Cancers du Sein Métastatiques

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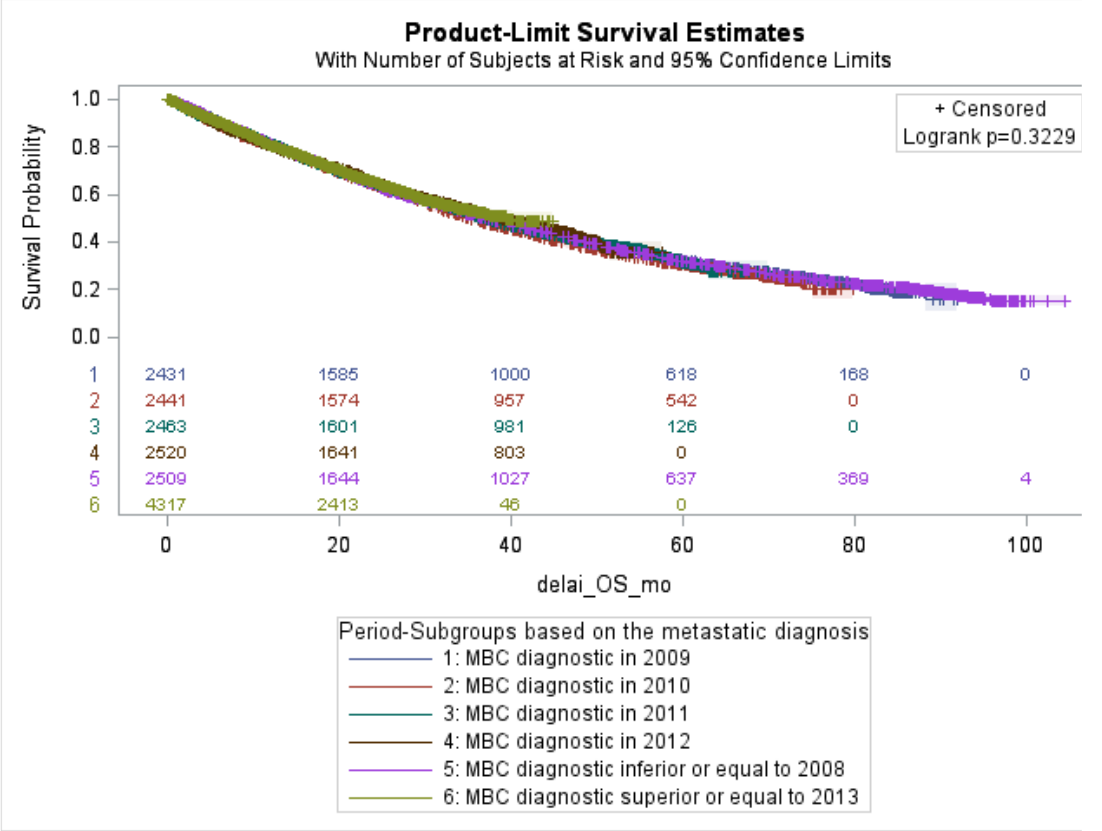
Rennes 18 mai 2018

Plan

- ESME
- Inhibiteurs CDK 4/6 RH+
- Inhibiteurs PARP
- Anticorps drogue-conjugués
- Perspectives 2018-2019

ESME

Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort

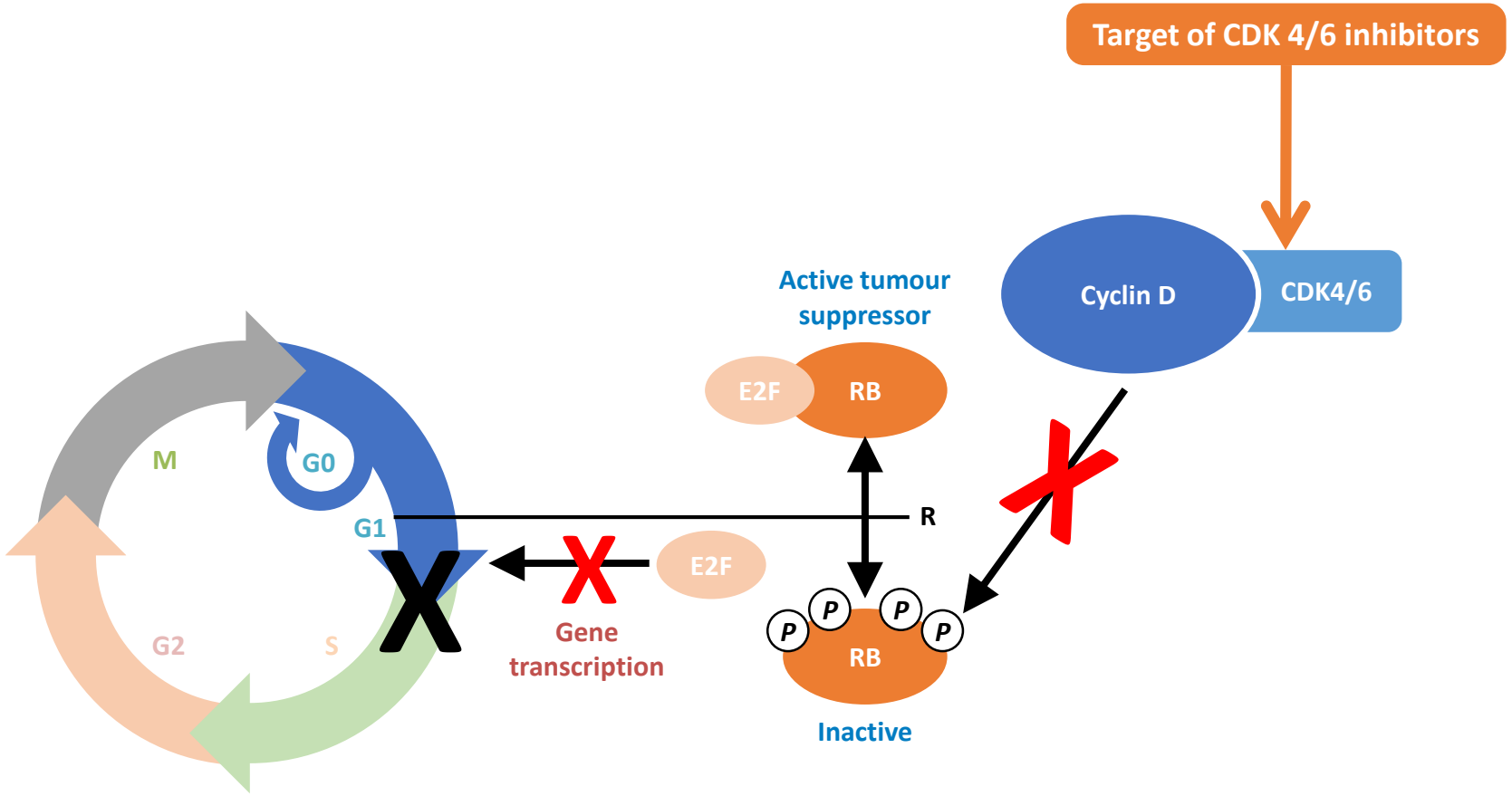


OS median (95 % of CI)	Year of diagnosis	2008	2009	2010	2011	2012	2013
HR+HER2- (n=9908)		43.7 [40.2-46.6]	42.0 [38.9-44.6]	40.9 [38.0-43.4]	42.0 [39.26-45.04]	44.5 [41.8-47.3]	40.3 [37.8-ND]
HER2+++ (n=2861)		38.67 [33.6-44.6]	42.3 [38.3-50.8]	40.1 [35.2-45.6]	42.38 [36.5-49.8]	51.1 [46.5-ND*]	Median not reached
HR-HER2- (n=2317)		15.1 [12.7-16.4]	15.1 [13.0-17.4]	14.7 [13.2-17.0]	14.0 [11.4-15.9]	13.9 [11.4-15.9]	14.1 [12.5-15.5]

Gobbini E, European Journal of Cancer 2018

INHIBITEURS CDK 4/6

Mechanism of action: selective CDK4/6 inhibition



Palbociclib arrests the cell cycle at G1 by selective inhibition of CDK4/6

Fry DW, et al. *Mol Cancer Ther.* 2004;3:1427; Carnero A. *Br J Cancer.* 2002;87:129.

CDK 4/6 inhibitors: Clinical programs

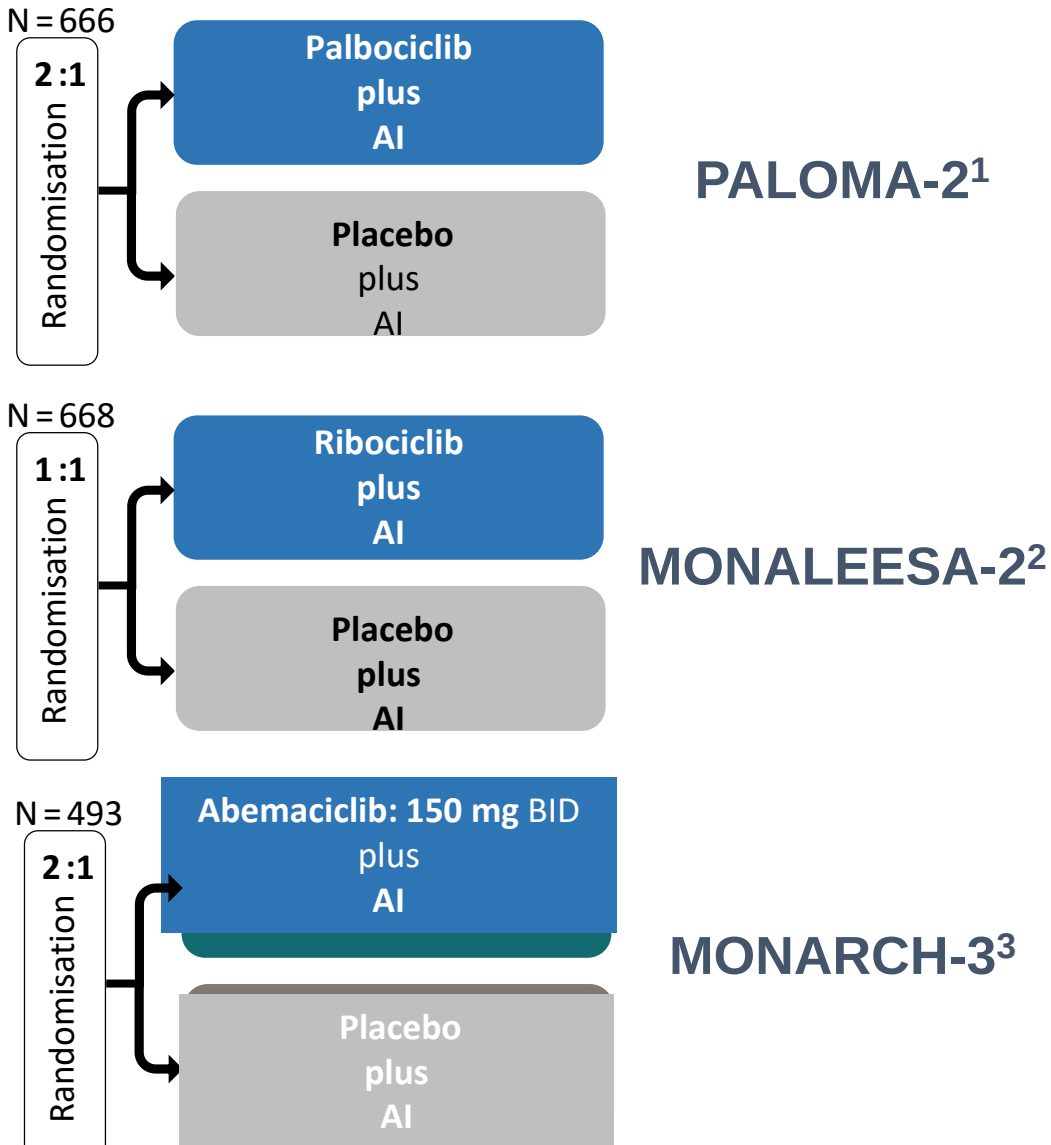
Palbociclib (PD0332991)	Ribociclib (LEE011)	Abemaciclib (LY28335219)
Pfizer	Novartis	Lilly
PALOMA	**MONALEESA**	**MONARCH**

Clinicaltrials.gov. Palbociclib: NCT01740427; Ribociclib : NCT01958021; Abemaciclib: NCT02057133.

