ASSOCIAZIONE DI ONCOLOGIA
"MARIANGELA PINNA" ODV

Sassari, 26/10/24

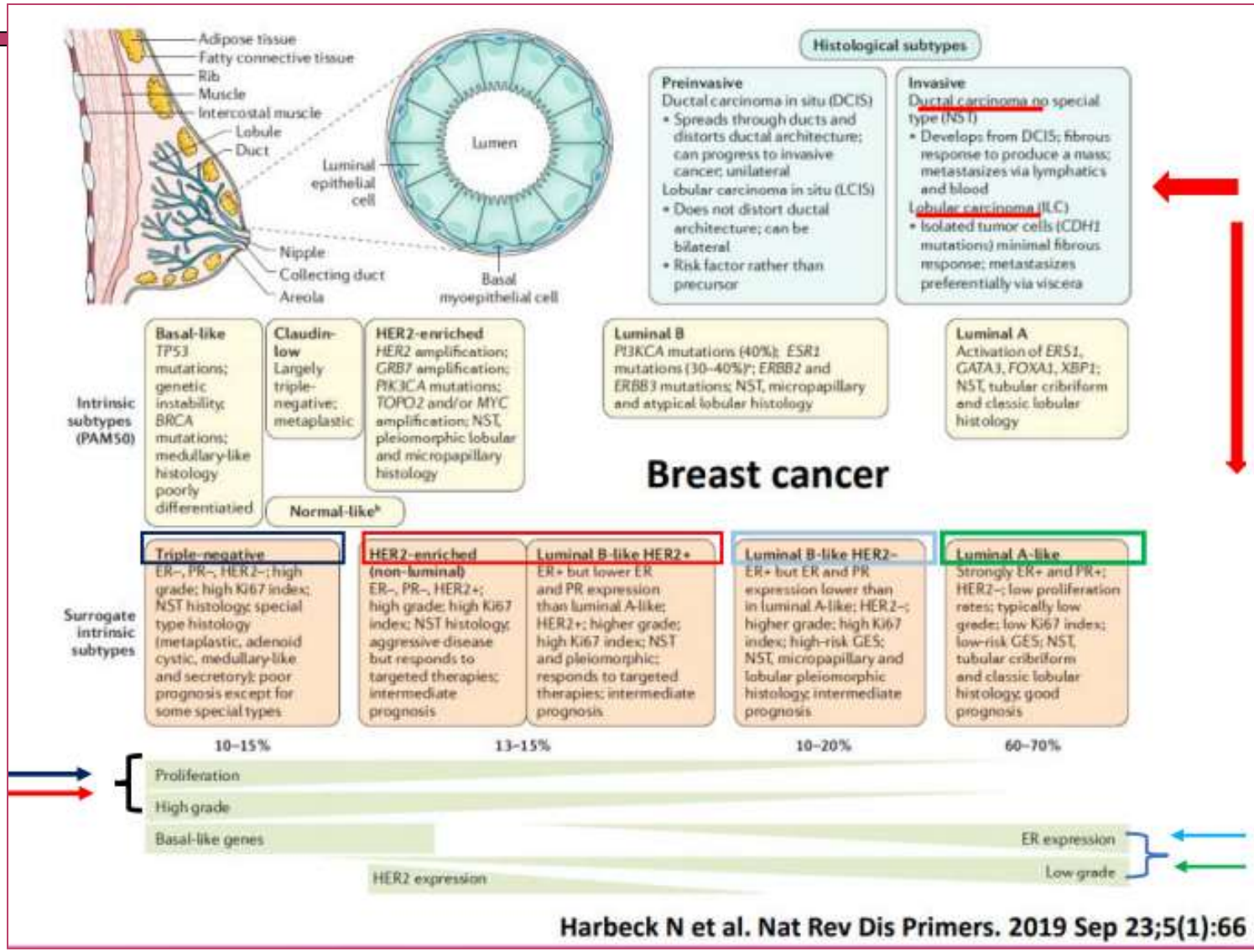
Il Tumore della mammella

Nuove strategie nella malattia avanzata Luminal

Dott.ssa Silvia Mura, U.O. Oncologia Medica , A.O.U. Sassari

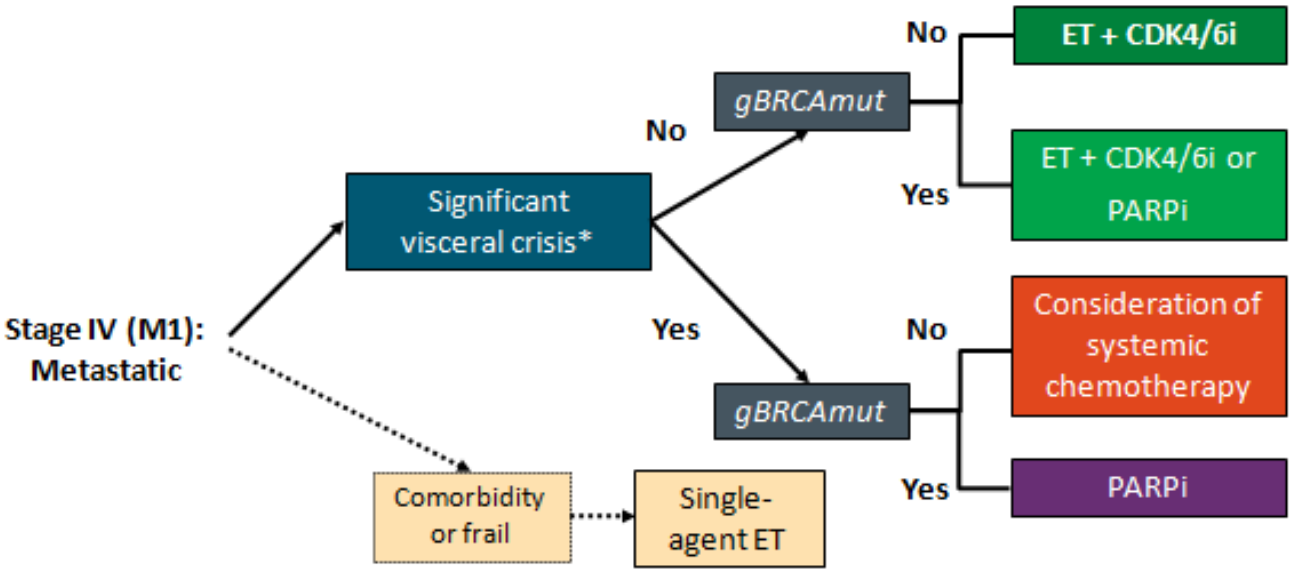
TERAPIA NELLA MALATTIA METASTATICA

- Solo il 5% dei tumori mammari si presenta metastatico *de novo*.
- La maggior parte delle diagnosi di malattia metastatica viene effettuata durante il follow-up.
- Il rischio di recidiva dipende dallo stadio alla diagnosi e dal sottotipo molecolare.
- Dopo una diagnosi di ripresa di malattia è opportuna una ristadiazione completa.



Harbeck N et al. Nat Rev Dis Primers. 2019 Sep 23;5(1):66

Risk Assessment Algorithm to Guide 1L Systemic Therapy Selection in HR+/HER2- MBC

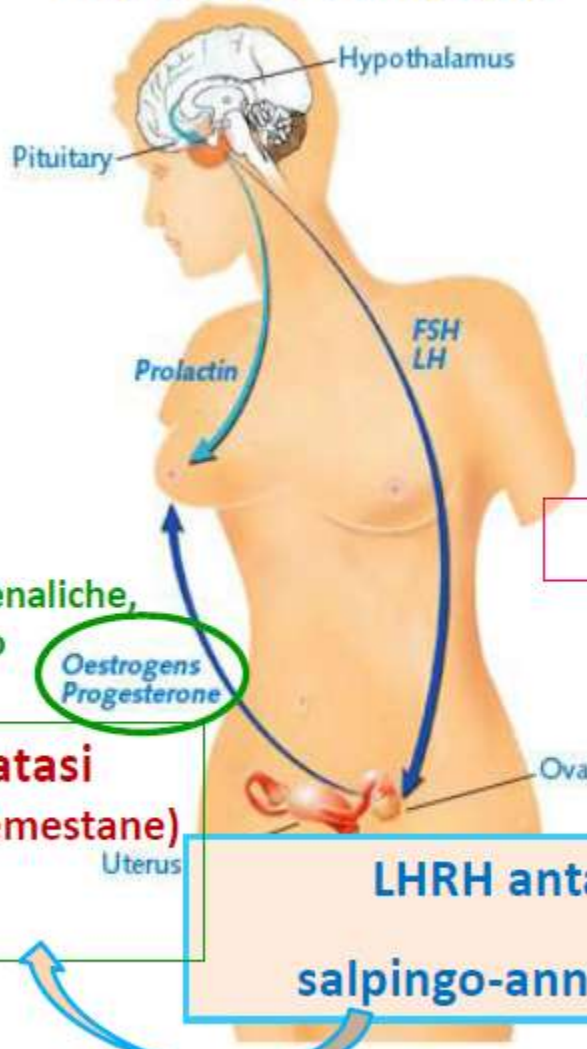


*Defined as patient with severe organ dysfunction, not solely presence of visceral metastases.
Severe organ disfunction assessed by signs and symptoms, laboratory values, and rapid disease progression.

