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DDR AND PARPi EXPERTS FORUM TOKYO

Prof. Keiichi Fujiwara, Dr. Shinji Ohno, Prof. Charlie Gourley, Dr. Simon Boulton

Tuesday 21st January 2020

Cerulean Tower Hotel, Tokyo, Japan

DDR AND PARPi EXPERTS FORUM

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THE OBJECTIVE:

TO LEARN ABOUT THE ROLE OF PARP INHIBITORS IN CLINICAL PRACTICE AND TARGETING DDR

- Mechanism of Action of PARP inhibition and targeting DDR
- Clinical profile of PARP inhibitors and their benefit in ovarian and breast cancer
- Appropriate patient selection for PARP inhibition
- Future of DDR and PARP inhibition

EXPERTS FORUM ASIA

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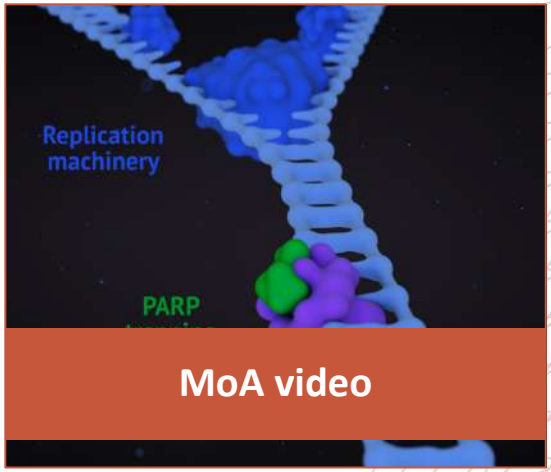
This Experts Forum is part of a larger suite of resources on DDR and PARP inhibition

BluePrints on DDR and PARPi

Review paper published in J Clin Oncol 2019[1]



MoA video

E-learning

ESMO OncologyPRO content

Experts Forum in Asia
Tokyo and Singapore

1. Gourley C, et al. J Clin Oncol 2019;37:2257-69

DISCLAIMER

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Please note:

The views expressed within this presentation are the personal opinions of the experts. They do not necessarily represent the views of the expert's academic institution.

AstraZeneca has provided a sponsorship grant towards this independent programme.

AGENDA

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Time	Topic	Speaker
18:00 - 18:30	Welcome Dinner and Registration	
18:30 - 18:35	Introduction	Prof. Keiichi Fujiwara
18:35 - 19:00	State-of-the-art presentation on DDR	Dr. Simon Boulton
19:00 - 19:25	State-of-the-art presentation on PARPi in ovarian cancer	Prof. Charlie Gourley
19:25 -19:50	State-of-the-art presentation on PARPi in breast cancer	Dr. Shinji Ohno
19:50 - 20:05	Management of PARPi adverse events	Prof. Charlie Gourley
20:05 - 20:50	Q&A session - Local experiences with PARPi and targeting DDR	Led by Prof. Keiichi Fujiwara
20:50 - 21:00	Closing comments	Prof. Keiichi Fujiwara

EXPLOITING DNA REPAIR VULNERABILITIES IN CANCER

Simon J. Boulton

THE FRANCIS CRICK INSTITUTE

artios DNA DAMAGE RESPONSE

DISCLOSURES

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- Artios Pharma Ltd.
  - Co-founder & SVP Science Strategy
  - Niall Martin (CEO) & Graeme Smith (CSO)
    - Co-discovered Olaparib (KuDos)

DNA DAMAGE – DNA REPAIR MECHANISMS

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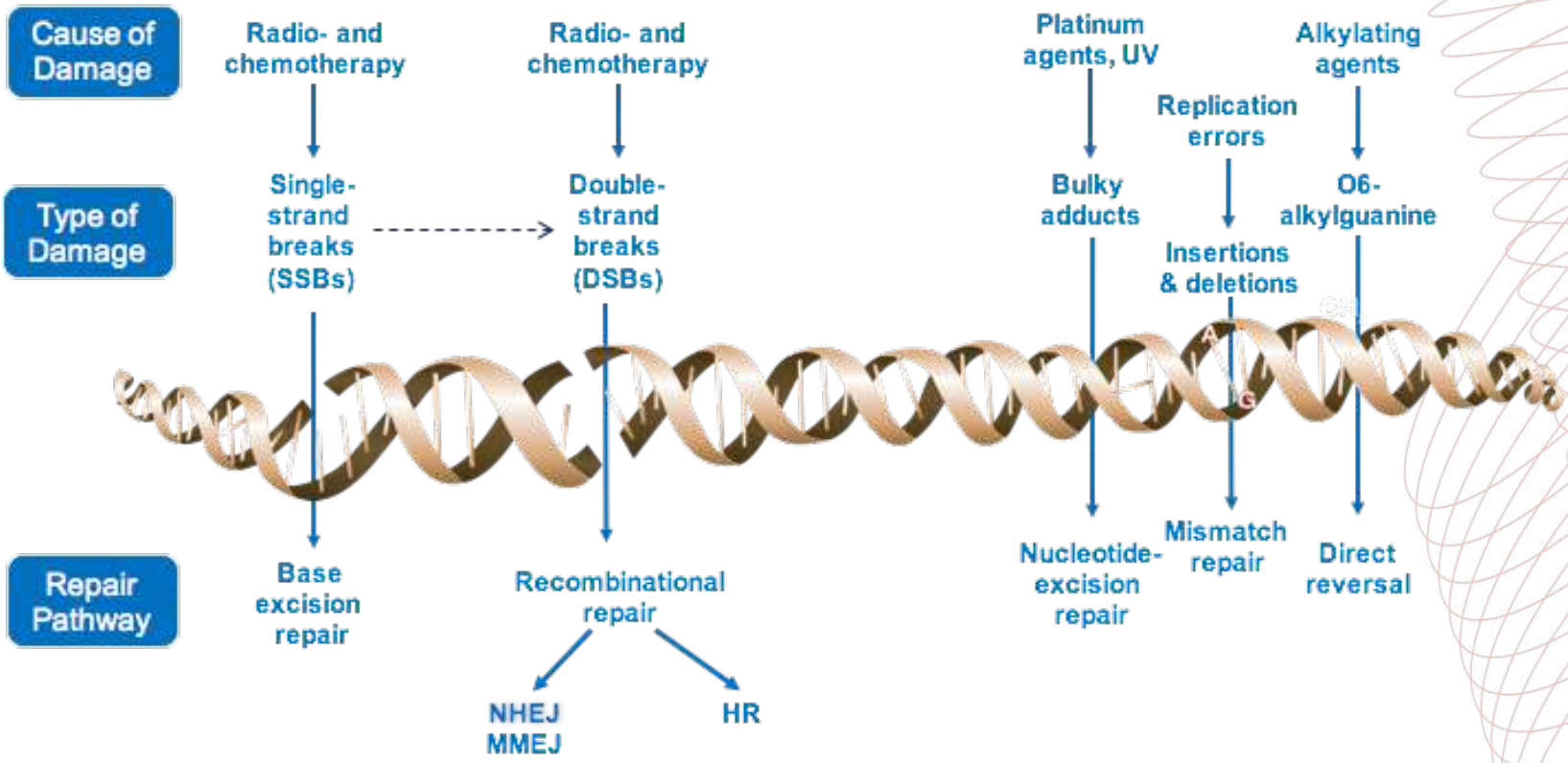

HR, homologous recombination; MMEJ, microhomology-mediated end joining; NHEJ, non-homologous end joining; UV, ultraviolet

ABERRANT DSB REPAIR: GENOME INSTABILITY

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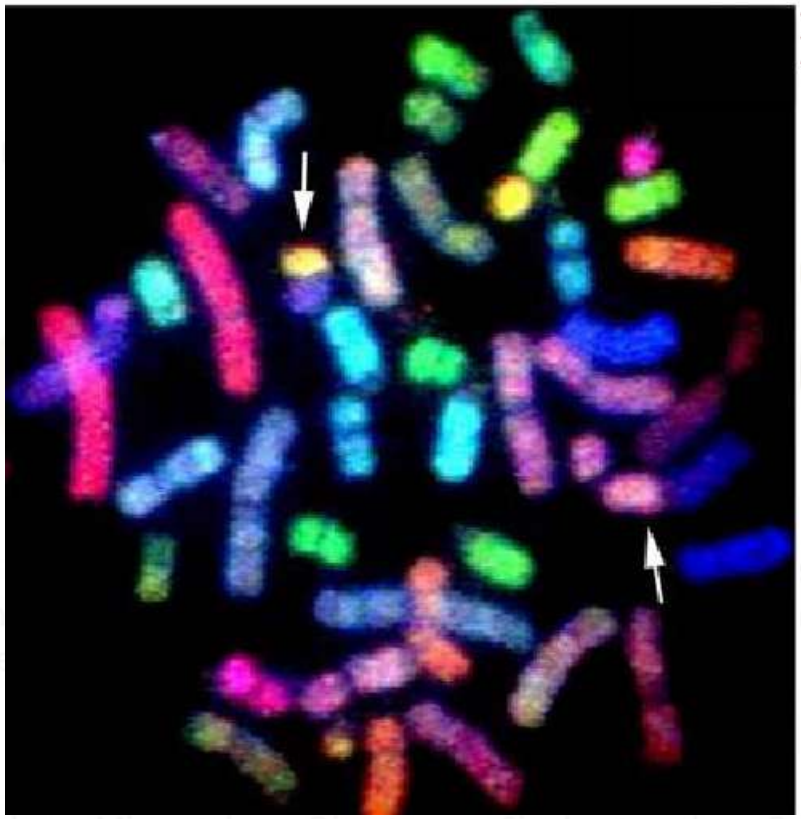
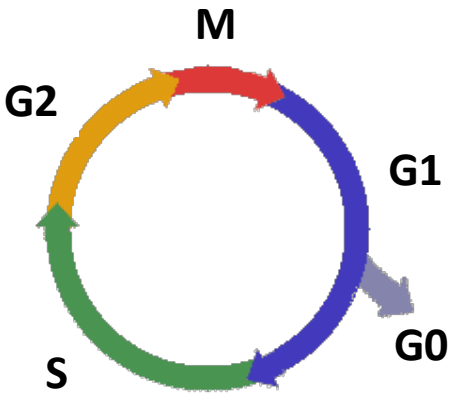
Spontaneous
(Fork collapse)



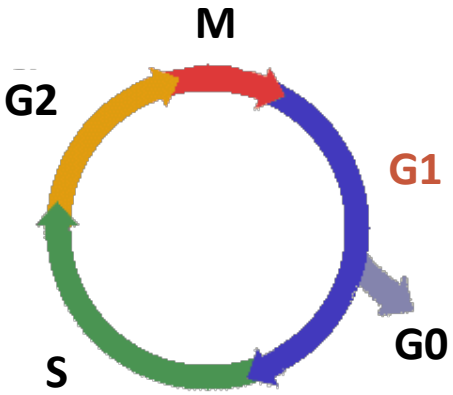
DSB, double-strand break

DSB REPAIR: CELL CYCLE



DSB, double-strand break

DSB REPAIR: CELL CYCLE



"NHEJ"

DSB

"Error prone"

DSB, double-strand break; NHEJ, non-homologous end joining

DSB REPAIR: CELL CYCLE

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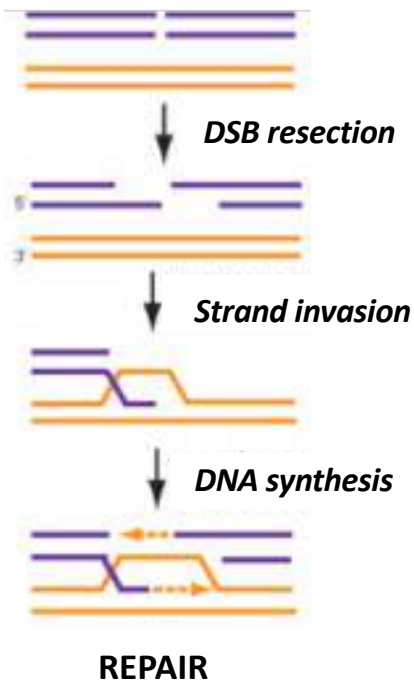
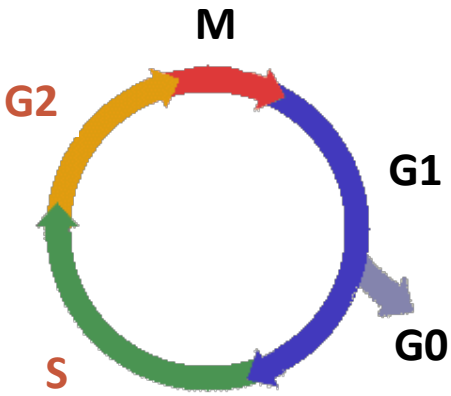
"HR"

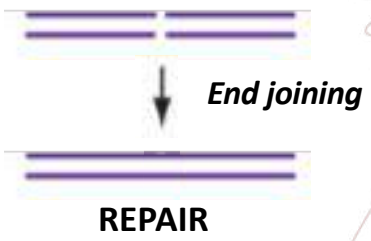


"Error free"



BRCA1/53BP1

"NHEJ"



"Error prone"

53BP1, tumour suppressor p53-binding protein 1; BRCA1, breast cancer type 1 susceptibility protein; DSB, double-strand break; HR, homologous recombination; NHEJ, non-homologous end joining

DSB REPAIR

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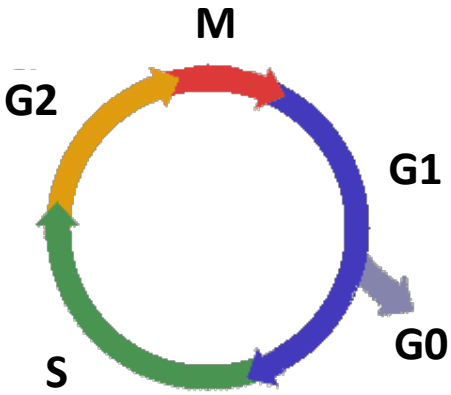
"HR"

DSB

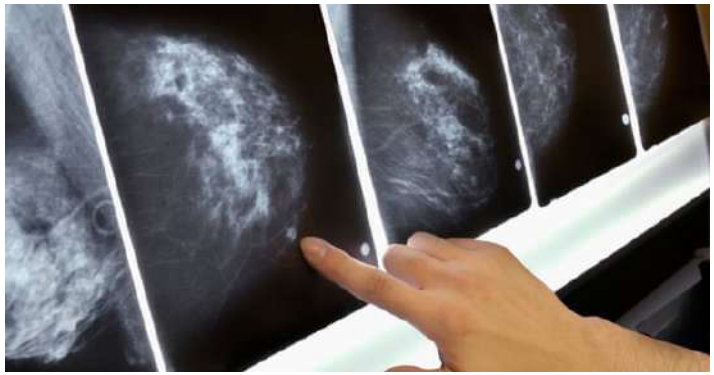


"NHEJ"

DSB

Mono-allelic

Breast, ovarian, prostate and others



DSB, double-strand break; HR, homologous recombination; NHEJ, non-homologous end joining

DSB REPAIR DEFECTS: THERAPEUTIC EXPLOITATION IN CANCER

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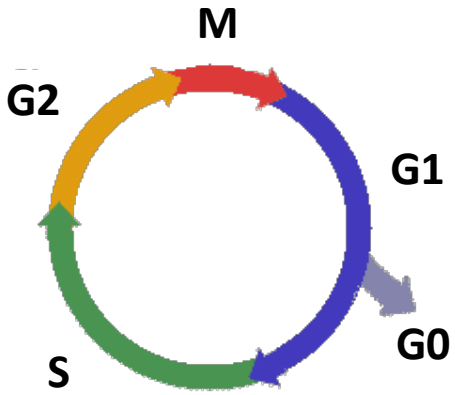
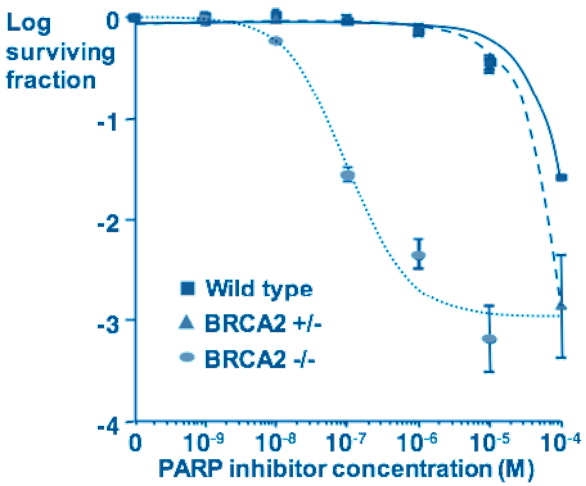
"HR"

"NHEJ"



DSB

DSB



Helleday, Jackson, Ashworth

Bryant HE, et al. Nature 2005; 434:913-917
Farmer H, et al. Nature 2005; 434:917-921

BRCA2, breast cancer type 2 susceptibility protein; DSB, double-strand break; HR, homologous recombination; M, molarity; NHEJ, non-homologous end joining; PARP, poly-ADP ribose polymerase

PARP INHIBITORS: THERAPEUTIC EXPLOITATION IN CANCER

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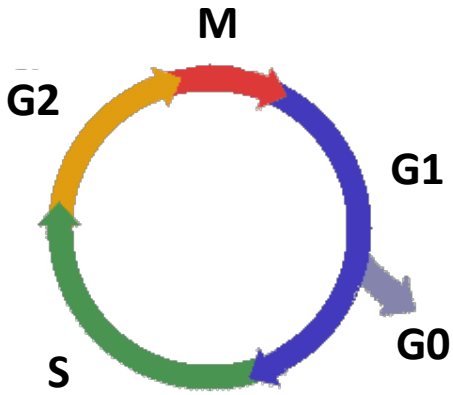
"HR"

"NHEJ"



DSB

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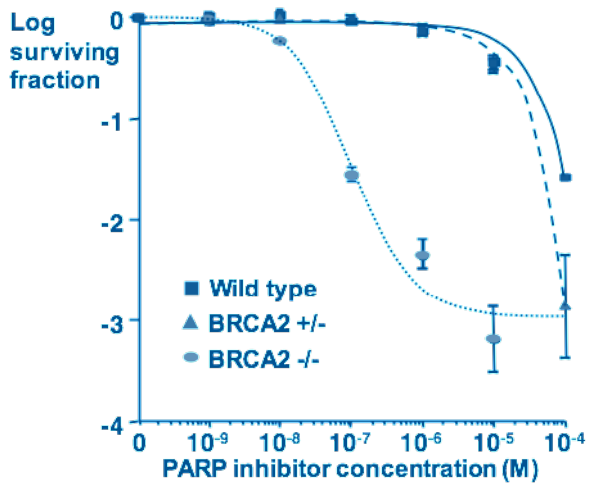

Lynparza® olaparib

Zejula™ niraparib

Rubraca® (rucaparib) 300 mg tablets

TALZENNA™ talazoparib 1 mg capsules

BRCA2, breast cancer type 2 susceptibility protein; DSB, double-strand break; HR, homologous recombination; M, molarity; NHEJ, non-homologous end joining; PARP, poly-ADP ribose polymerase

PARP INHIBITORS: THERAPEUTIC EXPLOITATION IN CANCER

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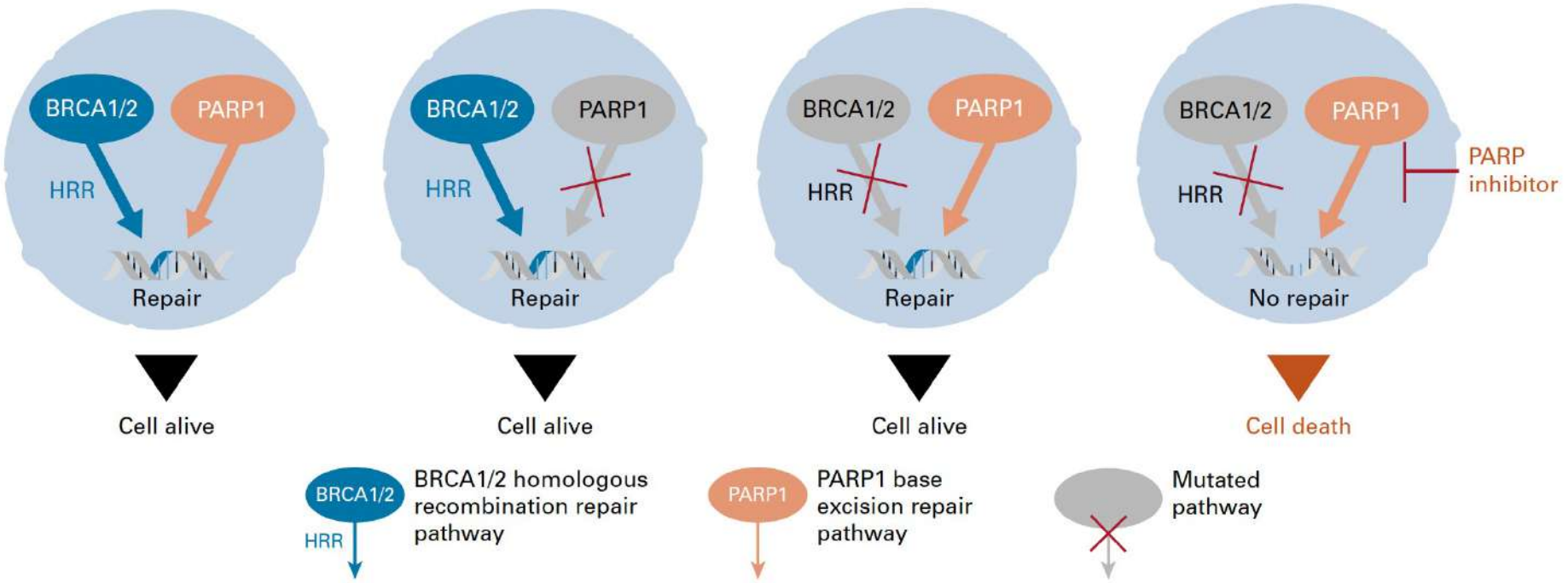
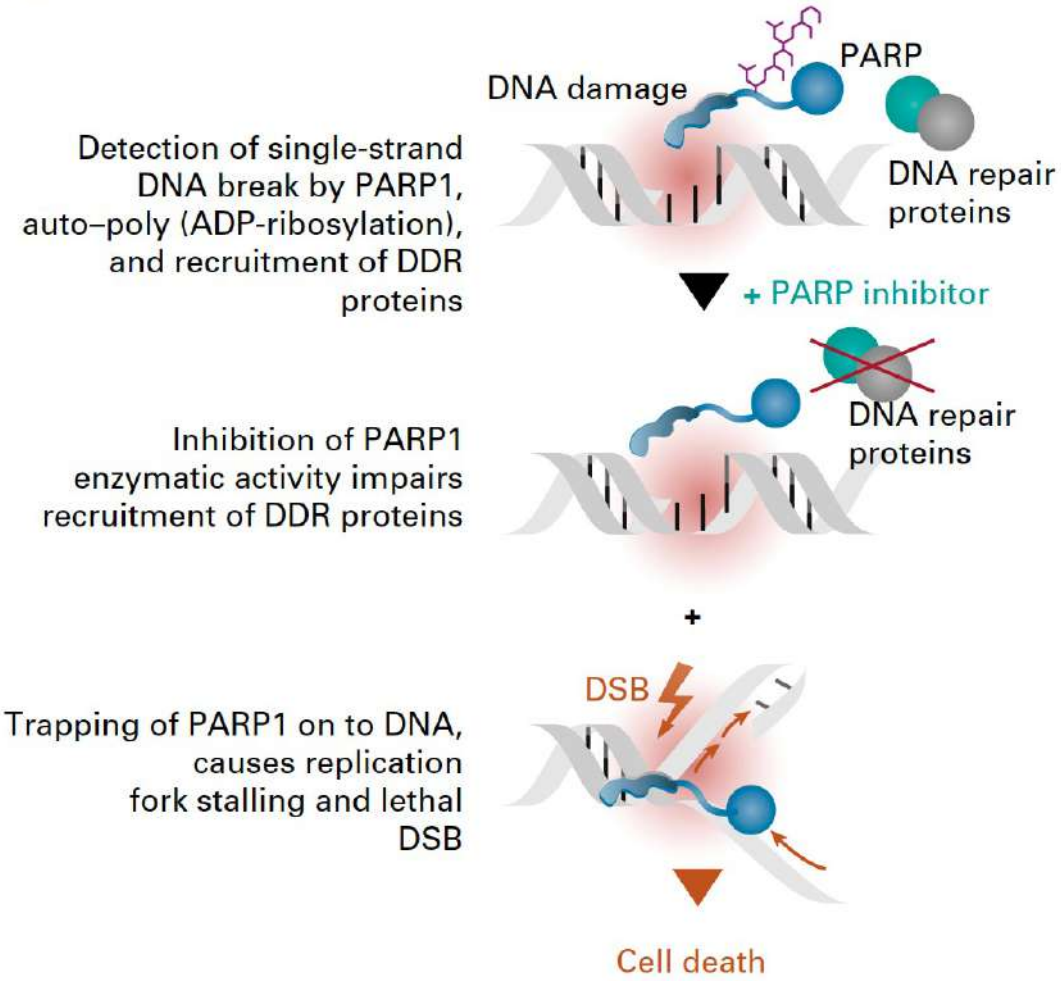


PARP is required for single strand break repair (and BER)

MOA – inhibiting SSB/BER synthetic lethal with HRD

BER, base excision repair; BRCA1/2, breast cancer type 1/2 susceptibility protein; HRD, homologous recombination deficiency; HRR, homologous recombination repair; MOA, mode of action; PARP, poly-ADP ribose polymerase; SSB, single-strand break

PARP INHIBITORS: EFFICACY (AND TOXICITY) – PARP TRAPPING



MOA – trapping PARP is synthetic lethal with HRD

ADP, adenosine diphosphate; DDR, DNA damage response; DSB, double-strand break; HRD, homologous recombination deficiency; MOA, mode of action; PARP, poly-ADP ribose polymerase

PARP INHIBITORS: CLINICAL IMPACT (OVARIAN)

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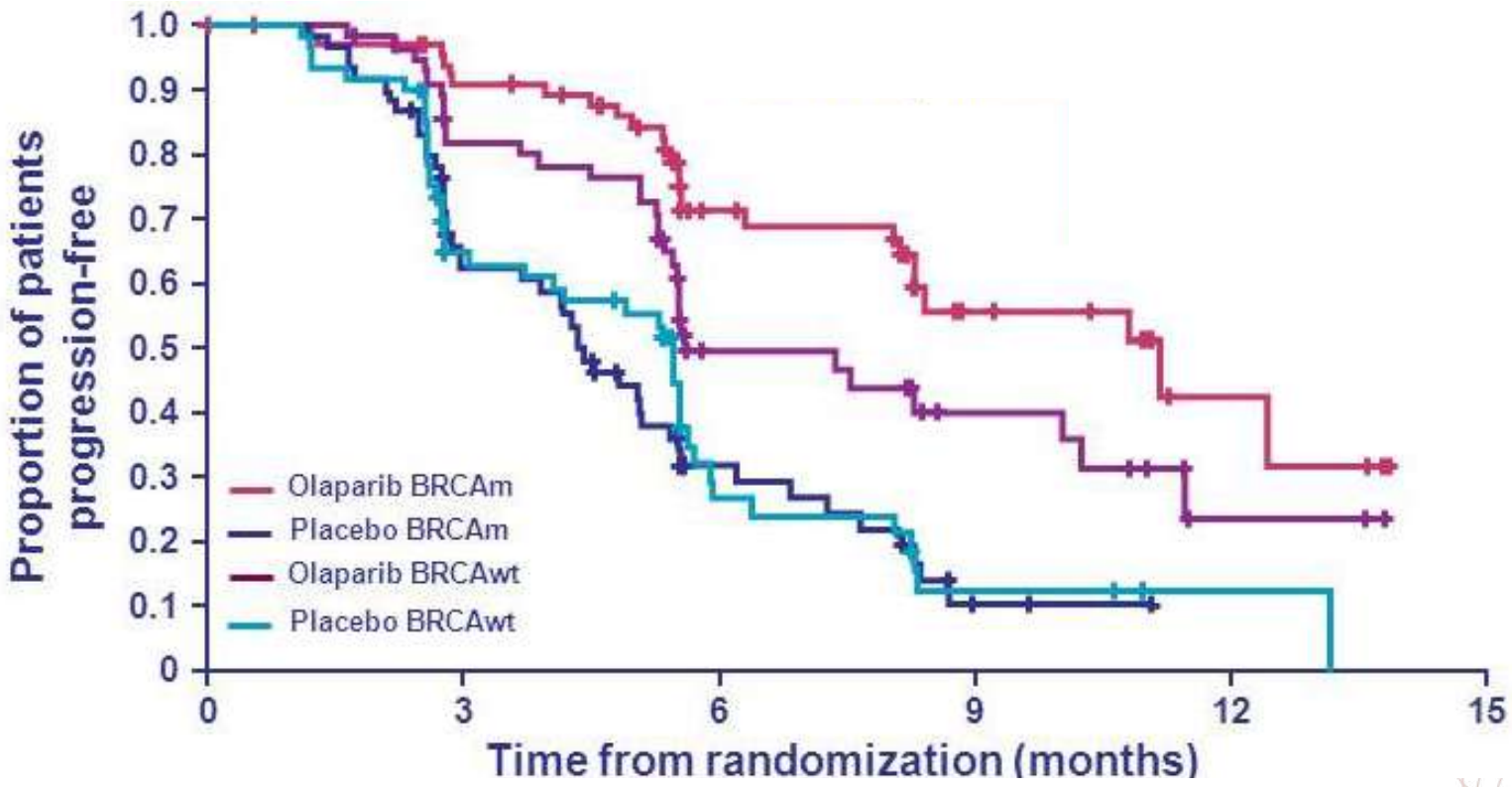

Super-responders – germline *Brca* (HRD)

~25% patients have no progression for >2 years (cf 5% placebo) germline *Brca* (HRD)

~17% patients for >3 years (cf 3% placebo)

BRCA, breast cancer susceptibility protein; BRCAm, BRCA mutated; BRCAwt, BRCA wild type; HRD, homologous recombination deficiency; PARP, poly-ADP ribose polymerase
Ledermann J, et al. J Clin Oncol 2013; 31(15S):abstr 5505

PARP INHIBITORS RESISTANCE MECHANISMS

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Resistance mechanisms	Cause of resistance	Clinical evidence
(i) Increased drug efflux	- Upregulation of ABC transporters	- No evidence
(ii) Decreased PARP trapping	- Loss or decreased trapping of PARP1 - Loss of PARG	- Trapping-diminishing PARP1 mutation in PARPi-resistant tumour - No evidence
(iii) Restoration of HR	- Reactivation of *BRCA1/2* - Loss of 53BP1 - Loss of Shieldin factors - Loss of CTC/Polα - Loss of DYNLL1/ATMIN	- Mutations in patients and PDXs - Low expression and mutations in PDXs - Low expression and mutations in PDXs - No evidence - No evidence
(iv) Stabilization of stalled forks	- Loss of PTIP - Loss of EZH2	- No evidence - No evidence

53BP1, tumour suppressor p53-binding protein 1; ABC, ATP-binding cassette; ATMIN, ATM interactor; BRCA, breast cancer susceptibility protein; DYNLL1, dynein light chain 1, cytoplasmic; EZH2, enhancer of zeste homolog 2; pARG, poly (ADP-ribose) glycohydrolase; PARP, poly-ADP ribose polymerase; PDX, patient derived xenograft; Polα, DNA polymerase alpha; PTIP, PAX-interacting protein 1

DSB REPAIR DEFECTS: THERAPEUTIC EXPLOITATION IN CANCER

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Large disease burden

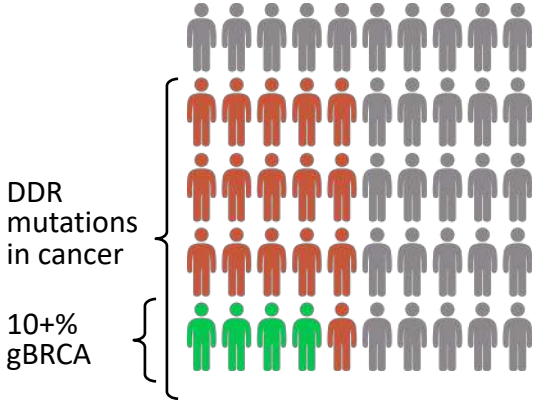
14.1 million — # of people diagnosed every year with cancer, worldwide

3 million — # of people diagnosed with ovarian (0.2m), breast (1.7m) and prostate cancer (1.1m) every year, worldwide

200K-300K ovarian, breast and prostate cancer patients with **BRCA** 1/2 mutations

50% of **BRCA** patients respond to PARPi (just one example of DDR/SL)

Resistance & mutations drives continuing need for new drug therapies



Cancers that are potentially DDR targetable:
- ❑ *BRCA mutation, BRCA epigenetic*
- ❑ *Beyond-BRCA e.g. Homologous recombination deficiency (ATM, CHEK2, FA)*
- ❑ *Other DOR losses MMR, NHEJ, BER pathways*

= **40-50%**

% **BRCA** patients becoming resistant to PARPi (unless cured) = **>90%**

Intrinsic and acquired PARPi resistance – need for novel medicines

ATM, ataxia telangiectasia mutated gene; BRCA1/2, breast cancer type 1/2 susceptibility protein; CHEK2, checkpoint kinase 2; DDR, DNA damage response; DSB, double-strand break; FA, Fanconi anaemia gene; gBRCA, germline BRCA; PARPi, poly-ADP ribose polymerase inhibitor; SL, synthetic lethality

DDR INHIBITORS: THERAPEUTIC EXPLOITATION IN CANCER

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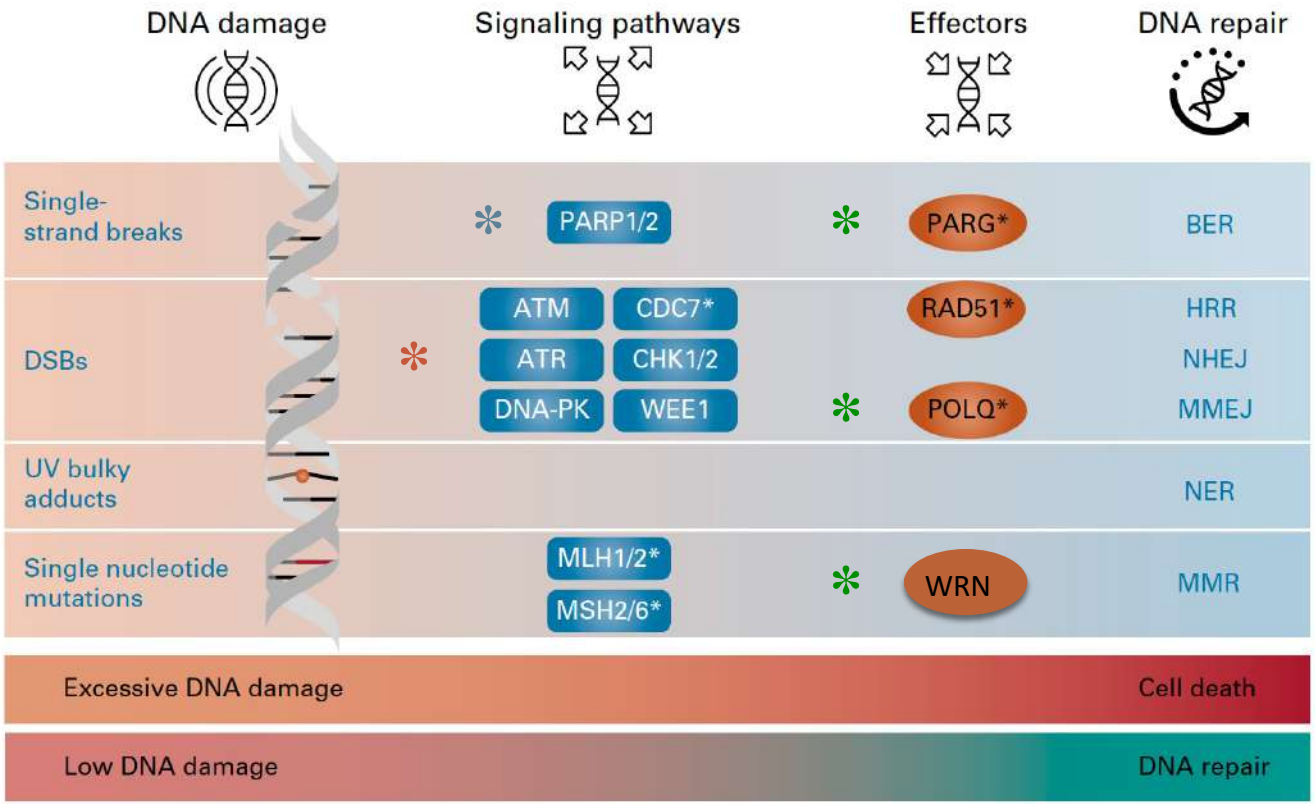

Pharmacologically targeted:

PARP1/2	Olaparib (AstraZeneca)
	Rucaparib (Clovis)
	Niraparib (Tesaro)
	Talazoparib (Pfizer)
ATR	AZD-6738 (AstraZeneca)
	M-4344 (Merck)
DNA-PK	Asi DNA (Onxeo)
	CC-125 (Celgene)
	LY-3023414 (Eli Lilly)
	M-3814 (Merck)
WEE1	AZD-1775 (AstraZeneca)
CHK1/2	CBP-501 (CanBas)
	Prexasertib (Eli Lilly)
	GDC-0575 (Genentech)
	SRA-737 (Sierra Oncology)
ATM	AZD-0156 (AstraZeneca)

*** FDA approved; * clinical development; * pre-clinical development**

ATM, ataxia telangiectasia mutated gene; ATR, ataxia telangiectasia and Rad3-related protein; BER, base excision repair; CDC7, cell division cycle 7-related protein kinase; DDR, DNA damage response; DNA-PK, DNA-dependent protein kinase; DSB, double-strand break; HRR, homologous recombination repair; MMEJ, microhomology-mediated end joining; MMR, mismatch repair; NER, nucleotide excision repair; NHEJ, non-homologous end joining; PARP1/2, poly-ADP ribose polymerase 1/2; UV, ultraviolet

ATM AND ATR: DAMAGE RESPONSIVE KINASES

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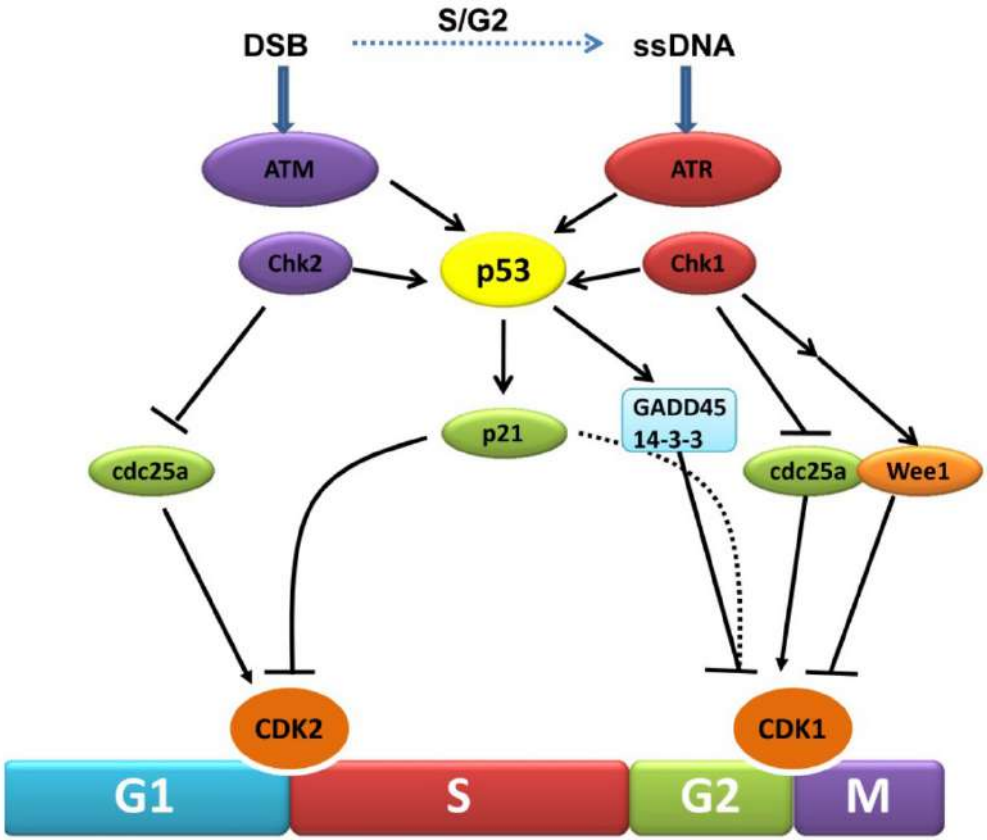
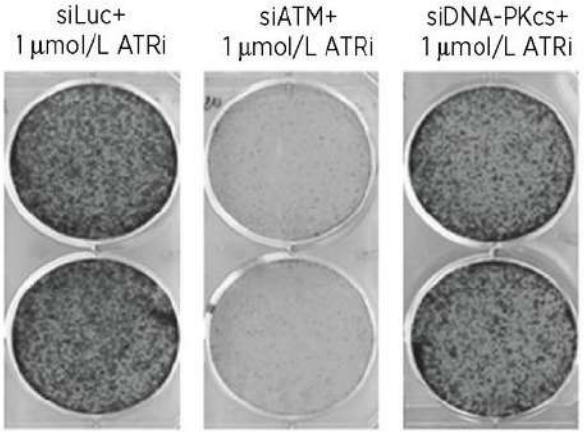
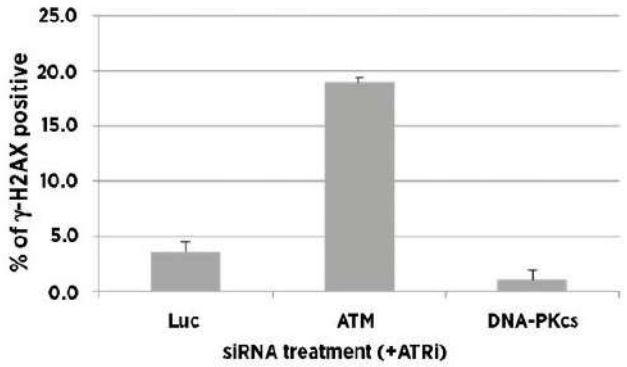


