NCCN 2021 Virtual Congress: Breast Cancer
with Updates from the 2020 San Antonio Breast Cancer Symposium

Friday, February 12, 2021
1:15 PM – 2:15 PM EST

Adjuvant and Neoadjuvant Therapies for Breast Cancer, Including SABCS Updates

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National Comprehensive Cancer Network®

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Neoadjuvant Therapies for Breast Cancer, Including SABCS Updates

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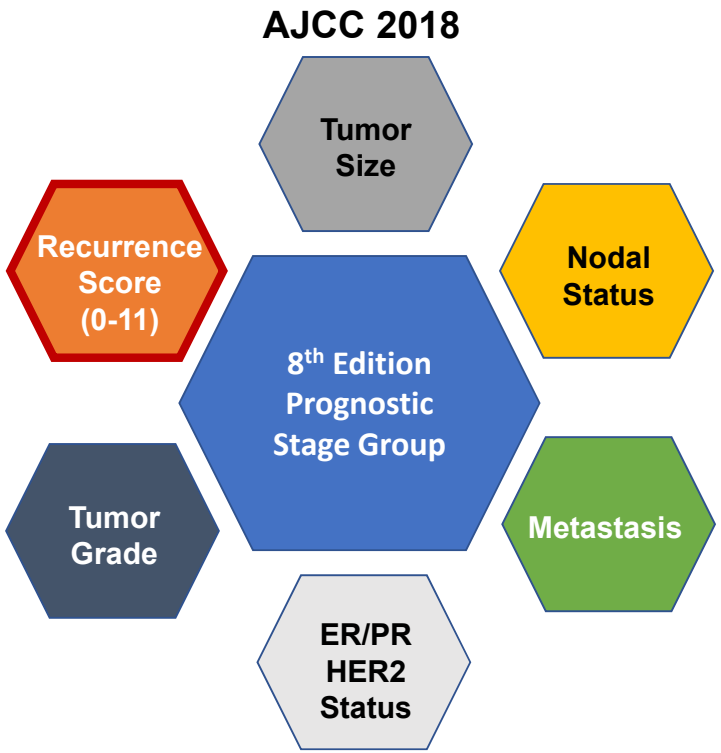
Treatment decisions: personalized risk assessment



Gene Expression Assays

Created to help de-escalate treatment in HR+ BC

Assay	Nodal Involvement	Predictive	Prognostic	Category of Preference
Oncotype DX (21-gene)	pN0 or node negative	Yes	Yes	Preferred[a]
	pN+ or node positive	Yes	Yes	Preferred[a]
MammaPrint (70-gene)	Node negative and 1-3 positive nodes	Not determined	Yes	Other[a]
PAM50 (50-gene)				Other[b]
EndoPredict (12-gene)				
Breast Cancer Index	NS			

Adapted from the NCCN Guidelines for Breast Cancer

Recurrence Score®: Continuous predictor of recurrence risk

16 Cancer and 5 Reference Genes From 3 Studies

PROLIFERATION
Ki-67
STK15
Survivin
Cyclin B1
MYBL2

ESTROGEN
ER
PR
Bcl2
SCUBE2

GSTM1

BAG1

INVASION
Stromelysin 3
Cathepsin L2

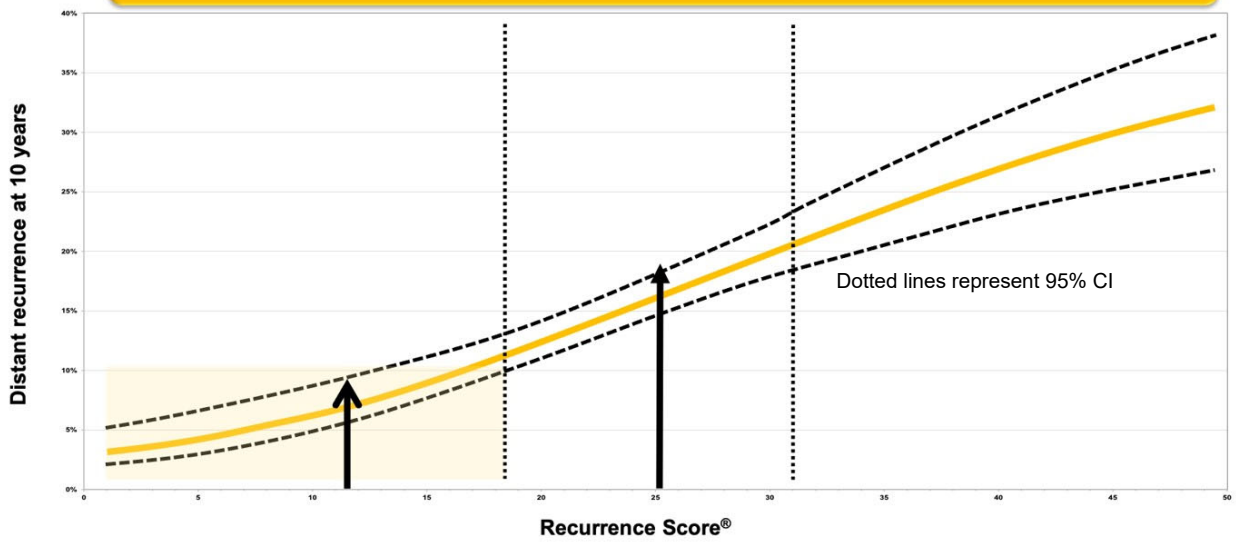
CD68

HER2
GRB7
HER2

REFERENCE
Beta-actin
GAPDH
RPLPO
GUS
TFRC

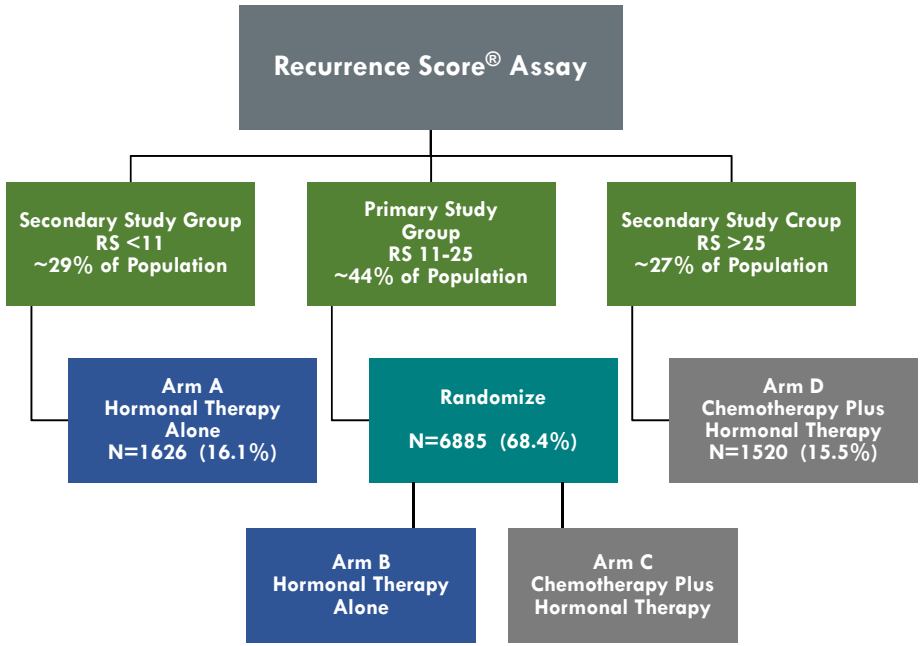
RS = + 0.47 x HER2 Group Score
- 0.34 x ER Group Score
+ 1.04 x Proliferation Group Score
+ 0.10 x Invasion Group Score
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x B

RS of 11 and 25 chosen as they represent the upper confidence interval for 10% and 20% risk of distant recurrence



Paik et al. NEJM 2004

TAILORx: prospective validation of a 21-gene expression assay in breast cancer



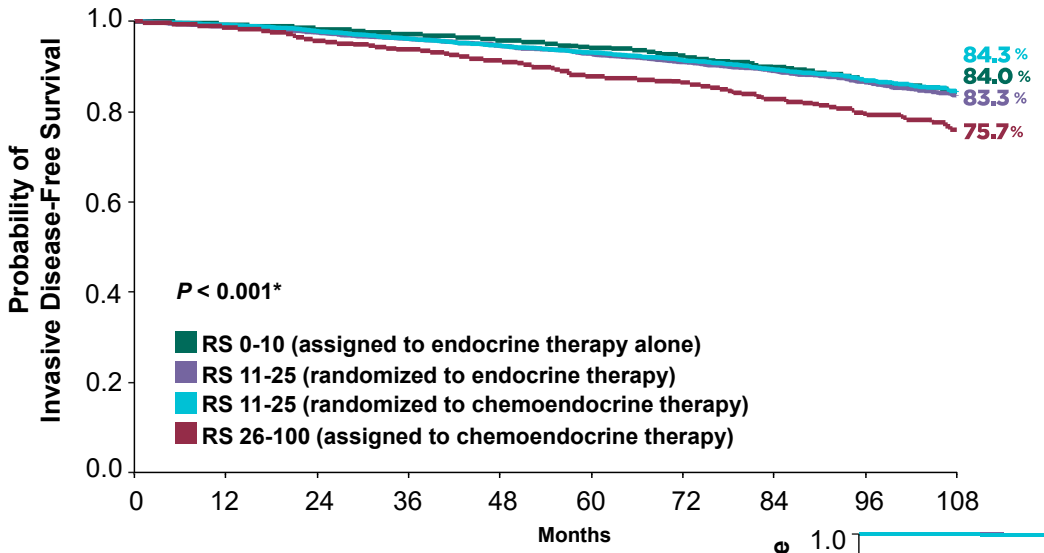
Eligible 10,253 pts prospectively enrolled (2006-2010)

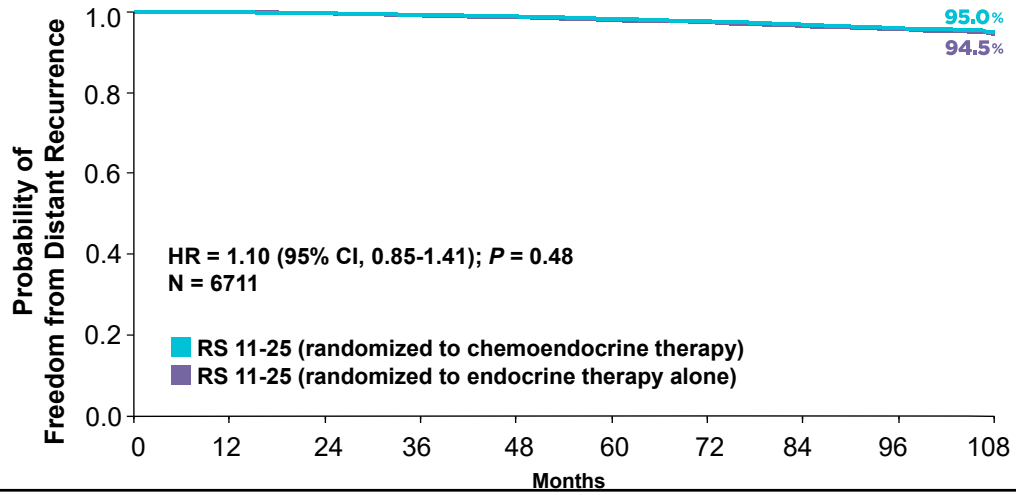
- Age < 50 years = 33-34%
- Age < 40 years = 5%
- ER and PR positive = 92%
- T size 2.1-3 cm = 19%
- T size > 3 cm = 5%
- Grade III = 13%
- Low clinical risk (per MINDACT criteria) = 74%

Sparano et al. NEJM 2015

TAILORx
iDFS and RFS

(IIT population)
9-Year Event Rates





Sparano et al. NEJM 2018

Are there subgroups that might derive some benefit from chemotherapy? Women ≤ 50 years of age

Statistically significant chemo treatment interactions

Age (≤ 50, 51-65, > 65 years) and chemo benefit

- IDFS (p = 0.003)
- DRFI (p = 0.02)

Age, Menopause, RS (11-15, 16-20, 21-25), and chemo benefit

- IDFS - Age-RS (p = 0.004)
- IDFS - Menopause-RS (p = 0.02)

RS 0-15: 3% distant recurrence with ET alone, no evidence for chemo benefit

RS 16-20: 9% fewer IDFS events with ET + Chemo, including **3.4% fewer** local + distant recurrences

RS 21-25: 6% fewer IDFS events with ET + Chemo, including **9.7% fewer** local + distant recurrences

Sparano et al. NEJM 2018

("TAILORx in 1-3 +LN")

RxPONDER a clinical trial

Rx for Positive Node, Endocrine Responsive Breast Cancer

Key Entry Criteria

- Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- breast cancer with 1*-3 LN+ without distant metastasis
- Able to receive adjuvant taxane and/or anthracycline-based chemotherapy**
- Axillary staging by SLNB or ALND

REGISTRATION

N = 5,000 pts

Recurrence Score 0-25

Recurrence Score > 25

Off Study
Chemotherapy Followed by
Endocrine Therapy Recommended

RANDOMIZATION

Arm 1:
Chemotherapy Followed by
Endocrine Therapy

Arm 2:
Endocrine Therapy Alone

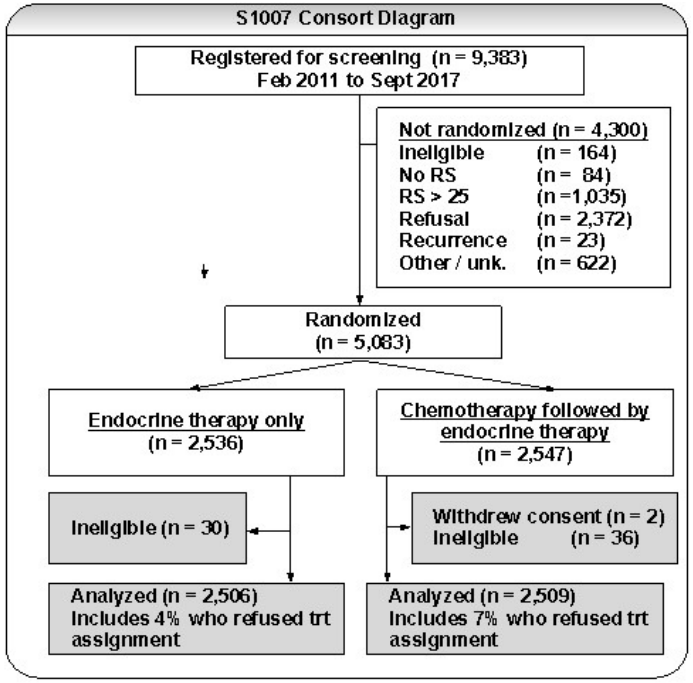
Stratification Factors
Recurrence Score: 0-13 vs.14-25
Menopausal Status: pre vs. post
Axillary Surgery: ALND vs. SLNB

Primary Objective: Determine the effect of chemotherapy on invasive disease-free survival (IDFS) in pts with 1-3 LN+ breast cancer and a RS ≤ 25 and assess whether the effect depends on the RS

* After randomization of 2,493 pts, the protocol was amended to exclude enrollment of pts with pN1mic as only nodal disease.
** Approved chemotherapy regimens included TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T). AC alone or CMF not allowed.

