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OlympiA
Olaparib in adjuvant BRCAm breast cancer

Pre-specified analyses of IDFS, DDFS and OS 10 years from First Patient In (FPI) in the OlympiA trial of adjuvant olaparib in germline *BRCA1/2* mutation-associated breast cancer

BIG Breast International Group
frontier science
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Declaration of interests

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I have the following relationships to disclose:

Co-PI, NRG-55 (OlympiA adjuvant olaparib trial: Astra-Zeneca co-sponsor)

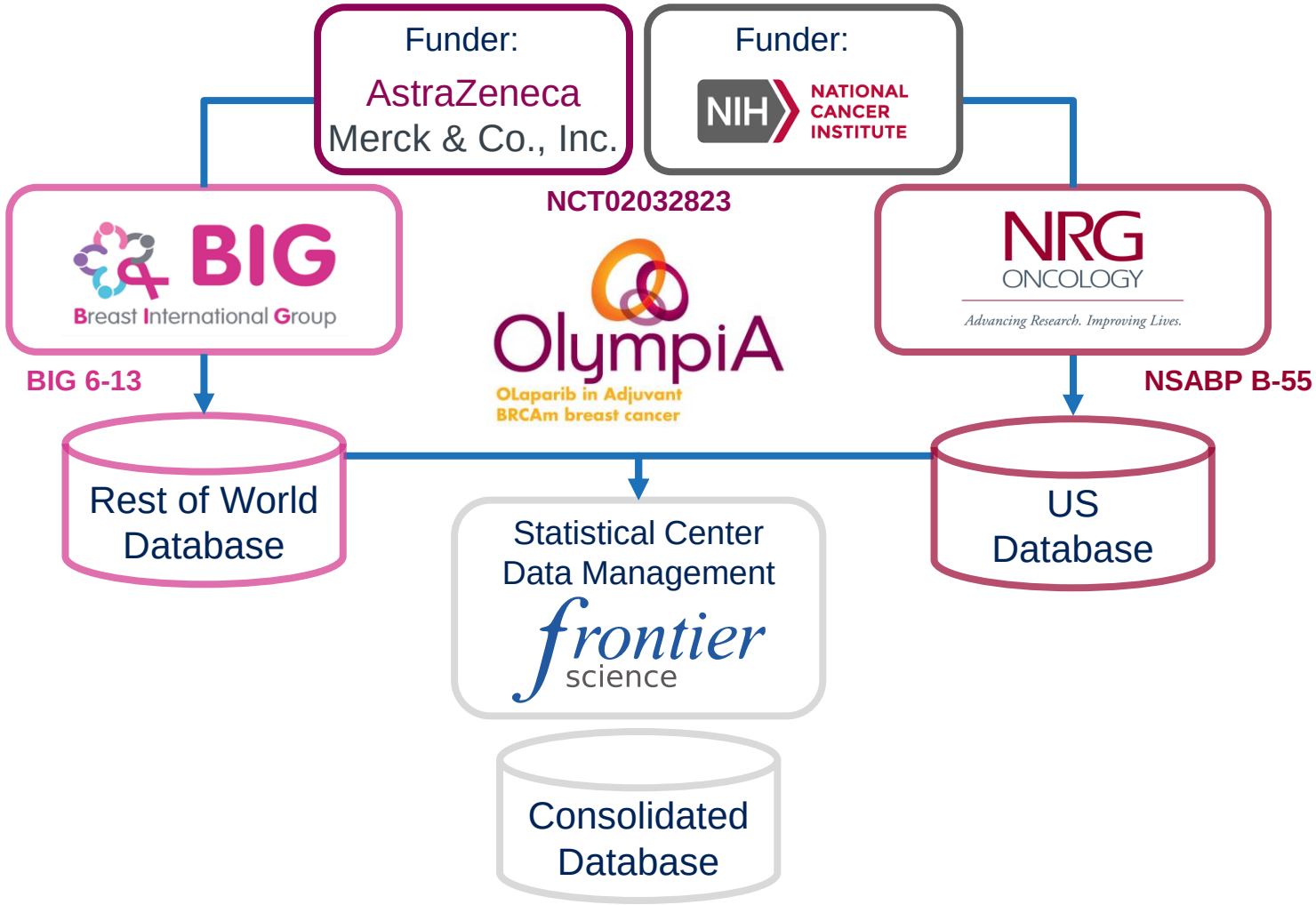
Co-PI, BRCA-P Trial (Amgen)

Spouse: Kronos Pharmaceuticals, others

Research support: Ambry Genetics, Invitae Genetics

I will discuss the following off-label uses of the product in approved research protocols in my presentation:
None

OlympiA: Academia-industry partnership



OlympiA: Study History

Rationale

- Inhibition and trapping of PARP1 on DNA results in synthetic lethality with loss of function of *BRCA1* and *BRCA2* proteins and homologous recombination DNA repair.
- Loss of function Germline “Pathogenic Variants” in *BRCA1/2* (g*BRCA*pv) predispose to both ER positive and TNBC.

