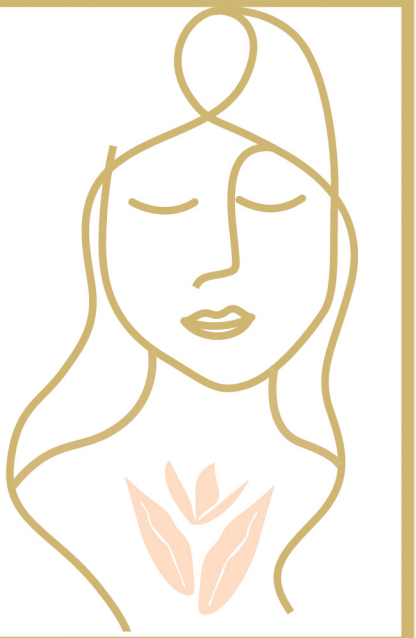
實體・線上會議

台灣東部婦產科臨床學術研討會

2022
06/11



EASTERN TAIWAN

THE OBSTETRICS AND GYNECOLOGY

台灣東部婦產科
臨床學術研討會

實體．線上會議

掃描或點擊
連結報名頁面

- 會議時間：2022 年 6 月 11 日（六）14:30–18:05
- 會議地點：花蓮福容大飯店 2F 宴會 A 廳

請先掃描或點擊右方 QRcode 報名此會議

Time	Topic	Speaker	Moderator
14:30-14:55	報到		
14:55-15:00	Opening	丁大清 醫師 花蓮慈濟醫院	
15:00-15:30	女性骨盆底肌肉筋膜炎 (Female Myofascial Pelvic Pain Syndrome)	龐浸醛 醫師 花蓮慈濟醫院	丁大清 醫師 花蓮慈濟醫院
15:30-15:50	Haploinsufficient tumor suppressor gene, BRCA1/2 Case sharing	廖基元 醫師 門諾醫院	
15:50-16:20	Expert Insight on Niraparib Trial Data from SGO 2022 to Optimize Clinical Outcomes for First-Line Maintenance in Ovarian Cancer	魏凌鴻 醫師 臺大醫院	
16:20-16:50	Niraparib Maintenance Therapy for Recurrent Ovarian Cancer	魏佑吉 醫師 花蓮慈濟醫院	
16:50-17:00	Break		
17:00-17:30	Therapeutic Roles of Leuplin in Endometriosis	蔡啟智 醫師 門諾醫院	廖基元 醫師 門諾醫院
17:30-17:50	陰道雷射用於女性應力性尿失禁之經驗分享	李佩蓁 醫師 花蓮慈濟醫院	
17:50-18:00	達文西手術運用於婦癌治療	陳盈希 醫師 花蓮慈濟醫院	
18:00-18:05	Closing	廖基元 醫師 門諾醫院	

主辦單位：
花蓮慈濟醫院婦科微創手術中心

Takeda　Zejula niraparib capsules 100 mg　LEUPLIN® Leuprorelin DEPOT 3.75 11.25

EASTERN TAIWAN

THE OBSTETRICS AND GYNECOLOGY

C-APROM/TW/LEU/0279 May2022

題目 1:　「骨盆底肌肉筋膜炎」(Myofascial Pelvic Pain Syndrome, 簡稱 MFPPS)

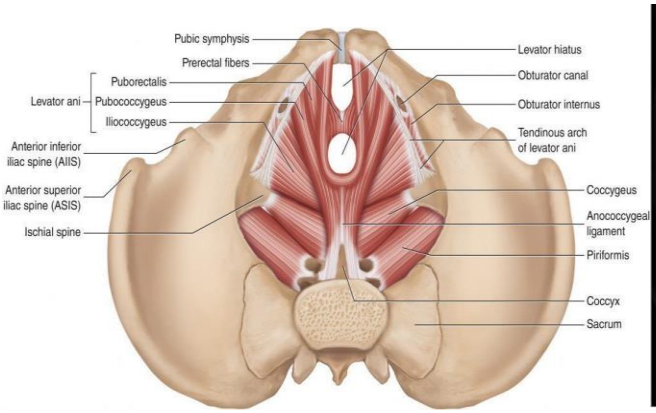
龐浸醛
花蓮慈濟醫院婦產部婦科主任
婦科微創手術中心主任

摘要

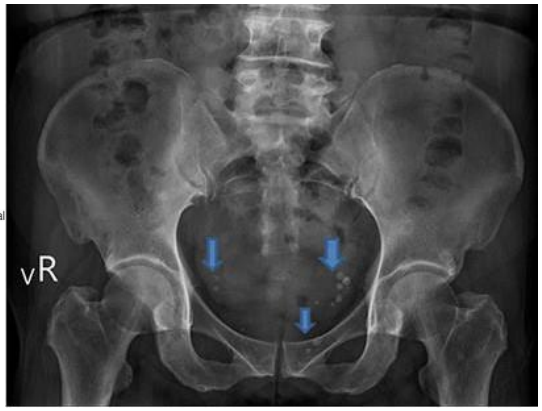
女性慢性下腹痛的原因很多種，可以是很複雜的狀況，各種各樣的疾病都有可能，因此診斷過程需要更多的耐心和專業。而女性「骨盆底肌肉筋膜炎」(Myofascial Pelvic Pain Syndrome, 簡稱 MFPPS) 更是常見、但經常沒被診斷出來的病症。MFPPS 需要排除其他的問題後內診碰觸骨盆底肌肉筋膜時會有觸結節性痛點(nodular triger point)典型的還會伴隨或 tender band， 在醫院不會教，婦產科住院醫師訓練過程也沒有 MFPPS，因此即便婦產科醫師也很少知道 MFPPS，何況是其他科的醫師？MFPPS 會反覆性下腹痛、頻尿、性交疼痛等症狀，有的嚴重影響病人的情緒、工作表現、性生活、生活品質、甚至人際關係。多數 MFPPS 的病人，常被當作骨盆腔發炎、膀胱發炎或是膀胱過動症來治療而無效。其實目前 MFPPS 治療的選擇也相當有限。由於 MFPP 是經年累月造成的慢性病, 因此需要至少 1-3 個月的療程, 才會慢慢康復。

其治療分為兩類:(1)**藥物治療**: 急性期經陰道施用局部消炎藥、肌肉鬆弛劑和止痛藥 2-4 周，來放鬆骨盆底肌肉。再補充一些肌肉筋膜修復所需的維他命或營養，就較不易復發。頑固型 MFPP 需要侵入性藥物注射治療才能改善，但是屬於侵入性治療，先前有些病人反映過程會很不舒服。(2)**理物理治療**:A. 溫水坐浴，避免做凱格爾骨盆底肌肉強化的運動，以避免刺激骨盆底肌肉收縮，惡化病症。B. 體外震波（附件 2）:可有效地讓深部骨盆肌肉有效放鬆並解除症狀。

女性慢性下腹痛的原因很多種，可以很複雜的狀況，因此診斷過程需要更多的耐心和專業，MFPPS 是經常被忽略的其中一種原因。病人經常在各科繞了一大圈問題依舊沒有得到解決而且吃了不少沒有必要的藥物。本次報告將整理本人 MFPPS 的臨床治療經驗和介紹新治療武器--體外震波儀來作分享和討論。



（圖 1）



（圖 2）

參考資料:

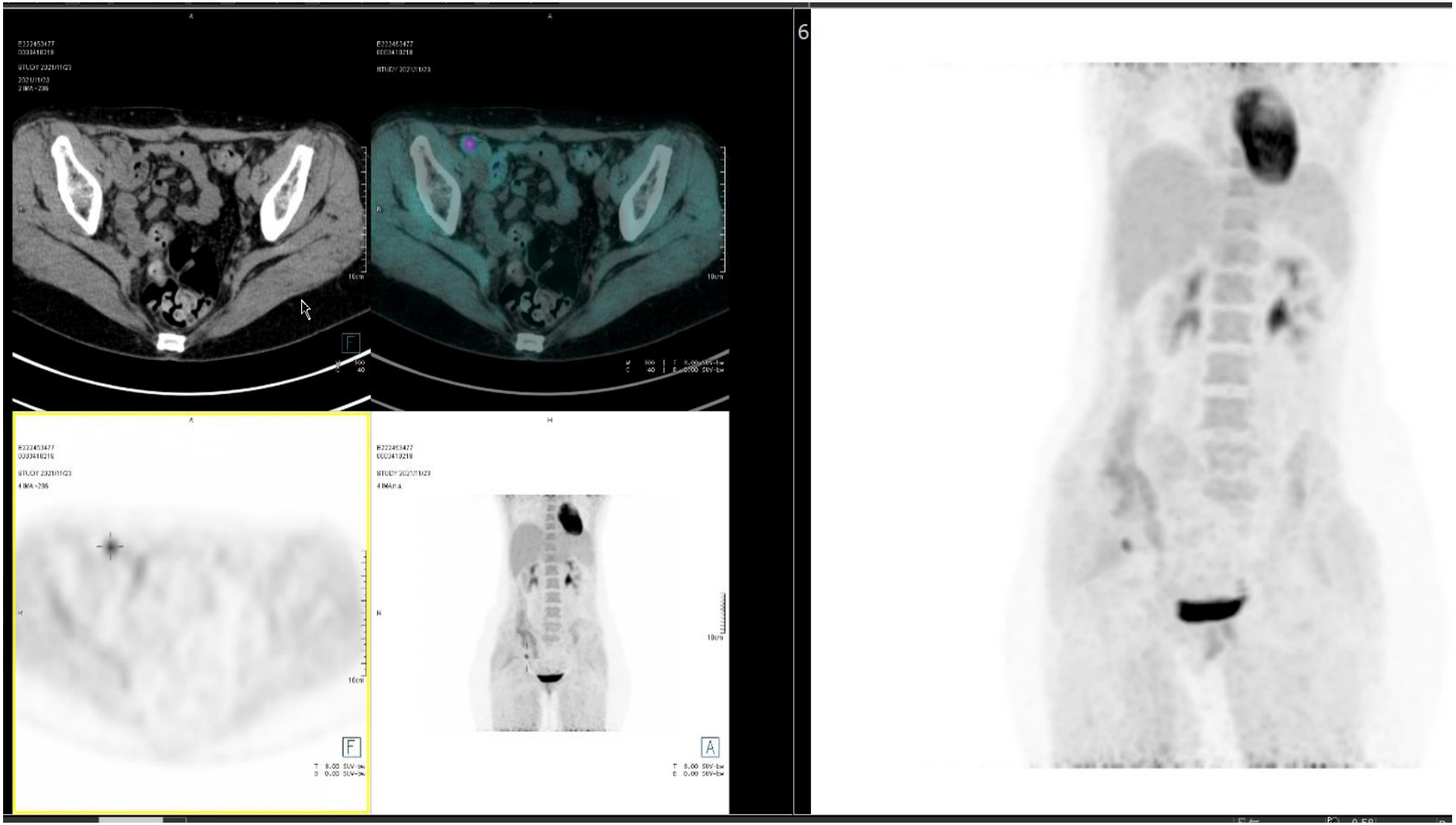
1. Myofascial Pelvic Pain and Related Disorders.Phys Med Rehabil Clin N Am. 2017 Aug;28(3):501-515.
2.Recognizing Myofascial Pelvic Pain in the Female Patient with Chronic Pelvic Pain J Obstet Gynecol Neonatal Nurs. 2012 September; 41(5): 680–691.

heterozygous mutation of BRCA1/2 gene

- BRCA1 and BRCA2 are the most commonly mutated breast cancer susceptibility genes that convey a high risk of breast and ovarian cancer. Most BRCA1 or BRCA2 mutation carriers have inherited a single heterozygous mutation.
- Haploinsufficiency of tumor suppressor genes (TSGs) indicates that the reduced levels of proteins in cells that lack one allele of the genomic locus results in the inability of the cell to execute normal cellular functions contributing to tumor development.

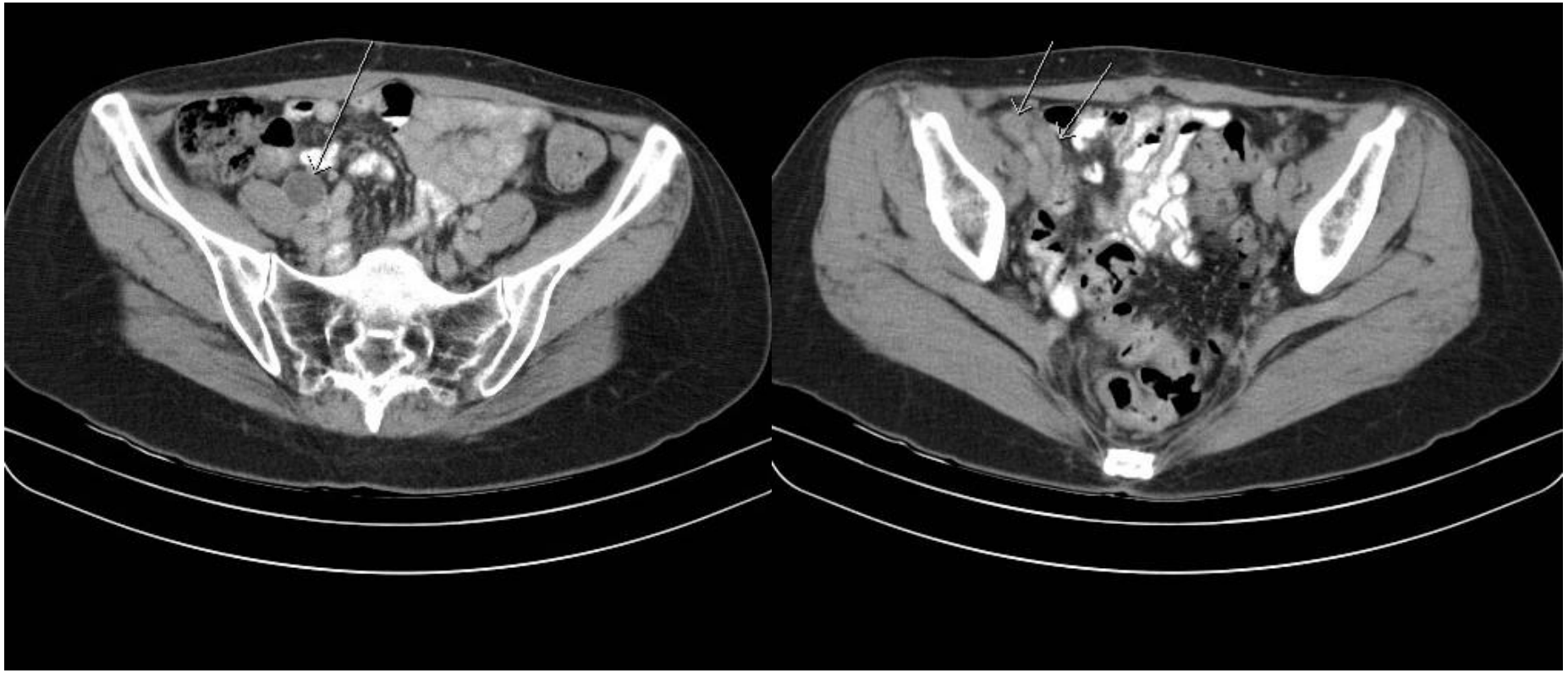
- This 44-year-old female
- IMP : Bilateral ovarian endometrioid carcinoma, stage IC1, grade 3
- On 2020/02/12 , Laparoscopic bilateral ovarian cystectomy →with Frozen section of both bilateral specimens show a picture of poorly-differentiated carcinoma , surgical spill found during first manipulation of rt cyst by scope →Laparotomy staging with Washing cytology+ATH+ BSO+ BPLND+Paraaortic nodes dissection+ liver, Diaphgram smear +Appendectomy Omentectomy+Multiple biopsies .CEA 0.72, CA125 37.56, CA199 10.36 before operation.
- ….Pathological report: Bil endometrioid carcinoma 1C3G3.
- Patient accepted chemotherapy for Taxol 175mg/m2 + Carboplatin AUC 5 x 6 # course (2020/02/27~2020/06/13)
- She has regular follow up . and last tumor maker 2021/11/18 CEA:0.96 ng/ml CA 125:24.95 U/mL CA 19-9:7.73 U/mL

- 2021/08/16 CT : Stationary in size of residual seromas along with RIGHT side iliac vessels first considered.
- 2021/11/23 CT A borderline enlarged LN along with RIGHT side external iliac artery, comparing with recent PET scan, a metastatic LN considered. (Revised 2021/11/25)
- The GYN sonogram sonar again Rt para-external LN involvement close to exiternal iliac a. 2.3 x 2.5 cm.
- 2021/11/25 PET A glucose hypermetabolic lesion in the pelvic region, nature to be determined. Normal bowel radioactivtity could show this picture. However, lympadenopathy could not be excluded completely. Please correlate with CT findings. Tumor markers ok.
- Retrospective review CT same site nodule 1.8 x 1.5cm.
- Need secondary debulking ?



IMPAX 6.5.3.117 "Enterprise Unlimited"

2021/11/23 CT

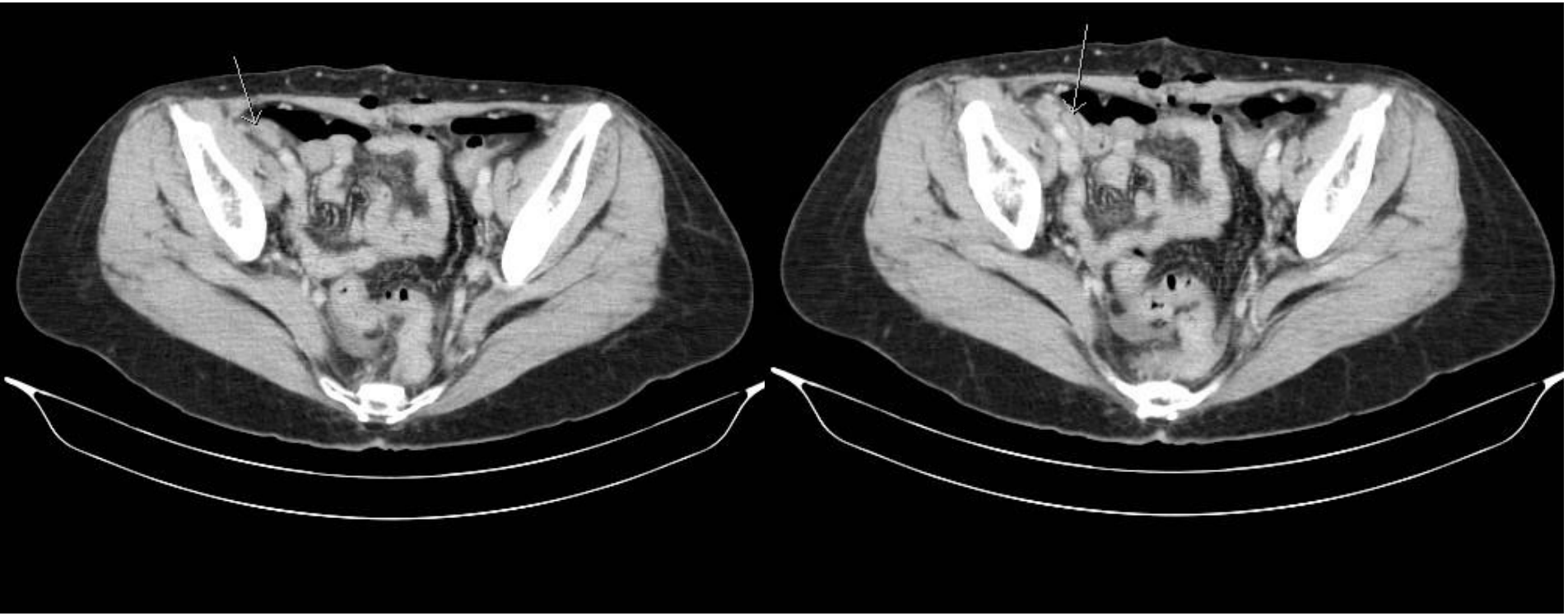


2021/12/20 secondary look

- 8:43~11:30
- #1 Soft tissue, right external iliac area, excision biopsy --- cyst degeneration lesion with stitches granuloma and mixed inflammatory infiltrate
- #2 Soft tissue, sigmoid mesentery, excision biopsy --- fat necrosis with foci of fibrosis and reactive mesothelial cells

- 因為早上開刀取出的冰凍切片病理科醫師看是良性的.
- 術後下午再次照腹部電腦斷層發現外腸骨處有一淋巴結跟之前比較仍然存在.
- 所以早上取的是另一個結節冰凍切片病理報告是良性.原來的外腸骨處有一淋巴結還存在.

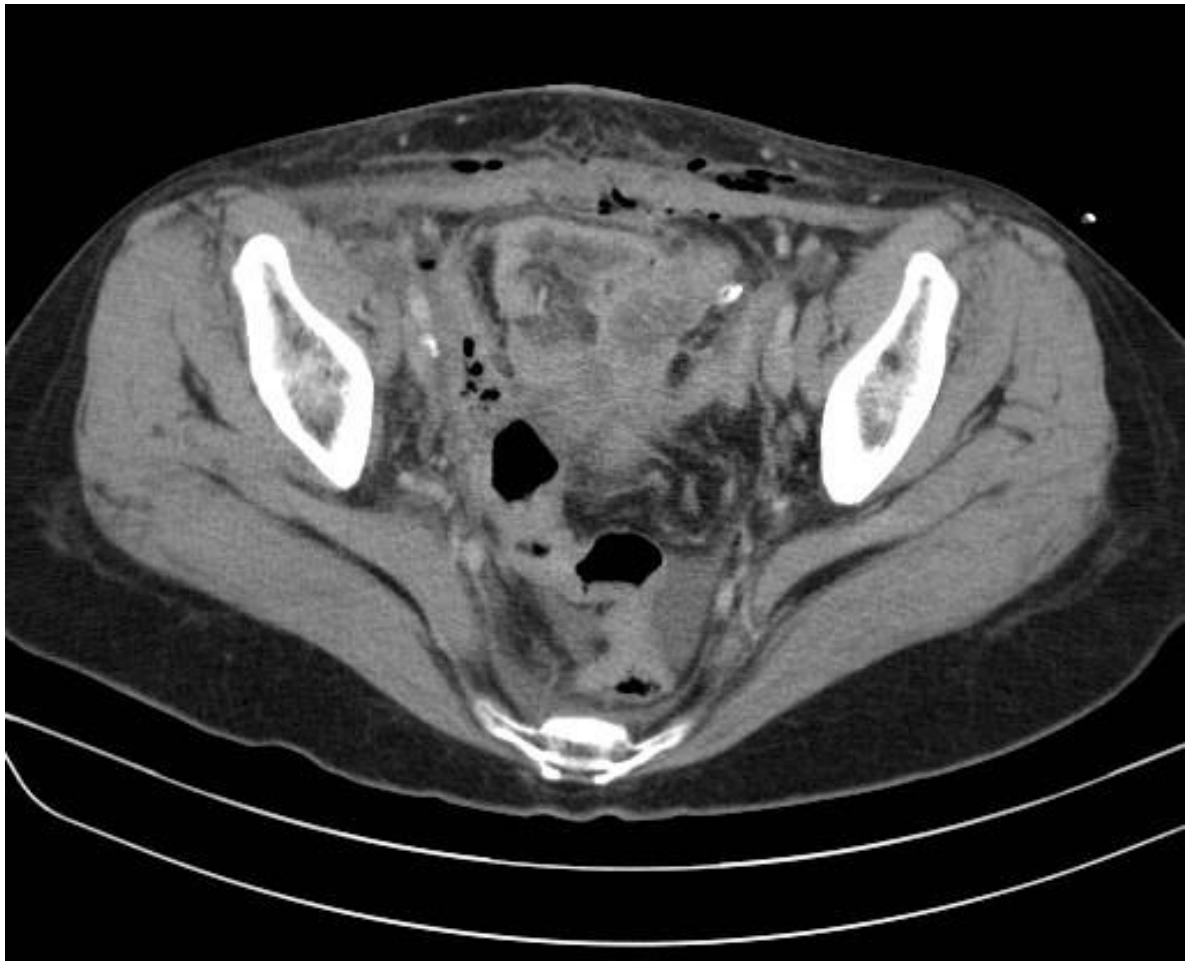
2022/12/20



- Lymph node, external iliac, dissection --- carcinoma, metastatic, consistent with ovary origin
- Lymph node and soft tissue, right external iliac area, excision biopsy --- carcinoma, metastatic
- Immunohistochemical study for MSI (microsatellite instability):
- MLH1: positive (70%)
- PMS2: positive (60%)
- MSH2: positive (>90%)
- MSH6: positive (>90%)
- Conclusion
- MMR-I (mismatch repair-intact, MSI-L/S): both MLH1(PMS2) and MSH2(MSH6) positive

- Post second look
- 2021/12/24 follow CT again
- S/P recent dissection of a metastatic LN along with RIGHT side external iliac artery, with mild increased surrounding soft tissue fatty strandings, in favor of post-OP fibrosis.
- 3. Probable small bowel ileus.

2021/12/24



- Chemotherapy Taxol 175mg/m2 + carboplatin9 AUC5) x 6 courses and Avastin 15mg /kg 5 courses Q3W
- Now maintenance Olaparib

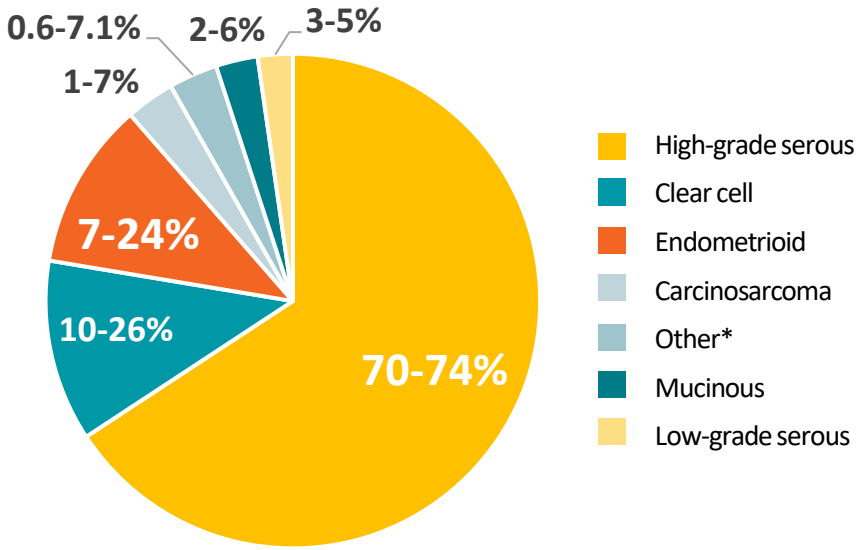
Most patients were with serous ovarian cancer in Taiwan

- ***For epithelial carcinomas, serous is the most common subtype (75%)***[1]

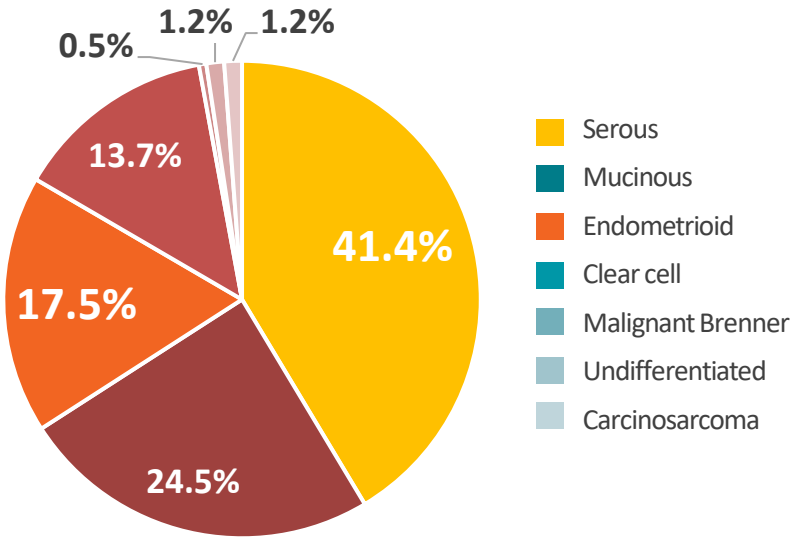
The WHO histological typing of epithelial ovarian tumors[2]

- Serous
- Endometrioid
- Clear cell
- Mucinous
- Brenner (transitional cell)
- Mixed epithelial tumors
- Undifferentiated
- Unclassified

Percentage of cases by major OC subtype[3]



Distribution of OC histologic type in Taiwan[4]



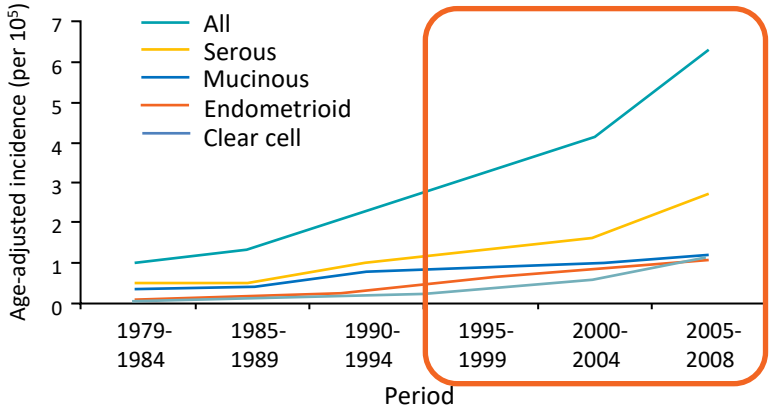
OC, ovarian cancer; WHO, World Health Organization.

1. Chen LM, et al (UpToDate). Overview of epithelial carcinoma of the ovary, fallopian tube, and peritoneum. Available at: https://www.uptodate.com/contents/overview-of-epithelial-carcinoma-of-the-ovary-fallopian-tube-and-peritoneum/ (Accessed in Sep 2020); 2. Ledermann JA, et al. Ann Oncol. 2013;24 (Suppl 6):vi24-vi32; 3. Committee on the State of the Science in Ovarian Cancer Research, Board on Health Care Services, Institute of Medicine, & National Academies of Sciences, Engineering, and Medicine. (2016). *Ovarian Cancers: Evolving Paradigms in Research and Care.* National Academies Press (US); 4. Chiang YC, et al. J Gynecol Oncol. 2013;24:342-351.

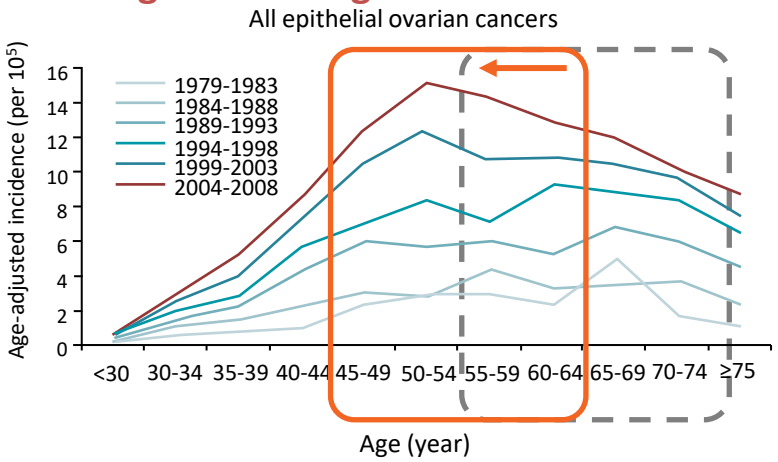
The incidence of OC increased over time and the patients were younger than before

- 9,491 patients with OC between 1979 and 2008 from National Cancer Registration System of Taiwan

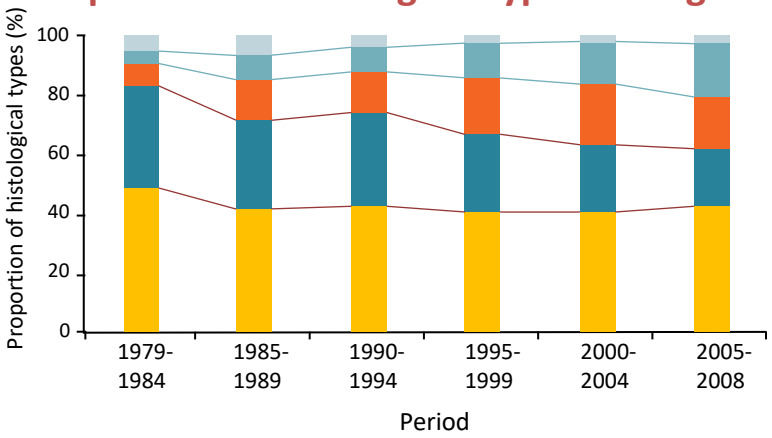
Incidence of OC increased



Age of OC diagnosis decreased



Proportion of histological types changed



- *Decreased in mucinous carcinoma*
- *Increased in clear cell carcinoma*

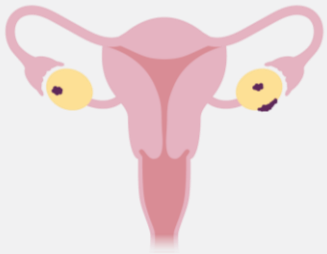
OC, ovarian cancer.

Chiang YC, et al. J Gynecol Oncol. 2013;24:342-351.

Ovarian cancer staging system

Stage **1**

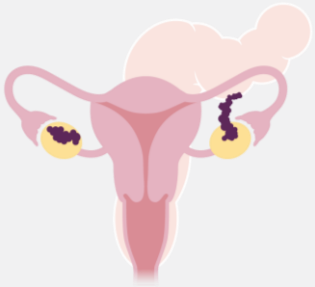
Cancer is in only one or both ovaries and **has not spread** to any other organs or tissues



1A	**1** ovary/fallopian tube
1B	**Both** ovaries/fallopian tubes
1C	**≥ 1** ovaries/fallopian tubes with: • Surgical spill/capsule ruptured • Malignant cells in the ascites/ peritoneal washings

Stage **2**

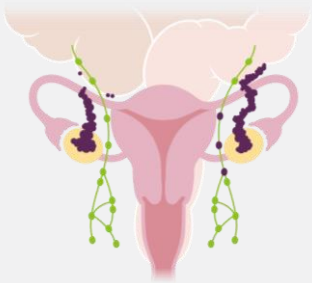
Cancer has spread to other organs or tissues **within the pelvis**



2A	**Extension** ± implants on uterus ± fallopian tubes ± ovaries
2B	**Extension** to other pelvic intraperitoneal tissues

Stage **3**

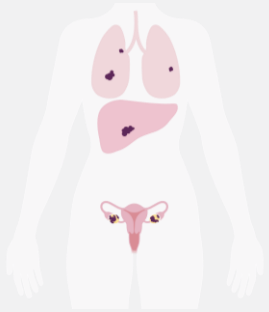
Cancer has **spread outside the pelvis** to abdominal areas



3A	**Lymph nodes**/extrapelvic peritoneal involvement
3B	**Peritoneal metastasis** beyond pelvic **≤ 2 cm** ± metastatsis to lymph nodes
3C	**Peritoneal metastasis** beyond pelvic **> 2 cm** ± metastatsis to lymph nodes

Stage **4**

Cancer has **spread to other organs** or distant lymph nodes

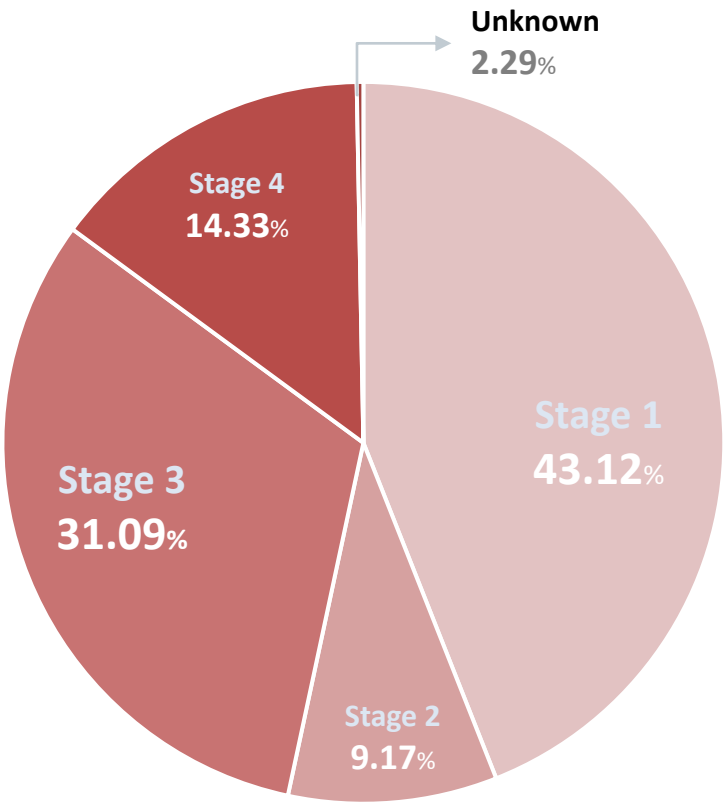


4A	**Pleural effusion** + cytology (+)
4B	**Parenchymal metastases** & metastases to **extra-abdominal organs**

1. National Comprehensive Cancer Network Guidelines for Patients/Ovarian Cancer, 2019. Available at: https://www.nccn.org/patients/guidelines/cancers.aspx (Accessed in Jun 2020); 2. Prat J, et al. Int J Gynaecol Obstet. 2014;124:1-5.

Most of patients were diagnose with stage I or III OC in Taiwan

Most of OC cases were diagnosed at FIGO stage 1 and 3[1]



FIGO stage 1 of OC has the highest 5-survival rates[2]

	FIGO 2014 stage definitions	Invasive epithelial
I	Tumor limited to one or both ovaries	92%
II	Tumor involves one or both ovaries with pelvic extension	73–78%
III	Tumor involves one or both ovaries with metastasis outside the pelvis and/or regional lymph node metastasis	39–59%
IV	Distant metastases other than peritoneal metastases	17–28%

In compared to serous carcinoma, other histological type of OC has lower risk of death*[3]

Histological type	N	HR	95% CI	*p*-value
Serous	3364	1	Reference	-
Mucinous	1872	0.65	0.59-0.72	<0.001
Endometrioid	1518	0.72	0.65-0.79	<0.001
Clear cell	1224	0.80	0.72-0.89	<0.001
Undifferentiated	81	1.98	1.52-2.58	<0.001

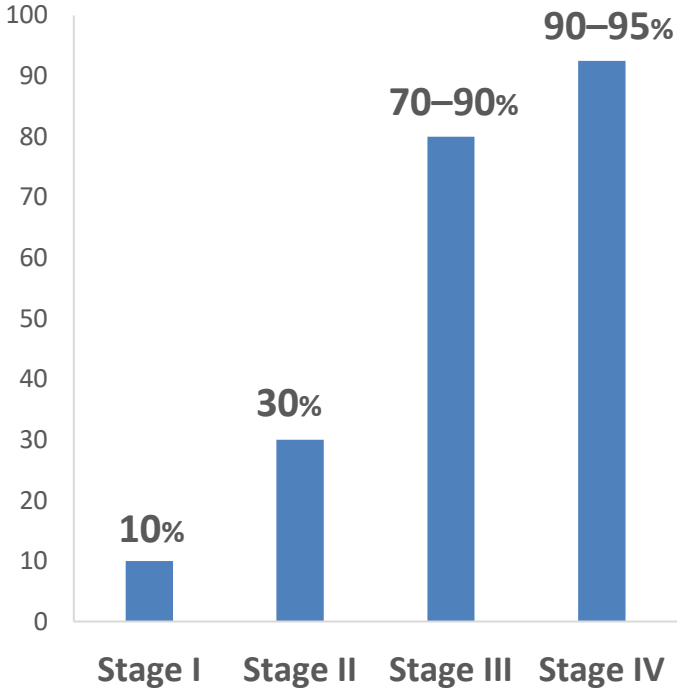
*Other than the undifferentiated carcinoma.

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; OC, ovarian cancer.

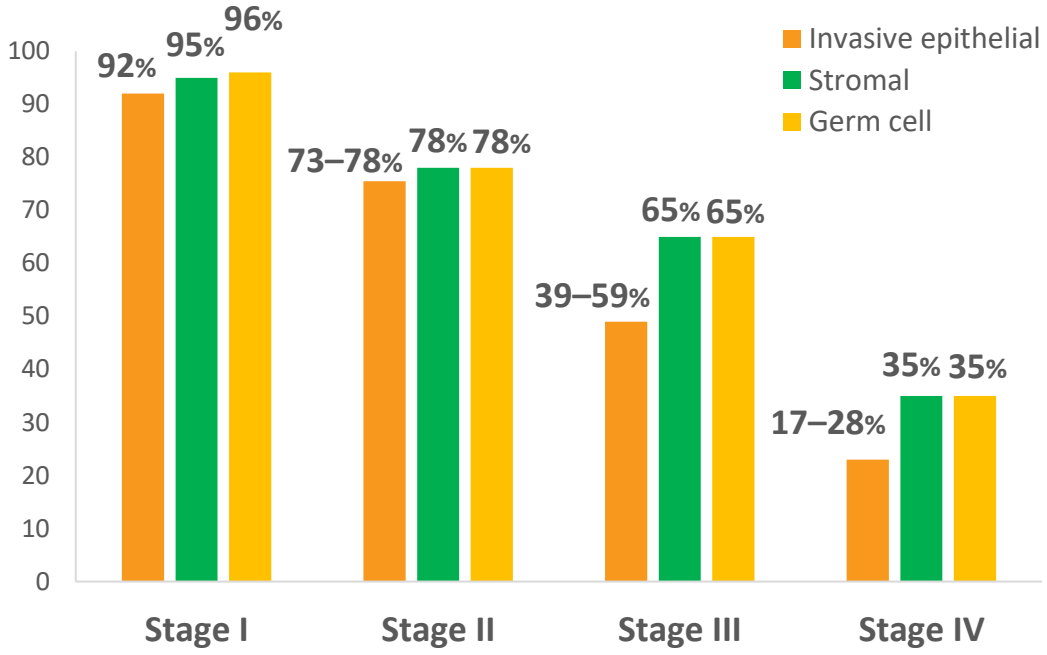
1.衛生福利部國民健康署. 中華民國 106 年癌症登記報告. 2019); 2. Doubeni CA, et al. Am Fam Physician. 2016;93:937-944; 3. Chiang YC, et al. J Gynecol Oncol. 2013;24:342-351.

Advanced stages have higher recurrence rates and lower 5-year survival rates

Recurrence rates of OC by stage[1]



5-year survival of OC by tumor stage and type[2]



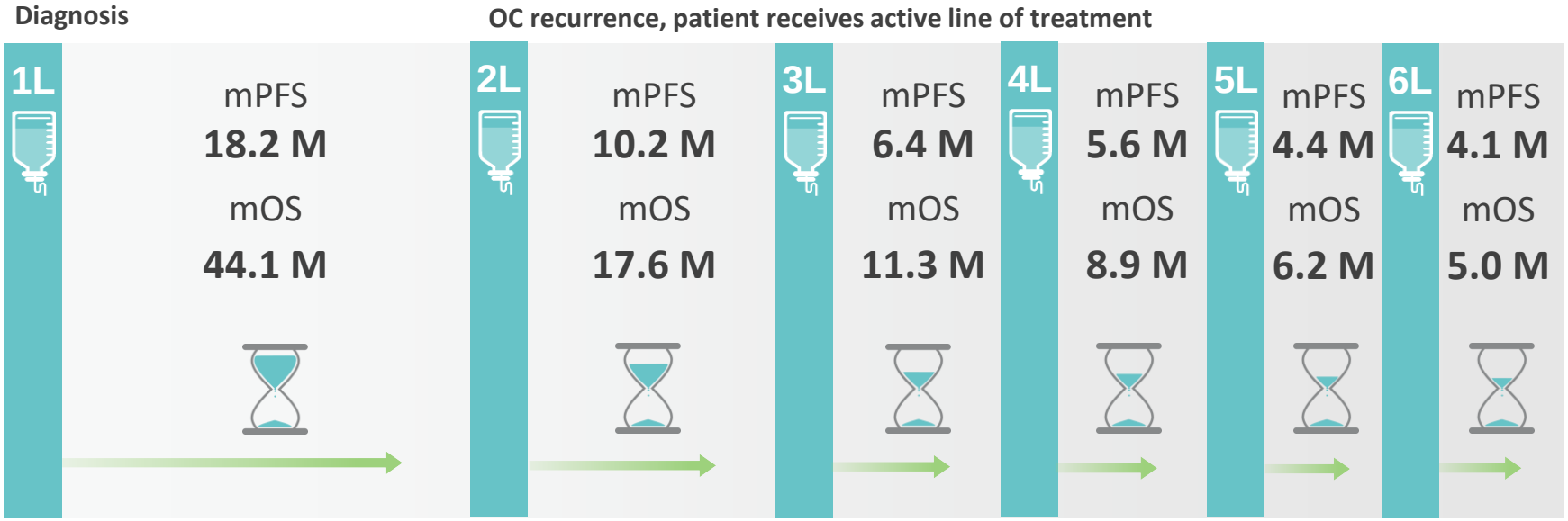
OC, ovarian cancer.

1. Ovarian cancer research alliance. Available at: https://ocrahope.org/patients/about-ovarian-cancer/recurrence/ (Accessed in Jun 2020);
2. Doubeni CA, et al. Am Fam Physician. 2016;93:937-944.

