NSGO Symposium: Ovarian Cancer Major Advances

A Decade of Maintenance therapy

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Disclosures

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PARP inhibitors……. in the beginning……..

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olaparib Maintenance Therapy in Platinum-Sensitive Relapsed Ovarian Cancer

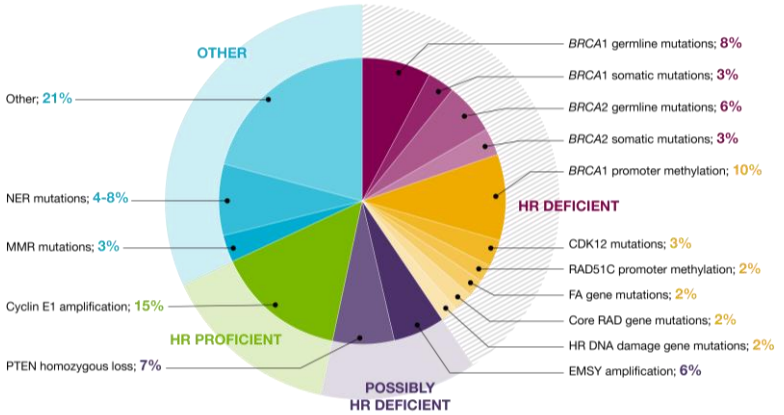
Jonathan Ledermann, M.D., Philipp Harter, M.D., Charlie Gourley, M.B., Ph.D., Michael Friedlander, M.B., Ph.D., Ignace Vergote, M.D., Ph.D., Gordon Rustin, M.D., Clare Scott, M.B., Ph.D., Werner Meier, M.D., Ph.D., Ronnie Shapira-Frommer, M.D., Tamar Safra, M.D., Daniela Matei, M.D., Euan Macpherson, M.Sc., Claire Watkins, M.A., M.Sc., James Carmichael, M.D., and Ursula Matulonis, M.D.

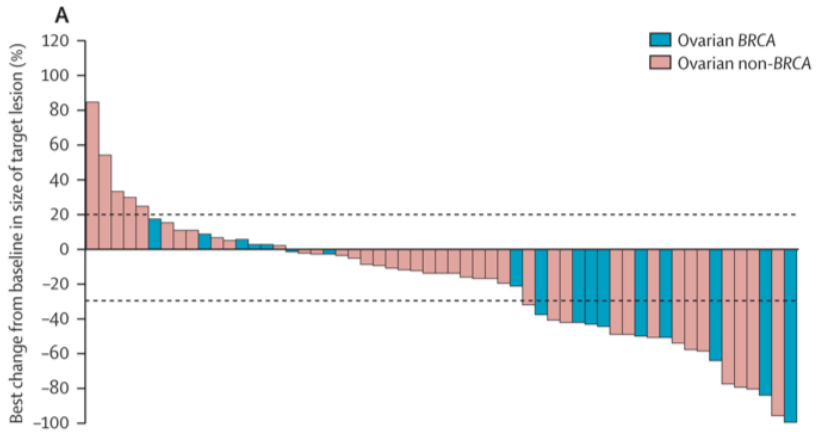
N Engl J Med 2012;366:1382–1392

How did we get there?……..

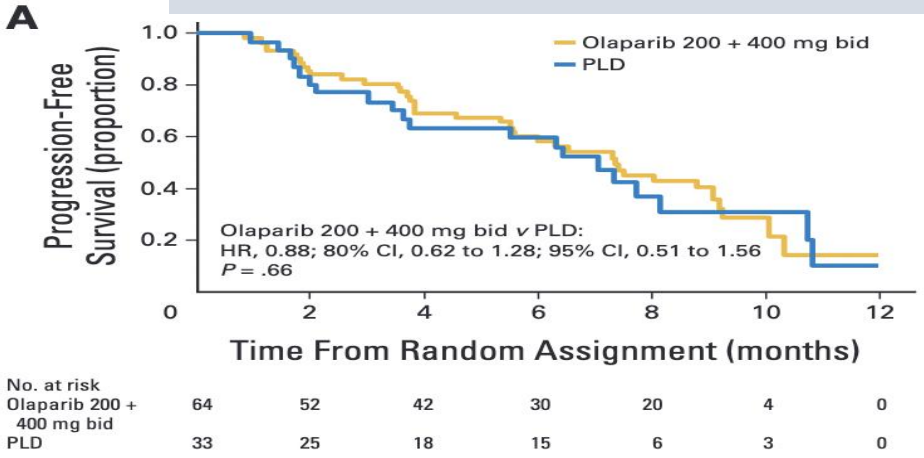
Background to Maintenance therapy

- Emerging evidence that olaparib was active beyond *BRCA*^{mut} tumours
- More active in platinum-sensitive tumours
- Compared to chemotherapy-no benefit





Study 12 – a randomised phase II trial of olaparib *versus* PLD for recurrent ovarian cancer



Maintenance hypothesis testing high grade serous ovarian cancer **following a response to platinum**

Enriched for PARP responders

Volume of disease reduced by platinum

Will it delay recurrence- improving PFS?

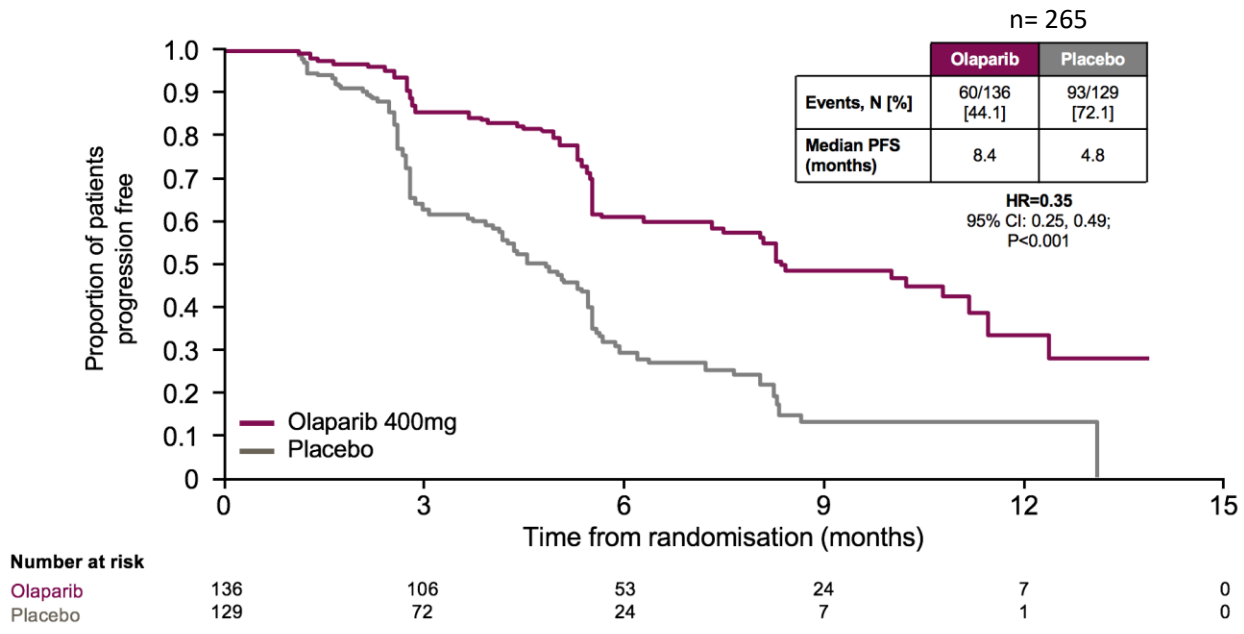
Gelmon KA *et al. Lancet Oncol* 2011;12:852–861

