Clinical impact

Who really need adj Abemaciclib?

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Outline

- Ki67>20%
- N+
- Genomic testing
- Chemo-refractory
- Follow up
- BRCA

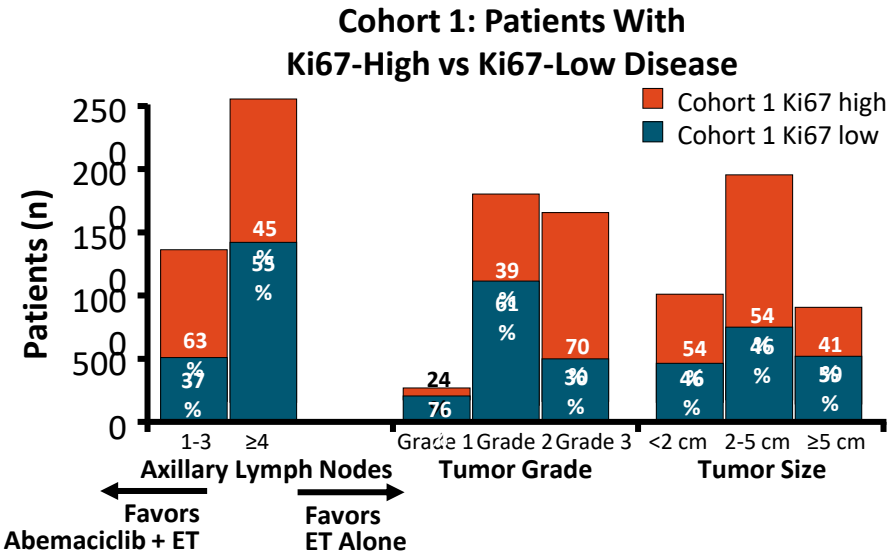
Adjuvant Abemaciclib for High-Risk HR+/HER- EBC: Approved by FDA

On October 12, 2021, based on the results of the phase III monarchE trial, the FDA approved abemaciclib with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with HR+/HER2-, node-positive early breast cancer at high risk of recurrence and a Ki67 score ≥20%, as determined by an FDA-approved test

Harbeck. Ann Oncol. 2021;32:1571. Abemaciclib PI.

monarchE: Analysis of Patients With ≥4 Axillary Lymph Nodes

- **55% of patients with ≥4 ALN on the monarchE trial had Ki67-low disease**
- Despite a very high risk of recurrence, patients with ≥4 ALN would currently be excluded from treatment with abemaciclib



	Abemaciclib + ET		ET Alone			
iDFS	**N**	**Events**	**N**	**Events**	**HR (95% CI)**	**Interaction *P* Value**
Overall	2808	232	2829	333	0.70 (0.59-0.82)	
Positive lymph nodes, n						.597
1-3	1118	75	1142	105	0.72 (0.54-0.97)	
4-9	1107	75	1126	126	0.61 (0.46-0.81)	
≥10	575	80	554	102	0.74 (0.55-0.99)	

Favors Abemaciclib + ET

Favors ET Alone

Harbeck. Ann Oncol. 2021;32:1571. O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

monarchE: Ki67 Assay Scoring Algorithm

In the monarchE trial, trained pathologists assessed Ki67 expression as follows:

- Ki67 staining: defined by convincing and complete nuclear staining corresponding to tumor cell chromatin at ≥1+ grade intensity (using a 0-3+ scale)

$$\textbf{Ki67 Score (\%)} = \frac{\text{Ki67 staining viable invasive tumor cells, n}}{\text{Total staining and nonstaining viable invasive tumor cells, N}} \times 100$$

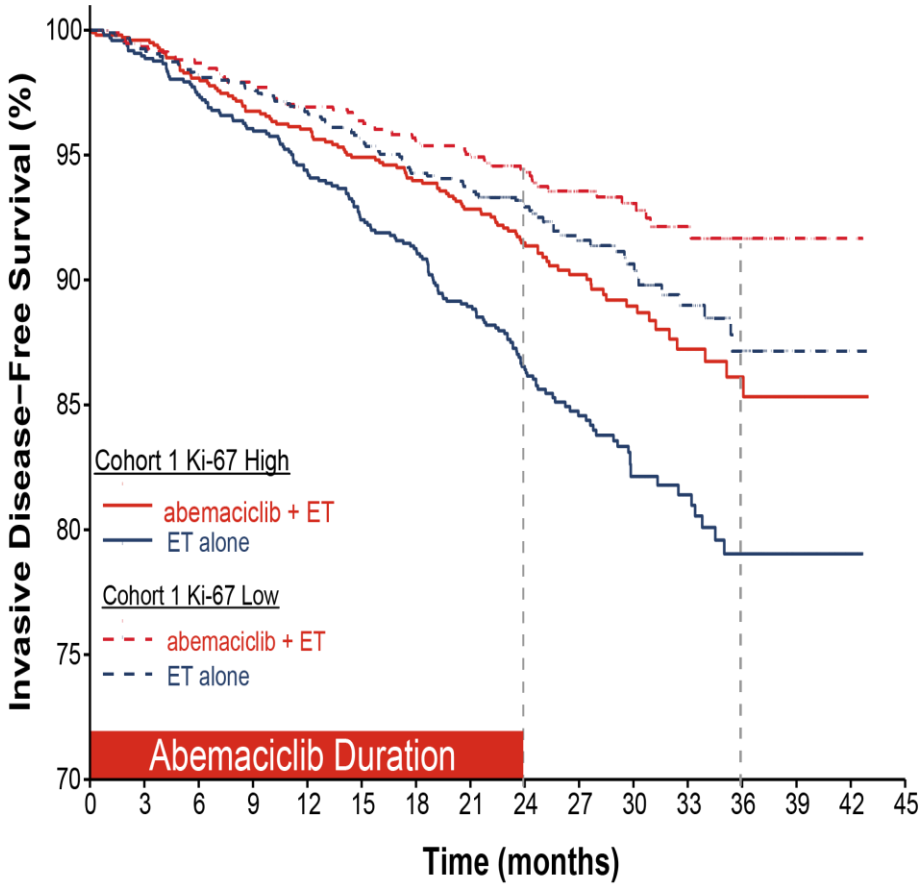
Ki67 Score <20%	Ki67 Score ≥20%
Ki67 Low	Ki67 High

2021 St Gallen Consensus Ki67 of at least 30% for recommending CT

42% of the panelists (36% stated KI67 threshold is not known)

Nielsen. ESP 2020. Abstr PS-01-045 2021 St Gallen (Bursttein)

