XXIII JORNADA DE REVISIÓN DEL

CONGRESO AMERICANO DE ONCOLOGÍA

ASCO'23: *Highlights* en Cáncer de mama metastásico

23 de junio de 2023

Ana Godoy Ortiz

Hospitales Regional Universitario y
Virgen de la Victoria, Málaga

COIs Disclosures

Employment: UGCI O. Médica de Málaga: Hospitales Regional Universitario y Virgen de la Victoria de Málaga

Consultant or Advisory Role: Novartis, Pfizer, Roche, Astra-Zeneca, Daichii-Sankyo, SeaGen, Gilead, MSD, and Lilly

Research Funding (clinical trial participation as PI): Novartis, Lilly, Gilead, Sermonix, MSD, GSK

Speaking: Novartis, Roche, Lilly , Pfizer, MSD

Optimizing 1st Line Therapy for HR+/HER2- MBC

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- **#Q3#** **Early switch after biological progression:** is there a benefit to early therapy based on ctDNA dynamics?

- **#Q4#** **Extend CDK4/6i:** Does endocrine backbone switch (with continued CDK4/6i) effectively extend 1st line therapy?
  - *Previous evidence: Neither phase III; favorable outcomes for continued ribociclib after CDK4/6i progression (MAINTAIN); PEACE trial with negative results.*

#Q1# Personalize CDK4/6i

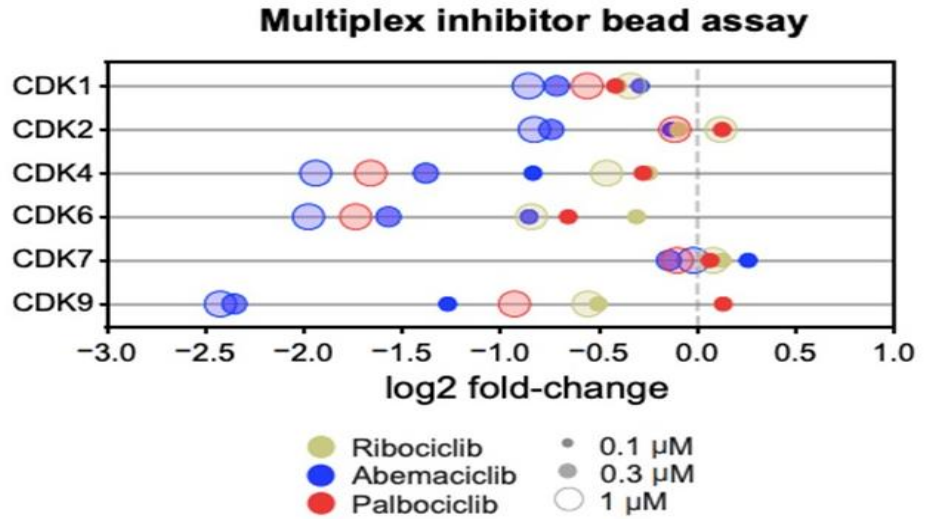
PFS-OS data → Different studies, different designs, different study populationts and subgroup definitions

	PALOMA-2	MONALEESA-2	MONARCH-3
Phase	Phase 3	Phase 3	Phase 3
Line	1st line	1st line	1st line
Endocrine tx	Letrozole	Letrozole	Letrozole or anastrozole
CDK4/i	Palbociclib	Ribociclib	Abemaciclib
Patients (n)	666	668	493
PFS Hazard Ratio	0.58	0.56	0.54
PFS (months)	24.8 vs 14.5	25.3 vs 16	28.2 vs 14.8
OS Hazard Ratio	0.96	0.76	0.75
OS (months)	53.9 vs 51.2	63.9 vs 51.4	67.1 vs 54.5

Finn *NEJM* 2016; Hortobagyi *NEJM* 2016; Goetz *J Clin Oncol* 2017; Finn, *ASCO* 2022; Hortobagyi *NEJM* 2022; Goetz *ESMO* 2022

CDK4/6i are NOT identical pharmacologically

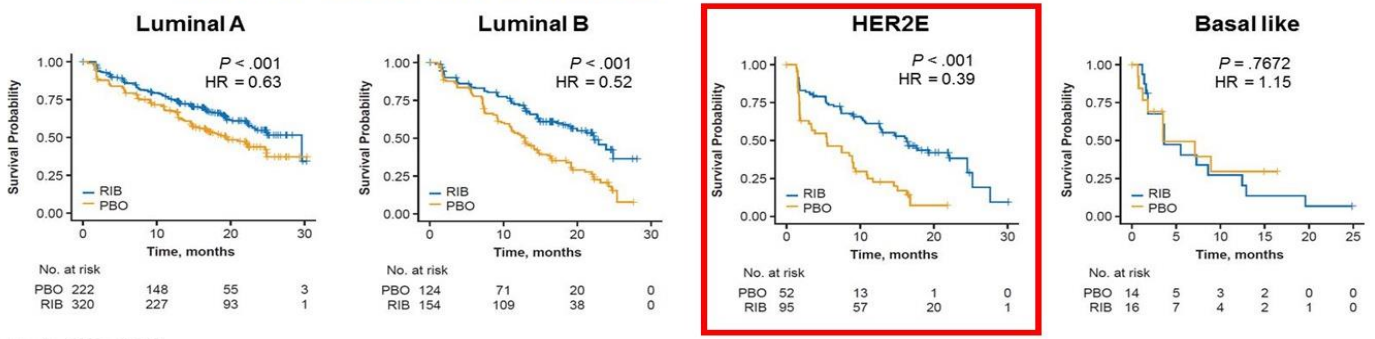
(Ribo CDK4>6; Abema CDK1, CDK2)



Hafner *Cell Chem Bio* 2019

Differences by molecular subtype?

- MONALEESA studies:



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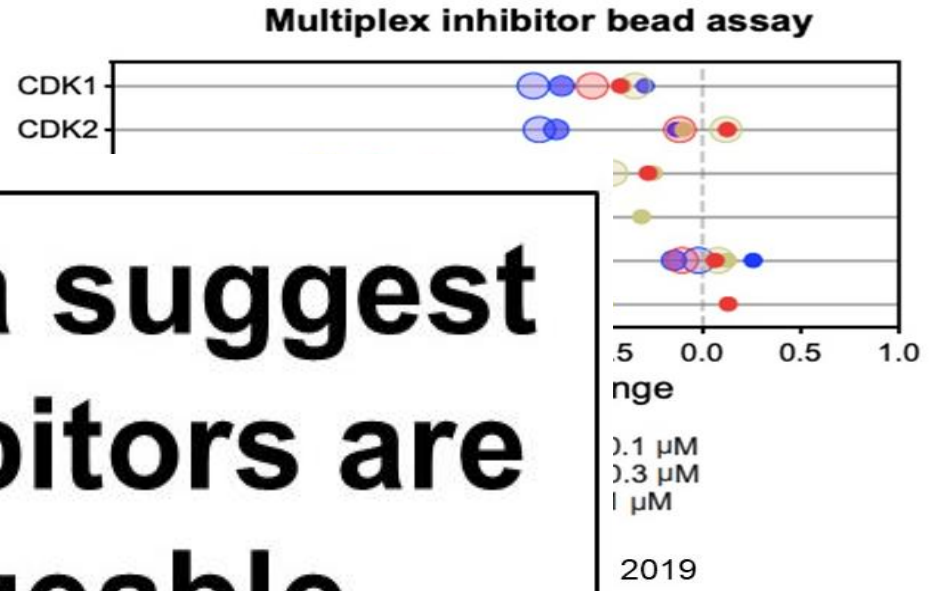
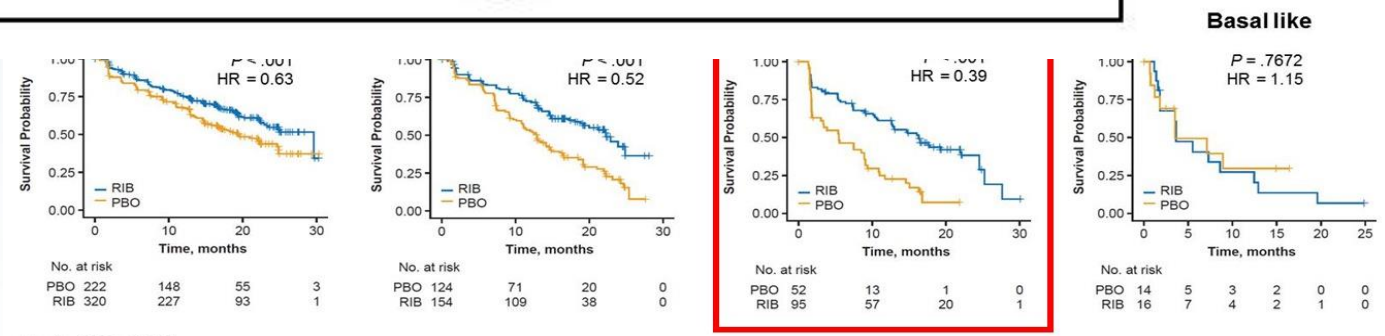


Increasingly, data suggest that CDK4/6 inhibitors are not interchangeable

Differences by molecular subtype?



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#Q2# Can certain patients delay CDK4/6i

Patients with HR+/HER2- ABC
- Pre- and postmenopausal women
- Measurable or evaluable disease
- (Neo)adjuvant therapy allowed *
- No prior therapy for ABC
- No visceral crisis
- N = 1050

Randomization (1:1)

Stratified by CDK4/6i, visceral disease and prior (neo)adjuvant endocrine treatment

- non-steroidal AI + CDK4/6i → Fulvestrant
- non-steroidal AI → Fulvestrant + CDK4/6i

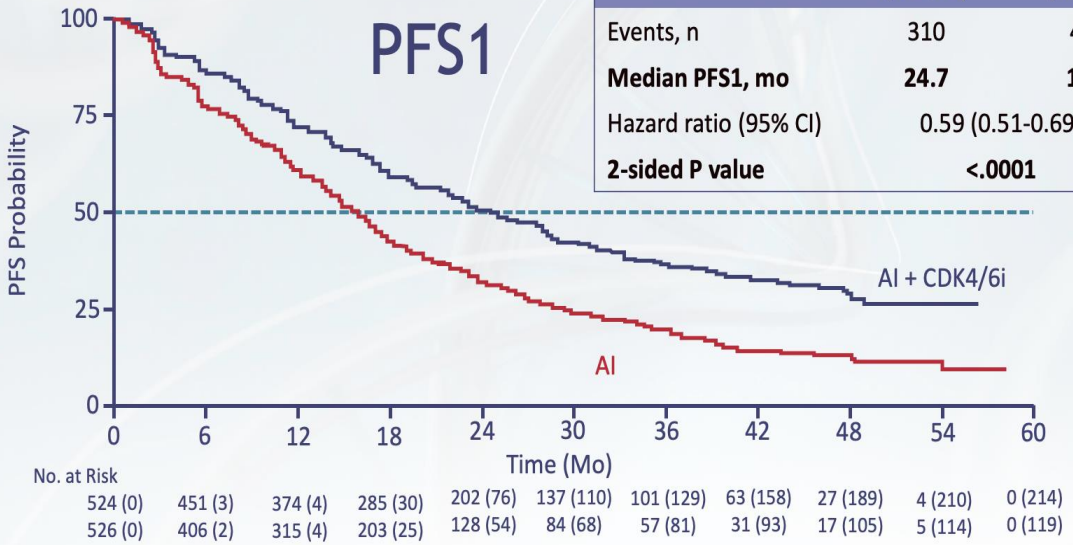
Primary endpoint
- PFS after 2 lines (PFS2)

Secondary endpoints
- Quality of life
- Overall survival
- Cost-effectiveness

Primary outcome analysis of the phase 3 SONIA trial (BOOG 2017-03)

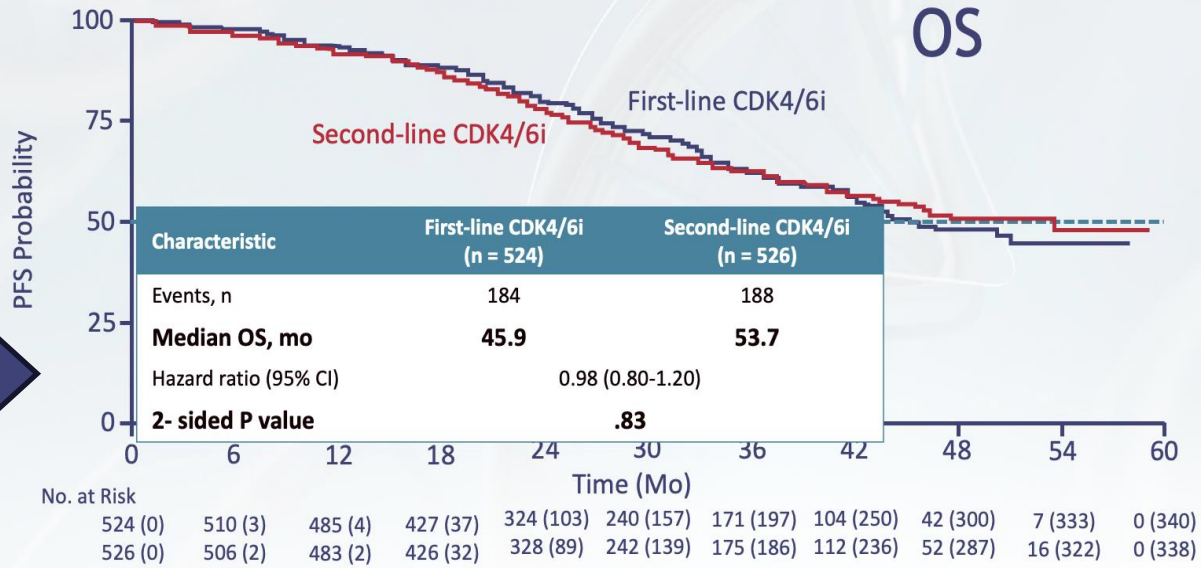
Gabe Sonke, Annemiek van Ommen - Nijhof, Noor Wortelboer, Vincent van der Noort, Astrid Swinkels, Hedwig Blommestein, Aart Beeker, Karin Beelen, Lisanne Hamming, Joan Heijns, Aafke Honkoop, Paul de Jong, Quirine van Rossum - Schornagel, Christa van Schaik - van de Mheen, Jolien Toi, Cathrien Tromp - van Driel, Suzan Vrijaldenhoven, Elise van Leeuwen - Stok, Inge Konings, Agnes Jager

PFS1



Characteristic	AI + CDK4/6i (n = 524)	AI (n = 526)
Events, n	310	407
Median PFS1, mo	**24.7**	**16.1**
Hazard ratio (95% CI)	0.59 (0.51-0.69)	
2-sided P value	**<.0001**	

OS



Characteristic	First-line CDK4/6i (n = 524)	Second-line CDK4/6i (n = 526)
Events, n	184	188
Median OS, mo	**45.9**	**53.7**
Hazard ratio (95% CI)	0.98 (0.80-1.20)	
2- sided P value	**.83**	

Median follow up: 37.3 mo

- Majority of patients posmenopausal (>80%)
  DFI > 24mo around 47% with 1/3 de novo stage IV
- Visceral disease in more than 55 % of patients
  CDK4/6i employed: 91% palbociclib

Sonke. ASCO 2023. Abstr LBA1000.

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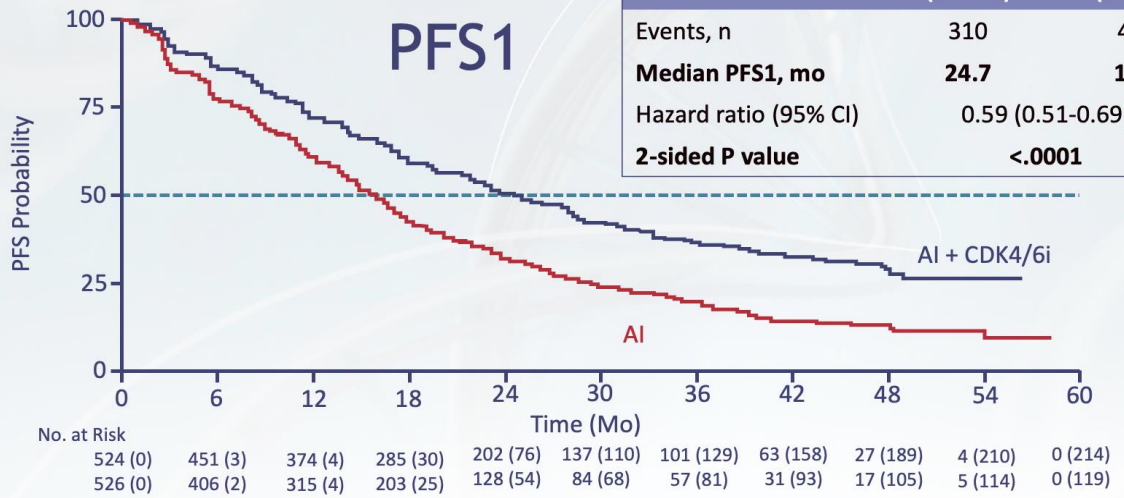
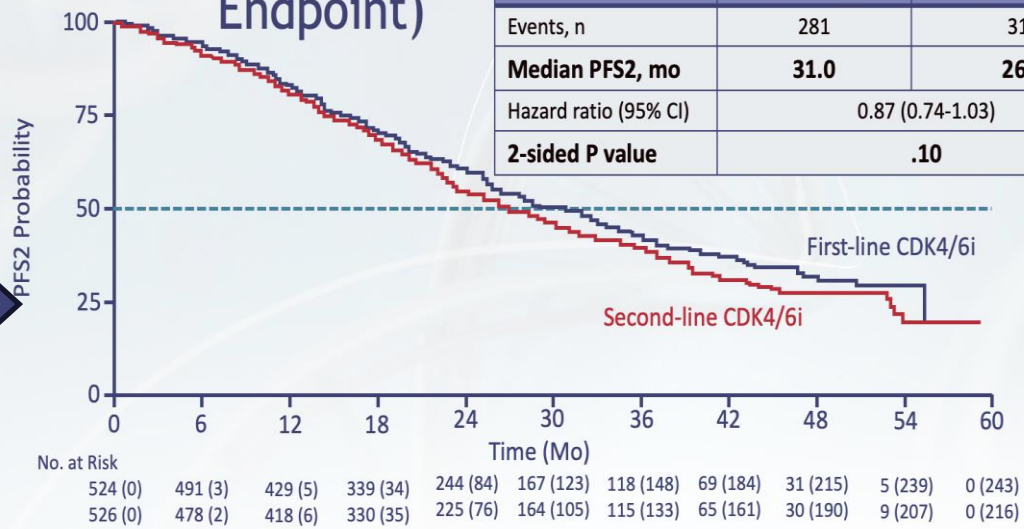


