Il Carcinoma Mammario HR+/HER2-

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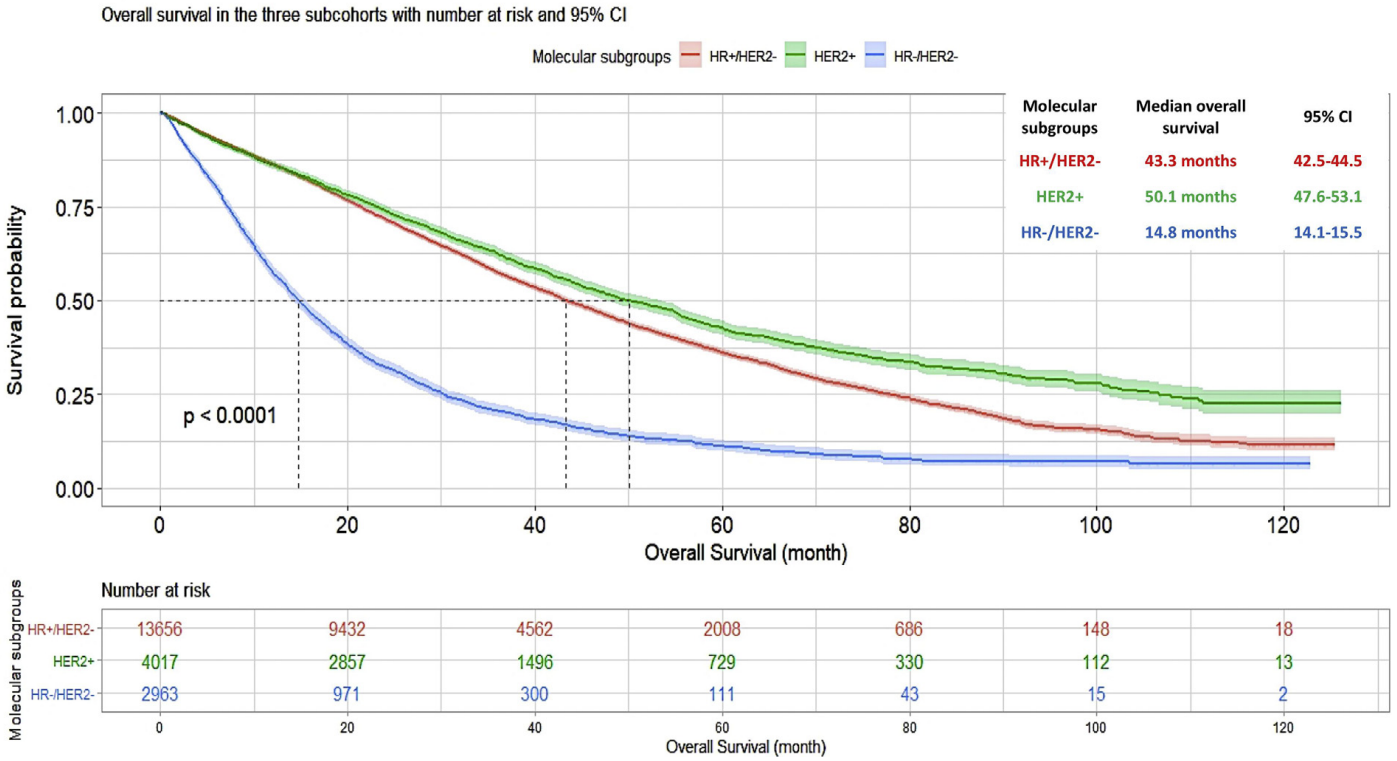
Unita' Medicina di Precisione in Senologia

Gemelli

The Outcome in The New ERA

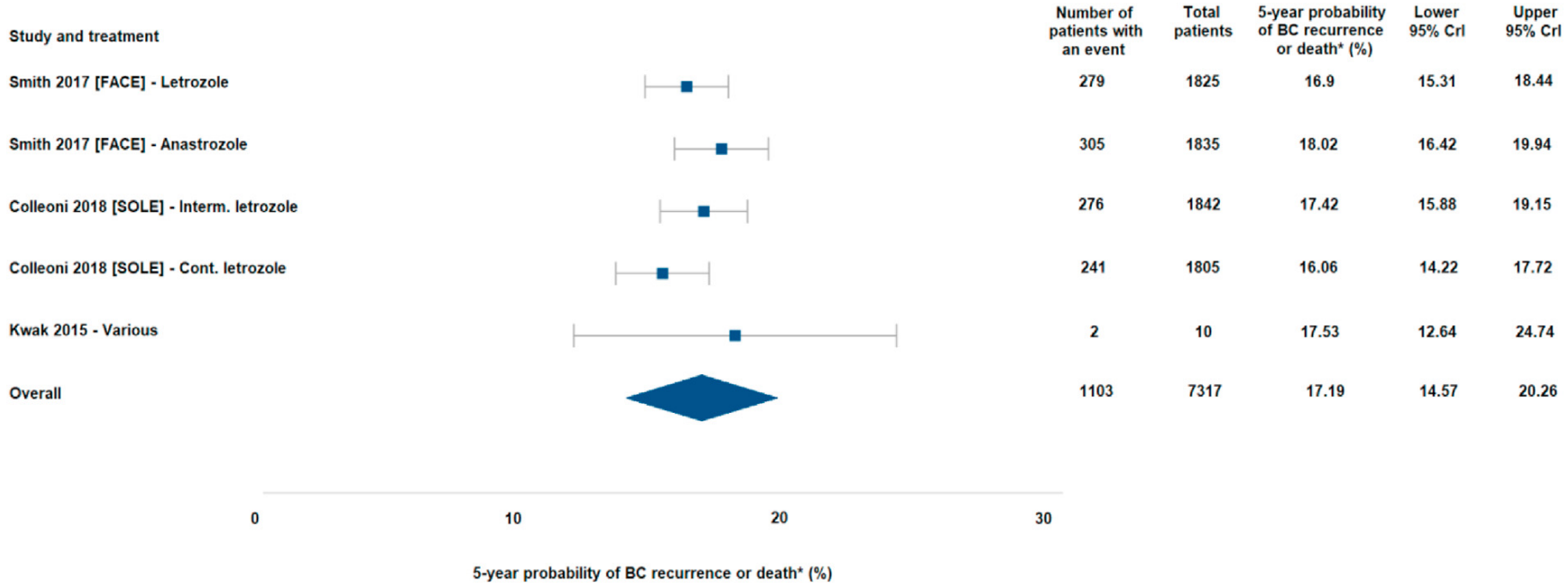
ESME cohort (n=22,109 patients between 2008 and 2016)



Deluche E et al, Eur J Cancer 2020

Risk of Recurrence among patients with HR-positive, HER2-negative, EBC receiving adjuvant endocrine therapy

17% 5-years probability of BC recurrence or death



1 in 6 women with node-positive HR+/HER2- early-stage BC receiving endocrine therapy experience recurrence or death within 5-years of initiating treatment

Salvo EM et al Breast 2021

Topics of my Talk

1. CDK4/6i in Adjuvant setting: myth or reality?
2. …In small steps towards NAHT
3. the delay of today the precocity of tomorrow

2020 in Early BC Disease

CDK4/6i

Screening & Covid-19

1. CDK4/6i in Adjuvant setting: myth or reality?

2. …In small steps towards NAHT

3. the delay of today the precocity of tomorrow

monarchE
EARLY BREAST CANCER

PALLAS

Penelope B

MonarchE

Age 51 Prem~50% No CT 5% >4LN 60%
TAM 30% LHRH 20%

HR+, HER2-, Node+ high risk early breast cancer

Cohort 1: Inclusion based on clinicopathological risk factors:
- ≥4 ALN OR
- 1-3 ALN and at least 1 of the below:
  - Histolgic Grade 3
  - Tumor size ≥5 cm

Cohort 2: Inclusion based on Ki-67:
- 1-3 ALN and
- Centrally tested Ki-67 ≥20%[d]
- Not Grade 3 and tumor size not ≥5 cm

ITT includes both C1 and C2

N = 5637[a]

R 1:1

Abemaciclib (150mg twice daily for up to 2 years[b]) **+ Standard of Care Endocrine Therapy**[c] (5 to 10 years as clinically indicated)

Standard of Care Endocrine Therapy[b,c] (5 to 10 years as clinically indicated)

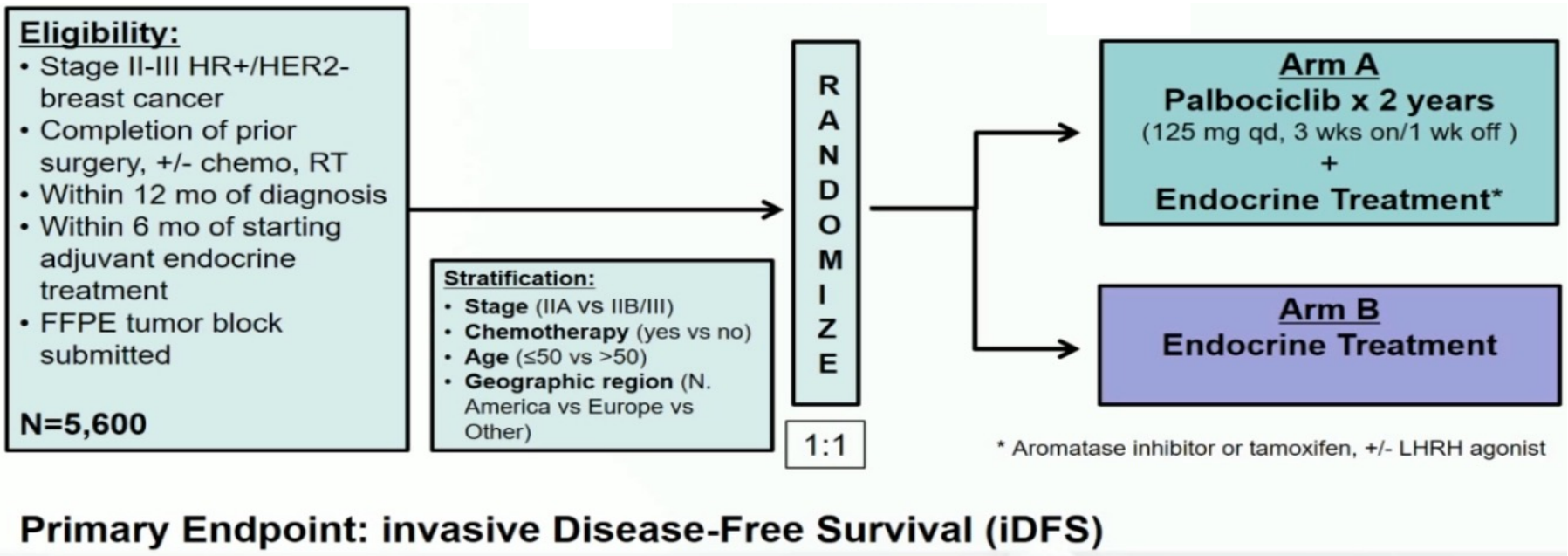
Stratified for:
- Prior chemotherapy
- Menopausal status
- Region

