

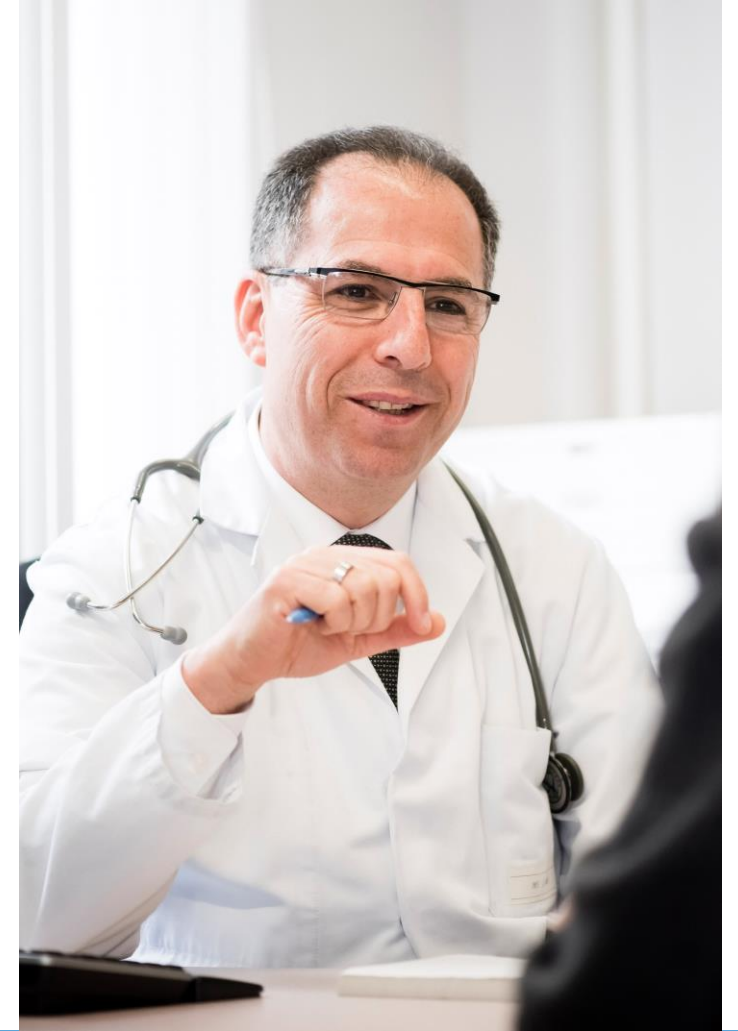
CDK4/6 inhibitoren in de praktijk

ONCOCLINICS 21.01.2025

DR. ANNELIES REQUILÉ



“De grootste revolutie
voor patiënten met
hormoongevoelige
borstkanker sinds de
uitvinding van
tamoxifen in 1973.”



Prof. Ahmad Awada, Chirec Cancer Institute

Tijdens Breast Cancer Debate of the year, 17.01.2025

Inhoud



Wat zijn CDK4/6 inhibitoren?



Welke CDK4/6 inhibitoren zijn er?



Waarvoor worden ze gebruikt?



Wat zijn de voornaamste
nevenwerkingen?

Inhoud



Wat zijn CDK4/6 inhibitoren?



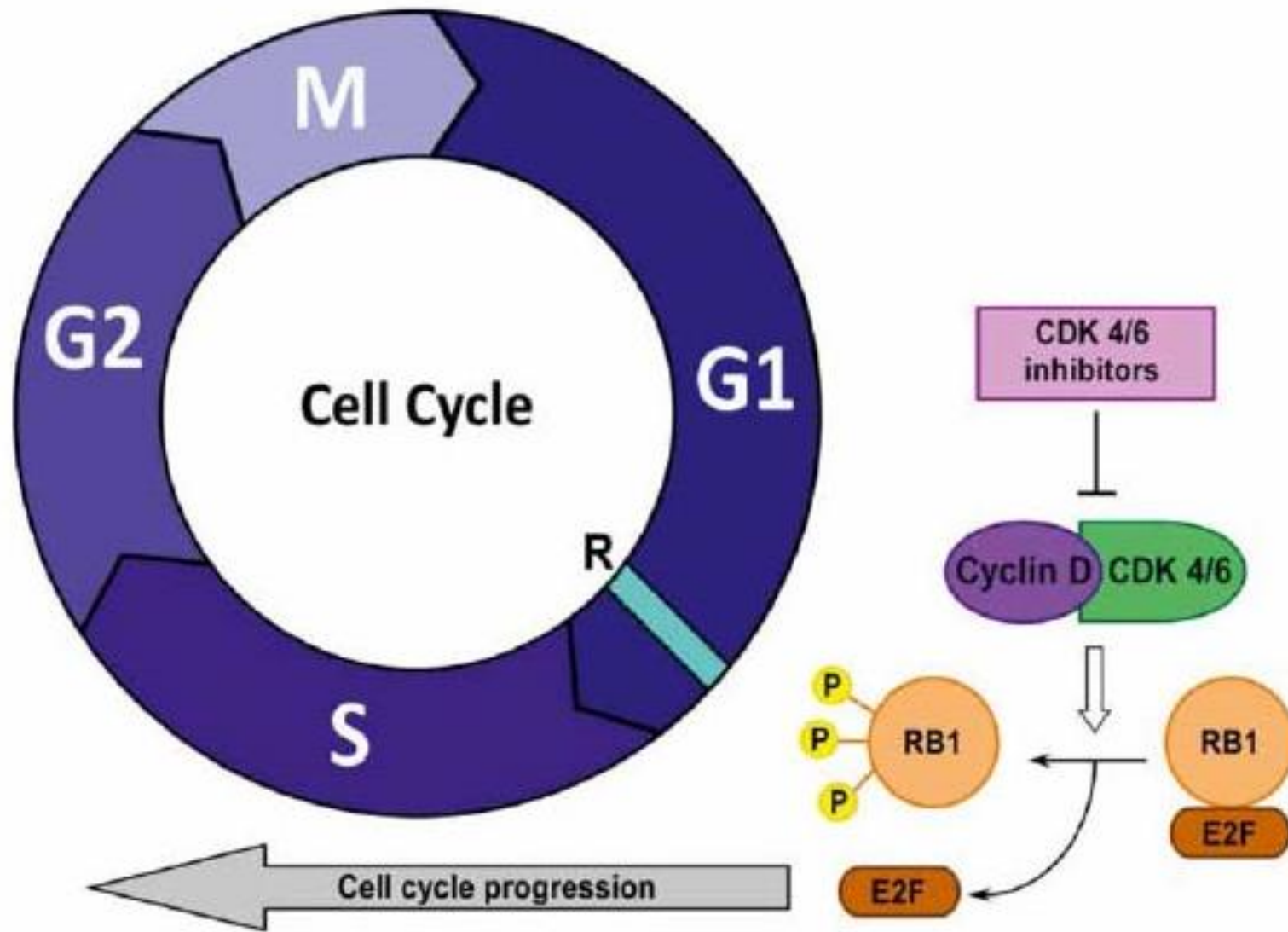
Welke CDK4/6 inhibitoren zijn er?



Waarvoor worden ze gebruikt?



Wat zijn de voornaamste
nevenwerkingen?



CDK:
Cycline D dependent Kinase

CDK4/6 Inhibitor=

“Celgroeiremmmer”

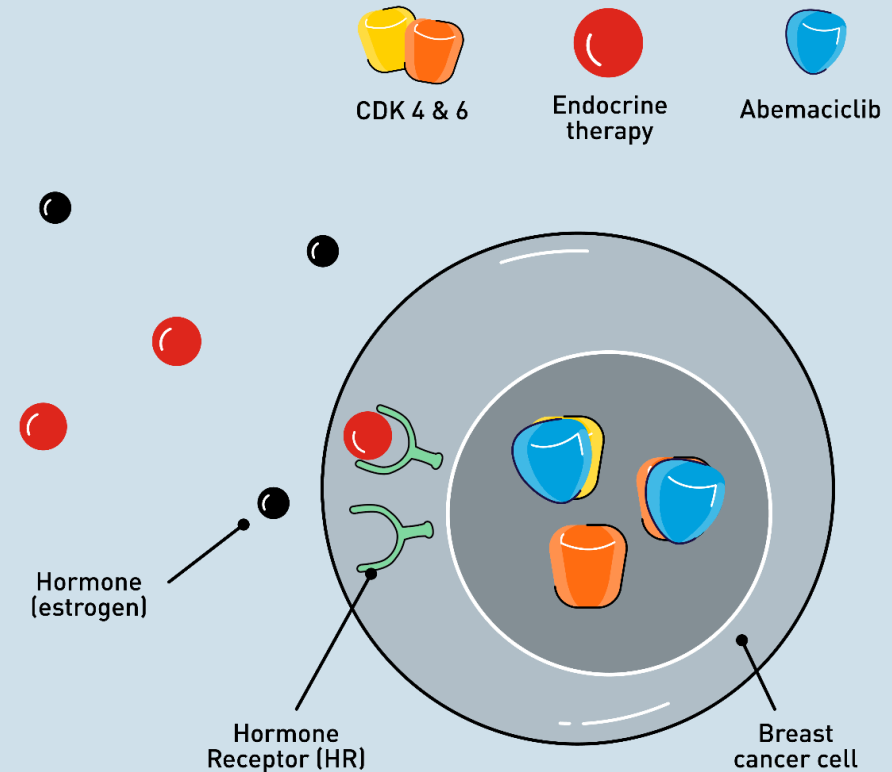
Abemaciclib: Mechanism of Action

Endocrine therapy (ET), or hormone therapy, is the standard treatment for patients with HR+, HER2- early breast cancer, and removes or blocks hormones to prevent cancer from returning

Adding abemaciclib to endocrine therapy can further reduce the risk of cancer recurrence in patients with high-risk HR+, HER2- early breast cancer

There are two proteins inside the cancer cells, cyclin-dependent kinase (CDK) 4 and 6, that help control how fast the cancer cells grow

Abemaciclib blocks the activity of these two proteins, which means it can help stop the growth of cancer cells



Inhoud



Wat zijn CDK4/6 inhibitoren?



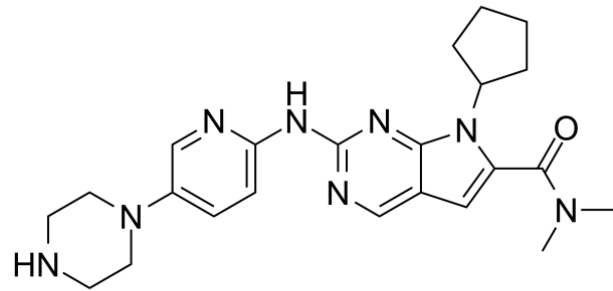
Welke CDK4/6 inhibitoren zijn er?



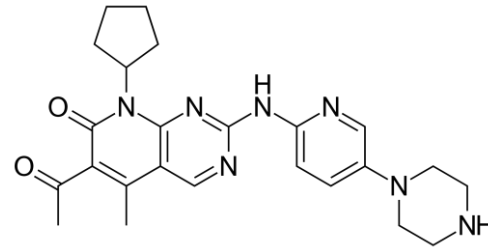
Waarvoor worden ze gebruikt?



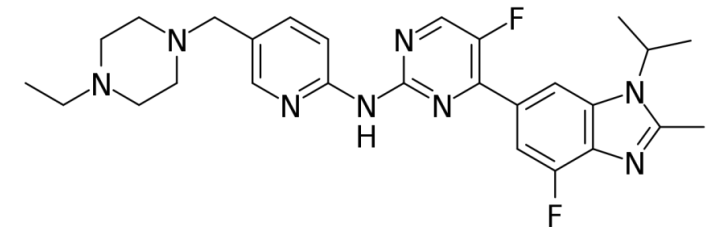
Wat zijn de voornaamste
nevenwerkingen?