The interval of recurrence will shorten after each lines of treatments

From platinum-sensitive to platinum-resistant

- Most ovarian cancers will recur, leading to shorter treatment intervals[1]



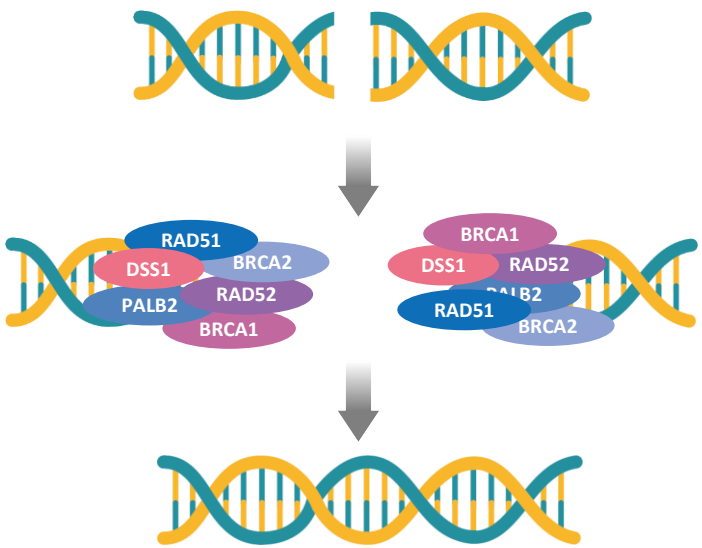
- About **80% of advanced ovarian cancers will recur** during or after first-line treatment[1]
- Until recent years, there were essentially no treatment options other than repeated courses of chemotherapy in patients with 2 or more prior lines of chemotherapy[2]

M, months; ; mOS, median overall survival; mPFS, median progression-free survival.

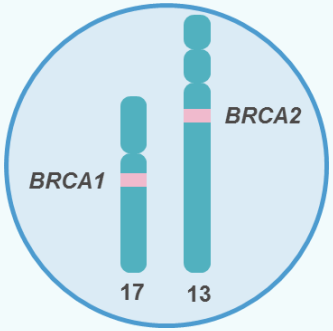
1. Hanker LC, et al. Ann Oncol. 2012;23:2605-2612; 2. Herzog TJ, Monk BJ. Gynecol Oncol Res Pract. 2017;4:13.

BRCA1/2 attribute in the DNA repair process

HRR mechanism[1]



1. DNA damage constantly occurs within cells; this needs to be repaired to maintain genomic integrity[2]
2. HR (homologous recombination) is an important pathway that allows repair of DSB[2]
3. HR relies on many proteins including **BRCA1 and BRCA2**[2]



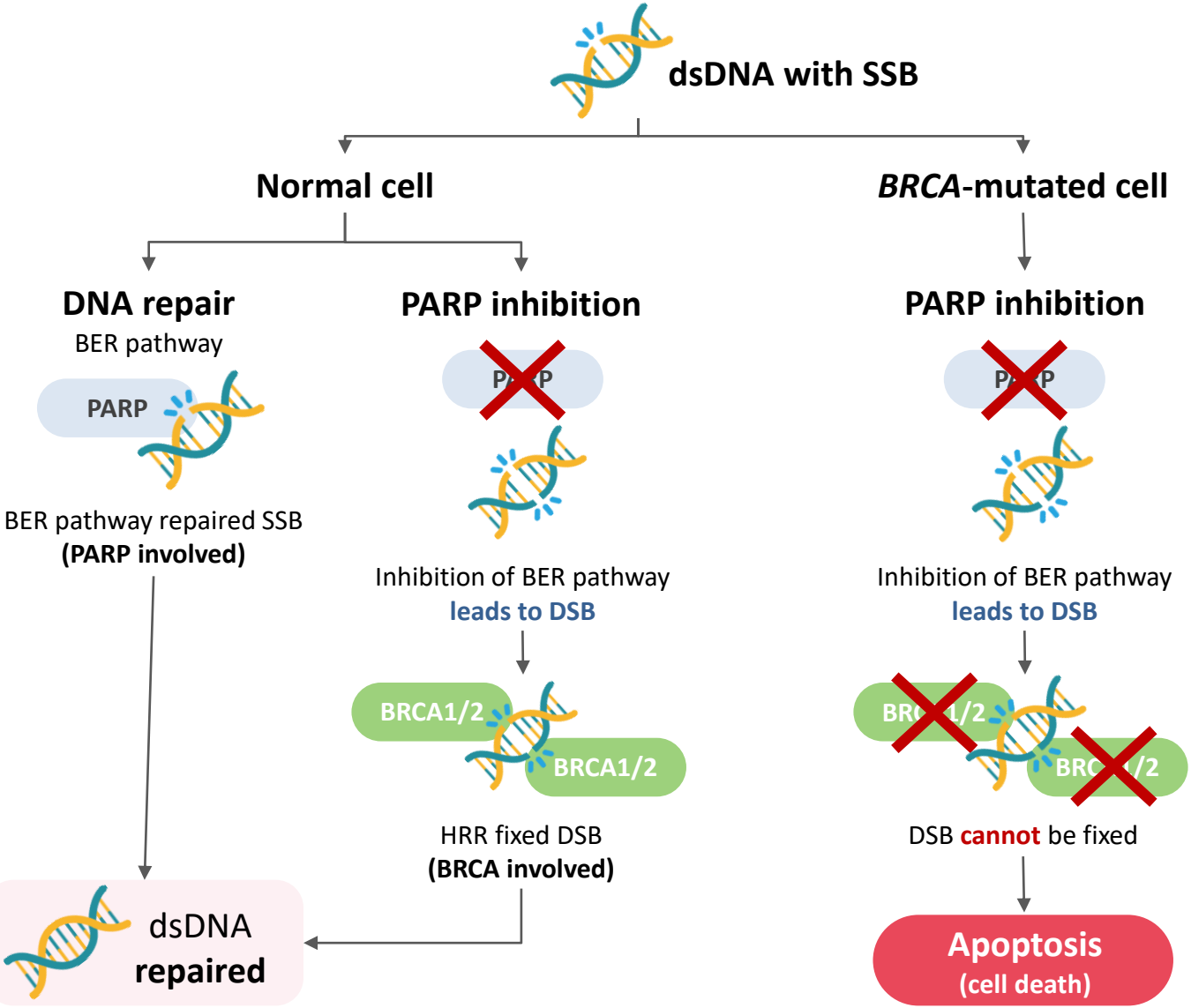
*BRCA*1 and *BRCA*2 gene

- *BRCA*1 and *BRCA*2 are key proteins in homologous repair of DSB[3]
- *BRCA*1 is involved in regulating cell cycle progression and interacts with multiple transcription factors, including ER-α, p53, STAT1 and c-Myc[4]

BRCA, breast cancer susceptibility gene; BRCA, breast cancer susceptibility protein; DNA, deoxyribonucleic acid; DSB, double-strand break; ER, estrogen receptor; HRR, homologous recombination repair; PALB2, Partner and localizer of BRCA2.

1. LaFargue CJ, Tewari KS. Recent Pat Biotechnol. 2016;9:86-101; 2. Frey MK and Pothuri B. Gynecol Oncol Res Pract 2017;4:4;
3. Powell SN, Kachnic LA. Oncogene. 2003;22:5784-5791; 4. Mullan PB, et al. *Oncogene* 2006;25:5854-5863.

Blocking the BER pathway in *BRCA*-mutated patients will lead to cell apoptosis



BER, base excision repair; *BRCA,* breast cancer susceptibility gene; BRCA, breast cancer susceptibility protein; DSB, double-strand break; dsDNA, double-strand deoxyribonucleic acid; HRR, homologous recombination repair; PARP, poly(ADP-ribose) polymerase; SSB, single-strand break.

1. Kedar PS, et al. Mol Cancer Res. 2012;10:360-368; 2. McLornan DP, et al. N Engl J Med. 2014; 371:1725-1735.

Examples of PARP inhibition in DNA repair

Normal cell

DNA repair
BER pathway
(PARP involved)

dsDNA **repaired**

PARP inhibition
HRR pathway
(BRCA involved)

dsDNA **repaired**

***BRCA*-mutated cell**

PARP inhibition
✕ BER pathway
✕ HRR pathway

dsDNA **cannot be repaired**

A building with 4 pillar, solid & stable

ONE pillar has broken, it stands but unstable

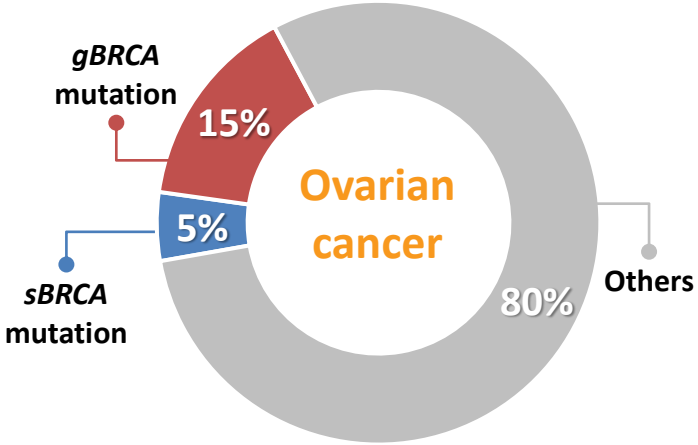
TWO pillars have broken, the temple collapsed

BER, base excision repair; *BRCA,* breast cancer susceptibility gene; dsDNA, double-strand deoxyribonucleic acid; HRR, homologous recombination repair; PARP, poly(ADP-ribose) polymerase.

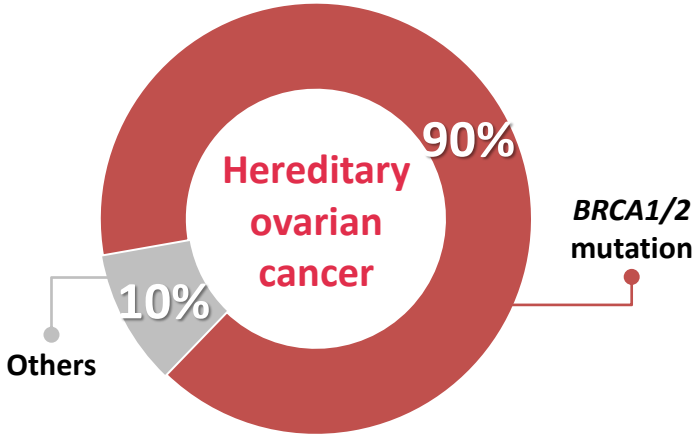
1. Kedar PS, et al. Mol Cancer Res. 2012;10:360-368; 2. McLornan DP, et al. N Engl J Med. 2014; 371:1725-1735.

BRCA mutation occurs in about 1/4 ovarian cancer cases in Taiwan

- Either germline or somatic mutations in *BRCA* account for **20%** of all the ovarian cancers[1]

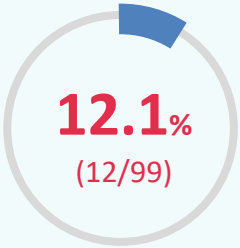


- *BRCA*1/2 mutations account for **90%** of all hereditary ovarian cancer cases[1]



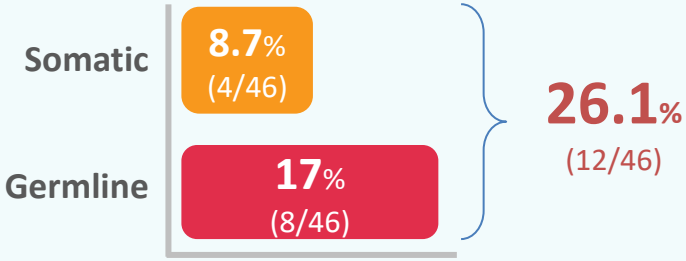
99 Taiwanese patients with ovarian cancer (46 serous; 24 endometrioid; 29 clear cell)[2]

Pathogenic variants



BRCA1: n=7; *BRCA2*: n=6

***BRCA*mut among serous OC**

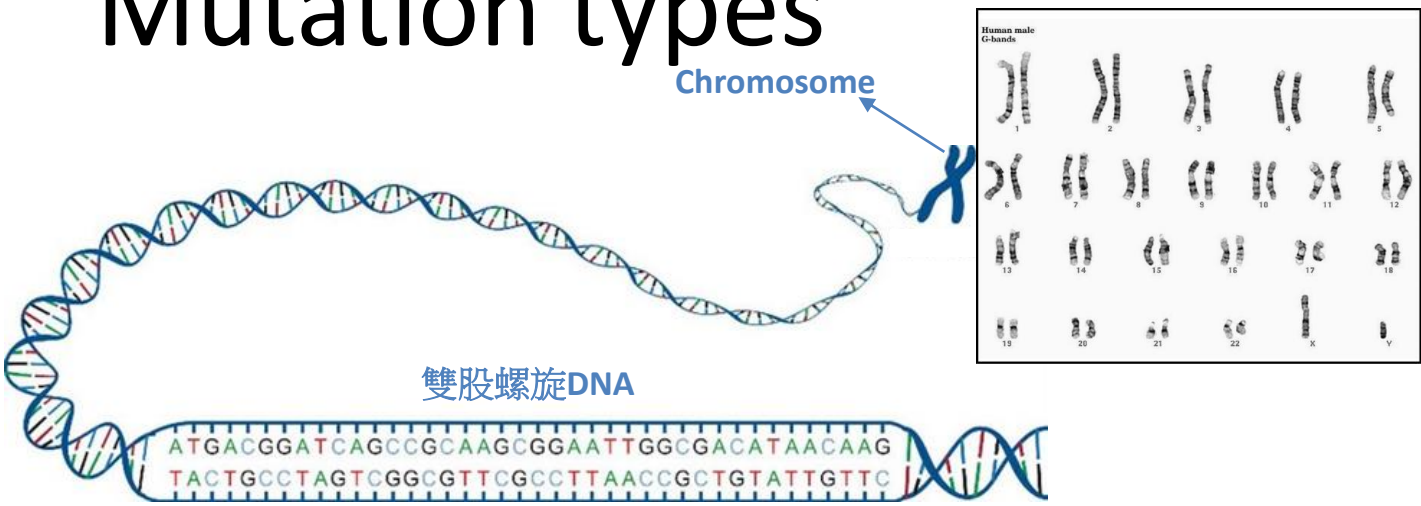


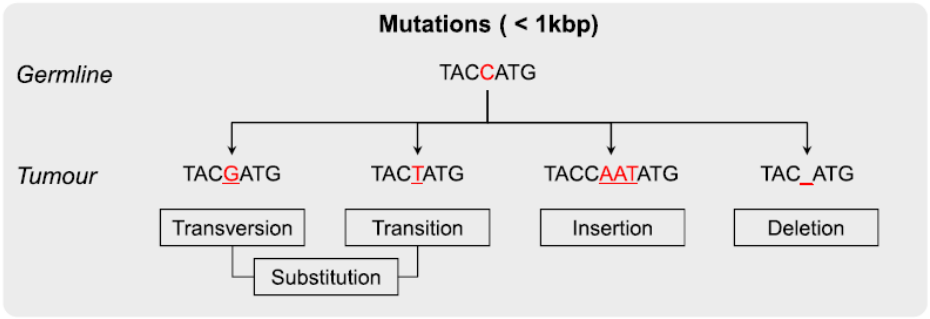
All pathogenic *BRCA*1/2 mutations were identified in serous carcinoma samples

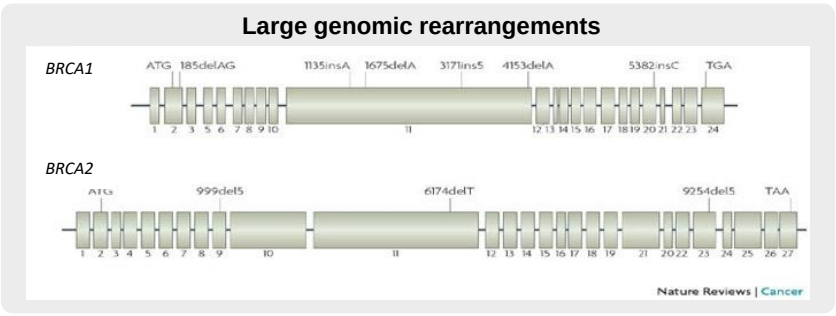
g, germline; *BRCA*, breast cancer susceptibility gene; OC, ovarian cancer; s, somatic.

1. Pan Z, Xie X. Oncotarget 2017;8:97657-97670; 2. Chao A, et al. Oncotarget. 2016;7:85529-85541.

Mutation types







文獻指出BRCAm中約有 10% 為大片段重組 (LGR)
NGS技術無法檢測到，需靠其他檢測幫忙：e.g. MLPA

Platform to detect:

NGS or Sanger Sequencing

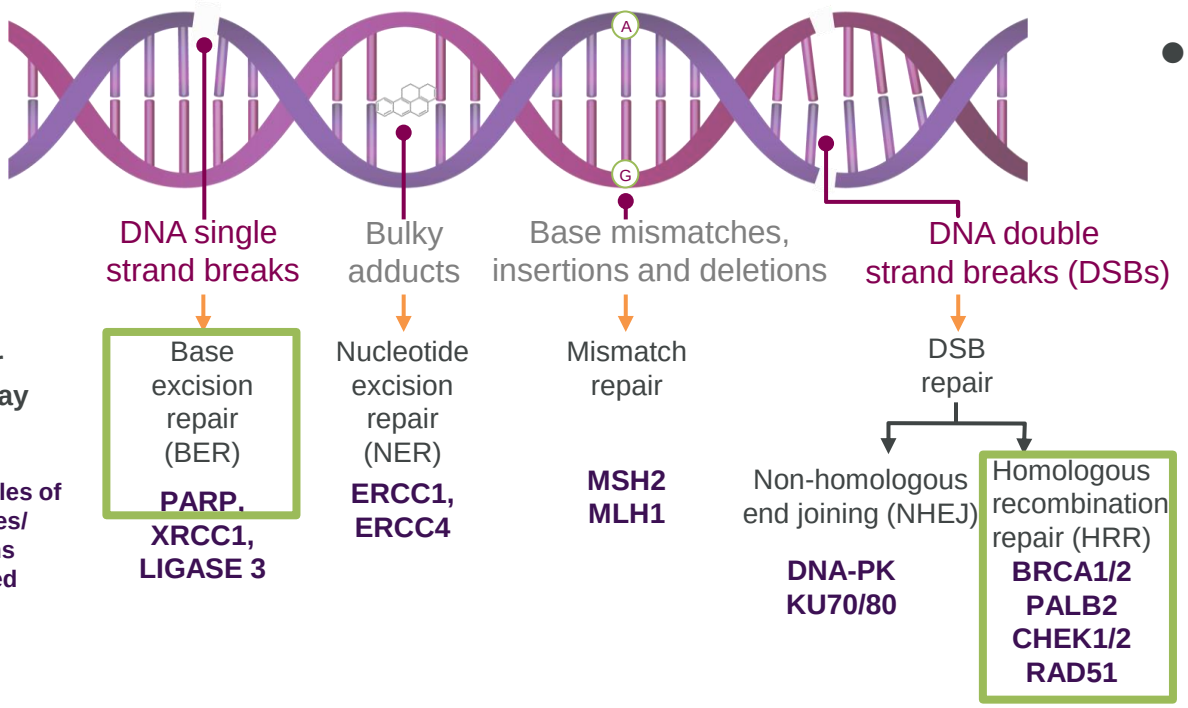
Platform to detect:

MLPA or BioInfo

1. Watkins, J.A., et al., Breast Cancer Res, 2014. 16(3): p. 211 ; 2. James, P.A., et al., Fam Cancer, 2015. 14(2): p. 287-95

Homologous Recombination Repair (HRR) 同源重組修復

- HRR 是一種修復精確度高的修復機制
- 可修復DNA雙股螺旋斷裂

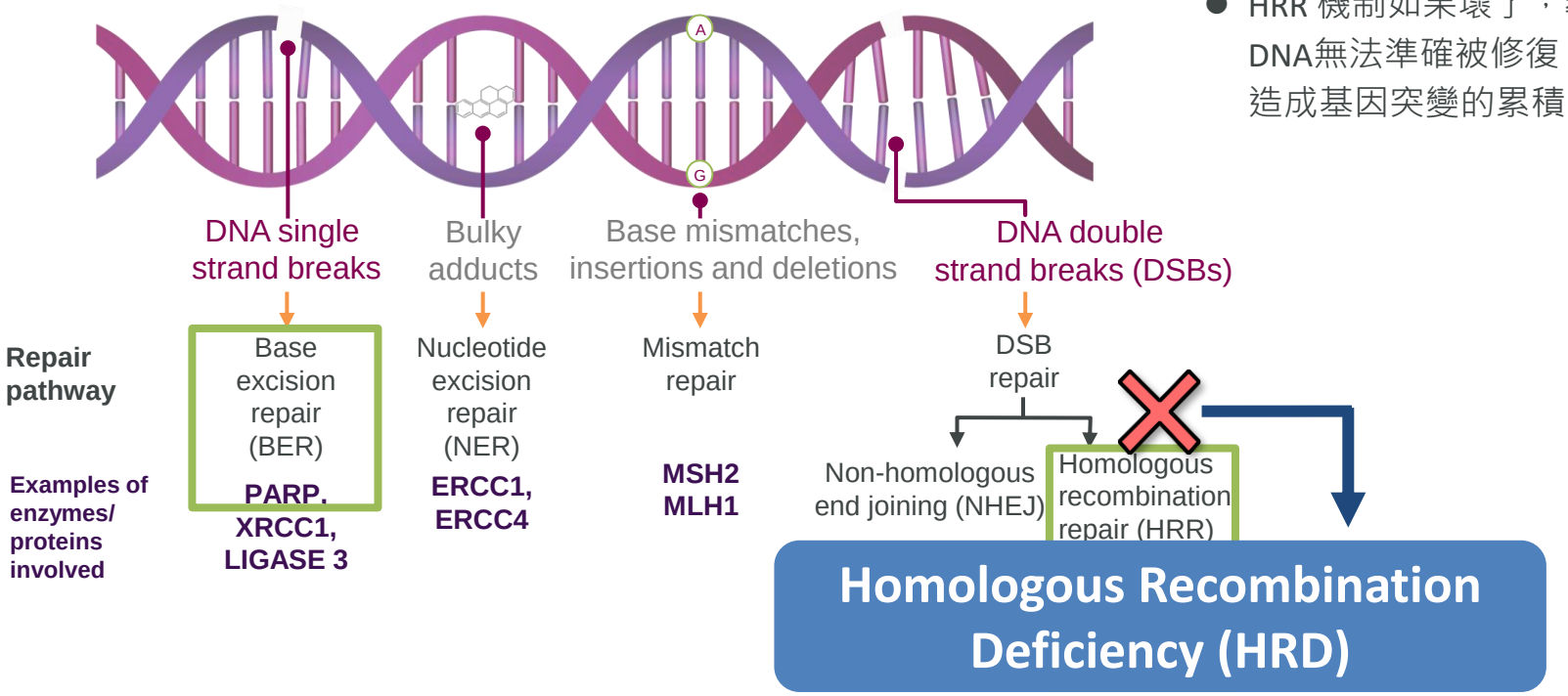


BER=base excision repair; DDR=DNA damage response; DNA=deoxyribonucleic acid; DSB=double stand break; HRR=homologous recombination repair; NER=nucleotide excision repair; NHEJ=non-homologous end joining

Figure adapted from: 1. Lord CJ, and Ashworth A. Nature. 2012;481:287–294

Homologous Recombination Deficiency (HRD) 同源重組修復缺失

- HRR 機制如果壞了，導致DNA無法準確被修復，進而造成基因突變的累積



BER=base excision repair; DDR=DNA damage response; DNA=deoxyribonucleic acid; DSB=double stand break; HRR=homologous recombination repair; NER=nucleotide excision repair; NHEJ=non-homologous end joining

Figure adapted from: 1. Lord CJ, and Ashworth A. Nature. 2012;481:287–294

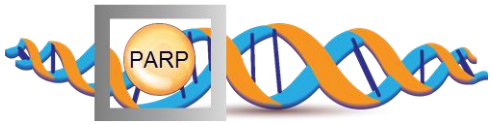
BRCA function and PARP inhibitor

BRCA1 & BRCA2 的功能為修復受傷缺損的**DNA**，特別是雙股螺旋斷裂

PARP 的功能為修復 **DNA** 單股螺旋斷裂

BRCA1/2 基因突變

DNA無法修補



PARP 協助修復

BRCA function and PARP inhibitor

BRCA1 & BRCA2 的功能為修復受傷缺損的**DNA**，特別是雙股螺旋斷裂

PARP 的功能為修復 **DNA** 單股螺旋斷裂

BRCA1/2 基因突變
DNA無法修補

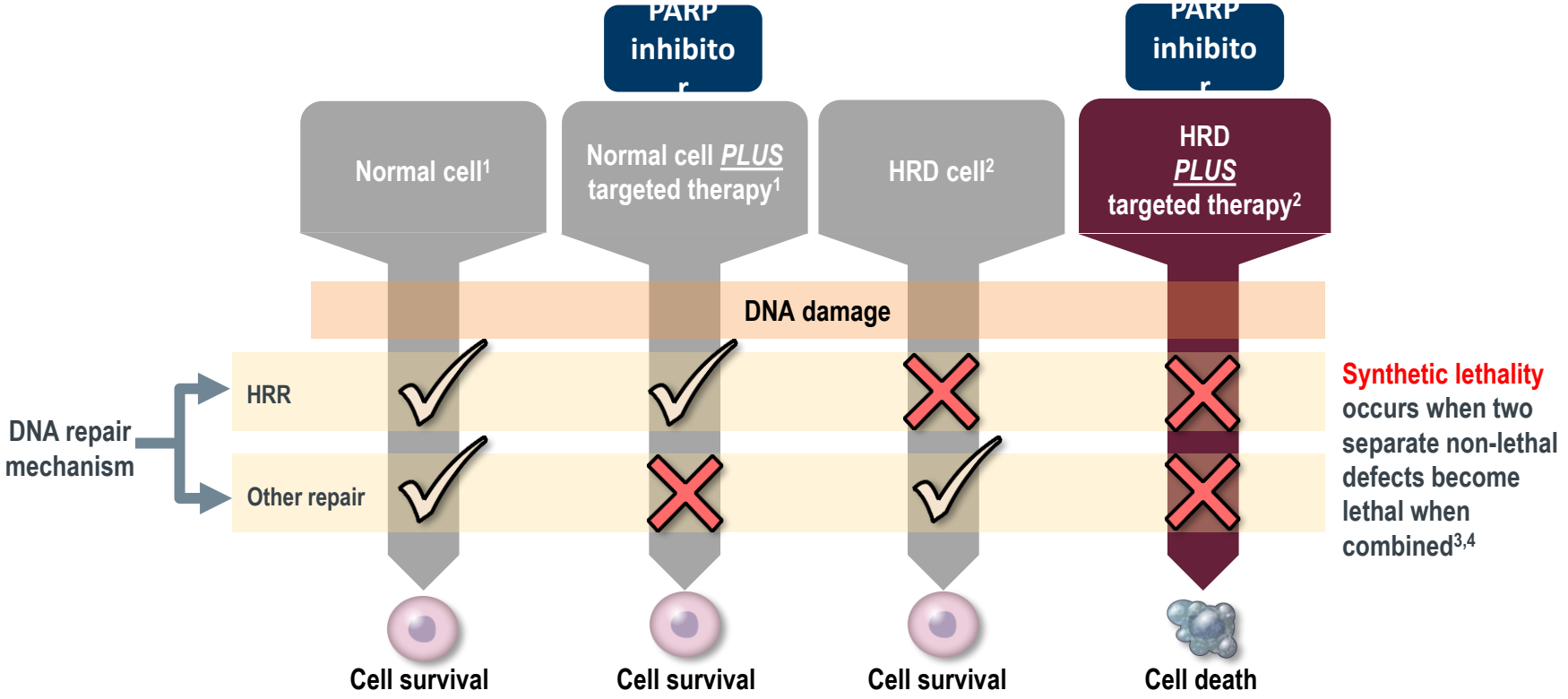
PARP 抑制劑

Cell death

失去修復**DNA**功能
細胞走向死亡

BRCA1/2 基因檢測

PARP Inhibition targets DNA repair–deficient cells by exploiting synthetic lethality



DNA, deoxyribonucleic acid; HR, homologous recombination; HRR, homologous recombination repair; PARP, poly (ADP-ribose) polymerase

1. Walsh CS. *Gynecol Oncol.* 2015;137(2):343-350. 2. Konecny GE, et al. *Br J Cancer.* 2016;115:1157-1173. 3. George A, et al. *Nat Rev Clin Oncol.* 2017;14(5):284-296.

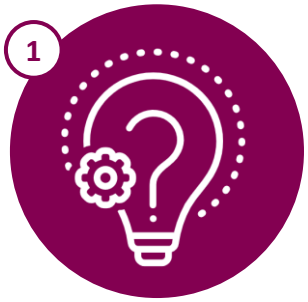
Three approaches to identify HRD

Cause of HRD

Function of HRR

Effect of HRD

Approach 1: Cause of HRD



Cause of HRD

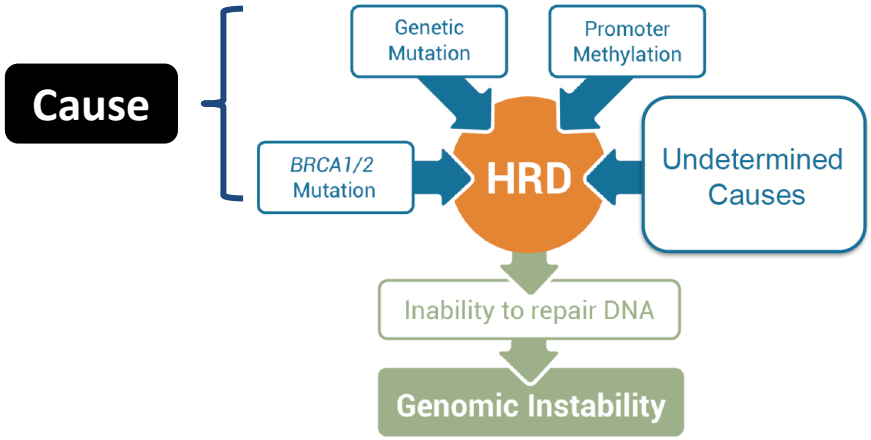
Causes of HRD

*BRCA1/2*m	HRRm Gene panels
Germline / Tumor • Including point mutation / InDel detected by NGS • Large DNA deletion detected by MLPA	• Loss of function of key HRR genes (tumor test) • 15 genes in AZ panel: *BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*

1. O'Kane GM et al. Trends Mol Med. 2017;23(12):1121-1137. 2. Hoppe MM, et al. J Natl Cancer Inst. 2018;110(7):704-713

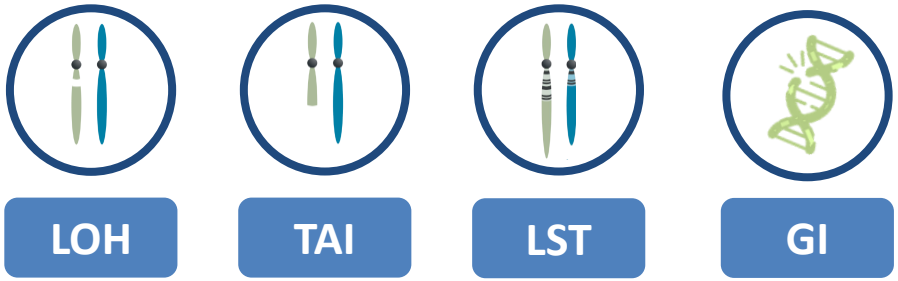
Approach 3: Effect of HRD

Effect of HRD



Genomic Scar

Methods to detect genetic scar

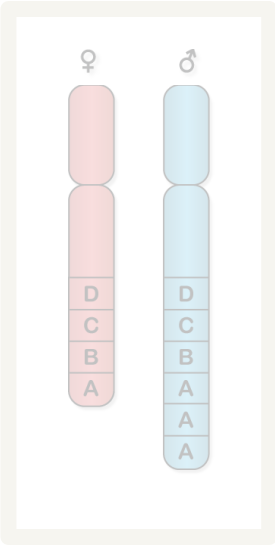


LOH: Loss of heterozygosity ; TAI: Telomeric allelic imbalance ; LST: Large-scale state transitions ; GI: Genomic integrity

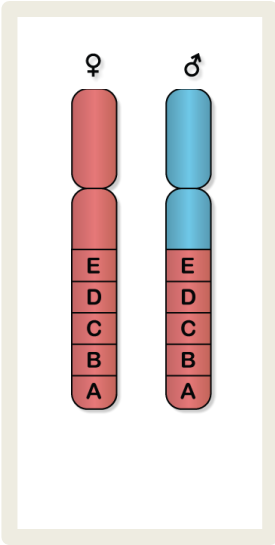
1. Serra Elizalde V, Llop-Guevara A, Pearson A, et al. Detection of homologous recombination repair deficiency (HRD) in treatment-naive early triple negative breast cancer (TNBC) by RAD51 foci and comparison with DNA-based tests.

2. Llop-Guevara A, Vladimirova V, Schneeweiss A, et al. Association of RAD51 with Homologous Recombination Deficiency (HRD) and clinical outcomes in untreated triple-negative breast cancer (TNBC): analysis of the GeparSixto randomized clinical trial.

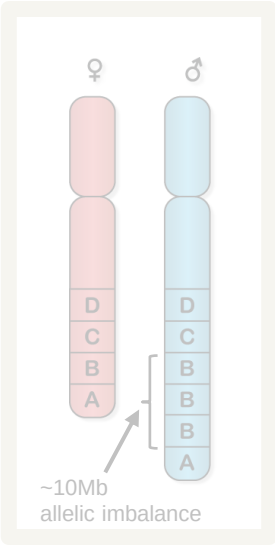
Genomic Scars
HRD-LOH Score



Telomeric Allelic Imbalance Score



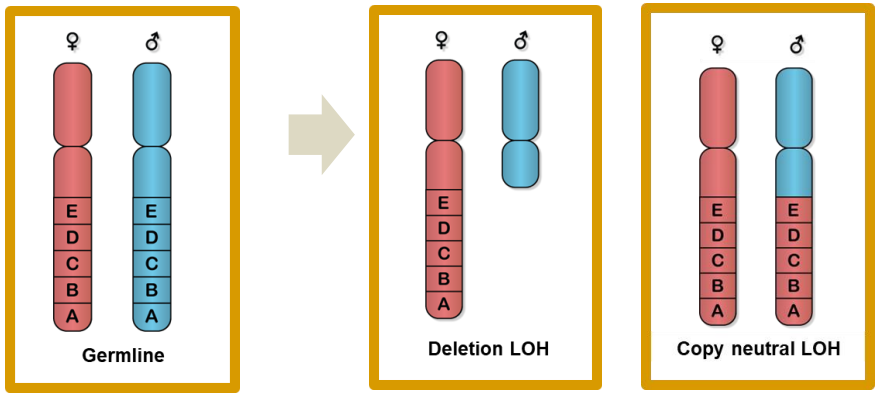
Loss of heterozygosity (LOH) HRD Score



Large Scale Transition Score

1. 學術定義: Loss of heterozygosity (LOH) is a common genetic event in many cancer types

Transition from a heterozygous state in the germline to an apparently homozygous state in the tumour



Heterozygosity

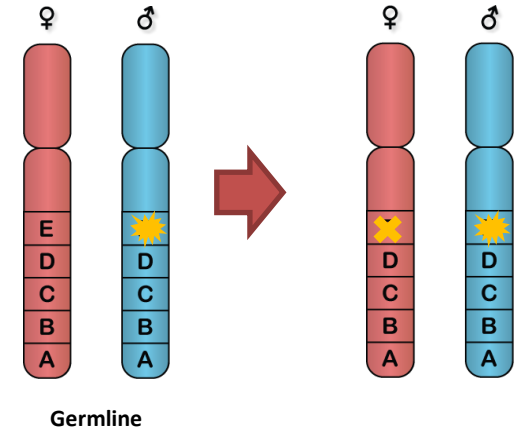
Loss of heterozygosity (LOH)

2. For a patient with germline mutation

Ryland GL. et al. *BMC Medical Genomics* 2015;8:45

Genomic Scars
HRD-LOH Score

2. For a patient with germline mutation[1]



- **Complete loss of BRCA1/2 function** requires bi-allelic loss, and this is hypothesized to be required for PARP inhibitor sensitivity.[2,3]
- **Loss of the non-mutated (wild-type) allele** at the BRCA1 or BRCA2 locus, termed locus-specific loss of heterozygosity (LOH) is observed in tumors [4, 5].
- Cells with complete loss of BRCA1 or BRCA2 function and resultant HR-based DNA repair deficiency (HRD) have exquisite sensitivity to DNA damaging agents, such as platinum-based chemotherapeutics [6] and PARP inhibitors [7,8].

1. Maxwell, Kara N., et al. "BRCA locus-specific loss of heterozygosity in germline BRCA1 and BRCA2 carriers." *Nature communications* 8.1 (2017): 319. 2. Antoniou, Anthony, et al. "Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies." *The American Journal of Human Genetics* 72.5 (2003): 1117-1130. 3. Cancer risks in BRCA2 mutation carriers. The Breast Cancer Linkage Consortium. J. Natl Cancer. Inst. 91, 1310–1316 (1999). 4. Smith, S. A., Easton, D. F., Evans, D. G. & Ponder, B. A. Allele losses in the region 17q12-21 in familial breast and ovarian cancer involve the wild-type chromosome. Nat. Genet. 2, 128–131 (1992). 5. Gudmundsson, J. et al. Different tumor types from BRCA2 carriers show wild-type chromosome deletions on 13q12-q13. Cancer Res. 55, 4830–4832 (1995). 6. Bhattacharyya, A., Ear, U. S., Koller, B. H., Weichselbaum, R. R. & Bishop, D. K. The breast cancer susceptibility gene BRCA1 is required for subnuclear assembly of Rad51 and survival following treatment with the DNA cross-linking agent cisplatin. J. Biol. Chem. 275, 23899–23903 (2000). 7. Bryant, H. E. et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature 434, 913–917 (2005). 8. Farmer, H. et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 434, 917–921 (2005).

TW-10999_LYN_25/02/2020

Rebbeck *et al. Breast Cancer Research* (2016) 18:112
DOI 10.1186/s13058-016-0768-3

Breast Cancer Research

RESEARCH ARTICLE Open Access

Inheritance of deleterious mutations at both *BRCA1* and *BRCA2* in an international sample of 32,295 women

Heterozygous mutation

Abstract

Background: Most *BRCA1* or *BRCA2* mutation carriers have inherited a single (heterozygous) mutation. Transheterozygotes (TH) who have inherited deleterious mutations in both *BRCA1* and *BRCA2* are rare, and the consequences of transheterozygosity are poorly understood.

