BRCA 突變的晚期乳癌及卵巢癌病人的治療考量

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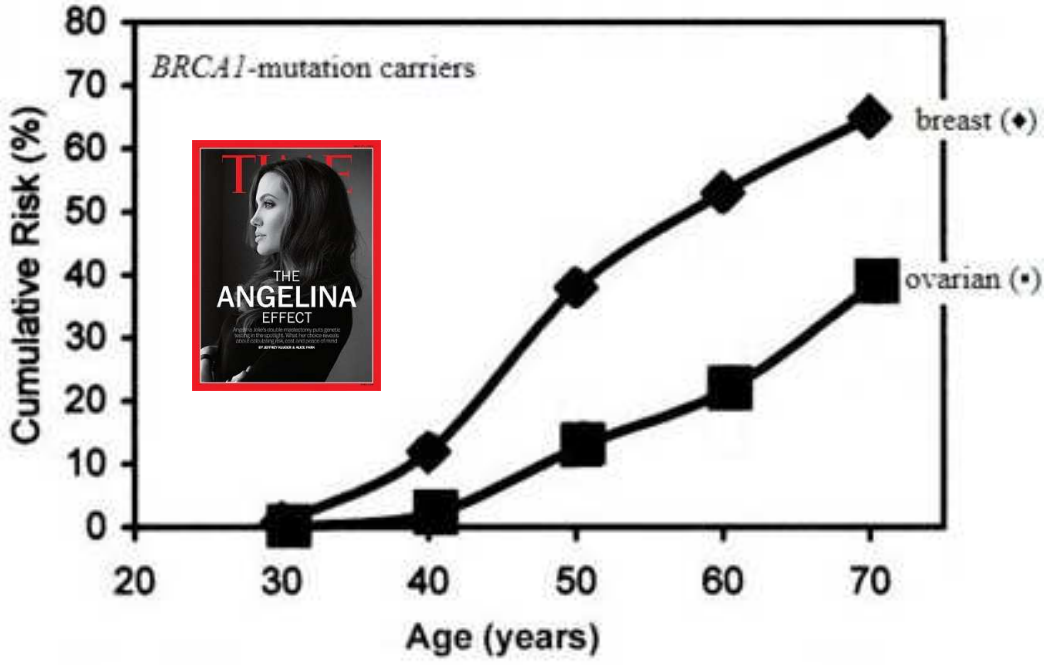
Outline

- BRCA genes mutations and cancers
- What is a PARP inhibitor, how it works?
- Pivotal trials in Ovarian and breast cancers
- Current practice considerations and future

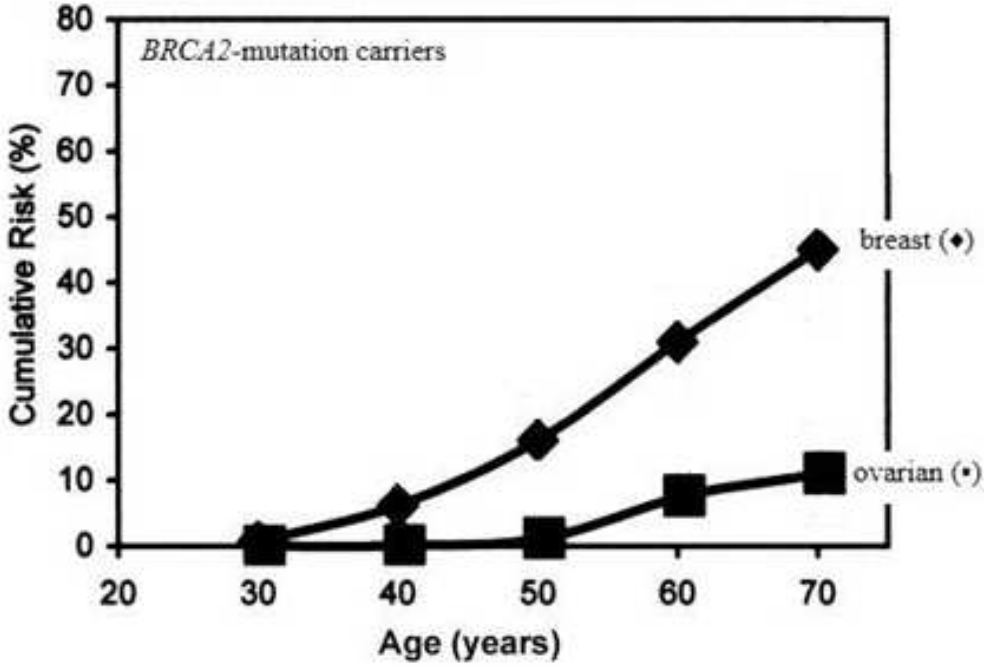
乳癌基因

Average Risks of Breast and Ovarian Cancer Associated with BRCA1 or BRCA2 carriers

gBRCA1 and risk of BC/OC

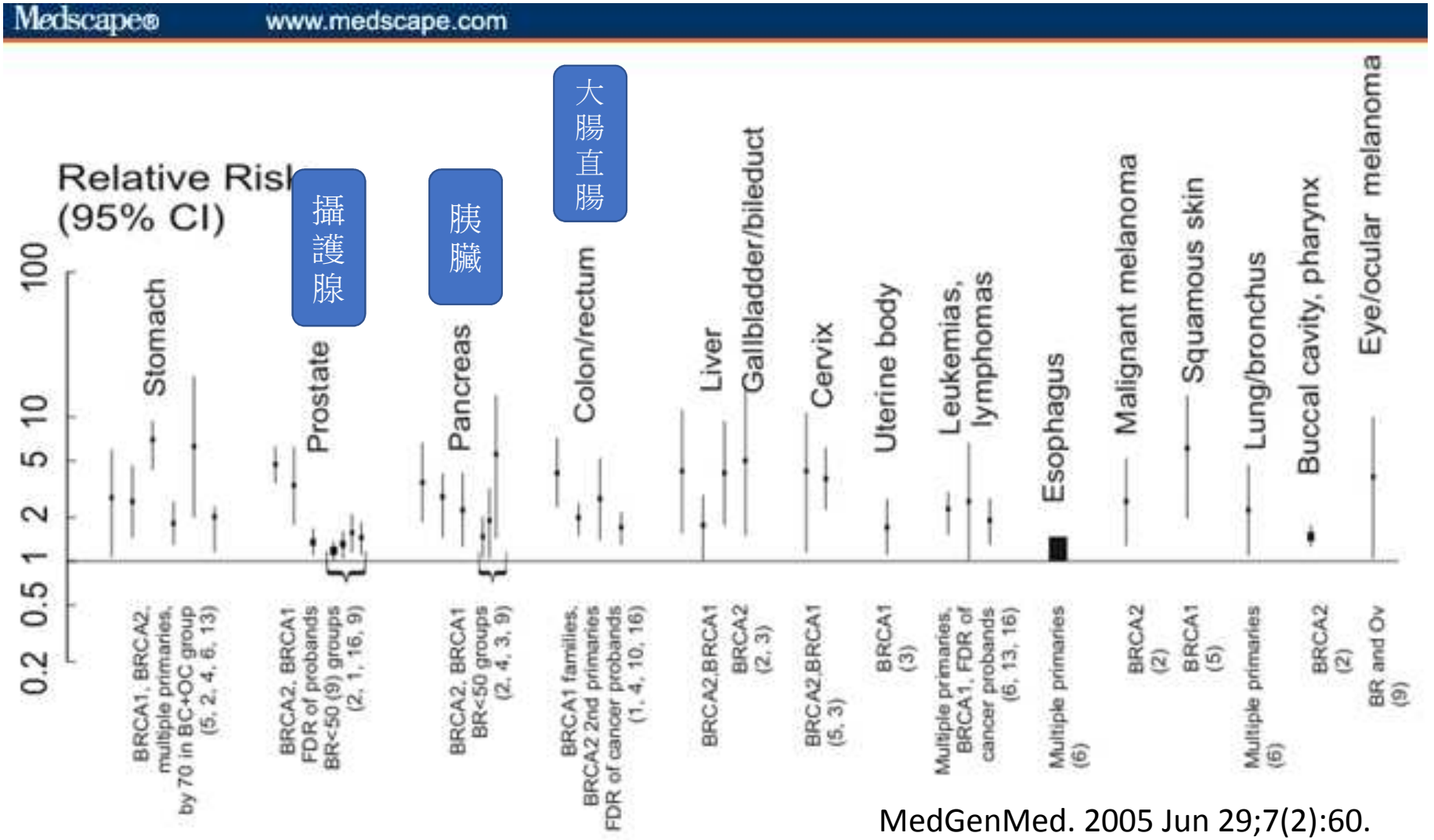


gBRCA2 and risk of BC/OC



Am J Hum Genet. 2003 May; 72(5): 1117–1130

gBRCA-related cancers: risk beyond BC and OC



MedGenMed. 2005 Jun 29;7(2):60.

Who (for a known breast cancer patient) to test ?

Box 1. Characteristics that should trigger testing for germline *BRCA*1/2 mutation in patients already diagnosed with breast cancer

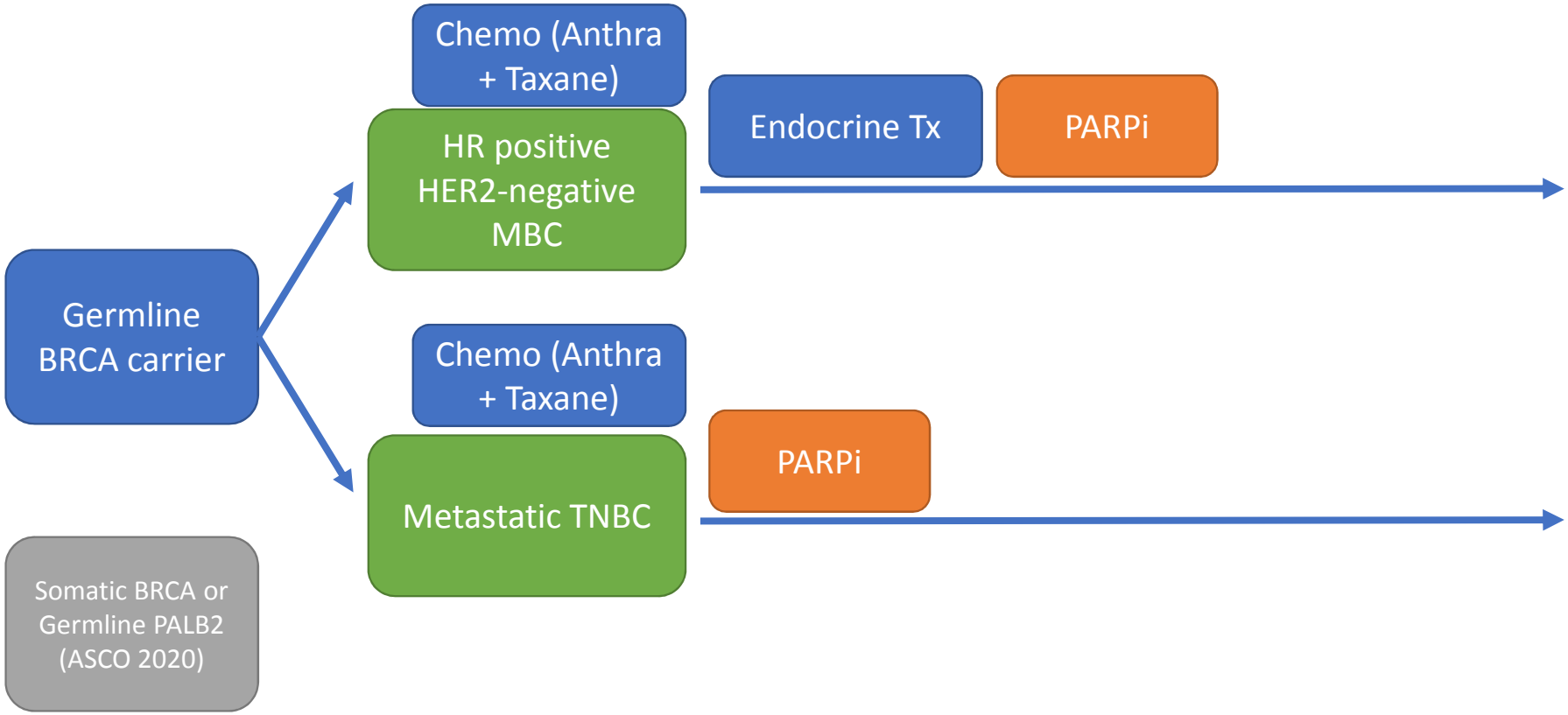
- Family history of breast, ovarian/tubal/peritoneal cancer, pancreatic, or aggressive prostate cancer
- Young age at diagnosis (<50 years)
- Triple-negative breast cancer (ER-negative, PgR-negative, and HER2-negative)
- Breast cancer in a male
- Ashkenazi Jewish heritage
- Personal history of ovarian or pancreatic cancer
- Detection of somatic *BRCA*1/2 mutation
- Patient with metastatic HER2-negative breast cancer who is eligible for treatment with a PARPi[19]

ER-negative oestrogen receptor-negative, *HER2-negative* human epidermal growth factor receptor 2-negative, *PgR-negative* progesterone receptor-negative

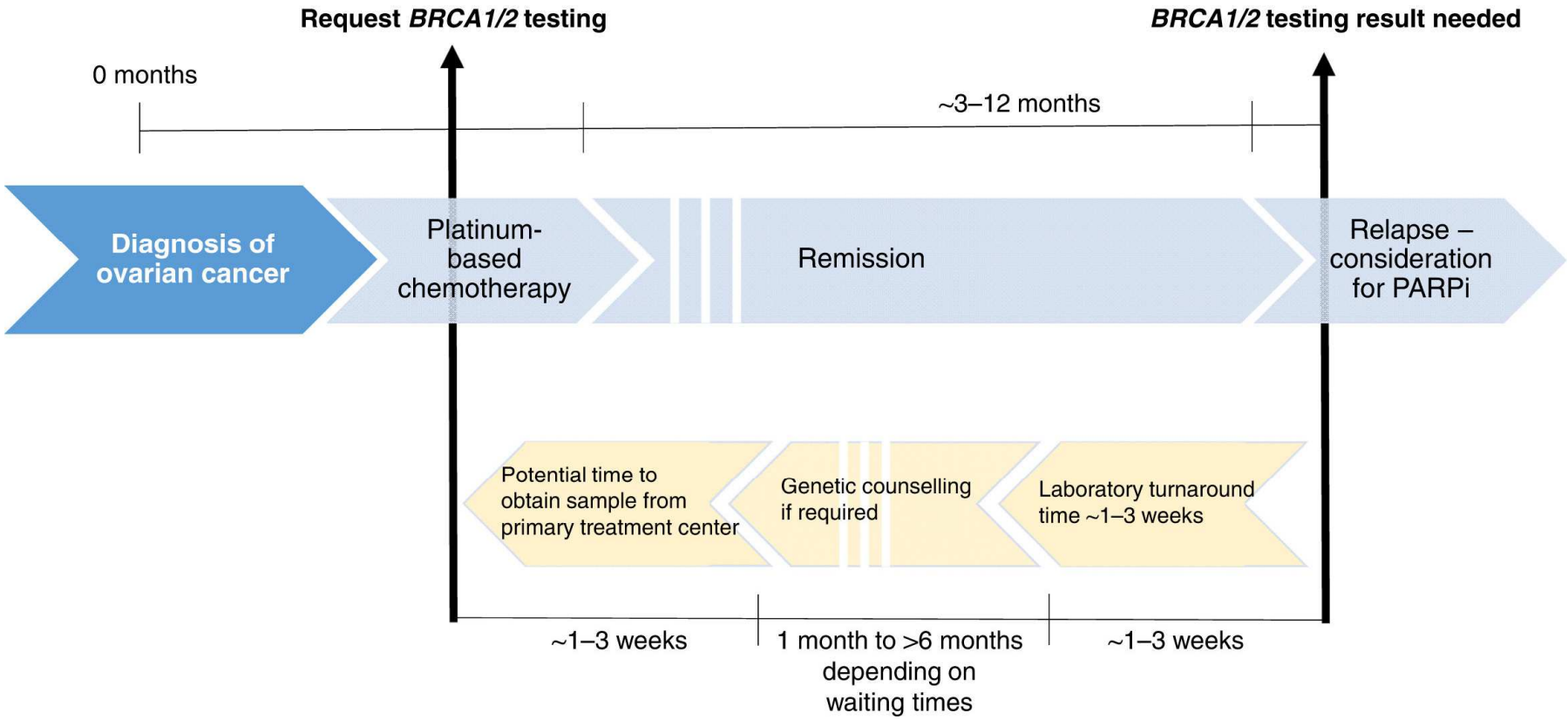
晚期荷爾蒙受體陽性或三陰性乳癌病患計畫使用PARP-抑制劑時

British Journal of Cancer (2018) 119:141–152

Current Treatment Landscape for PARPi in Breast Cancer

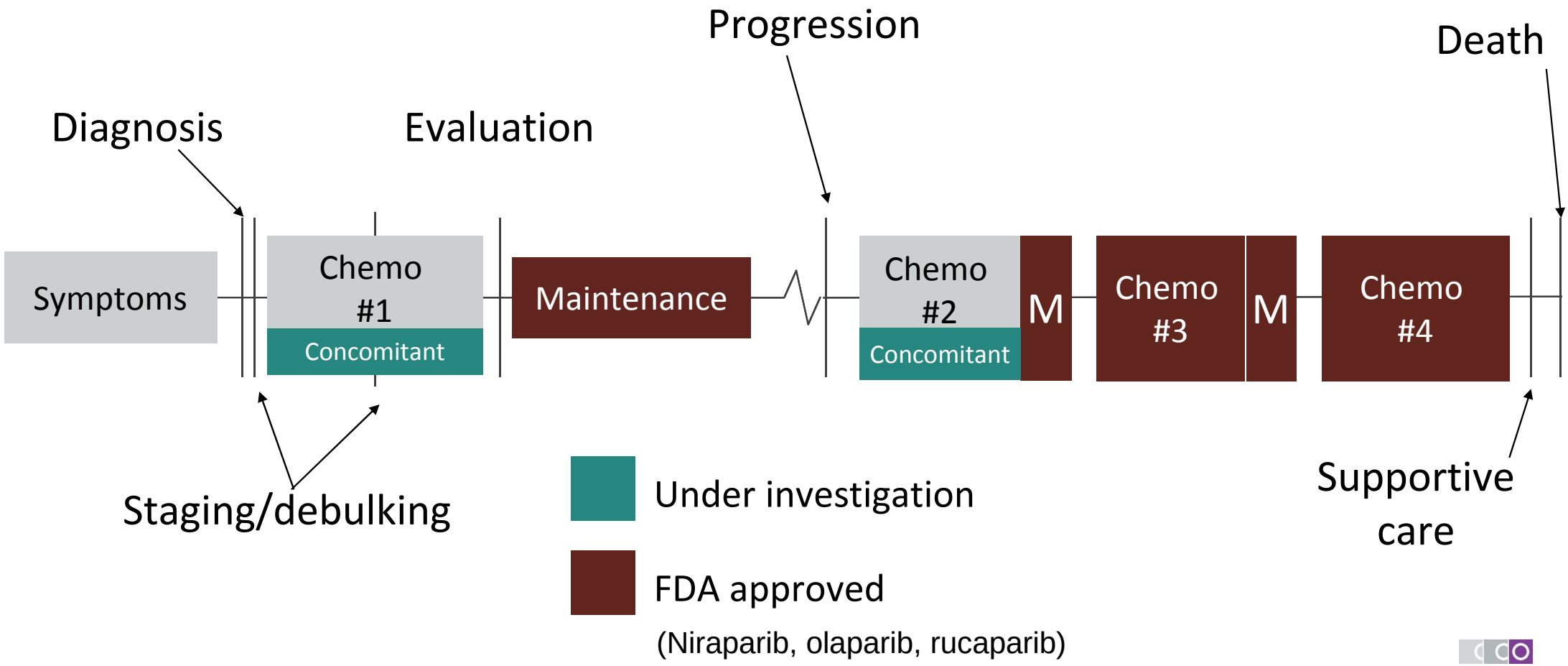


An estimated 10%–20% of OC patients are likely to harbor either a germline or somatic BRCA1/2 mutation



Semin Oncol. 2017 Jun;44(3):187-197.

Current Treatment Landscape for PARPi in Ovarian Cancer



LaFargue. Lancet Oncol. 2019;20:e15.

Slide credit: clinicaloptions.com

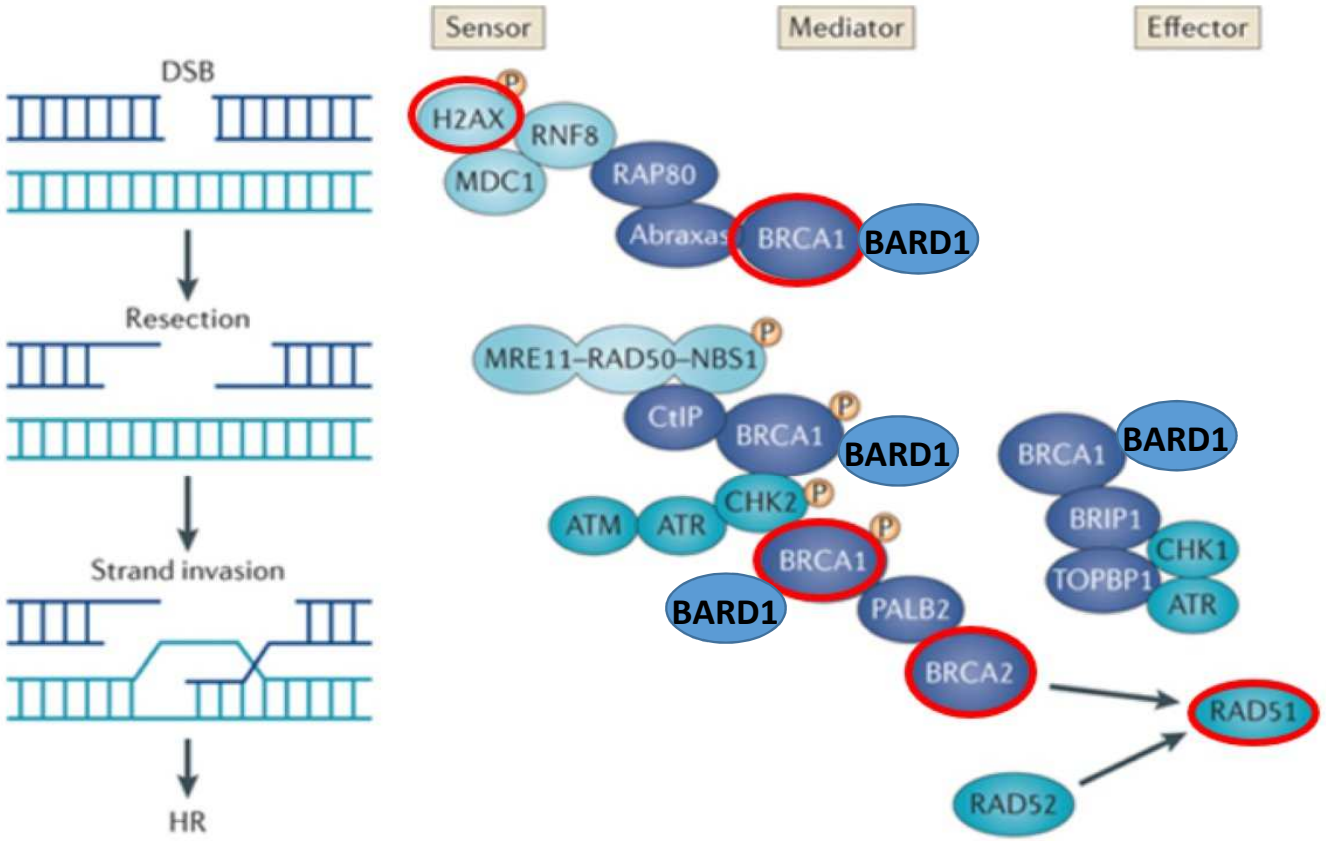
PARP Inhibitors: Current Indications for OC

Olaparib	Niraparib	Rucaparib
▪ First-line maintenance therapy for *BRCA*-mutated advanced ovarian cancer		
▪ Maintenance therapy for recurrent ovarian cancer regardless of *BRCA* mutation status	▪ Maintenance therapy for recurrent ovarian cancer regardless of *BRCA* mutation status	▪ Maintenance therapy for recurrent ovarian cancer regardless of *BRCA* mutation status
▪ Fourth-line and beyond treatment for advanced ovarian cancer with germline *BRCA* mutations		▪ Third-line and beyond treatment for advanced ovarian cancer with *BRCA* mutations

Olaparib PI 2018; Rucaparib PI 2018; Niraparib PI 2019.

Slide credit: clinicaloptions.com

BRCA-related genes (BRCAness) involves DNA homologous recombinant repair (HR) and DNA-damage response (DDR)



Reprinted by permission from Springer Nature: Nature Reviews Cancer. Roy R, et al. Nat Rev Cancer. 2011;12:68. BRCA1 and BRCA2: different roles in a common pathway of genome protection, Roy R, et al., Copyright © 2011, Springer Nature.

Presumed rationale for the synthetic lethality of BRCA 1/2 deficiency in tumours and PARP inhibition

*BRCA*wt tumour cells

In *BRCA*wt tumour cells, there are multiple ways to repair DNA damage, allowing cell survival.

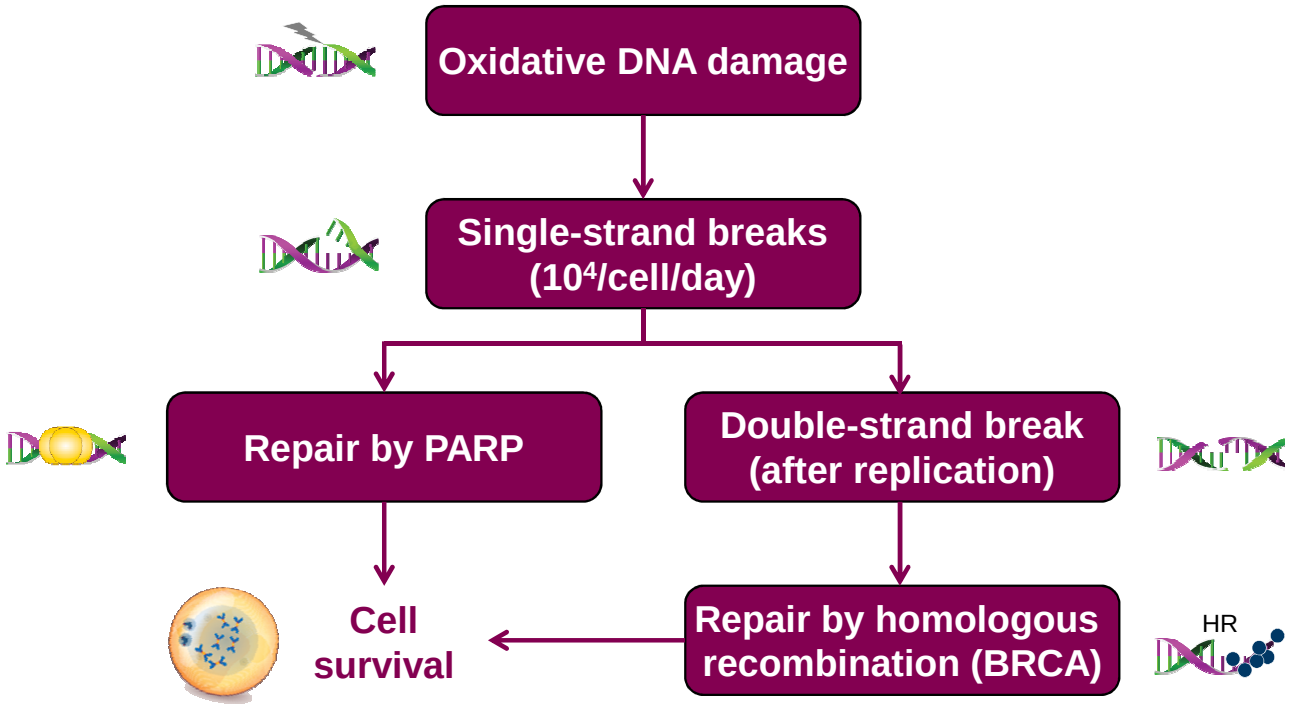


Figure adapted from Hoeijmakers JH, 2009. PARP, poly ADP-ribose polymerase.

Hoeijmakers JH. *N Engl J Med* 2009;361:1475–1485.

Presumed rationale for the synthetic lethality of BRCA 1/2 deficiency in tumours and PARP inhibition

*BRCA*m tumour cells

In *BRCA*m cells, one of the repair pathways is lost, leaving the cell dependent on a less accurate repair mechanism that can allow accumulation of DNA damage, leading to a cancer phenotype.

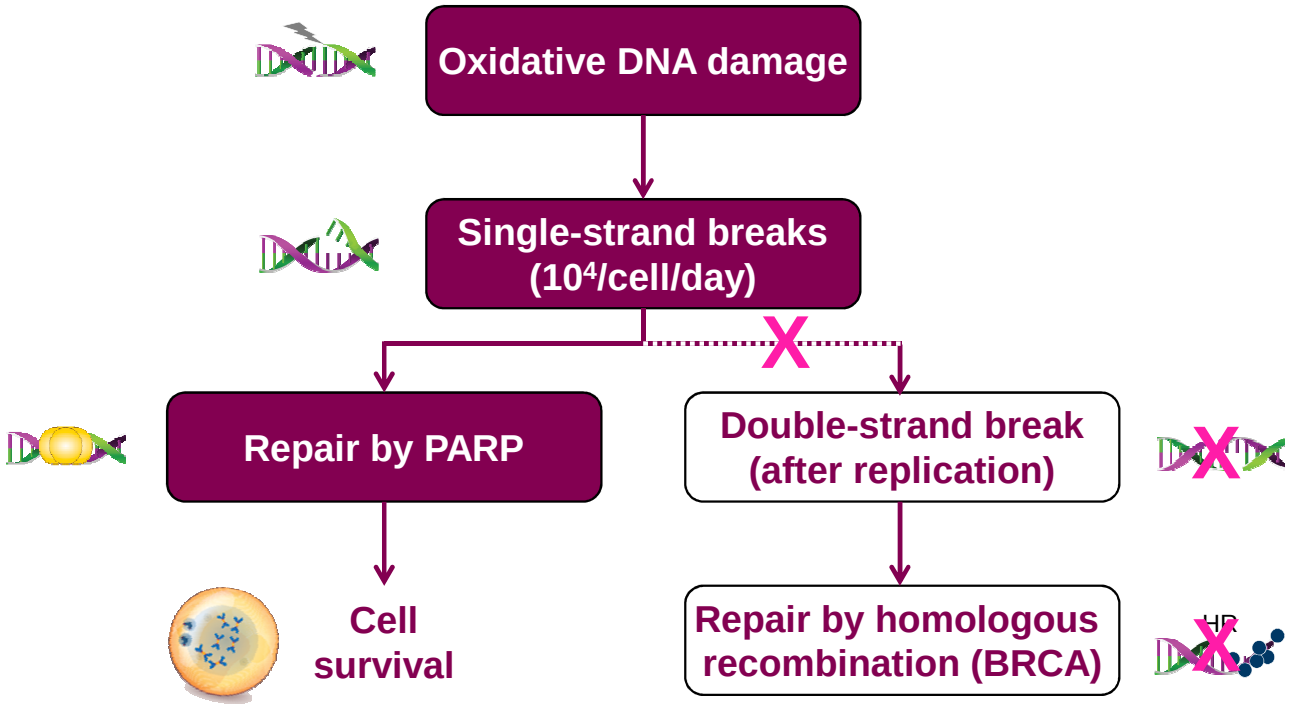


Figure adapted from Hoeijmakers JH, 2009. BRCAm, BRCA mutated; PARP, poly ADP-ribose polymerase.

Hoeijmakers JH. *N Engl J Med* 2009;361:1475–1485.

Presumed rationale for the synthetic lethality of BRCA 1/2 deficiency in tumours and PARP inhibition

*BRCA*m tumour cells + PARP inhibitor

In *BRCA*m cells treated with a PARP inhibitor, neither repair pathway is available meaning double-strand breaks accumulate, eventually triggering apoptosis.

