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Date: 12 Jan 2024

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Sample Information

Patient Name: 黃完女 Gender: Female ID No.: P221443439 History No.: 49238699

Age: 55

Ordering Doctor: DOC3577C 黃楷中

Ordering REQ.: 0CVNKYR Signing in Date: 2024/1/9

Path No.: M113-00009 **MP No.:** BR24002

Assay: Oncomine BRCA1/2 Assay

Sample Type: FFPE Block No.: S112-68409J Percentage of tumor cells: 35%

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

Note:

Sample Cancer Type: Ovarian Cancer

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Report Highlights

- 1 Relevant Biomarkers
- 8 Therapies Available
- 1 Clinical Trials

Relevant Ovarian Cancer Variants

Gene	Finding
BRCA1	BRCA1 p.(S1286Rfs*20) c.3858_3861delTGAG
BRCA2	None detected

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	BRCA1 p.(S1286Rfs*20) c.3858_3861delTGAG BRCA1 DNA repair associated Allele Frequency: 63.12%	bevacizumab + olaparib 1,2 olaparib 1,2 rucaparib 1 niraparib	abiraterone + niraparib 1,2 bevacizumab + olaparib 1,2 olaparib 1,2 rucaparib 1 talazoparib + hormone therapy 1 olaparib + hormone therapy	1

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

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Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
			talazoparib	

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

Variant Details

DNA Sequence Variants								
Gene	Amino Acid Change	Coding	Locus	Allele Frequency	Transcript	Variant Effect	ClinVar ¹	Coverage
BRCA1	p.(S1286Rfs*20)	c.3858_3861delTGAG	chr17:41243686	63.12%	NM_007294.4	frameshift Deletion	Pathogenic	1974
BRCA2	p.(?)	c26G>A	chr13:32890572	62.19%	NM_000059.3	unknown	Benign	1997
BRCA2	p.(N372H)	c.1114A>C	chr13:32906729	38.45%	NM_000059.3	missense	Benign	2000
BRCA2	p.(K1132=)	c.3396A>G	chr13:32911888	62.90%	NM_000059.3	synonymous	Benign	2000
BRCA2	p.(L1521=)	c.4563A>G	chr13:32913055	99.95%	NM_000059.3	synonymous	Benign	1995
BRCA2	p.(V2171=)	c.6513G>C	chr13:32915005	100.00%	NM_000059.3	synonymous	Benign	1999
BRCA2	p.(S2414=)	c.7242A>G	chr13:32929232	62.33%	NM_000059.3	synonymous	Benign	1999
BRCA2	p.(V2466A)	c.7397T>C	chr13:32929387	99.90%	NM_000059.3	missense	Benign	1996
BRCA1	p.(S1613G)	c.4837A>G	chr17:41223094	62.73%	NM_007294.4	missense	Benign	1996
BRCA1	p.(S1436=)	c.4308T>C	chr17:41234470	61.55%	NM_007294.4	synonymous	Benign	2000
BRCA1	p.(K1183R)	c.3548A>G	chr17:41244000	63.13%	NM_007294.4	missense	Benign	1999
BRCA1	p.(E1038G)	c.3113A>G	chr17:41244435	62.80%	NM_007294.4	missense	Benign	2000
BRCA1	p.(P871L)	c.2612C>T	chr17:41244936	59.37%	NM_007294.4	missense	Benign	1996
BRCA1	p.(L771=)	c.2311T>C	chr17:41245237	62.50%	NM_007294.4	synonymous	Benign	2000
BRCA1	p.(S694=)	c.2082C>T	chr17:41245466	63.50%	NM_007294.4	synonymous	Benign	2000