Other criteria:
- Women or men
- Pre-/ post menopausal
- With or without prior neo- and/or adjuvant chemotherapy
- No distant metastasis
- Maximum of 16 months from surgery to randomization and 12 weeks of ET following the last non-ET

Primary Objective: Invasive disease-free survival (IDFS) (STEEP criteria)
Key Secondary Objectives: IDFS in Ki-67 high (≥20%) population, Distant relapse-free survival (DRFS), Overall survival, Safety, Patient reported outcomes, and Pharmacokinetics

[a]Recruitment from July 2017 to August 2019; [b]Treatment period = first 2 years on study treatment after randomization; [c]Endocrine therapy of physician's choice [e.g., aromatase inhibitors, tamoxifen, LHRH agonist]; [d]Ki-67 expression assessed in all patients from both cohorts with suitable untreated breast tissue using Ki-67 immunohistochemistry Assay by Dako/Agilent
Abbreviations: ALN, positive axillary lymph nodes; R, randomized

PALLAS



85% power, HR 0.75, 1-sided α 0.0025
2 IA planned

Mayer E, ESMO 2020

Population

Pallas

- Between 9/2015 and 11/2018, 5,760 patients were randomized and included in the ITT set.
- The majority had higher stage disease and had received prior chemotherapy.
- 58·7% had high clinical risk disease, described as:
  - ≥4 nodes involved (≥N2), or
  - 1-3 nodes with either T3/T4 and/or G3 disease

Variable	Palbociclib + ET (N=2,883)	ET (N=2,877)
Age (y) – median (range)	52 (25 – 90)	52 (22 – 85)
Stage		
IIA	504 (17·5%)	509 (17·7%)
IIB	968 (33·6%)	951 (33·1%)
III	1402 (48·6%)	1408 (48·9%)
T-Stage		
T0/T1/Tis/TX	557 (19·3%)	500 (17·4%)
T2	1603 (55·6%)	1636 (56·9%)
T3/T4	722 (25·0%)	741 (25·8%)
N-Stage		
N0	267 (12·7%)	283 (13·3%)
N1	1427 (49·5%)	1415 (49·2%)
N2	703 (24·4%)	709 (24·6%)
N3	385 (13·4%)	370 (12·9%)
Histologic Grade		
G1	300 (10·4%)	313 (10·9%)
G2	1622 (56·3%)	1658 (57·6%)
G3	836 (29·0%)	767 (26·7%)
Prior Chemotherapy	2384 (82·7%)	2370 (82·4%)
Initial Adjuvant Endocrine Therapy		
Aromatase inhibitor	1954 (67·8%)	1918 (66·7%)
Tamoxifen	923 (32·0%)	949 (33·0%)
Concurrent Adjuvant LHRH Agonist	532 (18·5%)	604 (21.1%)

PALLAS | Sponsored by AFT and ABCSG, in cooperation with PrECOG, BIG, GBG, NSABP, and supp

MonarchE

		Abemaciclib + ET N = 2808, n (%)	ET Alone N = 2829, n (%)
Number of positive lymph nodes	0	7 (0.2)	7 (0.2)
	1-3	1119 (39.9)	1143 (40.4)
	≥4 or more	1680 (59.8)	1679 (59.3)
Histological grade	Grade 1	209 (7.4)	215 (7.6)
	Grade 2	1373 (48.9)	1395 (49.3)
	Grade 3	1090 (38.8)	1066 (37.7)
Primary tumor size by pathology following definitive surgery	<2 cm	780 (27.8)	765 (27.0)
	2-5 cm	1369 (48.8)	1419 (50.2)
	≥5 cm	610 (21.7)	612 (21.6)
Central Ki-67	<20%	953 (33.9)	973 (34.4)
	≥20%	1262 (44.9)	1233 (43.6)
	Unavailable	593 (21.1)	623 (22.0)
Progesterone receptor status	Positive	2421 (86.2)	2453 (86.7)
	Negative	298 (10.6)	294 (10.4)

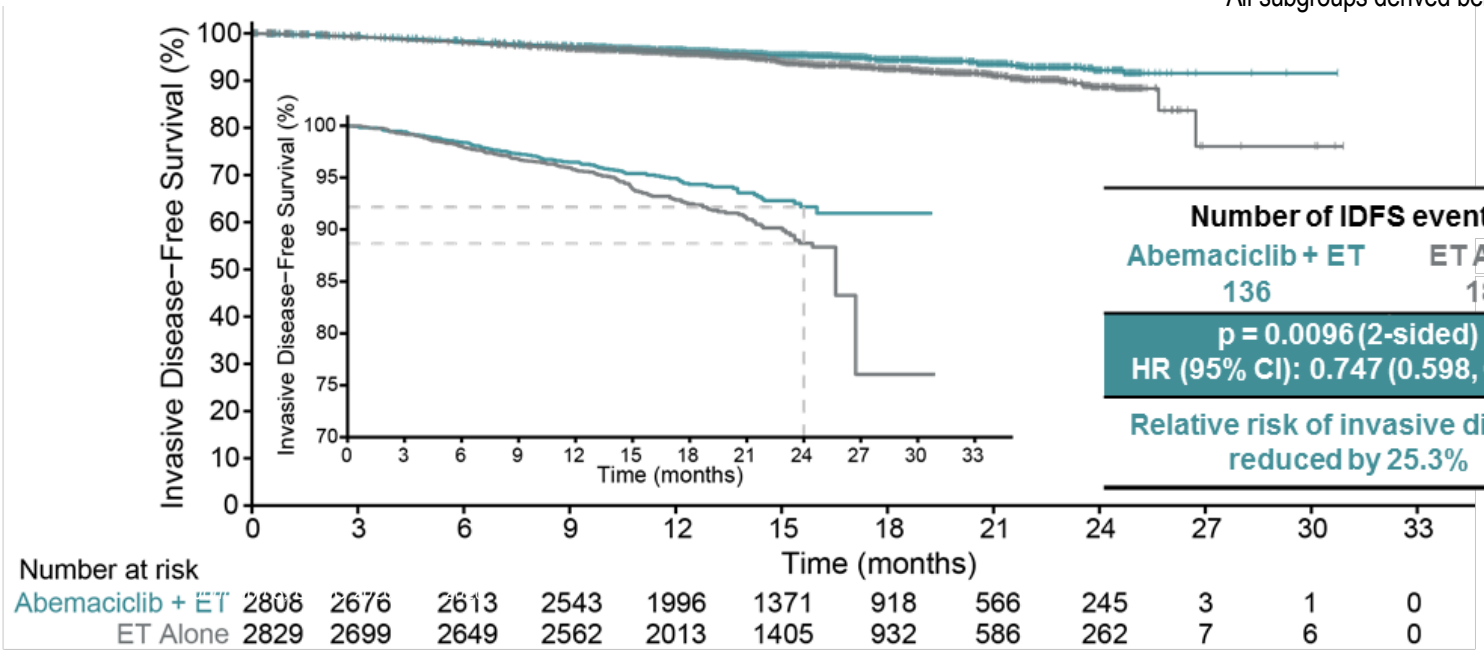
Note: where values do not add up to 100%, remaining data are missing, unavailable or could not be assessed

Additional high risk eligibility criteria for patients with 1-3 nodes	Abemaciclib + ET N = 2808, n (%)	ET Alone N = 2829, n (%)
Tumor size ≥5 cm (pathology) [a]	249 (8.9)	236 (8.3)
Tumor size ≥5 cm (imaging) [a, b]	152 (5.4)	158 (5.6)
Histologic grade 3 [a]	629 (22.4)	618 (21.8)
Central Ki-67 ≥20% only [c]	216 (7.7)	237 (8.4)

[a] Patients could be counted in more than one of the sub-categories under 1-3 positive lymph nodes; [b] Patients who received neoadjuvant chemotherapy may have been eligible based on imaging tumor size prior to receiving systemic therapy; [c] Patients not double counted; patients did not have tumor size ≥5 cm (either by pathology or imaging) or histologic grade 3