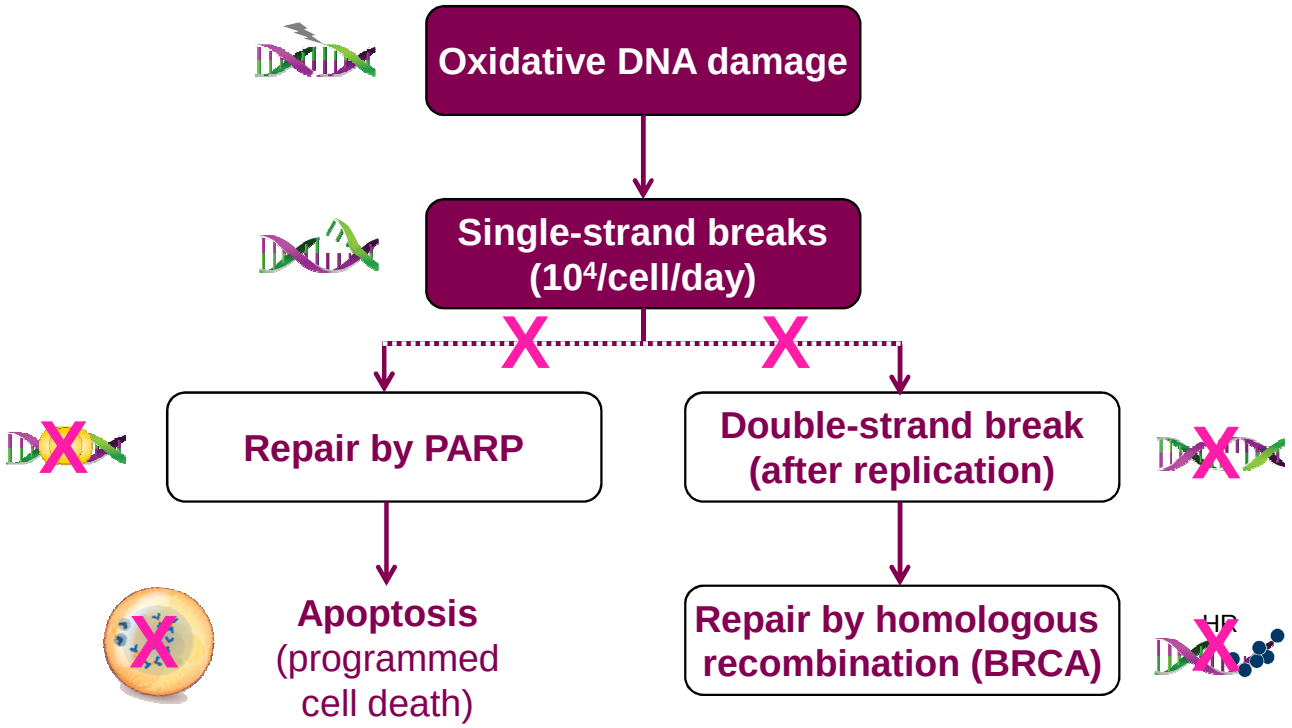
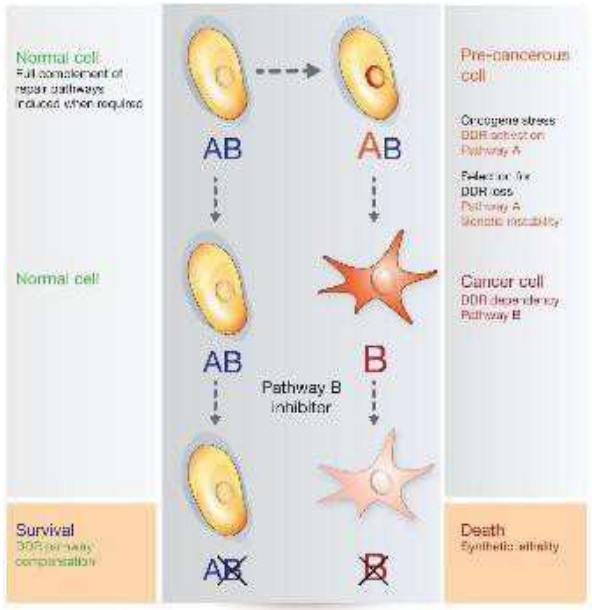


Figure adapted from Hoeijmakers JH, 2009. PARP, poly ADP-ribose polymerase.

Hoeijmakers JH. *N Engl J Med* 2009;361:1475–1485.

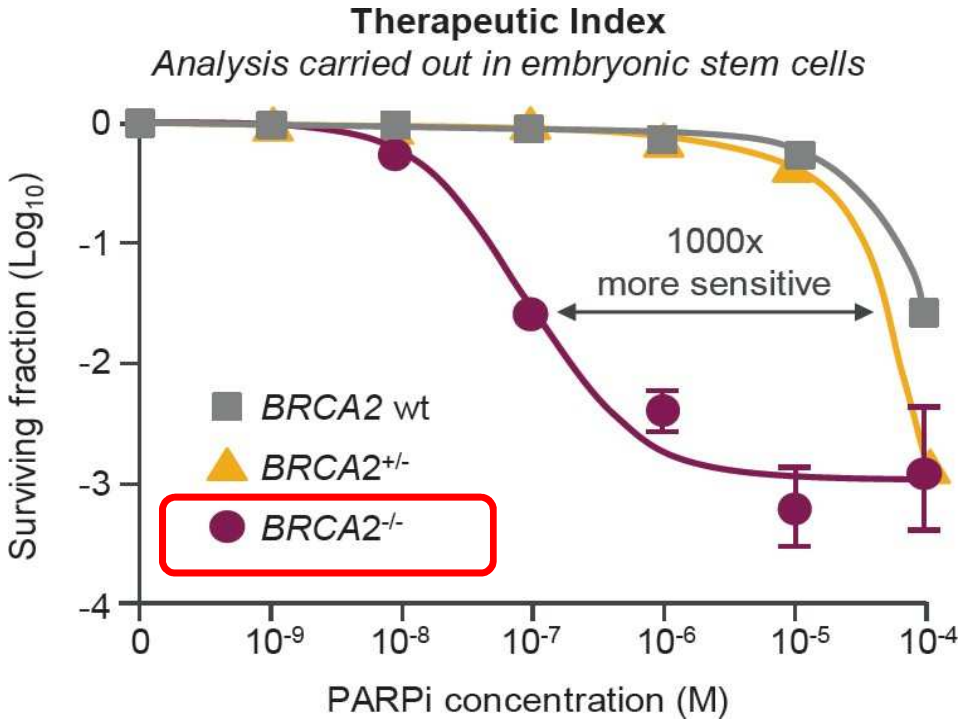
Loss of DDR Pathways during Tumorigenesis Results in DDR Dependencies



Gene A	Gene B	
A	B	Viable
A	b	Viable
a	B	Viable
a	b	Lethal

LOH: Loss of Heterozygosity
Double-Hit, Bi-allelic loss theory

Synthetic lethality: PARPi monotherapy

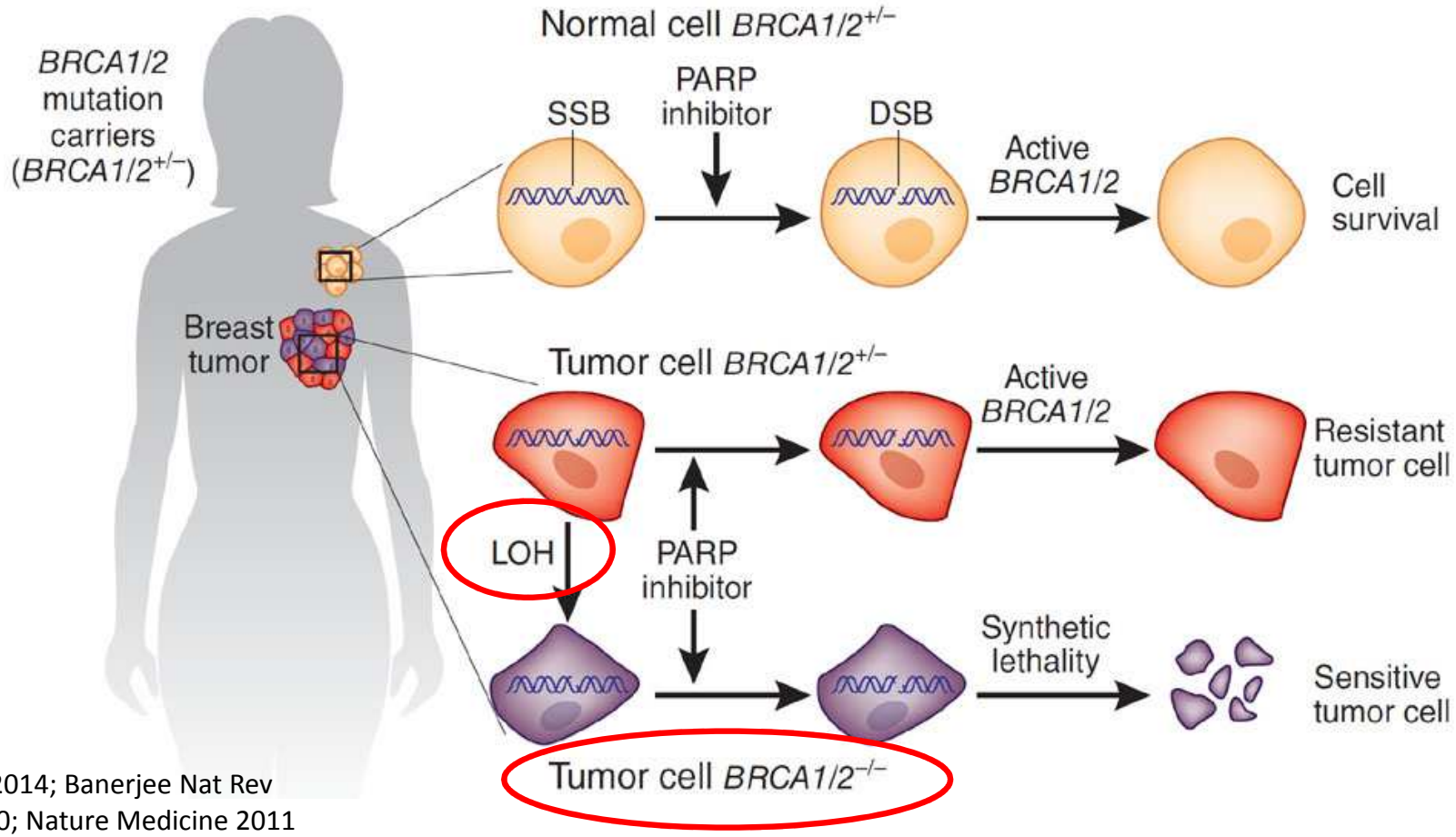


Wide therapeutic window between wild-type and BRCA-/-

Selectivity

1. Bryant HEet al. Nature 2005;434:913–917; 2. Farmer H et al. Nature 2005:434:917–921

Why we test germline BRCA (gBRCA) status?



Rustgi G&D 2014; Banerjee Nat Rev Clin Onc 2010; Nature Medicine 2011

Mechanisms of biallelic loss at the germline locus in gBRCA1/2 mutated tumors

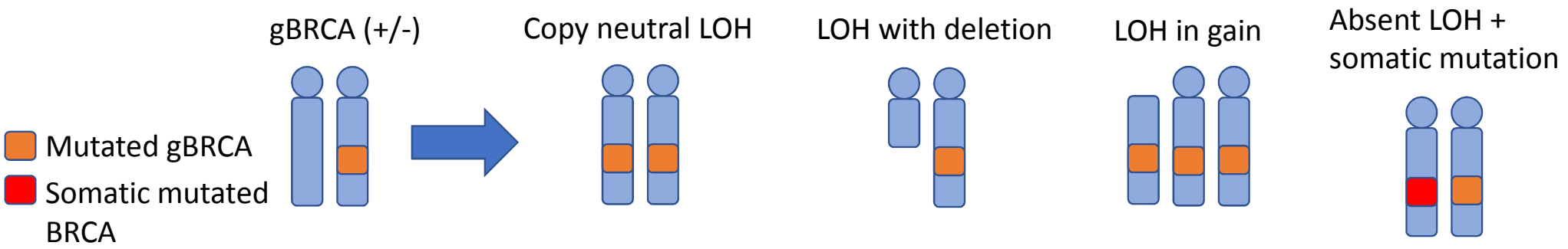


Table 1 Mechanisms of biallelic loss at the germline locus in BRCA1 and BRCA2 mutation germline mutation-associated tumors

ASCN analysis of locus-specific LOH[a]	BRCA1 germline mutation				BRCA2 germline mutation			
	TCGA (n = 55)		Local (n = 38)		TCGA (n = 45)		Local (n = 22)	
LOH with deletion	9	16%	8	21%	8	18%	6	27%
Copy neutral LOH	23	42%	13	34%	15	34%	5	23%
LOH in gain	20	36%	11	29%	7	16%	4	18%
Absent locus-specific LOH	2	4%	6	16%	13	29%	8	36%
Absent LOH + somatic mutation[b]	1	2%	0	0%	1	2%	0	0%

[a]Allele-specific copy number analysis (*ASCN*) at *BRCA1* or *BRCA2* genomic locus. Categories of allele-specific copy number loss are defined as per the output of the Sequenza program: loss of heterozygosity (LOH) with deletion refers to copy number state of one with one mutant allele; copy neutral LOH refers to copy number state of two with two mutant alleles; LOH in gain refers to copy number state of ≥3 with all mutant alleles; absent locus-specific LOH refers to copy number state of ≥2 and at least one wildtype allele
[b]Identification of a somatic mutation in the corresponding gene in the tumor

Nature Communications 2017. 8: 319

Biallelic loss of germline BRCA mutations is common in breast cancer and ovarian cancer

Table 2. Bi-allelic loss of germline and somatic BRCA mutations in TCGA ovarian and breast cancer cohorts

n/N (%)	Ovarian*		Breast	
	Germline	Somatic	Germline	Somatic
BRCA1	34/34 (100)	13/16 (81)	22/23 (96)†	10/12 (83)
BRCA2	24/26 (92)	8/8 (100)	21/27 (78)‡	8/10§ (80)
Total	58/60 (97)	21/24 (88)	43/50 (86)	18/22§ (82)

*As a result of limitations of access to raw data, only 60 of 70 germline mutations and 24 of 36 somatic mutations in the ovarian cohort were analyzed for bi-allelic loss; †One patient had one germline and one somatic *BRCA1* mutation assumed to be bi-allelic; ‡One patient had one germline and one somatic *BRCA1* mutation assumed to be bi-allelic; two patients have both germline and homozygous deletions counted as bi-allelic; §Two samples with large rearrangements could not be determined for bi-allelic status and were therefore excluded in the bi-allelic calculation

Table 4. Bi-allelic loss of germline and somatic BRCA mutations in Foundation Medicine ovarian and breast cancer cohorts

n/N (%)	Ovarian		Breast	
	Germline	Somatic	Germline	Somatic
BRCA1 bi-allelic loss	96/100 (96)	82/85 (96)	77*/85 (91)	48†‡/56 (86†)
BRCA2 bi-allelic loss	34/38 (89)	47/52 (90)	95†/111 (86†)	51†§/68 (75†)

*One tumor lost a germline but gained a homozygous somatic mutation; †Composite heterozygous mutations are considered as bi-allelic loss; ‡The patient with a compound heterozygous loss had two somatic frameshift mutations; §Of the five patients with compound heterozygous loss, four had both germline and somatic mutations and one had two somatic mutations

BRCA1 biallelic loss (LOH): ≥ 80-90%
BRCA2 biallelic loss (LOH): ≥ 50-80%

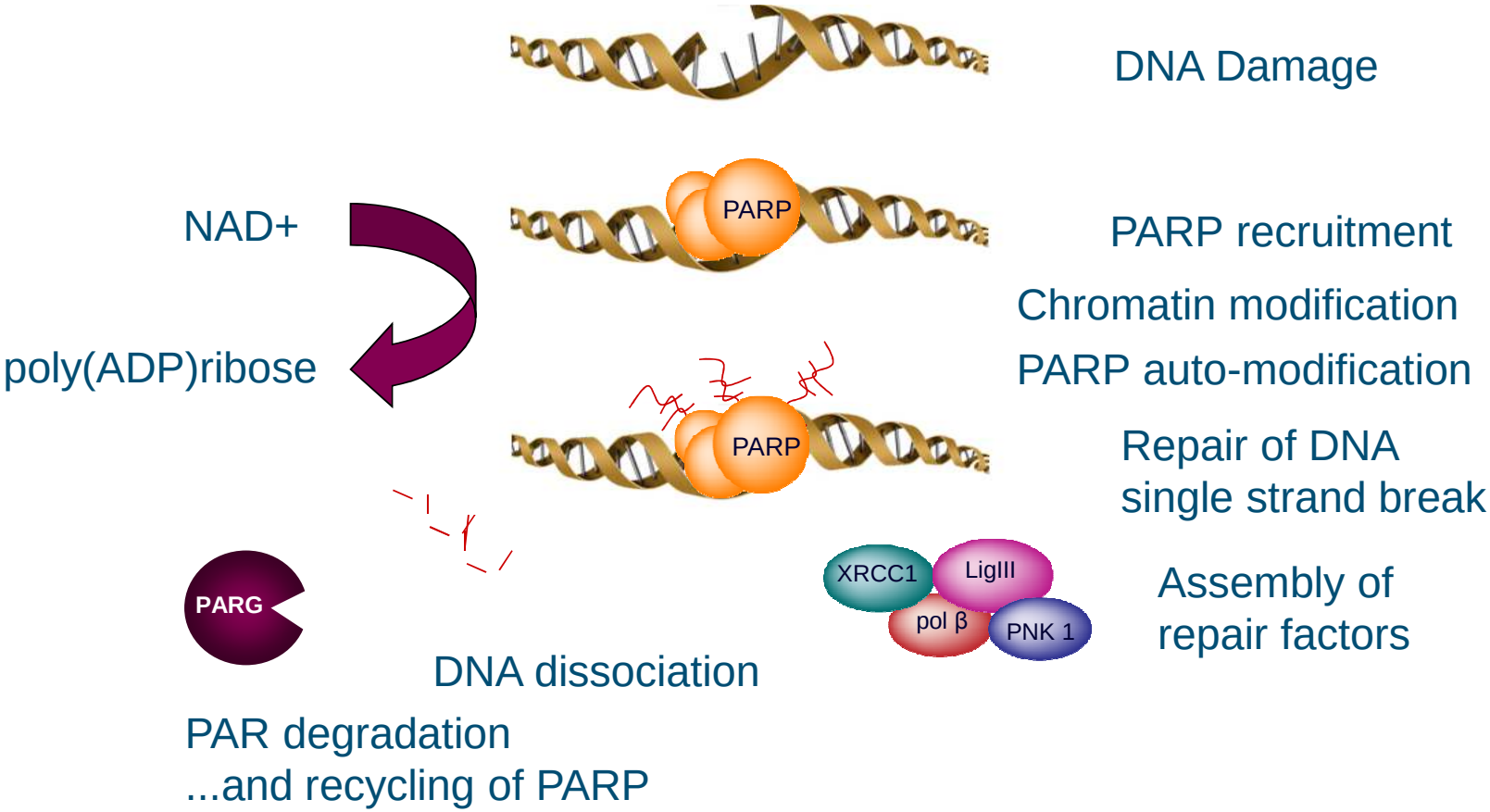
Table 2 LOH and promoter methylation of tumors from *BRCA* carriers

	Breast	Ovarian	Total
BRCA1			
LOH	28/35 (80%)	3/3 (100%)	31/38 (82%)
Methylation	0/11 (0%)	NA	0/11 (0%)
No LOH and no methylation	0/7 (0%)	NA	0/7 (0%)
BRCA2			
LOH	13/19 (68%)	1/4 (25%)	14/23 (61%)
Methylation	1/11 (9%)	0/2	1/13 (8%)
No LOH and no methylation	1/6 (17%)	0/2	1/8 (12.5%)

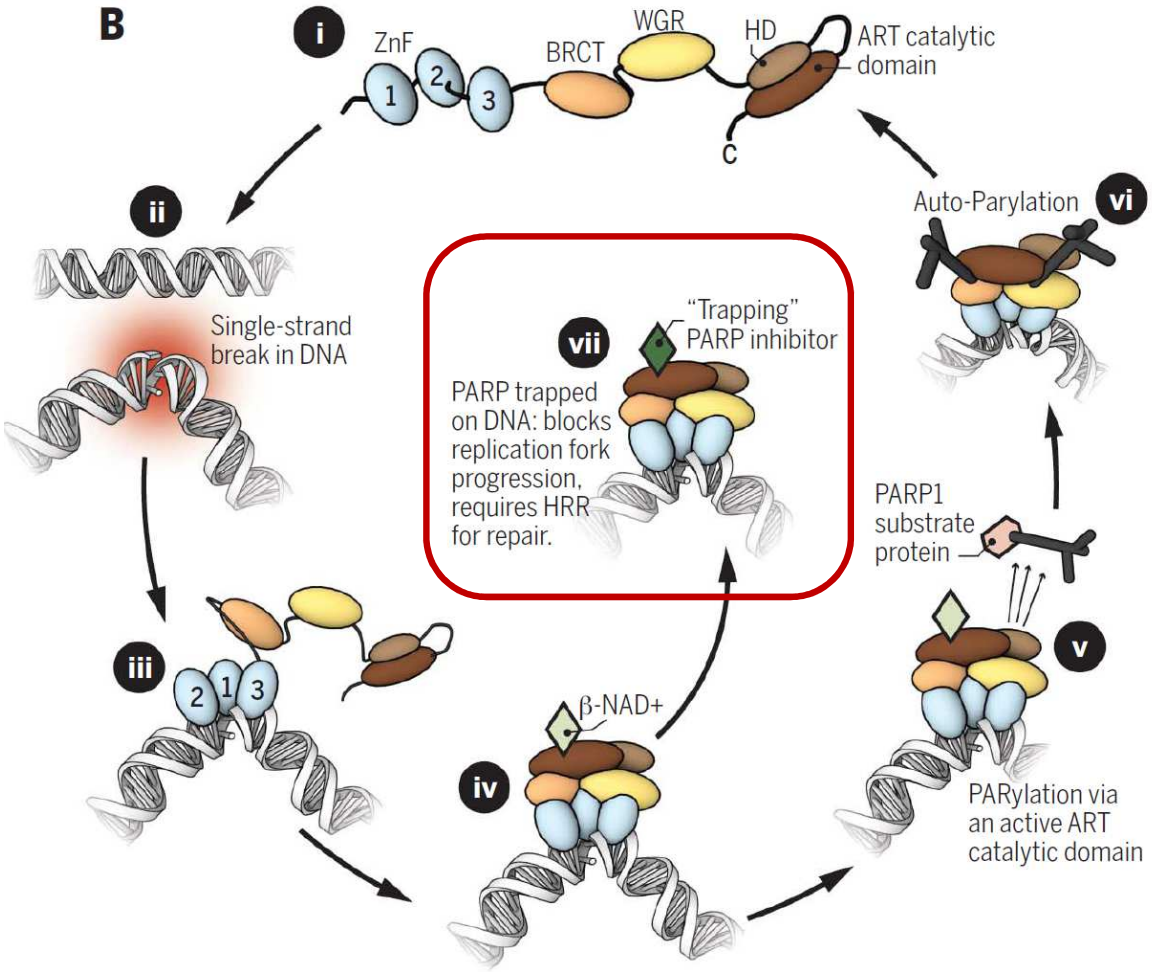
LOH, loss of heterozygosity; NA, not applicable as all tumors in this category showed LOH

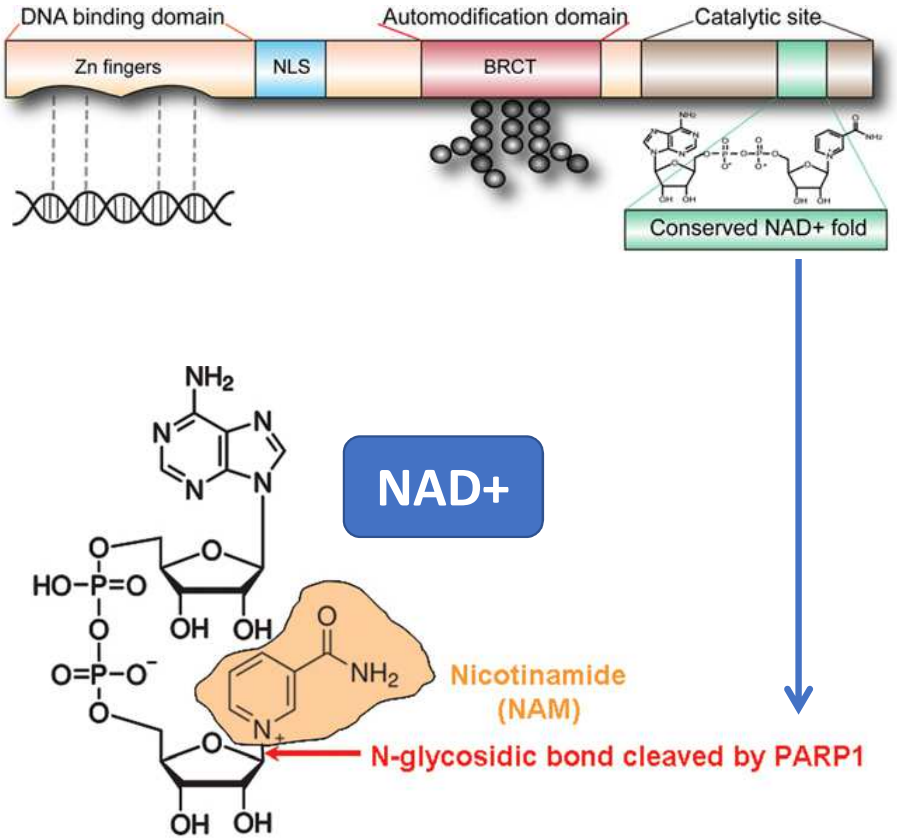
Familial Cancer (2009) 8:339–346
AACR 2019 Abstract #1747 (Lai Z et al.)

PARP and DNA repair



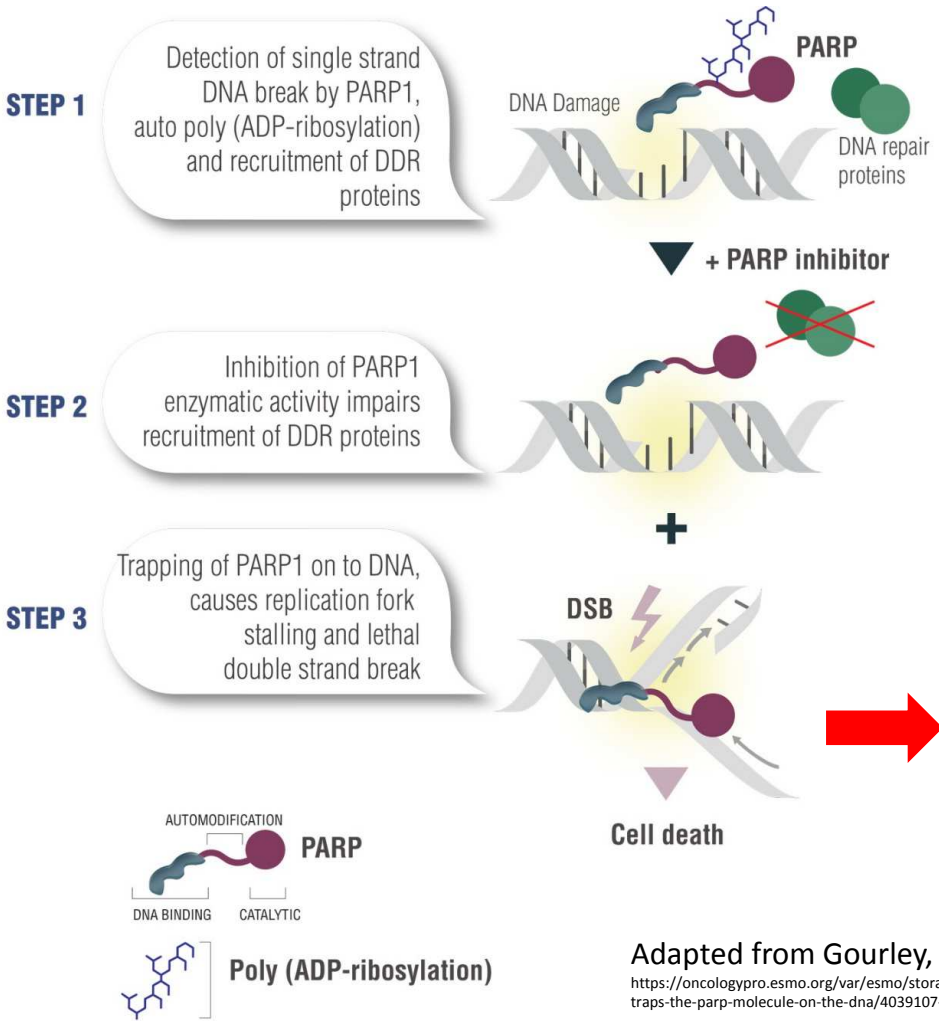
Mechanisms of PARP-1 function in DNA repair

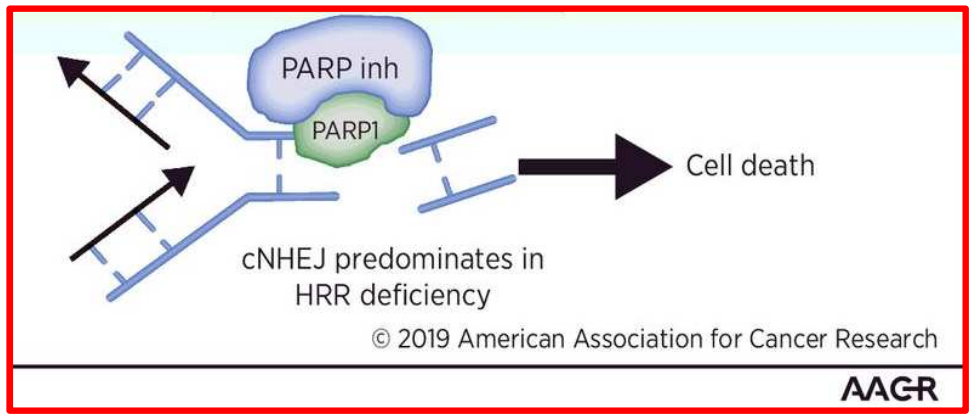




Science. 2017;355(6330):1152-1158

Hallmark (consequence) of PARP inhibition in BRCA-deficient cells: DNA double-strand break (DSB) and replication fork stalling





Adapted from Gourley, et al., J Clin Oncol 2019 & Clin Cancer Res; 25(13), 2019

https://oncologypro.esmo.org/var/esmo/storage/images/media/images-op/oncology-in-practice/parp-inhibition-and-dna-damage-response/figure-2-parp-inhibition-traps-the-parp-molecule-on-the-dna/4039107-1-eng-GB/Figure-2-PARP-inhibition-traps-the-PARP-molecule-on-the-DNA.jpg

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

- Multicenter phase II clinical trial of olaparib 400 mg BID (Capsule) 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)
▪ Early death	8 (4)	7 (11)

Kaufman. JCO 2015;33:244.

Slide credit: clinicaloptions.com

Olaparib tablets vs capsule formulations: better bioavailability and PK profile thus reduced pill-burden

Table 2 Steady-state PK parameters (day 29) for olaparib following multiple dosing with TAB and CAP during the efficacy expansion phase of groups 1 and 6

Day 29[a]	Olaparib CAP and TAB dose during the dose-expansion phase				
	Dose expansion 1 (group 1)		Dose expansion 2 (group 6)		
	200 mg BD TAB ($n = 11$)	400 mg BD CAP ($n = 10$)	300 mg BD TAB ($n = 17$)	400 mg BD TAB ($n = 10$)	400 mg BD CAP ($n = 17$)
$C_{max,ss}$, μg/mL	6.88 (4.01–10.4)	5.70 (2.38–10.9)	9.37 (2.28–14.7)	12.0 (8.45–16.9)	6.36 (3.88–13.3)
$C_{min,ss}$, μg/mL	1.00 (0.28–3.10)	1.86 (0.53–6.67)	1.84 (0.34–3.83)	2.01 (0.76–3.61)	1.04 (0.23–8.49)
$AUC_{0-12,ss}$, μg h/mL	36.1 (16.0–69.0)	43.1 (18.1–98.6)	58.4 (23.1–96.0)	72.8 (44.8–106)	41.5 (18.7–147)

[a] Only subjects remaining on the starting dose at day 29 were included in the summary statistics. All data expressed as gmean (range)

Target Oncol. 2016 Jun;11(3):401-15.

PARP inhibitor trials in breast cancer

Phase II studies of olaparib in breast cancer

	Tutt *et al*[1] (n=54)	Gelmon *et al*[2] (n=26, 10 g *BRCA*m)	Kaufman *et al*[3] (n=62)
Patient population	Locally advanced/ metastatic *BRCA*m BC, ≥1 chemotherapy regimen	Advanced metastatic or recurrent BC, triple negative or known *BRCA*m	Advanced *BRCA*m BC that progressed despite ≥3 previous lines of chemotherapy for advanced/metastatic BC
Prior lines of therapy for advanced disease	3 (median, including adjuvant)	3 (median, including adjuvant)	4.6 (mean, metastatic only)
ORR	41%	0% (50% unconfirmed in *BRCA*m)	13%
Median DoR	144 days	–	204 days

BC, breast cancer; DoR, duration of response; ORR, objective response rate

1. Tutt A *et al Lancet* 2010;376:235–244; 2. Gelmon KA *et al Lancet Oncol* 2011;12:852–861; 3. Kaufman B *et al J Clin Oncol* 2015;33:244–250

OlympiAD is a Phase III study investigating olaparib vs TPC in g*BRCA*m HER2-negative metastatic breast cancer[1]

Germline BRCA mutation

and taxane

HER2 negative

there should be.

