



Update endocriene therapie

Dr. Annelies Requilé
Medisch oncoloog Jessa en Sint-Franciscus

Nieuws vers van de pers



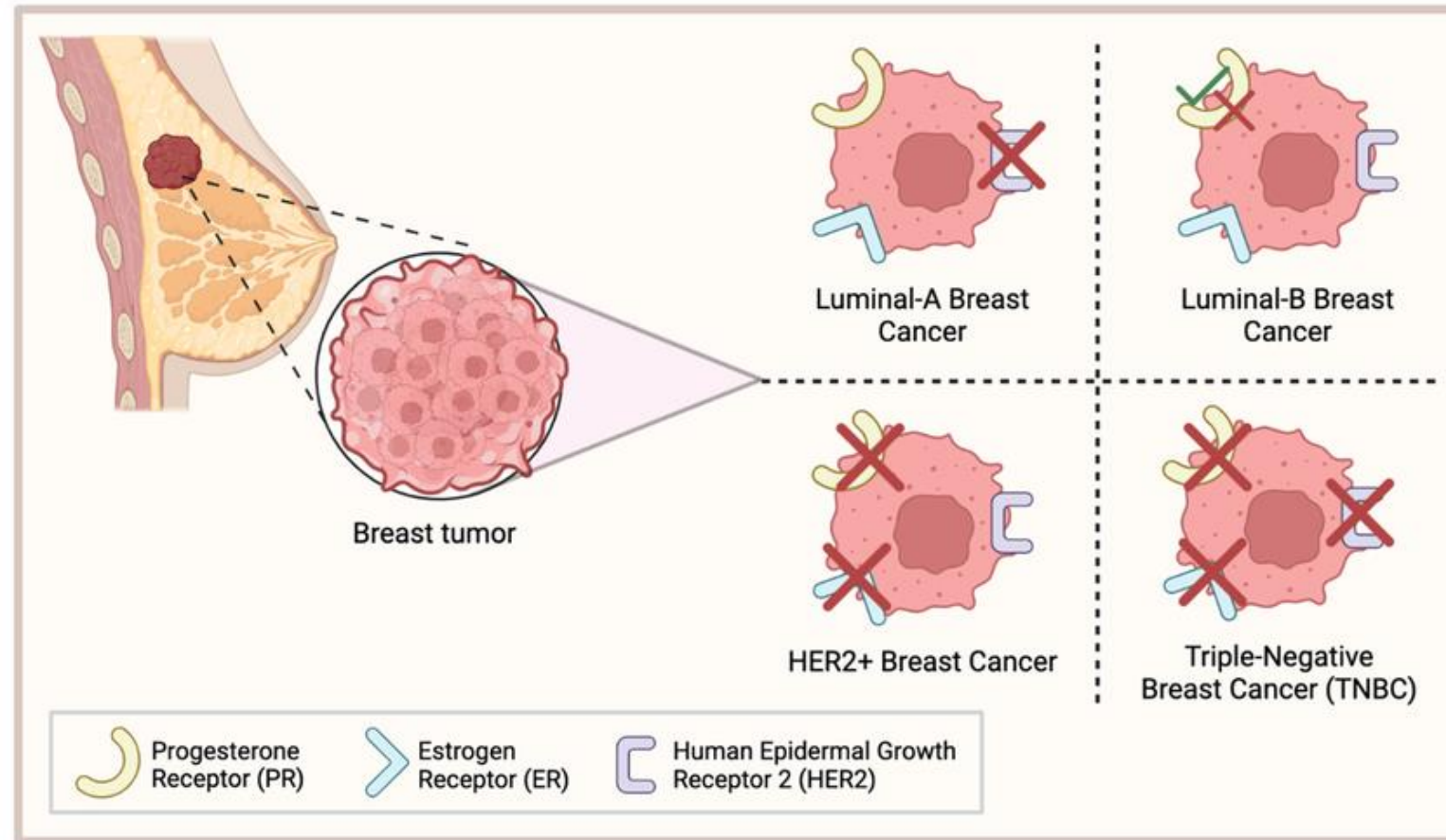
2025 **ESMO BREAST CANCER**

Annual Congress

MUNICH GERMANY
14-17 MAY 2025



Intro: hormoongevoelig borstcarcinooma



Overzicht



Een beetje geschiedenis



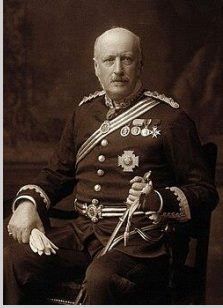
Huidige en nieuwe
endocriene behandelingen



Casussen



Tipje van de sluier:
toekomstige behandelingen



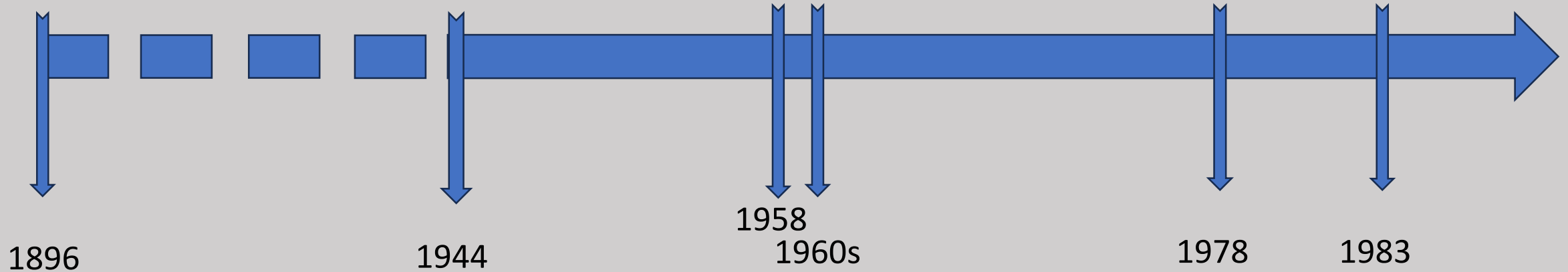
Bilaterale ovariectomie
(George Beatson)

