9e ÉDITION

JOURNÉES DU **GFCO 2023**

Biomarqueurs et analyses moléculaires en oncologie

Avec la participation scientifique du GFCO

Innovations dans les cancers du sein

Pr Nicolas ISAMBERT

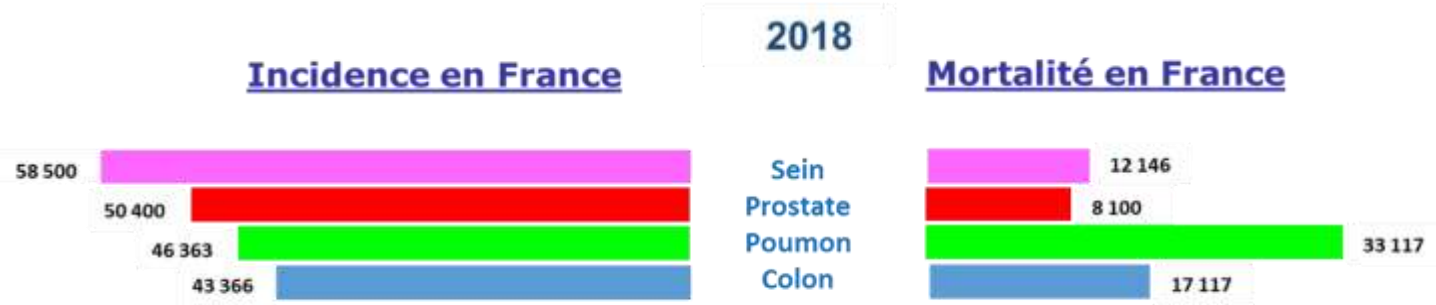
Pôle Régional de Cancérologie, CHU de Poitiers

8 décembre 2023

Liens d’intérêt

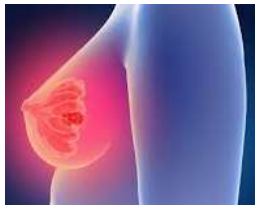
Activité de consultant, intervention dans des réunions scientifiques	Amgen, BMS, Daiichi-Sankyo, Eisai, GSK, Lilly, Novartis, Pfizer, Transgene, GILEAD, Deciphera, AstraZeneca
Participation congrès, voyages, hébergements	Novartis, Pfizer, PharmaMar, Roche Genentech, GILEAD

Généralités



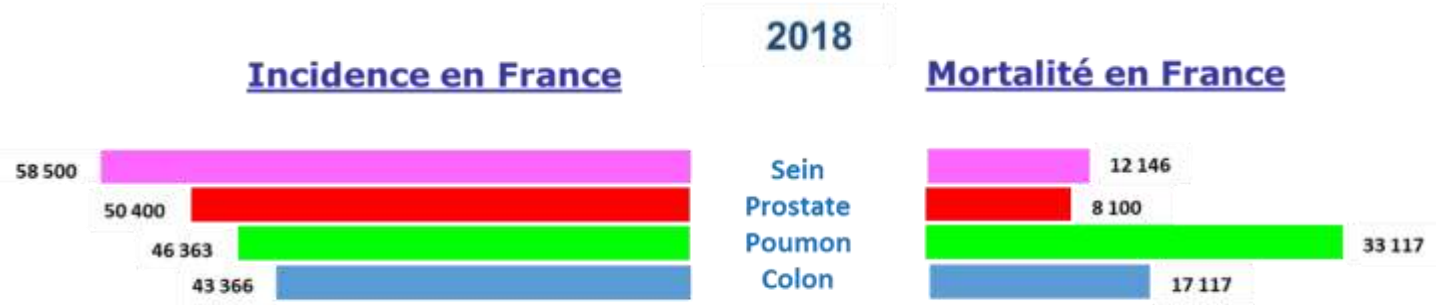
- 1er cancer chez la femme en terme d'incidence et de mortalité : 58 000 nouveaux cas/an et 12 000 décès/an
- Age médian au diagnostic : 63 ans
- Age médian au décès : 74 ans

chirurgie | **chimiothérapie** | **radiothérapie** | **hormonothérapie**



INCa, 2019

Généralités



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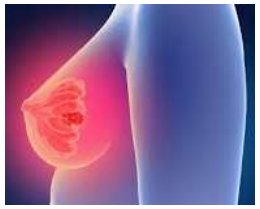
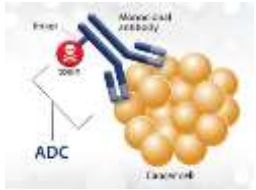
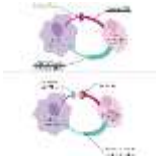


Situation métastatique puis adjuvante

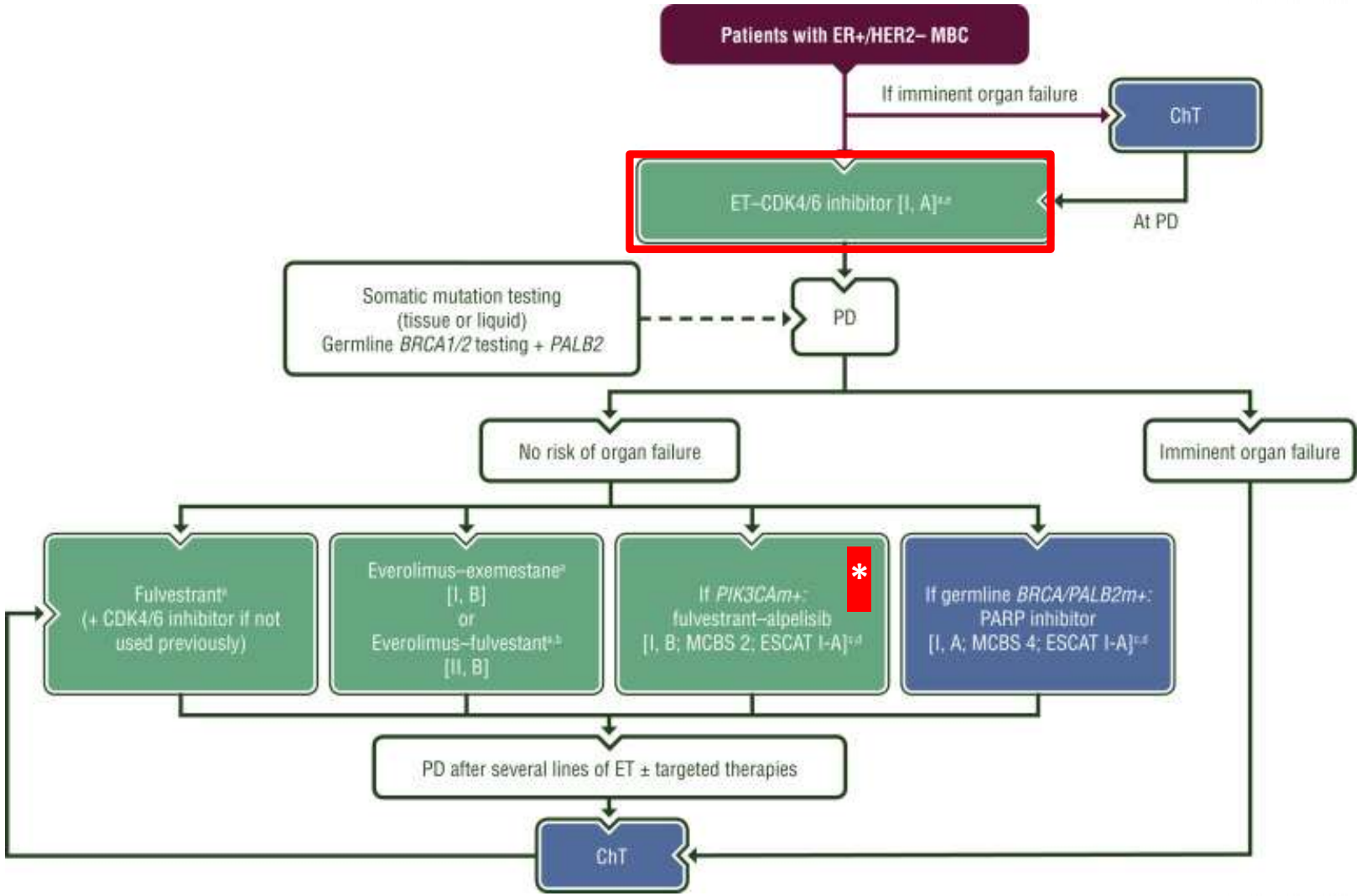
thérapies ciblées | **ADC** | **immunothérapie**





INCa, 2019

Guidelines ESMO 2023 – M+, RH+, HER2-



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Données non validées par les Autorités de Santé à ce jour

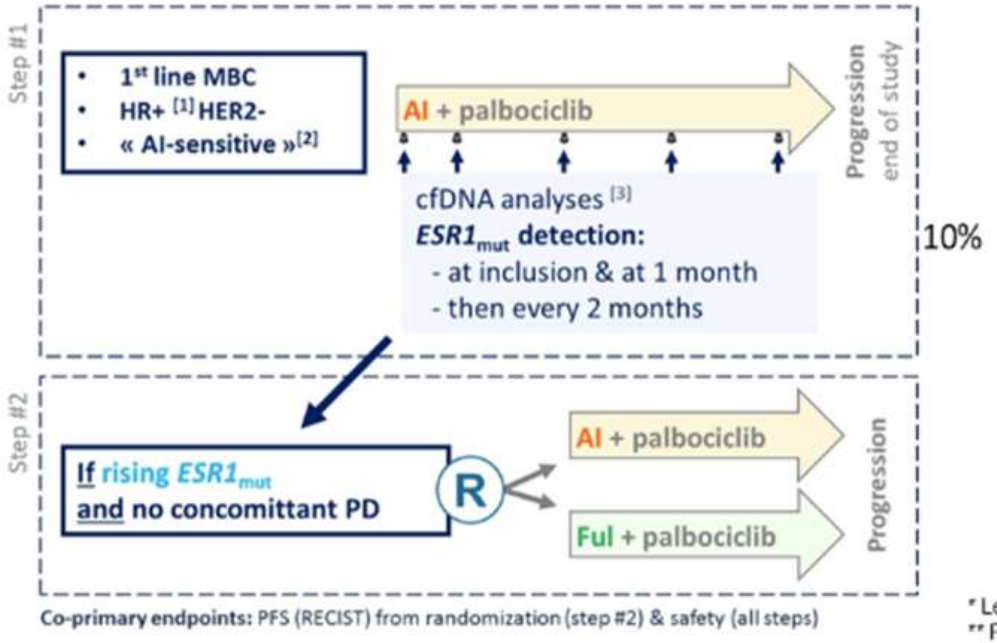
Gennari et *al*. Ann Oncol. 2021

1ère ligne métastatique

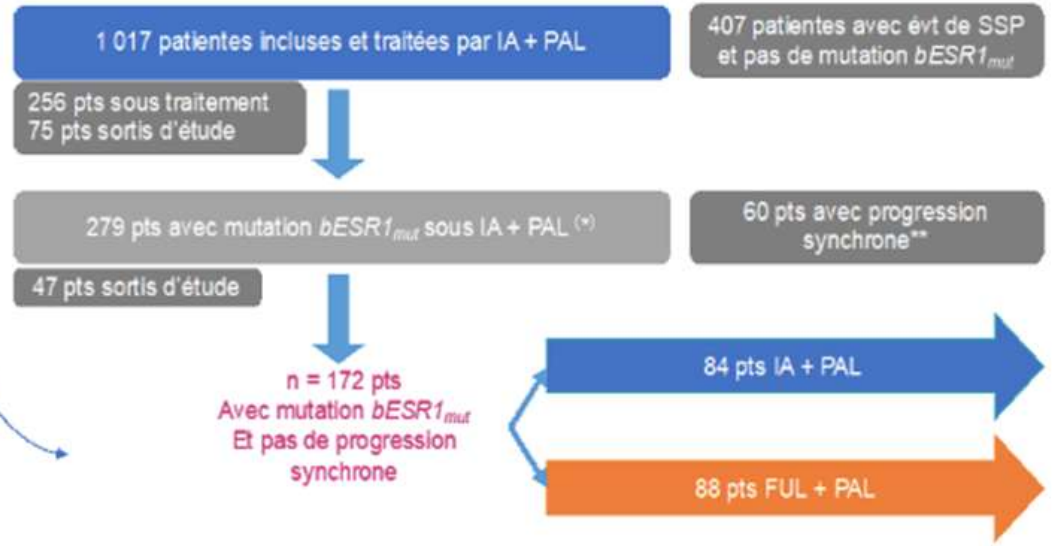
	Ribociclib			Abémaciclib		Palbociclib	
Trial	**MONALEESA-2**	**MONALEESA-3**	**MONALEESA-7**	**MONARCH-2**	**MONARCH-3**	**PALOMA-2**	**PALOMA-3**
Line of therapy	1L	1L & 2L	1L	1L & 2L	1L	1L	1L & 2L
Menopausal status	Post (N-668)	Post (N=726)	Pre (N=672 [ITT]) (N=495 [NSAI])	Post (N=666)	Post (N=413) Pre (N=108)	Post (N=493)	Post (N=551) Pre (N=114)
Endocrine partner	AI	Fulvestrant	AI	Fulvestrant	AI	AI	Fulvestrant
Patient population	No prior systemic therapy for advanced disease	No prior therapy for advanced disease; progressed after ET	No prior ET for advanced disease; 1L of chemotherapy for advanced disease allowed	No prior systemic therapy for advanced disease	Progressed on or after prior ET; 1L of chemotherapy for advanced disease allowed	No prior systemic therapy for advanced disease	Progressed on or after prior ET
Significant OS	✓	✓	✓	✓	Pending ✓	✗	✓ ✗
	G.N. Hortobagyi, et al., ESMO® 2021, Abs LBA17	ASCO 2021 - D'après Slamon DJ et al., abstr. 1001, actualisé	UPDATE Lu et al. Clin Can Res décembre 2021	Sledge JAMA ONCOL 2020: Sledge Jr GW, at al., SABCS 2022	Goetz ESMO 2022	Finn et al ASCO 2022	ASCO 2021 - D'après Cristofalli M et al., abstr. 1000, actualisé

Les 3 inhibiteurs CDK 4-6 n'ont pas été comparés directement entre eux dans le cadre d'un essai clinique

PADA-1



10%

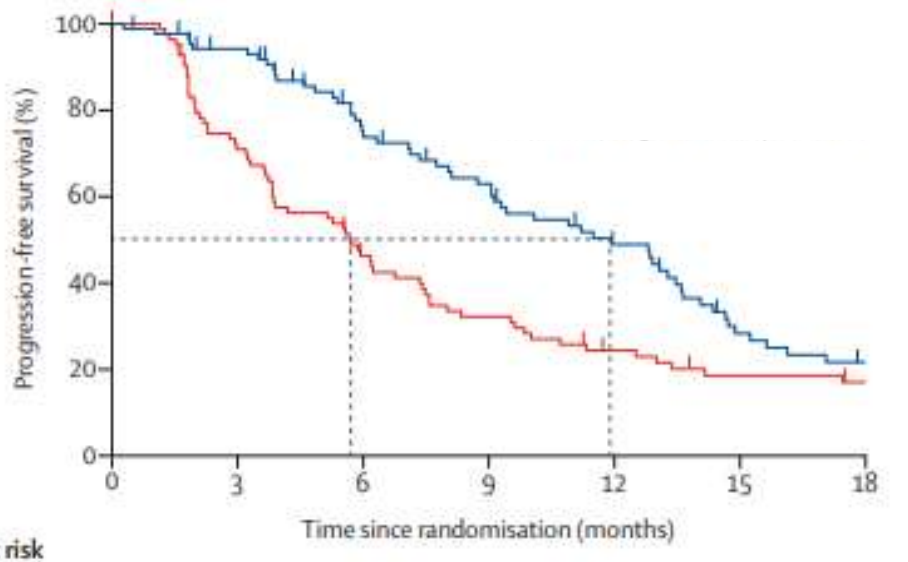


* Le temps médian entre l'inclusion et la détection de l'augmentation de la mutation *bESR1mut* était de 14,2 mois (2,8-47,1)
** Progression synchrone : progression observée (± 30 jours) après la détection des mutations *bESR1mut*

