Antoine Lacassagne
CENTRE DE LUTTE CONTRE LE CANCER DE NICE

CHANGEMENTS DE PARADIGMES DANS LES CANCERS DU SEIN A HAUT RISQUE

Pr Jean-Marc FERRERO

Définition du haut risque

Risque de récidive à distance à 5 ans

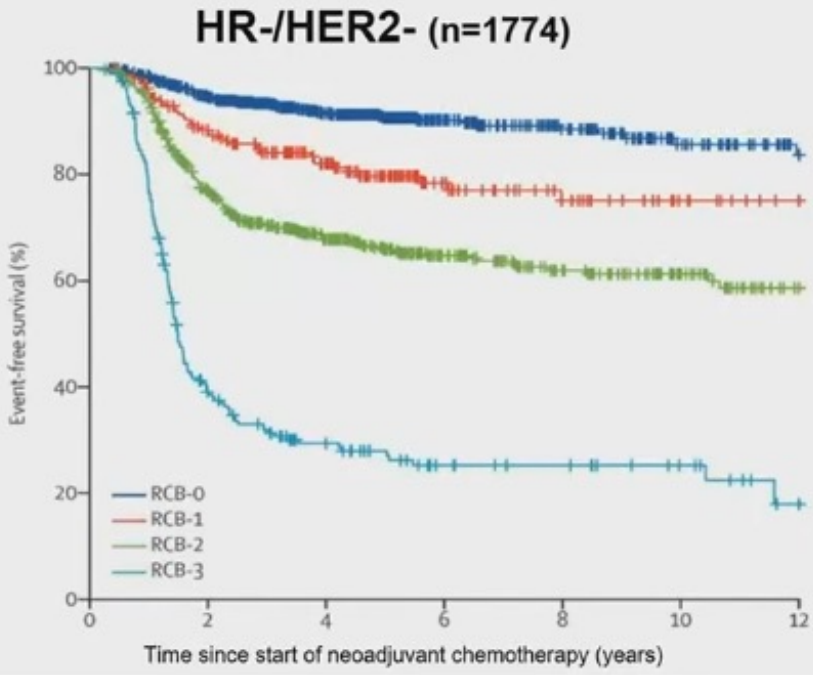
- < 10 % faible risque
- ≥ 10 % et < 20%: risque intermédiaire
- > 20 % : haut risque

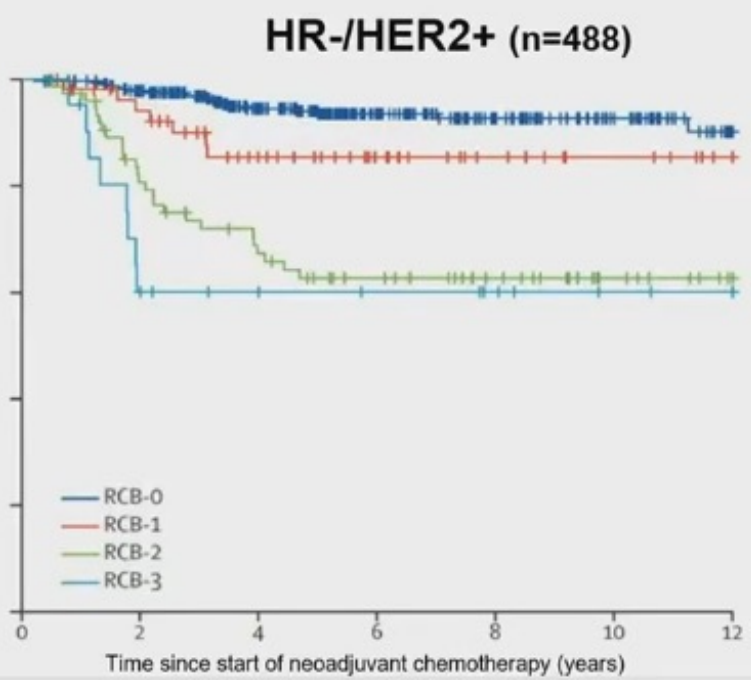
Antoine Lacassagne
CENTRE DE LUTTE CONTRE LE CANCER DE NICE

Cancer du sein à haut risque de rechute

- **Résidu tumoral après CTNA (TN et HER2 +)**
- **RH+ avec plus de 4 N+ ou 1 à 3 N+ et FdR**

Why give neoadjuvant vs. adjuvant treatment?





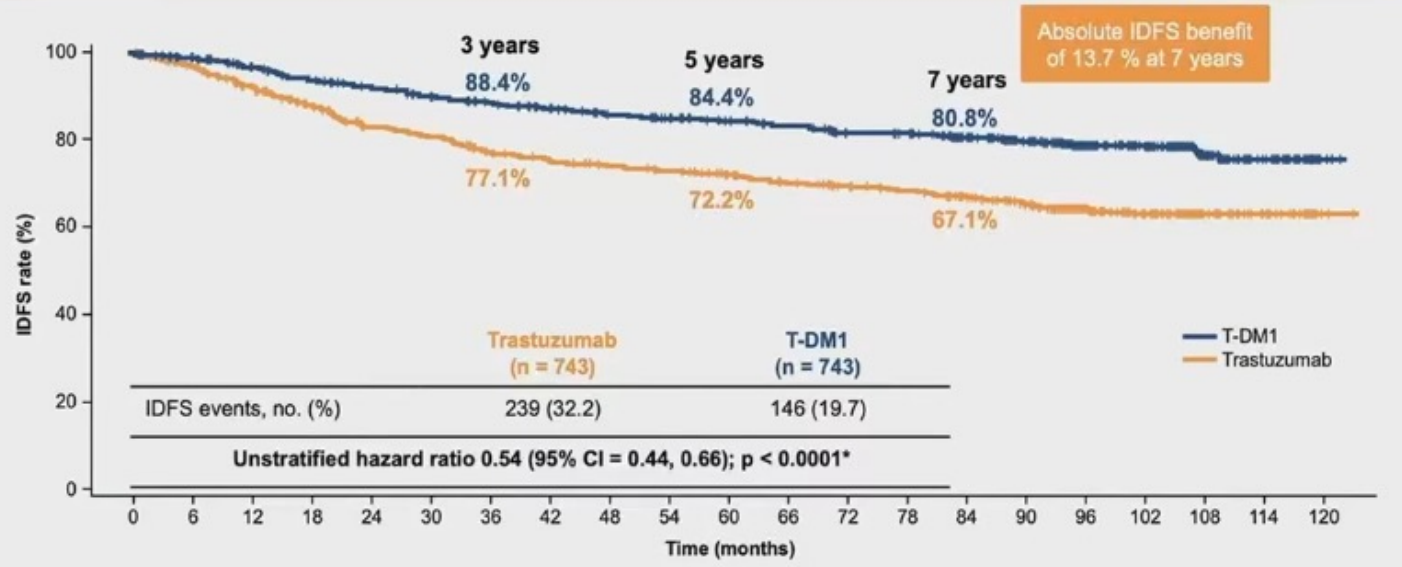
Yau et al. *Lancet Onc*. 2022

Comment améliorer le pronostic en cas de maladie résiduelle après CTNA ?

