INIBITORI DI PARP NELLA TERAPIA ADIUVANTE DEL CARCINOMA MAMMARIO

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Early Drug Development for Innovative Therapies

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DISCLOSURES

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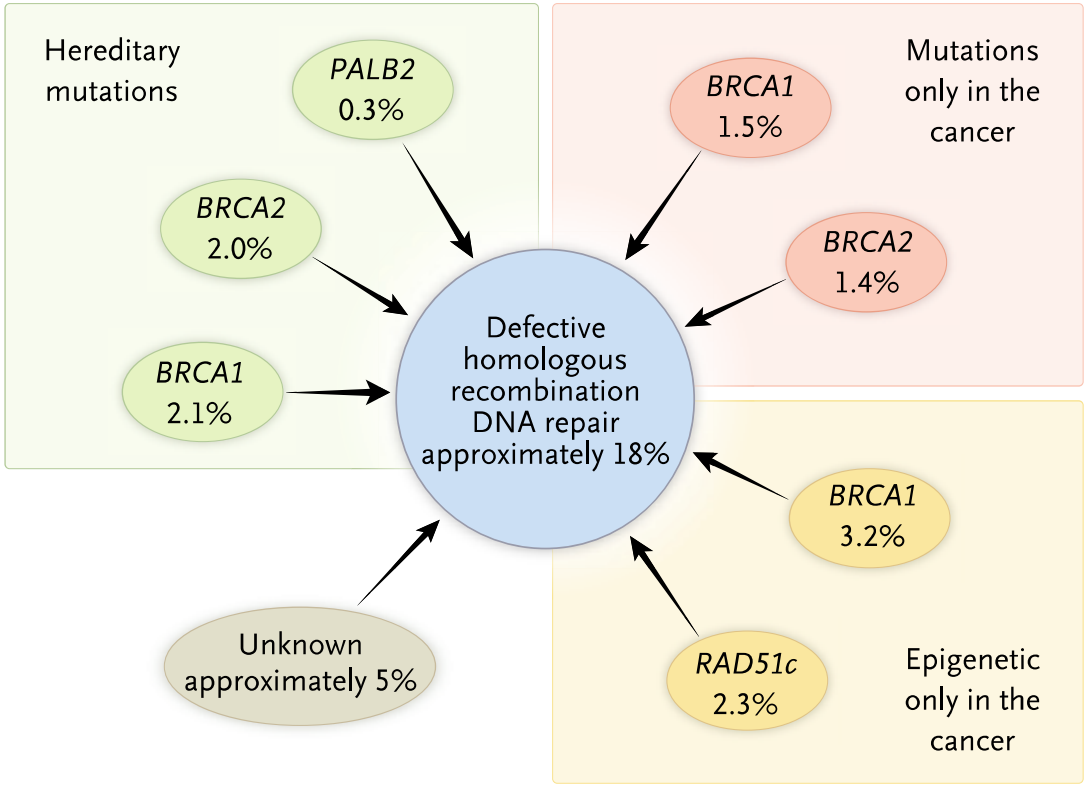
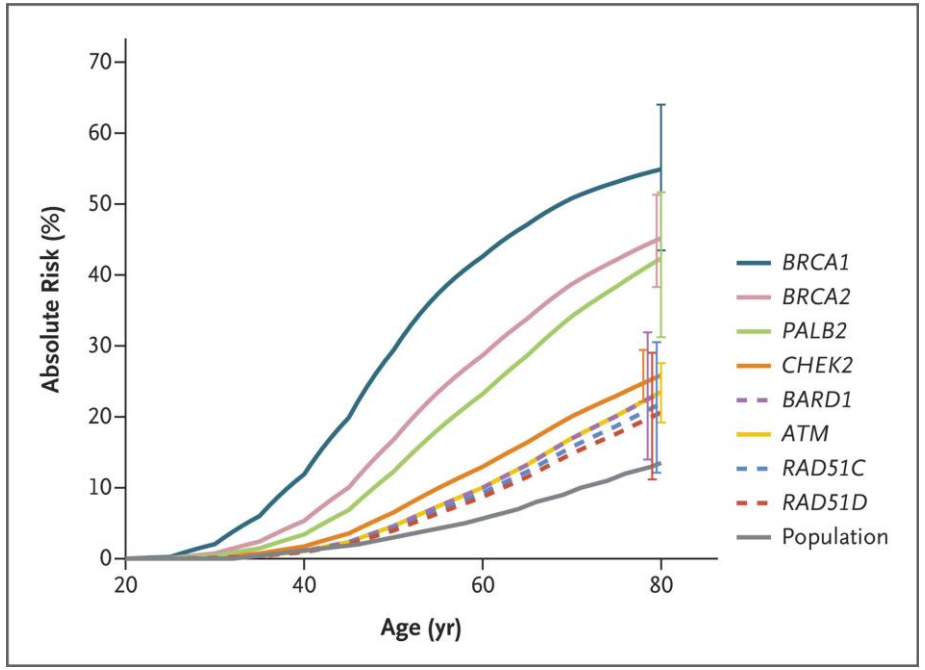
OUTLINE

- Homologous Recombination Deficiency in Breast Cancer
- PARP Inhibitors in Early Breast Cancer
- Current Dilemmas
- Future Perspectives

HOMOLOGOUS RECOMBINATION DEFICIENCY IN BREAST CANCER



Absolute risk of breast cancer in carriers of pathogenic/likely pathogenic variants of putative cancer susceptibility genes



Turner, NEJM 2017; Breast Cancer Association Consortium, NEJM 2021

HOMOLOGOUS RECOMBINATION DEFICIENCY IN BREAST CANCER

BRCA1 and *BRCA2* germline mutations vary according to subtype

BRCA1

- ER-/PR-/HER2- phenotype (85%)
- Grade 3
- Pushing borders
- Brisk lymphocytic infiltrate
- Up to 14% of consecutive TNBCs

BRCA2

- ER+/HER2- phenotype (Luminal B – 75%)
- Grade 3
- Pushing borders
- 5%-8% of Luminal cancers

HOW TO EVALUATE HOMOLOGOUS RECOMBINATION DEFICIENCY IN BREAST CANCER

Alterations of HRR genes (germline, somatic, epigenetic)

↓

DNA sequencing
Methylation assays

Large DNA changes / genomic instability

↓

Genomic scars (LOH/nTAi/LST)
Mutational signatures
Combinations (HRDetect)

