Post ESMO 2021

Actualités Séno-Gynécologie

Le 14 octobre 2021

Domaine de la Tuilerie

Dr JONCOUR Anthony

Breast Cancer

Metastatic setting

DESTINY Breast03
(2nd line T-DXd HER2+)

KEYNOTE 355
(1st line Pembrolizumab TN)

MONALEESA 2
(1st line Ribociclib Luminal)

Neoadjuvant setting

BRIGHTNESS
(Carboplatine TNBC)

KEYNOTE 522
(Pembrolizumab TNBC)

Gynecological Cancers

EMPOWER
(2nd line Cemeplimab in metastatic cervical cancer)

KEYNOTE 826
(1st line Pembrolizumab in metastatic cervical cancer)

OReO-ENGOT-Ov38
(Olaparib retreatment in late recurrent ovarian cancer)

Breast Cancer

Metastatic setting

DESTINY Breast03
(2nd line T-DXd HER2+)
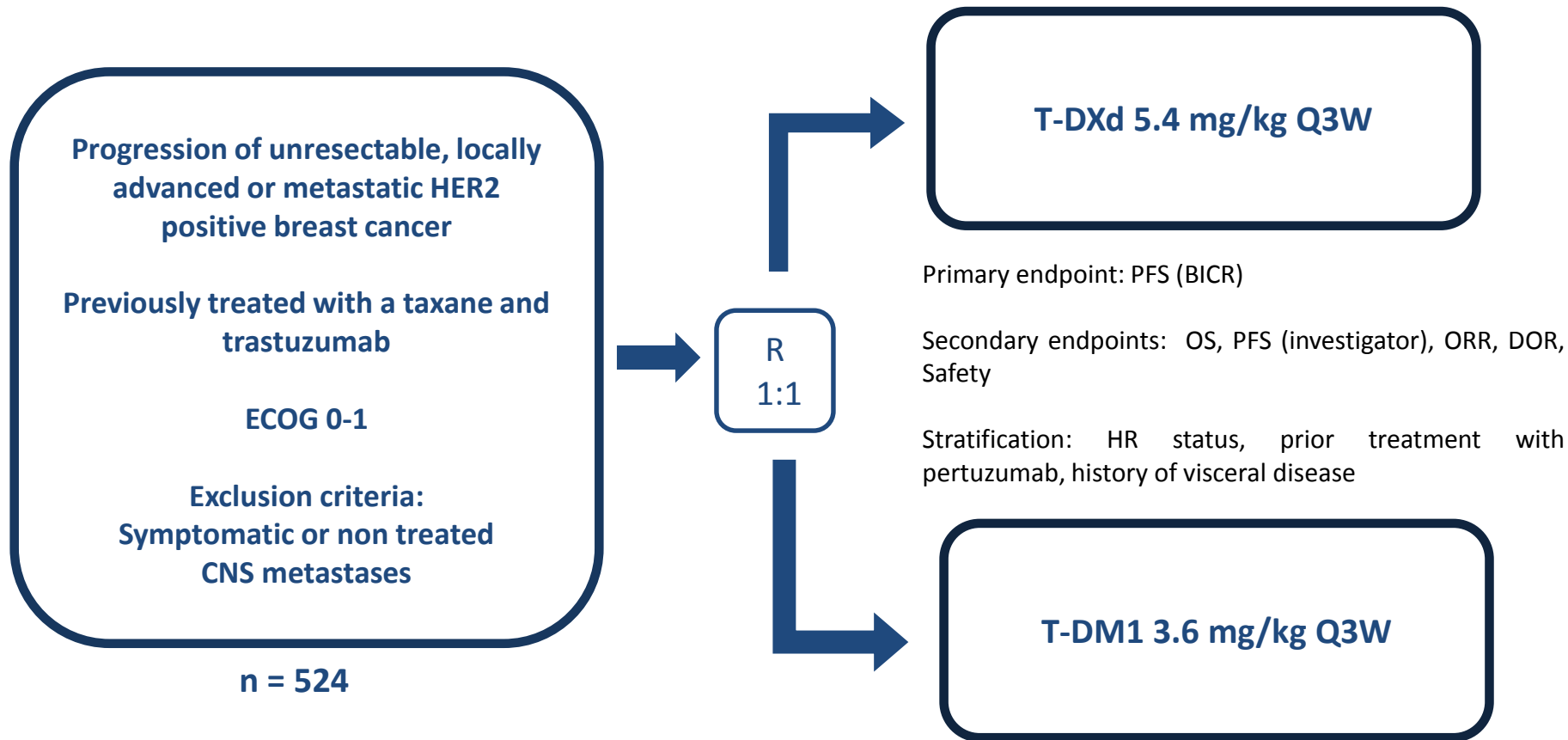
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(Pembrolizumab TNBC)

DESTINY Breast03: Phase III Trial

Progression of unresectable, locally advanced or metastatic HER2 positive breast cancer

Previously treated with a taxane and trastuzumab

ECOG 0-1

**Exclusion criteria:
Symptomatic or non treated CNS metastases**

n = 524

R
1:1

T-DXd 5.4 mg/kg Q3W

T-DM1 3.6 mg/kg Q3W

Primary endpoint: PFS (BICR)

Secondary endpoints: OS, PFS (investigator), ORR, DOR, Safety

Stratification: HR status, prior treatment with pertuzumab, history of visceral disease

HR expression ≈ 50%

Brain metastases: 23.8% *vs* 19.8%
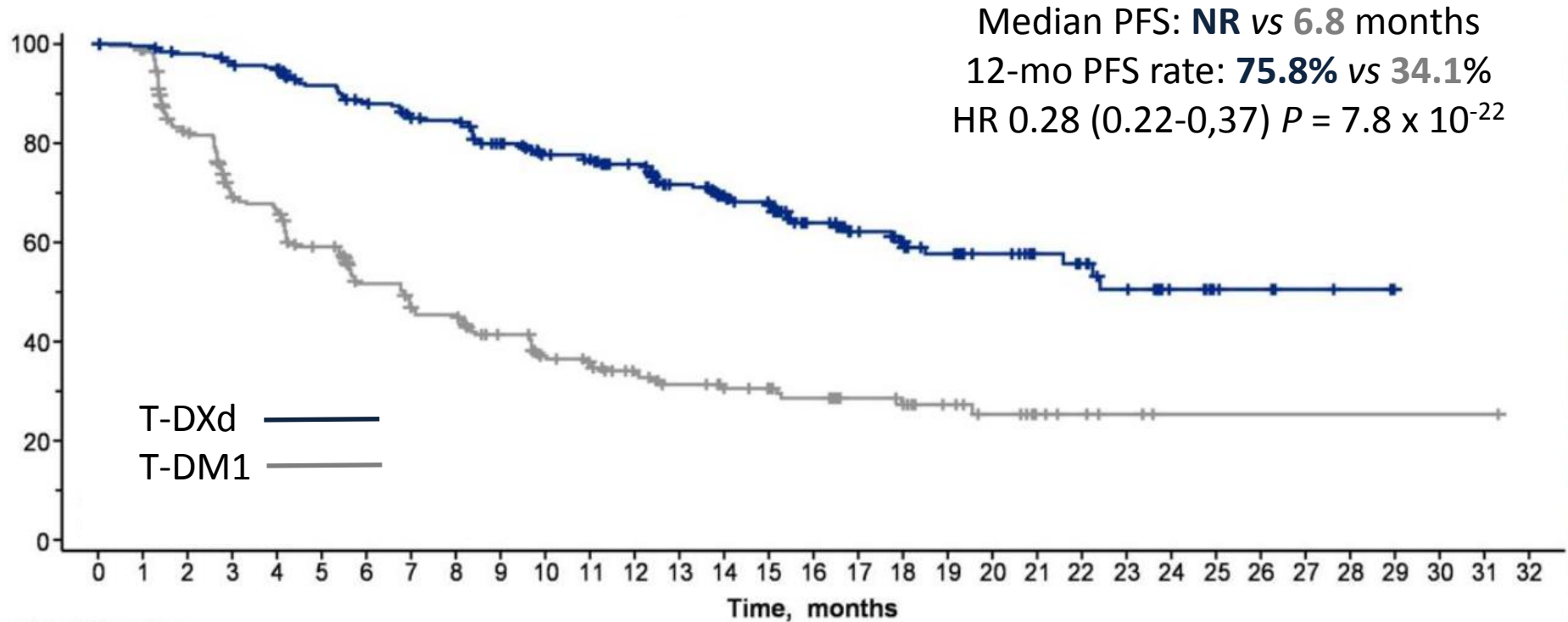
Median age: 54 years