HER2 +

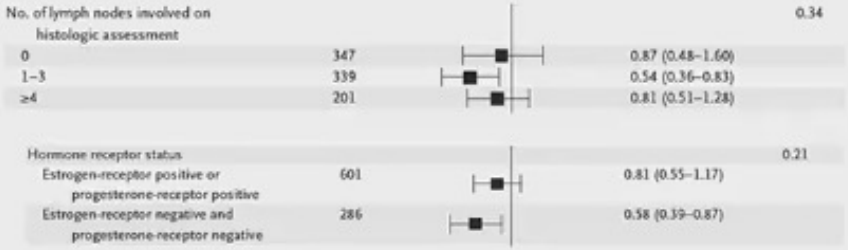
Tailored Adjuvant Therapy Improves Outcomes

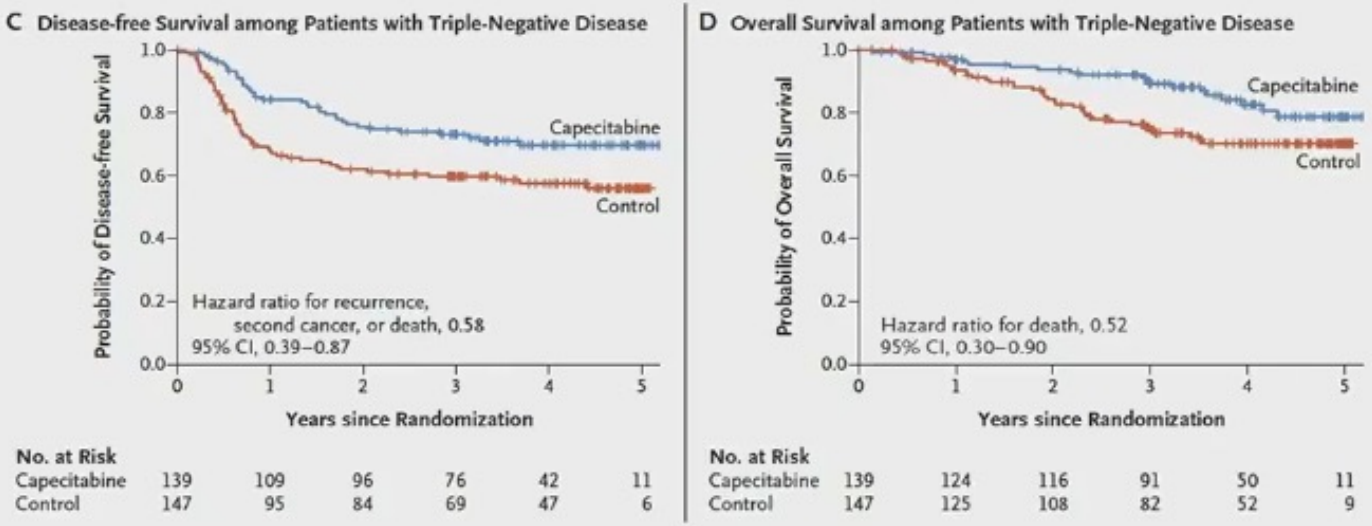
KATHERINE IDFS final analysis; median follow-up 8.4 years (101 months)



Loibl et al.
SABCS 2023

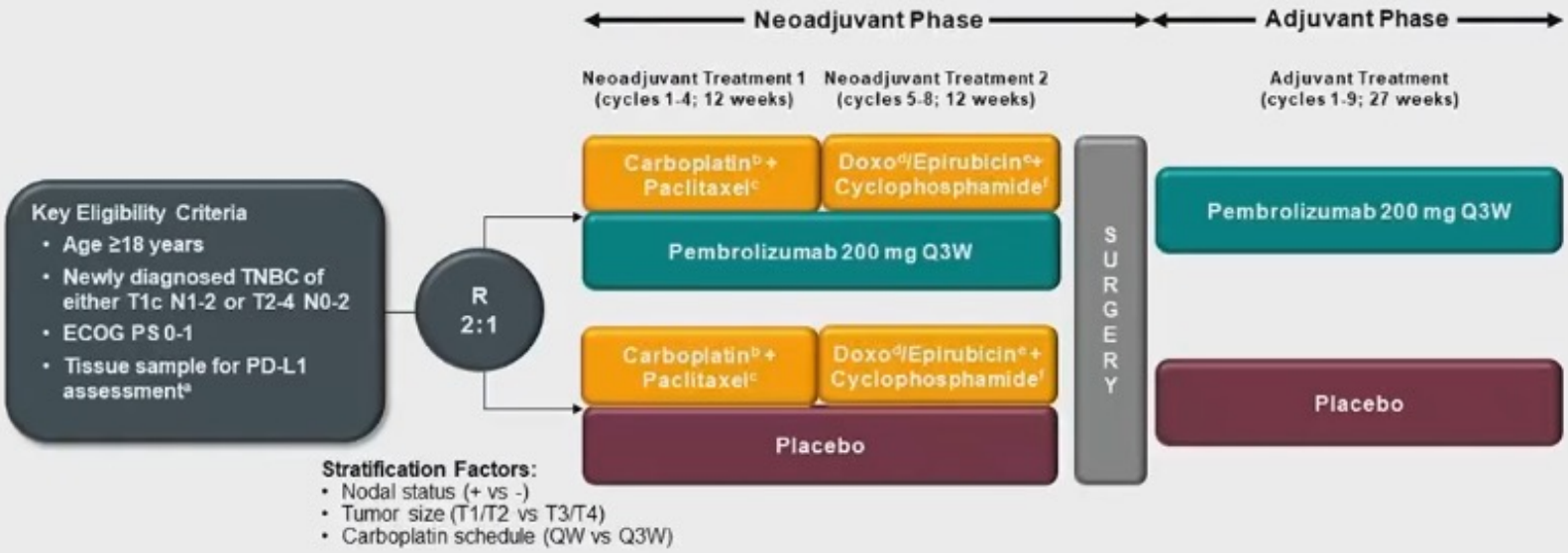
Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy





Masuda et al. N Engl J Med. 2017

KEYNOTE-522 Study Design (NCT03036488)