Sense and signal DNA damage in cells

ATM, ataxia telangiectasia mutated gene; ATR, ataxia telangiectasia and Rad3-related protein; DSB, double-strand break; ssDNA, single-stranded DNA

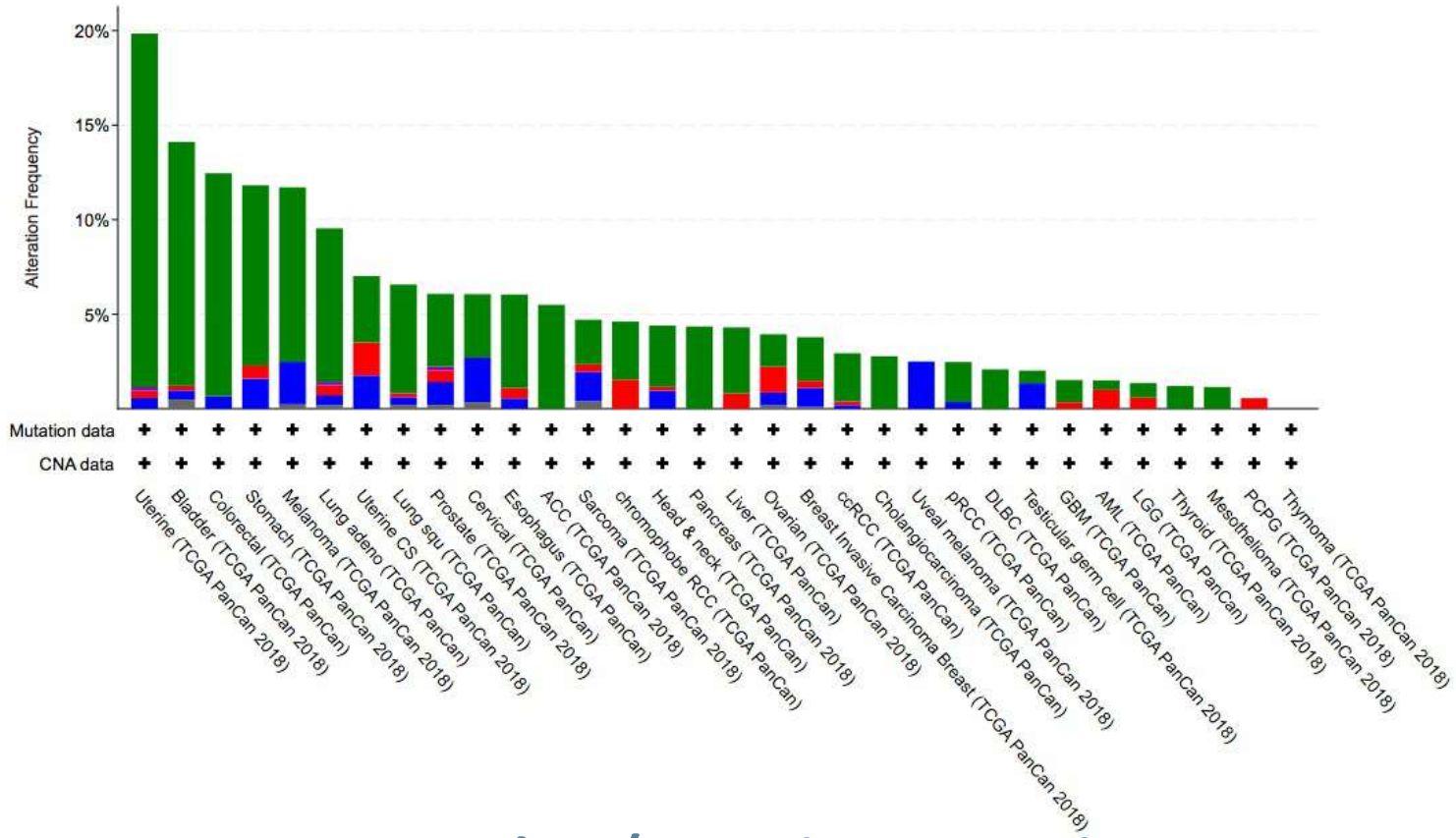
ATM LOSS: SYNTHETIC LETHAL WITH ATRi *IN VITRO*





ATM, ataxia telangiectasia mutated gene; ATR, ataxia telangiectasia and Rad3-related protein; ATRi, ATR inhibitor; DNA-PKcs, catalytic subunit of DNA-dependent protein kinase; DSB, double-strand break; H2AX, H2A histone family member X; Luc, luciferase; siRNA, small-interfering RNA; siATM, siRNA targeting ATM; siDNA-PKcs, siRNA targeting DNA-PKcs; siLuc, siRNA targeting luciferase; ssDNA, single-stranded DNA

ATM LOSS: SYNTHETIC LETHAL WITH ATRi



Atm loss/mutation occurs in many cancers

ACC, adenoid cystic carcinoma; AML, acute myeloid leukaemia; ATM, ataxia telangiectasia mutated gene; ATR, ataxia telangiectasia and Rad3-related protein; ATRi, ATR inhibitor; CAN, copy number alteration; ccRCC, clear cell renal cell carcinoma; CS, carcinosarcoma; DLBC, diffuse large B-cell lymphoma; GBM, glioblastoma; LGG, low grade glioma; PCPG, pheochromocytoma/paraganglioma; pRCC, papillary renal cell carcinoma

ATM LOSS: SYNTHETIC LETHAL WITH ATRi *IN PATIENTS*

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ATM null cancer

Presented by Johann De Bono at 2019 ASCO Annual Meeting

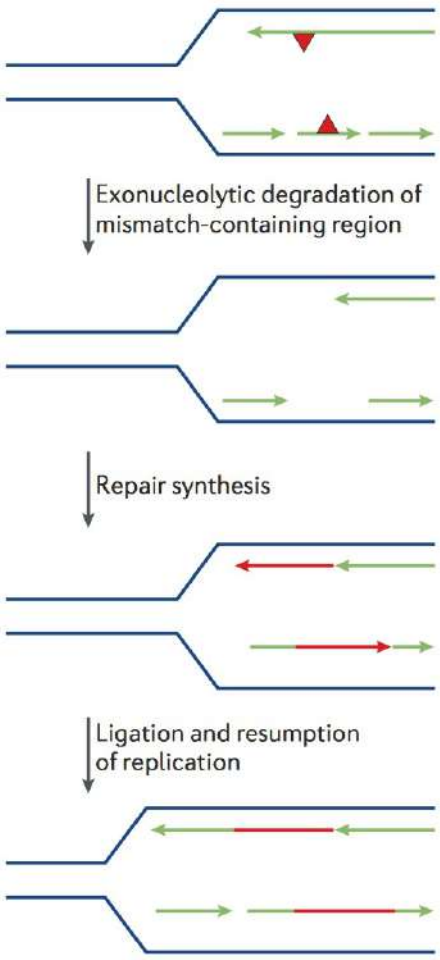
"Super-responders *Atm* null"

Bayer ATRi caused prolonged (>1 year) stable disease

ATM, ataxia telangiectasia mutated gene; ATR, ataxia telangiectasia and Rad3-related protein; ATRi, ATR inhibitor; MTD, maximum tolerated dose

De Bono J, et al. ASCO 2019. Abstract #3007

MISMATCH REPAIR: MMR



MMR – detects, removes, repairs mismatches introduced during DNA replication

Germline MMRD – Lynch Syndrome

Somatic MMRD – MSI cancers

MMR, mismatch repair; MMRD, mismatch repair deficiency; MSI, microsatellite instability

MSI IS COMMON IN MANY CANCER TYPES

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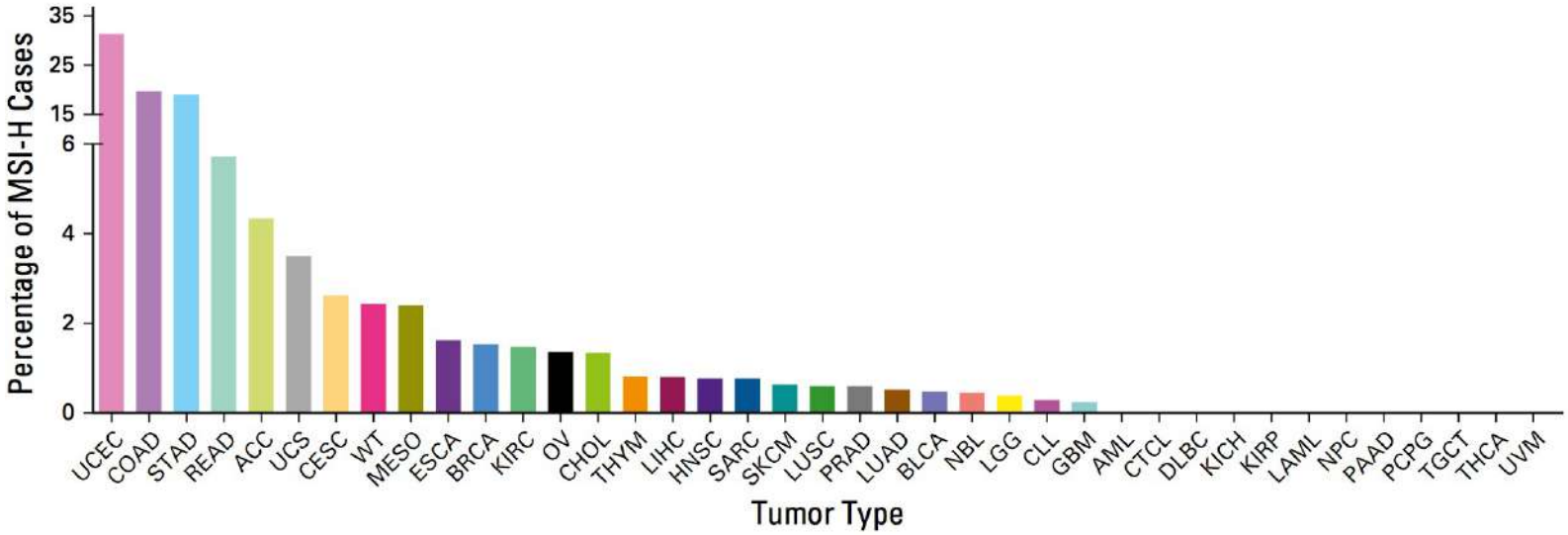

ACC, adenoid cystic carcinoma; AML, acute myeloid leukaemia; BLCA, bladder urothelial carcinoma; BRCA, breast cancer; CESC, cervical squamous cell carcinoma; CHOL, cholangiocarcinoma; CLL, chronic lymphocytic leukaemia; COAD, colon adenocarcinoma; CTCL, cutaneous T-cell lymphoma; DLBC, diffuse large B-cell lymphoma; ESCA, oesophageal carcinoma; GBM, glioblastoma; HNSC, head-neck squamous cell carcinoma; KICH, chromophobe renal cell carcinoma; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukaemia; LGG, low grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; MSI, microsatellite instability; MSI-H, microsatellite instability-high; NBL, neuroblastoma; NPC, nasopharyngeal cancer; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma/paraganglioma; PRAD, prostate adenocarcinoma; OV, ovarian; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TGCT, tenosynovial giant cell tumour; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma; WT, Wilm's tumour

MSI CANCERS: SYNTHETIC LETHALITY?

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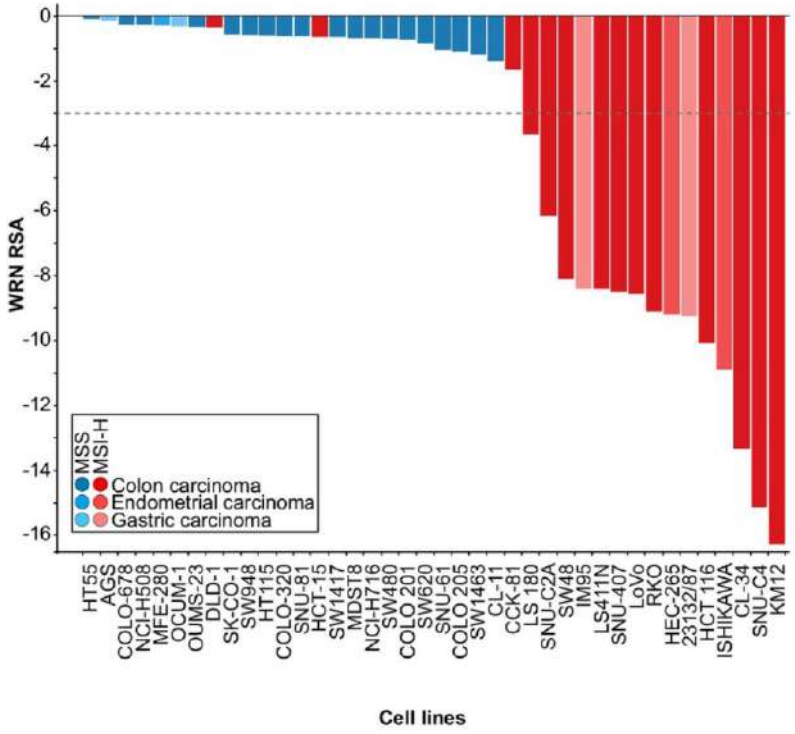
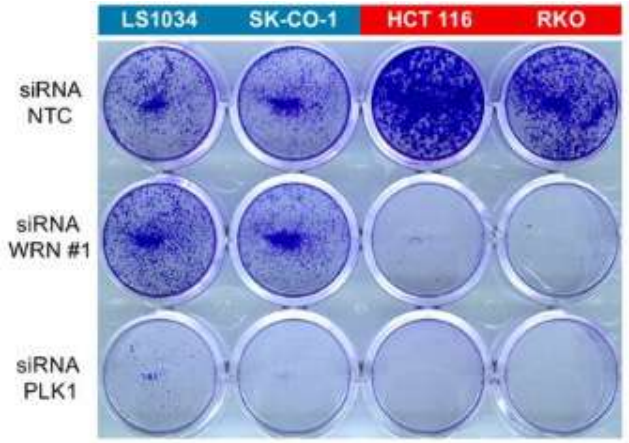
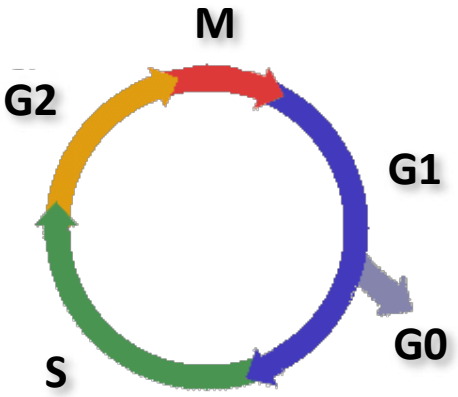




Loss of the Werner Helicase is synthetic lethal in MSI cancers

MSI, microsatellite instability; MSI-H, microsatellite instability-high; NTC, non-targeting control; PLK1, polo-like kinase 1; RSA, redundant siRNA activity; siRNA, small-interfering RNA, WRN, Werner syndrome protein

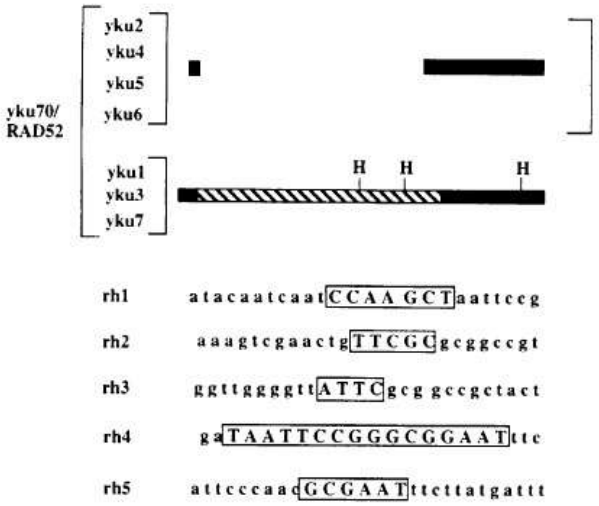
DSB REPAIR:
BACK UP PATHWAY (MMEJ)



"NHEJ"

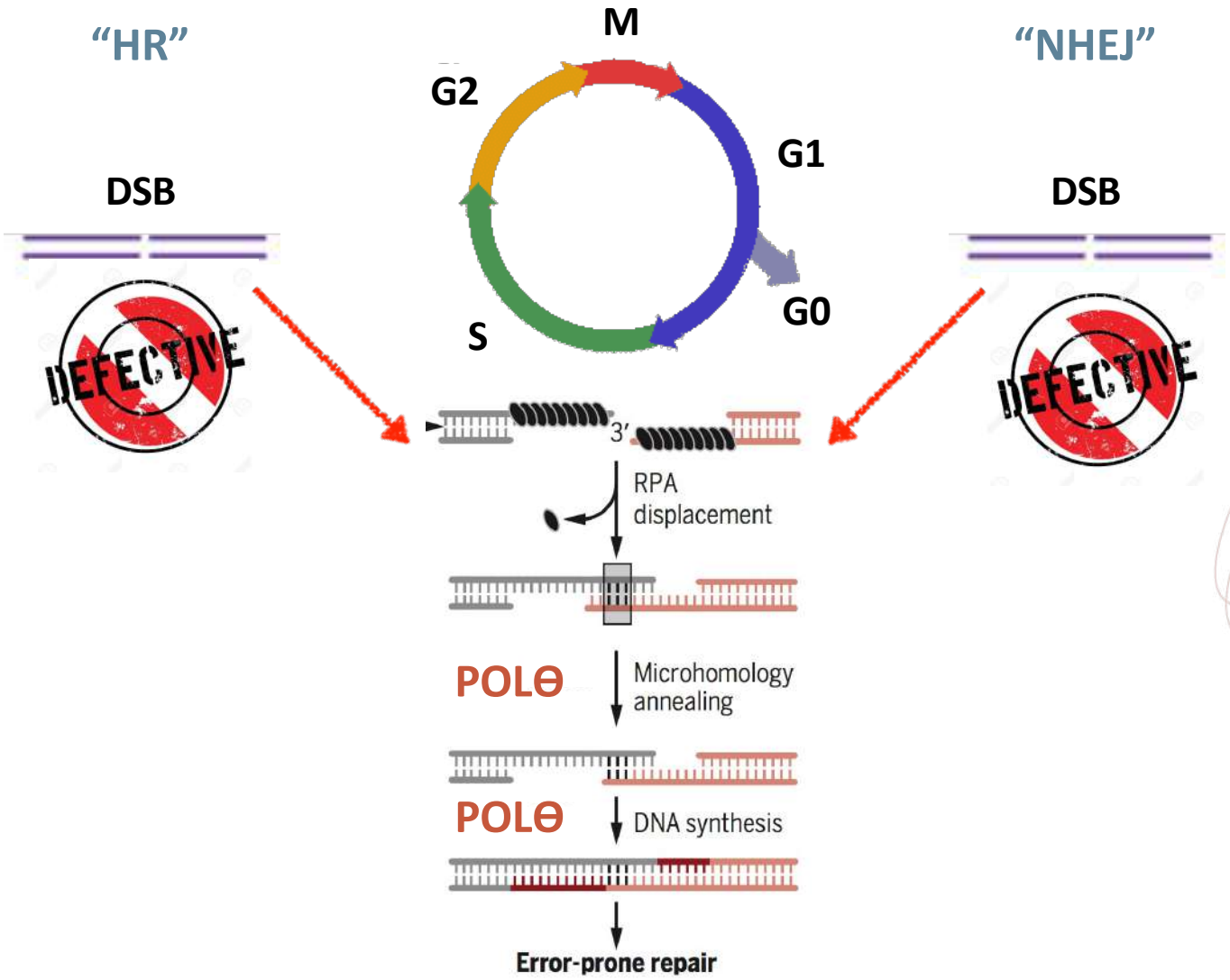
***Saccharomyces cerevisiae* Ku70 potentiates illegitimate DNA double-strand break repair and serves as a barrier to error-prone DNA repair pathways**

Boulton & Jackson *EMBO J*. 1996



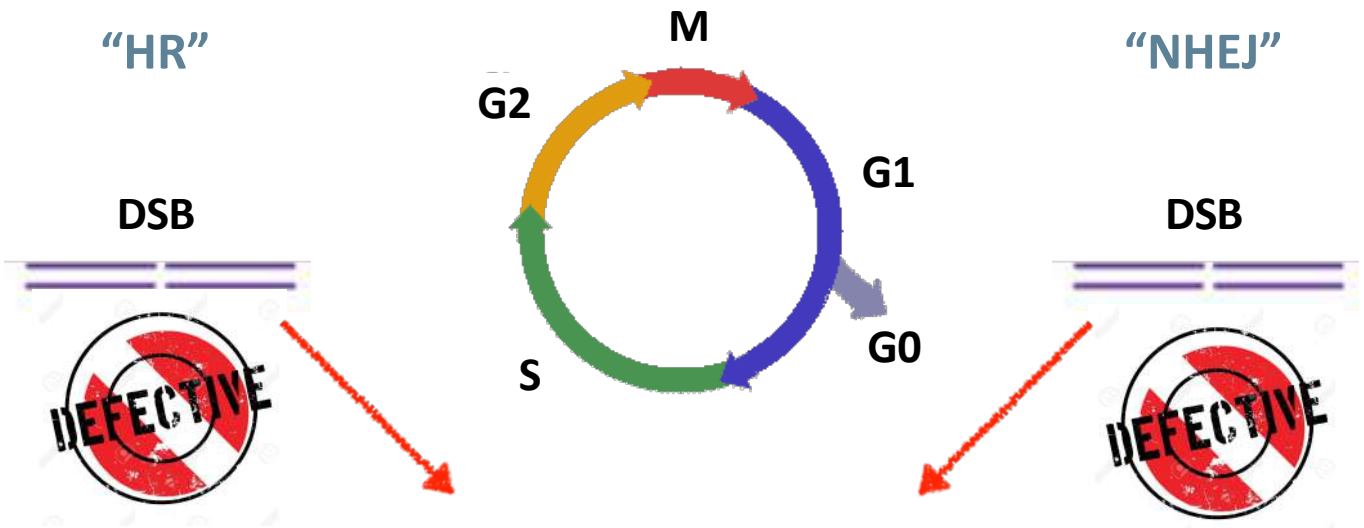
DSB, double-strand break; MMEJ, microhomology-mediated end joining; NHEJ, non-homologous end joining

DSB REPAIR DEFECTS: BACK UP PATHWAY (MMEJ)



DSB, double-strand break; HR, homologous recombination; MMEJ, microhomology-mediated end joining; NHEJ, non-homologous end joining; POLΘ, DNA polymerase theta; RPA, replication protein A

POLΘ IN CANCER



POLΘ:

- Absent in normal cells
- O/E in many cancers
- Tumour heterogeneity
- Drives resistance

DSB, double-strand break; HR, homologous recombination; NHEJ, non-homologous end joining; O/E, overexpressed; POLΘ, DNA polymerase theta

Ceccaldi R, et al. Nature 2015; 518:258-262; Higgins GS and Boulton SJ. Science 2018; 359:1217-1218

POLΘ HAS NUMEROUS CLINICAL OPPORTUNITIES

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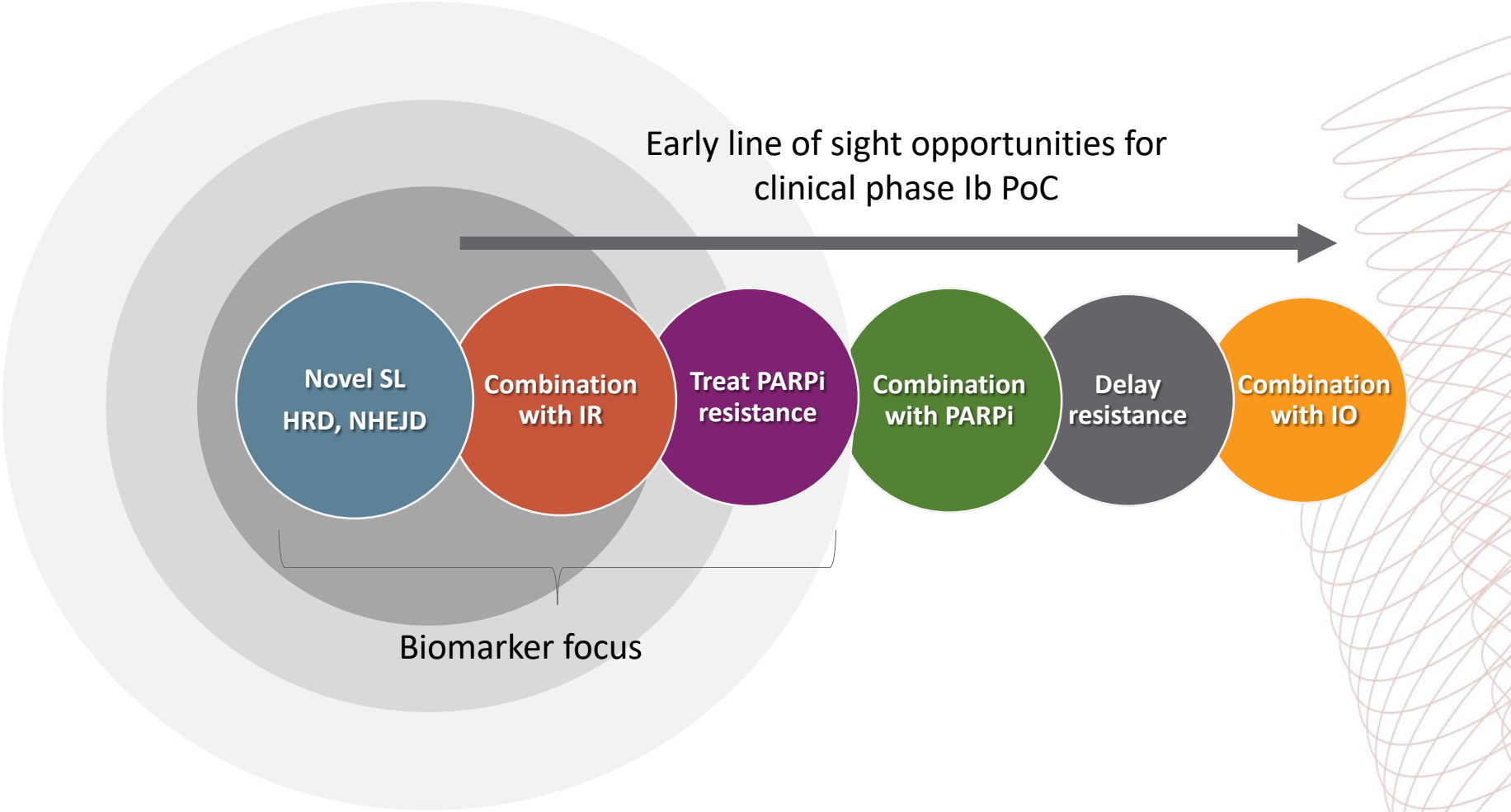

HRD, homologous recombination deficiency; IO, immuno-oncology; IR, ionising radiation; NHEJD, non-homologous end joining deficiency; PARPi, poly-ADP ribose polymerase inhibitor; PoC, proof-of-concept; POLΘ, DNA polymerase theta; SL, synthetic lethality

Higgins GS and Boulton SJ. Science 2018; 359:1217-1218

DDR INHIBITORS: THERAPEUTIC EXPLOITATION IN CANCER

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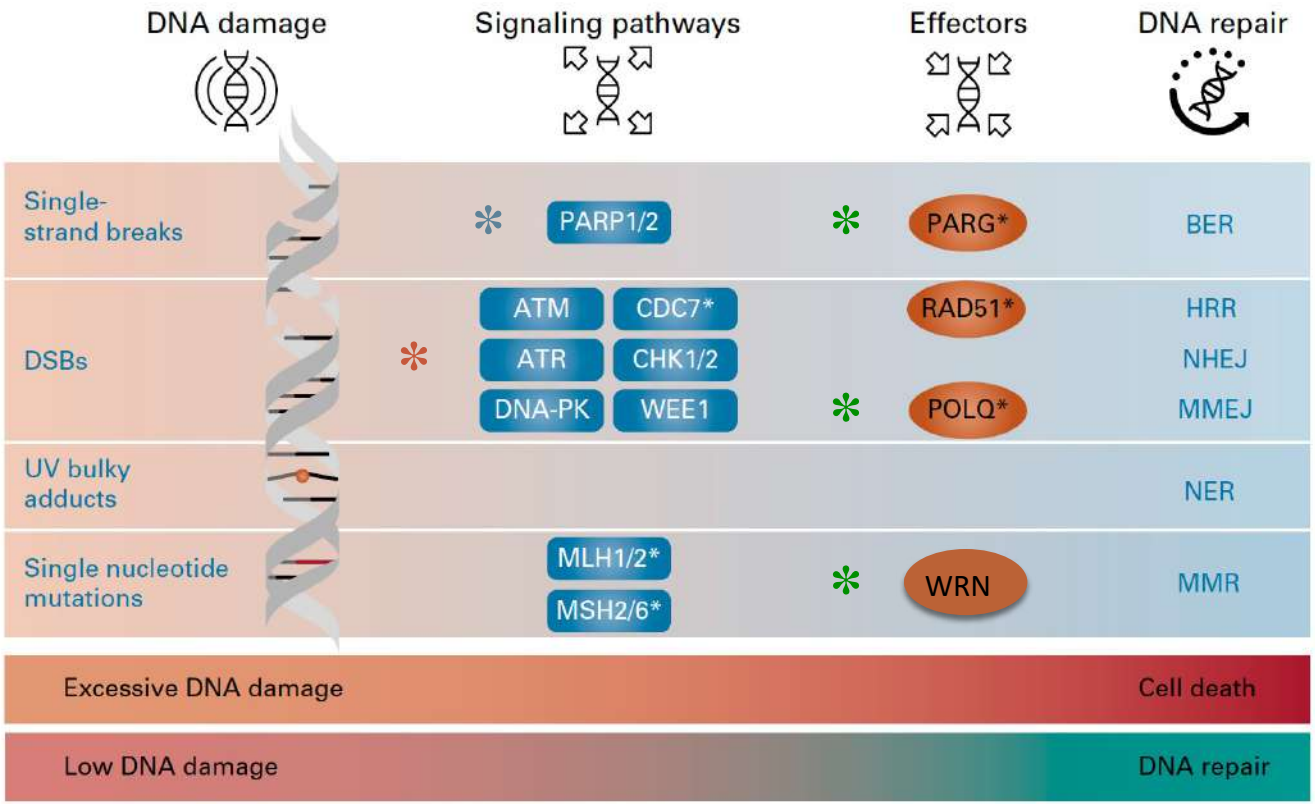

Pharmacologically targeted:

PARP1/2	Olaparib (AstraZeneca)
	Rucaparib (Clovis)
	Niraparib (Tesaro)
	Talazoparib (Pfizer)
ATR	AZD-6738 (AstraZeneca)
	M-4344 (Merck)
DNA-PK	Asi DNA (Onxeo)
	CC-125 (Celgene)
	LY-3023414 (Eli Lilly)
	M-3814 (Merck)
WEE1	AZD-1775 (AstraZeneca)
CHK1/2	CBP-501 (CanBas)
	Prexasertib (Eli Lilly)
	GDC-0575 (Genentech)
	SRA-737 (Sierra Oncology)
ATM	AZD-0156 (AstraZeneca)

*** FDA approved; * clinical development; * pre-clinical development**

ATM, ataxia telangiectasia mutated gene; ATR, ataxia telangiectasia and Rad3-related protein; BER, base excision repair; CDC7, cell division cycle 7-related protein kinase; DNA-PK, DNA-dependent protein kinase; DDR, DNA damage response; DSB, double-strand break; HRR, homologous recombination repair; MMEJ, microhomology-mediated end joining; MMR, mismatch repair; NER, nucleotide excision repair; NHEJ, non-homologous end joining; PARP1/2, poly-ADP ribose polymerase 1/2; UV, ultraviolet

PARP INHIBITORS AS TARGETED THERAPY FOR PERSONALIZED MEDICINE

Charlie Gourley
Professor of Medical Oncology,
University of Edinburgh

CONFLICTS OF INTEREST

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Personal interests:

- Roche, AstraZeneca, MSD, Tesaro, Nucana, Clovis, Foundation One, Sierra Oncology, Cor2Ed
- Named co-inventor on five patents:
  - issued: PCT/US2012/040805
  - pending: PCT/GB2013/053202, 1409479.1, 1409476.7 and 1409478.3

Non-personal interests (research funding):

- AstraZeneca, Novartis, Aprea, Nucana, Tesaro

PARP INHIBITORS: 50 YEARS ON FROM PARP1 DISCOVERY

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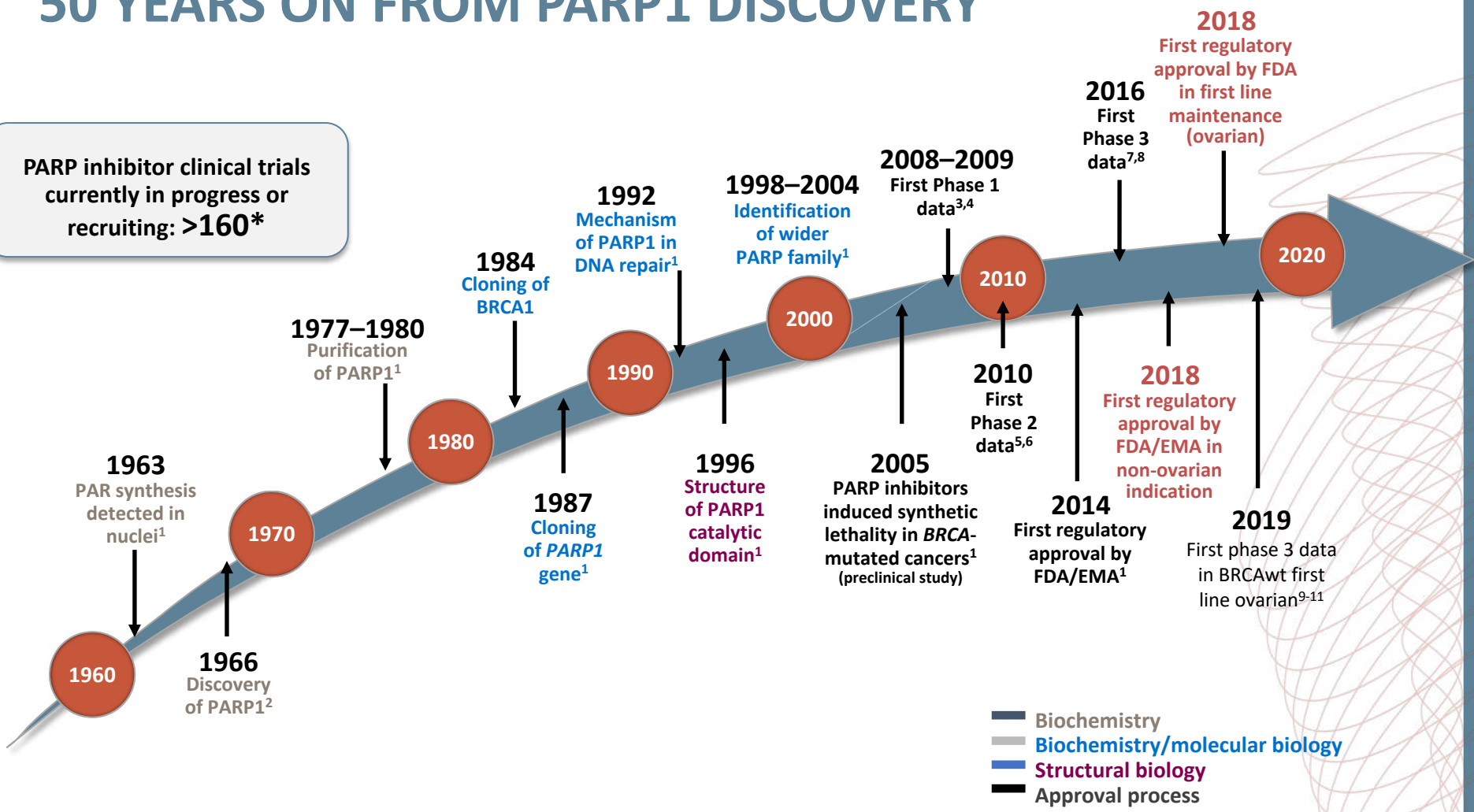
PARP inhibitor clinical trials currently in progress or recruiting: >160*



*Source: ClinicalTrials.gov.

EMA, European Medicines Agency; FDA, Food and Drug Administration; PARP, poly ADP-ribose polymerase.

