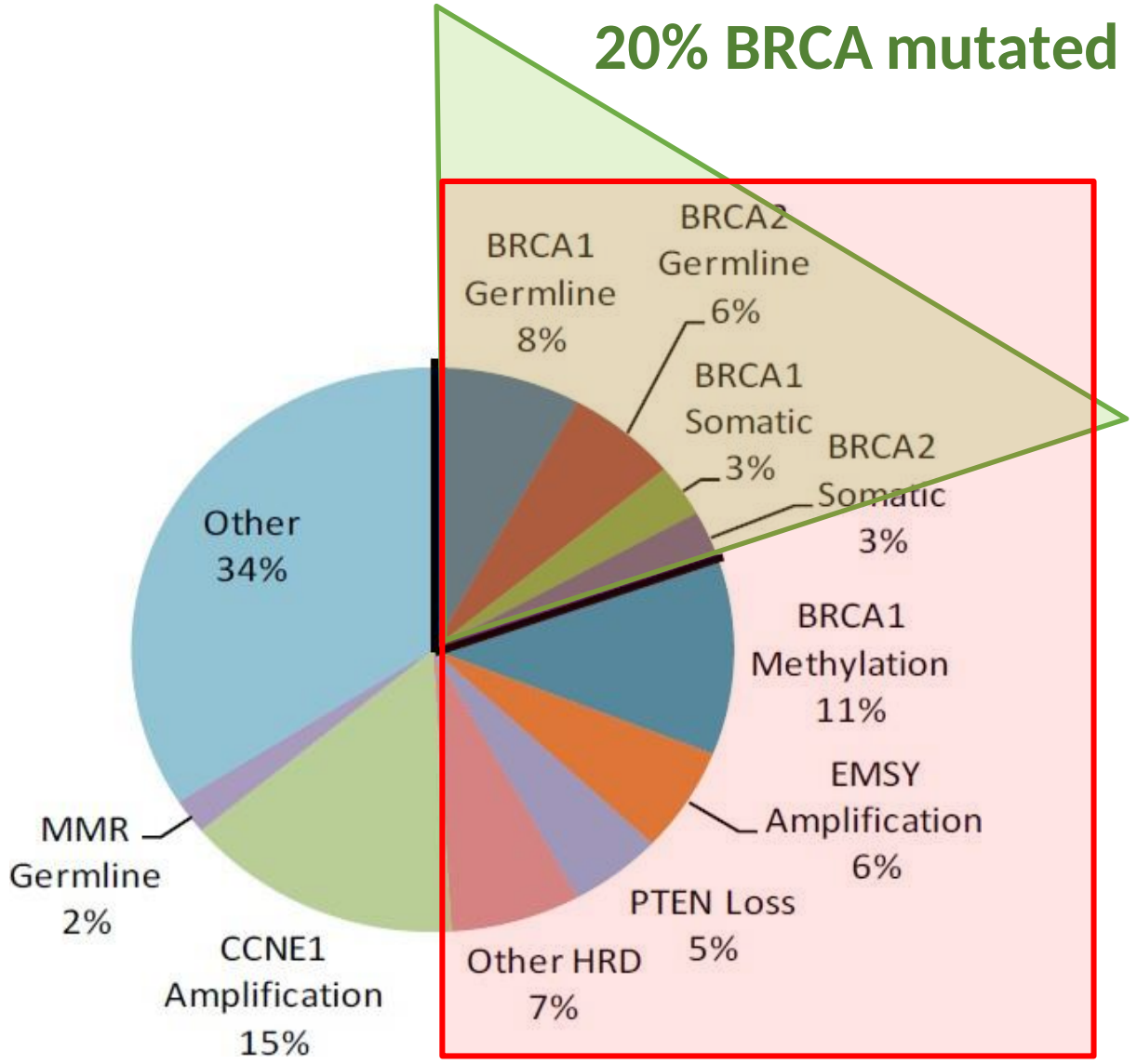
PARPi monotherapy in recurrent ovarian cancer

