Artist and Researcher 2020

The heat wave of an anti-tumor response- Karen Karlsson

Updates in Immunotherapy in Breast Cancer

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California Cancer Consortium Conference, Pasadena

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Outline

I. Background on immunotherapy
II. Clinical trials in breast cancer → recent approvals / standard of care
III. Areas of ongoing research
IV. Summary / Questions

Objectives

- Review basics of immune checkpoint inhibition and relevant clinical trials leading to approval for use in breast cancer
- Discuss ongoing research in the field of checkpoint inhibition in breast cancer

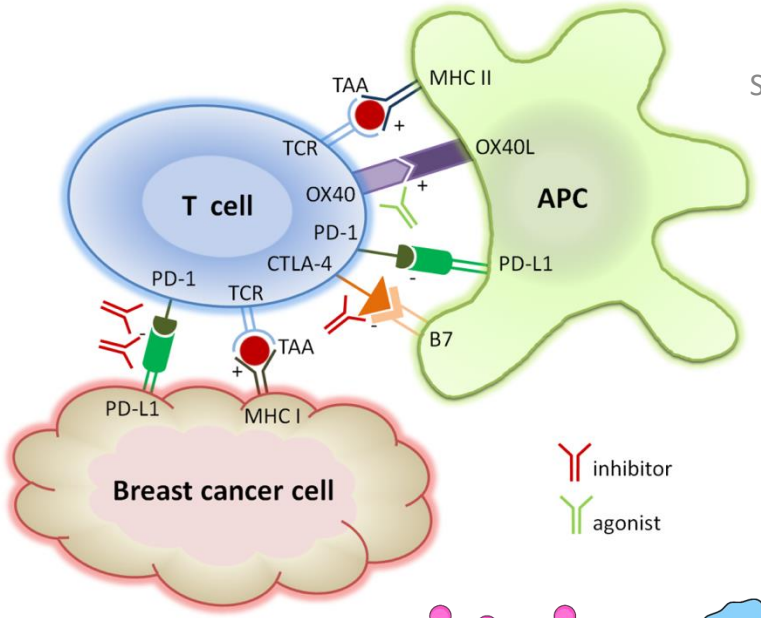
I. Background: Immune checkpoints in cancer

- Types of immunotherapy
  - Cancer Vaccines
  - Adoptive Cellular Therapy (ACT)
  - Immune Checkpoint Blockade

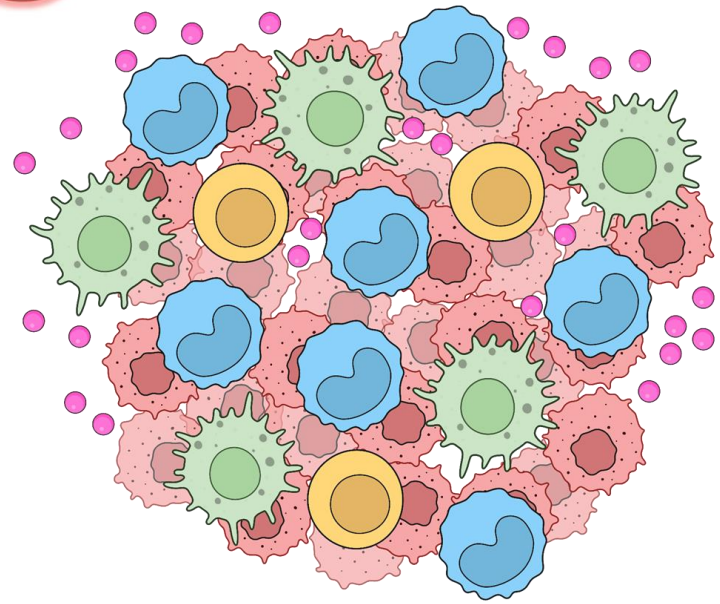
- Checkpoints control T cell activation through various mechanisms

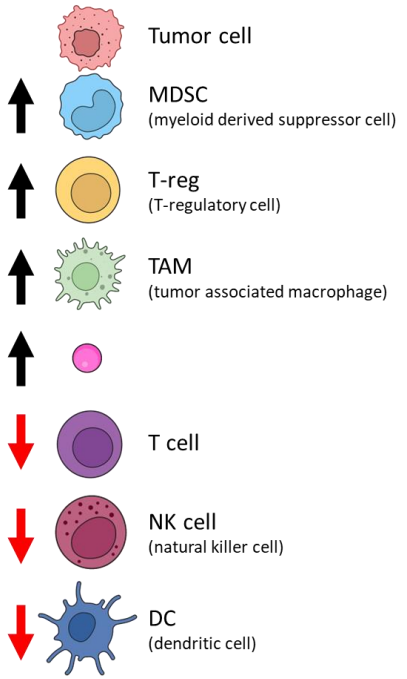
- PD1/PDL1 blockade active in many cancers

- Breast cancer historically considered to have a “cold” immunophenotype in part due to immunosuppression

