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: 念碧玉
Gender: Female
ID No.: Z200004664
History No.: 48312114
Age: 64

Ordering Doctor: DOC3697E 陳怡仁
Ordering REQ.: 0BTKMQD
Signing in Date: 2022/03/23

Path No.: S111-98808
MP No.: BR22023
Assay: Oncomine BRCA Assay
Sample Type: FFPE
Block No.: S111-65866I
Percentage of tumor cells: 80%

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

Note:

Sample Cancer Type: Ovarian Cancer

Table of Contents	Page

Report Highlights

1 Relevant Biomarkers
4 Therapies Available
0 Clinical Trials

Relevant Ovarian Cancer Variants

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

Relevant Biomarkers

Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
BRCA2 deletion BRCA2 DNA repair associated **Prognostic significance:** None **Diagnostic significance:** None	**niraparib** [1] bevacizumab + olaparib	niraparib olaparib rucaparib	0

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, ESMO
Public data sources included in prognostic and diagnostic significance: NCCN, ESMO

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Locus	Allele Frequency	Transcript	Variant Effect	ClinVar[1]	Coverage
BRCA2	p.(?)	c.-26G>A	chr13:32890572	83.64%	NM_000059.3	unknown	Benign	3997
BRCA2	p.(N372H)	c.1114A>C	chr13:32906729	17.20%	NM_000059.3	missense	Benign	4000
BRCA2	p.(K1132=)	c.3396A>G	chr13:32911888	82.74%	NM_000059.3	synonymous	Benign	3998
BRCA2	p.(L1521=)	c.4563A>G	chr13:32913055	99.90%	NM_000059.3	synonymous	Benign	3991
BRCA2	p.(V2171=)	c.6513G>C	chr13:32915005	99.97%	NM_000059.3	synonymous	Benign	4000
BRCA2	p.(S2414=)	c.7242A>G	chr13:32929232	81.52%	NM_000059.3	synonymous	Benign	3999
BRCA2	p.(V2466A)	c.7397T>C	chr13:32929387	99.82%	NM_000059.3	missense	Benign	4000
BRCA2	p.(P2507=)	c.7521A>G	chr13:32930650	82.11%	NM_000059.3	synonymous	Benign	3992

[1] Based on Clinvar version 20200329

Copy Number Variations

Gene	Locus	Copy Number	ClinVar[1]
BRCA2	chr13:32890490	1	

[1] Based on Clinvar version 20200329

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 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

Biomarker Descriptions (continued)

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 deletion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
niraparib	●	◑	✖	●	✖
olaparib	✖	○	✖	✖	✖
rucaparib	✖	○	✖	✖	✖
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.

BRCA2 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.

BRCA2 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]

○ niraparib

Cancer type: Uterine Leiomyosarcoma **Variant class:** BRCA2 deletion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Second-line therapy); Useful in certain circumstances, Consider

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2022]

○ olaparib

Cancer type: Uterine Leiomyosarcoma **Variant class:** BRCA2 deletion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Second-line therapy); Useful in certain circumstances, Consider

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2022]

○ rucaparib

Cancer type: Uterine Leiomyosarcoma **Variant class:** BRCA2 deletion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- (Second-line therapy); Useful in certain circumstances, Consider

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2022]

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.

BRCA2 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)]

Signatures

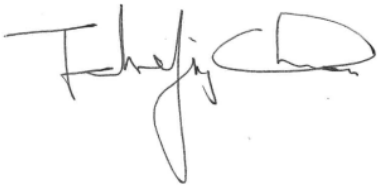
Testing Personnel:

2022.03.28
13:45:35 +08'00'

Laboratory Supervisor:

2022.03.28
13:45:46 +08'00'

Pathologist:



2022.03.28
13:45:56 +08'00'

References

1. Liu et al. Distinct functions of BRCA1 and BRCA2 in double-strand break repair. Breast Cancer Res. 2002;4(1):9-13. PMID: 11879553
2. Jasin. Homologous repair of DNA damage and tumorigenesis: the BRCA connection. Oncogene. 2002 Dec 16;21(58):8981-93. PMID: 12483514
3. Kuchenbaecker et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017 Jun 20;317(23):2402-2416. PMID: 28632866
4. Tai et al. Breast cancer risk among male BRCA1 and BRCA2 mutation carriers. J. Natl. Cancer Inst. 2007 Dec 5;99(23):1811-4. PMID: 18042939
5. Levy-Lahad et al. Cancer risks among BRCA1 and BRCA2 mutation carriers. Br. J. Cancer. 2007 Jan 15;96(1):11-5. PMID: 17213823
6. NCCN Guidelines® - NCCN-Genetic/Familial High-Risk Assessment: Breast and Ovarian [Version 1.2018]. NCCN-Genetic/Familial High-Risk Assessment: Breast and Ovarian
7. ARUP Laboratories University of Utah Department of Pathology.. https://arupconsult.com/ati/hereditary-breast-and-ovarian-cancer
8. Petrucelli et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. GeneReviews® [Internet]. PMID: 20301425
9. 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
10. 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
11. 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
12. 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
13. 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
14. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
15. 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
16. Hodgson et al. Candidate biomarkers of PARP inhibitor sensitivity in ovarian cancer beyond the BRCA genes. Br. J. Cancer. 2018 Nov;119(11):1401-1409. PMID: 30353044
17. Bryant et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005 Apr 14;434(7035):913-7. PMID: 15829966
18. Farmer et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005 Apr 14;434(7035):917-21. PMID: 15829967
19. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208558s019s020lbl.pdf
20. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209115s009lbl.pdf
21. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211651s008lbl.pdf
22. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208447s022s024lbl.pdf
23. 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
24. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair (Amst.). 2018 Nov;71:172-176. PMID: 30177437