Ribociclib

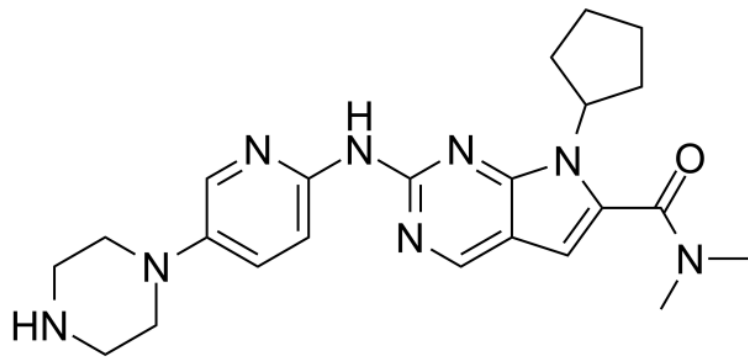


Palbociclib

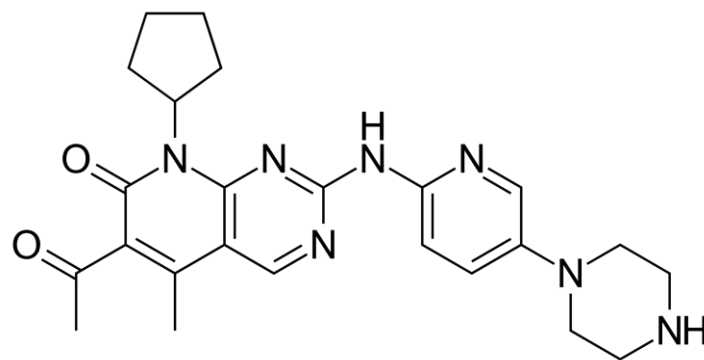


Abemaciclib

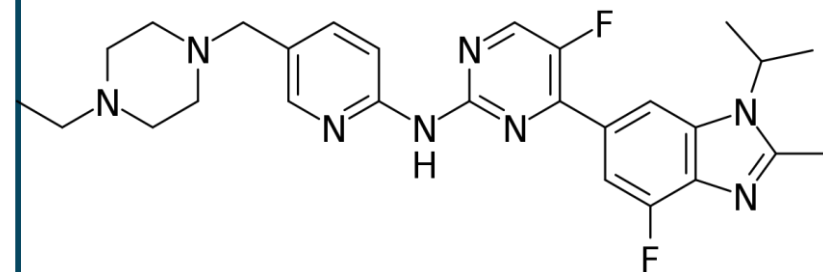
Zoek de 10 verschillen 🕒



Ribociclib

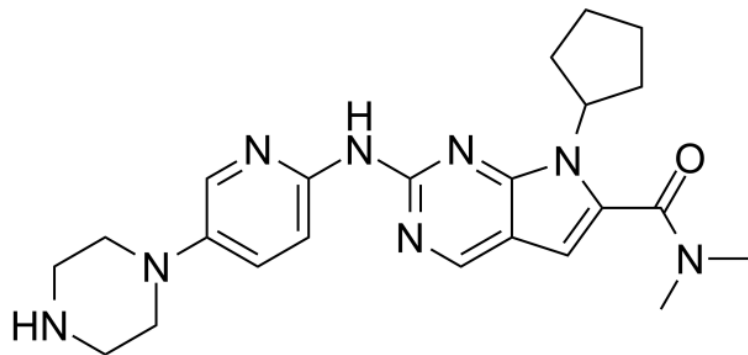


Palbociclib

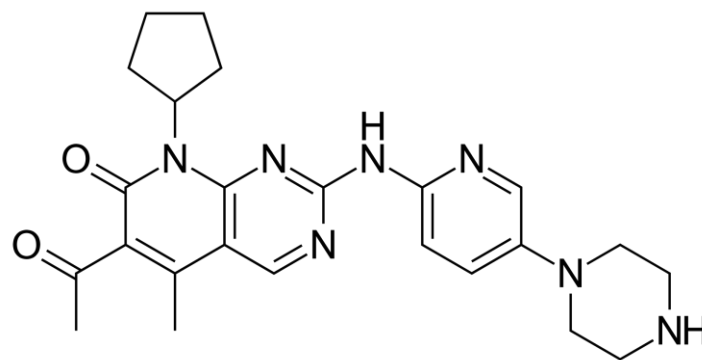


Abemaciclib

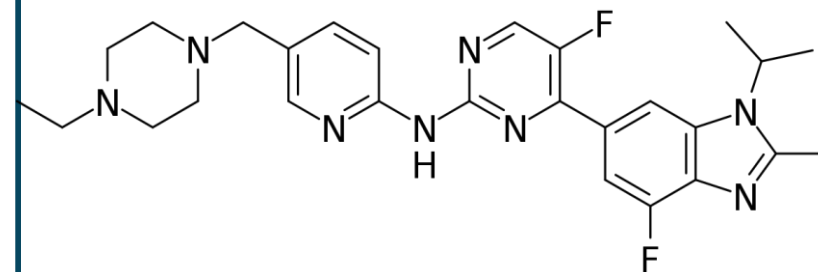
Zoek de 10 verschillen 🕒



Ribociclib



Palbociclib



Abemaciclib

Inname niet continu ▶▶

Inname continu ▶

Inhoud



Wat zijn CDK4/6 inhibitoren?



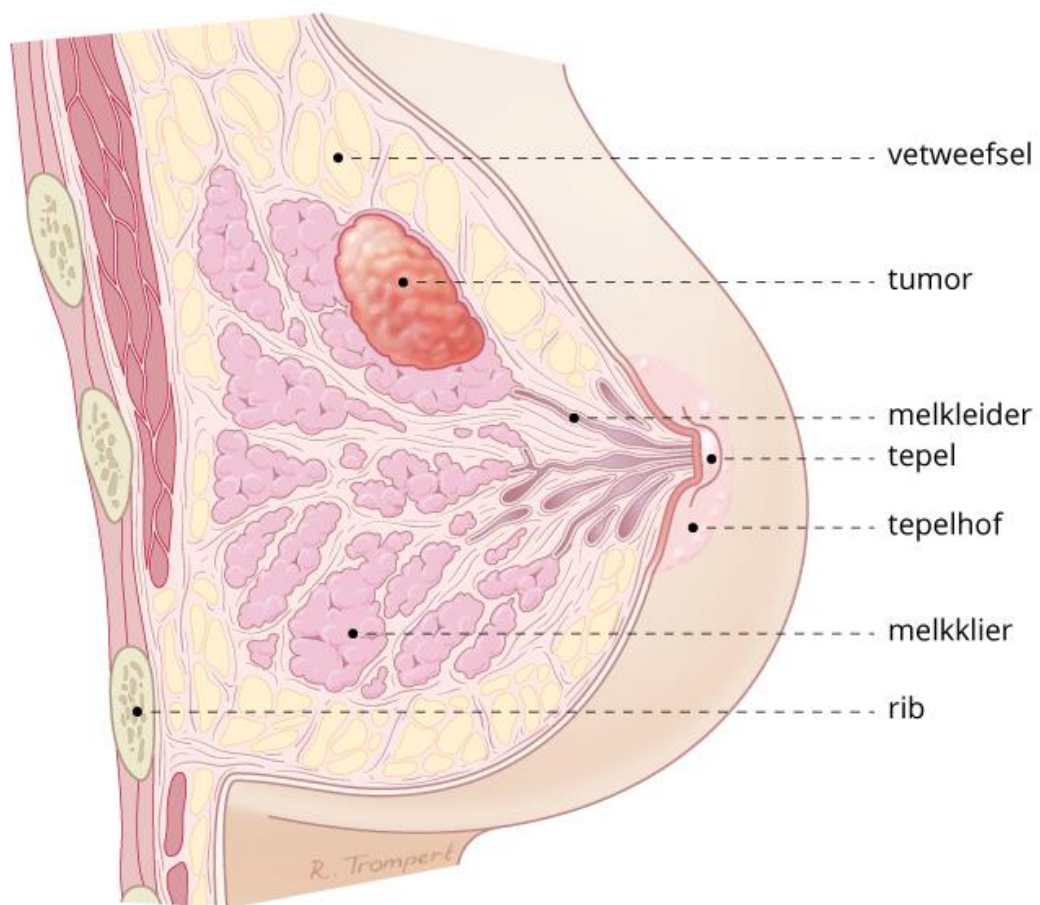
Welke CDK4/6 inhibitoren zijn er?



Waarvoor worden ze gebruikt?



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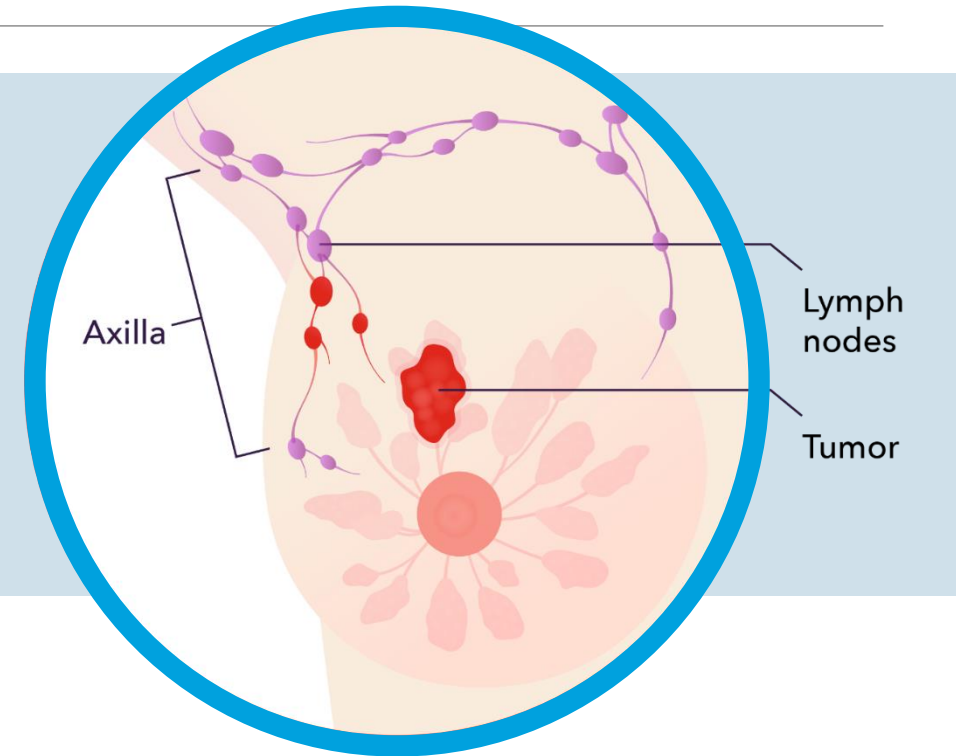


Borstkanker
- Gemetastaseerd
- Vroege setting
(high risk)

Defining Early Breast Cancer

- Early breast cancer has no spread detected beyond the breasts and lymph nodes in and around the breasts and has gone only as far as the lymph nodes in the armpit(s)¹
- Some patients with early breast cancer have cancer cells that are more aggressive and more likely to grow and spread quickly, which means there is a higher risk of the cancer recurring^{2,3}

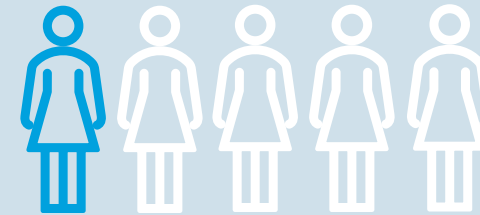
The cancer has not spread **beyond the breast and axillary lymph nodes.**



1. National Cancer Institute. Definition of early-stage breast cancer. Accessed October 2023. www.cancer.gov/publications/dictionaries/cancer-terms/def/early-stage-breast-cancer
2. National Cancer Institute. Definition of recurrent cancer. Accessed October 2023. <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/recurrent-cancer>
3. National Cancer Institute. Definition of aggressive. Accessed October 2023. <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/aggressive>

Defining Breast Cancer Recurrence

- Some cancer cells are more likely to grow and spread quickly, which means there is a higher risk of cancer recurrence and metastasis^{1,2}
- HR+, HER2- early breast cancer can be cured, but approximately 1 in 5 of patients will experience disease recurrence within the first 10 years³
- Taking early action with certain treatments can potentially improve a patient's chances of becoming cancer-free



Diagnosis

Treatment

Potentially
improve
chances of
becoming
cancer-free

HER2, human epidermal receptor 2; HR, hormone receptor.

1. National Cancer Institute. Definition of recurrent cancer. Accessed October 2023. <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/recurrent-cancer>

2. National Cancer Institute. Definition of metastasis. Accessed October 2023. <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/metastasis>

3. Early Breast Cancer Trialists' Collaborative Group. *Lancet*. 2015;386:1341-1352.

Defining High Risk Breast Cancer

Some factors associated with **high risk of cancer recurrence** include:



Positive nodal status: Cancer cells have been found in the lymph nodes



High tumor grade: Cancer cells appear and grow very differently from normal, healthy breast cells



Large tumor size: tumor is the size of a lime (5 centimeters or 2 inches) or larger



Ribociclib



Palbociclib



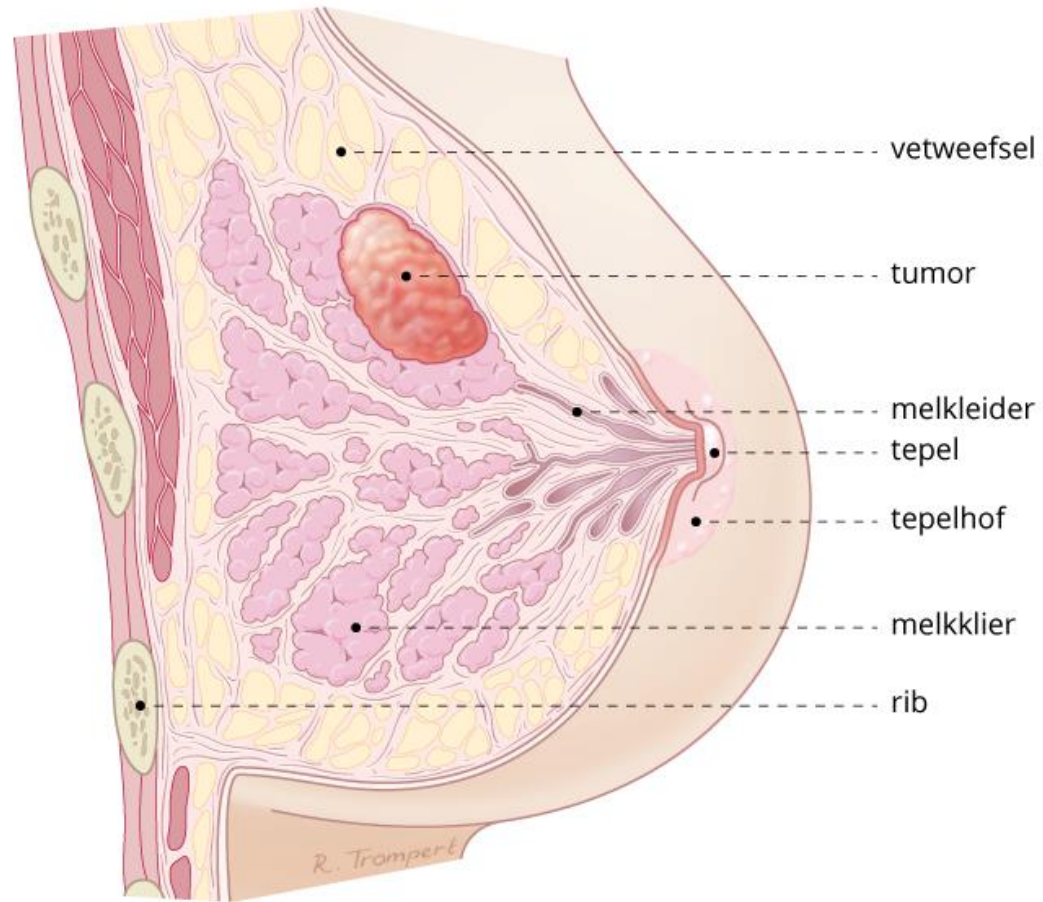
Abemaciclib

Gebruik CDK4/6 inhibitoren

← Samen met hormoontherapie



Welke hormoontherapie combineren?