Ki-67 as a prognostic marker in Cohort 1



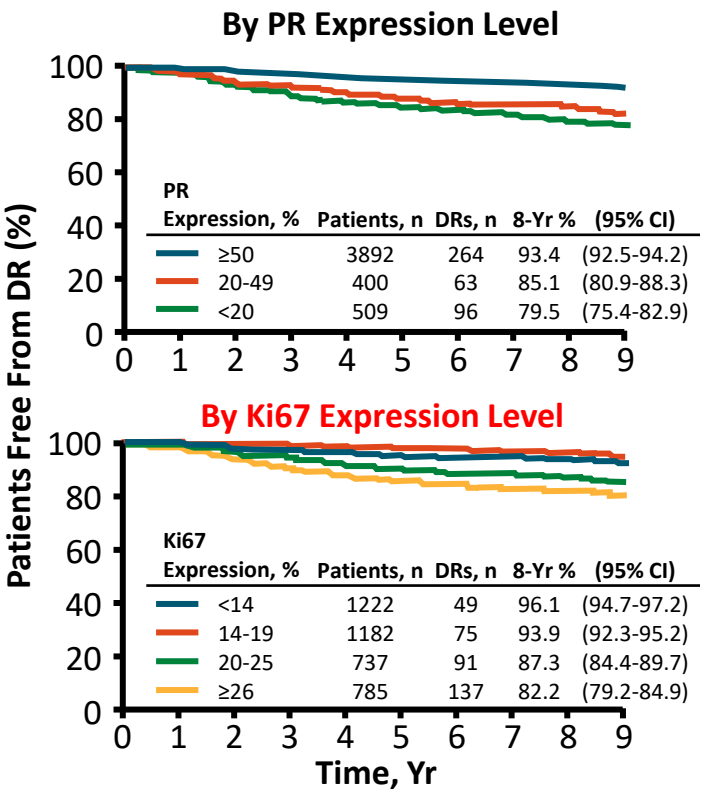
	Abemaciclib + ET	ET alone	HR (95% CI)
Cohort 1 Ki-67 High, N = 2003			
Patients, N	1017	986	0.626 (0.488, 0.803)
Events, n	104	158	
3-Year Rates	86.1%	79.0%	
Cohort 1 Ki-67 Low, N = 1914			
Patients, N	946	968	0.704 (0.506, 0.979)
Events, n	62	86	
3-Year Rates	91.7%	87.2%	

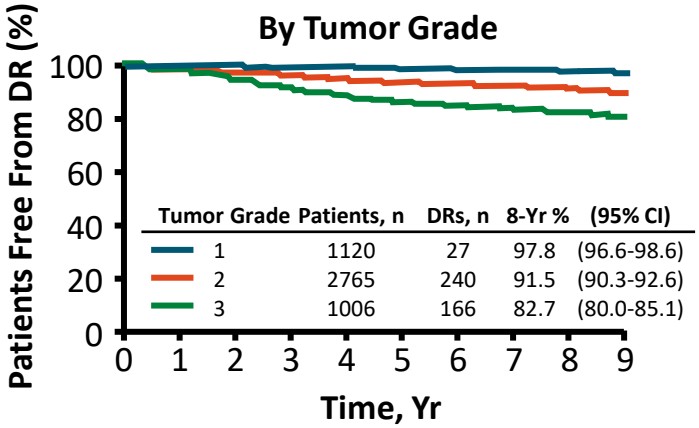
Ki-67 is prognostic

Ki-67 is not predictive of abemaciclib benefit

As expected, high Ki-67 index was prognostic of worse outcome. However, abemaciclib benefit was consistent regardless of Ki-67 index.

Prognostic Factors for Premenopausal ER+ Patients: SOFT/TEXT Trials





Pagani. JCO. 2020;38:1293.

Adjuvant Abemaciclib for High-Risk HR+/HER- EBC: Approved by FDA

On October 12, 2021, based on the results of the phase III monarchE trial, the FDA approved abemaciclib with endocrine therapy (tamoxifen or an aromatase inhibitor)

ASCO and NCCN guideline panels endorse adjuvant Abemaciclib for the whole monarchE ITT population

of recurrence and a Ki67 score ≥20%,
as determined by an FDA-approved test

In February 24, 2022 the CHMP of EMA adopted a positive opinion for marketing authorization of adjuvant Abemaciclib for the whole monarchE ITT population

Harbeck. Ann Oncol. 2021;32:1571. Abemaciclib PI.

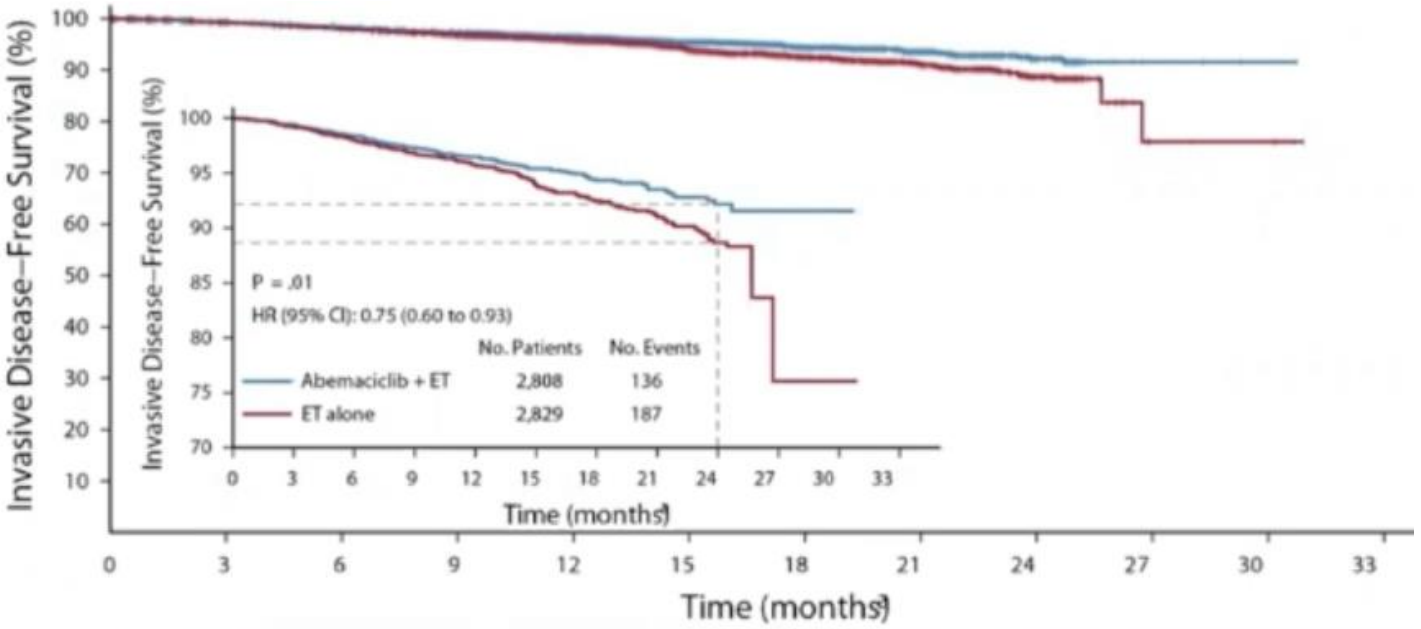
N+

- Ki67>20%
- N+
- Genomic testing
- Chemo-refractory
- Follow up
- BRCA

monarchE N+

		Abemaciclib + ET N=2808, %	ET Alone N=2829, %
Age	Median (range)	51 (23-89)	51 (22-86)
Age categories	<65 years	84.4	85.4
Gender	Female	99.3	99.5
Menopausal Status[1]	Premenopausal	43.5	43.5
	Postmenopausal	56.5	56.5
Prior Chemotherapy[1]	Neoadjuvant	37.0	37.0
	Adjuvant	58.5	58.2
	None	4.5	4.7
Baseline ECOG PS	0	85.7	83.8
Pathologic Tumor Size	<2 cm	27.8	27.1
	2 - 5 cm	48.9	50.2
	≥5 cm	21.6	21.6
Number of Positive Lymph Nodes	1-3	39.8	40.4
	≥4	59.9	59.6
Histological Grade	Grade 1	7.4	7.6
	Grade 2	49.0	49.3
	Grade 3	38.7	37.6
Central Ki-67	<20%	33.9	34.4
	≥20%	44.9	43.6
	Unavailable	21.1	21.8

monarchE target population



Eligibility

≥ 4+ nodes	1-3 + nodes AND T ≥ 5 cm Grade 3 Ki67 > 20%
Lower prevalence	Higher prevalence