Kaye et al *J Clin Oncol* 2011

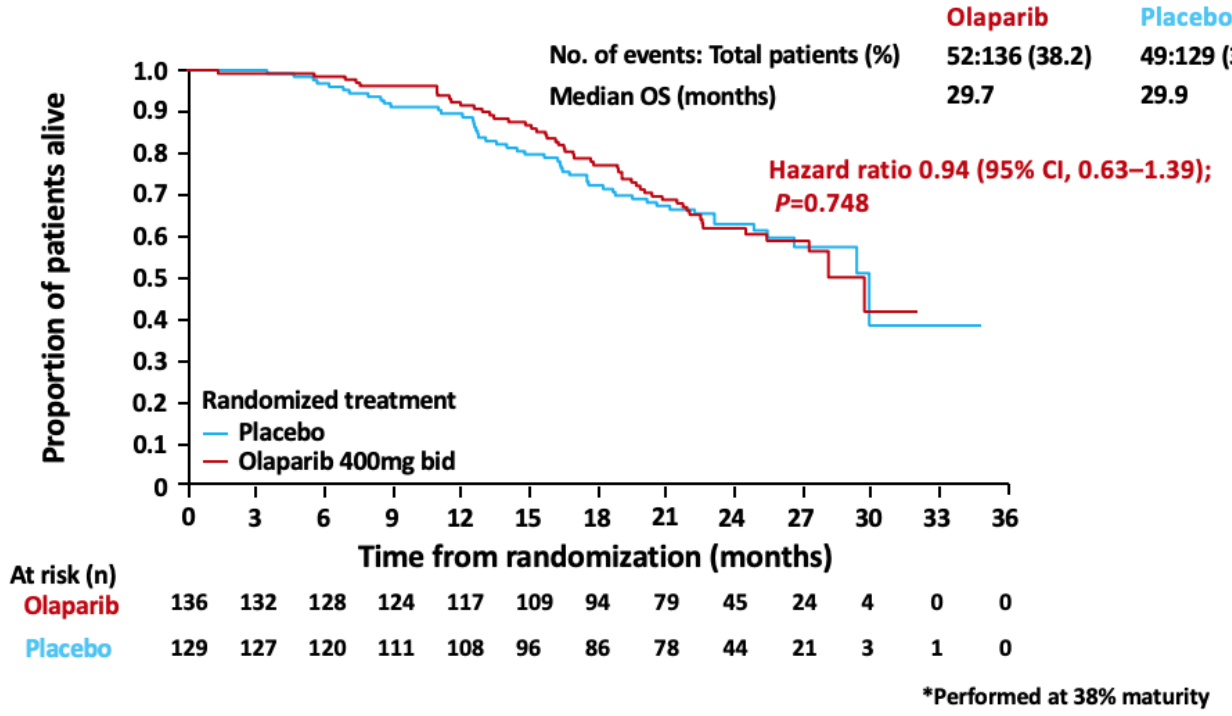
Konstantinopoulos PA, et al. *Cancer Discov*. 2015;5(11):1137–54

Progression-free survival with olaparib maintenance in Study 19

Whole population with HGSOC



Overall survival: interim analysis*



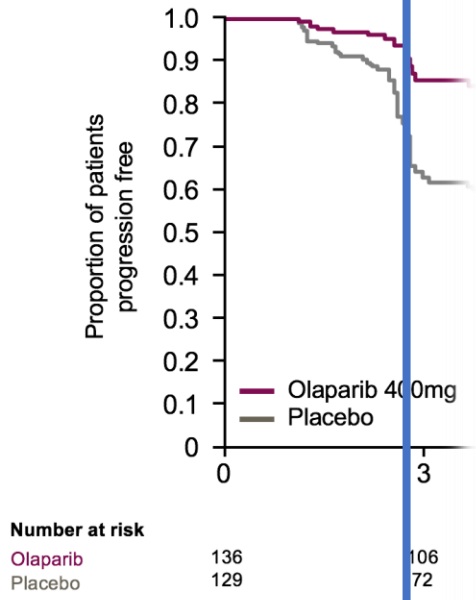
*Performed at 38% maturity

Ledermann J et al. N Engl J Med 2012;366:1382–1392

Progression-free survival with olaparib maintenance in Study 19

December 20, 2011

Whole pop



News Release AstraZeneca

ASTRAZENECA UPDATES ON OLAPARIB AND TC-5214 DEVELOPMENT PROGRAMMES

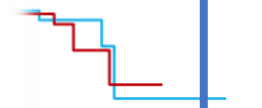
With Associated Impairment Charges, Company Confirms Full Year Financial Target, But Guides to Lower Half of Its Core EPS Range

AstraZeneca today announced that its investigational compound olaparib will not progress into Phase III development for the maintenance treatment of serous ovarian cancer. In addition, AstraZeneca announced that the second RENAISSANCE Phase III study of TC-5214 for patients with major depressive disorder did not meet its primary end point. As a result, AstraZeneca will take pre-tax impairment charges totalling $381.5 million to R&D expense in the fourth quarter of 2011. The company confirms its expectation for full year Core EPS in the range of $7.20 to $7.40, but with the inclusion of these intangible impairments, Core EPS is likely to be in the lower half of this range.

im analysis*

	Olaparib	Placebo
atients (%)	52:136 (38.2)	49:129 (38.0)
	29.7	29.9

azard ratio 0.9 (95% CI, 0.63–1.39);
P=0.748

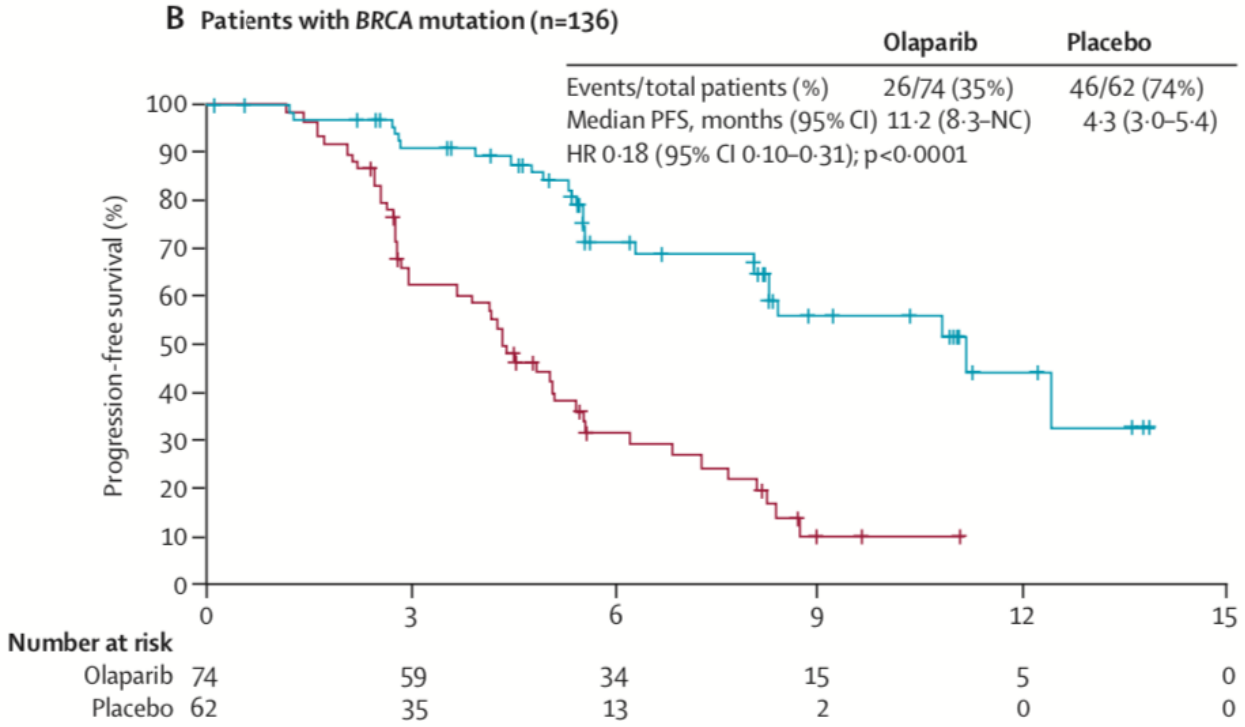


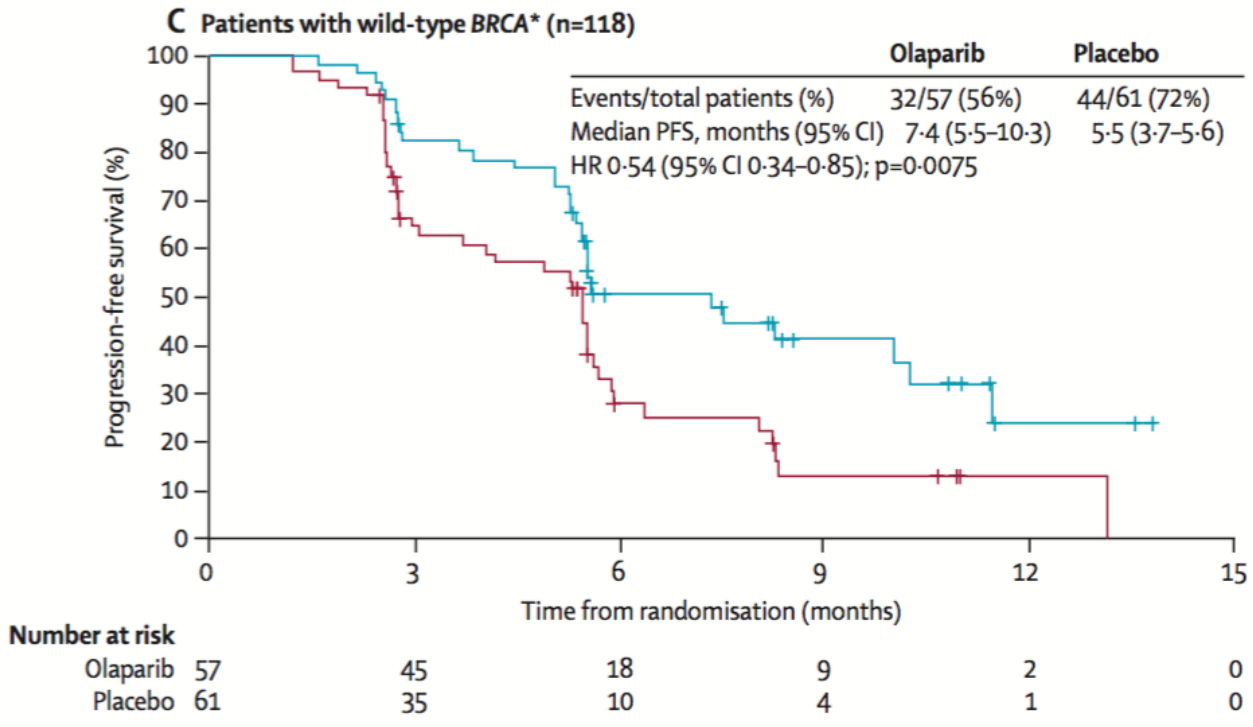
27 30 33 36
ths)
24 4 0 0
21 3 1 0

*Performed at 38% maturity

Ledermann J et al. N Engl J Med 2012;366:1382–1392

Study 19: olaparib subgroup analysis by BRCA mutational status





Ledermann J, et al. Lancet Oncol 2014.