Median follow up: 37.3 mo

PFS2 (Primary Endpoint)

Characteristic	First-line CDK4/6i (n = 524)	Second-line CDK4/6i (n = 526)
Events, n	281	310
Median PFS2, mo	**31.0**	**26.8**
Hazard ratio (95% CI)	0.87 (0.74-1.03)	
2-sided P value	**.10**	



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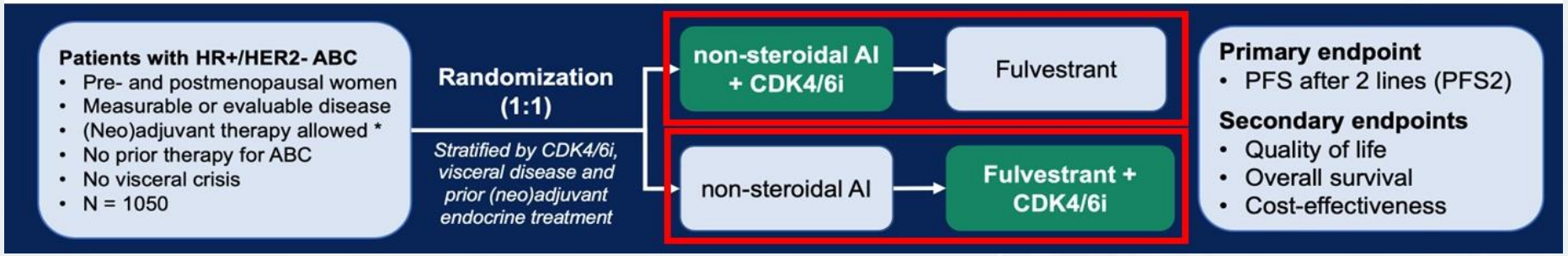

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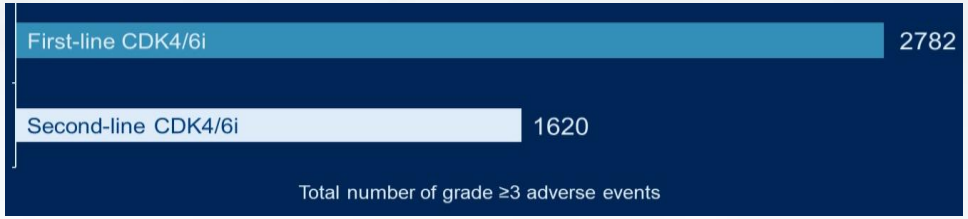
PFS2 Subgroup Analyses

Subgroup, n/N	First-line CDK4/6i (n = 524)	Second-line CDK4/6i (n = 526)	Hazard Ratio (95% CI)	P Value
Prior (neo)adjuvant ET				
▪ No	126/266	151/272	0.81 (0.64-1.02)	.34
▪ Yes	155/258	159/254	0.95 (0.76-1.19)	
Prior (neo)adjuvant CT				
▪ No	153/312	183/316	0.78 (0.63-0.97)	.12
▪ Yes	128/212	127/210	1.01 (0.79-1.30)	
De novo metastatic disease				
▪ No	186/342	202/344	0.89 (0.73-1.09)	.62
▪ Yes	95/182	108/182	0.79 (0.59-1.05)	
Visceral disease				
▪ No	118/233	136/234	0.80 (0.62-1.02)	.42
▪ Yes	163/291	174/292	0.93 (0.75-1.15)	
Bone-only disease				
▪ No	237/433	258/435	0.90 (0.75-1.08)	.33
▪ Yes	44/91	52/91	0.64 (0.42-0.98)	
CDK4/6 inhibitor				
▪ Pabociclib	257/472	267/447	0.86 (0.72-1.02)	.55
▪ Ribociclib	24/51	39/72	1.05 (0.61-1.79)	

Limited signal on WHO can delay CDK4/6i treatment

Safety and QoL

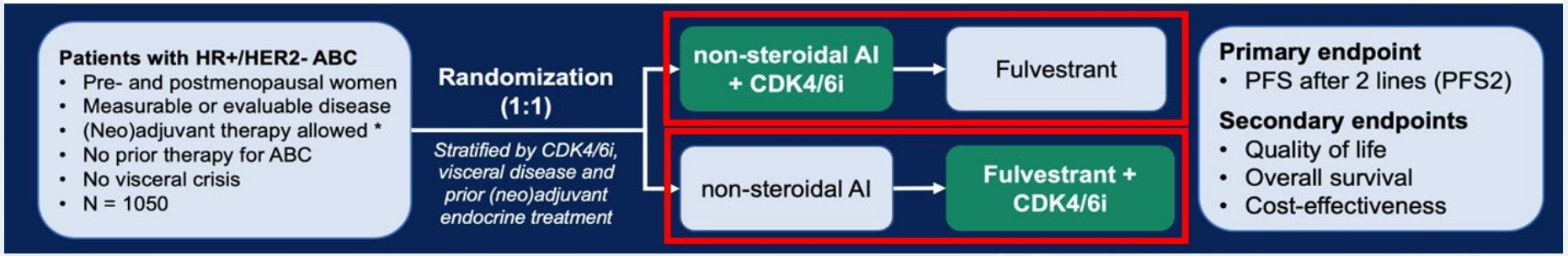
Substantially (42%) more ≥ grade 3 AEs with 1st line vs 2nd line CDK4/6 inhibitors use



- QoL *(FACT-B and EQ-5D-5L at up to 11 time points)*
  - ✓ No difference observed between study arms (p = 0.4)

Sonke. ASCO 2023. Abstr LBA1000.

SONIA: Summary



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CDK4/6 inhibition in 1st line compared to 2nd line

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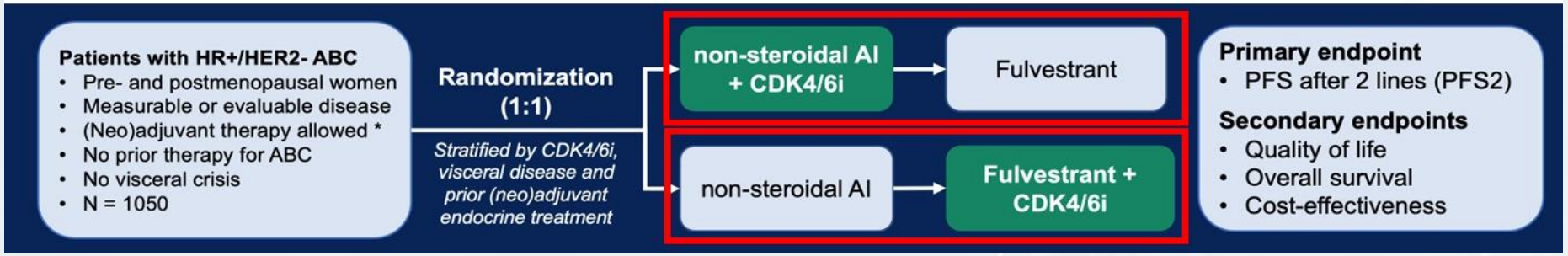

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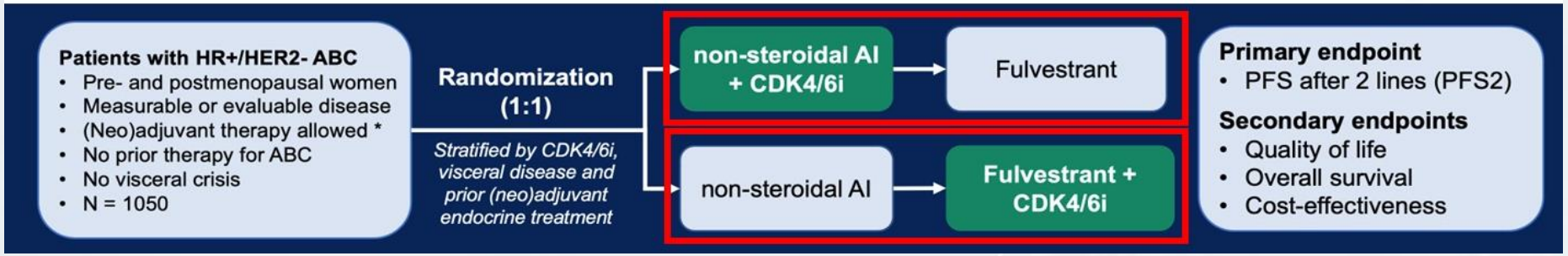

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- Increase incidence of grade 3-4 toxicity by 42%

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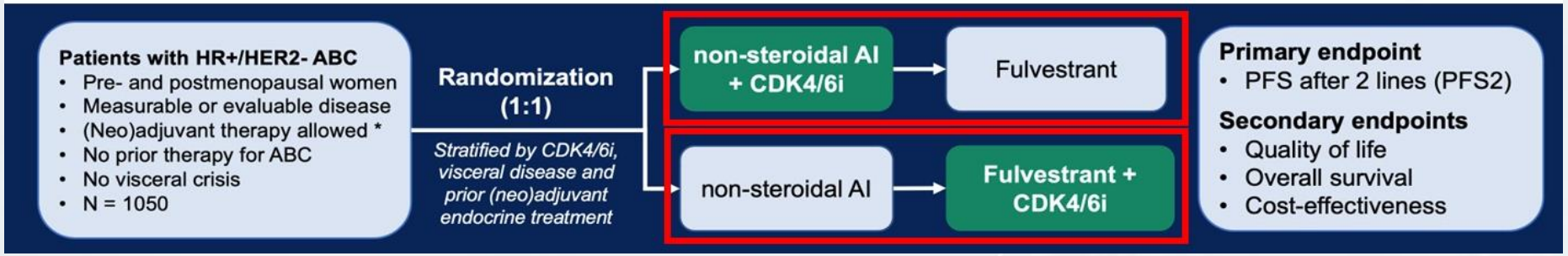

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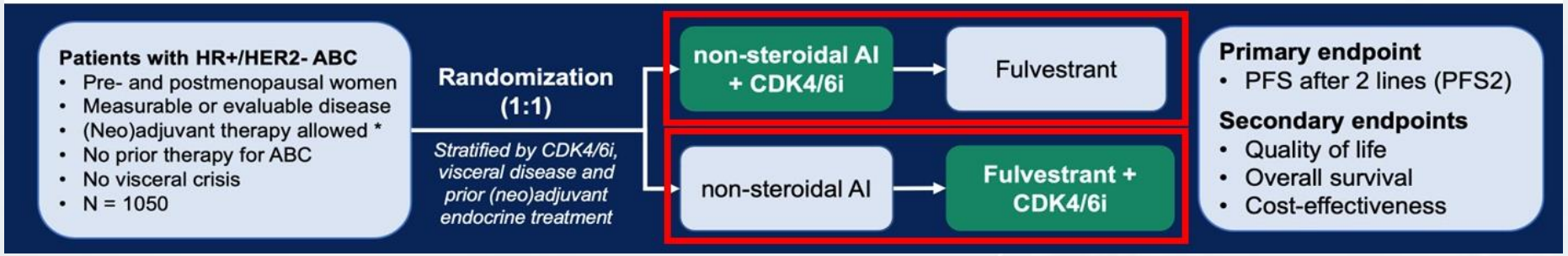

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BUT…

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#Q2# Can certain patients delay CDK4/6i

Key outstanding questions:

- **Optimal 2nd line therapy? …Probably NOT…**
- **Does CDK4/6i matter?** Over 90% received Palbociclib
  - ✓ Better outcomes for OS with ribociclib and abemaciclib
- **Patients reported outcomes:**
  - ✓ Duration on CDK4/6i: 24.6 mo (1st line) vs 8.4 mo(2nd line) --< fewer AEs 2nd line
  - ✓ Inferior costs

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Who are the very good risk patients who can delay CDK4/6i?

- Historically, a consistent subset of patients have good and prolonged disease control with ET alone
- Urgently need of additional biomarkers: ctDNA profiling and dinamycs, microbiome, RNA-based?

Sonke. ASCO 2023. Abstr LBA1000.

#Q3# Benefit of early switch based on ESR1mut ctDNA

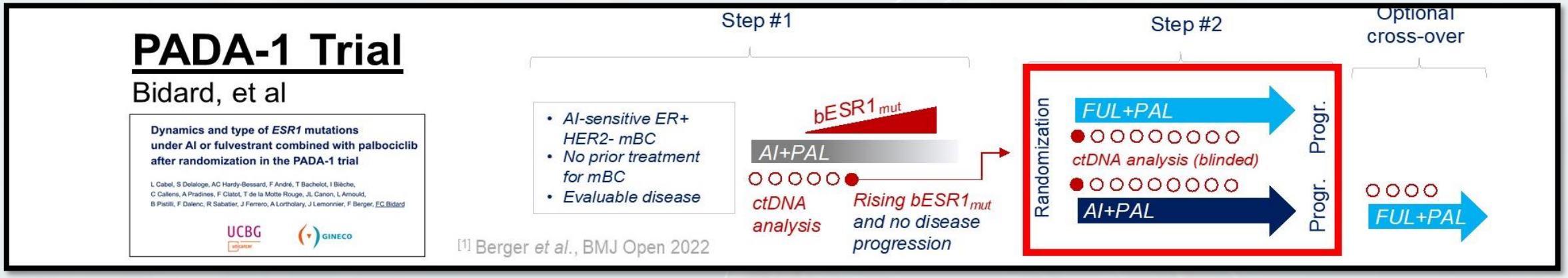
PADA-1 Trial

Bidard, et al

Dynamics and type of *ESR1* mutations under AI or fulvestrant combined with palbociclib after randomization in the PADA-1 trial

L Cabel, S Delaloge, AC Hardy-Bessard, F André, T Bachelot, I Bièche, C Callens, A Pradines, F Clatot, T de la Motte Rouge, JL Canon, L Arnould, B Pistilli, F Dalenc, R Sabatier, J Ferrero, A Lortholary, J Lemonnier, F Berger, FC Bidard

UCBG GINECO



[1] Berger *et al.*, BMJ Open 2022

N= 1,017 pts enrolled in step #1

N= 283 pts with a rising *bESR1*$_{mut}$

while the study was ongoing

N= 172 pts randomized

- N= 88 pts allocated to FUL+PAL
- N= 84 pts allocated to AI+PAL

Data cut-off: June 21, 2022

Median FU from randomization: 28.2 months; N= 152 PFS events (89% maturity)

[2] Bidard *et al.*, Lancet Oncol 2022

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Step #1

- *AI-sensitive ER+ HER2- mBC*
- *No prior treatment for mBC*
- *Evaluable disease*

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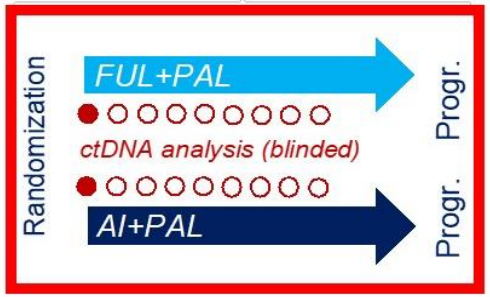
Step #2



Optional cross-over

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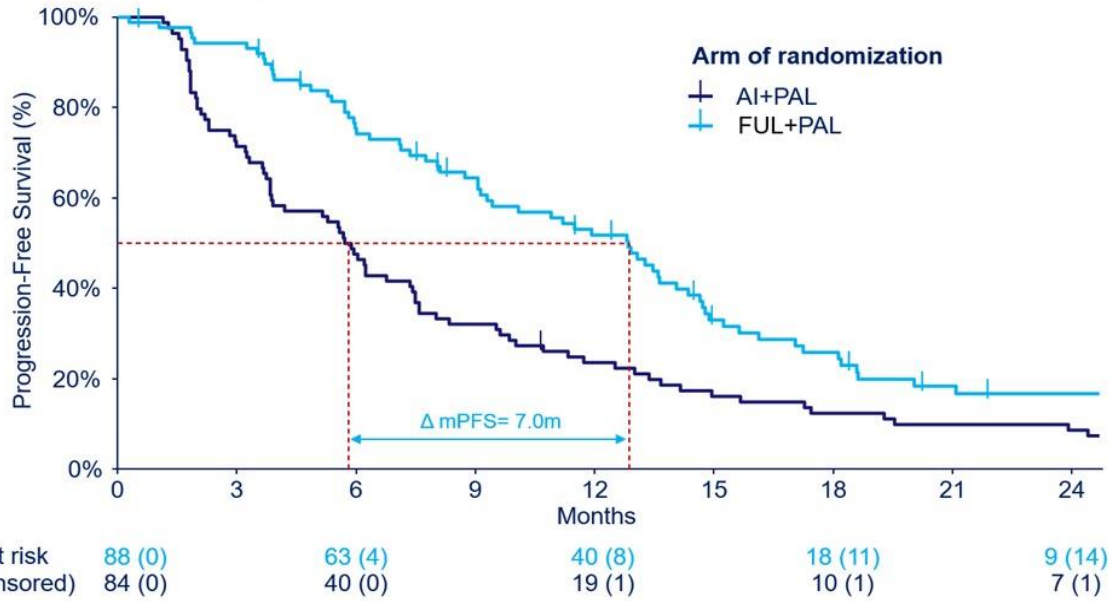
Progression-Free Survival, from randomization



FUL+PAL mPFS: 12.8 months, 95%CI [9.3;14.7]

AI+PAL mPFS: 5.8 months, 95%CI [3.9;7.5]

PFS HR= 0.54 [0.38;0.75]

Optional cross-over (N=49 patients)

mPFS: 3.5 months, 95%CI [2.4;5.4]

2021 analysis [2]