Johnston JCO 2020

N+ varies according with HR/HER2

MSKCC 1998-2010 N 11.496

	HR+/HER2-	HR+ HER2+	HR-/HER2+	TN
N (%)	8440 (73%)	915 (8%)	621 (5%)	1520 (13%)
Mean T size	1.6 cm	1.6 cm	1.7 cm	1.7 cm
N+	25%	32%	36%	28%
N+ > 4	9%	16%	22%	13%

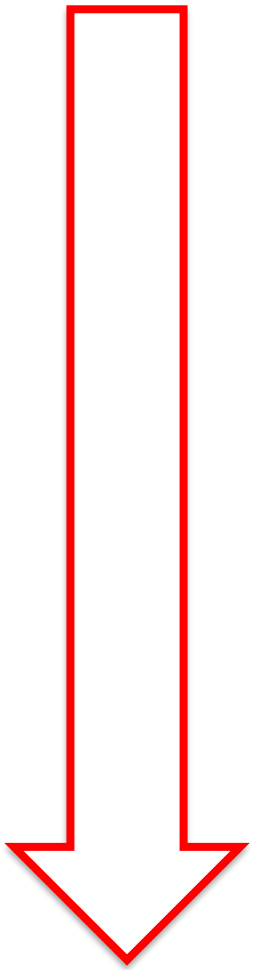
Ugras S, Ann Surg Oncol 2014

The risk of pN+ in cN0 & neg US

	SOUND	INSEMA
N	146	1001
Meadian Age	82%>50y	61y
HR+	88%	97%
G3	-	5%
SN macro	8.6%	14%
N+>3	0.5%	1.3%

Reimer T 2017; Veronesi P St Gallen 2021

Can we omit ALND in eBC ?



1970: ALND

1990: SN for N0

2000: SN + RT for N+

2011: SN+ w/o ALND

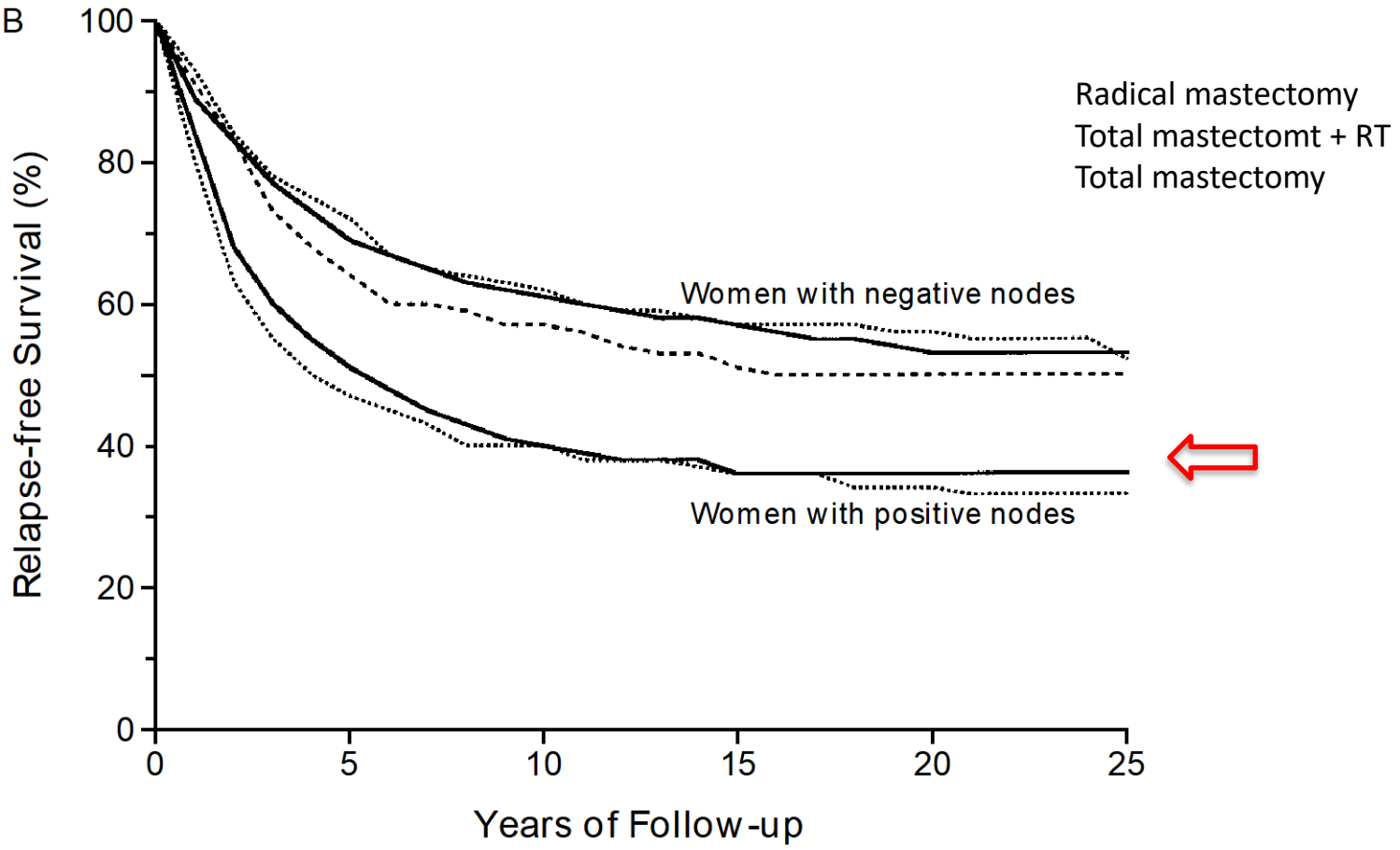
2022: ALND omission ?

ALND historical belifs

- Survival benefit
- Loco-regional disease control
- Staging/Adj Rx indication

ALND does not improve BC survival

NSABP B04



No differences among the 2 groups of pN+ pts receiving or not ALND

Fisher B NEJM 2002

ALND historical belifs

- Survival benefit
- Loco-regional disease control
- Staging/Adj Rx indication

Rate of LRR w/o ALND

IBCSG 10-93

N 473 pts; median Age 74 (elegible >60y and cN0)
42% T>2cm
80% ER+, all received TAM
45% mastectomy, 33% BCS + RT, 23% BCS

cN0, median follow up 6.6y

Axillary First Events		
ALND n = 239 (28% N+)		No ALND n = 239
2 (1%)	p=NS	6 (3%)

IBCSG, JCO 2006

ALND historical belifs

- Survival benefit
- Loco-regional disease control
- Staging/Adj Rx indication

Is ALND necessary for the choice of optimal adjuvant RX?

HR+/HER2-

(NCCN 2020/St Gallen 2021)

T1ab N0	T1c N0	N+1-3 nodes	N+>3 nodes
ET	ET/CT (genomic test)	ET/CT (genomic test)	ET/CT

Menopausal status matters

Burstein Ann Oncol 2021

Genomic testing

- Ki67>20%
- N+
- Genomic testing
- Chemo-refractory
- Follow up
- BRCA

The role of ALND according to RxPONDER in pre-menop

- Nodal mets indicate the need for CT regardless of RS (sufficit SLNB pN0 vs pN1)

Axillary staging with SLNB is crucial

No strict need for ALND

The role of ALND according to RxPONDER in post-menop

- 37% of pts SLB+ only. No trend for CT benefit as number of nodes involved incresed (1 vs 2-3)

Axillary staging with SLNB is crucial

Unfavorable risk/benefit ratio for ALND

The role of ALND according to monarchE

- In pts at higher risk of additional pos nodes not meeting criteria for 1-3N+ (T>5cm, G3, Ki67>20%)

Then, ALND can be selectively performed

RegioneLombardia

LA GIUNTA

DELIBERAZIONE N° XI / 1986 Seduta del 23/07/2019

Per le paz HR+/HER2- a rischio intermedio per le quali il clinico potrebbe porre una indicazione a chemioterapia adiuvante.