Kalinsky et al, SABCS 2020

RxPONDER Results: Accrual and ITT population



- ✓ 50% randomized to chemotherapy received TC (4 or 6 cycles)
- ✓ Ovarian function suppression use in premenopausal pts (6-month post randomization data)
  - 16% in the ET arm and 3% in Chemotherapy + ET arm
- ✓ 2 treatment-related deaths in ET arm (stroke) and 3 in chemotherapy + ET arm (sepsis, typhlitis, and liver necrosis)

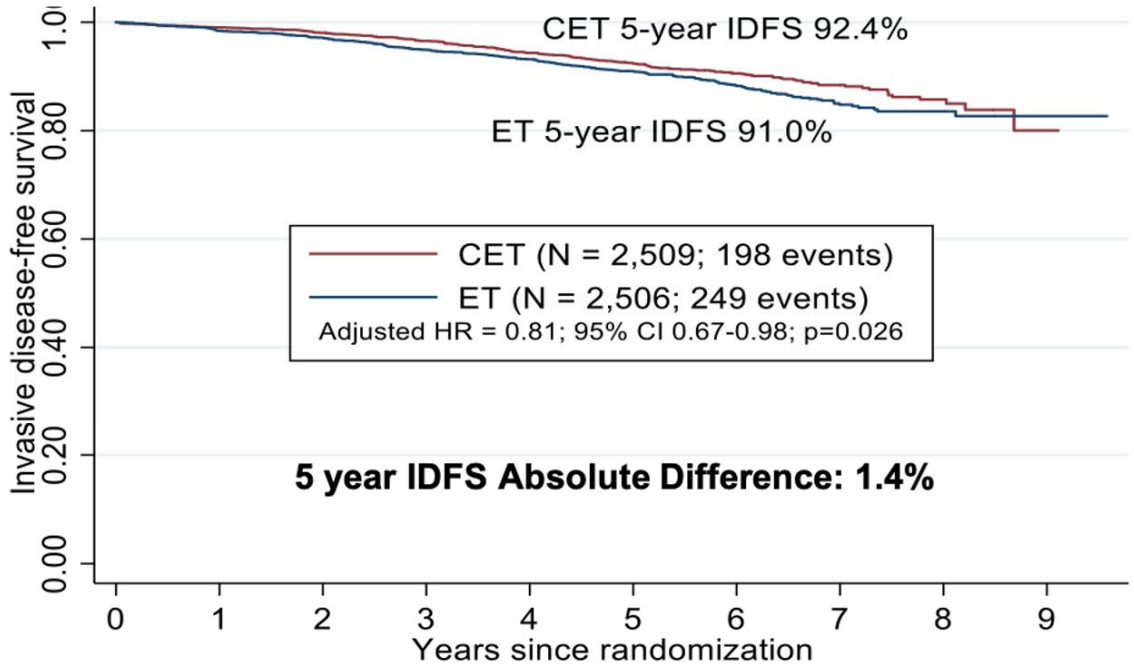
Kalinsky et al, SABCS 2020

Baseline variable	Endocrine Therapy (n=2,506)	Chemotherapy (n=2,509)	Overall (n=5,015)
Race			
White	64.9%	66.4%	65.7%
Black	4.8%	5.1%	5.0%
Asian	6.8%	6.1%	6.5%
Other/Unknown	23.5%	22.3%	22.9%
Hispanic			
Yes	13.0%	11.9%	12.4%
No	67.6%	68.9%	68.3%
Unknown	19.4%	19.3%	19.3%
Menopausal status			
Premenopausal	33.2%	33.2%	33.2%
Postmenopausal	66.8%	66.8%	66.8%
Recurrence Score			
RS 0-13	42.7%	42.9%	42.8%
RS 14-25	57.3%	57.1%	57.2%
Nodal Dissection			
Full ALND	62.7%	62.5%	62.6%
Sentinel nodes only	37.4%	37.5%	37.4%
Positive Nodes			
1 node	65.9%	65.0%	65.5%
2 nodes	24.9%	25.7%	25.3%
3 nodes	9.2%	9.2%	9.2%
Grade			
Low	24.6%	24.7%	24.7%
Intermediate	64.1%	66.1%	65.1%
High	11.3%	9.2%	10.3%
Tumor size			
T1	58.5%	57.7%	58.1%
T2/T3	41.5%	42.3%	41.9%

Baseline Characteristics

Kalinsky et al, SABCS 2020

IDFS in Overall Population by Treatment Arm



Number at risk

CET	2509	2277	2104	1893	1648	1397	857	403	122	4
ET	2506	2327	2161	1910	1696	1404	846	397	135	11

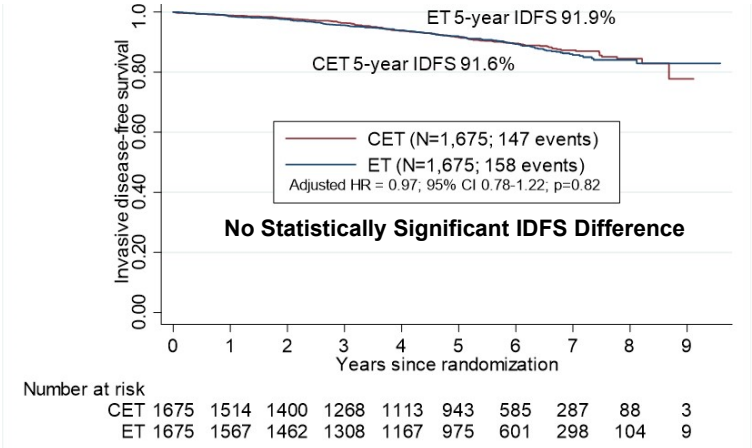
CET = Chemotherapy + Endocrine Therapy; ET = Endocrine Therapy Alone

447 observed IDFS events (54% of expected at final analysis) at a median follow-up of 5.1 years

Kalinsky et al, SABCS 2020

IDFS Stratified by Menopausal Status

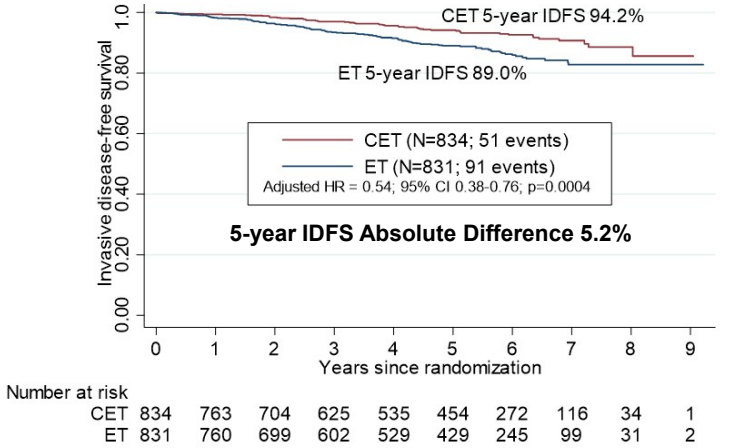
Postmenopausal



IDFS Event	CET	ET	Total (%)
Distant	39	44	83 (27%)
Local-Regional	10	14	24 (8%)
Contralateral	10	9	19 (6%)
Non-Breast Primary	44	47	91 (30%)
Recurrence Not Classified	9	7	16 (5%)
Death not due to Recurrence or Second Primary	35	37	72 (24%)

Absolute Difference in Distant Recurrence as 1st site: 0.3% (2.3% CET vs. 2.6% ET)

Premenopausal



IDFS Event	CET	ET	Total (%)
Distant	26	50	76 (54%)
Local-Regional	8	17	25 (18%)
Contralateral	4	8	12 (8%)
Non-Breast Primary	10	10	20 (14%)
Recurrence Not Classified	1	1	2 (1%)
Death not due to Recurrence or Second Primary	2	5	7 (5%)

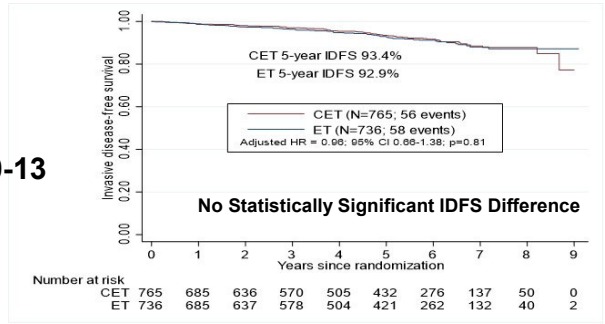
Absolute Difference in Distant Recurrence as 1st site: 2.9% (3.1% CET vs. 6.0% ET)

Kalinsky et al, SABCS 2020

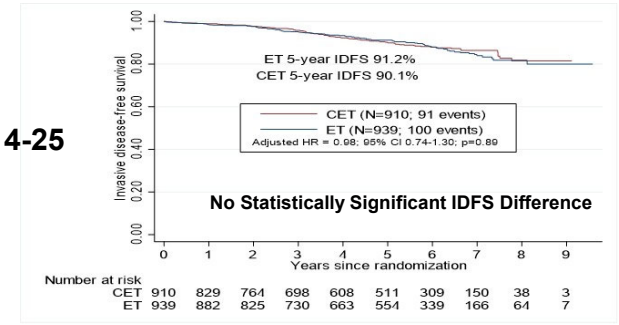
IDFS Stratified by Recurrence Score and Menopausal Status

Postmenopausal

RS 0-13

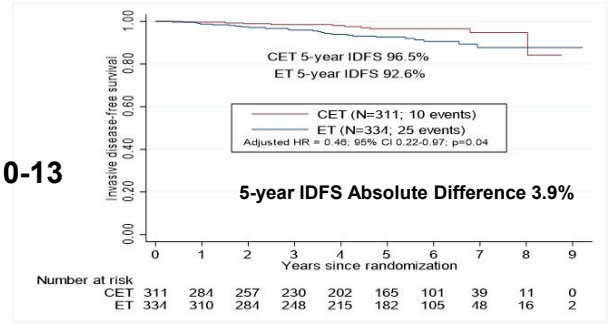


RS 14-25

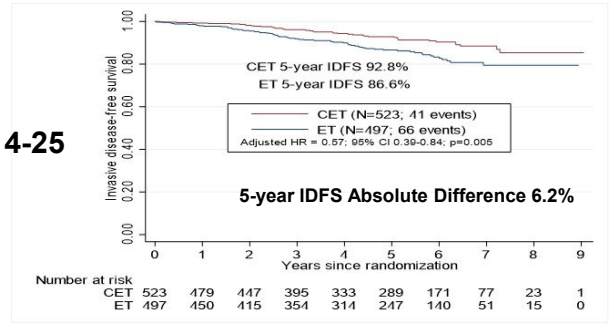


Premenopausal

RS 0-13



RS 14-25

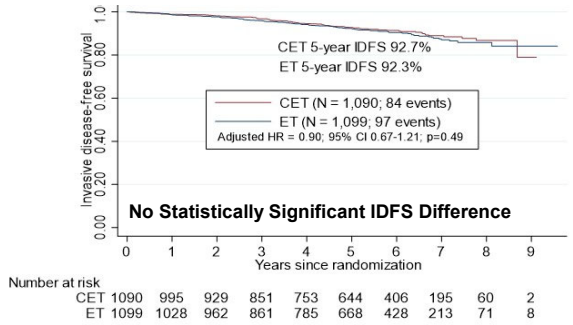


Kalinsky et al, SABCS 2020

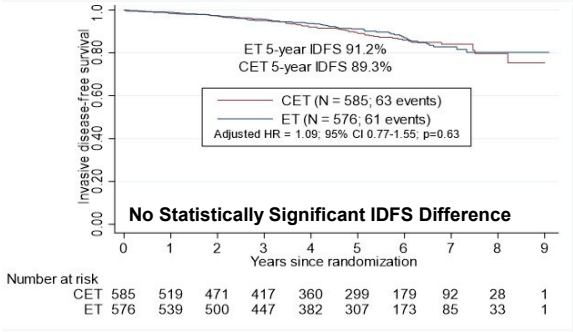
IDFS Stratified by Number of Nodes and Menopausal Status