N=134 events

11.9 months

5.7 months

0.61

3.5 months

[2] Bidard *et al.*, Lancet Oncol 2022

#Q3# Benefit of early switch based on ESR1mut ctDNA

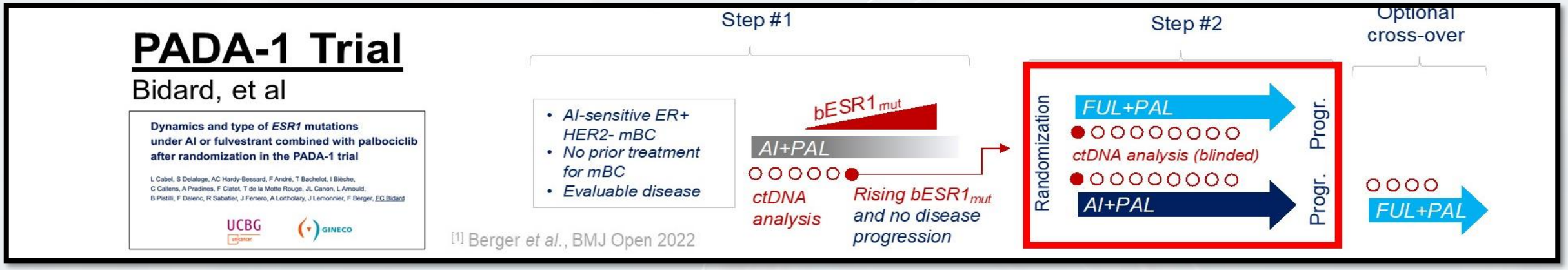
PADA-1 Trial

Bidard, et al

Dynamics and type of *ESR1* mutations under AI or fulvestrant combined with palbociclib after randomization in the PADA-1 trial

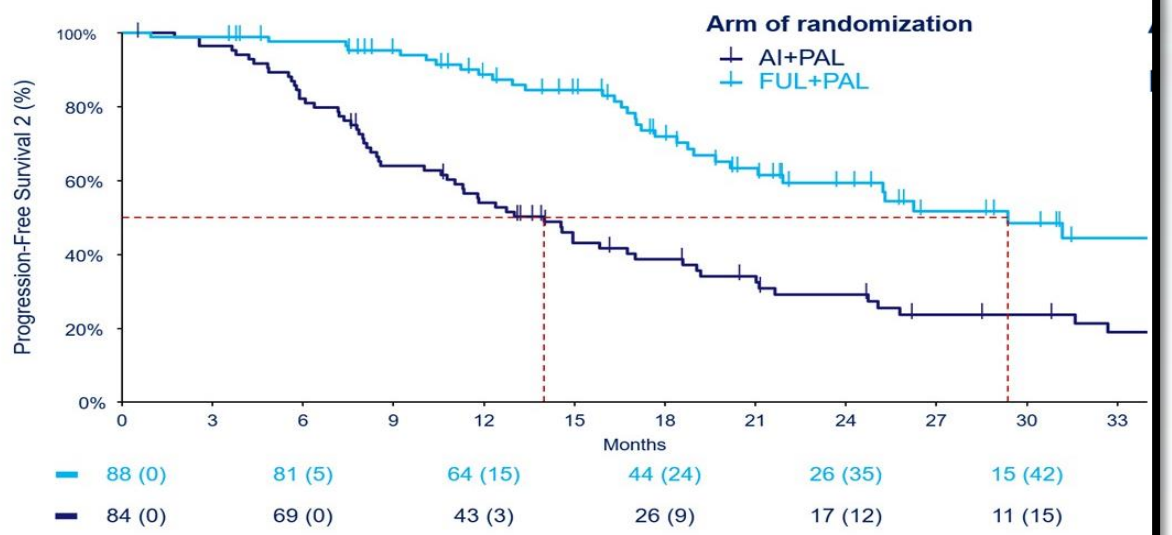
L Cabel, S Delaloge, AC Hardy-Bessard, F André, T Bachelot, I Bièche, C Callens, A Pradines, F Clatot, T de la Motte Rouge, JL Canon, L Arnould, B Pistilli, F Dalenc, R Sabatier, J Ferrero, A Lortholary, J Lemonnier, F Berger, FC Bidard

UCBG GINECO



[1] Berger *et al.*, BMJ Open 2022

Data cut-off: June 21, 2022 N= 93 PFS2 events (54% maturity)



Update results PFS2

FUL+PAL mPFS2: 29.4 months, 95%CI [21.9;NR]

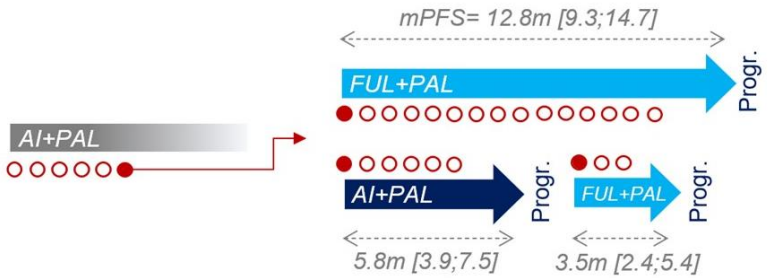
AI+PAL mPFS2: 14.0 months, 95%CI [11.0;18.6]

PFS2 HR= 0.37 [0.24;0.56]

#Q3# Benefit of early switch based on ESR1mut ctDNA

Mutation features & dynamics:

ctDNA kinetics: methods



Exploring *bESR1$_{mut}$* kinetics in a new clinical setting with **low ctDNA levels** (≠ usual liquid biopsy)

- *bESR1$_{mut}$* detection was performed using a laboratory-developed ddPCR assay [2,3]
- QC & feasability in PADA-1 have been previously reported [4]
- Mutation typing was performed on left-over plasma samples by panel NGS [4] in N=95 patients, of whom 88 were randomized

Rising *bESR1$_{mut}$*

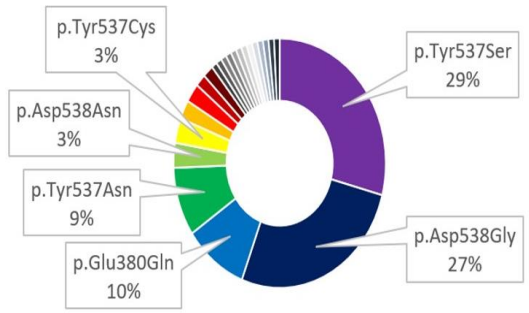
Among 172 randomized patients

Median level of *bESR1$_{mut}$*: 14 copies /ml$_{plasma}$ range: 4-1033 copies

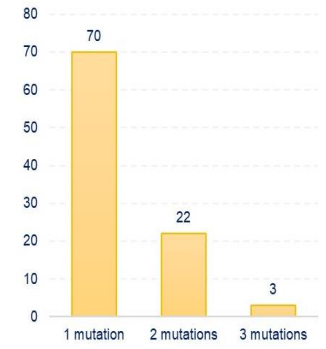
0.8% MAF range: 0.1-25 %

No imbalance observed between arms

Mutation type

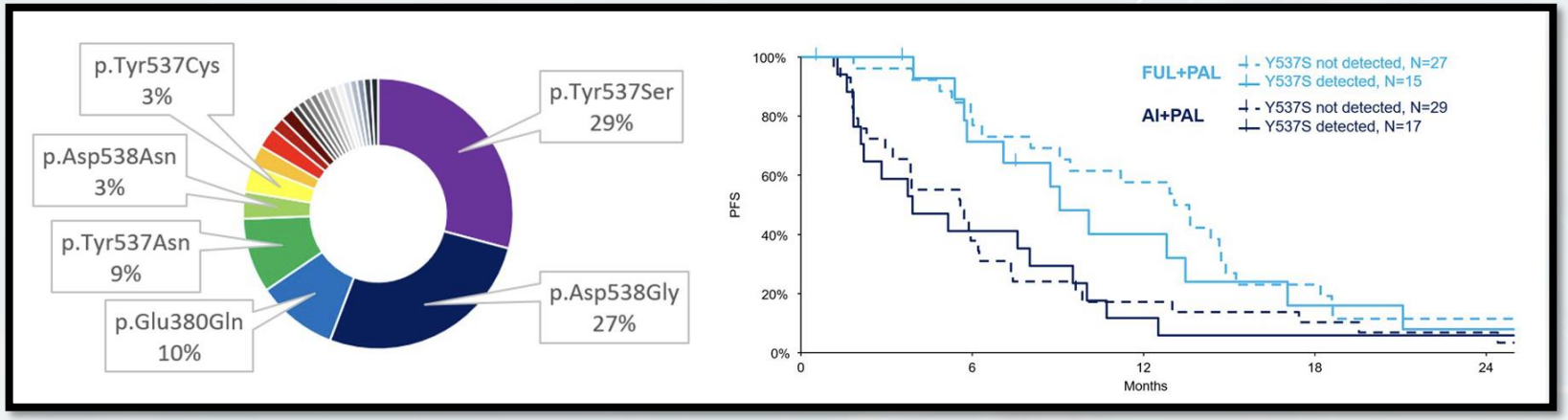


Polyclonality observed in 26% of pts

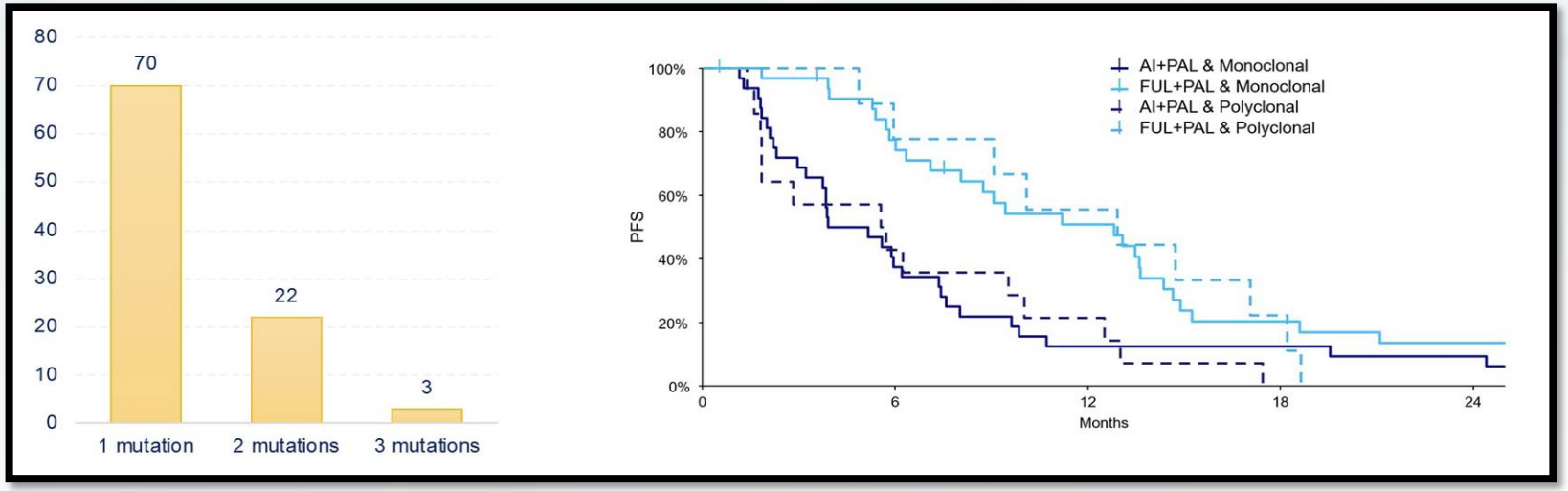


#Q3# Benefit of early switch based on ESR1mut ctDNA

Mutation features & dynamics did not significantly predict switch benefit



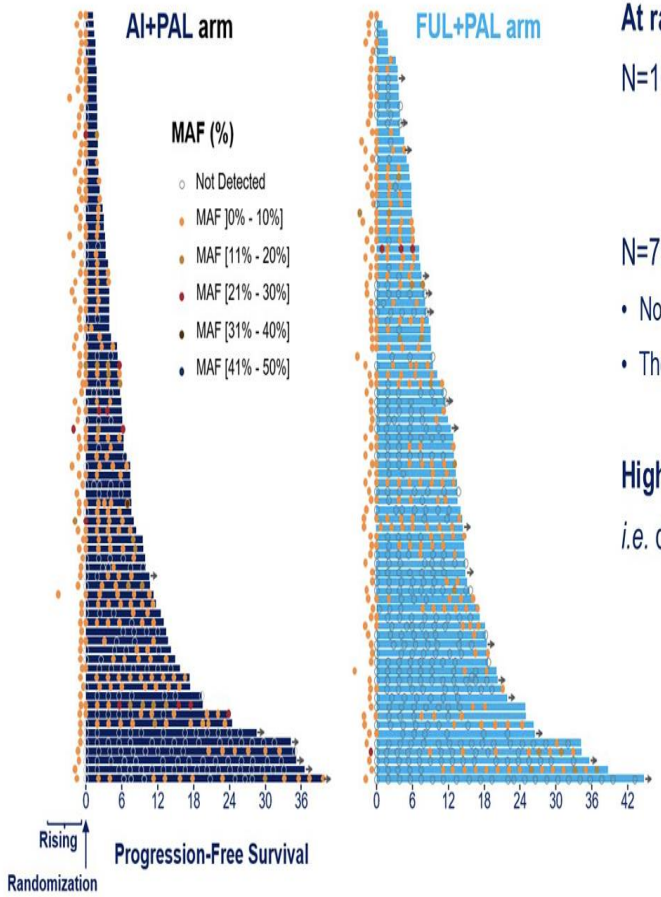
- No difference by which ESR1mut



- No difference if polyclonal ESR1mut

#Q3# Benefit of early switch based on ESR1mut ctDNA

bESR1$_{mut}$ kinetics from randomization



At randomization

N=161 pts had a 2nd ctDNA result available

(AI+PAL was continued until randomization)

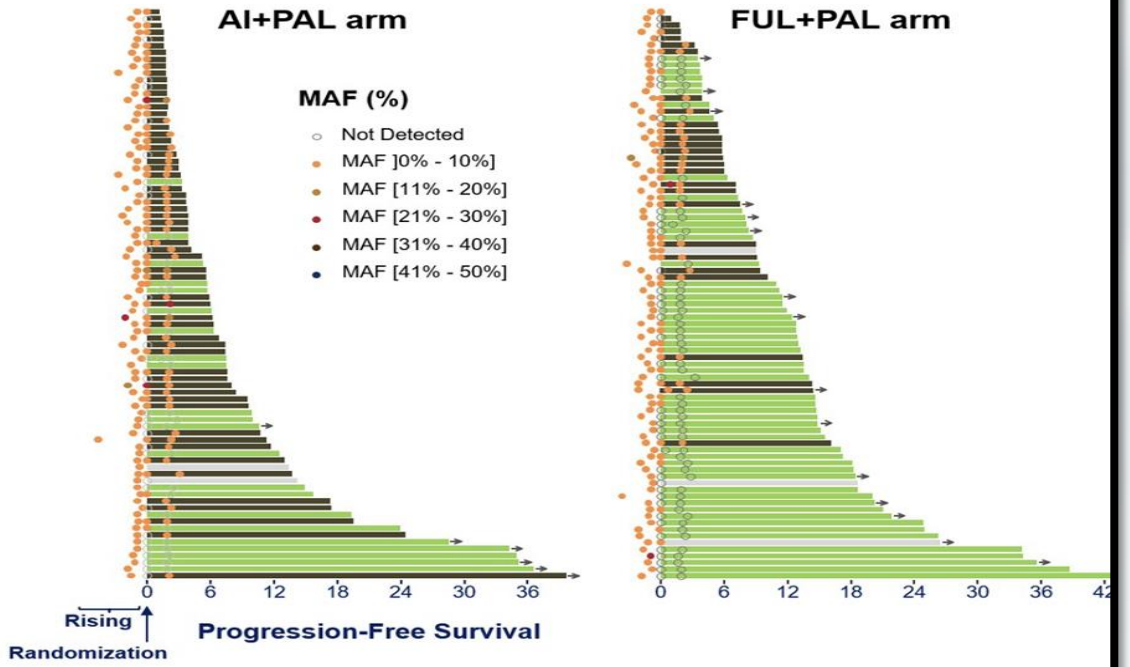
N=75/161 (46.6%) had no *bESR1*$_{mut}$ detected

- No difference between arms
- These patients globally had lower levels of rising *bESR1*$_{mut}$ (p=0.01)

Highlight the specific context of 'rising' mutations

i.e. detection made at the limit of sensitivity of the ctDNA assay

bESR1$_{mut}$ after 2 months on therapy



N=163 pts with ctDNA results available at 2 months

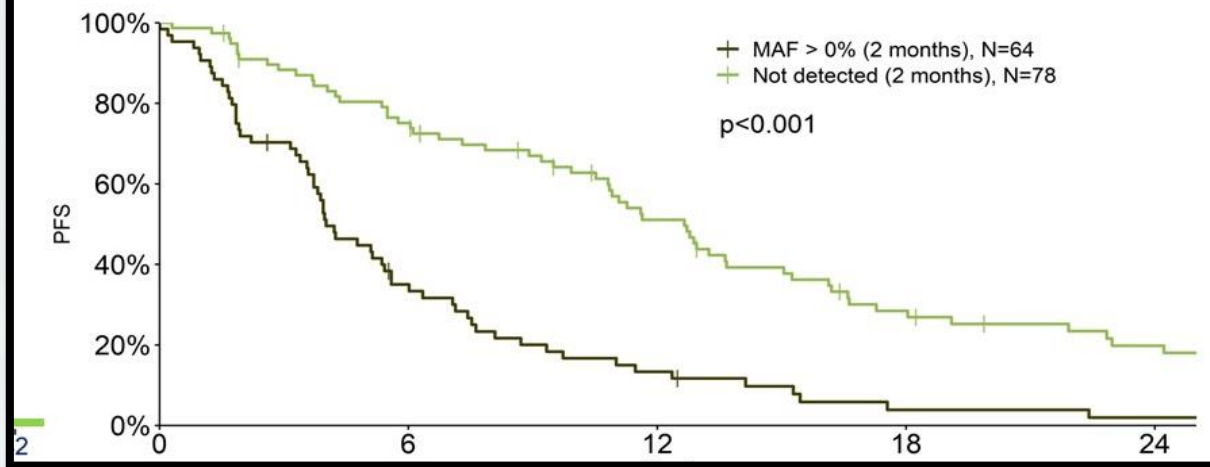
Undetectability rate:

FUL+PAL: N=58/85 68.2% [58.3%;78.1%]

AI+PAL: N=25/78 32.1% [21.7%;42.4%]

#Q3# Benefit of early switch based on ESR1mut ctDNA

PFS by mutation status at 2 months (landmark analysis)

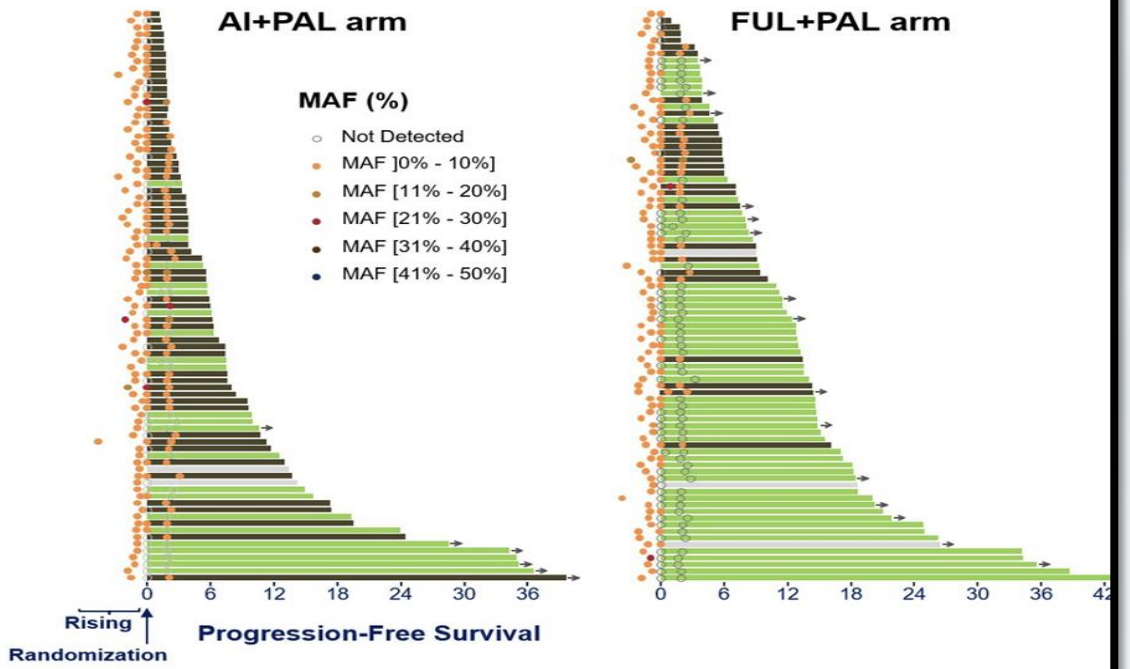


bESR1$_{mut}$ status at 2mo = **independent prognostic factor for PFS**
(Cox model with landmark analysis)

- In all randomized pts, **HR=0.35** [0.24;0.52])
- In pts with *bESR1*$_{mut}$ detected at randomization, **HR=0.52** [0.29;0.93]

The other prognostic factor in multivariate analysis was age >60
HR=0.57 [0,38; 0,87]

bESR1$_{mut}$ after 2 months on therapy



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#Q3# Benefit of early switch based on ESR1mut ctDNA

bESR1$_{mut}$ at progression and during cross-over

Detection rate at progression

- N=144 pts with available results at progression
- N=111 (78.2%) had a *bESR1*$_{mut}$ detected at progression
  82.7% in AI+PAL arm *vs* 73.1% in FUL+PAL arm (NS)

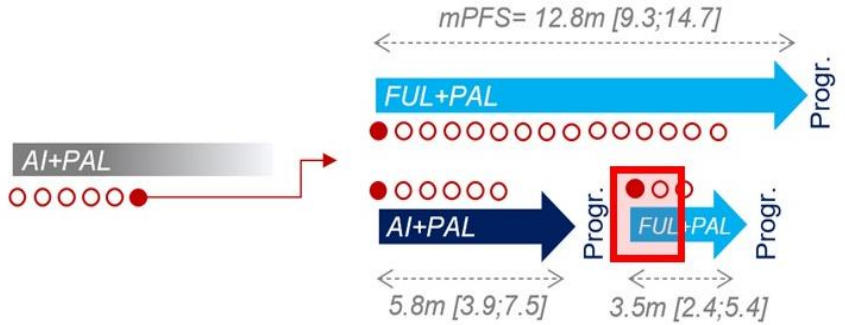
Levels of *bESR1*$_{mut}$ at progression

- Median (copies): 68/mL, range: 0-3557
- Median (MAF): 2.4%, range: 0-40.8
- No significant difference between arms

Increased *vs* 'rising'

Type of *bESR1*$_{mut}$ at progression (NGS done in N=26 pts)

- More frequent polyclonal mutations: N=18/26 (69.2%)
- More frequent Y537S mutations: N=13/26 (50%)
- No significant difference between arms



Kinetics during cross-over (N=33 pts assessable at 2 mo)

- Undetectability rate at 2 months: 27% (N=9/33)

Limited 'molecular efficacy' of FUL in the cross-over cohort

#Q3# Benefit of early switch based on ESR1mut ctDNA

Key outstanding questions:

- **Overall survival data**
  - ✓ Very interesting PFS2 data – *types of therapy post-FULV+Palbo treatment??*
- **Does CDK4/6i matter?**
- **Logistical challenges and cost of serial ctDNA?**

ctDNA clearance at 2 months associated with good PFS & irrespective of arm

Sonke. ASCO 2023. Abstr LBA1000.

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ctDNA clearance at 2 months associated with good PFS & irrespective of arm

Are there certain situations where this may be particularly useful?

- Indeterminate progression (biological progression alone)
- Bone only/bone dominant metastatic breast cancer?

Sonke. ASCO 2023. Abstr LBA1000.

#Q3# Benefit of early switch based on ESR1mut ctDNA

ASCO Guidelines

Testing for *ESR1* Mutations to Guide Therapy for Hormone Receptor–Positive, Human Epidermal Growth Factor Receptor 2–Negative Metastatic Breast Cancer: ASCO Guideline Rapid Recommendation Update

Testing for *ESR1* Mutations to Guide Therapy for HR-Positive, HER2-Negative Metastatic Breast Cancer: ASCO Guideline Rapid Recommendation Update			
Recommendation	**Type**	**Evidence Quality**	**Strength**
To aid in treatment selection, the Expert Panel recommends routine testing for emergence of *ESR1* mutations at recurrence or progression on ET (with or without CDK4/6 inhibitor) in patients with ER-positive, HER2-negative MBC. Testing with a CLIA-certified assay should be performed on blood or tissue obtained at the time of progression, as ESR1 mutations develop in response to selection pressure during treatment and are typically undetectable in the primary tumor;[1] blood-based ctDNA is preferred owing to greater sensitivity.[2] If not performed earlier, testing for *PIK3CA* mutations should also be performed to guide further therapy. Patients whose tumor or ctDNA tests remain *ESR1* wildtype may warrant retesting at subsequent progression(s) to determine if an *ESR1* mutation has arisen.	EB	H	S
Patients previously treated with ET and a CDK4/6 inhibitor for advanced breast cancer have several therapeutic options if choosing to continue endocrine-based approaches. For patients with prior CDK4/6 inhibitor treatment and *ESR1* wildtype tumors, appropriate subsequent ET options include fulvestrant, aromatase inhibitor, or tamoxifen monotherapy, or ET in combination with targeted agents such as alpelisib (for *PIK3CA* mutated tumors), or everolimus. For patients with prior CDK4/6 inhibitor treatment and a detectable *ESR1* mutation, options include elacestrant, or other ET either alone or in combination with targeted agents such as alpelisib (for *PIK3CA* mutated tumors) or everolimus. Elacestrant has comparable or greater activity than SOC ET monotherapy. Currently, there are no data on safety or clinical efficacy to support the use of elacestrant in combination with targeted agents.	EB	H	S

Abbreviations. ctDNA, circulating tumor DNA; EB, evidence based; ER, estrogen receptor; ET, estrogen therapy; H, high; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MBC, metastatic breast cancer; S, strong; SOC, standard-of-care

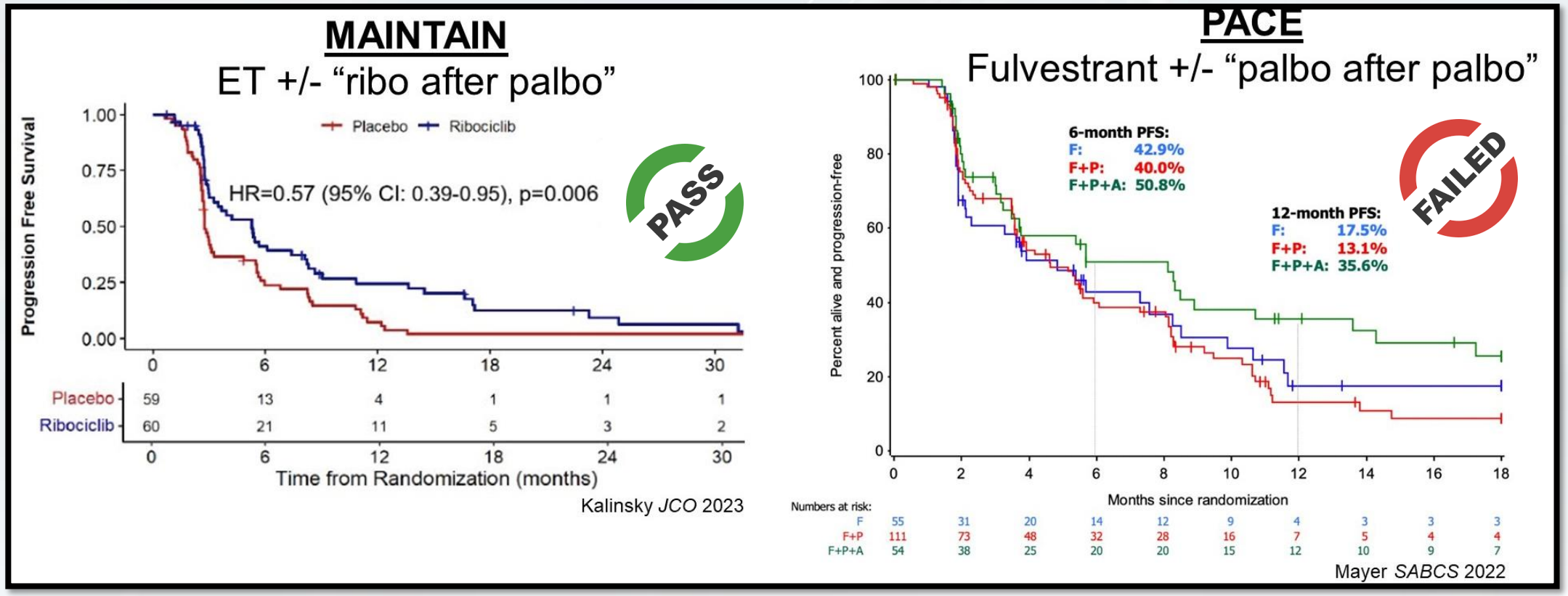
References.

[1] Grinshpun A, Sandusky ZM, Jeselsohn R: The Clinical Utility of ESR1 Mutations in Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer. Hematol Oncol Clin North Am 37:169-181, 2023

[2] Turner NC, Kingston B, Kilburn LS, et al: Circulating tumour DNA analysis to direct therapy in advanced breast cancer (plasmaMATCH): a multicentre, multicohort, phase 2a, platform trial. Lancet Oncol 21:1296-1308, 2020

#Q4# Can ET switch extend CDK4/6i?

Previous evidence: phase II trials



Significant PFS benefit in ribociclib group

Non-significant PFS benefit in palbociclib group

#Q4# Can ET switch extend CDK4/6i?

2023 ASCO ANNUAL MEETING

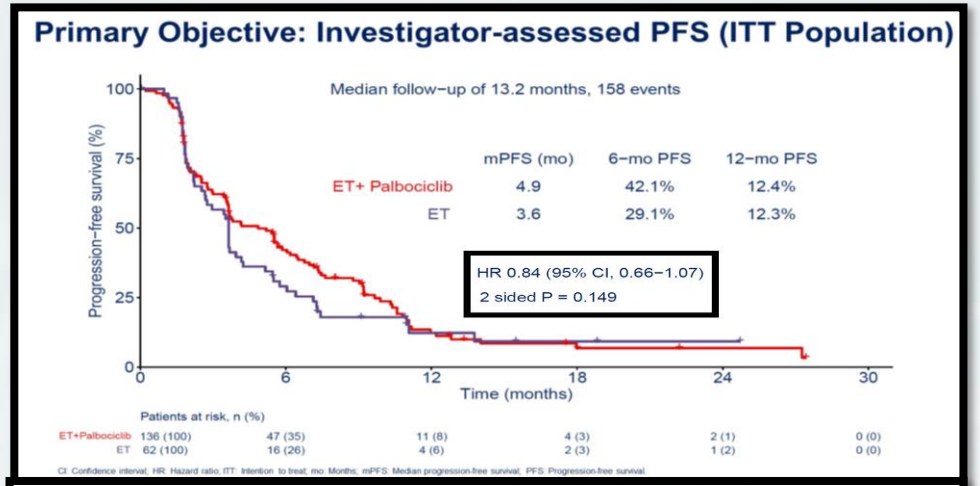
Second-line endocrine therapy with or without palbociclib maintenance in patients with HR[+]/HER2[-] advanced breast cancer: PALMIRA trial

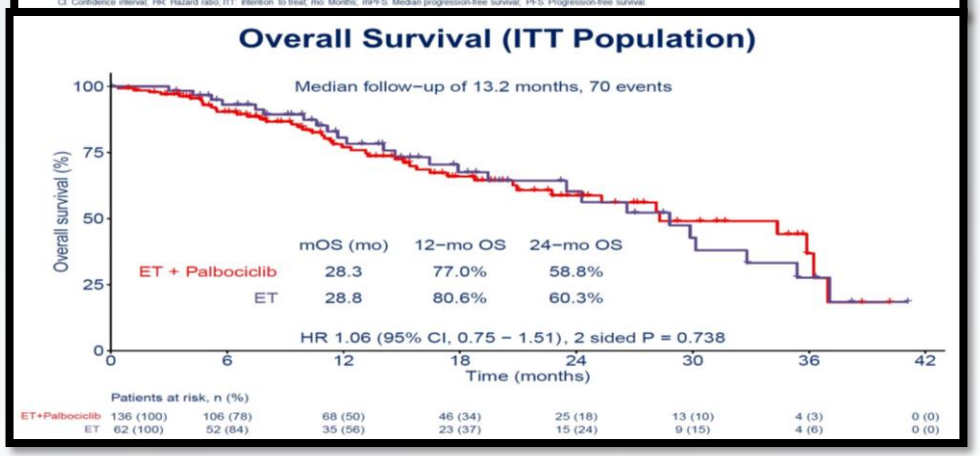
Antonio Llombart-Cussac[1], Catherine Harper-Wynne[2], Antonia Perelló[3], Audrey Hennequin[4], Adela Fernández[5], Marco Colleoni[6], Vicente Carañana[7], Vanesa Quiroga[8], Jacques Medioni[9], Vega Iranzo[10], Duncan Wheatley[11], Sonia del Barco Berrón[12], Antonio Antón[13], Erion Dobi[14], Manuel Ruiz[15], Daniel Alcalá-López[16], Jhudit Pérez-Escuredo[17], Miguel Sampayo-Cordero[18], José Manuel Pérez-García[19], Javier Cortés[20]

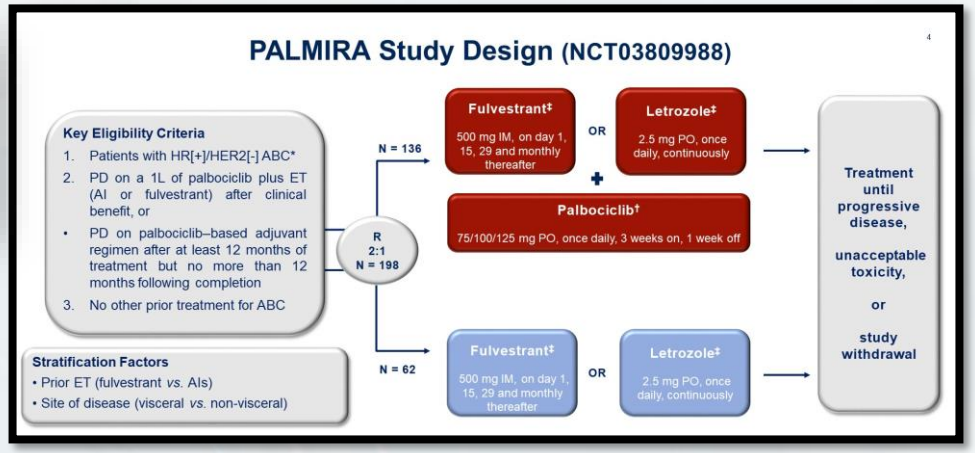
PALMIRA

Llombart-Cussac, et al

ET +/- "palbo after palbo"







- **Without differences in the subgroups analyses** (visceral disease OR duration prior palbociclib [6-12 m vs ≥12 m)
- Mutation status (ESR1, PIK3CA, ctDNA dinamycs) not reported yet

NCT03809988. Llombart-Cussac. ASCO 2023. Abstr 1001.

#Q4# Can ET switch extend CDK4/6i?

	MAINTAIN	PACE	PALMIRA
Patients (n)	120	166	198
1st line CDK4/6i	Palbociclib (84%)	Palbociclib (90%)	Palbociclib (100%)
% 1st line CDK4/6i >12mo	67%	75%	86%
Endocrine therapy	Fulvestrant (83%) or exemestane	Fulvestrant (100%)	Fulvestrant (90%) or letrozole
'Continuation' CDK4/6i	Ribociclib	Palbociclib	Palbociclib
PFS ET only	**2.8mo**	**4.8mo**	**3.6mo**
PFS Fulv + CDK4/6i	**5.3mo**	**4.6mo**	**4.9mo**

Different studies, different designs, different study populations and subgroup definitions

Kalinsky *JCO* 2023; Mayer *SABCS* 2022; Llombart-Cussac *ASCO* 2023

#Q4# Can ET switch extend CDK4/6i?

