Strategies to treat High Risk ER+/HER2- Residual Disease (CDK 4/6i, IO, ADCs)

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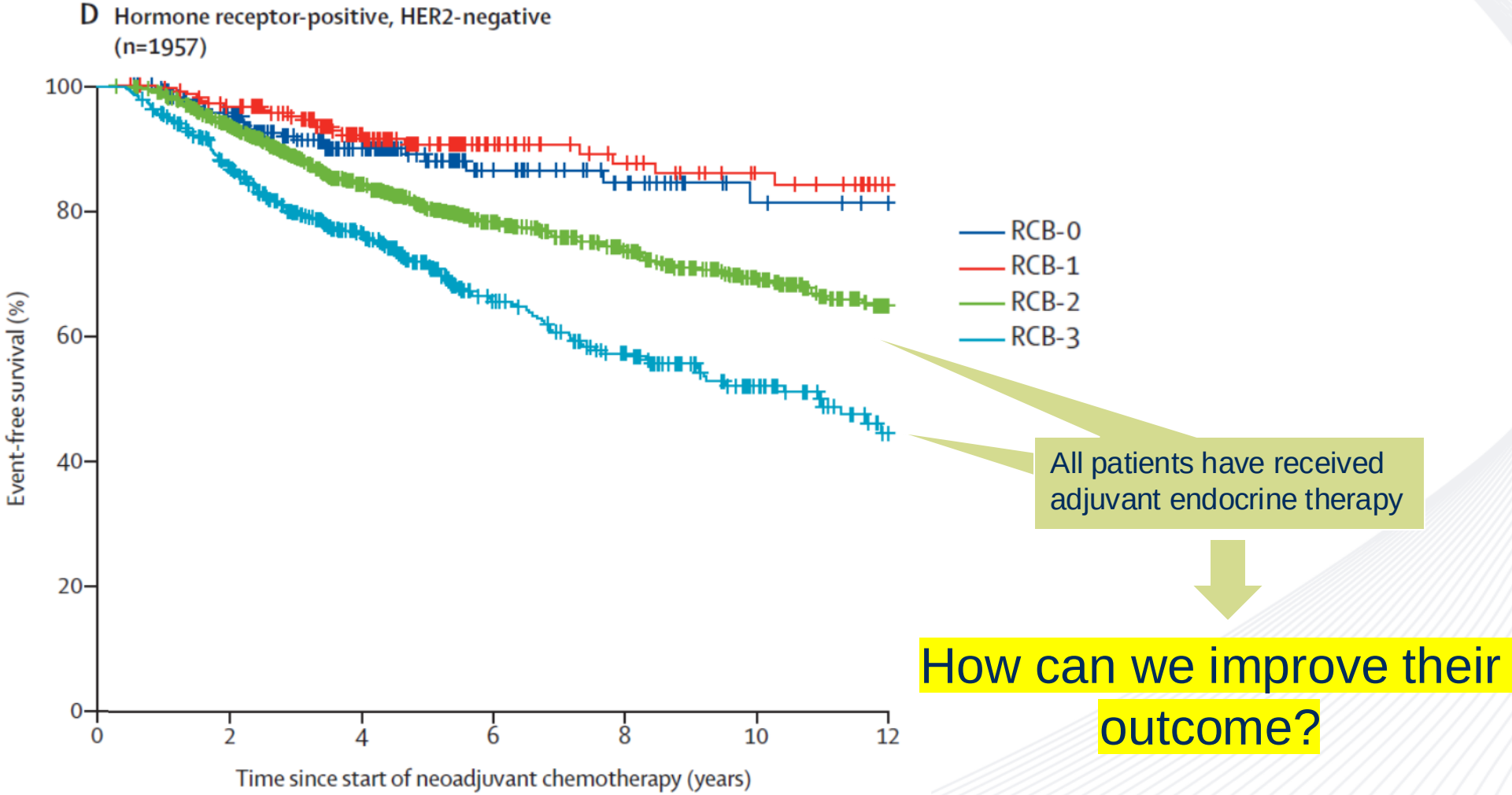
Under what circumstances one should consider neoadjuvant chemotherapy for an ER+/HER2- stage II/III breast cancer ?