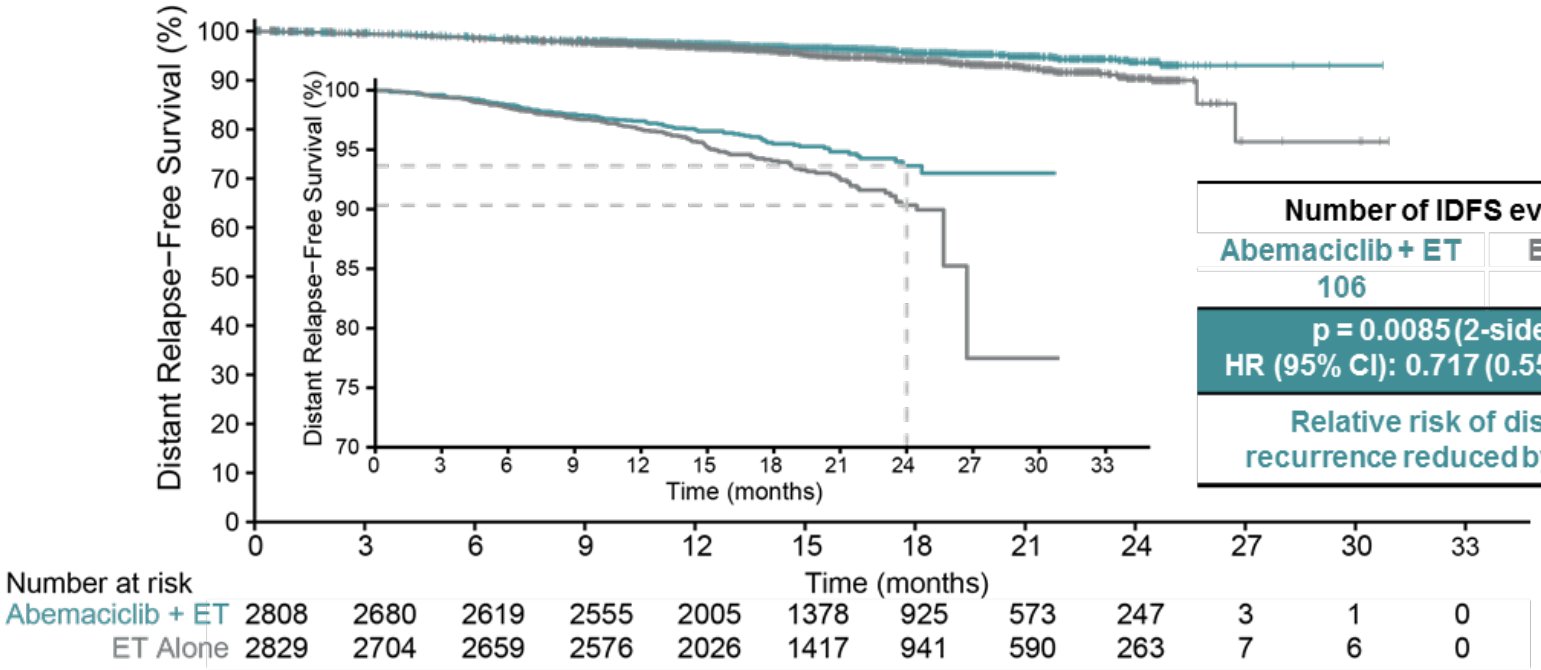
MonarchE: primary endpoint iDFS

12.5% pts completed 2 yr
72.8% pts still in the 2-yr period
All subgroups derived benefit



Two-year IDFS rates were 92.2% (abemaciclib + ET arm) and 88.7% (ET arm) – 3.5% absolute difference

MonarchE: primary endpoint DRFS



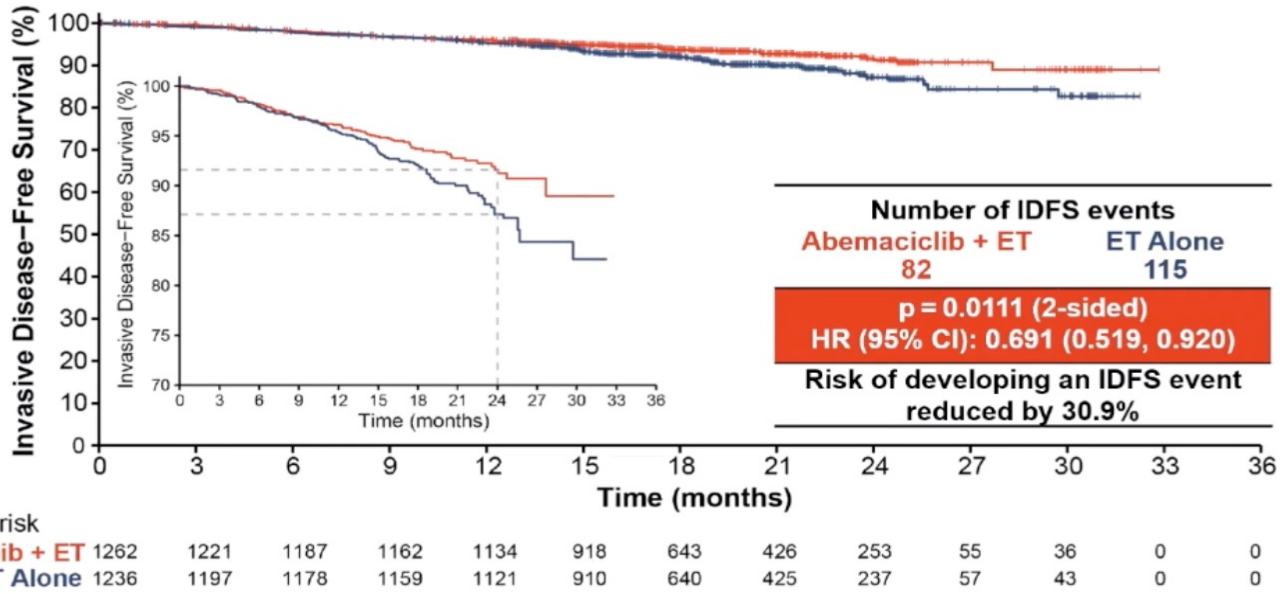
Number at risk												
Abemaciclib + ET	2808	2680	2619	2555	2005	1378	925	573	247	3	1	0
ET Alone	2829	2704	2659	2576	2026	1417	941	590	263	7	6	0

Number of IDFS events	
Abemaciclib + ET	ET Alone
106	152
p = 0.0085 (2-sided) HR (95% CI): 0.717 (0.559, 0.920)	
Relative risk of distant recurrence reduced by 28.3%	

Two-year DRFS rates were 93.6% (abemaciclib + ET arm) and 90.3% (ET arm) – 3.3% absolute difference.
DRFS benefit consistent across all prespecified subgroups.

Johnston S, ESMO 2020, JCO 2020

Monarch E: IDFS in Ki-67 high (≥20%) in the ITT Population



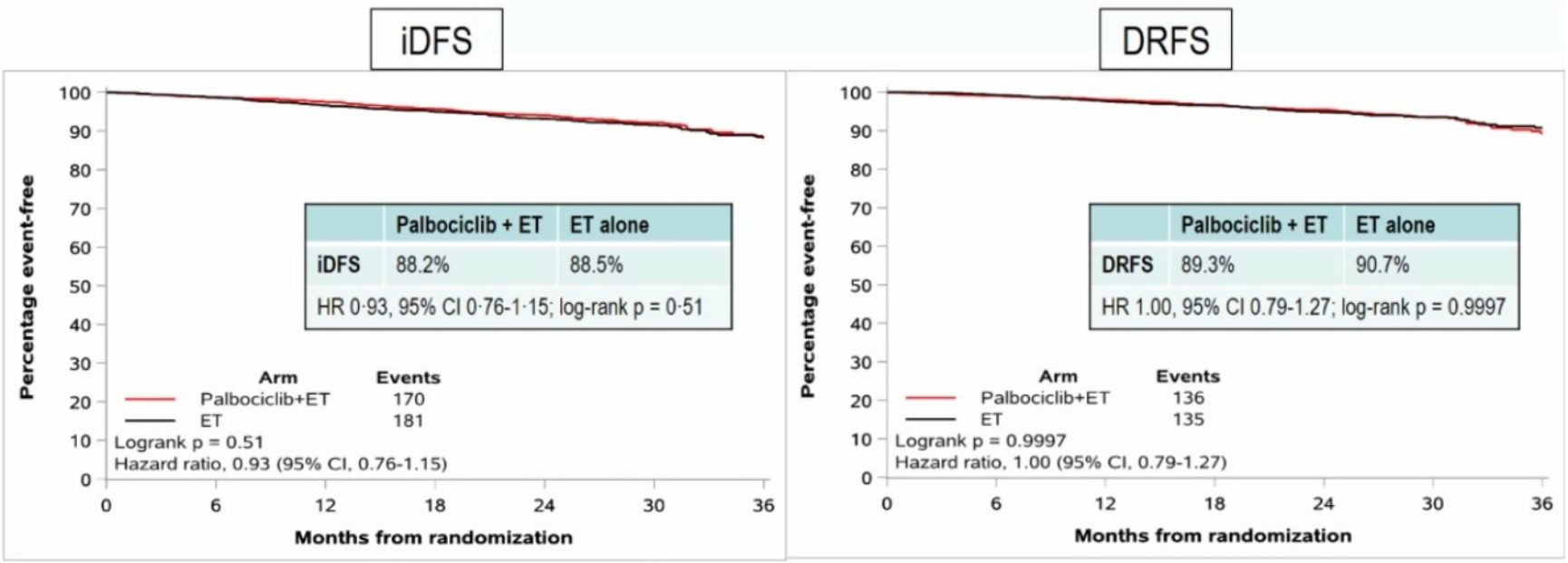
Number at risk													
Abemaciclib + ET	1262	1221	1187	1162	1134	918	643	426	253	55	36	0	0
ET Alone	1236	1197	1178	1159	1121	910	640	425	237	57	43	0	0

Ki-67 was tested in all eligible patients in cohorts 1 and 2 with suitable untreated breast tissue

Statistically significant and clinically meaningful improvement in IDFS in patients with high Ki-67 tumors
Two-year IDFS rates were 91.6% in the abemaciclib + ET arm and 87.1% in the ET arm – 4.5% difference

Rastogi et al SABCS 2020

PALLAS: iDFS and DRFS



At a median follow-up of 23.7 months, no significant difference in either 3-year iDFS or DRFS was observed

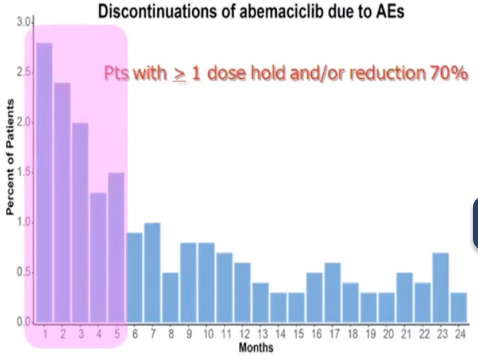
PALLAS and MonarchE: safety and treatment discontinuations

