bjclub breast Journal club

L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

04-05 Aprile
2024
Padova

PALAZZO BO - Aula Nievo - Via VIII Febbraio, 2

CENTRO ALTINATE - Auditorium - Via Altinate, 71

Il carcinoma mammario in fase precoce HR+

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Disclosure

Honoraria for Consultancy and Advisory Board from:

Roche, Novartis, Lilly, AstraZeneca, Pfizer, MSD, Daiichi Sankyo, Gilead, Seagen, Exact Sciences, Gentili.

Outline

1. Genomics and risk estimate (MGA)
2. Adjuvant and CDK4/6-i (NATALEE)
3. (Neo)adj and dynamic biomarker (POETIC/ADAPT)
4. Neoadj and IO (CM7FL, KN756)

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EPclin for risk estimate in prospective RCT (UNIRAD)

Prognostic value of EndoPredict test in patients screened for UNIRAD, a UCBG randomized, double blind, phase III international trial evaluating the addition of everolimus (EVE) to adjuvant hormone therapy (HT) in women with high risk HR+, HER2- early breast cancer (eBC)

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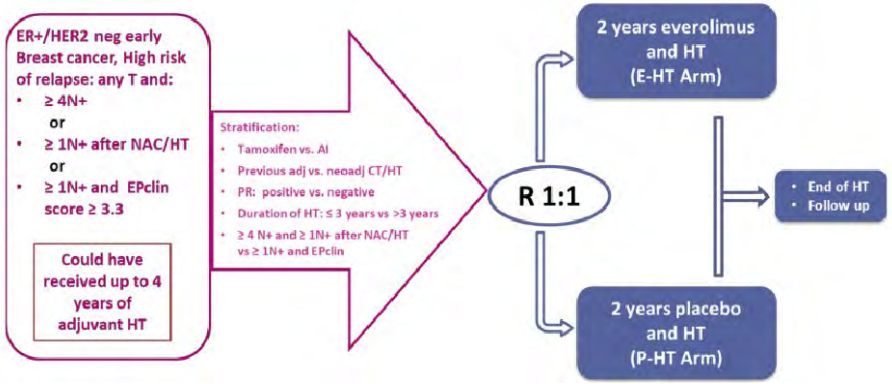
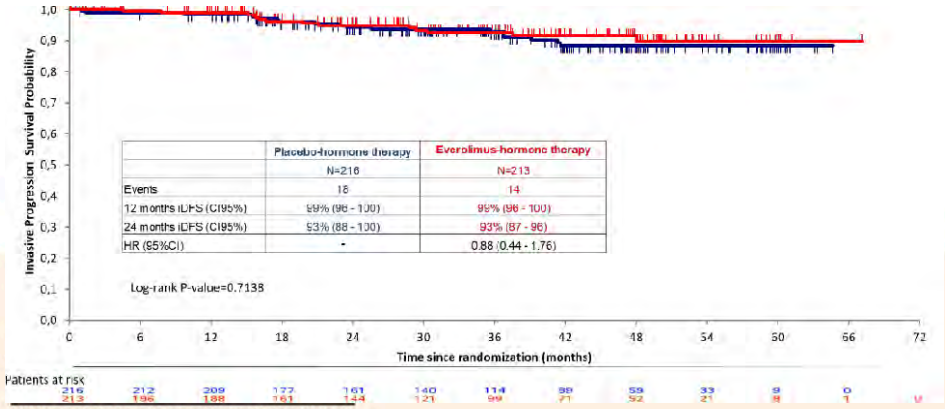
1. Centre Jean Perrin, Clermont-Ferrand, France; 2. Institut Claudius Régaud, Toulouse, France; 3. Centre Léon Bérard, Lyon, France; 4. Institut Curie, Paris, France; 5. Centre François Baclesse, Caen, France; 6. Western General Hospital,Edinburg, United Kingdom; 7. IC Lucien Neuwirth, Saint-Priest-en-Jarez, France; 8. Institut Sainte Catherine, Avignon, France; 9. CHU Dupuytren, Limoges, France; 10. Royal Stoke Hospital, Stoke-on-Trent, United Kingdom; 11. Institut de cancérologie de l'Ouest, Saint-Herblain & Angers, France; 12. Hopitaux du Léman - site Georges Pianta, Thonon-les-bains, France; 13. Institut Bergonié, Bordeaux, France; 14. Centre CARIO - HPCA, Plérin, France; 15. Hopital Saint Louis, Paris, France; 16. Institut de Cancérologie Strasbourg Europe, Strasbourg, France; 17. Centre Hospitalier Cotentin, Cherbourg en Cotentin, France; 18. Centre Oscar Lambret, Lille, France; 19. Centre Oncogard, Nîmes, France; 20. Clinique Pasteur, Toulouse, France; 21. Hopital Diaconnesses, Paris, France; 22. Hopital Laennec, Quimper, France; 23. Ninewells Hospital, Dundee - Scotland, United Kingdom; 24. Musgrove Park Hospital, Taunton, United Kingdom; 25. Centre hospitalier Annecy, Pringy, France; 26. Centre hospitalier Montélimar,Montélimar, France; 27. Weston Park Hospital, Sheffield, United Kingdom; 28. Centre Hospitalier Fleyriat, Bourg En Bresse, France; 29. Gustave Roussy, Villejuif, France; 30. The Institute of Cancer Research, London, United Kingdom; 31. Grand Hopital de Charleroi, Charleroi, Belgium; 32. UNICANCER, Paris, France.

PD9-08

San Antonio Breast Cancer Symposium - December 7-10, 2021

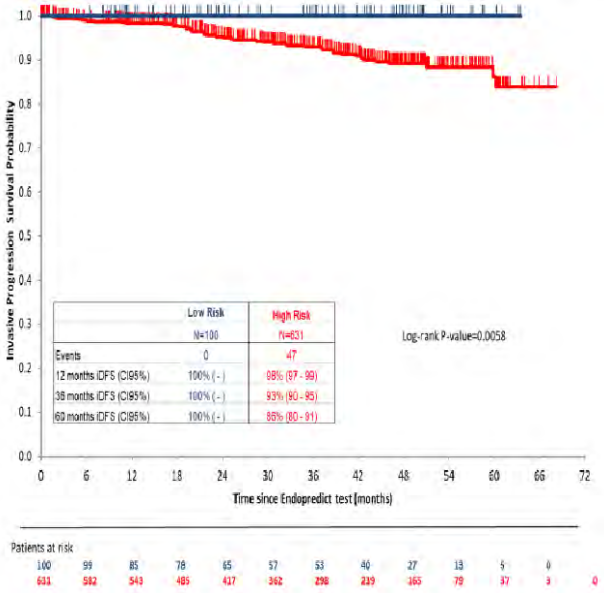


No predictive value of EPclin for EVE efficacy in HR pts



	Placebo-hormone therapy	Everolimus-hormone therapy
	N=216	N=213
Events	18	14
12 months iDFS (CI95%)	99% (96 - 100)	95% (96 - 100)
24 months iDFS (CI95%)	93% (88 - 100)	93% (87 - 96)
HR (95%CI)	-	0.88 (0.44 - 1.76)

Prognostic value of EPclin for iDFS in the whole population



	Low Risk	High Risk
	N=100	N=631
Events	0	47
12 months iDFS (CI95%)	100% (-)	98% (97 - 99)
36 months iDFS (CI95%)	100% (-)	93% (90 - 95)
60 months iDFS (CI95%)	100% (-)	85% (80 - 91)

Clinical implication

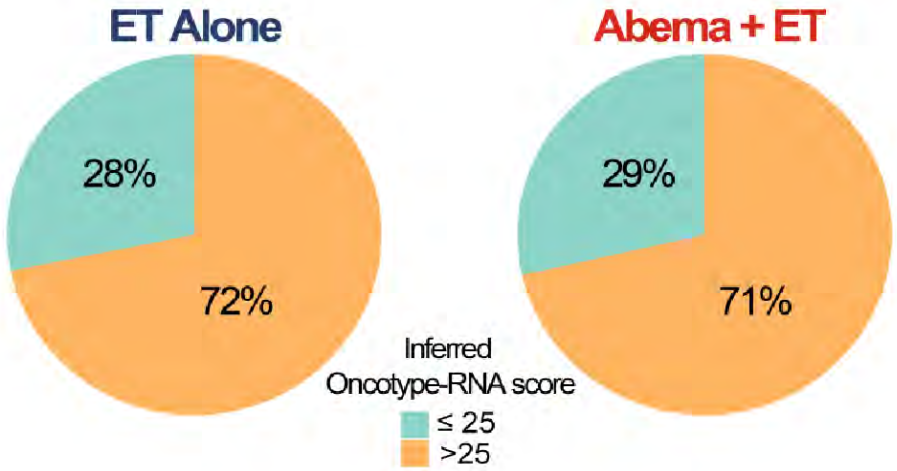
- Indipendent prognostic factors
- EPclin LoE 1A for prognosis
- EVE not effective in eBC

Penault-Llorca F et al SABCS 2021

The predictive role of ODX on CDK4/6-i

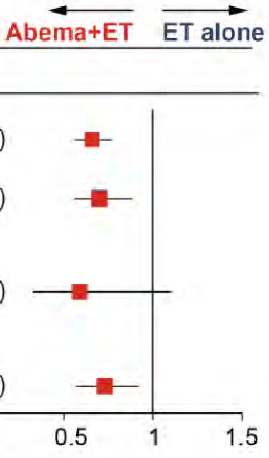
The impact of inferred ODX in MonarchE

Higher proportion of high RS samples



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

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

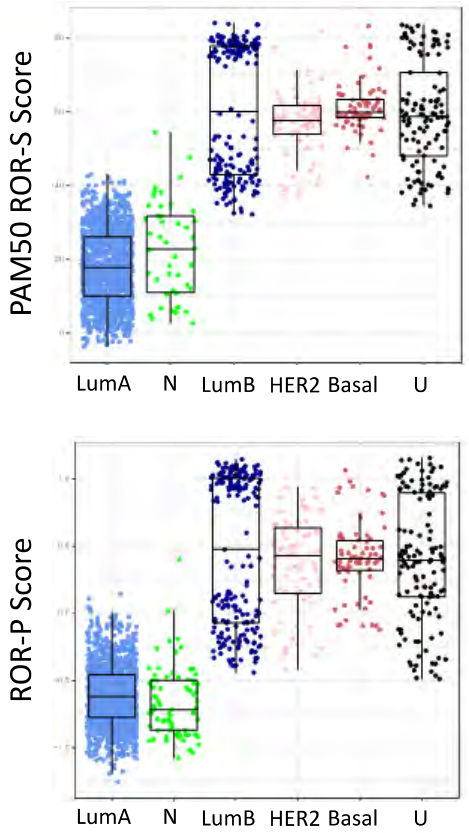


Interaction *p-value* (inferred high and low Oncotype scores) = 0.532

N. Turner, SABCS 2023

The predictive role of PROSIGNA on CDK4/6-i

The impact of PROSIGNA in PALLAS



ROR did not predict benefit to CDK4/6 inh

Subgroup	N	Events	Palbo + ET 5-yr IDFS (95% CI)	ET only 5-yr IDFS (95% CI)	Cox Model Hazard Ratio (95% CI)	Interaction P-Value
ROR subtype only	1748	230				0.051
low	865	92	90.3 (86.9 - 92.9)	86.2 (82.0 - 89.4)	0.68 (0.45 - 1.04)	.
med	583	89	82.3 (76.8 - 86.5)	84.2 (79.1 - 88.2)	1.04 (0.69 - 1.58)	.
high	300	49	89.2 (82.3 - 93.5)	76.1 (68.2 - 82.3)	0.44 (0.24 - 0.81)	.
ROR subtype proliferation	1748	230				0.201
low	688	72	88.8 (84.8 - 91.9)	88.5 (84.1 - 91.7)	0.92 (0.58 - 1.46)	.
med	774	113	85.5 (81.2 - 88.9)	82.0 (77.3 - 85.8)	0.77 (0.53 - 1.12)	.
high	286	45	89.3 (82.2 - 93.7)	77.5 (69.6 - 83.6)	0.46 (0.25 - 0.87)	.