吳華席

April, 2022

High grade serous carcinoma

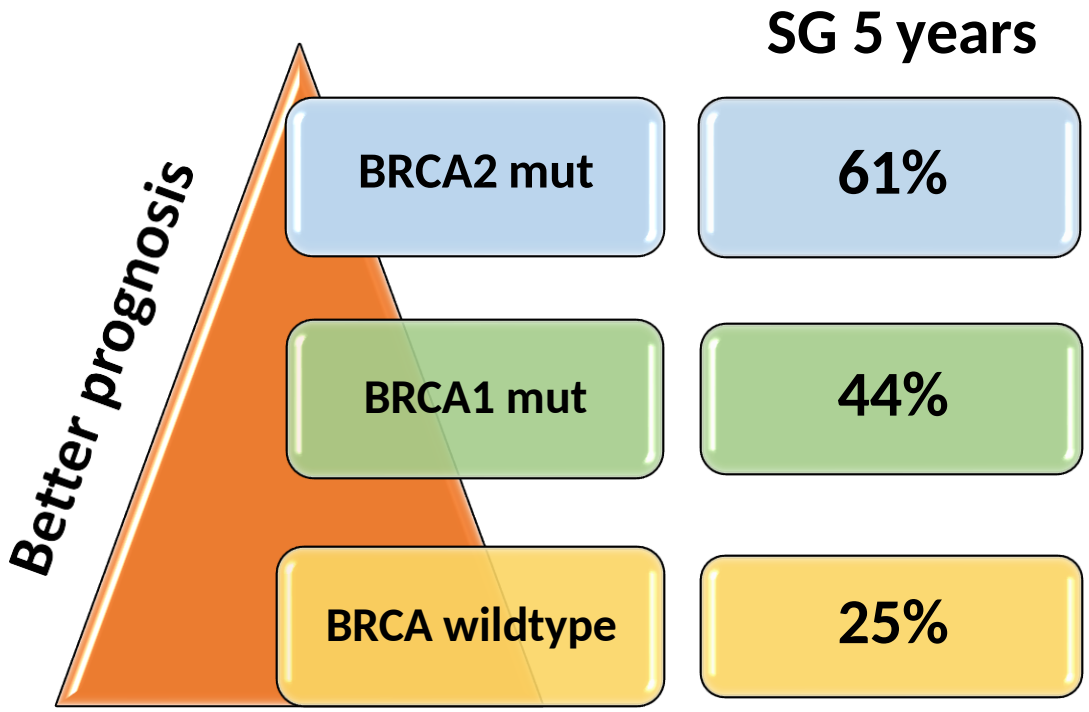
BRCA mutations and HRD



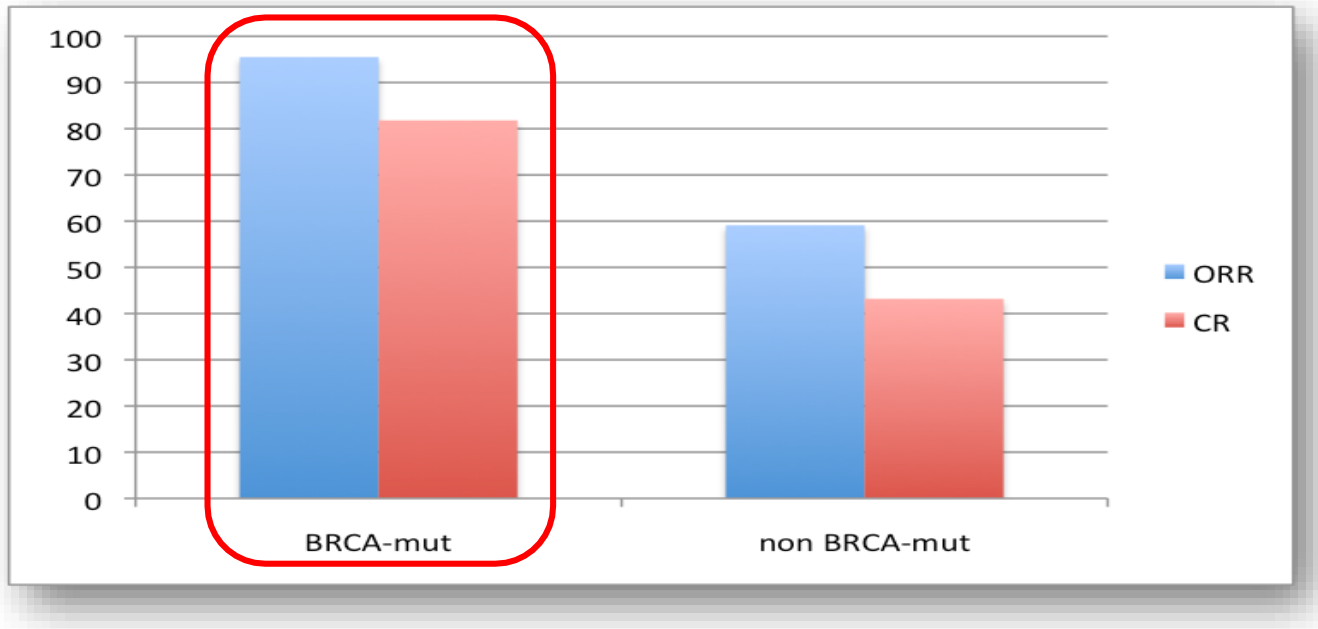
TGCA, Nature 2011

BRCA mutations

Prognostic and predictive role



<u>Responses to platinum</u> in BRCA and non-BRCA-mut



Yang et al. JAMA 2011
Tan et al. J Clin Oncol 2008

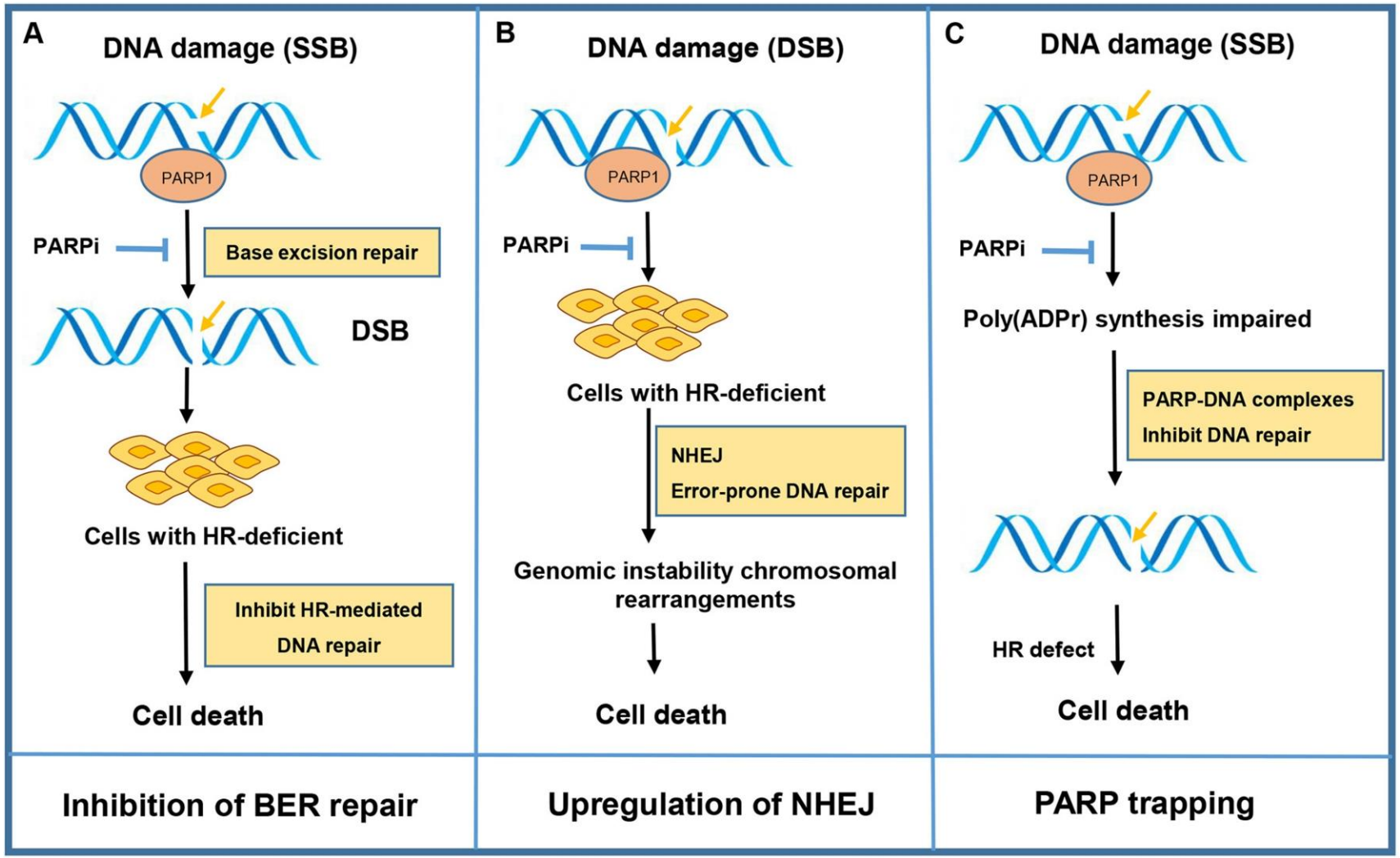
Homologous Recombination Deficiency (HRD)

How can we identify it?

- **DNA-based measures of genomic instability** reflecting underlying tumor HRD:
  - Loss of heterozygosity (LOH)
  - Telomeric allelic imbalance (TAI)
  - Large-scale state transitions (LST)

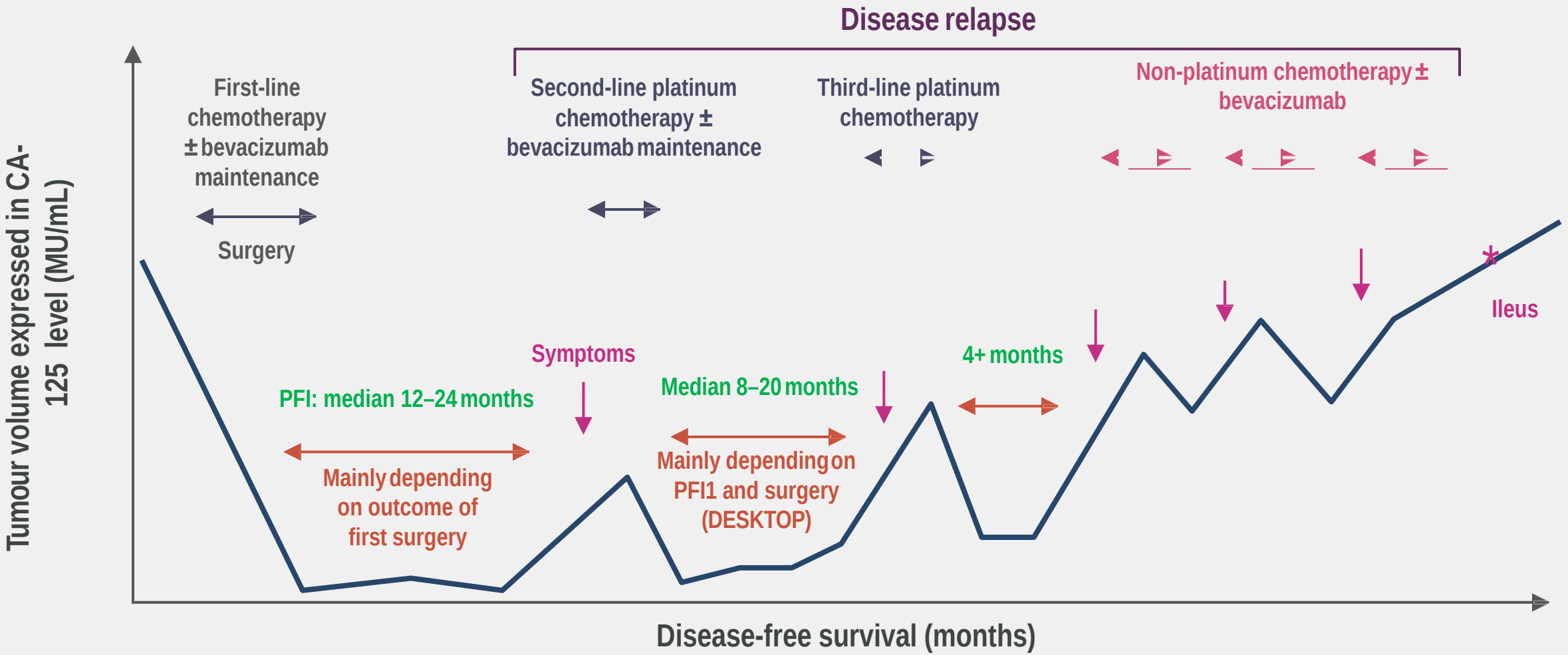
Test LOH Foundation Medicine	Test MyChoice® Myriad
LOH	LOH, LST, TAI
Rucaparib	Niraparib

