KEYNOTE – 355 (ESMO UPDATE)

	CPS ≥10		CPS ≥1	
	P + C n = 220	C n = 103	P + C n = 425	C n = 211
OS, mo, median[a] (95% CI)	23.0 (19.0 – 26.3)	16.1 (12.6 – 18.8)	17.6 (15.5 – 19.5)	16.0 (12.8 – 17.4)
OS, HR[b] (95% CI)	0.73[c] (0.55 – 0.95)		0.86[d] (0.72 – 1.04)	
PFS, mo, median[a] (95% CI)	9.7 (7.6 – 11.3)	5.6 (5.3 – 7.5)	7.6 (6.6 – 8.0)	5.6 (5.4 – 7.4)
PFS, HR[b] (95% CI)	0.66 (0.50 – 0.88)		0.75 0.62 – 0.91	
ORR, % (95% CI)	52.7 (45.9 – 59.5)	40.8 (31.2 – 50.9)	44.9 (40.1 – 49.8)	38.9 (32.2 – 45.8)

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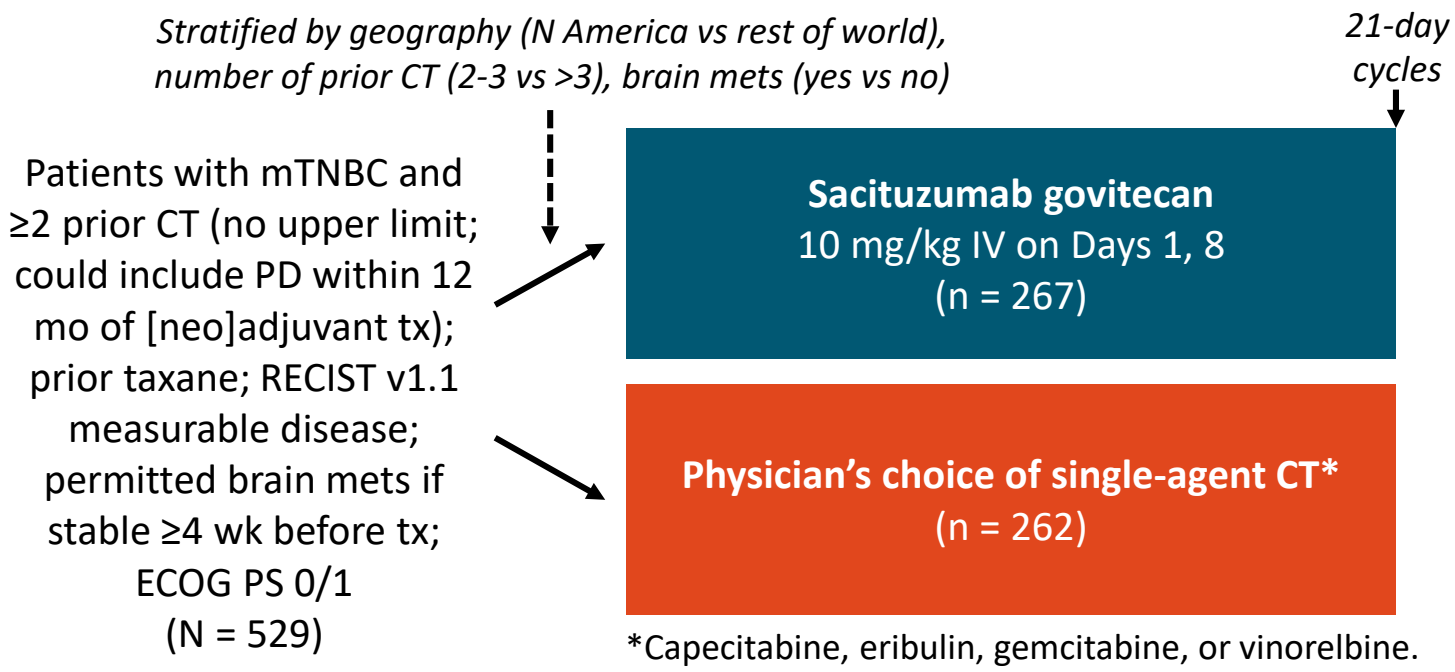
KEYNOTE-355

- Pembrolizumab + chemo approved
  - Chemo backbone: Taxane, Gemcitabine / Carboplatin
  - CPS≥ 10

SACITUZUMAB GOVITECAN – ASCENT TRIAL

STUDY SCHEMA



- **Primary endpoint:** PFS by BICR in patients without brain mets
- **Secondary endpoints:** investigator-assessed PFS, OS, ORR, DoR, TTR, safety

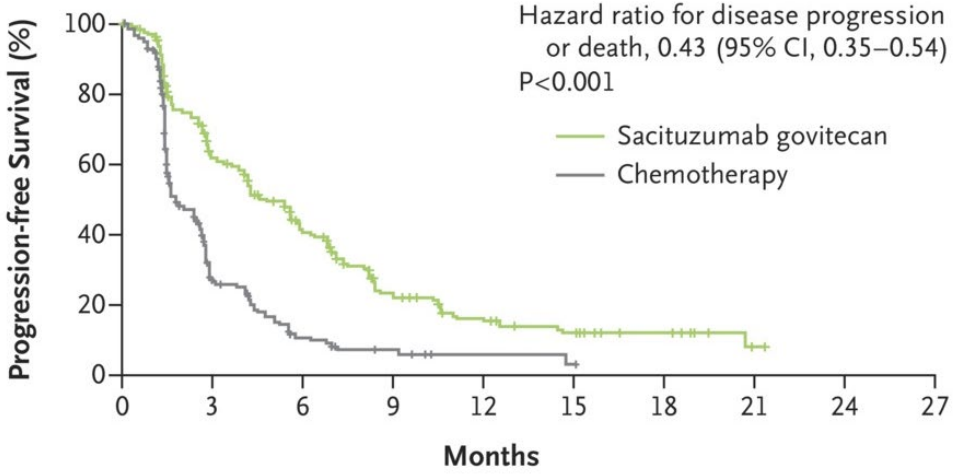
- **Trial halted early based on efficacy** per unanimous recommendation of DSMC