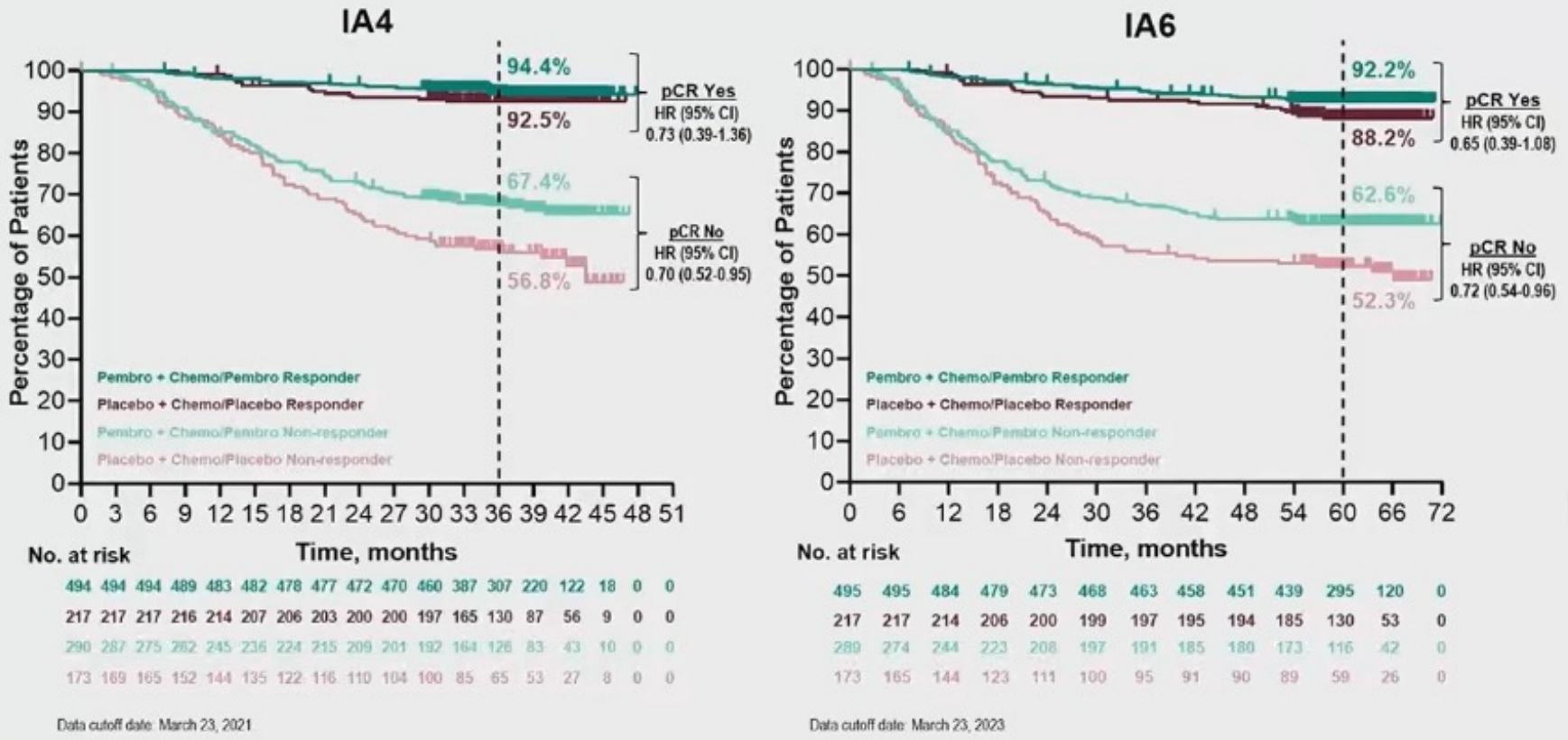


Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

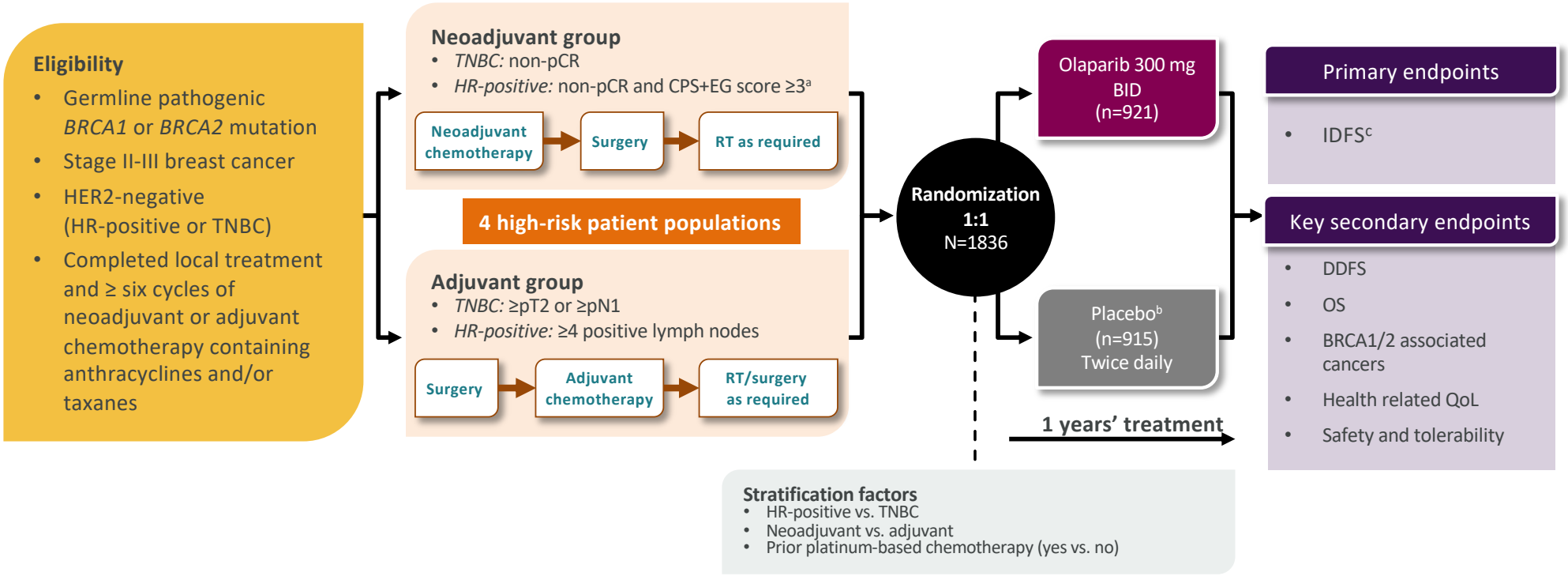
Schmid et al. N Engl J Med 2020

KEYNOTE-522 (Phase 3): Efficacy – EFS by pCR (ypT0Tis ypN0)



Schmid P, et al. ESMO 2023. Abstract LBA18

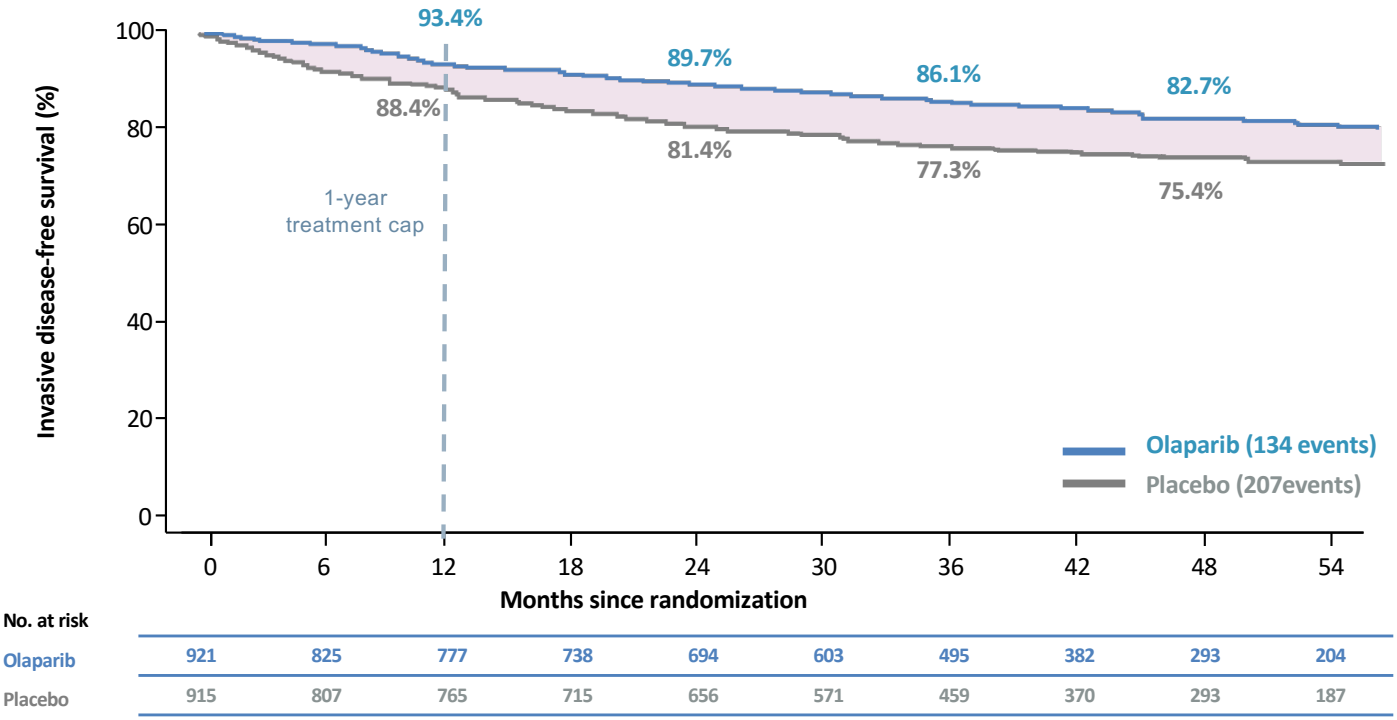
OlympiA: phase III study of olaparib versus placebo as adjuvant treatment for high risk gBRCA-mutated, HER2-negative BC