Borstkanker
- Gemetastaseerd
- Vroege setting
(high risk)

Overzicht studies- 1^{ste} lijn gemetastaseerde setting

Medicatie	Studie
Ribociclib + letrozole	MONALEESA-2
Palbociclib + letrozole	PALOMA-2
Abemaciclib + letrozole	MONARCH-3

3 fase-3 studies

Overzicht studies- 1^{ste} lijn gemetastaseerde setting

Medicatie	Studie
Ribociclib + letrozole	MONALEESA-2
Palbociclib + letrozole	PALOMA-2
Abemaciclib + letrozole	MONARCH-3



MONALEESA-2 studie

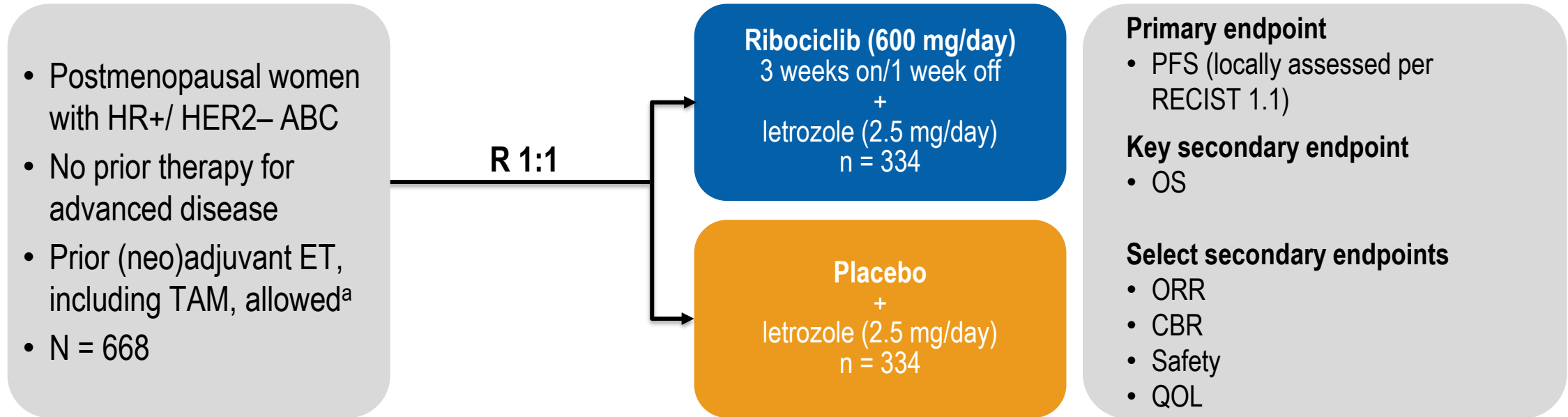
Post-menopauzale vrouwen

668 patiënten

Eerste lijnsbehandeling

Ribociclib + letrozole of placebo + letrozole

MONALEESA-2 study design

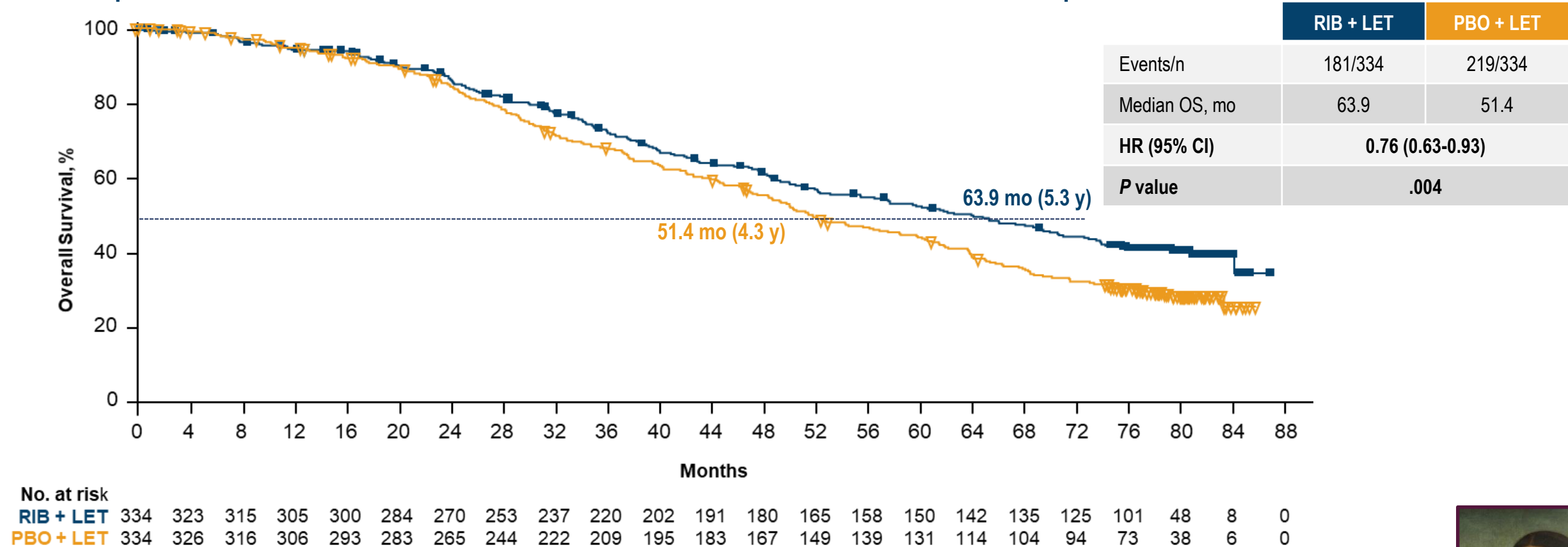


Stratified by the presence/absence of liver and/or lung metastases



Ribociclib achieved statistically significant OS benefit in ML-2

Improvement in median OS was 12.5 months with ribociclib plus letrozole



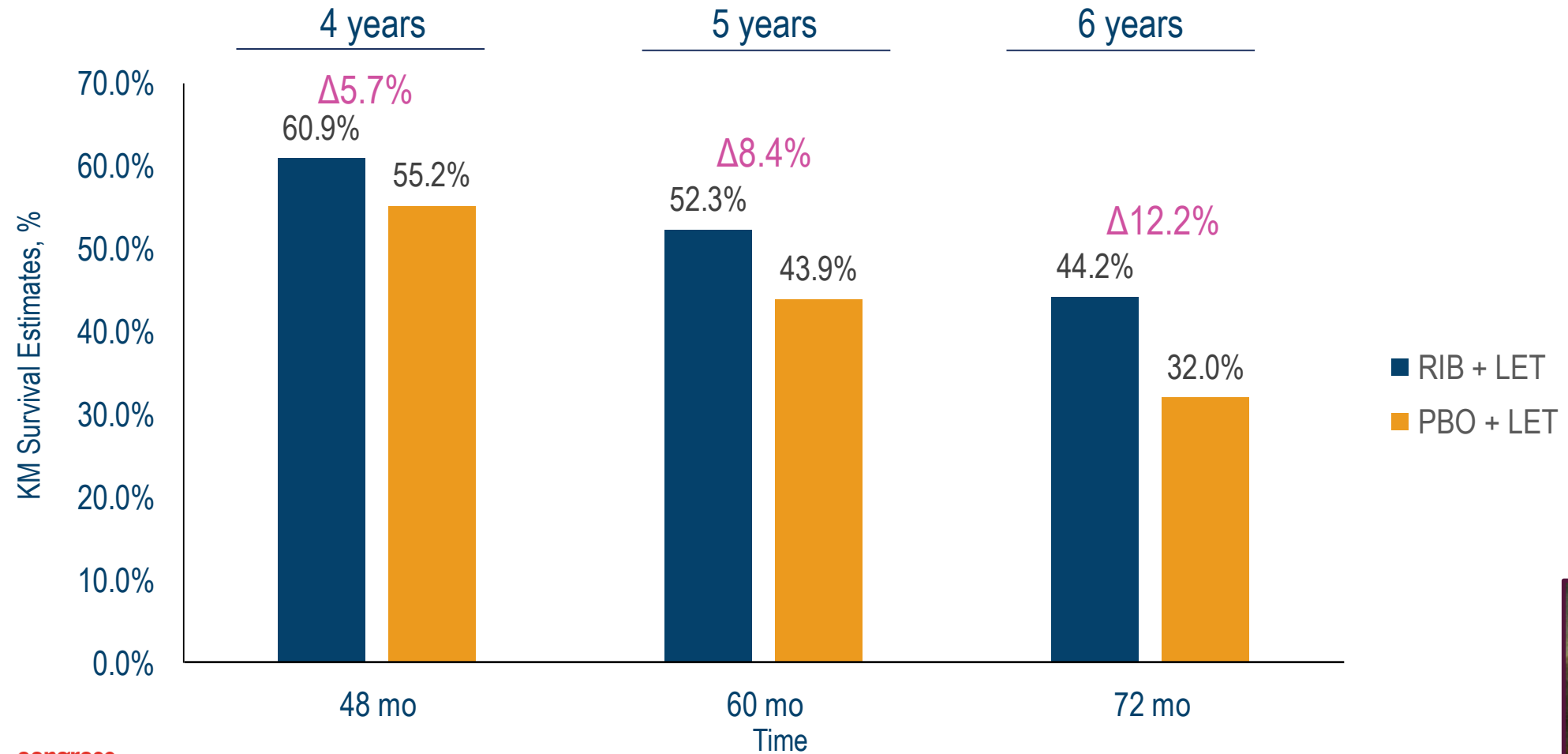
The P value of .004 crossed the prespecified boundary to claim superior efficacy



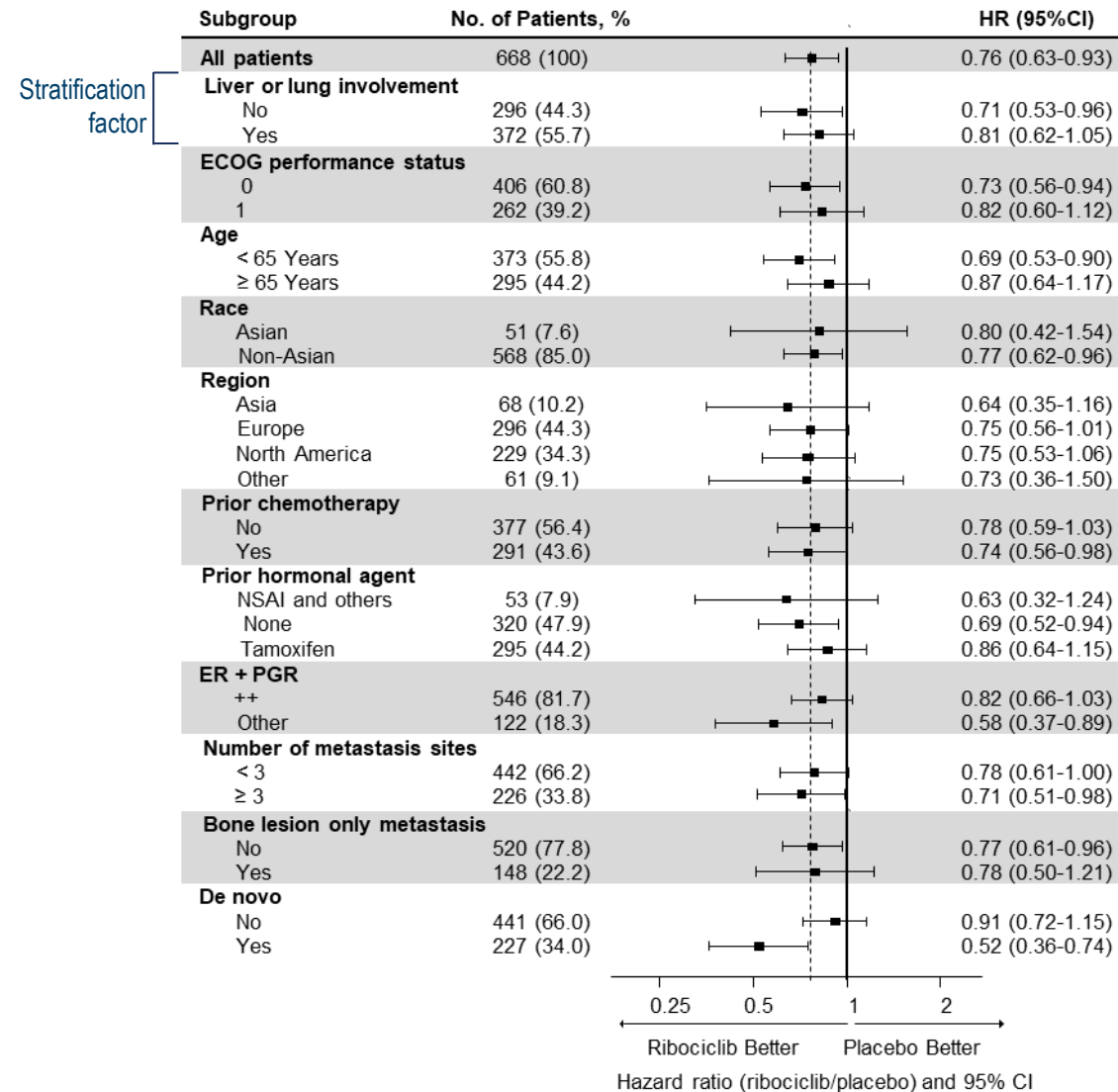
HR, hazard ratio; ML-2, MONALEESA-2; LET, letrozole; OS, overall survival; PBO, placebo; RIB, ribociclib.