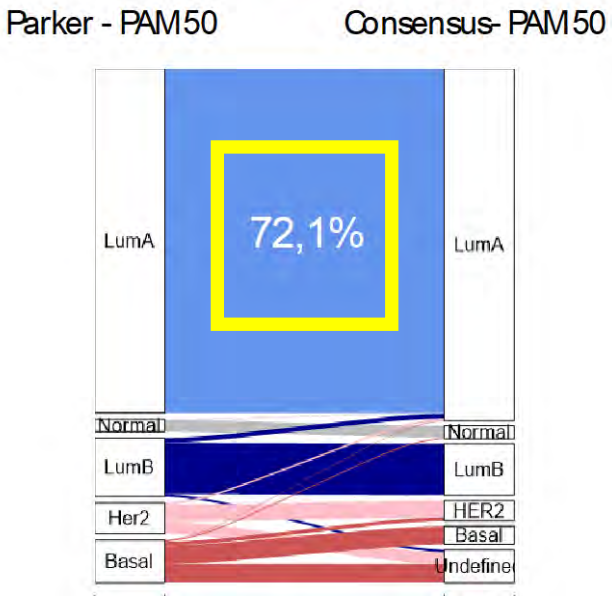
High ROR-S (ROR-P) tend to benefit more
→ need further investigation

D. Stover, SABCS 2023

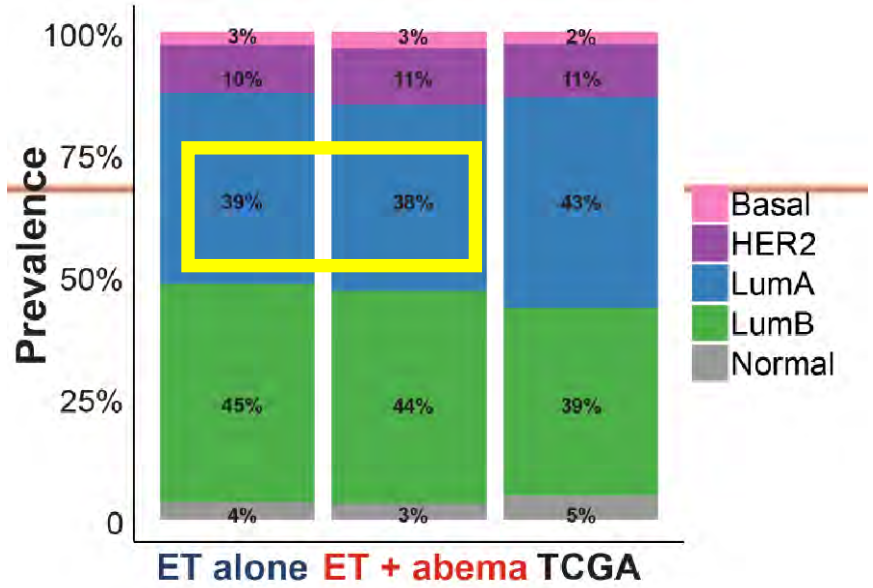
The predictive role of intrinsic signature on CDK4/6-i

PALLAS enriched LumA tumors *vs.* MonarchE

PALLAS



monarchE
EARLY BREAST CANCER



In PENELOPE B: 73% LumA, 7% LumB

LumA: 3-year iDFS 83.9% vs 79.5%, HR = 0.93 (0.68-1.28), no signficant interaction

LumB: 3-year iDFS 71.9% vs 44.8%, HR = 0.50 (0.24-1.05), no signficant interaction (limited sample size)

Denkert ASCO 2021

The predictive role of intrinsic signature on CDK4/6-i

The impact of molecular subtypes in PALLAS and MonarchE

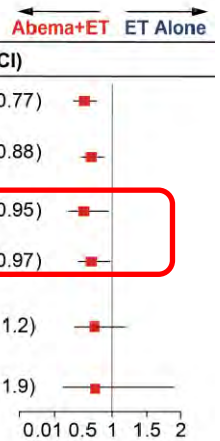
PALLAS

Subgroup	N	Events	Palbo + ET 5yr IDFS(95% CI)	ET only 5yr IDFS (95% CI)	Cox Model Hazard Ratio (95% CI)	Interaction P-Value
LumA	1748	230				0.145
Basal	67	15	72.8 (52.9 - 85.4)	78.6 (60.3 - 89.2)	1.33 (0.48 - 3.68)	.
HER2	73	12	93.3 (75.2 - 98.3)	72.7 (54.1 - 84.8)	0.25 (0.07 - 0.93)	.
LumA	1260	149	88.0 (85.0 - 90.5)	86.2 (82.9 - 88.9)	0.83 (0.60 - 1.15)	.
LumB	184	29	82.7 (72.5 - 89.4)	81.8 (71.7 - 88.7)	0.89 (0.43 - 1.85)	.
Normal	46	9	87.5 (66.0 - 95.8)	64.3 (36.4 - 82.5)	0.40 (0.10 - 1.62)	.
Undefined	118	16	94.1 (82.7 - 98.0)	77.1 (63.7 - 86.0)	0.25 (0.07 - 0.88)	.

Interaction *p-value* in all subtypes: 0,14

monarchE EARLY BREAST CANCER

	Abemaciclib + ET Events/n (%)	Abemaciclib + ET 4-yr IDFS Rate (95% CI)	ET Alone Events/n (%)	ET Alone 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)
HER2	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)



Interaction *p-value* in all subtypes: 0,62

MGA prognostic not predictive

(study-population enriched in HR)

C. Sotiriou, SABCS 2023

The relevance of MGA on CDK4/6-i use (IR/HR)

The impact of MGA in NATALEE trial

- 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*** **<2%**
      - 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

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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

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

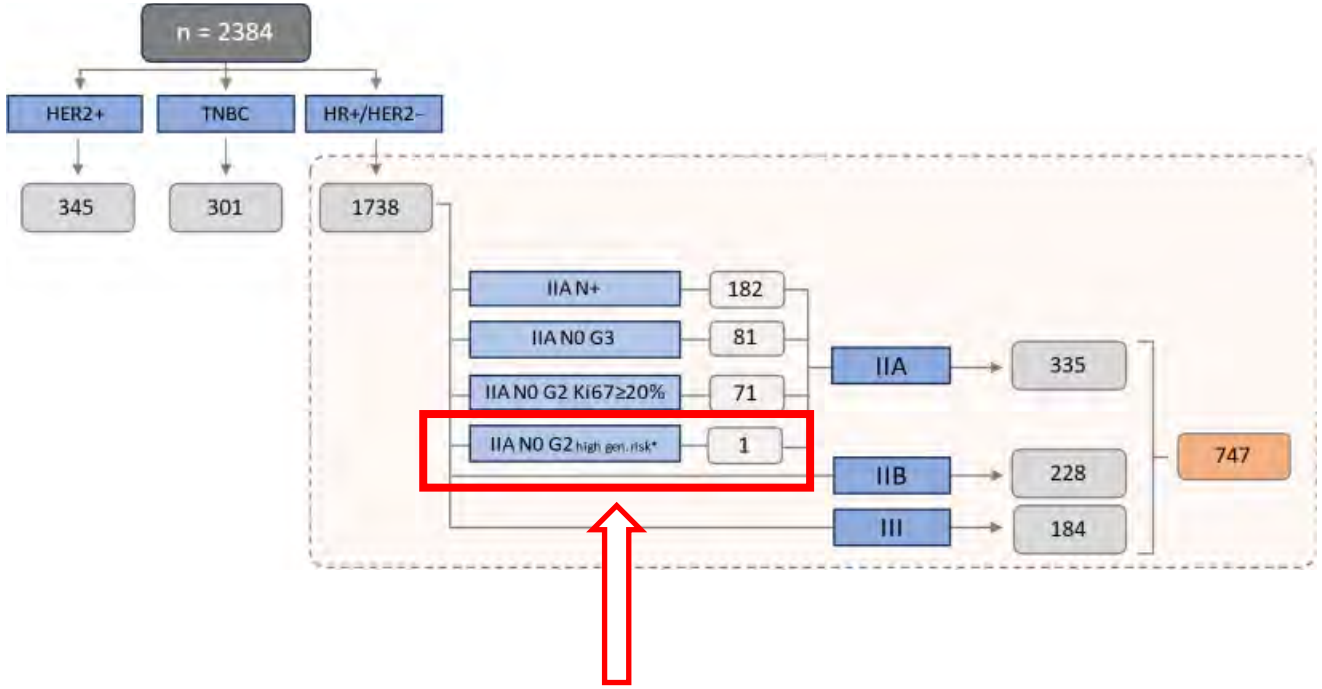
ct, circulating tumor; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from Jan 10, 2019 to April 20, 2021. [c] Open-label design. [d] Per investigator choice.
1. Slamon D, et al. ASCO 2023. Oral LBA500. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl). Abstract TPS597. 3. Slamon DJ, et al. *Ther Adv*

D. Slamon ASCO 2019

The relevance of MGA on CDK4/6-I use (IR/HR)

The potential impact of MGA in RW eBC

AJCC	TN (M0)	NATALEE	MonarchE	Difference
IIA	T0 N1	11	only if G3 or Ki-67 ≥ 20% 11	0
	T1 N1	170	only if G3 or Ki-67 ≥ 20% 59	111
	T2 N0	only if G3 or G2 with Ki-67 ≥ 20% or high genomic risk 154		154
IIB	T2 N1	199	only if G3 or Ki-67 ≥ 20% 87	112
	T3 N0	29		29
IIIA	T0 N2	2	1	1
	T1 N2	20	19	1
	T2 N2	46	43	3
	T3 N1	32	29	3
	T3 N2	13	13	0
IIIB	T4 N0	6		6
	T4 N1	16	only if tumor size ≥ 5 cm or Ki-67 ≥ 20% 6	10
	T4 N2	11	11	0
IIIC	Any TN3	38	37	1
	total	747/ 1738 (42.9%)	316/ 1738 (18.1%)	430



In RW the contribution of genomic test to CDK4/6-i elegibility appears limited

H Schaffler *Int. J. Mol. Sci* 2023

1. Genomics and risk estimate (MGA)
2. Adjuvant and iCDK4/6-i (NATALEE)
3. (Neo)adj and dynamic biomarker (POETIC/ADAPT)
4. Neoadj and IO (CM7FL, KN756)

NATALEE study design

Multicenter, randomized, open-label phase III trial

Patients with HR+, HER2- stage II (either N0 with grade 2/3 and/or Ki67 ≥20% or N1) or III EBC; pre/postmenopausal women or men, with or without prior (neo)adjuvant chemotherapy, no distant metastases (planned N = 4000)

The enrollment of patients with stage II was capped at 40%

Ribociclib 400 mg/day (3 wk on/1 wk off) for 3 yr + **ET (letrozole or anastrazole)*** for 60 mo + **Goserelin†**

ET for 60 mo

*Treatment may begin up to 1 year before study treatment start date. †Premenopausal women and men will also receive goserelin 3.6 mg/28 days.

Randomization stratification

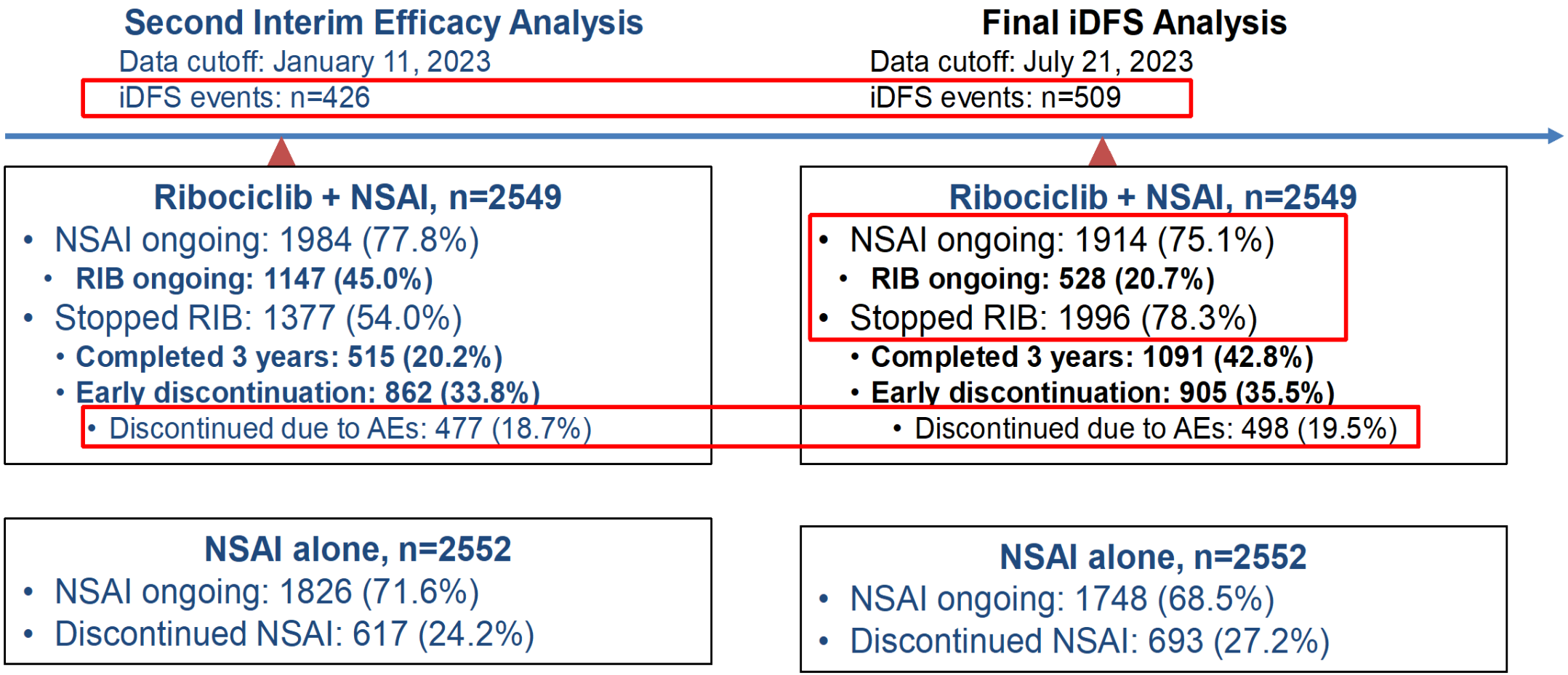
- **Anatomical stage:** II vs III
- **Menopausal status**: men and pre vs postmenopausal women
- **Receipt of prior (neo)adj CT:** yes vs no
- **Geographic location:** North America/Western EU/Oceania vs rest of world

Primary endpoint: invasive disease-free survival (STEEP criteria)

Key secondary endpoints: recurrence-free survival, distant DFS, overall survival, patient-reported outcomes, and pharmacokinetics; safety and tolerability will also be evaluated