Study 19: olaparib subgroup analysis by BRCA mutational status

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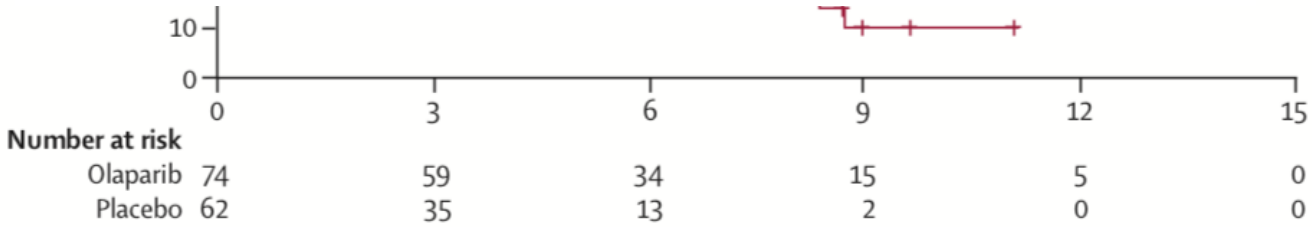
Lynparza recommended for approval in ovarian cancer

Press release 24/10/2014

The Committee for Medicinal Products for Human Use (CHMP) recommended that Lynparza be used as monotherapy for the maintenance treatment of adult patients with relapsed, platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer with mutations in one of two genes called *BRCA*, and who have responded to platinum-based chemotherapy.

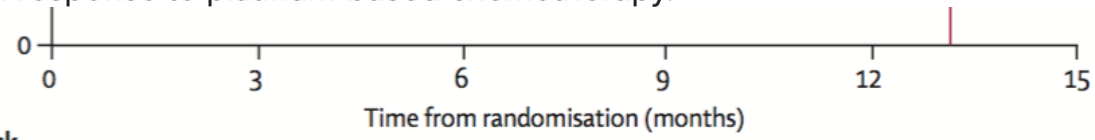


Number at risk						
Olaparib	74	59	34	15	5	0
Placebo	62	35	13	2	0	0

FDA Panel Votes Against Accelerated Approval for Olaparib

The Oncologic Drugs Advisory Committee (ODAC) of the US Food and Drug Administration (FDA) has voted, by a wide margin, not to recommend accelerated approval for use of a targeted cancer drug in a subset of ovarian cancer patients.

Panel members voted 11 to 2 against the approval of olaparib (AstraZeneca) as a maintenance treatment for women with platinum-sensitive relapsed ovarian cancer who have a germline *BRCA* mutation and who have had a complete or partial response to platinum-based chemotherapy.



nber at risk						
Olaparib	57	45	18	9	2	0
Placebo	61	35	10	4	1	0

Ledermann J, et al. Lancet Oncol 2014.

NOVA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer

M.R. Mirza, B.J. Monk, J. Herrstedt, A.M. Oza, S. Mahner, A. Redondo, M. Fabbro, J.A. Le
C. Marth, R. Mądry,
A. du Bois, A. González-
B.J. Rimel, J. Busc
for the

BACKGROUND
Niraparib is an oral poly(
1/2 inhibitor that has sh

Articles

SOLO2

Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/2* mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial

*Eric Pujade-Lauraine, Jonathan A Ledermann, Frédéric Selle, Val Gebski, Richard T Penson, Amit M Oza, Jacob Korach, Tomasz Huzarski, Andrés Poveda, Sandro Pignata, Michael Friedlander, Nicoletta Colombo, Philipp Harter, Keiichi Fujiwara, Isabelle Ray-Coquard, Susana Banerjee, Joyce Liu, Elizabeth S Lowe, Ralph Bloomfield, Patricia Pautier, the SOLO2/ENGOT-Ov21 investigators**

Summary

Background Olaparib, a poly(ADP-ribose) polymerase (PARP) inhibitor, has previously shown efficacy in a phase 2 study when given in capsule formulation to all-comer patients with platinum-sensitive, relapsed high-grade serous ovarian cancer. We aimed to confirm these findings in patients with a *BRCA1* or *BRCA2* (*BRCA1/2*) mutation using a tablet formulation of olaparib.

Methods This international, multicentre, double-blind, randomised, placebo-controlled, phase 3 trial evaluated olaparib tablet maintenance treatment in platinum-sensitive, relapsed ovarian cancer patients with a *BRCA1/2* mutation who had received at least two lines of previous chemotherapy. Eligible patients were aged 18 years or older with an Eastern

Articles

ARIEL 3

Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial

Robert L Coleman, Amit M Oza, Domenica Lorusso, Carol Aghajanian, Ana Oaknin, Andrew Dean, Nicoletta Colombo, Johanne I Weberpals, Andrew Clamp, Giovanni Scambia, Alexandra Leary, Robert W Holloway, Margarita Amenedo Gancedo, Peter C Fong, Jeffrey C Goh, David M O'Malley, Deborah K Armstrong, Jesus Garcia-Donas, Elizabeth M Swisher, Anne Floquet, Gottfried E Konecny, Iain A McNeish, Clare L Scott, Terri Cameron, Lara Maloney, Jeff Isaacson, Sandra Goble, Caroline Grace, Thomas C Harding, Mitch Raponi, James Sun, Kevin K Lin, Heidi Giordano, Jonathan A Ledermann*, on behalf of the ARIEL3 investigators†*

Summary

Background Rucaparib, a poly(ADP-ribose) polymerase inhibitor, has anticancer activity in recurrent ovarian carcinoma harbouring a *BRCA* mutation or high percentage of genome-wide loss of heterozygosity. In this trial we assessed rucaparib versus placebo after response to second-line or later platinum-based chemotherapy in patients with high-grade, recurrent, platinum-sensitive ovarian carcinoma.

Methods In this randomised, double-blind, placebo-controlled, phase 3 trial, we recruited patients from 87 hospitals and cancer centres across 11 countries. Eligible patients were aged 18 years or older, had a platinum-sensitive, high-

Published Online
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http://dx.doi.org/10.1016/S0140-6736(17)32440-6
See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(17)32418-2
*Contributed equally

Summary of PFS of trials of maintenance PARPi in recurrent ovarian cancer after a response to platinum-based therapy

			HR	Med PFS months Control	Med PFS months PARPi
Study 19	Olaparib	All	**0.35**	4.8	8.4
SOLO2*	Olaparib	*BRCAm*	**0.30**	5.5	19.1
NOVA	Niraparib	gBRCAm	**0.27**	5.5	21.0
		non-gBRCAm	**0.45**	3.9	9.3
ARIEL3	Rucaparib	ITT (all)	**0.36**	5.4	10.8
NORA	Niraparib	*gBRCA*	**0.22**	5.5	NR
		Non-gBRCA	**0.40**	3.9	11.1

Primary endpoint PFS was met in all trials in recurrent ova[illegible] cancer[illegible]gnificantly positive results

*BRCAm only trial

Ledermann et al, NEJM 2012; Pujade-Lauraine et al Lancet Oncol 2017 ; Mirza et al NEJM 2016; Coleman et al, Lancet 2017; Wu XH, Zhu JQ, Yin RT, et al. Ann Oncol. 2021

Summary of outcome and licence

Niraparib (ZEJULA)

FDA approves olaparib tablets for maintenance treatment in ovarian cancer

Listen to the F

On March 27,
Tesaro, Inc.), a
treatment of a
peritoneal can
chemotherapy

Share Tweet

On Aug. 17, 2017, the U.S. Food and Drug
olaparib tablets (Lynparza, AstraZeneca)
with recurrent epithelial ovarian, fallopia
complete or partial response to platinum

FDA approves rucaparib for maintenance treatment of recurrent ovarian, fallopian tube, or primary peritoneal cancer

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On April 6, 2018, the Food and Drug Administration approved rucaparib (Rubraca®, Clovis Oncology Inc.), a poly ADP-ribose polymerase (PARP) inhibitor, for the maintenance treatment of recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

Approval was based on ARIEL3 (NCT01968213), a randomized, double-blind, placebo-controlled trial in 561 patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who had been treated with at least two prior treatments of platinum-based chemotherapy and were in complete or partial response to the most recent platinum-based chemotherapy. Patients were randomized (2:1) to rucaparib 600 mg orally

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 September 2017
EMA/648982/2017
Committee for Medicinal Products for Human Use (CHMP)

Zejula is indicated for the maintenance treatment of adult patients with platinum-se
recurrent high grade serous epithelial ovarian, fallopian tube, or primary peritoneal
in response (complete response or partial response) to platinum-based chemothera

Following the CHMP positive opinion on this marketing authorisation, the Committee
Medicinal Products (COMP) reviewed the designation of Zejula as an orphan medicir
the approved indication. The outcome of the COMP review can be found on the Ager
ema.europa.eu/Find medicine/Human medicines/Rare disease designation.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/109273/2023
EMEA/H/C/004272

Rubraca (*rucaparib*)

An overview of Rubraca and why it is authorised in the EU

What is Rubraca and what is it used for?