Both Onco*type* DX Recurrence Score (RS) and MammaPrint (MP) predict benefit from adjuvant chemotherapy, and multiple studies showed that high-risk MP status and high RS are also associated with a higher pCR rates (Pease AM et al. *Annals Surg Onc* 26:366-371, 201; Blumencranz P, et al, *Annals Surg Onc*. 2023;30:8353-8361)

- Whenever adjuvant chemotherapy is indicated, neoadjuvant use of the same regimen may also be appropriate (Korde LA, et al. *J Clin Oncol*; 2021;39:1485-505)
  - Clinical response and tumor shrinkage is common but pCR (ypT0/is ypN0) is rare 6-10%
  - Higher pCR rates of 15-20% are seen in RS >30 and Mammaprint-High 2 cancers

- Why do neoadjuvant chemotherapy?
  - Pathologic downstaging can lead to smaller surgery (Boughey JC, et al. *Annals Surg*. 2006;244(3):464-470)
  - Additional prognostic information may be gained that can guide postoperative therapy
    - Residual disease guided therapy can improve survival in TNBC and HER2+ cancers, but this is yet to be demonstrated in ER+ disease (Pusztai L, et al. *Lancet Oncol*. 2019;20(7):e390-6)

The extent of residual cancer after neoadjuvant chemotherapy remains prognostic in ER+/HER2- patients



All patients have received adjuvant endocrine therapy

How can we improve their outcome?

Yau C, et al. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. *Lancet Oncol*. 2022;23(1):149-60.

Components of the most effective adjuvant endocrine therapy for high-risk ER+ patients

(i) Extended duration of endocrine therapy (ET) to 7-10 years (DFS HR: 0.57 - 0.88)

(Bekes I, Huober J. *Cancers*. 2023;15:4190)

The Breast Cancer Index (BCA) assay may help predicting benefit from extended ET

(ii) Zoledronic acid 4 mg I.V. q 6 mo x 2-3 years (OS HR: 0.82)

(Early Breast Cancer Trialists' Collaborative Group. *Lancet.* 2015;386:1353-61)

(iii) AI + OFS in premenopausal women (OS HR: 0.80)

(Francis PA, et al. *J Clin Oncol*. 2023;41:1370-75)

(iv) Adjuvant CDK4/6 inhibitor therapy (IDFS HR: 0.68 - 0.75)

(Caswell-Jin JL, et al ASCO Rapid Guideline Update Clinical Insights. *JCO Oncology Practice*. 2025:OP-24.)

(v) Adjuvant olaparib + ET for germline BRCA+ patients (IDFS HR: 0.68)

(Geyer CE, et al. *Annals Oncol*. 2022; 33:1250-68)

The NATALEE and MonarchE trials specifically included ER+ patients with residual disease post-neoadjuvant chemotherapy

NATALIE trial population

Characteristic	Ribociclib + NSAI (N = 2549)	NSAI Alone (N = 2552)	All Patients (N = 5101)
Median age (range) — yr	52 (24–90)	52 (24–89)	52 (24–90)
Menopausal status — no. (%)			
Premenopausal women	1115 (43.7)	1123 (44.0)	2238 (43.9)
Postmenopausal women	1423 (55.8)	1420 (55.6)	2843 (55.7)
Men	11 (0.4)	9 (0.4)	20 (0.4)
Anatomical stage — no. (%)†			
I	9 (0.4)	5 (0.2)	14 (0.3)
IIA	479 (18.8)	521 (20.4)	1000 (19.6)
IIB	532 (20.9)	513 (20.1)	1045 (20.5)
III	1528 (59.9)	1512 (59.2)	3040 (59.6)
Previous neoadjuvant or adjuvant chemotherapy — no. (%)			
Any	2249 (88.2)	2245 (88.0)	4494 (88.1)
Neoadjuvant	1085 (42.6)	1095 (42.9)	2180 (42.7)
Adjuvant	1223 (48.0)	1220 (47.8)	2443 (47.9)

ypN+ or Stages II (gr 3, Ki67>20, genomic high risk), or III at diagnosis or post-chemotherapy