The mechanisms of cytotoxicity of PARPi



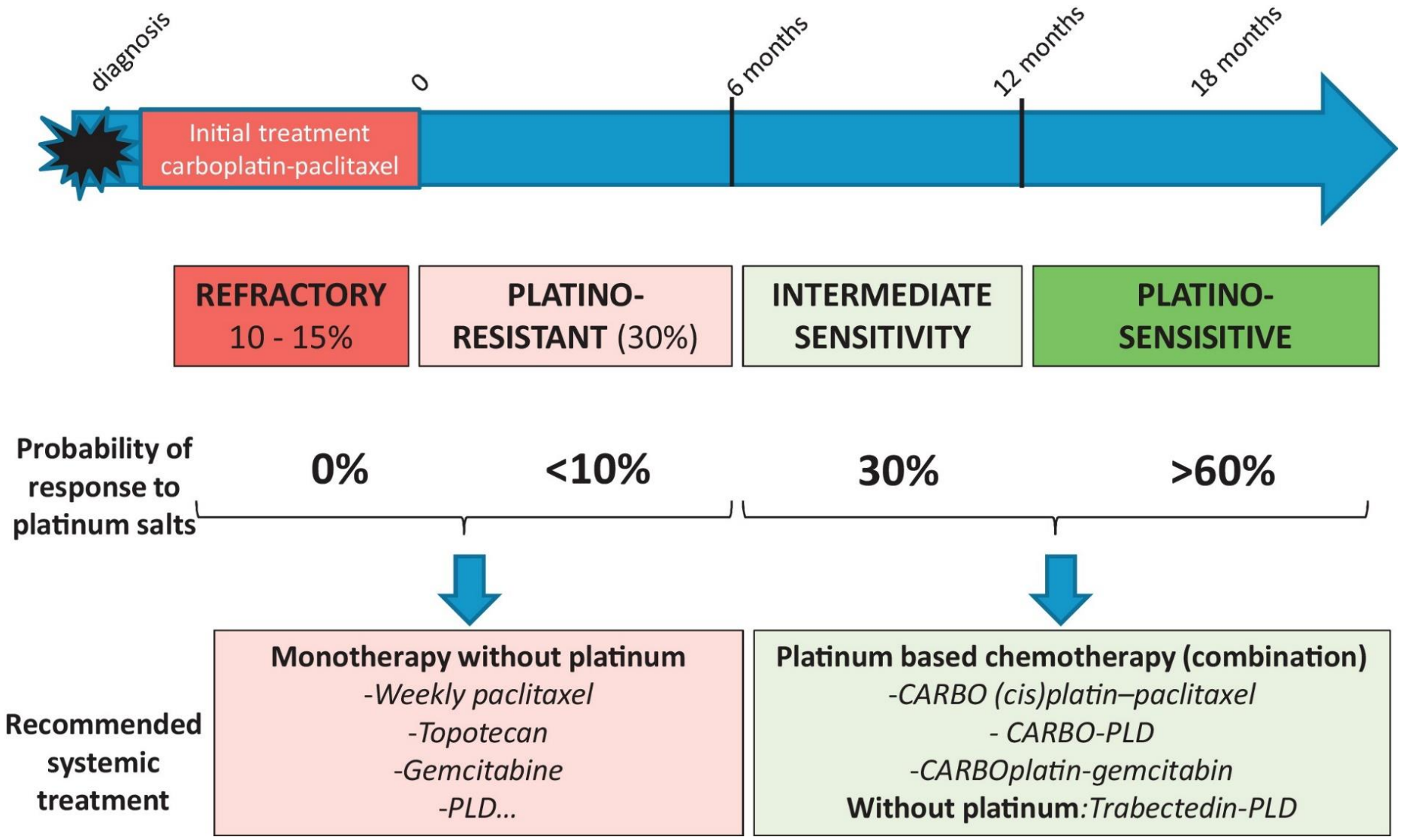
Biomedicine & Pharmacotherapy, Volume 127, July 2020

Advanced ovarian cancer is characterised by multiple relapses



CA-125, cancer antigen-125; PFI, progression-free interval Adapted from: Giornelli GH. *Springerplus* 2016;5:1197

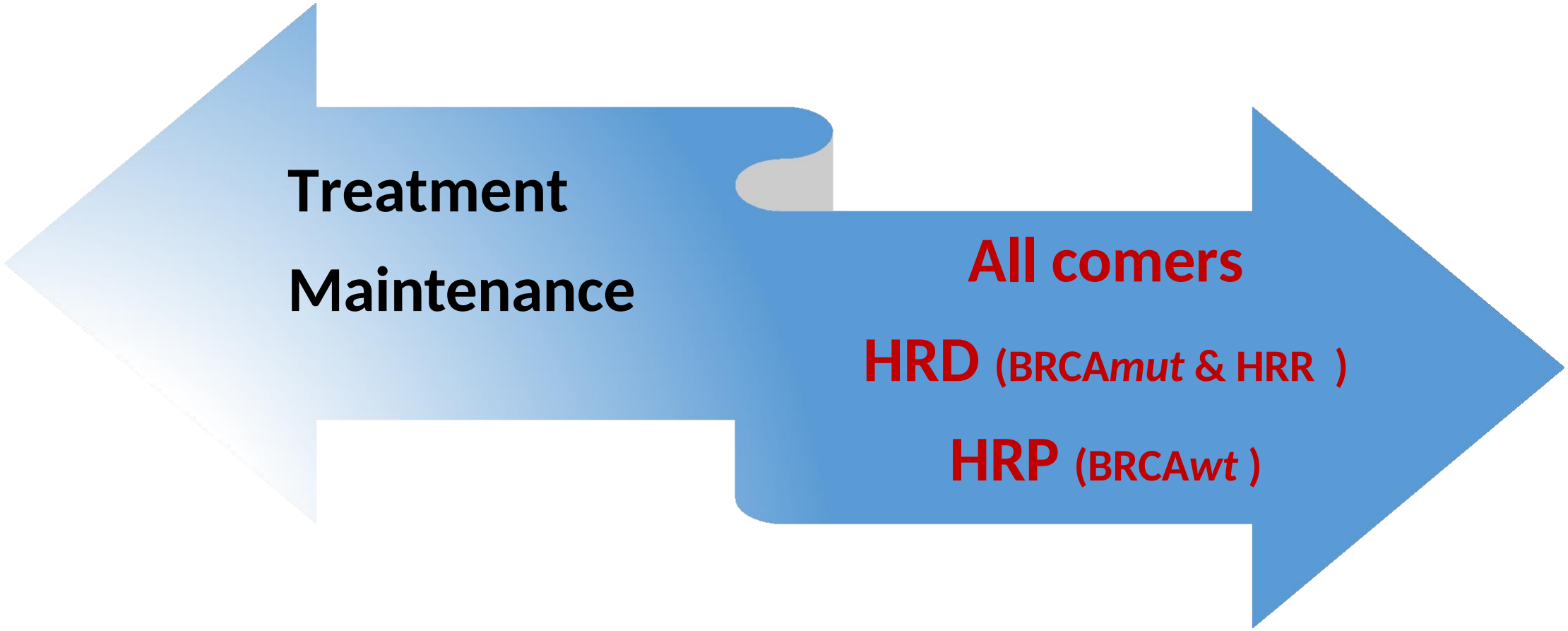
Clinical prediction of response to platinum salts