Rubraca is a cancer medicine for treating high-grade cancers of the ovary, fallopian tubes (the tubes connecting ovaries to the uterus) and the peritoneum (the membrane lining the abdomen).

It is used as maintenance treatment in patients whose recurring cancer has cleared (partially or completely) after treatment with platinum-based cancer medicines.

Rubraca contains the active substance rucaparib.

Lynparza tablets receive EU approval for the treatment of platinum-sensitive relapsed ovarian cancer

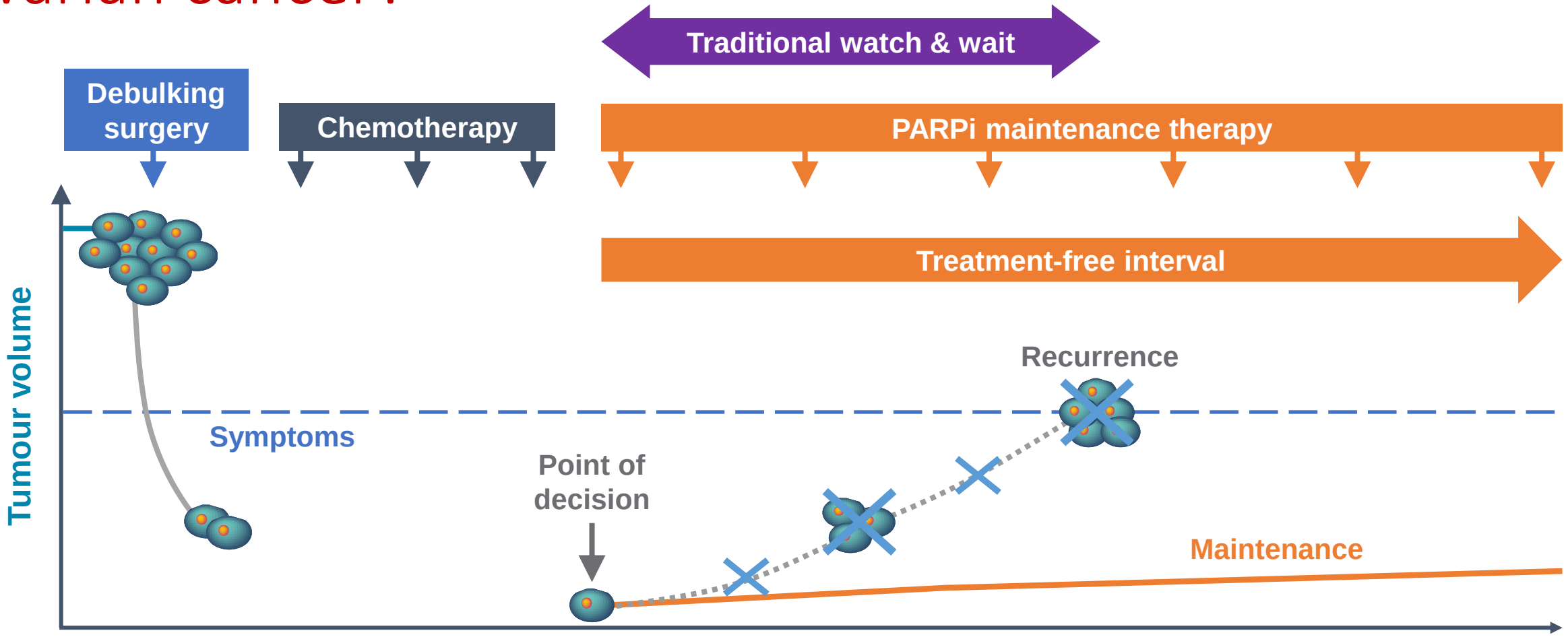
PUBLISHED
8 May 2018

Women with platinum-sensitive ovarian cancer now have access to maintenance therapy with AstraZeneca and MSD's Lynparza, regardless of BRCA status

Analysis	SOLO-2 (germline *BRCA*-mutated platinum-sensitive relapsed) n=295		Study 19 (platinum-sensitive relapsed) n=265	
	Lynparza	Placebo	*Lynparza*	Placebo
Reduction in the risk of disease progression or death (PFS)	70% (HR 0.30 [95% CI, 0.22-0.41], p<0.0001; median 19.1 vs 5.5 months)*		65% (HR 0.35 [95% CI, 0.25-0.49], p<0.00001; median 8.4 vs 4.8 months)*	

Analysis	Study 19 (platinum-sensitive relapsed) n=265	
	Lynparza	Placebo
Time to first subsequent therapy or death*	HR 0.39 (95% CI, 0.30-0.52), p<0.00001; median 13.3 months vs. 6.7 months	
OS	HR 0.73 (95% CI, 0.55-0.95), p=0.02138**; median 29.8 vs. 27.8 months***	

Can the benefits of maintenance therapy with a PARP inhibitor be applied to first line treatment of advanced ovarian cancer?



PARP, poly ADP ribose polymerase

Trials of PARP inhibitors in front line treatment of ovarian cancer

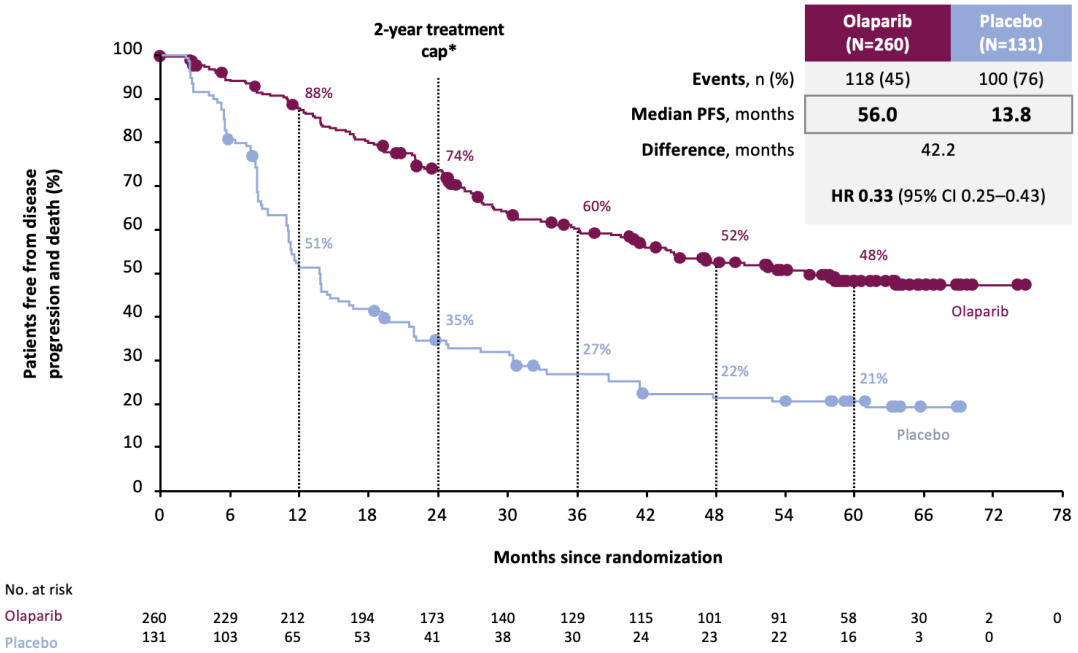
Maintenance PARPi post chemotherapy

	SOLO1	PAOLA-1	PRIMA	PRIME	ATHENA	VELIA
Entry	BRCA mutation	All comers	All comers ('high risk')	All comers	All comers	All comers
Drug	Olaparib	Bevacizumab + Olaparib	Niraparib	Niraparib	Rucaparib	Veliparib + Chemo followed by maintenance
Control	Placebo	Bevacizumab + Placebo	Placebo	Placebo	Placebo	Placebo
Duration	24 months	15 months bevacizumab 24 months olaparib	36 months or to progression	36 months or to progression	24 months	24 months maintenance

