



Sample Information

Patient Name: 唐鳳儀
Gender: Female
ID No.: A223532320
History No.: 36857939
Age: 59

Ordering Doctor: DOC3520C 顏明賢
Ordering REQ.: K2J7N7B
Signing in Date: 2023/10/19

Path No.: M112-00269
MP No.: BR23075
Assay: Oncomine BRCA1/2 Assay
Sample Type: Blood
Date of blood drawing: 2023/10/13

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

Note:

Sample Cancer Type: Ovarian Cancer

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Relevant Ovarian Cancer Variants

Gene	Finding
BRCA1	BRCA1 p.(L1086*) c.3257T>G (HR Deficient)
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.(L1086*) c.3257T>G HR Deficient BRCA1 DNA repair associated Allele Frequency: 51.14%	bevacizumab + olaparib ^{1, 2} olaparib ^{1, 2} olaparib + hormone therapy ¹ rucaparib ¹ niraparib	abiraterone + niraparib ^{1, 2} bevacizumab + olaparib ^{1, 2} olaparib ^{1, 2} olaparib + hormone therapy ¹ rucaparib ¹ talazoparib + hormone therapy ¹	1

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

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2023.09(003). The content of this report has not been evaluated or approved by FDA, EMA or other regulatory agencies.

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.(L1086*)	c.3257T>G	chr17:41244291	51.14%	NM_007294.4	nonsense	Pathogenic	3995
BRCA2	p.(N372H)	c.1114A>C	chr13:32906729	99.85%	NM_000059.3	missense	Benign	4000
BRCA2	p.(M1149V)	c.3445A>G	chr13:32911937	48.20%	NM_000059.3	missense	Conflicting interpretations of pathogenicity	3998
BRCA2	p.(L1521=)	c.4563A>G	chr13:32913055	99.97%	NM_000059.3	synonymous	Benign	3984
BRCA2	p.(V2171=)	c.6513G>C	chr13:32915005	100.00%	NM_000059.3	synonymous	Benign	4000
BRCA2	p.(V2466A)	c.7397T>C	chr13:32929387	99.68%	NM_000059.3	missense	Benign	4000
BRCA1	p.(S1613G)	c.4837A>G	chr17:41223094	48.52%	NM_007294.4	missense	Benign	3984
BRCA1	p.(S1436=)	c.4308T>C	chr17:41234470	50.29%	NM_007294.4	synonymous	Benign	3999
BRCA1	p.(K1183R)	c.3548A>G	chr17:41244000	51.23%	NM_007294.4	missense	Benign	4000
BRCA1	p.(E1038G)	c.3113A>G	chr17:41244435	51.92%	NM_007294.4	missense	Benign	4000
BRCA1	p.(P871L)	c.2612C>T	chr17:41244936	49.90%	NM_007294.4	missense	Benign	3996
BRCA1	p.(L771=)	c.2311T>C	chr17:41245237	50.25%	NM_007294.4	synonymous	Benign	3996
BRCA1	p.(S694=)	c.2082C>T	chr17:41245466	51.85%	NM_007294.4	synonymous	Benign	4000

¹ 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 DNA^{1,2}. Specifically, BRCA1/2 are required for the repair of chromosomal double strand breaks (DSBs) which are highly unstable and compromise genome integrity^{1,2}. 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 cancer^{3,4,5}. For individuals diagnosed with inherited pathogenic or likely pathogenic BRCA1/2 variants, the cumulative risk of breast cancer by 80 years of age was 69-72% and the cumulative risk of ovarian cancer by 70 years was 20-48%^{3,6}.

Alterations and prevalence: 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^{7,8,9,10,11,12,13,14}. 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^{15,16}.

Biomarker Descriptions (continued)

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)¹⁷. Inhibitors targeting PARP induce synthetic lethality in recombination deficient BRCA1/2 mutant cells^{18,19}. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib²⁰ (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, olaparib²⁰ 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. Rucaparib²¹ is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib²² (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Additionally, talazoparib²² in combination with enzalutamide is approved (2023) for metastatic castration-resistant prostate cancer (mCRPC) with mutations in HRR genes that includes BRCA1. Niraparib²³ (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. Niraparib in combination with abiraterone acetate²⁴ received FDA approval (2023) for the treatment of deleterious or suspected deleterious BRCA-mutated (BRCAm) mCRPC. Despite tolerability and efficacy, acquired resistance to PARP inhibition has been clinically reported²⁵. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality²⁶. 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, pidnarulex²⁷, 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.

HR Deficient

Background: Homologous recombination repair (HRR) is a DNA repair mechanism that targets double stranded breaks (DSBs) and interstrand cross-links (ICL) in DNA²⁸. Homologous recombination deficiency (HRD) is characterized by the cell's inability to repair these DSBs^{28,29}. 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 PALB2^{30,31,32,33}. A consequence of HRD due to the failure to repair DSBs is genomic instability^{34,35}. Genomic instability is an increased tendency towards acquiring genomic alterations during cell division^{36,37,38,39,40,41}. 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)^{37,42,43}. Variations of genomic instability include chromosomal instability, intrachromosomal instability, microsatellite instability, and epigenetic instability³⁶. 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^{44,45,46}. For this reason, the alterations characteristic of genomic instability are referred to as genomic scars^{47,48}. 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)^{28,49}. Current methods for HRD detection are heterogeneous and the definition for HRD positive tumors varies depending on the cancer type²⁸. Generally, these methods detect the causes of HRD (i.e., alterations in HRR genes) and/or the consequences (i.e., signatures of genomic instability/genomic scarring)^{28,34,50,51}.

