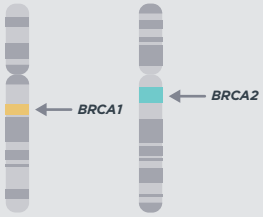


Chromosome 17 Chromosome 13

TOPIC OVERVIEW

BRCA1/2 & Actionability in Ovarian Cancer

A BRCA1/2 alteration can be classified as a deleterious tumor BRCA variant if it meets any of the three criteria in Table 1.[8]

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 maintenance therapy.[1,2]
- FoundationOne®CDx[§] was approved for detection of *BRCA1/2* sequence alterations and LOH from formalin-fixed, paraffin-embedded (FFPE) ovarian tumor tissue for rucaparib, based on the ARIEL3 study, in April 2019.[2,3,4]
- FoundationOne CDx was also approved as a companion diagnostic for olaparib as first-line maintenance therapy in *BRCA*-mutated advanced ovarian cancer, based on analysis of the SOLO1 clinical study, in July 2019.[5,6,7]
- Clinical performance of FoundationOne CDx was established in patients with either germline or somatic *BRCA*-mutated ovarian cancer, however, it does not distinguish between germline or somatic mutations.[1,2,7]

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. Moore K, et al. *N Engl J Med* 2018; 379:2495-2505
6. http://investors.foundationmedicine.com/news-releases/news-release-details/foundation-medicine-expands-indication-foundationonercdx
7. FoundationOne CDx Technical Info - Assessed on 16th Oct 2019 -Table 39.
8. https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019C.pdf
9. Pennington KP, et al. *Clin Cancer Res.* 2013;20(3):764-75

Acronyms/abbreviations: base pair (bp); Loss of heterozygosity (LOH); homologous recombination deficiency (HRD); Progression-free survival (PFS)

§ 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/flcdx.

Note: Images in this document designed internally

Last Updated Oct 24th, 2019

Table 1: Classification Criteria for Deleterious Tumor *BRCA* Mutations Covered by FoundationOne CDx.[8]

Sequence Classifications	Detailed Description
Protein truncation alterations	Premature stop codons anywhere in *BRCA1/2* coding regions with exception of *BRCA2* K3326* and any alteration 3' downstream of K3326
Splice slice alterations	Splice sequence alteration at intron/exon junctions -/+ 2 bp of exon starts/ends
Deleterious missense mutations	Listed in Table 2

Note: transcript IDs used in this table - *BRCA1* U14680 and *BRCA2* U43746

Table 2: Select Deleterious *BRCA* Missense Mutations Covered by FoundationOne CDx.[8]

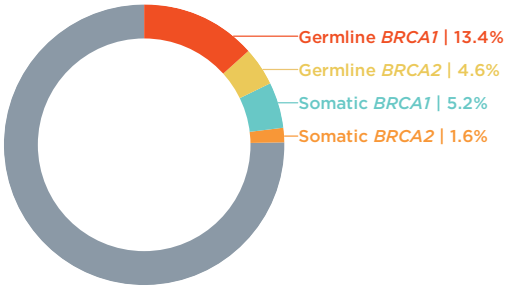
BRCA1 alterations (Protein Change)	*BRCA2* alterations (Protein Change)
c.1 A>G (M1V)	c.2T>G (M1R)
c.3G>T (M1I)	c.3G>T (M1I)
c.181T>G (C61G)	c.475G>A (V159M)
c.191G>A (C64Y)	c.631G>C (V211L)
c.211A>G (R71G)	c.631G>A (V211I)
c.212G>A (R71K)	c.7007G>C (R2336P)
c.4484G>T (R1495M)	c.7007G>A (R2336H)
c.4675G>A (E1559K)	
c.5074G>A (D1692N)	
c.5074G>C (D1692H)	
c.5095C>T (R1699W)	
c.5123C>A (A1708E)	
c.5363G>T (G1788V)	

ADDITIONAL INFORMATION

1. *BRCA1/2* reference database and transcript IDs used:[8]

- The curated list of deleterious *BRCA1/2* alterations is based on the Breast Cancer Information Core (BIC) database.
- The transcript IDs for the deleterious missense alterations listed in Table 2 are: *BRCA1* U14680 and *BRCA2* U43746.

2. Frequencies of germline and somatic *BRCA1/2* mutations in ovarian cancer[9]



- FoundationOne CDx may help identify more ovarian cancer patients who could benefit from PARP inhibitors, including rucaparib or olaparib, as compared to conventional test methods that only identify germline *BRCA* mutations.[1,2,5,6,9]

3. *BRCA1/2* detection considerations:[7]

- *BRCA1/2* alterations reported may include somatic (not inherited) or germline (inherited) alterations. FoundationOne CDx does not distinguish between germline and somatic mutations.
- Identification of BRCA1/2 short insertion/deletions (indels) is up to 13 bp.
- Alterations in polyT homopolymer runs may not be reliably detected in *BRCA1/2*
- Certain large rearrangements in *BRCA1/2* including large scale genomic deletions (affecting at least one whole exon), insertions or other deleterious genomic rearrangements including inversions or transversion events, may not be detected in an estimated 5% of ovarian cancer patients with *BRCA1/2* mutations by FoundationOne CDx.
- Certain potentially deleterious missense or small in-frame deletions in *BRCA1/2* may not be reported under the "CDx associated findings" but may be reported in the "Other alterations and biomarkers identified" section in the patient report.

FOUNDATION MEDICINE

Tel. 888.988.3639 Fax 617.418.2290