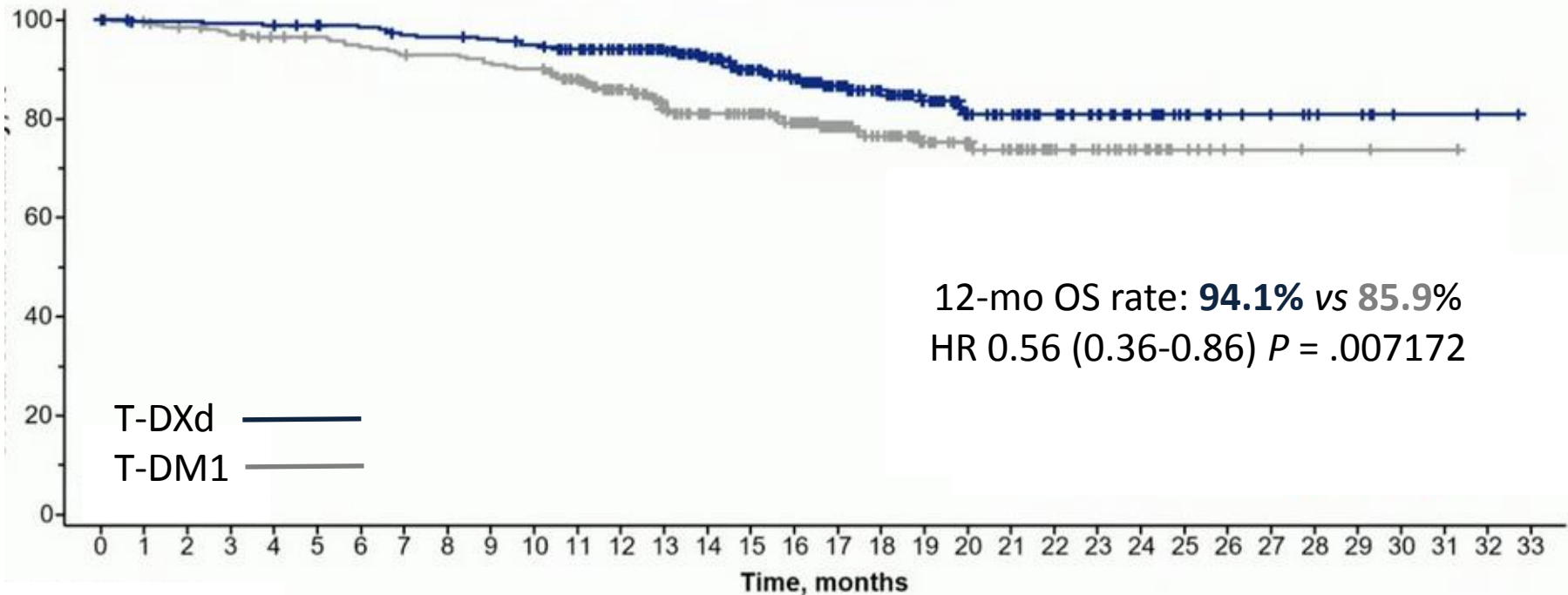Only one previous therapy : 49%

2 previous therapies: 21.5 *vs* 24.7%
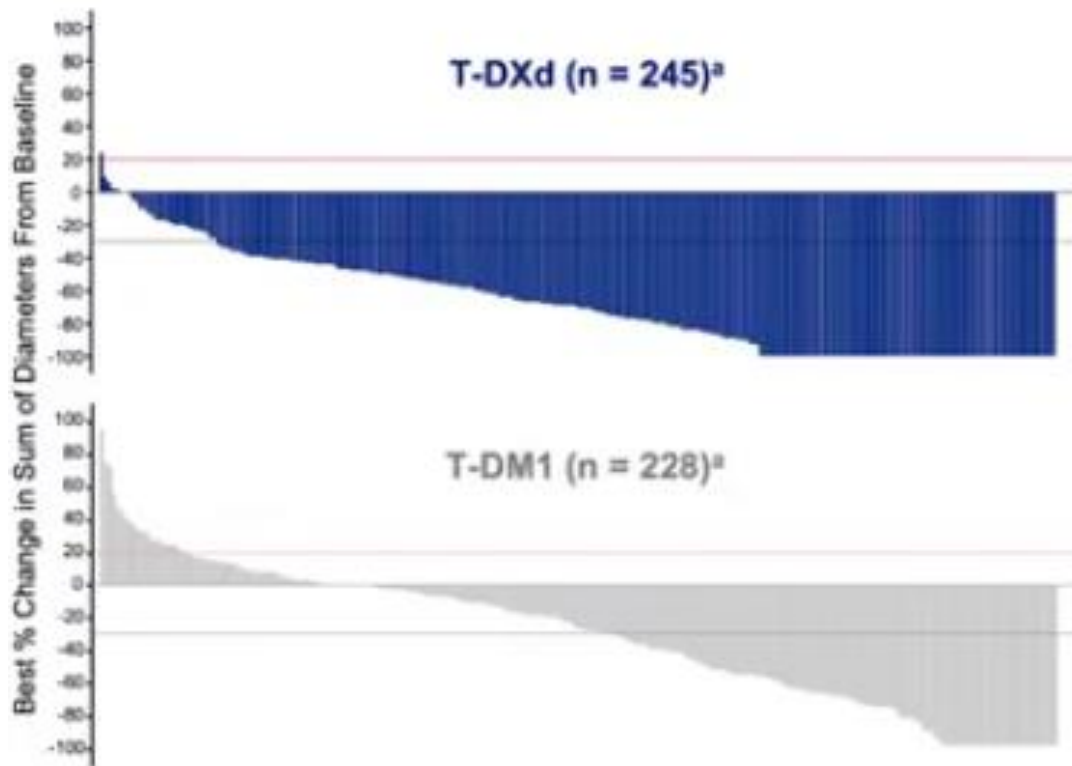
Prior Pertuzumab: 62.1% *vs* 60.1%

Prior ITK: 16.1% *vs* 13.7%

DESTINY Breast03: PFS (BICR)

Median PFS: **NR** *vs* **6.8** months
12-mo PFS rate: **75.8%** *vs* **34.1%**
HR 0.28 (0.22-0,37) *P* = 7.8 x 10^{-22}

T-DXd
T-DM1

DESTINY Breast03: Overall survival

12-mo OS rate: **94.1%** *vs* **85.9%**
HR 0.56 (0.36-0.86) *P* = .007172

T-DXd
T-DM1

	T-DXd (n = 261)	T-DM1 (n = 263)
Confirmed ORR		
n (%)[b]	208 (79.7)	90 (34.2)
[95% CI]	[74.3-84.4]	[28.5-40.3]
	P < .0001	
CR	42 (16.1)	23 (8.7)
PR	166 (63.6)	67 (25.5)
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
CR + PR + SD (DCR)	252 (96.6)	202 (76.8)

DESTINY Breast03: Safety profile

Adverse events G3/4 : **45.5%** vs **39.8%**
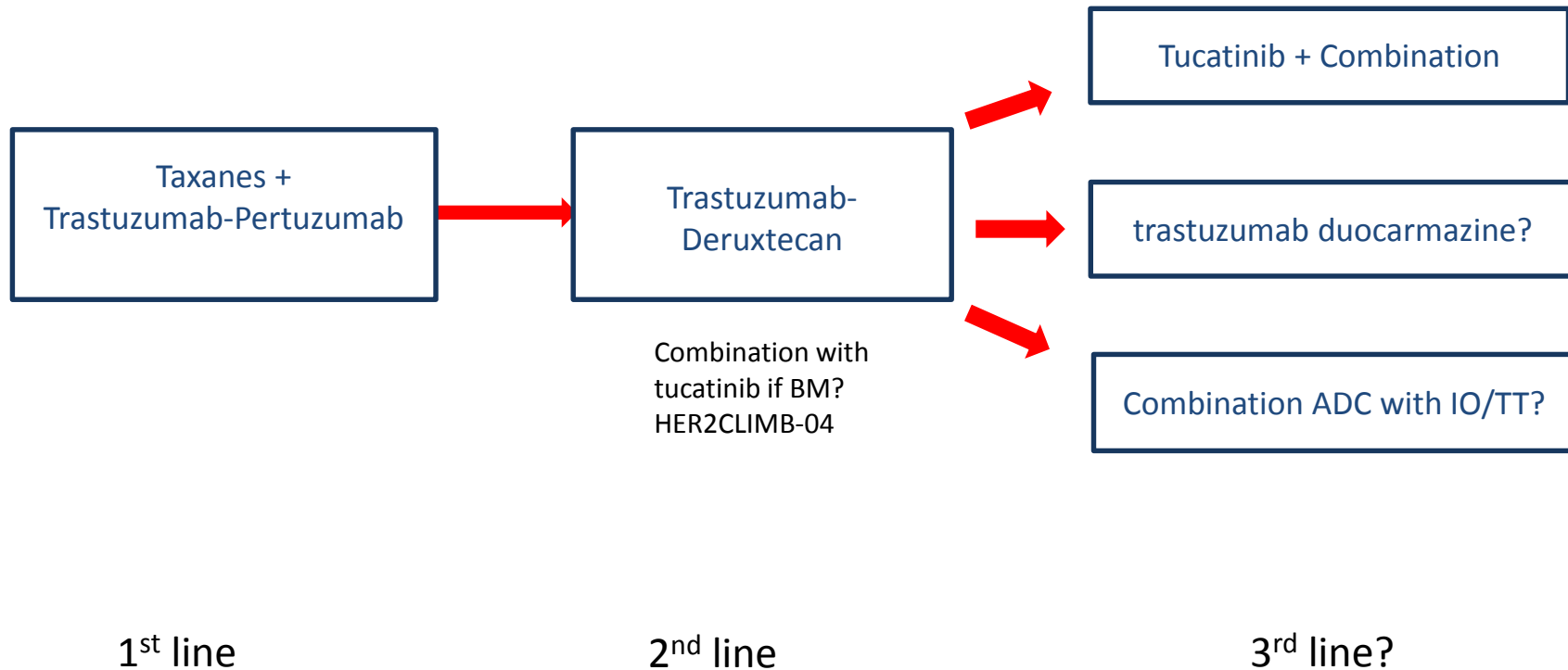
Neutropenia G3-4: **19.1%** vs **3.4%**

Thrombocytopenia G3-4: **7.0%** vs **24.9%**

Nausea G3-4: **6.6%** vs **0.4%**

Discontinuation: **21,4%** *vs* **12,6%**

27 cases of ILD (10.5%): low Grade (9.7%), no G4 or G5

A new treatment algorithm?

Taxanes + Trastuzumab-Pertuzumab

Trastuzumab-Deruxtecan

Combination with tucatinib if BM?
HER2CLIMB-04

Tucatinib + Combination

trastuzumab duocarmazine?

Combination ADC with IO/TT?

1st line

2nd line

3rd line?

Breast Cancer

Metastatic setting

DESTINY Breast03
(2nd line T-DXd HER2+)

KEYNOTE 355
(1st line Pembrolizumab TN)

MONALEESA 2
(1st line Ribociclib Luminal)

Neoadjuvant setting

BRIGHTNESS
(Carboplatine TNBC)

KEYNOTE 522
(Pembrolizumab TNBC)

KEYNOTE 355: a randomized, double-blind, placebo-controlled phase III trial

From January 2017 through June 2018

Locally advanced or metastatic TNBC

No previous therapy in metastatic setting or completion of previous therapy with curative intent ≥ 6 mo

ECOG 0-1

No active CNS metastases

No active autoimmune disease

n = 847

R 2:1

Pembrolizumab* + Chemotherapy
n = 566

Dual Primary EP: PFS and OS
- PD-L1 CPS ≥10
- PD-L1 CPS ≥ 1
- Intention-to-treat populations

Stratification factors
⇒ Chemotherapy (taxane or gemcitabine-carboplatin)
⇒ PD-L1 tumor expression (CPS ≥1 or <1)
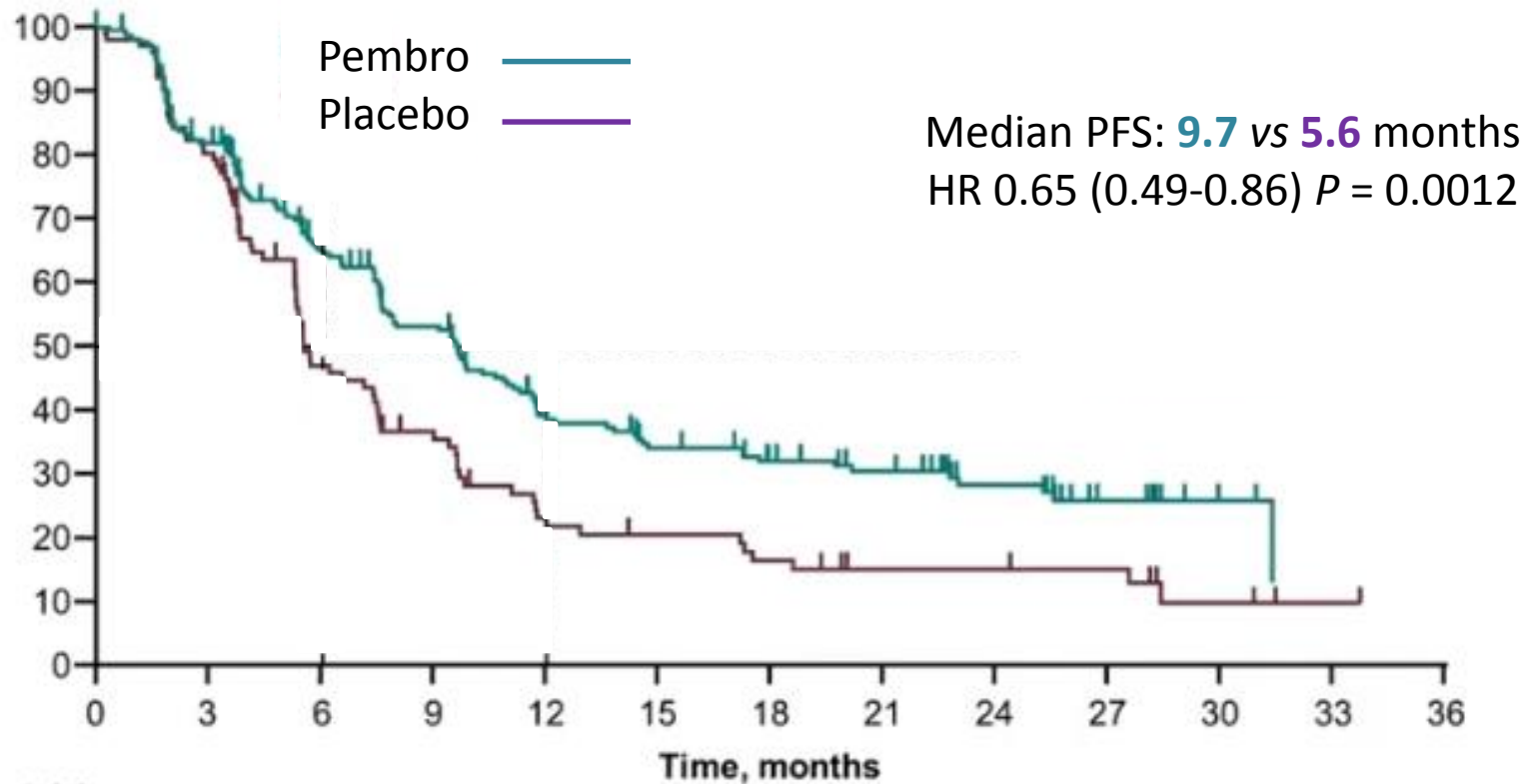⇒ Prior treatment with same class chemo in the neoadjuvant or adjuvant setting
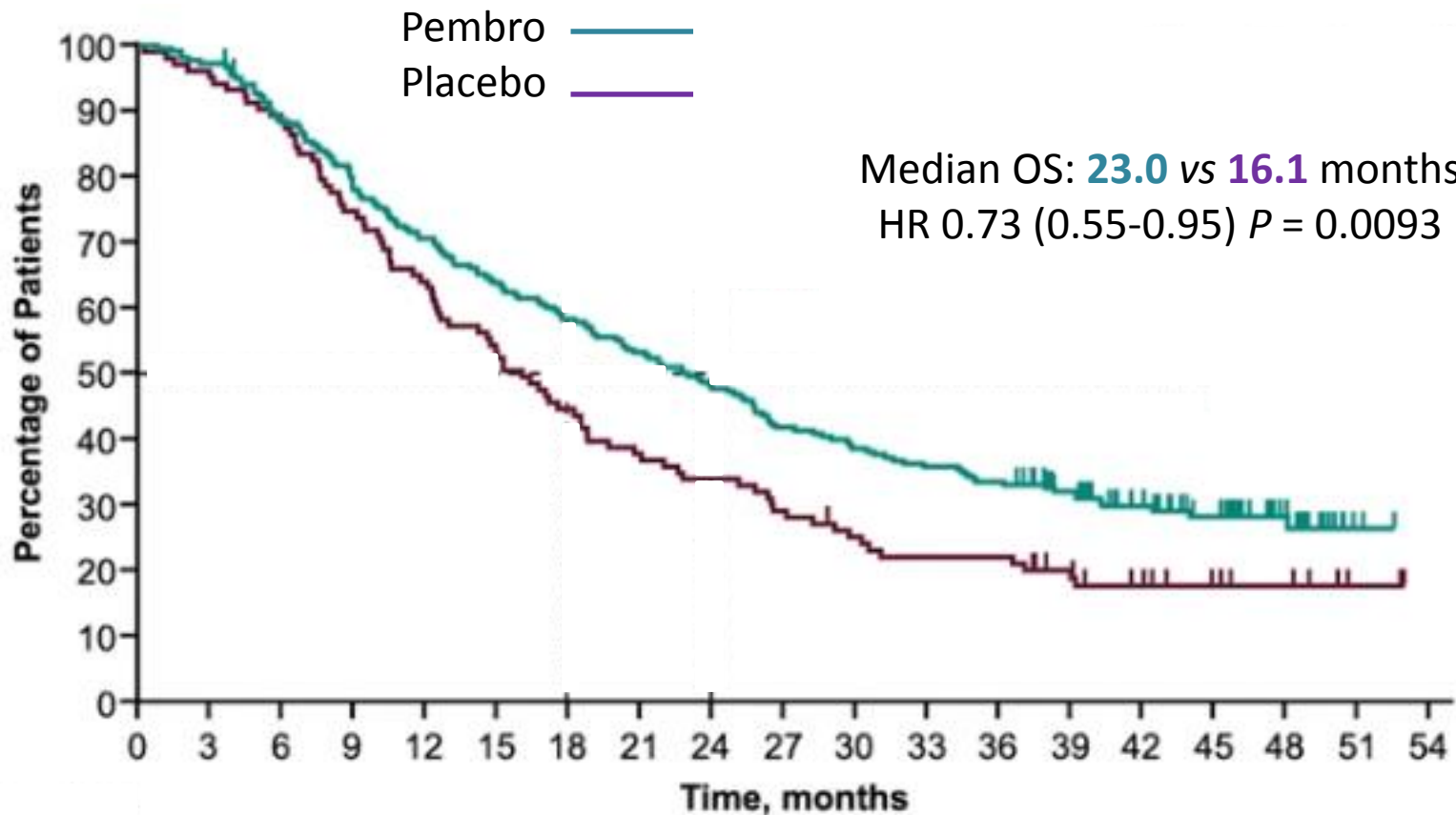
Placebo* + Chemotherapy
n = 281

