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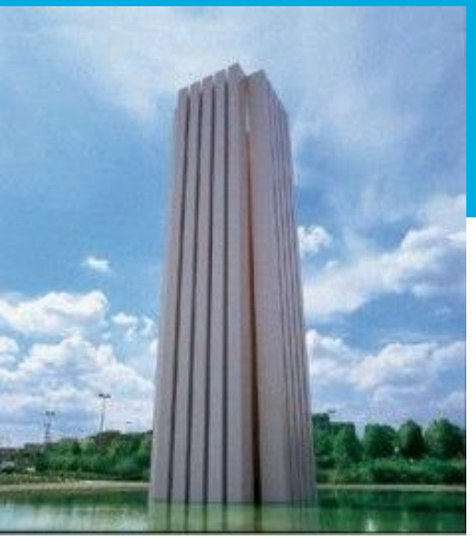
Immunotherapy and breast cancer: where are we?

Hans Wildiers

Medical oncologist, Leuven, Belgium



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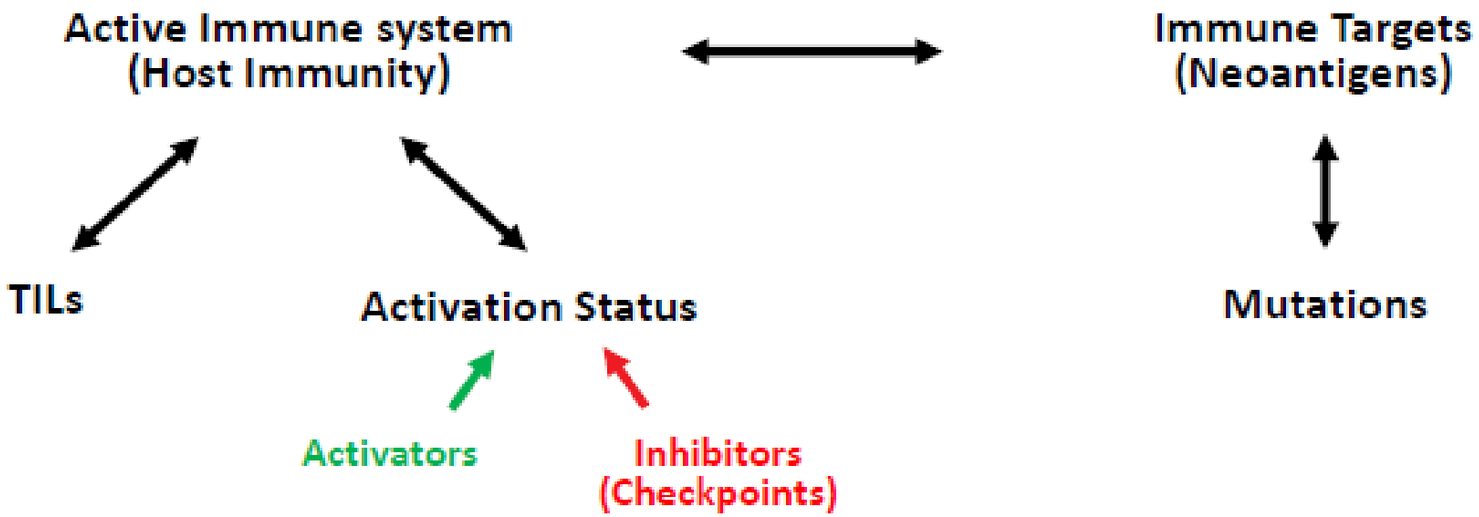
Courtesy to Peter Schmid

Disclosure slide

- **Institutional conflict**:
  - Consulting fees and honoraria to my institute from Abbvie, Amgen, Ariez International, AstraZeneca, Biocartes, DNA Prime, Lilly, Novartis, ORION corporation, Pfizer, PUMA Biotechnology, Roche, Sirtex, TRM Oncology, Vifor Pharma, Daiichi Sankyo.
  - Unrestricted research grant to my institute from Roche.

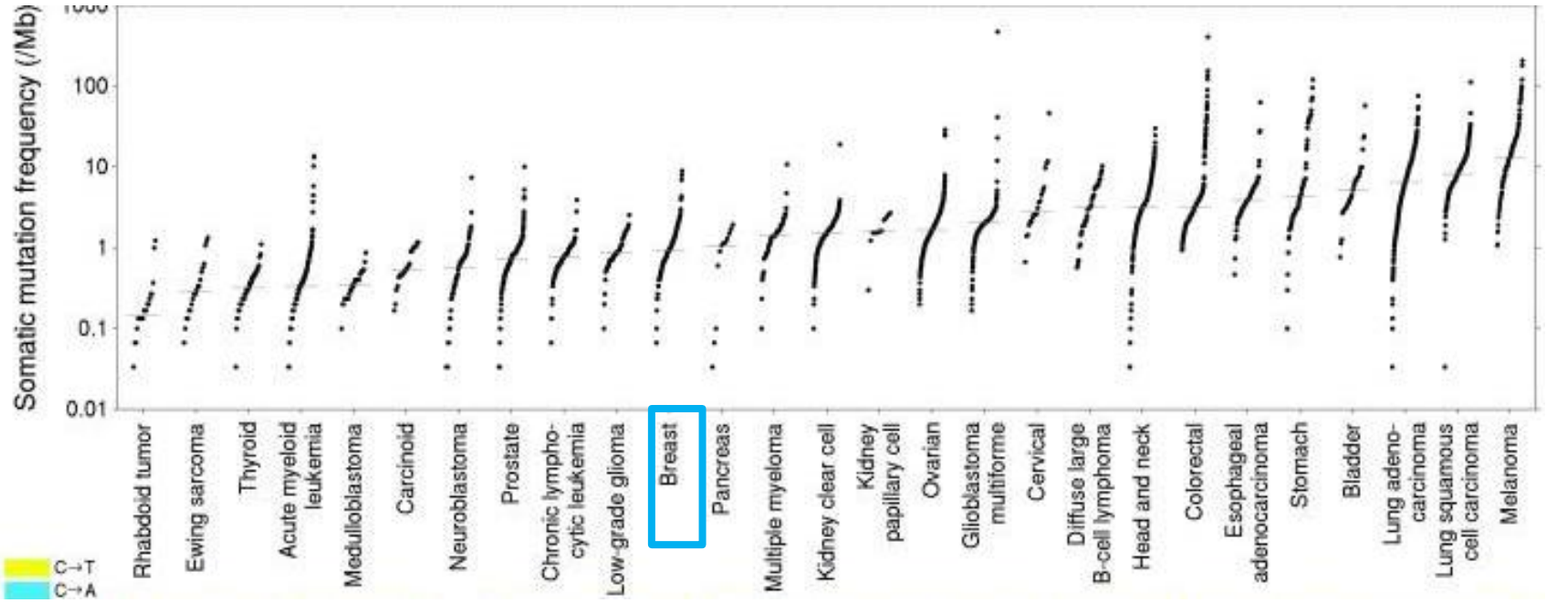
- **Travel support** from Roche and Pfizer.

Immune targeting in breast cancer



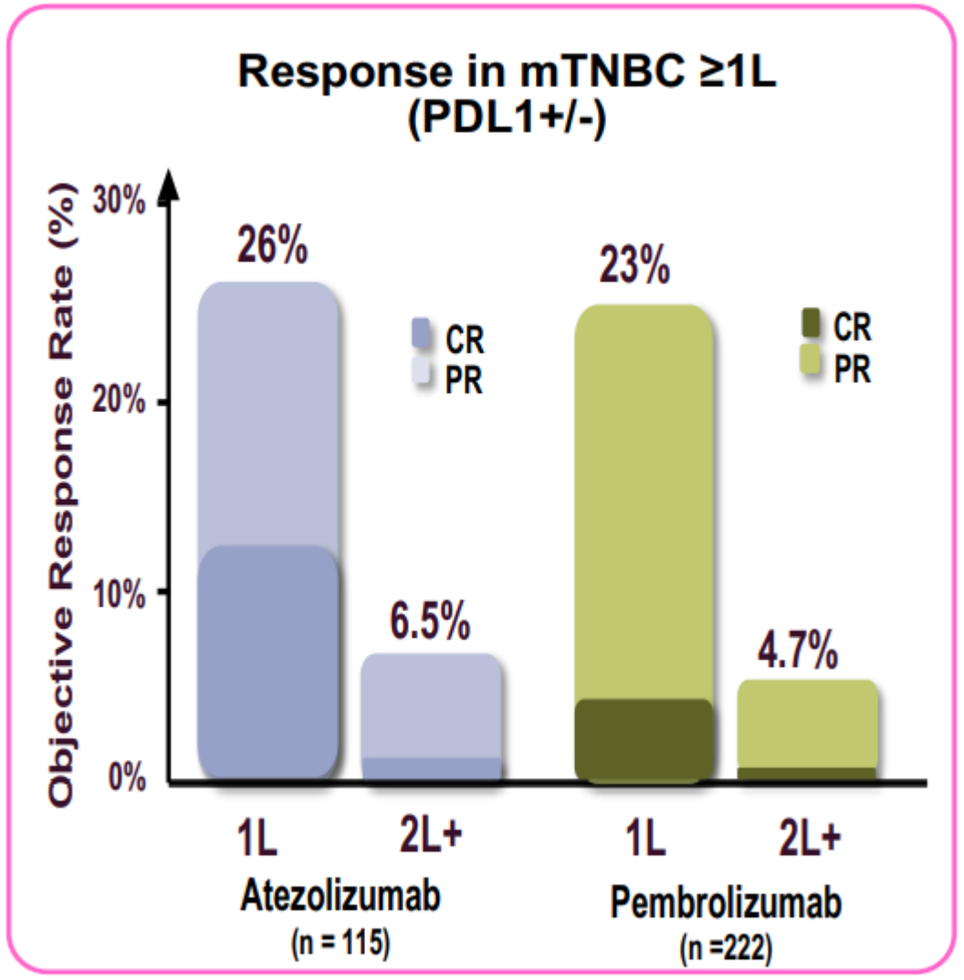
Triple negative breast cancer (**TNBC**) is genomically less stable and has higher **mutational burden** compared to luminal and HER2 + breast cancer