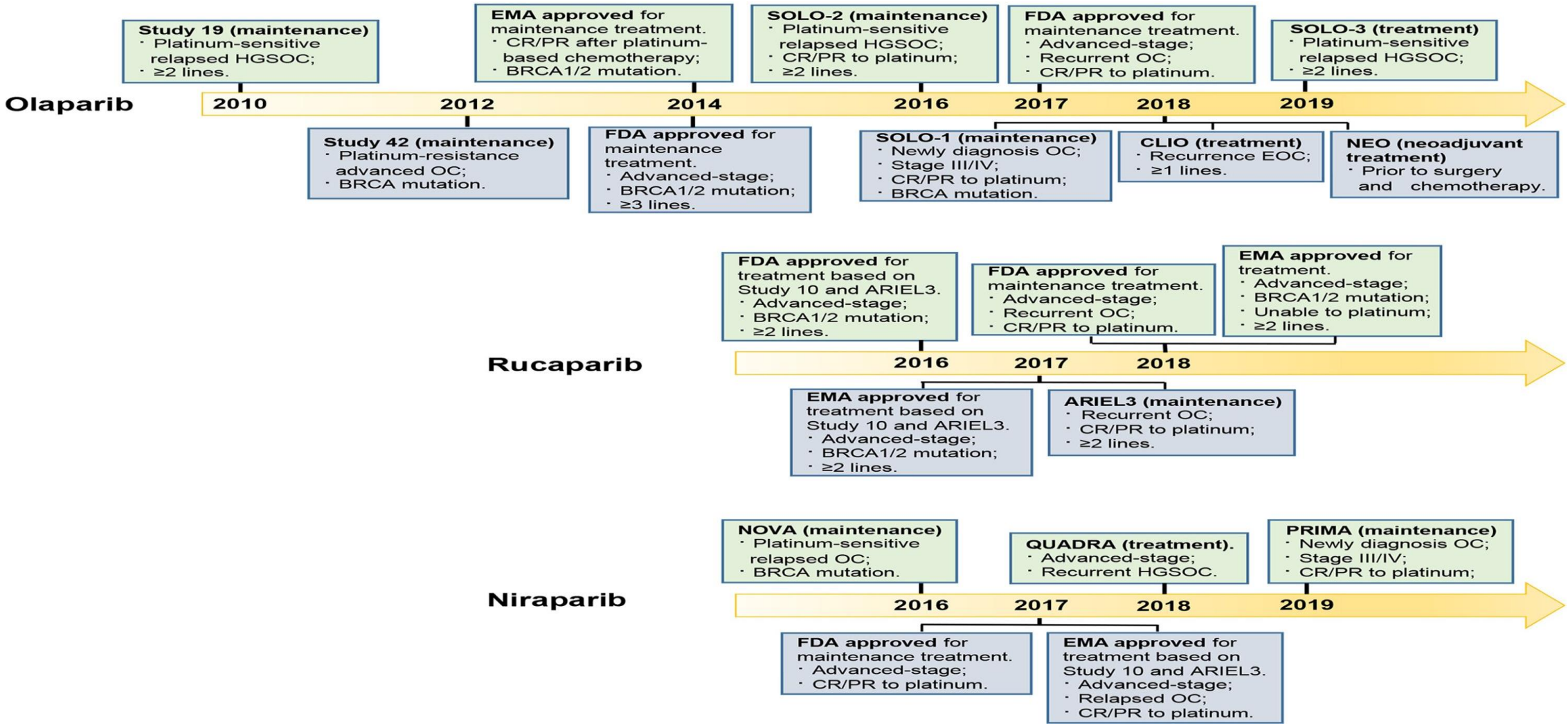
Critical Reviews in Oncology/Hematology
Volume 89, Issue 2, February 2014, Pages 207-216

Development of PARPi in recurrent ovarian cancer

Platinum-sensitive vs Platinum resistant



The developmental history of PARPi in the monotherapy or maintenance treatment for ovarian cancer patients.



PARP inhibitors in recurrent ovarian cancer
<Clinical trials>

Agent	Treatment Monotherapy		Maintenance	
	BRCA mut	All comers	BRCA mut	All comers
Olaparib	Ph II Study 42 Ph III SOLO-3	Ph IIR CLIO	Ph III SOLO-2	Ph IIR Study 19
Niraparib	-	Ph II Quadra	-	Ph III NOVA
Rucaparib	Ph II ARIEL-2 y St. 10	Ph II Ariel 2 Part1	-	Ph III ARIEL-3

PARPi monotherapy:

Olaparib, Rucaparib, Niraparib

<Phase II studies>

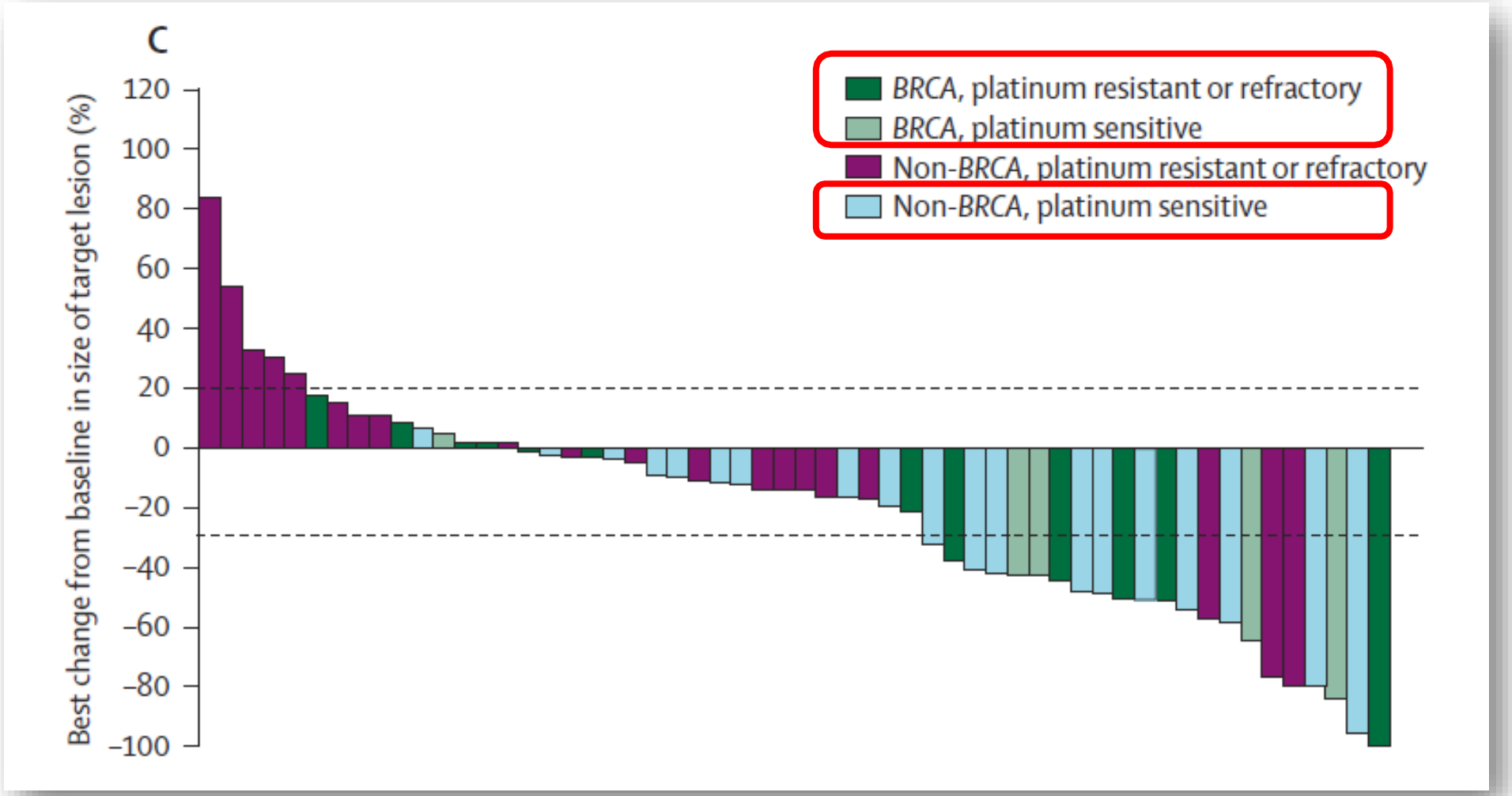
	Olaparib[1] Study 42	Rucaparib[2] Study-10 & ARIEL-2	Niraparib[3] QUADRA
Prior number of lines	≥ 3 lines	≥ 2 lines	> 3 lines
Biomarker	BRCAmut	BRCAmut	HRD+, Plat-S (expanded primary population)
N	137	106 (74.5% Plat-S)	51 (plat-S)
ORR	34%	53.8%	27%
Median PFS (months)	7	10	-
Median DOR (months)	7.9	9.2	9.4
Approval	FDA	FDA and EMA (Plat-S)	-

1. Kaufman B et al.. J Clin Oncol 2015; 33(3): 244–250. 2. Oza et al. Gyn Oncol 2017; 147 (2017) 267–275 3. Moore K et al. ASCO 2018

故事就是這樣開始

Monotherapy : Olaparib

<First study in ovarian cancer>



Gelmon KA *et al*. *Lancet Oncol* 2011

Study 42: "Olaparib Monotherapy" in Advanced Cancers With Germline *BRCA1/2* Mutations

- Multicenter phase II clinical trial of **olaparib 400 mg BID** in patients with germline *BRCA1/2* recurrent solid tumors (N = 298)
  - **Ovarian** cancer with platinum resistance
  - **Breast** cancer with ≥ 3 regimens for MBC
  - **Pancreatic** cancer with prior gemcitabine
  - **Prostate** cancer with 1 prior systemic therapy and progression on hormonal therapy
- Primary endpoint: tumor response rate
- **Results: responses to olaparib observed across tumor types with germline *BRCA1/2* mutations**

Response, n (%)	Ovarian Cancer (n = 193)	Breast Cancer (n = 62)
Tumor response	60 (31.1%) [95% CI: 24.6-38.1]	8 (12.9) [95% CI: 5.7-23.9]
▪ CR	6 (3%)	0 (0)
▪ PR	54 (28%)	8 (13)
SD ≥ 8 wks	78 (40%) [95% CI: 33.4-47.7]	29 (47) [95% CI: 34.0-59.9]
▪ SD	64 (33)	22 (36)
▪ PRu	12 (6)	7 (11)
PD	41 (21) [95% CI: 15.7-27.7]	23 (37) [95% CI: 25.2-50.3]
▪ PD by RECIST	33 (17)	16 (26)
		7 (11)

193 platinum-resistant/refractory patients or platinum-sensitive but in eligible to receive further platinum-based chemotherapy

Kaufman. JCO 2015;33:244.

Slide credit: clinicaloptions.com

On December 19, 2014, the FDA approved

ROC : ***gBRCAm*** **+** **>= 3 lines p-based C/T**

- **olaparib capsules** (Lynparza; AstraZeneca) for the treatment of patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.

- The **BRACAnalysis CDx** (Myriad Genetic Laboratories, Inc.) was approved concurrently.

真正考驗，就在這裡:

- SOLO-3是在2014美國FDA首次加速核准olaparib時作為上市後要求 (Post Marketing Requirement) 而進行的試驗。

- 隨著tablet劑型上市，且FDA 核准olaparib tablet於PSROC之維持治療後 (根據SOLO-2及study19結果)， FDA也要求補足olaparib tablet於以上適應症之相關實證。

Olaparib in gBRCAmut in PSROC

SOLO-3 trial (*Phase III Olaparib vs C/T*)

看看對於先前接受至少兩線含鉑化療、具對鉑敏感且BRCA遺傳性突變之復發性卵巢癌患者，olaparib之療效?

Study Design

- Relapsed, high-grade serous or endometrioid ovarian, primary peritoneal, and/or fallopian tube cancer
- Germline BRCAm
- ECOG performance status 0–2
- ≥2 previous lines of platinum-based chemotherapy*
- Platinum sensitive†

Open-label

Study treatment administered until disease progression

Olaparib tablets 300 mg bid (n=178)

2:1 randomization

Stratified by:
- Selected chemotherapy‡
- Number of prior lines of chemotherapy
- Time to progression after previous platinum-based chemotherapy

Non-platinum chemotherapy§ (n=88)
- PLD (n=47)
- Paclitaxel (n=20)
- Gemcitabine (n=13)
- Topotecan (n=8)

Primary endpoint
- ORR by BICR (RECIST v1.1)