Slamon D, et al. New Eng J Med. 2024; 390:1080-91

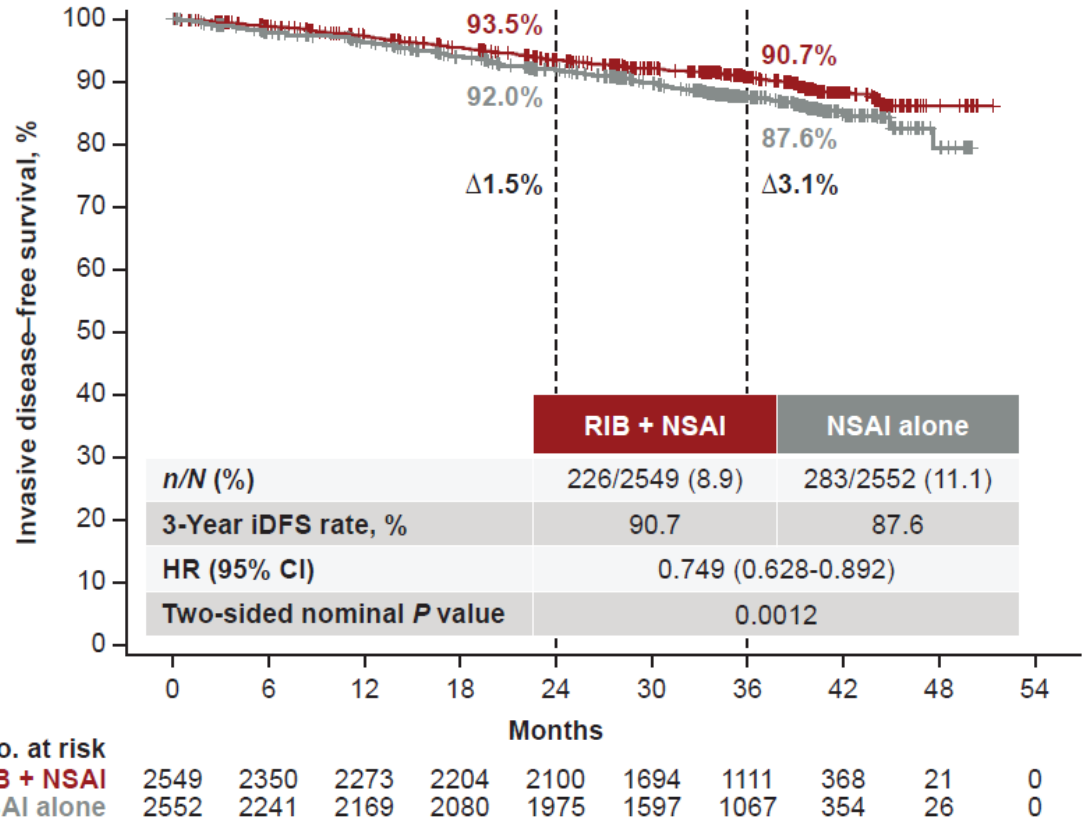
MonrachE trial population

Category	ITT population[d]		ITT Ki-67-high population (≥20%)	
	Abemaciclib + ET N = 2808, n (%)[a]	ET alone N = 2829, n (%)[a]	Abemaciclib + ET N = 1262, n (%)[a]	ET alone N = 1236, n (%)[a]
Age, median (range)	51 (23-89)	51 (22-86)	51 (23-88)	51 (24-86)
<65	2371 (84.4%)	2416 (85.4%)	1095 (86.8%)	1070 (86.6%)
≥65	437 (15.6%)	413 (14.6%)	167 (13.2%)	166 (13.4%)
Female	2787 (99.3%)	2814 (99.5%)	1250 (99.0%)	1227(99.3%)
Male	21 (0.7%)	15 (0.5%)	12 (1.0%)	9 (0.7%)
Hormone receptor status				
Estrogen receptor-positive	2786 (99.2%)	2810 (99.3%)	1251 (99.1%)	1224 (99.0%)
Estrogen receptor-negative	16 (0.6%)	17 (0.6%)	8 (0.6%)	11 (0.9%)
Progesterone receptor-positive	2426 (86.4%)	2456 (86.8%)	1062 (84.2%)	1043 (84.4%)
Progesterone receptor-negative	298 (10.6%)	295 (10.4%)	165 (13.1%)	152 (12.3%)
Menopausal status[b,c]				
Premenopausal	1221 (43.5%)	1232 (43.5%)	575 (45.6%)	564 (45.6%)
Postmenopausal	1587 (56.5%)	1597 (56.5%)	687 (54.4%)	672 (54.4%)
Prior chemotherapy[b]				
Neoadjuvant chemotherapy	1039 (37.0%)	1048 (37.0%)	457 (36.2%)	472 (38.2%)
Adjuvant chemotherapy	1642 (58.5%)	1647 (58.2%)	749 (59.4%)	704 (57.0%)
No chemotherapy	127 (4.5%)	134 (4.7%)	56 (4.4%)	60 (4.9%)
Region[b]				
North American/Europe	1470 (52.4%)	1479 (52.3%)	692 (54.8%)	674 (54.5%)
Asia	574 (20.4%)	582 (20.6%)	272 (21.6%)	280 (22.7%)
Other	764 (27.2%)	768 (27.1%)	298 (23.6%)	282 (22.8%)
Positive axillary lymph nodes				
0	7 (0.2%)	7 (0.2%)	2 (0.2%)	2 (0.2%)
1-3	1118 (39.8%)	1142 (40.4%)	672 (53.2%)	668 (54.0%)
≥4	1682 (59.9%)	1680 (59.4%)	588 (46.8%)	566 (45.8%)