1. Kraus WL. Mol Cell. 2015;58:902-10. 2. Chambon P, et al. Biochem Biophys Res Commun. 1966;25:638-43. 3. Plummer R, et al. Clin Cancer Res. 2008;14:7917-23. 4. Fong PC, et al. N Engl J Med. 2009:361:123-34. 5. Audeh MW, et al. Lancet. 2010;376:245-51. 6. Tutt A, et al. Lancet. 2010;376:235-44. 7. Bang Y-J, et al. ASCO 2016. Abstract #2742. 8. Mirza MR, et al. N Engl J Med. 2016;375:2154-64. 9. Coleman R, et al. ESMO 2019. Abstract #LBA3. 10. Ray-Coquard IL, et al. ESMO 2019. Abstract #LBA2_PR. 11. González Martín A, et al. ESMO 2019. Abstract #LBA1

TALK SUMMARY

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Clinical trial data

- Relapsed disease
- First-line setting

Main PARPi trials currently underway

Key issues for the future

- Patient selection criteria
- Prediction/detection of disease resistance
- Positioning in the patient journey
- What to do when patients relapse following PARP inhibitor therapy

CLINICAL TRIAL DATA: RELAPSED DISEASE

PROOF OF CONCEPT

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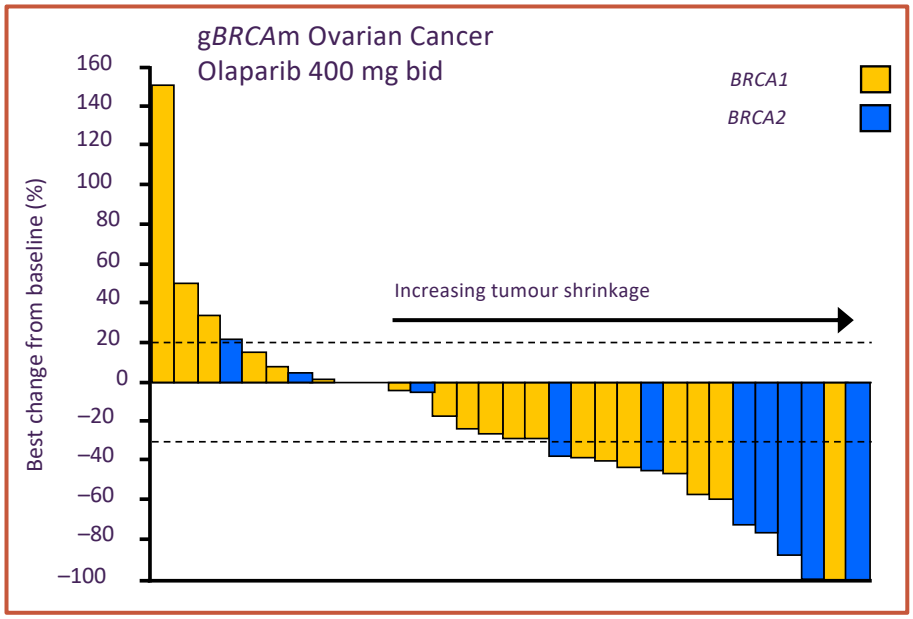

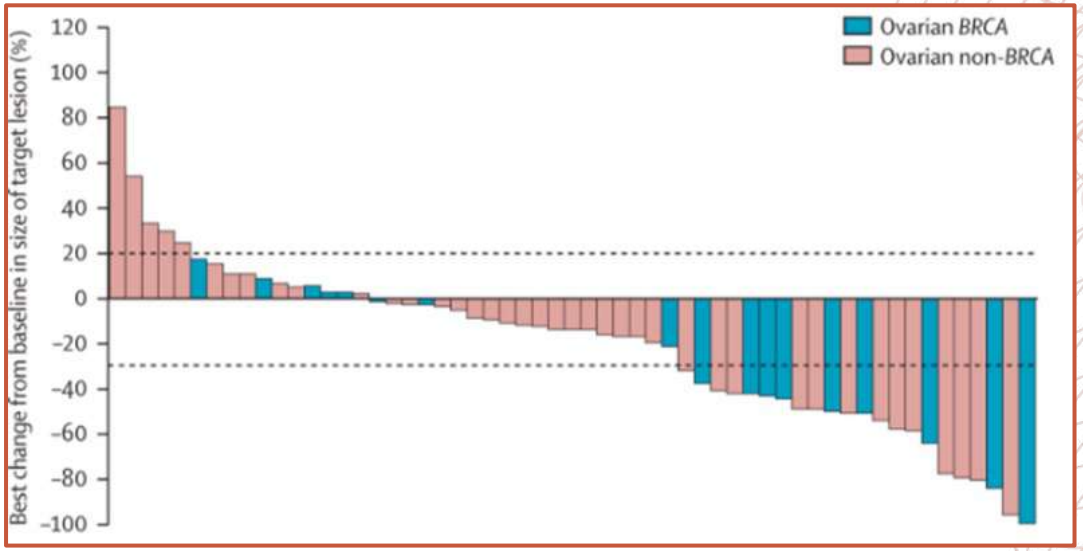

Audeh, et al. Lancet 2010;376:245-51. Gelmon, et al. Lancet Oncol 2011;12:852-61

RELAPSED DISEASE MAINTENANCE STUDIES; GENERAL FORMAT

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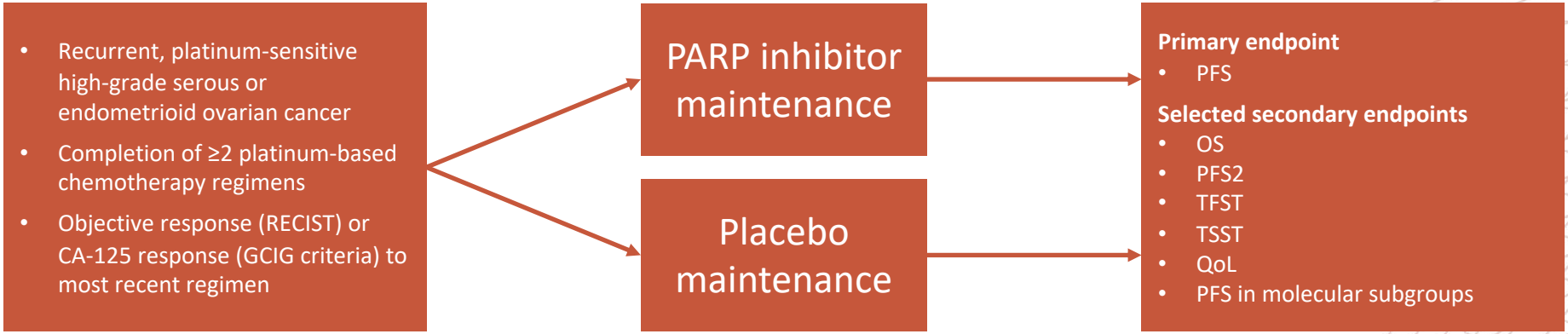

Study	PARP inhibitor	Patient population
Study 19	Olaparib	Platinum sens relapse
SOLO 2	Olaparib	Platinum sens relapse BRCA1/2 mutation
NOVA	Niraparib	Platinum sens relapse
ARIEL 3	Rucaparib	Platinum sens relapse

OS, overall survival; PFS, progression-free survival; PFS2, time to second progression or death; QoL, quality of life; sens, sensitive; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy

STUDY 19: PFS BENEFIT IRRESPECTIVE OF BRCA STATUS

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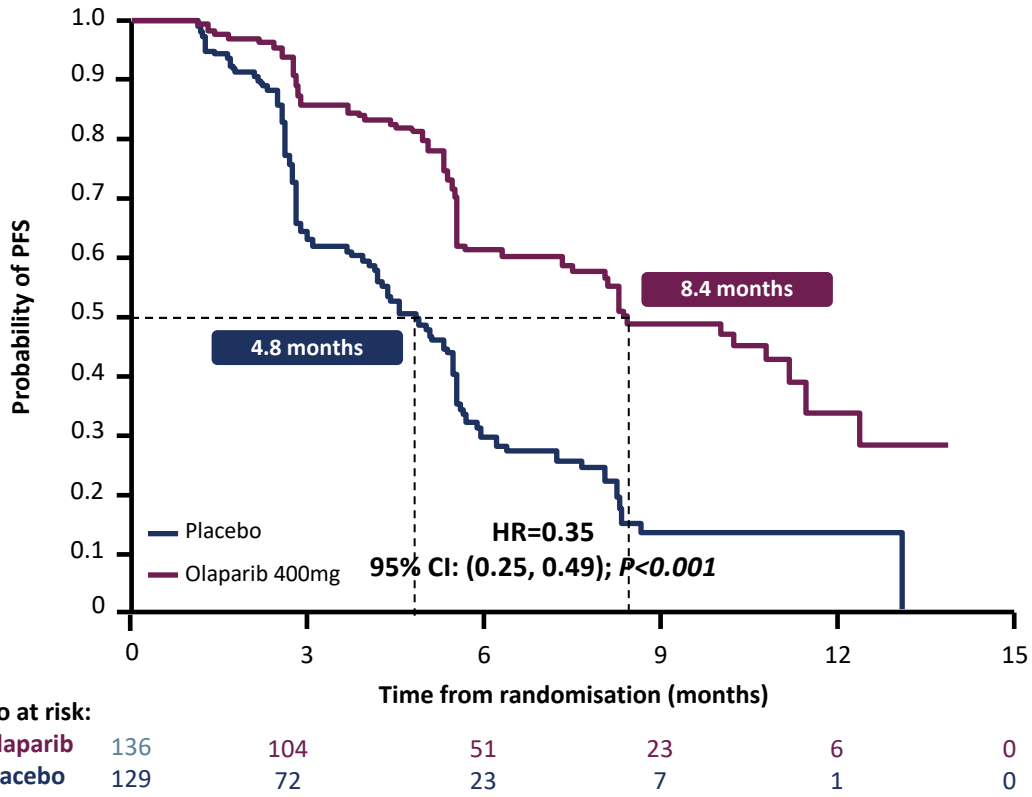
PFS in the full analysis set



PFS in BRCAm and BRCAwt patients

	BRCAm (n=136)		BRCAwt (n=118)	
	Olaparib	Placebo	Olaparib	Placebo
Events: total pts (%)	26:74 (35.1)	46:62 (74.2)	32:57 (56.1)	44:61 (72.1)
Median PFS, months	11.2	4.3	7.4	5.5
	HR=0.18 95% CI: 0.11-0.31; p<0.00001		HR=0.54 95% CI: 0.34-0.85; p=0.0075	

BRCAm, BRCA mutated; BRCAwt, BRCA wild type; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

1. Ledermann JA, et al. Lancet Oncol. 2014;15:852-6

STUDY 19: FINAL OS (79% MATURE) NUMERICALLY FAVOURS OLAPARIB[1]

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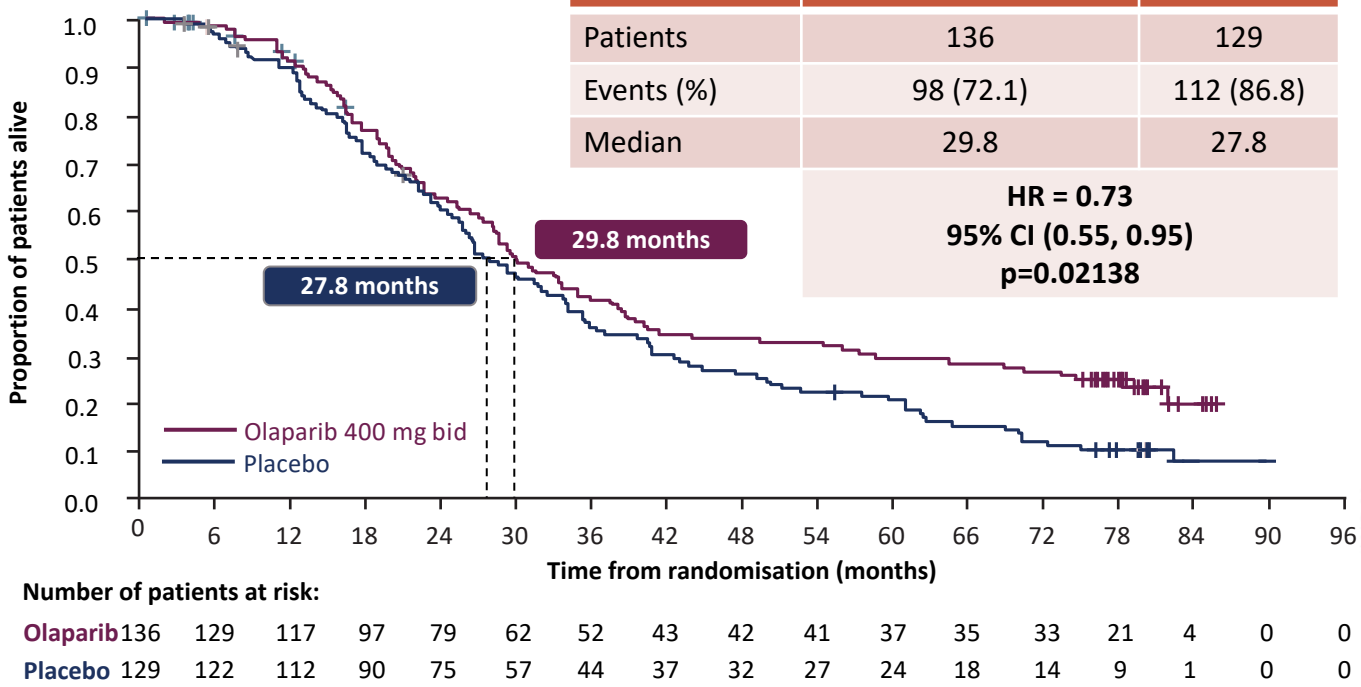
	Olaparib 400 mg bd	Placebo
Patients	136	129
Events (%)	98 (72.1)	112 (86.8)
Median	29.8	27.8
	HR = 0.73 95% CI (0.55, 0.95) p=0.02138	



Number of patients at risk:

Olaparib	136	129	117	97	79	62	52	43	42	41	37	35	33	21	4	0	0
Placebo	129	122	112	90	75	57	44	37	32	27	24	18	14	9	1	0	0

- **13% of placebo-receiving patients received post-discontinuation PARP inhibitor treatment in other studies**
- **11% of patients remained on treatment for ≥6 years[2]**

*To maintain statistical rigour with final analyses of OS, the threshold for statistical significance at this update was p<0.0095 which was not met
DCO: May 2016; data maturity 79%
CI, confidence interval; HR, hazard ratio; OS, overall survival
1. Ledermann JA, et al. Lancet Oncol 2016; 17: 1579–89. 2. Friedlander et al, Brit J Cancer 2018; 119: 1075–1085

STUDY 19: 11% OF PATIENTS REMAINED ON TREATMENT FOR ≥6 YEARS

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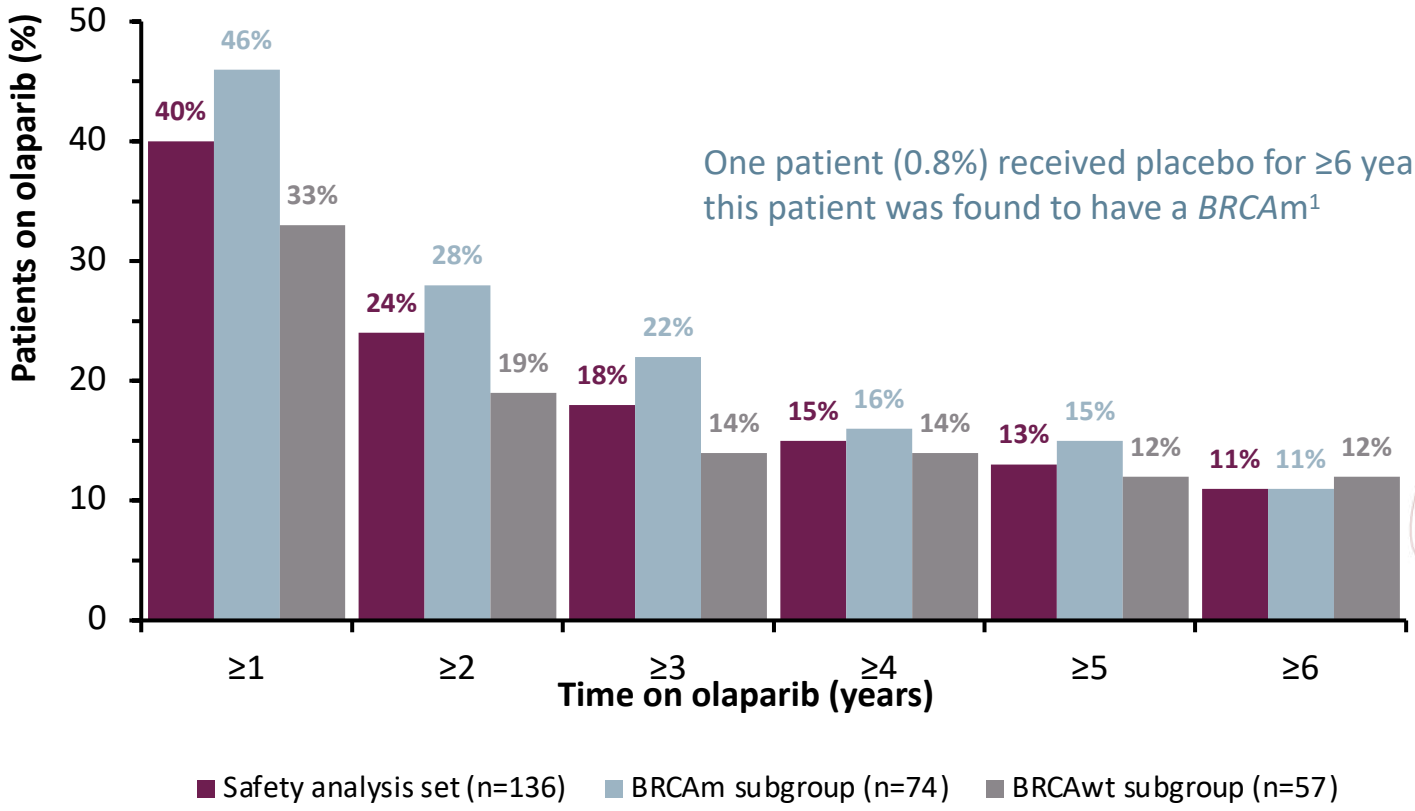

One patient (0.8%) received placebo for ≥6 years – this patient was found to have a *BRCA*m[1]

BRCAm, BRCA mutated; BRCAwt, BRCA wild type

1. Gourley C, et al. J Clin Oncol 2017;35:(suppl; poster related to abstr 5533). 2. Friedlander, et al. Brit J Cancer 2018;119:1075–85

SOLO2: PFS BY INVESTIGATOR ASSESSMENT

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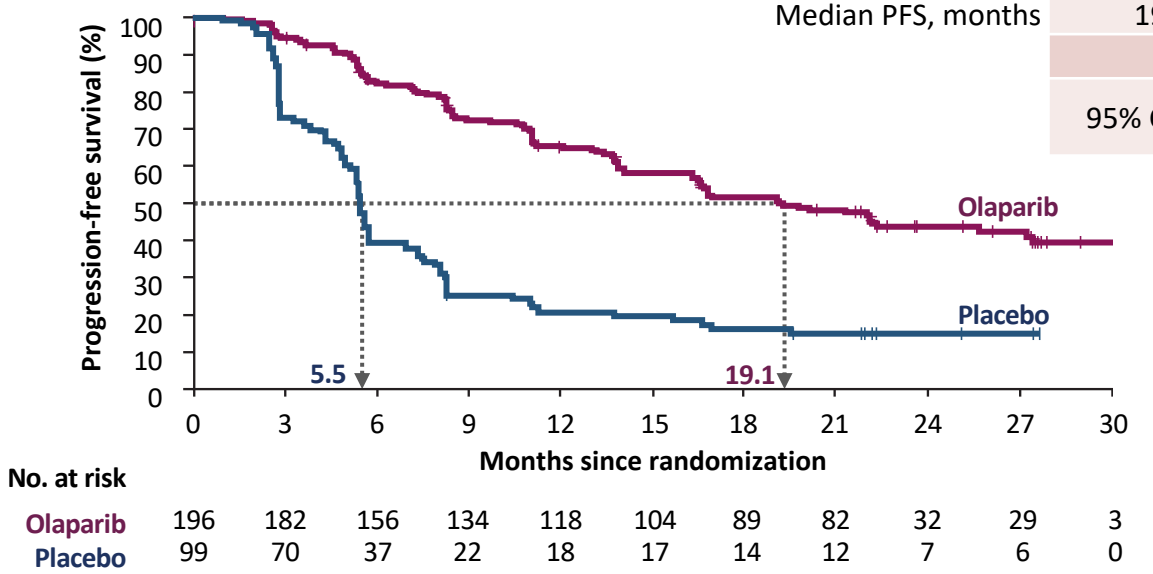
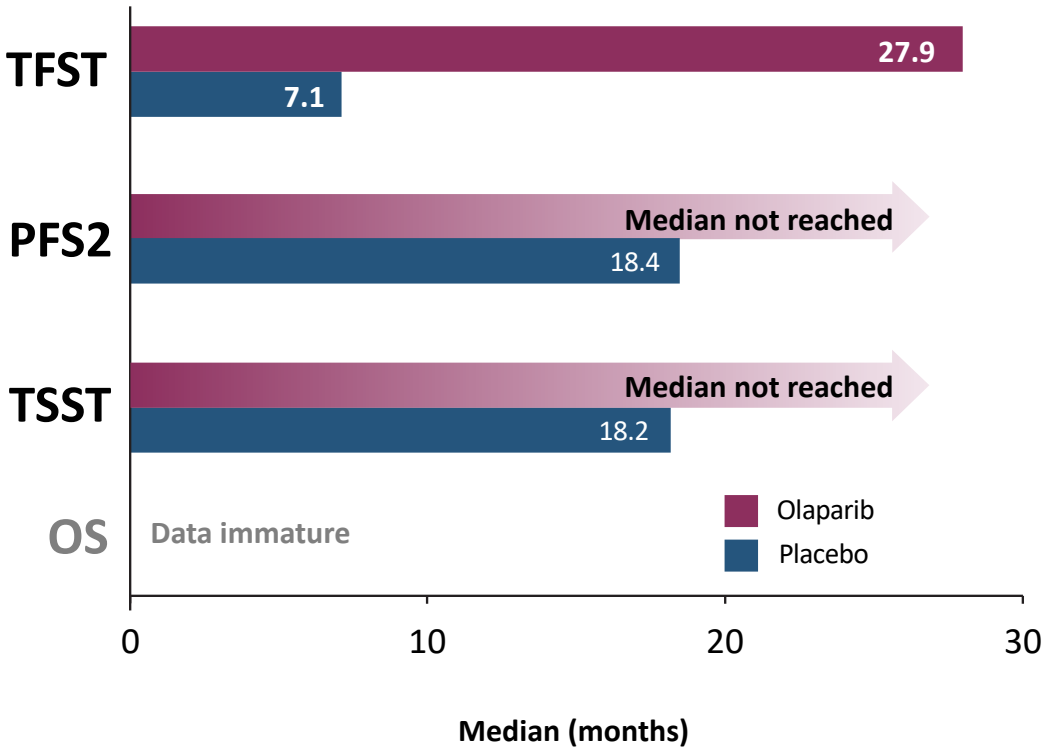
	Olaparib (n=196)	Placebo (n=99)
Events (%)	107 (54.6)	80 (80.8)
Median PFS, months	19.1	5.5
HR 0.30		
95% CI 0.22 to 0.41 P<0.0001		



Median follow-up was 22.1 months in the olaparib group and 22.2 months for placebo

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival
Slide obtained from Pujade-Lauraine, et al. SGO 2017

SECONDARY EFFICACY ENDPOINTS



HR 0.28
95% CI 0.21 to 0.38
P<0.0001

HR 0.50
95% CI 0.34 to 0.72
P=0.0002

HR 0.37
95% CI 0.26 to 0.53
P<0.0001

CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS2, time to second progression or death; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy

Slide obtained from Pujade-Lauraine, et al. SGO 2017

NOVA: NIRAPARIB MAINTENANCE FOLLOWING PLATINUM SENSITIVE RELAPSE

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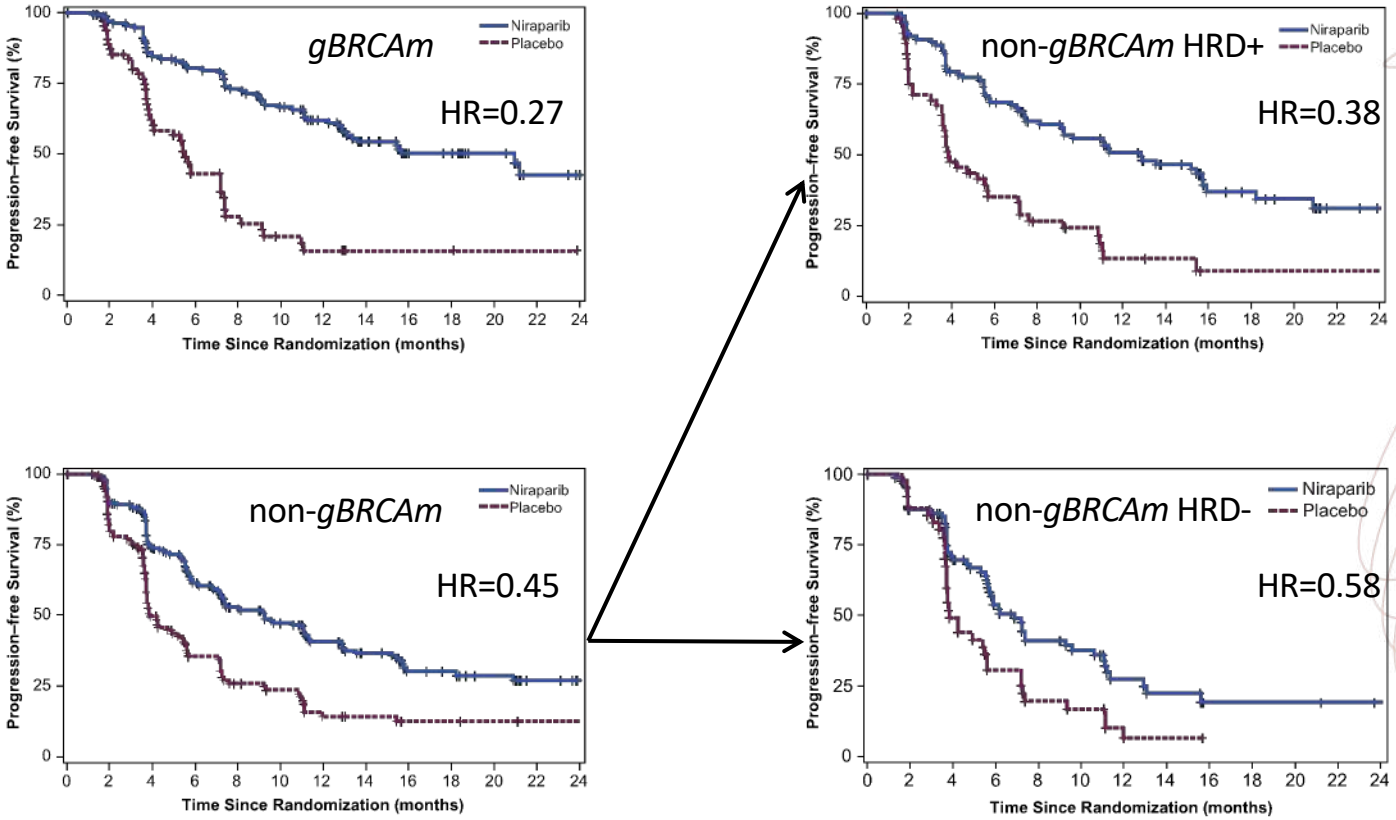

gBRCAm, germline BRCA mutation; HR, hazard ratio; HRD, homologous recombination deficiency
Mirza MR, et al. N Engl J Med. 2016;375:2154-64

ARIEL 3: RUCAPARIB MAINTENANCE FOLLOWING PLATINUM SENSITIVE RELAPSE

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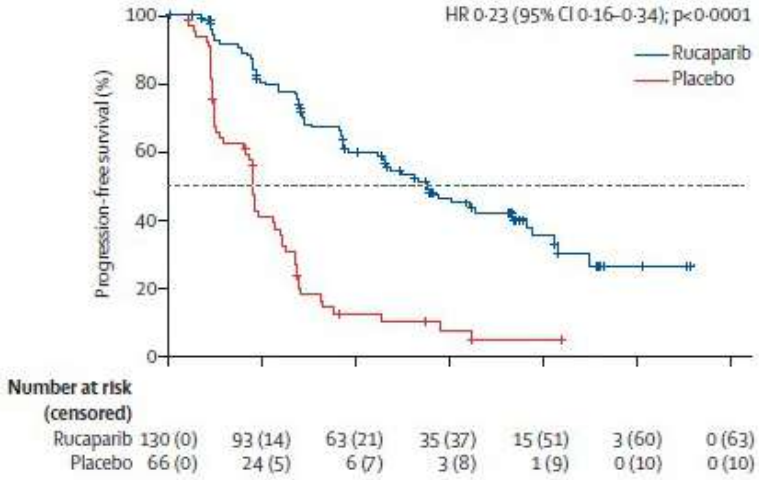
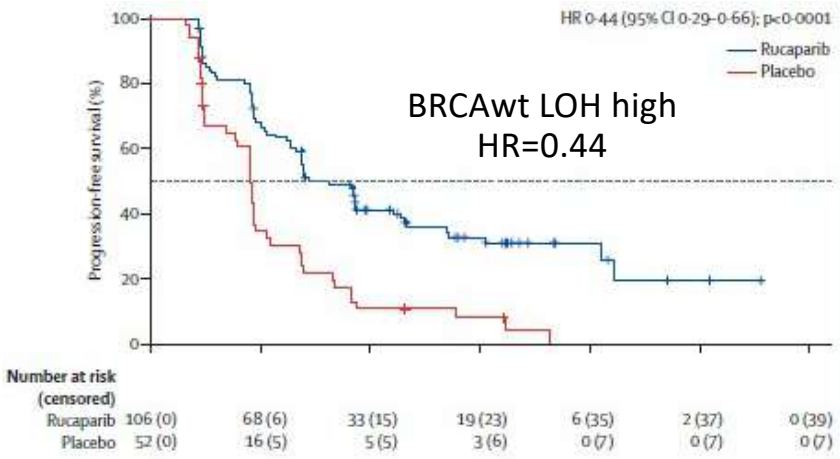
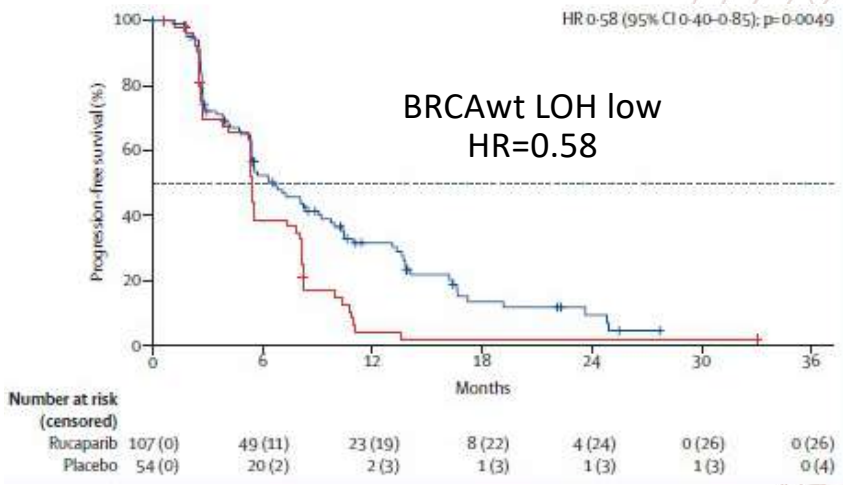


BRCAm
HR=0.23



BRCAwt LOH high
HR=0.44



BRCAwt LOH low
HR=0.58

BRCAm, BRCA mutant; BRCAwt, BRCA wild type; HR, hazard ratio; LOH, loss of heterozygosity
Coleman RL, et al. Lancet.2017;390:1949-61

OTHER IMPORTANT RELAPSED DISEASE STUDIES

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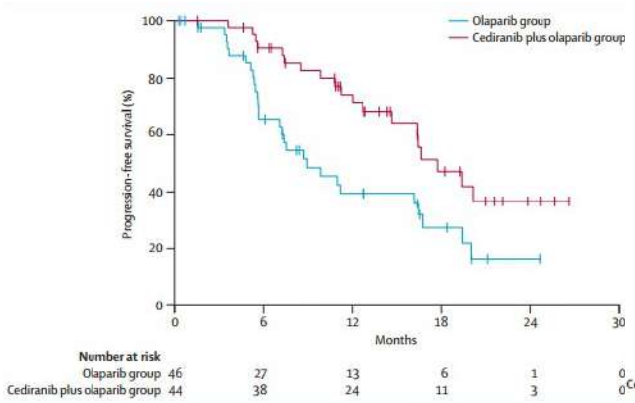
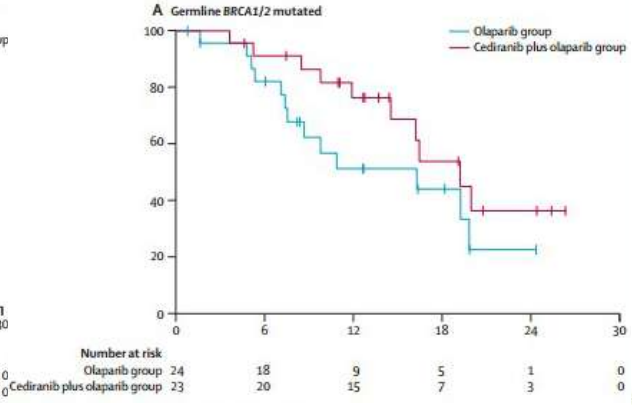
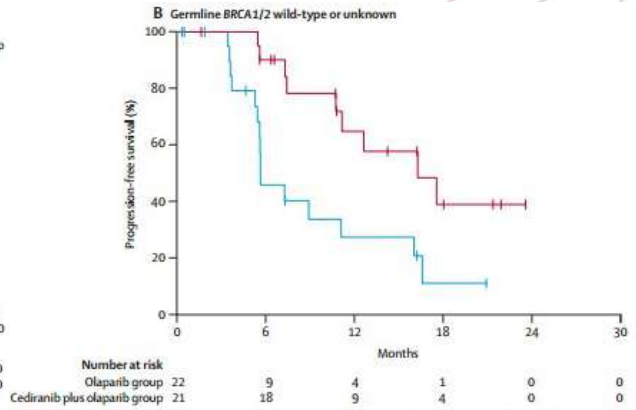
PHASE 1/2 OF OLAPARIB +/- CEDIRANIB







All patients
PFS: 17.7 v 9.0 months;
HR 0.42 (0.23-0.76, p=0.005)

Germline *BRCA1/2* mutant
PFS: 19.4 v 16.5 months;
HR 0.55 (0.24-1.27, p=0.16)

Germline *BRCA1/2* wild type
PFS: 16.5 v 5.7 months;
HR 0.32 (0.14-0.74, p=0.008)

HR, hazard ratio; PFS, progression-free survival
Liu, et al. Lancet Oncol 2014;15:1207-14

OTHER IMPORTANT RELAPSED DISEASE STUDIES

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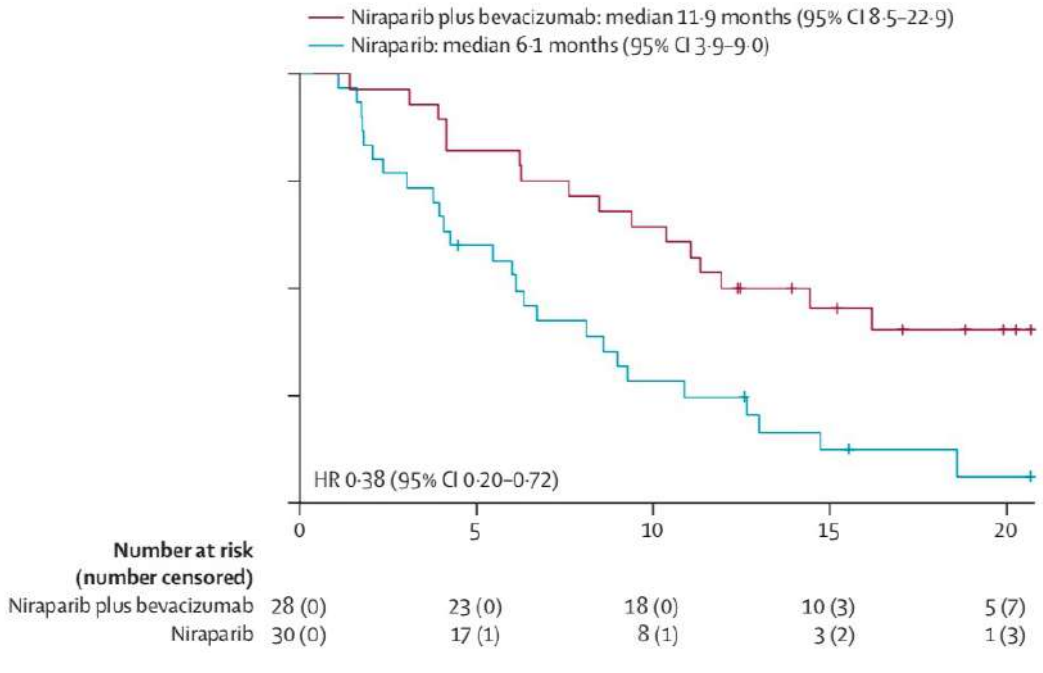
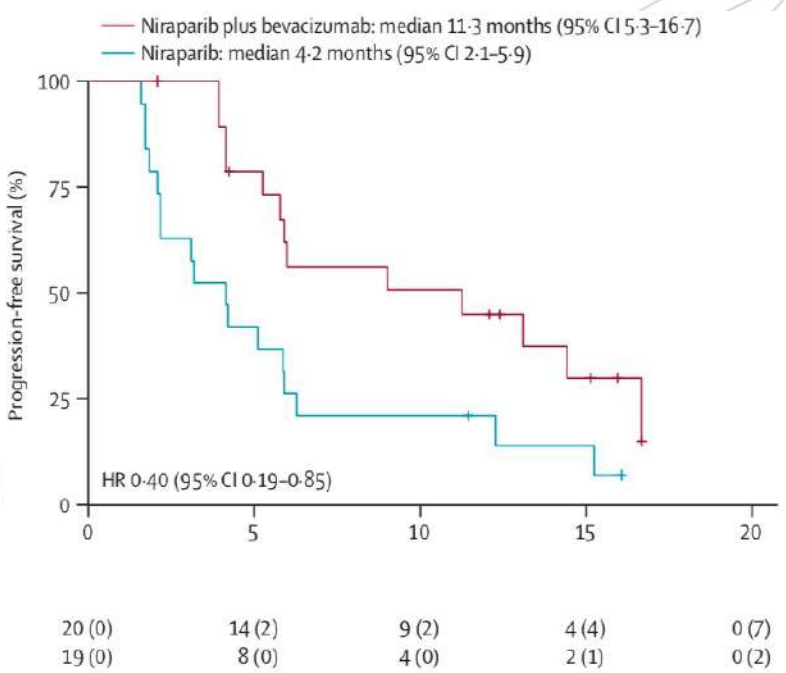
AVANOVA: PHASE 2 STUDY OF NIRAPARIB +/- BEVACIZUMAB

HRD+ subgroup



HRD- subgroup



CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency
Mirza, et al. Lancet Oncol 2019;20:1409-19

PLATINUM SENSITIVE RELAPSE MAINTENANCE STUDIES: KEY MESSAGES

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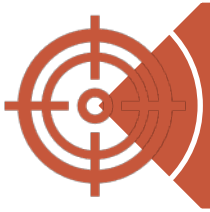

Olaparib, niraparib and rucaparib maintenance all result in a **substantial and significant improvement in PFS and PFS2** in patients with platinum sensitive relapse of high grade serous or high grade endometrioid ovarian cancer

The effect is **most marked in patients with *BRCA* mutations** but ***BRCA* wild-type patients also benefit** significantly

DNA 'scarring assays' (Myriad MyChoice or Foundation medicine LOH test) enrich for patients most likely to respond but do not identify patients who do not respond

The study with the longest follow-up (Study 19) demonstrates the **potential for long term disease-free survival** (possibly cure) in relapsed disease patients (including some without *BRCA* mutations)

CLINICAL TRIAL DATA: FIRST-LINE SETTING

SOLO1 STUDY DESIGN

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- Newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- Germline or somatic *BRCA*m
- ECOG performance status score 0–1
- Cytoreductive surgery*
- In clinical complete response or partial response after platinum-based chemotherapy

Olaparib tablet 300 mg bd (N=260)

2:1 randomisation

Stratified by response to platinum-based chemotherapy

Placebo (N=131)

- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with a partial response at 2 years could continue treatment

2 years' treatment if no evidence of disease

Primary endpoint

- Investigator-assessed PFS (modified RECIST 1.1)

Secondary endpoints

- PFS using BICR
- PFS2
- OS
- Time from randomization to first subsequent therapy or death
- Time from randomization to second subsequent therapy or death
- HRQoL (FACT-O TOI score)

*Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease.

bd, twice daily; BICR, blinded independent central review; ECOG, Eastern Cooperative Oncology Group; FACT-O, Functional Assessment of Cancer Therapy – Ovarian Cancer; FIGO, International Federation of Gynaecology and Obstetrics; HRQoL, health-related quality of life; PFS, progression-free survival; PFS2, time to second progression or death; RECIST, Response Evaluation Criteria in Solid Tumours; TOI, Trial Outcome Index

Moore K, et al. N Engl J Med 2018;379:2495-505

SOLO1: PFS BY INVESTIGATOR ASSESSMENT

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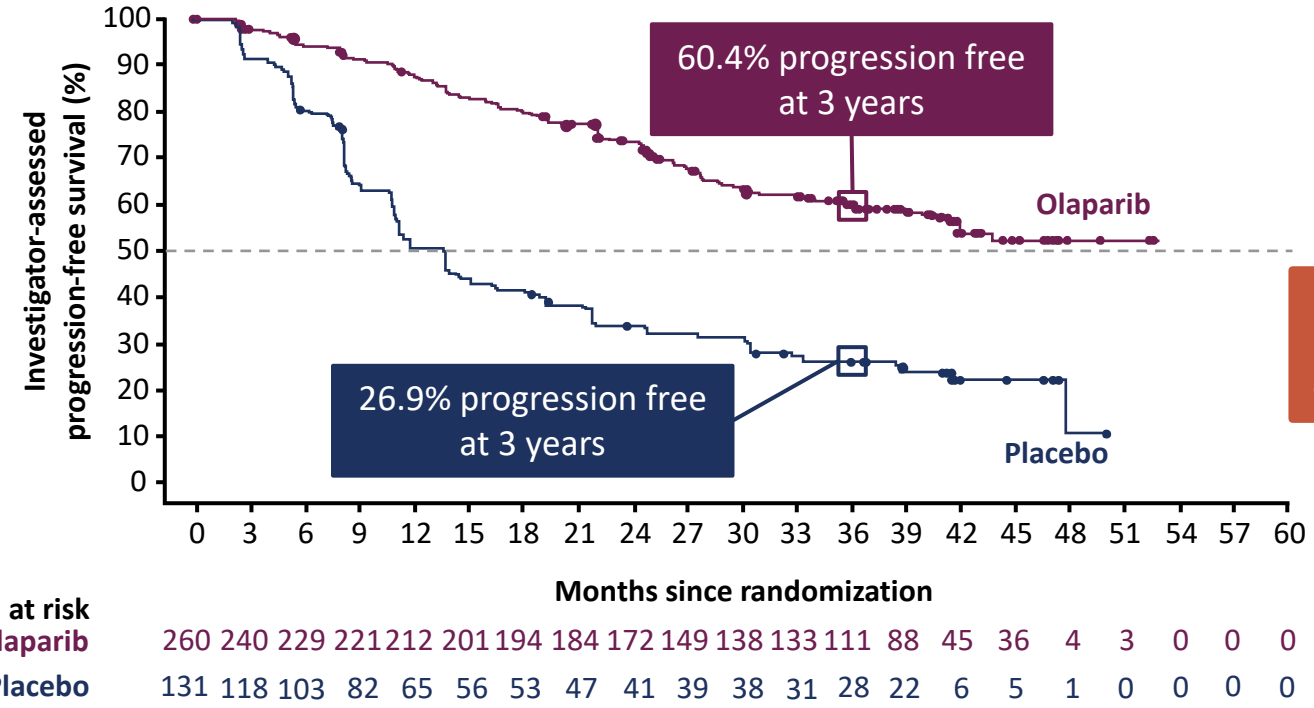
	Olaparib (N=260)	Placebo (N=131)
Events (%) [50.6% maturity]	102 (39.2)	96 (73.3)
Median PFS, months	NR	13.8
HR 0.30		
95% CI 0.23, 0.41; *P*<0.0001		



No. at risk																				
Olaparib	260	240	229	221	212	201	194	184	172	149	138	133	111	88	45	36	4	3	0	0	0
Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0	0	0

Median PFS benefit 36 months

CI, confidence interval; HR, hazard ratio; NR, not reached; PFS, progression-free survival

Moore K, et al. N Engl J Med 2018;379:2495-505

SOLO1: PFS SUBGROUP ANALYSIS

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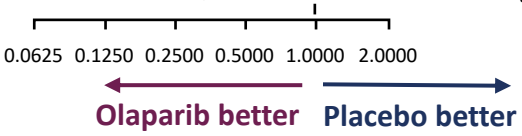
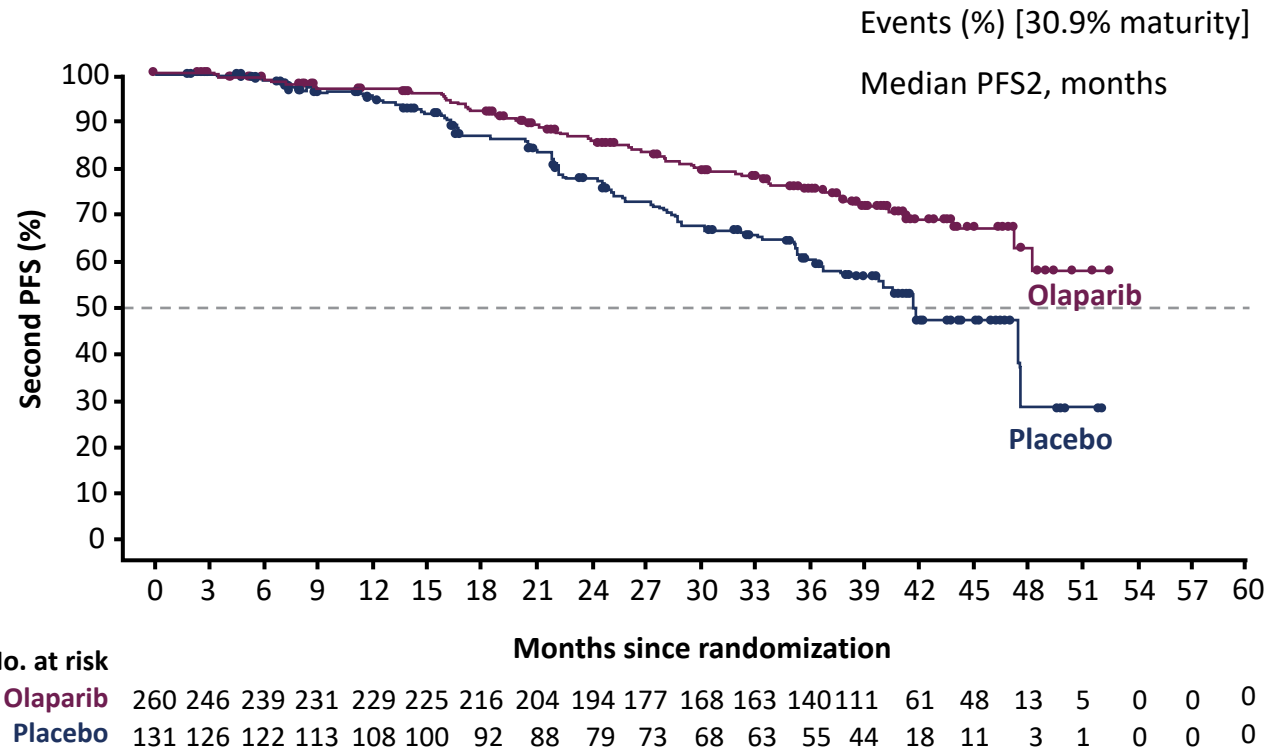
Subgroup	Olaparib 300 mg bd Number of patients with events/total number of patients (%)	Placebo bd Number of patients with events/total number of patients (%)	HR (95% CI)
All patients	102/260 (39.2)	96/131 (73.3)	0.30 (0.23, 0.41)
Response after surgery/platinum-based chemotherapy			
Clinical complete response	73/213 (34.3)	73/107 (68.2)	0.35 (0.26, 0.49)
Partial response	29/47 (61.7)	23/24 (95.8)	0.19 (0.11, 0.34)
ECOG performance status at baseline			
Normal activity	75/200 (37.5)	76/105 (72.4)	0.33 (0.24, 0.46)
Restricted activity	27/60 (45.0)	20/25 (80.0)	0.38 (0.21, 0.68)
Baseline CA-125 value			
≤ULN	92/247 (37.2)	89/123 (72.4)	0.34 (0.25, 0.46)
>ULN	10/13 (76.9)	7/7 (100.0)	NC
g*BRCA* mutation type by Myriad testing			
BRCA1	84/188 (44.7)	69/91 (75.8)	0.40 (0.29, 0.56)
BRCA2	15/62 (24.2)	26/39 (66.7)	0.20 (0.10, 0.38)
BRCA1/2 (both)	0/3	0/0	NC
Negative	3/7 (42.9)	1/1 (100.0)	
Age			
<65 years	85/225 (37.8)	82/112 (73.2)	0.33 (0.24, 0.45)
≥65 years	17/35 (48.6)	14/19 (73.7)	0.45 (0.22, 0.92)
Stage of disease at initial diagnosis			
Stage III	83/220 (37.7)	79/105 (75.2)	0.32 (0.24, 0.44)
Stage IV	19/40 (47.5)	17/26 (65.4)	0.49 (0.25, 0.94)
Following debulking surgery prior to study entry			
Residual macroscopic disease	29/55 (52.7)	23/29 (79.3)	0.44 (0.25, 0.77)
No residual macroscopic disease	70/200 (35.0)	69/98 (70.4)	0.33 (0.23, 0.46)



bd, twice daily; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PFS, progressiosn-free survival; ULN, upper limit of normal

Moore K, et al. N Engl J Med 2018;379:2495-505

SOLO1: PFS2



Olaparib (N=260)	Placebo (N=131)
69 (26.5)	52 (39.7)
NR	41.9
HR 0.50	
95% CI 0.35, 0.72; *P*=0.0002	

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

CI, confidence interval; HR, hazard ratio; PFS2, time to second progression or death

Moore K, et al. N Engl J Med 2018;379:2495-505

PRIMA: PHASE 3 TRIAL OF NIRAPARIB VS PLACEBO AS MAINTENANCE TREATMENT IN PATIENTS WITH ADVANCED OVARIAN CANCER

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- FIGO Stage III-IV high-grade serous or endometrioid*
- Stage III with visible residual disease post-surgery
- Inoperable Stage III disease
- Any Stage IV disease
- Had received NACT
- CR or PR (<2 cm†) and normalisation of CA-125‡

HRD testing prior to randomisation

Randomise 2:1
N=733

Stratify by:
- NACT
- CR/PR
- HRD-positive or negative/unknown

Niraparib
200/300 mg PO QD¶

Placebo

Primary endpoint
- PFS (BICR) in HRD-positive population and step down to all-comers (RECIST 1.1)

Secondary endpoints
- OS
- PFS2
- TFST
- Safety
- PRO/HRQoL

Niraparib is not approved for use outside the platinum-sensitive relapsed ovarian cancer setting.