Slide credit: clinicaloptions.com

Bardia et al, NEJM 2021

PFS – ENTIRE POPULATION

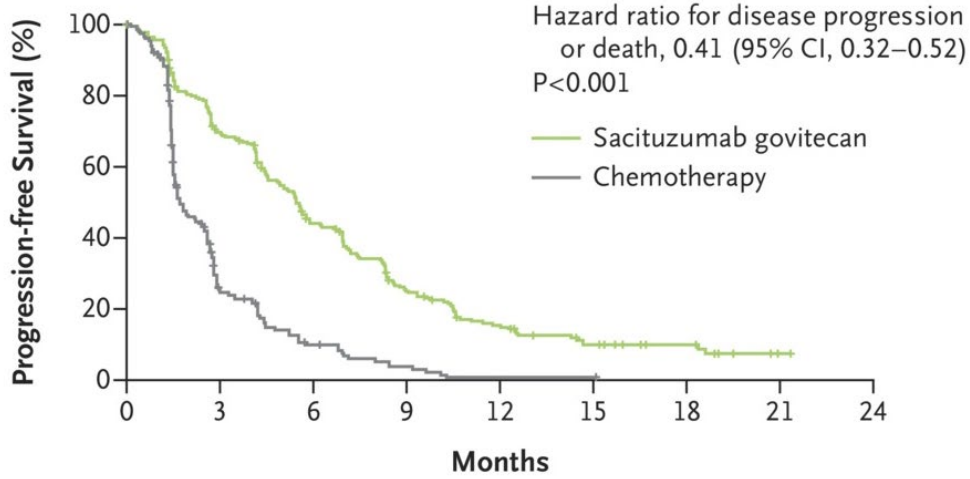
	No. of Patients	No. of Events	Median Progression-free Survival
			mo (95% CI)
Sacituzumab Govitecan	267	190	4.8 (4.1–5.8)
Chemotherapy	262	171	1.7 (1.5–2.5)



No. at Risk								
Sacituzumab govitecan	267	145	82	38	23	14	8	1
Chemotherapy	262	41	13	6	2	1	0	0

PFS – No Brain Mets

	No. of Patients	No. of Events	Median Progression-free Survival
			mo (95% CI)
Sacituzumab Govitecan	235	166	5.6 (4.3–6.3)
Chemotherapy	233	150	1.7 (1.5–2.6)



No. at Risk								
Sacituzumab govitecan	235	154	91	49	28	15	9	1
Chemotherapy	233	39	14	5	1	1	0	0

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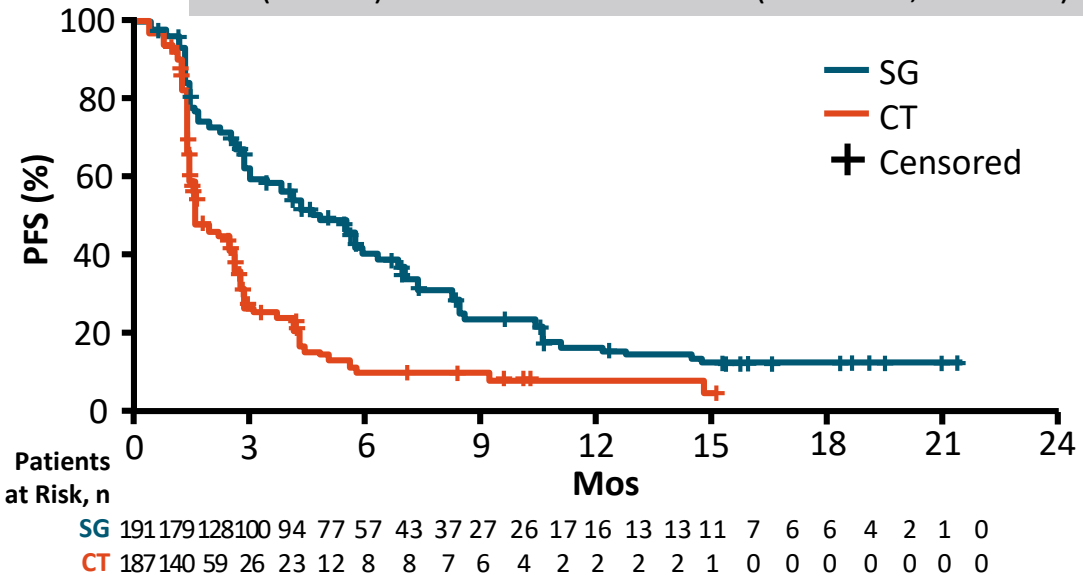
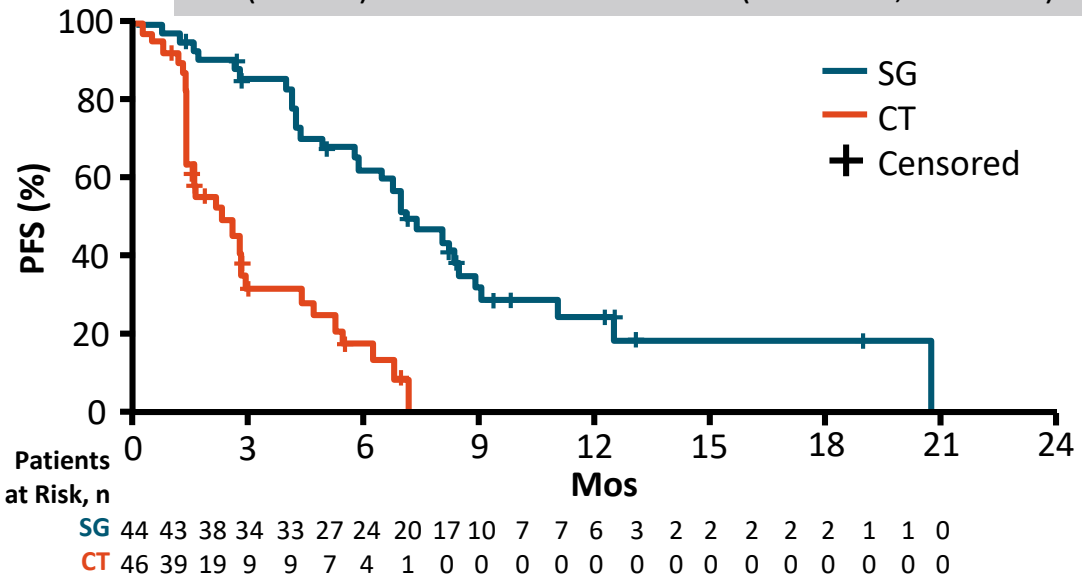
Bardia et al, NEJM 2021