FAILED

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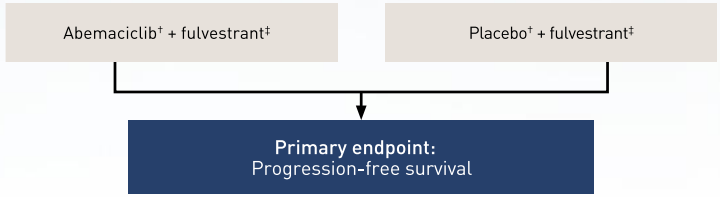
Different studies, different designs, different study populations and subgroup definitions

postMONARCH; NCT05169567

Awaited results

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study to Compare the Efficacy of Abemaciclib Plus Fulvestrant to Placebo Plus Fulvestrant in Participants With HR+, HER2-, Advanced or Metastatic Breast Cancer Following Progression on a CDK4 & 6 Inhibitor and Endocrine Therapy*



Kalinsky *JCO* 2023; Mayer *SABCS* 2022; Llombart-Cussac *ASCO* 2023

#Q4# Can ET switch extend CDK4/6i?

Key outstanding questions:

- **What are the alternative options?**
- **Does CDK4/6i matter?**
  - ✓ >80% 1st line Palbociclib in all studies
  - ✓ PFS benefit only in MAINTAIN (ribociclib)
- **Next-generation ET backbone?**
  - ✓ SERDs / SERMs / PROTACs/ CERANs
- **Adjuvant CDK4/6i ?**
- **Pending CDK4/6i→CDK4/6i trials:**
  - ✓ **PostMONARCH**
  - ✓ **EMBER-3:** ET vs imlunestrant vs imlunestrant/abema
  - ✓ **ELAINE-3 (ESR1mut):** lasofoxifene/abema vs FULV/abema

2ND LINE POST-CDK4/6i	PFS
Fulvestrant + alpelisib (BYLieve) – *PIK3CA*mut	7.3mo
Fulvestrant + capivasertib (CAPITELLO)	7.2mo
Camizestrant (SERENA-3) – *ESR1*mut	6.3-9.2mo
AI + albelisib (BYLieve) – *PIK3CA*mut	5.7mo
Fulvestrant + ribociclib (MAINTAIN)	5.3mo
Fulvestrant alone (PACE)	4.8mo
Fulvestrant + palbociclib (PACE)	4.6mo
Elacestrant (EMERALD) – *ESR1*mut	3.8mo
Fulvestrant alone (CAPITELLO)	3.6mo
Fulvestrant>AI alone (MAINTAIN)	2.8mo
Fulvestrant>AI alone (EMERALD)	1.9mo

Optimizing 1st Line Therapy for HR+/HER2- MBC

- **#Q1# Personalize CDK4/6i:**
- **#Q2# Delay CDK4/6i:** should **all** patients receive CDK4/6i as part of 1st line?
- **#Q3# Early switch after biological progression: serial monitoring for all?**
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- **#Q4# Extend CDK4/6i:** Most will **NOT** benefit
  - Awaited results with next-generation ET backbone
  - Mechanisms of intrinsic and acquired resistance remains largely unknown

HR status → *Subtype switch from 1º?*

HER2-low

ER + MBC

Relapsing after adjuvant treatment or *de novo* visceral metastasis or not

Biopsy for ER, HER2 reassessment and NGS

Visceral crisis

(Poly or mono) chemotherapy

RIGH-CHOICE trial

second line

First Line Therapy

-Most: ET + ribociclib or abemaciclib

-Select: ET alone | ET+Palbociclib | Chemo | Trial

Genomic testing to inform 2nd line

- ESR1# PIK3CA# sBRCA#
- Liquid biopsy

Genomic testing: tissue or ctDNA NGS if not done before

Definite progression

Liquid biopsy → *ESR1*mut

Second Line Therapy

-PIK3CAmut: Fulvestrant + alpelisib or capivasertib*

***-ESR1*mut**: Elacestrant

-gBRCA1/2 (gPALB2/sBRCA): Olaparib, talazoparib

-No mut: Fulvestrant +/- everolimus or CDK4/6i switch

-Rapid progression: Chemotherapy/ADC*

Indeterminate progression

?Repeat genomic testing:

-Liquid biopsy → *ESR1*mut

Consider ET switch:

AI→Fulvestrant

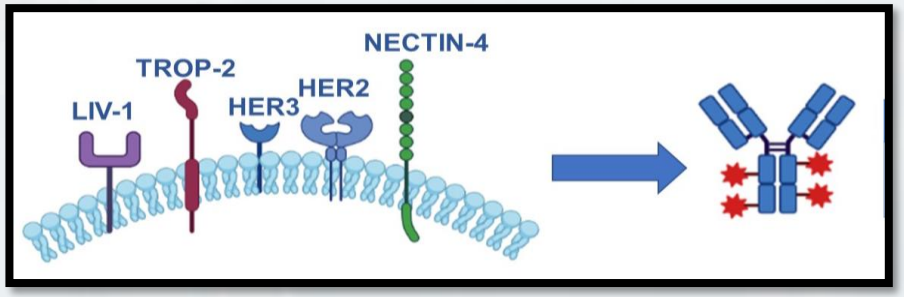
Patients progressing after 1-2 lines of chemotherapy

Sacituzumab govitecan

Trastuzumab deruxtecan (HER2-low: IHC 1+ or IHC 2+/FISH-)

ESMO Open 2023 8DOI: (10.1016/j.esmoop.2023.100882)

Targets in Antibody-Drug Conjugate Therapy



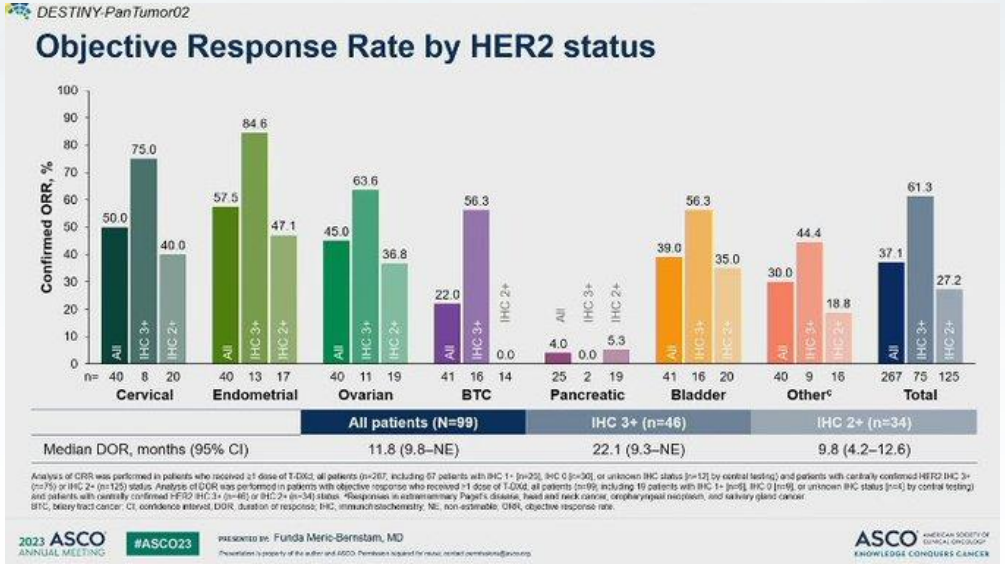
- The target landscape of ADCs is expanding rapidly

- 3RD generation ADCs showed activity across a wide range of target expression

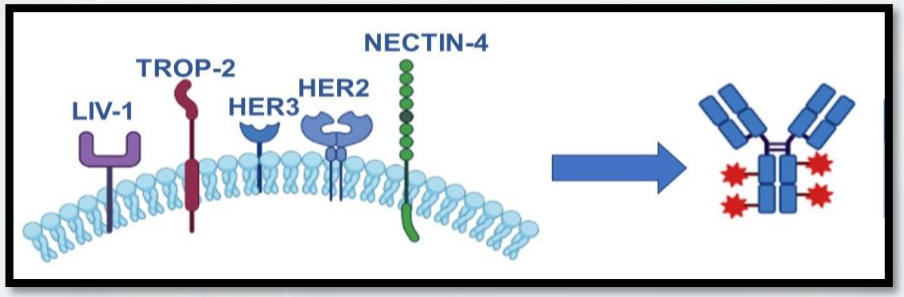
  ❑ Do we still need to know tumor TARGET EXPRESSION levels?

ASCO'23 ***Exciting data***

DESTINY-PanTumour02



Targets in Antibody-Drug Conjugate Therapy



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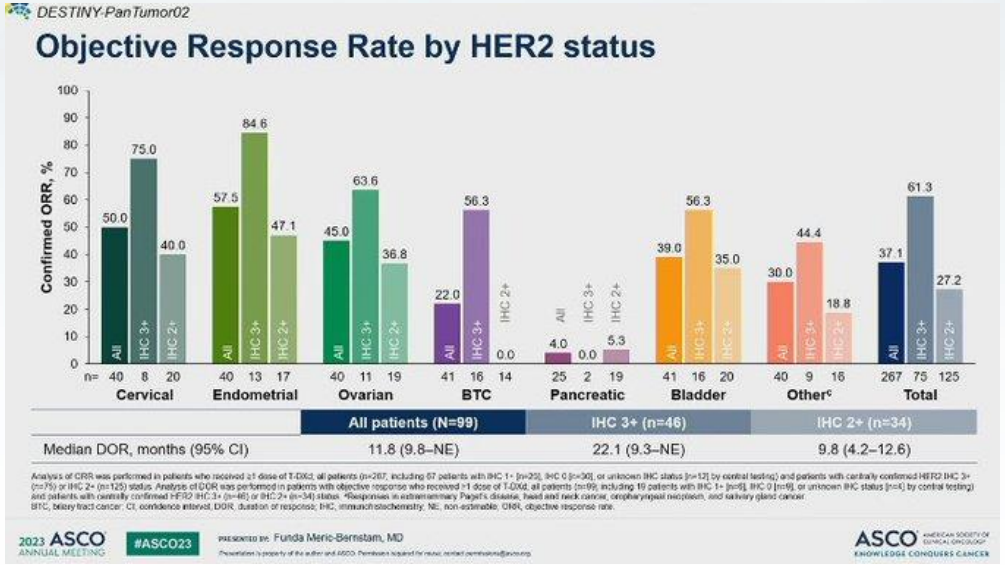
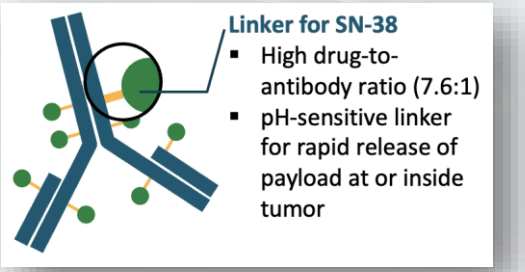
  - **ASCENT, TROPICS**
  - **DESTINY-Breast 03, 04**

ASCO'23 ***Exciting data***

DESTINY-PanTumour02



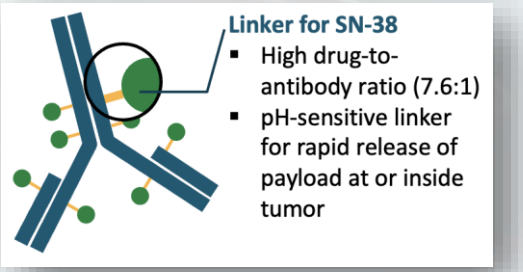
TROP-2 ADCs



#1# Datopotamab-deruxtecan results are awaited

#2# Sacituzumab Govitecan is approved irrespective of TROP-2 expression

TROP-2 ADCs



#1# Datopotamab-deruxtecan results are awaited

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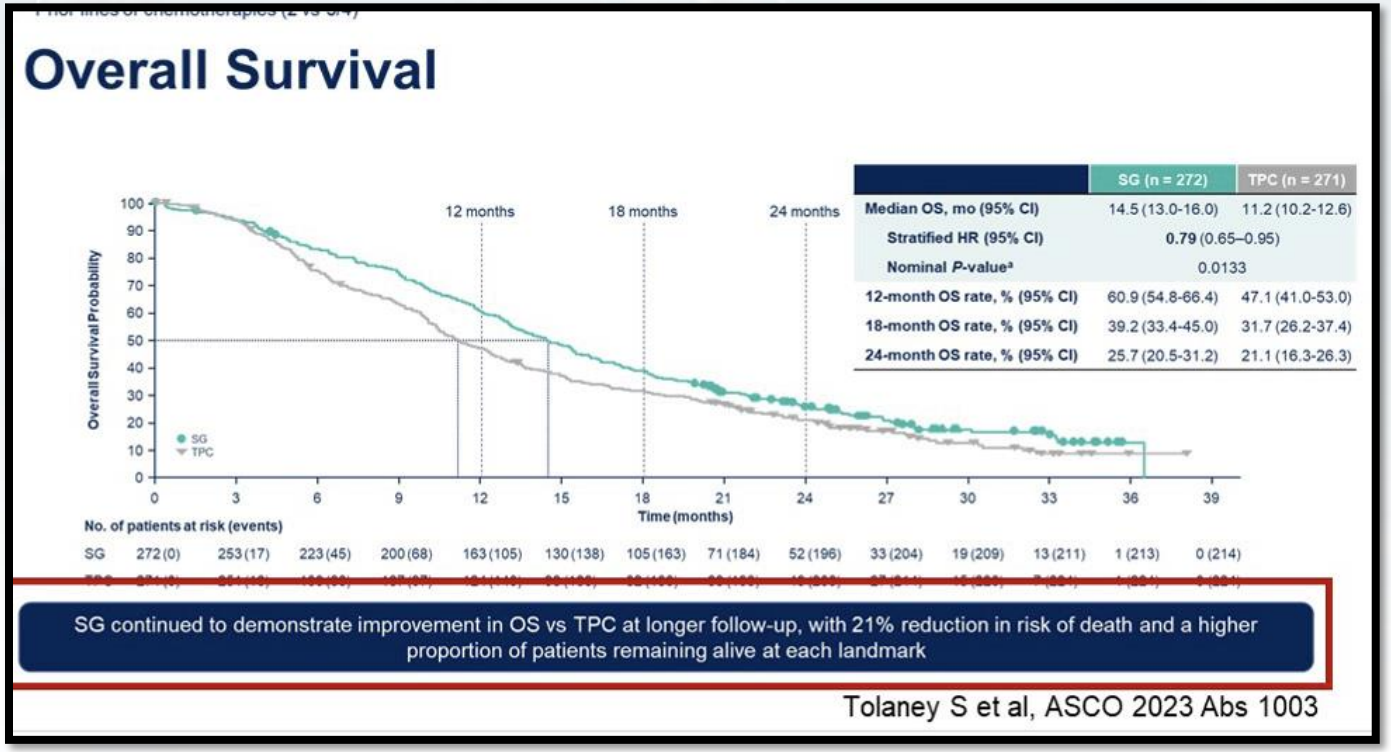
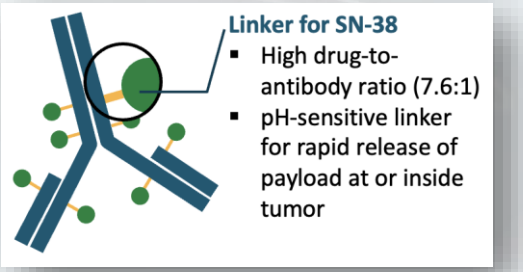
#3# **ASCO'23**

TROPiCS-02 final OS analysis confirms the efficacy of SG in HR+/HER2- MBC

- ✓ **unselected for TROP-2 expression**
- ✓ in HER2-low and HER2-0 patients (PFS and OS data)



TROP-2 ADCs



#1# Datopotamab-deruxtecan results are awaited

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#3# **ASCO'23**

TROPiCS-02 final OS analysis confirms the efficacy of SG in HR+/HER2- MBC

✓ **unselected for TROP-2 expression**

Insufficient data to recommend routine testing for TROP-2

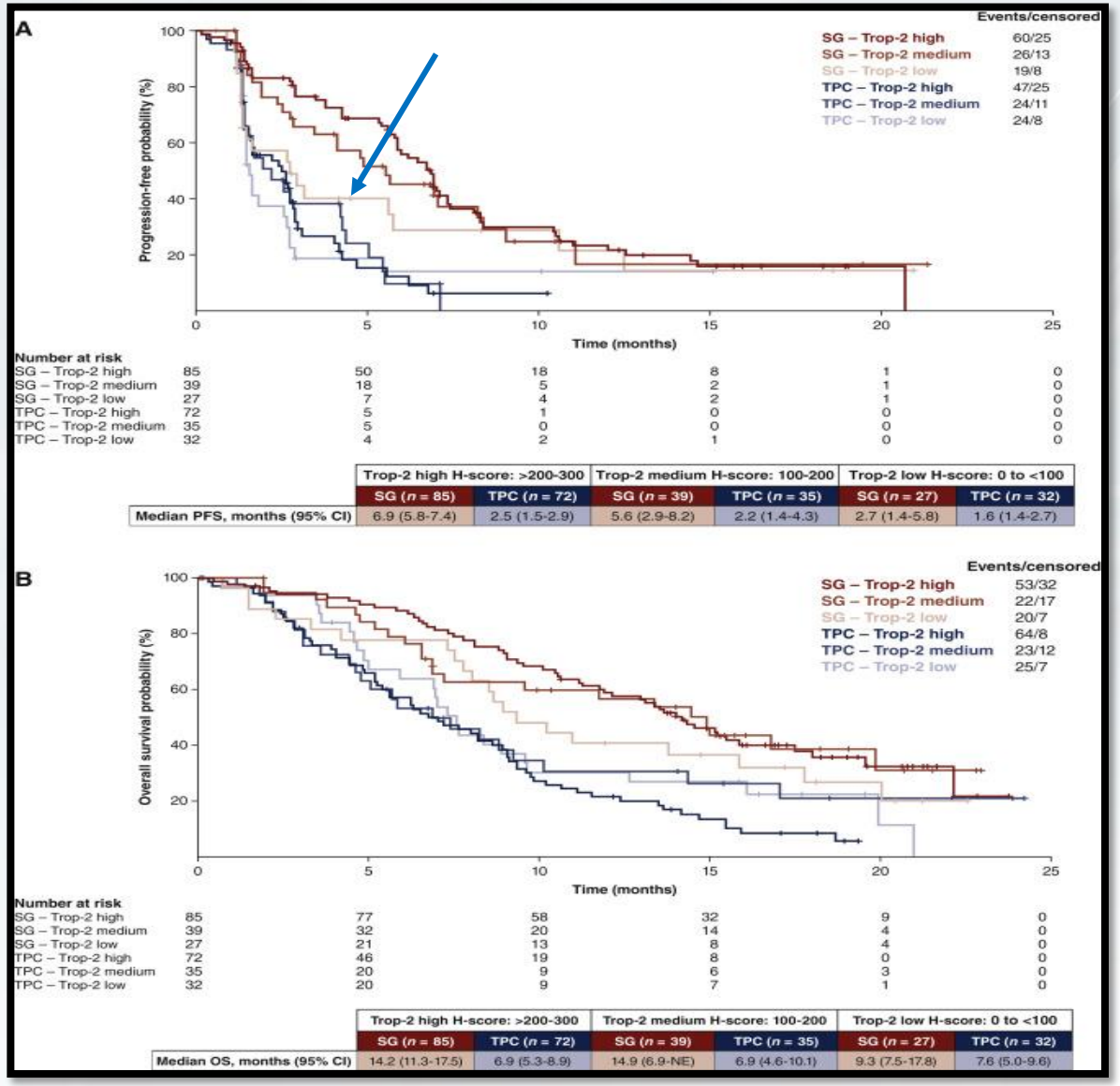
TABLE 1. At-a-Glance Guide to ASCO Biomarker Testing in Metastatic Breast Cancer Recommendations

