bjclub breast Journal club

L'IMPORTANZA DELLA RICERCA IN ONCOLOGIA

7-8 MARZO 2025
NAPOLI
Hotel Royal Continental
Via Partenope, 38

JOURNAL CLUB UPDATES

Luminal fase precoce

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IRCCS - Fondazione Pascale

Disclosures and potential conflicts of interest

- **Consulting/Advisor:** Roche, AstraZeneca, Lilly, GSK, Novartis, Pfizer, Gilead, Seagen, Daiichi Sankyo, MSD
- **Honoraria:** Roche, AstraZeneca, Lilly, GSK, Novartis, Pfizer, Gilead, Seagen, Daiichi Sankyo
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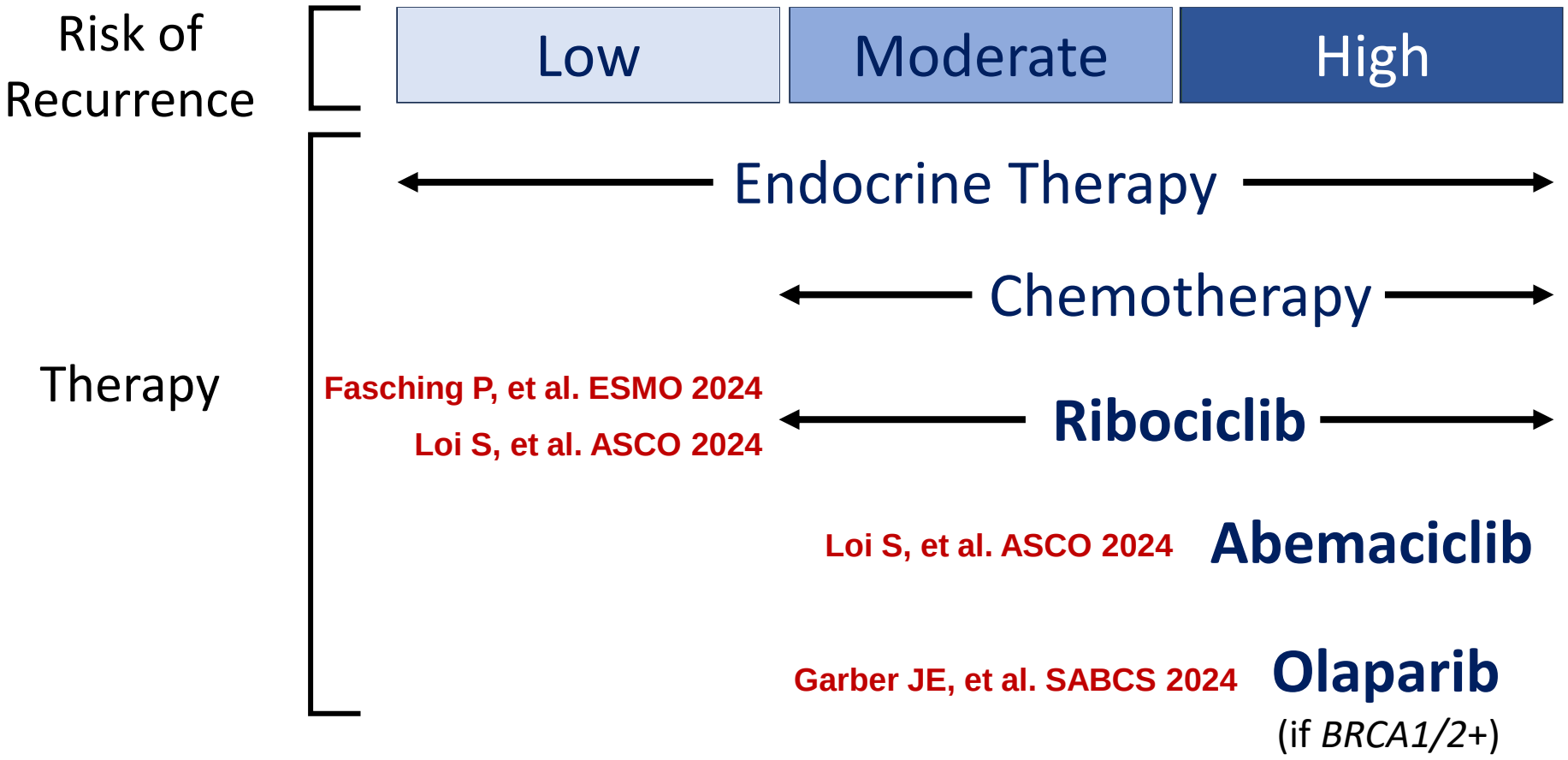
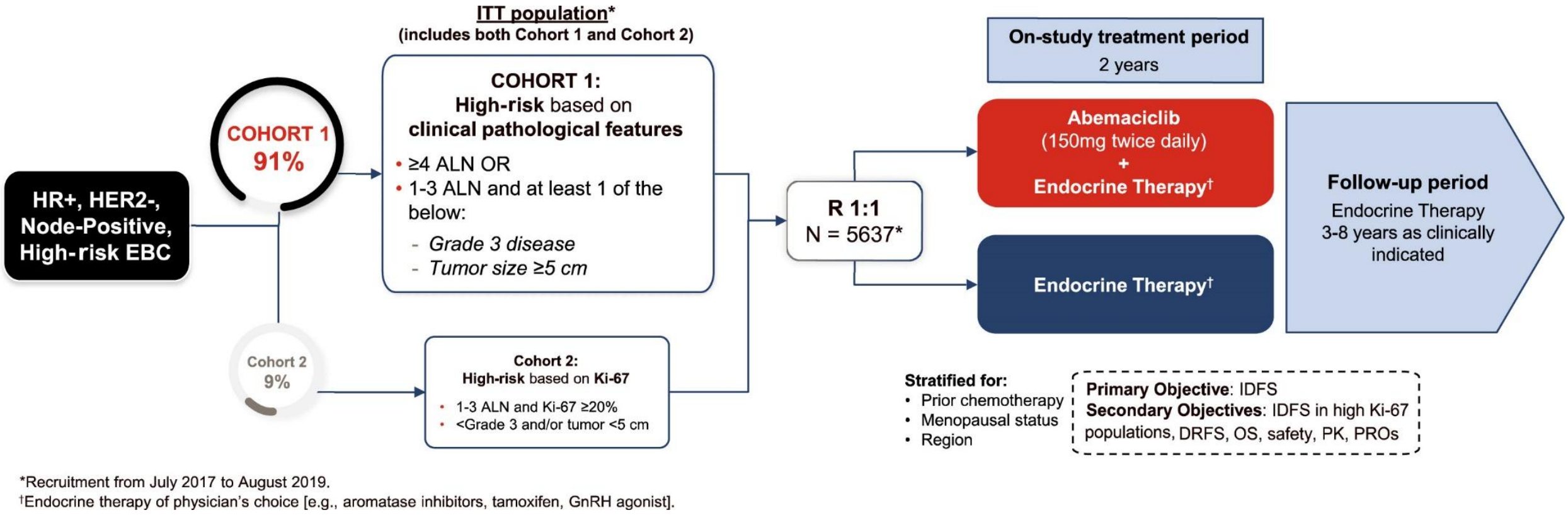
- **Travel, accommodation, expenses:** Roche, AstraZeneca, Lilly, GSK, Novartis, Celgene, Pfizer

Risk of Recurrence and Treatment Strategies for HR+/HER2- Early Breast Cancer Patients



monarchE: Adjuvant Abemaciclib for HR+/ HER2- High-Risk EBC

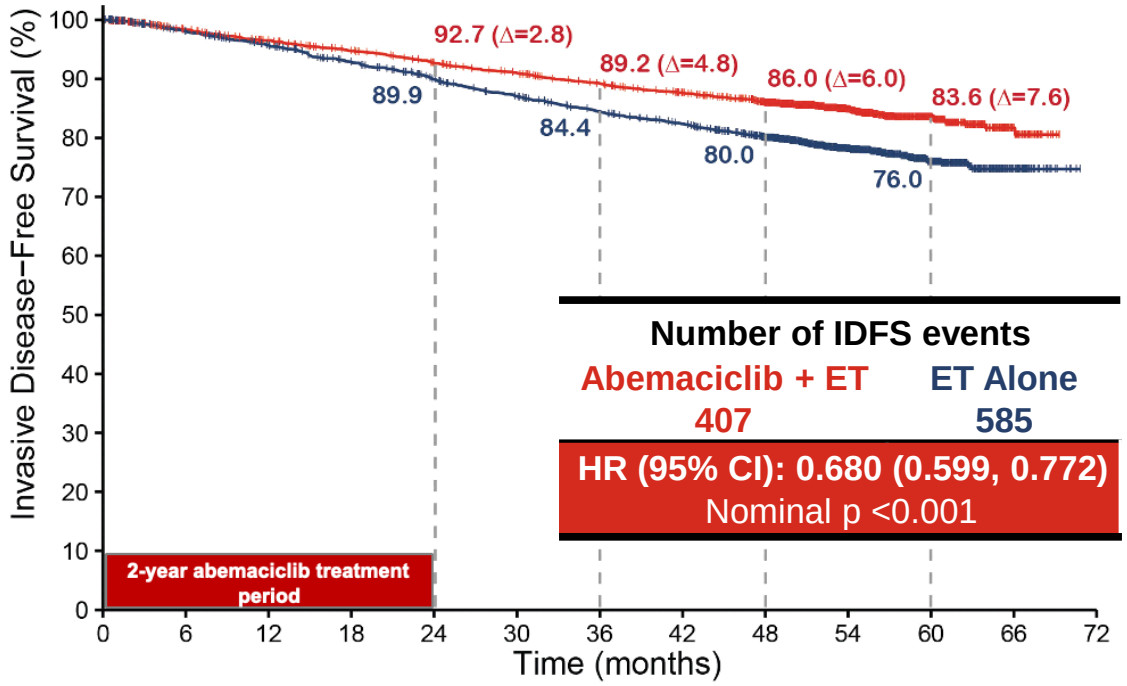


*Recruitment from July 2017 to August 2019.
†Endocrine therapy of physician's choice [e.g., aromatase inhibitors, tamoxifen, GnRH agonist].