Secondary endpoints
- PFS
- PFS2
- OS
- TFST
- TSST
- HRQoL
- Safety

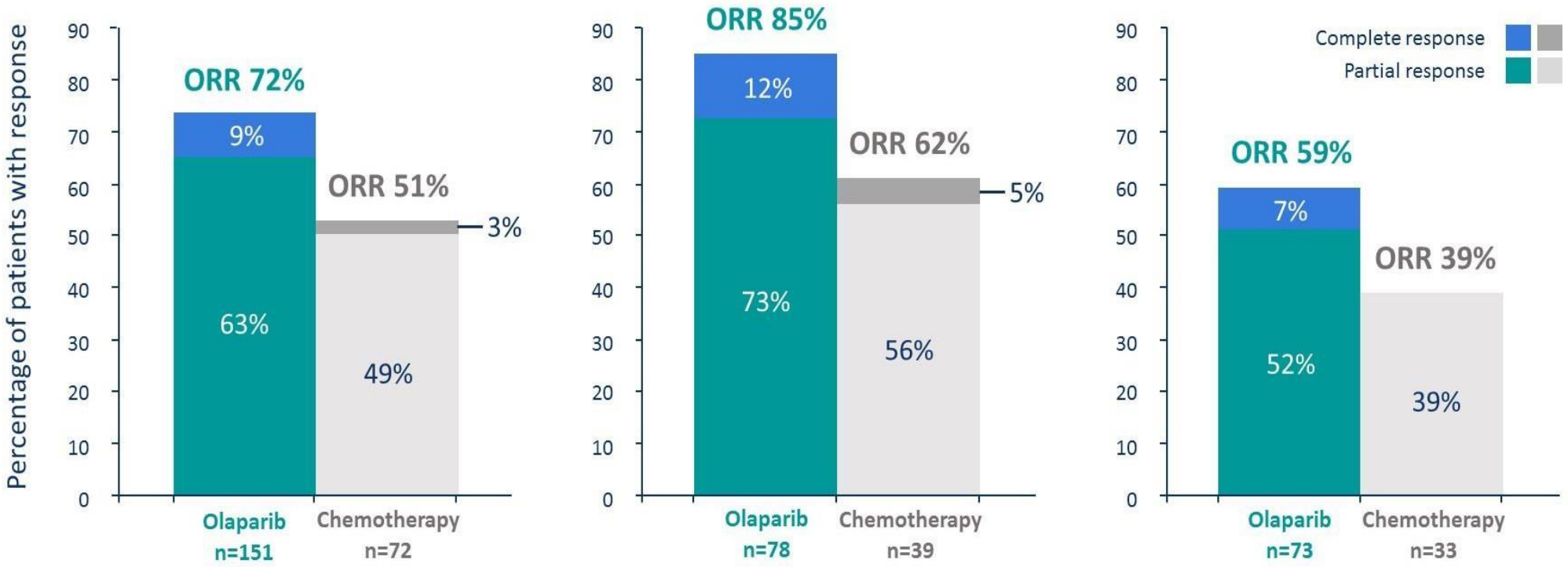
*Prior treatment with a PARP inhibitor was not permitted;

Penson at. ASCO 2019

Olaparib in *g*BRCAmut in PSROC

SOLO-3 trial (*Phase III Olaparib vs C/T*)

Primary Endpoint: ORR by BICR



All patients*

OR 2.53 (1.40, 4.58) *P*=0.002

Patients with 2 prior lines of chemotherapy*

OR 3.44 (1.42, 8.54)

Patients with ≥3 prior lines of chemotherapy*

OR 2.21 (0.96, 5.20)

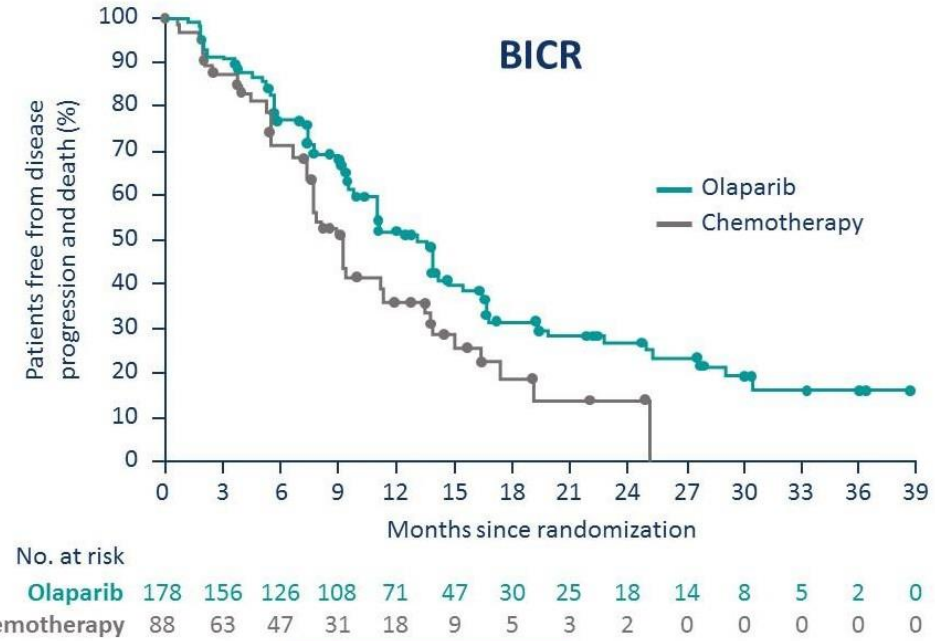
*Patients with measurable disease at baseline

Penson at. ASCO 2019

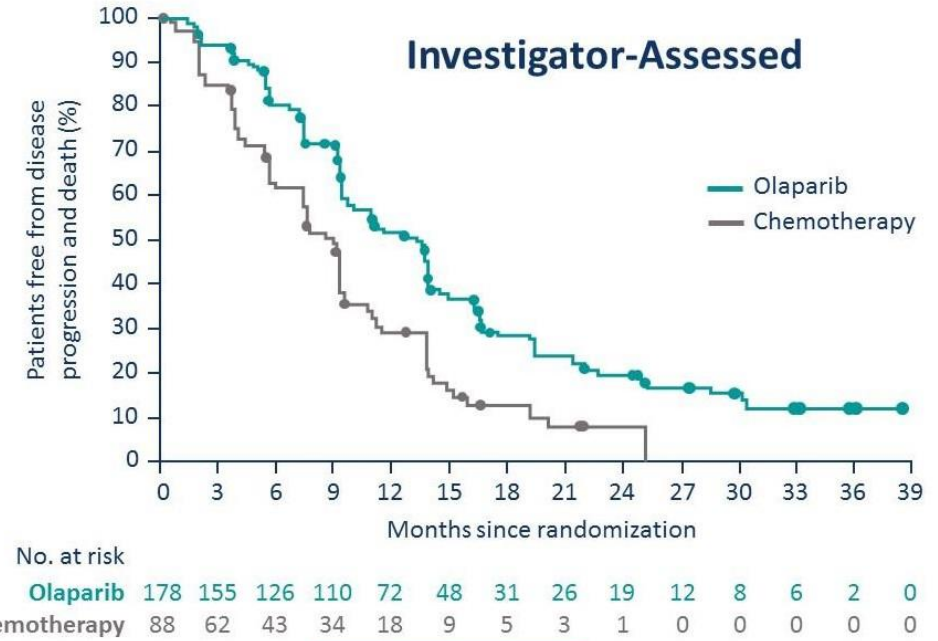
Olaparib in *g*BRCAmut in PSROC

SOLO-3 trial (*Phase III Olaparib vs C/T*)

PFS (Intention-To-Treat Population)



	Olaparib (n=178)	Chemotherapy (n=88)
PFS events, n (%)	110 (62)	49 (56)
Median PFS, months	**13.4**	**9.2**
HR (95% CI), *P* value	**0.62 (0.43, 0.91); *P*=0.013**	



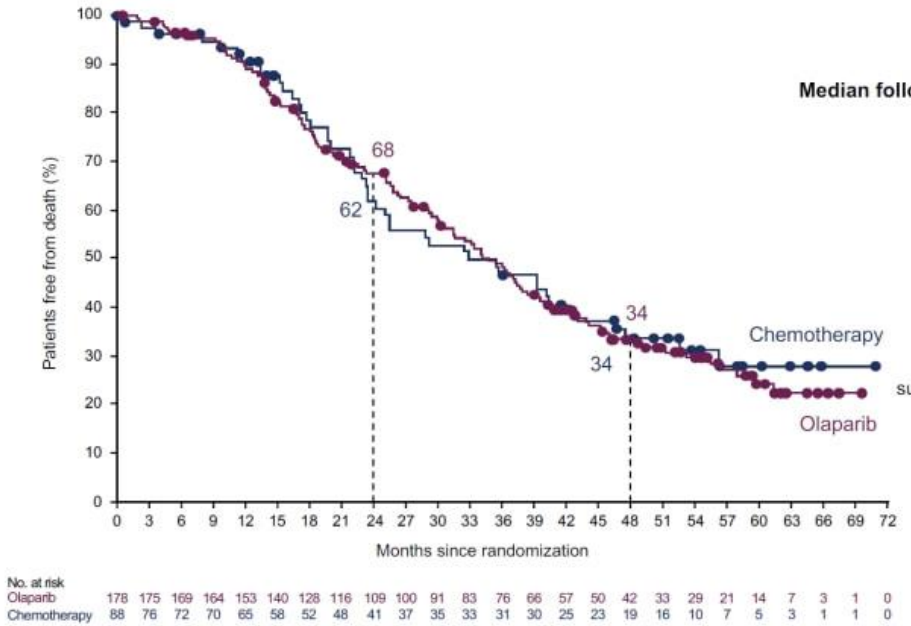
	Olaparib (n=178)	Chemotherapy (n=88)
PFS events, n (%)	123 (69)	63 (72)
Median PFS, months	**13.2**	**8.5**
HR (95% CI), *P* value	**0.49 (0.35, 0.70); *P*<0.001**	