¹ Based on Clinvar version 20200329

Biomarker Descriptions

BRCA1 p.(S1286Rfs*20) c.3858_3861delTGAG

BRCA1 DNA repair associated

Background: Homologous recombination repair (HRR) is a DNA repair mechanism that targets double stranded breaks (DSBs) and interstrand cross-links (ICL) in DNA¹. Homologous recombination deficiency (HRD) is characterized by the cell's inability to repair these DSBs¹.². HRD is caused by genetic or epigenetic alterations in the HRR pathway genes, most notably BRCA1 and BRCA2 along with other genes such as ATM and PALB2³.4.5.6. A consequence of HRD due to the failure to repair DSBs is genomic instability^{7,8}. Genomic instability is an increased tendency towards acquiring genomic alterations during cell division^{9,10,11,12,13,14}. These alterations include small structural variations (i.e., single nucleotide variants (SNVs), insertions, and deletions) as well as significant structural variations (i.e., loss or gain of large chromosome fragments)^{10,15,16}. Variations of genomic instability include chromosomal instability, intrachromosomal instability, microsatellite instability, and epigenetic instability⁹. Importantly, while the impact of frame-shift mutations in specific HRR genes can be mitigated by secondary mutations that restore the correct reading frame and thereby alleviate HRD, the effects of genomic instability are permanent and not reversible^{17,18,19}. For this reason, the alterations characteristic of genomic instability are referred to as genomic scars^{20,21}. Some of the genomic scar signatures that are characteristic of the HRD phenotype include loss of heterozygosity (LOH), telomeric allelic imbalance (TAI), and large-scale transition (LST)^{1,22}. Current methods for HRD detection are heterogeneous and the definition for HRD positive tumors varies depending on the cancer type¹. Generally, these

Biomarker Descriptions (continued)

methods detect the causes of HRD (i.e., alterations in HRR genes) and/or the consequences (i.e., signatures of genomic instability/genomic scarring)^{1,7,23,24}.

Alterations and prevalence: In a pan-cancer analysis of HRR gene mutations and genomic scar signatures in 8847 tumors across 33 cancer types, 17.5% of tumors were HRD-positive and 4% of tumors were positive for the BRCA1/2 mutation²⁵. Specifically, HRD-positive status was observed in over 50% of ovarian serous cystadenocarcinoma and lung squamous cell carcinoma, 35-45% of esophageal carcinoma, uterine carcinosarcoma, sarcoma, and lung adenocarcinoma, 20-30% of stomach adenocarcinoma, bladder urothelial carcinoma, breast invasive carcinoma, and head and neck squamous cell carcinoma, 5-15% of endometrial cancer, mesothelioma, cervical cancer, pancreatic adenocarcinoma, cutaneous melanoma, hepatocellular carcinoma, diffuse large B-cell lymphoma, and adrenocortical carcinoma, and 1-4% of rectum adenocarcinoma, prostate adenocarcinoma, colon adenocarcinoma, testicular germ cell tumors, kidney chromophobe, glioblastoma multiforme, low grade glioma, and renal clear cell carcinoma²⁵. Inherited BRCA1/2 mutations occur in 1:400 to 1:500 individuals and are observed in 10-15% of ovarian cancer, 5-10% of breast cancer, and 1-4% of prostate cancer^{26,27,28,29,30,31,32,33}. Somatic alterations in BRCA1 are observed in 5-10% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, diffuse large B-cell lymphoma, and cervical squamous cell carcinoma, 3-4% of lung squamous cell carcinoma, lung adenocarcinoma, stomach adenocarcinoma, ovarian serous cystadenocarcinoma, colorectal adenocarcinoma, and breast invasive carcinoma, and 2% of head and neck squamous cell carcinoma and glioblastoma multiforme^{34,35}. Somatic alterations in BRCA2 are observed in 5-15% of uterine corpus endometrial carcinoma, cutaneous melanoma, bladder urothelial carcinoma, stomach adenocarcinoma, colorectal adenocarcinoma, lung squamous cell carcinoma, lung adenocarcinoma, and uterine carcinosarcoma, 3-4% of cervical squamous cell carcinoma, head and neck squamous cell carcinoma, esophageal adenocarcinoma, ovarian serous cystadenocarcinoma, cholangiocarcinoma, breast invasive carcinoma, renal papillary cell carcinoma, and 2% of renal clear cell carcinoma, hepatocellular carcinoma, thymoma, prostate adenocarcinoma, sarcoma, and glioblastoma multiforme^{34,35}.