Functional assay

↓

RAD51 methylation

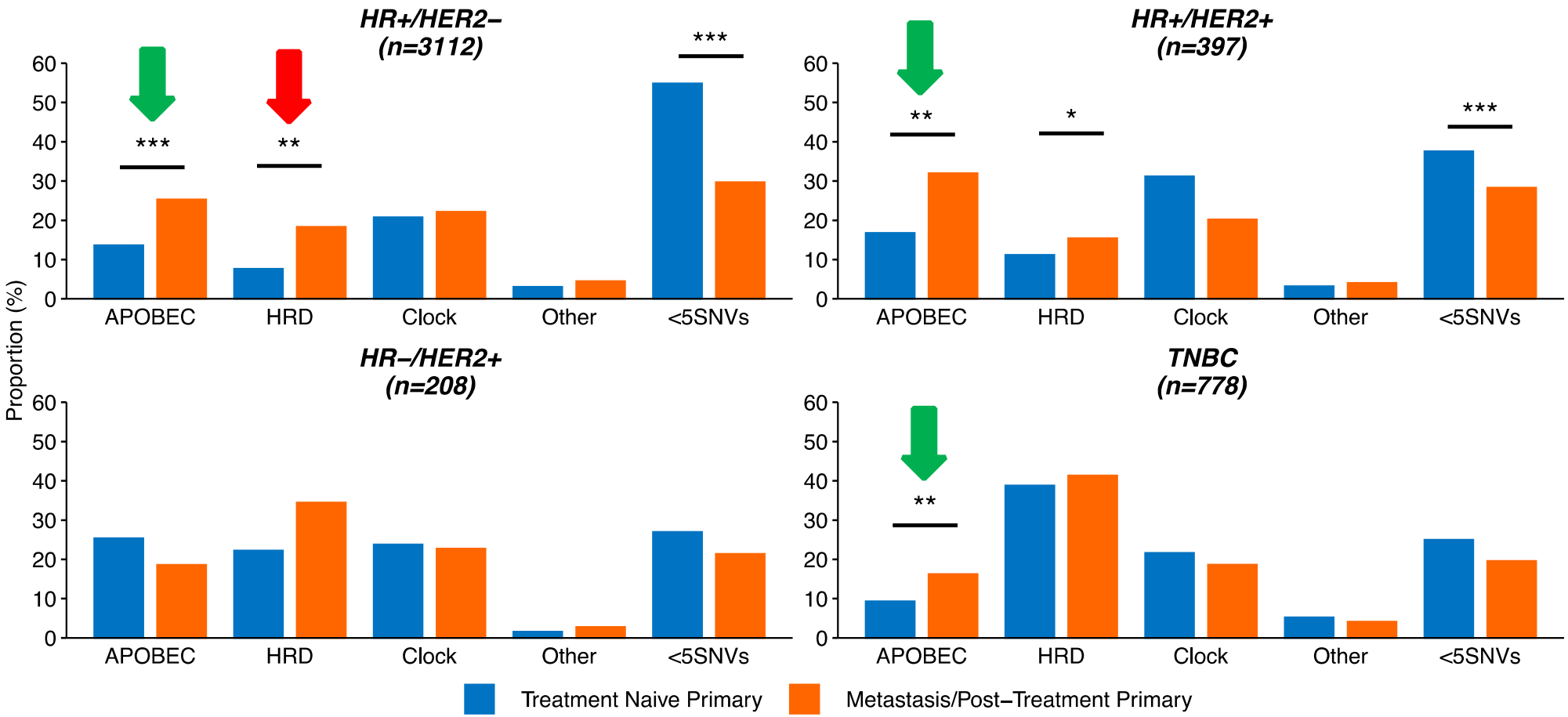
The CAUSE of HRD

Assess the cause of HRD by looking for loss of function of key HRR genes

The EFFECT of HRD

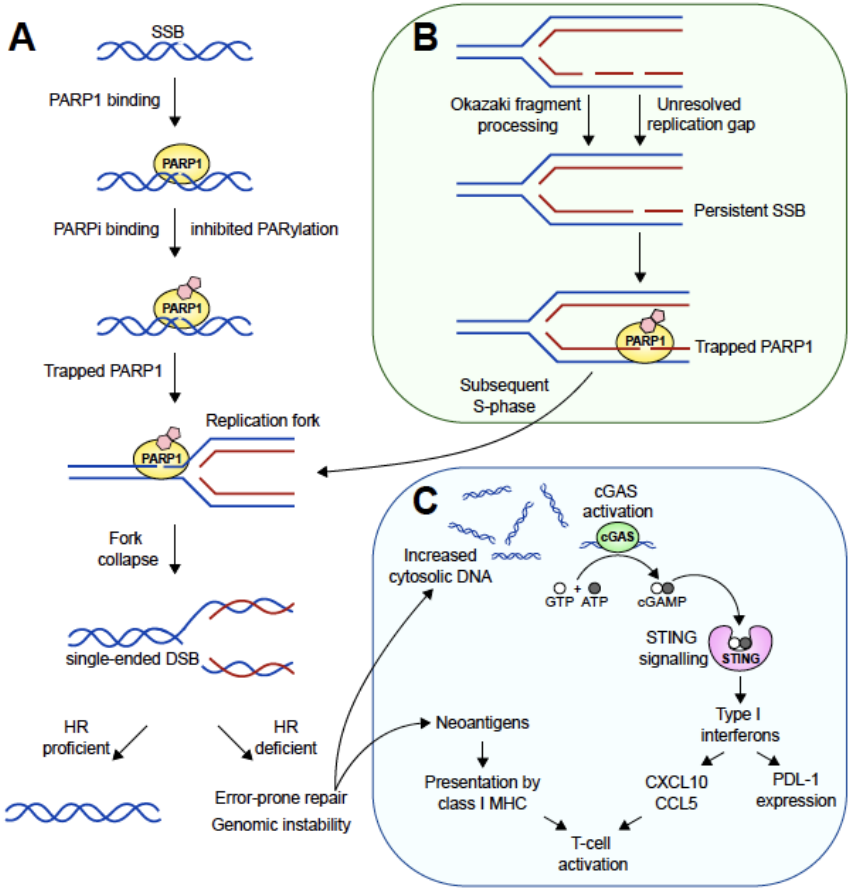
Look for indicators of genomic damage to identify the implications of HRD

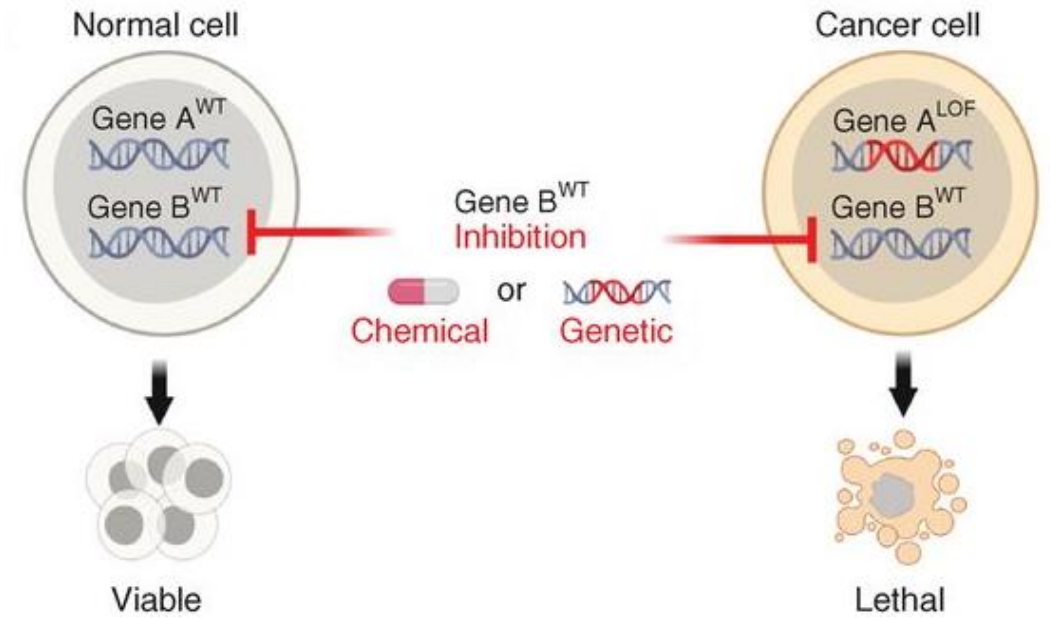
HRD TENDS TO BE HIGHER IN METASTATIC HR+/HER2-, WHILE IT IS STABLE IN TRIPLE-NEGATIVE TUMORS



Marra A, et al. ESMO 2022; manuscript under revision

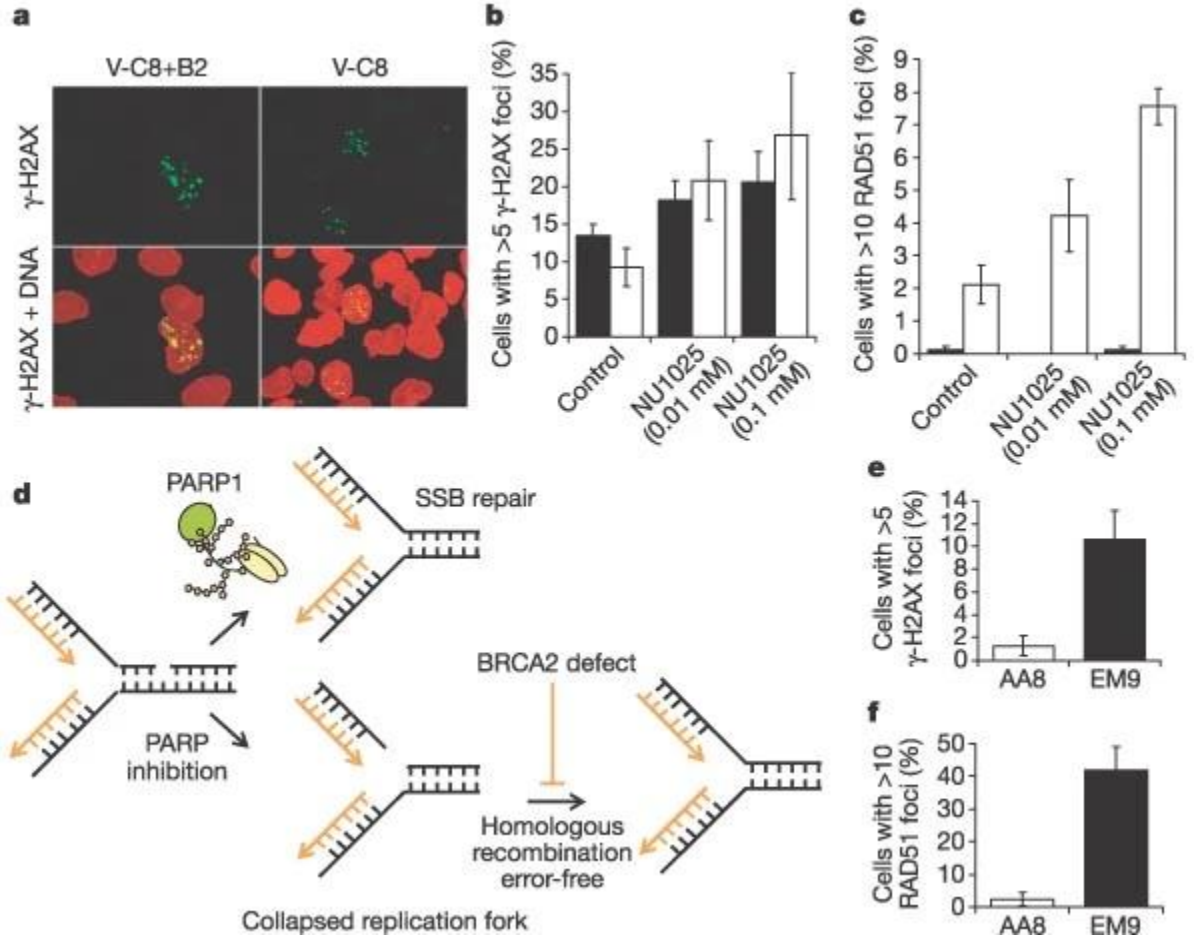
PARP INHIBITORS EXPLOIT "SYNTHETIC LETHALITY" TO TARGET BRCA-DEFICIENT TUMORS



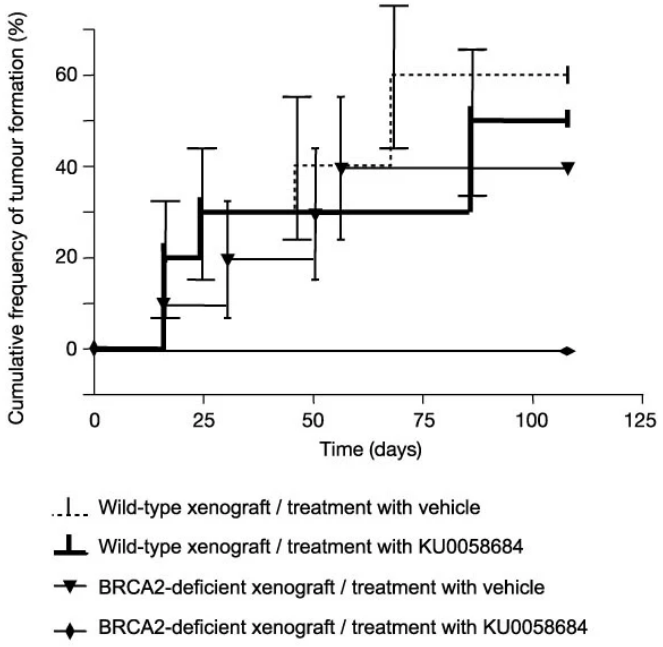


Setton et al. Cancer Discov. 2021; Wicks et al. Open Biol. 2022

BRCA2 DEFICIENT CELLS ARE KILLED BY PARP INHIBITORS



PARPi selectively blocks the growth of *BRCA2*-deficient tumors



Bryant et al. Nature 2005; Farmer et al. Nature 2005

PIVOTAL PHASE III TRIALS TESTING PARP INHIBITION IN ADVANCED BREAST CANCER

OLYMPIAD

- HER2-negative metastatic BC
  - ER+ and/or PR+ or TNBC
- Deleterious or suspected deleterious gBRCAm
- 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