Hoge dosis oestrogeen
(Haddow)

Ontdekking
oestrogeenreceptor
(Jensen)

Gosereline

Tamoxifen
adjuvant
(NATO trial)



Ontwikkeling tamoxifen
(ICI)

Soorten hormoontherapie

Oestrogeen receptor blokkers

- Tamoxifen (Adex)
- Fulvestrant (Faslodex)

Aromatase- inhibitoren

- Letrozole (BRA)
- Anastrozole (ARIMIDEX)
- Exemestane (AROMASIN)

Ovariële suppressie

- Chirurgisch
- Chemisch:
Gosereline (Zoladex)
 - LHRH-analoog

Casus: mevr. A, nu 77 jaar

1996 (48j): diagnose borstcarcinooma: lobulair, ER en PR positief, met axillaire kliermetastasen. Adjuvant chemo, RT, tamoxifen

2015 (67j): detectie van botmetastasen. APO: metastase ILA. ER+. Start tamoxifen + zolendronaat

2021 (73j): ziekteprogressie. Start letrozole + abemaciclib

2025: progressie thv botmetastasen lumbale wervelzuil

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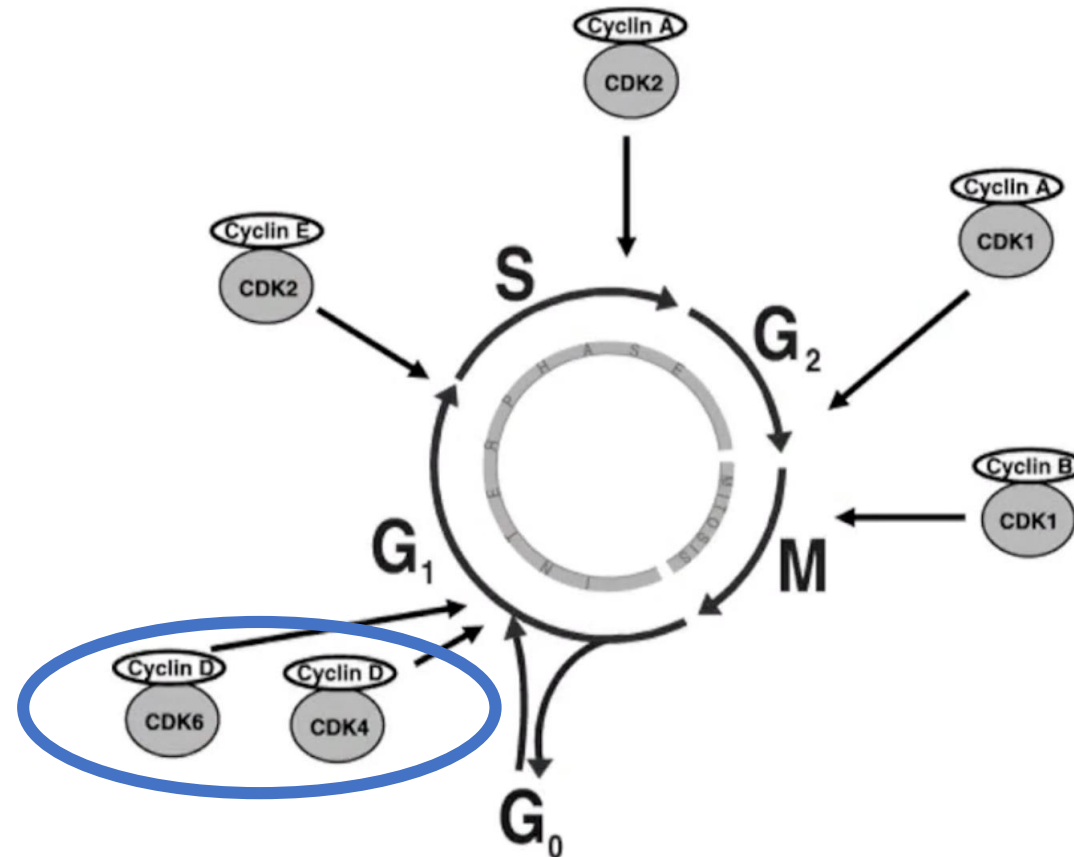
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Abemaciclib: werkingsmechanisme

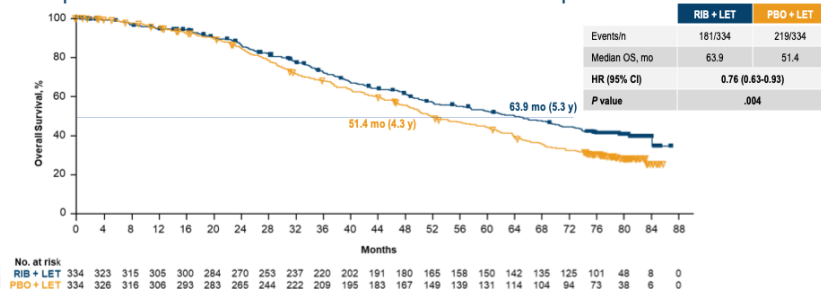


Cdk4/6 inhibitoren

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

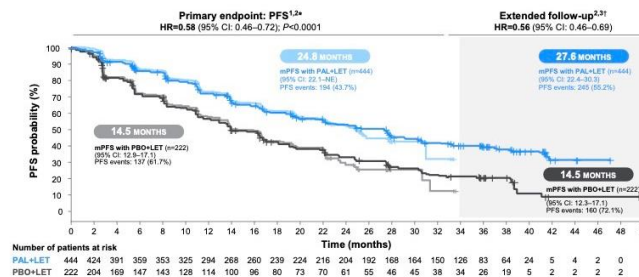
Ribociclib achieved statistically significant OS benefit in ML-2