44% premenopausal / 95% (neo)adjuvant CT / 60% ≥ 4+ LN / 44% Ki 67 ≥ 20%

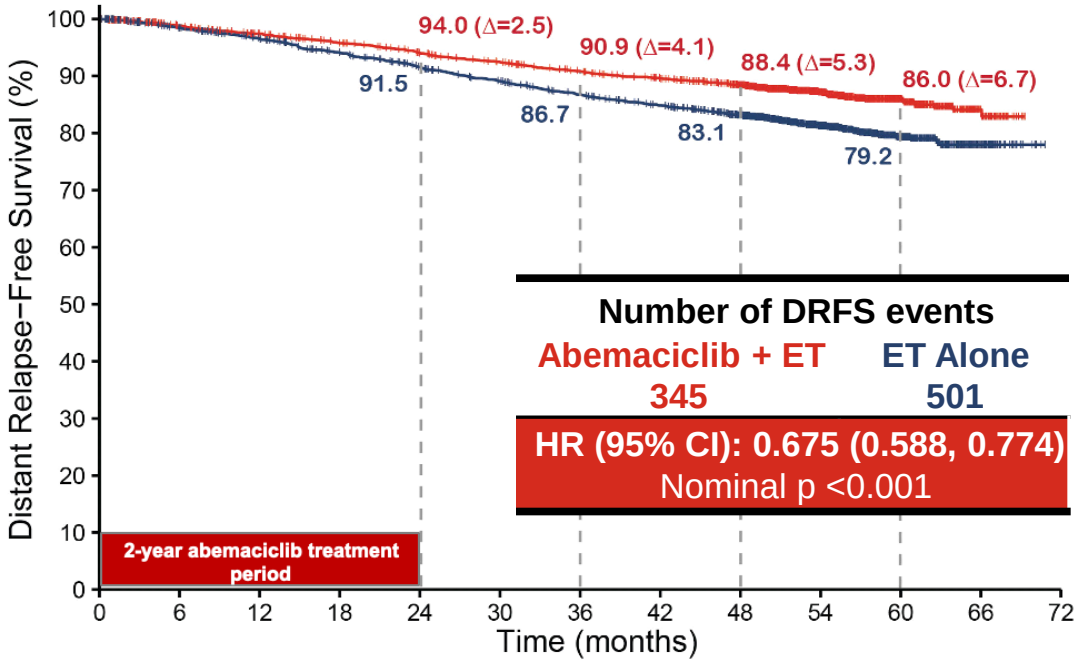
Harbeck N et al, ESMO 2023

monarch-E: Mature data on IDFS and DRFS benefit



Number at risk

Abemaciclib + ET	2808	2621	2549	2479	2408	2347	2284	2220	2095	1175	490	74	0
ET alone	2829	2653	2573	2474	2374	2281	2195	2125	1974	1124	473	67	0



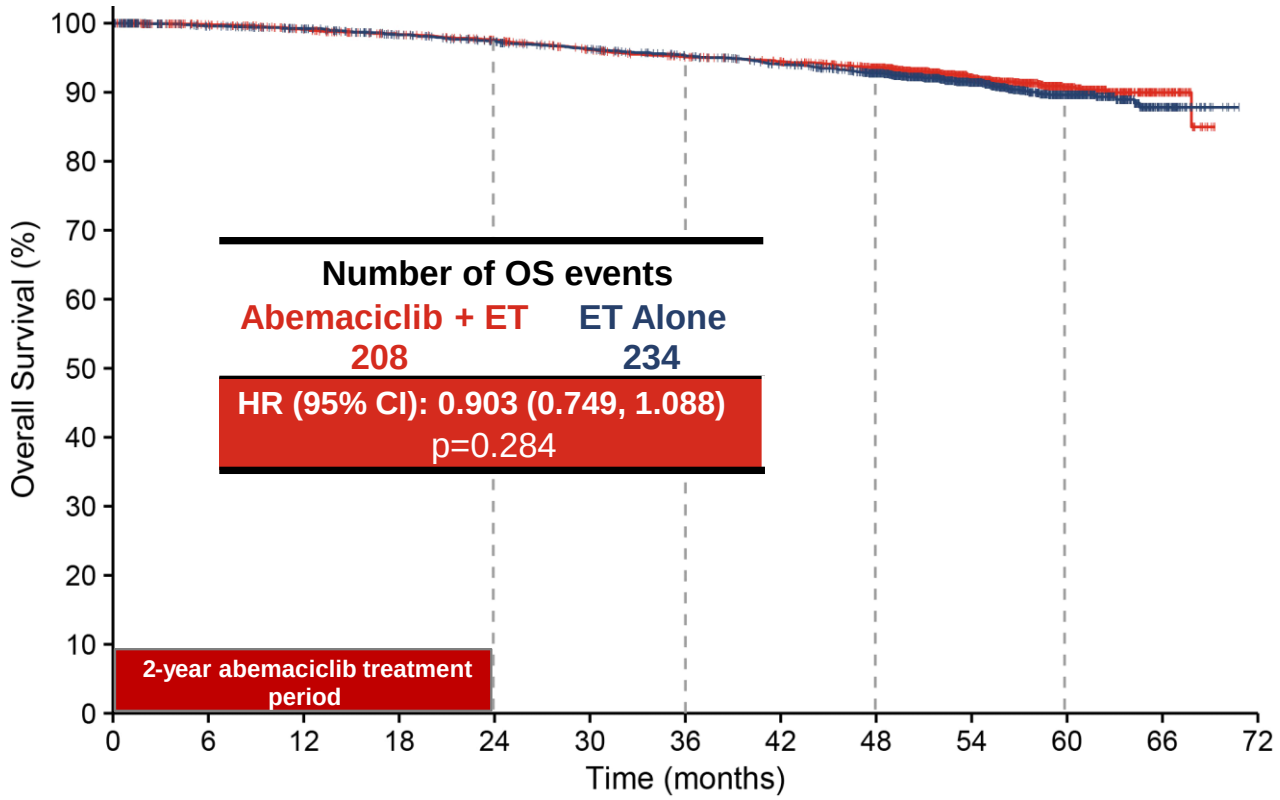
Number at risk

Abemaciclib + ET	2808	2630	2567	2500	2434	2375	2313	2258	2141	1202	500	75	0
ET alone	2829	2660	2590	2499	2410	2327	2243	2176	2032	1161	488	72	0

54 months median follow-up

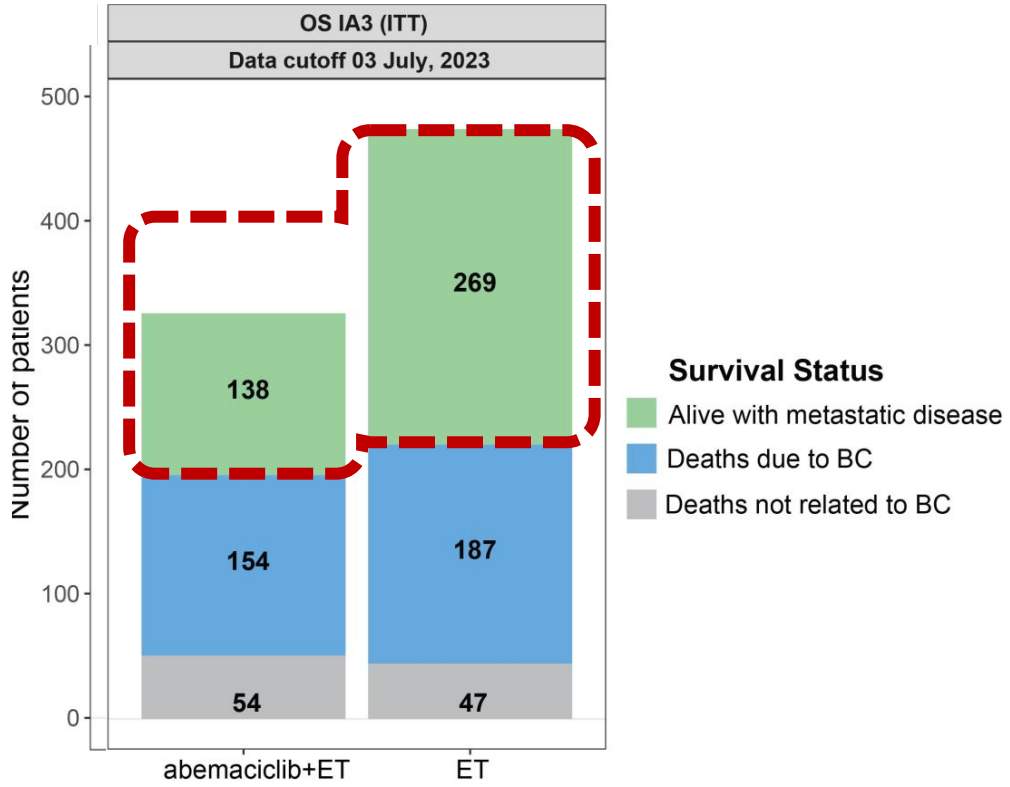
Harbeck N et al, ESMO 2023

monarch-E: Fewer deaths in the Abemaciclib Arm in ITT



Number at risk

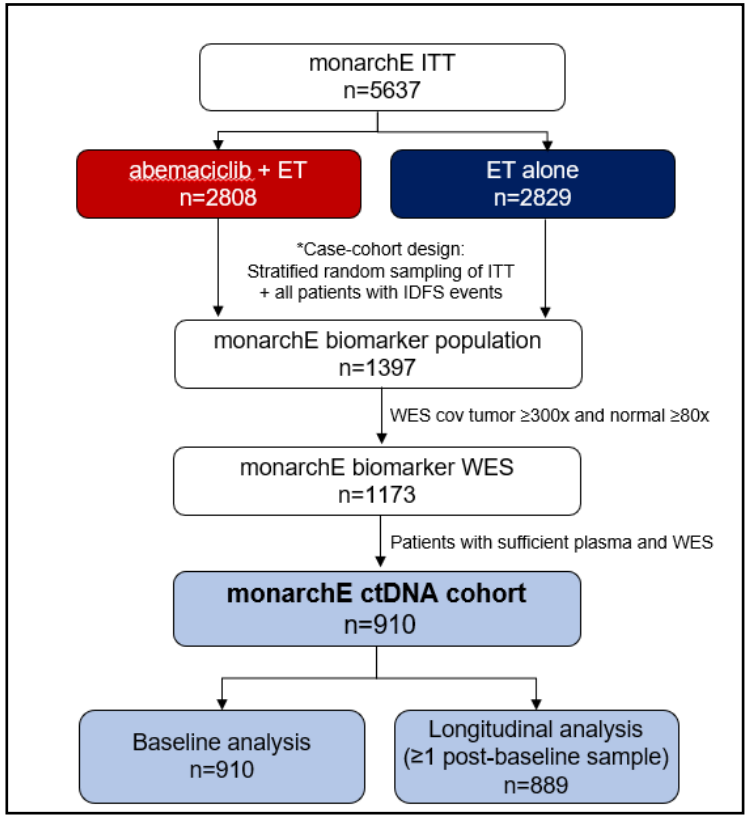
Abemaciclib + ET	2808	2666	2614	2566	2518	2455	2407	2373	2260	1271	528	80	0
ET alone	2829	2705	2664	2599	2545	2496	2440	2382	2243	1279	538	77	0



Harbeck N et al, ESMO 2023

Prognostic utility of ctDNA detection in the monarchE trial

Biomarker cohort (n=910)
enriched for IDFS events



Methods

- Serial Testing: **0**, **3**, **6**, **24** months
- ctDNA detection was performed in blood samples using the *personalized*, *tumor informed* **Signatera™** ctDNA assay (Natera, Inc) utilizing whole exome sequencing (WES) of the primary tumor to inform ctDNA assay development.
- Largest prospective evaluation of prognostic capacity of ctDNA