[a] CPS+EG score incorporates pretreatment clinical stage, oestrogen receptor status, nuclear grade and pathological stage after neoadjuvant chemotherapy
[b] Data to support adjuvant capecitabine was not available when the OlympiA study was initiated in 2014
[c] by STEEP system[2]
1. NEJM OlympiA; 2.Hudis CA. J Clin Oncol 2007;25:2127–32

Essai OlympiA

Survie sans maladie invasive



No. at risk										
Olaparib	921	825	777	738	694	603	495	382	293	204
Placebo	915	807	765	715	656	571	459	370	293	187

IDFS at DCO2‡

HR 0.63
95% CI 0.50–0.78

4-year IDFS rate

Olaparib (n=921) **82.7%**

Placebo (n=915) **75.4%**

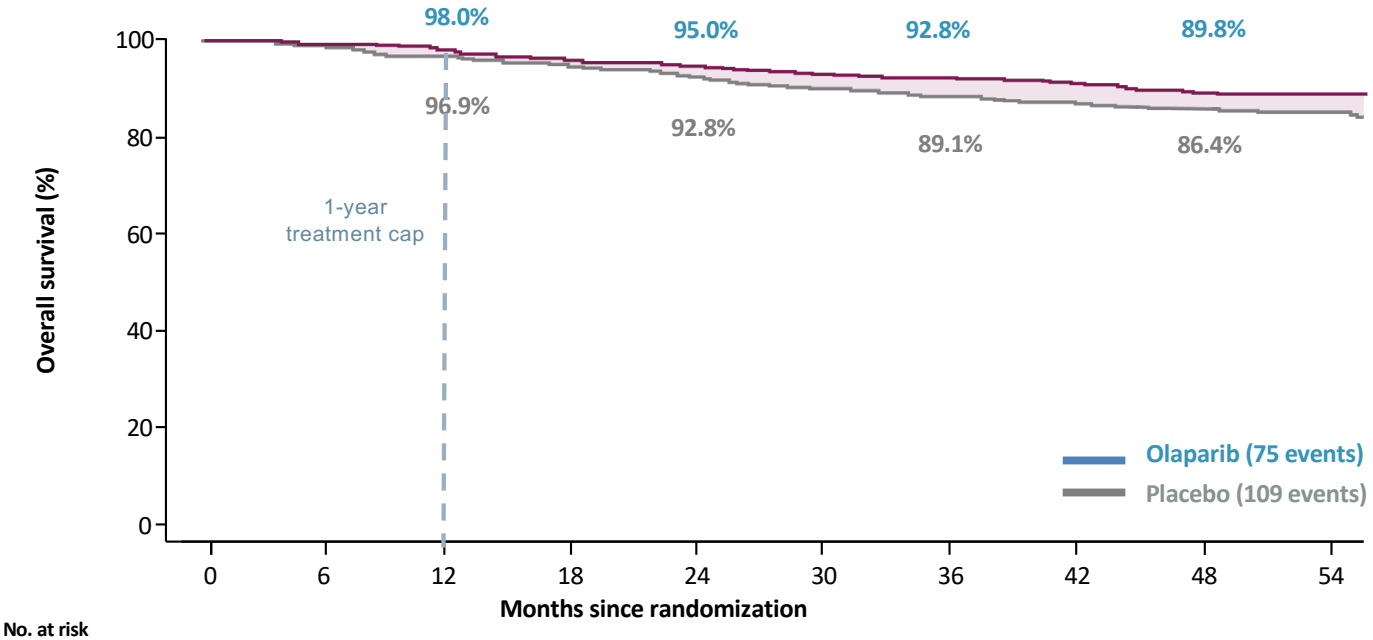
Difference 7.3%
95% CI 3.0–11.5

ǂIDFS analysis is descriptive at OS IA2; ‡DCO2 12 July 2021 (at 330 IDFS events, 25% data maturity)

Tutt J, Garber J, Gelber R, et al. Pre-specified event driven analysis of Overall Survival in the OlympiA Phase III trial of adjuvant olaparib in germline BRCA1/2 mutation associated breast cancer. [Presentation]. Presented at ESMO Virtual Plenary; March 16-18, 2022.

Essai OlympiA

Survie globale



No. at risk										
Olaparib	921	862	844	809	773	672	560	437	335	228
Placebo	915	868	843	808	752	647	530	423	333	218

OS at DCO2

HR 0.68†
98.5% CI 0.47–0.97
p=0.009

4-year OS rate

Olaparib (n=921) **89.8%**

Placebo (n=915) **86.4%**

Difference 3.4%
95% CI -0.1–6.8

*Data from the pre-specified second interim analysis of OS (at ~330 IDFS events); cut-off date July 2021 (DCO2), data maturity 9%; †Non-proportional hazards; 98.5% CI is shown for the HR for OS because p<0.015 is required to indicate statistical significance for this endpoint

1. Tutt A, Garber J, Gelber R, et al. Pre-specified event driven analysis of Overall Survival in the OlympiA Phase III trial of adjuvant olaparib in germline BRCA1/2 mutation associated breast cancer. [Presentation]. Presented at ESMO Virtual Plenary; March 16-18, 2022 2. In House Data, AstraZeneca. Data on file SD-2020-ALL-0088

PARPi et sein adjuvant : en Pratique

- **INDICATIONS**
- Mutation germinale de BRCA 1 ou 2
- Et traitées par chimiothérapie adjuvante ou néoadjuvante
- Et
  - triple négatif : et N+ ou T> 2cm ou avec résidu invasif post CNA
  - RH+ HER2 négatif : ≥4N+ ou résidu invasif post CNA

- **TRAITEMENT**
- Olaparib 300mg x2/jour pendant 1 an
- En association à l'hormonothérapie si RH positifs
- A débuter entre 2 et 12 semaines après la radiothérapie