Up to 35 cycles

KEYNOTE 355: Baseline characteristics

Characteristic, n (%)	All Subjects, N = 847	
	Pembro + Chemo N = 566	Placebo + Chemo N = 281
Age, median (range), yrs	53 (25-85)	53 (22-77)
ECOG PS 1	232 (41.0)	108 (38.4)
PD-L1–positive CPS ≥1	425 (75.1)	211 (75.1)
PD-L1–positive CPS ≥10	220 (38.9)	103 (36.7)

Pembro ——

Placebo ——

Median PFS: **9.7** *vs* **5.6** months

HR 0.65 (0.49-0.86) *P* = 0.0012

Cortes, Lancet 2020

KEYNOTE 355: Overall Survival (PD-L1 CPS ≥ 10)

Median OS: **23.0** *vs* **16.1** months
HR 0.73 (0.55-0.95) *P* = 0.0093

Pembro
Placebo

Median OS: **17.6** *vs* **16.0** months
HR 0.86 (0.72-1.04) *P* = 0.0563

Pembro ——————
Placebo ——————

Median OS: **17.2** *vs* **15.5** months
HR 0.89 (0.76-1.05)

Subgroup	N	Median OS (mo)		Hazard Ratio for Death (95%)
		Pembro + Chemo	Placebo + Chemo	
Overall	323	23.0	16.1	0.73 (0.55 to 0.95)
Age (years)				
<65	257	21.8	16.8	0.78 (0.58 to 1.05)
≥65	66	28.3	12.6	0.51 (0.28 to 0.92)
Geographic region				
N America/EU/ANZ	212	23.5	15.2	0.72 (0.52 to 1.00)
Asia	56	26.7	17.4	0.44 (0.23 to 0.84)
Rest of world	55	18.0	22.0	1.07 (0.57 to 1.98)
ECOG PS				
0	196	26.4	19.8	0.70 (0.49 to 1.00)
1	127	17.7	10.6	0.70 (0.47 to 1.05)
On-study chemotherapy				
Nab-paclitaxel	99	29.8	18.4	0.63 (0.39 to 1.03)
Paclitaxel	44	28.6	8.5	0.34 (0.16 to 0.72)
Gemcitabine-Carboplatin	180	19.1	16.2	0.88 (0.61 to 1.25)
Prior same-class chemotherapy				
Yes	65	23.5	14.9	0.60 (0.32 to 1.09)
No	258	22.8	16.9	0.74 (0.55 to 1.00)
Prior (neo)adjuvant chemotherapy				
Yes	193	20.3	17.1	0.86 (0.61 to 1.22)
No	130	28.3	13.0	0.53 (0.34 to 0.80)
Disease-free interval				
de novo metastasis	104	26.4	12.5	0.54 (0.34 to 0.86)
<12 months	65	17.1	19.7	1.44 (0.73 to 2.82)
≥12 months	153	24.9	17.1	0.65 (0.45 to 0.96)
Number of metastatic sites				
<3	184	32.1	18.8	0.63 (0.43 to 0.91)
≥3	138	13.2	10.5	0.75 (0.51 to 1.10)

Hazard Ratio (95% CI)

⟵ Favors Pembro + Chemo | Favors Placebo + Chemo ⟶

<u>Median overall survival in PD-L1+ population</u>

KEYNOTE 355 (Chemo +/- pembrolizumab)
=> (CPS ≥10): **23.0 *vs* 16.1 months; HR 0.73 (0.55-0.95); p = 0.0093**

Impassion 130 (Nab-paclitaxel +/- atezolizumab)
=> (IC 1%): 25.4 *vs* 17.9 months; HR 0.67 (0.53-0.86); p not formally tested

IMpassion 131 (Paclitaxel +/- atezolizumab)
=> (IC 1%): 22.1 *vs* 28.3 months; HR 1.11 (0.76-0.1.64); p not formally tested

Breast Cancer

Metastatic setting

DESTINY Breast03
(2nd line T-DXd HER2+)

KEYNOTE 355
(1st line Pembrolizumab TN)

MONALEESA 2
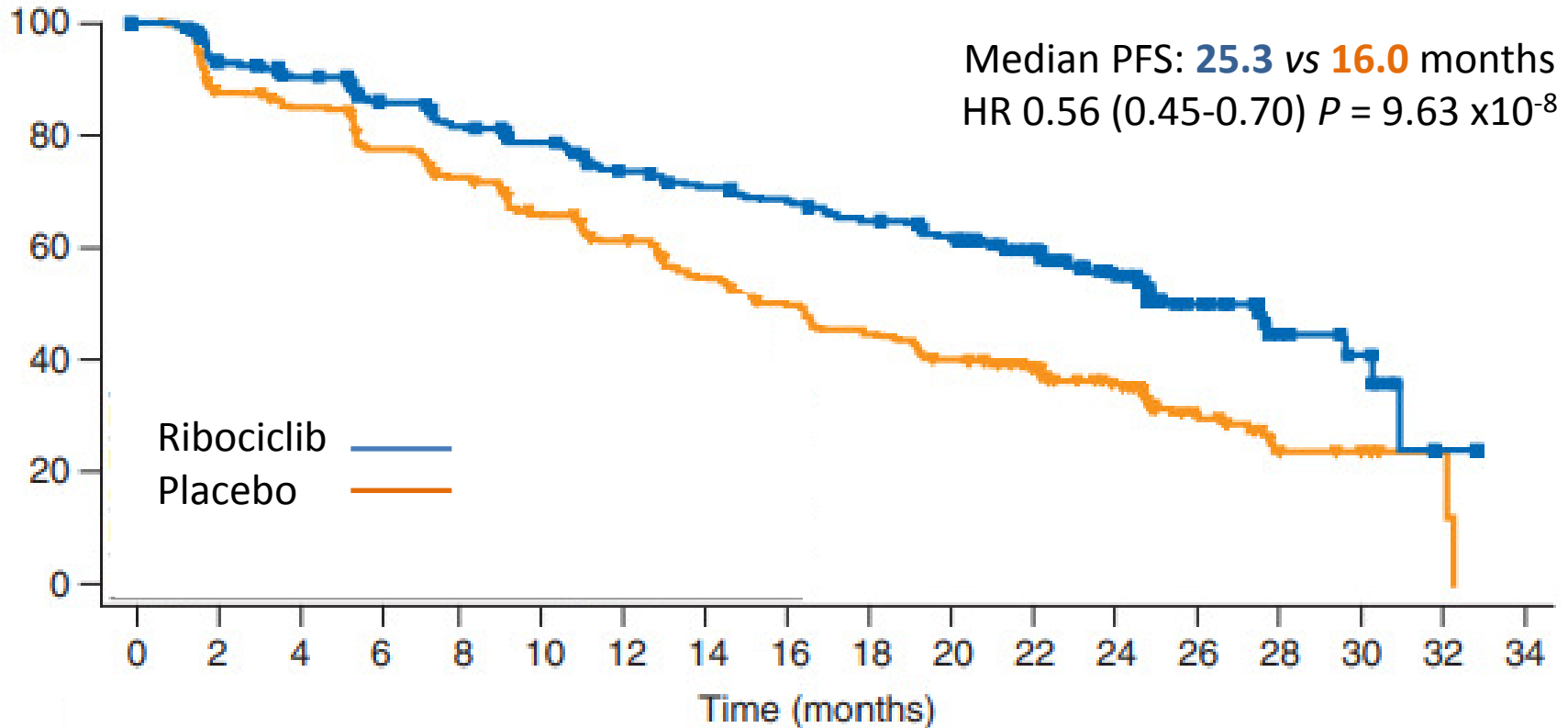(1st line Ribociclib Luminal)