R 2:1

Olaparib 300 mg tablets bd

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

EMBRACA

Patients with locally advanced or metastatic HER2 negative BC and a germline BRCA1/2 mutation

Stratification factors
- Number of prior CT regimens (0 or ≥1)
- TNBC or HR+
- History of CNS mets or no CNS mets

R 2:1

Talazoparib 1 mg PO daily

Treatment (21-day cycles) continues until progression or unacceptable toxicity

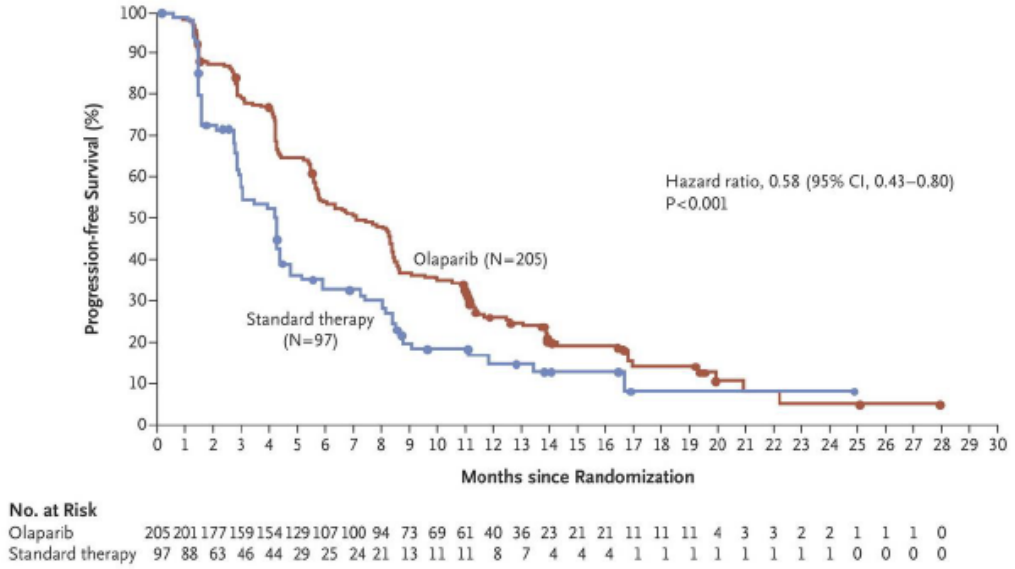
Physicians choice of therapy (PCT): capecitabine, eribulin, gemcitabine or vinorelbine

Robson, NEJM 2017; Litton, NEJM 2018

BOTH OLAPARIB AND TALAZOPARIB IMPROVES PFS IN GERMLINE BRCA1/2-MUT ADVANCED BREAST CANCER

OLYMPIAD

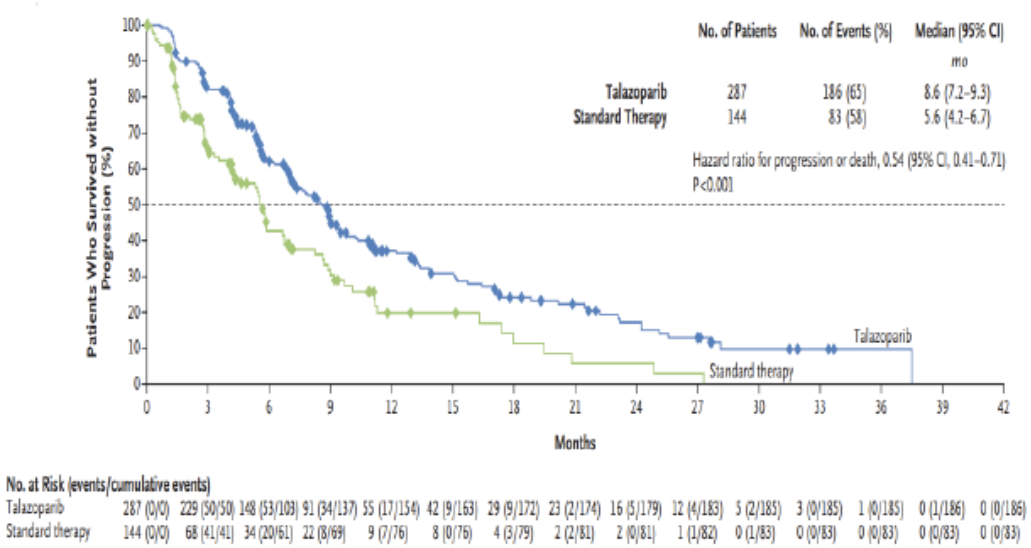
50% TN; A/T pretreated; 71% prior CT for MBC; TN: non-platinum resistant



Median PFS **7.0 vs 4.8 months**
HR 0.58, 95% CI: 0.43, 0-80; P<0.001
TNBC: HR 0.43, 95% CI: 0.29, 0.63

EMBRACA

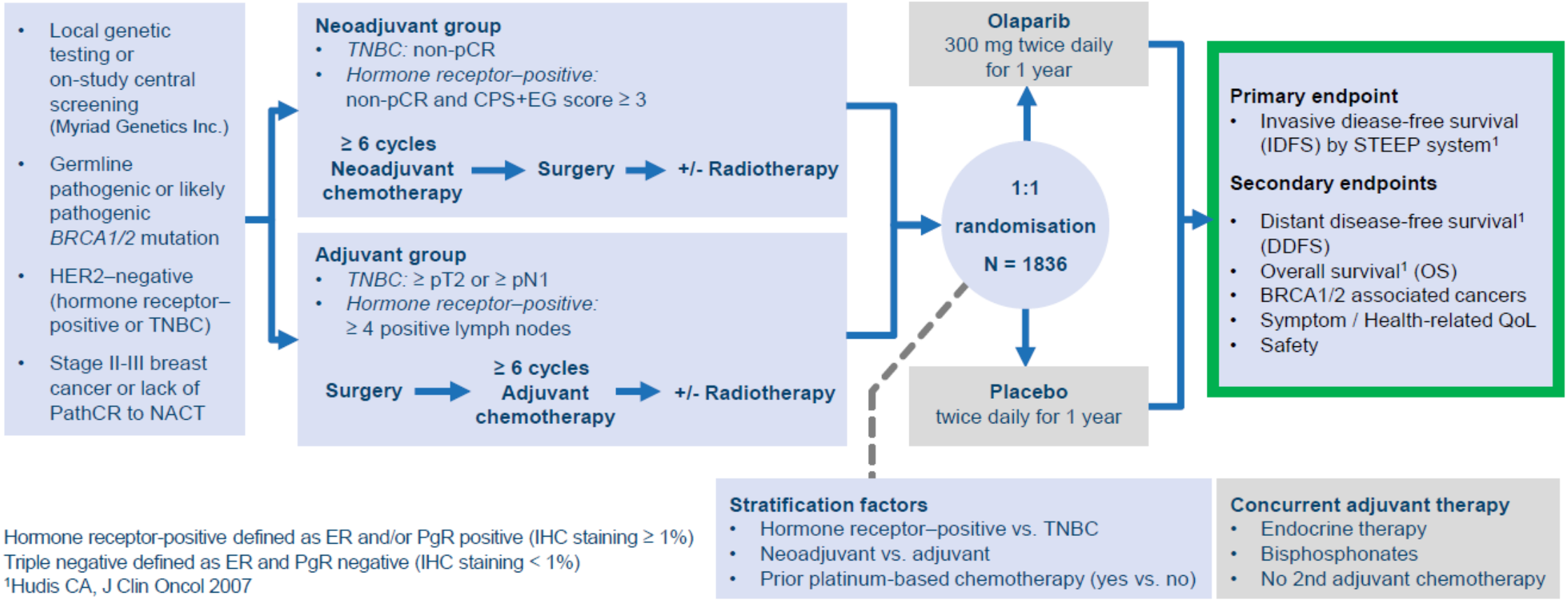
44% TN; A/T pretreated; 62% prior CT for MBC; TN: non-platinum resistant



Median PFS **8.6 vs 5.6 months**
HR 0.54, 95% CI: 0.41.0, 71; P<0.001
TNBC: HR 0.60, 95% CI: 0.41, 0.87

Robson, NEJM 2017; Litton, NEJM 2018

OLYMPIA TRIAL: MOVING PARP INHIBITORS TO EARLY BREAST CANCER



Hormone receptor-positive 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

Tutt et al. NEJM 2021; Tutt, ESMO VP 2022; Geyer et al. Ann Oncol. 2022

OLYMPIA: BASELINE CHARACTERISTICS

Characteristic	Olaparib (n = 921)	Placebo (n = 915)
Median age, yr (IQR)	42 (36-49)	43 (36-50)
g*BRCA* mutation(s),* n (%) ▪ *BRCA1* ▪ *BRCA2* ▪ *BRCA1* and *BRCA2*	 657 (71.3) 261 (28.3) 2 (0.2)	 670 (73.2) 239 (26.1) 5 (0.5)
Prior neo(adjuvant) CT,† n (%) ▪ Adjuvant ▪ Neoadjuvant ▪ Anthracycline + taxane regimen ▪ Anthracycline, no taxane regimen ▪ Taxane, no anthracycline regimen ▪ <6 cycles (neo)adjuvant CT ▪ Platinum-based (neo)adjuvant CT	 461 (50.1) 460 (49.9) 871 (94.6) 7 (0.8) 43 (4.7) 7 (0.8) 247 (26.8)	 455 (49.7) 460 (50.3) 849 (92.8) 13 (1.4) 52 (5.7) 15 (1.6) 239 (26.1)
Menopausal status (women only‡), n (%) ▪ Premenopausal ▪ Postmenopausal	n = 919 572 (62.2) 347 (37.8)	n = 911 553 (60.7) 358 (39.3)

*Data missing for n = 1 in each arm. †Regimen not reported in n = 1 (placebo arm). ‡Trial enrolled 6 men (olaparib, n = 2; placebo, n = 4).