Test	Type of Recommendation	Quality of Evidence	Strength of Recommendation
Biomarker tests recommended by the ASCO expert panel			
PIK3CA	Evidence-based	High	Strong
Germline *BRCA1* and *BRCA2*	Evidence-based	High	Strong
PD-L1	Evidence-based	Intermediate	Strong
dMMR/MSI-H	Informal consensus-based	Low	Moderate
TMB	Informal consensus-based	Low	Moderate
NTRK fusions	Informal consensus-based	Low	Moderate
Biomarker tests not recommended by the ASCO expert panel			
ESR1	Evidence-based	Insufficient	Moderate
PALB2	Evidence-based	Low	Moderate
HRD	Informal consensus-based	Low	Moderate
TROP2 expression	Informal consensus-based	Low	Moderate
ctDNA	Informal consensus-based	Low	Moderate
CTCs	Informal consensus-based	Low	Moderate

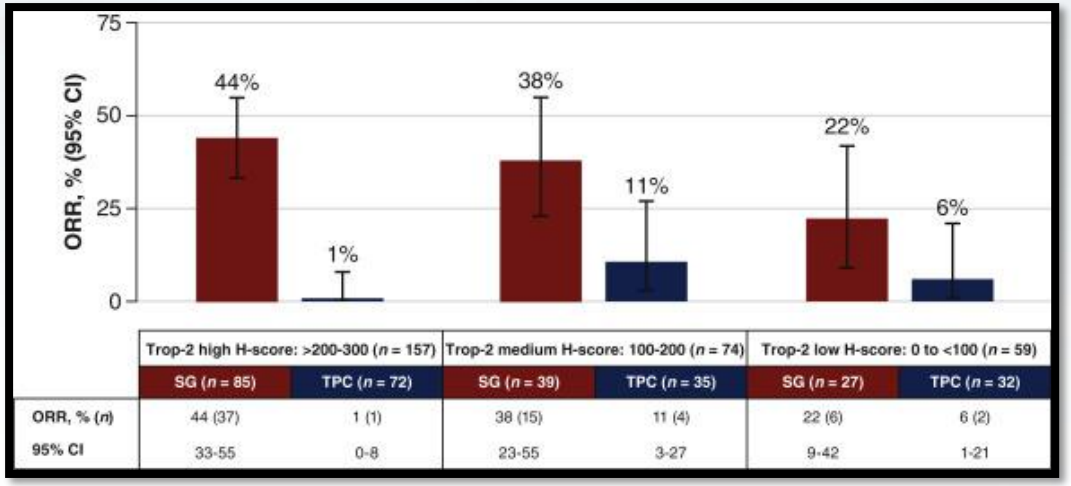
Henry NL, Somerfield MR, Dayao Z, et al. Biomarkers for Systemic Therapy in Metastatic Breast Cancer: ASCO Guideline Update. *J Clin Oncol*. 2022;40(27):3205-3221. doi:10.1200/JCO.22.01063

So, does TROP-2 expression matter ?

Clinical data

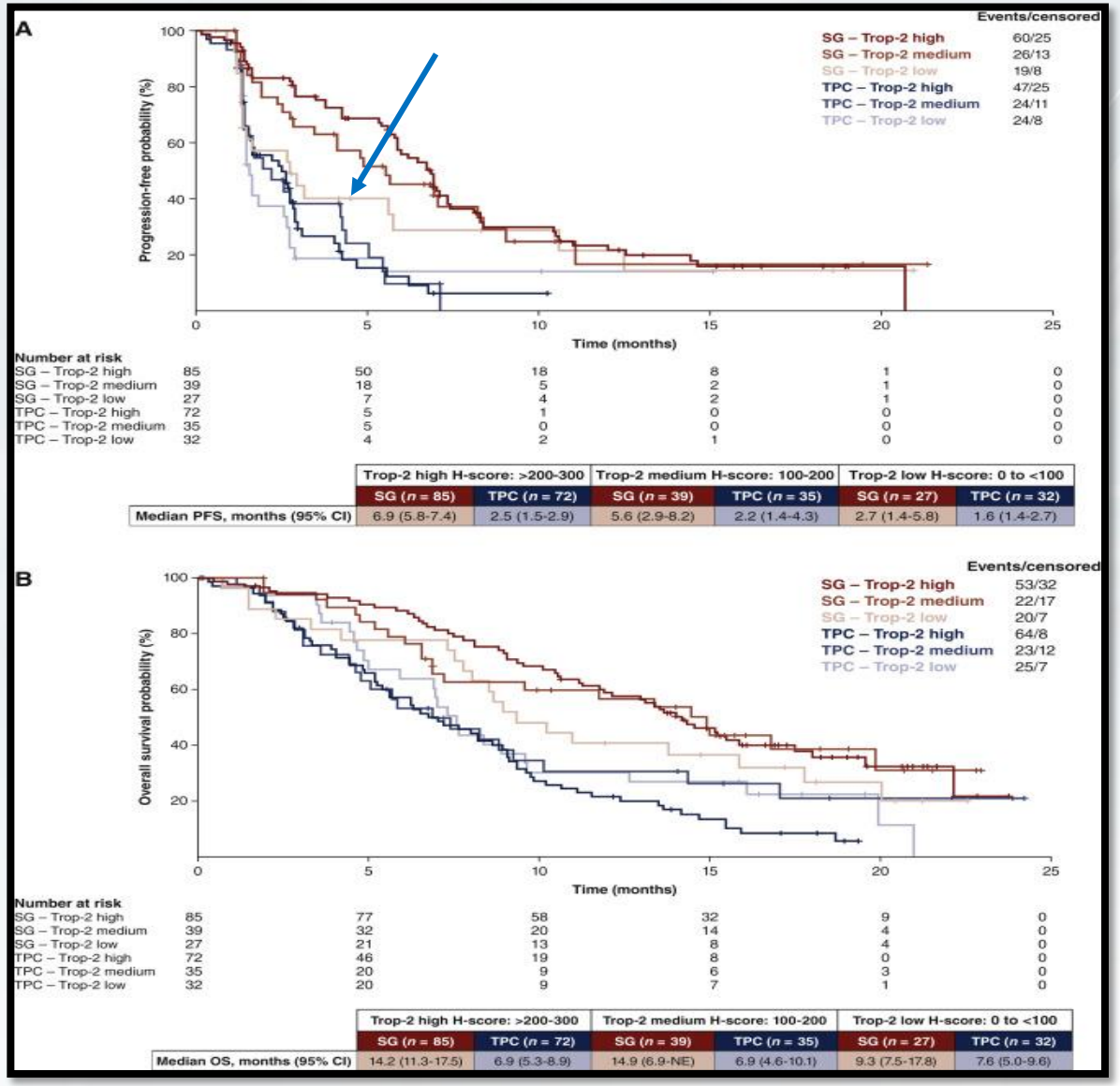


	Trop-2 high H-score: >200-300		Trop-2 medium H-score: 100-200		Trop-2 low H-score: 0 to <100	
	SG (n = 85)	TPC (n = 72)	SG (n = 39)	TPC (n = 35)	SG (n = 27)	TPC (n = 32)
Median PFS, months (95% CI)	6.9 (5.8-7.4)	2.5 (1.5-2.9)	5.6 (2.9-8.2)	2.2 (1.4-4.3)	2.7 (1.4-5.8)	1.6 (1.4-2.7)
Median OS, months (95% CI)	14.2 (11.3-17.5)	6.9 (5.3-8.9)	14.9 (6.9-NE)	6.9 (4.6-10.1)	9.3 (7.5-17.8)	7.6 (5.0-9.6)



	Trop-2 high H-score: >200-300 (n = 157)		Trop-2 medium H-score: 100-200 (n = 74)		Trop-2 low H-score: 0 to <100 (n = 59)	
	SG (n = 85)	TPC (n = 72)	SG (n = 39)	TPC (n = 35)	SG (n = 27)	TPC (n = 32)
ORR, % (n)	44 (37)	1 (1)	38 (15)	11 (4)	22 (6)	6 (2)
95% CI	33-55	0-8	23-55	3-27	9-42	1-21

So, does TROP-2 expression matter ?



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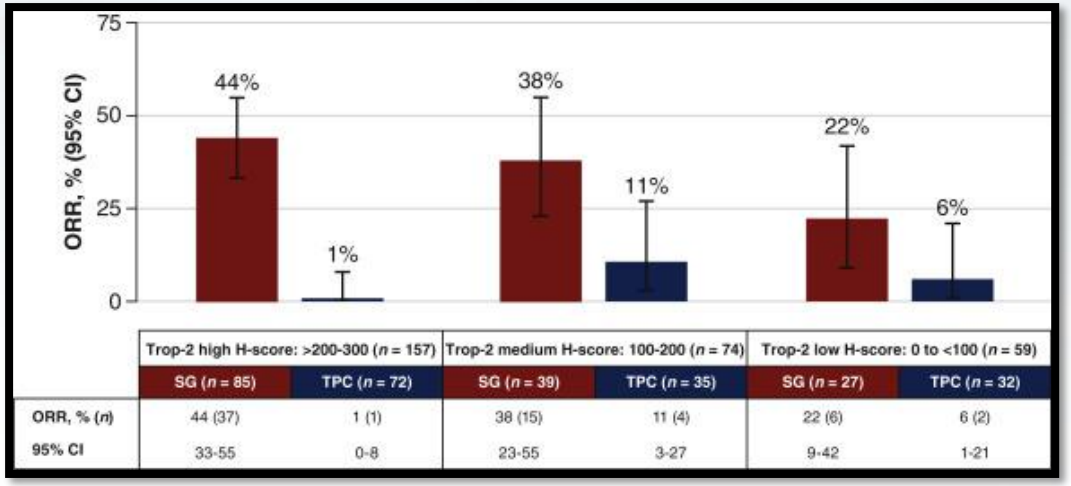
Clinical data

ASCENT trial

Numerically (NS) higher efficacy outcomes (mPFS, ORR) in high and medium TROP-2 expression subgroups



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So, does TROP-2 expression matter ?

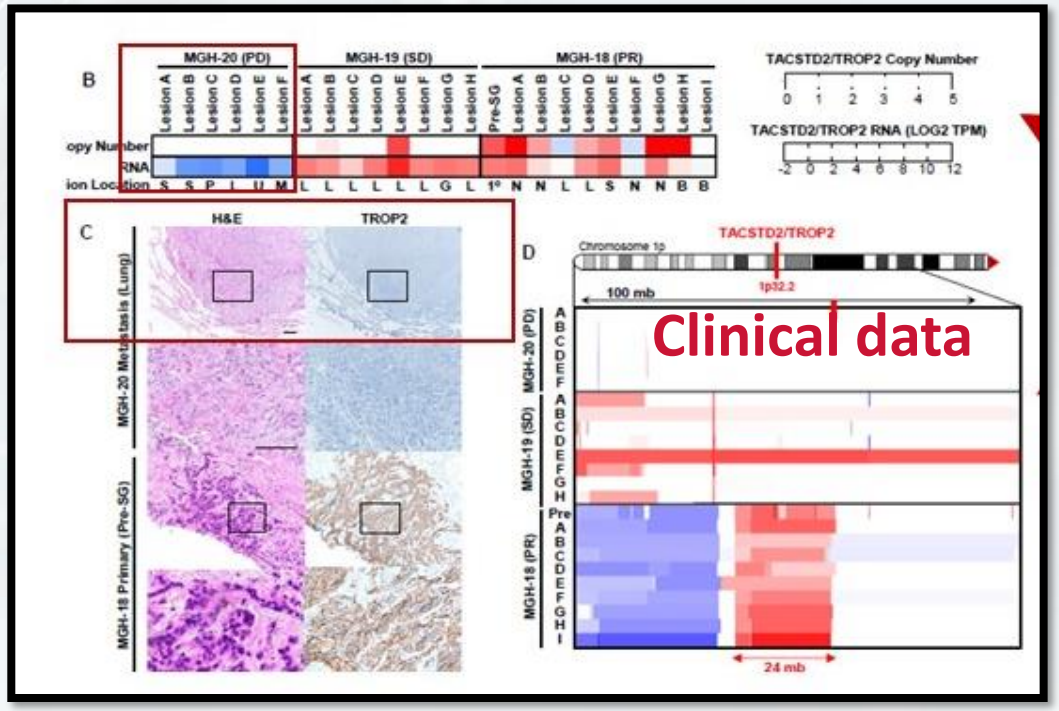
In vitro cytotoxic studies

Table 1. Expression of Trop-2 and *in vitro* cytotoxicity of SN-38 and hRS7-SN-38 in several solid tumor lines

Cell line	Trop-2 expression *via* FACS: Median fluorescence (background)	Trop-2 expression *via* FACS: Percent positive	Cytotoxicity results: SN-38	95% CI	hRS7-SN-38[a]	95% CI	ADC/free SN-38 ratio
			IC_{50} (nmol/L)	IC_{50} (nmol/L)	IC_{50} (nmol/L)	IC_{50} (nmol/L)	
Calu-3	282.2 (4.7)	99.6%	7.19	5.77–8.95	9.97	8.12–12.25	1.39
COLO 205	141.5 (4.5)	99.5%	1.02	0.66–1.57	1.95	1.26–3.01	1.91
Capan-1	100.0 (5.0)	94.2%	3.50	2.17–5.65	6.99	5.02–9.72	2.00
PC-3	46.2 (5.5)	73.6%	1.86	1.16–2.99	4.24	2.99–6.01	2.28
SK-MES-1	44.0 (3.5)	91.2%	8.61	6.30–11.76	23.14	17.98–29.7	2.69
BxPC-3	26.4 (3.1)	98.3%	1.44	1.04–2.00	4.03	3.25–4.98	2.80

[a]IC_{50}-value is shown as SN-38 equivalents of hRS7-SN-38.

IC50 ADC:free SN-38 was lower in the higher Trop-2-expressing cells



Enhanced ability to internalize the ADC when more antigen is present

Undetectable TROP2 RNA and absence of TROP2 (IHC) have been associated to de novo resistance to SG

Cardillo et al, Clin Cancer Res 2011; Bardia et al, Ann Oncol 2021; Coates et al, Cancer Discov, 2021

And what about HER3? *Promising results in mBC*

BRE354: Phase II study (NCT04699630) examines the efficacy and safety of patritumab deruxtecan administered in patients with locally advanced or metastatic BC (Part A)

- Multicenter, 3-part, open-label phase II trial; data for

Part A

Patients with HER2- locally advanced or MBC; 1 prior CDK4/6i, ≤2 prior CT, and unlimited ET regimens for HR+ BC, or 1-3 prior CT regimens for TNBC; no prior anti-HER3 agents or exatecan-based ADCs (N = 60)

→ **Patritumab deruxtecan** 5.6 mg/kg IV Q3W

- **Primary endpoints**: ORR, 6-mo PFS in HER2- MBC
- **Secondary endpoints**: DoR, CBR, PFS in HER2+ and HER2- MBC; safety

	(N=60) n (%)
Patients Enrolled*	61
Patients Treated (Safety Set)	60
Treatment Status	
Receiving study treatment	21 (35.0)
Discontinued from study treatment	39 (65.0)
Primary reason for discontinuation from study treatment	
Adverse event**	8 (13.1)
Clinical progression/objective disease progression	25 (41.7)
Death†	2 (3.3)
Physician/patient decision	4 (6.7)
Duration on Study (Months)	
Median (range)	5.9 (0.2, 14.5)

	(N=47) n (%)
Baseline HER3 Expression*	
≥75%	30 (63.8)
25% to 74%	13 (27.7)
<25%	4 (8.5)

*Membrane HER3 expression measured at 10X objective.