Neoadjuvant setting

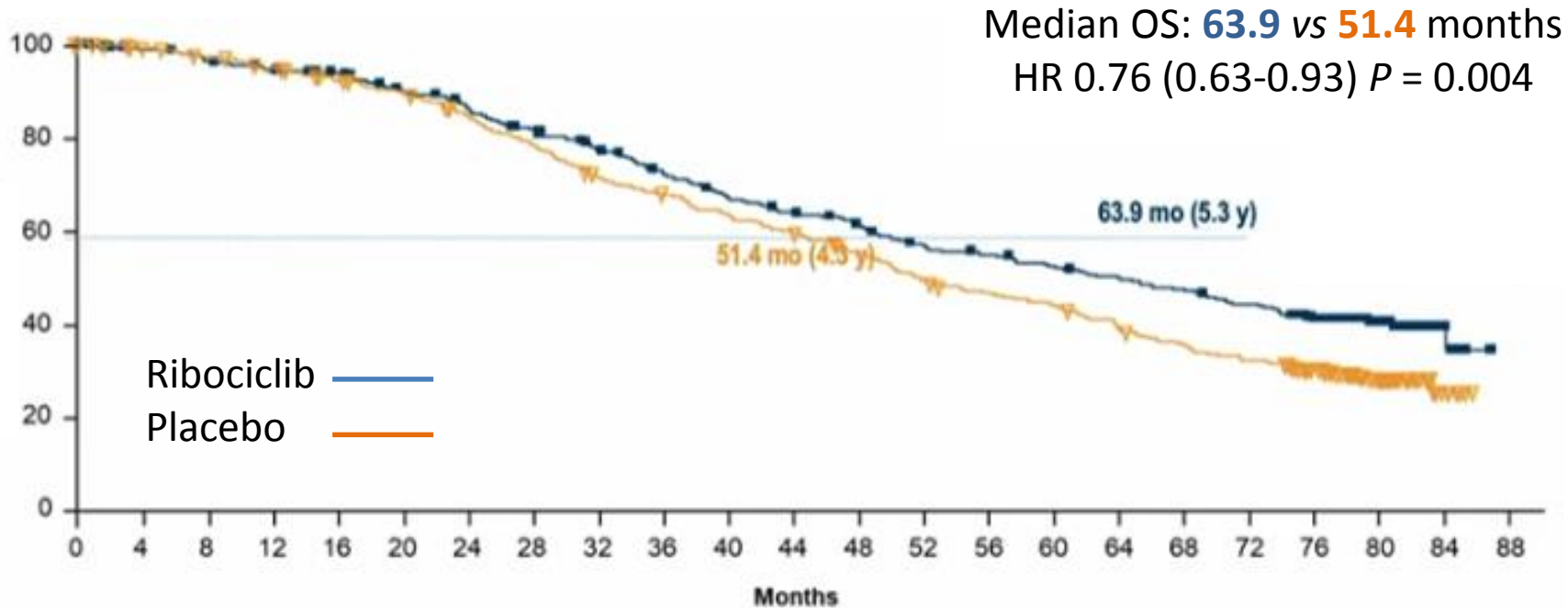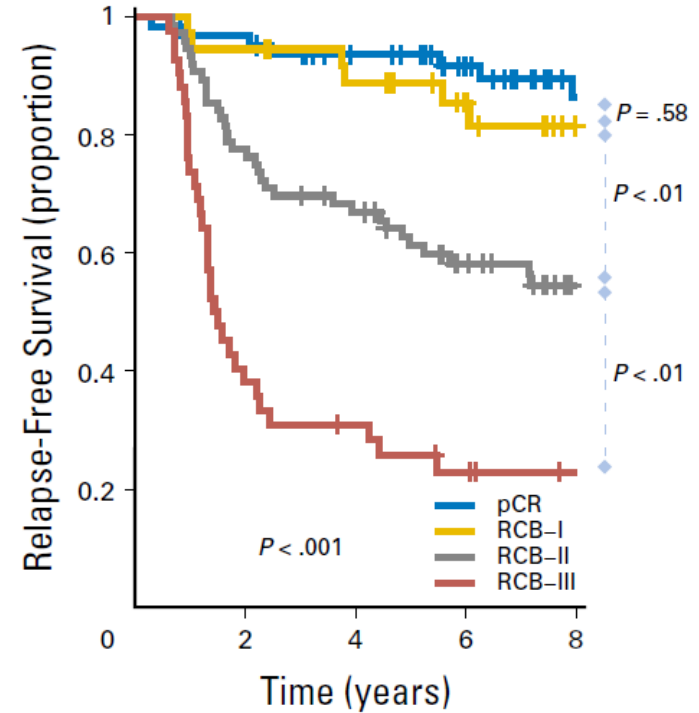**BRIGHTNESS**
(Carboplatine TNBC)

KEYNOTE 522
(Pembrolizumab TNBC)

MONALEESA-2: a randomized, double-blind, placebo-controlled phase III trial

From January 2014 through March 2015

HR+ HER2- advanced breast cancer

Postmenopausal women

No previous endocrine therapy in metastatic setting

n = 668

R
1:1

Ribociclib 600 mg once per day
(3 weeks on/1 week off)
+ Letrozole
n = 334

Primary EP: PFS

Secondary EP : OS, ORR, CBR, Safety, QOL

Stratification factors
⇒liver or lung metastases: yes/no

Placebo once per day
(3 weeks on/1 week off)
+ Letrozole
n = 334

Median PFS: **25.3** *vs* **16.0** months
HR 0.56 (0.45-0.70) *P* = 9.63 x10^{-8}

Ribociclib
Placebo

Time (months)
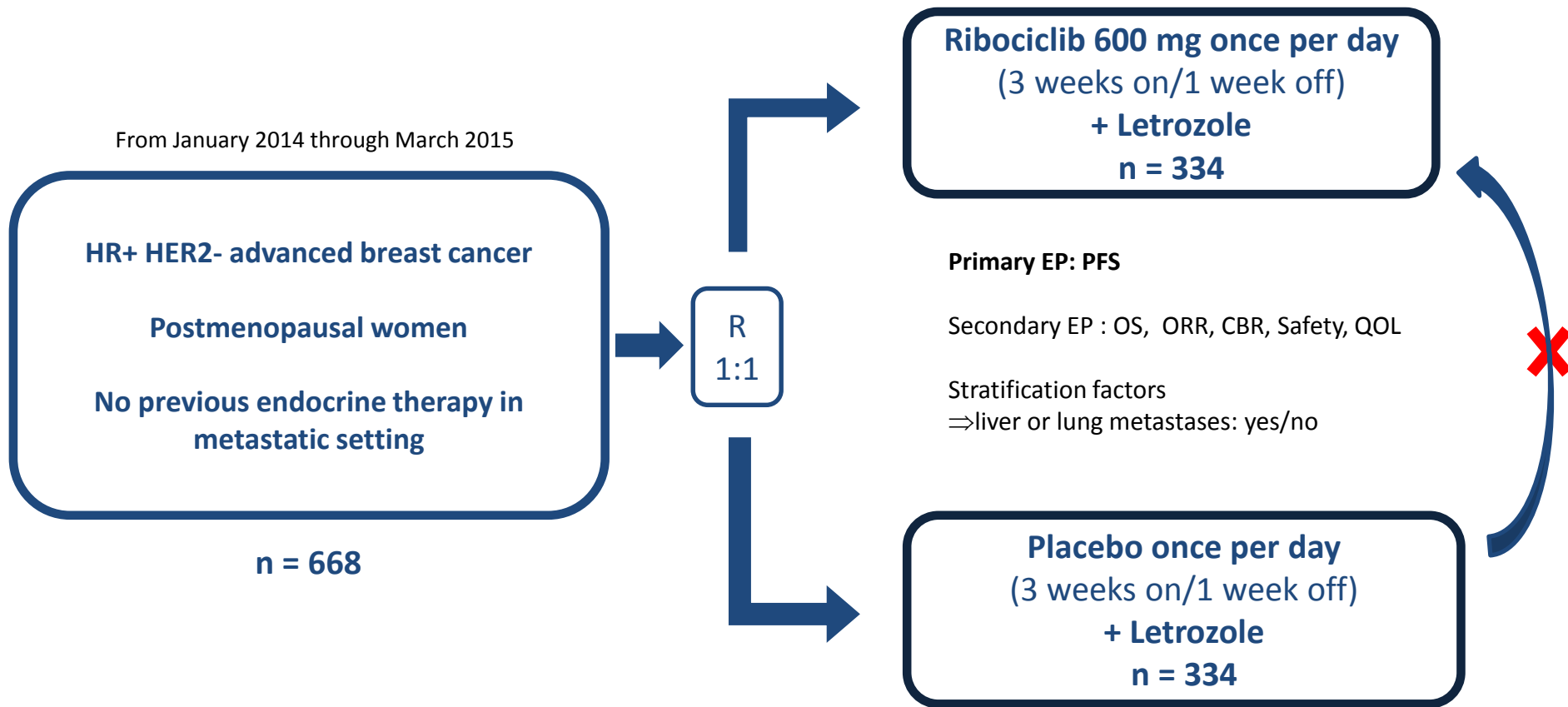
MONALEESA-2: Overall Survival

Median OS: **63.9** *vs* **51.4** months
HR 0.76 (0.63-0.93) *P* = 0.004

63.9 mo (5.3 y)

51.4 mo (4.3 y)

Ribociclib
Placebo

Months

Breast Cancer

Metastatic setting

DESTINY Breast03
(2nd line T-DXd HER2+)

KEYNOTE 355
(1st line Pembrolizumab TN)

MONALEESA 2
(1st line Ribociclib Luminal)

Neoadjuvant setting

BRIGHTNESS
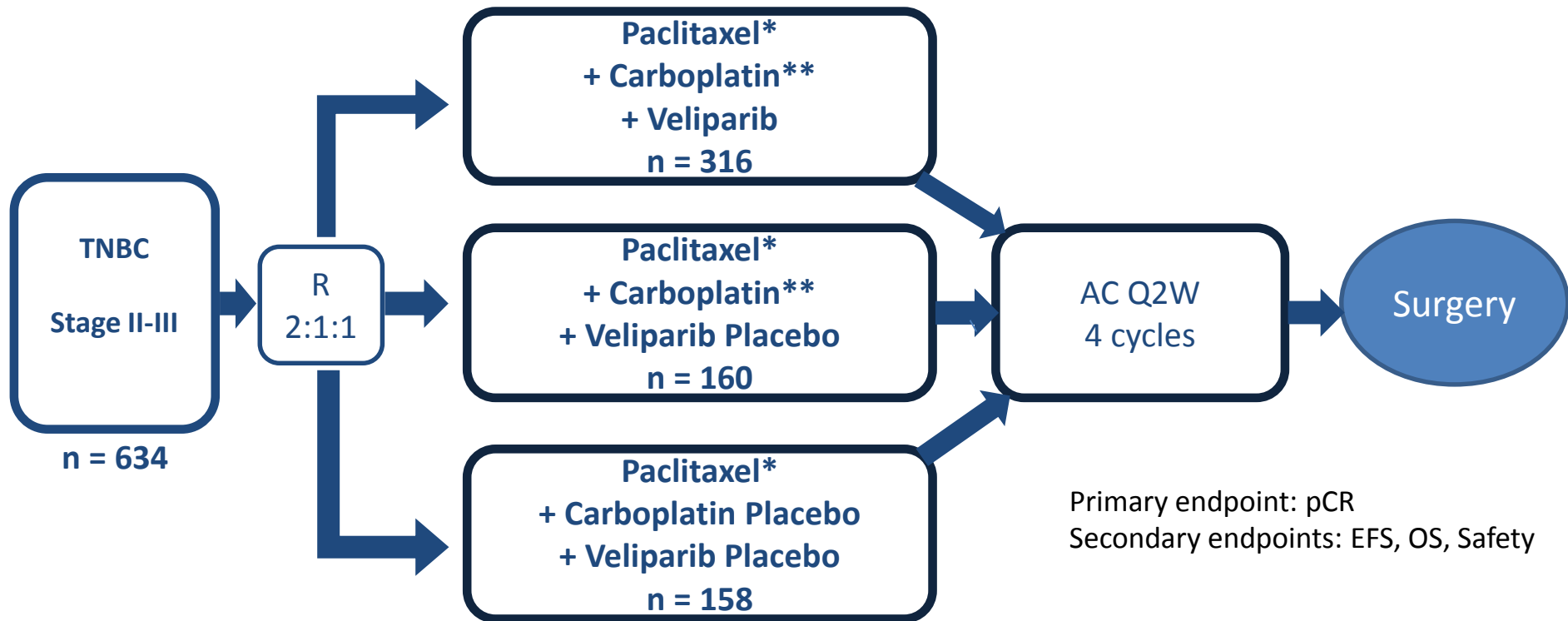(Carboplatine TNBC)

KEYNOTE 522
(Pembrolizumab TNBC)

SOC: EC-Paclitaxel dose dense (> 2 cm or N+)

Correlation between pathological response and prognostic
Symmans JCO 2017, Long-Term Prognostic Risk After Neoadjuvant Chemotherapy Associated With Residual Cancer Burden and Breast Cancer Subtype.