≤ 4+ LN, 1-3+ LN and T≥5 cm, grade 3, Ki-67 >20%,

Harbeck N. et al. Annals of Oncology. 2021; 32(12):1571-81

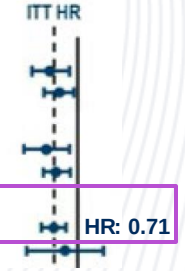
NATALEE results (3 years of ribociclib)



	RIB + NSAI	NSAI alone
n/N (%)	226/2549 (8.9)	283/2552 (11.1)
3-Year iDFS rate, %	90.7	87.6
HR (95% CI)	0.749 (0.628-0.892)	
Two-sided nominal *P* value	0.0012	

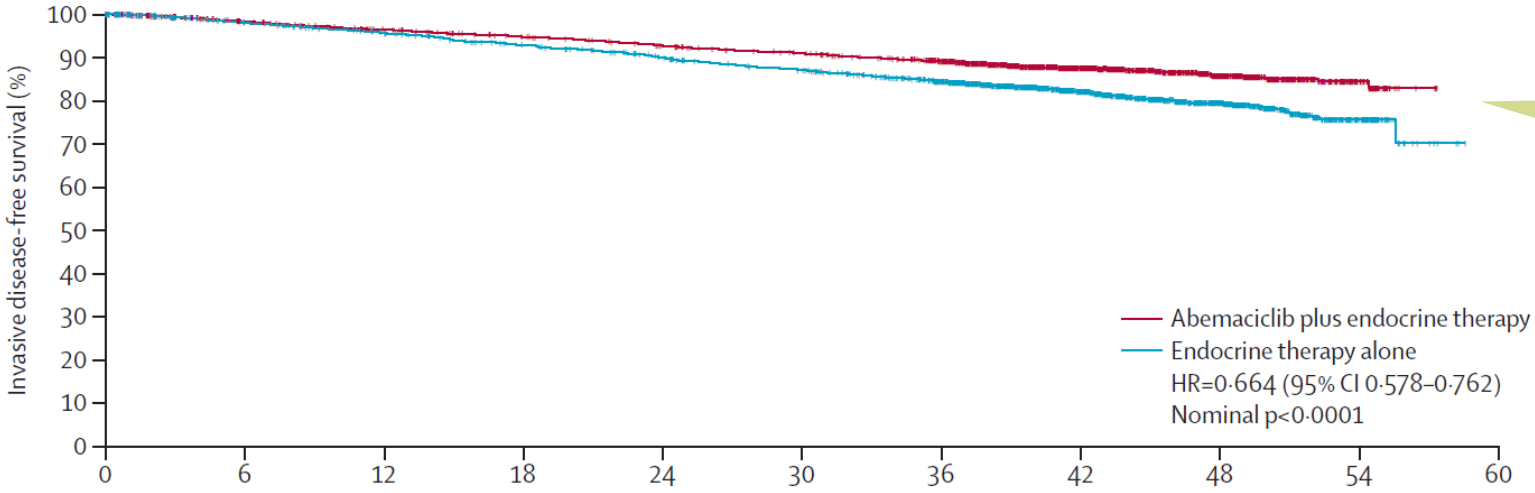
Type and site of first iDFS event, n (%)	RIB + NSAI n=2549	NSAI Alone n=2552
Distant recurrence	176 (6.9)	246 (9.6)
Local/regional invasive recurrence	25 (1.0)	49 (1.9)
Second primary nonbreast cancer	39 (1.5)	40 (1.6)
Death	17 (0.7)	11 (0.4)
Invasive contralateral breast tumor	11 (0.4)	10 (0.4)
Invasive ipsilateral breast tumor	8 (0.3)	9 (0.4)

