CANCER DU SEIN METASTATIQUE RH+ HER2-

CAS CLINIQUE

Dr Fanny LE DU

LIENS D'INTÉRÊT

	Consulting/ Advisory Board	Speaker/ Conferences	Research grants (Institutional Grant)	Travel fees
Amgen		x		
Daiichi / AZ	x	x	x	x
Lilly	x	x		x
Seagen	x	x		x
Novartis	x	x		x
Pierre Fabre		x		x
Pfizer	x			x
Roche	x			
Gilead	x	x		x
Myriad/ ExactSciences	x			

« L'intervenant déclare qu'il a été sollicité à la demande des laboratoires Novartis pour intervenir en tant qu'expert »

CAS CLINIQUE #1

Jeanne, née en 1941 (78 ans)

Veuve, vit à Rennes, conduit encore, isolée, quelques troubles de mémoire

ATCD :
- HTA
- Diverticulose

Traitements en cours : Valsartan/hydrochlorothiazide, Trimetazidine, Bisoprolol, Acide acétylsalicylique, Paracétamol.

1999 : CARCINOME CANALAIRE INFILTRANT T2 (24mm) N0 (0/13) du sein gauche, SBRI, RE 100%, RP 80%
– Tumorectomie + curage axillaire
– Radiothérapie adjuvante
– TAMOXIFENE pendant 5 ans

2019 : Découverte de METASTASES asymptomatiques osseuses et hépatiques multiples dans le cadre d'une rechute locale clinique avec CA15.3 élevé à 500 (PS 0, 44 kg/1.50 m, SC 1.36)
– Biopsie mammaire : ER+ 100% PR 0%, HER2- (score 1+), Ki67 20%

CAS CLINIQUE #1

Quels traitements de L1 envisager chez cette patiente ?

- HT (Anti-aromatase – Fulvestrant) en monothérapie
- HT (Anti-aromatase – Fulvestrant) – CDK4/6i
- Chimiothérapie par CAPECITABINE
- Chimiothérapie par PACLITAXEL

CAS CLINIQUE #1

G8 = 10

- Pas de perte de poids **+2** ni d'appétit **+3**
- Sort de chez elle **+2**
- Quelques doutes sur troubles cognitifs modérés **+1**
- IMC 19.6 **+1**
- Traitemement : valsartan/hydrochlorothiazide, trimetazidin bisoprolol, acide acétylsalicylique, paracétamol **+0**
- Etat de santé jugé « aussi bien » que les autres **+1**
- > 85 **+0**

Carey = 5

- Femme **+0**
- >80 **+2**
- Pas de difficulté pour toilette **+0**
- Pas de difficulté pour courses **+0**
- Difficulté pour marche prolongée **+2**
- Difficulté pour tirer ou pousser de gros objets **+1**

→ Mortalité à 2 ans 12%

Soubeyran et al. PLOS 2014
Carey et al. J Gen Intern Med 2004

CAS CLINIQUE #1

Quelle place pour la **CHIMIOTHERAPIE** en 1ère ligne ?

RIGHT

Premenopausal patients

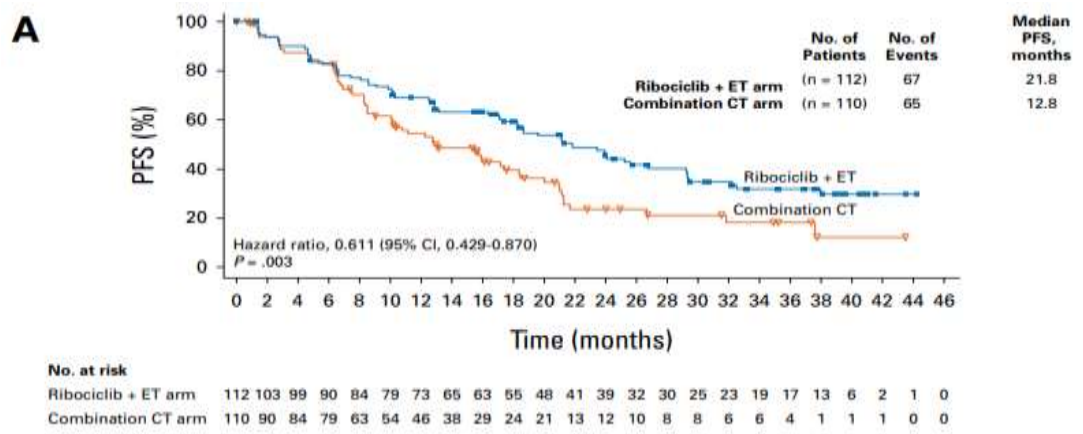
- RH+ HER2-
- **Critères d'agressivité** (métastases viscérales symptomatiques, progression rapide ou en "crise viscérale", métastases non viscérales très symptomatiques)
- Nécessitant, selon l'investigateur, une polychimiothérapie.

R

1:1
n = 222

AA + Goséréline + RIBOCICLIB

Polychimiothérapie (docétaxel-capécitabine, paclitaxel-gemcitabine, vinorelbine-capécitabine)



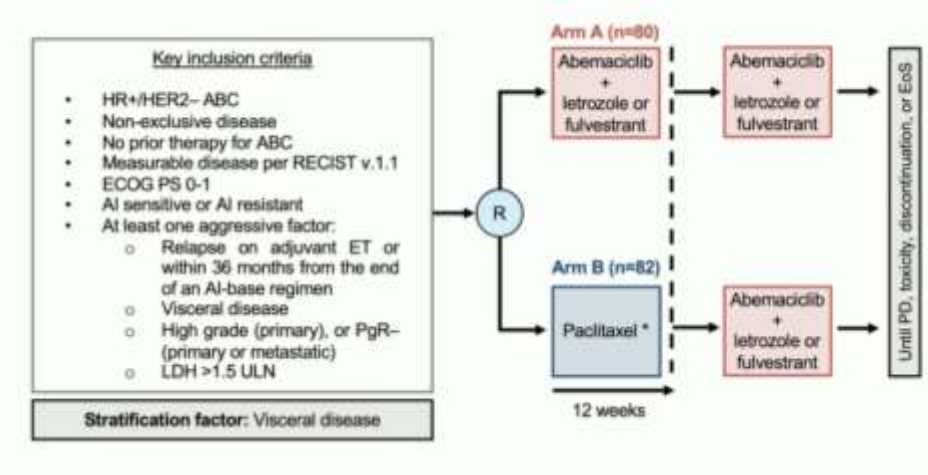
Bin Mohd Mahidin El et al., abstr. GS1-10, SABCS 2022
Lu et al. JCO 2024

CAS CLINIQUE #1

Quelle place pour la **CHIMIOTHERAPIE** en 1ère ligne ?

ABIGAIL

Median age 57 (26-82)
70% postménopausal



Primary objective:
Compare 12-week ORR per BICR in both groups.

Secondary endpoints:
PFS, OS, clinical benefit rate, time to response, duration of response, safety, maximum tumor shrinkage.

Newcombe hybrid score method was used. Based on 10% dropout rate, N ≥160 was necessary to attain 80% power at nominal level of two-sided α=0.05.

* According to response, clinicians can determine if patients extend paclitaxel to a maximum of 6 cycles after the first 12 weeks of treatment.

	Abemaciclib + ET N = 80	Paclitaxel N = 82	Odd ratio (95% CI)	p value
12-week ORR in ITT population				
Complete response, partial response	47 (58.8%)	33 (40.2%)	2.11 (1.13-3.96)	0.0193
Stable disease, progressive disease , or discontinuation	33 (41.2%)	49 (59.8%)		
Response at 12 weeks since randomization				
Complete response	0 (0%)	0 (0%)		
Partial response	47 (58.8%)	33 (40.2%)		
Stable disease	24 (30.0%)	37 (45.2%)		
Progressive disease	1 (1.2%)	7 (8.5%)		

Juan de la Hab-Rodriguez, ESMO2024

CAS CLINIQUE #1

Quels traitements de L1 envisager chez cette patiente ?

HT (Anti-aromatase – Fulvestrant) en monothérapie

HT (Anti-aromatase – Fulvestrant) – CDK4/6i

Chimiothérapie : CAPECITABINE

Chimiothérapie : PACLITAXEL

CAS CLINIQUE #1

Quelle place pour les CDK4/6i en 1ère ligne ?

L1

Study	CDK4/6 inhibitor	Endocrine therapy	Line	Menopausal status	Median FUP (PFS	HR PFS (95% CI)	Median PFS (CDK4/6i)	Median PFS (Placebo)	Median FUP (OS)	HR OS (95% CI)	Median OS (CDK4/6i)	Median OS (Placebo)
PALOMA-2[13,23]	Palbociclib	Letrozole	1st line	Post- menopausal	37.5 m	0.563 (0.461–0.687)	27.6 m	14.5 m	90.0 m	0.956 (0.777–1.177)	53.9 m	51.2 m
MONALEESA-2[6,24]	Ribociclib	Letrozole	1st line	Post-menopausal	26.4 m	0.568 (0.457–0.704)	25.3 m	16.0 m	79.2 m	0.760 (0.630–0.930)	63.9 m	51.4 m
MONALEESA-7[7,25]	Ribociclib	Tamoxifen/ NSAI + Goserelin	1st or 2nd line (after chemotherapy)	Pre-menopausal	19.2 m	0.553 (0.441–0.694)	23.8 m	13.0 m	53.5 m	0.763 (0.608–0.956)	58.7 m	48.0 m
MONARCH-3[15,26,27]	Abemaciclib	NSAI	1st line	Post-menopausal	39.3 m	0.525 (0.415–0.665)	28.2 m	14.8 m	70.2 m	0.754 (0.584–0.974)	67.1 m	54.5 m

FUP = follow-up. PFS = progression-free survival. OS = overall survival. HR = hazard ratio. m = months. ET = endocrine therapy.