ASCENT Subgroup Analyses: PFS in Patients Without Brain Mets Aged <65 Yr vs ≥65 Yr

PFS BICR Analysis	Aged <65 Yr	
	SG (n = 191)	CT (n = 187)
No. events	136	117
Median PFS, mo (95% CI)	4.6 (3.7-5.7)	1.7 (1.5-2.5)
HR (95% CI)	0.46 (0.35-0.59; *P* <.0001)	



PFS BICR Analysis	Aged ≥65 Yr	
	SG (n = 44)	CT (n = 46)
No. events	30	33
Median PFS, mo (95% CI)	7.1 (5.8-8.9)	2.4 (1.4-2.9)
HR (95% CI)	0.22 (0.12-0.40; *P* <.0001)	



- In those aged ≥65 yr, median PFS benefit with SG vs CT was similar to benefit in overall population (overall population: 5.6 vs 1.7 mo)

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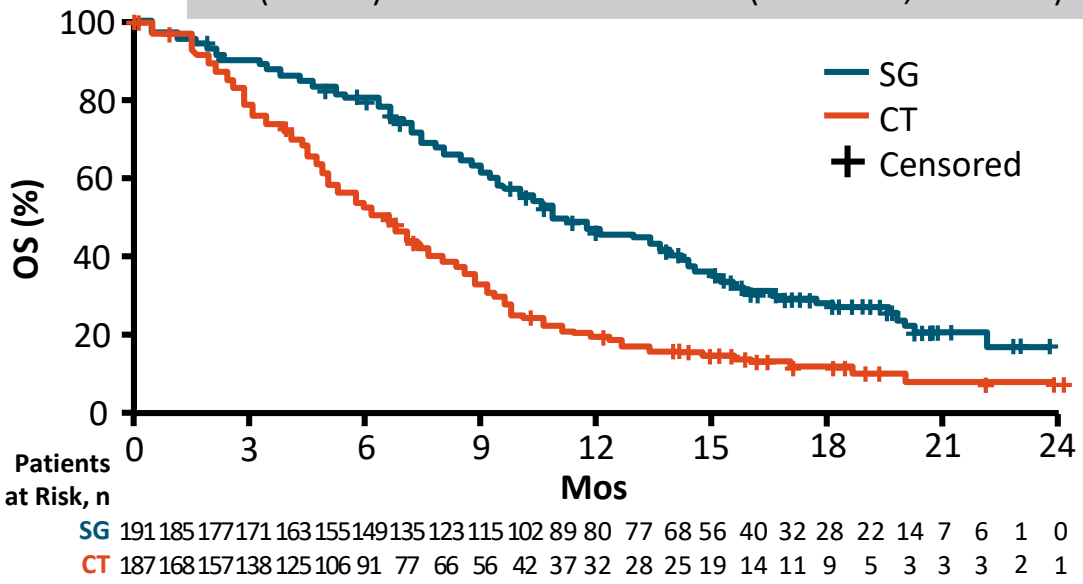
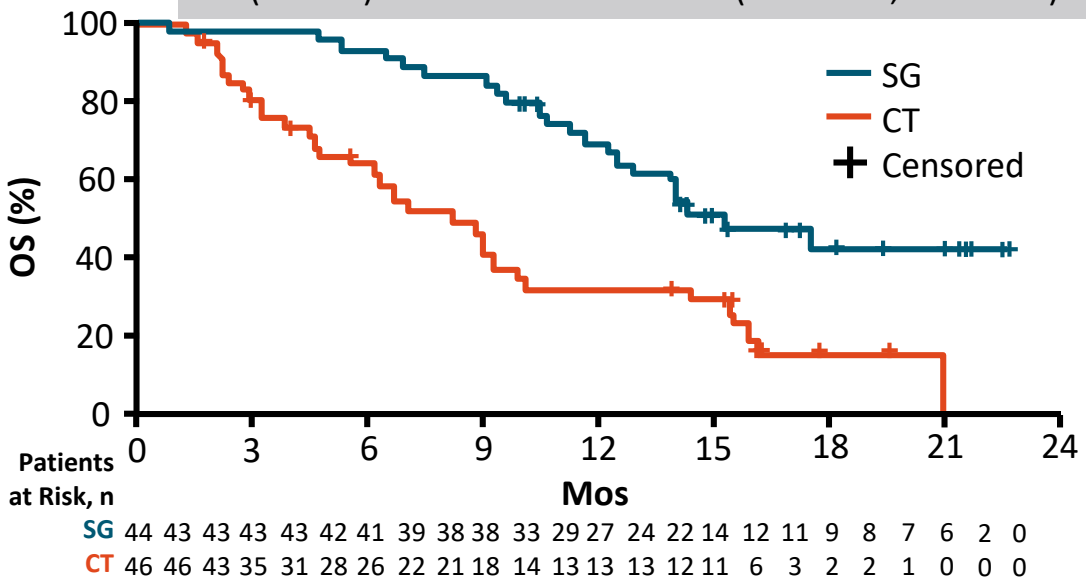
Slide credit: clinicaloptions.com

ASCENT Subgroup Analyses: OS in Patients Without Brain Mets Aged <65 Yr vs ≥65 Yr

OS BICR Analysis	Aged <65 Yr	
	SG (n = 191)	CT (n = 187)
No. events	133	150
Median OS, mo (95% CI)	11.2 (9.9-13.4)	6.6 (5.3-7.4)
HR (95% CI)	0.50 (0.40-0.64; *P* <.0001)	



OS BICR Analysis	Aged ≥65 Yr	
	SG (n = 44)	CT (n = 46)
No. events	22	35
Median OS, mo (95% CI)	15.3 (12.4-NE)	8.2 (5.6-9.8)
HR (95% CI)	0.37 (0.22-0.64; *P* = .0003)	



- In those aged ≥65 yr, median OS benefit with SG vs CT was similar to benefit in overall population (overall population: 12.1 vs 6.7 mo)

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BRCA-ASSOCIATED CANCER METASTATIC DISEASE

PARP Inhibitors

- Olaparib (OLYMPIAD trial)
- Talazoparib (EMBRACA trial)