Mutational burden for different tumor types

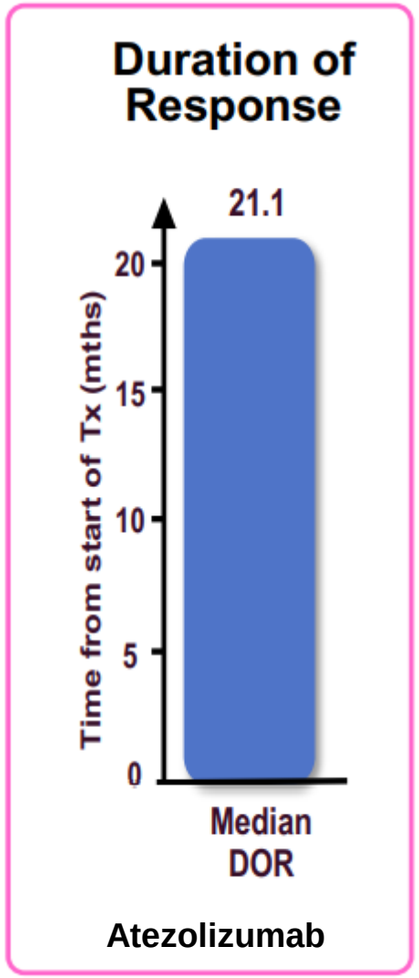


Lawrence MS, et al. Nature 2013; 499: 214-218
Schmid P. ESMO Congress 2017, Madrid

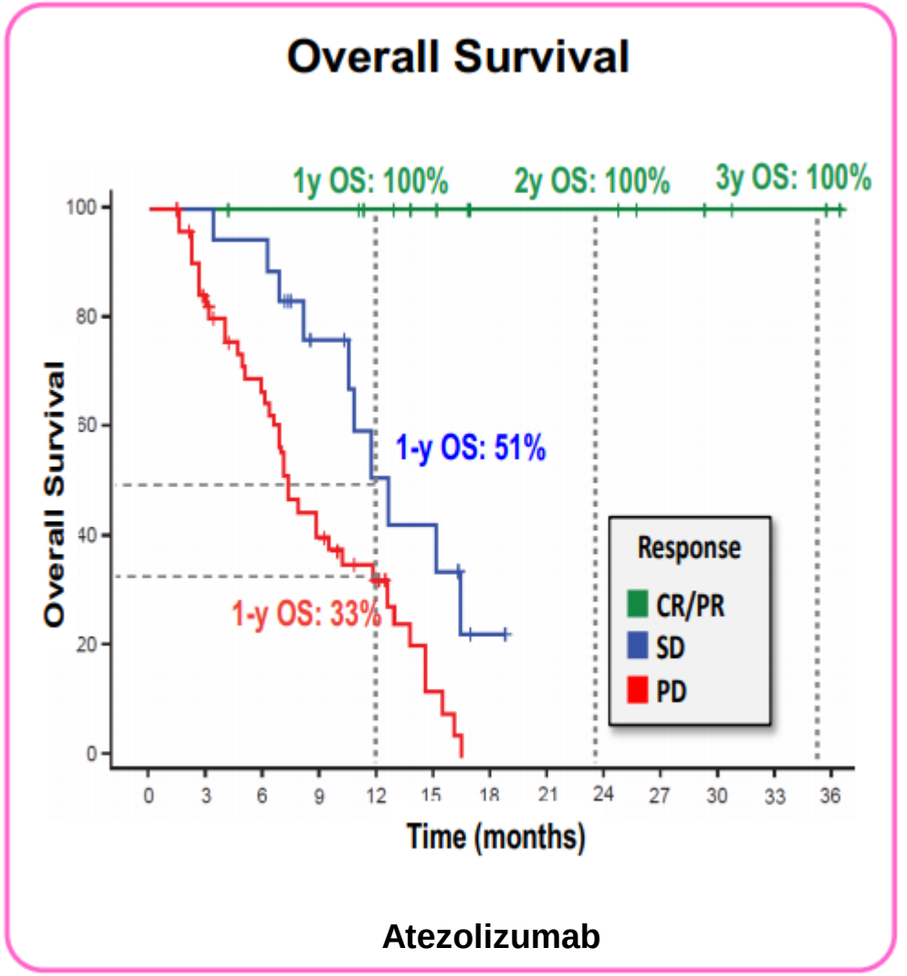
Activity of single agent anti-PD-L1/PD-1 in metastatic TNBC



Active in first line
Low response in later line

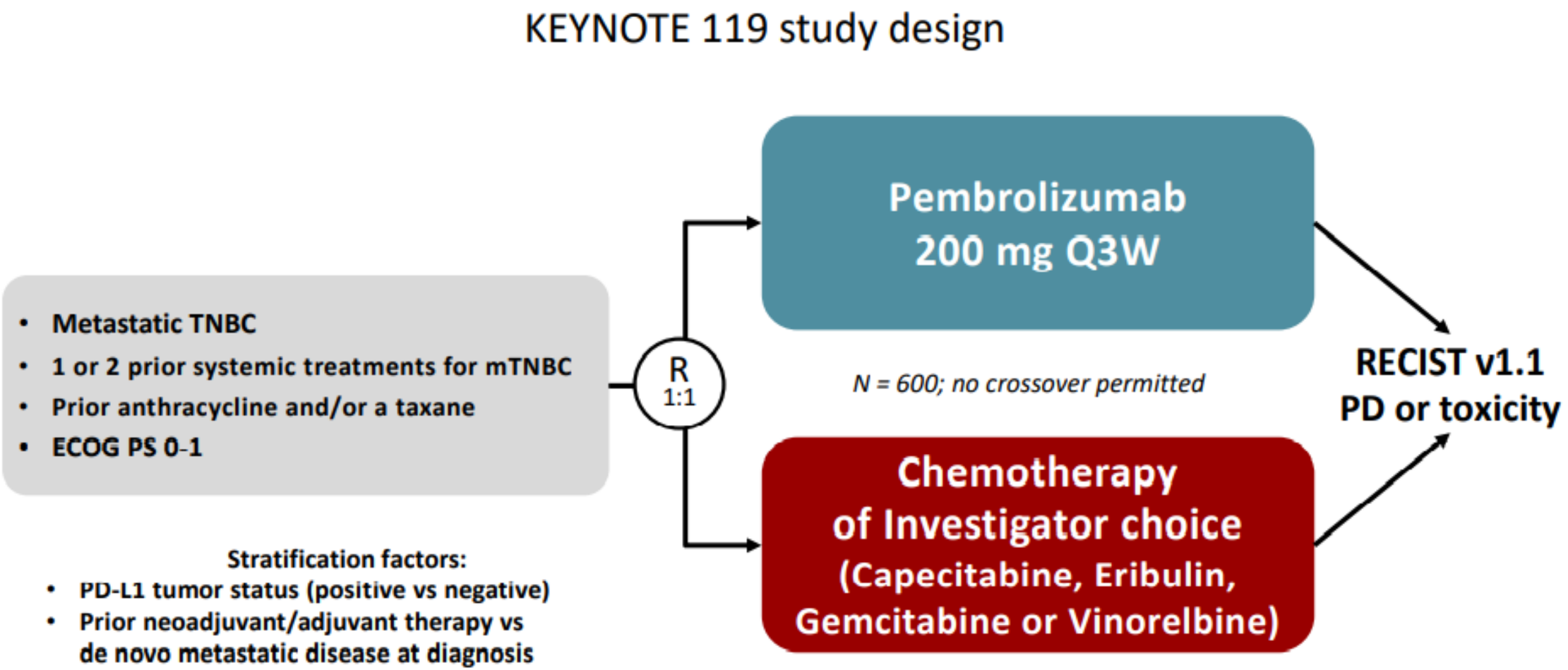


Duration of response is unseen in TNBC



Schmid P, et al. Cancer Res 2017; 77(suppl): Abstract 2986 ; Adams S, et al. J Clin Oncol 2017;35(suppl): Abstract 1008

Pembrolizumab vs chemo in 2L/3L metastatic TNBC

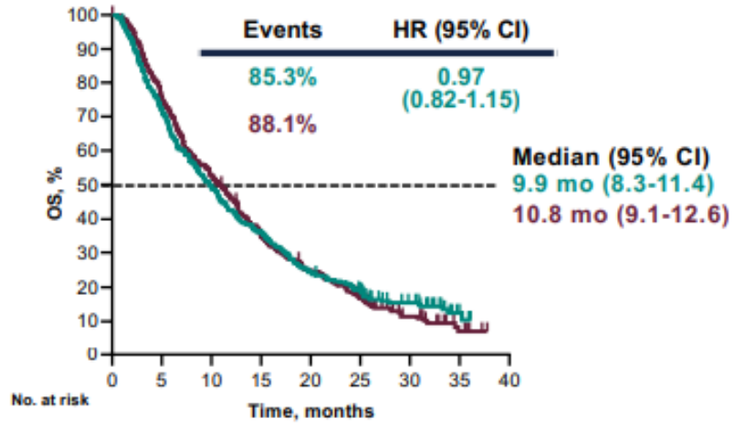


- **Co-primary endpoints were OS in the CPS ≥10, in the CPS ≥1, and in the ITT populations**

