7e ÉDITION

JOURNÉES DU **GFCO 2021**

Biomarqueurs et analyses moléculaires en oncologie

Avec la participation scientifique du GFCO

Biomarqueurs en oncologie : actualités et vision projective Cancer de la femme – Sein

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Liens d'intérêt

- **Advisory boards and honoraria:**

  - Roche, Novartis, Lilly, Amgen, Daiichi Sankyo , AstraZeneca, ExactSciences, Pfizer, Pierre Fabre Oncology, MSD, Celltrion, Ipsen, Sandoz, Seagen, Gilead, Mylan

- **Research funding (institution)**

  - Menarini Silicon Biosystems, Roche, Servier, Sanofi

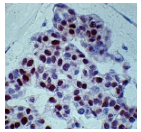
Plan

- **Tests génomiques au stade précoce**
  - Statut BRCA
  - Signatures génomiques (expression génique)
- **Tests génomiques au stade métastatiques**
  - PIK3CA
  - Statut BRCA
  - Autres tests
- **Perspectives**

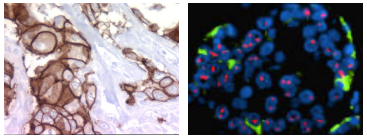
Biomarqueurs prédictifs dans le cancer du sein

Systématiquement évalués pour chaque cancer du sein précoce et si possible à la rechute

RE/RP



HER2



Nouveau
ER "low positive" 1-9%
Effet du traitement endocrine inconnu

cut-off RH
- 10% en France
- **1% ASCO**

HER2 cut-off
- **> 10%, ratio ≥2, HER2 ≥4**
- ASCO 2018

Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update

Kimberly H. Allison, MD[1]; M. Elizabeth H. Hammond, MD[2]; Mitchell Dowsett, PhD[3]; Shannon E. McKernin[4]; Lisa A. Carey, MD[5]; Patrick L. Fitzgibbons, MD[6]; Daniel F. Hayes, MD[7]; Sunil R. Lakhani, MD[8,9]; Mariana Chavez-MacGregor, MSc[10]; Jane Perlmutter, PhD[11]; Charles M. Perou, PhD[5]; Meredith M. Regan, ScD[12]; David L. Rimm, MD, PhD[13]; W. Fraser Symmans, MD[10]; Emina E. Torlakovic, MD, PhD[14,15]; Leticia Varella, MD[16]; Giuseppe Viale, MD[17,18]; Tracey F. Weisberg, MD[19]; Lisa M. McShane, PhD[20]; and Antonio C. Wolff, MD[21]

JCO 2020

Valeur predictive négative

Forte 95%

(<5% de chance de répondre au TT ciblé)

Valeur predictive positive

30-50%

HER2 low….

Remerciements à F. Penault Llorca

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 0: 1–10, 2019
doi:10.1093/annonc/mdz036
Published online 31 January 2019

REVIEW

Genomic alterations in breast cancer: level of evidence for actionability according to ESMO Scale for Clinical Actionability of molecular Targets (ESCAT)

R. Condorelli[1,2], F. Mosele[1*], B. Verret[1], T. Bachelot[3], P. L. Bedard[4], J. Cortes[5], D. M. Hyman[6], D. Juric[7], I. Krop[8], I. Bieche[9], C. Saura[10], C. Sotiriou[11], F. Cardoso[12], S. Loibl[13], F. Andre[1] & N. C. Turner[14]

Table 3. List of genomic alterations of LOE I/II

Alterations	Alteration considered	Alteration not considered	LOE	References
ERBB2 amplification	Focal amplification (DNA copy number ≥6; size ≤10 Mb)	DNA gain (DNA copy number <6)	IA	Romond et al. [13] Fehrenbacher et al. [14] Di Leo et al. [15] Perou CM, Nature 2000 [16]
Germline *BRCA1/2* mutations	Truncated mutations: InDel, splice-site, nonsense (except known truncating polymorphic variant, i.e. *BRCA2* K3326X). Rare known inactivating missense mutations (pathogenic variant class 5)	Most of missense variants (classes 1–4)	IA	Robson et al. [17] Litton et al. [18]
PIK3CA mutations	Major hot-spot activating missense mutations (E542K, E545K/A, H1047R/L)	Other missense mutations. Truncated mutations (InDel, splice-site, nonsense)	IA	Andre et al. [19] Hortobagyi et al. [20]
Microsatellite instability (MSI)			IC	Cortes-Ciriano et al. [21] Le et al. [22] Pembrolizumab package insert [23]
NTRK translocations			IC	Amatu et al. [24] Drilon et al. [25]

Table 3. List of genomic alterations of LOE I/II

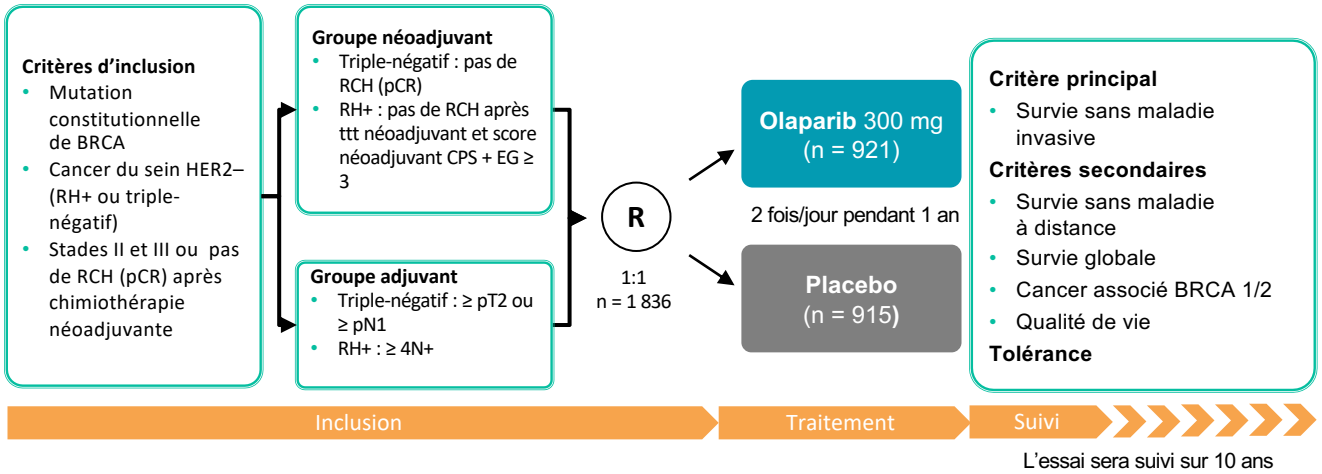
Alterations	Alteration considered	Alteration not considered	LOE	References
ESR1 mutations	Hot-spot activating missense mutations (E380Q, Y537S/C/N, D538G)	Other missense mutations. Truncated mutations (InDel, splice-site, nonsense)	IIA	Fribbens et al. [26]
PTEN loss	Homozygous deletions. Loss-of-function mutations: truncated mutations and known inactivating missense mutations (Ex: R130Q/G)	Other missense mutations	IIA	Schmid et al. [27]
AKT1 mutations	E17K	Other mutations	IIB	Hyman et al. [28] Emma Dean et al. [29]
ERBB2 mutations	Hot-spot activating missense mutations (e.g. S310F/Y, L755S, V777L) In-frame insertion exon 20 (Ex : Y772_A775dup)	Not hot-spot missense mutations. Truncated mutations (InDel, splice-site, nonsense)	IIB	Hyman et al. [30] Ma et al. [31]

Inhibiteur de PARP en adjuvant

Essai OlympiA

Méthodologie : étude de phase III randomisée en double aveugle

Schéma de l'étude



Stratification
- RH+ versus TN
- Néoadjuvant versus adjuvant
- CT antérieure à base de platine (oui versus non)

Traitement adjuvant
- HT
- Biphosphonates
- Pas de seconde CT adjuvante

Tutt A et al., ASCO 2021 NEJM 2021

OlympiA: Patient characteristics

	Olaparib (N = 921)	Placebo (N = 915)
Age, years, median (interquartile range)	**42** (36–49)	**43** (36–50)
BRCA gene affected in germline		
BRCA1	657 (**71.3%**)	670 (**73.2%**)
BRCA2	261 (**28.3%**)	239 (**26.1%**)
BRCA1 and *BRCA2*	2 (0.2%)	5 (0.5%)
BRCA testing available		
Local and central BRCA result*	550 (**59.7%**)	540 (**59.0%**)
Local testing only	130 (14.1%)	141 (15.4%)
Central Myriad testing only	240 (26.0%)	234 (25.6%)
No local or central Myriad testing available	1 (0.1%)	0 (0.0%)
Primary breast cancer surgery		
Mastectomy	698 (**75.8%**)	673 (**73.6%**)
Conservative surgery only	223 (24.2%)	240 (26.2%)
Missing	0 (0.0%)	2 (0.2%)

*Local/Central discordant results: Olaparib 12 (2.2%), Placebo 10 (1.9%), Total 22 (2.0%)

Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

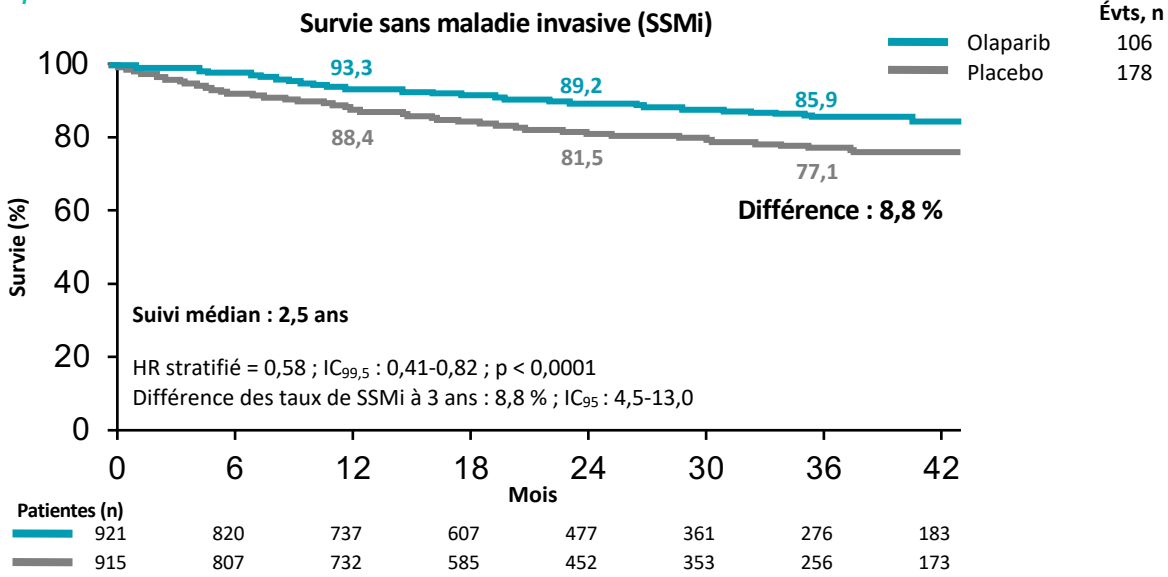
OlympiA: Patient characteristics

	Olaparib (N = 921)	Placebo (N = 915)
Hormone receptor status*		
Hormone receptor ≥ 1% / HER2-†	168 (**18.2%**)	157 (**17.2%**)
Triple Negative Breast Cancer‡	751 (**81.5%**)	758 (**82.8%**)
Menopausal status (female only)		
Premenopausal	572/919 (62.2%)	553/911 (60.7%)
Postmenopausal	347/919 (37.8%)	358/911 (39.3%)
Prior chemotherapy		
Adjuvant (ACT)	461 (**50.1%**)	455 (**49.7%**)
Neoadjuvant (NACT)	460 (**49.9%**)	460 (**50.3%**)
Anthracycline and taxane regimen	871 (**94.6%**)	849 (**92.8%**)
Neo(adjuvant) platinum-based therapy	247 (**26.8%**)	239 (**26.1%**)
Concurrent endocrine therapy (HR–positive only)	146/168 (86.9%)	142/157 (90.4%)

*Defined by local test results
†Following a protocol amended in 2015, the first patient with hormone receptor–positive disease was enrolled in December 2015
‡Two patients are excluded from the summary of the triple–negative breast cancer subset because they do not have confirmed HER2–negative status

Essai OlympiA

Résultats : critère principal



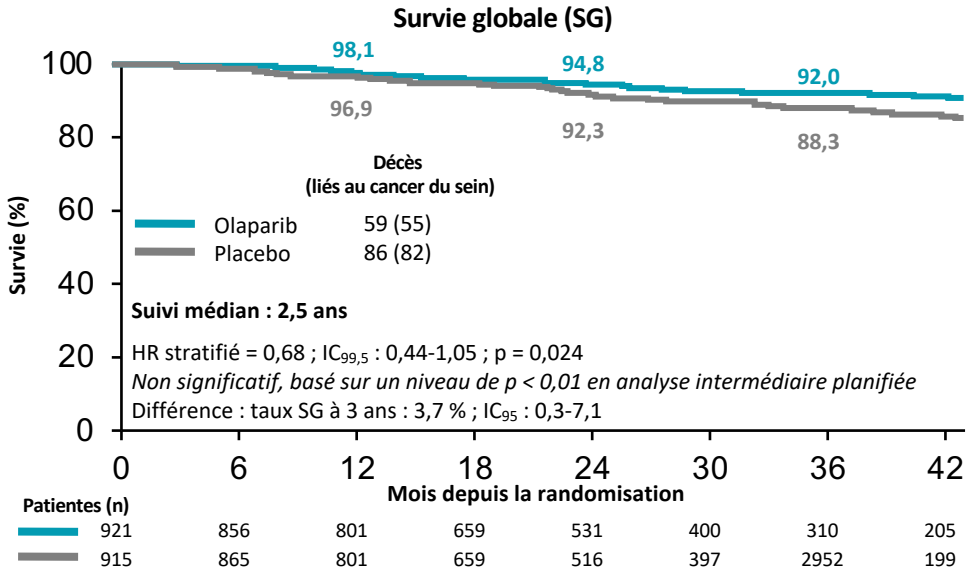
→ **Avec olaparib, diminution de 42 % du risque de maladie invasive :**

