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**Date:** 11 May 2023 1 of 14

## **Sample Information**

Patient Name: 高慧柔 Gender: Female ID No.: J222631644 History No.: 48937366

**Age:** 30

Ordering Doctor: DOC2589K 曾令民

Ordering REQ.: D75J8AH Signing in Date: 2023/05/11

**Path No.:** M112-00099 **MP No.:** BR23028

Assay: Oncomine BRCA1/2 Assay

Sample Type: Blood

Date of blood drawing: 2023/05/01

Reporting Doctor: DOC5424G 彭昱璟 (Phone: 8#5424)

Note:

## Sample Cancer Type: Breast Cancer

Table of Contents	Page
Variant Details	1
Biomarker Descriptions	2
Relevant Therapy Summary	3
Relevant Therapy Details	4
Alert Details	13

## Report Highlights 1 Relevant Biomarkers 5 Therapies Available

0 Clinical Trials

### **Relevant Biomarkers**

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	BRCA1 p.(R1751*) c.5251C>T BRCA1 DNA repair associated Allele Frequency: 46.59%	olaparib talazoparib	bevacizumab + olaparib 1,2 olaparib 1,2 rucaparib 1 niraparib	0

Public data sources included in relevant therapies: FDA1, NCCN, EMA2, ESMO

#### **Variant Details**

DNA	Sequence Varia	ants						
Gene	Amino Acid Change	Coding	Locus	Allele Frequency	Transcript	Variant Effect	ClinVar1	Coverage
Gene	Allillo Acid Charige	County	Locus	riequency	Transcript	Variant Enect	Ciliivai ·	Coverage
BRCA1	p.(R1751*)	c.5251C>T	chr17:41209095	46.59%	NM_007294.4	nonsense	Pathogenic	734

<sup>1</sup> Based on Clinvar version 20200329

## **Variant Details (continued)**

#### **DNA Sequence Variants (continued)**

Gene	Amino Acid Change	Coding	Locus	Allele Frequency	Transcript	Variant Effect	ClinVar <sup>1</sup>	Coverage
BRCA2	p.(?)	c26G>A	chr13:32890572	50.42%	NM_000059.3	unknown	Benign	1664
BRCA2	p.(K1132=)	c.3396A>G	chr13:32911888	50.68%	NM_000059.3	synonymous	Benign	1616
BRCA2	p.(L1521=)	c.4563A>G	chr13:32913055	100.00%	NM_000059.3	synonymous	Benign	648
BRCA2	p.(V2171=)	c.6513G>C	chr13:32915005	100.00%	NM_000059.3	synonymous	Benign	992
BRCA2	p.(S2414=)	c.7242A>G	chr13:32929232	49.71%	NM_000059.3	synonymous	Benign	865
BRCA2	p.(V2466A)	c.7397T>C	chr13:32929387	99.88%	NM_000059.3	missense	Benign	855

<sup>1</sup> Based on Clinvar version 20200329

## **Biomarker Descriptions**

#### **BRCA1 (BRCA1 DNA repair associated)**

Background: The breast cancer early onset gene 1 (BRCA1) encodes one of two BRCA proteins (BRCA1 and BRCA2) initially discovered as major hereditary breast cancer genes. Although structurally unrelated, both BRCA1 and BRCA2 exhibit tumor suppressor function and are integrally involved in the homologous recombination repair (HRR) pathway, a pathway critical in the repair of damaged DNA1,2. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity1,2. Inherited pathogenic mutations in BRCA1/2 are known to confer increased risk in women for breast and ovarian cancer and in men for breast and prostate cancer3,4,5. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, estimated lifetime risks range from 41% to 90% for developing breast cancer and 8 to 62% for developing ovarian cancer6.

Alterations and prevalence: Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer and 5-10% of breast cancer<sup>7,8,9,10,11,12,13</sup>. Somatic alterations in BRCA1 are observed in 2-8% of breast, ovarian, cervical, uterine, diffuse large B-cell lymphoma (DLBCL), melanoma, gastric, bladder, squamous lung, colorectal, and head and neck cancers<sup>14,15</sup>.