Subgroup	RIB + NSAI Events/n	RIB + NSAI 4-y iDFS rate, %	NSAI alone Events/n	NSAI alone 4-y iDFS rate, %
Menopausal status				
Men and premenopausal women	99/1125	90.7	137/1132	85.3
Postmenopausal women	164/1424	86.8	203/1420	82.2
AJCC stage				
Stage II	62/1012	93.9	96/1034	89.6
Stage III	200/1527	84.3	244/1512	78.4
Prior CT				
Yes	238/2249	88.2	309/2245	83.0
No	25/300	90.7	31/307	87.5



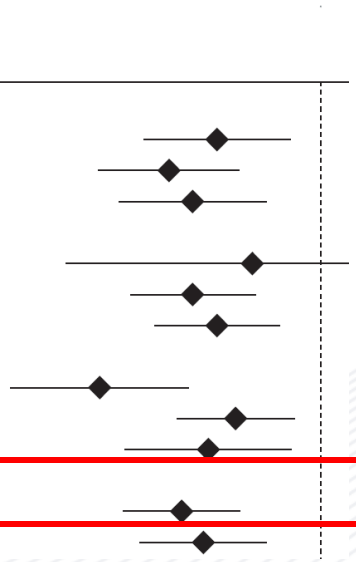
Hortobagyi GN, et al Annals of Oncology. 2025;36(2):149-57.

MonarchE results (2 years of abemaciclib)



4-year IDFS
85.8% *vs* 79.4%

	Abemaciclib plus endocrine therapy		Endocrine therapy alone	
	Events/N	3-year invasive disease-free survival	Events/N	3-year invasive disease-free survival
Number of positive lymph nodes				
1–3	111/1118	91·0 (89·0–92·5)	158/1142	87·3 (85·2–89·2)
4–9	113/1107	90·8 (88·8–92·4)	188/1126	85·4 (83·2–87·4)
10 or more	110/575	83·0 (79·6–85·9)	153/554	76·2 (72·2–79·6)
Histological grade				
Grade 1	18/209	92·9 (88·3–95·7)	23/216	91·6 (86·8–94·7)
Grade 2	148/1377	90·2 (88·4–91·7)	226/1395	85·9 (83·9–87·7)
Grade 3	157/1086	87·0 (84·8–89·0)	213/1064	82·0 (79·5–84·3)
Primary tumour size, cm				
<2	66/781	93·1 (91·0–94·7)	131/767	85·0 (82·2–87·5)
2–5	177/1371	88·2 (86·3–89·8)	242/1419	85·5 (83·5–87·3)
≥5	86/607	86·8 (83·7–89·3)	121/610	81·2 (77·7–84·2)
Previous chemotherapy				
Neoadjuvant	170/1039	84·8 (82·3–86·9)	261/1048	77·4 (74·7–79·9)
Adjuvant	147/1642	92·1 (90·6–93·3)	215/1647	88·7 (87·1–90·2)



