Quesito clinico 1: Nelle pazienti con carcinoma mammario HR+/ HER2- negativo stadio IIA-IIIC è raccomandabile l'aggiunta di inibitori di CDK4/6 (ribociclib/abemaciclib) all'endocrinoterapia adiuvante?

Quale impatto nella pratica clinica?

Luisa Carbognin, M.D., Ph.D.

Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Gemelli

Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

Verona, 29 Marzo 2025

Disclosure Information

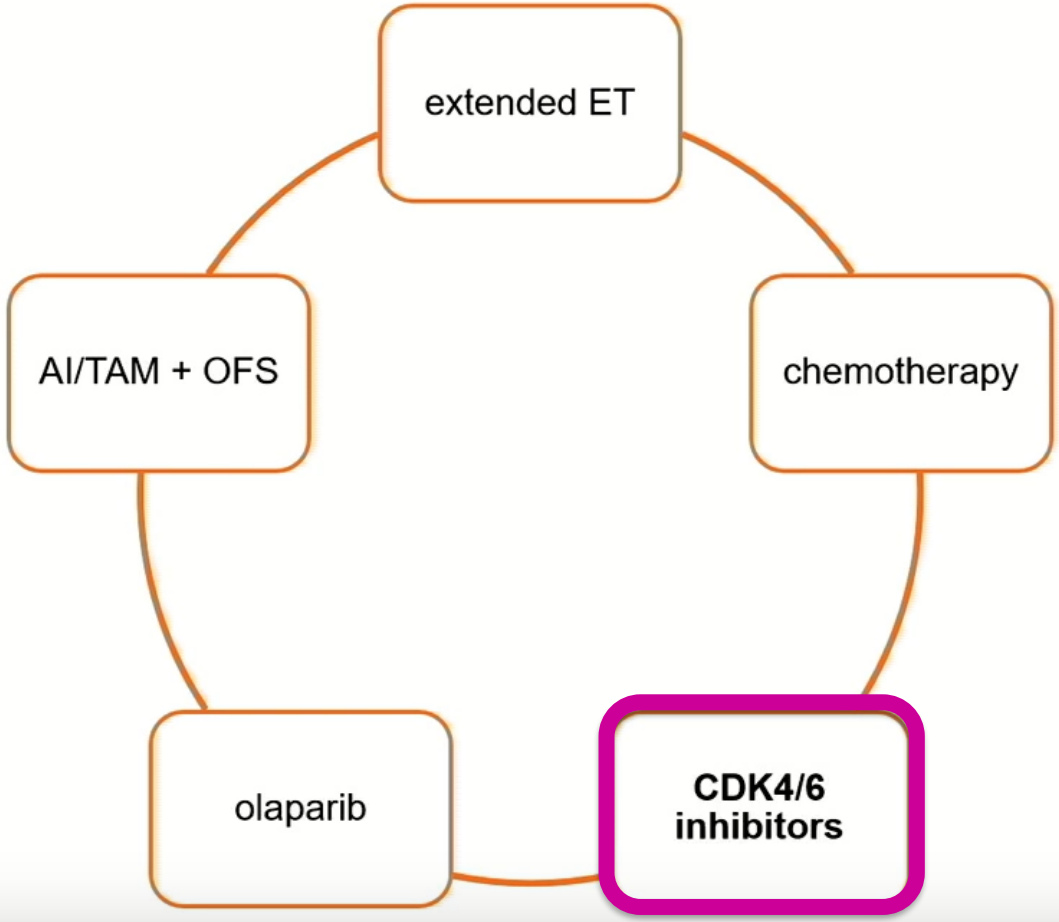
Luisa Carbognin, MD PhD

Relevant financial relationships to disclose:

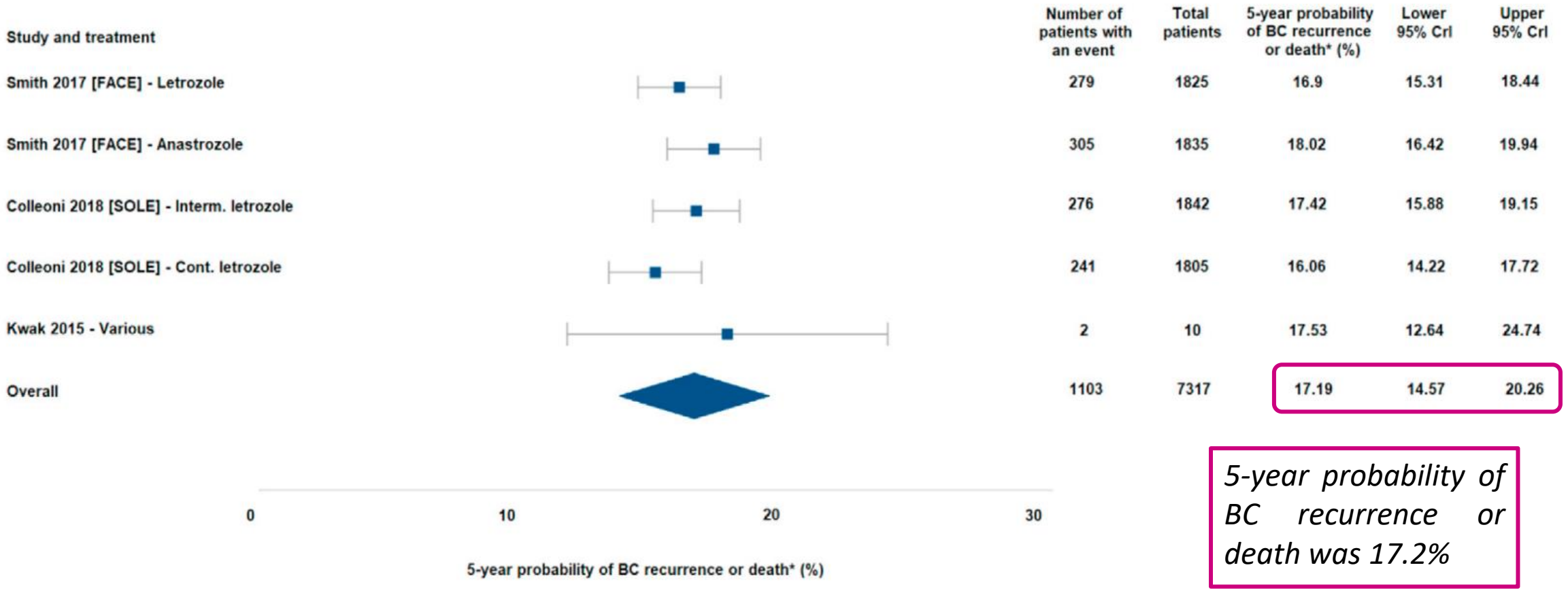
- Honoraria from: Novartis, Astrazeneca, Gilead, Menarini
- Grant/Research support from: AIRC

Adjuvant Strategy for Luminal-HER2-negative EBC

can we do something more?



Risk of Recurrence in ER+ EBC receiving Adjuvant ET

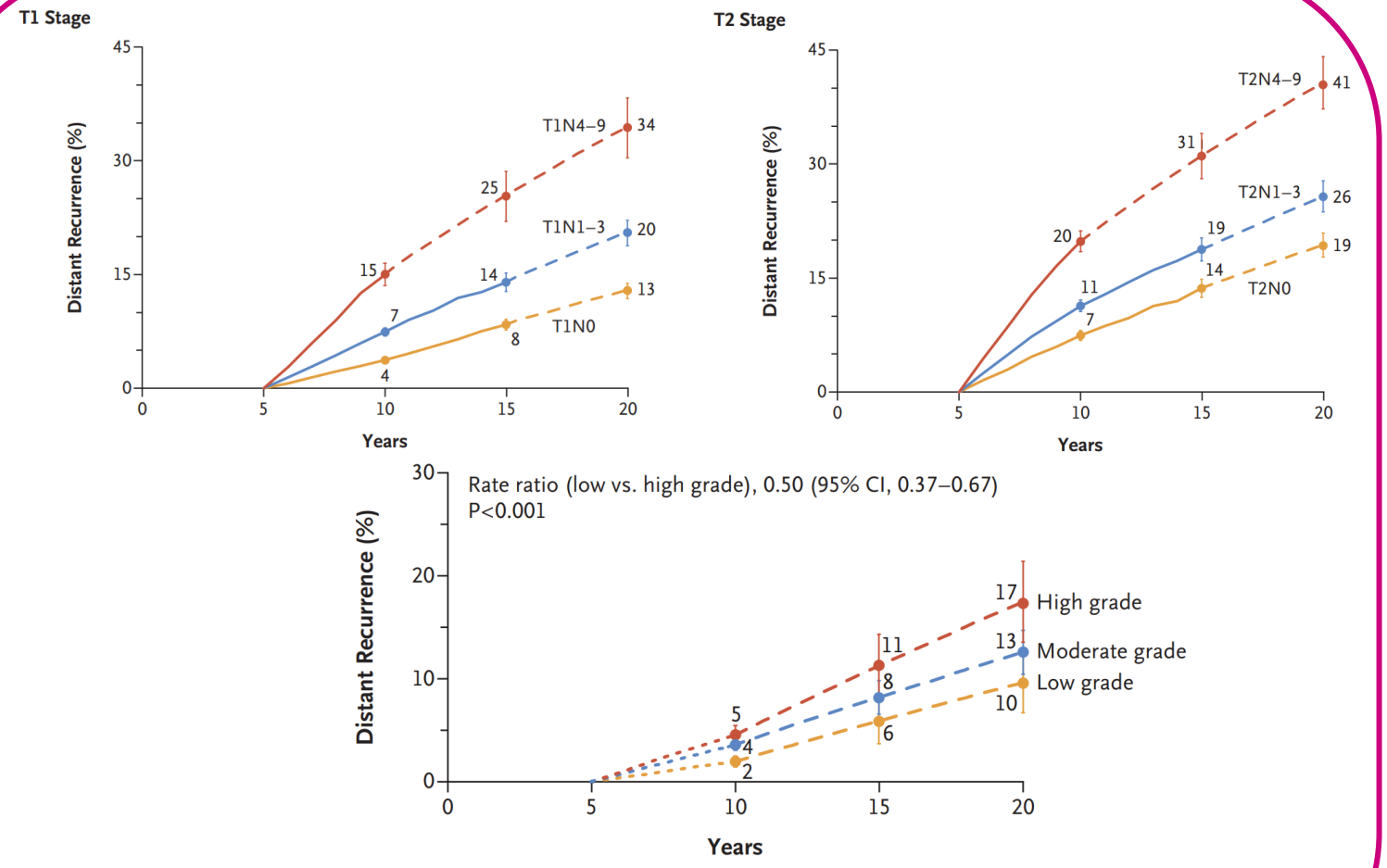


5-year probability of BC recurrence or death was 17.2%

1 in 6 women with node-positive HR+/HER2- early-stage BC receiving ET experience recurrence or death within 5-years of initiating treatment, suggesting a need for novel treatments for this population