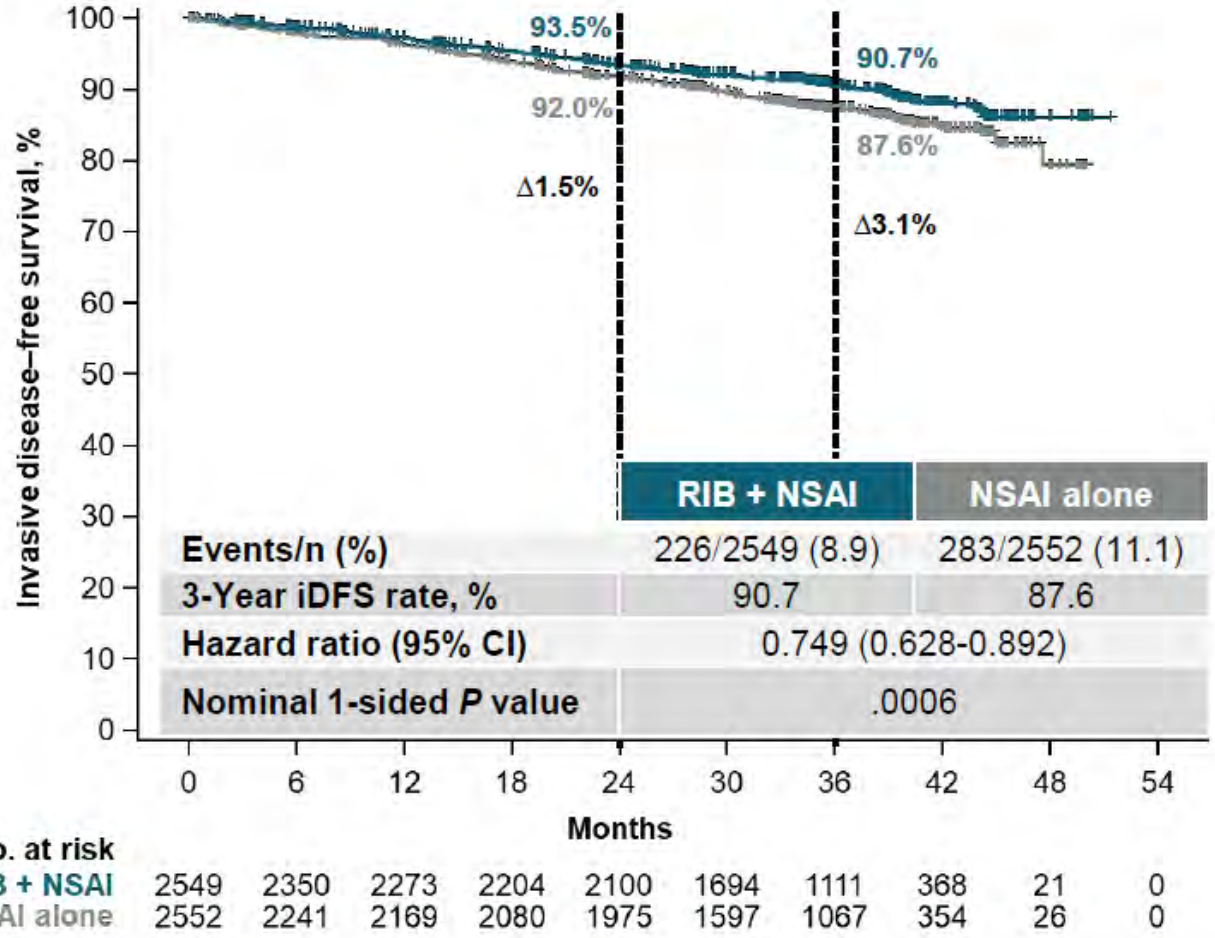
D. Slamon ASCO 2019

Patients disposition



G Hortobagiy, SABCS 2023

IDFS @33m of mFU



IDFS

- The absolute iDFS benefit with ribociclib plus NSAI was 3.1% at 3 years
- The risk of invasive disease was reduced by 25.1% with ribociclib plus NSAI vs NSAI alone

DDFS

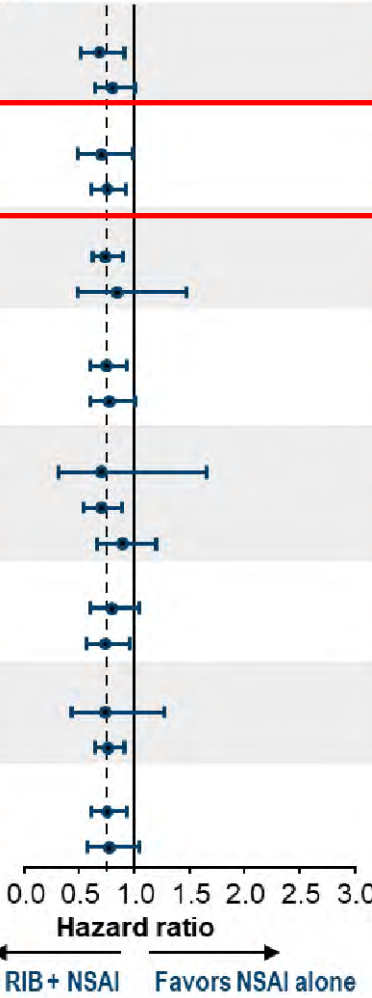
- The absolute DDFS[a] benefit with ribociclib plus NSAI was 2.7% at 3 years
- The risk of distant disease was reduced by 25.1% with ribociclib plus NSAI vs NSAI alone at the final analysis

G Hortobagiy, SABCS 2023

IDFS across pre-specified subgroups

42%

Subgroup	RIB + NSAI Events/n	RIB + NSAI 3-y iDFS rate, %	NSAI alone Events/n	NSAI alone 3-y iDFS rate, %	Hazard ratio	95% CI
Menopausal status						
Men and premenopausal women	83/1125	91.8	114/1132	88.2	0.688	0.519-0.913
Postmenopausal women	143/1424	89.7	169/1420	87.1	0.806	0.645-1.007
AJCC stage						
Stage II	55/1101	94.2	80/1034	92.6	0.700	0.496-0.986
Stage III	170/1528	88.1	203/1512	83.8	0.755	0.616-0.926
Prior CT						
Yes	203/2249	90.5	255/2245	87.1	0.746	0.620-0.897
No	23/300	92.0	28/307	91.2	0.852	0.491-1.479
Region						
North America/Western Europe/Oceania	131/1563	91.1	166/1565	87.5	0.748	0.595-0.941
Rest of world	95/986	90.1	117/987	87.6	0.774	0.591-1.015
Histological grade at time of surgery						
Grade 1	9/213	95.1	13/217	93.1	0.708	0.303-1.657
Grade 2	118/1460	91.5	155/1432	88.0	0.696	0.548-0.885
Grade 3	80/684	87.5	89/702	85.9	0.890	0.658-1.204
Ki-67 status[a]						
Ki-67 ≤20%	93/1199	91.8	117/1236	89.8	0.794	0.605-1.042
Ki-67 >20%	98/920	89.0	125/937	84.9	0.743	0.570-0.988
Nodal status[b,c]						
N0	20/285	93.2	31/328	90.6	0.723	0.412-1.288
N1-N3	206/2261	90.3	251/2219	87.1	0.759	0.631-0.912
Prior ET						
Yes	150/1826	91.4	186/1805	88.4	0.755	0.609-0.936
No	76/723	88.9	97/747	85.8	0.771	0.571-1.040



AJCC, American Joint Committee on Cancer; CT, chemotherapy.
[a] From archival tumor tissue. [b] Nodal status classification according to AJCC staging.
[c] Nodal status is from the worst stage derived per surgical specimen or at diagnosis.

G Hortobagiy, SABCS 2023

Stage II: implication for surgery

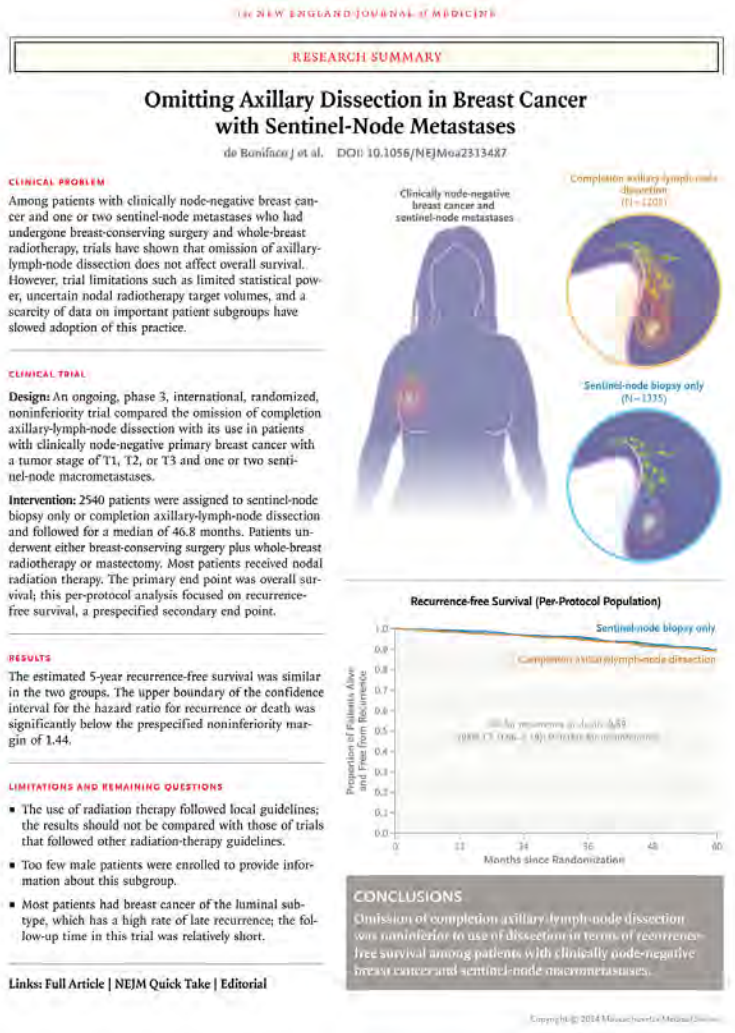
N0 not allowed in monarchE

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

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

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

G Hortobagiy, SABCS 2023



THE NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Omitting Axillary Dissection in Breast Cancer with Sentinel-Node Metastases

de Bonifacio J et al. DOI: 10.1056/NEJMoa2314847

CLINICAL PROBLEM

Among patients with clinically node-negative breast cancer and one or two sentinel-node metastases who had undergone breast-conserving surgery and whole-breast radiotherapy, trials have shown that omission of axillary-lymph-node dissection does not affect overall survival. However, trial limitations such as limited statistical power, uncertain nodal radiotherapy target volumes, and a scarcity of data on important patient subgroups have slowed adoption of this practice.

CLINICAL TRIAL

Design: An ongoing, phase 3, international, randomized, noninferiority trial compared the omission of completion axillary-lymph-node dissection with its use in patients with clinically node-negative primary breast cancer with a tumor stage of T1, T2, or T3 and one or two sentinel-node macrometastases.

Intervention: 2540 patients were assigned to sentinel-node biopsy only or completion axillary-lymph-node dissection and followed for a median of 46.8 months. Patients underwent either breast-conserving surgery plus whole-breast radiotherapy or mastectomy. Most patients received nodal radiation therapy. The primary end point was overall survival; this per-protocol analysis focused on recurrence-free survival, a prespecified secondary end point.

RESULTS

The estimated 5-year recurrence-free survival was similar in the two groups. The upper boundary of the confidence interval for the hazard ratio for recurrence or death was significantly below the prespecified noninferiority margin of 1.44.

LIMITATIONS AND REMAINING QUESTIONS

- The use of radiation therapy followed local guidelines; the results should not be compared with those of trials that followed other radiation-therapy guidelines.
- Too few male patients were enrolled to provide information about this subgroup.
- Most patients had breast cancer of the luminal subtype, which has a high rate of late recurrence; the follow-up time in this trial was relatively short.

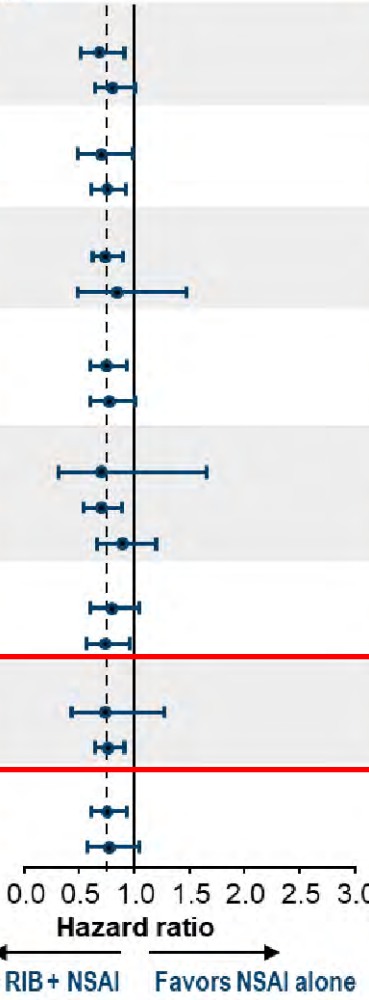
Links: Full Article | NEJM Quick Take | Editorial

CONCLUSIONS

Omission of completion axillary-lymph-node dissection was noninferior to use of dissection in terms of recurrence-free survival among patients with clinically node-negative breast cancer and sentinel-node macrometastases.