Johnston SRD. et al. The Lancet, 2023; 24:77-90

Adjuvant olaparib (OlympiA) for germline BRCA1/2+ and ER+/HER2- cancers

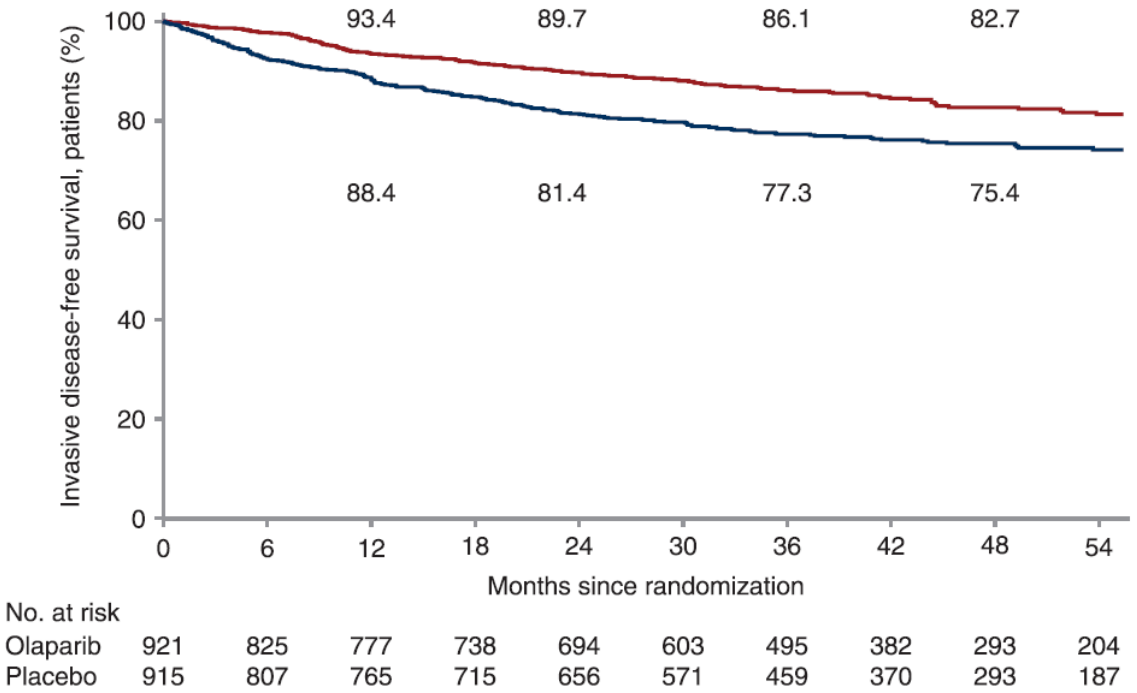
Characteristic	Olaparib (n = 921)	Placebo (n = 915)
Age, median (interquartile range), years	42 (36-49)	43 (36-50)
g*BRCA* P/LP gene—*n* (%)[b]		
BRCA1	656 (71.2)	669 (73.1)
BRCA2	260 (28.2)	238 (26.0)
BRCA1 and *BRCA2*	2 (0.2)	5 (0.5)
No g*BRCA* P/LP variant	2 (0.2)	3 (0.3)
Missing	1 (0.1)	0 (0.0)
Prior adjuvant/neoadjuvant chemotherapy, *n* (%)		
Adjuvant	461 (50.1)	455 (49.7)
Neoadjuvant	460 (49.9)	460 (50.3)
Anthracycline and taxane regimen	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 (0.0)	1 (0.1)
<6 cycles of (neo)adjuvant chemotherapy	7 (0.8)	13 (1.4)
Platinum-based (neo)adjuvant therapy		
No	674 (73.2)	677 (74.0)
Yes	247 (26.8)	238 (26.0)
Concurrent hormone therapy (hormone receptor positive only), *n* (%)	146/168 (86.9)	146/157 (93.0)
Hormone receptor status, *n* (%)[c]		
Hormone receptor positive/HER2 negative[d]	168 (18.2)	157 (17.2)
Triple-negative breast cancer[e]	751 (81.5)	758 (82.8)

