *BRCA1* or *BRCA2* mutation, receive oral rucaparib 600mg BID continuously in 28-day cycles until disease progression.
- 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.
- Trial duration:
  - Inclusion period: 1 year
  - Post-treatment follow-up period: 24 months
  - Overall trial duration: 3.5 years

Study design



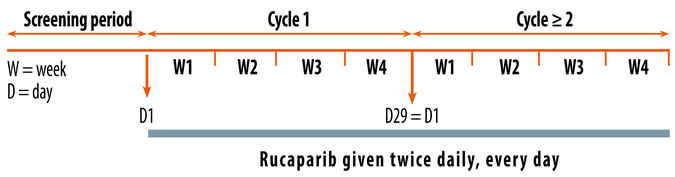
Study assessment and procedure



The screening phase is covered by the SAFIR02 Breast patient informed consent form.

After the consent form is signed for the RUBY study and the results from the baseline assessment are validated, eligible patients will be validated by UNICANCER.

Treatment scheme



Eligibility

INCLUSION CRITERIA:

- Women age ≥18 years with histologically proven breast cancer
- WHO Performance Status 0/1
- No Her2 over-expression
- Progressive metastatic disease previously treated with at least one line of chemotherapy in the metastatic setting
- Molecular analysis using the Affymetrix (CytoScan HD,SNP 6.0, or OncoScan) array available from the SAFIR02 protocol, or from other programs
- High genomic LOH as defined by the Clovis genomic signature or inactivating *BRCA1/2* somatic mutation (without known germline *BRCA* mutation)
- Presence of measurable target lesion according to RECIST criteria v1.1
- Patients will have had at least a 21-day wash-out period from last chemotherapy or targeted therapy administration prior to inclusion and should have recovered (grade ≤1) from all residual toxicities, excluding alopecia

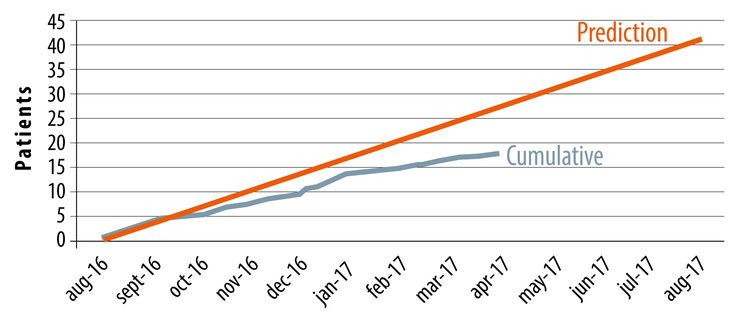
EXCLUSION CRITERIA:

- *BRCA1* or *BRCA2* germline known mutation
- Life expectancy <3 months
- Patients previously treated with a PARP inhibitor
- Patients with all target lesions in a previously irradiated region, except if clear progression has been observed prior to study in at least one of them
- Toxicities of grade ≥2 from any previous anti-cancer therapy, with the exception of alopecia
- Altered haematopoietic or organ function, as indicated by the following criteria:
  - Polynuclear neutrophils <1.5 x 10^9/L
  - Platelets <100 x 10^9/L
  - Haemoglobin ≤90 g/L
  - ALT/AST >2.5 x ULN in the absence of or >5 x ULN in the presence of liver metastases
  - Bilirubin >1.5 x ULN
- Creatinine clearance ≤30 mL/min (measured or calculated by Cockcroft and Gault formula

Study progress

- Study initiated in August 2016
- To date
  - 344 SNP array data have been screened by Clovis
  - 18 pts have been enrolled, with enrollment ongoing

Current enrollment



Acknowledgments

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