≦ 2L Chemo for MBC
Prior Anthra + Taxane

RECIST v1.1

FSI May 2014[3]

Global Study in 19 countries and approximately 141 sites[1]

Randomise 2:1
N=302[4]

Stratification by[2]

- *Prior chemotherapy regimens for metastatic breast cancer*
- *Hormonal receptor (HR) status*
- *Prior platinum therapy*

Olaparib 300mgpo* bid**

Treatment of Physician's Choice (TPC)
Capecitabine or Eribulin or Vinorelbine

Primary endpoint
- PFS (RECIST 1.1, Independent Review)

Secondary endpoints
- OS
- PFS2
- ORR
- PFS, PFS2 and OS based on Myriad g*BRCA*m status
- HRQoL (EORTC-QLQ-C30)
- Safety and tolerability

1. https://clinicaltrials.gov/ct2/show/NCT02000622; 2. Robson et al. Poster OT1-1-04, San Antonio Breast Cancer Symposium 2014; 3. AZ data on file (2017),
4. Robson et al. N Engl J Med. 2017; 377:523-533

OlympiAD: Baseline Characteristics

Characteristic, n (%)	Olaparib (n = 205)	CT (n = 97)
Median age, yrs (range)	44 (22-76)	45 (24-68)
Male	5 (2)	2 (2)
White race	134 (65)	63 (65)
BRCA mutation status ▪*BRCA1* ▪*BRCA2* ▪Both	 117 (57) 84 (41) 4 (2)	 51 (53) 46 (47) 0
HR status ▪ER+ and/or PgR+ ▪TNBC	 103 (50) 102 (50)	 49 (51) 48 (49)
Previous CT for metastasis	146 (71)	69 (71)
Previous platinum tx	**60 (29)**	**26 (27)**

Characteristic, n (%)	Olaparib (n = 205)	CT (n = 97)
De novo MBC	26 (13)	12 (12)
Measurable disease ▪≥ 2 sites ▪Bone metastases only	167 (82) 159 (78) 16 (8)	66 (68) 72 (74) 6 (6)
No. CT lines for MBC ▪0 ▪1 ▪2	 66 (33) 80 (39) 57 (28)	 31 (32) 42 (43) 24 (25)
Physician choice CT **▪Capecitabine** **▪Eribulin** **▪Vinorelbine**	N/A	 **41 (45)** **34 (37)** **16 (18)**

Robson ME, et al. ASCO 2017. Abstract LBA4.

Slide credit: clinicaloptions.com

Baseline patient characteristics were generally well balanced[1]

Patients had a median age of 44, and generally had good performance status[1]

		Olaparib n=205 n (%)	TPC n=97 n (%)	Total n=302 n (%)
Median age (min, max)		44 (22, 76)	45 (24, 68)	44 (22, 76)
Male		5 (2.4)	2 (2.1)	7 (2.3)
ECOG PS	**0**	148 (72.2)	62 (63.9)	210 (69.5)
	1	57 (27.8)	35 (36.1)	92 (30.4)
Race	**White**	134 (65.4)	63 (64.9)	202 (66.9)
	Asian	66 (32.2)	28 (28.9)	94 (31.1)
	Other	5 (2.4)	6 (6.2)	11 (3.6)

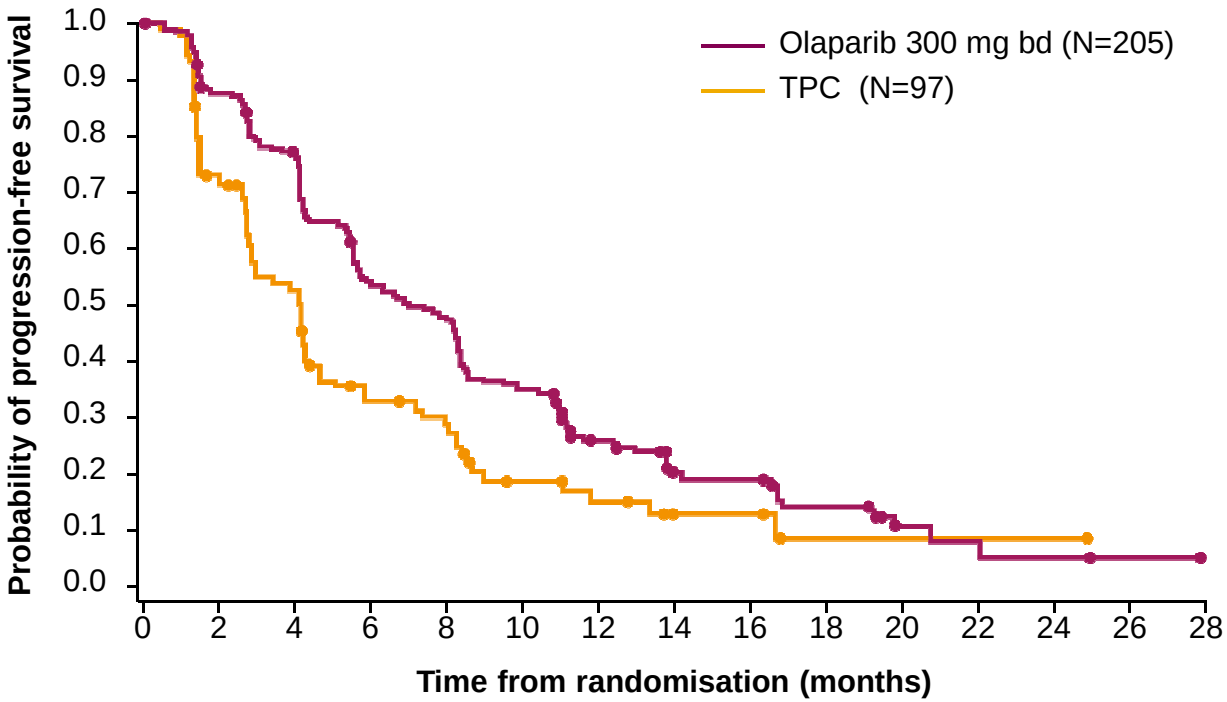
Adapted with permission[1,2]

Data Cutoff: 9th December 2016

1 Robson et al. N Engl J Med. 2017; 377:523-533; 2. AZ data on file (2017)

Primary endpoint: Olaparib treatment significantly improved PFS assessed by BICR compared to TPC[1]

The risk of progression or death over the course of the study was reduced by over 40%[1]



Number of patient's at risk

Olaparib	205	201	177	159	154	129	107	100	94	73	69	61	40	36	23	21	21	11	11	11	4	3	3	2	2	1	1	1	0
TPC	97	88	83	46	44	29	25	24	21	13	11	11	8	7	4	4	4	1	1	1	1	1	1	1	1	0	0	0	0

	Olaparib	TPC
n	205	97
Events (%)	163 (79.5%)	71 (73.2%)
Median (m)	**7.0**	**4.2**
	HR = 0.58 95 % CI (0.43, 0.80) p=0.0009	
PFS free at 6m (%)	54.1	32.9
PFS free at 12m (%)	25.9	15.0

- **2.8 months by BICR**
- **4 months by IA**

1. Robson et al. N Engl J Med. 2017; 377:523-533; 2. AZ data on file (2017)

Doubling of ORR in the olaparib arm compared to further supports the PFS findings[1]

ORR was 60% in the olaparib arm versus 29% in the TPC arm[1]

	Olaparib	TPC
Response Evaluable Population, n	167	66
ORR, n (%)	**100 (59.9)**	**19 (28.8)**
Complete Response, n (%)	15 (9.0)	1 (1.5)
Partial Response, n (%)	85 (51.0)	18 (27.3)
Median Duration of Response, months (95%CI)	6.4 (2.9-9.7)	7.1 (3.2-12.2)
Median Time to Onset of Response, days	47	45

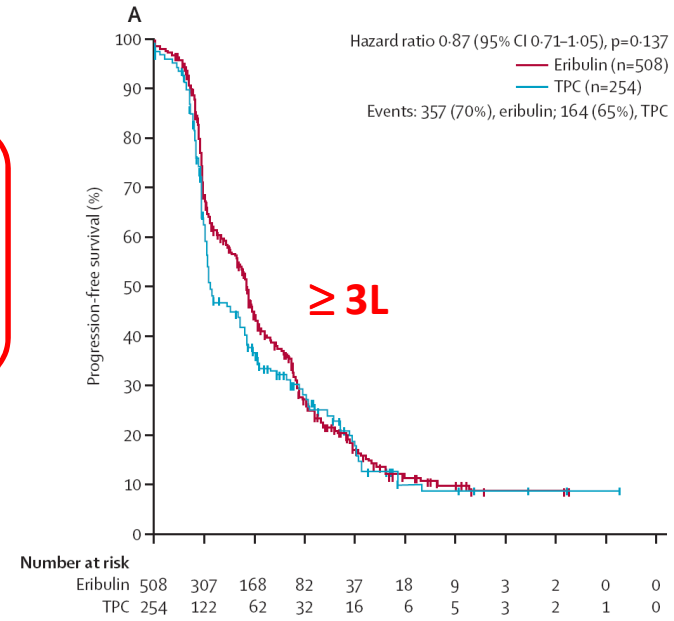
Adapted with permission[1]

BICR Review
Data Cutoff: 9th December 2016

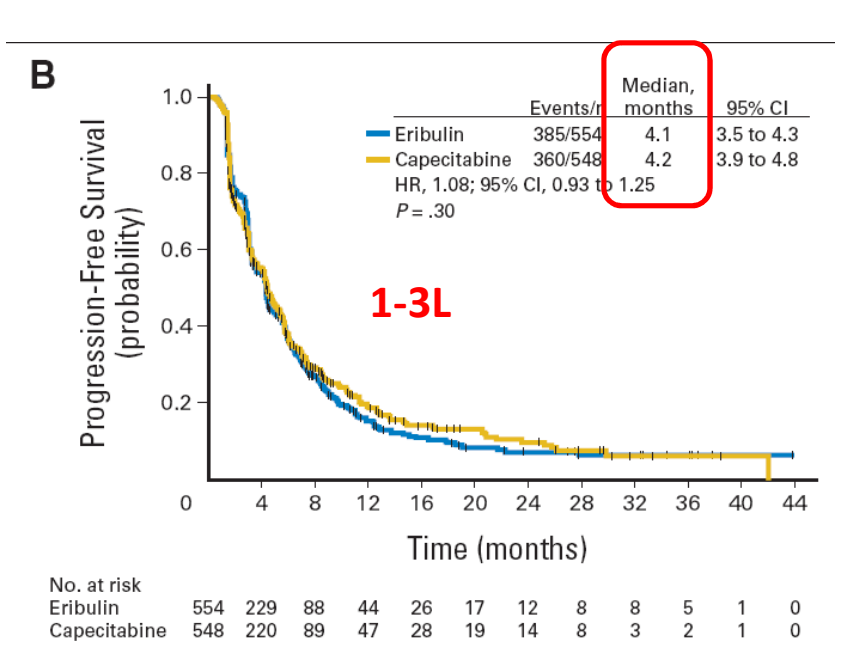
1. Robson et al. N Engl J Med. 2017; 377:523-533

Historical Chemotherapy efficacy in mBC

	Independent review		
	Eribulin	TPC	HR* (95% CI), p value
Progression-free survival			
Median (months)	3·7 (3·3–3·9)	2·2 (2·1–3·4)	0·87 (0·71–1·05) p=0·137
Best overall tumour response			
Tumour response			
Complete response	3 (1%)	0	..
Partial response	54 (12%)	10 (5%)	..
Stable disease	208 (44%)	96 (45%)	..
Progressive disease	190 (41%)	105 (49%)	..
Not evaluable	12 (3%)	3 (1%)	..
Unknown	1 (<1%)	0	..
Objective response rate†	57 (12%; 9·4–15·5)	10 (5%; 2·3–8·4)	p=0·002‡
Clinical benefit rate§	106 (23%; 18·9–26·7)	36 (17%; 12·1–22·5)	..



247 received TPC*
- 238 (96%) received chemotherapy†
  - 61 (25%) vinorelbine
  - 46 (19%) gemcitabine
  - 44 (18%) capecitabine
  - 38 (15%) taxanes‡
  - 24 (10%) anthracyclines§
  - 25 (10%) other chemotherapies¶
- 9 (4%) received hormonal therapy||

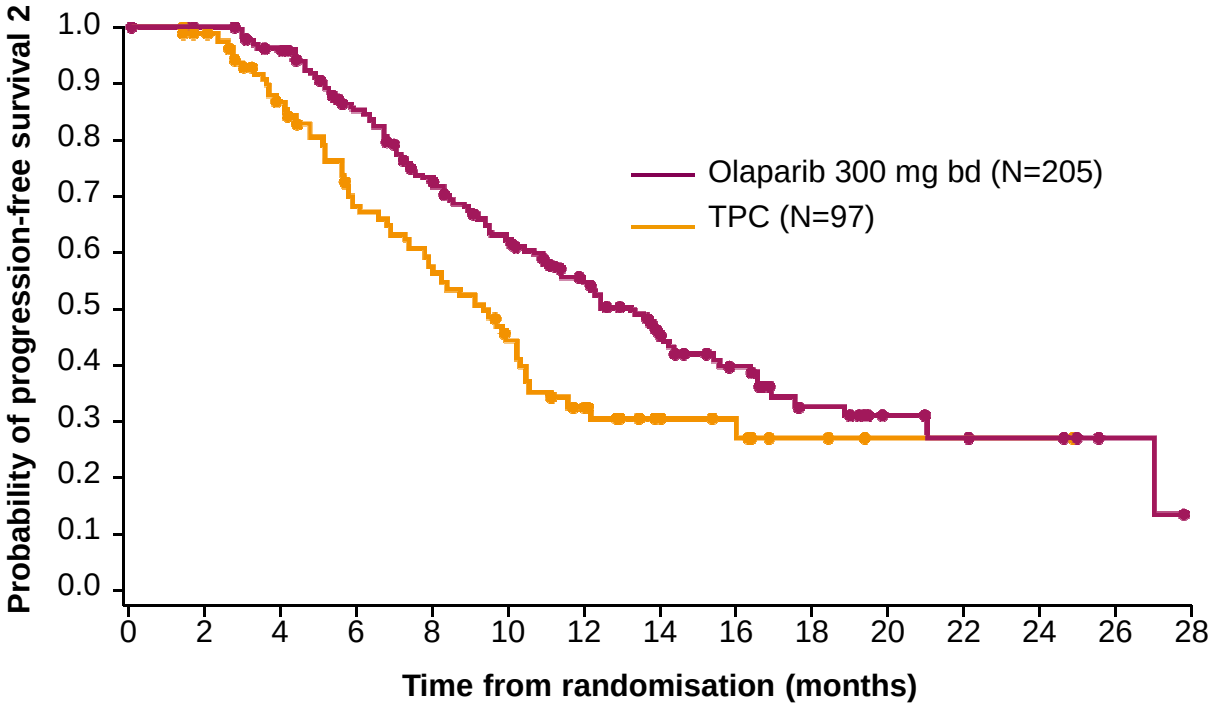


Eribulin vs Capacitabine

Objective response rate†		
No. of patients	61	63
%	11.0	11.5
95% CI	8.5 to 13.9	8.9 to 14.5
P‡	.85	

Lancet 2011; 377: 914–23; J Clin Oncol. 2015; 33(6): 594–601

PFS2 was also significantly increased with olaparib treatment versus TPC indicating benefit beyond first progression[1]



Number of patient's at risk

Olaparib	205	204	199	193	185	171	152	137	123	113	102	89	75	64	44	39	34	20	18	16	8	7	6	5	5	3	2	2	0
TPC	97	92	65	76	69	51	51	47	42	39	31	25	19	14	10	7	7	4	4	3	1	1	1	1	1	0	0	0	0

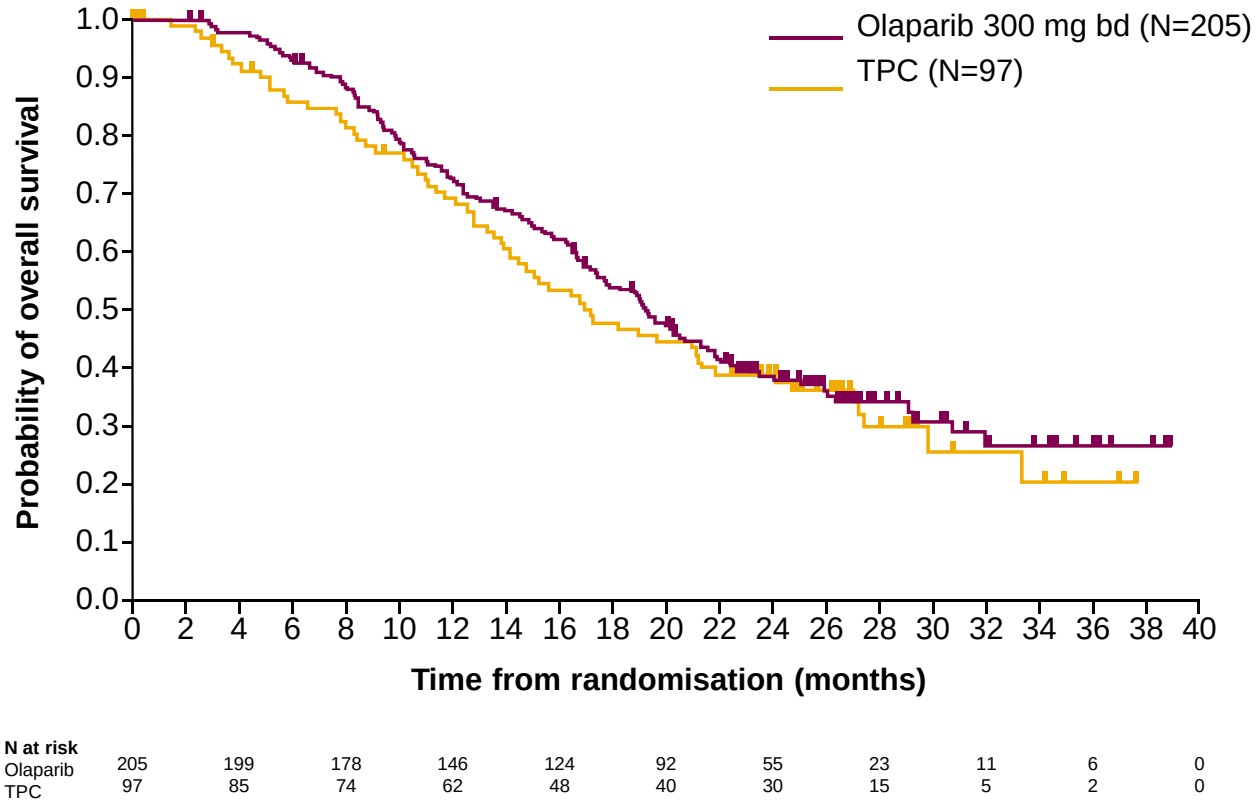
	Olaparib	TPC
n	205	97
Events (%)	104 (50.7%)	53 (54.6%)
Median (m)	**13.2**	**9.3**
	HR = 0.57 **95 % CI (0.40, 0.83)** **p=0.0033**	

PFS2= from randomization to 2nd PD

Data Cutoff: 9th December 2016

At the final DCO median overall survival in the olaparib arm was 19.3 months compared to 17.1 months in the TPC arm[1]

The difference did not reach statistical significance HR = 0.9 (95% CI: 0.66, 1.23) p=0.513

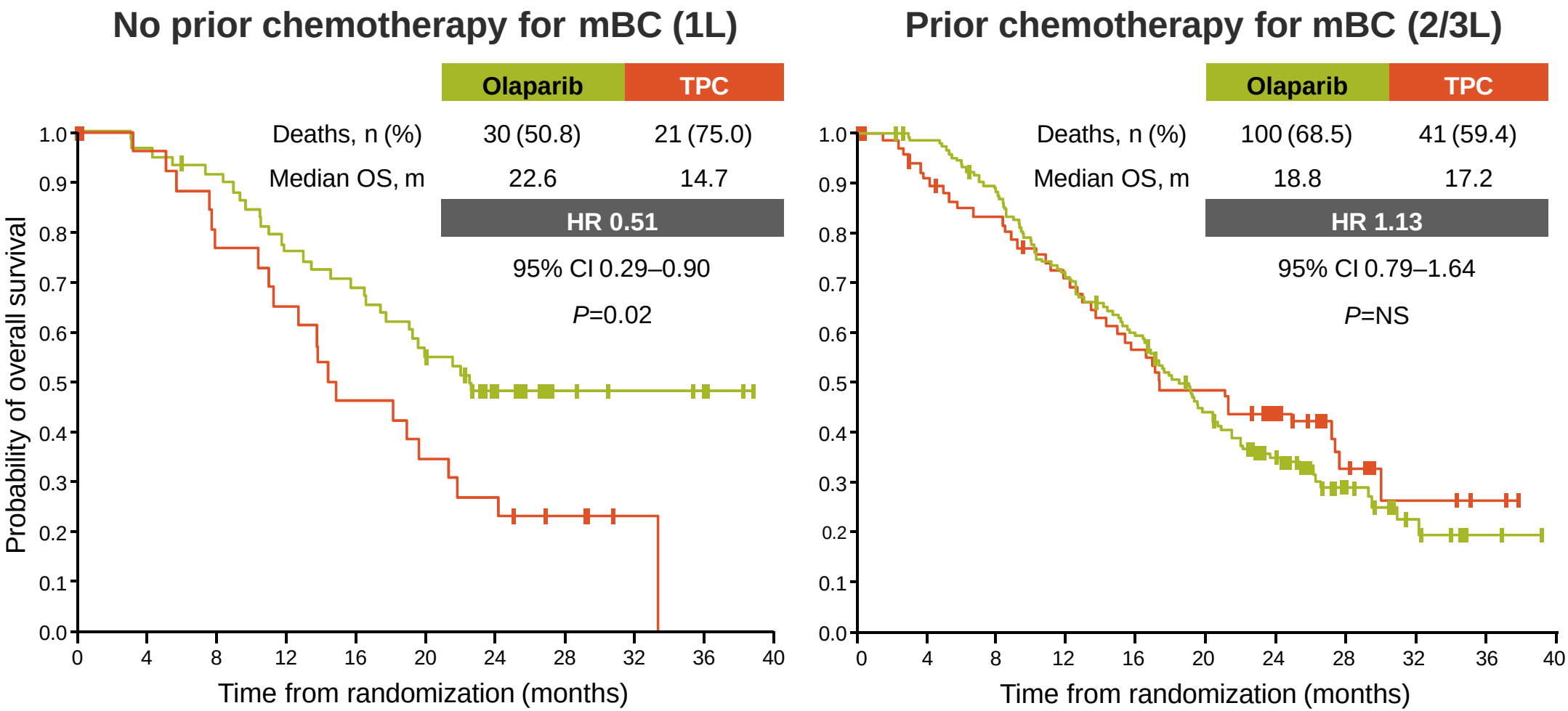


	Olaparib	TPC
n	205	97
Events (%)	130 (63)	62 (64)
Median (m)	**19.3**	**17.1**
	HR = 0.90 95% CI (0.66, 1.23) p=0.513	
Survival at 6m (%)	93.1	85.8
Survival at 18m (%)	54.1	48.0

OlympiAD was not powered to show an OS benefit[1]

1. Robson et al. AACR, 2018

Kaplan Meier plots for OS in patients with and without prior chemotherapy for mBC at baseline

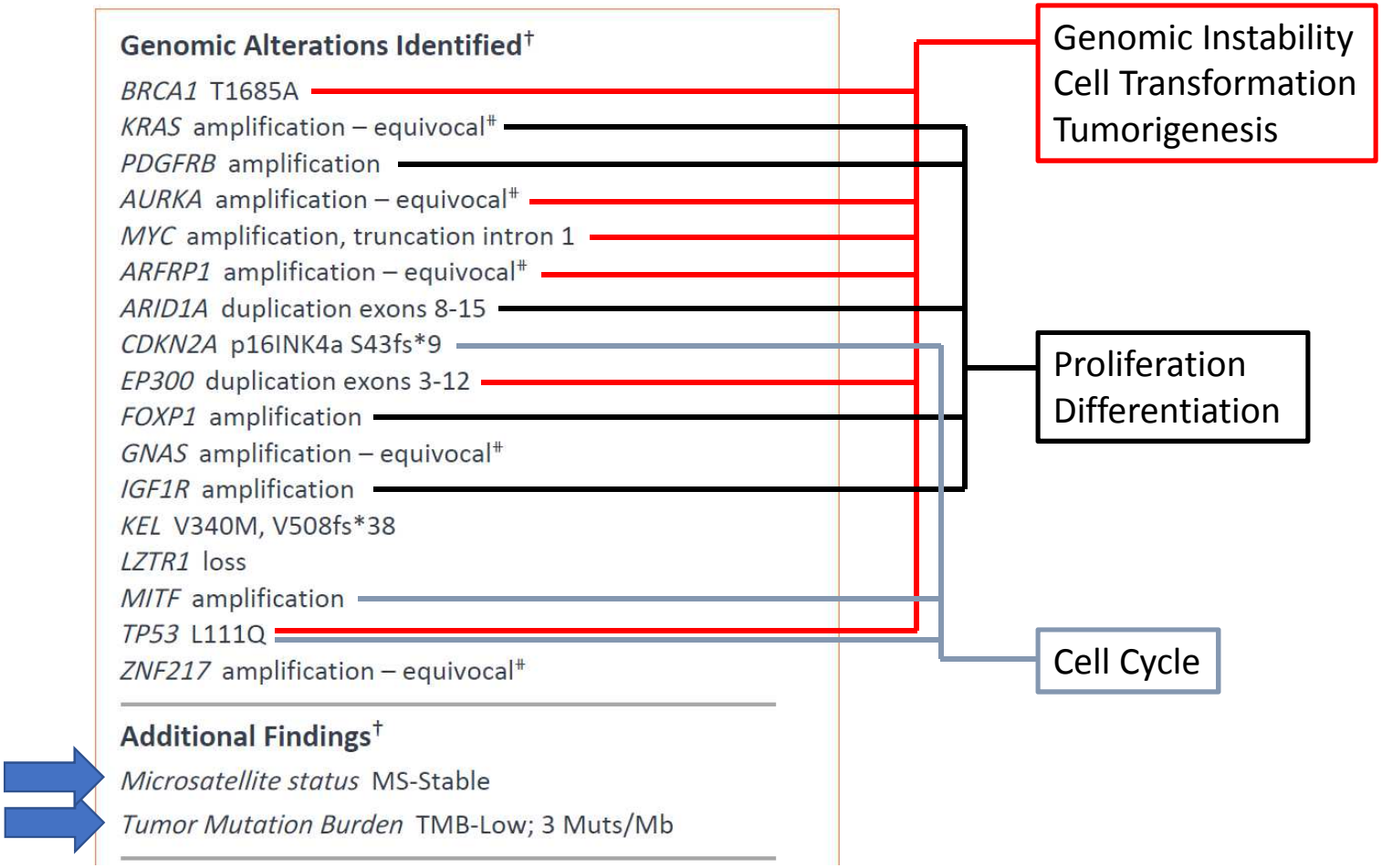


Nominal *P* values calculated using a likelihood ratio test; OS stratification factors were prespecified but not alpha controlled
1L, first line; 2/3L, second or third line; NS, not significant

Case History

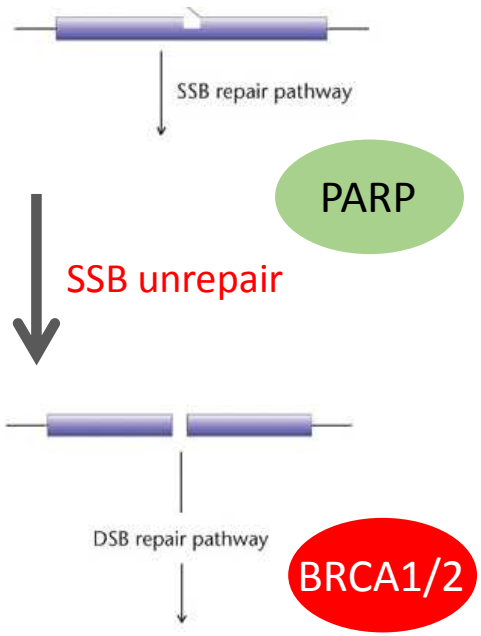
- Female, Breast Cancer, TNBC s/p adjuvant Taxotere/Carboplatin + FEC
- Recurrence as mTNBC
- - s/p Xeloda
  - s/p Eribulin
  - s/p lipo-Doxrubicin + cyclophosphamide
  - s/p vinorelbine + cisplatin + Avastin
  - s/p Pembrolizumab + paclitaxel + gemcitabine
- All lines of Tx are of short PFS,
- Tumor specimen (FFPE) from RECURRENT tumors sent for NGS study.

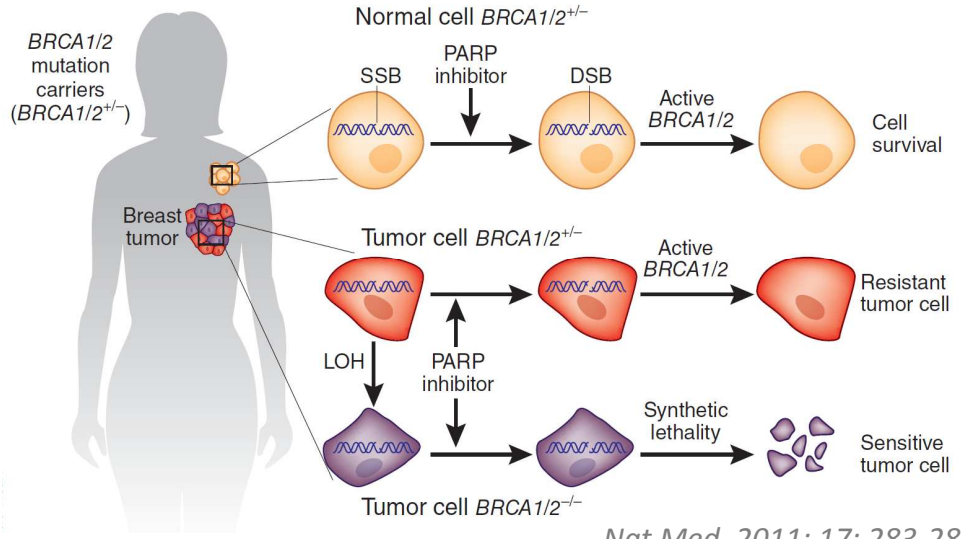
Co-occurrence of multiple genomic alterations



Prioritizing genomic alterations: BRCA1-T1685A

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)
BRCA1 T1685A	None	Niraparib Olaparib Rucaparib

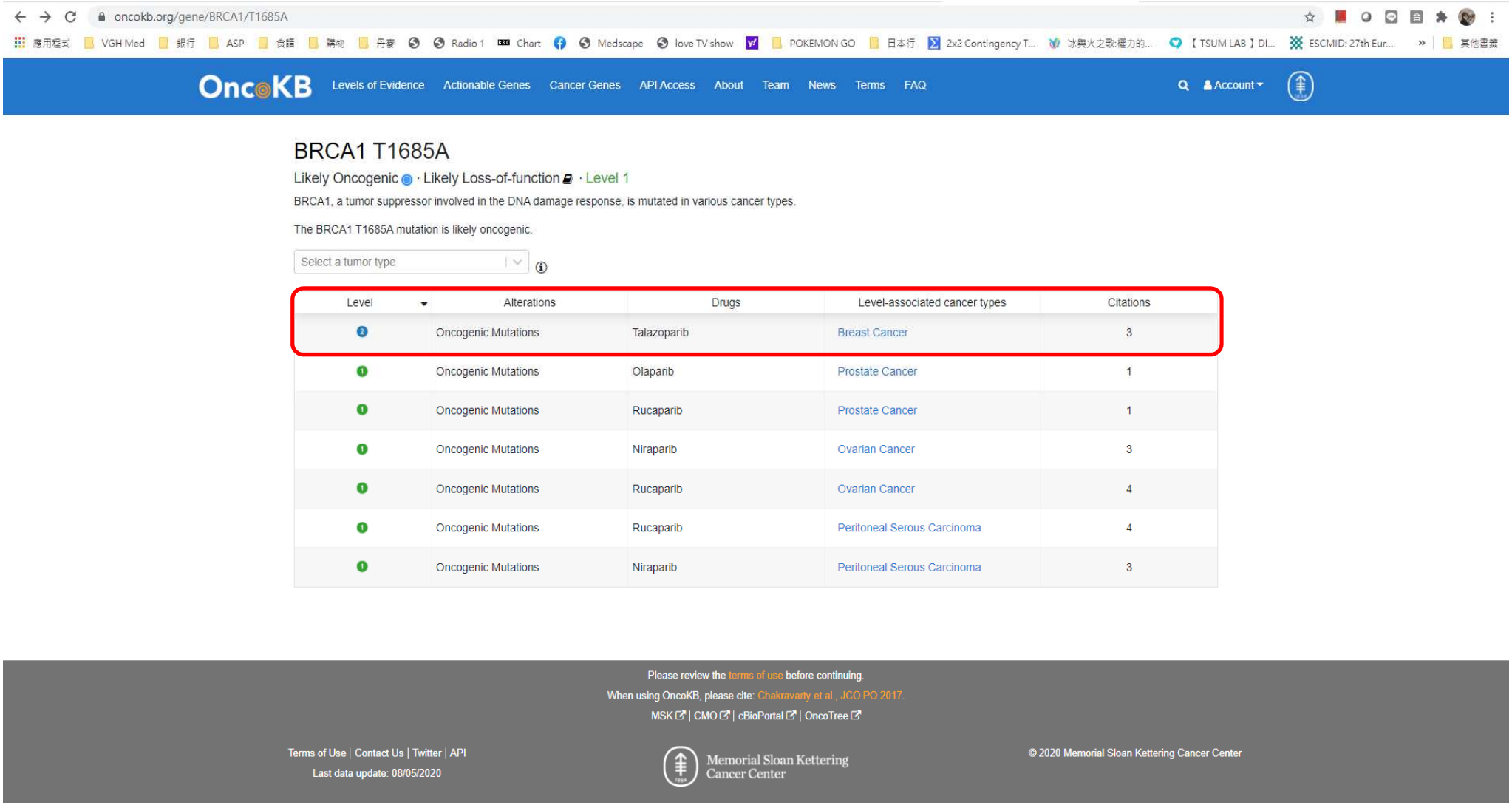




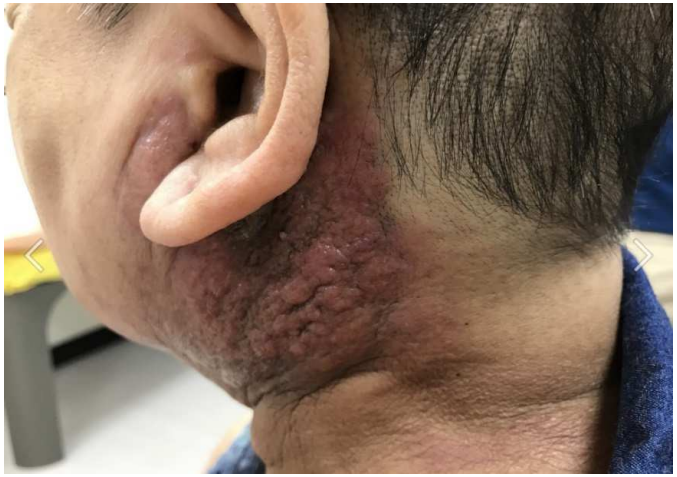
Nat Med. 2011; 17: 283-284

Allele frequency 75%, likely also gBRCA BUT UNconfirmed

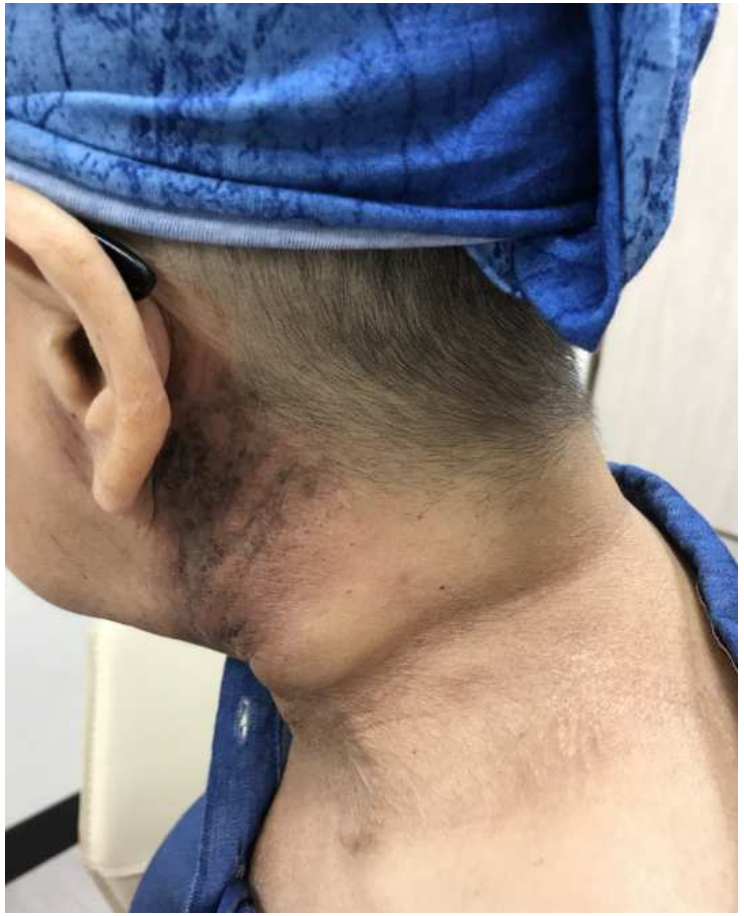
Prioritizing actionable targets



Aug. 23
Before PARP inhibitor treatment



Oct. 23
After 2 mons of PARP inhibitor treatment



Olaparib beyond gBRCA mutation in Breast cancer?