NCCN. Clinical practice guidelines in oncology: breast cancer. v4.2024. nccn.org.

ORMONOTERAPIA

POST-MENOPAUSA



PRE-MENOPAUSA

Tamoxifene

Fegato, ghiandole surrenaliche, tessuto adiposo

Inibitori dell'aromatasi
(letrozolo, anastrozolo, exemestane)

Fulvestrant

LHRH antagonisti/

salpingo-annessiectomia

Meccanismo d'azione degli inibitori delle cicline

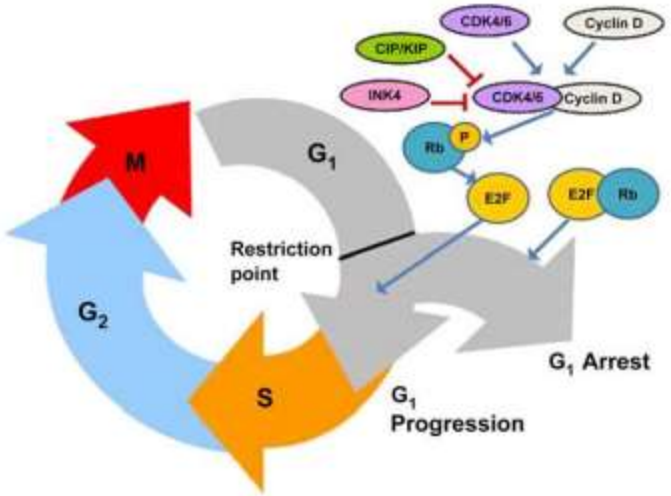


Figure 1. The interaction of Rb, cyclin D, and CDK4/6 in cell cycle progression. Hypophosphorylated Rb sequesters E2F family members, leading to decreased expression of genes involved in cell cycle progression from G_1 to S phases. CDK4/6-cyclin D complex phosphorylates Rb leading to loss of repression of E2F factors, resulting in cell cycle progression. Cip-Kip and INK4 family members inhibit cyclin-dependent kinase activity.

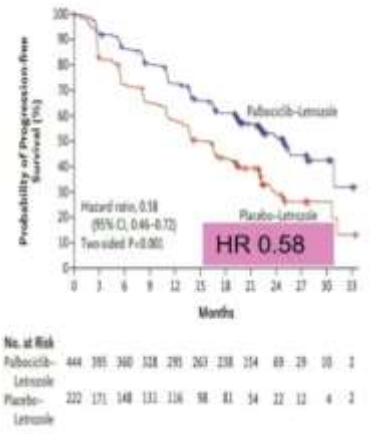
Abbreviations: CDK4/6, cyclin-dependent kinases 4 and 6; E2F, E2 transcription factor; P, phosphate group; Rb, retinoblastoma tumor suppressor protein.

Murphy The Oncol 2015

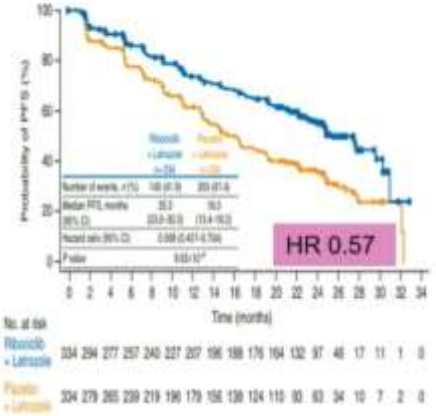
Endocrine Resistance/Sensitivity: PFS Data