NEJM OlympiA; Hudis CA. J Clin Oncol 2007;25:2127–32
HAS, 2023

CDK4/6 Inhibiteurs en adjuvant : les études

	PALLAS[1,2]	PENELOPE-B[3,4]	monarchE[5,6]	NATALEE[7,8]
N	5796	1250	5637	5101
Sex	Men and women	Women	Men and women	Men and women
Menopausal status	Pre- and postmenopausal	Pre- and postmenopausal	Pre- and postmenopausal	Pre- and postmenopausal
Disease severity	• Stage II • Stage III • N0, N1, N2, N3	• Residual invasive disease after neoadjuvant therapy ≥16 weeks (including 6 weeks of taxane) • CPS-EG ≥3 or score 2 if ypN+ • N0, N1, N2, N3	• Cohort 1: ≥4 ALN or 1-3 ALN + tumor size ≥5 cm and/or grade 3 • Cohort 2: 1-3 ALN + Ki-67 ≥20%	• Stage III (N0 and N1) • Stage IIB and IIA N1 • Stage IIA N0 G3 or N0 G2 with Ki-67 ≥20% or high risk by genetic test • Stage II pts capped at 40% of enrollment
CDK4/6i, dose	PAL 125 mg QD* (3 weeks on/1 week off)	PAL 125 mg QD * (3 weeks on/1 week off)	ABE 150 mg BID	RIB 400 mg QD * (3 weeks on/1 week off)
ET partner	AI or TAM ± LHRH agonist	Standard adjuvant ET	Standard adjuvant ET (eg, AI, TAM, LHRH agonist)	LET or ANA
Duration of CDK4/6i therapy	2 years	~13 months	Up to 2 years	3 years

References: 1. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT02513394. Accessed March 15, 2022; 2. Mayer E, et al. *Lancet Oncol*. 2021;22:212-222. 3. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT01864746. Accessed March 15, 2022; 4. Loibl S, et al. *J Clin Oncol*. 2021;39:1518-1530; 5. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03155997. Accessed March 15, 2022; 6. Johnston S, et al. J Clin Oncol. 2020;38:3987-3998. 7. Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed March 15, 2022; 8. Slamon D, et al. ASCO 2019. Poster TPS597.

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	pas d'AMM dans cette indication		***AMM dans cette indication***	***pas d'AMM dans cette indication***

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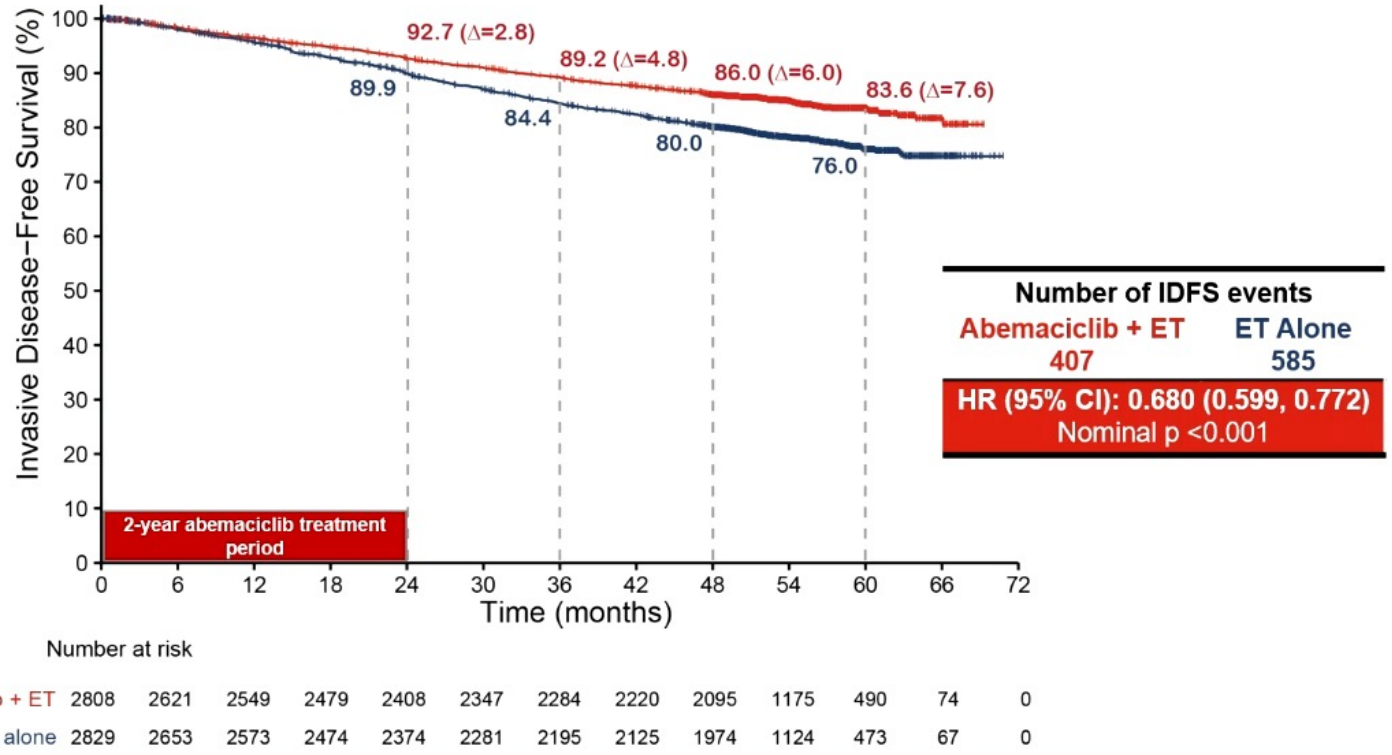
monarchE
Bénéfice maintenue en IDFS à 5 ans



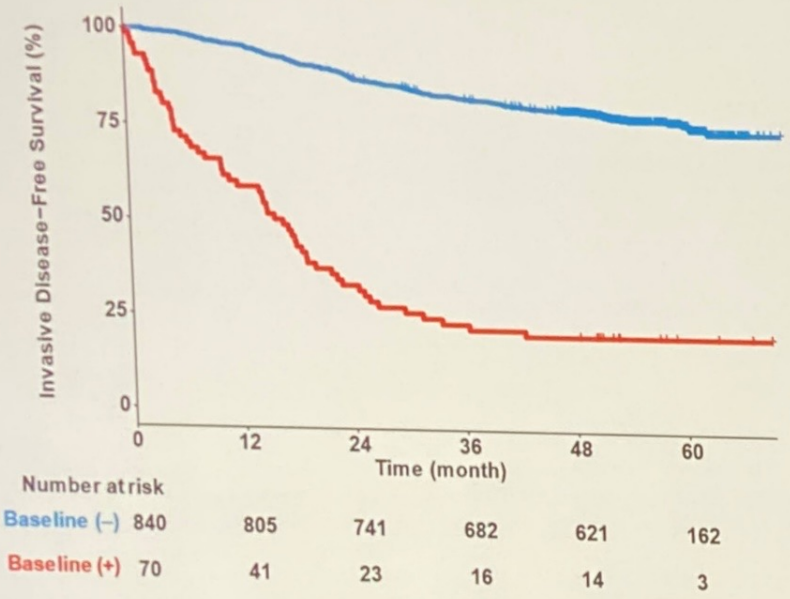
32% reduction in the risk of developing an IDFS event.
The KM curves continue to separate and the absolute difference in IDFS rates between arms was 7.6% at 5 years

