GÉNÉTIQUE CONSTITUTIONNELLE, GÉNÉTIQUE TUMORALE :UNE NOUVELLE ÈRE

Génomique tumorale : une révolution ?

Jean-Yves Pierga
Département d'Oncologie Médicale
Institut Curie

Université Paris Cité

SiRIC Institut Curie Site de Recherche Intégrée sur le Cancer

institutCurie

Liens d’intérêt

- Stock options: None
- Travel expenses:

  - Roche, Novartis, Pfizer, Lilly, AstraZeneca, Daiichi Sankyo
- Honoraria:

  - Consultant/ Advisory Boards: Roche/Genentech, Novartis, Lilly, Pfizer, AstraZeneca, AbbVie, MSD, Daiichi Sankyo, Seattle Genetics, Gilead, Eisai, Pierre Fabre Oncologie

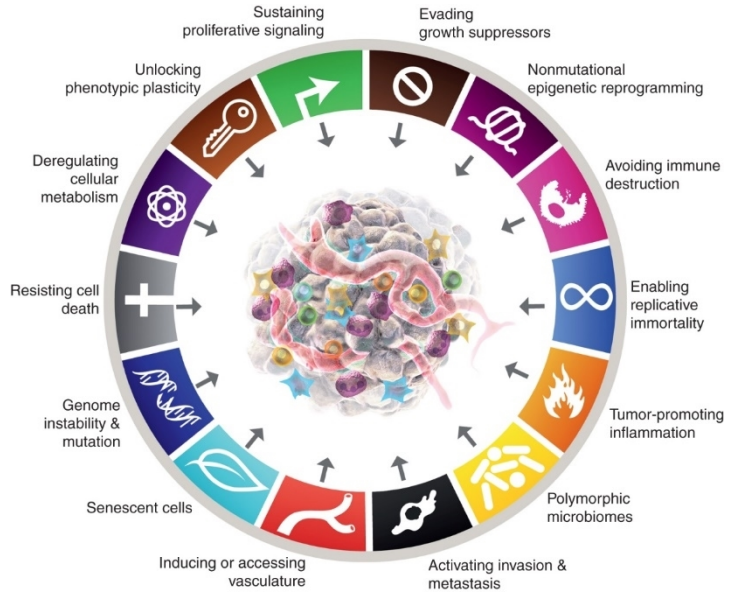
  - Symposia: Roche, Novartis, Pfizer, Lilly, Astra Zeneca, Daiichi Sankyo, Gilead

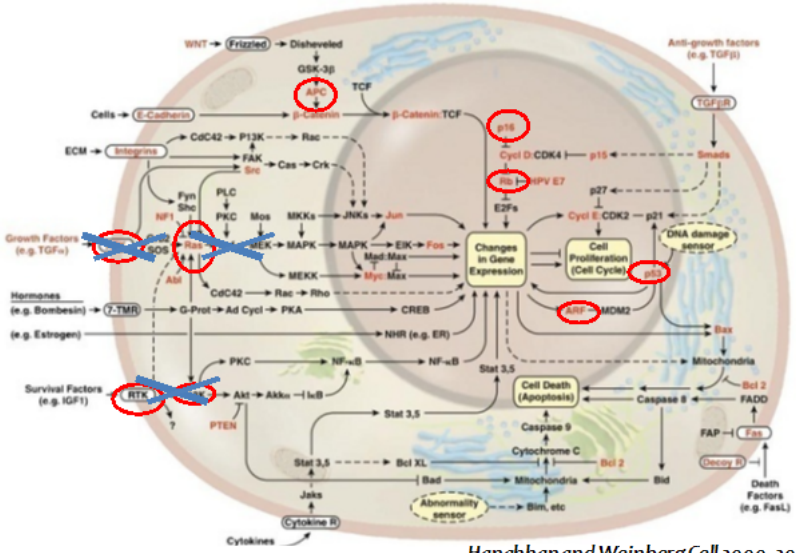
Essor du génomique et la médecine personnalisée/précision

Essor du génomique et connaissance de la biologie de la tumeur:

- Comprendre les mécanismes tumoraux
- Faire l'épidémiologie moléculaire des tumeurs
- Aider au **diagnostic**
- Affiner la **classification** des tumeurs
- Identifier le « Tendon d'Achille » des tumeurs (**mutations drivers)**
- **Développement des essais** guidé par la génomique
- Mise en place d'une **médecine de précision**

Profilage moléculaire des tumeurs
Carte d'identité des tumeurs





Hanahhan and Weinberg Cell 2000, 2011, 2022

Signatures génomiques

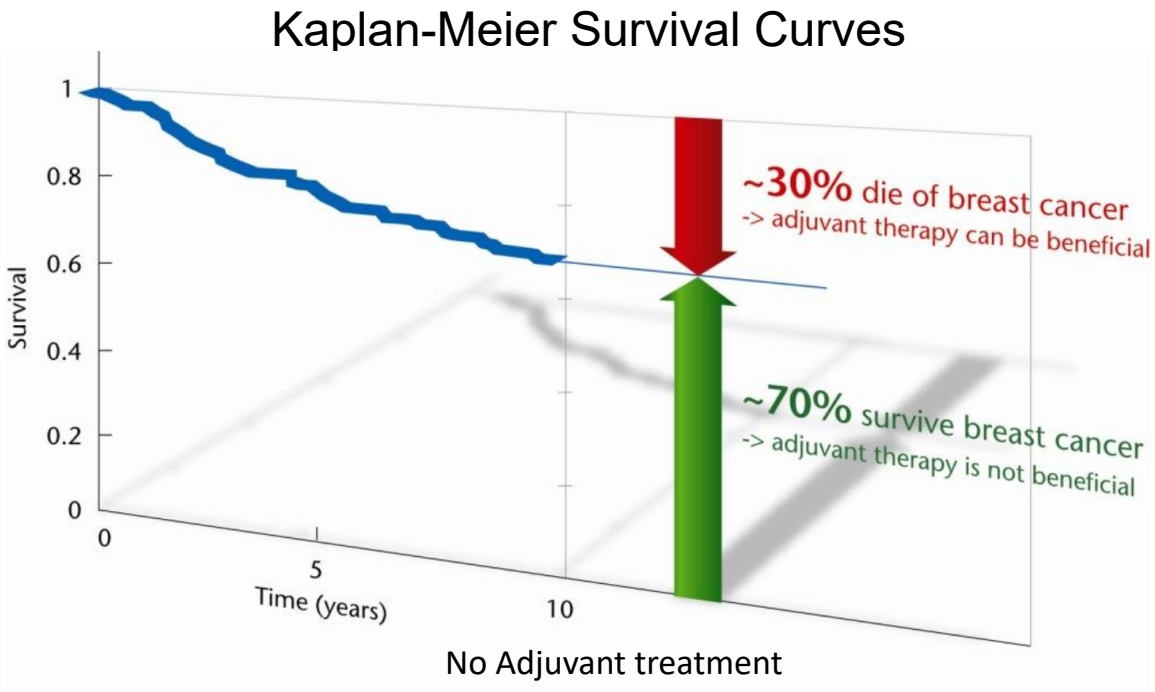
Salgado; Vincent-Salomon. Ann Onco 2021

Table 1. Summary of the gene expression assays discussed, including methodological, clinical and evidence levels[a]

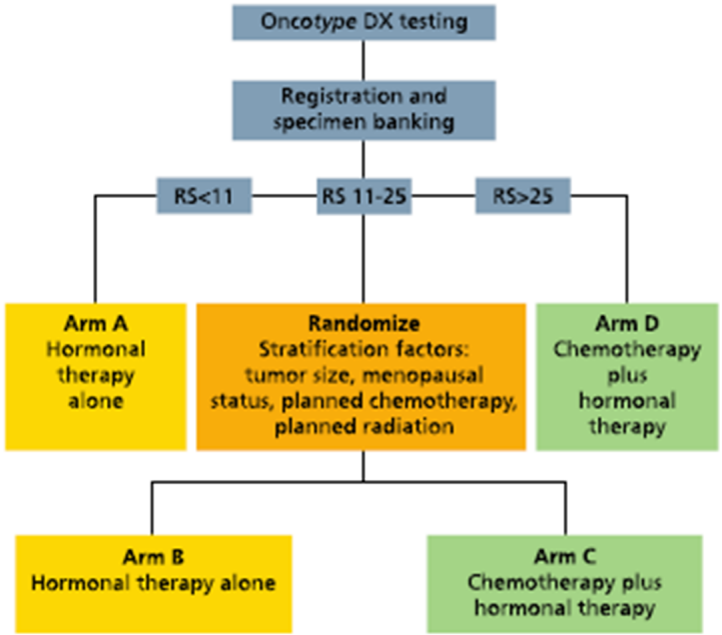
Multigene test	MammaPrint®	Oncotype DX®	Breast Cancer Index®	Prosigna®	Endopredict®
Central lab	Yes	Yes	Yes	No	No
Genomic scores	Genomic risk score	Recurrence score (RS 0-100)	Risk score (0-10)	ROR score (0-100) Intrinsic subtype	EP score (0-15) EPClin score (1-6, 9)
Risk category	Low High	Low Intermediate High	Low High	Low Intermediate High	Low High
Clinical parameters	No clinical parameters taken into account in risk scores	Interpretation of RS using pN−/+ RSPC = RS + age + pT + grade (N0)	No clinical parameters taken into account in risk scores	ROR = PAM50 + pT (+/− 2 cm) + pN(−/+)	EPClin = EP score + pT + pN
Indication for testing	Invasive breast cancer pT1-2 pN0/pN1	Invasive breast cancer pT1-2 ER+/HER2− pN0/pN1	Invasive breast cancer pT1-2-3 ER+/HER2− pN0 Adjuvant ET	Invasive breast cancer pT1-2 /pN0 or pT2 /pN1 ER+ Adjuvant ET Postmenopausal status	Invasive breast cancer pT1-2 ER+/HER2− pN0/pN1 postmenopausal status
Clinical validation	Yes	Yes	Yes	Yes	Yes
Validated for prognosis (resp late recurrences after 5 years)	Not separately shown	Yes	Yes	Yes	Yes
Validated for prediction	Yes	Yes	No	No	No
Prospective evidence	MINDACT	TAILORx PlanB RxPONDER ADAPT	No	No	No
Prospective-retrospective evidence	Multicenter validation	NSABPB-14 NSABPB-20 ECOG 9127 SWOG 8814 ATAC	Trans-aTTom	MA.12 MA.5 ABCSG 8 ATAC	ABCSG 6 ABCSG 8 GEICAM-9906 ATAC

ABCSG, Austrian Breast and Colorectal Cancer Study Group; ATAC, Arimidex, Tamoxifen alone or in combination; ECM, extracellular matrix; ECOG, Eastern Cooperative Oncology Group; EP, Endopredict; ER, estrogen receptor; ET, endocrine therapy; FFPE, formalin-fixed paraffin-embedded; GEICAM, Grupo Español de Investigación en Cáncer de Mama; GR

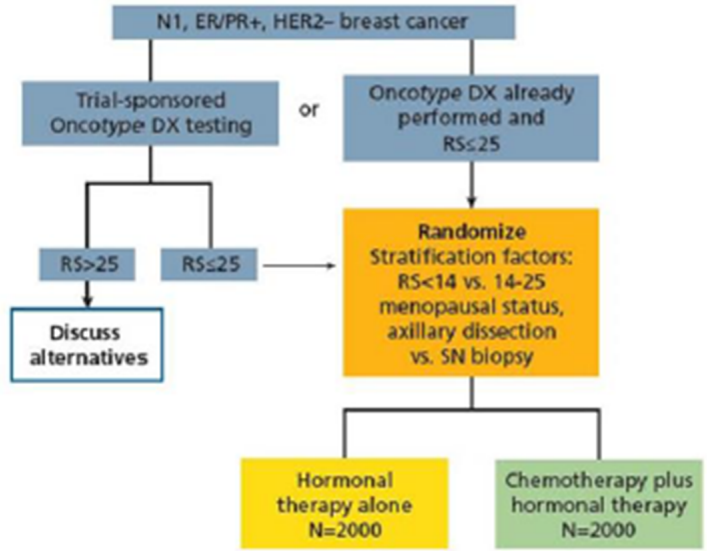
Qui va récidiver ?



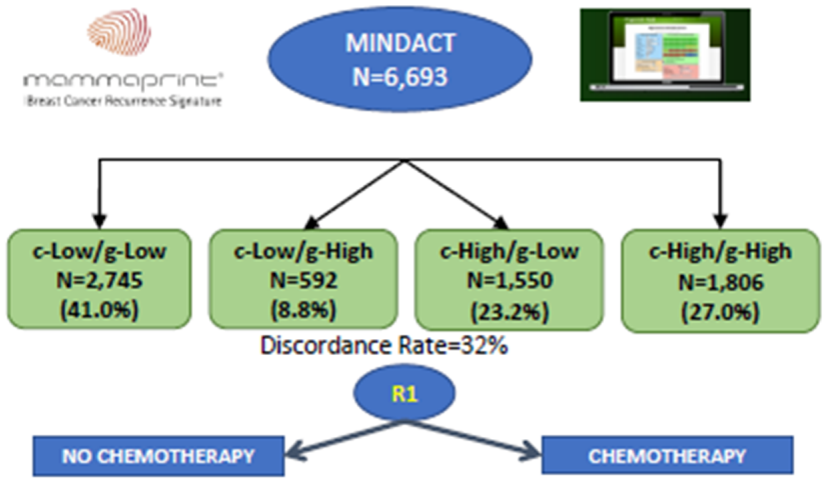
TAILORx
Node negative
All ER+/HER2-
N=9719



RxPONDER
Node positive (1-3 N+)
All ER+/HER2-
N=5083

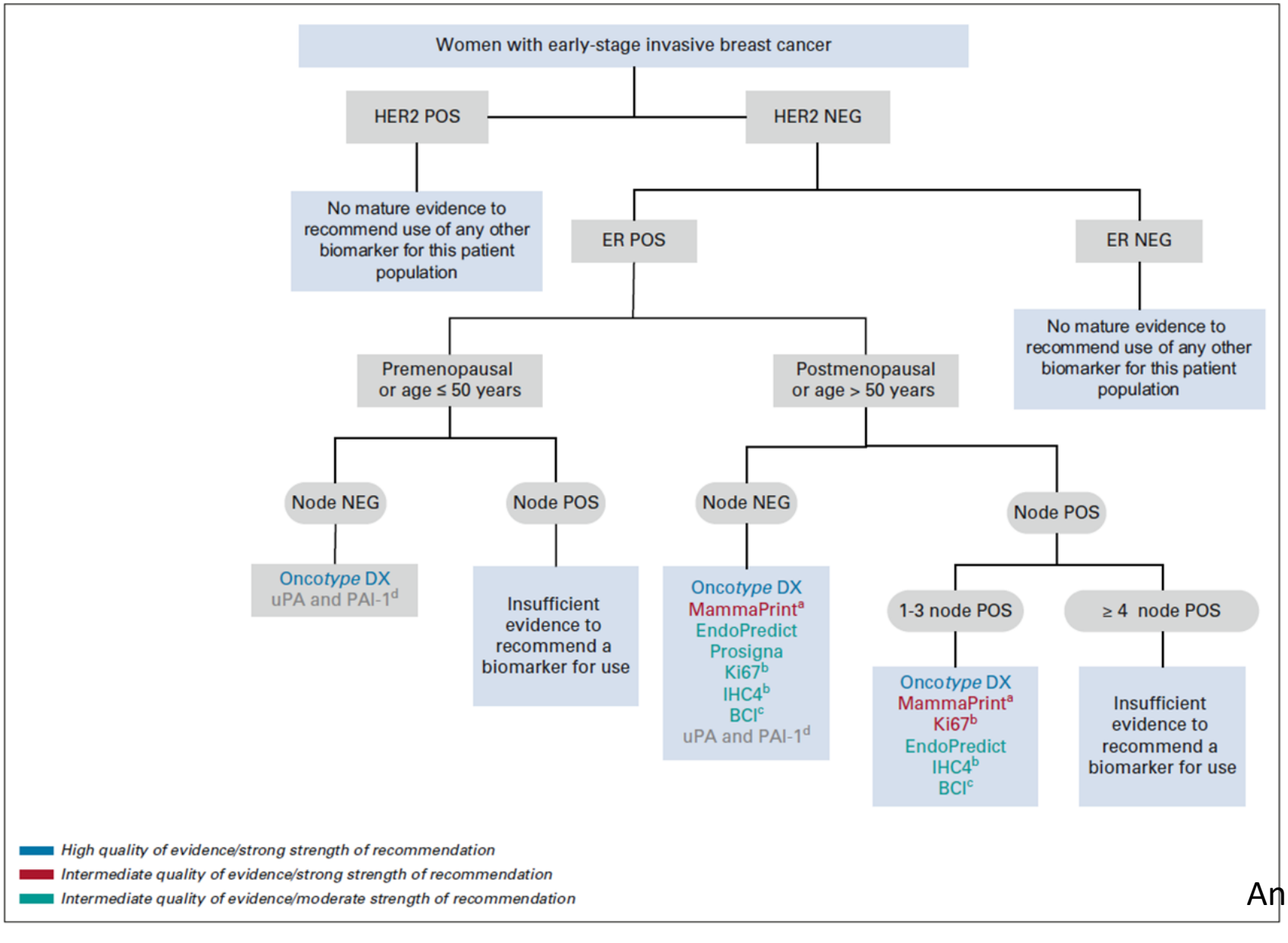


MINDACT
Node negative/positive
(1-3 N+ 21%)
81% ER+/HER2-
N=6693



21,495 patients

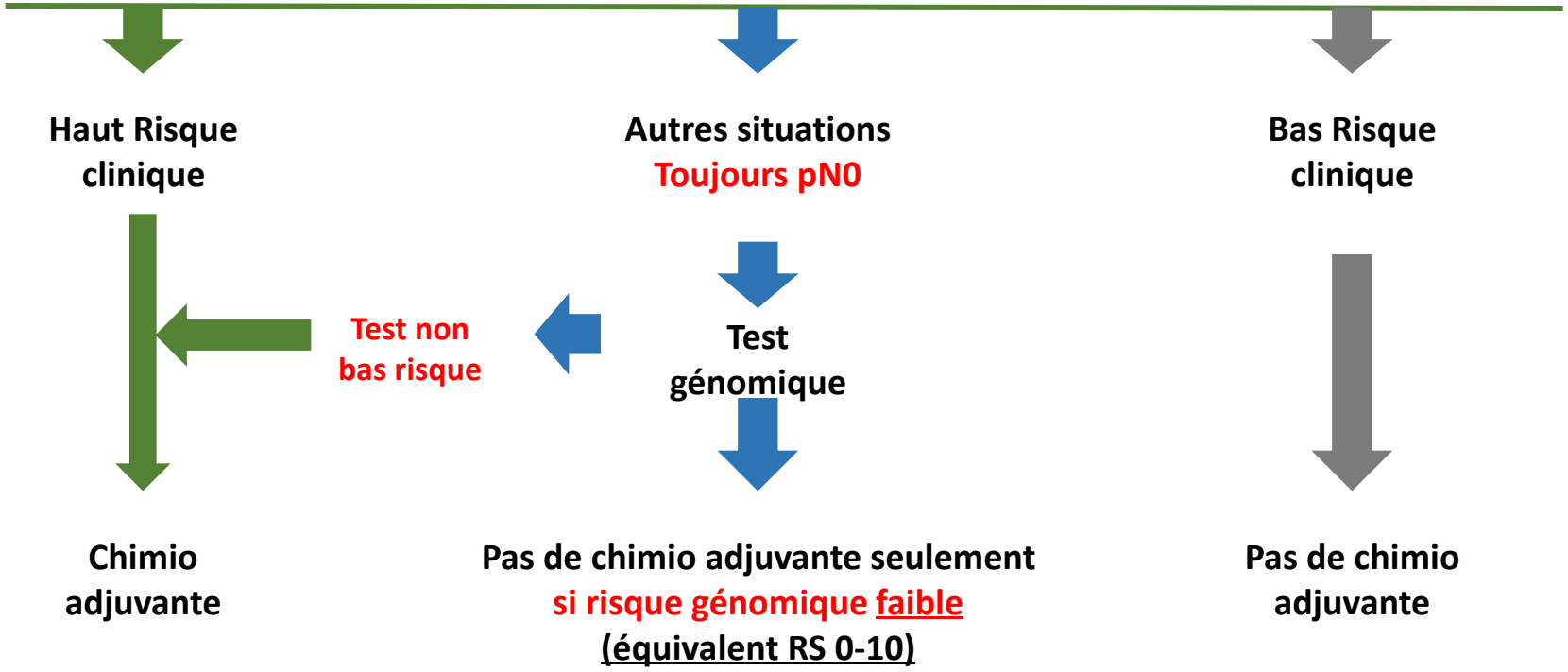
Biomarqueurs pour le cancer du sein précoce Recommandations de l'ASCO 2022