- OlympiA uniquely examined olaparib as adjuvant therapy in patients with g*BRCA*pv and high-risk early HER2-negative BC.
- Olaparib significantly improved IDFS and DDFS at first pre-specified interim analysis (IA), and significantly improved OS at the second pre-specified IA.
- **This updated analysis reports the results of the third pre-specified analysis at 10 years from first patient in with a median follow-up of 6.1 years (max, 9.6 years), an additional 2.6 years follow-up since the previous analysis.**

TNBC Triple negative breast cancer; IDFS Invasive disease-free survival; DDFS Distant disease-free survival; OS Overall survival;

OlympiA: Trial schema

- Local genetic testing or on-study central screening (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (ER and/or PgR positive or TNBC)
- Stage II-III Breast Cancer or lack of PathCR to NACT

Neoadjuvant Group
- *TNBC:* non-pCR
- *ER and/or PgR positive:* non-pCR and CPS+EG score ≥ 3

≥ 6 cycles Neoadjuvant Chemotherapy → **Surgery** → **+/- Radiotherapy**

Adjuvant Group
- *TNBC:* ≥ pT2 or ≥ pN1
- *ER and/or PgR positive:* ≥ 4 positive lymph nodes

Surgery → **≥ 6 cycles Adjuvant Chemotherapy** → **+/- Radiotherapy**

1:1 Randomization N=1836

Olaparib 300 mg twice daily for 1 year

Placebo twice daily for 1 year

Primary End Point
- Invasive disease-free survival (IDFS) by STEEP system[1]

Secondary End Points
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Symptom / Health related QoL
- Safety

Stratification Factors
- ER and/or PgR positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

Concurrent Adjuvant Therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd Adjuvant Chemotherapy

ER and/or PgR positive defined as IHC staining ≥1%.
Triple Negative defined as ER and PgR negative (IHC staining < 1%)

[1]Hudis CA, *J Clin Oncol* 2007

OlympiA: Patient characteristics

	Olaparib (N = 921)	Placebo (N = 915)
Age, years, median (interquartile range)	**42 (36–49)**	**43 (36–50)**
BRCA gene altered in germline		
BRCA1	**657 (71.3%)**	**670 (73.2%)**
BRCA2	**261 (28.3%)**	**239 (26.1%)**
BRCA1 and *BRCA2*	2 (0.2%)	5 (0.5%)
Menopausal status (female only)		
Premenopausal	**572/919 (62.2%)**	**552/911 (60.6%)**
Postmenopausal	347/919 (37.8%)	359/911 (39.4%)
Primary breast cancer surgery		
Mastectomy	**699 (75.9%)**	**673 (73.6%)**
Conservative surgery only	222 (24.1%)	240 (26.2%)
Missing	0 (0.0%)	2 (0.2%)

OlympiA: Patient characteristics

	Olaparib (N = 921)	Placebo (N = 915)
Hormone receptor status[1]		
ER and/or PgR + ≥1%/ HER2-[2]	**168 (18.2%)**	**157 (17.2%)**
Triple Negative Breast Cancer[3]	**751 (81.5%)**	**758 (82.8%)**
Prior chemotherapy		
Adjuvant (ACT)	461 (50.1%)	455 (49.7%)
Neoadjuvant (NACT)	460 (49.9%)	460 (50.3%)
Anthracycline and taxane regimen	871 (94.6%)	850 (92.9%)
Neo(adjuvant) platinum-based therapy	247 (26.8%)	238 (26.0%)
Concurrent endocrine therapy (HR–positive only)	**146/168 (86.9%)**	**146/157 (93.0%)**

[1] Defined by local test results
[2] Following a protocol amended in 2015, the first patient with ER and/or PgR positive disease was enrolled in December 2015
[3] Two patients are excluded from the summary of the triple–negative breast cancer subset because they do not have confirmed HER2-negative status

OlympiA: Protocol planned analyses

Summary of 2-sided significance levels across the endpoints and analyses Adapted from protocol V6 table 14				
	IA IDFS ***(165 IDFS events Mature cohort)*** *DCO 27 Mar 2020*	OS IA 2 ***(330 IDFS events ITT)*** *DCO 12 July 2021*	DDFS and OS analysis ***(10 years from FPI)*** *DCO 5 June 2024*	Final OS analysis ***(15 years from FPI)*** *June 2029**
IDFS	0.005	N/A	N/A	N/A
DDFS	0.005	N/A	N/A	N/A
OS	0.01	0.015	N/A	N/A

- This third pre-planned analysis was conducted 10 years from First Patient In (FPI – 5 June 2014).
- Median follow up at this point was 6.1 years with maximum follow-up of 9.6 years.
- Significance boundaries were crossed for IDFS and DDFS at the prior planned IA IDFS and for OS at OS IA2. No further significance testing was performed.
- All confidence intervals (CI) are 95% CIs and are descriptive.

* Estimated timing from FPI, 5 June 2014.