The OS benefit with ribociclib increased over time

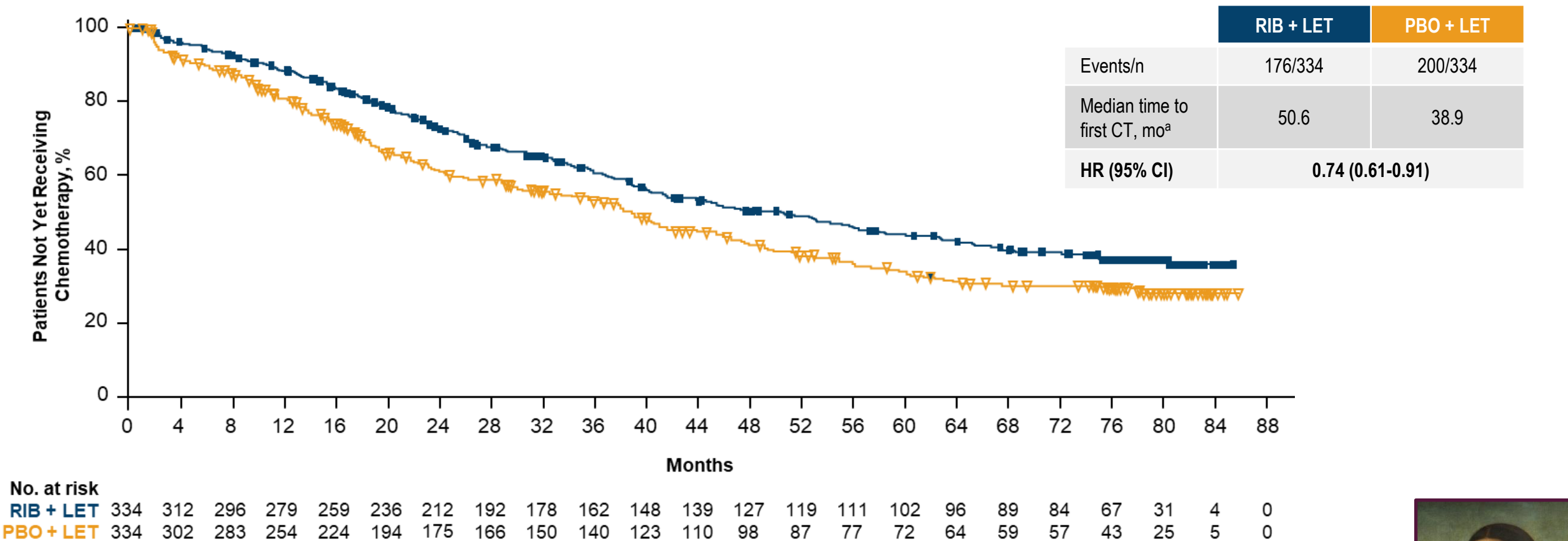
At 6 years, the survival rate of patients receiving ribociclib was 44.2%



Consistent OS benefit was seen across key subgroups



Ribociclib delayed time to first chemotherapy by ≈ 1 year



Overzicht studies- 1^{ste} lijn gemetastaseerde setting

Medicatie	Studie
Ribociclib + letrozole	MONALEESA-2
Palbociclib + letrozole	PALOMA-2
Abemaciclib + letrozole	MONARCH-3



PALOMA-2 studie

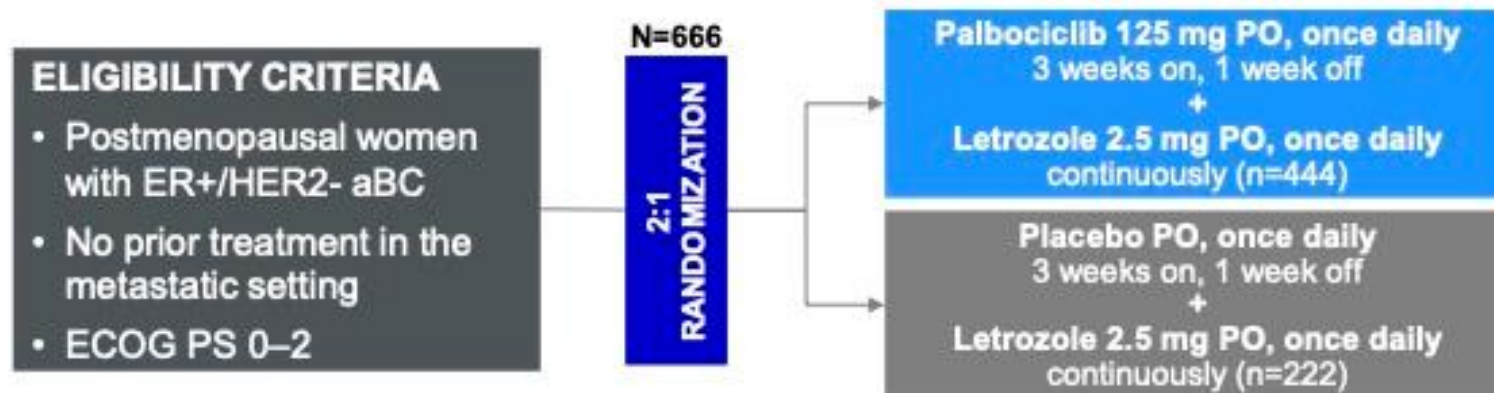
Post-menopauzale vrouwen

666 patiënten

Eerste lijnsbehandeling

Palbociclib + letrozole of placebo + letrozole

Randomized, Double-blind, Phase 3 Trial^{1,2}



Primary endpoint²
Investigator-assessed PFS

Secondary endpoints^{2,3}
ORR, OS, DOR, HRQoL, QTc evaluation, safety, and tolerability

Stratification factors^{1,2}

- Disease site (visceral, non-visceral)
- Disease-free interval (de novo metastatic, ≤12 months, >12 months)
- Prior neo/adjuvant hormonal therapy (yes, no)

Statistical Assumptions for PFS as primary endpoint⁴:

- Sample size determined to detect ~44% improvement in median PFS from 9 months for the control arm to 13 months for the palbociclib arm
- Assuming a true hazard ratio of 0.69 in favor of the palbociclib arm (90% power with 1-sided $\alpha=0.025$)

Statistical Assumptions for OS as secondary endpoint⁴:

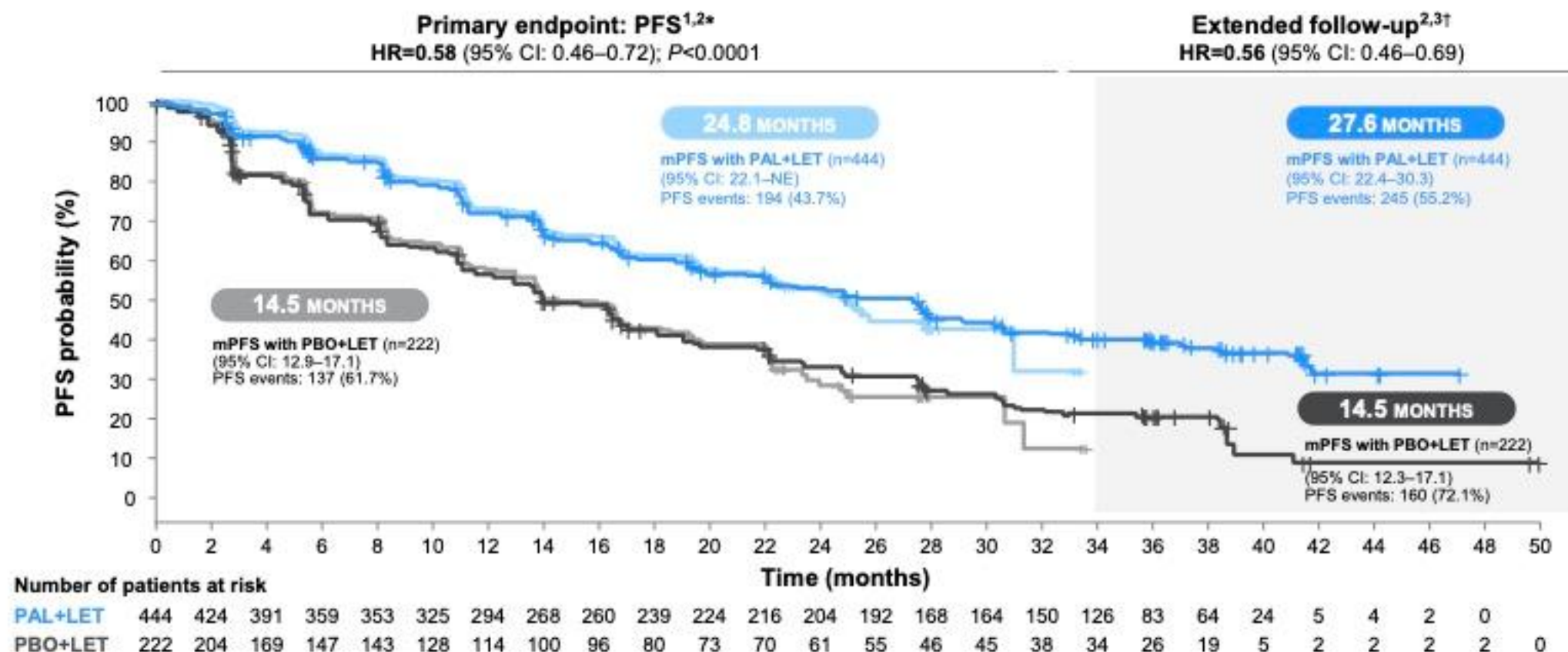
- Assumption for the control arm median OS of 34 to 46 months (~35% improvement)
- 390 events required to detect a hazard ratio of 0.74 or less (80% power with 1-sided $\alpha=0.025$)
- Final OS analysis was performed after required events were reached (November 2021) with median follow-up of 90 months⁴
- Results of the final OS analysis are reported⁴

aBC=advanced breast cancer; DOR=duration of response; ECOG PS=Eastern Cooperative Oncology Group performance status;

1. Ibrance SmPC 2. Finn RS, et al. *N Engl J Med*. 2016;375:1925-1936.
3. Data on file (63). Pfizer Inc., New York, NY. 4. Finn RS, et al. Abstract LBA1003. ASCO 2022.



PALOMA-2: PFS Analyses



*Intent-to-treat population. Data cutoff: February 26, 2016.¹

†Intent-to-treat population. Data cutoff: May 31, 2017; post hoc analysis.²

CI=confidence interval; HR=hazard ratio; LET=letrozole; NE=not estimable; PAL=palbociclib;

PBO=placebo; mPFS=median progression-free survival

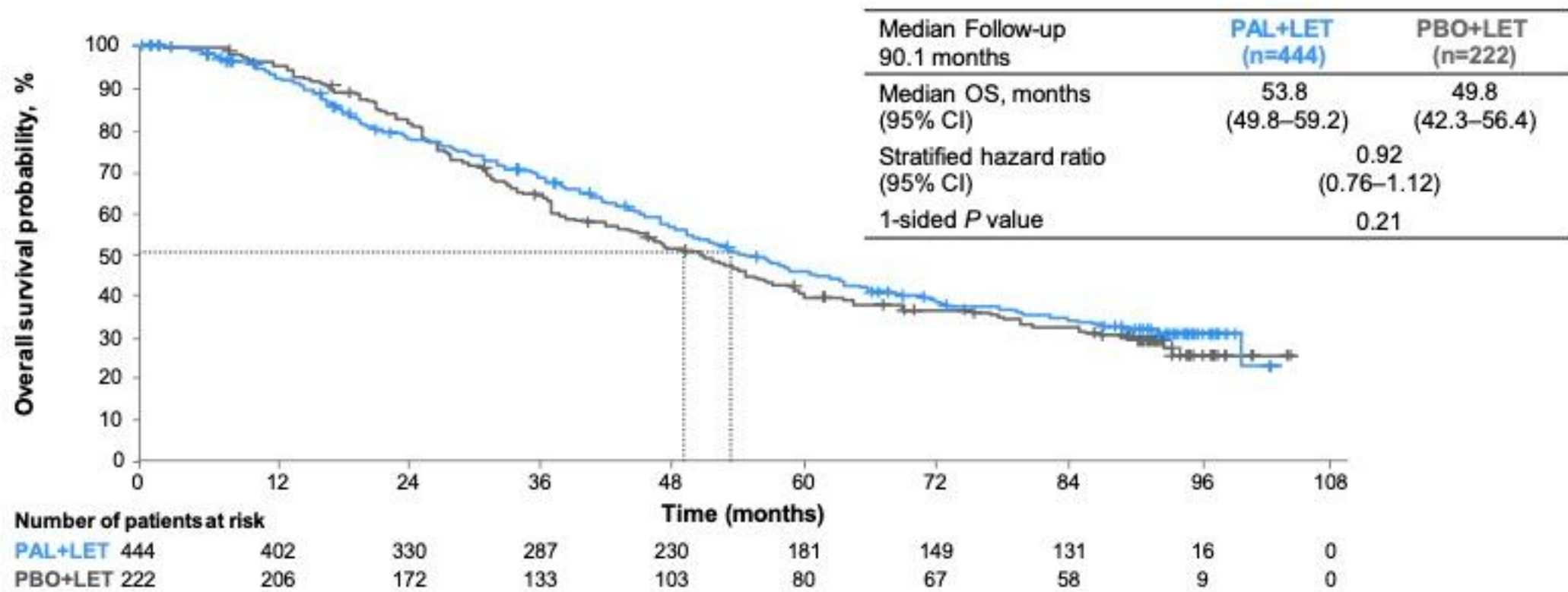
1. Finn RS, et al. *N Engl J Med*. 2016;375:1925-1936. 2. Rugo, HS, et al. *Breast Cancer Res Treat*. 2019;174:719-729.