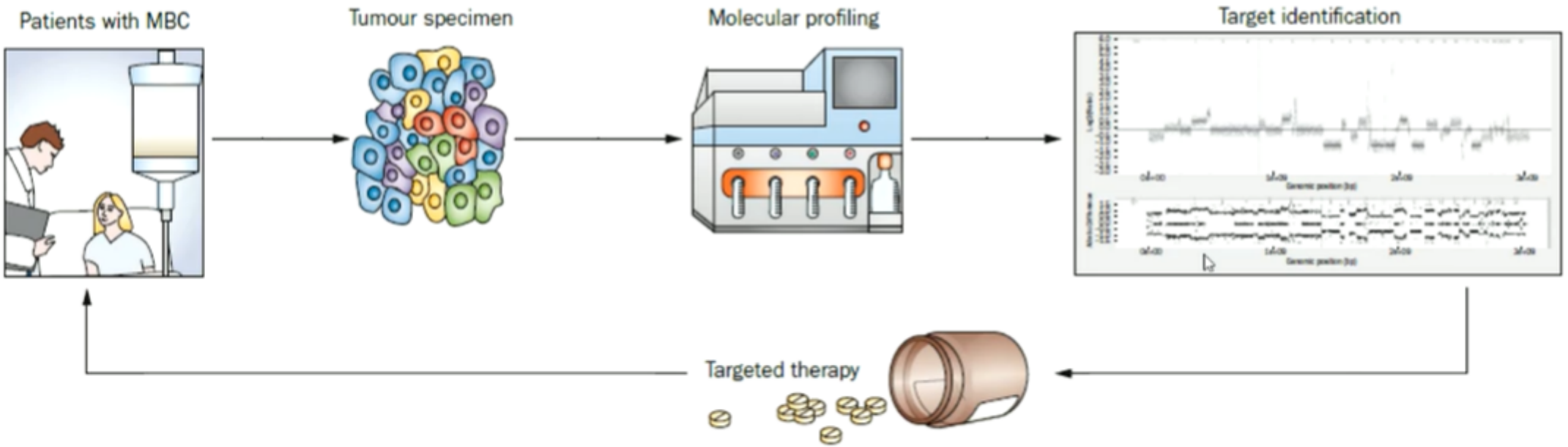
André F. et al J Clin Oncol 202

Arbres adjuvant RE+/HER2-

Patiente non ménopausée

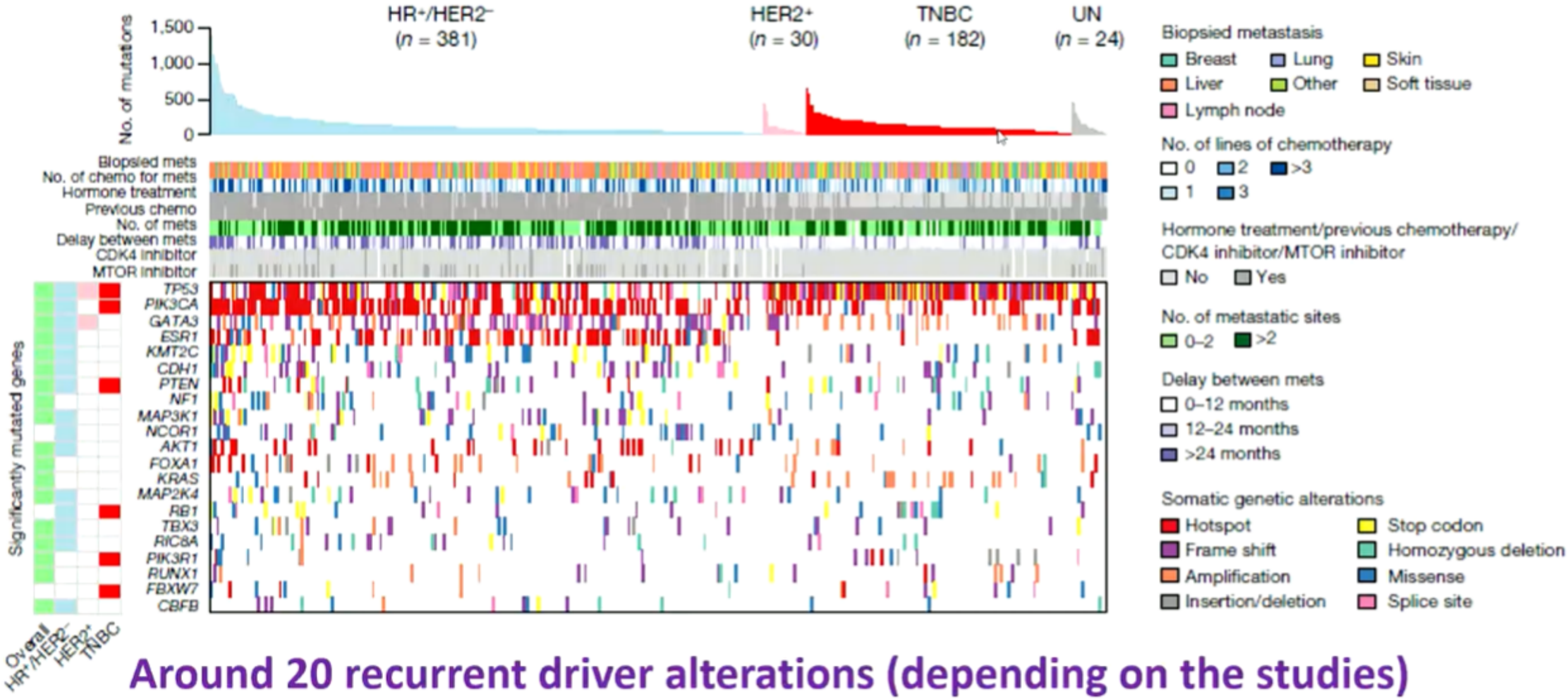


Hypothesis: if we identify the mechanisms of cancer progression in each patient and we can block them, it should improve PFS and OS



Arnedos et al, Nat Rev Clin Oncol, 2015

Are they recurrent genomic drivers in metastatic breast cancers ?



Around 20 recurrent driver alterations (depending on the studies)

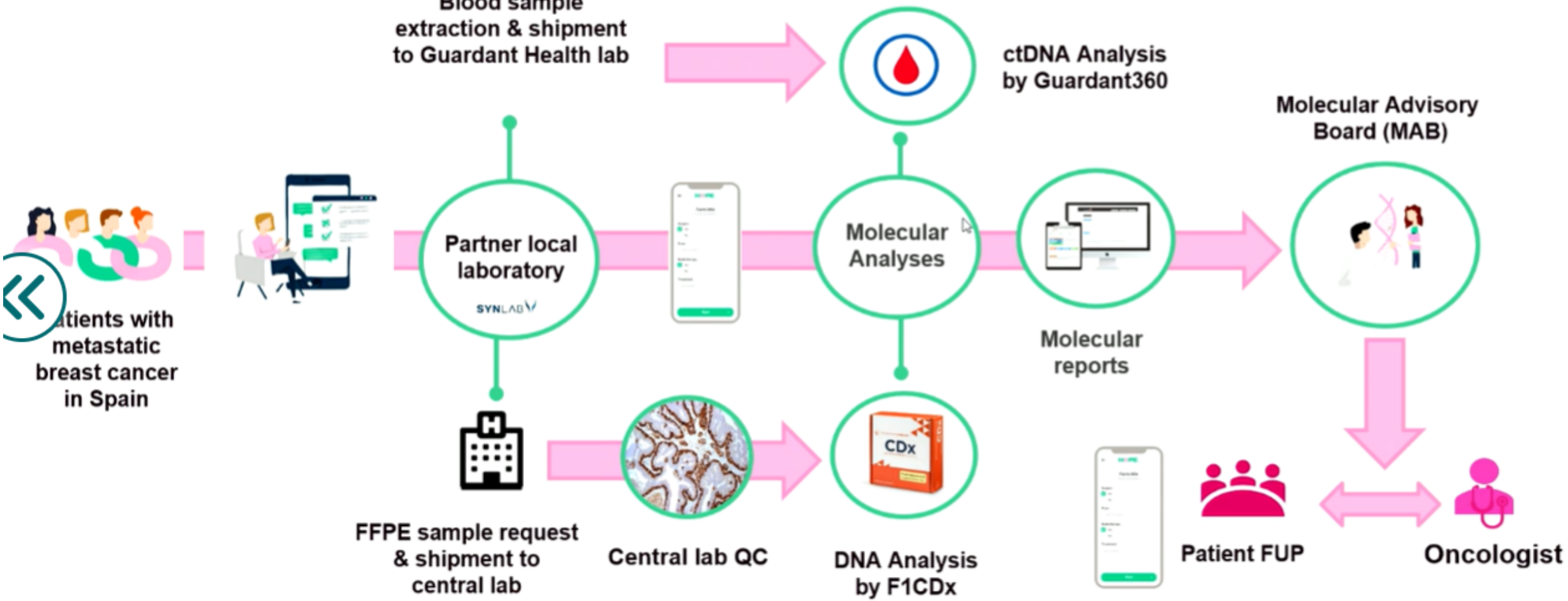
Bertucci, Nature, 2019

SOLTI-1903 HOPE Study Design

A Patient-Centric Molecular Screening Program in ABC

NCT04497285

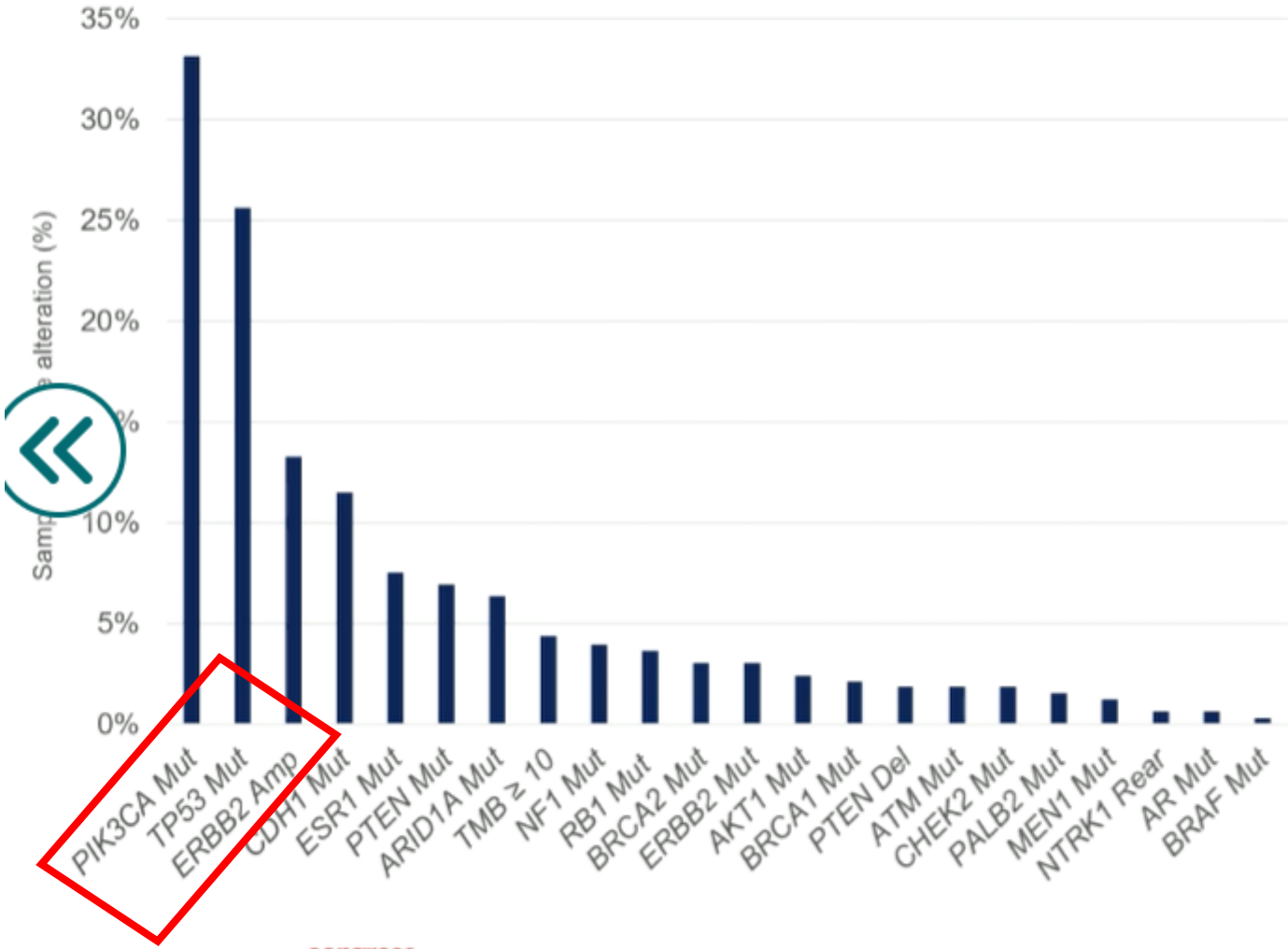
www.soltihope.com



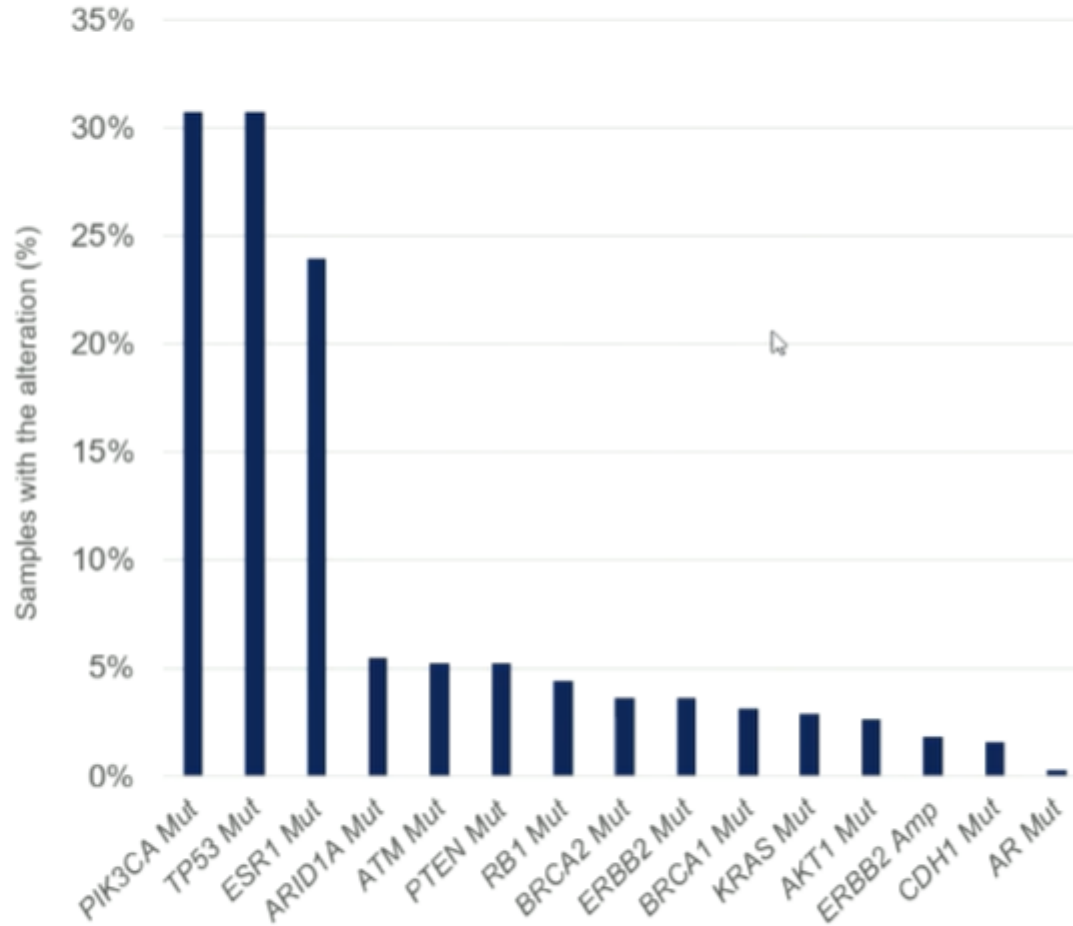
Tomás Pascual Martínez, MD

RESULTS: Molecular Results

Tissue DNA sequencing (F1CDx, N=334)