Type of first IDFS event

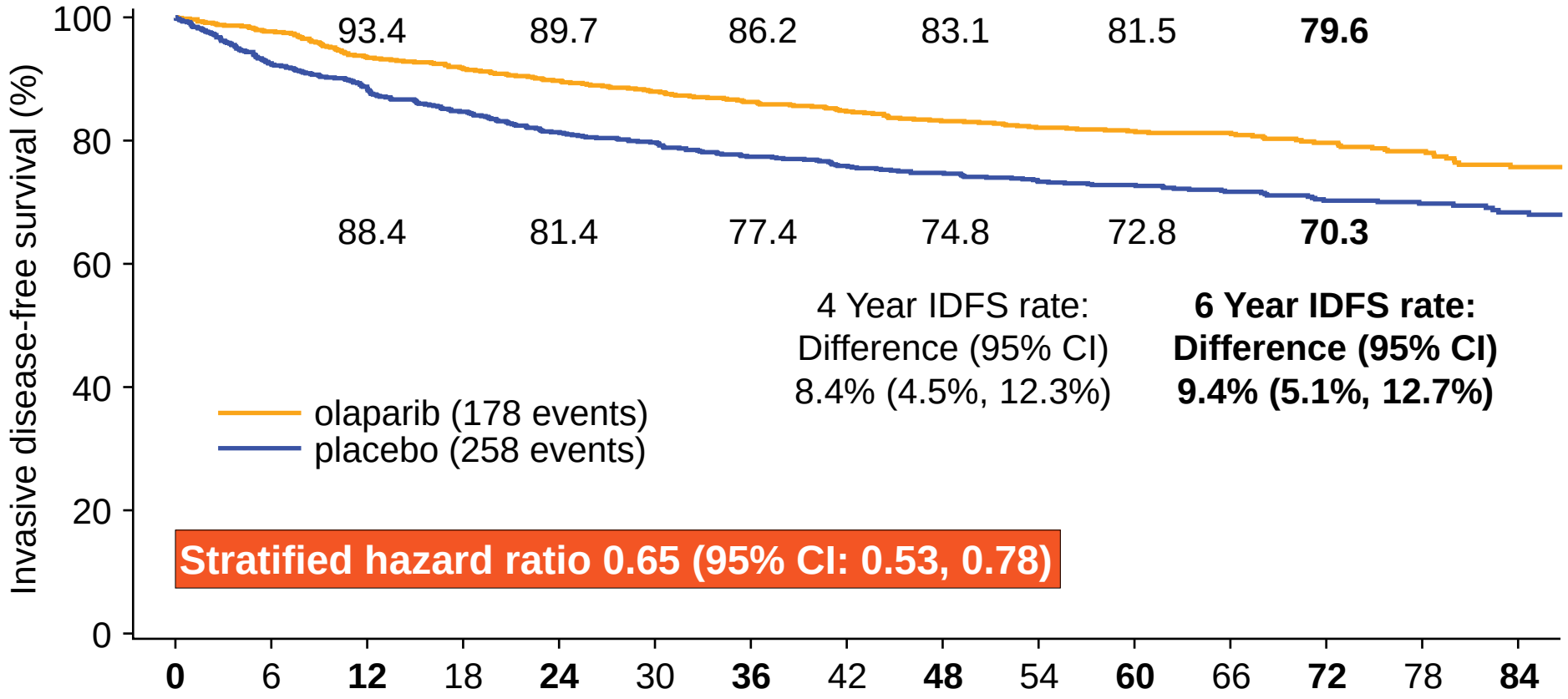
	Olaparib (N = 921)		Placebo (N = 915)	
	Current	**Previous***	**Current**	**Previous***
Number of patients with a first IDFS event	**178 (19.3%)**	*[134 (14.5%)]*	**258 (28.2%)**	*[207 (22.6%)]*
Distant recurrence	**106 (11.5%)**	*[88 (9.6%)]*	**149 (16.3%)**	*[136 (14.9%)]*
Distant CNS Recurrence	**26 (2.8%)**	*[24 (2.6%)]*	**40 (4.4%)**	*[38 (4.2%)]*
Distant excluding CNS Recurrence	**80 (8.7%)**	*[64 (6.9%)]*	**109 (11.9%)**	*[98 (10.7%)]*
Regional (Ipsilateral) Recurrence	**11 (1.2%)**	*[9 (1.0%)]*	**22 (2.4%)**	*[18 (2.0%)]*
Local (Ipsilateral) Recurrence	**11 (1.2%)**	*[9 (1.0%)]*	**12 (1.3%)**	*[12 (1.3%)]*
Contralateral invasive breast cancer	**26 (2.8%)**	*[15 (1.6%)]*	**36 (3.9%)**	*[18 (2.0%)]*
Second primary non-breast malignancies	**20 (2.2%)**	*[11 (1.2%)]*	**37 (4.0%)**	*[23 (2.5%)]*
Deaths without a prior IDFS event [1]	**4 (0.4%)**	*[2 (0.2%)]*	**2 (0.2%)**	*[0 (0.0%)]*

*Previous data from OS IA2

There can only be one first IDFS event per patient

[1] **olaparib**: cardiac arrest (n = 1), heart failure with preserved ejection fraction (n = 1), unknown cause (n = 2);
placebo: COVID19 (n = 1), cardiogenic shock (n = 1)

Analysis of IDFS (ITT)

