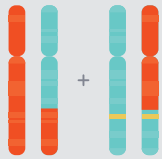
Retention of Heterozygosity



Loss of Heterozygosity

TOPIC OVERVIEW

LOH & Actionability in Ovarian Cancer

LOH scoring and cutoff value as part of an algorithm to determine the HRD status

LOH results from genomic scarring events if a tumor is HRD+. It is summarized as a score, with a cutoff of 16% being associated with a greater benefit from the PARP inhibitor rucaparib in ovarian cancer patients with platinum-sensitive disease, based on the ARIEL3 study[2,4]. *BRCA*-positive and/or LOH high are used to determine the status of HRD [1,2].

Trial Study Design Population	Interventions	Biomarker Prevalence in ARIEL3[4]		Results by HRD subgroup[2]
ARIEL3[2], phase 3, double-blind, randomized, ovarian carcinoma, n=564	Rucaparib vs. placebo; following ≥2 prior platinum chemo,	*BRCA*-mutant Germline Somatic Unknown**	34.8% 23.7% 9.6% 1.6%	Rucaparib vs Placebo mPFS: 16.6 vs 5.4 mo HR: 0.23; p<0.0001
		BRCA wild-type LOH ≥16% LOH <16% LOH indeterminate***	65.2% 27.9% 28.5% 8.7%	Rucaparib vs Placebo • BRCAwt/LOH-High mPFS: 9.7 vs 5.4 mo HR: 0.44; p<0.0001 • BRCAwt/LOH-Low mPFS: 6.7 vs 5.4 mo HR: 0.58; p=0.0049

* Confirmed objective responses by RECIST 1.1
** Tumor sample was *BRCA* mutant by FoundationOne CDx, but a blood sample was not available for central germline testing.
*** Tumor sample was not evaluable for percentage of genomic LOH due to low tumor content or low aneuploidy.

Acronyms/abbreviations: LOH-H: Loss of heterozygosity high; homologous recombination repair (HRR); Response rate (RR); Objective Response Rate (ORR); Progression-free Survival (PFS); median PFS (mPFS); radiographic progression-free survival (rPFS); Overall Survival (OS), median OS (mOS); Months (mo)

BACKGROUND

- Positive homologous recombination deficiency (HRD+) status, defined as deleterious tumor *BRCA1/2* variants and/or LOH high, in ovarian cancer patients is associated with improved progression-free survival (PFS) from rucaparib (Rubraca) maintenance therapy[1,2].
- FoundationOne® CDx§ was approved for qualitative detection of *BRCA1/2* sequence alterations and LOH from formalin-fixed, paraffin-embedded (FFPE) ovarian tumor tissue in April 2018[3,4].
- LOH with ≥16% score validated as HRD+ for ovarian tumor tissue run on FoundationOne®CDx§ only.

REFERENCES

1. Swisher EM, et al. Lancet Oncol 2017; 18:75–87
2. Coleman RL, et al. Lancet 2017; 390:1949–61
3. https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160018S001a.pdf
4. Oaknin A et al. JCO 2018; 36, no. 15_suppl 5545-5545 https://www.clovisoncology.com/media/1026/rucaparib_aoaknin_poster_asco2018.pdf
5. https://clovisoncology.com/media/1094/rubraca-prescribing-info.pdf
6. https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160018S001b.pdf

References 1-4 used an earlier laboratory developed version of FoundationOne®CDx test

§ FoundationOne®CDx is a next-generation sequencing based in vitro diagnostic device for detection of substitutions, insertion and deletion alterations, and copy number alterations in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens. For the complete intended use statement, including companion diagnostic indications, please see the FoundationOne CDx Technical Information, www.foundationmedicine.com/f1cdx. FoundationOne Liquid and FoundationOne Heme have not been cleared or approved by the U.S. FDA. For more information visit us at www.foundationmedicine.com

Note: Images in this document designed internally

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ADDITIONAL INFORMATION

LOH Score

- The LOH score is determined by leveraging estimated copy number and minor allele count of SNPs across the interrogated genomic regions[6].
- Because the LOH score represents accumulated genomic scarring events as a result of positive HRD, LOH is expected to only ever increase over time for a particular tumor. However, for the final binary classification of LOH positive vs LOH negative in these patients, a cutoff of 16% is imposed on the LOH score[2,4,6].

LOH actionability as reported on FoundationOne CDx§ or FoundationOne Heme§

- LOH high in ovarian cancer patients is associated with improved progression-free survival (PFS) from PARP inhibitor Rubraca (rucaparib) maintenance therapy in accordance with the RUBRACA product label[3,5].

Caveats of LOH measurement and cutoff

- For cases with LOH score between 13-19%, a caveat will appear on the claims page per FDA requirement due to its proximity to the cutoff value of 16%[6].
- For samples with insufficient tumor purity (< 35%) or for which the pipeline is unable to generate a copy number alteration model, the LOH score cannot be confidently calculated. In these scenarios the status will be FAIL and the finding listed as "Cannot Be Determined"[6]. A complete list of scenarios to determine HRD status are listed in the table on the right.

LOH Score≥16%	Mutant *BRCA1/2*	HRD Status
Yes	Yes	**HRD+**
Yes	No	**HRD+**
No	Yes	**HRD+**
No	No	**HRD-**
Cannot Be Determined	Yes	**HRD+**
Cannot Be Determined	No	**HRD-**

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