TBCRC 048: A phase II study of olaparib monotherapy in metastatic breast cancer patients with germline or somatic mutations in homologous recombination (HR) pathway genes (Olaparib Expanded)

Nadine Tung, Mark E. Robson, Steffen Ventz, Cesar Santa-Maria, Paul Kelly Marcom, Rita Nanda, Payal D. Shah, Tarah J. Ballinger, Eddy Yang, Michelle Melisko, Adam Brufsky, Shaveta Vinayak, Michelle DeMeo, Colby Jenkins, Susan Domchek, Gerburg Wulf, Ian E. Krop, Antonio C. Wolff, Eric P. Winer, Judy E. Garber

Presented By Nadine Tung at 2020 ASCO virtual meeting.

TBCRC 048: Study Schema (Olaparib expand)

non-randomized, Ph II study of olaparib in pts with mutations in HR pathway genes other than gBRCA

- Stage IV invasive breast cancer
- ≥1 measurable lesion per RECISTv1.1
- ≤2L prior chemotherapy for mBC
- PARPi naïve
- Non-platinum refractory disease
- Germline or somatic (likely) pathogenic variant (mutation) in:
  - *ATM, ATR, BARD1, BRIP1 (FANCJ), CHEK2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCM, MRE11A, NBN, PALB2, PTEN, RAD50, RAD51C, RAD51D* (+ others at PIs discretion)

--OR--

- Somatic BRCA1/2m (by tumour biopsy or cfDNA) in the absence of g*BRCA*m
- Germline testing only required to exclude g*BRCA*m if s*BRCA*m was present

***N*=54**
Cohort 1 Germline Mutation (n=27)
Cohort 2 Somatic Mutation (n=27*)
sBRCAm allowed if gBRCA (-)

Research biopsy prior to treatment

Tumour assessment q6w x 24w, then q12w

Olaparib
300 mg* *po* bid q3w

Optional research biopsy at progression

Primary Endpoint
- ORR (CR + PR by RECIST 1.1)

Secondary Endpoints
- CBR (CR + PR + SD ≥ 18w)
- DoR
- PFS
- Toxicity

Hypothesis: In patients with a g/s mutation in a HR pathway gene other than *BRCA*m, or patients with s*BRCA*m, olaparib will have an ORR ≥ 20%

***1 patient in Cohort 2 (s*BRCA2*) later found to be g*BRCA2*+; excluded from analysis**
Patients continued treatment if they experienced CR, PR, or SD and discontinued treatment if they experienced PD or toxicity requiring discontinuation
See notes for abbreviations

1. Tung N et al. Presented at: ASCO 2020 Congress; May 29-31, 2020; Chicago, Illinois; 2. Clinicaltrials.gov identifier: NCT03344965

Patient and Tumor Characteristics

	Total N=53	Cohort 1 Germline N=27	Cohort 2 Somatic N=26
Age – median (range)- yrs	59 (30-87)	54 (30-87)	59 (34-79)
Subtype*			
ER+ HER2-neg#	75%	85%	65%
TNBC	19%	7%	31%
HER2+	5%	7%	4%
# lines chemo in met setting- mean (range)	1 (0-4)	0 (0-2)	1 (0-4)
No prior chemotherapy	19%	22%	15%
Prior platinum	5%	4%	8%
Prior CDK4/6i among ER+ HER2-neg	93%	96%	88%

* Subtype of primary tumor # ER, HER2 determined locally

Tung N et al. Presented at: ASCO 2020 Congress; May 29-31, 2020.

Gene Mutation

Germline (Cohort 1)		Somatic (Cohort 2)[4]	
• *CHEK2*[1,2]	n=8	• *sBRCA1*[5]	n=6
• *ATM*	n=4	• *sBRCA2*	n=9
• *ATM & CHEK2*[1]	n=2		
• *PALB2*[3]	n=11	• *ATM*[6]	n=4
• *BARD1*	n=1	• *PALB2*	n=2
• *RAD50*	n=1	• *CDK12*	n=2
		• *BRIP1*	n=1
		• *BLM*	n=1
		• *FANCA*	n=1

14 *ATM CHEK2*

15 *sBRCA1/2*

[1] CHEK2: 5 missense, 5 frameshift/truncating
[2] 1 pt with missense CHEK2 found to also have sBRCA1 mutation (not listed with Cohort 2)
[3] 1 gPALB2 also had gATM mutation (not listed with ATM group)
[4] For 8 patients in Cohort 2, germline status is unknown
[5] One sBRCA1 also had sATM (not listed with ATM group)
[6] 1 sATM also had also had a sFANCF mutation

87% had a mutation in *ATM, CHEK2, PALB2* or *sBRCA1/2*

- Germline or somatic (likely) pathogenic variant (mutation) in:

  ATM, ATR, BARD1, BRIP1 (FANCJ), CHEK2 , FANCA, FANCC, FANCD2, FANCE, FANCF, FANCM, MRE11A, NBN, PALB2, PTEN, RAD50, RAD51C, RAD51D (+ others at PI's discretion)

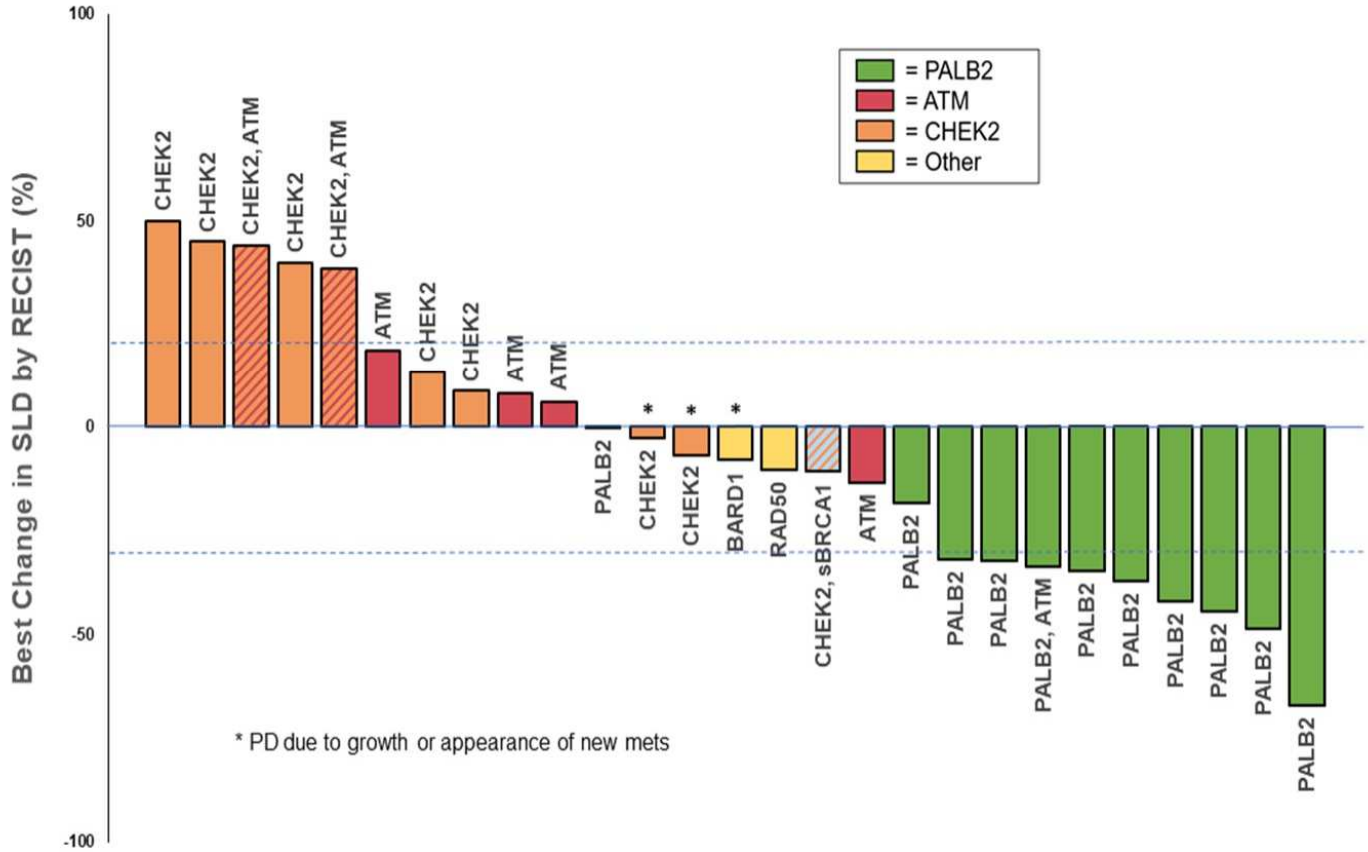
Tung N et al. Presented at: ASCO 2020 Congress; May 29-31, 2020.

Best Overall Responses: Cohort 1 (Germline)

Cohort 1 (Total) N=27	
Best Response	**Responses (rate, %)**
Complete Response (CR)	0 (0%)
Partial Response (PR)	9 (33%)
Stable Disease (SD)	8 (30%)
Progressive Disease (PD)	10 (37%)
ORR = 33% (9/27, 90%-CI: 19%-51%)	
CBR (18 weeks) = 44% (11/25, 90%-CI: 27%-62%)	

Results for g*PALB2*

g*PALB2* N=11	
Best Response	**Responses (rate, %)**
Complete Response (CR)	0 (0%)
Partial Response (PR)	9 (82%)
Stable Disease (SD)	2 (18%)
Progressive Disease (PD)	0 (0%)
ORR = 82% (9/11, 90%-CI: 48%-98%)	
CBR (18 wks) = 100% (10/10, 90%-CI: 74%-100%)	



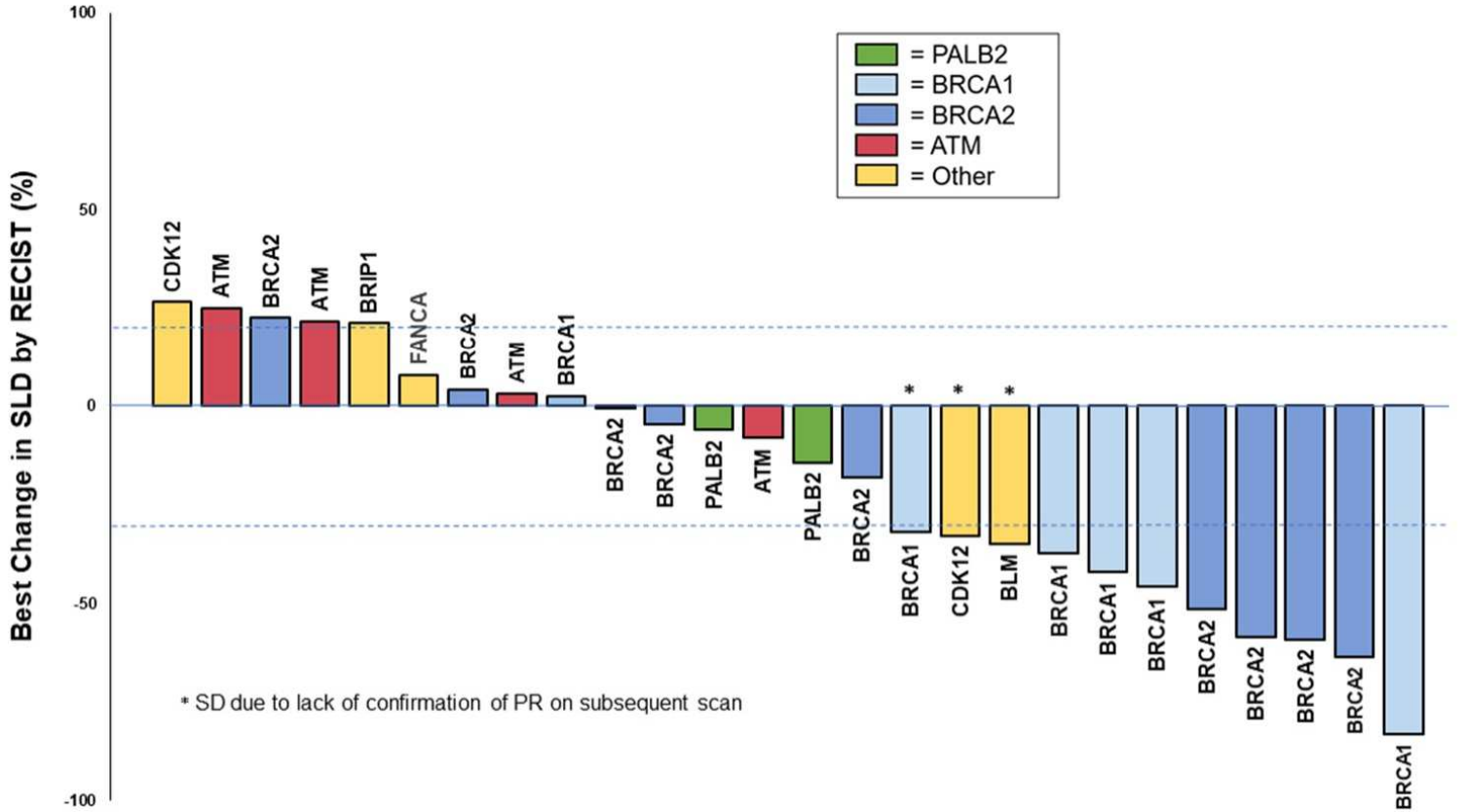
Datacut May 4, 2020

Presented By Nadine Tung at TBD

Best Overall Responses: Cohort 2 (Somatic)

Results for s*BRCA1/2*

s*BRCA1/2* N=16*	
Best Response	**Responses, (rate, %)**
Complete Response (CR)	0 (0%)
Partial Response (PR)	8 (50%)
Stable Disease (SD)	6 (38%)
Progressive Disease (PD)	2 (12%)
ORR = 50% (8/16, 90%-CI: 25%-75%)	
CBR (18 wks) = 67% (10/15, 90%-CI: 47%-87%)	



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Presented By Nadine Tung at TBD

Responses for 5 most common genes (somatic and germline mutations)

PALB2 N=13	*sBRCA1/2* N=17^	*ATM & CHEK2*** N=17
Germline: 9/11 PR (82%) 10/11 had tumor regression; 1 SD > 1 yr **Somatic: 0/2 – both SD*** **(limited assessments)**	**8/16 PR (50%)**	**0/13 germline** **0/4 somatic**

15 patients remain on study

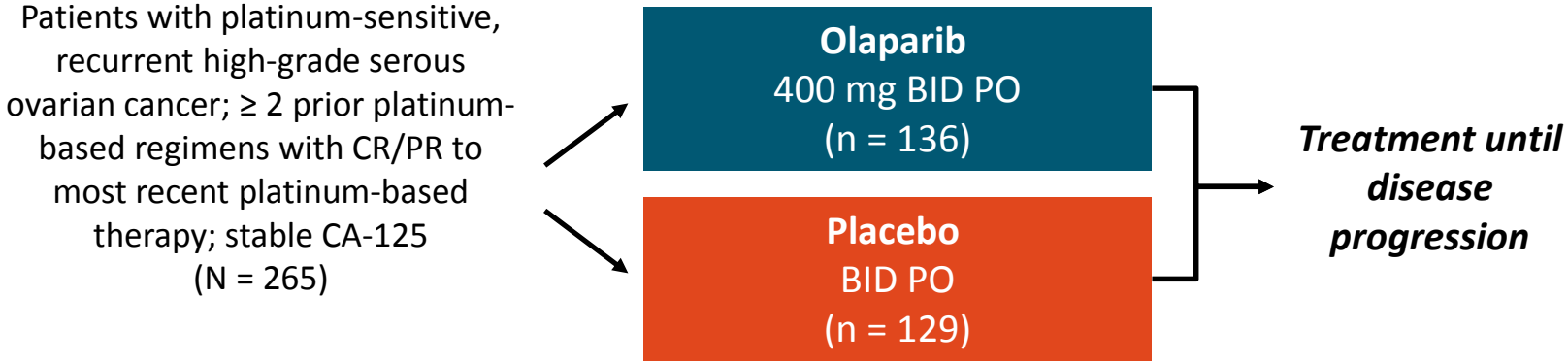
* 1 sPALB2- lost to follow-up after 1st tumor assessment with skin and tumor marker response
^ includes patient from Cohort 1 with sBRCA1 and gCHEK2
** Not included: patient with both gCHEK2 & sBRCA1; patient with gATM and gPALB2

Datacut May 4, 2020

PARP inhibitor trials in ovarian cancer

Phase II Study 19 of Olaparib Maintenance in Platinum-Sensitive Recurrent Ovarian Cancer

- Randomized, double-blind phase II clinical trial

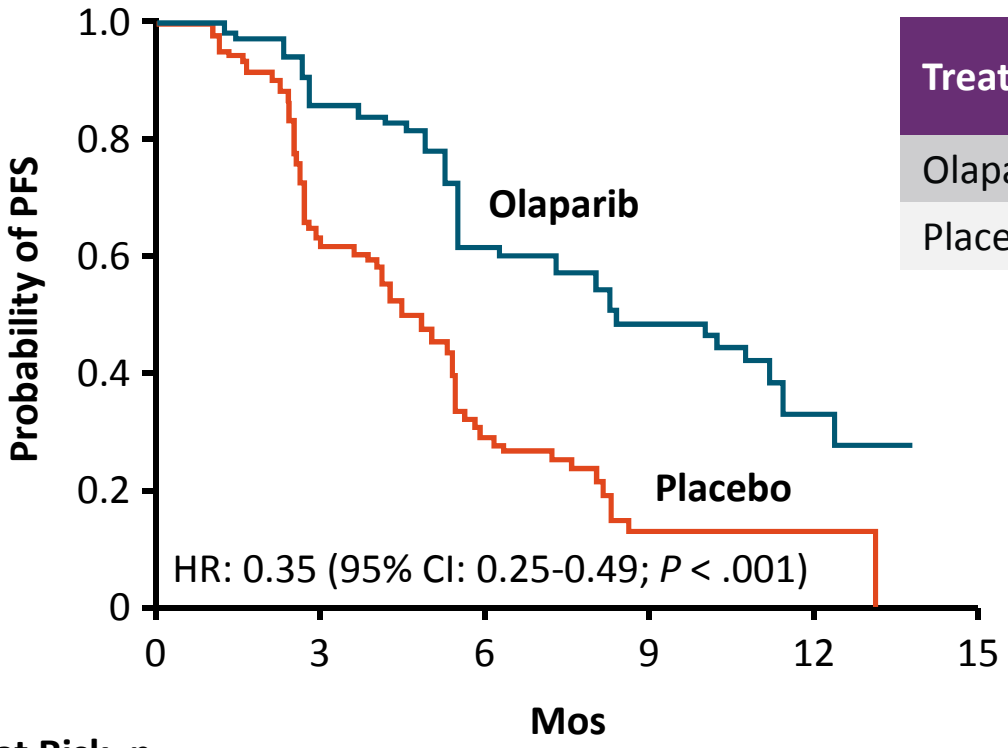


- Primary endpoint: PFS (RECIST 1.0)
- Secondary endpoints: OS, safety, tolerability
- Exploratory endpoints: time to first subsequent therapy or death, time to second subsequent therapy or death

Ledermann. NEJM. 2012;366:1382.

Slide credit: clinicaloptions.com

Study 19: PFS



Patients at Risk, n						
Olaparib	136	104	51	23	6	0
Placebo	129	72	23	7	1	0

Treatment	Number of Patients With Event (%)	Median PFS, Mos
Olaparib	60 (44.1)	8.4
Placebo	93(72.1)	4.8

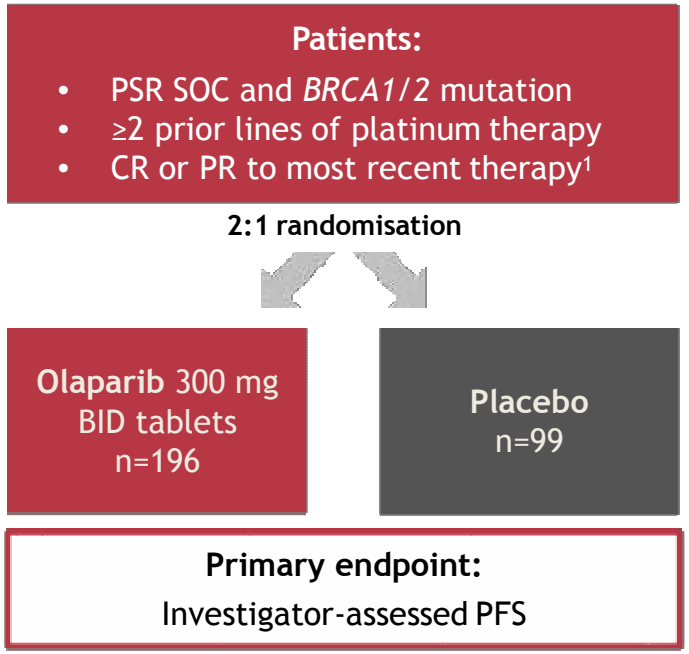
Ledermann. NEJM. 2012;366:1382.

Slide credit: clinicaloptions.com

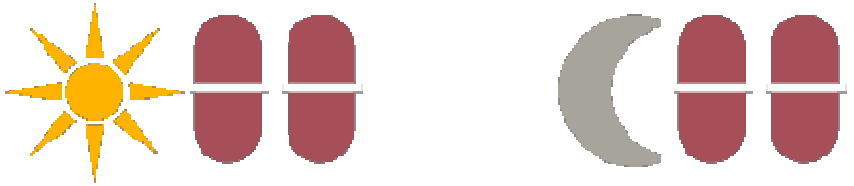
SOLO-2: Study Design

First phase 3 study testing olaparib tablets (300mg bd)

SOLO-2, a phase 3 study, was designed to provide additional evidence for the benefit of olaparib maintenance therapy in patients with *BRCA*m PSR ovarian cancer[1,2]



- SOLO-2 reported data on the new film-coated tablet formulation of olaparib[1-3]
- The tablet formulation used in SOLO-2 was chosen based on data from Study 24[4]
- The recommended **tablet dose was 300 mg** administered as 2 x 150-mg tablets, twice daily[4]

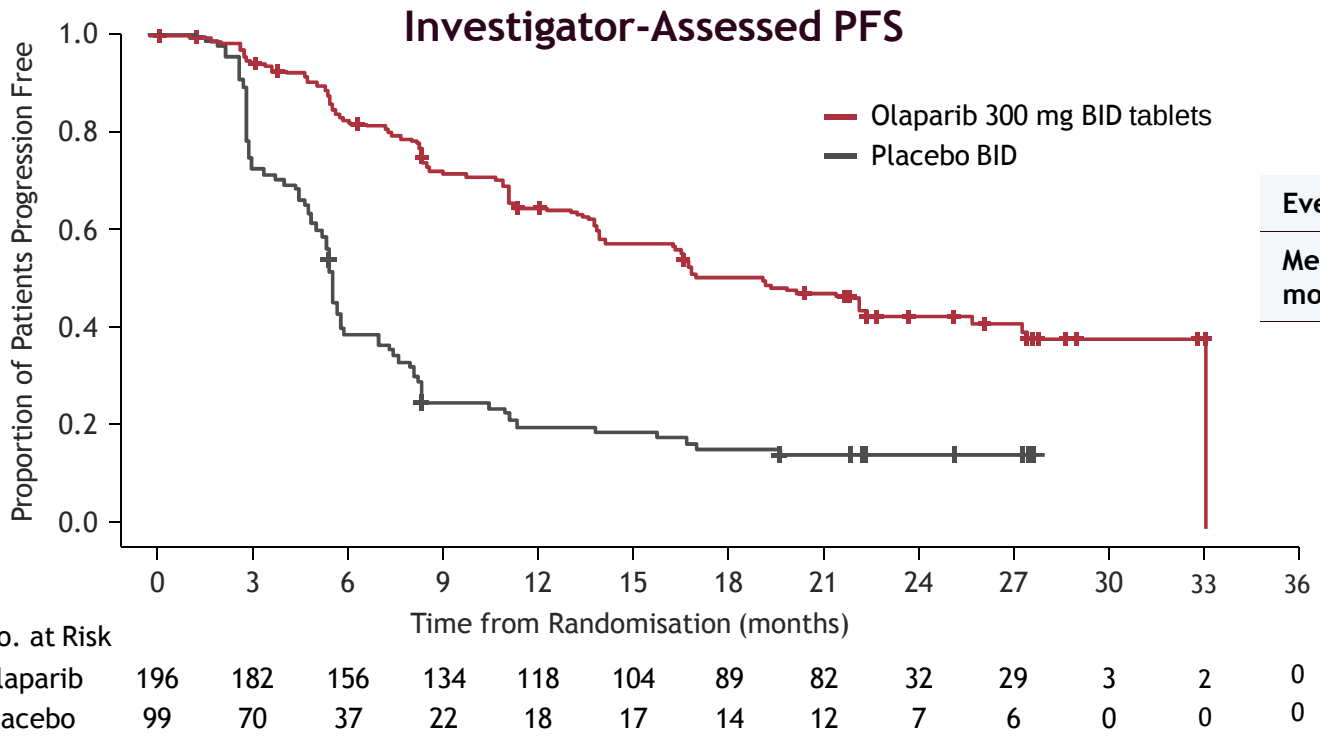


BID=twice daily; *BRCA*m=*BRCA* mutated; CR=complete response; PFS=progression-free survival; PR=partial response; PSR=platinum-sensitive relapsed; SOC=standard of care.

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01874353. Accessed 24 September 2018. 2. Pujade-Lauraine E et al. *Lancet Oncol*. 2017;18(9):1274-1284. 3. Ledermann J et al. *N Engl J Med*. 2012;366:1382–1392. 4. Mateo J et al. *Target Oncol*. 2016;11(3):401–415.

SOLO-2: Investigator-Assessed Progression-Free Survival

Risk of progression or death during the study was reduced by 70% for patients taking olaparib vs placebo[1,2]



	Olaparib 300 mg BID tablets	Placebo BID
Events, n (%)	107/196 (54.6)	80/99 (80.8)
Median PFS, mo	**19.1**	**5.5**

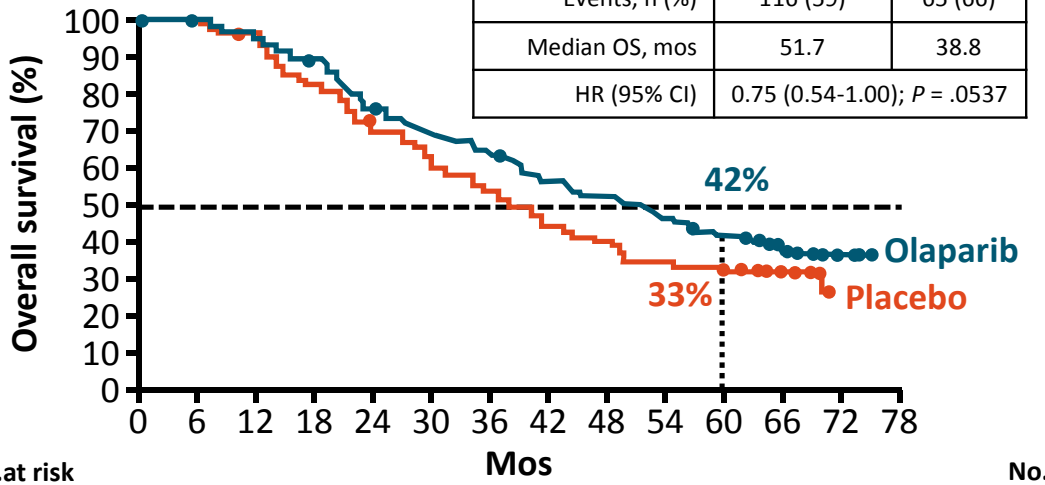
HR=0.30
(95% CI, 0.22-0.41)
P<0.0001

Investigator-assessed PFS at 63% maturity. Median follow-up for PFS was 22.1 months in the olaparib group and 22.2 months for placebo. Full assessment set N=295. Data cutoff: 9/19/2016.
BID=twice daily; CI=confidence interval; HR=hazard ratio; PFS=progression-free survival.
1. Pujade-Lauraine E et al. *Lancet Oncol*. 2017;18(9):1274-1284. 2. Pujade-Lauraine E et al. Presented at: SGO Annual Meeting; 2017.

SOLO2: Final OS Analysis

OS

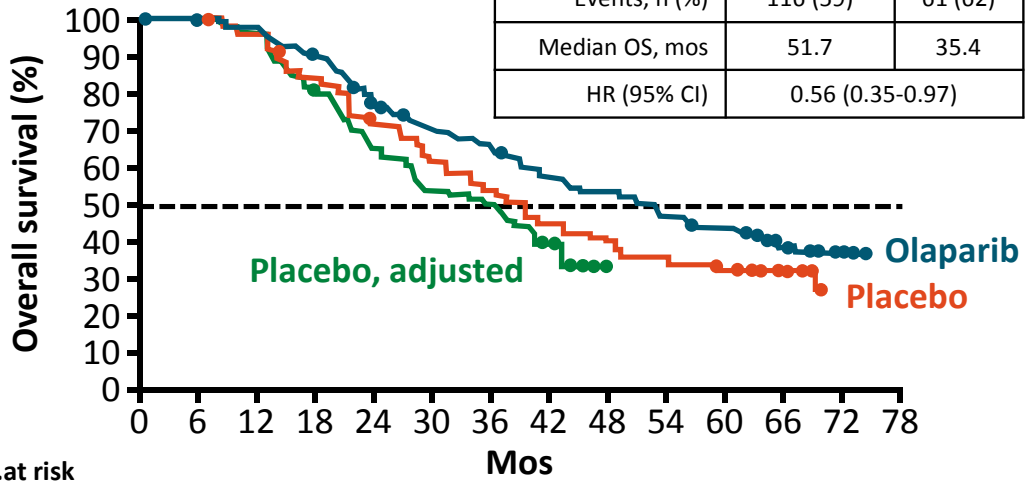
	Olaparib (n = 196)	Placebo (n = 99)
Events, n (%)	116 (59)	65 (66)
Median OS, mos	51.7	38.8
HR (95% CI)	0.75 (0.54-1.00); *P* = .0537	



No.at risk														
Olaparib	196	192	187	172	145	130	120	105	98	86	77	39	7	0
Placebo	99	99	93	79	66	57	50	42	38	33	31	16	0	0

Adjusted for subsequent PARP inhibitor use
(in 38% placebo, 10% olaparib pts)

	Olaparib (n = 196)	Placebo (n = 99)
Events, n (%)	116 (59)	61 (62)
Median OS, mos	51.7	35.4
HR (95% CI)	0.56 (0.35-0.97)	



No.at risk														
Olaparib	196	192	187	172	145	130	120	105	98	86	77	39	7	0
Placebo	99	99	93	79	66	57	50	42	38	33	31	16	0	0
Placebo adjusted	99	99	92	75	60	50	46	34	0	0	0	0	0	0

- HR 0.70 (95% CI: 0.52-0.96) per eCRF in full analysis set (posthoc)
- HR 0.71 (95% CI: 0.52-0.97) in gBRCA mutation subgroup (prespecified)

Poveda. ASCO 2020. Abstr 6002. Reproduced with permission.

