

Post-ESMO 2019 L'essentiel en Sénologie

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Cancer du sein RH+ Her2-

MONARCH 2 / Sledge G.W. et al. - ESMO 2019 – LBA6

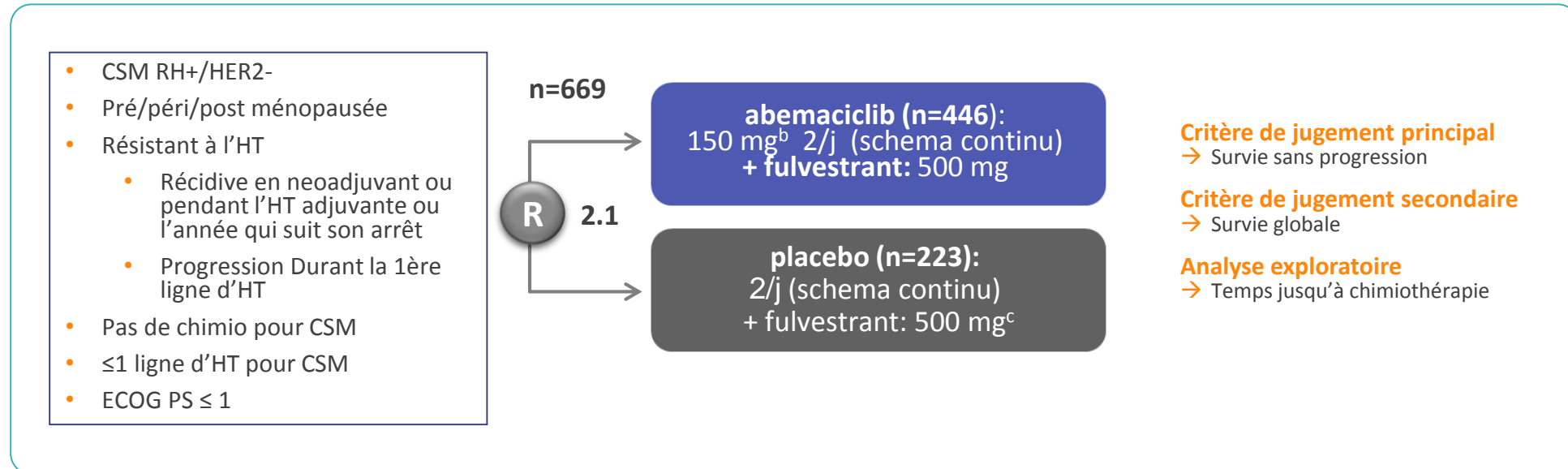
MONALESSA 3 / Slamon D.J. et al. - ESMO 2019 – LBA7

MONARCH 2

Sledge G.W. et al. - ESMO 2019 – LBA6

MONARCH 2

schéma de l'étude



Facteurs de stratification:

- Site métastatique (viscérale, os uniquement, ou autre)
- Résistance à l'HT (primaire ou secondaire)

→ Données au 20 Juin 2019

→ Médiane de suivi: 47,7 mois

→ 17% des patients dans le bras abemaciclib vs 4% dans le bras placebo sont toujours en traitement

^aRecevant un analogue de la LHRH

^bDose réduite par amendement de 200 à 150 mg

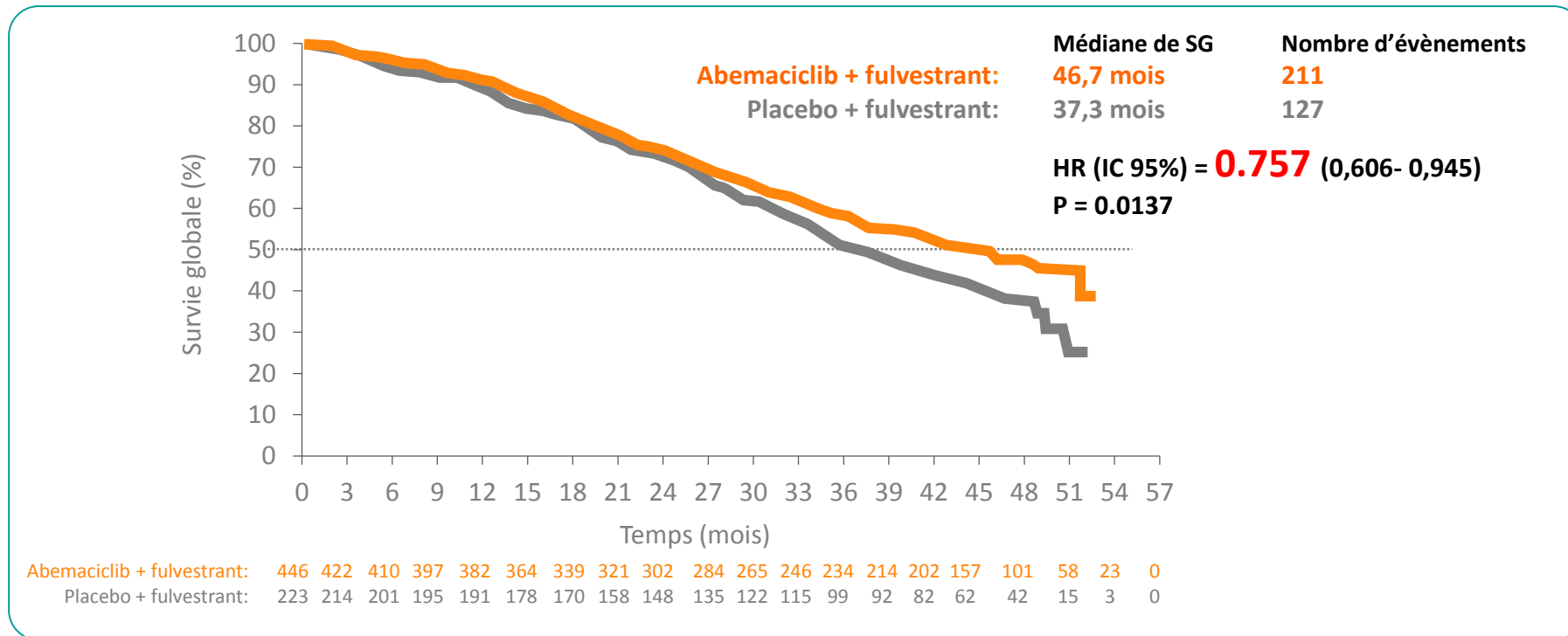
^cFulvestrant administré par voie intra-musculaire

Abbréviations: CSM= cancer du sein métastatique, n= nombre de patients, HT= hormonothérapie

MONARCH 2

Survie globale

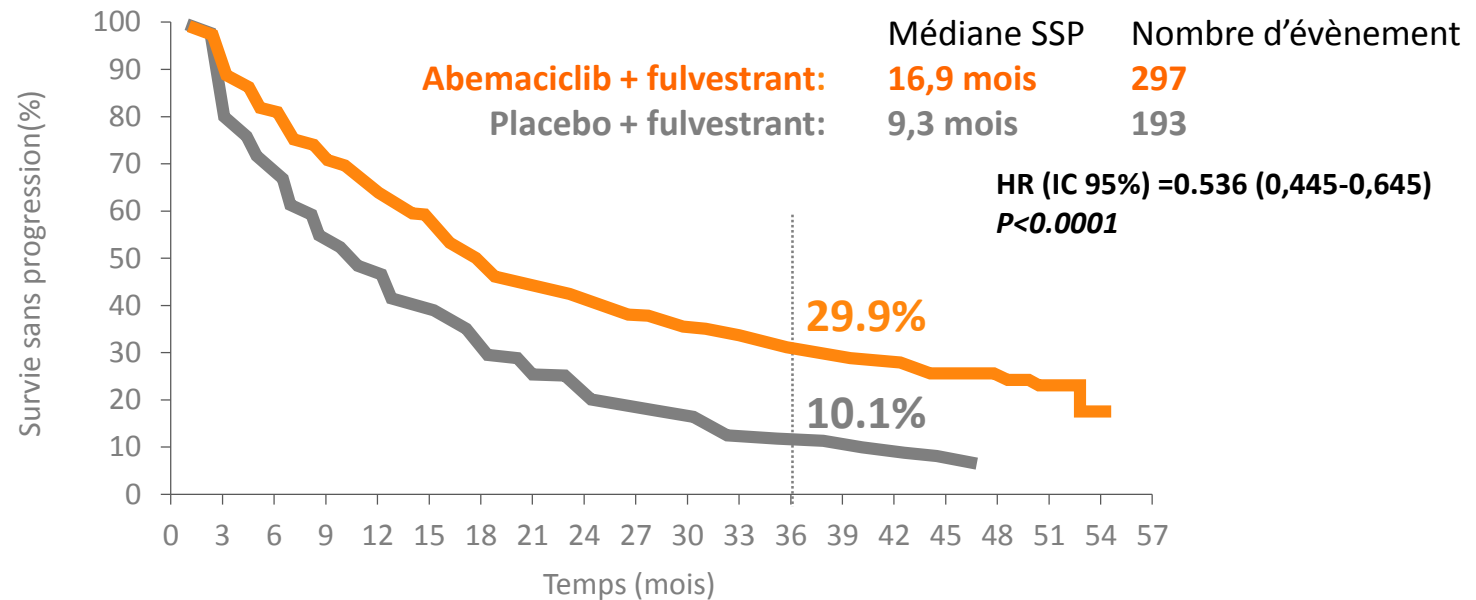
L'abemaciclib apporte un bénéfice significatif de survie globale de 9,4 mois supplémentaire.



MONARCH 2

Survie sans progression: données mises à jour

Survie sans progression : critère de jugement principal



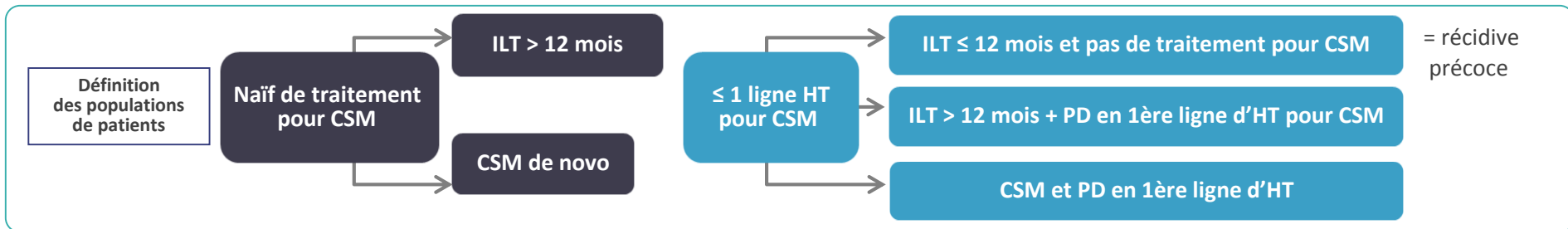
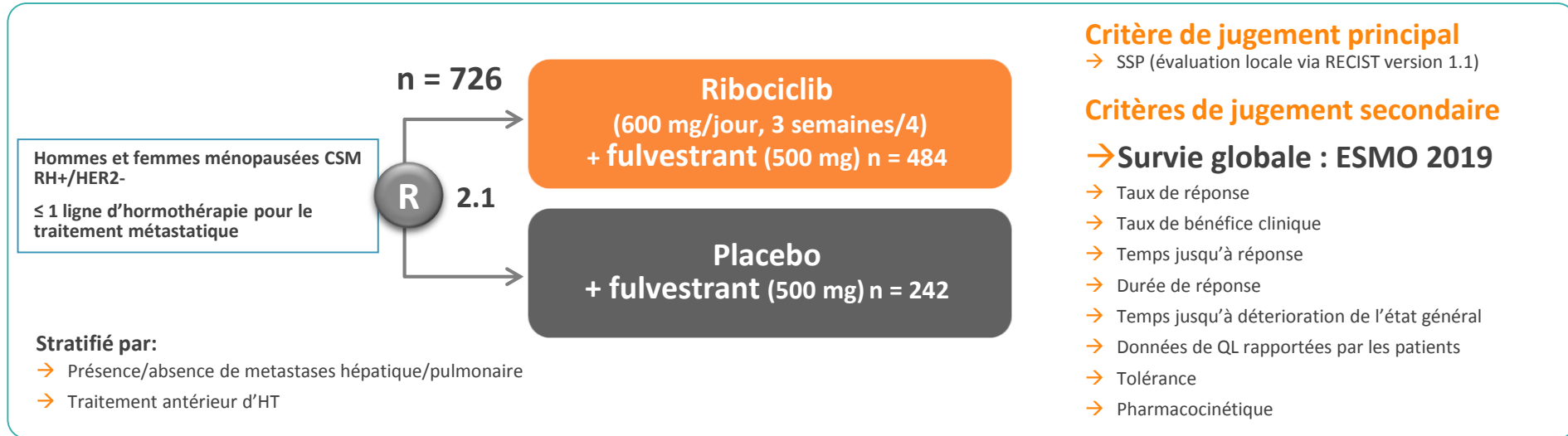
Abemaciclib + fulvestrant:	446	365	312	280	242	206	176	158	147	132	121	114	104	97	78	53	26	16	4	0
Placebo + fulvestrant:	223	165	124	103	61	72	54	47	36	31	26	16	17	14	9	7	0	0	0	0