Potential relevance: HRD status is an important biomarker in advanced ovarian and prostate cancer because it predicts response to certain treatments including poly-ADP ribose polymerase (PARP) inhibitors and platinum chemotherapies^{36,37,38}. Disruption of HRR or inhibition of PARP, are tolerated by cells through the utilization of complementary DNA repair pathways. However, presence of HRD and subsequent treatment with PARP inhibitors block DNA repair, causing accumulation of DNA damage and cell death through synthetic lethality^{1,39,40,41}. Several PARP inhibitors are approved by the FDA for various cancers associated with markers of HRD. Olaparib⁴² was the first PARP inhibitor originally approved in 2014 for ovarian cancer with germline mutations in BRCA1/2 (gBRCAm). The utility of olaparib has since expanded to include genomic instability markers and mutations in other HRR genes. Specifically, olaparib as monotherapy is now indicated for gBRCAm and somatic BRCA1/2 mutated (sBRCAm) ovarian cancer and in combination with bevacizumab for BRCA1/2 mutated or genomic instability positive ovarian cancer⁴². In addition, olaparib is approved in prostate cancer with germline or somatic mutations in HRR genes including ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L4,42,43, Olaparib is also approved for gBRCAm HER2 negative breast cancer and as maintenance therapies for gBRCAm pancreatic cancers⁴². Other PARP inhibitors that are FDA approved for BRCA mutated cancers include rucaparib44 (2016) that is indicated for gBRCAm or sBRCAm ovarian and prostate cancers, niraparib45 (2017) that is indicated for gBRCAm ovarian cancer, and talazoparib46 (2018) that is indicated for gBRCAm HER2-negative metastatic breast cancer. Niraparib is also recommended for the treatment of HRD-positive ovarian cancer, defined by BRCA1/2 mutations and/or genomic instability⁴⁷. In addition to PARP inhibitors, other drugs which promote synthetic lethality have been investigated for BRCA1/2 mutations. In 2022, the FDA granted fast track designation to the small molecule inhibitor, pidnarulex⁴⁸, for BRCA1/2, PALB2, or other HRR gene mutations in breast and ovarian cancers. Like PARP inhibitors, pidnarulex⁴⁸ causes synthetic lethality but through an alternative mechanism which involves stabilization of G-quadruplexes at the replication fork leading to DNA breaks and genomic instability. Despite tolerability and efficacy, acquired resistance to PARP inhibitors such as olaparib has been clinically reported⁴⁹. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality⁵⁰. Other potential mechanisms of resistance to PARP inhibitors include restoration of HRR activity, stabilization of the replication forks, inhibition of PARP trapping, increased drug efflux mediated by P-glycoprotein, and cell cycle control alterations^{50,51,52,53}.

Relevant Therapy Summary

In this cancer type	O In other cancer type	In this cancer t	type and other car	ncer types	X No evidence	ee
BRCA1 p.(S128	6Rfs*20) c.3858_386	1delTGAG				
Relevant Therapy		FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib		0	•	•	•	×

^{*} Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

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Relevant Therapy Summary (continued)

BRCA1 p.(S1286Rfs*20) c.3858_3861delTGAG (continued) **Relevant Therapy FDA** NCCN **EMA ESMO Clinical Trials*** rucaparib × × bevacizumab + olaparib × abiraterone + niraparib 0 0 0 × × talazoparib + enzalutamide 0 0 × × × niraparib × × × olaparib + abiraterone acetate × × × × talazoparib × × × 0 × senaparib, IMP-9064 (I/II) × X × ×

^{*} Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Relevant Therapy Details

Current FDA Information

FDA information is current as of 2023-11-15. For the most up-to-date information, search www.fda.gov.

BRCA1 p.(S1286Rfs*20) c.3858_3861delTGAG

olaparib, bevacizumab + olaparib

Cancer type: Castration-Resistant Prostate Label as of: 2023-11-06 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 deleterious or suspected deleterious germline or somatic BRCA-mutated recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA®. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA®.

