Early Breast Cancer
Highlights of the year 2023

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Disclosures

- Consultancy (Honoraria): AstraZeneca, Lilly, Novartis, Roche, Seagen, Menarini, MSD, Medimix.
- Travel/congresses grants: AstraZeneca, Gilead, Roche

Outline

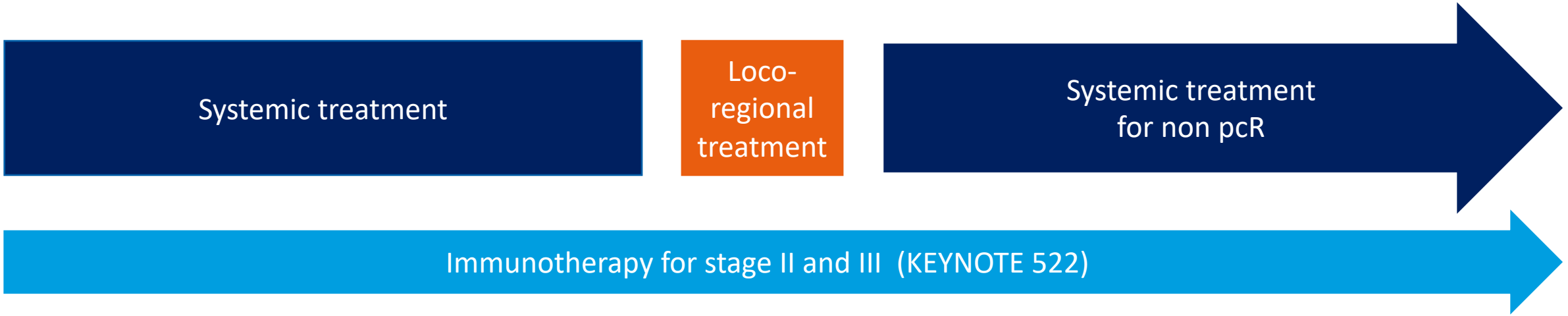
1/ Immunotherapy (ICI) in Early Breast Cancer (EBC)

2/ HER2 amplified EBC (KATHERINE update)

3/ Adjuvant CDK4/6 inhibitors in HR+ HER2- EBC

Immunotherapy (ICI) in Early Breast Cancer (EBC)

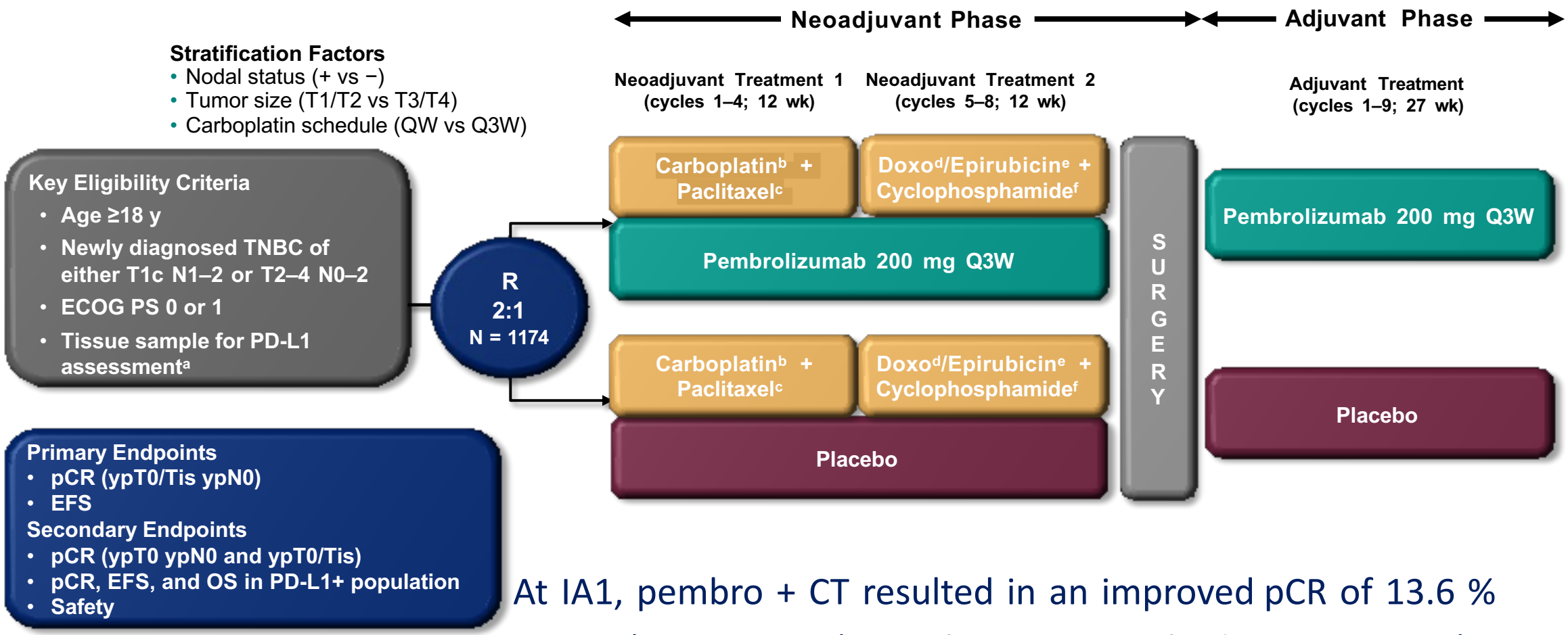
Immunotherapy in early TNBC in 2023



What are we still learning from KEYNOTE- 522?

What questions remain?

KEYNOTE-522 : 5-year update



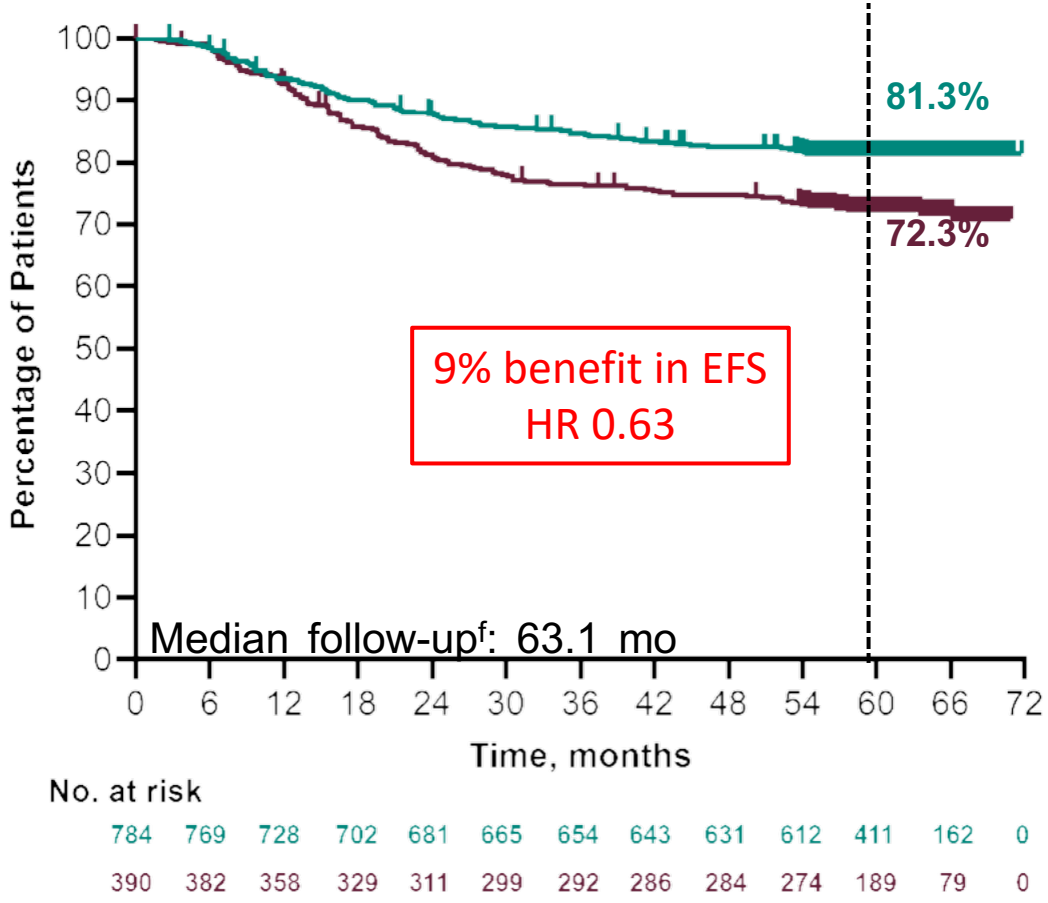
At IA1, pembro + CT resulted in an improved pCR of 13.6 %

At IA4 (mFU, 39.1m), pembro + CT resulted in EFS gain (HR, 0.63)

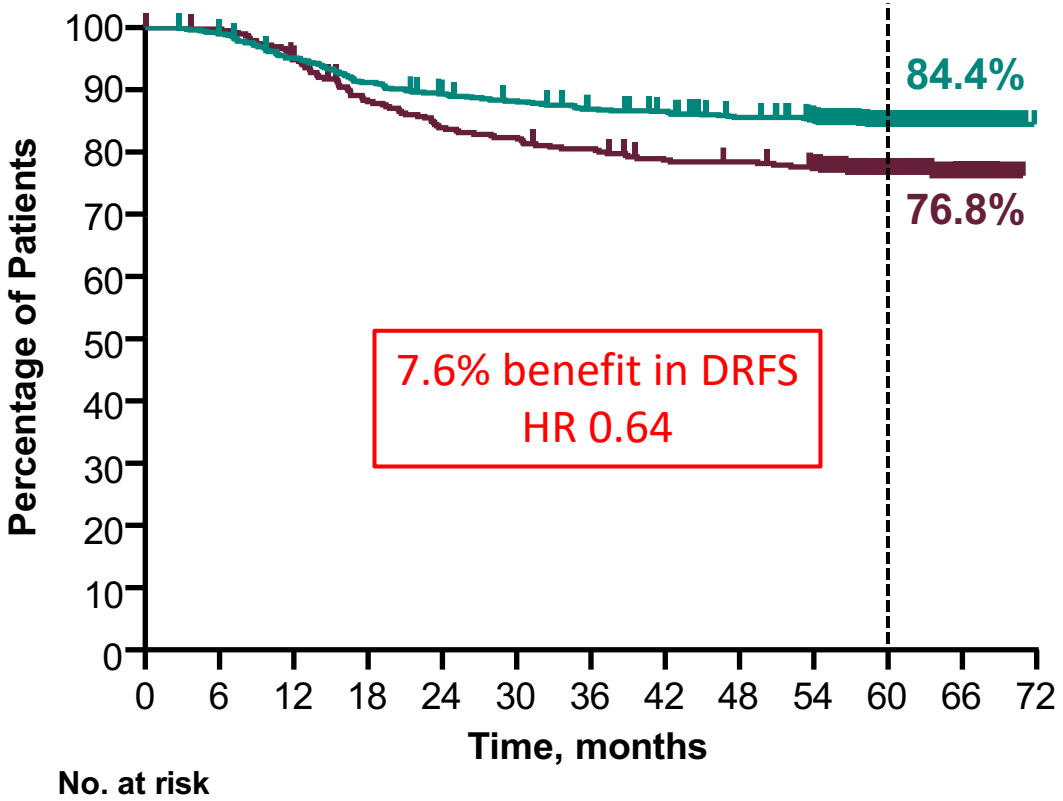
Peter Schmid ESMO 2023 and SABCS 2023

at IA6: EFS and Distant Recurrence-Free Survival

IA6[b]	Events	HR (95% CI)
Pembro + Chemo/Pembro	18.5%	0.63[c] (0.49–0.81)
Placebo + Chemo/Placebo	27.7%	



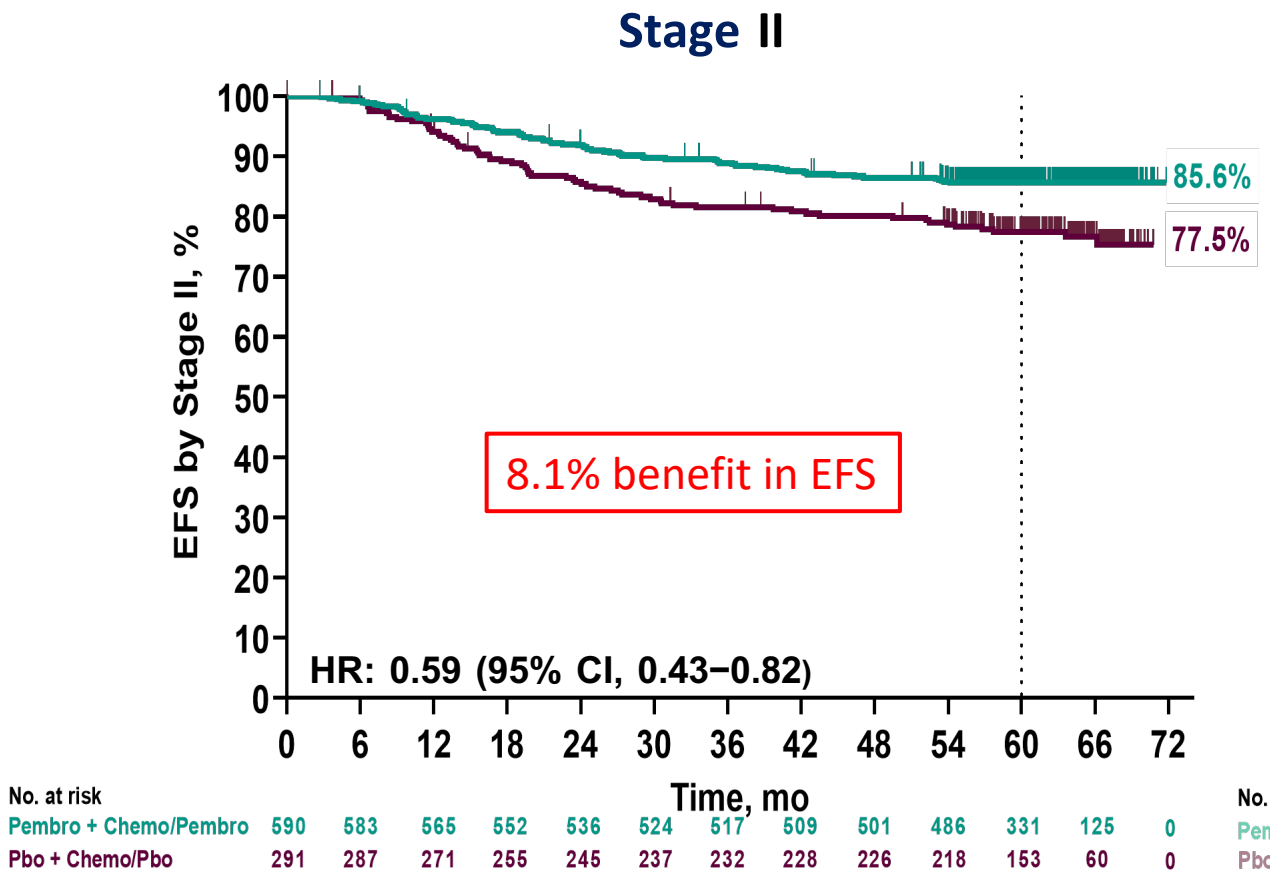
IA6	Events	HR (95% CI)
Pembro + Chemo/Pembro	15.3%	0.64[a] (0.49-0.84)
Placebo + Chemo/Placebo	23.1%	

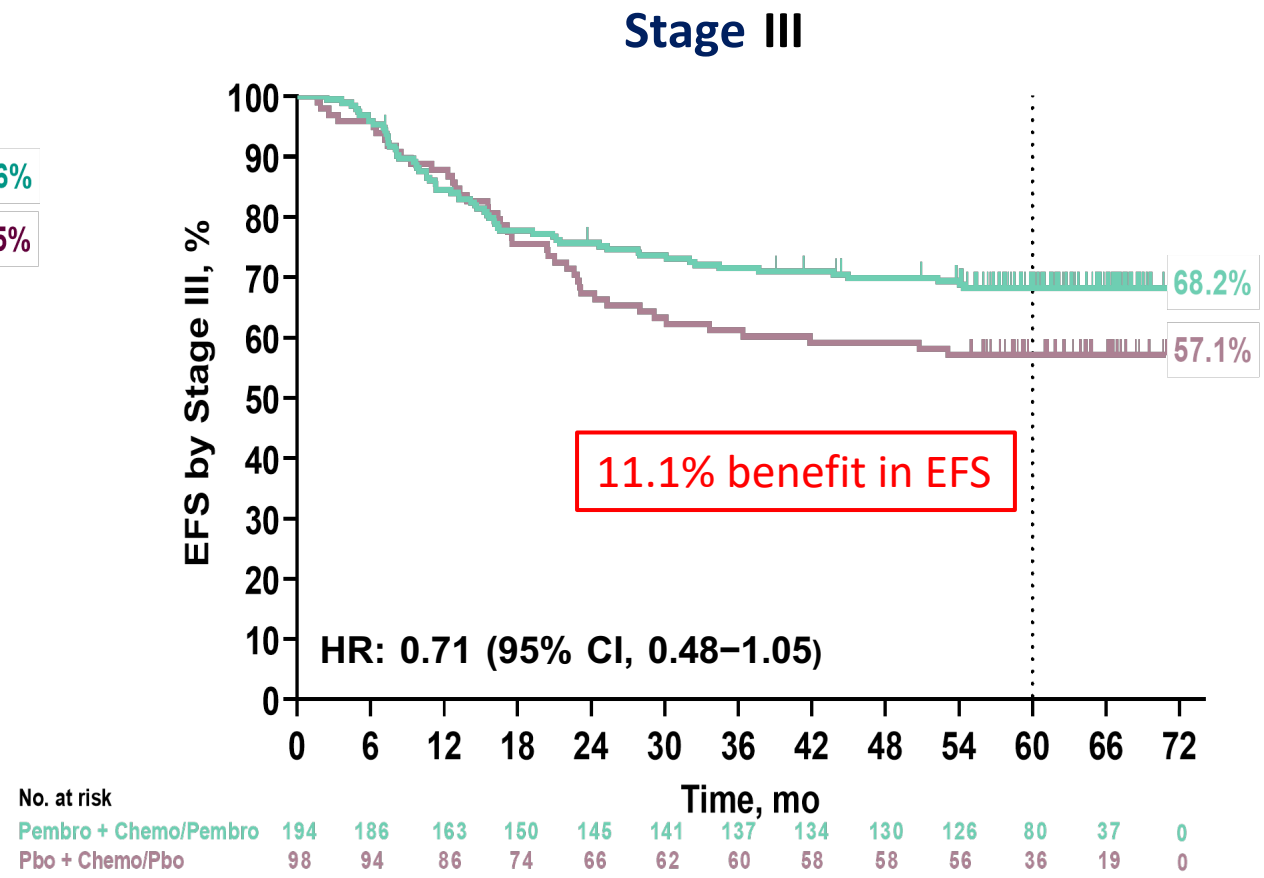


Data cutoff date: March 23, 2023.