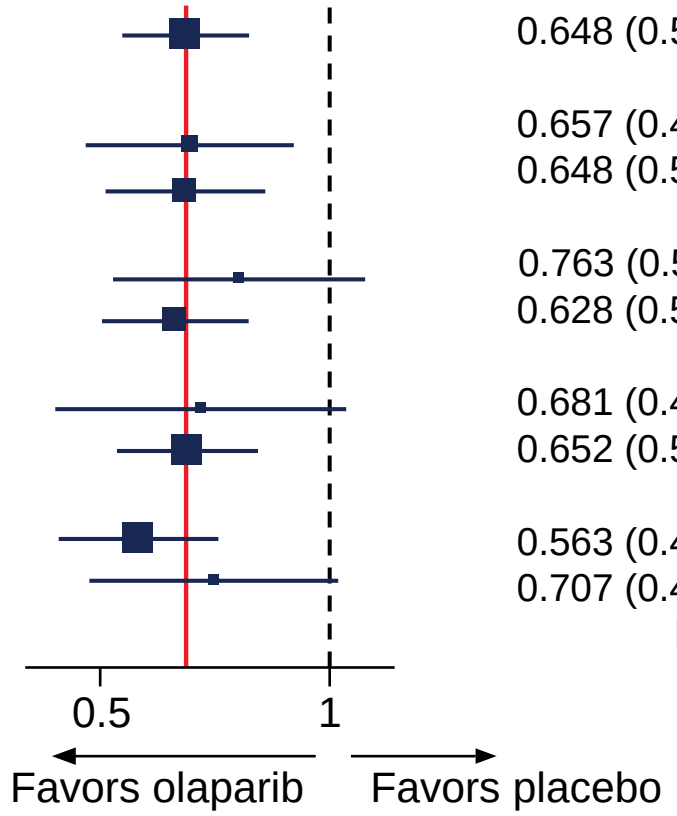


Number at risk

olaparib	921	778	712	670	632	570	361	194
placebo	915	766	683	628	588	512	327	181

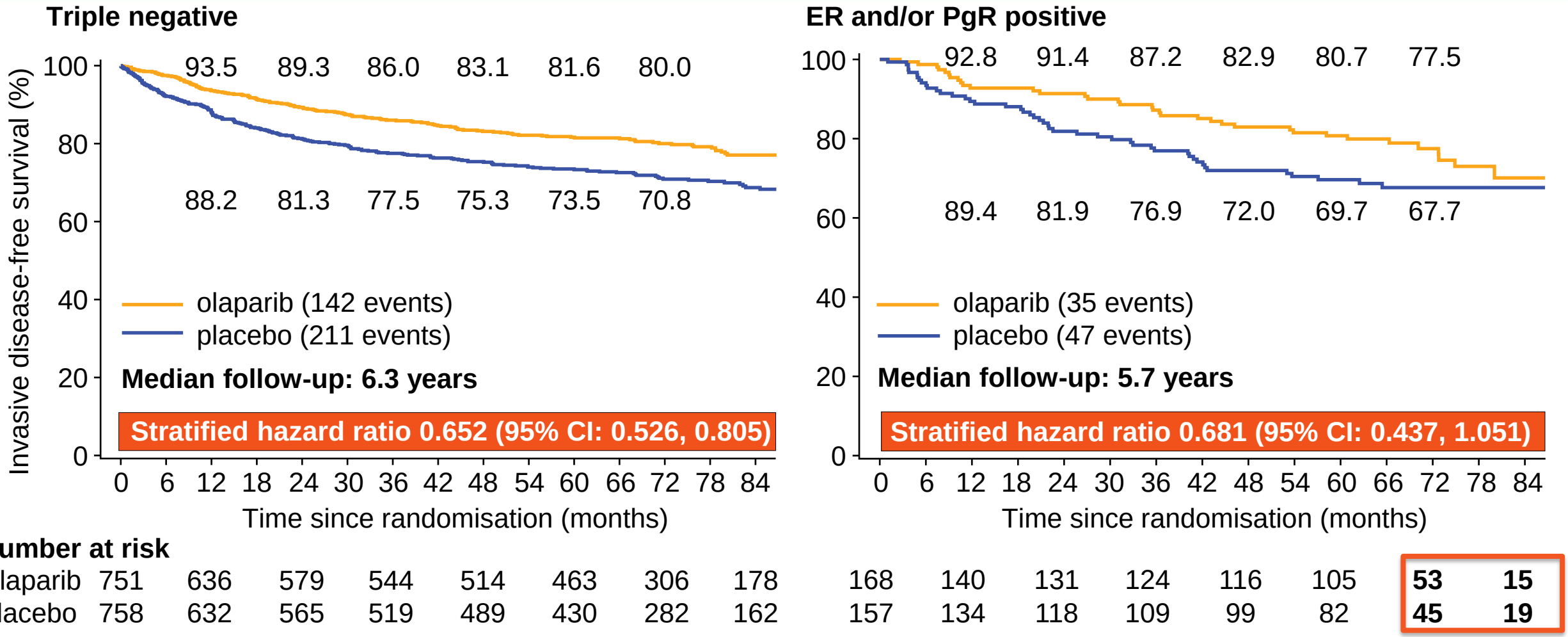
Subgroup analysis of IDFS

Subgroup	Olaparib	Placebo	Stratified hazard ratio for invasive disease-free survival (95% CI)	P value for heterogeneity
	Number of patients with an invasive-disease event/total number			
All patients	178/921	258/915	0.648 (0.535 – 0.784)	NA
Prior Chemo				
Adjuvant	65/461	98/455	0.657 (0.479 – 0.897)	0.94
Neoadjuvant	113/460	160/460	0.648 (0.508 – 0.823)	
Prior Platinum				
Yes	48/247	60/238	0.763 (0.520 – 1.113)	0.39
No	130/674	198/677	0.628 (0.503 – 0.783)	
HR status				
HR+/HER2–	35/168	47/157	0.681 (0.437 – 1.051)	0.86
TNBC	142/751	211/758	0.652 (0.526 – 0.805)	
BRCA				
BRCA1	106/579	177/588	0.563 (0.441 – 0.715)	0.61
BRCA2	49/235	62/216	0.707 (0.484 – 1.026)	
BRCA1/2 both	0/2	0/3	NC	



All subgroup hazard ratio estimates are <1 and all confidence intervals include the ITT population hazard ratio (shown by solid red line as per Cuzick J., Lancet 2005; 365:1308)