Bidard et *al*. Lancet Oncol 2022

PADA-1

	Palbociclib + IA	Palbociclib + FUL
SSP médiane, mois (IC_{95})	5,7 mois (1,9-7,5)	11,9 (9,1-13,6)
HR (IC_{95}), p	0,63 0,61 (0,45-0,88); 0,007	
HR stratifié (IC_{95}), p	0,61 (0,43-0,86); 0,004	

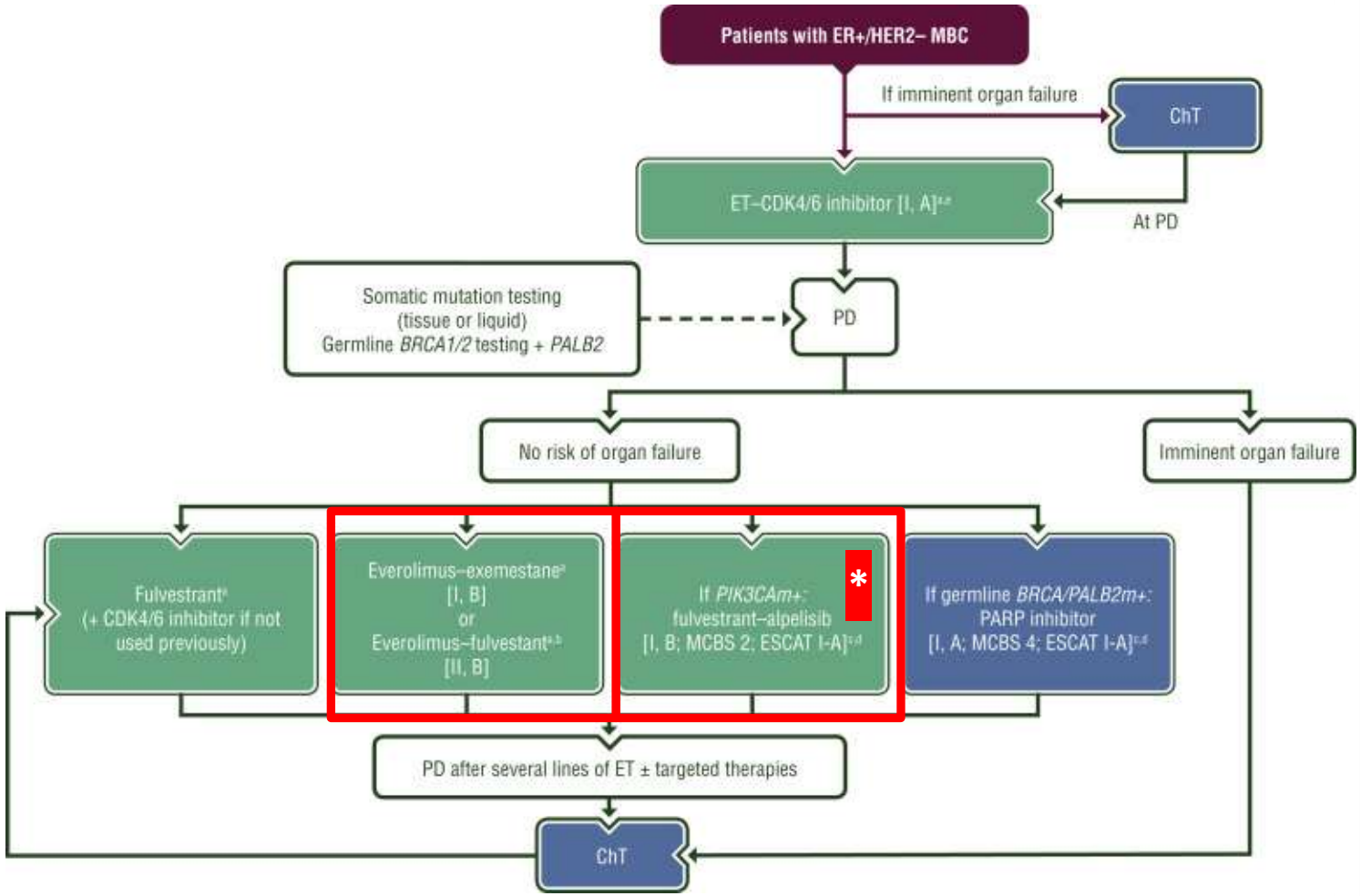


Number at risk (number censored)							
Fulvestrant and palbociclib	88 (0)	78 (5)	57 (11)	46 (13)	32 (17)	17 (19)	12 (20)
Aromatase inhibitor and palbociclib	84 (1)	58 (2)	36 (4)	25 (4)	17 (6)	12 (7)	10 (8)

	First step: aromatase inhibitor and palbociclib (n=1017)	Second step (n=172)		Crossover: fulvestrant and palbociclib (n=47)
		Aromatase inhibitor and palbocidib (n=84)	Fulvestrant and palbociclib (n=88)	
Neutropenia				
Grade 3	614 (60·4%)	33 (39·3%)	38 (43·2%)	16 (34·0%)
Grade 4	85 (8·4%)	2 (2·4%)	1 (1·1%)	0
Grade 5	0	0	0	0
Febrile neutropenia				
Grade 3	5 (0·5%)	0	0	0
Grade 4	1 (0·1%)	0	0	0
Grade 5	0	0	0	0
Lymphopenia				
Grade 3	60 (5·9%)	3 (3·6%)	4 (4·5%)	1 (2·1%)
Grade 4	5 (0·5%)	0	0	0
Grade 5	0	0	0	0
Anaemia				
Grade 3	12 (1·2%)	1 (1·2%)	1 (1·1%)	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Thrombocytopenia				
Grade 3	16 (1·6%)	1 (1·2%)	2 (2·3%)	0
Grade 4	2 (0·2%)	0	0	0
Grade 5	0	0	0	0

Bidard et *al*. Lancet Oncol 2022

Guidelines ESMO 2023 – M+, RH+, HER2-



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Données non validées par les Autorités de Santé à ce jour

Gennari et *al*. Ann Oncol. 2021

BOLERO 2

n = 724
- Patientes postménopausées ER+ HER2–
- Maladie localement avancée métastatique
- Récidive ou progression après létrozole ou anastrozole

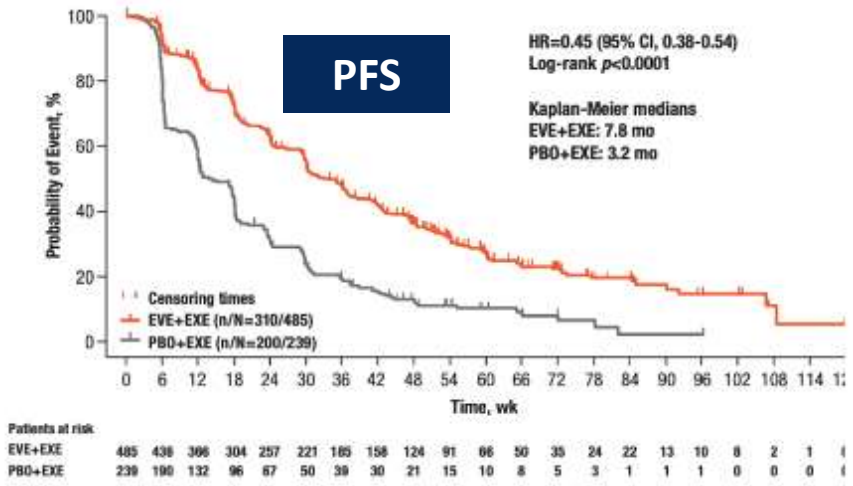
R 2:1

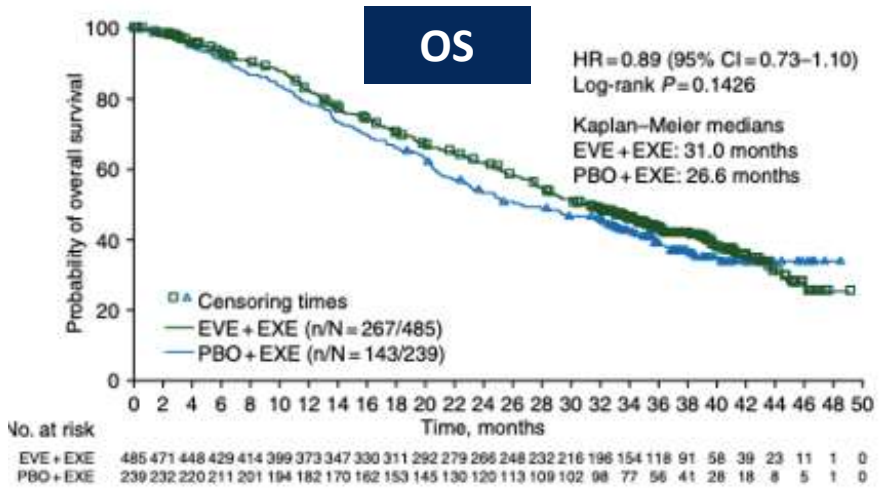
Évérolimus 10 mg/j + Exémestane 25 mg/j (n = 485)

Placebo + Exémestane 25 mg/j (n = 239)

- Critères de jugement
  - Primaires : SSP (évaluation locale)
  - Secondaires : SG, RO, bénéfice clinique, QdV, tolérance, marqueurs osseux, PK
- Stratification :
  1. Sensibilité à l'hormonothérapie antérieure
  2. Présence de métastase viscérale
- Pas de crossover

	Patients, *n* (%)	
	EVE + EXE (*n* = 482)	PBO + EXE (*n* = 238)
Serious adverse events	157 (32.6)	37 (15.5)
Suspected to be drug-related	63 (13.1)	4 (1.7)
Grade 3/4 adverse events	266 (55.2)	70 (29.4)
Suspected to be drug-related	197 (40.9)	20 (8.4)
Adverse events leading to treatment discontinuation	140 (29.0)	12 (5.0)





Piccart et *al*. Ann Oncol. 2014

SOLAR 1

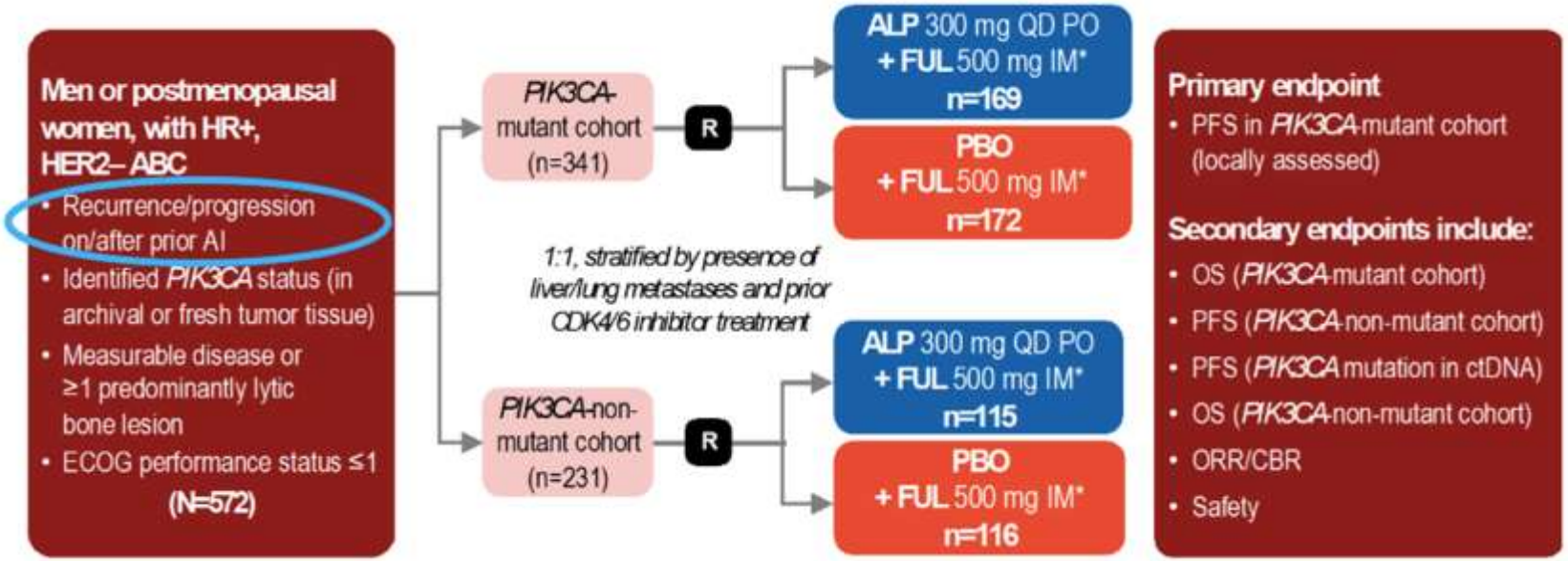


Table 3. Updated adverse events

Most frequent AEs (≥20% in either arm), *n* (%)	Alpelisib + fulvestrant (*n* = 284)*			Placebo + fulvestrant (*n* = 287)*		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Any AE	282 (99.3)	187 (65.8)	35 (12.3)	267 (93.0)	90 (31.4)	17 (5.9)
Hyperglycemia	184 (64.8)	94 (33.1)	11 (3.9)	27 (9.4)	2 (0.7)	1 (0.3)
Diarrhea	169 (59.5)	20 (7.0)	0	47 (16.4)	2 (0.7)	0
Nausea	133 (46.8)	8 (2.8)	0	65 (22.6)	1 (0.3)	0
Decreased appetite	103 (36.3)	2 (0.7)	0	30 (10.5)	1 (0.3)	0
Rash	103 (36.3)	28 (9.9)	0	20 (7.0)	1 (0.3)	0
Vomiting	81 (28.5)	2 (0.7)	0	29 (10.1)	1 (0.3)	0
Weight decreased	79 (27.8)	15 (5.3)	0	7 (2.4)	0	0
Fatigue	72 (25.4)	10 (3.5)	0	51 (17.8)	3 (1.0)	0
Stomatitis	71 (25.0)	7 (2.5)	0	20 (7.0)	0	0
Asthenia	64 (22.5)	7 (2.5)	0	39 (13.6)	0	0
Alopecia	58 (20.4)	0	0	7 (2.4)	0	0

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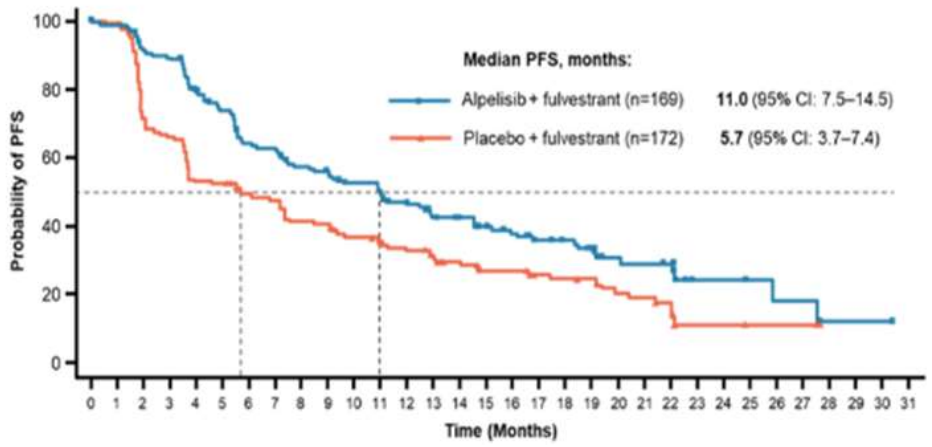
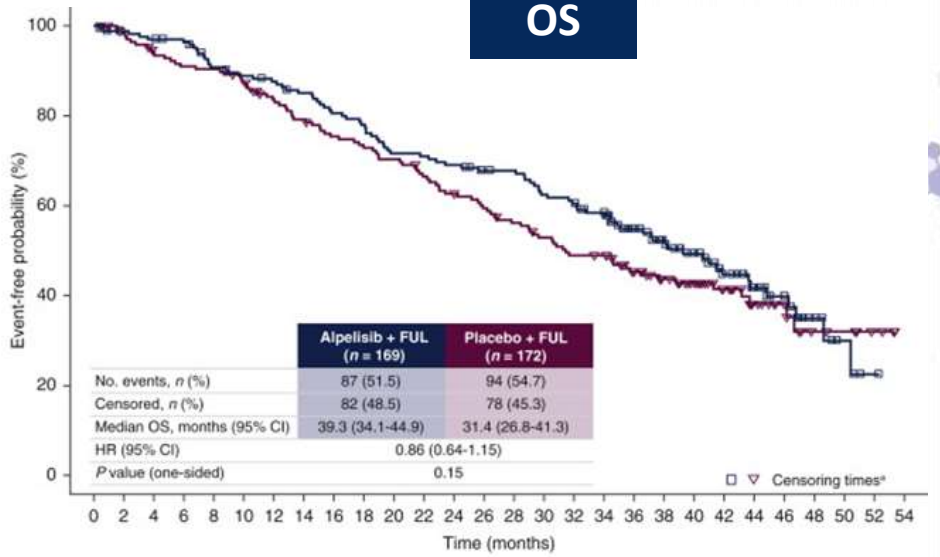
André et *al*. Ann Oncol 2021