MONALEESA 3

Slamon D.J. et al. - ESMO 2019 – LBA7

MONALEESA 3

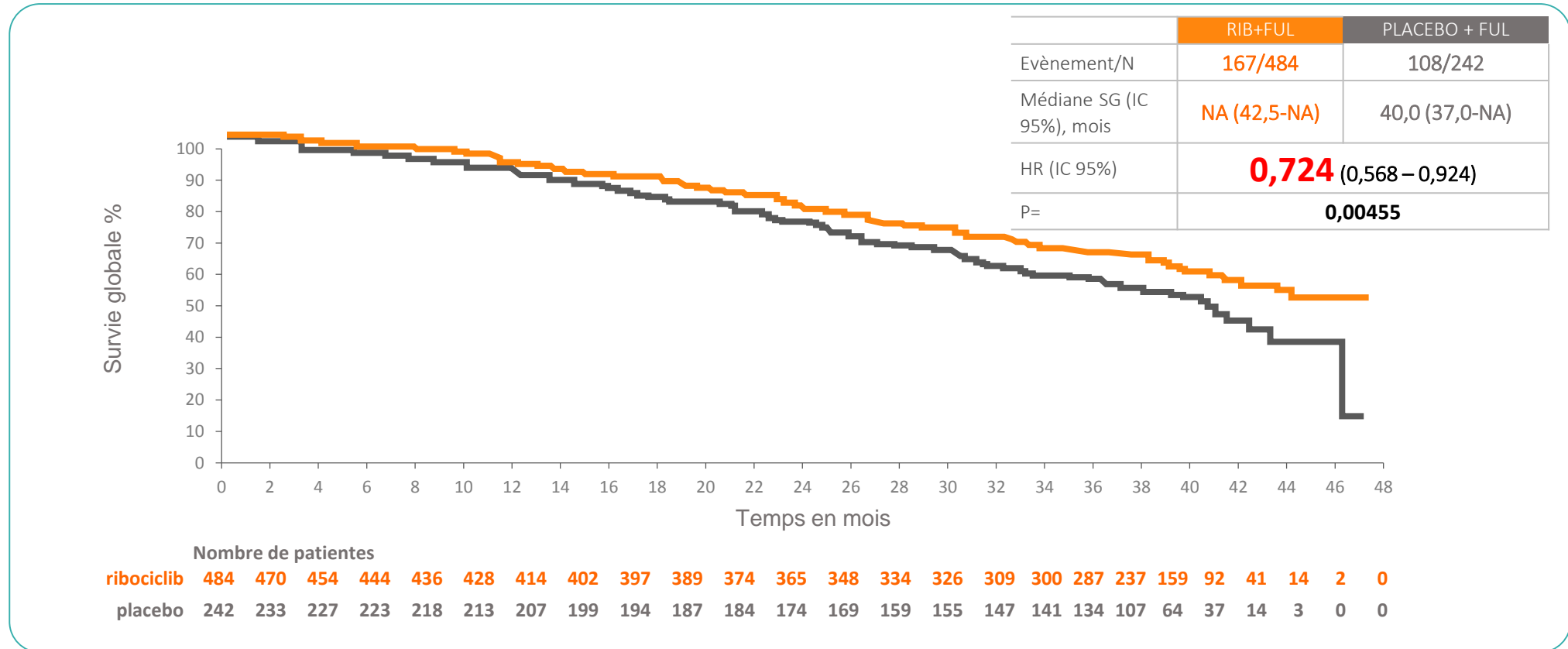
schéma de l'étude



MONALEESA 3

Survie globale

Le risque relatif de décès est diminué de 28% au profit du bras ribociclib



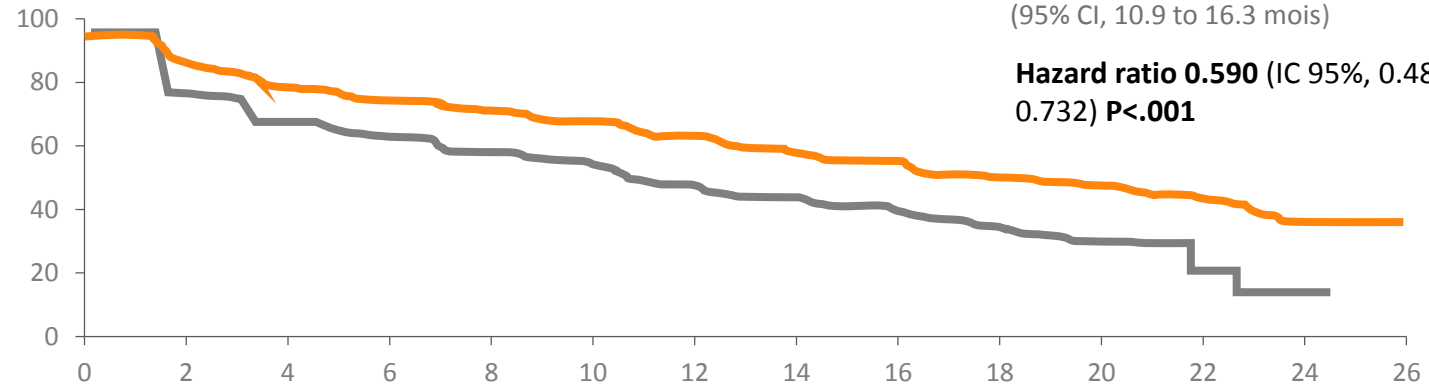
RIB: ribociclib; FUL: fulvestrant; SG: survie globale; NA: non atteint; HR: Hazard ratio

MONALEESA 3

Survie sans progression: données mises à jour

MONALEESA3

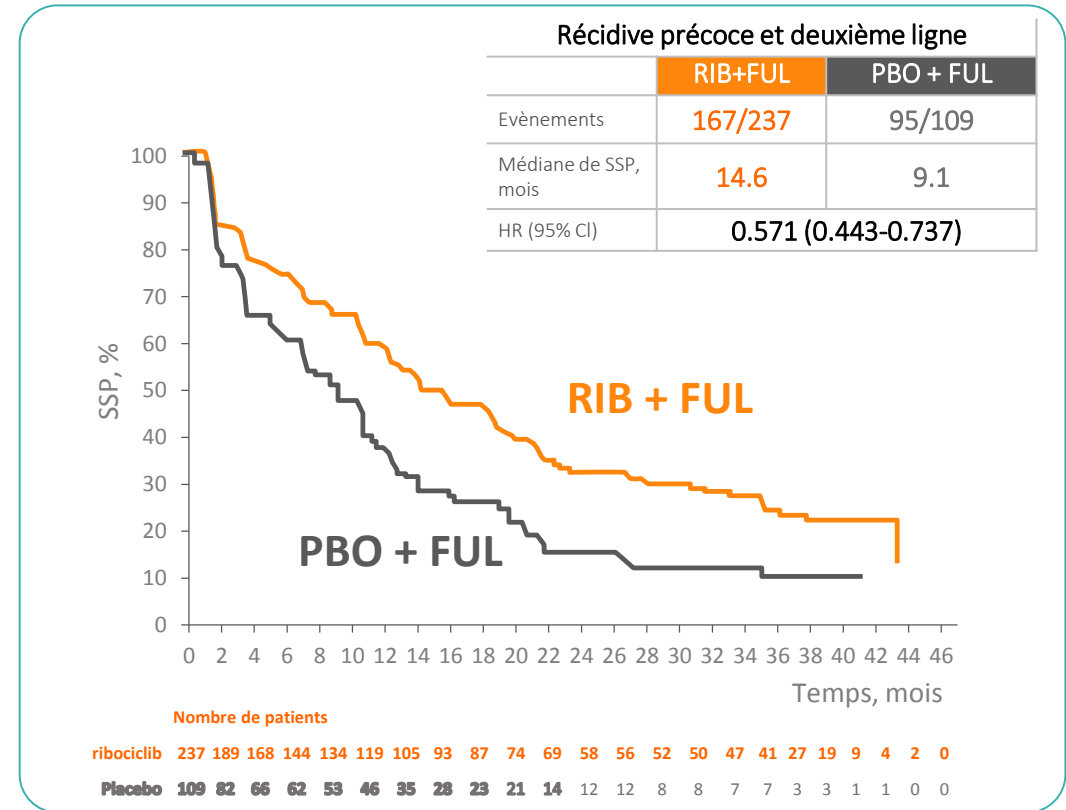
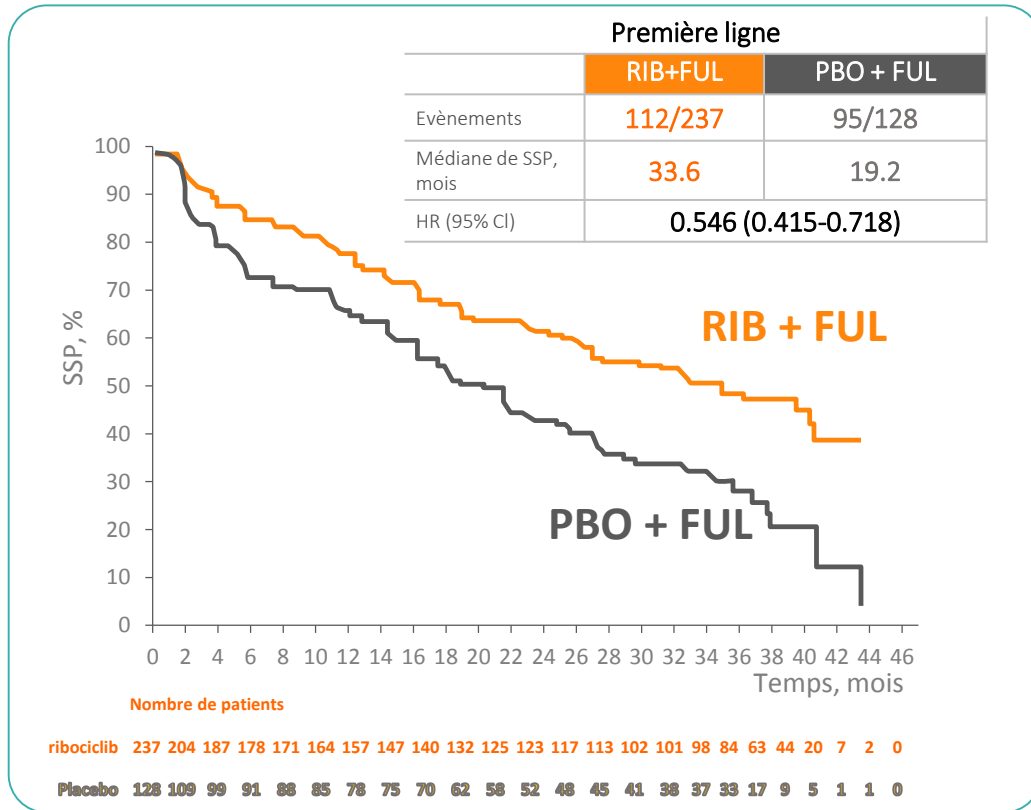
Survie sans progression (%)



ribociclib + fluevestrant	484	403	365	347	324	305	282	259	235	155	78	52	13	0
placebo + fluevestrant	242	195	168	156	144	134	116	106	95	53	27	14	4	0