(Continued on next page)

Olaparib TFDA核准適應症 (Ovarian cancer)

晚期高度惡性上皮卵巢癌、輸卵管腫瘤或原發性腹膜癌，且具遺傳性或體細胞BRCA1/2（germline or somatic BRCA1/2）致病性或疑似致病性突變，對第一線含鉑化療有反應（完全反應或部分反應）之成年病人作為維持治療。

對先前含鉑藥物敏感且復發之高度惡性上皮卵巢、輸卵管腫瘤或原發性腹膜癌，在復發後對含鉑化療有反應（完全反應或部分反應）之成人病人，作為維持治療。

Lynparza 併用 bevacizumab 可用於晚期高度惡性上皮卵巢癌、輸卵管腫瘤或原發性腹膜癌，且對第一線含鉑化療合併bevacizumab有反應有完全反應或部分反應之成年病人，做為維持治療。且其癌症帶有下列任一定義的DNA同源修復系統缺失 (homologous recombination deficiency, HRD)：致病性或疑似致病性 BRCA 突變，及/或基因體不穩定 (genomic instability)

TFDA核准適應症

晚期高度惡性上皮卵巢癌、輸卵管腫瘤或原發性腹膜癌，且具遺傳性或體細胞BRCA1/2（germline or somatic BRCA1/2）致病性或疑似致病性突變，對第一線含鉑化療有反應（完全反應或部分反應）之成年病人作為維持治療。

對先前含鉑藥物敏感且復發之高度惡性上皮卵巢、輸卵管腫瘤或原發性腹膜癌，在復發後對含鉑化療有反應（完全反應或部分反應）之成人病人，作為維持治療。

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卵巢癌

Lynparza單一療法可用於治療曾接受前導性、術後輔助性或轉移性化療，且具遺傳性BRCA1/2（germline BRCA1/2）致病性或疑似致病性突變的HER2（-）轉移性乳癌成人病人。針對荷爾蒙受體陽性的乳癌病人，本品應在曾經接受過荷爾蒙治療、或不適合使用荷爾蒙治療之狀況下使用。

乳癌

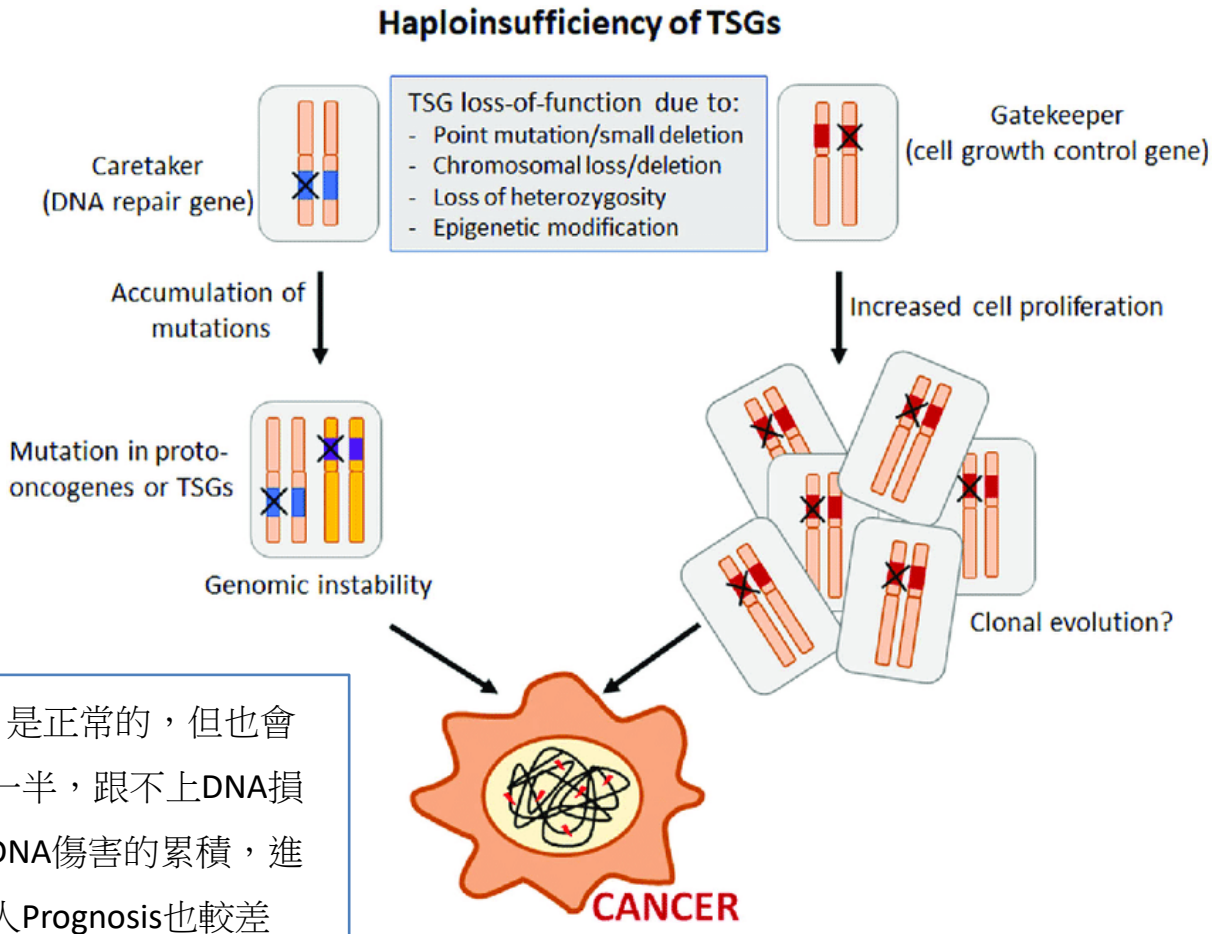
Lynparza 單一療法之維持治療，可用於遺傳性 BRCA 突變且經第一線含鉑化療至少 16 週後疾病未惡化之轉移性胰腺癌成年病人。

胰臟癌

TFDA核准適應症

用於去勢療法無效的轉移性攝護腺癌(metastatic castration-resistant prostate cancer，mCRPC)，且具BRCA1/2(遺傳性及/或體細胞)致病性或疑似致病性突變、先前曾接受新荷爾蒙藥物(novel hormonal agents)治療後惡化之成人病人。

前列腺癌



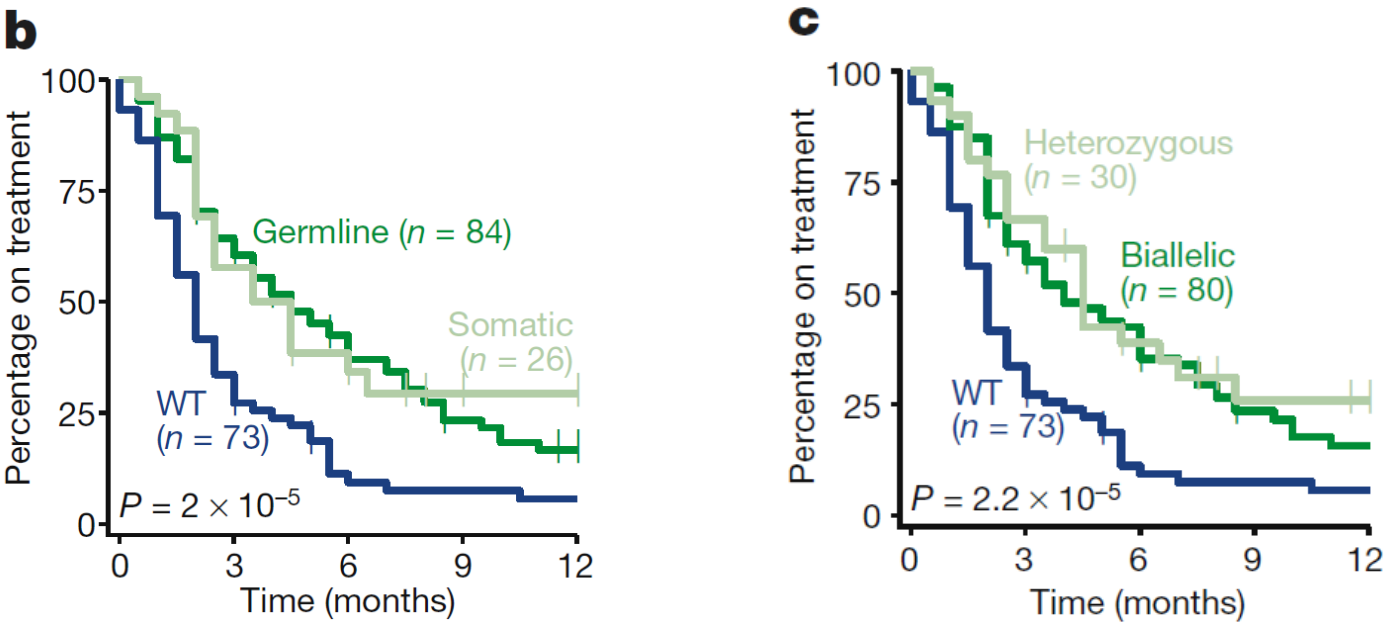
即使有一個 allele 是正常的，但也會因修復能力只剩一半，跟不上DNA損傷的速度，造成DNA傷害的累積，進而走向癌化、病人Prognosis也較差

LETTER

https://doi.org/10.1038/s41586-019-1382-1

Tumour lineage shapes BRCA-mediated phenotypes

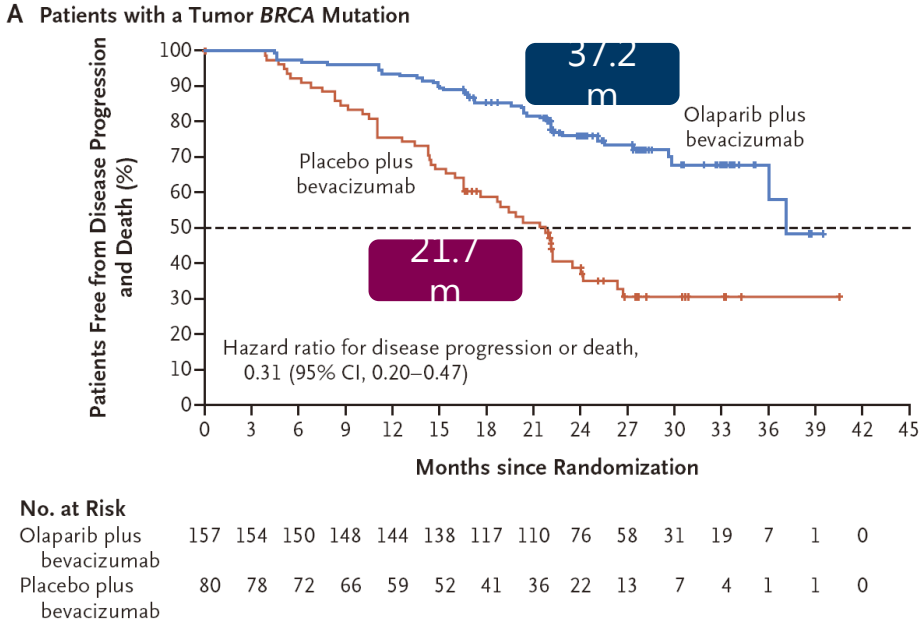
Philip Jonsson[1,2,3], Chaitanya Bandlamudi[1], Michael L. Cheng[4,7], Preethi Srinivasan[5], Shweta S. Chavan[1], Noah D. Friedman[2,3], Ezra Y. Rosen[4], Allison L. Richards[1], Nancy Bouvier[1], S. Duygu Selcuklu[1], Craig M. Bielski[1,2,3], Wassim Abida[4], Diana Mandelker[5], Ozge Birsoy[5], Liying Zhang[5], Ahmet Zehir[5], Mark T. A. Donoghue[1], José Baselga[4,8], Kenneth Offit[4], Howard I. Scher[4], Eileen M. O'Reilly[4], Zsofia K. Stadler[4], Nikolaus Schultz[1,3], Nicholas D. Socci[1], Agnes Viale[1], Marc Ladanyi[2,5], Mark E. Robson[4], David M. Hyman[4,6], Michael F. Berger[1,5,6*], David B. Solit[1,2,4,6*] & Barry S. Taylor[1,2,3,6*]

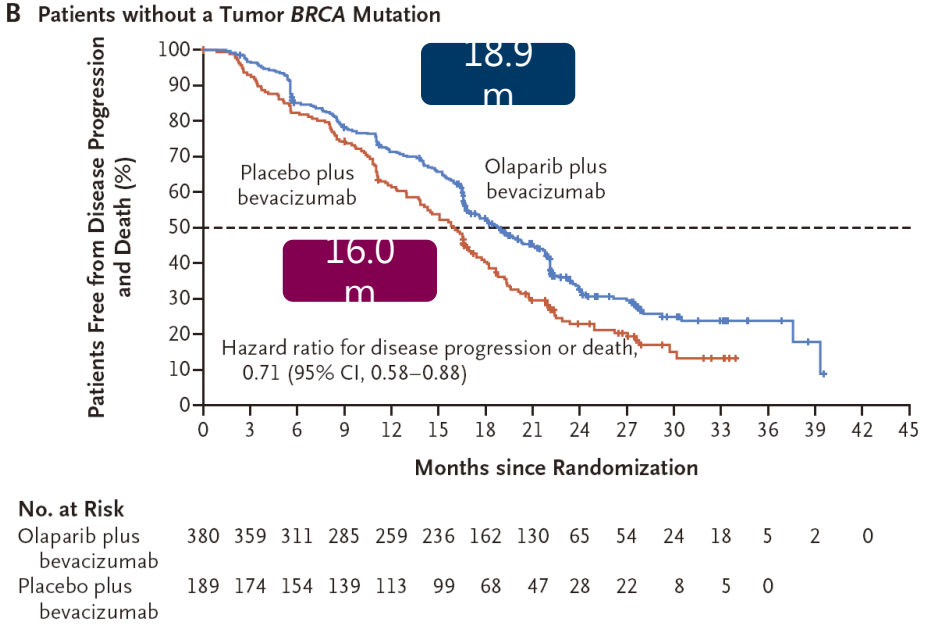


Olaparib + Bevacizumab provide more PFS benefit in patients with mBRCA

With mBRCA

w/o mBRCA

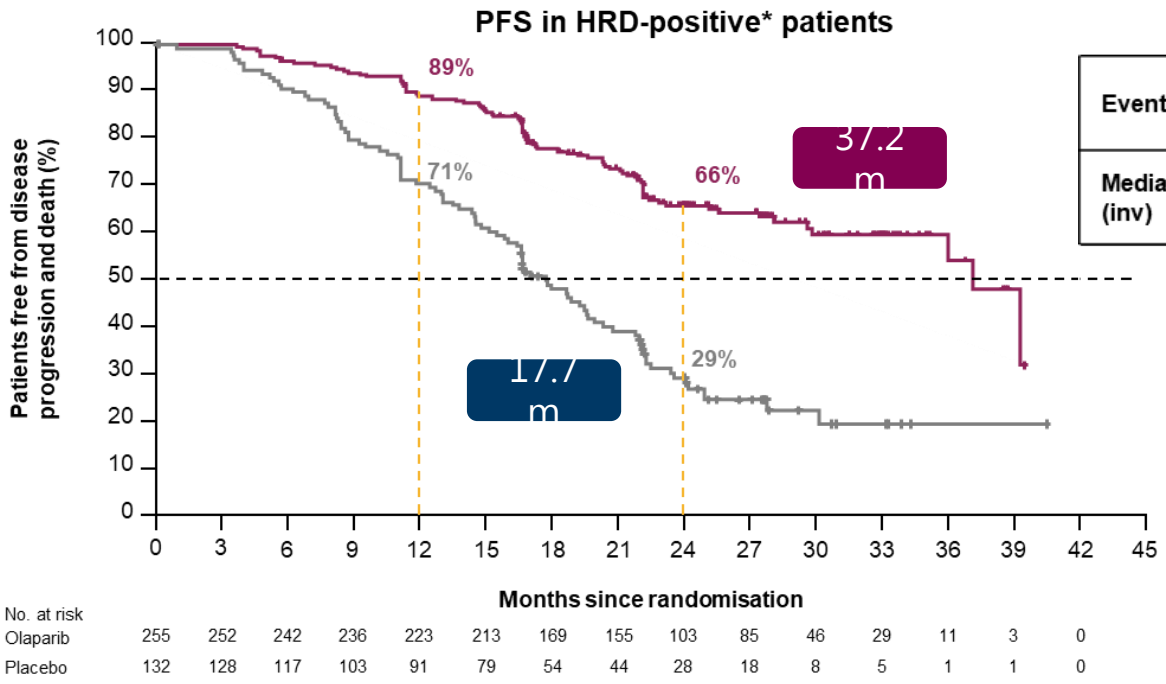




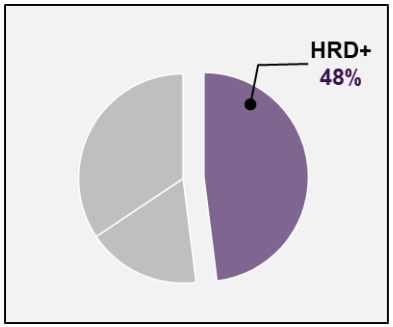
mBRCA: BRCA mutation

Ray-Coquard, I., et al., (2019). N Engl J Med 381(25): 2416-2428

Olaparib + Bevacizumab group showed a substantial PFS benefit in HRD-positive (including tBRCAm) patients



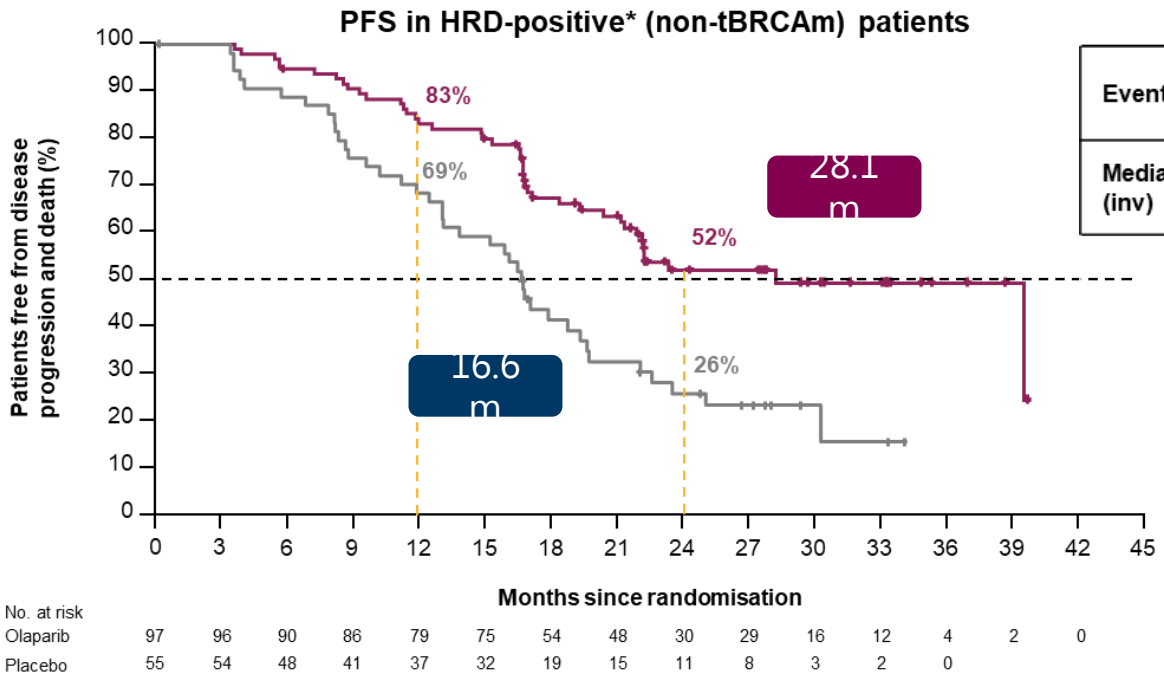
	Olaparib + bevacizumab n=255	Placebo + bevacizumab n=132
Events, n (%)	87 (34)	92 (70)
Median PFS, months (inv)	37.2	17.7
	HR 0.33 (95% CI 0.25-0.45)	



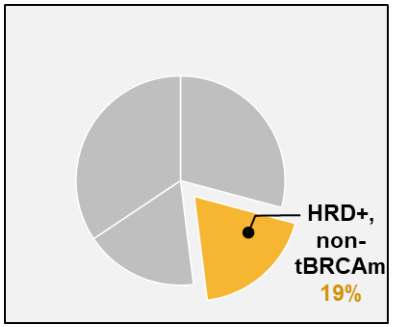
*HRD-positive defined as tBRCAm or a genomic instability score ≥42 in the Myriad myChoice® Plus assay

Ray-Coquard, I., et al., (2019). N Engl J Med 381(25): 2416-2428

Olaparib + Bevacizumab group showed PFS benefit in HRD-positive, non-tBRCAm patients



	Olaparib + bevacizumab n=97	Placebo + bevacizumab n=55
Events, n (%)	43 (44)	40 (73)
Median PFS, months (inv)	28.1	16.6
	HR 0.43 (95% CI 0.28-0.66)	

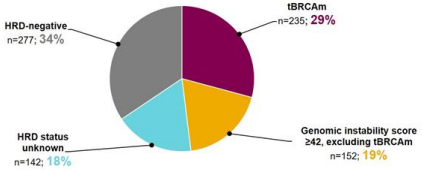


*HRD-positive defined as tBRCAm or a genomic instability score ≥42 in the Myriad myChoice® Plus assay

Ray-Coquard, I., et al., (2019). N Engl J Med 381(25): 2416-2428

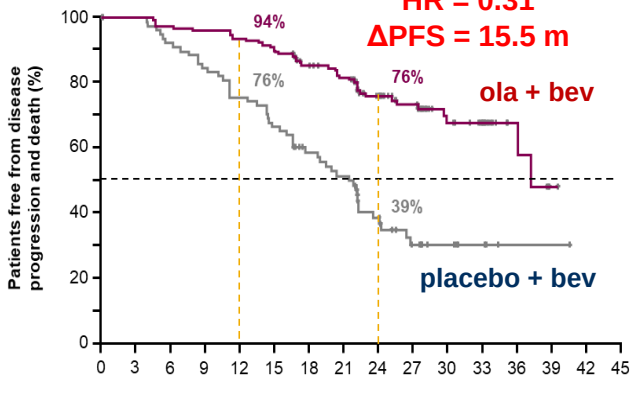
PAOLA-1: PFS by HRD status

PAOLA-1



HRD-positive

*BRCA*m

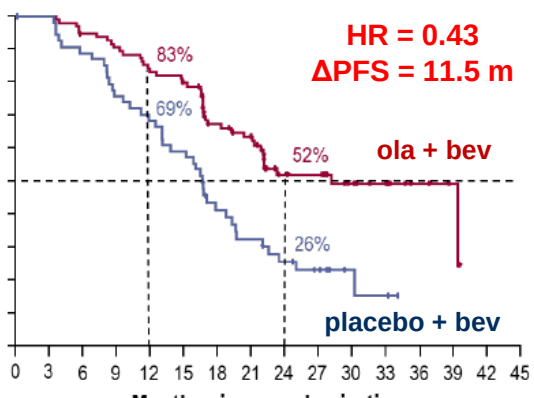


No. at risk

Olaparib	157	154	150	148	144	138	117	110	76	58	31	19	7	1	0
Placebo	80	78	72	66	59	52	41	36	22	13	7	4	1	1	0

	Olaparib + bevacizumab n=157	Placebo + bevacizumab n=80
Events, n (%)	41 (26)	49 (61)
Median PFS, months	37.2†	21.7
	HR 0.31; 95% CI 0.20–0.47	

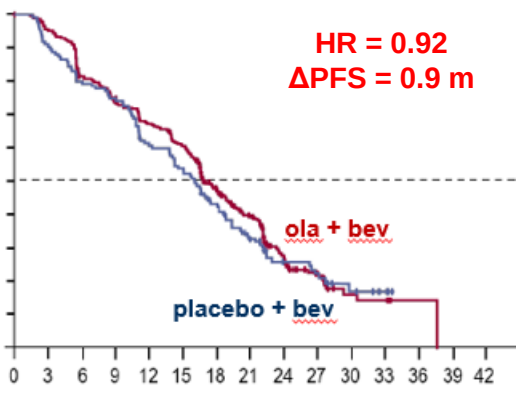
*BRCA*wt, HRD-positive



97	96	90	86	79	75	54	48	30	29	16	12	4	2	0
55	54	48	41	37	32	19	15	11	8	3	2	0		

Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
43 (44)	40 (73)
28.1*	**16.6**
HR 0.43 (95% CI 0.28–0.66)	

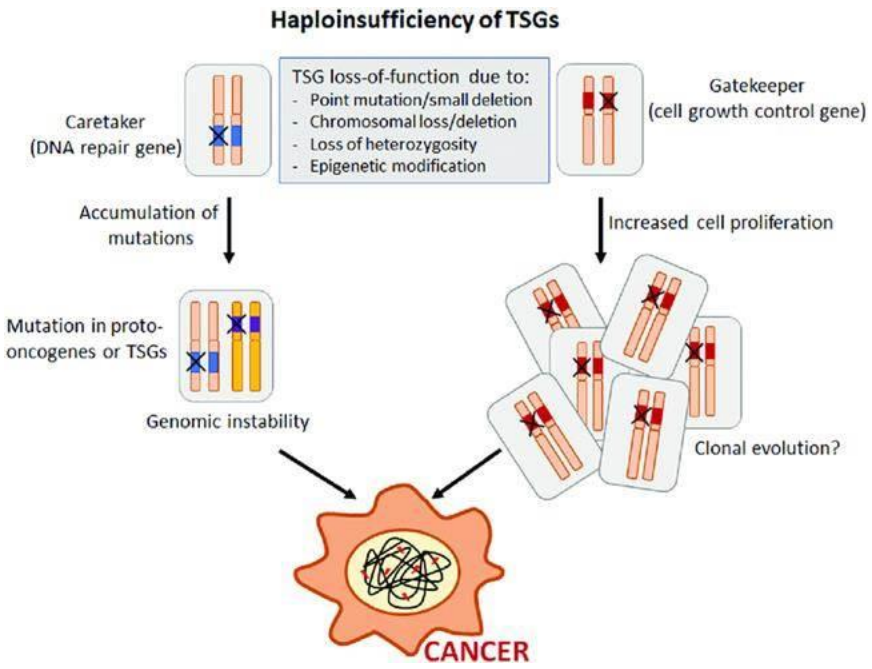
HRD negative / unknown



282	261	219	197	180	161	110	85	38	27	9	8	1	0	
137	124	109	102	81	72	55	39	22	17	7	4	0		

Olaparib + bevacizumab (N=282)	Placebo + bevacizumab (N=137)
193 (68)	102 (74)
16.9	**16.0**
HR 0.92 (95% CI 0.72–1.17)	

Ray-Coquard, I., et al., (2019). N Engl J Med 381(25): 2416-2428


Haploinsufficiency of TSGs
TSG loss-of-function due to:
- Point mutation/small deletion
- Chromosomal loss/deletion
- Loss of heterozygosity
- Epigenetic modification
Caretaker
(DNA repair gene)
Gatekeeper
(cell growth control gene)
Accumulation of
mutations
Increased cell proliferation
Mutation in proto-
oncogenes or TSGs
Genomic instability
Clonal evolution?
CANCER

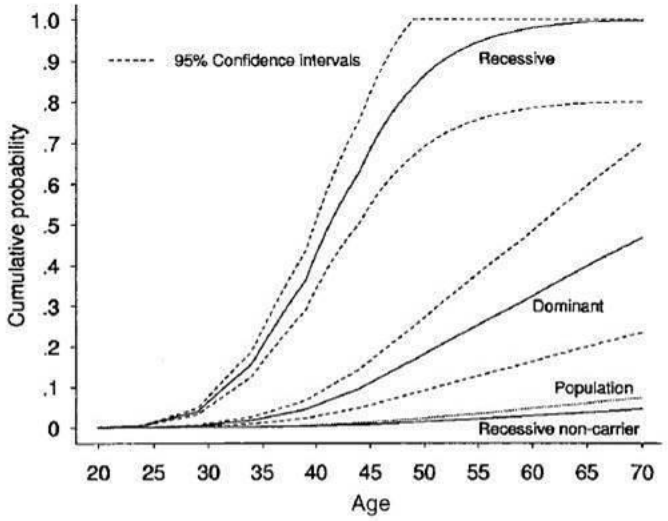


Figure 3 Age-specific cumulative probabilities of breast cancer for the population, for carriers of a dominantly inherited and a recessively inherited risk, and for noncarriers of the recessively inherited risk, with 95% CIs, on the basis of the 824 families with known BRCA1 and BRCA2 mutation carriers and their relatives excluded, under the multiplicative two-locus model.

Niraparib – PRIME Study

Efficacy and Safety of Niraparib as Maintenance Treatment in Patients with Newly Diagnosed Advanced Ovarian Cancer Using an Individualized Starting Dose (PRIME Study): A Randomized, Double-blind, Placebo-controlled, Phase 3 Trial

Ning Li*, Jianqing Zhu, Rutie Yin, Jing Wang, Lingya Pan, Beihua Kong, Hong Zheng, Jihong Liu, Xiaohua Wu, Li Wang, Yi Huang, Ke Wang, Dongling Zou, Hongqin Zhao, Chunyan Wang, Weiguo Lu, An Lin, Ge Lou, Guiling Li, Pengpeng Qu, Hongying Yang, Xiaoa Zhen, Wenzhao Hang, Jianmei Hou, Lingying Wu*

* National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

ANNUAL MEETING ON WOMENS' CANCER®
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Society of Gynecologic Oncology

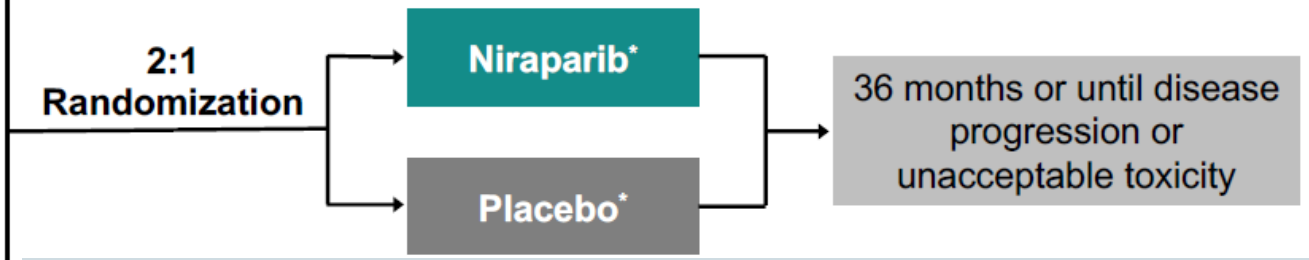
Study Design

- PRIME is a randomized, double-blind, placebo-controlled phase III trial (NCT03709316).

Schema

Eligible Patients
- Age ≥18 years
- FIGO stage III/IV ovarian cancer
- High-grade serous or endometroid tumor[a]
- Receipt of primary or interval cytoreductive surgery, irrespective of postoperative residual disease status
- CR/PR to 1L Pt-based chemotherapy

Stratified randomization
- Status of g*BRCA* mutations (g*BRCA*mut/non-g*BRCA*mut)
- Tumor HRD status[b] (positive/negative)
- Receipt of neoadjuvant chemotherapy (Y/N)
- Response to 1L Pt-based chemotherapy (CR/PR)



*Individualized starting dose (ISD) was adopted in **ALL** patients:
*starting dose of 200 mg administered orally, once daily, but 300 mg for patients with body weight ≥77 kg **AND** platelet count ≥150,000/μL*

(Individualized starting dosing was used in ~35% of patients in the PRIMA study[1])

Primary Endpoint
- **PFS by BICR in the ITT population**

Secondary Endpoints
- OS and TFST in the ITT population
- PFS and OS in the HRD subgroup[c]
- Safety

(The PRIMA study did not include stage III patients who had no residual disease after primary debulking surgery[1])

a There was no histological restriction for patients carrying g*BRCA* mutations.
b **Tumor HRD status testing was conducted with BGI assay (BGI Genomics, Shenzhen, China). The positive stratum consisted of patients who tested positive for tumor HRD with the BGI assay, and the other patients were grouped as the negative stratum.**
c The HRD subgroup consisted of patients with a g*BRCA* mutations and/or tumor with homologous recombination deficiency

BICR: blinded independent central review; CR, complete response; HRD, homologous recombination deficiency; ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; PR, partial response; Pt, platinum; TFST, time to first subsequent anti-cancer therapy.

1. Gonzalez-Martin A, et al. N Engl J Med 2019; 381(25): 2391-2402.

Demographics and Baseline Characteristics

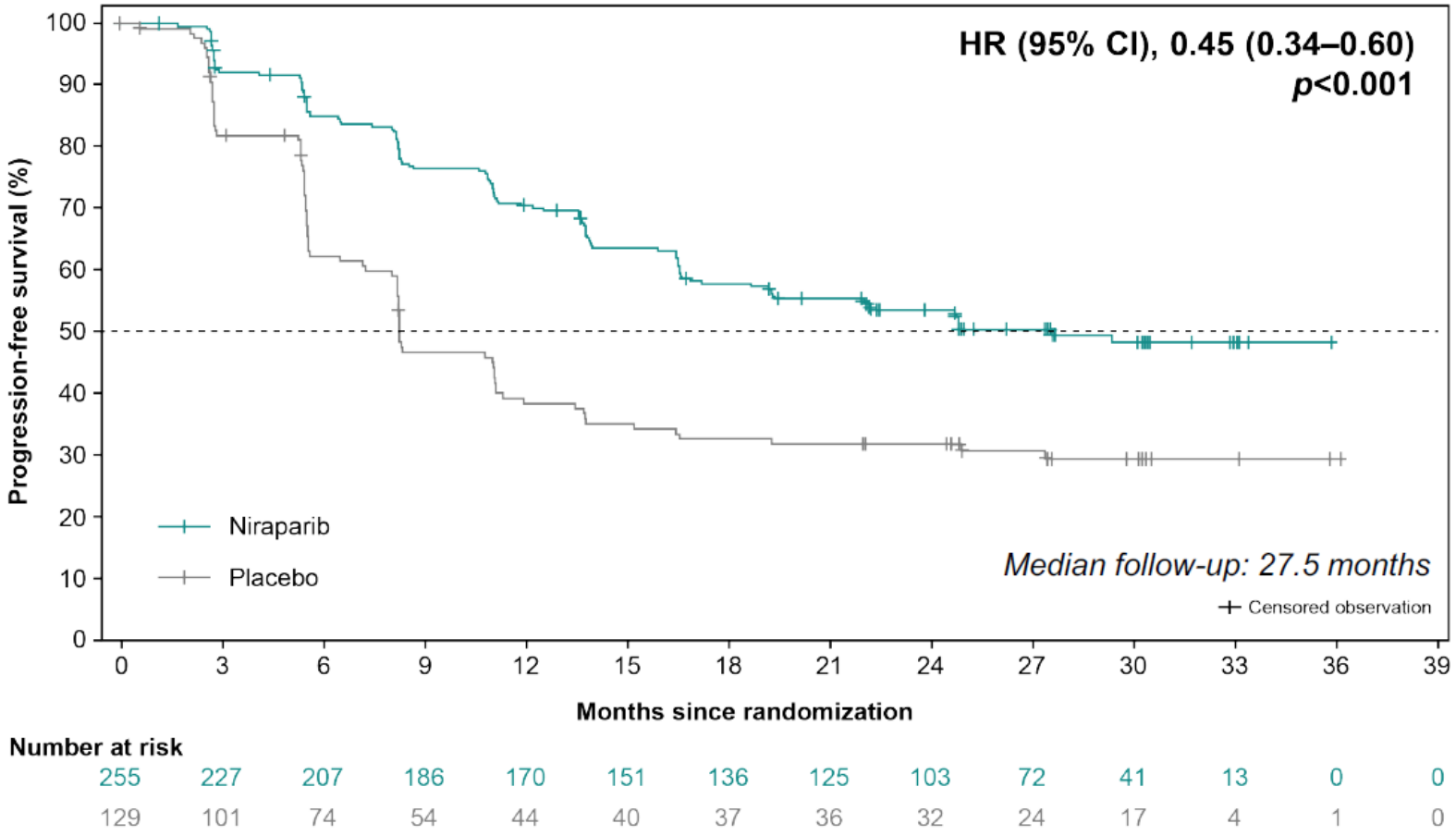
Characteristic	Niraparib (N=255)	Placebo (N=129)
Median age (range), years	53.0 (32–77)	54.0 (33–77)
Median weight (range), kg	59.0 (39.5–100.0)	57.0 (37.0–97.0)
ECOG performance status, n (%)		
0	98 (38.4)	52 (40.3)
1	157 (61.6)	77 (59.7)
FIGO stage, n (%)		
III	182 (71.4)	94 (72.9)
IV	73 (28.6)	35 (27.1)
Primary tumor location, n (%)		
Ovary	229 (89.8)	117 (90.7)
Fallopian tube	19 (7.5)	9 (7.0)
Peritoneum	7 (2.7)	3 (2.3)
Histologic subtype, n (%)		
Serous ovarian cancer	253 (99.2)	128 (99.2)
Endometrioid carcinoma	2 (0.8)	0
Other	0	1 (0.8)

Characteristic	Niraparib (N=255)	Placebo (N=129)
Neoadjuvant chemotherapy, n (%)		
Yes	121 (47.5)	59 (45.7)
No	134 (52.5)	70 (54.3)
Response to Pt-based CT, n (%)		
CR	212 (83.1)	103 (79.8)
PR	43 (16.9)	26 (20.2)
g*BRCA* mutation status, n (%)		
g*BRCA*mut	85 (33.3)	40 (31.0)
Non-g*BRCA*mut	170 (66.7)	89 (69.0)
Homologous recombination[a], n (%)		
Deficient	170 (66.7)	87 (67.4)
Proficient	85 (33.3)	42 (32.6)
Postoperative residual disease status, n (%)		
Optimal (R0/R1)	193 (75.7)	105 (81.4)
Suboptimal (R2) or missing	52 (24.3)	24 (18.6)

- The niraparib and placebo groups were well-balanced.

a. Homologous recombination deficiency was defined as the presence of a g*BRCA* mutation and/or tumor with homologous recombination deficiency; the other statuses were grouped as homologous recombination proficient.

PFS (by BICR) in the ITT Population – Primary Endpoint



16.5 months longer median PFS with niraparib versus placebo

	Niraparib (N=255)	Placebo (N=129)
PFS (54.4% data maturity)		
Events, n (%)	123 (48.2)	86 (66.7)
mPFS (95% CI), months	24.8 (19.2–NE)	8.3 (7.3–11.1)
Patients without PD or death (%)		
24 months	52.6	30.4

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mPFS, median progression-free survival; NE, not estimable; PD, progressive disease.

PFS Benefit in Pre-specified Subgroups

Subgroup	Events/patients (%)		Hazard ratio for PFS (95% CI)
	Niraparib	Placebo	
Overall	123/255 (48.2)	86/129 (66.7)	0.45 (0.34–0.60)
Age			
<65 years	108/229 (47.2)	73/114 (64.0)	0.47 (0.34–0.63)
≥65 years	15/26 (57.7)	13/15 (86.7)	0.24 (0.09–0.66)
Neoadjuvant chemotherapy			
Yes	62/121 (51.2)	46/59 (78.0)	0.32 (0.21–0.48)
No	61/134 (45.5)	40/70 (57.1)	0.63 (0.42–0.94)
Response to Pt-based chemotherapy			
Complete response	98/212 (46.2)	66/103 (64.1)	0.45 (0.32–0.61)
Partial response	25/43 (58.1)	20/26 (76.9)	0.45 (0.23–0.86)
***gBRCA* mutation status**			
*gBRCA*mut	35/85 (41.2)	25/40 (62.5)	0.40 (0.23–0.68)
Non-g*BRCA*mut	88/170 (51.8)	61/89 (68.5)	0.48 (0.34–0.67)
Homologous recombination			
Deficient	75/170 (44.1)	57/87 (65.5)	0.48 (0.34–0.68)
Proficient	48/85 (56.5)	29/42 (69.0)	0.41 (0.25–0.65)
Postoperative residual disease status			
Optimal	94/193 (48.7)	71/105 (67.6)	0.44 (0.32–0.61)
Suboptimal or missing	29/62 (46.8)	15/24 (62.5)	0.43 (0.21–0.87)

CI, confidence interval; FIGO, International Federation of Gynecology and Obstetric;
PFS, progression-free survival; Pt, platinum.

The analysis in PRIME study

Patients with stage III/IV ovarian cancer, high-grade serous or endometroid tumor, CR/PR to 1L platinum-based therapy (N = 384)

g*BRCA*mut

Niraparib, n = 85; mPFS: **NR**
Placebo, n = 40; mPFS: 10.8 months
Hazard ratio 0.40 (0.23 – 0.68)

non-g*BRCA*mut

Niraparib, n = 170; mPFS: 19.3 months
Placebo, n = 89; mPFS: 8.3 months
Hazard ratio 0.48 (0.34 – 0.67)

non-gBRCAmut/HRD

Niraparib, n = 85; mPFS: **24.8** months
Placebo, n = 47; mPFS: 11.1 months
Hazard ratio 0.58 (0.36 – 0.93)

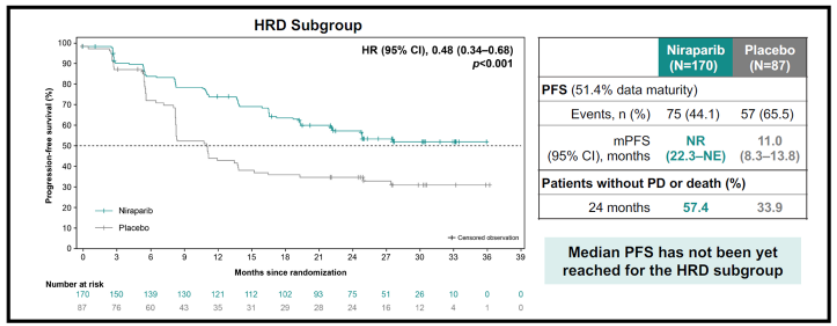
non-gBRCAmut/HRP

Niraparib, n = 85; mPFS: 14 months
Placebo, n = 42; mPFS: 5.5 months
Hazard ratio 0.41 (0.25 – 0.65)

s*BRCA*mut

***BRCA*wt/HRD**

Secondary Endpoints : PFS (HRD Subgroup)

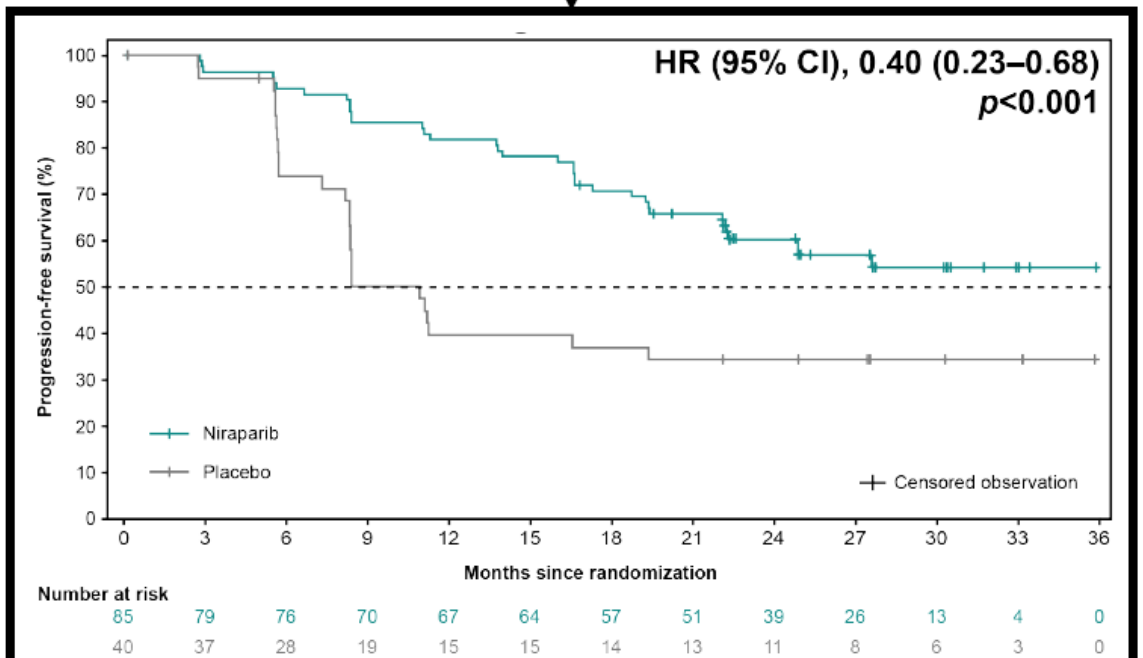


	Niraparib (N=170)	Placebo (N=87)
PFS (51.4% data maturity)		
Events, n (%)	75 (44.1)	57 (65.5)
mPFS (95% CI), months	NR (22.3–NE)	11.0 (8.3–13.8)
Patients without PD or death (%)		
24 months	57.4	33.9

Median PFS has not been yet reached for the HRD subgroup

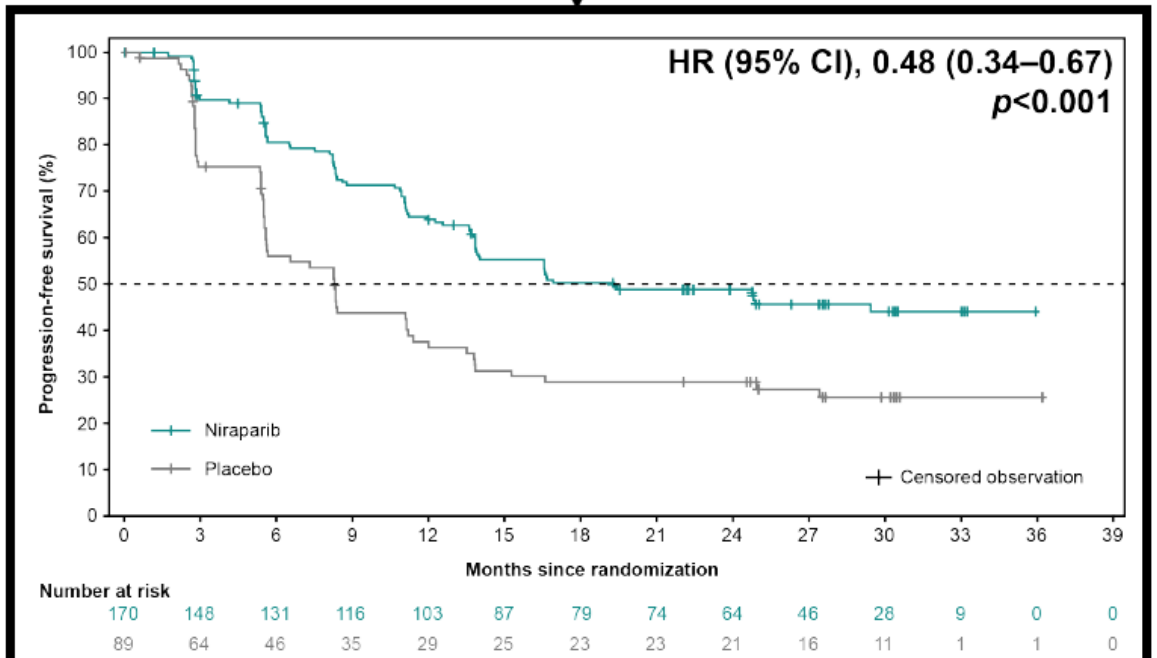
PFS Benefit by g*BRCA*mut Status – Prespecified Subgroup Analysis

g*BRCA*mut



	Niraparib (N=85)	Placebo (N=40)
mPFS (95% CI), months	NR (22.3–NE)	10.8 (8.3–19.3)

Non-g*BRCA*mut

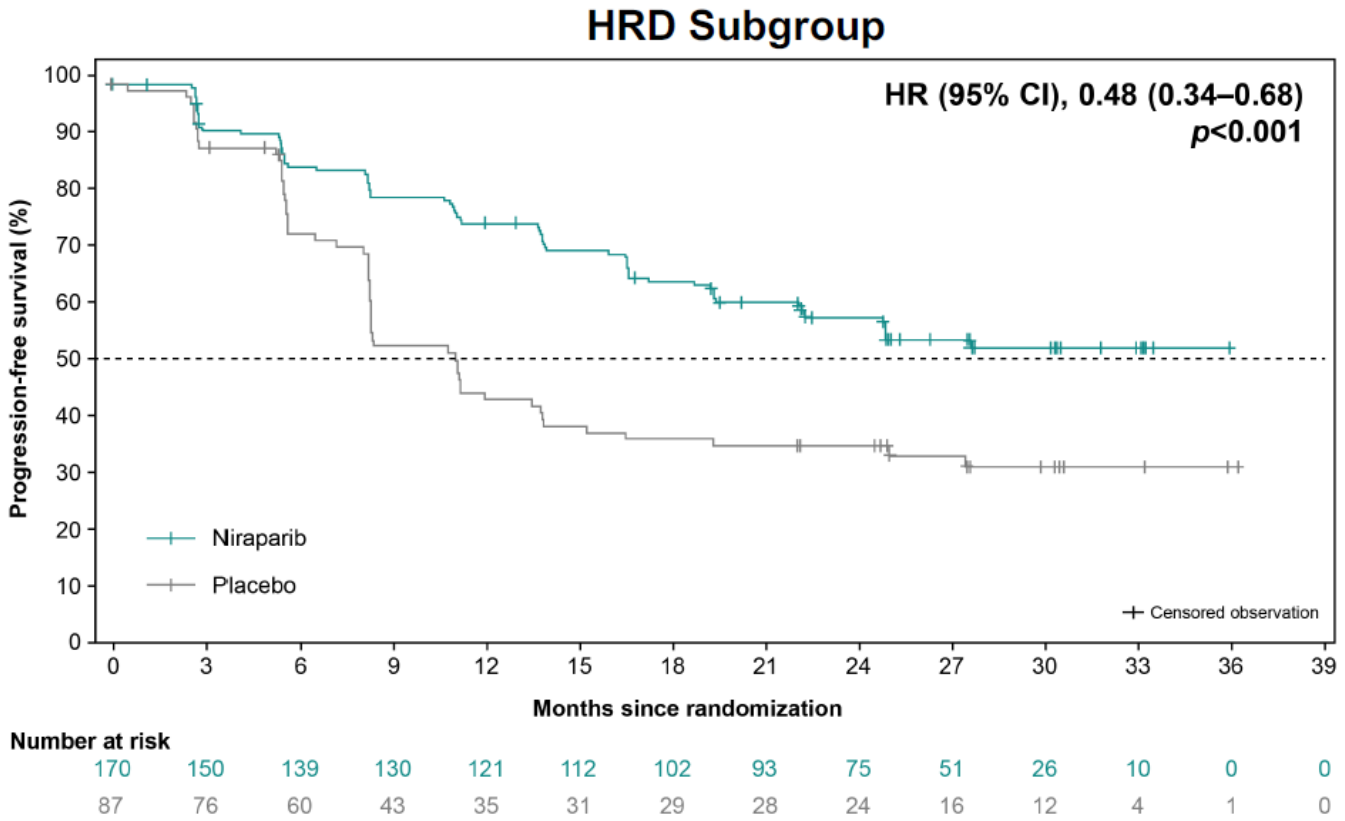


	Niraparib (N=170)	Placebo (N=89)
mPFS (95% CI), months	19.3 (13.8–NE)	8.3 (5.6–11.2)

- Median PFS has not been yet reached for the g*BRCA*mut population.
- The benefit of niraparib in the non-g*BRCA*mut population is confirmed.