Table 1: **Characteristics of studies included in the primary analysis.**

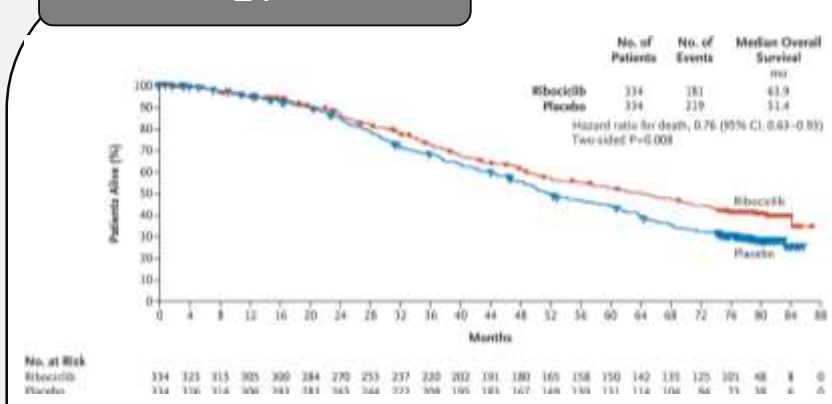
- Résultats remarquables et cliniquement significatifs en **PFS**
- Standard dans les **cancers du sein avancés RE+ 1ère ligne**
- Profils de tolérance permettant une préservation de la QoL

Mastrantoni L et al. EClinicalMedicine . 2023

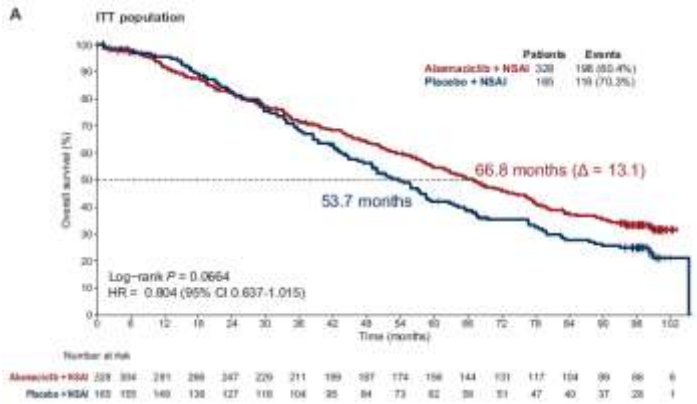
CAS CLINIQUE #1

Quelle place pour les CDK4/6i en 1ère ligne ?

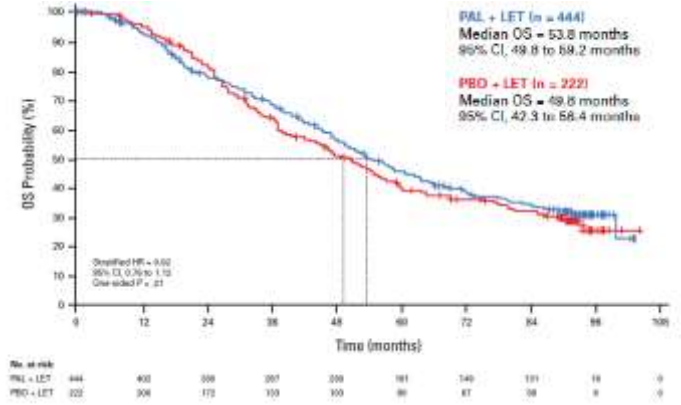
L1



MONALEESA2



MONARCH3



PALOMA2

- Amélioration cliniquement et statistiquement significative de la **survie globale** en 1ère ligne (ribociclib)
- Amélioration cliniquement significative de la **survie globale** en 1ère ligne (abemaciclib)
- Pas d'amélioration significative de la **survie globale** en 1ère ligne (palbociclib)

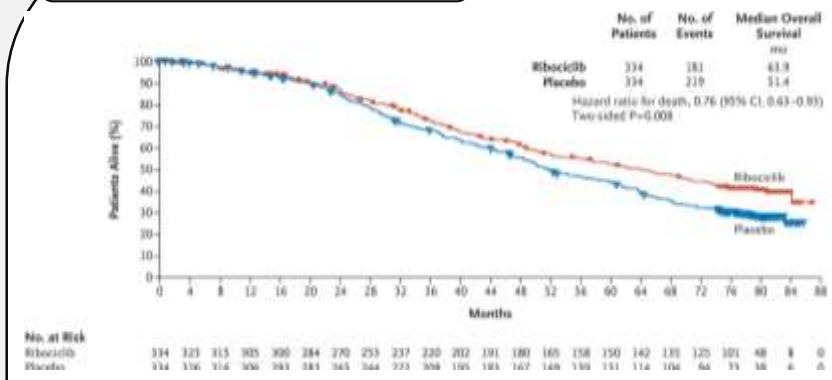
Mastrantoni L et al. EClinicalMedicine . 2023

CAS CLINIQUE #1

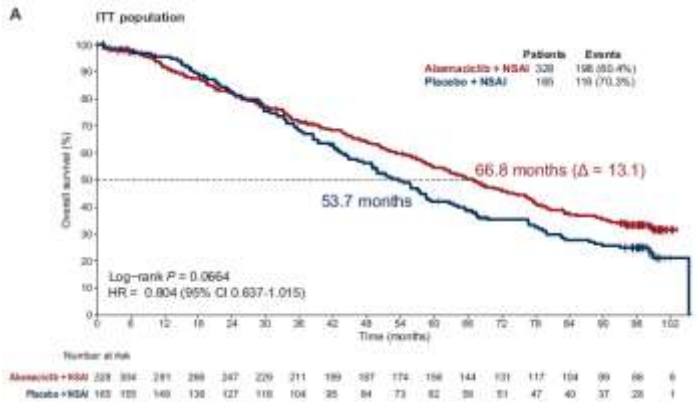
Quelle place pour les CDK4/6i en 1ère ligne ?

Profils de tolérance

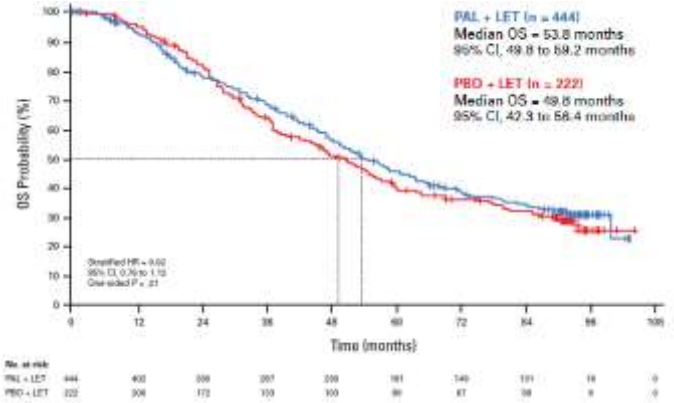
L1



MONALEESA2



MONARCH3



PALOMA2

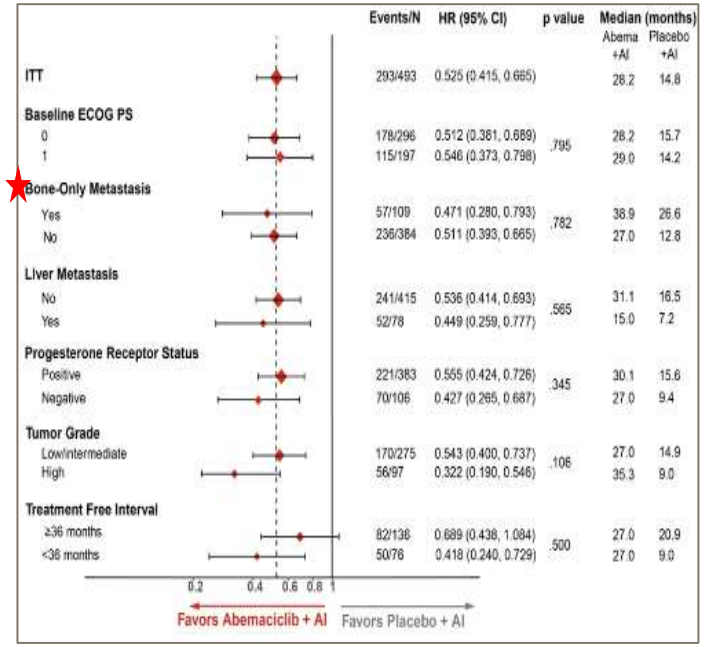
- Amélioration cliniquement et statistiquement significative de la **survie globale** en 1ère ligne (ribociclib)
- Amélioration cliniquement significative de la **survie globale** en 1ère ligne (abemaciclib)
- Pas d'amélioration significative de la **survie globale** en 1ère ligne (palbociclib)

Mastrantoni L et al. EClinicalMedicine . 2023

CAS CLINIQUE #1

Il y a-t-il un sous-groupe qui ne bénéficierait pas des CDK4/6i ?