Endocrine sensitive

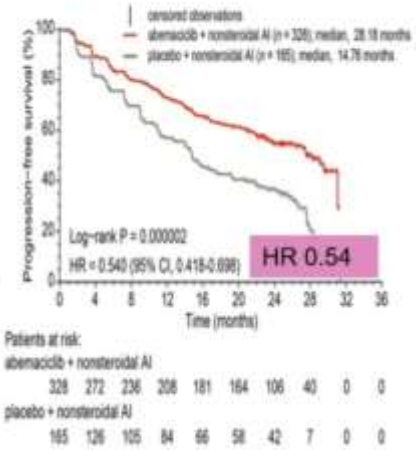
PALOMA-2

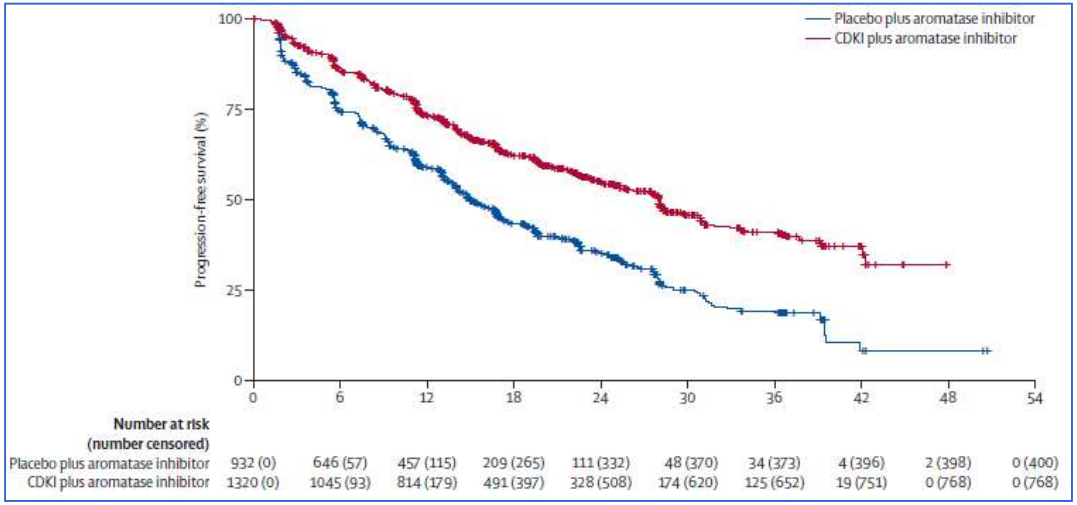


MONALEESA-2



MONARCH 3



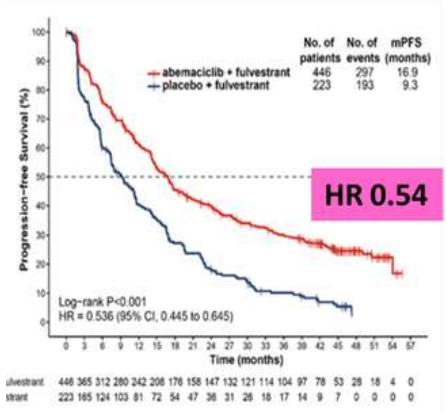


Gao JJ et al, Lancet Oncol 2020;21(2):250-60

Endocrine Resistance/Sensitivity: PFS Data

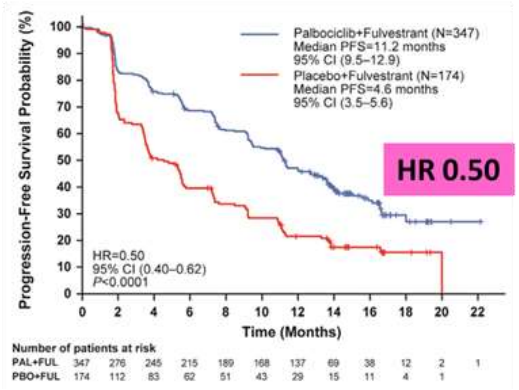
Endocrine resistant

MONARCH-2



HR 0.54

PALOMA-3



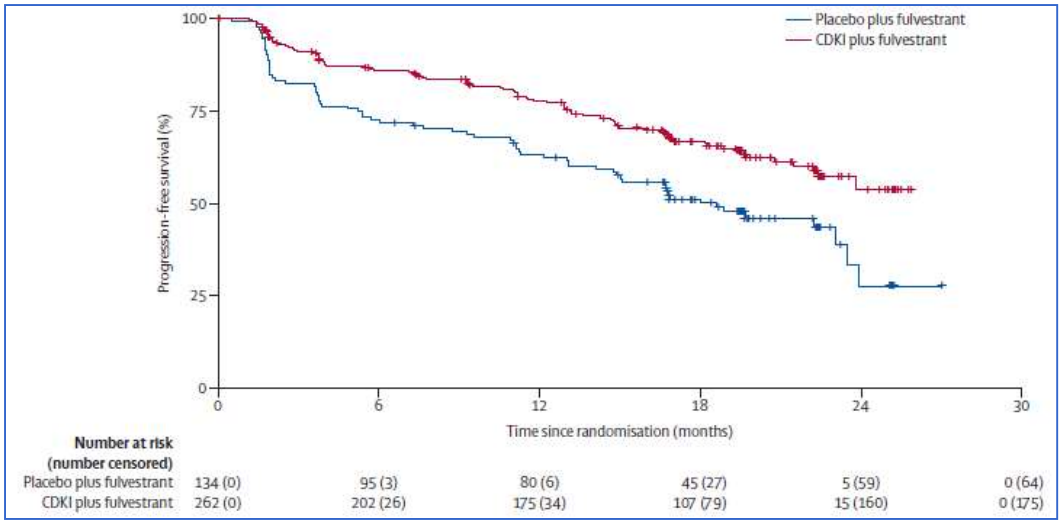
HR 0.50

MONALEESA-3

HR 0.56

MONALEESA-7

HR 0.56



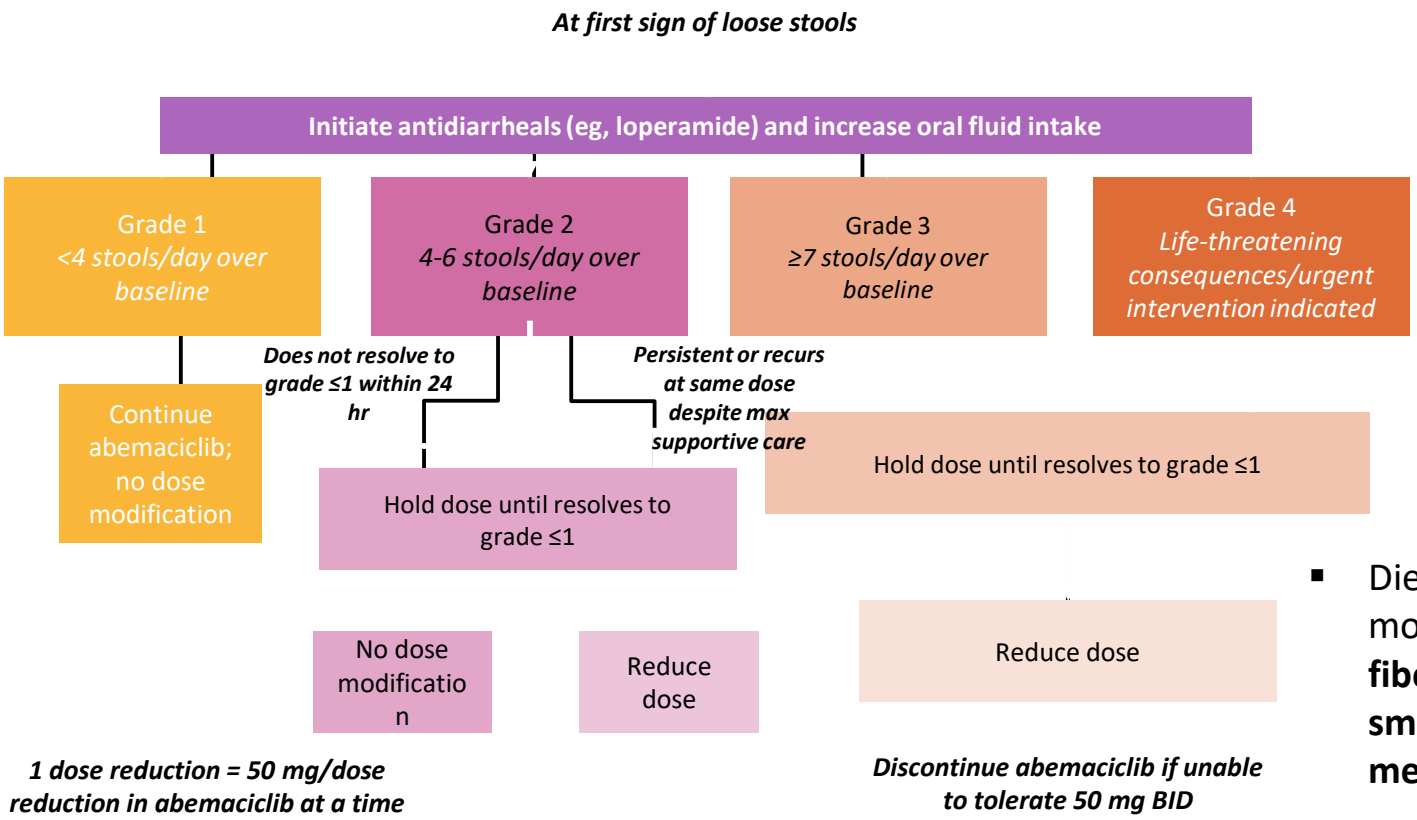
Gao JJ et al, Lancet Oncol 2020;21(2):250-60

Key AEs With CDK4/6 Inhibitors: Monitoring and Prevention to Maximize Adherence

Diarrhea	Hepatobiliary Toxicity	Neutropenia	VTE	ILD/ Pneumonitis
Abemaciclib **Palbociclib** **Ribociclib**	**Abemaciclib** **Ribociclib**	**Abemaciclib** **Palbociclib** **Ribociclib**	**Abemaciclib**	**Abemaciclib** **Palbociclib** **Ribociclib**
Antidiarrheal therapy Increase oral hydration Notify healthcare professional Dietary modification	LFTs before starting treatment, Q2W x 2 mo, then: ▪ *Abemaciclib*, QM x 2 mo, then as indicated ▪ *Ribociclib*, at start of cycle x 4 cycles	CBC before starting treatment, then: ▪ *Abemaciclib*, Q2W x 2 mo, QM x 2 mo, then as indicated ▪ *Palbociclib*, D1 and D15 of C1-2, then as indicated ▪ *Ribociclib*, Q2W x 2 cycles, start of next 4 cycles, then as indicated	Monitor for signs and symptoms of thrombosis or pulmonary embolism	Monitor for pulmonary symptoms indicative of ILD or pneumonitis (eg, hypoxia, cough, dyspnea)

Abemaciclib PI. Palbociclib PI. Ribociclib PI.

Management of Abemaciclib-Induced Diarrhea

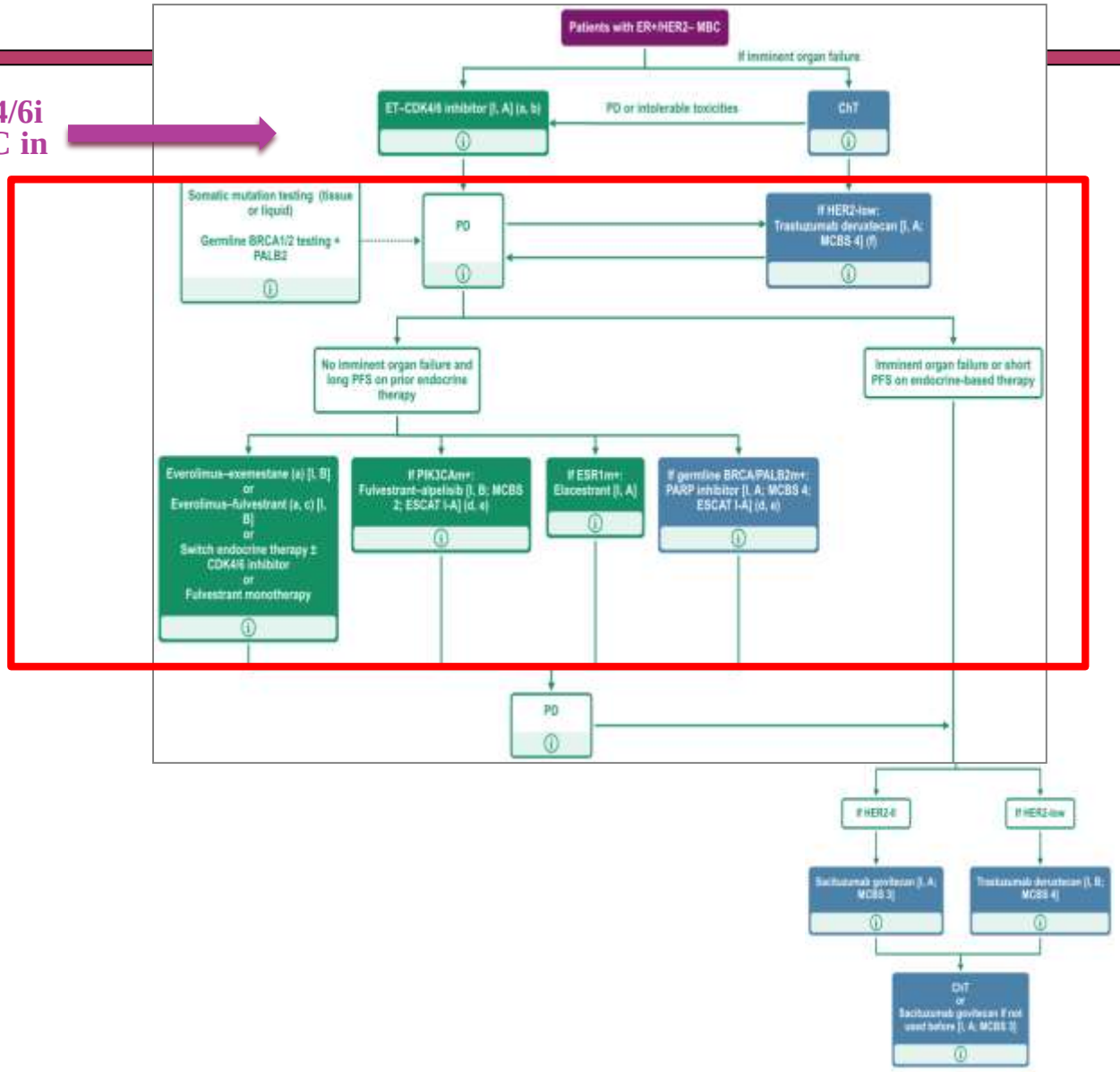


- Dietary modification: **Low fiber, low fat, smaller frequent meals**

Abemaciclib PI. Rugo. Ann Oncol. 2022;33:616. Sammons. Exp Rev Anticancer Ther. 2022;22:805.