First-line CDK inhibitors study designs

- HR+, HER2- ABC
- Postmenopausal
- **No prior systemic therapy in this setting**
- If neoadjuvant or adjuvant ET administered, a disease-free interval of >12 months since completion of ET
- ECOG PS ≤1

Primary endpoint:
Investigator-assessed PFS



ABC, advanced breast cancer; BID, twice a day; ET, endocrine therapy

1.Finn RS, et al. N Engl J Med 2016;375:1925–1936; 2. Hortobagyi G, et al. N Engl J Med 2016;375:1738–1748; 3. Goetz MP et al. J Clin Oncol. 2017;35:3638–3646.

Populations in recent phase 3, first-line, ER+ mBC trials

	PALOMA-2[1] (n=666)	MONALEESA-2[2] (n=668)	MONARCH-3[3*] (n=493)	FALCON[4] (n=462)
Disease-free interval				
De-novo mBC	37%	34%	39%	mBC: 87% laBC: 13%
<12 months	22%	2%	Not reported	
>12 months	41%	64%	Not reported	
Prior treatment				
Adjuvant endocrine therapy	56%	52%	47%	<1%
Adjuvant chemotherapy	40%	44%	39%	13%
Chemotherapy for mBC	nil	nil	nil	18%
Site of disease				
Visceral	49%	59%	53%	55%
Bone only	23%	22%	22%	10%[a]

Cross-trial comparisons need to be taken with caution due to differences in trial design
Abemaciclib is not approved for use in metastatic breast cancer in the EU
[a]Bone or musculoskeletal only
laBC, locally advanced breast cancer; mBC, metastatic breast cancer; nil, not included
1. Finn R et al. New Eng J Med 2016;375:1925-1936; 2. Hortobagyi G et al. New Eng J Med 2016;375:1738-1748; 3. Goetz MP et al. J Clin Oncol 2017;35:3638-3646; 4. Robertson J et al. Lancet 2016;388:2997-2305

Selective CDK4/6 inhibitors: Efficacy in first-line mBC

PALOMA-2[1]

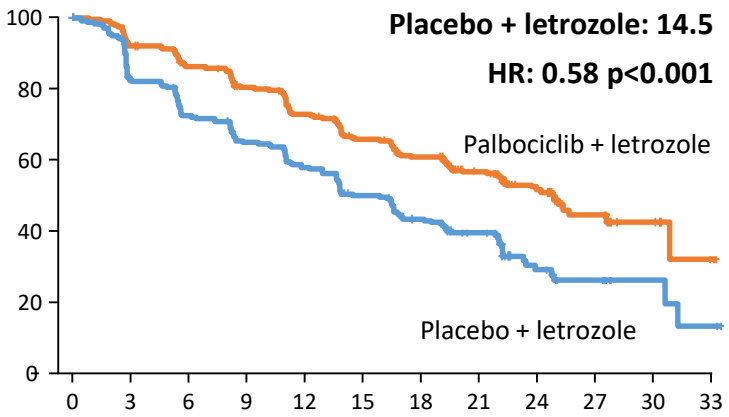
Palbociclib + letrozole

Median PFS (months)

Palbociclib + letrozole: 24.8

Placebo + letrozole: 14.5

HR: 0.58 p<0.001



MONALEESA-2[2]

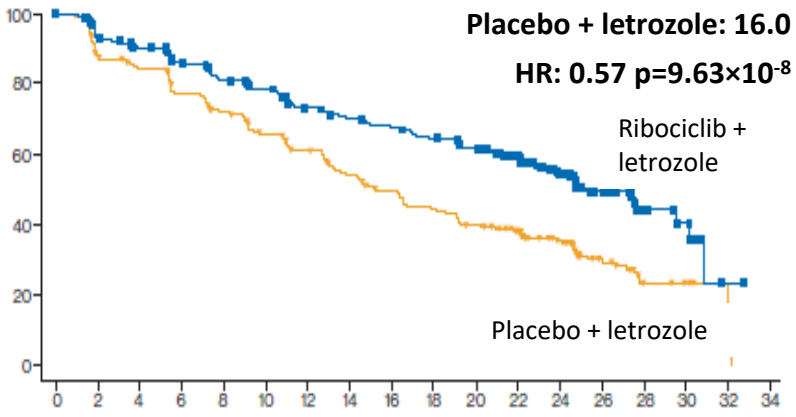
Ribociclib + letrozole

Median PFS (months)

Ribociclib + letrozole: 25.3

Placebo + letrozole: 16.0

HR: 0.57 p=9.63×10^{-8}



MONARCH-3[3]

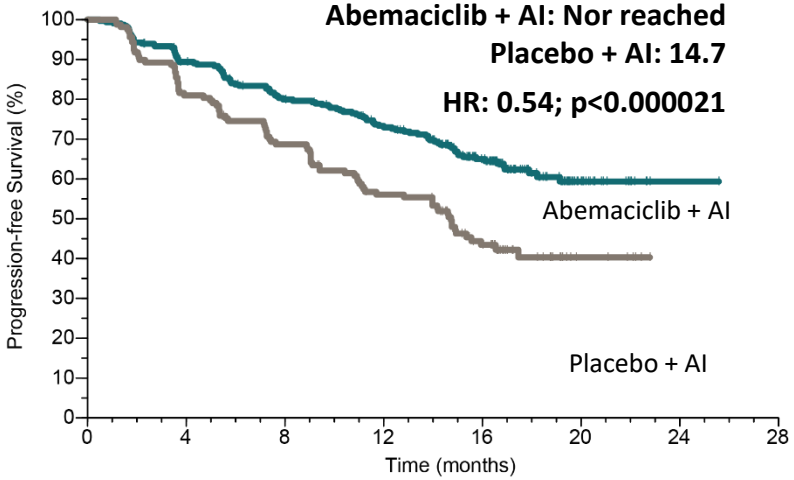
Abemaciclib + AI

Median PFS (months)

Abemaciclib + AI: Nor reached

Placebo + AI: 14.7

HR: 0.54; p<0.000021



Cross-trial comparisons need to be taken with caution due to differences in trial design

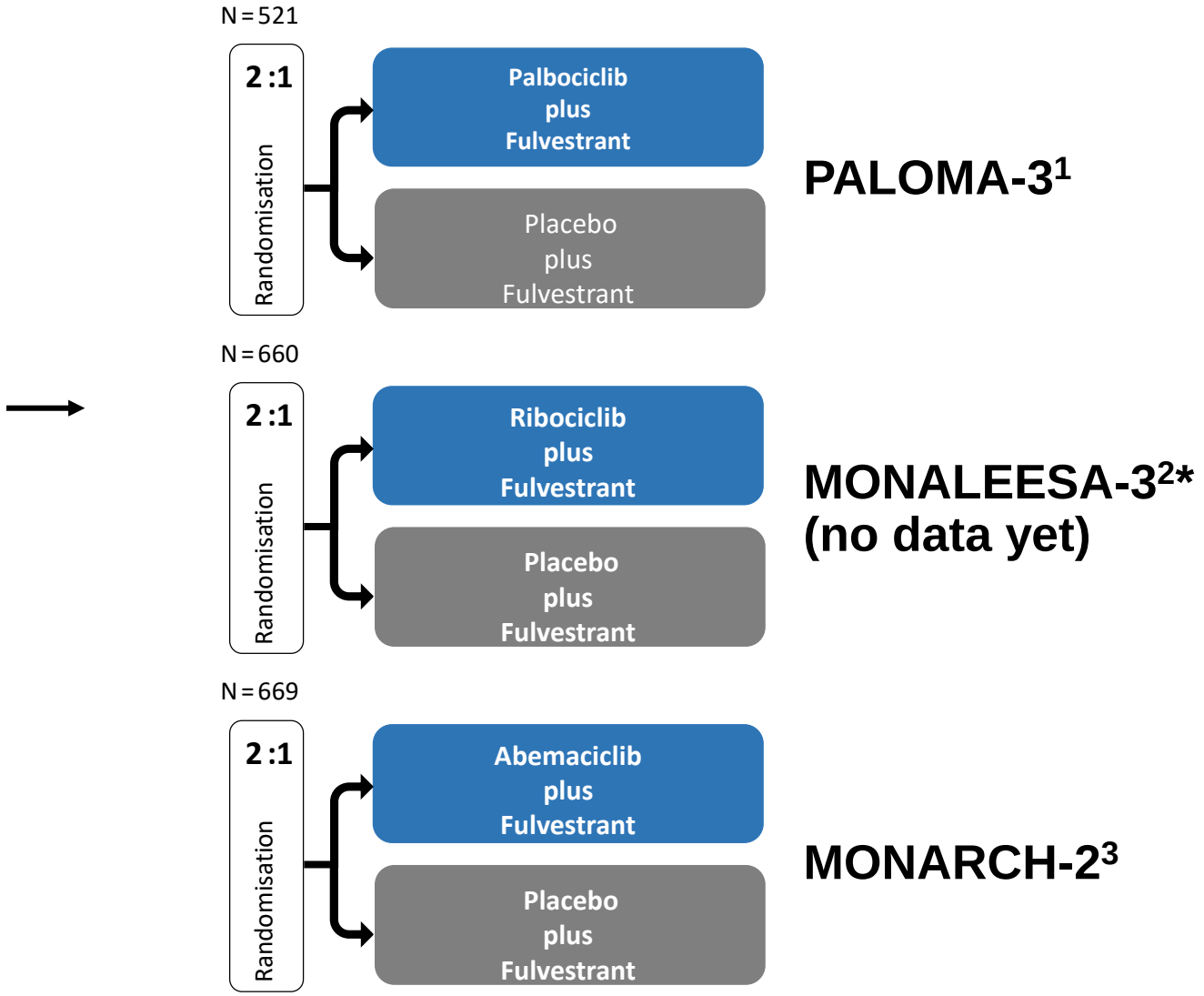
1. Finn R et al. New Eng J Med 2016;375:1925-1936; 2.Ribociclib SmPC, August 2017, accessed March 2018 3. Goetz MP et al. J Clin Oncol 2017;35:3638-3646 and AACR 2018