Postmenopausal

1 Node

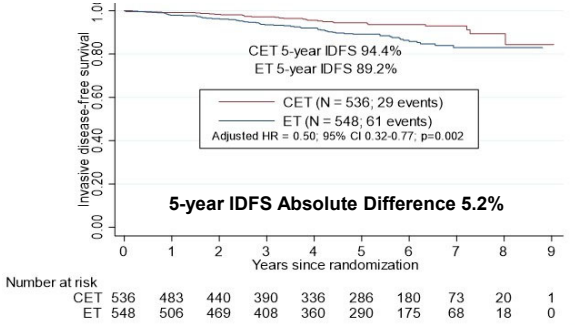


2-3 Nodes

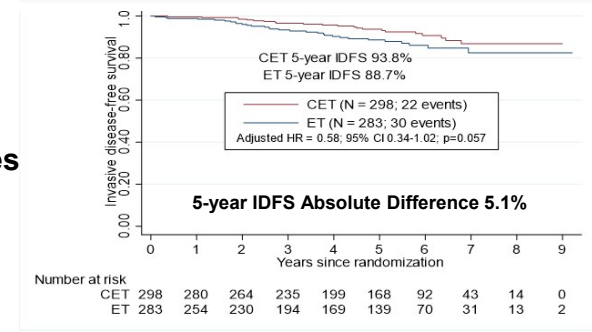


Premenopausal

1 Node



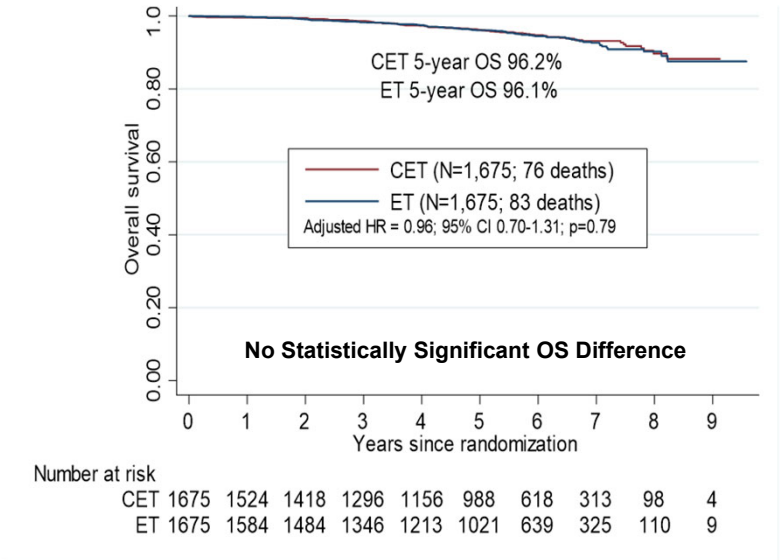
2-3 Nodes



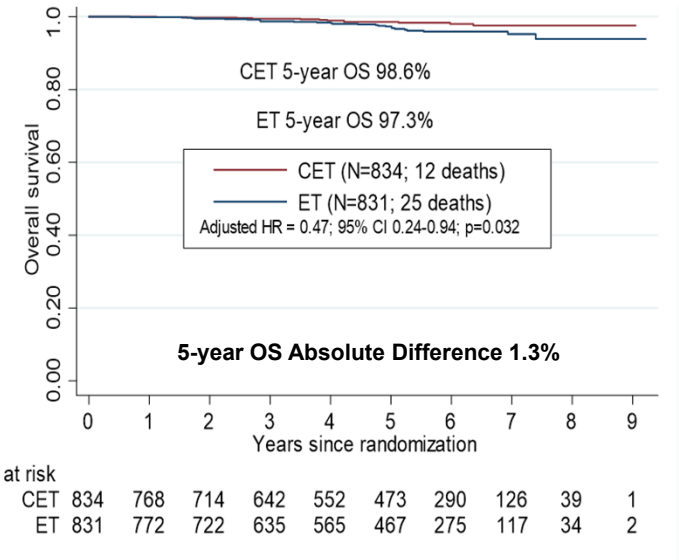
Kalinsky et al, SABCS 2020

Overall Survival by Menopausal Status

Postmenopausal

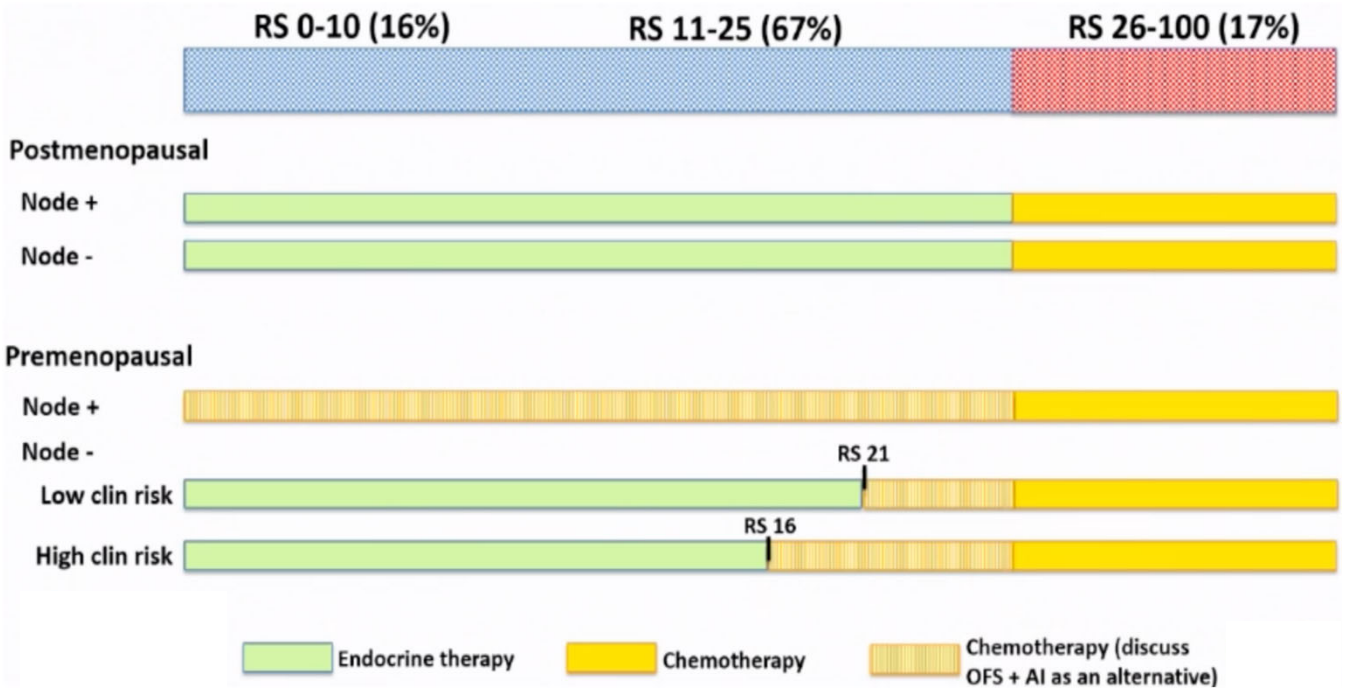


Premenopausal



Kalinsky et al, SABCS 2020

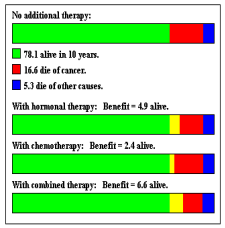
So how do we incorporate this into practice?



Since postmenopausal women don't seem to benefit from chemo, do they really need ALND if + SNLB?

How much benefit do premenopausal women really get from chemo vs. ovarian suppression??

MINDACT Trial Design: 8.7 years median follow-up

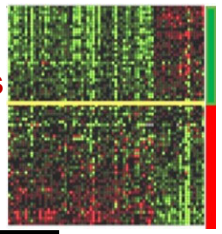


MINDACT population:

HR+/HER2-	**81%**
HER2+	9.5%
TNBC	9.6%
Enrollment 2007-2011	

Registration & Screening
Surgery

6693 patients | **112 hospitals, 9 countries**



Clinical-Pathological (C) risk
(Adjuvant! Online)

Genomic (G) risk
(70-gene signature)

C-low/G-low

Discordant cases
C-low/G-high or C-high/G-low

C-high/G-high

C-Low per modified Adjuvant! Online: 10-year BCS without AT of >88% for ER+ and >92% for ER-

1st randomization to treatment
use Clinical vs. Genomic risk

MINDACT main hypothesis:
can C-High / G-Low patients safely forego chemotherapy?

No Chemotherapy

2nd randomization
Anthracycline –based vs. Capecitabine-Docetaxel

Chemotherapy

HR+

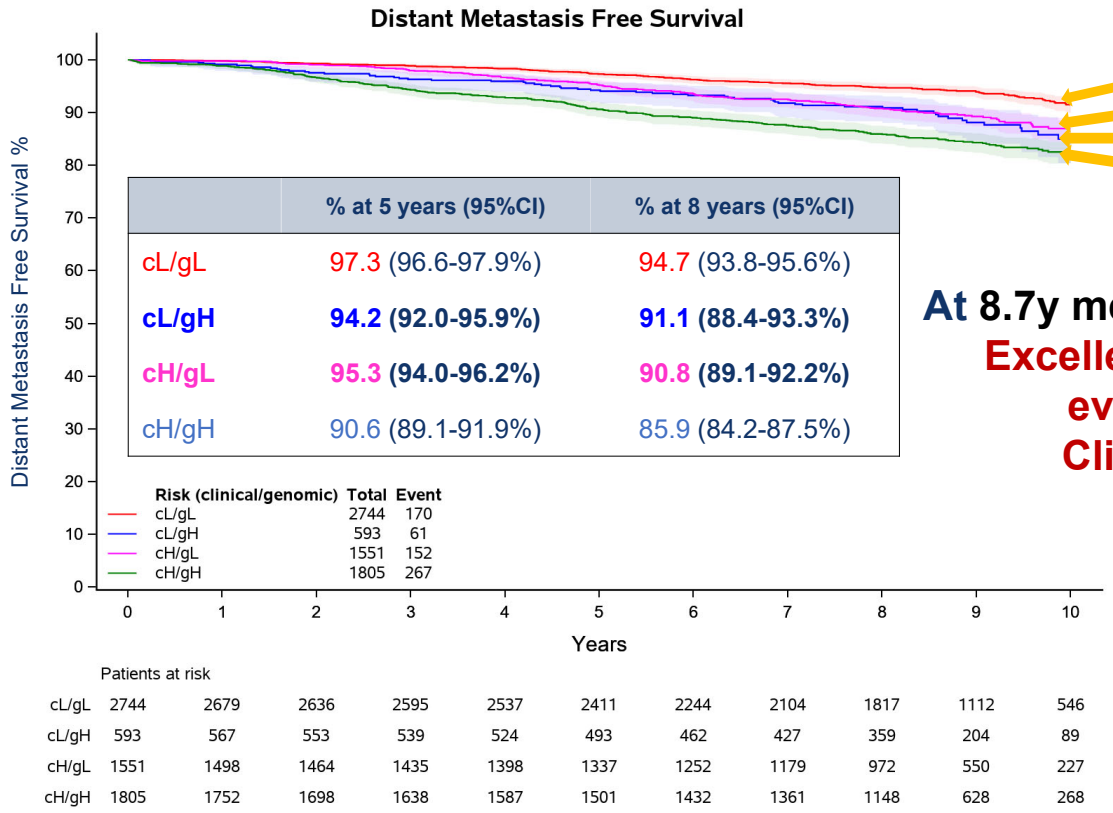
HR+

Endocrine therapy

3rd randomization
Tamoxifen 2y / Letrozole 5y vs. Letrozole 7y

Vantveer et al., SABCS 2020

MINDACT results: all patients across 4 risk groups



	% at 5 years (95%CI)	% at 8 years (95%CI)
cL/gL	97.3 (96.6-97.9%)	94.7 (93.8-95.6%)
cL/gH	**94.2 (92.0-95.9%)**	**91.1 (88.4-93.3%)**
cH/gL	**95.3 (94.0-96.2%)**	**90.8 (89.1-92.2%)**
cH/gH	90.6 (89.1-91.9%)	85.9 (84.2-87.5%)

Concordant C-Low / G-Low N=2744
Discordant C-Low / G-High N=593
Discordant C-High / G-Low N=1551
Concordant C-High / G-High N=1805

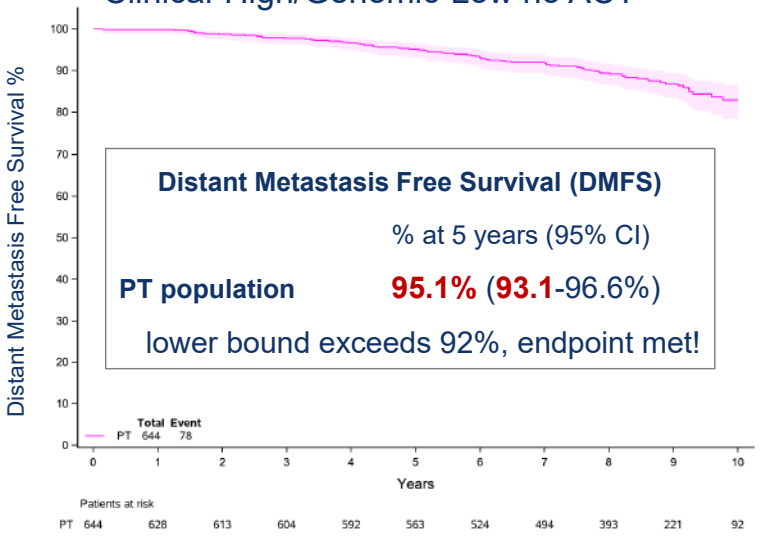
At 8.7y median FU, DMFS in 4 risk groups
Excellent prognosis and low rate of events in all groups except Clinical High/Genomic High

Type of first event (n = 650)
- distant recurrences: 68.8%
- death of any cause: 31.2%

Vantveer et al., SABCS 2020

PRIMARY ENDPOINT

Clinical-High/Genomic-Low no ACT



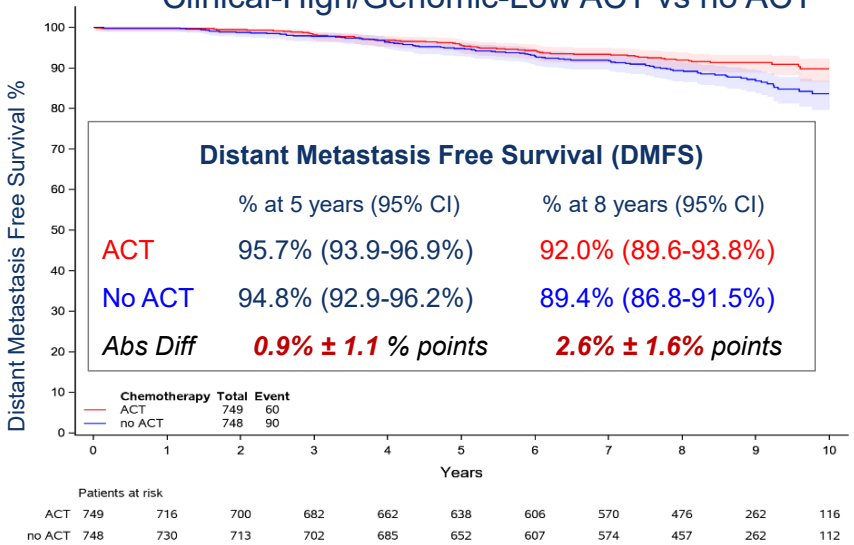
Distant Metastasis Free Survival (DMFS)

	% at 5 years (95% CI)
PT population	**95.1%** (**93.1**-96.6%)

lower bound exceeds 92%, endpoint met!

SECONDARY ENDPOINT

Clinical-High/Genomic-Low ACT vs no ACT



Distant Metastasis Free Survival (DMFS)

	% at 5 years (95% CI)	% at 8 years (95% CI)
ACT	95.7% (93.9-96.9%)	92.0% (89.6-93.8%)
No ACT	94.8% (92.9-96.2%)	89.4% (86.8-91.5%)
Abs Diff	***0.9% ± 1.1** % points*	***2.6% ± 1.6%** points*

At 8.7 years medium F/U:

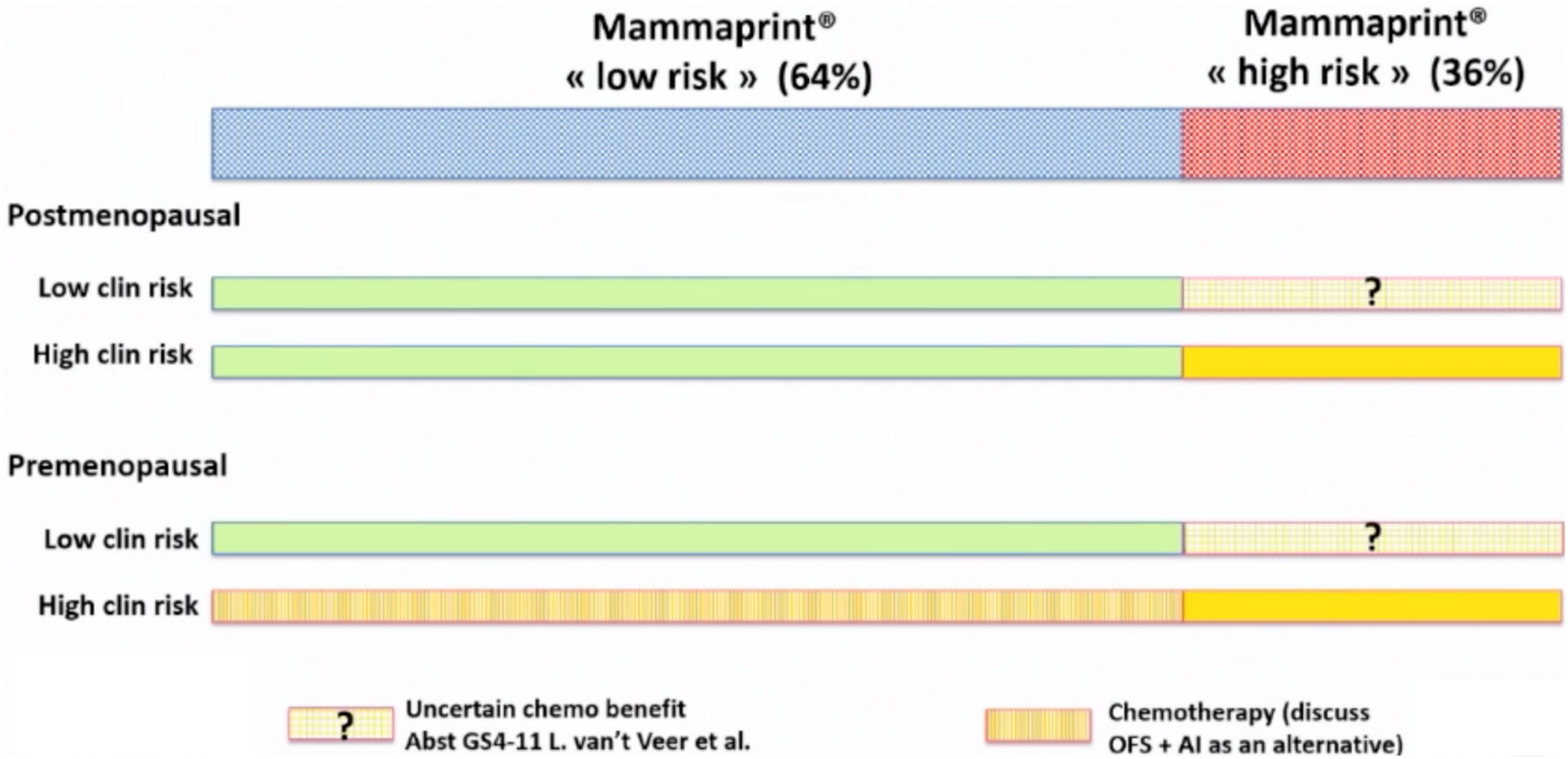
- **Primary endpoint continues to be met in CT untreated C-High/G-Low risk patients**, **confirming MINDACT as a positive de-escalation study**
- The estimated **DMFS gain for CT administration** in **C-High/G-Low is 2.6%** and must be balanced with CT harmful side effects
- Among clinical high-risk patients, **reduction of the use of CT in 46% patients,** when following genomic risk strategy

