Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
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11217, R.O.C.
Tel: 02-2875-7449

Sample Information

Patient Name: 陳素娟
Gender: Female
ID No.: G220020016
History No.: 42780438
Age: 62

Ordering Doctor: DOC3697E 陳怡仁
Ordering REQ.: 0BTBSKV
Signing in Date: 2022/03/18

Path No.: S111-98723
MP No.: BR22021
Assay: Oncomine BRCA Assay
Sample Type: FFPE
Block No.: S105-02999L
Percentage of tumor cells: 80%

Reporting Doctor: DOC5452C 周德盈 (Phone: 8#5452)

Note:

Sample Cancer Type: Ovarian Cancer

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Relevant Ovarian Cancer Variants

Gene	Finding
BRCA1	***BRCA1 deletion***
BRCA2	None detected

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*BRCA1 deletion* BRCA1 DNA repair associated **Prognostic significance:** None **Diagnostic significance:** None	**niraparib** [1] bevacizumab + olaparib	None	0

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, ESMO
Public data sources included in prognostic and diagnostic significance: NCCN, ESMO
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
BRCA2	p.(N372H)	c.1114A>C	.	chr13:32906729	73.61%	NM_000059.3	missense	1997
BRCA2	p.(L1521=)	c.4563A>G	.	chr13:32913055	99.85%	NM_000059.3	synonymous	1995
BRCA2	p.(V2171=)	c.6513G>C	.	chr13:32915005	99.95%	NM_000059.3	synonymous	1996
BRCA2	p.(V2466A)	c.7397T>C	.	chr13:32929387	99.75%	NM_000059.3	missense	2000
BRCA1	p.(S1613G)	c.4837A>G	.	chr17:41223094	75.60%	NM_007294.4	missense	2000
BRCA1	p.(S1436=)	c.4308T>C	.	chr17:41234470	76.00%	NM_007294.4	synonymous	2000
BRCA1	p.(K1183R)	c.3548A>G	.	chr17:41244000	75.45%	NM_007294.4	missense	2000
BRCA1	p.(E1038G)	c.3113A>G	.	chr17:41244435	77.19%	NM_007294.4	missense	1999
BRCA1	p.(P871L)	c.2612C>T	.	chr17:41244936	74.05%	NM_007294.4	missense	2000
BRCA1	p.(L771=)	c.2311T>C	.	chr17:41245237	75.89%	NM_007294.4	synonymous	1999
BRCA1	p.(S694=)	c.2082C>T	.	chr17:41245466	75.38%	NM_007294.4	synonymous	1998

Copy Number Variations

Gene	Locus	Copy Number
BRCA1	chr17:41197601	1

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. 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 BRCA1 are observed in 2-8% of breast, ovarian, cervical, uterine, diffuse large B-cell lymphoma (DLBCL), melanoma, gastric, bladder, squamous lung, colorectal, and head and neck cancers[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 BRCA1. 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 gBRCAm or sBRCAm mCRPC. Talazoparib[21] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or

Biomarker Descriptions (continued)

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

BRCA1 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
niraparib	●	●	✖	●	✖
bevacizumab + olaparib	✖	✖	✖	●	✖

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 2022-01-19. For the most up-to-date information, search www.fda.gov.

BRCA1 deletion

● niraparib

Cancer type: Ovarian Cancer **Label as of:** 2021-07-27 **Variant class:** HR Deficient

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 3 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 6 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/2021/208447s022s024lbl.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 2022-01-04. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

BRCA1 deletion

● niraparib

Cancer type: Ovarian Cancer **Variant class:** HR Deficient

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Epithelial, Less Common Ovarian Cancers, Fallopian Tube, Primary Peritoneal; Recurrent (Recurrence therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 3.2021]

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 2022-01-04. For the most up-to-date information, search www.esmo.org.

BRCA1 deletion

● bevacizumab + olaparib

Cancer type: Ovarian Cancer **Variant class:** 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:** HR Deficient

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

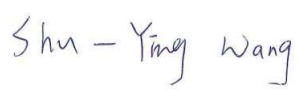
Population segment (Line of therapy):
- Epithelial; Relapsed (Maintenance therapy); ESMO-MCBS v1.1 score: 3

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)]

Clinical Trials in Taiwan region:

Signatures

Testing Personnel:



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Laboratory Supervisor:

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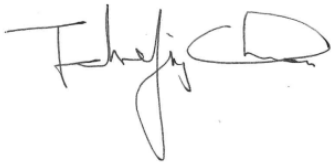
Pathologist:



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