MONARCH3



Bénéfice en PFS dans tous les **sous-groupes cliniques**

MONALEESA7

Bénéfice en PFS dans tous les **sous-groupes biologiques ou moléculaires** (excepté peut être les BL PAM50)

Johnston et al. Npj breast cancer 2021
*MONALEESA2 Hortobagyi et al. NEJM 2022
*MONALEESA7Johnston et al. Npj breast cancer 2021

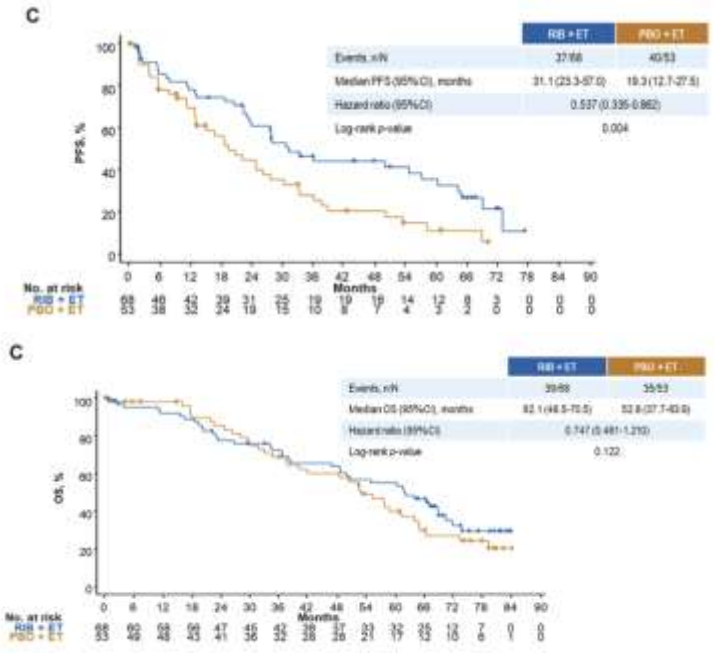
Bardia et al. JCO Prec Onco 2021

CAS CLINIQUE #1

Quid de la population agée ?

MONALEESA 2,3 et 7

>75ans



Bénéfice en PFS dans tous les **sous-groupes quel que soit l'âge**

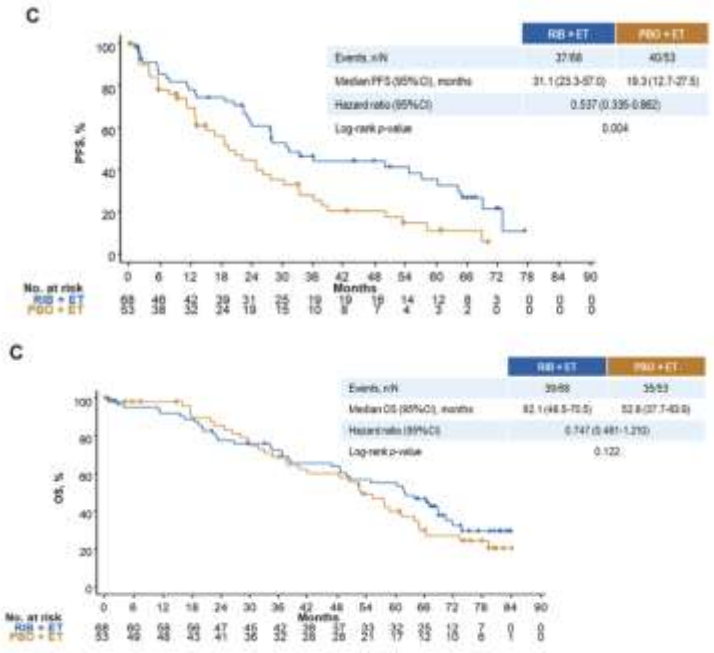
Hart et al. EJC 2025

CAS CLINIQUE #1

Quid de la population agée ?

MONALEESA 2,3 et 7

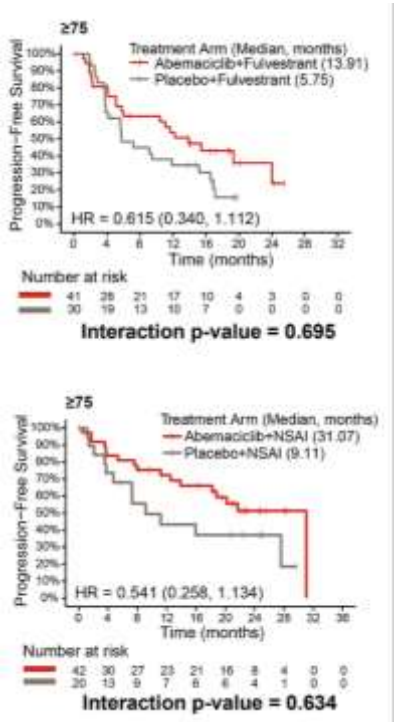
>75ans



Bénéfice en PFS dans tous les **sous-groupes quel que soit l'âge**

Hart et al. EJC 2025

MONARCH2 et 3



Bénéfice en PFS dans tous les **sous-groupes quel que soit l'âge**

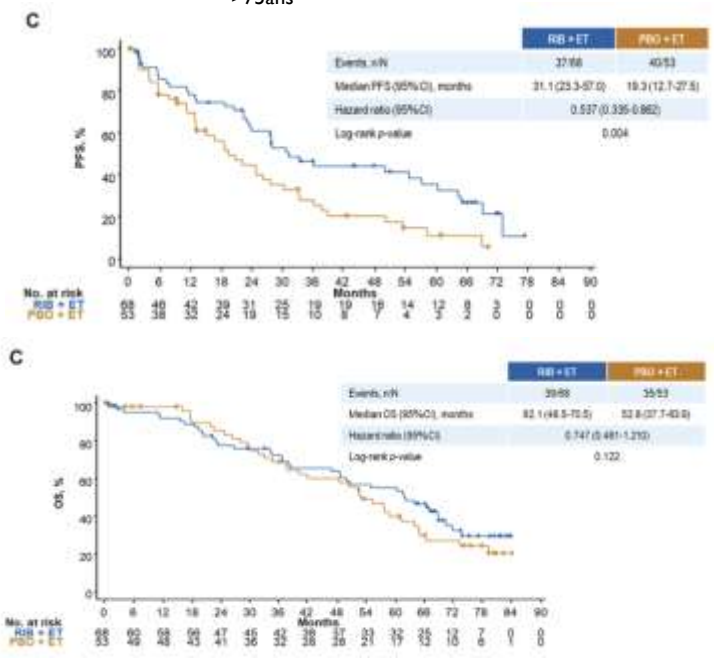
Goetz et al. JCO BCRT 2021

CAS CLINIQUE #1

Quid de la population agée ?