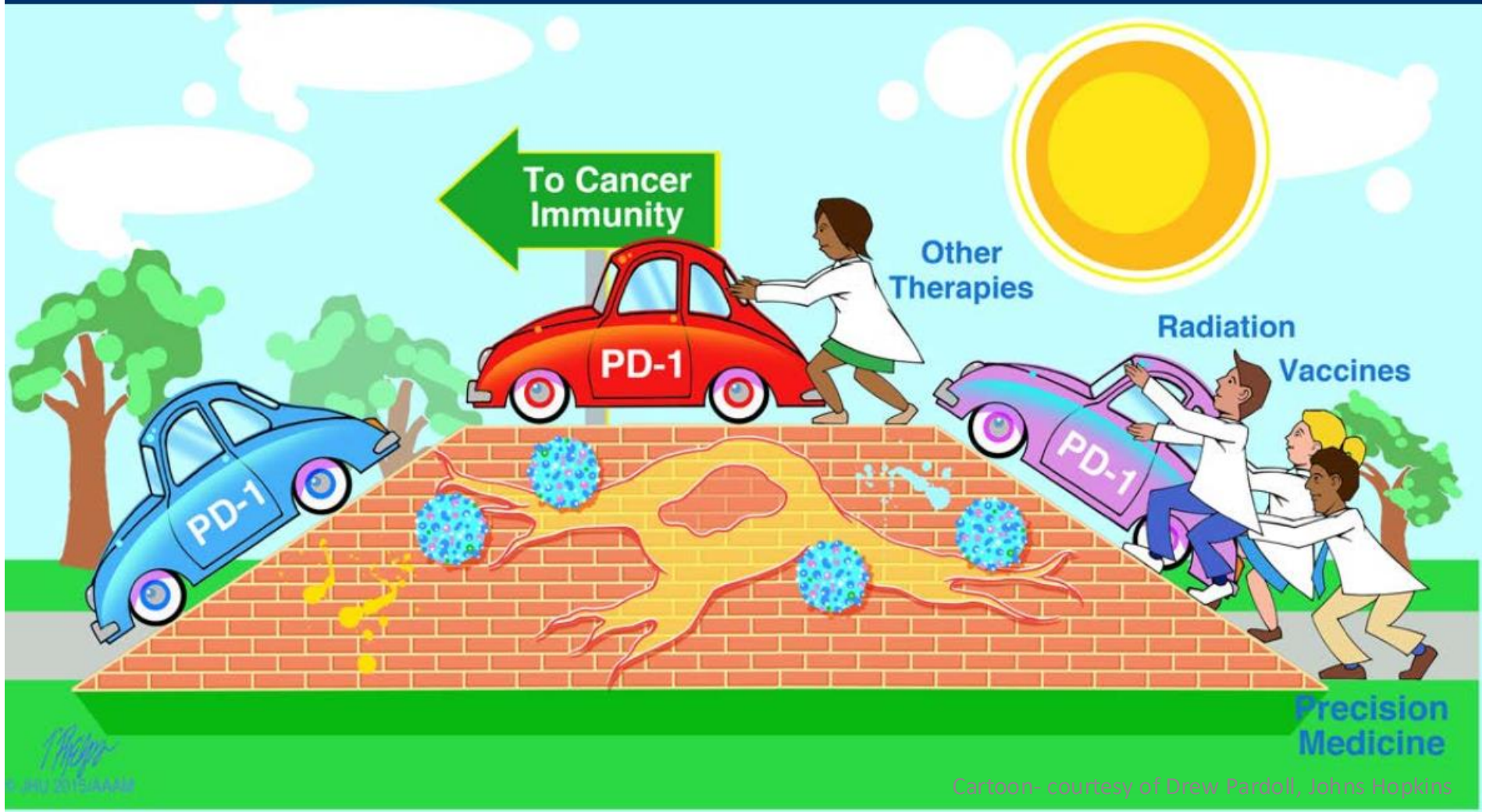


Santa-Maria et al. Expert Rev Anticancer Ther 2015





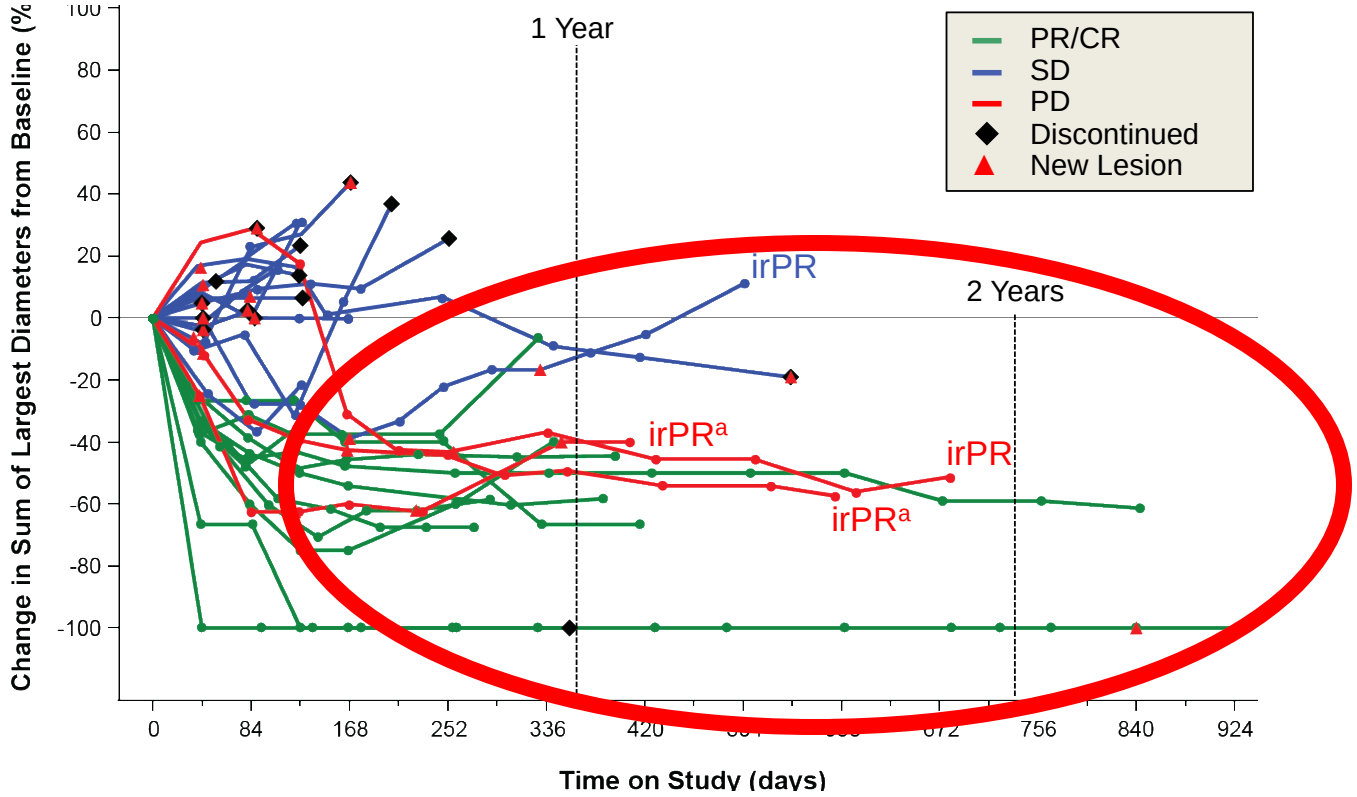
THE ROAD TO CANCER IMMUNITY: "IF A CAR IS SITTING AT THE TOP OF A HILL WITH THE FRONT POINTING DOWNHILL, IT MAY ONLY NEED THE PARKING BRAKE RELEASED TO START MOVING. ANOTHER CAR SITTING ON A FLAT ROAD MAY NEED THE BRAKE RELEASED AND A PUSH TO GET GOING. A CAR SITTING AT THE BOTTOM OF A HILL AND FACING UPHILL WILL NEED THE BRAKE RELEASED AND A LOT OF GAS TO GET MOVING," SAYS DREW PARDOLL, DIRECTOR, THE BLOOMBERG~KIMMEL INSTITUTE FOR CANCER IMMUNOTHERAPY



Cartoon- courtesy of Drew Pardoll, Johns Hopkins

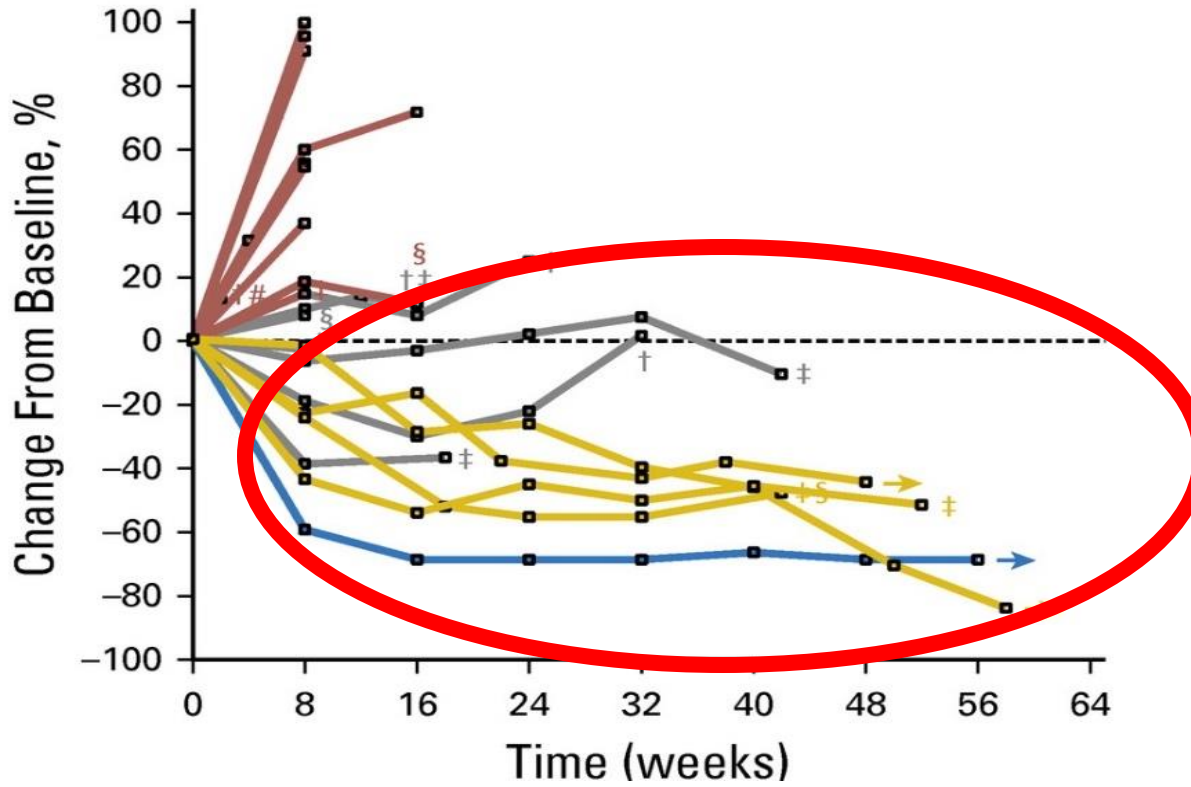
II. Clinical trials in METASTATIC breast cancer:
Checkpoint blockade confers durable responses…

Atezolizumab



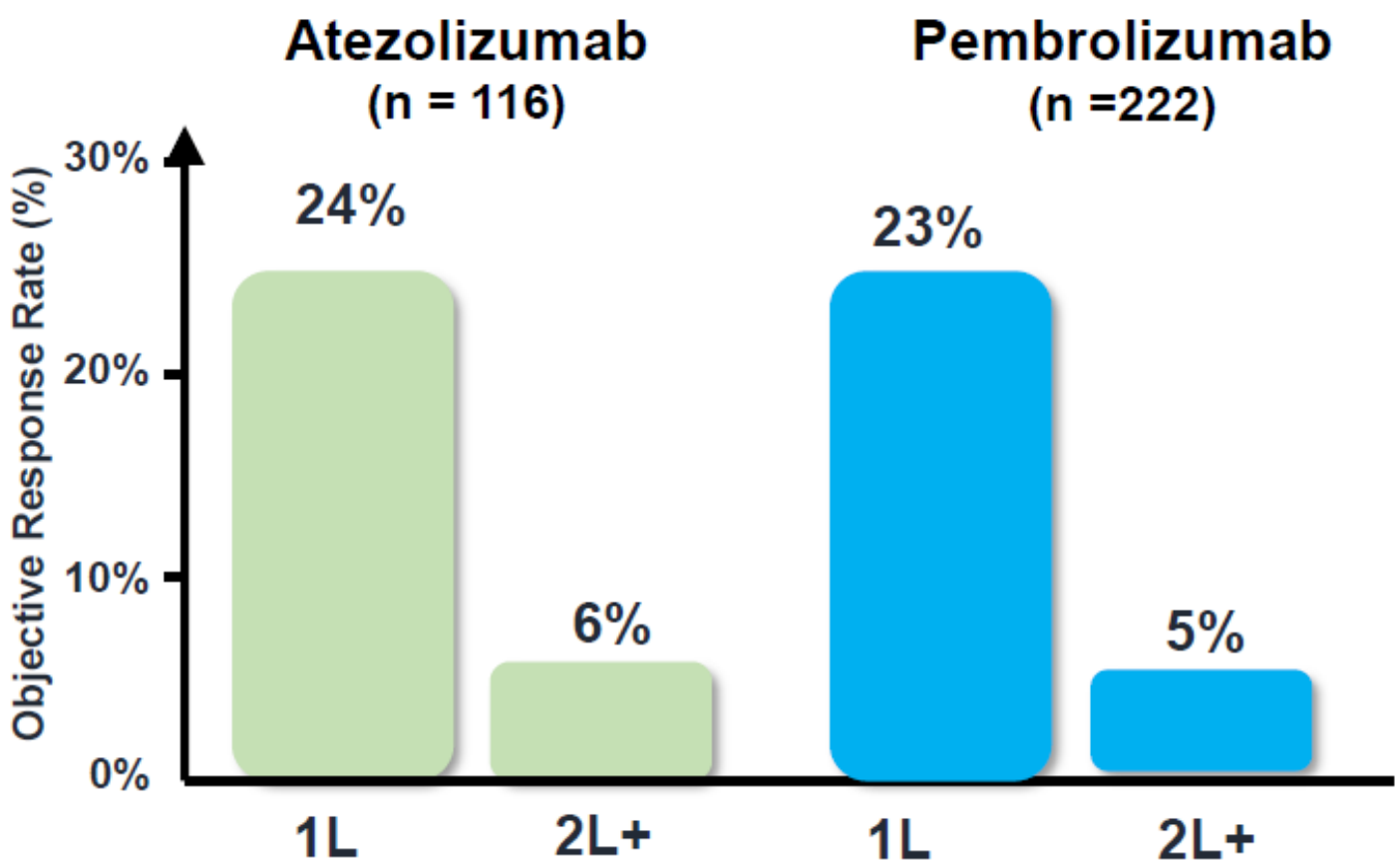
Schmid et al. AACR 2017;
Emens JAMA Oncol 2018