	(N=48) n (%)
Baseline ER	
High (>10% expression)	24 (50.0)
Low (1-10% expression)	1 (2.1)
Negative	23 (47.9)
Baseline PR	
High (>10% expression)	22 (45.8)
Low (1-10% expression)	3 (6.3)
Negative	23 (47.9)
Baseline Triple-Negative	19 (39.6)

≈ 40% TNBC

4 (8.5%) HER3 IHC < 25%

Median prior lines of systemic therapies for ABC: 3 [1-9]

≈8.3 % of patients: prior SG

And what about HER3? *Promising results in mBC*

BRE354: Phase II study (NCT04699630) examines the efficacy and safety of patritumab deruxtecan administered in patients with locally advanced or metastatic BC (Part A)

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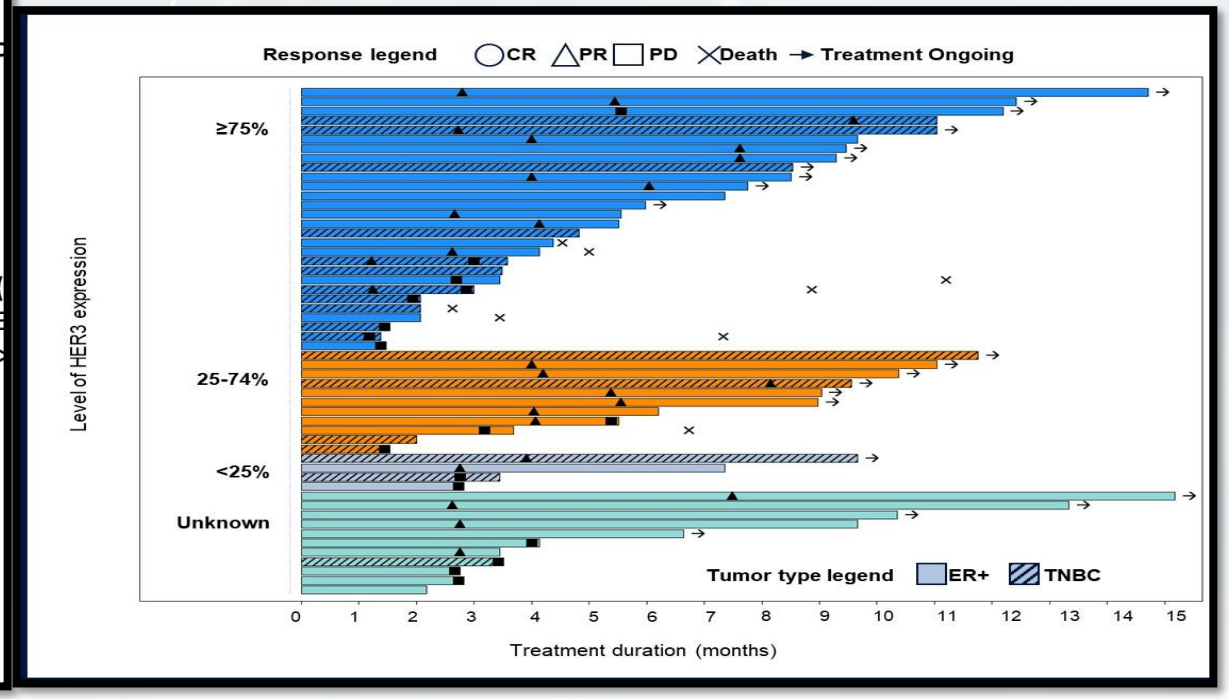

Among patients with heavily pretreated BC, all-comer ORR was 35%, overall CBR was 43%, and DoR was at least 6 months in nearly half of all patients who responded.

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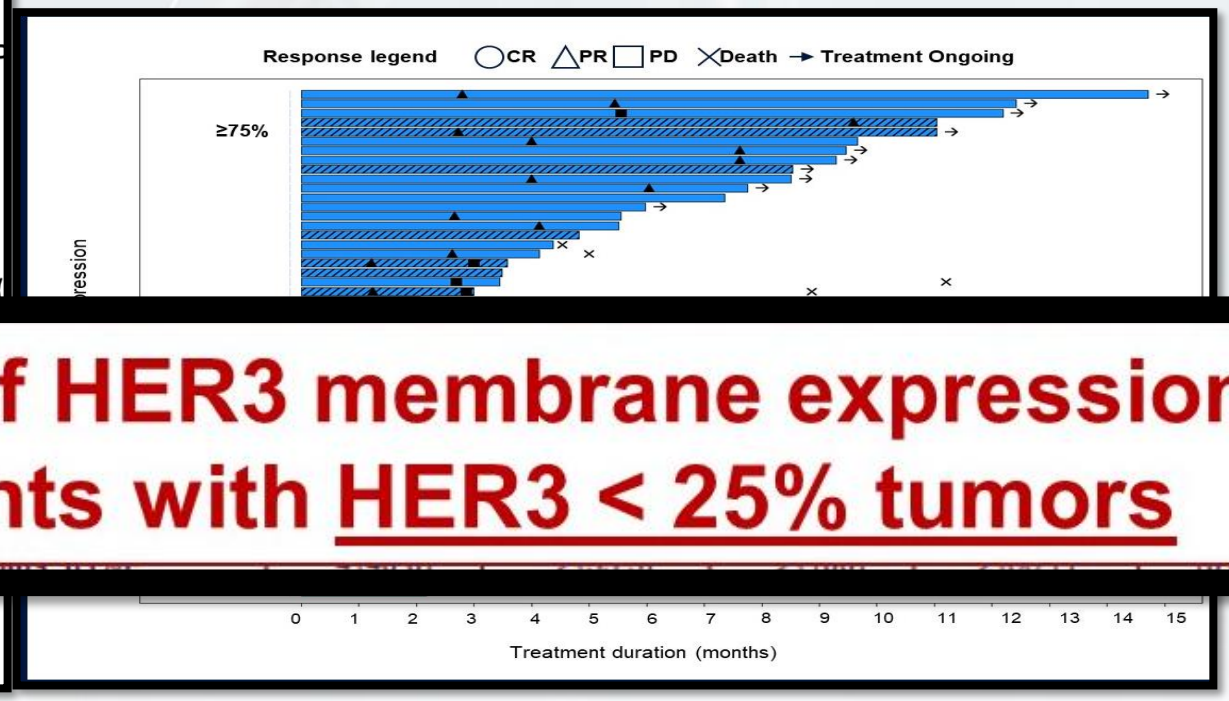
→ **Patritumab deruxtecan**

and HER2- MBC; safety



Activity regardless of HER3 membrane expression, but very few patients with HER3 < 25% tumors

Among patients with heavily pretreated BC, all-comer ORR was 35%, overall CBR was 43%, and DoR was at least 6 months in nearly half of all patients who responded.

3RD generation ADCs showed activity across a wide range of target expression

- ❑ Do we still need to know tumor TARGET EXPRESSION levels?

- ❑ **Surface protein expression is not enough** **Targets "move" !!!!**

Then WHEN and HOW to assess TARGET EXPRESSION to maximize ADCs EFFICACY?

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HER2	YES	TROP-2	Preferable..	HER3	Still unclear

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HER2	TROP-2	HER3
YES	Preferable..	Still unclear

- ❑ **Surface protein expression is not enough** **Targets "move" !!!!**

Over time

Across metastases sites (spatial heterogeneity)

Across tumor cell membrane and internal compartments (internalization)

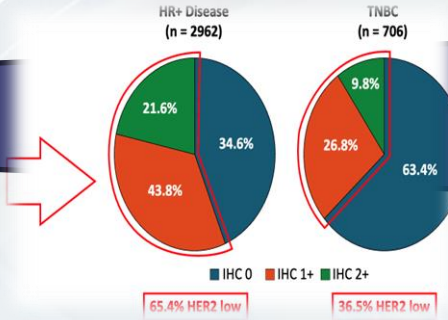
Then WHEN and HOW to assess TARGET EXPRESSION to maximize ADCs EFFICACY?

Assessment of HER2-expression

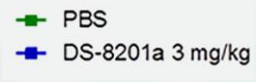
NEGATIVE

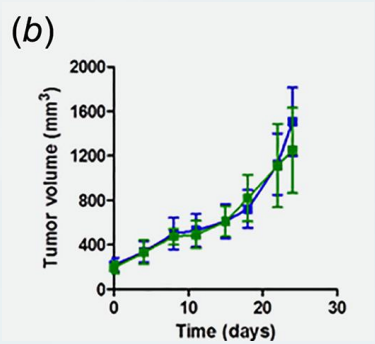
LOW

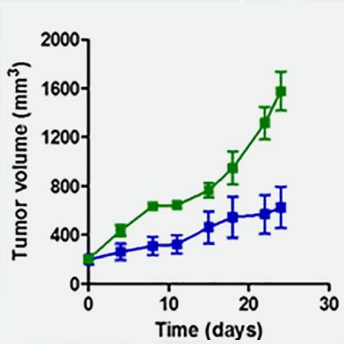
HIGH

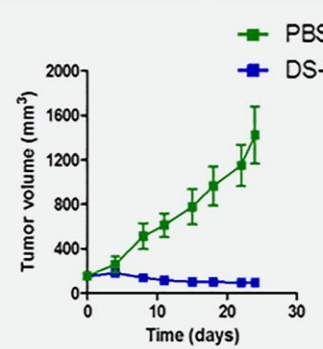


In vitro

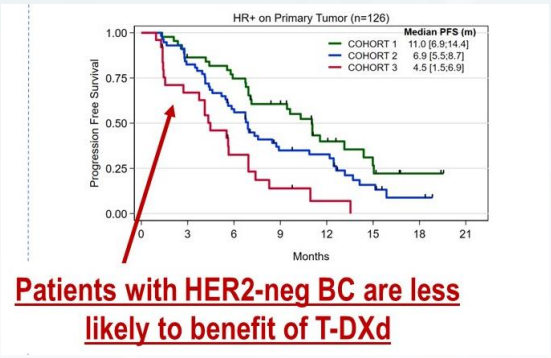




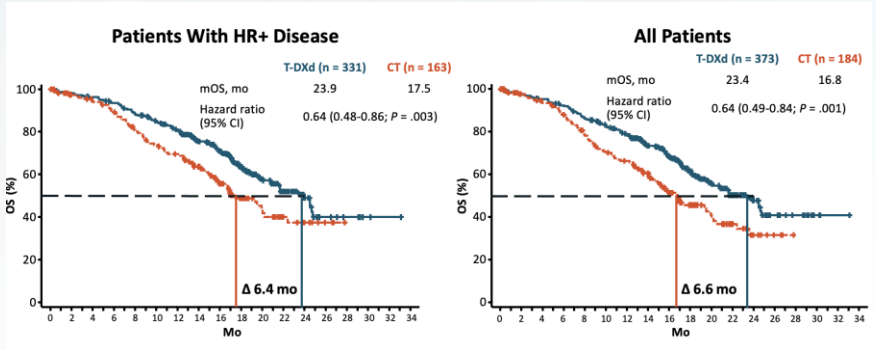




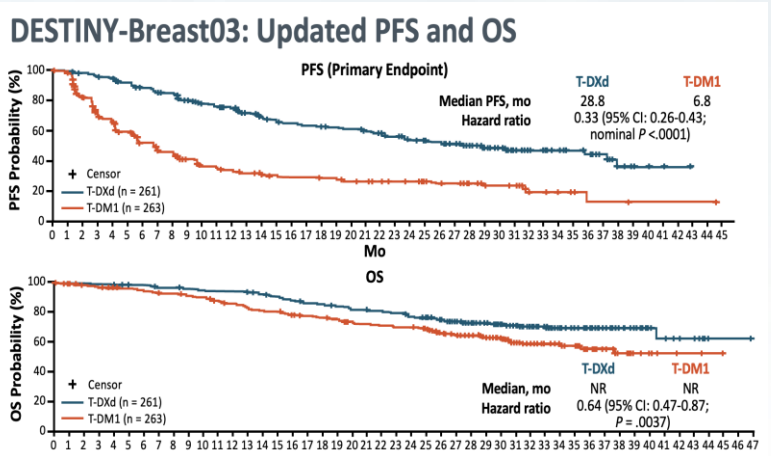
Clinical data



DESTINY-Breast04: OS



DESTINY-Breast03: Updated PFS and OS



Cortes et al, NEJM 2022; Ogitani et al, Clin Cancer Res 2016; Modi et al, NEJM 2022; Dieras et al, SABCS 2021

2023 ASCO ANNUAL MEETING

An Age-Specific Pooled Analysis of Trastuzumab Deruxtecan (T-DXd) in Patients With HER2-Positive Metastatic Breast Cancer (mBC) From DESTINY-Breast01, -02, and -03

≥ 65 age

2023 ASCO ANNUAL MEETING

An Age-Specific Pooled Analysis of Trastuzumab Deruxtecan (T-DXd) in Patients With HER2-Positive Metastatic Breast Cancer (mBC) From DESTINY-Breast01, -02, and -03

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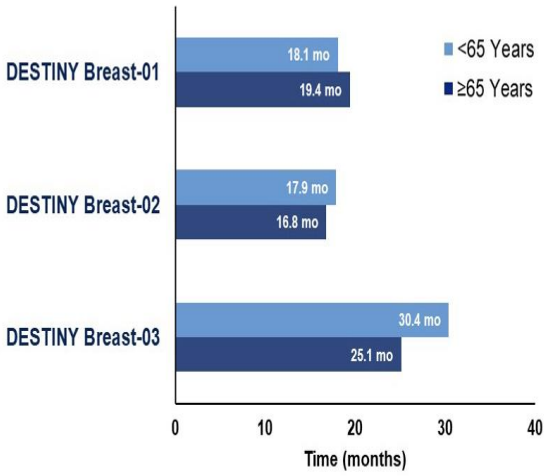
An Age-Specific Pooled Analysis of Trastuzumab Deruxtecan (T-DXd) in Patients With HER2-Positive Metastatic Breast Cancer (mBC) From DESTINY-Breast01, -02, and -03

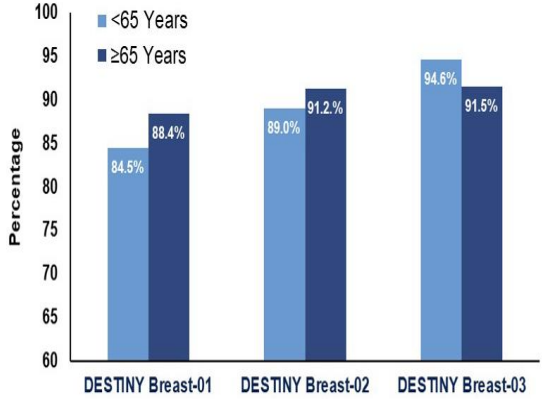
Median Progression Free Survival



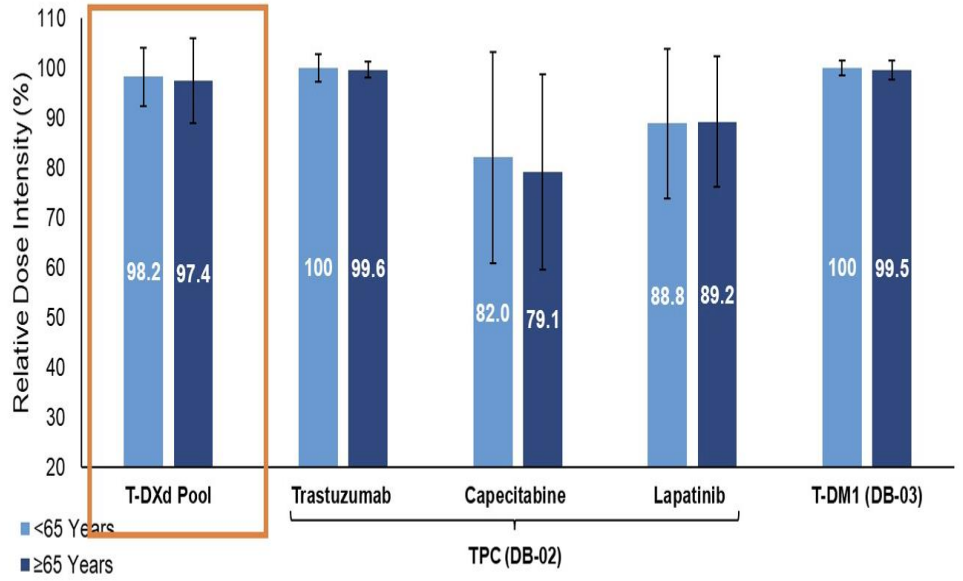
Median Overall Survival

	DESTINY-Breast01		DESTINY-Breast02		DESTINY-Breast03	
	<65 (n = 140)	≥65 (n = 44)	<65 (n = 321)	≥65 (n = 85)	<65 (n = 212)	≥65 (n = 49)
mOS, months (95% CI)	28.1 (23.3-36.1)	30.9 (21.9-NE)	NR (35.5-NE)	30.2 (22.3-39.2)	NR (40.5-NE)	NR (26.3-NE)

12-month Landmark Overall Survival



- Efficacy in patients aged <65 and ≥65 years treated with T-DXd was generally similar; however no formal comparison was made



- Relative dose intensity was similar between <65 and ≥65 age groups, regardless of treatment received

2023 ASCO ANNUAL MEETING

An Age-Specific Pooled Analysis of Trastuzumab Deruxtecan (T-DXd) in Patients With HER2-Positive Metastatic Breast Cancer (mBC) From DESTINY-Breast01, -02, and -03

	T-DXd Pool			TPC (DB-02)			T-DM1 (DB-03)		
	<65 (n = 673)	≥65 (n = 178)	≥75 (n = 34)	<65 (n = 164)	≥65 (n = 38)	≥75 (n = 8)	<65 (n = 206)	≥65 (n = 57)	≥75 (n = 8)
Disorders									
Blood and lymphatic system disorders (SOC)	73 (10.8)	26 (14.6)	5 (14.7)	12 (7.3)	6 (15.8)	1 (12.5)	14 (6.8)	6 (10.5)	1 (12.5)
Anemia	41 (6.1)	18 (10.1)	3 (8.8)	9 (5.5)	4 (10.5)	1 (12.5)	6 (2.9)	2 (3.5)	1 (12.5)
Cardiac disorders (SOC)	57 (8.5)	21 (11.8)	4 (11.8)	7 (4.3)	3 (7.9)	0	8 (3.9)	5 (8.8)	0
Diabetes mellitus	29 (4.3)	17 (9.6)	4 (11.8)	7 (4.3)	3 (7.9)	2 (25.0)	6 (2.9)	8 (14.0)	1 (12.5)
Renal and urinary disorders (SOC)	23 (3.4)	16 (9.0)	6 (17.6)	3 (1.8)	4 (10.5)	1 (12.5)	3 (1.5)	11 (19.3)	0
Vascular disorders (SOC)	174 (25.9)	109 (61.2)	28 (82.4)	43 (26.2)	24 (63.2)	5 (62.5)	52 (25.2)	31 (54.4)	6 (75.0)
Hypertension	123 (18.3)	93 (52.2)	26 (76.5)	30 (18.3)	24 (63.2)	5 (62.5)	35 (17.0)	28 (49.1)	5 (62.5)
Baseline renal function[b]									
Normal function	432 (64.2)	34 (19.1)	0	104 (63.4)	8 (21.1)	0	124 (60.2)	8 (14.0)	0
Mild renal impairment	205 (30.5)	91 (51.1)	14 (41.2)	54 (32.9)	22 (57.9)	3 (37.5)	77 (37.4)	28 (49.1)	3 (37.5)
Moderate renal impairment	35 (5.2)	53 (29.8)	20 (58.8)	6 (3.7)	8 (21.1)	5 (62.5)	4 (1.9)	21 (36.8)	5 (62.5)
Baseline hepatic function[c]									
Normal function	406 (60.3)	101 (56.7)	20 (58.8)	78 (47.6)	21 (55.3)	2 (25.0)	162 (78.6)	50 (87.7)	8 (100.0)
Mild hepatic impairment	260 (38.6)	75 (42.1)	14 (41.2)	86 (52.4)	17 (44.7)	6 (75.0)	43 (20.9)	7 (12.3)	0
Moderate hepatic impairment	2 (0.3)	2 (1.1)	0	0	0	0	0	0	0