MONALEESA 3

Survie sans récurrence par ligne de traitement



Cancer du sein triple négatif

Impassion 130 / PD-L1 IHC assays / Rugo H.D et al.- ESMO 2019 – LBA20

KEYNOTE 119 / Cortes J. et al., ESMO 2019 – LBA21

KEYNOTE 522 / Schmid P. et al. ESMO 2019 – LBA8

IMPASSION 130

Impassion 130 / PD-L1 IHC assays / Rugo H.D et al.- ESMO 2019 – LBA20

Impassion 130

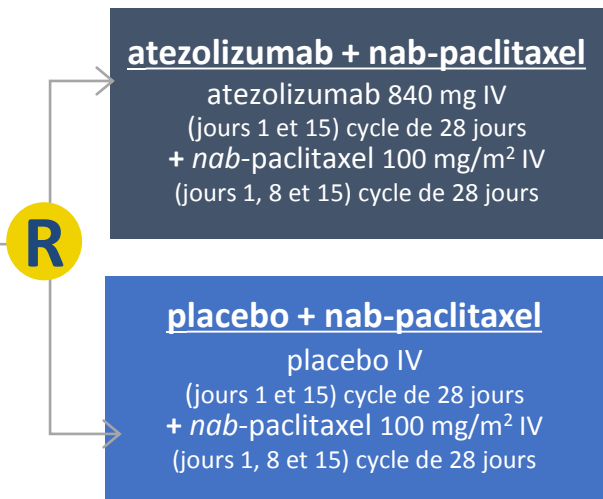
performances techniques IHC PD-L1

Critères d'éligibilité

- 1 Cancer triple-négatif métastatique ou localement avancé inopérable
- 2 Pas de traitement préalable en phase méta
- 3 chimiothérapie incluant taxanes autorisée en situation (néo)adjuvante si TFI ≥ 12 mois

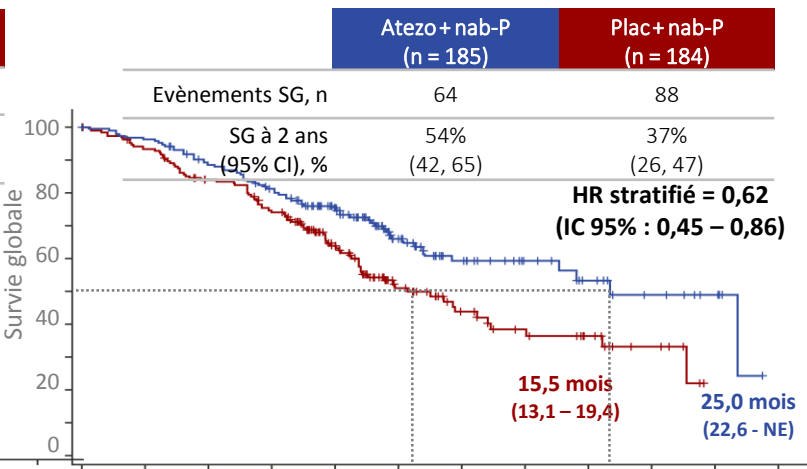
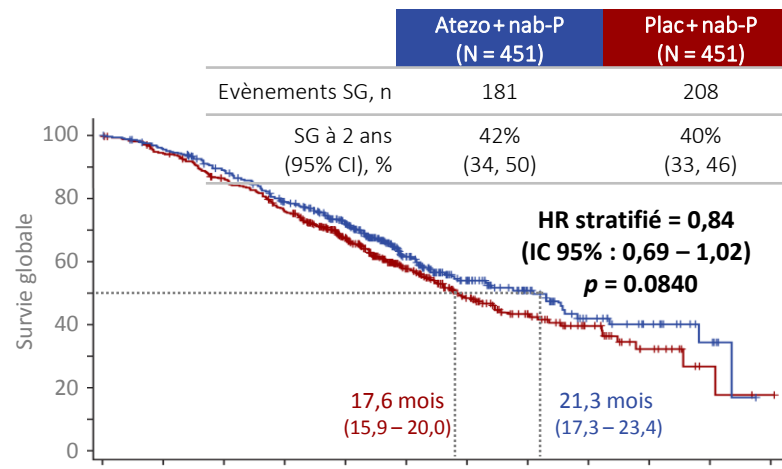
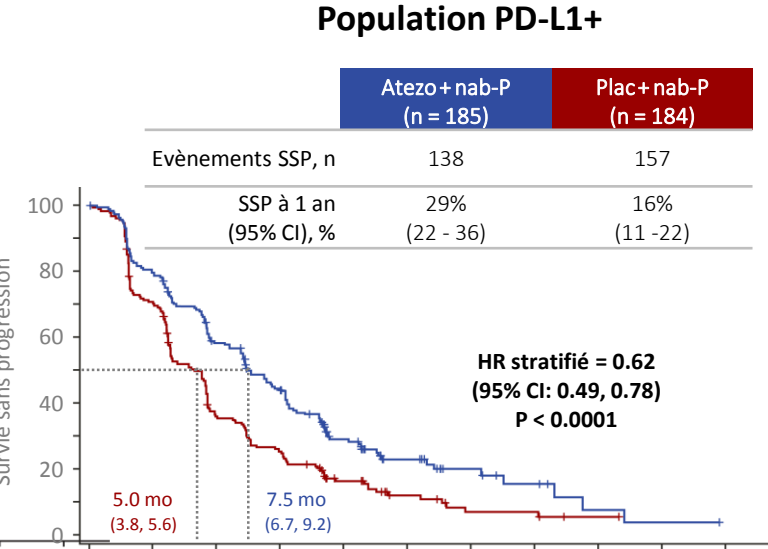
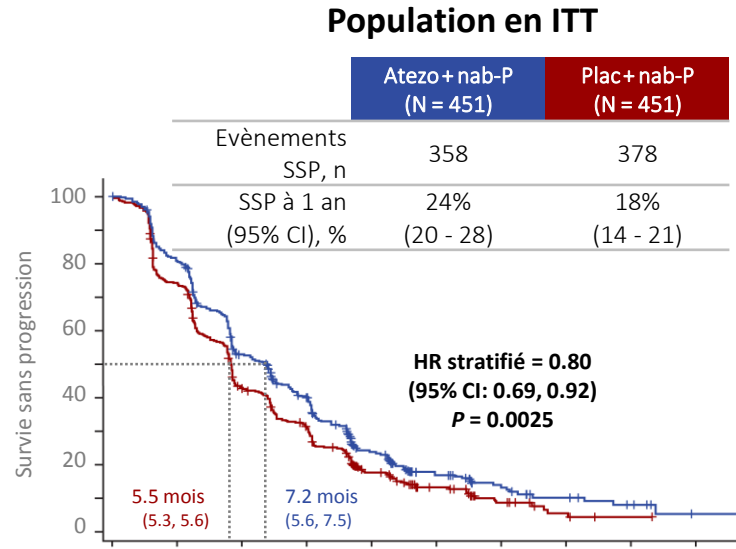
Facteurs de stratification :

- 1 Statut PD-L1 sur IC (positif [≥ 1%] vs négatif [< 1%])



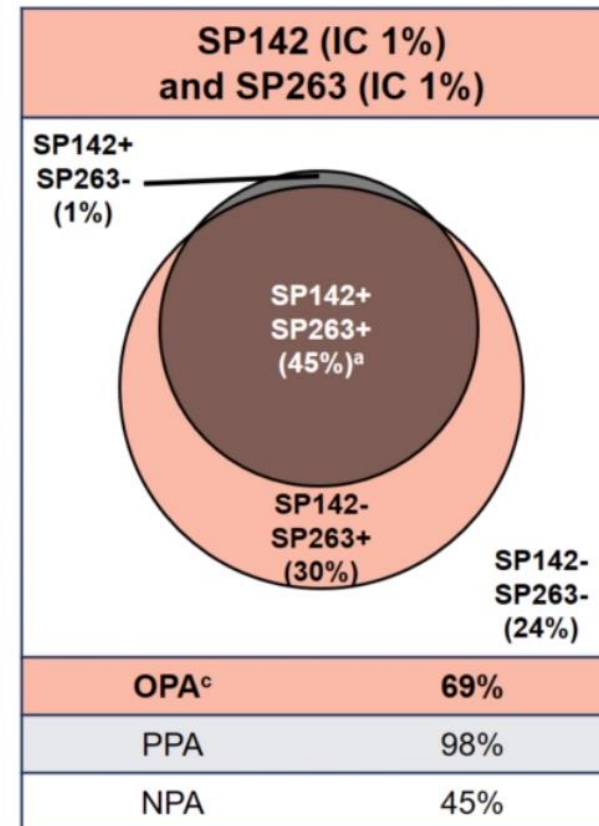
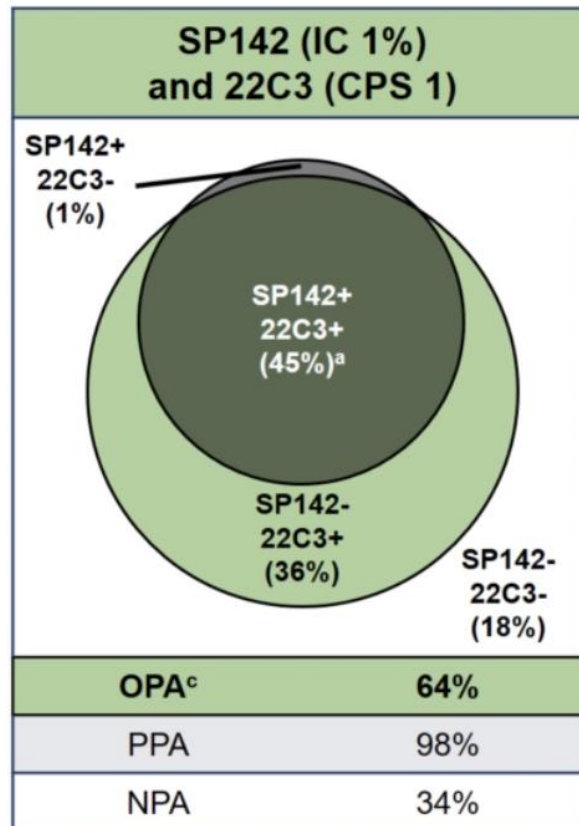
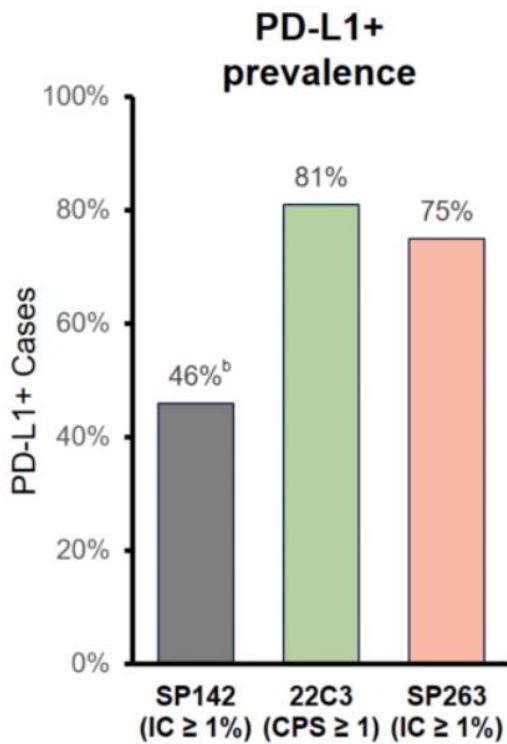
• Comparer 3 tests PD-L1

- SP-142 (IC 1%) (Atézolizumab)
- 22C3 (CPS 1) (Pembrolizumab)
- SP263 (IC 1%) (Durvalumab)



Impassion 130

performance techniques IHC PD-L1



- SP 142 validé FDA/ATU pour atézolizumab en combinaison pacli/nab-pacli en 1^{ère} ligne métastatique TNBC
- Nécessité d'identifier autres biomarqueurs de bénéfice de l'association chimio-immuno