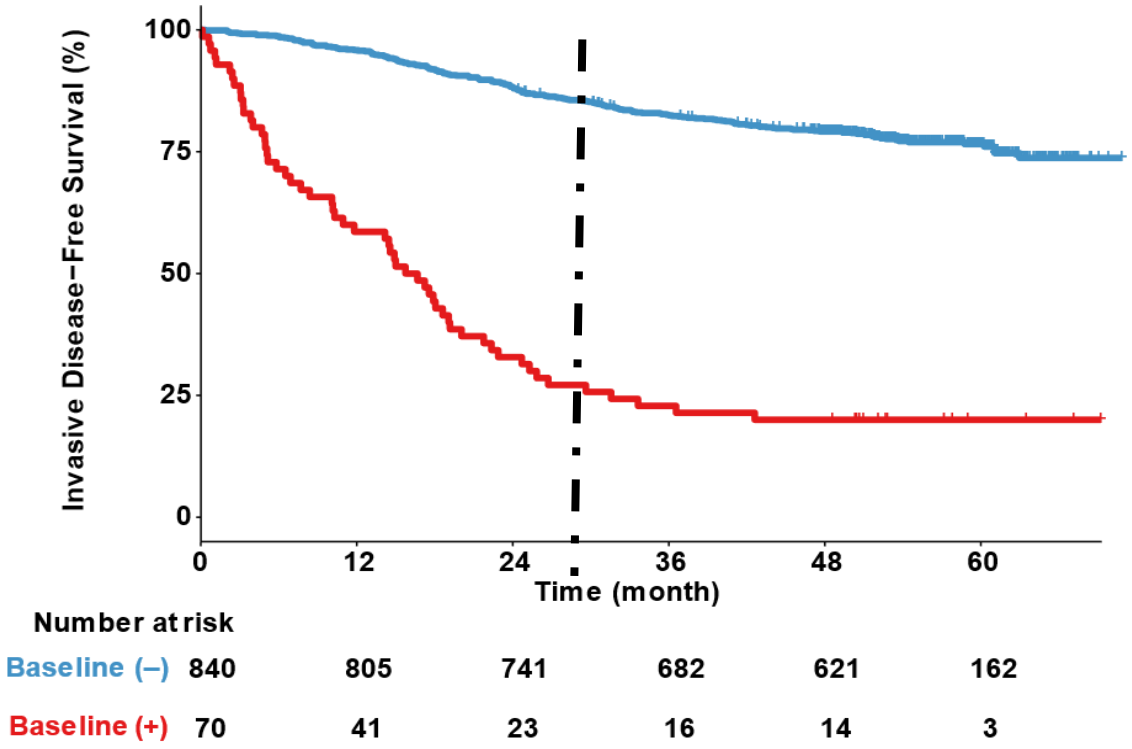
ctDNA detection

ctDNA cohort (N=910)	ctDNA detection, n (%)
Baseline Negative (–), undetected	840 (92)
Persistently –	749/831* (90)
Became +	82/831* (10)
Baseline Positive (+), detected	70 (8)
Persistently +	34/58** (59)
Became – (undetected)	24/58** (41)

Loi S, et al. ASCO 2024

Prognostic utility of ctDNA detection in the monarchE trial

Baseline ctDNA Detection is Associated with Worse Outcomes



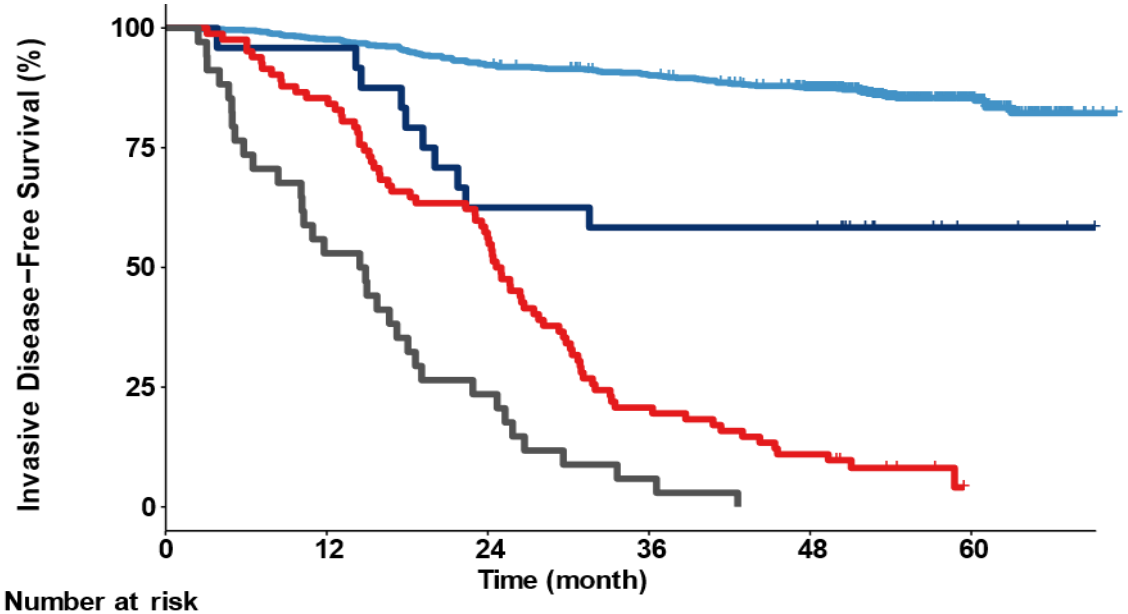
	Baseline Analysis* N=910	
	Baseline (–), undetected N=840	Baseline (+), detected N=70
IDFS event, n (%)	191 (23)	56 (80)
4-year IDFS rate, % (95% CI)	79.1 (76.4-82.0)	20.0 (12.5-32.0)
Log-rank test	Nominal p-value < 0.0001	

Patients who were ctDNA+ at baseline were more likely to experience an IDFS event compared to those who were ctDNA– at baseline (80% vs 23%, respectively)

Loi S, et al. ASCO 2024

Prognostic utility of ctDNA detection in the monarchE trial

Dynamics of ctDNA Detection on Treatment is Associated with Outcomes



Number at risk						
Persistently –	749	731	691	664	611	162
Became –	24	23	15	14	14	3
Became +	82	70	46	17	9	0
Persistently +	34	18	8	2	0	0

	Longitudinal Analysis (N=889)*			
	Baseline (–), undetected N=831		Baseline (+), detected N=58	
	Persistently –	Became +	Persistently +	Became – (undetected)
N	749 (90)	82 (10)	34 (60)	24 (40)
IDFS event, n (%)	107 (14)	76 (93)	34 (100)	10 (42)
4-year IDFS rate, % (95% CI)	87.5 (85.1-89.9)	11.0 (5.9-20.3)	NA	58.3 (41.6-81.8)

Patients who remained Persistently + or Became + on treatment were more likely to experience an IDFS event compared to those who Became – (undetected) or remained Persistently – on treatment

Loi S, et al. ASCO 2024

Prognostic utility of ctDNA detection in the monarchE trial

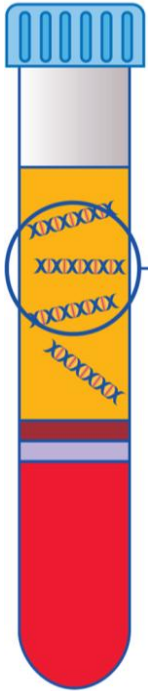
Median Lead Times from ctDNA Detection to IDFS Event

ctDNA subgroup	N	IDFS event (%)	Median time to IDFS event, months (range)
Baseline +	70*	56 (80)	12 (0-43)†
Persistently +	34/58**	34 (100)	15 (2-43)†
Became – (undetected)	24/58**	10 (42)	19 (4-32)†
Became + (Baseline –)	82	76 (93)	7 (0-48)‡

Overall, patients who were ctDNA+ had a relatively short lead time from ctDNA detection to IDFS event, with shortest lead time observed in patients who Became + on treatment

Loi S, et al. ASCO 2024

Implication of early ctDNA detection



- Detection of ctDNA+ provides an opportunity to
  I. Identify **molecular relapse** prior clinical recurrence
  II. Allow **introduction of therapy** to delay or reverse recurrence
- While ctDNA is *prognostic*, is it also *predictive* of treatment response?
- Which is the optimal assay?
- Does the early detection of ctDNA translated to **cost-effective** modifiable early interventions?
- Otherwise, creating unnecessary **anxiety** (if positive) and **false reassurance** (if negative)

Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2− early breast cancer: primary results from the Phase III 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*
      - 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/day
3 weeks on/1 week 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

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

Primary End Point
- iDFS using STEEP criteria

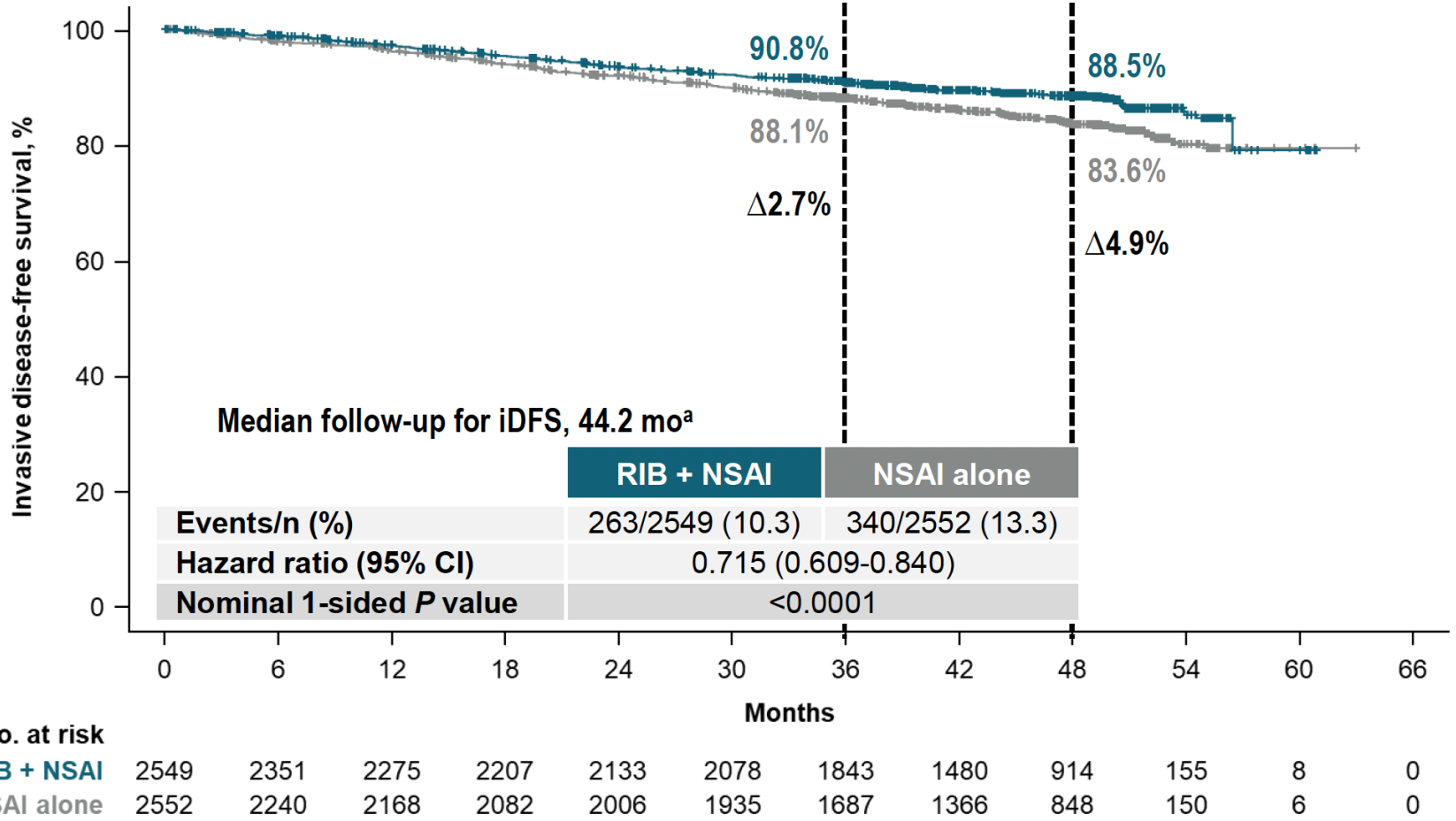
Secondary End Points
- Recurrence-free survival
- Distant disease–free survival
- OS
- PROs
- Safety and tolerability
- PK