Exploratory analysis by age (≤ 50 and > 50 years) **omitting CT** in C-High/G-Low in:

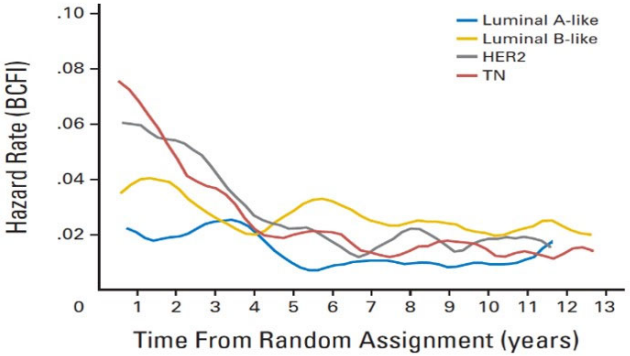
- **postmenopausal women** continues to be **safe** (DMFS gain 0.2% ± 2.3%) at 8 years
- **premenopausal women** show a **clinically relevant difference** of DMFS gain 5% ± 2.8% at 8 years. ***This later effect may possibly be related to chemotherapy-induced ovarian function suppression***

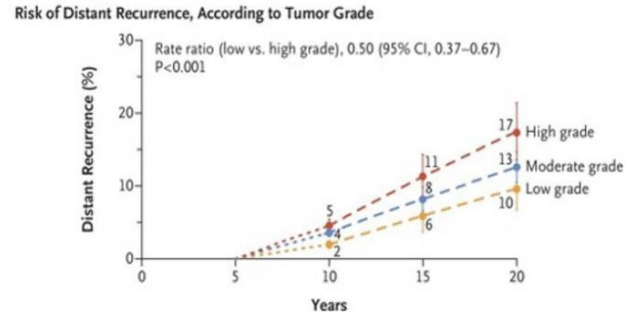
Vantveer et al., SABCS 2020

So how do we incorporate this into practice?



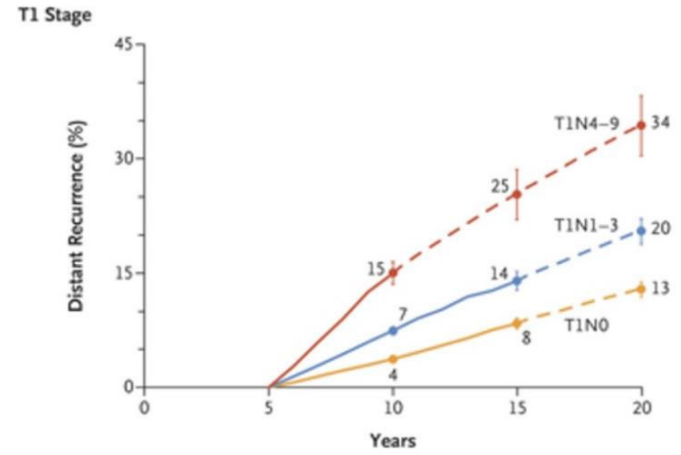
Risk of recurrence remains after 5 years adjuvant ET across all clinical stages





No. at Risk

High grade	3054	1010	188	2
Moderate grade	7363	2761	474	6
Low grade	3524	1258	239	6



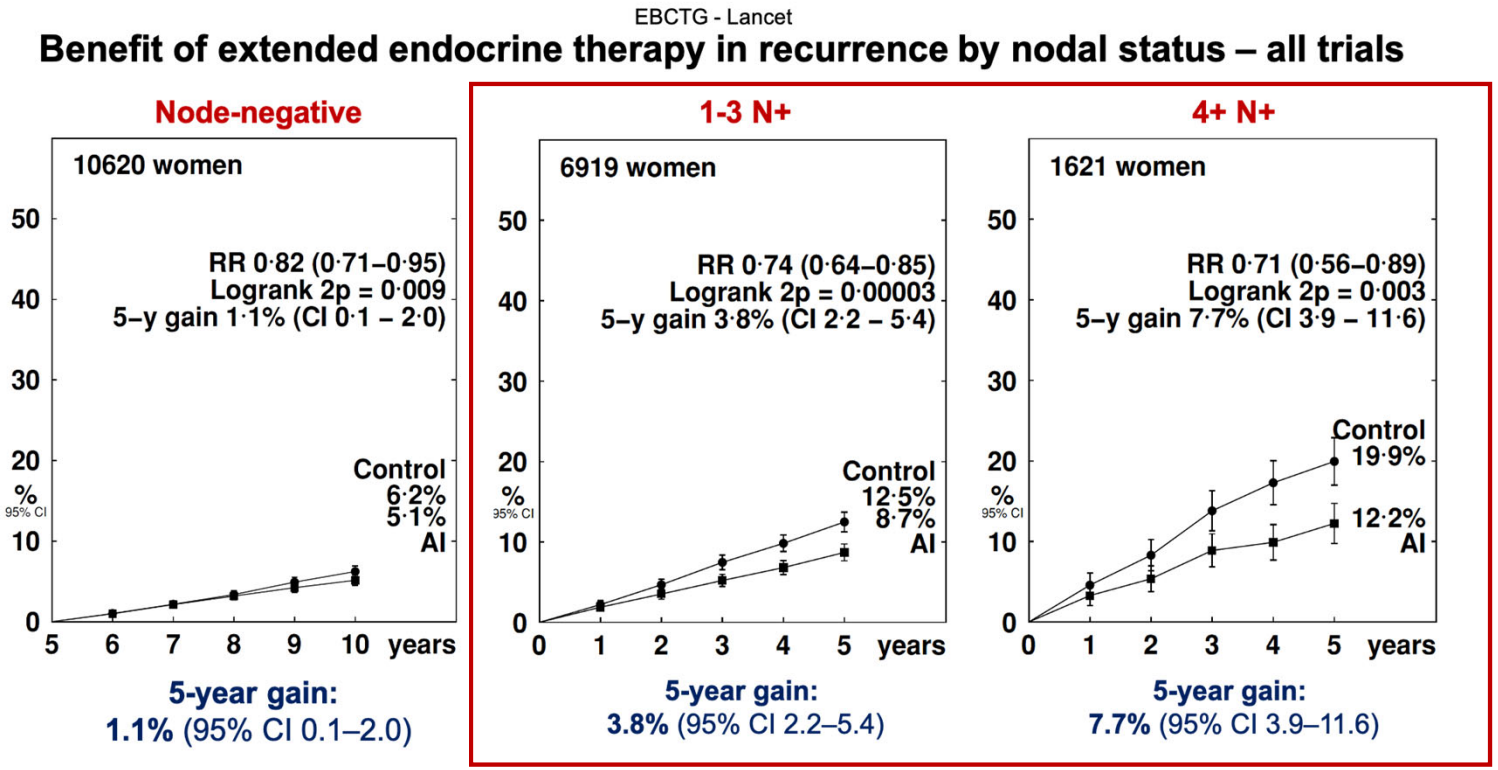
No. at Risk

T1N4–9	3,832	1193	214	32
T1N1–3	14,342	5138	817	154
T1N0	19,402	8020	2345	440

…especially in patients with high-risk features

Metzger-Filho et al. JCO 2013; Pan et al. NEJM 2017

EBCTG metanalysis: benefit of extended ET in +LNs



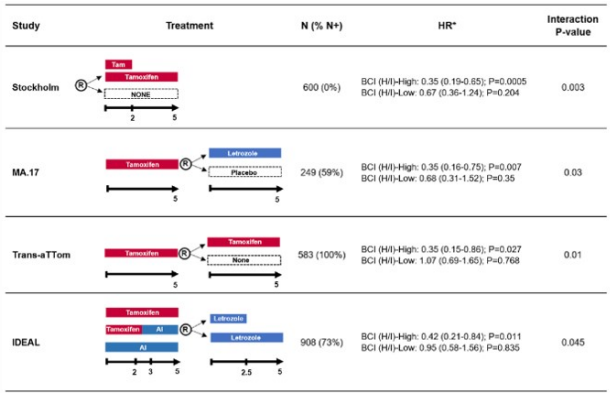
Can we refine who needs extended (~10 years) endocrine therapy?

Breast Cancer Index (BCI)

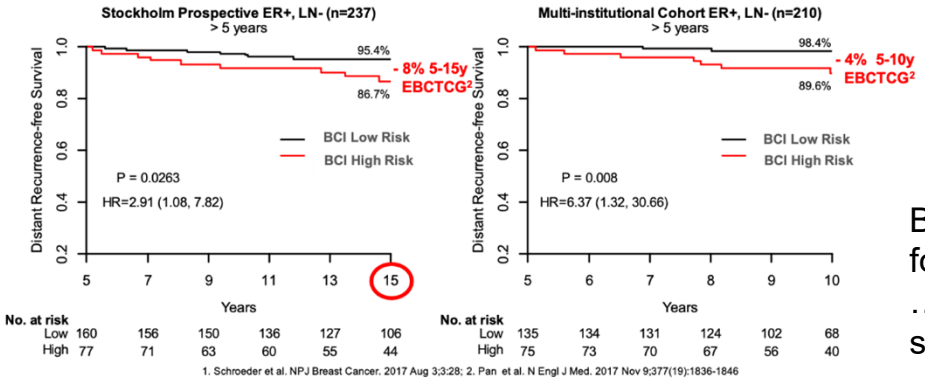
BCI Prognostic
Molecular Grade Index (MGI): *BUB1, CENPA, NEK2, RACGAP1, RRM2*
+
H/I
HOXB13/IL17BR

BCI Predictive
H/I
HOXB13/IL17BR

Noordhoek I et al, CCR 2020

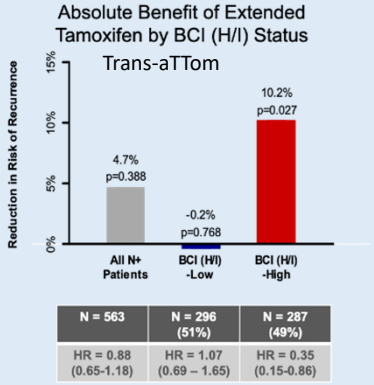


BCI risk analysis in T1N0 patient subset from 2 published study cohorts[1]



1. Schroeder et al. NPJ Breast Cancer. 2017 Aug 3;3:28; 2. Pan et al. N Engl J Med. 2017 Nov 9;377(19):1836-1846

It is reasonable to use BCI (H/I) to detect patients with +LNs that could be SPARED of (over)extended ET, but longer follow-up may be needed



Bartlett et al. Annals of Oncol 2019 doi:10.1093/annonc/mdz289

More data is needed to explore the PREDICTIVE role of BCI (H/I) for extended ET in clinical low risk patients

BCI (H/I) High: detects clinically low risk patients at risk for late recurrence (prognosis)
… But we don't know if and how much benefit this specific group derives from extended ET (prediction???)

Which ER+ breast cancers can safely forego, or need adjuvant chemotherapy in addition to endocrine therapy?

- **Anatomical risk**
  - Tumor size
  - Nodal status

Defines risk of recurrence but not sensitivity to any treatment modality

- **Baseline gene expression profiles (GEP)**
  - Recurrence Score®
  - MammaPrint
  - EndoPredict
  - Breast Cancer Index
  - Prosigna ROR

Capture elements of endocrine and chemotherapy sensitivity AND are prognostic risk variables independent of anatomical risk

Accurate **absolute risk** prediction requires both anatomic and GEP variables

- **Endocrine therapy response-guided**
  - Ki-67 response
  - PEPI score

1. Could early (week 2-4) Ki67 response identify patients who do, or do not, need chemo?
2. Is this strategy “superior” or “additive” to GEP-based treatment recommendations?

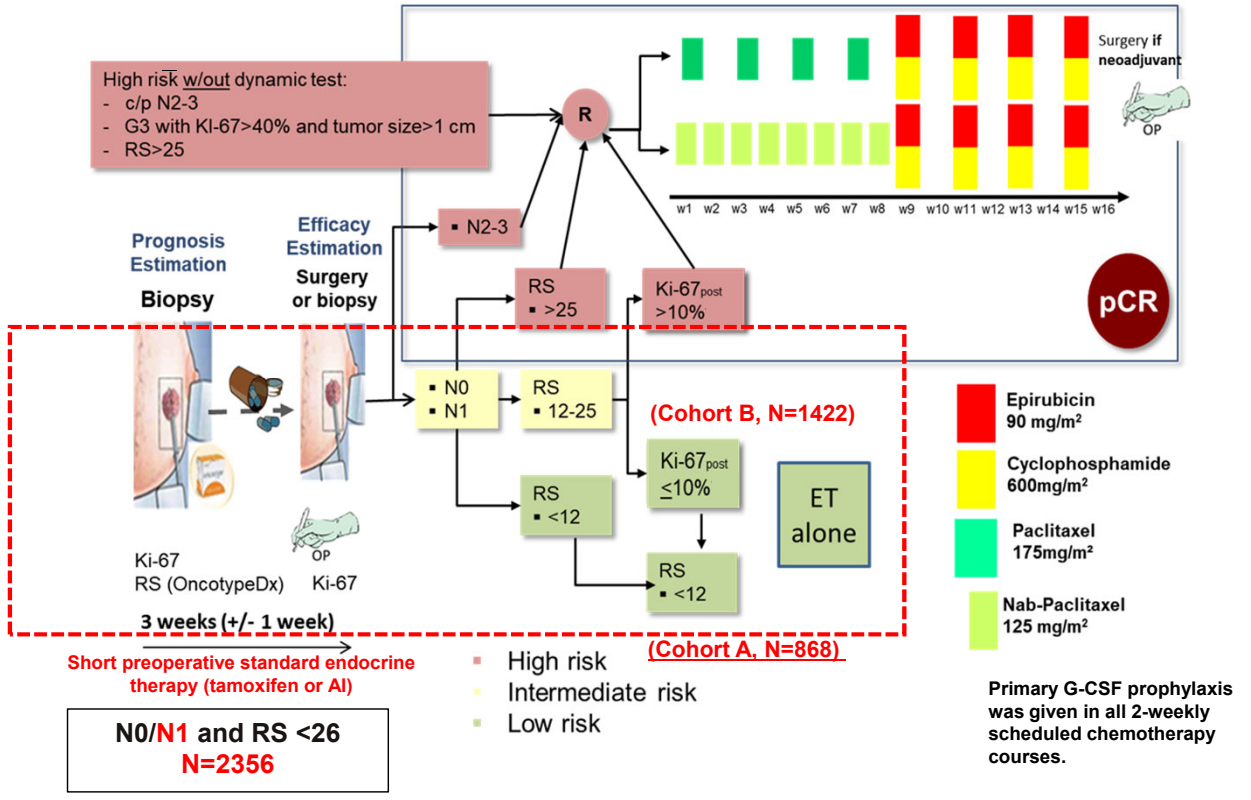
ADAPT HR+/HER2- trial

Do patients with an RS between 12 - 25 who had a Ki67 response to < 10% after 3-4 weeks of ET have the same excellent outcome as patients with RS < 12 when treated with ET alone?