Liquid Biopsy (G360, N=384)



MADRID 2023 ESMO congress

Tomás Pascual Martínez, MD

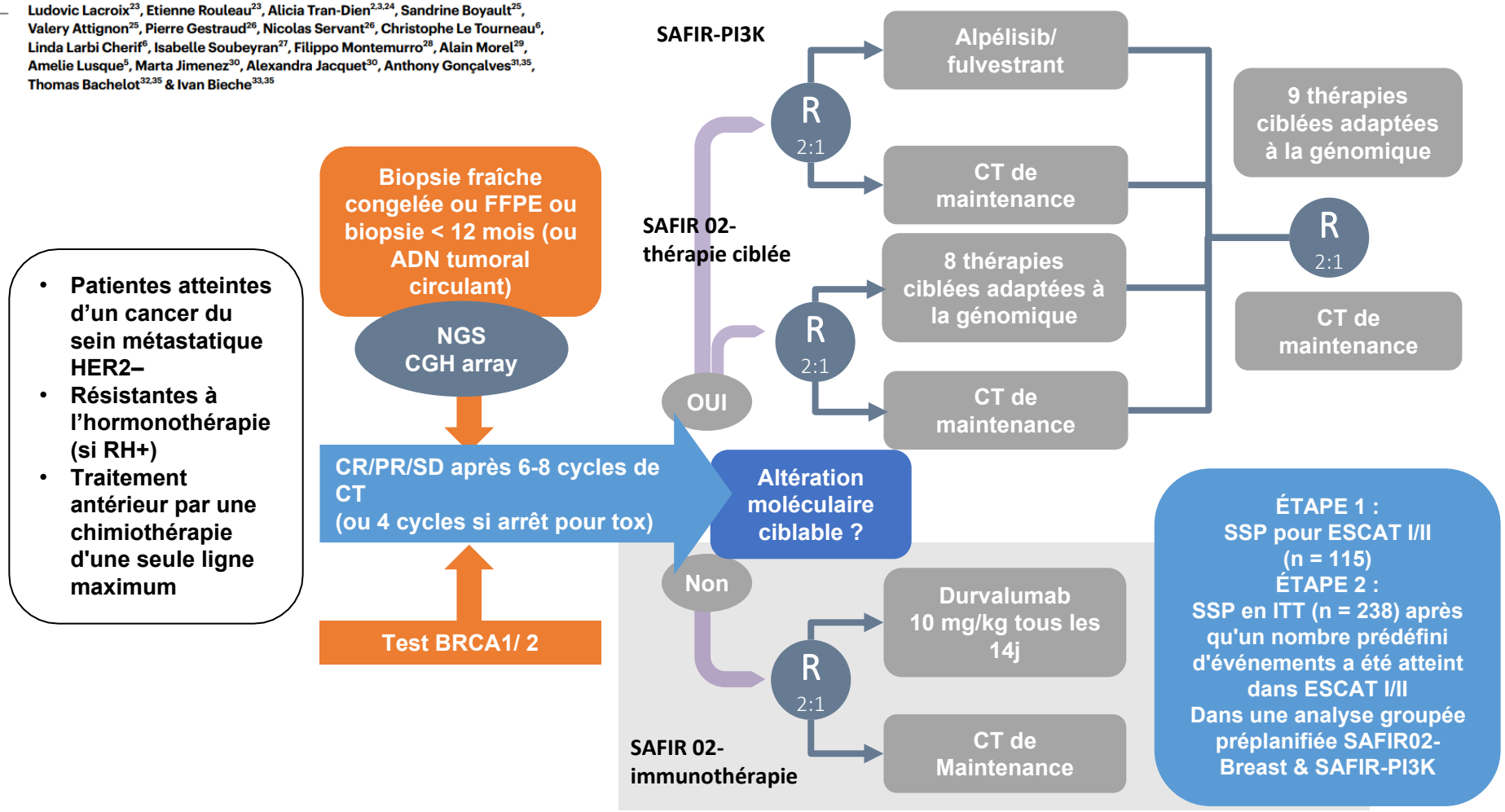
Genomics to select treatment for patients with metastatic breast cancer

https://doi.org/10.1038/s41586-022-05068-3
Received: 24 October 2021
Accepted: 3 July 2022
Published online: 7 September 2022
Check for updates

Fabrice Andre[1,2,3,4,34], Thomas Filleron[5,34], Maud Kamal[6,34], Fernanda Mosele[2], Monica Arnedos[1], Florence Dalenc[7], Marie-Paule Sablin[6,8], Mario Campone[9], Hervé Bonnefoi[10], Claudia Lefeuvre-Plesse[11], William Jacot[12], Florence Coussy[13], Jean-Marc Ferrero[14], George Emile[15], Marie-Ange Mouret-Reynier[16], Jean-Christophe Thery[17], Nicolas Isambert[18], Alice Mege[19], Philippe Barthelemy[20], Benoit You[21], Nawale Hajjaji[22], Ludovic Lacroix[23], Etienne Rouleau[23], Alicia Tran-Dien[2,3,24], Sandrine Boyault[25], Valery Attignon[25], Pierre Gestraud[26], Nicolas Servant[26], Christophe Le Tourneau[6], Linda Larbi Cherif[6], Isabelle Soubeyran[27], Filippo Montemurro[28], Alain Morel[29], Amelie Lusque[5], Marta Jimenez[30], Alexandra Jacquet[30], Anthony Gonçalves[31,35], Thomas Bachelot[32,35] & Ivan Bieche[33,35]

Étude SAFIR 02

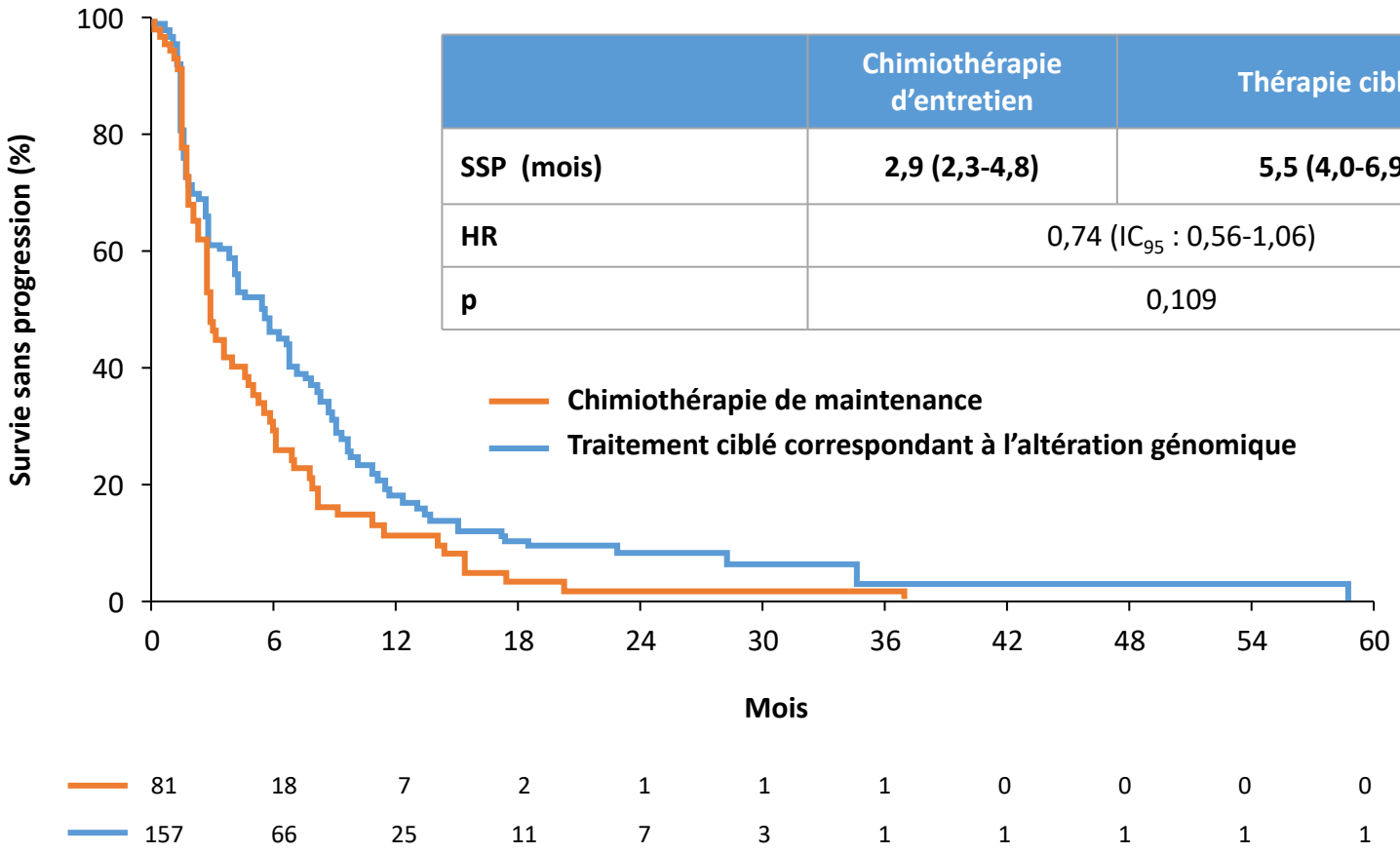
Schéma de l'étude



André F et al., Nature 2022

SSP dans la population totale (n = 238)

	Chimiothérapie d'entretien	Thérapie ciblée
SSP (mois)	**2,9 (2,3-4,8)**	**5,5 (4,0-6,9)**
HR	0,74 (IC_{95} : 0,56-1,06)	
p	0,109	



SABCS 2021 - D'après André F et al., abstr. GS1-10, actualisé

La Détermination du Profilage Moléculaire et Actionnabilité

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29: 1895–1902, 2018
doi:10.1093/annonc/mdy263
Published online 21 August 2018

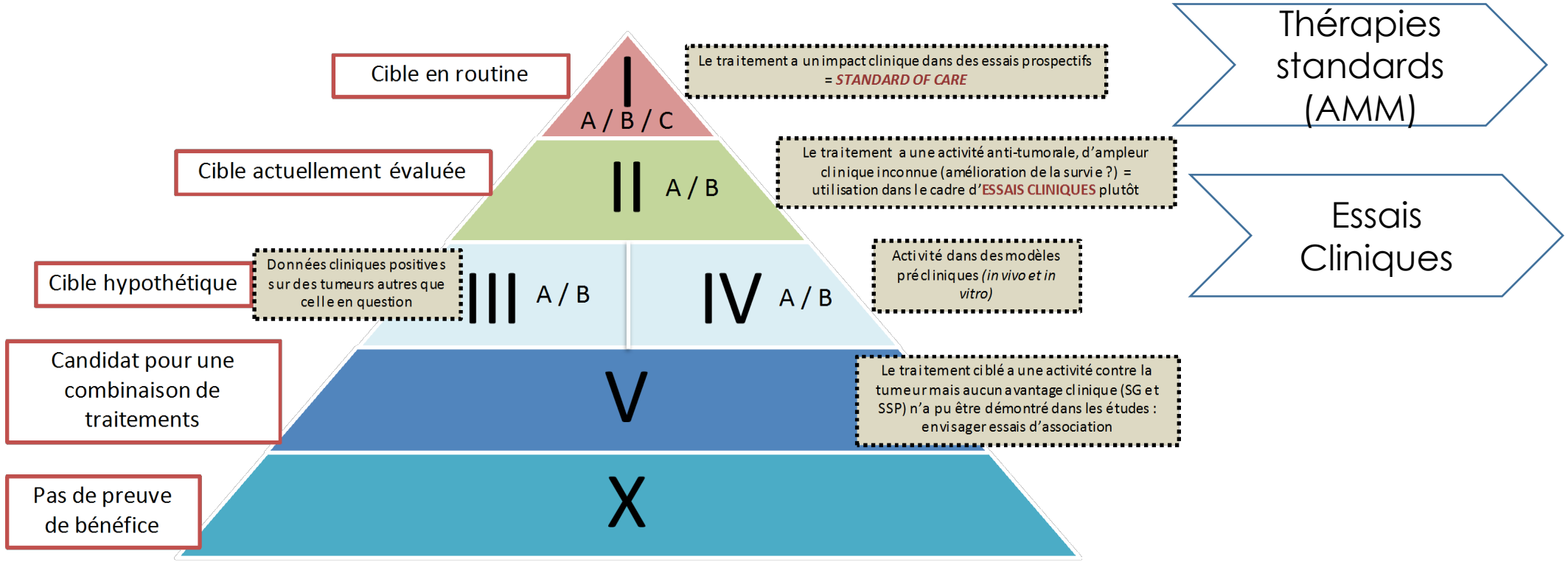
SPECIAL ARTICLE

L'échelle ESCAT 2018

A framework to rank genomic alterations as targets for cancer precision medicine: the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

J. Mateo[1], D. Chakravarty[2], R. Dienstmann[1], S. Jezdic[3], A. Gonzalez-Perez[4], N. Lopez-Bigas[4,5], C. K. Y. Ng[6], P. L. Bedard[7], G. Tortora[8,9], J.-Y. Douillard[3], E. M. Van Allen[10], N. Schultz[2], C. Swanton[11], F. André[12*] & L. Pusztai[13]

Objectif :
Aider à distinguer les altérations pertinentes de celles qui ne le sont pas, en un langage harmonisé



Cancer du sein métastatique

Table 4. List of genomic alterations level I/II/III according to ESCAT in metastatic breast cancer (mBC)

Gene	Alteration	Prevalence	ESCAT	References
ERBB2	Amplifications	15%–20%	IA	Slamon D, et al. *N Engl J Med.* 2001[65] Swain S, et al. *N Engl J Med.* 2015[66] Verma S, et al. *N Engl J Med.* 2012[67] Krop I, et al. *Lancet Oncol.* 2014[68] Murthy R, et al. *N Engl J Med.* 2020[69]
	Hotspot mutations	4%	IIB	Hyman D, et al. *Nature.* 2018[55]
PIK3CA	Hotspot mutations	30%–40%	IA	André F, et al. *N Engl J Med.* 2019[72]
BRCA1/2	Germline mutations	4%	IA	Robson M, et al. *N Engl J Med.* 2017[70] Litton J, et al. *N Engl J Med.* 2018[71]
	Somatic mutations	3%	IIIA	Balasubramaniam S, et al. *Clin Cancer Res.* 2017[63]
	MSI-H	1%	IC	Marcus L, et al. *Clin Cancer Res.* 2019[73]
NTRK	Fusions	1%	IC	Doebele RC, et al. *Lancet Oncol.* 2020[50]
ESR1	Mutations (mechanism of resistance)	10%	IIA	Fribbens C, et al. *J Clin Oncol.* 2016[74]
PTEN	Mutations	7%	IIA	Schmid P, et al. *J Clin Oncol.* 2018[75]
AKT1^{E17K}	Mutations	5%	IIB	Hyman D, et al. *J Clin Oncol.* 2017[76]
NF1	Mutations (resistance biomarker)	6%	Not applicable	Pearson A, et al. *Clin Cancer Res.* 2020[77]
MDM2	Amplifications	~1%	IIIA	Dembla V, et al. *Oncotarget.* 2018[78]
ERBB3	Mutations	2%	IIIB	Hyman D, et al. *Nature.* 2018[55]

ESCAT, European Society for Medical Oncology (ESMO) Scale for Clinical Actionability of molecular Targets; MSI-H, microsatellite instability-high.

