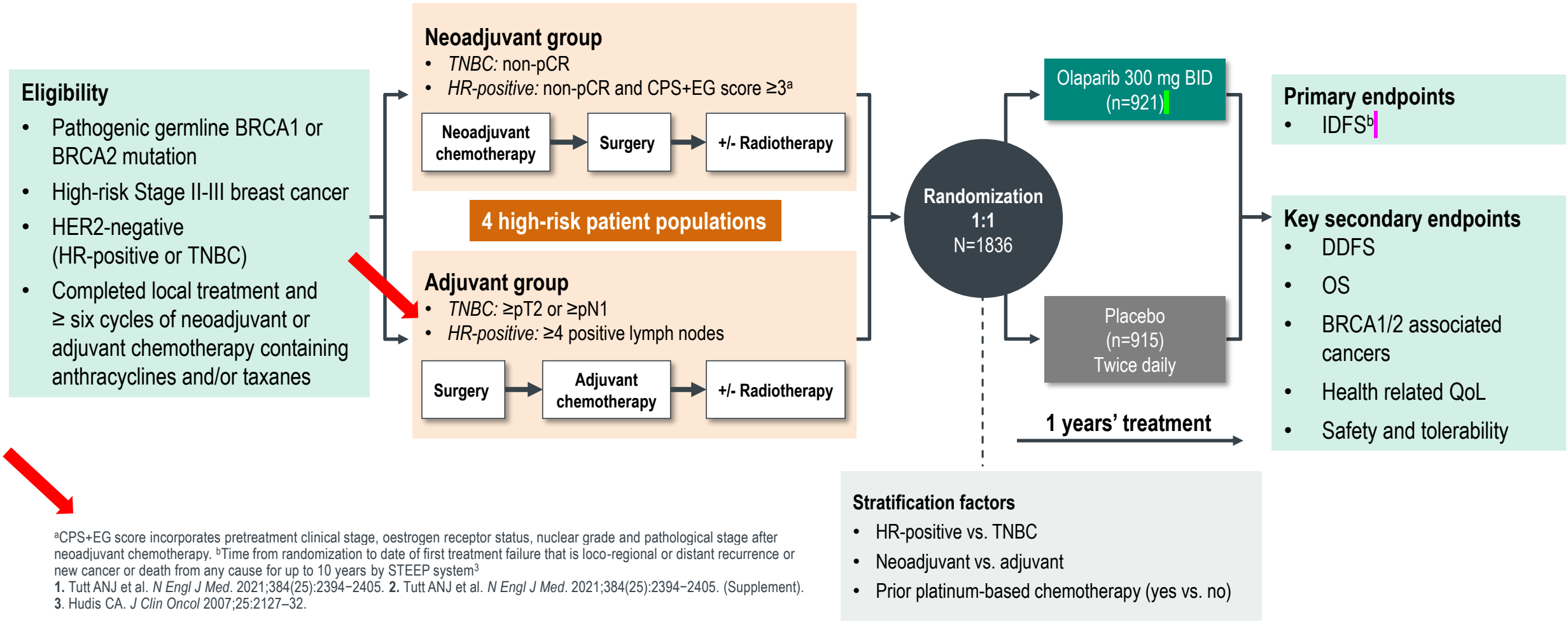
Nelle pazienti con ca mammario HER2-neg ad alto rischio e portatrici di VP gBRCA1/2, che abbiano completato chemioterapia (neo)-adiuvante, è raccomandabile olaparib?

Alberto Zambelli
Humanitas University Research Hospital
Rozzano (Mi)

OlympiA Study Design



[a]CPS+EG score incorporates pretreatment clinical stage, oestrogen receptor status, nuclear grade and pathological stage after neoadjuvant chemotherapy. [b]Time from randomization to date of first treatment failure that is loco-regional or distant recurrence or new cancer or death from any cause for up to 10 years by STEEP system[3]

1. Tutt ANJ et al. *N Engl J Med*. 2021;384(25):2394−2405. **2.** Tutt ANJ et al. *N Engl J Med*. 2021;384(25):2394−2405. (Supplement).
3. Hudis CA. *J Clin Oncol* 2007;25:2127–32.

OlympiA: Pathological Characteristics

CPS+EG scorea (Neoadjuvant only)

n (%)	Olaparib N=460	Placebo N=460
HR+/HER2-		
CPS+EG score ≤ 2[a]	13 (2.8)	6 (1.3)
CPS+EG score of 3 or 4	88 (19.1)	85 (18.5)
CPS+EG score of 5 or 6	3 (0.7%)	1 (0.2)
Not recorded	0 (0)	0 (0)
Triple Negative Breast Cancer		
CPS+EG score ≤ 2	151 (32.8)	144 (31.3)
CPS+EG score of 3 or 4	179 (38.8)	197 (42.8)
CPS+EG score of 5 or 6	19 (4.1)	14 (3.0)
Not recorded	7 (1.5)	13 (2.8)

Pathological AJCC stage (Adjuvant only)

n (%)	Olaparib N=461	Placebo N=455
0	0 (0.0)	0 (0.0)
IA[a]	5 (1.1)	2 (0.4)
IB	15 (3.3)	11 (2.4)
IIA	264 (57.3)	250 (54.9)
IIB	70 (15.2)	11 (2.4)
IIIA	73 (15.8)	70 (15.4)
IIIB	0 (0.0)	2 (0.4)
IIIC	28 (6.1)	41 (9.0)
NA[b]	6 (1.3)	4 (0.9)

aCPS+EG score is a staging system for disease specific survival in patients with breast cancer treated with neoadjuvant chemotherapy incorporating pretreatment clinical stage, estrogen receptor status, nuclear grade and post-neoadjuvant chemotherapy patholocial stage.

[a]Reported as protocol deviations. [b]These include 2 occult BC (placebo, n=2), 6 pTx (Olaparib, n=4; placebo, n=2) and 2 pNx (Olaparib, n=2).

Tutt ANJ et al. *N Engl J Med*. 2021;384(25):2394−2405. (Supplement).

Patients characteristics

Table 1. Demographic and Disease Characteristics of the Patients at Baseline.*

Characteristic	Olaparib (N=921)	Placebo (N=915)
Median age (interquartile range) — yr	42 (36–49)	43 (36–50)
Germline *BRCA* mutation — no. (%)†		
BRCA1	657 (71.3)	670 (73.2)
BRCA2	261 (28.3)	239 (26.1)
BRCA1 and *BRCA2*	2 (0.2)	5 (0.5)
Missing data	1 (0.1)	1 (0.1)
Previous adjuvant or neoadjuvant chemotherapy — no. (%)		
Adjuvant	461 (50.1)	455 (49.7)
Neoadjuvant	460 (49.9)	460 (50.3)
Regimen with both anthracycline and taxane	871 (94.6)	849 (92.8)
Anthracycline regimen, without taxane	7 (0.8)	13 (1.4)
Taxane regimen, without anthracycline	43 (4.7)	52 (5.7)
Regimen not reported	0	1 (0.1)
<6 Cycles of neoadjuvant or adjuvant chemotherapy	7 (0.8)	15 (1.6)
Platinum-based neoadjuvant or adjuvant therapy		
No	674 (73.2)	676 (73.9)
Yes	247 (26.8)	239 (26.1)
Concurrent hormone therapy (hormone-receptor–positive patients only) — no./total no. (%)	146/168 (86.9)	142/157 (90.4)
Hormone-receptor status — no. (%)‡		
Hormone-receptor positive and HER2 negative§	168 (18.2)	157 (17.2)
Triple-negative breast cancer¶	751 (81.5)	758 (82.8)
Menopausal status (women only) — no./total no. (%)		
Premenopausal	572/919 (62.2)	553/911 (60.7)
Postmenopausal	347/919 (37.8)	358/911 (39.3)
Surgery for primary breast cancer — no. (%)		
Mastectomy	698 (75.8)	673 (73.6)
Conservative surgery only	223 (24.2)	240 (26.2)
Missing data	0	2 (0.2)