Treatment of HR+/HER2- MBC in 2024

Adding a CDK4/6i is the global SoC in 1st line MBC treatment



Gennari A et al, Ann Oncol 2021;32(12):1475-95 – Living Guidelines Update May 2023

What to Do beyond CDK4/6 Inhibitors ?

- **CDK 4/6 inhibitor beyond CDK 4/6 inhibitor**
  - PostMONARCH (Kalinsky K, ASCO 2024)
  - MAINTAIN (Kalinsky K et al, JCO 2023)
  - PACE (Mayer E et al, JCO 2024)
  - PALMIRA (Llombart-Cussac A et al, ASCO 2023)
- Oral SERD
  - EMERALD (Bidard FC et al, JCO 2022)
  - SERENA-2 (Oliveira M et al, SABCS 2022)
- Other combinations of ET + targeted agents
  - SOLAR-1 (Andre F et al, NEJM 2019 & Ann Oncol 2021)
  - CAPItello-291 (Turner NC et al, NEJM 2023 & Rugo HS et al ESMO Breast 2024)
  - INAVO120 (Jhaveri KL et al, SABCS 2022 & Juric D et al, ASCO 2024)
- PARP inihibitors (in carriers of germline *BRCA* pathogenic variants)
- ADCs

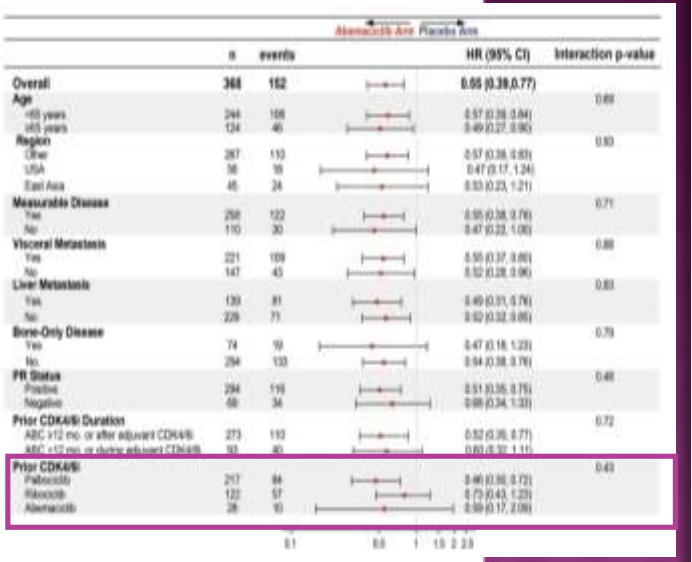
2ND LINE POST-CDK4/6I	PFS
Fulvestrant + alpelisib (BYLieve) – *PIK3CA*mut	7.3mo
Fulvestrant + capivasertib (CAPITELLO)	7.2mo
Camizestrant (SERENA-3) – *ESR1*mut	6.3-9.2mo
AI + albelisib (BYLieve) – *PIK3CA*mut	5.7mo
Fulvestrant + ribociclib (MAINTAIN)	5.3mo
Fulvestrant alone (PACE)	4.8mo
Fulvestrant + palboiclib (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

CDK4/6 Inhibitors beyond Progression

	postMONARCH		MAINTAIN		PALMIRA		PACE	
ARM	ABEMA	PLAC	RIBO	PLAC	PALBO	CONT	PALBO	CONT
PFS	6.0 mos.	5.3 mos.	5.3 mos.	2.8 mos.	4.9 mos.	3.6 mos.	4.6 mos	4.8 mos.
▲	0.7 mos.		2.5 mos.		1.3 mos		-0.2 mos	
HR	0.73		0.57		0.84		1.11	
P value	0.02		0.006		0.149		0.06	

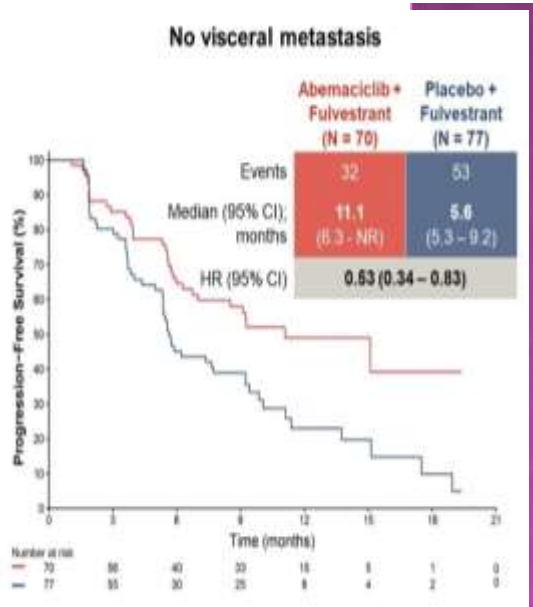
Control arm had longer PFS in postMONARCH likely indicating more ET-sensitive disease

Kalinsky et al ASCO 2024, Kalinsky et al J Clin Oncol 2023, Llombart-Cussac et al ASCO 2023, Mayer et al SABCS 2022



What about use after adjuvant CDK4/6i ?

		Abemaciclib + Fulvestrant N=182 (%)	Placebo + Fulvestant N=186 (%)
Measurable Disease		72	68
Visceral metastasis		62	59
Site of Metastasis	Liver	37	38
	Bone-Only	18	23
Prior CDK4/6i Setting	ABC	100	98
	Adjuvant	0	2
Prior CDK4/6i	Palbociclib	59	59
	Ribociclib	34	33
	Abemaciclib	8	8



O'Regan R, ASCO 2024. Kalinsky K et al, ASCO 2024

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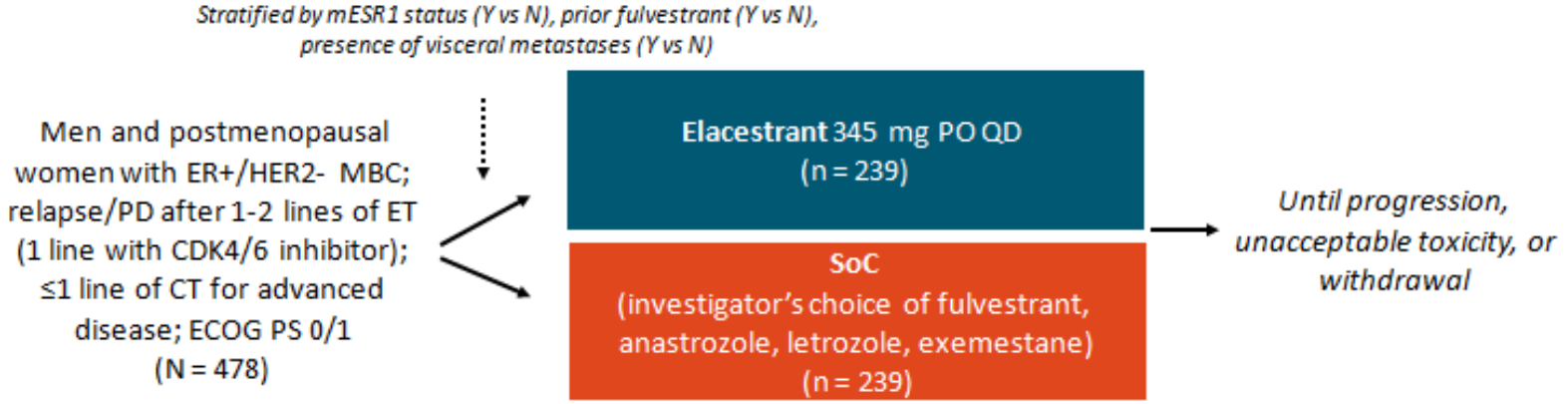
EMERALD: Elacestrant vs Investigator's Choice SoC ET in ER+/HER2- MBC

- Randomized, open-label, active-controlled phase III trial



- **Coprimary endpoints:** PFS in all patients, PFS in patients with *ESR1* mutation, both by BICR
- **Key secondary endpoint:** OS
- Current analysis examined impact of prior CDK4/6i duration on PFS

Bidard. JCO. 2022;40:3246. Bardia. SABCS 2022. Abstr GS3-01. Elacestrant PI.