- récidive locale du cancer du sein
- récidive métastatique du cancer du sein
- autres nouveaux cancers
- décès toutes causes confondues

Tutt A et al., ASCO 2021 NEJM 2021

Essai OlympiA

Résultats : critère secondaire



→ **Moins de décès dans le bras olaparib que dans le bras placebo mais la différence n'est pas statistiquement significative**

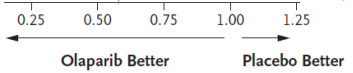
→ **Le suivi de l'étude est en cours**

Tutt A et al., ASCO 2021 NEJM 2021

Inhibiteur de PARP

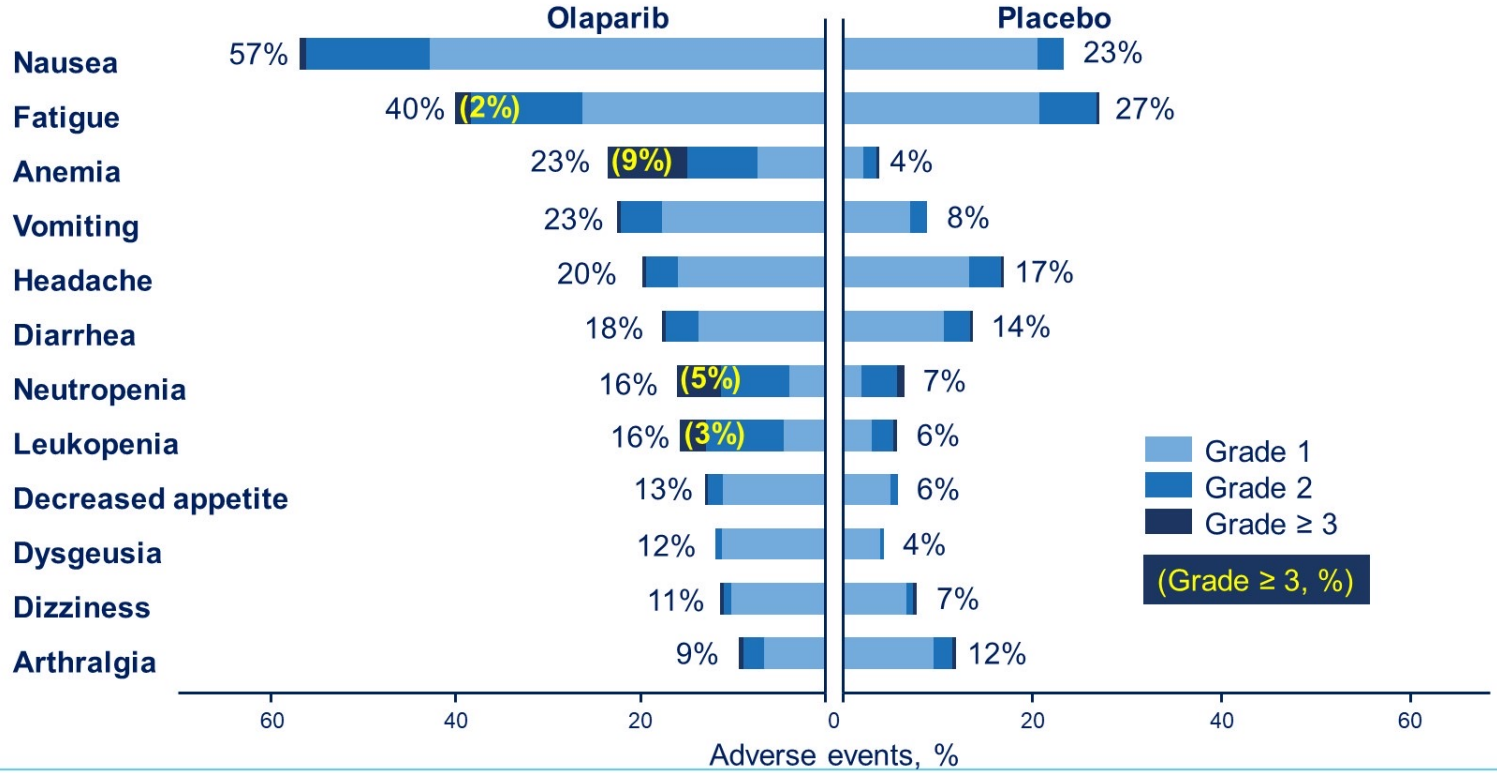
Essai OlympiA

Subgroup	Olaparib	Placebo	3-Y. Invasive Disease-free Survival Olaparib	3-Y. Invasive Disease-free Survival Placebo	Stratified Hazard Ratio for Invasive Disease or Death (95% CI)
	no. of patients with an event/total no.		%		
All patients	106/921	178/915	85.9	77.1	0.58 (0.46–0.74)
Timing of previous chemotherapy					
Neoadjuvant	70/460	117/460	82.5	68.0	0.56 (0.41–0.75)
Adjuvant	36/461	61/455	89.3	85.4	0.60 (0.39–0.90)
Previous platinum-based chemotherapy					
Yes	34/247	43/239	82.0	77.0	0.77 (0.49–1.21)
No	72/674	135/676	87.3	77.1	0.52 (0.39–0.69)
Hormone-receptor status					
HR+ and HER2–	19/168	25/157	83.5	77.2	0.70 (0.38–1.27)
TNBC	87/751	153/758	86.1	76.9	0.56 (0.43–0.73)
Germline *BRCA* mutation					
BRCA1	70/558	126/558	85.0	73.4	0.52 (0.39–0.70)
BRCA2	22/230	38/209	88.6	78.0	0.52 (0.30–0.86)
BRCA1 and *BRCA2*	0/1	0/3	NC	NC	NC
Hormone-receptor status and timing of previous chemotherapy					
HR+ and HER2–, NACT	13/104	20/92	86.0	67.0	0.52 (0.25–1.04)
HR+ and HER2–, ACT	6/64	5/65	76.4	89.3	1.36 (0.41–4.71)
TNBC, NACT	57/354	97/368	81.4	67.7	0.57 (0.41–0.79)
TNBC, ACT	30/397	56/390	90.3	84.8	0.54 (0.34–0.83)
Previous platinum-based chemotherapy and timing of previous chemotherapy					
Yes, NACT	26/169	39/169	81.8	70.1	0.66 (0.40–1.07)
Yes, ACT	8/78	4/70	NC	NC	NC
No, NACT	44/291	78/291	83.1	66.8	0.51 (0.35–0.73)
No, ACT	28/383	57/385	90.4	84.2	0.51 (0.32–0.79)
CPS+EG score in patients with previous NACT					
Score of 2, 3, or 4	55/398	96/387	84.3	68.9	0.51 (0.37–0.71)
Score of 5 or 6	11/22	10/15	50.0	17.9	0.44 (0.19–1.06)
Primary database					
Breast International Group	95/810	160/806	86.0	76.7	0.58 (0.45–0.75)
NRG Oncology (United States)	11/111	18/109	85.0	80.6	0.57 (0.26–1.18)



Tutt A et al., ASCO 2021 NEJM 2021

OlympiA: Adverse events of any grade ≥ 10%



Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

OlympiA: Summary of adverse events

	Olaparib (N = 911)	Placebo (N = 904)
Any adverse event	835 (91.7%)	753 (83.3%)
Serious adverse event (SAE)	**79 (8.7%)**	**76 (8.4%)**
Adverse event of special interest	**30 (3.3%)**	**46 (5.1%)**
MDS/AML	**2 (0.2%)**	**3 (0.3%)**
Pneumonitis	9 (1.0%)	11 (1.2%)
New primary malignancy	**20 (2.2%)**	**32 (3.5%)**
Grade ≥ 3 adverse event	221 (24.3%)	102 (11.3%)
Grade 4 adverse event	**17 (1.9%)**	**4 (0.4%)**
Adverse event leading to permanent discontinuation of treatment*	**90 (9.9%)**	**38 (4.2%)**
Adverse event leading to death†	1 (0.1%)	2 (0.2%)

Includes adverse events with an onset date on or after the first dose date and up to and including 30 days following date of last dose of study medication. AML denotes acute myeloid leukemia; MDS myelodysplastic syndrome

*Adverse events leading to permanent discontinuation of treatment in the olaparib group that occurring in > 1% were; nausea, anemia and fatigue

†Adverse events leading to death are cardiac arrest (olaparib, n = 1), AML (placebo, n = 1), and ovarian cancer (placebo, n = 1)

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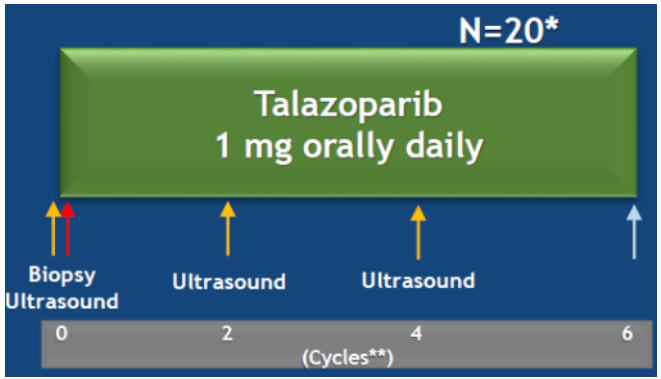
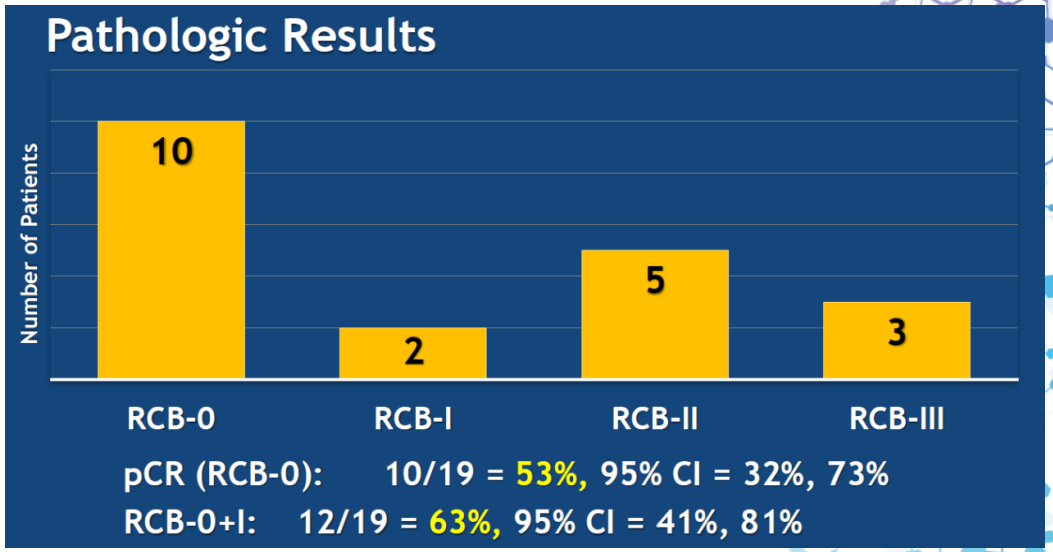
PARP INHIBITOR NEOADJUVANT SETTING

Talazoparib alone, BRCA carriers

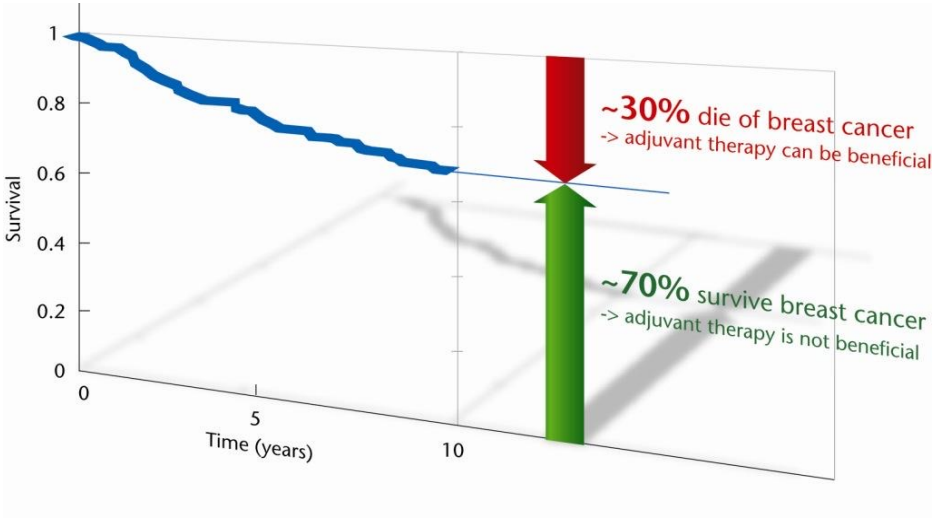




Litton J et al J Clin Oncol 2019

Qui va récidiver ? Désescalade thérapeutique

Kaplan-Meier Survival Curves



No Adjuvant treatment

Signatures génomiques

70-gene signature	21-gene signature	PAM50 (prosigna)	Genomic grade	HOXB13:IL17BR 2-gene ratio	11-gene assay
MammaPrint™ **(Agendia)**	**Oncotype DX®** **(Genomic health)**	**Prosigna** **(Nanostring)**	**MapQuant DX** **(Ipsogen/Haliodx)**	**BCI** **(biotheranostics)**	**Endopredict®** **(Sividon/Myriad)**
Microarray / NGS Centralisé / Décentralisé	qRT-PCR Centralisé	Mesure directe quantité d'ARNm : N-counter; Décentralisé	Microarray / qRT-PCR	RT-PCR Centralisée	qRT-PCR Décentralisé
-1 à +1 High vs Low Classe moléculaire	RS = 0 -100 High / Low **Cut-off à 25**	ROR= 0 - 100 High / Low / **Intermediate** Classe moléculaire	High / Low **Equivocal**	0 - 10 High / Low / **Intermediate**	0-15 (EP) 0-6(Epclin) High vs Low
70 gènes (croissance, prolifération, angiogenèse, invasion, survie)	*ER, PR, BCL2, SCUBE2, Ki67, STK15, BIRC5, CCNB1, MYBL2, HER2, GRB7, MMP11, CTSL2, GSTM1, CD68, BAG1*	50 gènes (dont prolif) **+ T** **+ pondération N**	97 gènes Simplifié *: MYBL2, KPNA2, CDC2, CDC20*	*HOXB13, IL17BR, BUB1, CENPA, NEK2, RACGAP1, RRM2*	*DHCR7, AZGP1, MGP, STC2, BIRC5, UBE2C, RBBP8, IL6ST* (prolif, voie RE) **+ T et N**
→ **M+ 5 et 10 ans** RE+ / RE- HER2-/+ N- / N+ (1-3) pre/post-menop.	→ **M+ 10 ans** RE+ sous HT N- / N+ (1-3) pre/post-menop.	→ **M+ 10 ans** RE+/HER2- sous HT N- / N+ (1-3) post-menop.	→ **M+ 10 ans** RE+ sous tamoxifène	→ **M+ 5 et 10 ans**	→ **M+ 10 ans** **RE+**/HER2- sous HT N- / N+ (1-3) pre/post-menop.
CT adjuvante (high)	CT adjuvante et néoadjuvante (high)		HT adjuvante et CT néoadjuvante (high)	HT adj > 5 ans (high)	
MINDACT	TAILORx RxPONDER	OPTIMA UK	ASTER 70s		