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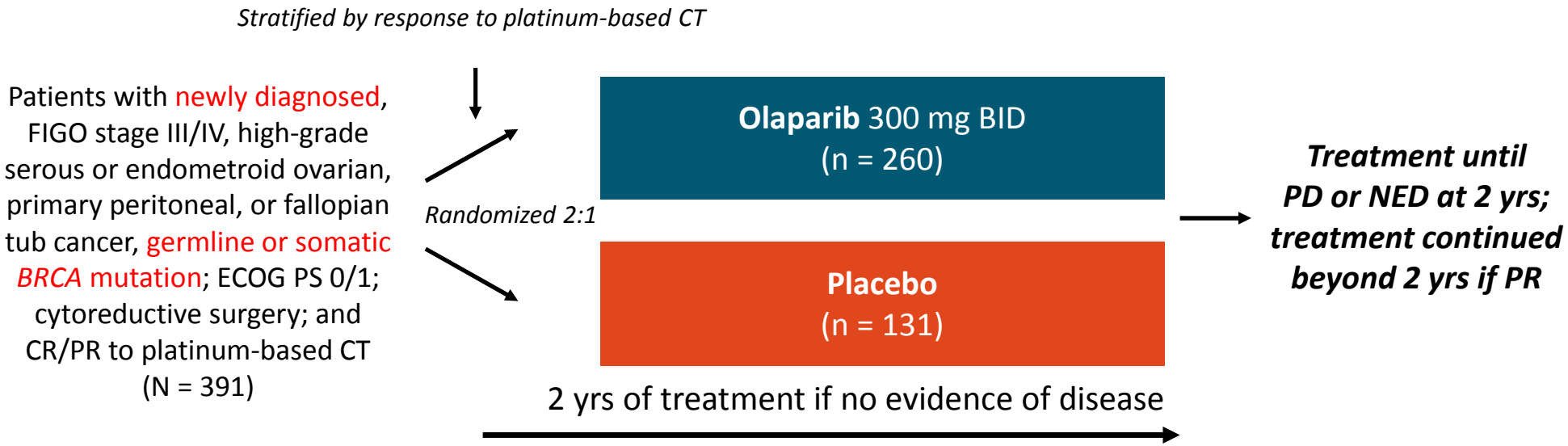
Phase III SOLO1 Trial of Olaparib vs Placebo as First-line Maintenance Therapy in Ovarian Cancer With *BRCA* Mutation

- Randomized, double-blind, placebo-controlled, multicenter phase III trial

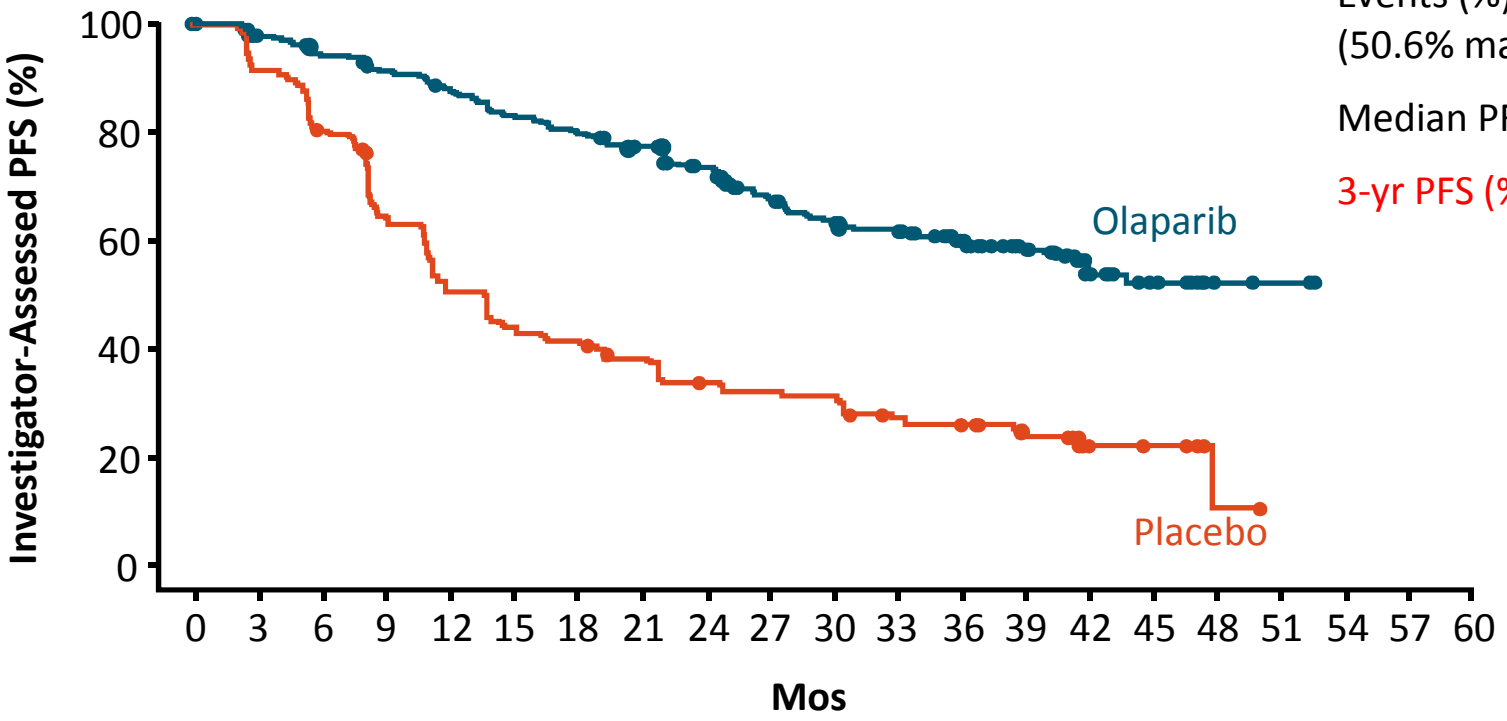


- Primary endpoint: investigator-assessed PFS (RECIST 1.1)
- Secondary endpoints: PFS by BICR, PFS2, OS, TSST or death, HRQoL (FACT-O TOI score)

Moore. NEJM. 2018;379:2495.

Slide credit: clinicaloptions.com

SOLO1: Investigator-Assessed PFS



Parameter	Olaparib (n = 260)	Placebo (n = 131)
Events (%) (50.6% maturity)	102 (39)	96 (73)
Median PFS, mos	NR	13.8
3-yr PFS (%)	60	27
HR: 0.30		
95% CI: 0.23-0.41; *P* < .0001		

Moore. NEJM. 2018;379:2495.

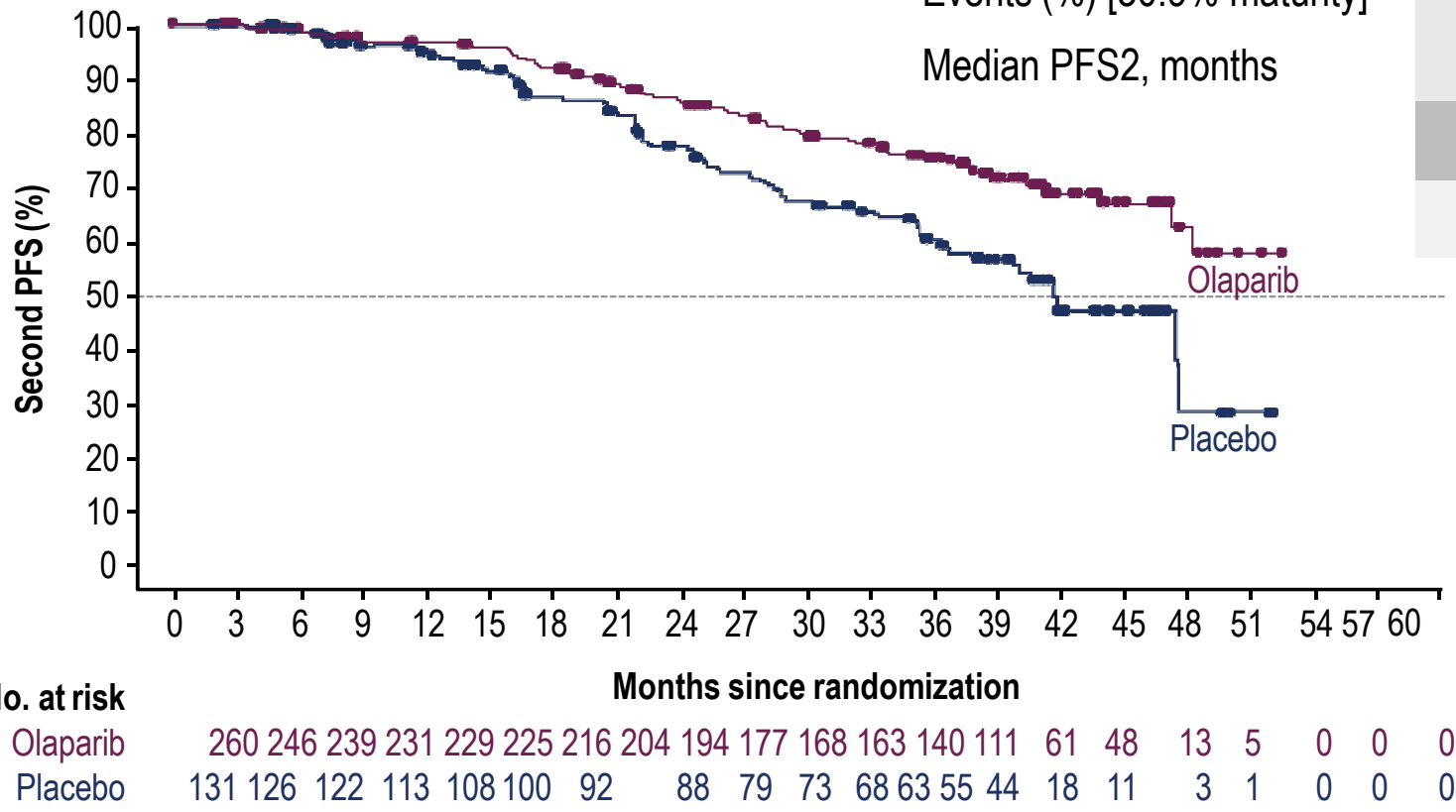
Slide credit: clinicaloptions.com

Patient disposition

	Olaparib	Placebo
Randomized, n	260	131
Treated, n	260	130
Discontinued treatment before 2 years	111 (42.7)	92 (70.8)
Completed treatment at 2 years per protocol	123 (47.3)	35 (26.9)
Continued treatment beyond 2 years	26 (10.0)	3 (2.3)
Still receiving treatment at data cut-off	13 (5.0)	1 (0.8)
Discontinued treatment for reason other than protocol-defined 2-year stopping rule	124 (47.7)	94 (72.3)
Objective disease progression	51 (19.6)	78 (60.0)
Adverse event	30 (11.5)	3 (2.3)
Patient decision	22 (8.5)	2 (1.5)
Other*/unknown reason	21 (8.1)	11 (8.5)
Median (range) duration of treatment, months	24.6 (0–52.0)	13.9 (0.2–45.6)
Median (IQR) duration of follow-up, months	40.7 (34.9–42.9)	41.2 (32.2–41.6)

*Other includes study-specific discontinuation criteria, severe non-compliance to protocol and lost to follow-up, among other reasons. IQR, interquartile range

PFS2*



	Olaparib (N=260)	Placebo (N=131)
Events (%) [30.9% maturity]	69 (26.5)	52 (39.7)
Median PFS2, months	NR	41.9
HR 0.50		
95% CI 0.35, 0.72; *P*=0.0002		

No. at risk																					
Olaparib	260	246	239	231	229	225	216	204	194	177	168	163	140	111	61	48	13	5	0	0	0
Placebo	131	126	122	113	108	100	92	88	79	73	68	63	55	44	18	11	3	1	0	0	0

In second line, a PARP inhibitor was used in 33/94 (35%) patients in the placebo arm and 10/91 (11%) patients in the olaparib arm

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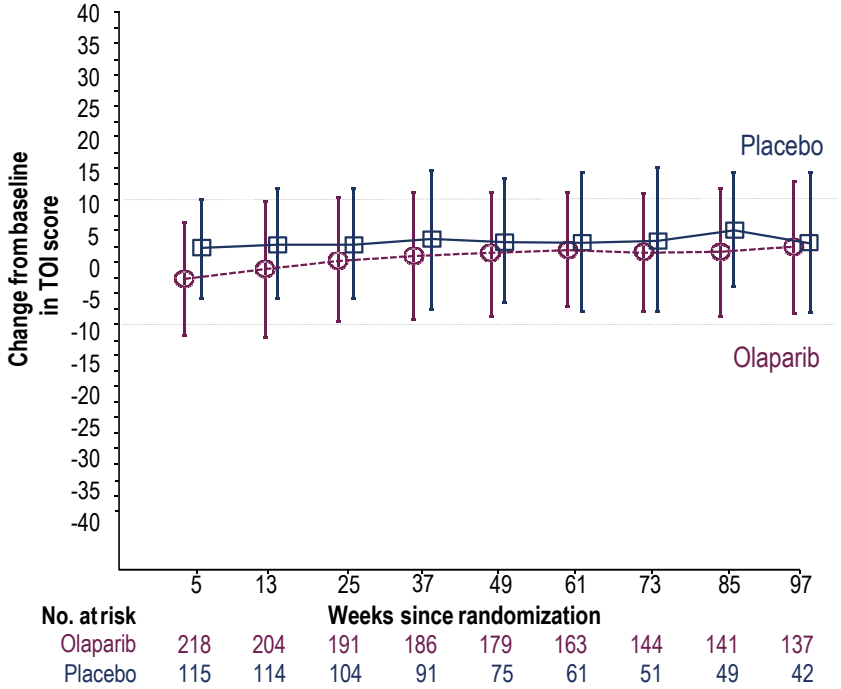
*Time from randomization to second progression or death

SOLO-1: Quality of life maintained in Olaparib treatment arm

Health-related quality of life: FACT-O TOI score*



The difference between olaparib and placebo in the mean change from baseline in TOI score over 24 months (−3.00; 95% CI −4.779, −1.216) was not clinically meaningful

*TOI scores range from 0 to 100, with higher scores indicating better HRQoL and a clinically meaningful difference defined as ±10 points

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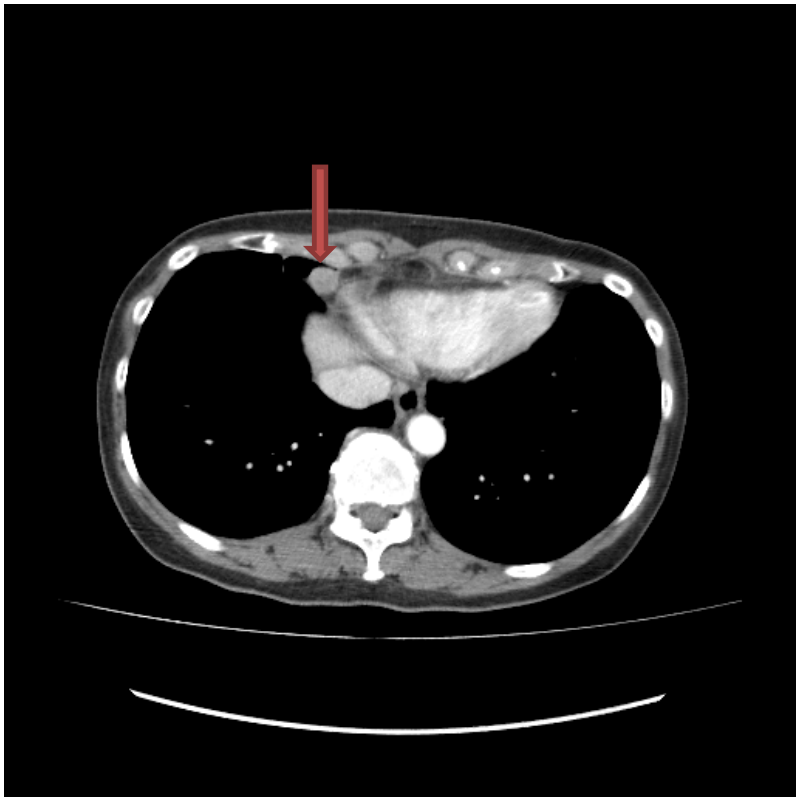
OC Case

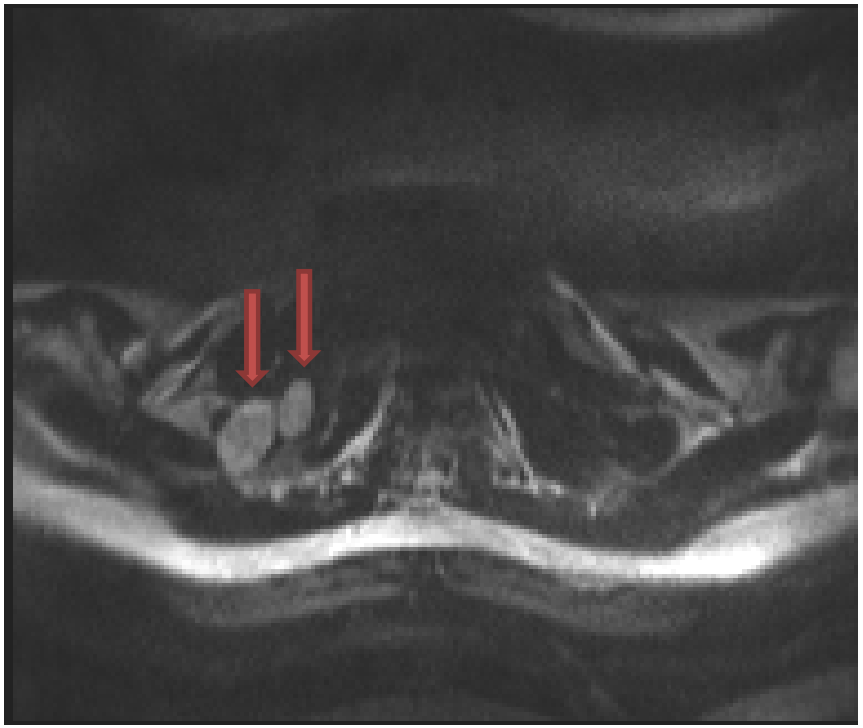
- 68 y/o Female
- History of Papillary thyroid carcinoma s/p total thyroidectomy, central zone neck LN dissection pT1N1aM0, AJCC stage II
  - s/p oral I-131 treatment (2014/11), on Eltroxin supplement

- Diagnosed as Metastatic carcinoma with unknow origin, poor differentiated s/p mediastinal tumor excision and RUL. RML wedge resection on 2014/8
- Recurrence with LAP over right supraclavicular and upper abdominal region in 2015/8.

- MUO 1st (2014-08)



- MUO 2nd (2015-08)



Pathology (1st OP and 2nd biopsy)

- (S103-27970) PATHOLOGICAL DIAGNOSIS: Metastatic carcinoma
- Sections show lymph node tissue with metastatic carcinoma, composed of solid nests of poorly differentiated carcinoma cells.
- Psammoma bodies are seen.
- Tumor cells are immunoreactive for CK AE1/AE3 and PAX8, while negative for S-100, LCA, thyroglobulin and TTF-1.

- 2nd Biopsy:
- The immunostain profile is similar to previous biopsy (S103-27970), and the tumor cells are immunoreactive for PAX8 and CK7, while negative for mTG and TTF-1.
- The tumor from organ other than thyroid should be considered.

The origin of the tumor cannot be determined based on morphological or immunohistochemical findings

- metastatic poorly differentiated carcinoma not favored thyroid origin (consulted with pathologist Chief Chou)
- s/p paclitaxel + cisplatin 2-2 (2015/9/23-2015/11/11) with CR.
- s/p start Glivec according to PDGFR mutation (since 2015/12/30)

- Disease free until 2019-01, left thigh swelling edema

3rd recurrence

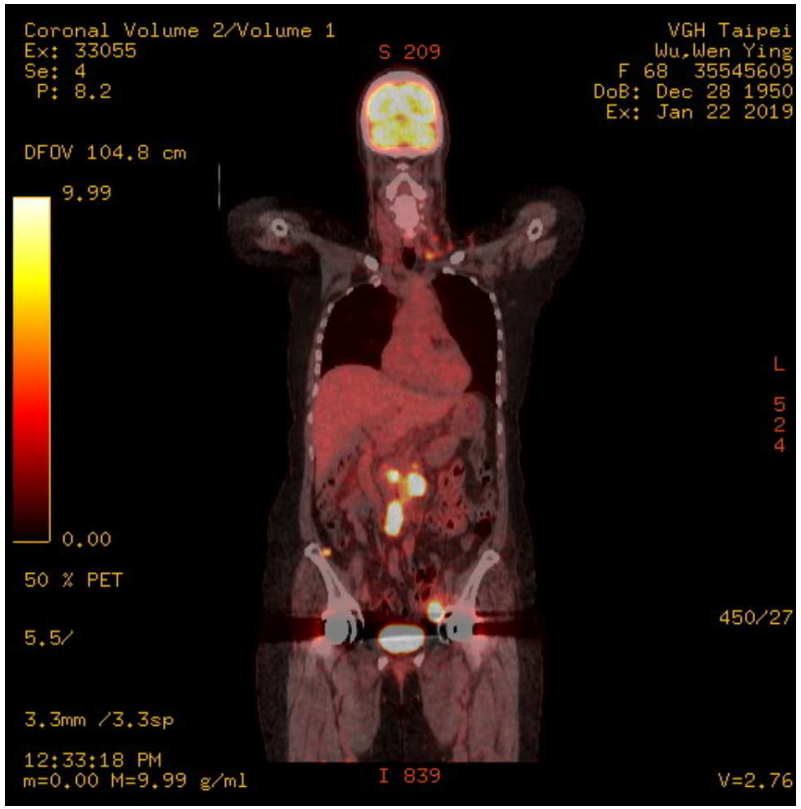
- - with left inguinal & right neck LAP (振興 abd to leg CT, 2019/1/17),
- - s/p biopsy on 1/23, patho: recurrence of previous MUO (adenocarcinoma, CK7+);

Pathology (3rd MUO)

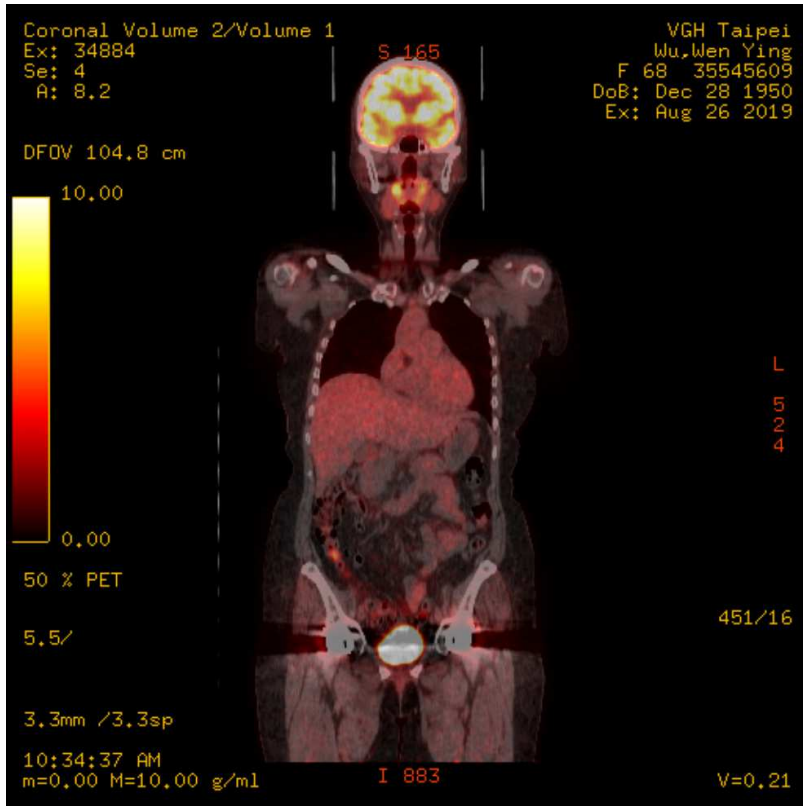
- Sections show tumor tissue composed of solid nests of poorly differentiated carcinoma in vague glandular pattern.
- The immunophenotypes are similar to previous biopsy (S103-27970)
- Tumor cells are immunoreactive for CK7, while negative for CK20, CDX2, GATA3 and TTF-1.

Platinum sensitive

- Before Chemo



- Post Chemo * C6



Tissue biopsy (FFPE)

TIER 2: VARIANTS OF POTENTIAL CLINICAL SIGNIFICANCE

Predictive Variants

Marker	Alteration	Therapies approved in this indication	Therapies approved in other indications	May indicate resistance to therapies	Trials
BRCA2	V1804fs*10	None	Talazoparib (C.1), Olaparib (C.1), Rucaparib (C.1), Niraparib (C.2)	None	Yes
TP53	R248Q	None	None	None	Yes

Prognostic and Diagnostic Variants: None

GUIDELINES: NONE

INTERACTIONS: NONE

OTHER ALTERATIONS

TIER 3: VARIANTS OF UNCERTAIN CLINICAL SIGNIFICANCE: NONE

TIER 4: BENIGN OR LIKELY BENIGN VARIANTS: NONE

LABORATORY TECHNICAL DATA

Marker	Alteration	Map Location	Variant Allele Frequency	Coding Sequence Change	Transcript ID
BRCA2	V1804fs*10	chr13:32913900	75.49%	c.5409_5412delTGTA	NM_000059
TP53	R248Q	chr17:7577538	57.53%	c.743G>A	NM_000546

The data in this table was generated by the laboratory in the course of molecular testing. It has not been altered in any way by CellMax.

2. Detailed Biomarker Information

2.1. BRCA2-V1804fs*10 (p.Val1804MetfsTer10)

TIER 2: Variant of Potential Clinical Significance

2.1.1 BIOMARKER RESULTS SUMMARY

Marker	Result	Summary
BRCA2	- MUTN (seq): p.Val1804MetfsTer10 (V1804fs*10)	BRCA2-V1804fs*10 is an inactivating mutation.
	Clinical relevance	BRCA2 inactivation may impair the DNA damage repair process and result in a loss of cell cycle checkpoint control leading to tumorigenesis (Holloman, 2011; 21731065, Kolinjivadi et al., 2017; 28079255). Inactivating BRCA2 alterations have been reported to predict sensitivity to platinum-based chemotherapy and PARP inhibitors, including olaparib, rucaparib, niraparib, and talazoparib, which are FDA-approved in specific indications (Litton et al., 2018; 30110579, Hollis et al., 2017; 28546758, Kim et al., 2015; 26187614, Swisher et al., 2017; 27908594, Scott, 2017; 28474297).

2.1.2 BIOLOGICAL RELEVANCE of BRCA2-V1804fs*10 (p.Val1804MetfsTer10)

BRCA2 alterations in Carcinoma of unknown primary (CUP)	
Molecular function	The alteration reported here is expected to effectively truncate the Brca2 protein prior to the C-terminal Rad51 binding domain and three nuclear localization signals crucial to Brca2 protein function; truncating mutations including T3195* and Y3308* have been reported to result in Brca2 inactivation (Davies and Pellegrini, 2007; 17515903, Spain et al., 1999; 10570174, Kim et al., 2015; 25847274, Hucl et al., 2008; 18593900). Therefore, this alteration is expected to be inactivating.
Incidence in disease	BRCA2 mutations have been reported in 3.0% (1386/46612) of all tumor samples analyzed in COSMIC (Jan 2019). Diseases in COSMIC with high incidence of BRCA2 mutations include Endometrial carcinoma (11%, 57/540), Bladder carcinoma (6.9%, 39/565), and Colorectal carcinoma (CRC) (6.0%, 200/3349) (Jan 2019). A literature study has reported BRCA2 mutations in 5.5% (11/200) of carcinoma of unknown primary (CUP) cases (Ross et al., 2015; 26182302).

Liquid biopsy (cfDNA) report

1. Summary

CLINICALLY RELEVANT ALTERATIONS

TIER 1: VARIANTS OF STRONG CLINICAL SIGNIFICANCE: NONE

TIER 2: VARIANTS OF POTENTIAL CLINICAL SIGNIFICANCE

Predictive Variants

Marker	Alteration	Therapies approved in this indication	Therapies approved in other indications	May indicate resistance to therapies	Trials
BRCA2	V1804fs*10	None	Niraparib (C), Talazoparib (C), Olaparib (C), Rucaparib (C)	None	Yes
TP53	R248Q	None	None	None	Yes

Prognostic and Diagnostic Variants: None

GUIDELINES: NONE

INTERACTIONS: NONE

OTHER ALTERATIONS

TIER 3: VARIANTS OF UNCERTAIN CLINICAL SIGNIFICANCE:

Marker	Alteration
BRCA2	p.Thr1803= (T1803T)
BRCA2	p.Val1804= (V1804V)
NOTCH1	p.Ser1708Leu (S1708L)

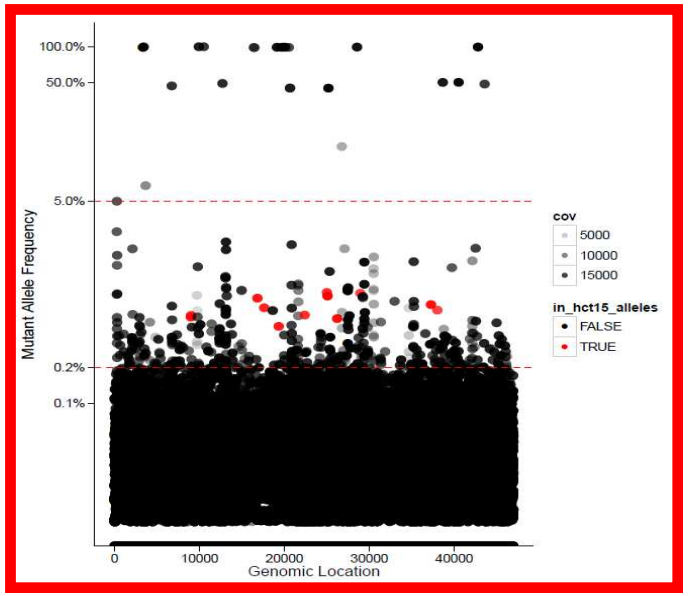
cfDNA: gBRCA2 mutation confirmed according to the NGS algorithm

LABORATORY TECHNICAL DATA

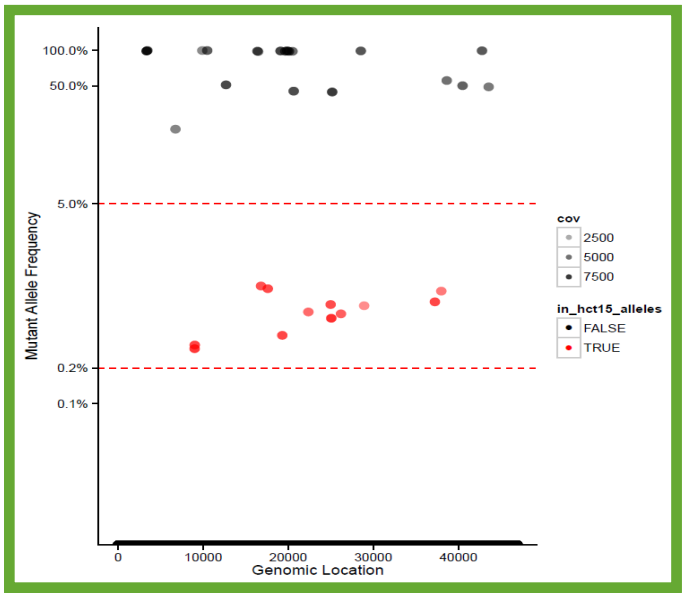
Marker	Alteration	Map Location	Variant Allele Frequency	Coding Sequence Change	Transcript ID
BRCA2	V1804fs*10	chr13:32913900	60.25%	c.5409_5412delTGTA	NM_000059
TP53	R248Q	chr17:7577538	22.88%	c.743G>A	NM_000546
BRCA2	T1803T	chr13:32913901	0.46%	c.5409T>A	NM_000059
BRCA2	V1804V	chr13:32913904	0.16%	c.5412A>C	NM_000059
NOTCH1	S1708L	chr9:139397678	0.2%	c.5123C>T	NM_017617

The data in this table was generated by the laboratory in the course of molecular testing. It has not been altered in any way by CellMax.