CI, confidence interval; HR, hazard ratio; mPFS, median progression-free survival; NE, not estimable; NR, not reached.

Secondary Endpoints : PFS (HRD Subgroup)



	Niraparib (N=170)	Placebo (N=87)
PFS (51.4% data maturity)		
Events, n (%)	75 (44.1)	57 (65.5)
mPFS (95% CI), months	NR (22.3–NE)	11.0 (8.3–13.8)
Patients without PD or death (%)		
24 months	57.4	33.9

Median PFS has not been yet reached for the HRD subgroup

CI, confidence interval; HR, hazard ratio; HRD: homologous recombination deficiency; ; mPFS, median progression-free survival; NE, not estimable; NR, not reached; PD, progressive disease.

PRIME Safety Overview (vs. PRIMA Study)

- The median relative dose intensity[a] was 100.0% for both niraparib (range: 26.0%–147.0%) and placebo (range: 36.0%–147.0%) groups.

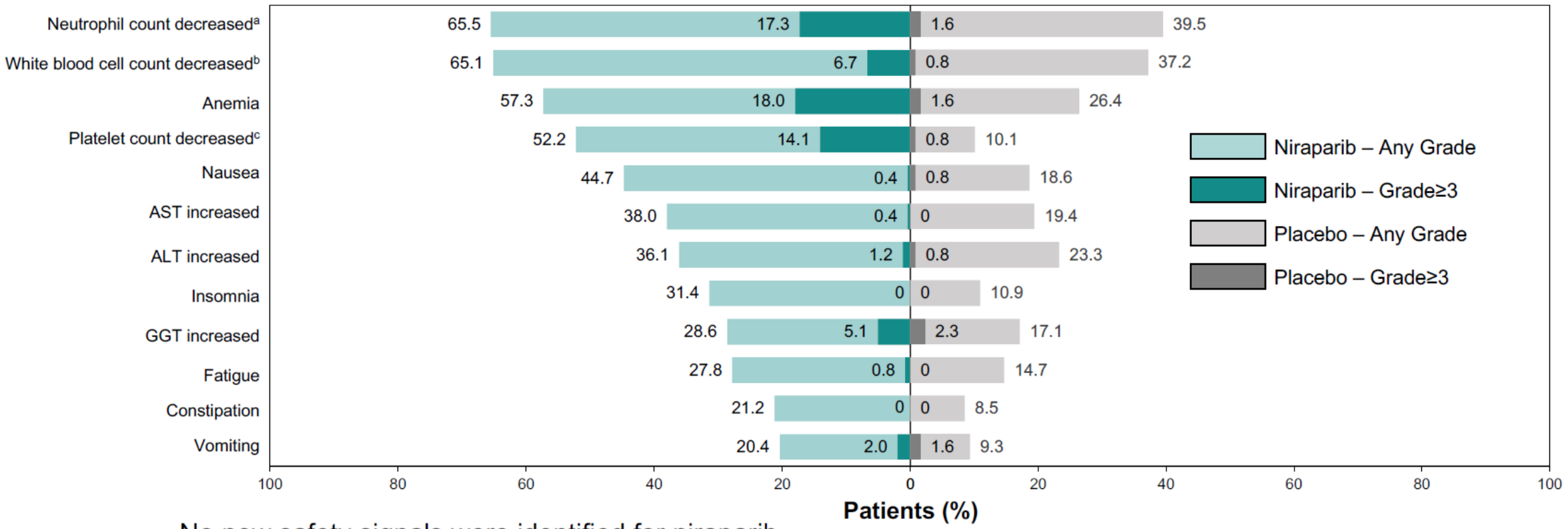
	PRIME		PRIMA[1]	
TEAEs, n (%)	**Niraparib (N=255)**	**Placebo (N=129)**	**Niraparib (N=484)**	**Placebo (N=244)**
Any TEAEs	253 (99.2)	121 (93.8)	478 (98.8)	224 (91.8)
Treatment-related	249 (97.6)	111 (86.0)	466 (96.3)	168 (68.9)
Grade≥3 TEAEs	139 (54.5)	23 (17.8)	341 (70.5)	46 (18.9)
Treatment-related	125 (49.0)	9 (7.0)	316 (65.3)	16 (6.6)
Serious TEAEs	48 (18.8)	11 (8.5)	156 (32.2)	32 (13.1)
Treatment-related	38 (14.9)	5 (3.9)	118 (24.4)	6 (2.5)
TEAEs leading to treatment interruption	160 (62.7)	25 (19.4)	385 (79.5)	44 (18.0)
TEAEs leading to dose reduction[b]	103 (40.4)	8 (6.2)	343 (70.9)	20 (8.2)
TEAEs leading to discontinuation	17 (6.7)	7 (5.4)	58 (12.0)	6 (2.5)
TEAEs leading to death	1 (0.4)	0	2 (0.4)	1 (0.4)

- TEAEs were manageable and consistent with the PARP inhibitor class.
- Dose reduction in all patients was numerically lower than in the previous niraparib trials[1,2] using fixed starting dosing.
- In the niraparib group, 6.7% of patients discontinued treatment, comparable to 5.4% in the placebo group.

a The relative dose intensity was defined as the percentage of administered doses to planned doses.
b Does reduction includes both direct dose reduction and dose reduction following treatment interruption.

1. Gonzalez-Martin A, et al. N Engl J Med 2019; 381(25): 2391-2402.
2. Mirza MR, et al. N Engl J Med 2016; 375(22): 2154-2164.

TEAEs Occurring in ≥ 20% of Either Group



- No new safety signals were identified for niraparib.
- The most common TEAEs were hematological and gastrointestinal events.
- One case each of acute myeloid leukemia and myelodysplastic syndrome was reported in the niraparib group and the acute myeloid leukemia case died of this secondary malignancy adverse event.

The term of **neutrophile count decreased here includes reports of neutrophile count decreased, neutropenia, and febrile neutropenia**.
The term of **white blood cell count decreased here includes reports of white blood cell count decreased and leukopenia**.
The term of **platelet count decreased here includes reports of platelet count decreased and thrombocytopenia**.
ALT, alanine transaminase; AST, aspartate transaminase; GGT, γ- glutamyltransferase; TEAE, treatment-emergent adverse event.

PRIME Conclusions

PRIME is a phase 3 randomized placebo-controlled trial which prospectively assessed the efficacy and safety of Niraparib as maintenance therapy in Chinese patients with newly diagnosed advanced OC

PRIME is the second Phase 3 trial to demonstrate benefit of Niraparib monotherapy as maintenance therapy Following response to first line platinum-based chemotherapy

PRIME differs from PRIMA because it enrolled patients irrespective of post-operative residual disease status and Prospectively investigated ISD in all participants

PRIME demonstrated a statistically significant and clinically meaningful improvement in PFS, with a 16.5 month Median improvement for patients receiving Niraparib (24.8 vs 8.3 months, HR 0.45, p <0.001)

- **ITT population**: mPFS, 24.8 vs 8.3 months; HR, 0.45; *p*<0.001
- **HRD subgroup:** mPFS, NR vs 11.0 months; HR, 0.48; *p*<0.001
- **g*BRCA*mut patients**: mPFS, NR vs 10.8 months; HR, 0.40; *p*<0.001
- **Non-g*BRCA*mut patients**: mPFS, 19.3 vs 8.3 months; HR, 0.48; *p*<0.001

Prospective Niraparib ISD in PRIME demonstrated improved tolerability compared to prior study using FSD; Only 6.7% of patients discontinued due to AEs, allowing patients to remain on long term maintenance therapy

Different HRD assay were used in PRIME and PRIMA

	BGI HRD Test	Myriad myChoice CDx HRD
Sequencing Method	NGS	NGS
Sample Type	FFPE/Tissue	FFPE
Includes BRCA	Yes	Yes
Genomic Instability Score	LOH, TAI, LST	LOH, TAI, LST
Score Cut Off	30	42
Validated in clinical trial	YES (PRIME)	YES

Once-daily oral
Zejula®
niraparib
capsules 100 mg

截永樂® Zejula®

niraparib capsules 100 mg

A PARP Inhibitor to
Bring Ovarian Cancer Patients to the Future

STAY BETTER, STAY LONGER
REGARDLESS OF GENOMIC MUTATION STATUS

2022.06.11 花蓮慈濟醫院婦產科魏佑吉醫師

Outline

01
Overview of OC

02
Unmet needs in OC

03
HRD and *BRCA* mutation in OC

04
NCCN guidelines for treatment of OC

05
Clinical evidence of Zejula®: NOVA trial

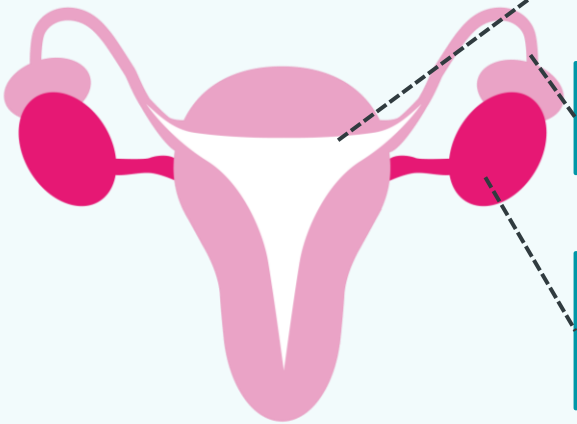
BRCA, breast cancer susceptibility gene; HRD, homologous recombination deficiency; NCCN, National Comprehensive Cancer Network; OC, ovarian cancer.

Overview of ovarian cancer

95% of ovarian cancer are epithelial tumors

Potential cellular origins of ovarian carcinomas[1]

- ***Most ovarian malignancies (95%) are epithelial***; the remainder arise from other ovarian cell types (germ cell tumors, sex cord-stromal tumors)[2]
- The sources of epithelial carcinoma includes the ovary, fallopian tube, or peritoneum[2]



Endometrium → Clear cell carcinoma (CCC)

Endometrium → Endometrioid carcinoma (EC)

Fallopian tube epithelium → High-grade serous carcinoma (HGSC)

Ovarian surface epithelium → High-grade serous carcinoma (HGSC)

Fallopian tube epithelium → Low-grade serous carcinoma (LGSC)

Ovarian surface epithelium → Low-grade serous carcinoma (LGSC)

Unknown → Mucinous carcinoma (MC)

1. Committee on the State of the Science in Ovarian Cancer Research, Board on Health Care Services, Institute of Medicine, & National Academies of Sciences, Engineering, and Medicine. (2016). *Ovarian Cancers: Evolving Paradigms in Research and Care.* National Academies Press (US); 2. Chen LM, et al (UpToDate). Overview of epithelial carcinoma of the ovary, fallopian tube, and peritoneum. Available at: https://www.uptodate.com/contents/overview-of-epithelial-carcinoma-of-the-ovary-fallopian-tube-and-peritoneum/ (Accessed in Sep 2020).

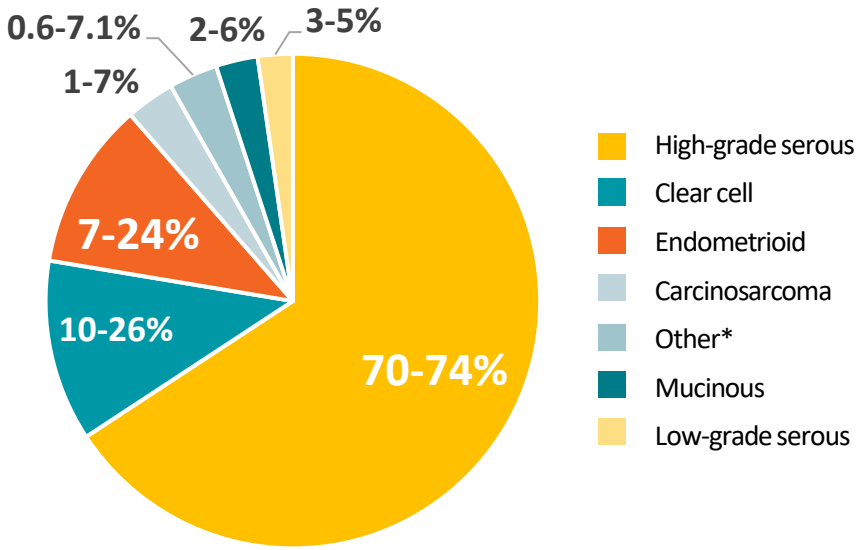
Most patients were with serous ovarian cancer in Taiwan

- ***For epithelial carcinomas, serous is the most common subtype (75%)***[1]

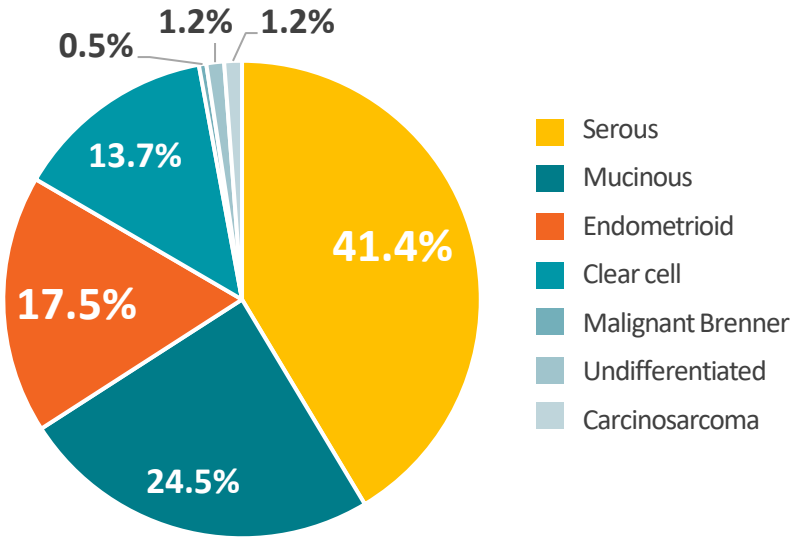
The WHO histological typing of epithelial ovarian tumors[2]

- Serous
- Endometrioid
- Clear cell
- Mucinous
- Brenner (transitional cell)
- Mixed epithelial tumors
- Undifferentiated
- Unclassified

Percentage of cases by major OC subtype[3]



Distribution of OC histologic type in Taiwan[4]

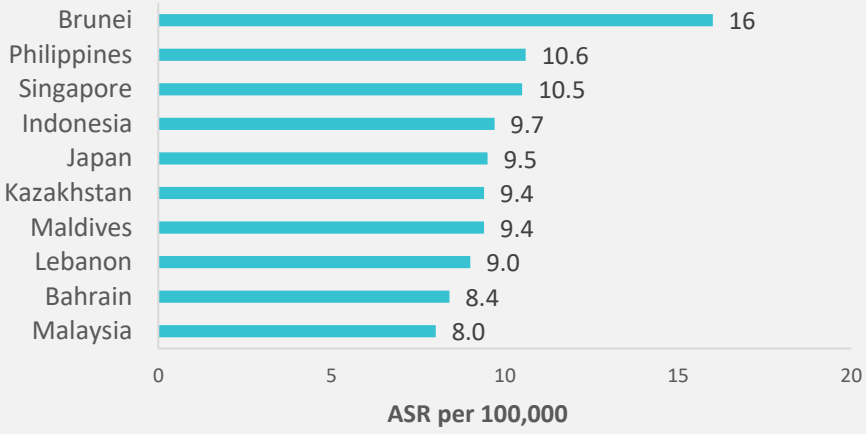


OC, ovarian cancer; WHO, World Health Organization.

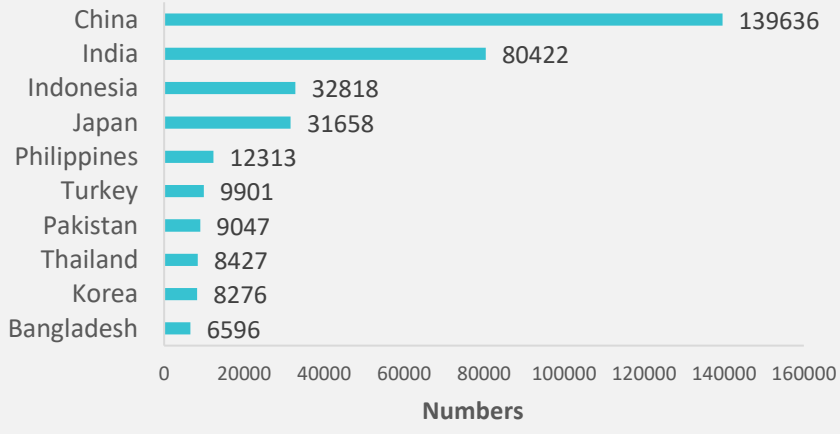
1. Chen LM, et al (UpToDate). Overview of epithelial carcinoma of the ovary, fallopian tube, and peritoneum. Available at: https://www.uptodate.com/contents/overview-of-epithelial-carcinoma-of-the-ovary-fallopian-tube-and-peritoneum/ (Accessed in Sep 2020); 2. Ledermann JA, et al. Ann Oncol. 2013;24 (Suppl 6):vi24-vi32; 3. Committee on the State of the Science in Ovarian Cancer Research, Board on Health Care Services, Institute of Medicine, & National Academies of Sciences, Engineering, and Medicine. (2016). *Ovarian Cancers: Evolving Paradigms in Research and Care.* National Academies Press (US); 4. Chiang YC, et al. J Gynecol Oncol. 2013;24:342-351.

The estimated incidence and prevalence varied from countries to countries in Asia

Estimated incidence rates in 2018 among Asian countries*[1]

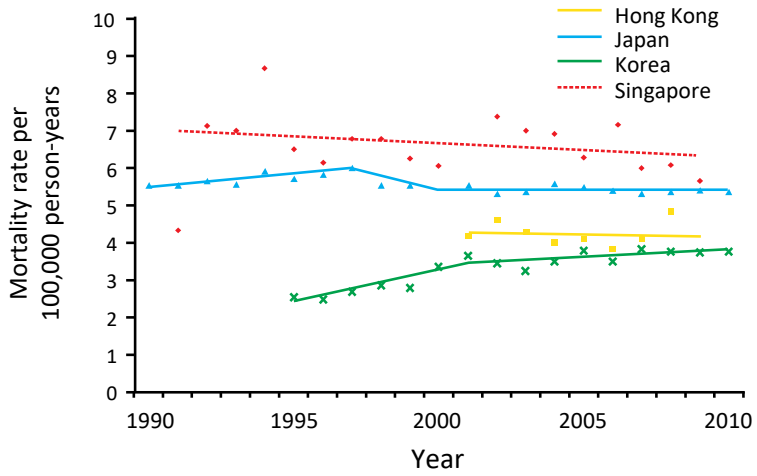


Estimated number of prevalent cases (5-year) among Asian countries*[1]



*Figures show only the top ten countries.

Trends in ovarian cancer mortality rates[2]



Overall, ***no significant changes in OC mortality were observed, except in Korea and Japan***. In Korea, OC mortality rates significantly increased across the study period (1995–2010), while in Japan, OC mortality rates decline following an increase during 1990–1997

ASR, age-standardized incidence rate; OC, ovarian cancer.

1. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available at: https://gco.iarc.fr/today (Accessed in May 2020);
2. Lee JY, et al. J Gynecol Oncol. 2014;25:174-182.

OC is the 7th leading cause of cancer death in Taiwan

In 2017,

New cases: 1,521

Deaths: 644

7th leading cause of cancer death in female in Taiwan

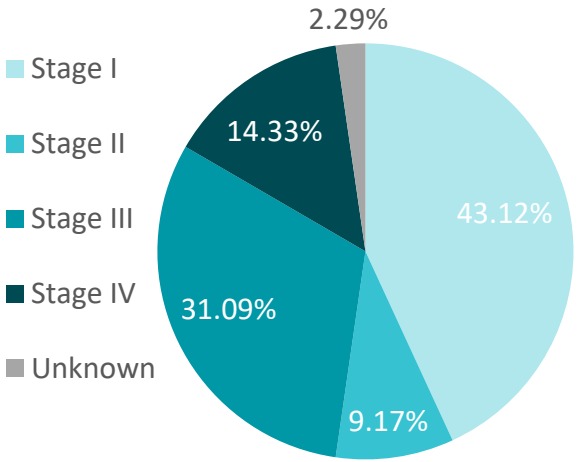
Incidence
New cases in 2017[1]

Crude	Age-standardized
12.83 per 100,000	**8.54** per 100,000

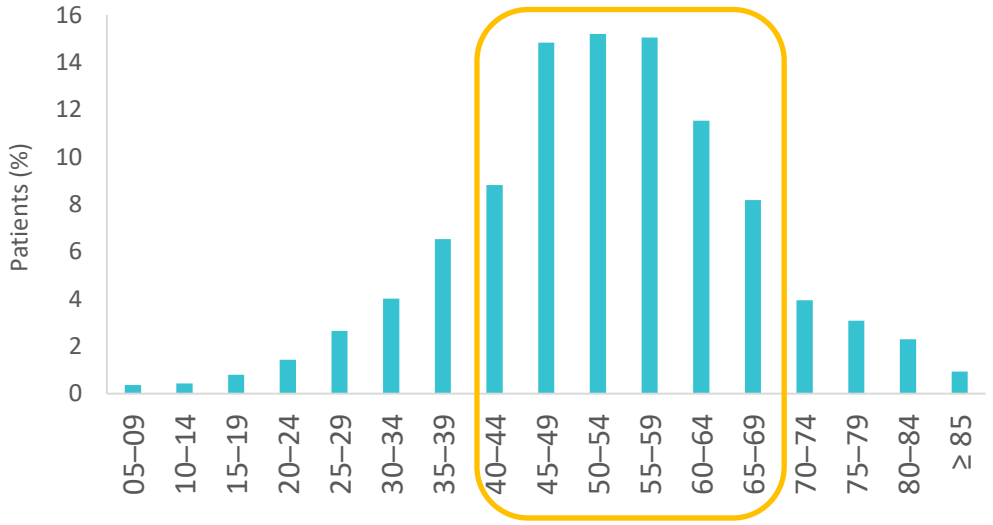
Mortality
Deaths in 2017[1]

Crude	Age-standardized
5.43 per 100,000	**3.09** per 100,000

OC patients in Taiwan by stage



OC patients in Taiwan by age



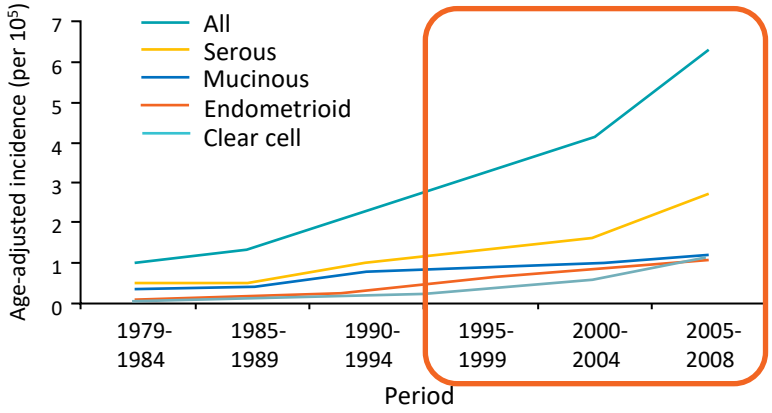
OC, ovarian cancer.

衛生福利部國民健康署. 中華民國 106 年癌症登記報告. 2019.

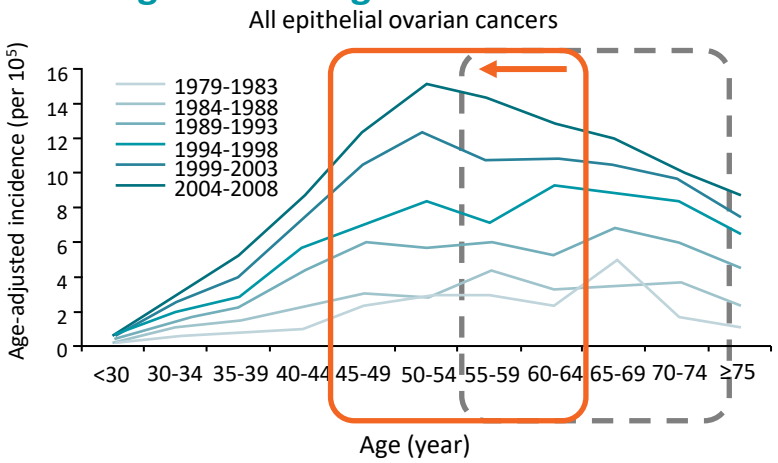
The incidence of OC increased over time and the patients were younger than before

- 9,491 patients with OC between 1979 and 2008 from National Cancer Registration System of Taiwan

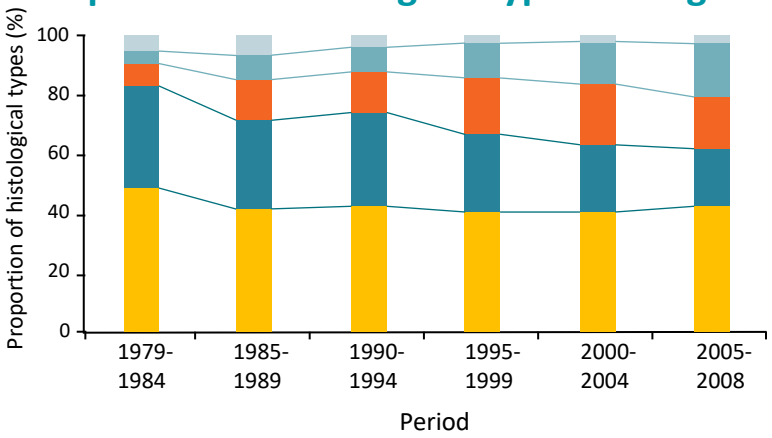
Incidence of OC increased



Age of OC diagnosis decreased



Proportion of histological types changed



- ***Decreased in mucinous carcinoma***
- ***Increased in clear cell carcinoma***

OC, ovarian cancer.

Chiang YC, et al. J Gynecol Oncol. 2013;24:342-351.

Ovarian cancer is asymptomatic in early stages and with nonspecific features in late stages

~60% of women with ovarian cancers have ***metastatic disease at the time of diagnosis*** because early-stage disease is usually asymptomatic.

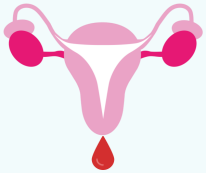
Symptoms

Late-stage ovarian cancers often have symptoms that are usually ***nonspecific and not recognized as symptoms of cancer.***

- Back pain
- Pelvic pain

- Abdominal pain
- Bloating
- Constipation

- Difficulty eating
- Early satiety



- Abnormal uterine bleeding
- Virilization
- Precocious puberty

- Urinary symptoms
- Fatigue

- Advanced disease may present with symptoms of regional spread or metastasis, such as ***bowel or ureteral obstruction, or shortness of breath***
- Ovarian cancer may also present with ***paraneoplastic syndromes***

Doubeni CA, et al. Am Fam Physician. 2016;93:937-944.

Diagnosis requires results from multiple examinations includes laboratory and imaging

Clinical presentation[1]

1. **Detection of pelvic mass on exam**
2. **Symptoms: bloating, pelvic or abdominal pain, early satiety, urinary symptoms**
3. **Concern raised on screening assays (e.g., CA-125)**
4. **Incidental findings on previous surgery or tissue biopsy**

Physical examinations[2,3]

General physical

Pelvic or abdominal pain, bloating, GI symptoms), infrequently, VTE

Lungs

Shortness of breath due to a malignant pleural effusion

Abdomen

Malignancy-related ascites (causes abdominal distension) or an abdominal mass

Pelvic

Perform pelvic exam to detect adnexal mass

Obtain family history[1,2]

Laboratory tests[1,2]

CBC, LFT, **CA-125**, other serum biomarkers (e.g., inhibin, AFP, beta-HCG)

Imaging[1,2,4]

Ultrasound, abdominal and/or **pelvic CT, Chest CT**/X-ray

Surgical or laparoscopic biopsy[4]

Histological assessment of ovarian tissue via primary surgery, image-guided biopsy, or laparoscopic biopsy

Cytological assessment of aspirated fluid if tissue diagnosis not feasible

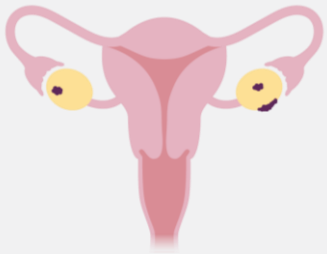
AFP, alpha-fetoprotein; CA-125, cancer antigen 125; CBC, complete blood count; CT, computed tomography; LFT, liver function test; GI, gastrointestinal; HCG, human chorionic gonadotropin; VTE, venous thromboembolism.

1. Committee on the State of the Science in Ovarian Cancer Research, Board on Health Care Services, Institute of Medicine, & National Academies of Sciences, Engineering, and Medicine. (2016). *Ovarian Cancers: Evolving Paradigms in Research and Care.* National Academies Press (US); 2. Doubeni CA, et al. Am Fam Physician. 2016;93:937-944; 3. Chen LM, et al (UpToDate). Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Clinical features and diagnosis. Available at: https://www.uptodate.com/contents/epithelial-carcinoma-of-the-ovary-fallopian-tube-and-peritoneum-clinical-features-and-diagnosis/ (Accessed in Sep 2020); 4. Ledermann JA, et al. Ann Oncol. 2013;24(suppl 6):v24-32.

Ovarian cancer staging system

Stage **1**

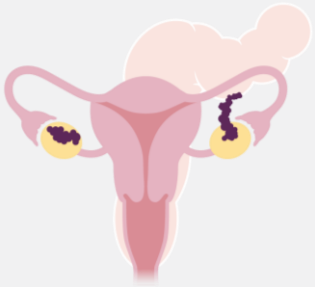
Cancer is in only one or both ovaries and **has not spread** to any other organs or tissues



1A	**1** ovary/fallopian tube
1B	**Both** ovaries/fallopian tubes
1C	**≥ 1** ovaries/fallopian tubes with: • Surgical spill/capsule ruptured • Malignant cells in the ascites/ peritoneal washings

Stage **2**

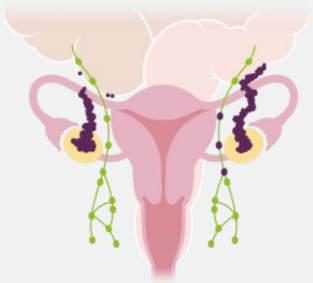
Cancer has spread to other organs or tissues **within the pelvis**



2A	**Extension** ± implants on uterus ± fallopian tubes ± ovaries
2B	**Extension** to other pelvic intraperitoneal tissues

Stage **3**

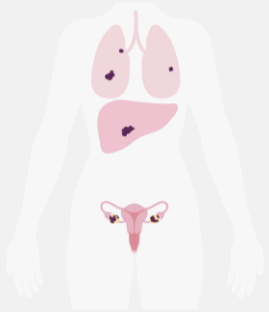
Cancer has **spread outside the pelvis** to abdominal areas



3A	**Lymph nodes**/extrapelvic peritoneal involvement
3B	**Peritoneal metastasis** beyond pelvic **≤ 2 cm** ± metastatsis to lymph nodes
3C	**Peritoneal metastasis** beyond pelvic **> 2 cm** ± metastatsis to lymph nodes

Stage **4**

Cancer has **spread to other organs** or distant lymph nodes

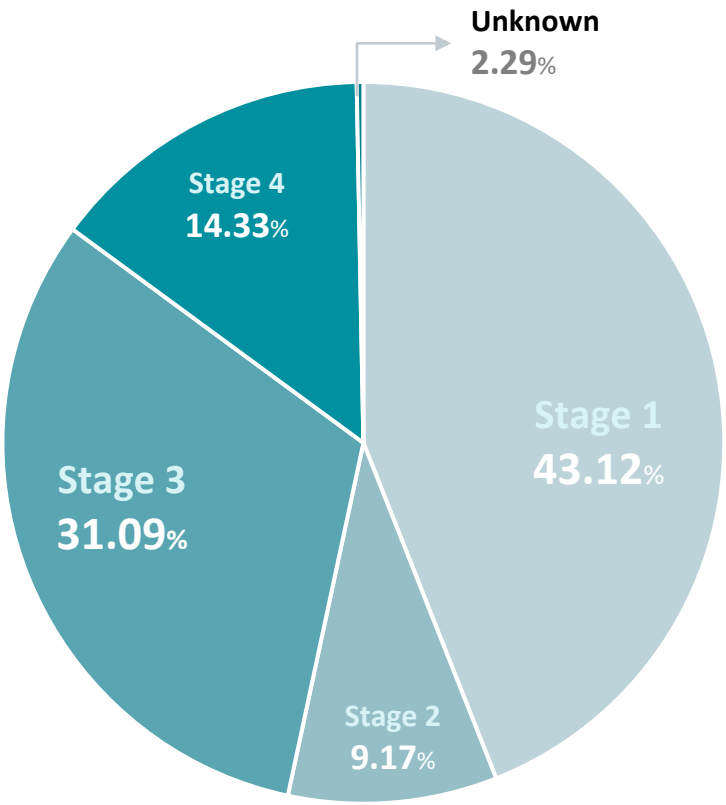


4A	**Pleural effusion** + cytology (+)
4B	**Parenchymal metastases** & metastases to **extra-abdominal organs**

1. National Comprehensive Cancer Network Guidelines for Patients/Ovarian Cancer, 2019. Available at: https://www.nccn.org/patients/guidelines/cancers.aspx (Accessed in Jun 2020);
2. Prat J, et al. Int J Gynaecol Obstet. 2014;124:1-5.

Most of patients were diagnose with stage I or III OC in Taiwan

Most of OC cases were diagnosed at FIGO stage 1 and 3[1]



FIGO stage 1 of OC has the highest 5-survival rates[2]

	FIGO 2014 stage definitions	Invasive epithelial
I	Tumor limited to one or both ovaries	92%
II	Tumor involves one or both ovaries with pelvic extension	73–78%
III	Tumor involves one or both ovaries with metastasis outside the pelvis and/or regional lymph node metastasis	39–59%
IV	Distant metastases other than peritoneal metastases	17–28%

In compared to serous carcinoma, other histological type of OC has lower risk of death*[3]

Histological type	N	HR	95% CI	*p*-value
Serous	3364	1	Reference	-
Mucinous	1872	0.65	0.59-0.72	<0.001
Endometrioid	1518	0.72	0.65-0.79	<0.001
Clear cell	1224	0.80	0.72-0.89	<0.001
Undifferentiated	81	1.98	1.52-2.58	<0.001

*Other than the undifferentiated carcinoma.

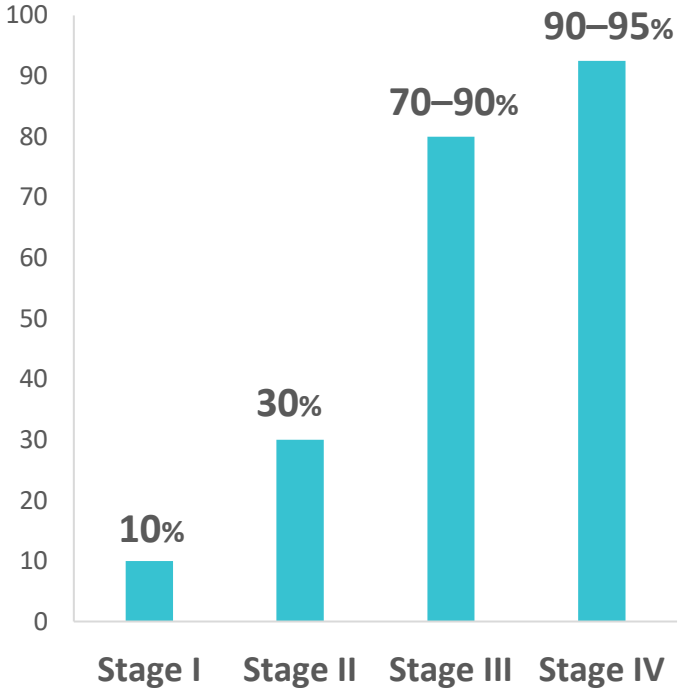
CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; OC, ovarian cancer.

1.衛生福利部國民健康署. 中華民國 106 年癌症登記報告. 2019); 2. Doubeni CA, et al. Am Fam Physician. 2016;93:937-944; 3. Chiang YC, et al. J Gynecol Oncol. 2013;24:342-351.

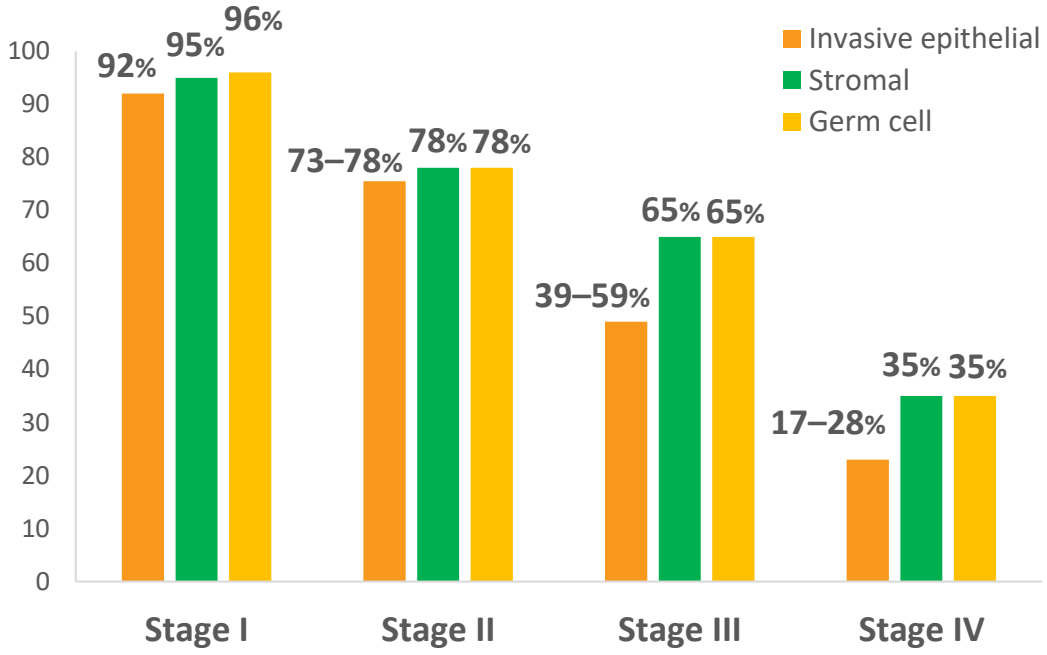
Unmet needs in ovarian cancer

Advanced stages have higher recurrence rates and lower 5-year survival rates

Recurrence rates of OC by stage[1]



5-year survival of OC by tumor stage and type[2]



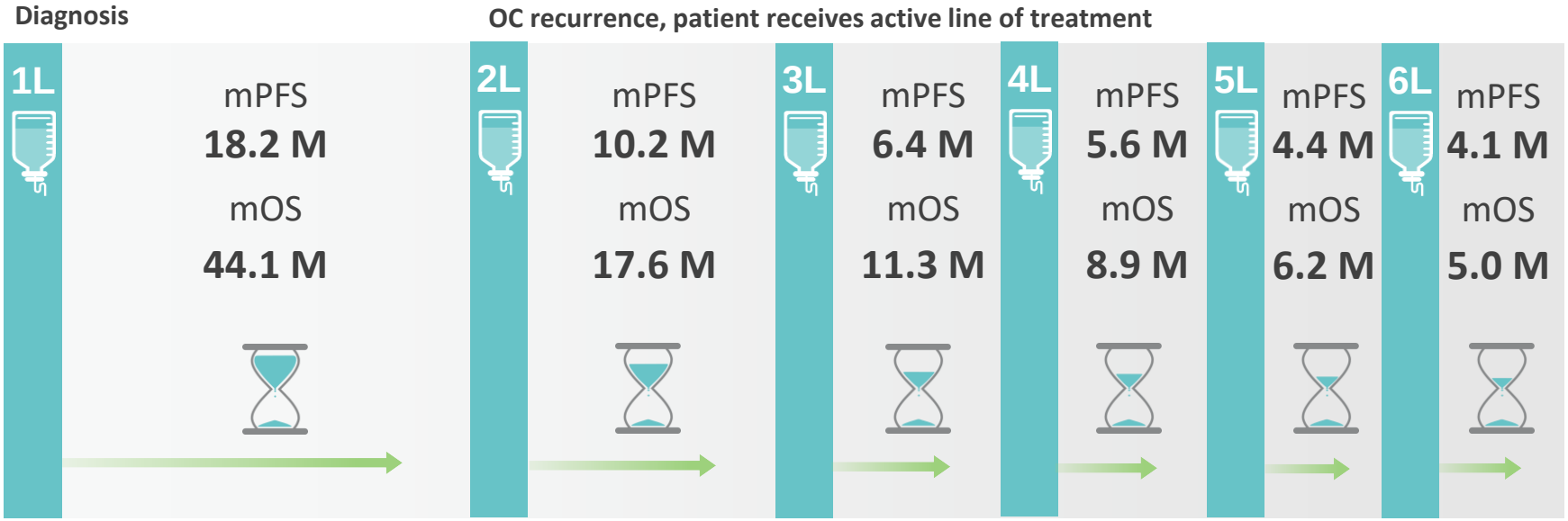
OC, ovarian cancer.

1. Ovarian cancer research alliance. Available at: https://ocrahope.org/patients/about-ovarian-cancer/recurrence/ (Accessed in Jun 2020);
2. Doubeni CA, et al. Am Fam Physician. 2016;93:937-944.

The interval of recurrence will shorten after each lines of treatments

From platinum-sensitive to platinum-resistant

- Most ovarian cancers will recur, leading to shorter treatment intervals[1]



- About **80% of advanced ovarian cancers will recur** during or after first-line treatment[1]
- Until recent years, there were essentially no treatment options other than repeated courses of chemotherapy in patients with 2 or more prior lines of chemotherapy[2]

M, months; ; mOS, median overall survival; mPFS, median progression-free survival.

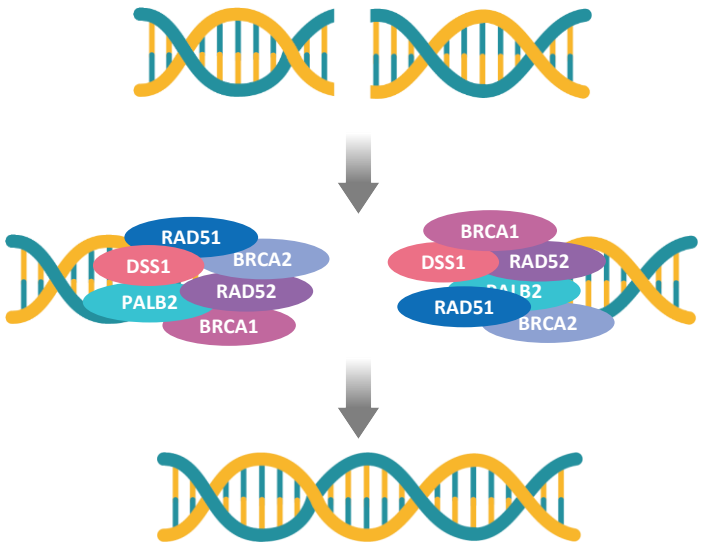
1. Hanker LC, et al. Ann Oncol. 2012;23:2605-2612; 2. Herzog TJ, Monk BJ. Gynecol Oncol Res Pract. 2017;4:13.

HRD and *BRCA* mutation in ovarian cancer

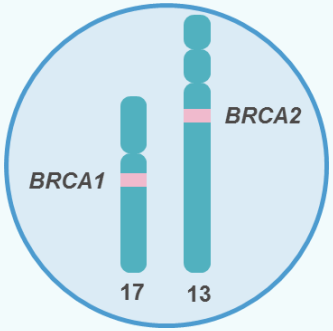
BRCA, breast cancer susceptibility gene; HRD, homologous recombination deficiency.