Moore et al NEJM 2018; Ray-Coquard et al NEJM 2019; Gonzalez-Martin et al NEJM 2019; Li et al SGO 2022; Monk et al J Clin Oncol 2022; Coleman et al NEJM 2019

SOLO1: A new paradigm for frontline treatment of *BRCA*^{mut} advanced ovarian cancer

Progression-Free survival at 5 years follow up

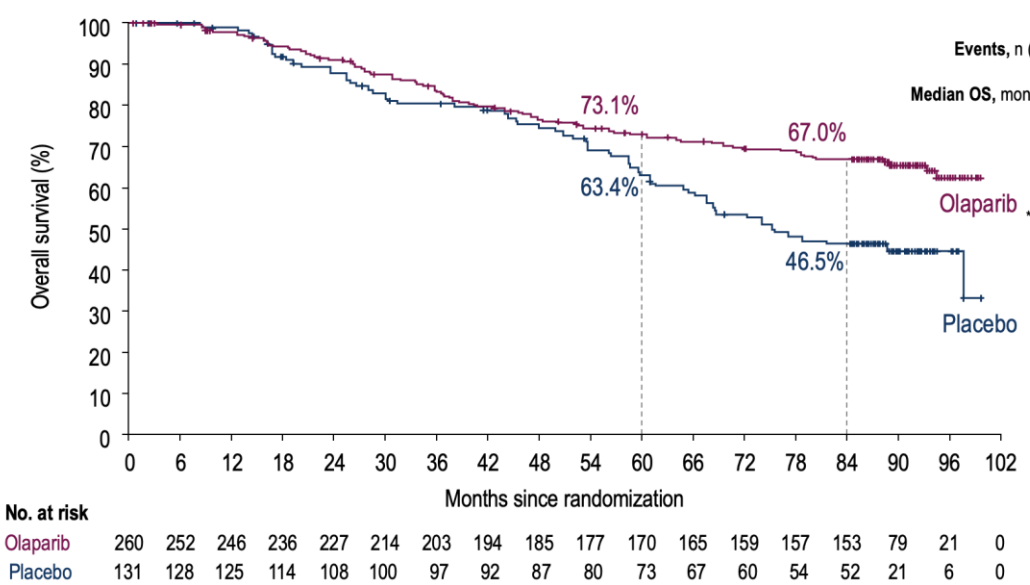


	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	118 (45)	100 (76)
Median PFS, months	**56.0**	**13.8**
Difference, months	42.2	
HR 0.33 (95% CI 0.25–0.43)		

*13 patients, all in the olaparib arm, continued study treatment beyond 2 years; †n=130 (safety analysis set).
Investigator-assessed by modified RECIST v1.1. DCO: March 5, 2020.

Bradley et al SGO 2021; Banerjee et al Lancet Oncol 2021

Survival at 7 years of follow up

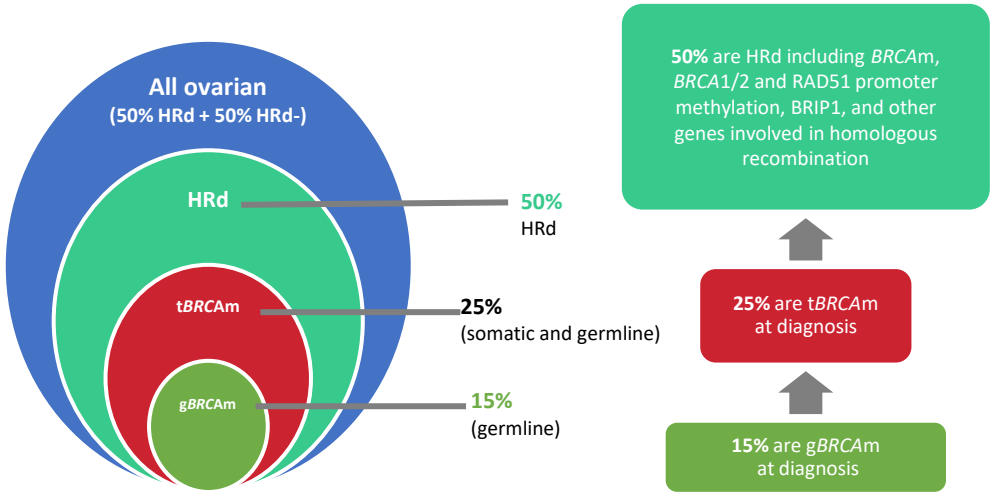


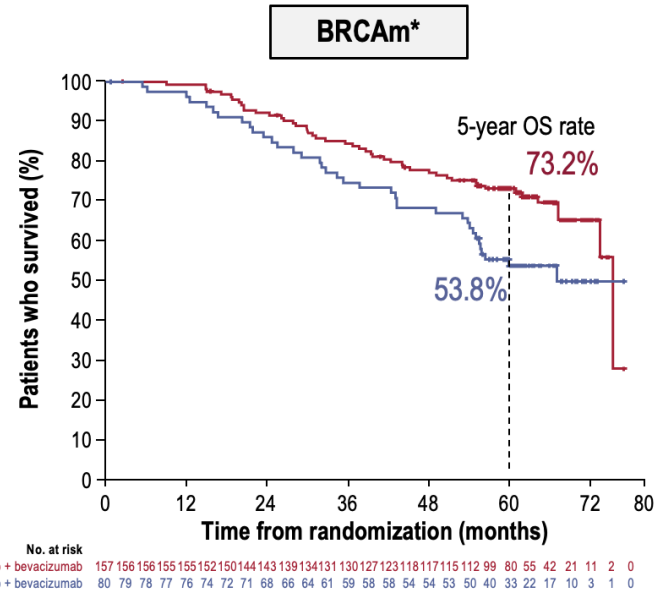
	Olaparib (N=260)	Placebo (N=131)
Events, n (%)	84 (32.3)	65 (49.6)
Median OS, months	**NR**	**75.2**
HR 0.55 (95% CI 0.40–0.76); *P*=0.0004*		

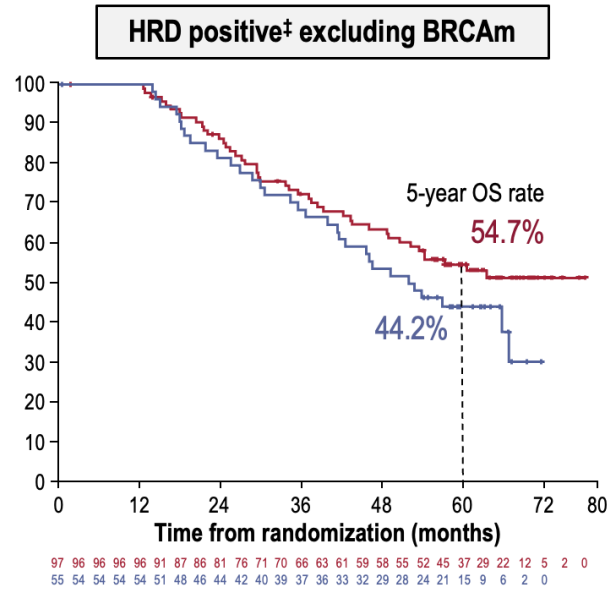
**P*<0.0001 required to declare statistical significance

DiSilvestro et al ESMO 2022; J Clin Oncol 2022

Overall survival beyond BRCA- HRD positive group







	Olaparib + bevacizumab (N=157)	Placebo + bevacizumab (N=80)
Events, n (%)	48 (30.6)	37 (46.3)
Median OS, months	75.2 (unstable)†	66.9
5-year OS rate, %	**73.2**	**53.8**
PARPi as subsequent treatment, n (%)	38 (24.2)	44 (55.0)
	HR 0.60 (95% CI 0.39–0.93)	

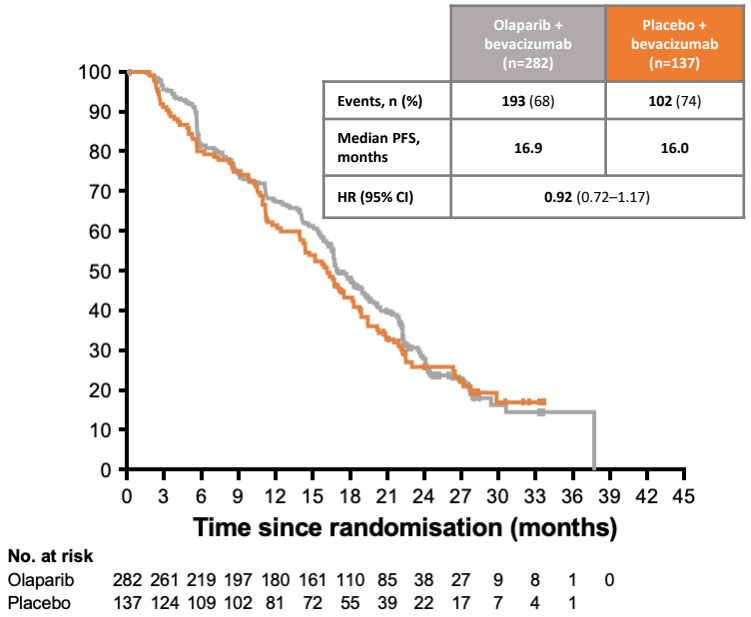
Olaparib + bevacizumab (N=97)	Placebo + bevacizumab (N=55)
44 (45.4)	32 (58.2)
NR	52.0
54.7	**44.2**
9 (9.3)	23 (41.8)
HR 0.71 (95% CI 0.45–1.13)	

*By central labs; †Unstable median; <50% data maturity; ‡By Myriad myChoice HRD Plus. NR, not reported.