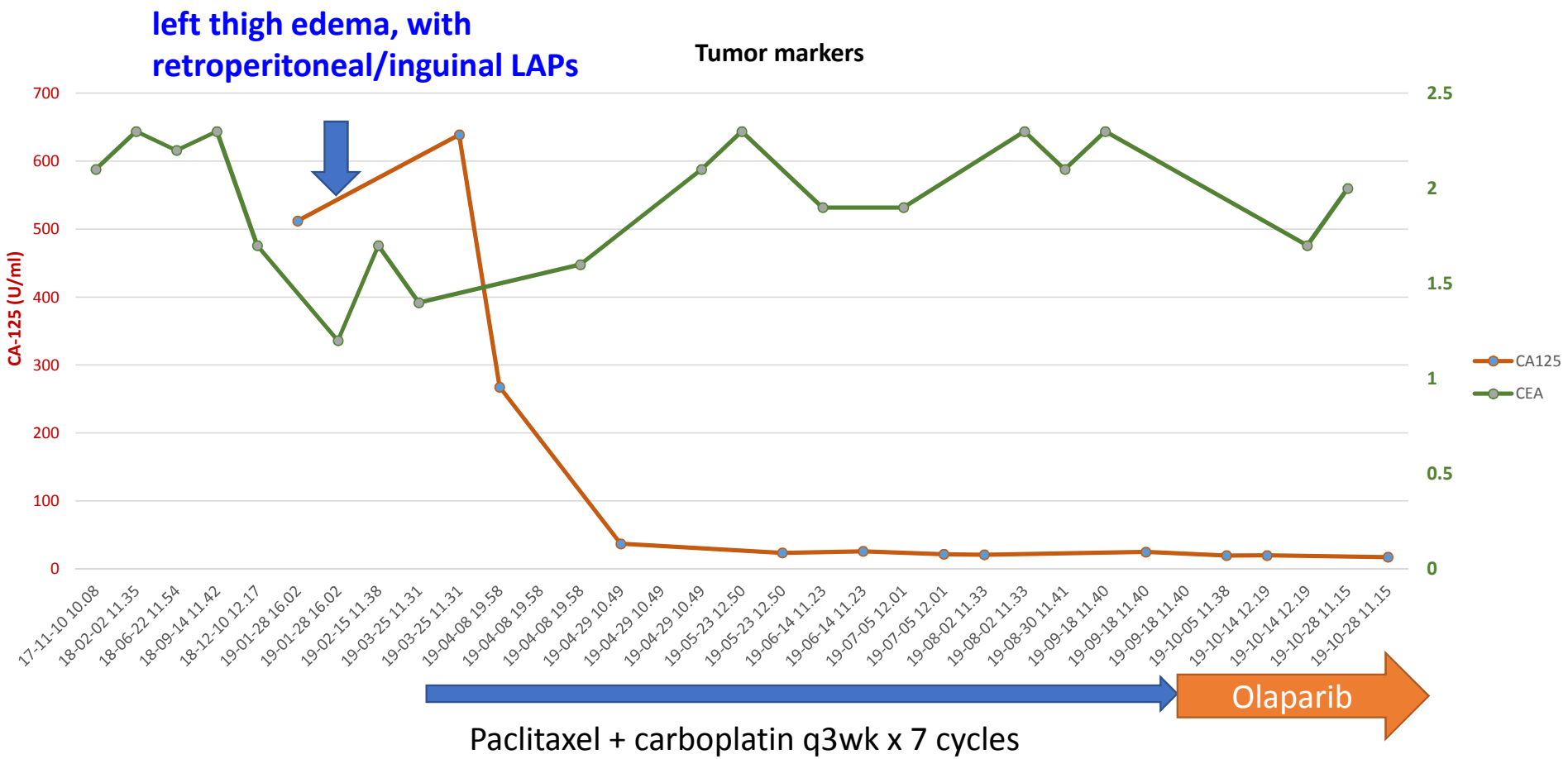
Standard NGS



SMSEQ™



OC Case: clinical course



PAOLA1

PAOLA-1: Olaparib maintenance in newly diagnosed advanced OC patients treated with chemotherapy and bevacizumab

Sponsored by ARCAGY research

- FIGO stage III–IV high-grade ovarian cancer (serous or endometrioid)* or non mucinous BRCAm
- Surgery (upfront or interval)
- Platinum-taxane based chemotherapy
- ≥3 cycles of bevacizumab†

NED/ CR/PR

Olaparib (300mg bid) x 2 years

+ bevacizumab†

2:1 randomisation; **n=806**

Stratification by tBRCA status‡ and 1L treatment outcome

Active control arm

Placebo x 2 years

+ bevacizumab†

2 years' Maintenance treatment

Primary endpoint

- Investigator-assessed PFS (RECIST 1.1)
  Sensitivity analysis by BICR

Secondary endpoints

- PFS2
- TSST
- OS
- Safety
- PRO/HRQoL

Pre-specified exploratory endpoints

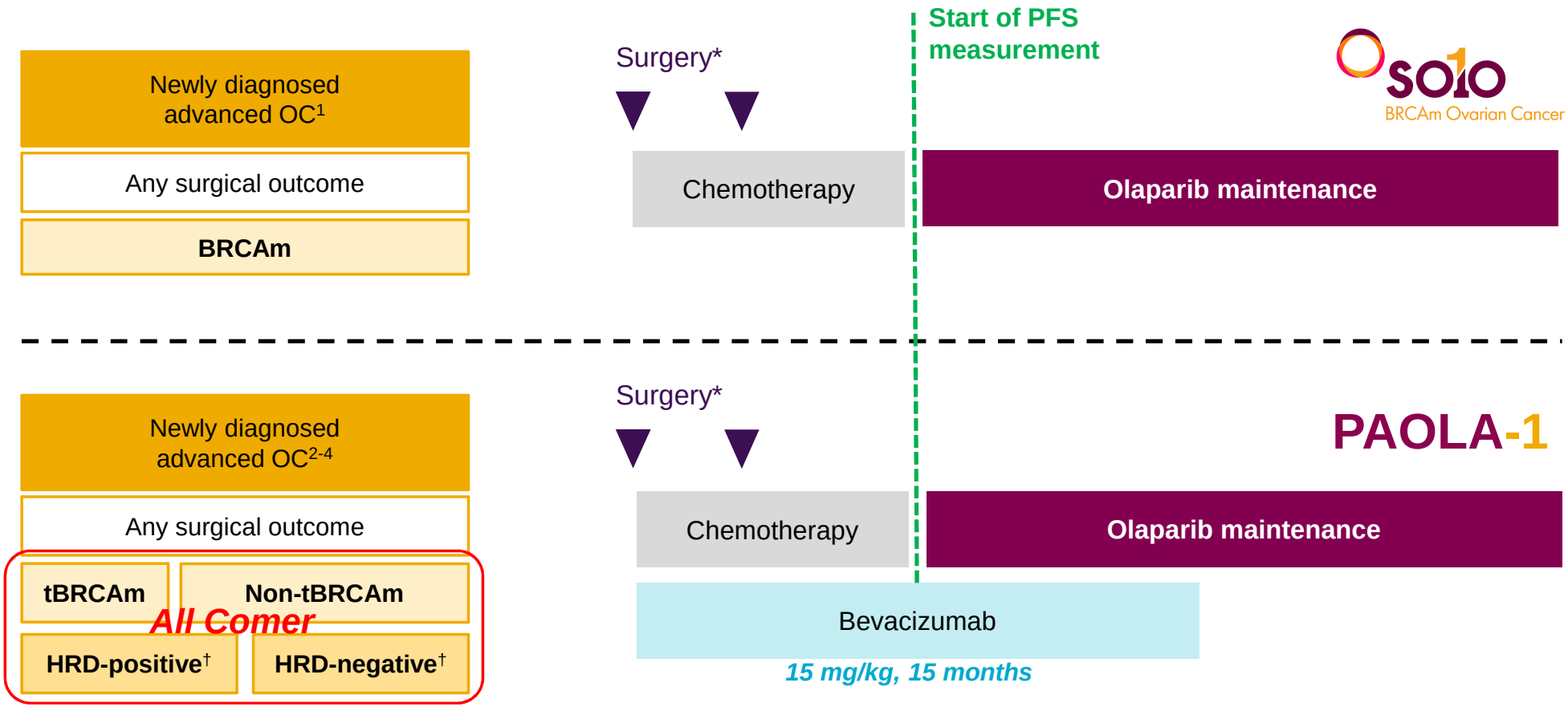
- PFS in pre-defined subgroups including tBRCAm and Myriad myChoice CDx

n=762 patients were planned to be randomised in the study so that maturity of the PFS1 data is ~60%. 458 events will give >80% power, at 5% alpha, to show HR 0.75, mPFS from 15.8 months (control) to 21.1 months (olaparib)
*Also includes fallopian tube and primary peritoneal cancer; †Bevacizumab: 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy. ‡By central labs
1L= first line; bid=twice daily; BICR=blinded independent centralised review; CDx=companion diagnostic test; CR=complete response; FIGO=Fédération Internationale de Gynécologie Obstétrique; gBRCAm=germline mutation in *BRCA1/2*; HRD=homologous recombination repair deficiency; HRQoL=health-related quality of life; MTX=maintenance; NED=no evidence of disease; OS=overall survival; PFS=progression-free survival; PFS2= time to second progression or death; PR=partial response; PRO=patient reported outcomes; RECIST=Response Evaluation Criteria in Solid Tumours; tBRCA=tumour BRCA; TSST=time to subsequent treatment

1. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 2. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428 Supplementary appendix;
3. Study NCT02477644. Available at https://clinicaltrials.gov/ct2/show/NCT02477644. Last accessed December 2019

PAOLA1

Olaparib maintenance treatment has been investigated in newly diagnosed advanced OC in two Phase III studies: SOLO1 & PAOLA1



*Surgery may be upfront or interval debulking
†HRD-positive determined by tBRCAm or Myriad myChoice CDx genomic instability score ≥42. HRD-negative determined by non-tBRCAm and Myriad myChoice CDx genomic instability score <42
BRCAm=mutation in *BRCA1/2*; CDx=companion diagnostic test; HRD=homologous recombination deficient; OC=ovarian cancer; tBRCAm=tumour BRCA mutation

1. Moore K et al. N Engl J Med. 2018;379(26):2495-2505; 2. Study NCT02477644. Available at https://clinicaltrials.gov/ct2/show/NCT02477644. Last accessed December 2019;
3. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 4. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428 Supplementary appendix.

PAOLA1

Baseline patient characteristics were well balanced between arms

		Olaparib + bevacizumab (n=537)	Placebo + bevacizumab (n=269)
Age, median years (range)		61 (32–87)	60 (26–85)
ECOG performance*, n (%)	0	378 (70)	189 (70)
	1	153 (28)	76 (28)
Primary tumour location, n (%)	Ovary	456 (85)	238 (88)
	Fallopian tubes	39 (7)	11 (4)
	Primary peritoneal	42 (8)	20 (7)
Histology, n (%)	Serous†	519 (97)	253 (94)
	Endometrioid	12 (2)	8 (3)
	Other‡	6 (1)	8 (3)
tBRCAm status, n (%)	tBRCAm	161 (30)	80 (30)
	No tBRCAm¶	376 (70)	189 (70)
FIGO stage, n (%)	III	378 (70)	186 (69)
	IV	159 (30)	83 (31)

* ECOG performance was missing for six patients in the olaparib arm and four patients in the placebo arm
† Two patients had low grade serous carcinoma with a BRCAm
‡ Other includes clear cell, undifferentiated and other histology
¶ No deleterious mutation, including tumour BRCA wild-type, a variant of uncertain significance, or an unknown result
BRCAm=mutation in *BRCA1/2*; ECOG=Eastern Cooperative Oncology Group; FIGO=Fédération Internationale de Gynécologie et d'Obstétrique; tBRCAm=mutation in tumour *BRCA1/2*

1. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 2. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428 Supplementary appendix; 3. Ray-Coquard I et al. Presentation LBA2_PR presented at ESMO Annual Conference 2019, 27 September - 1 October, Barcelona, Spain

PAOLA1

The majority of patients had no evidence of disease or were in complete response

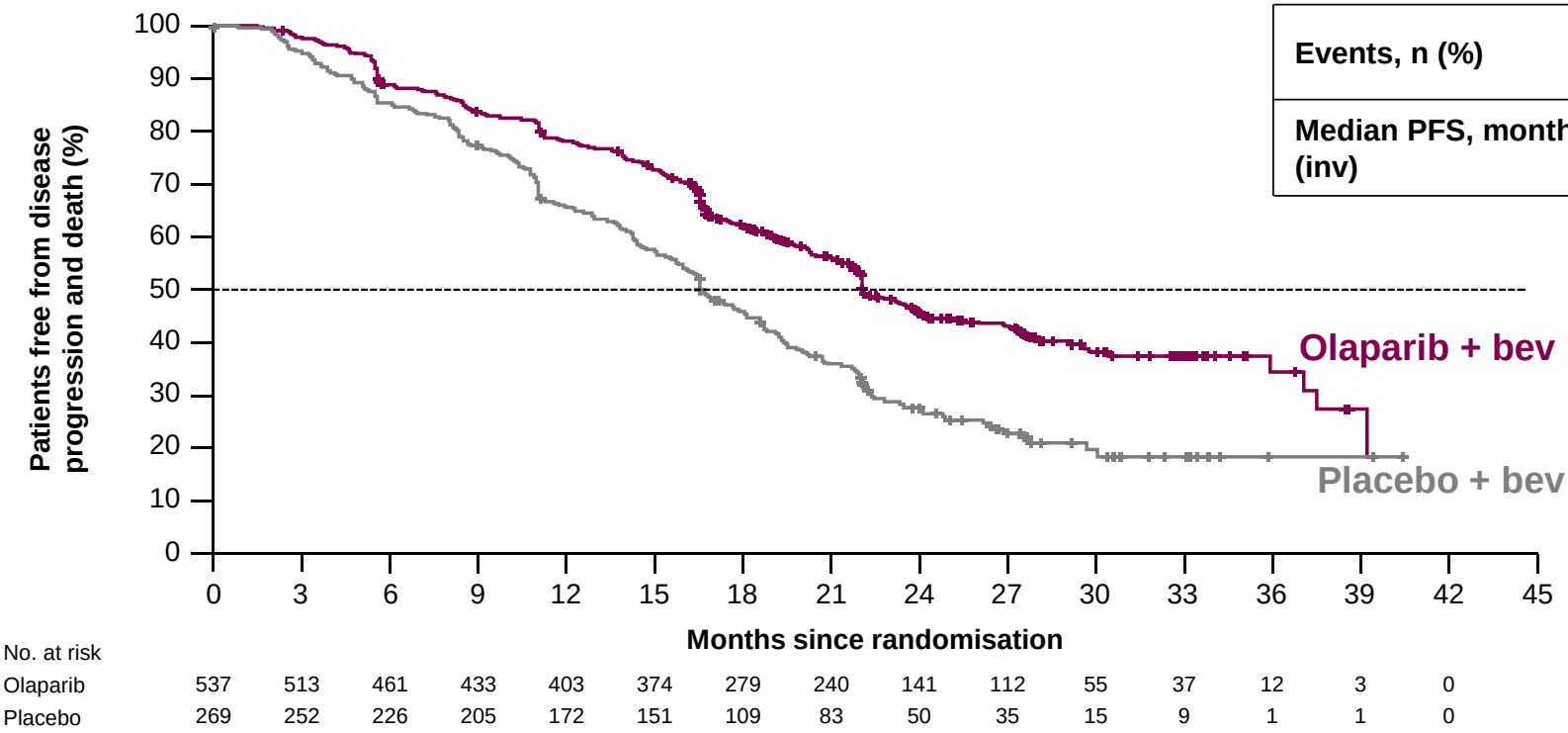
		Olaparib + bevacizumab (n=537)	Placebo + bevacizumab (n=269)
History of cytoreductive surgery, n (%)	**Upfront surgery**	271 (50)	138 (51)
	Residual macroscopic disease	111 (41)	53 (38)
	No residual macroscopic disease	160 (59)	85 (62)
	Interval cytoreductive surgery*	228 (42)	110 (41)
	Residual macroscopic disease	65 (29)	35 (32)
	No residual macroscopic disease	163 (71)	75 (68)
	No surgery	38 (7)	21 (8)
Response after surgery/platinum-based chemotherapy, n (%)	NED	290 (54)	141 (52)
	CR	106 (20)	53 (20)
	PR	141 (26)	75 (28)

*Neoadjuvant treatment may have included bevacizumab
CR=complete response; NED=no evidence of disease; PR=partial response

1. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 2. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428 PAOLA-1 Clinical Study Protocol

PAOLA1

Primary endpoint: PFS in the ITT population



	Olaparib + bevacizumab n=537	Placebo + bevacizumab n=269
Events, n (%)	280 (52)	194 (72)
Median PFS, months (inv)	**22.1**	**16.6**
	HR=0.59 95% CI (0.49–0.72) p<0.001	

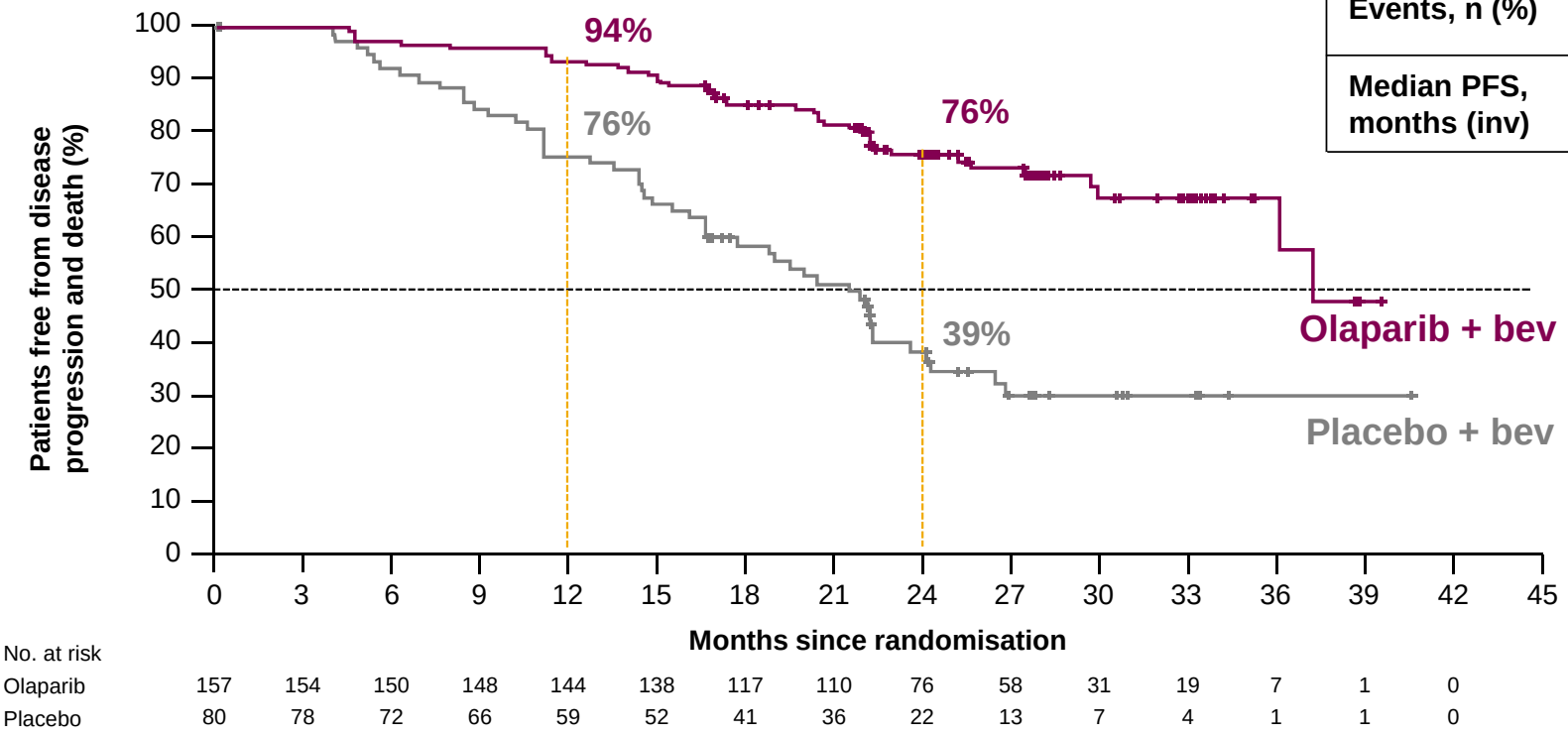
Median time from first cycle of chemotherapy to randomisation = **7 months**

PFS by investigator assessment; analysis per eCRF; data maturity = 59%
Median duration of follow-up for primary analysis: olaparib, 22.7 months; placebo, 24.0 months
Data cut-off: 22 March 2019
CI=confidence interval; HR=hazard ratio; inv=investigator-assessed; ITT=intent to treat; PFS=progression-free survival

1. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 2. Ray-Coquard I et al. Presentation LBA2_PR presented at ESMO Annual Conference 2019, 27 September - 1 October, Barcelona, Spain

PAOLA1

PFS in tBRCAm patients



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

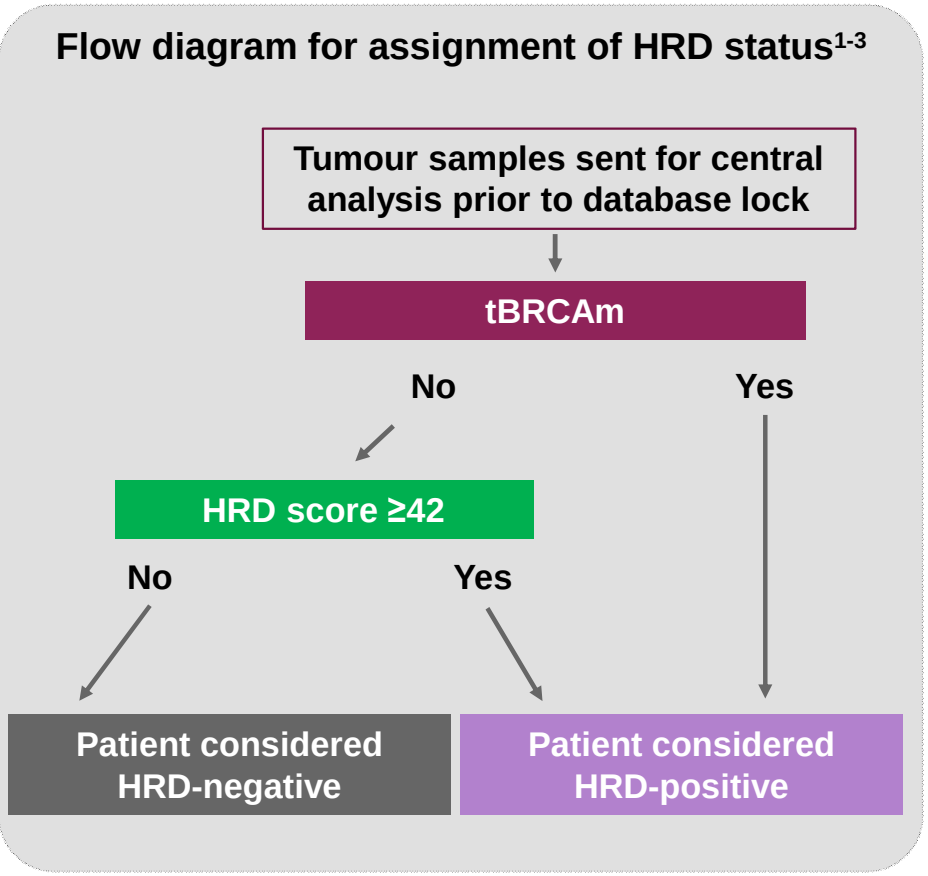
The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates
Analysis per eCRF, data maturity = 38%
*This median is unstable due to a lack of events – less than 50% maturity
CI=confidence interval; HR=hazard ratio; inv=investigator-assessed; PFS=progression-free survival; tBRCAm=mutation in tumour *BRCA1/2*

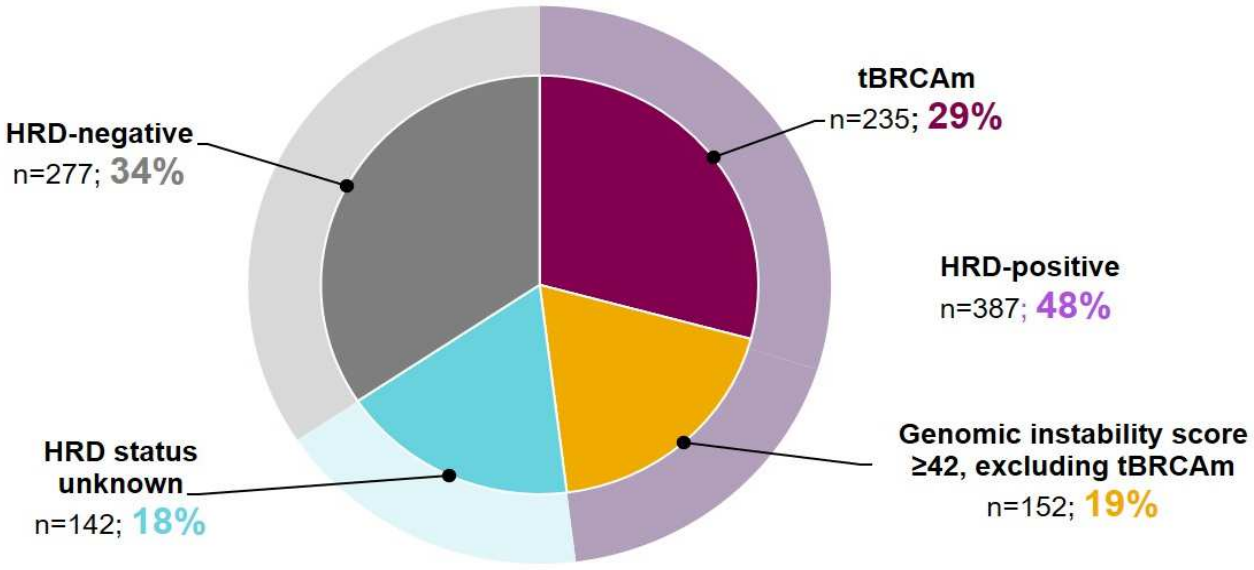
1. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 2. Ray-Coquard I et al. Presentation LBA2_PR presented at ESMO Annual Conference 2019, 27 September - 1 October, Barcelona, Spain

PAOLA1

Approximately 50% of patients in PAOLA-1 were HRD-positive identified by Myriad myChoice® Plus Assay

Flow diagram for assignment of HRD status[1-3]



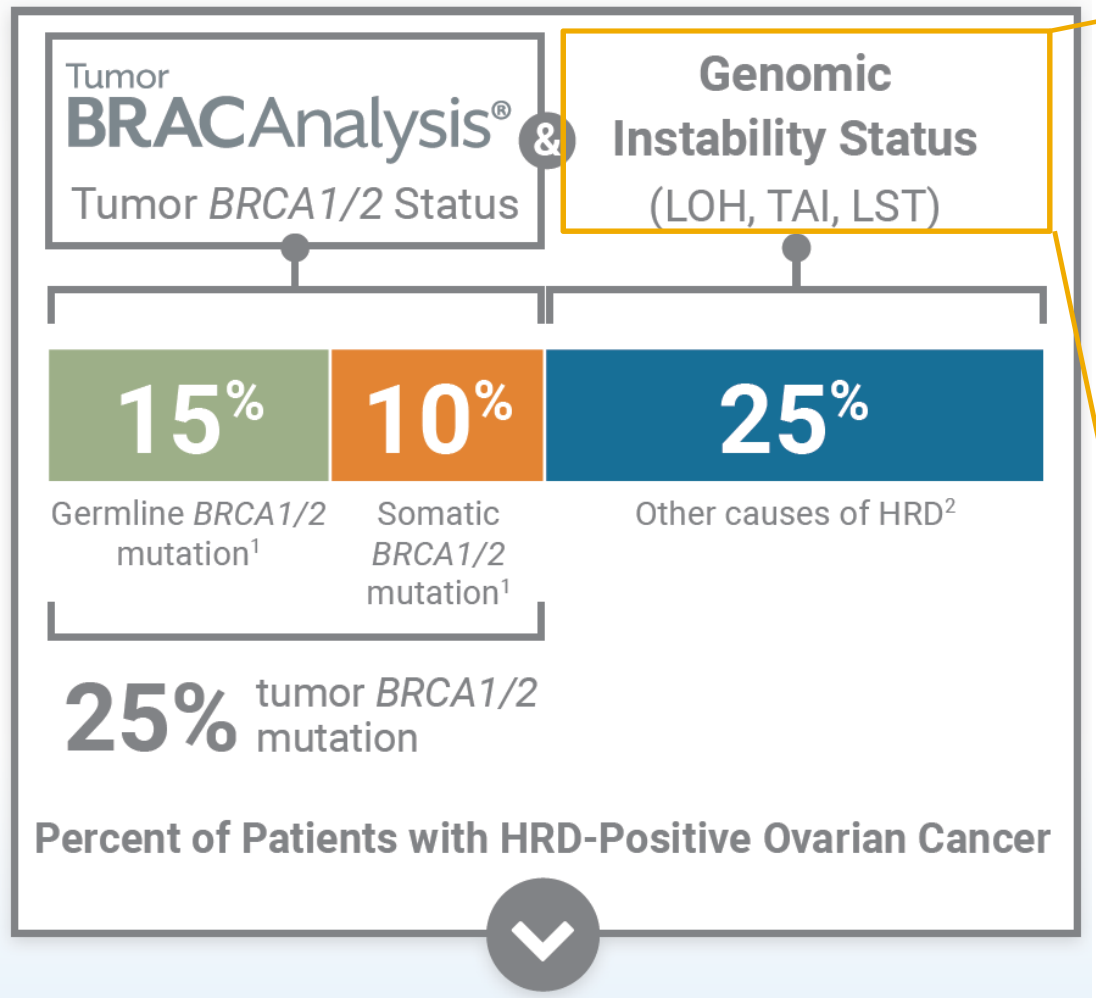


Reasons for HRD status unknown: 4.2% missing; 2.1% fail; 11.3% inconclusive

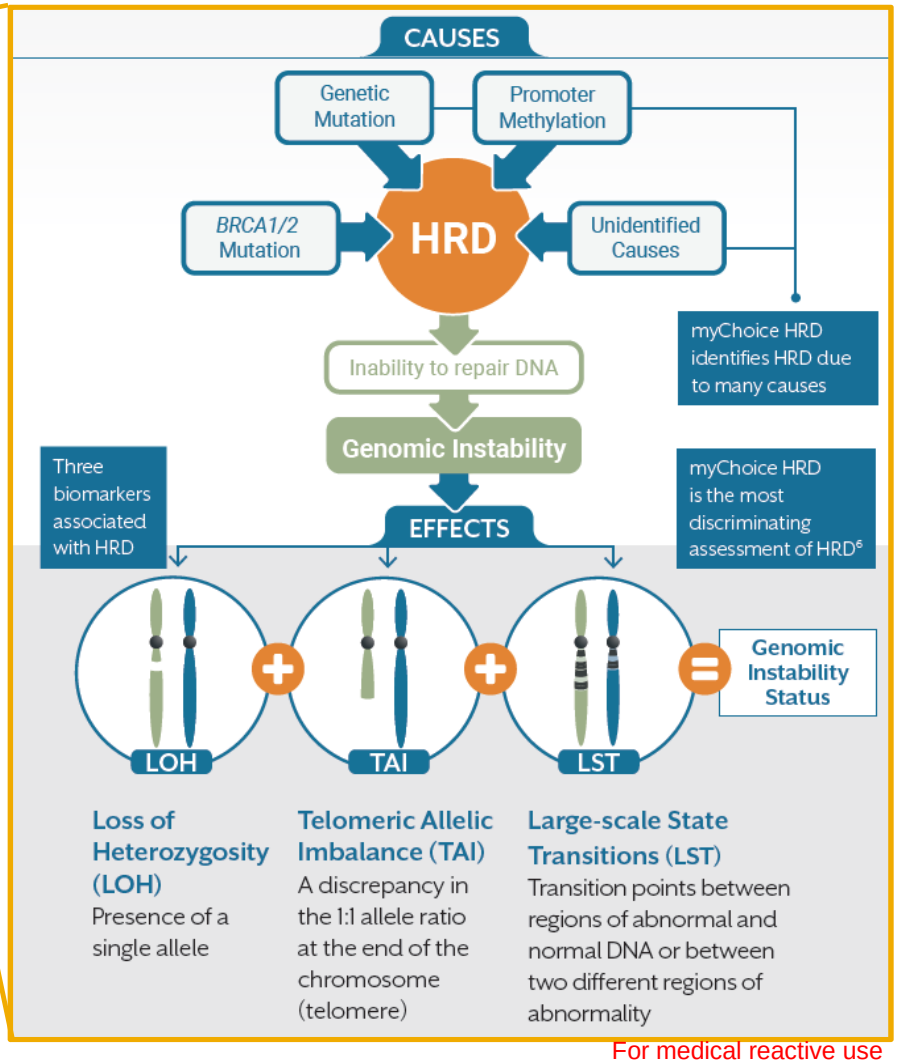
1. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 2. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428 Supplementary appendix; 3. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428 Clinical Study Protocol