Adverse Event	Adverse Events, incidence ≥ 15%					
	Palbociclib + ET (N=2,840)			ET (N=2,903)		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Any adverse event	2822 (99·4%)	1897 (66·8%)	159 (5·6%)	2571 (88·6%)	400 (13·8%)	24 (0·8%)
Neutropenia	2354 (82·9%)	1620 (57·0%)	122 (4·3%)	139 (4·8%)	11 (0·4%)	0
Leukopenia	1550 (54·6%)	843 (29·7%)	14 (0·5%)	213 (7·3%)	3 (0·1%)	0
Fatigue	1150 (40·5%)	60 (2·1%)	0	546 (18·8%)	10 (0·3%)	0
Arthralgia	992 (34·9%)	30 (1·1%)	0	1207 (41·6%)	31 (1·1%)	0
Upper respiratory tract infection	805 (28·3%)	32 (1·1%)	0	453 (15·6%)	3 (0·1%)	0
Hot flush	693 (24·4%)	7 (0·2%)	0	838 (28·9%)	7 (0·2%)	0
Anaemia	664 (23·4%)	13 (0·5%)	0	157 (5·4%)	4 (0·1%)	0
Thrombocytopenia	609 (21·4%)	25 (0·9%)	1 (0·0%)	49 (1·7%)	1 (0·0%)	0
Nausea	543 (19·1%)	8 (0·3%)	0	240 (8·3%)	4 (0·1%)	0
Alopecia	496 (17·5%)	0	0	144 (5·0%)	0	0
Diarrhoea	468 (16·5%)	21 (0·7%)	0	145 (5·0%)	5 (0·2%)	0
Headache	435 (15·3%)	7 (0·2%)	0	322 (11·1%)	7 (0·2%)	0

Patient Status	Palbociclib + ET	ET
Initiated Palbociclib	2840	
Ongoing Palbociclib at data cutoff	725 (25·5%)	
Completed Palbociclib per protocol	916 (32·3%)	
Early discontinuation of Palbociclib	1199 (42·2%)	
Adverse event (including unacceptable toxicity)	770 (64·2%)	
Patient non-compliance/non-adherence	128 (10·7%)	
Development of recurrent disease/secondary malignancy	104 (8·7%)	
Informed consent withdrawal	100 (8·3%)	
Other reasons	97 (8·1%)	
Initiated ET	2840	2903
Ongoing ET at data cutoff	2462 (86·7%)	2500 (86·1%)
Ongoing ET at end of study participation	182 (6·4%)	219 (7·5%)
Early discontinuation of ET	196 (6·9%)	184 (6·3%)
Development of recurrent disease/secondary malignancy	86 (43·9%)	84 (45·7%)
Informed consent withdrawal	49 (25·0%)	39 (21·2%)
Adverse event (including unacceptable toxicity)	28 (14·3%)	23 (12·5%)
Patient non-compliance/non-adherence	12 (6·1%)	10 (5·4%)
Other reasons	21 (10·7%)	28 (15·2%)

?

- Over half of the early discontinuations due to AEs occurred within the first 5 months of treatment



Treatment Discontinuation	Abemaciclib + ET N=2791, n (%)	ET alone N=2800, n (%)
For any reason	773 (27.7)[a]	410 (14.6)
Due to AEs, including deaths due to AEs	481 (17.2)[c]	23 (0.8)
Diarrhea	141 (5.1)	0
Fatigue	53 (1.9)	0
Neutropenia	26 (0.9)	0
Withdrawal by subject	156 (5.6)	169 (6.0)
IDFS/DRFS events	136 (4.9)	204 (7.3)
Deaths due to study disease	2 (<0.1)	2 (<0.1)
Noncompliance	8 (0.3)	0
Other[b]	32 (1.1)	21 (0.8)

[a]Some patients who discontinued abemaciclib and remained on ET may have been double counted for an early discontinuation due to a different reason once ET was discontinued
[b]Other includes lost to follow-up (0.3, 0.4), physician decision (0.5, 0.1), protocol deviation (0, 0.3), study terminated (0, 0.1) and other (0.3, 0) in the abemaciclib + ET alone and ET alone arm, respectively
[c]6.2% of patients discontinued both abemaciclib and ET due to AEs

Mayer E, ESMO 2020

Pallas vs MonarchE
27% over total pts
vs 17%

Penelope^{B}: Study Design

✓Age 49 Y
✓ypN2-3 50%
✓TAM 50% LHRH 18%

N=1250
- HR+/HER2- breast cancer
- no pCR after NACT
- CPS-EG score ≥3 or ≥2 with ypN+

Primary Endpoint: iDFS

Stratification factors
- Nodal status: ypN 0-1 vs ypN2-3
- Age: ≤50 vs >50 yrs
- Ki-67: >15% vs ≤ 15%
- Region: Asian vs non Asian
- CPS-EG Score: ≥3 vs 2 and ypN+

Neoadjuvant Chemotherapy → **Surgery +/- Radiotherapy** → **R 1:1**

Palbociclib
125 mg once daily p.o.
d1-21, q28d for 13 cycles

Placebo
d1-21, q28d for 13 cycles

All patients will receive concomitantly endocrine therapy according to local standards

Penelope-B: ClinicalTrials.gov NCT01864746

Loibl et al SABCS 2020

Penelope^{B}: Disposition of Patients

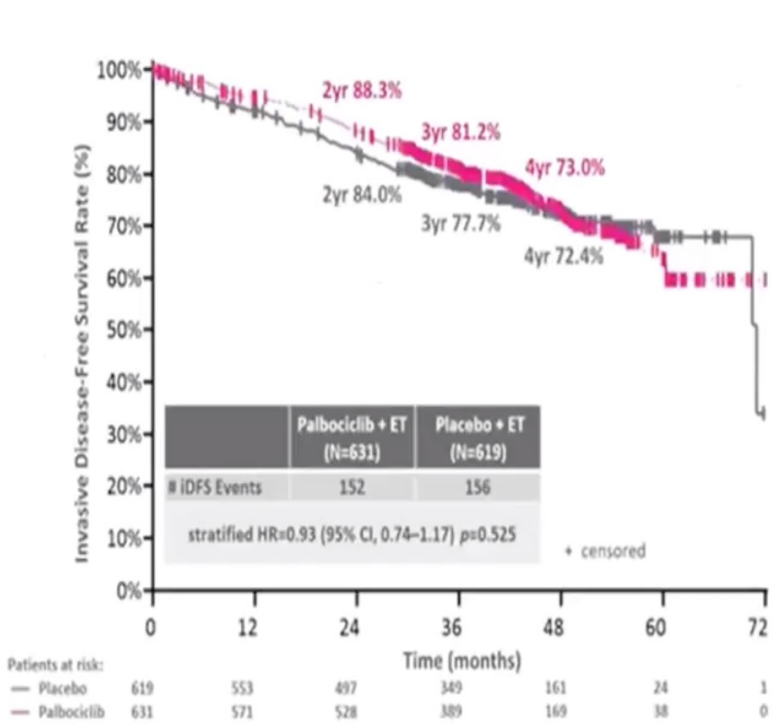
Patient Status	Palbociclib N (%)	Placebo N (%)	**Overall N (%)**
Number of patients screened			1708
Number of patients randomized	631	619	1250
Number of patients started treatment	628	616	1244
Completed at least 7 cycles of treatment	559 (88.6)	559 (90.3)	1118 (89.4)
Completed all 13 cycles regularly	508 (80.5)	523 (84.5)	1031 (82.5)
Discontinued endocrine therapy prematurely	28 (4.4)	36 (5.8)	64 (5.1)
Discontinued study treatment	123 (19.5)	96 (15.5)	219 (17.5)
- Disease recurrence	25 (4.0)	40 (6.5)	65 (5.2)
- Second primary (non-breast)	2 (0.3)	3 (0.5)	5 (0.4)
- Death	2 (0.3)	1 (0.2)	3 (0.2)
- Adverse event	33 (5.2)	5 (0.8)	38 (3.0)
- Patient´s wish	56 (8.9)	41 (6.6)	97 (7.8)
- Investigator´s decision	5 (0.8)	6 (1.0)	11 (0.9)

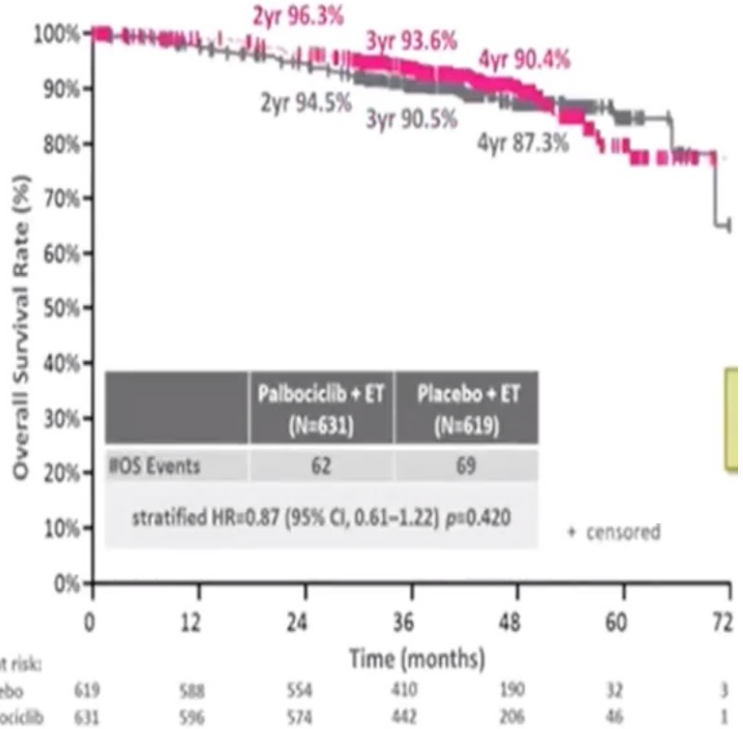
Dose reductions more common in Palbociclib arm