MONALEESA 2,3 et 7

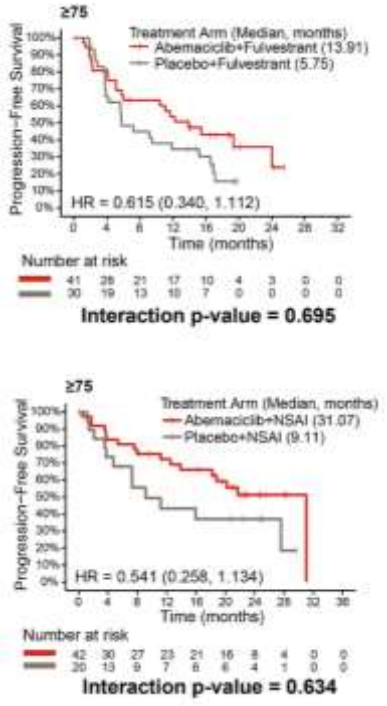
>75ans



Bénéfice en PFS dans tous les **sous-groupes quel que soit l'âge**

Hart et al. EJC 2025

MONARCH2 et 3



Bénéfice en PFS dans tous les **sous-groupes quel que soit l'âge**

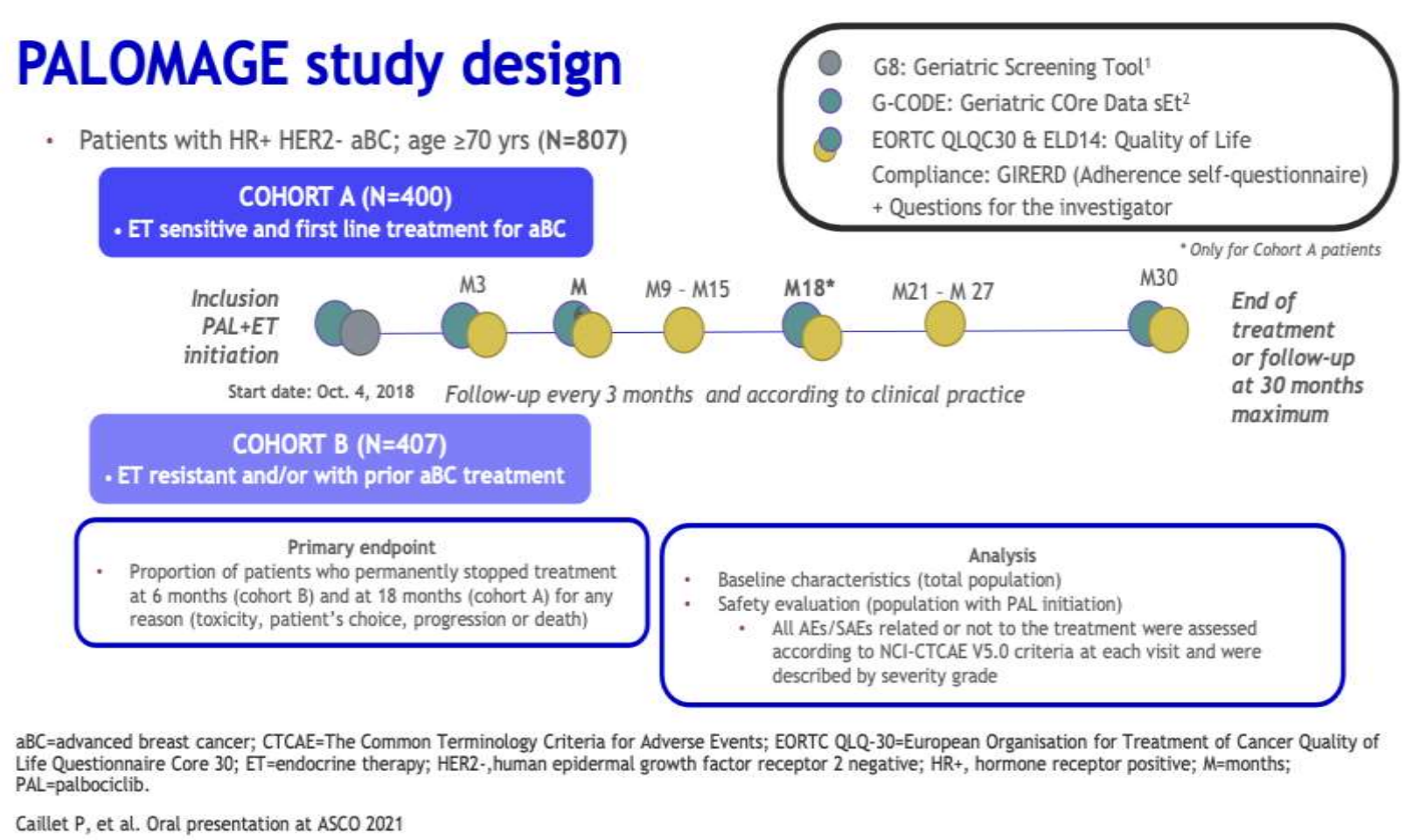
Goetz et al. JCO BCRT 2021

PalomAGE

- Etude de cohorte prospective de patientes **> 70 ans traitées par PALBOCICLIB+HT**

CAS CLINIQUE #1

Quid de la population agée ?



aBC=advanced breast cancer; CTCAE=The Common Terminology Criteria for Adverse Events; EORTC QLQ-30=European Organisation for Treatment of Cancer Quality of Life Questionnaire Core 30; ET=endocrine therapy; HER2-,human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive; M=months; PAL=palbociclib.

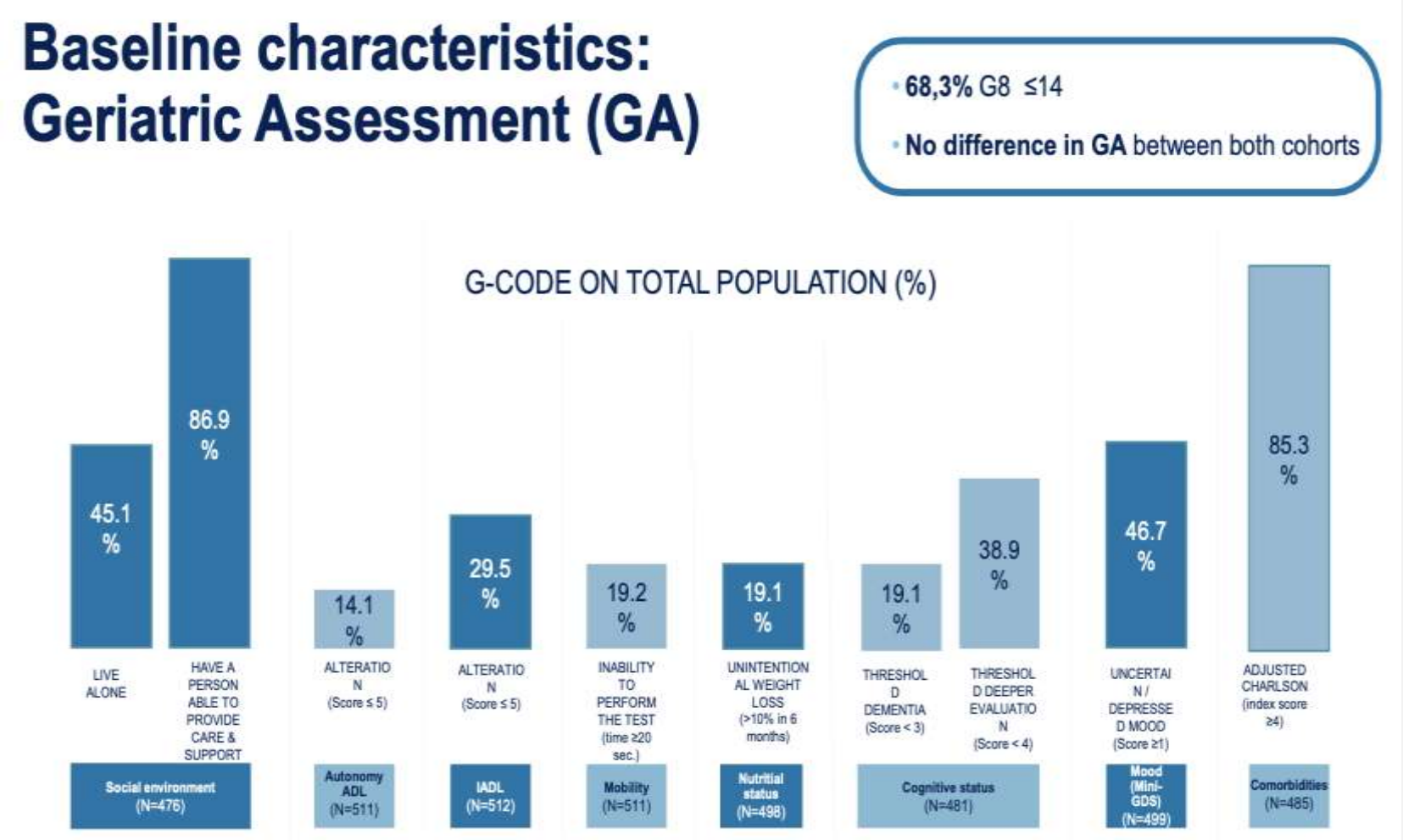
Caillet P, et al. Oral presentation at ASCO 2021

PalomAGE

- Etude de cohorte prospective de patientes **> 70 ans traitées par PALBOCICLIB+HT**
- Cohorte de 1ère ligne (362 patientes)
  - >50% à >80ans
  - G8 altéré dans 68% des cas
  - 40% de métastases viscérales
- **18-month discontinuation rate for PAL was 41.9%** due to disease progression (20.8%), toxicity (7.7%), patient's choice (6.7%), death (4.6%), or other reason (2.1%).
- Median PFS 28.1 months (95% CI: 25.6-not reached)

CAS CLINIQUE #1

Quid de la population agée ?



PalomAGE

- Etude de cohorte prospective de patientes **> 70 ans traitées par PALBOCICLIB+HT**
- Cohorte de 1ère ligne (362 patientes)
  - >50% à >80ans
  - G8 altéré dans 68% des cas
  - 40% de métastases viscérales
- Median PFS 28.1 months (95% CI: 25.6-not reached)

CAS CLINIQUE #1

Quels traitements de L1 envisager chez cette patiente ?