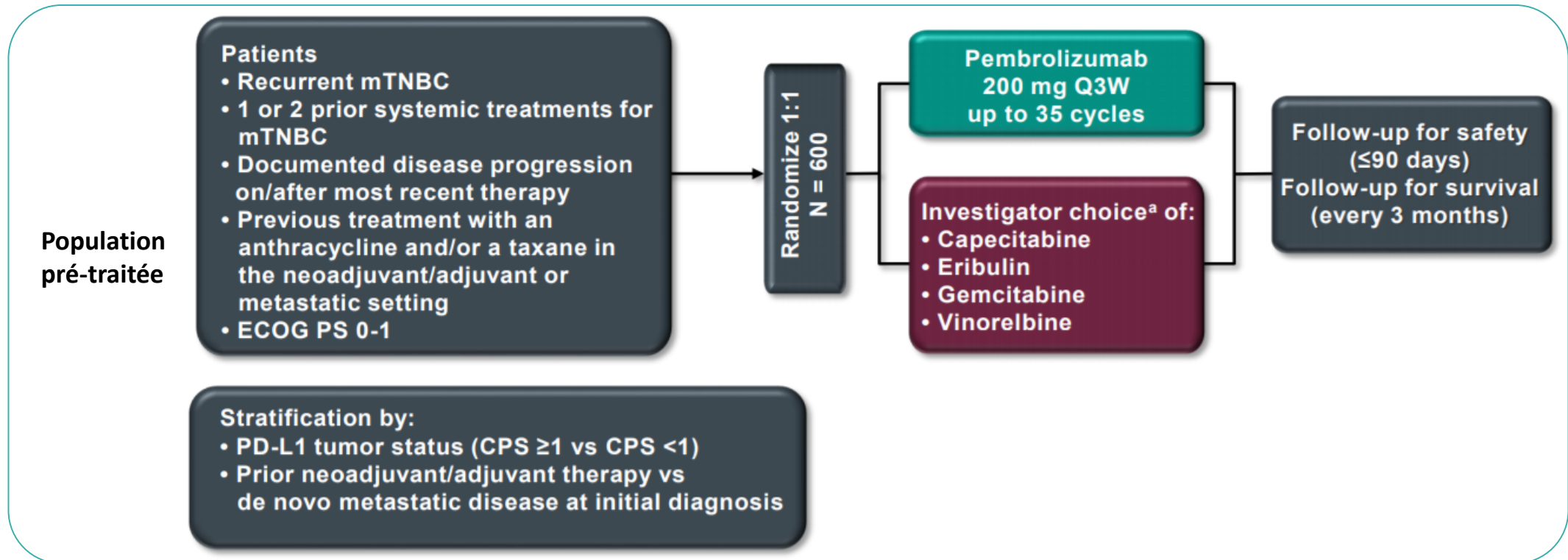
KEYNOTE 119

Cortes J. et al., ESMO 2019 – LBA21

Stade métastatique

KEYNOTE 119

schéma de l'étude



● Objectifs principaux

- SG population PD-L1+ (CPS ≥ 10)
- SG population PD-L1+ (CPS ≥ 1)
- SG population globale

● Objectifs secondaires

- SSP
- Taux de réponse objective
- Tolérance

● Analyses exploratoires

- SG, SSP, ORR population PD-L1+ définis selon autre CPS cutpoints

KEYNOTE 119

résultats

PD-L1 Expression Analysis

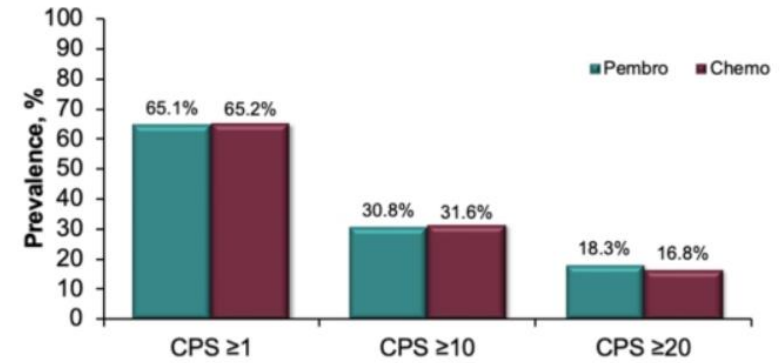
- Measure of PD-L1 expression: combined positive score (CPS)

$$\text{CPS} = \frac{\text{\# PD-L1-staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# viable tumor cells}} \times 100$$

- Assessed centrally in newly obtained core or excisional biopsy from metastatic, not previously irradiated, tumor lesion using PD-L1 IHC 22C3 pharmDx (Agilent Technologies)
- Positive PD-L1 expression: CPS ≥ 10 and CPS ≥ 1



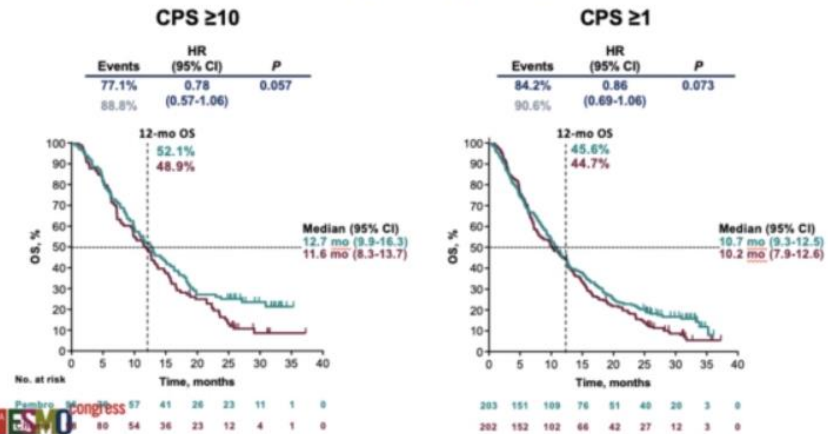
Prevalence of PD-L1 CPS Categories



CPS = combined positive score defined as the number of PD-L1-positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells $\times 100$. Data cutoff date: April 11, 2019.

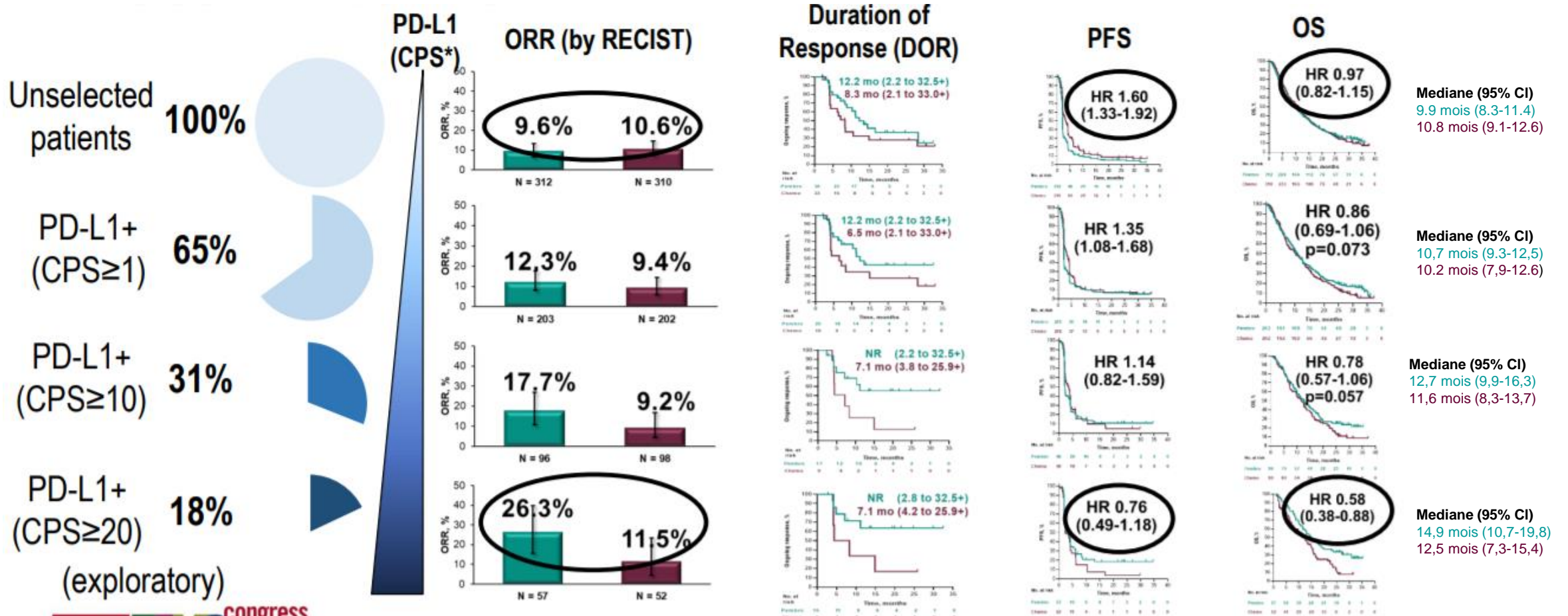
Overall Survival: Primary Endpoints

Chemotherapy \leftrightarrow Immune checkpoint blockade



KEYNOTE 119

discussion



CPS = combined positive score defined as the number of PD-L1-positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells × 100 (scored using 22C3 assay)

KEYNOTE 522

Schmid P. et al. ESMO 2019 – LBA8

Néo-adjuvant

KEYNOTE 522

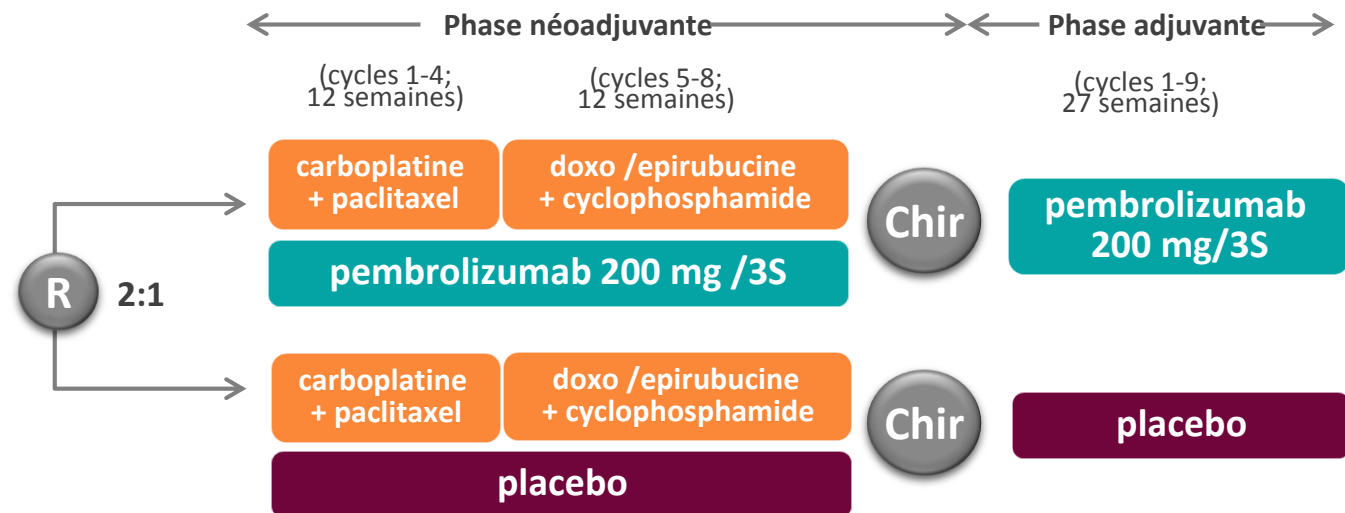
schéma de l'étude

● Critères d'inclusion

- Age ≥18 ans
- TNBC au diagnostic T1c N1-2 ou T2-4 NO-2
- PS 0-1
- Évaluation possible du statut PDL1

● Stratification:

- Envahissement ganglionnaire
- Taille tumorale
- Schéma du carboplatine qw vs q3w