Loibl et al SABCS 2020

Penelope^{B}: IDFS e OS

Median F/up 43 months

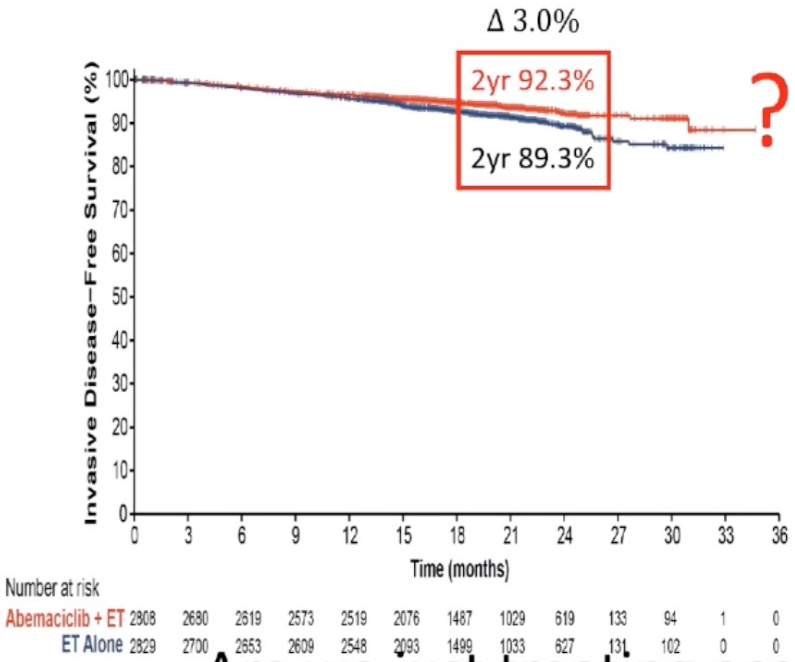




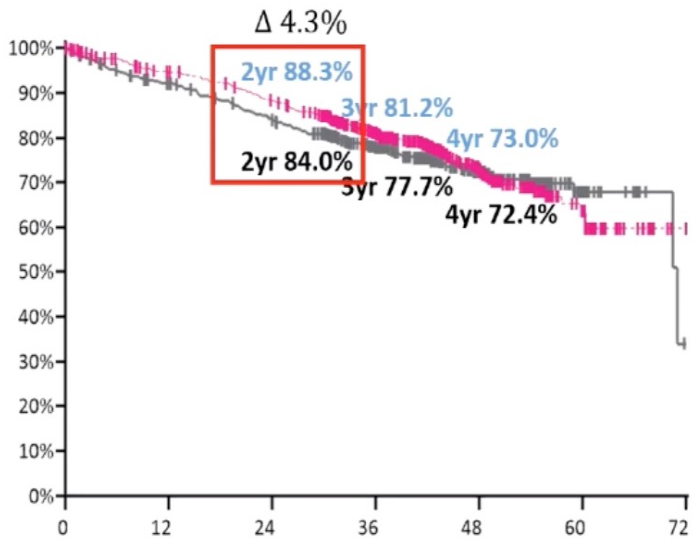
Loibl et al SABCS 2020

Why different outcomes across these trials (or is there

Monarch E



Penelope[B]



Are we just treating occult metastatic disease?

follow up too short to see benefits and too short to see failures?

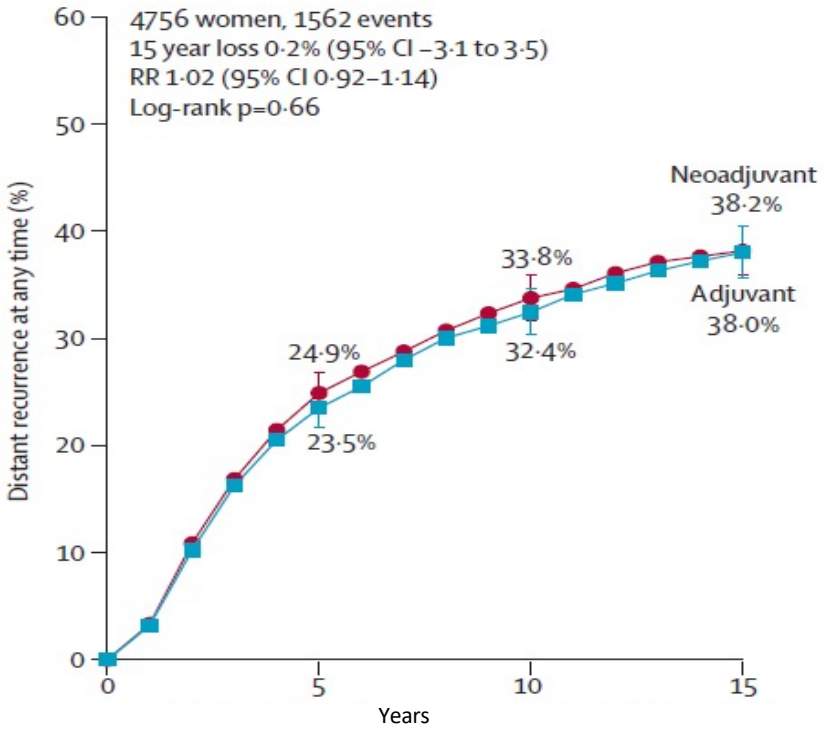
1. CDK4/6i in Adjuvant setting: myth or reality?

2. …In small steps towards NAHT

3. the delay of today, the precocity of tomorrow

CT has been shown to lead to similar long-term clinical outcome whether used in the neoadjuvant or adjuvant setting

DISTANT RECURRENCE overall population



EBCTCG Meta-analysis 10 clinical trials
NACT vs adjuvant CT in early breast cancer patients
N= 4,756

Rate of distant recurrence, BCSS, or OS were similar with NACT vs adjuvant CT

NACT had more frequent local recurrence (21.4% vs 15.9%)

In certain trials, some patients with a good response did not receive surgery. Hence, higher local recurrence frequencies have been attributed to omission of definitive local therapy.

NACT associated with increased BCS (65% vs 49%)

NACT= neoadjuvant chemotherapy

EBCTCG, *Lancet Onc* 2018

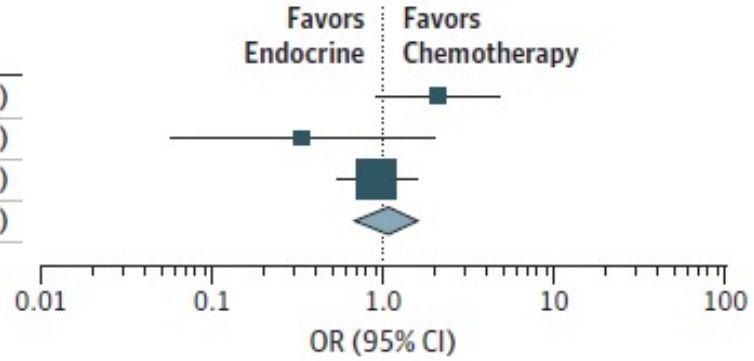
Neoadjuvant endocrine therapy has been shown to lead to similar response rates as neoadjuvant chemotherapy

Locally advanced HR+ HER2- T2+ N0-2 patients, without biomarker selection

Pooled analysis of three prospective randomized trials of NAET vs NACT (n=378 patients)

A Clinical response

Source	OR (95% CI)
Alba et al,[30] 2012	2.11 (0.92-4.82)
Palmieri et al,[31] 2014	0.34 (0.06-1.98)
Semiglazov et al,[32] 2007	0.93 (0.55-1.57)
Total	1.08 (0.50-2.35)
Heterogeneity: $\chi^2_2 = 4.47$ ($P = .11$), $I^2 = 55\%$	
Test for overall effect: $z = 0.19$ ($P = .85$)	



Clinical response (OR, 1.08; 95%CI, 0.50-2.35; P=.85; n = 378)

Radiological response (OR, 1.38; 95%CI, 0.92-2.07; P=.12; n = 378)

Breast-conserving surgery (OR, 0.65; 95%CI, 0.41-1.03; P=.07; n = 334)

Both neoadjuvant endocrine therapy and chemotherapy can be effective options for localized HR+ breast cancer

EXACT SCIENCES

Spring LM, et al. *JAMA Oncol*. 2016;2(11):1477-1486; Alba et al, Ann Onc 2012; Palmieri et al, BCRT 2014; Semiglazov et al, Cancer 2007.
CI, confidence interval; NACT, neoadjuvant chemotherapy; NAET, neoadjuvant endocrine therapy; OR, odds ratio.

>30% of early breast cancer patients do not respond to NACT

	Clinical response				
	Complete*	Partial†	Stable or progressive disease‡	Unknown	Total
Breast-conserving	452 (83%)	541 (68%)	246 (42%)	265 (68%)	1504 (65%)
Mastectomy	92 (17%)	258 (32%)	342 (58%)	124 (32%)	816 (35%)
Unknown	2 (NA)	4 (NA)	10 (NA)	51 (NA)	67 (NA)
Total response§	546/1947 (28%)	803/1947 (41%)	598/1947 (31%)	440 (NA)	2387 (100%)

EBCTCG Meta-analysis
10 clinical trials NACT vs adjuvant CT in HR+/- early breast cancer patients
N= 4,756

28% patients
- complete clinical response to NACT,
- 83% rate of BCS

RESPONDING TO NACT

31% patients
- no clinical response to NACT,
- higher rate of mastectomy

OVERTREATED WITH CT

EBCTCG, *Lancet Onc* 2018

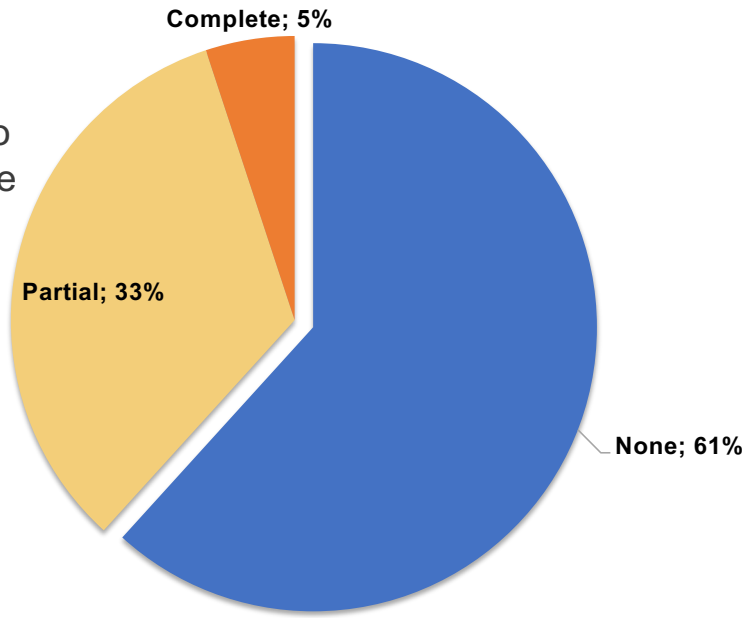
…..It is an important unmet need to identify those patients most likely to respond and spare chemotherapy for the others

Retrospective analysis of the National Cancer Database of HR+, HER2- early breast cancer patients receiving NACT
N= 1,377

Only 4.5% of patients achieve a complete pathological response to NACT, and 33% a partial response