2020

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

REVIEW ARTICLE

Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group

F. Mosele[1], J. Remon[2], J. Mateo[3], C. B. Westphalen[4], F. Barlesi[1], M. P. Lolkema[5], N. Normanno[6], A. Scarpa[7], M. Robson[8], F. Meric-Bernstam[9], N. Wagle[10], A. Stenzinger[11], J. Bonastre[12,13], A. Bayle[1,12,13], S. Michiels[12,13], I. Bièche[14], E. Rouleau[15], S. Jezdic[16], J-Y. Douillard[16], J. S. Reis-Filho[17], R. Dienstmann[18] & F. André[1,19,20*]

SAFIR 02 (phase III)

Evaluated the clinical utility of a molec. screen. program

N=1'462 → N=646 → N=238

Pts screened → Pts with targetable genomic alteration → Pts randomized 2:1 after 6-8 cycles of chemo

- HER2 neg mBC
- 0 or max 1L of chemo for metastic disease
- Resistant to endoc Ttt

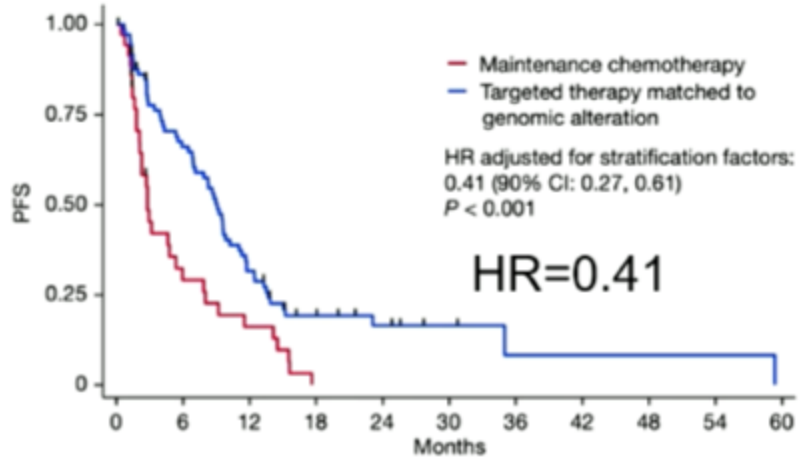
R → Maintenance targeted Ttt n=157

R → Maintenance chemo n=81

Pts with ESCAT I-II

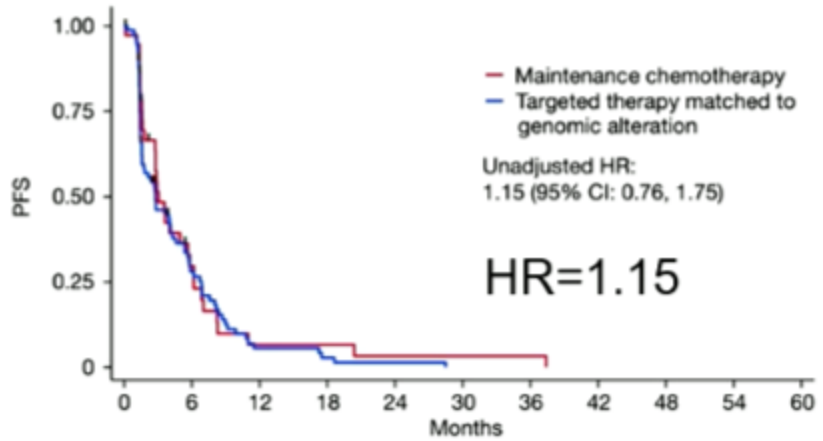
N=115

7.9% (115/1'462)



Pts beyond ESCAT I-II

N=123

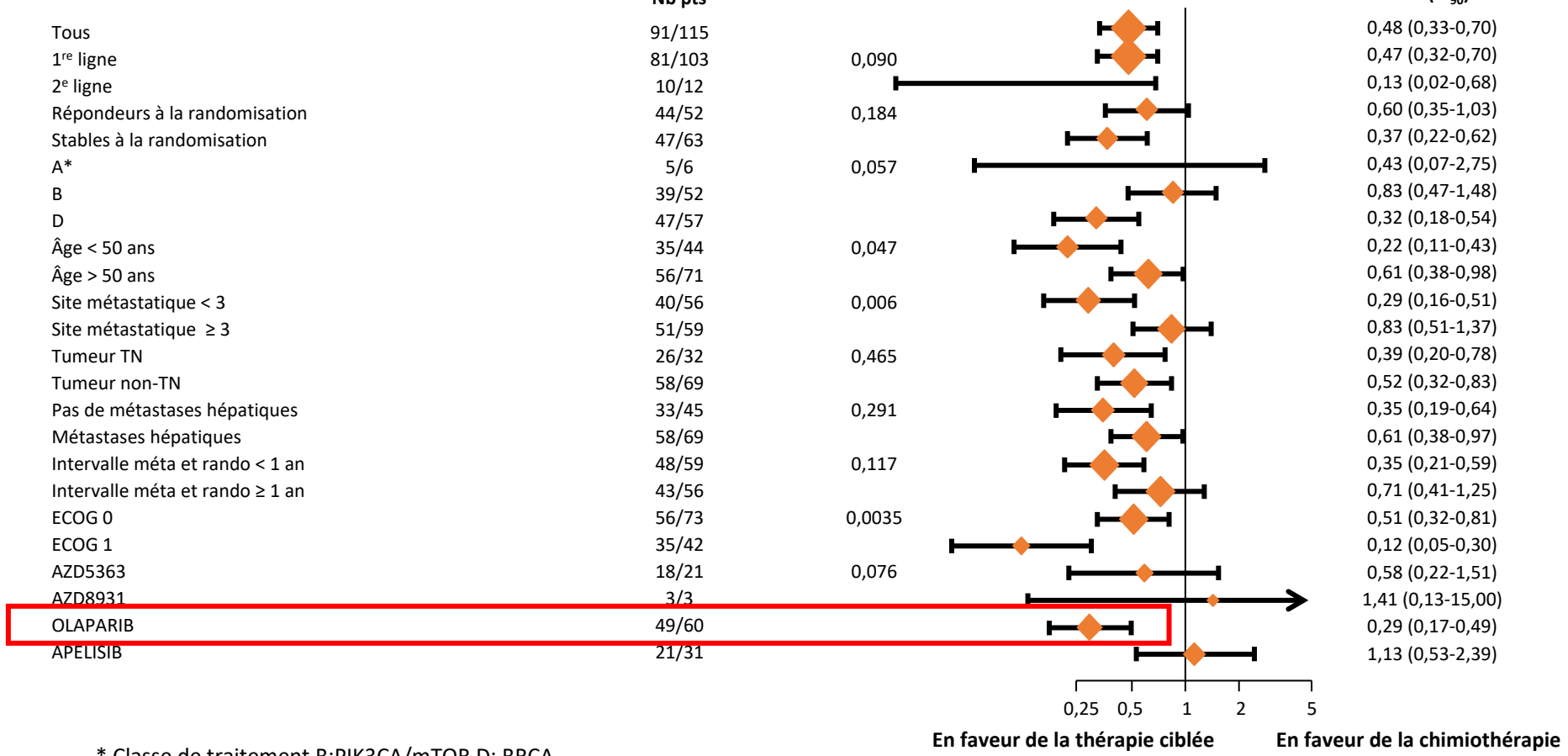


André F et al, Nature 2022

Étude SAFIR 02

Analyse en sous-groupe dans la population ESCAT I/II

Sous-groupe	Nb événements/ Nb pts	p	HR pour SSP (IC_{90})
Tous	91/115		0,48 (0,33-0,70)
1re ligne	81/103	0,090	0,47 (0,32-0,70)
2e ligne	10/12		0,13 (0,02-0,68)
Répondeurs à la randomisation	44/52	0,184	0,60 (0,35-1,03)
Stables à la randomisation	47/63		0,37 (0,22-0,62)
A*	5/6	0,057	0,43 (0,07-2,75)
B	39/52		0,83 (0,47-1,48)
D	47/57		0,32 (0,18-0,54)
Âge < 50 ans	35/44	0,047	0,22 (0,11-0,43)
Âge > 50 ans	56/71		0,61 (0,38-0,98)
Site métastatique < 3	40/56	0,006	0,29 (0,16-0,51)
Site métastatique ≥ 3	51/59		0,83 (0,51-1,37)
Tumeur TN	26/32	0,465	0,39 (0,20-0,78)
Tumeur non-TN	58/69		0,52 (0,32-0,83)
Pas de métastases hépatiques	33/45	0,291	0,35 (0,19-0,64)
Métastases hépatiques	58/69		0,61 (0,38-0,97)
Intervalle méta et rando < 1 an	48/59	0,117	0,35 (0,21-0,59)
Intervalle méta et rando ≥ 1 an	43/56		0,71 (0,41-1,25)
ECOG 0	56/73	0,0035	0,51 (0,32-0,81)
ECOG 1	35/42		0,12 (0,05-0,30)
AZD5363	18/21	0,076	0,58 (0,22-1,51)
AZD8931	3/3		1,41 (0,13-15,00)
OLAPARIB	49/60		0,29 (0,17-0,49)
APELISIB	21/31		1,13 (0,53-2,39)



* Classe de traitement B:PIK3CA/mTOR D: BRCA

SABCS 2021 - D'après André F et al., abstr. GS1-10, actualisé

OlympiAD

OlympiAD est une étude de phase III comparant l'olaparib au TPC dans le cancer du sein métastatique *gBRCA*m HER2-négatif[1]

- g*BRCA*m MBC
- TNBC or HER2-negative, ER/PR positive
- ≤2 prior chemotherapy lines for MBC
- Previous treatment must include anthracycline and taxane
- Hormone receptor positive (HR+) disease progressed on ≥1 endocrine therapy, or not suitable
- If patients have received platinum therapy there should be:
  - No evidence of progression during treatment in the advanced setting
  - At least 12 months since (neo)adjuvant treatment and randomisation
- ECOG PS 0-1
- At least one lesion that can be assessed by RECIST v1.1

FSI May 2014[3]

Global Study in 19 countries and approximately 141 sites[1]

Randomise 2:1 N=302[4]

Olaparib 300mg*po bid

Treatment of Physician's Choice (TPC)

Stratification by[2]
- *Prior chemotherapy regimens for metastatic breast cancer*
- *Hormonal receptor (HR) status*
- *Prior platinum therapy*

Primary endpoint
- PFS (RECIST 1.1, Independent Review)

Secondary endpoints
- OS
- PFS2
- ORR
- PFS, PFS2 and OS based on Myriad g*BRCA*m status
- HRQoL (EORTC-QLQ-C30)
- Safety and tolerability

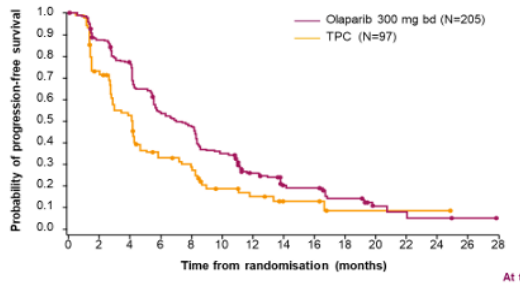
* Tablet formulation (2 tablets twice daily)
M=metastatic breast cancer, HER2=human epidermal growth factor 2, TNBC=triple negative breast cancer, TPC=treatment of physician's choice, OS=overall survival, PFS=progression-free survival, PFS2=progression-free survival 2, ORR=objective response rate, HRQoL=health-related quality of life, FSI=first subject in, RECIST=Response Evaluation Criteria in Solid Tumors, ER=oestrogen receptor, PR=progresterone receptor, ECOG PS= Eastern Cooperative Oncology Group Performance Status, g*BRCA*m=germline *BRCA* mutation; po=oral
1. https://clinicaltrials.gov/ct2/show/NCT02000622; 2. Robson et al. Poster OT1-1-04, San Antonio Breast Cancer Symposium 2014; 3. AZ data on file (2017), 4. Robson et al. N Engl J Med. 17 Aug 10;377(6):523-533

Olaparib et sa formulation comprimés évaluée dans l'étude OlympiaD sont hors du cadre de l'AMM de Lynparza[EN] à ce jour

14

Critère principal : le traitement par l'olaparib améliore significativement la PFS évaluée par le BICR par rapport au TPC[1]

Le risque de régression ou de décès au cours de l'étude a été réduit de plus de 40 %



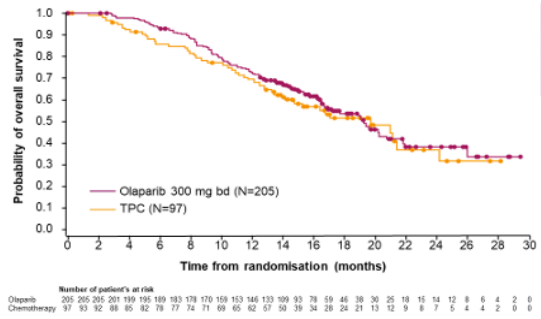
	Olaparib	TPC
n	205	97
Events (%)	163 (79.5%)	71 (73.2%)
Median (m)	7.0	4.2
	HR = 0.58 95 % CI (0.43, 0.80) p=0.0009	
PFS free at 6m (%)	54.1	32.9
PFS free at 12m (%)	25.9	15.0

At this time:
olaparib does not have an indication registered in breast cancer
olaparib in TABLETS does not have any indication registered

BICR: blind independent centralised review - FAS; Maturity rate: 234/302=77%
Stratified log rank test, stratified by previous chemotherapy for MBC (yes/no) and HR+ versus TNBC. 2 sided p value
1. Robson et al. N Engl J Med. 17 Aug 10;377(6):523-533; 2. AZ data on file (2017)

Olaparib et sa formulation comprimés évaluée dans l'étude OlympiaD sont hors du cadre de l'AMM de Lynparza[EN] à ce jour

16



	Olaparib	TPC
n	205	97
Events (%)	94 (45.9%)	46 (47.4%)
Median (m)	19.3	19.6
	HR = 0.90 95 % CI (0.63, 1.29) p=0.57	

Currently 8 patients in the TPC arm received subsequent treatment with PARP inhibitors[1]

Maturity rate: 140/302=46% 2 sided p value
8 control arm patients have received a subsequent PARPi
1. Robson et al. N Engl J Med. 17 Aug 10;377(6):523-533

Olaparib et sa formulation comprimés évaluée dans l'étude OlympiaD sont hors du cadre de l'AMM de Lynparza[EN] à ce jour

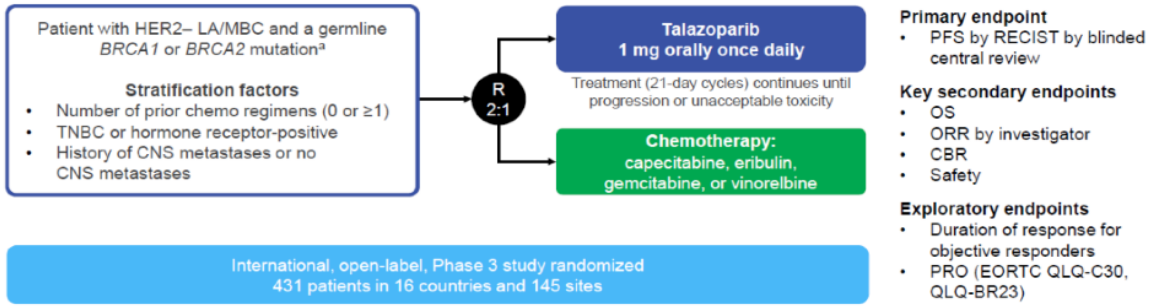
17

Il n'y a pas d'amélioration de la survie globale

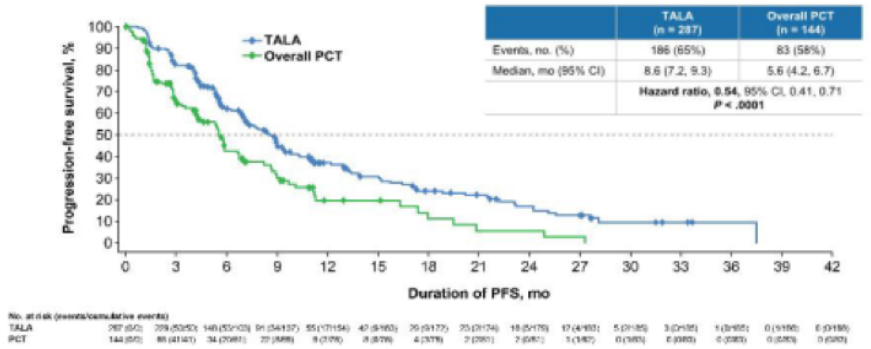
Robson M et al, , N Engl J Med. 2017 Aug 10: 377(6): 523-533

Etude EMBRACA (Talazoparib)

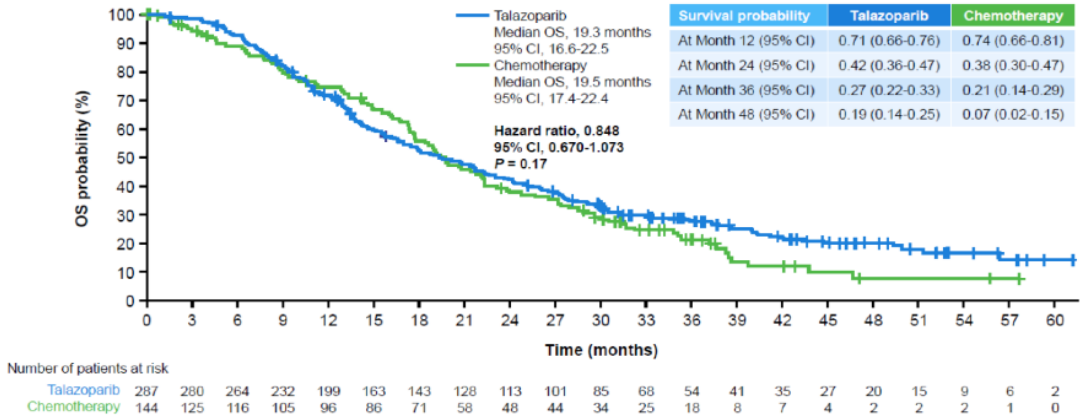
EMBRACA : Schéma de l'étude



Critère d'évaluation principal : PFS par examen central en aveugle



1-Year PFS 37 vs 20% Median follow-up time: 11.2 months



Survival probability	Talazoparib	Chemotherapy
At Month 12 (95% CI)	0.71 (0.66-0.76)	0.74 (0.66-0.81)
At Month 24 (95% CI)	0.42 (0.36-0.47)	0.38 (0.30-0.47)
At Month 36 (95% CI)	0.27 (0.22-0.33)	0.21 (0.14-0.29)
At Month 48 (95% CI)	0.19 (0.14-0.25)	0.07 (0.02-0.15)

OS finale : Les résultats de cette analyse préspécifiée n'ont révélé aucune différence statistiquement significative entre les groupes de traitement

Litton JK et al, N Engl J Med. 2018 Aug 23;379(8):753-763

RESULTS: MAB Outcomes

Median follow-up of 18.0 months (range 0,4 – 43)