Ray-Coquard et al ESMO 2022

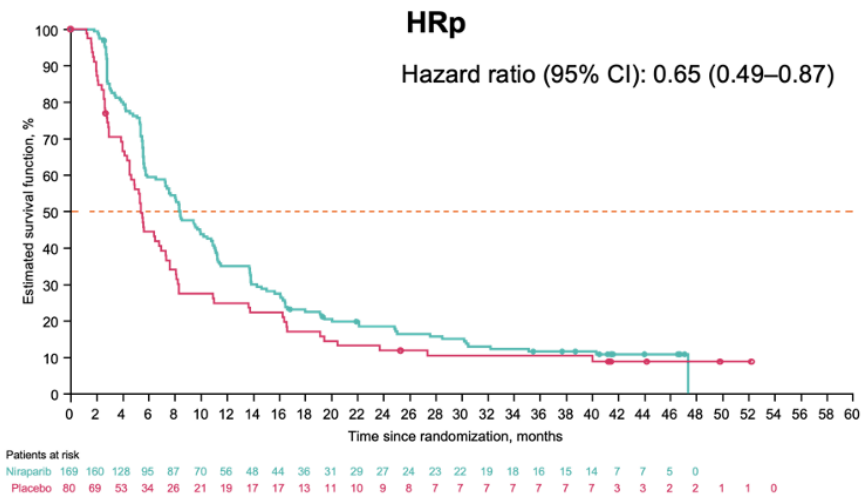
Progression-Free Survival in HRD negative (HR proficient) ovarian tumours

PAOLA-1: Bevacizumab + olaparib



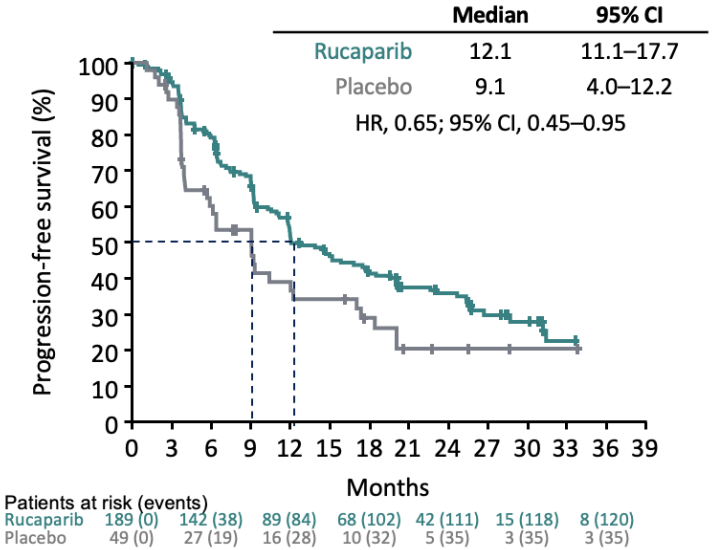
Myriad MyChoice: HRD -ve

PRIMA: Niraparib



Myriad MyChoice: HRD -ve

ATHENA-*mono*: Rucaparib



FoundationOne CDx: Low LOH

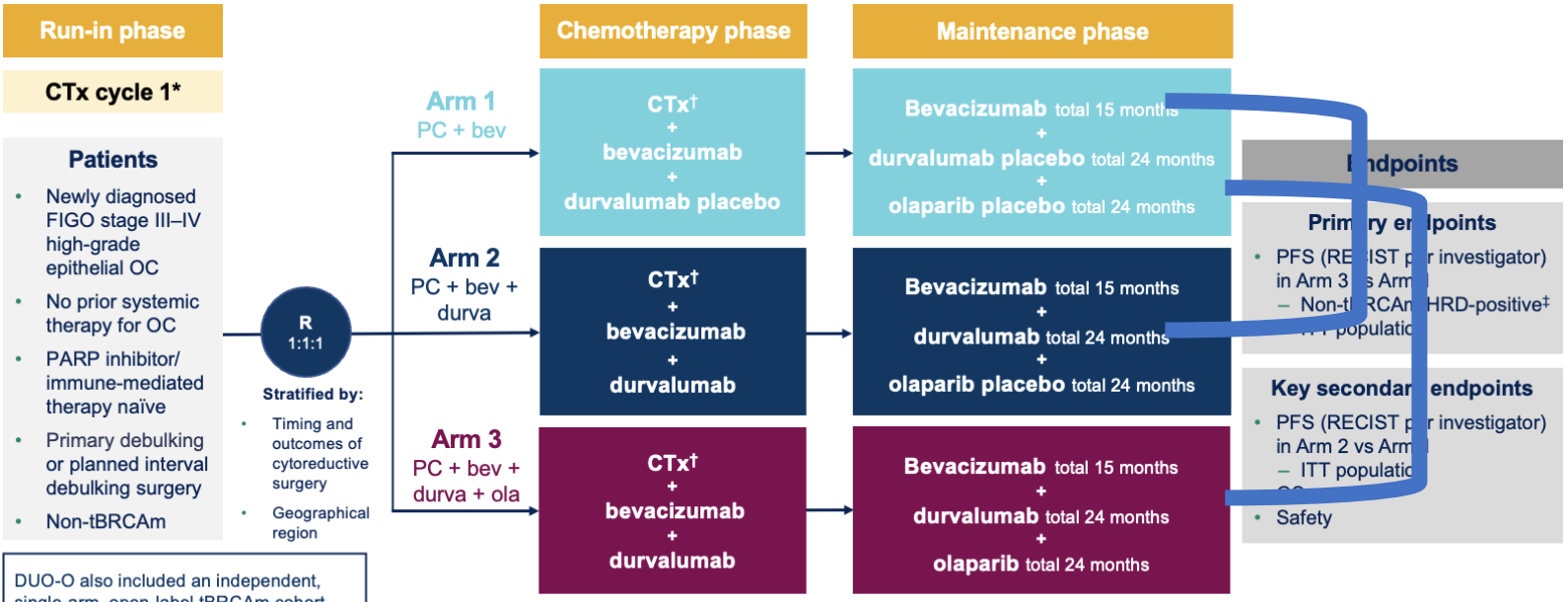
Ray-Coquard I, et al. N Engl J Med 2019

Gonzalez et al IGCS 2022

Monk et al. ASCO 2022; J Clin Oncol 2022

Is more better……?

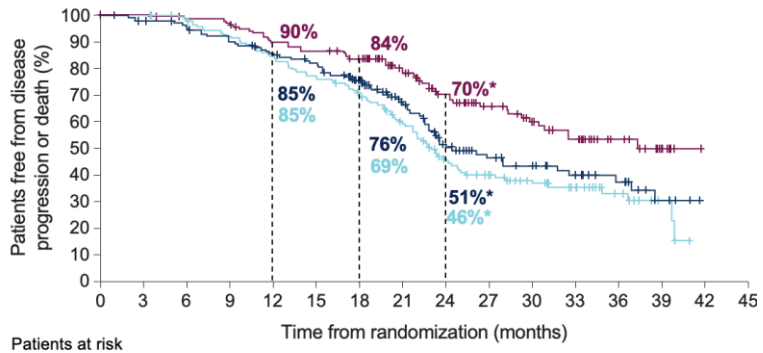
DUO-O study design



2023 ASCO ANNUAL MEETING
#ASCO23

PRESENTED BY: Dr Philipp Harter

Non-tBRCAm HRD-positive

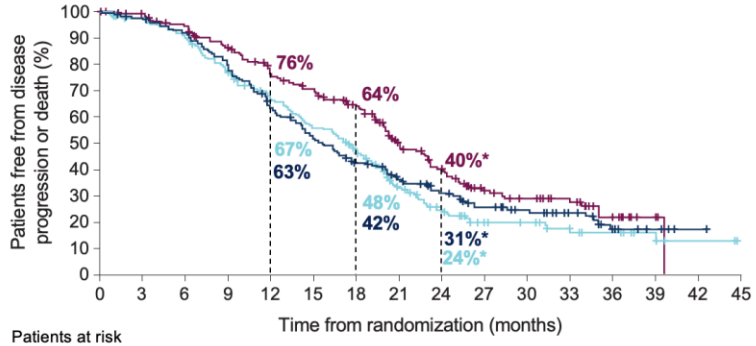


Patients at risk

Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0
Arm 2	148	142	137	128	118	112	94	66	45	34	28	21	15	7	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0