Improvement in median OS was 12.5 months with ribociclib plus letrozole

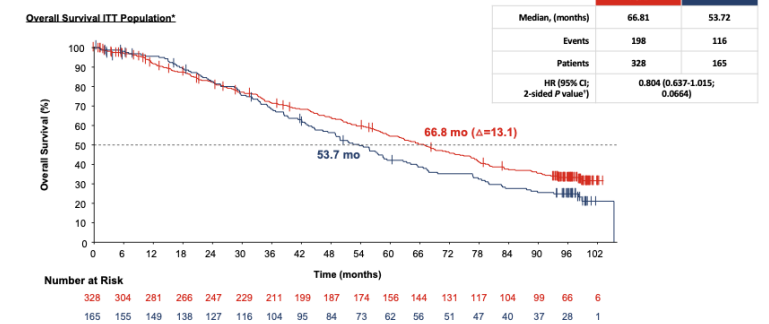


The P value of .004 crossed the prespecified boundary to claim superior efficacy

PALOMA-2: PFS Analyses



MONARCH 3: Final OS (ITT)



¹ Intent-to-treat population. Data cutoff: February 26, 2016.
² Intent-to-treat population. Data cutoff: May 31, 2017; post hoc analysis.
³ Confidence interval: HR=hazard ratio; LET=letrozole; NE=not estimable; PAL=palbociclib; PBO=placebo; mPFS=median progression-free survival.
⁴ Finn RS, et al. N Engl J Med. 2016;375:1925-1936. 2. Ruqo, HS, et al. Breast Cancer Res Treat. 2019;173:1-11.

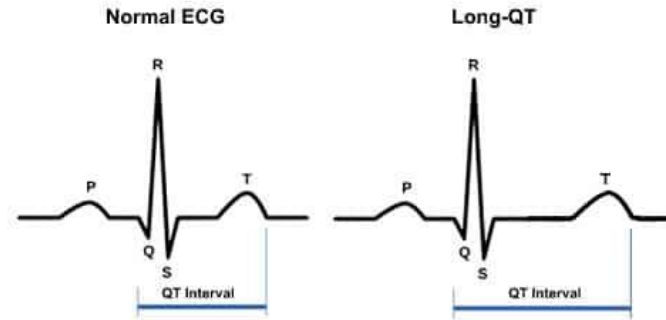
⁵ Data cutoff: September 28, 2023. *Calculated P-value threshold for statistical significance (2-sided) is 0.034.
 Abemaciclib, Circulone® (Abemaciclib); NSA=non-steroidal anti-inflammatory drug; OS=overall survival.
 Reference: Goss MF et al. Presented at: SABCS 2023. Abstract 5005.13.