Endocrine resistance CDK inhibitors study designs

- HR+, HER2- ABC
- Pre/peri and postmenopausal*
- Progressed on prior endocrine therapy:
  - On or within 12 month adjuvant
  - On therapy for ABC

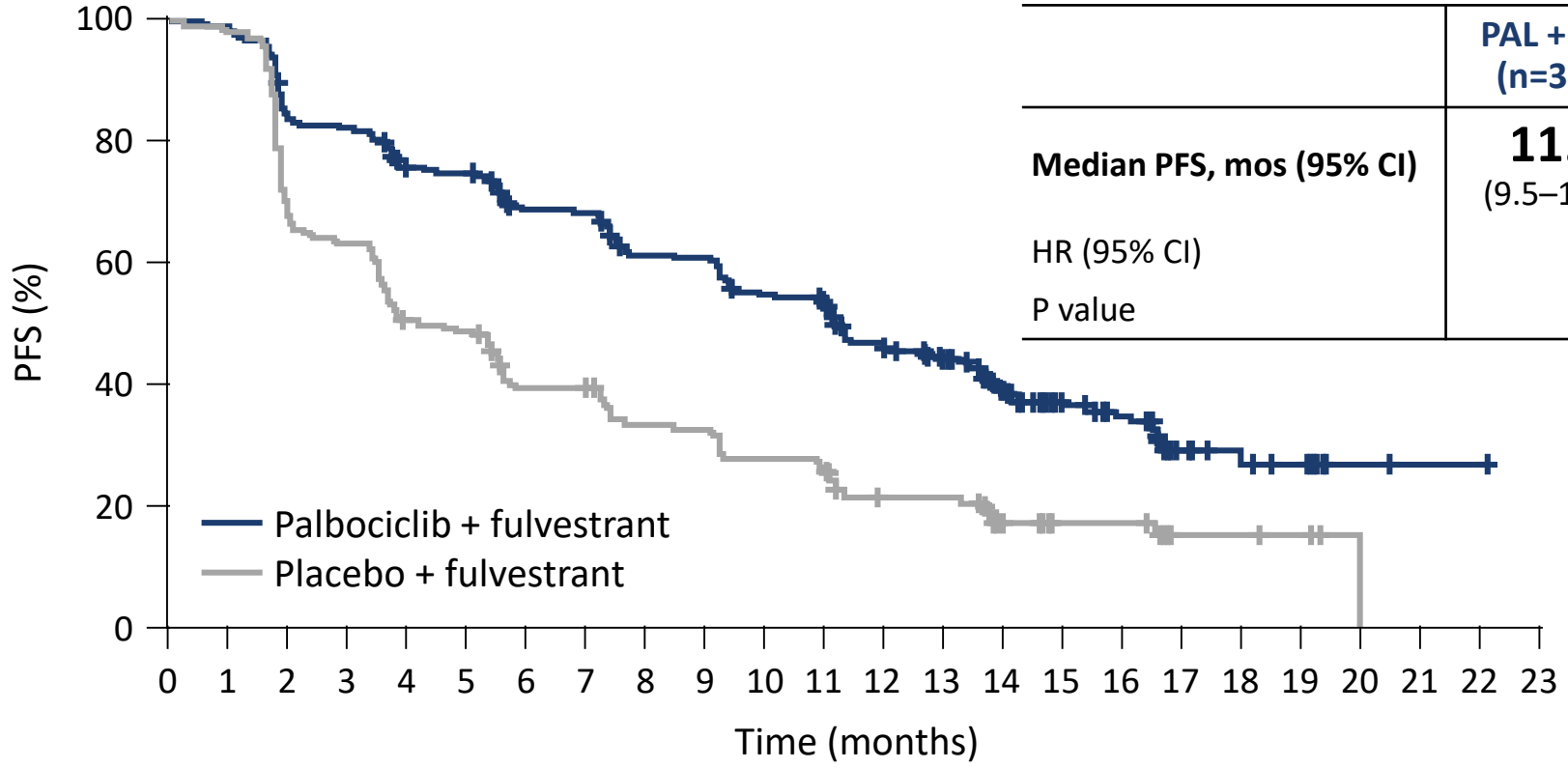
Primary endpoint:
Investigator-assessed PFS

*Only postmenopausal



1. Turner NC, et al. N Engl J Med 2015;373:209–219; 2. ClinicalTrials.gov Identifier: NCT02422615;
3. Sledge G, et al. J Clin Oncol 2017;35:2875–2884.

PALOMA-3 final analysis: Updated investigator-assessed PFS



	PAL + FUL (n=347)	PLACEBO + FUL (n=174)
Median PFS, mos (95% CI)	**11.2** (9.5–12.9)	**4.6** (3.5–5.6)
HR (95% CI)	0.50 (0.40–0.62)	
P value	<0.0001	

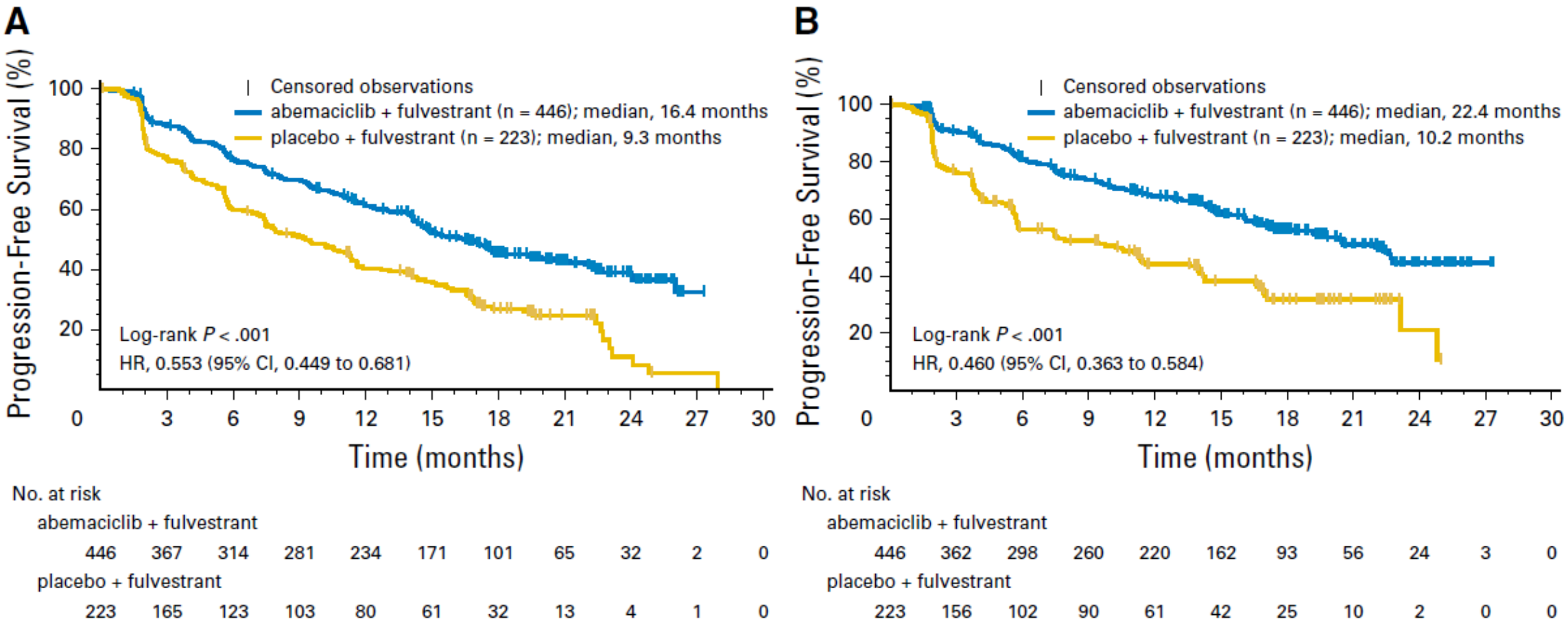
Number at risk

PAL + FUL	347	324	276	271	245	242	215	214	189	188	168	162	137	119	69	45	38	15	12	9	2	1	1	0
PCB + FUL	174	162	112	105	83	80	62	61	51	50	43	40	29	29	15	11	11	4	4	3	1	0		

- Palbociclib + fulvestrant doubled mPFS in patients with progression on/after ET in PALOMA-3

Data cut-off October 2015.
mPFS, median PFS.
Turner NC, et al. Poster presented at SABCS 2016 (Abstract P4-22-06).

MONARCH-2: Abemaciclib + Fulvestrant



Sledge GW Jr, et al. *J Clin Oncol.* 2017;35:2875–84

Summary of pivotal trials of CDK4/6 inhibitors: Endocrine-sensitive population

Efficacy	HR	95% CI
PALOMA-2	0.58	0.46–0.72
MONALEESA-2	0.56	0.43–0.72
MONARCH-3	0.54	0.41–0.72

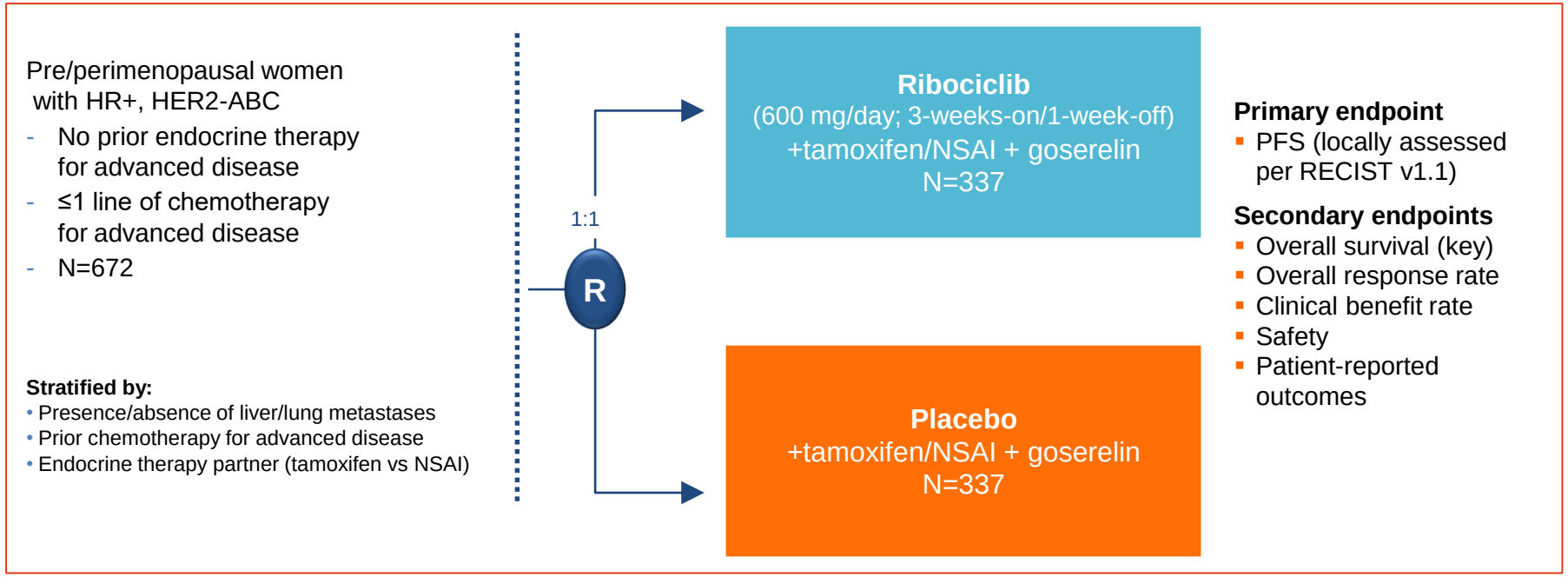
Safety	Neutropenia grade 3/4	Diarrhoea grade 3/4	Schedule
PALOMA-2	66%	1.4%	Intermittent
MONALEESA-2	59%	1.2%	Intermittent
MONARCH-3	21%	9.5%	Continuous