EMERALD: PFS by Duration (≥6, ≥12, and ≥18 Mo) of Prior CDK4/6i in All Patients and in *ESR1* Mutated

PFS Outcomes in All Patients	CDK4/6i ≥6 Mo (87.5%)		CDK4/6i ≥12 Mo (66.7%)		CDK4/6i ≥18 Mo (46.7%)	
	Elacestrant (n = 202)	SoC (n = 205)	Elacestrant (n = 150)	SoC (n = 160)	Elacestrant (n = 98)	SoC (n = 119)
Median PFS, mo (95% CI)	2.79 (1.94-3.78)	1.91 (1.87-2.14)	3.78 (2.33-6.51)	1.91 (1.87-3.58)	5.45 (2.33-8.61)	3.29 (1.87-3.71)
▪ HR (95% CI)	0.688 (0.535-0.884)		0.613 (0.453-0.828)		0.703 (0.482-1.019)	

PFS Outcomes in *ESR1* Mutated	CDK4/6i ≥6 Mo (92.3%)		CDK4/6i ≥12 Mo (71.6%)		CDK4/6i ≥18 Mo (50.0%)	
	Elacestrant (n = 103)	SoC (n = 102)	Elacestrant (n = 78)	SoC (n = 81)	Elacestrant (n = 55)	SoC (n = 56)
Median PFS, mo (95% CI)	4.14 (2.20-7.79)	1.87 (1.87-3.29)	8.61 (4.14-10.84)	1.91 (1.87-3.68)	8.61 (5.45-16.89)	2.10 (1.87-3.75)
▪ HR (95% CI)	0.517 (0.361-0.738)		0.410 (0.262-0.634)		0.466 (0.270-0.791)	

Bardia. SABCS 2022. Abstr GS3-01. Bidard. JCO. 2022; 40:3246.

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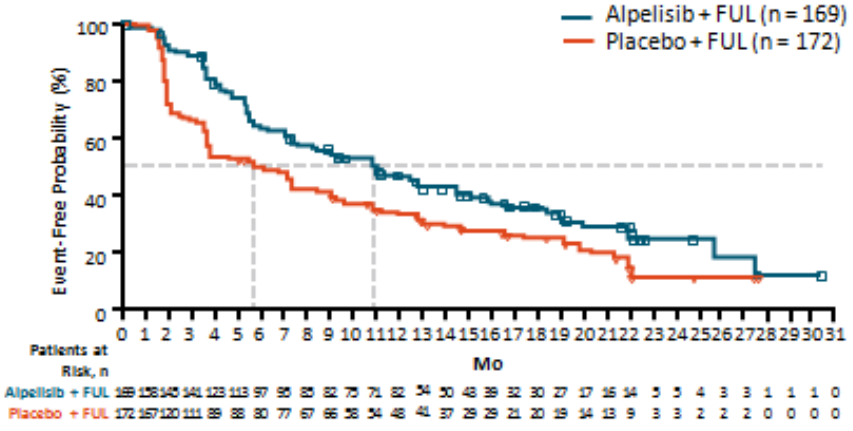
SOLAR-1: PFS and OS With Addition of Alpelisib to Fulvestrant in *PIK3CA*-Mutant, HR+, ABC

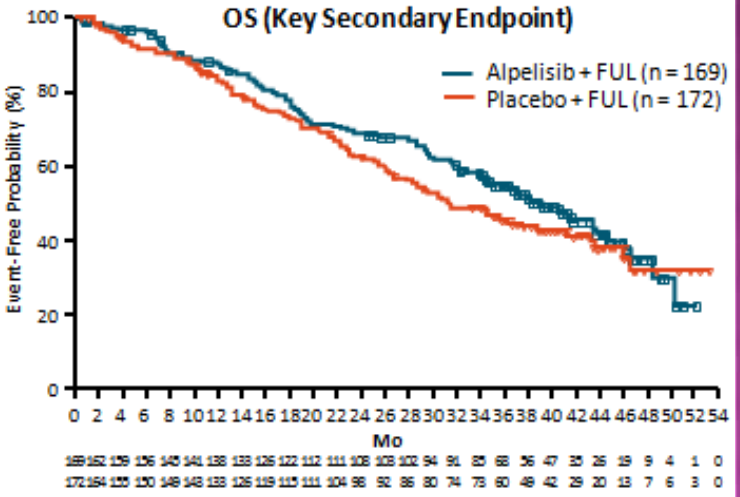
- Randomized double-blind, placebo controlled, phase III study of alpelisib plus fulvestrant in men and postmenopausal women with HR+/HER2-negative advanced breast cancer with disease progression on or after AI therapy

PFS (Primary Endpoint)



Median PFS: 11.0 vs 5.7 mo
Hazard ratio: 0.65 (0.50-0.85)
P = .00065

OS (Key Secondary Endpoint)



Median OS: 39.3 vs 31.4 mo
Hazard ratio: 0.86 (0.64-1.15)
P = .15

Andre. NEJM. 2019;380:1929. Andre. Ann Oncol. 2021;32:208.

BYLieve: Alpelisib + Fulvestrant in *PIK3CA*m HR+/HER2- ABC After CDK4/6 Inhibitor + AI (Cohort A)

- **Primary endpoint met** in cohort A in patients who received prior CDK4/6i + AI
  - 50.4% alive without PD at 6 mo per investigator assessment
  - Lower bound of 95% CI >30%
- Median PFS in mFAS*: 7.3 mo
- Reduction in tumor size (70.1%) comparable to cohort B patients who received alpelisib + letrozole after PD on prior CDK4/6i + fulvestrant (66.3%)

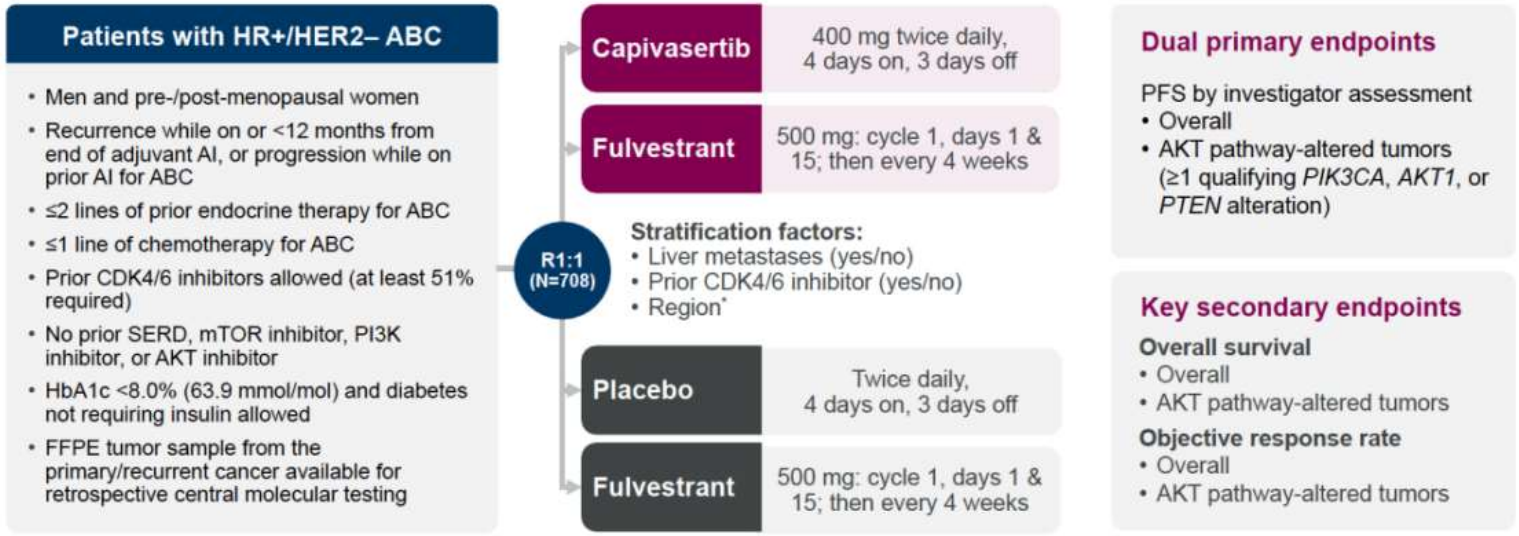
Investigator-Assessed Outcome, n (%)	mFAS* (n = 121)	mFAS* With Measurable Disease (n = 100)
Best overall response		
▪ CR	0	0
▪ PR	21 (17)	21 (21)
▪ Neither CR nor PR	16 (13)	0
▪ SD	55 (45)	55 (55)
▪ PD	14 (12)	11 (11)
▪ Unknown	15 (12)	13 (13)
ORR	21 (17)	21 (21)
Clinical benefit rate†	55 (45)	42 (42)

*Patients with centrally confirmed *PIK3CA* mutation.
†Clinical benefit rate = CR + PR + SD + non-CR/non-PD ≥24 wk.

Rugo. SABCS 2020. Abstr PD2-07 Rugo. Lancet Oncol. 2021;22:489.

Capitello-291

Phase III, randomized, double-blind, placebo-controlled study (NCT04305496)



Tirner et al, SABCS 2022

FDA approves capivasertib with fulvestrant for breast cancer

On November 16, 2023, the Food and Drug Administration approved capivasertib (Truqap, AstraZeneca Pharmaceuticals) with fulvestrant for adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer with one or more PIK3CA/AKT1/PTEN-alterations, as detected by an FDA-approved test, following progression on at least one endocrine-based regimen in the metastatic setting or recurrence on or within 12 months of completing adjuvant therapy.

