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:** 林淑芳
**Gender:** Female
**ID No.:** V200849679
**History No.:** 30152068
**Age:** 67

**Ordering Doctor:** DOC3730J 張燕後
**Ordering REQ.:** 0BDBFGX
**Signing in Date:** 2021/03/10

**Path No.:** S110-98351
**MP No.:** BR21008
**Assay:** Oncomine BRCA1/2 Assay
**Sample Type:** FFPE
**Block No.:** S109-68493J+L
**Percentage of tumor cells:** 30%
**Note:**

## Sample Cancer Type: Ovarian Cancer

| Table of Contents | Page |
|---|---|


### Report Highlights

1 Relevant Biomarkers
4 Therapies Available
28 Clinical Trials

## Relevant Ovarian Cancer Variants

| Gene | Finding |
|---|---|
| BRCA1 | ***BRCA1 p.(C1103*) c.3308_3309delGT*** |
| BRCA2 | Not detected |

## Relevant Biomarkers

| Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|---|---|---|---|
| *BRCA1 p.(C1103*) c.3308_3309delGT*<br>BRCA1, DNA repair associated<br>Allele Frequency: 24.98% | **bevacizumab + olaparib** [1]<br>**niraparib** [1]<br>**olaparib** [1, 2]<br>**rucaparib** [1, 2] | **bevacizumab + olaparib** [1]<br>**olaparib** [1]<br>**rucaparib** [1] | 28 |

**Public data sources included in relevant therapies: FDA**1, NCCN, **EMA**2, ESMO

# Variant Details

## DNA Sequence Variants

| Gene | Amino Acid Change | Coding | Locus | Allele Frequency | Transcript | Variant Effect | ClinVar[1] | Coverage |
|---|---|---|---|---|---|---|---|---|
| BRCA1 | p.(C1103*) | c.3308_3309delGT | chr17:41244238 | 24.98% | NM_007300.3 | nonsense | | 1133 |
| BRCA2 | p.(?) | c.-26G>A | chr13:32890572 | 31.47% | NM_000059.3 | unknown | Benign | 1999 |
| BRCA2 | p.(N372H) | c.1114A>C | chr13:32906729 | 70.16% | NM_000059.3 | missense | Benign | 1997 |
| BRCA2 | p.(=) | c.3396A>G | chr13:32911888 | 33.27% | NM_000059.3 | synonymous | Benign | 1999 |
| BRCA2 | p.(=) | c.4563A>G | chr13:32913055 | 100.00% | NM_000059.3 | synonymous | Benign | 229 |
| BRCA2 | p.(=) | c.6513G>C | chr13:32915005 | 99.95% | NM_000059.3 | synonymous | Benign | 1996 |
| BRCA2 | p.(V2466A) | c.7397T>C | chr13:32929387 | 99.66% | NM_000059.3 | missense | Conflicting interpretations of pathogenicity | 293 |
| BRCA1 | p.(S1634G) | c.4900A>G | chr17:41223094 | 62.13% | NM_007300.3 | missense | Benign | 1991 |
| BRCA1 | p.(=) | c.4308T>C | chr17:41234470 | 62.10% | NM_007300.3 | synonymous | Benign | 2000 |
| BRCA1 | p.(K1183R) | c.3548A>G | chr17:41244000 | 65.13% | NM_007300.3 | missense | Benign | 1999 |
| BRCA1 | p.(E1038G) | c.3113A>G | chr17:41244435 | 62.15% | NM_007300.3 | missense | Benign | 2000 |
| BRCA1 | p.(P871L) | c.2612C>T | chr17:41244936 | 60.60% | NM_007300.3 | missense | Benign | 2000 |
| BRCA1 | p.(=) | c.2311T>C | chr17:41245237 | 58.67% | NM_007300.3 | synonymous | Benign | 375 |
| BRCA1 | p.(=) | c.2082C>T | chr17:41245466 | 60.40% | NM_007300.3 | synonymous | Benign | 2000 |

[1] Based on Clinvar version 20180225

# 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

## 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

### BRCA1 p.(C1103*) c.3308_3309delGT

| 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

### BRCA1 p.(C1103*) c.3308_3309delGT (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.

## BRCA1 p.(C1103*) c.3308_3309delGT

### ◑ olaparib, bevacizumab + olaparib

**Cancer type:** Ovarian Cancer, Prostate Cancer **Label as of:** 2020-12-07 **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.
- 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

## BRCA1 p.(C1103*) c.3308_3309delGT (continued)

### rucaparib

**Cancer type:** Ovarian Cancer, Prostate Cancer **Label as of:** 2020-10-08 **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 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:** BRCA1 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.

## BRCA1 p.(C1103*) c.3308_3309delGT

### ● 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 remission, Complete remission (Maintenance therapy)

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

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### ● 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 remission, Complete remission (Maintenance therapy)

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

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### ● 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 remission, Complete remission (Maintenance therapy)

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

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### ● 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 remission, Complete remission (Maintenance therapy)

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

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## BRCA1 p.(C1103*) c.3308_3309delGT (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 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:** BRCA1 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:** BRCA1 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]

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## BRCA1 p.(C1103*) c.3308_3309delGT (continued)

### olaparib

**Cancer type:** Prostate Cancer **Variant class:** BRCA1 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.

## BRCA1 p.(C1103*) c.3308_3309delGT

### ● olaparib

**Cancer type:** Ovarian Cancer **Label as of:** 2020-11-06 **Variant class:** BRCA1 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:** BRCA1 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.

## BRCA1 p.(C1103*) c.3308_3309delGT

### ● 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:** BRCA1 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 2021.03.11 17:04:03 +08'00'

**Laboratory Supervisor:** 2021.03.11 17:04:16 +08'00'

**Pathologist:** 2021.03.11 17:04:30 +08'00'

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