Neoadjuvant chemotherapy sub-trial criteria:

- cN2-3 or
- Or RS 12-25 and KI67$_{post}$>10% in cN0-1 tumors or
- RS>25 or
- G3 with Ki67≥40% in tumors >1 cm

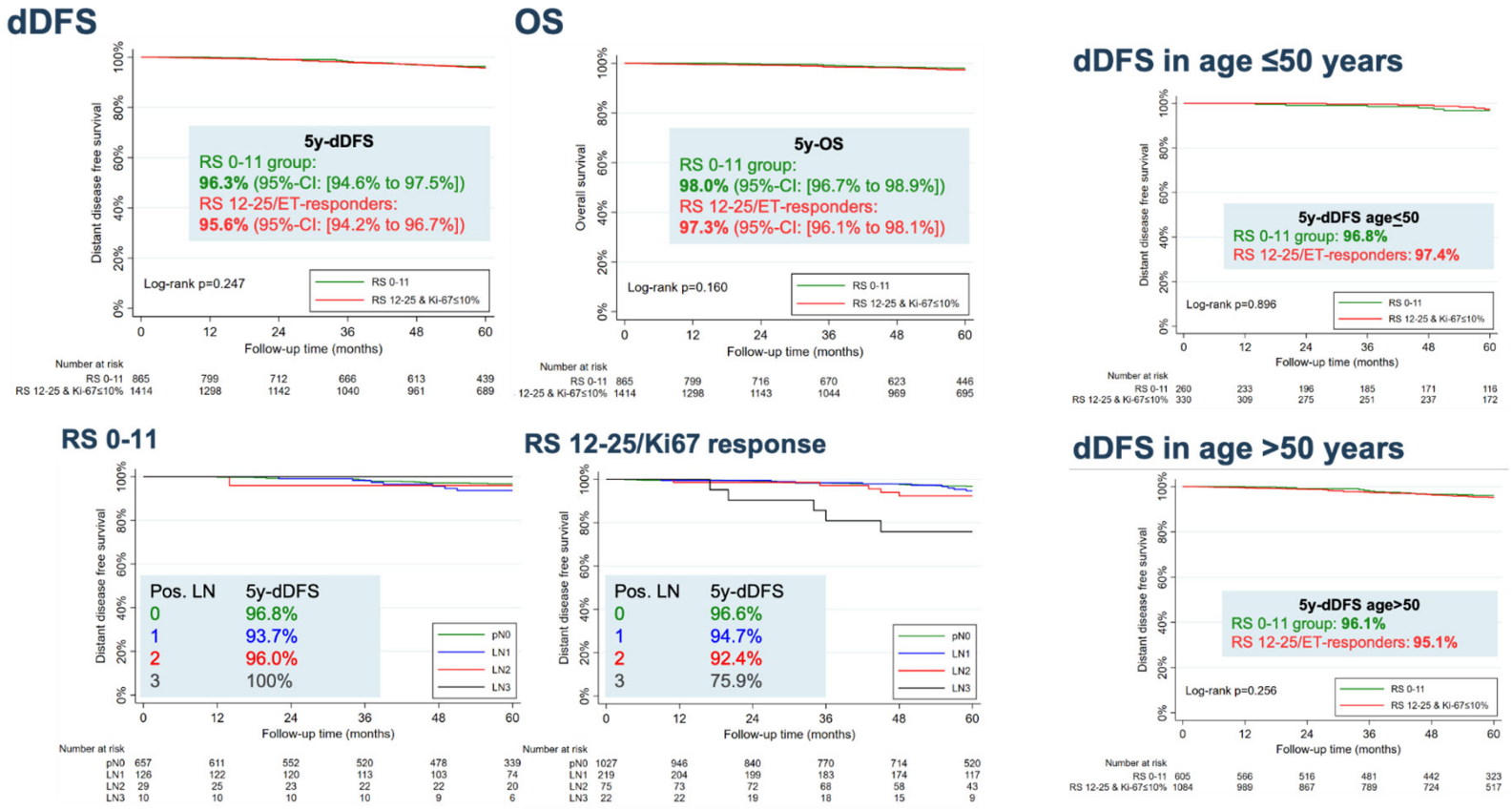
- Female patients ≥18 years old
- ER and/or PR positive (≥1%)/ HER2-negative unilateral EBC
- cT1-4c, cN0-3 stage
- **Candidates for adjuvant chemotherapy by conventional prognostic criteria:** cT2 or G3 or Ki67≥15% or <35 years old or cN+



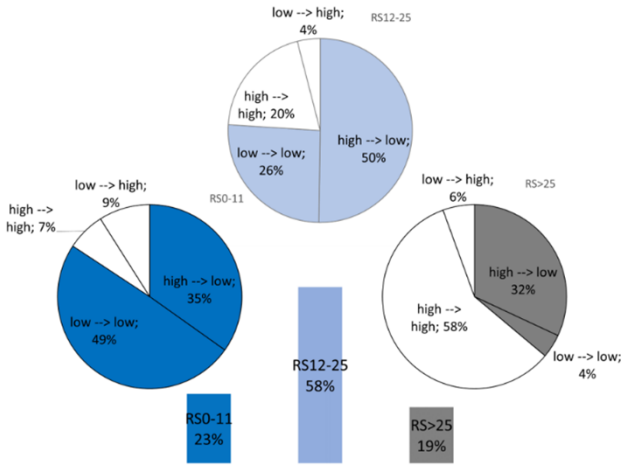
Harbeck et al. SABCS2020

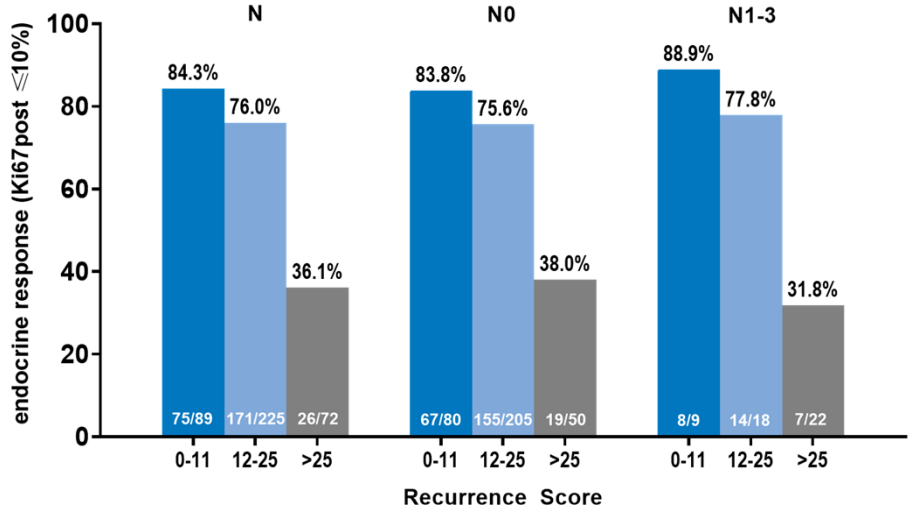
5-year iDFS is not significantly different by non-inferiority threshold between the two RS cohorts

Harbeck et al. SABCS2020



Ki67 response is more common in RS < 26





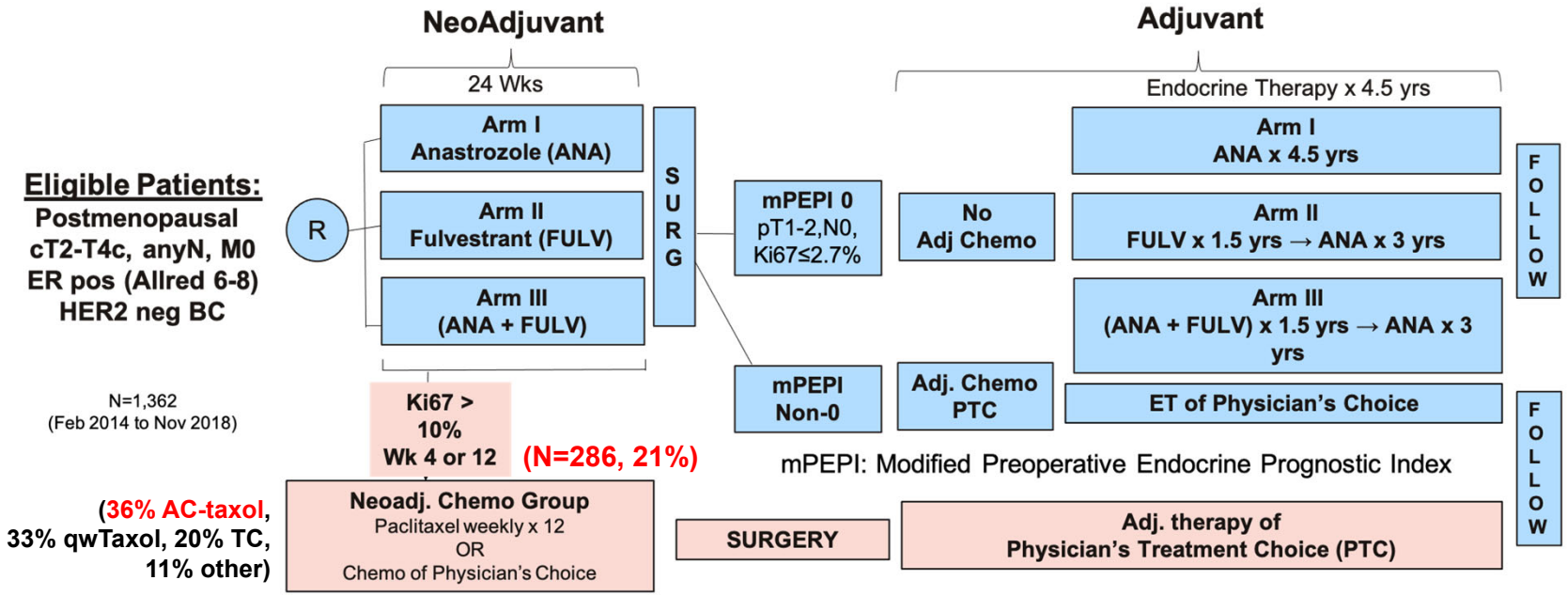
UNANSWERED QUESTIONS:

- **RS 12-25 group with Ki67 > 10% after 3 weeks of ET:**
  would they have done well with ET alone?

- **Is the week-3 Ki67 information necessary,**
  or is the RS score alone sufficient to recommend ET alone if RS <26?
  - **75% patients had < 10% Ki67**

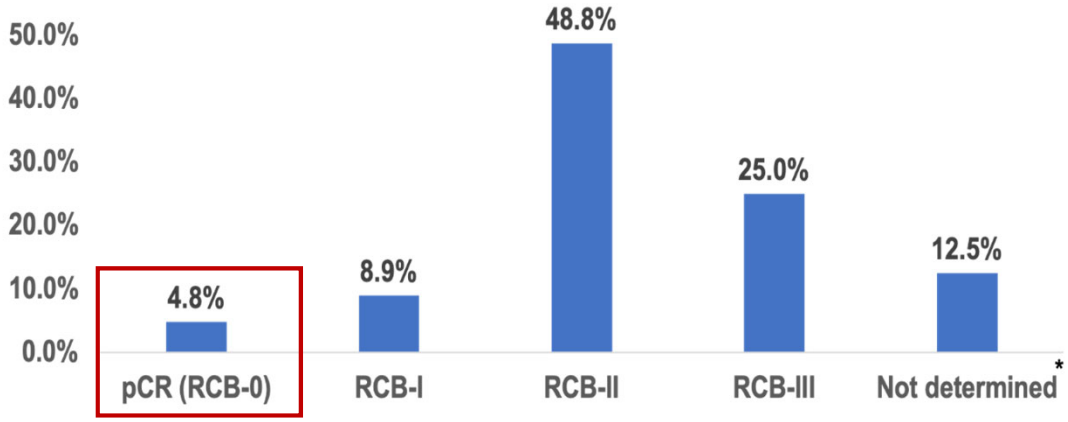
Harbeck et al. SABCS2020

Neoadjuvant chemotherapy response in postmenopausal women with clinical stage II or III ER+ BC resistant to endocrine therapy in the ALTERNATE trial (Alliance A011106)



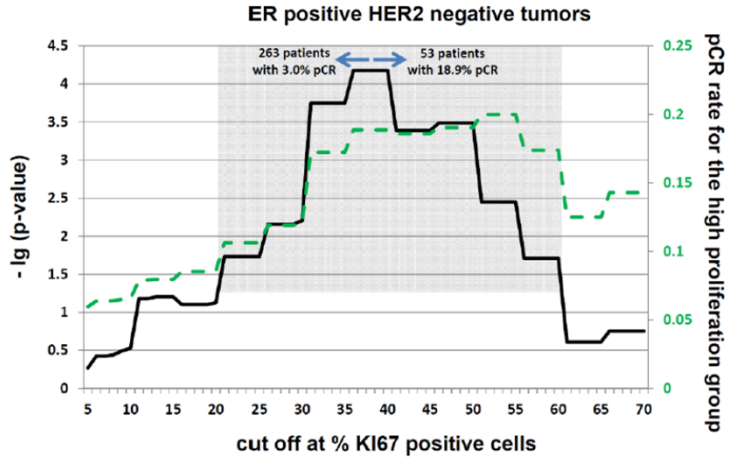
The Primary Endpoint: The Endocrine Sensitive Disease (ESD: pCR + mPEPI 0) rate in FULV or FULV + ANA arm was not significantly higher than that of the ANA arm (Ma, C et al ASCO 2020).