BRCA1/2 attribute in the DNA repair process

HRR mechanism[1]



1. DNA damage constantly occurs within cells; this needs to be repaired to maintain genomic integrity[2]
2. HR (homologous recombination) is an important pathway that allows repair of DSB[2]
3. HR relies on many proteins including **BRCA1 and BRCA2**[2]



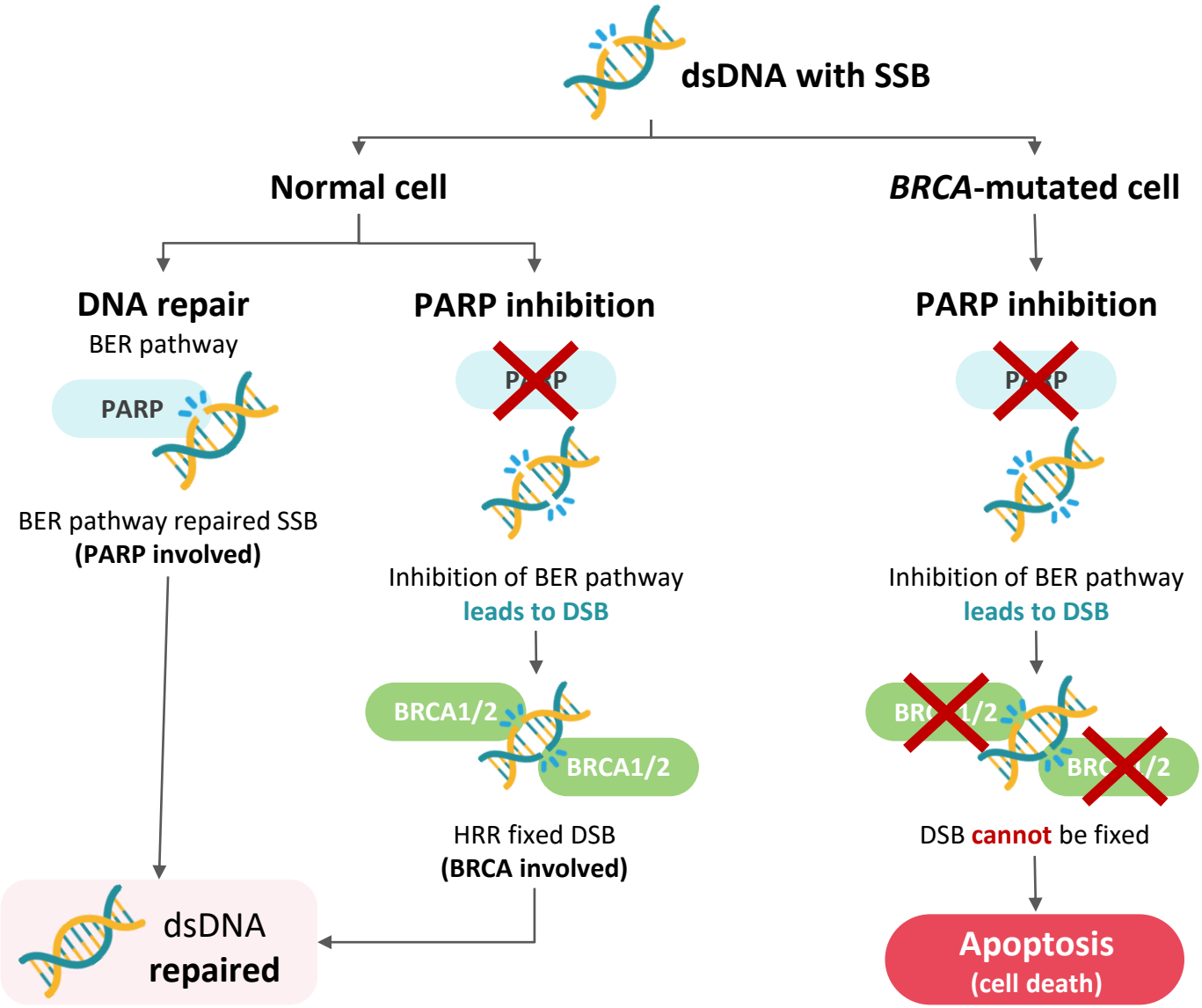
*BRCA*1 and *BRCA*2 gene

- *BRCA*1 and *BRCA*2 are key proteins in homologous repair of DSB[3]
- *BRCA*1 is involved in regulating cell cycle progression and interacts with multiple transcription factors, including ER-α, p53, STAT1 and c-Myc[4]

BRCA, breast cancer susceptibility gene; BRCA, breast cancer susceptibility protein; DNA, deoxyribonucleic acid; DSB, double-strand break; ER, estrogen receptor; HRR, homologous recombination repair; PALB2, Partner and localizer of BRCA2.

1. LaFargue CJ, Tewari KS. Recent Pat Biotechnol. 2016;9:86-101; 2. Frey MK and Pothuri B. Gynecol Oncol Res Pract 2017;4:4;
3. Powell SN, Kachnic LA. Oncogene. 2003;22:5784-5791; 4. Mullan PB, et al. *Oncogene* 2006;25:5854-5863.

Blocking the BER pathway in *BRCA*-mutated patients will lead to cell apoptosis



BER, base excision repair; *BRCA,* breast cancer susceptibility gene; BRCA, breast cancer susceptibility protein; DSB, double-strand break; dsDNA, double-strand deoxyribonucleic acid; HRR, homologous recombination repair; PARP, poly(ADP-ribose) polymerase; SSB, single-strand break.

1. Kedar PS, et al. Mol Cancer Res. 2012;10:360-368; 2. McLornan DP, et al. N Engl J Med. 2014; 371:1725-1735.

Examples of PARP inhibition in DNA repair

Normal cell

DNA repair
BER pathway
(PARP involved)

dsDNA **repaired**

PARP inhibition
HRR pathway
(BRCA involved)

dsDNA **repaired**

***BRCA*-mutated cell**

PARP inhibition
✕ BER pathway
✕ HRR pathway

dsDNA **cannot be repaired**

A building with 4 pillar, solid & stable

ONE pillar has broken, it stands but unstable

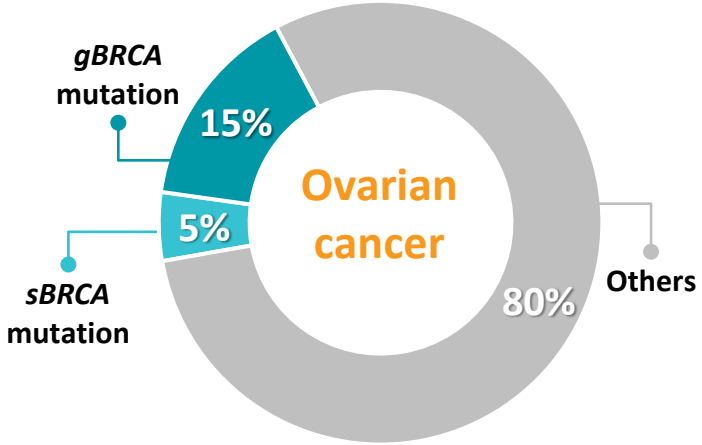
TWO pillars have broken, the temple collapsed

BER, base excision repair; *BRCA,* breast cancer susceptibility gene; dsDNA, double-strand deoxyribonucleic acid; HRR, homologous recombination repair; PARP, poly(ADP-ribose) polymerase.

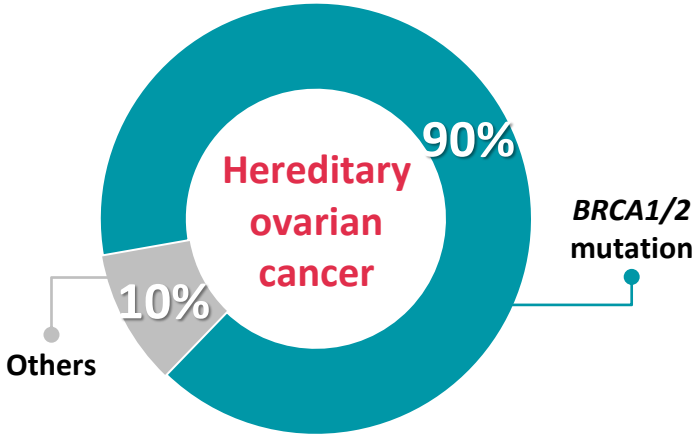
1. Kedar PS, et al. Mol Cancer Res. 2012;10:360-368; 2. McLornan DP, et al. N Engl J Med. 2014; 371:1725-1735.

BRCA mutation occurs in about 1/4 ovarian cancer cases in Taiwan

- Either germline or somatic mutations in *BRCA* account for **20%** of all the ovarian cancers[1]

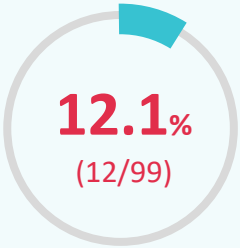


- *BRCA*1/2 mutations account for **90%** of all hereditary ovarian cancer cases[1]



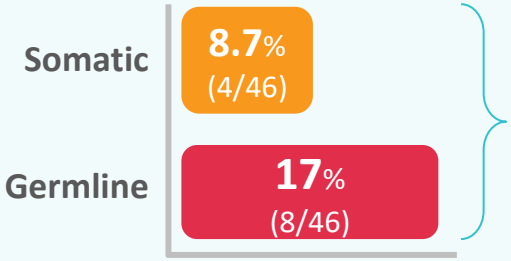
99 Taiwanese patients with ovarian cancer (46 serous; 24 endometrioid; 29 clear cell)[2]

Pathogenic variants



BRCA1: n=7; *BRCA2*: n=6

***BRCA*mut among serous OC**



All pathogenic *BRCA*1/2 mutations were identified in serous carcinoma samples

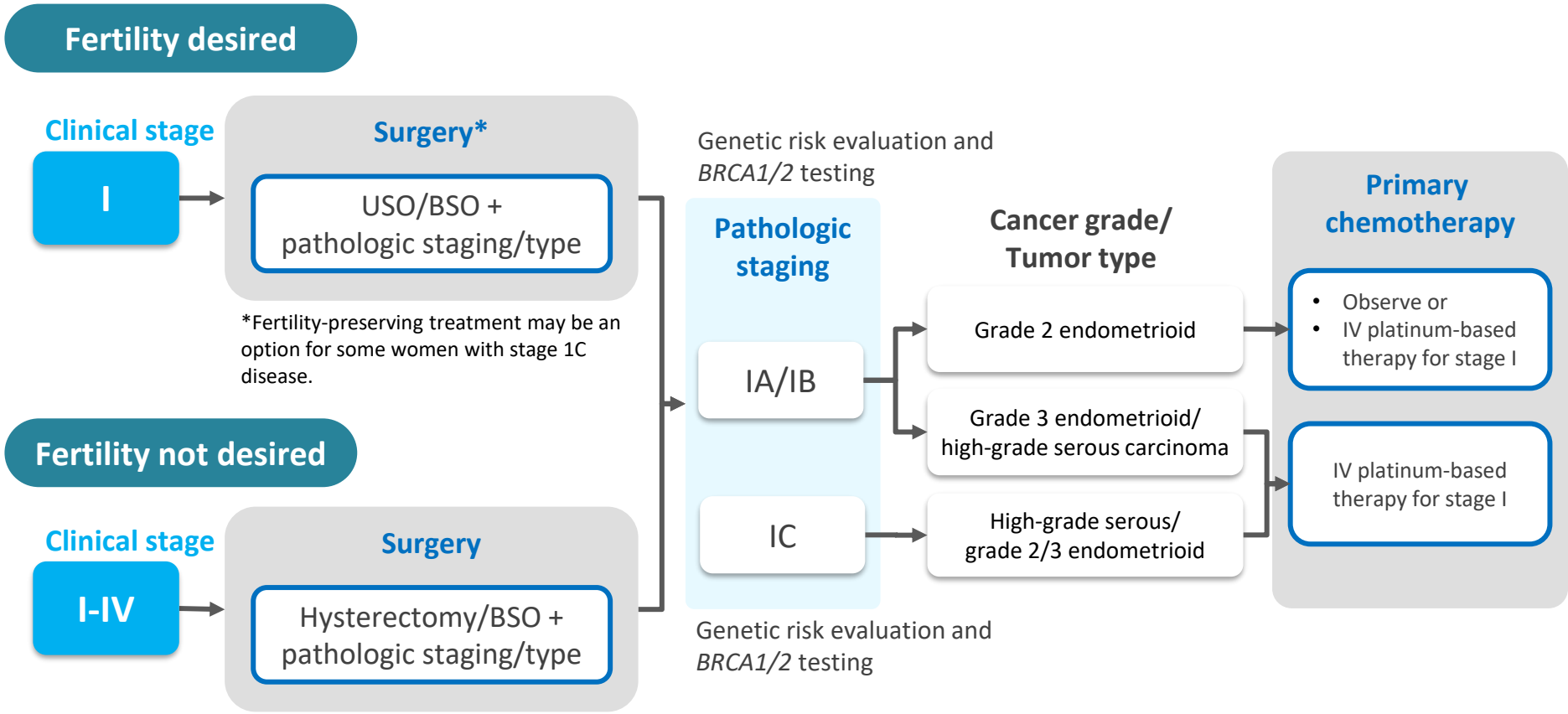
g, germline; *BRCA*, breast cancer susceptibility gene; OC, ovarian cancer; s, somatic.

1. Pan Z, Xie X. Oncotarget 2017;8:97657-97670; 2. Chao A, et al. Oncotarget. 2016;7:85529-85541.

NCCN guideline for treatment of ovarian cancer

C-APROM/TW/NIR/0029/2020OCT

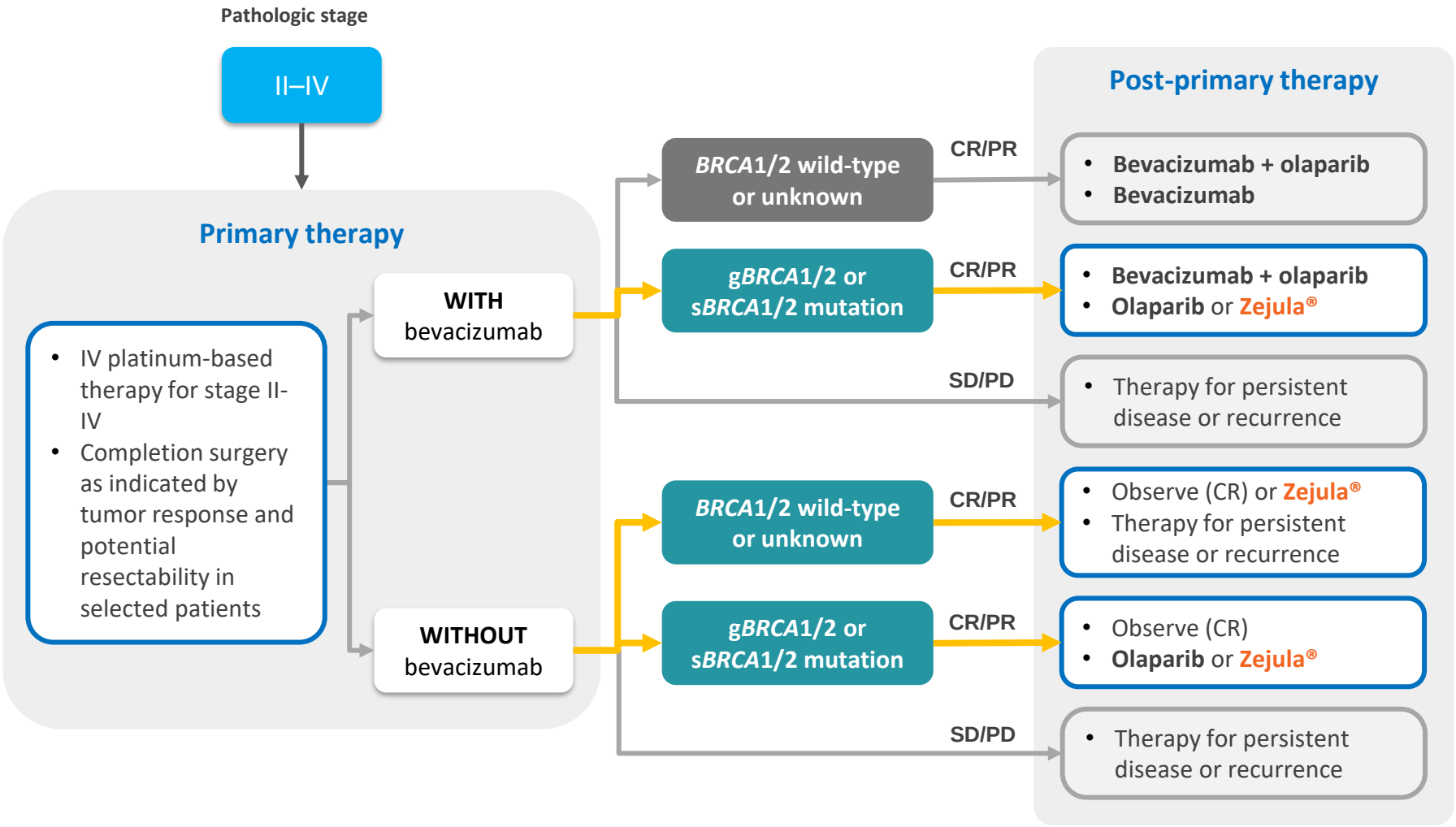
Patients with stage I ovarian cancer might be able to preserve their fertility



BRCA, breast cancer susceptibility gene; BSO, bilateral salpingo-oophorectomy; IV, intravenous; USO, unilateral salpingo-oophorectomy.

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology/Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 1.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf (Accessed in Aug 2020).

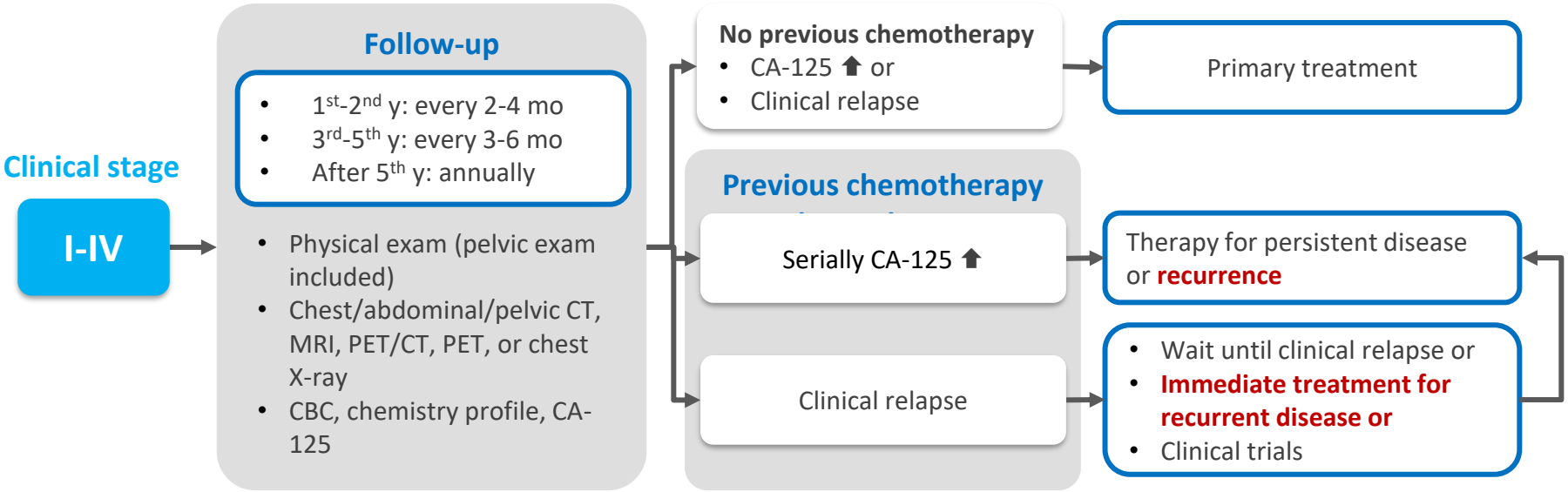
NCCN recommended Zejula® as post-primary therapy in patients with stage II-IV ovarian cancer



BRCA, breast cancer susceptibility gene; CR, complete clinical remission; *gBRCA*, germline breast cancer susceptibility gene; NCCN, National Comprehensive Cancer Network; PD, progressive disease; PR, partial remission; s*BRCA*, somatic breast cancer susceptibility gene; SD, stable disease.

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology/Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 1.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf (Accessed in Aug 2020).

Monitoring/follow-up after primary treatment with imaging and laboratory tests



CA-125, cancer antigen 125; CBC, complete blood count; CT, computerized tomography; MRI, magnetic resonance imaging; mo, months; PET, positron emission tomography; y, years.

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology/Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 1.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf (Accessed in Aug 2020).

Zejula® is one of the options in maintenance therapy for persistent disease or recurrence

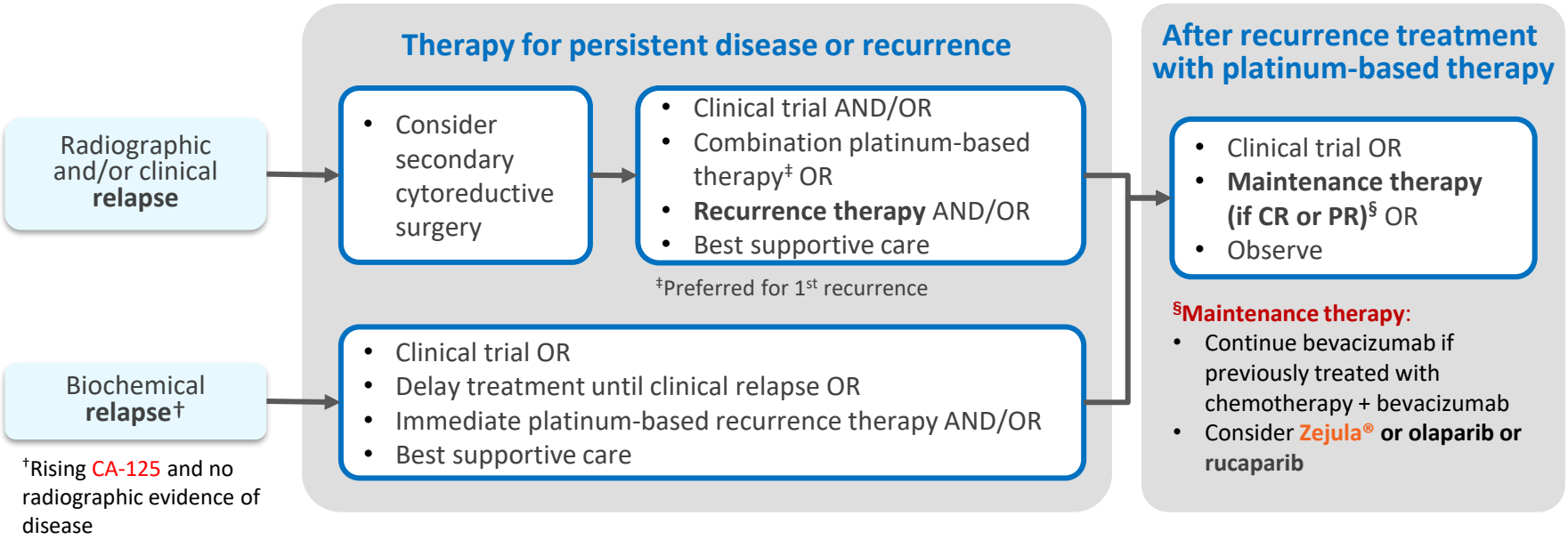
- **Progression** or **stable or persistent disease*** or **complete remission and relapse < 6 months after completing chemotherapy**

*If not on maintenance therapy

Therapy for persistent disease or recurrence

Clinical trial AND/OR best supportive care AND/OR **recurrence therapy**

- **Complete remission and relapse ≥ 6 months after completing prior chemotherapy**



CA-125, cancer antigen 125; CR, complete response; NCCN, National Comprehensive Cancer Network; PR, partial response.

National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology/Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 1.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf (Accessed in Aug 2020).

Regimens of platinum-based therapy

Platinum-based therapy for stage I

Medicine	Dosing	Cycles
Paclitaxel and carboplatin (preferred)	Q3W	• 3–6 cycles for endometrioid • 6 cycles for high-grade serous
Carboplatin and liposomal doxorubicin	Q4W	
Docetaxel and carboplatin	Q3W	

Platinum-based therapy for stage II–IV

Medicine	Dosing	Cycles
Paclitaxel and cisplatin (IP/IV)	Q3W	6 cycles
Paclitaxel and carboplatin	Q3W	6 cycles
	QW	18 weeks (a lower dose given more often)
Docetaxel and carboplatin	Q3W	6 cycles
Carboplatin and liposomal doxorubicin	Q4W	6 cycles
Paclitaxel, carboplatin, and bevacizumab	Q3W	5-6 cycles
	Q3W	• 6 cycles (paclitaxel and carboplatin) • Add bevacizumab for cycles 2–6 (up to 22 cycles)

IP, intraperitoneal; IV, intravenous; QW, every week; Q3W, every 3 weeks; Q4W, every 4 weeks.

NCCN Clinical Practice Guidelines in Oncology/Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer Version 3.2019.
Available at: https://www.nccn.org/professionals/physician_gls/default.aspx#site (Accessed in Jun 2020).

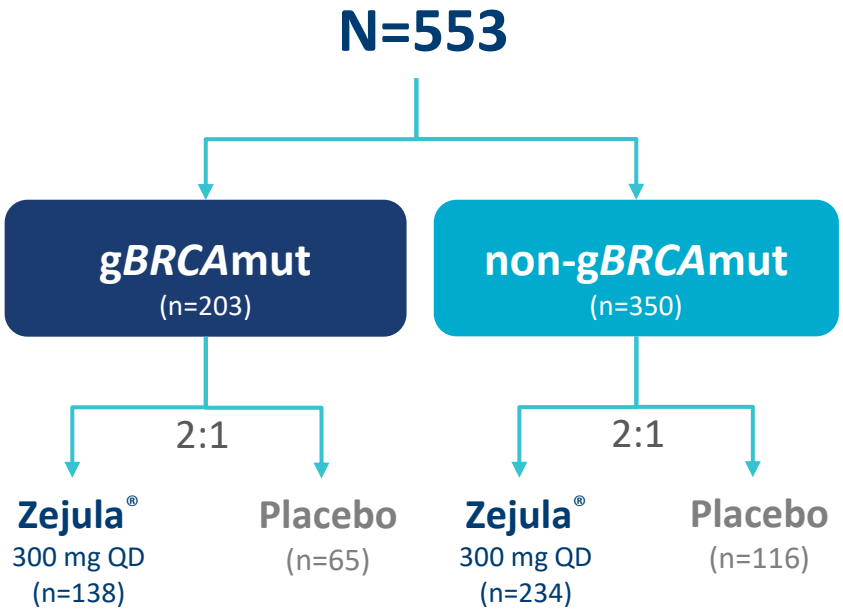
Clinical evidence of Zejula®: NOVA trial

NOVA study targeted patients with platinum-sensitive recurrent ovarian cancer

A randomized, double-blind trial to evaluate the efficacy of Zejula® as maintenance treatment in patients with platinum-sensitive, recurrent ovarian cancer

Study population

Patients with **platinum-sensitive, recurrent** ovarian cancer



Endpoints

Primary endpoint

- Progression-free survival

Secondary endpoints

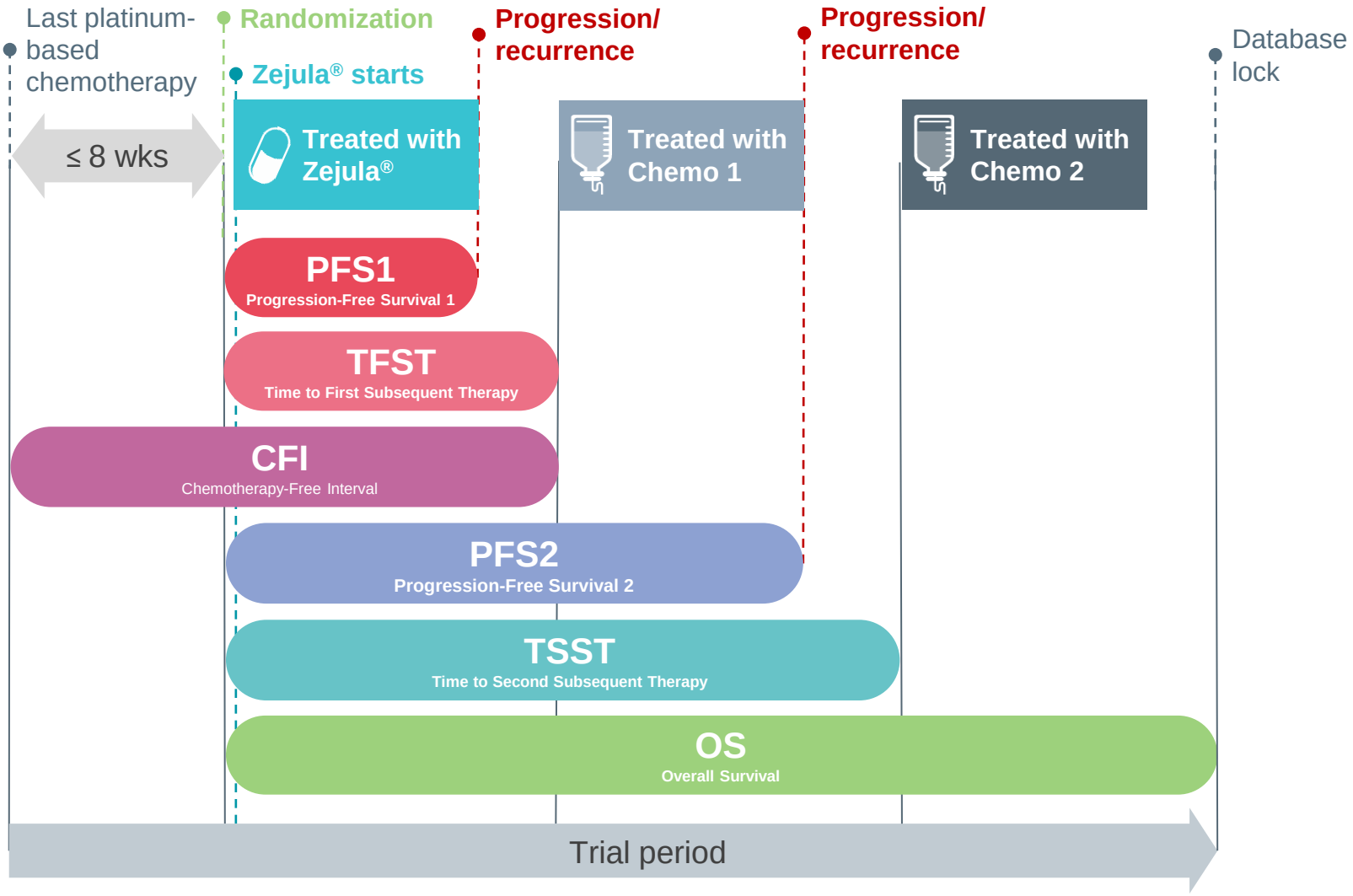
- Patient-reported outcomes
- Chemotherapy-free interval
- Time to first subsequent therapy
- Progression-free survival 2*
- Time to second subsequent therapy
- Overall survival

*The time from randomization until assessment of progression during receipt of the next anticancer therapy after the study treatment or until death

g*BRCA*, germline breast cancer susceptibility gene; mut, mutation; QD, once daily.

Mirza MR, et al. N Engl J Med. 2016;375:2154-2164.

NOVA designed multiple secondary endpoints to evaluate the patient-sensitivity to the treatment

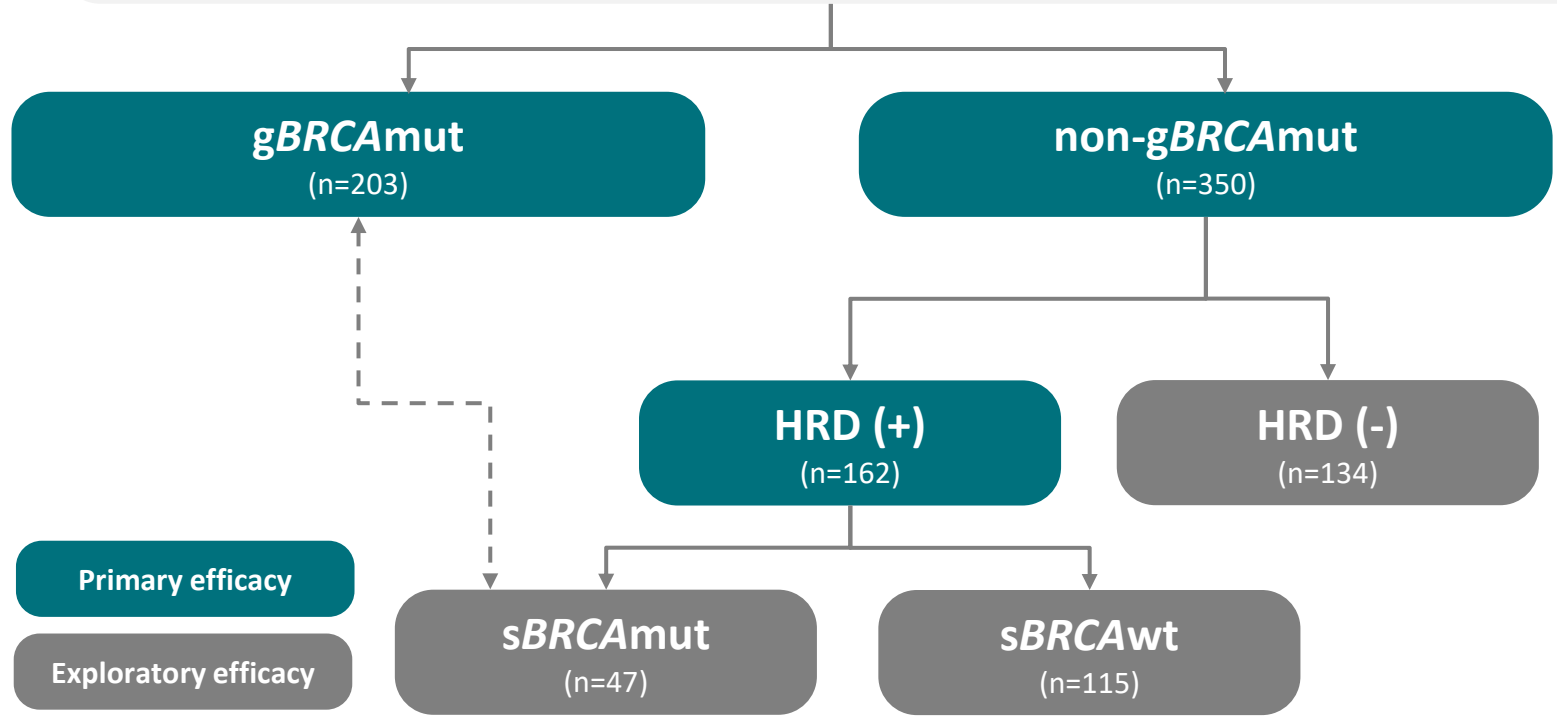


Chemo, chemotherapy; wks, weeks.

Mirza MR, et al. N Engl J Med. 2016;375:2154-2164. (suppl.)

The cohorts categorized according to patients' gene mutation status

Patients with **recurrent** ovarian cancer, fallopian tube cancer, or primary peritoneal cancer following **complete or partial response to platinum-based therapy (N = 553)**



BRCA, breast cancer susceptibility gene; g, germline; HRD, homologues recombination deficiency; mut, mutation; s, somatic; wt, wild-type.

Mirza MR, et al. N Engl J Med. 2016;375:2154-2164.

Patients with known *BRCA*1/2 mutation and priorly treated with platinum-based therapy enroll in NOVA study

- Patients must have no prior use of PARP inhibitor to participate in NOVA

Key inclusion criteria	Key exclusion criteria
Females aged ≥18 years	Known hypersensitivity to the components of Zejula®
Histologically diagnosed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer	**Invasive cancer other than ovarian cancer within 2 years** (except basal or squamous cell carcinoma of the skin that has been definitively treated)
Known *BRCA*1/2 mutation(s) or predominantly high-grade serous histology	**Symptomatic uncontrolled brain metastasis**
Completed ≥2 previous courses of platinum-containing therapy	Pregnant or breastfeeding
Achieved a CR or PR lasting ≥6 months following the penultimate treatment	Immunocompromised patients
Has responded to the last platinum regimen, and is **randomized in the study within 8 weeks of completion of the last platinum regimen***	Known active hepatic disease
ECOG performance status 0–1	**Prior treatment with a known PARP inhibitor**
Adequate hematologic, renal, and liver function	

*For the final platinum-containing therapy, patients were required to have received a minimum of 4 cycles of treatment and, following treatment, CA-125 levels within the normal range or a CA-125 decrease of more than 90%, and to have no measurable lesions >2 cm.

BRCA, breast cancer susceptibility gene; CA-125, cancer antigen 125; CR, complete response, ECOG, Eastern Cooperative Oncology Group; PARP, poly(adenosine diphosphate [ADP]–ribose) polymerase; PR, partial response.

Mirza MR, et al. N Engl J Med. 2016;375:2154-2164.

Demographic and clinical characteristics were well balanced in the two cohorts at baseline

n (%)	gBRCAmut		Non-gBRCAmut	
	Zejula® (n=138)	Placebo (n=65)	Zejula® (n=234)	Placebo (n=116)
Median age, y (range)	57 (36–83)	58 (38–73)	63 (33–84)	61 (34–82)
FIGO stage				
I/II	23 (16.7)	10 (15.4)	22 (9.4)	5 (4.3)
III	95 (68.8)	46 (70.8)	173 (73.9)	86 (74.1)
IV	20 (14.5)	9 (13.8)	38 (16.2)	24 (20.7)
Time to progression after penultimate platinum therapy				**Stratification factor**
6–<12 months	54 (39.1)	24 (40.0)	90 (38.5)	44 (37.9)
≥12 months	84 (60.9)	39 (60.0)	144 (61.5)	72 (62.1)
Best response to most recent platinum therapy				
CR	71 (51.4)	33 (50.8)	117 (50.0)	60 (51.7)
PR	67 (48.6)	32 (49.2)	117 (50.0)	56 (48.3)
Previous bevacizumab	33 (23.9)	17 (26.2)	62 (26.5)	30 (25.9)
Previous lines of chemotherapy				
1	1 (0.7)	0	0	0
2	70 (50.7)	30 (46.2)	155 (66.2)	77 (66.4)
≥3	67 (48.6)	35 (35.8)	79 (33.8)	38 (32.8)

Median age

57–63 across cohorts

≥3 prior lines of chemotherapy

Non-g*BRCA*mut **~33%**

g*BRCA*mut **~49%**

FIGO stage

III **69–74%**

IV **14–21%**

Previous bevacizumab

~26%

Time to progression after penultimate platinum therapy

6–<12 months **~40%**

≥12 months **~60%**

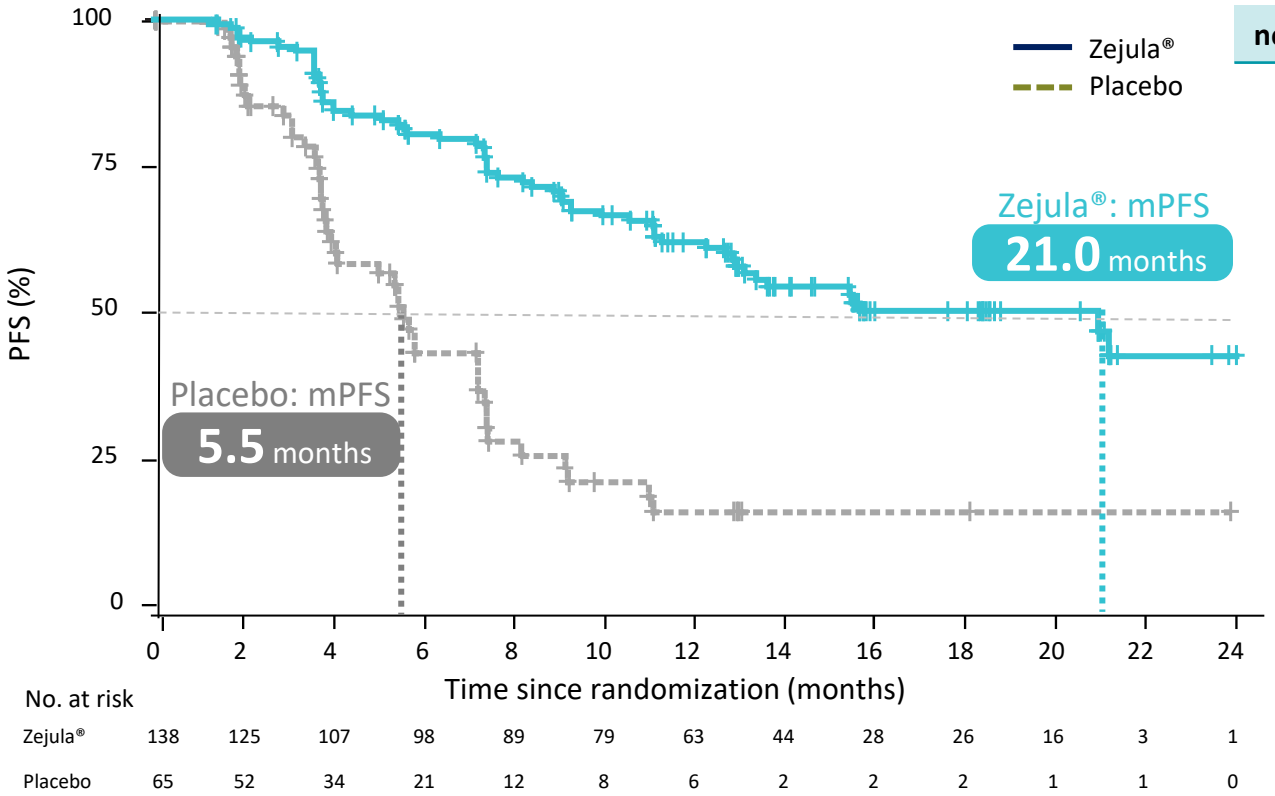
CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; g*BRCA*, germline breast cancer susceptibility gene; mut, mutation; PR, partial response; y, years

Mirza MR, et al. N Engl J Med. 2016;375:2154-2164.

The mPFS of Zejula® group in g*BRCA*mut were approximately 4 times longer than that of placebo group

- The efficacy analysis was performed after the occurrence of disease progression or death in 103 patients in the g*BRCA* cohort.

Median duration of follow-up, mo	
ITT population	16.9
g*BRCA* cohort	16.4
non-g*BRCA* cohort	17.5



Hazard ratio (95% CI)

0.27 (0.17–0.41)

p<0.001

Risk reduction

73%

Duration of ***PFS in the Zejula® group was significantly longer*** than that in the placebo group in all three primary efficacy populations.

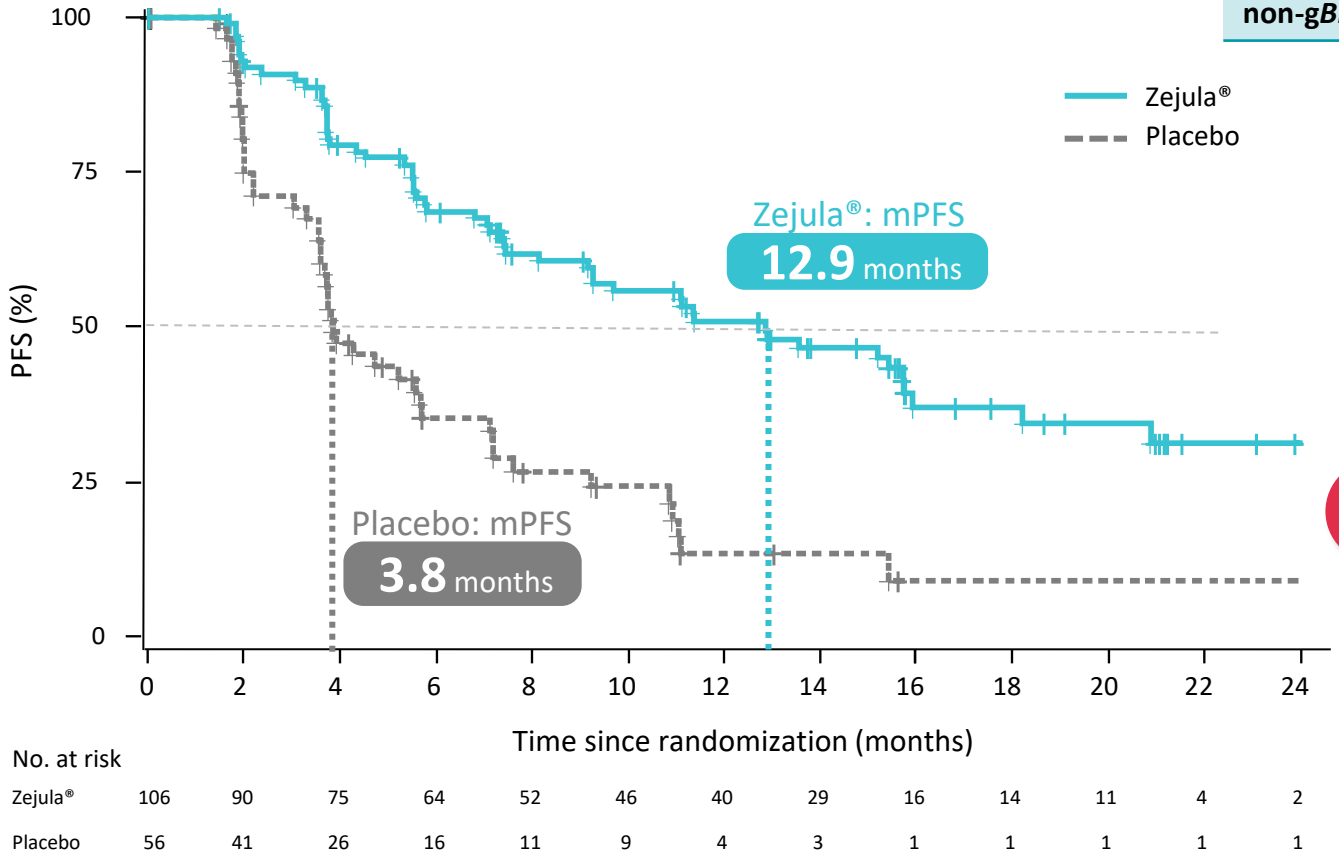
CI, confidence interval; g*BRCA*, germline breast cancer susceptibility gene; ITT, intention-to-treat; mo, months; mPFS, median progression-free survival; mut, mutation; PFS, progression-free survival.

Mirza MR, et al. N Engl J Med. 2016;375:2154-2164.