Signatures génomiques : les études

Mammaprint®	**MINDACT** *(Cardoso, NEJM 2016,2020. Piccart Lancet Oncol 2021)*	**Tous cancers localisés** **N- et 1- 3 N+ (21%)** **81% tumeurs luminales**
Oncotype DX®	**TAILOR X** *(Sparano, NEJM 2015, 2019)*	**Tumeurs luminales, N-**
	RXPONDER *(Kalinsky, SABCS 2020, NEJM 2021 in press)*	**Tumeur luminales, 1-3 N+**
Prosigna /PAM 50®	**OPTIMA** *(en cours)*	
Endopredict®	**Etudes rétrospectives**	

MINDACT
Microarray In Node-negative and 1 to 3 positive lymph node Disease may Avoid ChemoTherapy
EORTC 10041 / BIG 3-04

TRANSBIG

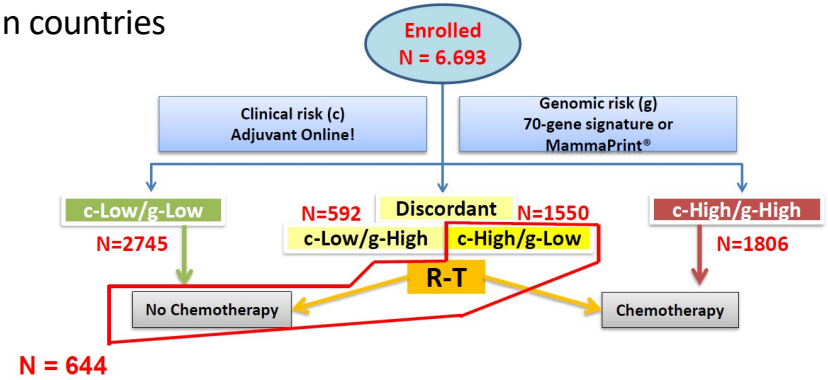

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 25, 2016 VOL. 375 NO. 8

70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer

F. Cardoso, L.J. van't Veer, J. Bogaerts, L. Slaets, G. Viale, S. Delaloge, J.-Y. Pierga, E. Brain, S. Causeret, M. DeLorenzi, A.M. Glas, V. Golfinopoulos, T. Goulioti, S. Knox, E. Matos, B. Meulemans, P.A. Neijenhuis, U. Nitz, R. Passalacqua, P. Ravdin, I.T. Rubio, M. Saghatchian, T.J. Smilde, C. Sotiriou, L. Stork, C. Straehle, G. Thomas, A.M. Thompson, J.M. van der Hoeven, P. Vuylsteke, R. Bernards, K. Tryfonidis, E. Rutgers, and M. Piccart, for the MINDACT Investigators*

- 6,600 pts **< 70**
  - 02/2007-08/2011
  - 112 institutions in 9 European countries
  - 11,291 registered patients
  - 6,673 enrolled (59.1%)

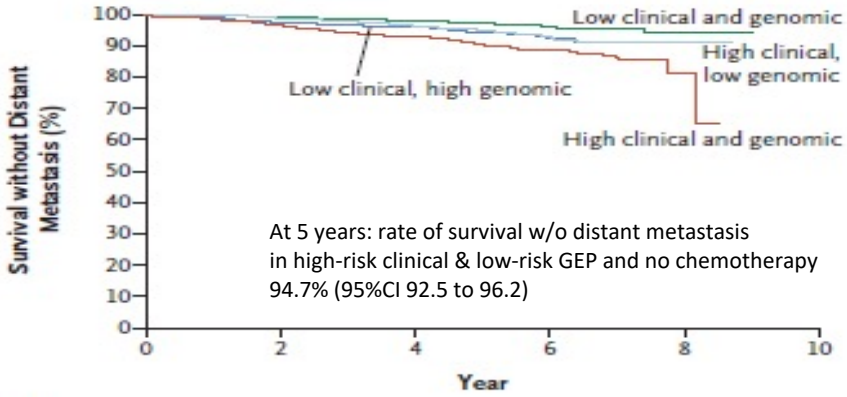
Mammaprint
Risk of distant recurrence
@ 5 years
w/ no treatment



Primary goal
In patients w/ high-risk clinical & low-risk GEP and no chemotherapy, lower boundary of the 95% CI for the rate of 5-yr survival w/o distant M+ ≥ 92% (i.e. the noninferiority boundary) at a 1-sided significance level of 0.025

(Cardoso, NEJM 2016,2020. Piccart Lancet Oncol 2021)

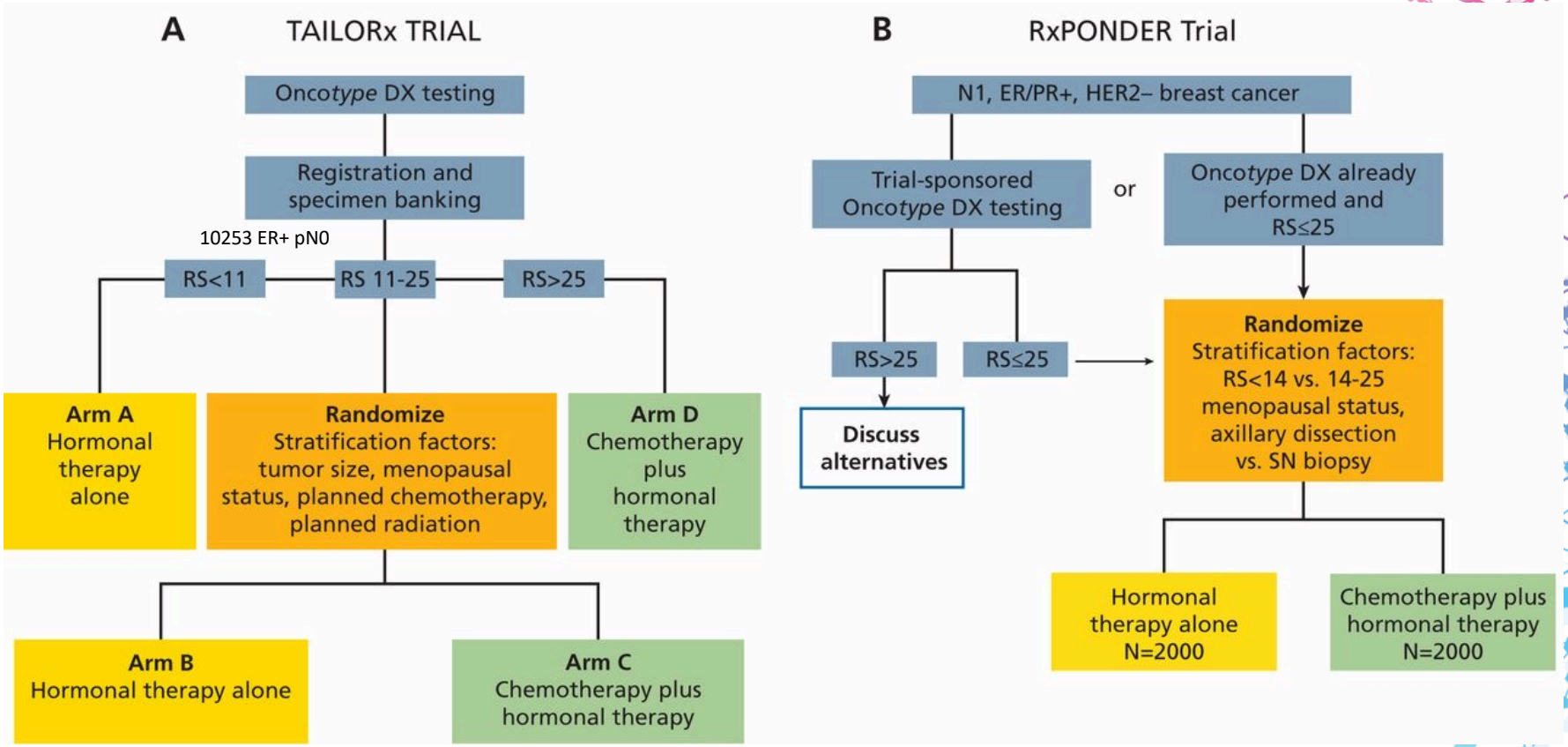
46% of decrease of chemotherapy indication in women w/ high clinical risk



At 5 years: rate of survival w/o distant metastasis in high-risk clinical & low-risk GEP and no chemotherapy 94.7% (95%CI 92.5 to 96.2)

No. at Risk					
Low clinical and genomic risk	2745	2628	2331	735	33
Low clinical, high genomic risk	592	550	484	136	2
High clinical, low genomic risk	1550	1457	1317	311	9
High clinical and genomic risk	1806	1689	1462	395	11

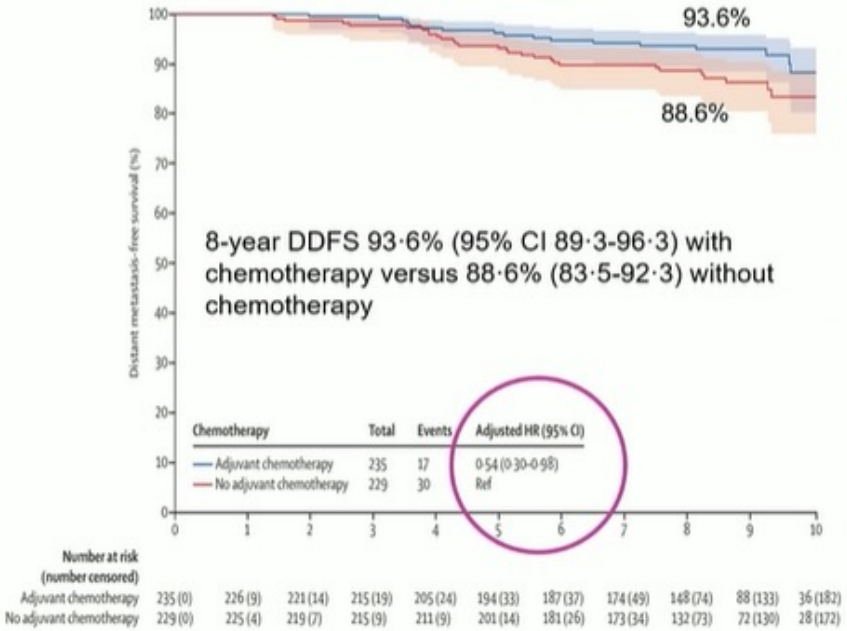
Figure 3. Survival without Distant Metastasis in the Four Risk Groups.
The analysis includes all enrolled patients, and the risk groups are based on corrected risk. The time-to-event curves were estimated by means of the Kaplan–Meier method.