Salvo EM, et Al. The Breast 57 (2021) 5-17

Long term Risk of Recurrence in ER+ EBC

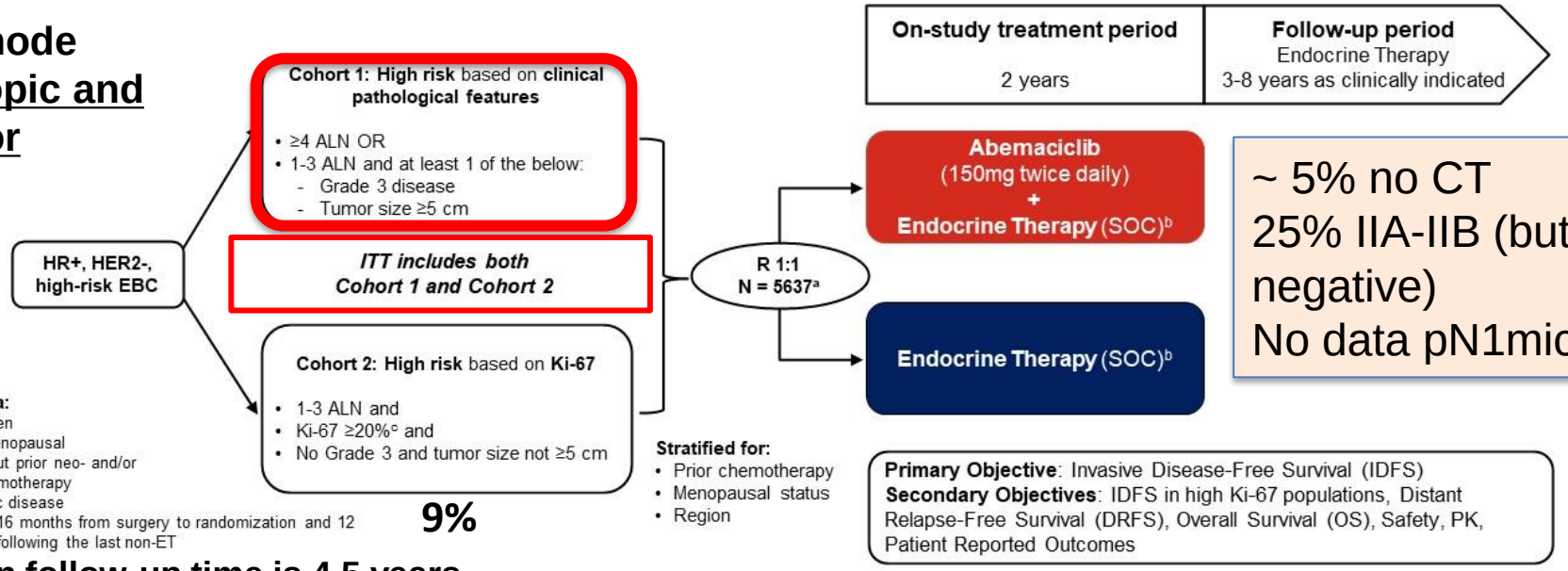


In a meta-analysis involving ~ 63.000 pts with BC who were disease-free after 5 years of ET, the risk of recurrence ranged from 10 to ~40% between years 5 and 20, depending on TN status and tumor grade ǂ

Pan H et al. N Engl J Med 2017 ;377:1836-1846

MonarchE Trial

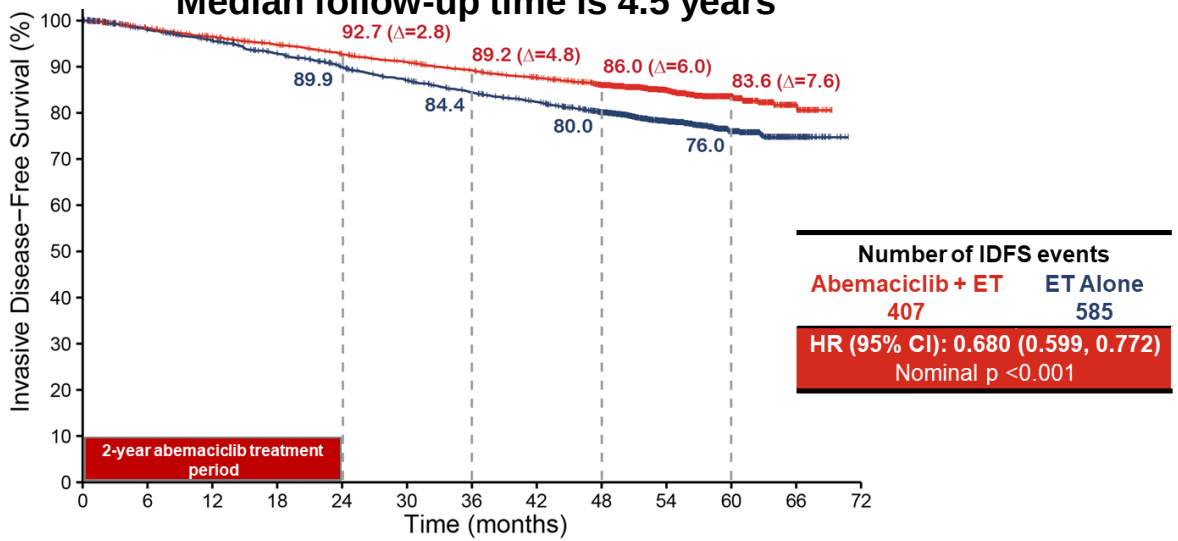
Patients must be node positive (<u>microscopic and macroscopic tumor involvements are allowed</u>).



~ 5% no CT
25% IIA-IIB (but not Node negative)
No data pN1mic

IDFS

Median follow-up time is 4.5 years



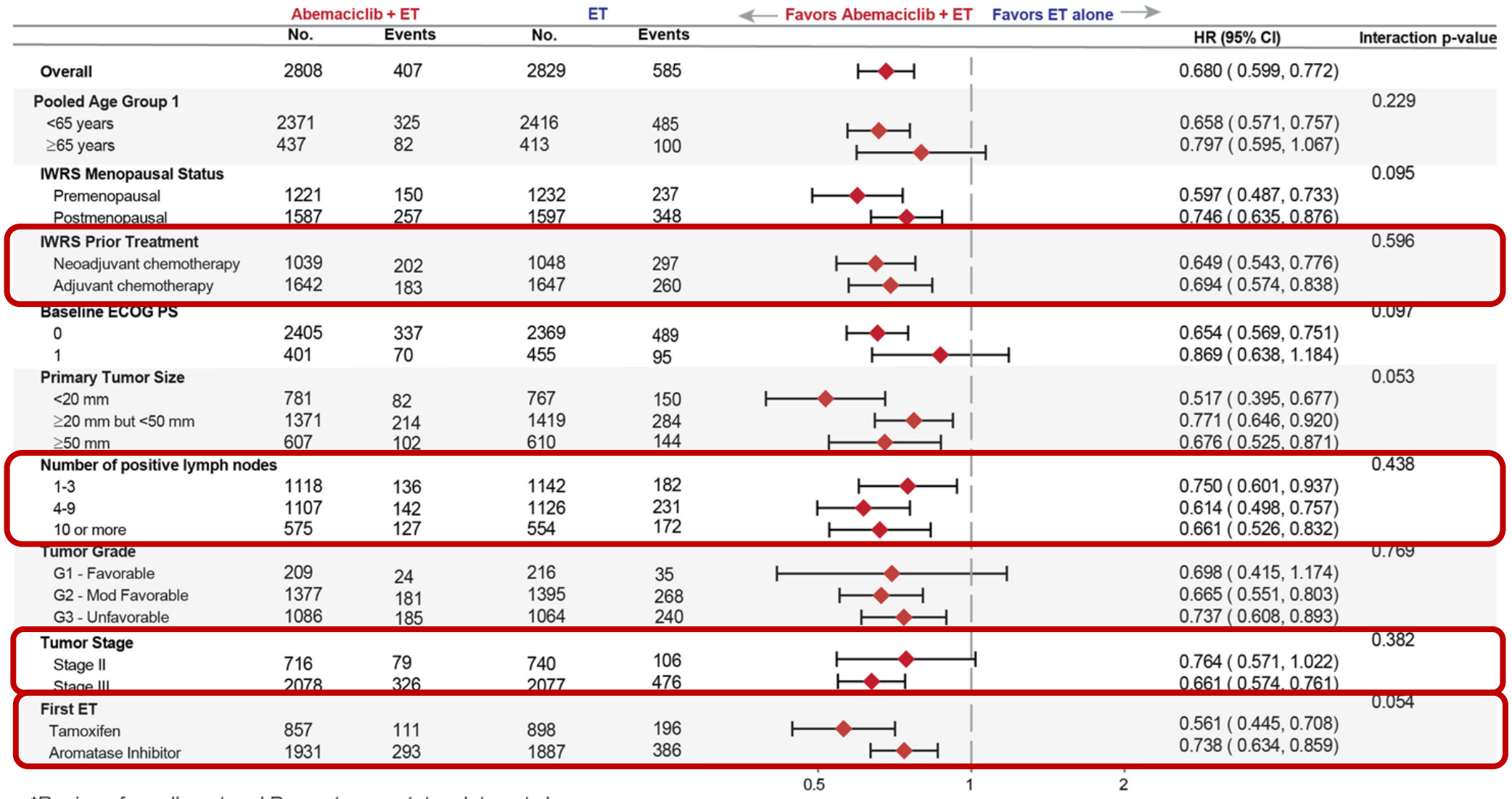
Number of IDFS events	
Abemaciclib + ET	ET Alone
407	585

HR (95% CI): 0.680 (0.599, 0.772)
Nominal p <0.001

- **The benefit of ABEMA is sustained beyond the completion of treatment with an absolute increase at 5 yrs**
- **No OS benefit, follow up is ongoing**