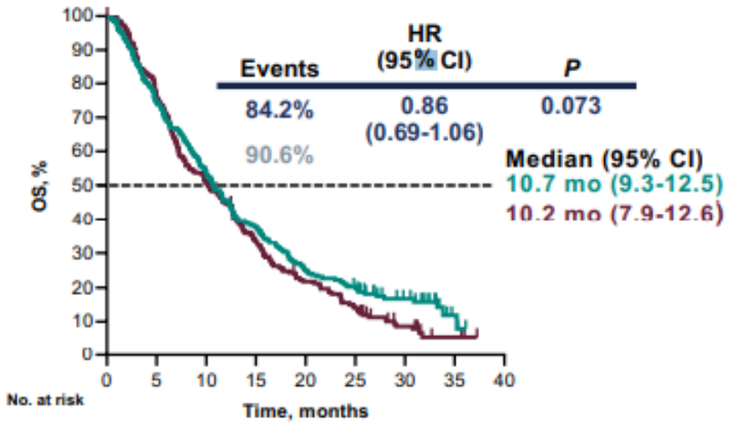
Cortes et al. ESMO 2019

Pembrolizumab vs chemo in 2L/3L metastatic TNBC

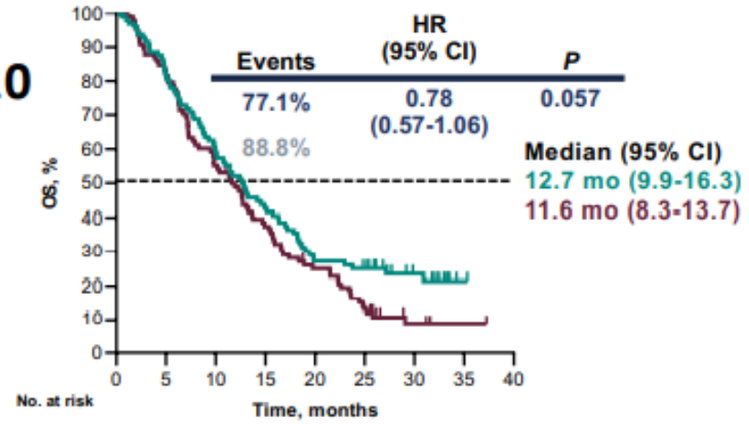
ITT



CPS ≥1

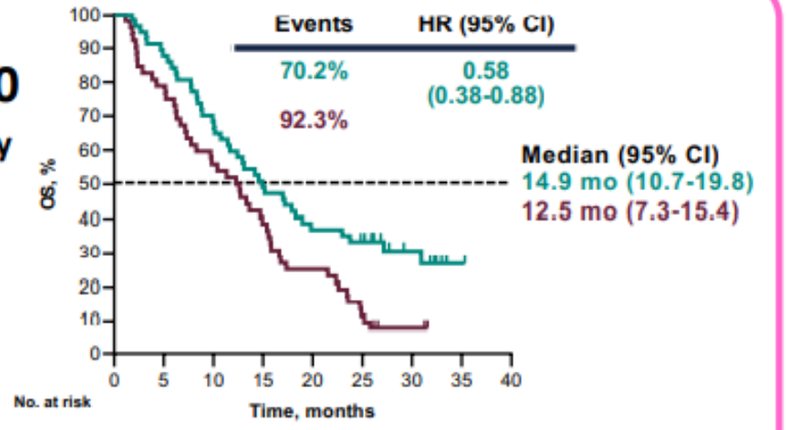


CPS ≥10



CPS ≥20

Exploratory

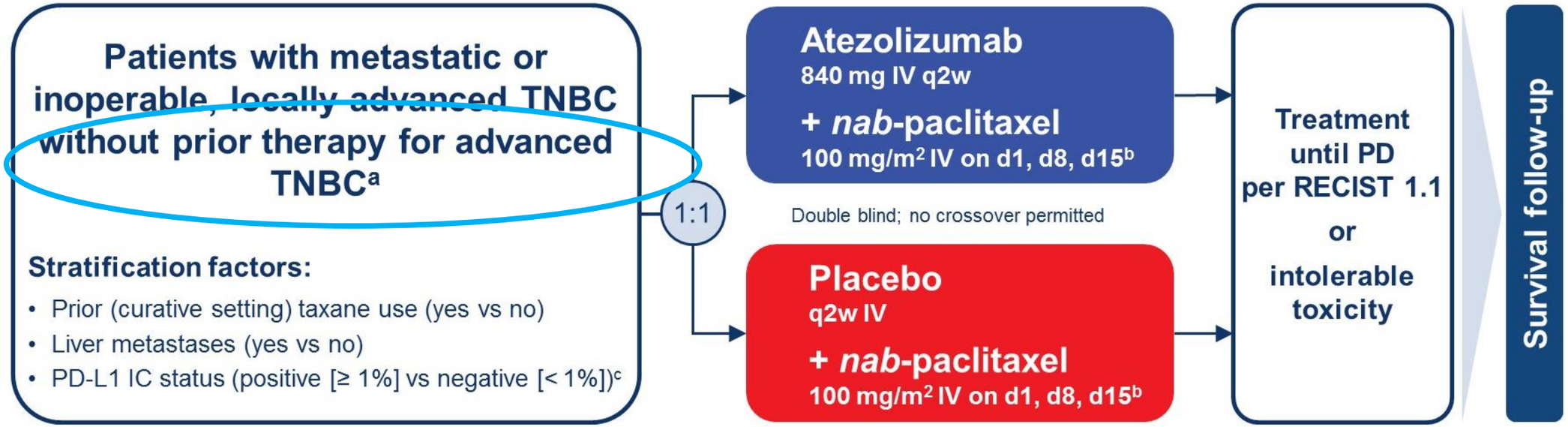


CPS = combined positive score
Measured by 22c3 assay
Measures PD-L1 positivity in tumor and immune cells
Different cut-offs: ≥1; ≥10; ≥20

Pembro mono has more or less similar antitumor activity as standard chemo

Cortes et al. ESMO 2019

Atezolizumab + chemo first line in triple negative breast cancer: IMpassion130 trial



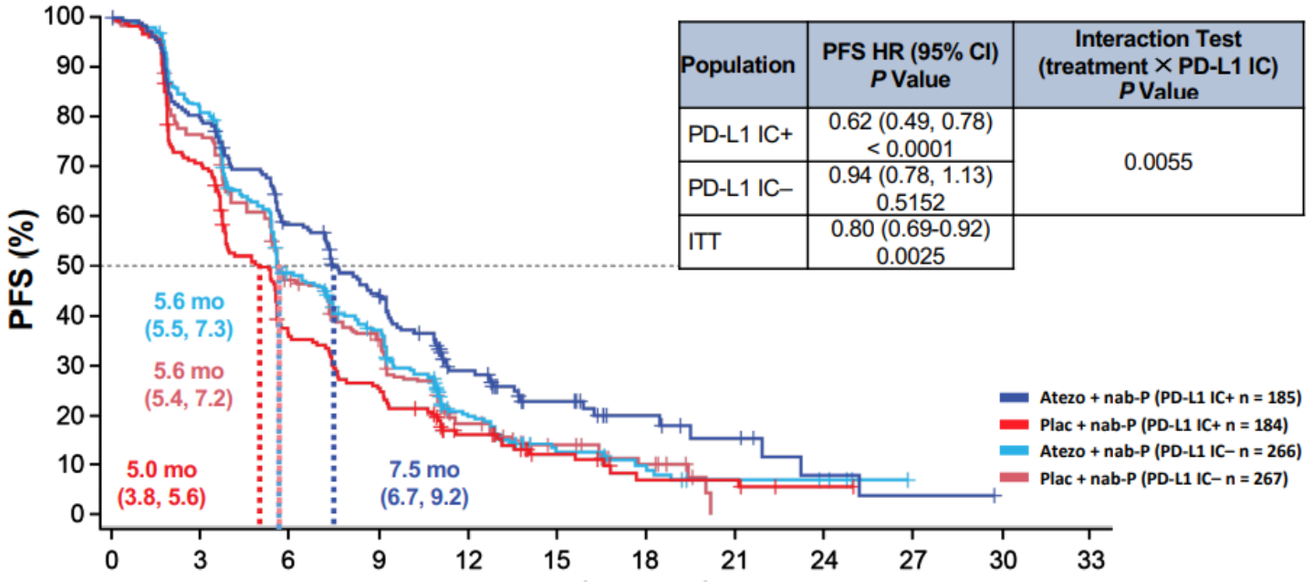
- Co-primary endpoints in ITT and PD-L1 IC+: PFS and OS[d]
- Pre-specified hierarchical testing of OS in ITT and, if significant, in PD-L1 IC+ patients
- In both treatment arms, 41% of patients were PD-L1 IC+

[a] Prior chemotherapy in the curative setting allowed if treatment-free interval ≥ 12 months. [b] 28-day cycle. [c] Centrally evaluated per VENTANA SP142 IHC assay.
[d] Efficacy endpoints assessed by investigators per RECIST 1.1. NCT02425891.

PD-L1 is measured by SP142 assay
PD-L1 positivity in **immune cells** = best marker
Positive if >1%

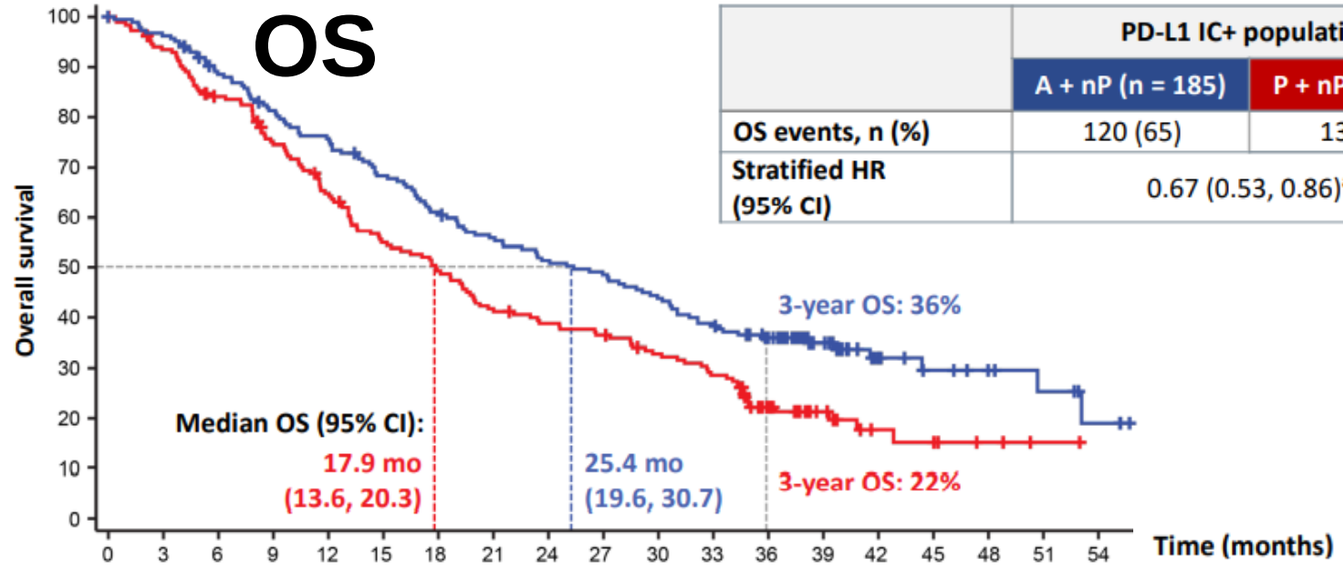
Schmid et al. NEJM 2018

Atezolizumab + chemo first line in triple negative breast cancer: IMpassion130 trial