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

Slamon D, et al ASCO 2023

NATALEE: iDFS in ITT population

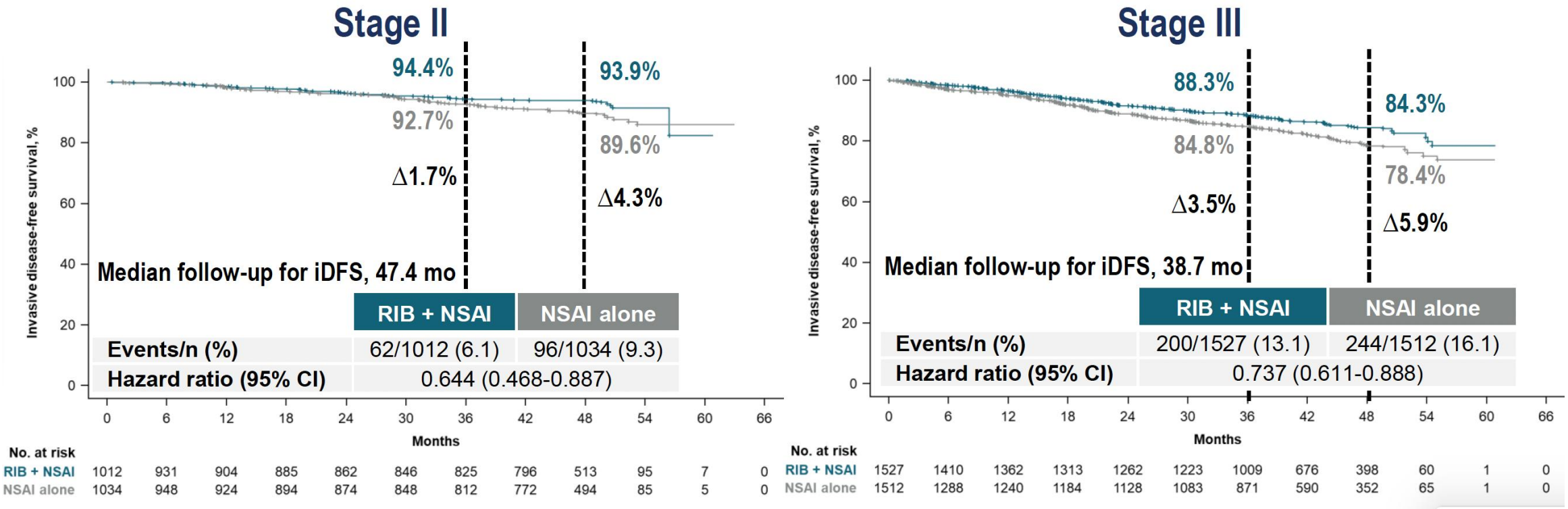
Significant iDFS benefit with RIB + NSAI after the planned 3-year treatment



Fasching P et al, ESMO 2024

NATALEE: iDFS by Stage

RIB + NSAI demonstrated an increasing magnitude of iDFS benefit over time for stage II/III disease

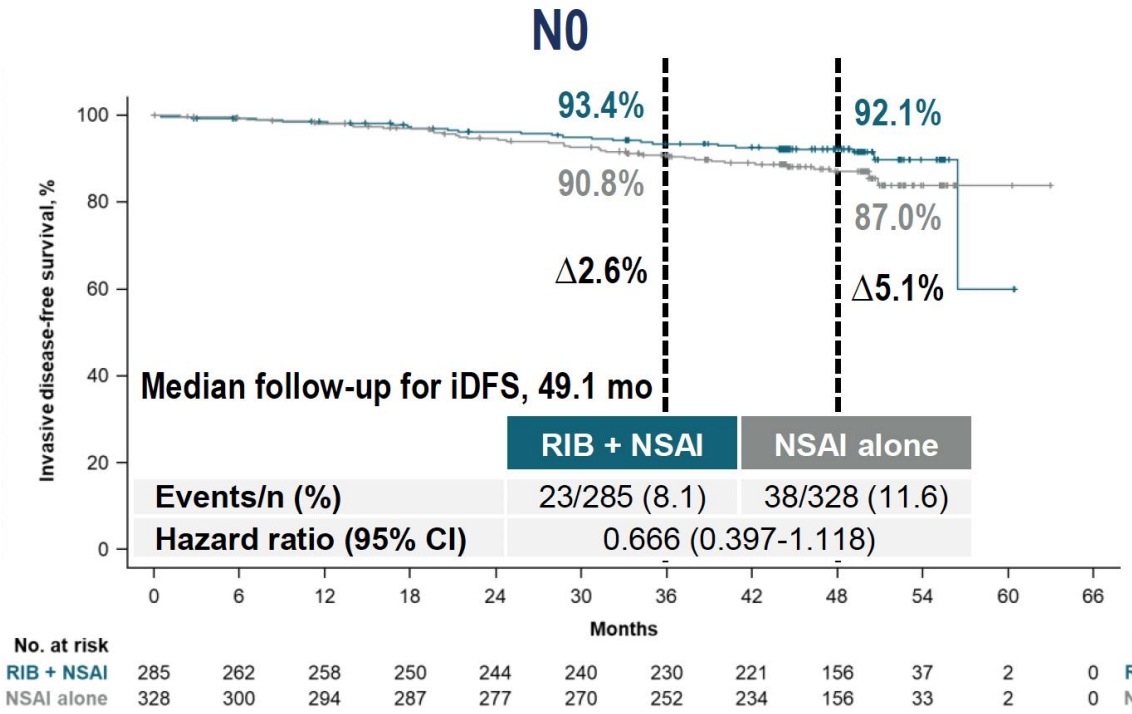


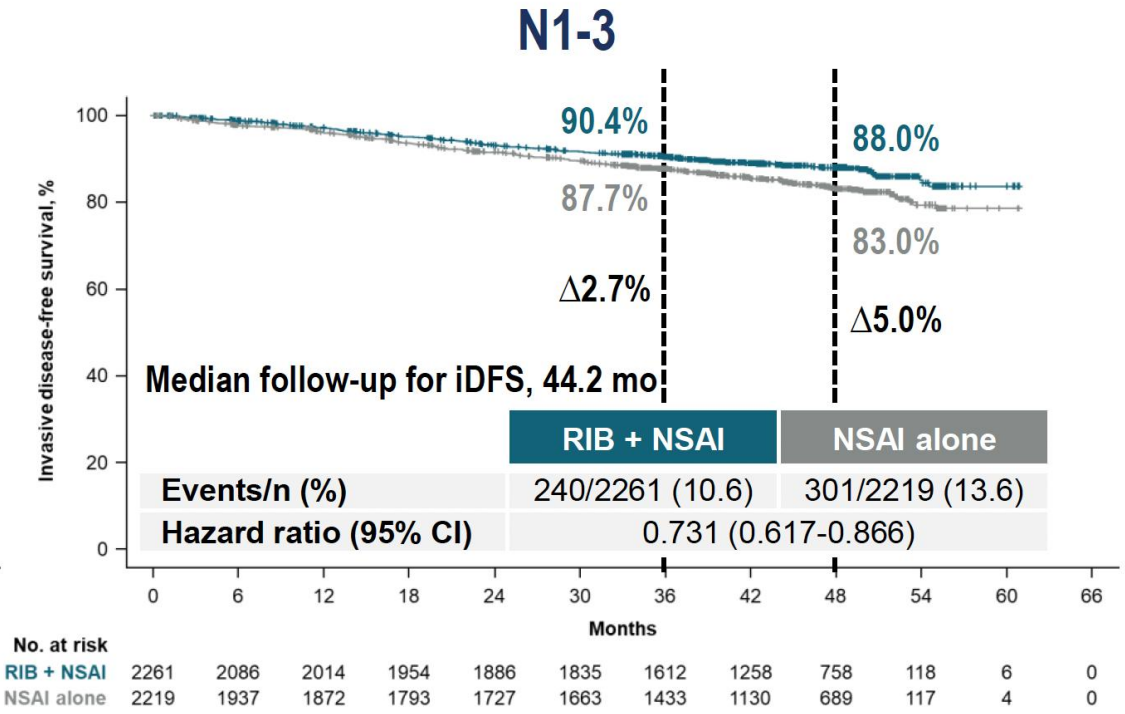
- **60% of patients**

Fasching P et al, ESMO 2024

NATALEE: by Nodal Status

RIB + NSAI showed an increasing magnitude of iDFS benefit over time for patients with N0 or N1-3 disease