Platinum-based chemo increase pCR, but no evidence in EFS
Poggio, Annals Of Oncology 2018; Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis
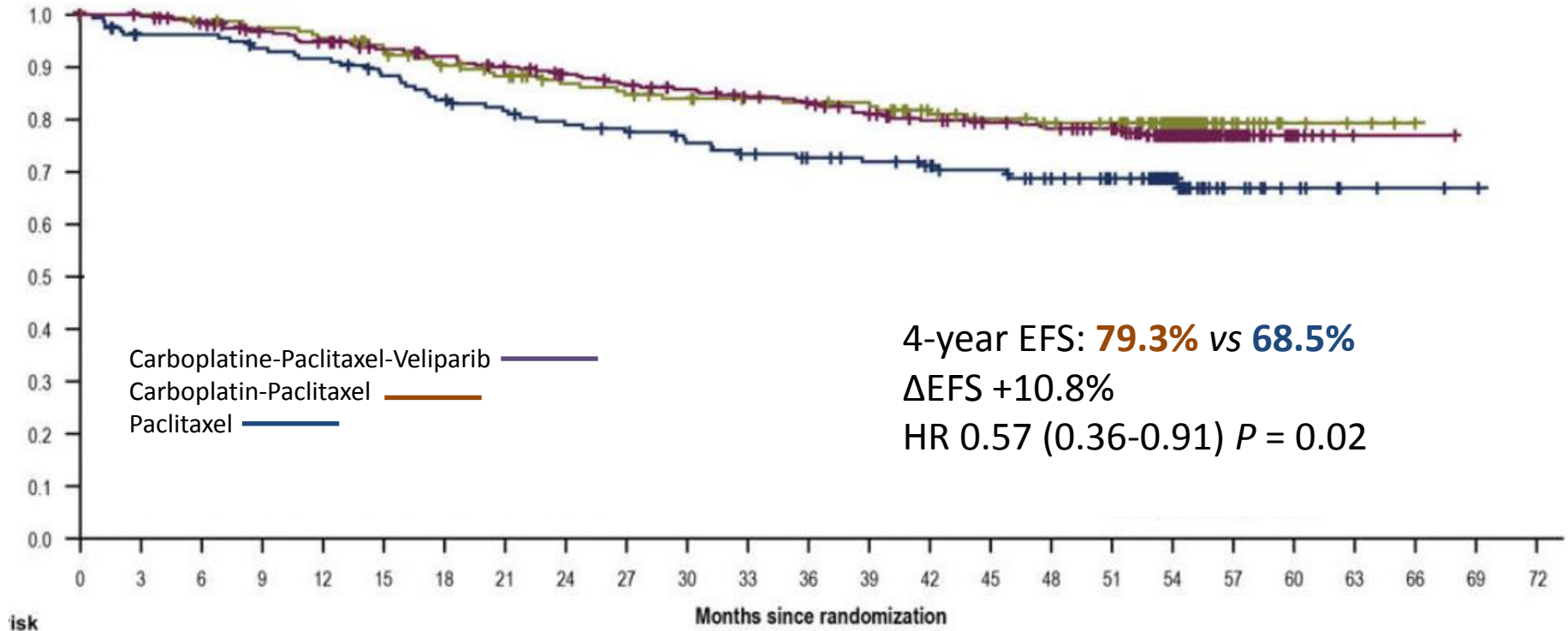
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                          ┌──────────────────────┐
                          │     Paclitaxel*      │
                          │   + Carboplatin**    │
                          │     + Veliparib      │
                          │       n = 316        │
                          └──────────────────────┘