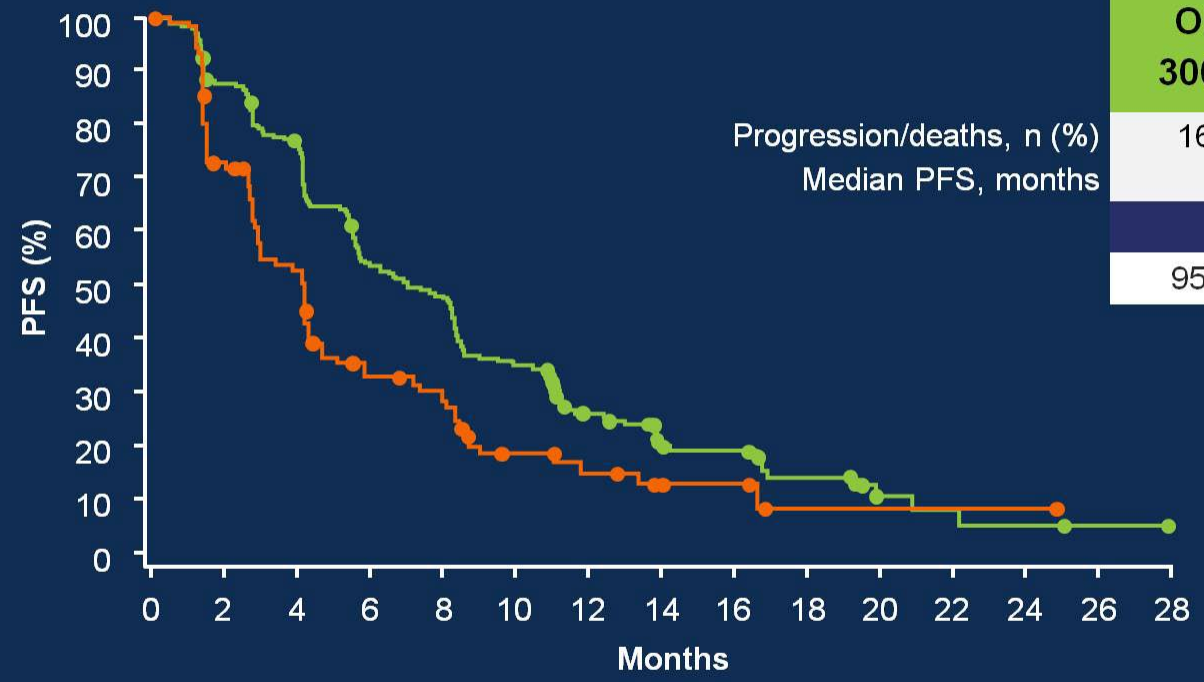
OlympiAD: Phase III trial of olaparib monotherapy versus chemotherapy for patients with HER2-negative metastatic breast cancer and a germline *BRCA* mutation

Mark Robson,[1] Seock-Ah Im,[2] Elżbieta Senkus,[3] Binghe Xu,[4] Susan M Domchek,[5] Norikazu Masuda,[6] Suzette Delaloge,[7] Wei Li,[8] Nadine Tung,[9] Anne Armstrong,[10] Wenting Wu,[11] Carsten Goessl,[11] Sarah Runswick,[12] Pierfranco Conte[13]

[1]Memorial Sloan Kettering Cancer Center, New York, USA; [2]Seoul National University Hospital, Seoul, Korea; [3]Medical University of Gdańsk, Gdańsk, Poland; [4]Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China; [5]Basser Center, University of Pennsylvania, Philadelphia, USA; [6]National Hospital Organization, Osaka National Hospital, Osaka, Japan; [7]Institut Gustave Roussy, Villejuif, France; [8]The First Hospital of Jilin University, Changchun, China; [9]Beth Israel Deaconess Medical Center, Dana-Farber Harvard Cancer Center, Boston, USA; [10]Christie Hospital NHS Foundation Trust, Manchester, UK; [11]AstraZeneca, Gaithersburg, USA; [12]AstraZeneca, Macclesfield, UK; [13]University of Padova and Istituto Oncologico Veneto IRCCS, Padova, Italy

ClinicalTrials.gov identifier: NCT02000622. This study was sponsored by AstraZeneca

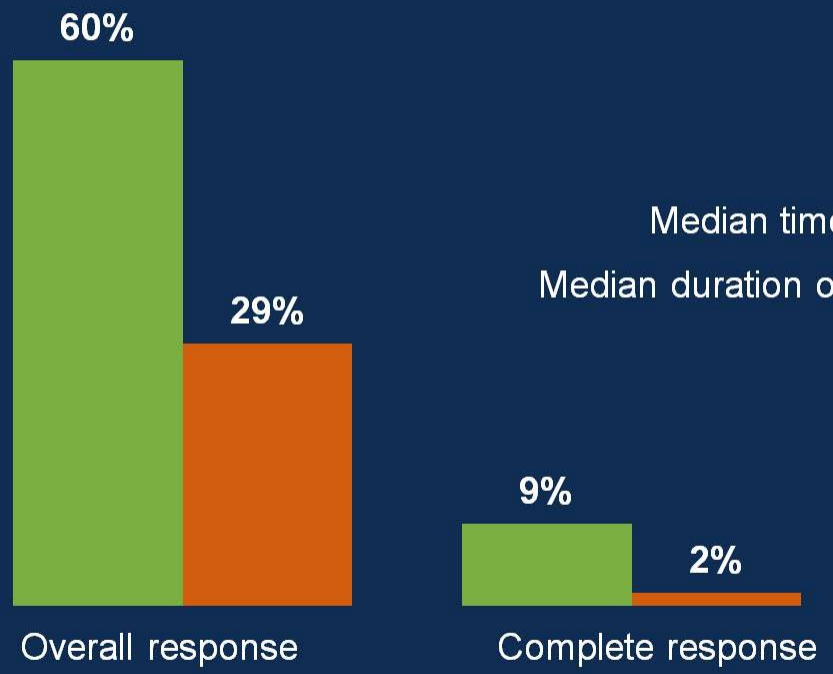
Primary endpoint: progression-free survival by BICR



	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		

At risk, n															
Olaparib 300 mg bd	205	177	154	107	94	69	40	23	21	11	4	3	2	1	0
Chemotherapy TPC	97	63	44	25	21	11	8	4	4	1	1	1	1	0	0