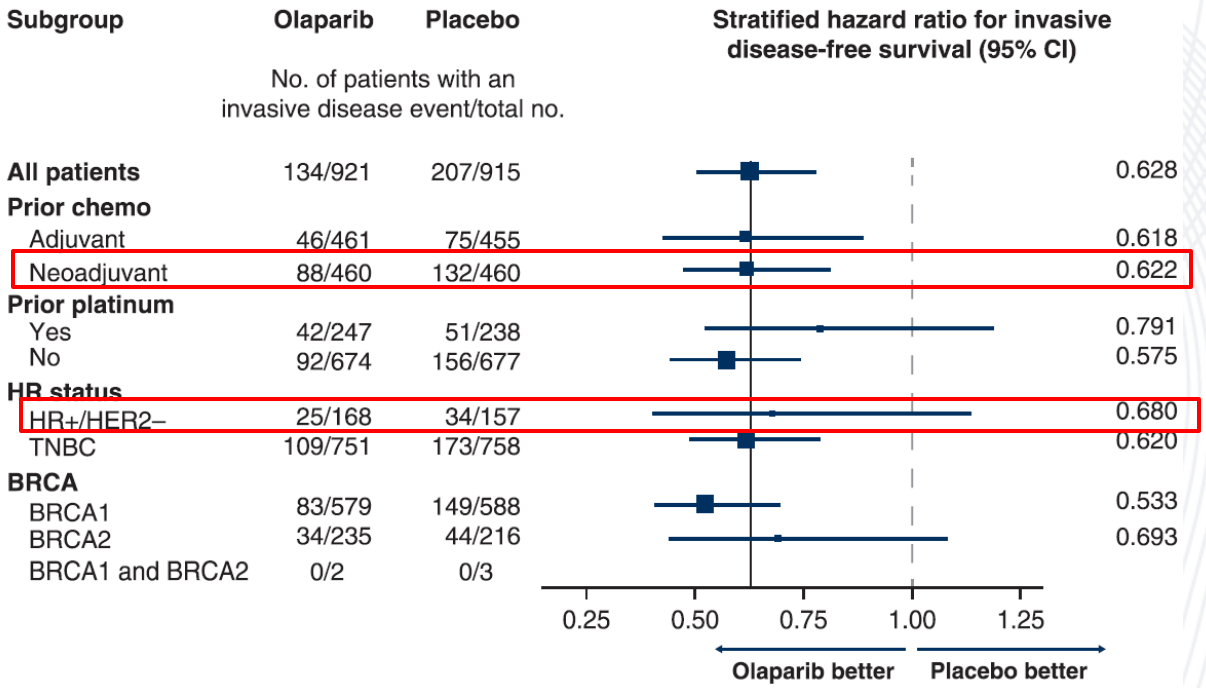
Geyer CE, et al. *Annals Oncol*. 2022; 33:1250-68

For eligibility, ER+ patients post-neoadjuvant chemo had to have CPS + EG score ≥ 3

CPS + EG Score			Points
Clincial Stage (Pre-Treatment)	I	T1N0, T0N1mi, T1N1mi	0
	IIA	T0N1; T1N1; T2N0	0
	IIB	T2N1; T3N0	1
	IIIA	T0-2 N2	1
	IIIB	T4 N0-N2	2
	IIIC	any T N3	2
Pathological Stage (Post-Treatment)	0	T0/isN0	0
	I	T1N0, T0N1mi, T1N1mi	0
	IIA	T0N1; T1N1; T2N0	1
	IIB	T2N1; T3N0	1
	IIIA	T0-2 N2	1
	IIIB	T4 N0-N2	1
	IIIC	any T N3	2
Receptor Status	ER +		0
	ER -		1
Nuclear Grade	1 or 2		0
	3		1

OlympiA Results



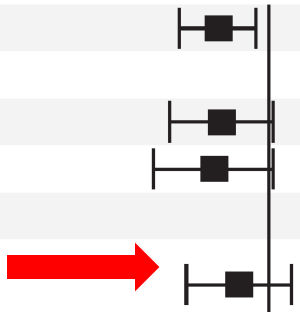


In ER+ patients, 1-yrear of olaparib was given concurrent with ET

Geyer CE, et al. *Annals Oncol*. 2022; 33:1250-68

Adjuvant capecitabine for patients with ER+/HER2- residual disease overall does not significantly improve outcome

Subgroup	No. of Patients	Hazard Ratio (95% CI)	P Value
Overall	887	0.70 (0.53–0.92)	0.01
Age			0.85
≤50 yr	532	0.72 (0.50–1.03)	
>50 yr	355	0.68 (0.45–1.04)	
Hormone receptor status			0.21
Estrogen-receptor positive or progesterone-receptor positive	601	0.81 (0.55–1.17)	
Estrogen-receptor negative and progesterone-receptor negative	286	0.58 (0.39–0.87)	