3. Data on File (97). Pfizer.

PALOMA-2: Overall Survival and Duration of Treatment



Secondary Endpoint: Revised Prespecified Analysis of Overall Survival (ITT)^{1*}



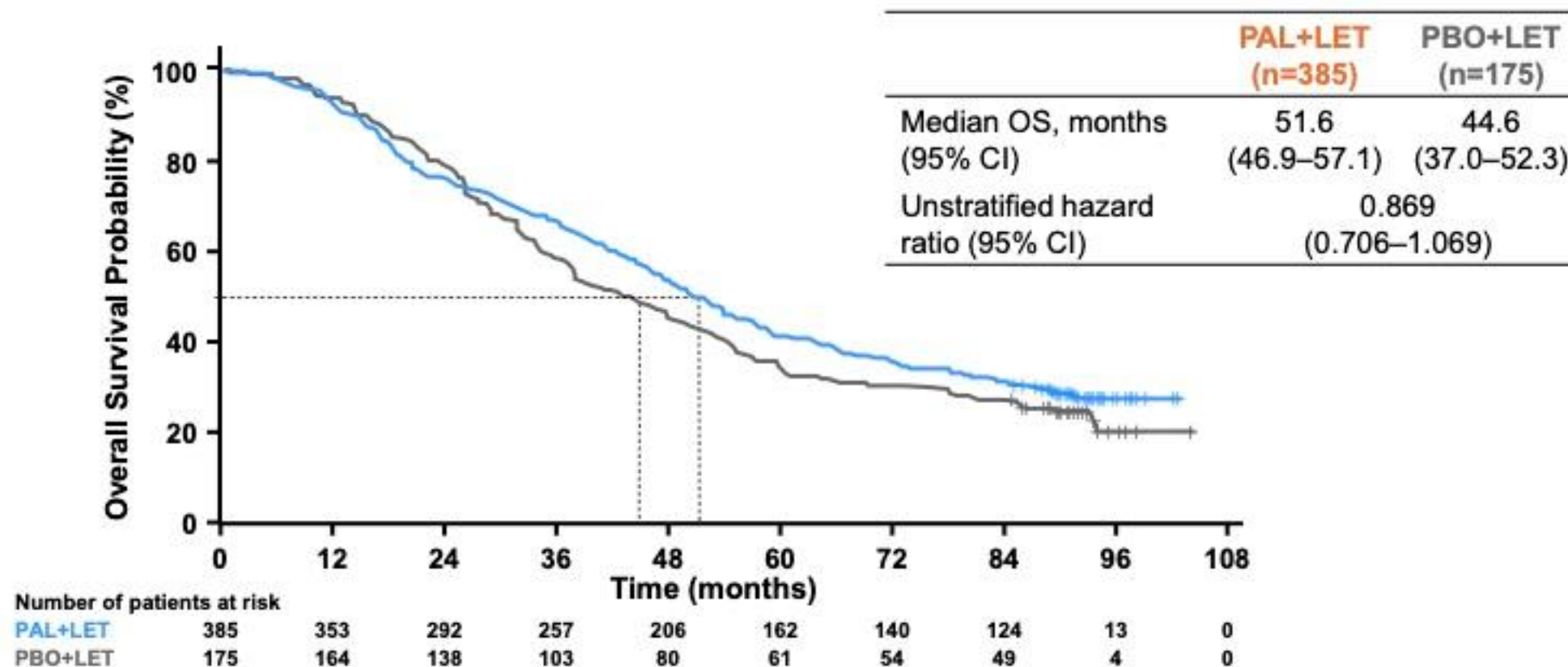
***The revised analysis includes recovered survival data from 39 additional patients.**

Data cutoff: November 15, 2021.
CI=confidence interval; ITT=intent to treat; LET=letrozole; OS=overall survival; PAL=palbociclib; PBO=placebo.

Slamon DJ, et al. *J Clin Oncol*. 2024; DOI:10.1200/JCO.23.00137

PALOMA-2: OS Excluding Patients With Unknown Survival Outcome^{1*}

Post hoc sensitivity analysis



Data cutoff: November 15, 2021.²

*This is a post hoc subgroup analysis. This analysis is not stratified or adjusted. Small patient numbers can be a limitation of subgroup analyses. These analyses may not be powered to detect significant differences and were not designed to compare across subgroups. Any comparison between groups should be approached with caution.

CI=confidence interval; LET=letrozole; PAL=palbociclib; PBO=placebo; OS=overall survival.

1. Finn RS, et al. Abstract LBA1003. ASCO 2022.

2. Data on File (170). Pfizer.

Overzicht studies- 1^{ste} lijn gemetastaseerde setting

Medicatie	Studie
Ribociclib + letrozole	MONALEESA-2
Palbociclib + letrozole	PALOMA-2
Abemaciclib + letrozole	MONARCH-3



MONARCH-3 studie

Post-menopauzale vrouwen

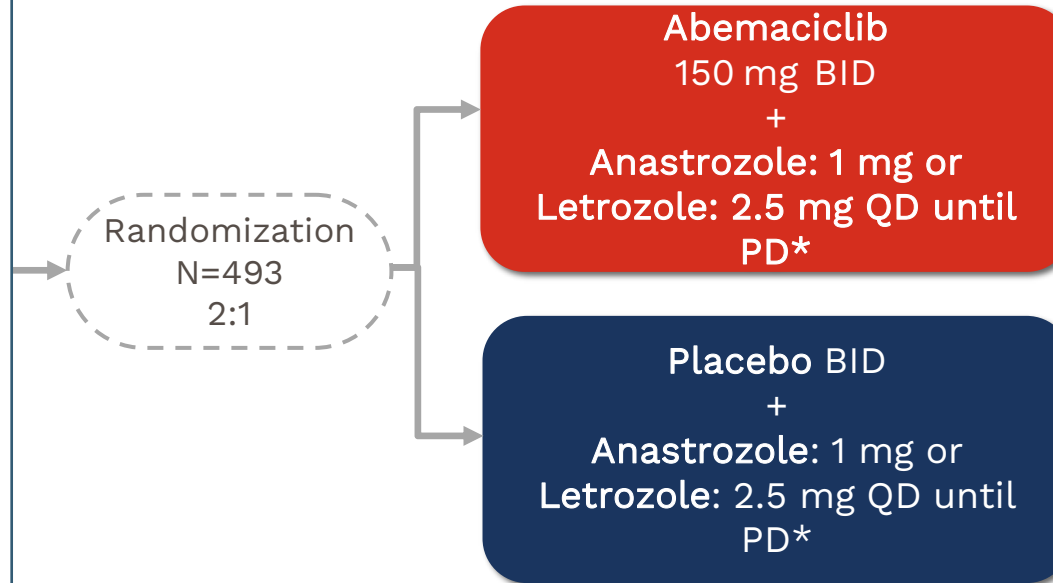
493 patiënten

Eerste lijnsbehandeling

Abemaciclib + letrozole/ anastrozole of placebo +
letrozole/ anastrozole

MONARCH 3: Study Design

- ◆ HR+/HER2- ABC
- ◆ Postmenopausal
- ◆ Metastatic or locally recurrent disease with no prior systemic therapy in this setting
- ◆ If neoadjuvant or adjuvant ET administered, a disease-free interval of >12 months since completion of ET
- ◆ ECOG PS ≤1
- ◆ Disease characteristics at baseline
 - Bone-only disease: 22%
 - Visceral disease: 53%
 - De novo metastatic disease: 40%



- Primary endpoint:**
Investigator-assessed PFS
- Secondary endpoints:**
OS, response rates, safety
- Exploratory endpoint:**
Chemotherapy-free survival
- Stratification factors**
- ◆ Metastatic site (visceral, bone only, or other)
 - ◆ Prior ET (NSAI, no ET, or other)

*Per physician's choice: 79.1% received letrozole and 19.9% received anastrozole.

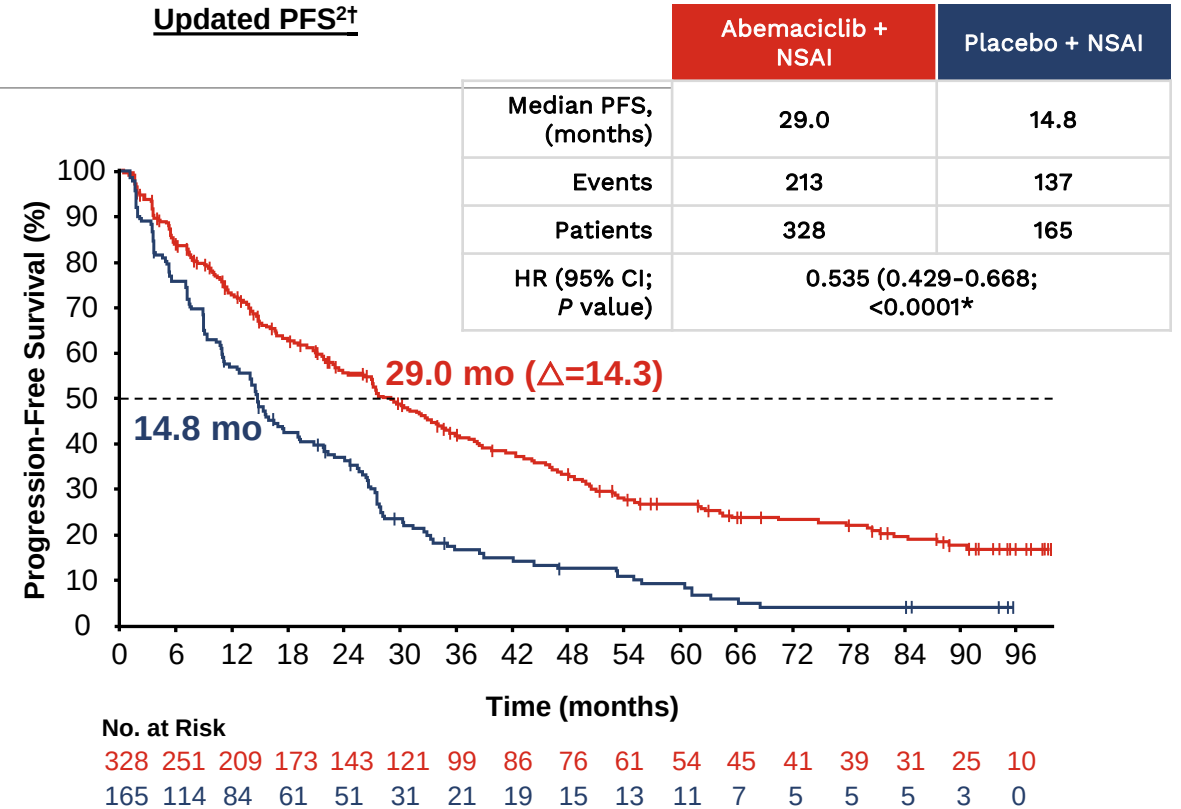
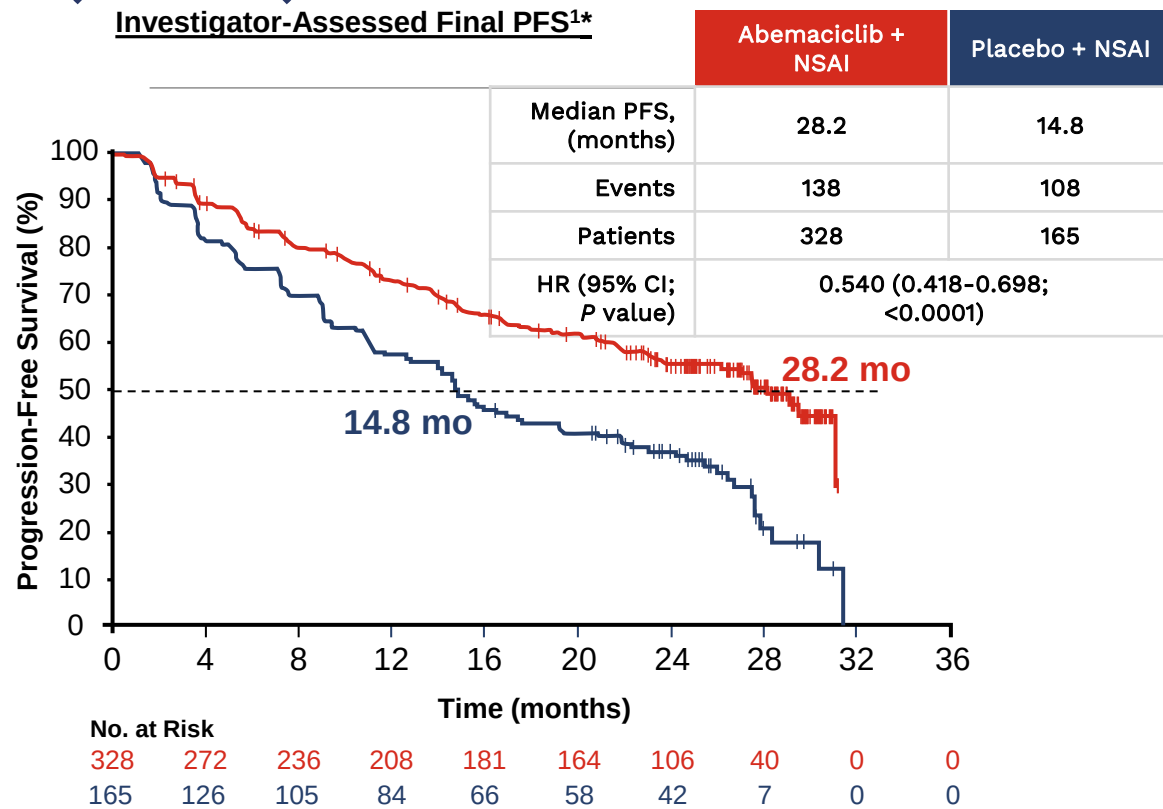
Abbreviations: ABC, advanced breast cancer; BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; MBC, metastatic breast cancer;

NSAI, non-steroidal aromatase inhibitor; OS, overall survival; PD, progressive disease; PFS, progression-free survival; QD, every day.