Population	PFS HR (95% CI) *P* Value	Interaction Test (treatment × PD-L1 IC) *P* Value
PD-L1 IC+	0.62 (0.49, 0.78) < 0.0001	0.0055
PD-L1 IC–	0.94 (0.78, 1.13) 0.5152	
ITT	0.80 (0.69-0.92) 0.0025	

Atezolizumab significantly improves PFS, but main effect on PFS and OS is seen in PD-L1+ tumors

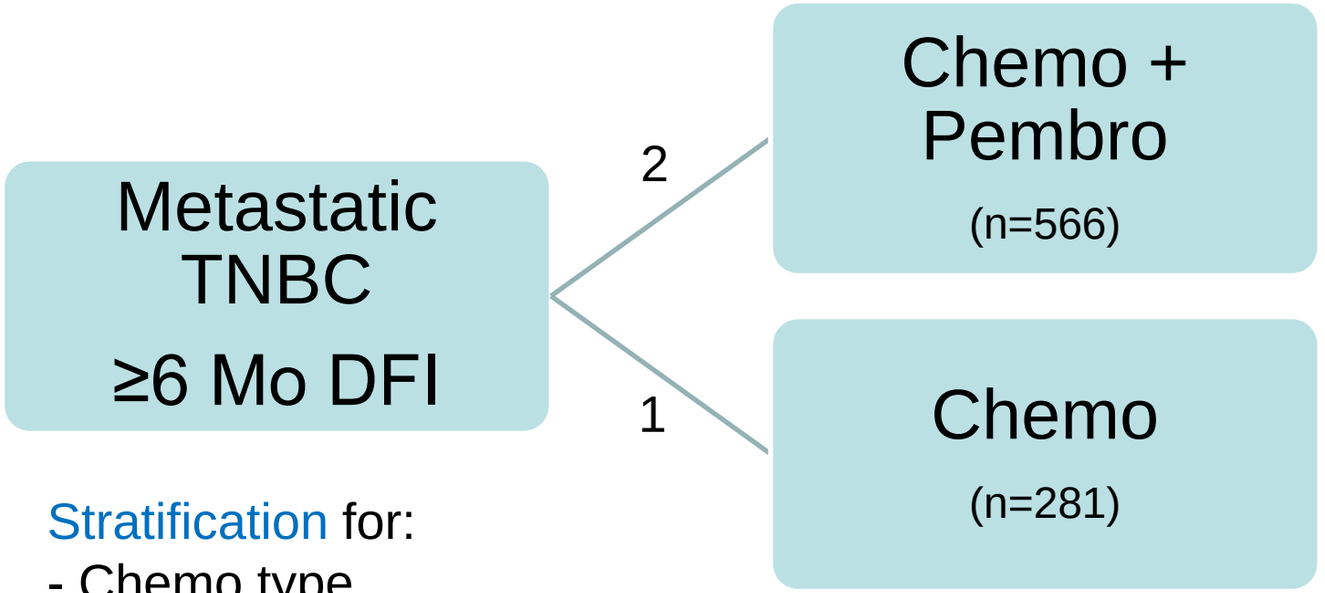


	PD-L1 IC+ population	
	A + nP (n = 185)	P + nP (n = 184)
OS events, n (%)	120 (65)	139 (76)
Stratified HR (95% CI)	0.67 (0.53, 0.86)[a]	

[a] p-value not formally tested per hierarchical study design

Emens et al, ESMO 2020

Pembrolizumab first line TNBC: Keynote-355



Chemo:
- Nab-paclitaxel
- Paclitaxel
- Gem/carbo

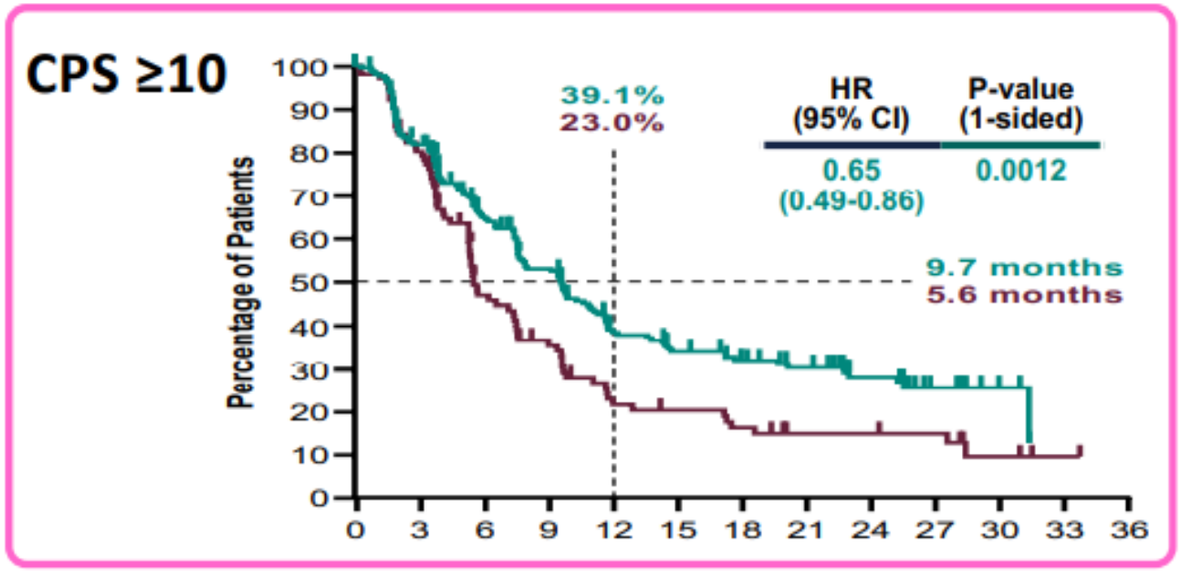
Primary endpoint:
PFS and OS by PD-L1 (CPS≥10, CPS≥1, and ITT)
(hierarchical testing: CPS10> CPS1 > ITT)

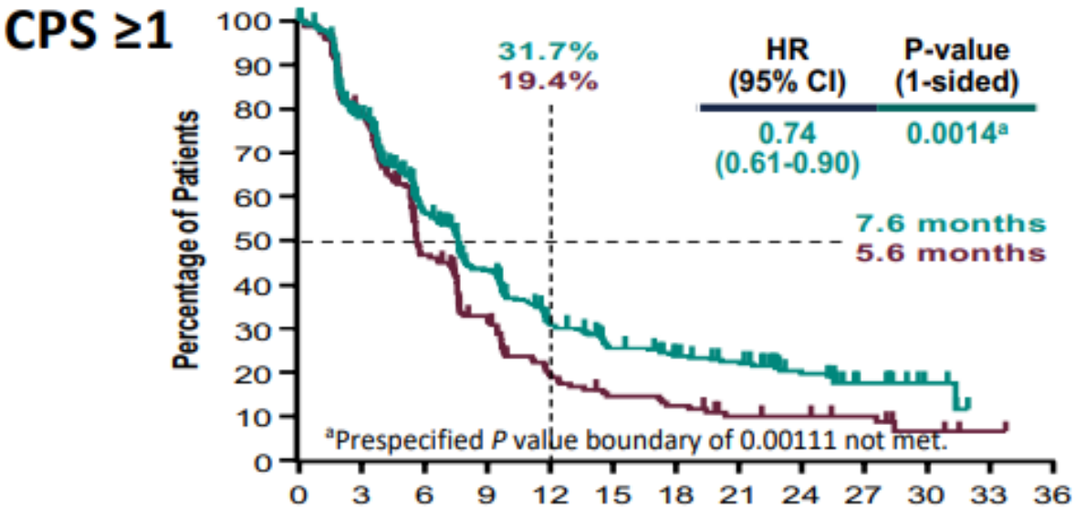
Stratification for:
- Chemo type
- PD-L1 status (CPS)
- Prior (neo)adj treatment with same-class chemo