Peter Schmid ESMO 2023

EFS at IA6 by Disease Stage

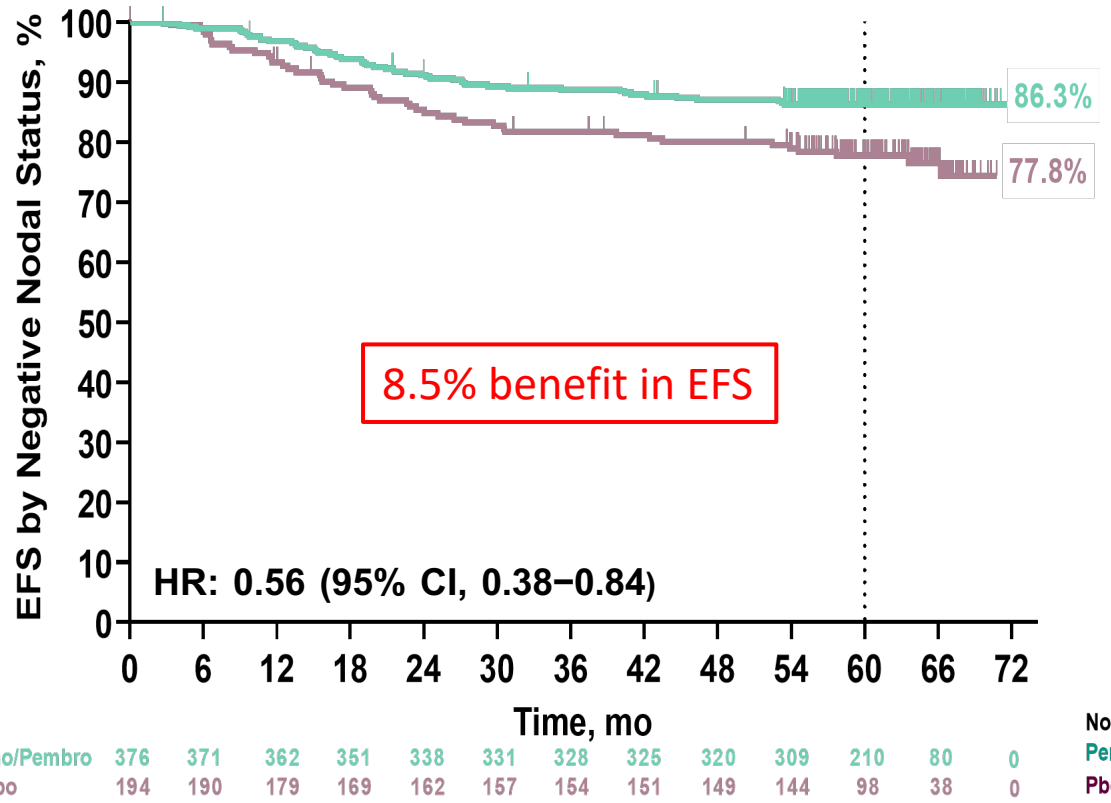




Peter Schmid SABCS 2023

EFS at IA6 by Nodal Status

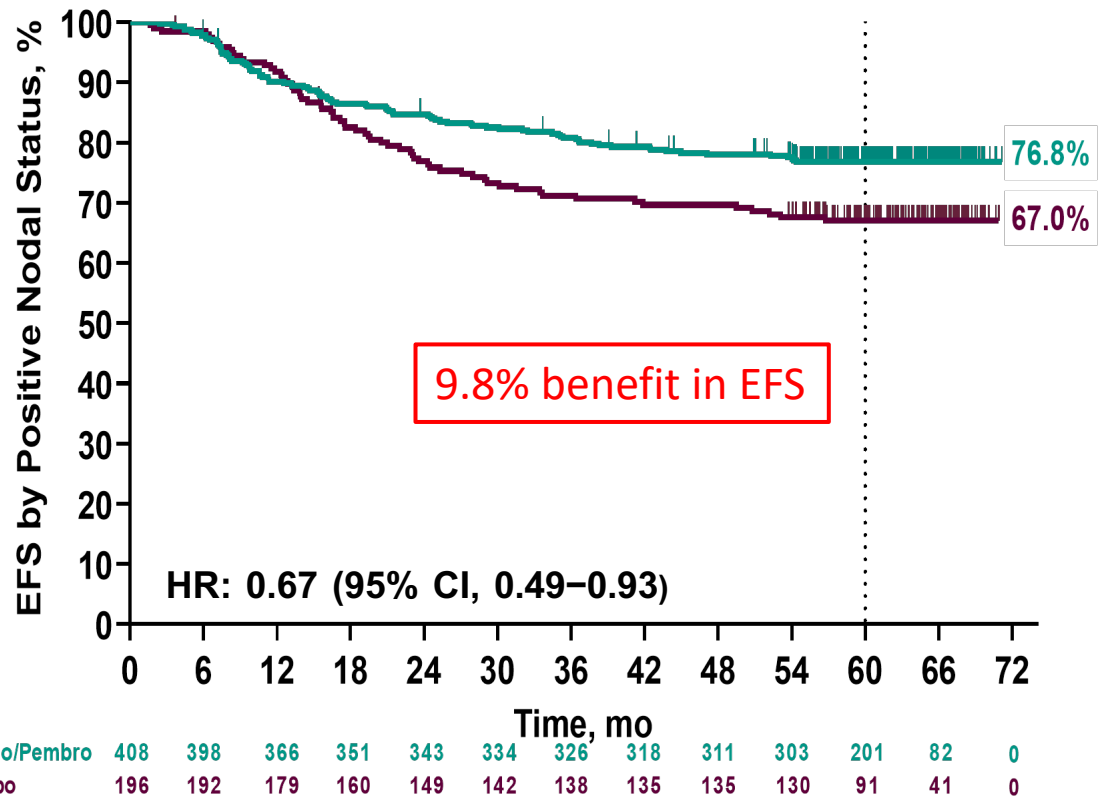
Negative Nodal Status



No. at risk

Pembro + Chemo/Pembro	376	371	362	351	338	331	328	325	320	309	210	80	0
Pbo + Chemo/Pbo	194	190	179	169	162	157	154	151	149	144	98	38	0

Positive Nodal Status



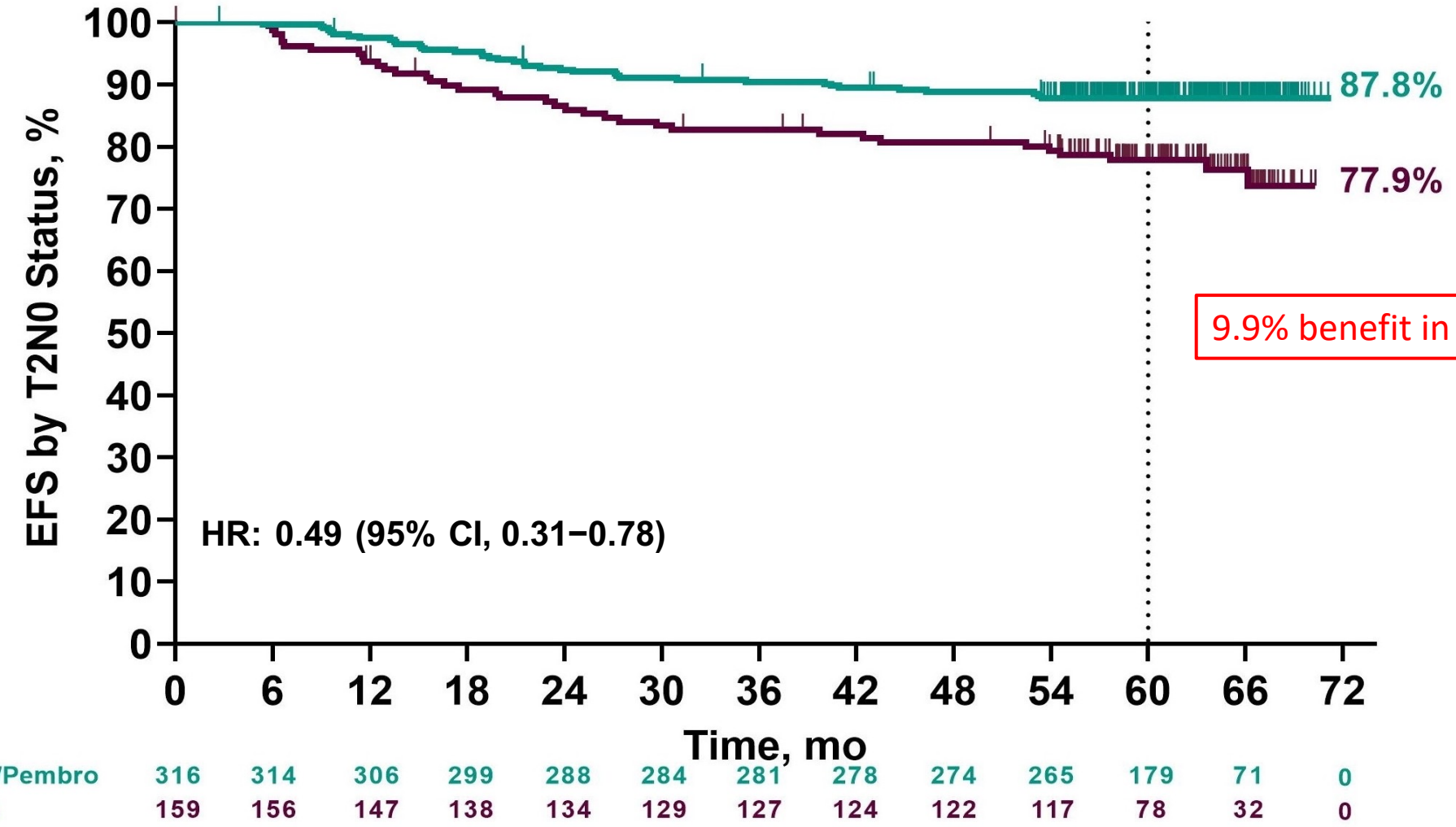
No. at risk

Pembro + Chemo/Pembro	408	398	366	351	343	334	326	318	311	303	201	82	0
Pbo + Chemo/Pbo	196	192	179	160	149	142	138	135	135	130	91	41	0

Data cutoff date of March 23, 2023.

EFS at IA6 by T2N0 Status

This group represents about 40% of the overall population



9.9% benefit in EFS

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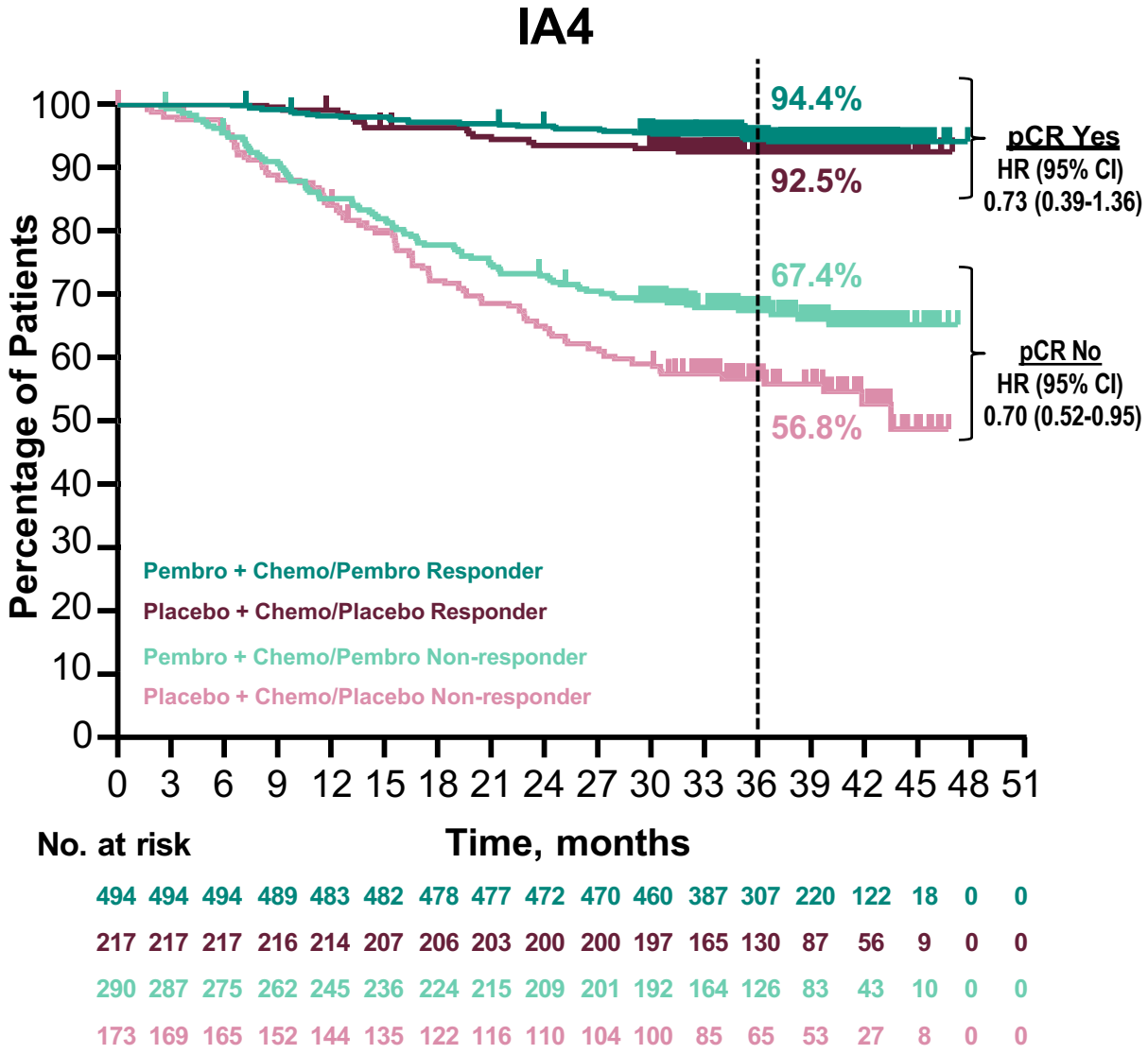
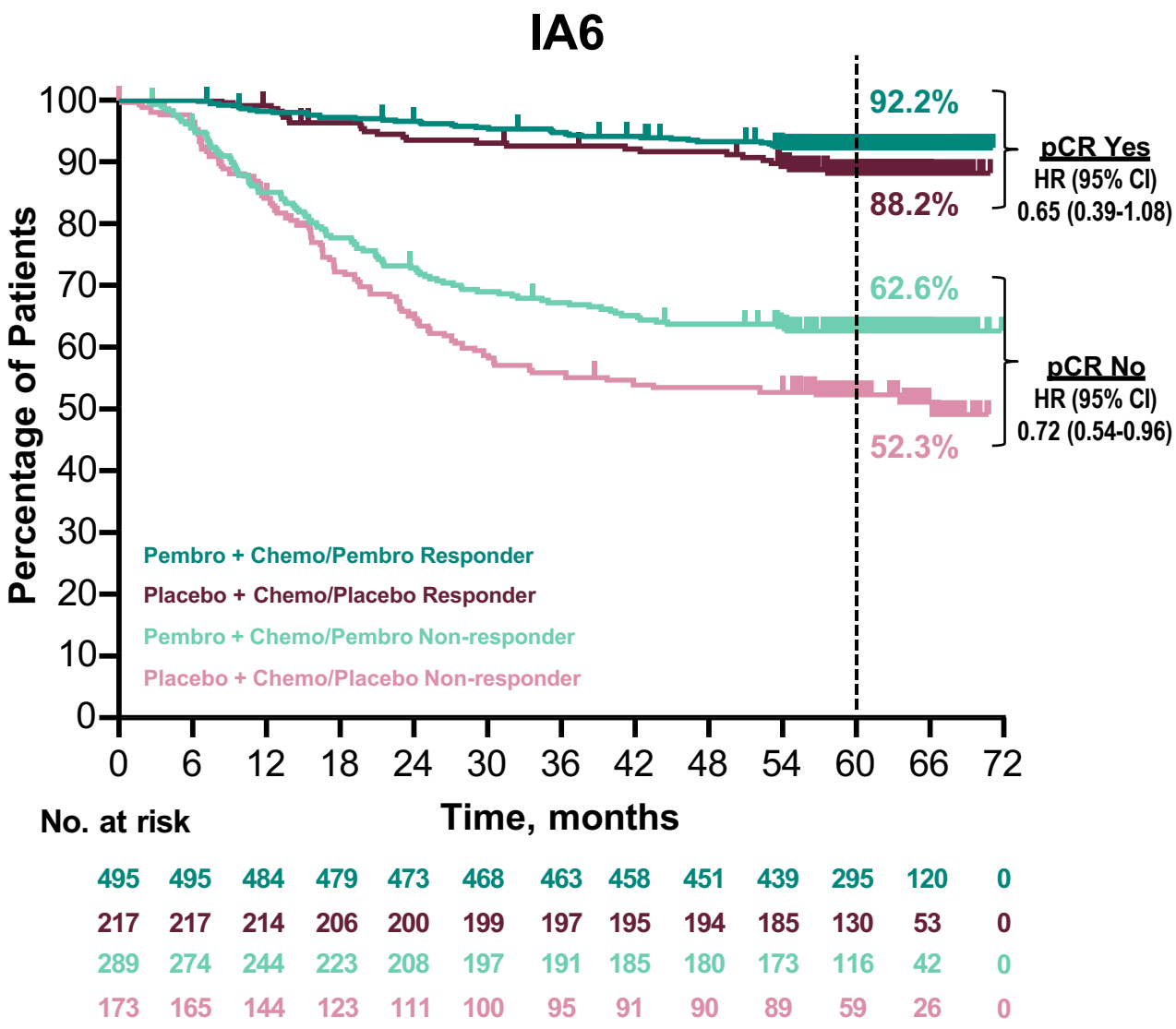
EFS by pCR (ypT0/Tis ypN0)



Data cutoff date: March 23, 2021.



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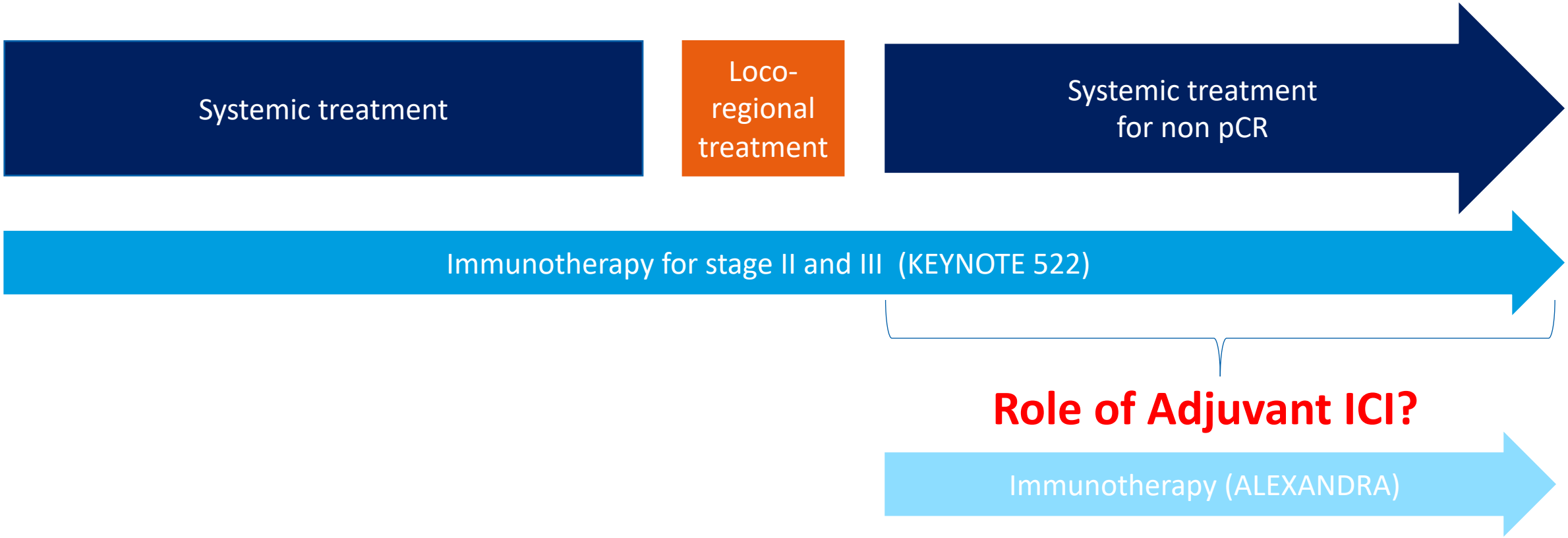
Immunotherapy in early TNBC in 2023

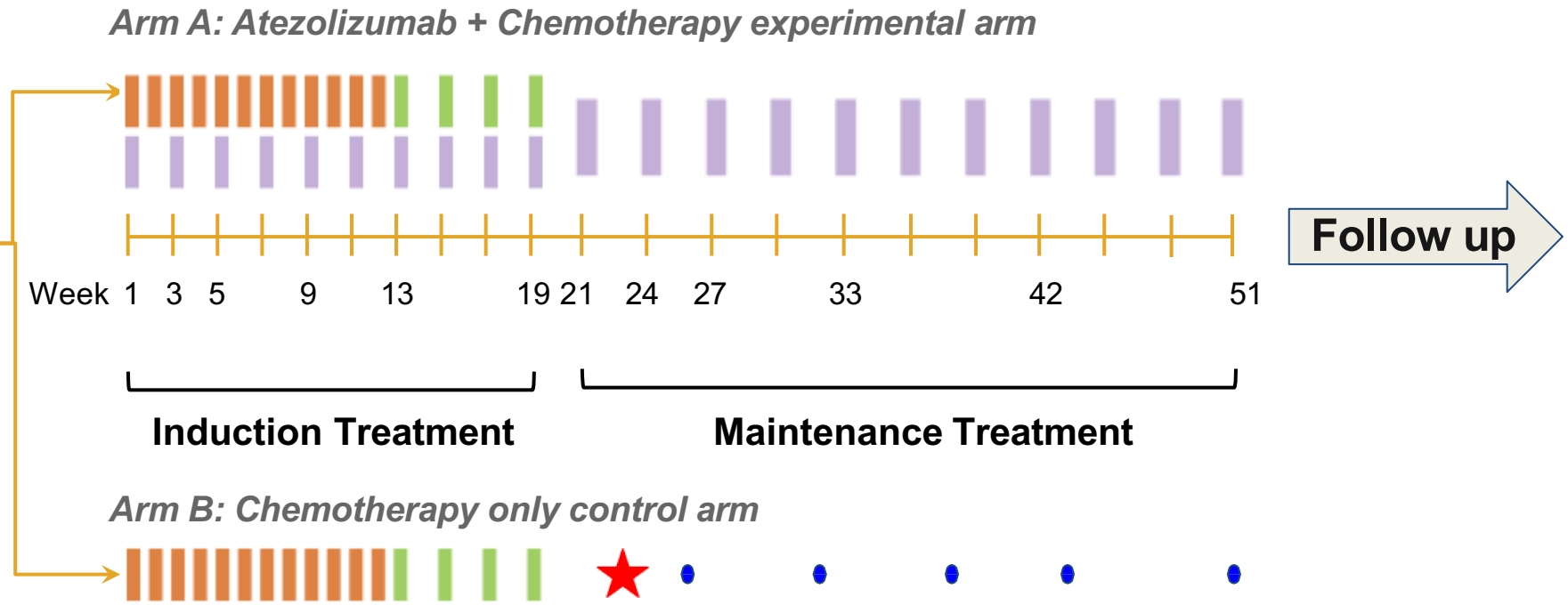


Alexandra/IMpassion030 ph3: Adjuvant Atezolizumab

SURGERY

Early TNBC
- **Stage II-III**
- **At least 50% node-positive**
- **N=2300**

R



Primary Endpoint: IDFS

Stratification factors:

Axillary nodal status
(0 vs. 1−3 vs. ≥ 4 positive lymph nodes)

Surgery
(breast conserving vs. mastectomy)

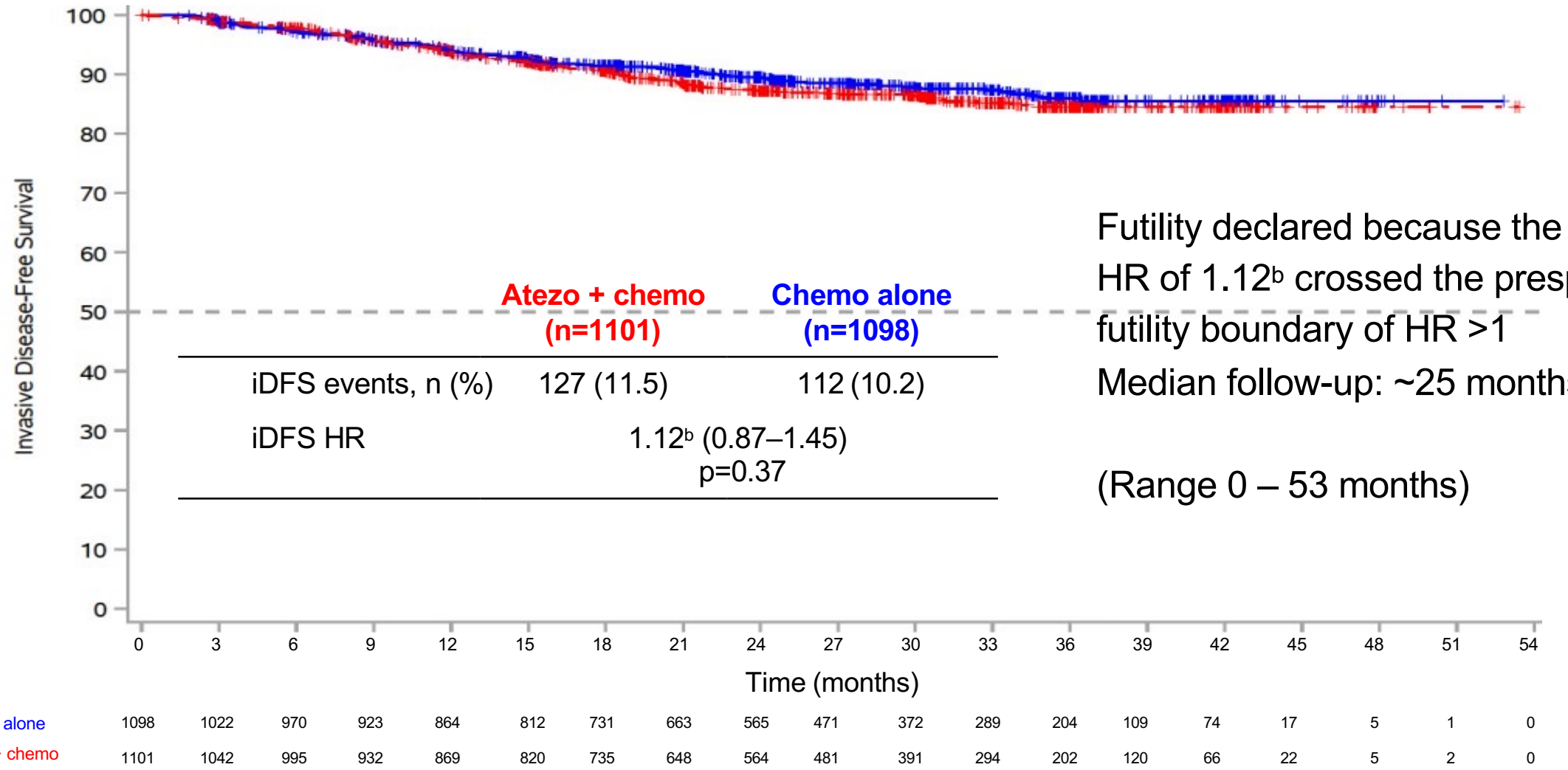
Tumor PD-L1 status
(IC0 vs. IC1/2/3)

- Paclitaxel qw for 12 weeks
- ddAC/EC q2w for 4 doses supported with G-CSF/GM-CSF
- Atezolizumab
  - Induction: 840 mg q2w for up to 10 doses
  - Maintenance: 1200 mg q3w to complete 1 year
- Monitoring visit Arm B

Baseline characteristics, ITT population

Characteristic, n (%)	Atezo + chemo (n=1101)	Chemo alone (n=1098)	Total (N=2199)
Primary Tumor Stage			
pT1-pT2	1024 (93.0)	1045 (95.2)	2069 (94.1)
pT3	71 (6.4)	51 (4.6)	122 (5.5)
Other[1]	6 (0.5)	2 (0.2)	8 (0.4)
Axillary Nodal Status (IxRS)			
0	577 (52.4)	573 (52.2)	1150 (52.3)
1-3	390 (35.4)	390 (35.5)	780 (35.5)
≥4	134 (12.2)	135 (12.3)	269 (12.2)
AJCC Stage at Surgery			
Stage II	935 (84.9)	940 (85.6)	1875 (85.3)
Stage III	161 (14.6)	157 (14.3)	318 (14.5)
Other[2]	5 (0.5)	1 (<0.1)	6 (0.3)
PD-L1 Status (IxRS)			
IC 0	316 (28.7)	316 (28.8)	632 (28.7)
IC 1/2/3	785 (71.3)	782 (71.2)	1567 (71.3)

Additional interim analysis: 1° endpoint: iDFS (ITT population)



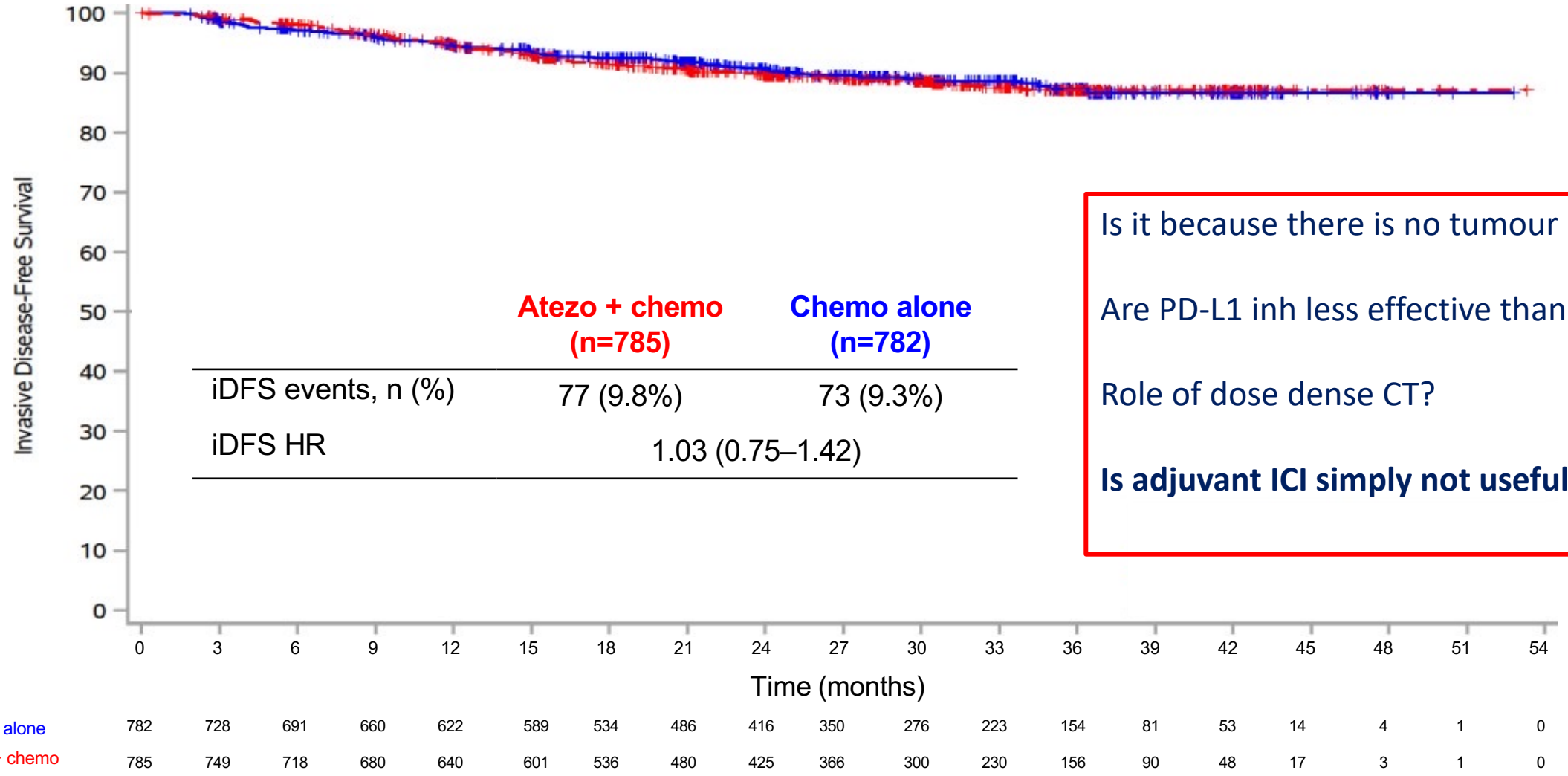
	Atezo + chemo (n=1101)	Chemo alone (n=1098)
iDFS events, n (%)	127 (11.5)	112 (10.2)
iDFS HR	1.12[b] (0.87–1.45) p=0.37	

Futility declared because the observed HR of 1.12[b] crossed the prespecified futility boundary of HR >1

Median follow-up: ~25 months

(Range 0 – 53 months)

Key 2° efficacy endpoint: iDFS in the PD-L1+ subgroup (71%)



	Atezo + chemo (n=785)	Chemo alone (n=782)
iDFS events, n (%)	77 (9.8%)	73 (9.3%)
iDFS HR	1.03 (0.75–1.42)	

Is it because there is no tumour in place?

Are PD-L1 inh less effective than PD-1 inh?

Role of dose dense CT?

Is adjuvant ICI simply not useful ?

Michail Ignatiadis SABCS 23

Real world toxicities with Keynote 522 regimen

- Multicenter retrospective cohort of patients (577 patients, 17 sites)
  - 360 unplanned care visits
  - High hospitalisation rates: 39% for black patients and 36% for white

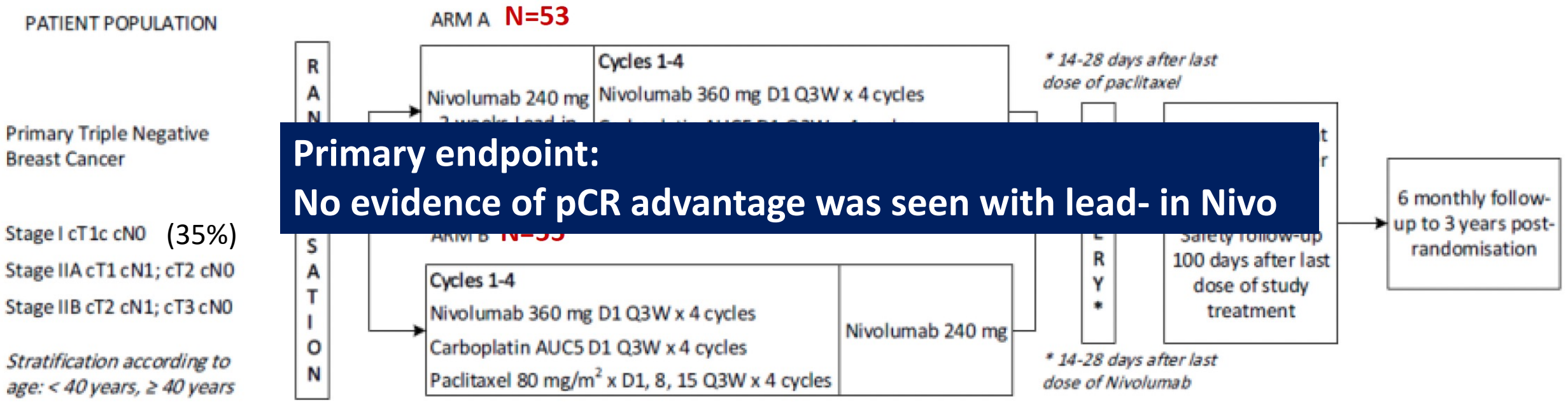
Safety	Any Grade (n=577)	Grade 3+	KN522, Any Grade (n= 783)	KN522 Grade 3+
Adverse Drug Event (ADE) Causing Dose Reductions	217 (37.6%)		No equivalent reported	
ADE Causing Early Discontinuation	228 (39.5%)		216 (27.7%)	
Patients who experienced an immune-related adverse effect (irAE)?	412 (71.4%)	184 (31.9%)	262 (33.5%)	101 (12.9%)

- High rates of all grade hepatitis/transaminitis (19.9%), hypothyroidism (18%), rash (23.4%), and adrenal insufficiency (7.8%), pneumonitis (3.6%), hypophysitis (1.4%) were observed.
- Lower pCR rates in patients having dose reductions

M. Hofherr SABCS 2023 poster session

Phase II Neoadjuvant Nivolumab (N) 2 week lead-in followed by 12 weeks of concurrent N+carboplatin plus paclitaxel (CbP) vs concurrent N+CbP in TNBC: (BCT1902/IBCSG 61-20 Neo-N)

Enrolment: N=108 evaluable at 14 centers from July '20 – Apr '22; Median follow-up 12 months



Primary endpoint:
No evidence of pCR advantage was seen with lead- in Nivo

Hypothesis: pCR=ypT0/is ypN0 (lower 90% CI, primary endpoint) greater than 40%

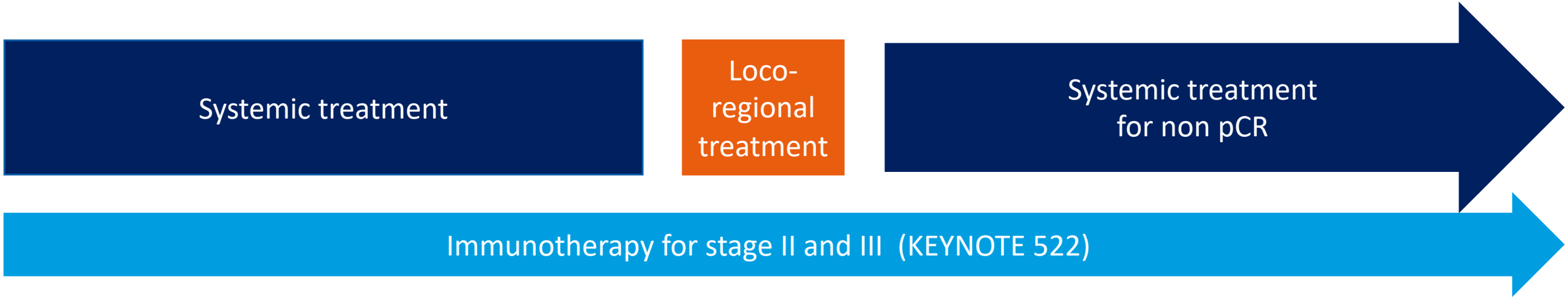
Secondary endpoints: RCB, safety, pCR by PD-L1 (≥1% SP-142) and TILs (≥30%), EFS

N.Zdenkowski SABCS 23

What should we remember from Neo-N?

- pCR rates in the overall population of 53%
- pCR in specific subgroups:
  - PD-L1 71% positive vs 33% negative; sTILs 67% high vs 47% low
- This study does support a 12 week neoadjuvant non- anthracycline chemotherapy regimen with nivolumab for Stage some I/II TNBC (immune enriched?)
- Need for EFS results and validation in larger trials

Immunotherapy in early TNBC in 2023



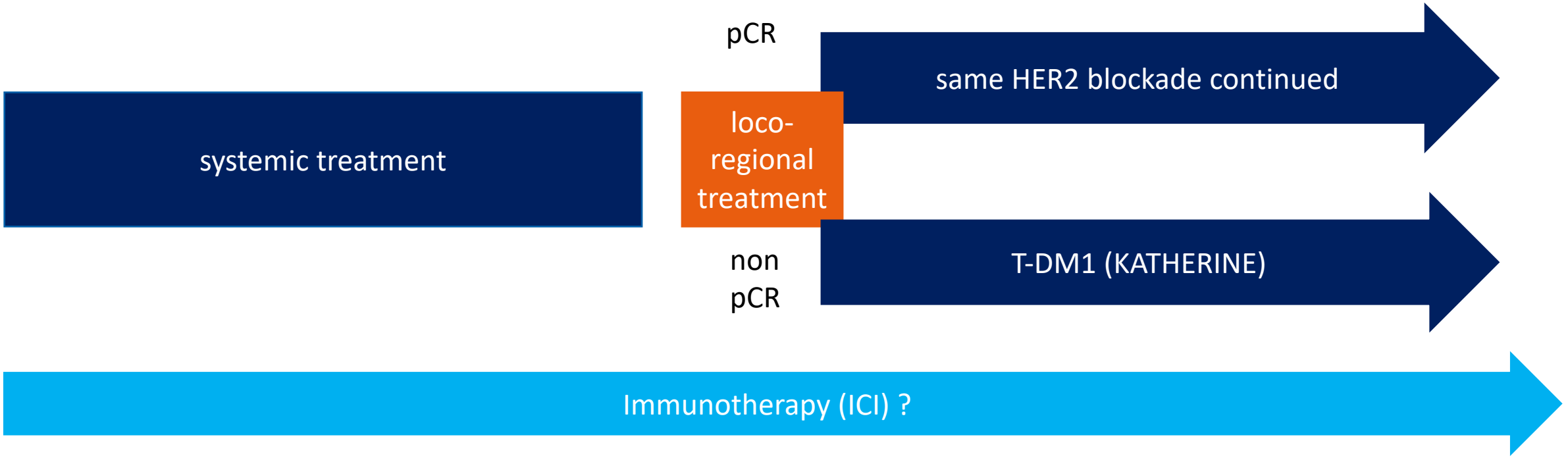
Keynote 522:

- Efficacy is clear even for smaller stages (II)
- Real world toxicities make this regimen unsuitable for all

Questions remaining for 2024:

- Why results with ICI are inconstant (NeoTRIP negative/GeparNuevo)?
- Place of adjuvant ICI (ALEXANDRA/GeparNuevo)? OptimICE-PCR
- De-escalation of chemo (ADAPT-TN/NIVO-N)? in high pro-immune profile? value of PDL1,TILS? signatures? lower volume? need for guidance in the clinic.