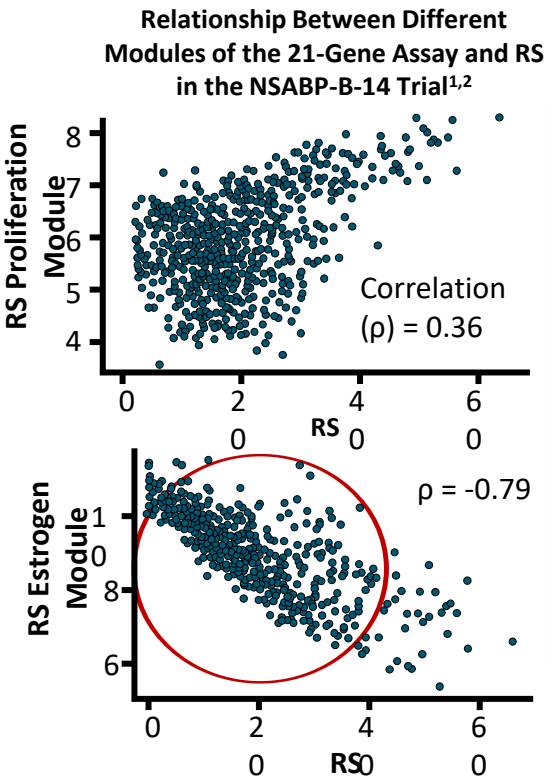
Vengono, pertanto, escluse dalla possibilità di effettuare il test gratuitamente tutte le pazienti a basso rischio, per le quali è indicata la sola ormonoterapia, e ad alto rischio per le quali è indicata l'associazione ormonoterapia- chemioterapia.

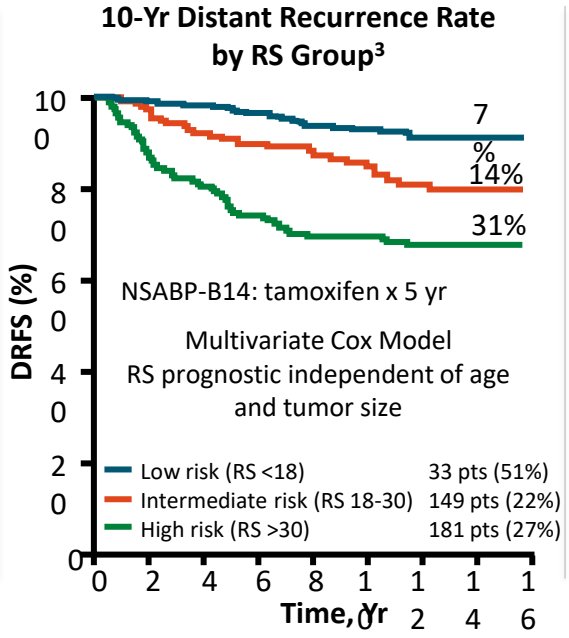
Le pazienti a basso e ad alto rischio sono definite in base alle caratteristiche descritte nella tabella seguente:

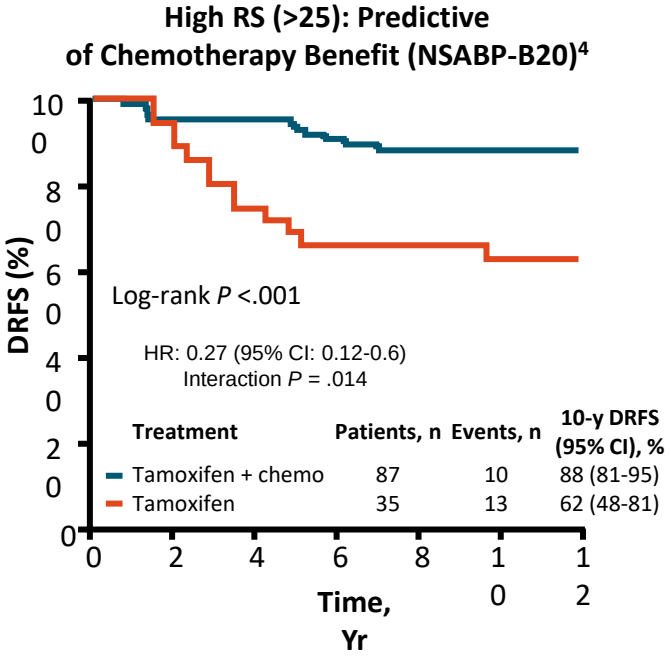
Basso rischio: almeno 4 delle seguenti caratteristiche	**Alto rischio: almeno 4 delle seguenti caratteristiche**
G1	G3
T1 (a-b)	T3-4
Ki 67<15%	Ki 67>30%
ER>80%	ER<30%
N 0	N positivo

La stima delle pazienti lombarde che usufruiranno della prestazione è pari a circa 1500 pazienti/anno con possibile riduzione in circa il 50%-75% dei casi del ricorso a chemioterapia.

Prospective Validation of the 21-Gene RS Assay for Prognosis and Prediction: Level 1B Evidence in ER+/Node- EBC



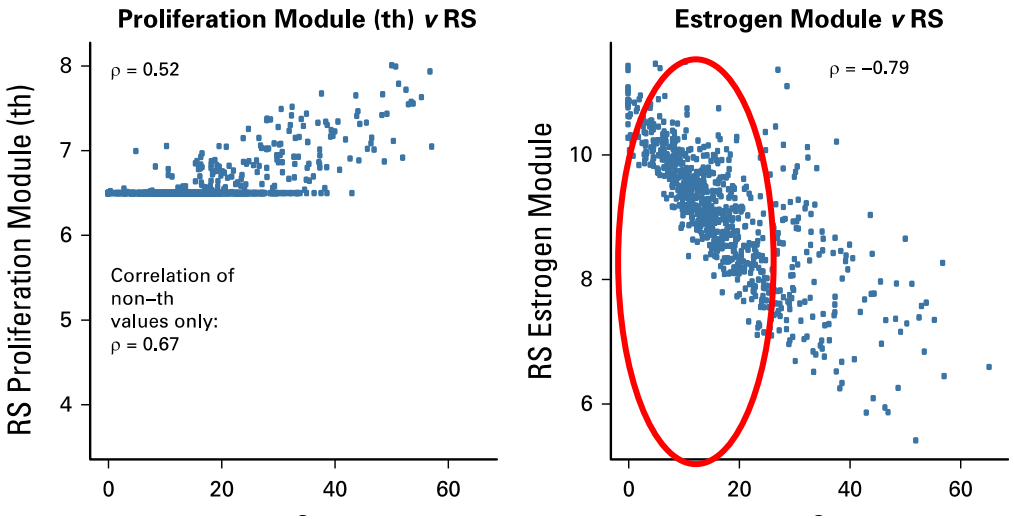




1. Paik. ASCO 2005. Abstr 510. 2. Buus. JCO. 2021;39:126. 3. Paik. NEJM. 2004;351:2817.
2. 4. Geyer. NPJ Breast Cancer. 2018;4:37.