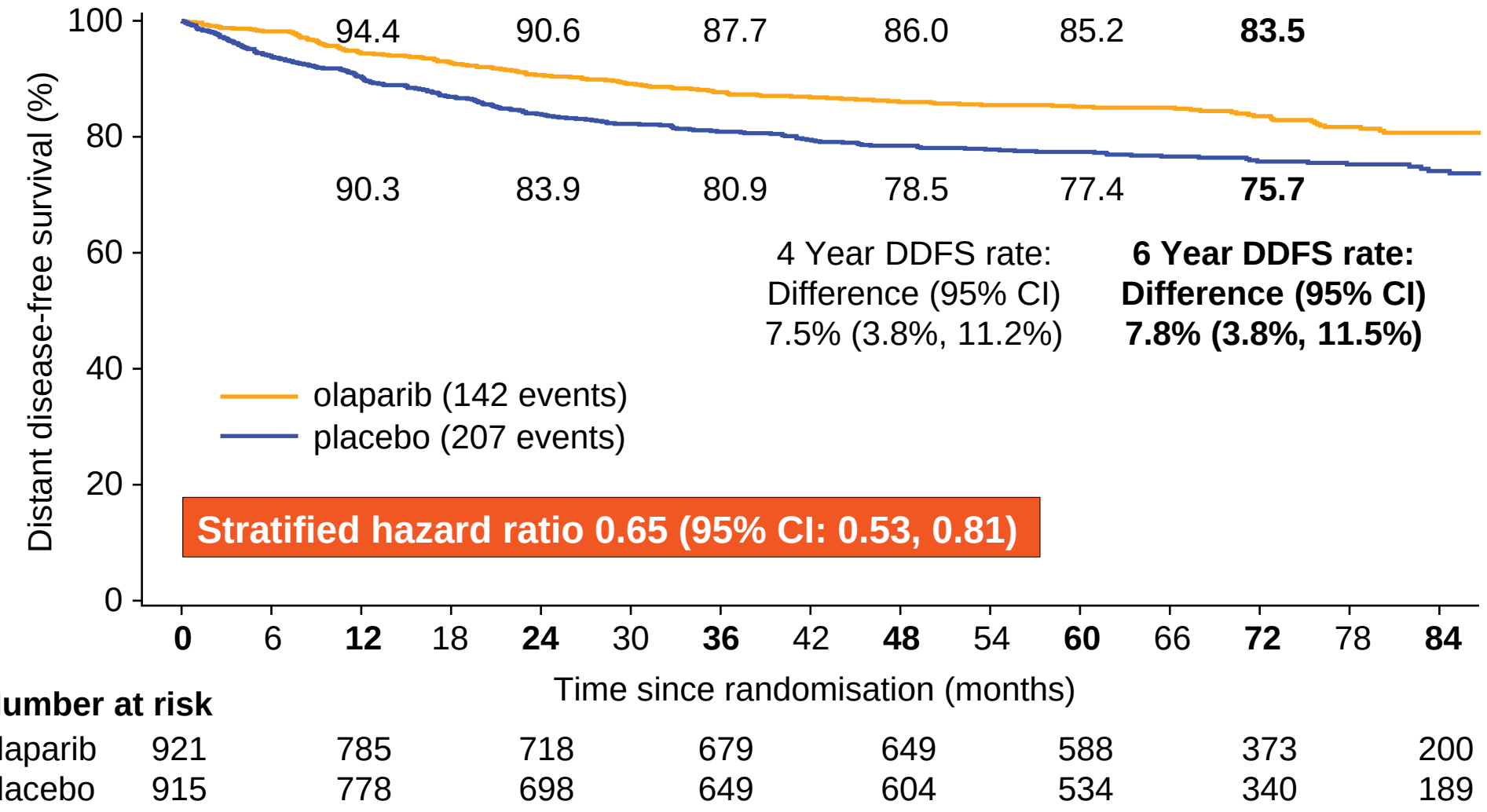
Analysis of IDFS by HR status



Number at risk

Olaparib	751	636	579	544	514	463	306	178	168	140	131	124	116	105	**53**	**15**
Placebo	758	632	565	519	489	430	282	162	157	134	118	109	99	82	**45**	**19**

Analysis of DDFS (ITT)