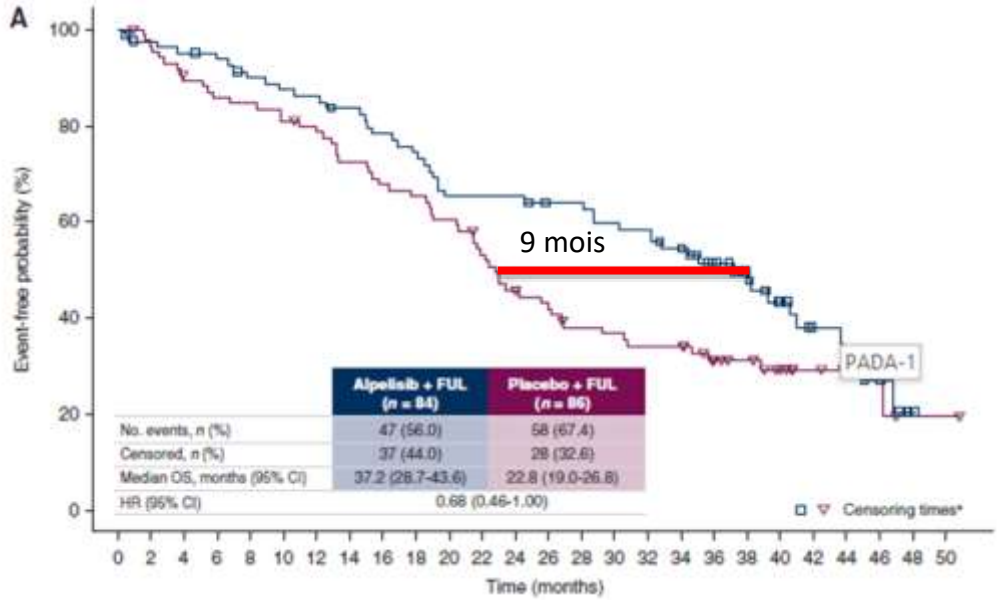
SOLAR 1

PFS



OS





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Données non validées par les Autorités de Santé à ce jour

André et *al*. Ann Oncol 2021

BYLieve

Hors AMM
Données non validées par les Autorités de Santé à ce jour

Femmes pré- ou post-ménauposées avec cancer du sein avancé RH+/HER2– et mutation *PIK3CA*
- Traitement antérieur : iCDK + HT, chimiothérapie ou HT
- ECOG PS ≤ 2
- Maladie mesurable (RECIST v1.1) ou ≥ 1 lésion osseuse à prédominance lytique

R

Patientes ayant reçu un iCDK + IA comme dernier traitement (n = 112)
Cohorte A
Alpélisib 300 mg oral 1 fois/j + fulvestrant 500 mg

Patientes ayant reçu iCDK + fulverstrant comme dernier traitement (n = 112)
Cohorte B
Alpelisib 300 mg oral 1 fois/j + letrozole 2,5 mg

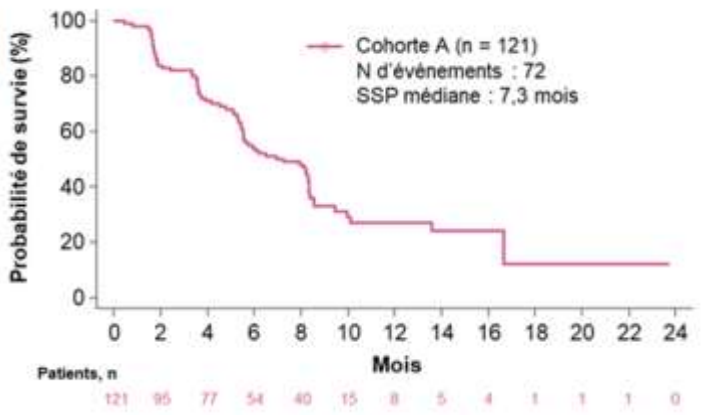
Patientes en progression sous/ou après IA ou ayant reçu de la CT ou HT comme dernier traitement (n = 112) Cohorte C
Alpelisib 300 mg oral 1 fois/j + fulvestrant 500 mg

Critère principal :
- Proportion de patientes sans progression à 6 mois (RECIST v1.1)

Critères secondaires
- SSP
- SSP2
- ORR, CBR, DOR
- SG
- Tolérance

Cross-over *entre les groupes non autorisé*

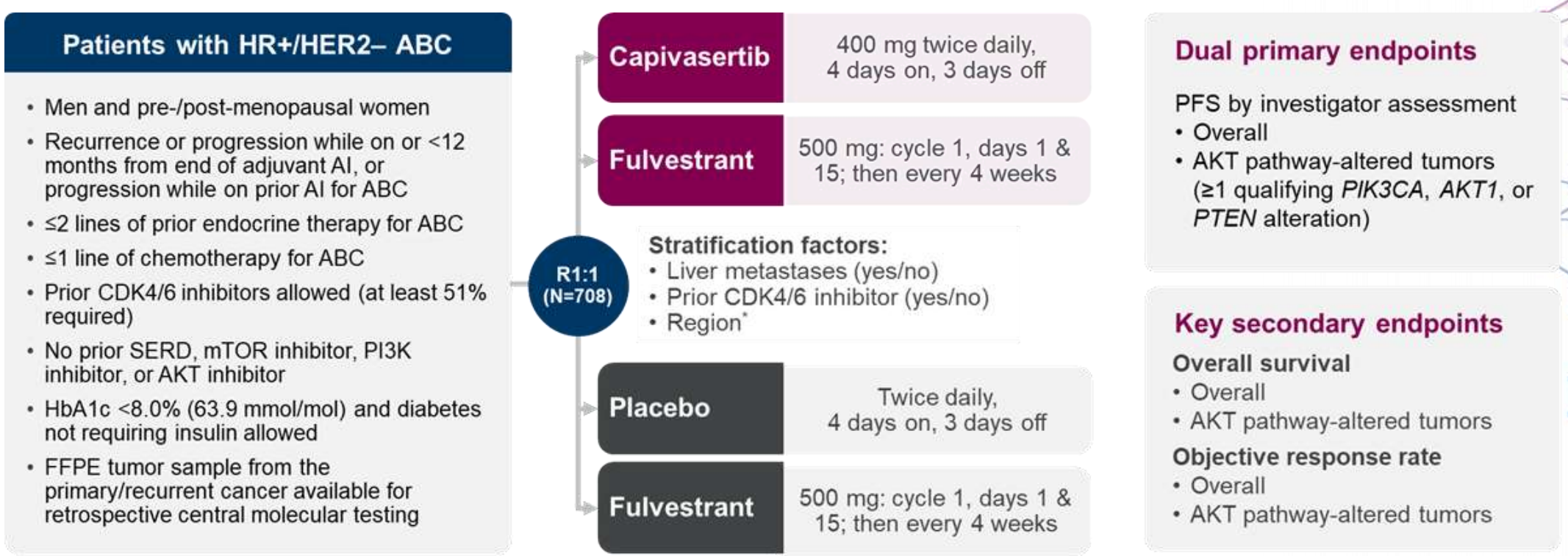
Critère	Cohorte iCDKi+ IA (n = 121)
Critère principal : taux de survie sans progression à 6 mois	**50,4 %** (n = 61 ; IC_{95} : 41,2-59,6)
Critère secondaire : SSP médiane	**7,3 mois** (n = 72 ; IC_{95} : 5,6-8,3)



Adverse events leading to dose interruption or adjustment		
Hyperglycaemia	37 (29%)	32 (25%)
Rash	16 (13%)	10 (8%)
Rash maculopapular	12 (9%)	11 (9%)
Diarrhoea	10 (8%)	6 (5%)
Vomiting	5 (4%)	1 (1%)
Asthenia	4 (3%)	1 (1%)
Pruritus	4 (3%)	2 (2%)
Stomatitis	4 (3%)	2 (2%)
Hypokalaemia	3 (2%)	3 (2%)
Pyrexia	3 (2%)	0
Weight decreased	3 (2%)	1 (1%)
Cough	2 (2%)	1 (1%)
Headache	2 (2%)	0
Lipase increased	2 (2%)	1 (1%)
Neutrophil count decreased	2 (2%)	2 (2%)
Urticaria	2 (2%)	2 (2%)

Rugo et *al*. Lancet Oncol 2021

CAPITELLO-291



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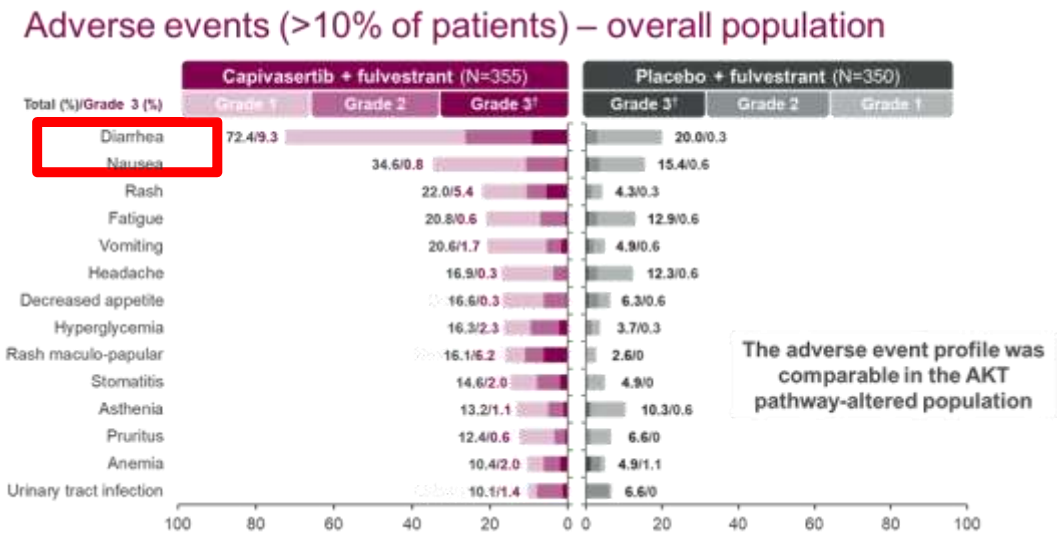
Turner et *al*. N Engl J Med. 2023

CAPITELLO-291

Alteration; n (%)		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Any AKT pathway alteration		**155 (43.7)**	**134 (38.0)**
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)
Non-altered		**200 (56.3)**	**219 (62.0)**
AKT pathway alteration not detected		142 (40.0)	171 (48.4)
Unknown		58 (16.3)	48 (13.6)
No sample available		10 (2.8)	4 (1.1)
Preanalytical failure		39 (11.0)	34 (9.6)
Post analytical failure		9 (2.5)	10 (2.8)



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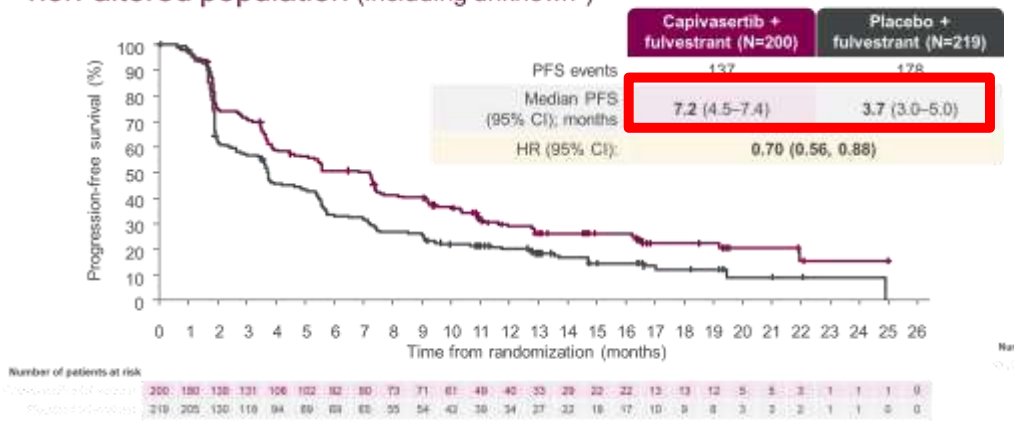
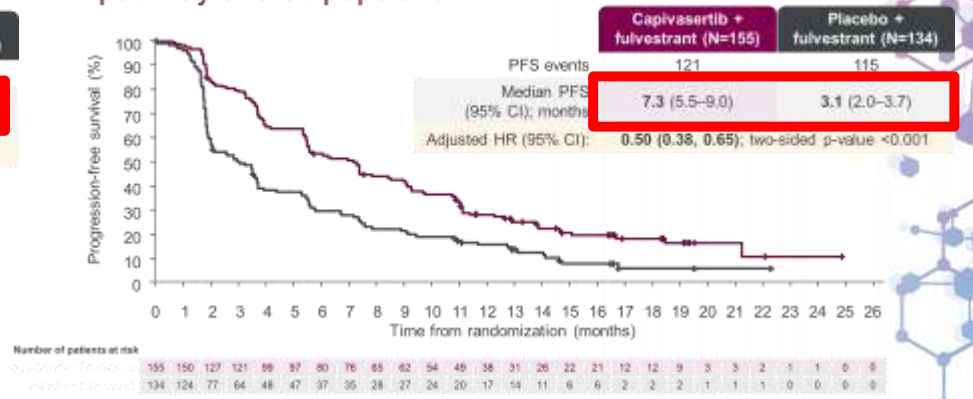
CAPITELLO-291

Exploratory analysis: Investigator-assessed PFS in the non-altered population (including unknown†)

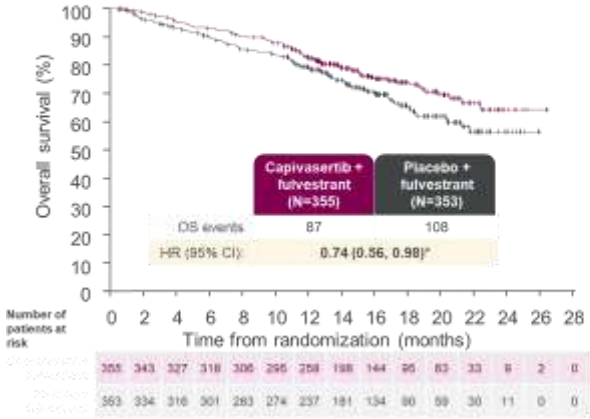


Dual-primary endpoint: Investigator-assessed PFS in the AKT pathway-altered population