Very low rate febrile neutropenia

Cross-trial comparisons need to be taken with caution due to differences in trial design
Abemaciclib is not approved for use in metastatic breast cancer in the EU

1. Finn R et al. New Eng J Med 2016;375:1925-1936; 2. Hortobagyi G et al. New Eng J Med 2016;375:1738-1748; 3. Goetz MP et al. J Clin Oncol 2017;35:3638-3646

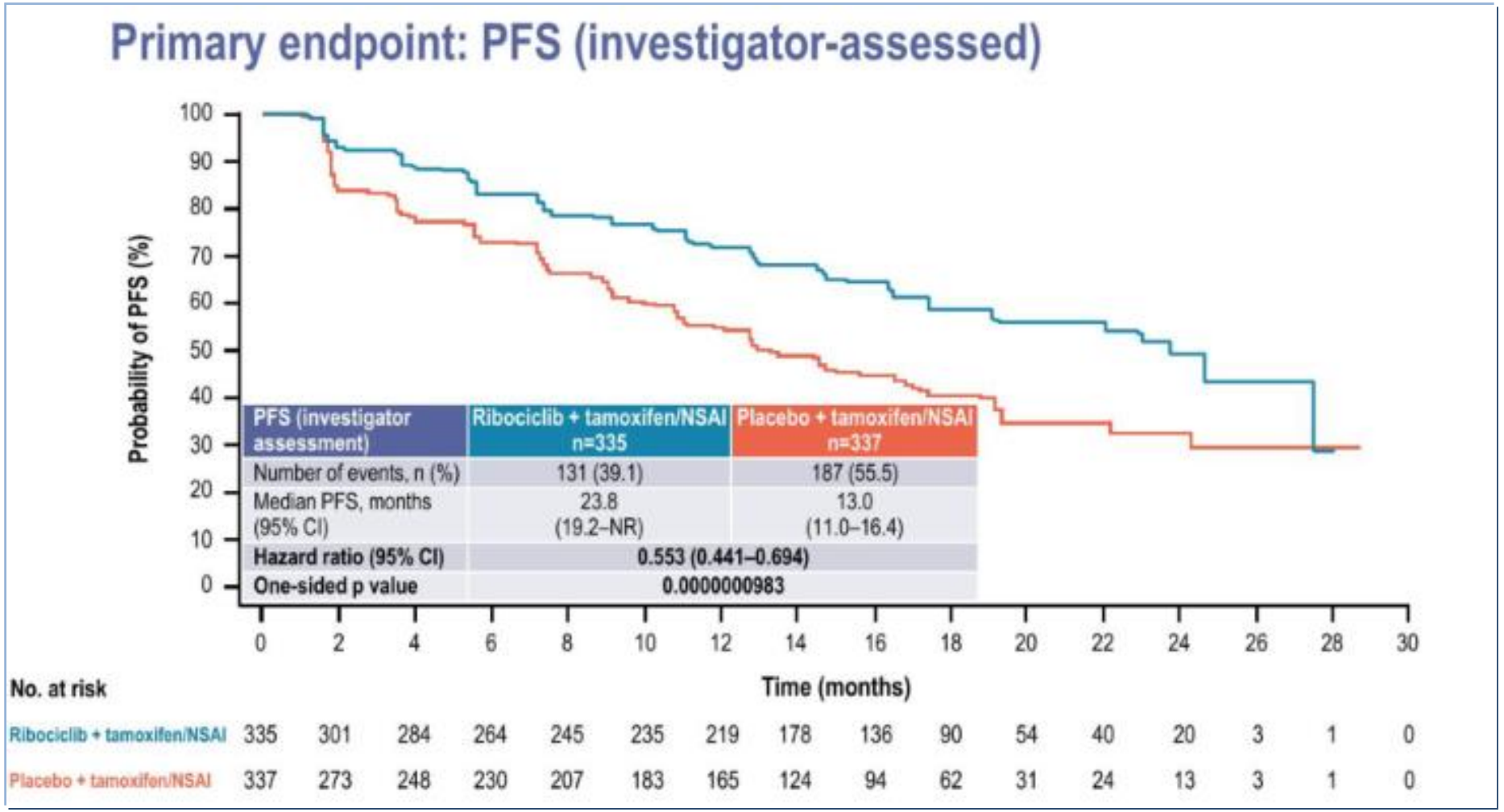
MONALEESA-7



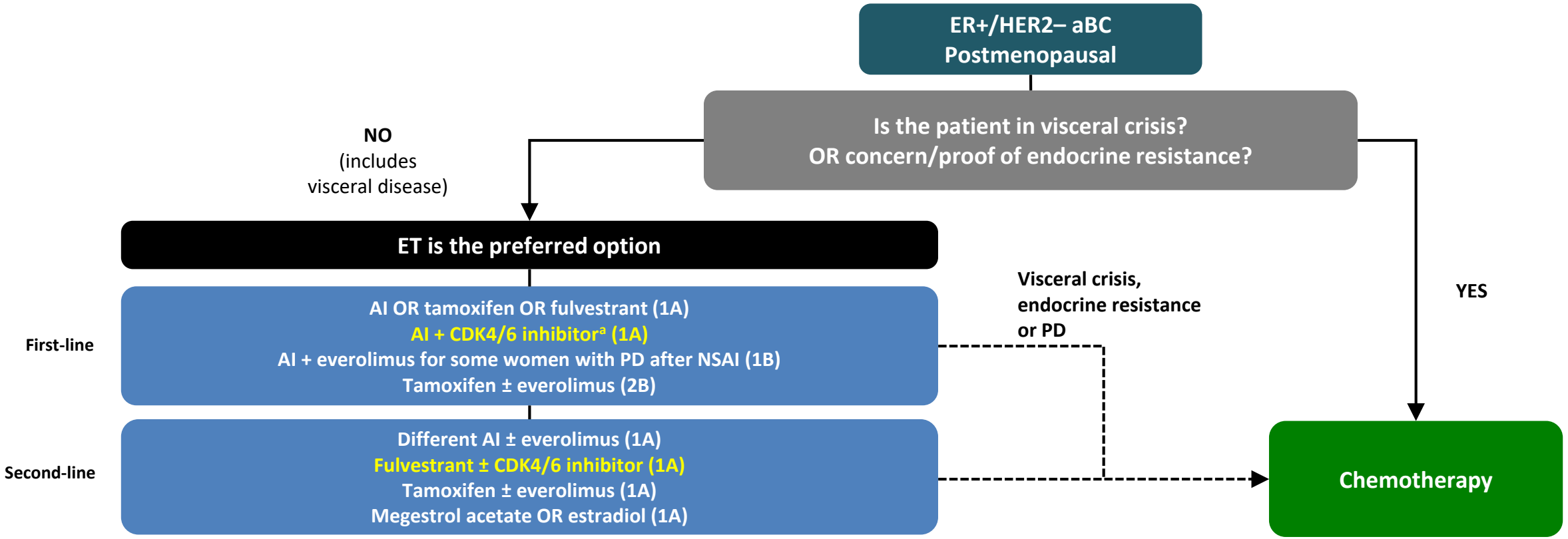
- Tumor assessments were performed every weeks for months, then every weeks thereafter
- Primary analysis planned after ~ 329 PFS events
  - 95% power to detect a 33% risk reduction (hazard ratio 0.67) with one-sided α=2.5%, corresponding to an increase in median PFS to 13.4 months (median PFS of 9 months for the placebo arm), and a sample size of 660 patients

Tripathy D.et al., SABCS 2017, GS2-05

MONALEESA-7


Primary endpoint: PFS (investigator-assessed)
Probability of PFS (%)
100
90
80
70
60
50
40
30
20
10
0
PFS (investigator assessment)
Ribociclib + tamoxifen/NSAI n=335
Placebo + tamoxifen/NSAI n=337
Number of events, n (%)
131 (39.1)
187 (55.5)
Median PFS, months (95% CI)
23.8 (19.2–NR)
13.0 (11.0–16.4)
Hazard ratio (95% CI)
0.553 (0.441–0.694)
One-sided p value
0.0000000983
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
Time (months)
No. at risk
Ribociclib + tamoxifen/NSAI 335 301 284 264 245 235 219 178 136 90 54 40 20 3 1 0
Placebo + tamoxifen/NSAI 337 273 248 230 207 183 165 124 94 62 31 24 13 3 1 0

ABC3 guidelines: Postmenopausal patients with ER+/HER2- aBC



[a]Except for relapse <12 months from finishing adjuvant AI

PD, progressive disease

Cardoso F, et al. Ann Oncol. 2017;28:16–33

RECOMMENDATIONS ABC4

HR+/HER2- ABC

- ✓ **Traitement identique pour patientes pre/postmenopausées**
- ✓ **Everolimus: en cas de résistance hormonothérapie option valide**
- ✓ **Addition CDK4/6 inhibiteur en première ligne à IA**
- ✓ **Addition CDK4/6 inhibiteur au fulvestrant en cas de résistance à l'hormonothérapie**
- ✓ **Séquence optimale ?**
- ✓ **Absence de biomarqueurs**

INHIBITEURS PARP

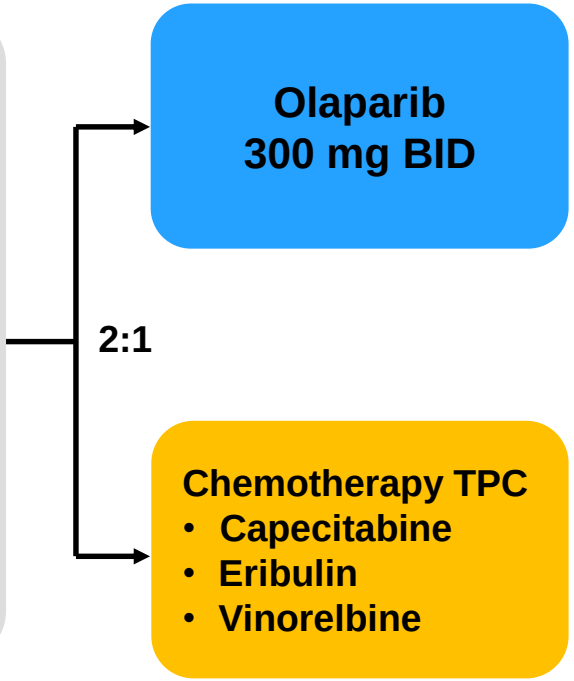
OLYMPIAD: STUDY DESIGN

Open-label, Phase III trial

HER2- MBC(N=302)