Algemene nevenwerkingen cdk4/6 inhibitoren



Allergie

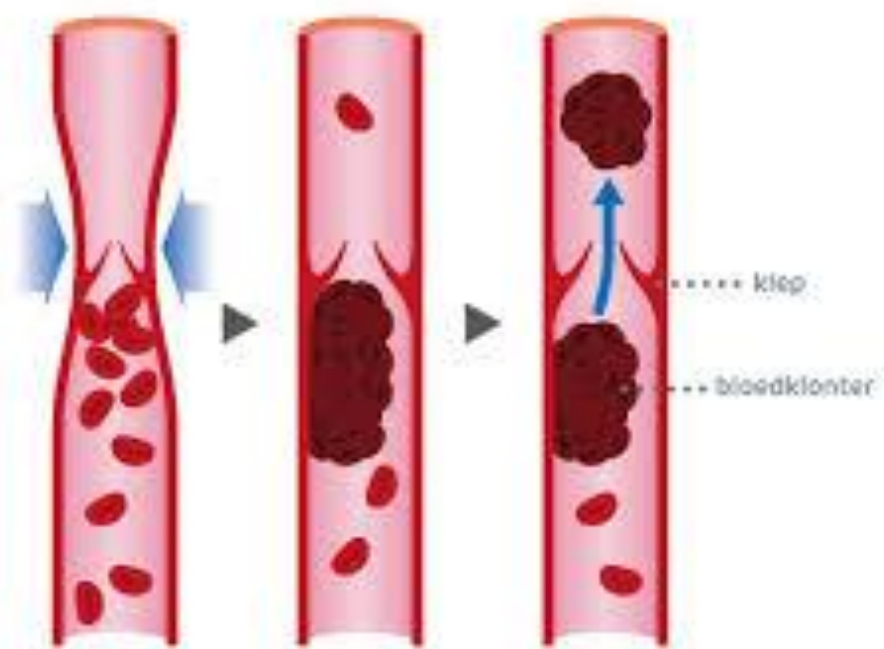


QT-verlenging

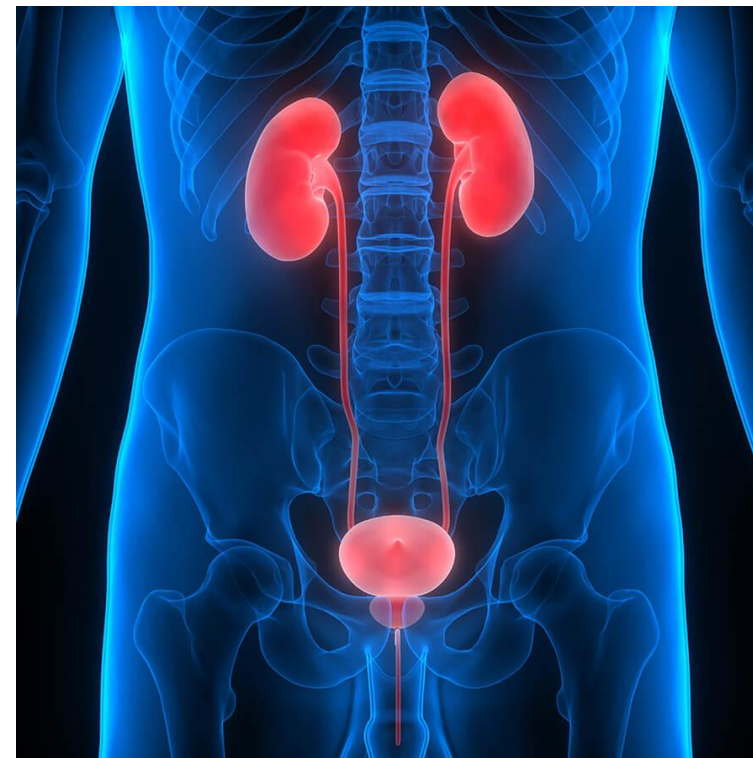


Leverfunctiestoornissen

Aandachtspunten ribociclib



Veneuze trombo-embolie



Creatinine stijging

Aandachtspunten abemaciclib

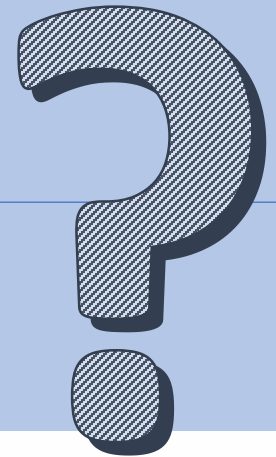
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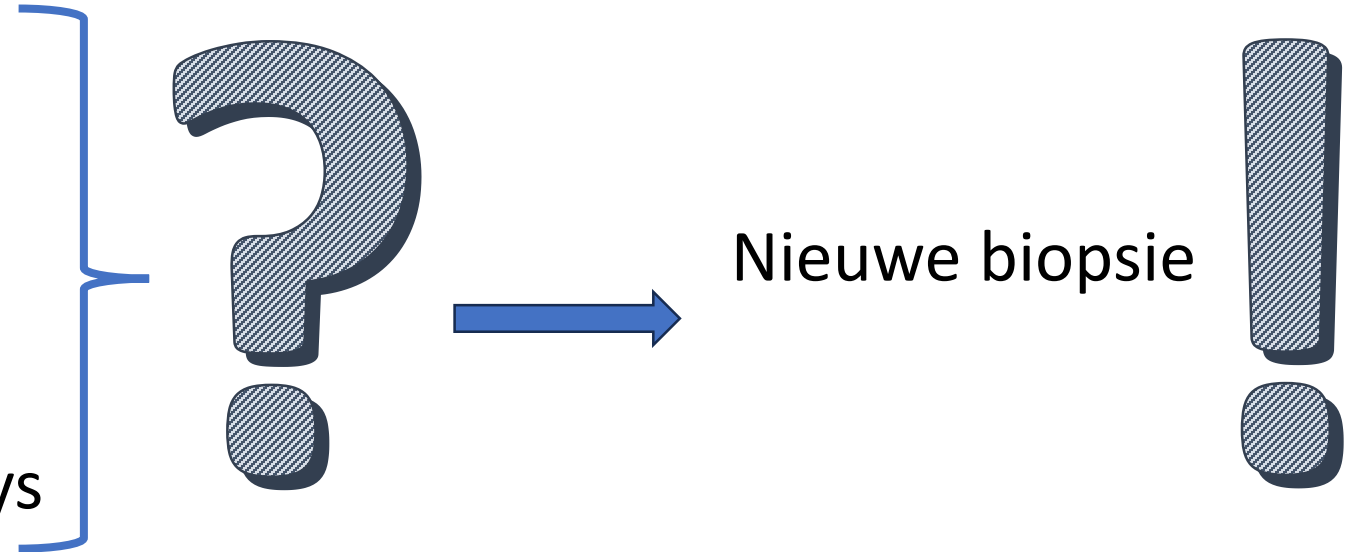
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Pathways voor endocriene resistentie

- Verlies van ER expressie
- Ontstaan van ESR1 mutatie
- Veranderde genexpressie
- Epigenetische veranderingen
- Activatie van nieuwe pathways



Nieuwe biopsie

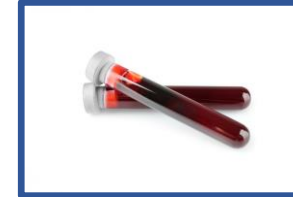


Bot



Bloed (liquid biopsy)