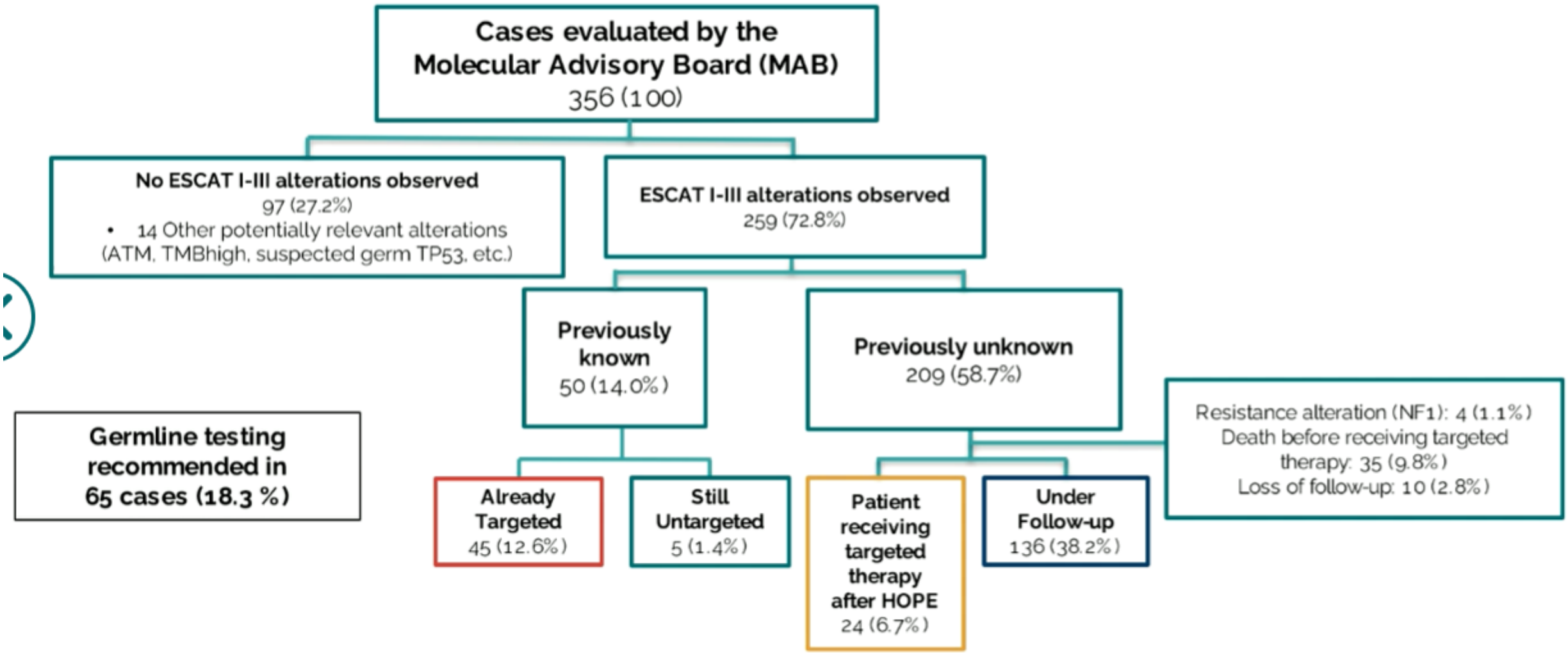


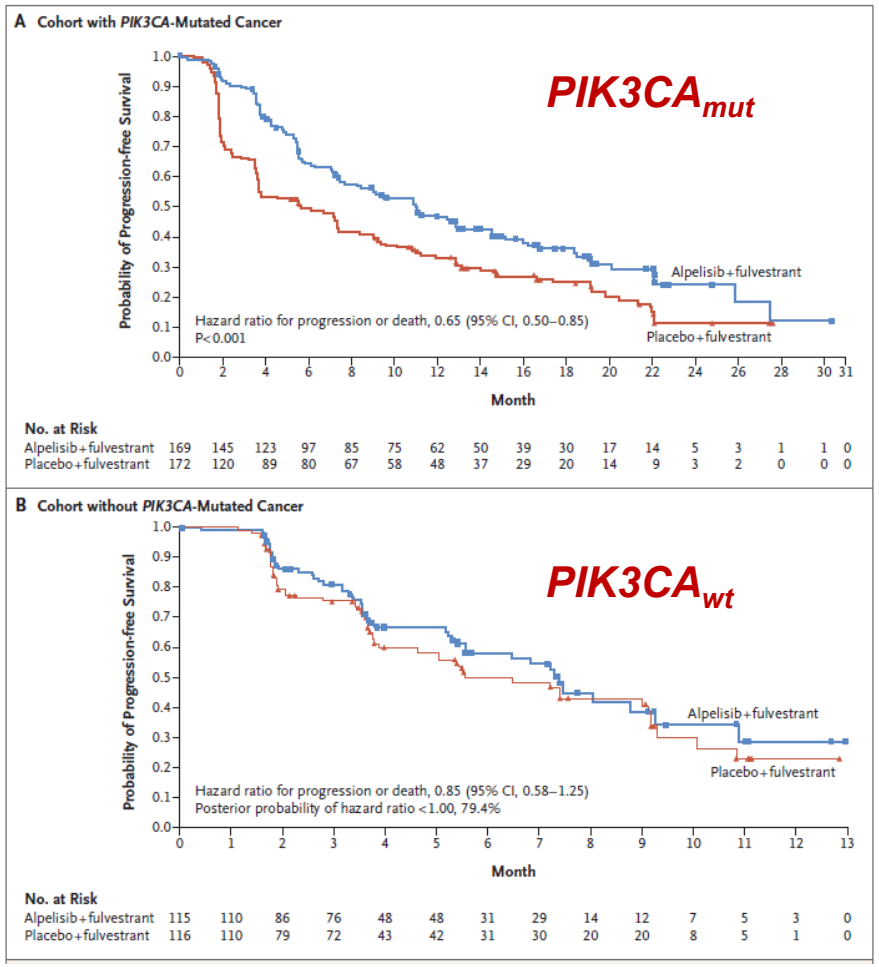
Table 4. List of genomic alterations level I/II/III according to ESCAT in metastatic breast cancer (mBC)

Gene	Alteration	Prevalence	ESCAT	References
ERBB2	Amplifications	15%–20%	IA	Slamon D, et al. *N Engl J Med.* 2001[65] Swain S, et al. *N Engl J Med.* 2015[66] Verma S, et al. *N Engl J Med.* 2012[67] Krop I, et al. *Lancet Oncol.* 2014[68] Murthy R, et al. *N Engl J Med.* 2020[69]
	Hotspot mutations	4%	IIB	Hyman D, et al. *Nature.* 2018[55]
PIK3CA	Hotspot mutations	30%–40%	IA	André F, et al. *N Engl J Med.* 2019[72]
BRCA1/2	Germline mutations	4%	IA	Robson M, et al. *N Engl J Med.* 2017[70] Litton J, et al. *N Engl J Med.* 2018[71]
	Somatic mutations	3%	IIIA	Balasubramaniam S, et al. *Clin Cancer Res.* 2017[63]

Mosele F. Ann Oncol 2020 Nov;31(11):1491-1505

SOLAR-1: a Phase 3 Randomized of Alpelisib in Double-Blind, Placebo-Controlled Trial

Tissue testing



Men or postmenopausal women with HR+, HER2– ABC

- Recurrence/progression on/after prior AI
- Identified *PIK3CA* status (in archival or fresh tumor tissue[a])
- Measurable disease or ≥ 1 predominantly lytic bone lesion
- ECOG performance status ≤ 1

(N = 572)

1:1, stratified by presence of liver/lung metastases and prior CDK4/6 inhibitor treatment

PIK3CA-mutant cohort (n = 341) → R
- **ALP** 300 mg PO QD **+ FUL** 500 mg IM[b] **n = 169**
- **PBO + FUL** 500 mg IM[b] **n = 172**

PIK3CA-non-mutant cohort (n = 231) → R
- **ALP** 300 mg PO QD **+ FUL** 500 mg IM[b] **n = 115**
- **PBO + FUL** 500 mg IM[b] **n = 116**

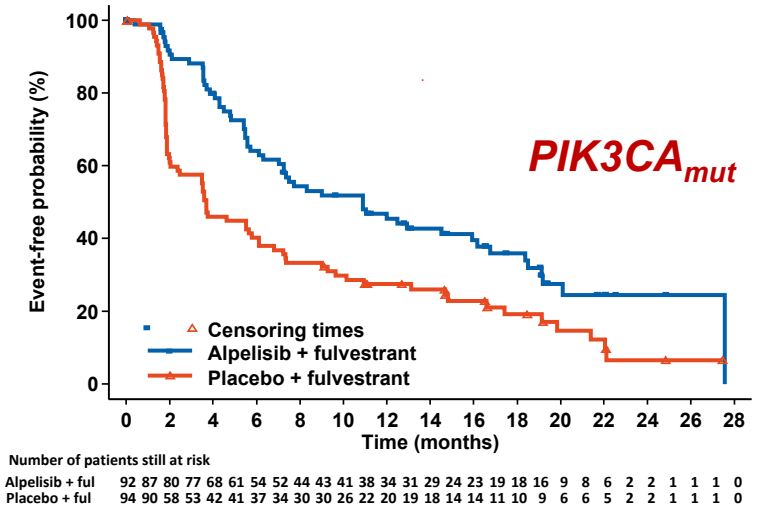
Primary endpoint

- PFS in *PIK3CA*-mutant cohort (locally assessed)

Secondary endpoints include

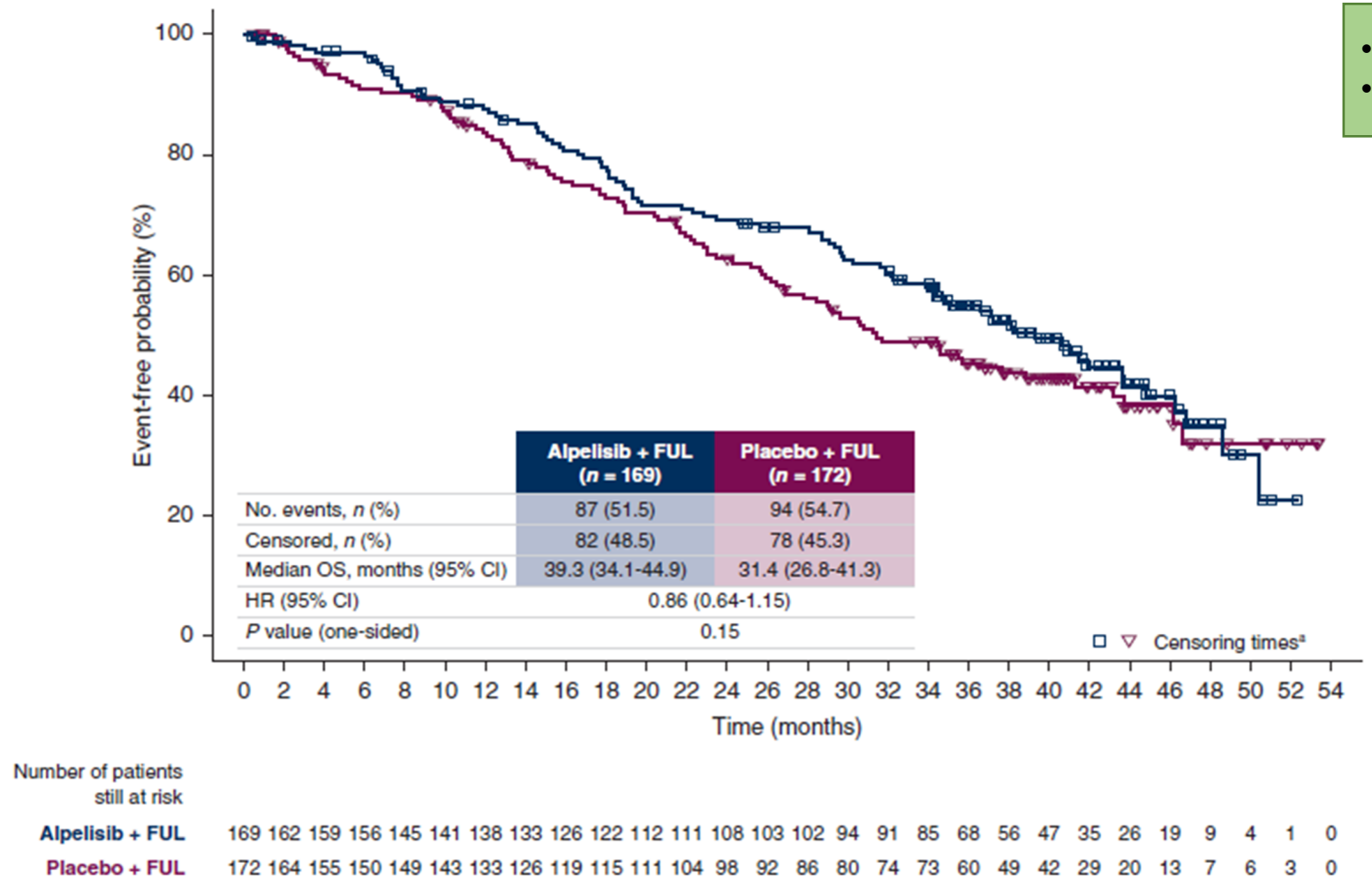
- OS (*PIK3CA*-mutant cohort)
- PFS (*PIK3CA*-non-mutant cohort)
- PFS (*PIK3CA* mutation in ctDNA)
- PFS (*PIK3CA*-non-mutant in ctDNA)
- ORR/CBR (both cohorts)
- Safety

ctDNA testing



André F N Engl J Med 2019;380:1929-40

SOLAR-1: final overall survival results



- **Non remboursé**
- **AMM en 2L post IA**

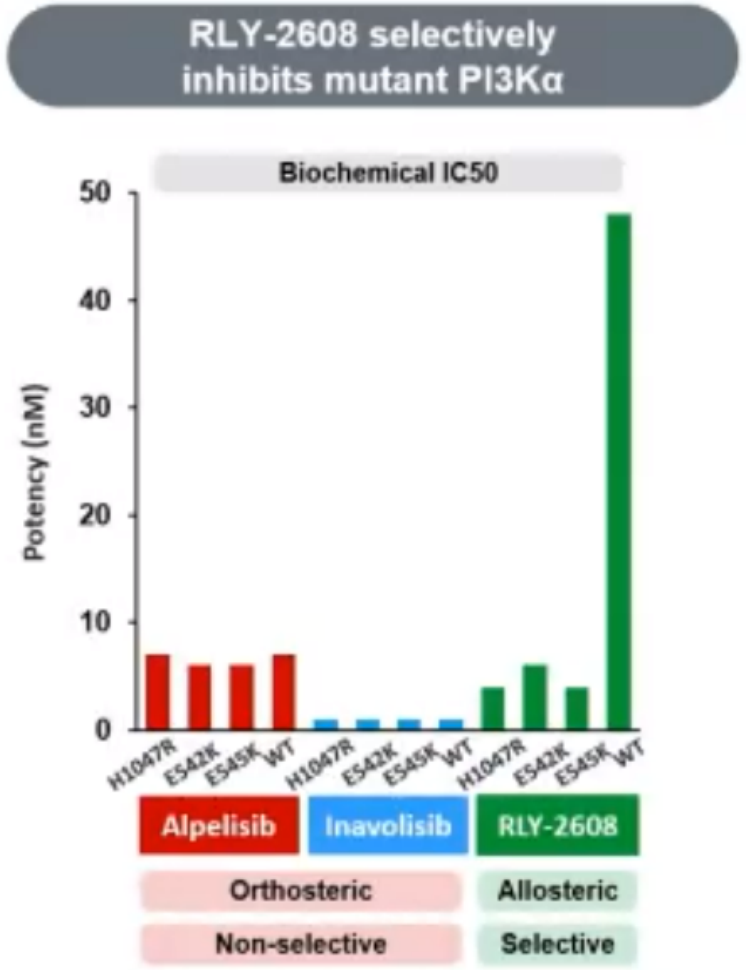
F. André et al. Annals Oncol 2021

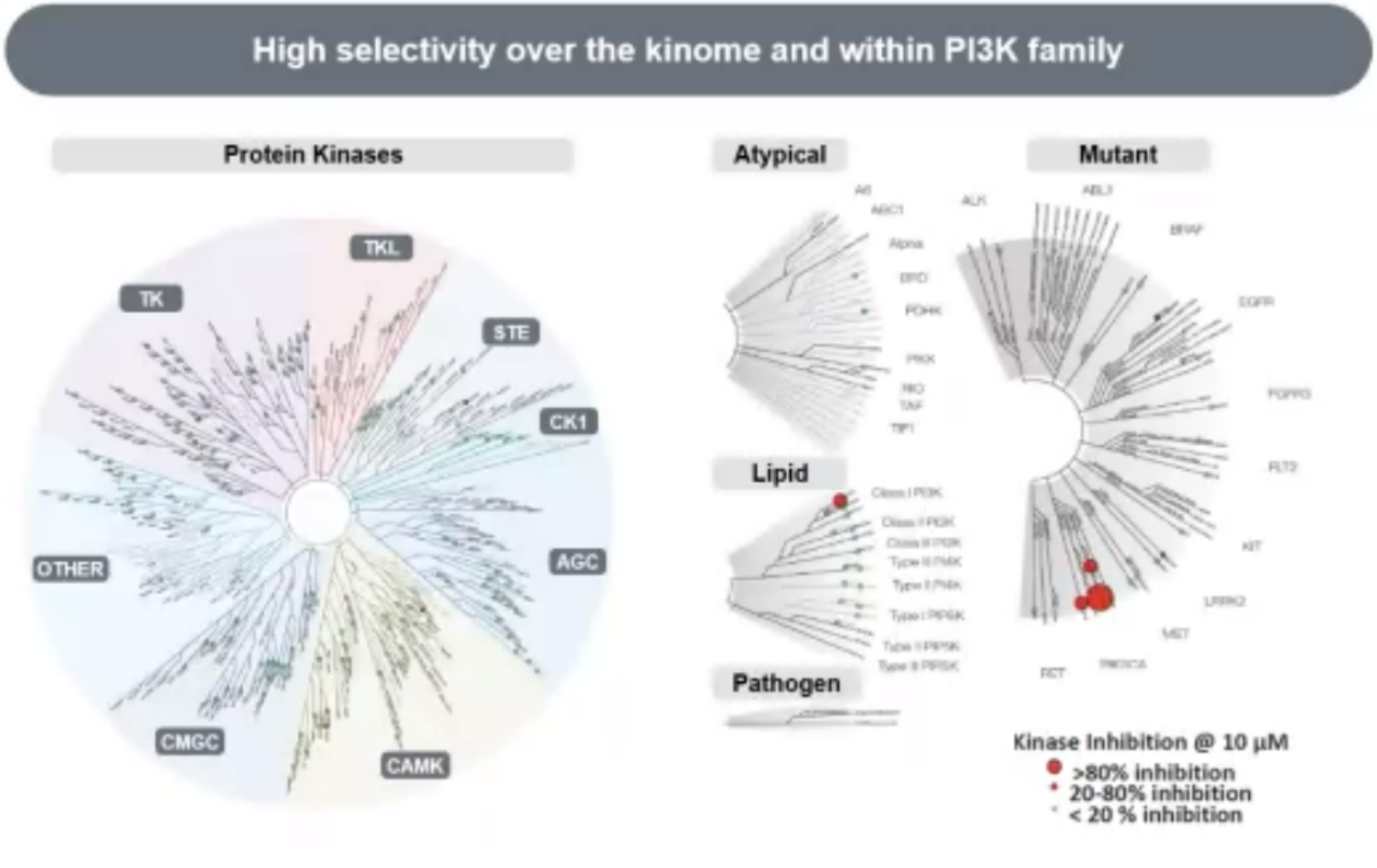
Biomarqueurs

- Hors screening pour un essai clinique, la recherche du statut *NTRK, PIK3CA*, MSI est inutile en l'absence de remboursement des drogues correspondantes

	Experts	Public
Oui	**87%**	**62%**
Non	**10%**	**33%**
Abstention	**3%**	**5%**

Autres agents ciblant PIK3CA en développement





Pazolli M, Discovery and characterization of RLY-2608, the first allosteric, mutant, and isoform-selective inhibitor of PI3Kα. Oral presentation at: AACR-NCI-EORTC Virtual International Conference on Molecular Targets Conference; October 7-10, 2021; Virtual.