Objective response by BICR

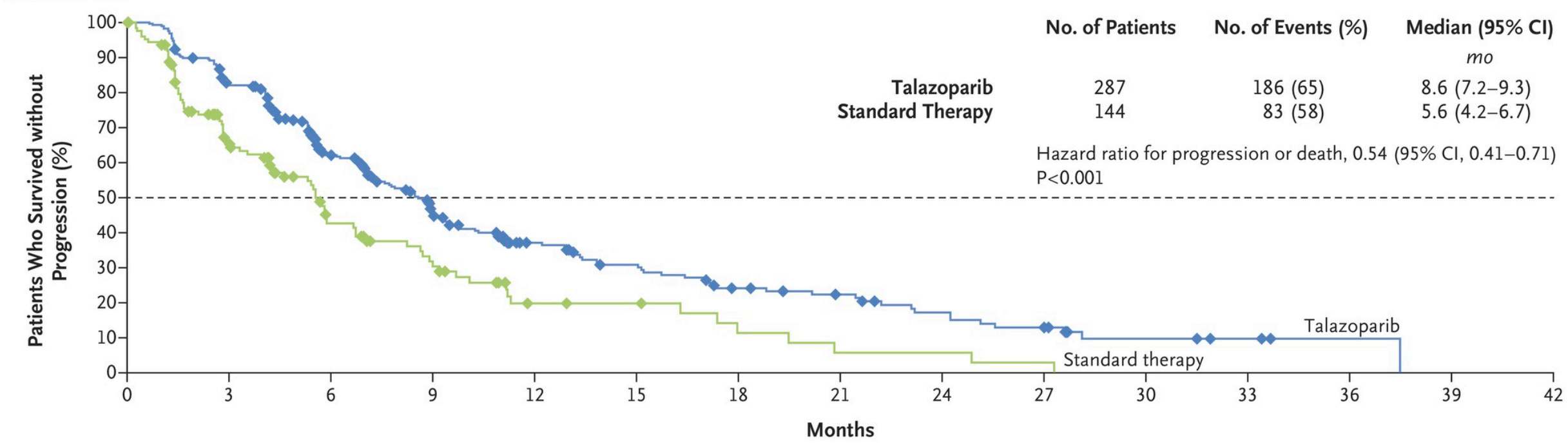


	Olaparib 300 mg bd	Chemotherapy TPC
n	167	66
Median time to response, days	47	45
Median duration of response, months	6.2 (4.6–7.2)	7.1 (2.8–12.2)

ORIGINAL ARTICLE

Talazoparib in Patients with Advanced Breast Cancer and a Germline *BRCA* Mutation

Jennifer K. Litton, M.D., Hope S. Rugo, M.D., Johannes Ettl, M.D., Sara A. Hurvitz, M.D., Anthony Gonçalves, M.D., Ph.D., Kyung-Hun Lee, M.D., Ph.D., Louis Fehrenbacher, M.D., Rinat Yerushalmi, M.D., Lida A. Mina, M.D., Miguel Martin, M.D., Ph.D., Henri Roché, M.D., Ph.D., Young-Hyuck Im, M.D., Ph.D., Ruben G.W. Quek, Ph.D., Denka Markova, Ph.D., Iulia C. Tudor, Ph.D., Alison L. Hannah, M.D., Wolfgang Eiermann, M.D., and Joanne L. Blum, M.D., Ph.D.



	No. of Patients	No. of Events (%)	Median (95% CI)
			mo
Talazoparib	287	186 (65)	8.6 (7.2–9.3)
Standard Therapy	144	83 (58)	5.6 (4.2–6.7)

Hazard ratio for progression or death, 0.54 (95% CI, 0.41–0.71)
P<0.001

The NEW ENGLAND JOURNAL of MEDICINE

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BRCA-ASSOCIATED CANCER EARLY STAGE

BIG Breast International Group

frontier science

NRG ONCOLOGY
Advancing Research. Improving Lives.

NIH NATIONAL CANCER INSTITUTE

A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline *BRCA1/2* mutations and high-risk HER2-negative early breast cancer

Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

2021 ASCO ANNUAL MEETING

OlympiA: Trial schema

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

Neoadjuvant Group
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS+EG score ≥ 3

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

Adjuvant Group
- *TNBC:* ≥ pT2 or ≥ pN1
- *Hormone receptor–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
- Hormone receptor–positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

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

Hormone receptor +ve defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple Negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

CPS + EG Score

Table 1. Point Assignments for the CPS + EG Staging System

Stage	Points
Clinical stage	
I	0
IIA	0
IIB	1
IIIA	1
IIIB	2
IIIC	2
Pathologic stage	
0	0
I	0
IIA	1
IIB	1
IIIA	1
IIIB	1
IIIC	2
Tumor marker	
ER negative	1
Nuclear grade 3	1

Abbreviations: CPS + EG, clinical-pathologic staging system incorporating ER-negative disease and nuclear grade 3 tumor pathology; ER, estrogen receptor.

http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=bcnt

Mittendorf et al, JCO 2011

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OlympiA: Patient characteristics

	Olaparib (N = 921)	Placebo (N = 915)
Age, years, median (interquartile range)	**42** (36–49)	**43** (36–50)
BRCA gene affected 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%)
BRCA testing available		
Local and central BRCA result*	550 (**59.7%**)	540 (**59.0%**)
Local testing only	130 (14.1%)	141 (15.4%)
Central Myriad testing only	240 (26.0%)	234 (25.6%)
No local or central Myriad testing available	1 (0.1%)	0 (0.0%)
Primary breast cancer surgery		
Mastectomy	698 (**75.8%**)	673 (**73.6%**)
Conservative surgery only	223 (24.2%)	240 (26.2%)
Missing	0 (0.0%)	2 (0.2%)