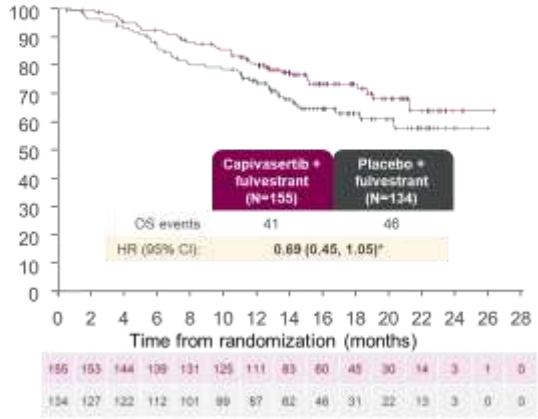


Overall survival at 28% maturity overall

Overall population



AKT pathway-altered population



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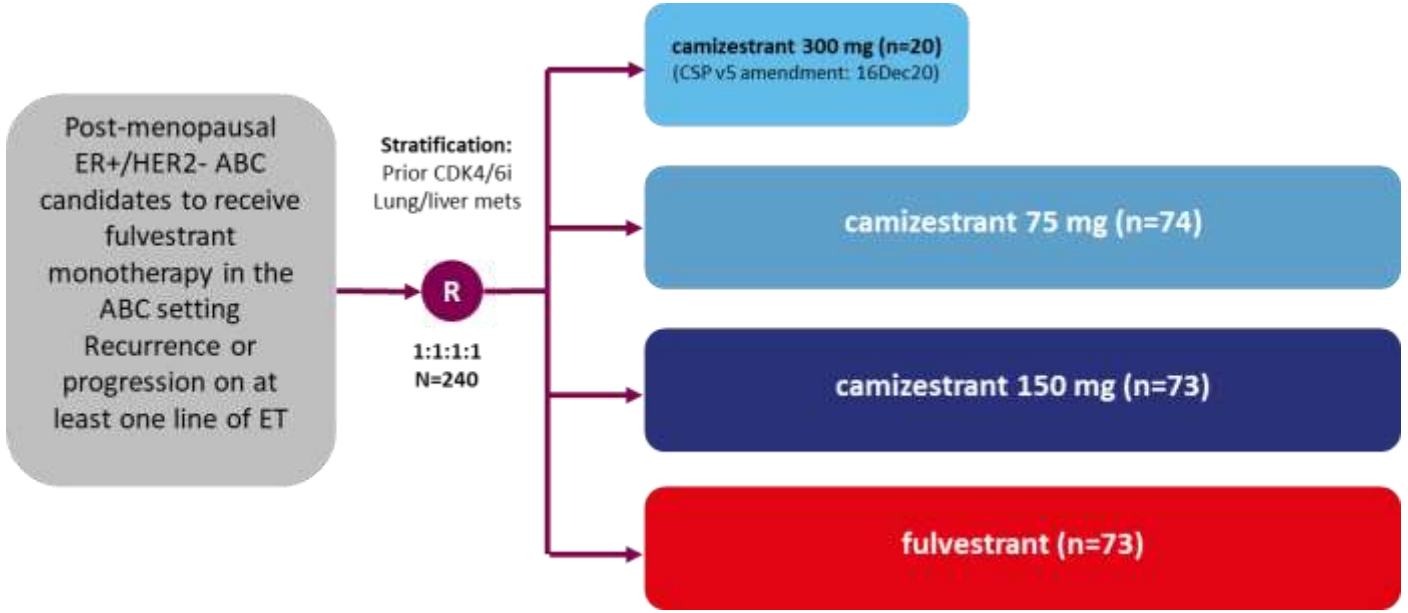
SERENA-2



- **Primary endpoint:** PFS (investigator assessment*)
- **Secondary endpoints:** CBR24, ORR, OS, safety
- **Translational endpoints:** serial ctDNA analysis including *ESR1*m, serial CTCs analysis

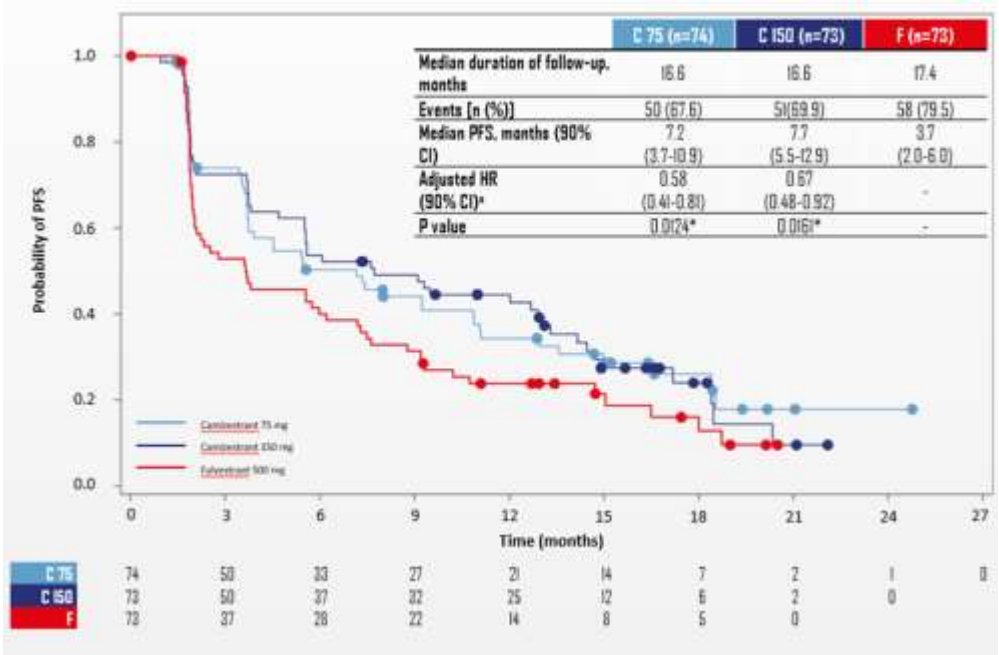
	C 75 (n=74)	C 150 (n=73)	F (n=73)	Total (n=240)
*ESR1*m detectable (%)[b]	29.7	35.6	47.9	36.7
D538G	18.9	19.2	31.5	22.9
Y537N	14.9	15.1	15.1	13.8
Y537S	6.8	13.7	19.2	12.5
E380Q	9.5	8.2	8.2	8.3
L536H	1.4	8.2	4.1	4.6
Y537C	4.1	4.1	2.7	3.3

AE, n (%)	C 75 (n=74)		C 150 (n=73)		C 300 (n=20)		F 500 (n=73)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any AE	57 (77.0)	9 (12.2)	66 (90.4)	16 (21.9)	19 (95.0)	3 (15)	50 (68.5)	10 (13.7)
Photopsia	9 (12.2)	0	18 (24.7)	0	7 (35.0)	0	0	0
(Sinus) bradycardia	4 (5.4)	0	19 (26.0)	0	8 (40.0)	0	0	0
Fatigue	4 (5.4)	0	13 (17.8)	1 (1.4)	4 (20.0)	0	3 (4.1)	0
Anemia	8 (10.8)	0	11 (15.1)	1 (1.4)	1 (5.0)	0	5 (6.8)	2 (2.7)
Asthenia	6 (8.1)	0	11 (15.1)	0	2 (10.0)	0	4 (5.5)	0
Arthralgia	3 (4.1)	0	9 (12.3)	1 (1.4)	2 (10.0)	0	2 (2.7)	0
AST increased	2 (2.7)	0	6 (8.2)	0	2 (10.0)	0	5 (6.8)	1 (1.4)
ALT increased	1 (1.4)	0	6 (8.2)	1 (1.4)	3 (15.0)	0	4 (5.5)	1 (1.4)
Covid-19	4 (5.4)	0	4 (5.5)	0	3 (15.0)	0	3 (4.1)	0
Diarrhea	4 (5.4)	0	4 (5.5)	0	3 (15.0)	1 (5.0)	2 (2.7)	1 (1.4)
Pain in extremity	1 (1.4)	0	4 (5.5)	1 (1.4)	2 (10.0)	0	3 (4.1)	0
Dyspepsia	1 (1.4)	0	3 (4.1)	0	2 (10.0)	0	1 (1.4)	0
Insomnia	1 (1.4)	0	3 (4.1)	0	2 (10.0)	0	1 (1.4)	0
Hyponatremia	0	0	3 (4.1)	1 (1.4)	2 (10.0)	0	1 (1.4)	1 (1.4)
Blood pressure increased	2 (2.7)	1 (1.4)	1 (1.4)	1 (1.4)	2 (10.0)	1 (5.0)	0	0
Cataract	2 (2.7)	0	0	0	2 (10.0)	0	0	0
Vitreous floaters	2 (2.7)	0	0	0	2 (10.0)	0	0	0

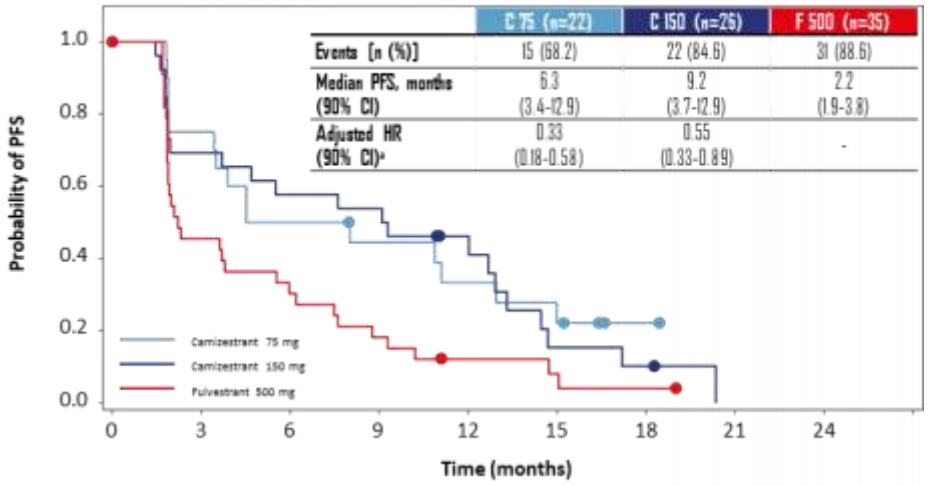
Hors AMM
Données non validées par les Autorités de Santé à ce jour

Oliveira et *al*. SABCS 2022

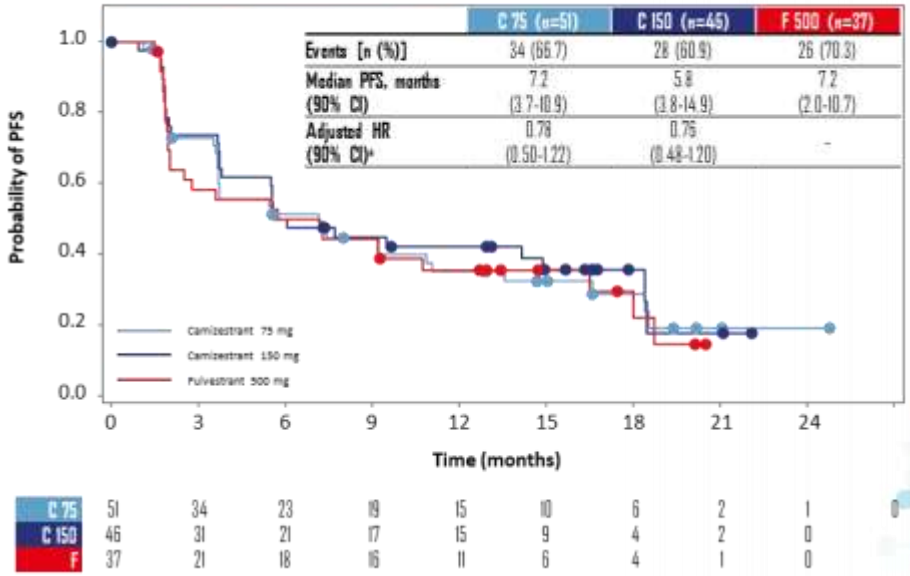
SERENA-2



*ESR1*m detectable at baseline



*ESR1*m not detectable at baseline



Hors AMM
Données non validées par les Autorités de Santé à ce jour

Oliveira et *al*. SABCS 2022

SERENA-6

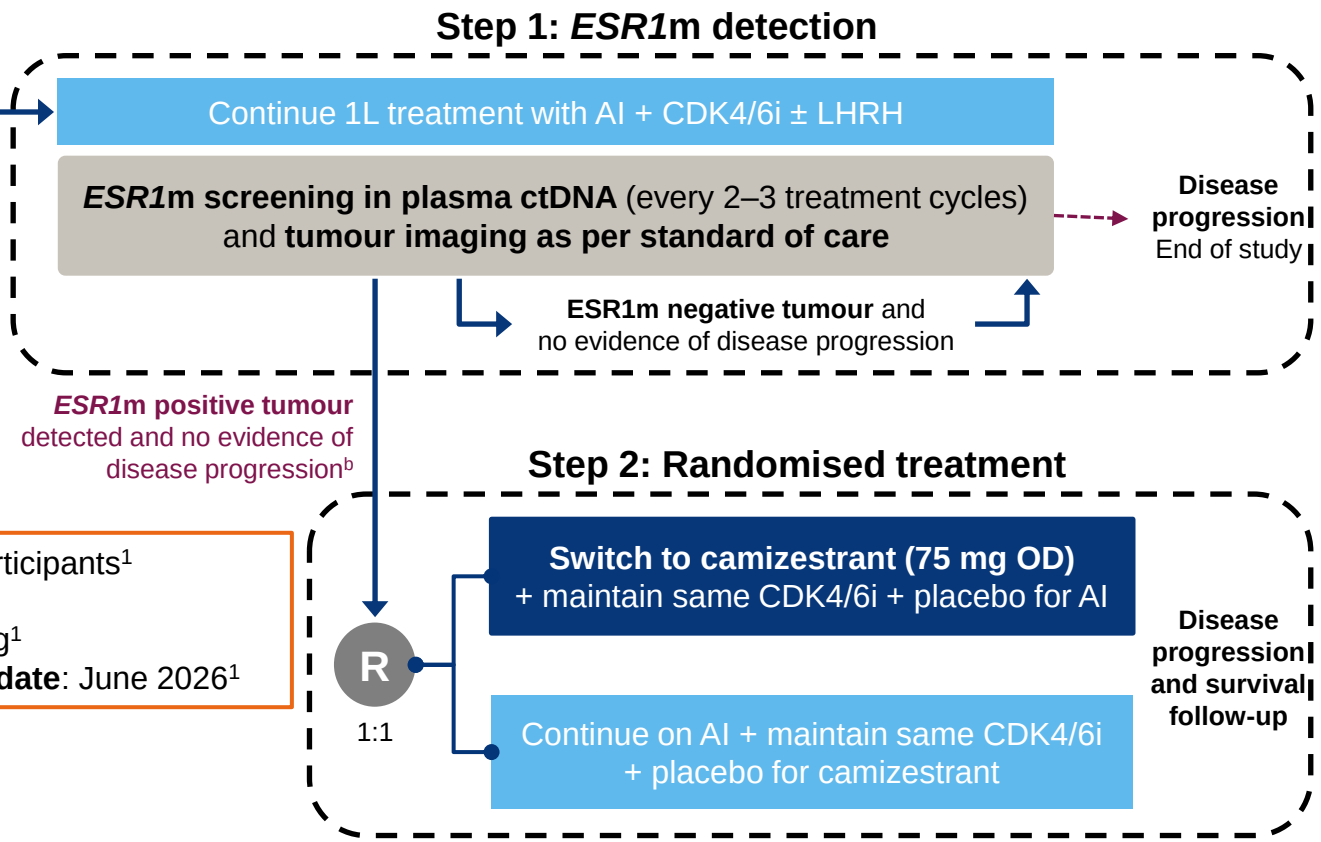
SERENA-6 (NCT04964934): a Phase III, randomized, multicenter, double-blind, ctDNA-guided switch study of AZD9833 (camizestrant) in patients with HR+/HER2– metastatic breast cancer with detectable *ESR1*m

- Adults with HR+/HER2– locally advanced (inoperable) or mBC[1,2]
- Currently receiving AI (anastrozole or letrozole) + CDK4/6i (palbociclib or abemaciclib) ± LHRH as 1L treatment for advanced disease for ≥6m with no evidence of disease progression by investigator assessment[1,2]
- ECOG 0 or 1[1,2]

Estimated enrolment: 302 participants[1]
Start date: June 2021[1]
Recruitment status: Recruiting[1]
Estimated study completion date: June 2026[1]