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TRASTUZUMAB DERUXTECAN

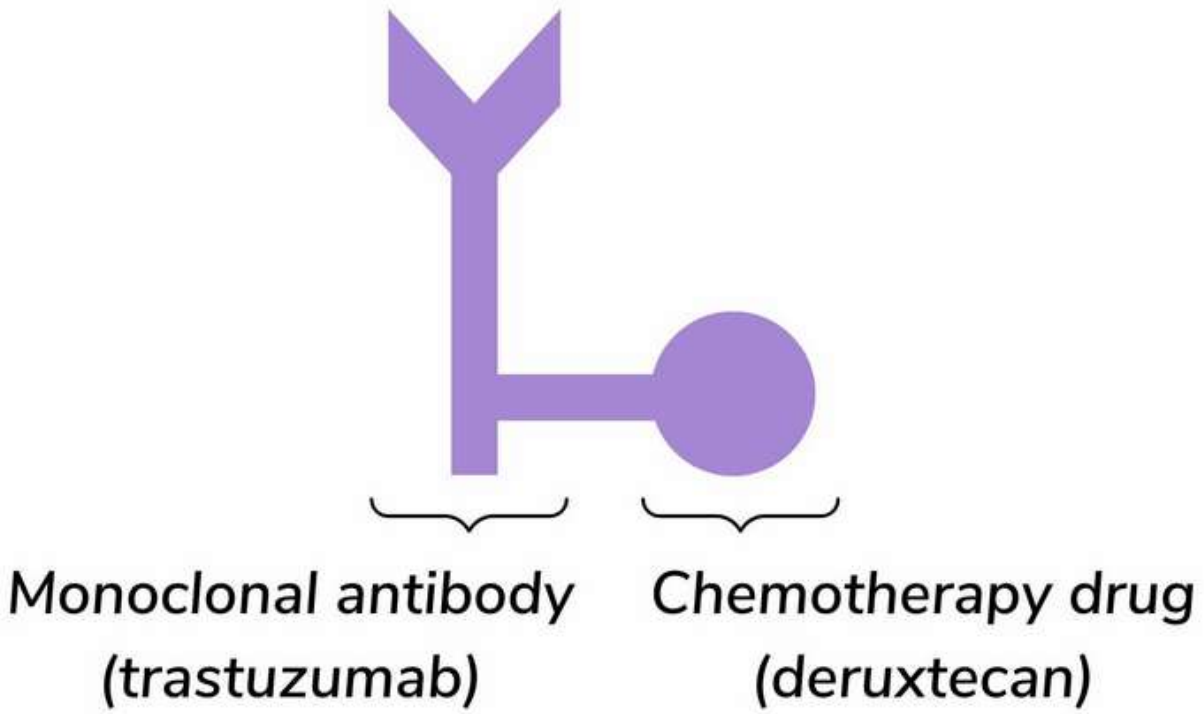
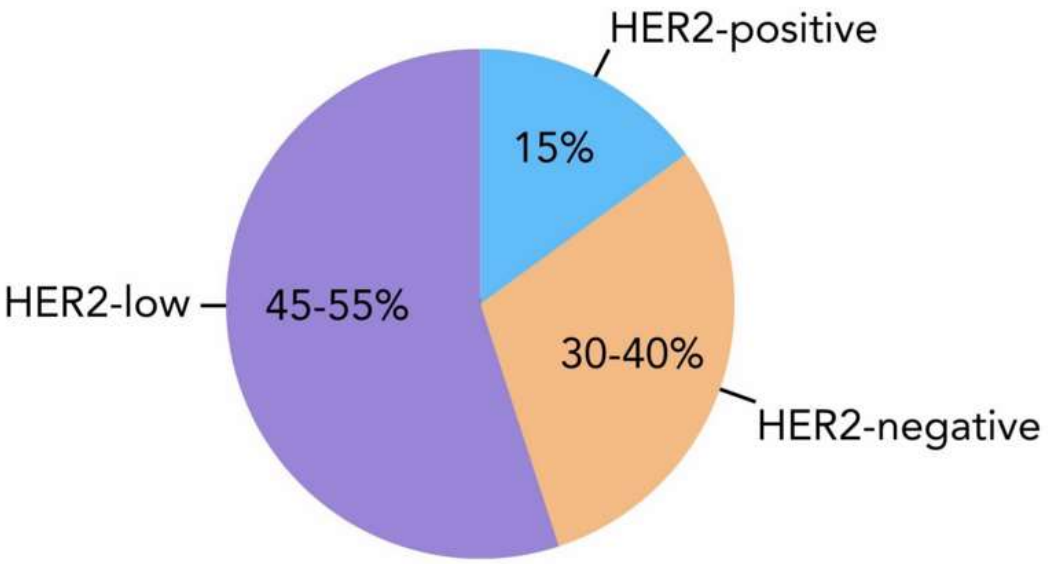


Figure 2. The structure of trastuzumab deruxtecan (Enhertu®).

HER2 status	Characteristics
HER2-negative	IHC 0
HER2-low	IHC 1+ or IHC 2+ (with a negative FISH)
HER2-positive	IHC 2+ (with a positive FISH) or IHC 3+



DESTINY-Breast 04 Updated Efficacy and safety

Patients[a]
- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

HR+ ≈ 480
HR− ≈ 60

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n=184)

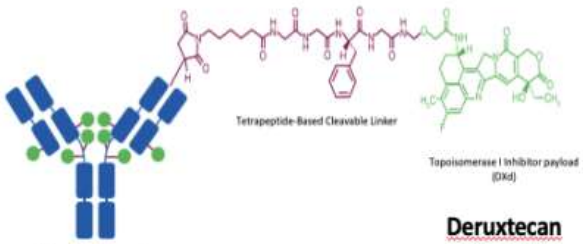
Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[b]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

Stratification factors
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

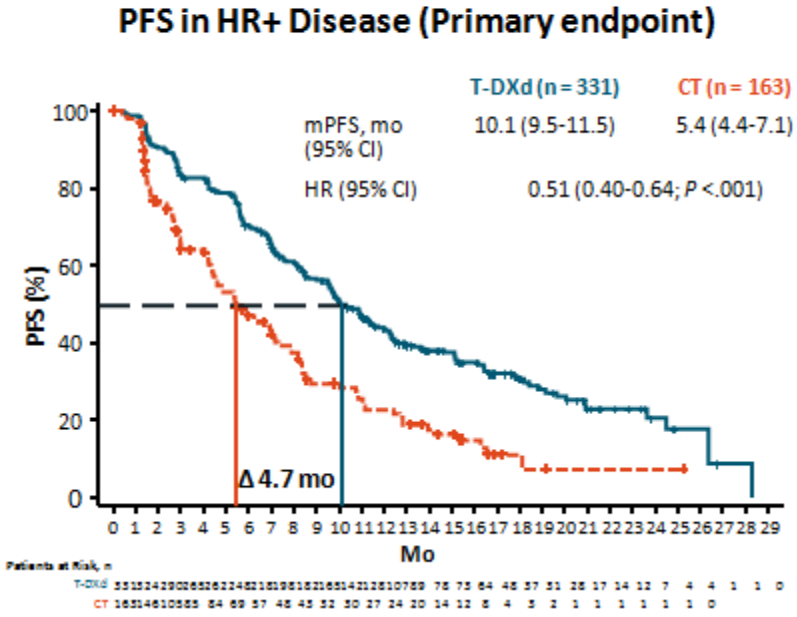
Trastuzumab Deruxtecan

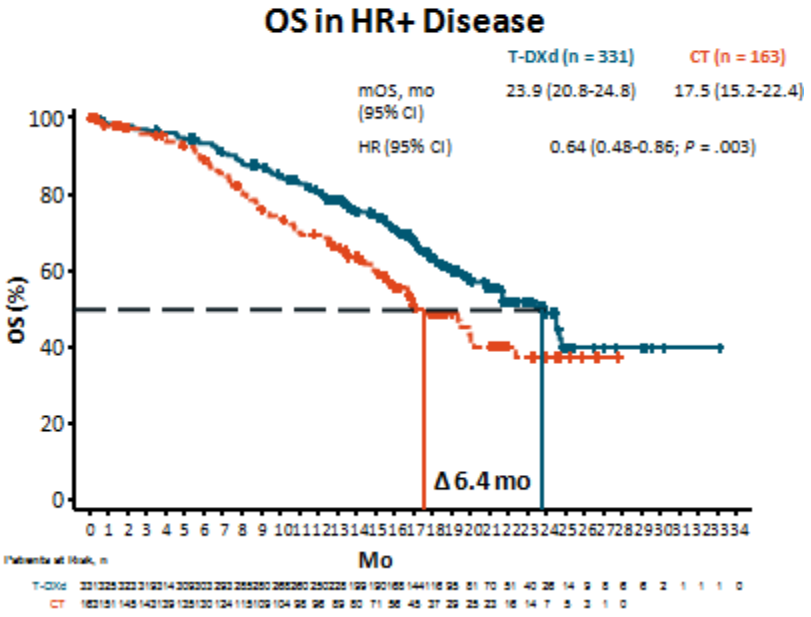
- A **humanized anti-HER2 IgG1 mAb** with the same amino acid sequence as trastuzumab
- A **topoisomerase I inhibitor payload**, an exatecan derivative
- A tetrapeptide-based cleavable linker



Modi et al, NEJM 2022

T-DXd vs Chemotherapy for Previously Treated HER2-Low ABC (DESTINY-Breast04): PFS and OS





special articles

US Food and Drug Administration Approval Summary: Fam-Trastuzumab Deruxtecan-nxki for Human Epidermal Growth Factor Receptor 2-Low Unresectable or Metastatic Breast Cancer

Preeti Narayan, MD[1]; Asma Dilawari, MD[1]; Christy Osgood, MD[1]; Zhou Feng, PhD[1]; Erik Bloomquist, PhD[1]; William F. Pierce, MD[1]; Samina Jafri, PhD[2]; Shyam Kalavar, PhD[2]; Marina Kondratovich, PhD[2]; Prakash Jha, MD[2]; Soma Ghosh, PhD[2]; Shenghui Tang, PhD[2]; Richard Pazdur, MD[1,3]; Julia A. Beaver, MD[1,3]; and Laleh Amiri-Kordestani, MD[1]

abstract

PURPOSE The US Food and Drug Administration approved fam-trastuzumab deruxtecan-nxki (DS-8201a, T-DXd) for the treatment of adult patients with unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-low (immunohistochemistry 1 + or immunohistochemistry 2+/in situ hybridization–) breast cancer who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy.