	Arm 1 PC + bev N=143	Arm 2 PC + bev + durva N=148	Arm 3 PC + bev + durva + ola N=140
Events, n (%)	86 (60)	69 (47)	49 (35)
Median PFS, months†	23.0	24.4‡	37.3‡
HR (95% CI) vs Arm 1		**0.82** (0.60–1.12)§	**0.51** (0.36–0.72)§

HRD-negative



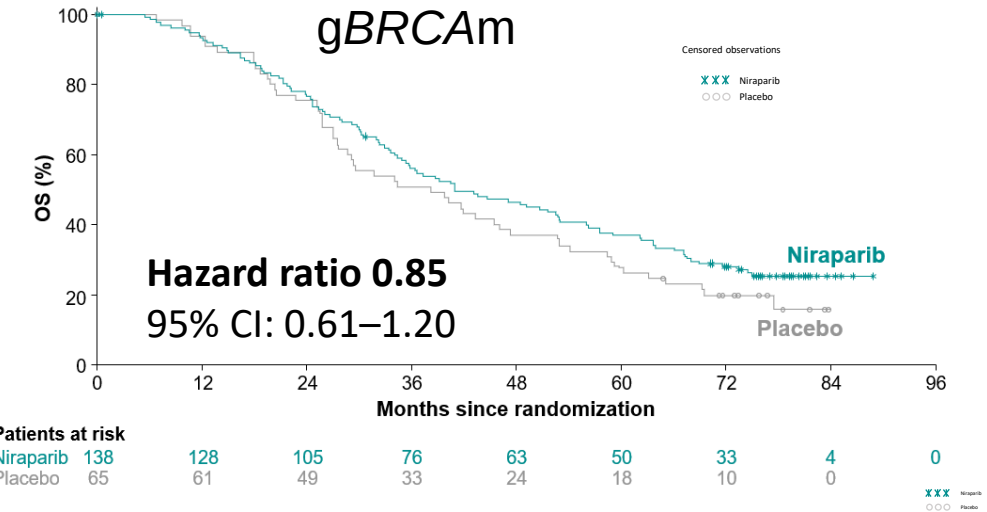
Patients at risk

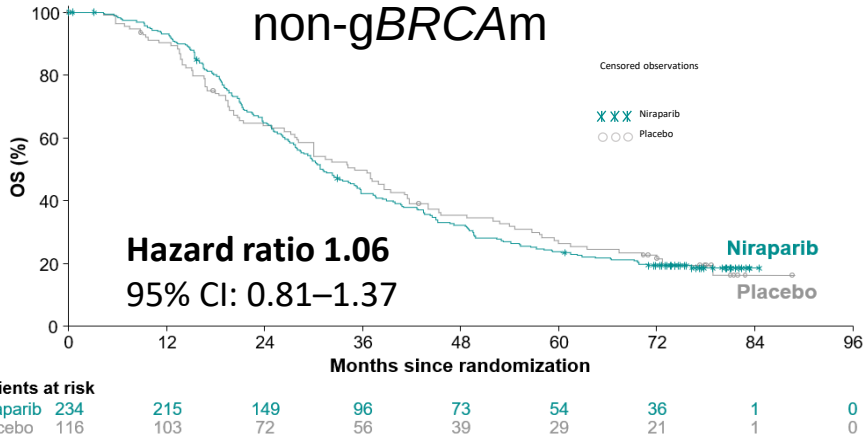
Arm 1	216	203	188	159	135	112	92	55	34	21	19	12	9	5	2	0
Arm 2	199	189	177	153	120	97	76	59	45	33	25	17	8	4	1	0
Arm 3	211	202	190	169	145	132	111	75	57	33	26	20	10	3	0	

	Arm 1 PC + bev N=216	Arm 2 PC + bev + durva N=199	Arm 3 PC + bev + durva + ola N=211
Events, n (%)	157 (73)	142 (71)	127 (60)
Median PFS, months†	17.4	15.4	20.9
HR (95% CI) vs Arm 1		**0.94** (0.75–1.18)§	**0.68** (0.54–0.86)§

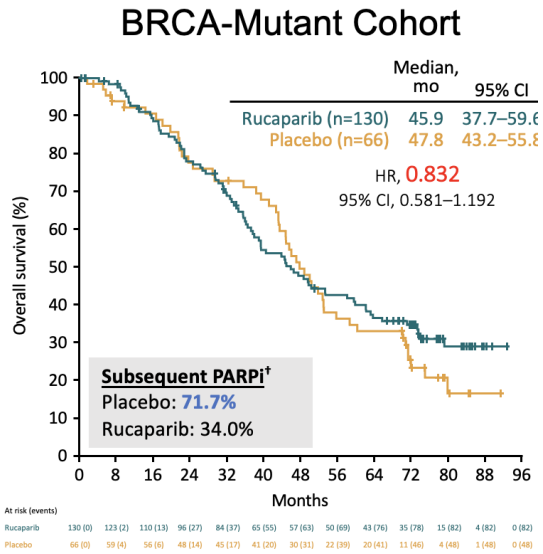
Survival analysis NOVA and ARIEL3 in recurrent ovarian cancer

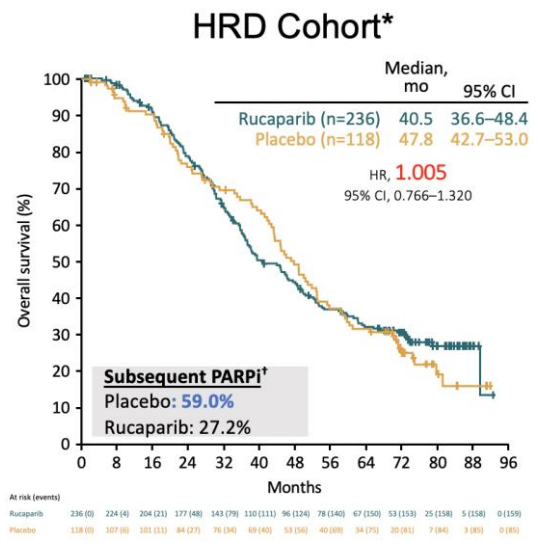
What do the results mean?