Harbeck N et al, ESMO 2023; Rastogi P. et al, JCO 2024

Consistent IDFS Benefit of ABEMA



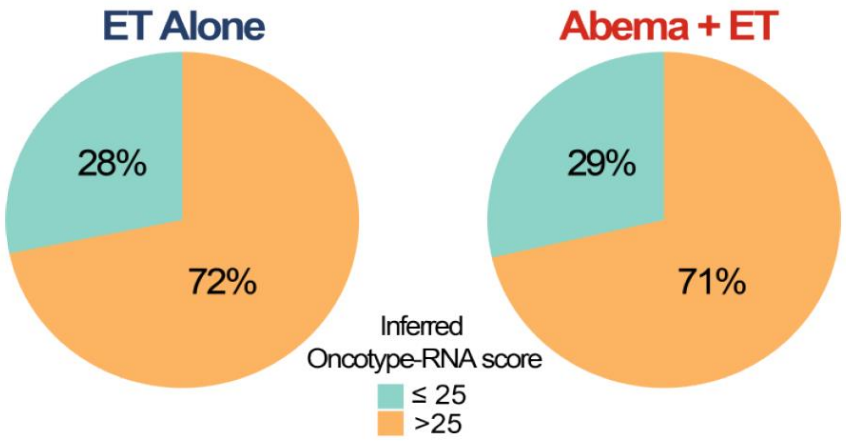
*Region of enrollment and Progesterone status data not shown

95% prior chemo; 60% had ≥ 4 LN+ at surgery

Harbeck N et al, ESMO 2023

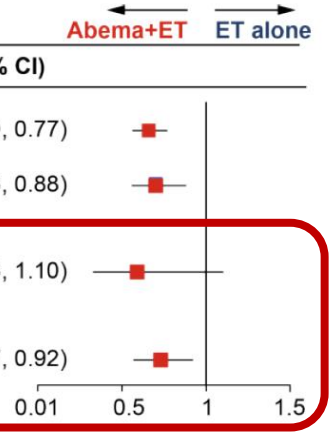
Similar results were seen with the inferred Oncotype

Higher proportion of high RS samples



No ***significant interaction*** between low (RS<25) and high (RS>25) Oncotype scores and benefit to abemaciclib

	Abemaciclib + ET		ET Alone		
	Events/n (%)	4yr IDFS Rate (95% CI)	Events/n (%)	4yr IDFS Rate (95% CI)	HR (95% CI)
ITT	407/2808 (14%)	86.0 (84.7–87.3)	585/2829 (21%)	80.0 (78.5–81.6)	0.68 (0.60, 0.77)
Biomarker Subset	138/605 (23%)	77.4 (74.1–80.9)	182/585 (31%)	69.8 (66.1–73.7)	0.70 (0.56, 0.88)
Inferred Oncotype-RNA score <=25	18/173 (10%)	90.2 (85.8–94.9)	28/165 (17%)	84.2 (78.7–90.1)	0.59 (0.33, 1.10)
Inferred Oncotype-RNA score>25	120/432 (28%)	72.3 (68.1–76.8)	154/420 (37%)	64.1 (59.6–69)	0.73 (0.57, 0.92)



Interaction *p-value* (inferred high and low Oncotype scores) = 0.532

Sotiriou C, SABCS 2023

ABEMACICLIB – Approval

On October 2021, the **FDA** approved Abemaciclib with ET (tamoxifen or an aromatase inhibitor) for adjuvant treatment of adult patients with HR-positive, HER2-negative, node-positive, EBC at high risk of recurrence and a Ki-67 score ≥20%, as determined by an FDA approved test (*A prespecified, controlled analysis of IDFS in patients with Ki-67 ≥ 20% in cohort 1 was statistically significant at the final IDFS analysis (July 2020; HR [95% CI], 0.643 [0.475 to 0.872]; P = .0042*).
On March 2023, **FDA removed the Ki-67 testing requirement** (*in cohort 2, more deaths were observed with Abemaciclib plus standard ET compared to standard ET alone (10/253 vs. 5/264*). Therefore, the indication was restricted to cohort 1.

On February 2022, **EMA** approved Abemaciclib in combination with ET for the adjuvant treatment of adult patients with HR-positive, HER2-negative, node-positive EBC at high risk of recurrence.

Giugno 2023: Approvazione **AIFA** con le stesse indicazioni EMA. Specifiche EMA/AIFA:
L'alto rischio di recidiva è stato definito da caratteristiche cliniche e patologiche:
≥4 pALN (linfonodi ascellari positivi) o 1-3 pALN, e almeno uno dei seguenti criteri: dimensione del tumore ≥ 5 cm o grado istologico 3

NATALEE Trial

- Adult patients with HR+/HER2− EBC
- Prior ET allowed ≤12 mo prior to randomization
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk:
      - Ki-67 ≥20%
      - Oncotype DX Breast Recurrence Score ≥26 *or*
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N = 5101[b]

R 1:1[c]

RIB
400 mg/day
3 weeks on/1 week off
for 3 years

+

NSAI
Letrozole or anastrozole[d]
for ≥5 years
+ goserelin in men and premenopausal women

NSAI
Letrozole or anastrozole[d]
for ≥5 years
+ goserelin in men and premenopausal women

Primary End Point
- iDFS using STEEP criteria

Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- Safety and tolerability
- PROs
- PK

Exploratory End Points
- Locoregional recurrence–free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

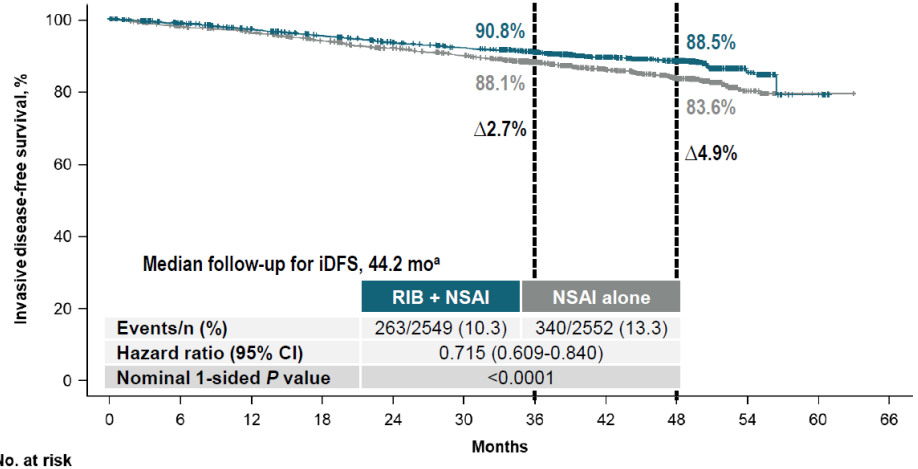
Enrollment of patients with stage II disease was capped at 40%.

Data cutoff: 29 April 2024

- Second interim efficacy analysis (miDFS FU, 27.7 mo): **HR, 0.748** (95% CI, 0.618-0.906); 1-sided *P*=0.0014
- Protocol-specified final iDFS analysis (miDFS FU, 33.3 mo): **HR, 0.749** (95% CI, 0.628-0.892); nominal 1-sided *P*=0.0006 [FDA requested]
- An exploratory 4-year landmark analysis of NATALEE, with an additional 10.9 months of FU
  Completed 3 years of RIB treatment: 63%

40% IIA-IIB | Node neg 28% | No CT 12%

Significant iDFS benefit with RIB + NSAI after the planned 3-year treatment

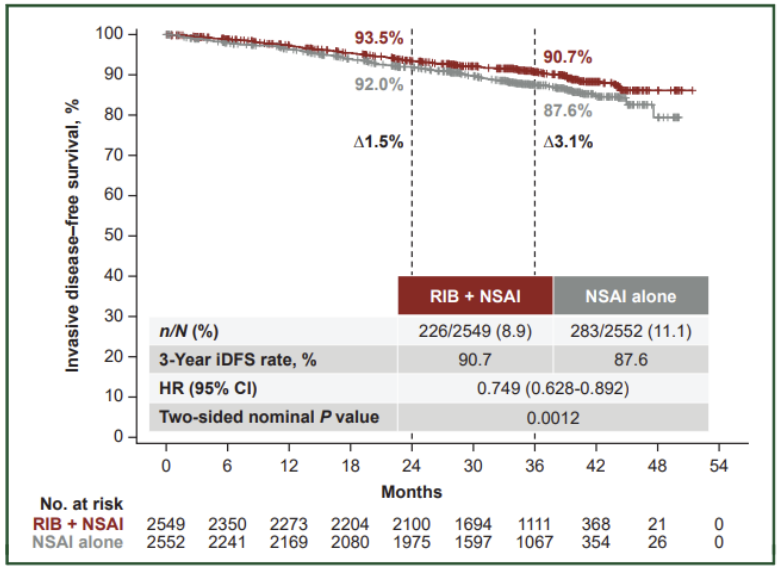


Median follow-up for iDFS, 44.2 mo[a]

	RIB + NSAI	NSAI alone
Events/n (%)	263/2549 (10.3)	340/2552 (13.3)
Hazard ratio (95% CI)	0.715 (0.609-0.840)	
Nominal 1-sided *P* value	<0.0001	

No. at risk												
RIB + NSAI	2549	2351	2275	2207	2133	2078	1843	1480	914	155	8	0
NSAI alone	2552	2240	2168	2082	2006	1935	1687	1366	848	150	6	0

iDFS, invasive disease–free survival; ITT, intent to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] An additional 10.9 months of follow-up compared with the protocol-specified final iDFS analysis.