Autres marqueurs

	MSI-H	1%	IC	Marcus L, et al. *Clin Cancer Res.* 2019[73]
NTRK	Fusions	1%	IC	Doebele RC, et al. *Lancet Oncol.* 2020[50]
ESR1	Mutations (mechanism of resistance)	10%	IIA	Fribbens C, et al. *J Clin Oncol.* 2016[74]
PTEN	Mutations	7%	IIA	Schmid P, et al. *J Clin Oncol.* 2018[75]
AKT1^{E17K}	Mutations	5%	IIB	Hyman D, et al. *J Clin Oncol.* 2017[76]
NF1	Mutations (resistance biomarker)	6%	Not applicable	Pearson A, et al. *Clin Cancer Res.* 2020[77]
MDM2	Amplifications	~1%	IIIA	Dembla V, et al. *Oncotarget.* 2018[78]
ERBB3	Mutations	2%	IIIB	Hyman D, et al. *Nature.* 2018[55]

Mosele F. Ann Oncol 2020 Nov;31(11):1491-1505

Nouvelles explorations biologiques de la voie PI3K/AKT/PTEN

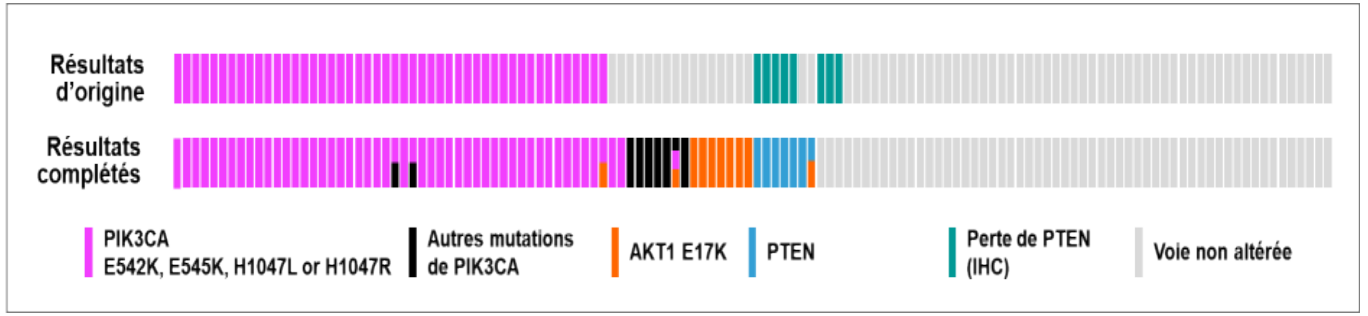
Méthodologie

- Une analyse génomique a été effectuée sur tissus et ADNtc avec respectivement les tests Foundation One CDx et GuardantOMNI.
- Une mutation activatrice de *PIK3CA* (exons 1,4,7,9,20) ou d'*AKT* (E17K) et/ou des altérations inactivatrices dans *PTEN* définissaient une altération de la voie.

Résultats

FAKTION : Nouvelles explorations biologiques permettant de détecter 25% de plus de patientes ayant une altération de la voie PI3K/AKT/PTEN

- 8 mutations E17K de *AKT1* (*AKT1* n'a pas été testé dans le panel d'origine)
- 5 mutations activatrices de *PIK3CA* non testées dans le panel d'origine
- 3 mutations de *PIK3CA* testée mais non détectée par le panel d'origine en raison d'une sensibilité limitée
- 1 une altération inactivatrice de *PTEN*
- 3 patientes présentaient plus d'un type d'altération sur *AKT1*, *PTEN* ou *PIK3CA*

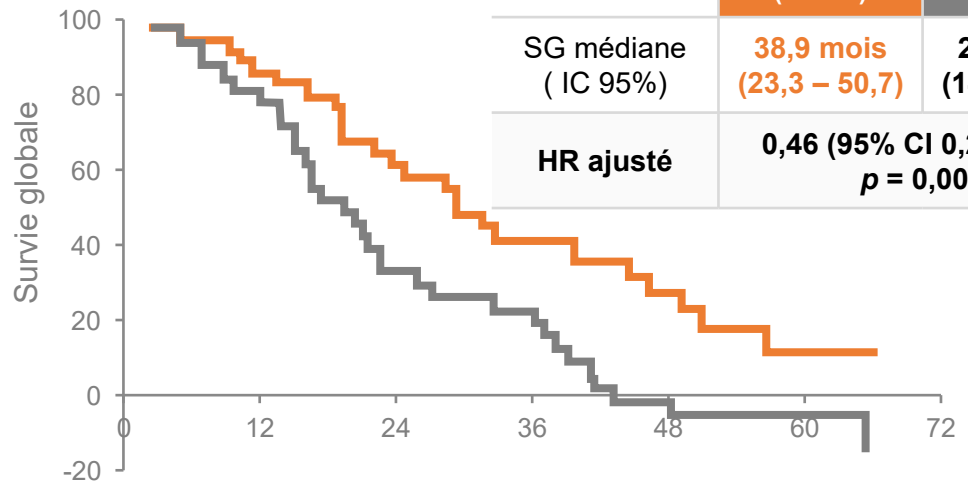


R.H. Jones, et al, Lancet Oncol. 2022 Jul;23(7):851-864.

FAKTION : SG selon altération de la voie PI3K/AKT/PTEN

Voie altérée

	Fulvestrant + capivasertib (n = 39)	Fulvestrant + placebo (n = 37)
SG médiane (IC 95%)	38,9 mois (23,3 – 50,7)	20,0 mois (14,8 – 31,4)
HR ajusté	0,46 (95% CI 0,27-0,79); *p* = 0,005	

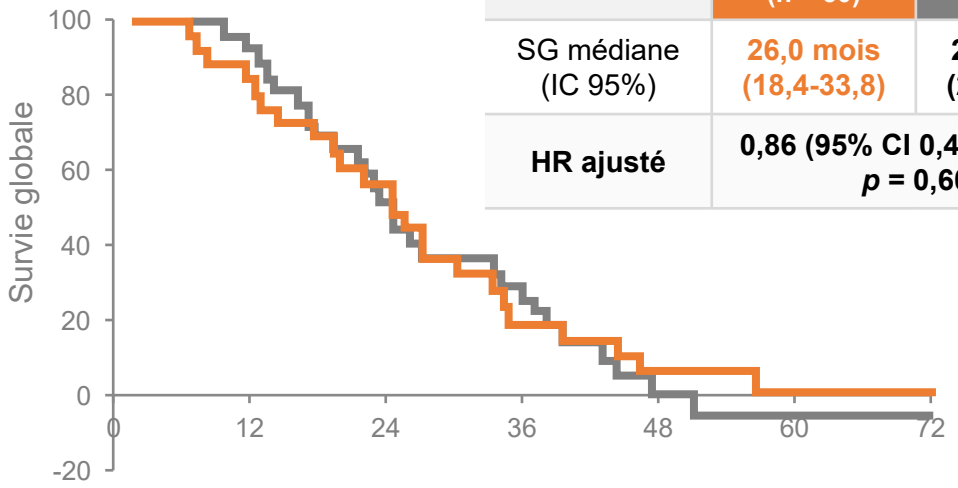


Nb à risque

Fulvestrant + placebo	37	27	14	10	3	3	0
Fulvestrant + capivasertib	39	33	23	17	10	3	0

Voie non altérée

	Fulvestrant + capivasertib (n = 30)	Fulvestrant + placebo (n = 34)
SG médiane (IC 95%)	26,0 mois (18,4-33,8)	25,2 mois (20,3-36,2)
HR ajusté	0,86 (95% CI 0,49 – 1,52) ; *p* = 0,60	



Nb à risque

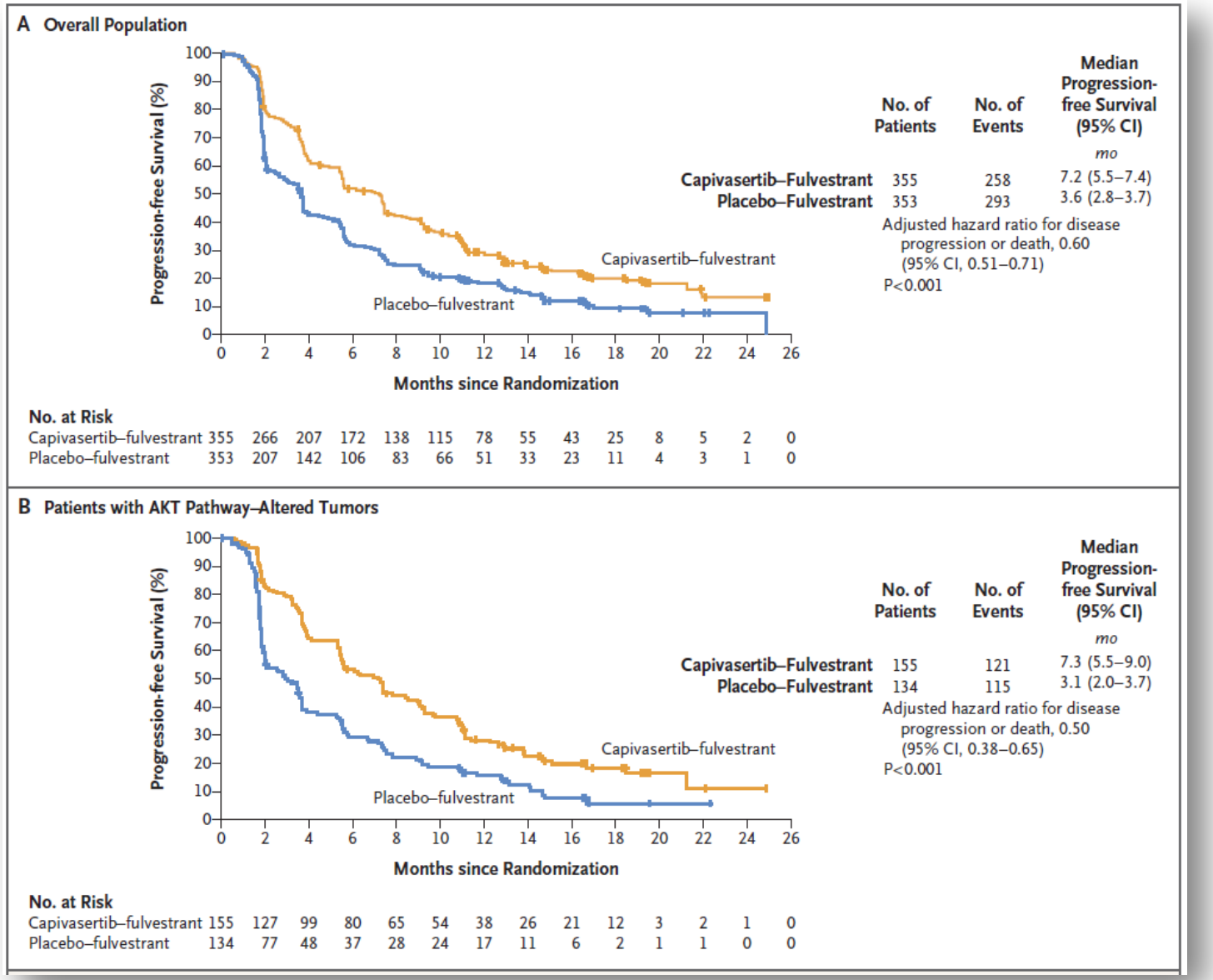
Fulvestrant + placebo	34	28	16	11	3	2	1
Fulvestrant + capivasertib	30	24	16	8	5	3	1

Amélioration de la SG uniquement chez les patientes ayant une altération de la voie PI3K/AKT/PTEN

R.H. Jones, et al, Lancet Oncol. 2022 Jul;23(7):851-864.

AKT: CAPITELLO phase III

Post CDKi 70%



Turner, NEJM 2023

ESCAT Esmo Scale for Clinical Actionability of molecular Targets (DNA level only)

	LOE			Clinical implication
ESCAT evidence tier	A	B	C	
I. Adm* → improved outcome in clinical trials	Prospective R trials and increased survival outcomes Ex: HER2 amplif, gBRCA1/2, PIK3CA mut	Prospect. Non R trials and ESMO MCBS 1.1 (clinical meaningful) Ex: sBRCA1/2, gPALB2	Basket trial Ex: NTRK transloc, MSI	Should be considered standard of care
dm* → anti-our activity but magnitude of benefit unk.	Retrospective trials → clinical meaningful benefit Ex: PTEN loss, ESR1 mut	Prosepective trials → clinical responsiveness but no survival data Ex: AKT1 mut, HER2 mut	NA	Treatment to be considered « preferable »
III. Adm* → improved outcome in other tumour types	Clinical benefit but in a different tumour type Ex: MDM2 amplif	Ex: HER3 mut	NA	Clinical trials to be discussed with patients
IV. Preclinical evid. of actionability				

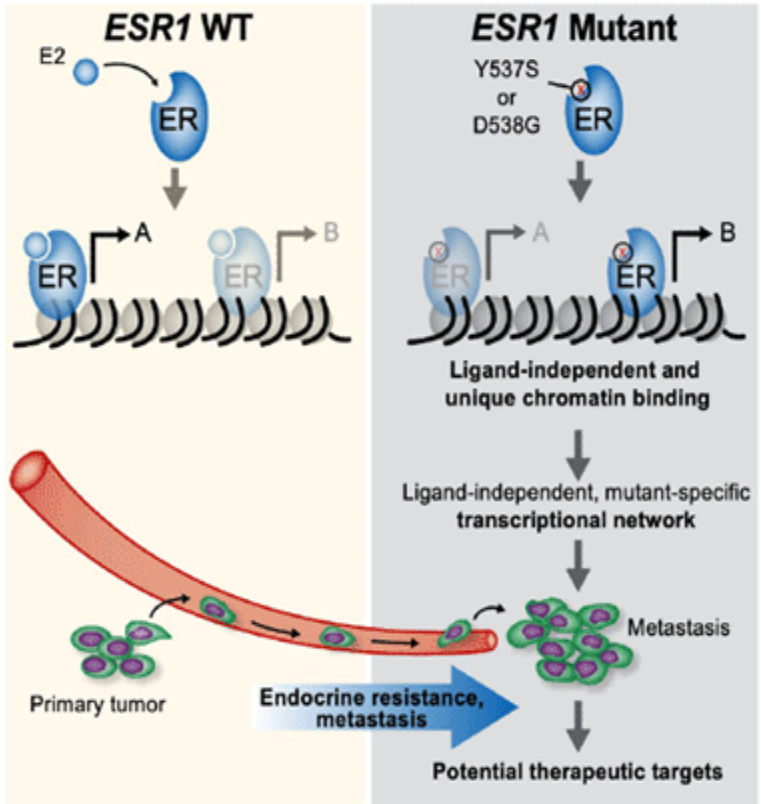
MADRID 2023 ESMO congress

* Adm: Aleteration-drug match

Condorelli R et al, Ann Oncol 2019;
Mosele F et al, Ann Oncol 2020;
Tung N et al, JCO 2020

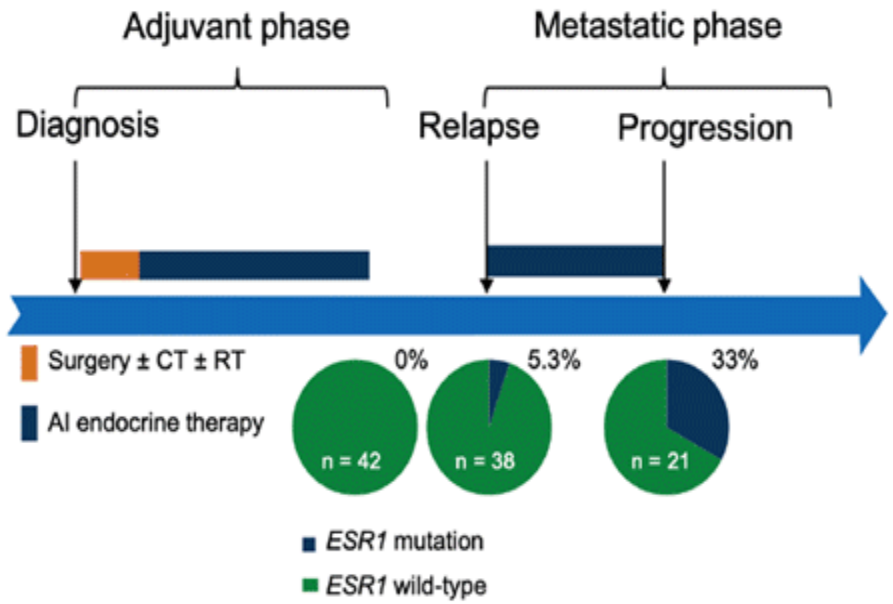
La biopsie liquide

Activating *ESR1* Mutations: Mechanism of Action[1,2]



Polling question answer option 2
ESR1 mutations allow ERα to be activated in the absence of its ligand (estradiol)

- Primary tumors: **not detectable**
- First relapse: **rare (<5%)**
- Progression on AI: **frequent**



Polling question answer option 3
ESR1 mutations are often selected during ~~adjuvant~~ **first-line** AI-based therapy