┌──────────┐   ┌──────┐   ┌──────────────────────┐   ┌──────────────┐   ╭─────────╮
│   TNBC   │   │  R   │   │     Paclitaxel*      │   │   AC Q2W     │   │ Surgery │
│          │──▶│ 2:1:1│──▶│   + Carboplatin**    │──▶│   4 cycles   │──▶│         │
│Stage II-III│ │      │   │  + Veliparib Placebo │   │              │   ╰─────────╯
│          │   └──────┘   │       n = 160        │   └──────────────┘
│ n = 634  │              └──────────────────────┘
└──────────┘
                          ┌──────────────────────┐
                          │     Paclitaxel*      │
                          │ + Carboplatin Placebo│
                          │  + Veliparib Placebo │
                          │       n = 158        │
                          └──────────────────────┘
```

Primary endpoint: pCR
Secondary endpoints: EFS, OS, Safety

*Paclitaxel 80 mg/m2 weekly (12 doses in up to 16 weeks) **Carboplatin AUC 6 Q3W (4 cycles)

Carboplatine-Paclitaxel-Veliparib
Carboplatin-Paclitaxel
Paclitaxel

4-year EFS: **79.3%** *vs* **68.5%**
ΔEFS +10.8%
HR 0.57 (0.36-0.91) *P* = 0.02

Breast Cancer

Metastatic setting

DESTINY Breast03
(2nd line T-DXd HER2+)

KEYNOTE 355
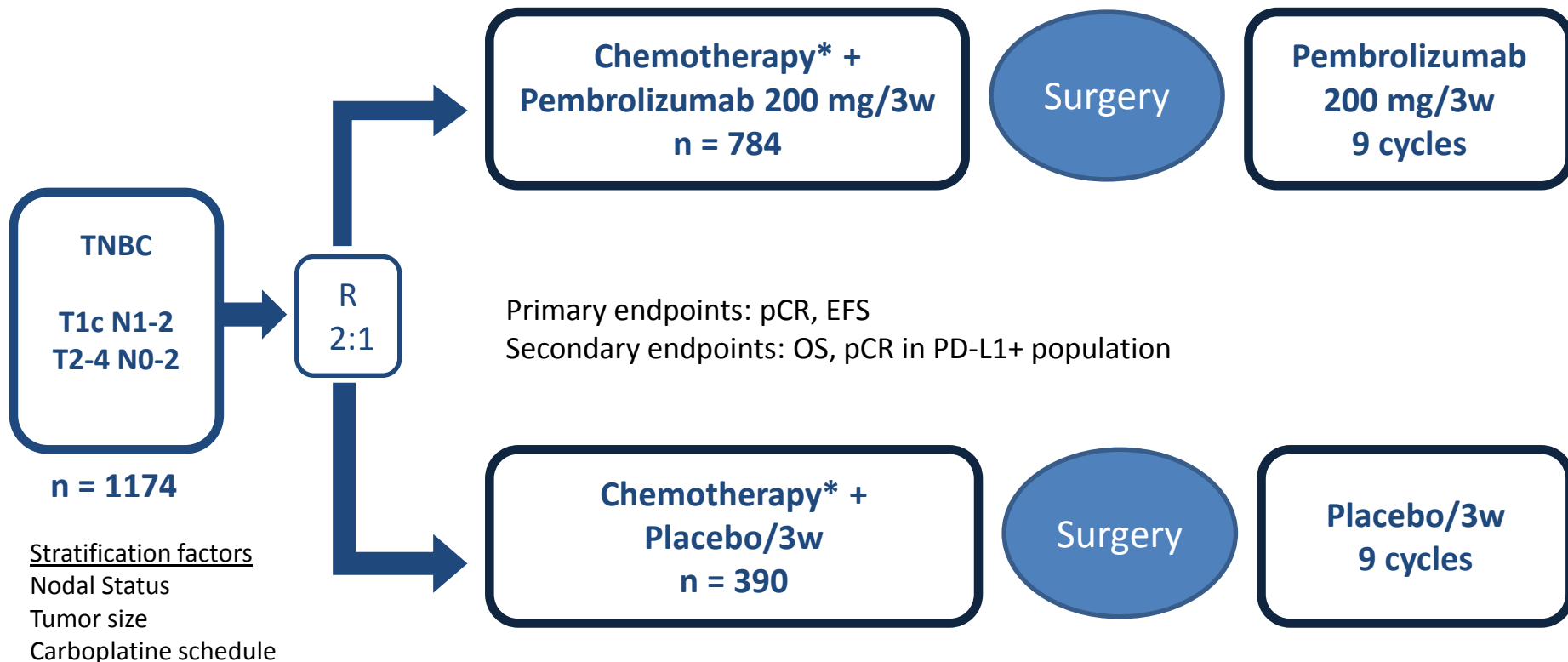(1st line Pembrolizumab TN)

MONALEESA 2
(1st line Ribociclib Luminal)

Neoadjuvant setting

BRIGHTNESS
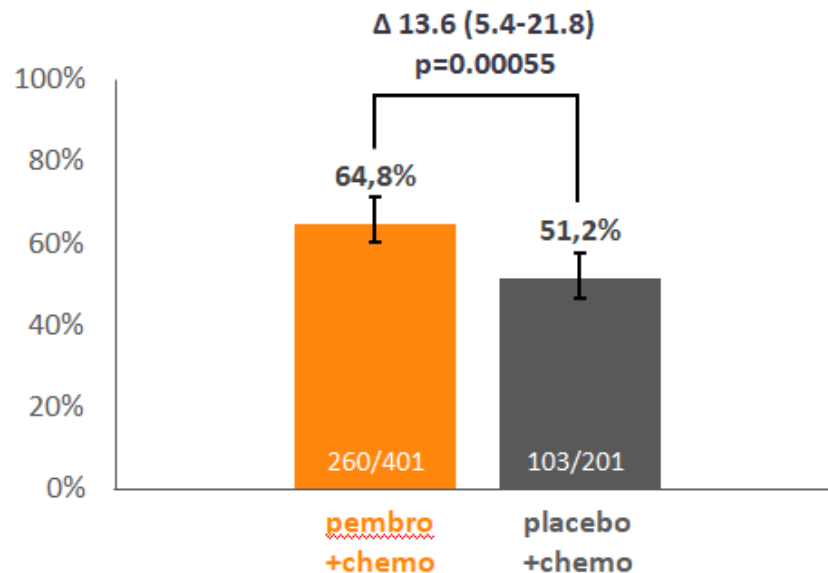(Carboplatine TNBC)

KEYNOTE 522
(Pembrolizumab TNBC)

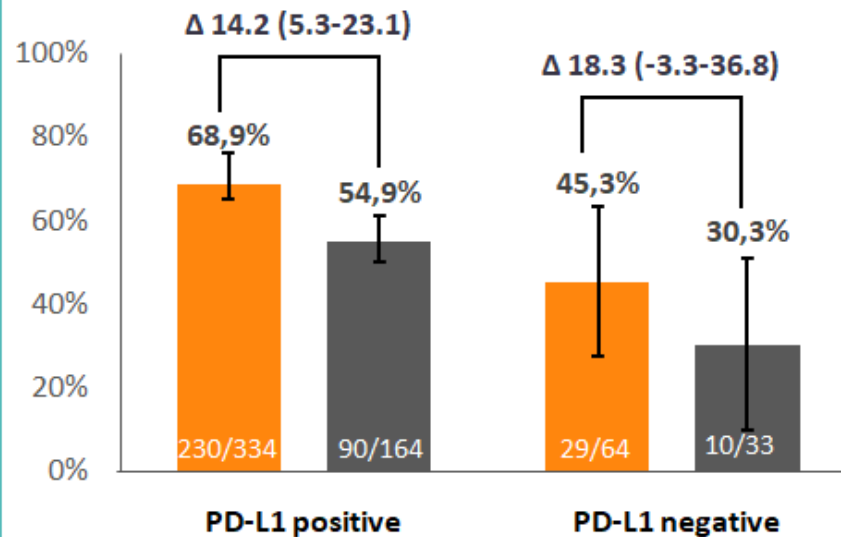# KEYNOTE-522 : a randomized, double-blind, placebo-controlled phase III trial

TNBC

T1c N1-2
T2-4 N0-2

n = 1174

<u>Stratification factors</u>
Nodal Status
Tumor size
Carboplatine schedule

R
2:1

Chemotherapy* +
Pembrolizumab 200 mg/3w
n = 784

Surgery

Pembrolizumab
200 mg/3w
9 cycles

Primary endpoints: pCR, EFS
Secondary endpoints: OS, pCR in PD-L1+ population

Chemotherapy* +
Placebo/3w
n = 390

Surgery

Placebo/3w
9 cycles

* 12 weeks of Carboplatine/paclitaxel followed by 4 cycles of EC or AC (Q3W)

KEYNOTE-522 : pCR

3 year EFS: **84.5%** *vs* **76.8%** HR
0.63 (0.48-0.82) *P* = 0.00031

Pembro
Placebo

3 year MRFS: **87.0%** *vs* **80.7%** HR 0.61 (0.46-0.82)

Pembro
Placebo

3 year OS: **89.7%** *vs* **86.9%**
HR 0.72 (0.51-1.02)

Pembro ———
Placebo ———

	Pembro + chemo n =783	Placebo + chemo n = 389
Any grade	43.6%	21.9%
Grade 3-5	14.9%	2.1%
Led to death	0.3%	0
Led to disconstinuation	10.9%	2.6%

Endocrine adverse events in early setting => Potentially irreversible

KEYNOTE 522

PD-L1 status correlation: ypT0/Tis ypN0

Δ 14.2 (5.3-23.1)
Δ 18.3 (-3.3-36.8)

68,9%
54,9%
45,3%
30,3%

230/334 90/164 29/64 10/33