Pembrolizumab



Nanda et al. JCO 2016;34:2460-7

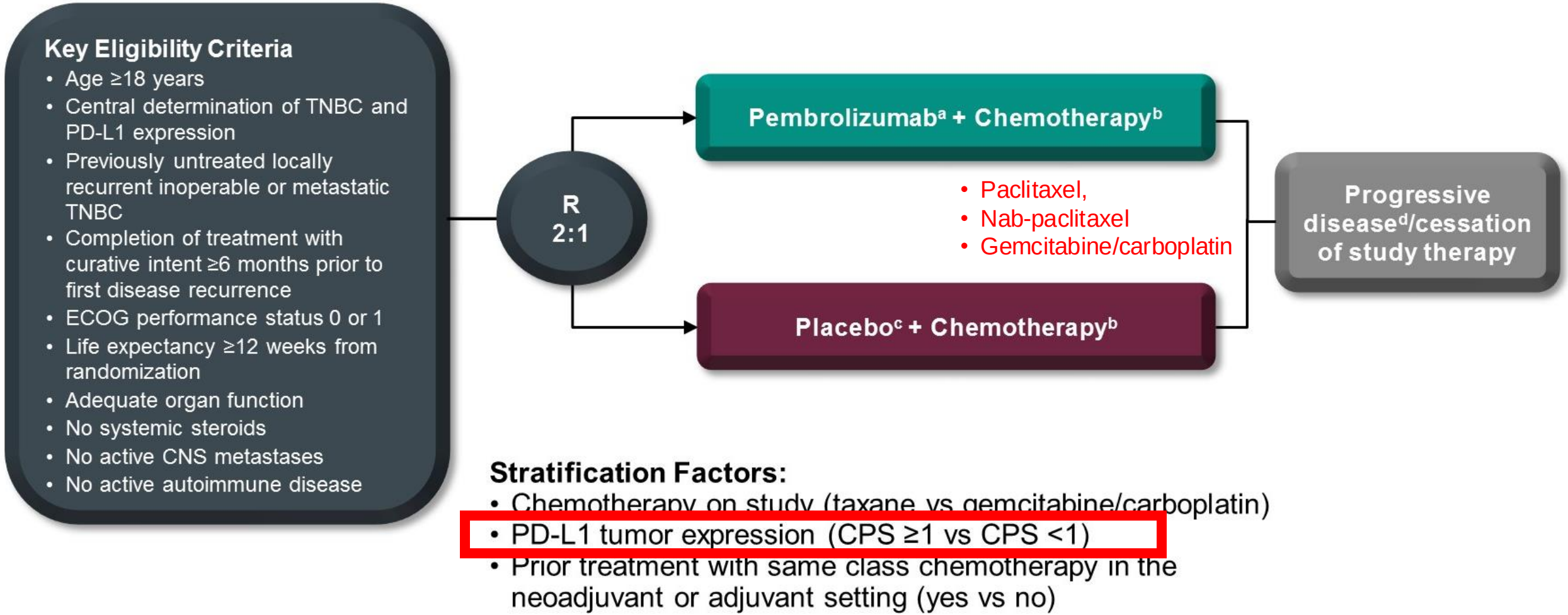
Lack of robust response to single agent therapy:



Metastatic Population	Agent	Evaluable (N)	ORR
TNBC	Avelumab	58	5%
HER2+	Avelumab	26	0%
HR+ HER2-	Pembrolizumab Avelumab	25 72	12% 3%

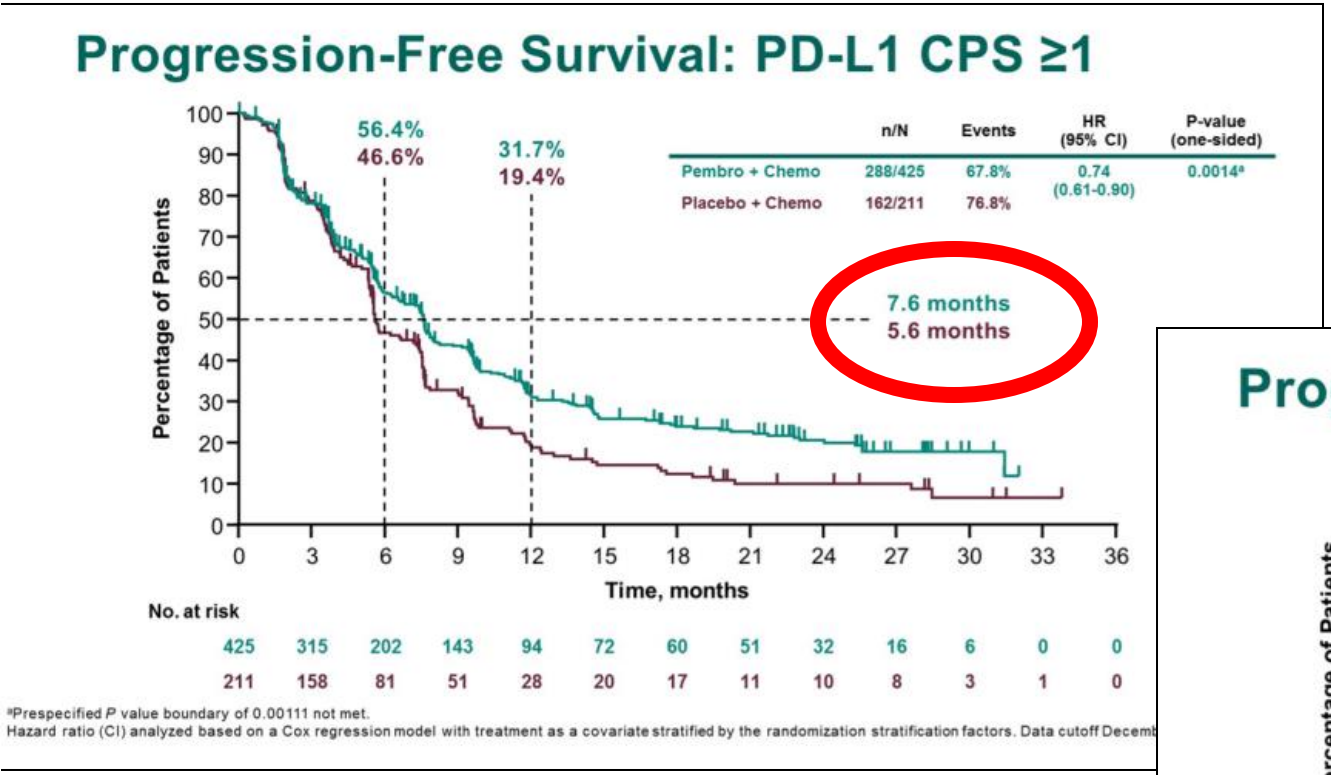
Emens JAMA Oncol 2018; Adams et al. SABCS 2017; Dirix Breast Cancer Res Treat 2018; Rugo Clin Cancer Res 2018.

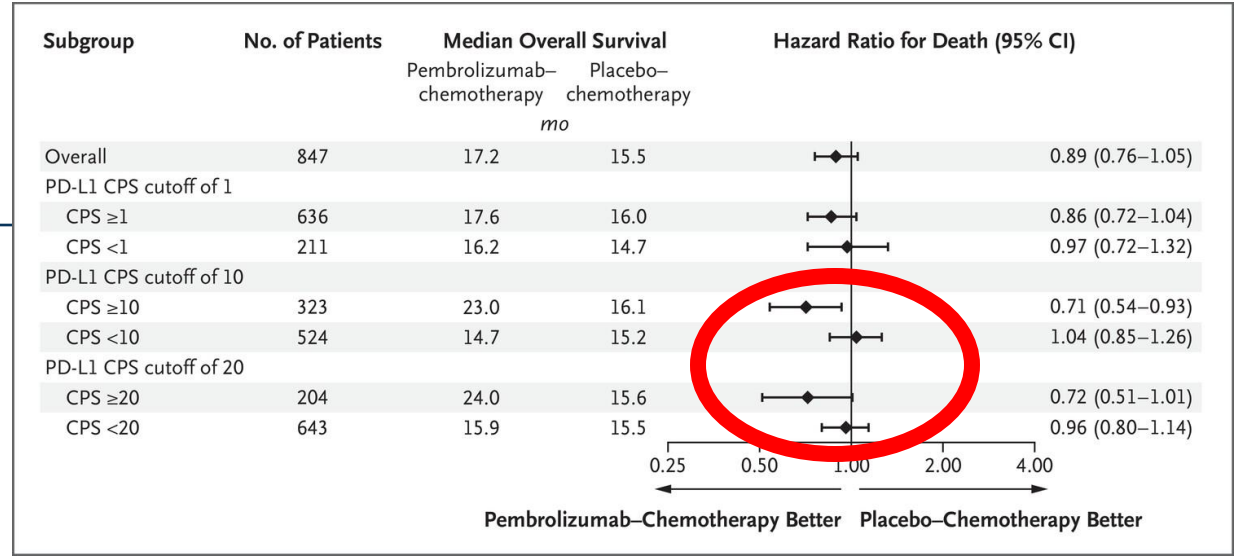
KEYNOTE-355 Study Design (NCT02819518)