(Sparano, NEJM 2015, 2019)

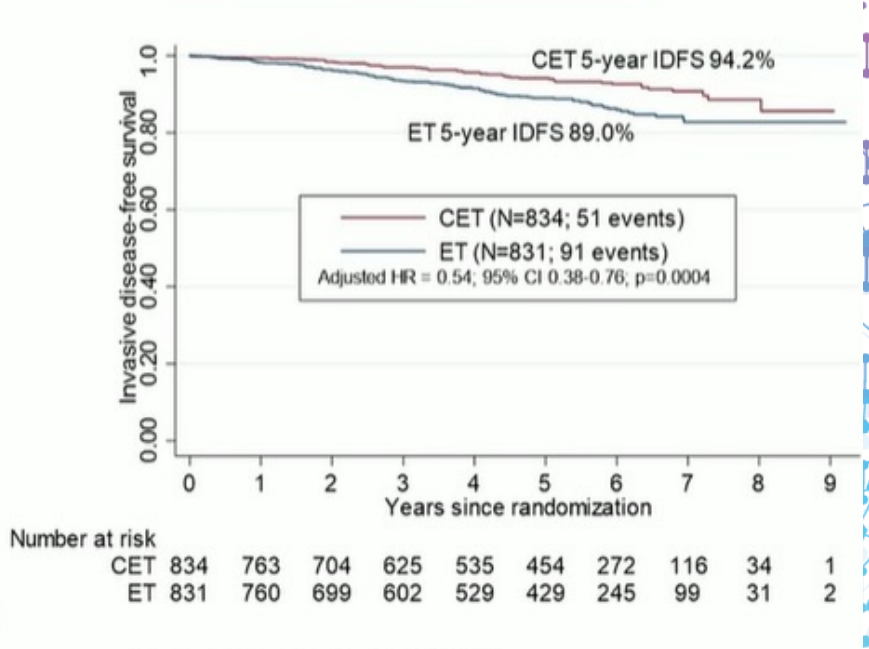
Essai Mindact et RxPonder chez les femmes non ménopausées

Mindact: clinical high risk/genomical low risk<50



Piccart M et al Lancet Oncol 2021

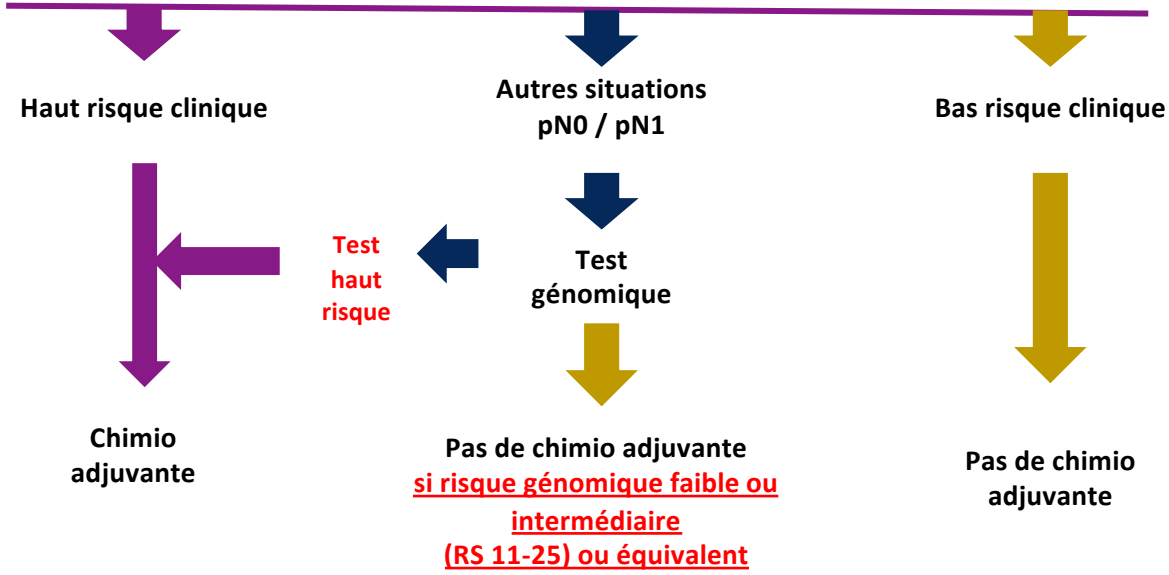
RxPonder: RS 11-25



Kalinsky et al. SABCS 2020

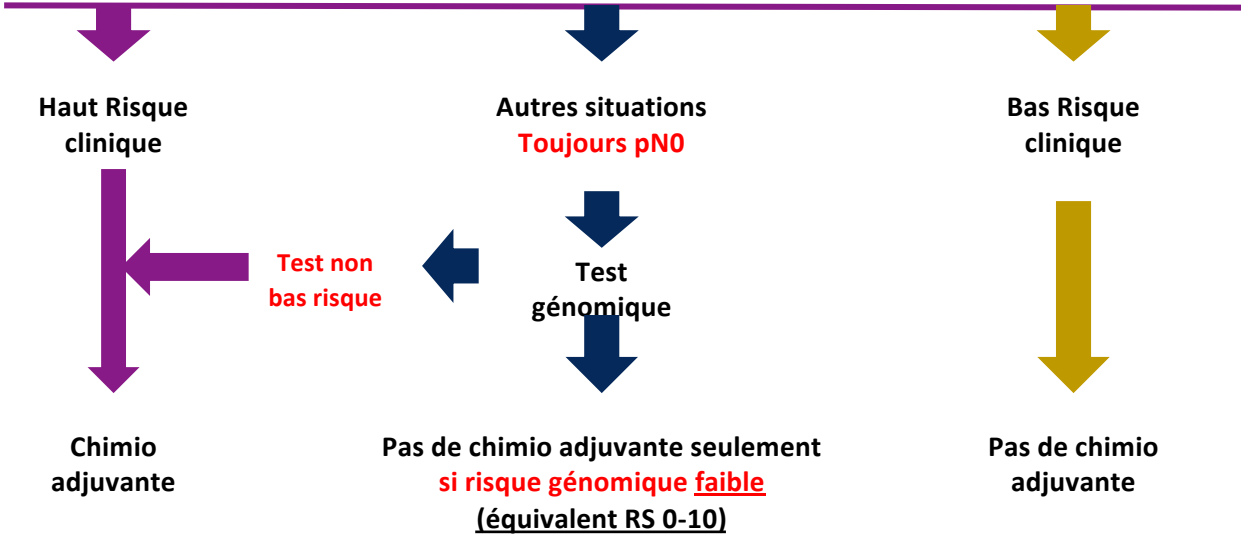
Arbres adjuvant RE+/HER2-

Patiente Ménopausée



Arbres adjuvant RE+/HER2-

Patiente non ménopausée



Au total en phase précoce

- Choix des traitements médicaux adjuvants (chimiothérapie plus ou moins thérapie ciblée anti HER2, hormonothérapie).
- Décision prise en fonction des critères anatomopathologiques et immunohistochimiques
- Référentiels nationaux et internationaux clairs pour les bas et hauts risques cliniques
- **Zone grise : recours aux signatures moléculaires**
- **En cas de haut risque (triple negatif ou RH+)➔ test BRCAg. Si g*BRCA*m éligibilité à olaparib**

Stade métastatique

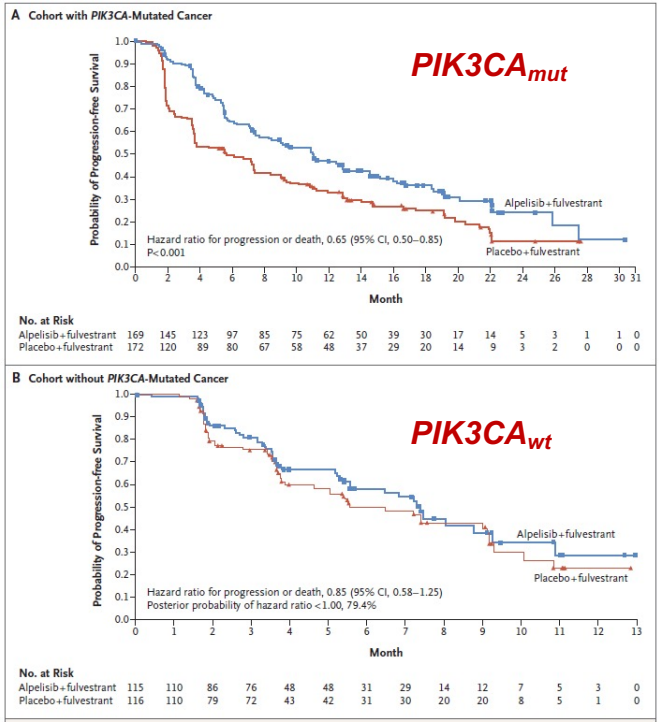
Table 4. List of genomic alterations level I/II/III according to ESCAT in metastatic breast cancer (mBC)

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]

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)

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

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

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

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

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

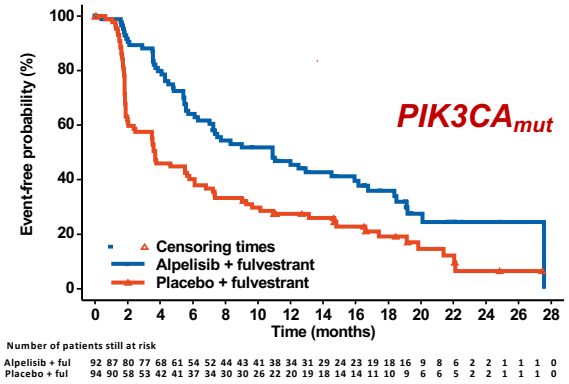
Primary endpoint

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

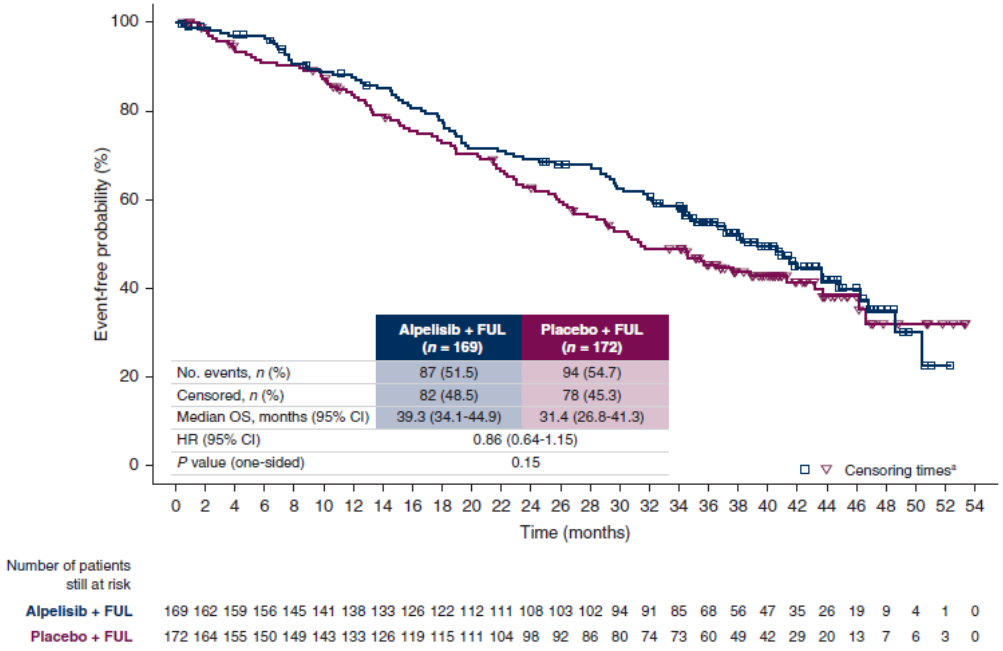
Secondary endpoints include

- 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



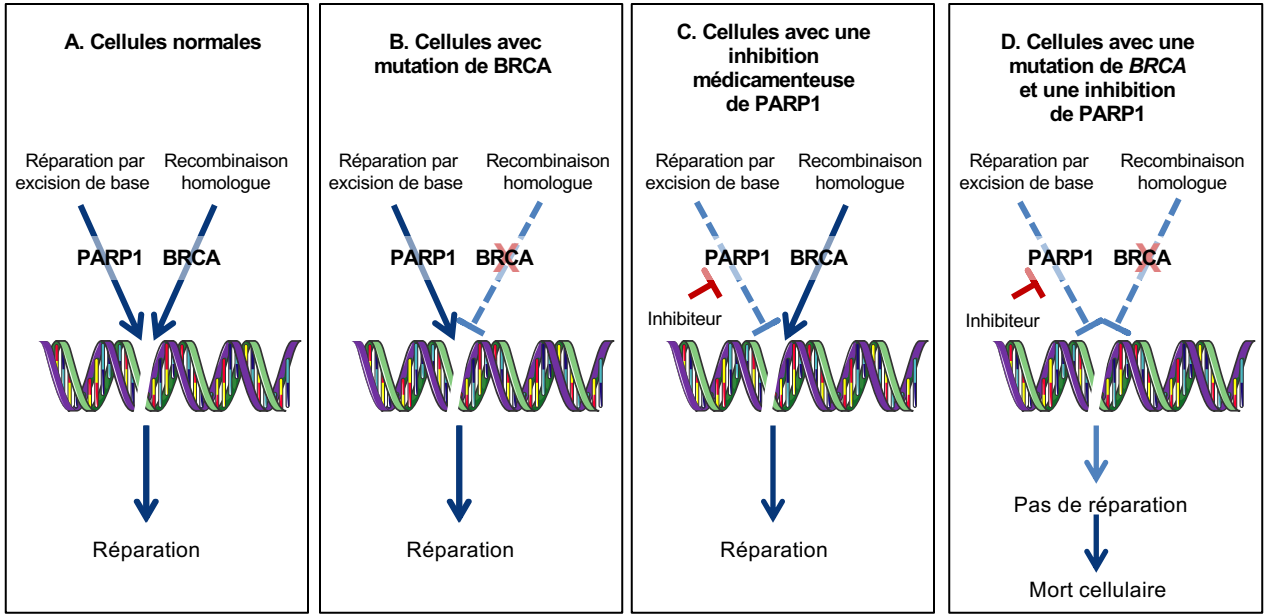
Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2enegative advanced breast cancer: final overall survival results from SOLAR-1



F. André et al. Annals Oncol 2021

Cancers du sein

- **Voie BRCA altérée : concept d'inhibition de PARP et létalité synthétique**



➔ **Chez les patientes avec mutations de BRCA, les inhibiteurs de PARP bloquent les voies de réparation de l'ADN**

Phase III Trial designs

- **HER2- MBC**
- **gBRCAm**
- **Prior anthracycline and taxane**
- **≤ 2 prior CT lines in MBC**
- **ER+ disease progressed on ≥ 1 ET, or not suitable**
- **If prior platinum use:**
  - **No evidence of progression during TT in advanced setting**
  - **≥ 12 months since (neo)adjuvant setting**

Olaparib
300 mg Tablets bd

CT TPC
- Capecitabine
- Eribulin
- Vinorelbine

OlympiAD

- **Patients with locally advanced or metastatic breast cancer**
- **Germline BRCA1 or BRAC2**
- **Prior anthracycline and taxane**
- **≤ 2 prior CT lines in MBC**
- **ER+ disease progressed on ≥ 1 ET**
- **Stratification factors:**
  - **# prior CT regimens (0 or ≥ 1**
  - **TNBC or ER+**
  - **History of CNS mets (Y/N)**