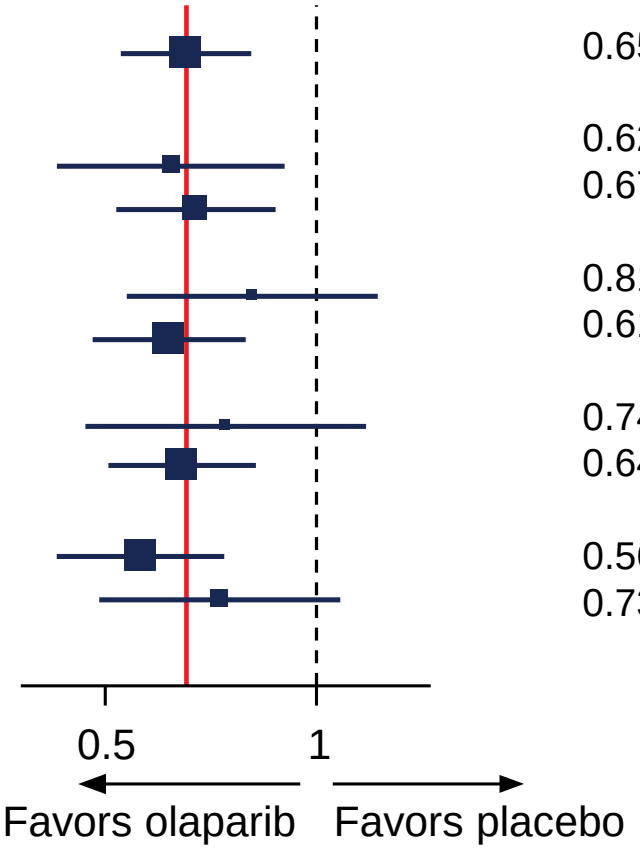


Number at risk

olaparib	921	785	718	679	649	588	373	200
placebo	915	778	698	649	604	534	340	189

Subgroup analysis of DDFS

Subgroup	Olaparib	Placebo	Stratified hazard ratio for distant disease-free survival (95% CI)	P value for heterogeneity
	Number of patients with a distant-disease event/total number			
All patients	142/921	207/915	0.653 (0.526 – 0.807)	NA
Prior Chemo				
Adjuvant	45/461	72/455	0.623 (0.427 – 0.901)	0.73
Neoadjuvant	97/460	135/460	0.675 (0.518 – 0.874)	
Prior Platinum				
Yes	42/247	50/238	0.812 (0.537 – 1.222)	0.27
No	100/674	157/677	0.618 (0.480 – 0.793)	
HR status				
HR+/HER2–	33/168	41/157	0.745 (0.469 – 1.177)	0.59
TNBC	109/751	166/758	0.645 (0.505 – 0.820)	
BRCA				
BRCA1	81/579	138/588	0.563 (0.426 – 0.739)	0.57
BRCA2	45/235	55/216	0.730 (0.490 – 1.081)	
BRCA1/2 both	0/2	0/3	NC	



All subgroup hazard ratio estimates are <1 and all confidence intervals include the ITT population hazard ratio (shown by solid red vertical line as per Cuzick J., Lancet 2005; 365:1308)

All Deaths (ITT Population)

	Olaparib (N = 921)		Placebo (N = 915)	
	Current	**Previous***	**Current**	**Previous***
Total number of deaths	**107 (11.6%)**	*[75 (8.1%)]*	**143 (15.6%)**	*[109 (11.9%)]*
Primary cause of death				
Breast cancer recurrence	**94 (10.2%)**	*[70 (7.6%)]*	**128 (14.0%)**	*[103 (11.3%)]*
Other [1]	**13 (1.4%)**	*[5 (<1%)]*	**15 (1.6%)**	*[6 (<1%)]*
Missing	**0 (0.0%)**	*[0 (0.0%)]*	**0 (0.0%)**	*[0 (0.0%)]*