- ER+ and/or PR+ (HR+) or
- TNBC

- Deleterious or suspected deleterious g*BRCA* mutation
- ≤2 prior CT lines in metastatic setting
- Prior anthracycline and taxane
- HR+ disease progressed on ≥1 ET, or not suitable
- If prior platinum use
  - No evidence of progression under treatment
  - ≥12 months since (neo)adjuvant treatment



- **Primary endpoint:** PFS (RECIST 1.1, BICR)
- **Secondary endpoints:** OS, time to second progression or death, ORR, global HRQoL (EORTC-QLQ-C30), safety and tolerability

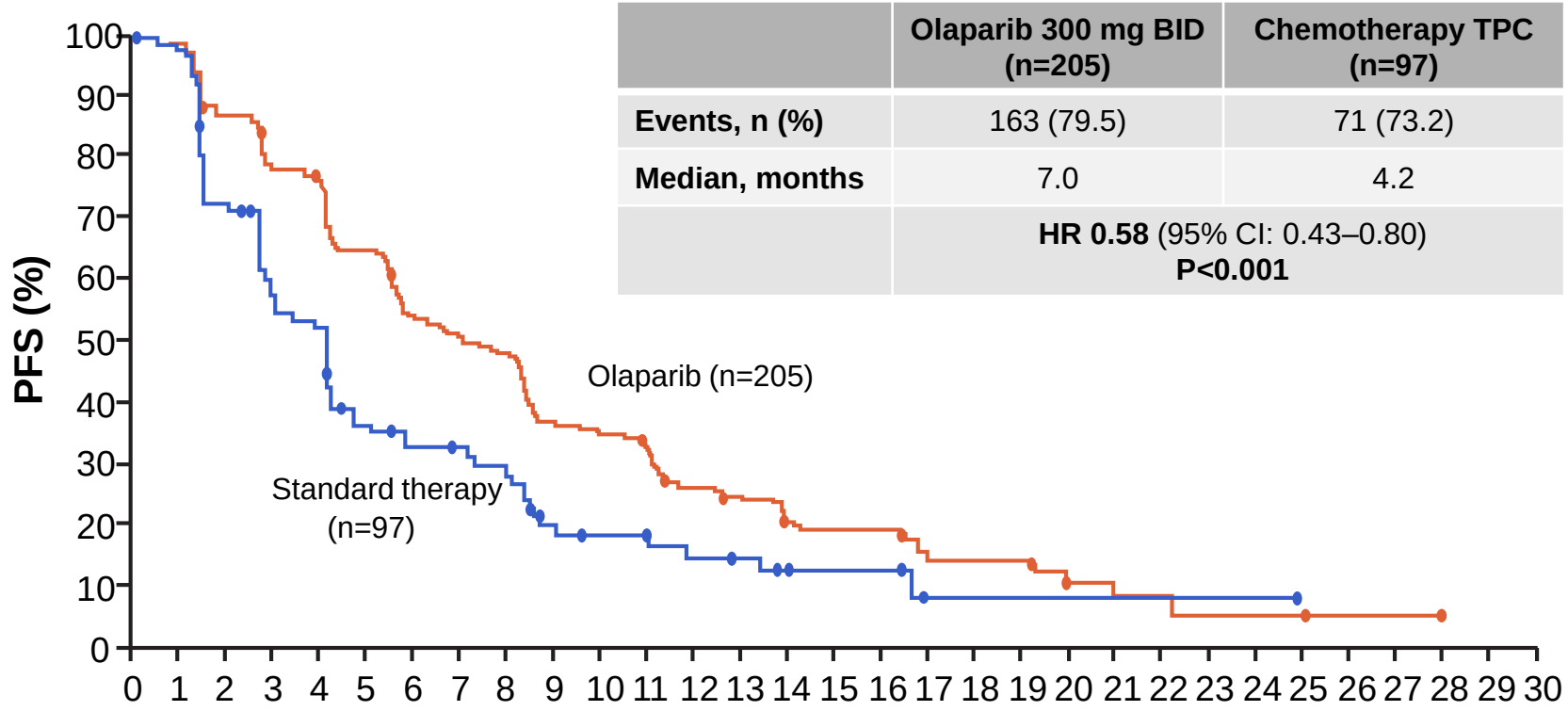
Investigational drug: olaparib is not approved for use breast cancer in Europe.

BICR, blinded independent central review; BID, twice daily; EORTC; European Organisation for Research and Treatment of Cancer; ER, oestrogen receptor; g*BRCA*, germline *BRCA*; HRQoL, health-related quality of life; PR, progesterone receptor; QLQ, quality of life questionnaire; RECIST, Response Evaluation Criteria In Solid Tumours; TPC, treatment of physician's choice

Robson M, et al. *N Engl J Med*. 2017;377:523–533.

OLYMPIAD: PFS (CENTRALLY EVALUATED)

	Olaparib 300 mg BID (n=205)	Chemotherapy TPC (n=97)
Events, n (%)	163 (79.5)	71 (73.2)
Median, months	7.0	4.2
	HR 0.58 (95% CI: 0.43–0.80) **P<0.001**	



No. at Risk

Olaparib	205	201	177	159	154	129	107	100	94	73	69	61	40	36	23	21	21	11	11	11	4	3	3	2	2	1	1	1	0
Standard therapy	97	88	63	46	44	29	25	24	21	13	11	11	8	7	4	4	4	1	1	1	1	1	1	1	1	0	0	0	0

Investigational drug: olaparib is not approved for use breast cancer in Europe.
Olaparib is approved by US FDA for the treatment of patients with deleterious or suspected deleterious g*BRCA* mutation, HER2- MBC who have previously been treated with CT in the neoadjuvant, adjuvant or metastatic setting. Patients with HR+ BC should have been treated with a prior ET or be considered inappropriate for ET
FDA, US Food and Drug Administration

Robson M, et al. *N Engl J Med*. 2017;377:523–533.

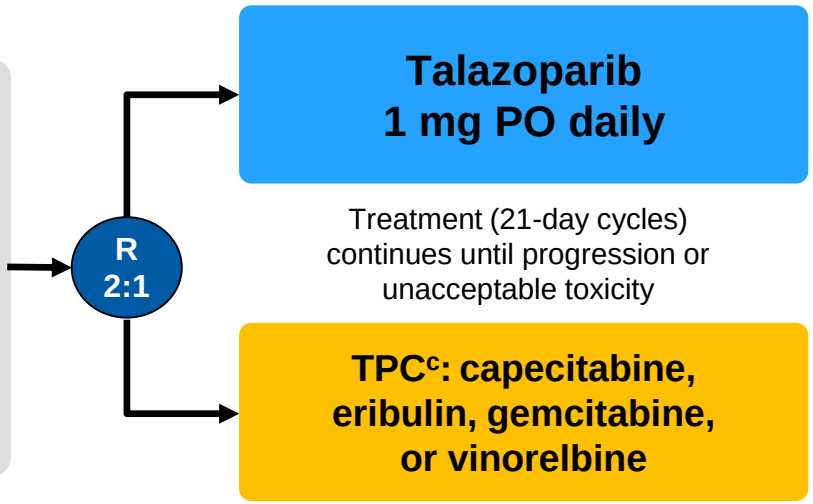
EMBRACA: STUDY DESIGN

Open-label, Phase III trial

Patients with locally advanced or metastatic HER2-negative breast cancer and a germline *BRCA1* or *BRCA2* mutation (n=431)[a,b]

Stratification factors:

- Number of prior chemo regimens (0 or ≥1)
- TNBC or HR+
- History of CNS metastasis or no CNS metastasis



- **Primary endpoint:** PFS by blinded central review
- **Secondary endpoints:** OS, ORR, safety
- **Exploratory endpoints:** DoR for objective responders, QoL (EORTC QLQ-C30, QLQ-BR23)

Investigational drug: talazoparib is not approved for use in breast cancer in Europe.

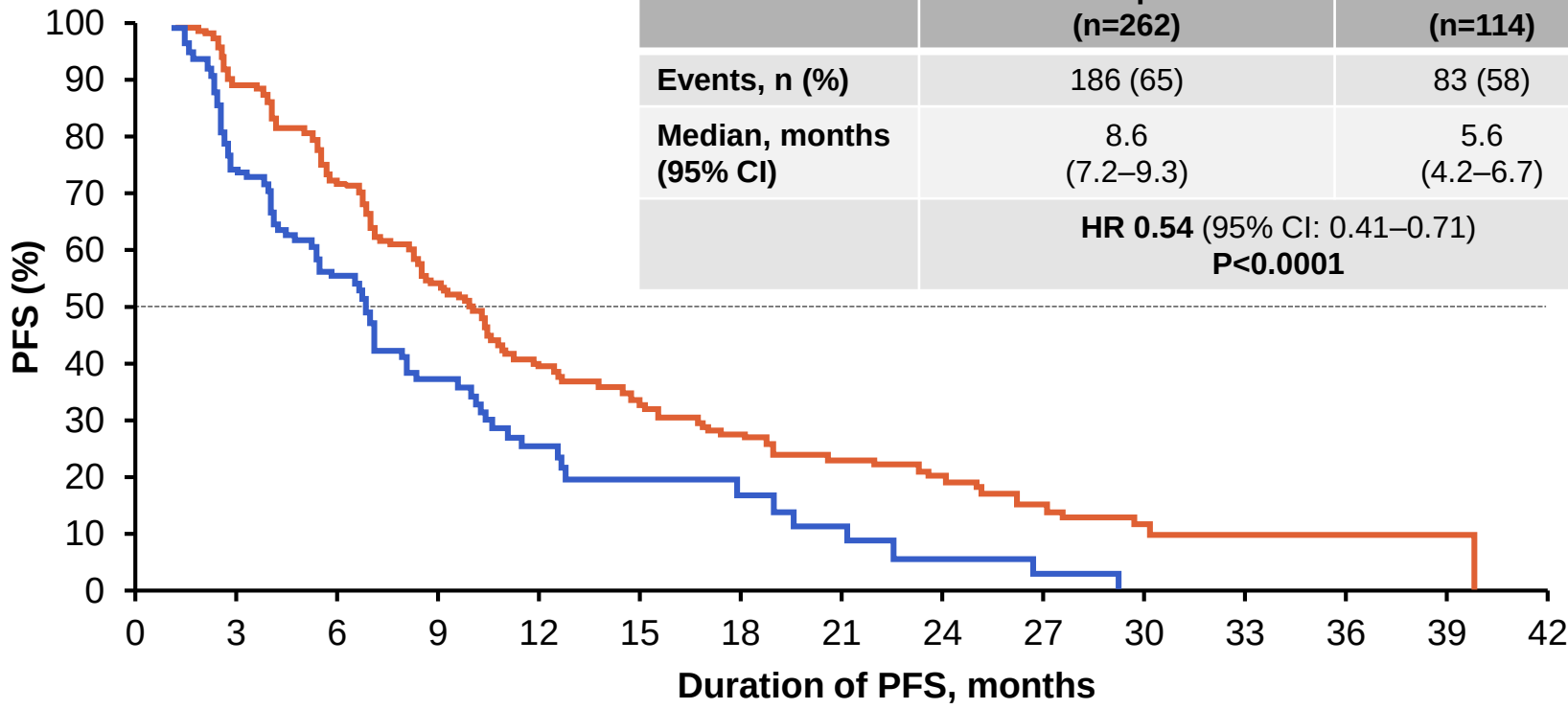
[a]Additional inclusion criteria: no more than 3 prior cytotoxic CT regimens for locally advanced or metastatic disease; prior treatment with a taxane and/or a anthracycline unless medically contraindicated; [b]HER2+ disease is excluded; [c] Physician's choice of therapy must be determined prior to randomisation

PO, by mouth

Litton J, et al. Presented at SABCS 2017. Abstract GS6-07.