RS gene module

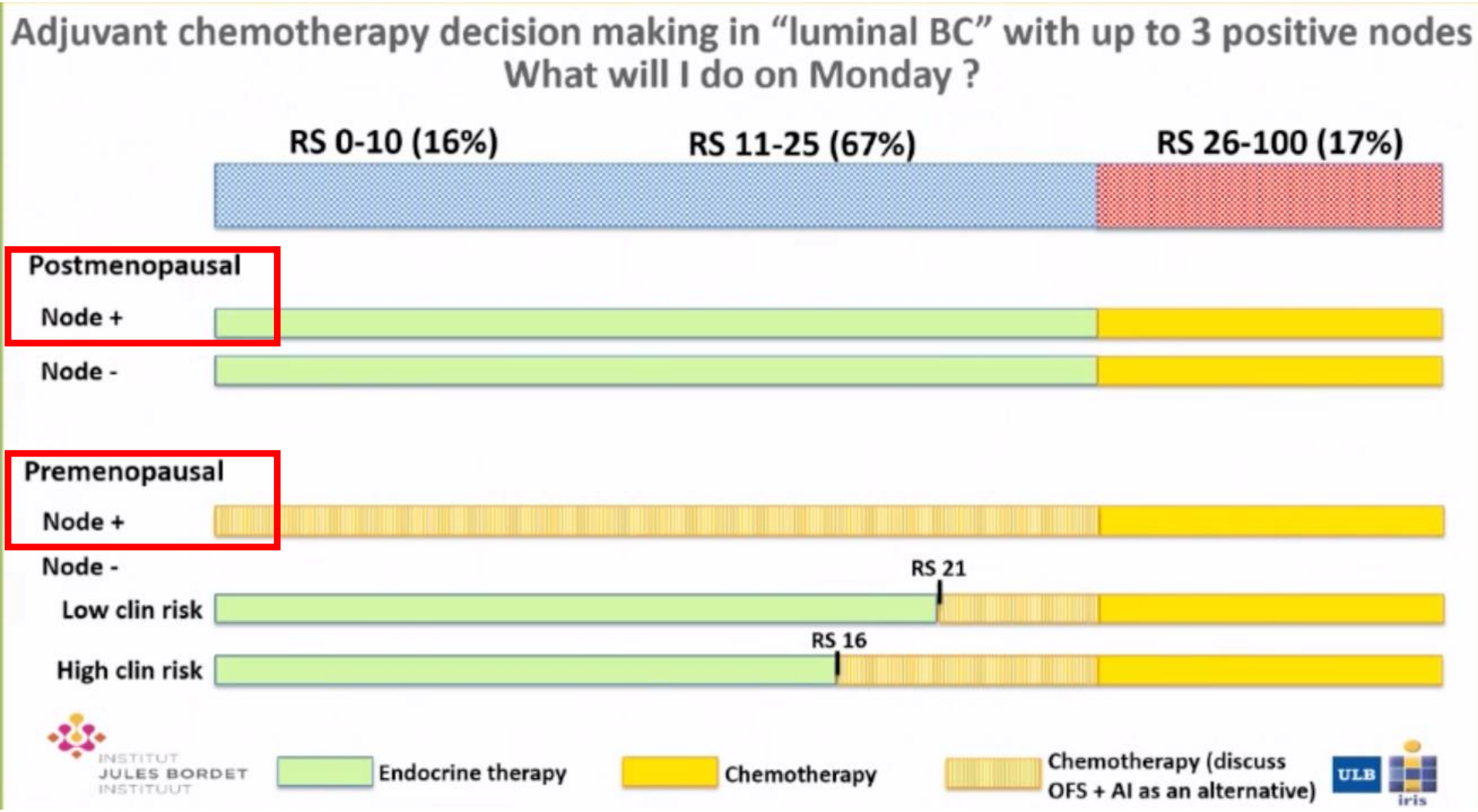
The prevalence of ER module in case of RS low
while a prevalence of proliferation module in case of high RS



The score from the proliferation module is thresholded

R Buus JCO 2020

21-gene RS assay clinical practice implication



Piccart SABCS 2020

CT refractory

- Ki67>20%
- N+
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Baseline Characteristics

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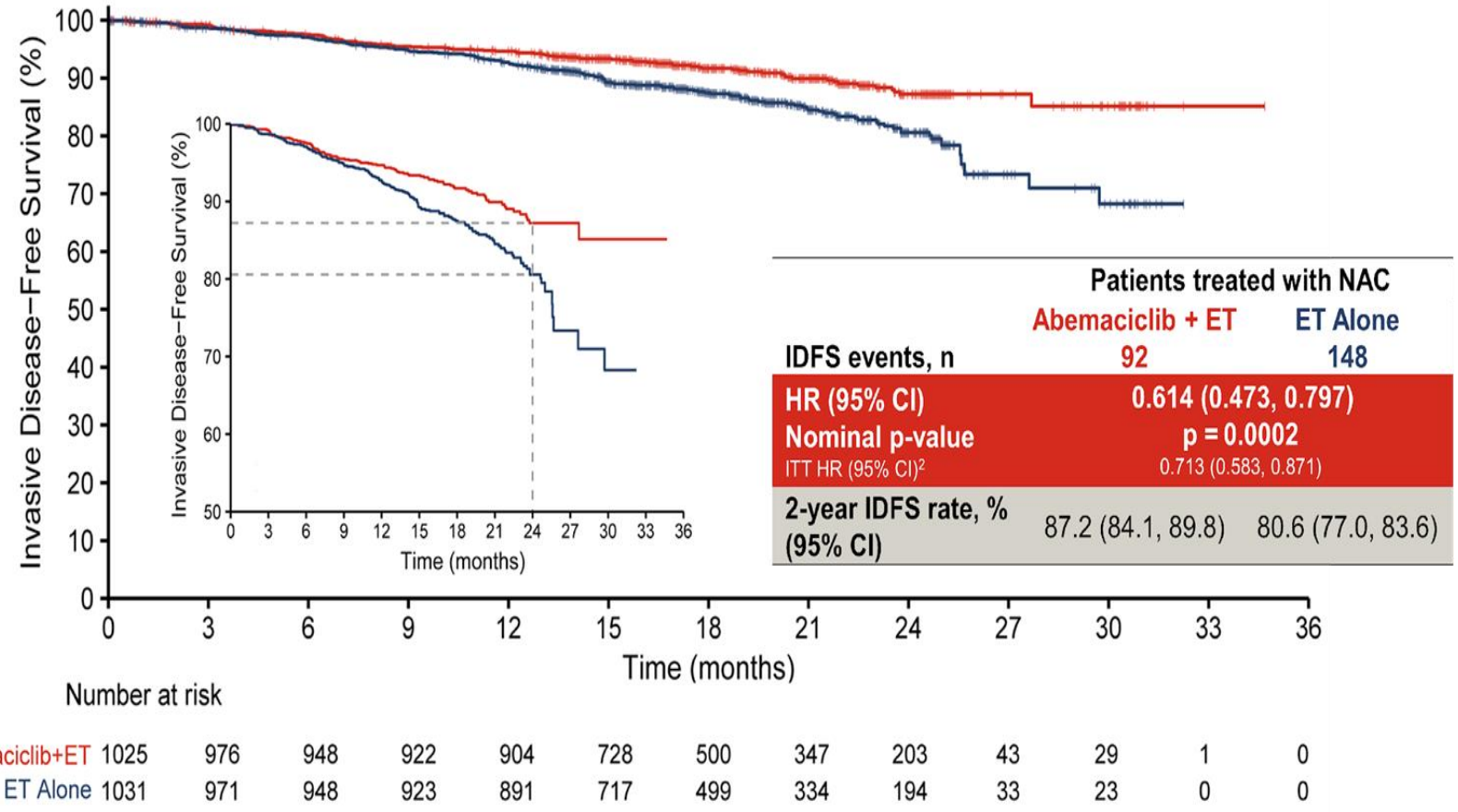
IDFS in Patients Who Received NAC