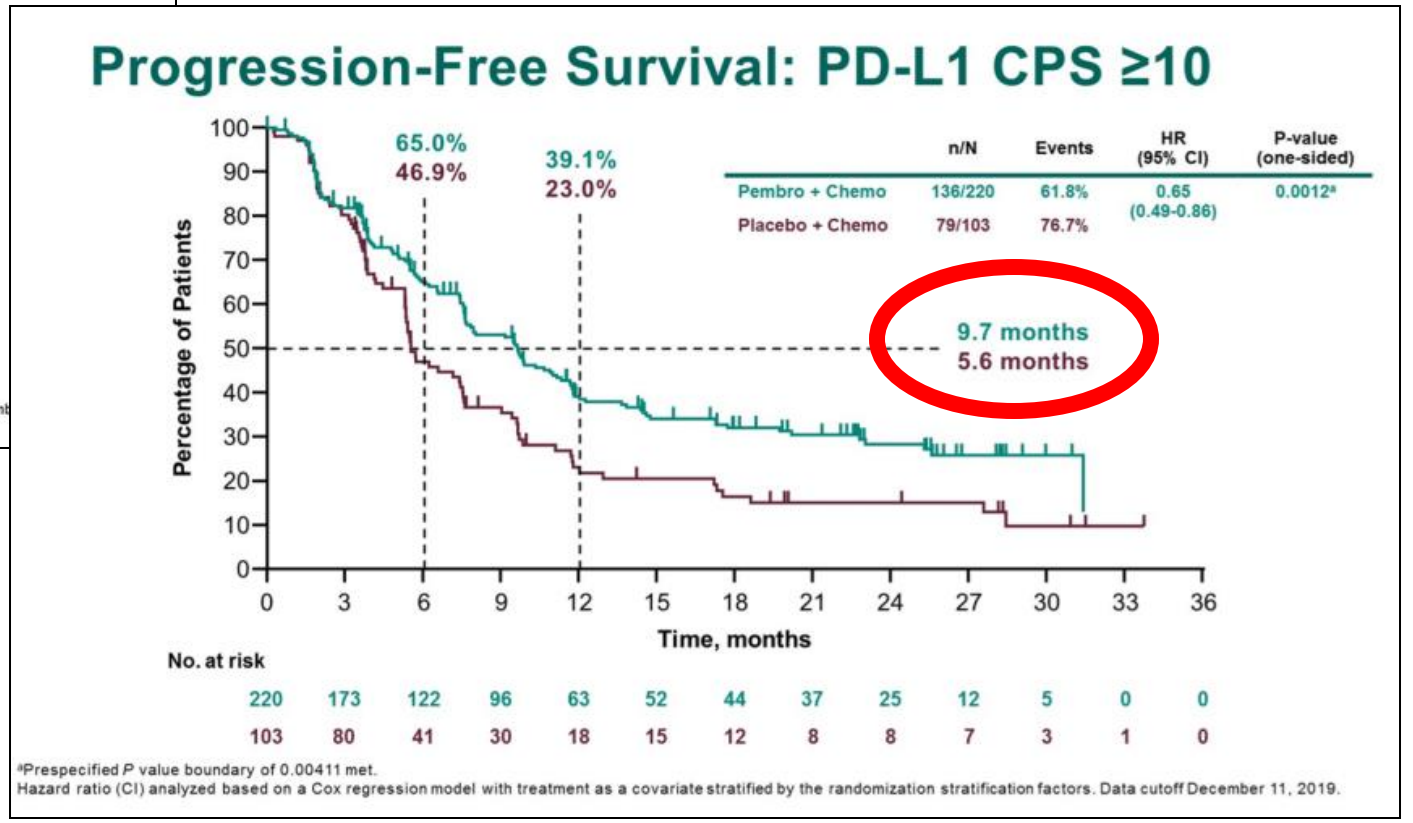


Cortes J et al. NEJM 2022

KEYNOTE-355







Cortes J et al. ASCO 2020. Abstract 1000.
Cortes et al. Lancet. 2020;396(10265):1817-1828.
Cortes et al. NEJM 2022

FDA-Approval

On 11/13/20, the FDA granted accelerated approval to **pembrolizumab** in combination with chemotherapy for patients with unresectable or metastatic TNBC whose tumors express **PD-L1 (CPS ≥10)** as determined by an FDA-approved test.

What about the early-stage disease?

KEYNOTE-522

Eligibility

- Newly diagnosed TNBC (central confirmation)
- T1c N+ or T≥2 N0-2
- PD-L1+ or PD-L1-

Stratification

- T1/T2 vs T3/T4
- N0 vs N+
- Carboplatin Q1W vs Q3W

N = 1,174

R

Neoadjuvant chemo **+ pembrolizumab** → Surgery → Adjuvant **pembrolizumab** 9 cycles

Neoadjuvant chemo **+ placebo** → Surgery → Adjuvant **placebo** 9 cycles

Within 3-6 weeks

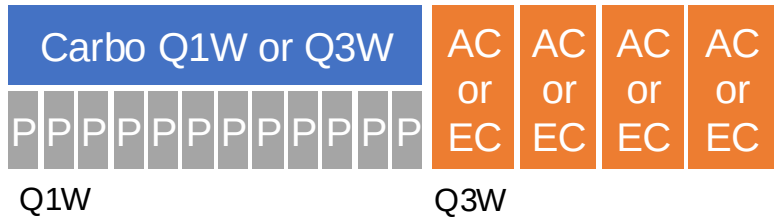
Primary endpoints

- pCR rate (ypT0/Tis ypN0)
- EFS

Secondary endpoints

- Alternative pCR rate (ypT0 ypN0)
- pCR rate in PD-L1+
- EFS in PD-L1+
- OS

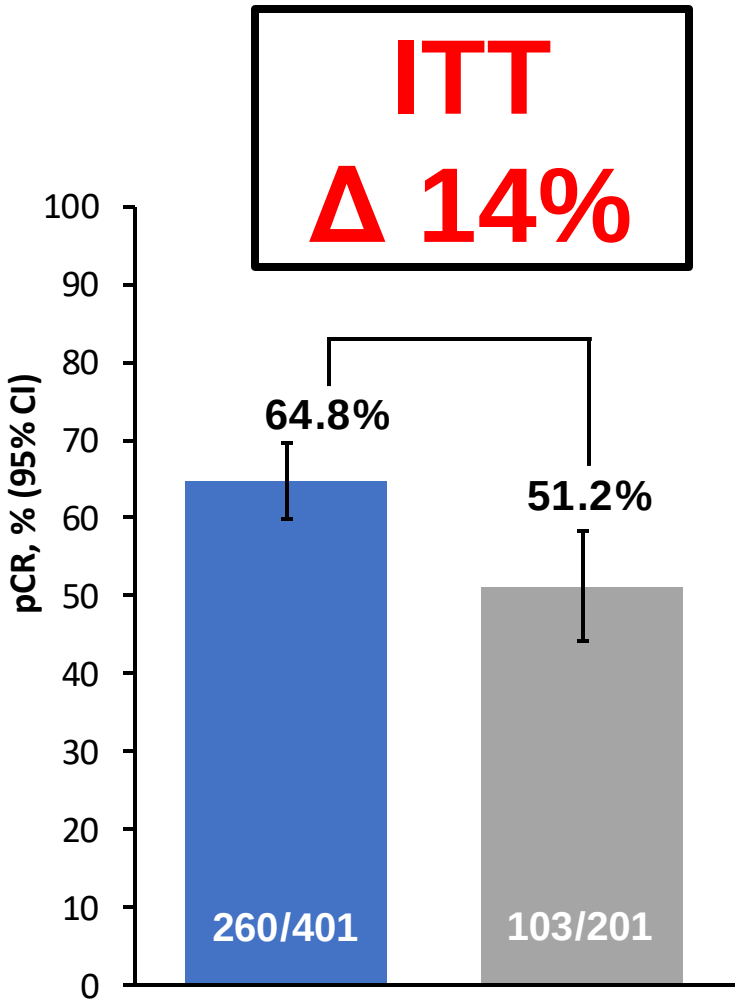
Study Treatment

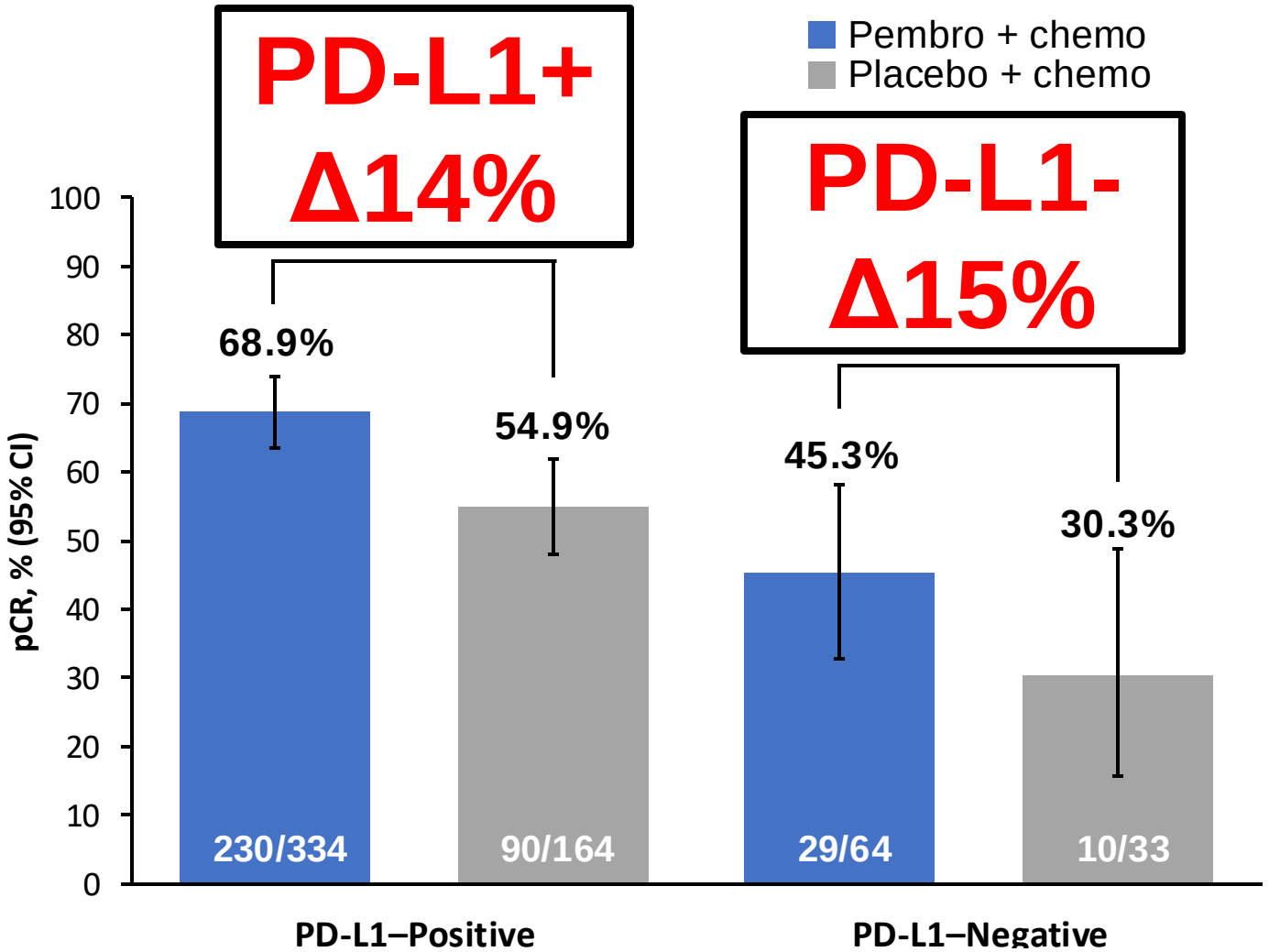


Paclitaxel 80 mg/m^2 IV weekly
Carboplatin weekly (AUC 1.5) or Q3W (AUC5)
Doxorubicin 60 mg/m^2 IV Q3W
(Epirubicin 90 mg/m^2 IV Q3W)
Cyclophosphamide 600 mg/m^2 IV Q3W
Pembrolizumab 200 mg IV Q3W

Schmid P et al. NEJM 2019.