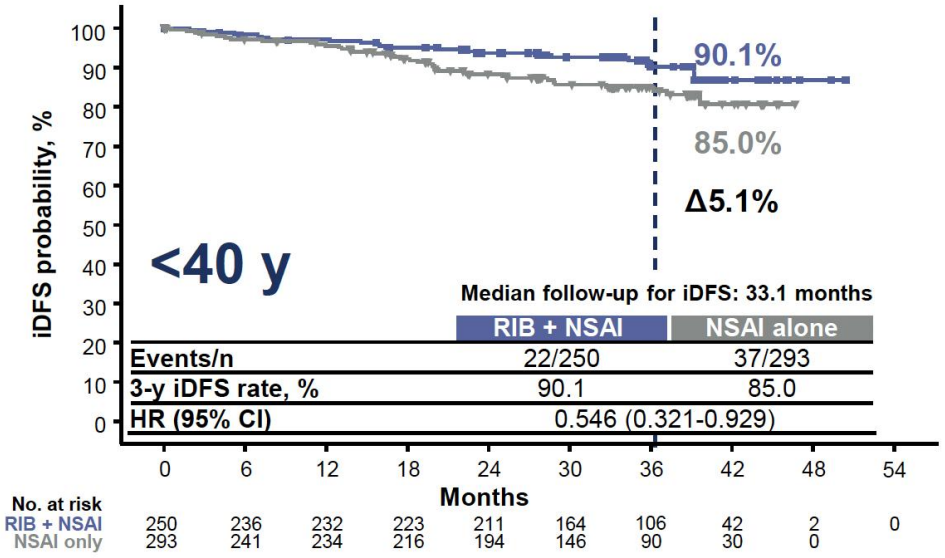


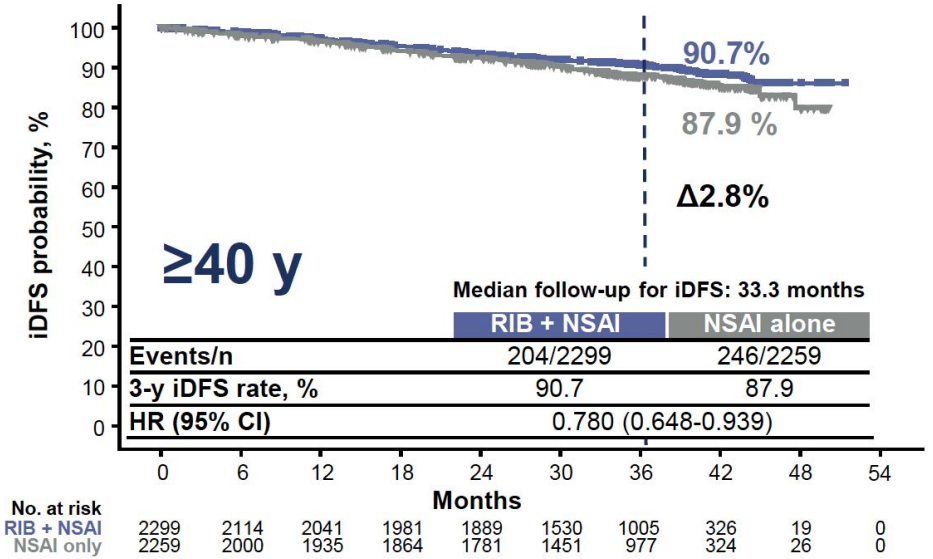
- **28%** of patients, **T2** = 75%, mostly **G2-3**
- **60% of patients (41% N1, 19% N2/3)**

Fasching P et al, ESMO 2024

NATALEE: Age group analysis

RIB + NSAI showed iDFS benefit in patients aged <40 and ≥40 years





- iDFS benefit of RIB + NSAI was observed regardless of menopausal status[a]
  - <40 y: premenopausal (n=513)—HR, 0.592 (95% CI, 0.345-1.015); postmenopausal (n=30)—not estimable due to small sample size
  - ≥40 y: premenopausal (n=1744)—HR, 0.730 (95% CI, 0.522-1.019); postmenopausal (n=2814)—HR, 0.812 (95% CI, 0.649-1.016)
- The absolute differences in 3-y iDFS rates between the RIB + NSAI and NSAI-only arms, when adjusted for menopausal status and prior neoadjuvant CT, were similar to those without adjustment (Δ4.0% for pts <40 y and Δ2.9% for pts ≥40 y)

Loi S et al, ESMO 2024

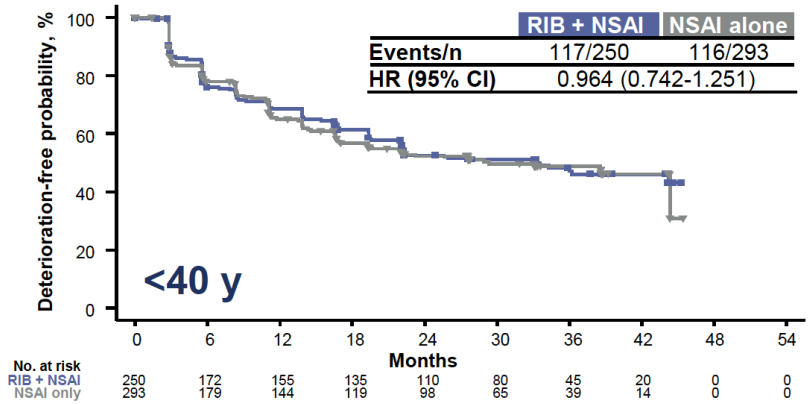
NATALEE: Age group analysis

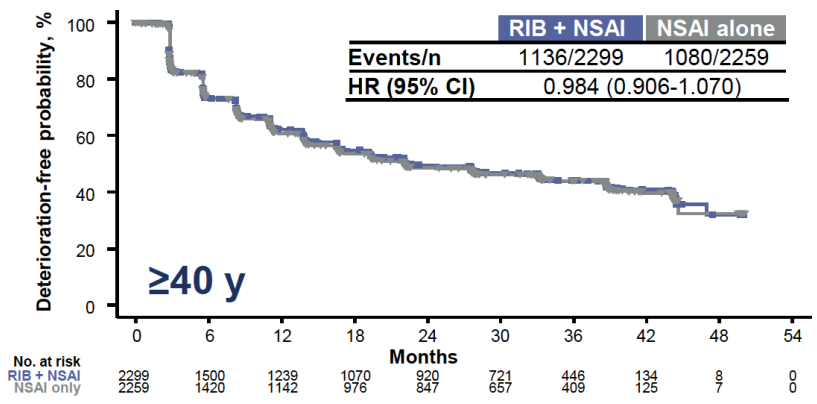
Patients aged <40 and ≥40 years had similar safety profiles

QoL was similar between arms in patients aged <40 and ≥40 years

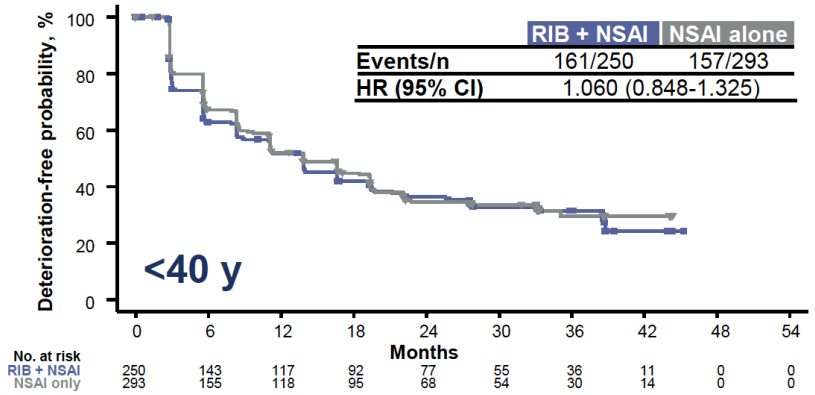
EORTC QLQ-C30 physical functioning and global health status were not altered by addition of RIB regardless of age

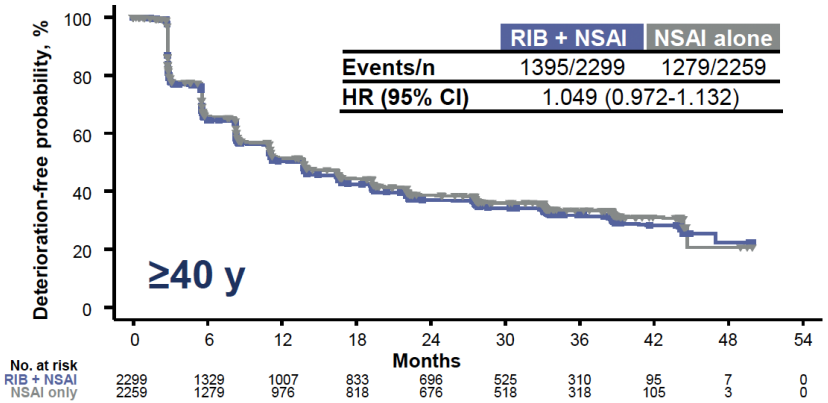
TTFD of physical functioning[a]





TTFD of global health status[b]