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 mutation⁵². 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 carcinoma⁵². 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^{7,8,9,10,11,12,13,14}. 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^{15,16}. 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^{15,16}.

Biomarker Descriptions (continued)

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^{5,53,54}. 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^{28,55,56,57}. Several PARP inhibitors are approved by the FDA for various cancers associated with markers of HRD. Olaparib²⁰ 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 cancer²⁰. 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 RAD54L^{20,31,58}. Olaparib is also approved for gBRCAm HER2 negative breast cancer and as maintenance therapies for gBRCAm pancreatic cancers²⁰. Other PARP inhibitors that are FDA approved for BRCA mutated cancers include rucaparib²¹ (2016) that is indicated for gBRCAm or sBRCAm ovarian and prostate cancers, niraparib²³ (2017) that is indicated for gBRCAm ovarian cancer, and talazoparib²² (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 instability⁵⁹. 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, pidnarulex²⁷, for BRCA1/2, PALB2, or other HRR gene mutations in breast and ovarian cancers. Like PARP inhibitors, pidnarulex²⁷ 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 reported²⁵. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality²⁶. 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^{26,60,61,62}.

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ① In this cancer type and other cancer types ✕ No evidence

BRCA1 p.(L1086*) c.3257T>G

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib	①	①	①	①	✕
rucaparib	①	①	✕	●	✕
bevacizumab + olaparib	①	●	①	●	✕
olaparib + abiraterone acetate + prednisolone	①	✕	✕	✕	✕
olaparib + abiraterone acetate + prednisone	①	✕	✕	✕	✕
abiraterone + niraparib	○	✕	○	✕	✕
talazoparib + enzalutamide	○	✕	✕	✕	✕
niraparib	✕	●	✕	●	✕
olaparib + abiraterone acetate	✕	○	✕	✕	✕
talazoparib	✕	✕	✕	○	✕
senaparib, IMP-9064	✕	✕	✕	✕	● (I/II)

* 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

☒ In this cancer type ☐ In other cancer type ☒ In this cancer type and other cancer types

FDA information is current as of 2023-08-16. For the most up-to-date information, search www.fda.gov.

BRCA1 p.(L1086*) c.3257T>G

☒ olaparib, bevacizumab + olaparib, olaparib + abiraterone acetate + prednisolone, olaparib + abiraterone acetate + prednisone

Cancer type: Castration-Resistant Prostate Cancer, Ovarian Cancer

Label as of: 2023-05-31

Variant class: BRCA1 mutation

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®.
- 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/2023/208558s025lbl.pdf

BRCA1 p.(L1086*) c.3257T>G (continued)**① rucaparib**

Cancer type: Castration-Resistant Prostate Cancer, Ovarian Cancer

Label as of: 2022-12-21

Variant class: BRCA1 mutation

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 taxane-based 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 Cancer

Label as of: 2023-08-11

Variant class: BRCA1 mutation

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

○ talazoparib + enzalutamide

Cancer type: Castration-Resistant Prostate Cancer

Label as of: 2023-06-20

Variant class: BRCA1 mutation

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

Current NCCN Information

☒ In this cancer type ☐ In other cancer type ☒ In this cancer type and other cancer types

NCCN information is current as of 2023-08-01. For the most up-to-date information, search www.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.

BRCA1 p.(L1086*) c.3257T>G

● 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 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 III, Stage IV; Partial response, Complete response (Maintenance therapy)

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; Partial response, Complete response, Recurrent (Maintenance therapy); Useful in certain circumstances

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

BRCA1 p.(L1086*) c.3257T>G (continued)**● 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 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]**● 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 2.2023]

BRCA1 p.(L1086*) c.3257T>G (continued)**● 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]**○ 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 2.2023]

BRCA1 p.(L1086*) c.3257T>G (continued)**○ 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 2.2023]

○ 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]

○ 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 2.2023]

○ 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]

○ 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 2.2023]

BRCA1 p.(L1086*) c.3257T>G (continued)**○ 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 2.2023]

Current EMA Information

- ☒ In this cancer type ☐ In other cancer type ☒ In this cancer type and other cancer types

EMA information is current as of 2023-08-16. For the most up-to-date information, search www.ema.europa.eu/ema.

BRCA1 p.(L1086*) c.3257T>G

☒ olaparib, bevacizumab + olaparib

Cancer type: Castration-Resistant Prostate Cancer, Ovarian Cancer

Label as of: 2023-05-04

Variant class: BRCA1 mutation

Reference:

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

☐ abiraterone + niraparib

Cancer type: Castration-Resistant Prostate Cancer

Label as of: 2023-06-02

Variant class: BRCA1 mutation

Reference:

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

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 2023-08-01. For the most up-to-date information, search www.esmo.org.

BRCA1 p.(L1086*) c.3257T>G

● 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)]

● 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)]

● 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)]

● 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)]

BRCA1 p.(L1086*) c.3257T>G (continued)**○ 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>]**○ 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: 4

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

Clinical Trials Summary

BRCA1 p.(L1086*) c.3257T>G

NCT ID	Title	Phase
NCT05269316	A First-in-human, Phase I/II, Open-label, Multi-center, Dose-escalation and Dose-expansion Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Anti-tumor Activity of the ATR Inhibitor IMP9064 Monotherapy and in Combination With PARP Inhibitor Senaparib in Patients With Advanced Solid Tumors	I/II

Alerts Informed By Public Data Sources

Current FDA Information

 Contraindicated  Not recommended  Resistance  Breakthrough  Fast Track

FDA information is current as of 2023-08-16. For the most up-to-date information, search www.fda.gov.

BRCA1 p.(L1086*) c.3257T>G

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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