Reference: Goetz MP et al. *J Clin Oncol*. 2017;35:3638-3646.



MONARCH 3: Primary Endpoint PFS (ITT)



The addition of abemaciclib to NSAI resulted in a **14.3-month** improvement in median PFS with continued separation of the curves at longer follow-up.

*Primary endpoint was met at the preplanned interim analysis with a data cutoff of January 31, 2017. Final PFS analysis data cutoff was November 3, 2017. †Data Cutoff: September 29, 2023.

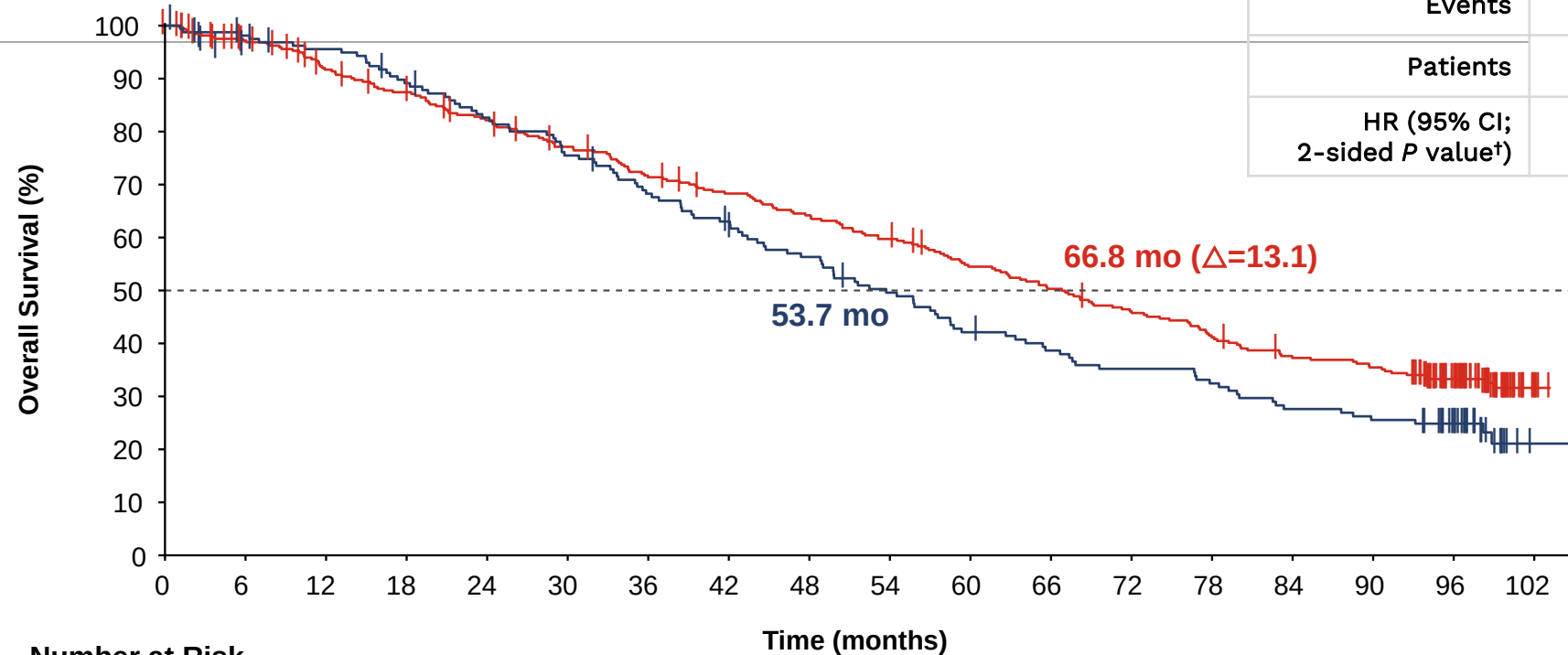
Abbreviations: ABC=Advanced Breast Cancer; CI=Confidence Interval; ET=Endocrine Therapy; HR=Hormone Receptor; HR=Hazard Ratio; HER2=Human Epidermal Growth Factor Receptor; ITT=intent-to-treat; mPFS=Median Progression-Free Survival; NSAI=Non-steroidal Aromatase Inhibitor.

References: 1. Verzenio [package insert]. Indianapolis, IN: Eli Lilly and Company; 2024. <https://uspl.lilly.com/verzenio/verzenio.html#pi> 2. Goetz MP et al. Presented at: SABCS 2023. Abstract GS01-12.



MONARCH 3: Final OS (ITT)

Overall Survival ITT Population*



Number at Risk

328	304	281	266	247	229	211	199	187	174	156	144	131	117	104	99	66	6
165	155	149	138	127	116	104	95	84	73	62	56	51	47	40	37	28	1



Abemaciclib in combination with a NSA resulted in longer OS compared to NSA alone; however, statistical significance[†] was not reached. The observed improvement in median OS was **13.1 months**.

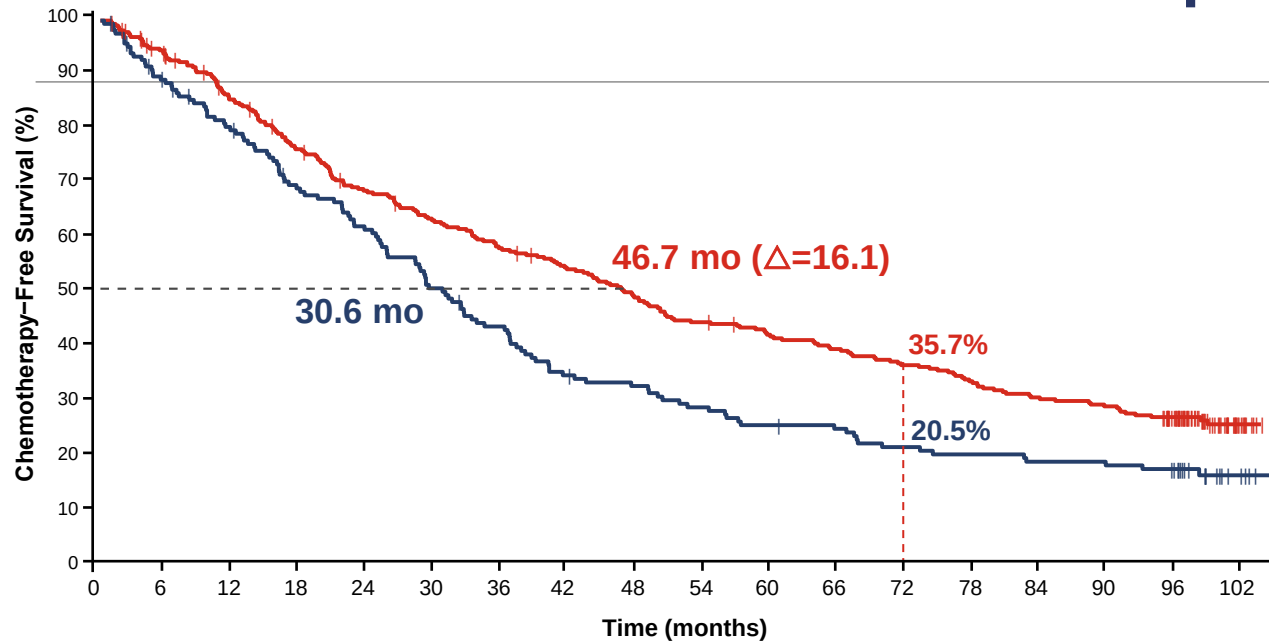
*Data Cutoff: September 29, 2023. [†]Calculated P-value threshold for statistical significance (2-sided) ≤ 0.034 .

Abbreviations: CI=Confidence Interval; HR=Hazard Ratio; ITT=Intent-to-Treat Analysis; NSA=Non-steroidal Aromatase Inhibitor; OS=Overall Survival.

Reference: Goetz MP et al. Presented at: SABCS 2023. Abstract GS01-12.



MONARCH 3: Chemotherapy-Free Survival in the ITT Population



	Abemaciclib + NSA	Placebo + NSA
Median, (months)	46.7	30.6
Events	230	132
Patients	328	165
HR (95% CI; 2-sided P value)	0.693 (0.557-0.863; 0.0010)	

Number at Risk

328	295	267	237	210	192	176	163	147	133	123	116	107	9	8	8	6	9
165	142	125	106	95	78	66	51	48	42	37	35	30	7	8	4	8	4
													2	2	2	2	
													8	6	5	2	



The addition of abemaciclib to NSA deferred the initiation of chemotherapy, with a **16.1 month** improvement in median chemotherapy-free survival.

^aData Cutoff: September 29, 2023.

Abbreviations: CI=Confidence Interval; HR=Hazard Ratio; ITT=Intent-to-Treat Analysis; mo=months; NSA=Non-steroidal Aromatase Inhibitor.

Reference: Goetz MP et al. Presented at: SABCS 2023. Abstract GS01-12.



Overzicht studies- adjuvante setting

Medicatie	Studie
Ribociclib + NSAï	NATALEE
Abemaciclib + NSAï	MONARCH-E

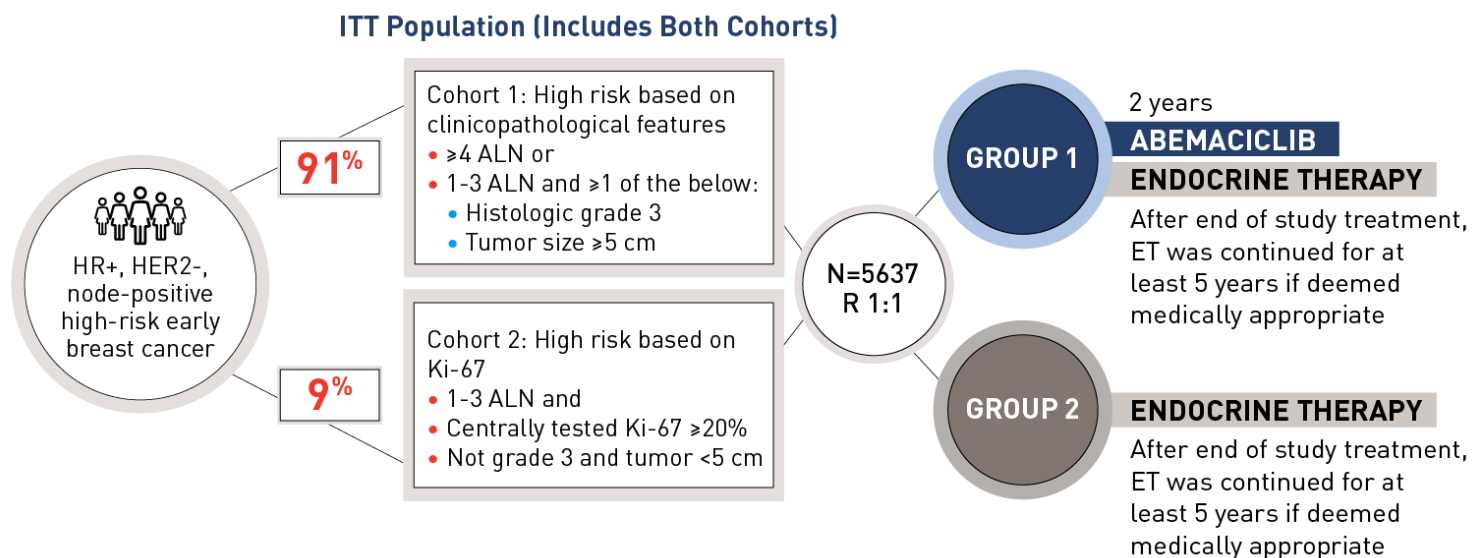
2 fase-3 studies



MonarchE studie

Abemaciclib: monarchE Clinical Trial Design

- **Primary Objective:** Invasive disease-free survival (IDFS), how long after starting the study treatment a person remains cancer-free
- **Secondary Objectives:** Distant relapse-free survival (DRFS), overall survival (OS), safety, PK, patient response outcomes