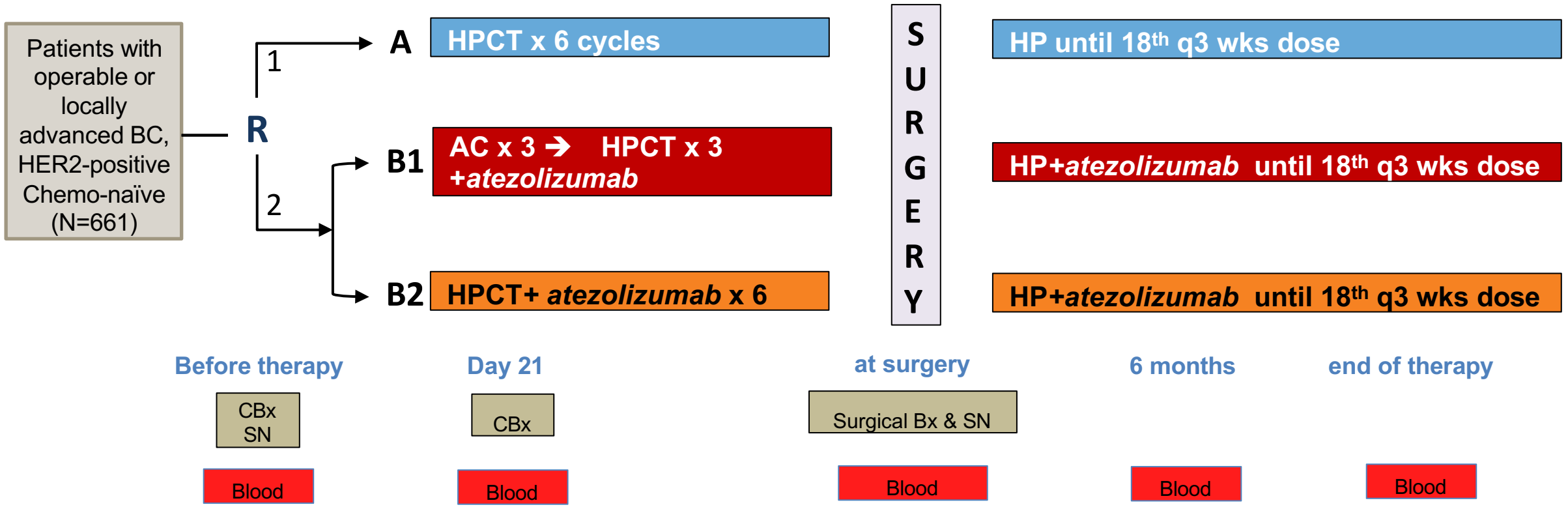
Immunotherapy and early **HER2 +** BC in 2023



There is a rationale in attempting to use ICI in HER2 disease (TILS: prognostic/predictive[1])
No strong evidence so far of efficacy in MBC (Kate 2) nor in EBC (Impassion 050)

1. Hills et al EBCTCG ASCO 23 Abs 508)

APTneo: Secondary endpoint pCR (Primary endpoint (5yr EFS) not reported)



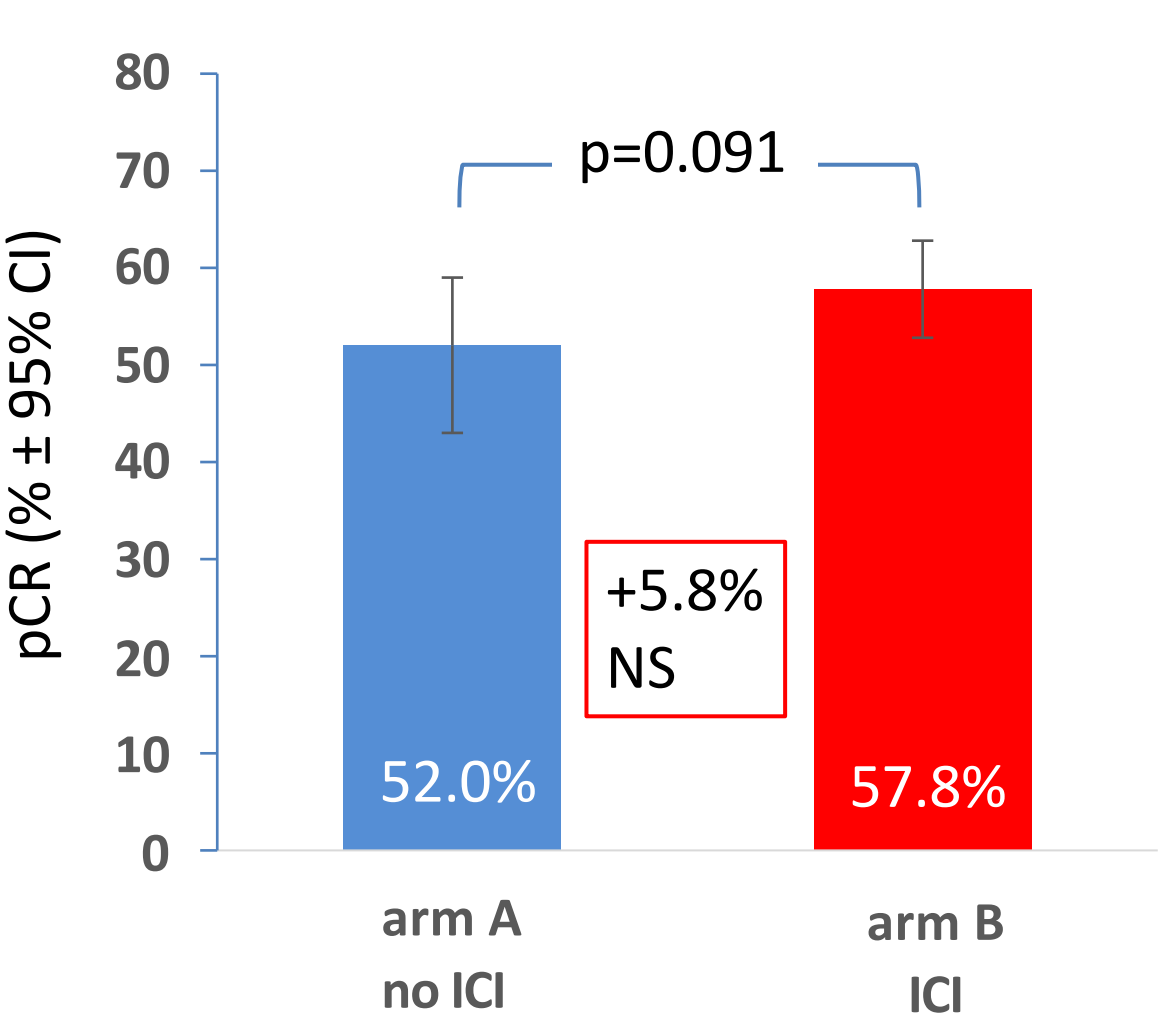
A = doxorubicin, 60 mg/m^2 q 21 days; Cy = Cyclophosphamide, 600 mg/m^2 q 21 days; C = Carboplatin, AUC 2 d1&8 q 21 days; T = paclitaxel, 90 mg/m^2 d1&8 q 21 days; H = Trastuzumab, 8 mg/kg on first dose, 6 mg/kg thereafter; P = Pertuzumab, 840 mg on first dose, 420 mg thereafter; Atezolizumab, 1200 mg i.v. infusion q 3 wks, S = surgery ; CBx = Core Biopsy; SN = Sentinel Node. As of May 2021, patients with RD at surgery could receive T-DM1

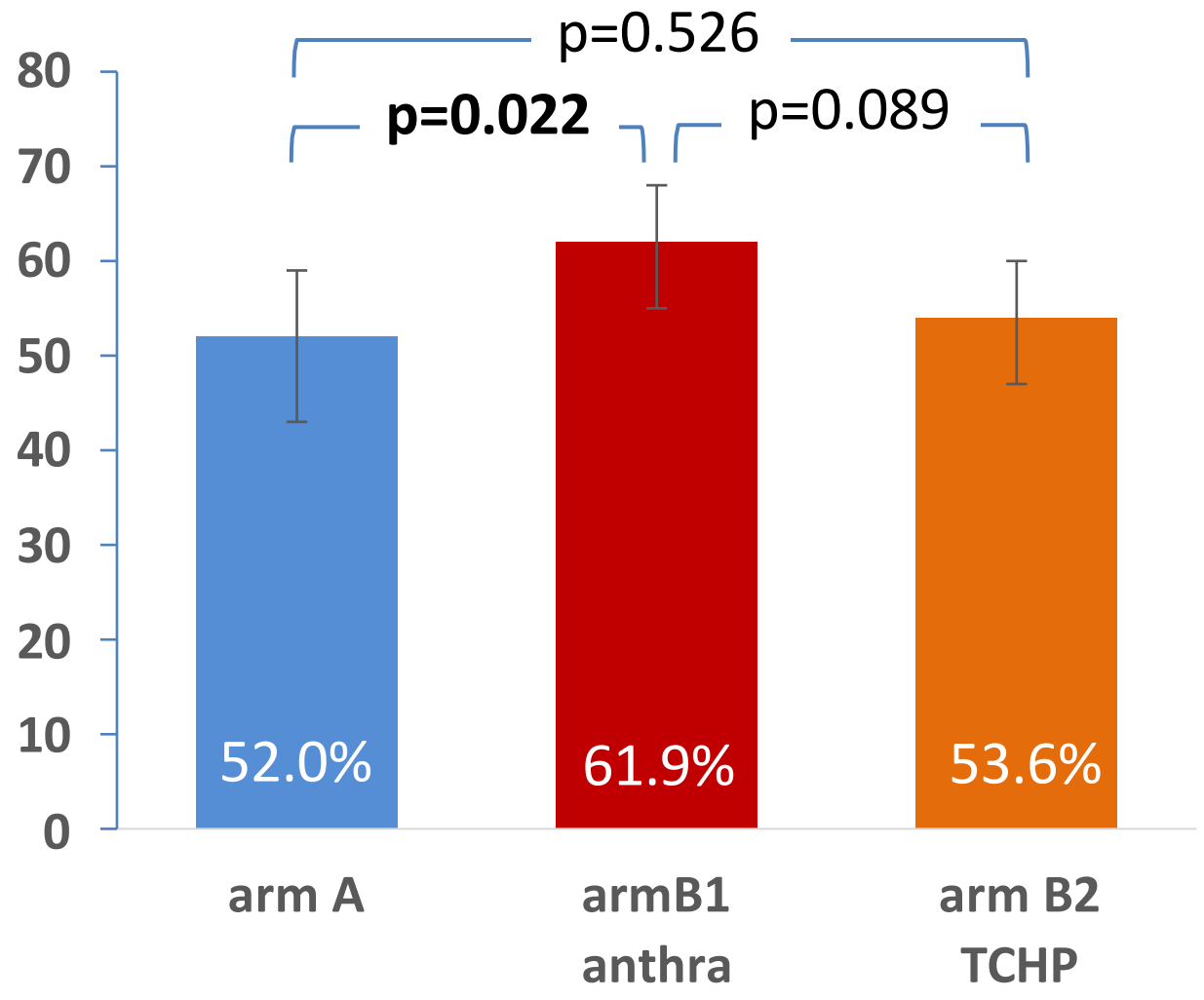
APTneo: patient characteristics at randomization (ITT population)

		Arm A (223)		Arm B1 (218)		Arm B2 (220)	
		#	%	#	%	#	%
Disease stage	Early high-risk	122	54.7	120	55.0	123	55.9
	Locally advanced	101	45.3	98	45.0	97	44.1
PD-L1*	Positive	68	30.5	65	29.8	68	30.9
	Negative	155	69.5	153	70.2	152	69.1
ER and/or PR	Positive	136	61.0	142	65.1	152	69.1
	Negative	87	39.0	76	34.9	68	30.9
Median age (range)		50 (29-79)		50 (21-81)		49 (24-78)	

* SP142; pos ≥ 1% IC

APTneo: Main Results: pCR rates (ypT0/is ypN0)





Wait for primary Endpoint: EFS

L.Gianni SABCS 2023

APTneo: Multivariate analysis of pCR

Variable	Effect	OR (95% CI)	P value
Treatment			22
			26
PD-L1			12
Disease stage			32
Hormonal rece			001
Age	<= 50 vs > 50	1.18 (0.86-1.63)	0.311
sTIls* (high vs low)	Arm B1 vs Arm A	1.58 (1.07-2.34)	0.021
sTILs* (high vs low)	Arm B2 vs Arm A	1.15 (0.78-1.69)	0.48

Wait for EFS results

*sTILS: stromal TILs; high = ≥30%

HR+ HER2 EBC and immunotherapy

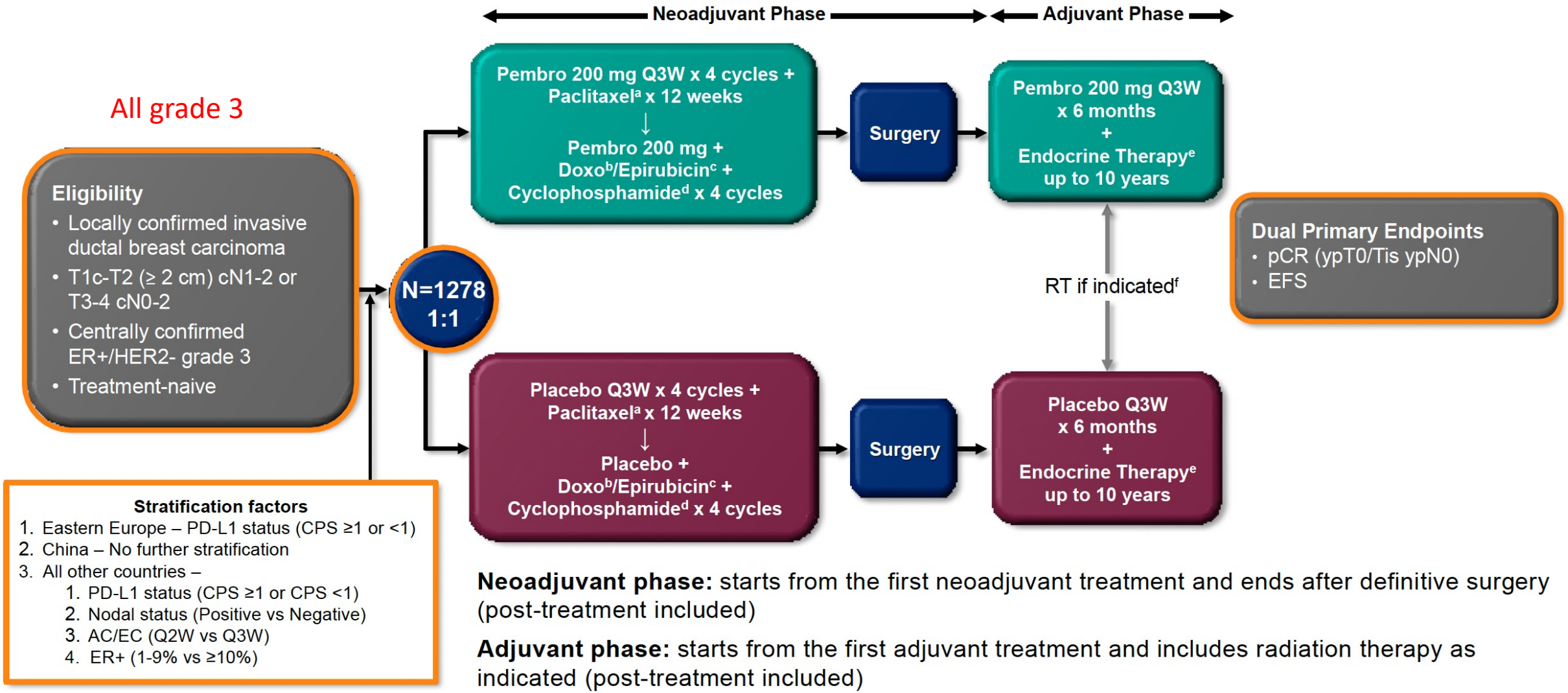
Immunotherapy is not approved in MBC and there is doubt as to real immunogenicity

There is some evidence of benefit from literature (I-SPY)

Heterogeneity (lum A, B, basal like…)

KEYNOTE-756

All grade 3



Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)

Cardoso et al, ESMO 2023; O'Shaughnessy SABCS 2023

Checkmate-7FL

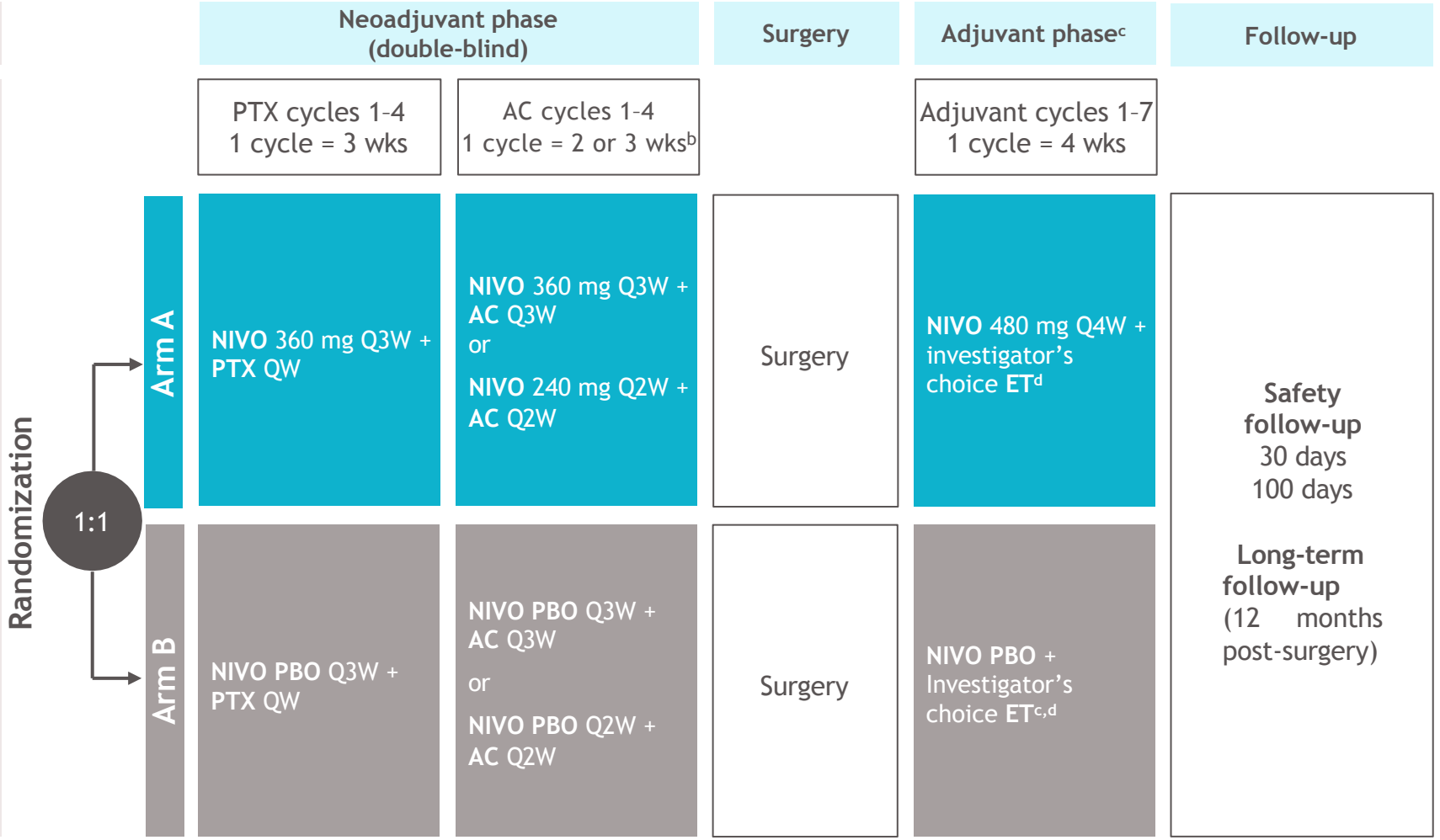
Screening

Key inclusion criteria

- Newly diagnosed ER+ HER2− breast cancer
- Confirmed ER+ breast cancer
- T1c (tumor size 2 cm only)-T2, cN1–cN2 or T3-T4, cN0-cN2
- Grade 3 with ER ≥ 1% or grade 2 with ER 1–10%[a]
- Adequate organ function
- Tissue available for biomarker assessment
- ECOG PS 0–1

Stratification factors

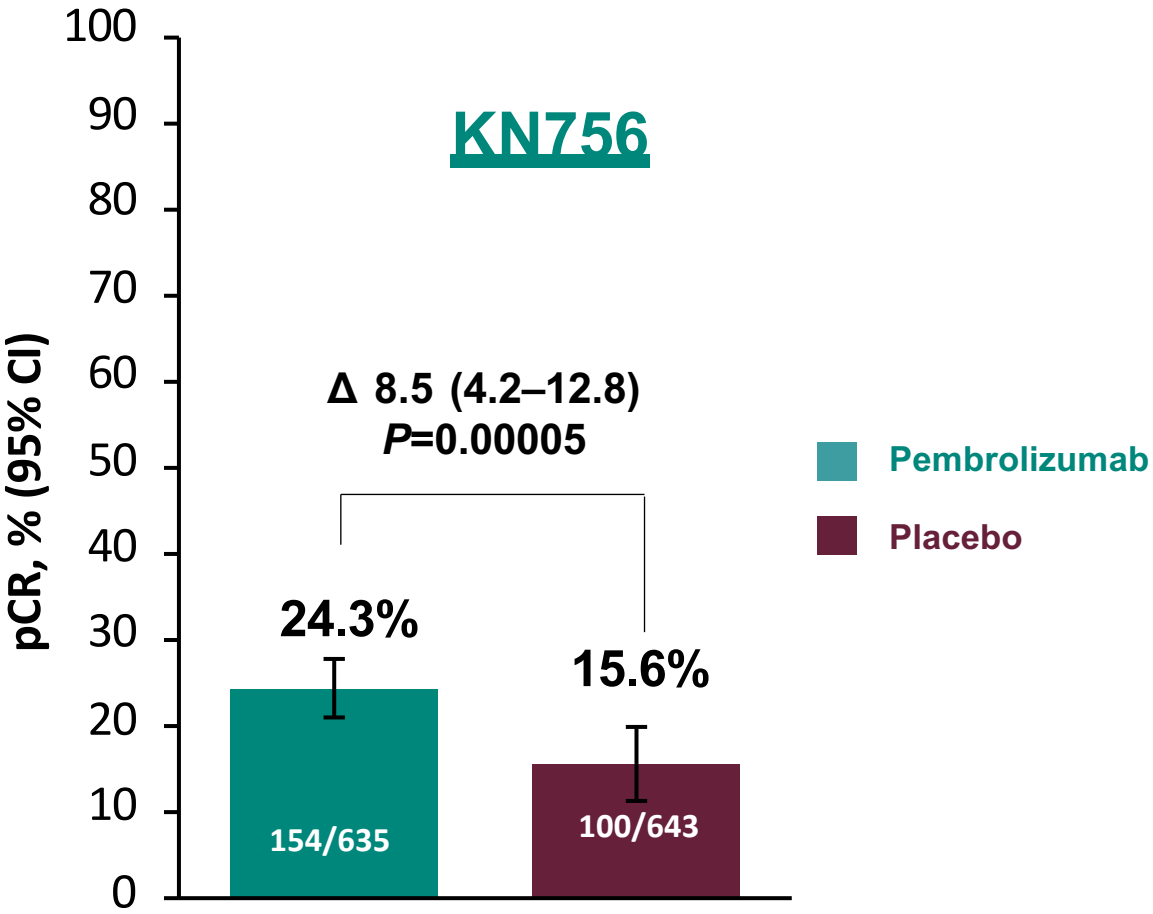
- PD-L1 IC (≥ 1% or < 1%) by SP142
- Tumor grade (3 or 2)
- Axillary nodal status (positive or negative)
- AC frequency (Q3W or Q2W)