*Includes patients with primary peritoneal and/or fallopian tube cancer. †Based on protocol modification. ‡Normal or >90% decrease in CA-125 with front-line treatment.

¶Modified starting dose permitted to mitigate for haematological toxicity following protocol amendment.

BICR, blinded independent central review; CA-125, cancer antigen-125; CR, complete response; FIGO, International Federation of Gynaecology and Obstetrics; HRD, homologous recombination deficiency; HRQoL, health-related quality of life; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival; PFS2, time to second progression; PO, by mouth; PR, partial response; PRO, patient-reported outcome; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumours; TFST, time to first subsequent therapy

1. Gonzalez-Martin A, et al. N Engl J Med. 2019. 2. Gonzalez-Martin A, et al. ESMO 2019. Abstract #LBA1. 3. Monk BJ, et al. SGO 2019. Abstract #3.
4. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02655016. Accessed 24 October 2019.

PRIMA: PFS BY MOLECULAR SUBGROUP

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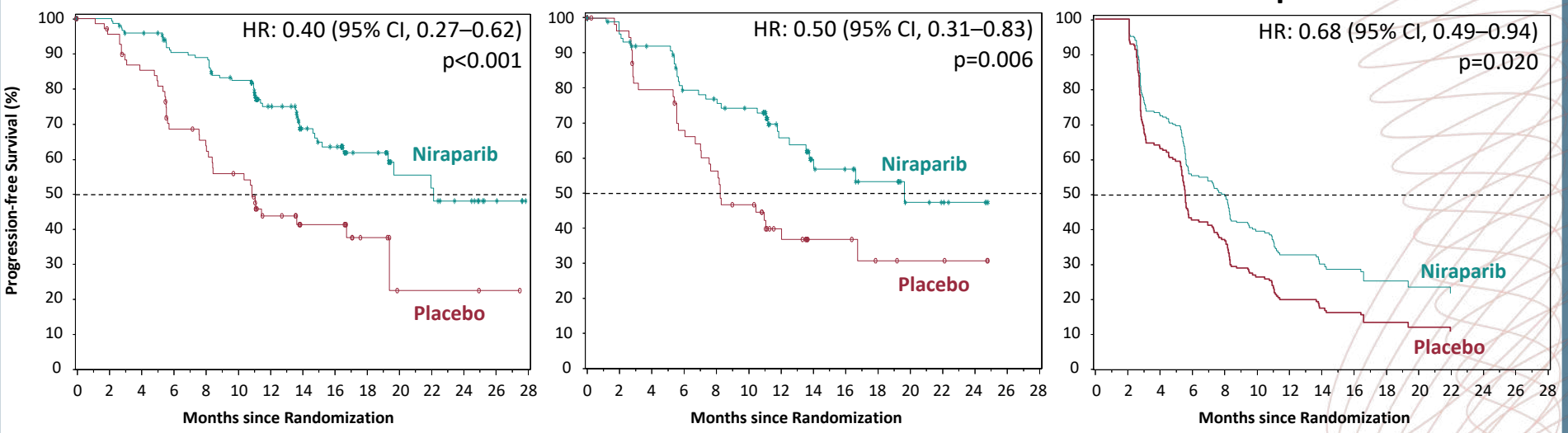

HRD by Myriad MyChoice

Gonzalez Martin et al, ESMO 2019; NEJM 2019

- Niraparib provided similar clinical benefit in the HRD subgroups (*BRCA*mut and *BRCA*wt)
- Niraparib provided clinically significant benefit in the HR-proficient subgroup with a 32% risk reduction in progression or death

CI, confidence interval; HR, hazard ratio; HRD, homologous recombination; HRD, homologous recombination deficient; mut, mutation; PFS, progression-free survival wt, wild-type

Gonzalez-Martin A, et al. ESMO 2019. Abstract #LBA1. Gonzalez-Martin A, et al. N Engl J Med 2019; 381:2391-2402

PAOLA-1: PHASE 3 TRIAL OF OLAPARIB MAINTENANCE IN NEWLY DIAGNOSED ADVANCED OVARIAN CANCER PATIENTS TREATED WITH CHEMOTHERAPY AND BEVACIZUMAB

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GINECO

ENGOT
European Network of Gynaecological Oncological Trial groups

GYNECOLOGIC CANCER INTERGROUP

Newly diagnosed FIGO IIIB-IV high-grade serous/endometrioid ovarian, fallopian tube, or primary peritoneal cancer*

FIRST-LINE
- **Surgery (upfront or interval)**
- **Platinum-taxane based chemotherapy**
- **≥3 cycles of bevacizumab†**

NED/CR/PR

N=806

Randomisation 2:1

Stratification
- Tumour *BRCA*m status‡
- First-line treatment outcome¶

Maintenance therapy

Olaparib (300 mg BID) x2 years
+ Bevacizumab†

Placebo x2 years
+ Bevacizumab†

Primary endpoint
Investigator-assessed PFS (RECIST v1.1)

Sensitivity analysis
PFS by BICR

Secondary endpoints
TFST
PFS2, TSST
OS
HRQoL
Safety and tolerability

*Patients with other epithelial non-mucinous ovarian cancer were eligible if they had a germline BRCA1 and/or BRCA2 mutation.

†Bevacizumab: 15 mg/kg, every 3 weeks for a total of 15 months, including when administered with chemotherapy.
‡By central labs.
¶According to timing of surgery and NED/CR/PR.

Addition of olaparib to bevacizumab for the first-line maintenance treatment of ovarian cancer is not an approved indication.

BICR, blinded independent central review; BID, twice daily; BRCAm, BRCA mutation; CR, complete response; FIGO, International Federation of Gynaecology and Obstetrics; NED, no evidence of disease; OS, overall survival; PFS, progression-free survival; PFS2, time to second progression; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; TFST, time to first subsequent therapy; TSST, time to second subsequent therapy.

Ray-Coquard I, et al. ESMO 2019. Abstract #LBA2. Ray-Coquard I, et al. N Engl J Med 2019; 381:2416-28

PAOLA-1: PFS BY MOLECULAR SUBGROUP

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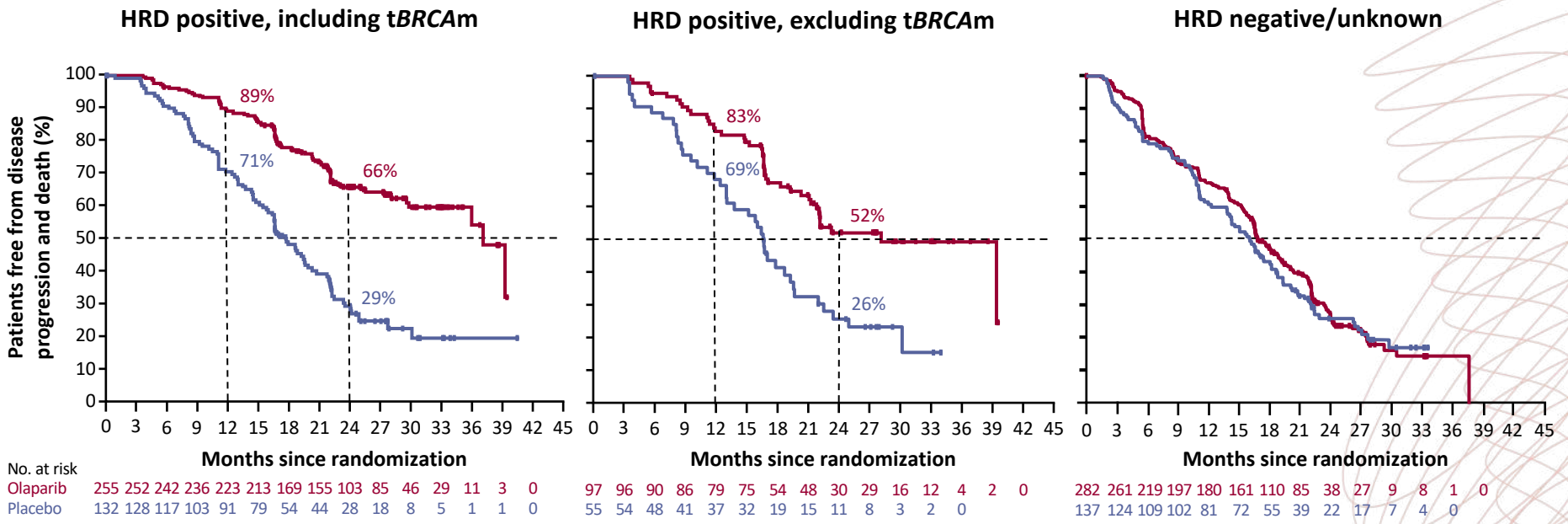
ARCAGY - GINECO | ENGOT European Network of Gynaecological Oncological Trial groups | GYNECOLOGIC CANCER INTERGROUP



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

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

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

HRD by Myriad MyChoice

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; tBRCAm, tumour BRCA mutation
The percentages of patients progression-free at 12 months and 24 months have been calculated based on Kaplan-Meier estimates. HRD positive is an HRD score ≥42. *This median is unstable due to a lack of events – less than 50% maturity
Ray-Coquard I, et al. ESMO 2019. Abstract #LBA2. Ray-Coquard I, et al. N Engl J Med 2019; 381:2416-28

VELIA: PHASE 3 TRIAL OF VELIPARIB WITH CARBOPLATIN AND PACLITAXEL AS CONTINUOUS MAINTENANCE[1,2]

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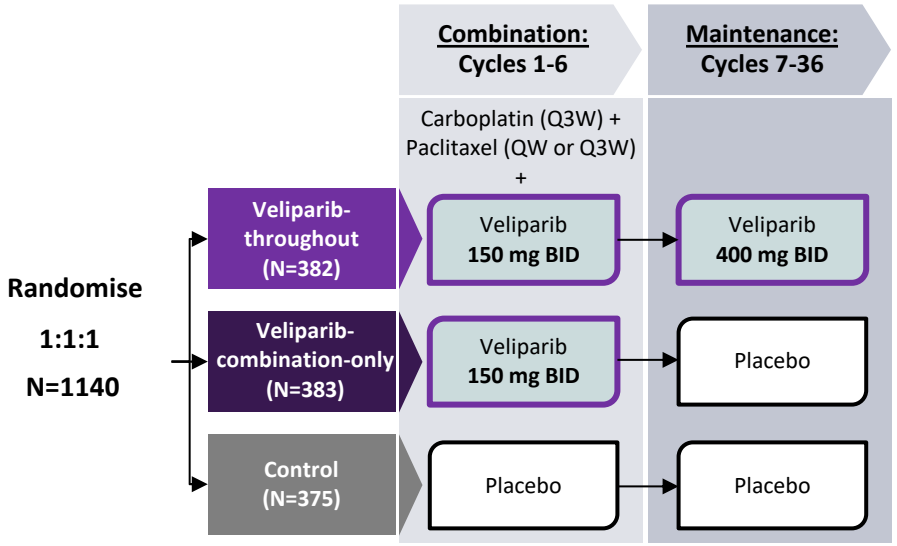
- High-grade serous cancer
- FIGO Stage III or IV
- No prior systemic therapy
- ECOG 0–2
- No CNS metastases



Primary endpoint

- PFS1 (RECIST 1.1)

Secondary endpoints

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

Stratify by:

- Stage of disease
- Region
- Primary vs interval cytoreduction
- Residual disease
- Chemotherapy regimen*
- *gBRCA* status†

Veliparib is not approved for use in ovarian cancer.
*Carboplatin AUC 6 Q3W + paclitaxel 80 mg/m^2 QW or 175 mg/m^2 Q3W.
†Added as a stratification factor ~14 months after trial initiation due to noted imbalance.

BID, twice daily; *BRCA*m, *BRCA* mutation; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; g*BRCA*, germline *BRCA*; HRQoL, health-related quality of life; OS, overall survival; PFS1, time to first progression; PFS2, time to second progression; PRO, patient-reported outcome; Q3W, every 3 weeks; QW, every week; RECIST, Response Evaluation Criteria in Solid Tumours; TSST, time to second subsequent therapy.

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02470585. Accessed 1 October 2018. 2. Coleman RL et al. ESMO 2019. Abstract #LBA3

VELIA: PFS DATA BY MOLECULAR SUBGROUP

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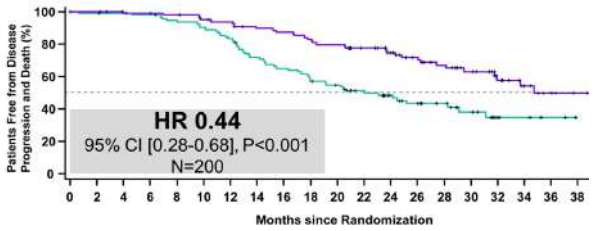
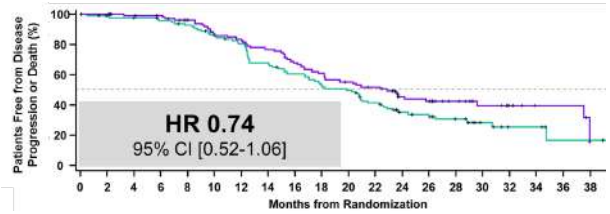
Veliparib
Control

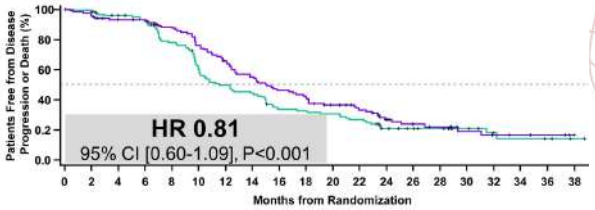
BRCA mutant



*BRCA*wt HRD



Non-HRD



CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficient; wt, wild type
Coleman, RL et al. ESMO 2019. Abstract #LBA3. Coleman RL, et al. N Engl J Med 2019; 381:2403-15

VELIA: ORR AT END OF COMBINATION PHASE

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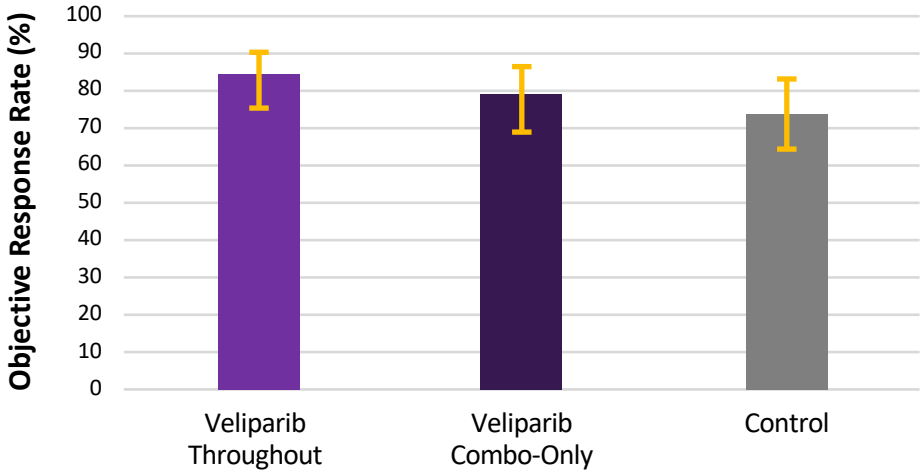
ORR at End of Combination Phase in ITT Patients with Primary Surgery and Measurable Disease



ORR (CR+PR), n/N % (95% CI)

Veliparib-Throughout	Veliparib-Combo-Only	Control
82/98	78/99	69/93
84% (75, 90)	79% (69, 86)	74% (64, 83)

N=290 (25% of ITT Patients)

Veliparib is not approved for use in ovarian cancer.
CI, confidence interval; CR, complete response; ITT, intent-to-treat; ORR, objective response rate; PR, partial response

Coleman, RL et al. ESMO 2019. Abstract #LBA3

VELIA: PFS FOR VELIPARIB-COMBO-ONLY VERSUS CONTROL

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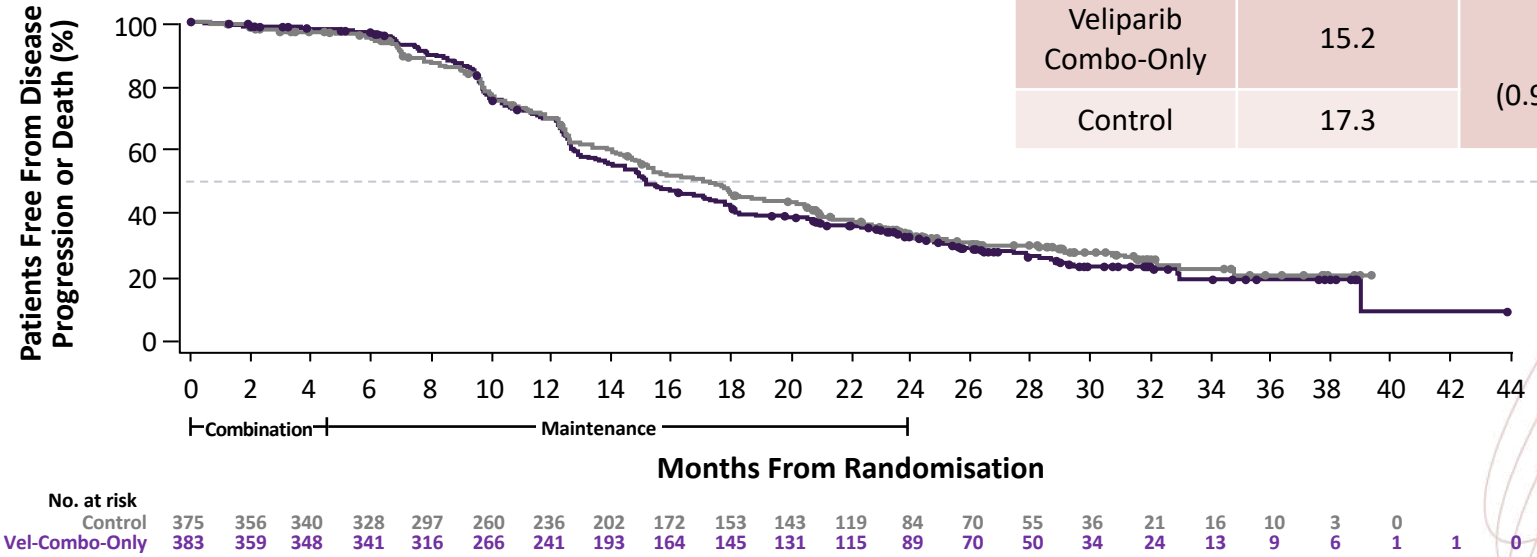
ITT

Treatment	mPFS, mo	HR (95% CI)
Veliparib Combo-Only	15.2	1.07 (0.90–1.29)
Control	17.3	



Across *BRCA*m, HRD and ITT, the veliparib-combo-only arm and the control arm demonstrated similar PFS

PFS in the veliparib-combination-only group as compared with the control group is a secondary endpoint that will be formally analysed for statistical significance at a later date if the comparisons for overall survival in the veliparib-throughout group meet the threshold for significance.

Veliparib is not approved for use in ovarian cancer.

*BRCA*m, *BRCA* mutation; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intent-to-treat; mPFS, median PFS; PFS, progression-free survival

Coleman, RL et al. ESMO 2019. Abstract #LBA3. Coleman RL, et al. N Engl J Med 2019; 381:2403-15

FIRST LINE MAINTENANCE STUDIES: KEY MESSAGES

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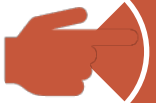
First-line PARP inhibitor maintenance therapy **significantly increases PFS and PFS2** in high grade serous or high grade endometrioid patients



The **lack of selection** for clinical 'platinum sensitivity' does **not seem to be an issue**

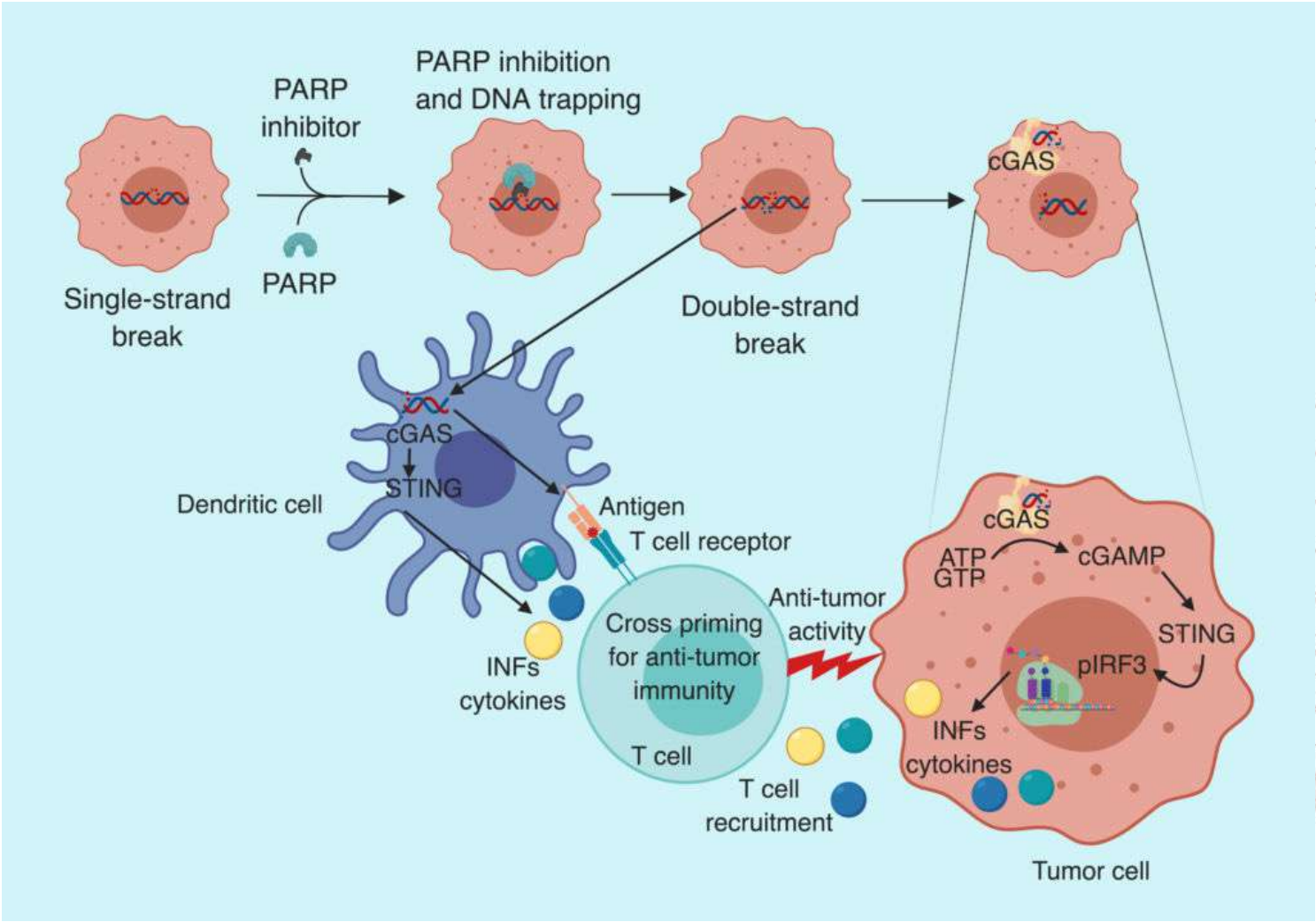
The effect is **most marked in patients with *BRCA* mutations** but there is **also a significant effect in *BRCA* wild type** patients

There doesn't seem to be a particular advantage in co-administering PARP inhibitors with chemotherapy (in contrast with PARPi maintenance only)

The first-line studies looked at heterogeneous populations and some combined with bevacizumab; we need to decide whether we believe the **results translate outside of each particular trial population**

HRD testing again provides enrichment for patients most likely to respond, but with the exception of PAOLA-1 and VELIA, does not identify patients who will not respond

MAIN PARPi TRIALS CURRENTLY UNDERWAY



Pant S, chasing cancer blog 2019

TRIALS OF PARP INHIBITORS IN COMBINATION WITH IMMUNE CHECKPOINT INHIBITORS

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	ENGOT Ov43	ENGOT Ov44 FIRST (BRCAm)	ENGOT Ov44 FIRST (BRCAwt)	ENGOT Ov45 ATHENA	ENGOT Ov46 DUO-O
Arm 1	CP +/- bev placebo-placebo	CP +/- bev **niraparib**-Placebo	CP +/- bev placebo-Placebo	rucaparib **nivolumab**	CP + Bev placebo-placebo
Arm 2	CP +/- bev **pembro**-placebo	CP +/- bev **niraparib-TSR042**	CP +/- bev **niraparib**-placebo	**rucaparib** placebo	CP + bev **durvalumab**-placebo
Arm 3	CP +/- bev **pembro-olaparib**		CP +/- bev **niraparib-TSR042**	**placebo nivolumab**	CP + bev **durvalumab-olaparib**
Arm 4				placebo placebo	

Maintenance

bev, bevacizumab; CP, paclitaxel-carboplatin; pembro, pembrolizumab
Slide courtesy of Antonio Gonzalez Martin

KEY ISSUES FOR THE FUTURE:

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- **Patient selection criteria**

- Prediction/detection of disease resistance
- Positioning in the patient journey

- What to do when patients relapse following PARP inhibitor therapy

PATIENT SELECTION CRITERIA:
VALUE OF HRD TESTING

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- Patients with BRCA mutations (germline or somatic) should all be considered for PARP inhibitors
- False-negative results remain a problem
  - Patients testing negative had some benefit in NOVA, ARIEL3 and PRIMA
  - Patients testing negative did not seem to benefit in PAOLA-1 or VELIA
- False-positive results are an issue; there are clearly patients harbouring PARP inhibitor resistant cells who test positive for HRD
  - This is presumably because the cancer was HR deficient at some point in its development but resistance mechanisms have occurred

- THE VALUE OF TESTING REMAINS UNCLEAR
- BETTER TESTS ARE REQUIRED (PERHAPS TAKING ACCOUNT OF RESISTANCE MECHANISMS)

HR, homologous recombination; HRD, homologous recombination deficiency

KEY ISSUES FOR THE FUTURE:

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- Patient selection criteria

- **Prediction/detection of disease resistance**
- **Positioning in the patient journey**

- What to do when patients relapse following PARP inhibitor therapy

STUDY 19: 11% OF PATIENTS REMAINED ON TREATMENT FOR ≥6 YEARS

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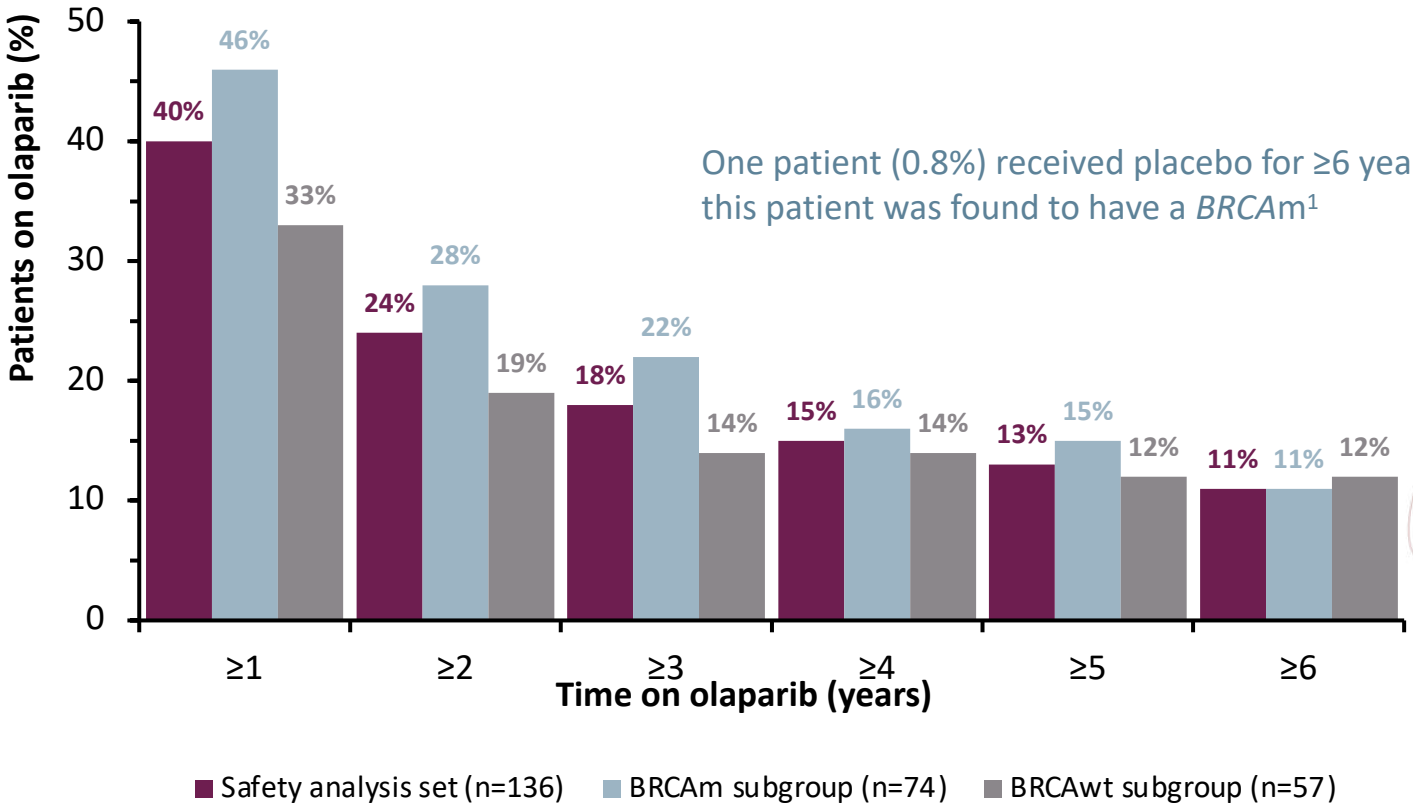

One patient (0.8%) received placebo for ≥6 years – this patient was found to have a *BRCA*m[1]

BRCAm, BRCA mutated; BRCAwt, BRCA wild type

1. Gourley C, et al. J Clin Oncol 2017;35:(suppl; poster related to abstr 5533). 2. Friedlander, et al. Brit J Cancer 2018;119:1075–85

CLINICAL FACTORS ASSOCIATED WITH EXCEPTIONAL RESPONDERS

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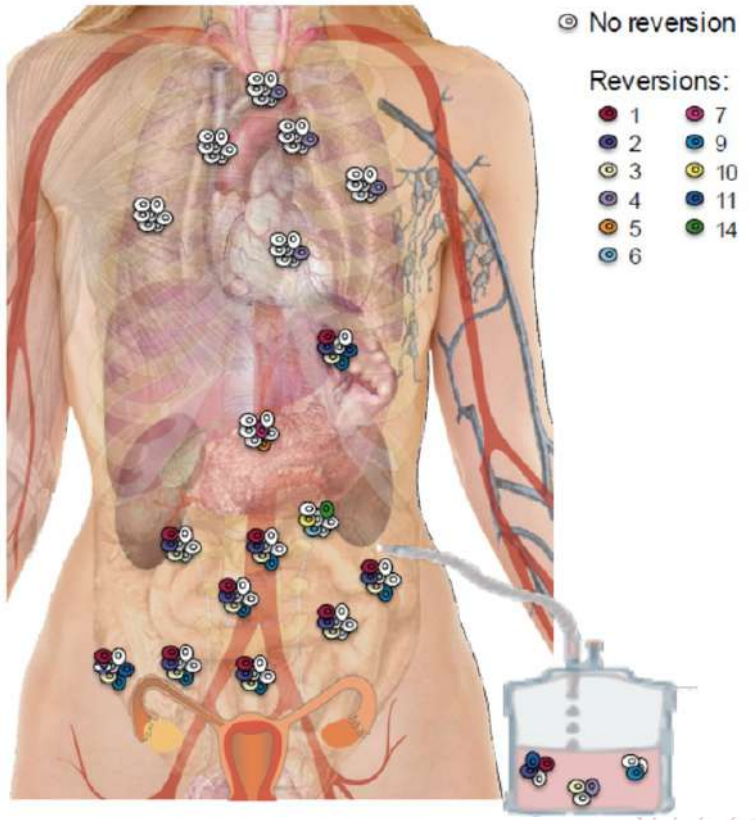
Study 19 suggests long-term olaparib response (>2 years) more likely if:

- Complete response to preceding chemotherapy (P<0.05)



1. Lheureux S, et al. Clin Can Res 2017;23:4086-94. 2. Patch AM, et al. Nature 2015; 521:489-94.

CLINICAL FACTORS ASSOCIATED WITH EXCEPTIONAL RESPONDERS

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Study 19 suggests long-term olaparib response (>2 years) more likely if:

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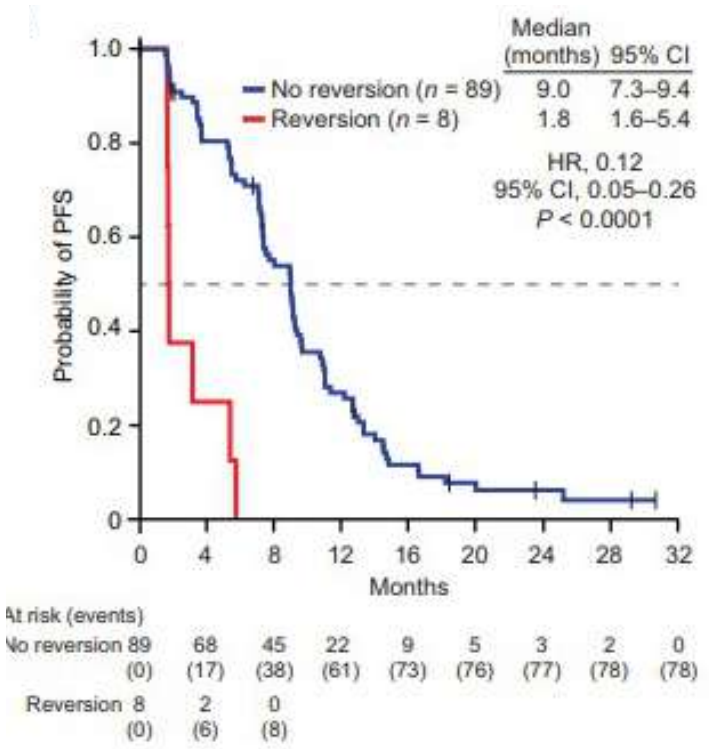

CI, confidence interval; HR, hazard ratio

1. Lheureux S, et al. Clin Can Res 2017;23:4086-94. 2. Lin, et al. Cancer Disc 2019;9:210-9

TREATING IN THE CONTEXT OF MINIMAL RESIDUAL DISEASE MAY BE THE BEST WAY TO ACHIEVE LONG TERM CONTROL

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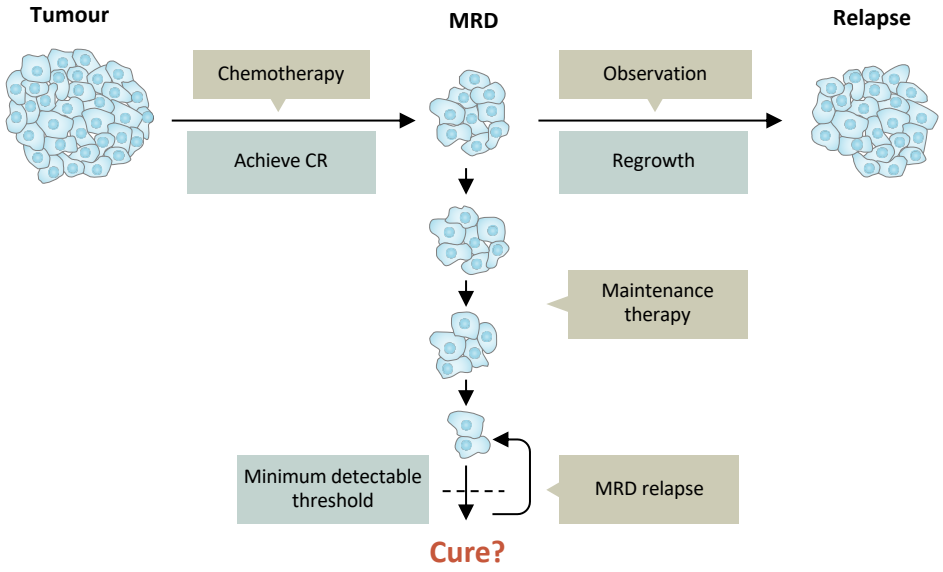
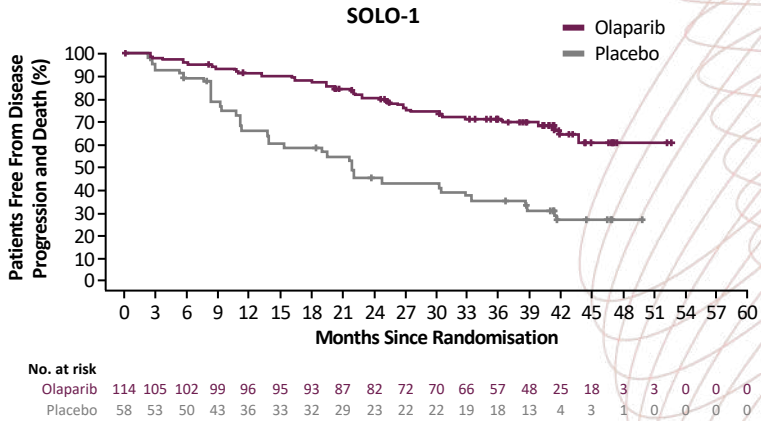
Paradigm for the management of Minimal Residual Disease (MRD)[1]



Investigator-assessed PFS in Stage III patients who underwent upfront surgery and had no residual disease[2]



CR, complete response; MRD, minimal residual disease; PFS, progression-free survival.

