TOPIC OVERVIEW

LOSS OF HETEROZYGOSITY IN OVARIAN CANCER

Loss of heterozygosity (LOH) scoring and cutoff value as part of an algorithm to determine the homologous recombination deficiency (HRD) status

LOH results from genomic scarring events if a tumour is HRD+. It is summarised 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]

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LOH IN OVARIAN CANCER

BACKGROUND

- Positive homologous recombination deficiency (HRD+) status, defined as deleterious tumour *BRCA1/2* variants and/or LOH high, in ovarian cancer patients is associated with improved progression-free survival (PFS) from rucaparib 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 tumour tissue in April 2018.[3,4]
- LOH with ≥16% score validated as HRD+ for ovarian tumour tissue run on FoundationOne®CDx[§] only.

ARIEL3: HRD+ status (*BRCA*-mutation and/or LOH high) was associated with improved PFS with rucaparib vs. placebo

TRIAL STUDY POPULATION[2]	INTERVENTIONS	BIOMARKER PREVALENCE IN ARIEL3[2]		INVESTIGATOR-ASSESSED PFS BY HRD SUBGROUP[2]
		RUCAPARIB ARM	PLACEBO ARM	
ARIEL3, phase III, double-blind, randomised, ovarian carcinoma, n=564	Rucaparib vs. placebo; following ≥2 prior lines of platinum-based chemotherapy	*BRCA*-mutant: 35% Germline: 22% Somatic: 11% Unknown: 2%*	*BRCA*-mutant: 35% Germline: 25% Somatic: 8% Unknown: 1%*	Rucaparib vs. placebo *BRCA*-mutant mPFS: 16.6 vs 5.4 mo HR: 0.23; p<0.0001
		BRCA-wild type: 65% LOH high (≥16%): 28% LOH low (<16%): 29% LOH intermediate: 9%†	*BRCA*-wild type: 65% LOH high (≥16%): 28% LOH low (<16%): 29% LOH intermediate: 9%†	Rucaparib vs. placebo • *BRCA*wt/LOH high mPFS: 9.7 vs 5.4 mo HR: 0.44; p<0.0001 • *BRCA*wt/LOH-Low mPFS: 6.7 vs 5.4 mo HR: 0.58; p=0.0049

*Tumour sample was *BRCA* mutant by FoundationOne®CDx, but a blood sample was not available for central germline testing.
†Tumour sample was not evaluable for percentage of genomic LOH due to low tumour content or low aneuploidy.

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.[5]
- 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 tumour. 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.[2,4,5]

LOH actionability as reported on FoundationOne®CDx[§]

- LOH high in ovarian cancer patients is associated with improved progression-free survival (PFS) from PARP inhibitor rucaparib maintenance therapy.[3]

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%.[5]
- For samples with insufficient tumour purity (<35% of tumour cells) 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".[5] 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–**

ABBREVIATIONS AND REFERENCES

HR, hazard ratio; HRD, homologous recombination repair deficiency; HRR, homologous recombination repair; mo, months; mOS, median overall survival; mPFS; median progression-free survival; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; rPFS, radiographic progression-free survival; RR, response rate; SNP, single nucleotide polymorphism; wt, wild type.

1. Swisher EM, *et al. Lancet Oncol* 2017;18:75–87.
2. Coleman RL, *et al. Lancet* 2017;390:1949–1961.
3. FoundationOne®CDx FDA approval for RUBCARA®, 2018. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160018S001a.pdf (Accessed December 2019).
4. Oaknin A, *et al.* Presented at ASCO Annual Meeting 2018, Chicago (Illinois), US: Poster no. 5545. Available at: https://www.clovisoncology.com/media/1026/rucaparib_aoaknin_poster_asco2018.pdf (Accessed December 2019).
5. FDA. FoundationOne®CDx Summary of Safety and Effectiveness Data (SSED). Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf16/P160018S001b.pdf (Accessed December 2019).

References 1–5 used an earlier laboratory-developed version of the 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 tumour mutational burden (TMB) using DNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumour 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.rochefoundationmedicine.com.

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