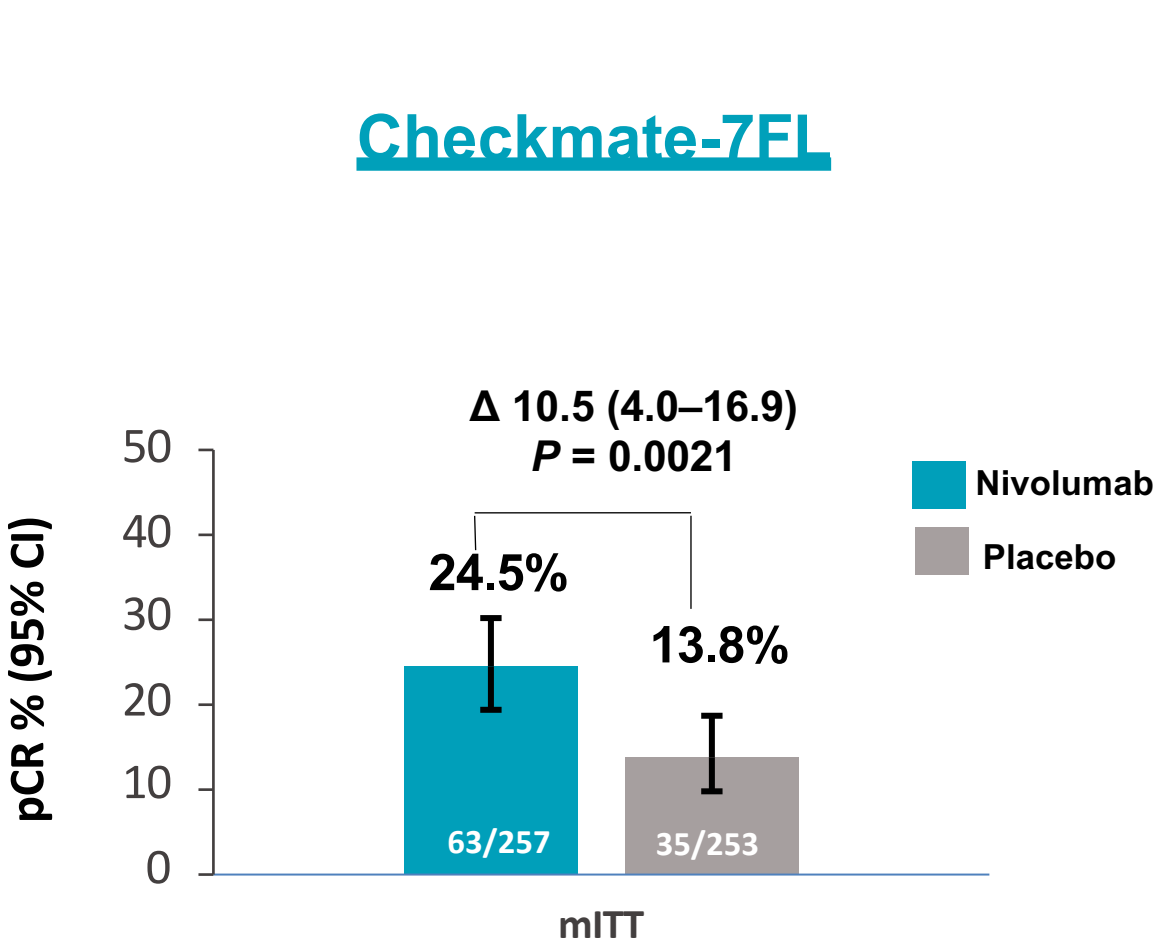
Some grade 2 and N0
but vast majority high grade and N+

Loi et al, LBA 20, ESMO 2023; Loi et al, SABCS 2023

Pathological Complete Response (ypT0/Tis ypN0)



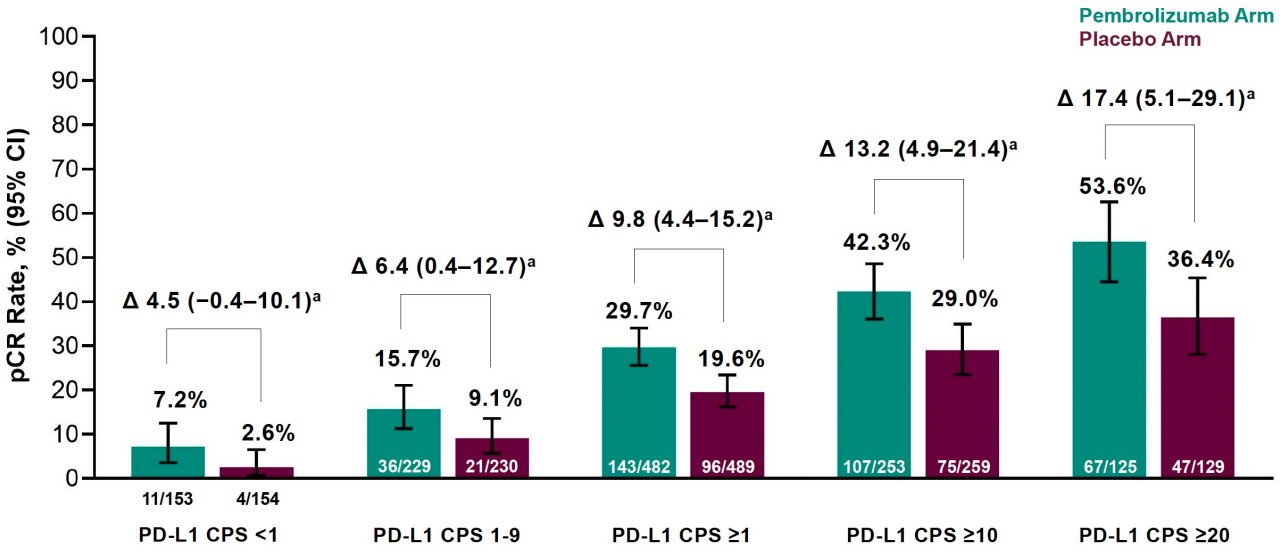
Cardoso et. al. ESMO 2023



Loi et. al. ESMO 2023

KEYNOTE-756: Key subgroup and biomarker analyses

PD-L1 status (22C3 CPS)



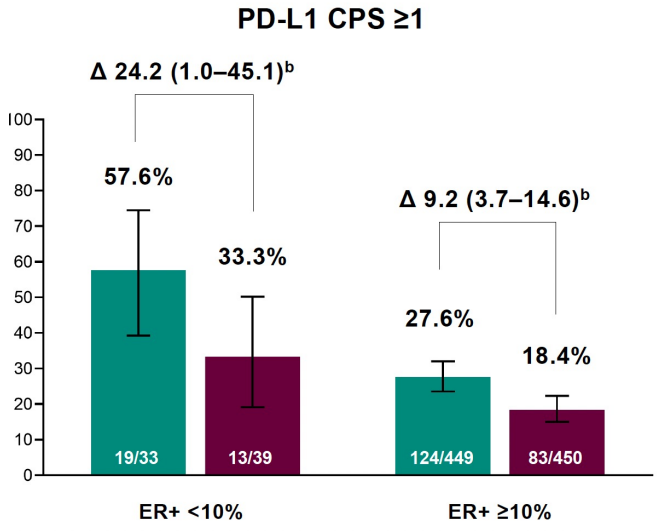
CPS <1
n=307 (24%)

CPS ≥1
n=971 (76%)

CPS ≥10
n=512 (40%)

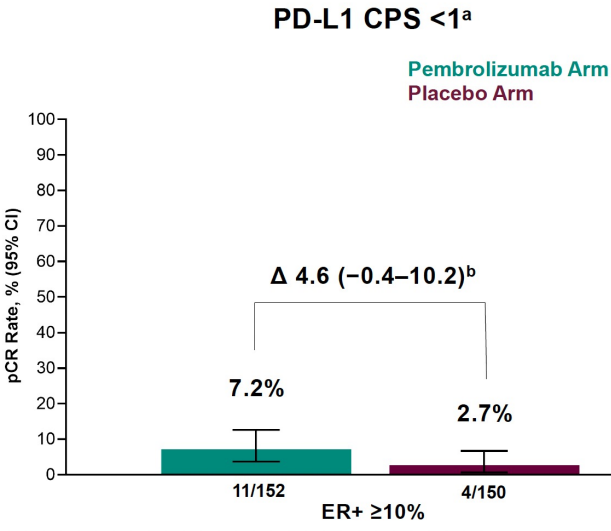
CPS ≥20
n= 254 (20%)

ER status



ER+ < 10%

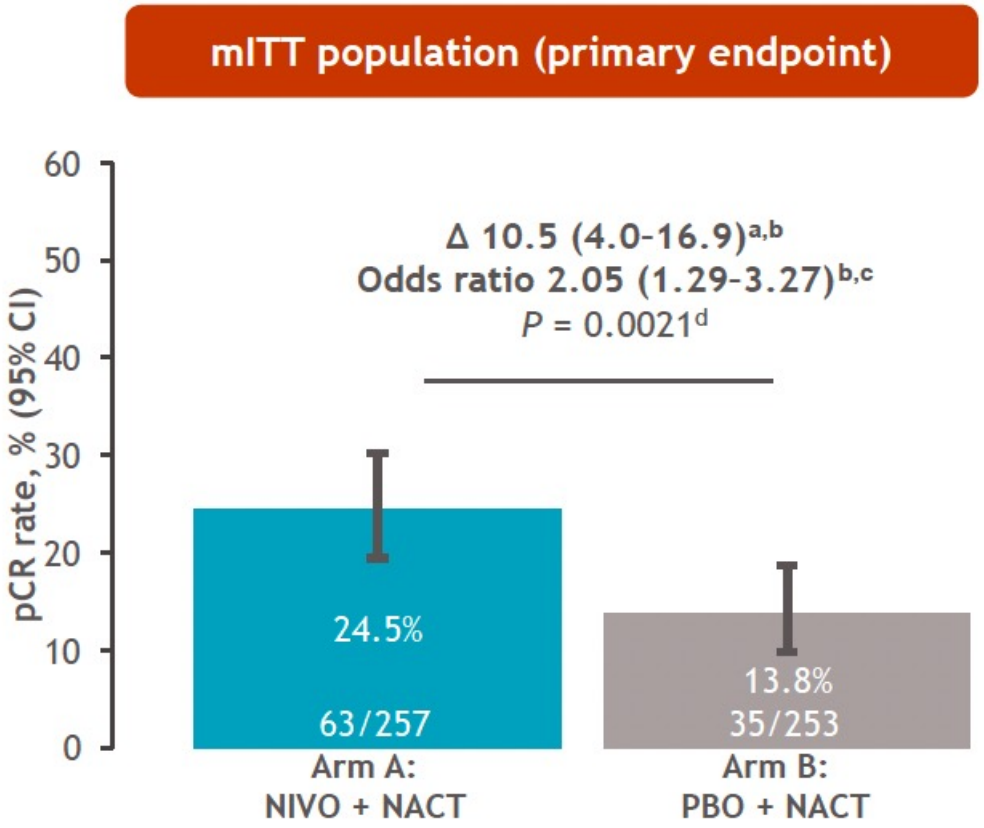
ER+ ≥10%

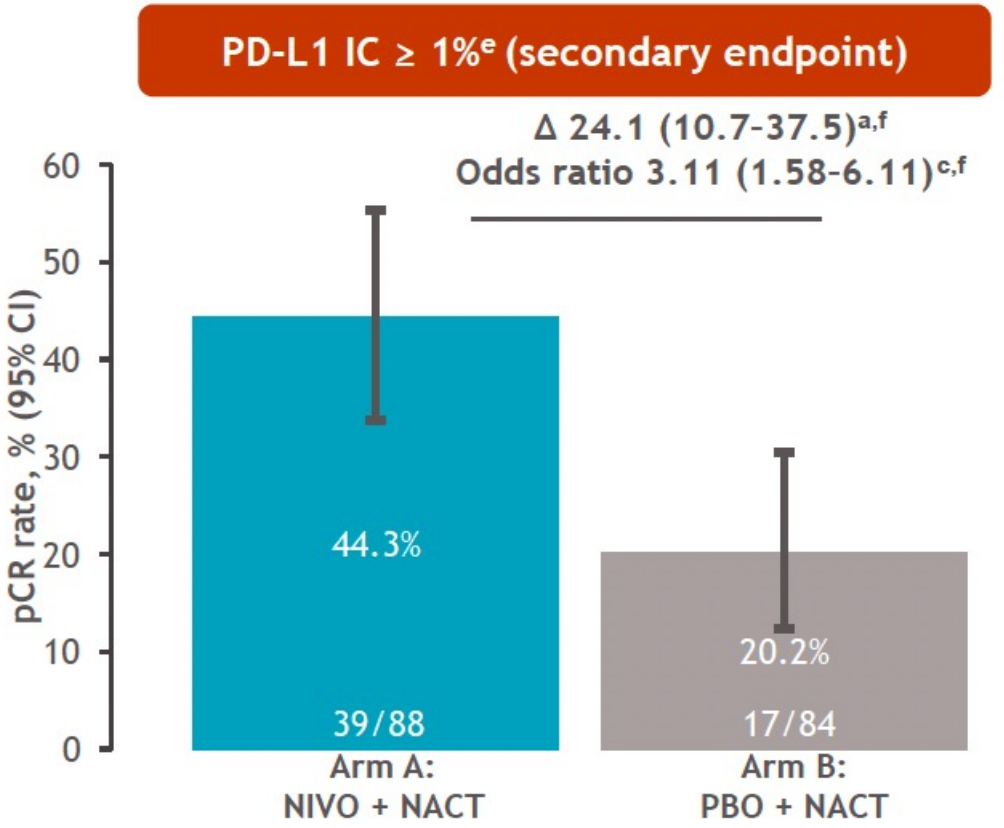


ER+ ≥10%

Cardoso et. al. SABCS 2023

Checkmate-7FL: pCR rate in mITT population and by PD-L1 IC ≥ 1%

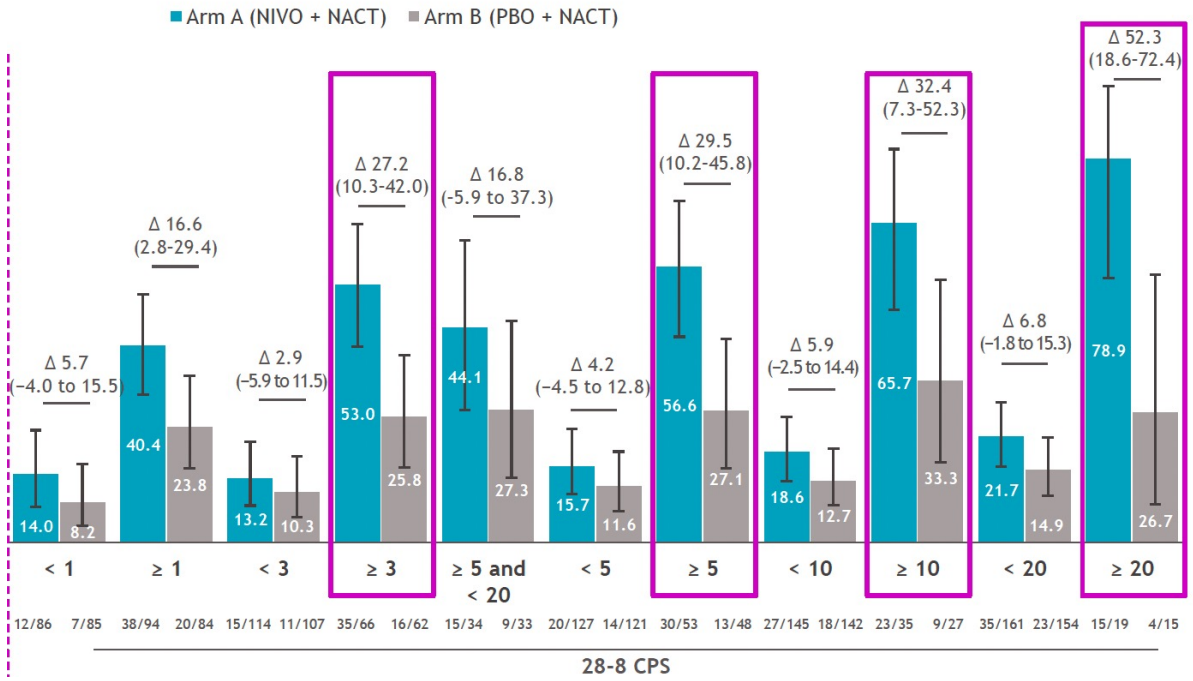




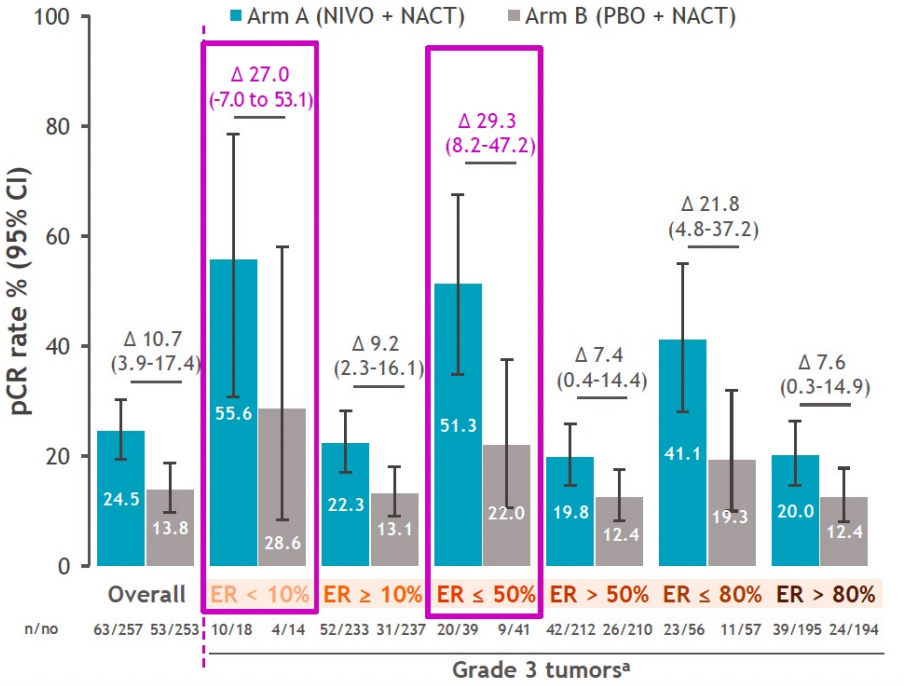
Loi et. al. ESMO 2023

Checkmate-7FL: biomarkers

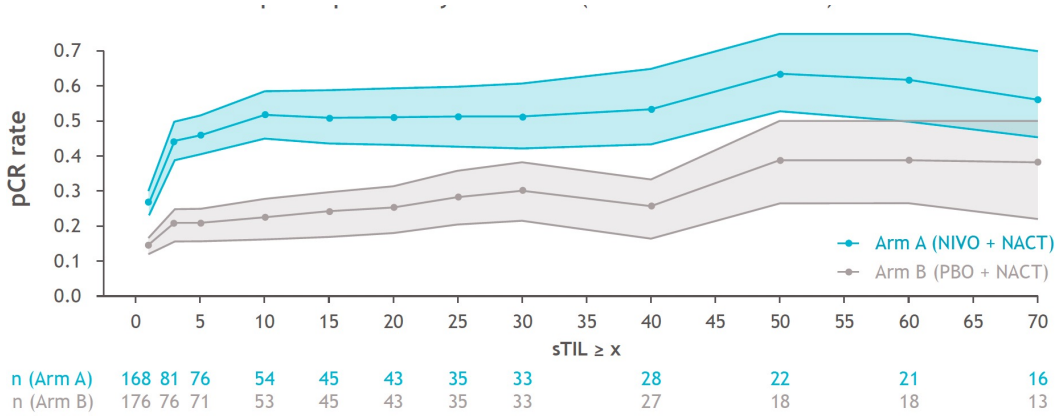
PD-L1 status (CPS)



pCR by ER

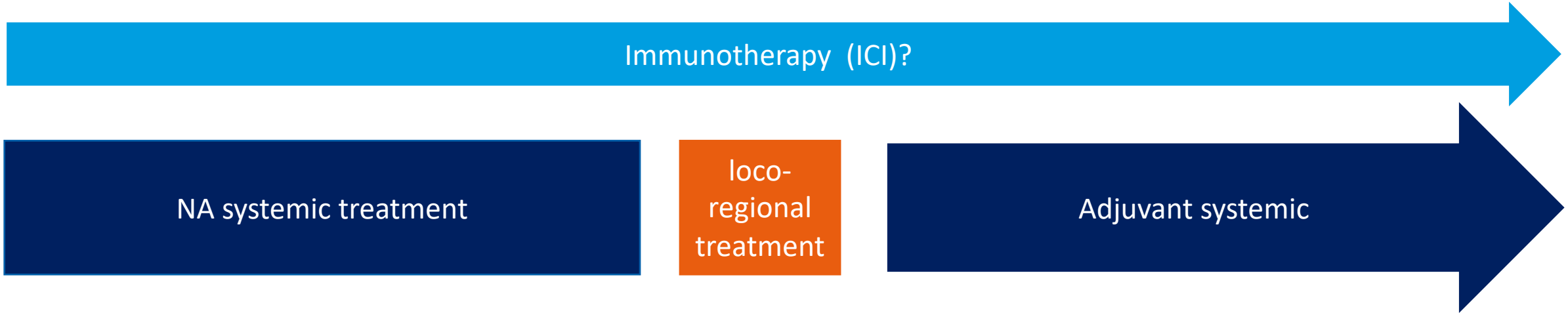


pCR by TILS



Loi et. al. ESMO 2023

HR+ HER2 – EBC and immunotherapy



Robust data on pCR (is pCR a valid endpoint?). EFS results awaited

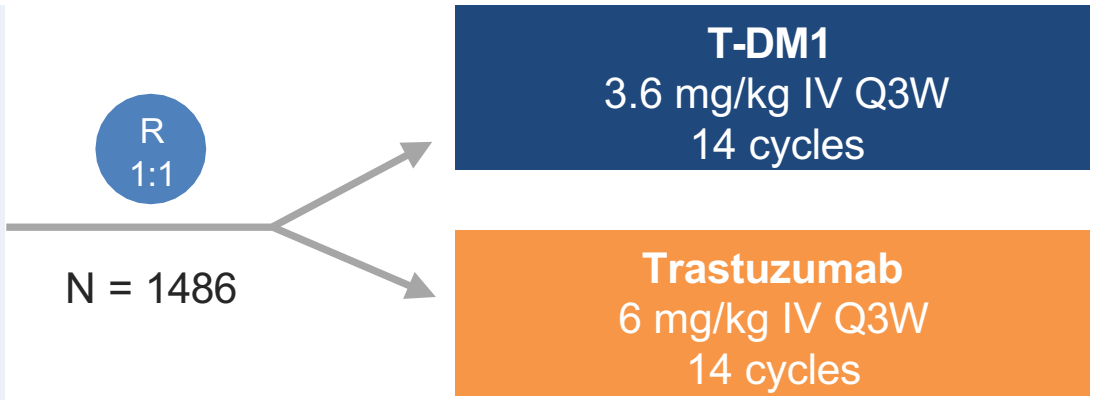
Higher pCR rate in higher CPS thresholds and lower ER scores (selection by intrinsic subtypes (lum B)/ and immune expression profile?)