● Objectifs principaux

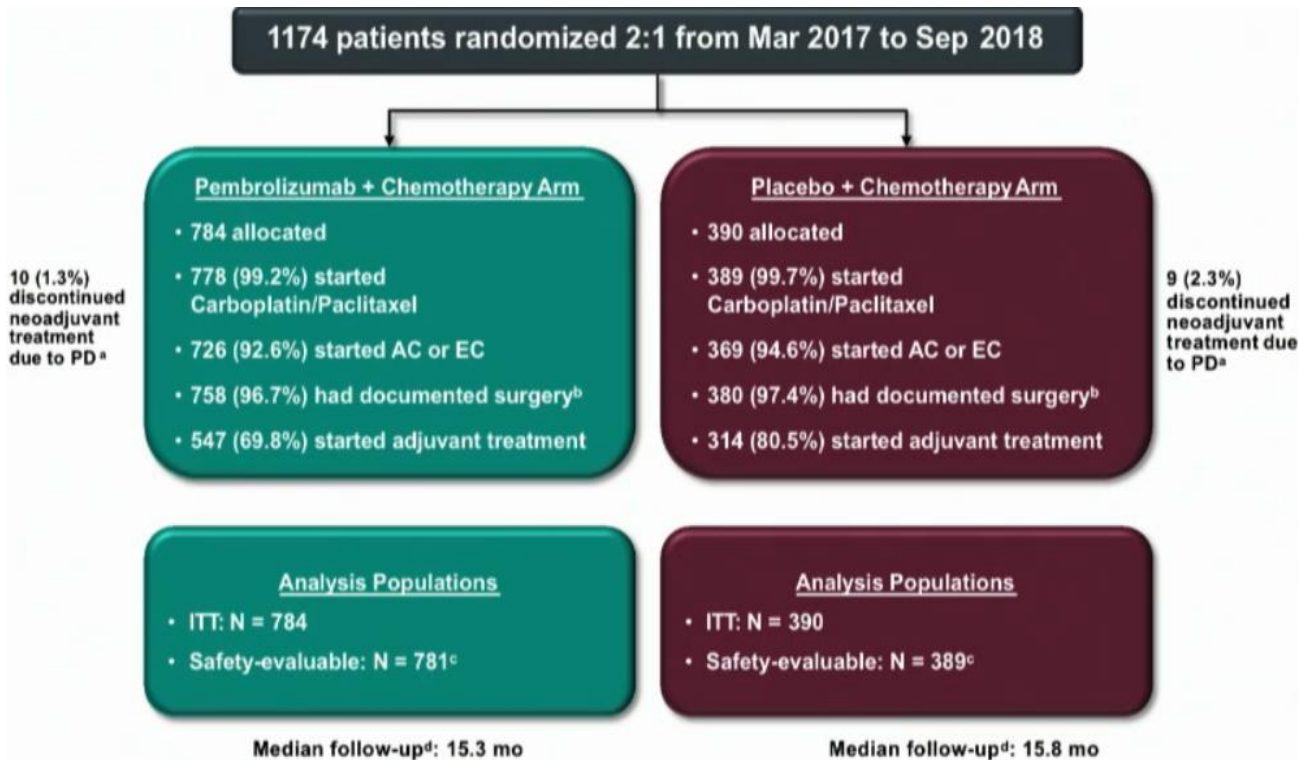
- pCR (ypT0/Tis ypN0) ⇔ population en ITT
- Survie sans évènement (SSE) ⇔ population en ITT

● Objectifs secondaires

- pCR : autres définitions (ypT0 ypN0 and ypT0/Tis)
- Survie globale (SG)
- pCR, SSE and SG dans la population PD-L1-positive
- Tolérance

KEYNOTE 522

caractéristiques



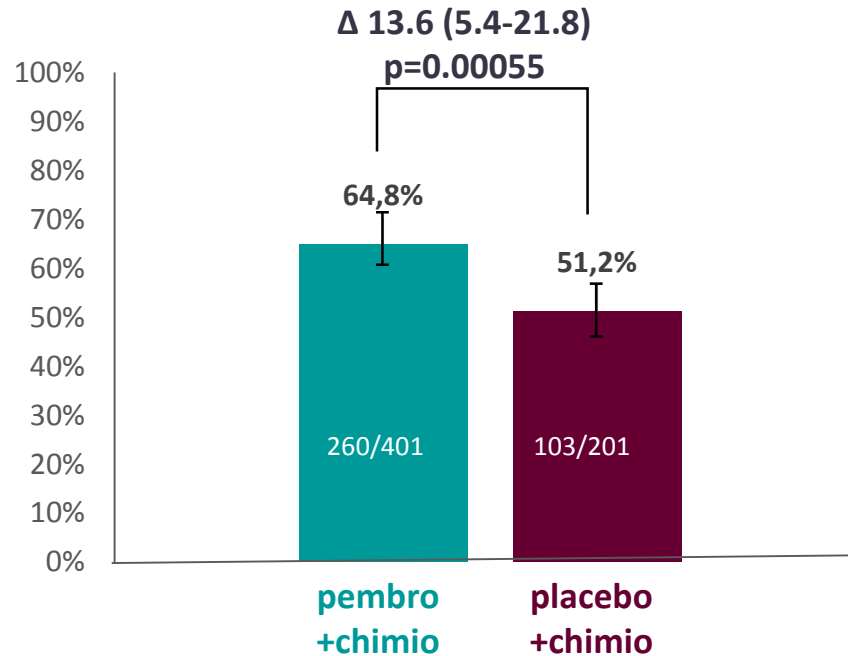
Characteristic, n (%)	All Subjects, N = 1174	
	Pembro + Chemo N = 784	Placebo + Chemo N = 390
Age, median (range), yrs	49 (22-80)	48 (24-79)
ECOG PS 1	106 (13.5)	49 (12.6)
PD-L1–positive ^a	656 (83.7)	317 (81.3)
Carboplatin schedule		
QW	449 (57.3)	223 (57.2)
Q3W	335 (42.7)	167 (42.8)
Tumor size		
T1/T2	580 (74.0)	290 (74.4)
T3/T4	204 (26.0)	100 (25.6)
Nodal involvement		
Positive	405 (51.7)	200 (51.3)
Negative	379 (48.3)	190 (48.7)

^aPD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100); PD-L1–positive = CPS ≥1.

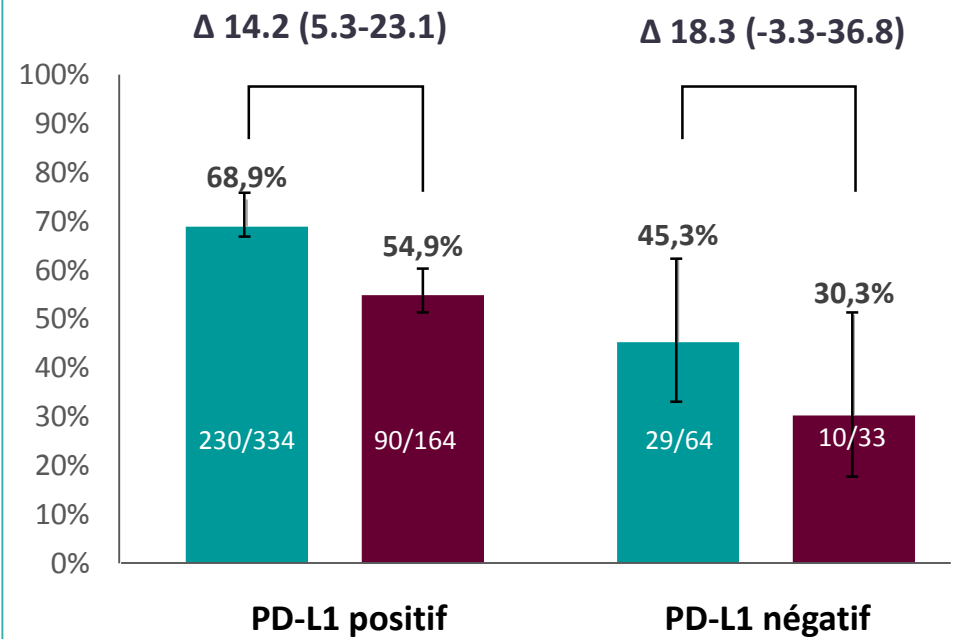
KEYNOTE 522

réponse histologique complète

Objectif principal: ypT0/Tis ypN0

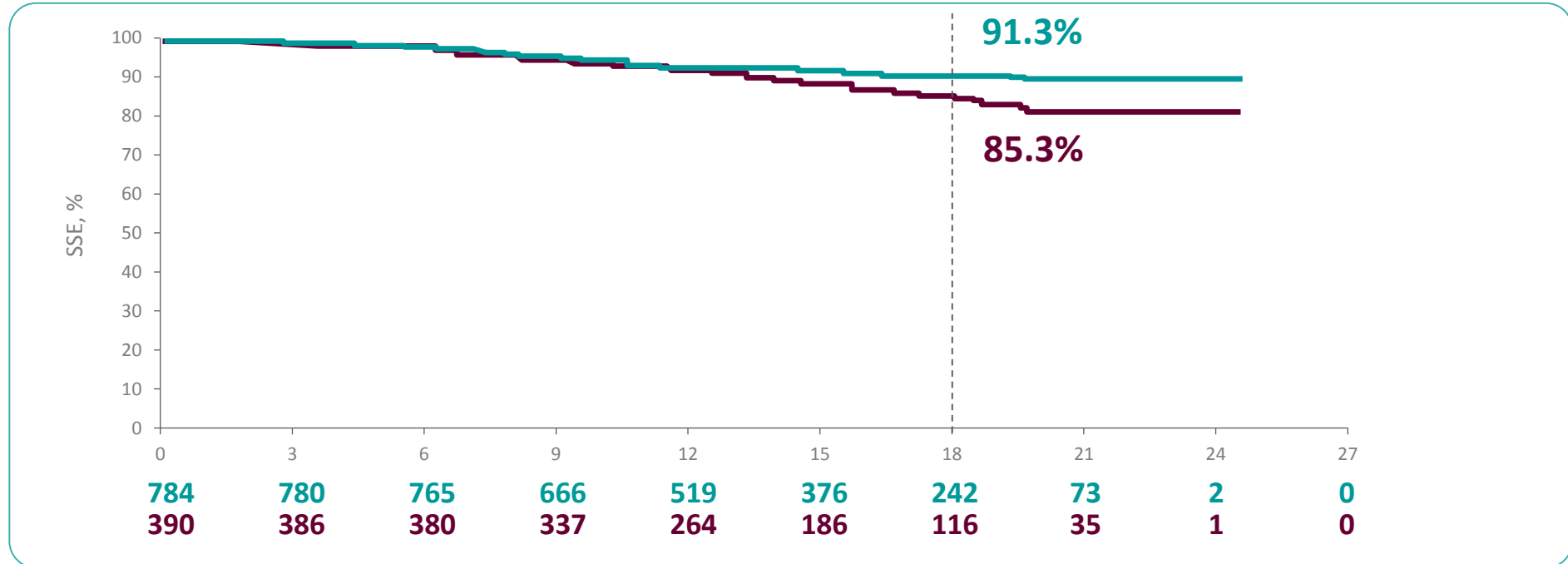


Fonction du statut PD-L1: ypT0/Tis ypN0



KEYNOTE 522

survie sans évènement

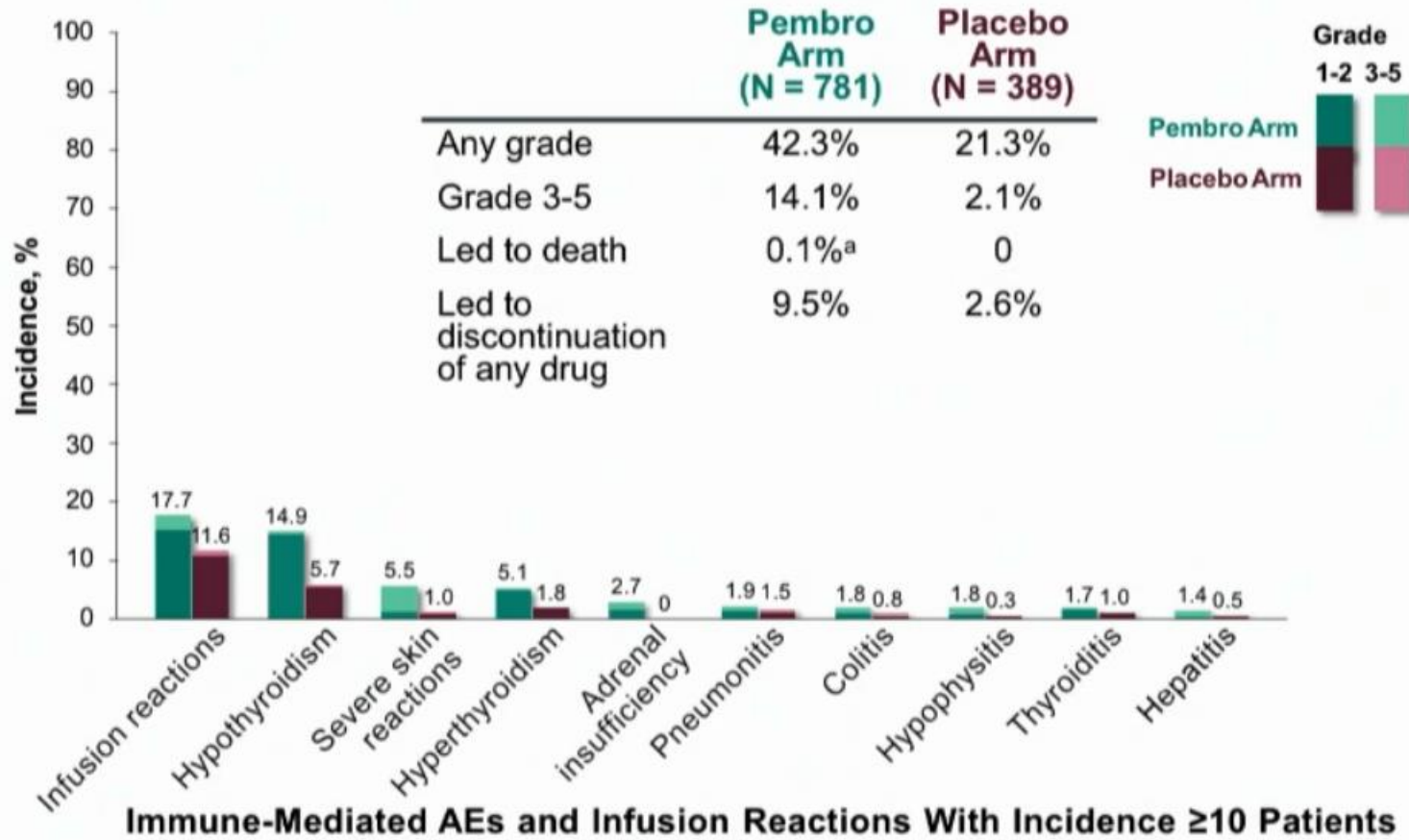


784	780	765	666	519	376	242	73	2	0
390	386	380	337	264	186	116	35	1	0

	Evènements	HR (95% CI)
pembro + chimio/pembro	7,4%	0,63
placebo + chimio/placebo	11,8%	(0.43-0.93)