Ma et al, SABCS2020

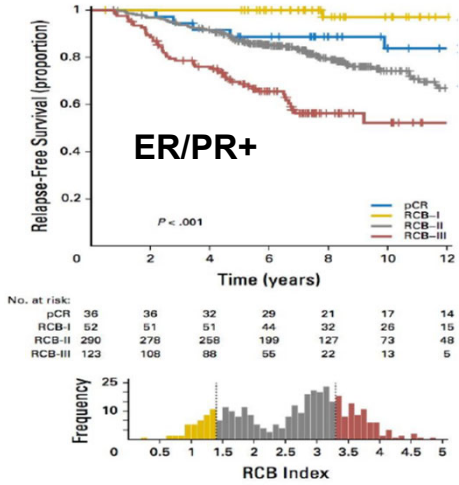


Ma et al, SABCS2020

Ki67 is not a very strong predictor of pCR



Fasching et al. BMC Cancer 2011



Symmans et al. JCO 2017

As the bulk of the Ki67 levels were between 10-30% in the ALTERNATE trial, the low pCR rate is not surprising

Longer f/u needed to know if the lack of pCR will indeed imply lack of IDFS benefit from chemotherapy in these patients

Conclusions

"Less is more":

- **Tailoring chemotherapy recommendations for patients with HR+ BC:**

➢ **RS < 26 in post-menopausal women with 0-3+LNs – no chemo needed**

➢ **Jury still out in pre-menopausal women with RS < 26**

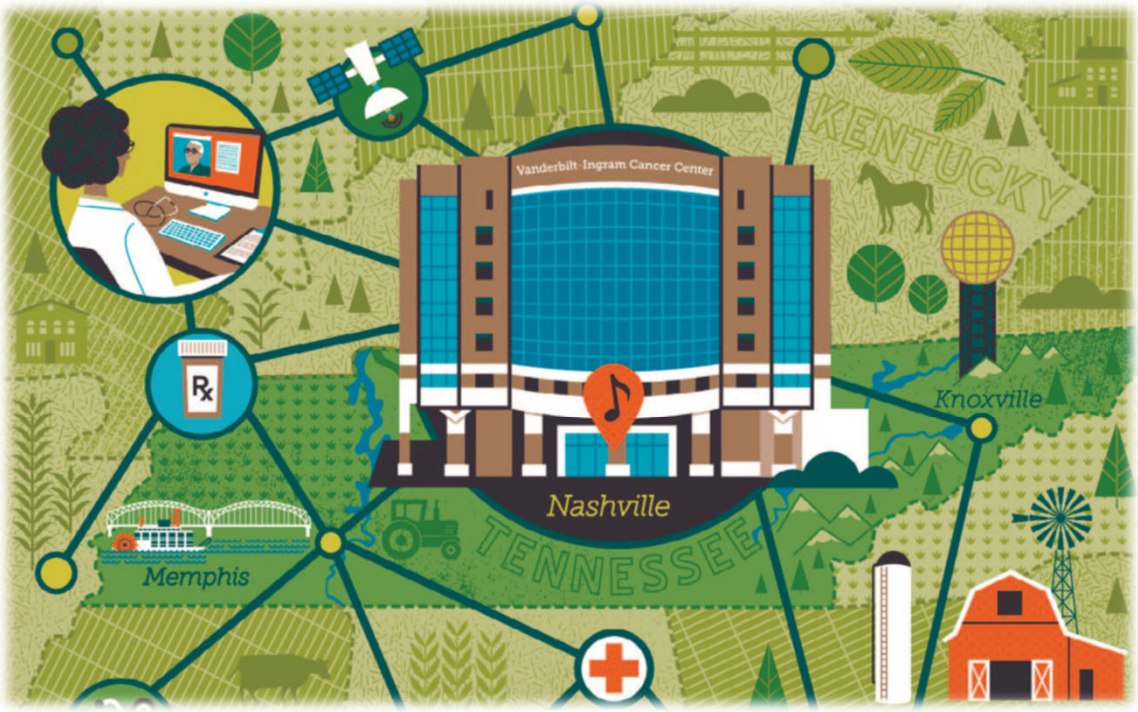
- ❑ **No point in ordering RS in LN+ disease for now**
- ❑ **(VERY limited) benefit of chemo in LN- disease in RS 16 – 25 may be due to ovarian suppression**

- **Extended AI therapy could be considered in high-risk post-menopausal patients with HR+**

➢ **BCI (H/I) low may spare women with LN+ from prolonged treatment**

- **Ki67 as a "triage" marker for chemo or endocrine therapy benefit may not be so useful in the era of gene expression signatures…**

THANK YOU!



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NCCN 2021 Virtual Congress: Breast Cancer
with Updates from the 2020 San Antonio Breast Cancer Symposium

Adjuvant Therapies for Breast Cancer, Including SABCS Updates

Erica M. Stringer-Reasor, MD
O'Neal Comprehensive Cancer Center at UAB

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ADJUVANT THERAPY UPDATES -- OUTLINE

- **De-escalation**
  - RxPonder (SABCS 2020)
  - RS-Clin - - > validation of individualization tool (SABCS 2020)
  - ADAPT HR+/HER2-: Short pre-op ET to select patients for ET alone (SABCS 2020)
- **Extended Adjuvant Endocrine Therapy**
  - BCI (SABCS 2020)
- **CDK4/6 inhibitors**
  - MonarchE (SABCS 2020)
  - PENELOPE-B (SABCS 2020)
  - PALLAS (ESMO 2020)

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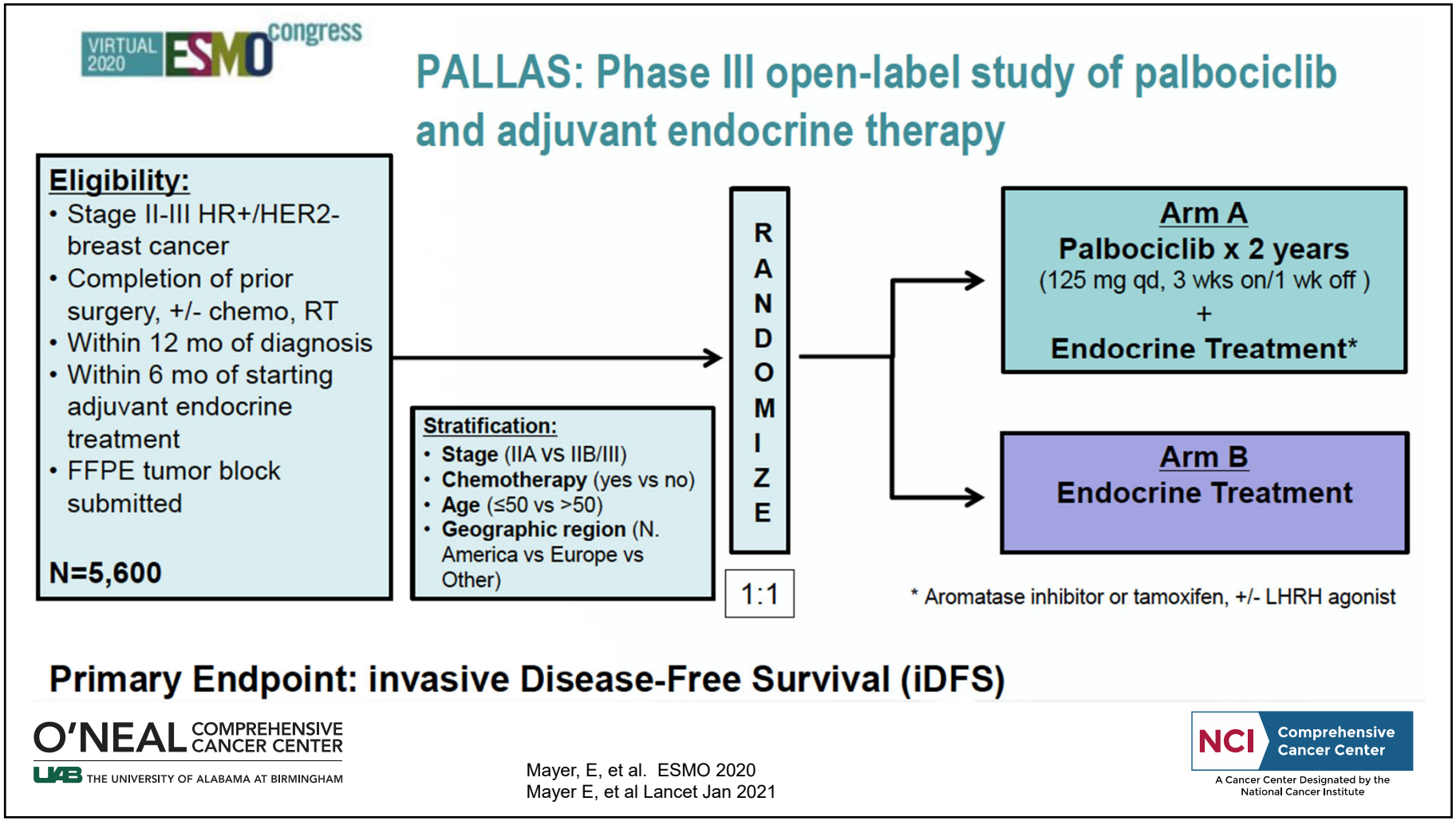


VIRTUAL 2020 ESMO congress

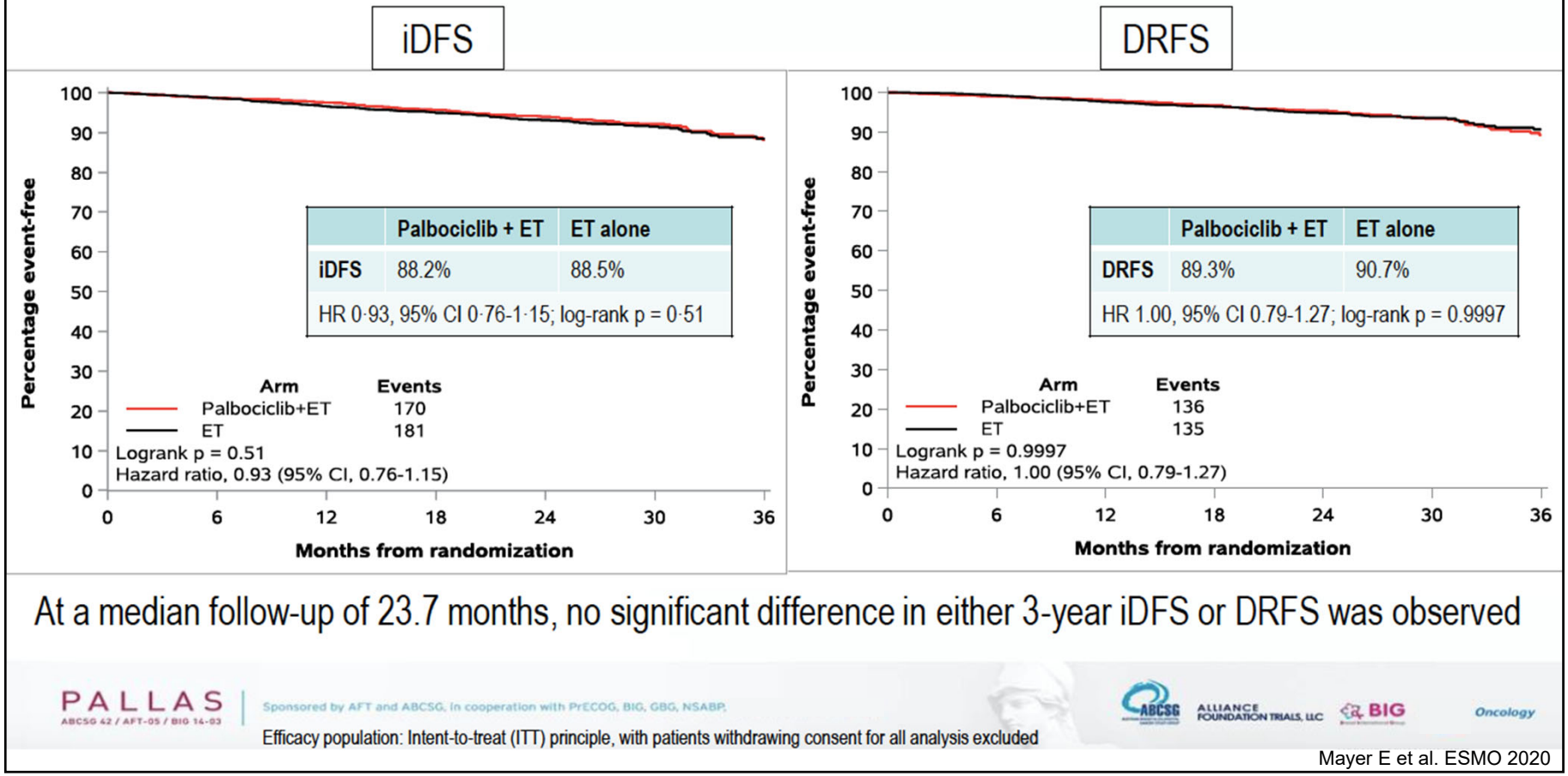
PALLAS: Patient Characteristics

- 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	367 (12·7%)	383 (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
ABCSG 42 / AFT-05 / BIG 14-03
Sponsored by AFT and ABCSG, in cooperation with PrECOG, BIG, GBG, NSABP, and supp

PALLAS: Primary Endpoint iDFS



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

PALLAS
ABCSG 42 / AFT-05 / BIG 14-03

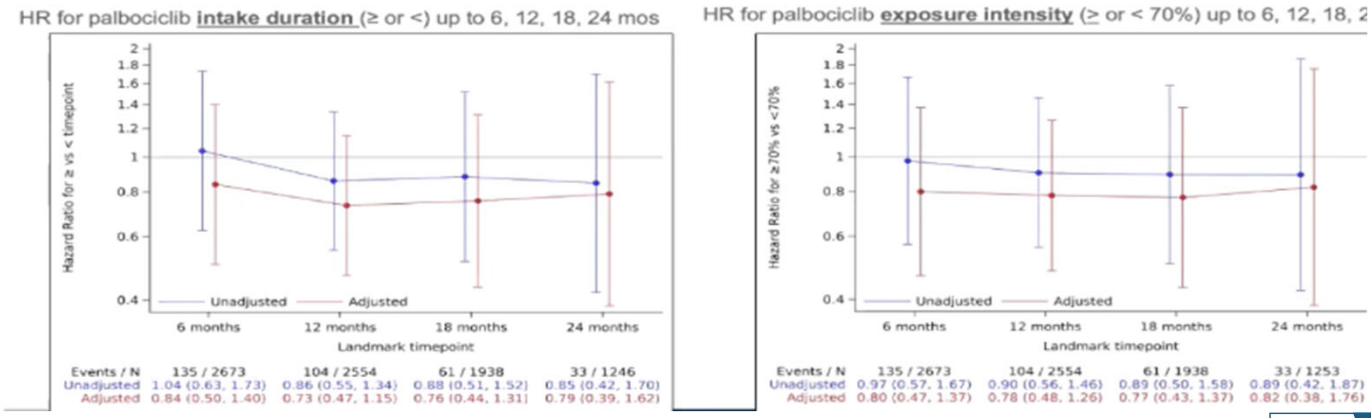
Sponsored by AFT and ABCSG, in cooperation with PrECOG, BIG, GBG, NSABP

Efficacy population: Intent-to-treat (ITT) principle, with patients withdrawing consent for all analysis excluded

Mayer E et al. ESMO 2020

PALLAS – IMPACT OF TREATMENT MODIFICATION

- Did treatment discontinuation or decreased treatment intensity affect outcome?
  - Looked at both dose of drug as well as question of whether time off drug more important
  - 42% discontinued drug early (27.2% due to AE)
  - 55% dose reduced to 100 mg, 34% to 75 mg at some point during treatment
    - Evaluated the relationship between exposure and iDFS
      - Duration of palbociclib
      - Exposure intensity of palbociclib



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PENELOPE-B

GBG-78 - BIG 1-13 - NSABP-B-54-I

Phase III study of palbociclib combined with endocrine therapy in patients with hormone-receptor-positive, HER2-negative primary breast cancer and high relapse risk after neoadjuvant chemotherapy: First results from PENELOPE-B