Need of a clear clinical benefit on this population experiencing already added toxicity (and benefit) from the adjuvant setting.

HER2 positive EBC highlight

KATHERINE final IDFS and updated OS analysis

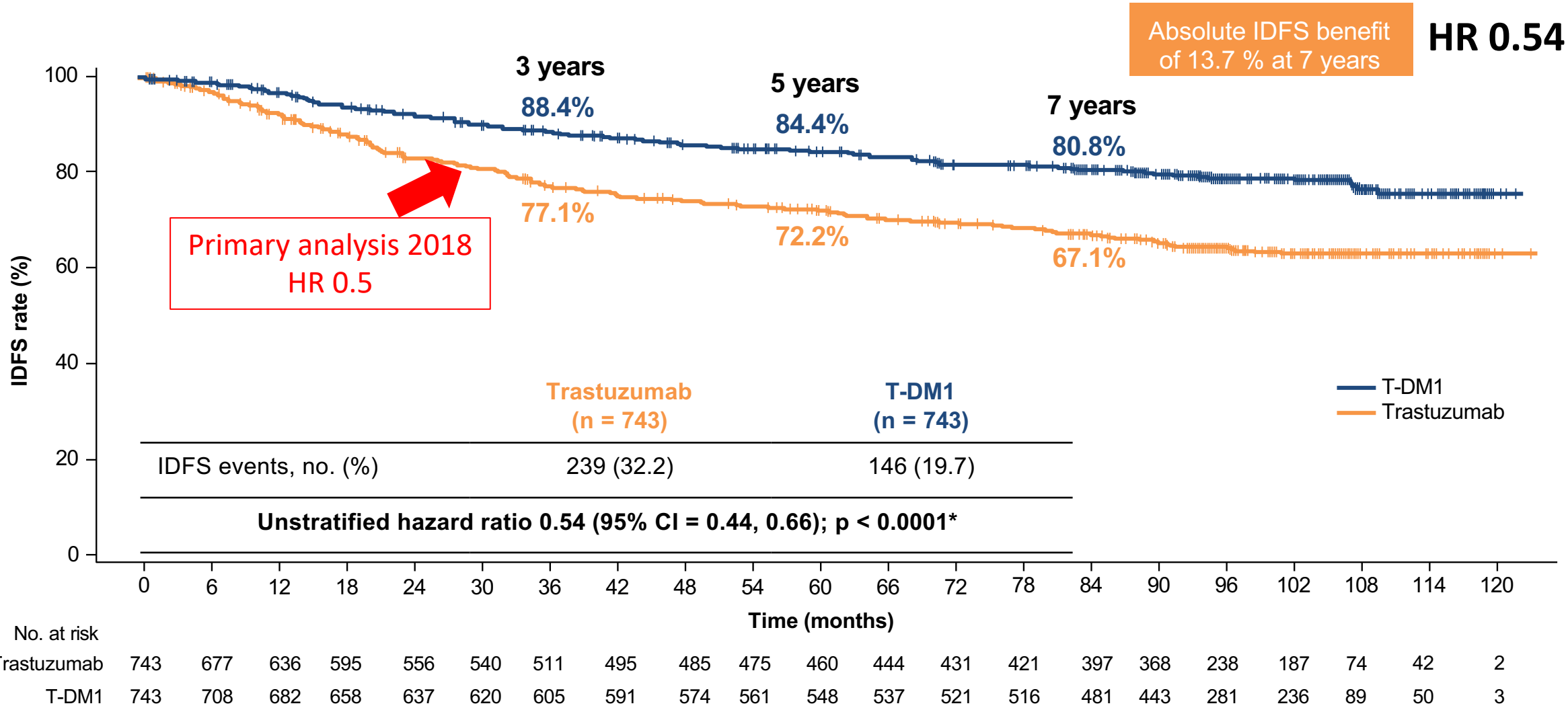
- Prior neoadjuvant therapy consisting of:
  - Minimum 6 cycles of chemotherapy
  - Minimum 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery



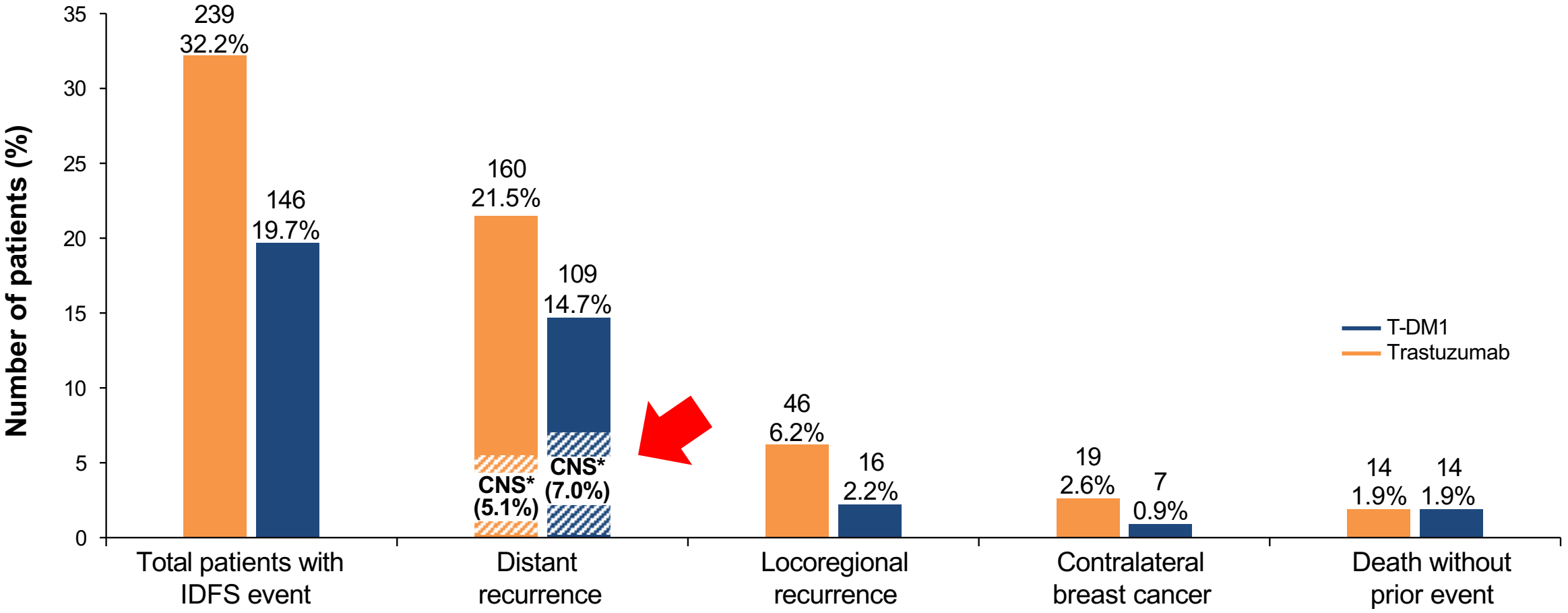
- Radiation and endocrine therapy per protocol and local guidelines
- Switch to trastuzumab permitted if T-DM1 discontinued due to AEs

- **Primary endpoint:** IDFS
- **Secondary endpoints:** IDFS with second primary non-breast cancers included, DFS, OS, DRFI, safety, and QoL
- **Stratification factors:** Clinical stage at presentation (inoperable vs operable), HR status, preoperative HER2-directed therapy, pathologic nodal status after preoperative therapy

KATHERINE IDFS final analysis; median follow-up 8.4 years (101 months)



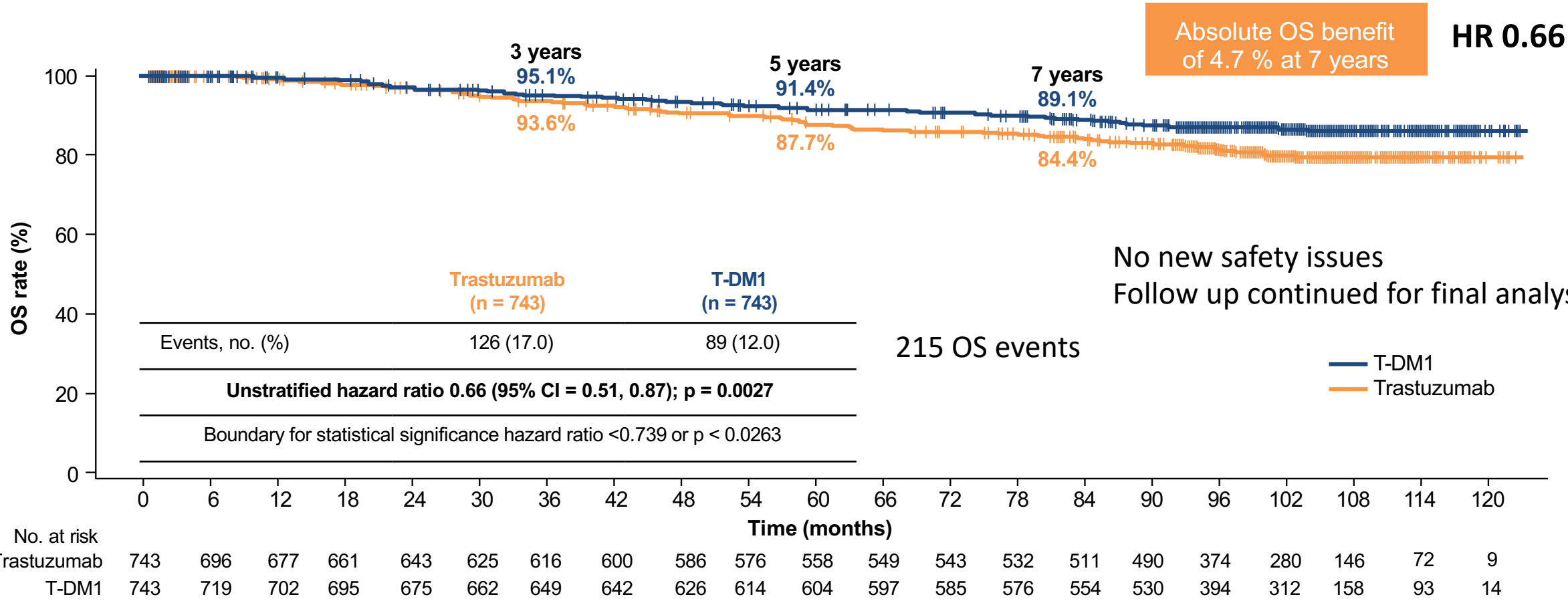
Site of first occurrence of an IDFS event



* **CNS metastases as component of distant recurrence (isolated or with other sites).**

CNS recurrence after first IDFS event: 19 patients (2.6%) in the trastuzumab arm and four patients (0.5%) in the T-DM1 arm.
CNS, central nervous system; IDFS, invasive disease-free survival; T-DM1, ado-trastuzumab emtansine.

KATHERINE 2nd OS interim analysis; median follow-up 8.4 years (101 months)



Significant reduction in risk of death by 34% with T-DM1

CI, confidence interval; OS, overall survival; T-DM1, ado-trastuzumab emtansine.

HR+/HER2 highlight: CDK 4/6inh in the adjuvant setting

Luminal EBC: de-escalation or escalation or both ?

DE-ESCALATION

↓ lymphadenectomies (ACOZOG, AMAROS,SENOMAC)

↓ chemotherapies (TAILORx, RxPONDER, MINDACT)

↑? Immunotherapy? (KEYNOTE 756/Checkmate 7FL)

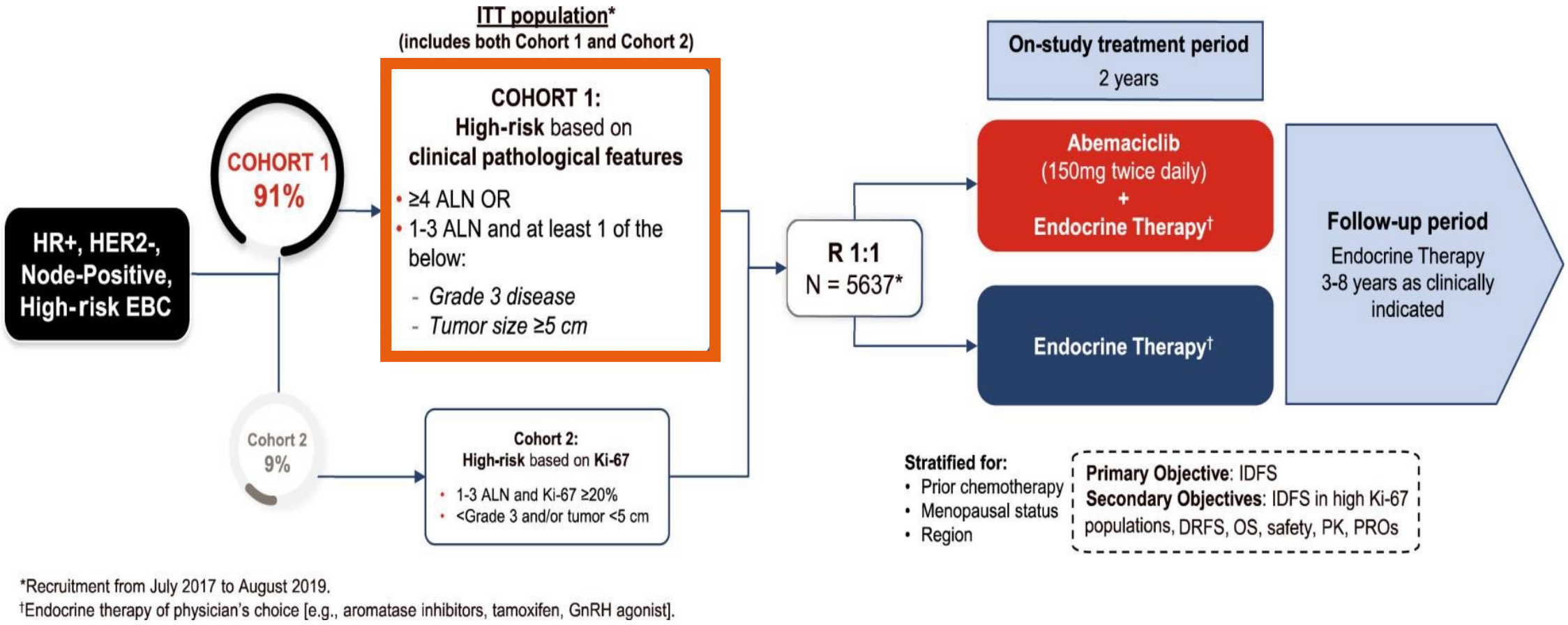
↑? Immunotherapy (KEYNOTE 756/Checkmate 7FL)

↑ OFS for premenopausal women (SOFT/TEXT/EBCTCG meta)

ESCALATION

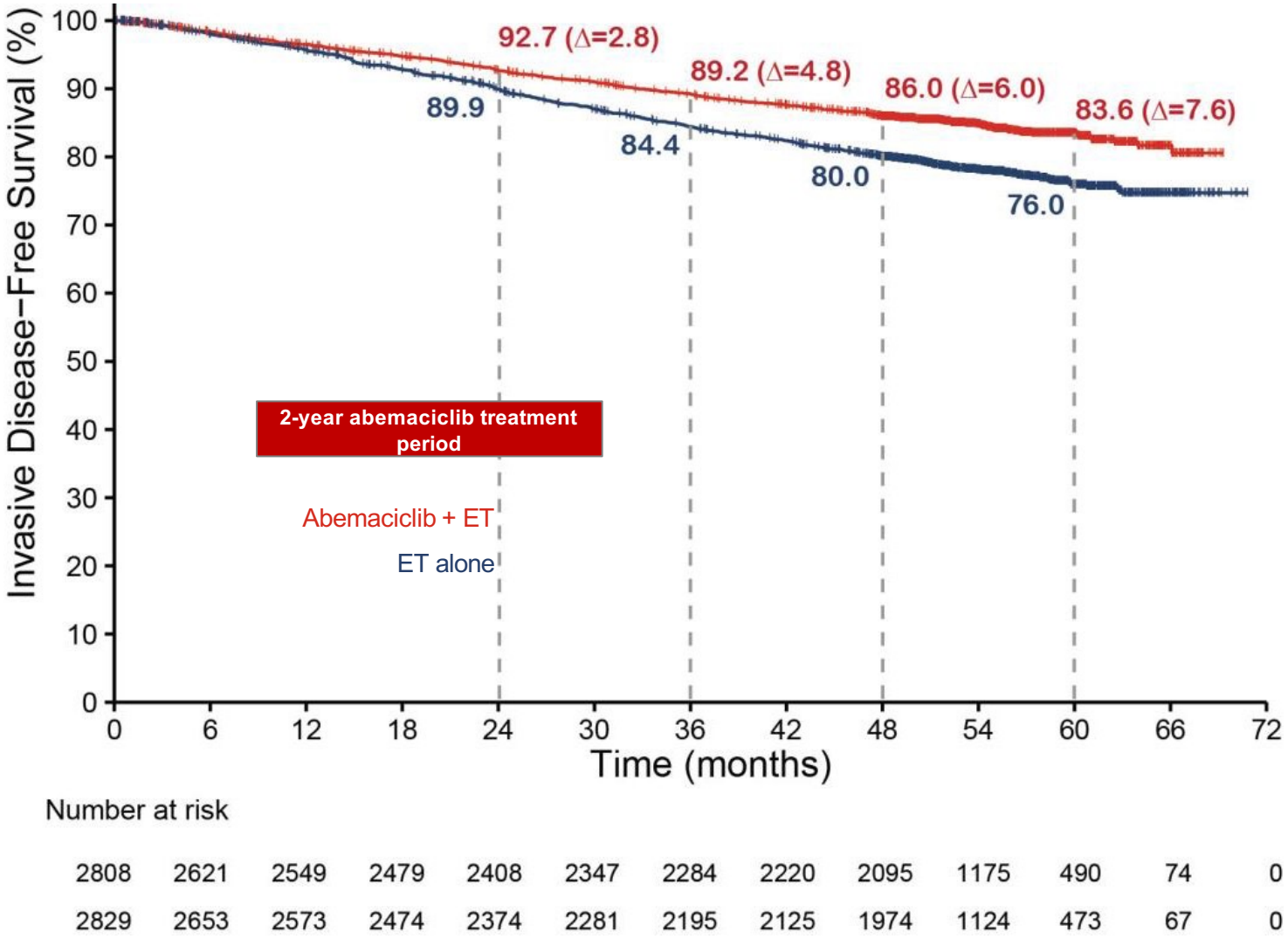
↑ **CDK 4/6i for high risk EBC,** and for intermediate risk? (MonarchE, NATALEE)

monarchE: CDK4/6inh in high-risk patients



*Recruitment from July 2017 to August 2019.
†Endocrine therapy of physician's choice [e.g., aromatase inhibitors, tamoxifen, GnRH agonist].