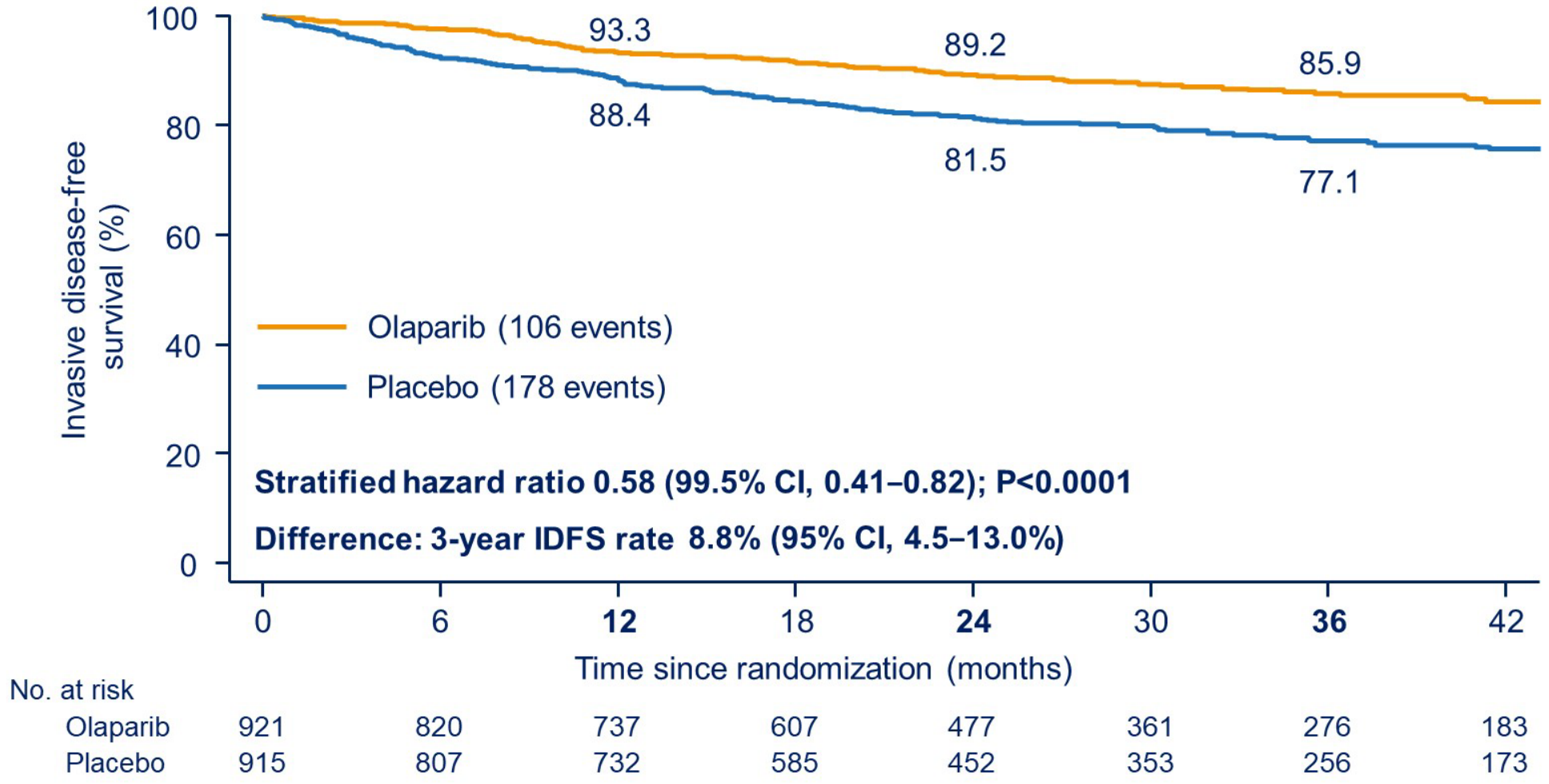
*Local/Central discordant results: Olaparib 12 (2.2%), Placebo 10 (1.9%), Total 22 (2.0%)

OlympiA: Patient characteristics

	Olaparib (N = 921)	Placebo (N = 915)
Hormone receptor status*		
Hormone receptor ≥ 1% / HER2-†	168 (**18.2%**)	157 (**17.2%**)
Triple Negative Breast Cancer‡	751 (**81.5%**)	758 (**82.8%**)
Menopausal status (female only)		
Premenopausal	572/919 (62.2%)	553/911 (60.7%)
Postmenopausal	347/919 (37.8%)	358/911 (39.3%)
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%**)	849 (**92.8%**)
Neo(adjuvant) platinum-based therapy	247 (**26.8%**)	239 (**26.1%**)
Concurrent endocrine therapy (HR–positive only)	146/168 (86.9%)	142/157 (90.4%)

*Defined by local test results
†Following a protocol amended in 2015, the first patient with hormone receptor–positive disease was enrolled in December 2015
‡Two patients are excluded from the summary of the triple–negative breast cancer subset because they do not have confirmed HER2–negative status

OlympiA: Invasive disease-free survival (ITT)



No. at risk

Olaparib	921	820	737	607	477	361	276	183
Placebo	915	807	732	585	452	353	256	173

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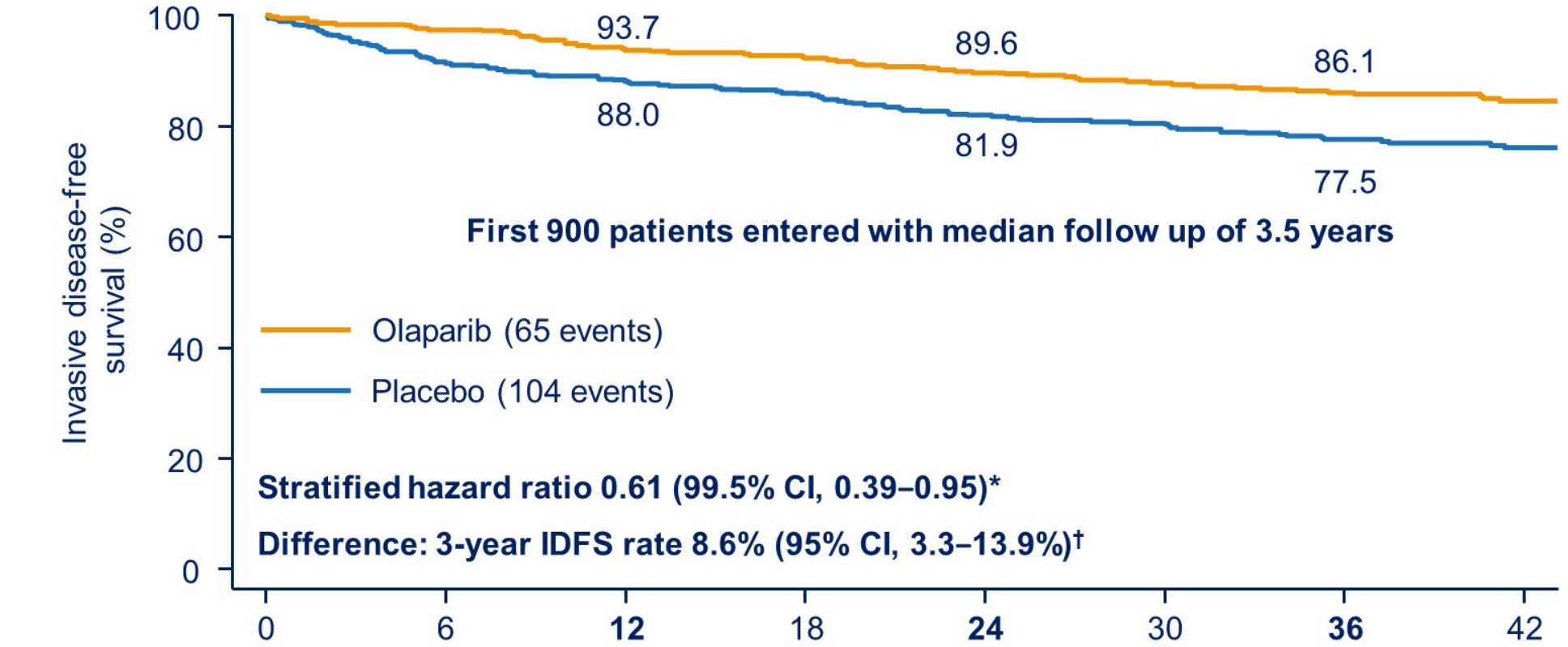
The Institute of Cancer Research and Kings College London