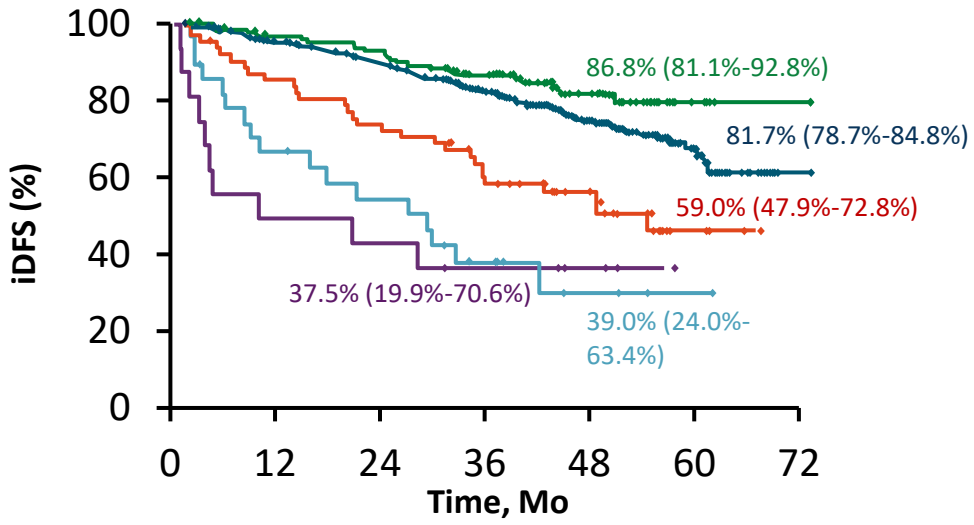


Clinically meaningful improvement in IDFS – 38.6% reduction in the risk of developing an IDFS event

Two-year IDFS rates were 87.2% in the abemaciclib + ET arm and 80.6% in the ET arm – 6.6% difference

[2]Rastogi P. et al. SABCS 2020; presentation number GS1-01

PENELOPE-B: iDFS by Absolute Intrinsic Molecular Subtyping



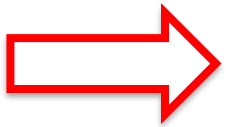
- Gene expression data: 906 of 1250 patients (72%)
  - 663 LumA
  - 64 LumB
  - 135 NormL
  - 16 BasalL and 28 HER2E

Denkert. ASCO 2021. Abstr 519.

Chemorefractory

Not to add but to replace

+



The real challange has not yet begun

FU

- Ki67>20%
- N+
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- Follow up
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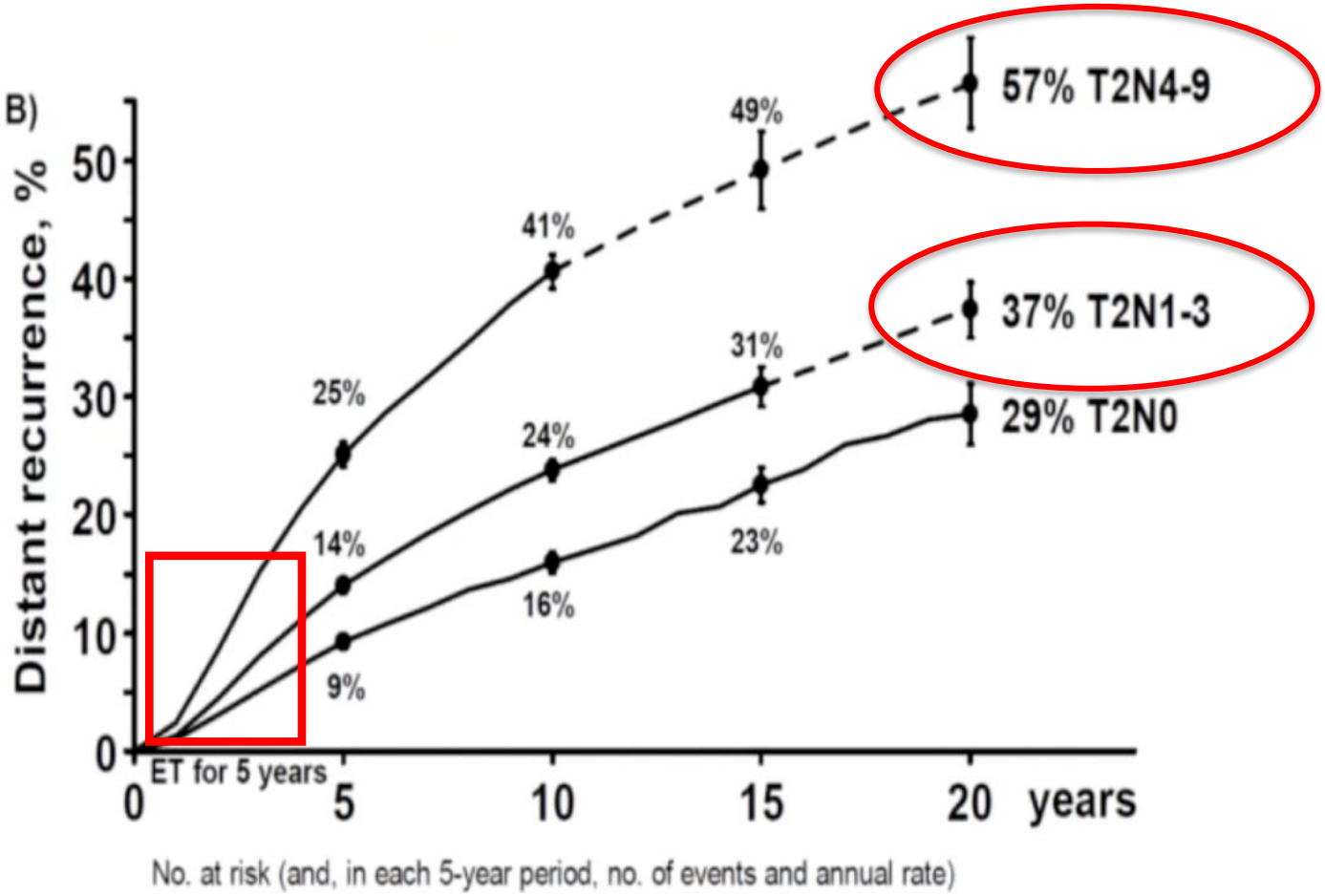
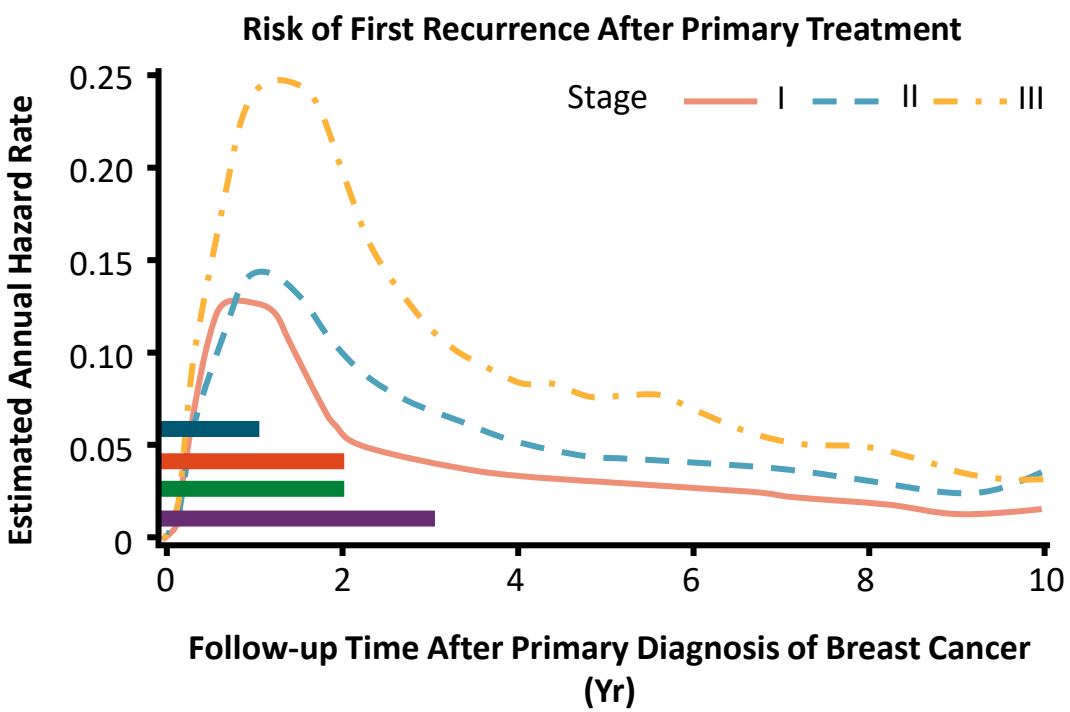
Follow Up