SERIE GENERALE

Spediz. abb. post. - art. 1, comma 1
Legge 27-02-2004, n. 46 - Filiale di Roma

Anno 164° - Numero 296

GAZZETTA UFFICIALE

DELLA REPUBBLICA ITALIANA

PARTE PRIMA **Roma - Mercoledì, 20 dicembre 2023** SI PUBBLICA TUTTI I GIORNI NON FESTIVI

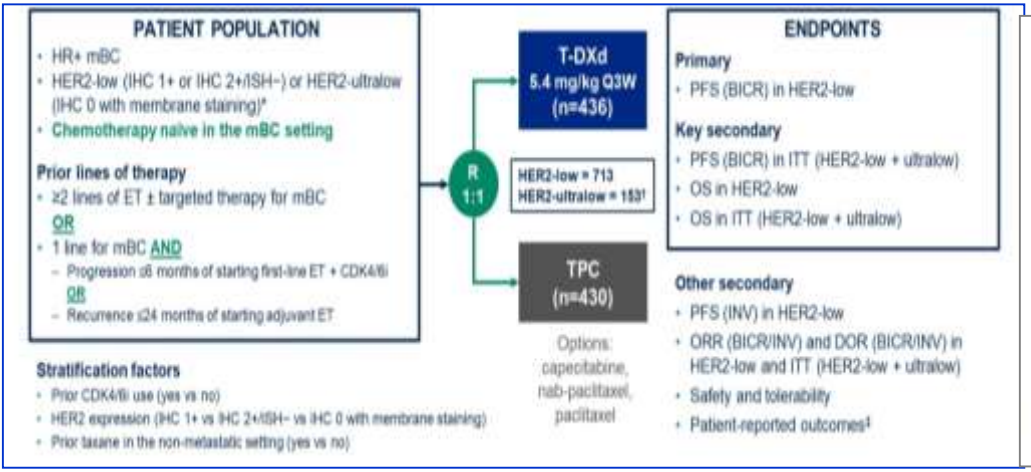
"Enhertu" in monoterapia è indicato per il trattamento di pazienti adulti con cancro della mammella HER2-low non resecabile o metastatico, che hanno ricevuto precedente chemioterapia per malattia metastatica o che hanno sviluppato recidiva della malattia durante o entro sei mesi dal completamento della chemioterapia adiuvante»

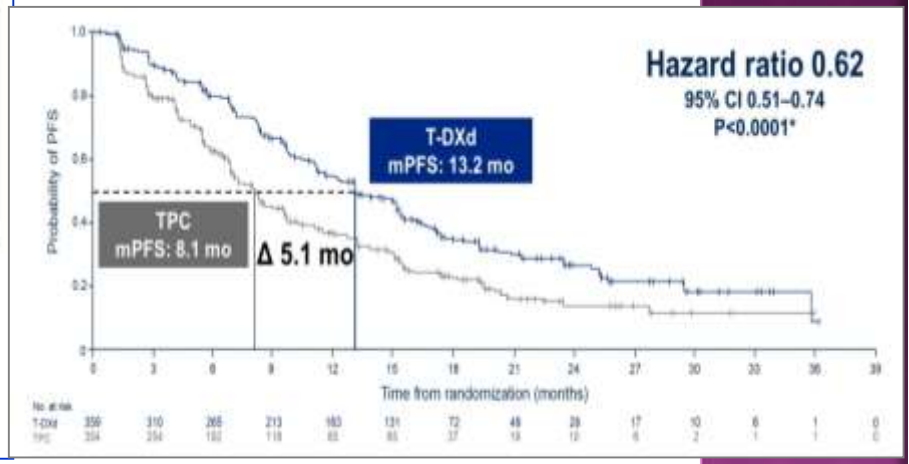
Enhertu (trastuzumab deruxtecan) - Carcinoma della mammella HER2low

AGENZIA ITALIANA DEL FARMACO

ADCs in HR+/HER2-low MBC: Trastuzumab Deruxtecan

DESTINY-Breast06 trial



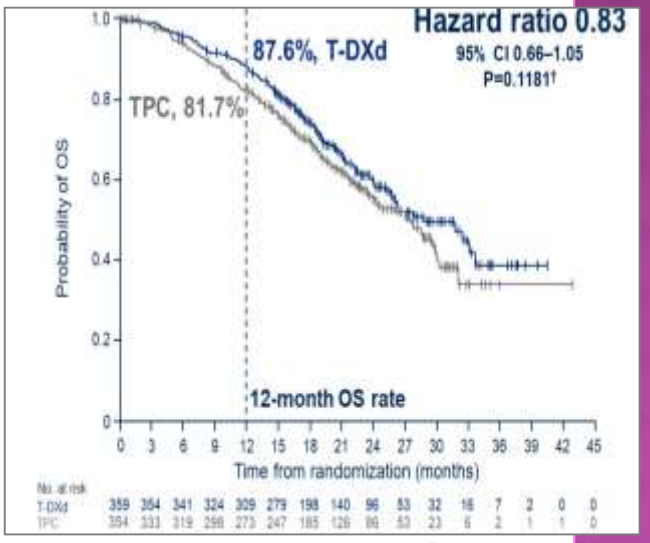


Median previous lines for MBC: 2 (1-5)

Median previous CT lines for MBC: 0

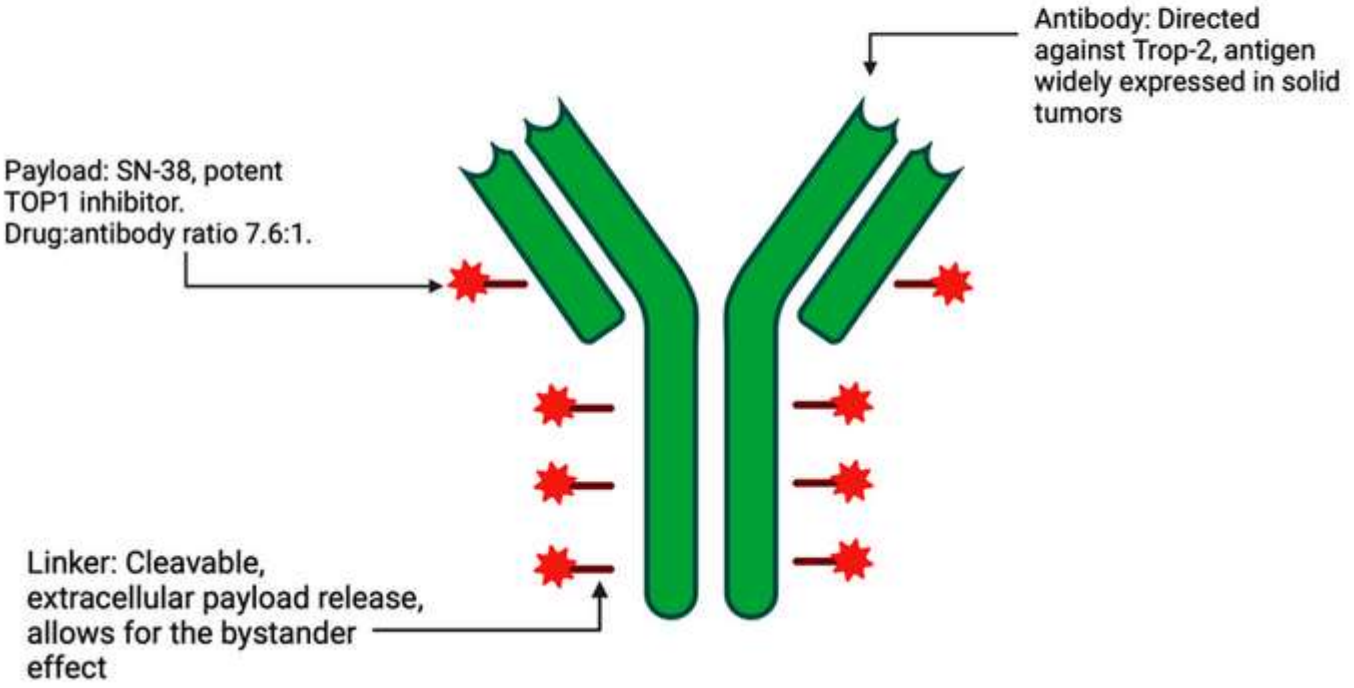
Pretreatment with CDK4/6i: 89%

HER2 1+ = 54% / HER2 2+&ISH- = 27% / HER2 ultralow 17%



Curigliano G et al, ASCO 2024

Sacituzumab Govitecan: First-in-class Trop2 ADC



TROPiCS-02: A Phase 3 Study of SG in HR+/HER2- Locally Recurrent Inoperable or Metastatic Breast Cancer