OlympiA: Type of first IDFS event

	Olaparib (N = 921)	Placebo (N = 915)
Number of patients with a first IDFS event	**106 (11.5%)**	**178 (19.5%)**
Distant recurrence	**72 (7.8%)**	**120 (13.1%)**
Distant CNS Recurrence	22 (2.4%)	36 (3.9%)
Distant excluding CNS Recurrence	50 (5.4%)	84 (9.2%)
Regional (Ipsilateral) Recurrence	6 (0.7%)	14 (1.5%)
Local (Ipsilateral) Recurrence	7 (0.8%)	11 (1.2%)
Contralateral invasive breast cancer	8 (0.9%)	12 (1.3%)
Second primary non-breast malignancies	11 (1.2%)	21 (2.3%)
Ovarian	1 (0.1%)	4 (0.4%)
Peritoneal	0 (0.0%)	0 (0.0%)
Fallopian tube	1 (0.1%)	4 (0.4%)
Other	9 (1.0%)	13 (1.4%)
Deaths without a prior IDFS event*	2 (0.2%)	0 (0.0%)

There can only be one first IDFS event per patient
*1 death due to cardiac arrest and 1 patient with unknown cause of death

OlympiA: Invasive disease-free survival (mature cohort)



No. at risk

Olaparib	449	399	378	365	343	324	276	183
Placebo	451	396	378	361	340	321	256	173

*Stratified Cox proportional hazards model, †Kaplan–Meier estimates

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The Institute of Cancer Research and Kings College London