monarchE: IDFS in ITT at 5yrs



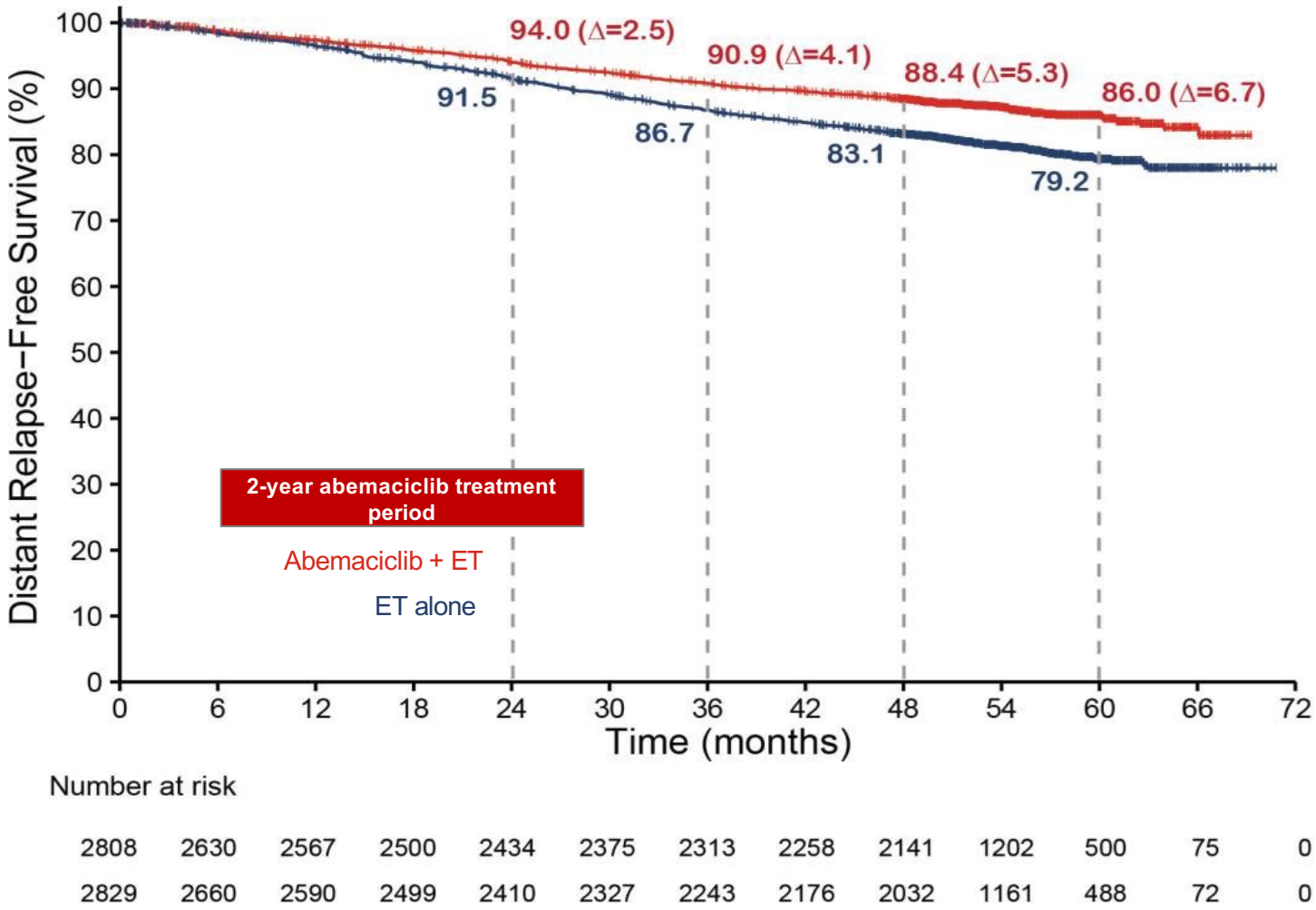
7.6% benefit in iDFS at 5yrs

Number of IDFS events	
Abemaciclib + ET	ET Alone
407	585

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

Nadia Harbeck, ESMO 23

monarchE: DRFS in ITT at 5 yrs



6.7% DRFS benefit at 5yrs

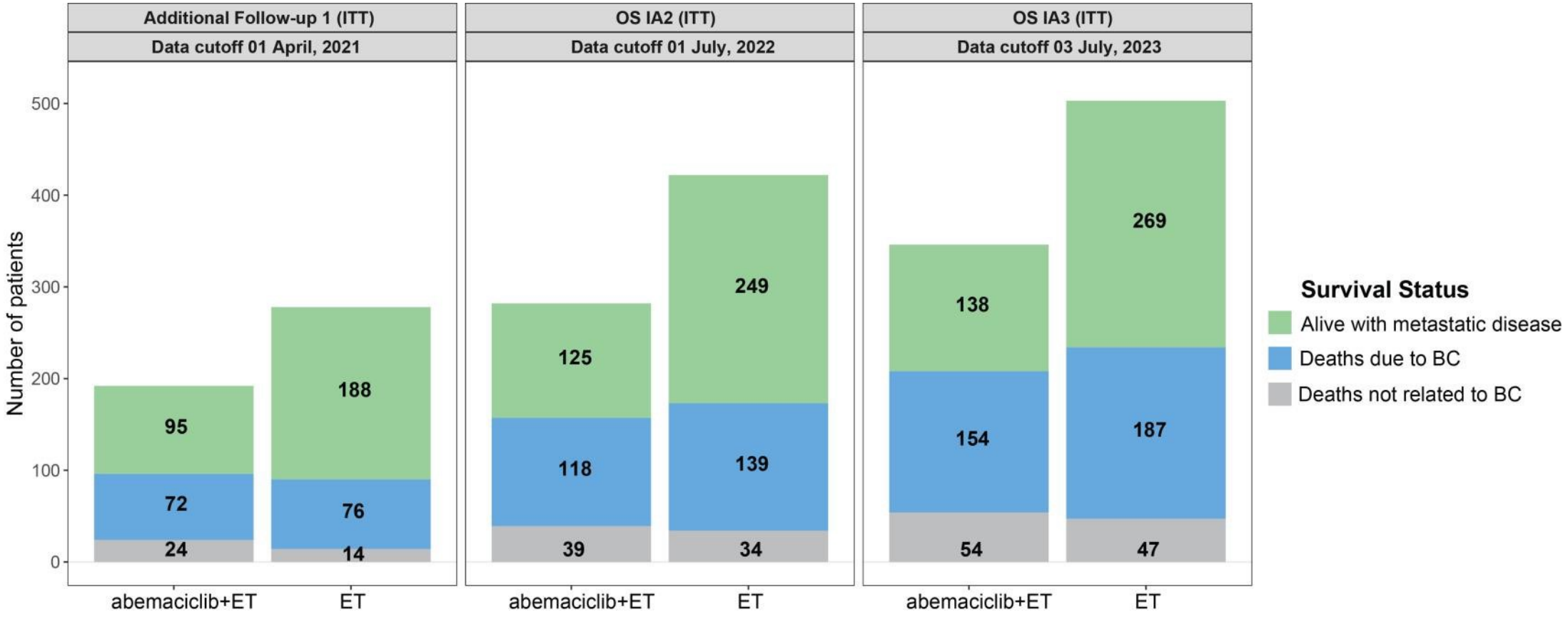
Number of DRFS events	
Abemaciclib + ET	ET Alone
345	501

HR (95% CI): 0.675 (0.588, 0.774)
Nominal p <0.001

Nadia Harbeck, ESMO 23

monarchE: overall survival

[1] [2]



OS benefit: Not significant at 5 yr update – wait for final assessment

Nadia Harbeck, ESMO 23

NATALEE: CDK4/6i in intermediate and high-risk patients

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 mo
- **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]

Ribociclib 400 mg/d
3 wk on/1 wk off
for 3 y

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

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

Primary End Point
– iDFS using STEEP criteria

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

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

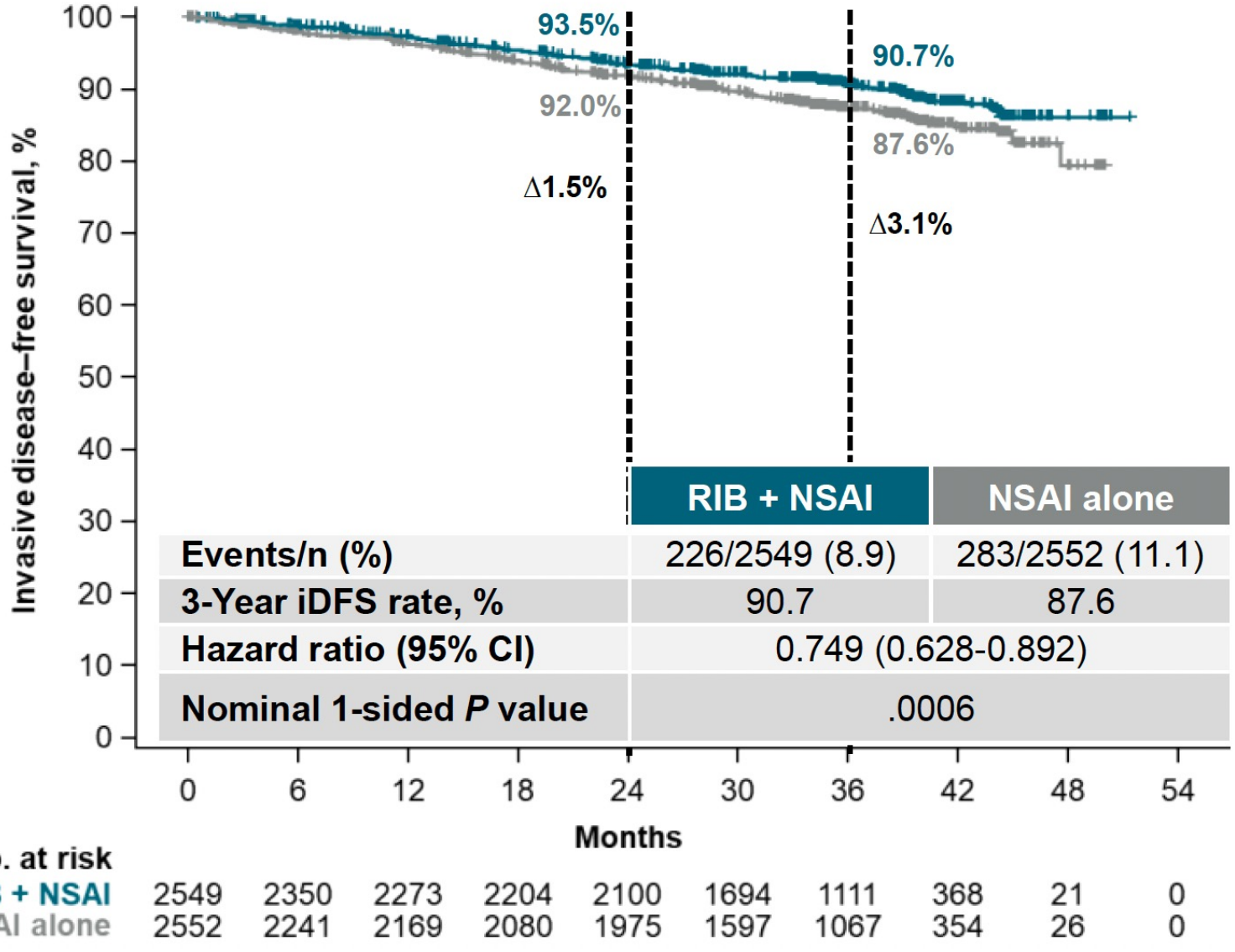
Prior chemo in 88%
Stage IIA 20%
Stage IIB 20%
Stage III 60%
28% N0

Final protocole-specified analysis of iDFS at a Data cut off at 509 events

20% still on going RIB in the RIB and NSAI arm

G.Hortobagyi at SABCS 2023

NATALEE: Final iDFS analysis



	RIB + NSAI	NSAI alone
Events/n (%)	226/2549 (8.9)	283/2552 (11.1)
3-Year iDFS rate, %	90.7	87.6
Hazard ratio (95% CI)	0.749 (0.628-0.892)	
Nominal 1-sided *P* value	.0006	

Median FU: 33.3 months
(additional 5.6 m to 2nd analysis)

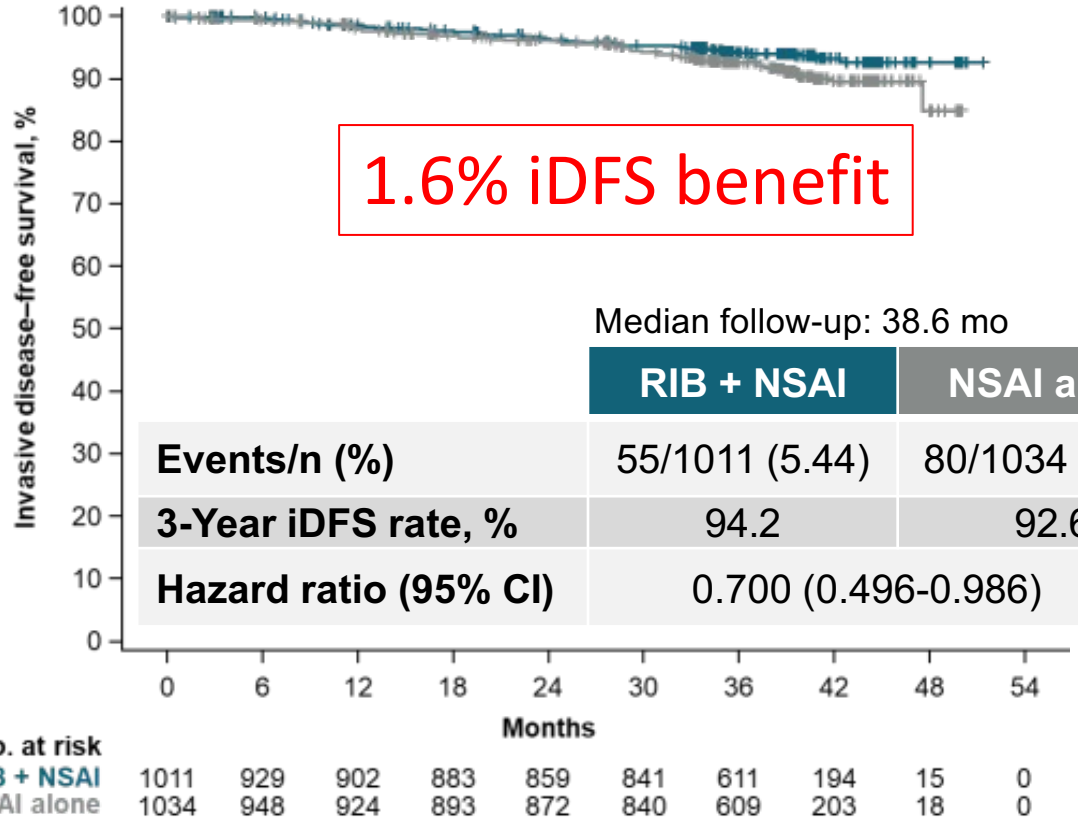
3.1% iDFS benefit at 3yrs

RR by 25.1% with RIB+NSAI

G.Hortobagyi SABCS 2023

NATALEE: iDFS by Anatomical Stage

Stage II

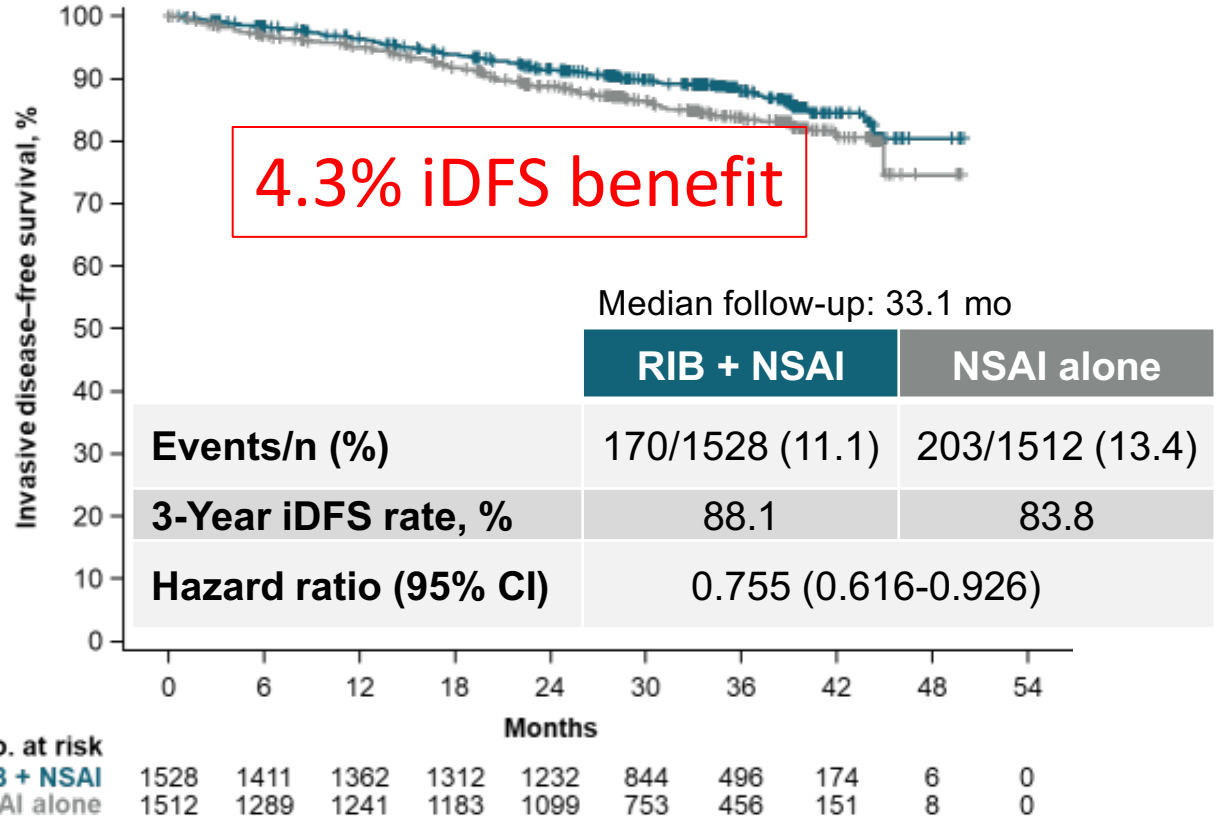


1.6% iDFS benefit

Median follow-up: 38.6 mo

	RIB + NSAI	NSAI alone
Events/n (%)	55/1011 (5.44)	80/1034 (7.74)
3-Year iDFS rate, %	94.2	92.6
Hazard ratio (95% CI)	0.700 (0.496-0.986)	

Stage III



4.3% iDFS benefit

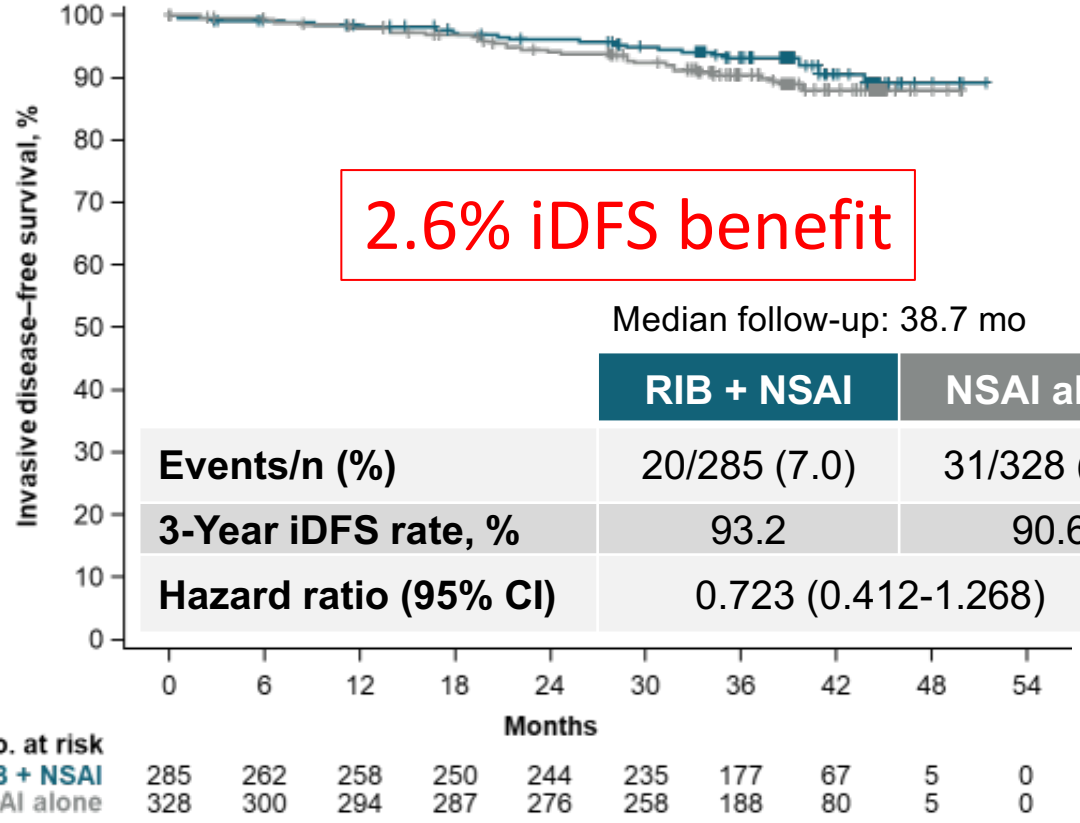
Median follow-up: 33.1 mo

	RIB + NSAI	NSAI alone
Events/n (%)	170/1528 (11.1)	203/1512 (13.4)
3-Year iDFS rate, %	88.1	83.8
Hazard ratio (95% CI)	0.755 (0.616-0.926)	