Hors AMM
Données non validées par les Autorités de Santé à ce jour

Ongoing



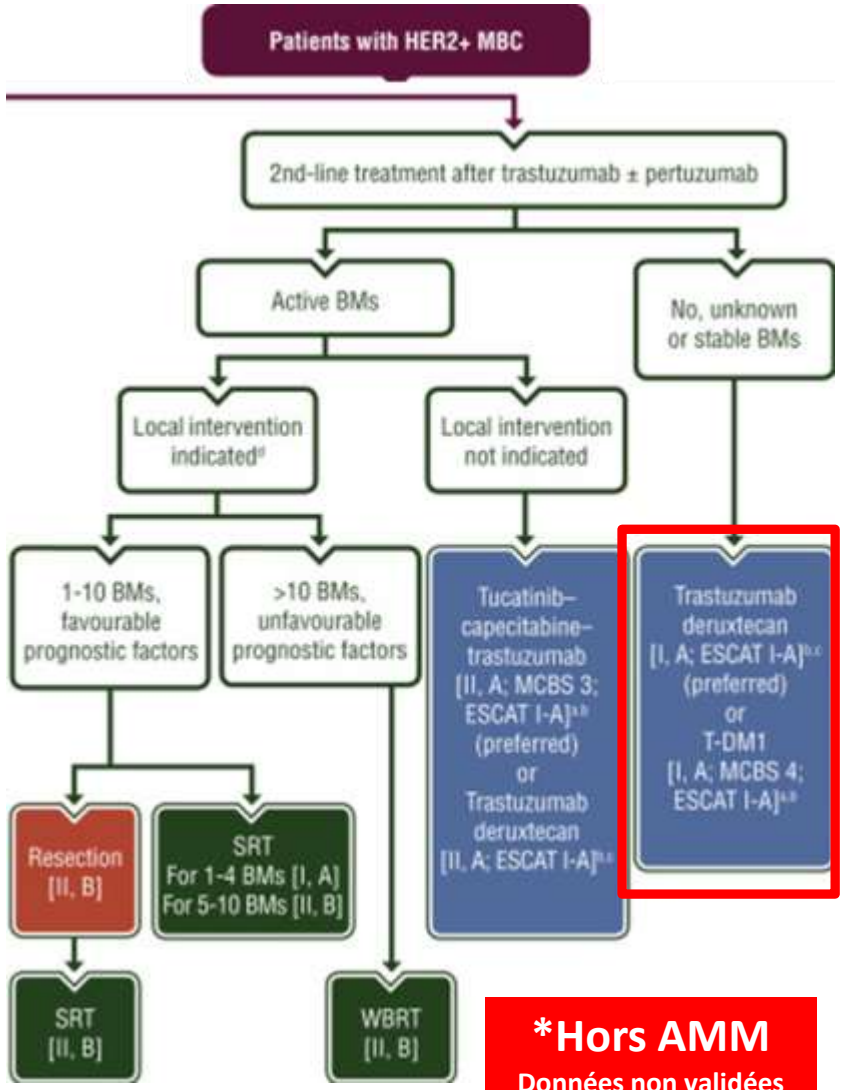
Primary endpoint[1,2]
- PFS[a]

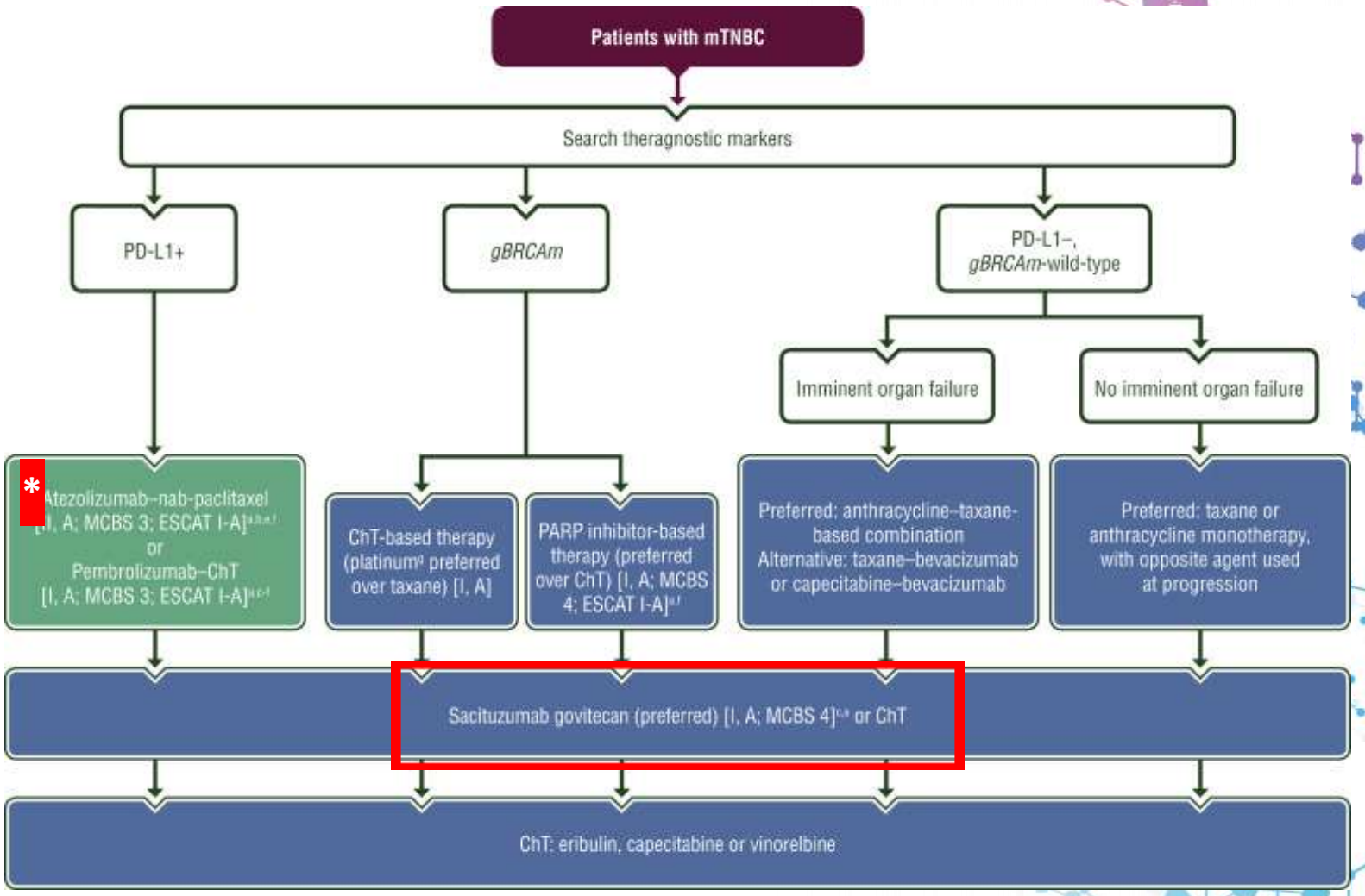
Secondary endpoints[1,2]
- PFS2
- OS
- Chemotherapy-free survival
- ORR
- CBR_{24}
- PROs

Safety and tolerability[2]
- AEs, SAEs, vital signs, clinical safety laboratory assessments

1. Study NCT04964934. ClinicalTrials.Gov website. 2. Bidard et *al*. Poster OT2-11-05 SABCS

Guidelines ESMO 2023 - ADC



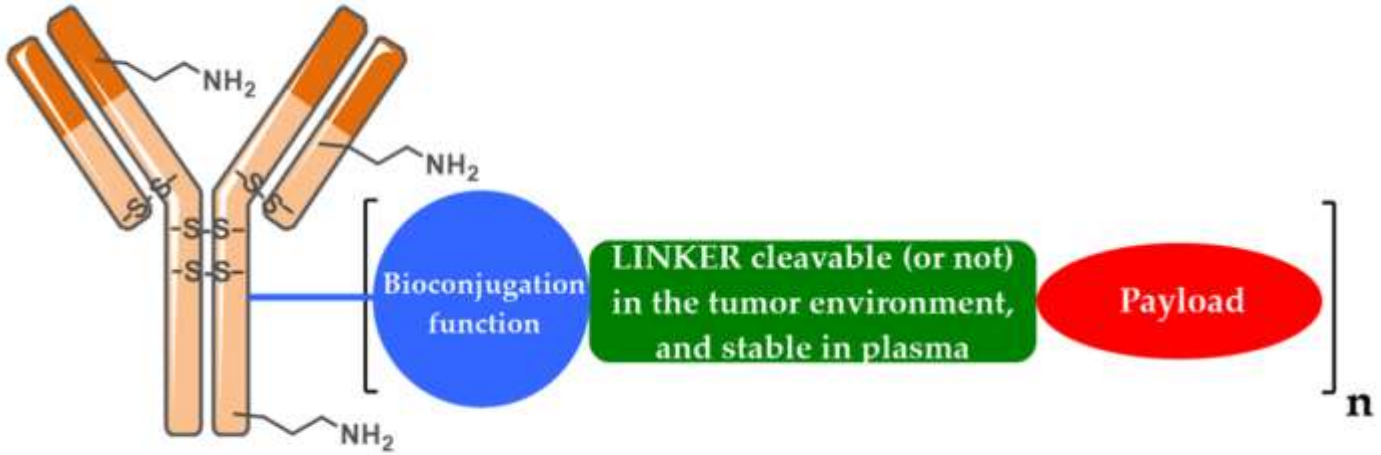


***Hors AMM**

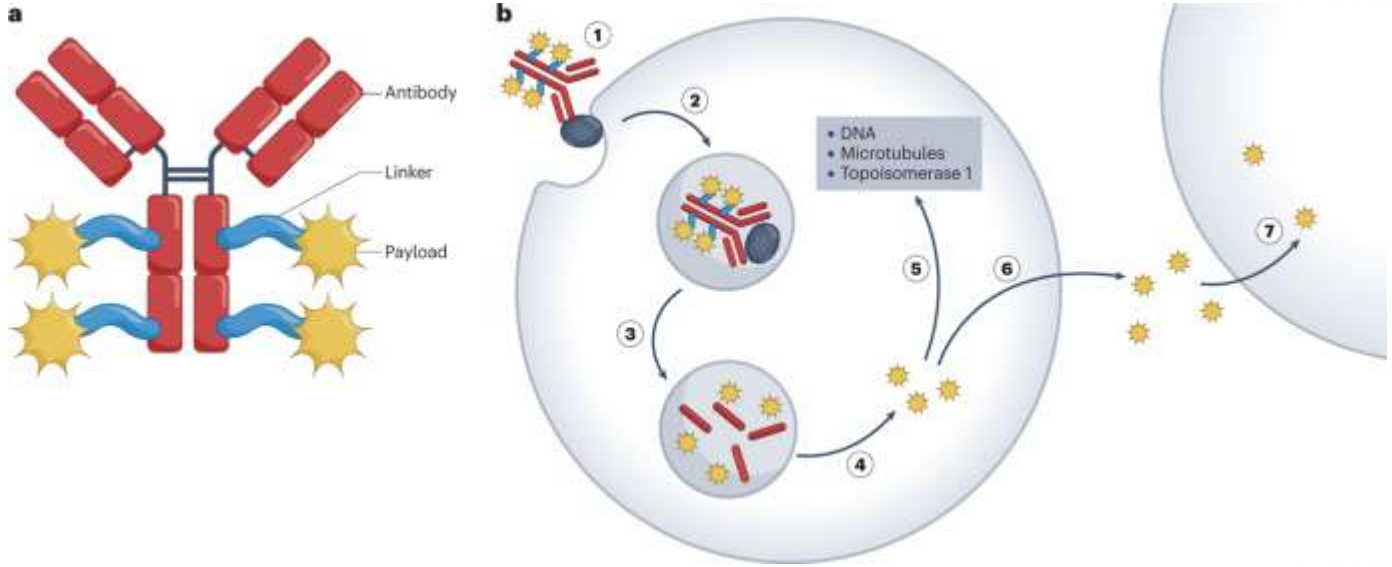
Données non validées par les Autorités de Santé à ce jour

Gennari et *al*. Ann Oncol. 2021

ADC



n = DAR (drug-to-antibody ratio)



Dumontet C *et al.* . Nat Rev Drug Discov 2023

DESTINY Breast 03

Patients (N = 524)

- Unresectable or metastatic HER2 positive breast cancer that has been previously treated with trastuzumab and taxane
- Could have clinically stable, treated brain metastases
  - ≥2 weeks between end of whole brain radiotherapy and study enrollment

Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

R 1:1

- **T-DXd** 5.4 mg/kg Q3W (n = 261)
- **T-DM1** 3.6 mg/kg Q3W (n = 263)

Primary endpoint

- PFS (BICR)

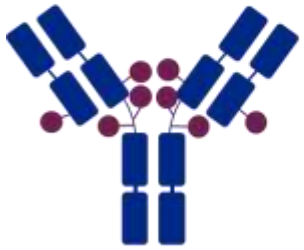
Key secondary endpoint

- OS

Secondary endpoints

- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Trastuzumab deruxtecan (T-DXd)[1]

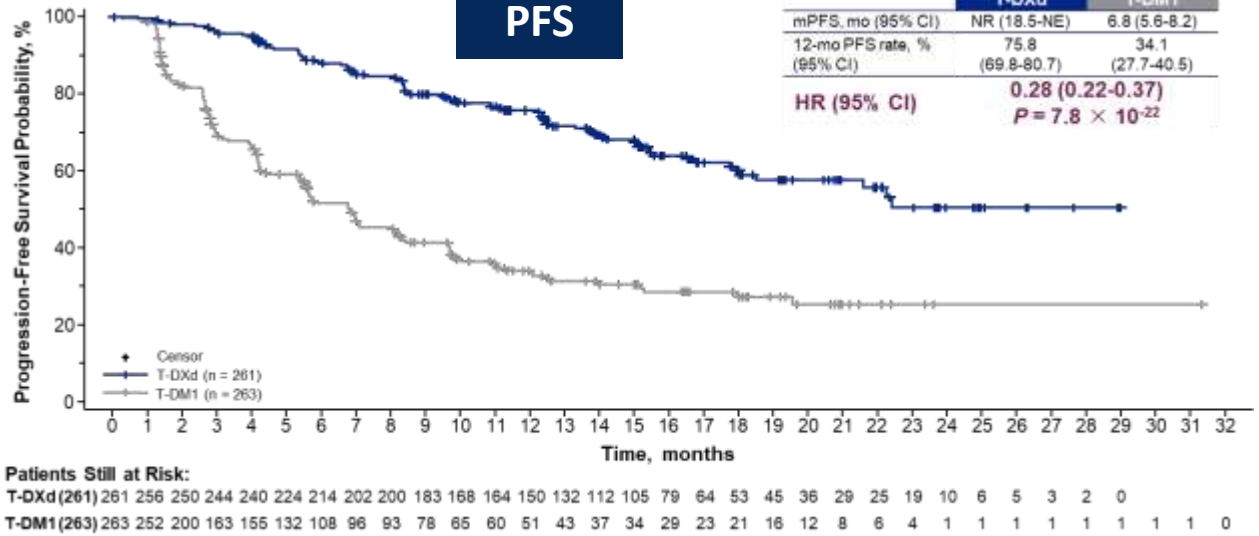


T-DXd[1-4]	Caractéristiques ADC
Inhibiteur de topoisomerase I	Payload MoA
~8:1	Drug-to-antibody ratio
Oui	Tumor-selective cleavable linker?
Oui	Evidence of bystander anti-tumor effect?