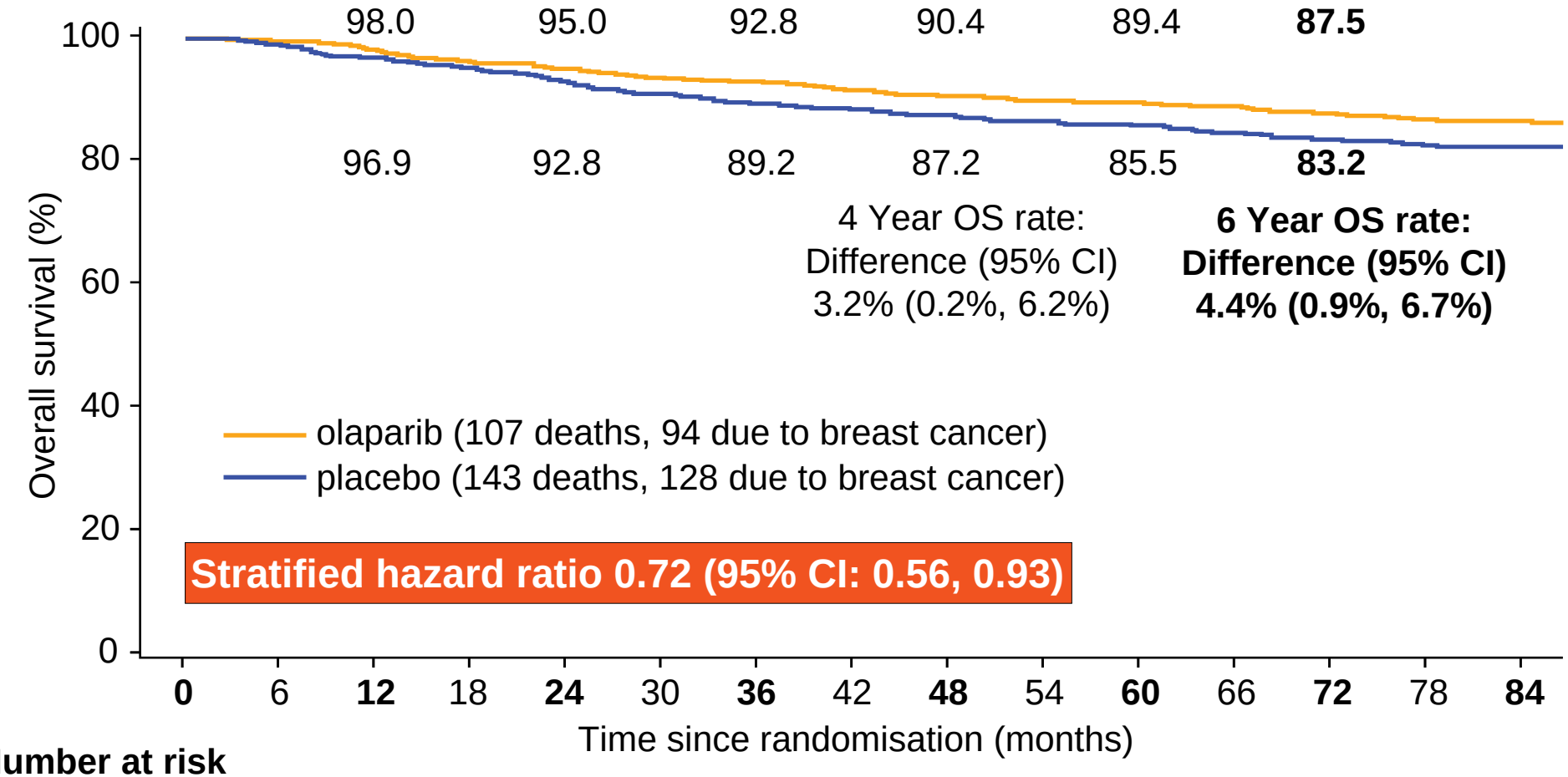
*Previous data from OS IA2

[1] Other cause of death (including fatal AEs):

olaparib: **pancreatic carcinoma (n = 1), acute myeloid leukemia (n = 3),** cardiovascular (n= 4), multiple organ dysfunction syndrome (n = 1), neutropenic sepsis (n = 1), unknown (n = 3)

placebo: **ovarian cancer (n = 2), pancreatic carcinoma (n = 1), pharyngeal carcinoma (n = 1), acute myeloid leukaemia (n = 3), myelodysplastic syndrome (n = 1), pneumonitis (n = 1),** cardiovascular (n = 2), superior vena cava occlusion (n = 1), covid-19 (n = 1), unknown (n = 2)

Analysis of OS (ITT)

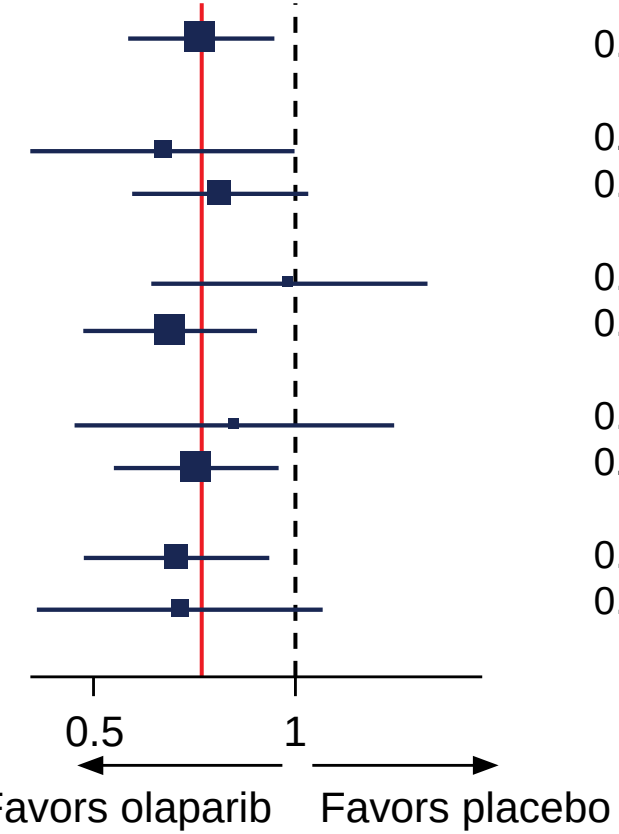


Number at risk

olaparib	921	846	795	765	728	660	420	224
placebo	915	843	788	739	698	616	390	221

Subgroup analysis of OS

Subgroup	Olaparib	Placebo	Stratified hazard ratio for overall survival (95% CI)	P value for heterogeneity
	Number of patients with a death/total number			
All patients	107/921	143/915	0.725 (0.563 – 0.930)	NA
Prior Chemo				
Adjuvant	31/461	48/455	0.638 (0.402 – 0.997)	0.49
Neoadjuvant	76/460	95/460	0.774 (0.571 – 1.045)	
Prior Platinum				
Yes	35/247	34/238	0.979 (0.610 – 1.574)	0.15
No	72/674	109/677	0.653 (0.483 – 0.876)	
HR status				
HR+/HER2–	24/168	28/157	0.814 (0.469 – 1.404)	0.67
TNBC	83/751	115/758	0.713 (0.536 – 0.944)	
BRCA				
BRCA1	64/579	94/588	0.667 (0.484 – 0.914)	1.00
BRCA2	28/235	38/216	0.676 (0.412 – 1.098)	
BRCA1/2 both	0/2	0/3	NC	



All subgroup hazard ratio estimates are <1 and all confidence intervals include the ITT population hazard ratio (shown by solid red vertical line as per Cuzick J., Lancet 2005; 365:1308)

Summary of adverse events of special interest

	Olaparib (N = 911)		Placebo (N = 904)	
	Current	Previous*	Current	Previous*
Adverse event leading to death[1]	**5 (<1%)**	*[2 (<1%)]*	**10 (1.1 %)**	*[4 (<1%)]*
Adverse event of special interest at any time	**57 (6.3%)**	*[31 (3.4%)]*	**84 (9.3%)**	*[51 (5.6%)]*
On treatment AESIs[2]	**14 (1.5%)**	*[14 (1.5%)]*	**28 (3.1%)**	*[27 (3.0%)]*
AESI > 30 days after last dose	**44 (4.8%)**	*[18 (2.0%)]*	**57 (6.3%)**	*[24 (2.7%)]*
MDS/AML	**4 (0.4%)**	*[2 (0.2%)]*	**6 (0.7%)**	*[3 (0.3%)]*
Pneumonitis	**9 (1.0%)**	*[9 (1.0%)]*	**13 (1.4%)**	*[12 (1.3%)]*
New primary malignancy	**45 (4.9%)**	*[21 (2.3%)]*	**68 (7.5%)**	*[36 (4.0%)]*