PD-L1 positive PD-L1 negative

84.5%
76.8%

Months

$\Delta EFS + 7.7\%$

Favorable trend in OS
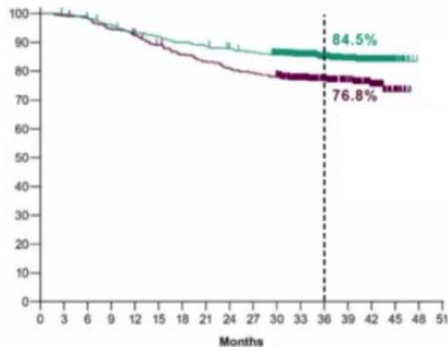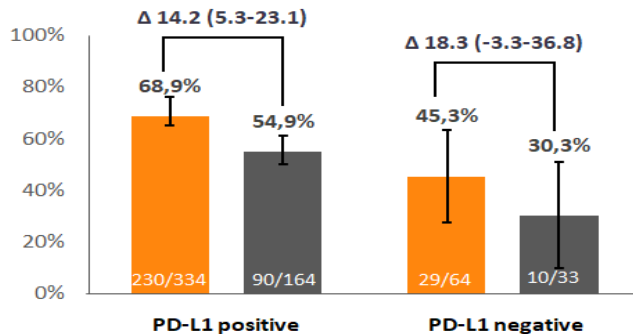
IMpassion 031

pCR (IC95%), ypT0/is ypN0 (PD-L1-positive)

Δ 19,5% (4,2-34,8)
P=0,021[b]
Limite de significativité non
atteinte 0,0184

68,8%
49,3%

53/77 37/75

Atezolizumab – Chimio   Placebo – Chimio
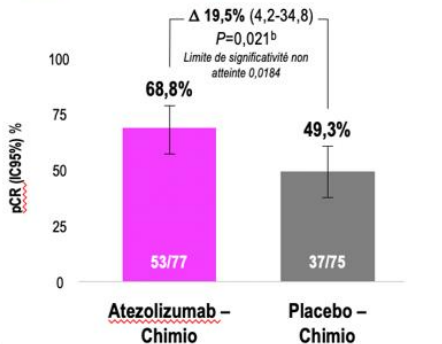
pCR (IC95%), ypT0/is ypN0 (PD-L1-negative)

Δ 13,3%
(-0,9-27,5)

47,7%
34,4%

42/88 39/93

Atezolizumab – Chimio   Placebo – Chimio
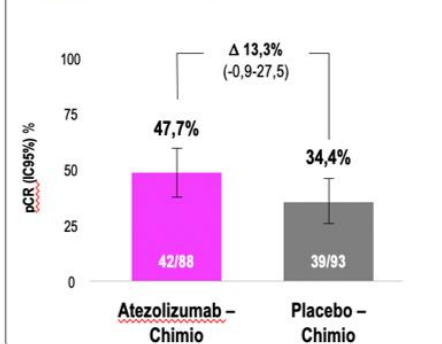
EFS and OS non evaluated

Breast Cancer

Metastatic setting

DESTINY Breast03
(2nd line T-DXd HER2+)

KEYNOTE 355
(1st line Pembrolizumab TN)

MONALEESA 2
(1st line Ribociclib Luminal)

Δ1YPFS +41.7%

ΔOS +6.9 months

ΔOS +12.5 months

Neoadjuvant setting

BRIGHTNESS
(Carboplatine TNBC)

KEYNOTE 522
(Pembrolizumab TNBC)

Δ4YEFS +10.8%

Δ3YEFS +7.7%

Gynecological Cancers

EMPOWER
(2nd line Cemeplimab in metastatic cervical cancer)

KEYNOTE 826
(1st line Pembrolizumab in metastatic cervical cancer)

OReO-ENGOT-Ov38
(Olaparib retreatment in late recurrent ovarian cancer)

EMPOWER
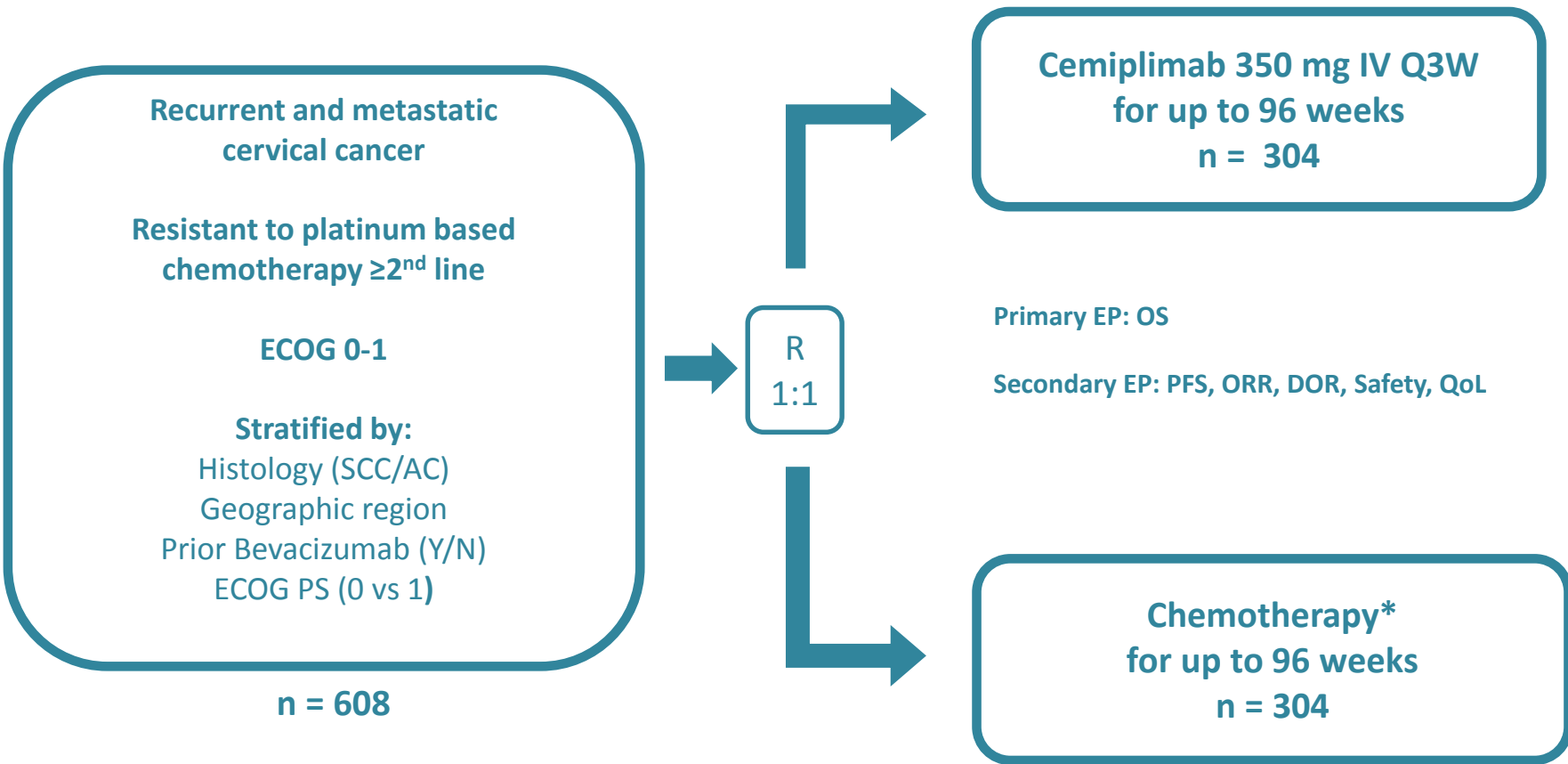(2nd line Cemeplimab in metastatic cervical cancer)

KEYNOTE 826
(1st line Pembrolizumab in metastatic cervical cancer)
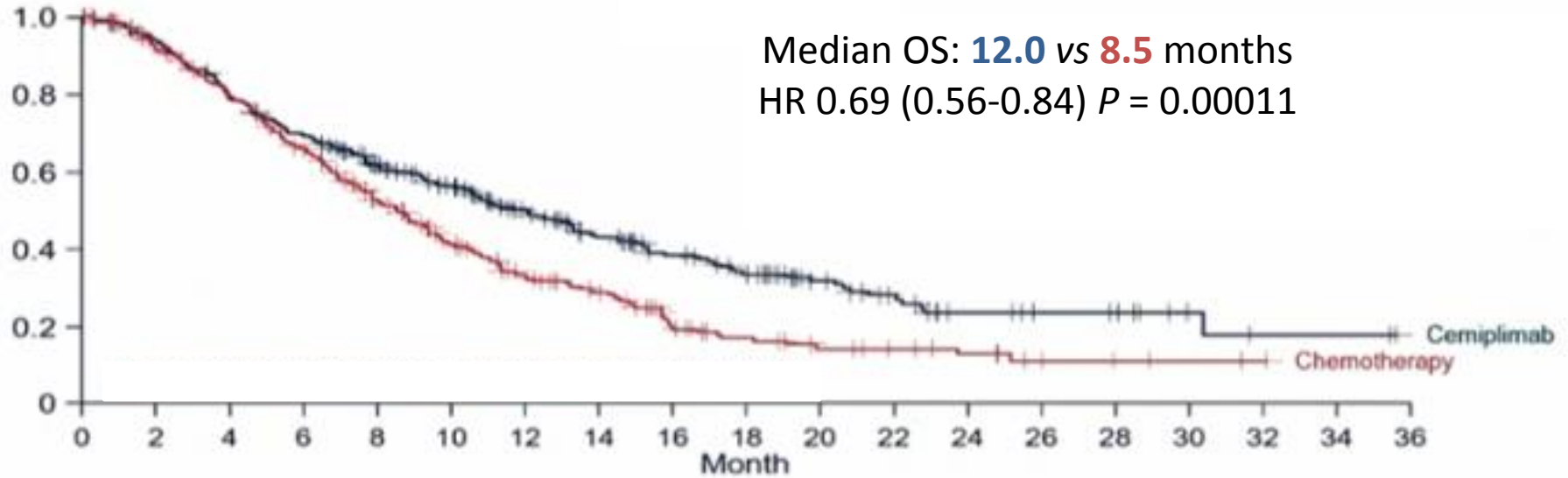
OReO-ENGOT-Ov38
(Olaparib retreatment in late recurrent ovarian cancer)

EMPOWER cervical: phase III trial

Recurrent and metastatic cervical cancer

Resistant to platinum based chemotherapy ≥2nd line

ECOG 0-1

Stratified by:
Histology (SCC/AC)
Geographic region
Prior Bevacizumab (Y/N)
ECOG PS (0 vs 1)

n = 608

R
1:1

Cemiplimab 350 mg IV Q3W for up to 96 weeks n = 304

Primary EP: OS

Secondary EP: PFS, ORR, DOR, Safety, QoL

Chemotherapy* for up to 96 weeks n = 304

Pemetrexed, Gemcitabine, Topotecan, Irinotecan, Vinorelbine

EMPOWER cervical: Overall Survival

Median OS: **12.0** *vs* **8.5** months
HR 0.69 (0.56-0.84) *P* = 0.00011

KEYNOTE 826: phase III trial

Persistent, Recurrent or metastatic cervical cancer not amenable to curative treatment

No prior systemic chemotherapy (prior chemoradiotherapy permetted)

ECOG 0-1

Stratified by:
Metastatic disease at diagnosis (Y/N)
PD-L1 CPS
Planned Bevacizumab use (Y/N)

n = 617

R
1:1

Pembrolizumab 200 mg IV Q3W*
+
Paclitaxel + Cisplatin/Carboplatin IV Q3W
+
Bevacizumab 15 mg/kg IV Q3W

Dual Primary EP: OS, PFS (investigator)

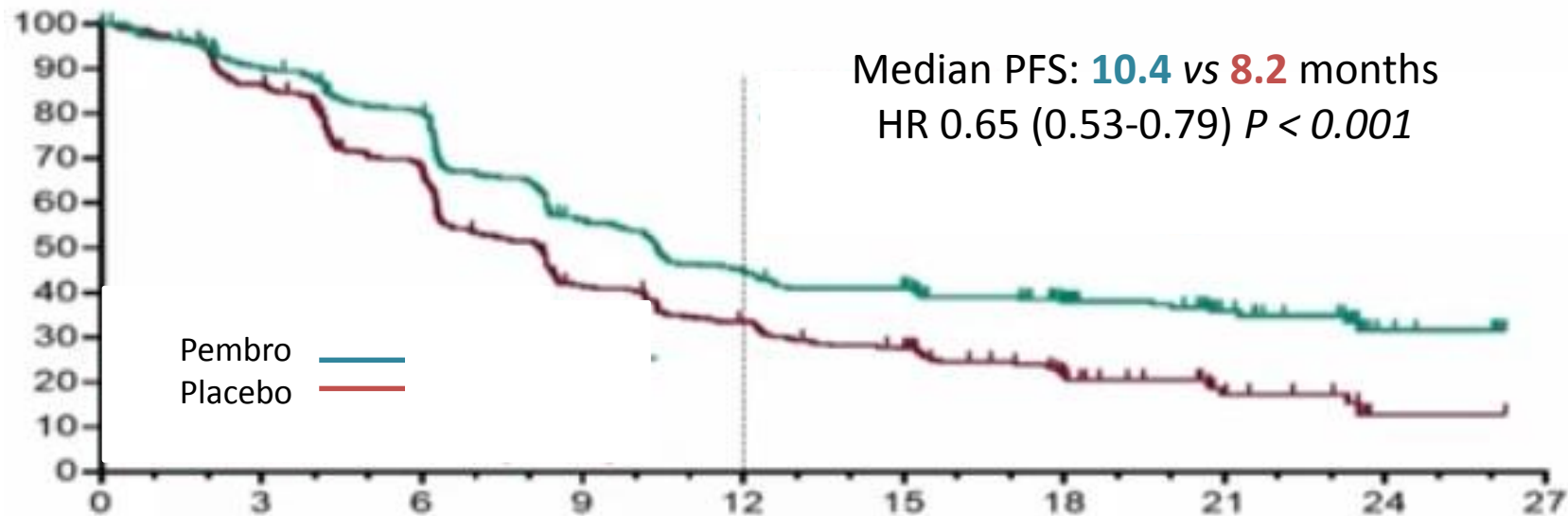**Secondary EP: ORR, DOR, PFS (BICR) Safety**

Placebo IV Q3W*