Nieuwe biopsie



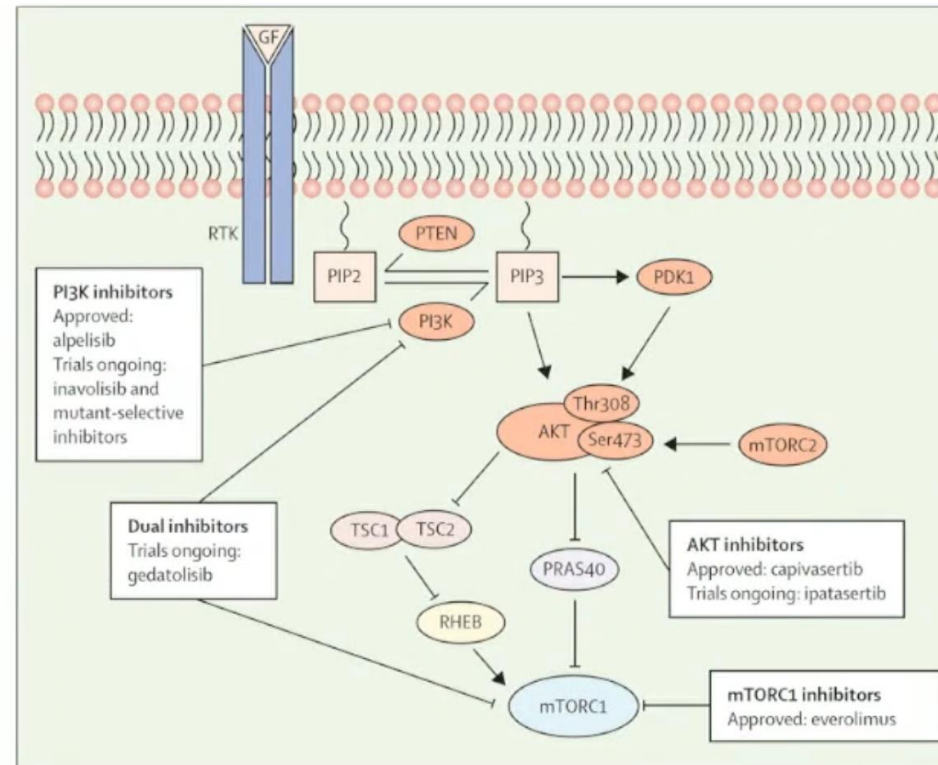
Weefselbiopsie	Liquid biopsy
Invasief	Niet invasief
Moeilijker te herhalen	Kan makkelijk herhaald worden
Representatief? (heterogene tumor)	Representatief
Langere turnover tijd	Snel resultaat (+/- 1 week)
Weefseldiagnostiek	Geen weefseldiagnostiek

Casus: mevr. A

- Resultaat botbiopsie:
 - Metastase lobulair borstcarcinooma, ER +
 - Next Generation Sequencing (NGS): **PIK3CA mutatie**



THE PI3K/AKT PATHWAY



Physiological functions:

- Cell growth and proliferation
- Cell survival and apoptosis inhibition
- Metabolism Regulation: glucose and lipid metabolism
- Neural development and function
- Angiogenesis
- Muscle growth and maintenance
- Immune system regulation

Browne IM et al. Lancet Oncol. 2024 Apr;25(4):e139-e151 | TCGA Nature 490:61-70, 2012; Ciriello G, Cell 163:506-19, 2015; Nik-Zainal S, Nature 534:47-54, 2016; Pereira B, Nat Commun 7:11479, 2016

2025 **ESMO BREAST CANCER**

Mafalda Oliveira, MD PhD

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APPROVED DRUGS TARGETING THE PI3K/AKT PATHWAY

HR+/HER2-negative advanced breast cancer

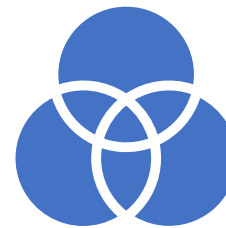
	Everolimus	Alpelisib	Inavolisib	Capivasertib
Mechanism of action	mTORC1 inhibitor	PI3K α -specific, non mutant selective inhibitor	PI3K α -specific, mutant-selective inhibitor	ATP-competitive pan-AKT inhibitor
Indication	After an AI	<i>PIK3CA</i> -mut, after ET-based regimen	<i>PIK3CA</i> -mut, progressing on or <12 months after adjuvant ET	At least one <i>PIK3CA</i> , <i>AKT1</i> or <i>PTEN</i> alteration, after ≥ 1 ET

ABC: advanced breast cancer; ET: endocrine therapy; HR: hormone receptor

Casus: mevr. A



Helaas geen nieuwe doelgerichte therapie beschikbaar momenteel



Opties zijn:

- Faslodex (fulvestrant) + verderzetten abemaciclib (?)
- Faslodex (fulvestrant) monotherapie
- Everolimus + endocriene therapie
- Start chemotherapie
- Deelname aan een klinische studie

Volgende casus: mevr. B, 76j

2017 (68j): bilateraal borstcarcinoma met klier-en botmetastasen

- APO (links + rechts): luminal B invasief ductaal carcinoma, ER en PR sterk positief.
- Start letrozole + ribociclib (+ deelname observationele studie)
- Langdurige partiële respons

2024 (75j): ziekteprogressie: levermetastasen

- Start fulvestrant
- Biopsie voor NGS + liquid biopsy

Casus: mevr. B, 76j.