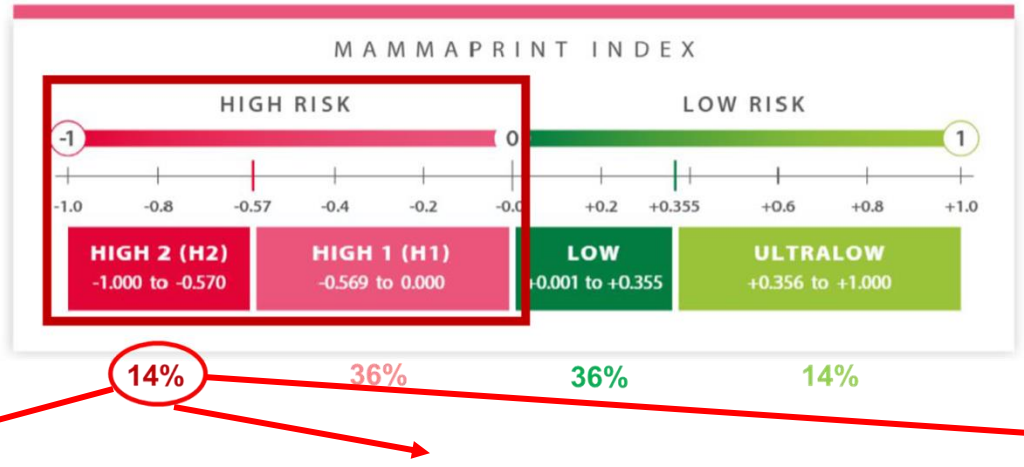


Masuda N, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. *N Engl J Med*. 2017;376:2147-59.

In the future ….

- ctDNA monitoring for molecular relapse and possible “2L adjuvant therapy” (DARE NCT04567420) ?
- Second generation SERDs/SERMs (ELEGANT NCT06492616; CAMBRIA-2 NCT05952557), and switching strategies (AMBER-4 NCT05514054, CAMBRIA-1 NCT05774951) ?
- (*in the more distant future next generation adjuvant CDK inhibitors and PIK3Ca/AKT/mTOR inhibitors*…) ?

An emerging unique subset of ER+ / HER2- breast cancers that resemble TNBC in its biology and clinical course



Clinical Features

Mostly grade 3
Mostly Recurrence Score ≥ 25
Mostly low/intermediate ER %
Often PD-L1 +

Biological Features

Low endocrine sensitivity gene expression
High proliferation
High immune gene expression
Overall gene expression similarity with TNBC

Clinical Course

High pathologic CR rate with chemo +IO
Benefit from anthracycline + taxane over TC
Higher rate of recurrence
Early recurrence in 1-3 years

Rios-Hoyo A, et al. Hormone Receptor–Positive HER2-Negative/MammaPrint High-2 Breast Cancers Closely Resemble Triple-Negative Breast Cancers. *Clinical Cancer Res*. 2025;31:403-13.
Huppert LA, et al. Pathologic complete response (pCR) rates for HR+/HER2-breast cancer by molecular subtype in the I-SPY2 Trial. *Annals Oncol*. 2-25;36:172-84.

Currently accruing: SWOG S2206 Neoadjuvant chemotherapy +/- durvalumab for Stage II/III MP High2 ER+ breast cancers (NCT 06058377)

Summary

- Moderate and extensive residual invasive cancer after neoadjuvant chemotherapy qualifies as high-risk ER+/HER2- disease (RCB II-III, CPS/EG ≥ 3)

- The most aggressive, most effective, adjuvant therapy for high-risk ER+/HER2- patients includes
  - 7-10 years of extended adjuvant endocrine therapy
  - 2-3 years of CDK4/6 inhibition
  - 3-years of adjuvant Zoledronic acid
  - Combined modality OFS + AI if premenopausal
  - (1 year of olaparib concurrent with ET, if gBRCA1/2 positive)

- Currently recruiting ER+/HER2- adjuvant trials might change standard of care for high-risk patients in the next 5-10 years.
  - An emerging clinically and biologically distinct subset of ER+/HER2- cancers that is characterized by ultra-high genomic risk (i.e MammaPrint High 2) shares many characteristics with TNBC and might require similar treatment strategies
    - (…neoadjuvant IO + chemo, … adjuvant Capecitabine or ADC if RD after neoadjuvant chemo..?)