Tutt et al, *NEJM* 2021

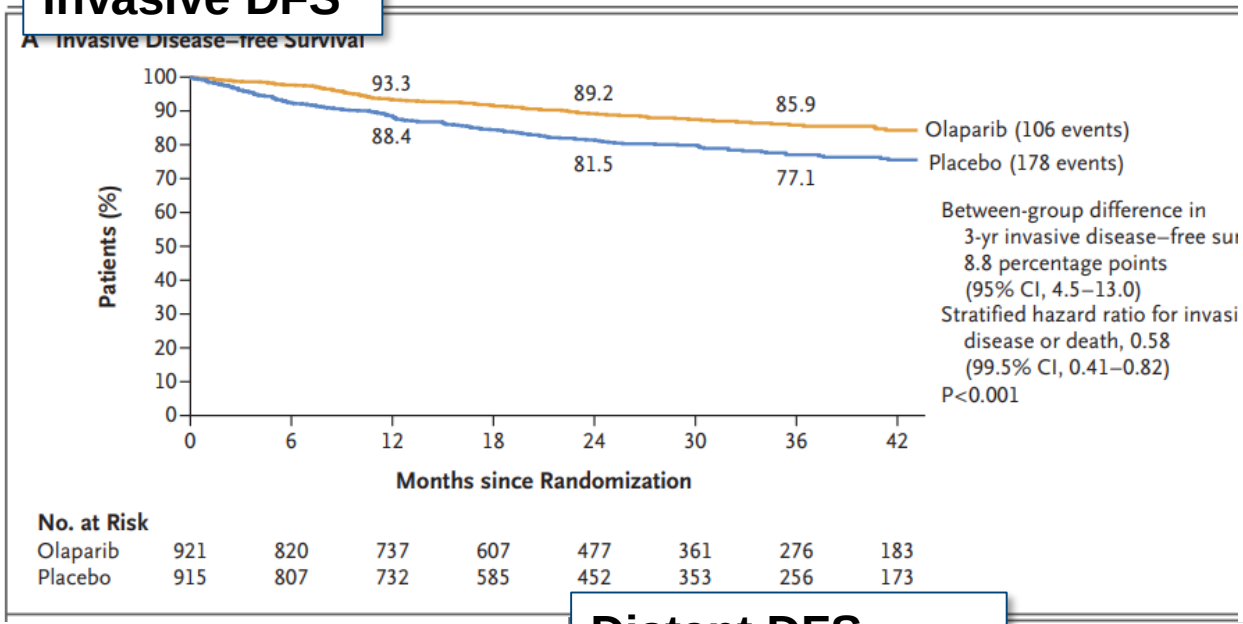
Comment on study population

- Very young (median 42-43, 25% > 50)
- 72.3% gBRCA1m
- 82.2% TNBC, no HER2+ (by design)
- 74.7% treated with mastectomy (46.5% bilateral)
- RRSO in ~60%

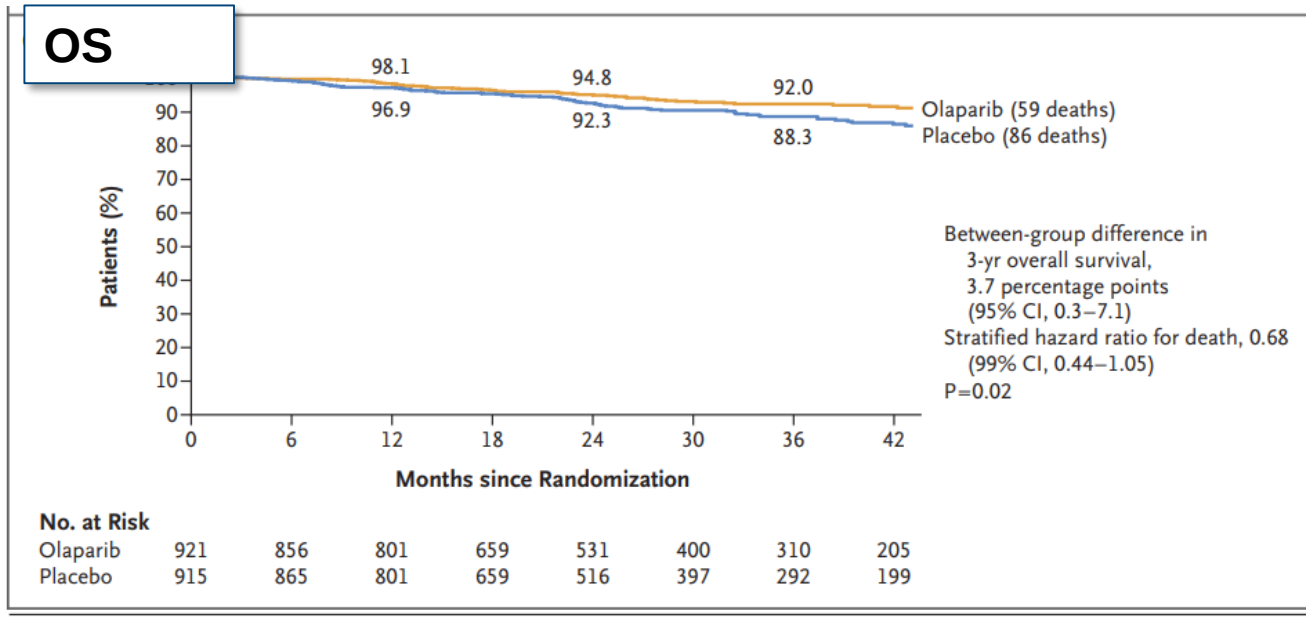
- CPS+EG score unfamiliar to many
  - http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=bcnt