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®.
- in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated (BRCAm) metastatic castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA®.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208558s028lbl.pdf

BRCA1 p.(S1286Rfs*20) c.3858_3861delTGAG (continued)

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

abiraterone + niraparib

Cancer type: Castration-Resistant Prostate Label as of: 2023-08-11 Variant class: BRCA1 mutation

Cancer

Indications and usage:

AKEEGA® is a combination of niraparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, and abiraterone acetate, a CYP17 inhibitor indicated with prednisone for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated (BRCAm) metastatic castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved test for AKEEGA®.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216793s000lbl.pdf

O talazoparib + enzalutamide

Cancer type: Castration-Resistant Prostate Label as of: 2023-06-20 Variant class: BRCA1 mutation

Cancer

Indications and usage:

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

Breast Cancer

 As a single agent, for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) HER2-negative locally advanced or metastatic breast cancer. Select patients for therapy based on an FDA-approved companion diagnostic for TALZENNA®.

HRR Gene-mutated mCRPC

In combination with enzalutamide for the treatment of adult patients with HRR gene-mutated metastatic castration-resistant prostate cancer (mCRPC).

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211651s010lbl.pdf

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Current NCCN Information

In this cancer type

O In other cancer type

In this cancer type and other cancer types

NCCN information is current as of 2023-11-01. To view the most recent and complete version of the guideline, go online to NCCN.org.

For NCCN International Adaptations & Translations, search www.nccn.org/global/what-we-do/international-adaptations.

Some variant specific evidence in this report may be associated with a broader set of alterations from the NCCN Guidelines. Specific variants listed in this report were sourced from approved therapies or scientific literature. These therapeutic options are appropriate for certain population segments with cancer. Refer to the NCCN Guidelines® for full recommendation.

All guidelines cited below are referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) National Comprehensive Cancer Network, Inc. 2023. All rights reserved. NCCN makes no warranties regarding their content.

BRCA1 p.(S1286Rfs*20) c.3858_3861delTGAG

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 IV; Partial response, Complete response (Maintenance therapy)

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

niraparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

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

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

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 IV; Partial response, Complete response (Maintenance therapy)

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

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BRCA1 p.(S1286Rfs*20) c.3858_3861delTGAG (continued)

olaparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

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

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

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 IV; Partial response, Complete response (Maintenance therapy)

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

rucaparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):

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

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

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 2.2023]

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BRCA1 p.(S1286Rfs*20) c.3858_3861delTGAG (continued)

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 IV; Partial response, Complete response (Maintenance therapy)

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

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 2.2023]

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, Persistent (Recurrence therapy);
 Other recommended intervention

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

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, Persistent (Recurrence therapy);
 Other recommended intervention

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

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BRCA1 p.(S1286Rfs*20) c.3858_3861delTGAG (continued)

O abiraterone + niraparib

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

NCCN Recommendation category: 1

Population segment (Line of therapy):

 Adenocarcinoma; Non Visceral Metastasis, Visceral Metastases (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 4.2023]

O olaparib

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

NCCN Recommendation category: 1

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 4.2023]

O olaparib + abiraterone acetate

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

NCCN Recommendation category: 1

Population segment (Line of therapy):

 Adenocarcinoma; Non Visceral Metastasis, Visceral Metastases (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 4.2023]

O talazoparib + enzalutamide

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

NCCN Recommendation category: 1

Population segment (Line of therapy):

Adenocarcinoma; Metastatic (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 4.2023]

abiraterone + niraparib

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 4.2023]

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BRCA1 p.(S1286Rfs*20) c.3858_3861delTGAG (continued)

O olaparib + abiraterone acetate

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 4.2023]

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 2.2023]

O rucaparib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 4.2023]

talazoparib + enzalutamide

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 4.2023]

O abiraterone + niraparib

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 4.2023]

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BRCA1 p.(S1286Rfs*20) c.3858_3861delTGAG (continued)

O 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 4.2023]

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 4.2023]

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 4.2023]

talazoparib + enzalutamide

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):

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

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 4.2023]

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Current EMA Information

In	this	cancer	type
Ш	uns	cancer	type

O In other cancer type

In this cancer type and other cancer types

EMA information is current as of 2023-11-15. For the most up-to-date information, search www.ema.europa.eu/ema.