IDFS across pre-specified subgroups

Subgroup	RIB + NSAI Events/n	RIB + NSAI 3-y iDFS rate, %	NSAI alone Events/n	NSAI alone 3-y iDFS rate, %	Hazard ratio	95% CI
Menopausal status						
Men and premenopausal women	83/1125	91.8	114/1132	88.2	0.688	0.519-0.913
Postmenopausal women	143/1424	89.7	169/1420	87.1	0.806	0.645-1.007
AJCC stage						
Stage II	55/1101	94.2	80/1034	92.6	0.700	0.496-0.986
Stage III	170/1528	88.1	203/1512	83.8	0.755	0.616-0.926
Prior CT						
Yes	203/2249	90.5	255/2245	87.1	0.746	0.620-0.897
No	23/300	92.0	28/307	91.2	0.852	0.491-1.479
Region						
North America/Western Europe/Oceania	131/1563	91.1	166/1565	87.5	0.748	0.595-0.941
Rest of world	95/986	90.1	117/987	87.6	0.774	0.591-1.015
Histological grade at time of surgery						
Grade 1	9/213	95.1	13/217	93.1	0.708	0.303-1.657
Grade 2	118/1460	91.5	155/1432	88.0	0.696	0.548-0.885
Grade 3	80/684	87.5	89/702	85.9	0.890	0.658-1.204
Ki-67 status[a]						
Ki-67 ≤20%	93/1199	91.8	117/1236	89.8	0.794	0.605-1.042
Ki-67 >20%	98/920	89.0	125/937	84.9	0.743	0.570-0.988
Nodal status[b,c]						
N0	20/285	93.2	31/328	90.6	0.723	0.412-1.288
N1-N3	206/2261	90.3	251/2219	87.1	0.759	0.631-0.912
Prior ET						
Yes	150/1826	91.4	186/1805	88.4	0.755	0.609-0.936
No	76/723	88.9	97/747	85.8	0.771	0.571-1.040



12%

AJCC, American Joint Committee on Cancer; CT, chemotherapy.
[a] From archival tumor tissue. [b] Nodal status classification according to AJCC staging.
[c] Nodal status is from the worst stage derived per surgical specimen or at diagnosis.

G Hortobagiy, SABCS 2023

The N0/+ migration from baseline to randomization

Table S1. Nodal Status at Diagnosis, Surgery, and Stage

Nodal Status, n (%)[a]	At Diagnosis (clinical)		Post Surgery (pathological)		Used in AJCC Staging (worst of 2)	
	RIB + NSAI (n=2549)	NSAI alone (n=2552)	RIB + NSAI (n=2549)	NSAI alone (n=2552)	RIB + NSAI (n=2549)	NSAI alone (n=2552)
NX[b]	272 (11)	264 (10)	2 (0.1)	5 (0.2)	3 (0.1)	5 (0.2)
N0[c]	694 (27)	737 (29)	378 (15)	418 (16)	285 (11)	328 (13)
N1[d]	1050 (41)	1049 (41)	1062 (42)	1039 (41)	1088 (43)	1039 (41)
N2[e]	332 (13)	292 (11)	733 (29)	690 (27)	752 (30)	711 (28)
N3[f]	151 (6)	175 (7)	372 (15)	399 (16)	421 (17)	469 (18)

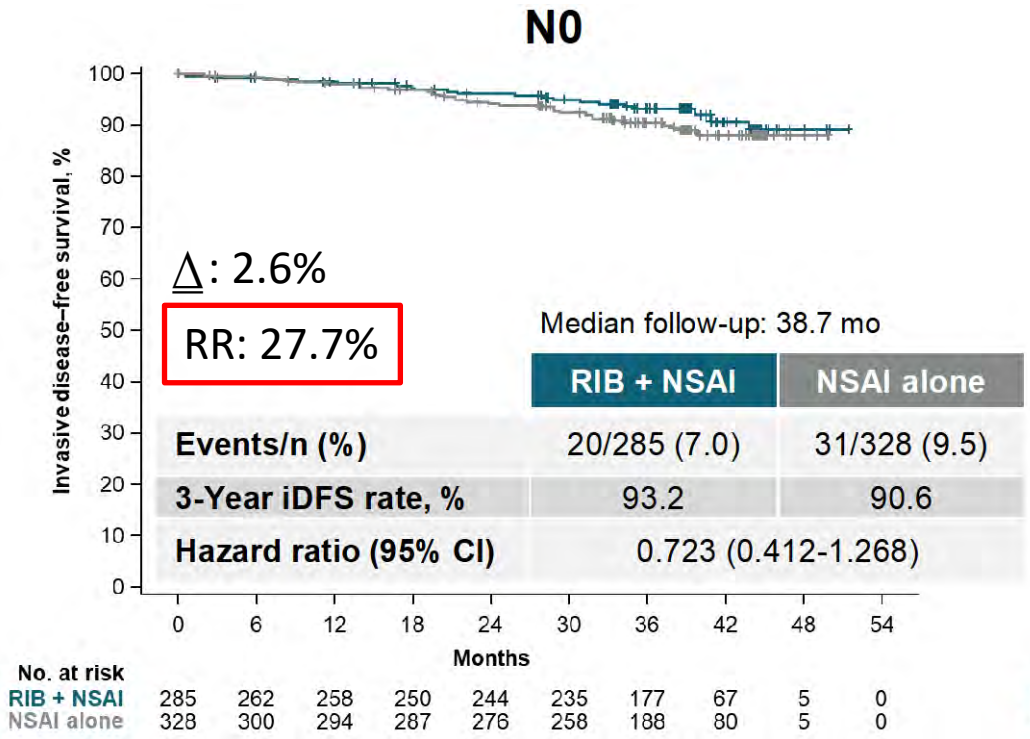
N0 28->12%

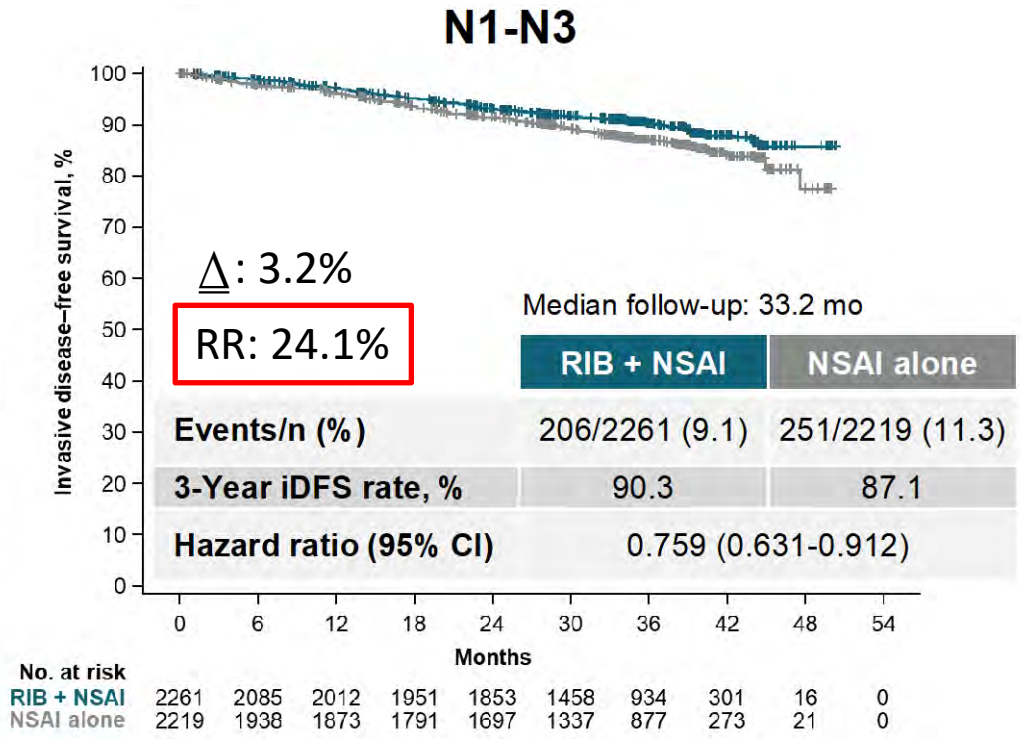
N2 12->29%

@ baseline the clinical staging was use to describe patients characteristics
@ randomization the worse staging (c/p) was use to define the extent of the disease

D Slamon NEJM 2024

N0: implication for adj treatment





The N0 cases derive similar benefit as compare to N1-3 (with imprecision)

IDFS across pre-specified subgroups

12%

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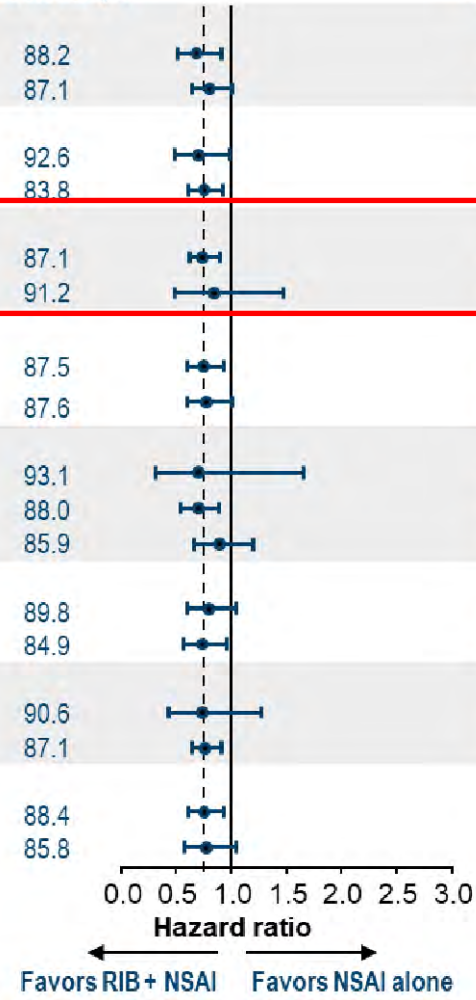


AJCC, American Joint Committee on Cancer; CT, chemotherapy.
[a] From archival tumor tissue. [b] Nodal status classification according to AJCC staging.
[c] Nodal status is from the worst stage derived per surgical specimen or at diagnosis.

Clinical relevance NATALEE in RWE

AJCC	TN (M0)	NATALEE	MonarchE	Difference
IIA	T0 N1	11	only if G3 or KI-67 ≥ 20% 11	0
	T1 N1	170	only if G3 or KI-67 ≥ 20% 59	111
	T2 N0	only if G3 or G2 with KI-67 ≥ 20% or high genomic risk 154		154
IIB	T2 N1	199	only if G3 or KI-67 ≥ 20% 87	112
	T3 N0	29		29
IIIA	T0 N2	2	1	1
	T1 N2	20	19	1
	T2 N2	46	43	3
	T3 N1	32	29	3
	T3 N2	13	13	0
IIIB	T4 N0	6		6
	T4 N1	16	only if tumor size ≥ 5 cm or KI-67 ≥ 20% 6	10
	T4 N2	11	11	0
IIIC	Any TN3	38	37	1
	total	747/ 1738 (42.9%)	316/ 1738 (18.1%)	430

Notable difference NATALEE vs RWD

	NATALEE	RWD
Age	52	59.1
Stage		
• IIA	18.8	44.8
• IIB	20.9	30.5
• III	59.9	24.6
Nodes neg (N0)	11.2	27.6
Chemotherapy	88.2	49.4
ECOG 0	82.6	NA
Premenopausal	44.2	32

In the RW context **43%** of pts may enter the NATALEE vs **18%** the MonarchE
In RW cohort pts were: **older,** received **less chemotherapy** and presented with **less advanced tumor stages** *vs* RCT

H Schaffler *Int. J. Mol. Sci* 2023

No standard definition of High-Risk Luminal eBC

Definition of high risk patients with HR+/HER2- EBC for escalating adjuvant therapy