Cortés J et *al*. N Engl J Med. 2022

DESTINY Breast 03

PFS

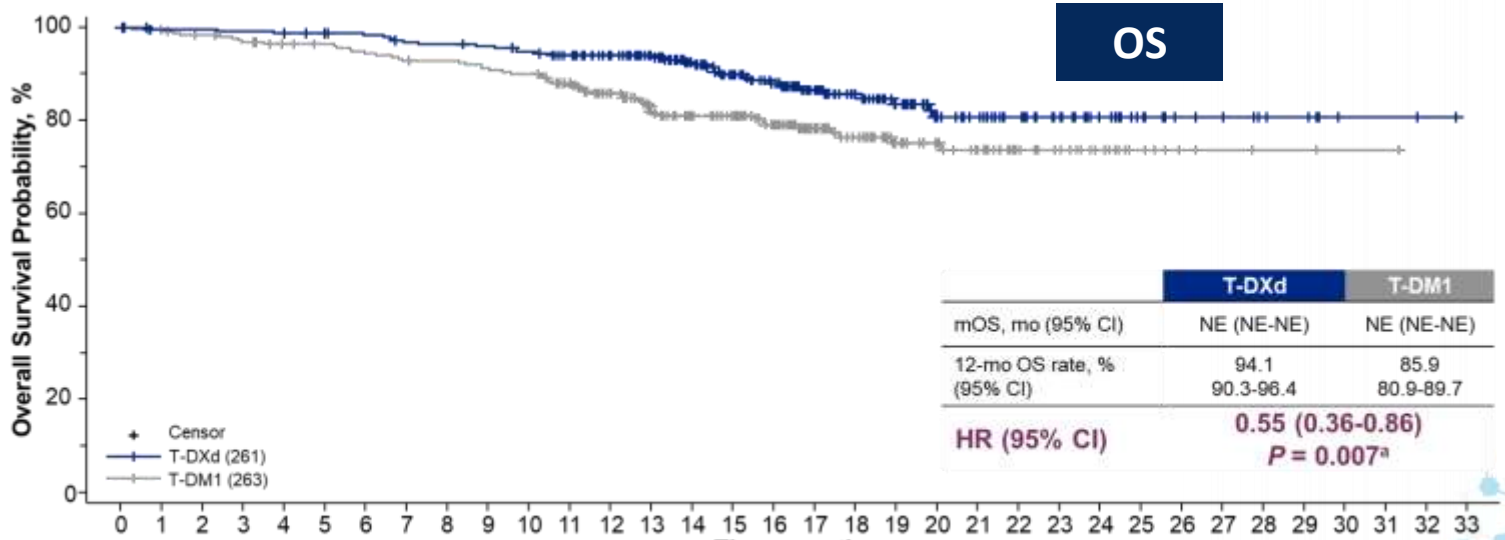


	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	

Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	1	0

OS



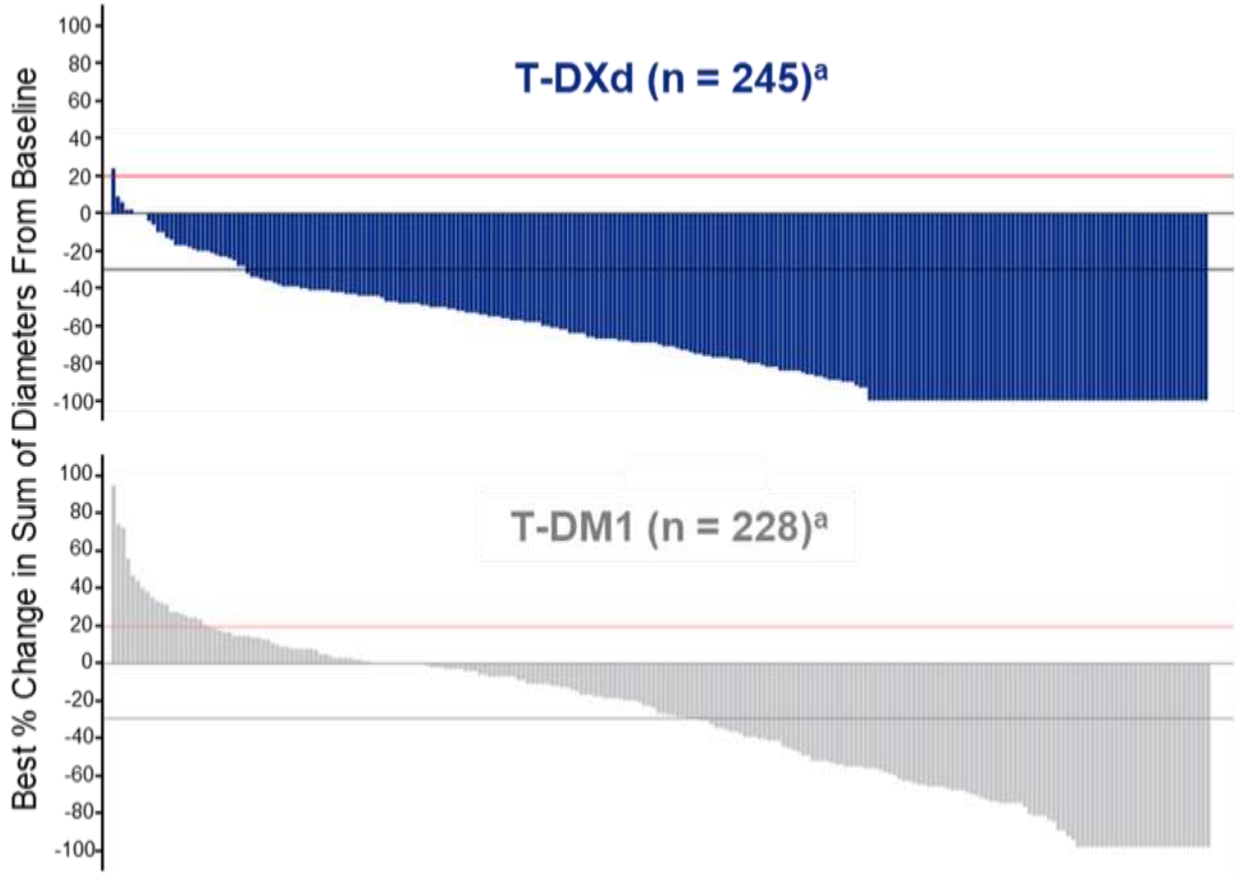
	T-DXd	T-DM1
mOS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS rate, % (95% CI)	94.1 (90.3-96.4)	85.9 (80.9-89.7)
HR (95% CI)	0.55 (0.36-0.86)	
	$P = 0.007^a$	

Patients Still at Risk:

T-DXd (261)	261	256	256	255	254	251	249	244	243	241	237	230	218	202	180	158	133	108	86	71	56	50	42	33	24	18	11	10	7	6	2	2	1	0
T-DM1 (263)	263	258	253	248	243	241	236	232	231	227	224	210	188	165	151	140	120	91	75	58	52	44	32	27	18	11	5	4	3	3	1	1	0	

Cortés J et *al*. N Engl J Med. 2022

DESTINY Breast 03



	T-DXd (n = 261)	T-DM1 (n = 263)
Confirmed ORR		
n (%)	208 **(79.7)**	90 **(34.2)**
[95% CI]	[74.3-84.4]	[28.5-40.3]
	P < 0.0001	
CR	42 **(16.1)**	23 **(8.7)**
PR	166 **(63.6)**	67 **(25.5)**
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
CR + PR + SD (DCR)	252 (96.6)	202 (76.8)

Cortés J et *al*. N Engl J Med. 2022

DESTINY Breast 03

System Organ Class Preferred term, n (%)	T-DXd (n = 257)		T-DM1 (n = 261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Drug-related blood and lymphatic system disorders				
Neutropenia	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Drug-related gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0

Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis, n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd
- In the T-DXd arm, 21 patients (8.2%) discontinued treatment due to ILD/pneumonitis
- In the T-DM1 arm, 3 patients (1.1%) discontinued treatment due to ILD/pneumonitis

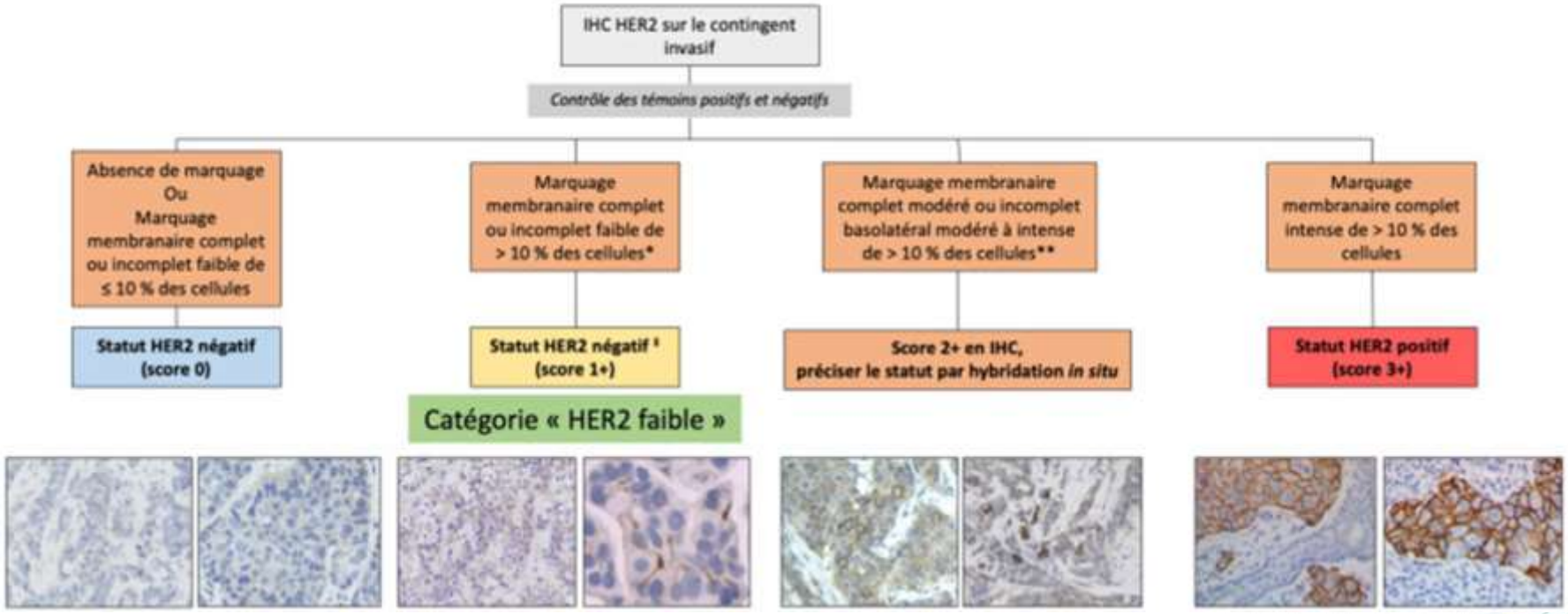
=> Majorité des effets secondaires étaient troubles gastro-intestinaux et hématologiques

Cortés J et *al*. N Engl J Med. 2022

Emergence du concept de HER faible (HER low)

- Traitements anti-HER2 sont réservés aux patientes avec surexpression de HER2 (IHC 2+ amplifié et 3+)
- Avènement de nouvelles drogues cytotoxiques conjuguées à des anticorps anti-HER2 a montré une activité thérapeutique prometteuse chez les patientes atteintes d'un cancer du sein avec un niveau plus faible d'expression de HER2

Concept de tumeur HER faible (GEFPICS 2021)



DESTINY Breast 04

Patients
- 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

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

R 2:1

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

HR+ = 494
HR− = 63

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

Primary endpoint
- PFS by BICR (HR+)

Key Secondary Endpoints
- PFS by BICR (all patients)
- OS (HR+ and all patients)

Secondary endpoints
- PFS (investigator)
- ORR (BICR and investigator)
- DOR (BICR)
- Safety
- Patient-reported outcomes (HR+)

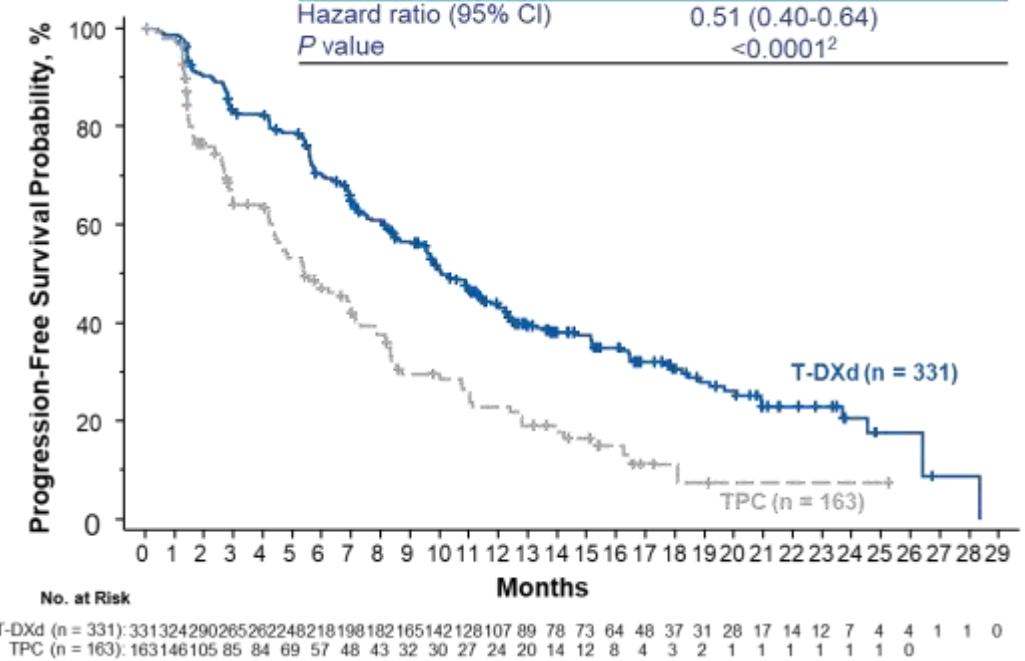
Table 3. Most Common Drug-Related Adverse Events (in ≥20% of Patients) in the Safety Analysis Set.*

Event	Trastuzumab Deruxtecan (N=371)		Physician's Choice of Chemotherapy (N=172)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Blood and lymphatic system disorders				
Neutropenia†	123 (33.2)	51 (13.7)	88 (51.2)	70 (40.7)
Anemia‡	123 (33.2)	30 (8.1)	39 (22.7)	8 (4.7)
Thrombocytopenia§	88 (23.7)	19 (5.1)	16 (9.3)	1 (0.6)
Leukopenia¶	86 (23.2)	24 (6.5)	54 (31.4)	33 (19.2)
Gastrointestinal disorders				
Nausea	271 (73.0)	17 (4.6)	41 (23.8)	0
Vomiting	126 (34.0)	5 (1.3)	17 (9.9)	0
Diarrhea	83 (22.4)	4 (1.1)	31 (18.0)	3 (1.7)
Constipation	79 (21.3)	0	22 (12.8)	0
Investigations: increased aminotransferase levels‖	87 (23.5)	12 (3.2)	39 (22.7)	14 (8.1)
General disorders: fatigue**	177 (47.7)	28 (7.5)	73 (42.4)	8 (4.7)
Metabolism and nutrition disorders: decreased appetite	106 (28.6)	9 (2.4)	28 (16.3)	2 (1.2)
Skin and subcutaneous tissue disorders: alopecia	140 (37.7)	0	56 (32.6)	0

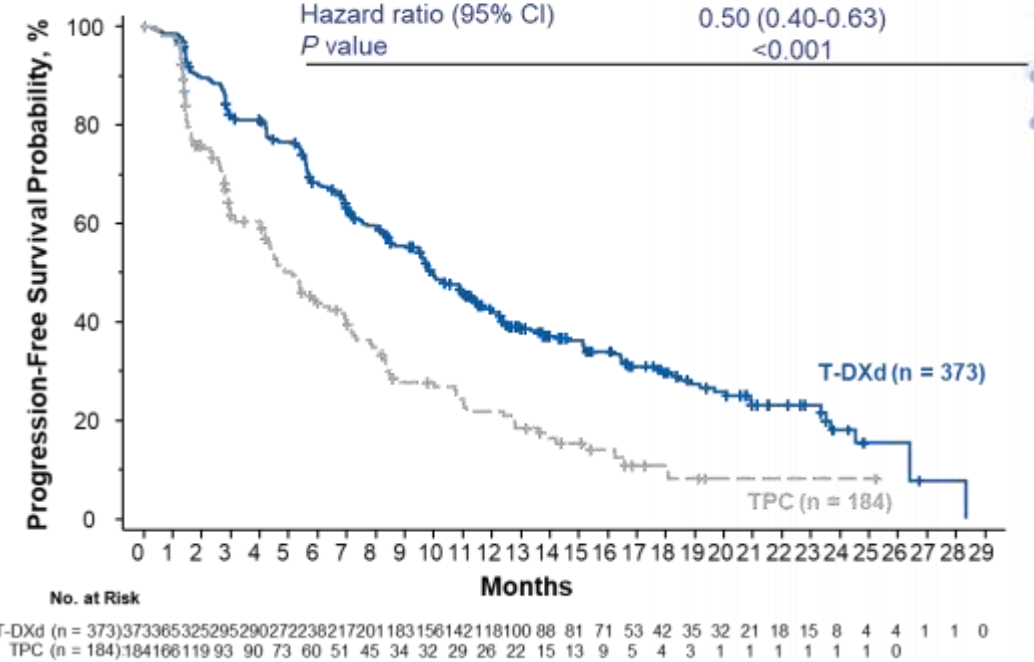
Modi S et *al.* N Engl J Med. 2022

DESTINY Breast 04

	Hormone receptor-positive	
	T-DXd (n = 331)	TPC (n = 163)
mPFS (95% CI), mo	10.1 (9.5-11.5)	5.4 (4.4-7.1)
Hazard ratio (95% CI)	0.51 (0.40-0.64)	
P value	<0.0001[2]	