Nadia Harbeck et al., ESMO 2023, LBA17

Indications de l'Abemaciclib en adjuvant

- Cancer du sein RH +/HER2 – avec envahissement ganglionnaire et haut risque de rechute
- 4 ou plus N +
- 1 à 3 N+ **et** grade 3 ou T3 ou T4
- Traitement pendant 2 ans

Baseline ctDNA Detection is Associated with Worse Outcomes



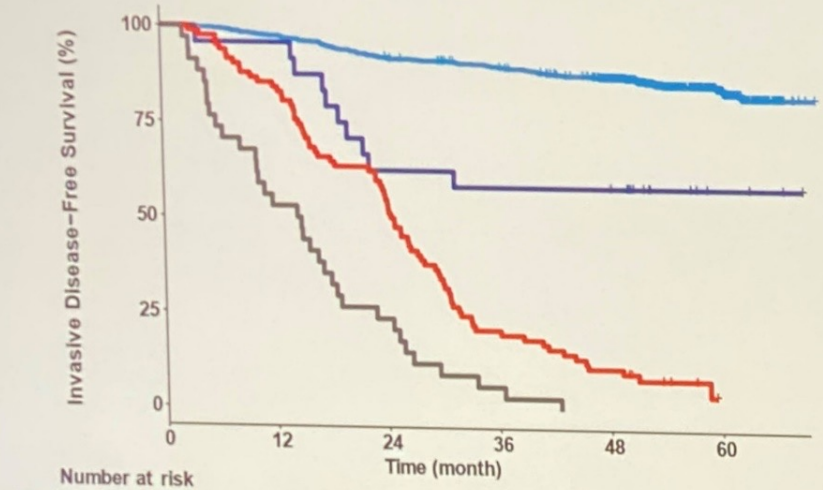
	Baseline Analysis* N=910	
	Baseline (–), undetected N=840	Baseline (+), detected N=70
IDFS event, n (%)	191 (23)	56 (80)
4-year IDFS rate, % (95% CI)	79.1 (76.4-82.0)	20.0 (12.5-32.0)
Log-rank test	Nominal p-value < 0.0001	

*The ctDNA subset was enriched by patients with IDFS events within 24 months; therefore, the estimated IDFS rates in each subgroup are not reflective of that in the overall population

Patients who were ctDNA+ at baseline were more likely to experience an IDFS event compared to those who were ctDNA– at baseline (80% vs 23%, respectively)

PRESENTED BY: Sherene Loi, MD; PhD

Dynamics of ctDNA Detection on Treatment is Associated with Outcomes



Number at risk						
Persistently –	749	731	691	664	611	162
Became –	24	23	15	14	14	3
Became +	82	70	46	17	9	0
Persistently +	34	18	8	2	0	0

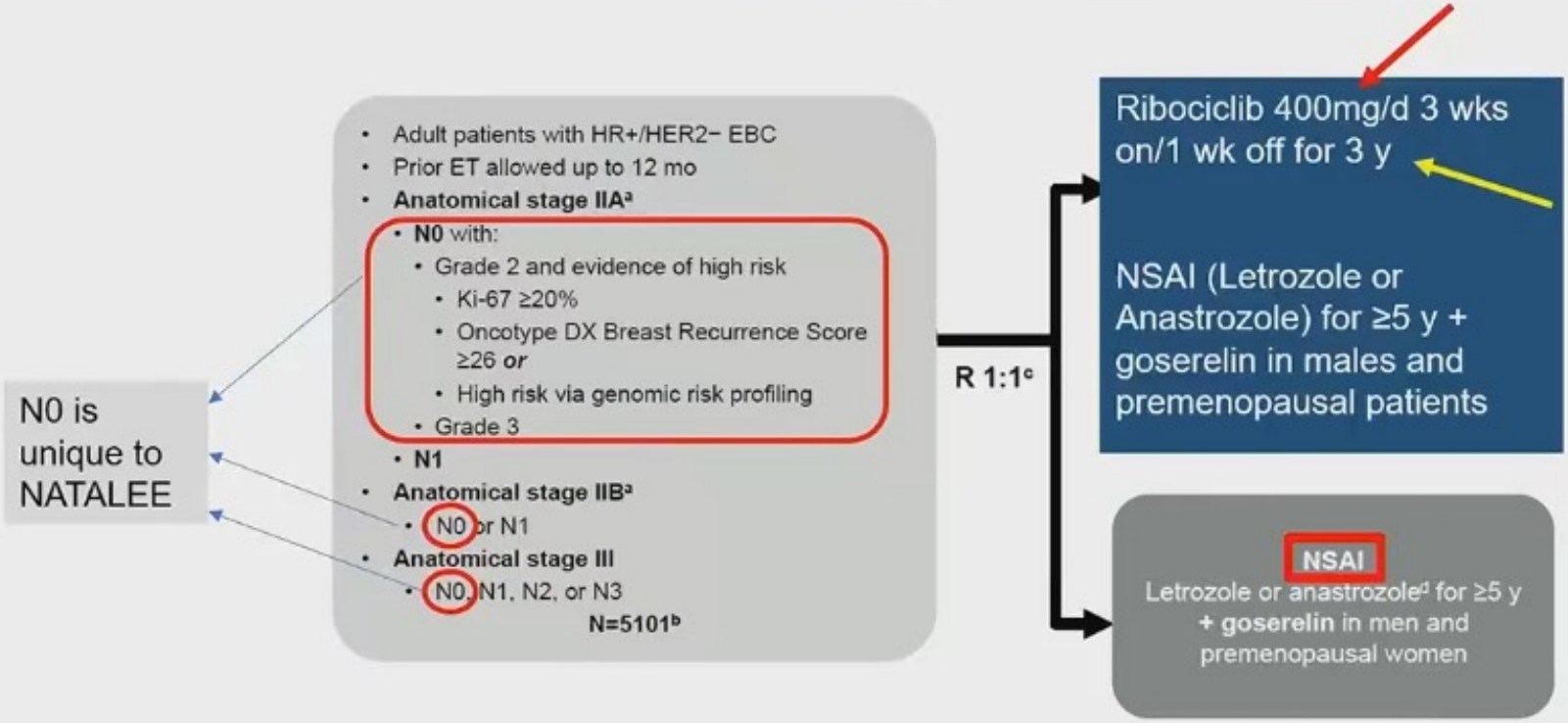
Longitudinal Analysis (N=889)*	Baseline (–), undetected N=831		Baseline (+), detected N=58	
	Persistently –	Became +	Persistently +	Became – (undetected)
N	749 (90)	82 (10)	34 (60)	24 (40)
IDFS event, n (%)	107 (14)	76 (93)	34 (100)	10 (42)
4-year IDFS rate, % (95% CI)	87.5 (85.1-89.9)	11.0 (5.9-20.3)	NA	58.3 (41.6-81.8)

*The ctDNA subset was enriched by patients with IDFS events within 24 months; therefore, the estimated IDFS rates in each subgroup are not reflective of that in the overall population. Robust assessment was limited in 194 patients with <3 post-baseline timepoints and there may be differences in IDFS; total events 227.