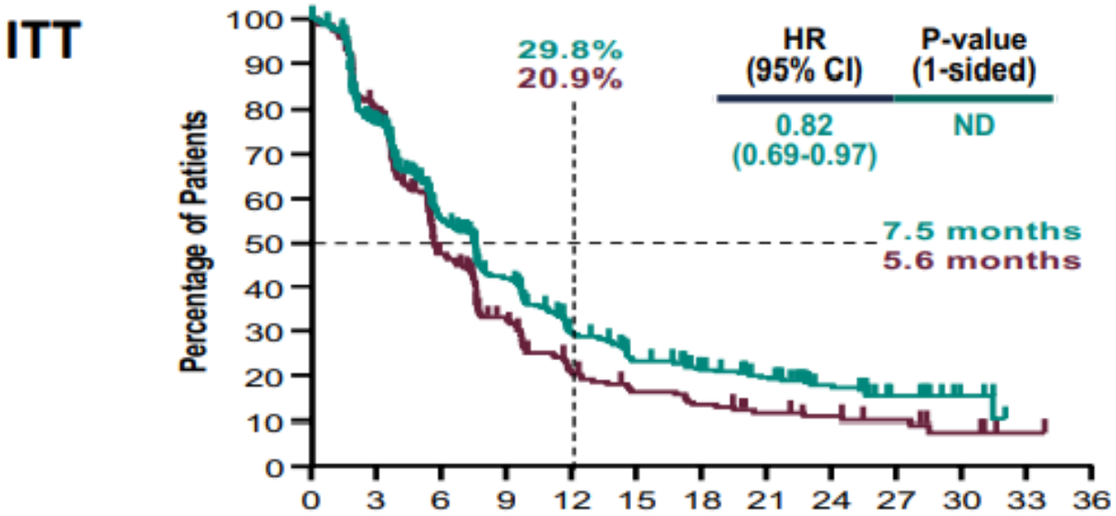
Study population:
- CPS≥10 38% ; CPS≥1 75% ; CPS <1% 25%
- Taxane 45% ; Gem/carbo 55%
- Prior treatment with same class chemo 22%
- De novo MBC 30% ; DFI 6-12Mo 21% ; DFI >12Mo 49%

Cortes et al. ASCO 2020

Pembrolizumab first line TNBC: Keynote-355





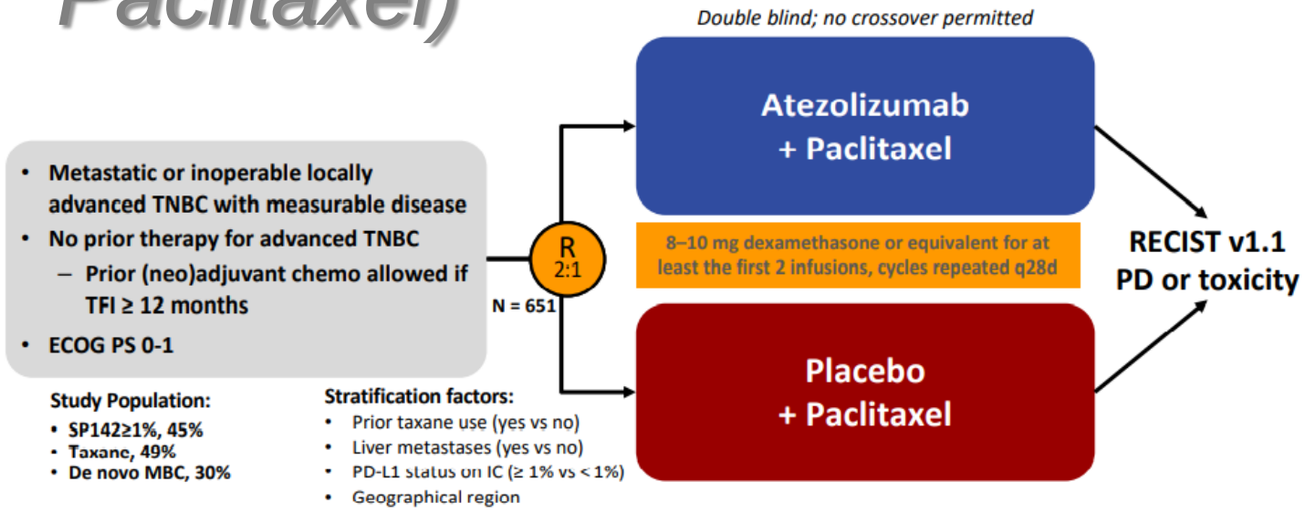


Subgroup analysis revealed no subgroups with different benefit

Pembro added to chemo improves PFS in CPS ≥10 TNBC

Cortes et al. ASCO 2020

Atezolizumab + chemo first line in triple negative breast cancer: IMpassion131 trial *(Paclitaxel instead of Nab-Paclitaxel)*

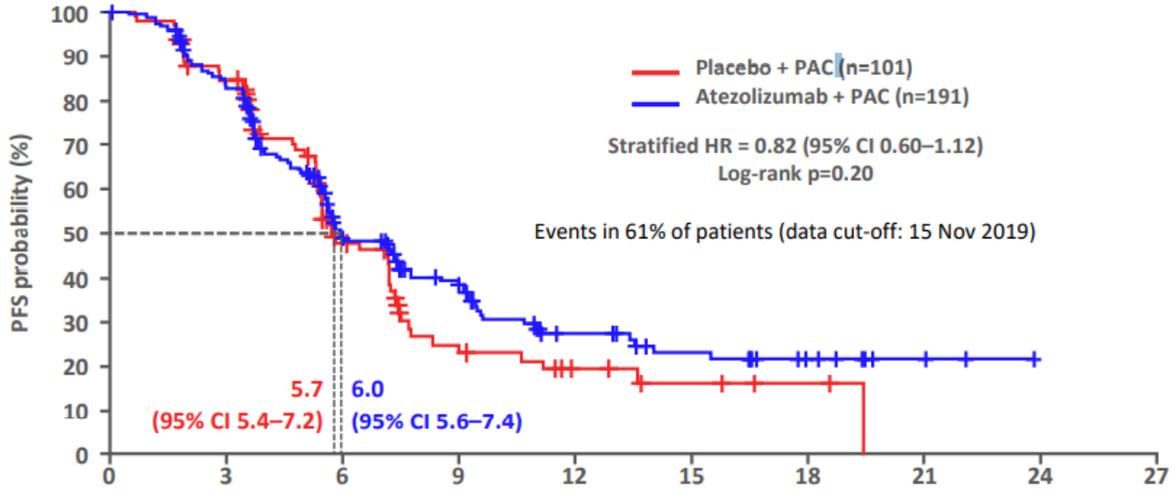


NO benefit of Atezolizumab when added to paclitaxel

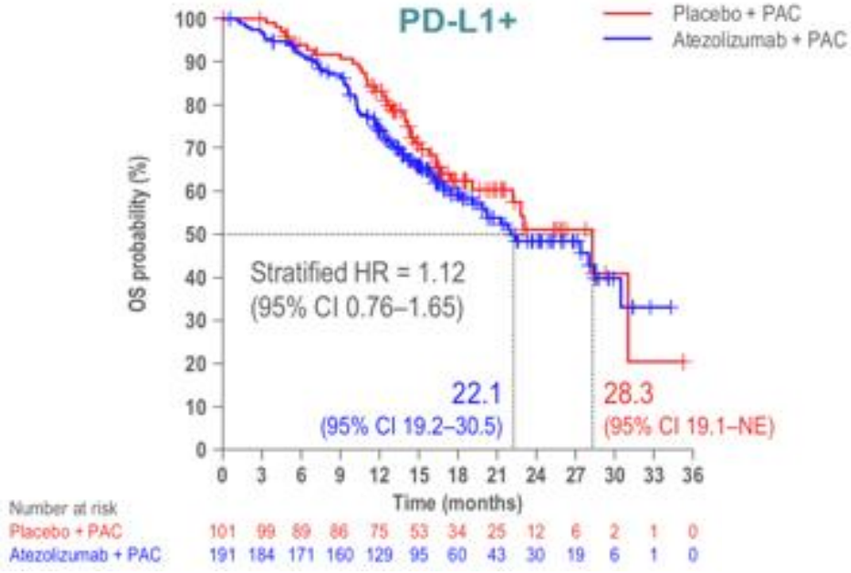
Unexpected long OS in control arm! (28,3 Mo)

- **Co-primary endpoints were PFS (investigator assessed) in the PD-L1+ and ITT populations**