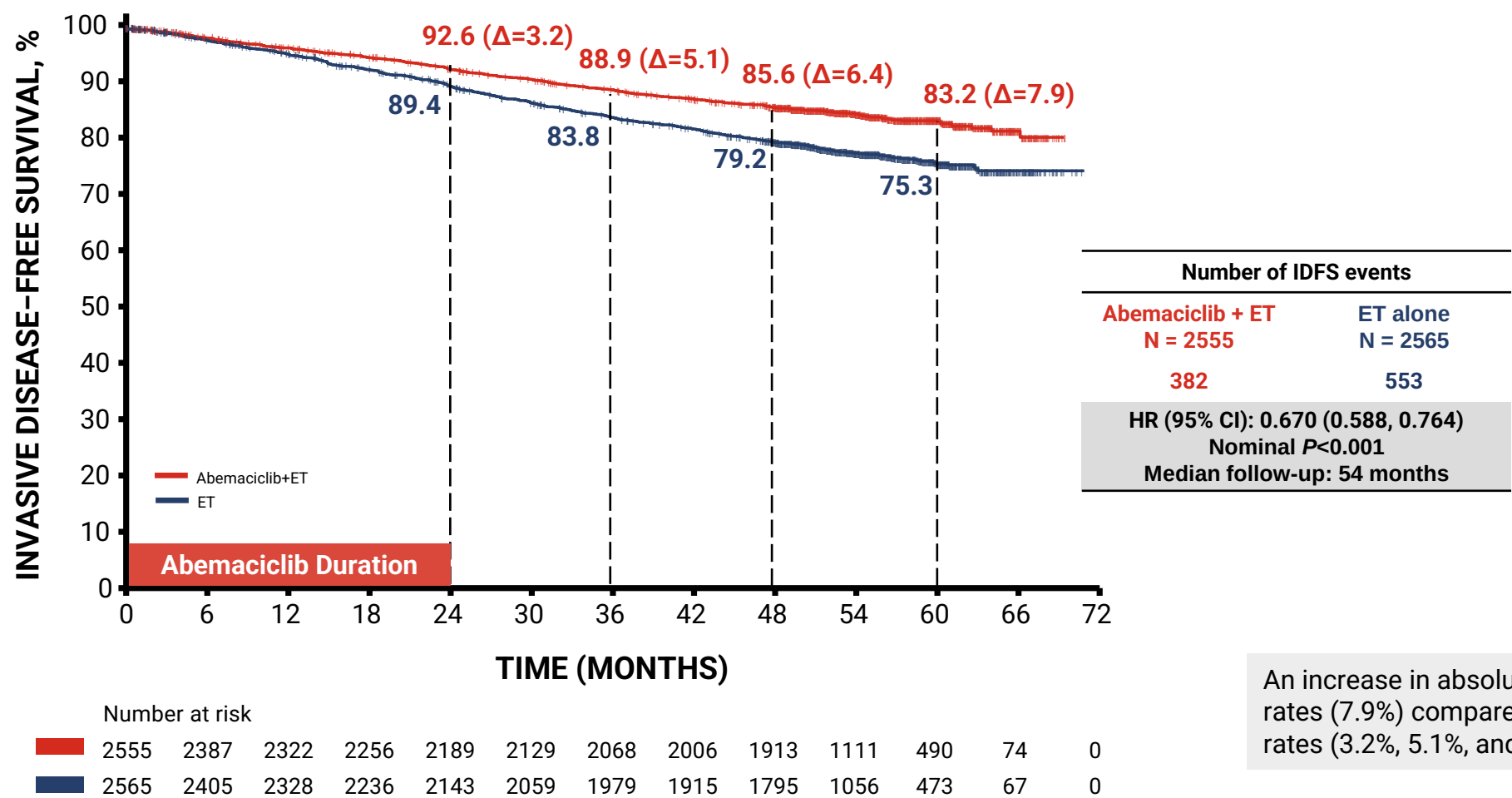
ALN, positive axillary lymph nodes; HER2, human epidermal receptor 2; HR, hormone receptor; ITT, intent-to-treat population; N, number of patients in ITT population; PK, pharmacokinetics; R, randomized.

1. Johnston SRD et al. Oral presentation at San Antonio Breast Cancer Symposium (SABCS). December 2022.

2. Johnston SRD et al. *Lancet Oncol.* 2023;24:77-90.

monarchE: IDFS in Cohort 1 Population, 5-Year Data

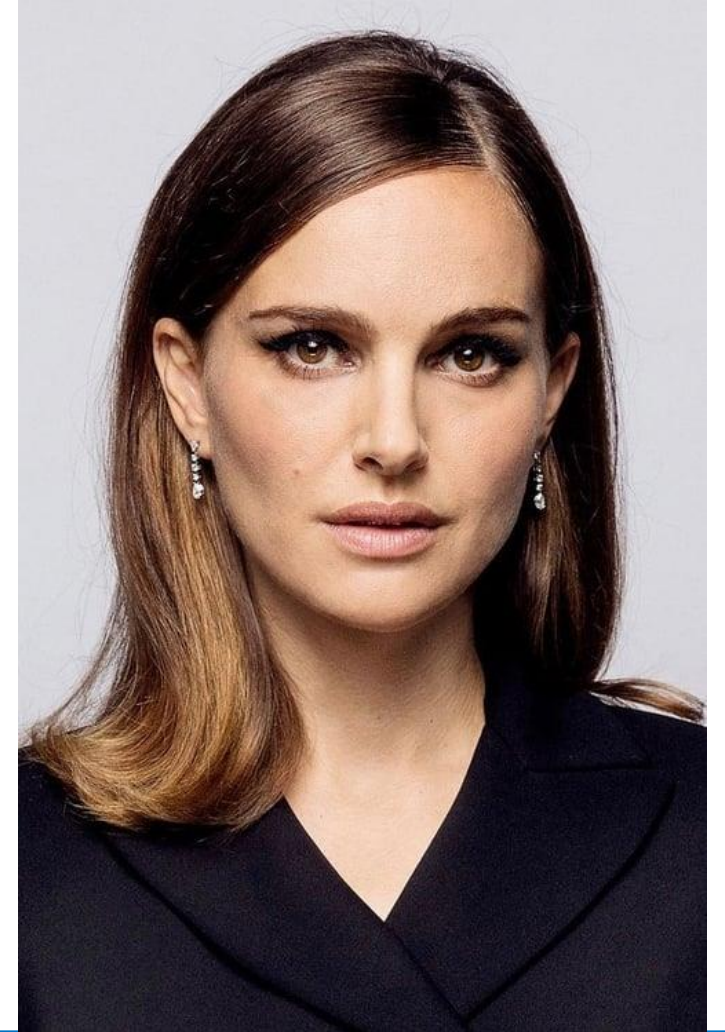
Absolute difference in efficacy was 7.9% at 5 years.



An increase in absolute benefit in IDFS 5-year rates (7.9%) compared to 2-, 3-, and 4-year IDFS rates (3.2%, 5.1%, and 6.4% respectively).



Absolute differences were calculated by subtraction of the IDFS rates between the two arms at each year.
IDFS analysis for this subpopulation was not powered or alpha controlled for testing statistical significance.
Harbeck N, et al. Adjuvant abemaciclib plus endocrine therapy for HR+, HER2-, high-risk early breast cancer: Results from a preplanned monarchE overall survival interim analysis, including 5-year efficacy outcomes. Abstract LBA17. Presented at: European Society for Medical Oncology (ESMO); October 20, 2023; Munich, Germany. © 2024 Eli Lilly and Company



NATALEE Studie

Study Design and Methods

- Adult patients with HR+/HER2- EBC
 - Prior ET allowed ≤ 12 mo prior to randomization
 - **Anatomical stage IIA^a**
 - N0 with:
 - Grade 2 and evidence of high risk:
 - Ki-67 $\geq 20\%$
 - 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

RIB
400 mg/day
3 weeks on/1 week off
for 3 years

+

NSAI
Letrozole or anastrozole^d
for ≥ 5 years
+ **goserelin** in men and
premenopausal women

NSAI
Letrozole or anastrozole^d
for ≥ 5 years
+ **goserelin** in men and
premenopausal women

Primary End Point

- iDFS using STEEP criteria

Secondary End Points

- Recurrence-free survival
- Distant disease-free survival
- OS
- Safety and tolerability
- PROs
- PK

Exploratory End Points

- Locoregional recurrence-free survival
- Gene expression and alterations in tumor ctDNA/ctRNA samples

Endpoints included in this presentation

Statistical comparisons were performed using a Cox proportional hazards model and the Kaplan-Meier method

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

Data cutoff: 29 April 2024

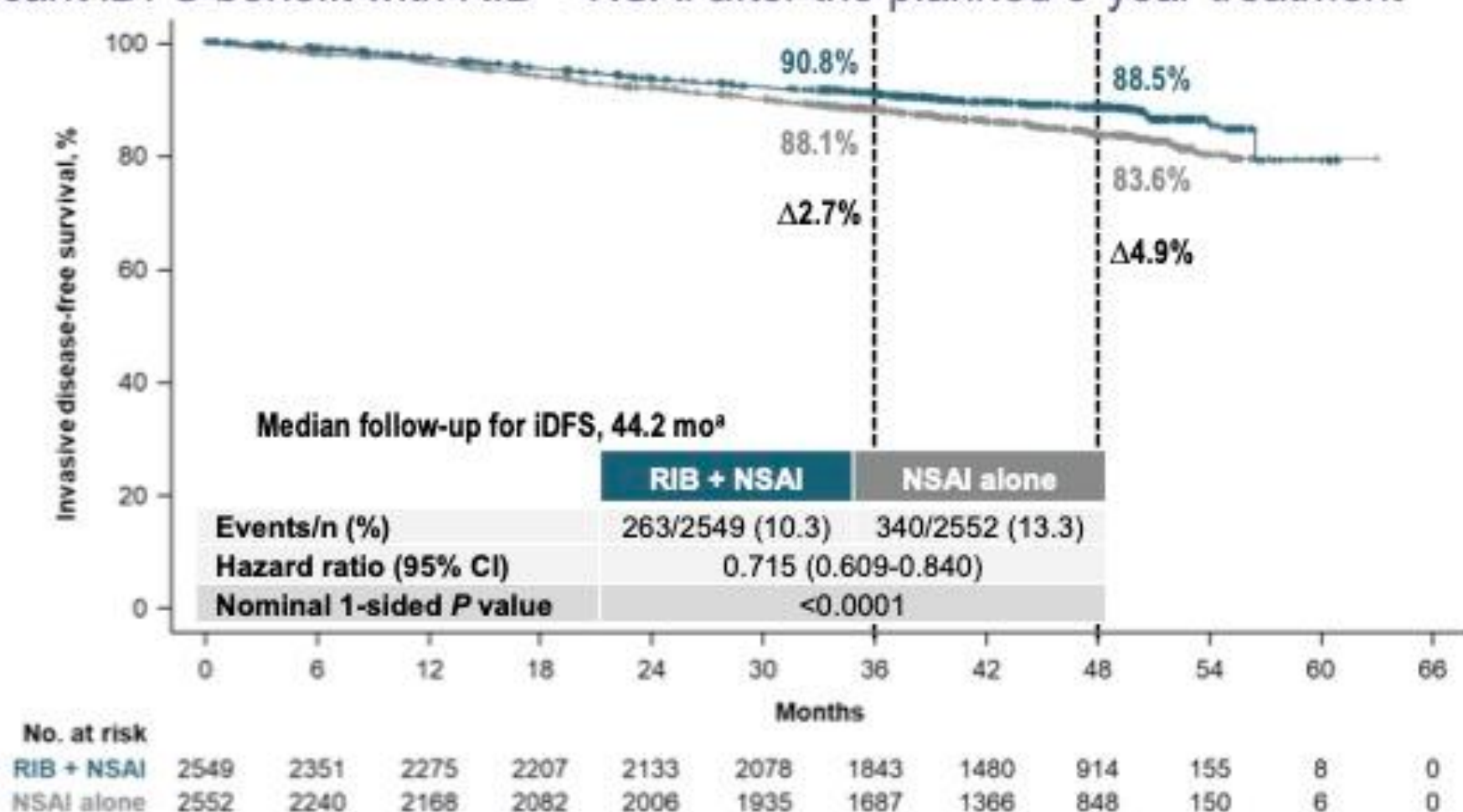
ctDNA/ctRNA, circulating tumor DNA/RNA; EBC, early breast cancer; ET, endocrine therapy; iDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome; R, randomized; RIB, ribociclib; STEEP, Standardized 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 10 Jan 2019 to 20 April 2021. ^c Open-label design. ^d Per investigator choice.

1. ClinicalTrials.gov. Accessed March 15, 2024. <https://clinicaltrials.gov/ct2/show/NCT03701334>. 2. Slamon DJ, et al. Poster presented at: ASCO 2019. Poster TPS587. 3. Slamon DJ, et al. *Ther Adv Med Oncol*. 2023;15:1-16. 4. Horisbagi G, et al. Oral presentation at: SABCS 2023. Oral GS03-03.

iDFS in ITT Population

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



iDFS, invasive disease-free survival; ITT, intent to treat; NSAID, nonsteroidal anti-inflammatory drug; RIB, ribociclib.
^a An additional 10.9 months of follow-up compared with the protocol-specified final iDFS analysis.

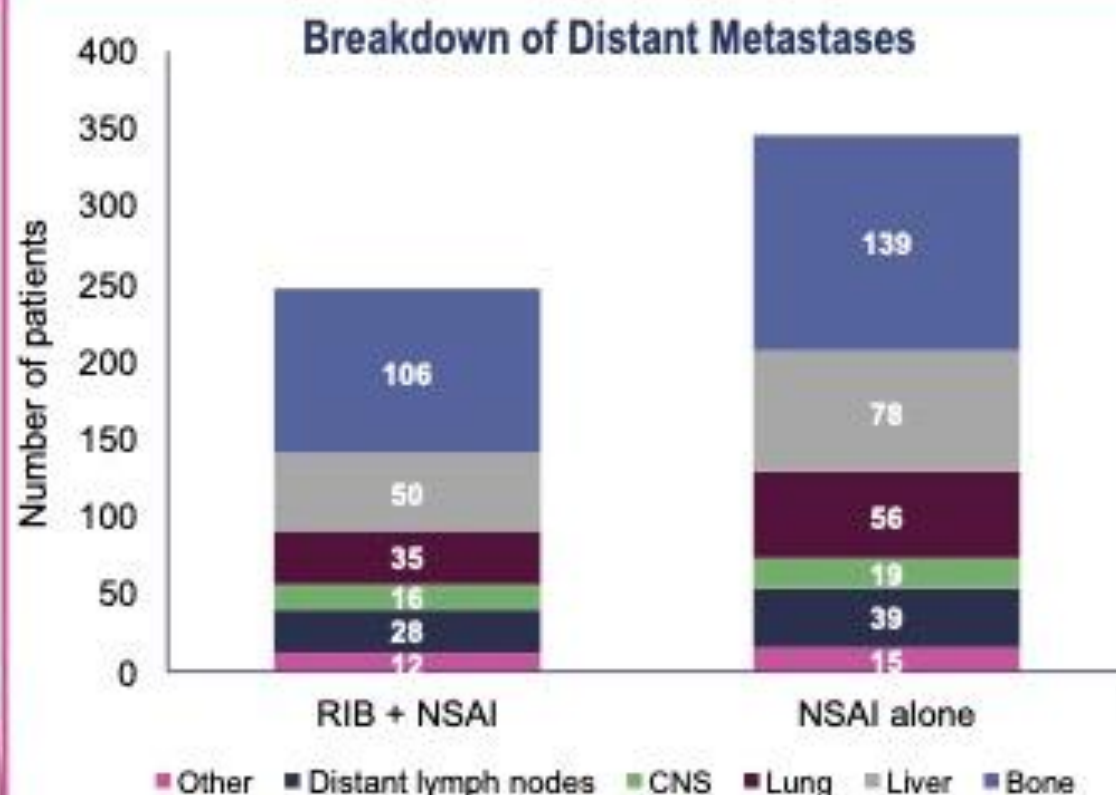
Peter A. Fasching

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iDFS Events in ITT Population

The majority of iDFS events were distant recurrences, which were more common in the NSAI only arm

Type and site of first iDFS event, n (%)	RIB + NSAI n=2549	NSAI Alone n=2552
Distant recurrence	176 (6.9)	246 (9.6)
Local/regional invasive recurrence	25 (1.0)	49 (1.9)
Second primary nonbreast cancer	39 (1.5)	40 (1.6)
Death	17 (0.7)	11 (0.4)
Invasive contralateral breast tumor	11 (0.4)	10 (0.4)
Invasive ipsilateral breast tumor	8 (0.3)	9 (0.4)



Inhoud



Wat zijn CDK4/6 inhibitoren?