HT (Anti-aromatase – Fulvestrant) en monothérapie

HT (Anti-aromatase – Fulvestrant) – CDK4/6i

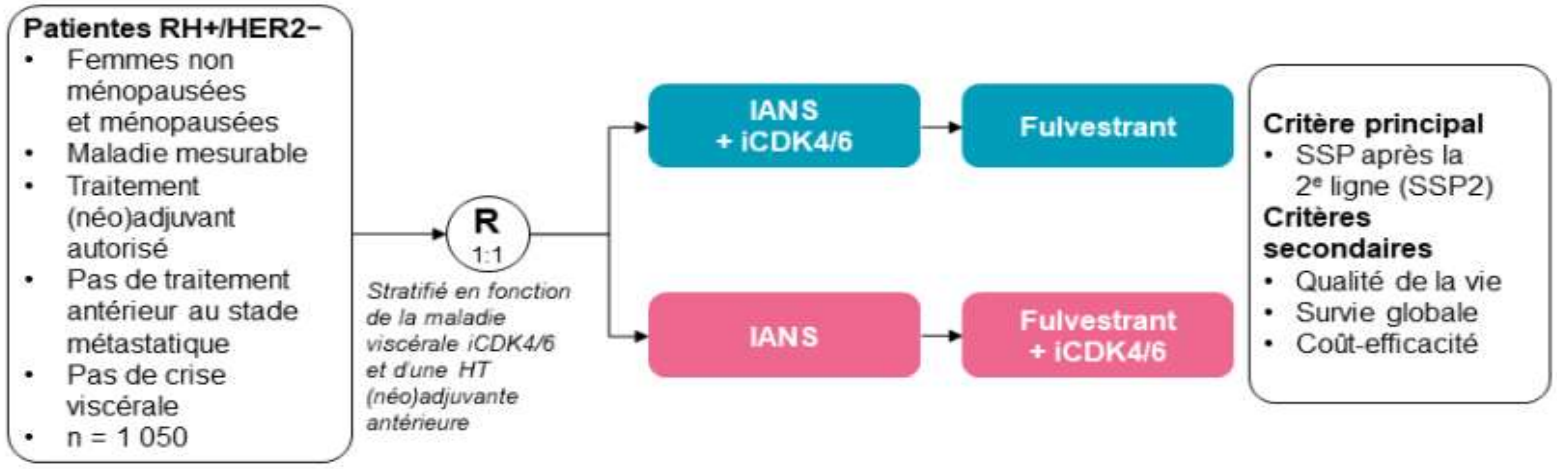
Chimiothérapie : CAPECITABINE

Chimiothérapie : PACLITAXEL

CAS CLINIQUE #1

Peut-on encore faire de l'HT en monothérapie en LI ?

SONIA



- Évaluation toutes les 12 semaines
- SSP évaluée localement selon RECIST v1.1
- Analyse primaire prévue après 574 événements de SSP2
  - 89 % de puissance pour détecter une supériorité selon l'ESMO MCBS (limite inférieure HR IC ≤ 0,65 et Δ ≥ 3 mois) avec α bilatéral = 5 %

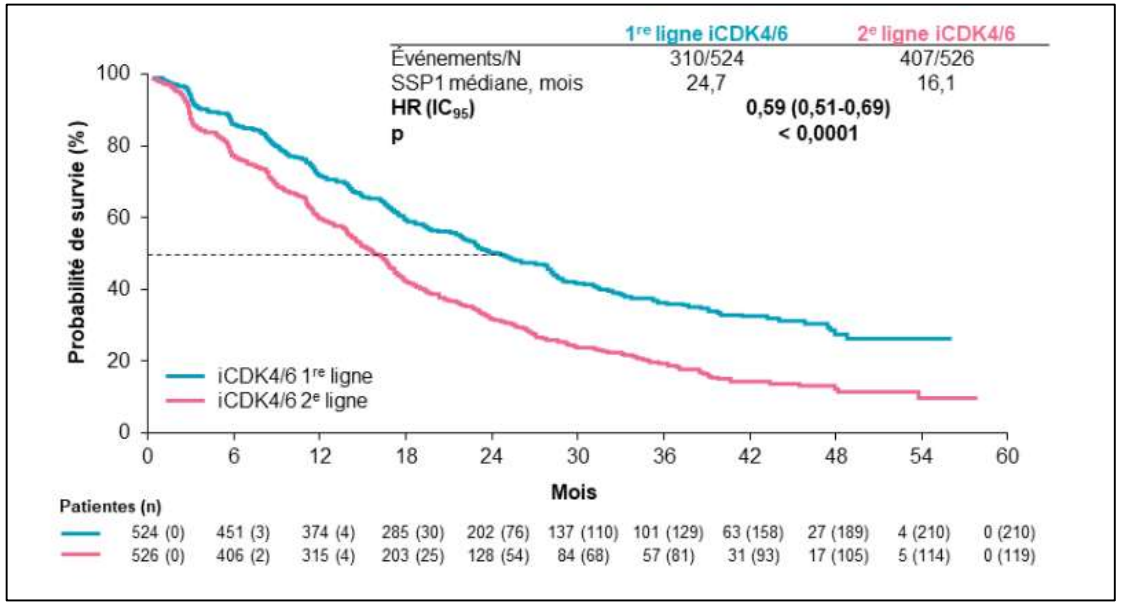
Sonke et al. abstr LBA100. ASCO 2023

CAS CLINIQUE #1

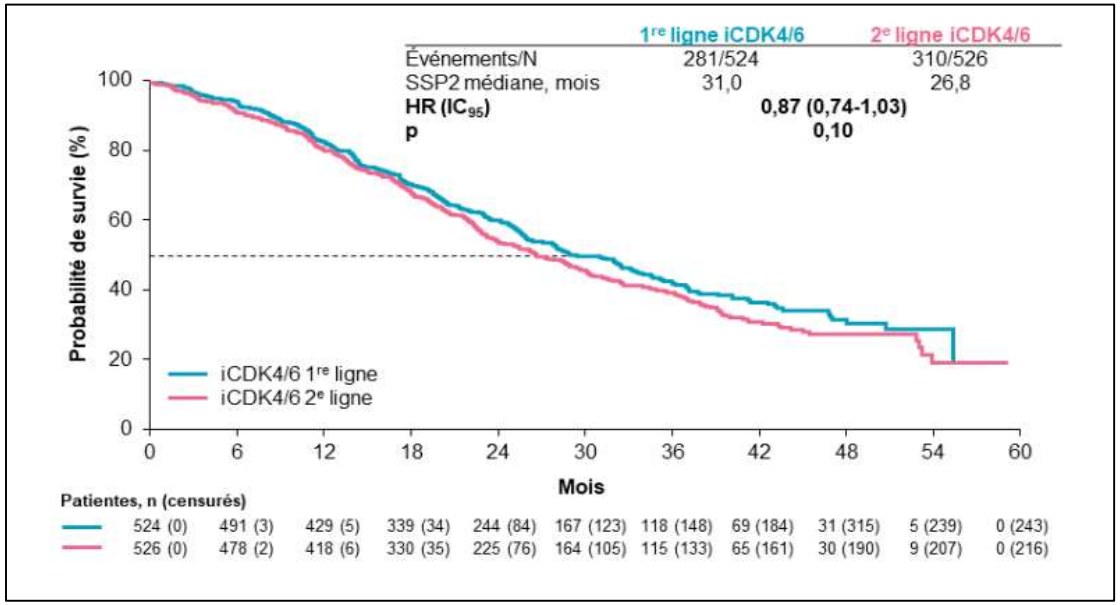
Peut-on encore faire de l'HT en monothérapie en LI ?

SONIA

Median age 64 (24-88)
88% postménopausal



SSP1

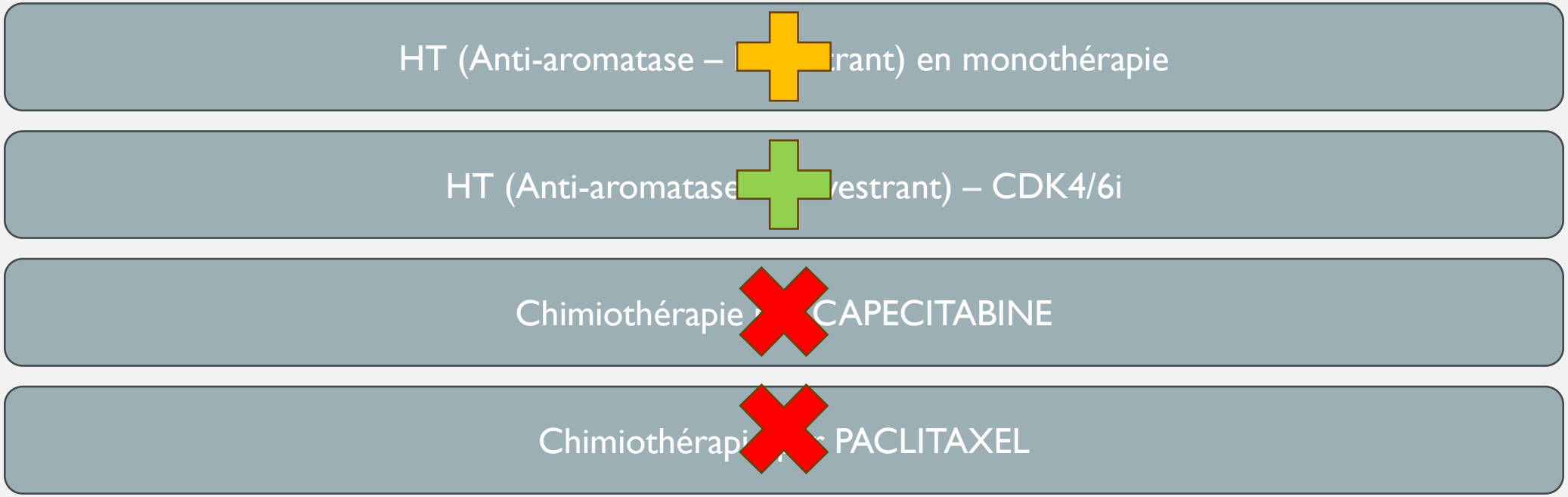


SSP2

Sonke et al. abstr LBA100. ASCO 2023

CAS CLINIQUE #1

Quels traitements de L1 envisager chez cette patiente ?