Patients who remained Persistently + or Became + on treatment were more likely to experience an IDFS event compared to those who Became – (undetected) or remained Persistently – on treatment

PRESENTED BY: Sherene Loi, MD; PhD

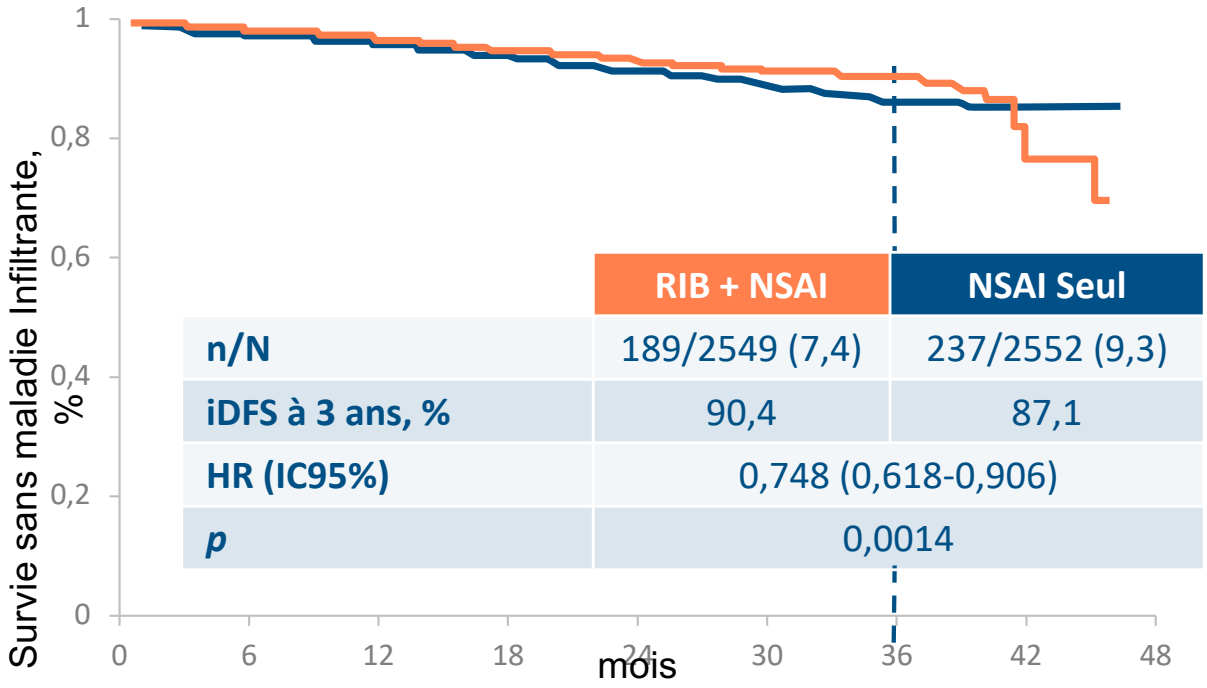
NATALEE Trial: Ribociclib + Nosteroidal Aromatase Inhibitor as Adjuvant Treatment in Patients with HR+/HER2- Early Breast Cancer



Primary End Point: iDFS

Slamon D, et al. ASCO 2023. Gabriel N. Hortobagyi, MD. SABCS 2023

Etude NATALEE : Survie sans maladie infiltrante



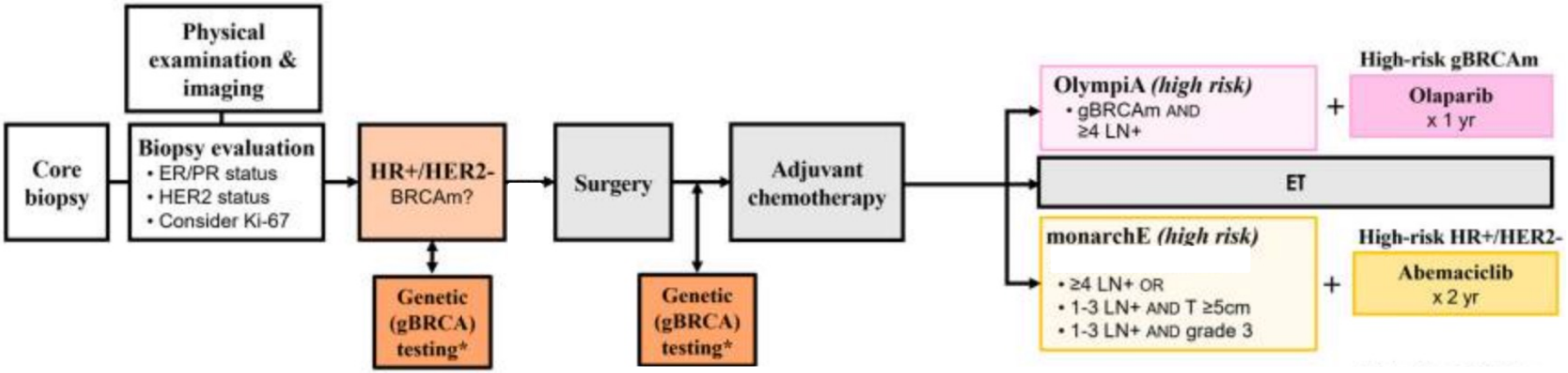
	RIB + NSAI	NSAI Seul
n/N	189/2549 (7,4)	237/2552 (9,3)
iDFS à 3 ans, %	90,4	87,1
HR (IC95%)	0,748 (0,618-0,906)	
p	0,0014	

Nbe à risque									
RIB + NSAI	2 549	2 350	2 274	2 193	1 718	1 111	311	12	0
NSAI seul	2 552	2 240	2 166	2 071	1 631	1 067	286	13	0

Pour le bras expérimental avec ribociclib :

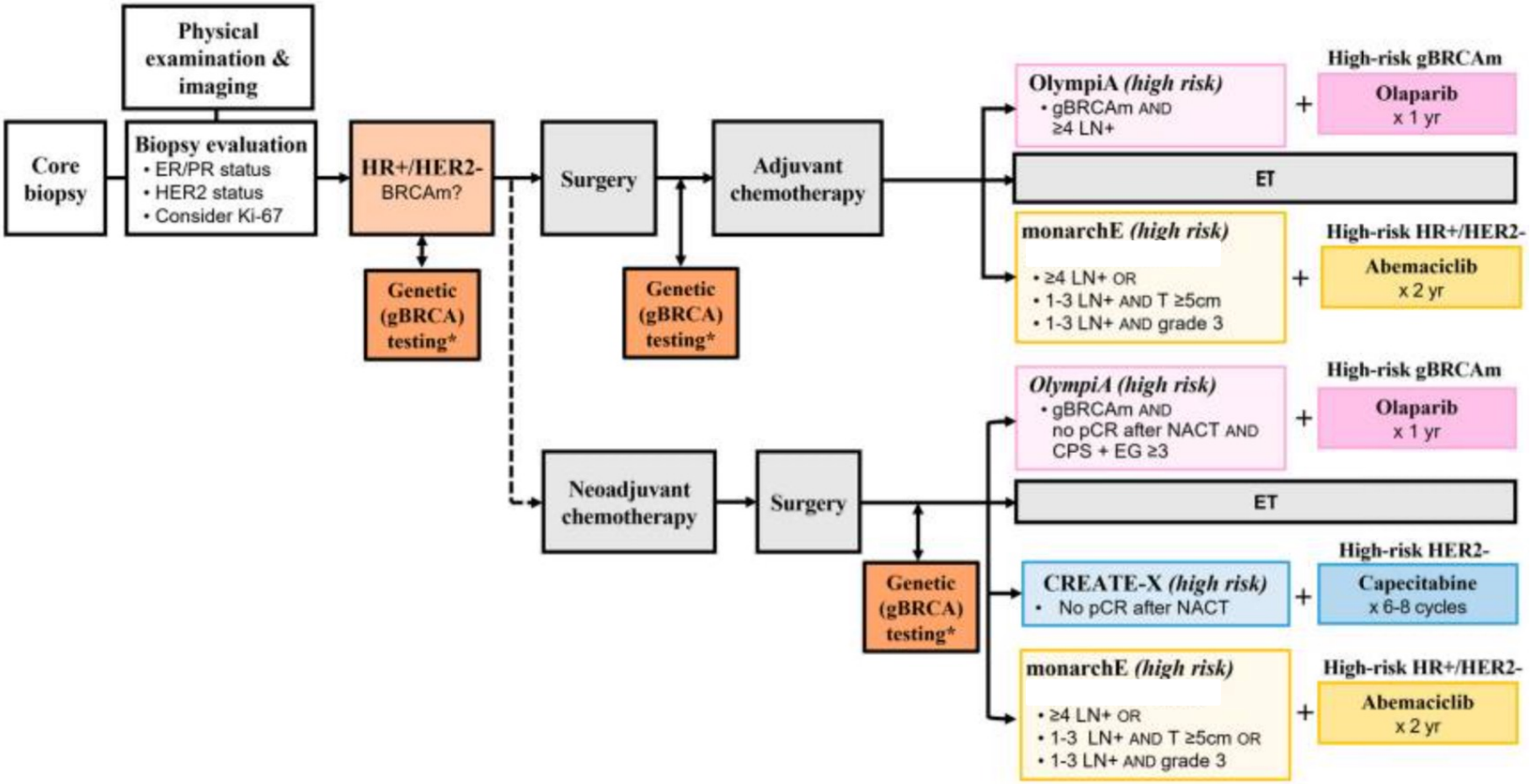
- **Bénéfice absolu en IDFS à 3 ans = 3,3 %**
- **Réduction du risque de maladie infiltrante = 25,2 %**