EMBRACA: PFS BY BLINDED CENTRAL REVIEW

	Talazoparib (n=262)	Overall TPC (n=114)
Events, n (%)	186 (65)	83 (58)
Median, months (95% CI)	8.6 (7.2–9.3)	5.6 (4.2–6.7)
	HR 0.54 (95% CI: 0.41–0.71) **P<0.0001**	



No. at risk (event/cumulative events)

Talazoparib	287 (0/0)	229 (50/50)	148 (53/103)	91 (34/137)	55 (17/154)	42 (9/163)	29 (9/172)	23 (2/174)	12 (4/183)	5 (2/185)	3 (0/185)	1 (0/185)	0 (1/86)	0 (1/86)	287 (0/0)
TPC	144 (0/0)	68 (41/41)	34 (20/61)	22 (8/69)	9 (7/76)	8 (0/76)	4 (3/79)	2 (2/81)	1 (1/82)	0 (1/83)	0 (0/83)	0 (0/83)	0 (0/83)	0 (0/83)	144 (0/0)

Investigational drug: talozaparib is not approved for use in breast cancer in Europe.

Litton J, et al. Presented at SABCS 2017. Abstract GS6-07.

Inhibiteurs de PARP monothérapie versus Chimiothérapie

Etudes OLYMPIAD et EMBRACA

- Critère d'exclusion: résistance aux sels de platine[1]
- Pas de sels de platine dans le bras contrôle[1,2]
- Absence de stratification selon mutation *BRCA*[1,2]
- Amélioration PFS PARP inhibiteur vs chimiothérapie cytotoxique[1,2]

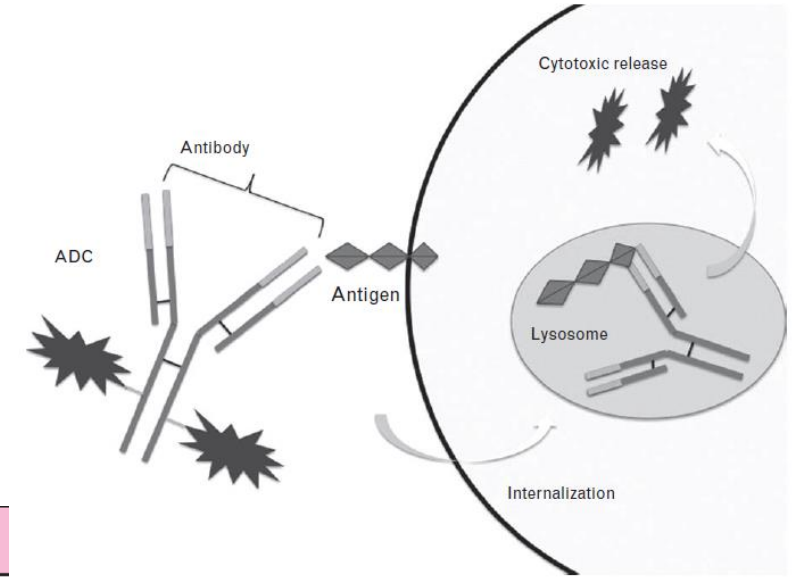
- **Autres essais de Phase III:** BRAVO (niraparib vs TPC)[3]
- **Autres stratégies:** traitement de maintenance?

Investigational drugs: olaparib and talozaparib are not approved for use in breast cancer in Europe.
SOC, standard of care

1. Robson M, et al. *N Engl J Med*. 2017;377:523–533;
2. Litton J, et al. Presented at SABCS 2017. Abstract GS6-07;
3. NCT01905592. Available at: www.clinicaltrials.gov.

ANTICORPS DROGUE-CONJUGUES

Anticorps drogue-conjugués

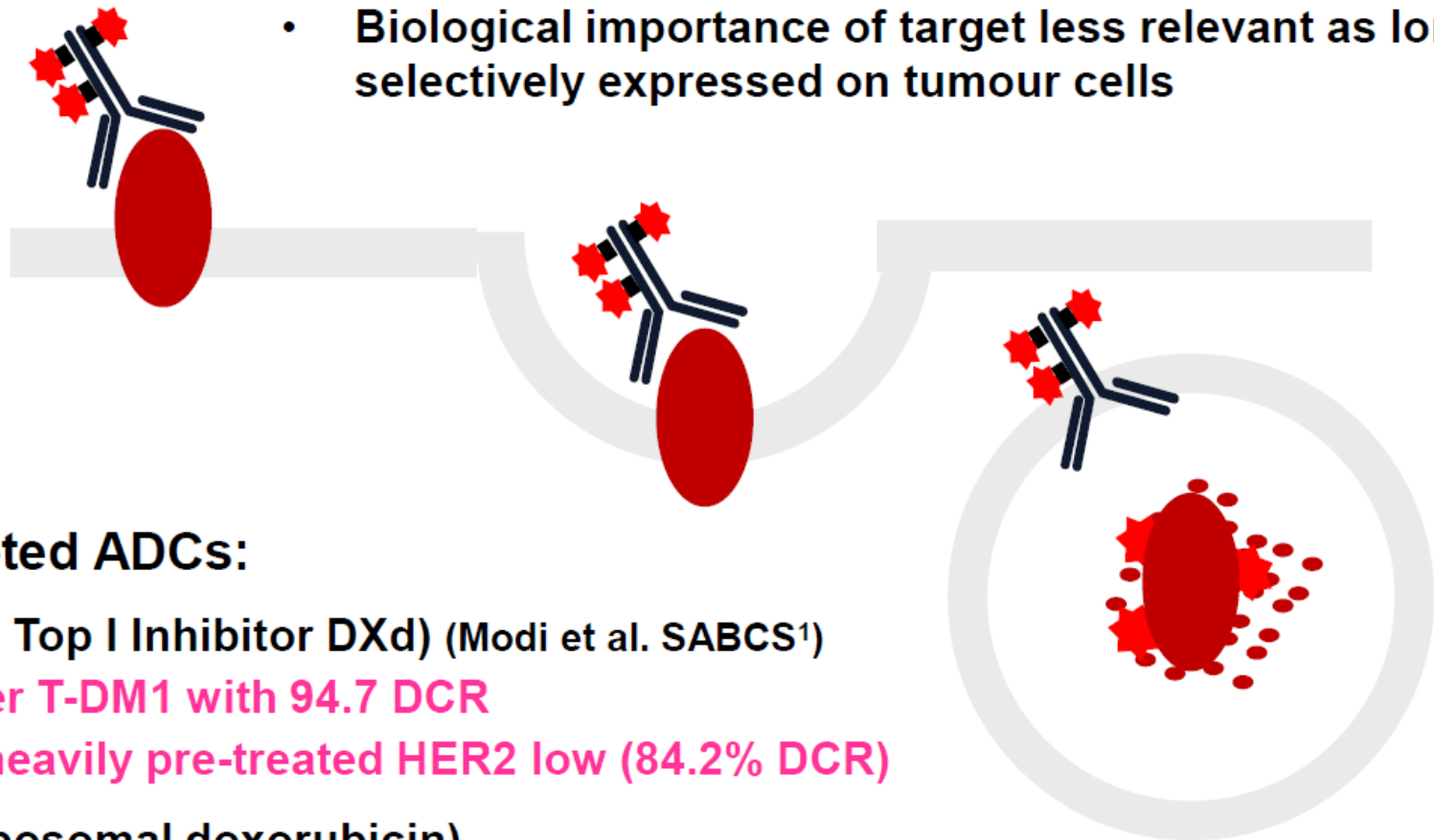


Agent	Status	Indication	Antigen	
Vandortuzumab vedotin	Phase I	Hormone refractory prostate cancer	STEAP1	Monomethyl auristatin E
Vorsetuzumab mafodotin SGN-75	Phase I	Metastatic renal carcinoma	CD70	Monomethyl auristatin F
AMG595	Phase I	Glioblastoma	EGFRvIII	DM1
IMGN853	Phase I	Epithelial ovarian cancer	Folate receptor 1	DM4
Enfortumab vedotin	Phase I	Bladder, breast, lung, pancreatic cancer	Cell surface protein nectin 4	Monomethyl auristatin E
Vintafolide	Phase I/IIb	Nonsmall cell lung cancer, ovarian cancer	Folate receptor	Vinblastine
ABT-414	Phase I/II	Glioblastoma	EGFRvIII	Monomethyl auristatin F
Sacituzumab govitecan IMMU-132	Phase I/II	Triple negative BC epithelial cancers	TROP-2	SN38
Indusatumab vedotin	Phase II	Gastrointestinal, pancreatic cancer	Guanylyl cyclase C	Monomethyl auristatin E
Glembatumumab vedotin	Phase II	Metastatic BC advanced melanoma, recurrent or refractory osteosarcoma	Glycoprotein NMB	Monomethyl auristatin E
PSMA-ADC	Phase II	Hormone refractory prostate cancer	PSMA	Monomethyl auristatin E
Lifastuzumab vedotin	Phase II	Platinium-resistant ovarian cancer	SLC34A2	Monomethyl auristatin E
Lorvotuzumab mertansine	Phase II	Small-cell lung, ovarian cancer	CD56	DM1

New antibody–drug conjugates

Targets for ADC:

- **Potentially enriched on tumour-initiating cells / stem cells**
- **Biological importance of target less relevant as long as selectively expressed on tumour cells**



New HER2-targeted ADCs:

DS-8201a (payload Top I Inhibitor DXd) (Modi et al. SABCS[1])

- **ORR 61.4% after T-DM1 with 94.7 DCR**
- **ORR 31.6% in heavily pre-treated HER2 low (84.2% DCR)**