KEYNOTE 522

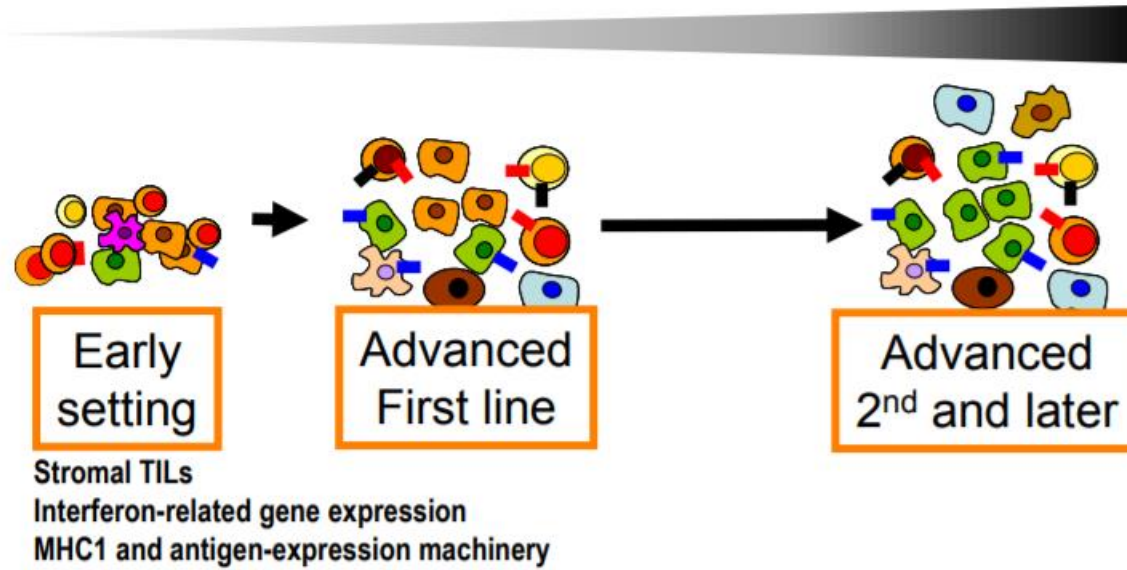
tolérance



Immunothérapie des cancers du sein TN

Tumor/immune co-evolution leads to an increasing immunoediting and immune subversion

Immune escape

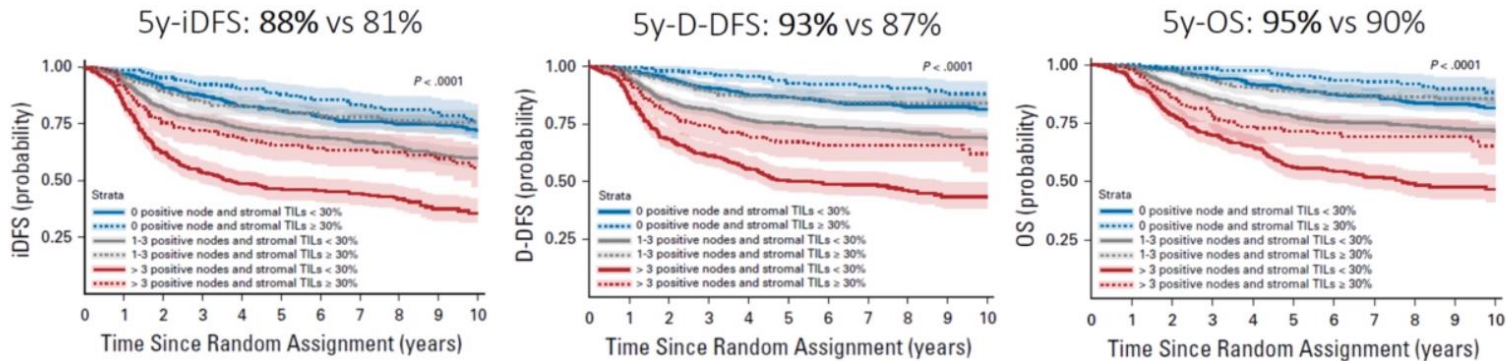


TILs et cancers du sein TN de stade précoce

Niveau élevé de TILs associé à excellent pronostic à stade précoce traité par chimiothérapie adjuvante Anthra +/- taxane

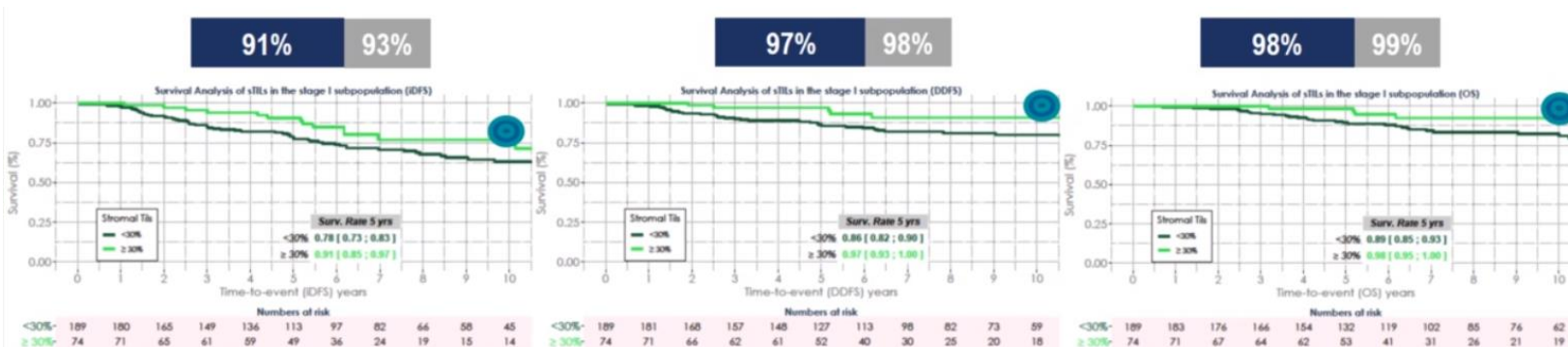
N=2148

In patients with *node-negative disease*: TILs \geq 30% vs < 30%:



Loi S. et al, JCO 2019

Niveau élevé de TILs associé à excellent pronostic à stade précoce pStade I sans chimiothérapie ajuvante



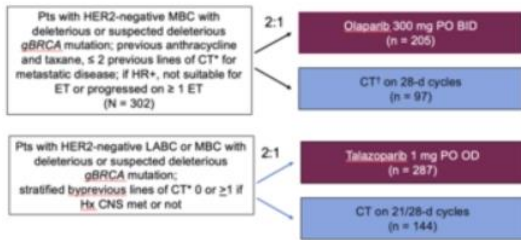
Park J.H. et al, ESMO 2019 Abst 1750

Cancer du sein et mutation constitutionnelle de BRCA

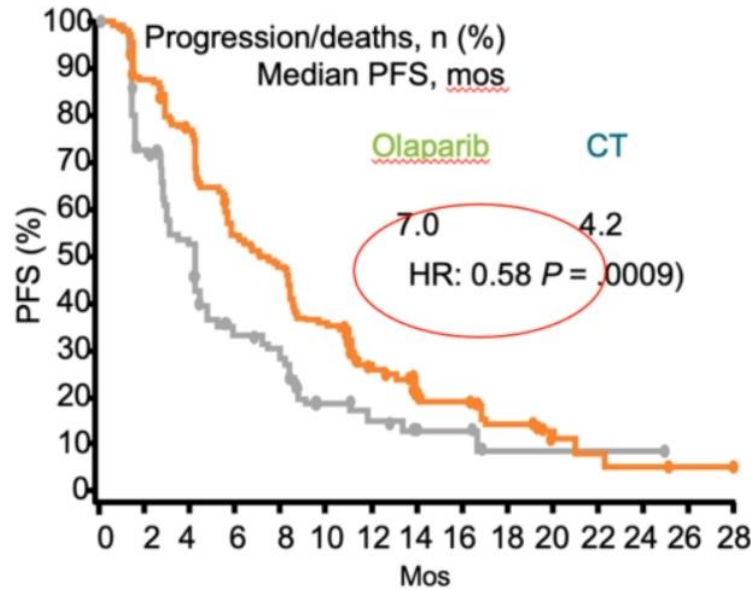
BROCADE 3 / Dieras V.C., et al., ESMO 2019, Abs LBA9

PARPi en situation métastatique

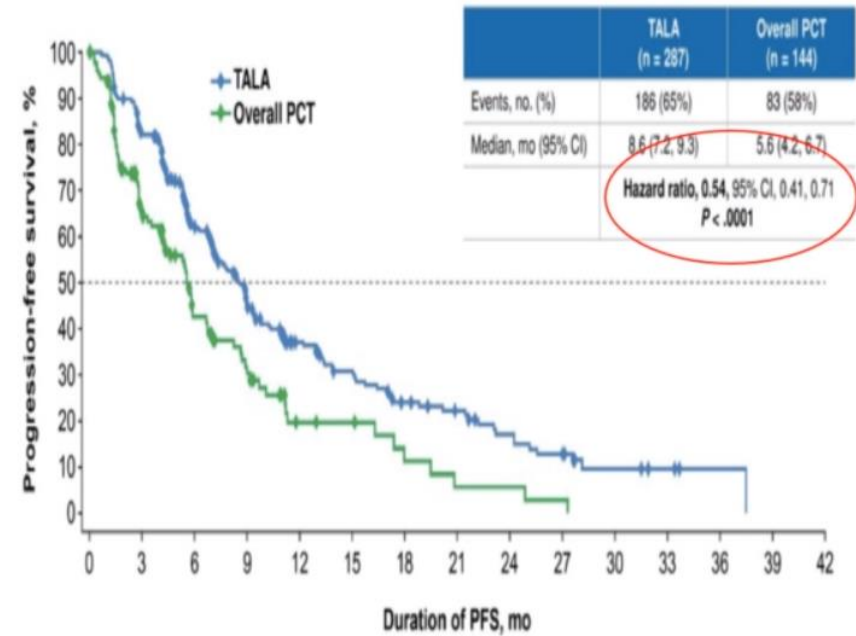
OLYMPIA-D & EMBRACA; Phase III PARPi Trials