Non-g*BRCA*mut, HRD-positive patients treated with Zejula® had 3 times longer mPFS

- The efficacy analysis was performed after the occurrence of disease progression or death in 101 patients in the HRD-positive subgroup of the non-g*BRCA* cohort

Median duration of follow-up, mo	
ITT population	16.9
g*BRCA* cohort	16.4
non-g*BRCA* cohort	17.5



Hazard ratio (95% CI)

0.38 (0.24–0.59)

p<0.001

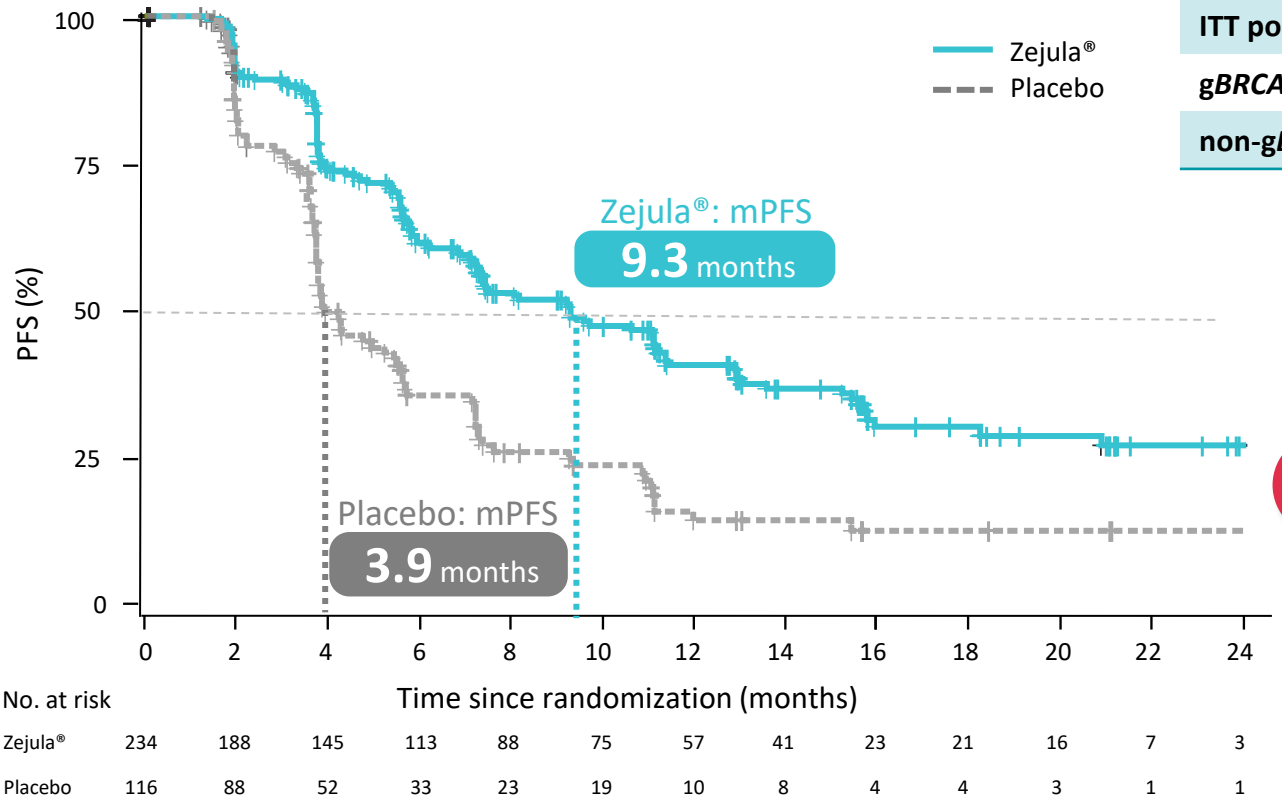
Risk reduction

62%

CI, confidence interval; g*BRCA*, germline breast cancer susceptibility gene; HRD, homologous recombination deficiency; ITT, intention-to-treat; mo, months; mPFS, median progression-free survival; mut, mutation; PFS, progression-free survival.

Mirza MR, et al. N Engl J Med. 2016;375:2154-2164.

The mPFS in non-g*BRCA*mut patients treated with Zejula® were about 2 times longer than who treated with placebo



Median duration of follow-up, mo	
ITT population	16.9
g*BRCA* cohort	16.4
non-g*BRCA* cohort	17.5

Hazard ratio (95% CI)

0.45 (0.34–0.61)

p<0.001

Risk reduction

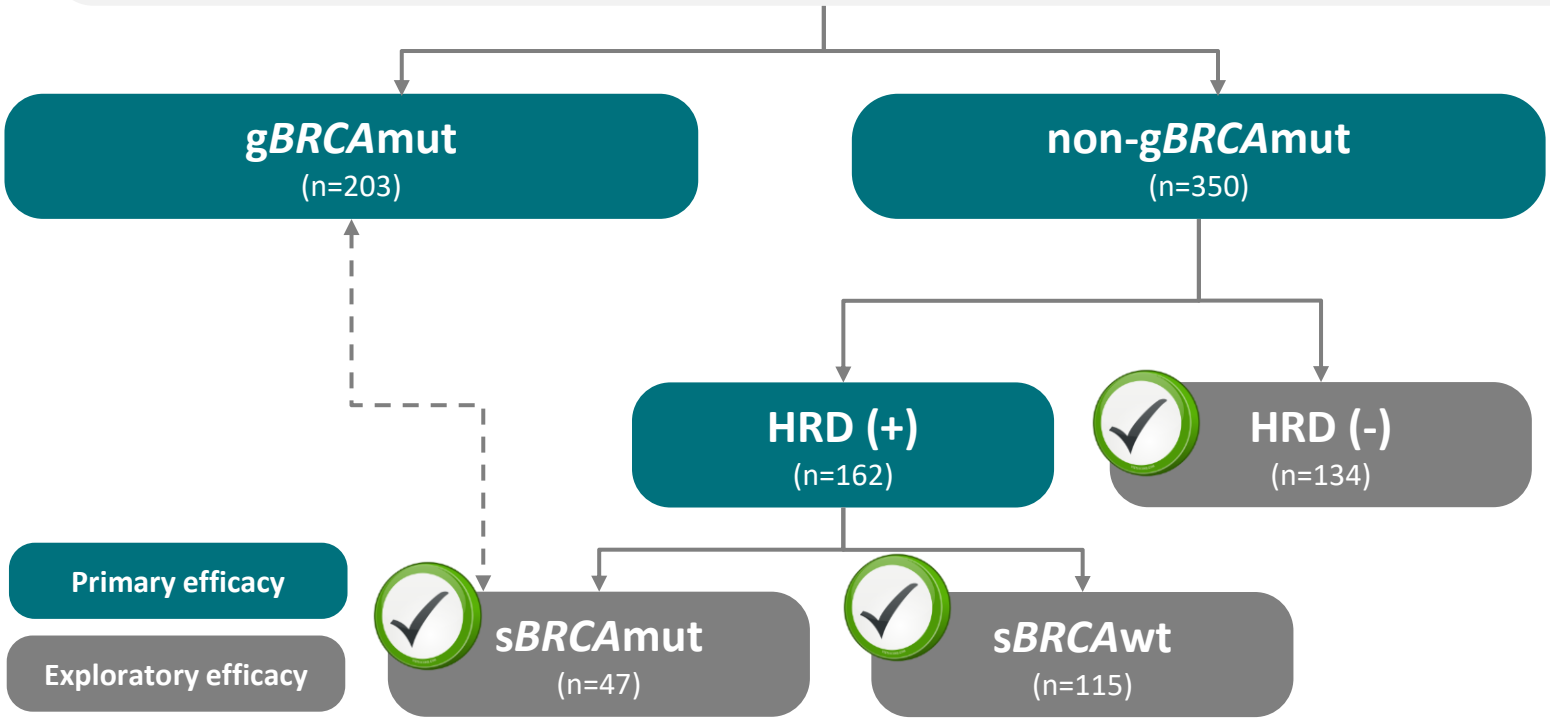
55%

CI, confidence interval; g*BRCA*, germline breast cancer susceptibility gene; ITT, intention-to-treat; mPFS, median progression-free survival; mo, months; mut, mutation; PFS, progression-free survival.

Mirza MR, et al. N Engl J Med. 2016;375:2154-2164.

The exploratory analysis of HRD(-), s*BRCA*mut, and s*BRCA*wt patients

Patients with **recurrent** ovarian cancer, fallopian tube cancer, or primary peritoneal cancer following **complete or partial response to platinum-based therapy (N = 553)**



BRCA, breast cancer susceptibility gene; g, germline; mut, mutation; s, somatic; wt, wild-type.

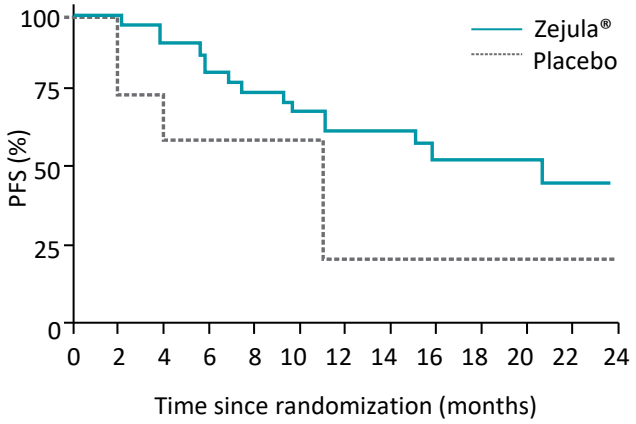
Mirza MR, et al. N Engl J Med. 2016;375:2154-2164.

Patients with or without HRD in Zejula® group both showed significant longer PFS

HRD (+) (n=162)

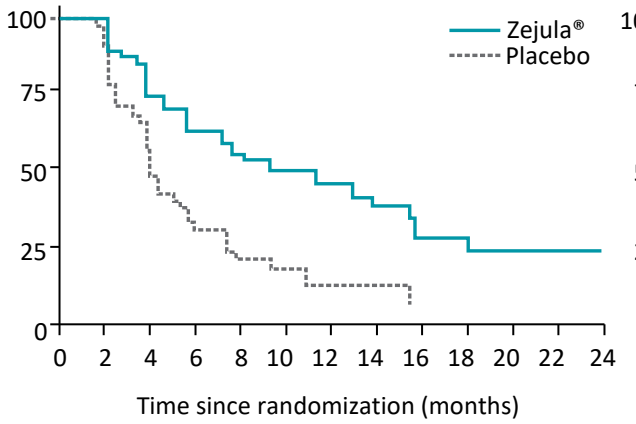
s*BRCA*mut (n=47)

	Zejula® (n=35)	Placebo (n=12)
mPFS, months	**20.9**	**11.0**
Hazard ratio (95% CI)	0.27 (0.08–0.90)	
***p* value**	*p*=0.02	



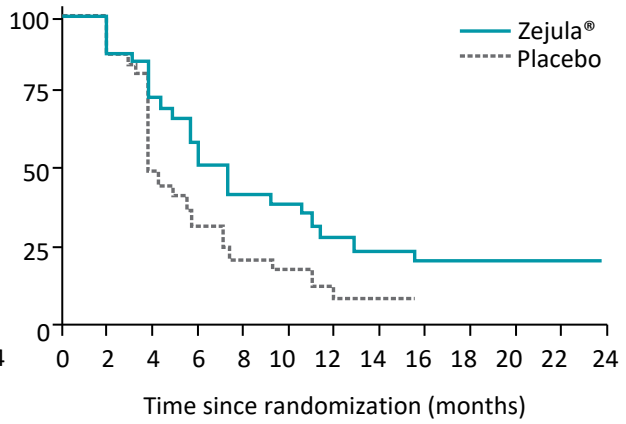
s*BRCA*wt (n=115)

	Zejula® (n=71)	Placebo (n=44)
mPFS, months	**9.3**	**3.7**
Hazard ratio (95% CI)	0.38 (0.23–0.63)	
***p* value**	*p*<0.001	



HRD (-) (n=134)

	Zejula® (n=92)	Placebo (n=42)
mPFS, months	**6.9**	**3.8**
Hazard ratio (95% CI)	0.58 (0.36–0.92)	
***p* value**	*p*=0.02	



CI, confidence interval; HRD, homologous-recombination deficiency; mPFS, median progression-free survival; PFS, progression-free survival; s*BRCA*, somatic breast cancer susceptibility gene; wt, wild type.

Mirza MR, et al. N Engl J Med. 2016;375:2154-2164

Summary of mPFS in NOVA trial

Patients with **recurrent** ovarian cancer, fallopian tube cancer, or primary peritoneal cancer following **complete or partial response to platinum-based therapy (N = 553)**[1]

ITT population[2]
Zejula® (n = 372) vs Placebo (n = 181)
mPFS 11.3 mo vs 4.7 mo, HR 0.42

g*BRCA*mut
Zejula® (n = 138) vs Placebo (n = 65)
mPFS 21 mo vs 5.5 mo, HR 0.27, *p*<0.001

non-g*BRCA*mut
Zejula® (n = 234) vs Placebo (n = 116)
mPFS 9.3 mo vs 3.9 mo, HR 0.45, *p*<0.001

HRD (+)
Zejula® (n = 106) vs Placebo (n = 56)
mPFS 12.9 mo vs 3.8 mo, HR 0.38 , *p*<0.001

HRD (-)
Zejula® (n = 92) vs Placebo (n = 42)
mPFS 6.9 mo vs 3.8 mo, HR 0.58, *p*=0.02

s*BRCA*mut
Zejula® (n = 35) vs Placebo (n = 12)
mPFS 20.9 mo vs 11.0 mo, HR 0.27, *p*=0.02

s*BRCA*wt
Zejula® (n = 71) vs Placebo (n = 44)
mPFS 9.3 mo vs 3.7 mo, HR 0.38, *p*<0.001

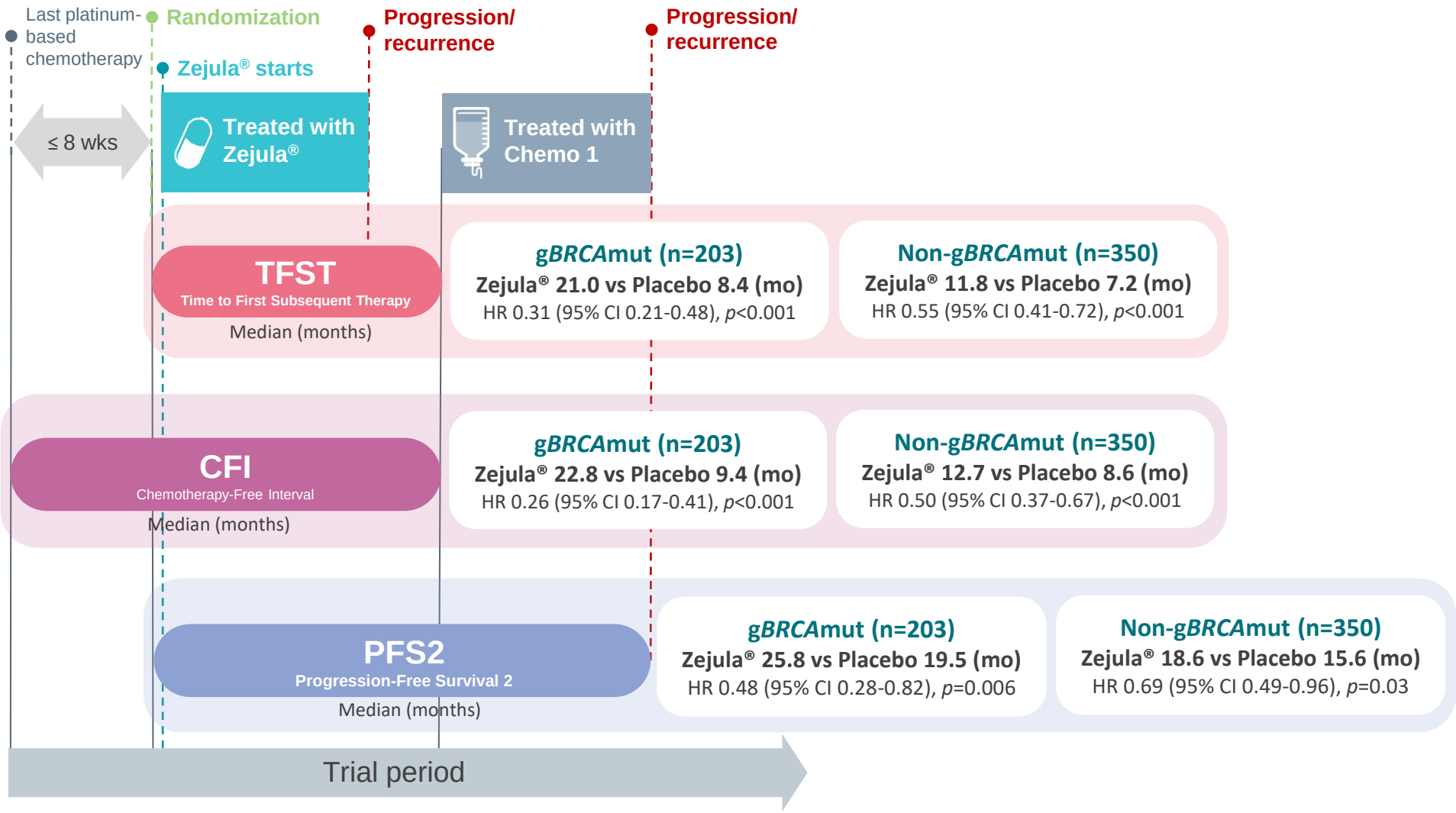
Primary efficacy

Exploratory efficacy

BRCA, breast cancer susceptibility gene; g, germline; HR, hazard ratio; HRD, homologues recombination deficiency; mut, mutation; mo, months; mPFS, median progression-free survival; s, somatic; wt, wild-type.

1. Mirza MR, et al. N Engl J Med. 2016;375:2154-2164; 2. Ison G, et al. Clin Cancer Res. 2018;24:4066-71.

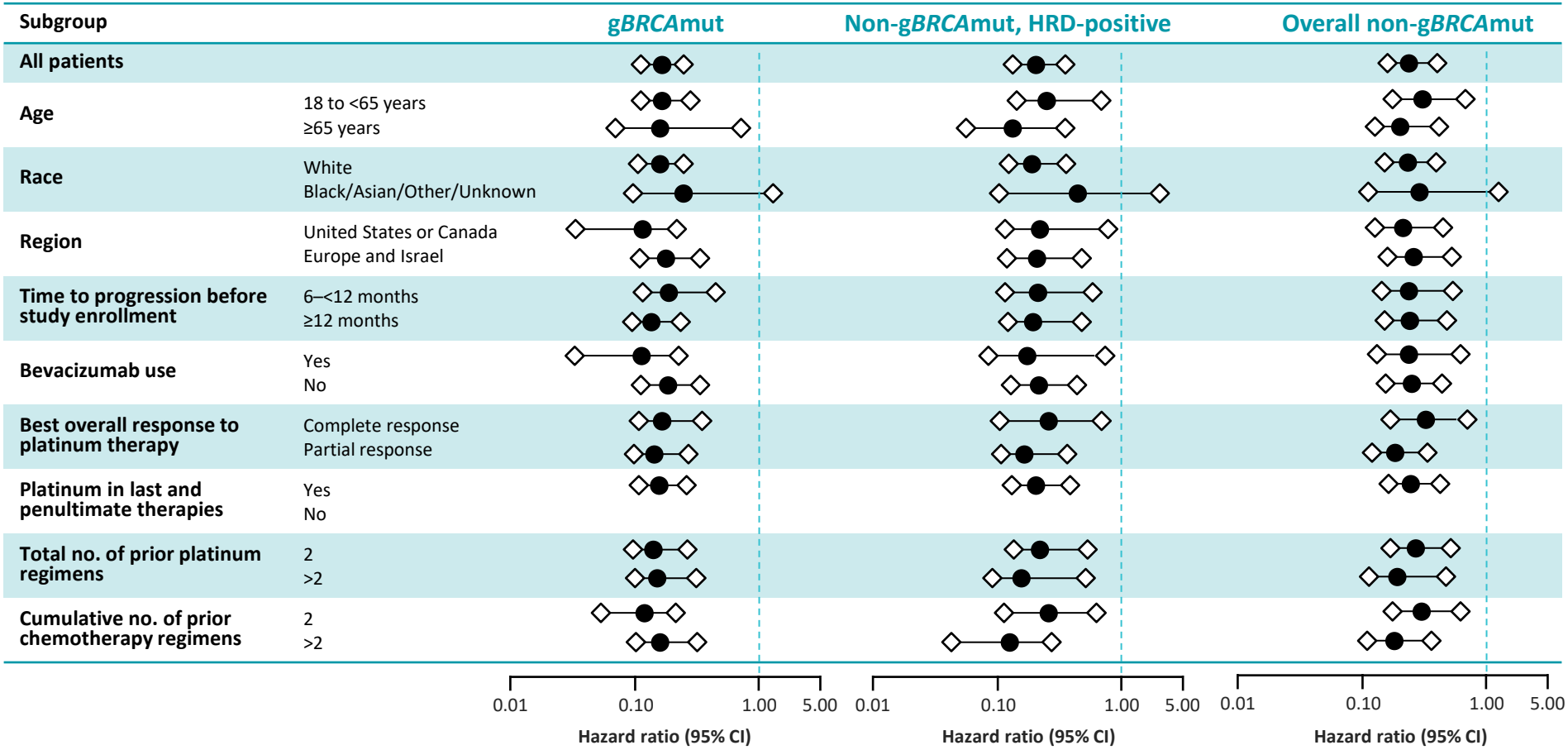
The results of TFST, CFI, and PFS2 are similar to that of the primary endpoint, which was better than the placebo



Chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; wks, weeks.

Mirza MR, et al. N Engl J Med. 2016;375:2154-2164.

All the subgroup analysis showed that the Zejula® group had longer mPFS than placebo



➢ ***Consistency of the significant superiority of Zejula® with respect to PFS* was shown *in all three primary efficacy populations***, with upper two-sided 95% confidence limits of <1.00 for all subgroup hazard ratios, except for the category of nonwhite race (due to small sample size).

CI, confidence interval; g*BRCA*, germline breast cancer susceptibility gene; HRD, homologous recombination deficiency; mut, mutation; PFS, progression-free survival.

Mirza MR, et al. N Engl J Med. 2016;375:2154-2164.

TEAEs were manageable and the discontinuation rate decrease after dose adjustment

Summary of AE

Reported, n (%)	Zejula® (n=367)	Placebo (n=179)
TEAE	367 (100.0)	171 (95.5)
Related TEAE	358 (97.5)	127 (70.9)
CTCAE Grade ≥3 TEAE	272 (74.1)	41 (22.9)
Related CTCAE Grade ≥3 TEAE	237 (64.6)	8 (4.5)
Serious TEAE	110 (30.0)	27 (15.1)
Related serious TEAE	62 (16.9)	2 (1.1)
TEAE leading to treatment interruption	253 (68.9)	9 (5.0)
TEAE leading to dose reduction	244 (66.5)	26 (14.5)
TEAE leading to treatment DC	54 (14.7)	4 (2.2)
TEAE leading to death	0	0

Treatment DC due to myelosuppression AE

Event, n (%)	Zejula® (n=367)	Placebo (n=179)
Thrombocytopenia*	12 (3.3)	1 (0.6)
Neutropenia†	7 (1.9)	0
Leukopenia‡	7 (1.9)	0
Anemia§	5 (1.4)	0
Pancytopenia	3 (0.8)	0

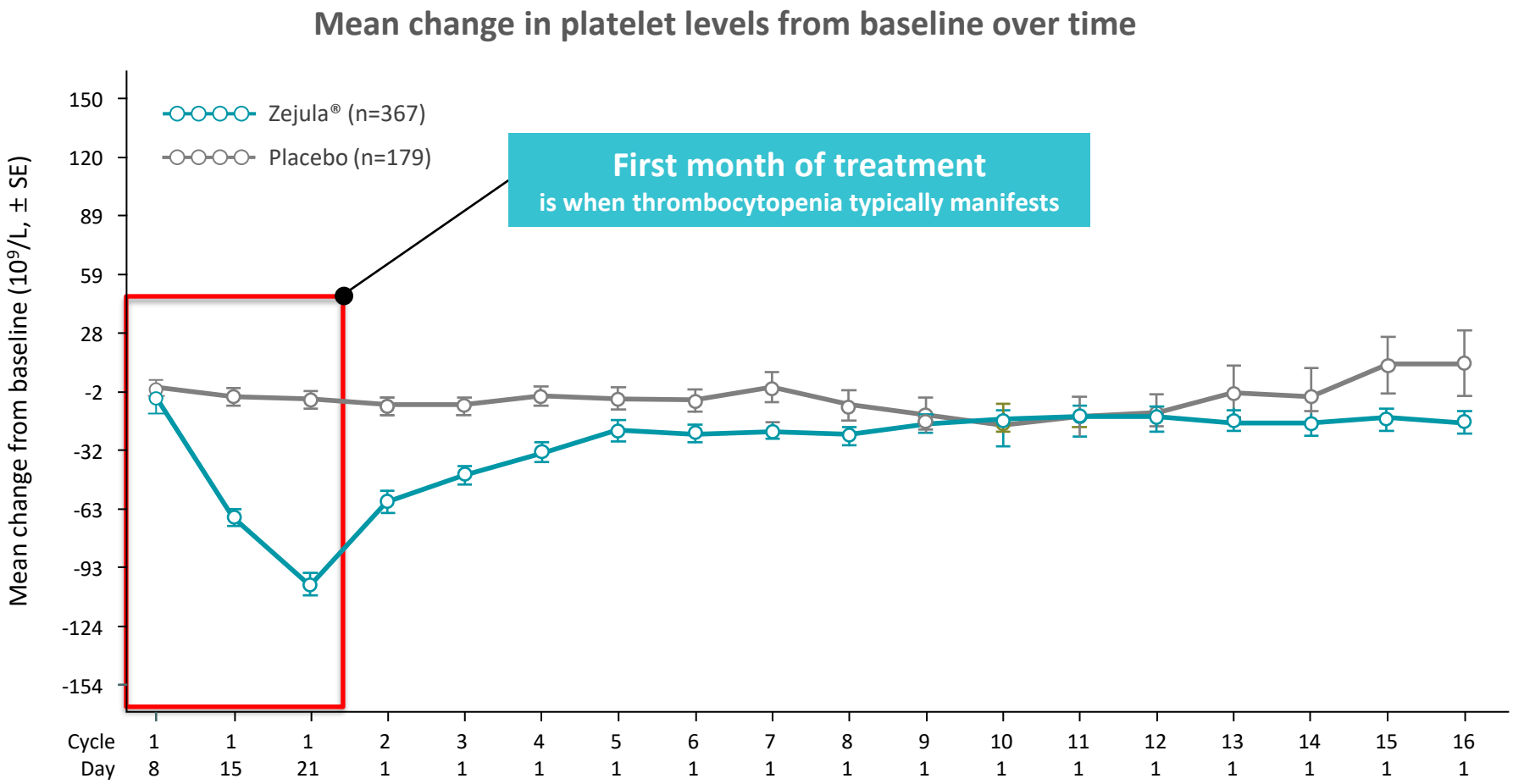
*Thrombocytopenia includes reports of thrombocytopenia and decreased platelet count.
†Neutropenia includes reports of neutropenia, decreased neutrophil count, and febrile neutropenia.
‡Leukopenia includes reports of neutropenia, neutrophil count decrease, white blood cell count decreased, leukopenia, lymphocyte count decreased, lymphopenia, febrile neutropenia, and monocyte count decreased.
§Anemia includes reports of anemia and decreased hemoglobin counts.

- *Treatment discontinuations* because of myelosuppression AE were *infrequent.*
- During the follow-up period, 3 patients (1 in the Zejula® group and 2 in the placebo group) died from the MDS or AML; *1 in each group were considered treatment-related.*

AE, adverse event; AML, acute myeloid leukemia; CTCAE, Common Terminology Criteria for Adverse Events; DC, discontinuation; MDS, myelodysplastic syndrome; TEAE, treatment-emergent adverse event.

Mirza MR, et al. N Engl J Med. 2016;375:2154-2164.

Thrombocytopenia was transient and typically manifested during the first month of treatment



SE, standard error.

Mirza MR, et al. N Engl J Med. 2016;375:2154-2164.

Dose reduction for non-hematologic toxicities

Treatment was interrupted for any non-hematologic NCI-CTCAE Grade 3/4 AE which the investigator considered to be treatment-related.

Initial dose		**3 capsules QD (300 mg/d)** 
1st dose reduction	NCI-CTCAE Grade 3/4 treatment-related SAE/AE where prophylaxis is not considered feasible	**2 capsules QD (200 mg/d)** 
2nd dose reduction	NCI-CTCAE Grade 3/4 treatment-related SAE/AE where prophylaxis is not considered feasible	**1 capsules QD (100 mg/d)** 
Continued NCI-CTCAE Grade 3/4 treatment-related SAE/AE **≥28 days**		**Discontinue treatment** 

- Dose interruption and/or reduction may be implemented at any time for any grade toxicity considered intolerable by the patient
- Dose not to be decreased below 100 mg QD

AE, adverse event; d, day; NCI-CTCAE, National Cancer Institute - Common Terminology Criteria for Adverse Events; QD, once daily; SAE, serious adverse event.

Mirza MR, et al. N Engl J Med. 2016;375:2154-2164. (suppl.)

NOVA provided hematologic guidance for dose adjustment

If blood cell counts or the level of Hb decreased, medication dose reduced

- Monitor CBC weekly until recovery; monitor for additional 4 weeks after the AE resolves
- Continue monitoring every 4 weeks thereafter

Hematologic AE		Interrupt study treatment until	Resume
Platelet count	1st occurrence: 75,000–99,999/µL (Grade 1)	≥100,000/µL	**At same or reduced dose** based on clinical judgement
	2nd occurrence: 75,000–99,999/µL (Grade 1) OR <75,000/µL (Grade ≥2)	≥100,000/µL	**At a reduced dose**
Neutrophil count	<1,000/µL (Grade ≥3)	≥1,500/µL	
Hemoglobin	<8 g/dL (Grade ≥3)	≥9 g/dL	

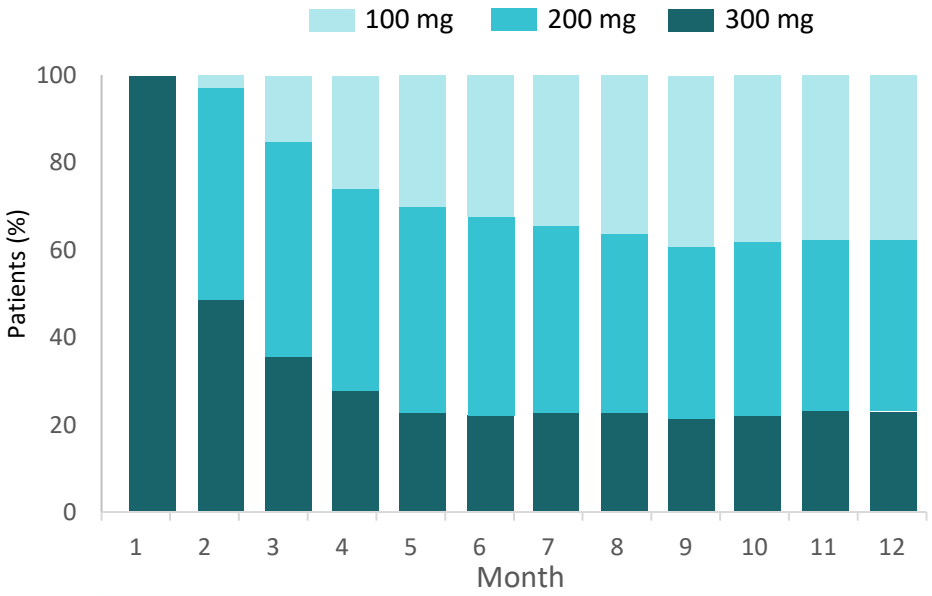
- **Resume at a reduced dose** upon recovery if patient required **transfusion** of platelets or red blood cells (≥1 units) or hematopoietic growth factor support
- **Permanently discontinue** study treatment if the **blood count has not returned to the specified levels within 28 days** or if the patient has already undergone maximum dose reductions
- **Discontinue** study treatment **if MDS/AML or secondary cancers** (new malignancies other than MDS/AML) is confirmed by a hematologist

AE, adverse event; AML, acute myeloid leukemia; CBC, complete blood count; MDS, myelodysplastic syndrome.

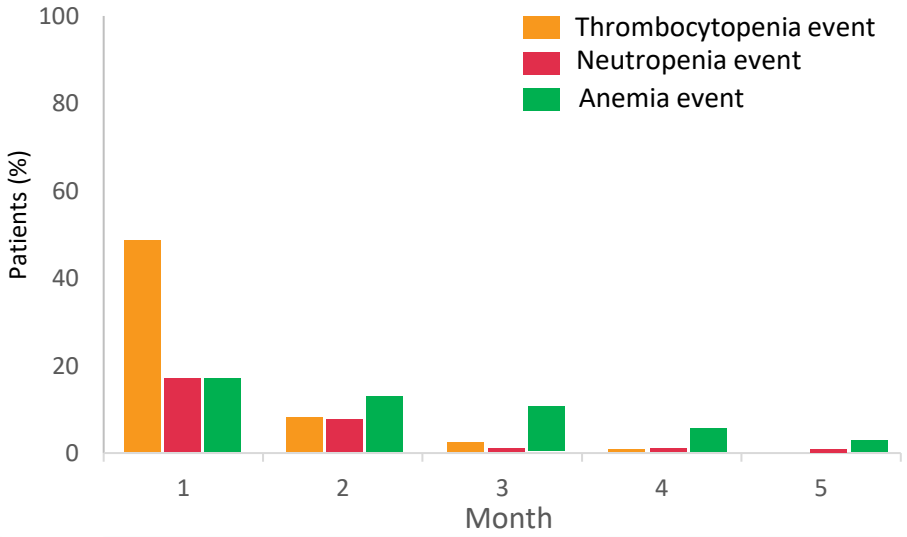
Mirza MR, et al. N Engl J Med. 2016;375:2154-2164. (suppl.)

The dose stabilized after 3 months and most of TEAEs resolved with dose reduction

Zejula® dose level by month on treatment



Any grade hematologic TEAEs in Zejula® arm (Month 1–5)



- Most patients reached their individual-adjusted dose level ***at the end of month 3 of treatment***
- ***200 mg*** was the most commonly administered dose

- ***Incidences of hematologic Grade ≥3 events decreased*** to 0.7% for thrombocytopenia and 1.6% for neutropenia after month 3, when only 27.6% of patients remained on the 300mg dose

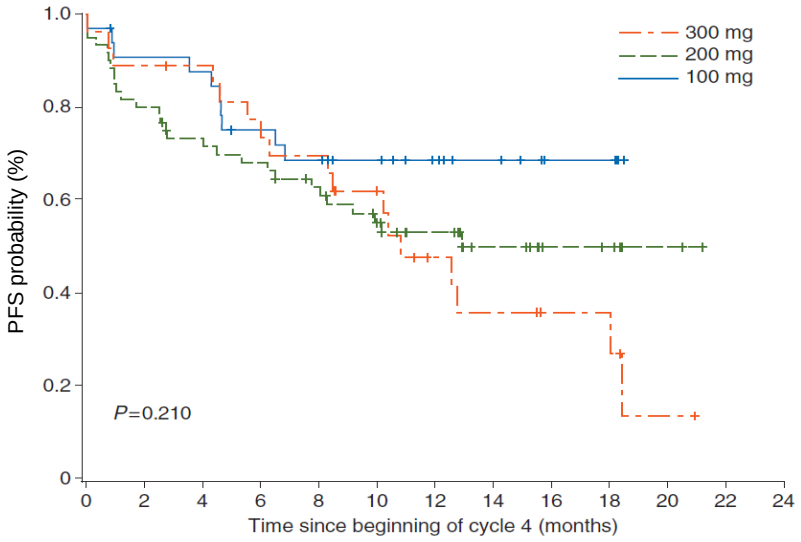
TEAE, treatment-emergent adverse event.

Berek JS, et al. Ann Oncol. 2018;29:1784-1792.

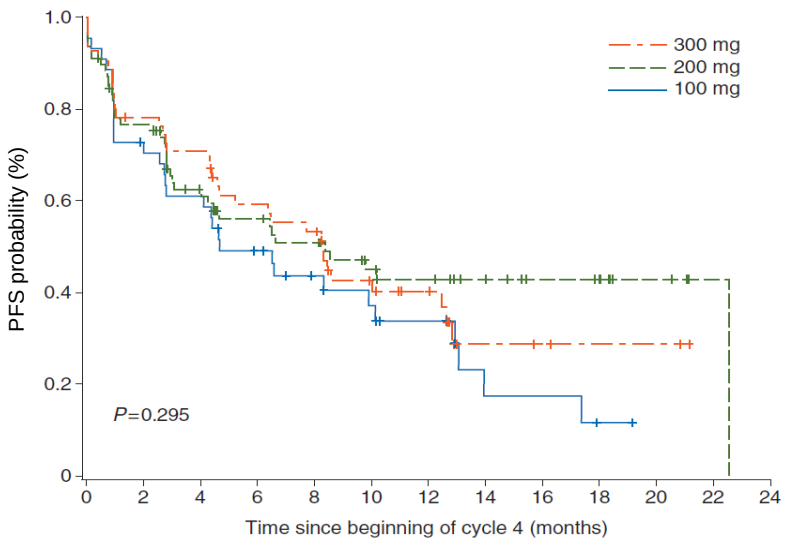
Dose reductions did not compromise efficacy

Estimated PFS probability by dose level measured after month 3

*gBRCA*mut



Non-g*BRCA*mut



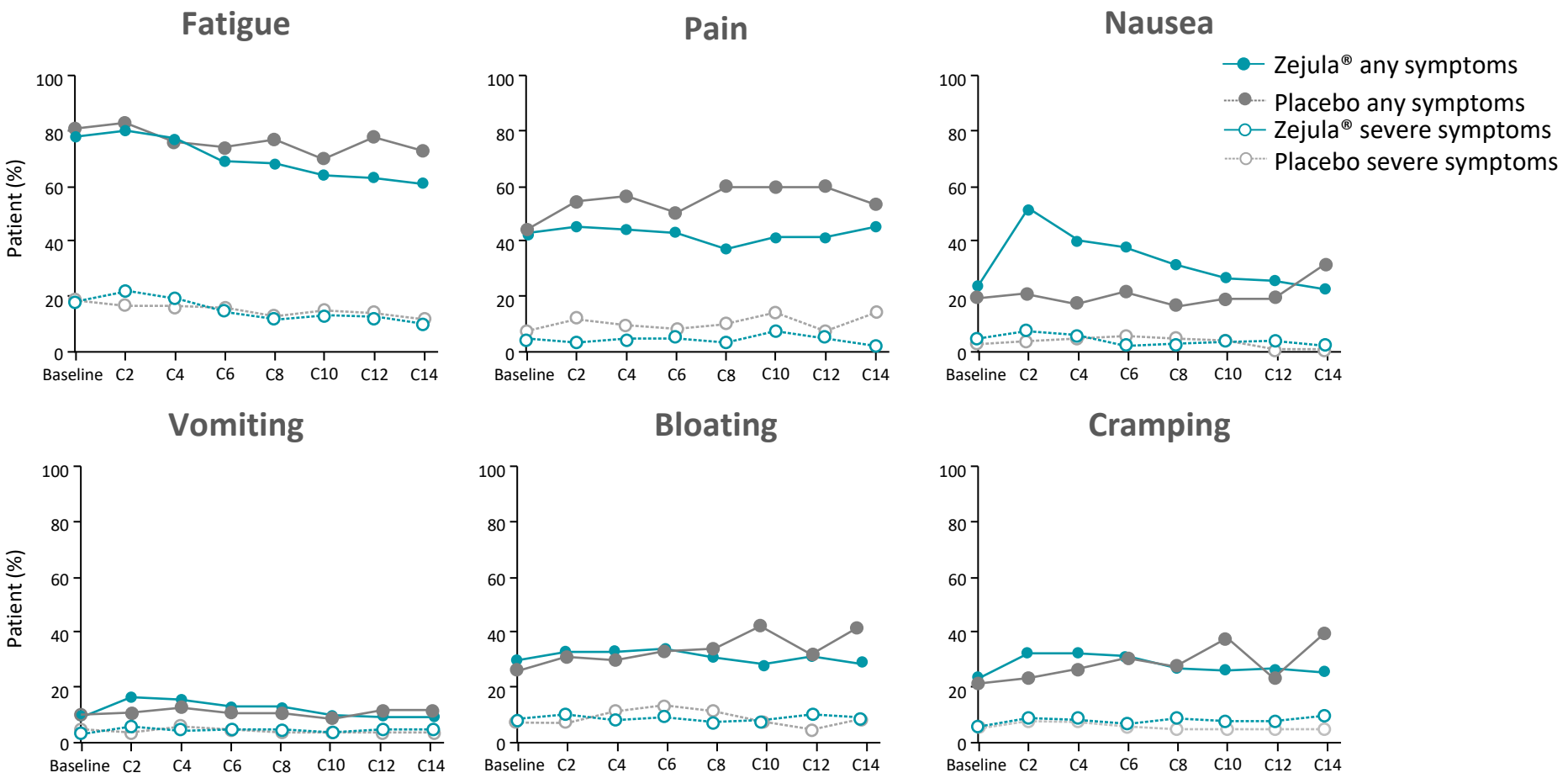
- PFS from month 4, when the majority of patients had achieved a stable dose, was assessed for the patients remaining on treatment.
- PFS in patients who were dose reduced to either 200 mg or 100 mg was **consistent with that of patients who remained at the 300 mg starting dose.**

g*BRCA*, gemline breast cancer susceptibility gene; mut, mutation; PFS, progression-free survival.

Berek JS, et al. Ann Oncol. 2018;29:1784-1792.

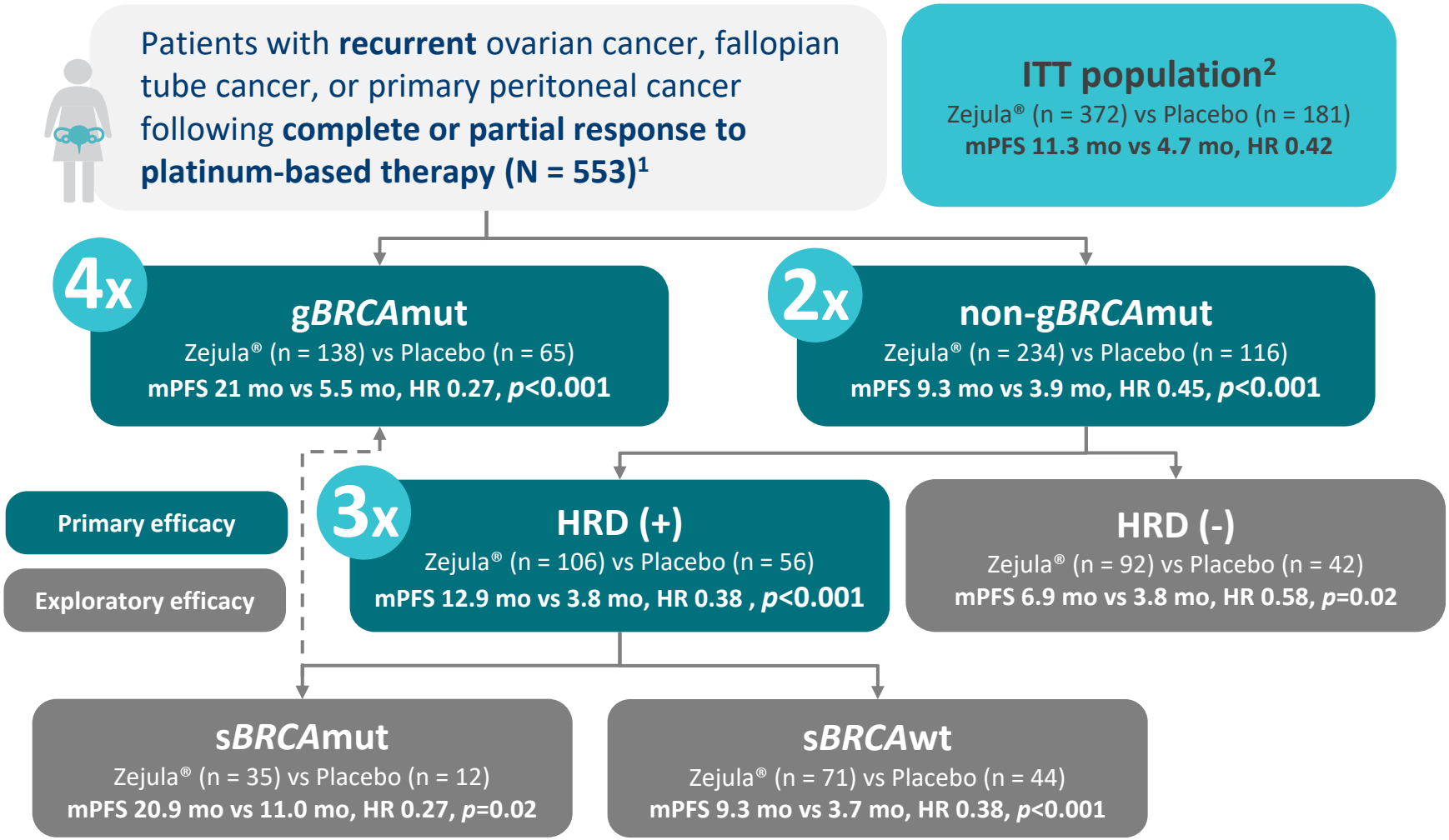
Zejula® did not adversely affect the patients' quality of life over the course of treatment

All symptoms, with the exception of nausea, either ***remained stable or improved over time with Zejula® treatment***



C, cycle; FOSI, Functional Assessment of Cancer Therapy–Ovarian Symptom Index.
Oza AM, et al. Lancet Oncol. 2018;19:1117-1125.