Results

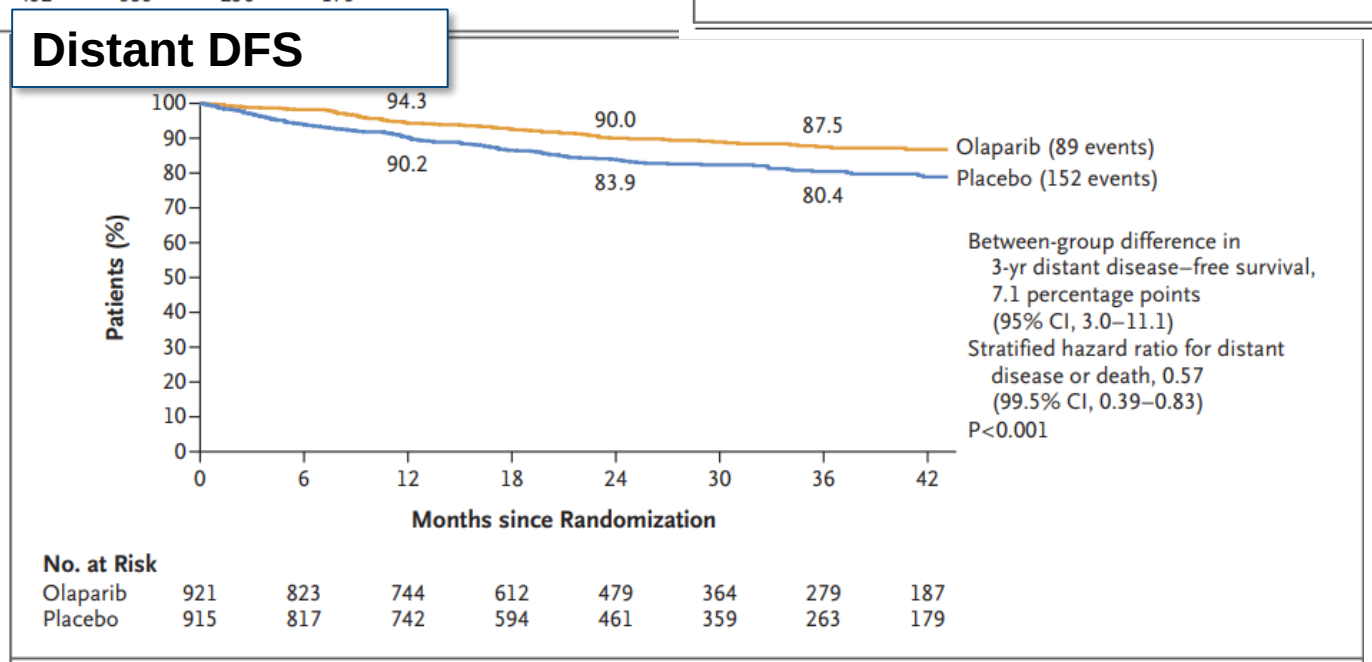
Invasive DFS



OS

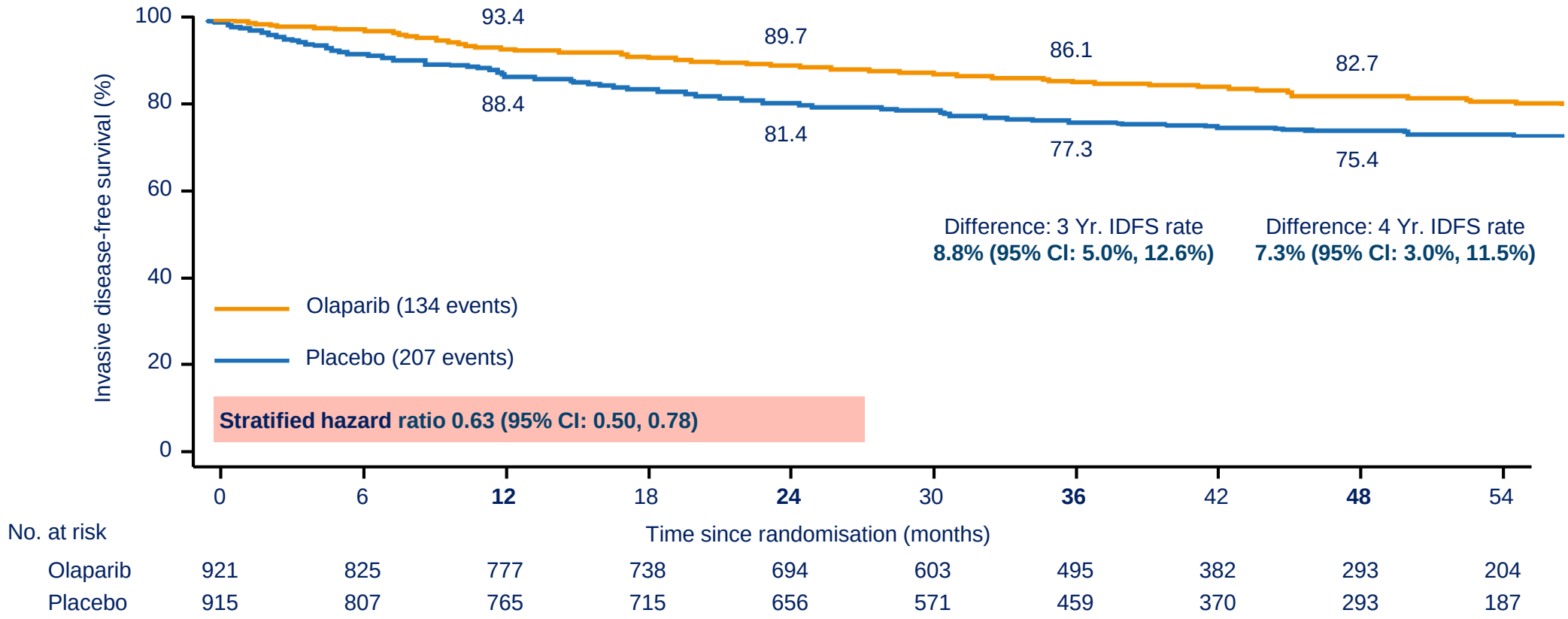


Distant DFS



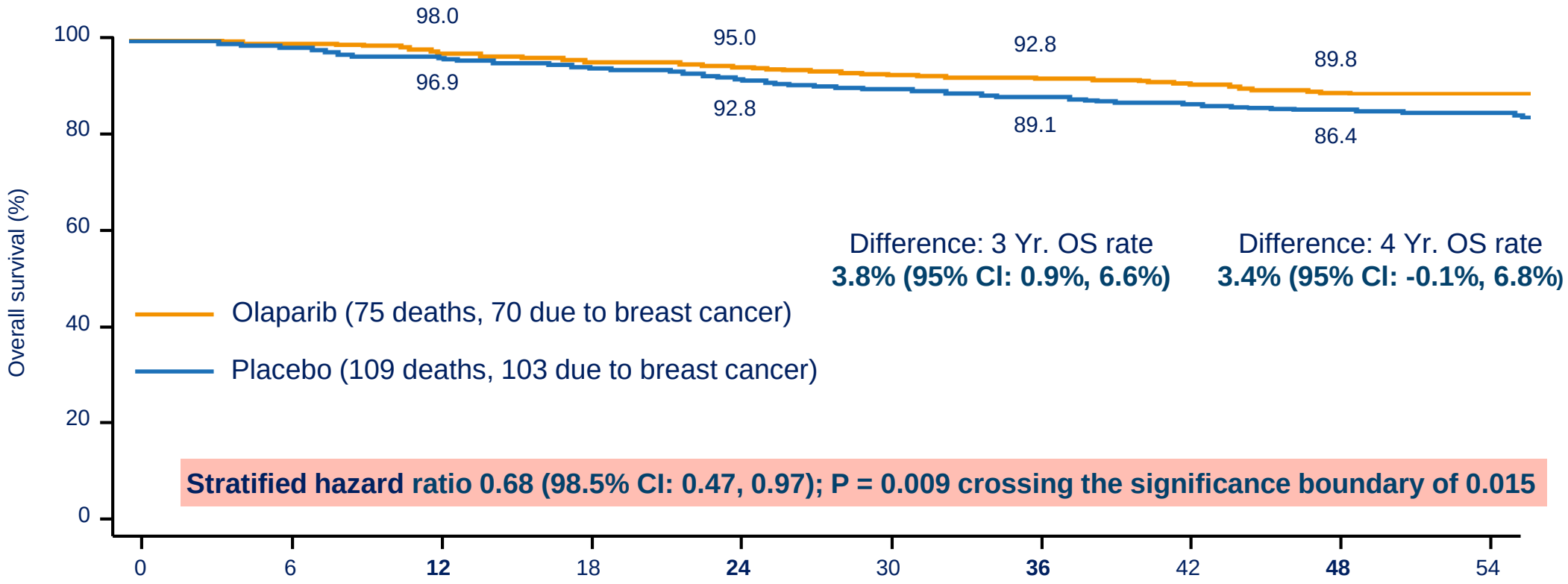
Tutt et al, *NEJM*, 2021

Updated IDFS



Tutt et al, Annals of Oncology, 2022

Second overall survival interim analysis - OS IA 2 (ITT)

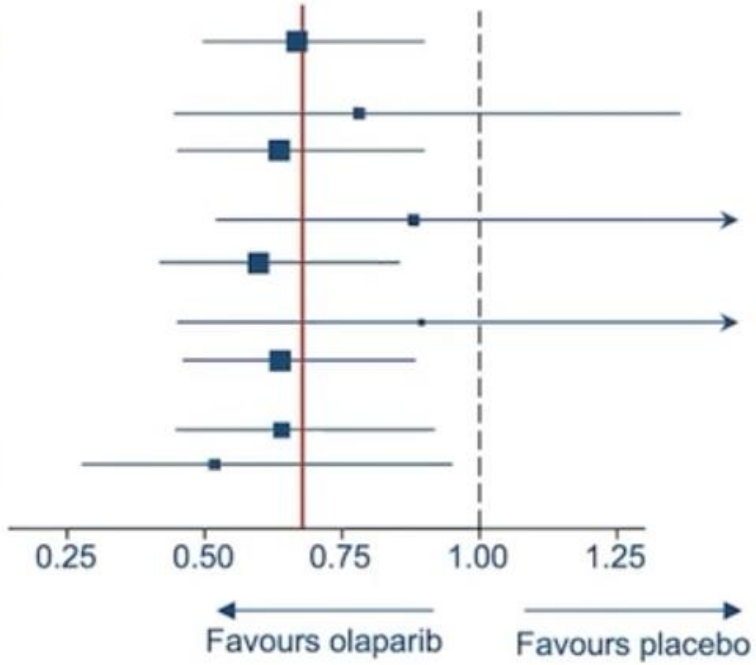


No. at risk										
Olaparib	921	862	844	809	773	672	560	437	335	228
Placebo	915	868	843	808	752	647	530	423	333	218