Welke CDK4/6 inhibitoren zijn er?

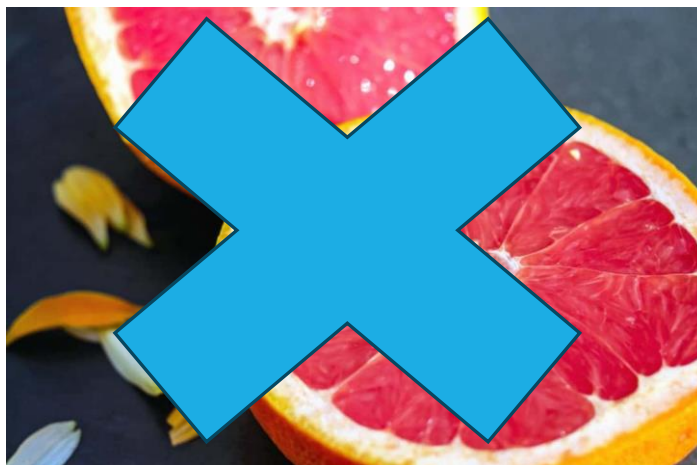


Waarvoor worden ze gebruikt?



Wat zijn de voornaamste
nevenwerkingen?

Inname medicatie



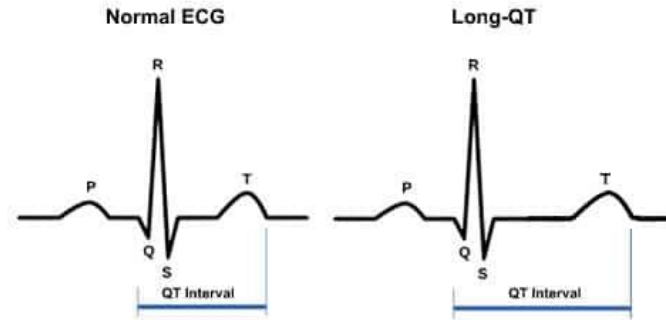
Geen pinda-allergie bij
Kisqali



Algemene nevenwerkingen



Allergie

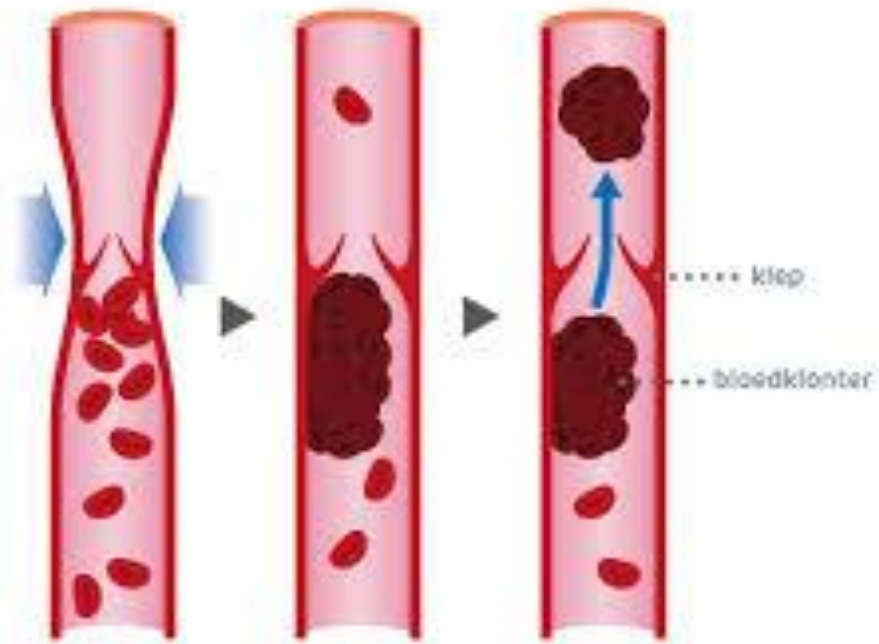


QT-verlenging

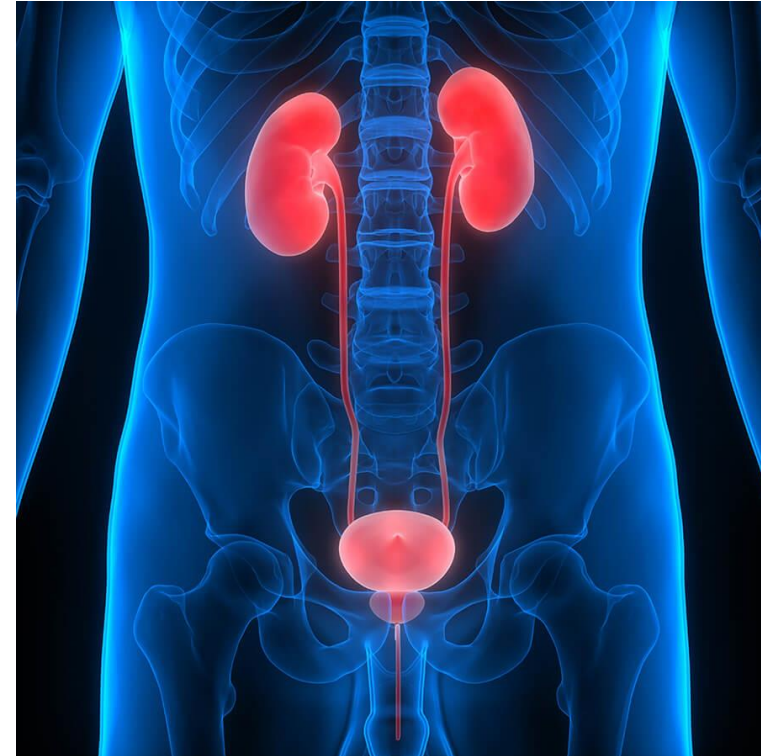


Leverfunctiestoornissen

Aandachtspunten Kisqali



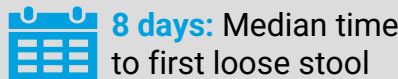
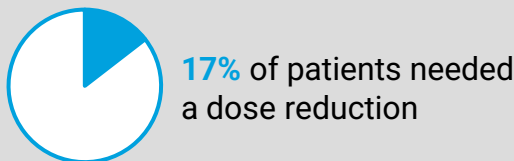
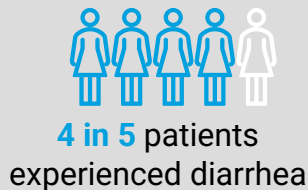
Veneuze trombo-embolie



Creatinine stijging

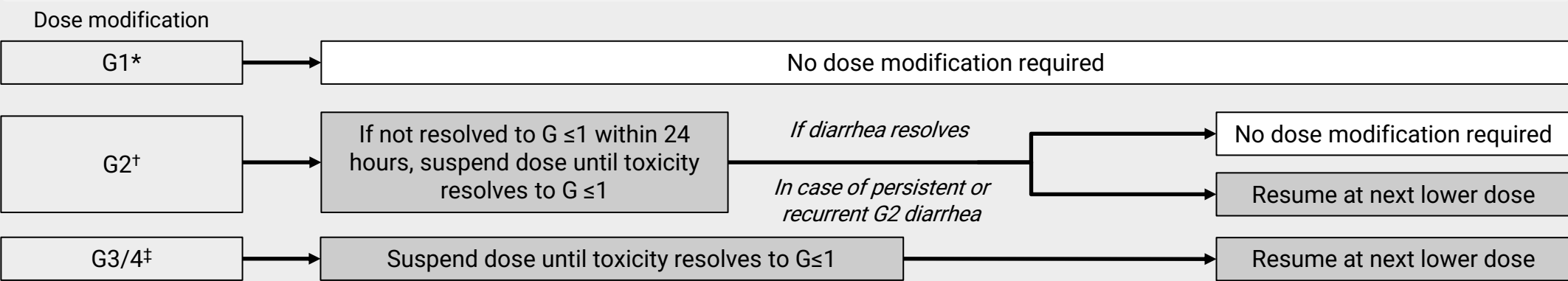
Aandachtspunten Verzenios

Diarrhea in All Abemaciclib-Treated Patients

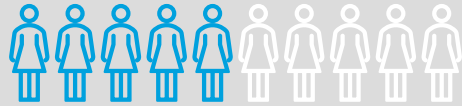


Management of Diarrhea

Instruct patients to initiate antidiarrheal therapy at the first sign of loose stools, increase fluids, and notify their healthcare provider.



Neutropenia in All Abemaciclib-Treated Patients



5 in 10 patients
experienced neutropenia



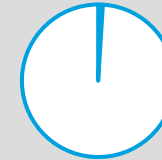
16% of patients had to
hold at least one dose



8% of patients needed
a dose reduction



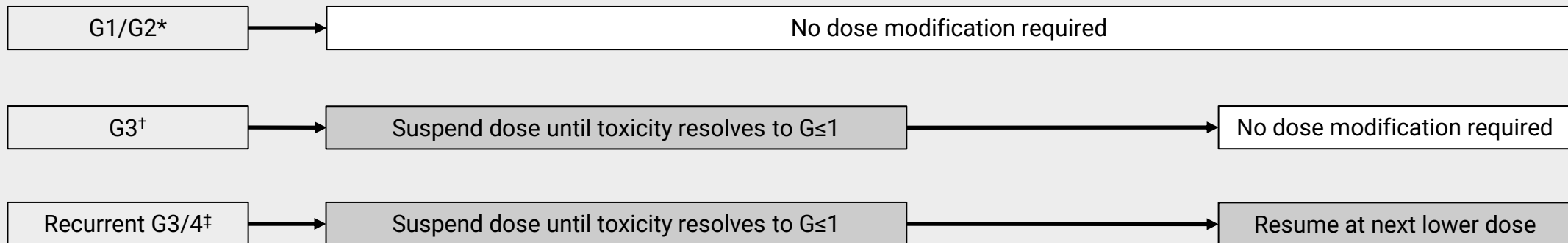
1 in 5 patients experienced
severe neutropenia



1% of patients
discontinued

Management of Neutropenia

Dose modification



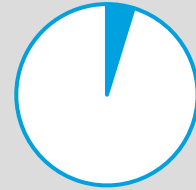
Fatigue in All Abemaciclib-Treated Patients



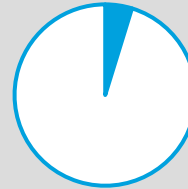
4 in 10 patients experienced fatigue or tiredness



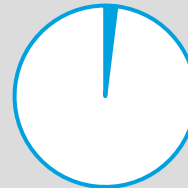
3% experienced severe fatigue



5% of patients had to hold at least one dose



5% of patients needed a dose reduction



2% of patients discontinued

Management of Fatigue²

Physical exercise is the most established evidence-based approach for management of fatigue.

Serious Side Effects in Abemaciclib-Treated Patients

Interstitial Lung Disease/Pneumonitis
Lung problems



Trouble breathing or shortness of breath, cough with or without mucus, or chest pain.

Hepatotoxicity
Liver problems



Feeling very tired, abdominal pain, loss of appetite, bleeding or bruising more easily than normal.

Venous Thromboembolism
Blood Clots in veins, arteries of lungs



Pain or swelling of arms or legs, shortness of breath, chest pain, rapid breathing, rapid heart rate.

Events of interest, any grade	ILD	Hepatotoxicity ALT, AST increase (lab)	VTE, PE
Abemaciclib + ET N = 2791, %	3.3	38.7, 32.9	2.5, 1.0
ET Alone N = 2800, %	1.3	24.4, 18.3	0.7, 0.1

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ET, endocrine therapy; ILD, interstitial lung disease; PE, pulmonary embolism; VTE, venous thromboembolism.

1. Eli Lilly. Verzenio (abemaciclib) US Prescribing Information. Published 2023. Accessed March 2023. <https://pi.lilly.com/us/verzenio-uspi.pdf?s=pi>

2. Johnston SRD et al. Oral presentation at San Antonio Breast Cancer Symposium (SABCS). December 2022.

3. Johnston SRD et al. *Lancet Oncol.* 2023;24:77-90.

Brochures

Voor oncocoachen
en
verpleegkundigen

HELP UW PATIËNTEN IN GOEDE
TE LEVEN MET KISQALI®





“Zijn er nog vragen?”



Dr. Annelies Requilé, Jessa ziekenhuis

Tijdens Oncoclinics 21.01.2025