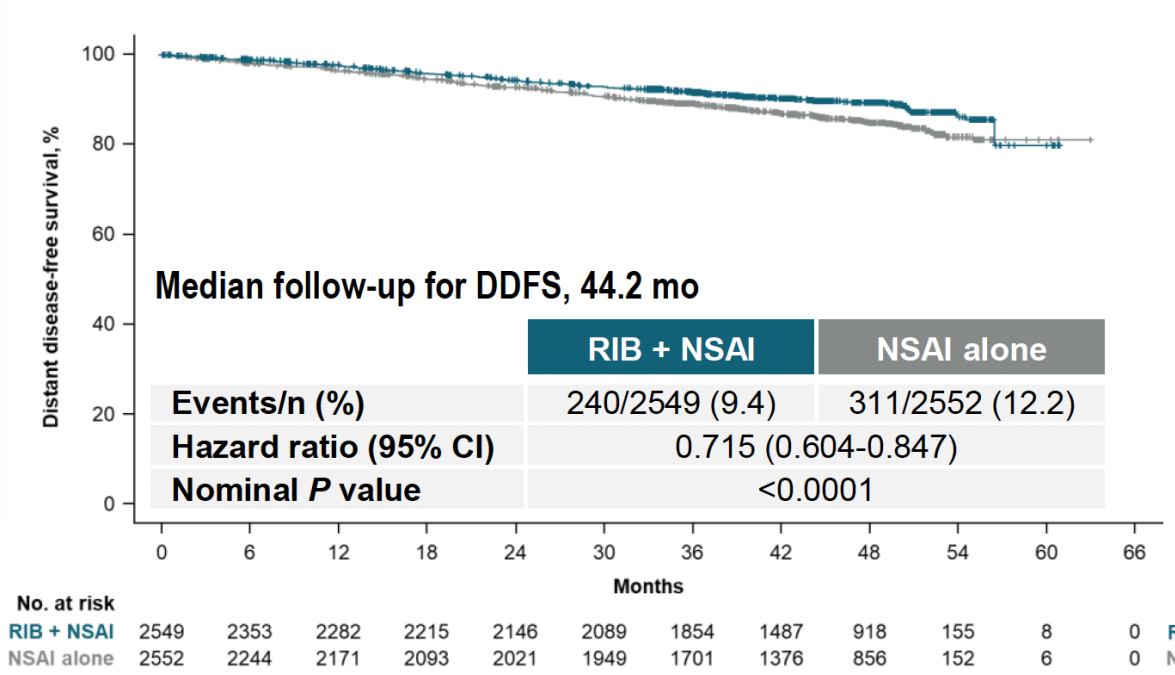


Loi S et al, ESMO 2024

NATALEE: Key Secondary Endpoints

RIB + NSAI continued to improve DDFS and showed a positive trend for OS

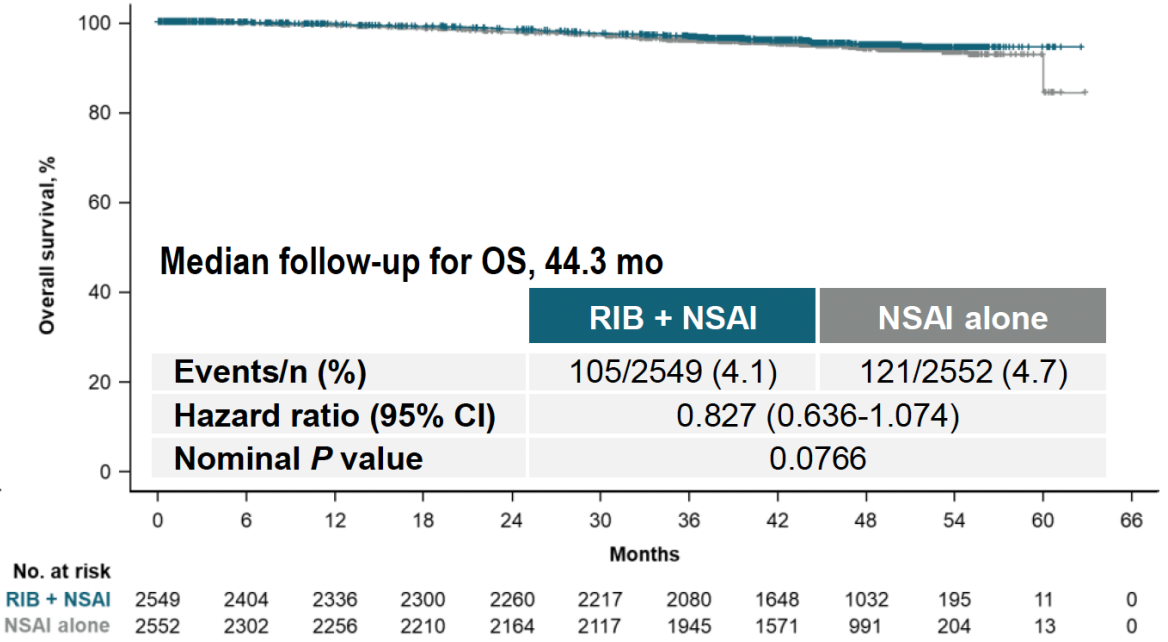
DDFS



Median follow-up for DDFS, 44.2 mo

	RIB + NSAI	NSAI alone
Events/n (%)	240/2549 (9.4)	311/2552 (12.2)
Hazard ratio (95% CI)	0.715 (0.604-0.847)	
Nominal *P* value	<0.0001	

OS



Median follow-up for OS, 44.3 mo

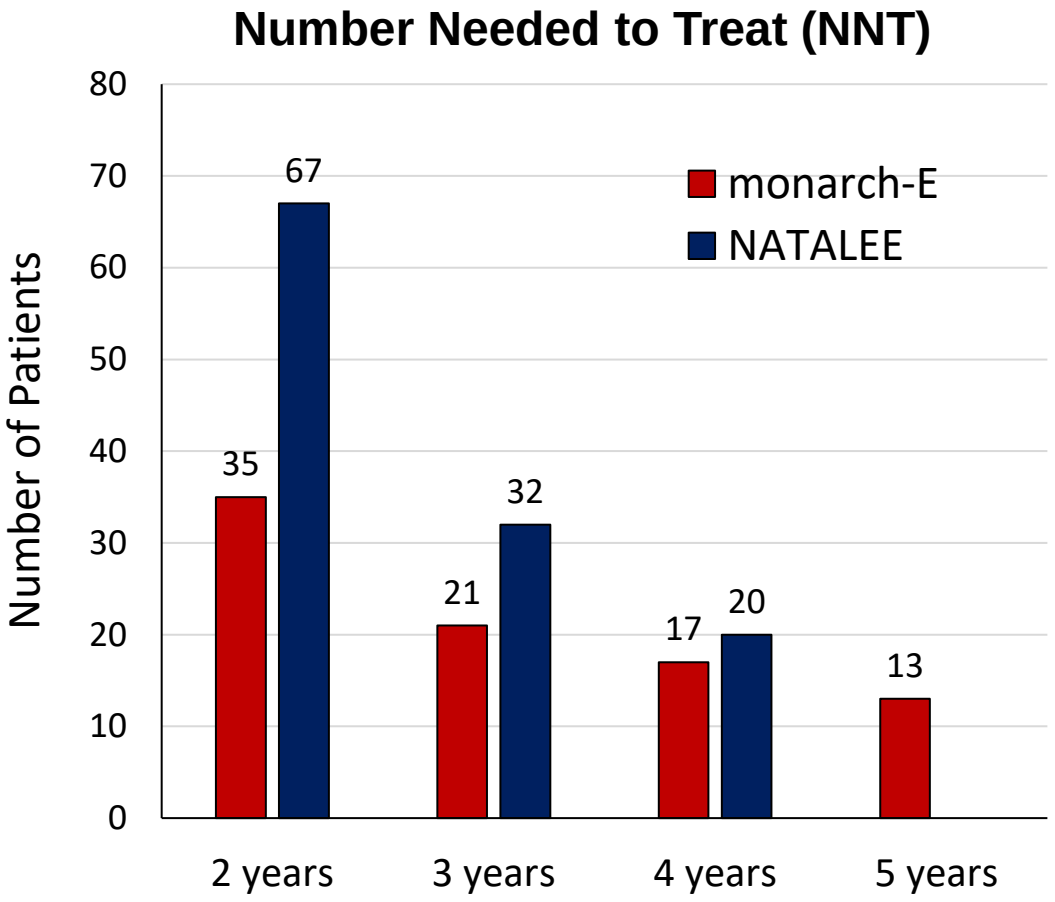
	RIB + NSAI	NSAI alone
Events/n (%)	105/2549 (4.1)	121/2552 (4.7)
Hazard ratio (95% CI)	0.827 (0.636-1.074)	
Nominal *P* value	0.0766	

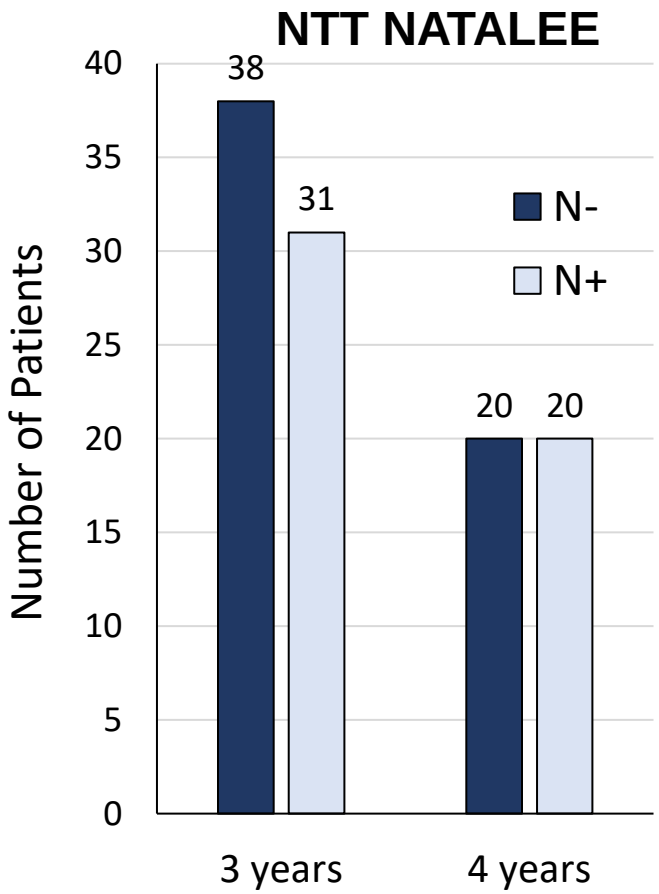
Fasching P et al, ESMO 2024

Adjuvant CDK4/6 Inhibitors for Early Breast Cancer:

Abemaciclib vs Ribociclib

Adjuvant CDK4/6 Inhibitors for Early Breast Cancer:

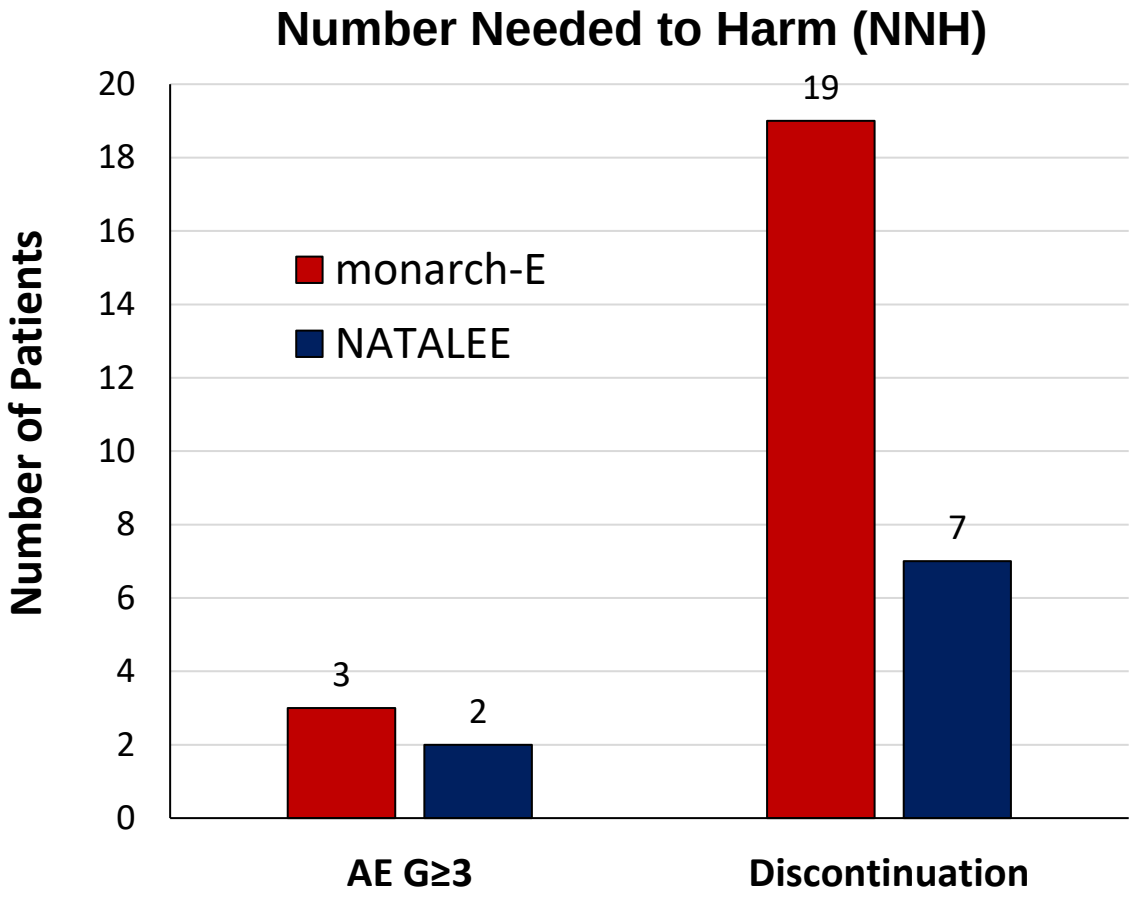




$$NNT = \frac{1}{Absolute\ Risk\ Reduction}$$

Thanks to **Roberto Buonaiuto**, *Manuscript in preparation*

Adjuvant CDK4/6 Inhibitors for Early Breast Cancer:



$$NNT = \frac{1}{Absolute\ Risk\ Increase}$$

monarch-E: Discontinuation rate due to AEs = **18.5%**

NATALEE: Discontinuation rate due to AEs = **20.0%**

Thanks to **Roberto Buonaiuto**, *Manuscript in preparation*

Adjuvant CDK4/6 Inhibitors for Early Breast Cancer:

Abemaciclib

Schedule
150 mg twice daily

Duration
2 years

Most frequent AEs	Any G	G ≥3
Diarrhea	75%	7%
Fatigue	38%	3%
Abdominal pain	34%	1%
Neutropenia	26%	11%
Leucopenia	26%	11%
VTEs	1.2%	1.1%

Ribociclib

Schedule
400 mg/day 3 weeks on/1 week off

Duration
3 years

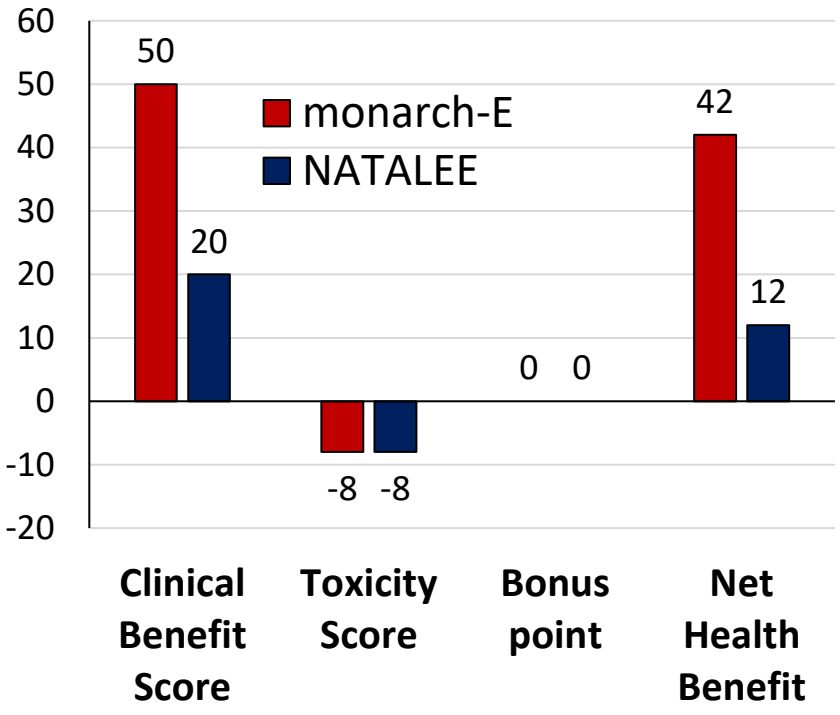
Most frequent AEs	Any G	G ≥3
Neutropenia	63%	44%
Arthralgia	39%	1%
Liver-related AEs	27%	9%
QT prolongation	5%	1%
ILD	1.6%	0%
VTEs	1.1%	0.6%

Harbeck N et al, ESMO 2023; Fasching P et al, ESMO 2024

Adjuvant CDK4/6 Inhibitors for Early Breast Cancer:

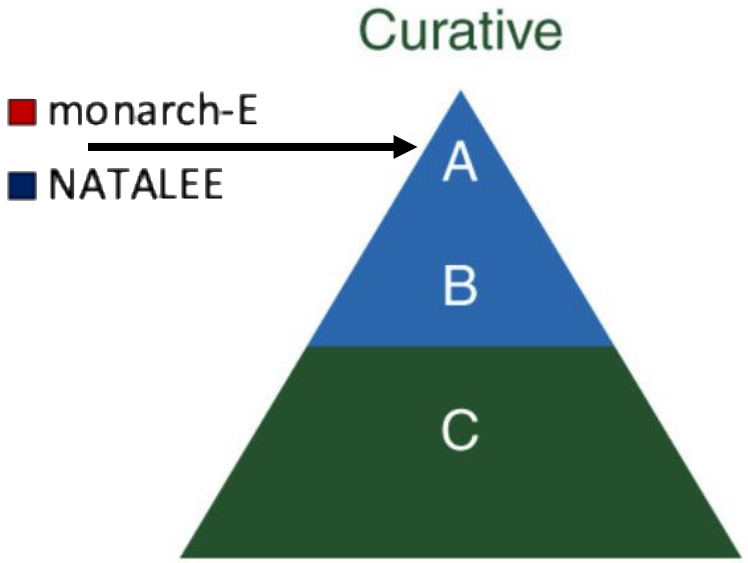
ASCO®

Value Framework Net Health Benefit
Adjuvant Setting



ESMO-MCBS

ESMO-Magnitude of Clinical Benefit Scale



Thanks to **Alessandra Longobardi**, *Manuscript in preparation*

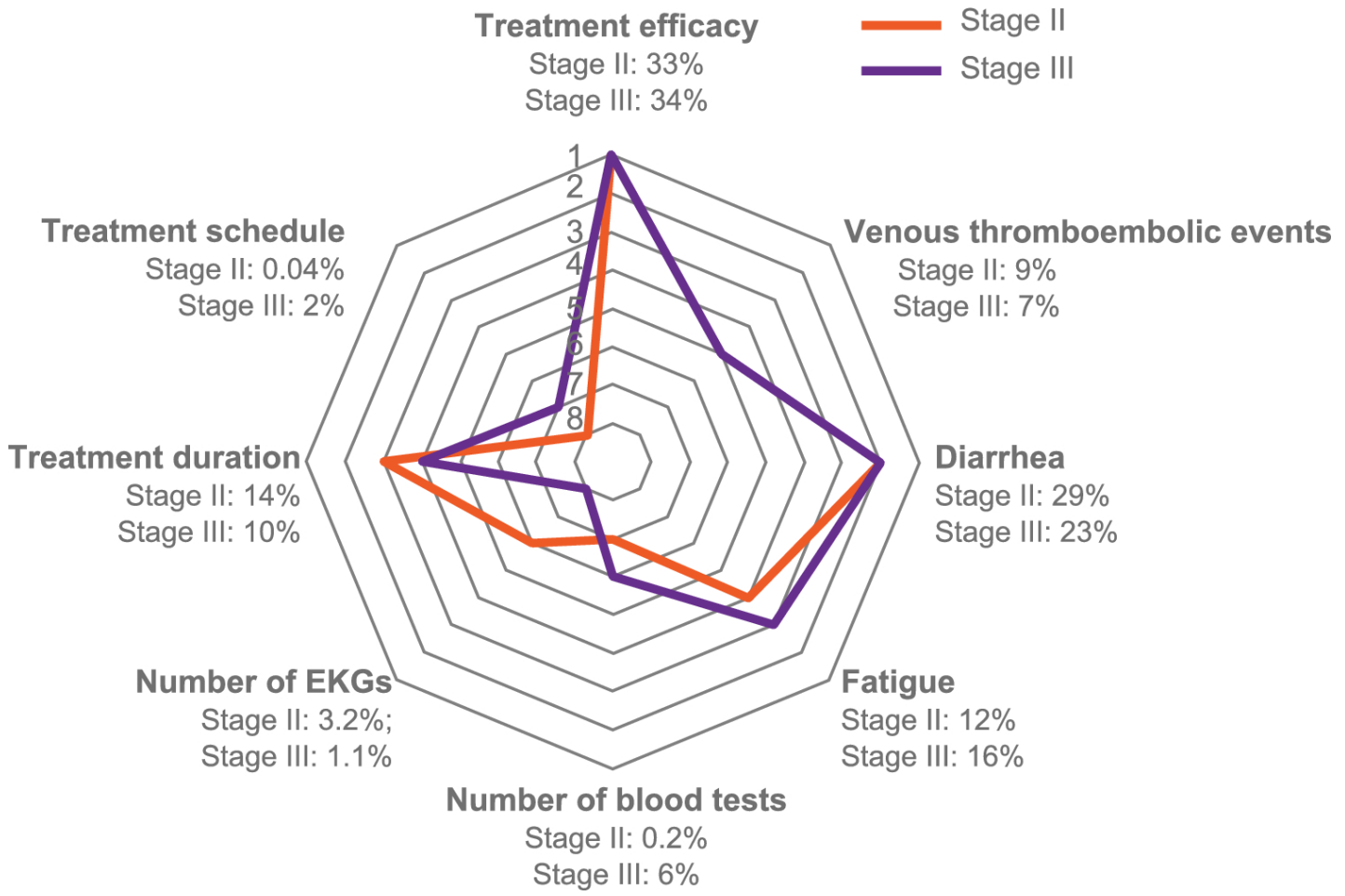
Patient preferences for CDK4/6 inhibitor treatments in HR+/HER2- early breast cancer: a discrete choice survey study

Methods:

- A web-based discrete choice experiment survey was conducted among US-based adult women with self-reported stage II/III HR+/HER2- EBC
- 409 women participated