Does the treatment duration matter?

Abemaciclib in the context



PENELOPE-B
Palbociclib
After neoadjuvant, high risk

monarchE
Abemaciclib
High-risk CPR factors, Ki67

PALLAS
Palbociclib
Stage II, III

NATALEE
Ribociclib
Stage II, III

Cheng. Cancer Epidemiol Biomarkers Prev. 2012;21:800.

monarchE: Abemaciclib Treatment Effect Over Time

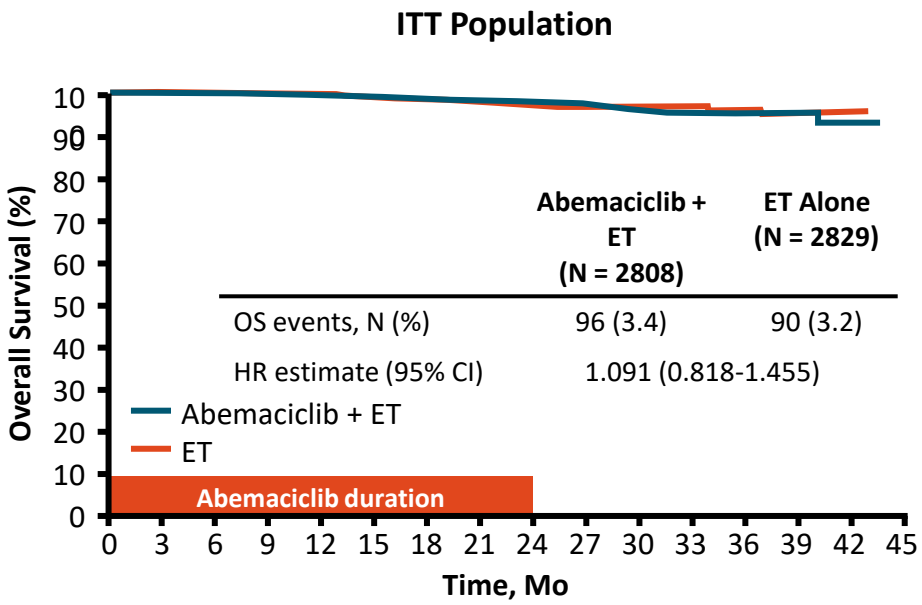
Analysis Landmark	iDFS (Events)			DRFS (Events)		
	Abema + ET (n)	ET Alone (n)	HR (95% CI)	Abema + ET (n)	ET Alone (n)	HR (95% CI)
Yr 0-1	93	116	0.795 (0.589-1.033)	67	91	0.732 (0.520-0.987)
Yr 1-2	98	146	0.681 (0.523-0.869)	85	129	0.675 (0.507-0.875)
Yr 2→	41	71	0.596 (0.397-0.855)	39	58	0.692 (0.448-1.032)

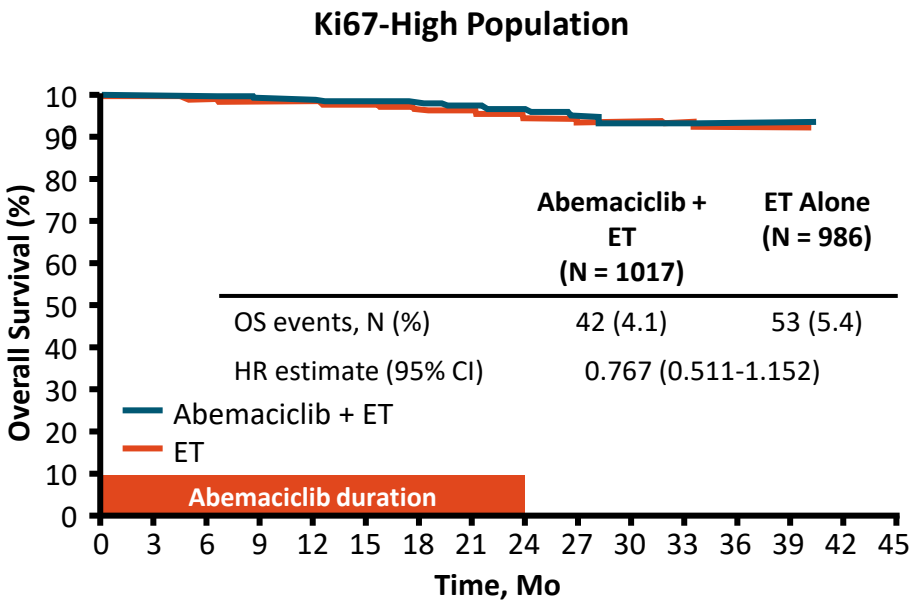
- From Yr 1 to Yr 2: iDFS and DRFS increased in the magnitude of effect size
- Yr 2 and beyond: maintained treatment benefit

Harbeck. Ann Oncol. 2021;32:1571. O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

Slide credit: clinicaloptions.com

monarchE: Preliminary Overall Survival Results





- Death rate was similar in both treatment arms: 3.4% vs 3.2%

Harbeck. Ann Oncol. 2021;32:1571. O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