Characteristic	Olaparib (n = 921)	Placebo (n = 915)
HR+/HER2-, n (%)	168 (18.2)	157 (17.2)
TNBC, n (%)	751 (81.5)	758 (82.8)
Concurrent ET (HR+ only), n/N (%)	146/168 (86.9)	142/157 (90.4)
Primary BC surgery, n (%) ▪ Mastectomy ▪ Conservative surgery only ▪ Missing	 698 (75.8) 223 (24.2) 0	 673 (73.6) 240 (26.2) 2 (0.2)

- Among those treated with neoadjuvant CT only, most common CPS + EG score was 3/4 in HR+/HER2- subgroup (18.5% pbo, 19.1% olap); in TNBC subgroup, ≤2 (31.3% pbo, 32.8% olap) and 3/4 (42.8% pbo, 38.8% olap)
- Among those treated with adjuvant CT only, most common pathologic AJCC stages were IIA (54.9% pbo, 57.3% olap) and IIB (16.5% pbo, 15.2% olap)

Tutt et al. NEJM 2021; Tutt, ESMO VP 2022; Geyer et al. Ann Oncol. 2022

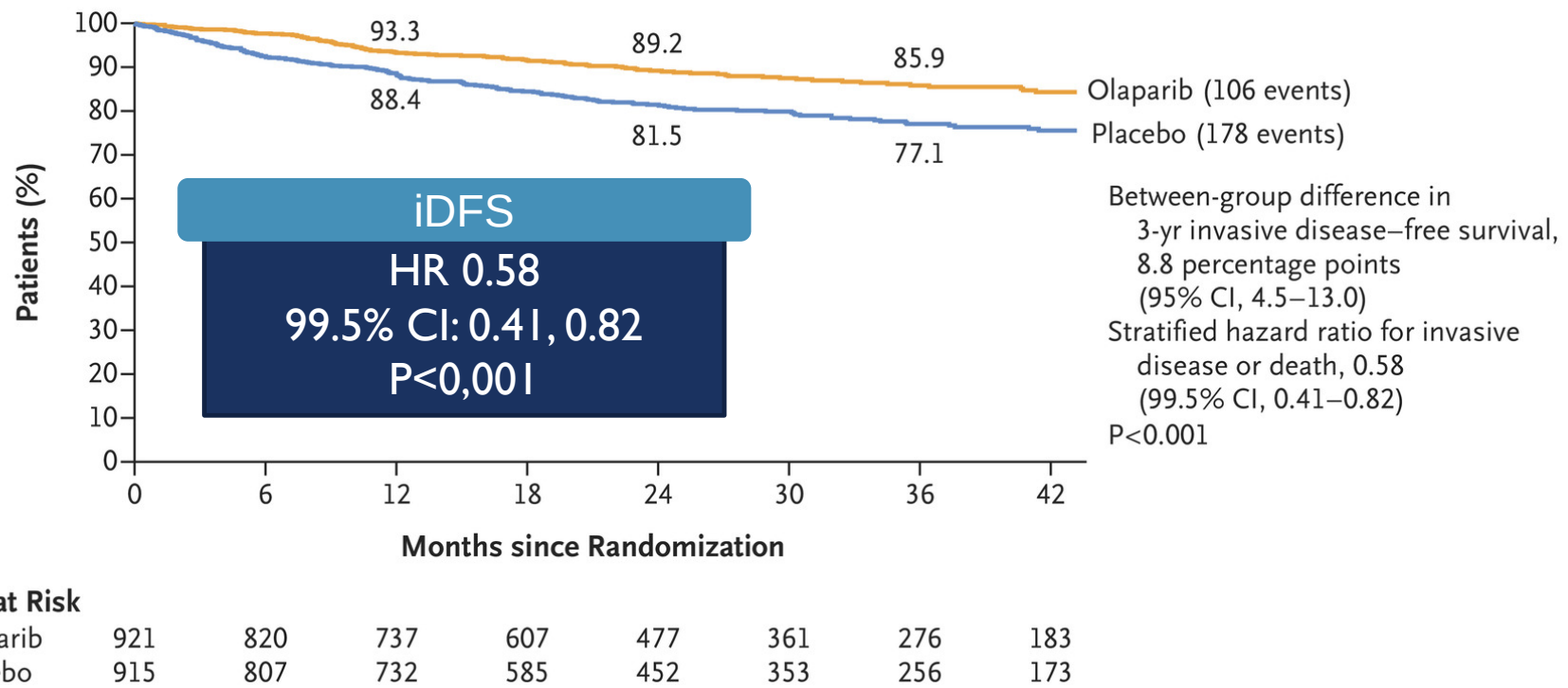
COMMENTS ON THE PATIENT POPULATION

- Very young (median 42-43, 25% > 50)
- 72.3% gBRCA1 mutated
- 82.2% TNBC, no HER2+ (by design)
- 74.7% treated with mastectomy (46.5% bilateral)
- Risk-reducing salpingo-oophorectomy in ~60%

- CPS+EG score unfamiliar to many

(https://www3.mdanderson.org/app/medcalc/index.cfm?pagename=bcnt)

OLYMPIA: FIRST INTERIM ANALYSIS FOR IDFS



3-year iDFS rate

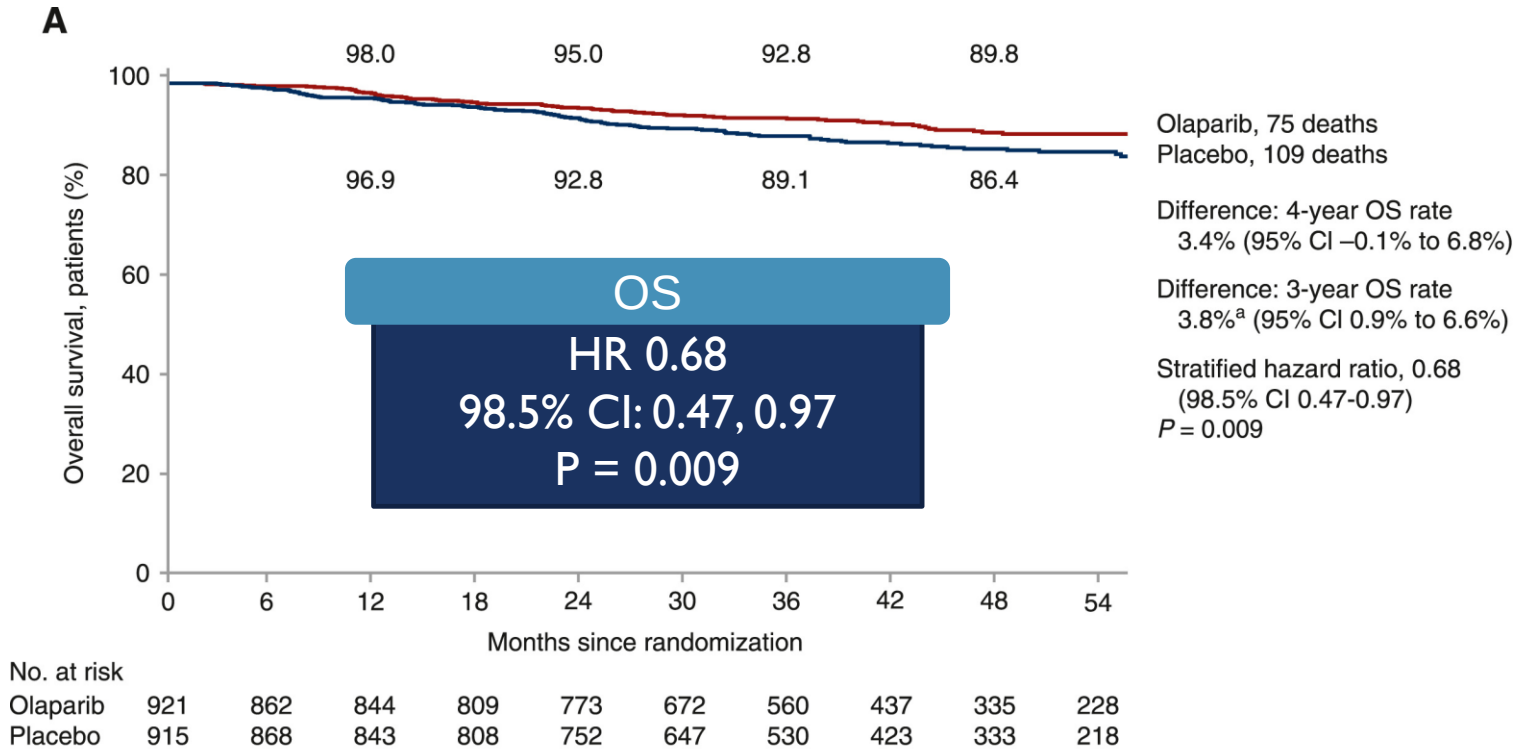
Olaparib (n=921)	**85.9%**
Placebo (n=915)	**77.1%**

Difference: 8.8%
95% CI: 4.5, 13

2022 Global approvals as post chemotherapy adjuvant therapy in “high risk” HER2-negative gBRCAmut breast cancer regardless of ER status

Tutt et al. NEJM 2021; Tutt, ESMO VP 2022; Geyer et al. Ann Oncol. 2022

OLYMPIA: PLANNED EVENT DRIVEN OVERALL SURVIVAL INTERIM ANALYSIS (2022)



Olaparib, 75 deaths
Placebo, 109 deaths

Difference: 4-year OS rate
3.4% (95% CI –0.1% to 6.8%)

Difference: 3-year OS rate
3.8%[a] (95% CI 0.9% to 6.6%)