1. Luskin MR, et al. Nat Rev Cancer 2018;18:255-63. 2. Matthews C, et al. ASCO 2019. Abstract #5541

ABSOLUTE PFS IMPROVEMENT IN SOLO-1 IS SUBSTANTIALLY GREATER THAN THAT SEEN WITH OLAPARIB IN THE RELAPSED DISEASE SETTING (SOLO-2)

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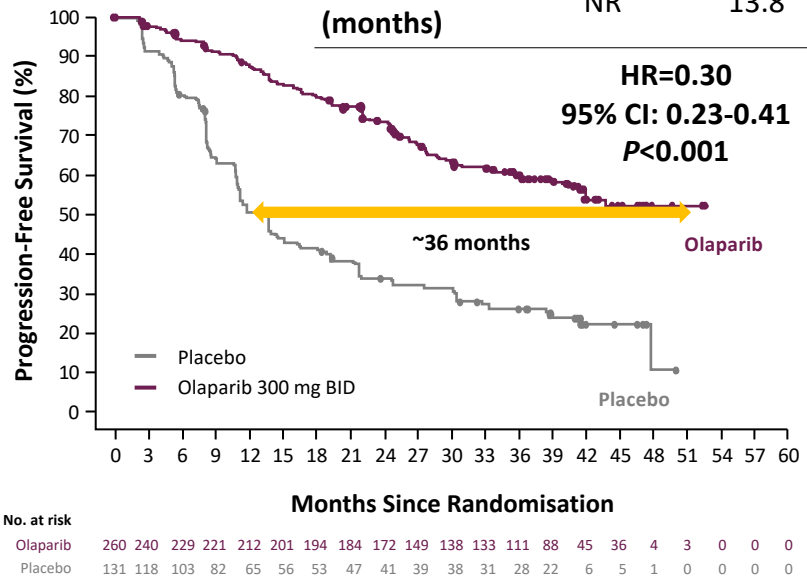
PFS: SOLO-1

	Olaparib	Placebo
Events, n (%)	102 (39.2)	96 (73.3)
Median PFS (months)	NR	13.8

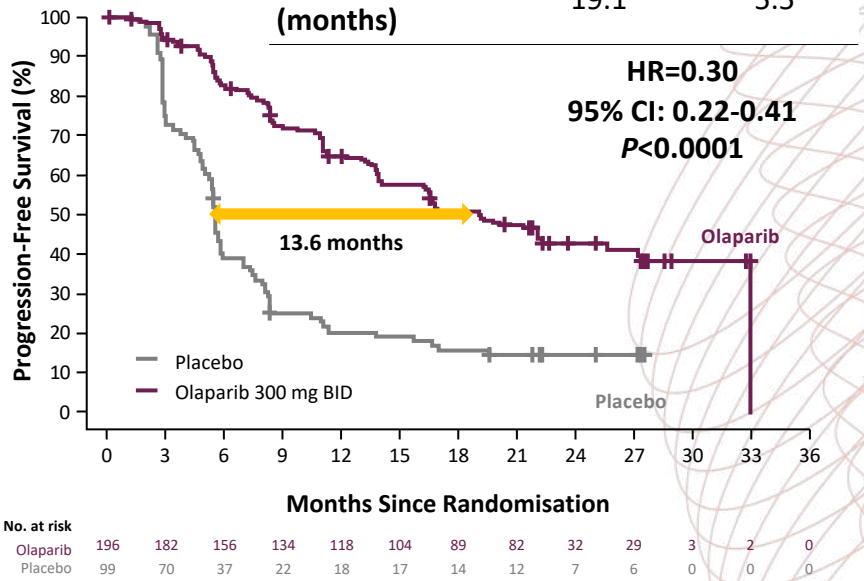


No. at risk

Olaparib	260	240	229	221	212	201	194	184	172	149	138	133	111	88	45	36	4	3	0	0	0
Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0	0	0

PFS: SOLO-2

	Olaparib	Placebo
Events, n (%)	107 (54.6)	80 (80.8)
Median PFS (months)	19.1	5.5



No. at risk

Olaparib	196	182	156	134	118	104	89	82	32	29	3	2	0
Placebo	99	70	37	22	18	17	14	12	7	6	0	0	0

DO WE CURE MORE PATIENTS FIRST LINE?

Comparisons across trials should not be made as they were not head-to-head trials. For presentation only.
BID, twice daily; HR, hazard ratio; NR, not reached; PFS, progression-free survival.

1. Moore K, et al. N Engl J Med 2018;379:2495-505; 2. Pujade-Lauraine E, et al. Lancet Oncol 2017;18:1274-84.

KEY ISSUES FOR THE FUTURE:

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- Patient selection criteria

- Prediction/detection of disease resistance
- Positioning in the patient journey

- **What to do when patients relapse following PARP inhibitor therapy**

RETREAT WITH PLATINUM?

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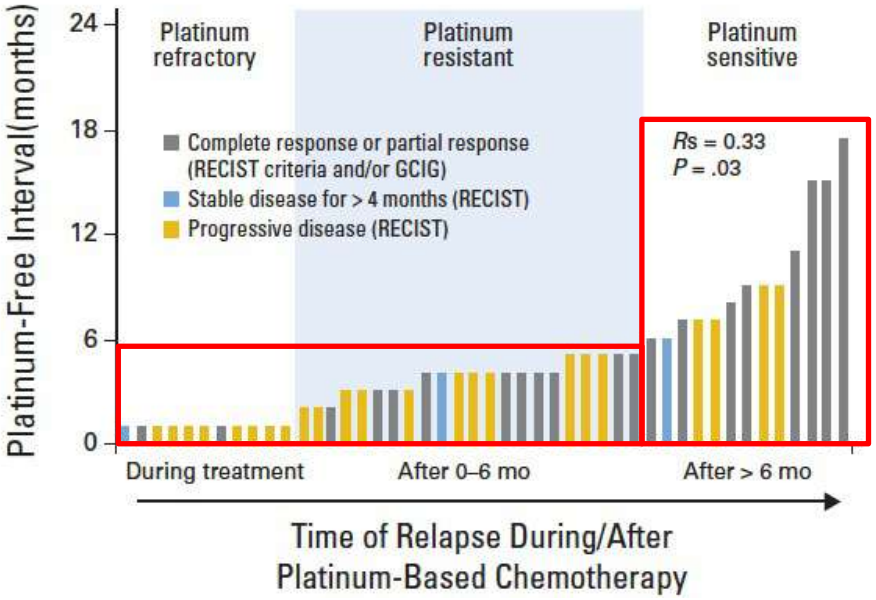
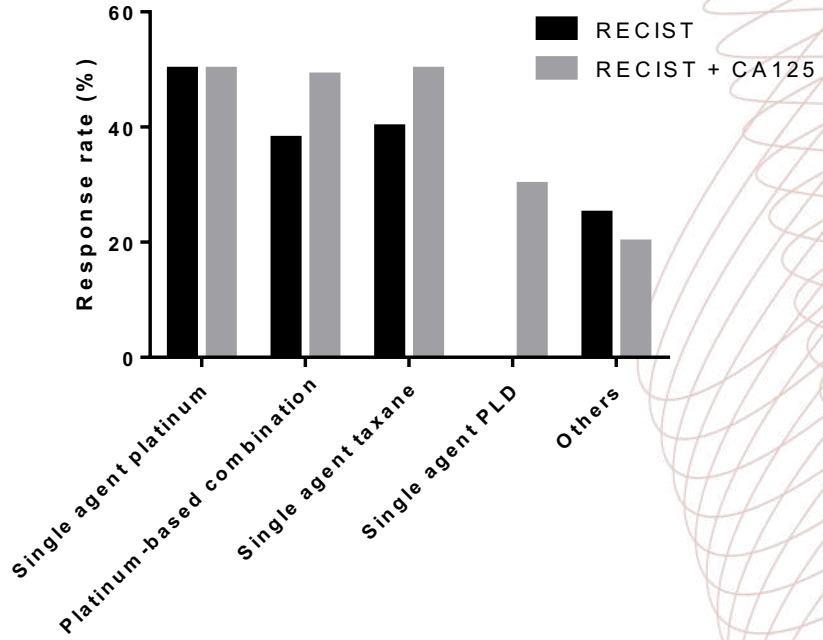
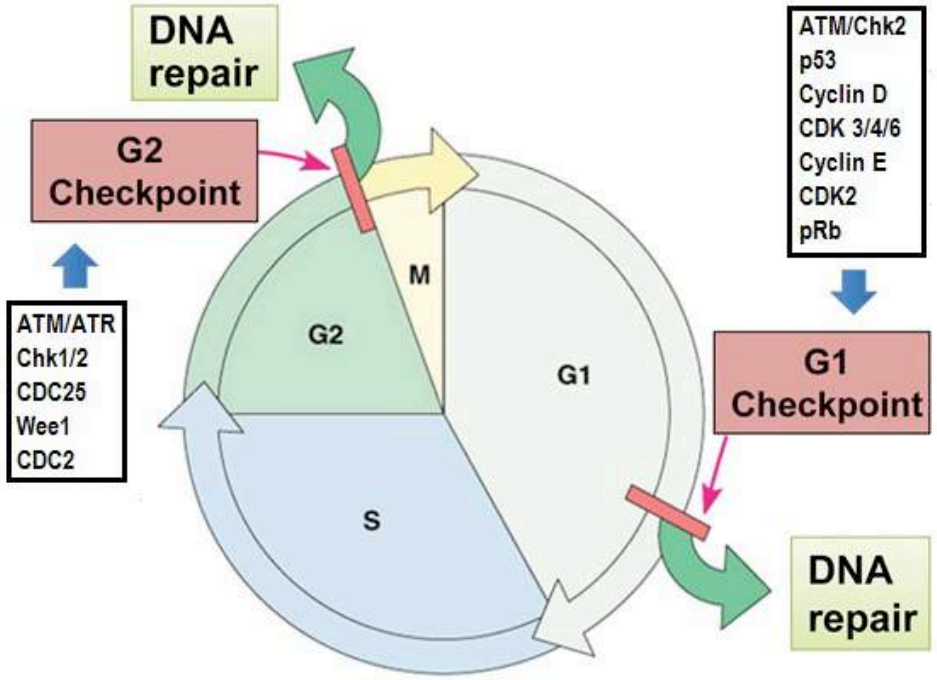
General assumption: Platinum sensitivity = PARPi sensitivity





1. Fong PC, et al. J Clin Oncol 2010;28(15):2512-9. 2. Ang, et al. Clin Can Res 2013;19:5485-93

TRIALS OF NEW DRUGS THAT TARGET THE CELL CYCLE?



Wee1 inhibitor?
ATR inhibitor?

CONCLUSION

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PARP inhibitor maintenance therapy represents a massive step forward in terms of delaying relapse and delaying the requirement for subsequent chemotherapy

It may also result in increased cure rate but more follow-up of the key trials is required to state this definitively

Molecular tools for patient selection remain suboptimal but HRD testing seems to be the most informative current strategy

We must understand more about ways to detect, prevent and abrogate PARP inhibitor resistance to maximise the utility of these drugs

STATE-OF-THE-ART ON PARPi IN BREAST CANCER

Shinji Ohno, M.D., Ph.D.

Breast Oncology Center
Cancer Institute Hospital of JFCR

Breast International Group

PARPi FOR BREAST CANCER

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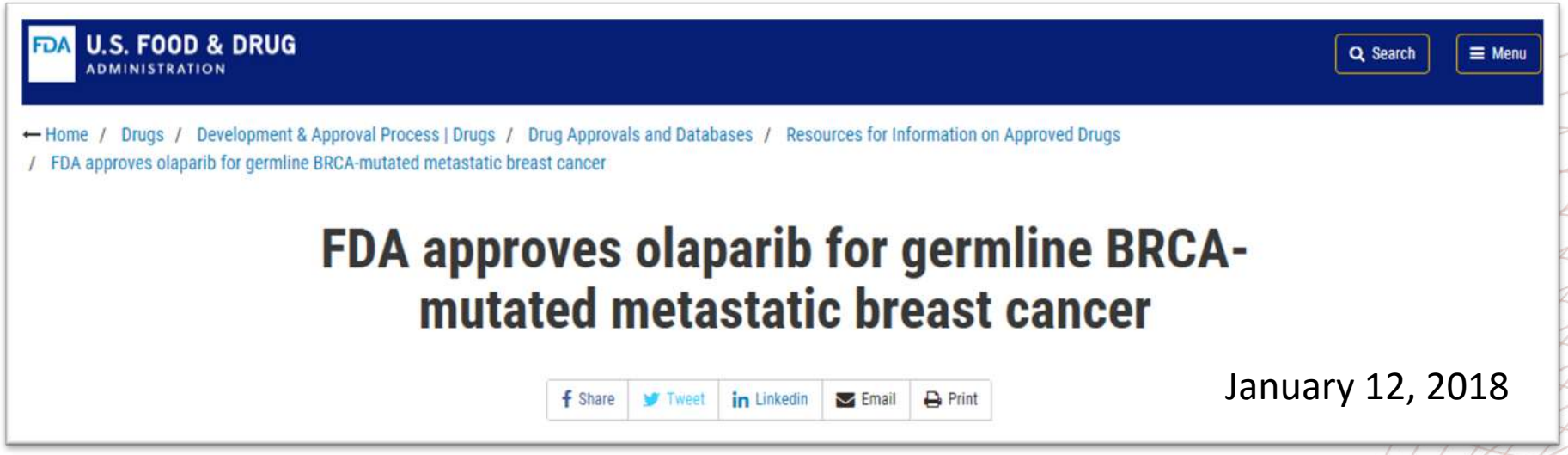
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FDA approves olaparib for germline BRCA-mutated metastatic breast cancer

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January 12, 2018


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FDA approves talazoparib for gBRCAm HER2-negative locally advanced or metastatic breast cancer

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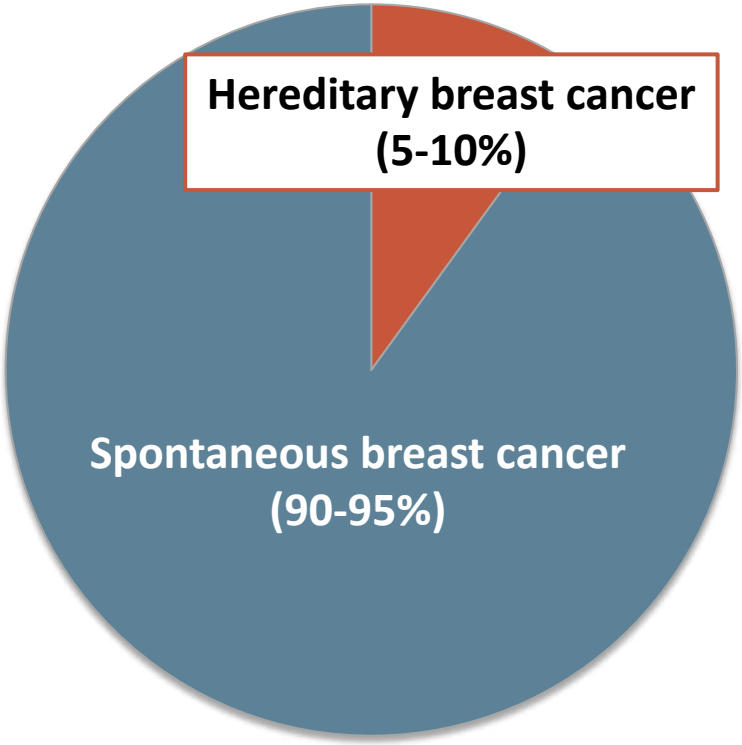
October 16, 2018

BRCA, breast cancer susceptibility gene; FDA, Food and Drug Administration; gBRCAm, germline BRCA mutated; HER2, human epidermal growth factor receptor 2; PARPi, poly-ADP ribose polymerase inhibitor


PREV
Francine, second cousin
Breast cancer, age mid-40s
Stella, great aunt
Breast cancer, had a double mastectomy, died later in her 70s
Rolland Bertrand, grandfather
Sweat gland cancer, age 61
Marcheline Bertrand, mom
Ovarian cancer, age 56
Angelina Jolie
Debbie Martin, aunt
Breast cancer, age 61
Raleigh Bertrand, uncle
Prostate cancer, age mid-50s

HEREDITARY BREAST CANCER



***BRCA1* mutation:**

- **Female:** Risk of breast cancer and ovarian cancer

***BRCA2* mutation:**

- **Female:** Risk of breast cancer and ovarian cancer
- **Male:** Risk of breast cancer, pancreas cancer, prostate cancer

BC, breast cancer; BRCA1/2, breast cancer type 1/2 susceptibility gene

Nakamura S, et al. Breast Cancer 2015;22:462-8

BRCA1, *BRCA2* MUTATION AND RISK OF CANCER

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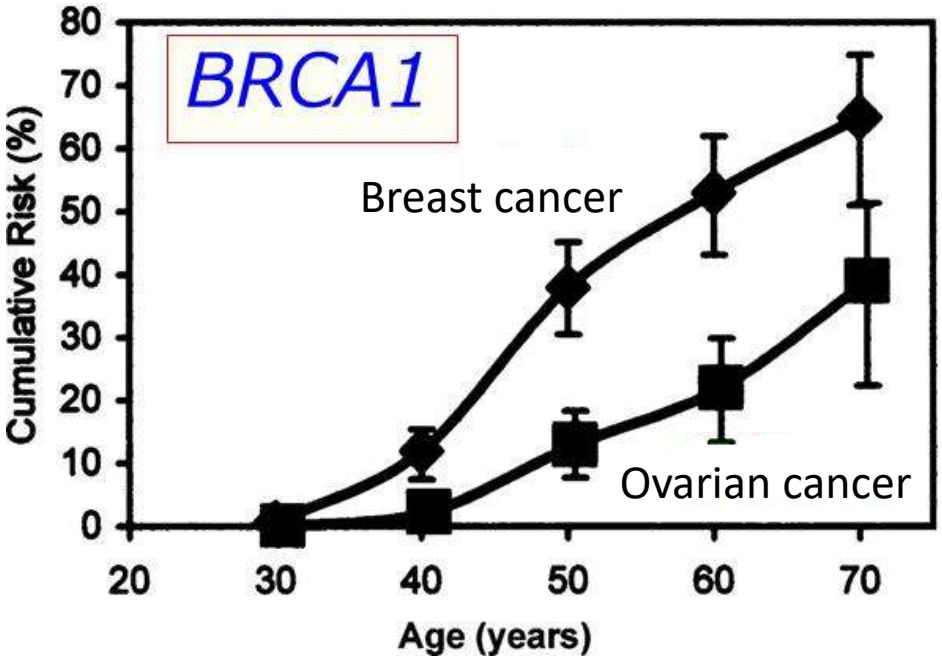

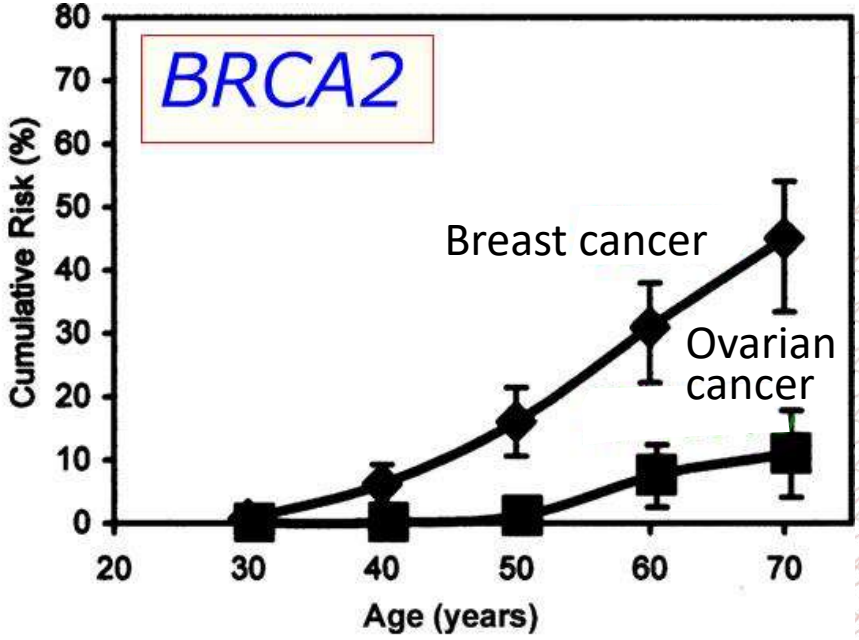

Morbidity rate until 70 years old

Mutation	Breast cancer	Ovarian cancer
*BRCA*1	65% (44-78)	39% (18-54)
*BRCA*2	45% (31-56)	11% (2.4-19)

BRCA1/2, breast cancer type 1/2 susceptibility gene

Antoniou A, et al. Am J Hum Genet 2003;72:1117-30

BRCA MUTATION AND SUBTYPE

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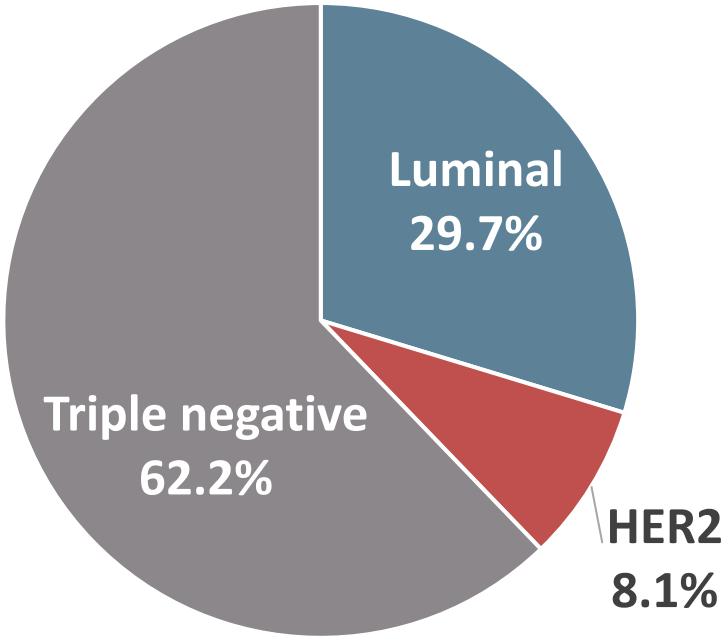
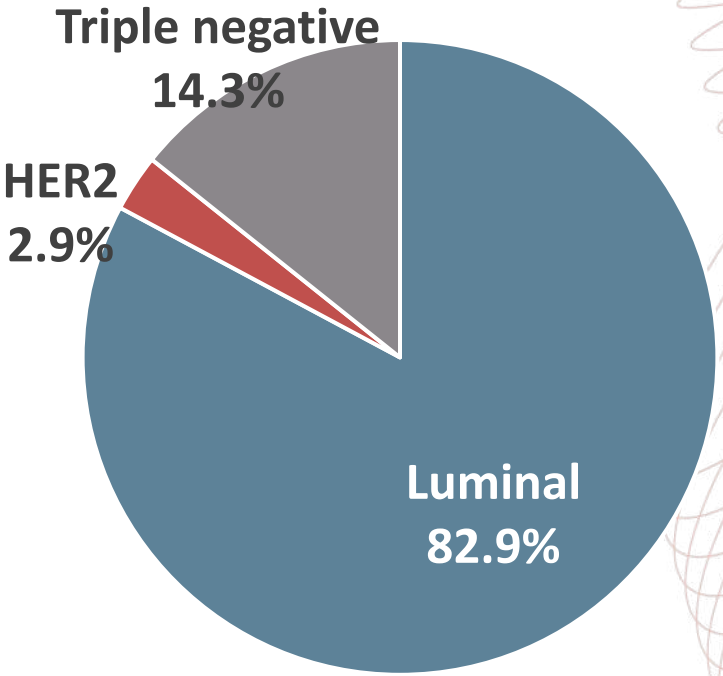
BRCA1 mutated



BRCA2 mutated



BRCA, breast cancer susceptibility gene; BRCA1/2, BRCA type 1/2; HER2, human epidermal growth factor receptor 2

Nakamura S, et al. Breast Cancer 2015;22:462-8

SUBTYPE OF BREAST CANCER

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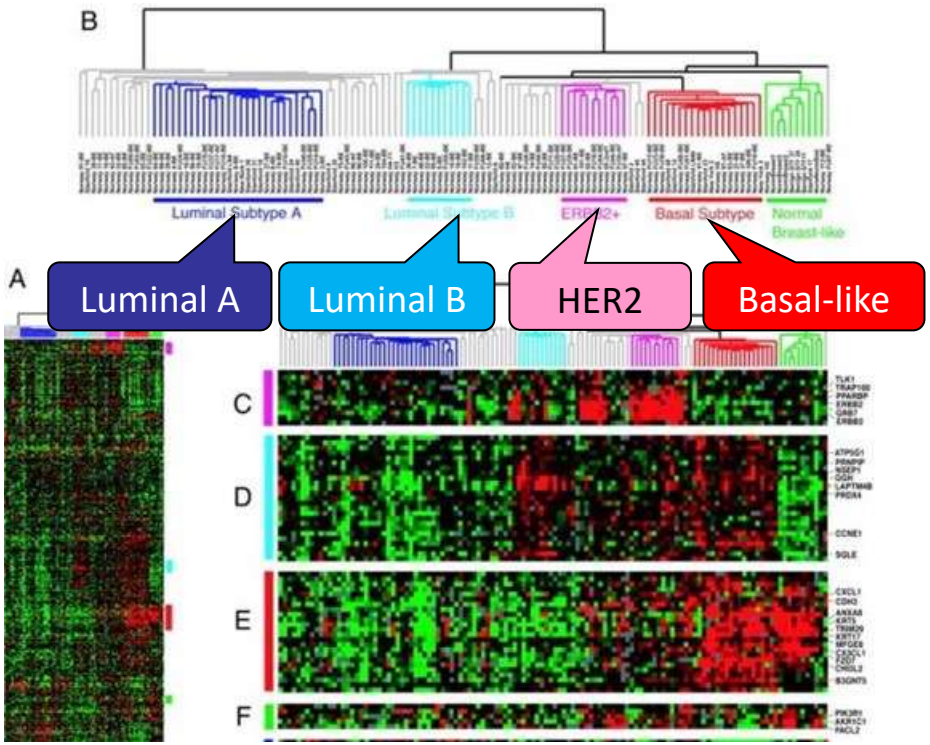
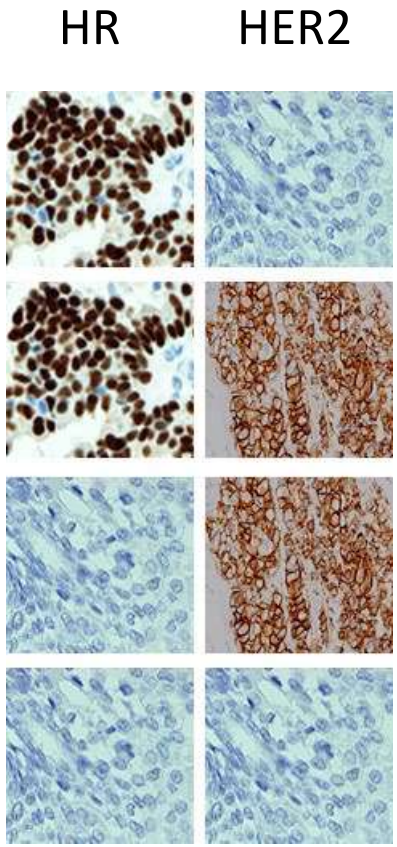
Genomic profile



Intrinsic subtype by immuno-histochemistry



Luminal type

Luminal HER2 type

HER2 type

Triple negative type

HER2, human epidermal growth factor receptor 2; HR, hormone receptor
CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OS, overall survival

Sorlie T, et al. PNAS 2001;98:10869-10874

STATISTICS: TNBC

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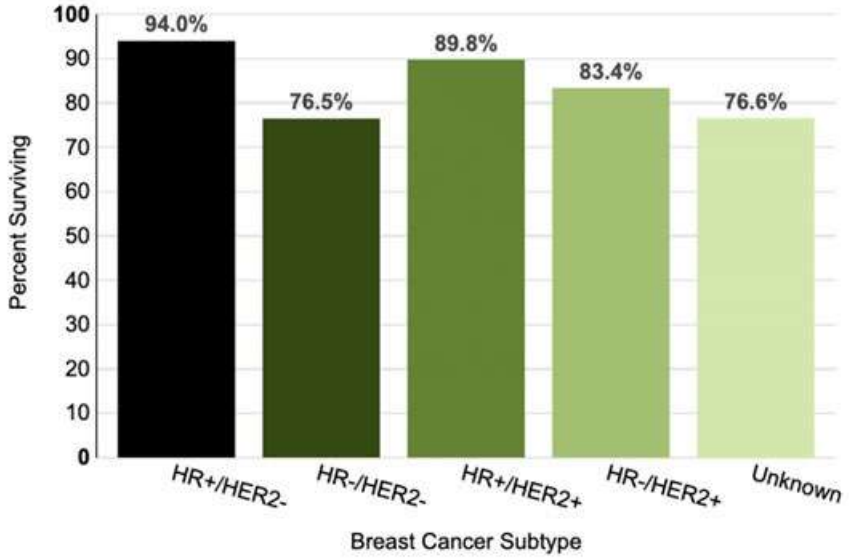
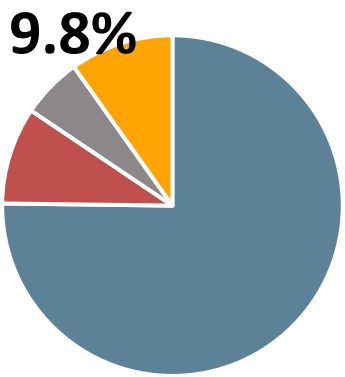
Rate of new breast cases per 100,000 women, SEER 21 2012-2016

Subtype	New cases
HR+/HER2-	85.8
HR-/HER2-	13.0
HR+/HER2+	12.9
HR-/HER2+	5.4
Unknown	10.4
Total	**127.5**



5-year relative survival with distant disease 11.2%



Japan Breast Cancer Society
95,257 cases (2016)

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; SEER, Surveillance, Epidemiology, and End Results; TNBC, triple negative breast cancer

SUBTYPE AND PROGNOSIS AFTER RECURRENCE

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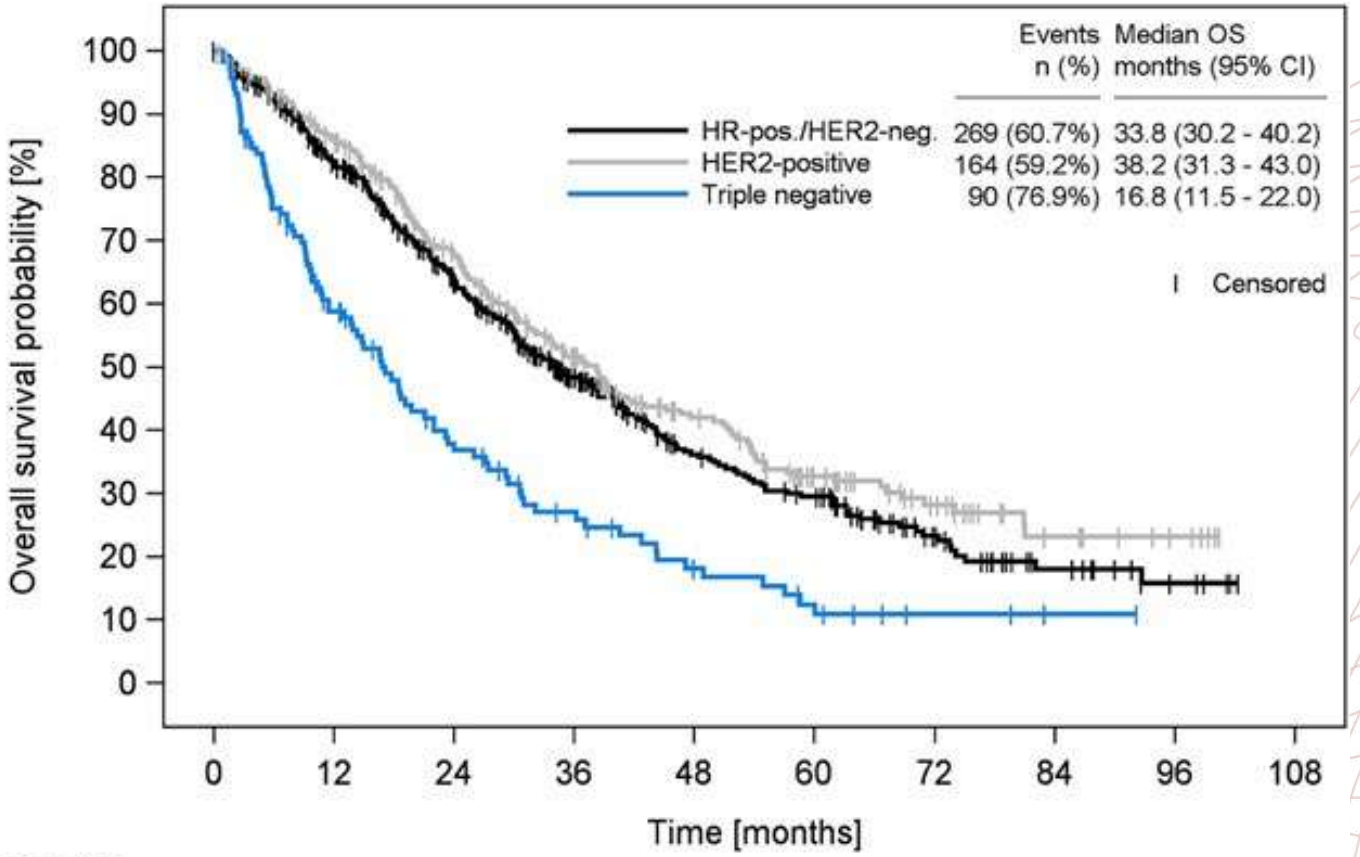

Number at risk

HR-pos./HER2-neg.	443	344	239	147	83	65	31	14	5	0
HER2-positive	277	226	163	111	74	46	26	11	5	0
Triple negative	117	63	37	23	13	8	3	1	0	

CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; OS, overall survival

Fietz T, et al. The Breast 2017;34:122-30

HR-POSITIVE BREAST CANCER WITH RESISTANCE TO HORMONE THERAPY

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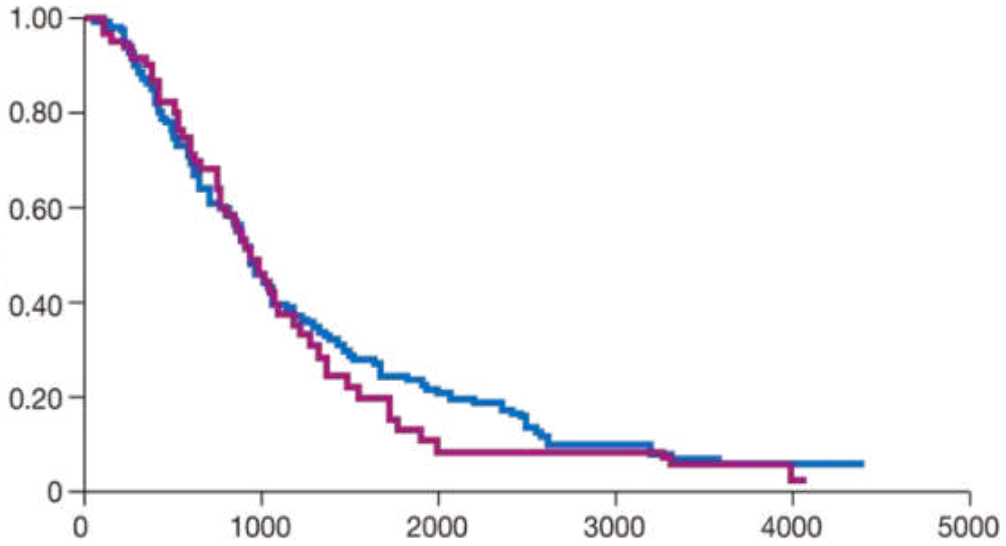
Prognosis of HR-positive breast cancer with resistance to hormone therapy and that of TNBC



Subtype	N	Death	OS	[95%]	p value
Luminal	205	76.1%	941.0 日	[294.0-2880.0]	NS
Triple N	62	79.4%	933.0 日	[416.0-1717.0]	

Shizuoka cancer center 2002 Oct – 2014 Nov

HR, hormone receptor; N, number; NS, not significant; OS, overall survival; TNBC, triple negative breast cancer

Data of Shizuoka Cancer Center

BASAL-LIKE BREAST CANCER AND BRCA1 MUTATION

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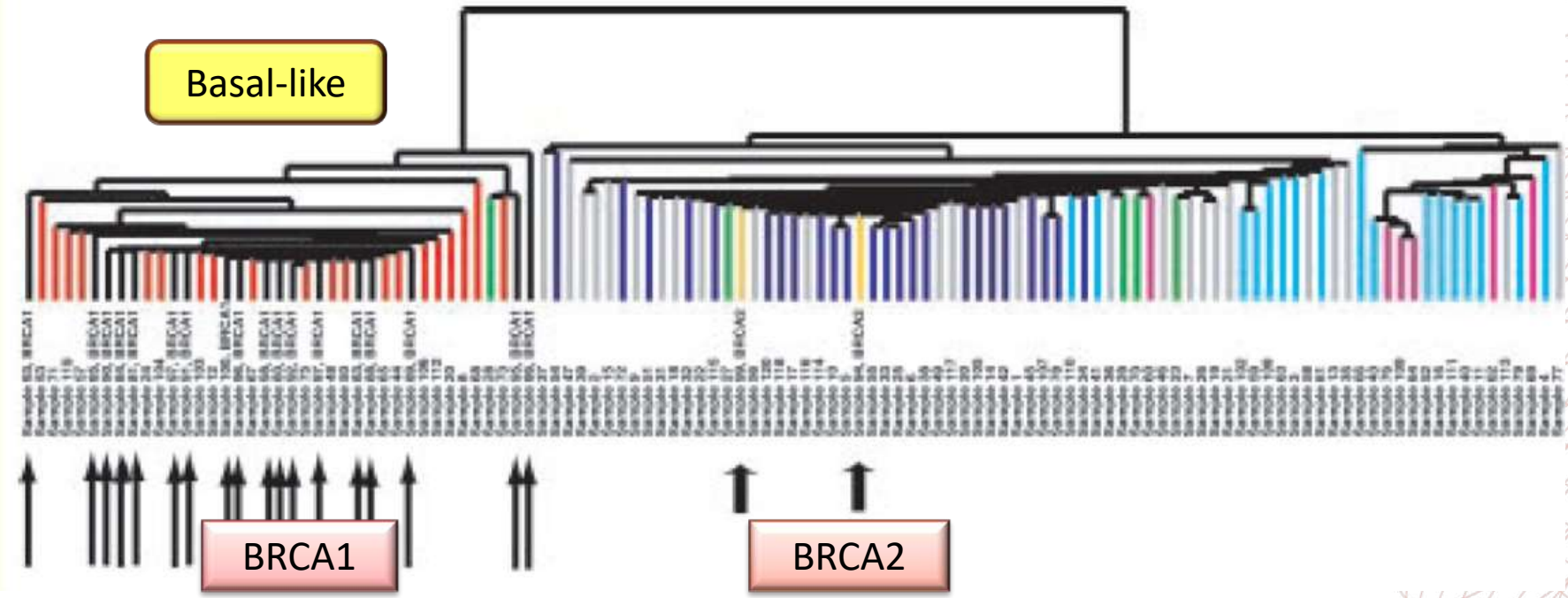
BRCA1 tumours associated with a basal tumour profile



Dendrogram showing all tumours from van 't Veer et al., including:

- 18 tumours from *BRCA1* mutation carriers (black branches)
- 2 tumours from *BRCA2* mutation carriers (yellow branches)
- *BRCA1* tumours: longer arrows; *BRCA2* tumours: shorter arrows

Cluster of genes characteristic of basal tumours and highly expressed in tumours from *BRCA*1-carriers.