Talazoparib 1mg
PO daily

R
2:1

CT TPC
- Capecitabine
- Eribulin
- Vinorelbine
- Gemcitabine

EMBRACA

OLYMPIAD

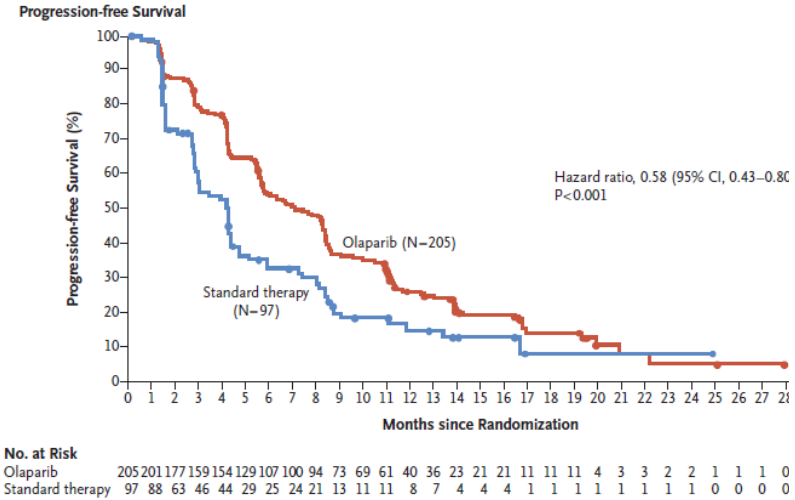
PFS

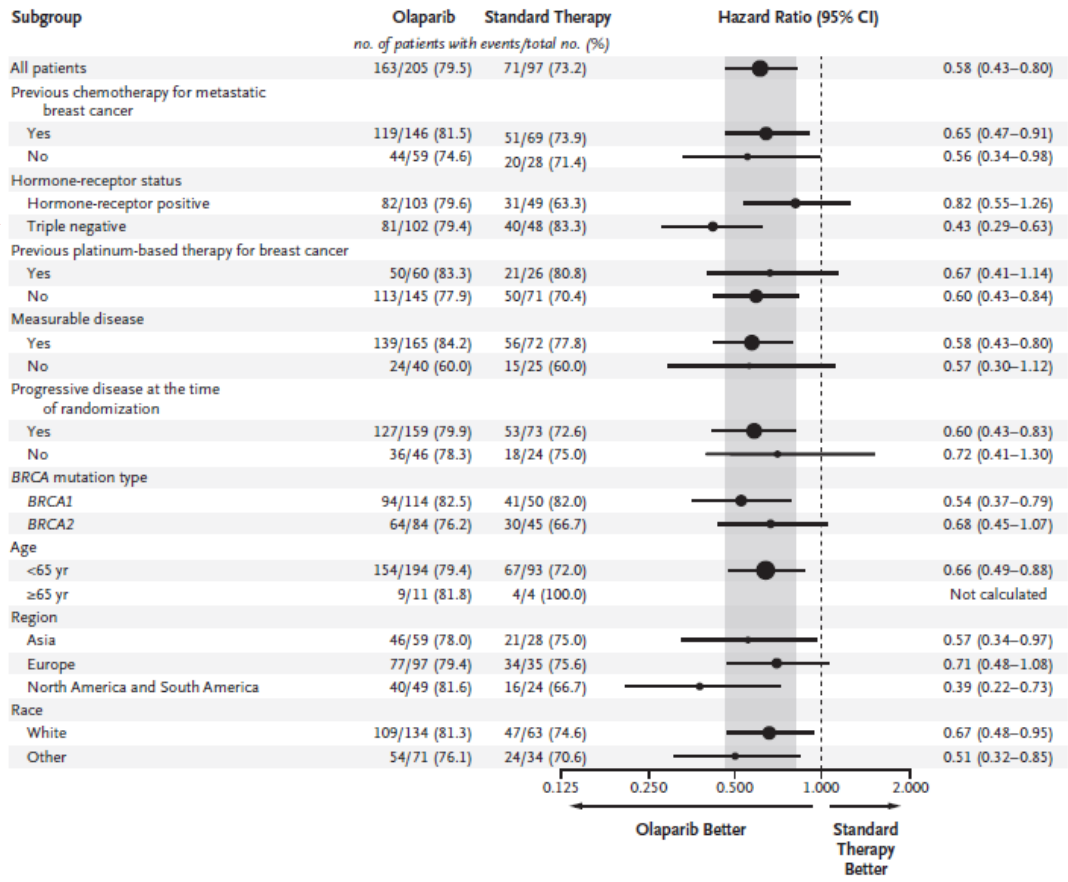
Olaparib 7 months

TPC 4.2 months

HR 0.58 (IC95% 0.43-0.80)

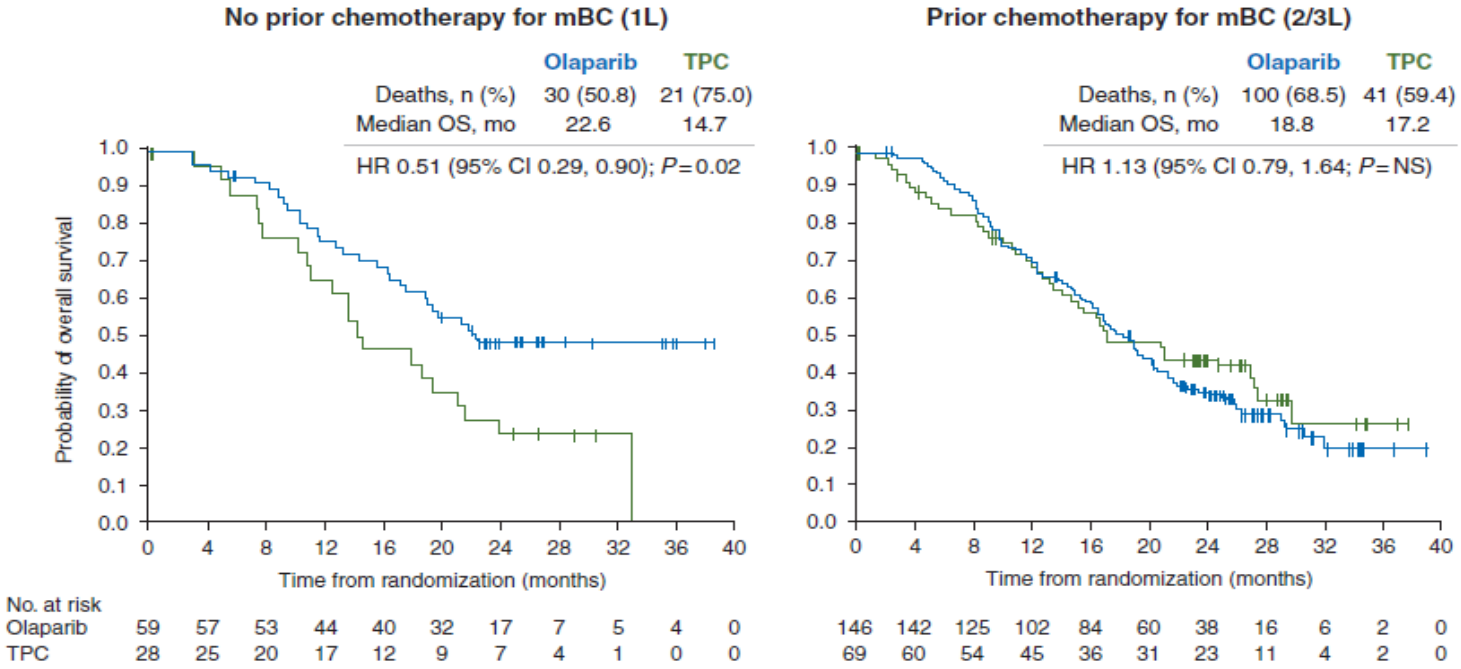
p= 0.0009





Robson M NEJM 2017

OlympiAD: Survie globale et chimiothérapie



Robson, Ann Oncol 2019

EMBRACA

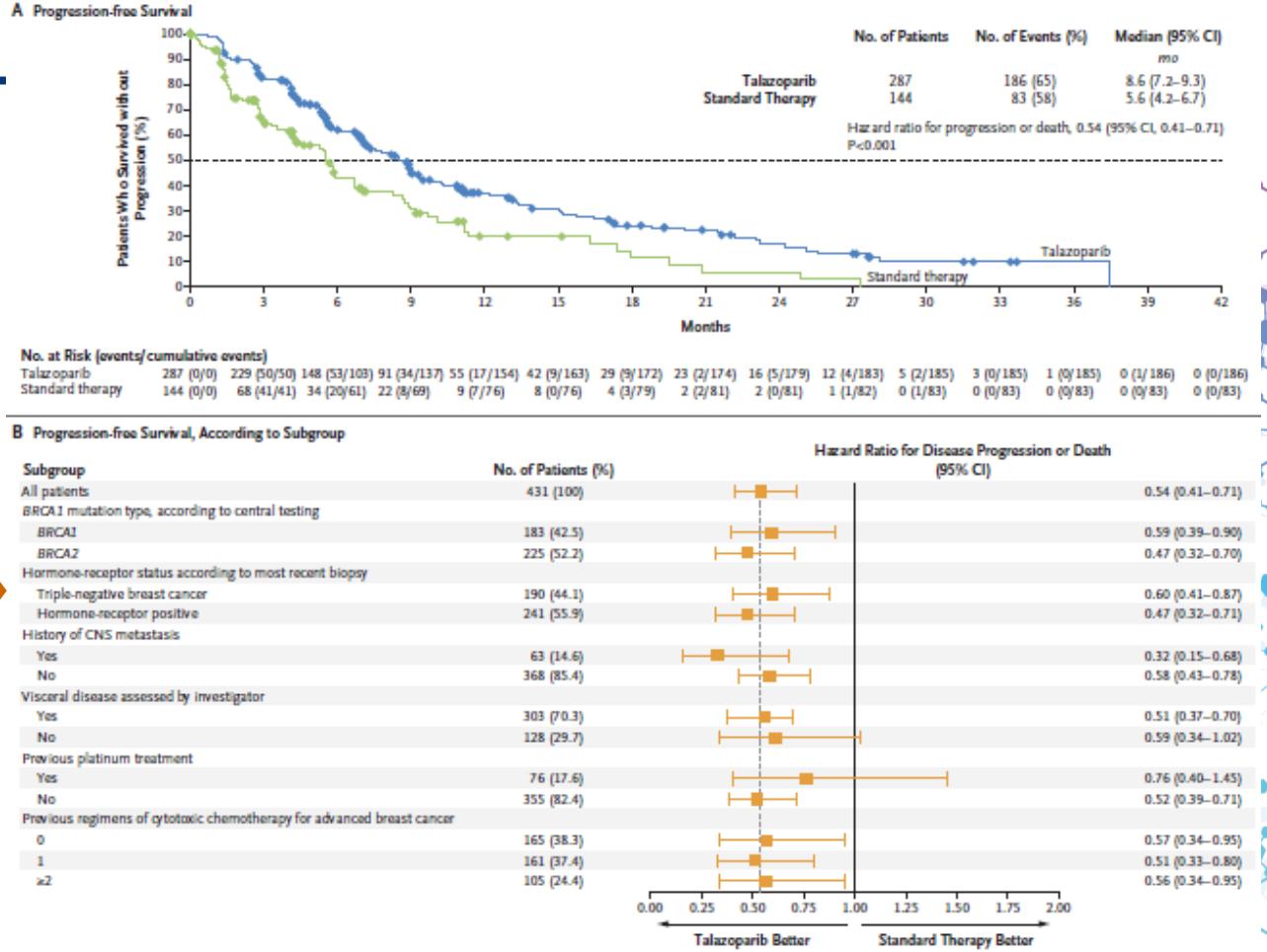
PFS

Talazoparib 8.6 months

TPC 5.6 months

HR 0.54 (0.41-0.71)

P< 0.01



Litton J NEJM 2018

AMM Olaparib

- **04/2019** : **Forme comprimé/ Extension d'AMM** dans le traitement en monothérapie du **« cancer du sein localement avancé ou métastatique HER2-négatif** et présentant une mutation germinale des gènes **BRCA1/2**.
- Les patients doivent avoir été précédemment traités avec une anthracycline et un taxane au stade (néo)adjuvant ou métastatique sauf si les patients n'étaient pas éligibles à ces traitements.
- Les patients présentant des récepteurs hormonaux-positifs doivent également avoir présenté une progression pendant ou après une hormonothérapie antérieure ou être considérés comme non éligible à l'hormonothérapie ».

