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:** 曾佳瑩
**Gender:** Female
**ID No.:** K221333319
**History No.:** 37168040
**Age:** 46

**Ordering Doctor:** DOC3581L 張哲維
**Ordering REQ.:** 0CMGERR
**Signing in Date:** 2023/06/28

**Path No.:** M112-00159
**MP No.:** BR23047
**Assay:** Oncomine BRCA1/2 Assay
**Sample Type:** Blood
**Date of blood drawing:** 2023/06/16

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

**Note:**

## Sample Cancer Type: Ovarian Cancer

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


### Report Highlights

1 Relevant Biomarkers
5 Therapies Available
1 Clinical Trials

## Relevant Ovarian Cancer Variants

| Gene | Finding |
|---|---|
| BRCA1 | None detected |
| BRCA2 | ***BRCA2 p.(E2198Nfs*4) c.6591_6592delTG*** |

## Relevant Biomarkers

| Tier | Genomic Alteration | Relevant Therapies (In this cancer type) | Relevant Therapies (In other cancer type) | Clinical Trials |
|---|---|---|---|---|
| **IA** | *BRCA2 p.(E2198Nfs*4) c.6591_6592delTG*<br>BRCA2 DNA repair associated<br>Allele Frequency: 48.82% | **bevacizumab + olaparib** [1, 2]<br>**olaparib** [1, 2]<br>**rucaparib** [1]<br>niraparib | **bevacizumab + olaparib** [1, 2]<br>**olaparib** [1, 2]<br>**rucaparib** [1]<br>niraparib<br>talazoparib | 1 |

**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 |
|---|---|---|---|---|---|---|---|---|
| BRCA2 | p.(E2198Nfs*4) | c.6591_6592delTG | chr13:32915082 | 48.82% | NM_000059.3 | frameshift Deletion | Pathogenic | 3980 |
| ZAR1L | p.(?) | c.-4433A>G | chr13:32890495 | 50.11% | NM_001136571.2 | unknown | | 3999 |
| BRCA2 | p.(N289H) | c.865A>C | chr13:32906480 | 49.22% | NM_000059.3 | missense | Benign | 3998 |
| BRCA2 | p.(N372H) | c.1114A>C | chr13:32906729 | 50.83% | NM_000059.3 | missense | Benign | 3998 |
| BRCA2 | p.(S455=) | c.1365A>G | chr13:32906980 | 46.15% | NM_000059.3 | synonymous | Benign | 3998 |
| BRCA2 | p.(H743=) | c.2229T>C | chr13:32910721 | 49.66% | NM_000059.3 | synonymous | Benign | 3999 |
| BRCA2 | p.(N991D) | c.2971A>G | chr13:32911463 | 49.91% | NM_000059.3 | missense | Benign | 2270 |
| BRCA2 | p.(L1521=) | c.4563A>G | chr13:32913055 | 99.95% | NM_000059.3 | synonymous | Benign | 3988 |
| BRCA2 | p.(V2171=) | c.6513G>C | chr13:32915005 | 100.00% | NM_000059.3 | synonymous | Benign | 4000 |
| BRCA2 | p.(V2466A) | c.7397T>C | chr13:32929387 | 99.70% | NM_000059.3 | missense | Benign | 4000 |
| BRCA2 | p.(K2729N) | c.8187G>T | chr13:32937526 | 49.62% | NM_000059.3 | missense | Benign | 3996 |
| BRCA1 | p.(S1613G) | c.4837A>G | chr17:41223094 | 99.88% | NM_007294.4 | missense | Benign | 3999 |
| BRCA1 | p.(S1436=) | c.4308T>C | chr17:41234470 | 99.90% | NM_007294.4 | synonymous | Benign | 4000 |
| BRCA1 | p.(K1183R) | c.3548A>G | chr17:41244000 | 99.50% | NM_007294.4 | missense | Benign | 3998 |
| BRCA1 | p.(E1038G) | c.3113A>G | chr17:41244435 | 99.53% | NM_007294.4 | missense | Benign | 4000 |
| BRCA1 | p.(P871L) | c.2612C>T | chr17:41244936 | 99.87% | NM_007294.4 | missense | Benign | 3996 |
| BRCA1 | p.(L771=) | c.2311T>C | chr17:41245237 | 99.87% | NM_007294.4 | synonymous | Benign | 3994 |
| BRCA1 | p.(S694=) | c.2082C>T | chr17:41245466 | 99.85% | NM_007294.4 | synonymous | Benign | 3996 |

[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[1,2]. 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 and in men for breast and prostate cancer[3,4,5]. 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, 5-10% of breast cancer, and 1-4% of prostate cancer[7,8,9,10,11,12,13,14]. 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: 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. Olaparib[20] (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[20] 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[21] is also approved (2020) for deleterious gBRCAm or sBRCAm mCRPC. Talazoparib[22] (2018) is indicated for the treatment of gBRCAm HER2-negative locally advanced or metastatic breast cancer. Niraparib[23] (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[24]. One of the most common mechanisms of resistance includes secondary intragenic mutations that restore BRCA1/2 functionality[25]. 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, pidnarulex[26], 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.

## Relevant Therapy Summary

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

### BRCA2 p.(E2198Nfs*4) c.6591_6592delTG

| Relevant Therapy | FDA | NCCN | EMA | ESMO | Clinical Trials* |
|---|---|---|---|---|---|
| olaparib | ◑ | ◑ | ◑ | ◑ | ✖ |
| rucaparib | ◑ | ◑ | ✖ | ● | ✖ |
| bevacizumab + olaparib | ◑ | ● | ◑ | ● | ✖ |
| niraparib | ✖ | ◑ | ✖ | ● | ✖ |
| 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 2023-04-19. For the most up-to-date information, search www.fda.gov.