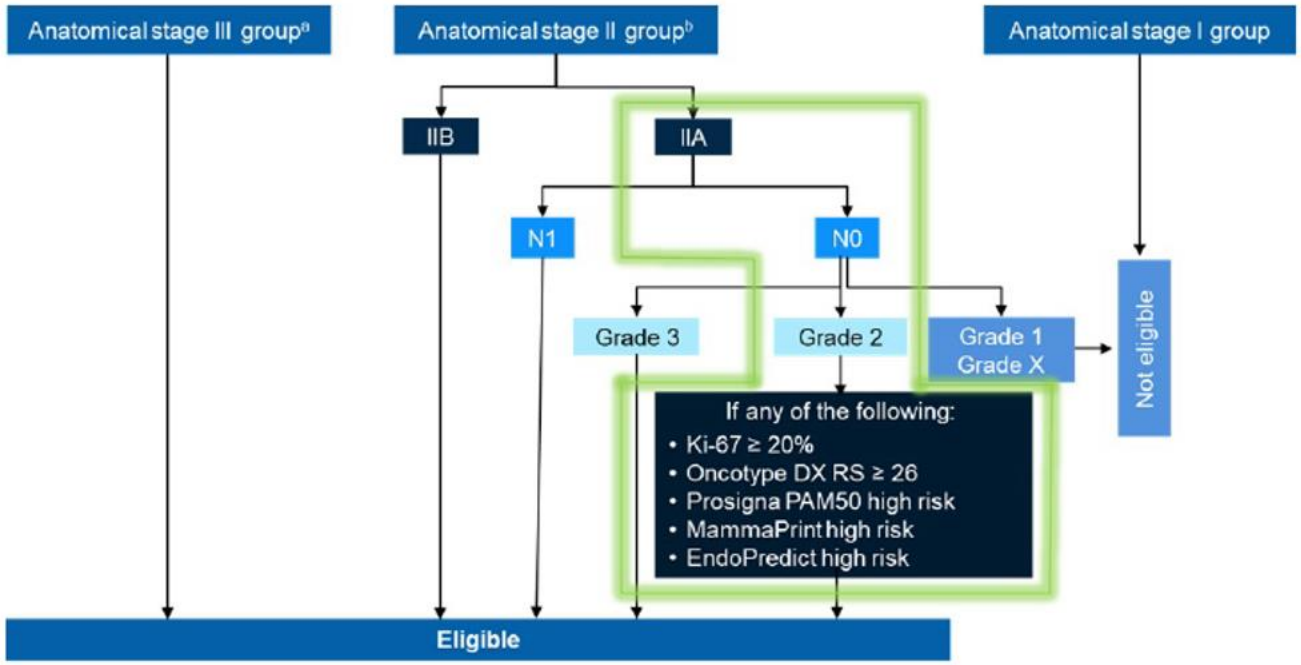
	RIB + NSAI	NSAI alone
n/N (%)	226/2549 (8.9)	283/2552 (11.1)
3-Year iDFS rate, %	90.7	87.6
HR (95% CI)	0.749 (0.628-0.892)	
Two-sided nominal *P* value	0.0012	

No. at risk										
RIB + NSAI	2549	2350	2273	2204	2100	1694	1111	368	21	0
NSAI alone	2552	2241	2169	2080	1975	1597	1067	354	26	0

- **No OS benefit, follow up is ongoing**

Desmedt C & et al, ESMO 2024; Hortobagyi GN et al, AO 2025

NATALEE: eligible patients



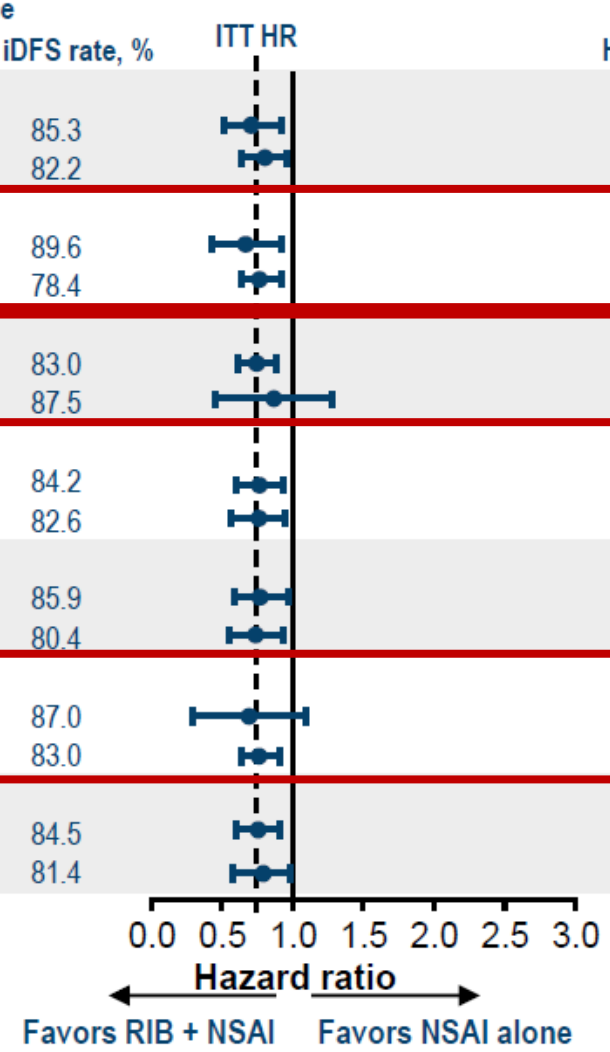
AJCC anatomical staging[1]	TN (M0)	NATALEE[2,3]
Stage IA	T1N0	✗
Stage IB	T0N1mi	✗
	T1N1mi	✗
Stage IIA	T0N1	✓
	T1N1	✓
	T2N0	G3, or G2 with Ki-67 ≥ 20% or high genomic risk[c]
Stage IIB	T2N1	✓
	T3N0	✓
Stage IIIA	T0N2	✓
	T1N2	✓
	T2N2	✓
	T3N1	✓
	T3N2	✓
Stage IIIB	T4N0	✓
	T4N1	✓
	T4N2	✓
Stage IIIC	Any TN3	✓

AJCC, American Joint Committee on Cancer; G, grade; M, metastasis; N0, no nodal involvement;; N1mi, nodal micrometastases; N1, 1-3 axillary lymph nodes; N2, 4-9 axillary lymph nodes; N3, ≥ 10 axillary lymph nodes or collarbone lymph nodes; RS, Recurrence Score; T, tumor; T0, no evidence of primary tumor; T1, tumor is 2cm or less; T2, Tumor is more than 2cm bu less than 5cm; T3, tumor is more than 5cm; T4, tumor of any size growing into the chest wall or skin, includes inflammatory breast cancer.
[a] Including stage IIIA (N1/N2), IIIB (N0/N1/N2), or IIIC (N3). [b] Capped at 40% (~ 2000 patients). Simplified inclusion criteria are used in the illustration. [c] High risk as determined by Oncotype DX, Prosigna PAM50, MammaPrint, or EndoPredict EPclin Risk Score.
References: 1. Amin MB, Edge SB, Greene FL, et al, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017:587-636. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(suppl 15) [abstract TPS597]. 3. Data on file. NATALEE CLEE011O12301C (TRIO033). Clinical study protocol. V4.0. Novartis Pharmaceuticals Corp; August 27, 2020.

Slamon D, ASCO 2023

Consistent IDFS Benefit of RIBO

Subgroup	RIB + NSAI Events/n	RIB + NSAI 4-y iDFS rate, %	NSAI alone Events/n	NSAI alone 4-y iDFS rate, %	Hazard ratio	95% CI
Menopausal status						
Men and premenopausal women	99/1125	90.7	137/1132	85.3	0.677	0.523-0.877
Postmenopausal women	164/1424	86.8	203/1420	82.2	0.760	0.619-0.933
AJCC stage						
Stage II ~ 40%	62/1012	93.9	96/1034	89.6	0.644	0.468-0.887
Stage III	200/1527	84.3	244/1512	78.4	0.737	0.611-0.888
Prior CT						
Yes	238/2249	88.2	309/2245	83.0	0.715	0.604-0.846
No	25/300	90.7	31/307	87.5	0.827	0.488-1.401
Region						
North America/Western Europe/Oceania	151/1563	88.9	195/1565	84.2	0.726	0.587-0.898
Rest of world	112/986	88.0	145/987	82.6	0.722	0.564-0.925
Ki-67 status[a]						
Ki-67 ≤20%	106/1199	89.9	142/1236	85.9	0.737	0.573-0.948
Ki-67 >20%	113/920	86.3	149/937	80.4	0.709	0.555-0.905
Nodal status[b,c]						
N0 ~ 20%	23/285	92.1	38/328	87.0	0.666	0.397-1.118
N1-N3	240/2261	88.0	301/2219	83.0	0.731	0.617-0.866
Prior ET						
Yes	176/1830	89.2	227/1807	84.5	0.718	0.589-0.874
No	87/719	86.7	113/745	81.4	0.752	0.568-0.994



AJCC, American Joint Committee on Cancer; CT, chemotherapy; ET, endocrine therapy; iDFS, invasive disease–free survival; ITT, intent to treat; N, node; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] From archival tumor tissue. [b] Nodal status classification according to AJCC staging. [c] Nodal status is from the worst stage derived per surgical specimen or at diagnosis.

88% prior chemo; 43% had ≥ 4 LN+ at surgery

Fasching PA, ESMO 2024

ASCO Guideline Update: Adjuvant CDK 4/6 Inhibitors

Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer—Cyclin-Dependent Kinase 4 and 6 Inhibitors: ASCO Guideline Rapid Recommendation Update

Rachel A. Freedman, MD, MPH[1]; Jennifer L. Caswell-Jin, MD[2]; Michael Hassett, MD, MPH[1]; Mark R. Somerfield, PhD[3]; and Sharon H. Giordano, MD, MPH[4]; for the Optimal Adjuvant Chemotherapy and Targeted Therapy for Early Breast Cancer Guideline Expert Panel

DOI https://doi.org/10.1200/JCO.24.00886

ASCO Journal of Clinical Oncology®

Published Online April 24, 2024

Recommendation 2

The Panel recommends, based on the phase III NATALEE trial, that adjuvant Ribociclib (400 mg once daily, 3 weeks on followed by 1 week off) for 3 years plus ET may be offered to patients with anatomic stage II or III breast cancer who would have met criteria for study entry and have a high risk of recurrence (Evidence quality: High; Strength of recommendation: Conditional).

Qualifying Statements for Recommendations 1 and 2 on the Use of Adjuvant Abemaciclib and Ribociclib

The Panel believes that adjuvant CDK4/6 inhibitor therapy may not provide meaningful clinical benefit to all patients who would have been eligible for the available trials, especially the lower-risk patients who were included in the NATALEE trial. For example, for most patients with node negative disease, the risks of Ribociclib may outweigh the benefits, with the exception of some patients with the highest risk, node-negative disease. However, the Panel acknowledges that there are insufficient data to specify which subgroups of patients do or do not warrant therapy. The Panel thus recommends considering the benefits, risks, costs, and preferences for each individual patient when deciding whether to recommend therapy.

Freedman RA et al. J Clin Oncol. 2024; 20;42(18) 2233-35

RIBOCICLIB – Approval

FDA Regulatory Actions

September 17, 2024: regular approval – ribociclib USPI

1.1 Early Breast Cancer

KISQALI is indicated in combination with an aromatase inhibitor for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative stage II and III early breast cancer at high risk of recurrence.