Tutt et al Annals of Oncology, March 2022

Subgroup Analysis for OS

Subgroup	Olaparib	Placebo	Stratified hazard ratio for overall survival (95% CI)	P value for heterogeneity
	No. of patients who died /total no.			
All patients	75 / 921	109 / 915	0.678 (0.503, 0.907)	NA
Prior chemo				0.543
Adjuvant	22 / 461	28 / 455	0.783 (0.444, 1.365)	
Neoadjuvant	53 / 460	81 / 460	0.638 (0.449, 0.900)	
Prior platinum				0.236
Yes	27 / 247	29 / 238	0.882 (0.520, 1.491)	
No	48 / 674	80 / 677	0.601 (0.417, 0.855)	
HR status				0.381
HR+/HER2-	16 / 168	17 / 157	0.897 (0.449, 1.784)	
TNBC	59 / 751	92 / 758	0.640 (0.459, 0.884)	
BRCA				0.845
BRCA1	49 / 579	75 / 588	0.643 (0.446, 0.918)	
BRCA2	16 / 235	28 / 216	0.521 (0.276, 0.951)	
BRCA1/2 both	0 / 2	0 / 3	NC	



All subgroup hazard ratio point estimates are < 1 and confidence intervals include the hazard ratio for olaparib treatment effect in the overall ITT population

Should we wait for a longer FU to confirm the benefit , at least for HR+ population ?

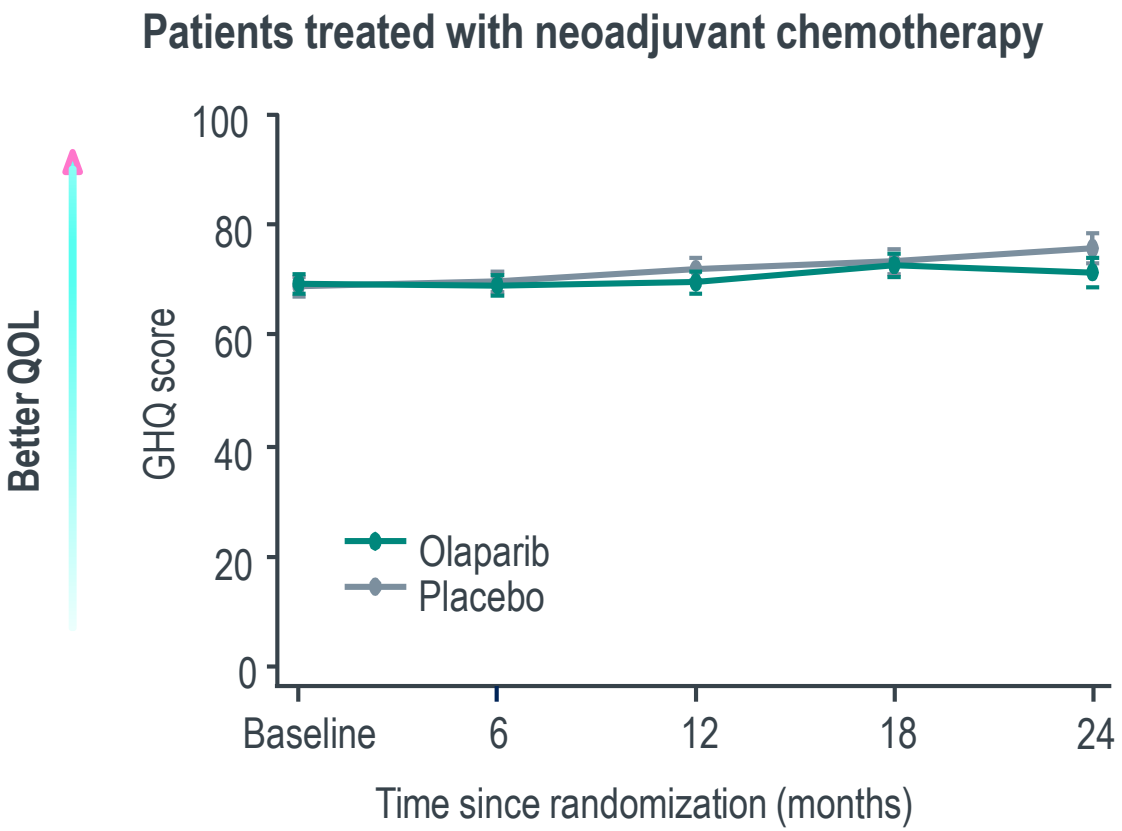
Other cancers?

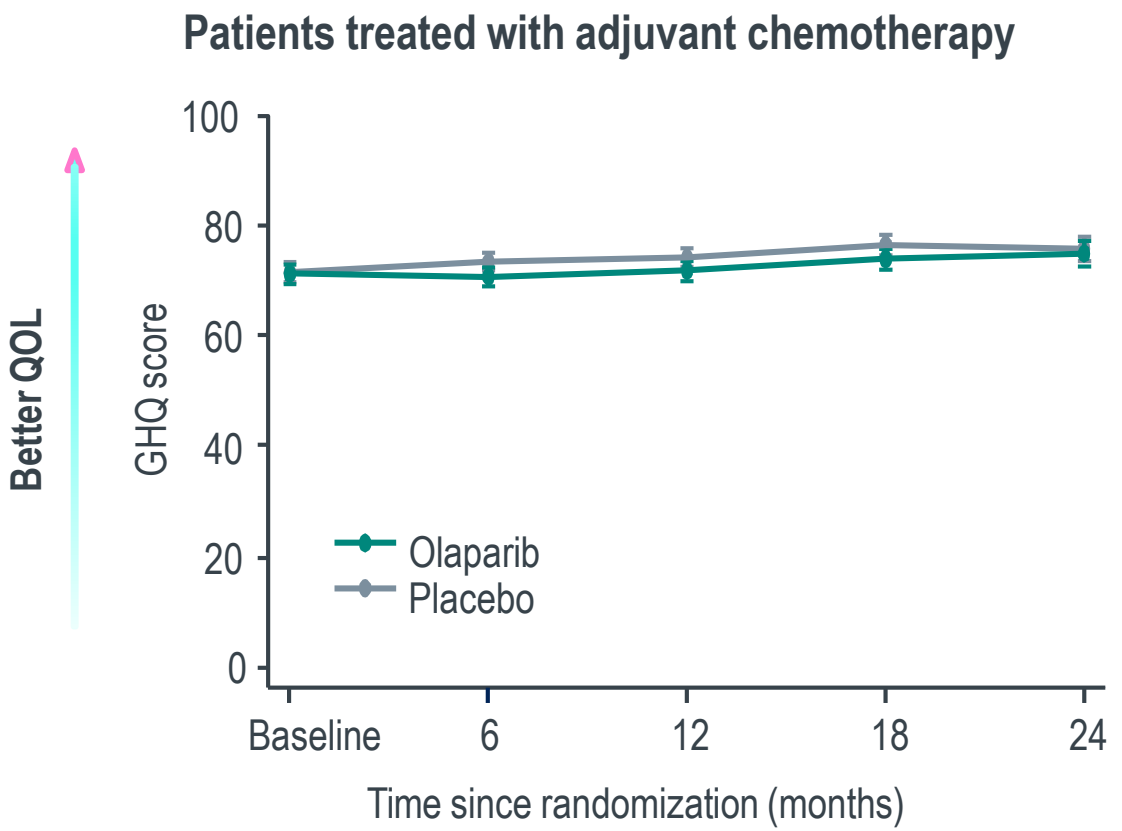
Table 3. Summary of Adverse Events in the Safety Analysis Set.*