Au final ?

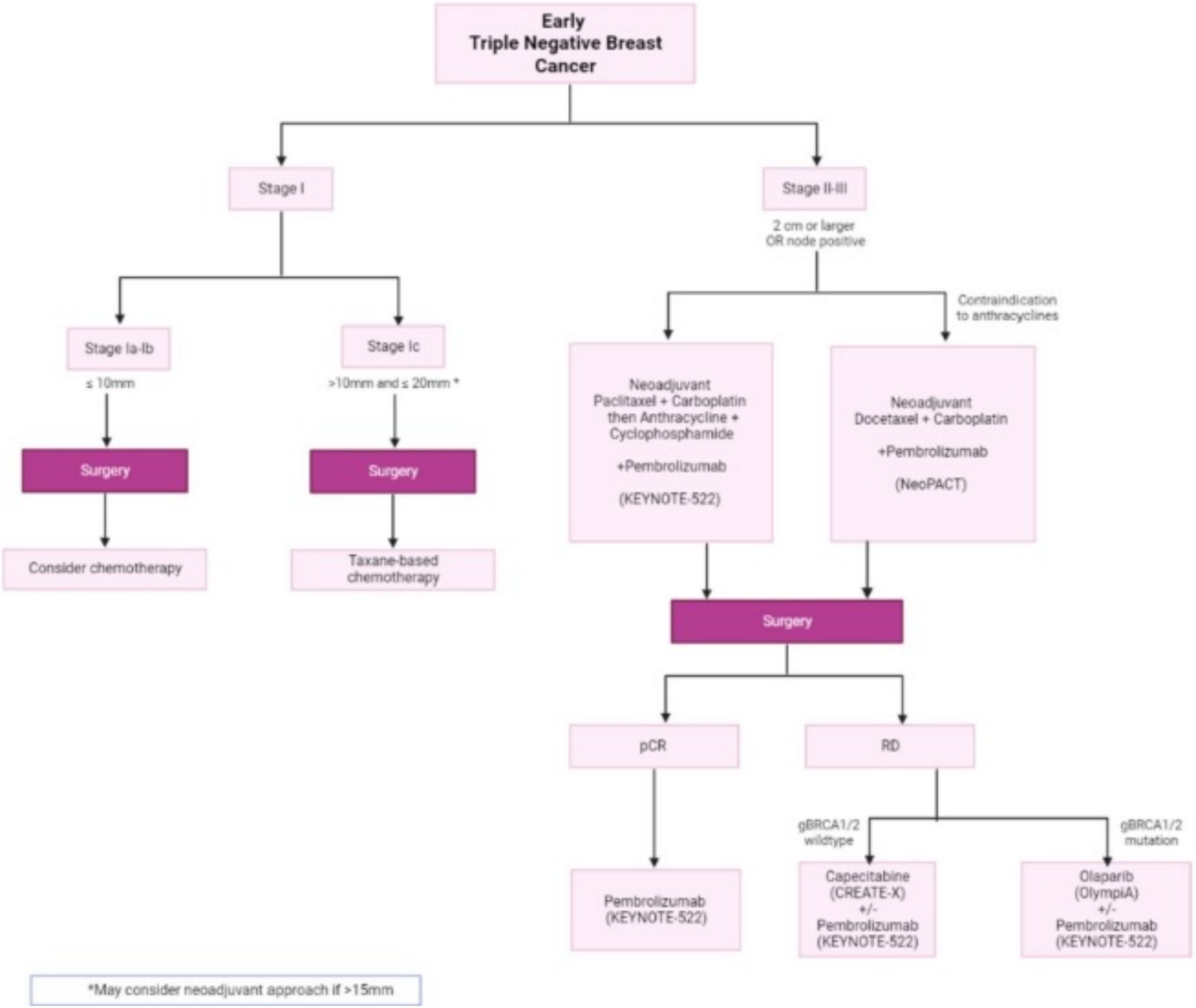


From Henning et al, Current oncology 2023

Au final ?



From Henning et al, Current oncology 2023


Early
Triple Negative Breast
Cancer
Stage I
Stage II-III
2 cm or larger
OR node positive
Stage Ia-Ib
≤ 10mm
Stage Ic
>10mm and ≤ 20mm *
Contraindication
to anthracyclines
Surgery
Surgery
Consider chemotherapy
Taxane-based
chemotherapy
Neoadjuvant
Paclitaxel + Carboplatin
then Anthracycline +
Cyclophosphamide
+Pembrolizumab
(KEYNOTE-522)
Neoadjuvant
Docetaxel + Carboplatin
+Pembrolizumab
(NeoPACT)
Surgery
pCR
RD
Pembrolizumab
(KEYNOTE-522)
gBRCA1/2
wildtype
gBRCA1/2
mutation
Capecitabine
(CREATE-X)
+/-
Pembrolizumab
(KEYNOTE-522)
Olaparib
(OlympiA)
+/-
Pembrolizumab
(KEYNOTE-522)
*May consider neoadjuvant approach if >15mm

Conclusions

- L'introduction de nouvelles molécules a permis d'améliorer le pronostic des cancers du sein à haut risque

- Sélection de patientes à très haut risque avec de nouvelles technologies (ADNc)

- Prochaines étapes :
  - Associations : anti-PDL1 + Capécitabine ou IPARP
  - Nouvelles molécules : SERD oraux
  - Nouvelles indications : Ac Conjugués (TdXD, Sacituzumab govitecan)