- Comorbidities were generally low in the overall population due to selection criteria

2023 ASCO ANNUAL MEETING

An Age-Specific Pooled Analysis of Trastuzumab Deruxtecan (T-DXd) in Patients With HER2-Positive Metastatic Breast Cancer (mBC) From DESTINY-Breast01, -02, and -03

	T-DXd Pool			TPC (DB-02)			T-DM1 (DB-03)		
	<65 (n = 668)	≥65 (n = 177)	≥75 (n = 33)	<65 (n = 157)	≥65 (n = 38)	≥75 (n = 8)	<65 (n = 204)	≥65 (n = 57)	≥75 (n = 8)
Median treatment duration, mo (range)	13.1 (0.7-44.0)	12.4 (0.7-45.1)	9.0 (0.7-35.6)	N/A[b]	N/A[b]	N/A[b]	6.9 (0.7-38.9)	8.3 (0.7-39.3)	7.7 (2.0-29.4)
TEAE, n (%)	**665 (99.6)**	**177 (100.0)**	**33 (100.0)**	**148 (94.3)**	**37 (97.4)**	**8 (100.0)**	**194 (95.1)**	**55 (96.5)**	**8 (100.0)**
Drug-related	653 (97.8)	176 (99.4)	33 (100.0)	144 (91.7)	36 (94.7)	8 (100.0)	178 (87.3)	50 (87.7)	8 (100.0)
TEAEs grade ≥3, n (%)	**358 (53.6)**	**116 (65.5)**	**17 (51.5)**	**68 (43.3)**	**18 (47.4)**	**6 (75.0)**	**100 (49.0)**	**35 (61.4)**	**4 (50.0)**
Drug-related	291 (43.6)	96 (54.2)	13 (39.4)	48 (30.6)	12 (31.6)	5 (62.5)	82 (40.2)	28 (49.1)	3 (37.5)
Serious TEAEs, n (%)	**162 (24.3)**	**57 (32.2)**	**10 (30.3)**	**39 (24.8)**	**7 (18.4)**	**1 (12.5)**	**33 (16.2)**	**25 (43.9)**	**4 (50.0)**
Drug-related	77 (11.5)	29 (16.4)	5 (15.2)	13 (8.3)	2 (5.3)	1 (12.5)	11 (5.4)	9 (15.8)	2 (25.0)
TEAEs associated with drug discontinuation, n (%)	**125 (18.7)**	**45 (25.4)**	**8 (24.2)**	**15 (9.6)**	**4 (10.5)**	**1 (12.5)**	**13 (6.4)**	**11 (19.3)**	**3 (37.5)**
Drug-related	100 (15.0)	42 (23.7)	8 (24.2)	8 (5.1)	2 (5.3)	1 (12.5)	9 (4.4)	8 (14.0)	2 (25.0)
TEAEs associated with dose reduction, n (%)	**163 (24.4)**	**51 (28.8)**	**10 (30.3)**	**67 (42.7)**	**22 (57.9)**	**7 (87.5)**	**23 (11.3)**	**15 (26.3)**	**2 (25.0)**
Drug-related	156 (23.4)	47 (26.6)	8 (24.2)	67 (42.7)	22 (57.9)	7 (87.5)	23 (11.3)	15 (26.3)	2 (25.0)
TEAEs associated with dose interruption, n (%)	**302 (45.2)**	**94 (53.1)**	**15 (45.5)**	**73 (46.5)**	**17 (44.7)**	**5 (62.5)**	**53 (26.0)**	**23 (40.4)**	**3 (37.5)**
Drug-related	226 (33.8)	74 (41.8)	11 (33.3)	61 (38.9)	15 (39.5)	5 (62.5)	30 (14.7)	15 (26.3)	3 (37.5)
TEAEs associated with death, n (%)	**17 (2.5)**	**10 (5.6)**	**0**	**6 (3.8)**	**1 (2.6)**	**0**	**4 (2.0)**	**2 (3.5)**	**1 (12.5)**
Drug-related	4 (0.6)	3 (1.7)	0	0	0	0	0	0	0

Patients ≥65 years of age experienced ”ACCEPTABLE” TEAEs

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DRUG-RELATED ILD/PNEUMONITIS

	T-DXd Pool			TPC (DB-02)			T-DM1 (DB-03)		
	<65 (n = 668)	≥65 (n = 177)	≥75 (n = 33)	<65 (n = 157)	≥65 (n = 38)	≥75 (n = 8)	<65 (n = 204)	≥65 (n = 57)	≥75 (n = 8)
Any grade, n (%)	**79 (11.8)**	**31 (17.5)**	**5 (15.2)**	**0**	**1 (2.6)**	**0**	**6 (2.9)**	**2 (3.5)**	**1 (12.5)**
1	21 (3.1)	7 (4.0)	0	0	0	0	3 (1.5)	1 (1.8)	0
2	**48 (7.2)**	**20 (11.3)**	**5 (15.2)**	0	0	0	2 (1.0)	1 (1.8)	1 (12.5)
3	4 (0.6)	3 (1.7)	0	0	1 (2.6)	0	1 (0.5)	0	0
4	0	0	0	0	0	0	0	0	0
5	6 (0.9)	1 (0.6)	0	0	0	0	0	0	0
≥3	10 (1.5)	4 (2.3)	0	0	1 (2.6)	0	1 (0.5)	0	0

Rates of adjudicated ILD/pneumonitis were higher in patients ≥65 years

Maximizing the Benefits of Capecitabine

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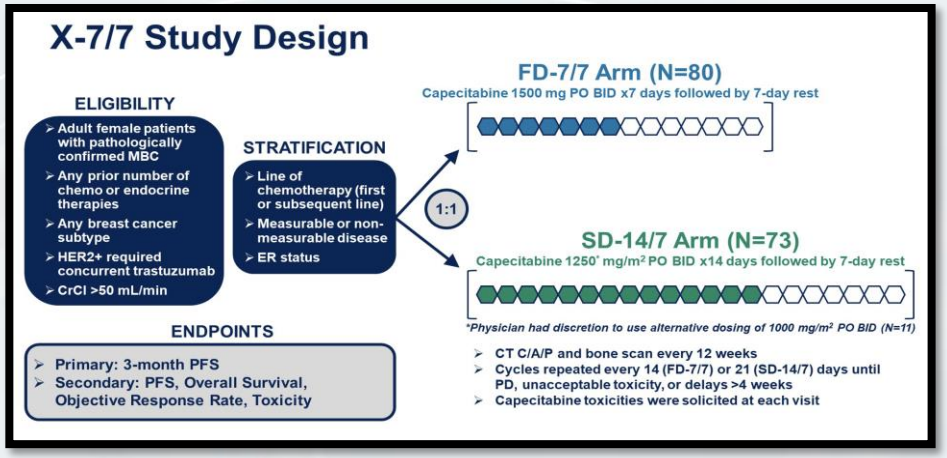
Randomized Trial of Fixed Dose Capecitabine Compared to Standard Dose Capecitabine in Metastatic Breast Cancer: X-7/7 trial

Qamar Khan, Colleen Bohnenkamp, Taylor Monson, Holly Smith, Milind Phadnis, Vinay Raja, Manana Elia, Anne O'Dea, Gregory Crane, Mark Fesen, Lauren Nye, Maureen Sheehan, Robert Pluenneke, Raed Al-Rajabi, Joaquina Baranda, Anup Kasi, Richard McKittrick, Laura Mitchell, Stephanie LaFaver, Priyanka Sharma



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X-7/7 Study Design

ELIGIBILITY
- Adult female patients with pathologically confirmed MBC
- Any prior number of chemo or endocrine therapies
- Any breast cancer subtype
- HER2+ required concurrent trastuzumab
- CrCl >50 mL/min

STRATIFICATION
- Line of chemotherapy (first or subsequent line)
- Measurable or non-measurable disease
- ER status

1:1

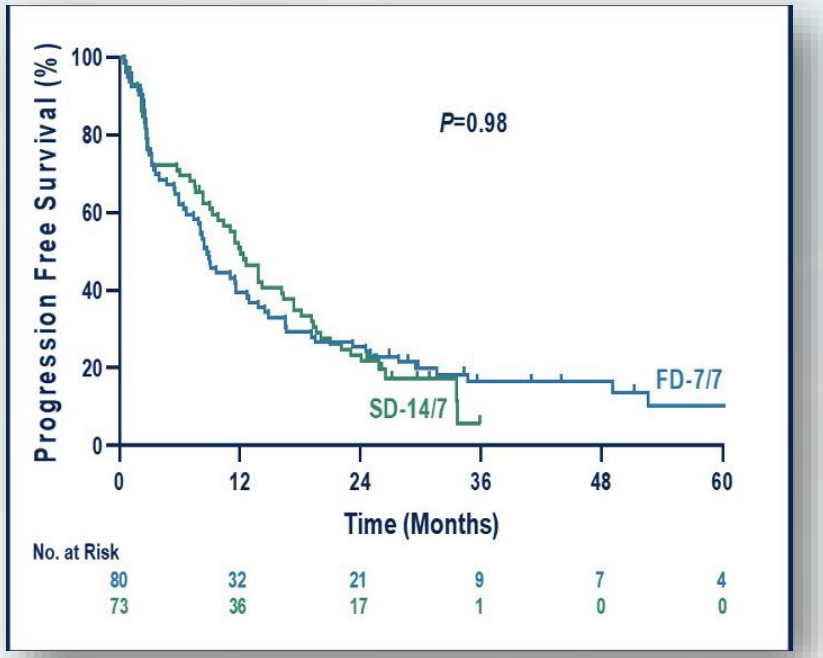
FD-7/7 Arm (N=80)
Capecitabine 1500 mg PO BID x7 days followed by 7-day rest

SD-14/7 Arm (N=73)
Capecitabine 1250* mg/m² PO BID x14 days followed by 7-day rest

*Physician had discretion to use alternative dosing of 1000 mg/m² PO BID (N=11)

ENDPOINTS
- Primary: 3-month PFS
- Secondary: PFS, Overall Survival, Objective Response Rate, Toxicity

- CT C/A/P and bone scan every 12 weeks
- Cycles repeated every 14 (FD-7/7) or 21 (SD-14/7) days until PD, unacceptable toxicity, or delays >4 weeks
- Capecitabine toxicities were solicited at each visit



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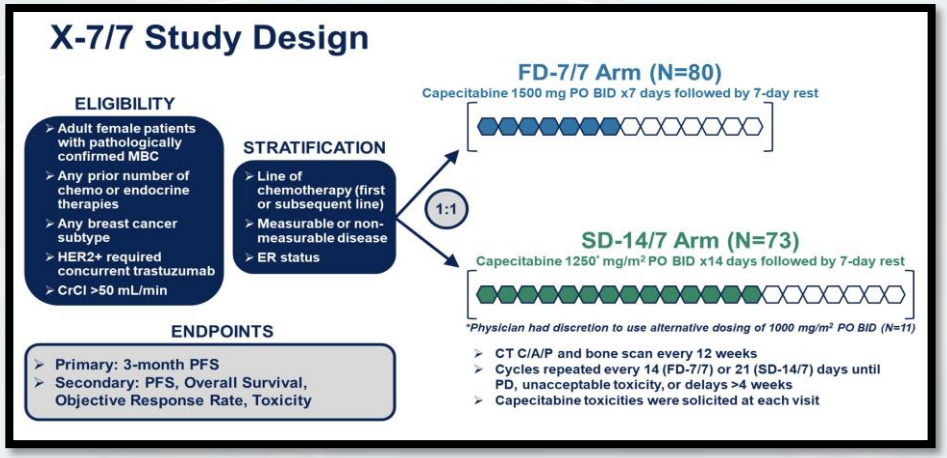

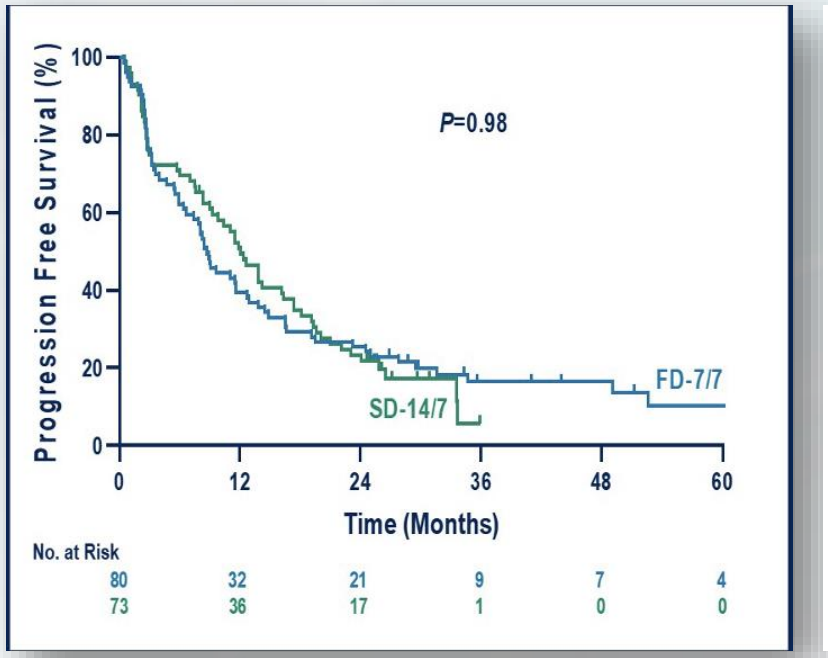

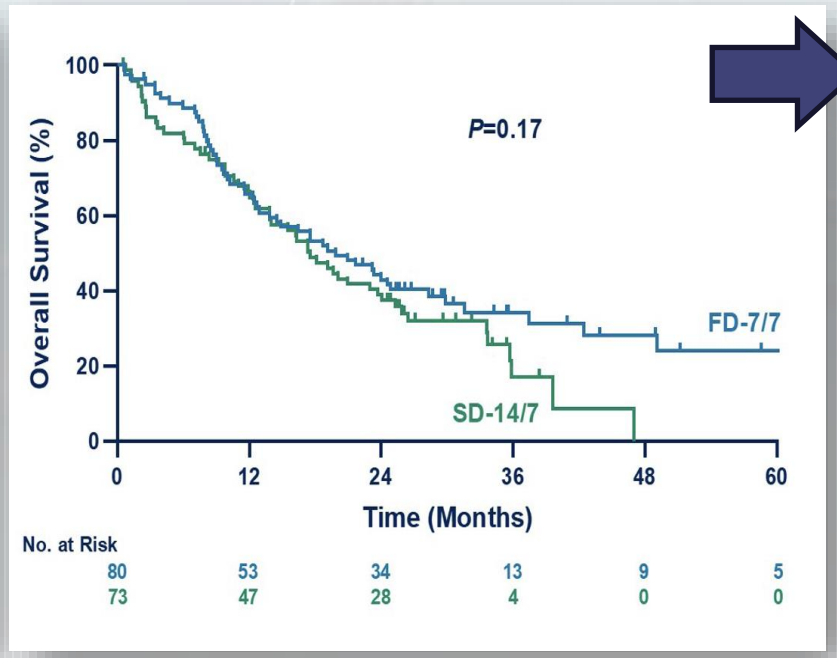

Overall Survival, Landmark Analysis

OS	FD-7/7 (N=80)	SD-14/7 (N=73)	P-value
3-month OS	58 (94%)	56 (85%)	0.16
12-month OS	35 (56%)	40 (63%)	0.59
24-month OS	**19 (30%)**	**21 (33%)**	**0.85**
36-month OS	**16 (23%)**	**16 (23%)**	**1**
48-month OS	12 (17%)	10 (14%)	0.82

PRESENTED BY: Qamar Khan, MD

Maximizing the Benefits of Capecitabine

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	FD-7/7 (N=80)	SD-14/7 (N=73)	P-Value
Diarrhea			
Any Grade	16 (20)	45 (61.6)	0.0039
Grade 2-4	**2 (2.5)**	**15 (20.5)**	**0.0008**
Hand Foot Syndrome			
Any Grade	22 (27.5)	39 (53.4)	0.0033
Grade 2-4	**3 (3.8)**	**11 (15.1)**	**0.0019**
Oral Mucositis			
Any Grade	3 (3.75)	20 (27.4)	0.0001
Grade 2-4	**0**	**4 (5.5)**	**0.0001**
Neutropenia			
Any Grade	30 (37.5)	31 (42.5)	0.67
Grade 2-4	**17 (21.3)**	**20 (27.4)**	0.68

Grade 3-4 toxicity:
27.4% in SD-14/7
11.3% in FD-7/7
p=0.02

Treatment Discontinuation:
28.7% in SD-14/7
7.5% in FD-7/7
p<0.0006

Dose Modification:
23.3% in SD-14/7
7.5% in FD-7/7
p=0.0063

XXIII JORNADA DE REVISIÓN DEL

CONGRESO AMERICANO DE ONCOLOGÍA

Muchas gracias