14.1 Early Breast Cancer

NATALEE: KISQALI in Combination with a Non-steroidal Aromatase Inhibitor (NSAI) with or without Goserelin

Adults with HR-positive, HER2-negative Stage II and III Early Breast Cancer at High Risk of Recurrence

Early breast cancer

17 October 2024
EMA/CHMP/512303/2024
Committee for Medicinal Products for Human Use (CHMP) Corr.1[1]

Kisqali in combination with an aromatase inhibitor is indicated for the adjuvant treatment of patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence.

In pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with a LHRH agonist.

Documento reso disponibile da AIFA il 13/12/2024

Cancro della mammella in fase iniziale

Kisqali in associazione a un inibitore dell'aromatasi è indicato per il trattamento adiuvante di pazienti con cancro della mammella in fase iniziale positivo per il recettore ormonale (HR) e negativo per il recettore di tipo 2 per il fattore di crescita epidermico umano (HER2), ad alto rischio di recidiva (vedere paragrafo 5.1 per i criteri di selezione).

Managed Access Program (MAP)* Cohort Treatment Plan CLEE011A2006M to provide access to ribociclib for patients diagnosed with early-stage HR+HER2- (stages II and III) breast cancer requiring adjuvant treatment with an ET based regimen

MAP medical inclusion criteria for cohort patients

- Anatomic Stage Group III, or
- Anatomic Stage Group IIB, or
- Anatomic Stage Group IIA that is either:
  - N1, or
  - N0, with:
    - Grade 3, or
    - Grade 2, with any of the following criteria:
      - Ki67 ≥ 20%, or
      - Oncotype DX Breast Recurrence Score ≥ 26, or
      - Prosigna/PAM50 categorized as high risk, or
      - MammaPrint categorized as high risk, or
      - EndoPredict EPclin Risk Score categorized as high risk.

The patient to be treated has no alternative authorized option.
The patient is not eligible or able to enroll in a clinical trial.

Comparison of NATALEE & MonarchE Population

N0 not allowed in monarchE

AJCC Anatomical Staging[1]	TN (M0)	NATALEE[2,3]	monarchE[4]
Stage IIA	T0N1	✓	Only if grade 3 or Ki-67 ≥20%
	T1N1	✓	Only if grade 3 or Ki-67 ≥20%
	T2N0	Only if G3 or G2 with Ki-67 ≥20% or high genomic risk[a]	✗
Stage IIB	T2N1	✓	Only if grade 3 or Ki-67 ≥20%
	T3N0	✓	✗
Stage IIIA	T0N2	✓	✓
	T1N2	✓	✓
	T2N2	✓	✓
	T3N1	✓	✓
	T3N2	✓	✓
Stage IIIB	T4N0	✓	✗
	T4N1	✓	Only if tumor size ≥5 cm or grade 3 or Ki-67 ≥20%
	T4N2	✓	✓
Stage IIIC	Any TN3	✓	✓

In monarchE, relatively few patients with stage II were allowed:
- N1 allowed only if grade 3 or Ki-67 ≥20%

In monarchE, within stage III,
- N0 not allowed (in IIIB)
- N1 (whether in IIIA or IIIB) allowed only if tumor size ≥5 cm, grade 3, or Ki-67 ≥20%

Slamon D at al, Ther Adv Med Oncol 2023

Prognosis of patients with HR+/HER2-negative eBC according to monarchE and NATALEE trials risk categories: patient-level analysis of MIG and GIM randomized trials

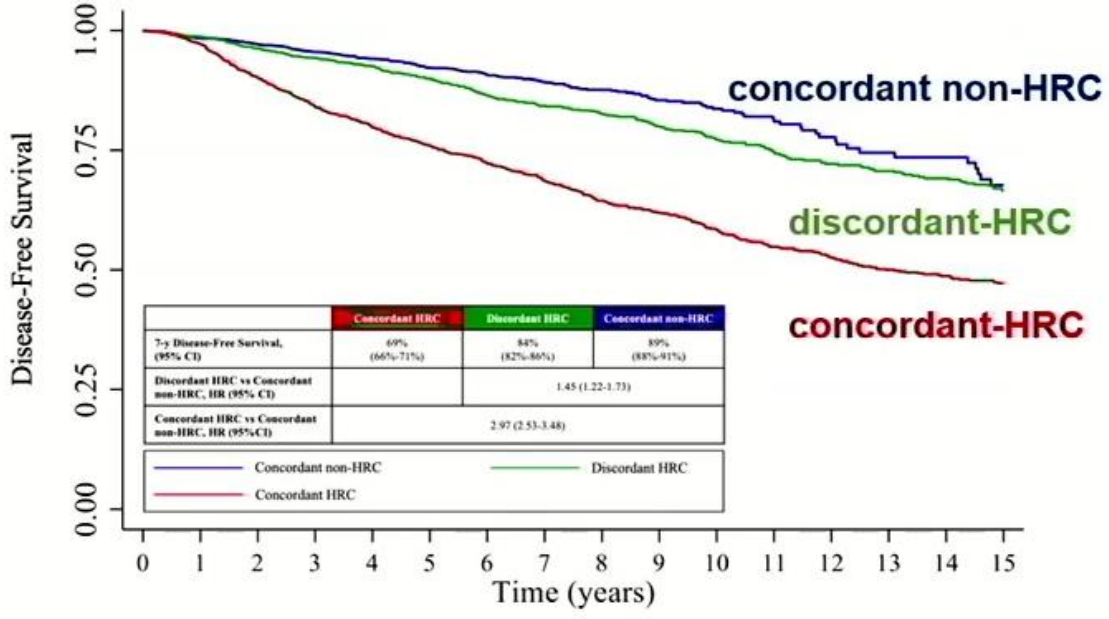
- Individual patient-level data from 3 adjuvant phase III randomized trials conducted by the MIG and GIM study groups (MIG1, GIM2, and GIM3 trials) = 7002 patients

- Pts were categorized in 3 cohorts according to inclusion criteria of the monarchE and NATALEE trials:

Cohorts	MonarchE	NATALEE
Concordant non-High Risk (pts at non-high-risk for both trials)	🟢	🟢
Concordant High-Risk (pts at high-risk for both trials)	🟢	🟢
Discordant High Risk (pts at high-risk for one trial but not for the other)	🔴	🟢

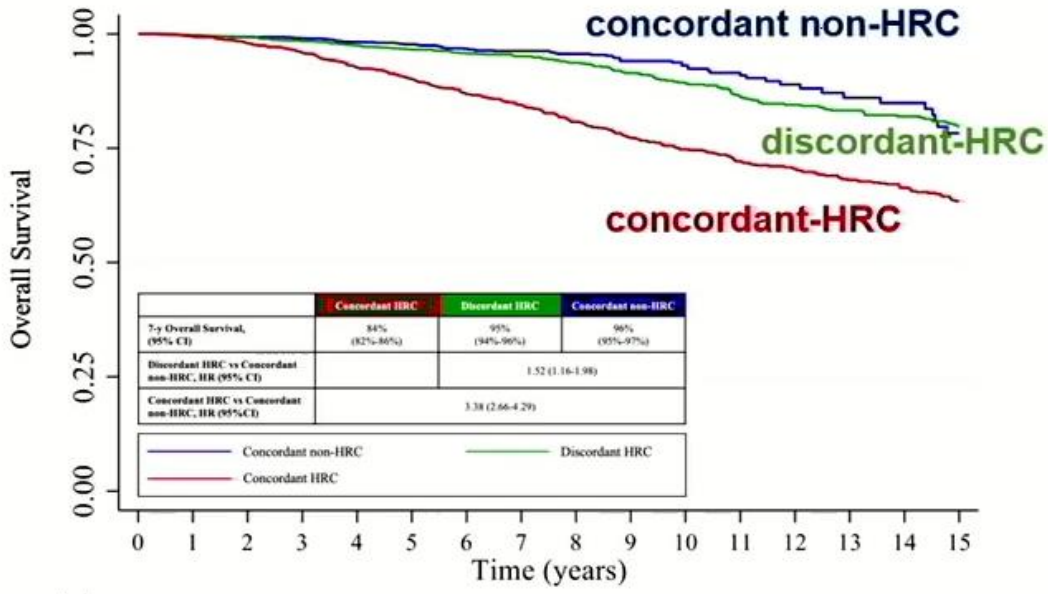
Arecco L, et al. *JNCI* 2025

Results: Disease-free Survival and Overall Survival



Number at risk

Concordant non-high-risk	2106	2008	1936	1828	1622	1282	937	692	484	360	250	153	102	76	73	54
Discordant risk	1346	1306	1252	1180	1094	961	775	677	559	471	372	323	296	282	271	235
Concordant high-risk	1343	1278	1156	1050	953	830	717	619	512	436	366	317	293	277	265	235



Number at risk

Concordant non-high-risk	2106	2035	1979	1886	1682	1349	991	740	519	386	270	165	108	80	74	54
Discordant risk	1346	1320	1288	1225	1137	1018	845	748	624	532	423	368	343	327	314	278
Concordant high-risk	1343	1305	1249	1177	1088	966	838	742	621	523	449	402	378	362	346	303

7-y DFS:
89% in **concordant non-HRC**
84% in **discordant HRC**
69% in concordant HRC

7-y OS:
96% in **concordant non-HRC**
95% in **discordant HRC**
84% in concordant HRC

Arecco L, et al. *JNCI* 2025

Adjuvant CDK4/6 Inhibitors for Early Breast Cancer:

Abemaciclib

Schedule
150 mg twice daily

Duration
2 years

Most frequent AEs	Any G	G ≥3
Diarrhea	75%	7%
Fatigue	38%	3%
Abdominal pain	34%	1%
Neutropenia	26%	11%
Leucopenia	26%	11%
VTEs	1.2%	1.1%

Discontinuation rate due to AEs = **18.5%**

Ribociclib

Schedule
400 mg/day 3 weeks on/1 week off

Duration
3 years

Most frequent AEs	Any G	G ≥3
Neutropenia	63%	44%
Arthralgia	39%	1%
Liver-related AEs	27%	9%
QT prolongation	5%	1%
ILD	1.6%	0%
VTEs	1.1%	0.6%

Discontinuation rate due to AEs = **20.0%**

Harbeck N et al, ESMO 2023; Fasching P et al, ESMO 2024

ADJUVANT CDK 4/6i in ER+ eBC

Discontinuations due to Adverse Events – compliance

MONARCH-E

- **18.5% discontinued Abemaciclib due to AE**
- Most frequent all-grade AEs leading to discontinuation:
  - Diarrhea: 5.3%
  - Fatigue: 2.0%
- Most of ABEMA AE discontinuations occurred early in treatment
  - Majority in 1st 3 months