Adverse Event	Olaparib (N=911)	Placebo (N=904)
	no. of patients (%)	
Any adverse event	835 (91.7)	753 (83.3)
Serious adverse event	79 (8.7)	76 (8.4)
Adverse event of special interest†	30 (3.3)	46 (5.1)
MDS or AML	2 (0.2)	3 (0.3)
Pneumonitis‡	9 (1.0)	11 (1.2)
New primary cancer§	19 (2.1)	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 olaparib or placebo‖	90 (9.9)	38 (4.2)
Adverse event leading to death**	1 (0.1)	2 (0.2)

Tutt et al, *NEJM*, 2021

Health-Related Quality of Life Results





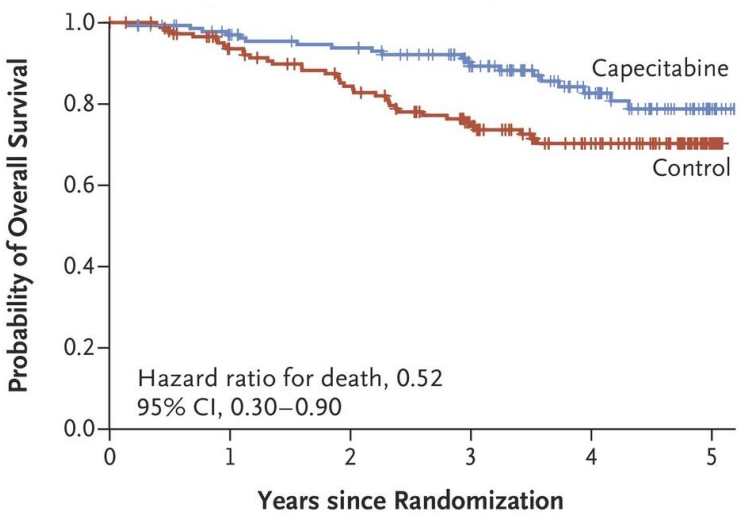
Global Health Quality (GHQ) score ranges from 0 to 100, higher score indicates better QOL. Adjusted least-square mean responses and 95% CI for time points other than baseline are obtained from mixed model for repeated measures analysis of the GHQ score. The model includes treatment, time and treatment by time interaction, corresponding baseline score, and the baseline score by time interaction.

Reproduced with permission from Tutt ANJ et al. *N Engl J Med*. 2021;384(25):2394−2405.

Tutt ANJ et al. *N Engl J Med*. 2021;384(25):2394−2405.

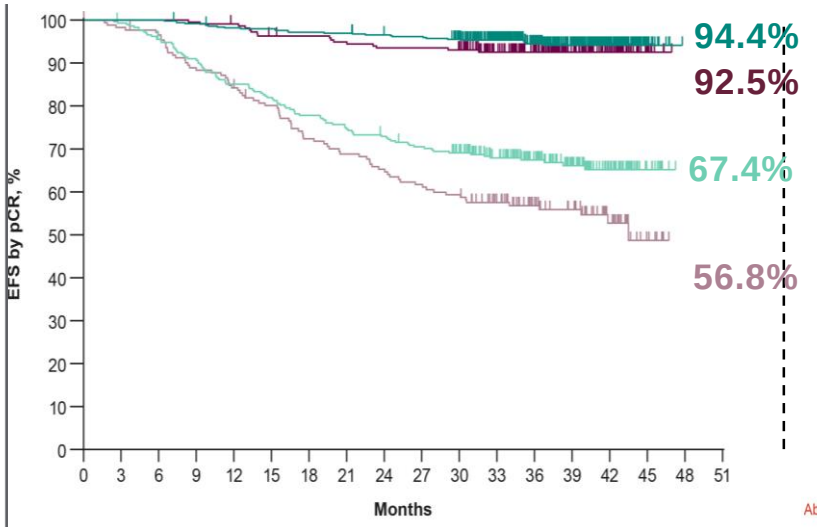
Olaparib in the context (TNBC neoadj)

OS CREATE-X TNBC



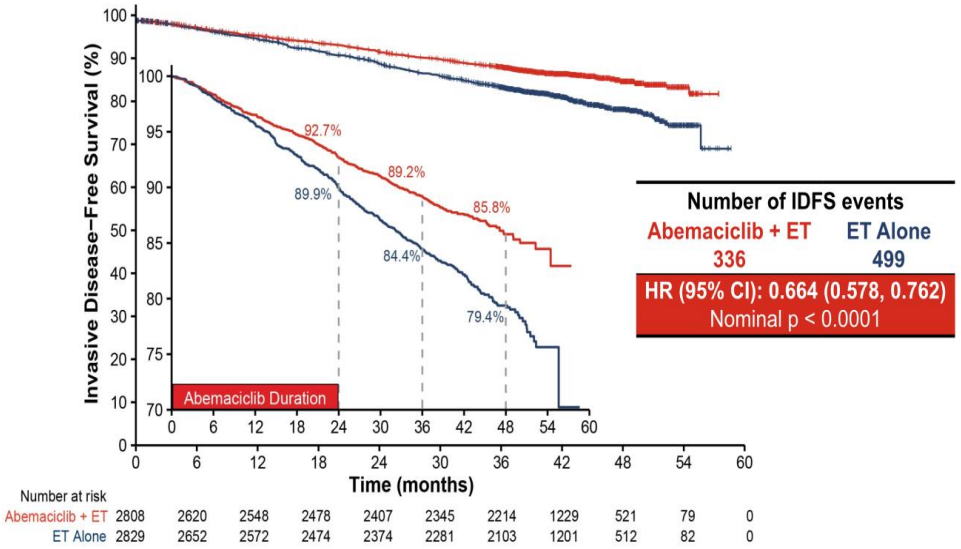
Masuda et al. NEJM 2017

EFS KN 522 TNBC EFS



Schmid et al. ESMO Virtual Plenary. July 15, 2021.

EFS MonarchE

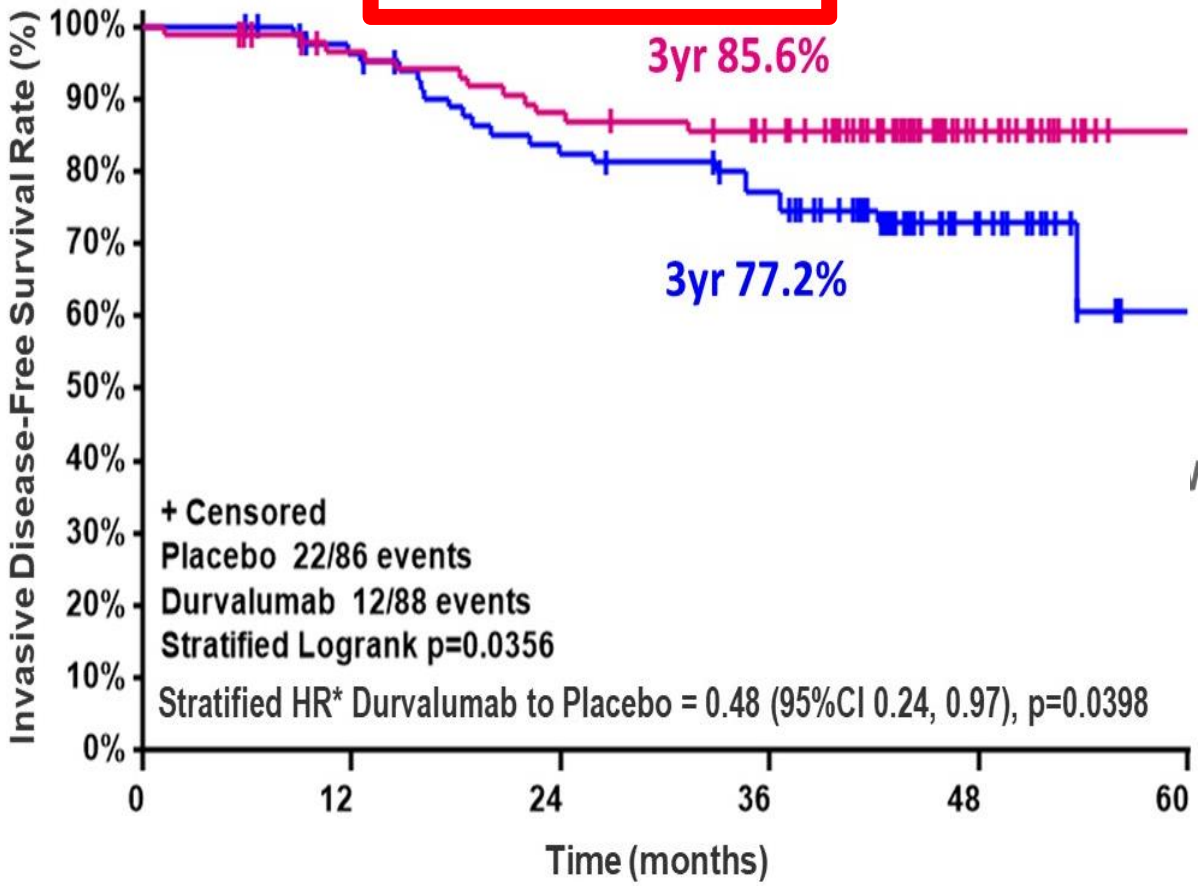


Johnston et al SABCS 2022

ICI post neoadj administration ?