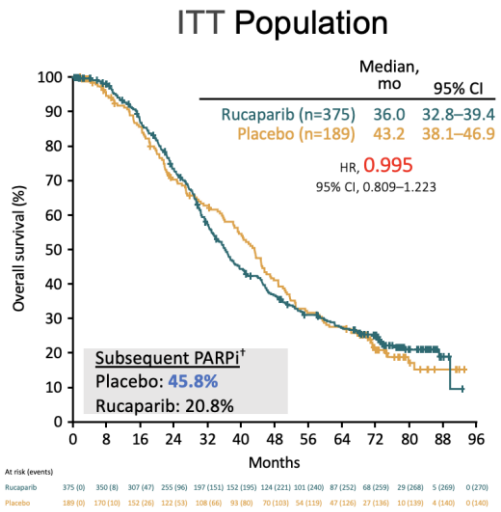




Matulonis et al SGO 2023



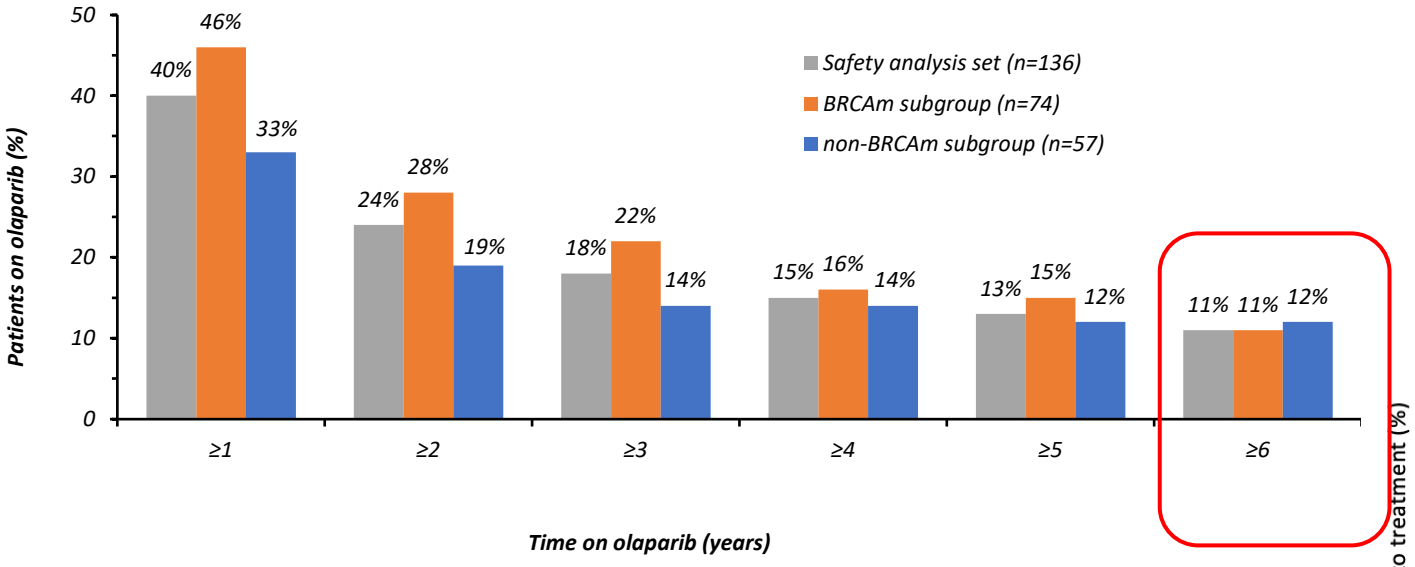




Coleman et al IGCS 2022

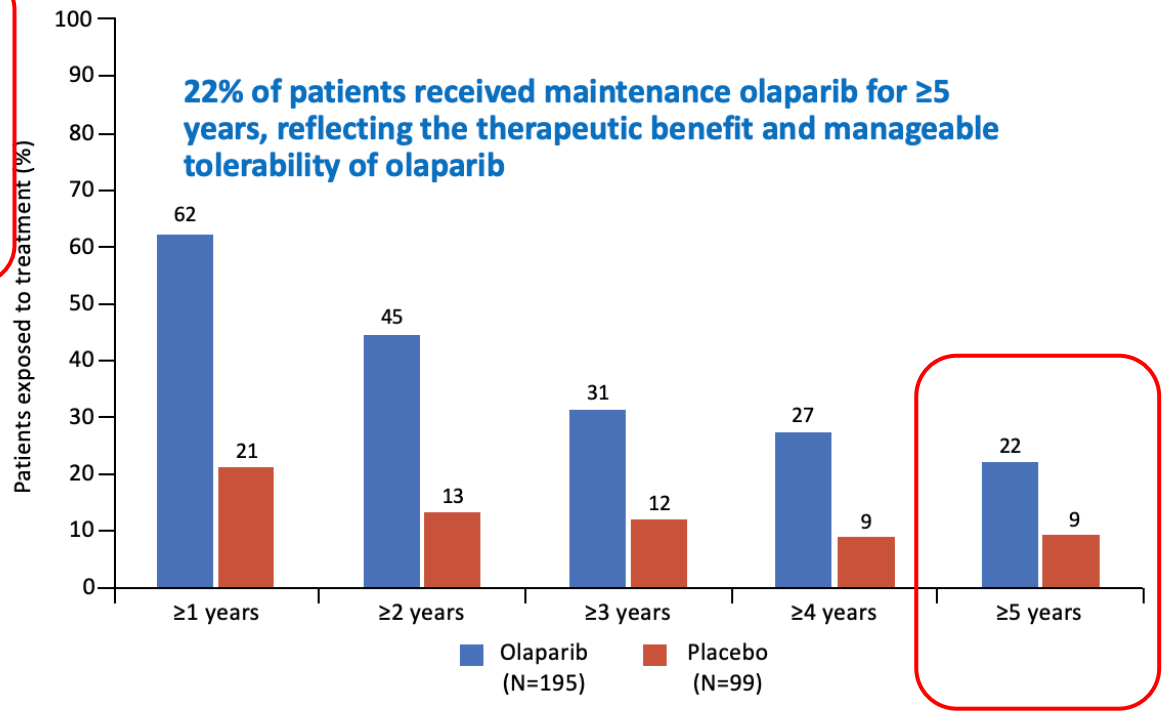
Long-term ‘super’ responders to olaparib

Study 19



Gourley C et al. J Clin Oncol 35, 2017 (suppl; poster related to abstr 5533)

SOLO2

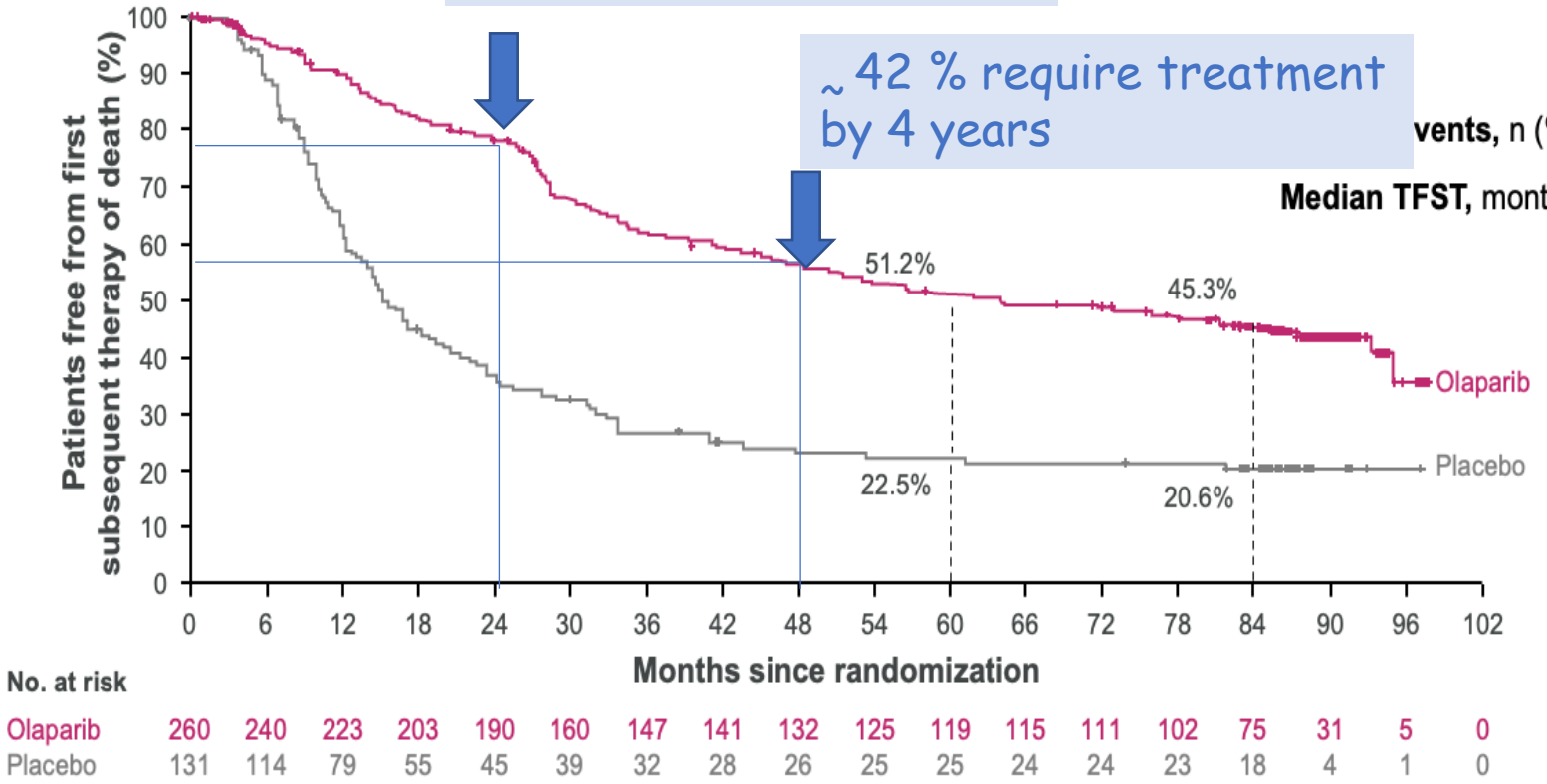


Poveda et al ASCO 2020; Lancet Oncol 2021

SOLO1- Time to First Subsequent Therapy in patients with a *BRCA*^{mut}

~ 22 % require treatment by 2 years

~ 42 % require treatment by 4 years



	Olaparib (N=260)	Placebo (N=131)
vents, n (%)	135 (51.9)	98 (74.8)
Median TFST, months	**64.0**	**15.1**
HR 0.37 (95% CI 0.28–0.48)		

In the olaparib arm **45%** of patients who were still alive at 7 years had **yet to receive any subsequent treatment**

DiSilvestro et al ESMO2022

What has the decade achieved……?

- Recognition of the importance of *BRCA* testing in high grade ovarian cancer
- Molecularly directed therapy with PARP inhibitors being particularly effective in $BRCA^{mut}$ tumours and those with HR Deficiency
- Maintenance with PARP inhibitors significantly prolongs PFS in recurrent ovarian cancer responding to platinum-based therapy
- Overall survival benefit with olaparib in frontline treatment of advanced $BRCA^{mut}$ ovarian cancer
- Overall survival benefit in HRD population when olaparib combined with bevacizumab

Outstanding issues for the next decade

- Clear survival benefit of front-line PARPi in *BRCA^{mut}* ovarian cancer - but 50% patients will progress
  - *How can this be reduced?*
- Many patients with recurrence will have previously been exposed to PARPi
  - *Rechallenge with PARPi (alone or in combination)?*
- What drugs may best prevent resistance to PARPi
  - *Cell cycle inhibitors or DNA repair pathways?*
- Will it be possible to demonstrate overall survival results in recurrent ovarian cancer with PARPi, or is the PFS benefit sufficient?
  - *Engagement with Regulators*


Thank you