AMM Talazoparib

- **« TALZENNA est indiqué en monothérapie pour le traitement des patients adultes atteints d'un cancer du sein localement avancé ou métastatique HER2 négatif et présentant des mutations germinales BRCA1/2.**
- **Les patients doivent avoir déjà reçu un traitement (néo)adjuvant par une anthracycline et/ou un taxane pour un cancer localement avancé ou métastatique, sauf s'ils n'étaient pas éligibles à ce type de traitement (voir rubrique 5.1 du RCP).**
- **Les patients atteints d'un cancer du sein positif aux récepteurs hormonaux (RH) doivent préalablement avoir reçu une hormonothérapie ou être considérés comme non-éligibles à une hormonothérapie. »**

BROCADE3 : veliparib

Patient Population

- Advanced HER2-negative breast cancer
- Germline *BRCA1* or *BRCA2* mutation
- ≤2 prior lines cytotoxic therapy for metastatic disease
- ≤1 prior lines of platinum; no progression ≤12 months of completing

Stratification Factors

- Hormone Receptor Expression
- Prior Platinum
- CNS Metastasis

2:1 Randomization
N=513

- Veliparib + Carboplatin/paclitaxel
- Placebo + Carboplatin/paclitaxel

Treat to progression:
If carboplatin and paclitaxel were discontinued prior to progression, dosing of veliparib/placebo increased to 300mg BID continuous, and then 400mg BID if tolerated

Optional open-label crossover to veliparib

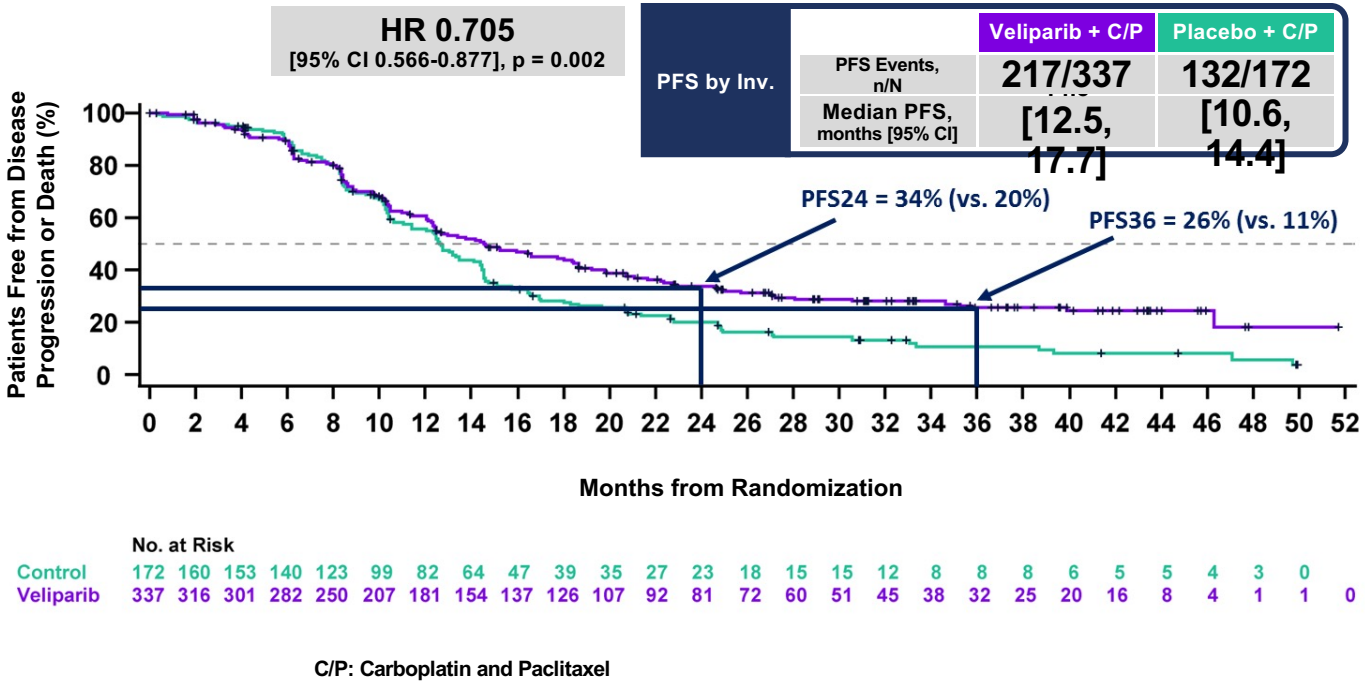
Primary Endpoint:
Investigator-assessed PFS per RECIST 1.1

21-Day Cycles:
- Carboplatin (C): AUC 6 on Day 1
- Paclitaxel (P): 80 mg/m^2 on Days 1, 8, 15
- Veliparib or Placebo: 120mg BID on Days -2 to 5

Diéras et al, Lancet Oncol 2020

BROCADE3 : veliparib

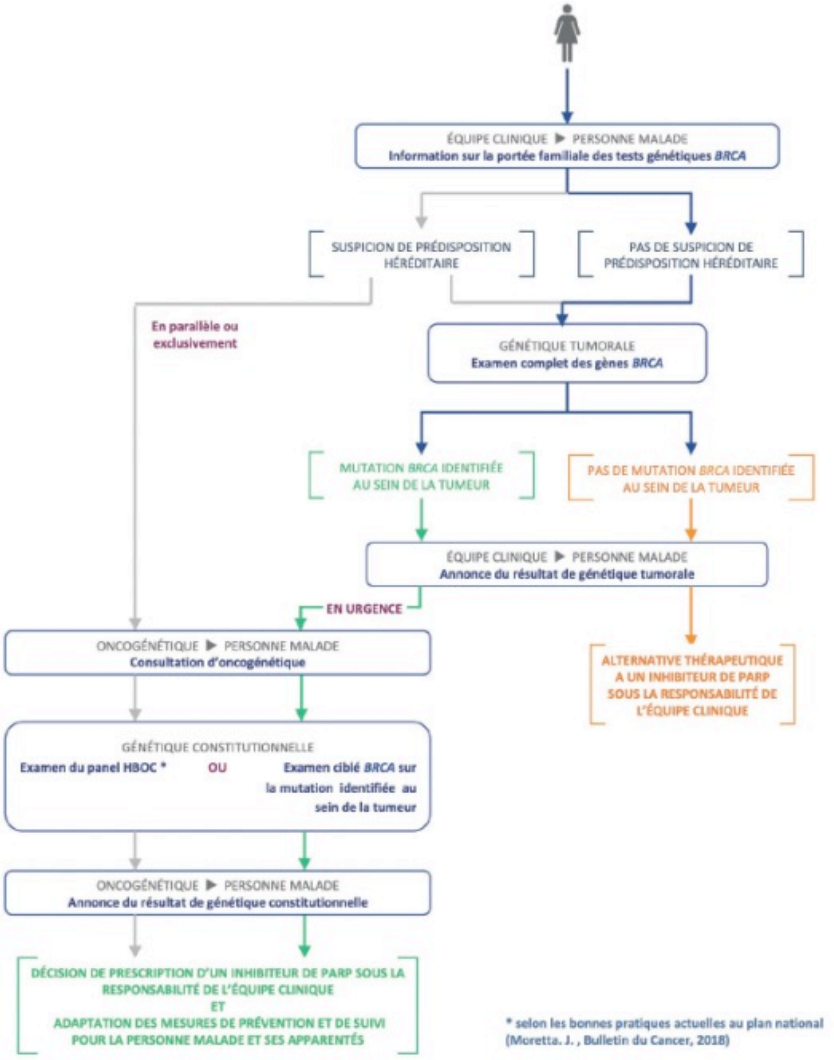
Primary Endpoint: PFS by Investigator Assessment



C/P: Carboplatin and Paclitaxel

Diéras et al, Lancet Oncol 2020

PARCOURS EN GÉNÉTIQUE ONCOLOGIQUE EN VUE D'UNE PRESCRIPTION D'UN INHIBITEUR DE PARP CONDITIONNÉE PAR LA PRÉSENCE D'UNE MUTATION *BRCA* CONSTITUTIONNELLE



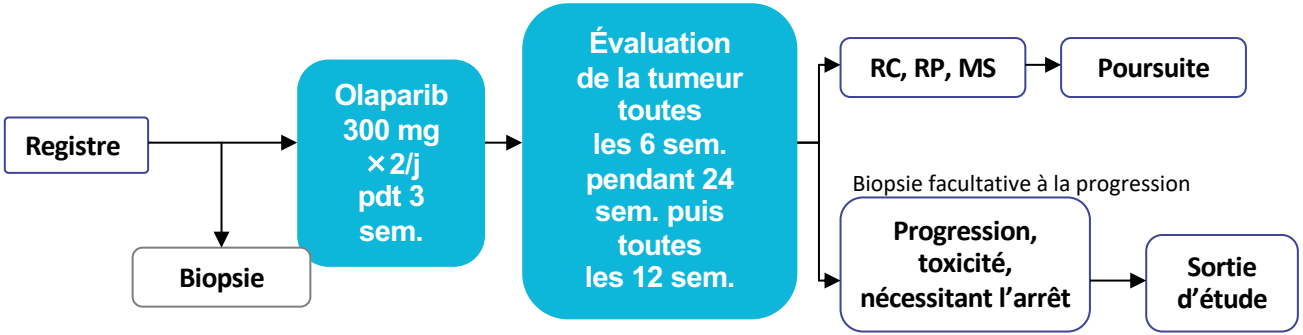
Cancers du sein

Cancer du sein métastatique triple-négatif

Étude TBCRC 048 *(1)*

Phase II, simple bras

Schéma de l'étude



- Cohorte 1 : mutations germinales
- Cohorte 2 : mutations somatiques
  - sBRCA1/2 autorisée si gBRCA négative

ATM, ATR, BAP1, BARD1, BLM, BRIP1 (FANCJ), CHK1 (CHECK1), CHECK2, CDK12, FANCA, FANCC, FANCD2, FANCF, MRE11A, NBN (NBS1), PALB2, RAD50, RAD51C, RAD51D, WRN

RC : réponse complète ; RP : réponse partielle ; MS : maladie stable

Tung N et al., J Clin Oncol. 2020 Dec 20;38(36):4274-4282.

Cancers du sein

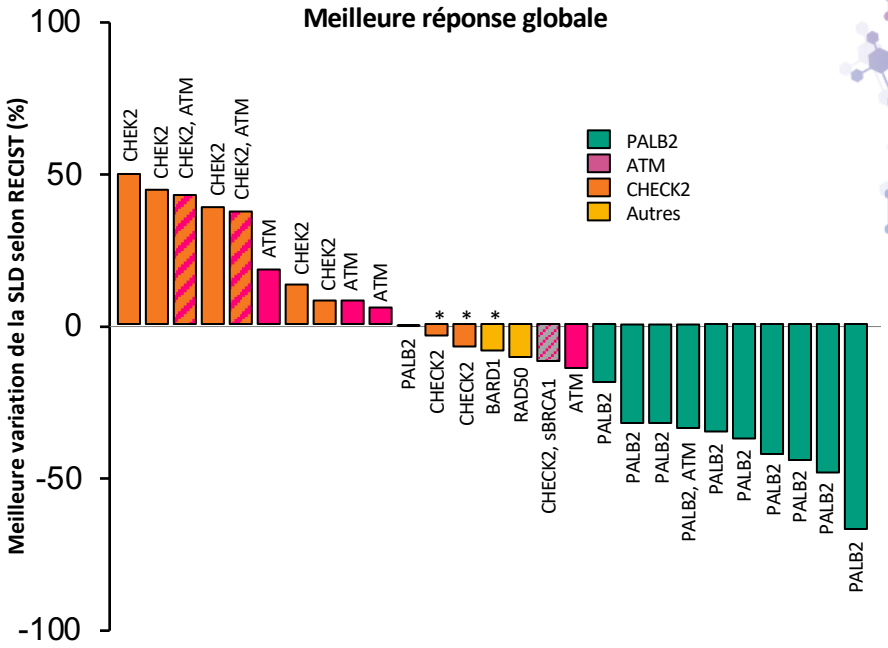
Cancer du sein métastatique triple-négatif

Étude TBCRC 048 *(2)*

Résultats de la cohorte 1 (mutations germinales)

Cohorte 1 (total) (n = 27)	
Meilleure réponse	Taux de réponse (%)
Réponse complète	0 (0 %)
Réponse partielle	9 (33 %)
Maladie stable	8 (30 %)
Progression	10 (37 %)
TRO = 33 % (9/27 ; IC_{90} : 19-51)	
Bénéfice clinique (18 sem.) = 44 % (11/25 ; IC_{90} : 27-62)	

Tous les répondeurs présentaient une mutation PALB2



* Progression due à une croissance de la tumeur ou à une nouvelle métastase

Cut-off : 4 mai 2020

TRO : taux de réponse objective ; SLD : somme des diamètres.

Tung N et al., J Clin Oncol. 2020 Dec 20;38(36):4274-4282.

Cancers du sein

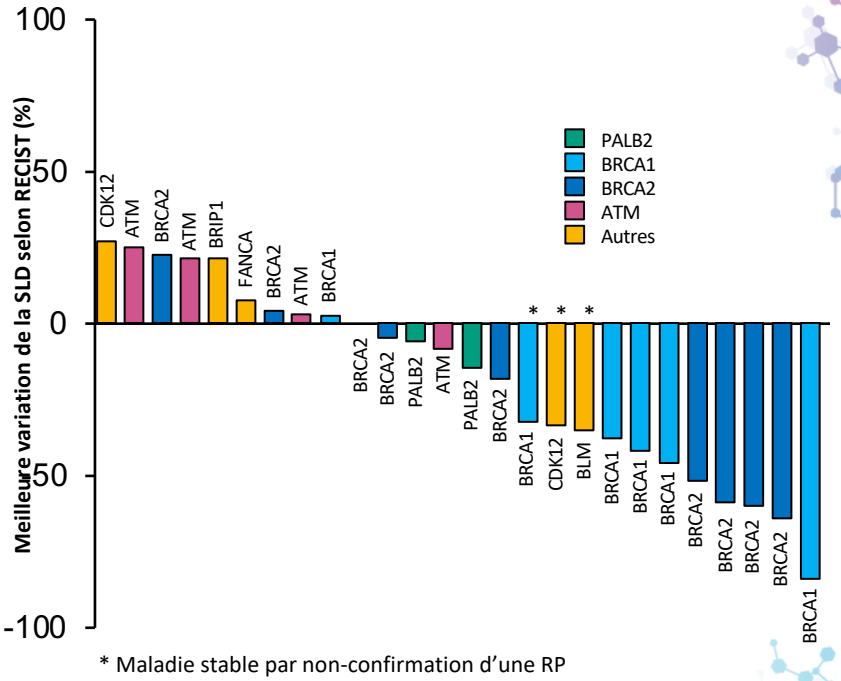
Cancer du sein métastatique triple-négatif

Étude TBCRC 048 *(3)*

Résultats cohorte 2 (mutations somatiques)

Cohorte 2 (total) (n = 26)	
Meilleure réponse	Taux de réponse (%)
Réponse complète	0 (0 %)
Réponse partielle	8 (31%)
Maladie stable	10 (38 %)
Progression	8 (31 %)
TRO = 31 % (8/26 ; IC_{90} : 16-49)	
Bénéfice clinique (18 sem.) = 44 % (11/25 ; IC_{90} : 27-62)	

Toutes les RP confirmées présentaient une mutation BRCA somatique :
4 sBRCA1 et 4 sBRCA2
RP sans confirmation : 1 sBRCA1, 1 CDK12, 1 BLM



* Maladie stable par non-confirmation d'une RP

TRO : taux de réponse ojective ; SLD : somme des diamètres.