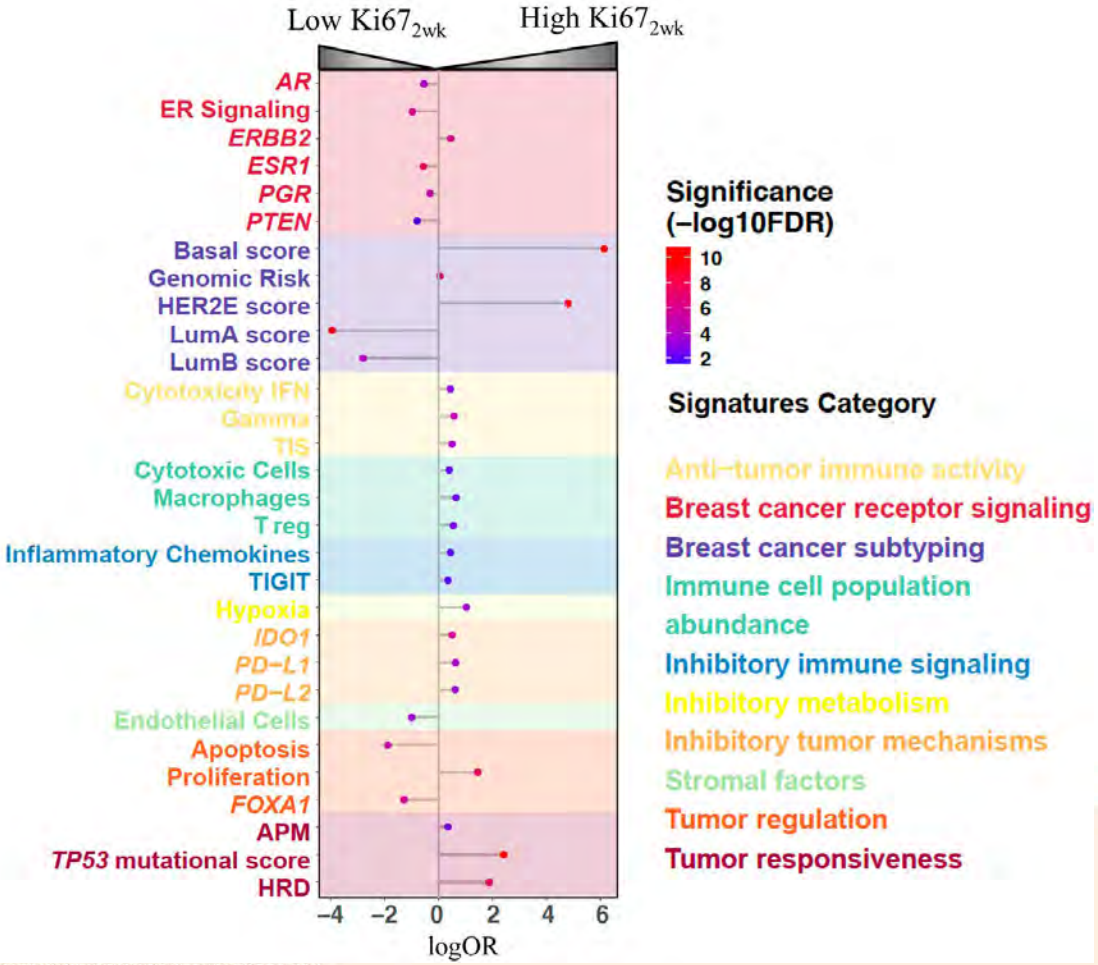
MONARCHE	NATALEE	OLYMPIA	WSG-ADAPT
-High risk based on <u>clinical-pathological features:</u> • ≥4 positive nodes • 1-3 positive nodes + 1 of the following: Tumor size ≥5 cm Grade 3 -High risk based on <u>highly proliferative disease:</u> 1-3 positive nodes + Ki-67 ≥20%	-stage II (either N0 with grade 2/3 and/or Ki67 ≥20% or N1) -or stage III	-After NACT: No pCR and CPS + EG ≥3 -After ACT: ≥4 positive nodes	cT2-4 OR clinically N+ OR G3 OR Ki67>15%

Tutt et al, NEJM. 2021; Slamon et al, ASCO 2019; Johnston et al, JCO. 2020; Gluz et al, ASCO 2022

Can we predict the poor responders in the first biopsy?

Can we predict the poor responders in the first biopsy?

Hypothesis: intrinsic subtyps and genomic signatures predict response
PR reduction <50%, IR 50-75%, GR <75%, based on Ki67$_{@2wks}$ (POETIC trial)



Ki67 response categories

Arm	TREATED				
	All	Basal	HER2-E	LumA	LumB
	226 (100.0%)	3 (1.3%)	95 (42.1%)	45 (19.9%)	83 (36.7%)
GR	70 (31·0%)	0 (0·0%)	15 (15·8%)	18 (40·0%)	37 (44·6%)
IR	51 (22·5%)	0 (0·0%)	17 (16·5%)	11 (24·4%)	23 (27·7%)
PR	105 (46·5%)	3 (100%)	63 (66·3%)	16 (35·5%)	23 (27·8%)

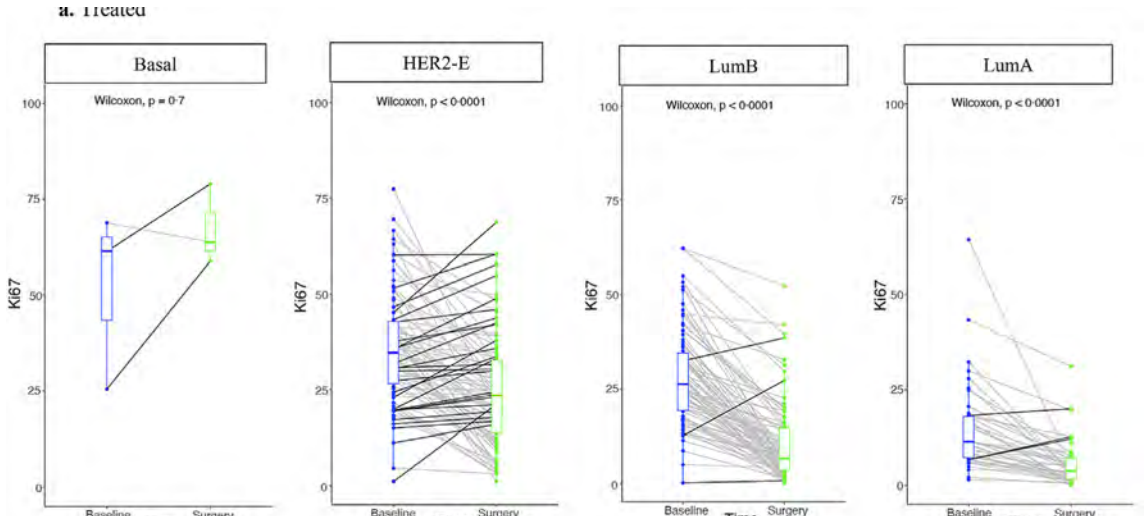
Chi -squared 27·69, $P<0·00001$

HER2 enriched subtype poor responders
Basing decisions on baseline biopsy- missing >50% of the PR in the Lum A and Lum B subtypes

Adapted from Bergamino MA, et al. eBioMedicine 2022

Can we predict the poor responders in the first biopsy?

Gene expression profiles at baseline were assessed in association with the response to AI
Luminal A tumors have lower Ki67 at baseline



But GEX classification of the initial biopsy still misses
 49% of Lum tumours that have persistent high Ki67 after 2 weeks of AI

Ki67 response categories

Arm	TREATED All 226 (100.0%)	Basal 3 (1.3%)	HER2-E 95 (42.1%)	LumA 45 (19.9%)	LumB 83 (36.7%)
GR	70 (31·0%)	0 (0·0%)	15 (15·8%)	18 (40·0%)	37 (44·6%)
IR	51 (22·5%)	0 (0·0%)	17 (16·5%)	11 (24·4%)	23 (27·7%)
PR	105 (46·5%)	3 (100%)	63 (66·3%)	16 (35·5%)	23 (27·8%)
		Chi -squared 27·69, $P<0·00001$			
					$Ki67_{2wks}$
HIGH	118 (52·0%)	3 (100·0%)	80 (84·2%)	7 (15·6%)	28 (33·7%)
LOW	109 (48·0%)	0 (0·0%)	15 (15·8%)	38 (84·4%)	55 (66·3%)
		Chi-squared 67·98, $P<0·00001$			

Adapted from Bergamino MA, et al. eBioMedicine 2022

1. Genomics and risk estimate (MGA)
2. Adjuvant and iCDK4/6-i (NATALEEI)
3. (Neo)adj and dynamic biomarker (POETIC/ADAPT)
4. Neoadj and IO (CM7FL, KN756)

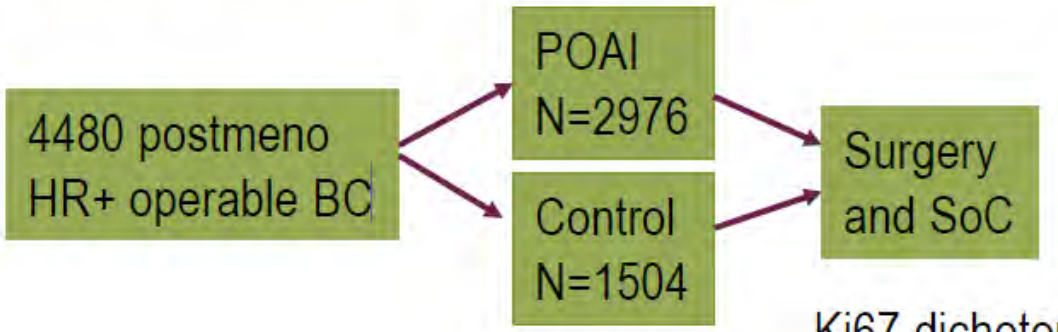
Dynamic Tx-response prediction

POETIC trial

Postmenopausal W ER+ eBC were randomly assigned (2:1) to POAI (letrozole or anastrozole) for 14 days before/following surgery or no POAI (control).

Perioperative Aromatase Inhibitor-

AI 14 days before and after surgery



Ki67 dichotomized

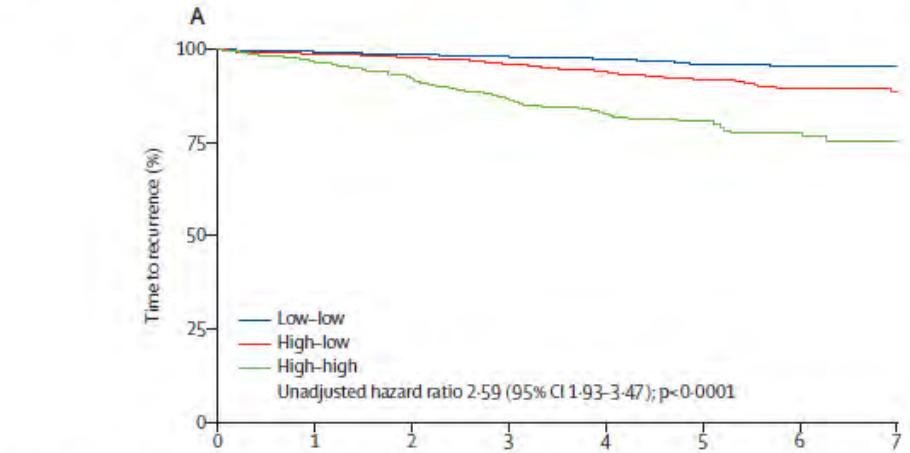
Low < 10%

High ≥ 10%

HR relapse high-high vs high-low: 2.59 (1.93-3.47)

Primary endpoint TTR (no differences)

Secondary- explore association of changes in ki67 and TTR



Number at risk (number censored)								
Low–low	704 (11)	688 (18)	676 (34)	657 (100)	585 (235)	443 (434)	243 (580)	97 (··)
High–low	1097 (7)	1077 (21)	1052 (44)	1011 (130)	902 (378)	638 (678)	327 (882)	121 (··)
High–high	406 (5)	387 (9)	366 (17)	336 (35)	302 (111)	220 (227)	98 (290)	33 (··)

Adapted from Smith I, et al. Lancet Oncol 2020

Abema: POETIC-A trial

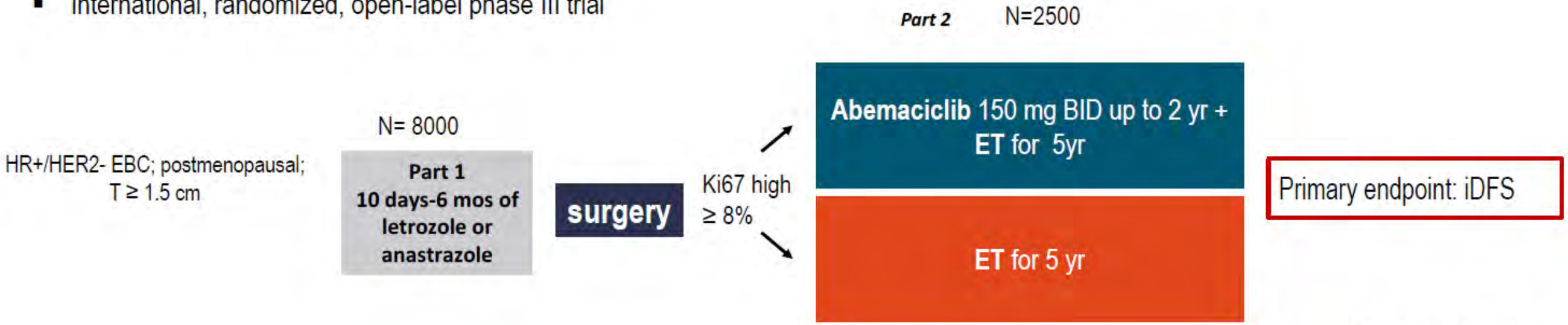
CANCER RESEARCH UK

POETIC-A

Pre-Operative Endocrine Therapy for Individualised Care with Abemaciclib

Part 1 uses samples from peoples' BC surgery to assess their cancer's sensitivity to ET
Part 2 is the treatment part of the trial. Pts found to not be very sensitive to ET will be randomized to ET *vs* ET+A