PFS in PD-L1+



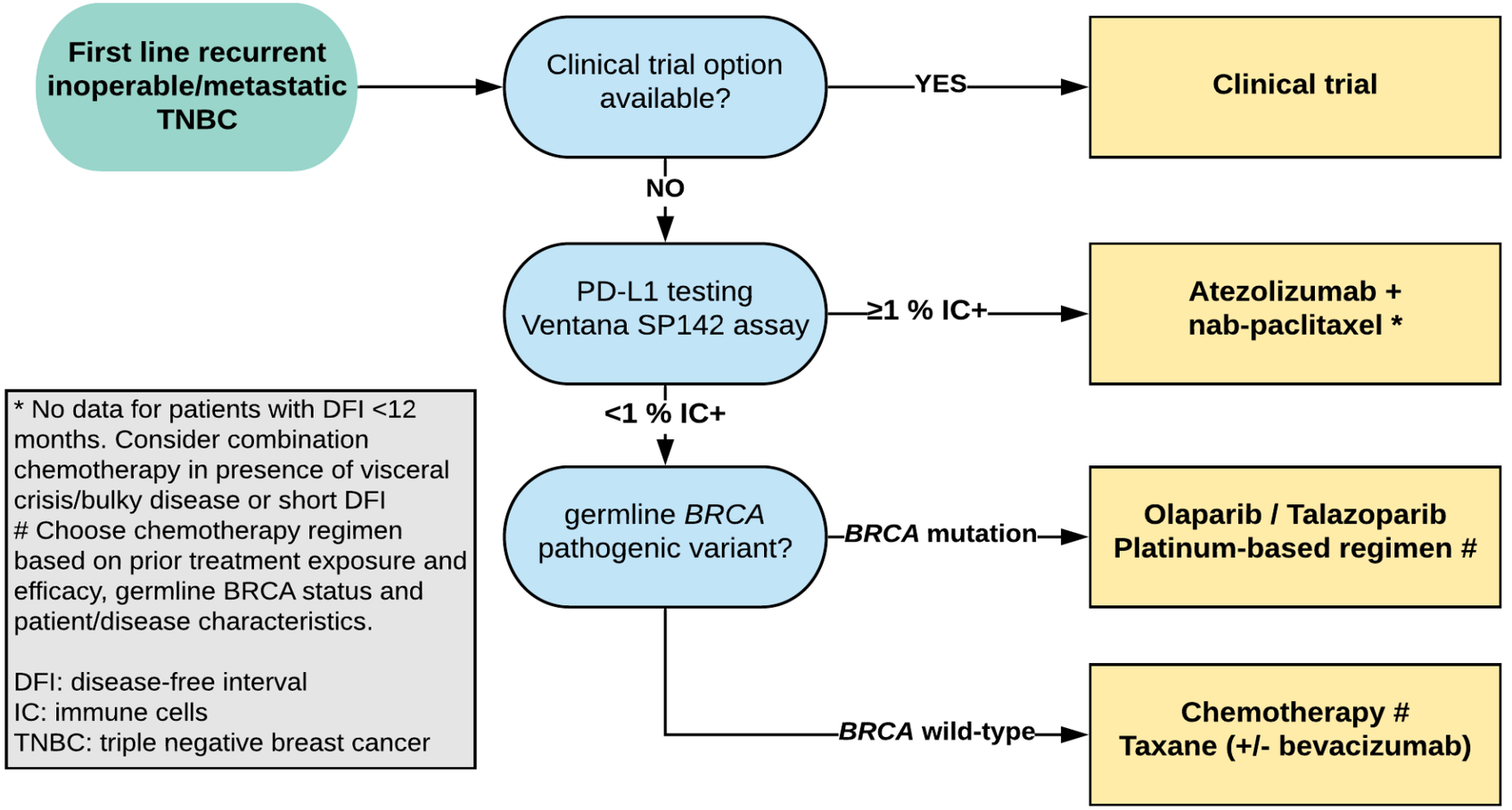
OS in PD-L1+



Miles et al, ESMO 2020

CLINICAL MANAGEMENT OF FIRST-LINE ADVANCED TNBC

BSMO breast cancer task force



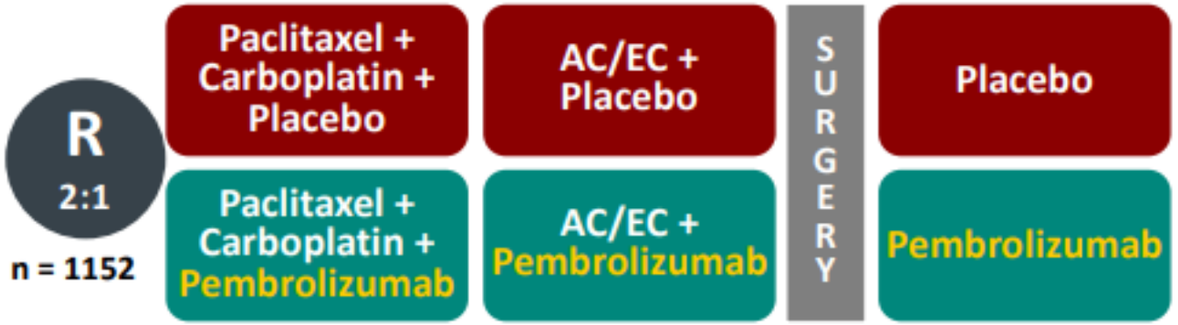
Mattia Rediti, Kevin Punie, Evandro de Azambuja, Eline Naert, Donatienne Taylor, Francois P Duhoux, Hannelore Denys, Ahmad Awada, Hans Wildiers, Michail Ignatiadis.

BJMO 2020, in press

Neoadjuvant immunotherapy in early TNBC

Phase III trial in stage II/III TNBC

Keynote 522



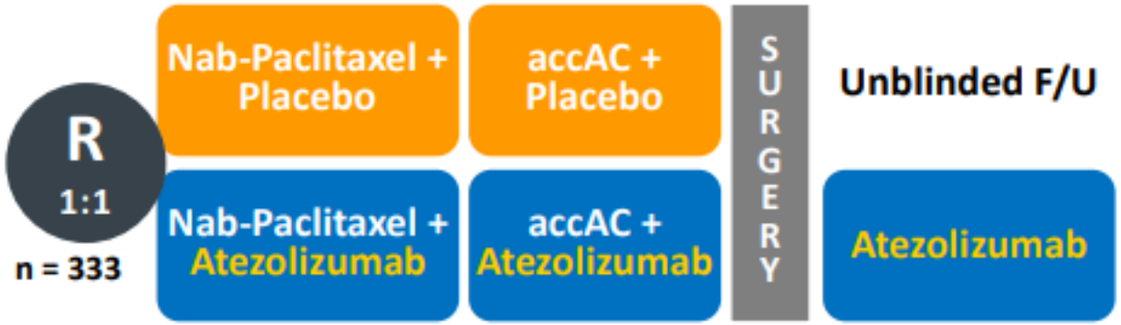
- PDL1+ (22C3 CPS1) 82%
- N+ 52%, T3/4 26%
- Carbo QW 41%

Co-primary endpoints:

- pCR (ypT0/Tis ypN0)
- Event-free Survival

Pembrolizumab: 200 mg given IV q3w
Paclitaxel: 80 mg/m² given IV qw for 12 weeks;Carboplatin: AUC5 q3w x 4 or AUC1.5 qw x 12
Doxorubicin: 60 mg/m² given IV q2w/Cyclophosphamide: 600 mg/m² given IV q2w

Impassion 031



- PDL1+ (SP142≥1%) 53%
- N+ 38% (34% Ate; 43% Pla)
- T3/4 28%

Primary endpoint:

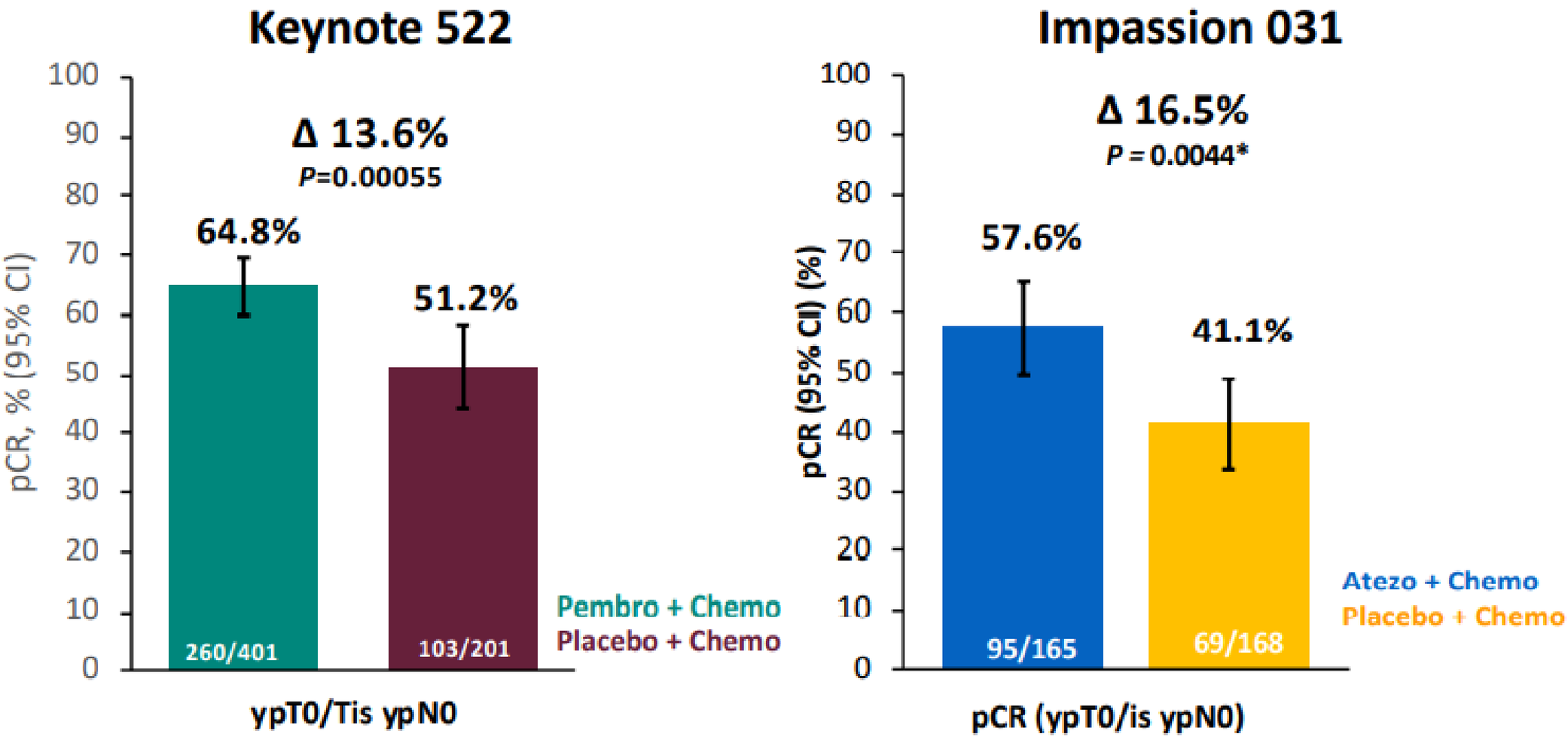
- pCR (ypT0/Tis ypN0) in ITT & PD-L1+

Atezolizumab: 840 mg given IV q2w (neoadjuvant); 1200 mg IV q3w x 11 (adjuvant)
Nab-paclitaxel: 125 mg/m² given IV qw for 12 weeks
Doxorubicin: 60 mg/m² given IV q2w/Cyclophosphamide: 600 mg/m² given IV q2w