Myriad myChoice®

HRD testing

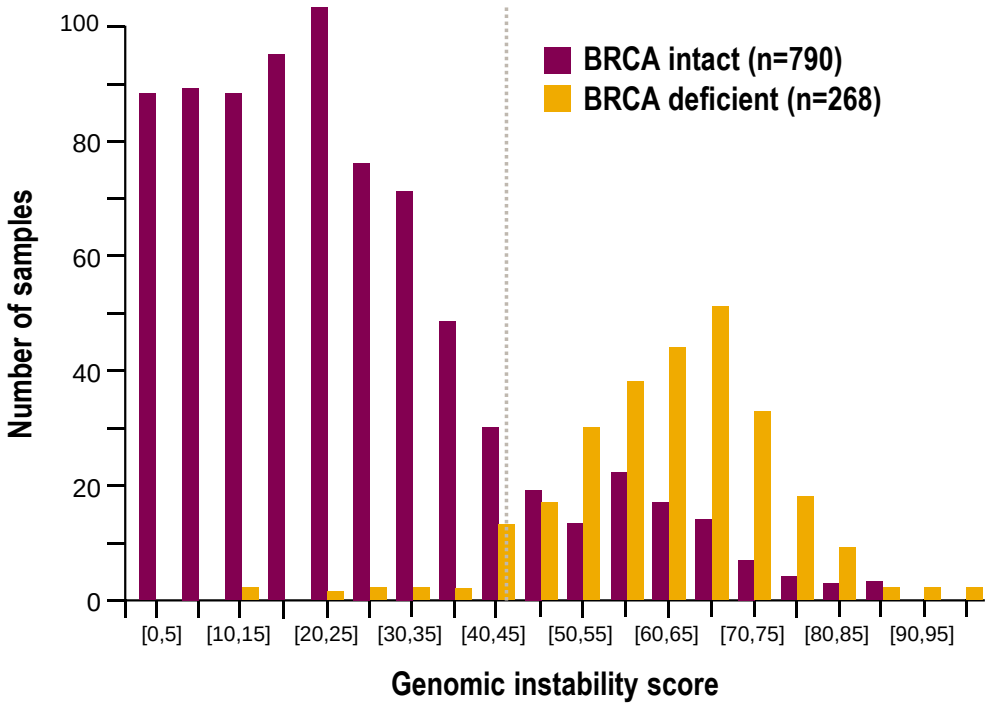


Genomic Instability Status



The HRD-positive Cut-off Score of ≥42 Was Initially Developed in a Training Cohort

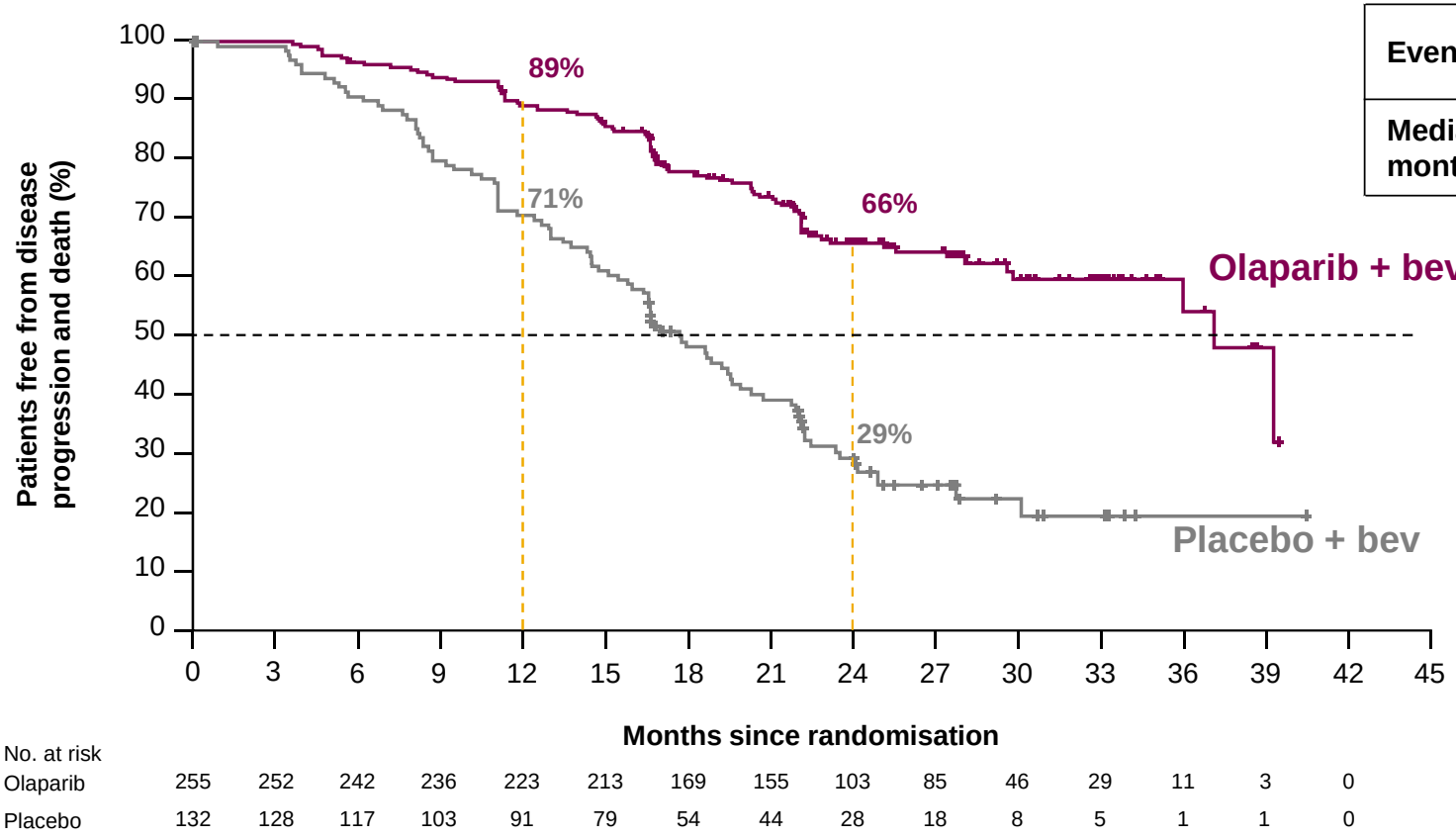
- A cut-off of point of 42 was developed in a training cohort (n=1,058) of chemotherapy naïve OC and BC tumors using 95% sensitivity to detect BRCA1/2 deficient tumors
- Tumors with a high HRD score (≥42) were defined as HRD-positive



BC=breast cancer; HRD=homologous recombination deficient; OC=ovarian cancer.
Mills GB, et al. Presented at SGO Annual Congress; March 19-22, 2016: San Diego, CA, USA.

PAOLA1

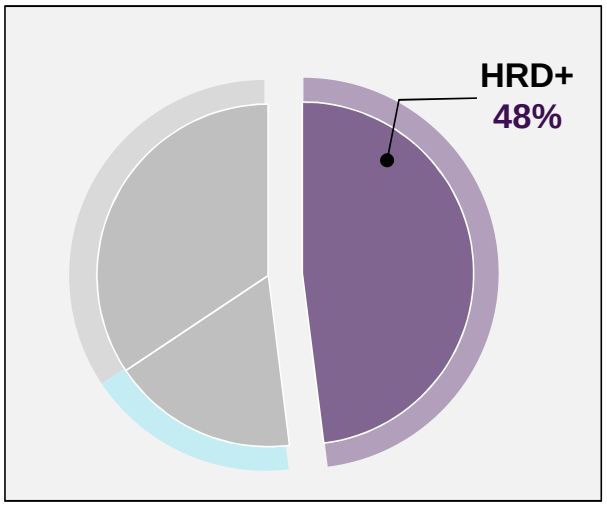
PFS in HRD-positive (including tBRCAm) patients



No. at risk

Olaparib	255	252	242	236	223	213	169	155	103	85	46	29	11	3	0
Placebo	132	128	117	103	91	79	54	44	28	18	8	5	1	1	0

	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)	



The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates

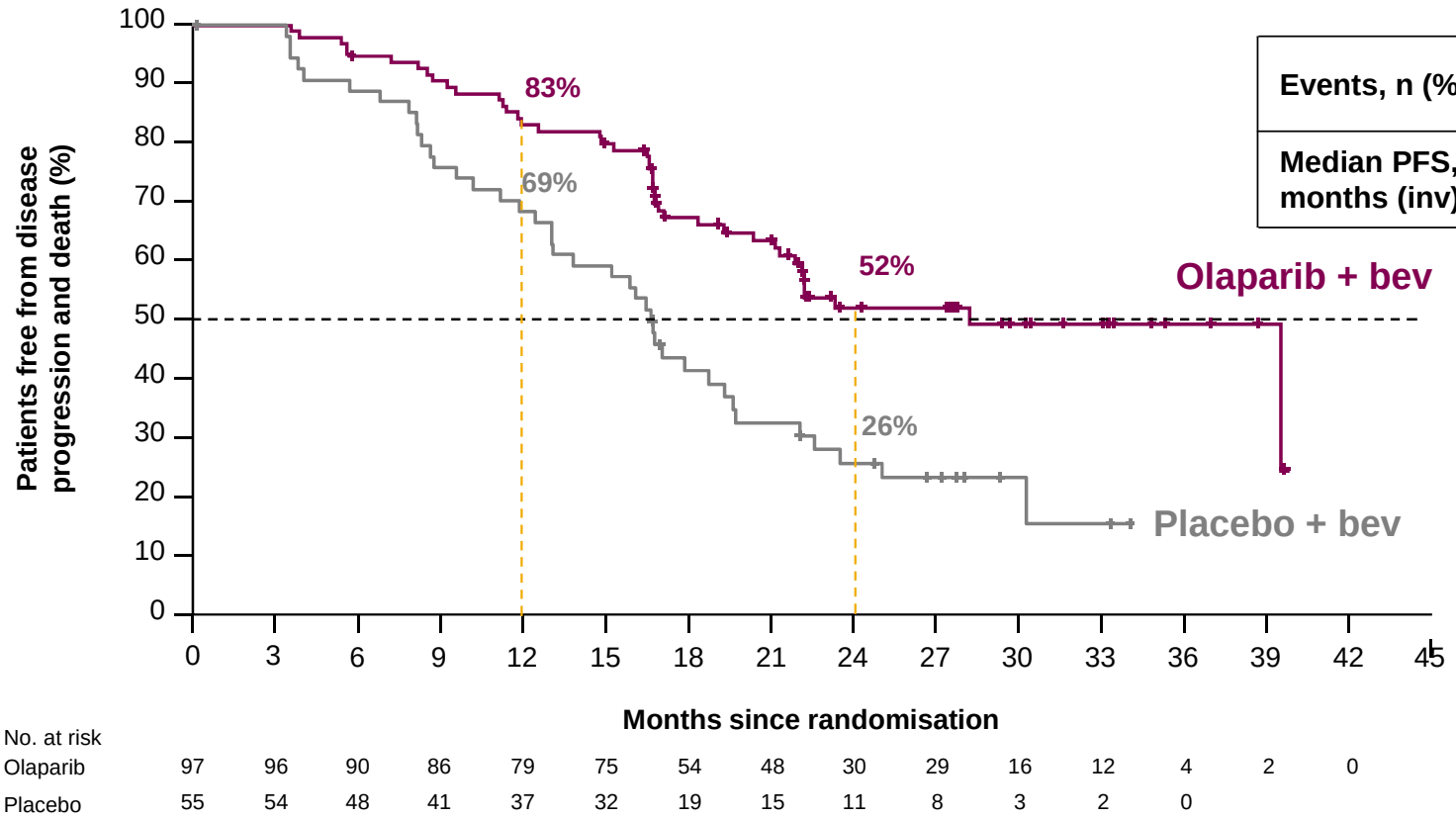
†This median is unstable due to a lack of events – less than 50% maturity ; Data maturity = 46%

CDx=companion diagnostic test; CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficient; inv=investigator-assessed; (m)PFS=median progression-free survival; tBRCAm=mutation in tumour *BRCA1/2*

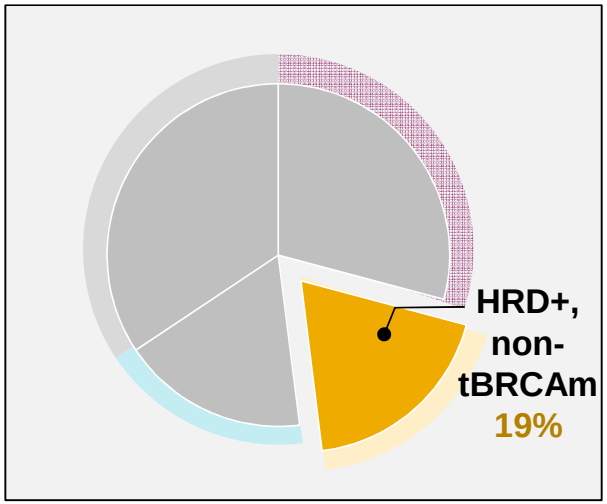
1. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 2. Ray-Coquard I et al. Presentation LBA2_PR presented at ESMO Annual Conference 2019, 27 September - 1 October, Barcelona, Spain

PAOLA1

PFS 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)	



The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates

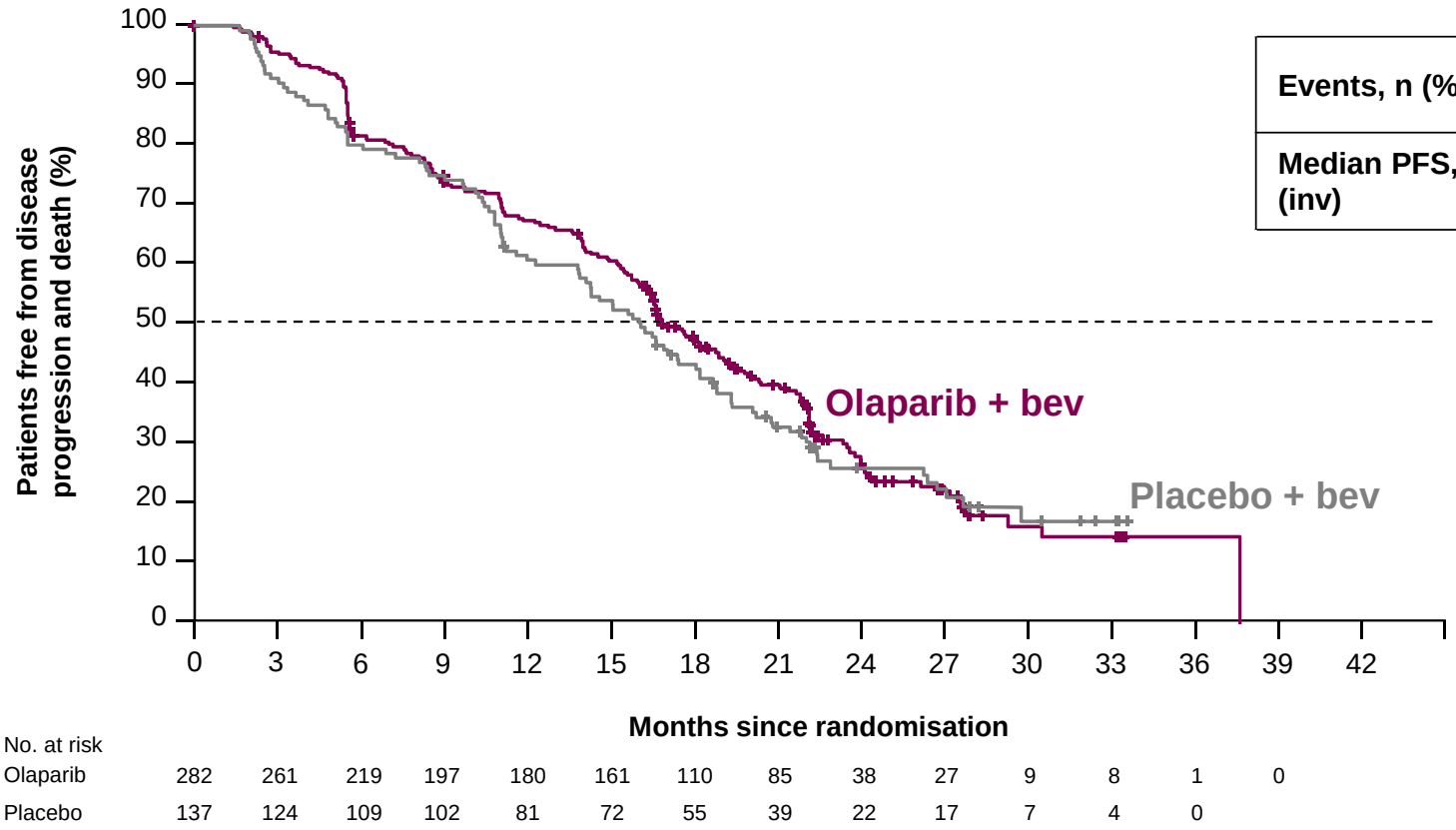
† This median is unstable due to a lack of events – less than 50% maturity ; Data maturity = 55%

CDx=companion diagnostic test; CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficient; inv=investigator-assessed; PFS=progression-free survival; tBRCAm= mutation in tumour *BRCA1/2*

1. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 2. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428 Supplementary appendix;
3. Ray-Coquard I et al. Presentation LBA2_PR presented at ESMO Annual Conference 2019, 27 September - 1 October, Barcelona, Spain

PAOLA1

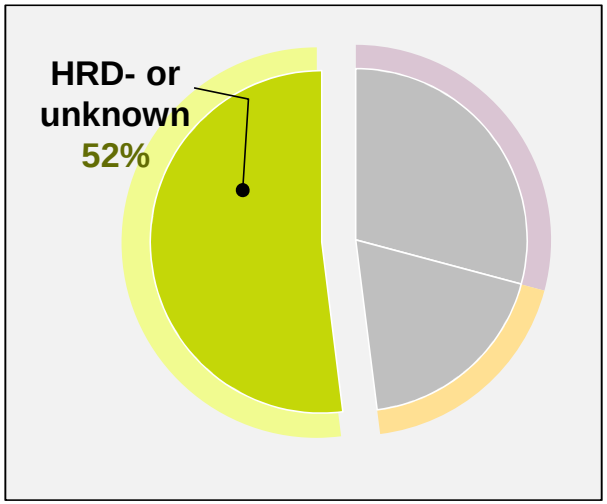
PFS in HRD-negative or unknown patients



No. at risk

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

	Olaparib + bevacizumab n=282	Placebo + bevacizumab n=137
Events, n (%)	193 (68)	102 (74)
Median PFS, months (inv)	**16.9**	**16.0**
	HR=0.92 95% CI (0.72–1.17)	



Data maturity = 70%.
CDx=companion diagnostic test; CI=confidence interval; HR=hazard ratio; HRD=homologous recombination deficient; inv=investigator-assessed; PFS=progression-free survival

1. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 2. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428 Supplementary appendix;
3. Ray-Coquard I et al. Presentation LBA2_PR presented at ESMO Annual Conference 2019, 27 September - 1 October, Barcelona, Spain

Managing Adverse Events Associated With PARP Inhibitors

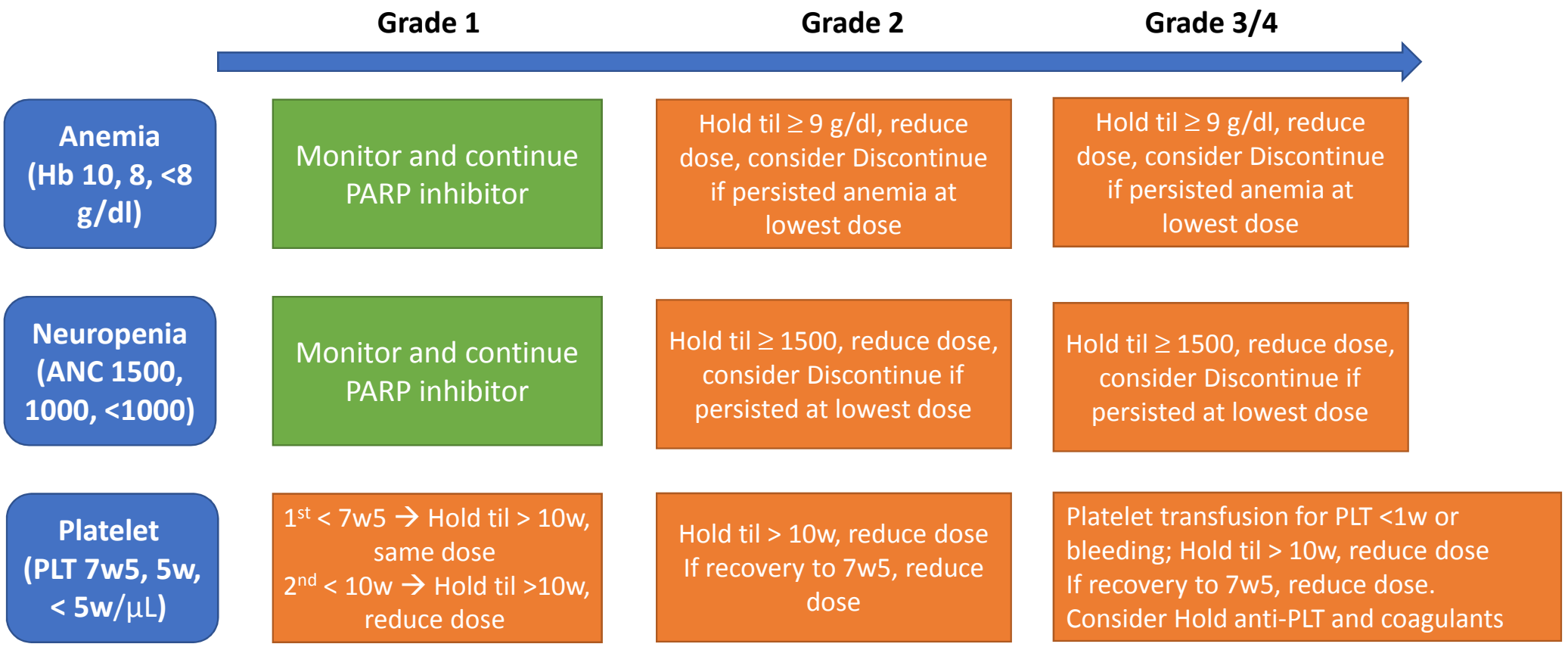
Common AEs of PARP-inhibitors

	Niraparib (n=367)		Placebo (n=179)		Olaparib (n=195)		Placebo (n=99)		Rucaparib (n=372)		Placebo (n=189)	
	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4	All grades	Grade 3 or 4
Anaemia	184 (50%)	93 (25%)	12 (7%)	0	85 (44%)	38 (19%)	8 (8%)	2 (2%)	139 (37%)	70 (19%)	11 (6%)	1 (<1%)
Thrombocytopenia	225 (61%)	124 (34%)	10 (6%)	1 (<1%)	27 (14%)	2 (1%)	3 (3%)	1 (1%)	104 (28%)	19 (5%)	5 (3%)	0
Neutropenia	111 (30%)	72 (20%)	11 (6%)	3 (2%)	38 (19%)	10 (5%)	6 (6%)	4 (4%)	67 (18%)	25 (7%)	9 (5%)	2 (1%)
Nausea	270 (74%)	11 (3%)	63 (35%)	2 (1%)	148 (76%)	5 (3%)	33 (33%)	0	280 (75%)	14 (4%)	69 (37%)	1 (<1%)
Constipation	146 (40%)	2 (<1%)	36 (20%)	1 (<1%)	40 (21%)	0	20 (20%)	3 (3%)	136 (37%)	7 (2%)	45 (24%)	2 (1%)
Vomiting	126 (34%)	7 (2%)	29 (16%)	1 (<1%)	73 (37%)	5 (3%)	19 (19%)	1 (1%)	136 (37%)	15 (4%)	28 (15%)	2 (1%)
Decreased appetite	93 (25%)	1 (<1%)	26 (15%)	1 (<1%)	43 (22%)	0	11 (11%)	0	87 (23%)	2 (<1%)	26 (14%)	0
Abdominal pain	83 (23%)	4 (1%)	53 (30%)	3 (2%)	47 (24%)	5 (3%)	31 (31%)	3 (3%)	111 (30%)	9 (2%)	49 (26%)	1 (<1%)
Diarrhoea	70 (20%)	1 (<1%)	37 (21%)	2 (1%)	64 (33%)	2 (1%)	20 (20%)	0	118 (32%)	2 (<1%)	41 (22%)	2 (1%)
Dyspepsia	42 (11%)	0	17 (10%)	0	22 (11%)	0	8 (8%)	0	54 (15%)	1 (<1%)	9 (5%)	0
Dysgeusia	37 (10%)	0	7 (4%)	0	52 (27%)	0	7 (7%)	0	146 (39%)	0	13 (7%)	0
Fatigue	218 (59%)	30 (8%)	74 (41%)	1 (<1%)	128 (66%)	8 (4%)	39 (39%)	2 (2%)	258 (69%)	25 (7%)	83 (44%)	5 (3%)
Dizziness	61 (17%)	0	13 (7%)	0	26 (13%)	1 (<1%)	5 (5%)	0	54 (15%)	0	15 (8%)	1 (<1%)
Headache	95 (26%)	1 (<1%)	17 (10%)	0	49 (25%)	1 (<1%)	13 (13%)	0	67 (18%)	1 (<1%)	30 (16%)	1 (<1%)
Dyspnoea	71 (19%)	4 (1%)	15 (8%)	2 (1%)	23 (12%)	2 (1%)	1 (1%)	0	50 (13%)	1	14 (7%)	0
Nasopharyngitis	41 (11%)	0	13 (7%)	0	21 (11%)	0	11 (11%)	0	41 (11%)	0	6 (3%)	2 (1%)
Cough	55 (15%)	0	8 (5%)	0	33 (17%)	1 (<1%)	5 (5%)	0	54 (15%)	0	25 (13%)	0
Arthralgia	43 (12%)	1 (<1%)	22 (12%)	0	29 (15%)	0	15 (15%)	0	57 (15%)	2 (1%)	24 (13%)	0

Table 2: Toxicities of poly (ADP-ribose) polymerase (PARP) inhibitors described in the three phase 3 trials

Lancet Oncol 2019; 20: e15–28

Management for hematological adverse events for PARP-inhibitor (olaparib etc)



*Withhold for maximum of 28 days and monitor blood counts weekly

Lancet Oncol 2019; 20: e15–28

Panel:* Management of non-haematological adverse events (according to the Common Terminology Criteria for Adverse Events) for poly (ADP-ribose) polymerase PARP inhibitors

Grade 1[28,30,33]

- Continue PARP inhibitor
- Symptomatic treatment if necessary

Grade 2[28,30,33]

- Continue PARP inhibitor
- Consider dose interruption, reduction, or both, if toxicity remains uncontrolled despite symptomatic or prophylactic therapies

Grade 3 or 4[14,15,18]

- Withhold until resolution of adverse event for niraparib is classified grade 1 or less for olaparib (ie, resolved or grade 1 event), or grade 2 or less for rucaparib (resolved, grade 1, or grade 2)
- Might continue treatment if adverse event is nausea, vomiting, or diarrhoea, and controlled on medication
- If treatment was interrupted, consider dose reduction upon resumption (particularly if after second time withholding)

Grade 3 or 4 lasting more than 28 days with the lowest dose of PARP inhibitor[7,27,30]

- Discontinue PARP inhibitor

* Although these guidelines are specific for niraparib (except where indicated in the panel), they can also be applied to the other PARP inhibitors.

Lancet Oncol 2019; 20: e15–28

Dose Reduction Guide for PARP Inhibitors

PARP Inhibitor	Starting Dose	First Dose Reduction	Second Dose Reduction	Third Dose Reduction	Presence of Hepatic Impairment*	Presence of Renal Impairment†‡
Olaparib	300 mg BID	250 mg BID	200 mg BID	Discontinue	Mild: no dose adjustment; moderate or severe: unknown	Mild: no dose adjustment; moderate: 200 mg BID; severe or ESRD: unknown
Niraparib	300 mg QD	200 mg QD	100 mg QD	Discontinue	Mild: no dose adjustment; moderate or severe: unknown	Mild or moderate: no dose adjustment; severe or ESRD: unknown
Rucaparib	600 mg BID	500 mg BID	400 mg BID	300 mg BID	Mild: no dose adjustment; moderate or severe: unknown	Mild or moderate: no dose adjustment; severe or ESRD: unknown

*Hepatic impairment defined according to Organ Dysfunction Working Group criteria.
†Mild: CrCl = 60-89 mL/min; moderate: CrCl = 30-59 mL/min; severe: CrCl < 30 mL/min.
‡Consider evaluating GFR by noninvasive imaging to differentiate acute kidney injury.

LaFargue. Lancet Oncol. 2019;20:e15.

Nursing Implications: Patient Education and Assessment

- Consider implementing drug adherence strategies that are tailored to the patient
- Provide patient education on how to take the drug before implementation of the treatment
- Provide patients with appropriate education and regimen for managing gastrointestinal toxicities
- Patients should be assessed for a baseline level of fatigue/energy and educated on ways to counteract fatigue
- Patients should be counseled on monitoring blood counts, creatinine levels, and liver functions
- Early intervention to control these symptoms is important; establishing an open and trusting communication pattern with your patient is key to ensuring their safety and success with this treatment regimen

Daugherty. Oncol Nurse. 2010;3.

Pharmacist Considerations for Use of PARP Inhibitors

PARP Inhibitor Dosing and Administration

	Olaparib	Rucaparib	Niraparib
Dosing	300 mg PO BID (150-mg, 100-mg tablets)	600 mg PO BID (300-mg, 250-mg, 200-mg tablets)	300 mg PO daily (100-mg capsules)
How to take	With/without food (taking at bedtime or 30-60 min after meal may help with nausea)		
Renal impairment (baseline dosing)	200 mg PO BID for CrCl 31-50 mL/min	—	—
CYP interactions	Inhibits CYP3A and induces CYP2B6; metabolized by CYP3A4	Inhibits CYP2C19, 2C9, 3A4, 1A2; metabolized by CYP2D6, lesser extent 1A2 and 3A4	Other hepatic metabolism*
PARP inhibitor dose reductions for CYP interactions	Avoid strong CYP3A inhibitors 150 mg PO BID with moderate CYP3A inhibitors 100 mg PO BID with strong CYP3A inhibitors	No dose reductions	No dose reductions

*Carboxylesterase-catalyzed amide hydrolysis vs rucaparib and olaparib via CYP450.

LaFargue. Lancet Oncol. 2019;20:e15. Olaparib PI. Rucaparib PI. Niraparib PI.

Significant Drug Interactions With PARP Inhibitors

- Olaparib: inhibits CYP3A and induces CYP2B6; metabolized by CYP3A4
  - Avoid moderate/strong CYP3A inhibitors (amiodarone, verapamil, diltiazem, azole antifungals, etc) and inducers (rifampin, St John's wort, phenytoin, etc)
  - Avoid grapefruit juice or Seville oranges
  - Dose reductions required to manage these interactions
- Rucaparib: inhibits CYP2C19, 2C9, 3A4, 1A2; metabolized by CYP2D6, lesser extent 1A2 and 3A4
  - Can affect/increase concentrations of drugs, monitor patient
    - Substrates of 2C19: citalopram, sertraline, etc
    - Substrates of 2C9: warfarin, candesartan, etc
- Niraparib: no significant CYP interactions due to alternate metabolic pathway

Olaparib PI. Rucaparib PI. Niraparib PI.

Slide credit: clinicaloptions.com

PARP Inhibitors: General Patient Counseling Points

- There may be overlapping disease and treatment-related toxicity; prophylactic management may increase success
  - eg, if patients have baseline nausea or baseline diarrhea that may be worsened by PARP inhibitors, prophylactic medications can be used
- Set realistic expectations for patients and caregivers regarding timing and severity of adverse events; it is okay to reduce or hold doses and restart to maintain the treatment
  - eg, reducing the dose for fatigue will still allow for effective PARP inhibitor therapy

Moore. Oncologist. 2016;21:954.

Slide credit: clinicaloptions.com

PARP Inhibitors: Additional Patient Counseling Points

- Safe handling and storage at home
  - Keep at room temperature in original packaging
  - Keep out of reach of children, pets
  - If family member is administering, they should wear gloves
- Drug disposal
  - Medication take-back programs (do not flush)
- Missed doses
  - If within a few hrs, okay to take missed dose; otherwise skip until next dose
- Miscellaneous
  - Do not chew or crush

Slide credit: clinicaloptions.com

PARP Inhibitors: Financial Factors

- PARP inhibitors are considered "high-cost" therapy:
  $16,000 to $23,000/month wholesale price
  - Copays, deductibles may vary based on specific patient insurance plan
    - Many patients may pay less than $100/month; others may pay thousands
  - Prior authorizations to allow filling of prescription
  - Medication assistance programs available from manufacturers
    - Each program with specific requirements and assistance offered
  - Often requires specialty pharmacy for dispensing

Slide credit: clinicaloptions.com

用法用量/價格

- 目前台灣有150mg. 乳癌、卵巢癌都是600mg/day = 2tab bid
- 150mg/顆　台北榮總自費價約**2500元/顆**
- 一盒56顆 = 14天藥量，換算自費價格28天需要負擔**280,000元**
- 健保給付價格150mg： 一顆 **1600元** 100mg:一顆**1500元**

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生活首頁 總覽 新冠肺炎 Campus

首頁 / 生活

乳癌最惡性殺手 三陰性乳癌藥首納健保 5年內152人受惠

11:57 2020/09/08 中時 林周義

yahoo! 新聞

搜尋 搜尋新聞

熱搜： 總統府發言人 蘋果發表會 不沾炒鍋 余苑綺化療18次 燕窩禮盒 美

首頁 政治 論壇 財經 娛樂 運動 社會地方 國際 生活 健康 科技 天氣

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台灣新生報 | 2k 人追蹤 追蹤

【記者鍾佩芳 / 台北報導】
2020年9月8日 下午9:51

HEHO health & hope

Search...