Potential relevance: Individuals possessing BRCA1/2 pathogenic germline or somatic mutations are shown to exhibit sensitivity to platinum based chemotherapy as well as treatment with poly (ADP-ribose) polymerase inhibitors (PARPI)16. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells<sup>17,18</sup>. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib19 (2014) was the first PARPI to be approved by the FDA for BRCA1/2 aberrations. Originally approved for the treatment of germline variants, olaparib is now indicated (2018) for the maintenance treatment of both germline BRCA1/2-mutated (gBRCAm) and somatic BRCA1/2-mutated (sBRCAm) epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responsive to platinum-based chemotherapy. Olaparib is also indicated for the treatment of patients with gBRCAm HER2-negative metastatic breast cancer and metastatic pancreatic adenocarcinoma. Additionally, olaparib<sup>19</sup> is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA1. Rucaparib<sup>20</sup> is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib<sup>21</sup> (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib<sup>22</sup> (2017) is another PARPi approved for the treatment of epithelial ovarian, fallopian tube, or primary peritoneal cancers with a deleterious or suspected deleterious BRCA mutation. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported<sup>23</sup>. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality<sup>24</sup>. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex<sup>25</sup>, for BRCA1/2, PALB2, or other homologous recombination deficiency (HRD) mutations in breast and ovarian cancers. Like PARPi, pidnarulex promotes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability.

**Date**: 11 May 2023 3 of 14

# **Relevant Therapy Summary**

■ In this cancer type
O In other cancer type
In this cancer type and other cancer types
X No evidence

BRCA1 p.(R1751*) c.5251C>T					
Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	0	0	0	•	×
bevacizumab + olaparib	0	0	0	0	×
rucaparib	0	0	×	0	×
niraparib	×	0	×	0	×
talazoparib	×	×	×	•	×

Date: 11 May 2023 4 of 14

## **Relevant Therapy Details**

#### **Current FDA Information**

In this cancer type

In other cancer type

In this cancer type and other cancer types

FDA information is current as of 2023-03-15. For the most up-to-date information, search www.fda.gov.

## BRCA1 p.(R1751\*) c.5251C>T

### O olaparib, bevacizumab + olaparib

Cancer type: Castration-Resistant Prostate Label as of: 2022-10-27 Variant class: BRCA1 mutation

Cancer, Ovarian Cancer

#### Indications and usage:

LYNPARZA® is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated:

#### Ovarian cancer

- for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA®.
- in combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either:
  - a deleterious or suspected deleterious BRCA mutation, and/or
  - genomic instability.

Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA®.

• for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy.

#### Breast cancer

- for the adjuvant treatment of adult patients with deleterious or suspected deleterious gBRCAm human epidermal growth factor receptor 2 (HER2)-negative high risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA®.
- for the treatment of adult patients with deleterious or suspected deleterious gBRCAm, HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA®.

#### Pancreatic cancer

for the maintenance treatment of adult patients with deleterious or suspected deleterious gBRCAm metastatic pancreatic adenocarcinoma whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA®.

#### Prostate cancer

for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA®.

#### Reference:

https://www.accessdata.fda.gov/drugsatfda\_docs/label/2022/208558s024lbl.pdf

**Date**: 11 May 2023 5 of 14

## BRCA1 p.(R1751\*) c.5251C>T (continued)

### O rucaparib

Cancer type: Castration-Resistant Prostate Label as of: 2022-12-21 Variant class: BRCA1 mutation

Cancer, Ovarian Cancer

#### Indications and usage:

RUBRACA® is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated:

#### Ovarian cancer

• for the maintenance treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)- associated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

#### Prostate cancer

for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor-directed therapy and a taxanebased chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for RUBRACA®.

This indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

#### Reference:

https://www.accessdata.fda.gov/drugsatfda\_docs/label/2022/209115s013lbl.pdf

**Date:** 11 May 2023 6 of 14

#### **Current NCCN Information**

NCCN information is current as of 2023-03-01. For the most up-to-date information, search www.nccn.org. For NCCN International Adaptations & Translations, search www.nccn.org/global/international\_adaptations.aspx.