- International, randomized, open-label phase III trial



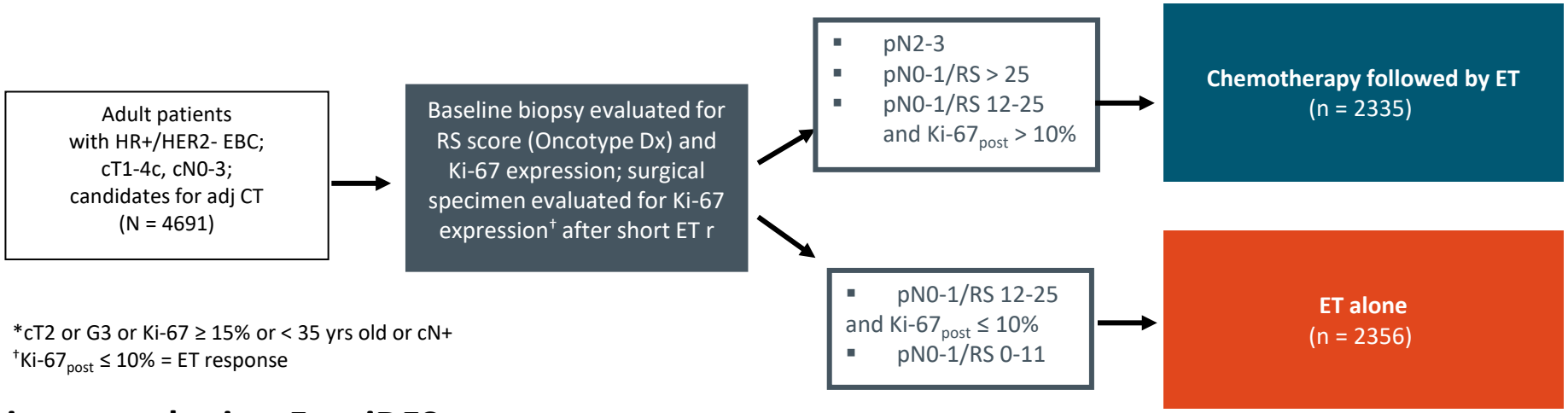
P.I. Stephen Johnston

Dynamic Tx-response prediction
ADAPT Trial HR+/HER2-

Adj ET ± CT in Intermediate/High-Risk, HR+/HER2- eBC

2-part, prospective phase III trial

Part 1: current analysis evaluated prognostic impact of RS < 26 and Ki-67 decrease after short-course of preoperative ET in the ET alone arm and is not a randomized comparison



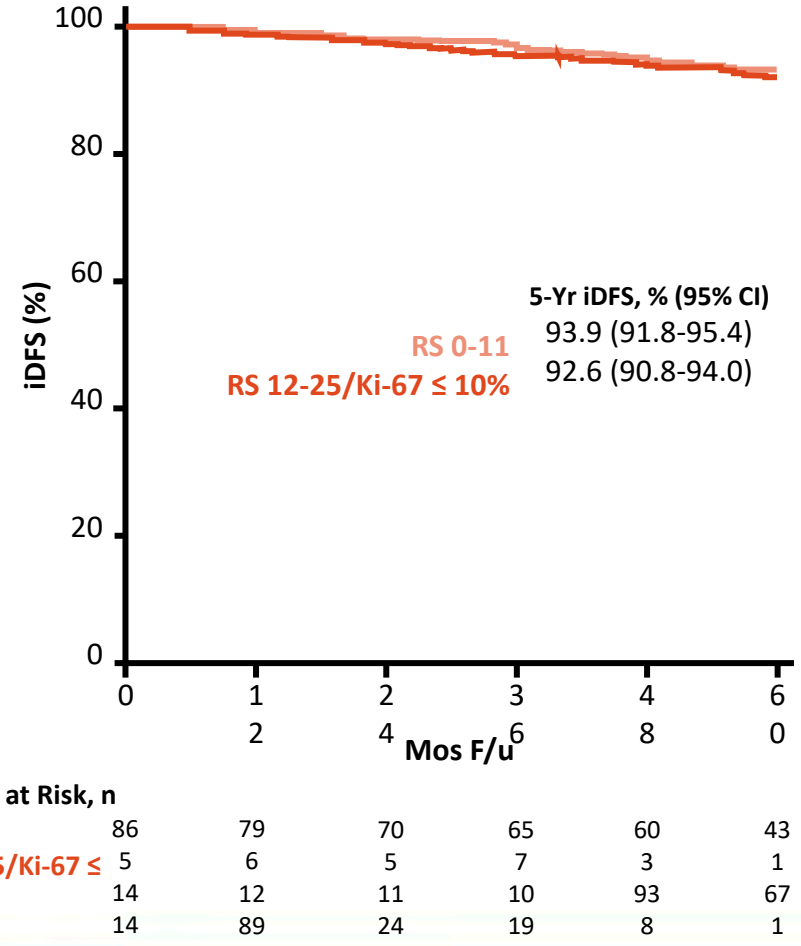
*cT2 or G3 or Ki-67 ≥ 15% or < 35 yrs old or cN+
†Ki-67$_{post}$ ≤ 10% = ET response

Primary endpoint: 5-yr iDFS Part 1: noninferiority for pN0-1/RS 12-25/Ki-67$_{post}$ ≤ 10% vs pN0-1/RS 0-11. Key secondary endpoints: dDFS, OS, translational research

Harbeck. SABCS 2020. Abstr GS4-04

ADAPT Trial HR+/HER2-: 5-Yr iDFS

Primary Endpoint

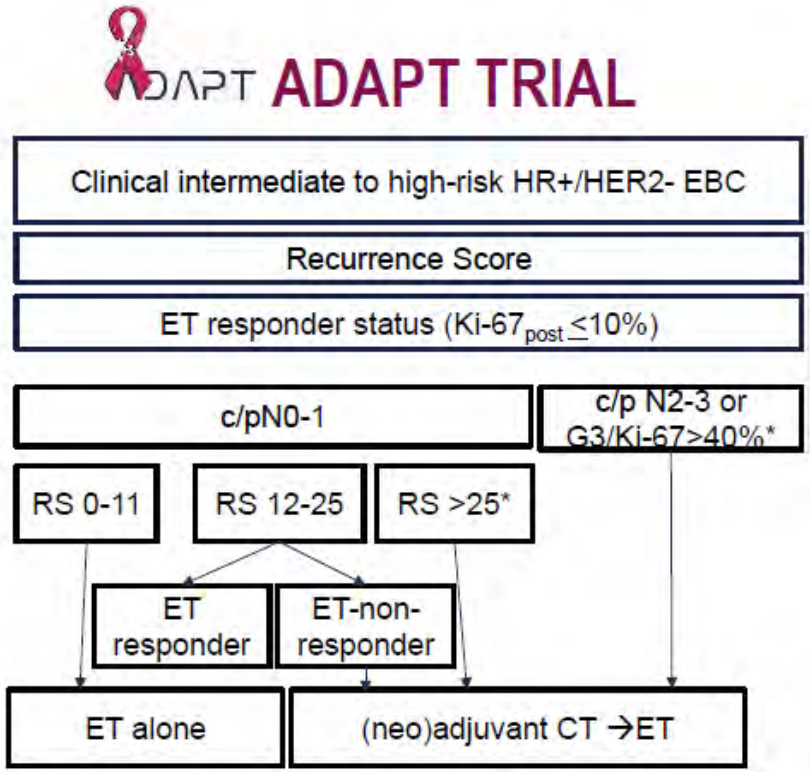


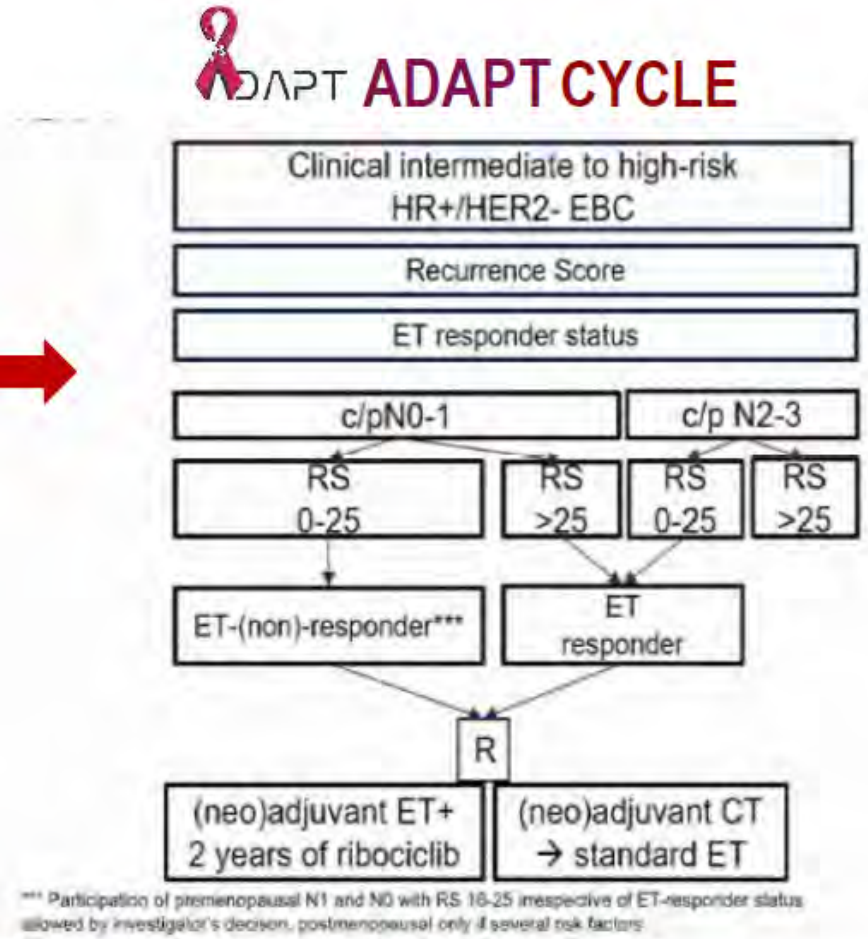
- Primary endpoint met
  - 5-yr iDFS difference: -1.3%
    (95% CI: -3.3% to 0.6%)
  - 95% lower confidence limit of -3.3% met prespecified criterion for **non-inferiority** of pN0-1/RS 12-25/Ki-67$_{post}$ ≤ 10% ***vs*** pN0-1/RS 0-11 (P = .05)

- 5-yr OS rate
  - 97.3% for pN0-1/RS 12-25/Ki-67 ≤ 10% ***vs*** 98.0% for pN0-1/RS 0-11(P = .160)

Harbeck. SABCS 2020. Abstr GS4-04

Ribo: ADAPT-Cycle Trial





Ribo: RIBOLARIS Trial

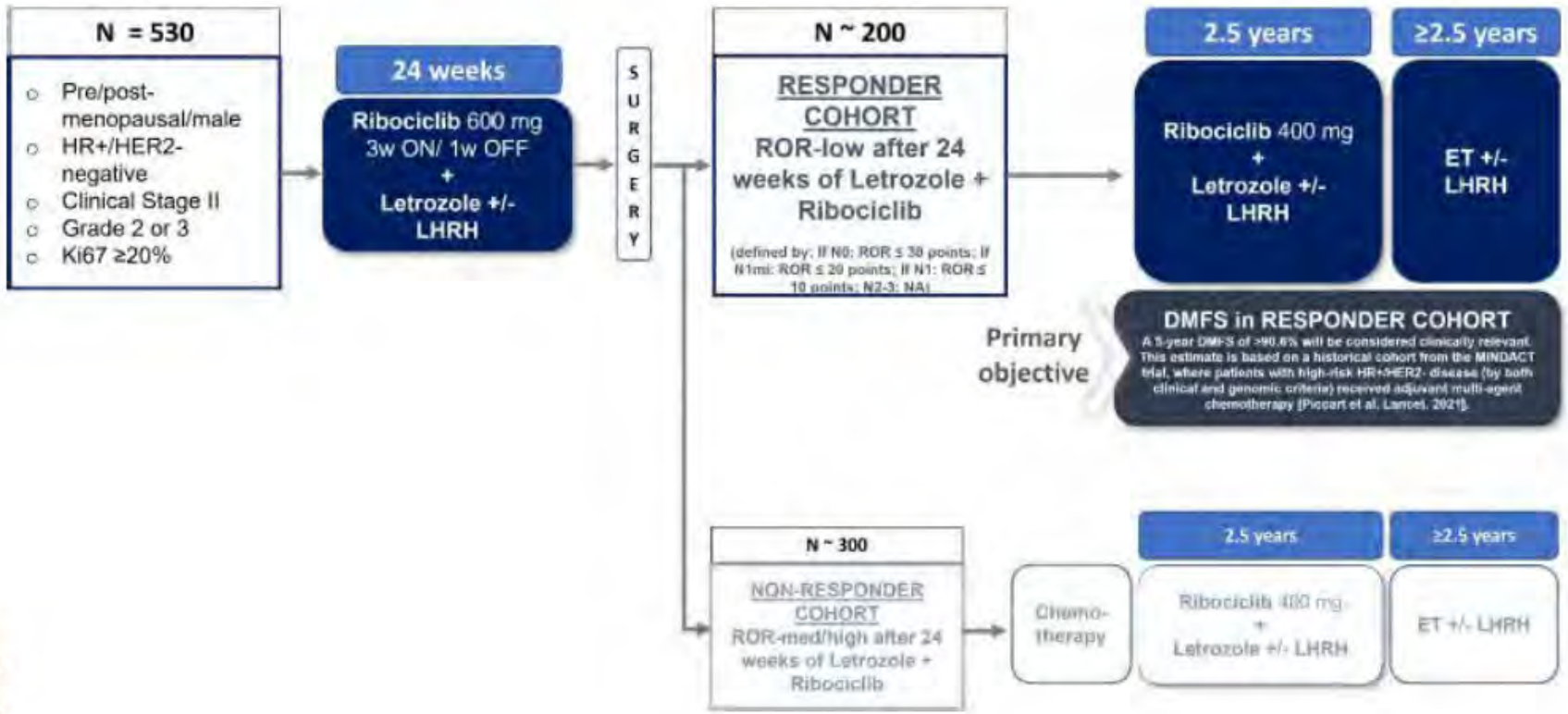
(Neo)adjuvant Ribociclib and ET (6mo) for High-Risk ER+/HER2- eBC