BRCA1 p.(S1286Rfs*20) c.3858_3861delTGAG

olaparib, bevacizumab + olaparib

Cancer type: Castration-Resistant Prostate

Label as of: 2023-09-21

Variant class: BRCA1 mutation

Cancer, Ovarian Cancer

Reference:

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

O abiraterone + niraparib

Cancer type: Castration-Resistant Prostate

Label as of: 2023-06-02

Variant class: BRCA1 mutation

Cancer

Reference:

 $https://www.ema.europa.eu/en/documents/product-information/akeega-epar-product-information_en.pdf$

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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 2023-11-01. For the most up-to-date information, search www.esmo.org.

BRCA1 p.(S1286Rfs*20) c.3858_3861delTGAG

bevacizumab + olaparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation or HR Deficient

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

Population segment (Line of therapy):

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Newly Diagnosed and Relapsed Epithelial Ovarian Carcinoma [Ann Oncol 2023; Volume 34 issue 10 pp:833-848 https://doi.org/10.1016/j.annonc.2023.07.011(Published)]

niraparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation or HR Deficient

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

Population segment (Line of therapy):

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Newly Diagnosed and Relapsed Epithelial Ovarian Carcinoma [Ann Oncol 2023; Volume 34 issue 10 pp:833-848 https://doi.org/10.1016/j.annonc.2023.07.011(Published)]

niraparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation

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

Population segment (Line of therapy):

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Newly Diagnosed and Relapsed Epithelial Ovarian Carcinoma [Ann Oncol 2023; Volume 34 issue 10 pp:833-848 https://doi.org/10.1016/j.annonc.2023.07.011(Published)]

olaparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation

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

Population segment (Line of therapy):

■ Epithelial; Recurrent (Maintenance therapy); ESMO-MCBS v1.1 score: 2

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Newly Diagnosed and Relapsed Epithelial Ovarian Carcinoma [Ann Oncol 2023; Volume 34 issue 10 pp:833-848 https://doi.org/10.1016/j.annonc.2023.07.011(Published)]

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BRCA1 p.(S1286Rfs*20) c.3858_3861delTGAG (continued)

rucaparib

Cancer type: Ovarian Cancer Variant class: BRCA1 mutation

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

Population segment (Line of therapy):

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

Reference: ESMO Clinical Practice Guidelines - ESMO-Newly Diagnosed and Relapsed Epithelial Ovarian Carcinoma [Ann Oncol 2023; Volume 34 issue 10 pp:833-848 https://doi.org/10.1016/j.annonc.2023.07.011(Published)]

O 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); ESMO-MCBS v1.1 score: 3

Reference: ESMO Clinical Practice Guidelines - ESMO-Cancer of the Prostate [Ann Oncol (2020) (eUpdate 21 March 2023) Published]

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BRCA1 p.(S1286Rfs*20) c.3858_3861delTGAG (continued)

O 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 [Ann Oncol (2023), doi: https://doi.org/10.1016/

j.annonc.2022.10.506]

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated

Not recommended

Resistance

◆ Breakthrough

A Fast Track

Variant class: HR Deficient

FDA information is current as of 2023-11-15. For the most up-to-date information, search www.fda.gov.

BRCA1 p.(S1286Rfs*20) c.3858_3861delTGAG

pidnarulex

Cancer type: Breast Cancer, Ovarian Cancer

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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References