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乳癌標靶藥物首納健保！共4種癌症新藥獲給付11/1上路

日期：2020-09-08 作者：林 以瑨

康健 For a better life

健康城市

全部 試試搜尋「燃脂、抗老」...

健保署今（8日）天公布，將4類藥物納入健保給付及擴大給付範圍，其中包含有「乳癌最惡性殺手」——三陰性乳癌的標靶藥物Olaparib。這項藥物可以有效控制癌細胞，提升病患生活品質，每個病人每月更可省下約20萬元醫療費用。


THE DAY AFTER
TOMORROW

TFDA核准適應症

1st line OCa BRCA1/2m - maintenance therapy

Recurrence OCa platinum sensitive - maintenance therapy

1st line OCa HRD/Genomic instability – combine bevacizumab as maintenance therapy

HER2- mBC gBRCA1/2m (post chemo/HT)

1st line mPaC gBRCA1/2m maintenance therapy

Lynparza副作用

令癌莎（Lynparza)的常見副作用

		說明
貧血	40.0%[1]	• 醫師會在令癌莎（Lynparza)治療前、及治療期間定期監測全血球計數，評估治療期間全血球計數變化[2]。
嗜中性白血球減少	27.3%[1]	
白血球減少	16.1%[1]	
 噁心	58.0%[1]	• 出現輕度或中度噁心，可服用醫師處方的止吐藥[4]
 嘔吐	29.8%[1]	• 出現輕度或中度嘔吐，可服用醫師處方的止吐藥[4]
 腹瀉	20.5%[1]	• 症狀不複雜的輕度腹瀉者，建議少量多餐、或採用BRAT飲食（香蕉、米飯、蘋果、吐司）[4] • 服用醫師處方的止瀉藥[4]
 倦怠、無力	28.8%[1]	• 節省體力的消耗、和適度運動，能有效改善症狀[4] • 服用醫師處方的精神振奮藥[4]

令癌莎（Lynparza)的其他副作用

		說明
 骨髓造血不良 症候群（MDS)/急性骨髓性白血病（AML）	< 1.5%[2]	• 若出現疑似MDS/AML 症狀，包括：虛弱、疲倦、發燒、體重減輕、頻繁感染、瘀血、容易出血、呼吸困難、血尿或血便、血球計數降低、需要輸血，請告知醫護人員[3]。
 非感染性肺炎	< 1%[2]	• 若出現新的呼吸症狀或症狀惡化，例如呼吸困難、咳嗽和發燒，或是發生胸腔放射影像異常，請立即告知您的醫師，並由醫師檢查評估是否罹患非感染性肺炎[2]。

1. Robson M, et al. N Engl J Med. 2017;377(6):523-33.
2. Lynparza 中文仿單，版本日期：2018 年 08 月。
3. Friedlander M, et al. Asia Pac J Clin Oncol. 2016;12(4):323-31
4. Moore KN, Monk BJ. Oncologist. 2016;21(8):954-63.

Take Home Message

- Olaparib is indicated for:
  - gBRCA mutated HER2-negative MBC (from Expert point of view: may extend to sBRCA/gPALB2 patients after failed all SOC)

- Olaparib is also indicated for recurrent platinum-sensitive ovarian cancer
  - 1st-Line maintenance (g/sBRCA)
  - 2nd-Line maintenance (no biomarkers needed)
  - 4th-Line or beyond (Monotherapy for gBRCA)

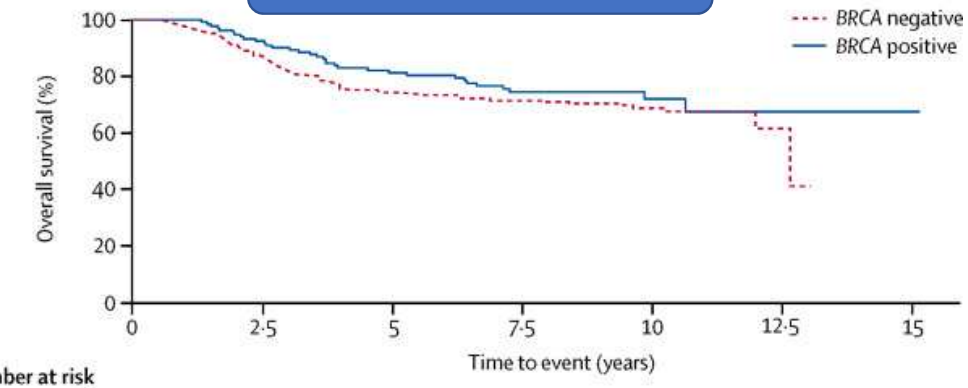
- AE management:
  - Anemia, Neurtopenia, Thrombocytopenia
  - Moderate emetic potential and diarrhea
  - Fatigue, headache

Thank you !

Young-onset gBRCA breast cancer patients have a similar overall survival to non-carriers.

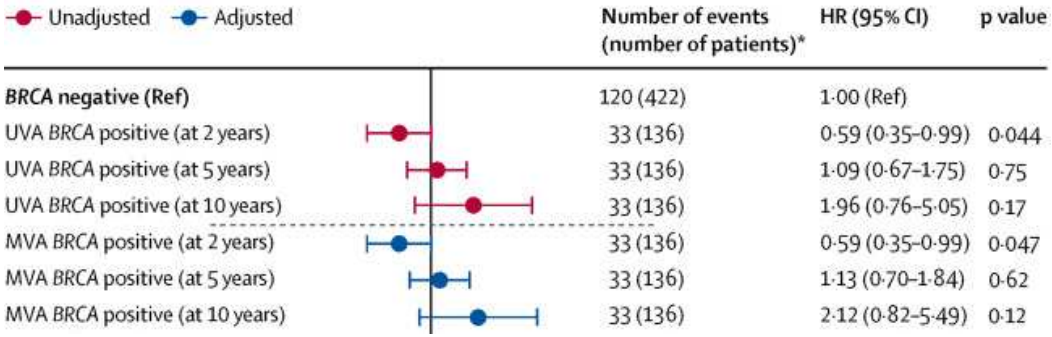
TNBC type

A



Number at risk (number censored)							
BRCA negative	422 (52)	361 (53)	267 (8)	165 (4)	62 (2)	4 (1)	0 (0)
BRCA positive	136 (10)	120 (14)	94 (7)	63 (1)	26 (1)	2 (0)	1 (0)

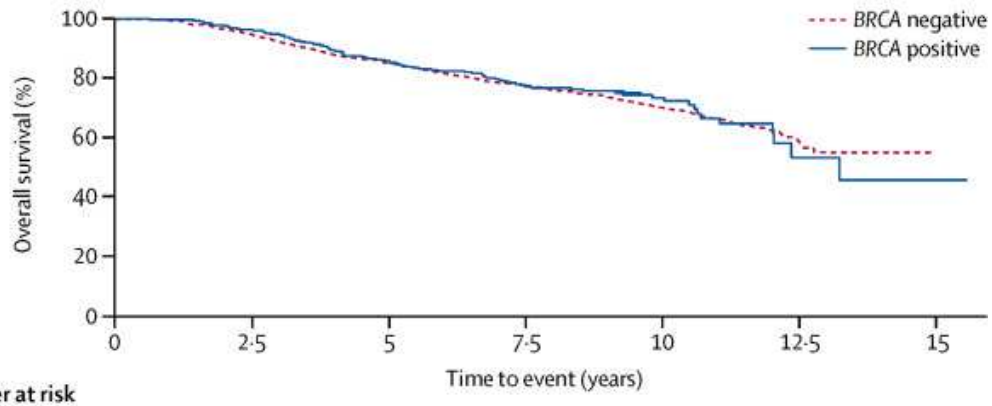
B



	Number of events (number of patients)*	HR (95% CI)	p value
***BRCA* negative (Ref)**	120 (422)	1·00 (Ref)	
UVA *BRCA* positive (at 2 years)	33 (136)	0·59 (0·35–0·99)	0·044
UVA *BRCA* positive (at 5 years)	33 (136)	1·09 (0·67–1·75)	0·75
UVA *BRCA* positive (at 10 years)	33 (136)	1·96 (0·76–5·05)	0·17
MVA *BRCA* positive (at 2 years)	33 (136)	0·59 (0·35–0·99)	0·047
MVA *BRCA* positive (at 5 years)	33 (136)	1·13 (0·70–1·84)	0·62
MVA *BRCA* positive (at 10 years)	33 (136)	2·12 (0·82–5·49)	0·12

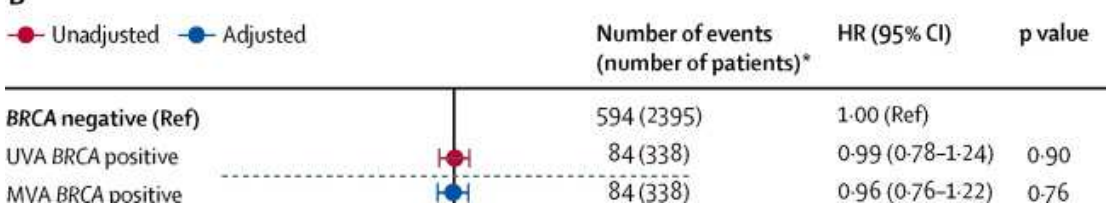
All BC type

A



Number at risk (number censored)							
BRCA negative	2395 (125)	2217 (217)	1805 (141)	1160 (78)	452 (30)	48 (3)	0 (0)
BRCA positive	338 (13)	313 (38)	245 (18)	163 (5)	71 (9)	10 (1)	2 (0)

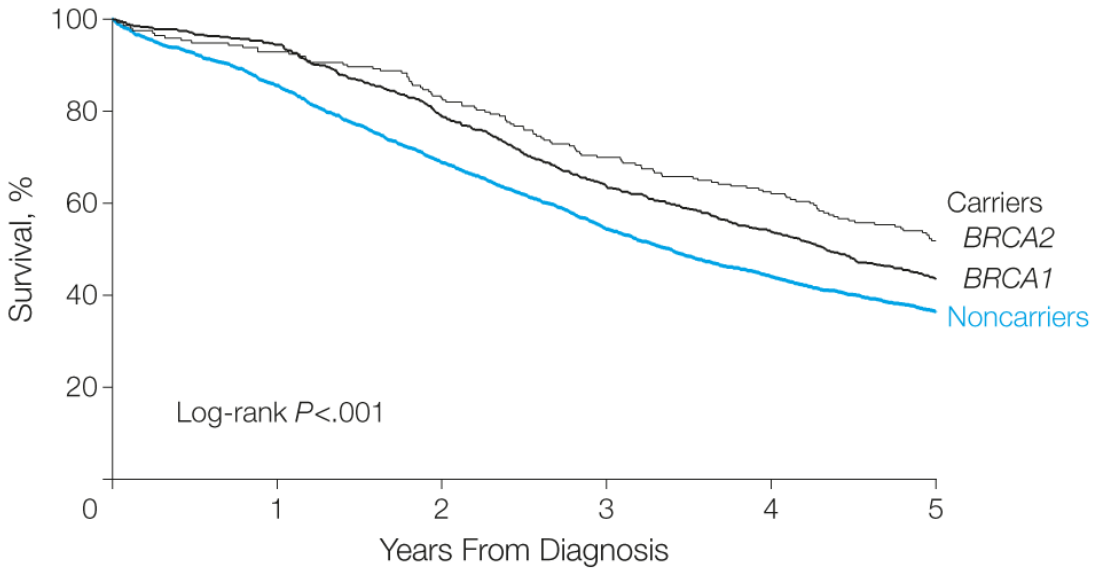
B



	Number of events (number of patients)*	HR (95% CI)	p value
***BRCA* negative (Ref)**	594 (2395)	1·00 (Ref)	
UVA *BRCA* positive	84 (338)	0·99 (0·78–1·24)	0·90
MVA *BRCA* positive	84 (338)	0·96 (0·76–1·22)	0·76

Lancet Oncol. 2018 Feb;19(2):169-180.

Prognosis of gBRCA1/2 in ovarian cancer



No. at risk						
Noncarriers	1047	1687	1540	1395	1225	1044
Carriers						
BRCA1	327	593	569	490	408	342
BRCA2	117	199	192	179	164	125

From: Association Between BRCA1 and BRCA2 Mutations and Survival in Women With Invasive Epithelial Ovarian Cancer

JAMA. 2012;307(4):382-389

SOLO-2: Study Design

SOLO-2, a phase 3 study, was designed to provide additional evidence for the benefit of olaparib maintenance therapy in patients with *BRCA*m PSR ovarian cancer[1,2]

Patients:
- PSR SOC and *BRCA1/2* mutation
- ≥2 prior lines of platinum therapy
- CR or PR to most recent therapy[1]

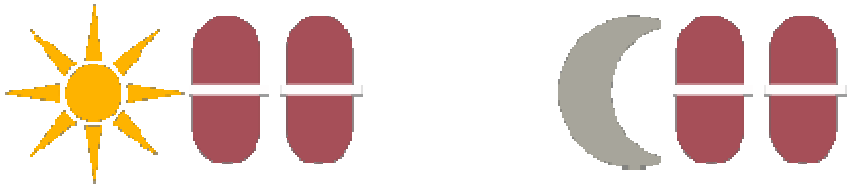
2:1 randomisation

Olaparib 300 mg BID tablets n=196

Placebo n=99

Primary endpoint:
Investigator-assessed PFS

- SOLO-2 reported data on the new film-coated tablet formulation of olaparib[1-3]
- The tablet formulation used in SOLO-2 was chosen based on data from Study 24[4]
- The recommended **tablet dose was 300 mg** administered as 2 x 150-mg tablets, twice daily[4]

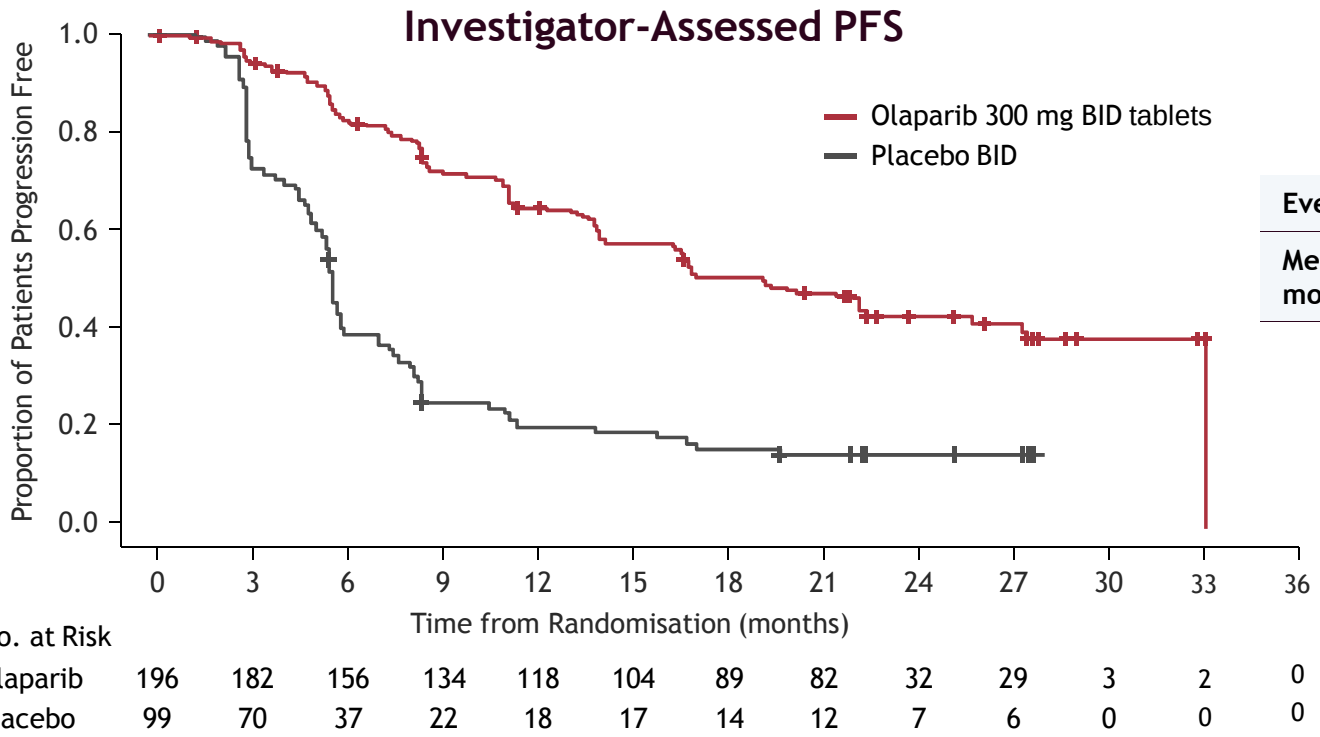


BID=twice daily; *BRCA*m=*BRCA* mutated; CR=complete response; PFS=progression-free survival; PR=partial response; PSR=platinum-sensitive relapsed; SOC=standard of care.

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01874353. Accessed 24 September 2018. 2. Pujade-Lauraine E et al. *Lancet Oncol*. 2017;18(9):1274-1284. 3. Ledermann J et al. *N Engl J Med*. 2012;366:1382–1392. 4. Mateo J et al. *Target Oncol*. 2016;11(3):401–415.

SOLO-2: Investigator-Assessed Progression-Free Survival

Risk of progression or death during the study was reduced by 70% for patients taking olaparib vs placebo[1,2]

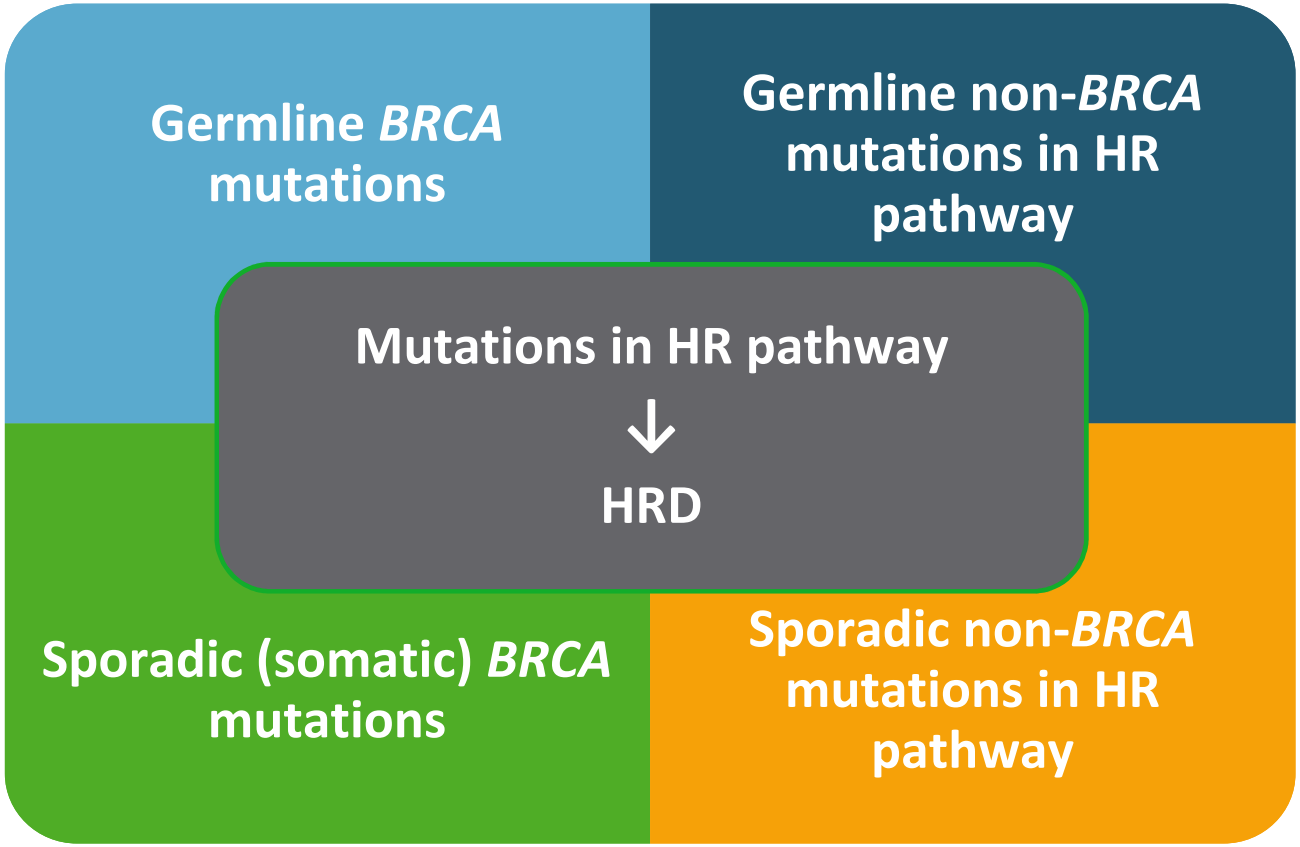


	Olaparib 300 mg BID tablets	Placebo BID
Events, n (%)	107/196 (54.6)	80/99 (80.8)
Median PFS, mo	**19.1**	**5.5**

HR=0.30
(95% CI, 0.22-0.41)
P<0.0001

Investigator-assessed PFS at 63% maturity. Median follow-up for PFS was 22.1 months in the olaparib group and 22.2 months for placebo. Full assessment set N=295. Data cutoff: 9/19/2016.
BID=twice daily; CI=confidence interval; HR=hazard ratio; PFS=progression-free survival.
1. Pujade-Lauraine E et al. *Lancet Oncol*. 2017;18(9):1274-1284. 2. Pujade-Lauraine E et al. Presented at: SGO Annual Meeting; 2017.

HRD and *BRCA* Mutations

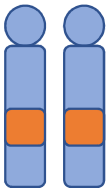


Slide credit: clinicaloptions.com

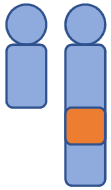
BRCA locus-specific loss of heterozygosity (LOH positive) in germline BRCA1 and BRCA2 carriers

BRCA LOH positive

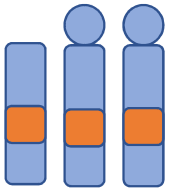
Copy neutral LOH



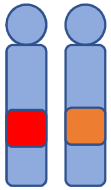
LOH with deletion

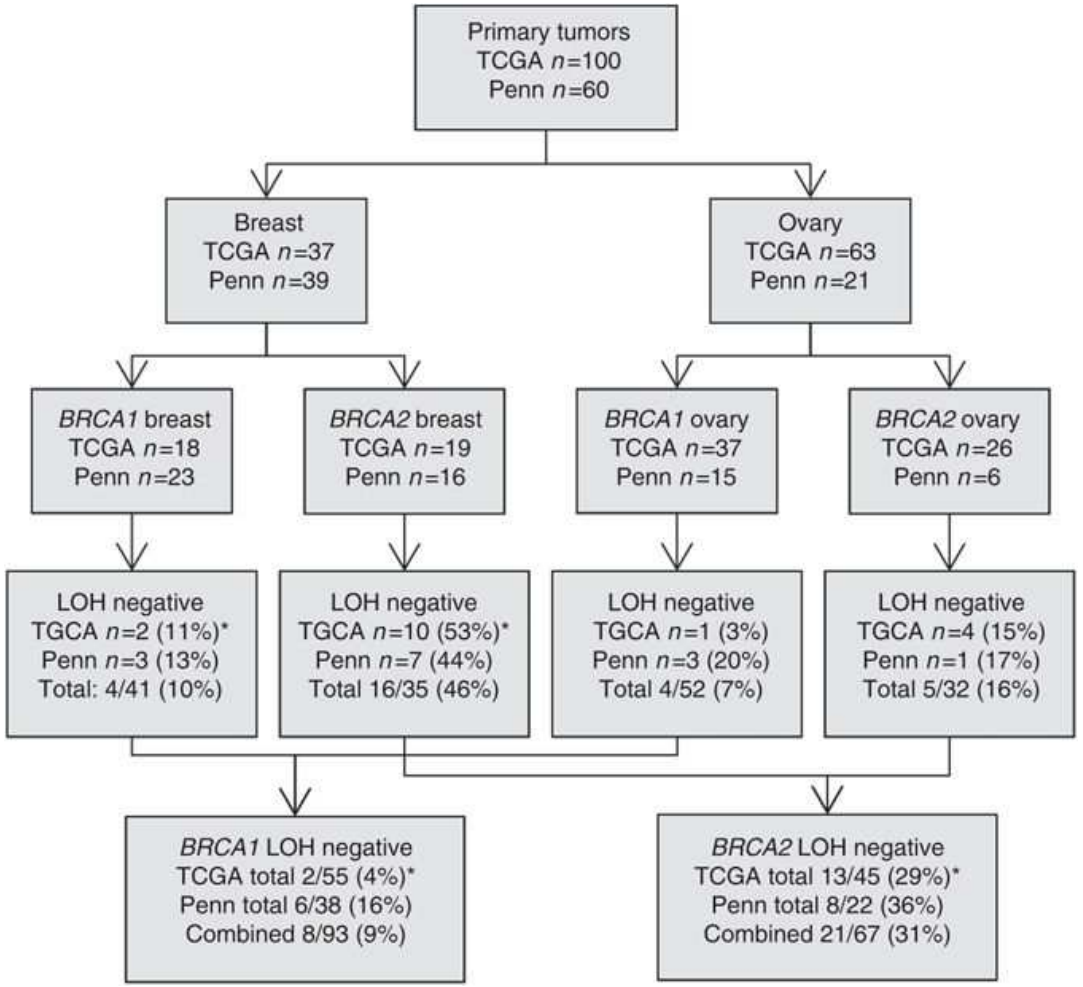


LOH in gain



Absent LOH + somatic mutation





Nature Communications 2017: 319

副作用

- AE乳癌和卵巢癌相似

The most common AEs were nausea, anaemia and vomiting[1]

AE	Olaparib (N=205) n (%)	TPC (N=91) n (%)
Nausea	119 (58.0)	32 (35.2)
Anaemia	82 (40.0)	24 (26.4)
Vomiting	66 (32.2)	14 (15.4)
Fatigue	61 (29.8)	22 (24.2)
Neutropenia*	56 (27.3)	45 (49.5)
Cough	35 (17.1)	6 (6.6)
Decreased appetite	35 (17.1)	11 (12.1)
Back pain	30 (14.6)	8 (8.8)
Alanine aminotransferase increased	24 (11.7)	16 (17.6)
Aspartate aminotransferase increased	20 (9.8)	15 (16.5)
Alopecia	7 (3.4)	12 (13.2)
Hand-foot syndrome	1 (0.5)	19 (20.9)

最常見的副作用： 噁心嘔吐、疲倦、貧血

Anaemia was the most common Grade ≥3 adverse event

Grade ≥3 AE	Olaparib (N=205) n (%)	TPC (N=91) n (%)
Anaemia*	33 (16.1)	4 (4.4)
Neutropenia*	19 (9.3)	24 (26.4)
White blood cell count decreased	7 (3.4)	9 (9.9)
Fatigue	7 (3.4)	1 (1.1)
Platelet count decreased	5 (2.4)	1 (1.1)
Leukopenia	5 (2.4)	3 (3.3)
Gamma-glutamyltransferase increased	4 (2.0)	1 (1.1)
Back pain	4 (2.0)	1 (1.1)
Dyspnoea	2 (1.0)	2 (2.2)
Headache	2 (1.0)	2 (2.2)
Hand-foot syndrome	0	2 (2.2)

% patients in either arm, with ≥5% arms

最常見的>G3副作用： 貧血、嗜中性球缺乏

對比化療組。除了貧血外，Olaparib較少血液學副作用

* Combined term
AE=adverse event
Grade ≥3 adverse events occurring in ≥2% patients in either arm
Data Cutoff: 25 September 2017
1. Robson et al. AACR, 2018

Dose reduction recommendation for PARPi

	Starting dose	1st dose reduction	2nd dose reduction	3rd dose reduction	Presence of hepatic impairment*	Presence of renal impairment†
Niraparib[15,33]	300 mg daily‡	200 mg daily	100 mg daily	Discontinue	Mild: no dose adjustment; moderate or severe: unknown	Mild or moderate: no dose adjustment; severe or ESRD: unknown
Rucaparib[14,28]	600 mg twice daily	500 mg twice daily	400 mg twice daily	300 mg twice daily	Mild: no dose adjustment; moderate or severe: unknown	Mild or moderate: no dose adjustment; severe or ESRD: unknown
Olaparib[18,30]	300 mg twice daily	250 mg twice daily	200 mg twice daily	Discontinue	Mild: no dose adjustment; moderate or severe: unknown	Mild: no dose adjustment; moderate: 200 mg twice daily; severe or ESRD: unknown

*Hepatic impairment defined according to Organ Dysfunction Working Group criteria. †Mild: creatinine clearance=60–89 mL/min. Moderate: creatinine clearance=30–59 mL/min. Severe: creatinine clearance <30 mL/min. ESRD: end-stage renal disease. ‡Although not yet in the US prescribing information, for patients with baseline body weight of less than 77 kg or a baseline platelet count less than 150 000/mL, starting dose of 200 mg daily should be considered.

Table 4: **Dose reduction guide**

Lancet Oncol 2019; 20: e15–28

Nonhematologic AEs in Phase III Trials of PARP Inhibitors as Maintenance Therapy in Recurrent Ovarian Cancer

AE, n (%)	Olaparib (n = 195)		Niraparib (n = 367)		Rucaparib (n = 372)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	148 (76)	5 (3)	270 (74)	11 (3)	280 (75)	14 (4)
Constipation	40 (21)	0	146 (40)	2 (< 1)	136 (37)	7 (2)
Vomiting	73 (37)	5 (3)	126 (34)	7 (2)	136 (37)	15 (4)
Diarrhea	64 (33)	2 (1)	70 (20)	1 (< 1)	118 (32)	2 (< 1)
Dyspepsia	22 (11)	0	42 (11)	0	54 (15)	1 (< 1)
Dysgeusia	52 (27)	0	37 (10)	0	146 (39)	0
Fatigue	128 (66)	8 (4)	218 (59)	30 (8)	258 (69)	25 (7)
Dizziness	26 (13)	1 (< 1)	61 (17)	0	54 (15)	0
Headache	49 (25)	1 (< 1)	95 (26)	1 (< 1)	67 (18)	1 (< 1)
Dyspnea	23 (12)	2 (1)	71 (19)	4 (1)	50 (13)	1 (< 1)

LaFargue. Lancet Oncol. 2019;20:e15.

Slide credit: clinicaloptions.com

Managing Nonhematologic AEs Associated With PARP Inhibitors

Grade	Intervention
Grade 1	Continue treatment; may initiate symptomatic management if necessary
Grade 2	Continue treatment; may consider dose interruption/reduction if toxicity remains uncontrolled, despite initiation of symptomatic management or prophylactic therapy
Grade 3/4	Withhold until resolution of AE: ▪ For olaparib or niraparib, hold until AE is grade 1 or resolved ▪ For rucaparib, hold until AE is grade 2, grade 1, or resolved If the grade 3/4 AE was nausea, vomiting, or diarrhea and became controlled on medication, treatment may continue If treatment was interrupted, dose reduction should be considered when treatment is resumed If the grade 3/4 AE lasts more than 28 days despite dose reduction/interruption, treatment should be discontinued

LaFargue. Lancet Oncol. 2019;20:e15.

Hematologic AEs in Phase III Trials of PARP Inhibitors as Maintenance Therapy in Recurrent Ovarian Cancer

AE, n (%)	Olaparib (n = 195)		Niraparib (n = 367)		Rucaparib (n = 372)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Anemia	85 (44)	38 (19)	184 (50)	93 (25)	139 (37)	70 (19)
Thrombocytopenia	27 (14)	2 (1)	225 (61)	124 (34)	104 (28)	19 (5)
Neutropenia	38 (19)	10 (5)	111 (30)	72 (20)	67 (18)	25 (7)

LaFargue. Lancet Oncol. 2019;20:e15.

Slide credit: clinicaloptions.com

Managing Hematologic AEs Associated With PARP Inhibitors

AE	Grade 1	Grade 2	Grade 3/4
Anemia	Monitor and continue tx	Hold tx for max 28 days and monitor blood counts weekly until Hb returns to ≥ 9 g/dL; restart treatment at reduced dose; discontinue if Hb has not recovered after 28 days	Consider transfusion; hold tx for max 28 days; restart tx at reduced dose; discontinue if Hb has not recovered after 28 days or if patient was on lowest dose of tx
Thrombocytopenia	Hold tx for max 28 days and monitor blood counts weekly until platelets ≥ 100,000/µL; restart tx at same or reduced dose; discontinue if platelets have not recovered after 28 days or if patient was on lowest dose of tx	Hold tx for max 28 days and monitor blood counts weekly until platelets returns to ≥ 100,000/µL; restart tx at reduced dose (in case of rucaparib where tx can restart at grade 2, consider dose reduction if platelets remain < 75,000/µL)	Give platelet transfusion if platelets < 10,000/µL or bleeding; restart tx at reduced dose; if already at the lowest dose, discontinue; consider interruption of anticoagulation and antiplatelet therapy
Neutropenia	Monitor and continue tx	Hold tx for max 28 days and monitor blood counts weekly until neutrophil counts return to ≥ 1500 cells/µL; restart tx at reduced dose; discontinue if neutrophils have not recovered after 28 days	Hold tx for max 28 days; restart tx at reduced dose; discontinue if neutrophils have not recovered after 28 days or if patient was on lowest dose of tx

LaFargue. Lancet Oncol. 2019;20:e15.