Stratified hazard ratio, 0.68
(98.5% CI 0.47-0.97)
P = 0.009

4-year OS rate

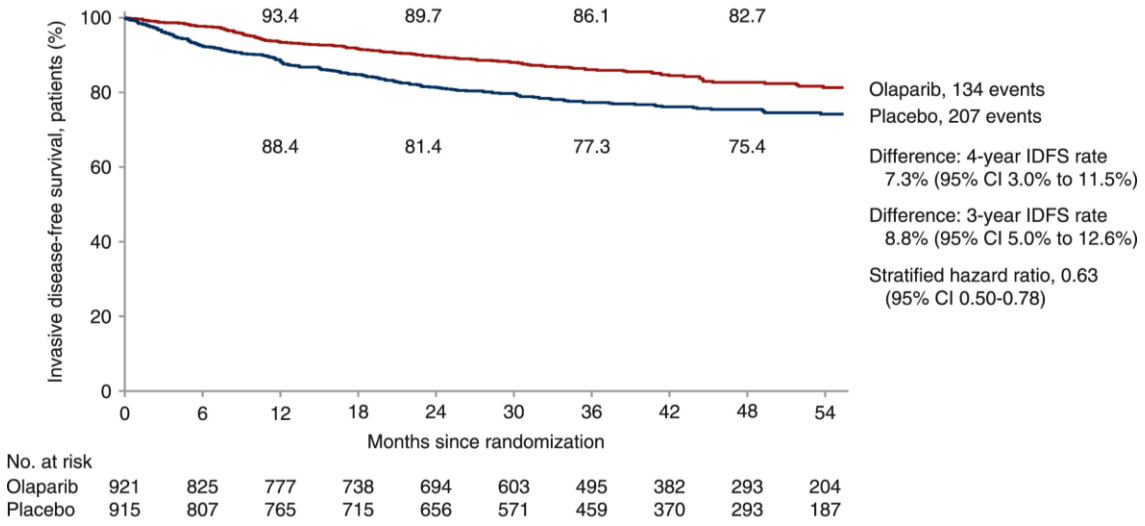
Olaparib (n=921)	**89.8%**
Placebo (n=915)	**86.4%**

Difference: 3.4%
95% CI: −0.1, 6.8

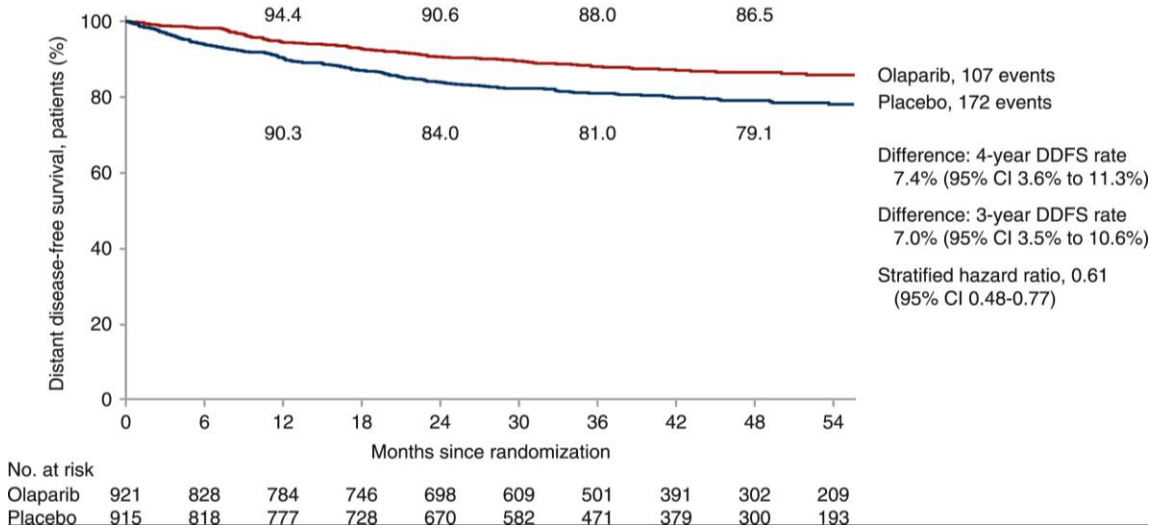
Tutt et al. NEJM 2021; Tutt, ESMO VP 2022; Geyer et al. Ann Oncol. 2022

OLYMPIA: UPDATED IDFS AND DDFS

Updated iDFS



Updated DDFS



iDFS

HR 0.63
95% CI: 0.50, 0.78

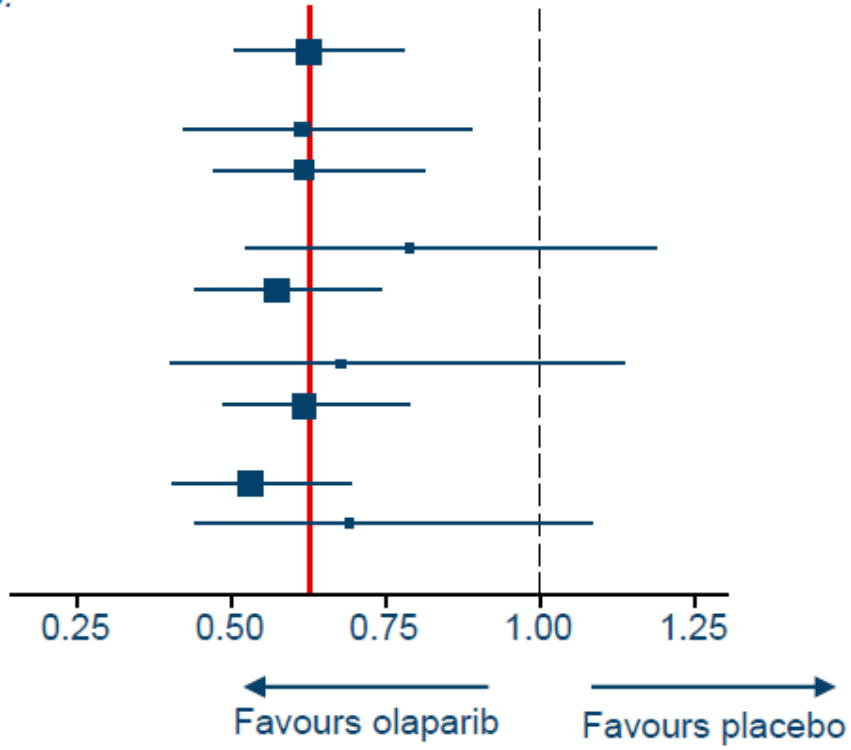
DDFS

HR 0.61
95% CI: 0.48, 0.77

Tutt et al. NEJM 2021; Tutt, ESMO VP 2022; Geyer et al. Ann Oncol. 2022

OLYMPIA: SUBGROUP ANALYSIS OF IDFS

Subgroup	Olaparib	Placebo	Stratified hazard ratio for invasive disease-free survival (95% CI)	P value for heterogeneity
	No. of patients with an invasive disease event/total no.			
All patients	134 / 921	207 / 915	0.628 (0.504, 0.779)	NA
Prior chemo				0.977
Adjuvant	46 / 461	75 / 455	0.618 (0.425, 0.888)	
Neoadjuvant	88 / 460	132 / 460	0.622 (0.473, 0.813)	
Prior platinum				0.197
Yes	42 / 247	51 / 238	0.791 (0.523, 1.187)	
No	92 / 674	156 / 677	0.575 (0.443, 0.742)	
HR status				0.754
HR+/HER2-	25 / 168	34 / 157	0.680 (0.402, 1.134)	
TNBC	109 / 751	173 / 758	0.620 (0.487, 0.787)	
BRCA				0.615
BRCA1	83 / 579	149 / 588	0.533 (0.406, 0.695)	
BRCA2	34 / 235	44 / 216	0.693 (0.440, 1.082)	
BRCA1/2 both	0 / 2	0 / 3	NC	



Tutt et al. NEJM 2021; Tutt, ESMO VP 2022; Geyer et al. Ann Oncol. 2022

OLYMPIA: TREATMENT-RELATED ADVERSE EVENTS AND QOL

AE in ≥10% of Patients, n (%)	Olaparib (n = 911)		Placebo (n = 904)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Nausea	518 (56.9)	7 (0.8)	211 (23.3)	0
Fatigue	365 (40.1)	16 (1.8)	245 (27.1)	4 (0.4)
Anemia	214 (23.5)	79 (8.7)	35 (3.9)	3 (0.3)
Vomiting	206 (22.6)	6 (0.7)	74 (8.2)	0
Headache	180 (19.8)	2 (0.2)	152 (16.8)	1 (0.1)
Diarrhea	160 (17.6)	3 (0.3)	124 (13.7)	3 (0.3)
Decreased neutrophil count	146 (16.0)	44 (4.8)	59 (6.5)	7 (0.8)
Decreased WBC count	143 (15.7)	27 (3.0)	52 (5.8)	3 (0.3)
Decreased appetite	119 (13.1)	2 (0.2)	53 (5.9)	0
Dysgeusia	107 (11.7)	0	38 (4.2)	0
Dizziness	104 (11.4)	1 (0.1)	67 (7.4)	1 (0.1)
Arthralgia	84 (9.2)	2 (0.2)	107 (11.8)	2 (0.2)

- In the olaparib arm, anemia was the most frequent AE at grade ≥3 in >1% patients
  - Transfusions: olaparib, 5.8%; placebo, 0.9%
- Median percentage of intended dose received: olaparib, 94.8%; placebo, 98.9%
- For the olaparib vs placebo arms:
  - Dose reductions: 25.0% vs 5.2%
  - Discontinuations due to AEs: 9.9% vs 4.2% (with olaparib, most commonly due to nausea, 2.0%; anemia, 1.8%; fatigue, 1.3%; decreased neutrophil count, 1.0%)
- No declines or clinically significant differences observed between arms in global health quality during tx