RESPONDING TO NACT

Pathological Response to Neoadjuvant CT

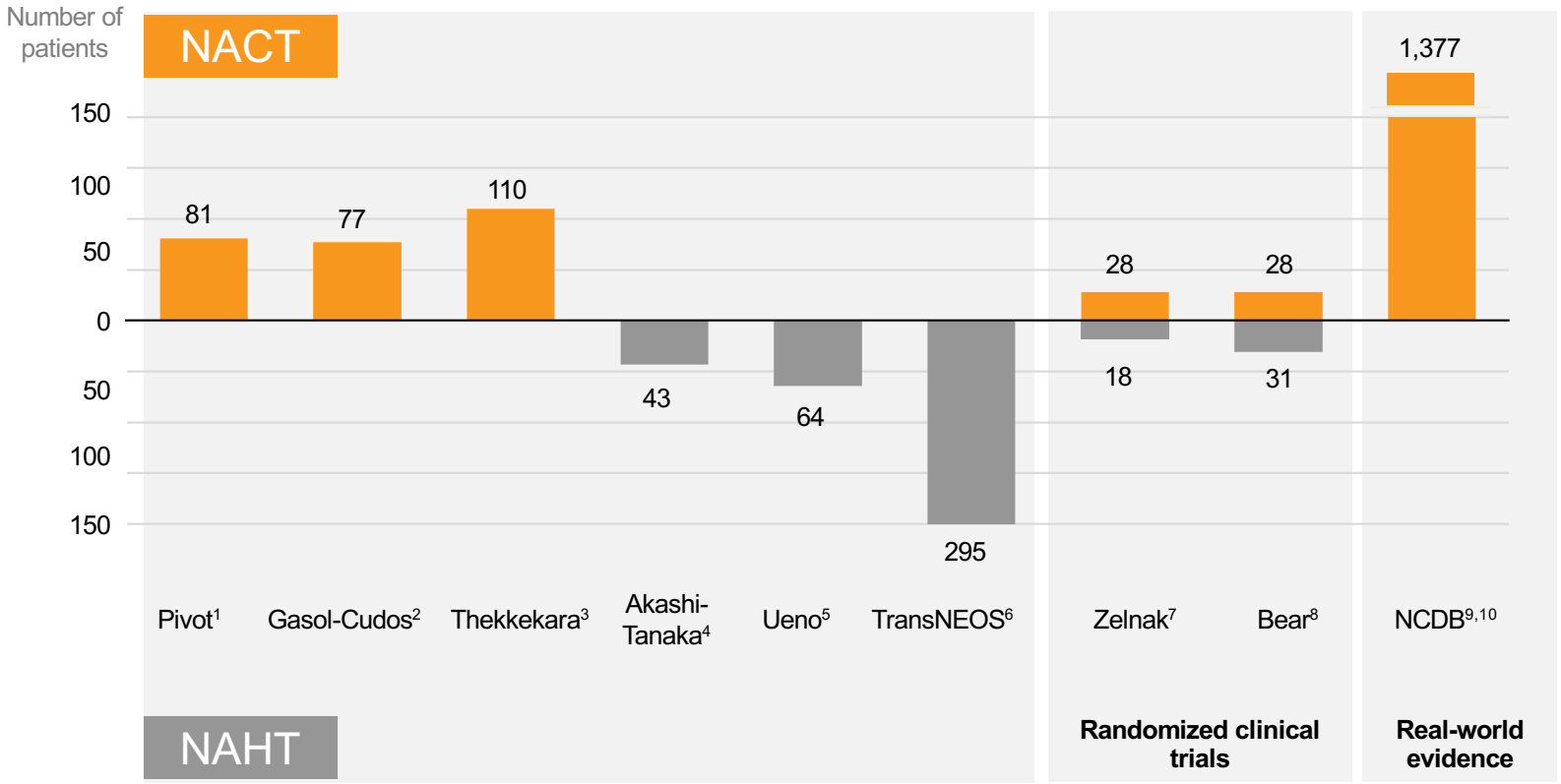


61% patients with **no significant pathological response to NACT**

OVERTREATED WITH CT

Kantor et al, Ann Surg Oncol 2019

Overview of key evidence supporting the clinical utility of the Oncotype DX® test to guide neoadjuvant treatment decisions



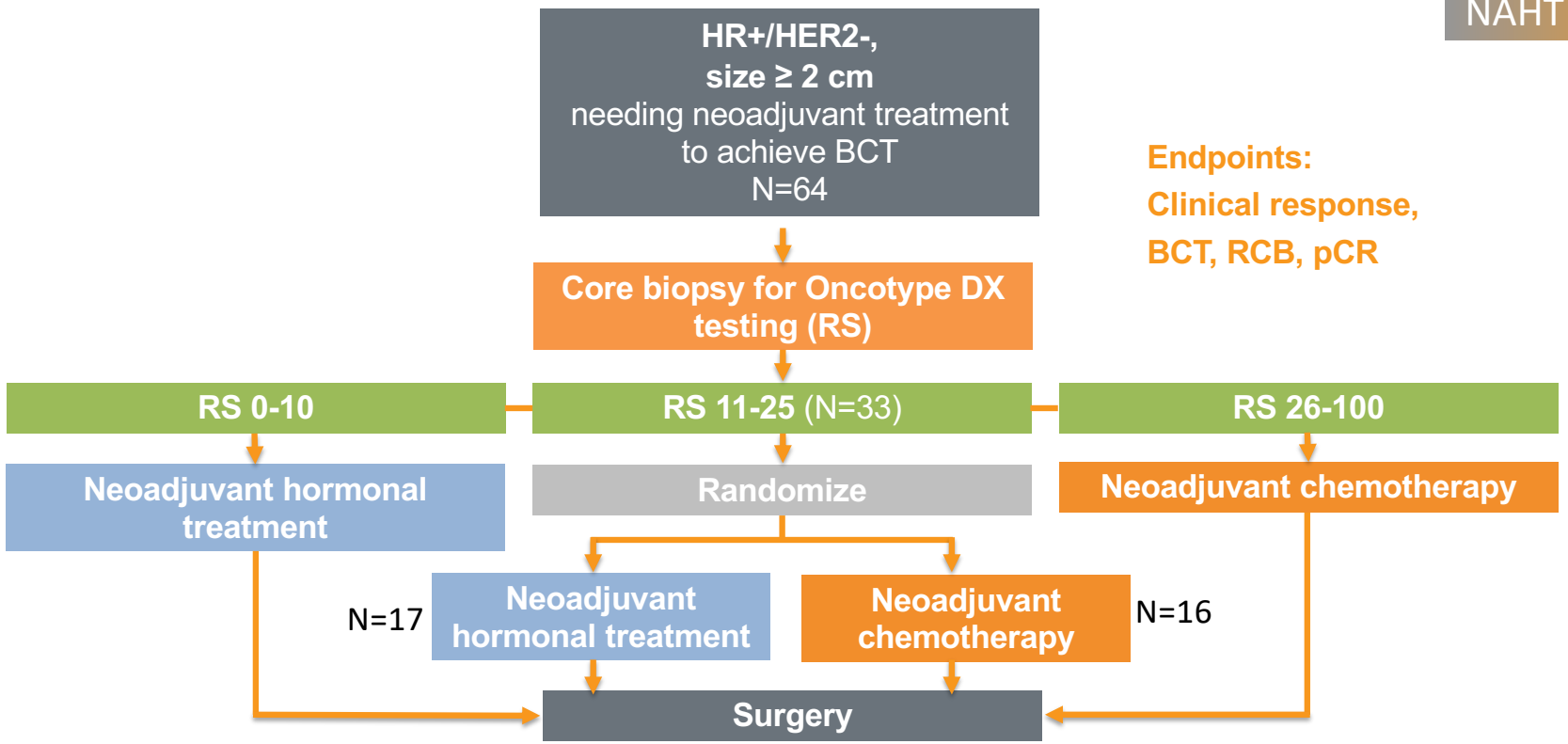
Excludes 3 studies with mixed populations ER+/-

1. Pivot et al. *Oncologist* 2015; 2. Gasol-Cudos et al. *St. Gallen conference* 2019; 3. Thekkekara et al. *ASCO* 2019; 4. Akashi-Tanaka et al *Breast* 2009; 5. Ueno et al. *Int J Clin Oncol* 2014; 6. Iwata et al. *Breast Can Res Treat* 2019; 7. Zelnak et al. *ASCO* 2013; 8. Bear et al. *J Surg Oncol* 2017; 9. Pease et al. *Ann Surg Oncol* 2018; 10. Kantor et al. *Ann Surg Oncol* 2019

Prospective multicenter trial evaluating NACT vs NAHT

Massey Cancer Center (Richmond, VA)

NAHT vs. NACT



Endpoints:
Clinical response,
BCT, RCB, pCR

1Bear et al. *J Surg Oncol.* 2017.

BCT – breast-conserving therapy; pCR – pathologic complete response;
RCB – residual cancer burden; RS – Recurrence Score® result

Surgical outcome when treatment decisions are guided by Recurrence Score results

NAHT vs. NACT

HR+/HER2- EBC pts with tumour size ≥ 2 cm (N=64)

	RS 0-10	RS 11-25		RS 26-100
Treatment Group	**NAHT N=12 (%)**	**NAHT N=18 (%)**	**NACT N=11 (%)**	**NACT N=14 (%)**
cCR	8.3	22.2	36.4	28.6
cPR	75.0	27.8	36.4	64.3
pCR breast	**8.3**	**6.0**	**0**	**21.4**
pCR breast + nodes	0	0	0	14.3
Successful BCS	**75.0**	**72.2**	**63.6**	**57.1**

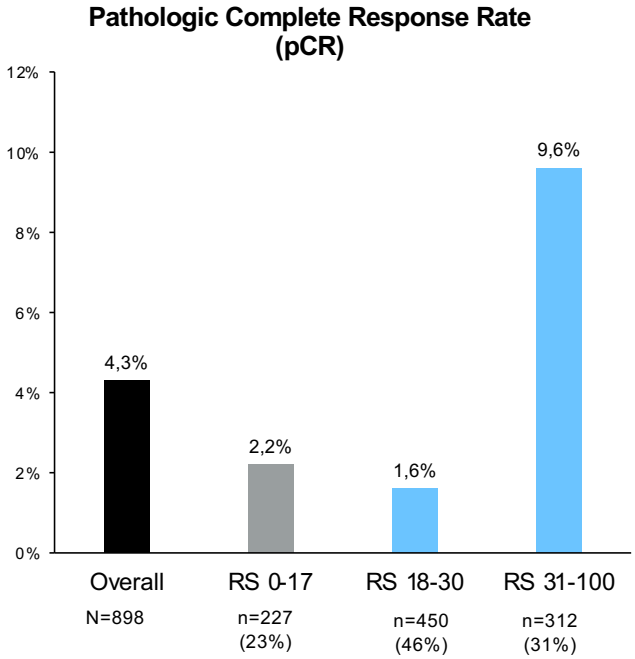
- Patients with RS 26 to 100 with NACT showed the highest clinical response rates
- 100% of patients with pCRs for breast and nodes had a RS 26 to 100
- Confirm prior studies showing that patients with a lower RS results have little to no benefit from chemotherapy, similar to the adjuvant setting

Bear et al. *J Surg Oncol.* 2017.