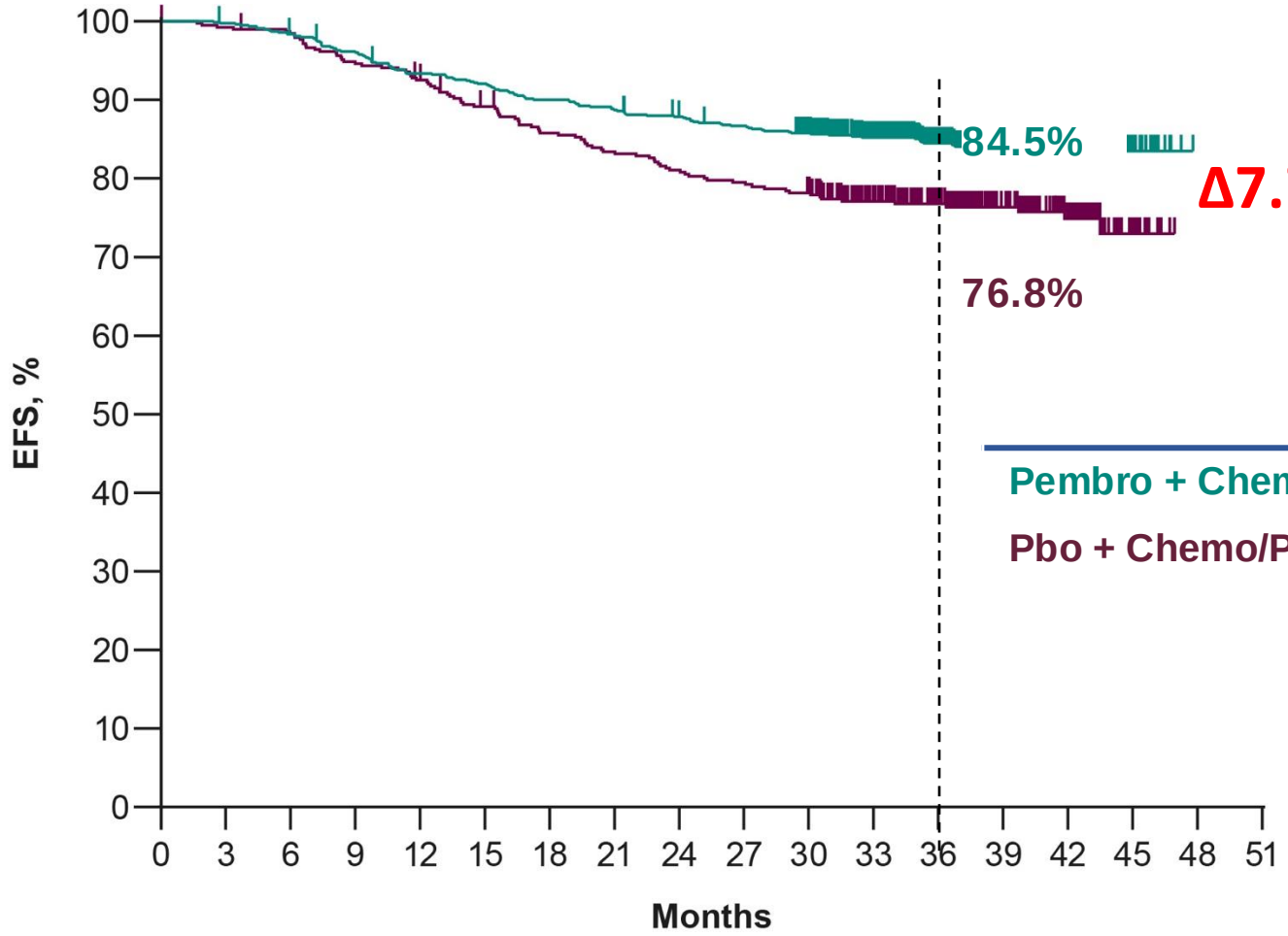
KEYNOTE-522: Higher pathologic complete response (pCR) at interim analysis 1





Schmid P et al. NEJM 2019.

KEYNOTE-522: EFS update at interim analysis at 63 months



81.3%

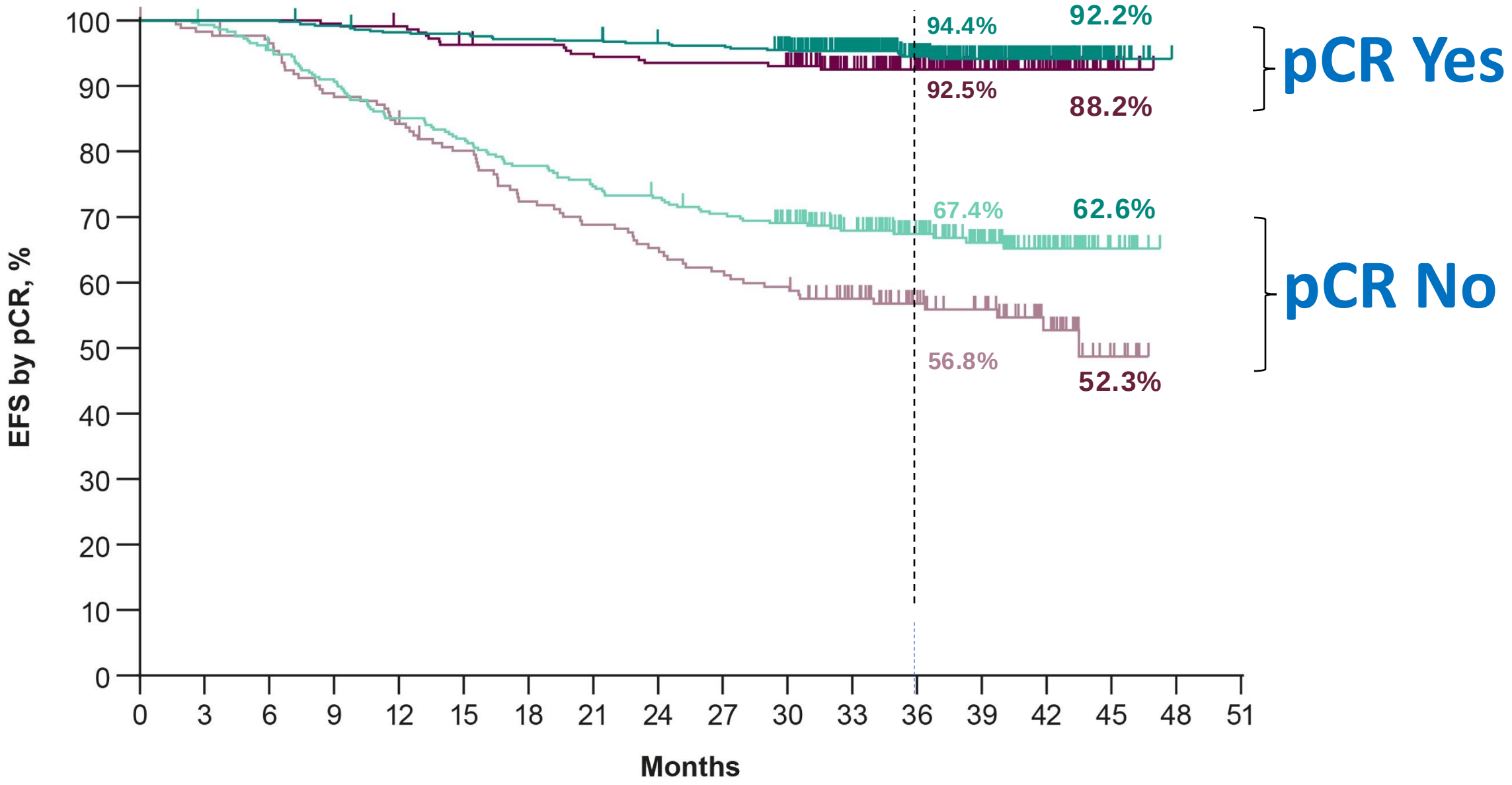
72.3%

Δ9%

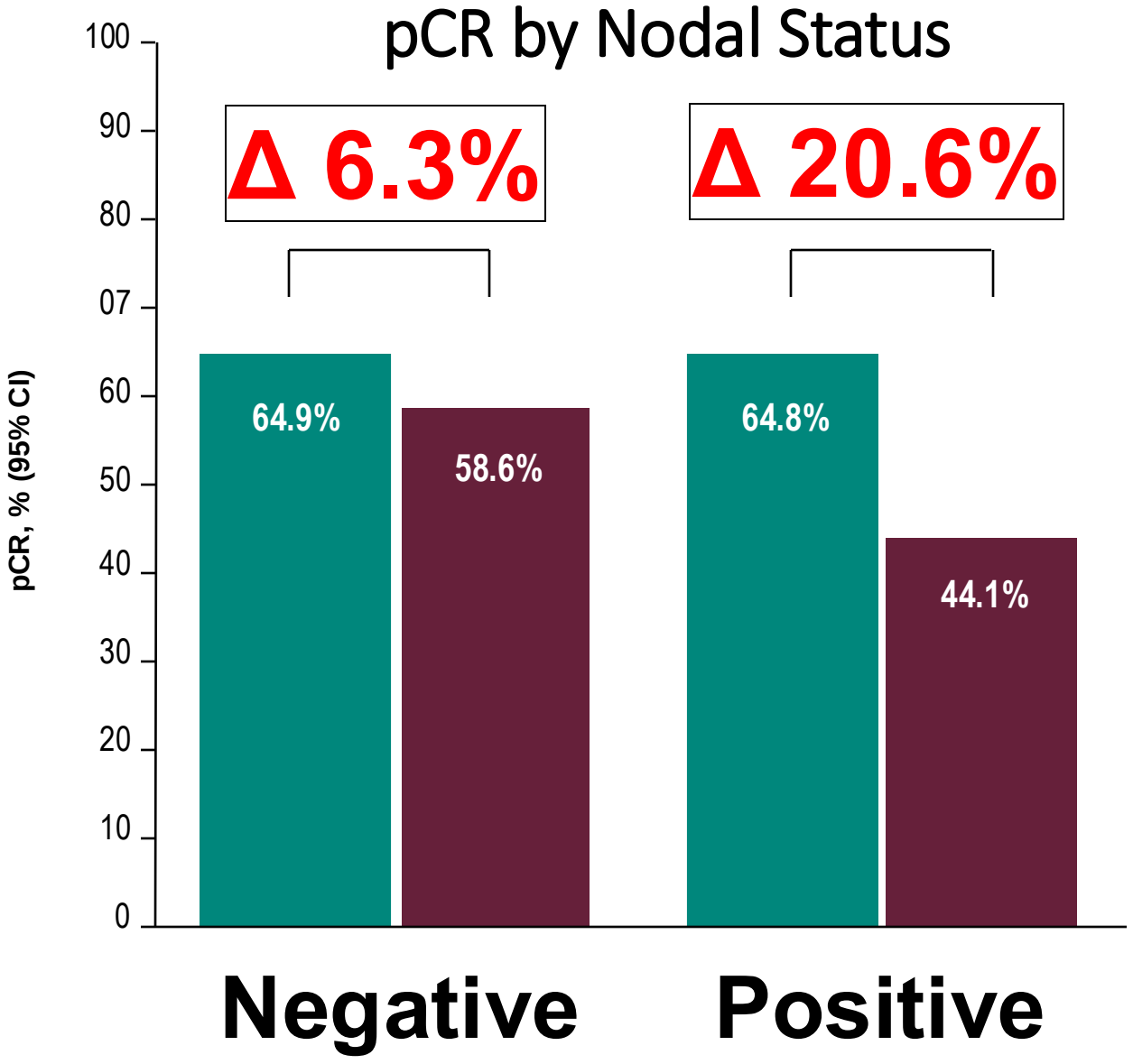
	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	15.7%	0.63[a]	0.00031[b]
Pbo + Chemo/Pbo	23.8%		