Rugo HS, et al. Ann. Oncol. 2022; 33(6):616-27

NATALEE

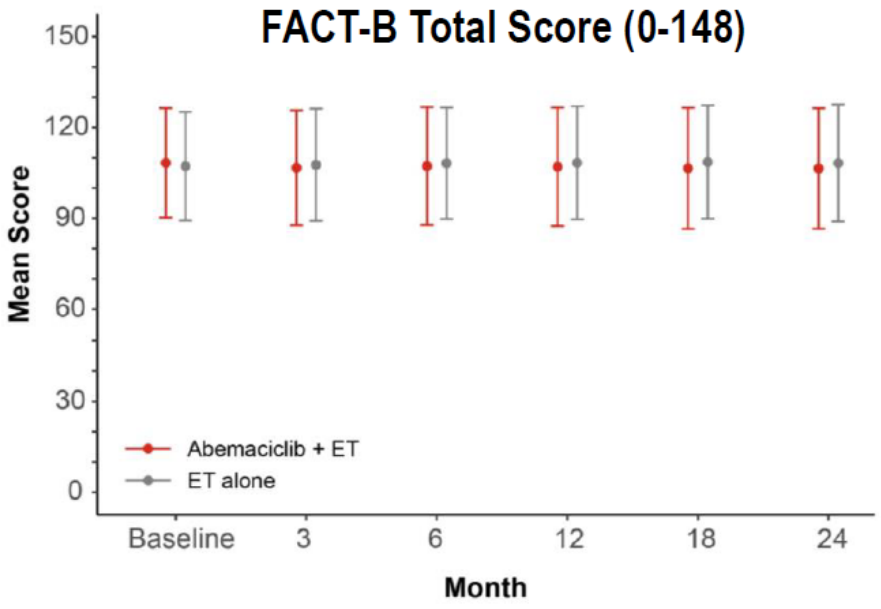
- **19% discontinued ribociclib due to AE**
- Most frequent all-grade AEs leading to discontinuation:
  - Liver-related AEs: 8.9%
  - Arthralgia: 1.3%
- Most of RIB AE discontinuations occurred early in treatment:
  - Median time of these discontinuations was 4 months

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

ADJUVANT CDK4/6 INHIBITORS IN ER+ EBC

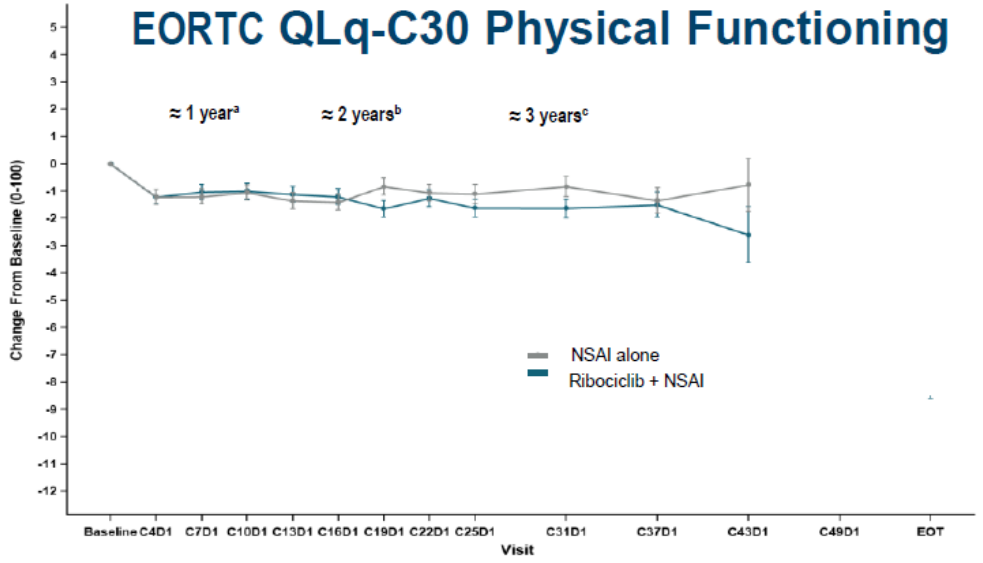
QOL scores maintained over time on treatment

MONARCH-E



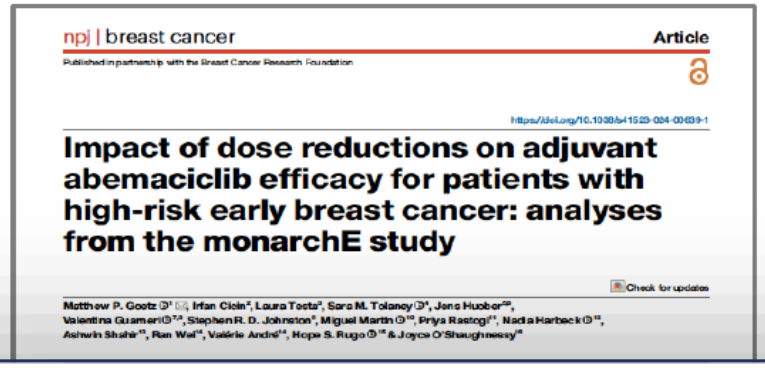
Harbeck N, et al. ESMO Breast 2023 Ann Oncol 8 (s4) 101219

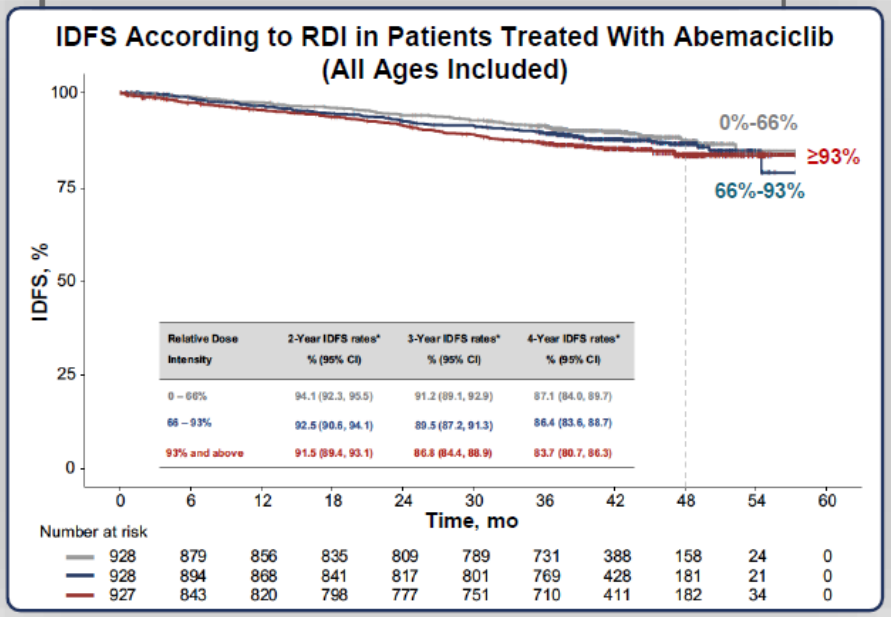
NATALEE



Fasching P, et al. ESMO Virtual Plenary 2023

MonarchE: Impact of Dose Reductions on Efficacy





BARCELONA 2024 ESMO congress

- Dose adjustments result in lower relative dose intensity (RDI)[a]
- To explore the impact of dose adjustments on abemaciclib efficacy:
  - Patients treated with abemaciclib were classified into 3 equal-sized subgroups according to their RDI
  - IDFS rates were estimated within each subgroup
- 4-year IDFS rates were generally consistent (87.1% vs 86.4% vs 83.7% from the lowest RDI group to the highest)
  - Similar findings were observed in patients treated with abemaciclib in Cohort 1

[a] RDI is defined as the average daily dose of abemaciclib received over the treatment duration, relative to the full dose (150mg BID)

Goetz MP et al. NPJ Breast Cancer 2024;10:34

ET non-Adherence and non-Persistence in BC Survivorship

Systematic review: 10 studies measuring the efects of endocrine treatment non-adherence (patients not taking treatment as prescribed) and non-persistence (patients stopping treatment prematurely) on survival

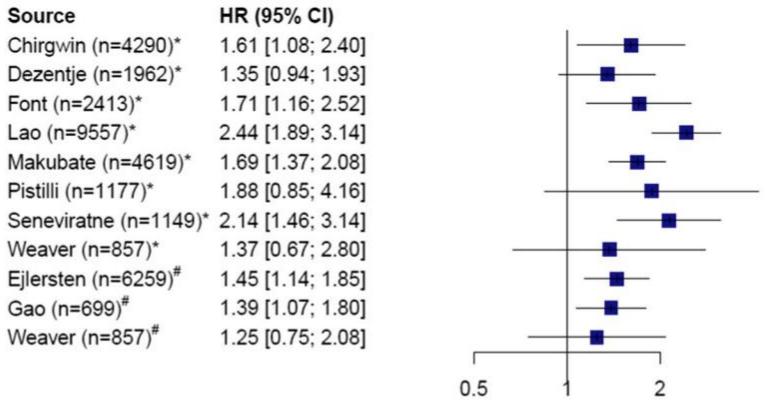


Fig. 2 Event-free survival Forest plot for event-free survival, reporting the hazard ratio (HR) for non-adherent (*) and non-persistent (#) patients with breast cancer. n = number of patients in the study