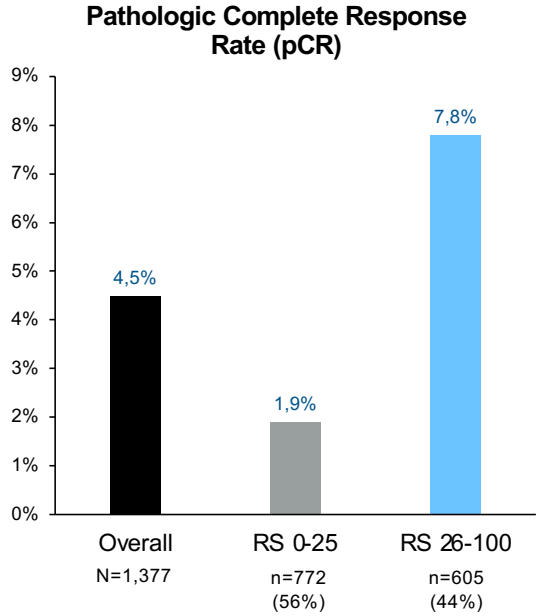
Large real-world dataset supports the association between Oncotype DX results and response to NACT

NACT

National Cancer Database : patients with T1-T3, ER+, HER2- early breast cancer from 2010-2015 who had Oncotype DX test and received NACT



Pease et al Ann Surg Oncol 2018



Kantor et al Ann Surg Oncol 2019

- pCR is rarely achieved in an overall HR+, HER2- unselected population
- **Patient group with higher RS results is significantly enriched in pCR**

Strong correlation between RS results and pathological response to neoadjuvant chemotherapy

NACT

Patients

63 early breast cancer HR+, HER2- patients who received NACT after having an Oncotype DX® test

Characteristics	
Median age (range)	54 years (31-84)
Median initial tumour size (range)	37 mm (12 -97)
Clinical node status Negative Positive	 35% 65%
Median Ki67 index (range)	34% (8 – 85)

Recurrence Score results distribution n (%)	
RS 0-10	*Excluded*
RS 11-25	25 (40%)
RS 26-100	38 (60%)

Results

- ✓ **100% patients who achieved a pCR had a RS result >25**
- ✓ Pathological response type 0 was achieved in 5 patients (8%) and type I in 16 (25%).
- ✓ **Strong correlation between pathological response type 0 and I and Recurrence Score result** in the univariable and multivariable analysis (OR 0.946 p-value 0.023)
- ✓ Threshold analysis showed the **Oncotype DX test was the most significant predictor of pathological response** (AUC 0.75 p-value 0.001) compared to Ki67 (AUC 0.61 p-value 0.171), Oestrogen receptor (AUC 0.41 p-value 0.21) and initial tumour size (AUC 0.671 p-value 0.028)

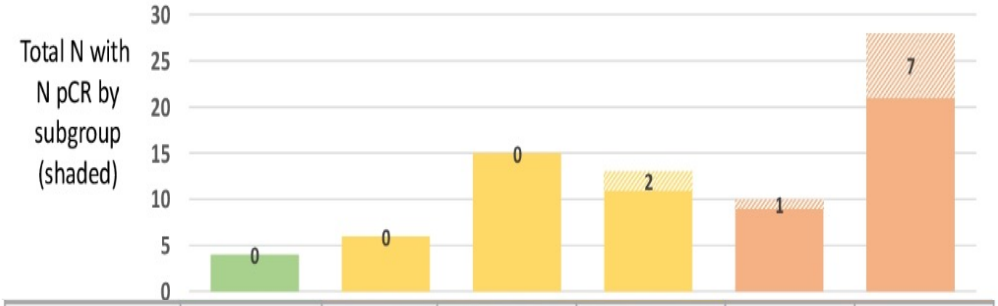
Morales Murillo et al. J Clin Oncol 38: 2020 (suppl; abstr e12630)

NACT: neoadjuvant chemotherapy

Disproportionate rate of pCR in response to neoadjuvant chemotherapy in young women (<40) with high RS results

NACT

Sub-study of 76 women ER+, HER2- patients <40 years who had received neoadjuvant chemotherapy from the Young Women's Breast Cancer Study[1,2]
26% cN0; 74% cN+



	<11	11-15	16-20	21-25	26-30	>30
pCR	0	0	0	2(15.4%)	1 (10%)	7(25%)
Non-pCR	4 (100%)	6 (100%)	15 (100)	11(84.6%)	9 (90%)	21 (75%)
Total	4	6	15	13	10	28

- A large proportion (~50%) of young patients <40 have Recurrence Score results 0 to 25
- **pCRs were seen in patients with high RS results 21 or higher**

1. Poorvu PD, et al J Clin Oncol. 38(7) 725-733, 2020
2. Sella et al. J Clin Oncol 38: 2020 (suppl; abstr 514)

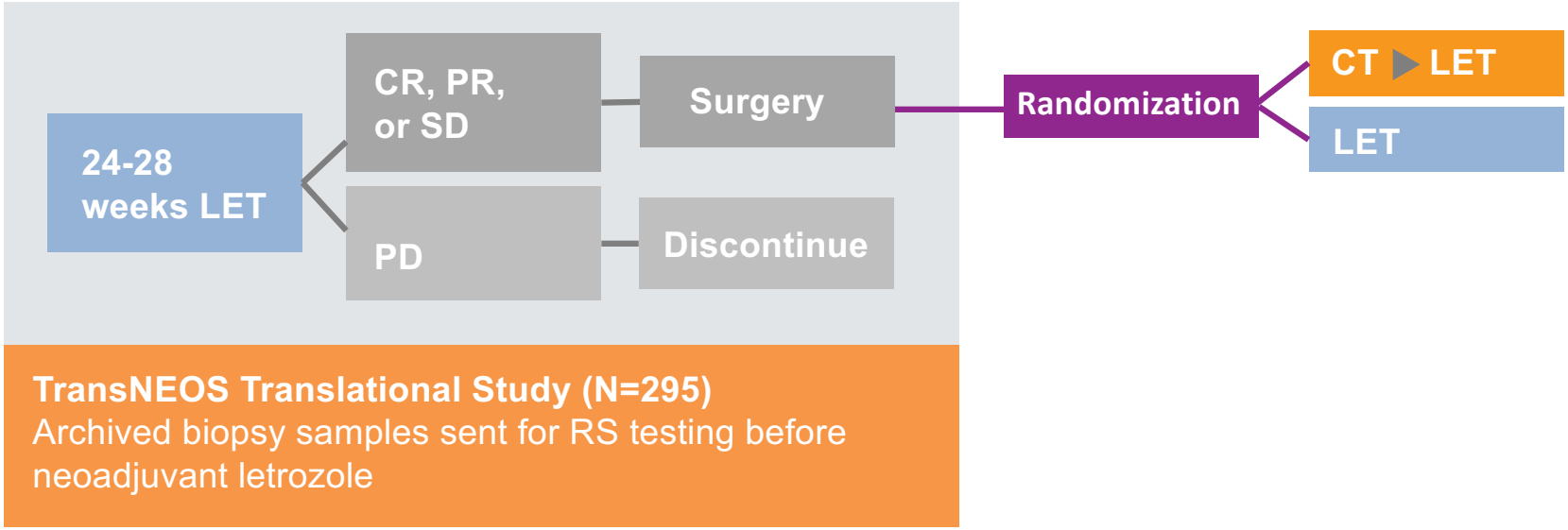
pCR: pathological complete response
RS: Recurrence Score results

TransNEOS: validation of RS result to select endocrine therapy in the neoadjuvant setting

NAHT

NEOS Parent Trial

(904 post-menopausal women; T1c-T2, N0, M0, ER+, HER2-)



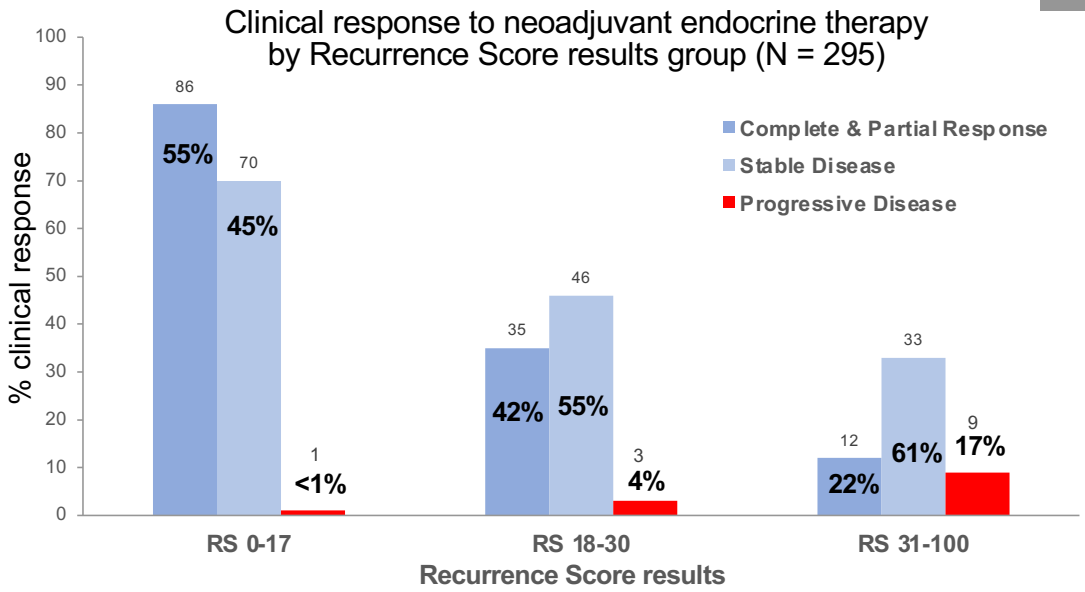
Iwata H, et al. *Breast Cancer Res Treat*. 2019