### BRCA1 p.(R1751\*) c.5251C>T

### olaparib

Cancer type: Breast Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 2B

#### Population segment (Line of therapy):

Stage IV; Invasive (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 2.2023]

### O bevacizumab + olaparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 1

#### Population segment (Line of therapy):

Epithelial, Fallopian Tube, Primary Peritoneal; Stage II, Stage III, Stage IV; Partial response, Complete response (Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

#### O niraparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 1

#### Population segment (Line of therapy):

 Epithelial, Fallopian Tube, Primary Peritoneal; Persistent, Recurrent, Partial response, Complete response (Maintenance therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

#### O niraparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 1

#### Population segment (Line of therapy):

Epithelial, Fallopian Tube, Primary Peritoneal; Stage II, Stage III, Stage IV; Partial response, Complete response (Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

**Date:** 11 May 2023 7 of 14

## BRCA1 p.(R1751\*) c.5251C>T (continued)

### O olaparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

■ Epithelial, Fallopian Tube, Primary Peritoneal; Persistent, Recurrent, Partial response, Complete response (Maintenance therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

### O olaparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

 Epithelial, Fallopian Tube, Primary Peritoneal; Stage II, Stage III, Stage IV; Partial response, Complete response (Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

#### O olaparib

Cancer type: Castration-Resistant Prostate Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

Adenocarcinoma; Metastatic (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 1.2023]

#### O rucaparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

■ Epithelial, Fallopian Tube, Primary Peritoneal; Persistent, Recurrent, Partial response, Complete response (Maintenance therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

Date: 11 May 2023 8 of 14

## BRCA1 p.(R1751\*) c.5251C>T (continued)

### O niraparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

Epithelial, Fallopian Tube, Primary Peritoneal; Stage II, Stage III, Stage IV; Partial response, Complete response (Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

### O olaparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

 Epithelial, Fallopian Tube, Primary Peritoneal; Stage II, Stage III, Stage IV; Partial response, Complete response (Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

### O rucaparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

 Epithelial, Fallopian Tube, Primary Peritoneal; Stage II, Stage III, Stage IV; Partial response, Complete response (Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

## O rucaparib

Cancer type: Pancreatic Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

Adenocarcinoma; Metastatic (Maintenance therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2022]

**Date**: 11 May 2023 9 of 14

## BRCA1 p.(R1751\*) c.5251C>T (continued)

### O rucaparib

Cancer type: Castration-Resistant Prostate Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):

Adenocarcinoma; Metastatic (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 1.2023]

#### O olaparib

Cancer type: Castration-Resistant Prostate Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

Adenocarcinoma; Visceral Metastases (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 1.2023]

### O rucaparib

Cancer type: Castration-Resistant Prostate Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):

Adenocarcinoma; Visceral Metastases (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 1.2023]

#### O niraparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 3

Population segment (Line of therapy):

 Epithelial, Less Common Ovarian Cancers, Fallopian Tube, Primary Peritoneal; Recurrent (Recurrence therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

#### O rucaparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 3

Population segment (Line of therapy):

 Epithelial, Less Common Ovarian Cancers, Fallopian Tube, Primary Peritoneal; Recurrent (Recurrence therapy); Other recommended intervention

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

**Date**: 11 May 2023 10 of 14

#### **Current EMA Information**

In this cancer type O In other cancer type	• In this cancer type and other cancer types
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EMA information is current as of 2023-03-15. For the most up-to-date information, search www.ema.europa.eu/ema.

## BRCA1 p.(R1751\*) c.5251C>T

## O olaparib, bevacizumab + olaparib

Cancer type: Castration-Resistant Prostate Label as of: 2023-02-02 Variant class: BRCA1 mutation Cancer, Ovarian Cancer

Reference:

https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information\_en.pdf

Date: 11 May 2023 11 of 14

#### **Current ESMO Information**

In this cancer type
In other cancer type
In this cancer type and other cancer types

ESMO information is current as of 2023-03-01. For the most up-to-date information, search www.esmo.org.

#### BRCA1 p.(R1751\*) c.5251C>T

### olaparib

Cancer type: Breast Cancer Variant class: BRCA1 mutation

Other criteria: ERBB2 negative, ER positive

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

■ Luminal A; Advanced, Metastatic (Second-line therapy); ESMO-MCBS v1.1 score: 4

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Breast Cancer [Ann Oncol (2021) VOLUME 32, ISSUE 12, P1475-1495, DECEMBER 01, 2021; DOI:https://doi.org/10.1016/j.annonc.2021.09.019]

