Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan
11217, R.O.C.
Tel: 02-2875-7449

Sample Information

Patient Name: 陳寶珠
Gender: Female
ID No.: G201307310
History No.: 8708358
Age: 69

Ordering Doctor: DOC3707G 洪煥程
Ordering REQ.: 0BCFZFY
Signing in Date: 2021/02/17

Path No.: S110-98244
MP No.: BR21004
Assay: Oncomine BRCA1/2 Assay
Sample Type: FFPE
Block No.: S109-68159D
Percentage of tumor cells: 40%
Note:

Sample Cancer Type: Ovarian Cancer

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Report Highlights

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Relevant Ovarian Cancer Variants

Gene	Finding
BRCA1	Not detected
BRCA2	***BRCA2 p.(T868fs) c.2600_2601insA***

Relevant Biomarkers

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
BRCA2 p.(T868fs) c.2600_2601insA BRCA2, DNA repair associated Allele Frequency: 8.16%	**bevacizumab + olaparib** [1] **niraparib** [1] **olaparib** [1, 2] **rucaparib** [1, 2]	**bevacizumab + olaparib** [1] **olaparib** [1] **rucaparib** [1]	28

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, ESMO

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Locus	Allele Frequency	Transcript	Variant Effect	ClinVar[1]	Coverage
BRCA2	p.(T868fs)	c.2600_2601insA	chr13:32911092	8.16%	NM_000059.3	frameshift Insertion		1986
BRCA2	p.(N372H)	c.1114A>C	chr13:32906729	99.65%	NM_000059.3	missense	Benign	1997
BRCA2	p.(=)	c.4563A>G	chr13:32913055	99.95%	NM_000059.3	synonymous	Benign	1997
BRCA2	p.(=)	c.6513G>C	chr13:32915005	99.70%	NM_000059.3	synonymous	Benign	1992
BRCA2	p.(V2466A)	c.7397T>C	chr13:32929387	99.80%	NM_000059.3	missense	Conflicting interpretations of pathogenicity	2000
BRCA1	p.(S1634G)	c.4900A>G	chr17:41223094	48.09%	NM_007300.3	missense	Benign	1986
BRCA1	p.(=)	c.4308T>C	chr17:41234470	47.16%	NM_007300.3	synonymous	Benign	1989
BRCA1	p.(E1221A)	c.3662A>C	chr17:41243886	49.87%	NM_007300.3	missense	Uncertain significance	1997
BRCA1	p.(K1183R)	c.3548A>G	chr17:41244000	58.68%	NM_007300.3	missense	Benign	1999
BRCA1	p.(E1038G)	c.3113A>G	chr17:41244435	46.70%	NM_007300.3	missense	Benign	2000
BRCA1	p.(P871L)	c.2612C>T	chr17:41244936	47.20%	NM_007300.3	missense	Benign	2000
BRCA1	p.(=)	c.2311T>C	chr17:41245237	48.70%	NM_007300.3	synonymous	Benign	1996
BRCA1	p.(=)	c.2082C>T	chr17:41245466	51.25%	NM_007300.3	synonymous	Benign	2000

[1] Based on Clinvar version 20180225

Biomarker Descriptions

BRCA2 (BRCA2, DNA repair associated)

Background: The breast cancer early onset gene 2 (BRCA2) 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. Specifically, BRCA1/2 are required for 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[3] and in men for breast and prostate cancer[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 cancer[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 and 5-10% of breast cancer[7,8,9,10,11,12,13]. Somatic alterations in BRCA2 are observed in 5-15% of melanomas, uterine, cervical, gastric, colorectal, esophageal, and lung cancers[14,15].

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[17,18]. Consequently, several PARP inhibitors have been FDA approved for BRCA1/2-mutated cancers. Olaparib[19] (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[19] is approved (2020) for metastatic castration-resistant prostate cancer (mCRPC) with deleterious or suspected deleterious, germline or somatic mutations in HRR genes that includes BRCA2. Rucaparib[20] (2016) was the first PARPi approved for the treatment of patients with either gBRCAm or sBRCAm epithelial ovarian, fallopian tube, or primary peritoneal cancers and is also approved (2020) for deleterious

Biomarker Descriptions (continued)

gBRCAm or sBRCAm mCRPC. Talazoparib[21] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[22] (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[23]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[24].

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

BRCA2 p.(T868fs) c.2600_2601insA

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
rucaparib	◑	◑	●	●	● (II)
olaparib	◑	◑	●	○	● (II)
bevacizumab + olaparib	◑	●	✖	✖	✖
niraparib	●	●	✖	✖	● (II)
atezolizumab, chemotherapy, niraparib	✖	✖	✖	✖	● (III)
cediranib, olaparib	✖	✖	✖	✖	● (III)
atezolizumab	✖	✖	✖	✖	● (II)
berzosertib	✖	✖	✖	✖	● (II)
ceralasertib, olaparib	✖	✖	✖	✖	● (II)
olaparib, chemotherapy	✖	✖	✖	✖	● (II)
olaparib, talazoparib	✖	✖	✖	✖	● (II)
Senaparib	✖	✖	✖	✖	● (II)
talazoparib	✖	✖	✖	✖	● (II)
AMXI-5001	✖	✖	✖	✖	● (I/II)
AT-406, nivolumab	✖	✖	✖	✖	● (I/II)
BAY-1895344	✖	✖	✖	✖	● (I/II)
durvalumab + olaparib + tremelimumab	✖	✖	✖	✖	● (I/II)
RP-3500, talazoparib	✖	✖	✖	✖	● (I/II)
rucaparib, nivolumab, ipilimumab	✖	✖	✖	✖	● (I/II)
BAY-1895344, niraparib	✖	✖	✖	✖	● (I)
copanlisib, olaparib, durvalumab	✖	✖	✖	✖	● (I)
HWH-340	✖	✖	✖	✖	● (I)
mirvetuximab, rucaparib	✖	✖	✖	✖	● (I)