OLYMPIAD



EMBRACA

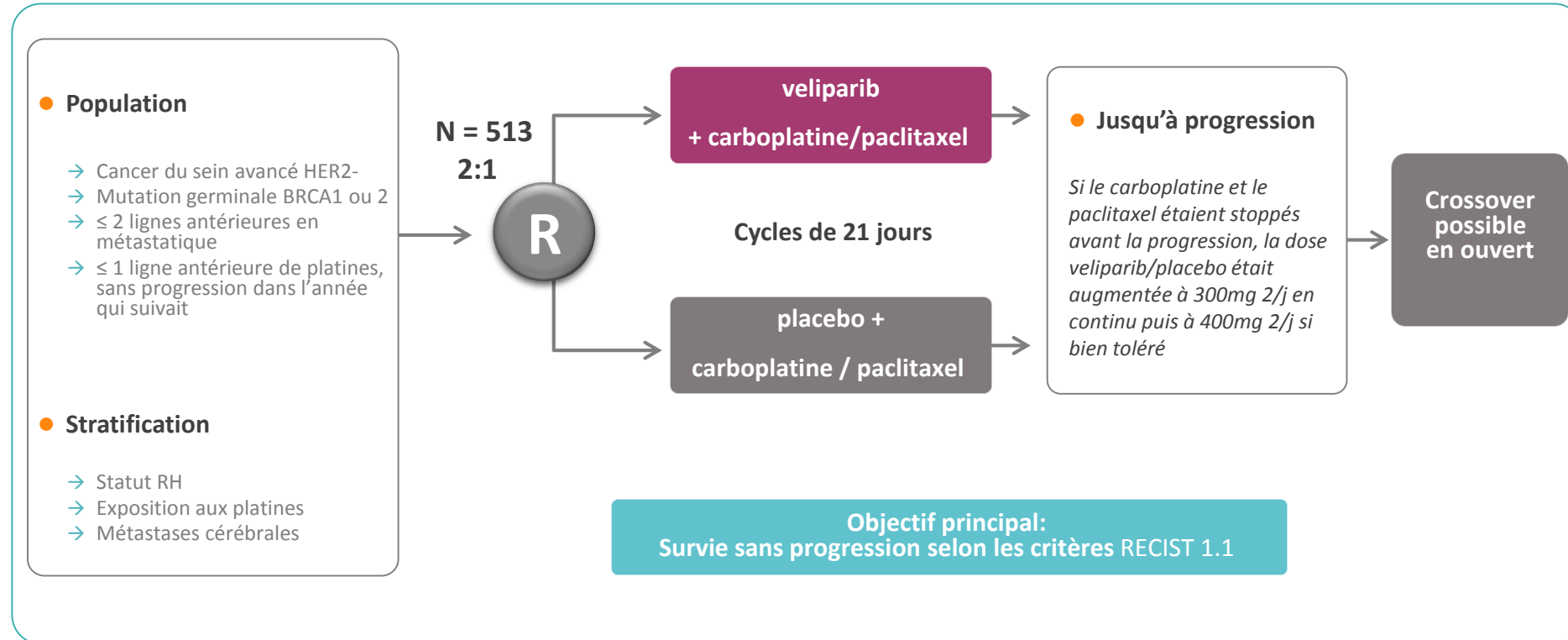


BROCADE 3

Dieras V.C., et al., ESMO 2019, Abs LBA9

BROCADE 3

schéma de l'étude



BROCADE 3

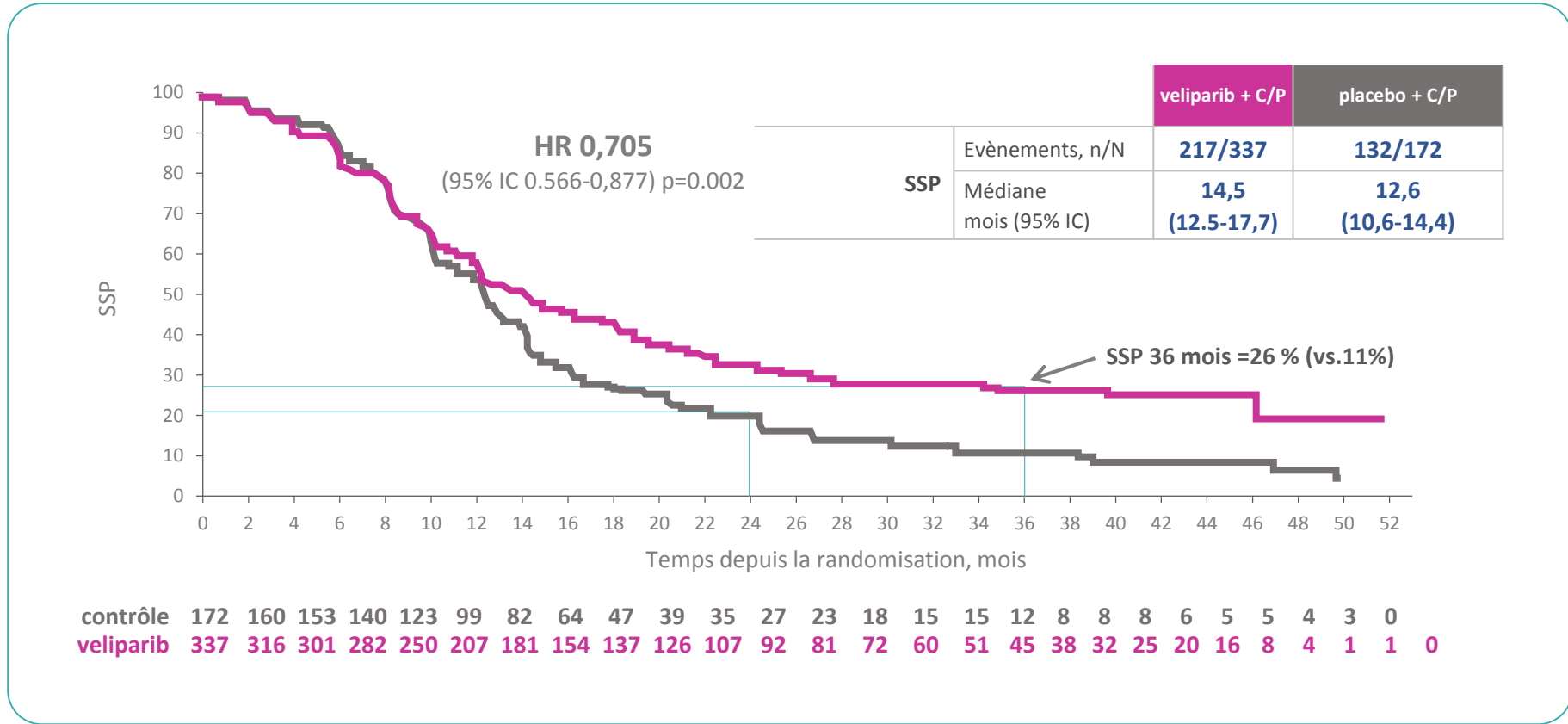
caractéristiques

Caractéristiques, no. (%)	veliparib +C/P (N = 337)	placebo + C/P (n=172)
Statut RH		
RE et/ou PR +	174 (52)	92 (54)
RE et PR -	163 (48)	80 (47)
Statut mutationnel BRCA		
Mutation BRCA1	177 (53)	89 (52)
Mutation BRCA2	167 (50)	86 (50)
Maladie Mesurable		
Oui	285 (85)	143 (84)
Non	52(15)	28 (16)
Performance Status		
0	208 (62)	102 (59)
1	121 (36)	63 (37)
2	8 (2)	7 (4)

Caractéristiques, no. (%)	veliparib +C/P (N = 337)	placebo + C/P (n=172)
Exposition aux platines		
Oui	27(8)	16(9)
Non	310 (92)	156 (91)
Chimiothérapie antérieure en peri-opératoire		
Oui	236 (70)	113 (66)
Non	101 (30)	59 (34)
Chimiothérapie antérieure au stade métastatique		
Oui	63 (19)	33 (19))
Non	274 (81)	139 (81)
Métastases cérébrales		
Oui	16 (5)	10 (6)
Non	320 (95)	161 (94)

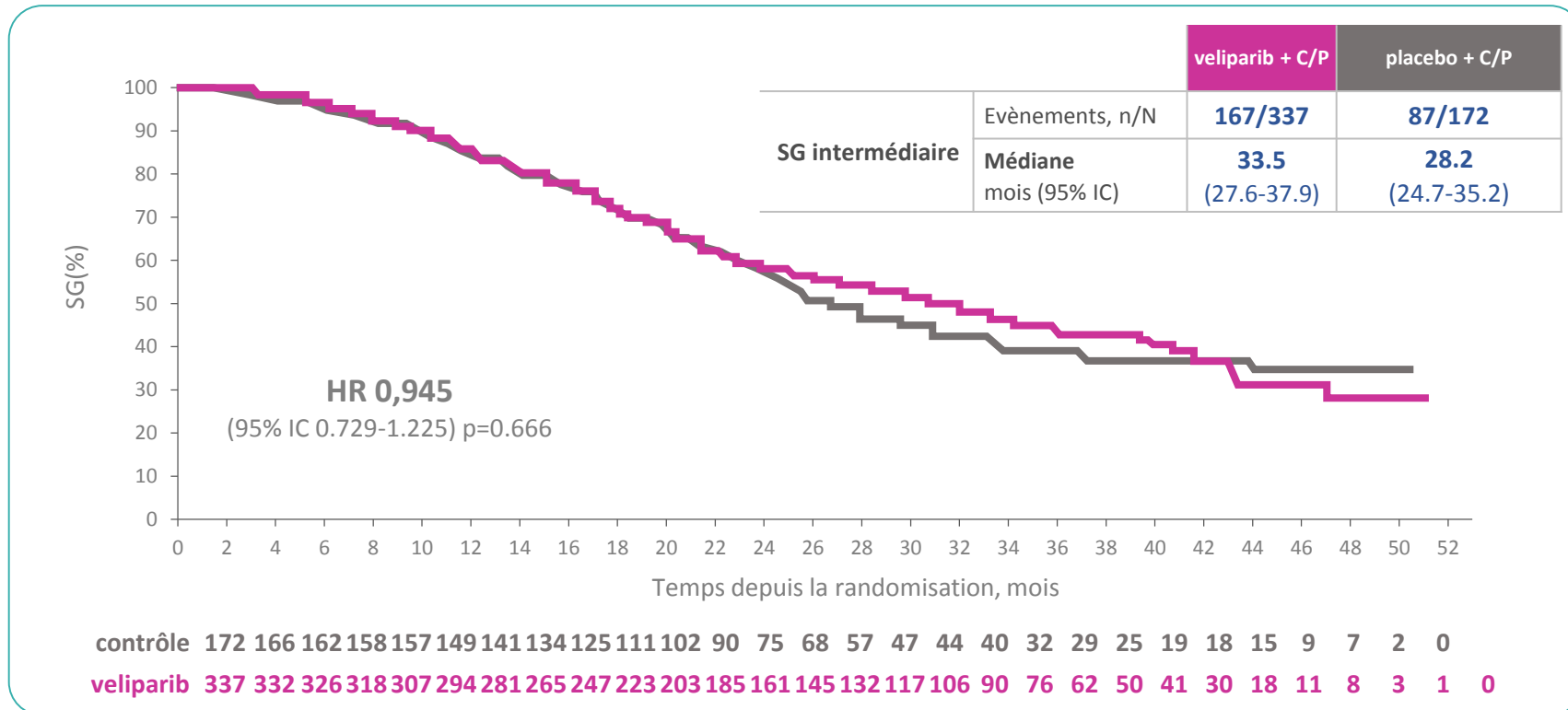
BROCADE 3

survie sans progression



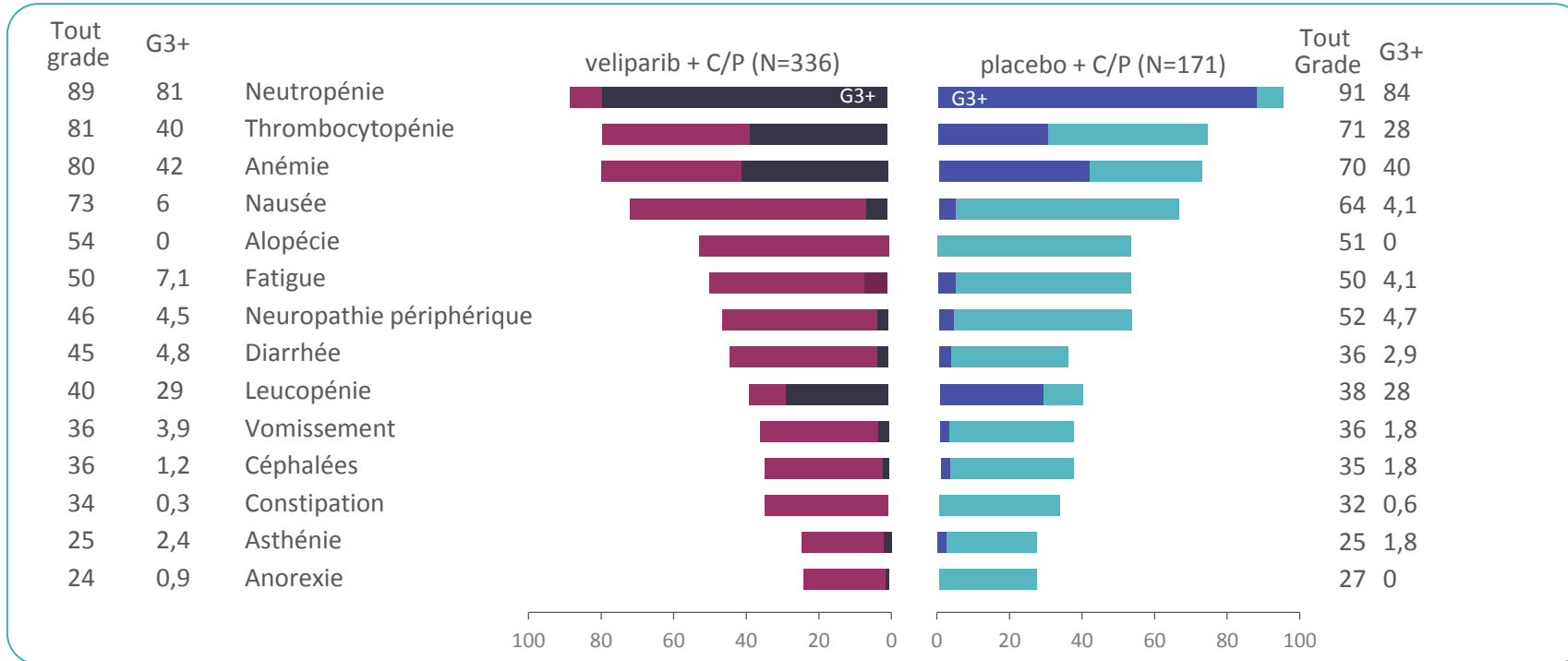
BROCADE 3

Survie Globale (analyse intermédiaire)