BRCA1/2, breast cancer type 1/2 susceptibility gene. Sørlie T, et al. PNAS 2003;100:8418-23

GENE ABNORMALITIES IN 7,051 JAPANESE WOMEN WITH BREAST CANCER

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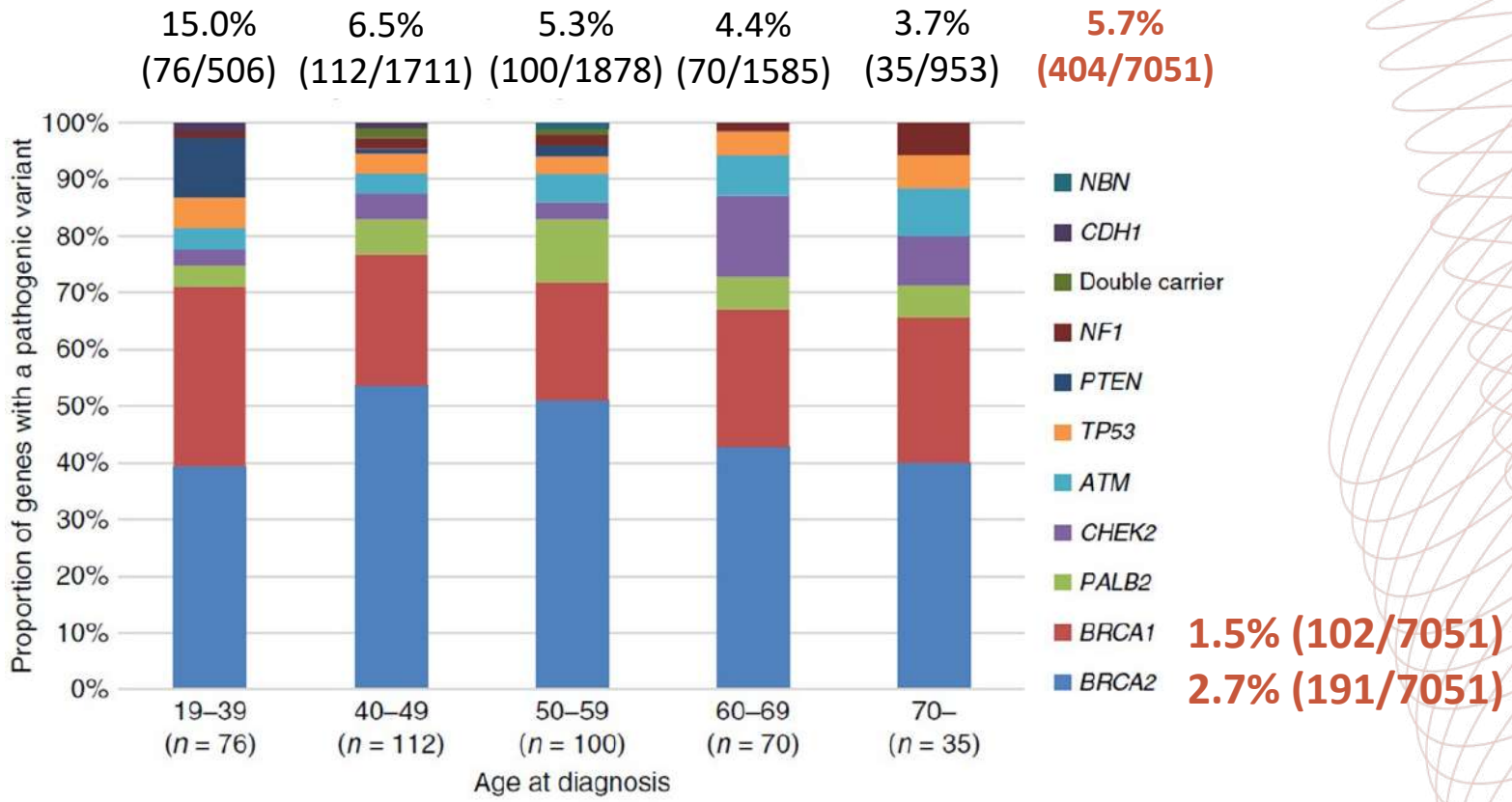

ATM, ataxia telangiectasia mutated gene; BRCA1/2, breast cancer type 1/2 susceptibility gene; CDH1, cadherin-1; CHEK2, checkpoint kinase 2; NF1, neurofibromin 1; PALB2, partner and localizer of BRCA2; PTEN, phosphatase and tensin homolog; TP53, tumour protein 53

Momozawa, et al. Nat Commun 2018;9:4083

CARBOPLATIN IN *BRCA* MUTANT BREAST CANCER

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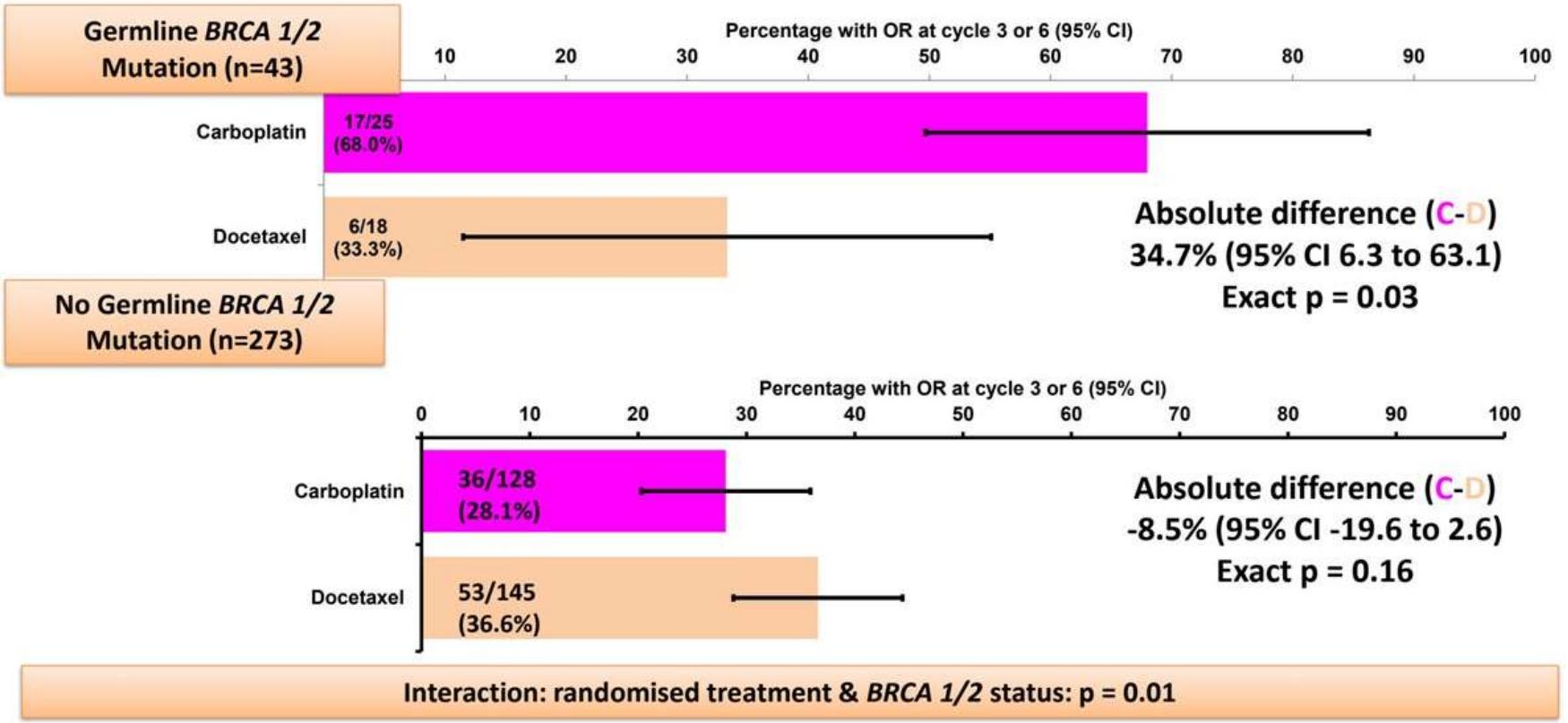

BRCA1/2, breast cancer type 1/2 susceptibility gene; C, carboplatin; CI, confidence interval; D, docetaxel; OR, objective response

Tutt A, et al. Nat Med 2018; 24: 628-637.

PARPI IN *BRCA* MUTANT BREAST CANCER

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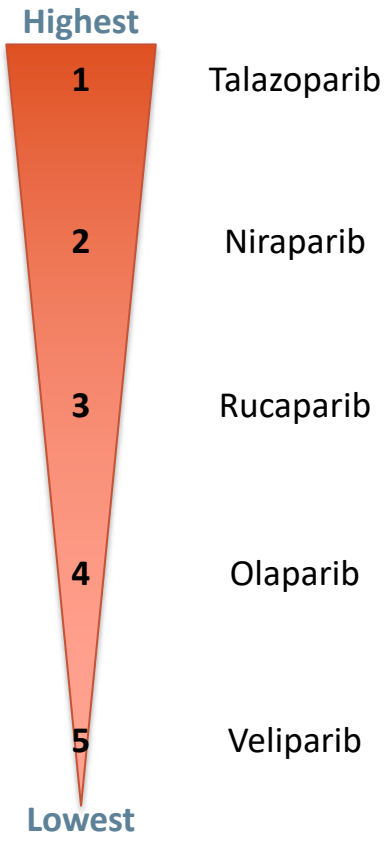
PARP Trapping Potency[1]*



PARP Catalytic Inhibition[3]

PARP Inhibitor	Catalytic Inhibition IC50 (nM)†
Talazoparib	4
Olaparib	6
Rucaparib	21
Veliparib	30
Niraparib	60

- Based on preclinical data, **talazoparib** is believed to inhibit PARP-mediated DNA SSBR through[2]:
  - Inhibition of catalytic activity of PARP1/2
  - Trapping PARP1/2 on sites of DNA damage

*The impact of PARP trapping and/or catalytic inhibition on clinical efficacy and safety is currently unknown.

†Concentration for 50% inhibition (IC_{50}) in PARP1 enzyme assay

BRCA, breast cancer susceptibility gene; PARP1/2, poly-ADP ribose polymerase 1/2; PARPi, PARP inhibitor; SSBR, single-stranded break repair

1. Lord CJ, Ashworth A. Science 2017;355:1152-8. 2. Murai J, et al. Mol Cancer Ther 2014;13:433-44.
3. Pommier Y. Presented at: TAT 13th International Congress; March 2015; Paris, France. Presentation 06.1.

OlympiAD STUDY DESIGN PHASE 3

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- **HER2-negative metastatic BC**
  - **ER+ and/or PR+ or TNBC**
- **Deleterious or suspected deleterious *gBRCA*m**
- **Prior anthracycline and taxane**
- **≤2 prior chemotherapy lines in metastatic setting**
- **HR+ disease progressed on ≥1 endocrine therapy, or not suitable**
- **If prior platinum use**
  - **No evidence of progression during treatment in the advanced setting**
  - **≥12 months since (neo)adjuvant treatment**

Olaparib
300 mg tablets bd

2:1 randomization

Chemotherapy treatment of physician's choice (TPC)
- Capecitabine
- Eribulin
- Vinorelbine

Treat until progression

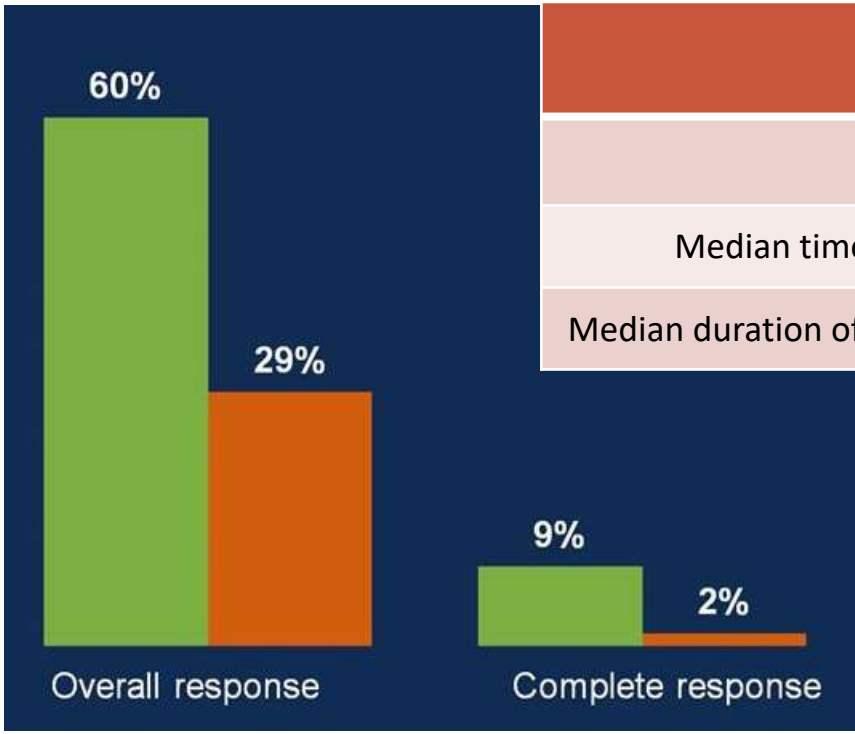
Primary endpoint:
- **Progression-free survival (RECIST 1.1, BICR)**

Secondary endpoints:
- Time to second progression or death
- Overall survival
- Objective response rate
- Safety and tolerability
- Global HRQoL (EORTC-QLQ-C30)

bd, twice daily; BICR, blinded independent central review; EORTC, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; ER, estrogen receptor; gBRCAm, germline BRCA mutated; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; HRQoL, health-related quality of life; PR, progesterone receptor; RECIST, Response Evaluation Criteria in Solid Tumours; TNBC, triple negative breast cancer

Robson, et al. ASCO 2017; N Engl J Med 2017;377:523

OBJECTIVE RESPONSE BY BICR



	Olaparib 300 mg bd	Chemotherapy TPC
N	167	66
Median time to response, days	47	45
Median duration of response, months	6.2 (4.6-7.2)	7.1 (2.8-12.2)

BICR, blinded independent central review; TPC, treatment of physician choice

Robson, et al. ASCO 2017; N Engl J Med 2017;377:523

PRIMARY ENDPOINT: PFS BY BICR

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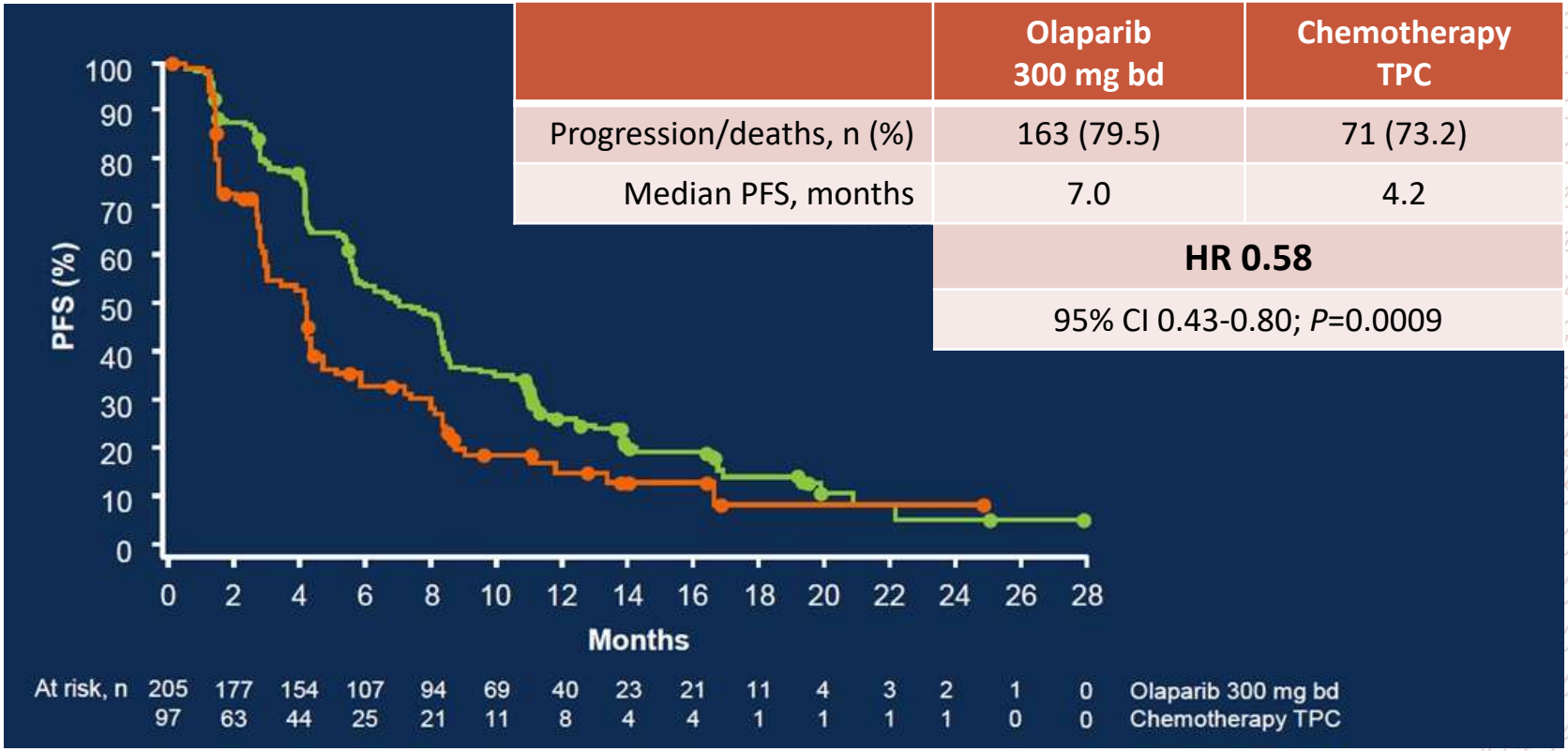

	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
	HR 0.58	
	95% CI 0.43-0.80; *P*=0.0009	

bd, twice daily; BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; TPC, treatment of physician choice

Robson, et al. ASCO 2017; N Engl J Med 2017;377:523

ADVERSE EVENTS (ANY GRADE) IN ≥15% OF PATIENTS

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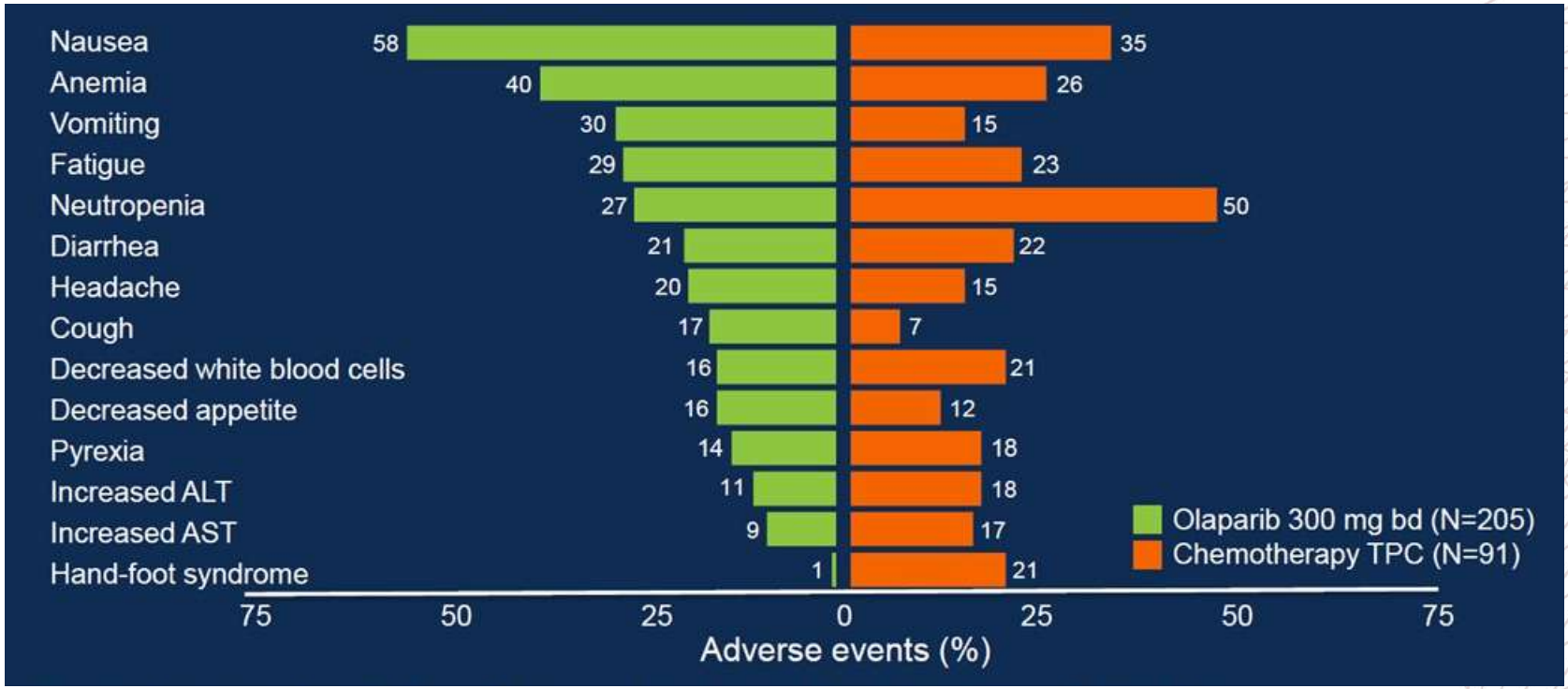

Irrespective of causality. MedDRA preferred terms for adverse events have been combined for 1) anaemia and 2) neutropenia

ALT, alanine aminotransferase; AST, aspartate aminotransferase; bd, twice daily; MedDRA, Medical Dictionary for Regulatory Activities; TPC, treatment of physician choice

Robson, et al. ASCO 2017; N Engl J Med 2017;377:523

GRADE ≥3 ADVERSE EVENTS IN ≥2% PATIENTS IN EITHER ARM

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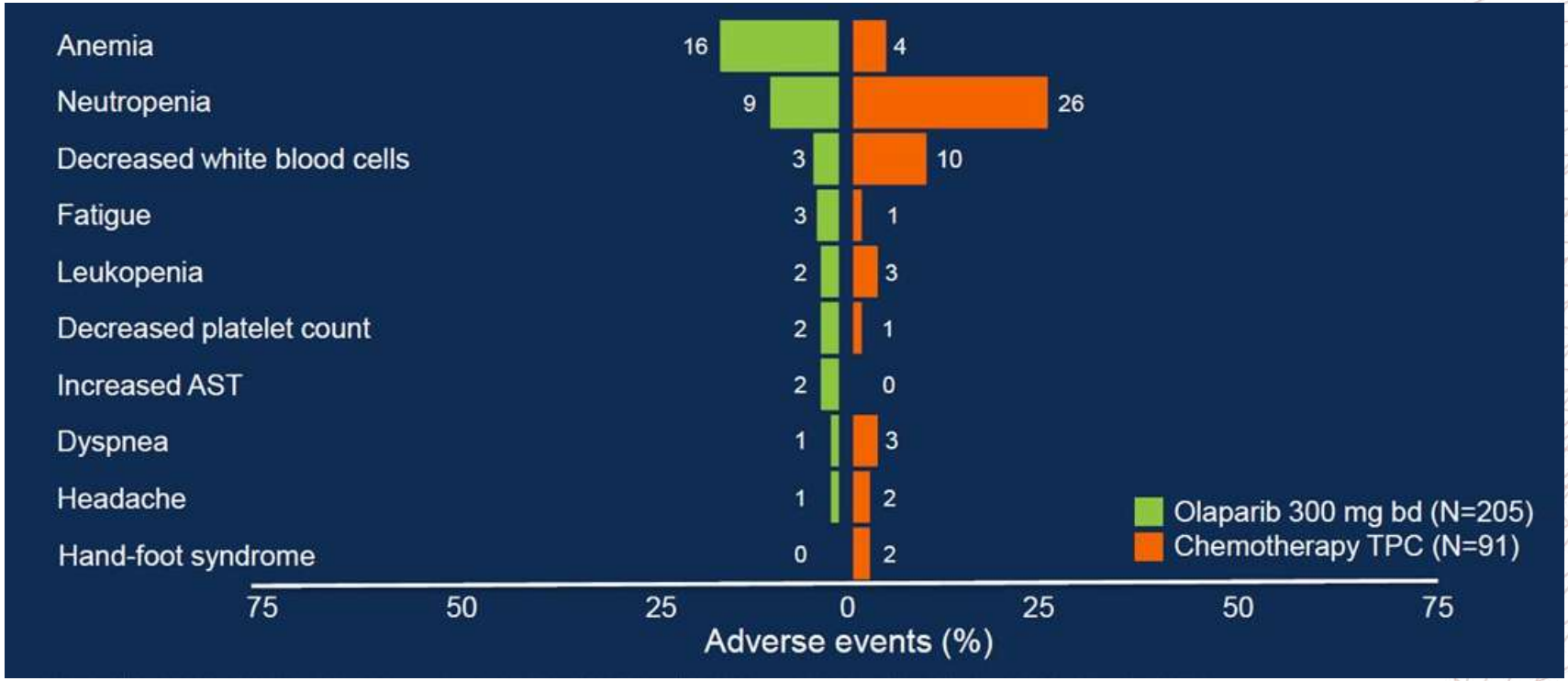

Irrespective of causality. MedDRA preferred terms for adverse events have been combined for 1) anemia and 2) neutropenia

AST, aspartate aminotransferase; bd, twice daily; MedDRA, Medical Dictionary for Regulatory Activities; TPC, treatment of physician choice

Robson, et al. ASCO 2017; N Engl J Med 2017;377:523

FINAL OVERALL SURVIVAL

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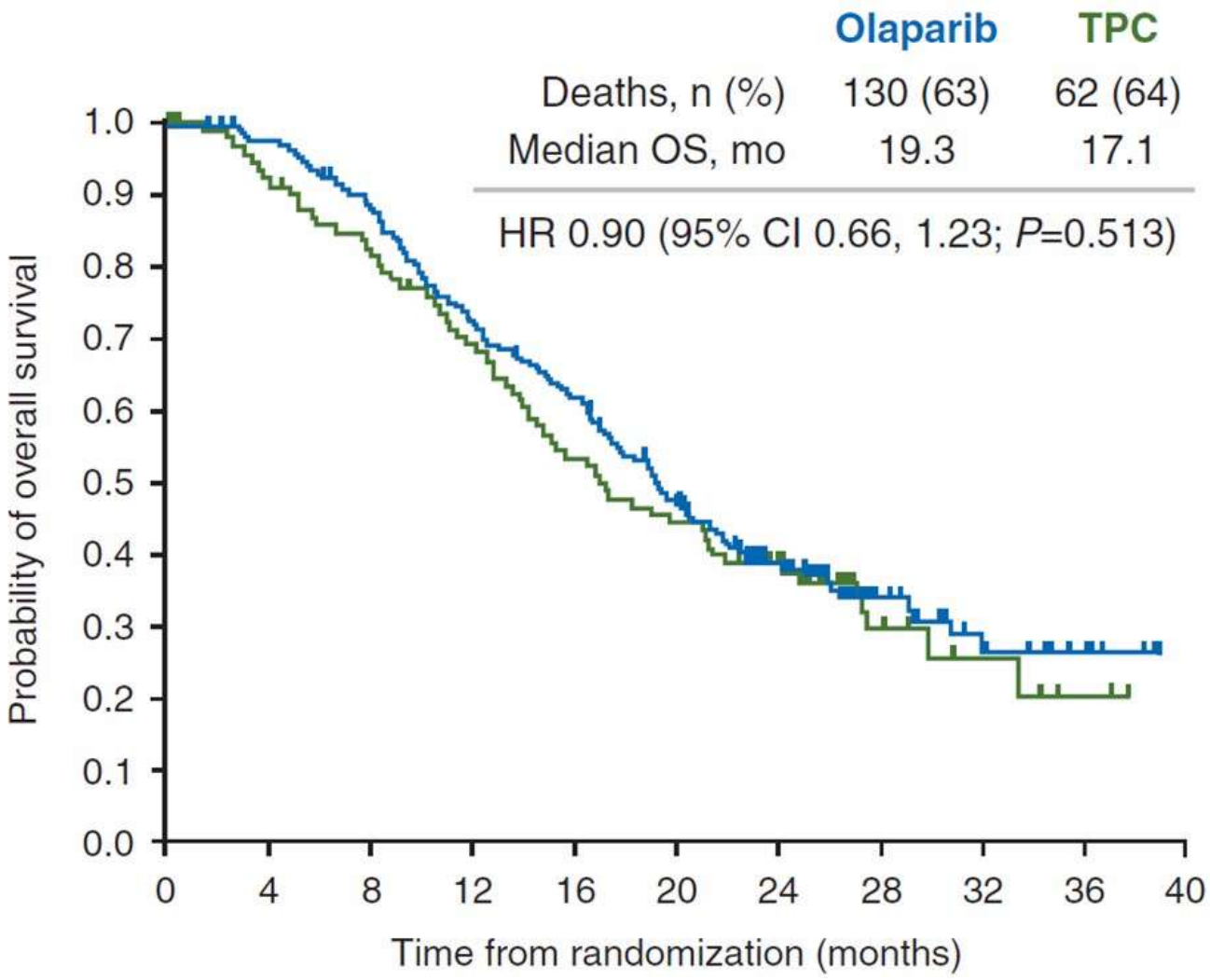

CI, confidence interval; HR, hazard ratio; OS, overall survival; TPC, treatment of physician choice

Robson, et al. Annals of Oncology 2019;30:558–66

FINAL OVERALL SURVIVAL

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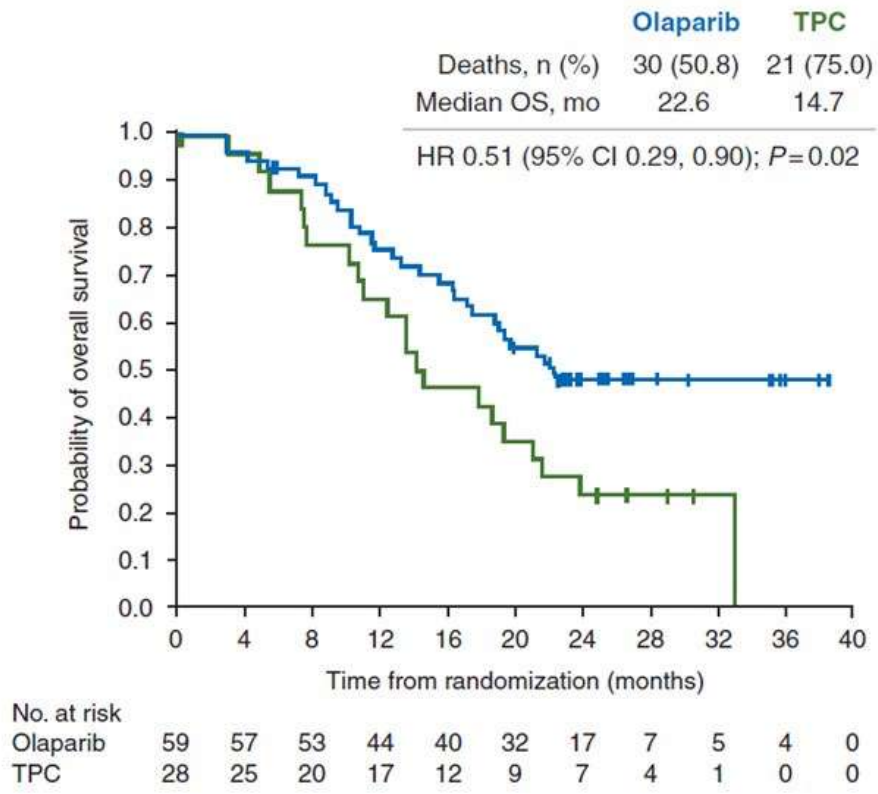
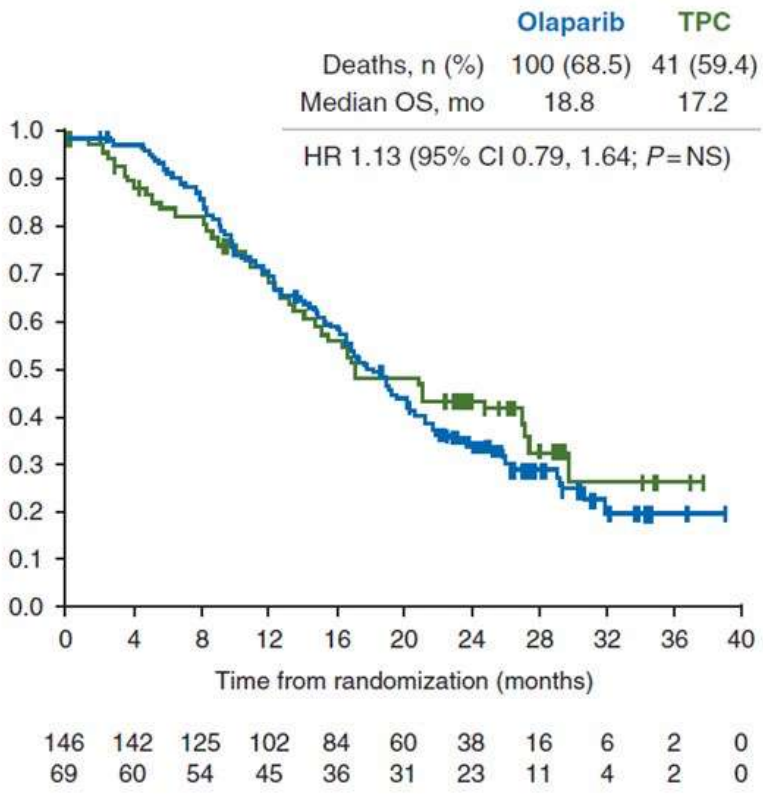
No prior chemotherapy for mBC



Prior chemotherapy for mBC



CI, confidence interval; HR, hazard ratio; mBC, metastatic breast cancer; NS, not significant; OS, overall survival; TPC, treatment of physician choice

Robson, et al. Annals of Oncology 2019;30:558–66

OLYMPIAD: CONCLUSIONS

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Olaparib tablet monotherapy provided a statistically significant and clinically meaningful **PFS benefit** versus standard-of-care chemotherapy for patients with **HER2-negative g*BRCA*m metastatic breast cancer**

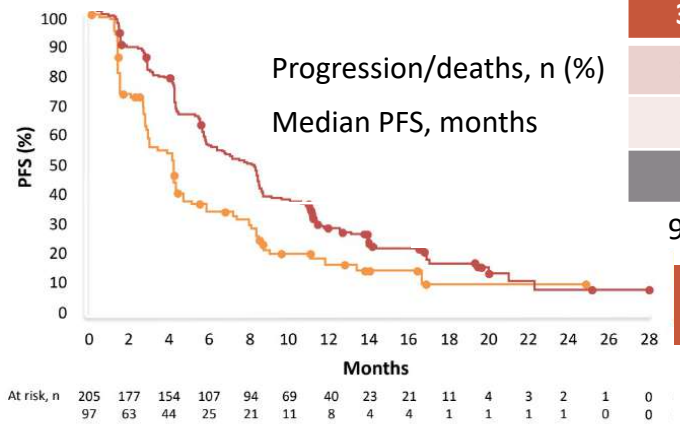
Olaparib was **generally well tolerated** with <5% discontinuing treatment for toxicity and lower rate of grade ≥3 AEs compared with chemotherapy

OlympiAD is the **first phase 3 study** in metastatic breast cancer patients **demonstrating benefit for a PARP inhibitor** over an active comparator

AE, adverse event; gBRCAm, germline breast cancer susceptibility gene mutated; HER2, human epidermal growth factor receptor 2; PARP, poly-ADP ribose polymerase; PFS, progression-free survival

Robson, et al. ASCO 2017; N Engl J Med 2017;377:523

OlympiAD

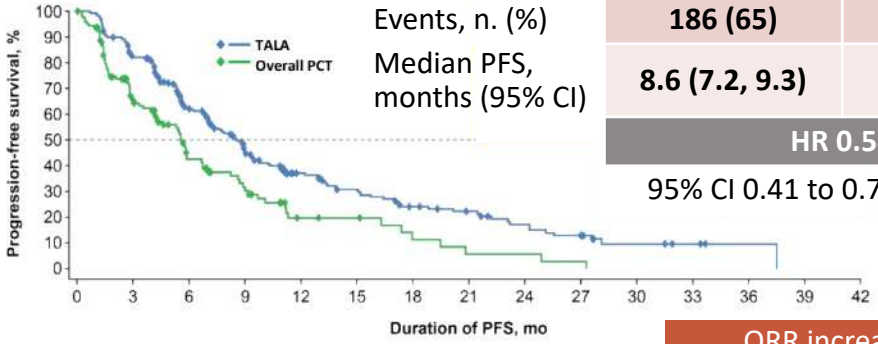


	Olaparib 300 mg bd	Chemotherapy TPC
Progression/deaths, n (%)	163 (79.5)	71 (73.2)
Median PFS, months	7.0	4.2
HR 0.58		

95% CI 0.43 to 0.80; *P*=0.0009

ORR increased from 29 to 60%

EMBRACA



	TALA (n=287)	Overall PCT (n=144)
Events, n. (%)	186 (65)	83 (58)
Median PFS, months (95% CI)	8.6 (7.2, 9.3)	5.6 (4.2, 6.7)
HR 0.54		

95% CI 0.41 to 0.71; *P*<0.0001

ORR increased from 27.2 to 62.6%

Toxicity

- Similar including nausea, anaemia

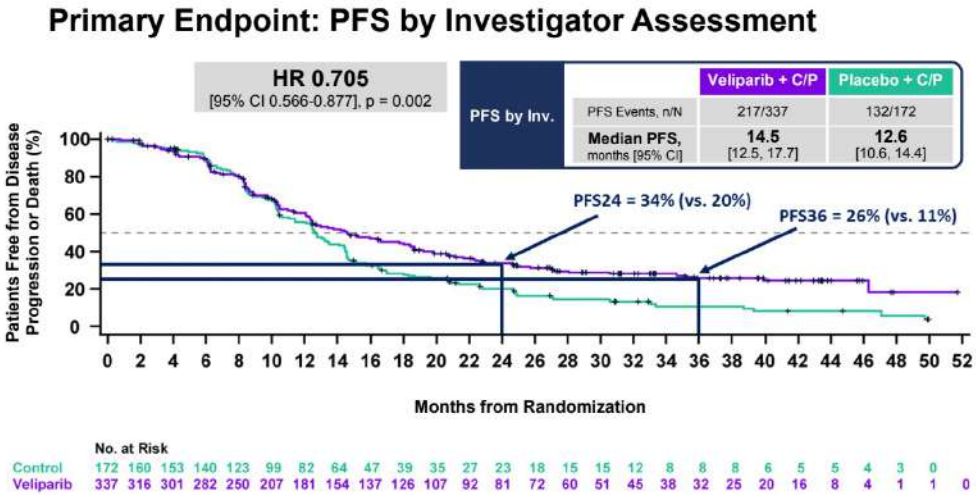
Overall survival

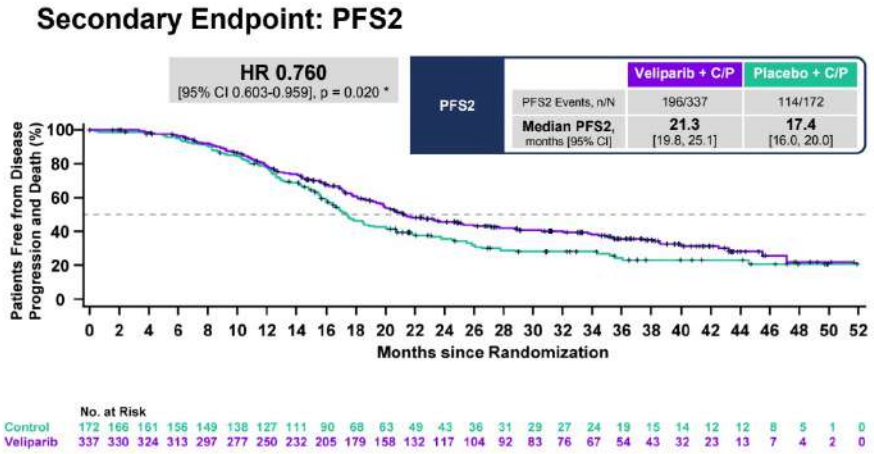
- OlympiAD:
  - No difference in ITT
  - Apparent improvement in first-line
- EMBRACA:
  - Not yet mature

bd, twice daily; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; ORR, objective response rate; PCT, physician's choice of therapy; PFS, progression-free survival; TALA, talazoparib; TPC, treatment of physician choice

BROCADE3 IN *BRCA*mut

VELIPARIB/CARBO/PACLITAXEL IMPROVES PFS VS CARBO/PACLITAXEL





N=513, 2:1 randomisation

- **Grade ≥3 toxicity**
  - Thrombocytopenia (40% vs 28%)
  - No change in neutropenia (80-81%), anaemia (40-42%)
- First phase 3 trial to evaluate the addition of PARPi to platinum-based chemotherapy in patients with mBC and g*BRCA* mutations
- **44% cross over** with PD from placebo to veliparib
  - OS endpoint challenging

BRCAmut, breast cancer susceptibility gene mutated; CI, confidence interval; C/P, carboplatin and paclitaxel; gBRCA, germline BRCA; HR, hazard ratio; mBC, metastatic breast cancer; N, number; OS, overall survival; PARPi, poly-ADP ribose polymerase inhibitor; PD, progressive disease; PFS, progression-free survival

Dieras, et al. ESMO 2019

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2019
Invasive Breast Cancer

RECURRENT/STAGE IV (M1) DISEASE

CLINICAL STAGE	WORKUP[a]
Recurrent or Stage IV (M1) →	• History and physical exam • Discuss goals of therapy, adopt shared decision-making, and document course of care • CBC • Comprehensive metabolic panel, including liver function tests and alkaline phosphatase • Chest diagnostic CT with contrast • Abdominal ± pelvic diagnostic CT with contrast or MRI with contrast • Brain MRI with contrast if suspicious CNS symptoms • Spine MRI with contrast if back pain or symptoms of cord compression • Bone scan or sodium fluoride PET/CT[j] (category 2B) • FDG PET/CT[l,yy] (optional) • X-rays of symptomatic bones and long and weight-bearing bones abnormal on bone scan • First recurrence of disease should be biopsied • Determination of tumor ER/PR and HER2 status on metastatic site[d,zz,aaa] • Assess for *PIK3CA* mutation with tumor or liquid biopsy if HR-positive/HER2-negative and if considering therapy with alpelisib[bbb] • For patients with HER2-negative tumors under consideration for chemotherapy, strongly consider germline BRCA1/2 testing. • For triple-negative breast cancer (TNBC), assess PD-L1 biomaker status on tumor-infiltrating immune cells to identify patients most likely to benefit from atezolizumab plus albumin-bound paclitaxel • Genetic counseling if patient is at risk[e] for hereditary breast cancer

BRCA1/2, breast cancer type 1/2 susceptibility gene; CBC, complete blood count; CNS, central nervous system; CT, computed tomography; ER, estrogen receptor; FDG, fluorodeoxyglucose; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MRI, magnetic resonance imaging; PD-L1, programmed death-ligand 1; PET, positron emission tomography; PR, progesterone receptor

INTERNATIONAL CONSENSUS CONFERENCE FOR ADVANCED BREAST CANCER

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ABC5 | Bridging the Gap

BRCA MUTATED TNBC

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A **PARP inhibitor** (olaparib or talazoparib) **is a reasonable treatment option** for patients with **BRCA-associated triple negative or luminal** (after progression on endocrine therapy) **ABC,** previously treated with an anthracycline with/without a taxane (in the adjuvant and/or metastatic setting), since its use is associated with a PFS benefit, improvement in QoL and a favourable toxicity profile.