Tutt et al. NEJM 2021; Tutt, ESMO VP 2022; Geyer et al. Ann Oncol. 2022

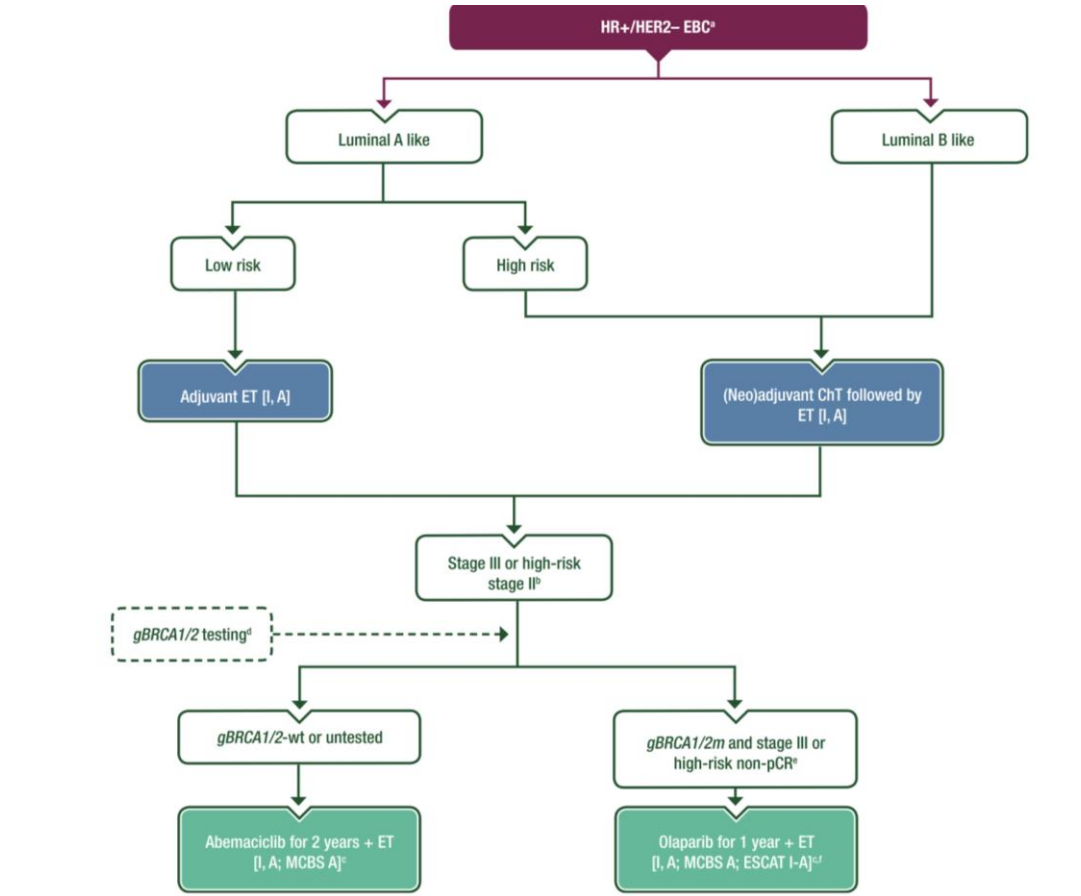
OLYMPIA: TREATMENT-RELATED ADVERSE EVENTS AND QOL

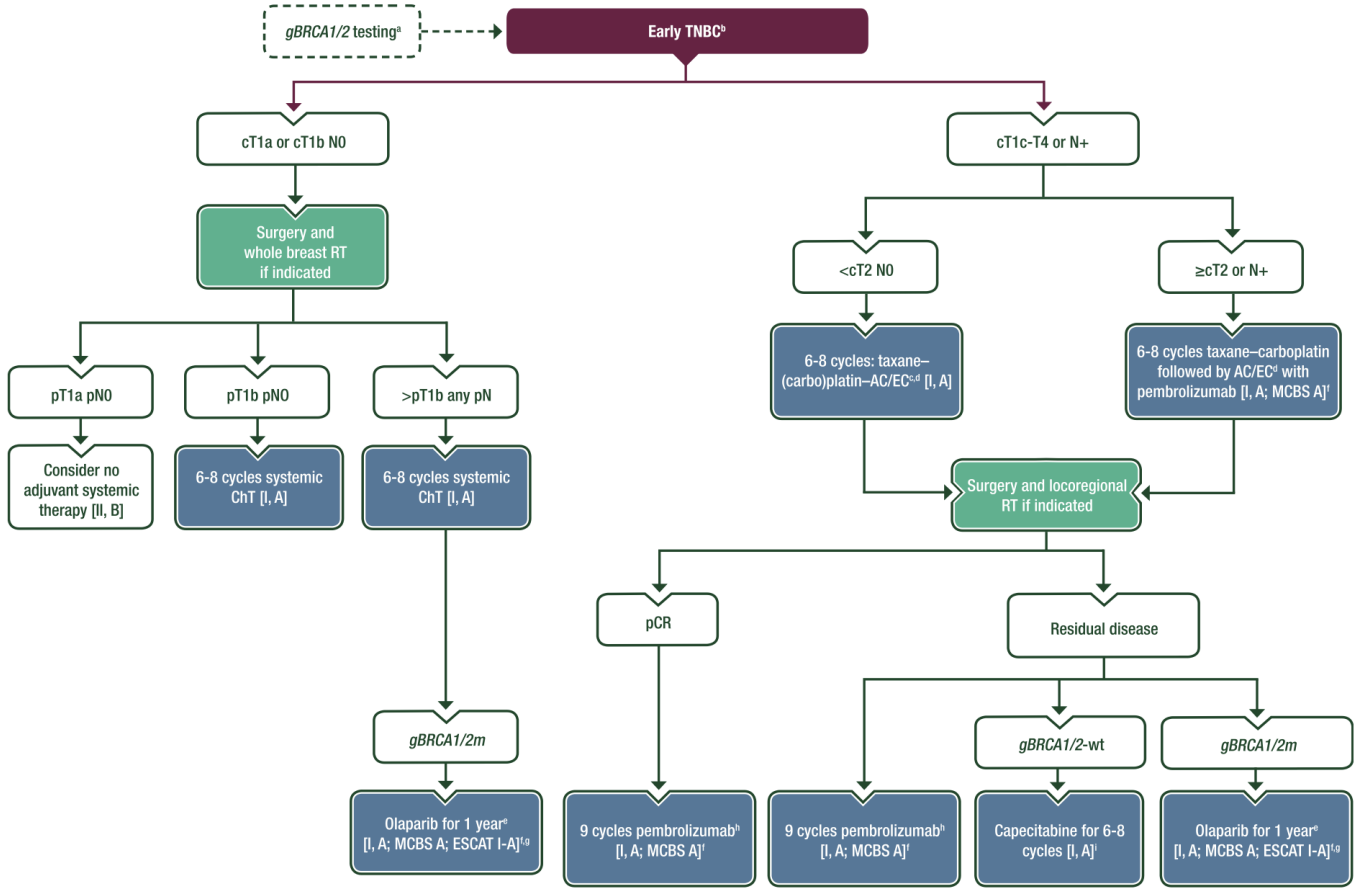
Safety Outcome, n (%)	Olaparib (n = 911)	Placebo (n = 904)
Any AE	835 (91.7)	753 (83.3)
Serious AE	79 (8.7)	76 (8.4)
AE of special interest ▪ MDS/AML ▪ Pneumonitis ▪ New primary malignancy	30 (3.3) 2 (0.2) 9 (1.0) 19 (2.1)	46 (5.1) 3 (0.3) 11 (1.2) 32 (3.5)
Grade ≥3 AE	221 (24.3)	102 (11.3)
Grade 4 AE	17 (1.9)	4 (0.4)
AE leading to permanent discontinuation	90 (9.9)	38 (4.2)

AEs leading to death: olaparib, n = 1 (cardiac arrest); placebo, n = 2 (AML, ovarian cancer)

Tutt et al. NEJM 2021; Tutt, ESMO VP 2022; Geyer et al. Ann Oncol. 2022

ADJUVANT OLAPARIB IS NOW APPROVED (LEVEL 1A) FOR BOTH HR+/HER2- AND TNBC





Loibl, et al. Ann Oncol. 2024

PRACTICAL CONSIDERATIONS

1. Should all women with breast cancer now be tested at diagnosis for germline BRCA1/2 alterations?
2. Overlapping indications in the adjuvant setting
   a) **Olaparib and pembrolizumb**: TNBC with residual after neoadjuvant chemo-immunotherapy
   b) **Olaparib and capecitabine**: TNBC with residual after neoadjuvant chemotherapy
   c) **Olaparib and abemaciclib**: High-risk early stage or locally advanced node-positive HR+/HER2- breast cancer

Q1. SHOULD ALL WOMEN WITH BREAST CANCER NOW BE TESTED AT DIAGNOSIS FOR BRCA1/2 ALTERATIONS?

Germline Testing in Patients With Breast Cancer: ASCO–Society of Surgical Oncology Guideline

Isabelle Bedrosian, MD[1]; Mark R. Somerfield, PhD[2]; Maria Isabel Achatz, MD, PhD[3]; Judy C. Boughey, MD[4]; Giuseppe Curigliano, MD, PhD[5,6]; Sue Friedman, DVM[7]; Wendy K. Kohlmann, MS[8]; Allison W. Kurian, MD, MSc[9]; Christine Laronga, MD[10]; Filipa Lynce, MD[11]; Barbara S. Norquist, MD[12]; Jennifer K. Plichta, MD, MS[13]; Patricia Rodriguez, MD[14]; Payal D. Shah, MD[15]; Marc Tischkowitz, MD, PhD[16]; Marie Wood, MD[17]; Siddhartha Yadav, MD[4]; Katherine Yao, MD[18]; and Mark E. Robson, MD[19]

BRCA1/2 mutation testing should be offered to all newly diagnosed patients with breast cancer ≤65 years and select patients >65 years based on personal history, family history, ancestry, or eligibility for poly(ADP-ribose) polymerase (PARP) inhibitor therapy

SPECIAL ARTICLE

Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

S. Loibl[1,2], F. André[3], T. Bachelot[4], C. H. Barrios[5], J. Bergh[6], H. J. Burstein[7], M. J. Cardoso[8,9], L. A. Carey[10], S. Dawood[11], L. Del Mastro[12,13], C. Denkert[14], E. M. Fallenberg[15], P. A. Francis[16], H. Gamal-Eldin[17], K. Gelmon[18], C. E. Geyer[19], M. Gnant[20], V. Guarneri[21,22], S. Gupta[23], S. B. Kim[24], D. Krug[25], M. Martin[26], I. Meattini[27,28], M. Morrow[29], W. Janni[30], S. Paluch-Shimon[31], A. Partridge[7], P. Poortmans[32,33], L. Pusztai[34], M. M. Regan[35], J. Sparano[36], T. Spanic[37], S. Swain[38], S. Tjulandin[39], M. Toi[40], D. Trapani[7], A. Tutt[41,42], B. Xu[43], G. Curigliano[44,45] & N. Harbeck[46], on behalf of the ESMO Guidelines Committee*

Germline testing and subsequent genetic counselling for PVs in BRCA1/2 should be offered to patients who meet the respective national criteria and to those who are candidates for adjuvant olaparib therapy [I, A; ESCAT score: I-A].