G.Hortobagyi SABCS 2023

NATALEE: iDFS by nodal status

N0

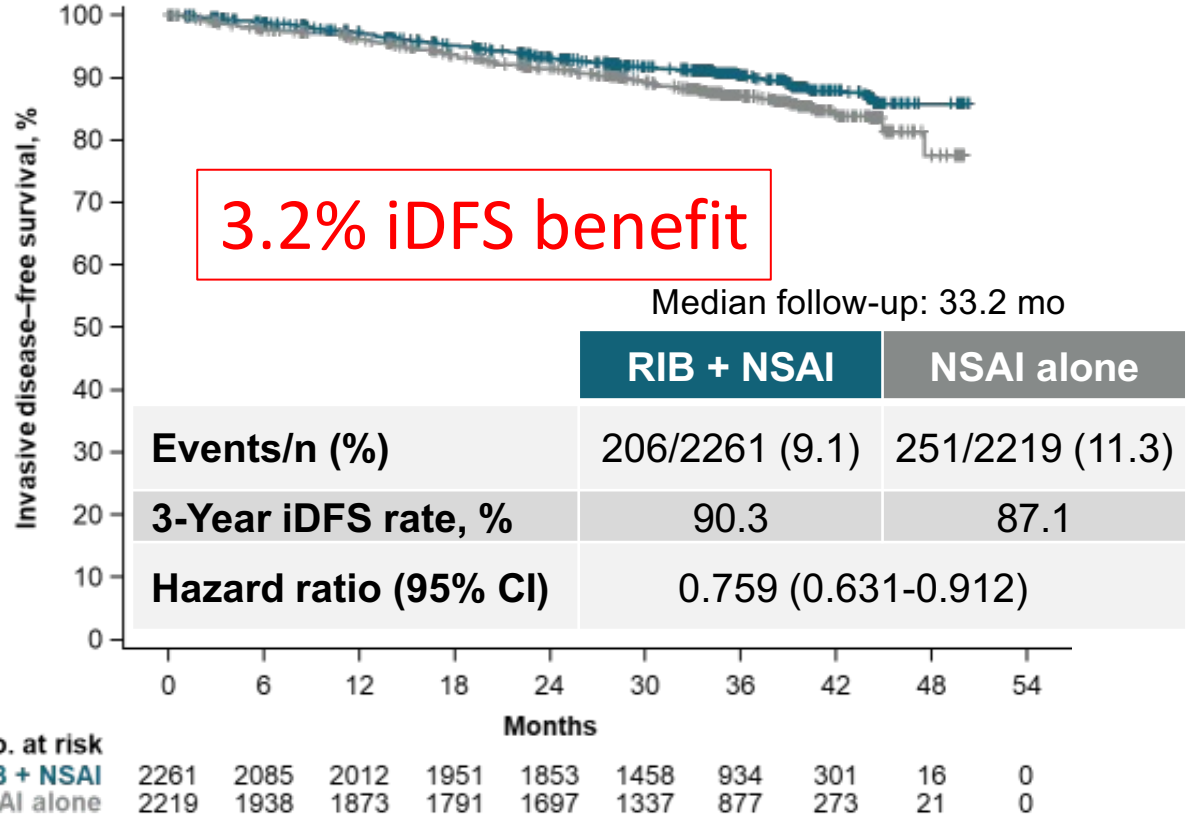


2.6% iDFS benefit

Median follow-up: 38.7 mo

	RIB + NSAI	NSAI alone
Events/n (%)	20/285 (7.0)	31/328 (9.5)
3-Year iDFS rate, %	93.2	90.6
Hazard ratio (95% CI)	0.723 (0.412-1.268)	

N1-N3



3.2% iDFS benefit

Median follow-up: 33.2 mo

	RIB + NSAI	NSAI alone
Events/n (%)	206/2261 (9.1)	251/2219 (11.3)
3-Year iDFS rate, %	90.3	87.1
Hazard ratio (95% CI)	0.759 (0.631-0.912)	

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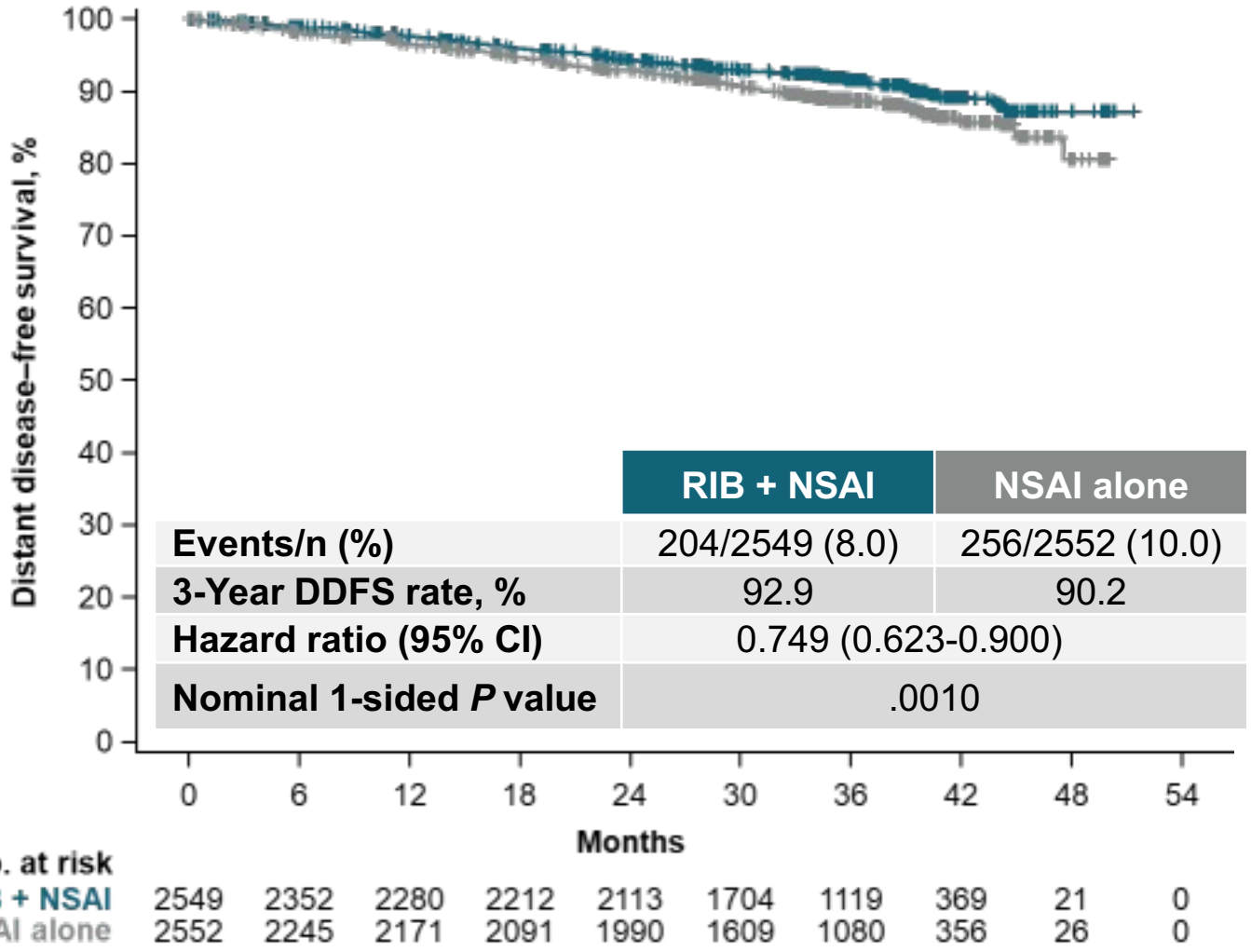
NATALEE: Distant Disease–Free Survival



	RIB + NSAI	NSAI alone
Events/n (%)	204/2549 (8.0)	256/2552 (10.0)
3-Year DDFS rate, %	92.9	90.2
Hazard ratio (95% CI)	0.749 (0.623-0.900)	
Nominal 1-sided *P* value	.0010	

2.7% DDFS benefit with RIB +NSAI at 3 yrs

OS data immature

G.Hortobagyi SABCS 2023

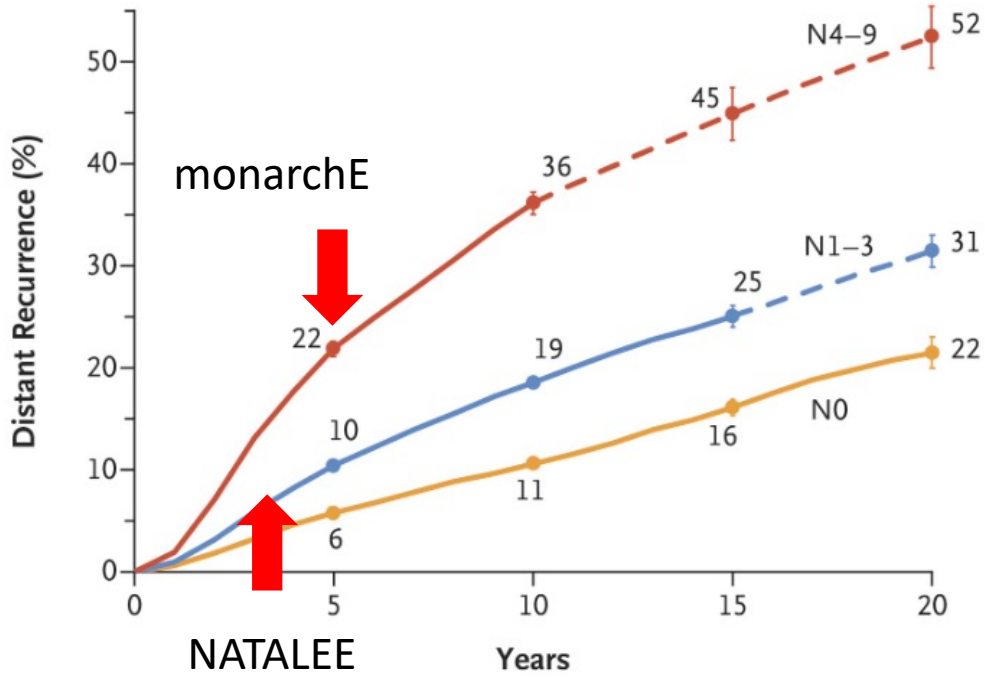
Thoughts on CDK4/6 inhibitors in the adjuvant setting:

<u>Follow up for distant recurrences :</u>

many events still to come

MonarchE: data are robust in terms of efficacy but.

<u>What magnitude of benefit is clinically meaningful</u>? stage II?



Pan H NEJM 2017

Thoughts on CDK4/6 inhibitors in the adjuvant setting:

<u>What % of breast clinic population does it represent? real Belgian clinic data</u>

CHU UCL NAMUR Ste E (2021,2022, 2023) with invasive breast cancer: 866 patients
Saint-Pierre Ottignies (2022, 2023) with invasive breast cancer: 525 patients

We extracted:
HR+, HER2-, eligible for Abema (according to the label) and for Ribo (according to NATALEE)
methods differed: p stage /or c stage (if NA chemo) for CHU, p stage only for SPO

	CHU UCL NAMUR (StE)	SPO
Total number invasive BC, n	866	525
Eligible for abema n, %	70 (8)	46 (9)
Eligible for ribo n, %	202 (23)	132 (25)

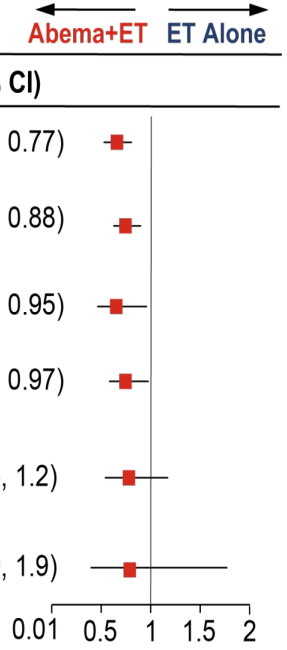
This is lower from reports from other reports (D.Dannehl)

Age, ECOG, comorbidities were not taken into account

Thank you to:
Shannon Mathelot (SPO)
Audrey Roegiers (CHU UCL Namur)

How can we better select the patients: intrinsic subtype or prognostic signatures?

	Abemaciclib + ET		ET Alone		
	Events/n (%)	4-yr IDFS Rate (95% CI)	Events/n (%)	4-yr 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)
LumA	28/230 (12%)	87.5 (83.2–92)	45/228 (20%)	81.4 (76.3–86.8)	0.59 (0.37, 0.95)
LumB	65/265 (25%)	76.3 (71.2–81.7)	88/262 (34%)	66.6 (61.1–72.7)	0.70 (0.51, 0.97)
HER2E	32/69 (46%)	52.6 (41.8–66.2)	34/59 (58%)	42.5 (31.4–57.5)	0.74 (0.46, 1.2)
Basal	9/21 (43%)	57.1 (39.5–82.8)	8/15 (53%)	46.7 (27.2–80.2)	0.75 (0.29, 1.9)



	Abemaciclib + ET		ET Alone		
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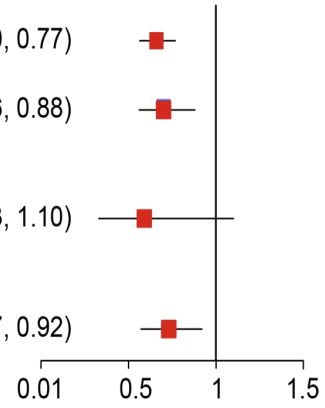
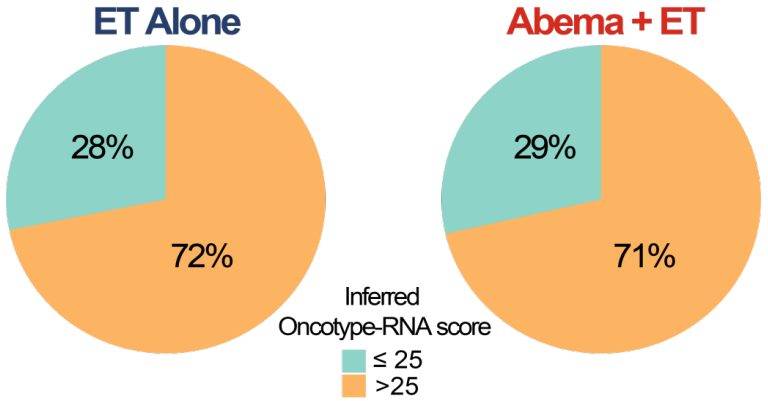
Biomarker Subset	138/605 (23%)	77.4 (74.1–80.9)	182/585 (31%)	69.8 (66.1–73.7)	0.70 (0.56, 0.88)
Inferred Oncotype-RNA score <=25	18/173 (10%)	90.2 (85.8–94.9)	28/165 (17%)	84.2 (78.7–90.1)	0.59 (0.33, 1.10)
Inferred Oncotype-RNA score>25	120/432 (28%)	72.3 (68.1–76.8)	154/420 (37%)	64.1 (59.6–69)	0.73 (0.57, 0.92)



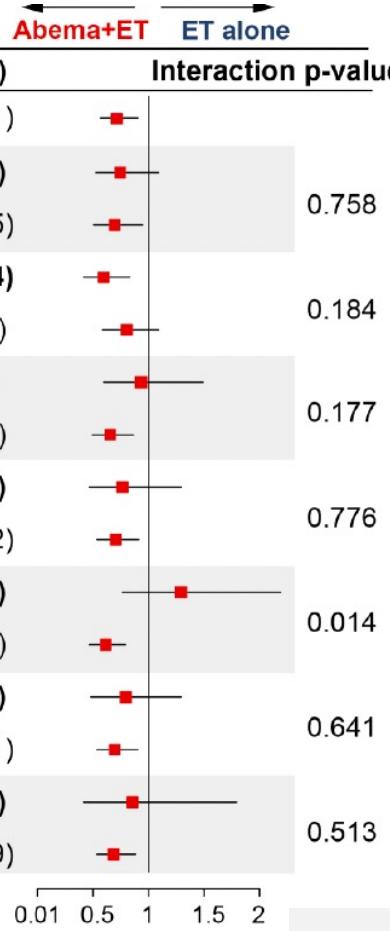
Intrinsic subtypes (Lum A/B) and prognostic signatures did not predict the benefit of abemaciclib



N.Turner SABCS 2023

How can we better select the patients? Genomic alterations

	Prevalence	Abemaciclib + ET Events/n (%)	ET Alone Events/n (%)	HR (95% CI)	Interaction p-value
All patients		123/580 (22%)	169/593 (28%)	0.72(0.57,0.91)	
PIK3CA mut	**38%**	**55/217 (26%)**	**73/229 (32%)**	**0.75(0.53,1.1)**	0.758
PIK3CA wt		68/363 (18%)	96/364 (26%)	0.70(0.51,0.95)	
TP53 mut/homdel	**32%**	**55/189 (30%)**	**82/184 (44%)**	**0.60(0.42,0.84)**	0.184
TP53 wt		68/391 (18%)	87/409 (22%)	0.81(0.59,1.1)	
CCND1 amp	**20%**	**36/113 (32%)**	**42/129 (32%)**	**0.94(0.6,1.5)**	0.177
CCND1 wt		87/467 (18%)	127/464 (28%)	0.66(0.5,0.87)	
ZNF703 amp	**16%**	**28/96 (30%)**	**37/100 (36%)**	**0.77(0.47,1.3)**	0.776
ZNF703 wt		95/484 (20%)	132/493 (26%)	0.71(0.54,0.92)	
MYC amp	**16%**	**34/92 (36%)**	**25/84 (30%)**	**1.30(0.77,2.2)**	0.014
MYC wt		89/488 (18%)	144/509 (28%)	0.62(0.47,0.8)	
FGFR1 amp	**16%**	**26/88 (30%)**	**35/98 (36%)**	**0.80(0.48,1.3)**	0.641
FGFR1 wt		97/492 (20%)	134/495 (28%)	0.70(0.54,0.91)	
GATA3 mut	**14%**	**13/73 (18%)**	**17/88 (20%)**	**0.86(0.42,1.8)**	0.513
GATA3 wt		110/507 (22%)	152/505 (30%)	0.69(0.54,0.89)	



MUT = mutation

HOMDEL = homozygous deletion

AMP = amplification

MYC, GATA3, FGFR1, ZNF703: analyses limited by small sample size

MYC amplifications seem associated with less benefit

(NF1 loss of function associated with endocrine R?)

Thoughts on CDK4/6 inhibitors in the adjuvant setting:

The vast majority of patients had received chemotherapy. Can adjuvant CDK4/6i replace chemotherapy? WSG ADAPT cycle trial

Compliance of CDK4/6i?

- AEs-associated discontinuation rates were in 18.5 and 19.5% (liver tox 8.6%) in monarchE and NATALEE respectively
- Real world data on compliance?

Thank you

CHU UCL NAMUR

back up

NATALEE: patient disposition

Second Interim Efficacy Analysis

Data cutoff: January 11, 2023
iDFS events: n=426

Ribociclib + NSAI, n=2549

- NSAI ongoing: 1984 (77.8%)
  - **RIB ongoing: 1147 (45.0%)**
- Stopped RIB: 1377 (54.0%)
  - **Completed 3 years: 515 (20.2%)**
  - **Early discontinuation: 862 (33.8%)**
    - Discontinued due to AEs: 477 (18.7%)

NSAI alone, n=2552

- NSAI ongoing: 1826 (71.6%)
- Discontinued NSAI: 617 (24.2%)

Final iDFS Analysis

Data cutoff: July 21, 2023
iDFS events: n=509

Ribociclib + NSAI, n=2549

- NSAI ongoing: 1914 (75.1%)
  - **RIB ongoing: 528 (20.7%)**
- Stopped RIB: 1996 (78.3%)
  - **Completed 3 years: 1091 (42.8%)**
  - **Early discontinuation: 905 (35.5%)**
    - Discontinued due to AEs: 498 (19.5%)

NSAI alone, n=2552

- NSAI ongoing: 1748 (68.5%)
- Discontinued NSAI: 693 (27.2%)

AE, adverse event; RIB, ribociclib.
Slamon D, et al. ASCO 2023. Oral LBA500.

Comparison of NATALEE and monarchE Populations

AJCC Anatomical Staging[1]	TN (M0)	NATALEE[2]	monarchE[3]
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	✓	✓

NATALEE allowed:
- Any **N1, N2, N3**
- **N0**: **T2** [(*G2 + high genomic risk or Ki-67≥ 20%) or G3*)], **T3, T4**

monarchE allowed:
- Any **N2**, **N3**
- **N1** only if G3 or tumor size ≥ 5cm or Ki-67≥20%

N0 not allowed in monarchE

[a] High risk as determined by Oncotype DX/Prosigna/MammaPrint/EndoPredict.

References: 1. Amin MB, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York, NY: Springer; 2017:587-636. 2. Slamon D, et al. ASCO 2023. LBA500 [Oral]. 3. Harbeck N, et al. *Ann Oncol.* 2021;32:1571-1581.