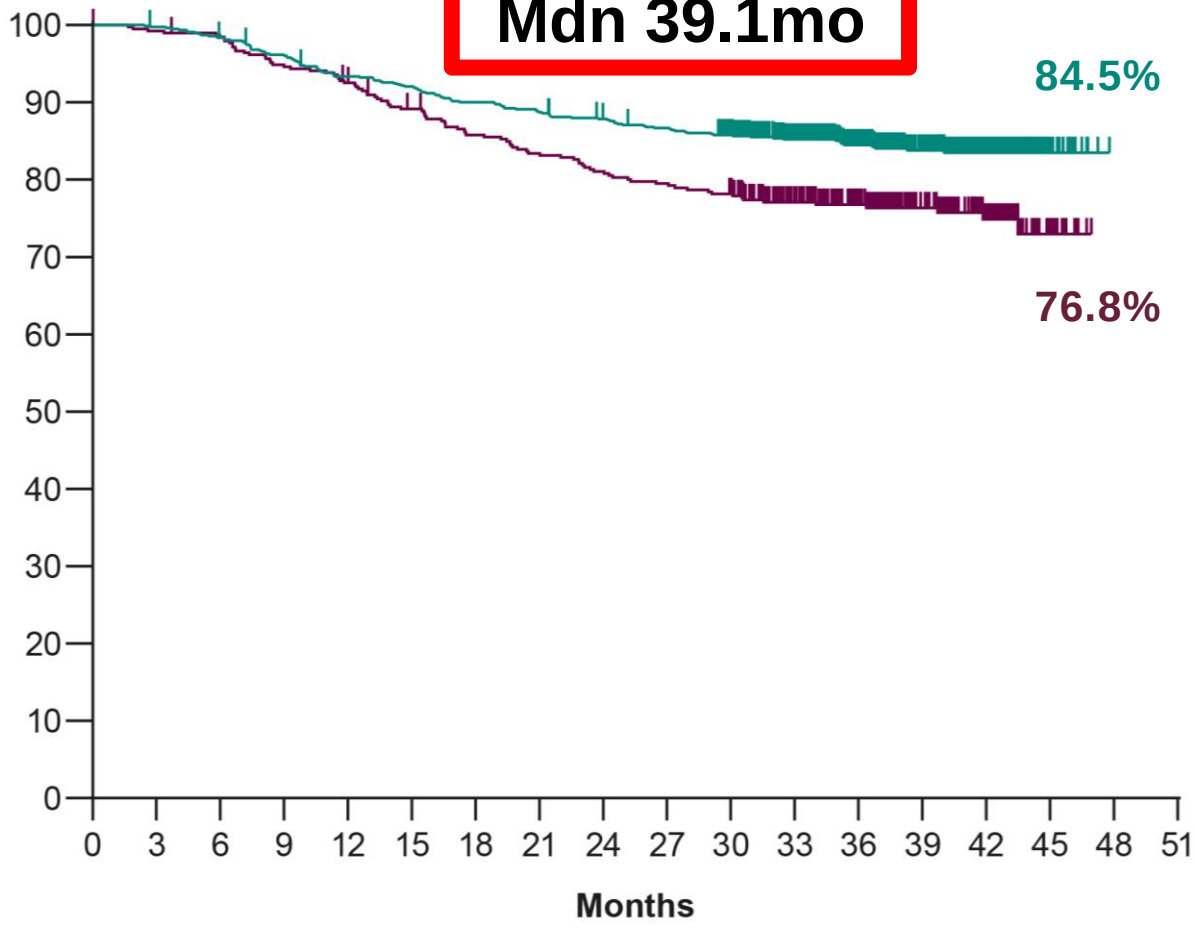
In case of pCR vs RD

GeparNuevo
Mdn 43.7mo



On going NeoTRIP

Keynote-522
Mdn 39.1mo

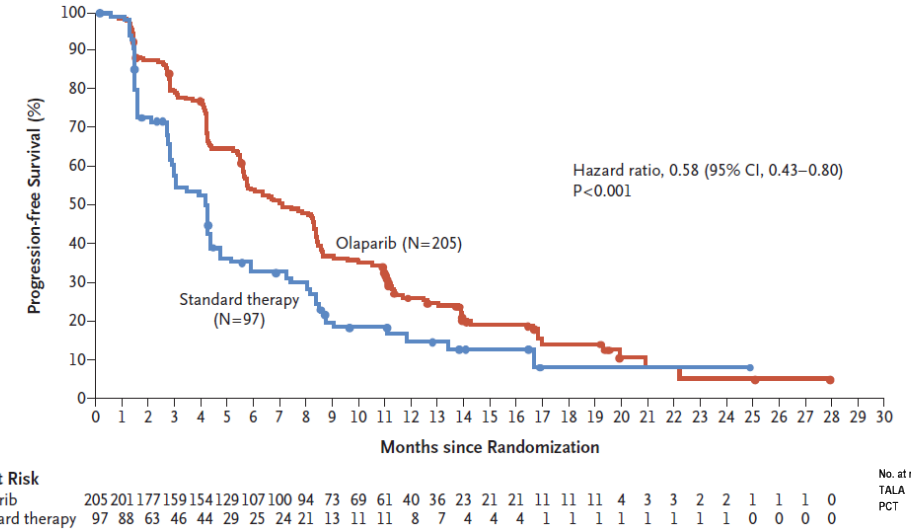


Loibl et al. ASCO 2021; Schmid ett al ESMO 2021.

Olaparib or Capecitabine ?

A data-free zone

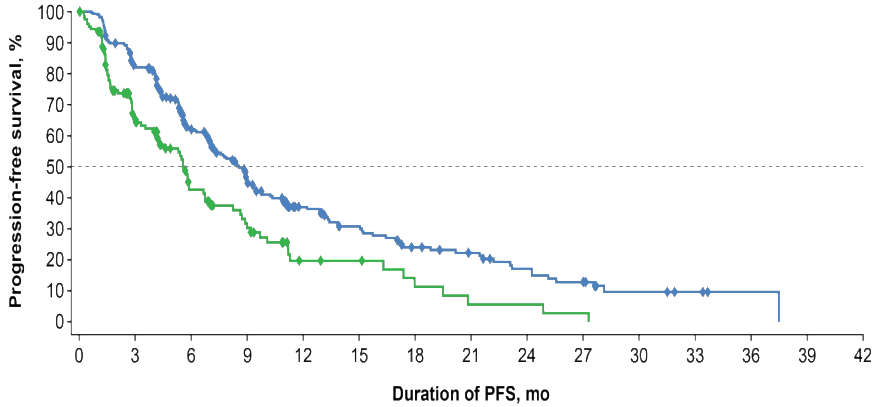
OlympiaD



No. at Risk

Olaparib	205	201	177	159	154	129	107	100	94	73	69	61	40	36	23	21	21	11	11	11	4	3	3	2	2	1	1	1	0
Standard therapy	97	88	63	46	44	29	25	24	21	13	11	11	8	7	4	4	4	1	1	1	1	1	1	1	1	0	0	0	0

EMBRACA



No. at risk (events/cumulative events)