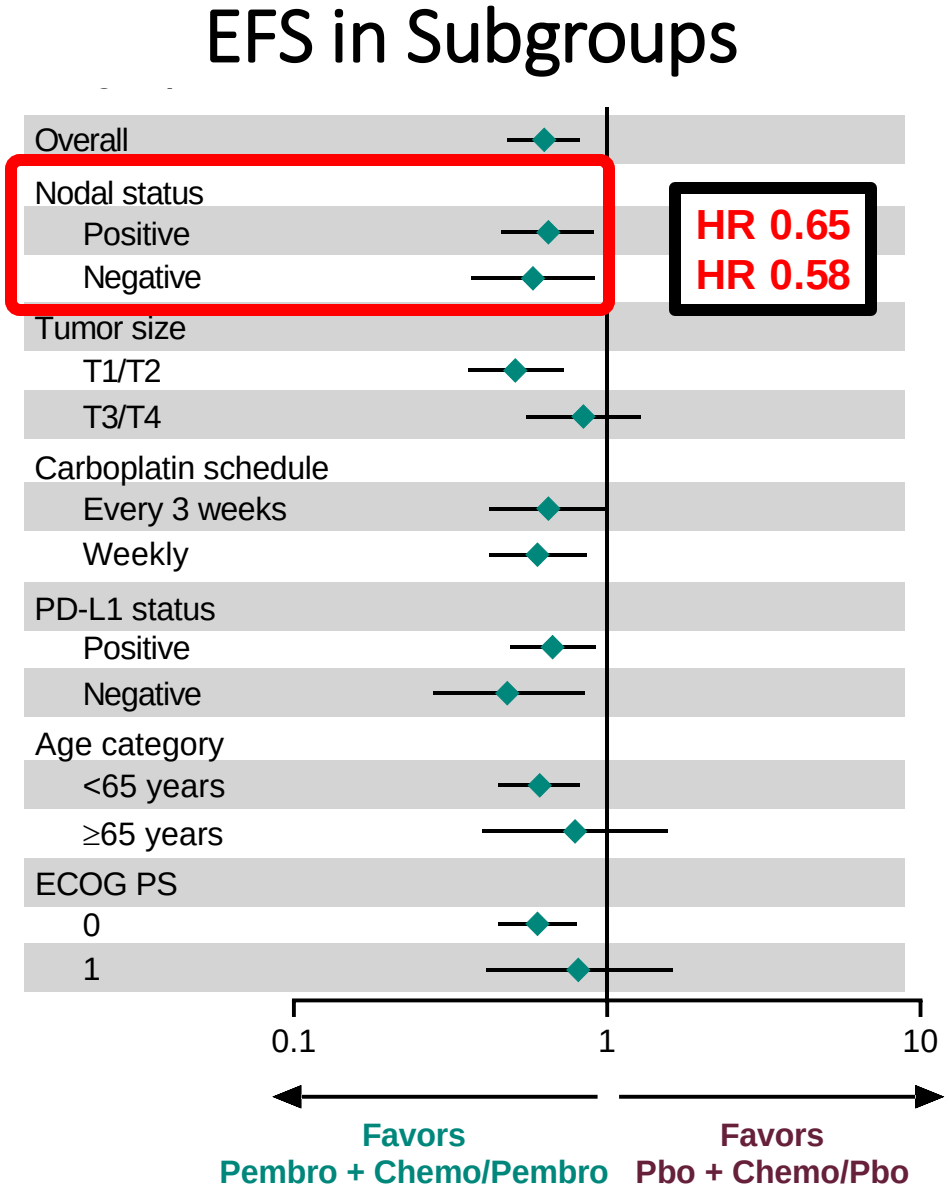
Schmid et al. ESMO Virtual Plenary. Abstract VP7-2021. Presented July 15, 2021.

EFS by pCR at 63 months



Schmid et al. ESMO Virtual Plenary. Abstract VP7-2021. Presented July 15, 2021.



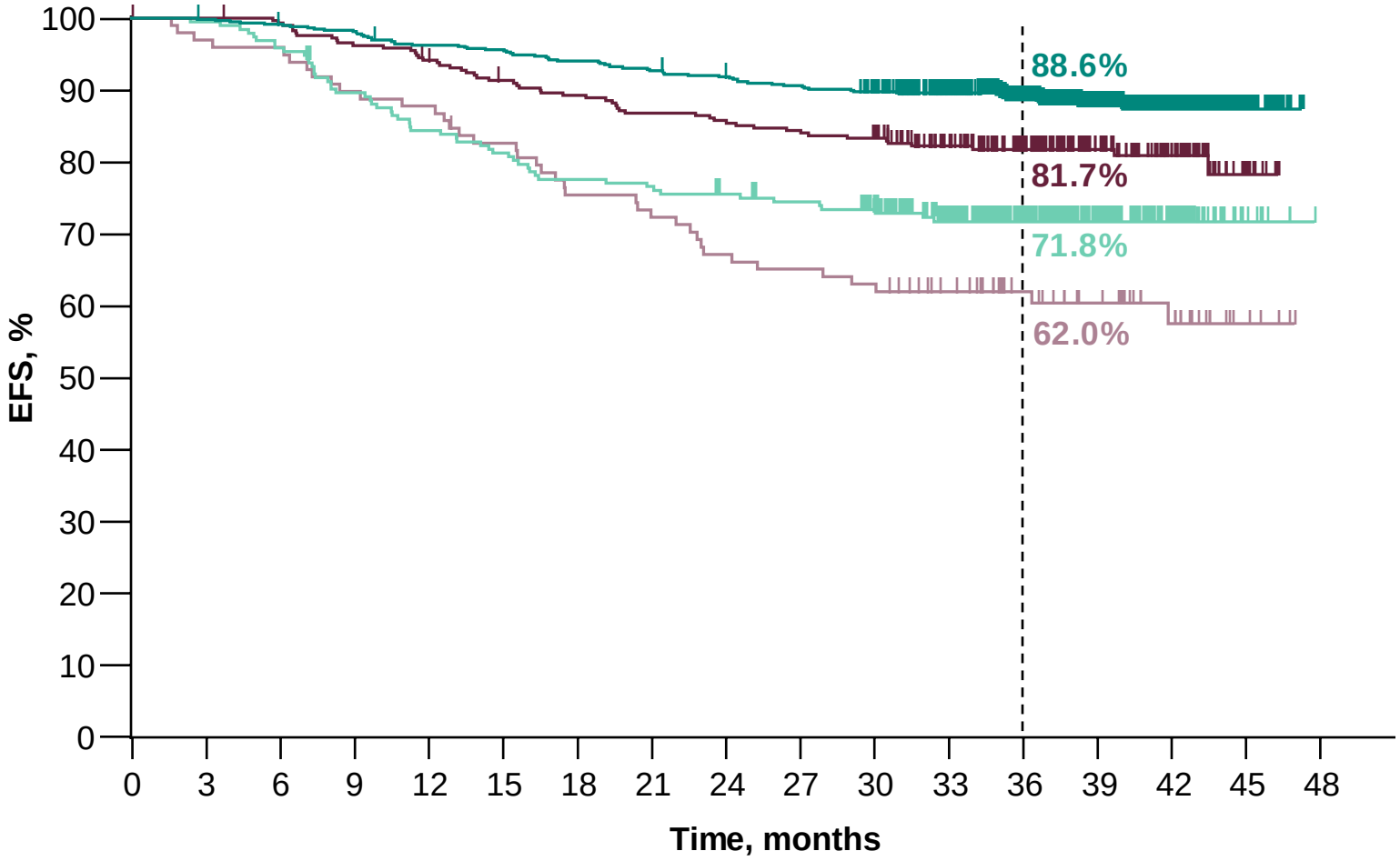


Schmid et al. ESMO Virtual Plenary. Abstract VP7-2021. Presented July 15, 2021.