BROCADE 3

Tolérance

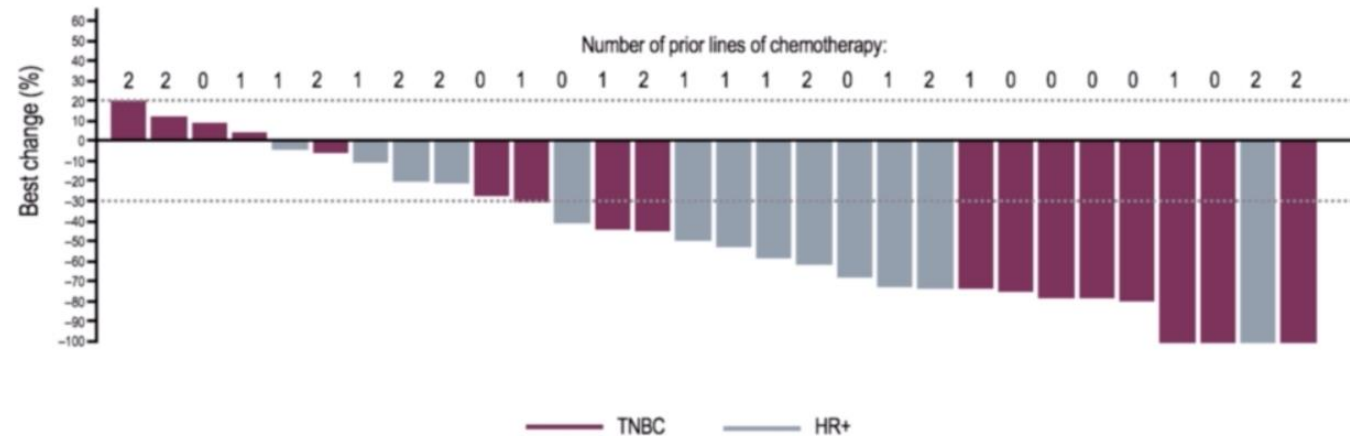
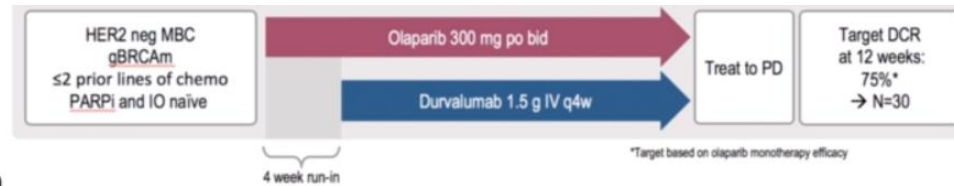


MEDIOLA

Association PARPi- Immune Checkpoint inhibiteur

Phase II study of olaparib and durvalumab (MEDIOLA): Updated results in patients with germline BRCA-mutated metastatic breast cancer

Susan M Domchek¹, Sophie Postel-Vinay², Seock-Ah Im³, Yeon Hee Park⁴, Jean-Pierre Delord⁵, Antoine Italiano⁶, Jerome Alexandre⁷, Benoit You⁸, Sara Bastian⁹, Matthew G Krebs¹⁰, Ding Wang¹¹, Saiama Waqar¹², Mark Lanasa¹³, Helen K Angell¹⁴, Zhongwu Lai¹⁵, Christopher Gresty¹⁴, Laura Opincar¹³, Pia Herbolzheimer¹³ and Bella Kaufman¹⁶



Endpoint	FAS, % n=30	TNBC, % n=17	HR+, % n=13	0-1 prior line, % n=20	Two prior lines, % n=10
ORR (95% CI)	63.3 (43.9, 80.1)	58.8 (32.9, 81.6)	69.2 (38.6, 90.9)	70.0 (45.7, 88.1)	50.0 (18.7, 81.3)

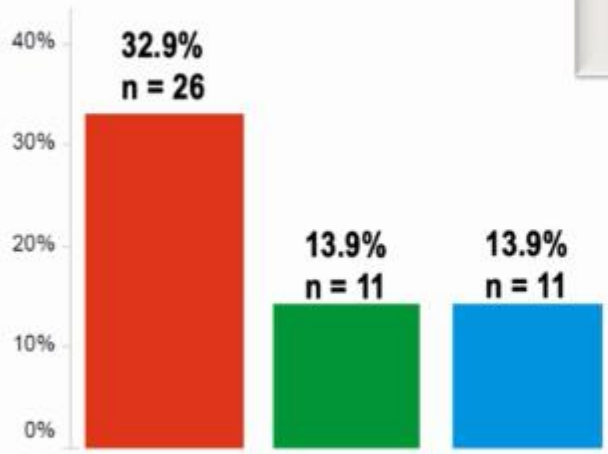
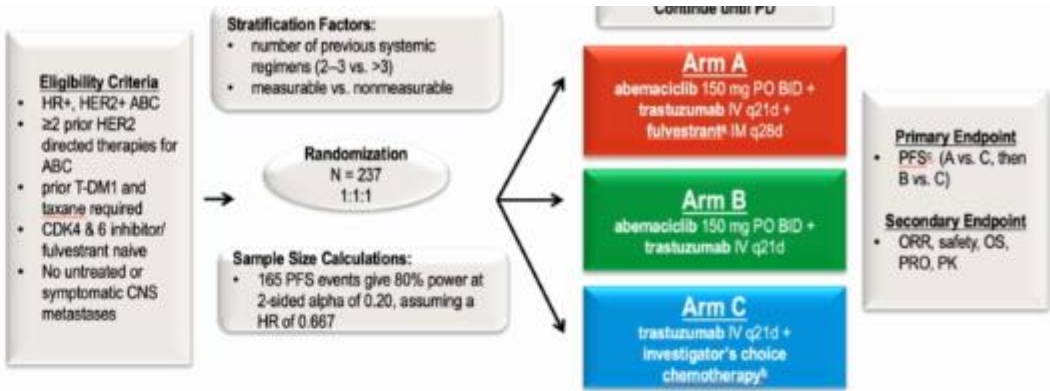
Conclusions

- Cancer du sein RH+ Her2- et inhibiteurs de CDK4/6
 - Stades avancés : « standard of care », efficacité confirmée 1^{ère}/2^{ème} ligne
 - translation aux stades précoces: essais néo-adjuvants, post-néo-adjuvants, adjuvants
- Cancer du sein triple négatif et immunothérapie
 - Stades avancés : précocement dans la population ciblée biomarqueur/test compagnon
 - Stades précoces: résultats prometteurs
- Population BRCA:
 - Sous-groupe moléculaire bénéficiant des PARPi
 - Séquence chimio/platine, association immune-checkpoints

Merci de votre attention

MonarchER: Tolaney et al (LBA23)

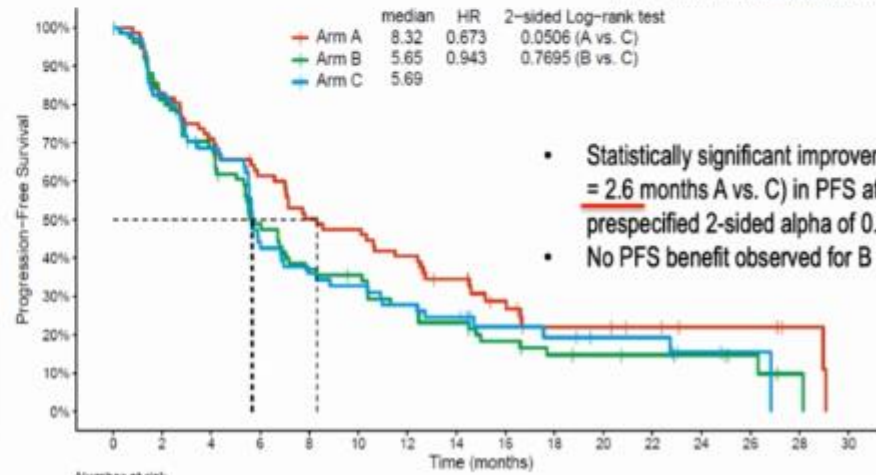
CDK4/6 inhibition + anti-HER2 therapy in HER2+ MBC



ITT Population
Total N = 237

	Arm A N=79	Arm B N=79	Arm C N=79
95% CI (%)	(22.5-43.3)	(6.3-21.6)	(6.3-21.6)
Stratified 2-sided p-value (vs Arm C)	0.0042	1.0000	-
Duration of Response, months	12.5	9.5	not reached

PRIMARY ENDPOINT: PFS



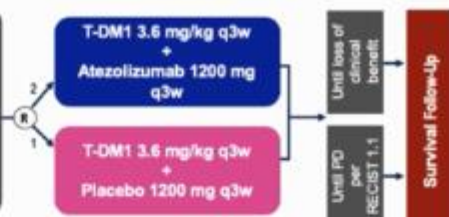
Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy

- Statistically significant improvement ($\Delta = 2.6$ months A vs. C) in PFS at prespecified 2-sided alpha of 0.2
- No PFS benefit observed for B vs. C

OVERALL SURVIVAL IN KATE2 (NCT02924883): A PHASE 2 STUDY OF PD-L1 INHIBITOR ATEZOLIZUMAB + TRASTUZUMAB EMTANSINE (T-DM1) VS PLACEBO + T-DM1 IN PREVIOUSLY TREATED HER2-POSITIVE ADVANCED BREAST CANCER

Leisha A. Emens,¹ Francisco Esteve,² Mark Beresford,³ Cristina Saura,⁴ Michelino De Laurentis,⁵ Sung-Bae Kim,⁶ Seock-Ah Im,⁷ Yifan Wang,⁸ Aruna Mani,⁹ Jigna Shah,⁹ Haiying Liu,⁹ Sanne de Haas,¹⁰ Monika Patre,¹⁰ Sherene Loi¹¹

HER2+ LABC or MBC
• Prior taxane and trastuzumab
• Progression on metastatic therapy or within 6 months of adjuvant therapy
• Measurable disease
(n=202)



Stratification factors:

- Tumour PD-L1 IC status (IC0 [$<1\%$] vs IC1/2/3 [$\geq 1\%$])^a
- World region (Western Europe vs North America vs rest of world)
- Presence of liver metastases (yes or no)

- Primary endpoint:**
- Investigator-assessed PFS
- Secondary endpoints:**
- OS
 - Objective response rate
 - Duration of response
- Exploratory endpoints:**
- PFS in patients with PD-L1+ disease
 - Exploratory biomarker subgroups (PD-L1, PIK3CA mutation status, HER2 expression, immune-related [TILs, CD8 IHC expression])
- Post hoc endpoint:**
- OS in PD-L1 subgroups

ITT

Small study – need phase III

PD-L1 IC+