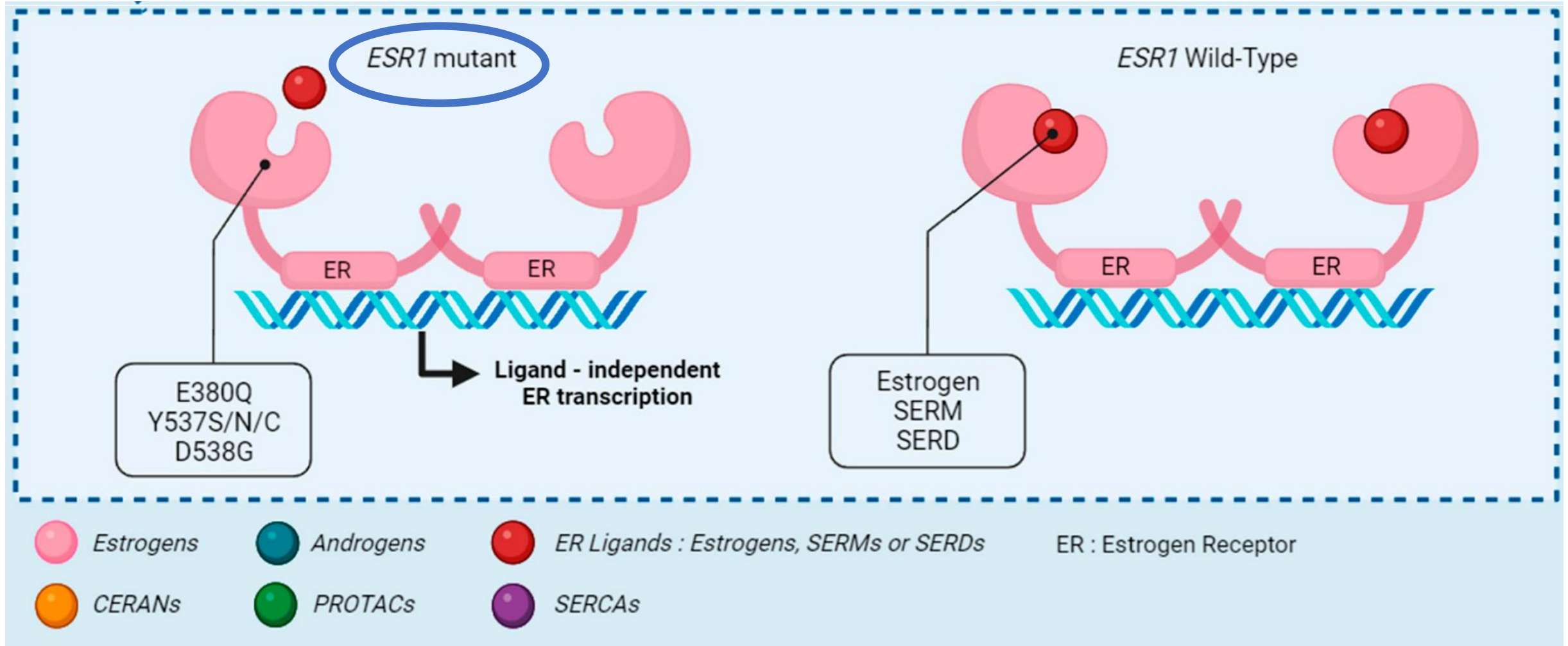


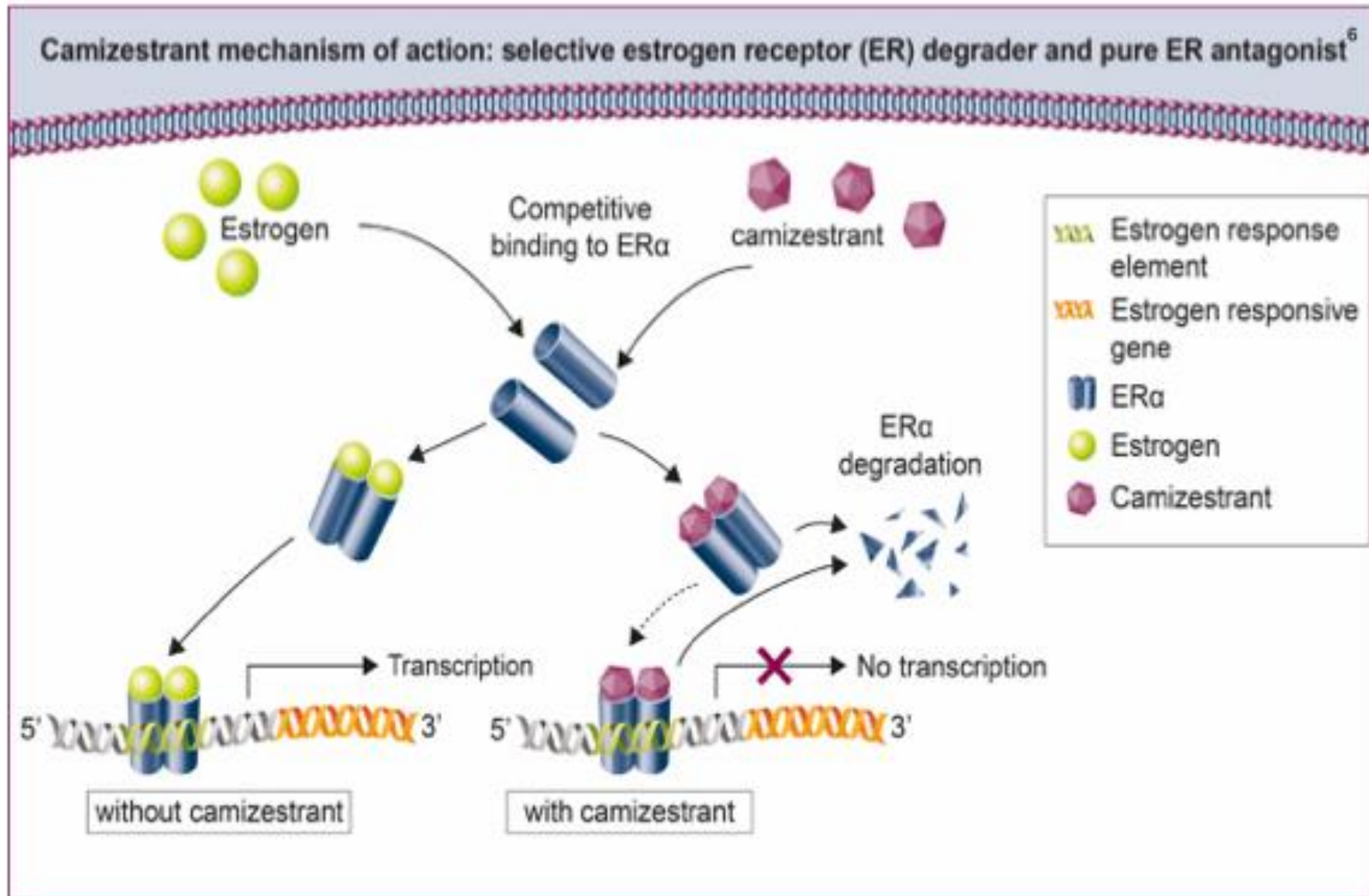
LIQUID BIOPSIE:
ESR1 MUTATIE



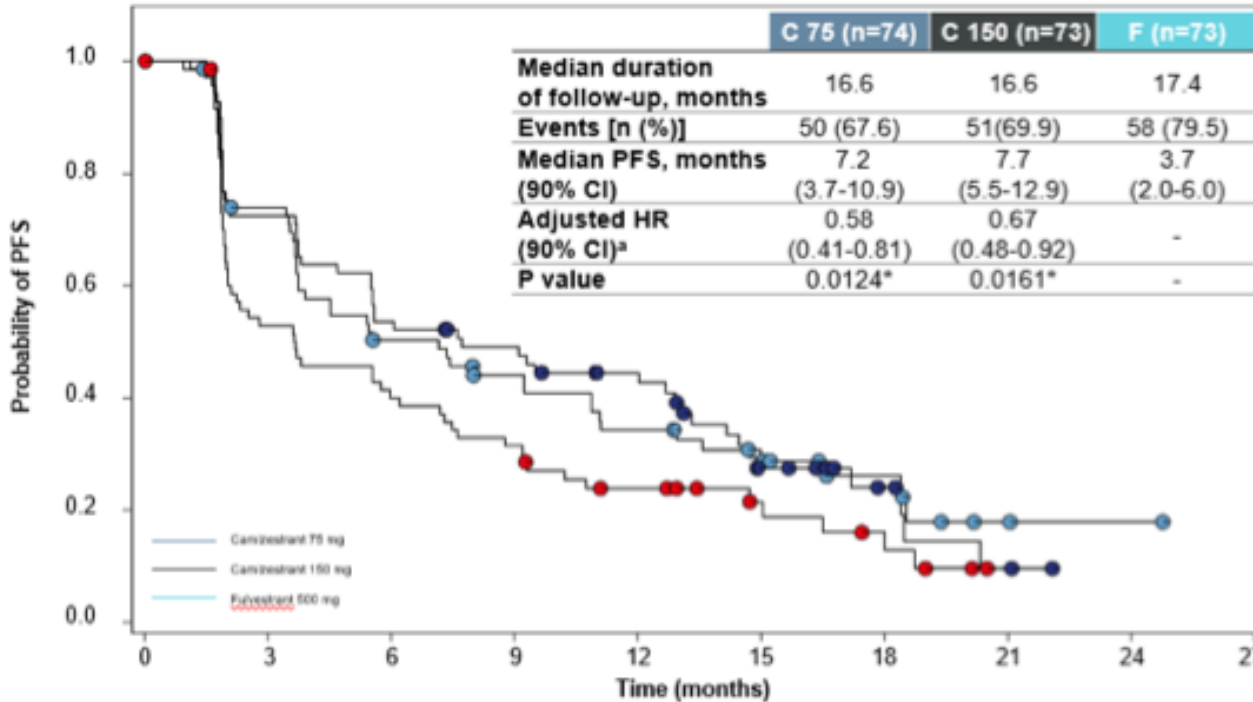
12/2024: START **ELACESTRANT**
(MEDICAL NEED PROGRAM)

SERD= Selective Estrogen Degradar





Primary endpoint: PFS by investigator assessment



Serena-2 studie

In the overall population, camizestrant produced a statistically significant and clinically meaningful improvement in PFS for both 75 and 150 mg camizestrant doses over fulvestrant