OS results are awaited.

It is unknown how PARP inhibitors compare with platinum compounds in this setting and their efficacy in truly platinum resistant tumours.

LoE/GoR: I/B (80%)

ABC, advanced breast cancer; BRCA, breast cancer susceptibility gene; GoR, grade of recommendations; LoE, level of evidence; OS, overall survival; PARP, poly-ADP ribose polymerase; PFS, progression-free survival; QoL, quality of life; TNBC, triple negative breast cancer

ESMO ABC4 Guidelines, Cardoso F, et al. Annals of Oncology 2018

TREATMENT CHOICE SHOULD TAKE INTO ACCOUNT AT LEAST THESE FACTORS:

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- HR & HER-2 status **and germline *BRCA* status**
- **Pi3K in HR+ and PD-L1 in TNBC, if targeted therapies are accessible**
- Previous therapies and their toxicities, disease-free interval,
- Tumour burden (defined as number and site of metastases),
- Biological age, Performance status, co-morbidities (including organ dysfunctions)
- Menopausal status (for ET)
- Need for a rapid disease/symptom control
- Socio-economic and psychological factors
- Available therapies in the patient's country
- Patient's preference

LoE/GoR: Expert opinion/A (95%)

ET, endocrine therapy; GoR, grade of recommendations; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LoE, level of evidence; PD-L1, programmed death-ligand 1; TNBC, triple negative breast cancer

GERMLINE GENETIC TESTING

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For ABC patients, results from germline genetic testing have therapeutic implications and should therefore be performed as early as possible.

Appropriate counselling should be provided, to patients and their families, if a pathogenic germline mutation is found.

LoE/GoR: I/A (88%)

ABC, advanced breast cancer; GoR, grade of recommendations; LoE, level of evidence

HEREDITARY ABC
PARPi

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For patients with a germline BRCA mutation single agent PARP inhibitor (**olaparib or talazoparib**) is a preferred treatment option for those with triple negative ABC.

LoE/GoR: I/A (78%)

In ER+ gBRCA-associated ABC, the optimal sequence between PARPi and ET with or without CDK4/6i is unknown. Given the OS benefit seen with CDK4/6i, the panel recommends their use before a PARPi.

LoE/GoR: Expert Opinion/B (78%)

Single agent PARP inhibitors (olaparib or talazoparib) are associated with a PFS benefit, improvement in QoL and a favourable toxicity profile.

Results suggest that any benefit in OS may be limited to the 1st line setting.

ABC, advanced breast cancer; BRCA, breast cancer susceptibility gene; CDK, cyclin-dependent kinase; ER, estrogen receptor; ET, endocrine therapy; gBRCA, germline BRCA; GoR, grade of recommendations; LoE, level of evidence; MCBS, magnitude of clinical benefit; OS, overall survival; PARP, poly-ADP ribose polymerase; PARPi, PARP inhibitor; PFS, progression-free survival; QoL, quality of life

MCBS: 4

HEREDITARY ABC
PARPi

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It is unknown how PARP inhibitors (olaparib or talazoparib) compare with platinum compounds in this setting, the optimal use with platinum (combined or sequential), and their efficacy in tumours progressing after platinum.

More research is needed to answer questions related to treatment sequencing.

LoE/GoR: Expert Opinion/NA (90%)

ABC, advanced breast cancer; GoR, grade of recommendations; LoE, level of evidence; NA, not applicable; PARP, poly-ADP ribose polymerase; PARPi, PARP inhibitor

CURRENT STANDARD OF CARE TREATMENTS IN TNBC AND FUTURE RESPECTIVE

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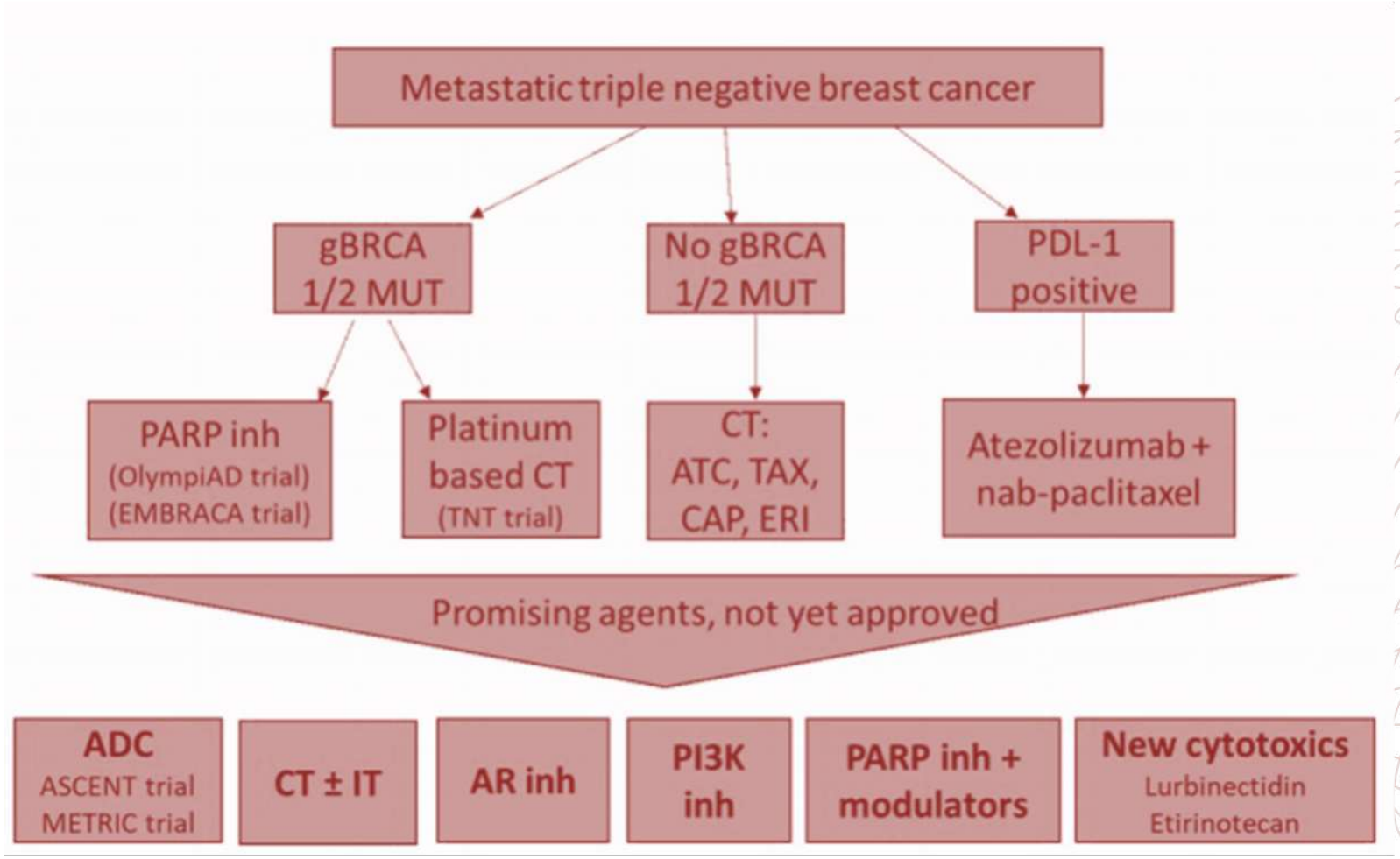

ADC, antibody drug conjugate; AR, androgen receptor; ATC, anthracycline; CAP, capecitabine; CT, chemotherapy; ERI, eribublin; gBRCA MUT, germline BRCAmutation; inh, inhibitor; IT, immunotherapy; PARP, poly (ADP-ribose) polymerase; PDL-1, programmed death ligand 1; PI3K, phosphoinositide-3 kinase; TAX, taxane; TNBC, triple negative breast cancer

Hachem GE, et al. F1000Research 2019

ONGOING CLINICAL TRIAL AS ADJUVANT THERAPY WITH OLAPARIB

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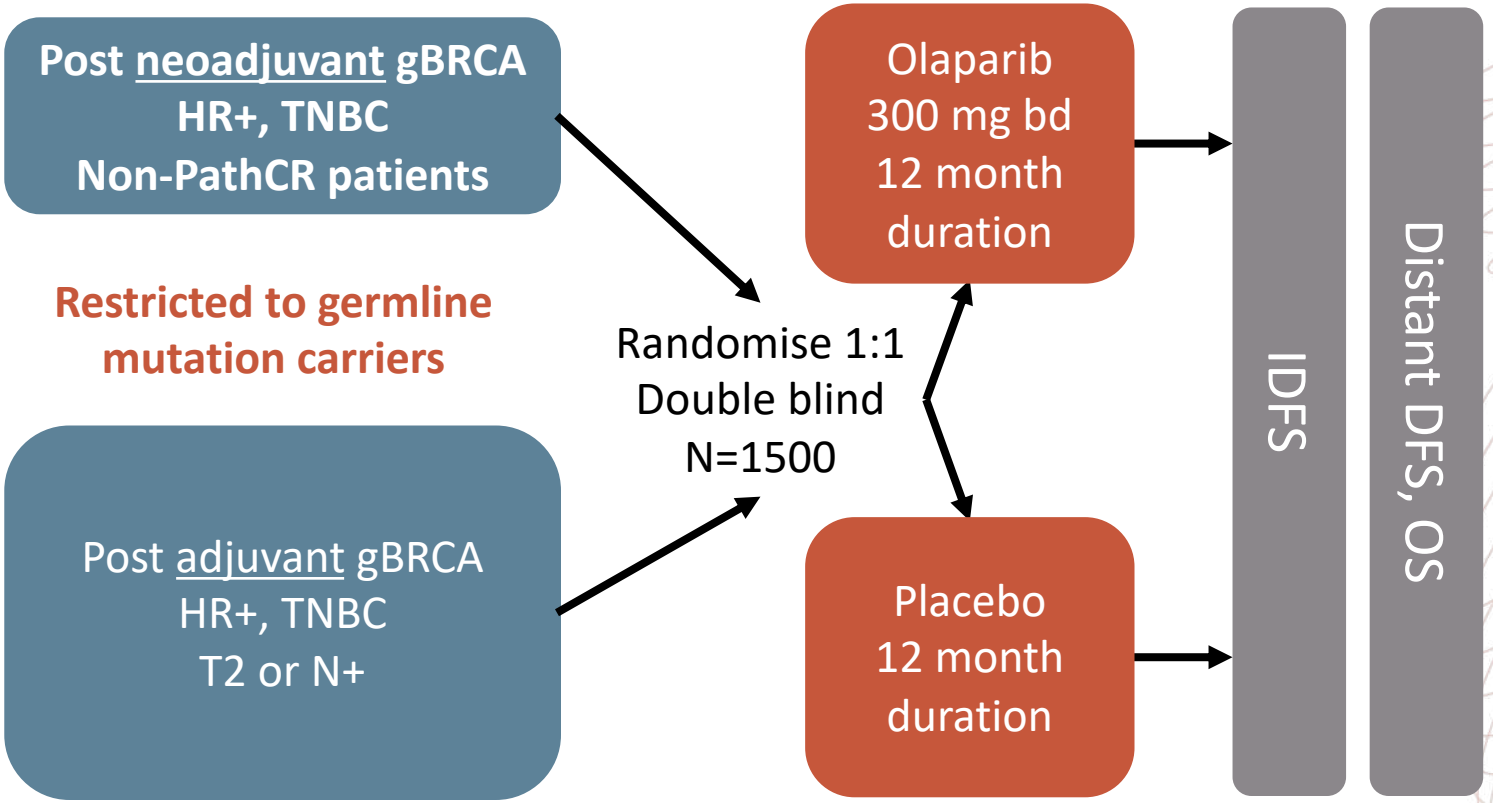

BIG Breast International Group

OlympiA
OLaparib in Adjuvant BRCAm breast cancer

frontier science

NRG ONCOLOGY
Advancing Research. Improving Lives.

gBRCA, germline breast cancer susceptibility gene mutation; DFS, disease-free survival; HR, hormone receptor; IDFS, invasive disease-free survival; OS, overall survival; PathCR, pathological complete response; TNBC, triple negative breast cancer

MECHANISMS OF RESISTANCE TO PARP INHIBITORS

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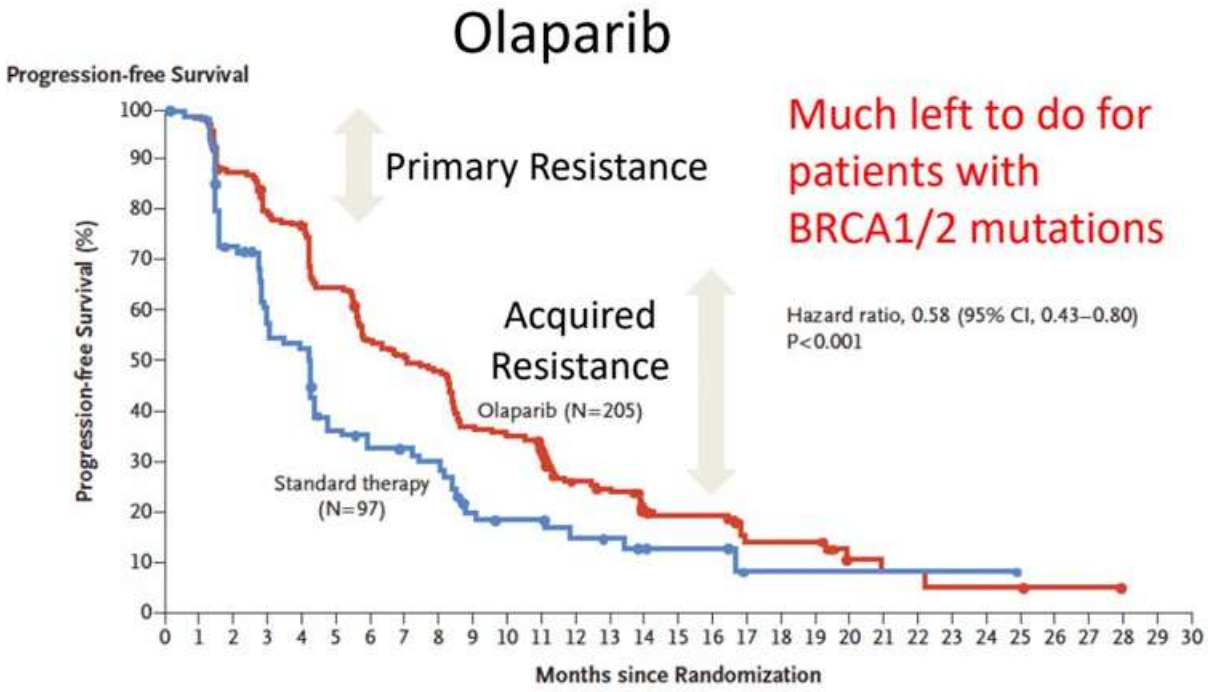
Resistance emerges rapidly in many patients with advanced HR deficient breast cancer

- BRCA1/2 deficient breast cancer
- PARP inhibitor resistance
- Selection of resistance by platinum treatment?



BRCA1/2, breast cancer type 1/2 susceptibility gene; CI, confidence interval; HR, hormone receptor; PARP, poly-ADP ribose polymerase

MECHANISMS OF RESISTANCE TO PARP INHIBITORS

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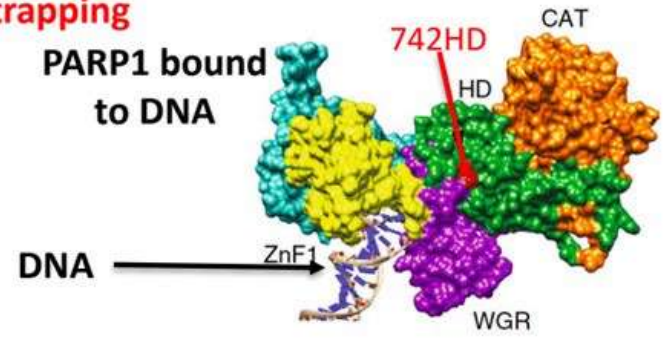
Mutations hat stop PARP1 trapping



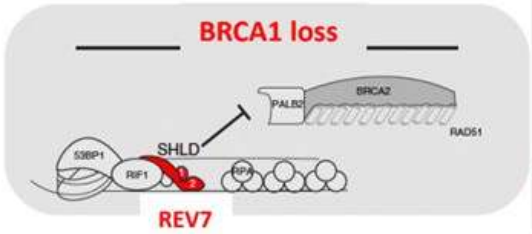
Pettitt ...Lord Nature Comms 2018

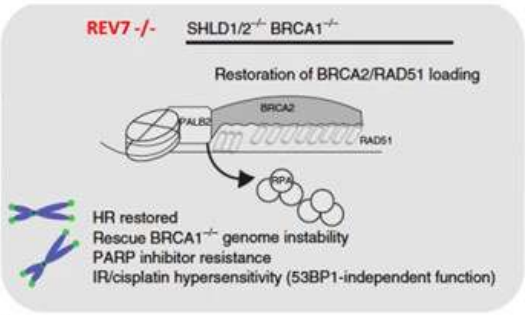
PARP1 DNA binding mutation

PARPi resistance

Retain HRD & Platinum sensitivity

Loss of REV7 and Shieldins re-enable HR and PARPi resistance



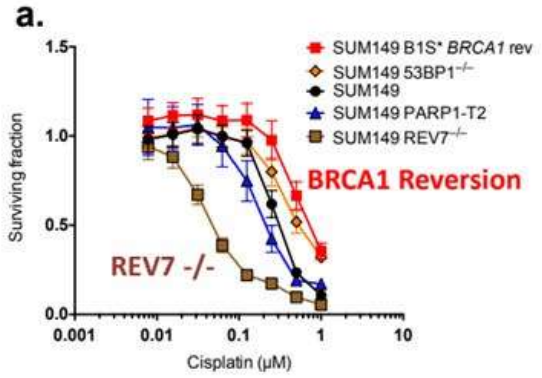


Noordermeer et al Nature 2018
Dev et al Nature Cell Biology 2018
Xu et al Nature 2015

REV7 / Shieldin mutation

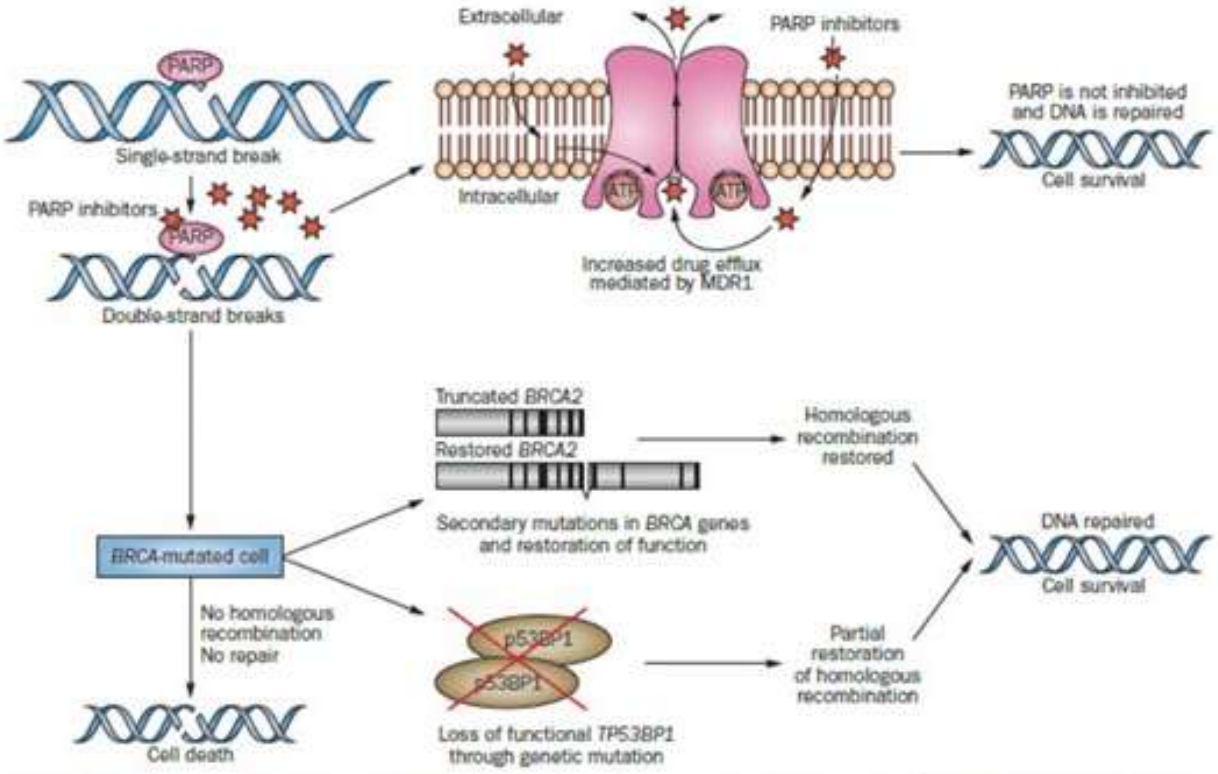
PARPi resistance

Extreme Platinum sensitivity



BRCA1, breast cancer type 1 susceptibility gene; HR, hormone receptor; HRD, homologous recombination deficiency; PARP, poly-ADP ribose polymerase; PARPi, PARP inhibitor

MECHANISMS OF RESISTANCE TO PARP INHIBITORS



- **Restoration of HR function:**
  - BRCA reversion mutations
  - Loss of TP53BP1
  - Reversal of epigenetic BRCA silencing
- **↑ P glycoprotein efflux pumps**
- **↓ levels of PARP-1 expression/activity**

BRCA, breast cancer susceptibility gene; HR, hormone receptor; HRD, homologous recombination deficiency; PARP, poly-ADP ribose polymerase; TP53BP1, tumour protein P53 binding protein 1

Sonnenblick, et al. Nat Rev Clin Onc 2015

MECHANISMS OF RESISTANCE TO PARP INHIBITORS

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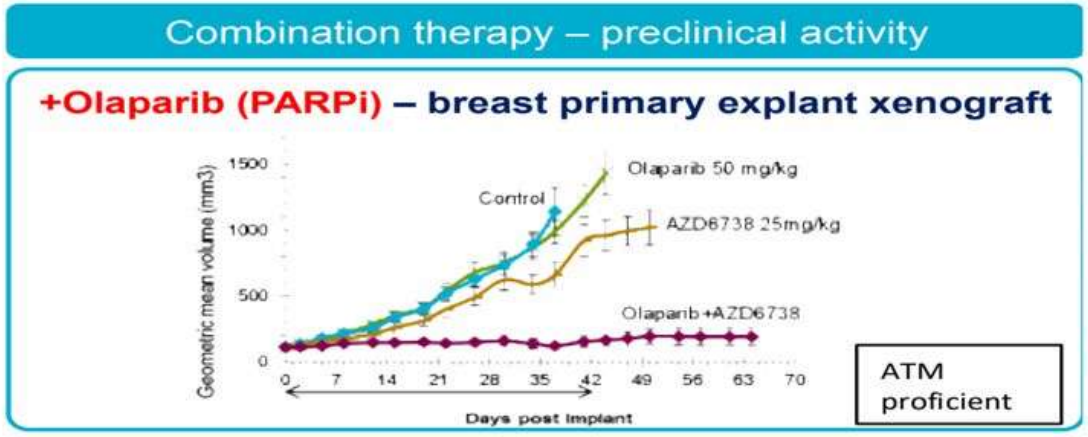
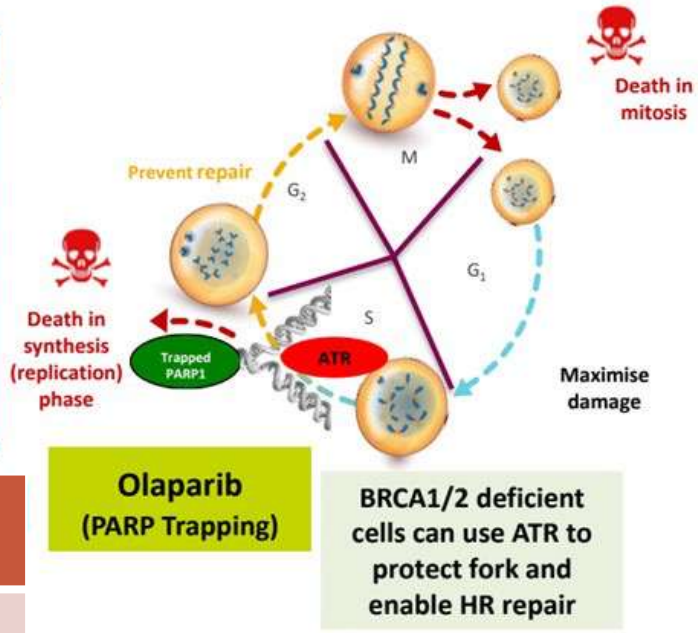


ATR enzyme (µM)	ATR cell (pCHK1??? µM)	mTOR cell (pAKT??? µM)	Pi3Ka cell (pAKT??? µM)	ATM cell (pATM??? µM)	DNAPK cell (pDNA-PK??? µM)	LoVo GI50 (µM)
0.001	0.074	>23	>30	>30	>30	0.44

Yap T, et al. Abstr AACR Mol Biomarkers Nov 2016



Yazinski, et al. Genes and Development
doi/10.1101/gad.290957.116.Nov 2016

ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related protein; BRCA1/2, breast cancer type 1/2 susceptibility gene; CHK1, checkpoint kinase 1; DNA-PK, DNA-dependent protein kinase; GI50, growth inhibition of 50%; mTOR, mechanistic target of rapamycin; p, phosphorylated; PARP, poly-ADP ribose polymerase; PARPi, PARP inhibitor

COMBINATIONS OF PARPi WITH ATRi OR WEE1i

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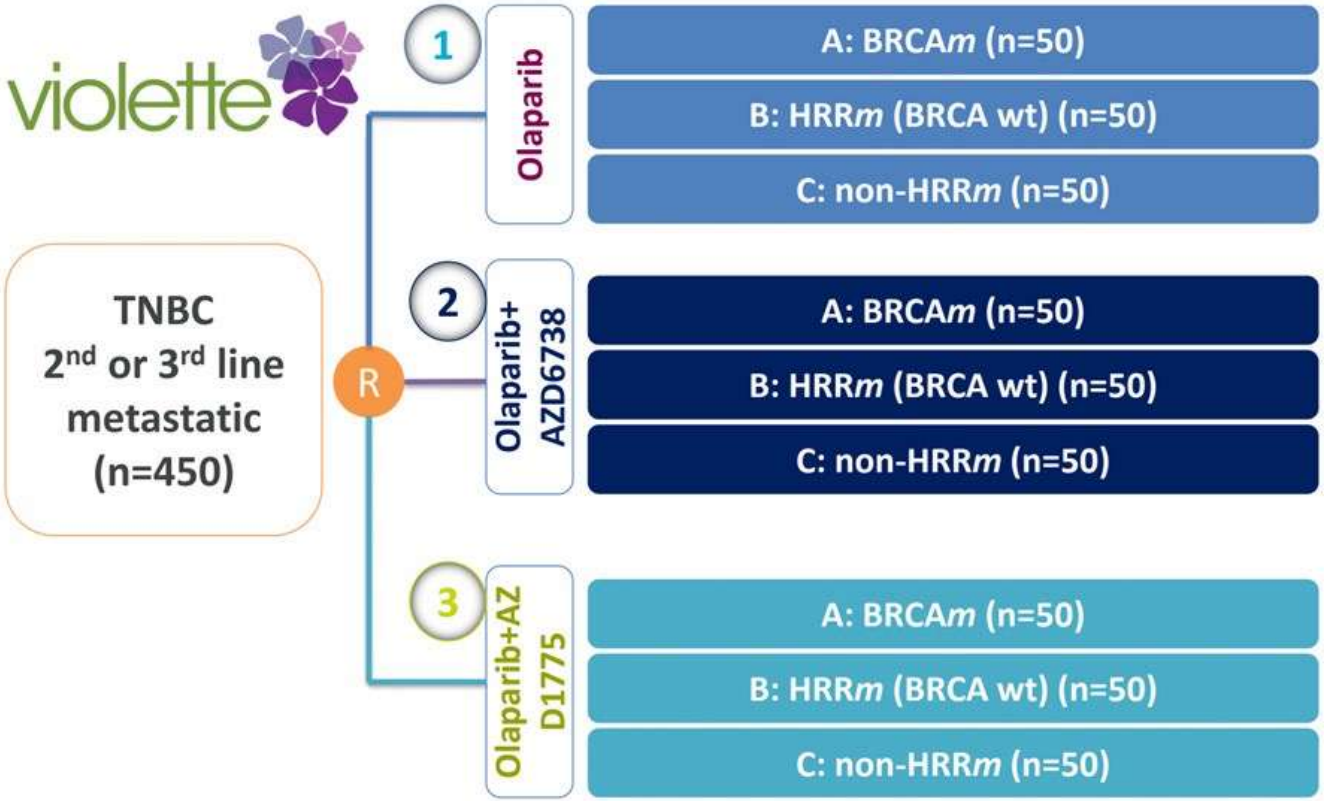

- 3 treatment arms:
- 3 prospective molecular strata
- Prospective stratification prior platinum
- Primary endpoint PFS
- Targeting improvement 6-11mths

ATRi, ataxia telangiectasia and Rad3-related protein inhibitor; BRCAm, breast cancer susceptibility gene mutated; BRCAwt, breast cancer susceptibility gene wild type; HRRm, homologous recombination repair mutation; PARPi, poly-ADP ribose polymerase inhibitor; PFS, progression-free survival; TNBC, triple negative breast cancer

COMBINATIONS OF PARPi

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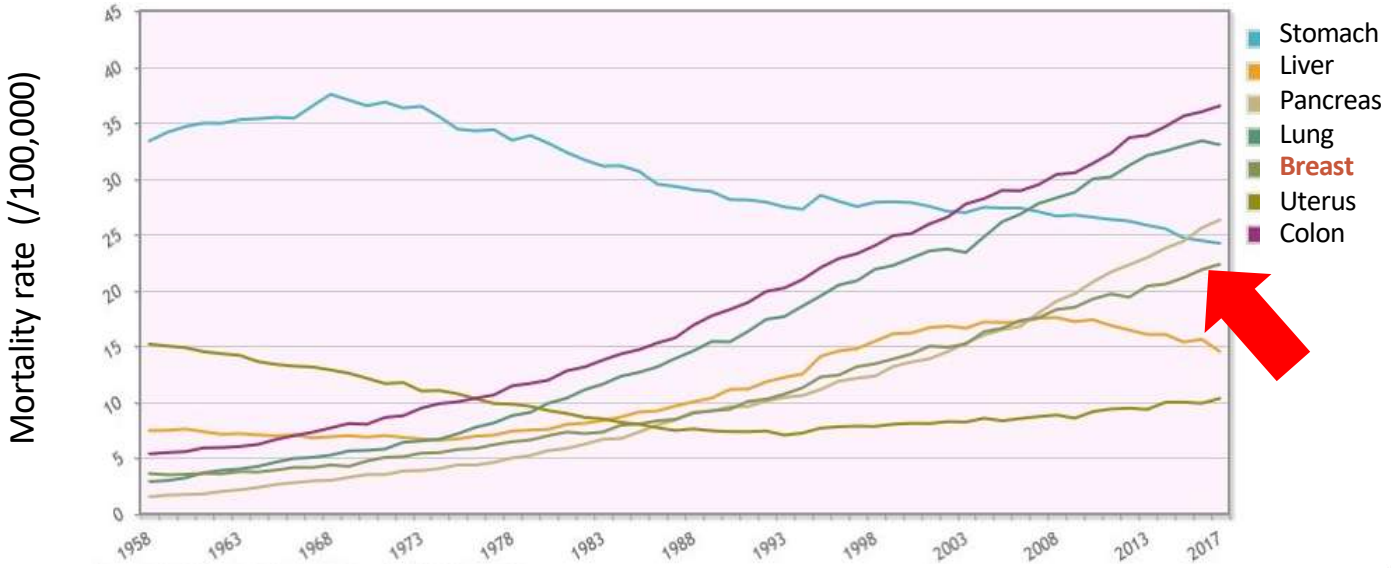
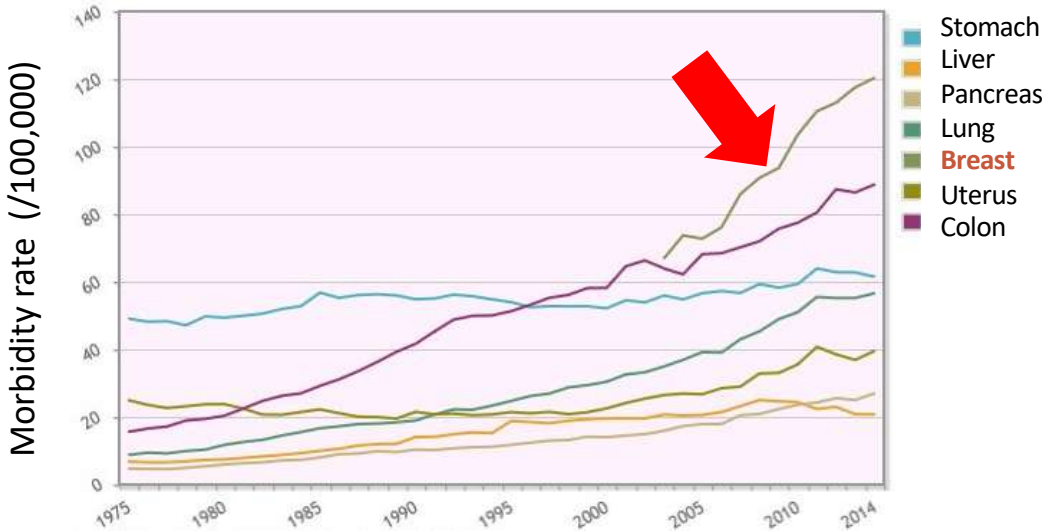
	Compounds
PARPi +	Immunotherapy Chemotherapy Radiotherapy
Novel agents +/- PARPi	ATR inhibitors, ATM, WEE1 inhibitors, PI3Ki, VEGFi, HSP90, G-quadruplex interacting compounds
Novel chemotherapeutic agents	BTP-114, a novel platinum product
Other	Lurbinectedin/Trabectedin – covalent DNA minor groove binder Sacituzumab govitecan (IMMU-132) – anti-Trop-2-SN-38 Antibody-Drug Conjugate with topoisomerase I (Topo I)-inhibitory activity

ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia and Rad3-related protein; HSP90, heat shock protein 90; PARPi, poly-ADP ribose polymerase inhibitor; VEGFi, vascular endothelial growth factor inhibitor

BREAST CANCER IN JAPAN

MORTALITY AND MORBIDITY RATES





Source: Cancer Information Services, National Cancer Center, Japan

BREAST CANCER IS THE MOST COMMON MALIGNANT DISEASE FOR WOMEN

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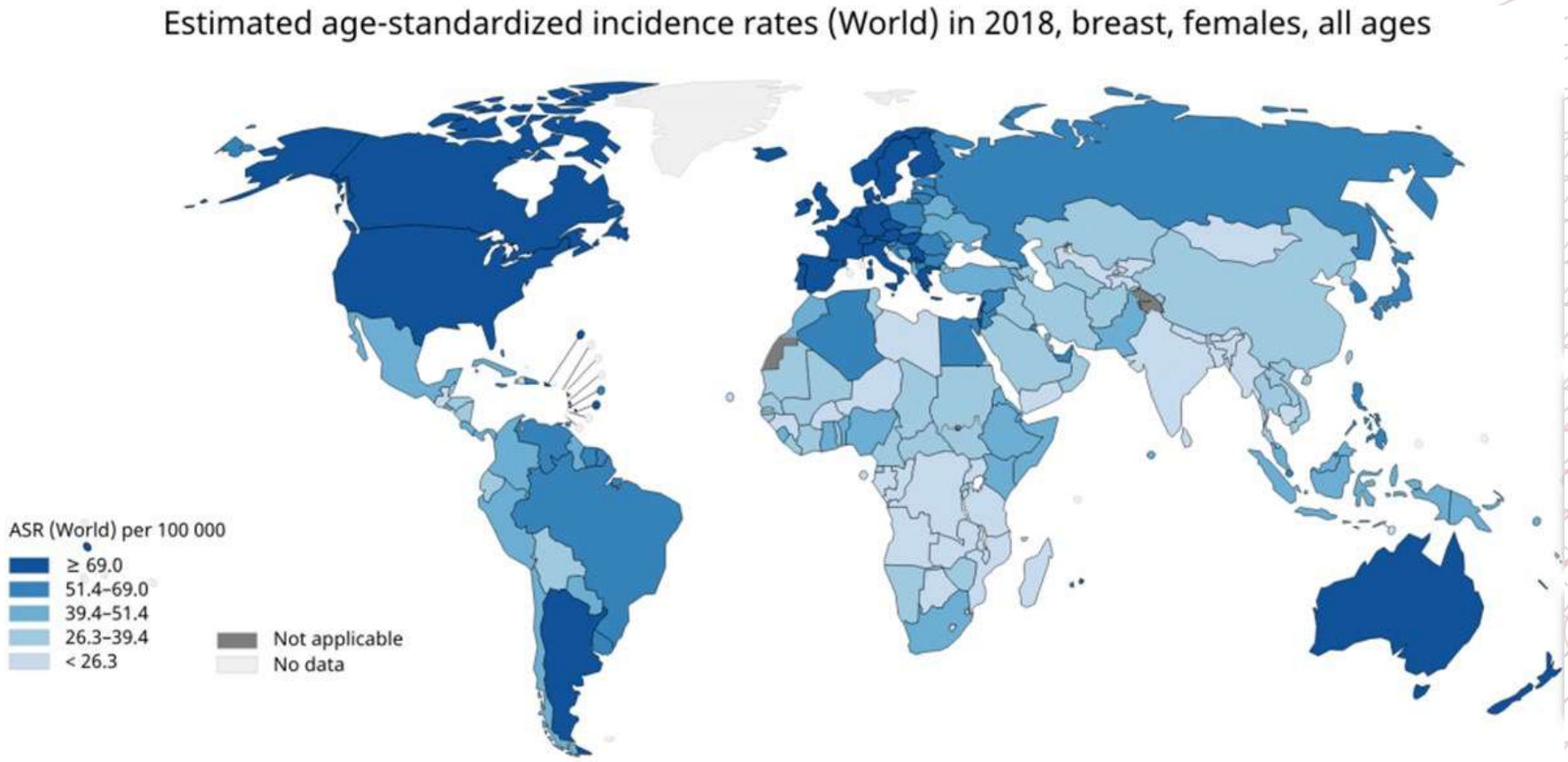

Thank you for your listening

MANAGEMENT OF PARP INHIBITOR ADVERSE EVENTS

Charlie Gourley
Professor of Medical Oncology,
University of Edinburgh

TALK SUMMARY

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- Frequency of the main adverse events from the key PARPi relapsed disease maintenance trials
- Timing of the main adverse events
- PARP inhibitor dose reductions over time in key studies
- Illustrative case presentation

PARP INHIBITOR TOXICITY PROFILE (RELAPSED DISEASE STUDIES)