RS results predict response to neoadjuvant endocrine therapy: TransNEOS study

NAHT

ER+, HER2- early breast cancer post-menopausal women, T1c-T2, N0, receiving 24 weeks letrozole
Oncotype DX performed on core biopsies

Patient demographics and disease characteristics (*N* = 295)	
Age Median (range)	63 (49–75)
Age ≤ 60	94 (31.9%)
Tumor size, Median mm (range)	25 (20–65)
T-stage	
T1c	44 (14.9%)
T2	251 (85.1%)
Nuclear grade	
1	195 (66.1%)
2	59 (20.0%)
3	27 (9.2%)
Ki-67 expression	
< 10%	86 (29.2%)
10–30%	123 (41.7%)
> 30%	61 (20.7%)



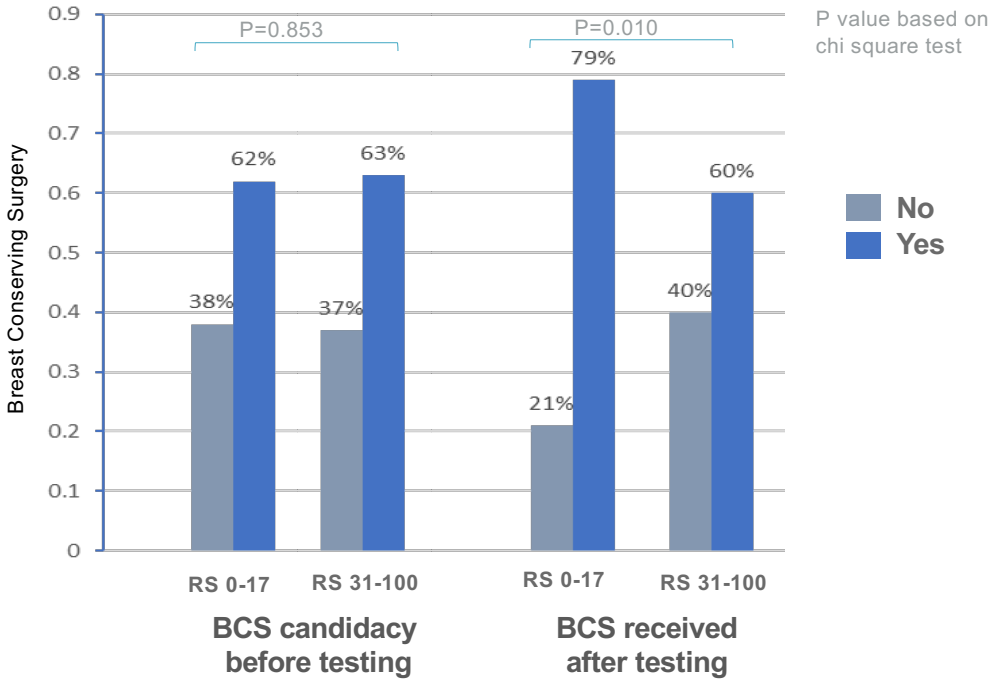
- **RS results group (0-17 vs 31-100) was significantly associated with clinical response rate (P < .001)**
- 99% of patients with results 0-17 had clinical response (CR, PR) or stable disease (SD), with low likelihood of progressive disease (<1%)

Iwata H et al. *Breast* Cancer *Res Treat*. 2019.

Patients with lower Recurrence Score® results were more likely to convert to breast conserving surgery
TransNEOS study

NAHT

ER+, HER2- early breast cancer post-menopausal women, T1c-T2, N0, receiving 24 weeks letrozole



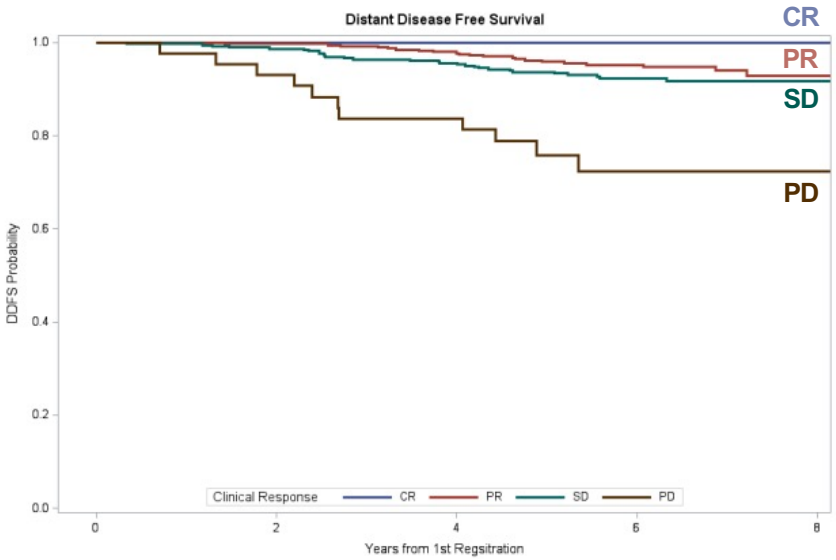
Iwata H et al. *Breast* Cancer *Res Treat*. 2018.

- Patients with **lowest Recurrence Score results were more likely to convert from non-candidates to actually receiving breast conserving surgery**
- RS results group was significantly associated with breast conserving surgery received after neoadjuvant endocrine treatment (p=0.010).

Patients treated with neoadjuvant endocrine therapy who did not progress had more favourable outcomes compared with those showing progressive disease

NAHT

Distant Disease-Free Survival according to clinical response (N=883)



- ✓ 95% of patients showed Complete / Partial Response or Stable Disease
- ✓ 5% of patients had progressive disease

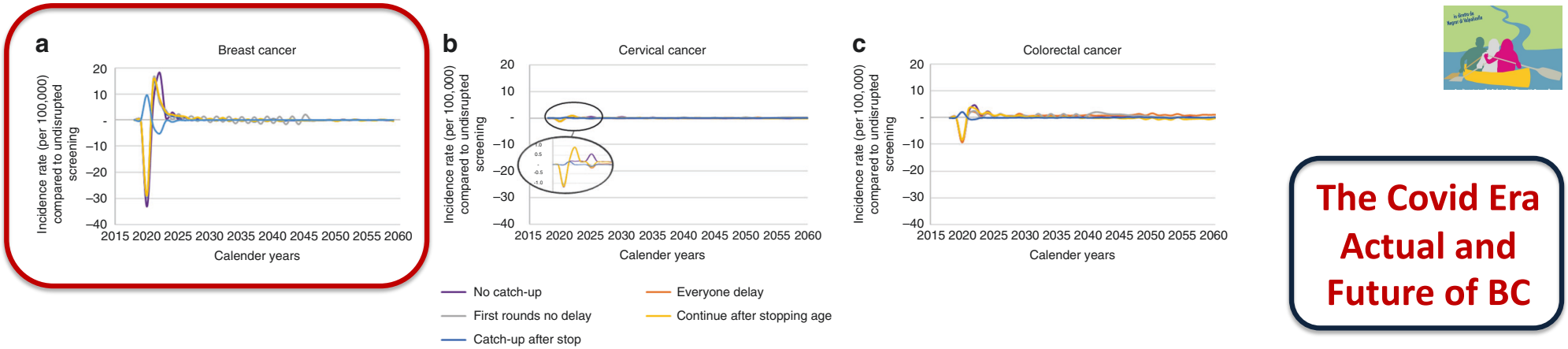
- ✓ **95% of patients treated with 24 wks of neoadjuvant letrozole showed complete / partial response or stable disease with more favourable 5-year DDFS outcomes compared with those showing progressive disease**

Iwata H, et al. ESMO 2018.

1. CDK4/6i in Adjuvant setting: myth or reality?

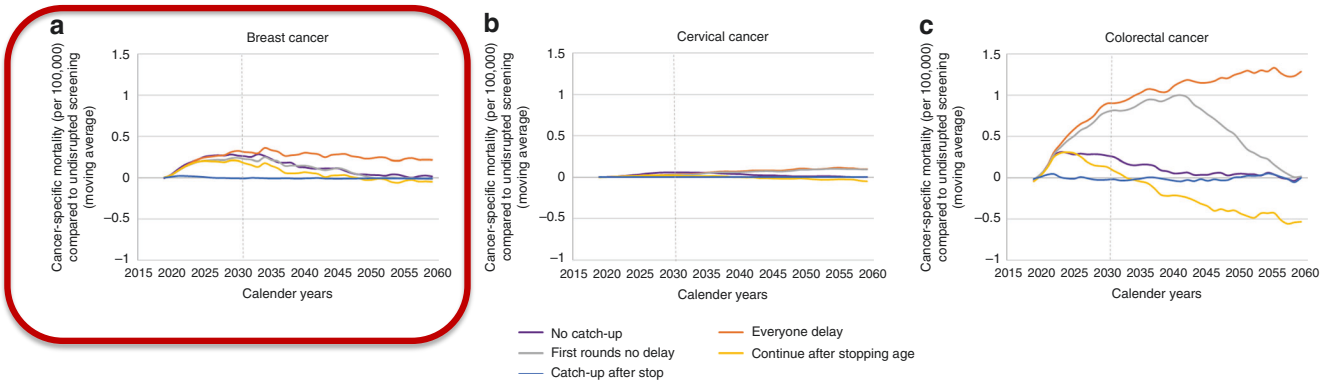
2. …In small steps towards NAHT

3. the delay of today, the precocity of tomorrow



The Covid Era Actual and Future of BC

Cancer incidence rate (per 100,000) after a 6-month disruption compared to undisrupted screening over time for the different restart strategies



Moving average of cancer-specific death rate (per 100,000) after a 6-month disruption compared to undisrupted screening over time for the different restart strategies

will we soon find ourselves treating more locally advanced BC ?