CAS CLINIQUE #1

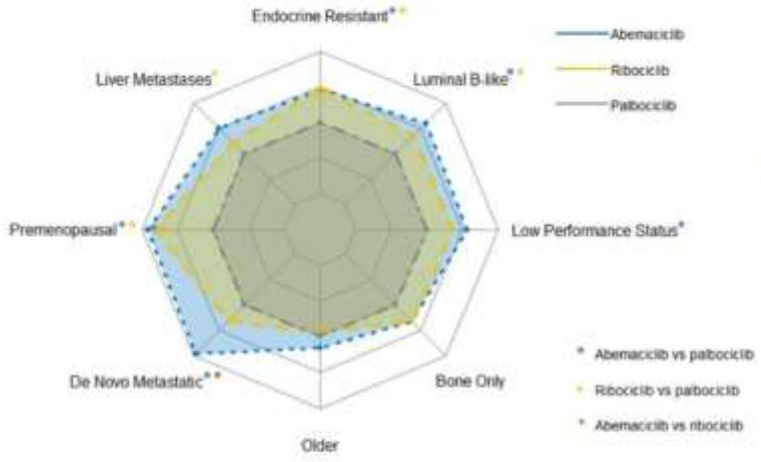
Si vous avez envisager les CDK4/6I, lequel privilégiez-vous (quelque soit votre partenaire d'HT) ?

- ABEMACICLIB *(150mg*2/jour en continu)*
- ABEMACICLIB *(100mg*2/jour en continu)*
- RIBOCICLIB *(600mg/jour 3W/4)*
- RIBOCICLIB *(400mg/jour 3W/4)*
- PALBOCICLIB *(125mg/jour 3W/4)*
- PALBOCICLIB *(100mg/jour 3W/4)*

CAS CLINIQUE #1

Quel CDK4/6i choisir ?

PALMARES



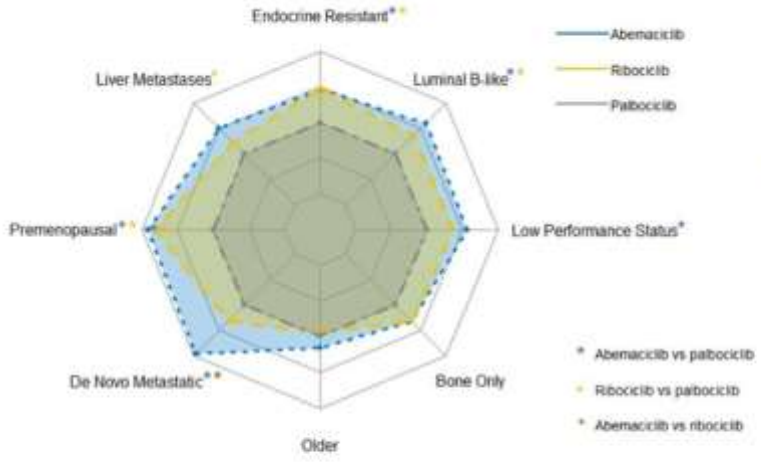
- Abemaciclib and ribociclib were more effective than palbociclib in patients with endocrine-resistant or luminal B-like disease, as well as in premenopausal patients
- Abemaciclib was superior to palbociclib in patients with poorer ECOG PS, and to both palbociclib and ribociclib in patients with de novo metastatic disease
- Both ribociclib and abemaciclib showed a trend towards higher efficacy in patients with liver metastases; however, this difference reached statistical significance only in patients treated with ribociclib
- The three CDK4/6i were similarly effective in patients who were older or had bone-only disease

Vernieri et al. ASCO 24

CAS CLINIQUE #1

Quel CDK4/6i choisir ?

PALMARES



- Abemaciclib and ribociclib were more effective than palbociclib in patients with endocrine-resistant or luminal B-like disease, as well as in premenopausal patients
- Abemaciclib was superior to palbociclib in patients with poorer ECOG PS, and to both palbociclib and ribociclib in patients with de novo metastatic disease
- Both ribociclib and abemaciclib showed a trend towards higher efficacy in patients with liver metastases; however, this difference reached statistical significance only in patients treated with ribociclib
- The three CDK4/6i were similarly effective in patients who were older or had bone-only disease

Profils de tolérance

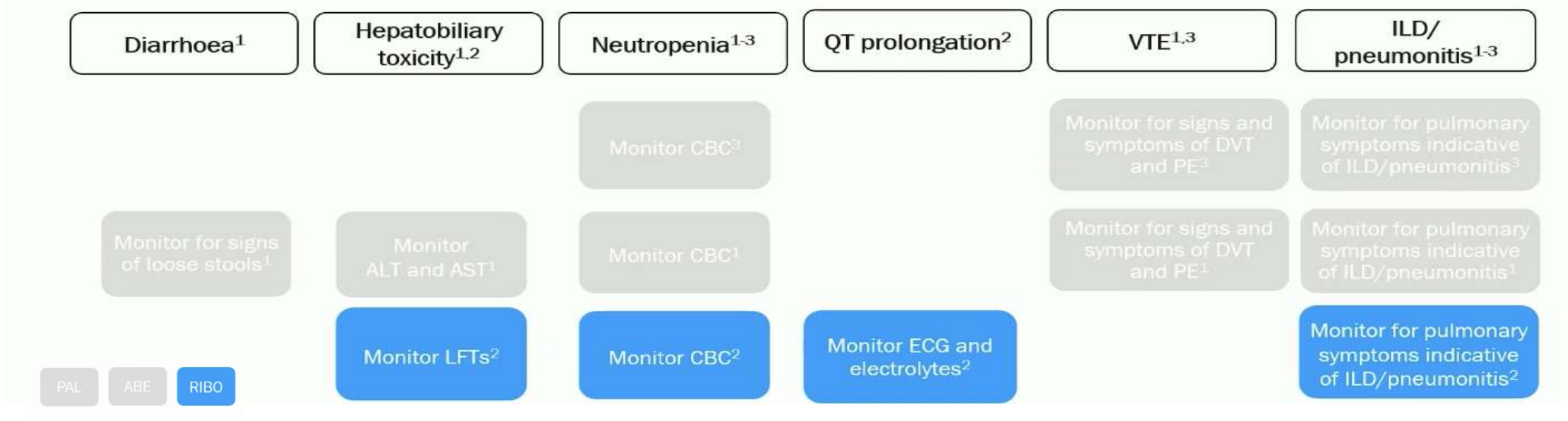
Données population AGÉE

Vernieri et al. ASCO 24

CAS CLINIQUE #1

Quel CDK4/6i choisir ?

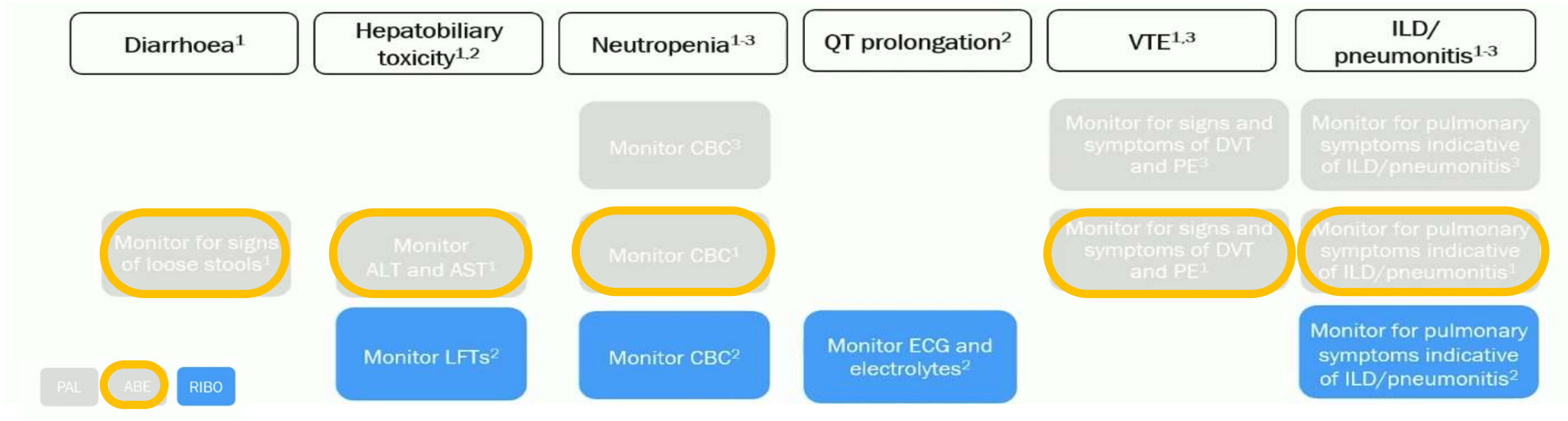
TOXICITE



CAS CLINIQUE #1

Quel CDK4/6i choisir ?