Cut-off : 4 mai 2020

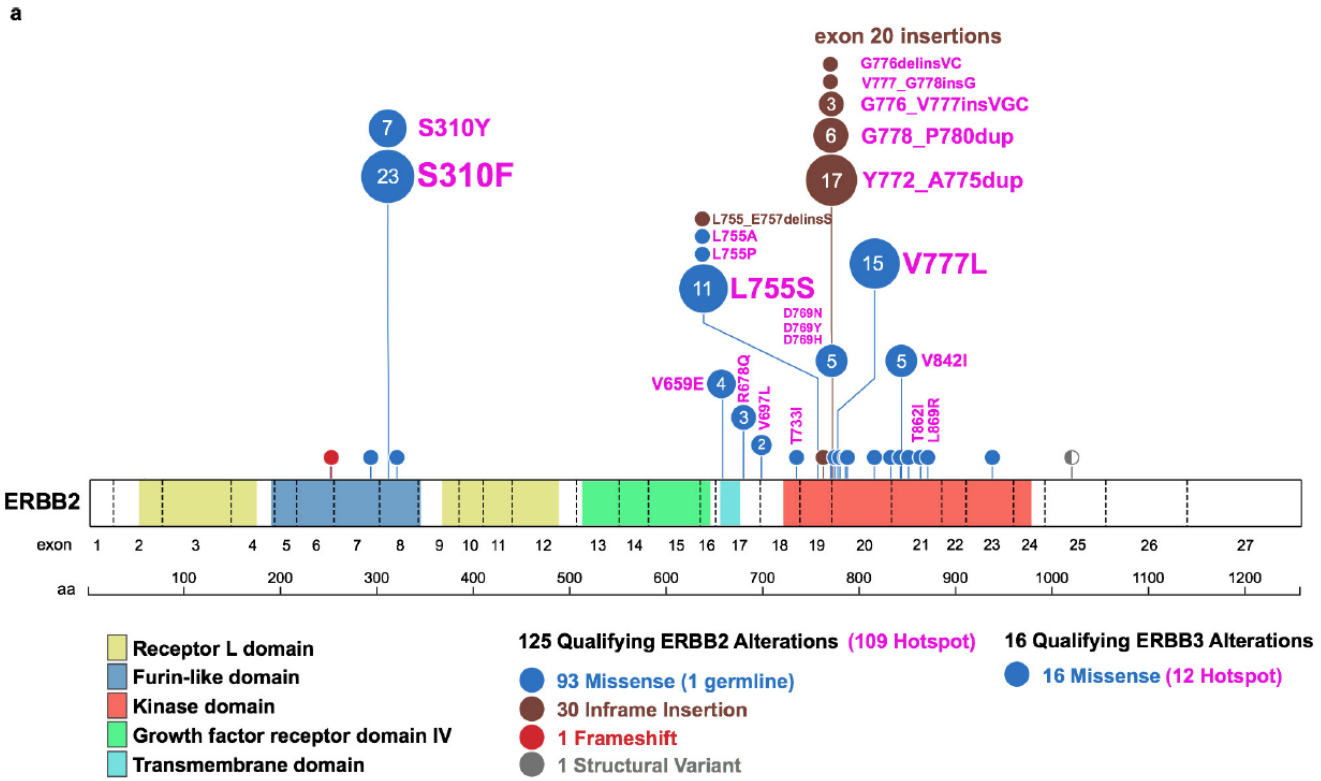
Tung N et al., J Clin Oncol. 2020 Dec 20;38(36):4274-4282.

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

HER kinase inhibition in patients with HER2- and HER3-mutant cancers SUMMIT TRIAL



HER kinase inhibition in patients with HER2- and HER3-mutant cancers
SUMMIT TRIAL

***HER2* or *HER3* mutations (documented by local testing)**

Primary endpoint

- Objective response rate at week 8 (ORR_8)

Secondary endpoints

- ORR (confirmed)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)
- Safety
- Biomarkers

Simon 2-stage design

- If ≥1 response in first evaluable 7 patients, expand cohort to Stage 2 (N=18)
- If ≥4 responses in Stage 2, expand or breakout

Tumor assessments

- RECIST v1.1 (primary criteria)
- PET response criteria (RECIST non-evaluable)

Statistical methods

- ORR_8, ORR, CBR: associated 95% CI
- Median PFS: Kaplan-Meier estimate with 95% CI

→ ***HER2*-mutant tumors**

- Endometrial
- Gastroesophageal
- Ovarian
- Colorectal
- Bladder/urinary tract
- Solid tumors (NOS)
- Breast
- Cervical
- Biliary tract
- Lung

***HER3*-mutant tumors**

- Solid tumors (NOS)

→ **Neratinib 240 mg daily**

PlasmaMATCH

- **ESR1 m 27%**
- **HER2m RH+ 2,7%**
- **AKT1m 4,2%**

- **Objectif principal**
- - Taux de réponse des traitements correspondant aux mutations de l'ADNct
  - Résultats obtenus en
    - 13 jours pour ddPCR
    - 10j pour séquençage

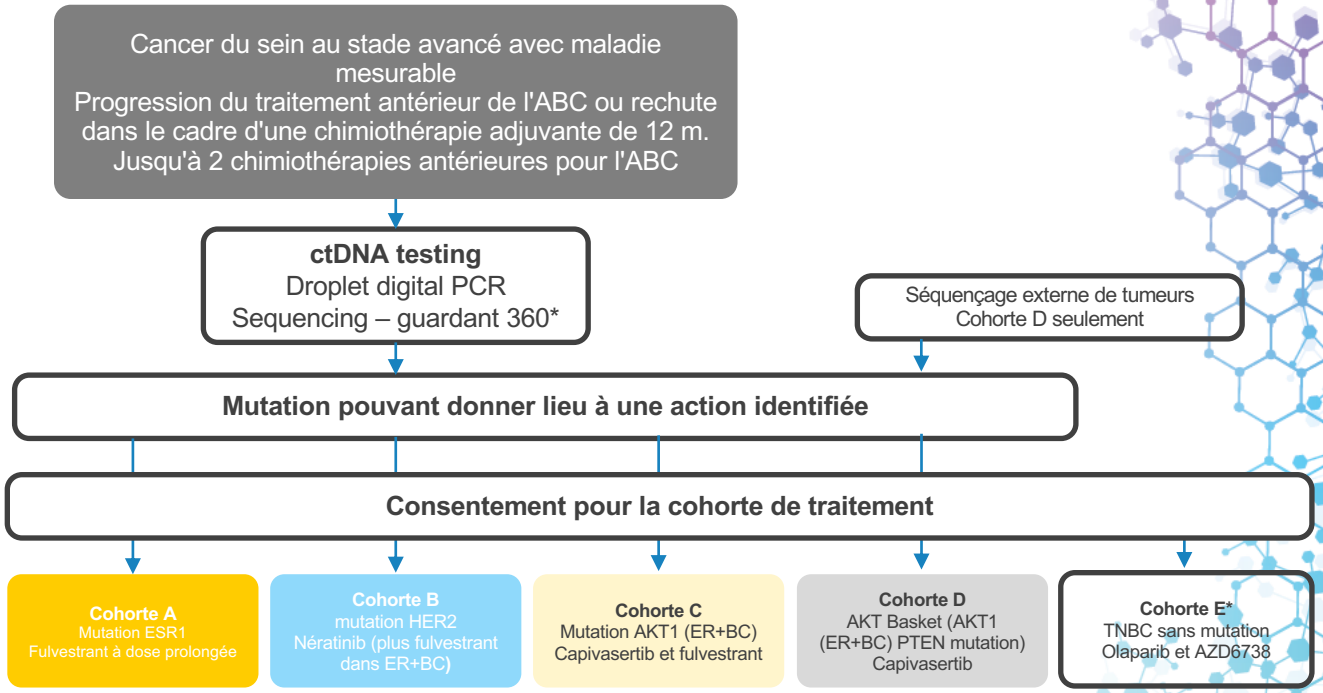
Objectifs secondaires

- Fréquence des mutations ciblées
- Précision du test d'ADNct

Proportion de patients entrant dans une cohorte

- Activité dans les mutations clonales dominantes vs sous-clonales ESR1

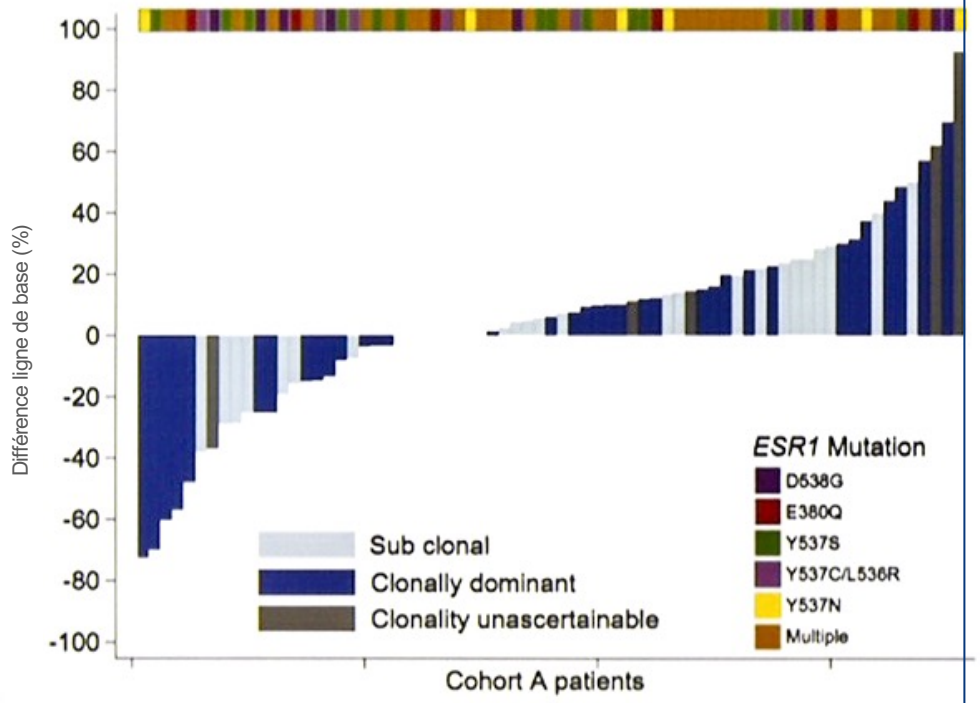
**prospective from part way through recruitment (n=364), retrospective in remaining patients (n=436)*
**cohort E to be reported separately*



Turner N. et al, SABCS 2019 GS3-06 - Kingston B. et al, SABCS 2019 GS3-07

PlasmaMATCH

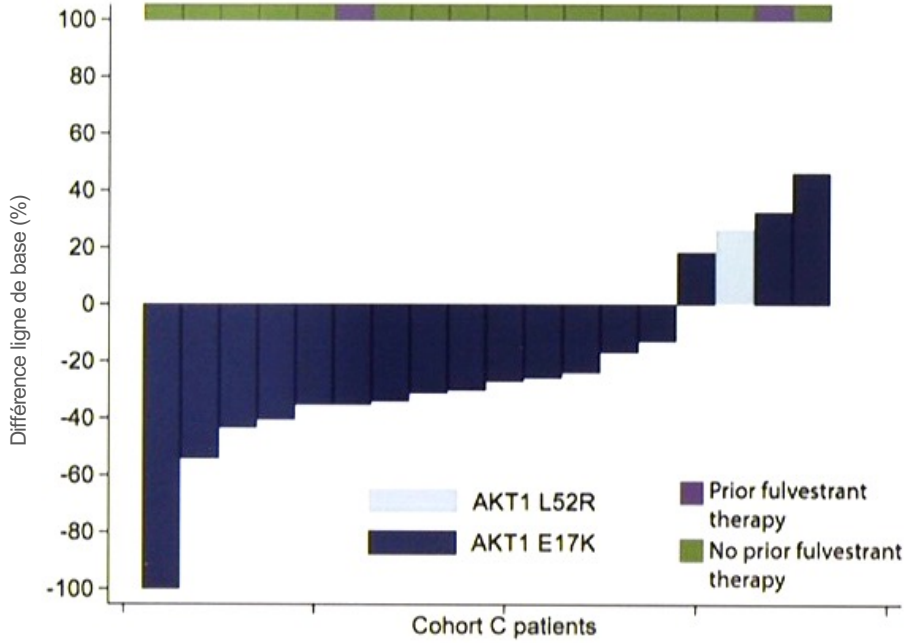
ESR1m (RH+)
avec fulvestrant « dose dense »
(**27%** de la population dont 84 pts incluses)
➔**résultats décevants** et PFS de 2,2 mois



Turner N. et al, Lancet Oncol 2020

PlasmaMATCH

Capivasertib + fulvestrant
en cas de mutations *AKT1 (RH+)* ctDNA
RR 25%, DFS 10,2 mois



Turner N. et al, SABCS 2019 GS3-06

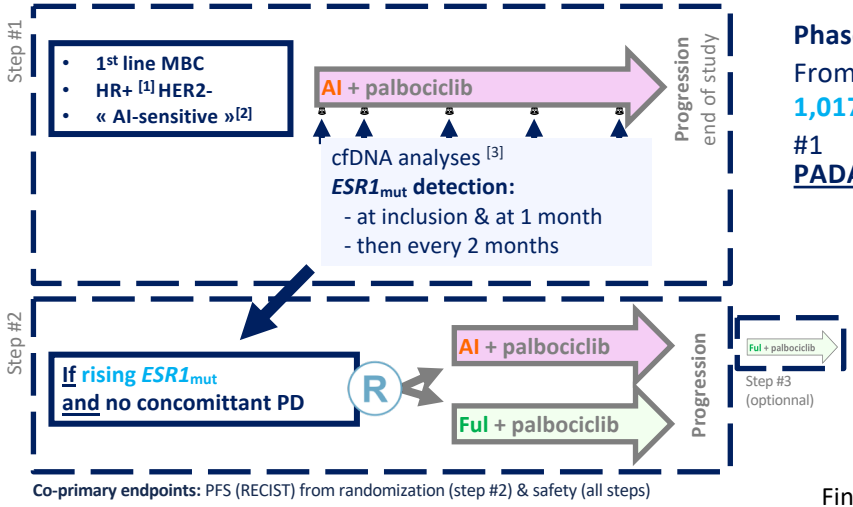
PlasmaMATCH

- **Au total**
  - Absence d'efficacité de la stratégie fulvestrant « haute dose » chez les pates ESR1m
  - Chez des patientes lourdement prétaitées (65%>2L), en particulier RH+ (64%) , la recherche systématique par biopsie liquide des mutations rares *HER2* et *AKT1* permet de faire bénéficier aux patientes de thérapies ciblées efficaces, comme le nératinib et le capivasertinib.
  - Cette stratégie est techniquement possible sans trop délai de prise en charge (~10-13j max)
  - Elle permet de mettre en evidence des anomalies rares