EFS by Overall Disease Stage

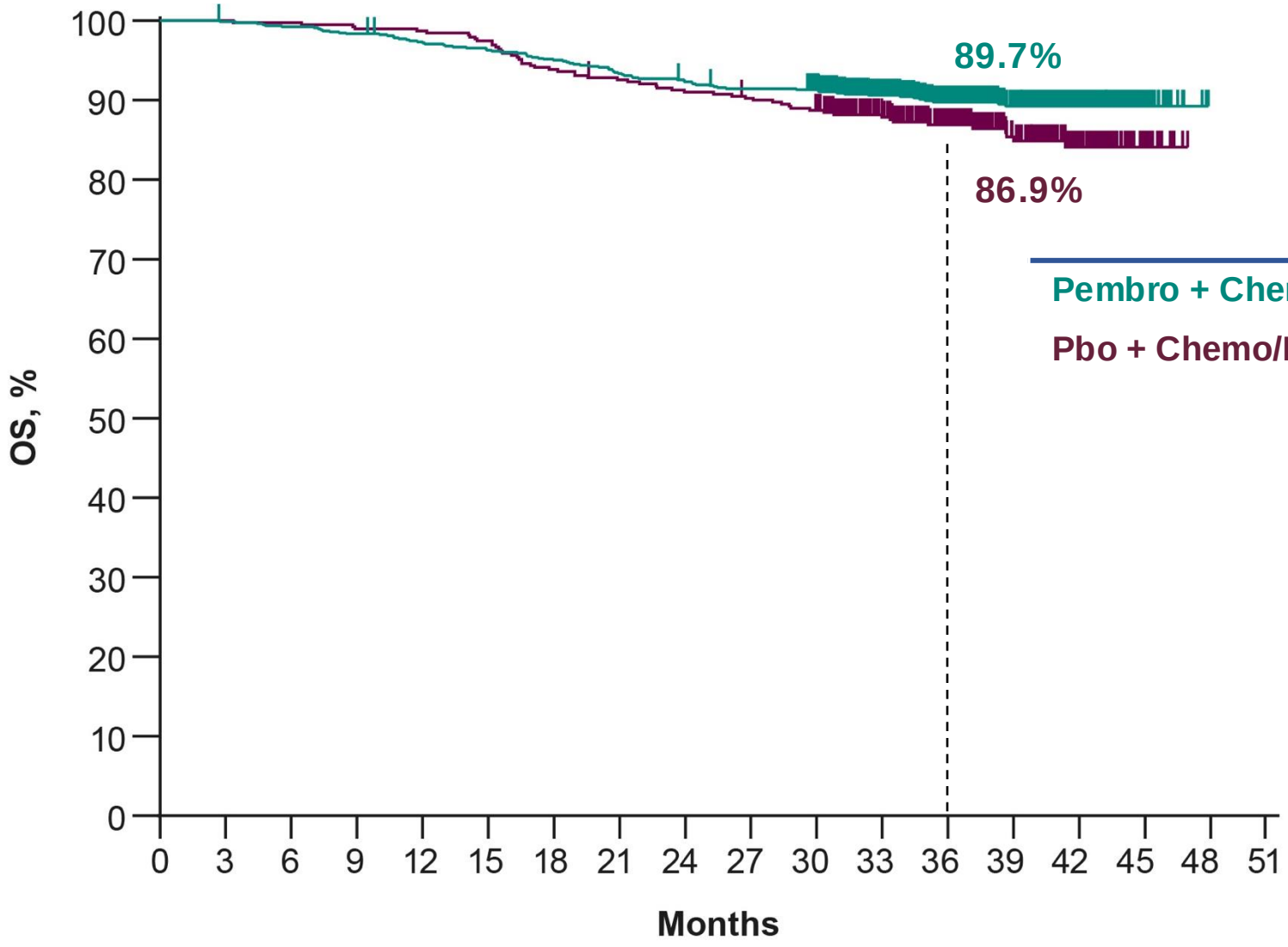
Stage II	Events	HR (95% CI)
Pembro+Chemo/Pembro	11.7%	0.60 (0.42-0.86)
Placebo+Chemo/Placebo	18.6%	

Stage III	Events	HR (95% CI)
Pembro+Chemo/Pembro	27.8%	0.68 (0.45-1.03)
Placebo+Chemo/Placebo	39.8%	



Schmid et al. SABCS 2021.

Overall Survival—met in May 2024



	Events	HR (95% CI)	*P*-value
Pembro + Chemo/Pembro	10.2%	0.72[a] (0.51-1.02)	0.03214[b]
Pbo + Chemo/Pbo	14.1%		

1st immunotherapy-based regimen demonstrating a statistically significant OS benefit in patients with high-risk early-stage TNBC—ESMO 2023

Schmid et al. ESMO Virtual Plenary. Abstract VP7-2021. https://www.annalsofoncology.org/article/S0923-7534(23)04152-2/fulltext

FDA-Approval

On **7/27/21July 27, 2021**, the FDA approved pembrolizumab for high-risk early-stage TNBC with chemotherapy as neoadjuvant treatment and then continued as a single agent as adjuvant treatment after surgery

Based on KEYNOTE-522, the indication for palliative pembrolizumab was converted from accelerated to full approval

www.fda.gov

FDA-Approval

On **7/27/21July 27, 2021**, the FDA … for high-risk early-stage TNBC wit… …djuvant treatment and then con… …as adjuvant treatment after su…

Bas… …indication for palliative …nverted from accelerated to full approval

NEW SOC!!
BUT MANY NEW QUESTIONS!

www.fda.gov

Studies to watch for HR+ disease:

1. **CheckMate-7FL**-LBA20 A randomized, double-blind trial of nivolumab (NIVO) vs placebo (PBO) with neoadjuvant chemotherapy (NACT) followed by adjuvant endocrine therapy (ET) ± NIVO in patients (pts) with high-risk, ER+ HER2− primary breast cancer (BC)
    1. pCR increased significantly in the nivolumab arm to 24.5% versus 13.8% in the control (P = .0021)
    2. PD-L1+ subset pCR rates increased from 20.2% to 44.3% (odds ratio [OR], 3.11 [95% CI, 1.58 to 6.11])
    3. PD-L1–negative cancers, pCR rates 14.2% versus 10.7%.

    (Loi et al Annals of Onc 2023).

2. **KEYNOTE-756** -pembrolizumab plus T-AC or placebo plus T-AC followed by surgery and continued pembrolizumab or placebo for 6 months and endocrine therapy for up to 10 years.
    1. pCR rate improved from 15.6% in the control arm to 24.3% in the pembrolizumab arm (P = .00005).
    2. PD-L1+ subpopulation, 29.7% versus 19.6%
    3. PD-L1–negative cancers, 7.2% versus 2.6%.
    4. The EFS results were immature and continue to be evaluated.

3. **iSPY2**—
    1. Three different immunotherapy arms demonstrated improved pCR rates with neoadjuvant immune checkpoint therapy in MammaPrint high ER+/HER2– cancers.
    2. Further molecular analysis revealed that among these cancers, only the MammaPrint High-2 (or MP2) subset had improvement in pCR rate.
    3. Integrating CDK4/6 inhibitors in adjuvant and neoadjuvant settings further enhances efficacy

In combination with CDK4/6?

Study	Recruitment Status	Treatment	Study Population	End Point
I-SPY2 (NCT01042379) Bayesian Adaptive phase II	Recruiting	Multiple arms; see: NCT01042379	cT2, MP high	pCR rate
Neo-CheckRay (NCT03875573) phase II	Recruiting	Durvalumab + oleclumab + AC + paclitaxel followed by preoperative radiation	cT1-3 cN-1, ER+/HER2–, Ki67 ≥15% or grade 3, or MP high risk	Safety run-in, tumor response, pCR, and RCB
SWOG S2206 (NCT06058377) phase III	Recruiting	Durvalumab plus neoadjuvant AC + paclitaxel followed by adjuvant ET	Stage II/III MP2/high2	Invasive disease-free survival, pCR

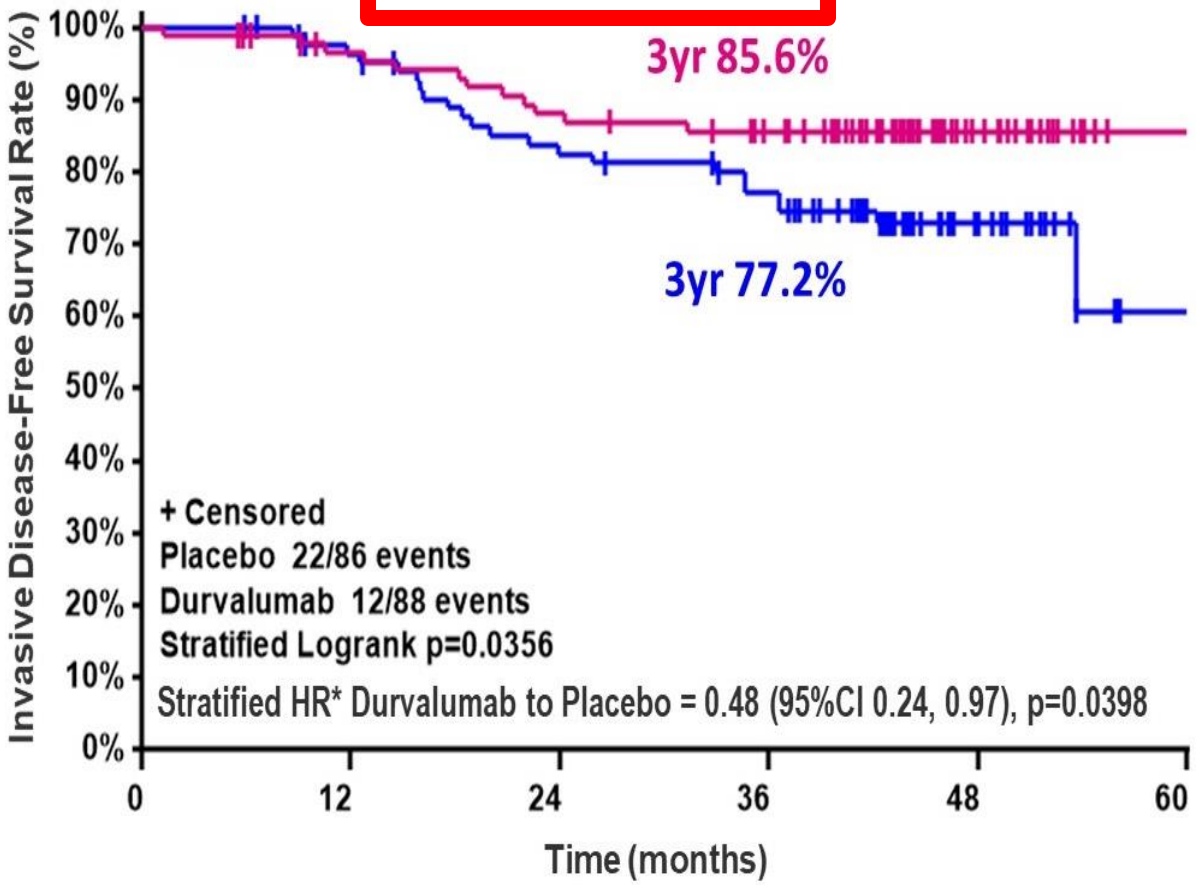
Need to determine who needs CDK4/6i vs. IO as unacceptably high rates of irAEs when combined