Overview of mPFS in NOVA trial



BRCA, breast cancer susceptibility gene; g, germline; HR, hazard ratio; HRD, homologues recombination deficiency; ITT, intent-to-treat; mut, mutation; mo, months; mPFS, median progression-free survival; s, somatic; wt, wild-type.

1. Mirza MR, et al. N Engl J Med. 2016;375:2154-2164; 2. Ison G, et al. Clin Cancer Res. 2018;24:4066-71.

Highlights of NOVA trial

4x

More mPFS for g*BRCAmut* patients[1]

3x

More mPFS for non-g*BRCA*mut/ HRD+ patients[1]

2x

More mPFS for non-g*BRCA*mut patients[1]

1

Once-a-day, enabling for long-term maintenance treatment[1,2]

g*BRCA*, germline breast cancer susceptibility gene; HRD, homologous recombination deficiency; mPFS, median progression-free survival; mut, mutation.

1. Mirza MR, et al. N Engl J Med. 2016;375:2154-2164; 2. Zejula 中文仿單（版本：2020年 3月）

Summary of NOVA trial

Efficacy

- The *only and first* Phase 3 study on gBRCAwt population
- *Significant longer duration of PFS* for all subgroup, no matter mutation or not
- Secondary endpoint *align with* primary endpoint

Safety

- *No new safety signals* were identified
- *Low incidence of discontinuation* because of the dose modifications
- *No efficacy impact after* dose adjustment

QoL

- Zejula® won't effect life quality, Zejula® could *maintain life quality and tolerate well*

PFS, progression-free survival; QoL, quality of life; wt, wild-type.

Mirza MR, et al. N Engl J Med. 2016;375:2154-2164.

截永樂® Zejula®

niraparib capsules 100 mg

A PARP Inhibitor to
Bring Ovarian Cancer Patients to the Future

STAY BETTER, STAY LONGER
REGARDLESS OF GENOMIC MUTATION STATUS

Zejula™
niraparib
capsules 100 mg

適應症

用於對含鉑化療有完全或部分反應的復發性表皮卵巢癌、輸卵管腫瘤或原發性腹膜癌成年病人之維持治療，病人須對復發前含鉑化療有敏感性

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.

Back up

Zejula® 可依病人狀況調整劑量 提供長期有效的治療

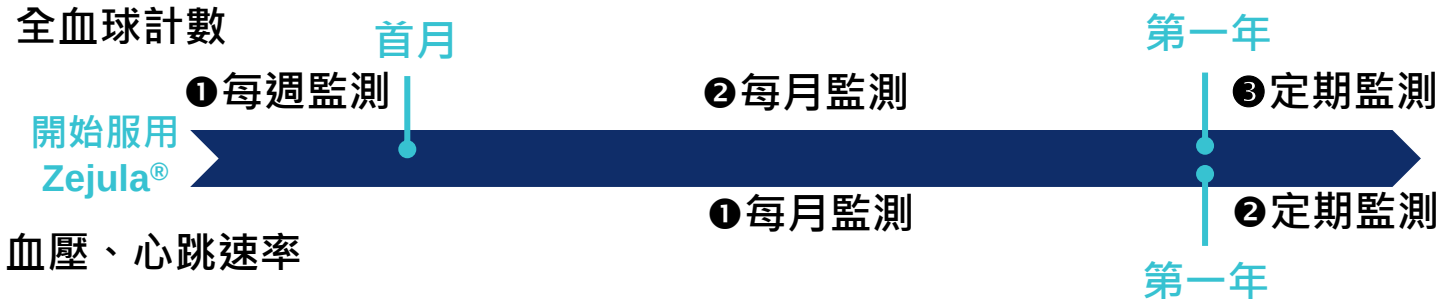
不良反應建議劑量調整方式

* 中斷治療直到不良反應緩解，但若不良反應於延後 Zejula® 治療 28 天後仍未緩解，或未回復可接受的數值，則應停用 Zejula® 。

體重 <77 kg 或 血小板 <150,000/μL

- 開始治療第一個月發生 Grade ≥ 3 血小板減少症之病人較體重 ≥77 kg 且血小板數量 ≥150,000/μL 高（35% v.s. 12%）處置：密切監測骨髓功能，並依**不良反應建議劑量調整方式**降低劑量

定期監測



C-APROM/TW/NIR/0029/2020OCT

仿單建議：不良反應之建議劑量調整方式

非血液不良反應（Non-hematologic ADRs）

Grade ≥3之不良反應（CTCAE）
無法採用預防治療或治療後
不良反應仍持續存在

↓

中斷治療
(延後 Zejula® 治療至最長 28 天)*

↓

不良反應緩解

↓

血液不良反應（Hematologic ADRs）

- **血小板數值（Platelet count）<100,000/μL *or***
- **嗜中性白血球數值（Neutrophil count）<1,000/μL *or***
- **血紅素數值（Hemoglobin）<8 g/dL *or***
- **需輸血的血液不良反應**

↓

中斷治療，並每週監測一次 CBC
(延後 Zejula® 治療至最長 28 天)*

↓

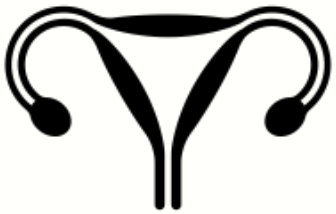
回復正常數值

↓

以Zejula®調降後劑量，重新開始服用#

* 若不良反應於延後 Zejula® 治療 28 天後仍未緩解，或未回復可接受的數值，則應停用 Zejula®。
# 若首次發生血小板低下，且血小板數值 ≥ 75,000/μL 時，可考慮使用 Zejula® 相同劑量，重新開始服用。

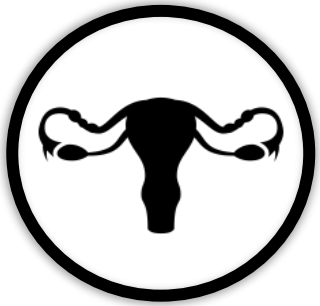
ADRs, adverse drug reactions; CBC, complete blood counts; CTCAE, Common Terminology Criteria for Adverse Events.



Therapeutic Roles of Leuplin® in Endometriosis

2022.06.11基督教門諾醫院蔡啟智醫師

Table of Contents



Endometriosis

- Epidemiology
- Signs, symptoms, comorbidity
- Pathophysiology

GnRH Agonist

- Treatment overview
- Mechanism
- Guideline recommendations

Leuprolide (Leupin®)

- Leuplin® clinical evidence for endometriosis
- Leuplin® product information

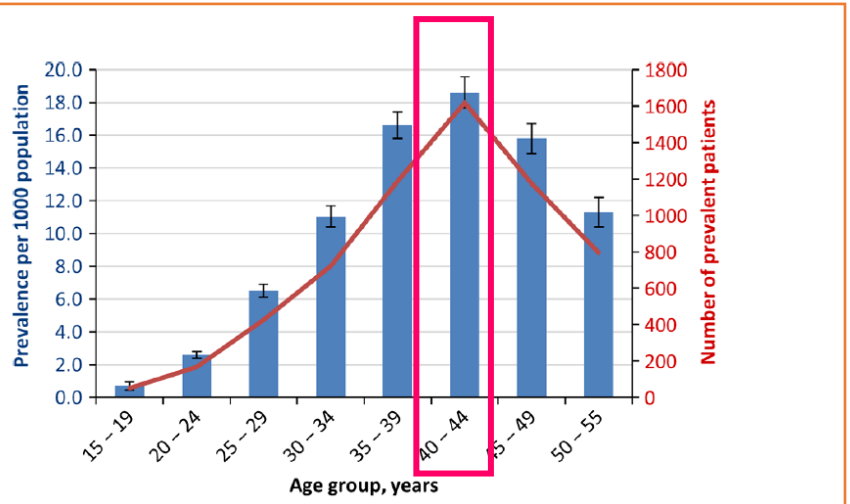
Endometriosis

- Epidemiology
- Pathophysiology
- Signs, symptoms, comorbidity

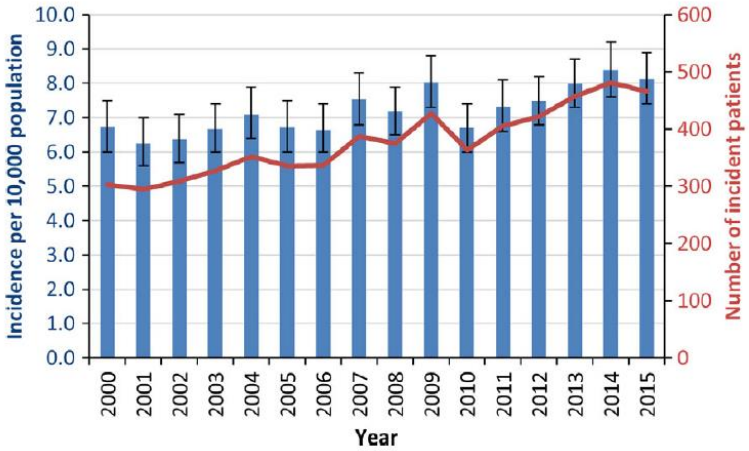
Prevalence of Endometriosis

Population-based study from a healthcare provider with 2 million members

- Prevalence of endometriosis was **10.8 per 1000** (95% CI 10.5–11.0)
- Women aged **40–44 years** had the **highest prevalence rate** of 18.6 per 1000(95% CI 17.7–19.5)
- The average annual incidence rate of **newly diagnosed** endometriosis was **7.2 per 10,000** (95% CI 6.5–8.0)



Age-specific point prevalence of diagnosed endometriosis



Annual incidence of newly diagnosed endometriosis

Eisenberg VH, et al. BJOG. 2018;125(1):55-62

Prevalence of Endometriosis in Taiwan

- The estimated prevalence was **8.9%.**[1]
- **Only 2/5** of those had a surgicopathological confirmation of endometriosis.
- **24.7%** patients were asymptomatic.

Indication	*Number of patients*	*Patients with Endometriosis*	*Percentage*
Pelvic adhesion	198	83	42%
Infertility	130	43	33%
Myoma	95	23	25%
Menorrhagia	79	15	20%
Tubal pregnancy	51	3	5%
Adnexal mass	50	9	17%
Sterilization	37	3	12%
Salpingoplasty	14	2	17%
Acute pain	13	1	7%
Cervical intraepithelial neoplasm	5	1	20%
Urinary stress incontinence	5	2	40%
Endometrial hyperplasia	3	1	33%

Prevalence of endometriosis related to indications for laparoscopic procedures in asymptomatic patients [2]

1. Teng SW, et al. J Chin Med Assoc. 2016;79(11):577-82. **2.** Chu KK. Diagn Ther Endosc. 1995;2(1):35-7.

Clinical Impact of Endometriosis

Infertility[1]

Endometriosis can further impair fertility by disturbing the function of the fallopian tube, embryo transport, and the eutopic endometrium.

- An estimated **25-50%** of women with infertility have endometriosis
- Around **30-50%** of women with endometriosis have infertility

Hysterectomy[2]

- In the USA, over **100,000** hysterectomies are performed each year for a primary diagnosis of endometriosis
- Approximately **12%** of women with endometriosis will eventually require a hysterectomy

1. Hickey M, et al. BMJ. 2014;348:g1752. **2.** Rizk B, et al. Facts Views Vis Obgyn. 2014;6(4):219-27.

Signs, Symptoms, Comorbidity

This conditions significantly affect women's everyday life, social relationships, sexuality and mental health.

Sign and symptoms[1]

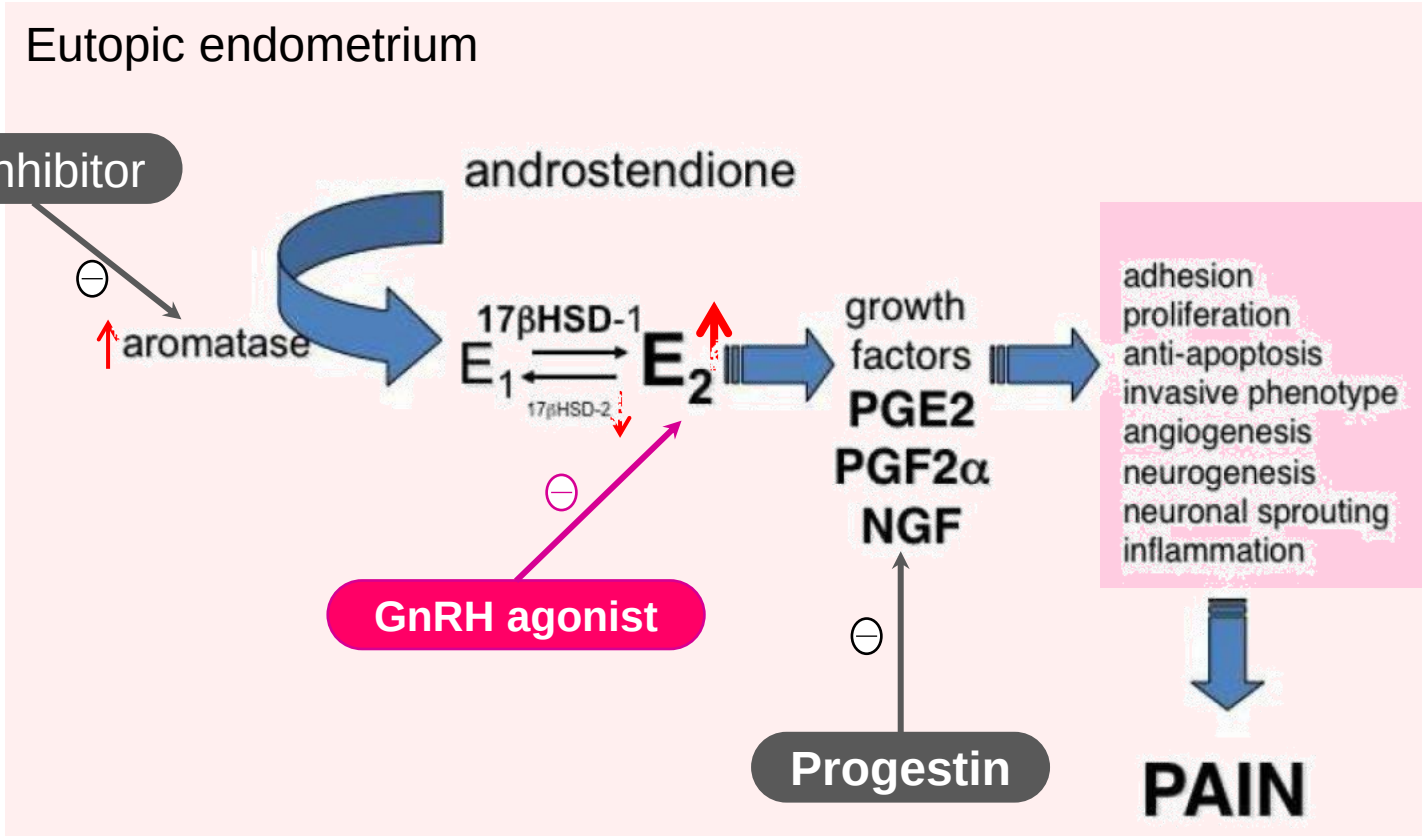
- Chronic pelvic pain
- Dysmenorrhea
- Deep dyspareunia
- Infertility
- Asymptomatic

Comorbidity[2]

- Pelvic inflammatory disease
- Infertility
- Malignant tumors
- (ovarian cancer**, breast cancer**, etc.)
- Irritable bowel syndrome
- CV disease
- Diabetes mellitus
- Chronic liver disease
- Chronic renal disease
- Rheumatic disease

1. Hickey M, et al. BMJ. 2014;348:g1752. **2.** Teng SW, et al. J Chin Med Assoc. 2016;79(11):577-82; 3.

Pathophysiology



Androgen Inducing a hypoestrogenic-hyperandrogenic state

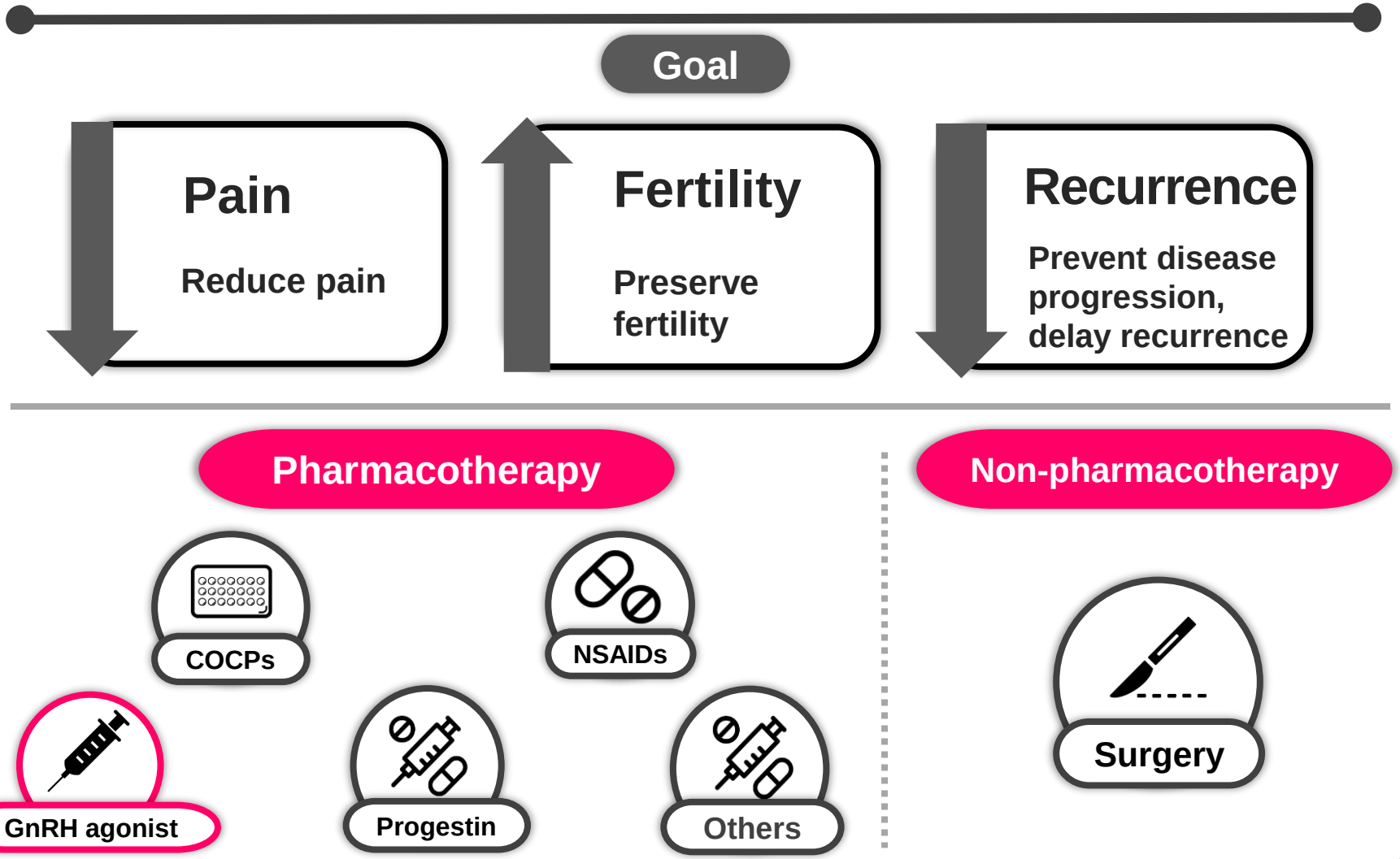
17βHSD = 17β hydroxysteroid dehydrogenase; E1= estrone; E2= estradiol; PGE2= prostaglandin E2; PGF2α= prostaglandin F2α; NGF= nerve growth factor.

Burney RO, Giudice LC. Fertil Steril. 2012;98(3):511-9.

GnRH Agonist

- Treatment overview
- Mechanism
- Guideline recommendations

Overview of Treatment

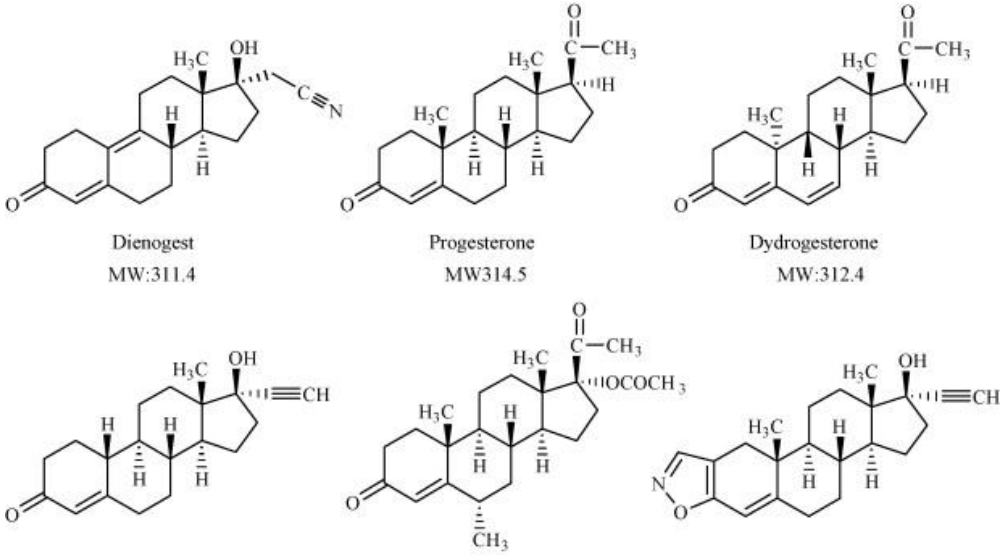


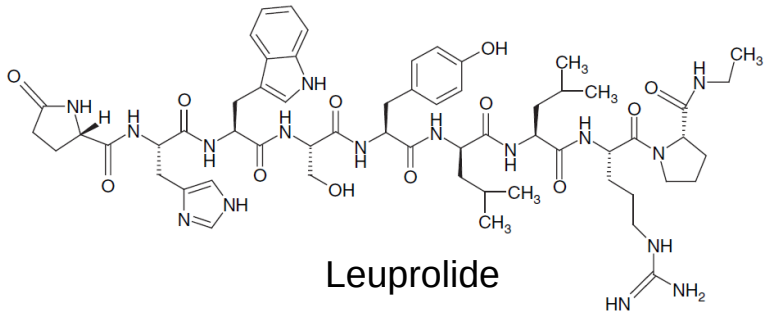
NSAIDs: non-steroid anti-inflammatory drugs; COCPs: combined oral contraceptive pills; GnRH: Gonadotropin-releasing hormone.

Parasar P, et al. Curr Obstet Gynecol Rep. 2017;6(1):34-41.

Comparison of Progestin and GnRH agonist

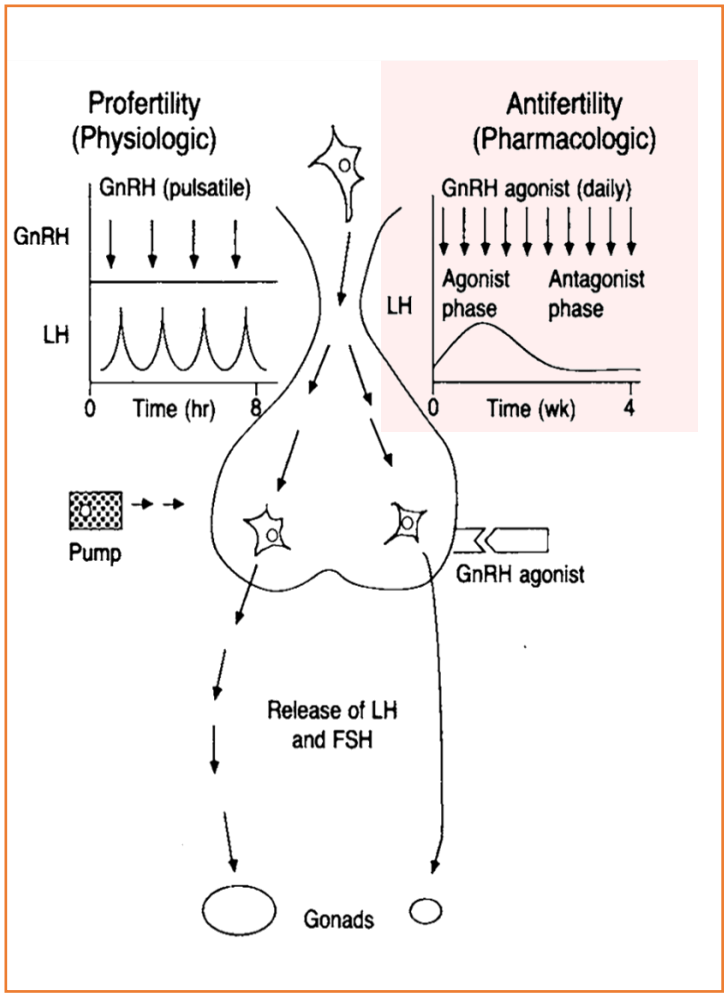
	Side effect[1]
Progestin[2]	**Thrombosis and hyperandrogenism**
GnRH agonist[3]	**Hypoestrogenic**





1. Zito G et al. Biomed Res Int. 2014;2014:191967; **2.** Sasagawa S, ey al. Steroids. 2008;73(2):222-31;
3. Wilson AC, et al. Expert Opin Investig Drugs. 2007;16(11):1851-63.

Mechanism of GnRH Agonists[1,2]



GnRH agonists

- Inhibit the secretion of FSH, preventing ovarian production of estrogen and creating a **hypoestrogenic state**.[2]

  ⇒ **Inhibit the development, maintenance, and growth of endometriosis**.[2]

Add-back therapy

- To increase sex-steroid hormones to a level sufficient to mitigate the menopause-like symptoms of the GnRH agonist without providing sufficient estrogen for endometriosis growth or maintenance.[2]

GnRH: Gonadotropin-releasing hormone.

1. Bulun SE. N Engl J Med. 2009;360:268-79. **2.** Olive DL. N Engl J Med. 2008;359(11):1136-42.

2014 & 2017 ESHRE recommendation for GnRH agonist

Pain relief [1] — A

- Clinicians are recommended to use **GnRH agonists**, as one of the options for **reducing endometriosis-associated pain.**
- **Hormonal add-back therapy**: to prevent bone loss and hypoestrogenic symptoms.

Infertility[1] — B

Clinicians can prescribe **GnRH agonists** for **3-6 months prior to treatment with assisted reproductive technologies** to improve clinical **pregnancy rates** in infertile women with endometriosis.

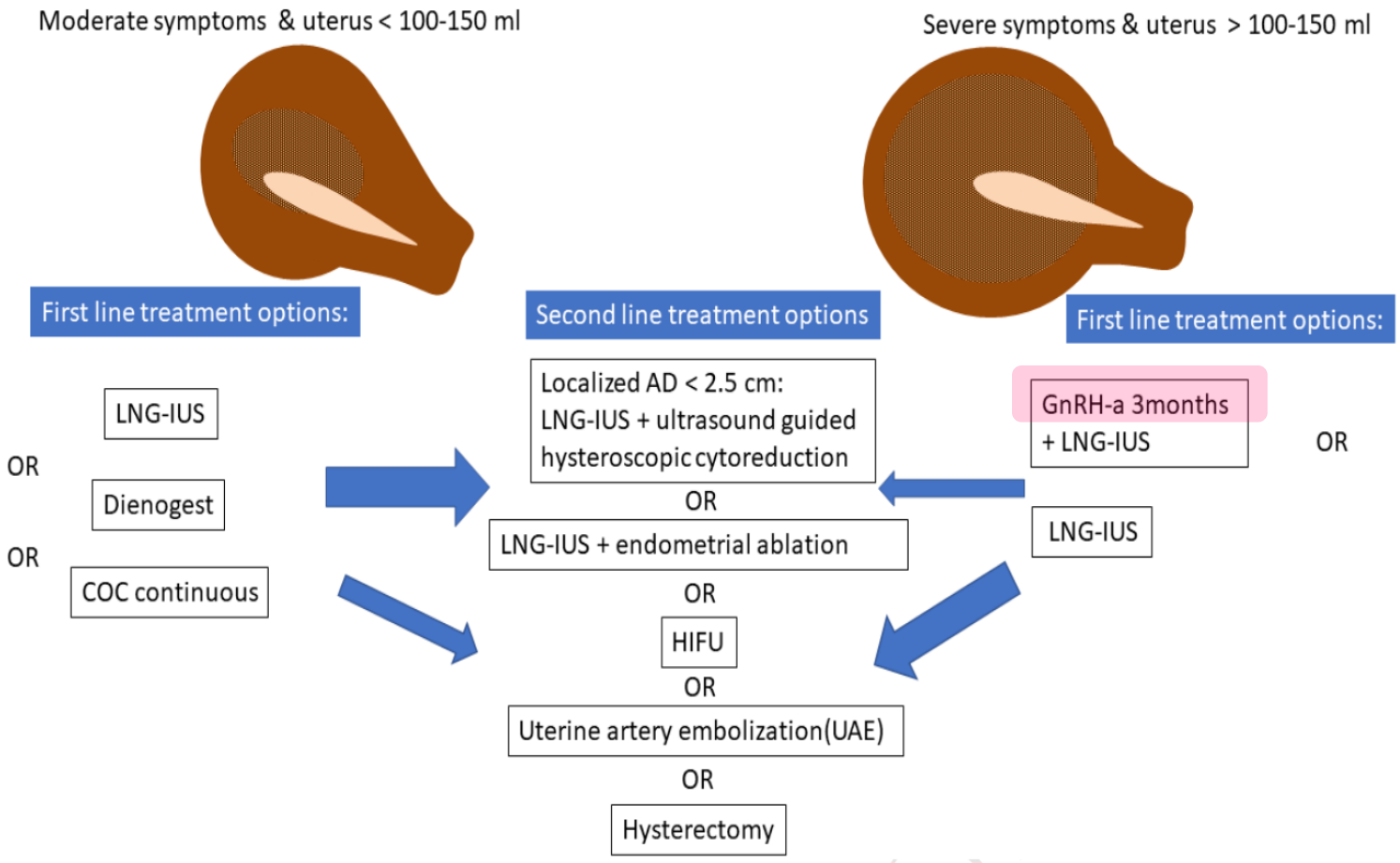
Large endometriomas[2] — Clinical expertise

Administer a **GnRH agonists** therapy for **3 months**, during which time the **thickness of the cyst wall significantly decreases**, with **atrophy and reduction in stromal vascularisation of the cyst**.

Grade of recommendation: A: Meta-analysis, systematic review or multiple RCTs (high quality); B: Meta-analysis, systematic review or multiple RCTs (moderate quality); Single RCT, large non-randomised trial, case-control or cohort studies (high quality).

1. Dunselman GA, et al. Hum Reprod. 2014;29:400-12. **2.** Working group of ESGE, ESHRE, and WES, et al. Gynecological Surgery 2017;14:27.

Treatment of Adenomyosis



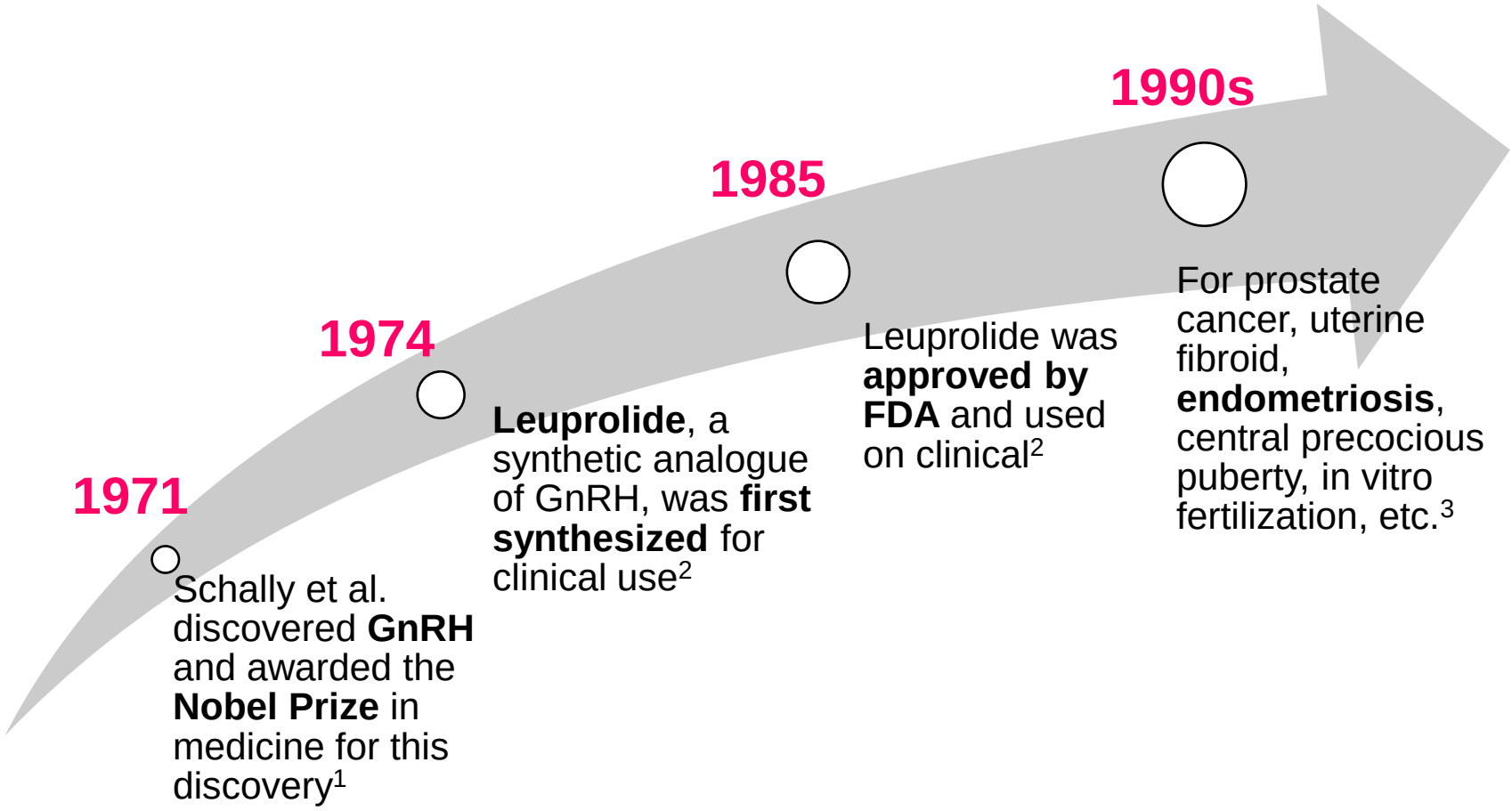
GnRH-a: Gonadotropin-releasing hormone agonist; LNG-IUS: levonorgestrel intrauterine system; COC: combined oral contraceptive.

Dueholm M. Best Pract Res Clin Obstet Gynaecol. 2018;1-19.

Leuprolide (Leuplin®)

- Efficacy
- Safety
- Quality of life
- Product information

Development of Leuprolide (Leuplin®)

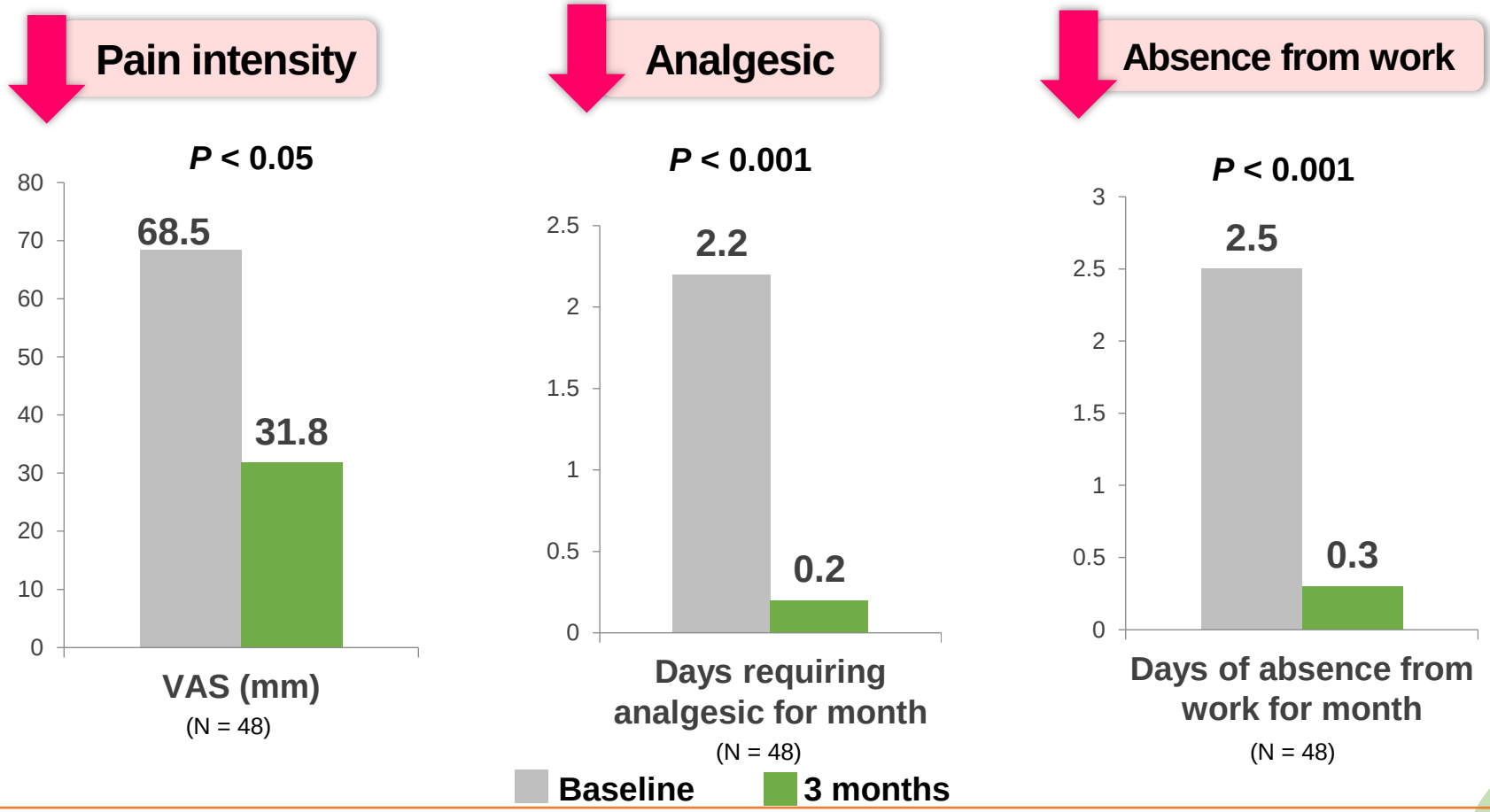


GnRH: Gonadotropin-releasing hormone; FDA: Food and Drug Administration.

1. Lepor H.Rev Urol. 2005;7 Suppl 5:S3-S12;
2. Sethi R, et al. Clin Interv Aging. 2009;4:259-67; **3.** Wilson AC, et al. Expert Opin Investig Drugs. 2007;16(11):1851-63.

Improvement in Pain with Leuprolide

After 3 months of leuprolide administration in women with endometriosis:



Morelli M, et al. Gynecol Endocrinol, 2013;29(4):305-8.

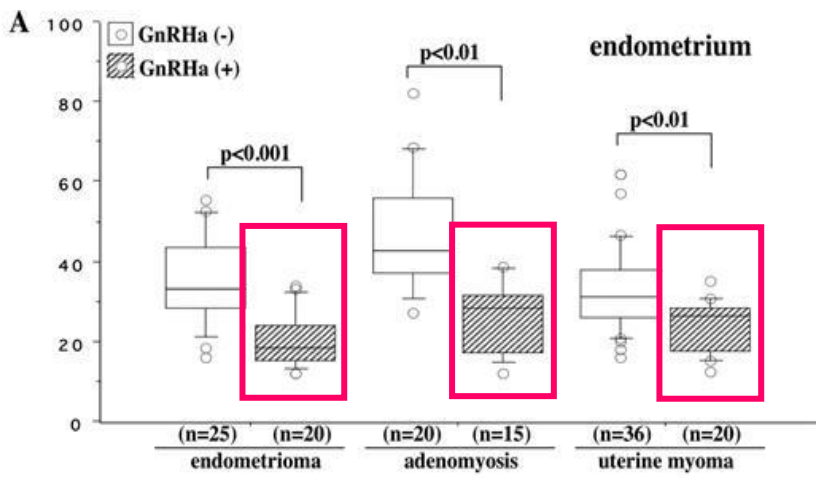
VAS: Visual Analogue Scale.

補充說明發炎反應與子宮內膜異位的關聯性

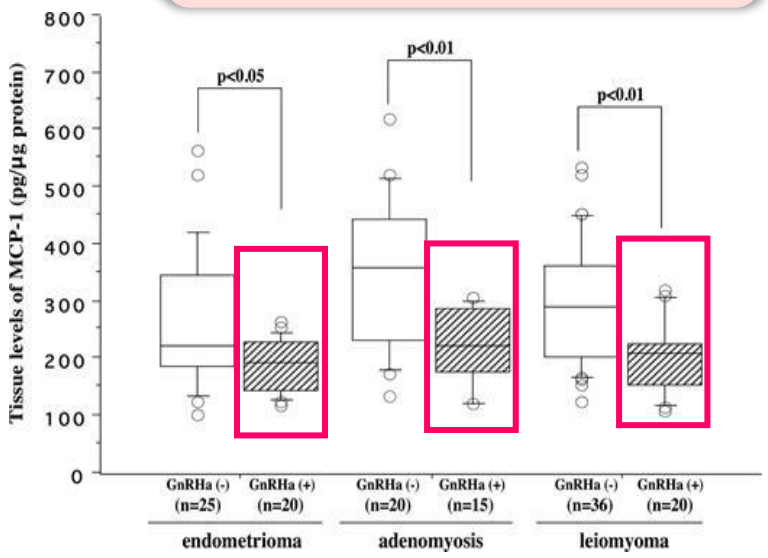
Leuprolide Reduced the Inflammation

- Endometriosis is an **oestrogen dependent** and **inflammatory disease.**[1]
- **GnRH-a** cause a **reduction in inflammation and angiogenesis** and **inducing apoptosis** so justifying alleviation of pain in women suffering from both adenomyosis and endometriosis.[2]

Macrophage



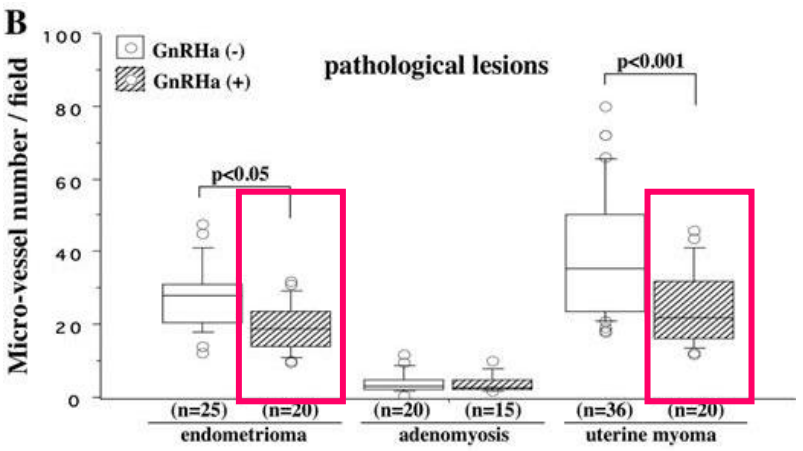
Monocyte chemotactic protein 1 (MCP-1)



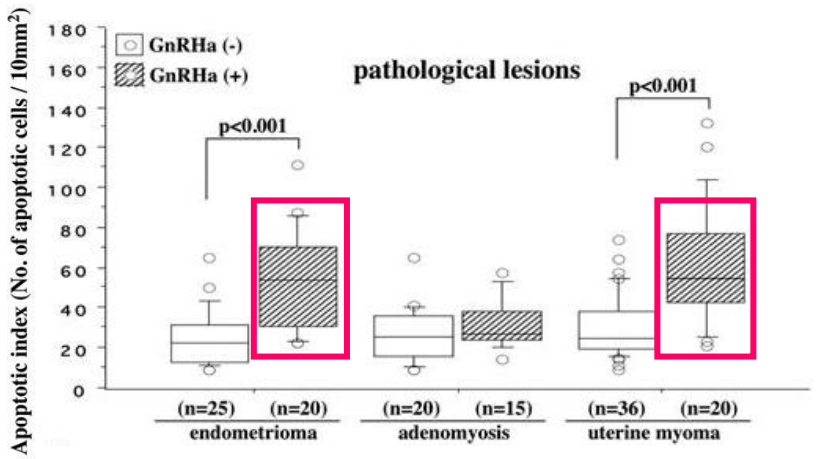
1. Hickey M, BMJ 2014, 348, g1752; 2. Morelli M et al. Gynecol Endocrinol, 2013;29(4);305-08;
3. Khan KN, et al. Hum Reprod. 2010;25(3):642–53.