	All patients (HR+ and HR−)	
	T-DXd (n = 373)	TPC (n = 184)
mPFS (95% CI), mo	9.9 (9.0-11.3)	5.1 (4.2-6.8)
Hazard ratio (95% CI)	0.50 (0.40-0.63)	
P value	<0.001	



Modi S et *al.* N Engl J Med. 2022

Etude ASCENT

Locally advanced or metastatic TNBC

> 2nd line of chemotherapy

No relapse within 12 months following adjuvant or neoadjuvant strategy

n = 529

R
1:1

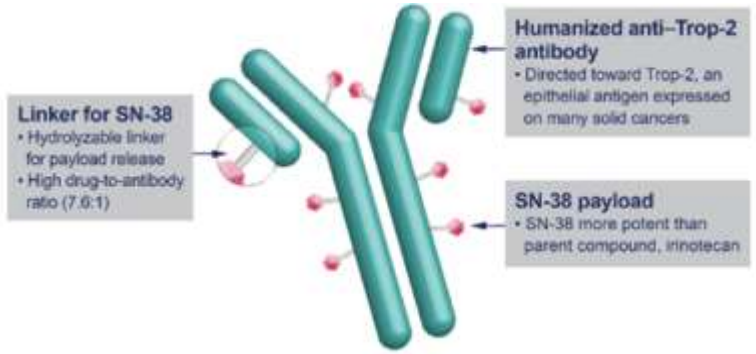
Sacituzumab-govitecan 10 mg/kg IV
D1-D8/21
n = 267

Investigator's choice
(Capecitabine, Eribuline, Vinorelbine, Gemcitabine)
n = 246

Primary end point: PFS in CNS- (independant central review)

Secondary end points: PFS, OS, ORR, DOR, TTR, Safety

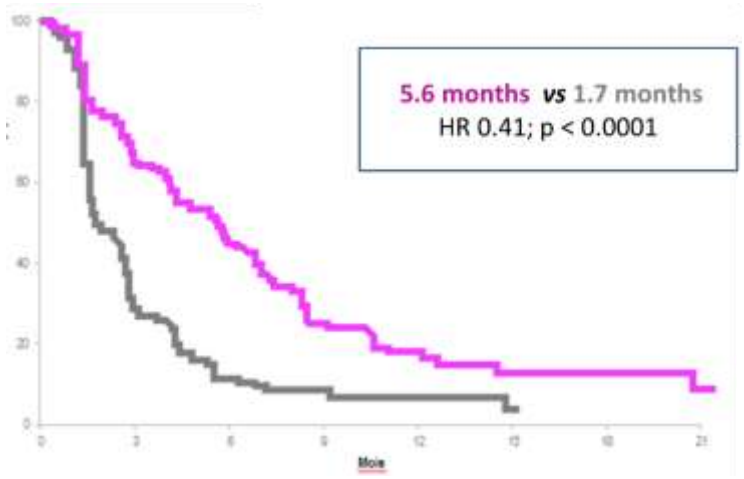
Stratification factors
- ⇒ Line of chemo: 2-3 vs > 3
- ⇒ Region: europa vs north-america
- ⇒ Brain metastases: yes or no



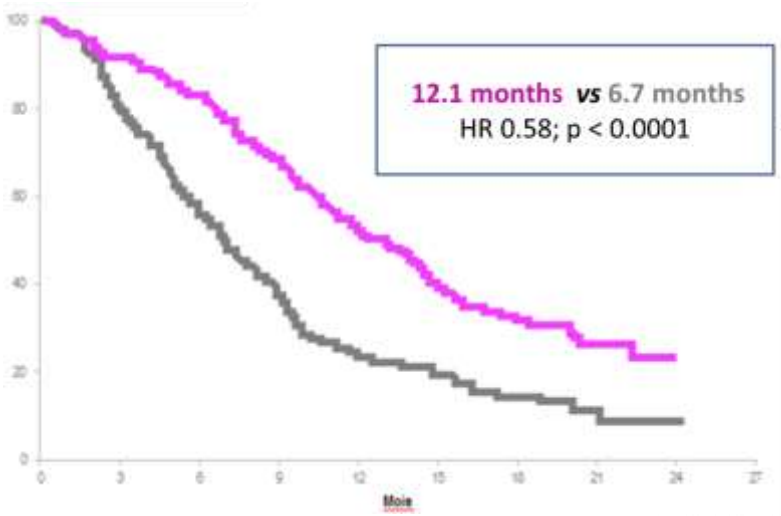
Bardia A et *al*. N Engl J Med. 2021

Etude ASCENT

PFS



OS

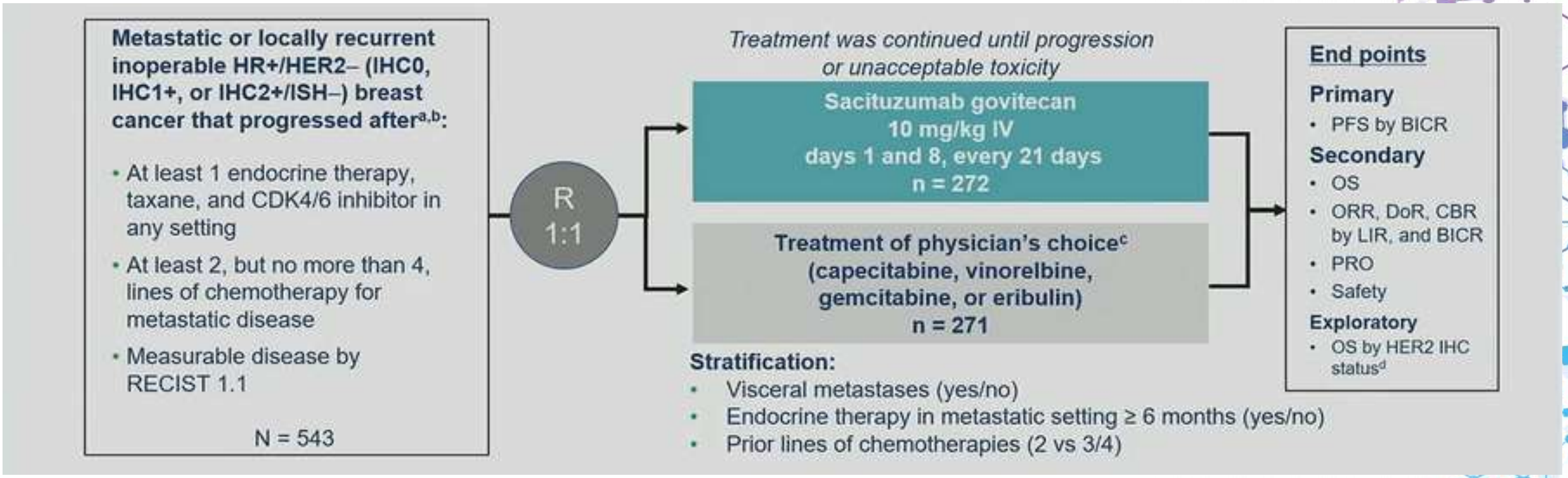


		SG (n=258)			TPC (n=224)		
		Tous grade %	Grade 3, %	Grade 4, %	Tous grade, %	Grade 3, %	Grade 4, %
Hematologique	Neutropenie[1]	63	46	17	43	27	13
	Anemie ±	34	8	0	24	5	0
	leucopénie	16	10	1	11	5	1
	Neutropenie fébrile	6	5	1	2	2	<1
Gastrointestinal	Diarrhée	59	10	0	12	<1	0
	Nausée	57	2	<1	26	<1	0
	Vomissement	29	1	<1	10	<1	0
autre	Fatigue	45	3	0	30	5	0
	Alopecie	46	0	0	16	0	0

- Utilisation du G-CSF: 49% (SG) vs 23% (TPC)
- Diminution de la posologie pour toxicité: 22 % (SG) vs 26% (TPC)
- Arrêt pour toxicité : SG et TPC: 4.7% et 5.4%

Bardia A et *al*. N Engl J Med. 2021

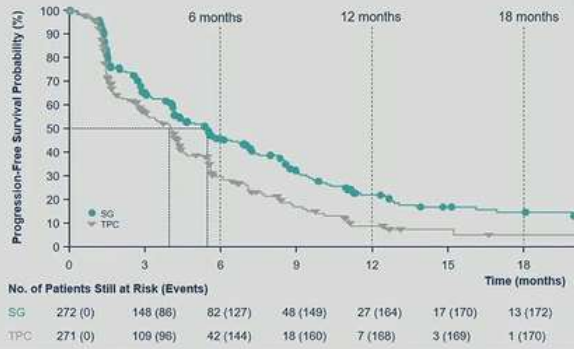
Etude TROPICS-02



Tolaney ASCO 2023

Etude TROPICS-02

Progression-Free Survival

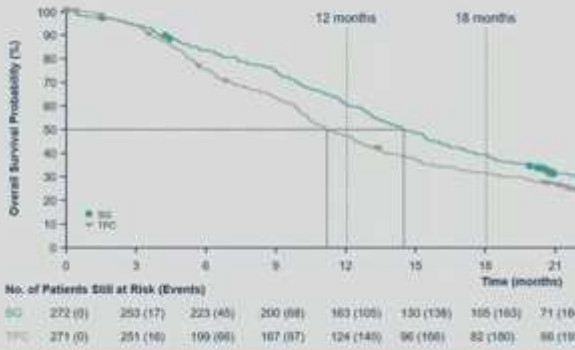


BICR analysis	SG (n = 272)	TPC (n = 271)
Median PFS, (95% CI) mo	5.5 (4.2-6.9)	4.0 (3.0-4.4)
Stratified HR (95% CI)	**0.65** (0.53-0.81)	
Nominal *P*-value[a]	.0001	
6-month PFS rate, % (95% CI)	45.6 (38.9-52.0)	29.4 (22.9-36.2)
12-month PFS rate, % (95% CI)	21.7 (15.8-28.3)	8.4 (4.2-14.5)
18-month PFS rate, % (95% CI)	14.4 (9.1-20.8)	4.7 (1.3-11.6)

SG continued to demonstrate improvement in PFS vs TPC at longer follow-up, with 35% reduction in risk of disease progression or death, and a higher proportion of patients remained alive and progression-free at each landmark

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
[a]Stratified log rank *P*-value.

Overall Survival



	SG (n = 272)	TPC (n = 271)
Median OS, mo (95% CI)	14.5 (13.0-16.0)	11.2 (10.2-12.6)
Stratified HR (95% CI)	**0.79** (0.65-0.95)	
Nominal *P*-value[a]	0.0133	
12-month OS rate, % (95% CI)	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-month OS rate, % (95% CI)	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-month OS rate, % (95% CI)	25.7 (20.5-31.2)	21.1 (16.3-26.3)

SG continued to demonstrate improvement in OS vs TPC at longer follow-up, with 21% reduction in risk of death and a higher proportion of patients remaining alive at each landmark

CI, confidence interval; HR, hazard ratio; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
[a]Stratified log rank *P*-value.

Tolaney ASCO 2023

Etude TROPICS-02

	Sacituzumab govitecan (n=268)	Chemotherapy (n=249)
Grade 3 or higher	198 (74%)	150 (60%)
Leading to treatment discontinuation	17 (6%)	11 (4%)
Leading to dose delay	178 (66%)	109 (44%)
Leading to dose reduction	90 (34%)	82 (33%)
Serious events	74 (28%)	48 (19%)
Leading to death*	6 (2%)	0
Treatment-related death	1 (<1%)	0

Treatment-emergent adverse events were defined as any adverse event that began or worsened on or after the start of the study drug until 30 days after the last dose of the study drug. *Of six treatment-emergent adverse events leading to death, only one was considered by the investigator to be treatment related (septic shock caused by neutropenic colitis). The other five deaths were caused by COVID-19 pneumonia, pulmonary embolism, pneumonia, nervous system disorder, and arrhythmia. Upon detailed review of the treatment-emergent adverse events leading to death, no patterns were identified.

71% de neutropénie (tous grades) +++
62% de diarrhées (tous grades)
59% de nausées (tous grades)
48% alopécie
37% anémie

Tolaney ASCO 2023

Etude TROPION Breast 01

Randomised, phase 3, open-label, global study

Key inclusion criteria:

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

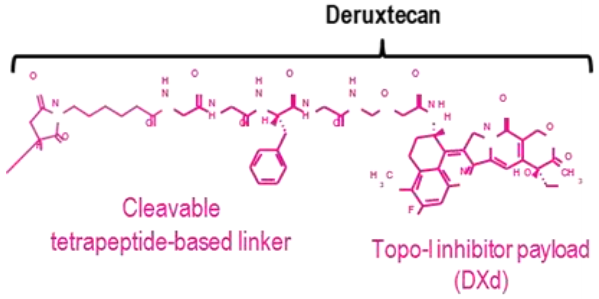
- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Key secondary:** ORR, PFS (investigator assessed) and safety

Randomisation stratified by:

- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs ROW)
- **Previous CDK4/6 inhibitor** (yes vs no)

- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

Dato-DXd: Humanised anti-TROP2 IgG1 monoclonal antibody



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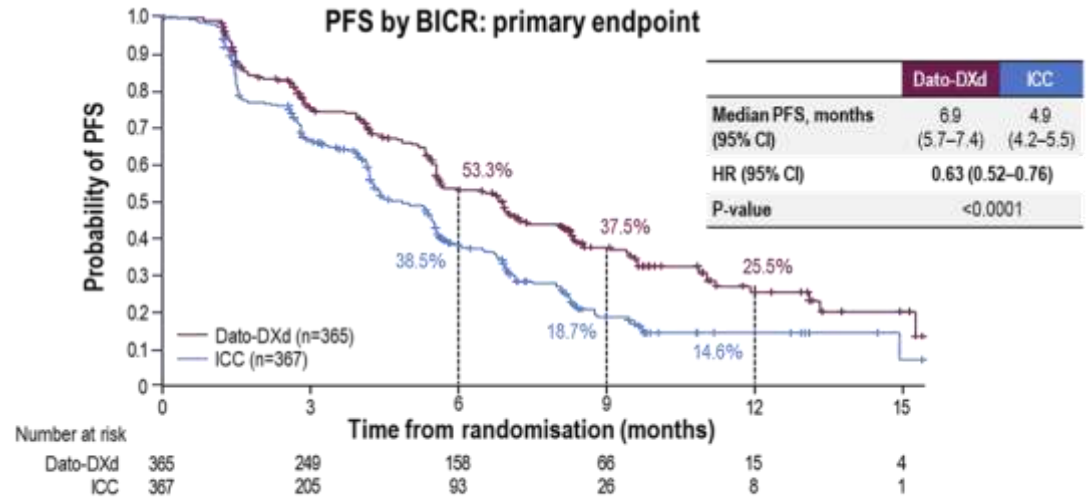
Bardia A et *al*. ESMO 2023 LBA11

Etude TROPION Breast 01

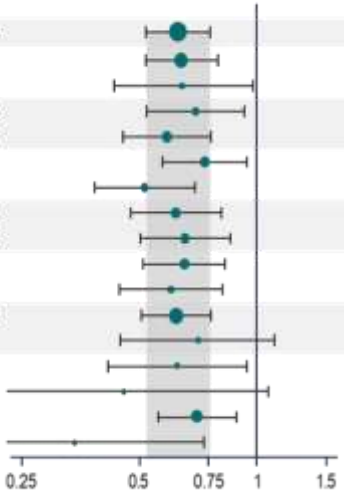


	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.7–7.4)	4.9 (4.2–5.5)
HR (95% CI)	0.63 (0.52–0.76)	
P-value	<0.0001	

PFS by investigator assessment: Median 6.9 vs 4.5 months; HR 0.64 (95% CI 0.53–0.76)

i; HR, hazard ratio

		Events/n Dato-DXd	Events/n ICC	Hazard ratio
All patients		212/365	235/367	0.63
Age at randomisation	<65 years	163/274	190/295	0.64
	≥65 years	49/91	45/72	0.65
Race	Asian	88/146	101/152	0.70
	Non-Asian	109/187	119/183	0.59
ECOG performance status	0	119/197	136/220	0.73
	1	91/165	98/145	0.52
Geographic region	US, Canada, Europe	110/186	112/182	0.62
	Rest of World*	102/179	123/185	0.66
Number of previous lines of chemotherapy	1	128/229	145/225	0.65
	2	84/135	90/141	0.60
Prior use of CDK4/6 inhibitor	Yes	177/299	190/286	0.62
	No	35/66	45/81	0.70
Prior use of taxane and/or anthracycline	Taxane alone	48/80	47/71	0.62
	Anthracycline alone	9/14	16/21	0.46
	Both taxane and anthracycline	141/236	155/247	0.70
	Neither taxane nor anthracycline	14/35	17/28	0.34



Size of circle is proportional to the number of events across both treatment groups
*Three patients from Canada were incorrectly stratified to Rest of World.