BRCA

- Ki67>20%
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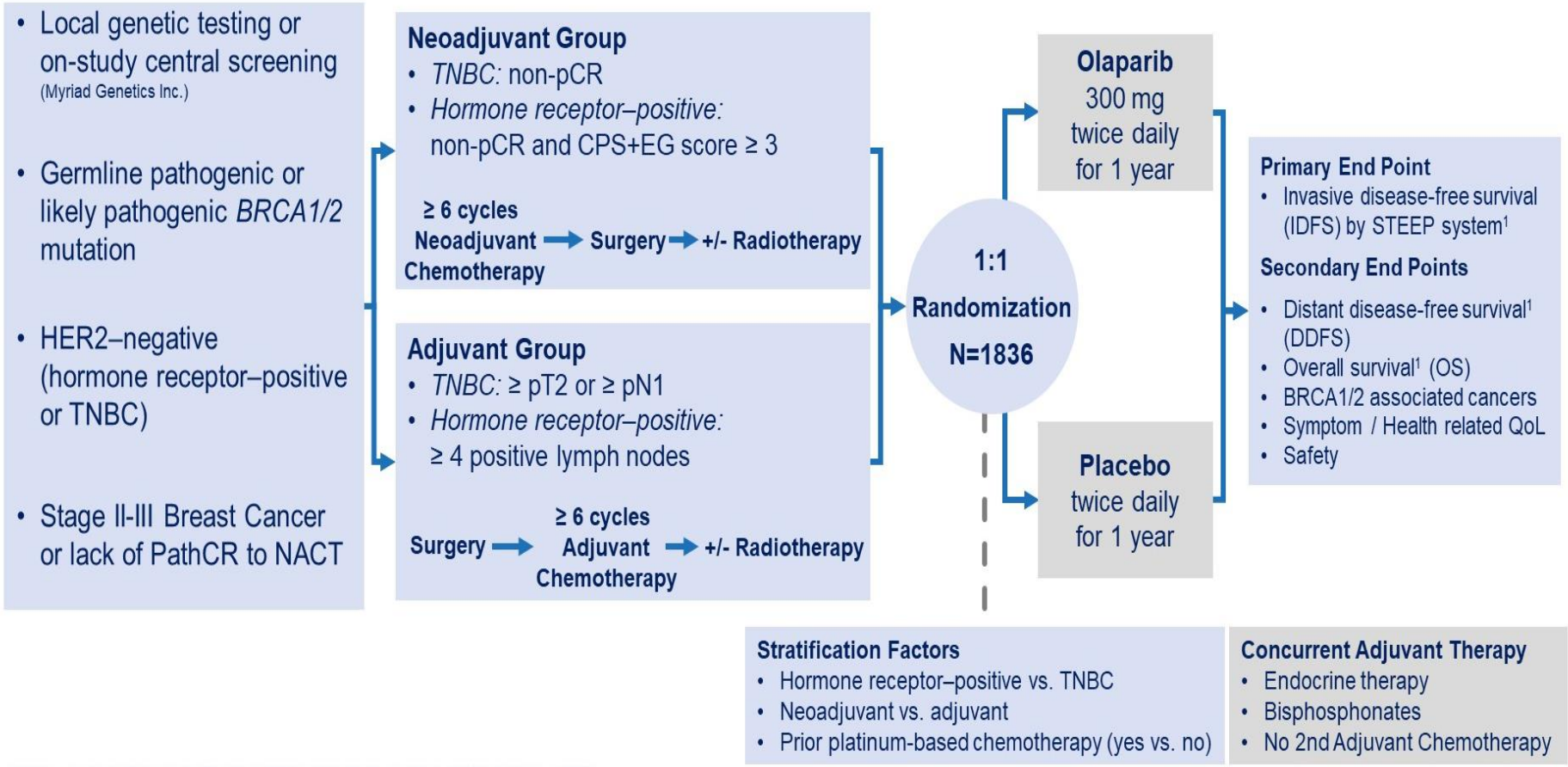
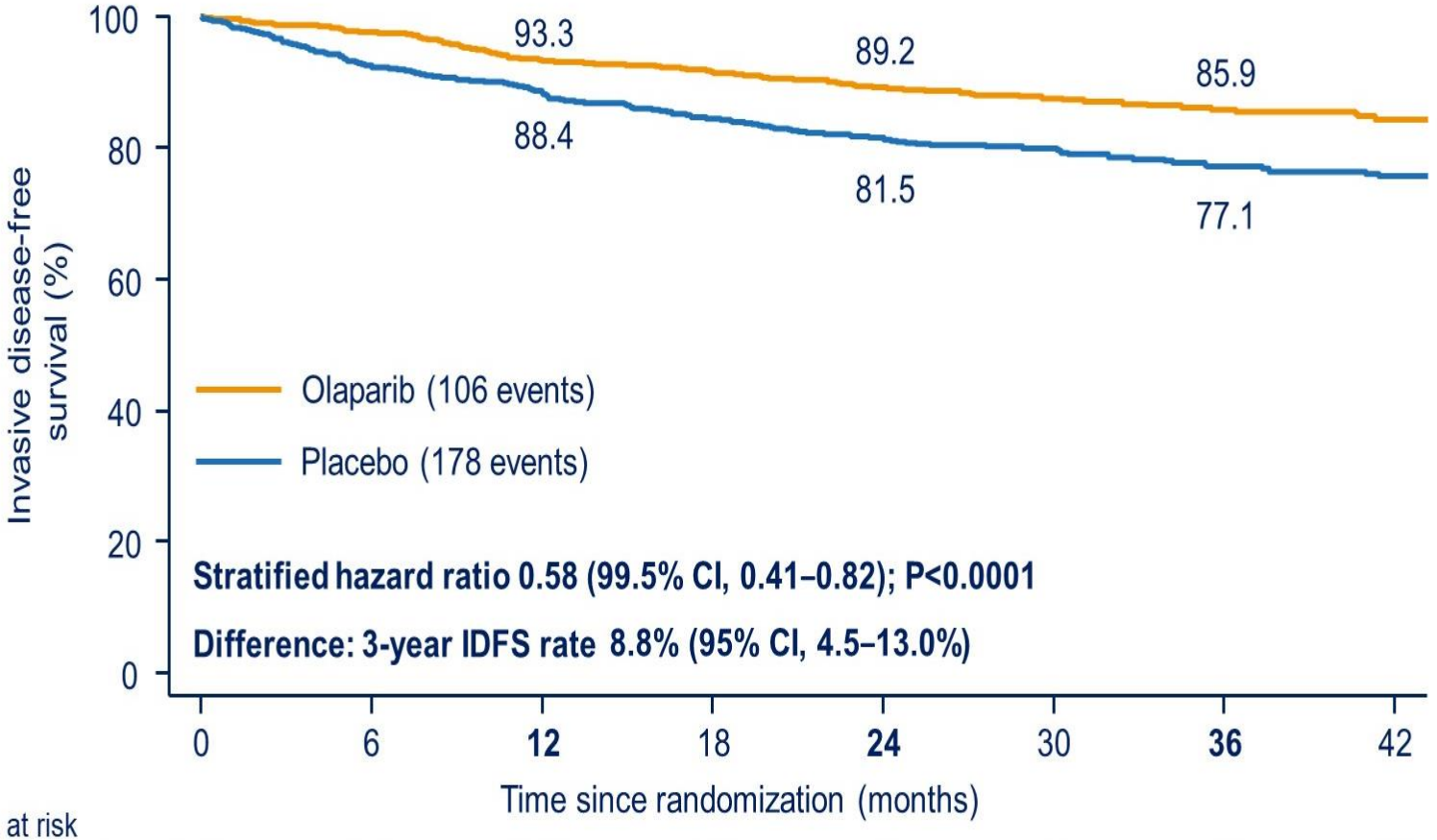
OlympiA trial design



Hormone receptor +ve defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple Negative defined as ER and PgR negative (IHC staining < 1%)
[1]Hudis CA, J Clin Oncol 2007

OlympiA results



No. at risk

Olaparib	921	820	737	607	477	361	276	183
Placebo	915	807	732	585	452	353	256	173