Schmid et al NEJM 2020 ; Harbeck et al, ESMO 2020

Neoadjuvant immunotherapy in early TNBC

Pathological complete response

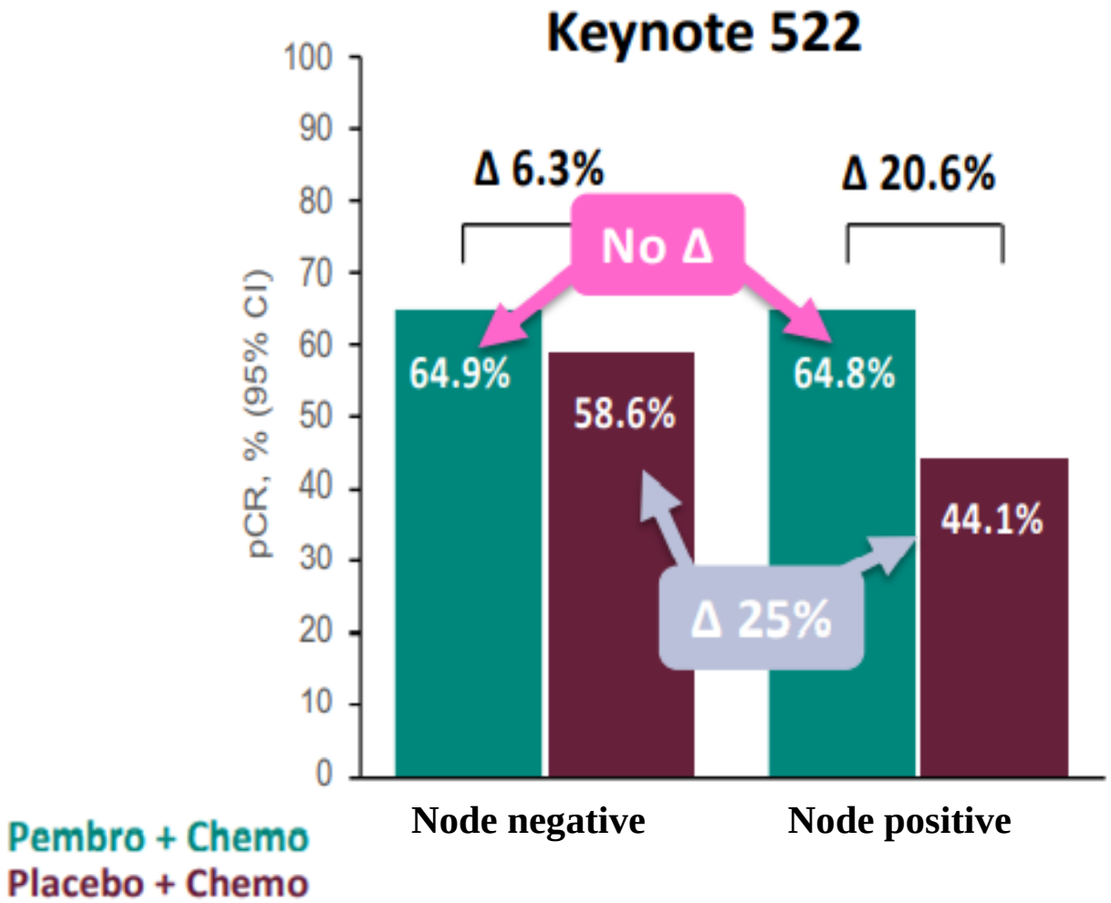


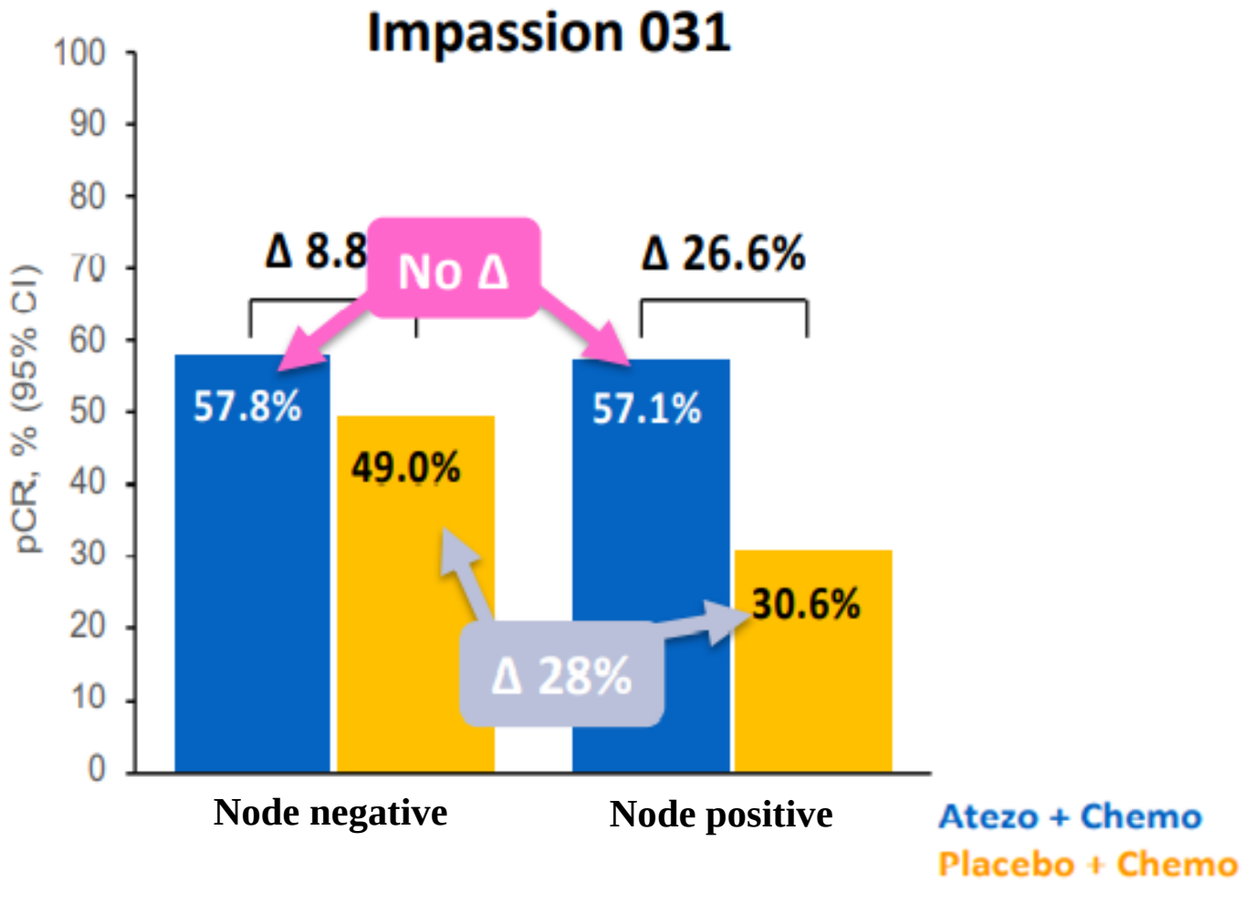
Immune therapy improves pCR +/- 15%

Schmid et al NEJM 2020 ; Harbeck et al, ESMO 2020

Neoadjuvant immunotherapy in early TNBC

Pathological complete response in relation to nodal status



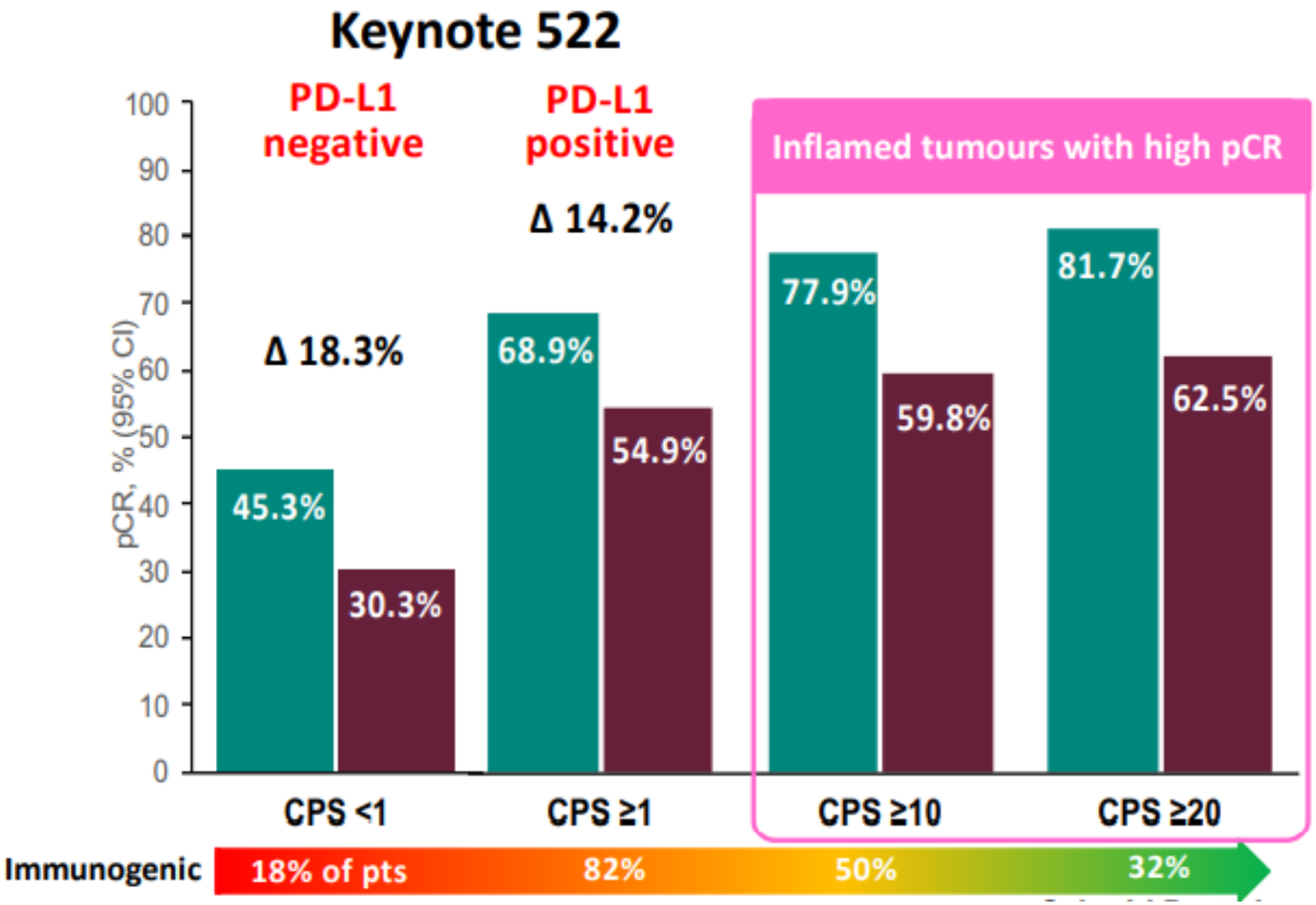


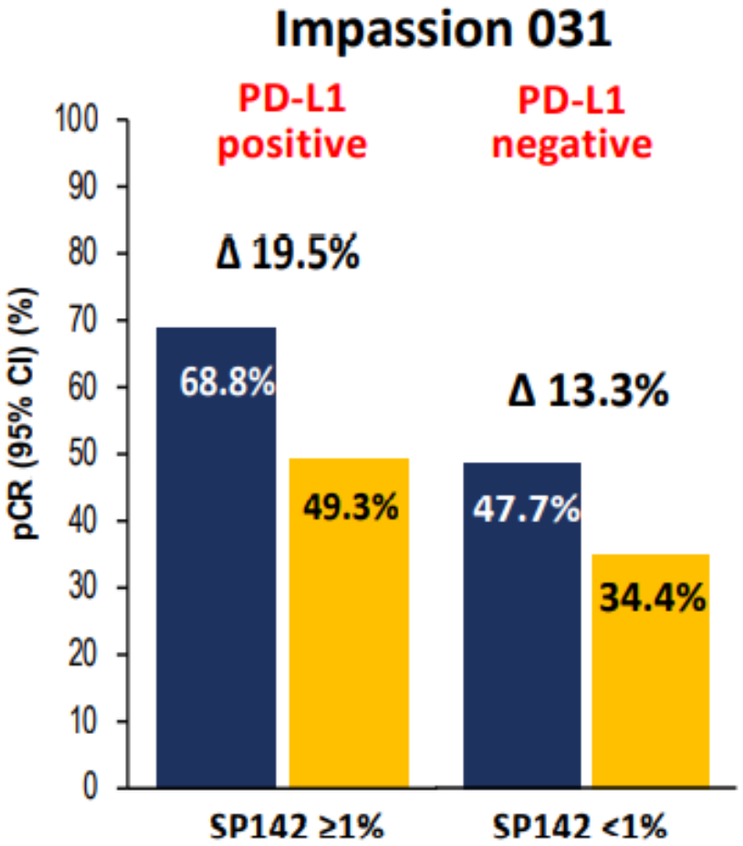
Immune therapy most effective in Node Positive tumors !

Schmid et al NEJM 2020 ; Harbeck et al, ESMO 2020

Neoadjuvant immunotherapy in early TNBC

pCR rates by PD-L1 expression



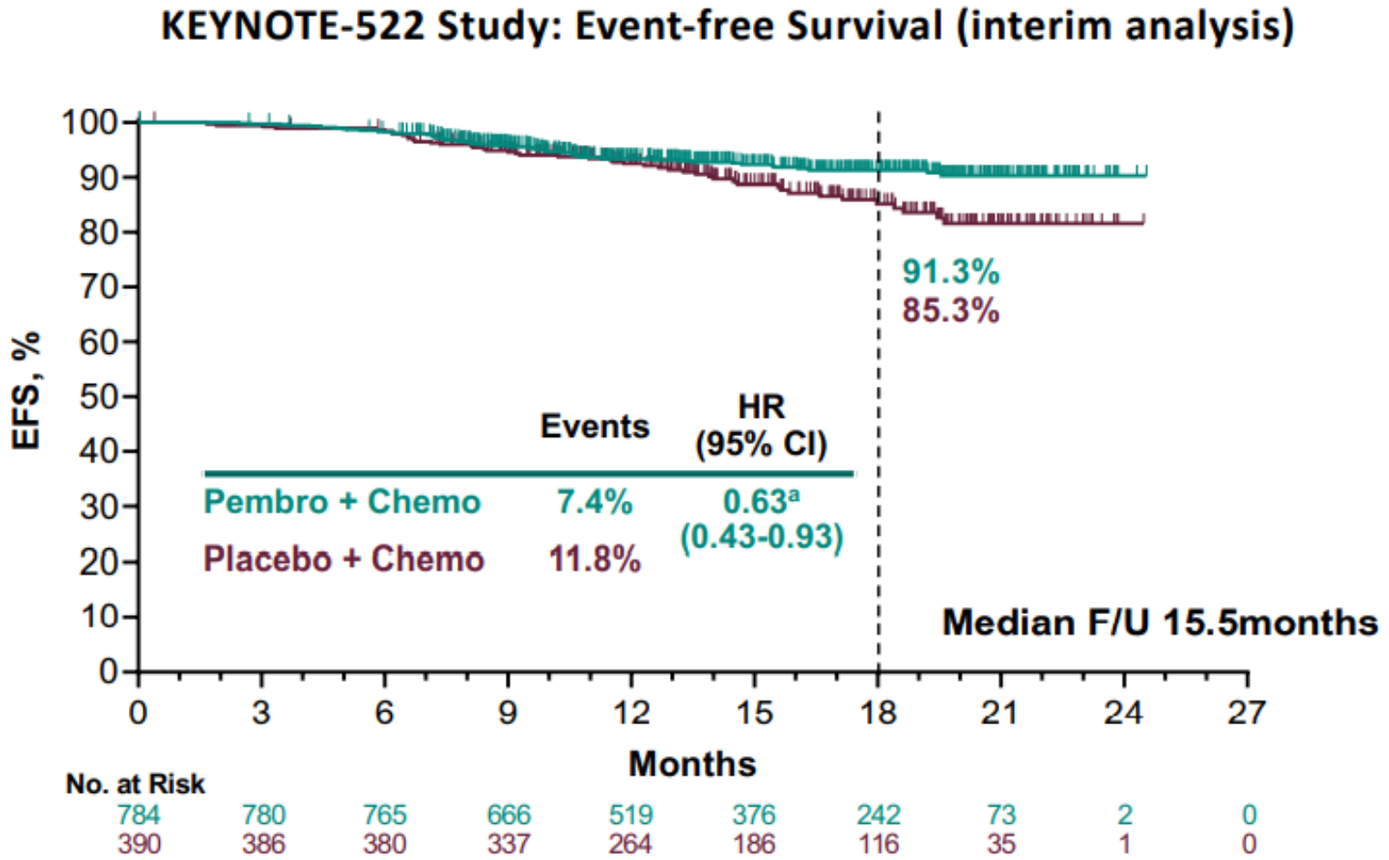


Both PD-L1+ and PD-L1- benefit from immune therapy!

Schmid et al NEJM 2020 ; Harbeck et al, ESMO 2020

Neoadjuvant immunotherapy in early TNBC

Event-free survival

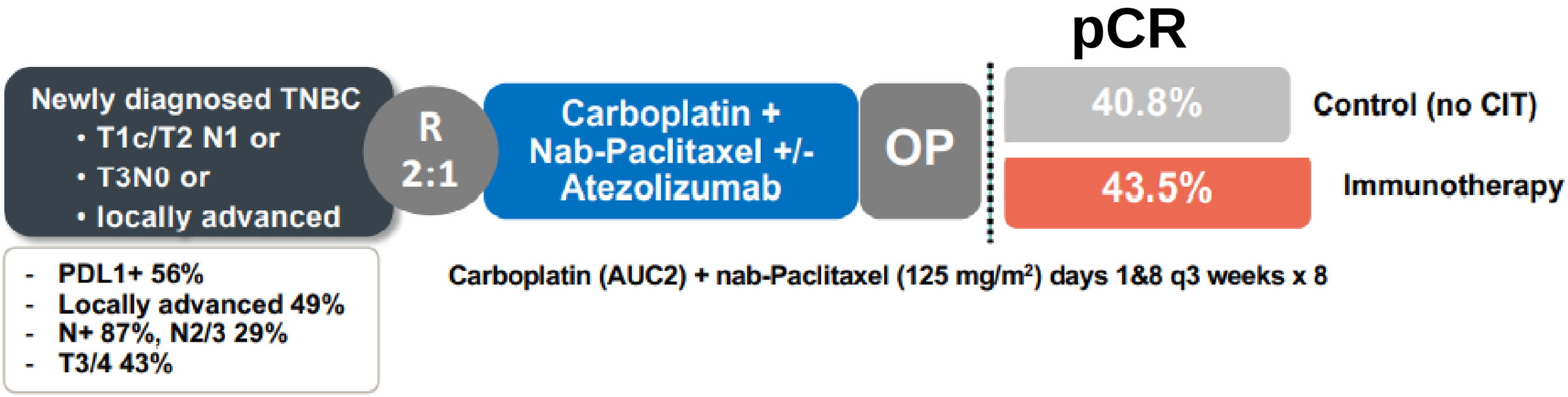


Immune therapy may improve longer term outcome but FUP is too short

Schmid et al NEJM 2020 ; Harbeck et al, ESMO 2020

Neoadjuvant immunotherapy in early TNBC

NeoTRIP study: anthracycline postoperative



Primary endpoint: Event-free survival at 5 years

Key secondary endpoints: pCR rates (ypT0/TisypN0), safety, predictive markers

Anthracyclines may be an important component also when immune therapy is used

Gianni et al, SABCS 2020

Conclusions: Immune therapy in TNBC

Metastatic TNBC

- Single agent activity in early lines in small subgroup, but with long responses
- When combined with chemo, Atezolizumab and Pembrolizumab both improve PFS, mainly in ‘inflamed’ TNBC (PD-L1+)
- Chemopartner may matter (e.g. nab-paclitaxel > paclitaxel)
- No major tolerability problems

Early TNBC

- When combined with chemo, Atezolizumab and Pembrolizumab improve pCR +/- 15% independently of PD-L1
- Most benefit in N+
- Encouraging trend for EFS benefit at 15 months FUP with Pembro

Open questions:

- Long term outcome?
- Best biomarker?
- Best chemopartner?
- Other checkpoints?