#### talazoparib

Cancer type: Breast Cancer Variant class: BRCA1 mutation

Other criteria: ERBB2 negative, ER positive

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

■ Luminal A; Advanced, Metastatic (Second-line therapy); ESMO-MCBS v1.1 score: 4

Reference: ESMO Clinical Practice Guidelines - ESMO-Metastatic Breast Cancer [Ann Oncol (2021) VOLUME 32, ISSUE 12, P1475-1495, DECEMBER 01, 2021; DOI:https://doi.org/10.1016/j.annonc.2021.09.019]

#### O olaparib

Cancer type: Castration-Resistant Prostate Cancer Variant class: BRCA1 mutation

ESMO Level of Evidence/Grade of Recommendation: I / B

Population segment (Line of therapy):

Metastatic, Progression (Line of therapy not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-Cancer of the Prostate [Ann Oncol (2020)]

#### olaparib

Cancer type: Biliary Tract Carcinoma Variant class: BRCA1 mutation

ESMO Level of Evidence/Grade of Recommendation: V / B

Population segment (Line of therapy):

(Second-line therapy)

Reference: ESMO Clinical Practice Guidelines - ESMO-Biliary Cancer [Annals of Oncology (2022), doi: https://doi.org/10.1016/

j.annonc.2022.10.506]

Date: 11 May 2023 12 of 14

# BRCA1 p.(R1751\*) c.5251C>T (continued)

### O bevacizumab + olaparib

Cancer type: Ovarian Cancer Variant class: BRCA mutation or HR Deficient

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

■ Epithelial; Relapsed (Maintenance therapy); ESMO-MCBS v1.1 score: 3

Reference: ESMO Clinical Practice Guidelines - ESMO-Newly Diagnosed and Relapsed Epithelial Ovarian Carcinoma [Ann Oncol 2013; 24 (Suppl 6): vi24-vi32. (eUpdate: 19 July 2021, 01 April 2020, 21 September 2016; Corrigendum: 03 October 2018)]

### O niraparib

Cancer type: Ovarian Cancer Variant class: BRCA mutation or HR Deficient

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

■ Epithelial; Relapsed (Maintenance therapy); ESMO-MCBS v1.1 score: 3

Reference: ESMO Clinical Practice Guidelines - ESMO-Newly Diagnosed and Relapsed Epithelial Ovarian Carcinoma [Ann Oncol 2013; 24 (Suppl 6): vi24-vi32. (eUpdate: 19 July 2021, 01 April 2020, 21 September 2016; Corrigendum: 03 October 2018)]

### O olaparib

Cancer type: Ovarian Cancer Variant class: BRCA mutation

ESMO Level of Evidence/Grade of Recommendation: I / A

Population segment (Line of therapy):

■ Epithelial; Relapsed (Maintenance therapy); ESMO-MCBS v1.1 score: 4

Reference: ESMO Clinical Practice Guidelines - ESMO-Newly Diagnosed and Relapsed Epithelial Ovarian Carcinoma [Ann Oncol 2013; 24 (Suppl 6): vi24-vi32. (eUpdate: 19 July 2021, 01 April 2020, 21 September 2016; Corrigendum: 03 October 2018)]

## O rucaparib

Cancer type: Ovarian Cancer Variant class: BRCA mutation

ESMO Level of Evidence/Grade of Recommendation: III / A

Population segment (Line of therapy):

■ Epithelial; Recurrent (Line of therapy not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-Newly Diagnosed and Relapsed Epithelial Ovarian Carcinoma [Ann Oncol 2013; 24 (Suppl 6): vi24-vi32. (eUpdate: 19 July 2021, 01 April 2020, 21 September 2016; Corrigendum: 03 October 2018)]

Date: 11 May 2023 13 of 14

## **Alerts Informed By Public Data Sources**

#### **Current FDA Information**

Contraindicated

Not recommended

Resistance

Breakthrough

Fast Track

FDA information is current as of 2023-03-15. For the most up-to-date information, search www.fda.gov.

## BRCA1 p.(R1751\*) c.5251C>T

#### pidnarulex

Cancer type: Breast Cancer, Ovarian Cancer

Variant class: HR Deficient

#### Supporting Statement:

The FDA has granted Fast Track Designation to the small molecule inhibitor, pidnarulex for BRCA1/2, PALB2, or other HRD mutations in breast and ovarian cancers.

#### Reference:

https://www.senhwabio.com//en/news/20220125

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