NCT03901339

Metastatic or locally recurrent inoperable HR+/HER2− breast cancer that progressed after[a]:

- At least 1 endocrine therapy, taxane, and CDK4/6i in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
  - (Neo)adjuvant therapy for early-stage disease qualified as a prior line of chemotherapy if disease recurred within 12 months
- Measurable disease by RECIST 1.1

N=543

R 1:1

Treatment was continued until progression or unacceptable toxicity

Sacituzumab govitecan
10 mg/kg IV
days 1 and 8, every 21 days
n=272

Treatment of physician's choice[b]
(capecitabine, vinorelbine, gemcitabine or eribulin)
n=271

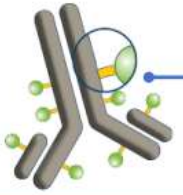
Endpoints

Primary
- PFS by BICR

Secondary
- OS
- ORR, DOR, CBR by LIR and BICR
- PRO
- Safety

Stratification:
- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥6 months (yes/no)
- Prior lines of chemotherapies (2 vs 3/4)

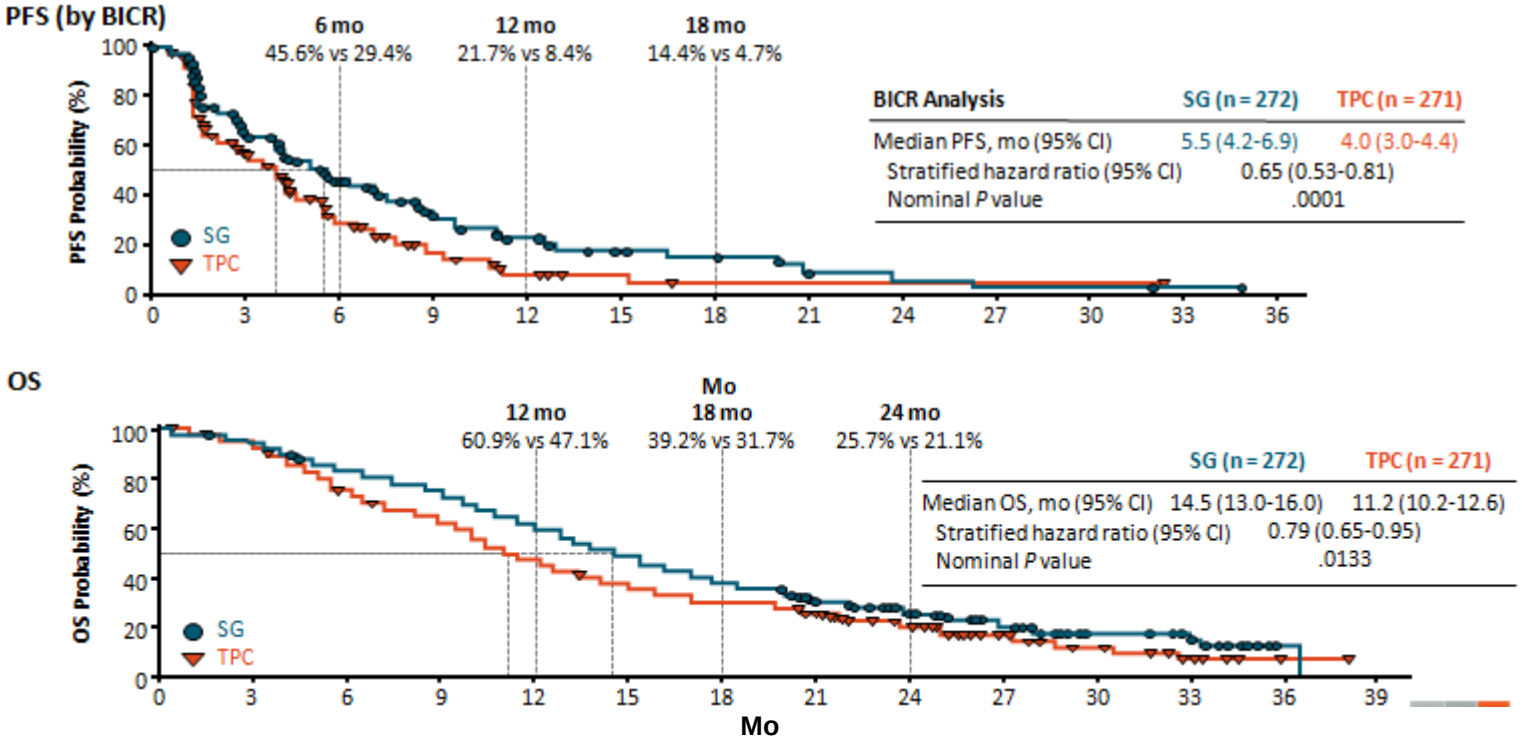
SN-38 payload (Topo1 inhibitor) more potent than parent compound, irinotecan



Humanized anti-Trop-2 Ab
- Targets Trop-2, an epithelial antigen expressed on many solid cancers, including mTNBC

Tolaney et al, ASCO 2023

TROPiCS-02: Sacituzumab Govitecan vs CT for Previously Treated HR+/HER2- ABC: Updated PFS/OS

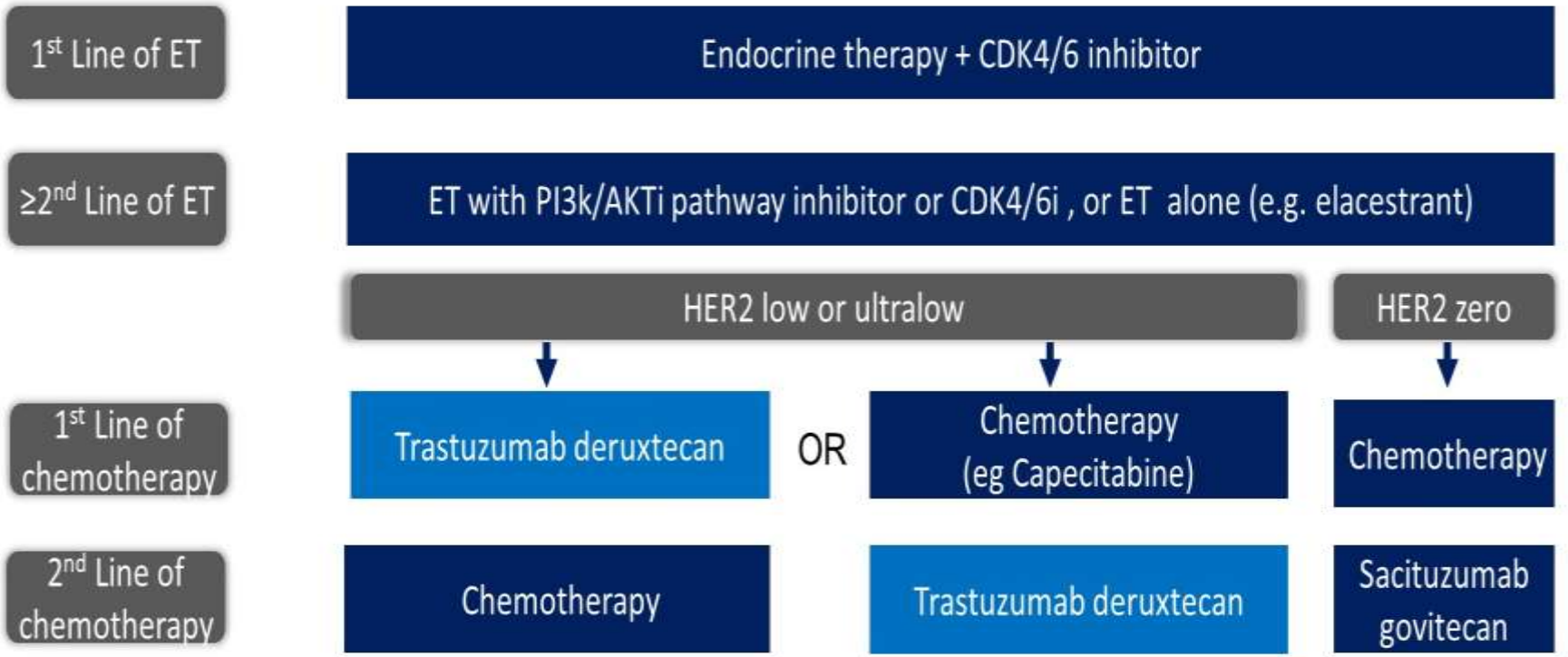


Tolaney. ASCO 2023. Abstr 1003.

FDA approves sacituzumab govitecan-hziy for HR-positive breast cancer

On February 3, 2023, the Food and Drug Administration (FDA) approved sacituzumab govitecan-hziy (Trodelvy, Gilead Sciences, Inc.) for patients with unresectable locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH-) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting.

ADCs in HR+/HER2- MBC after ASCO 2024



Krop I, ASCO 2024

Grazie
per l'attenzione