Leuprolide Reduced the Angiogenesis and Induced Apoptosis

Micro-vessels number



Apoptotic index



Khan KN, et al. Hum Reprod. 2010;25(3):642–53.

Therapy with Leuprolide after Laparoscopy was Associated with Lower Risk of Subsequent Surgery

Real-world Study

6 month Follow-up – Effect of LA Time-Invariant	Unadjusted HR (95% CI)	p-Value	Adjusted HR (95% CI)	p-Value
Surgery plus LA Only: Adherent vs. Surgery Only	0.273 (0.102–0.729)	0.010	**0.312** (0.117–0.835)	**0.020**
Surgery plus LA Only: Non-Adherent vs. Surgery Only	1.150 (0.836–1.582)	0.390	1.209 (0.877–1.667)	0.247
Surgery plus Other Therapies Only vs. Surgery Only	1.416 (0.934–2.145)	0.101	1.533 (1.010–2.328)	0.045

Lower risk

Adherent **LA** use was associated with significantly **lower risk of surgery**

Higher risk

Use of other therapies was associated with significantly higher risk of surgery

LA: leuprolide acetate. HR: hazard ratio.

Soliman AM, et al. Curr Med Res Opin. 2016;32(6):1073-82.

Higher Ongoing Pregnancy Rates and Higher Implantation Rates with Leuprolide

Leuprolide in infertile patients with endometriosis

51 IVF-ET candidates with endome-triosis

- Leuprolide 3.75 mg Q4W → Standard controlled ovarian hyperstimulation
- \- → Standard controlled ovarian hyperstimulation with mid–luteal phase GnRH agonist down-regulation or microdose flare regimens

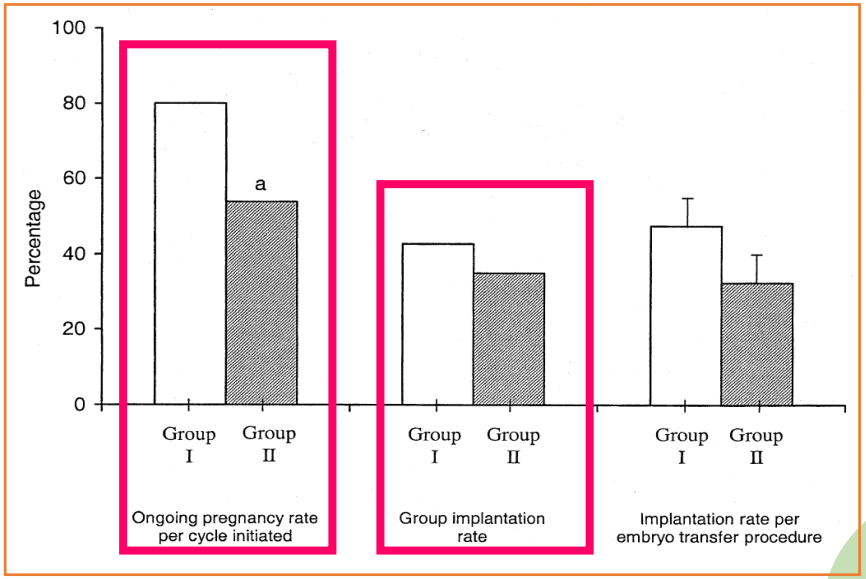
3 months

Outcomes:

- Ongoing pregnancy rates
- Group implantation rates
- Implantation rate per embryo transfer procedure

Results

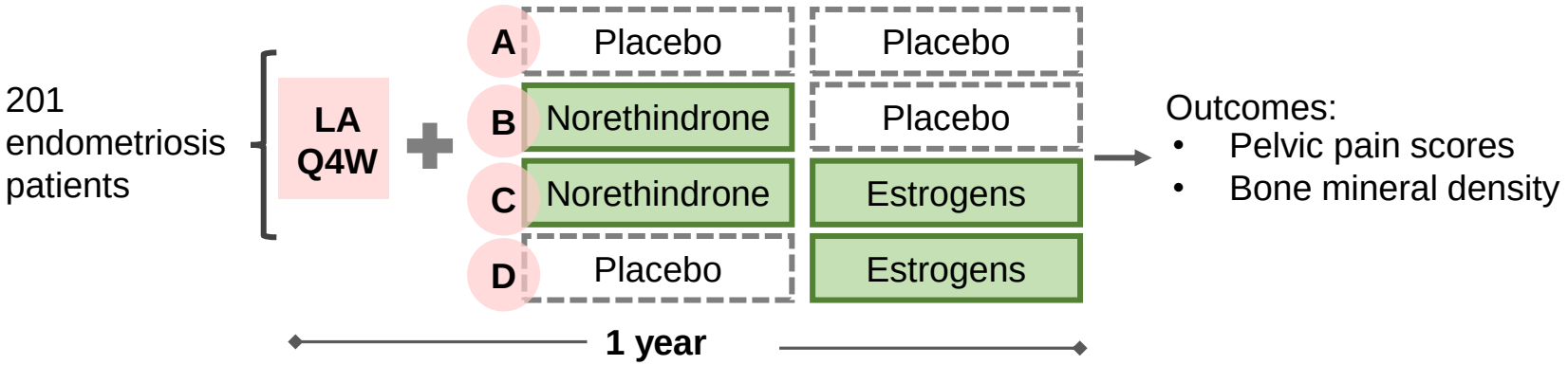
Patients who received the long-acting **GnRH regimen** before IVF-ET had significantly **higher ongoing pregnancy rates** and a trend toward **higher implantation rates**



GnRH: Gonadotropin-releasing hormone.

Surrey ES, et al. Fertil Steril. 2002;78(4);699-704.

Add-back Therapy and Bone Loss



Results

A Bone loss 6.3 ± 2.3% ($P \leq 0.001$)

Pelvic pain

A B C D

All improved

Bone density

B C D

Three preserved

Add-back therapy provided suppression of endometriosis related pain and against bone loss.

Hornstein MD, et al. Obstet Gynecol. 1998;91(1):16-24.

LA: leuprolide acetate.

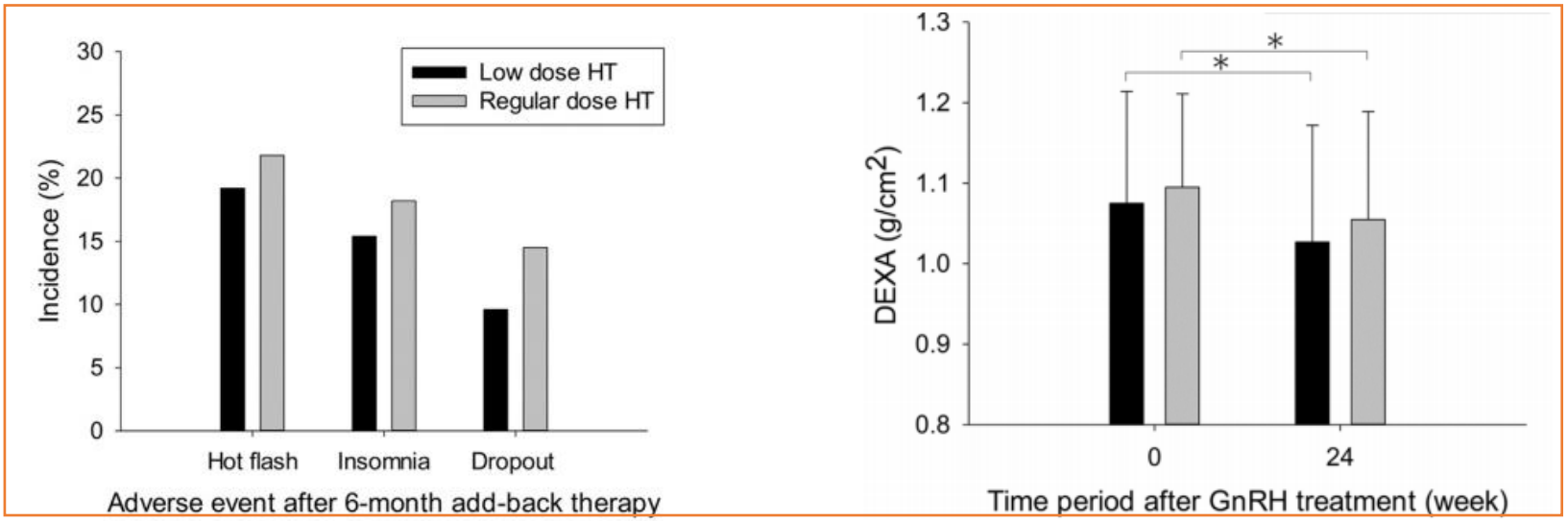
Low-dose Add-back Therapy

107 women with LA treatment

- Low-dose: +COCP **QD**
- Standard-dose: +COCP **BID**

20 weeks

Outcomes:
- Hypoestrogenic side effects
- Lumbar spine bone mineral density

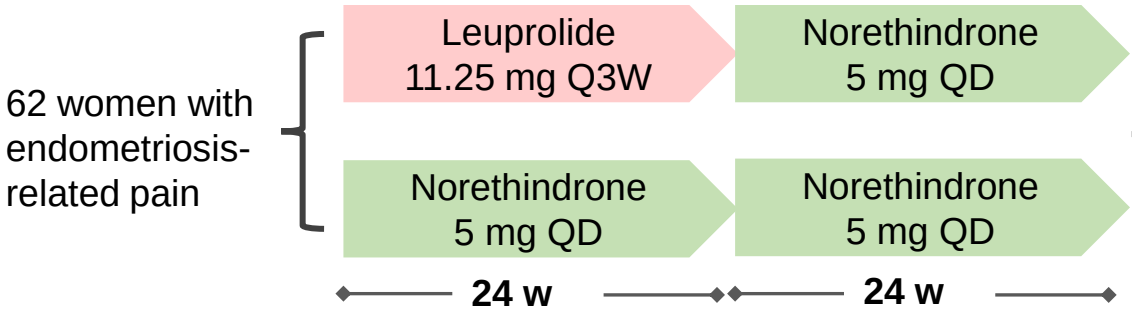


Low dose hormonal add-back therapy is equally effective with standard dose to ameliorate Leuprolide induced hypoestrogenic effects.

Tsai HW, et al. Taiwan J Obstet Gynecol. 2016;55(1);55-9.

LA: leuprolide acetate COCP: combined oral contraceptive pills

Quality of Life Improved after Treatment with Leuprolide



Results

Improvemts in HRQoL by Treatment Group

EHP-30 DIMENSIONS (Scale 0-100)	NA: ENTRY VS 24W	NA: 24W VS 52W	LD: ENTRY VS 24W	LD: 24W VS 52W
Pain	-31.6 ±23.0**	2.5 ±22.1	-37.5 ±25.3**	2.5 ±17.3
Control and Powerlessness	-33.0 ±26.4**	1.6 ±29.7	-34.4 ± 29.8**	-1.8 ±26.3
Emotional Well-Being	-15.9 ±23.0**	-1.4 ±18.6	-20.0 ±27.3*	0.7 ±20.6
Social Support	-17.5 ±19.6**	3.2 ±23.2	-29.2 ±36.5*	3.9 ±23.7
Self-Image	-12.9 ±22.3¶	-3.2 ±18.0	-18.8 ±36.5¶	3.1 ±25.3

NA: norethindrone acetate LD: leuprolide acetate depot

Muneyyirci-Delale O, et al. Fertility and Sterility. 2014;102(3):e14.

Leuprolide v.s. Dienogest

242 women aged 20–45 years with endometriosis and recurrent pelvic pain within 1 year

- Leuprolide 3.75 mg Q4W
- Dienogest 2 mg QD

12 weeks

Outcomes:
- Pelvic pain
- Back pain
- Dyspareunia
- Endometrioma size

- **VAS for pelvic pain**

	Dienogest (N = 101) Mean ± SD	**Leuprolide** (N = 96) Mean ± SD	**T**	**P value**
Baseline VAS	59.27 ± 11.02	58.73 ± 11.01	0.343	0.732
VAS by 12 weeks	30.61 ± 10.65	32.53 ± 8.74	- 1.377	0.170
Paired t	32.348	83.246	–	–
P	0.000	0.000	–	–

- **VAS for back pain**

	Dienogest (N = 72) Mean ± SD	**Leuprolide** (N = 68) Mean ± SD	**T**	**P value**
Baseline VAS	45.91 ± 3.33	46.68 ± 3.29	- 1.358	0.177
VAS by 12 weeks	26.92 ± 4.40	27.22 ± 1.79	- 0.529	0.597
Paired t	37.476	51.714	–	–
P	0.000**	0.000	–	–

Leuprolide and dienogest were associated with highly **significant reductions** in **pelvic pain** and **back pain**

VAS: Visual Analogue Scale.

Abdou AM, et al. J Obstet Gynecol India. 2018;68(4):306-13.

Leuprolide v.s. Dienogest

- **VAS for dyspareunia**

	Dienogest (N = 55) Mean ± SD	**Leuprolide** (N = 62) Mean ± SD	T	P value
Baseline VAS	36.53 ± 3.87	34.98 ± 4.96	1.859	0.066
VAS by 12 weeks	16.53 ± 3.10	17.11 ± 2.53	- 1.125	0.263
Paired t	48.076	25.656	–	–
P	0.000**	0.000**	–	–

- **Endometrioma size**

	Dienogest (N = 55) Mean ± SD	**Leuprolide** (N = 62) Mean ± SD	T	P value
Baseline VAS	32.48 ± 4.93	33.00 ± 5.29	- 0.330	0.743
VAS by 12 weeks	28.74 ± 6.39	30.11 ± 5.48	- 0.735	0.467
Paired t	4.789	3.886	–	–
P	0.000**	0.000**	–	–

Leuprolide and dienogest were associated with **highly significant reductions** in **dyspareunia** and **endometrioma size**

- **Drug-related adverse effects**

	Dienogest (N = 121)	Leuprolide (N = 121)	X^2	P value
Headache	17 (14%)	26 (21.5%)	2.29	0.13
Weight gain	13 (10.8%)	4 (3.3%)	5.1	0.020*
Vaginal bleeding	78 (64.5%)	26 (21.5%)	45.5	0.000**
Vaginal dryness	4 (3.3%)	19 (15.7%)	10.81	0.001**
Hot flushes	19 (15.7%)	56 (46.3%)	26.45	0.00**

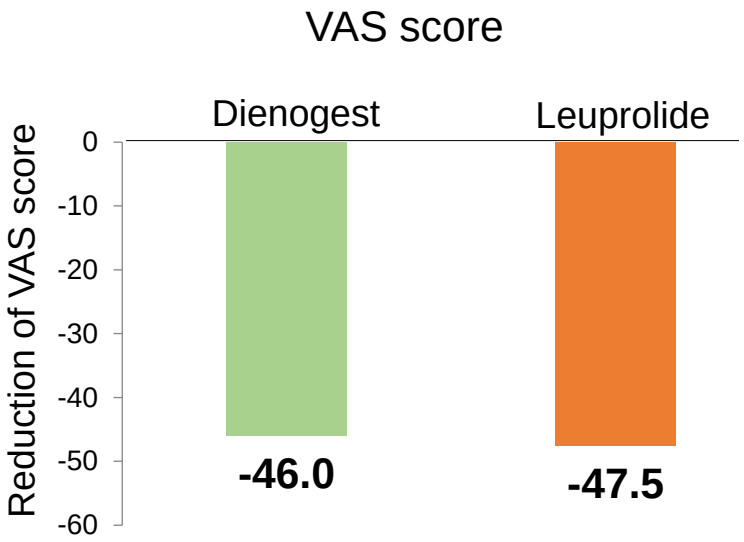
Leuprolide has **lower vaginal bleeding** and **weight gain**

VAS: Visual Analogue Scale.

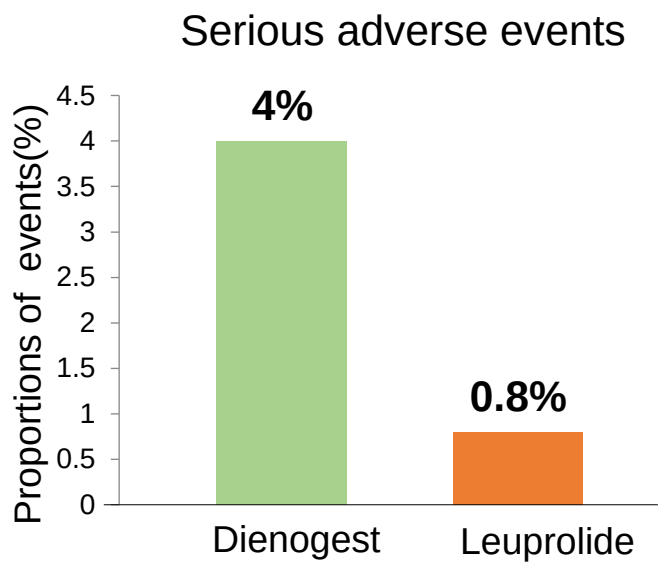
Abdou AM, et al. J Obstet Gynecol India. 2018;68(4):306-13.

Leuprolide v.s. Dienogest

Leuprolide is as effect as Dienogest and had less serious adverse events.



Dienogest was reported to be non-inferior to leuprolide



Leuprolide had less serious adverse events

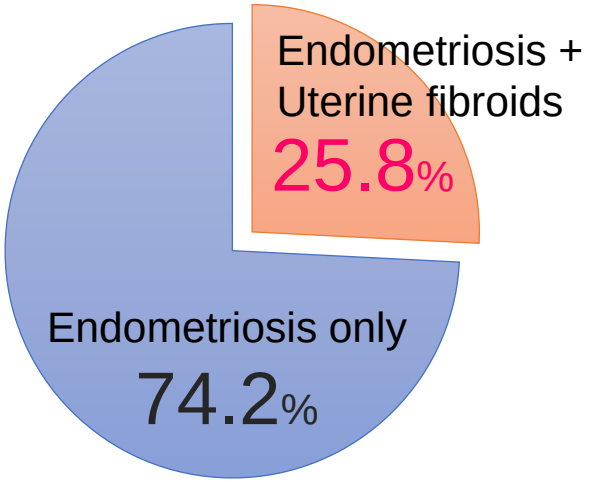
1. 異位寧 (Visanne) 醫療科技評估報告. Available at: http://nihta.cde.org.tw/ReadFile/?p=Assess&n=2755960d-5630-47c4-ac57-d60e216de157.pdf. Accessed on June, 2018; **2.** Common drug review. CADTH. Available at: https://www.cadth.ca/media/cdr/complete/cdr_complete_Visanne_April-20-12.pdf. Accessed on June, 2018.

Comorbidity of Endometriosis and Uterine Fibroids

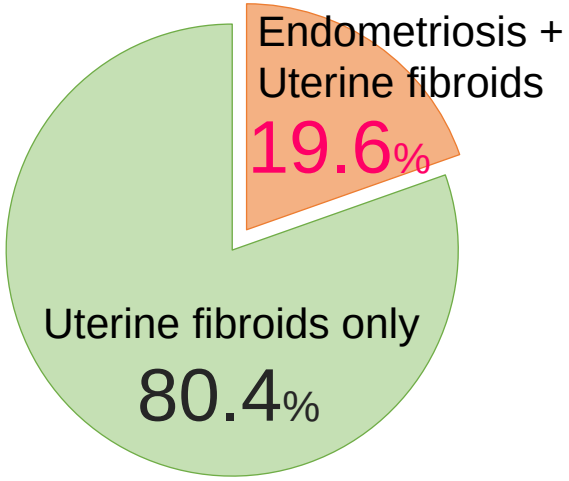
These two disorders may be **associated with each other** and that their **etiology has some similarities**

- Steroid hormone-dependent
- Inflammatory response

The prevalence of the comorbidity of endometriosis and uterine fibroids



Uterine fibroids were detected in 25.8% of patients with endometriosis.



Endometriosis was detected in 19.6% of patients with uterine fibroids.

Uimari O et al. J Hum Reprod Sci. 2011;4(1):34-8

Endometriosis and Breast Cancer

Kok et al. 2015

Endometriosis and breast cancer **share common risk factors:**[1]

- Hyperestrogenism
- Reproductive characteristics
- Obesity
- Hormone replacement therapy
- Type 2 diabetes

Mogensen et al. 2016

The risk for **breast cancer was increased** among women aged ≥50 years at first diagnosis of endometriosis (SIR 1.27; 95% CI: 1.12–1.42)[2]

SIR: Standardized incidence ratios

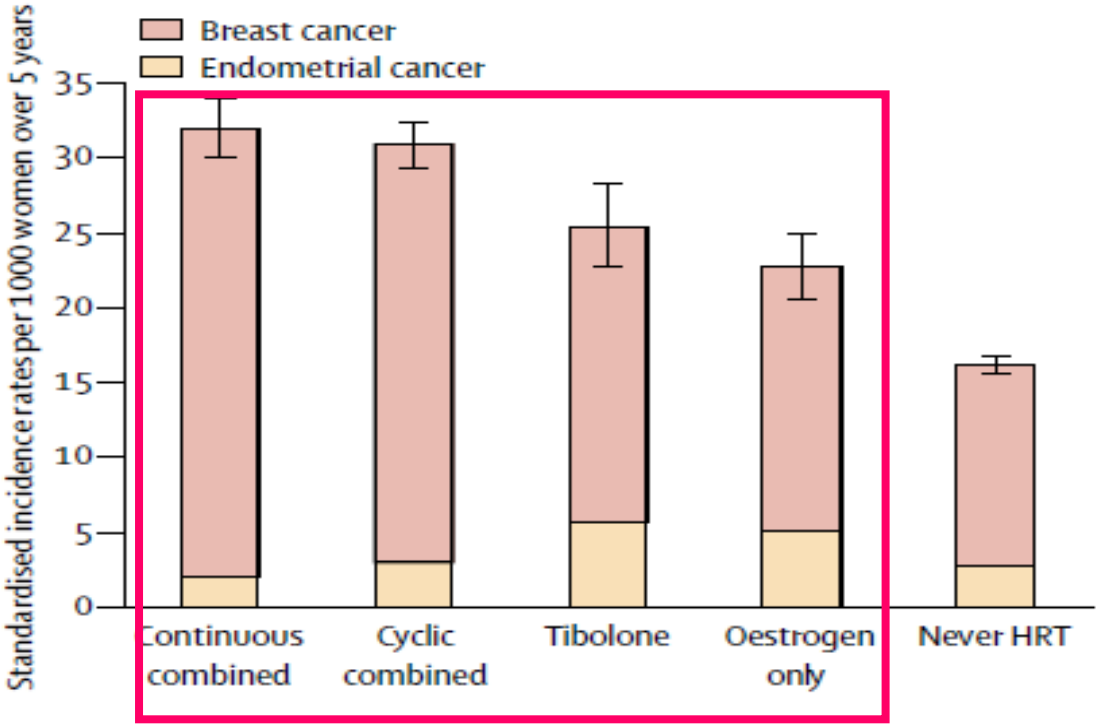
Choi et al. 2017

Adenomyosis exhibits comorbidity with leiomyoma, endometrial hyperplasia, endometrial cancer, and **breast cancer**[3]

1. Kok VC et al. Int J Gynecol Cancer. 2015;25(6):968-76; **2.** Mogensen JB, et al. Gynecol Oncol. 2016;143(1):87-92.
3. Choi EJ, et al. Obstet Gynecol Sci .2017;60(6):579-86.

HRT Causes a Greater Increase in Breast Cancer

- **Million Women Study**



Increased incidence in breast cancer

HRT: hormone replacement therapy.

Beral V, et al. Lancet 2005;365:1543-51.

The NEW ENGLAND JOURNAL of MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Contemporary Hormonal Contraception and the Risk of Breast Cancer

1.8 million women

Follow up

Average 10.9 years

11,517 cases of breast cancer occurred

Hormonal contraception

Variable	No. of Person-Yr	No. of Breast Cancer Events	Age-Adjusted Incidence Rate (no. of events/ 100,000 person-yr)	Adjusted Relative Risk (95% CI)	P Value	Age-Adjusted Risk Difference (95% CI) (no. of events/ 100,000 person-yr)
Never used hormonal contraception	7,815,180	5955	55	1.00 (Reference)		Reference
Used hormonal contraception >6 mo previously	4,348,722	2883	58	1.08 (1.03 to 1.13)		† 3 (1 to 6)
Duration of current or recent use of hormonal contraception						
Any hormonal contraception	7,308,437	2679	68	**1.20 (1.14 to 1.26)**	0.002	13 (10 to 16)
Combined oral contraceptives	6,424,088	1935	68	**1.19 (1.13 to 1.26)**	<0.001	13 (10 to 17)

Hormonal contraception causes a greater increase in breast cancer

Mørch LS, et al. N Engl J Med. 2017;377:2228-39.

Hormonal Contraceptive Increased the Risk of Breast Cancer

cer among Women
onal Contraception
ember 31, 2012.

Current or recent use of combined hormonal contraception	Were Followed until December 31, 2012.*		
	Adjusted Incidence Rate	Adjusted Relative Risk (95% CI†)	Age-Adjusted Risk Difference (95% CI)
			no. of events/100,000 person-yr
Oral combined ethinyl estradiol, 50 μg			
Norethisterone	55	1.00 (Reference)	Reference
Levonorgestrel	58	1.08 (1.03 to 1.13)	3 (1 to 6)
Oral combined ethinyl estradiol, 20 to 40 μg			
Norethisterone	46	1.01 (0.67 to 1.52)	−9 (−30 to 12)
Levonorgestrel	64	1.21 (0.93 to 1.59)	9 (−9 to 27)
Norgestimate	67	1.09 (0.80 to 1.50)	12 (−12 to 35)
Desogestrel	72	1.33 (1.20 to 1.48)	17 (9 to 25)
Gestodene	72	1.22 (1.20 to 1.48)	18 (5 to 30)
Drospirenone	64	1.12 (1.01 to 1.25)	9 (1 to 17)
Cyproterone	69	1.20 (1.11 to 1.30)	14 (8 to 20)
Estradiol valerate and dienogest	60	1.05 (0.86 to 1.28)	6 (−8 to 20)
Nonoral combined hormonal contraception	90	1.44 (1.15 to 1.81)	36 (11 to 60)
Patch	101	1.62 (0.77 to 3.41)	46 (−30 to 122)
Vaginal ring			
Current or recent use of progestin-only products			
Oral contraceptive	60	0.85 (0.21 to 3.41)	5 (−1 to 11)
Norethisterone	53	0.97 (0.62 to 1.50)	−2 (−32 to 28)
Levonorgestrel	58	1.00 (0.80 to 1.25)	3 (−10 to 16)
Desogestrel	102	1.93 (1.18 to 3.16)	47 (−4 to 99)
Nonoral contraceptive	69	1.18 (0.87 to 1.60)	14 (−8 to 36)
Implant	46	0.93 (0.48 to 1.79)	−9 (−42 to 25)
Levonorgestrel-releasing intrauterine system	70	1.21 (1.11 to 1.33)	16 (9 to 22)
Depot medroxyprogesterone acetate	51	0.95 (0.40 to 2.29)	−4 (−49 to 42)

sis, parity, and family history of premenopausal breast or ovarian cancer.

Leuprolide was NOT included

The risk of breast cancer was higher among women who **currently or recently used contemporary hormonal contraceptives** than among women who had never used hormonal contraceptives, and this **risk increased with longer durations of use**.

Mørch LS, et al. N Engl J Med. 2017;377:2228-39.

Contraceptives and Venous Thromboembolism

Monica V. Dragoman[1]
2018

Combined oral contraceptives (COCs) containing various progestogens could be associated with **differential risks for venous thromboembolism** (VTE)

EL. Moigne[2]
2016

- Choice of **contraception** after venous thromboembolism (VTE) is challenging because **hormonal contraception may increase the risk of recurrent VTE.**
- Estrogen contraception is usually **contraindicated in women with a personal history of VTE**

VTE: venous thromboembolism

1. Dragoman MV, et al. Int J Gynaecol Obstet. 2018;141(3)287-94. **2.** Le Moigne E, et al. Haematologica. 2016;101(1);e12-4.

HRT Causes a Greater Increase in Breast Cancer and Venous Thromboembolism

Medical treatment endometriosis[1]

NSAIDs

GnRH agonist

COCPs

Progestin

LNG-IUS

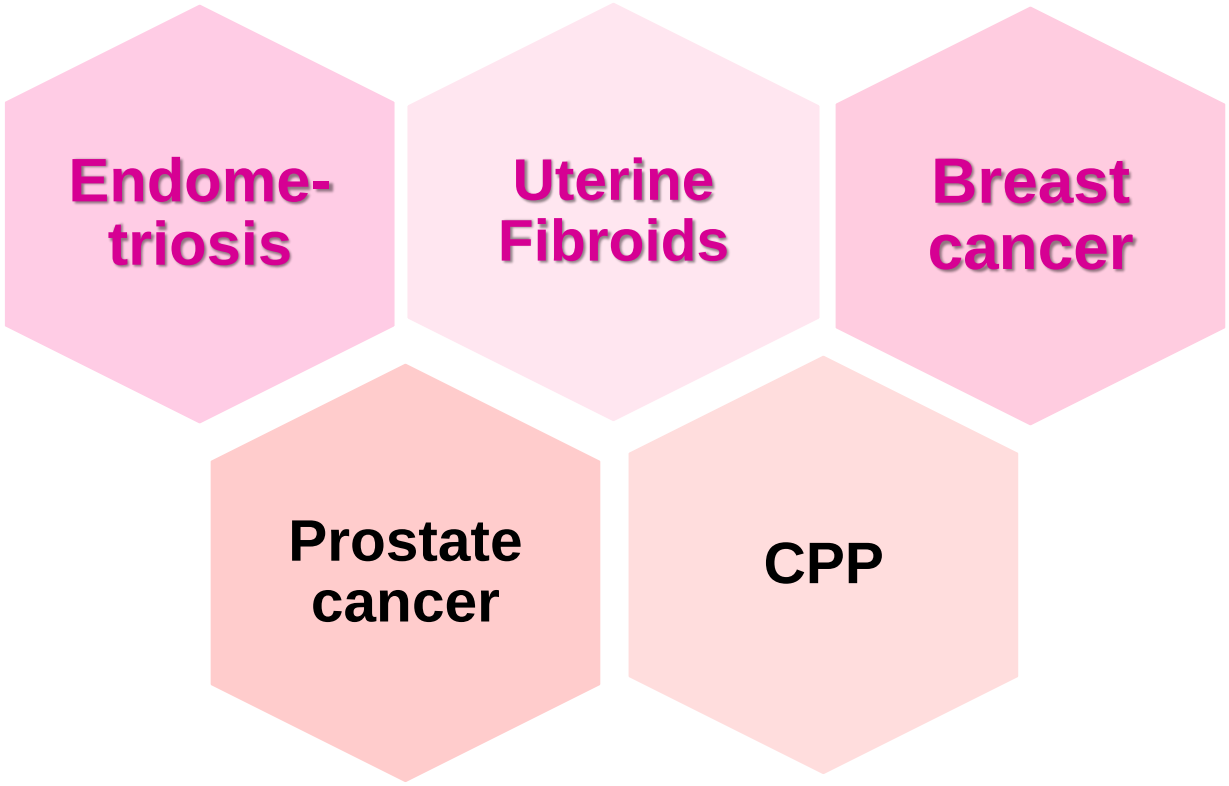
Hormone replacement therapy

May increase the development of **breast cancer and venous thromboembolism**[2,3]

HRT: hormone replacement therapy; NSAID: Non-steroidal anti-inflammatory drug
GnRH agonist: Gonadotropin-releasing hormone agonist; COCPs: combined oral contraceptive pills; LNG-IUS: Levonorgestrel-releasing intrauterine system

1. Parasar P, et al. Curr Obstet Gynecol Rep. 2017;6(1):34-41; **2.** Mørch LS, et al. N Engl J Med. 2017;377:2228-39.
3. Le Moigne E, et al. Haematologica. 2016;101(1);e12-4.

Leuplin® Indications



CPP: Central precocious puberty.

Leuplin® in WHO Model List

- 2017

World Health Organization

WHO Model List of Essential Medicines

Leuprolide - The best evidence for effectiveness and safety

20th Essential Medicines List (2017). Available at: http://www.who.int/medicines/news/2017/20th_essential_med-list/en/. Accessed on June, 2018.

Medical Treatment for Endometriosis[1-9]

	GnRH agonist Leuplin	Danazol 200 mg	Gestrinone 2.5 mg	MPA 5 mg	Dienogest 2 mg
適應症	子宮內膜異位症			子宮異常出血	子宮內膜異位症伴隨之骨盆腔疼痛
用法用量	每 4 週注射一次；長效 3 個月注射一次	200 - 800 mg/day	每週二次，每次一顆	30 - 60 mg/day	每日一錠
常見/特殊副作用	• 更年期障礙（抑鬱） • 骨質密度降低 • Add-back therapy 可改善副作用	皮膚產生粉刺、斑點及油膩、體重增加、熱潮紅、聲音改變等		乳房觸痛、不正常子宮出血、頭痛、敏感反應等	• 乳房不適、不正常子宮出血、頭痛、情緒低落、 痤瘡、水腫等 • **可能增加靜脈血栓栓塞、凝血功能異常、乳癌細胞增生等風險** • **嚴重不良事件發生率高於 leuprolide，分別為4.2%及0.8%[9]**
Estradiol	↓↓↓	↓↓	↓ (12~208 pg/ml)	-	↓ (39~79 pg/ml)
FSH	<1	Unchanged	Unchanged	-	Unchanged
LH	<1	Max 12	Max 12	-	Max 9.7
抑制排卵	✓ (E2濃度≒停經期)	✓	✓	✓	✓
懷孕分級	X	X	X	X	(B [AUS])
停藥後回復排卵	28+43-14 天	-	-	-	2 個月內

MPA: medroxyprogesterone acetate

1. Leuplin 仿單. **2.** Gestrinone 仿單. **3.** Danazol 仿單. **4.** MPA 仿單. 5. Dienogest 仿單. **6.** Klipping C, et al. J Clin Pharmacol. 2012;52:1704-13. **7.** Nobukata H, et al. Toxicol Lett. 1999;104:93-101. **8.** Klipping C, et al. J Clin Pharmacol. 2012;52:1704-13. **9.**.異位寧 (Visanne) 醫療科技評估報告. Available at: http://nihta.cde.org.tw/ReadFile/?p=Assess&n=2755960d-5630-47c4-ac57-d60e216de157.pdf. Accessed on June, 2018

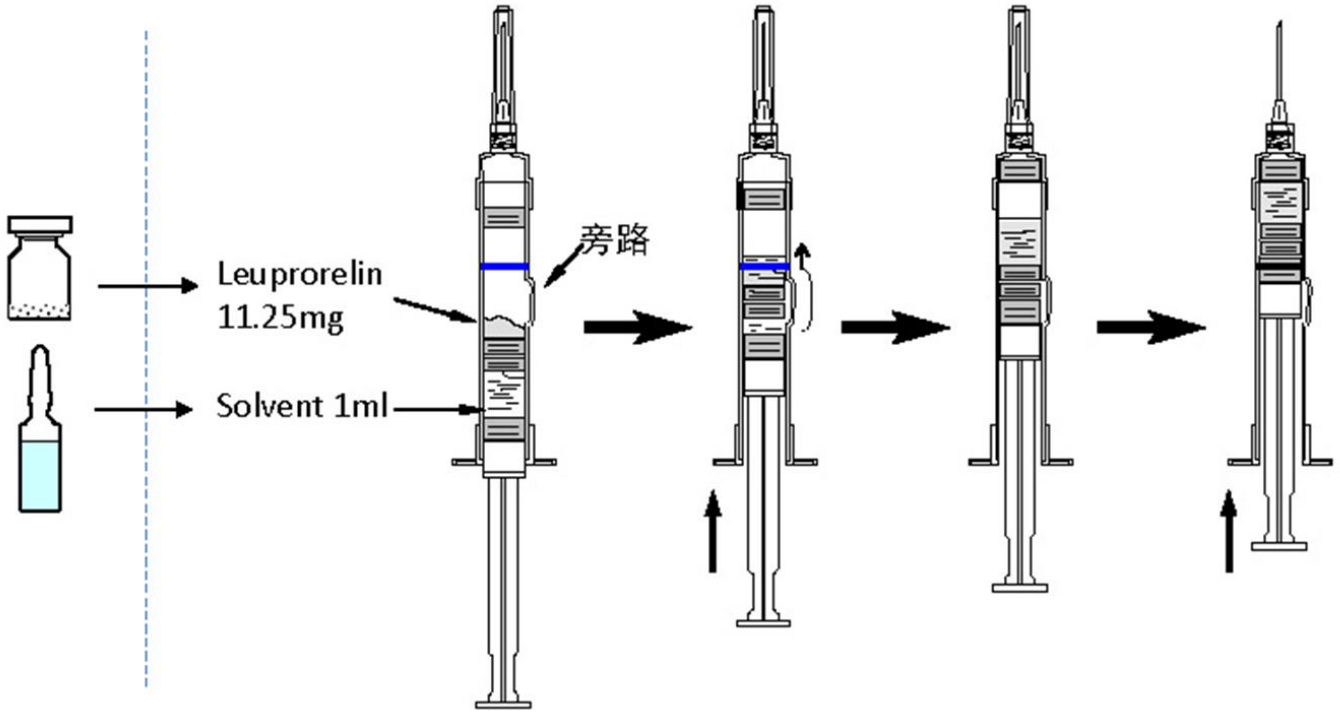
Advantages of Leuplin®

- 獨特微球體技術(20-30 μm)，穩定釋出維持3個月
- 23 或 25 號小針頭，減低患者不適，增加病患順從性
- 注射部位可選擇上臂、腹部或臀部
- 安定性佳，可存放於室溫25℃以下
- 每一個月或三個月注射一針，減少注射次數，
  對於交通不便或復發之患者，生活品質提高

1. Leuplin Depot 1M 3.75 mg S.C. Injection 中文仿單; 2.Leuplin Depot 3M 11.25 mg S.C. Injection 中文仿單.

Advantages of Leuplin®

- **All in one** **design which is simple and convenience.**
- **No reconstitution** **is needed.**



1. Leuplin Depot 1M 3.75 mg S.C. Injection 中文仿單; 2.Leuplin Depot 3M 11.25 mg S.C. Injection 中文仿單.

補充leuplin 1M及3M的用法用量

柳菩林®持續性藥效皮下注射劑

【適應症】

前列腺癌舒解治療、子宮內膜異位、中樞性性早熟症、因子宮肌瘤引起之經血過多及貧血而預計進行手術切除者、停經前乳癌。

【用法用量】

Leuplin®	子宮內膜異位症	子宮肌瘤	停經前乳癌
1M 3.75 mg	通常**每 4 週皮下注射** Leuprorelin acetate 3.75mg 一次，在月經開始的第 1~5 天打第一針，**推薦治療期為 6 個月**。	因子宮肌瘤引起之經血過多及貧血而預計進行手術切除者使用本藥時**建議不超過三個月**，通常**每 4 週皮下注射** Leuprorelin acetate 1.88~3.75mg 一次，依病人的症狀可適度調整用 量。在月經開始的第 1~5 天打第一針。	通常**每 4 週皮下注射** Leuprorelin acetate 3.75mg 一次。
3M 11.25 mg	單一療法或併用 norethindrone acetate 的合併療法，所建議的治療持續時間是 6 個月。 若結束 1 個療程後子宮內膜異位症的**症狀復發，可考慮重新接受 6 個月的柳菩林持續性藥效注射劑**合併每天norethindrone acetate 5 mg 的治療。不建議重新治療的持續時間超過 6 個月。 建議在開始重新治療前，先評估病人的骨密度，確定骨密度確實在正常範圍內。 不建議使用柳菩林持續性藥效注射劑單一療法進行重新治療。 若病人無法使用norethindrone acetate，則不建議進行重新治療。	柳菩林三個月持續性藥效注射劑 11.25 毫克的建議劑量是 1 次注射。在停止治療後，子宮肌瘤的相關症狀會復發。 若考慮額外進行柳菩林三個月持續性藥效注射劑 11.25 毫克治療，則在開始進行治療前應先評估病人的骨密度，確定骨密度確實在正常範圍內。	當以本品開始治療前，應按規定確認賀爾蒙受體表現力是否存在。當確認賀爾蒙受體表現力為陰性時則不能使用本品。

【副作用】

大部分因為**雌激素的降低**引起症狀、注射部位不適主觀及客觀的副作用。主要副作用有：潮熱感、熱感、肩僵硬、頭痛、失眠、眩暈、發汗等症狀。有時會出現像更年期障礙一樣的**抑鬱狀態**(0.1%-<5%)，故應充分觀察病人的狀態。

1. Leuplin Depot 1M 3.75 mg S.C. Injection 中文仿單; 2.Leuplin Depot 3M 11.25 mg S.C. Injection 中文仿單.

Take Home Messages

Leuprolide effectively:[1-5]

- **inhibited endometriosis-related pain** and **inflammation**
- **induced apoptosis**
- **reduced risk of subsequent surgery**
- **improved quality of life**
- **higher ongoing pregnancy rates**

Guidelines recommended **GnRH agonists (leuprolide)** use in endometriosis patients.[6]

Leuplin® provides 1-month and 3-month **depot microsphere formulation** with **finer needle** and **easy preparation.**[7,8]

WHO
Essential Medicines List

Leuprolide -
The best evidence for effectiveness and safety.[9]

1. Morelli M, et al. Gynecol Endocrinol, 2013;29(4):305-8; **2.** Khan KN, et al. Hum Reprod. 2010;25(3):642–53; **3.** Muneyyirci-Delale O, et al. Fertility and Sterility. 2014;102(3):e14. **4.** Soliman AM, et al. Curr Med Res Opin. 2016;32(6):1073-82; **5.** Surrey ES, et al. Fertil Steril. 2002;78(4);699-704; **6.** Working group of ESGE, ESHRE, and WES, et al. Gynecological Surgery 2017;14:27; **7.** Leuplin Depot 1M 3.75 mg S.C. Injection 中文仿單; **8**.Leuplin Depot 3M 11.25 mg S.C. Injection 中文仿單; **9.** 20th Essential Medicines List (2017). Available at: http://www.who.int/medicines/news/2017/20th_essential_med-list/en/. Accessed on June, 2018.

1110611台灣東部婦產科臨床學術研討會

題目—陰道雷射用於女性應力性尿失禁之經驗分享

李佩蓁
花蓮慈濟醫院婦產部主治醫師

摘要

應力性尿失禁定義為腹壓增高時的不自主漏尿, 在婦女盛行率約為25-45%, 影響族群非常廣泛, 並且隨著年齡的增長而增加, **懷孕、生產、停經、肥胖、便秘及吸菸等均是女性應力性尿失禁的危險因子**, 應力性尿失禁不僅嚴重降低女性患者的日常生活品質, 也會限制社交活動, 造成心理及生理的障礙。陰道雷射用於女性應力性尿失禁近年已有許多臨床研究發表, 主要原理是透過光熱效應, 加熱黏膜組織, 刺激陰道壁的膠原蛋白重組與增生, 達到骨盆筋膜與結締組織緊縮的效果, 陰道雷射治療適應症為產後陰道鬆弛、更年期生殖泌尿症候群，包括外陰部、陰道萎縮、乾燥、搔癢、輕度尿失禁、輕度膀胱、子宮、直腸膨出、急尿、頻尿、及膀胱過動症等患者。不需麻醉, 恢復期短, 一次治療即可改善, 可重複治療維持效果, 對於不想動刀的女性來說是很好的選擇。目前較廣泛應用的陰道雷射為波長2940 nm的鉺雅克雷射及波長10,600 nm的二氧化碳雷射，本院比較兩種陰道雷射用於輕度及中度尿失禁病患, 評估其對漏尿的改善效果。

Robotic surgery implemented indocyanine green in endometrial cancer

陳盈希

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Abstract

Robotic surgery has more advantages than laparoscopy surgery. Robotic surgery has 3D and in-depth perception, camera stability, no limited range of motion, and short learning curves [1]. The feasibility and safety are comparable to laparoscopic surgery.

Endometrial cancer has become the most prevalent gynecologic cancer. Endometrial cancer is also the most common indication for the use of the robotic platform in gynecology oncology, especially in obese and morbidly obese patients [2]. Robot-assisted hysterectomy may be a generally safer and better option than an open and laparoscopic hysterectomy for patients with endometrial cancer [3].

Sentinel lymph node (SLN) mapping is aimed to reduce the morbidity of a full staging procedure. Indocyanine green (ICG) is used to identify SLN and has a high degree of diagnostic accuracy. A multicenter prospective cohort study showed that SLN identified with ICG has a sensitivity of 97.2% (95% CI: 85 – 100), and a negative predictive value of 99.6% (95% CI: 97.9 – 100) in early-stage EC. This suggests that SLN detection by ICG can safely replace systematic lymphadenectomy [4].

In conclusion, robotic surgery can be safely applied to gynecologic oncology. ICG techniques implemented with robotic surgery can efficiently identify SLN in endometrial cancer surgeries. A video illustrating robotic surgery with

ICG in detecting SLN in a patient with endometrial cancer will be shown in th e lecture.

References

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