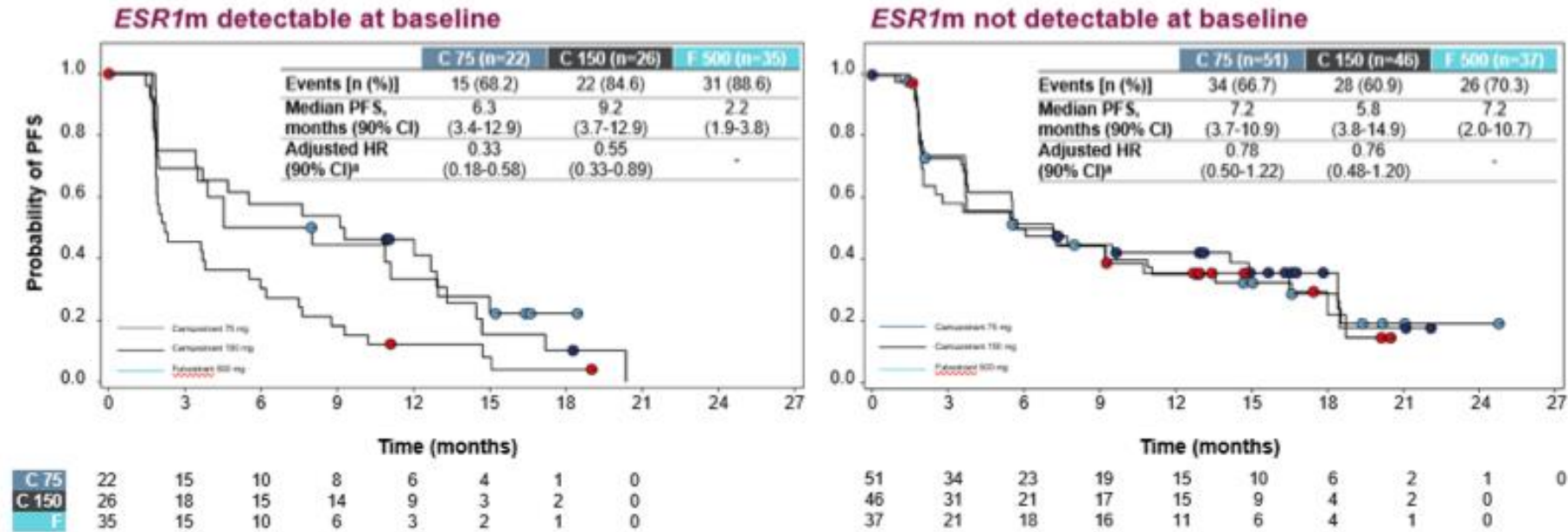
	C 75	C 150	F
74	50	33	27
73	50	32	25
73	37	22	14
			7
			2
			1
			0

aHRs adjusted for prior use of CDK4/6i and liver/lung metastases; bStatistically significant.

¹² C=camizestrant; CDK4/6i=cyclin dependent kinase 4/6 inhibitor; CI=confidence interval; F=fulvestrant; HR=hazard ratio; PFS=progression-free survival.

1. Oliveira M, et al. Presented at SABCS. 6–10 December 2022. San Antonio, TX. Abstract #GS3-02.

PFS in patients by detectable ESR1m



Serena-2 studie

In the sub-population of patients with detectable *ESR1m* at baseline, camizestrant at both doses produces a clinically meaningful improvement in PFS over fulvestrant

aHRs adjusted for prior use of CDK4/6i and liver/lung metastases.

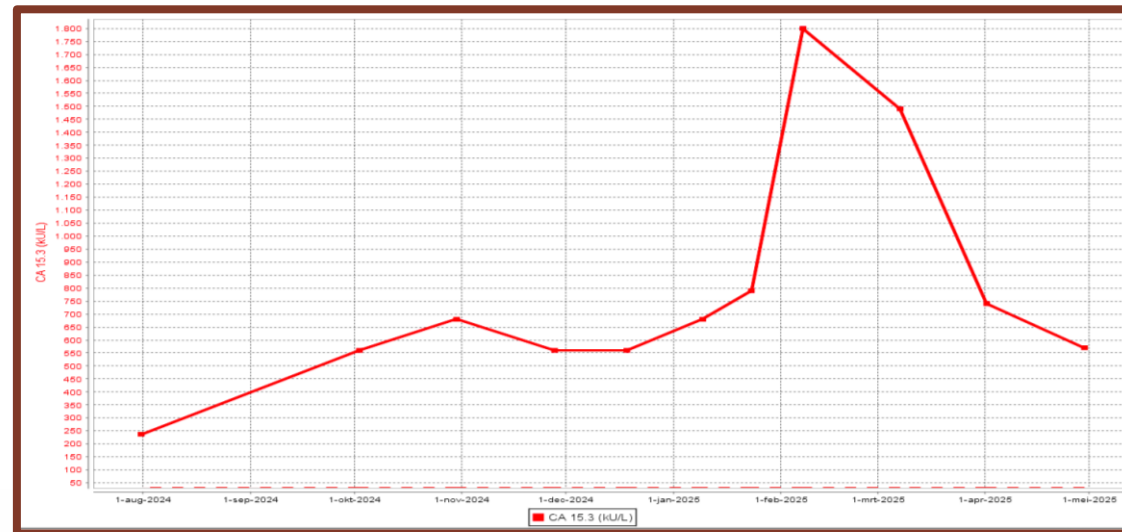
C=camizestrant; CDK4/6i=cyclin dependent kinase 4/6 inhibitor; CI=confidence interval; *ESR1m*: mutation in *estrogen receptor 1* gene; F=fulvestrant; HR=hazard ratio; PFS=progression-free survival.

15. Oliveira M, et al. Presented at SABCS. 6–10 December 2022. San Antonio, TX. Abstract #GS3-02.



Mevr. B

- 12/2024: start elacestrant (medical need programma)
- Partiële respons:
 - Dalende tumormerker CA15.3
 - Afname levermetastasen op PET-CT



Wat brengt de toekomst?

Nieuwe CDK inhibitoren: cdk2/4?

Nieuwe combinatie behandelingen

- SERD + CDK4/6?
- SERD + PI3K/AKT?
- Combinatie met immuuntherapie?

Meting ctDNA

- Snellere detectie van resistentie
- Snellere aanpassing van medicatie?
- Betere outcome?



Take home messages



Luminal borstkanker = hormoongevoelig borstkanker



Bij ziekteprogressie kan een nieuwe biopsie waardevolle info opleveren



Liquid biopsy als alternatief/ voorkeur



Compliance is belangrijk: motiveer uw patiënt!



Bij optreden endocriene resistentie:

Nieuwere doelgerichte therapie ifv mutatie

Deelname aan klinische studie

Chemotherapie

**Stay
tuned!
Volgende
keer
meer
nieuws**



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Bedankt voor uw aandacht!

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Medisch oncoloog Jessa en Sint-Franciscus