Penson at. ASCO 2019

SGO 2022, SOLO-3 final result

Overall Survival

OS was similar with olaparib and chemotherapy



	Olaparib (N=178)	Chemotherapy (N=88)
Median follow-up for OS, months	48.9	25.4
Events, n (%)	116 (65)	46 (52)
Median OS, months	**34.9**	**32.9**
HR 1.07 (95% CI 0.76–1.49); *P*=0.714		

	Olaparib	Chemotherapy
Subsequent anticancer therapy, n	119	54
PARP inhibitor as first subsequent therapy, n (%)	3 (3)	23 (43)
Any subsequent PARP inhibitor therapy, n (%)	9 (8)	33 (61)

11% of olaparib patients vs 25% of chemotherapy patients left the study prior to death

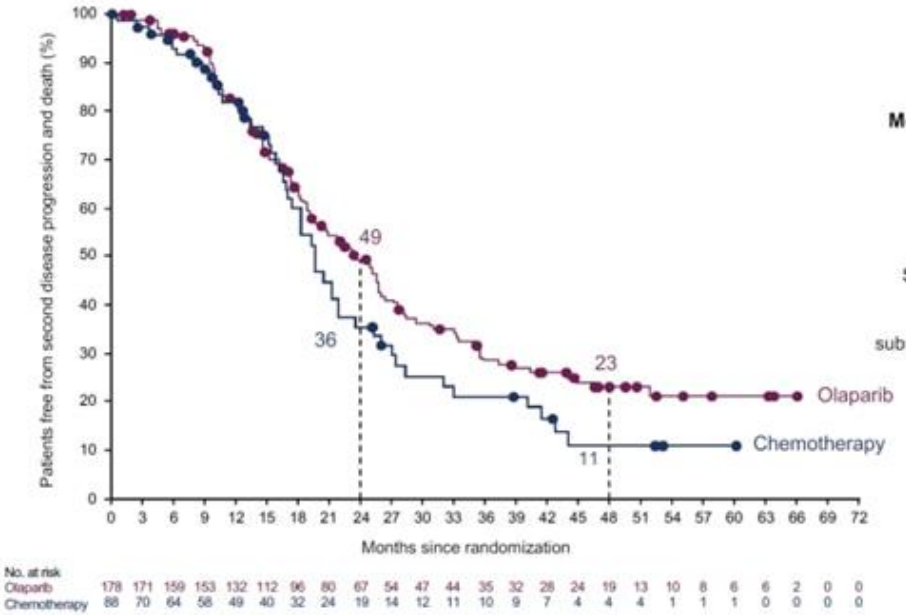
ANNUAL MEETING ON WOMENS' CANCER
BUILDING BRIDGES // BREAKING BARRIERS

Society of Gynecologic Oncology

SGO 2022, SOLO-3 final result

PFS2

PFS2 favored olaparib over chemotherapy



	Olaparib (N=178)	Chemotherapy (N=88)
Events, n (%)	114 (64)	48 (55)
Median PFS2, months	**23.6**	**19.6**
HR 0.80 (95% CI 0.56–1.15); *P*=0.229		

	Olaparib	Chemotherapy
Subsequent anticancer therapy, n	119	54
PARP inhibitor as first subsequent therapy, n (%)	3 (3)	23 (43)

ANNUAL MEETING ON WOMENS' CANCER
BUILDING BRIDGES // BREAKING BARRIERS

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SGO 2022, SOLO-3 final result

Adverse event

Similar safety profile to the primary DCO

	Primary ORR analysis (DCO 10 Oct 2018)		Final OS analysis (DCO 16 Apr 2021)	
	Olaparib (N=178)	Chemotherapy (N=76)	Olaparib (N=178)	Chemotherapy (N=76)
Median treatment duration, months (range)				
Olaparib	11.3 (0.1–39.5)	–	13.1 (0.1–67.5)	–
PLD	–	6.0 (0.9–15.4)	–	6.0 (0.9–15.4)
Paclitaxel	–	5.1 (1.8–18.2)	–	5.1 (1.8–20.0)
Gemcitabine	–	3.3 (0.7–14.3)	–	3.3 (0.7–14.3)
Topotecan	–	6.2 (2.3–9.7)	–	6.2 (2.3–9.7)
All-grade TEAEs, n (%)	174 (97.8)	73 (96.1)	175 (98.3)	73 (96.1)
Grade ≥3 TEAEs, n (%)	89 (50.0)	36 (47.4)	94 (52.8)	37 (48.7)
Serious TEAEs, n (%)	42 (23.6)	14 (18.4)	46 (25.8)	14 (18.4)
AESIs, n (%)				
MDS/AML	4 (2.2)	3 (3.9)*	5 (2.8)	3 (3.9)*
NPMs†	3 (1.7)	0	4 (2.2)	1 (1.3)
Pneumonitis	0	0	1 (0.6)	0
Dose interruption/delay due to TEAEs, n (%)	85 (47.8)	32 (42.1)	89 (50.0)	32 (42.1)
Dose reduction due to TEAEs, n (%)	48 (27.0)	25 (32.9)	53 (29.8)	25 (32.9)
Treatment discontinuation due to TEAEs, n (%)	13 (7.3)	15 (19.7)	18 (10.1)	15 (19.7)

*Two patients received PLD as study treatment and one patient received paclitaxel; two of these three patients received a PARP inhibitor as a subsequent treatment;

†At the primary DCO, NPMs were lung cancer (n=1), gastric cancer (n=1) and breast cancer (n=1) in the olaparib group. At the final DCO, additional NPMs were breast cancer (n=1) in the olaparib group and leukemia (n=1) in the chemotherapy group

AESI, adverse event of special interest; AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; NPM, new primary malignancy; TEAE, treatment-emergent adverse event

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BUILDING BRIDGES // BREAKING BARRIERS

Society of Gynecologic Oncology

SGO 2022, SOLO-3 final result

Conclusion

1. In a preliminary analysis of SOLO3, olaparib monotherapy improved ORR and PFS compared with single-agent non-platinum chemotherapy in gBRCAm PSROC patients previously treated with high-intensity therapy.

2. The final analysis showed better PFS2 performance in the olaparib group than in the TPC group, and OS was similar between the two treatment groups, supporting the use of olaparib as a chemotherapy-free strategy in this patient population.

3. No new safety signals were found.

故事還沒結束喔！

- SOLO-3: 對於先前接受至少兩線化療、具含鉑敏感且BRCA遺傳性突變之復發性卵巢癌患者，olaparib之療效 。

- PSROC with unknown or negative BRCAm ?
- PRROC?