1. Jeselsohn R et al. *Cancer Cell*. 2018;33:173-186.e5. 2. Allouchery V et al. *Breast Cancer Res*. 2018;20:40.

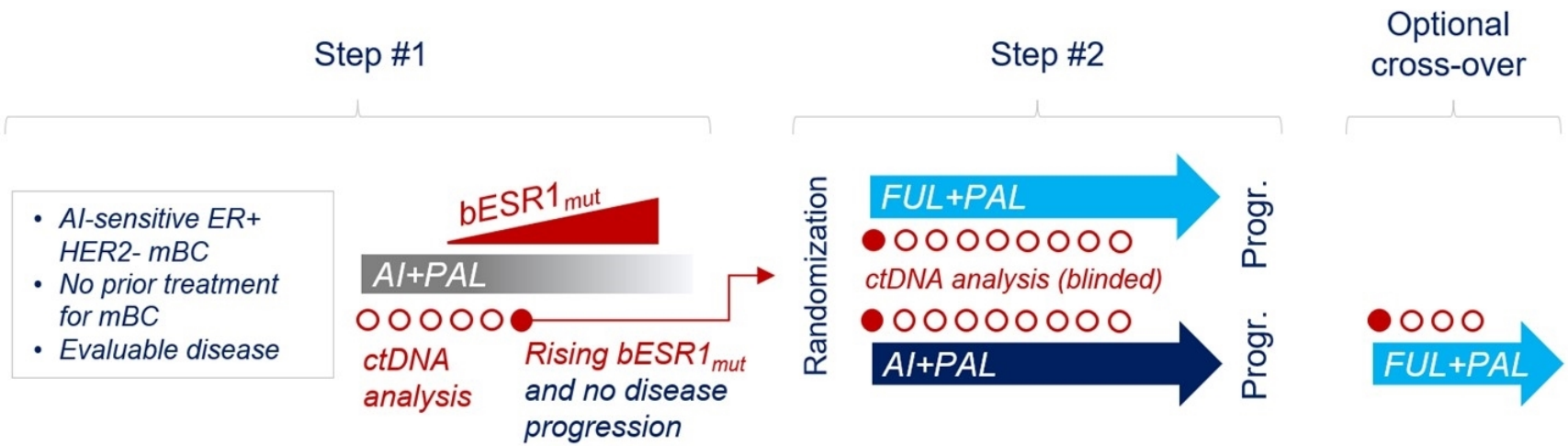
Background: *ESR1*$_{mut}$ & PADA-1 design

***ESR1* mutations**

- are acquired during aromatase inhibitors (AI) therapy in ~40% of ER+ HER2- mBC pts and drive resistance
- can be detected by ctDNA analysis in blood (*bESR1*$_{mut}$)
- retain partial sensitivity to fulvestrant (FUL), a selective estrogen receptor dégrader (SERD)

PADA-1

- Strategy: **targeting rising *bESR1*$_{mut}$ when they become detectable** under AI+Palbociclib (PAL) [1]

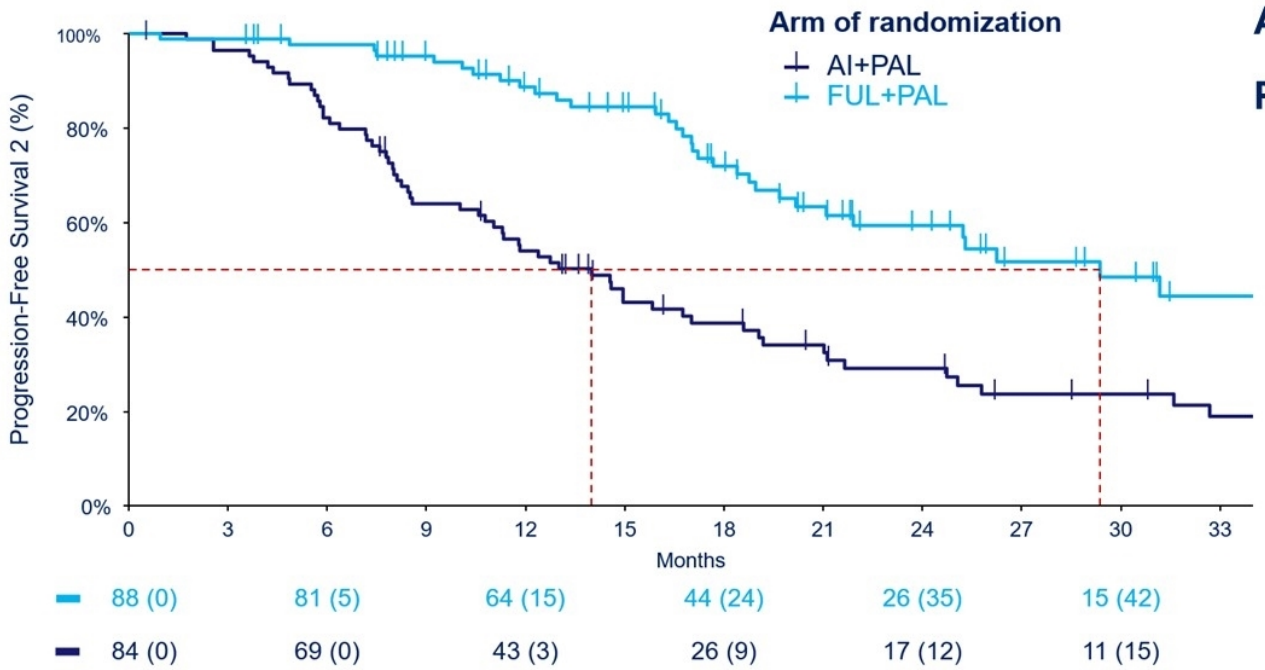


[1] Berger *et al.*, BMJ Open 2022

PFS2 results – secondary endpoint

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

Progression-Free Survival 2, from randomization



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

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

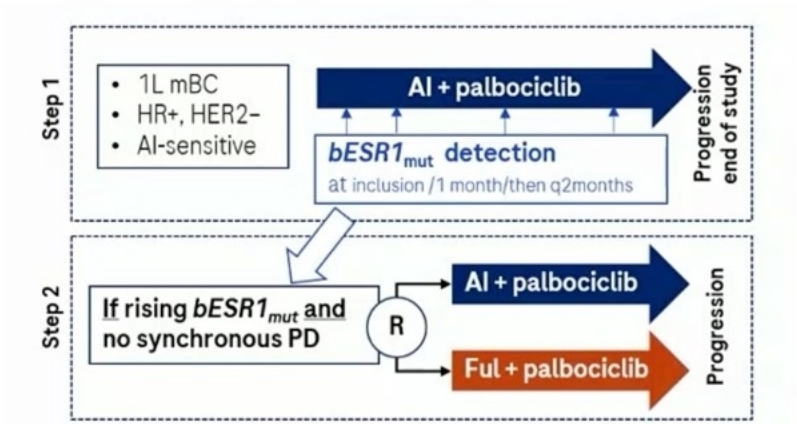
PFS2 HR= 0.37 [0.24;0.56]

Data cut-off: June 21, 2022; PFS2: time to 2nd progression or death in both arms

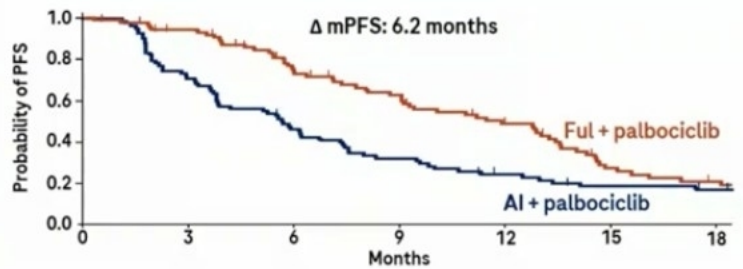
Cabel L ASCO 2023

ESR1 MUTATION MONITORING

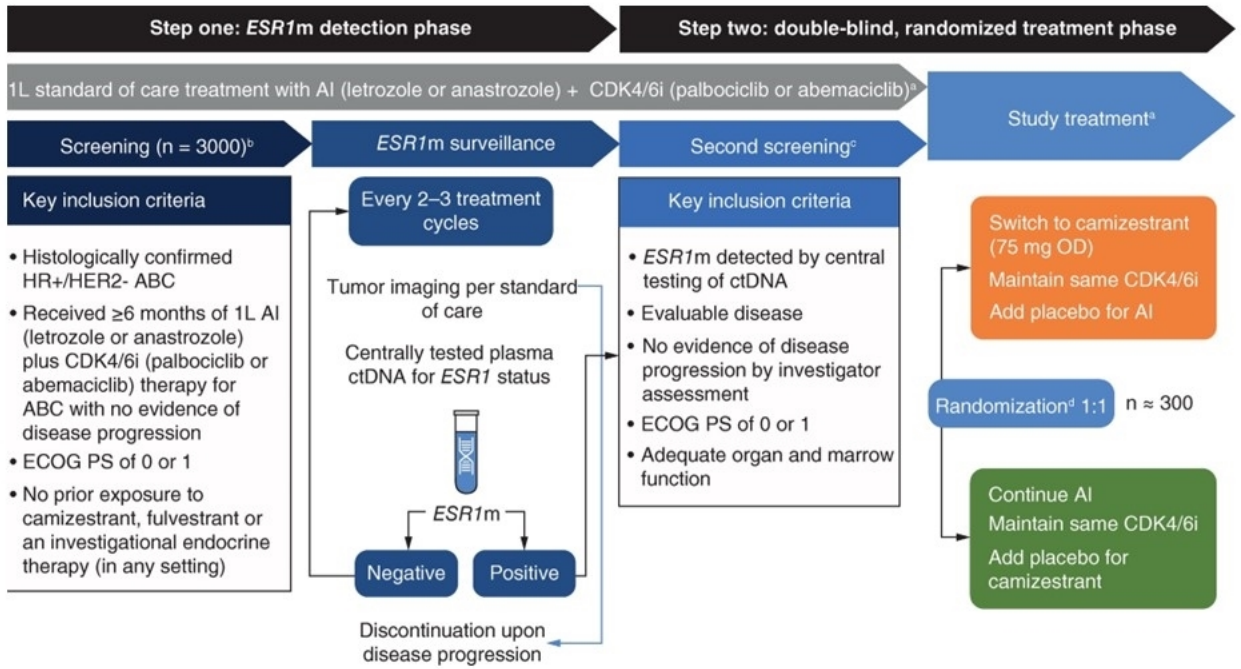
- **PADA -1**: ctDNA ESR1 mutation – guided change in therapy prior to disease progression. (1)



Step 2: PFS*	AI + palbociclib (n = 84)	Ful + palbociclib (n = 88)
mPFS, mo (95% CI)	5.7 (3.9, 7.5)	11.9 (9.1, 13.6)
Hazard ratio (95% CI)		**0.63** (0.45, 0.88)
p value		p = 0.007
Stratified hazard ratio (95% CI)		**0.61** (0.43, 0.86)
p value		p = 0.005



- **SERENA-6**: ctDNA ESR1 mutation – guided therapy. (2)



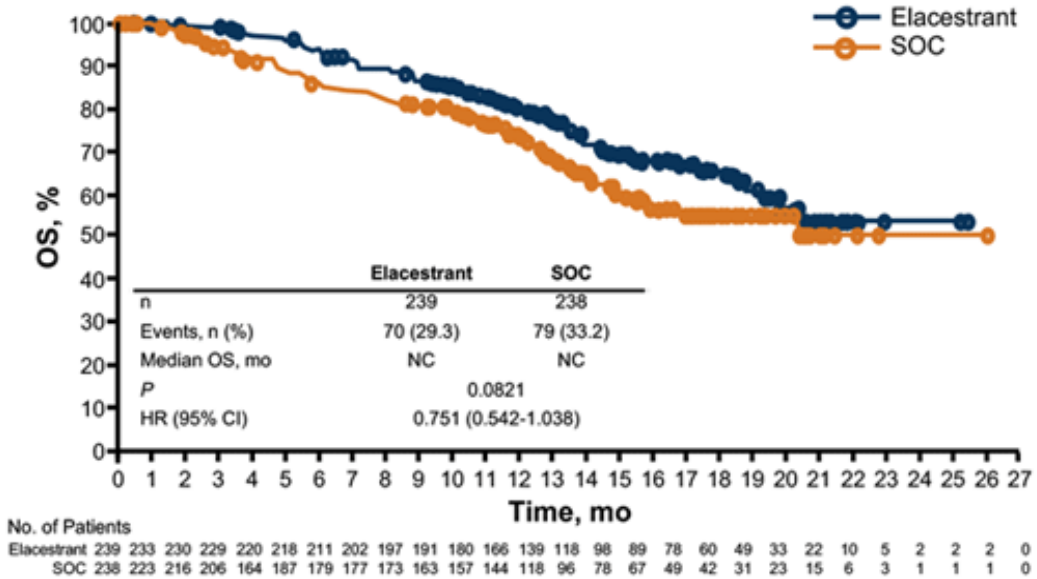
Can we tailor ET according to ***ESR1*** **mutations** or other biomarkers by analyzing **ctDNA**?

(1) Bidard FC SABCS 2021; Abstract GS3-05.
(2) Turner NC Future Oncol. 2023;19(8):559-573.

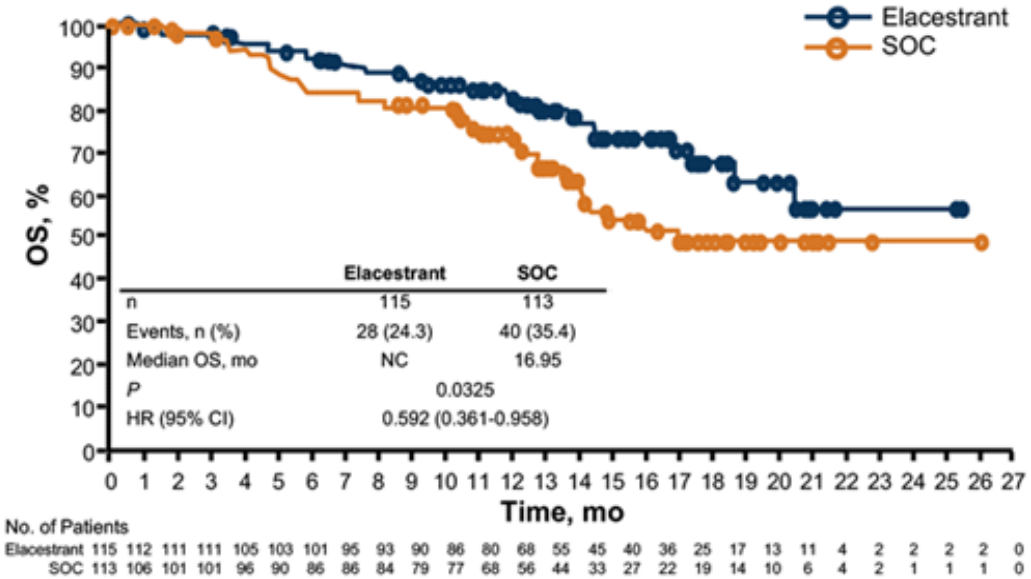
Phase 3 EMERALD: Study Design[1,2]

Overall Survival (Interim Analysis)[1,2]

All Patients



Patients With Tumors Harboring *ESR1*mut



- While no statistically significant differences were noted at the α = 0.0001 level in OS, an evident trend favoring elacestrant over SOC was noted in both groups
- Final analysis with mature data is expected to take place in late 2022/early 2023

1. Bardia A et al. SABCS 2021. Abstract GS2-02. 2. Bidard F-C et al. *J Clin Oncol*. 2022;JCO2200338.

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

Harold J. Burstein, MD, PhD[1]; Angela DeMichele, MD[2]; Mark R. Somerfield, PhD[3]; and N. Lynn Henry, MD, PhD[4]; for the Biomarker Testing and Endocrine and Targeted Therapy in Metastatic Breast Cancer Expert Panels

JCO May 18, 2023

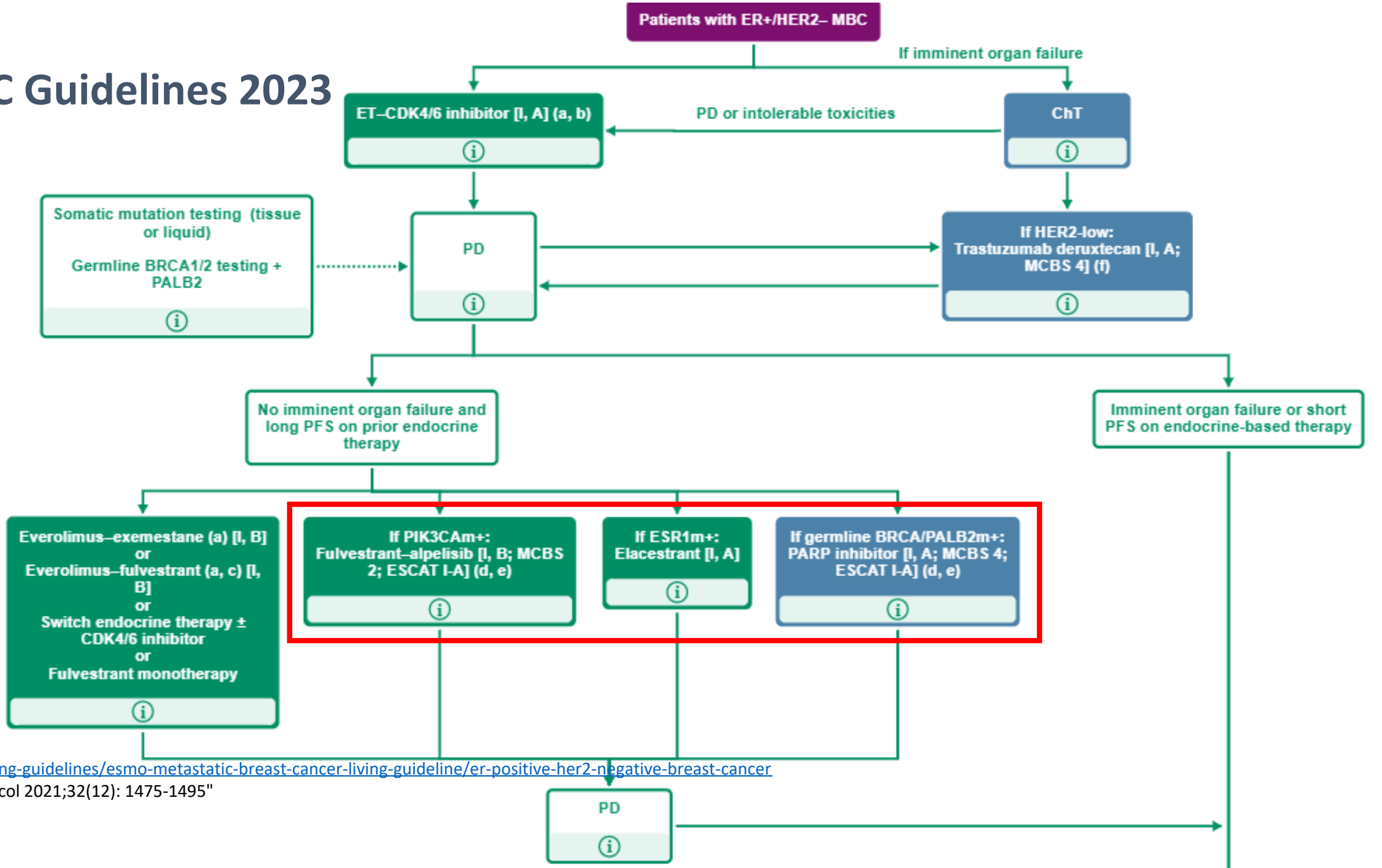
Expert Panel recommends routine testing for emergence of ESR1 mutations at recurrence or progression on ET+ or - CDK4-6 inhibitor