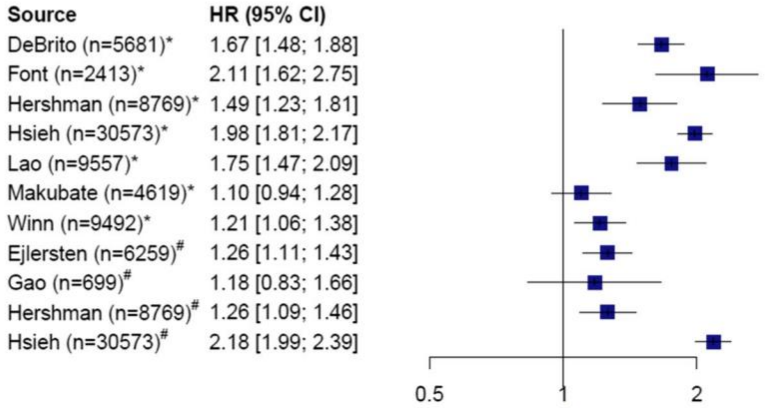
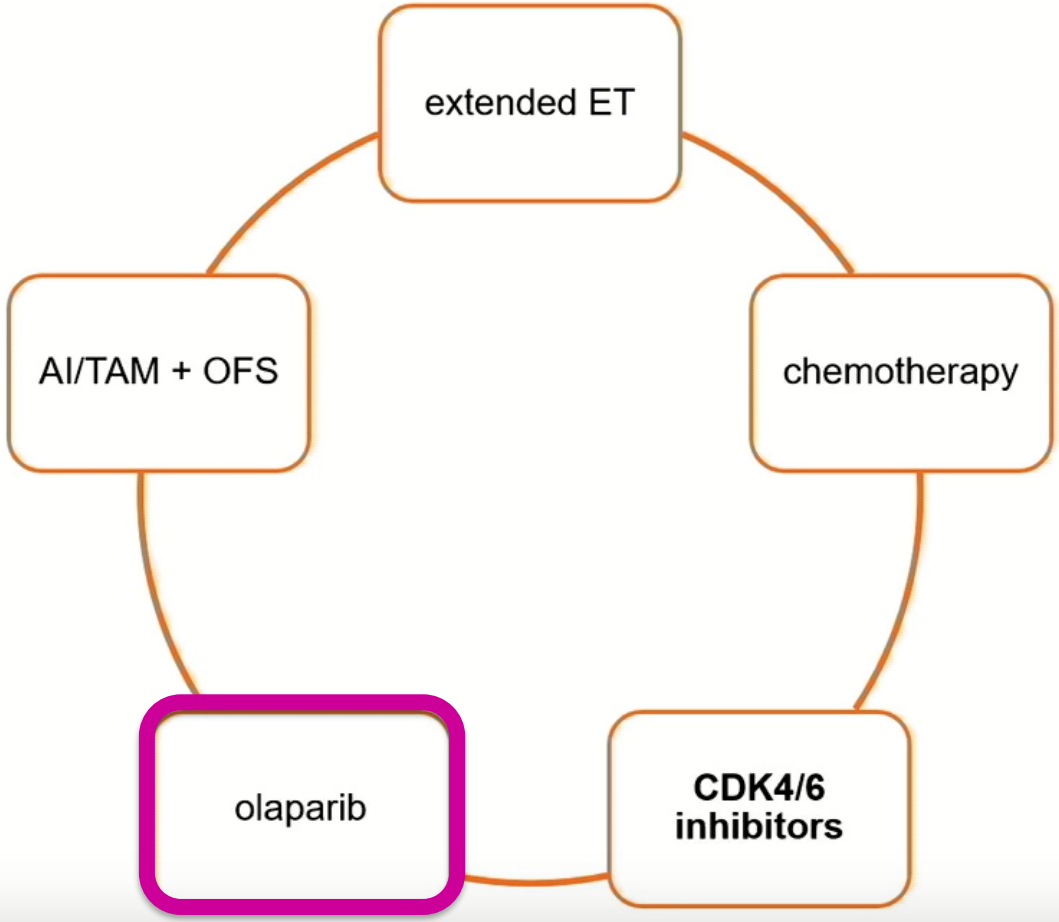


Fig. 3 Overall survival. Forest plot for overall survival, reporting the hazard ratio (HR) for non-adherent (*) and non-persistent (#) patients with breast cancer. n = number of patients in the study

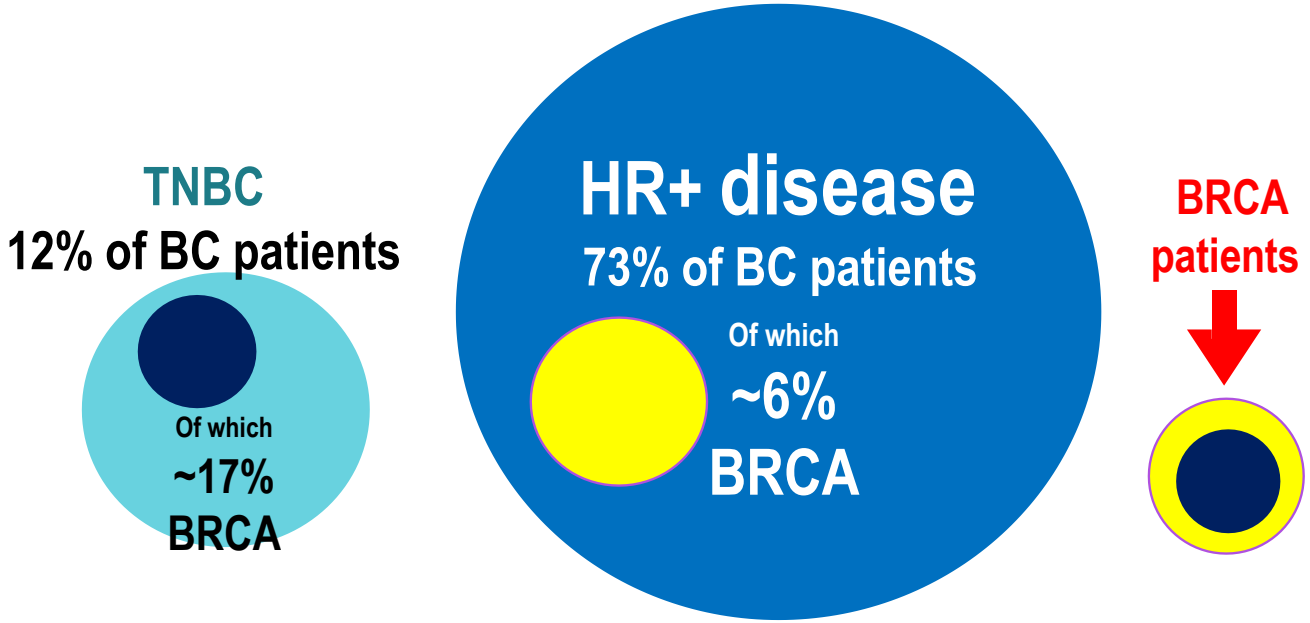
Eliassen *et al. BMC Cancer 2023*

Adjuvant Strategy for Luminal-HER2-negative EBC

can we do something more?



Prevalence of BRCA Mutation according to BC Immunophenotype



- A higher proportion of patients with TNBC have a BRCAm than those with HR+ disease.
- However, due to the relative prevalence, the majority of BRCA are found in patients with HR+ disease vs. TNBC

Winter et al. Ann Oncol. 2016 Aug; 27(8): 1532–1538

OlympiA Trial

- 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

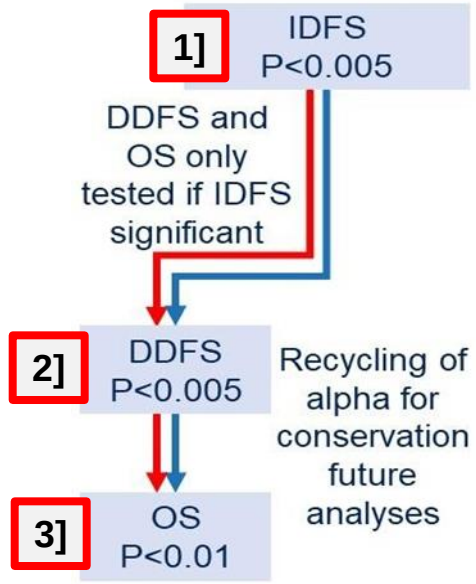
Placebo twice daily for 1 year

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



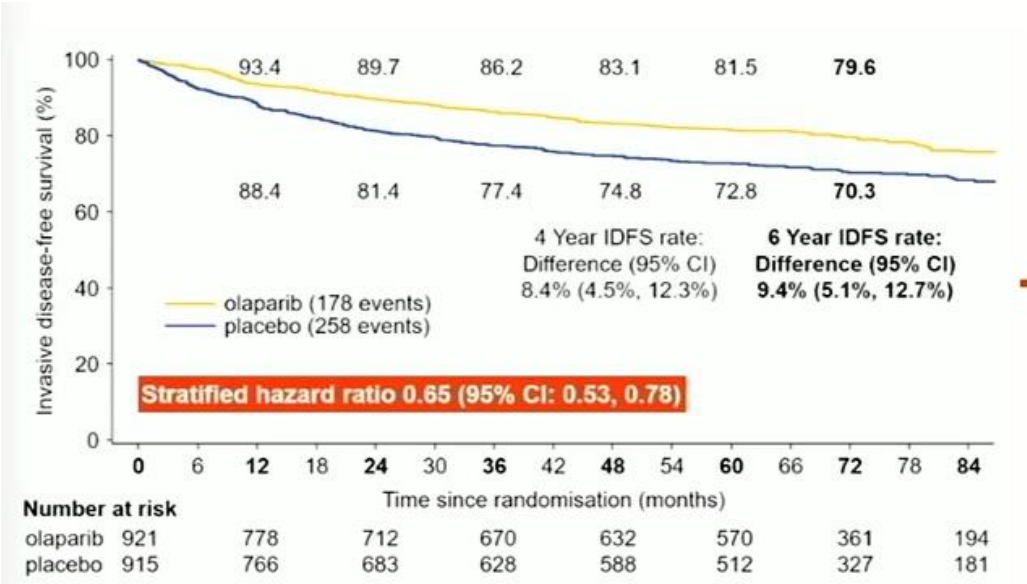
The original protocol that was activated in 2014 was developed for HER2-negative patients but included only patients with TNBC after regulatory review. When the safety rationale with respect to recurrence risk relative to combination therapy with Olaparib and ET was accepted by regulators, the protocol was amended in 2015 to include patients with high-risk HR-positive disease and to increase the sample size to the current number of 1800 patients. The first patient with HR-positive disease was enrolled 18 months after start of accrual.