Sibylle Loibl, Frederik Marmé, Miguel Martin, Michael Untch, Hervé Bonnefoi, Sung-Bae Kim, Harry Bear, Nicole Mc Carthy, Mireia Melé Olivé, Karen Gelmon, José García-Sáenz, Catherine M. Kelly, Toralf Reimer, Masakazu Toi, Hope S. Rugo, Sabine Seiler, Valentina Nekljudova, Carsten Denkert, Michael Gnant, Andreas Makris, Nicole Burchardi, Gunter von Minckwitz

on behalf of the PENELOPE-B investigators

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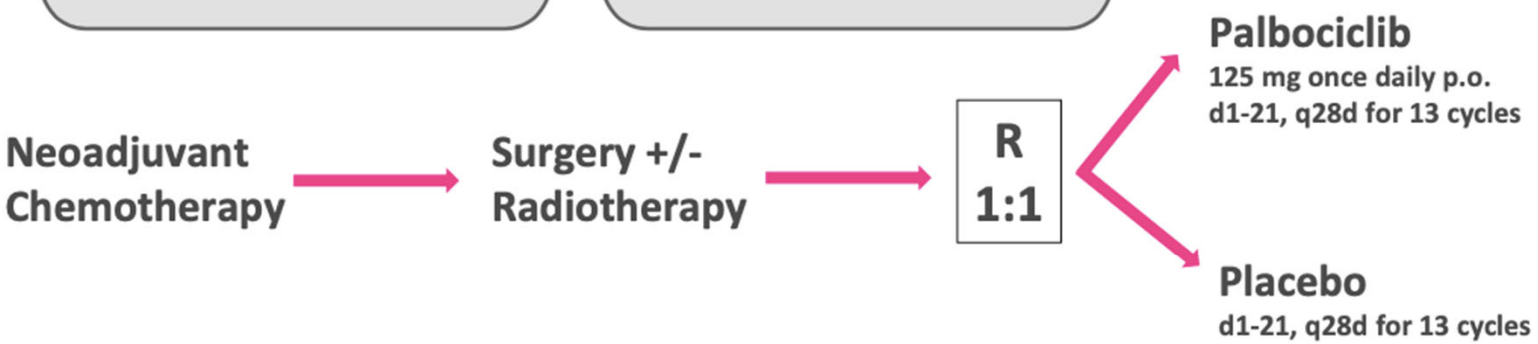
PENELOPE-B

Study Design

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+



All patients will receive concomitantly endocrine therapy according to local standards

CPS-EG: includes pretreatment clinical stage, pathological stage, plus estrogen receptor and grade

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Main Baseline Characteristics

PENELOPE-B

Parameter	Category	Palbociclib (N=631) N (%*)	Placebo (N=619) N (%*)	Overall (N=1250) N (%*)
Age	median (range)	49 (22.76)	48 (19.79)	49 (19.79)
Age, years	≤50	353 (55.9)	348 (56.2)	701 (56.1)
Histological lymph node status at surgery	ypN 0-1	310 (49.1)	310 (50.1)	620 (49.6)
	ypN 2-3	321 (50.9)	309 (49.9)	630 (50.4)
Ki-67%, central pathology	>15%	161 (25.5)	158 (25.5)	319 (25.5)
CPS-EG score	2 and ypN+	253 (40.1)	255 (41.2)	508 (40.6)
	≥3	378 (59.9)	364 (58.8)	742 (59.4)
Tumor stage at surgery	ypT0-1	238 (37.7)	208 (33.7)	446 (35.7)
	ypT2-3	368 (58.3)	389 (62.9)	757 (60.6)
	ypT4	25 (4.0)	21 (3.4)	46 (3.7)
Histological type	lobular	58 (9.2)	52 (8.5)	110 (8.8)
Grading	G3	294 (46.7)	297 (48.1)	591 (47.4)
Ovarian ablation		108 (17.1)	113 (18.3)	221 (17.7)
Endocrine therapy Tamoxifen	overall	314 (49.8)	308 (49.8)	622 (49.8)

stratification factors

*valid percent

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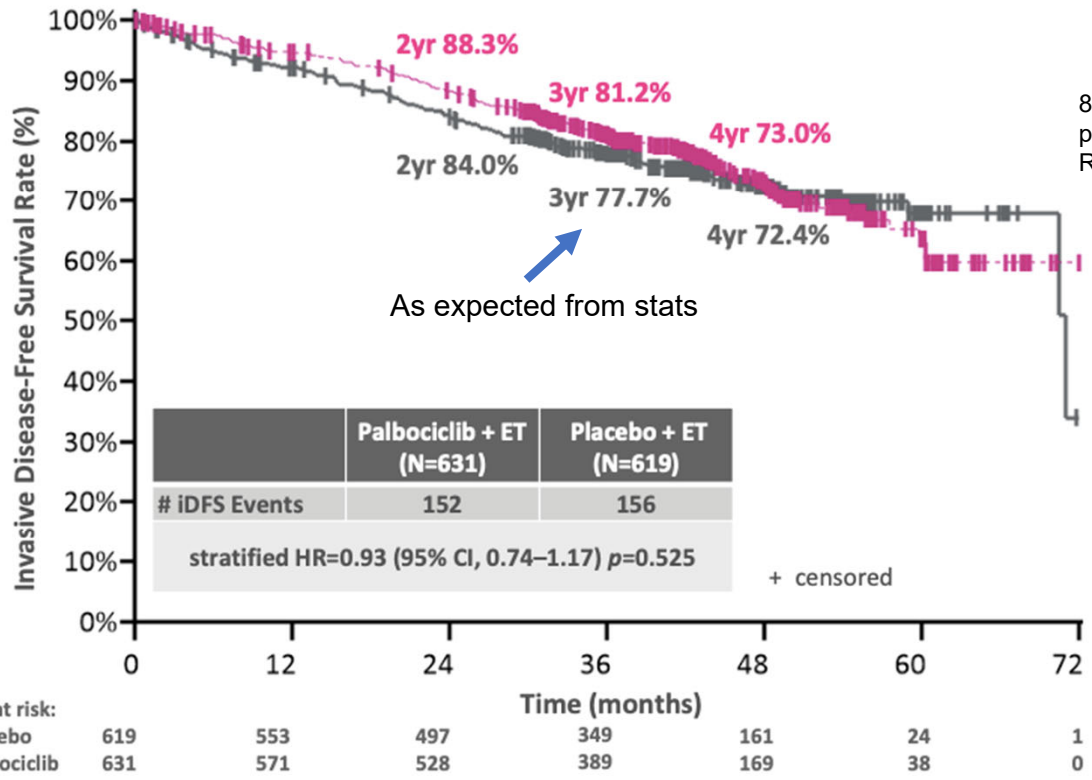
PENELOPE-B

Results Primary Endpoint iDFS



	Palbociclib + ET (N=631)	Placebo + ET (N=619)
# iDFS Events	152	156
stratified HR=0.93 (95% CI, 0.74–1.17) *p*=0.525		

Patients at risk:							
Placebo	619	553	497	349	161	24	1
Palbociclib	631	571	528	389	169	38	0

80% of patients completed all cycles of palbo
RDI palbo 82%; RDI placebo 89%

Median Follow-Up 42.8 Months

* Weighted log-rank test based on the CHW method, taking into account the adaptive sample size re-estimation and group-sequential nature of the design

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Please contact the presenter Sibylle.Loibl@gbg.de

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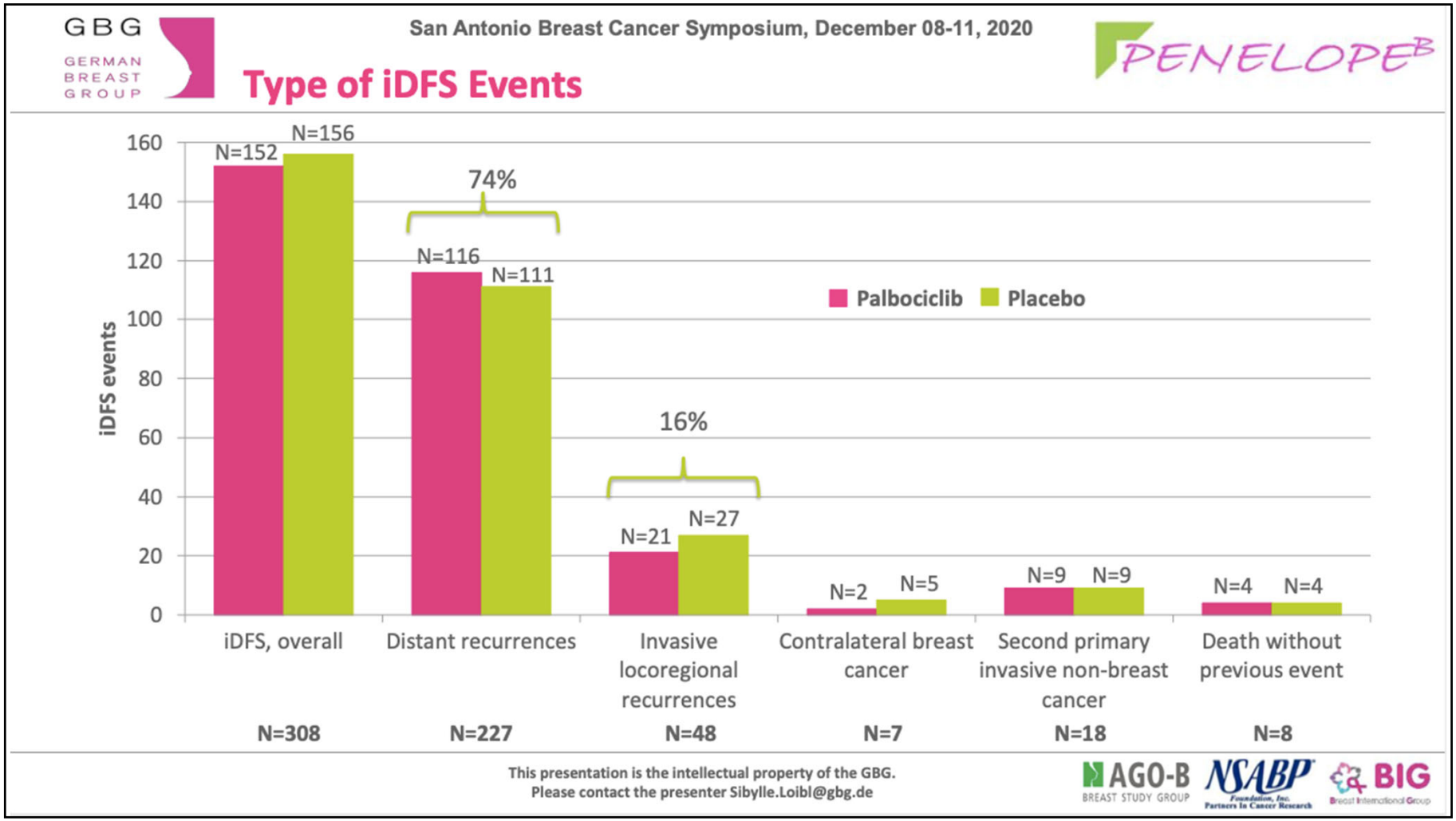

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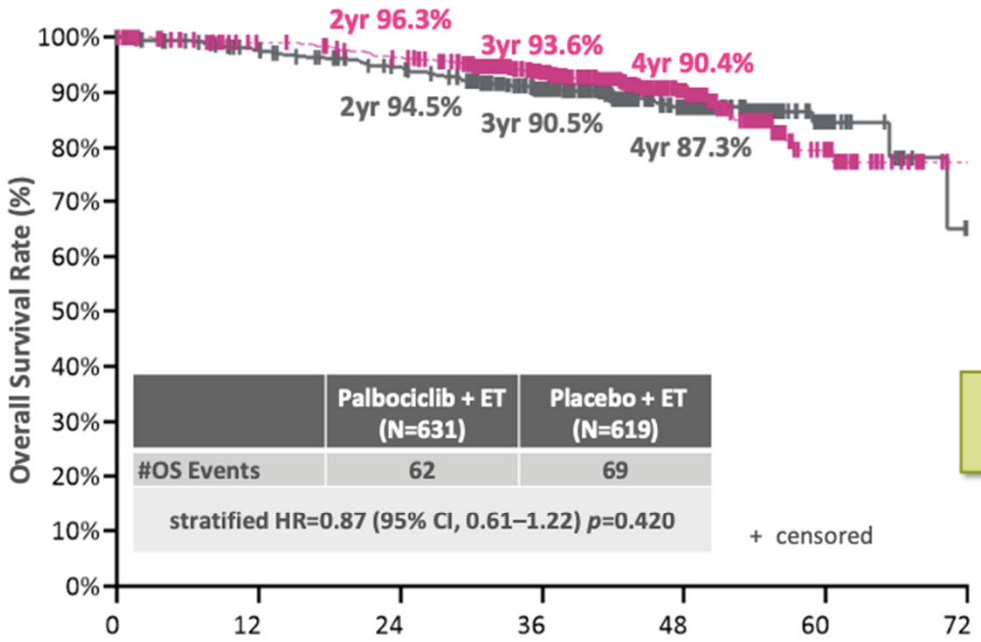
PENELOPE-B

Overall Survival (Interim Analysis)



	Palbociclib + ET (N=631)	Placebo + ET (N=619)
#OS Events	62	69
stratified HR=0.87 (95% CI, 0.61–1.22) *p*=0.420		

Median Follow-Up 42.8 Months

Patients at risk:							
Placebo	619	588	554	410	190	32	3
Palbociclib	631	596	574	442	206	46	1

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PENELOPE^{B} CONCLUSIONS

- With median follow-up of 43 months, no improvement in outcome with addition of 1 year of palbociclib to endocrine therapy
- Compliance declined over time but remained good
  - 80.5% vs 84.5% completed therapy
  - Relative total dose intensity 82% vs 99%

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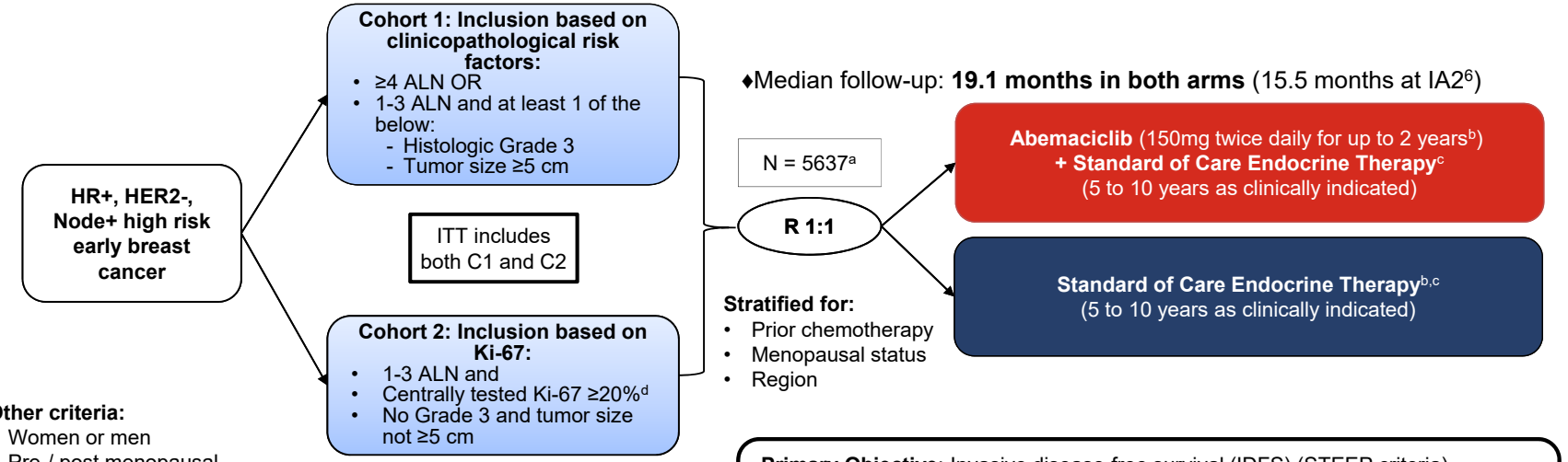
MONARCHE STUDY –PRIMARY OUTCOME ANALYSIS