*Previous data from OS IA2. *AML acute myeloid leukemia; MDS myelodysplastic syndrome*

[1] Adverse events leading to death are;

olaparib: **pancreatic carcinoma (n = 1), acute myeloid leukemia (n = 3),** cardiac arrest (n = 1);

placebo: **ovarian cancer (n = 2), pancreatic carcinoma (n = 1), pharyngeal carcinoma (n = 1), acute myeloid leukemia (n = 3), myelodysplastic syndrome (n = 1), pneumonitis (n = 1),** cardiogenic shock (n = 1)

[2] No patients were still on treatment at OS IA2.

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Summary of adverse events of special interest

	Olaparib (N = 911)		Placebo (N = 904)	
	Current	Previous*	Current	Previous*
New primary malignancy	**45 (4.9%)**	*[21 (2.3%)]*	**68 (7.5%)**	*[36 (4.0%)]*
Breast	**26 (2.9%)**	*[14 (1.5%)]*	**36 (4.0%)**	*[16 (1.8%)]*
Ovary/FT	**5 (<1%)**	*[2 (<1%)]*	**14 (1.5%)**	*[10 (1.1%)]*
Pancreas	**3 (<1%)**	*[0 (0%)]*	**1 (<1%)**	*[1 (<1%)]*
Other	**13 (1.4%)**	*[6 (<1%)]*	**21 (2.3%)**	*[10 (1.1%)]*

*Previous data from OS IA2.

Summary of new Breast and Ovarian cancers during follow-up

	Olaparib (N = 921)	Placebo (N = 915)
Bilateral mastectomy prior to randomization	339 (36.8%)	321 (35.1%)
Bilateral mastectomy post randomization	143 (15.5%)	163 (17.8%)
Patients with contralateral invasive breast cancer [1]	**34**	**42**
Patients with contralateral non-invasive breast cancer	**3**	**4**
Bilateral salpingectomy or BSO prior to randomization [2]	186 (20.2%)	168 (18.4%)
Bilateral salpingectomy or BSO post randomization [3]	239 (26.0%)	249 (27.2%)
Patients with new primary ovarian or fallopian tube cancer [4]	**5**	**14**

BSO Bilateral salpingo-oophorectomy

[1] 3 patients in the olaparib arm and 2 patients in the placebo arm had bilateral mastectomy prior to contralateral invasive breast cancer.

[2] Salpingectomy only recorded; **olaparib** (n = 1), **placebo** (n = 2); oophorectomy only recorded **olaparib** (n = 22), **placebo** (n = 13);

[3] Salpingectomy only recorded; **olaparib** (n = 2), **placebo** (n = 4); oophorectomy only recorded **olaparib** (n = 14), **placebo** (n = 13);

[4] 1 patient in the olaparib arm and 1 patient in the placebo arm had BSO prior to new primary ovarian cancer

Reported On-study Pregnancies and Outcomes

	Olaparib (N=911)	Placebo (N=904)
Number of patients (%)	**41 (4.5%)**	**40 (4.4%)**
Number of pregnancies*	**51**	**51**
Pregnancy outcomes		
Full Term	32	39
Premature Birth	2	3
Spontaneous Miscarriage	8	6
Termination	6	3
Missing	3	0

*In the olaparib arm 8 patients had 2 pregnancies and 1 patient had 3 pregnancies
In the placebo arm 7 patients had 2 pregnancies and 1 patient had 5 pregnancies

Exploratory

OlympiA: Conclusions

- At 6.1 years median follow-up (maximum, 9.6 years),12 months of olaparib after (neo)adjuvant chemotherapy continues to demonstrate clinically meaningful improvements in IDFS, DDFS and OS in patients with g*BRCA*pv and high-risk HER2-negative primary BC.
- Olaparib benefit was consistent across all key subgroups, including for patients with high-risk ER and/or PgR positive disease.
- Fewer new primary malignancies were observed in the olaparib arm.
- No new safety signals were observed with longer term follow-up, and there is no evidence of increased risk of MDS or AML.
- These data continue to support adjuvant olaparib as standard of care for patients with g*BRCA*pv high-risk HER2-negative primary BC and therefore highlight the importance of g*BRCA* testing for treatment planning.
- Blinded follow-up for the final planned analysis continues until June 2029.

Acknowledgments

- The patients and their families
- The study investigators and site staff
- The study partners: BIG, NRG, Frontier Science, NCI, AstraZeneca and Merck and Co., Inc.
- The current and former members of the OlympiA committees:
  - Steering Committee
  - Genetics Advisory Committee
  - Translational Advisory Committee
  - Independent Data Monitoring Committee

Ashworth, Jackson & Kudos Groups
For the underpinning HR Deficiency / PARPi olaparib concept funded by
Breast Cancer Now
Cancer Research UK

OlympiA
OLaparib in Adjuvant BRCAm breast cancer

We dedicate these results to our co-PI **Dr Bella Kaufman** who was instrumental to OlympiA design and conduct and died shortly before the primary analysis was published

An Inspiration in our field

May her memory be a blessing

Judy E. Garber, MD, MPH