Loibl et al. Ann Oncol. 2024; Bedrosian et al. J Clin Oncol. 2023

Q2A. OLAPARIB VS PEMBROLIZUMAB IN NON-PCR

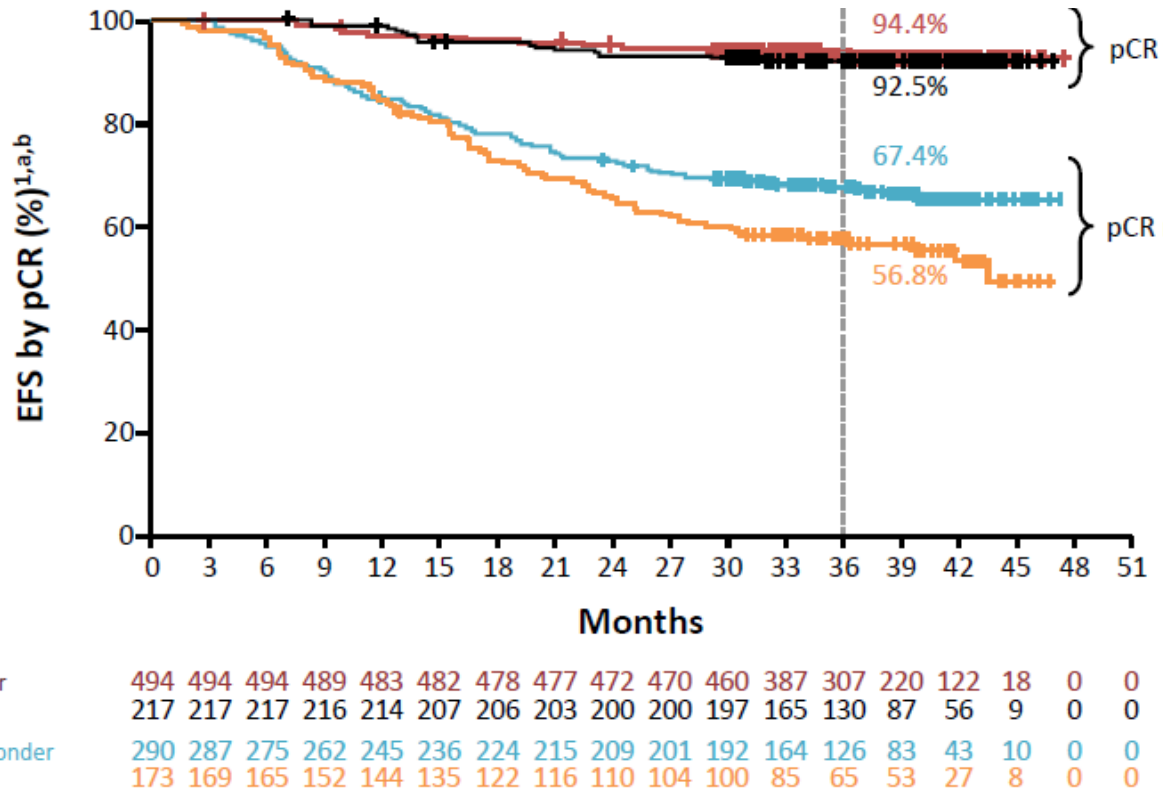
3-year EFS (Total population)[2]

Hazard ratio:

0.63

95% CI: 0.48, 0.82

P<0.001



No. at risk:

Pembro + CT / pembro responder	494	494	494	489	483	482	478	477	472	470	460	387	307	220	122	18	0	0
PBO + CT / PBO responder	217	217	217	216	214	207	206	203	200	200	197	165	130	87	56	9	0	0
Pembro + CT / pembro non-responder	290	287	275	262	245	236	224	215	209	201	192	164	126	83	43	10	0	0
PBO + CT / PBO non-responder	173	169	165	152	144	135	122	116	110	104	100	85	65	53	27	8	0	0

Outcomes are excellent if pCR

Role of adjuvant ICI is unknown

There is still an unmet need in the treatment of patients with no pCR

Schmid P et al. NEJM 2020

Q2A. OLAPARIB VS PEMBROLIZUMAB IN NON-PCR

- **Continue pembrolizumab and abstain from adjuvant olaparib**:
  - 32.6% EFS events at 36 months

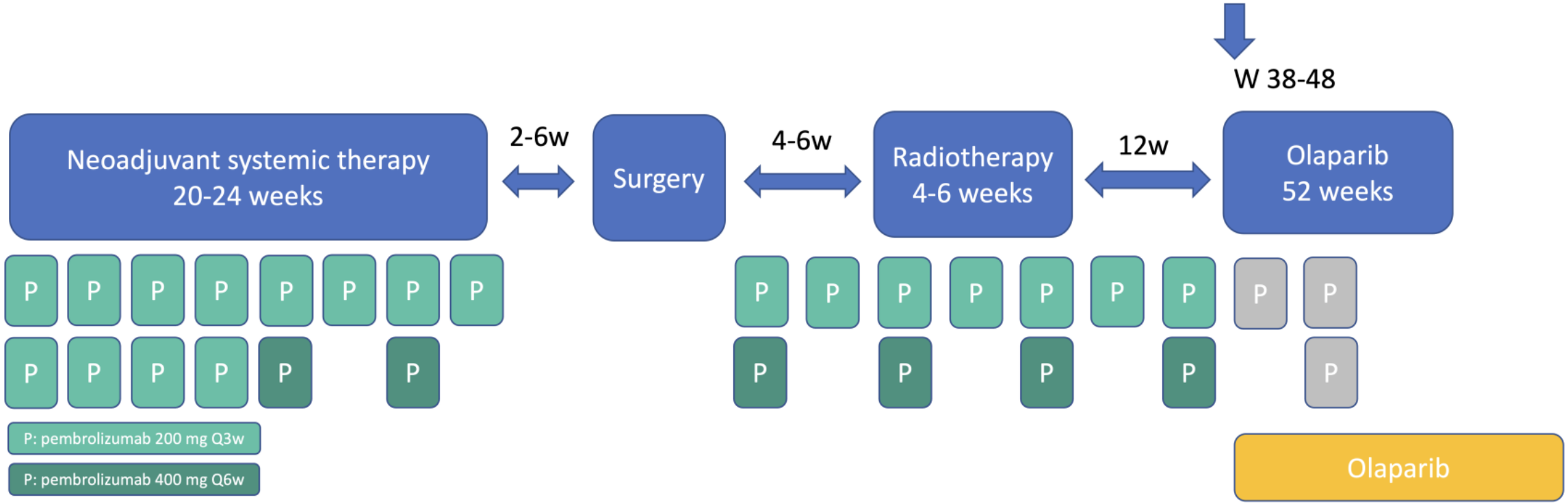
- **Discontinue pembrolizumab and prioritize olaparib single agent**:
  - Optimal duration of pembrolizumab in early TNBC is unknown
  - Trials needed to investigate whether shorter duration is non-inferior

- **Combine pembrolizumab and olaparib**:
  - No efficacy and safety data on combination in the early setting. Reassuring safety data reported with PARPi + PD-1/PD-L1 combinations in the advanced setting (MEDIOLA, KEYLYNK-009, DORA trials)
  - Off-label, problem with access / reimbursement

- **Option for sequential approach?**

Q2A. OLAPARIB VS PEMBROLIZUMAB: OPTION FOR SEQUENTIAL APPROACH?

In Olympia, olaparib could be initiated up to 12 weeks after the last local treatment



Punie K, ESMO Breast 2023

Q2B. OLAPARIB VS CAPECITABINE IN NON-PCR TNBC

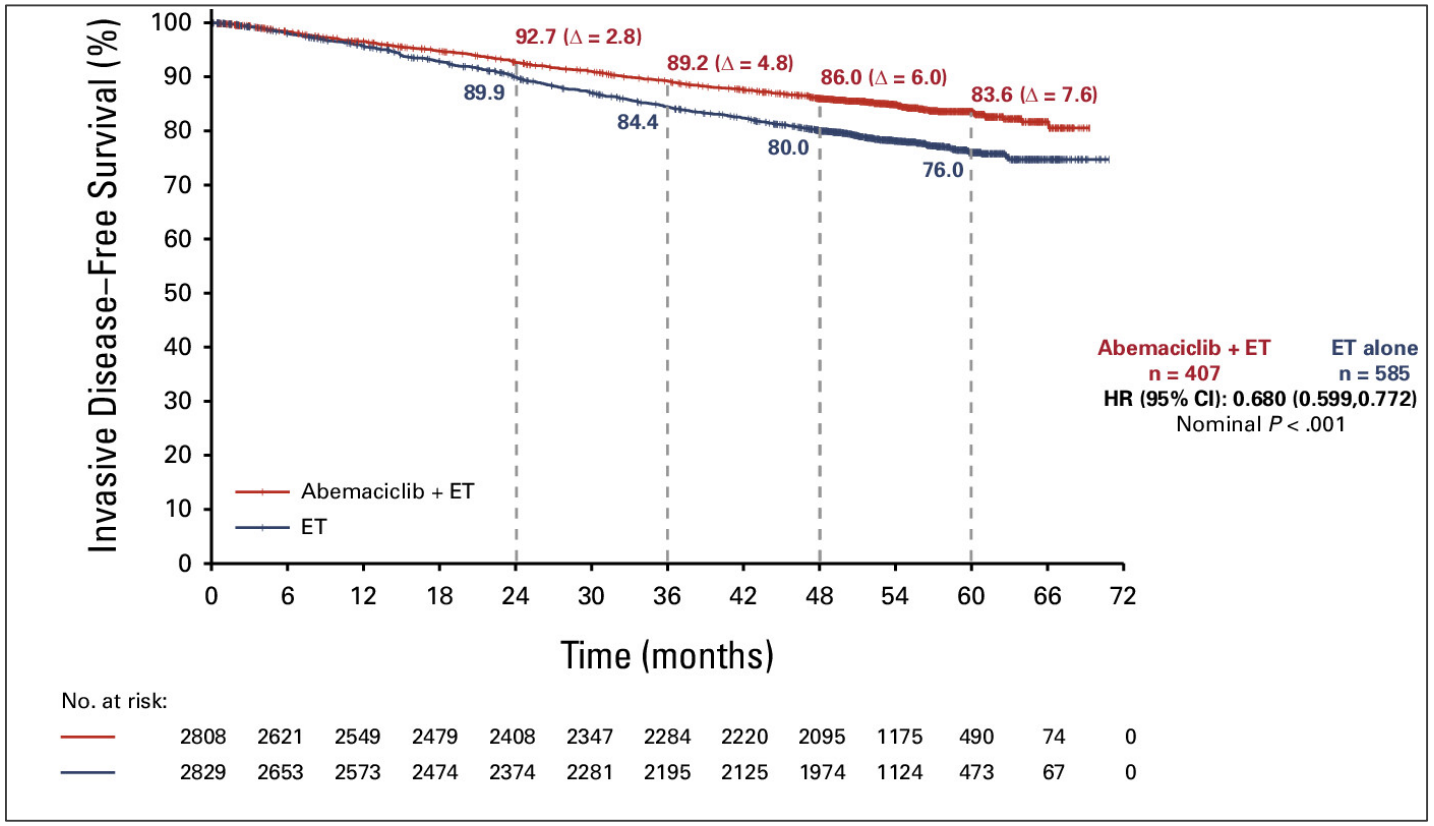
- CREATE-X was not conducted in a setting of either neoadjuvant carboplatin or chemo-immunotherapy
- Not focused in gBRCAm biological subset of TNBC
- PARPi superior to capecitabine as majority chemotherapy comparator in gBRCAm MBC (OLYMPIAD and EMBRACA)
- Combination has no adequate safety data