MOLECULAR DOWNSTAGING TO AVOID ADJUVANT CHEMOTHERAPY (CORALEEN)

- International, open-label phase III trial

SOLTI UCBG BIG

RIBOLARIS
SOLTI-1911 / BIG-21-02



Primary objective: to evaluate **if patients with initial high-risk clinical features and a ROR-low at surgery (RESPONDERS) after ribociclib and letrozole neoadjuvant treatment, can safely spare chemotherapy and maintain low risk of recurrence**

PI: Prat A

Palbo: TRAK-ER Trial

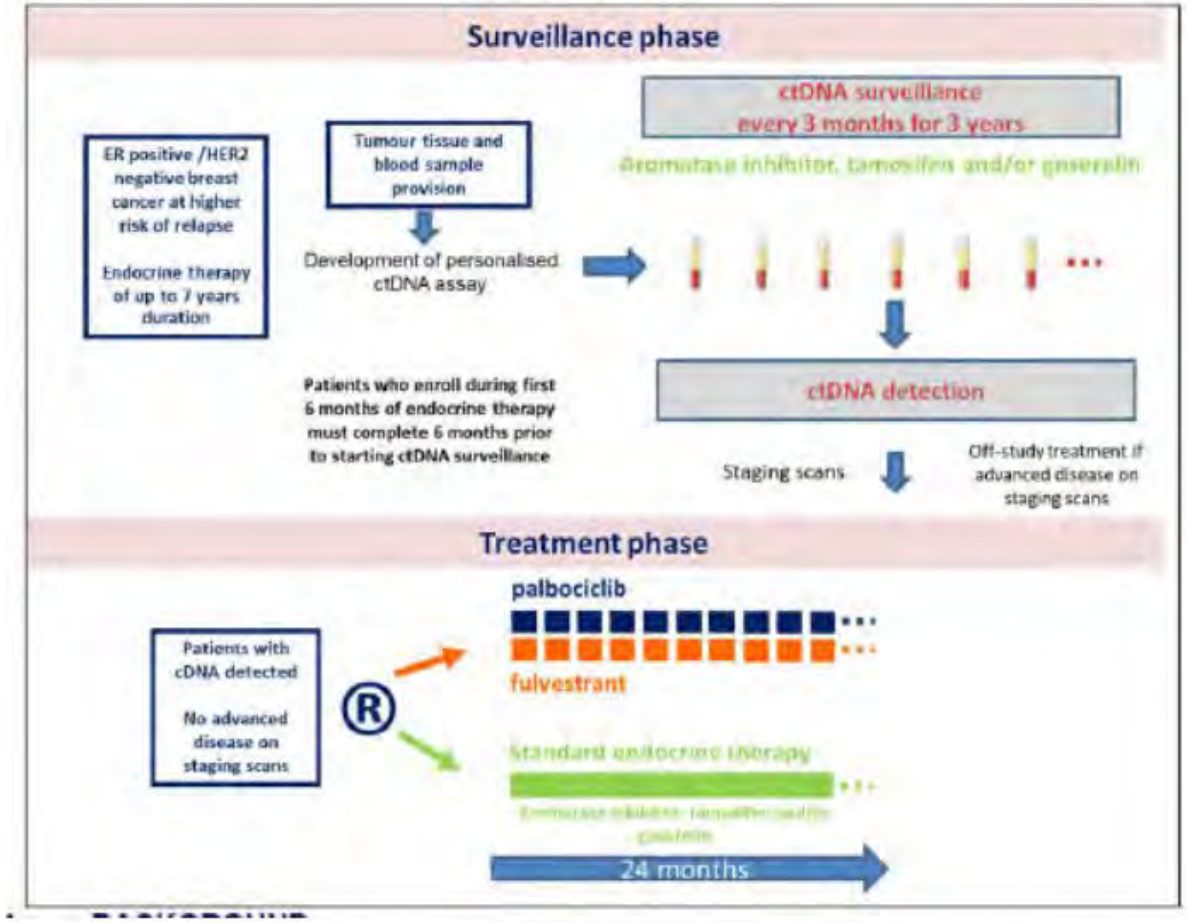
MOLECULAR DOWNSTAGING TO CALIBRATE ADJUVANT TX (TRAK-TN)

ICR The Institute of Cancer Research | The ROYAL MARSDEN | unicancer | UCBG

TRAK-ER

A randomised trial of early detection of molecular relapse with circulating tumour DNA tracking and treatment with palbociclib plus fulvestrant versus standard endocrine therapy in patients with ER positive HER2 negative breast cancer

A. Four or more involved axillary lymph nodes or positive supraclavicular lymph node at diagnosis, or
B. Tumour size > 5 cm, regardless of lymph node status, or
C. 1-3 involved axillary lymph nodes and at least one of the following; i) Tumour size > 3 cm, ii) histological grade 3 iii) high genomic risk defined as Oncotype Dx Recurrence Score >=26, Prosigna score >=60, EPclin risk score >=4.0, or Mammaprint high risk category, or
D. At least a 15% predicted residual risk of death within 10 years using NHS PREDICT (see appendix A3 on calculating predicted residual risk of death with PREDICT)



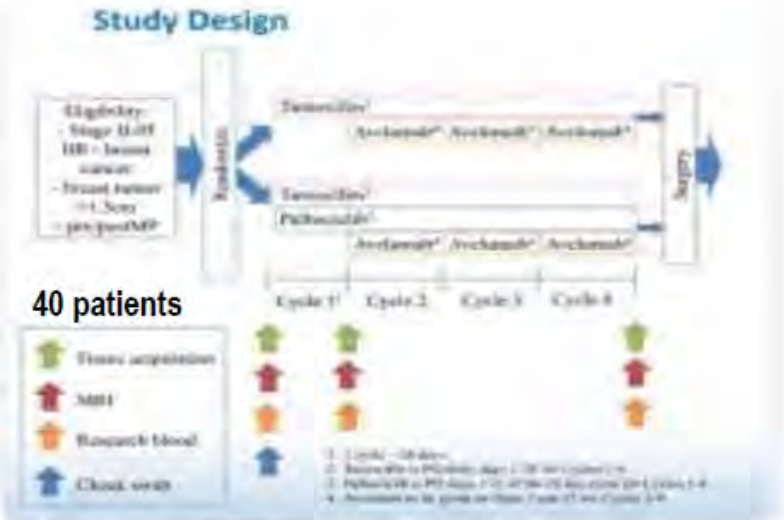
bjclub

N Turner, F André

Palbo: IMMUNOADAPT Trial

IMMUNEMODULATION WITH ADDITION OF AVELUMAB TO PALBOCICLIB AND TAMOXIFEN

IMMUNOADAPT



Primary objective: clinical complete response (cCR) rate by MRI
Secondary objectives :TILs (H&E), CD8 and FOXP3 by immunohistochemistry (IHC), T cell receptor (TCR) repertoire (TCR sequencing), multiplex gene expression panel (Nanostring), and multiplex IHC

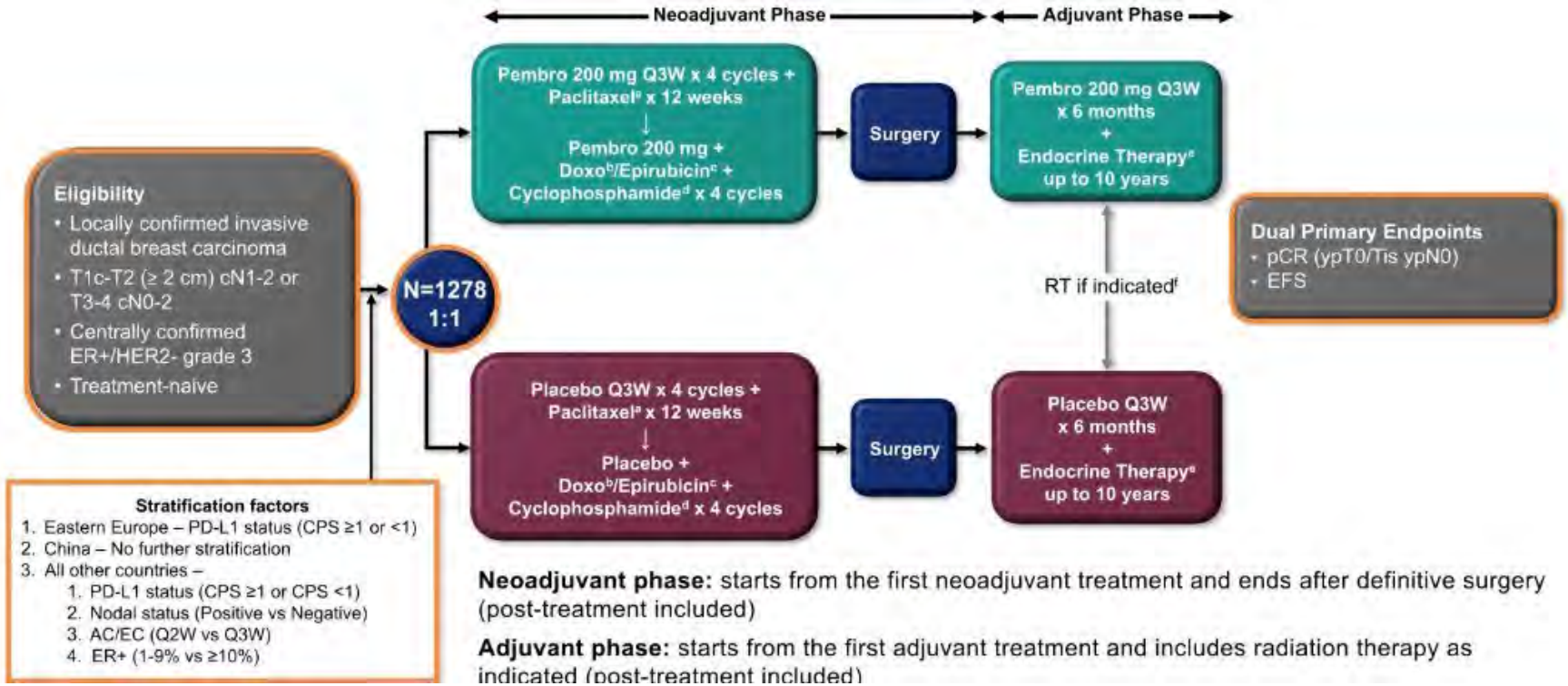
Santa-Maria et al, Cancer Res 2019

1. Genomics and risk estimate (MGA)
2. Adjuvant and iCDK4/6-i (NATALEE)
3. (Neo)adj and dynamic biomarker (POETIC/ADAPT)
4. Neoadj and IO (CM7FL, KN756)

IO in high-risk Luminal eBC

KN-756: IO in high risk HR+/HER2- eBC (neo)adj

KN-756 n=1278



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)

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IO in high-risk Luminal eBC

CM-7FL: IO in high risk HR+/HER2- eBC (neo)adj

CM-7FL n=510

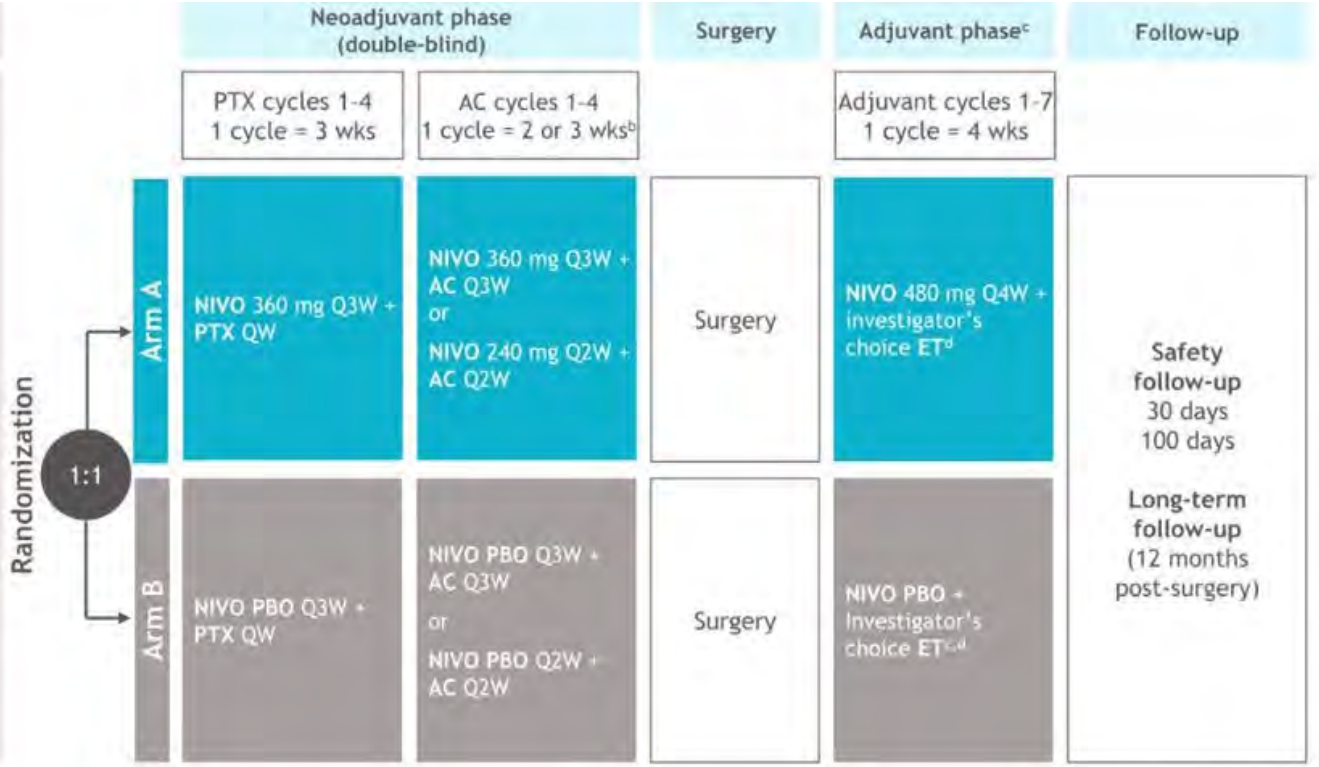
Screening

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)