OlympiA: Distant disease-free survival

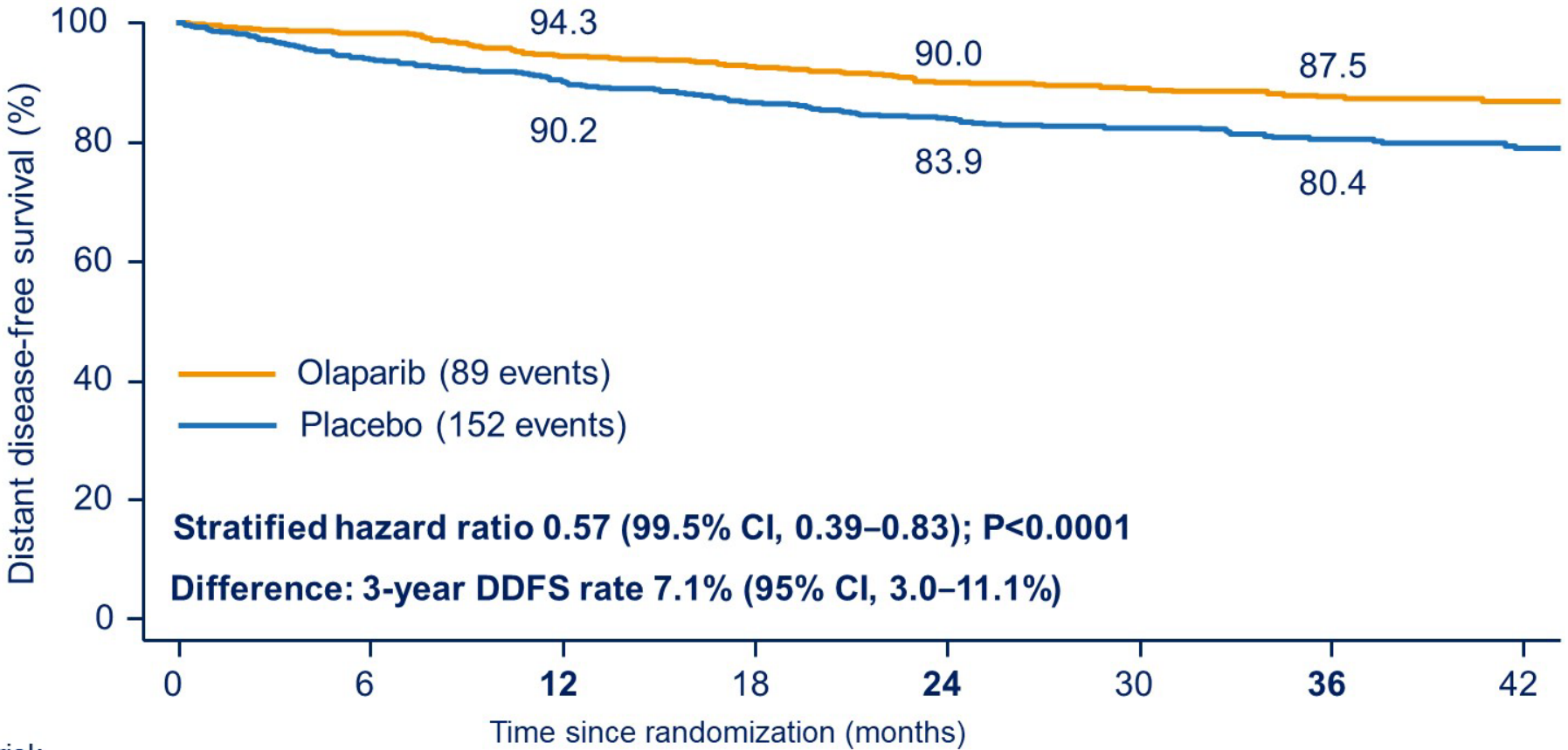
IDFS
P<0.005

DDFS and OS only tested if IDFS significant

DDFS
P<0.005

OS
P<0.01

Recycling of alpha for conservation future analyses



No. at risk

Olaparib	921	823	744	612	479	364	279	187
Placebo	915	817	742	594	461	359	263	179

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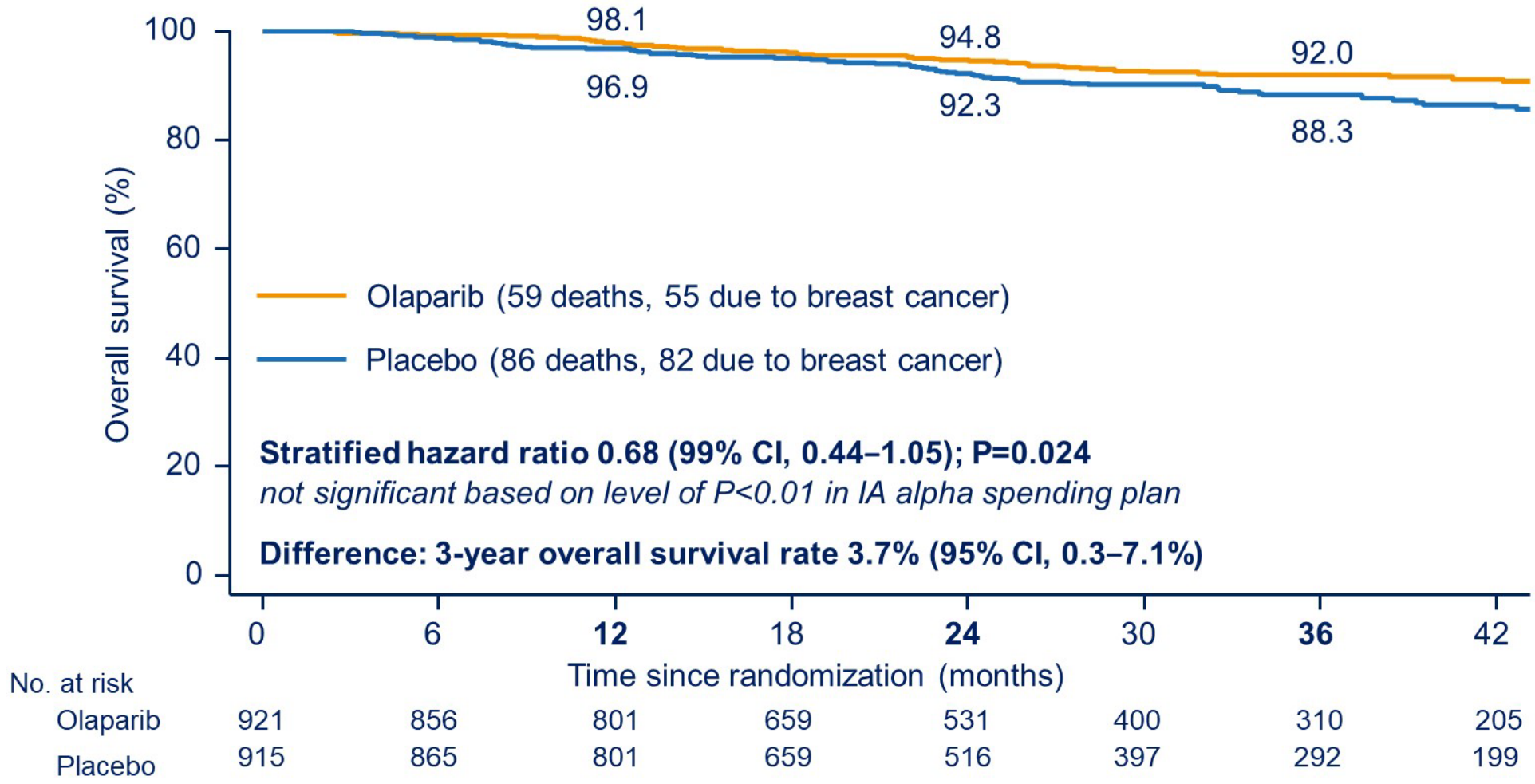
OlympiA: Overall survival



Presented By: Andrew Tutt MB ChB PhD FMedSci
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OlympiA: Summary of adverse events

	Olaparib (N = 911)	Placebo (N = 904)
Any adverse event	835 (91.7%)	753 (83.3%)
Serious adverse event (SAE)	**79 (8.7%)**	**76 (8.4%)**
Adverse event of special interest	**30 (3.3%)**	**46 (5.1%)**
MDS/AML	**2 (0.2%)**	**3 (0.3%)**
Pneumonitis	9 (1.0%)	11 (1.2%)
New primary malignancy	**20 (2.2%)**	**32 (3.5%)**
Grade ≥ 3 adverse event	221 (24.3%)	102 (11.3%)
Grade 4 adverse event	**17 (1.9%)**	**4 (0.4%)**
Adverse event leading to permanent discontinuation of treatment*	**90 (9.9%)**	**38 (4.2%)**
Adverse event leading to death†	1 (0.1%)	2 (0.2%)

Includes adverse events with an onset date on or after the first dose date and up to and including 30 days following date of last dose of study medication. AML denotes acute myeloid leukemia; MDS myelodysplastic syndrome

*Adverse events leading to permanent discontinuation of treatment in the olaparib group that occurring in > 1% were; nausea, anemia and fatigue

†Adverse events leading to death are cardiac arrest (olaparib, n = 1), AML (placebo, n = 1), and ovarian cancer (placebo, n = 1)

Presented By: Andrew Tutt MB ChB PhD FMedSci
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OLYMPIA: Conclusions

- Adjuvant Olaparib FDA Approved 3/2022
  - One year of therapy
- Effective / Well tolerated

OLYMPIA: Questions?

- TNBC with residual disease
  - Capecitabine or Olaparib or Sequence?
  - Keep Pembrolizumab with Olaparib?
- HR+ Eligible Patients
  - Calculate CPS + EG score
  - Abemaciclib or Olaparib?

THANK YOU


Questions?

SUPPLEMENTAL SLIDES?

- GeparNuevo
- Impassion 031