+
Paclitaxel + Cisplatin/Carboplatin IV Q3W
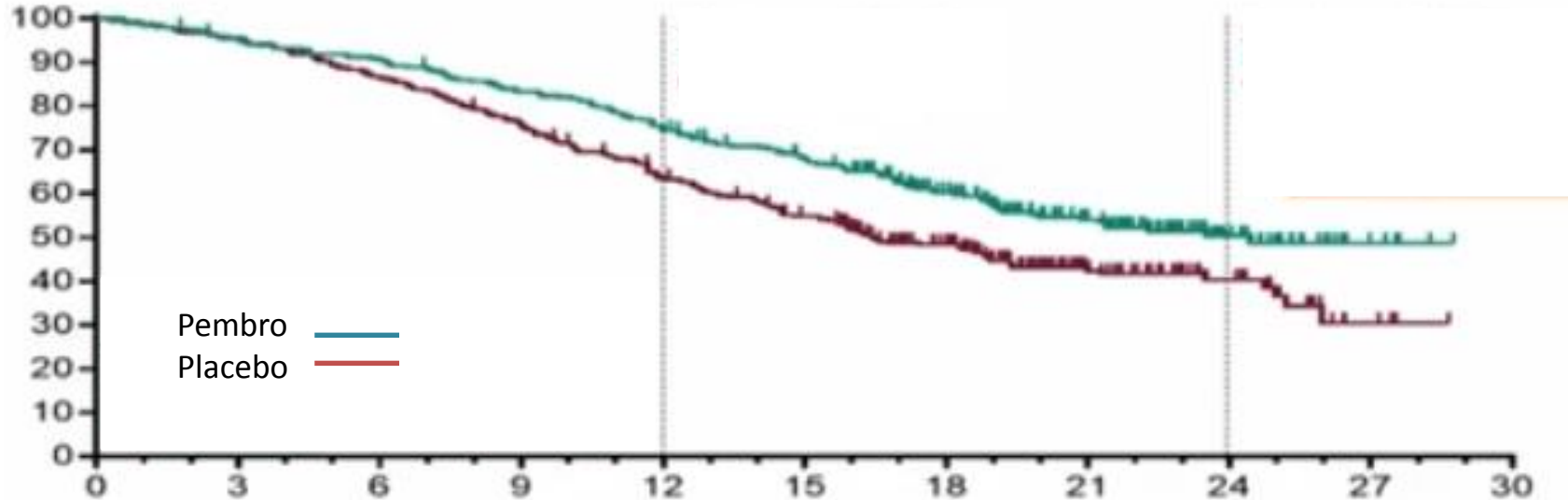**+**
Bevacizumab 15 mg/kg IV Q3W

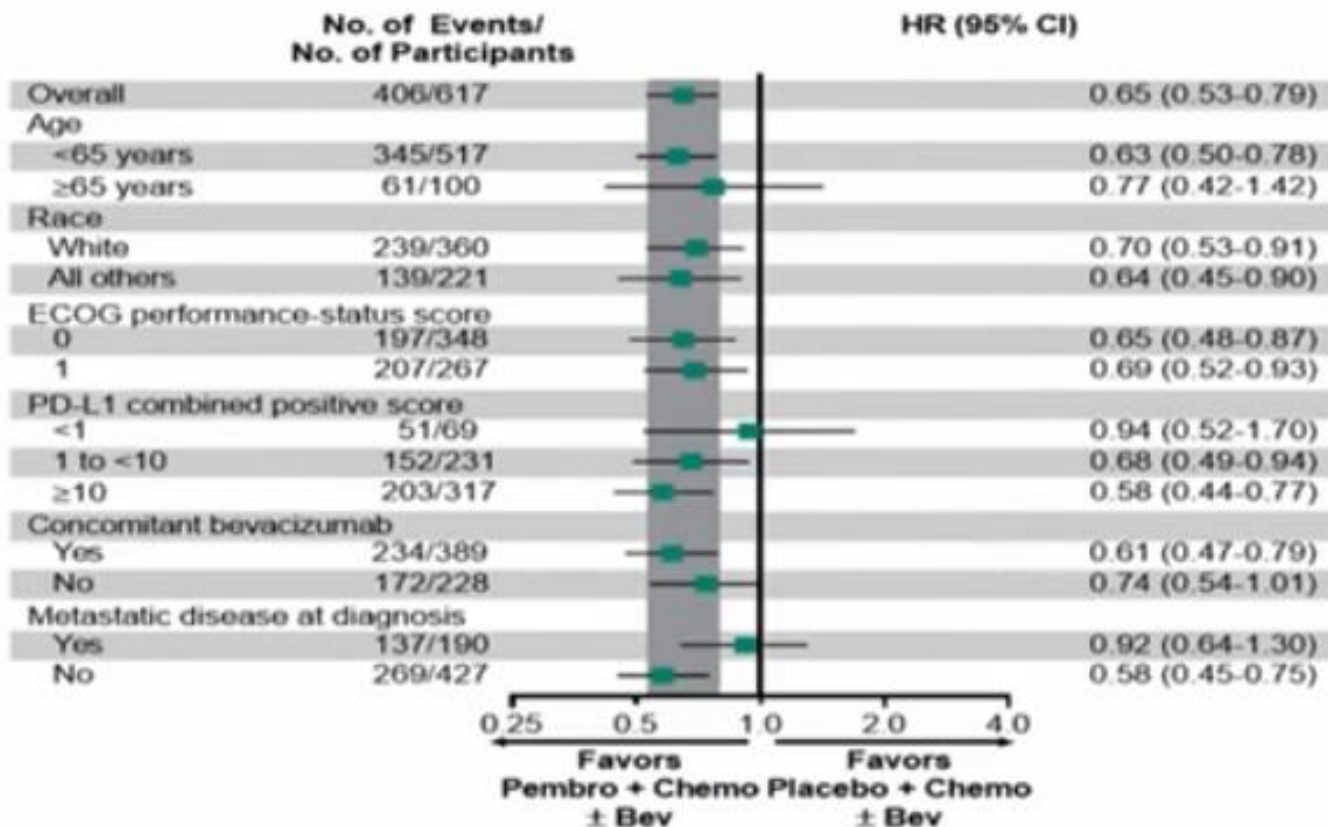*for up to 35 cycles*

KEYNOTE 826: Progression-Free Survival

Median PFS: **10.4** *vs* **8.2** months
HR 0.65 (0.53-0.79) *P < 0.001*

Pembro
Placebo

KEYNOTE 826: Subgroups Overall Survival

	No. of Events/ No. of Participants	HR (95% CI)
Overall	406/617	0.65 (0.53-0.79)
Age		
<65 years	345/517	0.63 (0.50-0.78)
≥65 years	61/100	0.77 (0.42-1.42)
Race		
White	239/360	0.70 (0.53-0.91)
All others	139/221	0.64 (0.45-0.90)
ECOG performance-status score		
0	197/348	0.65 (0.48-0.87)
1	207/267	0.69 (0.52-0.93)
PD-L1 combined positive score		
<1	51/69	0.94 (0.52-1.70)
1 to <10	152/231	0.68 (0.49-0.94)
≥10	203/317	0.58 (0.44-0.77)
Concomitant bevacizumab		
Yes	234/389	0.61 (0.47-0.79)
No	172/228	0.74 (0.54-1.01)
Metastatic disease at diagnosis		
Yes	137/190	0.92 (0.64-1.30)
No	269/427	0.58 (0.45-0.75)

Favors Pembro + Chemo ± Bev   Favors Placebo + Chemo ± Bev

Gynecological Cancers

EMPOWER
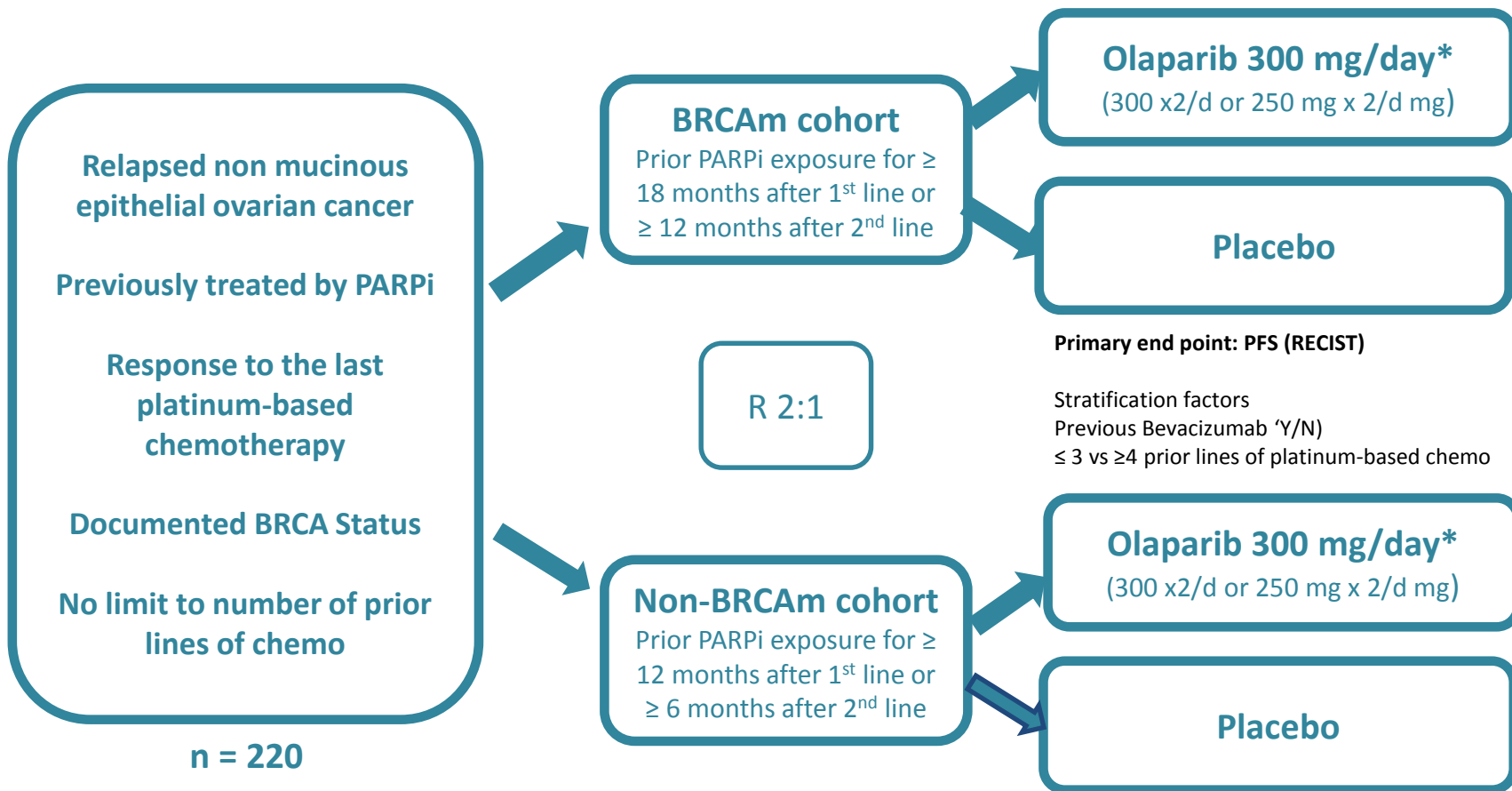(2nd line Cemeplimab in metastatic cervical cancer)

KEYNOTE 826
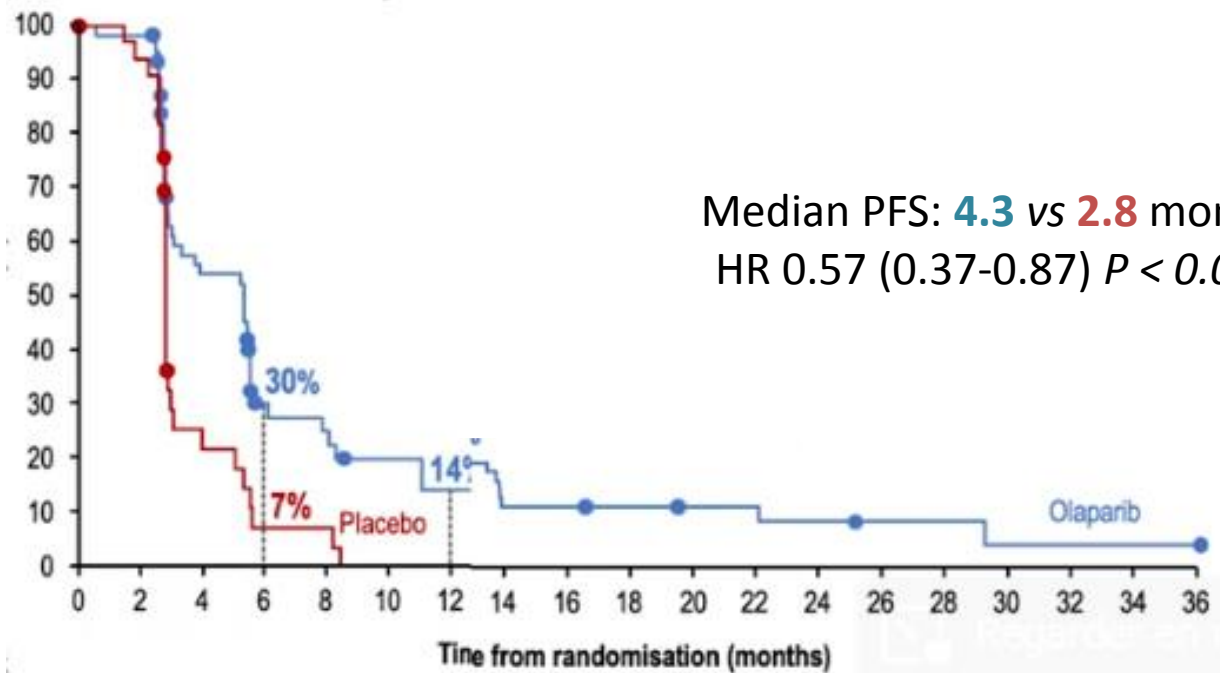(1st line Pembrolizumab in metastatic cervical cancer)

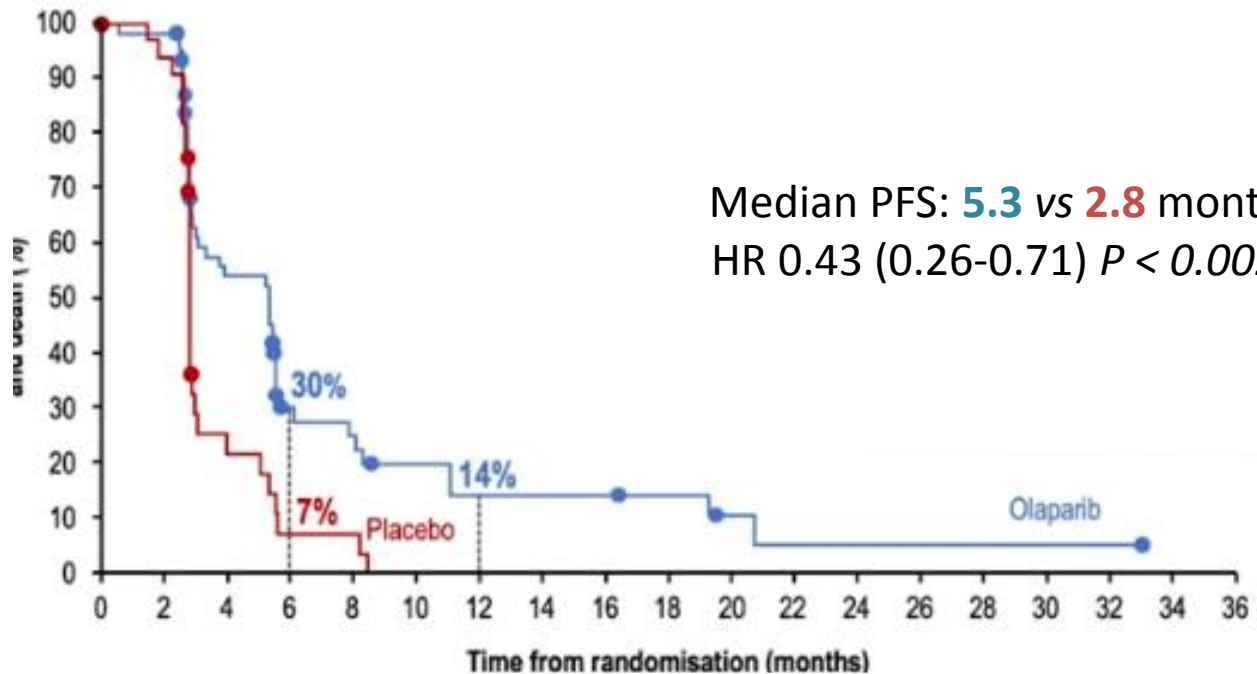**OReO-ENGOT-Ov38**
(Olaparib retreatment in late recurrent ovarian cancer)

OReO-ENGOT-Ov38

Relapsed non mucinous epithelial ovarian cancer

Previously treated by PARPi

Response to the last platinum-based chemotherapy

Documented BRCA Status

No limit to number of prior lines of chemo

n = 220

BRCAm cohort
Prior PARPi exposure for ≥ 18 months after 1st line or ≥ 12 months after 2nd line

R 2:1

Olaparib 300 mg/day*
(300 x2/d or 250 mg x 2/d mg)

Placebo

Primary end point: PFS (RECIST)

Stratification factors
Previous Bevacizumab 'Y/N)
≤ 3 vs ≥4 prior lines of platinum-based chemo

Non-BRCAm cohort
Prior PARPi exposure for ≥ 12 months after 1st line or ≥ 6 months after 2nd line

Olaparib 300 mg/day*
(300 x2/d or 250 mg x 2/d mg)

Placebo

Median PFS: **4.3** *vs* **2.8** months
HR 0.57 (0.37-0.87) *P < 0.022*

Median PFS: **5.3** *vs* **2.8** months
HR 0.43 (0.26-0.71) *P < 0.0023*

Gynecological Cancers

EMPOWER
(2nd line Cemeplimab in metastatic cervical cancer)
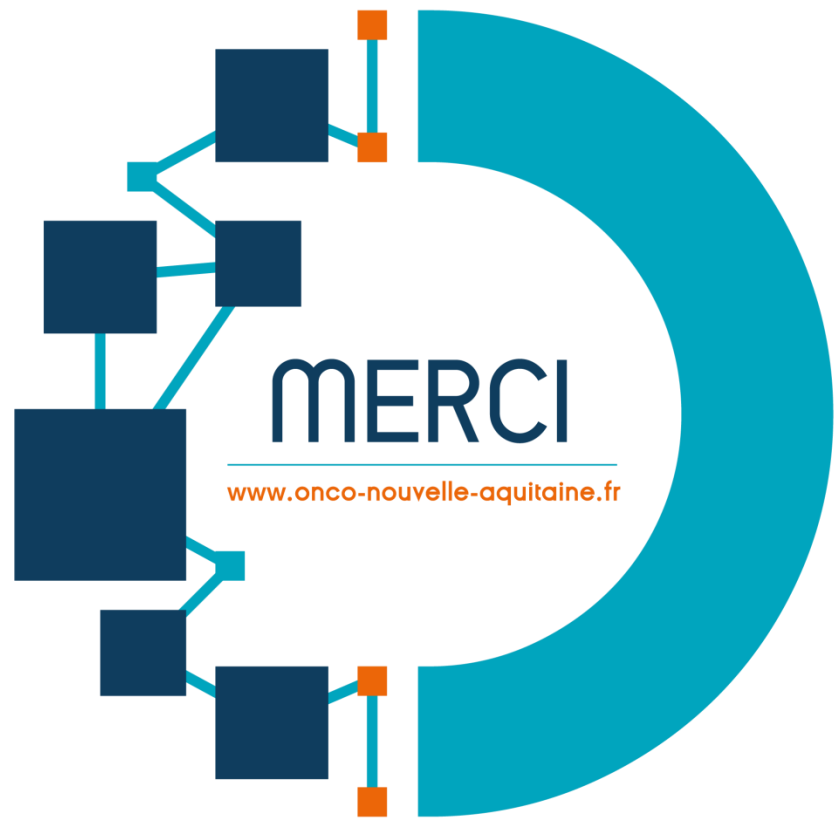
ΔOS +3.5 months

KEYNOTE 826
(1st line Pembrolizumab in metastatic cervical cancer)

ΔOS +7.9 months

OReO-ENGOT-Ov38
(Olaparib retreatment in late recurrent ovarian cancer)

ΔPFS +1.5-2.5 months

MERCI

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