PlasmaMATCH

Turner N. et al, SABCS 2019 GS3-06

Study design: PAlbociclib & ctDNA for *ESR1*$_{mut}$ detection (PADA-1)



Co-primary endpoints: PFS (RECIST) from randomization (step #2) & safety (all steps)

Phase 3

From 04.2017 to 01.2019

1,017 patients included in step #1

PADA-1 analysis is ongoing

N= 170 randomizations in step #2

Rising *ESR1mut* detected before progression;

Final results will be presented at San Antonio meeting December 2021 (SABCS)

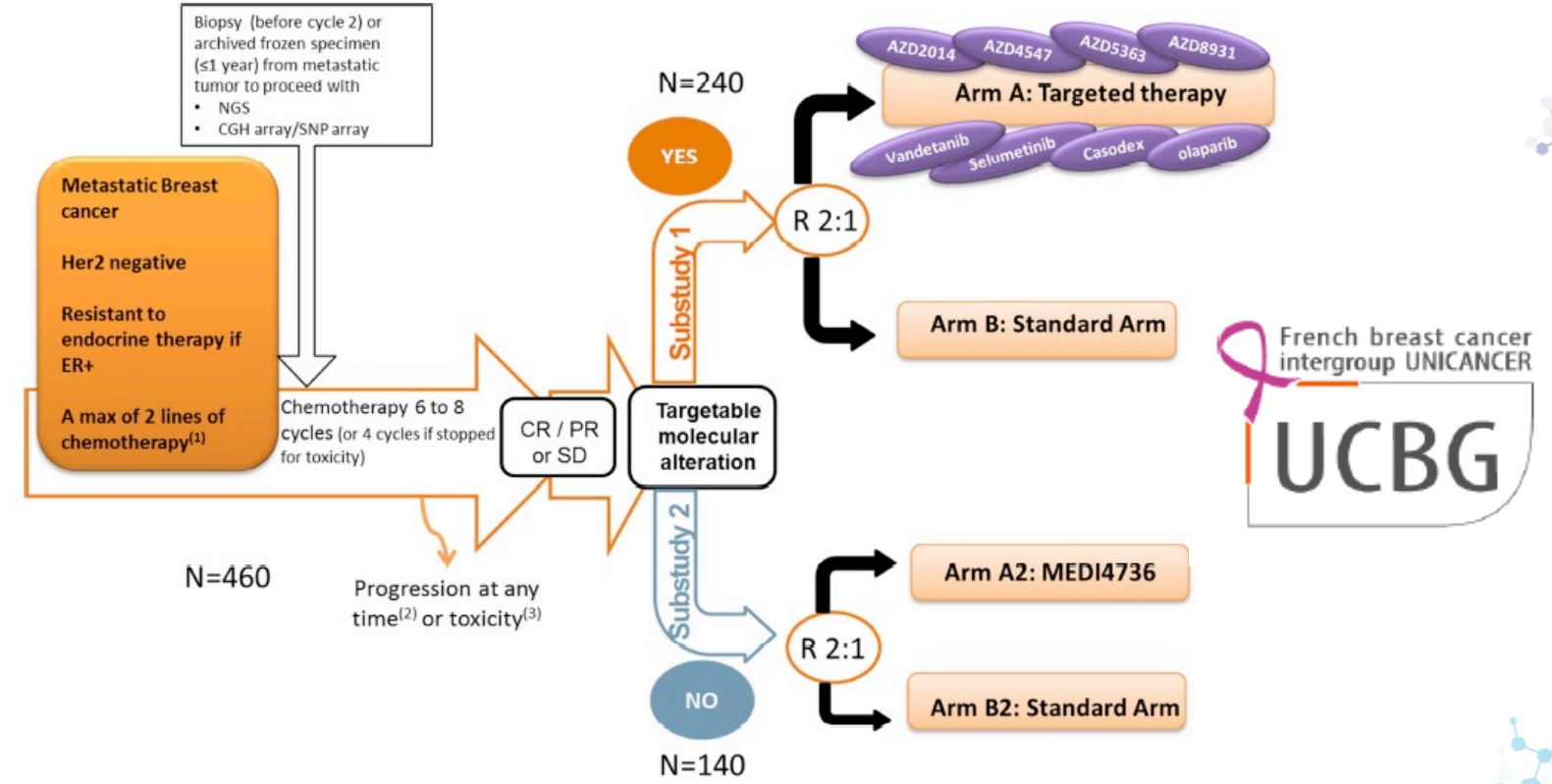
[1] ER and/or PR ≥ 10%

[2] "AI-sensitive": no prior AI or DFI>12 months from adjuvant AI completion

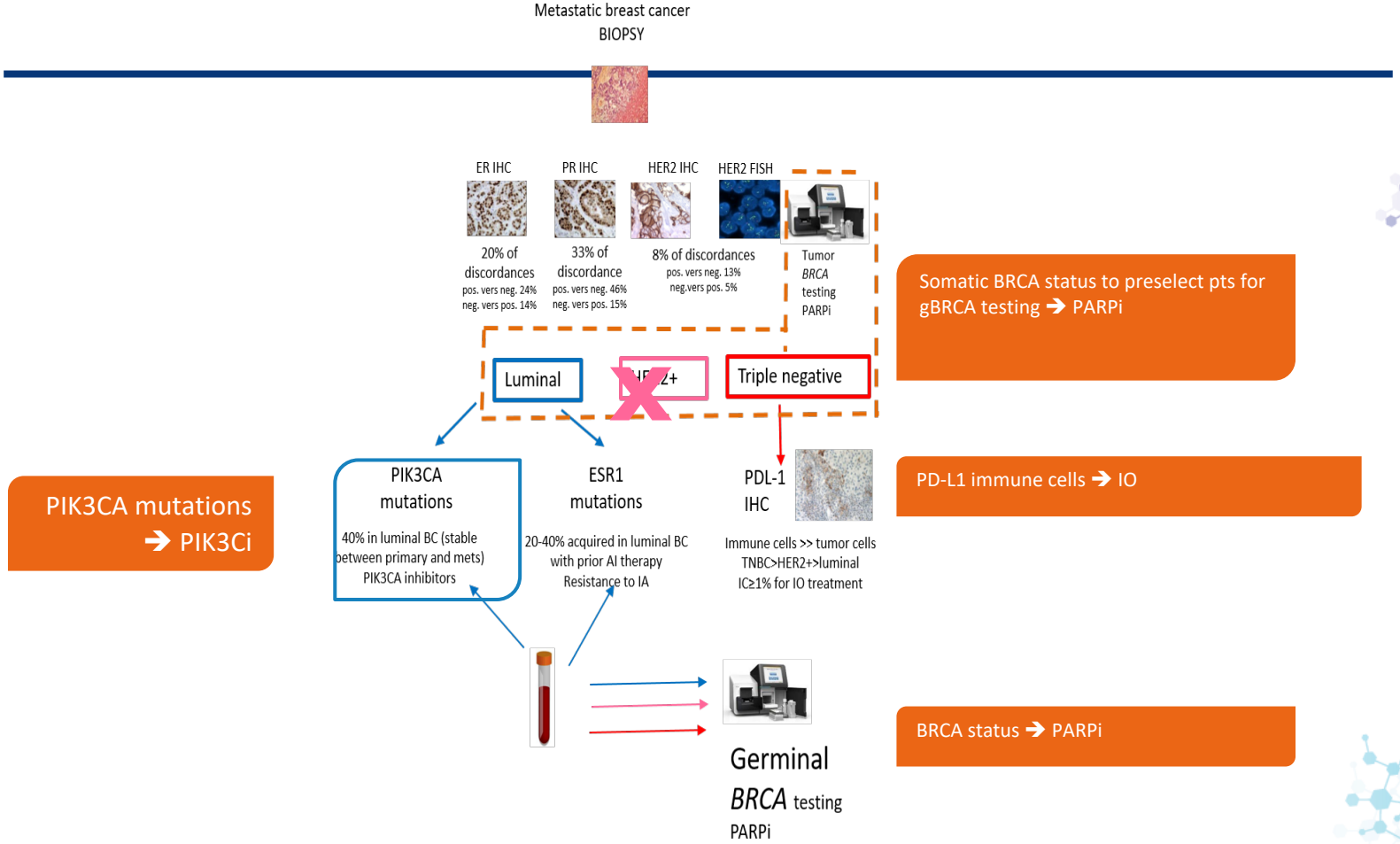
[3] centralized ddPCR assay cfcDNA from 4 mL of plasma (Jeannot, Oncogene 2020)

Francois-Clement BIDARD, MD PhD; fcbidard@curie.fr

Étude SAFIR02

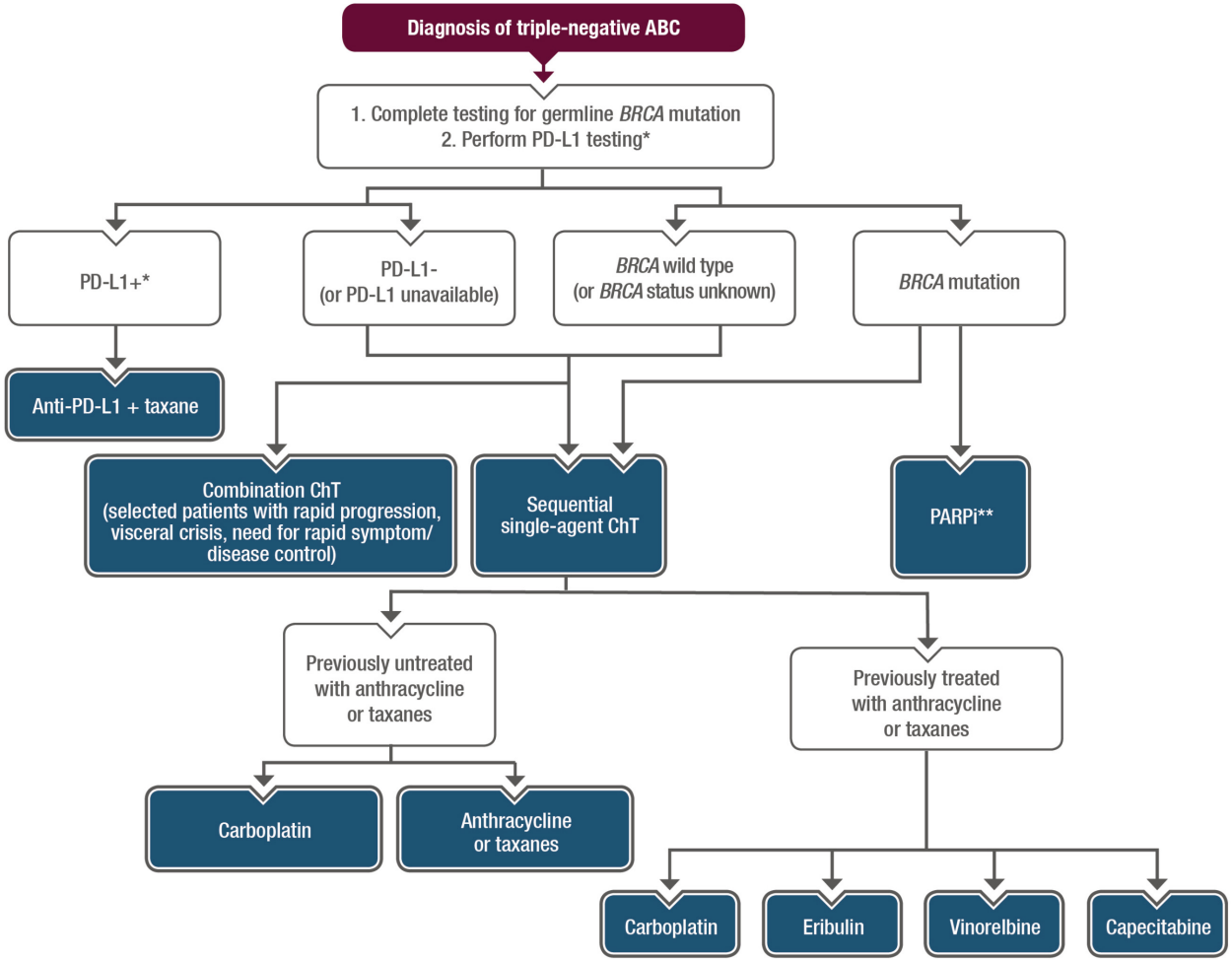


Current biomarkers in metastatic breast cancer



CLINICAL PRACTICE GUIDELINES

Treatment of triple-negative ABC



Include in clinical trials when available

For ESMO-MCBS scores, please refer to the manuscript and **www.esmo.org/Guidelines/ESMO-MCBS**

*Refer to relevant guidelines for PD-L1 testing

**If PARPi unavailable, preference should be given to a platinum agent

ESMO

Conclusions

- **Indication en situation adjuvante ou post néoadjuvante**
  - **BRCA :Olympia 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 (AMM restrictive non remboursé)**
  - **Programme de screening systématique pour tout cancer du sein métastatique**
    - **Recherche (RCP Moléculaire, SHIVA 02, MOST, SAFIR2)**

MERCI DE VOTRE ATTENTION