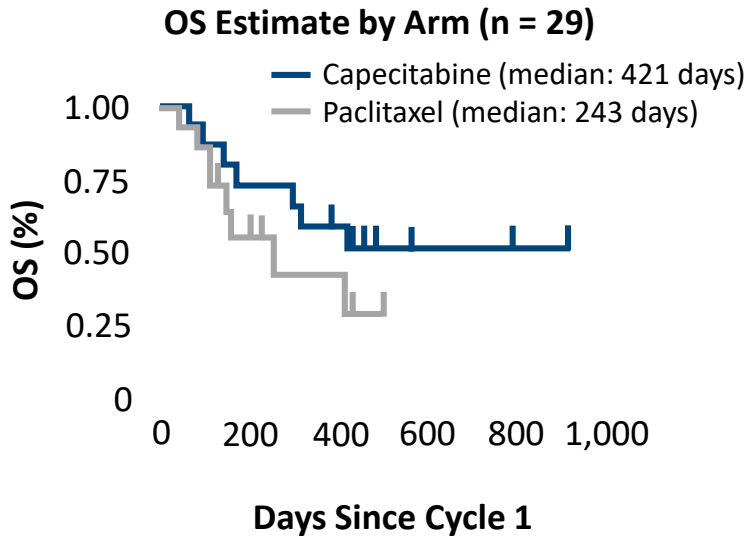
TALA	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	16 (5/179)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/186)	0 (0/186)										
PCT	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	2 (0/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)										

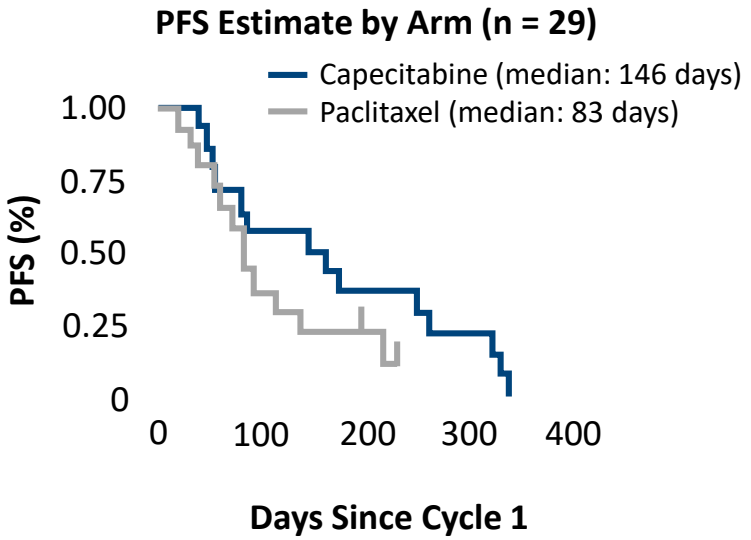
gBRCA testing is standard

45% of patients in OlympiAD received Capecitabine in the control arm

ICI and CT (Cape/Paclitaxel) ?

1L- or 2L Pembrowith Paclitaxel or Capecitabine in mTNBC





Week 12 ORR: 43% with pembro/capecitabine

Co-administration was safe

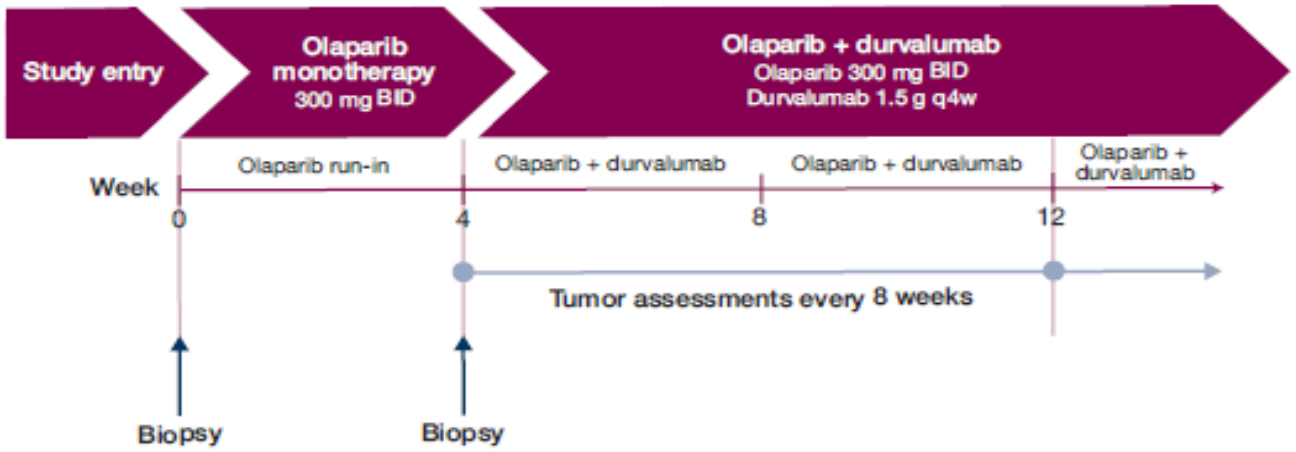
Co-administration of adjuvant pembro/capecitabine may be reasonable in selected high-risk patients with residual TNBC after NAC

Page et al. ASCO 2019. Abstr 1015.

ICI + PARPi?

MEDIOLA: Phase II basket trial of olaparib and durvalumab

Figure 1. Study schema



- **Primary endpoints:** DCR at 12 weeks, safety
- **Secondary endpoints:** DCR at 28 weeks, ORR, DoR, PFS, OS, PD-L1 expression
- **Exploratory endpoints:** TILs

Toxicity

34 patients were enrolled

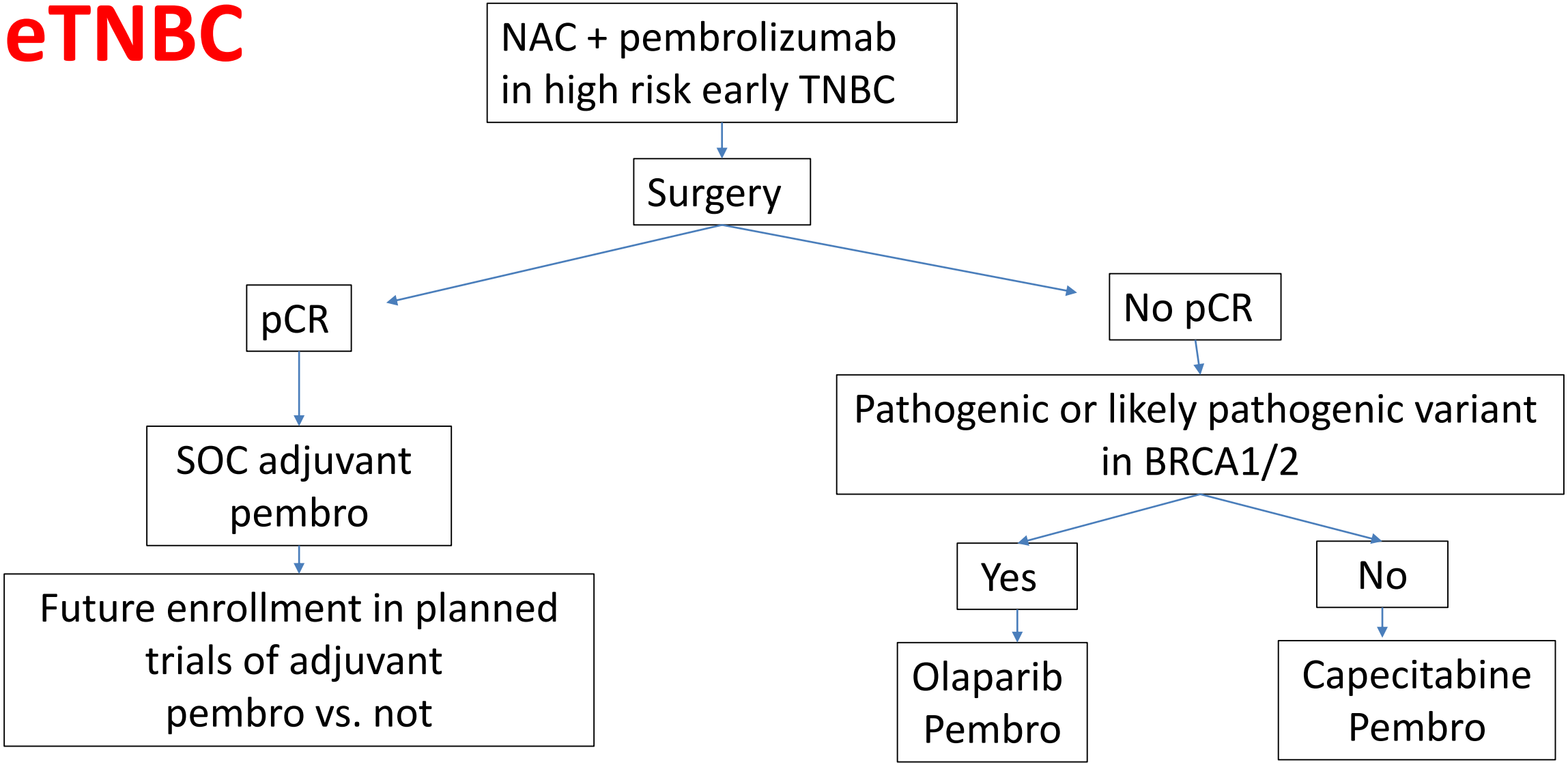
11 (32%) patients had =>G3
- Anaemia (12%),
- neutropenia (9%)
- pancreatitis (6%)