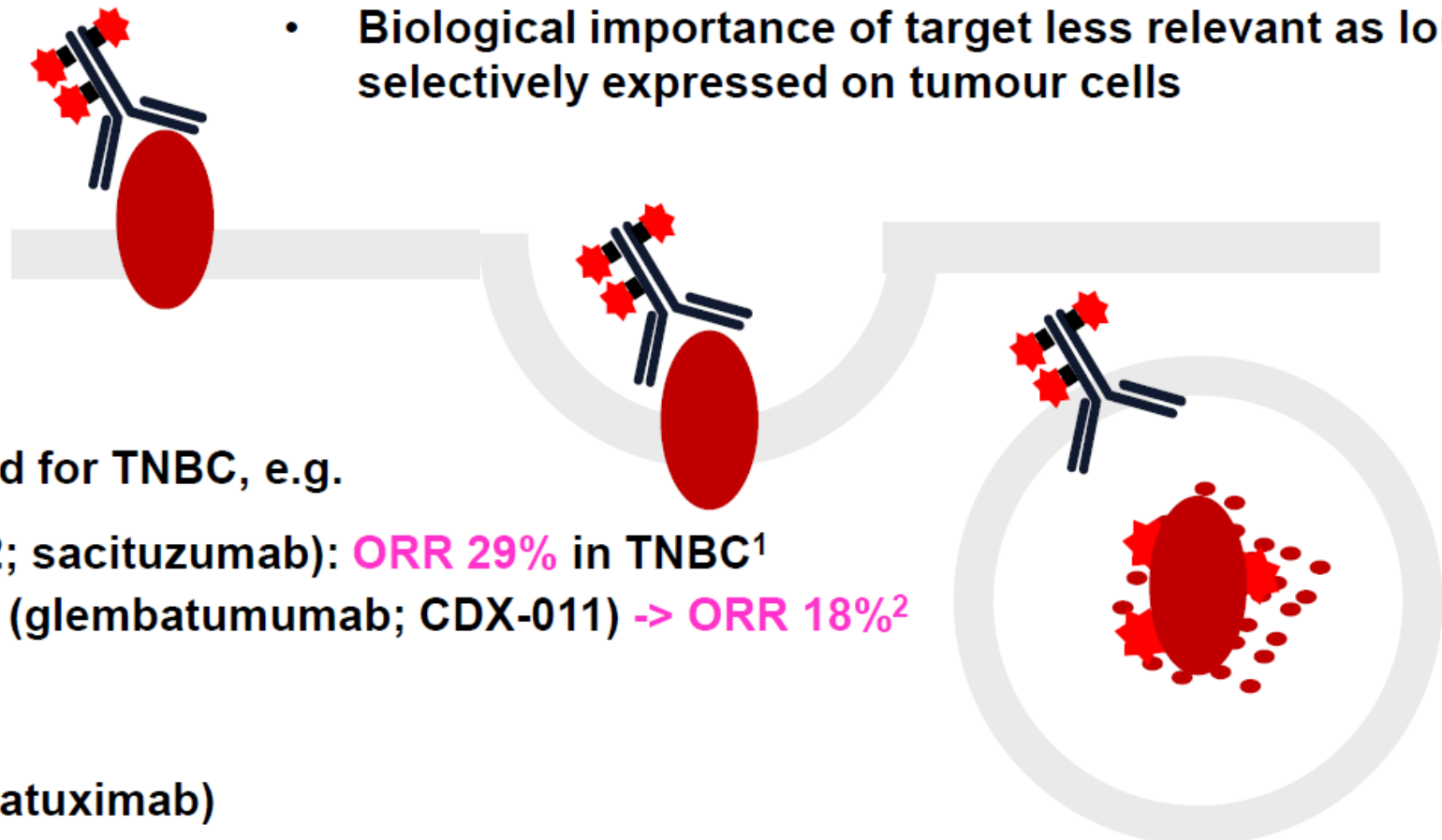
MM302 (payload liposomal doxorubicin)

ADC, antibody–drug conjugates; DCR, disease control rate
Modi S, et al. Presented at SABCS 2017. Abstract PD3-07.

New antibody–drug conjugates

Targets for ADC:

- **Potentially enriched on tumour-initiating cells / stem cells**
- **Biological importance of target less relevant as long as selectively expressed on tumour cells**



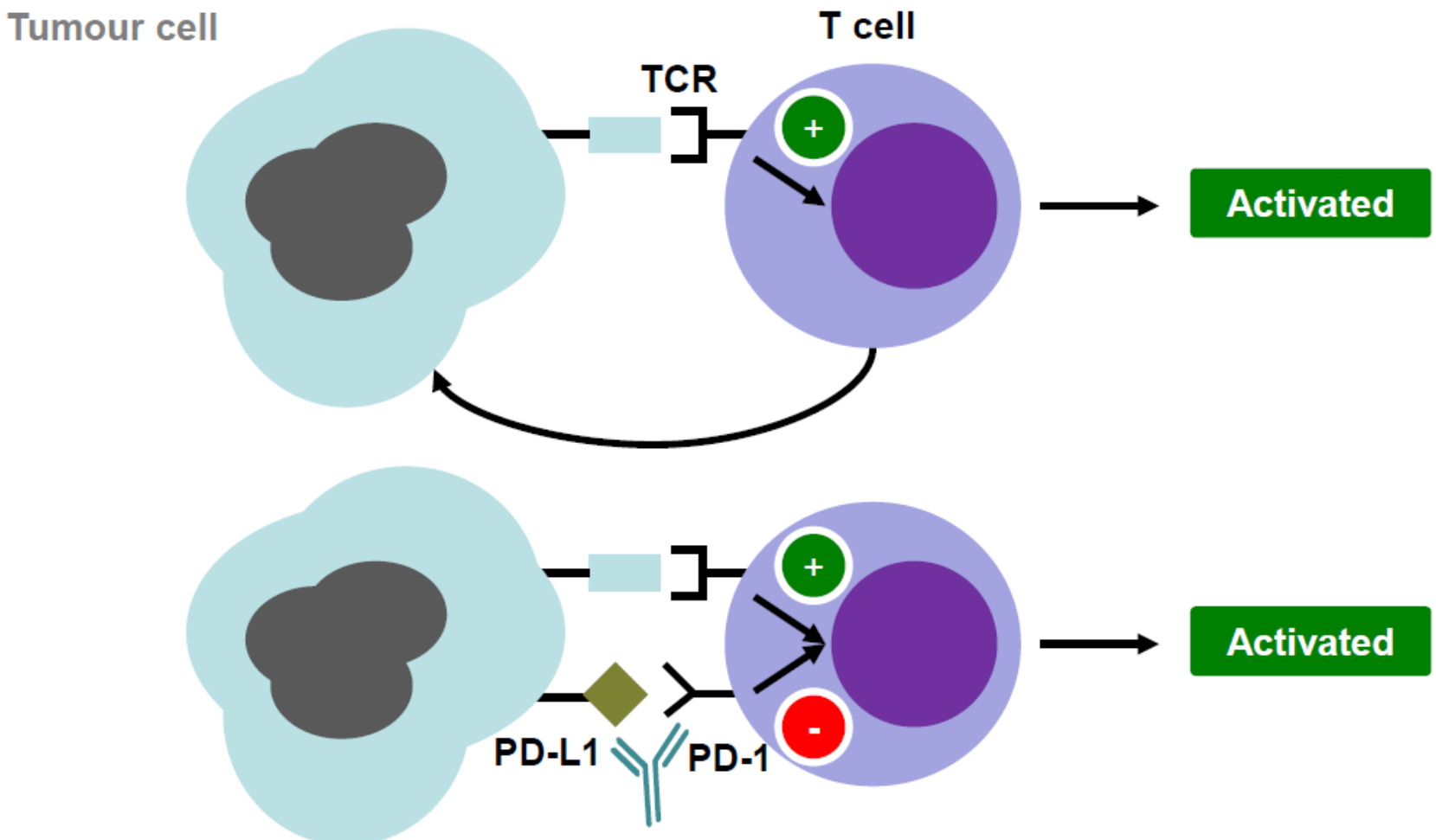
New targets identified for TNBC, e.g.

- **TROP-2 (IMMU 132; sacituzumab): ORR 29% in TNBC[1]**
- **Glycoprotein NMB (glembatumumab; CDX-011) -> ORR 18%[2]**
- **LIV-1 (SGN-LIV1A)**
- **NOTCH3, PTK7**
- **CD138 (BT062, indatuximab)**
- **Folate receptor (IMGN 853, mirvetuximab)**

1. Immunomedics Company Presentation, December 2017, http://www.immunomedics.com/pdfs/company-presentation.pdf; 2. Yardley DA, et al. *J Clin Oncol*. 2015;33:1609–1619.

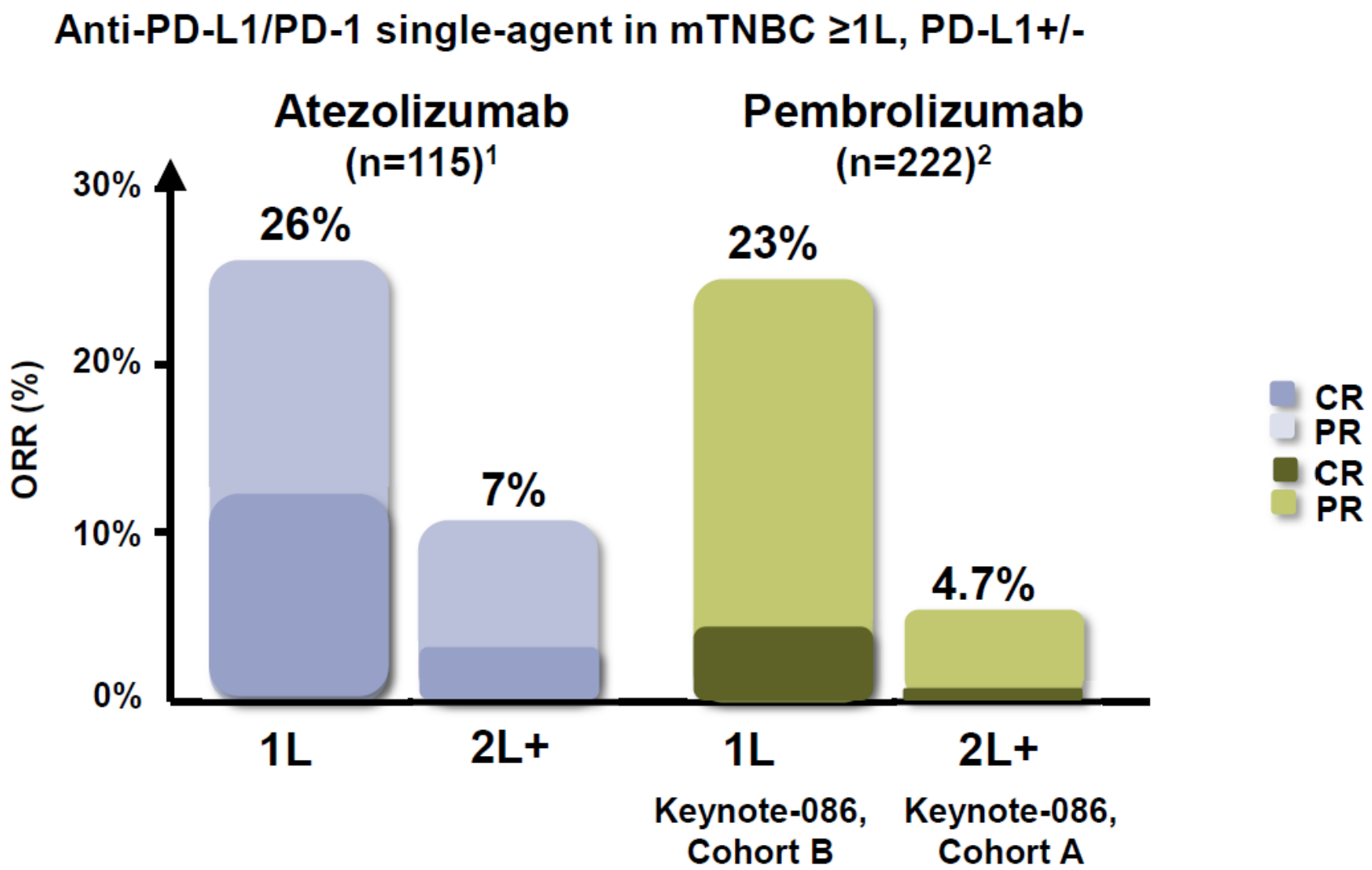
PERSPECTIVES 2018- 2019

Immune checkpoint inhibition: PD-1 and PD-L1



PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; TCR, T-cell receptor
Figure provided by Prof. Peter Schmid.