## BRCA2 p.(E2198Nfs*4) c.6591_6592delTG

### ◑ olaparib, bevacizumab + olaparib

**Cancer type:** Castration-Resistant Prostate Cancer, Ovarian Cancer **Label as of:** 2022-10-27 **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.

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®.

**Reference:**

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208558s024lbl.pdf

## BRCA2 p.(E2198Nfs*4) c.6591_6592delTG (continued)

### rucaparib

**Cancer type:** Castration-Resistant Prostate Cancer, Ovarian Cancer **Label as of:** 2022-12-21 **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 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

## 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 2023-04-03. 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.(E2198Nfs*4) c.6591_6592delTG

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

**Reference:** NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

---

### ● niraparib

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

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Epithelial, Fallopian Tube, Primary Peritoneal; Persistent, Recurrent, Partial response, Complete response (Maintenance therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

---

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

**Reference:** NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

---

### ● olaparib

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

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Epithelial, Fallopian Tube, Primary Peritoneal; Persistent, Recurrent, Partial response, Complete response (Maintenance therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

---

## BRCA2 p.(E2198Nfs*4) c.6591_6592delTG (continued)

### 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 response, Complete response (Maintenance therapy)

**Reference:** NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

---

### rucaparib

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

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Epithelial, Fallopian Tube, Primary Peritoneal; Persistent, Recurrent, Partial response, Complete response (Maintenance therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

---

### 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 response, Complete response (Maintenance therapy)

**Reference:** NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

---

### 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 response, Complete response (Maintenance therapy)

**Reference:** NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

---

## BRCA2 p.(E2198Nfs*4) c.6591_6592delTG (continued)

### rucaparib

**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 response, Complete response (Maintenance therapy)

**Reference:** NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

---

### niraparib

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

**NCCN Recommendation category:** 3

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

**Reference:** NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

---

### rucaparib

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

**NCCN Recommendation category:** 3

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

**Reference:** NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2023]

---

### olaparib

**Cancer type:** Castration-Resistant Prostate Cancer **Variant class:** BRCA2 mutation

**NCCN Recommendation category:** 1

**Population segment (Line of therapy):**
- Adenocarcinoma; Metastatic (Subsequent therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Prostate Cancer [Version 1.2023]

---

## BRCA2 p.(E2198Nfs*4) c.6591_6592delTG (continued)

### niraparib

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

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2023]

---

### olaparib

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

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2023]

---

### rucaparib

**Cancer type:** Pancreatic Cancer **Variant class:** BRCA2 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 2.2022]

---

### rucaparib

**Cancer type:** Castration-Resistant Prostate Cancer **Variant class:** BRCA2 mutation

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Adenocarcinoma; Metastatic (Subsequent therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Prostate Cancer [Version 1.2023]

---

### rucaparib

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

**NCCN Recommendation category:** 2A

**Population segment (Line of therapy):**
- Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

**Reference:** NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2023]

---

## BRCA2 p.(E2198Nfs*4) c.6591_6592delTG (continued)

### olaparib

**Cancer type:** Breast Cancer **Variant class:** BRCA2 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:** BRCA2 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 1.2023]

---

### rucaparib

**Cancer type:** Castration-Resistant Prostate Cancer **Variant class:** BRCA2 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 1.2023]

---

## 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 2023-04-19. For the most up-to-date information, search www.ema.europa.eu/ema.

## BRCA2 p.(E2198Nfs*4) c.6591_6592delTG

### ◑ olaparib, bevacizumab + olaparib

**Cancer type:** Castration-Resistant Prostate Cancer, Ovarian Cancer

**Label as of:** 2023-03-24

**Variant class:** BRCA2 mutation

**Reference:**

https://www.ema.europa.eu/en/documents/product-information/lynparza-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 2023-04-03. For the most up-to-date information, search www.esmo.org.

## BRCA2 p.(E2198Nfs*4) c.6591_6592delTG

### ● bevacizumab + 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: 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

**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)]

---

## BRCA2 p.(E2198Nfs*4) c.6591_6592delTG (continued)

### olaparib

**Cancer type:** Breast Cancer **Variant class:** BRCA2 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:** BRCA2 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:** BRCA2 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:** BRCA2 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

### BRCA2 p.(E2198Nfs*4) c.6591_6592delTG

| 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 |

## 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. Petrucelli et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. GeneReviews® [Internet]. PMID: 20301425
8. 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
9. 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
10. 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
11. 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
12. King et al. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. Science. 2003 Oct 24;302(5645):643-6. PMID: 14576434
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. Shao et al. A comprehensive literature review and meta-analysis of the prevalence of pan-cancer BRCA mutations, homologous recombination repair gene mutations, and homologous recombination deficiencies. Environ Mol Mutagen. 2022 Jul;63(6):308-316. PMID: 36054589
15. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
16. 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
17. 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
18. 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
19. 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
20. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208558s024lbl.pdf
21. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209115s013lbl.pdf
22. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211651s008lbl.pdf
23. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208447s025lbl.pdf
24. 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
25. D'Andrea. Mechanisms of PARP inhibitor sensitivity and resistance. DNA Repair (Amst.). 2018 Nov;71:172-176. PMID: 30177437
26. https://www.senhwabio.com//en/news/20220125