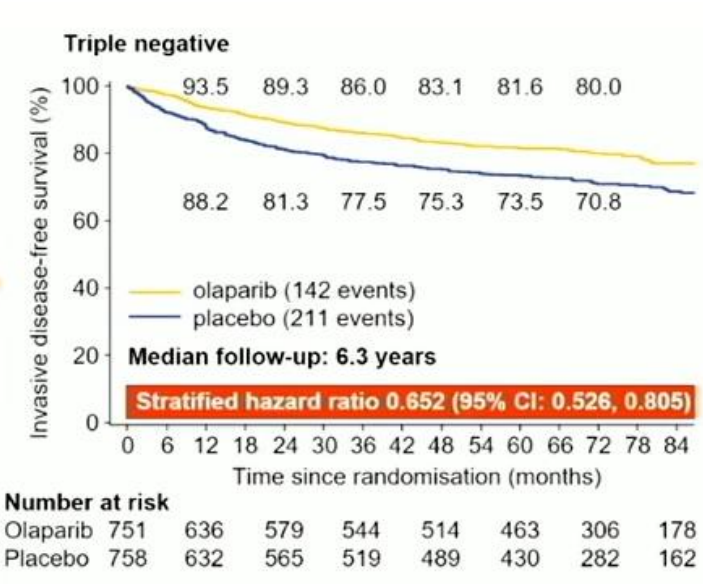
	Olaparib (N = 921)	Placebo (N = 915)
Hormone receptor status*		
Hormone receptor ≥ 1% / HER2-†	168 (**18.2%**)	157 (**17.2%**)
Triple Negative Breast Cancer‡	751 (**81.5%**)	758 (**82.8%**)
Menopausal status (female only)		
Premenopausal	572/919 (62.2%)	553/911 (60.7%)
Postmenopausal	347/919 (37.8%)	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%)

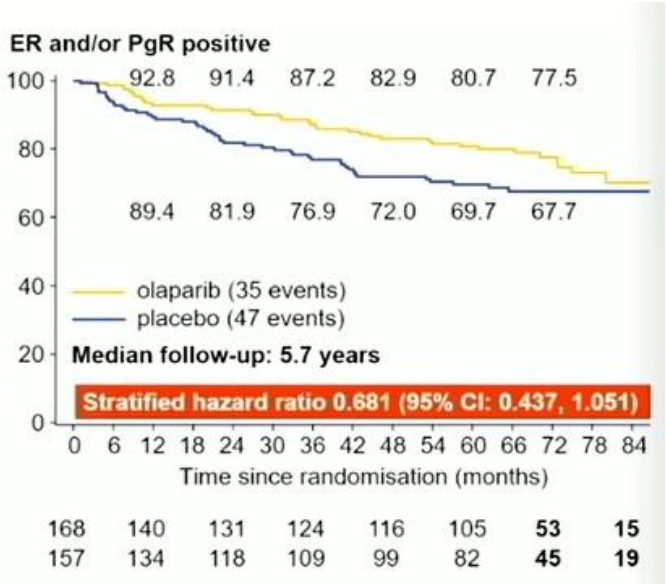
*Defined by local test results
†Following a protocol amended in 2015, the first patient with hormone receptor–positive disease was enrolled in December 2015
‡Two patients are excluded from the summary of the triple–negative breast cancer subset because they do not have confirmed HER2–negative status

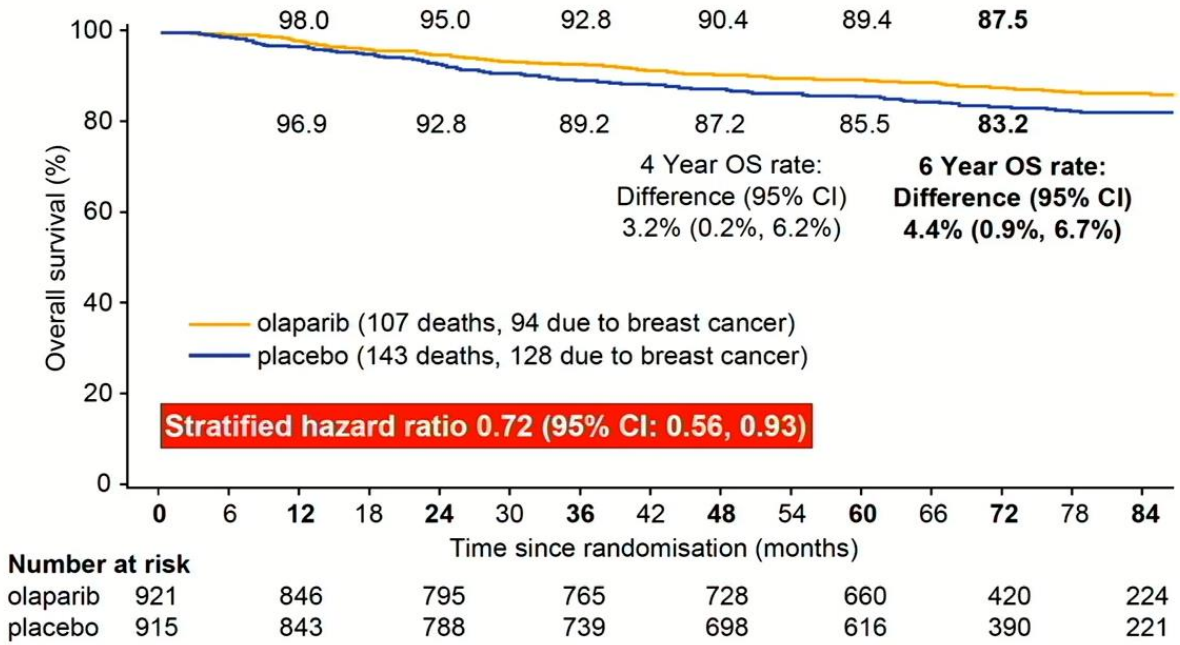
Tutt A. et al., ASCO 2021; NEJM 2021

OlympiA Trial: updated IDFS & OS results



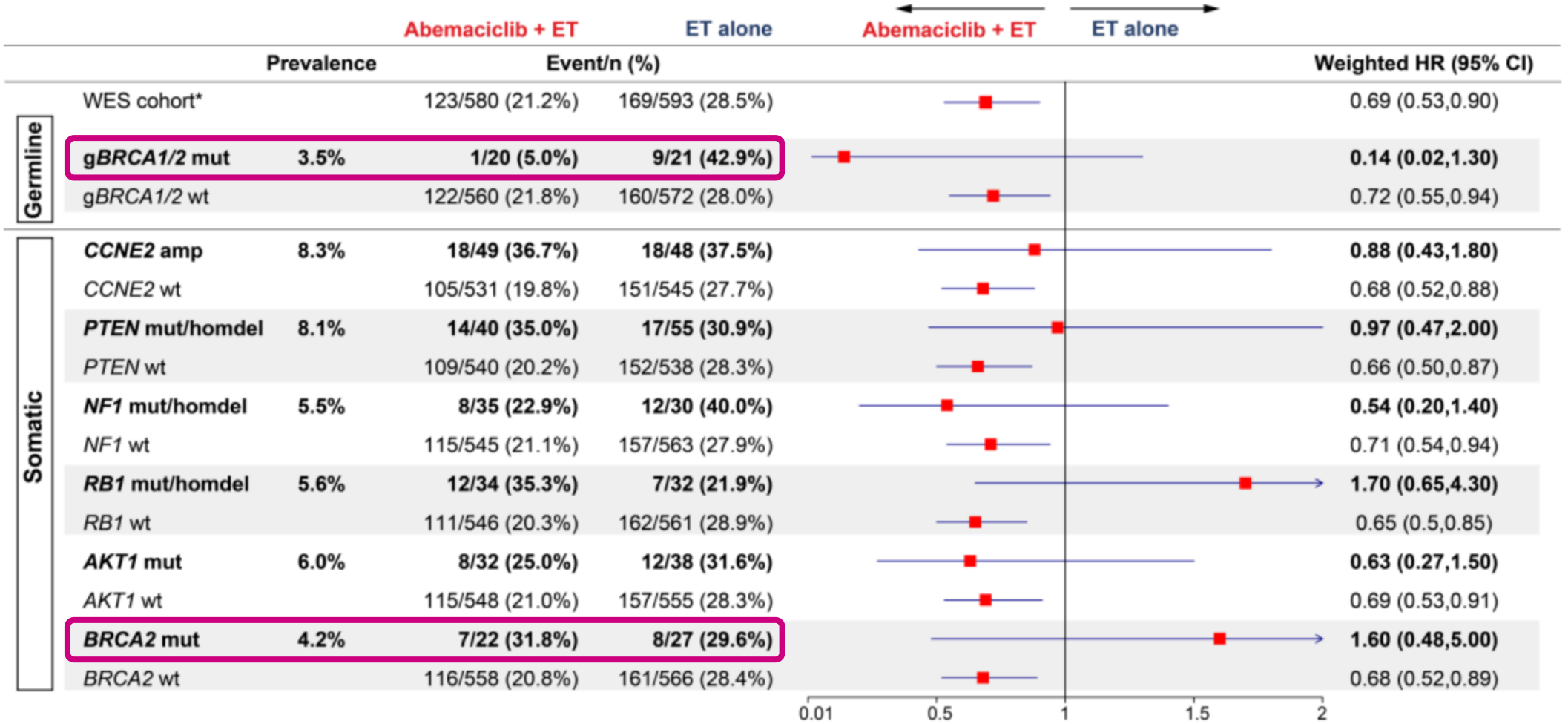






Garber JE, et al. SABCS 2024

Consistent IDFS Effect Observed Across Most Genomic Subgroups



*Due to the case-cohort design, effect size was estimated using weighted HRs of baseline factors (geographical region and prior chemotherapy). Given the small sample size and limited number of events, HR estimates are highly variable, may change over time, and thus should be interpreted with caution.

The results are exploratory, and caution is warranted given the case-cohort design, smaller sample sizes in genomic subgroups and limited number of events

Desmedt C et al, ESMO BC 2024

Conclusions & Open Questions

- **Currently Abemaciclib approval:** >4 lymph nodes positive nodes; 1-3 lymph nodes (pathologically positive) with one additional high-risk feature: grade 3 tumour, and/or tumour size >=5 cm
- **Currently Ribociclib approval:** Node-positive; Stage IIA Node-negative patients (ie. G3, G2 but Ki-67 >20% /high genomic risk). Lower level of risk more numbers of patients needed to treat to prevent each recurrence
- Theoretically, all N1 patients could benefit from the addition a Ribociclib (including T1N1: issue of **Omission of SLNB?**)
- Can Biomarkers Select for Adjuvant CDK4/6 inhibitors?
  - Similar benefit seen regardless of Intrinsic Subtype, Oncotype RS, Common Oncogenic Mutations
  - Don’t forget to use all available tests to better stratify the prognosis and to select our patients (safety/compliance issues)
- What about the role of extended ET? Can Adjuvant CDK4/6i replace Chemotherapy for some patients?
- **Addition of Olaparib to standard therapy improved iDFS/DDFS/OS for gBRCA1/2 carriers with HR+/HER2- (≥4 nodes) or NO pCR after NACT with CPS-EG ≥ 3**
  - Evidence and data are missing for patients candidates to receive both Olaparib and CDK4/6i (Abemaciclib or Ribociclib). Possible sequencing??
  - Patients with gBRCAmut have worse outcome with CDK4/6i than patients with gBRCAwt, in MBC
- **Treatment adherence and compliance is key for adjuvant therapy success**
  - Careful toxicity management and patients’ education are needed when new drugs are introduced in the adjuvant setting

Thank you for your attention