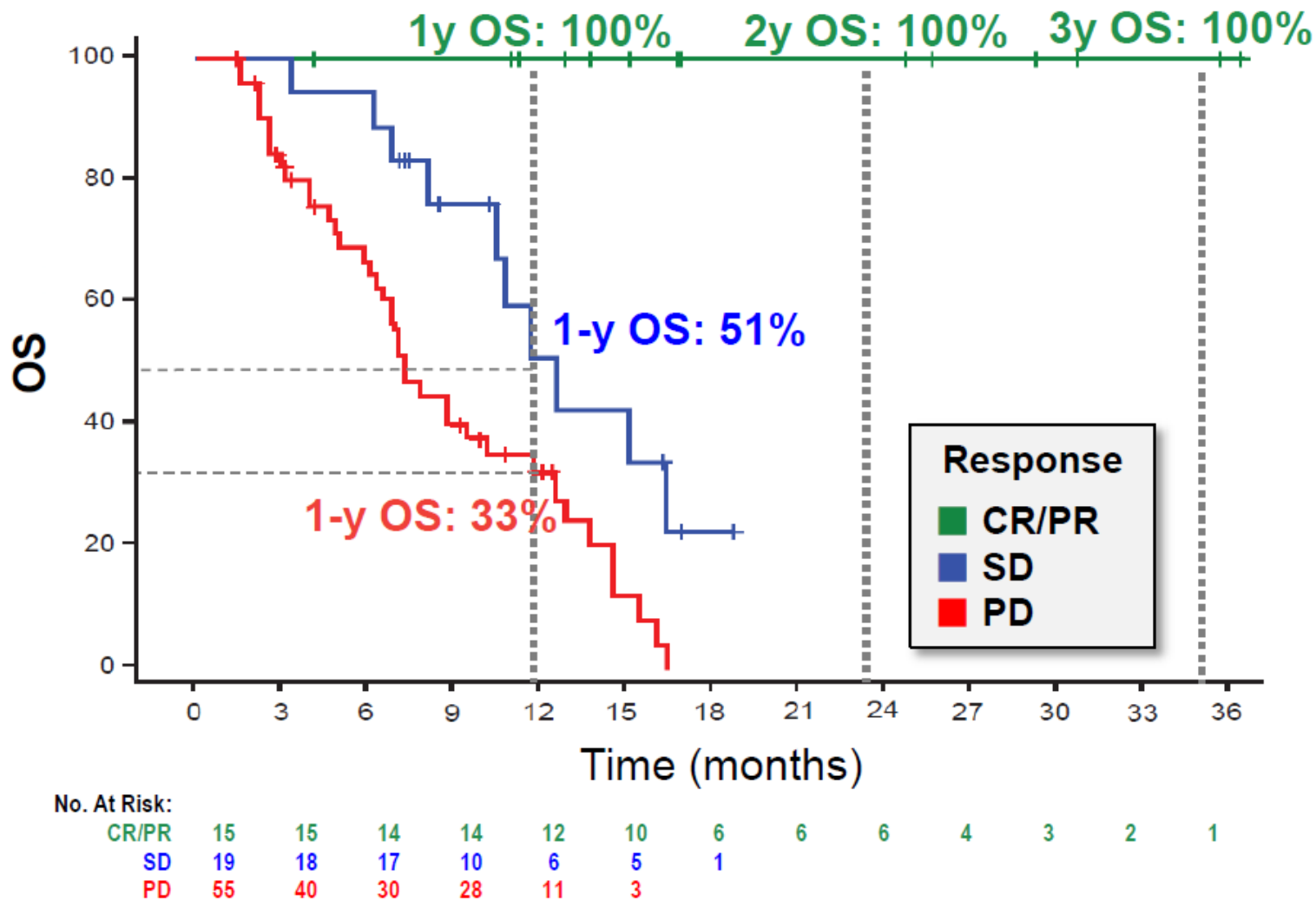
Response to single-agent anti-PD-L1/PD-1



1L, first line; 2L, second line; CR, complete response; mTNBC, metastatic TNBC; ORR, objecteive response rate; PR, partial response

1. Schmid P, et al. Presented at AACR 2017. Abstract 2986; 2. Adams S, et al. Presented at ASCO 2017. Abstract 1008.

OS by best response to anti-PD-L1



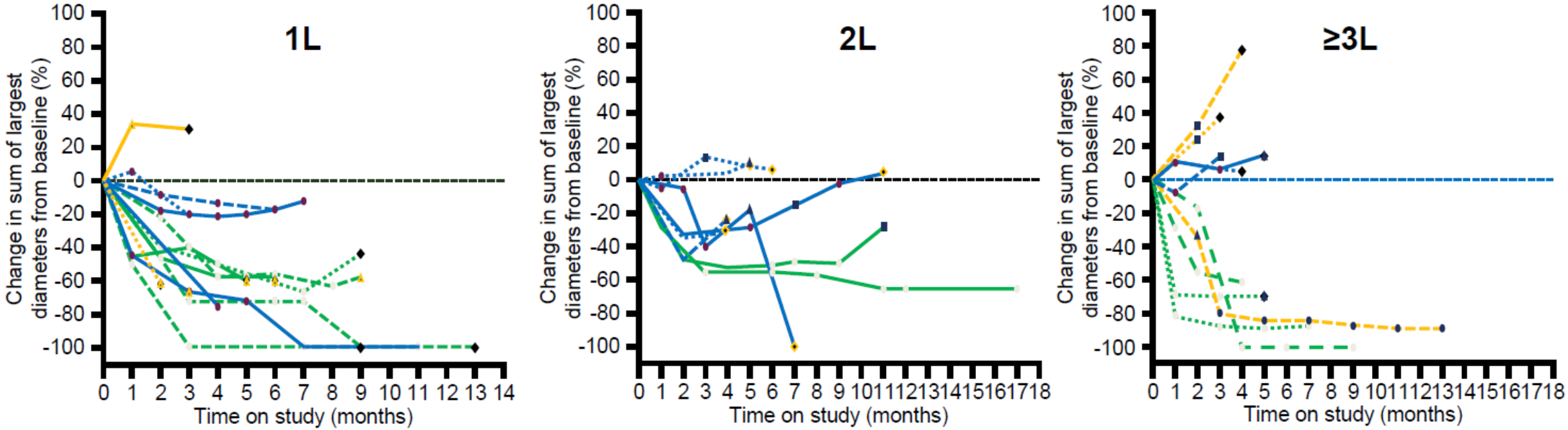
Atezolizumab single agent in mTNBC ≥1L, PD-L1+/-

Median OS follow-up (range) was 15.2 months (0.4+ to 36.7) in all patients, 17.0 mo (0.43+ to 36.7) in IC2/3 patients and 12.8 months (0.8+ to 16.9) in IC0/1 patients

IC, tumour-infiltrating immune cell

Schmid P, et al. Presented at AACR 2017. Abstract 2986.

Nab-paclitaxel + anti-PD-L1 (atezolizumab) in TNBC



	1L n=9	2L n=8*	3L+ n=7†
Confirmed ORR (95% CI)*	67% (30–75)	22% (3–60)	40% (12–74)
SD	18%	67%	30%
PD	15%	0	30%
DCR	85%	89%	70%

Best confirmed response

PR/CR: IC1/2/3, IC0, Unknown
SD: IC1/2/3, IC0, Unknown
PD: IC1/2/3, IC0, Unknown

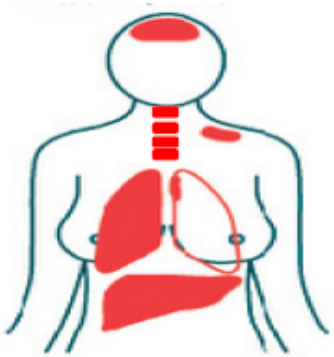
◆ Discontinued atezolizumab
▲ New lesion
■ Progressive disease

3L, third line

Graphs adapted from Adam S, et al. Presented at ASCO 2016. Abstract 1009.

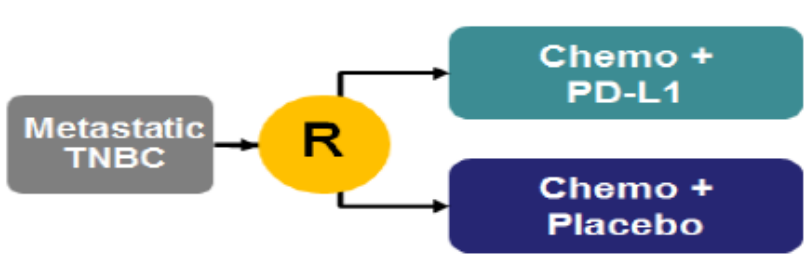
Nab-paclitaxel + anti-PD-L1 are not EMA approved in this indication.

Metastatic breast cancer

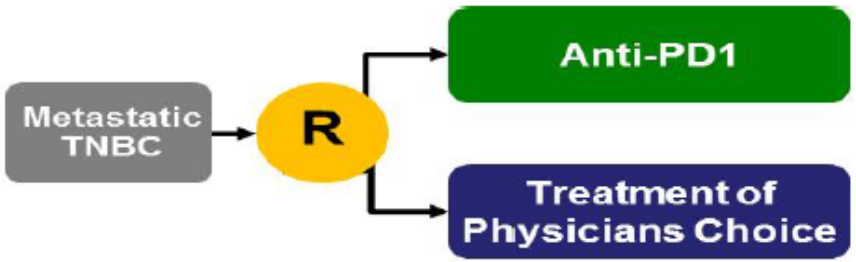


1st-line MBC

≥2nd-line MBC



IMpassion130, Keynote 355



Keynote 119

Figure provided by Prof. Peter Schmid.

CONCLUSION

Conclusions

- Multiples options thérapeutiques
- Limitations: hétérogénéité tumorale et mofication profil moléculaire à progression
- Séquence thérapeutique optimale non définie
- Nouvelles associations: amélioration des résultats mais toxicité (et prix!)
- Biomarqueurs +++
- Médecine de precision et médecine personalisée

Nouvelles directions

- Résistance hormonothérapie (et CDK 4/6 inhibiteurs !)
- Ciblage lésions ADN et léthalité synthétique
- Nouveaux anticorps drogue-conjugués
- Immunothérapies

Meilleure caractérisation biologie tumorale essentielle pour stratégies futures