- Stewart et al. Homologous Recombination Deficiency: Concepts, Definitions, and Assays. Oncologist. 2022 Mar 11;27(3):167-174. PMID: 35274707
- 2. Creeden et al. Homologous recombination proficiency in ovarian and breast cancer patients. BMC Cancer. 2021 Oct 28;21(1):1154. PMID: 34711195
- Sokol et al. Pan-Cancer Analysis of BRCA1 and BRCA2 Genomic Alterations and Their Association With Genomic Instability as Measured by Genome-Wide Loss of Heterozygosity. JCO Precis Oncol. 2020;4:442-465. PMID: 32903788
- 4. Heeke et al. Prevalence of Homologous Recombination-Related Gene Mutations Across Multiple Cancer Types. JCO Precis Oncol. 2018;2018. PMID: 30234181
- 5. Prakash et al. Homologous recombination and human health: the roles of BRCA1, BRCA2, and associated proteins. Cold Spring Harb Perspect Biol. 2015 Apr 1;7(4):a016600. PMID: 25833843
- 6. Kondrashova et al. Methylation of all BRCA1 copies predicts response to the PARP inhibitor rucaparib in ovarian carcinoma. Nat Commun. 2018 Sep 28;9(1):3970. PMID: 30266954
- 7. Hoppe et al. Biomarkers for Homologous Recombination Deficiency in Cancer. J. Natl. Cancer Inst. 2018 Jul 1;110(7):704-713. PMID: 29788099
- 8. Wagener-Ryczek et al. Biomarkers for Homologous Recombination Deficiency in Cancer. J Pers Med. 2021 Jun 28;11(7). PMID: 34203281
- 9. Negrini et al. Genomic instability--an evolving hallmark of cancer. Nat Rev Mol Cell Biol. 2010 Mar;11(3):220-8. PMID: 20177397
- 10. Yao et al. Genomic Instability and Cancer. J Carcinog Mutagen. 2014;5. PMID: 25541596
- 11. Chen et al. GSA: an independent development algorithm for calling copy number and detecting homologous recombination deficiency (HRD) from target capture sequencing. BMC Bioinformatics. 2021 Nov 23;22(1):562. PMID: 34814825
- 12. Popova et al. Ploidy and large-scale genomic instability consistently identify basal-like breast carcinomas with BRCA1/2 inactivation. Cancer Res. 2012 Nov 1;72(21):5454-62. PMID: 22933060
- 13. Timms et al. Association of BRCA1/2 defects with genomic scores predictive of DNA damage repair deficiency among breast cancer subtypes. Breast Cancer Res. 2014 Dec 5;16(6):475. PMID: 25475740
- 14. Birkbak et al. Telomeric allelic imbalance indicates defective DNA repair and sensitivity to DNA-damaging agents. Cancer Discov. 2012 Apr;2(4):366-375. PMID: 22576213
- 15. Duijf et al. Mechanisms of Genomic Instability in Breast Cancer. Trends Mol Med. 2019 Jul;25(7):595-611. PMID: 31078431
- 16. Stoler et al. The onset and extent of genomic instability in sporadic colorectal tumor progression. Proc Natl Acad Sci U S A. 1999 Dec 21;96(26):15121-6. PMID: 10611348
- 17. Sakai et al. Functional restoration of BRCA2 protein by secondary BRCA2 mutations in BRCA2-mutated ovarian carcinoma. Cancer Res. 2009 Aug 15;69(16):6381-6. PMID: 19654294
- 18. Sakai et al. Secondary mutations as a mechanism of cisplatin resistance in BRCA2-mutated cancers. Nature. 2008 Feb 28;451(7182):1116-20. PMID: 18264087
- 19. Swisher et al. Secondary BRCA1 mutations in BRCA1-mutated ovarian carcinomas with platinum resistance. Cancer Res. 2008 Apr 15;68(8):2581-6. PMID: 18413725
- 20. Watkins et al. Genomic scars as biomarkers of homologous recombination deficiency and drug response in breast and ovarian cancers. Breast Cancer Res. 2014 Jun 3;16(3):211. PMID: 25093514
- 21. Marquard et al. Pan-cancer analysis of genomic scar signatures associated with homologous recombination deficiency suggests novel indications for existing cancer drugs. Biomark Res. 2015;3:9. PMID: 26015868
- 22. Chao et al. Genomic scar signatures associated with homologous recombination deficiency predict adverse clinical outcomes in patients with ovarian clear cell carcinoma. J Mol Med (Berl). 2018 Jun;96(6):527-536. PMID: 29725737
- 23. Doig et al. Homologous Recombination Repair Deficiency: An Overview for Pathologists. Mod Pathol. 2023 Mar;36(3):100049. PMID: 36788098
- 24. Nguyen et al. Pan-cancer landscape of homologous recombination deficiency. Nat Commun. 2020 Nov 4;11(1):5584. PMID: 33149131
- 25. Rempel et al. Pan-cancer analysis of genomic scar patterns caused by homologous repair deficiency (HRD). NPJ Precis Oncol. 2022 Jun 9;6(1):36. PMID: 35681079
- 26. Petrucelli et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. GeneReviews® [Internet]. PMID: 20301425
- 27. Pruthi et al. Identification and Management of Women With BRCA Mutations or Hereditary Predisposition for Breast and Ovarian Cancer. Mayo Clin. Proc. 2010 Dec;85(12):1111-20. PMID: 21123638