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Preferred term	Percentage incidence any grade (grade 3/4)			
	Olaparib		Niraparib	Rucaparib
	Study 19[1] (400mg bd capsule)	SOLO2[2] (300mg bd tablet)	NOVA[3] (300mg od)	ARIEL2[4] (600mg bd)
Anaemia	21 (6)	44 (20)	50 (25)	36 (22)
Neutropenia	7 (4)	20 (5)	30 (20)	12 (7)
Thrombocytopenia	4 (1)	8 (0)	61 (34)	14 (2)
Nausea	71 (2)	76 (3)	74 (3)	79 (4)
Fatigue	63 (9)	66 (4)	60 (8)	78 (9)
Vomiting	35 (2)	37 (3)	34 (2)	44 (2)
Diarrhoea	27 (2)*	33 (1)		33 (3)
Dysgeusia		27 (0)	10 (0)	43 (0)
Headache		25 (1)	26 (0)	17 (0)
Decreased appetite		22 (11)	25 (0)	41 (2)
Constipation		21 (0)	40 (1)	46 (1)
Transaminitis		5		42 (12)
Hypertension			19 (8)	
Hypotension				3 (1)
MDS/AML	2**	2†	1‡	

* similar incidence in control arm [24(2)]; ** incidence in control arm 1%; † incidence higher in control arm (4%); ‡ similar incidence in control arm (1%)

AML, acute myeloid leukemia; bd, twice daily; MDS, myelodysplastic syndromes

1. Gourley C, et al. ASCO 2017. Abstract #5533; 2. Pujade-Lauraine E, et al. SGO 2017; 3. Mirza MR, et al. N Engl J Med. 2016 ;375:2154-64. 4. Swisher EM, et al. Lancet Oncology 2017;18:75-87

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PARP INHIBITOR TOXICITY PROFILE (RELAPSED DISEASE STUDIES)

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Preferred term	Percentage incidence any grade (grade 3/4)			
	Olaparib		Niraparib	Rucaparib
	Study 19[1] (400mg bd capsule)	SOLO2[2] (300mg bd tablet)	NOVA[3] (300mg od)	ARIEL2[4] (600mg bd)
Anaemia	21 (6)	44 (20)	50 (25)	36 (22)
Neutropenia	7 (4)	20 (5)	30 (20)	12 (7)
Thrombocytopenia	4 (1)	8 (0)	61 (34)	14 (2)
Nausea	71 (2)	76 (3)	74 (3)	79 (4)
Fatigue	63 (9)	66 (4)	60 (8)	78 (9)
Vomiting	35 (2)	37 (3)	34 (2)	44 (2)
Diarrhoea	27 (2)*	33 (1)		33 (3)
Dysgeusia		27 (0)	10 (0)	43 (0)
Headache		25 (1)	26 (0)	17 (0)
Decreased appetite		22 (11)	25 (0)	41 (2)
Constipation		21 (0)	40 (1)	46 (1)
Transaminitis		5		42 (12)
Hypertension			19 (8)	
Hypotension				3 (1)
MDS/AML	2**	2†	1‡	

* similar incidence in control arm [24(2)]; ** incidence in control arm 1%; † incidence higher in control arm (4%); ‡ similar incidence in control arm (1%)

AML, acute myeloid leukemia; bd, twice daily; MDS, myelodysplastic syndromes

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STUDY 19:
TIME TO ONSET OF MAIN TOXICITIES

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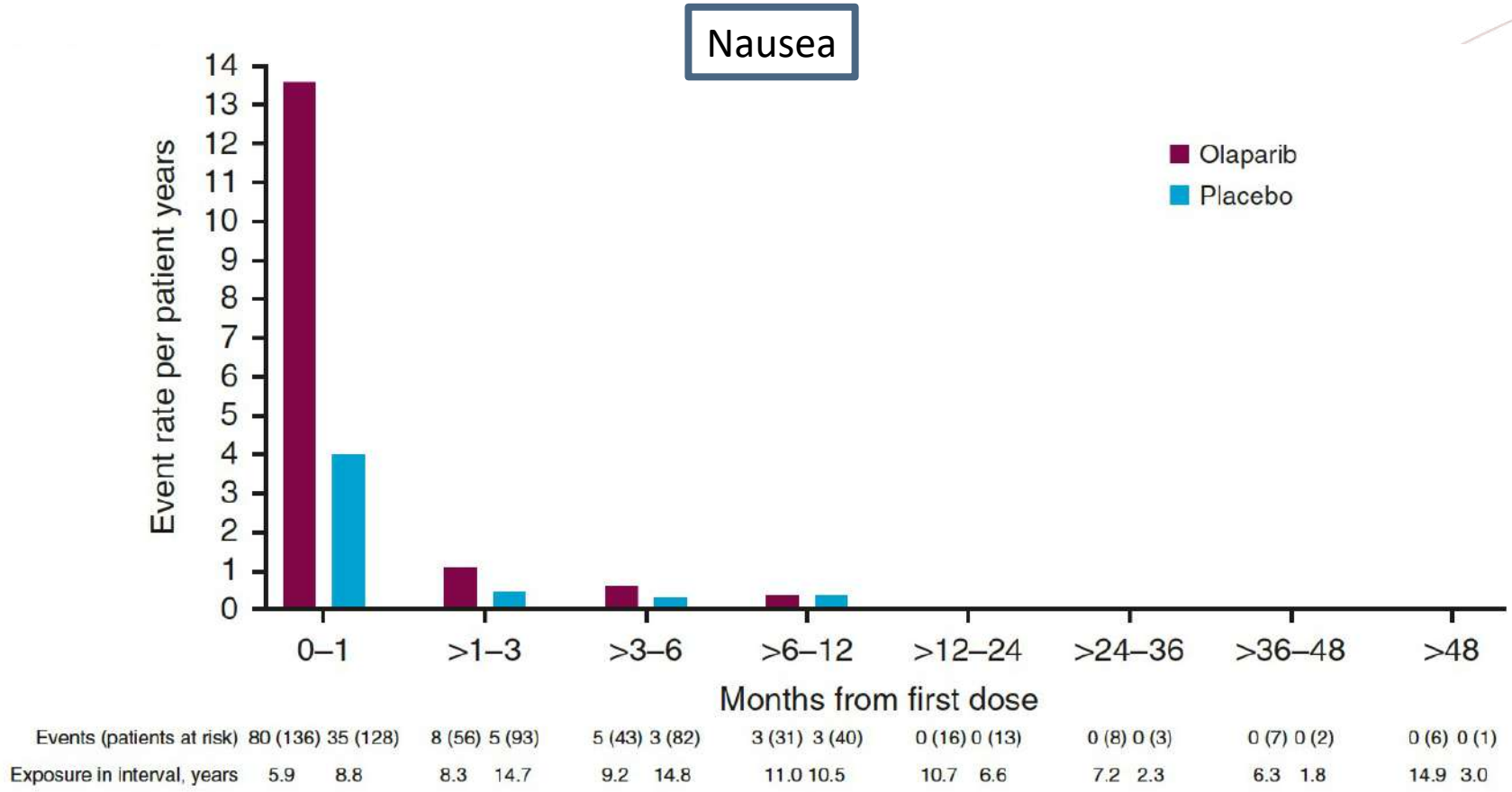

Friedlander M, et al. Br J Cancer. 2018;119:1075-85

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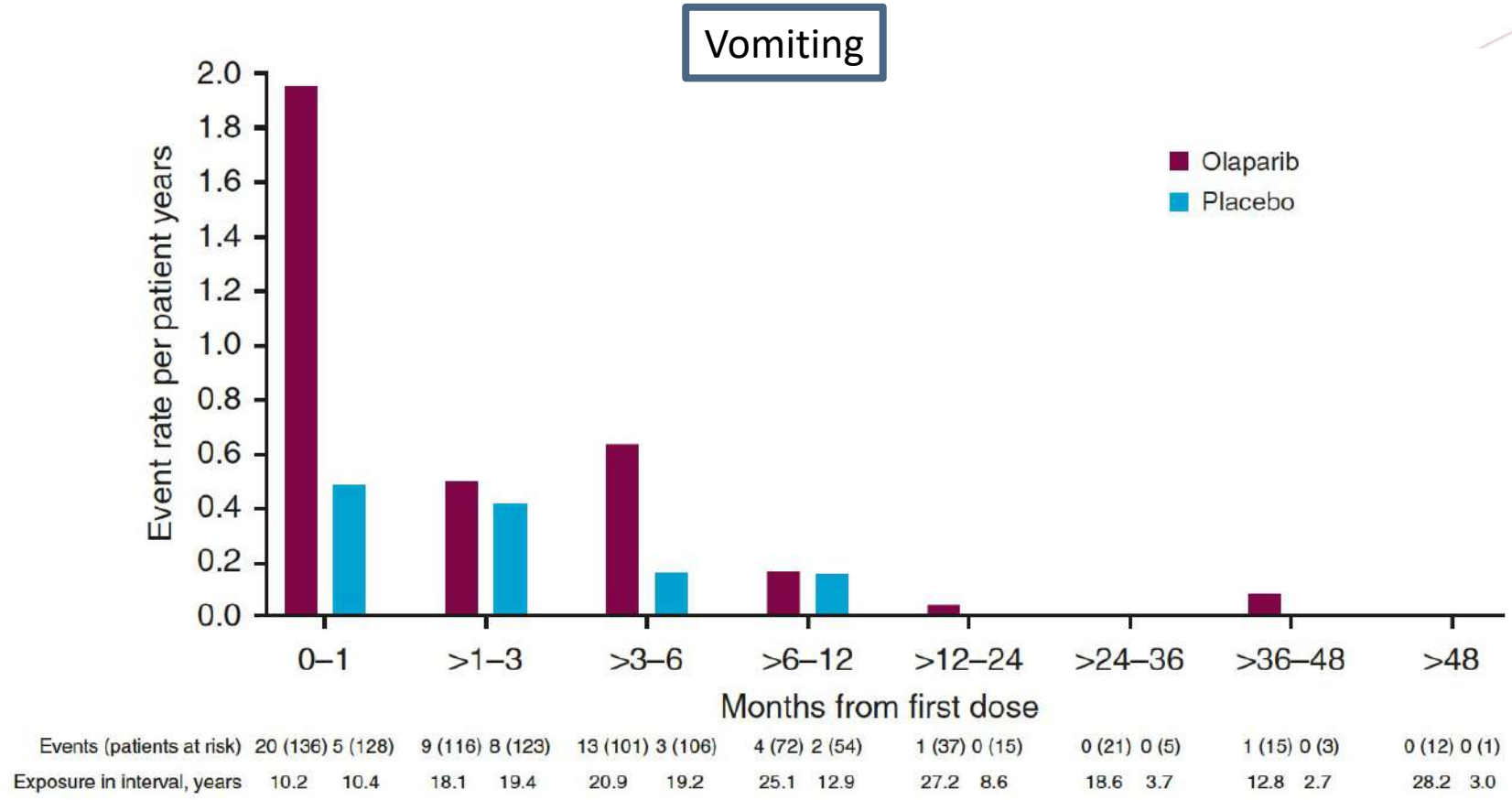

Friedlander M, et al. Br J Cancer. 2018;119:1075-85

STUDY 19:
TIME TO ONSET OF MAIN TOXICITIES

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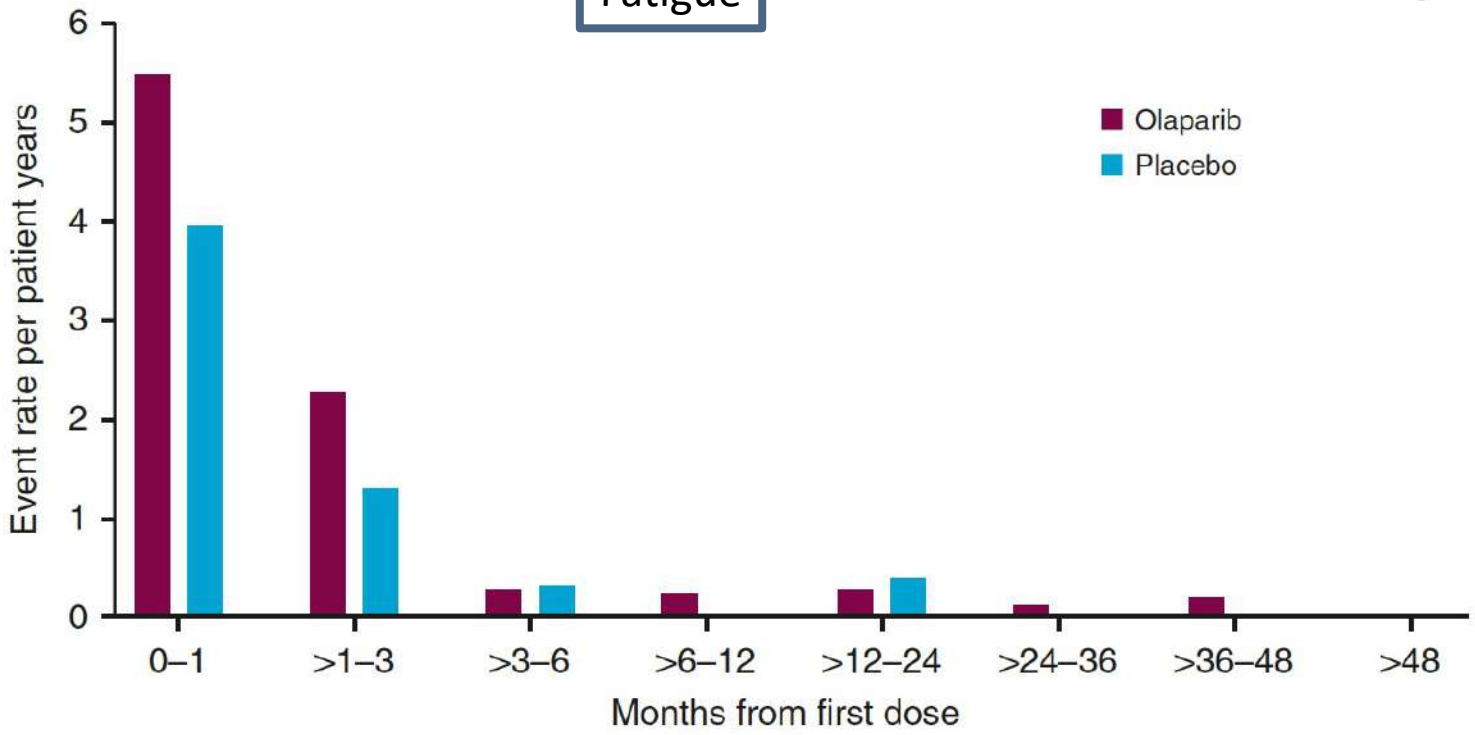
Fatigue



Events (patients at risk)	48 (136)	36 (128)	26 (88)	17 (92)	3 (54)	4 (67)	3 (43)	0 (35)	4 (21)	2 (11)	1 (13)	0 (3)	1 (7)	0 (2)	0 (5)	0 (1)
Exposure in interval, years	8.8	9.2	11.6	13.3	11.8	12.6	14.6	9.6	15.8	5.3	9.5	2.3	5.5	2.0	11.8	3.0

Friedlander M, et al. Br J Cancer. 2018;119:1075-85

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TIME TO ONSET OF MAIN TOXICITIES

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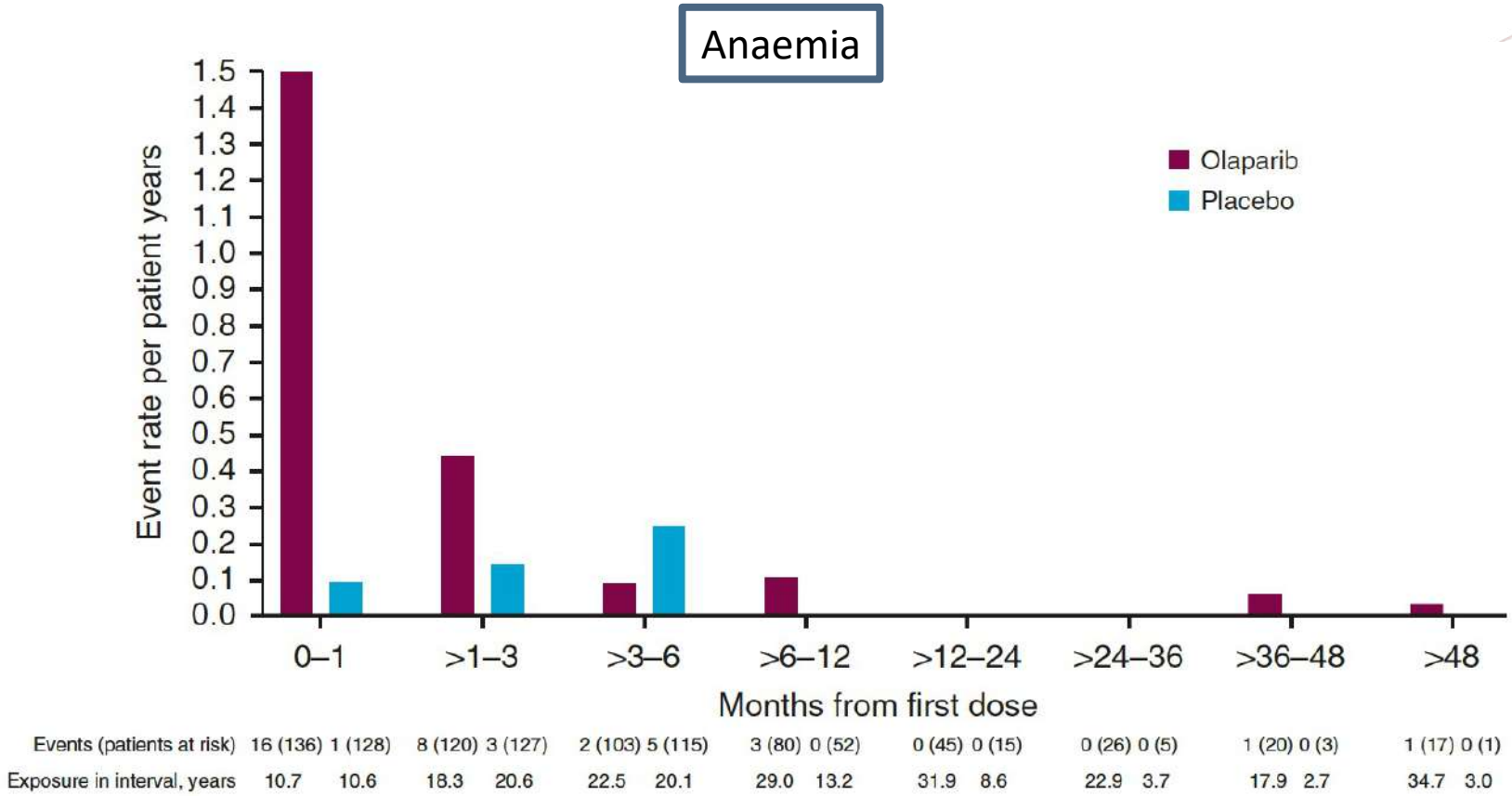

Friedlander M, et al. Br J Cancer. 2018;119:1075-85

PREVALENCE OF MAIN TOXICITIES

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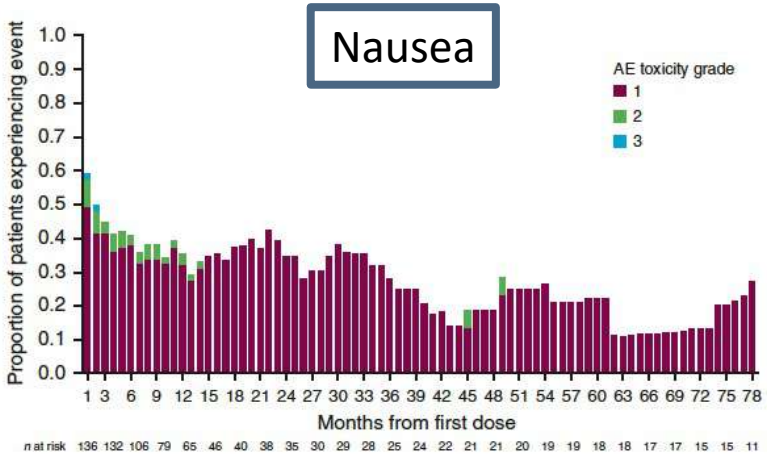
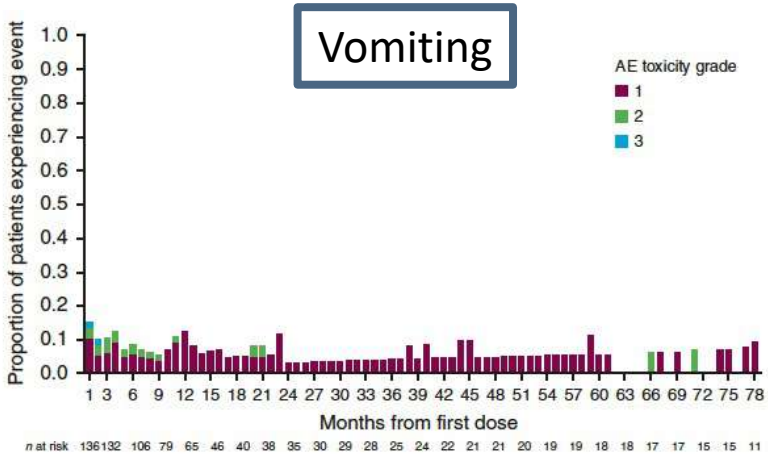
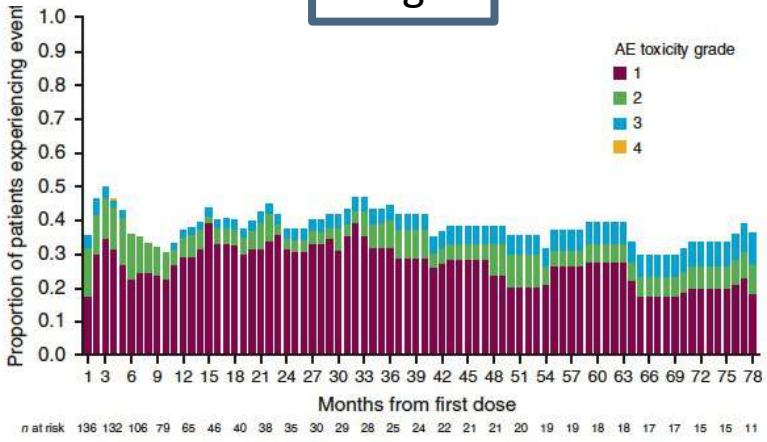
Nausea



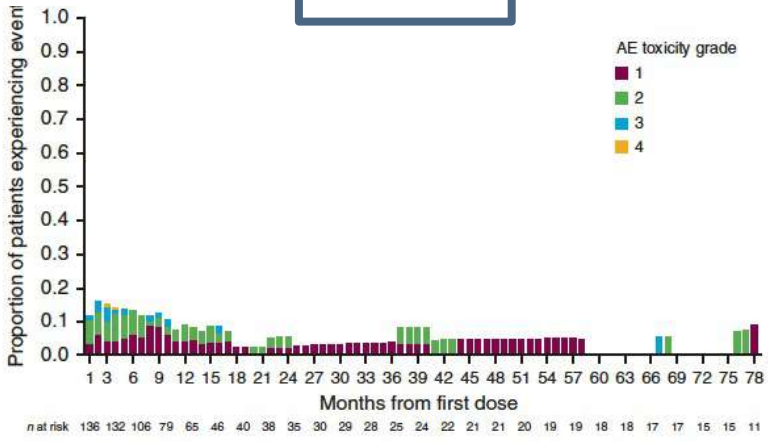
Vomiting



Fatigue



Anaemia



Friedlander M, et al. Br J Cancer. 2018;119:1075-85

SOLO1: MANAGEMENT AND OUTCOME OF THE MOST COMMONLY REPORTED NON-HEMATOLOGIC ADVERSE EVENTS*

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Non-hematologic adverse events	Nausea		Fatigue/asthenia‡		Vomiting	
	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
Patients with events (all grades), n (%)	201 (77)	49 (38)	165 (63)	54 (42)	104 (40)	19 (15)
Management, n (%)†						
Supportive treatment	117 (58)	15 (31)	11 (7)	0	28 (27)	3 (16)
Dose interruption	35 (17)	0	20 (12)	1 (2)	25 (24)	3 (16)
Dose reduction	10 (5)	0	15 (9)	1 (2)	0	0
Discontinuation	6 (3)	1 (2)	6 (4)	1 (2)	2 (2)	0
Outcome, n (%)†						
Recovered/resolved	183 (91)	46 (94)	103 (62)	41 (76)	100 (96)	19 (100)
Recovered/resolved with sequelae	1 (<1)	0	1 (1)	1 (2)	1 (1)	0
Recovering/resolving	2 (1)	1 (2)	13 (8)	3 (6)	1 (1)	0
Not recovered/resolved	15 (7)	2 (4)	48 (29)	9 (17)	2 (2)	0
Patients with grade ≥3 events, n (%)	2 (1)	0	10 (4)	2 (2)	1 (<1)	1 (1)

*The safety analysis set comprised 260 patients in the olaparib group and 130 in the placebo group; †Percentages were calculated from the number of patients with that event; ‡Grouped-term events.

Colombo N, et al. ASCO 2019. Abstract #5539

SOLO1: MANAGEMENT AND OUTCOME OF THE MOST COMMONLY REPORTED HEMATOLOGIC ADVERSE EVENTS*

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Hematologic AEs	Anemia‡		Neutropenia‡		Thrombocytopenia‡	
	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
Patients with events (all grades), n (%)	101 (39)	13 (10)	60 (23)	15 (12)	29 (11)	5 (4)
Management, n (%)†						
Supportive treatment	72 (71)	4 (31)	11 (18)	2 (13)	2 (7)	1 (20)
Dose interruption	58 (57)	1 (8)	30 (50)	5 (33)	6 (21)	0
Dose reduction	44 (44)	1 (8)	10 (17)	1 (7)	4 (14)	0
Discontinuation	6 (6)	0	1 (2)	0	1 (3)	0
Outcome, n (%)†						
Recovered/resolved	84 (83)	11 (85)	53 (88)	14 (93)	21 (72)	4 (80)
Recovered/resolved with sequelae	2 (2)	0	0	0	2 (7)	0
Recovering/resolving	5 (5)	0	1 (2)	0	0	0
Not recovered/resolved	10 (10)	2 (15)	6 (10)	1 (7)	6 (21)	1 (20)
Patients with grade ≥3 events, n (%)	56 (22)	2 (2)	22 (9)	6 (5)	2 (1)	2 (2)

*The safety analysis set comprised 260 patients in the olaparib group and 130 in the placebo group; †Percentages were calculated from the number of patients with that event; ‡Grouped-term events.

Colombo N, et al. ASCO 2019. Abstract #5539

SOLO1: OLAPARIB DOSE REDUCTIONS OVER TIME

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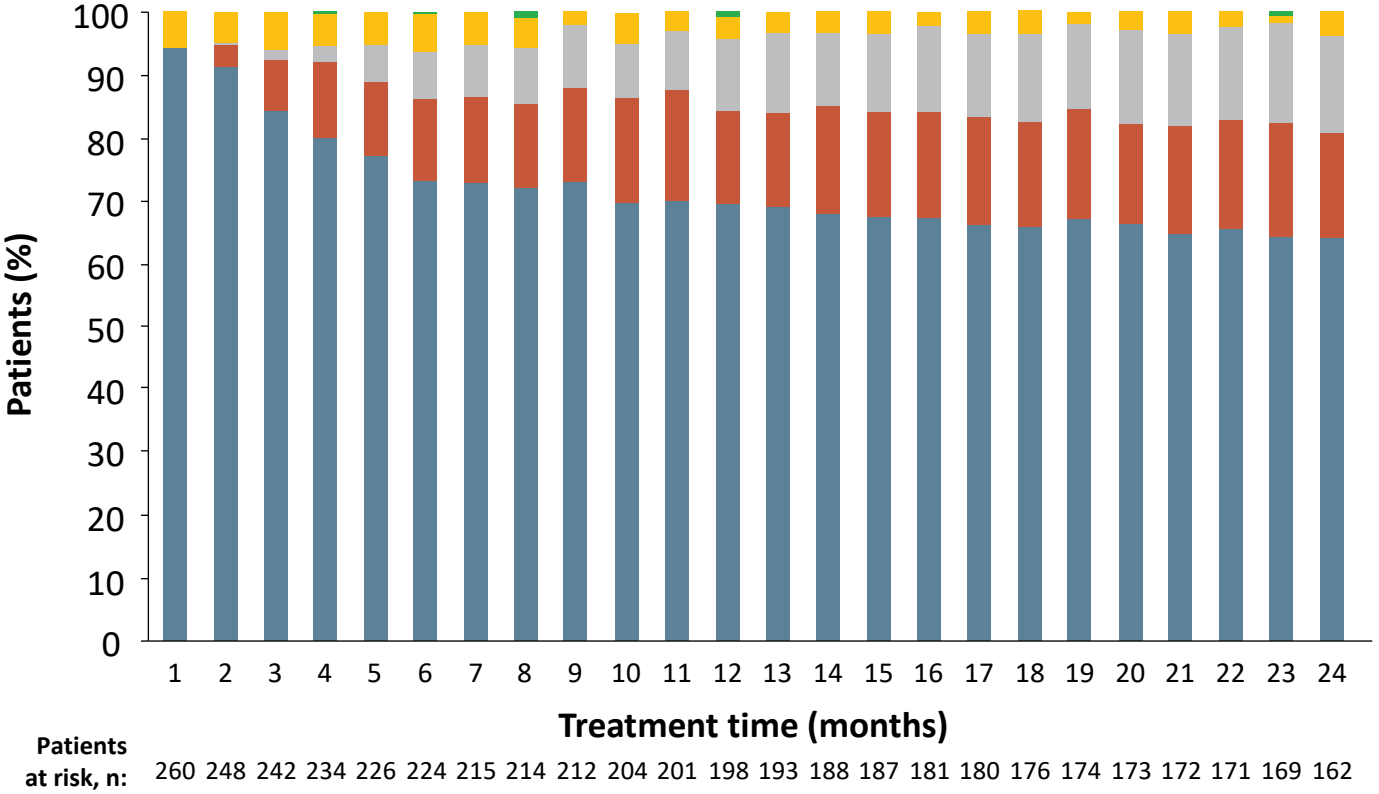

Number of patients treated at the start of each month.

*'Other regimen' includes 150 mg qd, 150 mg bid, 200 mg qd, 250 mg qd, 300 mg qd, and 450 mg bid;

†The category of 'no dosing' was assigned if the patient had dosing interrupted for the entire month window.

bid, twice daily; qd, once daily

Colombo N, et al. ASCO 2019. Abstract #5539

NOVA: MYELOSUPPRESSION ACCORDING TO NIRAPARIB DOSE

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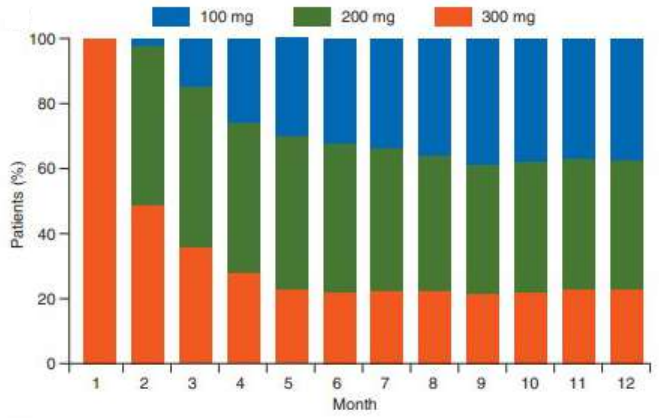
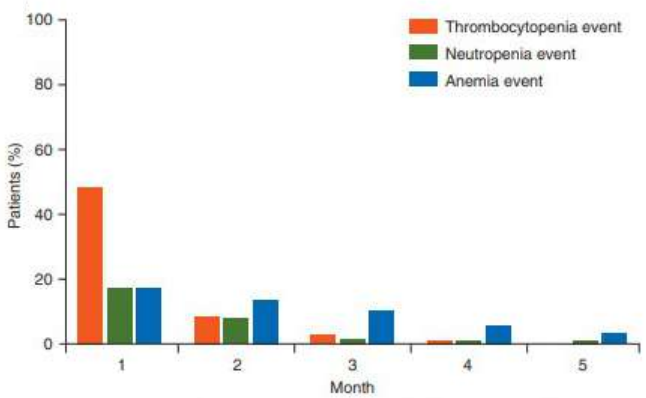
Niraparib dose by month



- Grade ≥3 within first 3 months:
  - Thrombocytopenia 33%
  - Neutropenia 18%
  - Anaemia 13%
- Grade ≥3 after month 3:
  - Thrombocytopenia 1%
  - Neutropenia 2%
  - Anaemia 15%

Treatment-emergent haematological adverse events (any grade)



- Patients who stayed on 300 mg after month 3 rarely experienced delayed Grade 3/4 thrombocytopenia
- Few patients discontinued due to haematological adverse events
  - Thrombocytopenia 3%
  - Neutropenia 2%
  - Anaemia 1%

Berek, JS, et al. Annals Oncol 2018;29:1784-92

CLINICAL CASE

BACKGROUND 1

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- **79-year old patient**
  - K/c/o BRCA1 mutation
  - Declined risk reducing bilateral salpingo-oophorectomy 10 years previously
- Presented in late **2013** with abdominal distension and pain
- Gross ascites
  - Large omental mass and right adnexal mass (8 cm)
- **High-grade serous cancer**
  - Biopsy: CA125 1980 U/ml

RRBSO, risk-reducing bilateral salpingo-oophorectomy
Case courtesy of Michael Friedlander

PRIMARY TREATMENT

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- Patient received 2 cycles **carboplatin and paclitaxel-CA125** and had clinical response
- **Interval debulking**
  - No residual disease
  - High grade serious cancer
- 4 additional cycles of carboplatin and paclitaxel
- Required 2 units of packed cells for symptomatic anaemia pre cycle 6

- CA125 normal at cycle 3
- CT CR completion of chemotherapy
  - CA125 4 U/mL

CR, complete response

PATIENT PUT ON SOLO 1 MAINTENANCE TRIAL

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March 2014:
Patient randomised to maintenance treatment with olaparib

PATIENT PUT ON SOLO 1 MAINTENANCE TRIAL – ON 01 MARCH 2014

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- Hb: 102 g/L CA125: 6 U/mL
- 10 March: **Hb dropped** to 98 g/L
- 28 March: **anaemic** Hb 74 g/L
  - 2 units packed cells transfused
- Restarted olaparib/placebo 300mg BD
- 23 June **anaemic** Hb 78 g/L
  - Once again, 2 units packed cells transfused
- Dose reduced to 250 mg bd

bd, twice daily; Hb, haemoglobin

TOXICITY ENCOUNTERED ON STUDY

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- **Hb stable** and patient well
- **January 2015**: **Hb 76 g/L**
  - Transfused 2 units packed cells
- Olaparib/Placebo reduced to 200 mg bid
- **March 2015**: **Hb 84 g/L**
  - 14 day-break
  - Hb came up to 101 g/L
- **March 2016**: Completed 2 years of treatment in
- **April 2016**: Hb 115 g/L

bd, twice daily; Hb, haemoglobin

HAEMOGLOBIN VALUE PROGRESSION WITH OLAPARIB DOSE

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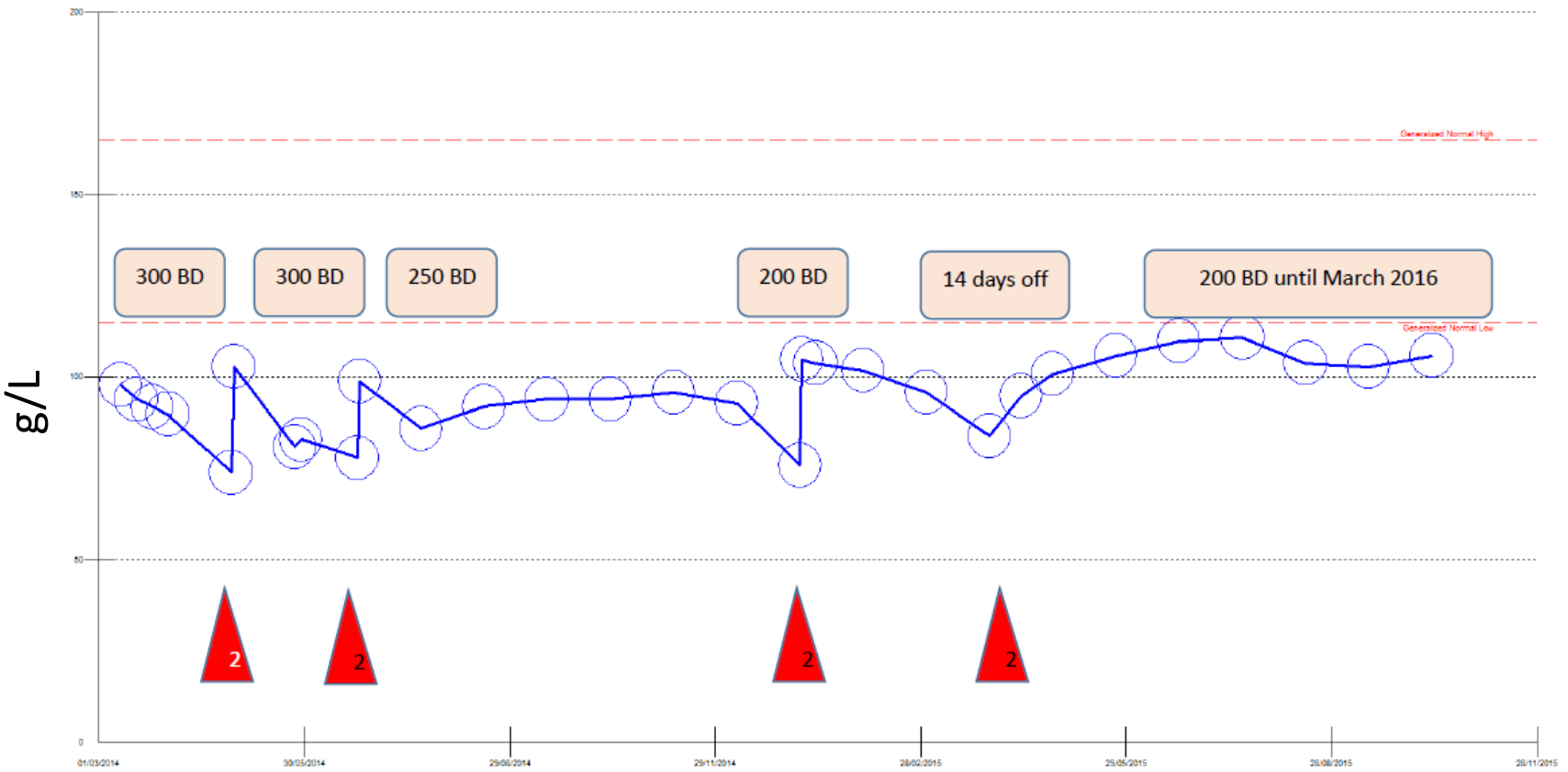

OLAPARIB ADVERSE-EVENT DOSE MODIFICATIONS FOR ANAEMIA

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- Any toxicity observed during the course of the treatment can be managed by interruption of the dose of treatment or dose reductions
- Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion (as per the SOLO1/SOLO2 trial)
- Treatment can be dose reduced to:
  - 250 mg twice daily as a first step
  - 200 mg twice daily as a second step

Initial Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300mg twice daily	250mg twice daily	200mg twice daily

SUBSEQUENT PROGRESS

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- **Remains well** – age 85
- Last review on 1 October 2019:
  - Hb: 130 g/L
  - CA125: 8 U/ml
- CT scan: normal
- Continues on surveillance **over 6 years from presentation** with stage 3c high grade serious ovarian cancer

Hb, haemoglobin

LEARNING POINTS

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Age not a barrier to treatment with maintenance olaparib

Anaemia can be managed by dose reductions, transfusions and dose delay and possible to complete treatment

WHAT IS THE MDS/AML RISK WITH PARP INHIBITORS?

MDS / AML RATES IN SOLO-1 WERE CONSISTENT WITH PRIOR STUDIES OF OLAPARIB IN OVARIAN CANCER[1-5]

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Trial, n/N (%)	AML / MDS rate in olaparib arm N	AML / MDS rate in comparator arm N	Comparator arm
SOLO-1[1,2] **Newly diagnosed OC, BRCAm**	3/260 (1.2)	0/130 (0)	Placebo
SOLO-2[3] **PSR OC, BRCAm**	4/195 (2.1)	4/99 (4)	Placebo
Study 19[4] **PSR OC**	2/136 (1.5)	1/129 (0.8)	Placebo
Ovarian Phase 3 comparative studies Combined (monotherapy)	9/591 (1.5)	5/358 (1.4)	
OlympiAD[5] **HER2- mBC, gBRCAm**	0/205 (0)	0/91 (0)	TPC – capecitabine, eribulin or vinorelbine

AML, acute myeloid leukaemia; gBRCAm, germline BRCA mutation; HER2-, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; MDS, myelodysplastic syndromes; OC, ovarian cancer; PSR, platinum-sensitive relapse

1. Moore K, et al. N Engl J Med 2018; 379:2495-2505. 2. Moore K, et al. N Engl J Med 2018; 379:2495-2505 [supplementary appendix]. 3. Gourley, C. et al. J Clin Oncol 35 (poster related to suppl; abstr 5533) (2017). 4. Pujade-Lauraine E, et al. Lancet Oncol 2017:181274-84. 5. Robson, et al. N Engl J Med 2017;377:523-33

CONCLUSION

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PARP inhibitors have a predictable side-effect profile dominated by nausea, fatigue and myelosuppression

In the vast majority of cases these can be managed by concomitant medications, dose reductions and drug holidays

Investigators must be vigilant for more severe events such as myelodysplastic syndromes, acute myeloid leukaemia or pneumonitis

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