→ CLIO trial

Olaparib for all comer in PSROC

CLIO trial (*Phase 2R, Olaparib vs C/T*)

CLIO Study Design

Randomized open-label study — ENGOT MODEL A

- **RELAPSED OVARIAN CANCER**: at least **1 previous line of chemotherapy**
- HISTOLOGY: High-grade serous, Endometrioid, Clear-Cell, Carcinosarcoma, Undifferentiated
- MEASURABLE DISEASE
- PREVIOUS PARPi ALLOWED

Platinum-sensitive / PSOC (n = 60)

- Relapse ≥ **6 months** after platinum-based chemotherapy
- **Exlusion of patients with known** germline or somatic **BRCA mutation** prior to screening

R → **OLAPARIB** 300mg BID (4 tablets/day) *crossover*

R → Physician's choice **CHEMOTHERAPY** (Carbo-Gemci / Carbo-Paclitaxel / Carbo-PLD) *crossover*

2:1 randomisation

Platinum-resistant / PROC (n = 100)

- Relapse < **6 months** after platinum-based chemotherapy), exclusion **primary platinum-refractory disease** (i.e. relapse during or < 28 days after first-line platinum)
- Germline or somatic BRCA mutation allowed

R → **OLAPARIB** 300mg BID (4 tablets/day) *crossover*

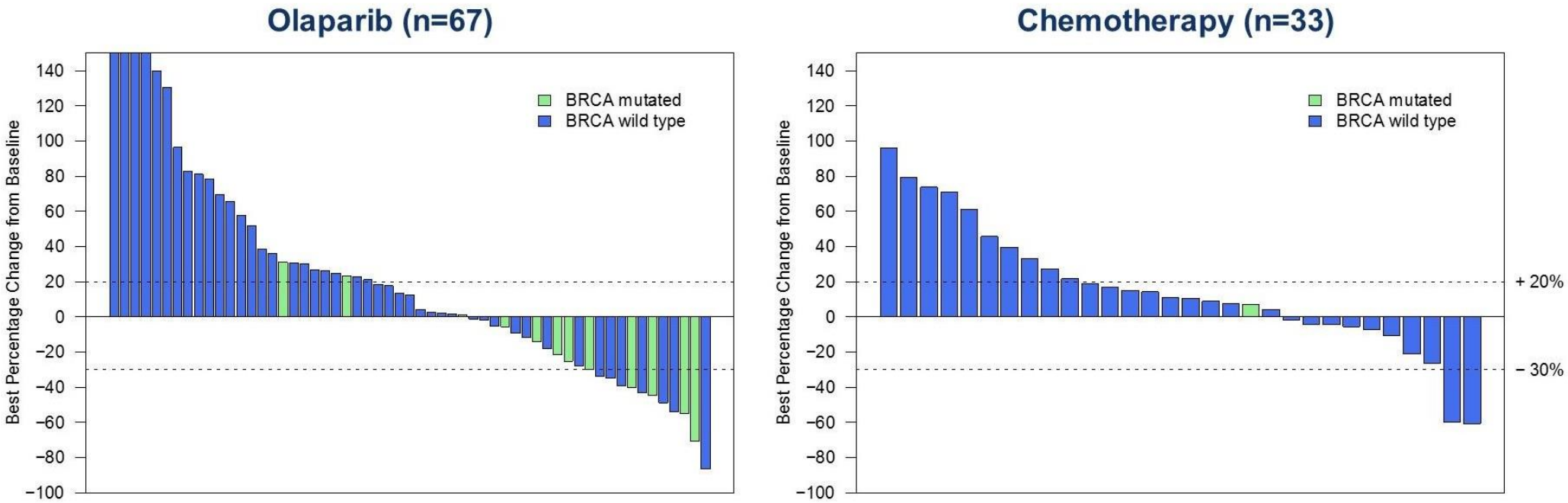
R → Physician's choice **CHEMOTHERAPY**
Paclitaxel 80mg/m² Topotecan 1.25mg/m²
PLD 40mg/m² Gemcitabine 1000mg/m²

Vanderstichele et at ASCO 2019

Single agent: Olaparib in all comers

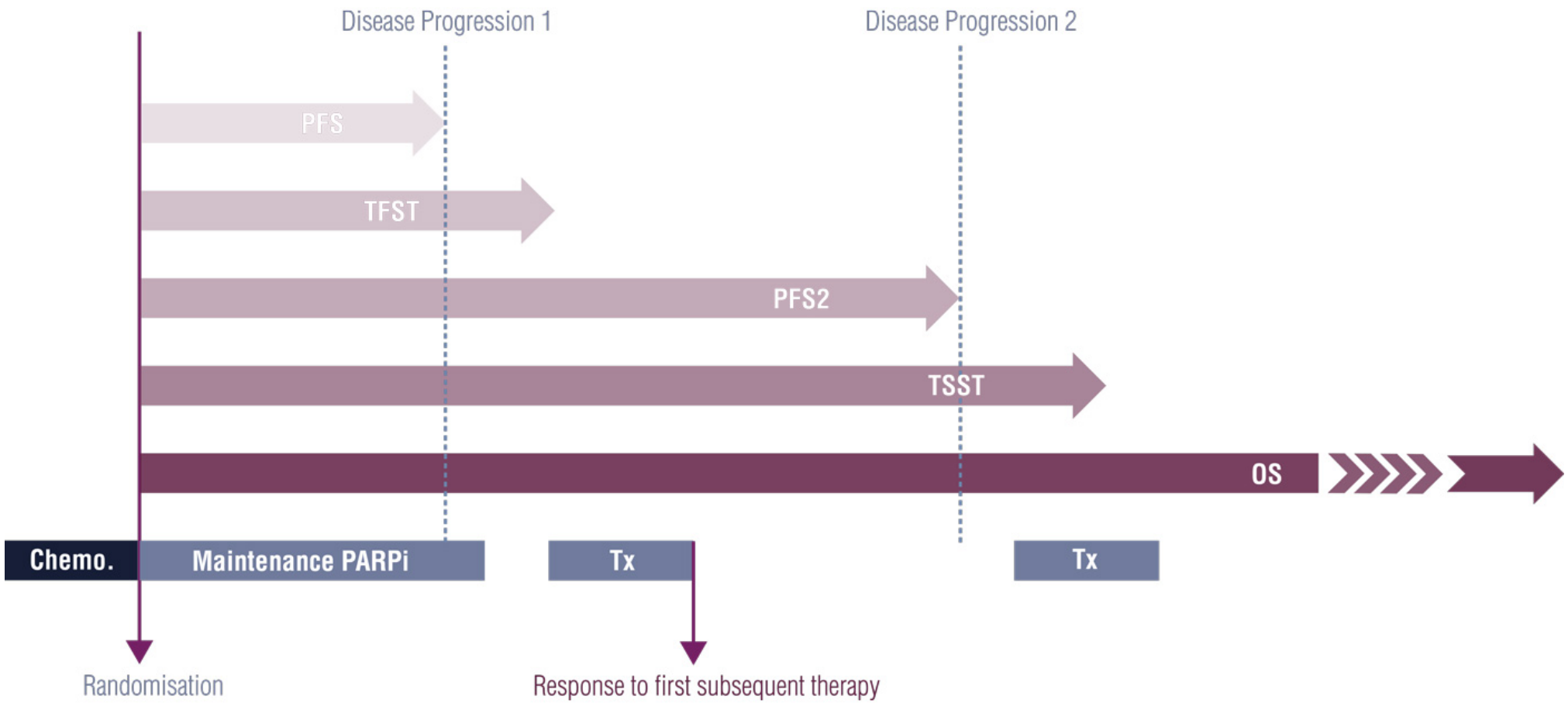
CLIO trial: Ph IIR

ORR according to BRCA status (PROC, n=100)



	OLAPARIB	CHEMOTHERAPY
BRCA mutated	36 % (5/14)	0 % (0/1)
BRCA wild type	13 % (7/53)	6 % (2/32)

Vanderstichele et at ASCO 2019


Disease Progression 1
Disease Progression 2
PFS
TFST
PFS2
TSST
OS
Chemo.
Maintenance PARPi
Tx
Tx
Randomisation
Response to first subsequent therapy