	N TNBC (Basal)	Capecitabine iDFS	Capecitabine OS
CREATE-X (v. obs, sig DFS, OS)	286 (N/A)	69.8% 5-year DFS (all)	78.9% 5-year (all)
GEICAM_CIBOMA (v. obs, NS)	876 (647)	79.6% 5-year DFS (all)	86.2% 5-year (all)
EA1131 (v. platinum, NSD)	410 (308)	49% 3-year IDFS (basal)	66% 3-year (basal)

Masuda et al. NEJM 2017; Lluch et al. J Clin Oncol. 2020; Mayer et al. J Clin Oncol. 2021

Q2C. OLAPARIB VS ABEMACICLIB IN HIGH-RISK HR+/HER2-

monarchE: abemaciclibib improves iDFS at 5-year follow up



5-year iDFS

HR, 0.680
95% CI: 0.599, 0.772
P<0.001

OS

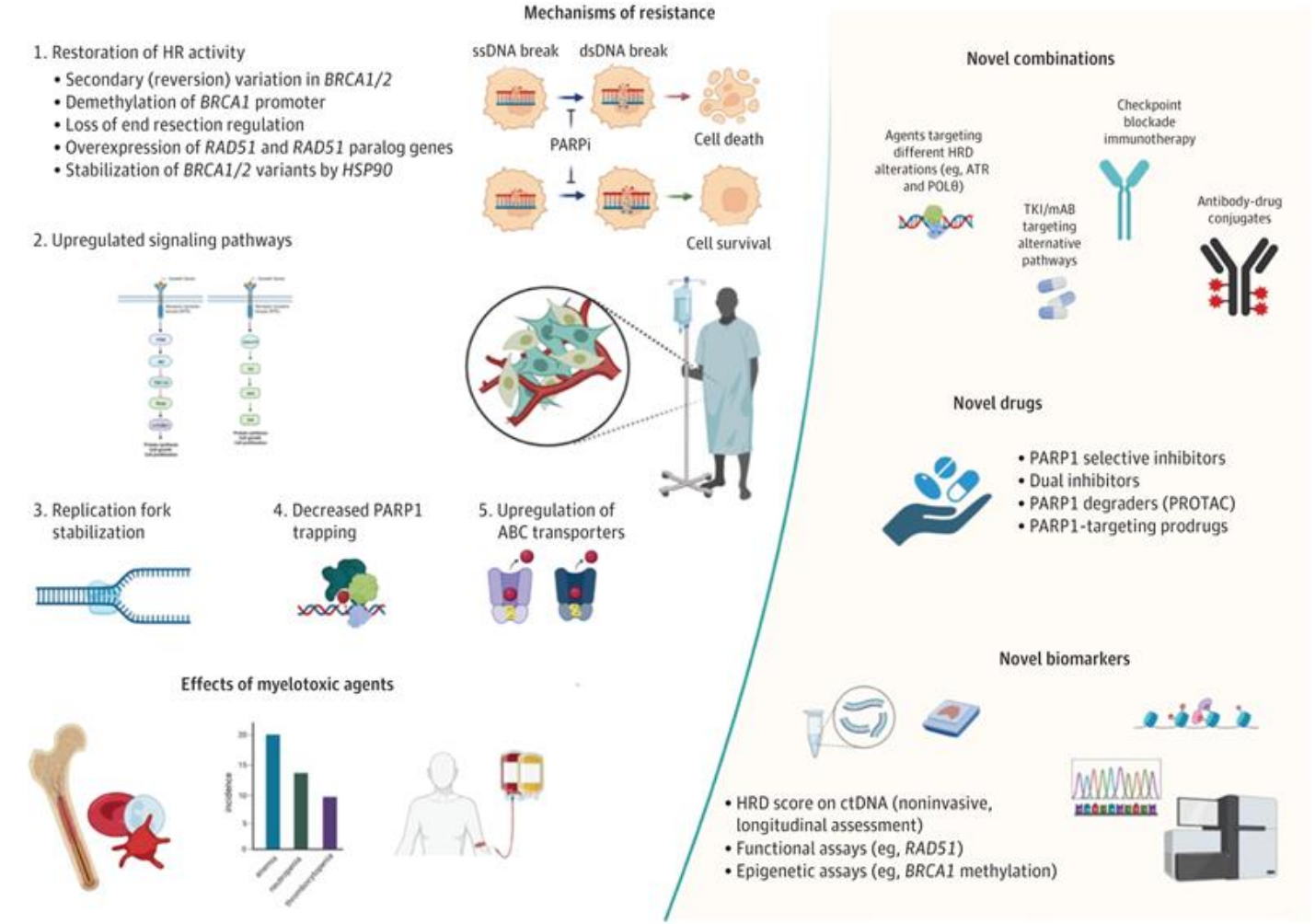
No difference in OS
(at 5-year analysis)

Johnston SRD, et al. Lancet Oncol 2023; Rastogi P, et al. J Clin Oncol 2024

Q2C. OLAPARIB VS ABEMACICLIB IN HIGH-RISK HR+/HER2-

- Abemaciclib improves iDFS at longer follow up but without overall survival benefit yet seen
- Olaparib improves iDFS with early and sustained separation of survival curves in a mechanism based biomarker selected population of HER2-negative breast cancer
- Inadequate safety data to support use of a combination of abemaciclib with olaparib
- Data from metastatic setting suggest BRCA-mediated resistance to CDK4/6i
- Sequential approach?

LIMITATIONS AND FUTURE DIRECTION OF PARP INHIBITORS IN BREAST CANCER



Understand and address resistance to PARPi in high recurrence risk gBRCA1/2 mutation carriers

Reduce toxicity to improve “low risk” and even “prevention” feasibility (PARP1-selective inhibitors)

Investigate potential for use in other forms of HR-deficient breast cancer

Improve biomarkers to detect breast cancer that is HR-deficient

Morganti S, Marra A, et al. JAMA Oncol. 2024

KEY ONGOING STUDIES INVESTIGATING PARP INHIBITORS IN EARLY BREAST CANCER

Registration identifier	Phase	Primary endpoint(s)	Disease(s)	Mutation status	Prior PARPi	N	Class(es)	Interventional cohort drug(s)
NCT05582499	I/II	pCR rate	BC	N.R.	//	716	PARPi + CDKi	Fluzoparib + Dalpiciclib/Fluzoparib + Chemotherapy
NCT05332561 (COGNITION-GUIDE)	II	iDFS	BC (TNBC cohort)	s/gBRCA1/2, gPALB2	//	240	PARPi	Olaparib
NCT05761470	II	pCR rate	HER2- BC	HRD	//	66	PARPi + IO	Fluzoparib + Camrelizumab + Chemotherapy
NCT02849496	II	PFS	HER2- BC	BRCA1/2	Not allowed	81	PARPi + IO	Olaparib + Atezolizumab
NCT04481113	I	MTD	HR+/HER2- BC	N.R.	Not allowed	8	PARPi + CDKi	Niraparib + Abemaciclib
NCT05834582	II	pCR rate	TNBC	gBRCA 1/2	Not allowed	60	PARPi	Fluzoparib + Chemotherapy
NCT03911453	I	PD-L1 expression	TNBC	N.R.	Not allowed	20	PARPi	Rucaparib
NCT05498155	II	pCR rate	TNBC	s/gBRCA 1/2	Not allowed	50	PARPi + IO	Olaparib ± Durvalumab
NCT04584255	II	pCR rate TILs change	HER2- BC	gBRCA1/2, gPALB2	Not allowed	62	PARPi + IO	Niraparib + Dostarlimab

Abbreviations: N = enrollment; PFS = progression free survival; N.R. = not required; PARPi = adenosine diphosphate polymerase inhibitor; sBRCA = somatic BRCA; gBRCA = germline BRCA; HR = hormone receptor; TNBC = triple negative breast cancer; ADC = antibody-drug conjugate; IO = immunotherapy; HRD = homologous recombination deficiency; pCR = pathological complete response

Morganti S, Marra A, et al. JAMA Oncol. 2024

CONCLUSIONS (…personal…)

- Germline *BRCA1* and *BRCA2* status is now an important systemic therapy defining-biomarker in early (and advanced) breast cancer → **PLEASE TEST YOUR PATIENT!**
- **Adjuvant olaparib improves iDFS, DDFS and OS** in HER2-negative gBRCA early disease
- **In TNBC with residual disease:** olaparib benefits unknown following KEYNOTE-522 regimen but lack of pCR is associated with substantial risk favors use of olaparib post surgery
- **In TNBC with residual disease:** OS adjuvant and MBC response and PFS data support choice of olaparib over capecitabine in gBRCAm specific context
- **In high risk ER+/HER2- disease:** ITT IDFS, DDFS and an OS benefit favour olaparib over abemaciclib but sequencing after 12 months olaparib could be considered