System Organ Class Preferred term, n (%)	Dato-DXd (n=360) Any Grade	Dato-DXd (n=360) Grade ≥3	ICC (n=351) Any Grade	ICC (n=351) Grade ≥3
Blood and lymphatic system				
Anaemia	40 (11)	4 (1)	69 (20)	7 (2)
Neutropenia*	39 (11)	4 (1)	149 (42)	108 (31)
Eye				
Dry eye	78 (22)	2 (1)	27 (8)	0
Gastrointestinal				
Nausea	184 (51)	5 (1)	83 (24)	2 (1)
Stomatitis	180 (50)	23 (6)	46 (13)	9 (3)
Vomiting	71 (20)	4 (1)	27 (8)	2 (1)
Constipation	65 (18)	0	32 (9)	0
General				
Fatigue	85 (24)	6 (2)	64 (18)	7 (2)
Skin and subcutaneous				
Alopecia	131 (36)	0	72 (21)	0

*Neutropenia includes the PTs neutropenia and neutrophil count decreased. †Oral stomatitis/mucositis events included PTs of aphthous ulcer, dysphagia, glossitis, stomatitis, tongue ulceration; all grade: 59% with Dato-DXd, 17% with ICC; grade 3: 7% with Dato-DXd, 3% with ICC. ‡Ophthalmologic assessments were required Corneal Disorder SMQ and select relevant PTs from Eye Disorder SOC; all grade: 49% with Dato-DXd, 23% with ICC; grade 3: 1% with Dato-DXd (one patient wit §ILD includes events that were adjudicated as ILD and related to use of Dato-DXd or ICC (includes cases of potential ILD/pneumonitis, based on MedDRA v23.0 fo respiratory failure). ¶One adjudicated drug-related grade 5 ILD event: attributed to disease progression by investigator. ILD, interstitial lung disease; PTs, preferred te

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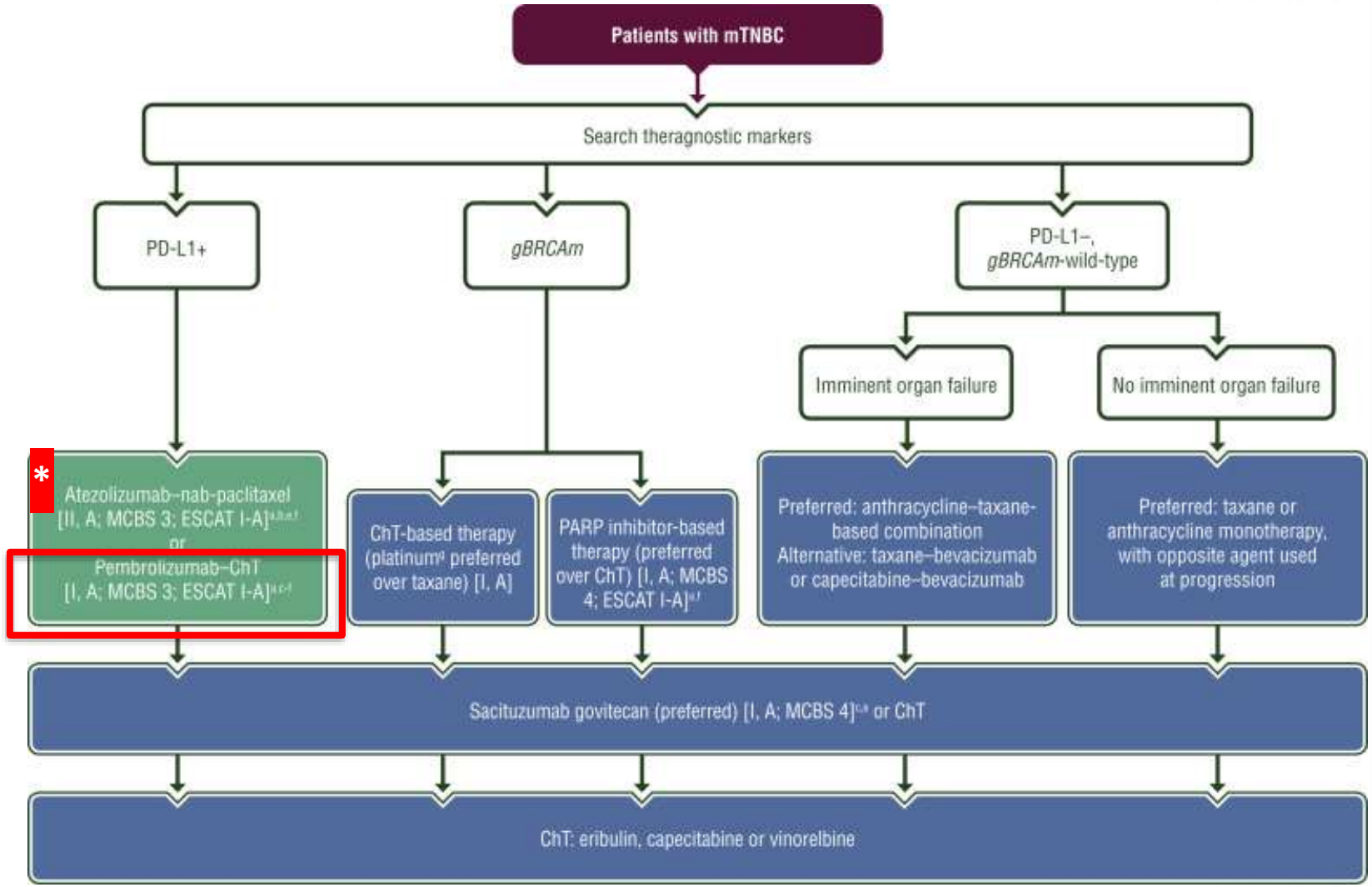
Bardia A et *al*. ESMO 2023 LBA11

Guidelines ESMO 2023 - immunothérapie



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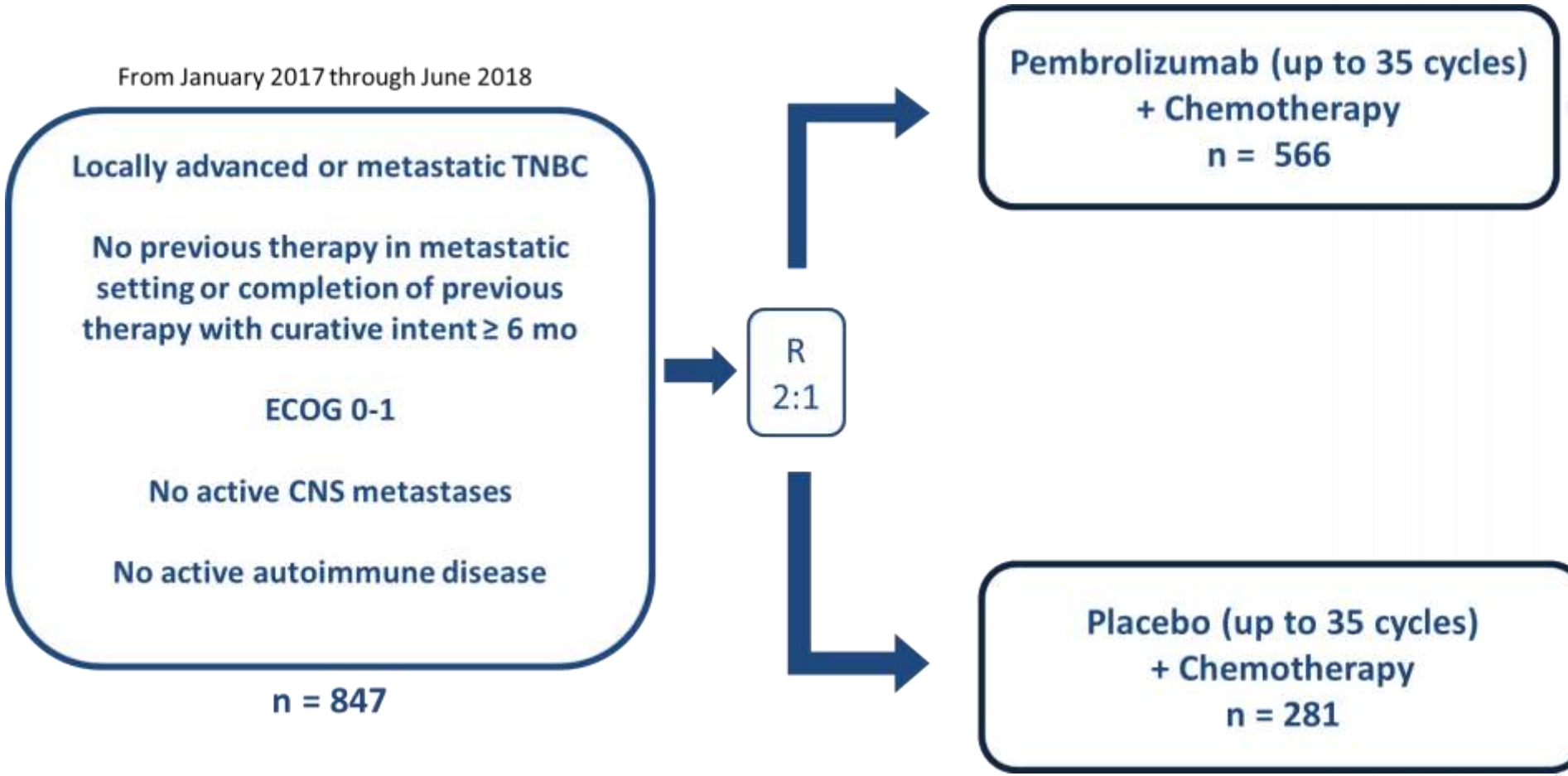
Gennari et *al*. Ann Oncol. 2021

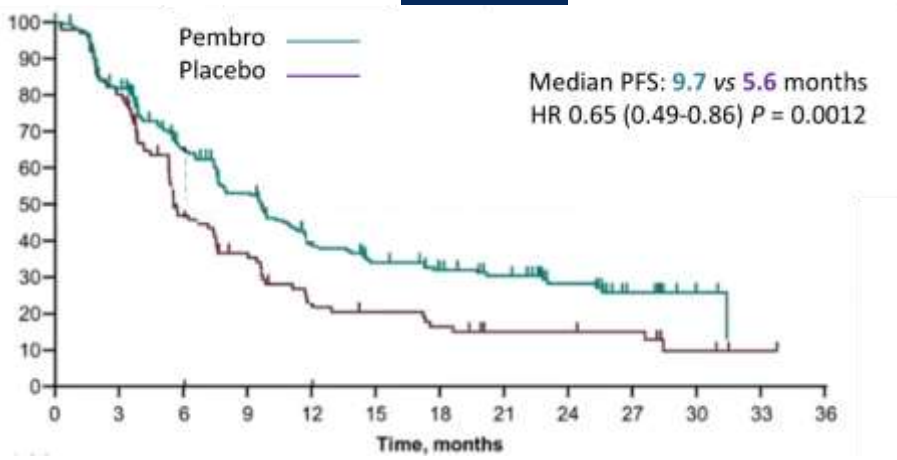
Etude KEYNOTE 355



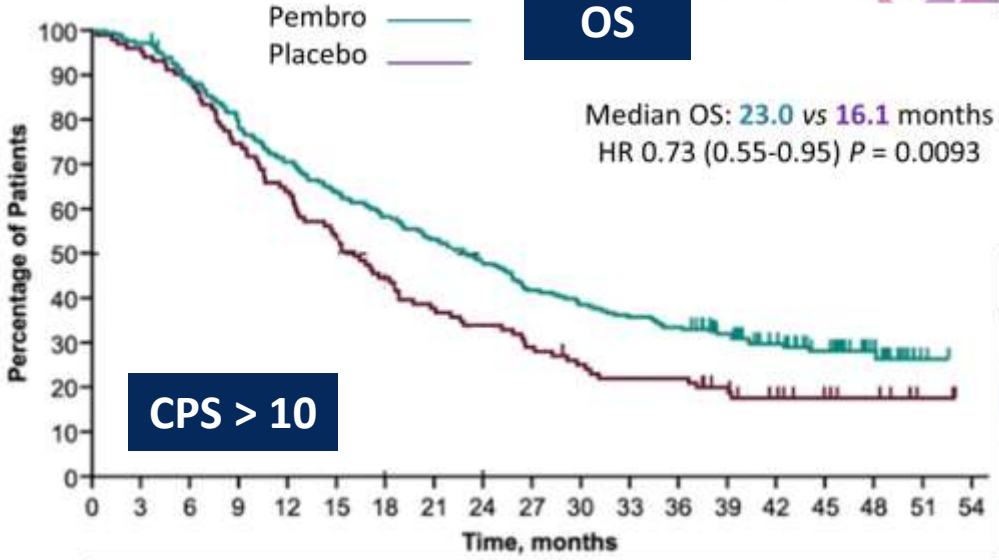
Cortes J et *al*. Lancet. 2020

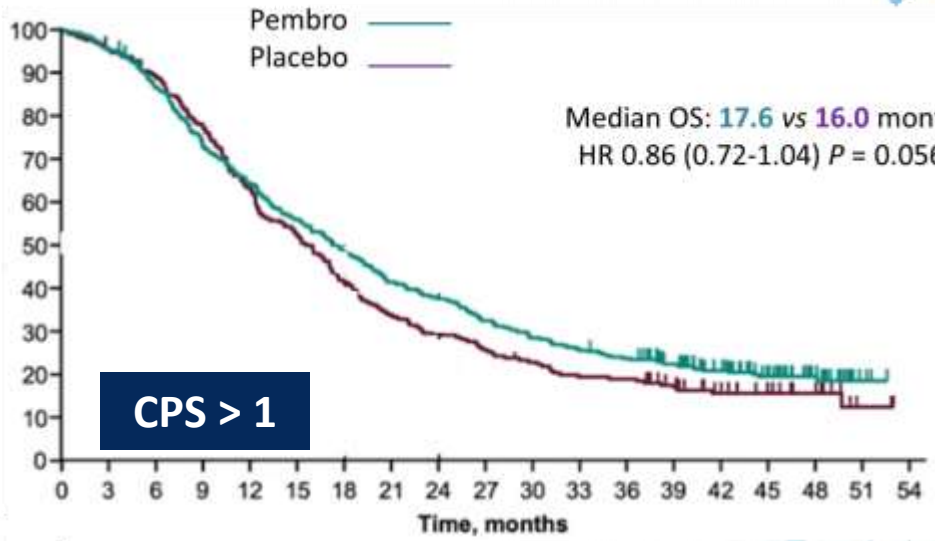
Etude KEYNOTE 355

PFS



OS





Event	Pembrolizumab–Chemotherapy (N=562)		Placebo–Chemotherapy (N=281)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
Immune-mediated adverse events‡	149 (26.5)	30 (5.3)	18 (6.4)	0
Hypothyroidism	89 (15.8)	2 (0.4)	9 (3.2)	0
Hyperthyroidism	24 (4.3)	1 (0.2)	3 (1.1)	0
Pneumonitis	14 (2.5)	6 (1.1)	0	0
Colitis	10 (1.8)	2 (0.4)	4 (1.4)	0
Severe skin reactions	10 (1.8)	10 (1.8)§	1 (0.4)	0

Cortes J et *al*. Lancet 2020

Conclusion

- Les traitements des cancers du sein sont actuellement en pleine mutation avec l'introduction des thérapies ciblées, des ADC ou de l'immunothérapie
- Toutefois, leur place nécessite d'être précisée notamment par rapport à la détermination et l'utilisation de biomarqueurs
- Place de plus en plus importante de la biologie moléculaire (ex: recherche mutation ESR1 sur ADNtc)

Merci de votre attention