Three (9%) pts discontinued due to Aes
Four (12%) pts had a total of 6 SAE.

There were no treatment-related deaths.

Domchek Lancet Oncol 2020

In eTNBC



Consider sequential Olaparib with radiation

[1]McArthur et al. SABCS 2022. PD3-01

Cost/effectivness

Cost Effectiveness of Adjuvant Olaparib for Breast Cancer Patients with Germline *BRCA1/2* Mutations

Christina M. Zettler, MPH[1], Dilanka L. De Silva, MD[2], Victoria S. Blinder, MD[3], Mark E. Robson, MD[3], Elena B. Elkin, PhD MPA[1]

#374

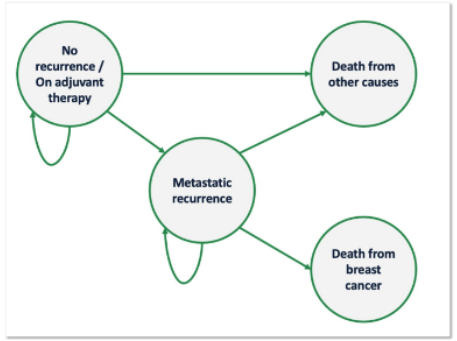
1 Columbia University Mailman School of Public Health • 2 Peter MacCallum Cancer Centre • 3 Memorial Sloan Kettering Cancer Center

Background

- In the OlympiA trial, one year of adjuvant olaparib improved 3-year distant-disease free survival and overall survival in breast cancer patients with a germline *BRCA1/2* mutation
- Olaparib, a PARP inhibitor taken orally, costs about $15,000 per month

Methods

- Markov model of disease recurrence and breast cancer mortality with and without one year of adjuvant olaparib in 42-year-old women with high-risk, early-stage breast cancer and a known germline *BRCA1/2* mutation
- Incremental cost effectiveness ratio (ICER) in 2021 $US per quality-adjusted life-year (QALY)
- Costs estimated from a health care system perspective; costs and QALYs discounted by 3% annually



Memorial Sloan Kettering Cancer Center | Columbia University Mailman School of Public Health | PeterMac

Adjuvant olaparib is a cost-effective option for patients with high-risk, early-stage breast cancer and a germline *BRCA1/2* mutation

Base-Case Results

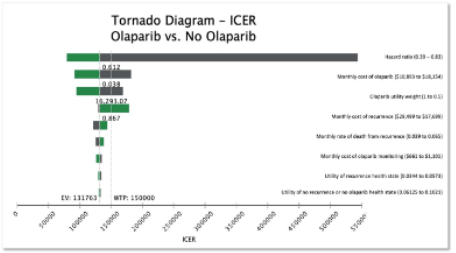
- Adjuvant olaparib costs about $131,800 per QALY gained, compared with no olaparib
- This ICER is within a commonly accepted US threshold of $150,000 per QALY and is favorable compared with the cost effectiveness of olaparib for other indications

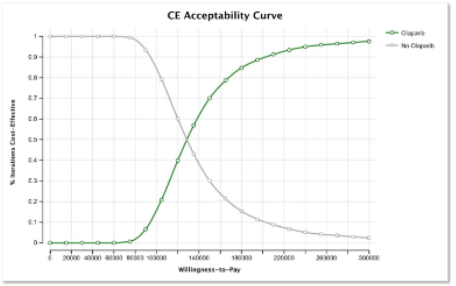
	Olaparib	No olaparib	Difference
Life-years	17.42	16.23	1.19
QALYs	16.87	15.75	1.12
Cost	$322,163	$174,761	$147,402
$ per LY gained	-	-	$123,867
$ per QALY gained	-	-	$131,763

Corresponding Author: Elena Elkin (elena.elkin@columbia.edu)

Sensitivity Analysis

- Results were most sensitive to assumptions about the effectiveness and cost of olaparib
- The ICER for adjuvant olaparib was <$150,000 per QALY in 69% of simulations in probabilistic sensitivity analysis





Conclusions and Future Research

- At a willingness-to-pay threshold of $150,000 per QALY, olaparib is cost effective at its current price
- Cost effectiveness of adjuvant olaparib in conjunction with strategies to identify patients with germline *BRCA1/2* mutations should be studied

Accesso al test (AIOM 2023)

Aggiornamento criteri per l'accesso al test

Aggiornamento Tabella 22 (precedentemente Tabella 26)

Storia personale di:
Variante patogenetica nota in un gene predisponente in un familiare
Uomo con carcinoma mammario
Donna con carcinoma mammario e carcinoma ovarico
Donna con carcinoma mammario ≤40 anni
Donna con carcinoma mammario triplo negativo
Donna con carcinoma mammario bilaterale < 50 anni
Donna con carcinoma mammario in stadio iniziale a recettori ormonali positivi e ≥ 4 linfonodi positivi
Donna con carcinoma mammario a recettori ormonali positivi con precedente CT neoadiuvante, residuo di malattia e CPS/EG score≥3
Donna con carcinoma mammario metastatico recettori ormonali positivi/HER2-negativo già sottoposta a chemioterapia con antracicline/taxani e trattamento endocrino (qualora possibili), in progressione dopo inibitori di CDK 4/6 per la malattia avanzata.
Storia personale di carcinoma mammario 46-50 anni e familiarità di primo grado* per:
Carcinoma mammario <50 anni
Carcinoma ovarico non mucinoso o borderline a qualsiasi età
Carcinoma mammario bilaterale
Carcinoma mammario maschile
Carcinoma del pancreas
Carcinoma della prostata
Storia personale di carcinoma mammario >50 anni e familiarità per carcinoma mammario, ovarico, pancreatico in 2 o più parenti in primo grado* tra loro (di cui uno in primo grado con lei)

**Presenza di un familiare di primo grado (genitore, fratello/sorella, figlio/a) con le caratteristiche di malattia specificate. Per il lato paterno della famiglia, considerare anche familiari di secondo grado (nonna, zie).*

A practice changing trial with some open questions

- **Q1 Olaparib vs Capecitabine (in non pCR TNBC)**: CreateX; Geicam; EA 1131 (Cape benefit non-basal phenotype)
- **Q2 Olaparib vs Pembrolizumab:** no OS benefit (yet) for Pembro: role of pembro post-operative (?); combo (Mediola)
- **Q3 Olaparib vs Abemaciclib:** no OS benefit (yet) for Abema; role of Abema in mBRCA (?); no combo (tox); possible sequencing (>12m post diagnosis)
- **Q4 Should all women with BC now be tested for BRCA1/2 ?** According to OLYMPIA criteria
- **Q5 Could Olaparib replace Platinum in pre/post-op in NAC ?** Trial is ongoing