[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

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[6]Johnston SD et al JCO 2020
Joyce O'Shaughnessy et al SABCS 2020

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High risk disease characteristics

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monarchE EARLY BREAST CANCER

		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)

- Median Age: 51 (15% age 65 or older)
- 56% postmenopausal
- 95% prior (neo)adjuvant chemo

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]	152 (5.4)	158 (5.6)
Tumor size ≥5 cm (imaging) [a, b]	629 (22.4)	618 (21.8)
Histologic grade 3 [a]	216 (7.7)	237 (8.4)
Central Ki-67 ≥20% only [c]		

[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

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

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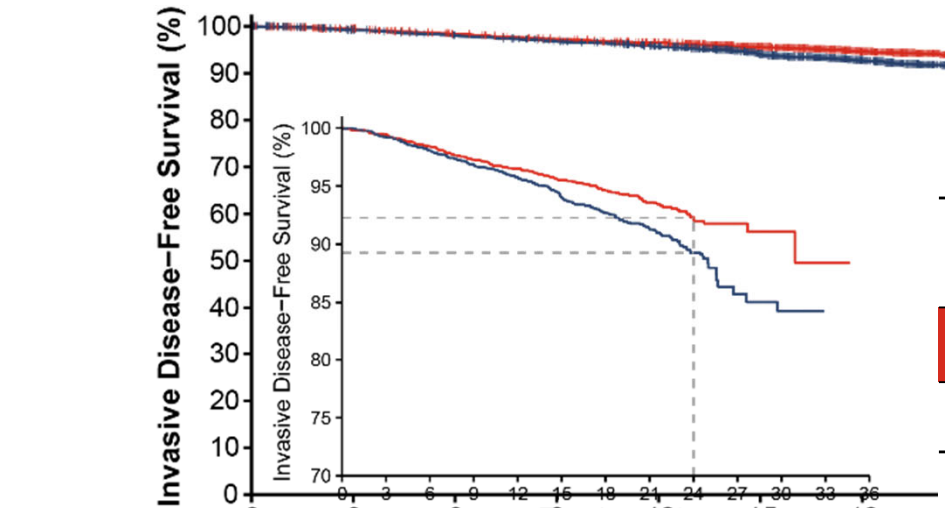
INVASIVE DISEASE-FREE SURVIVAL (ITT) AT PO ANALYSIS



Number of IDFS events

Abemaciclib + ET	ET Alone
163	232

Nominal p = 0.0009 (2-sided)
HR (95% CI): 0.713 (0.583, 0.871)

Risk of developing an IDFS event reduced by 28.7%

IA2 HR (95% CI)[6] = 0.747 (0.598, 0.932)

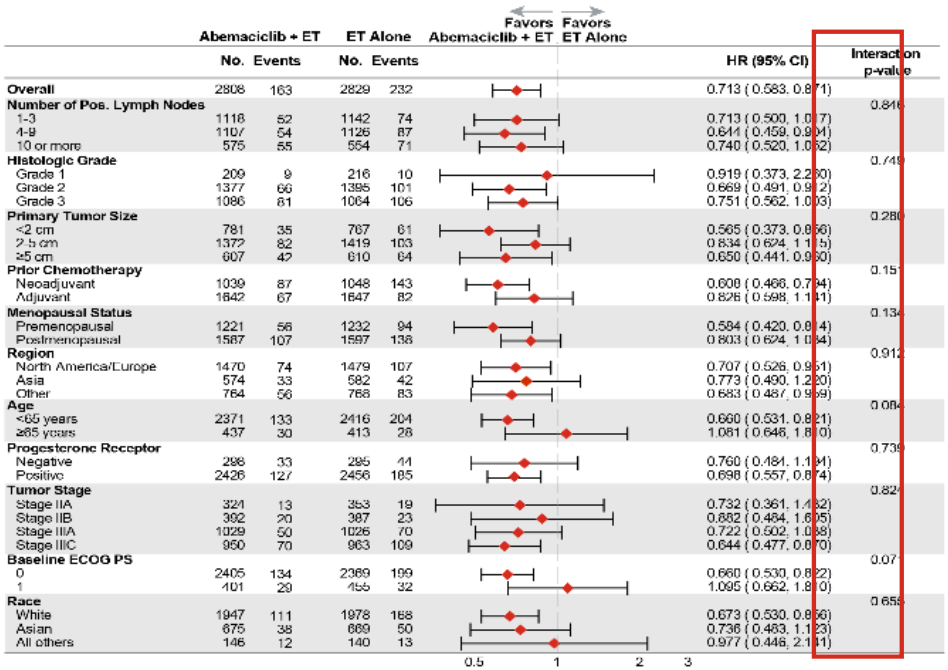
Number at risk

Abemaciclib + ET	2808	2680	2619	2573	2519	2076	1487	1029	619	133	94	1	0
ET Alone	2829	2700	2653	2609	2548	2093	1499	1033	627	131	102	0	0

Statistically significant and clinically meaningful improvement in IDFS with greater treatment benefit at PO analysis
Two-year IDFS rates were 92.3% in the abemaciclib + ET arm and 89.3% in the ET arm - 3.0% difference

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

IDFS IN PRESPECIFIED SUBGROUPS AT PO ANALYSIS



	Abemaciclib + ET		ET Alone		HR (95% CI)	Interaction p-value
	No.	Events	No.	Events		
Overall	2808	163	2829	232	0.713 (0.583, 0.871)	
Number of Pos. Lymph Nodes						0.846
1-3	1118	52	1142	74	0.713 (0.500, 1.017)	
4-9	1107	54	1126	87	0.644 (0.459, 0.904)	
10 or more	575	55	554	71	0.740 (0.520, 1.052)	
Histologic Grade						0.749
Grade 1	209	9	216	10	0.919 (0.373, 2.260)	
Grade 2	1377	66	1395	101	0.669 (0.491, 0.912)	
Grade 3	1086	81	1064	106	0.751 (0.562, 1.003)	
Primary Tumor Size						0.280
<2 cm	781	35	767	61	0.565 (0.373, 0.856)	
2-5 cm	1372	82	1419	103	0.834 (0.624, 1.115)	
≥5 cm	607	47	610	64	0.650 (0.441, 0.960)	
Prior Chemotherapy						0.15
Neoadjuvant	1039	87	1048	143	0.600 (0.466, 0.774)	
Adjuvant	1842	67	1847	82	0.826 (0.598, 1.141)	
Menopausal Status						0.134
Premenopausal	1221	56	1232	94	0.584 (0.420, 0.814)	
Postmenopausal	1587	107	1597	138	0.803 (0.624, 1.034)	
Region						0.912
North America/Europe	1470	74	1479	107	0.707 (0.526, 0.951)	
Asia	574	33	582	42	0.773 (0.490, 1.220)	
Other	764	56	768	83	0.683 (0.487, 0.959)	
Age						0.084
<65 years	2371	133	2416	204	0.660 (0.531, 0.821)	
≥65 years	437	30	413	28	1.081 (0.646, 1.810)	
Progesterone Receptor						0.739
Negative	298	33	295	44	0.760 (0.484, 1.194)	
Positive	2426	127	2456	185	0.698 (0.557, 0.874)	
Tumor Stage						0.824
Stage IIA	324	13	353	19	0.732 (0.361, 1.482)	
Stage IIB	392	20	387	23	0.882 (0.484, 1.605)	
Stage IIIA	1029	50	1026	70	0.722 (0.502, 1.038)	
Stage IIIC	950	70	963	109	0.644 (0.477, 0.870)	
Baseline ECOG PS						0.07
0	2405	134	2369	199	0.660 (0.530, 0.822)	
1	401	29	455	32	1.095 (0.662, 1.810)	
Race						0.655
White	1947	111	1978	168	0.673 (0.530, 0.856)	
Asian	675	38	669	50	0.736 (0.483, 1.123)	
All others	146	12	140	13	0.977 (0.446, 2.141)	

Favors Abemaciclib + ET | Favors ET Alone

0.5 1 2 3

No statistically significant interactions observed supporting consistent benefit across all subgroups at PO analysis

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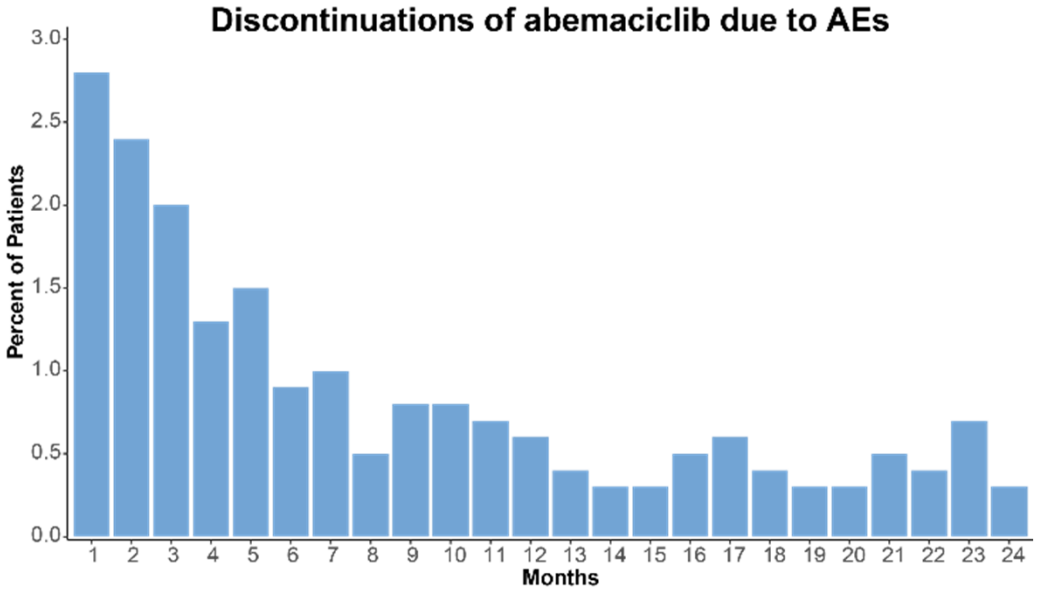
ABEMACICLIB DISCONTINUATIONS AT PO ANALYSIS

- 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)	160 (5.7)
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

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ADJUVANT TRIALS WITH CDK4/6I

	MonarchE	PALLAS	Penelope[B]
N	5637	5600	1250
CDKi	Abemaciclib	Palbociclib	Palbociclib
Eligibility	≥ N2 or ≥ N1 and G3 or T3 (1) N1 and Ki67 ≥ 20% (2)	Anatomic stage 2 or 3 (59% N2 or N1 and G3 or T3)	CPS-EG 3 or 2 with ypN+
CDKi duration	24 months	24 months	12 months
F/UP	19 months	24 months	43 months
IDFS 2 year (Δ)	92% vs 89% (3%)	NR	88% vs 84% (4%)
IDFS 3 year (Δ)	NR	88% vs 89% (-1%)	81% vs 78% (3%)
IDFS 4 year (Δ)	NR	NR	73% vs 72% (0.6%)
DRFS (Δ)	94% vs 91% (3%) @ 2 yr	89% vs 90% @ 3 yr	No difference
Discontinuation rate	28%	42%	20%
Discontinued due to AE	17%	27%*	5%
Completed Rx	72%	32%	80%

* 64% of discontinuations

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ADJUVANT CDK4/6I
WHY WAS MONARCHE POSITIVE AND PALBO TRIALS NEGATIVE?

- Different patient populations?
  - N2/N3 59% monarchE vs 37% in PALLAS
  - But no benefit in PALLAS high risk subset or PENELOPE[B]
- Duration of follow-up?
  - Benefit with palbo early in PENELOPE[B] that disappeared over time
  - Effect diminishing (a bit) over time: ▲3.5% (mF/U 15.5 mos) and ▲3.0% (mF/U 19.1 mos)
- Different drugs in terms of CDK4/6 inhibition and dosing (intermittent vs continuous)
  - Highly selective use of abemaciclib in the adjuvant setting
- High discontinuation rate in PALLAS
  - Analysis does not support a difference in benefit based on dose modification
- NATALEE (3 yrs adjuvant ribociclib) results pending
- Awaiting biomarker studies

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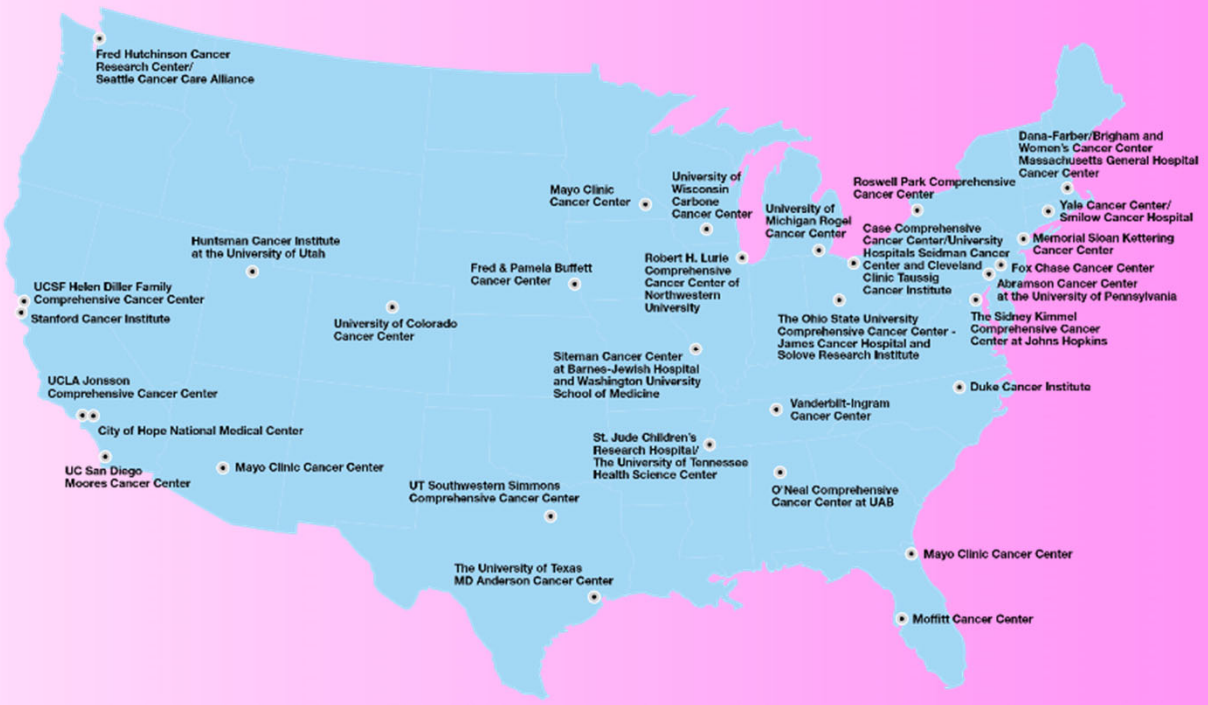
- **Who We Are**
  An alliance of leading cancer centers devoted to patient care, research, and education
- **Our Mission**
  To improve and facilitate quality, effective, efficient, and accessible cancer care so patients can live better lives
- **Our Vision**
  To define and advance high-quality, high-value, patient-centered cancer care globally



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