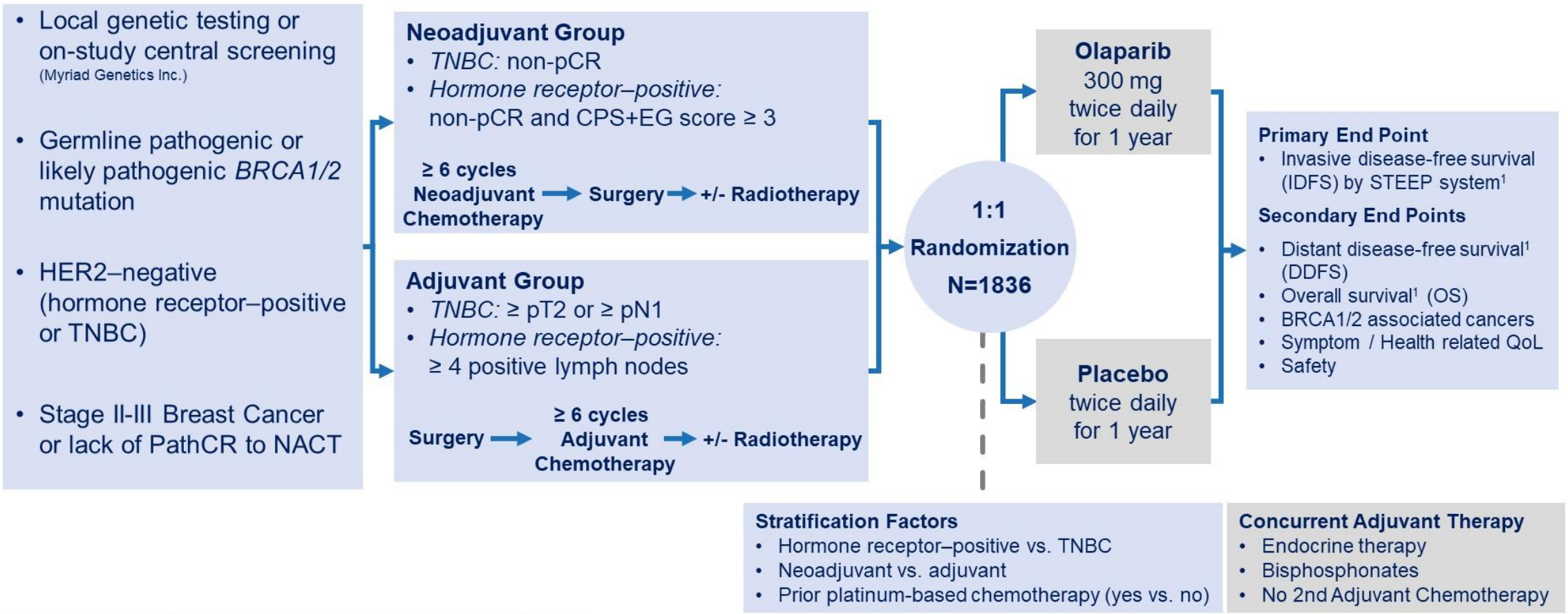
Results and Conclusions:

- Patients prefer adjuvant treatment with higher efficacy and lower risk of adverse events.
- Utility scores were higher for reconstructed treatment profiles that resembled **ribociclib**.



Erica L Mayer et al, BCRT 2025

OlympiA: Trial Schema



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

Tutt A et al, ASCO 2021, NEJM 2022

OlympiA: Patient characteristics

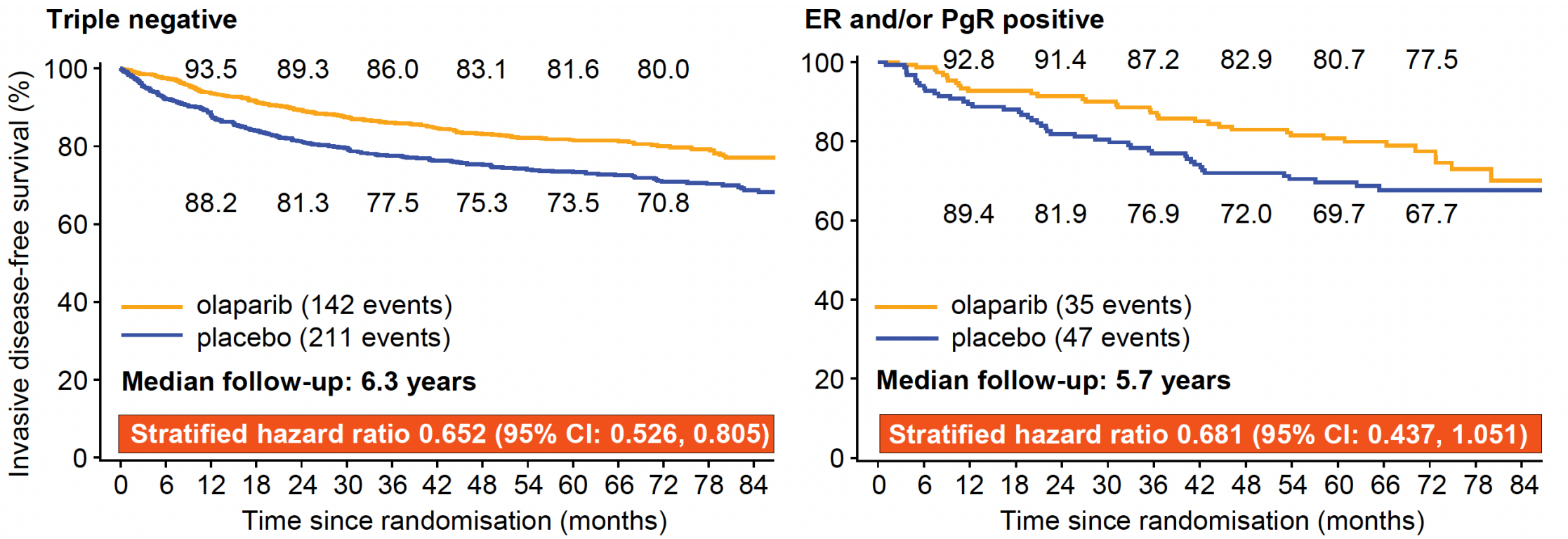
	Olaparib (N = 921)	Placebo (N = 915)
Hormone receptor status*		
Hormone receptor ≥ 1% / HER2-†	168 (**18.2%**)	157 (**17.2%**)
Triple Negative Breast Cancer‡	751 (**81.5%**)	758 (**82.8%**)
Menopausal status (female only)		
Premenopausal	572/919 (62.2%)	553/911 (60.7%)
Postmenopausal	347/919 (37.8%)	358/911 (39.3%)
Prior chemotherapy		
Adjuvant (ACT)	461 (**50.1%**)	455 (**49.7%**)
Neoadjuvant (NACT)	460 (**49.9%**)	460 (**50.3%**)
Anthracycline and taxane regimen	871 (**94.6%**)	849 (**92.8%**)
Neo(adjuvant) platinum-based therapy	247 (**26.8%**)	239 (**26.1%**)
Concurrent endocrine therapy (HR–positive only)	146/168 (86.9%)	142/157 (90.4%)

*Defined by local test results
†Following a protocol amended in 2015, the first patient with hormone receptor–positive disease was enrolled in December 2015
‡Two patients are excluded from the summary of the triple–negative breast cancer subset because they do not have confirmed HER2–negative status

Tutt A et al, ASCO 2021, NEJM 2022

OlympiA: Updated analysis of iDFS by HR status

median follow-up of 6.1 years



Number at risk

Olaparib	751	636	579	544	514	463	306	178	168	140	131	124	116	105	**53**	**15**
Placebo	758	632	565	519	489	430	282	162	157	134	118	109	99	82	**45**	**19**

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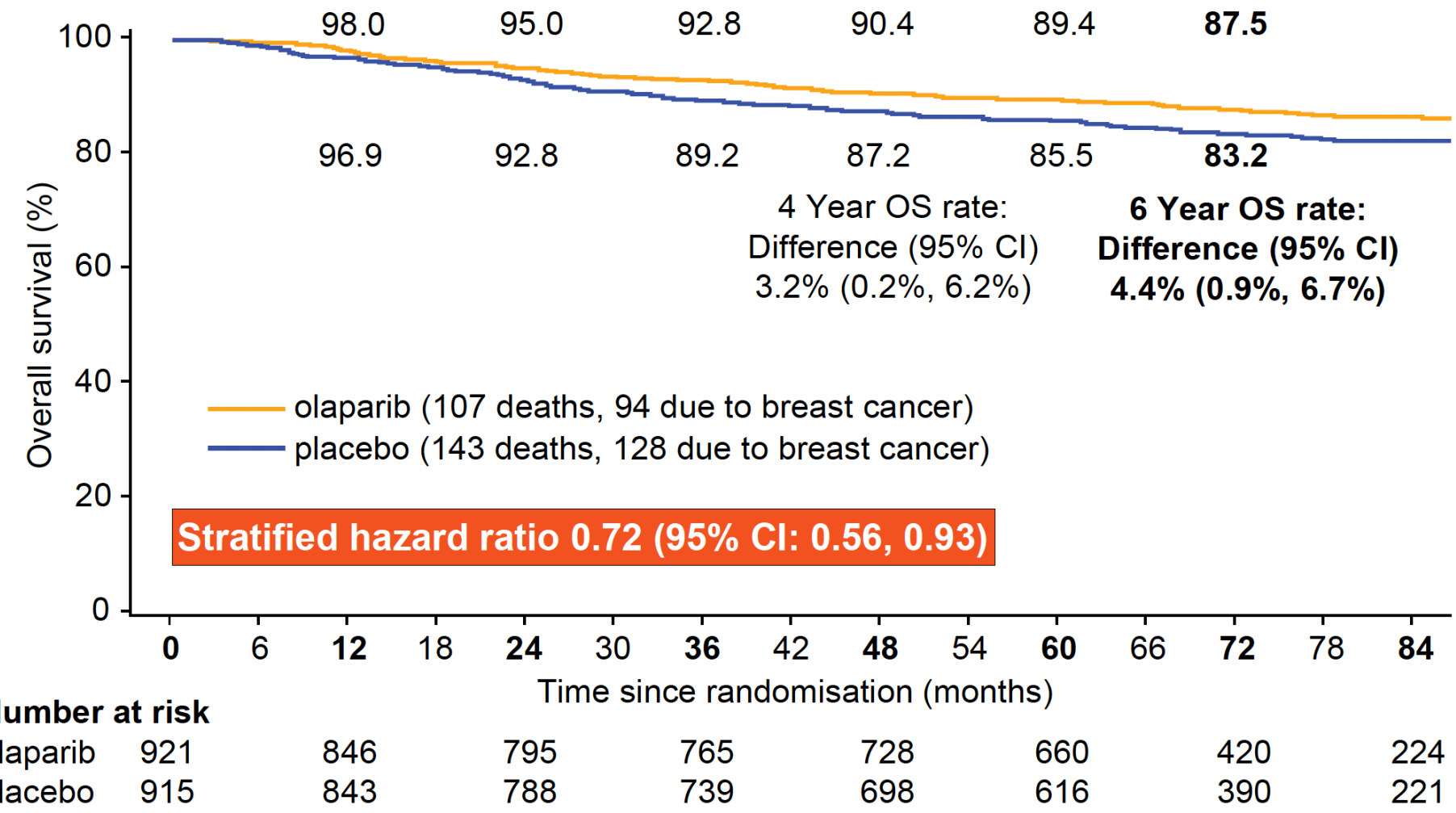
OlympiA: Updated analysis of OS (ITT)



Number at risk

olaparib	921	846	795	765	728	660	420	224
placebo	915	843	788	739	698	616	390	221

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Thanks for your attention

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