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

Relevant Therapy Summary (continued)

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

BRCA2 p.(T868fs) c.2600_2601insA (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
olaparib, adavosertib	✖	✖	✖	✖	● (I)

* 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 2020-12-16. For the most up-to-date information, search www.fda.gov.

BRCA2 p.(T868fs) c.2600_2601insA

◑ olaparib, bevacizumab + olaparib

Cancer type: Ovarian Cancer, Prostate Cancer **Label as of:** 2020-12-07 **Variant class:** BRCA2 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.
- for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA®.

Breast cancer

- 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/2020/208558s016lbl.pdf

BRCA2 p.(T868fs) c.2600_2601insA (continued)

rucaparib

Cancer type: Ovarian Cancer, Prostate Cancer **Label as of:** 2020-10-08 **Variant class:** BRCA2 mutation

Indications and usage:

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

Ovarian cancer

- for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.
- for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for RUBRACA®.

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/2020/209115s008lbl.pdf

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niraparib

Cancer type: Ovarian Cancer **Label as of:** 2020-04-29 **Variant class:** BRCA2 mutation

Indications and usage:

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

- for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.
- for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.
- for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:
  - a deleterious or suspected deleterious BRCA mutation, or
  - genomic instability and who have progressed more than six months after response to the last platinum-based chemotherapy.

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

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf

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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 2020-12-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

BRCA2 p.(T868fs) c.2600_2601insA

● bevacizumab + olaparib

Cancer type: Ovarian Cancer **Variant class:** BRCA2 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Epithelial, Fallopian Tube, Primary Peritoneal; Stage II, Stage III, Stage IV; Partial remission, Complete remission (Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2020]

● niraparib

Cancer type: Ovarian Cancer **Variant class:** BRCA2 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Epithelial, Fallopian Tube, Primary Peritoneal; Stage II, Stage III, Stage IV; Partial remission, Complete remission (Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2020]

● olaparib

Cancer type: Ovarian Cancer **Variant class:** BRCA2 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Epithelial, Fallopian Tube, Primary Peritoneal; Stage II, Stage III, Stage IV; Partial remission, Complete remission (Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2020]

● niraparib

Cancer type: Ovarian Cancer **Variant class:** BRCA2 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Epithelial, Fallopian Tube, Primary Peritoneal; Stage II, Stage III, Stage IV; Partial remission, Complete remission (Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2020]

BRCA2 p.(T868fs) c.2600_2601insA (continued)

olaparib

Cancer type: Ovarian Cancer **Variant class:** BRCA2 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Epithelial, Fallopian Tube, Primary Peritoneal; Stage II, Stage III, Stage IV; Partial remission, Complete remission (Maintenance therapy)

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2020]

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rucaparib

Cancer type: Ovarian Cancer **Variant class:** BRCA mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Epithelial, Fallopian Tube, Primary Peritoneal; Recurrent (Subsequent therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2020]

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olaparib

Cancer type: Prostate Cancer **Variant class:** BRCA2 mutation

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Castration-Resistant, Adenocarcinoma; Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 3.2020]

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rucaparib

Cancer type: Prostate Cancer **Variant class:** BRCA2 mutation

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Castration-Resistant, Adenocarcinoma; Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 3.2020]

BRCA2 p.(T868fs) c.2600_2601insA (continued)

olaparib

Cancer type: Prostate Cancer **Variant class:** BRCA2 mutation

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Castration-Resistant, Adenocarcinoma; Metastatic (Second-line therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Prostate Cancer [Version 3.2020]

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 2020-12-16. For the most up-to-date information, search www.ema.europa.eu/ema.

BRCA2 p.(T868fs) c.2600_2601insA

● olaparib

Cancer type: Ovarian Cancer **Label as of:** 2020-11-06 **Variant class:** BRCA2 mutation

Reference:

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

● rucaparib

Cancer type: Ovarian Cancer **Label as of:** 2019-05-24 **Variant class:** BRCA2 mutation

Reference:

https://www.ema.europa.eu/en/documents/product-information/rubraca-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 2020-12-01. For the most up-to-date information, search www.esmo.org.

BRCA2 p.(T868fs) c.2600_2601insA

● rucaparib

Cancer type: Ovarian Cancer **Variant class:** BRCA mutation

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

Population segment (Line of therapy):
- 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: 01 April 2020, 21 September 2016; Corrigendum: 03 October 2018)]

○ olaparib

Cancer type: Prostate Cancer **Variant class:** BRCA2 mutation

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

Population segment (Line of therapy):
- Castration-Resistant; Metastatic, Progression (Line of therapy not specified)

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

Signatures

Testing Personnel: Shin-Ying Lin 2021.02.19 08:14:32 +08'00'

Laboratory Supervisor: 2021.02.19 08:14:45 +08'00'

Pathologist: 2021.02.19 08:14:58 +08'00'

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