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IO in high-risk Luminal eBC (neo)adj

Trial element	Similarities	Differences

Trial design	• Both phase III, placebo-controlled RCTs that evaluated neoadj/adj PD1 inhibitors in combination with the same NACT regimen for high-risk HR+/HER2- EBC	• Use of different PD1 inhibitors:
		  • KN756: Pembrolizumab
		  • 7FL: Nivolumab
		• Keynote-756 enrolled over twice as many pts

Eligibility criteria	• Overall similar: pts with high-risk HR+/HER2- EBC	• Slight differences in enrollment criteria:
		  • KN756: All grade 3, T1c-T2/ N1-2 or T3/T4
		  • 7FL: Gr **2**/3, T1c-T2/N**0**-2 or T3/T4 N0-2

Stratification factors	• Similar: nodal status, AC/EC q2w/3w, PD-L1 status	• Use of different PD-L1 assays:
		  • KN756: 22C3 CPS
		  • 7FL: SP142 (and 28-8 CPS in biomarker analysis)

1º endpoint(s)	• Both powered to detect difference in pCR rates	• KN756 also powered to detect difference in EFS

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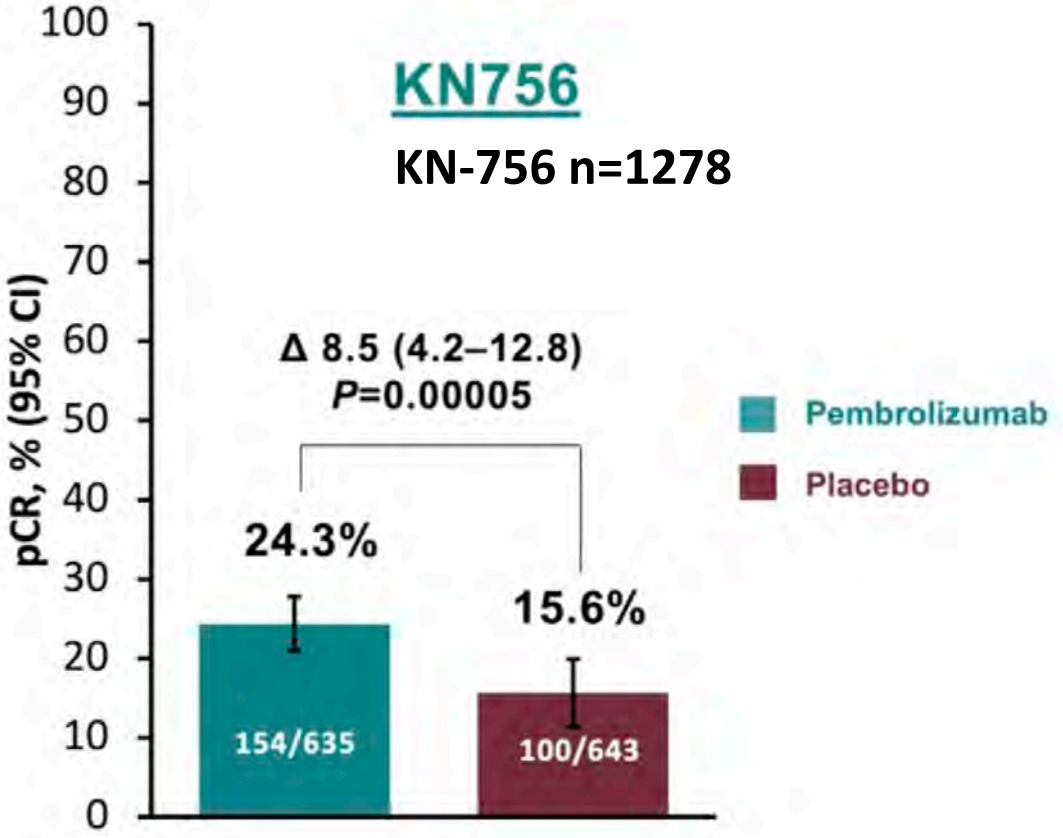
Results: activity (pCR)



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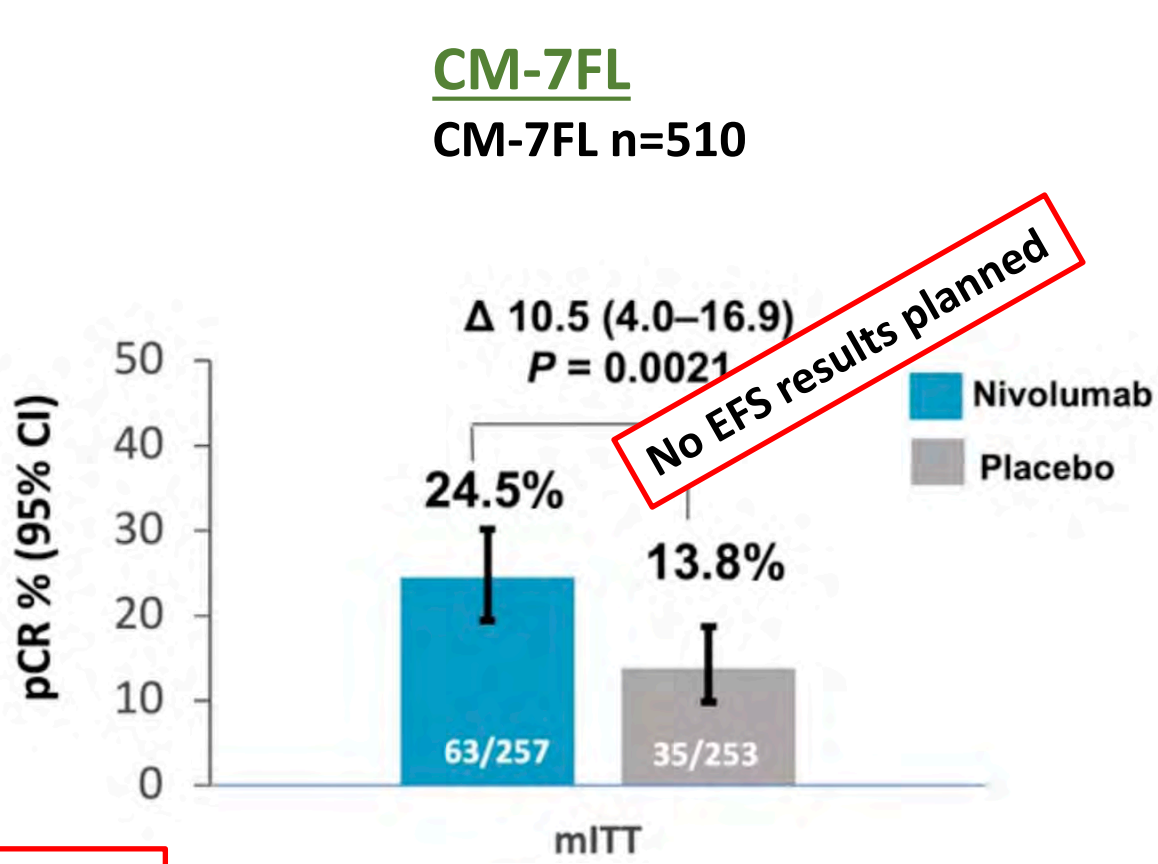

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Consider IR toxicities

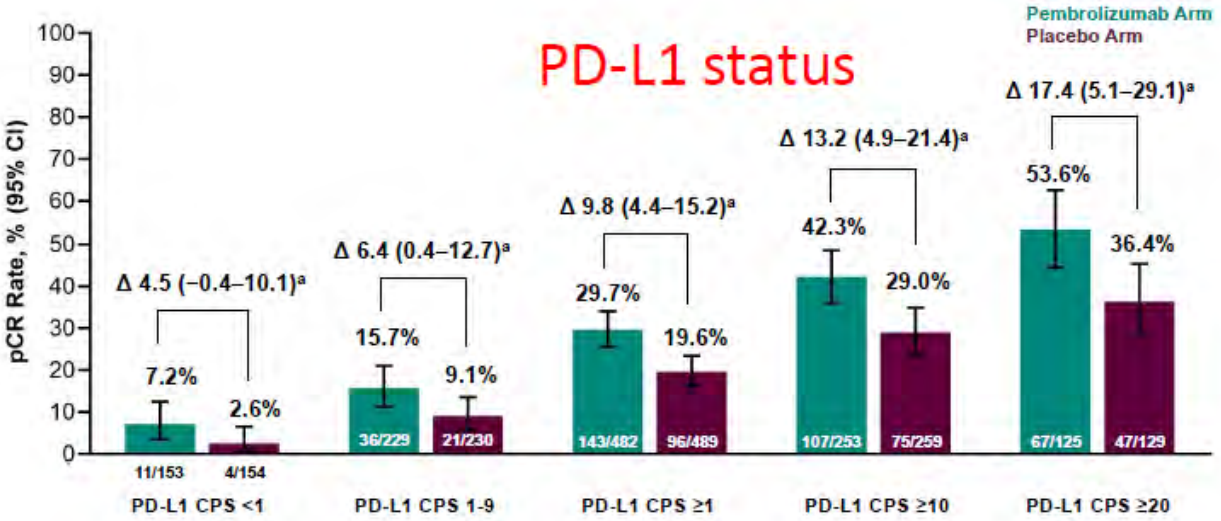
KN-756

Key subgroup and biomarkers analysis

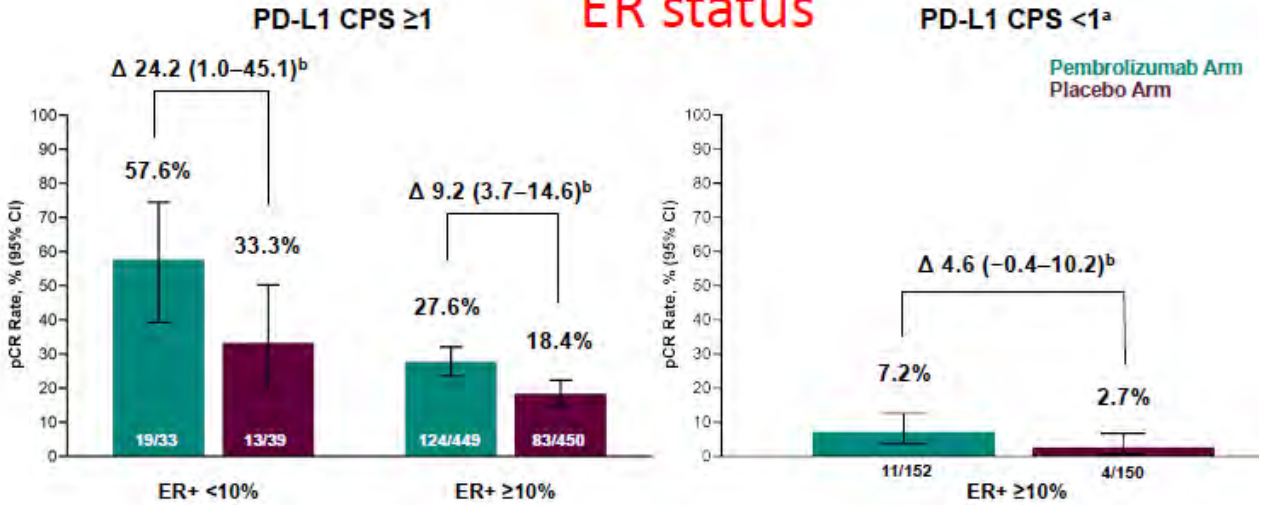
Clinical charact.	Impact of pembro on pCR rate
Stage II (n-807) III (n=471)	• Benefit regardless of stage - stage II (+Δ 9.1) and III (+Δ 8.0)
LN involvement pos (n=1152) neg (n=126)	• Benefit in LN pos (+Δ 9.3) • Benefit less clear LN neg (+Δ3.8)
Chemo exposure full (n=634) partial (n=641)	• Benefit regardless of whether chemotherapy completed

Biomarker	Impact of pembro on pCR rate
PD-L1 22C3 CPS	• Benefit if CPS ≥1. Higher pCR rates & larger Δ with higher CPS • Benefit less clear CPS <1
ER status Stratified by CPS score	• CPS ≥1: Benefit for all ER%, with larger benefit if ER <10% • CPS <1: Benefit less clear ER ≥10%

PD-L1 status



ER status



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Conclusion

- MGA are prognostic and not predictive for CDK4/6i in eBC
- Not everything con be revealed by the first BC biopsy (at least for now)
- Dynamic biomarkers (RR, Ki67, MGA; ctDNA) may add crucial information for optimal adjuvant Tx
- Neoadj approaches are relevant in HR+ eBC and deserve dedicated studies as for HER2/TNBC

Thank you

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