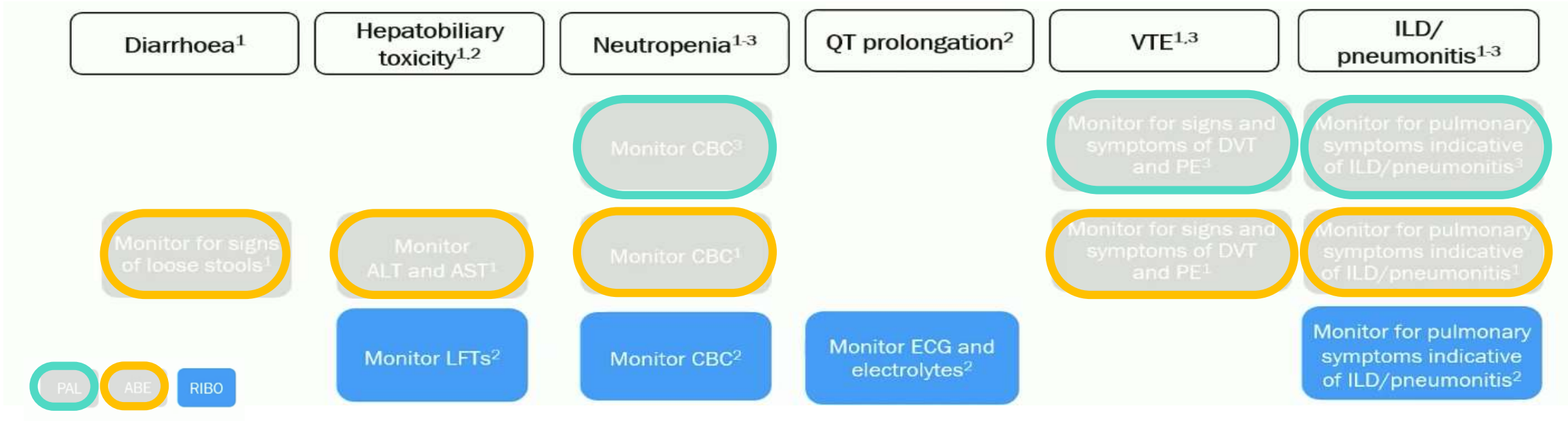
TOXICITE



CAS CLINIQUE #1

Quel CDK4/6i choisir ?

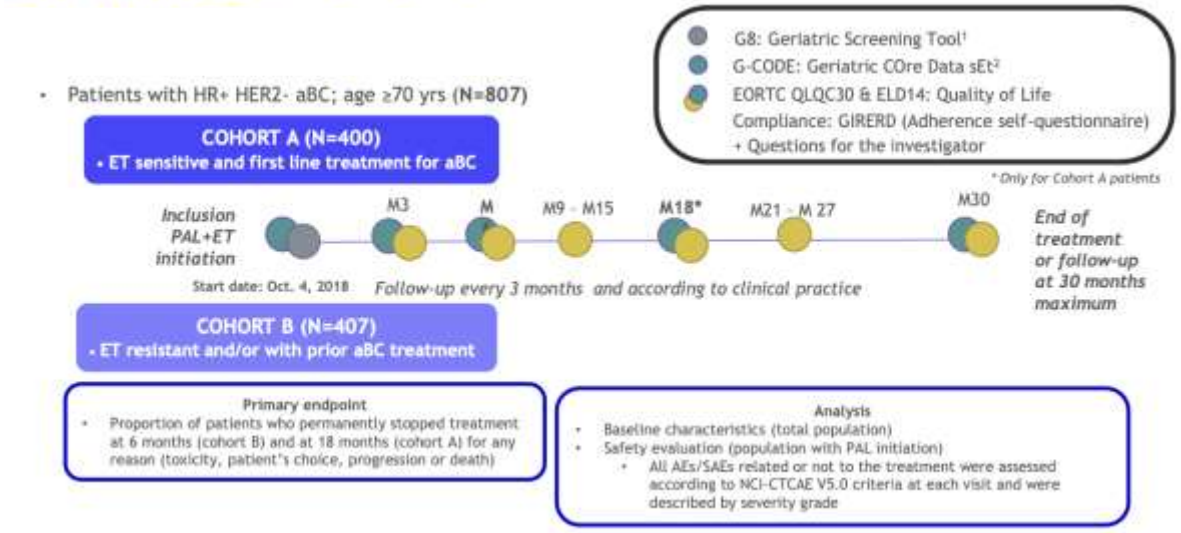
TOXICITE

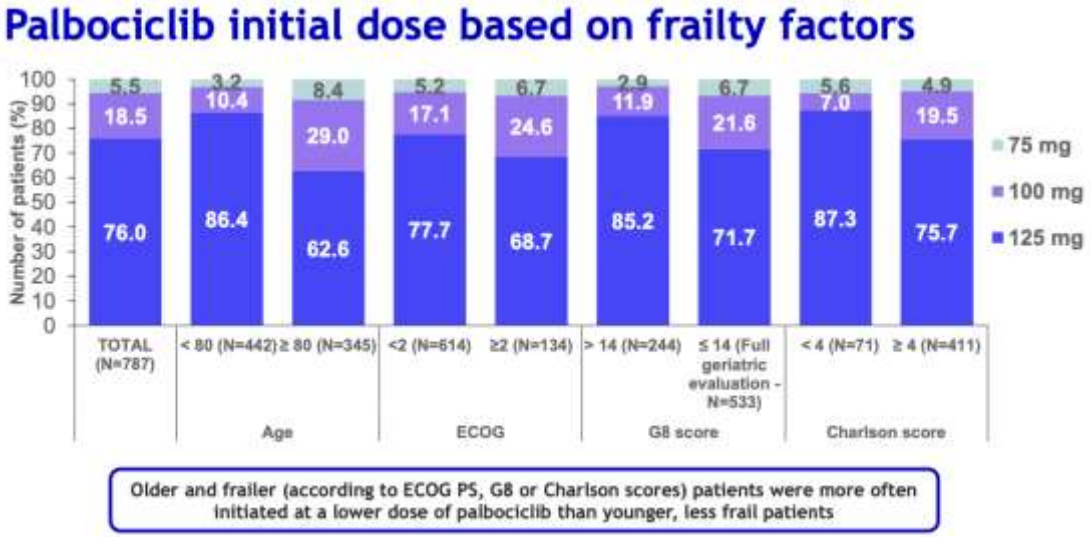


CAS CLINIQUE #1

A quel dosage débuté ?

PALOMAGE



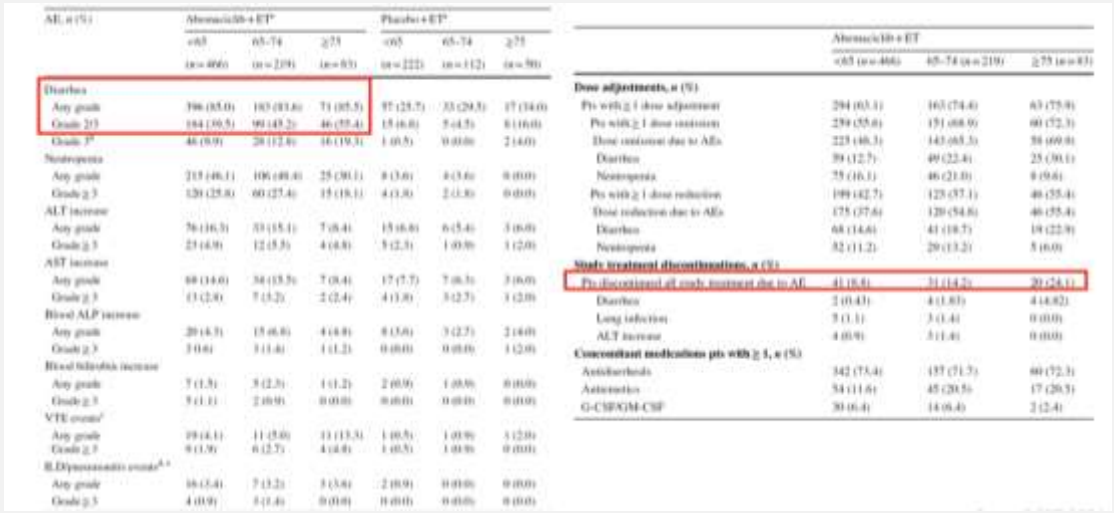


Caillet P, et al. Oral presentation at ASCO 2021.

CAS CLINIQUE #1

A quel dosage débuté ?