Date: 12 Jan 2024

References (continued)

- 28. Walsh et al. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. Proc. Natl. Acad. Sci. U.S.A. 2011 Nov 1;108(44):18032-7. PMID: 22006311
- 29. Alsop et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. J. Clin. Oncol. 2012 Jul 20;30(21):2654-63. PMID: 22711857
- 30. Whittemore et al. Prevalence of BRCA1 mutation carriers among U.S. non-Hispanic Whites. Cancer Epidemiol. Biomarkers Prev. 2004 Dec;13(12):2078-83. PMID: 15598764
- 31. King et al. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003 Oct 24;302(5645):643-6. PMID: 14576434
- 32. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. Anglian Breast Cancer Study Group. Br. J. Cancer. 2000 Nov;83(10):1301-8. PMID: 11044354
- 33. Shao et al. A comprehensive literature review and meta-analysis of the prevalence of pan-cancer BRCA mutations, homologous recombination repair gene mutations, and homologous recombination deficiencies. Environ Mol Mutagen. 2022 Jul;63(6):308-316. PMID: 36054589
- 34. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
- 35. Cerami et al. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov. 2012 May;2(5):401-4. PMID: 22588877
- 36. Levy-Lahad et al. Cancer risks among BRCA1 and BRCA2 mutation carriers. Br. J. Cancer. 2007 Jan 15;96(1):11-5. PMID: 17213823
- 37. Ferrone et al. BRCA germline mutations in Jewish patients with pancreatic adenocarcinoma. J Clin Oncol. 2009 Jan 20;27(3):433-8. PMID: 19064968
- 38. Cavanagh et al. The role of BRCA1 and BRCA2 mutations in prostate, pancreatic and stomach cancers. Hered Cancer Clin Pract. 2015;13(1):16. PMID: 26236408
- 39. Pilié et al. PARP Inhibitors: Extending Benefit Beyond BRCA-Mutant Cancers. Clin Cancer Res. 2019 Jul 1;25(13):3759-3771. PMID: 30760478
- 40. Lord et al. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017 Mar 17;355(6330):1152-1158. PMID: 28302823
- 41. Iglehart et al. Synthetic lethality-a new direction in cancer-drug development. N Engl J Med. 2009 Jul 9;361(2):189-91. PMID: 19553640
- 42. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208558s028lbl.pdf
- 43. de et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2020 May 28;382(22):2091-2102. PMID: 32343890
- 44. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf
- 45. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208447s027lbl.pdf
- 46. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/211651s010lbl.pdf
- 47. NCCN Guidelines® NCCN-Ovarian Cancer [Version 2.2023]
- 48. https://www.senhwabio.com//en/news/20220125
- 49. Barber et al. Secondary mutations in BRCA2 associated with clinical resistance to a PARP inhibitor. J. Pathol. 2013 Feb;229(3):422-9. PMID: 23165508
- 50. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair (Amst.). 2018 Nov;71:172-176. PMID: 30177437
- 51. Dias et al. Understanding and overcoming resistance to PARP inhibitors in cancer therapy. Nat Rev Clin Oncol. 2021 Dec;18(12):773-791. PMID: 34285417
- 52. Giudice et al. PARP Inhibitors Resistance: Mechanisms and Perspectives. Cancers (Basel). 2022 Mar 10;14(6). PMID: 35326571
- 53. Kim et al. Alternate therapeutic pathways for PARP inhibitors and potential mechanisms of resistance. Exp Mol Med. 2021 Jan;53(1):42-51. PMID: 33487630