Testing ESR1 should be performed on blood (preferred) 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

Blood-based ctDNA is preferred owing to greater sensitivity

2023: reimbursement of ctDNA test in breast cancer by Medicare

ESMO BC Guidelines 2023



https://www.esmo.org/living-guidelines/esmo-metastatic-breast-cancer-living-guideline/er-positive-her2-negative-breast-cancer

G Curigliano et al; "Ann Oncol 2021;32(12): 1475-1495"

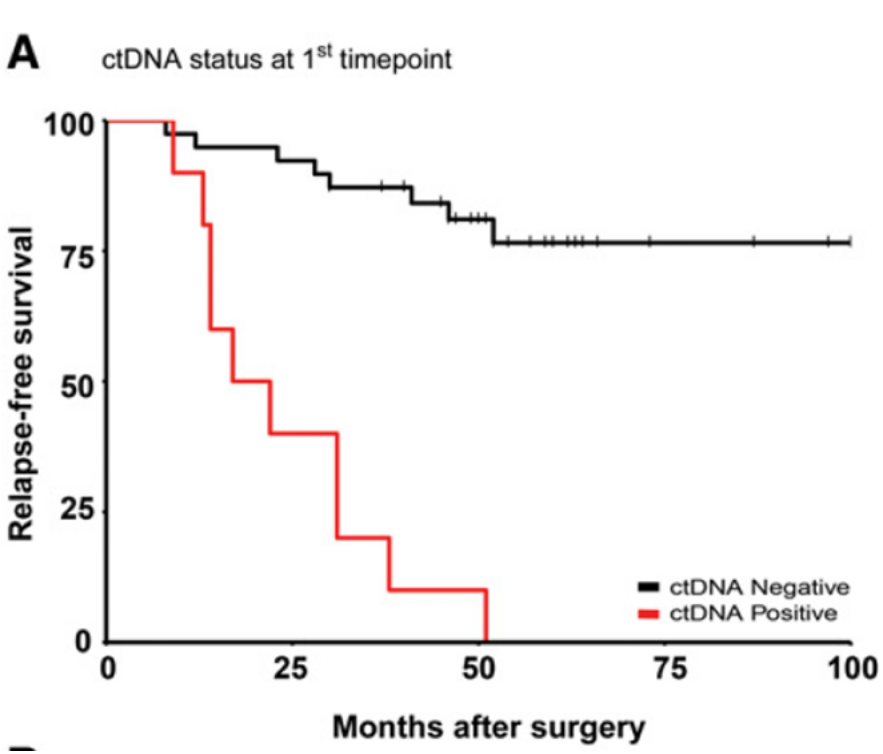
Genetic Tests: Medicare Expands Coverage of Molecular Cancer Screening Tests Publication Date: May 22, 2023

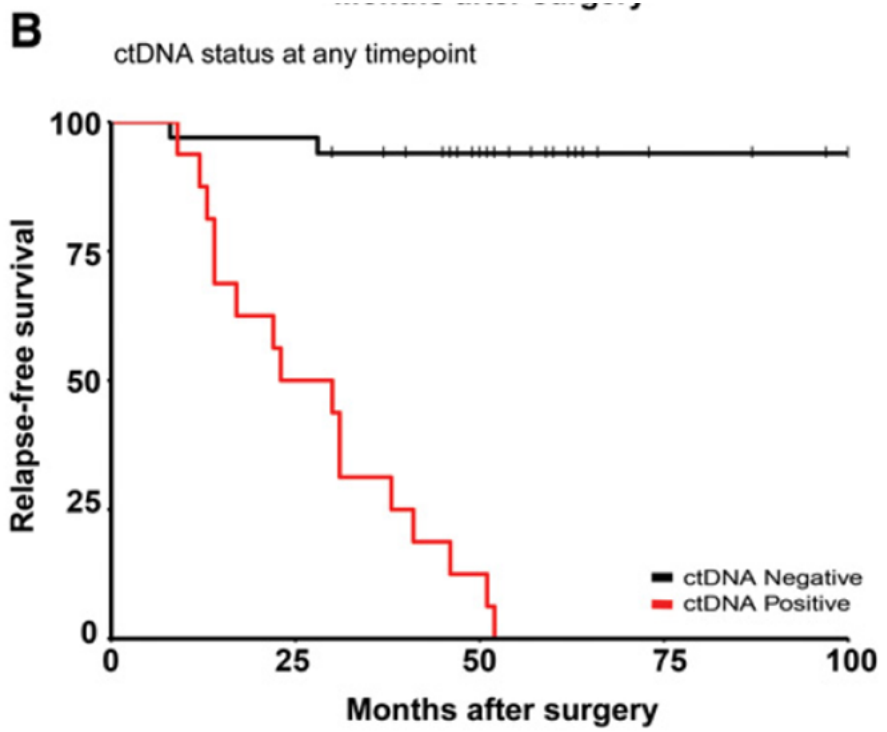
- **Epic Sciences' Breast Cancer Profiling ctDNA Test**
- Epic Sciences announced that it received a positive Medicare coverage decision from Palmetto MolDX® for a 56-gene circulating DNA (ctDNA) panel for genomic profiling of metastatic breast cancer.
- Medicare will reimburse the test at $1,934.21, according to media reports.

- **Others ctDNA circulating test are also reimbursed**

Minimal residual disease detection

Personalized Detection of Circulating Tumor DNA Antedates Breast Cancer Metastatic Recurrence





Coombes et al, Clin Cancer Res 2019

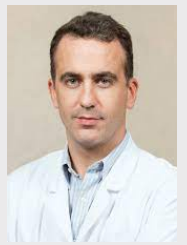
Understanding breast cancer complexity to improve patient outcomes: The St Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023

- The Food and Drug Administration (FDA) has granted approval for the use of liquid biopsy to detect circulating tumor DNA (ctDNA) in solid tumors in the early and in the metastatic setting.
- The approval of liquid biopsy in solid tumors by the FDA signifies its recognition as a potentially valuable diagnostic and monitoring tool in management of early-stage cancers. The panelists did not recommend routine ctDNA liquid biopsy testing at this time, awaiting studies showing clinical utility.

St Gallen Consensus Conference Panelists 2023 Ann Oncol sept 2023

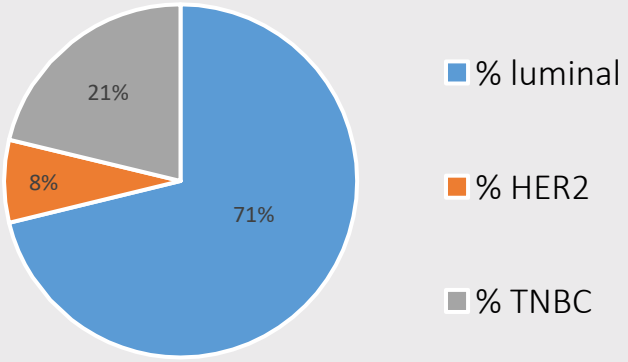
Une RCP en pleine expansion



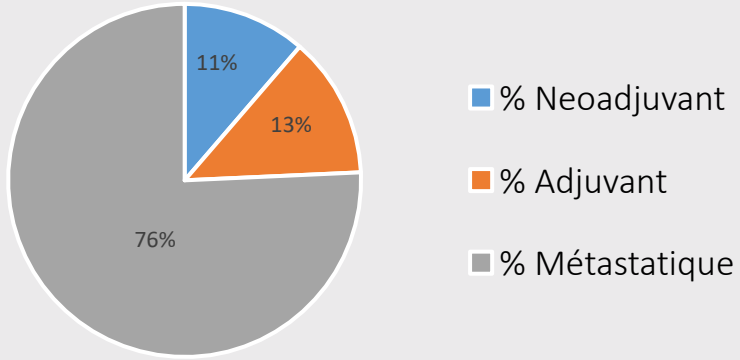


- Création : Février 2021
- Inclusions au fil de l'eau de toutes les patientes sein ayant une analyse génomique en routine
- Nombre de patientes incluses (02/21 – 01/23): 845 (en moyenne: 40 patientes /RCP)

Répartition par sous-types

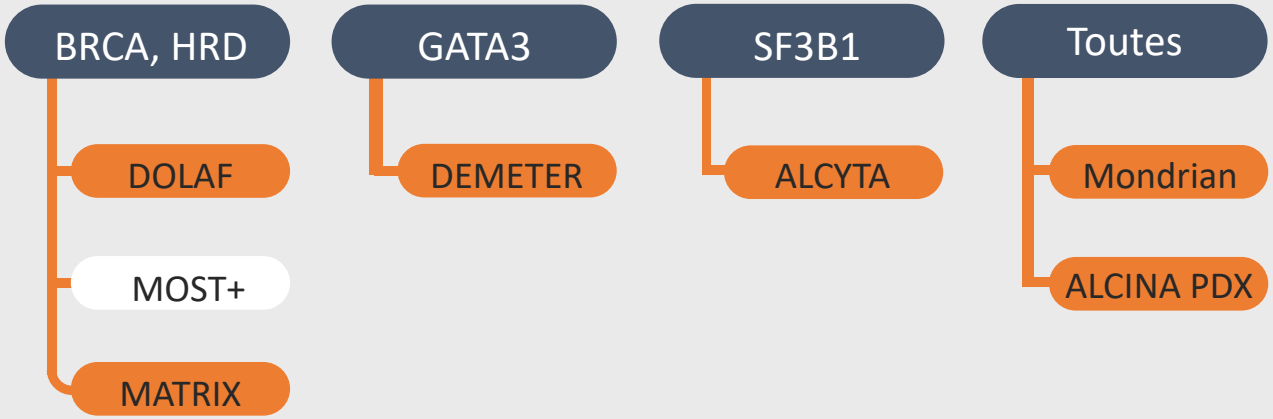


Répartition par phase de traitement

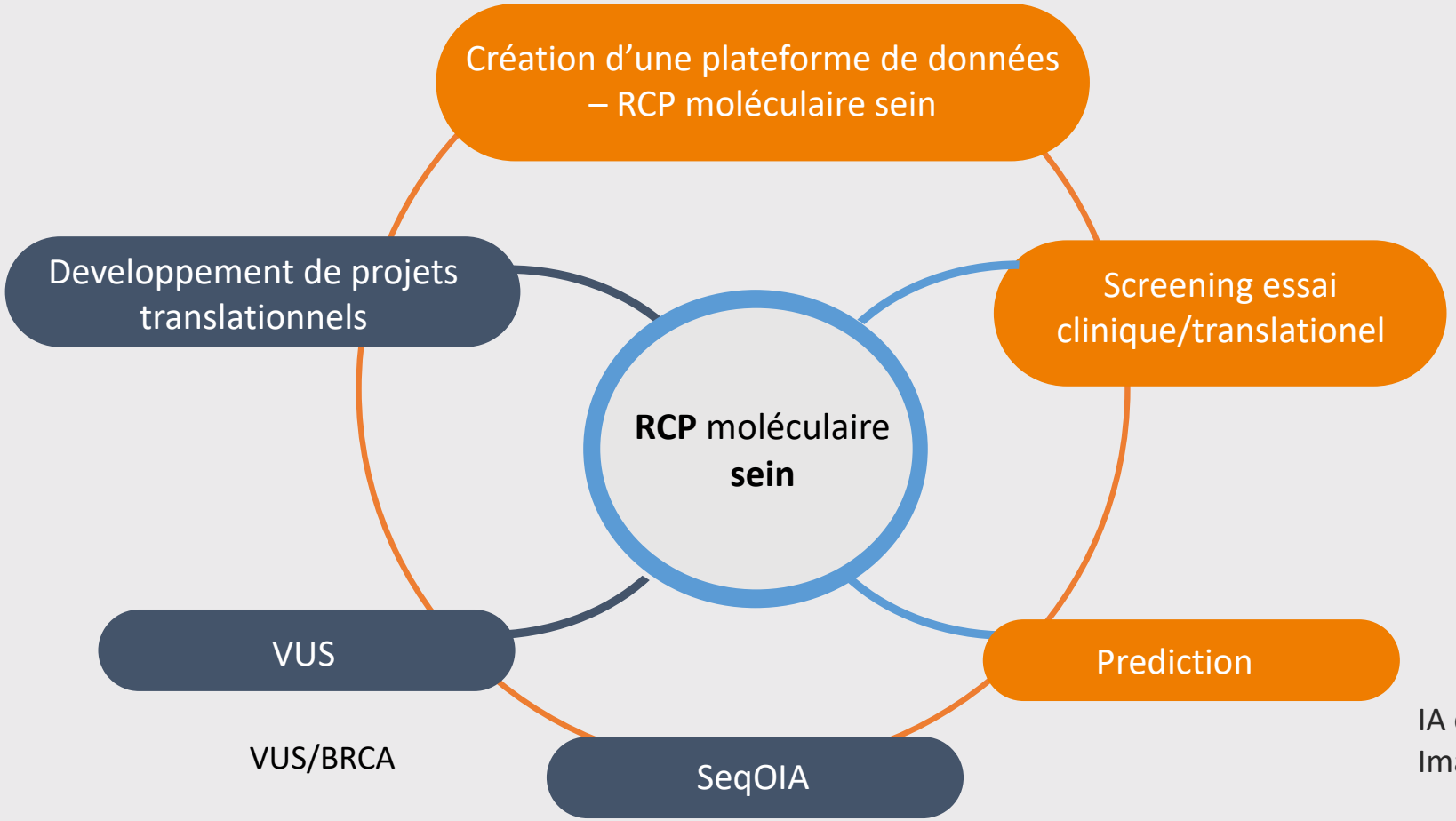


Décisions


Essai clinique
45%
Proposition
thérapeutique
15%


BRCA, HRD
DOLAF
MOST+
MATRIX
GATA3
DEMETER
SF3B1
ALCYTA
Toutes
Mondrian
ALCINA PDX

Une RCP en pleine évolution



Pop Art
ALCINA PDX
DEMETER
ALCYTA

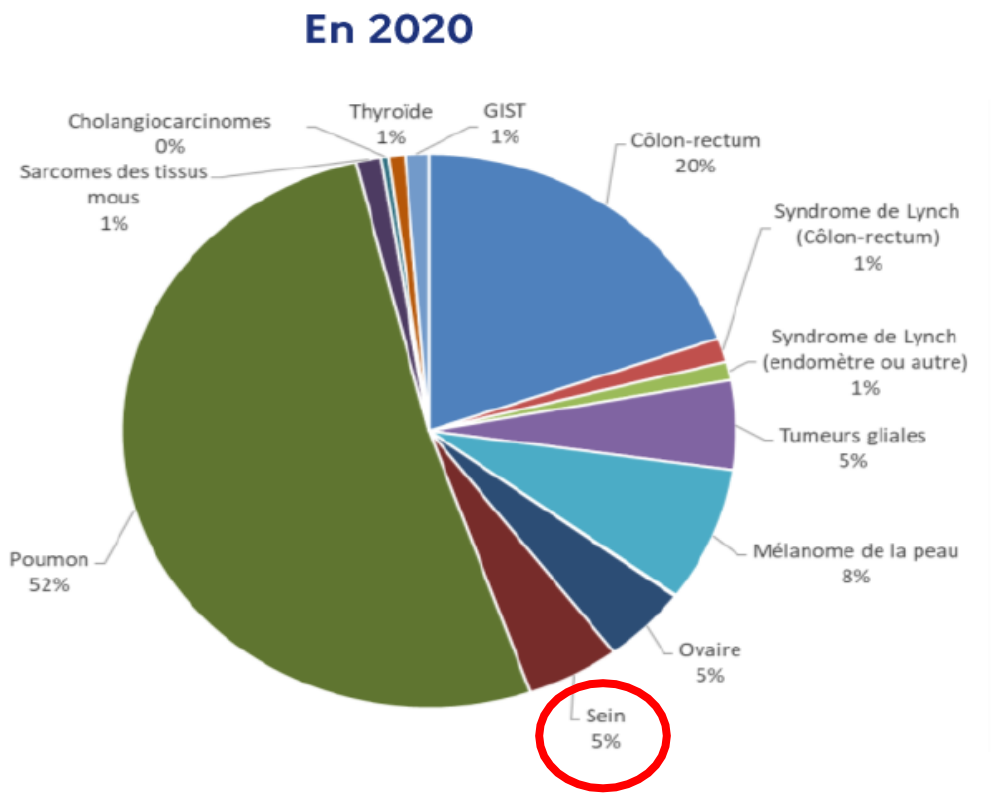
VUS/BRCA

IA et pathologie digitale
Imagerie

Implémentation de la NGS à partir de 2013
+
Implémentation de RNAseq à partir de 2020

Financement INCa

Patients ayant eu un test NGS



Conclusions

- **Indication en situation adjuvante ou post néoadjuvante**
  - BRCA : en adjuvant pour olaparib
  - Signatures génomiques: désescalade thérapeutique
- **En situation métastatique:**
  - Absence de bénéfice démontré en survie globale
  - Bénéfice en PFS pour :
    - **Inhibiteur de PARP mais mutations germinales**
    - **Inhibiteur de PI3KCA (non remboursé)**
    - **Mutation ESR1**
  - Programme de screening systématique pour tout cancer du sein métastatique
    - **Recherche (RCP Moléculaire, SEQOIA)**
    - **Inclusion dans les essais cliniques**
  - Autres marqueurs: en IHC pour les ADC HER2 faible, Trop2?

Evolution