ABEMACICLIB



RIBOCICLIB

Adverse events by age groups.

≥ 15 % in either arm, n (%)	< 65y				65–74y				≥ 75y			
	All-grade		Grade 3/4		All-grade		Grade 3/4		All-grade		Grade 3/4	
	RIB + ET n = 419	PBO + ET n = 350	RIB + ET n = 419	PBO + ET n = 350	RIB + ET n = 188	PBO + ET n = 147	RIB + ET n = 188	PBO + ET n = 147	RIB + ET n = 68	PBO + ET n = 52	RIB + ET n = 68	PBO + ET n = 52
Any AE	412 (98)	342 (98)	353 (84)	132 (38)	186 (99)	142 (97)	168 (89)	62 (42)	68 (100)	50 (96)	60 (88)	31 (60)

Dose modifications by age groups.

Modification	< 65y		65–74y		≥ 75y	
	RIB + ET n = 419	PBO + ET n = 350	RIB + ET n = 188	PBO + ET n = 147	RIB + ET n = 68	PBO + ET n = 52
Patients with permanent discontinuations, n (%)	347 (83)	327 (93)	164 (87)	142 (97)	64 (94)	52 (100)
Patients with discontinuation due to AE, n (%)	61 (15)	11 (3)	37 (20)	10 (7)	28 (41)	4 (8)

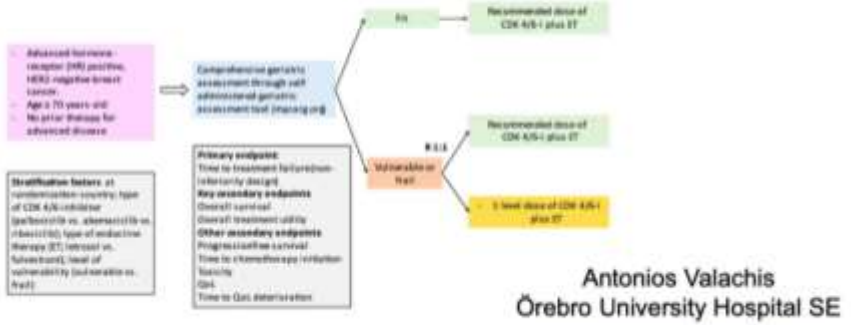
Hart et al. EJC 2025
Goetz et al. JCO BCRT 2021

CAS CLINIQUE #1

A quel dosage débuté ?

IMPORTANT

IMPlementing geriatric assessment for dose Optimization of CDK 4/6-inhibitors in older bReasT cAncer patieNTs – a pragmatic randomized-controlled trial (IMPORTANT trial)



Antonios Valachis
Örebro University Hospital SE

ClinicalTrials.gov ID: NCT06044623

supported by: HORIZON-MISS-2022-CANCER-01

Research In progress: Not yet recruiting

Comparing Oral Drug Dosing Strategies in Older Patients with Metastatic Breast Cancer to Maximize Tolerance and Reduce Discontinuation: The CDK4/6 Inhibitor Dosing Knowledge (CDK) Study

500 patients ≥ 65 yo
HR+/HER2- MBC
planned use of CDK4/6i (PAL or RIB) + ET
1st time in metastatic setting

Indicated dose (start high, deescalate if needed)
versus (1:1)
titrated dose (start low, escalate if tolerated)

Primary objective = time to discontinuation of CDK4/6i

32

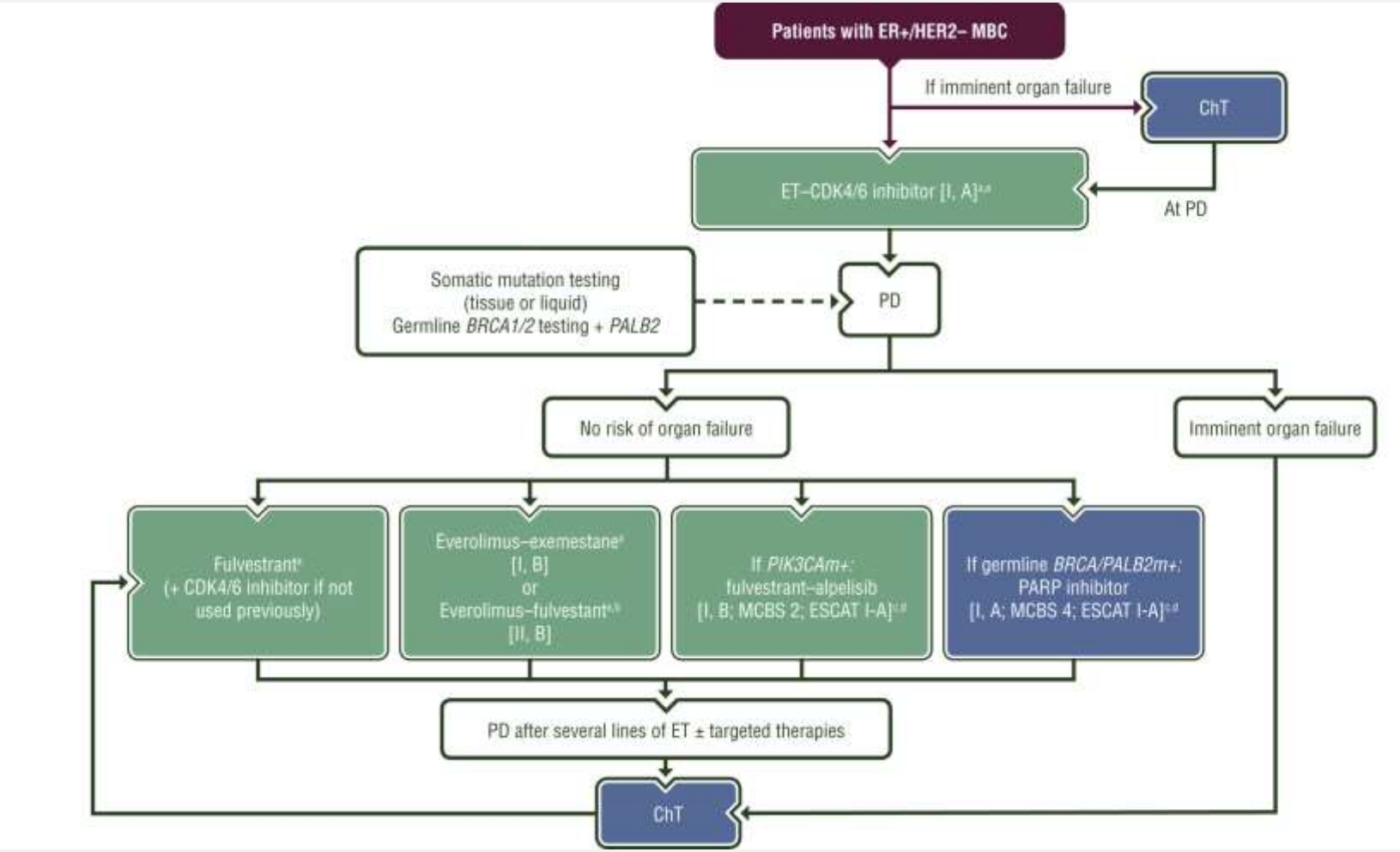
https://www.pcori.org/, https://clinicaltrials.gov/study/NCT06377852

QUESTION BONUS

A 80 ans soit après 24 mois de traitement par LETROZOLE-PALBOCICLIB, la patiente progresse au niveau hépatique avec cytolyse à 3N, PS1 ?

- FULVESTRANT
- FULVESTRANT-EVEROLIMUS
- TDXD
- TAXOL
- CAPECITABINE

CONCLUSION



ET alone in the first-line setting should be reserved for the small group of patients with comorbidities or a performance status (PS) that prevents the use of CDK4/6 inhibitor combinations; there are no clinical or biomarker data that can help to identify patients suitable for ET alone. Older age alone should not be used to select for endocrine monotherapy, although there may be a higher incidence of haematological adverse events (AEs) from CDK4/6 inhibitor therapy in older patients.[1]

Targeted therapies in luminal tumours

Efficacy of cyclin-dependent kinase 4/6 (CDK4/6) inhibition is age independent in the subgroup and pooled analyses of landmark studies of palbociclib, ribociclib, and abemaciclib,[95-98] with no age-related changes in pharmacokinetics. Nevertheless, patients age 75 years or older experience higher rates of toxicity and dose modifications.[98] Although endocrine therapy alone is still reasonable in particular patients, CDK4/6 inhibitors are a suitable treatment in older patients.[99]

Everolimus should be used with caution in older patients in view of its safety profile. A subgroup analysis of the BOLERO-2 study[100] revealed a higher rate of discontinuations in patients age 70 years or older and more on-treatment deaths. 26% of patients enrolled in the expanded access BALLET trial[101] were aged older than 70 years, which similarly reported more frequent adverse event-related dose discontinuations, reductions, and interruptions.

Biganzoli et al. Lancet 2021 (EUSOMA-SIOG)
Gennarie et al. Ann Oncol 2021 (ESMO)

MERCI DE VOTRE ATTENTION