https://ascopubs.org/doi/full/10.1200/JCO.23.02614

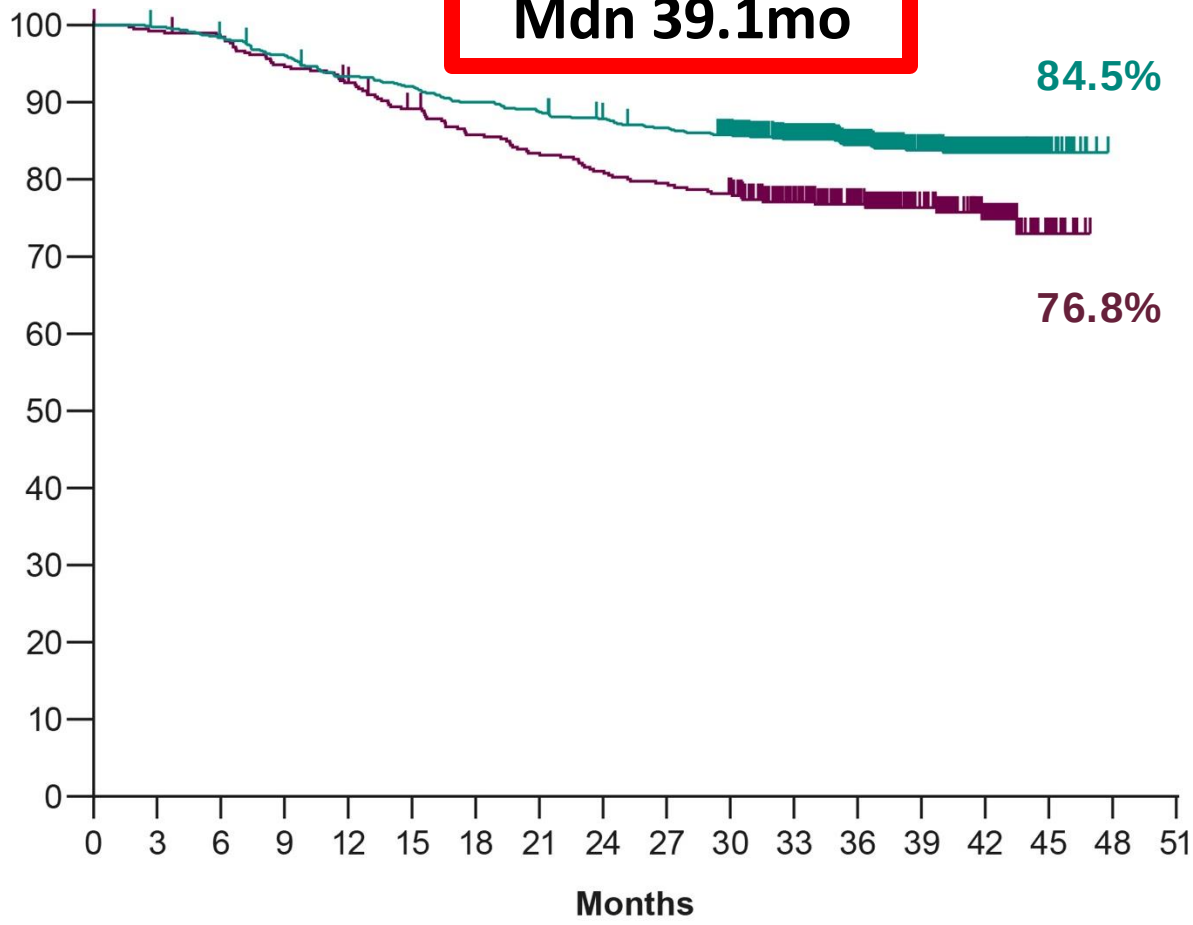
III. Ongoing research:

Q#1: Is all the IO benefit conferred with neoadjuvant administration?

GeparNuevo
Mdn 43.7mo

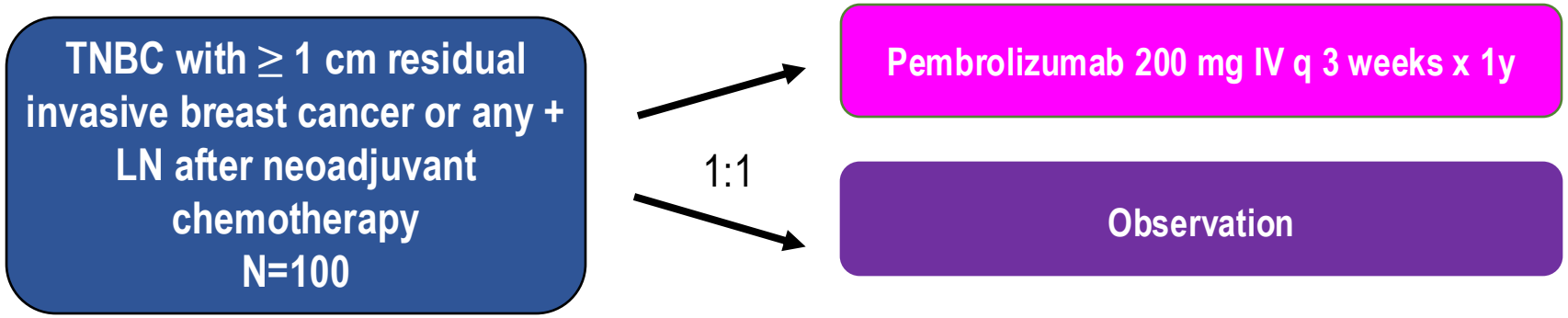


Keynote-522
Mdn 39.1mo



Loibl et al. ASCO 2021; Schmid ett al ESMO 2021.

SWOG 1418/NRG BR006
Pembrolizumab as adjuvant therapy for TNBC



- **Registration:**
  - Central PD-L1 testing
- **Stratification:**
  - Nodal stage ypNo vs ypN+
  - Residual tumor ≥2 vs < 2cm
  - PD-L1 pos vs neg
  - Prior adjuvant chemo yes vs no

- **Hypothesis:**
  - Pembrolizumab reduces IDFS by 33% c/w observation alone
- **Primary Endpoint:**
  - Invasive DFS in PD-L1-positive and overall cohort
- **Secondary Endpoints:**
  - Toxicity
  - OS
  - DRFS
  - QOL (PROMIS, PRO-CTCAE forms, inflammatory markers)
  - Tissue banking

PI Lajos Pusztai
NCT02954874

ALEXANDRA/IMpassion030
Pembrolizumab added to adjuvant chemotherapy for early stage TNBC

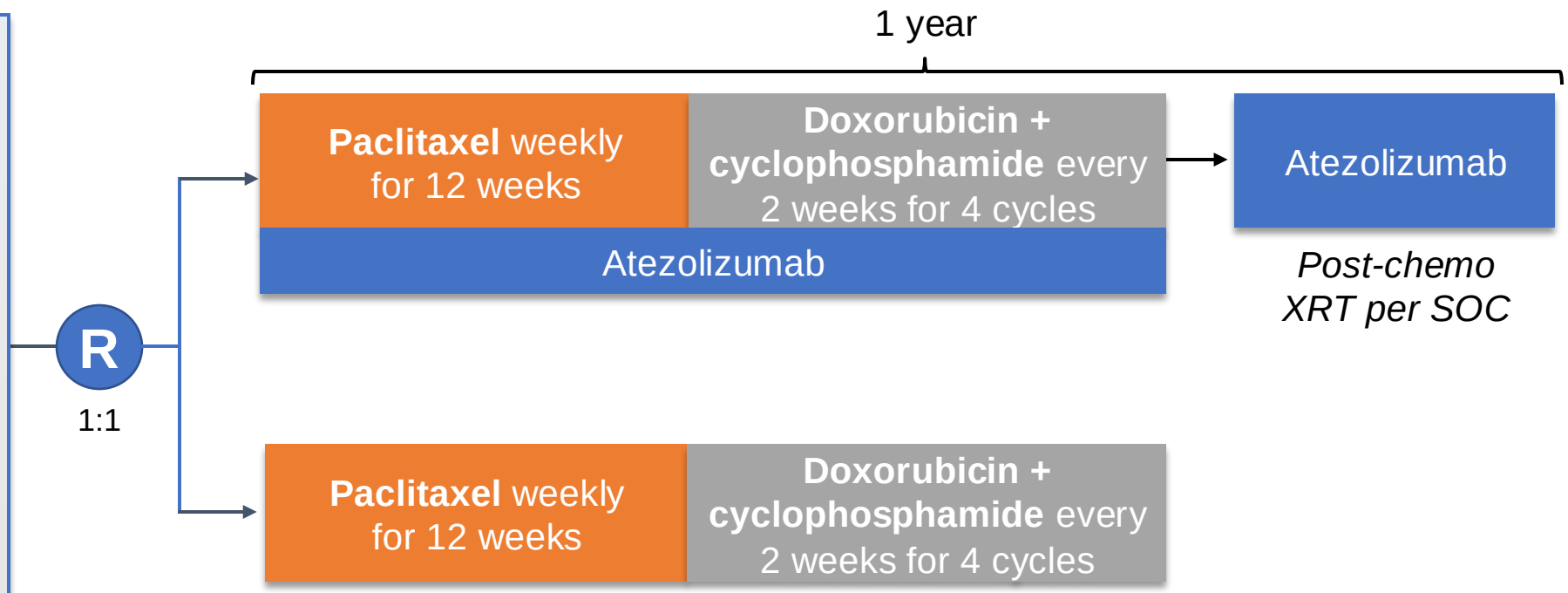
Eligibility

- **Adequately excised primary invasive TNBC (stage II/III)** 50:50 node negative/positive–enriched population

Stratification

- Axillary nodal status (0 vs 1-3 vs ≥4 positive lymph nodes)
- Surgery (breast conserving vs mastectomy)
- PD-L1 IC0 vs IC1/2/3

N = 2,300

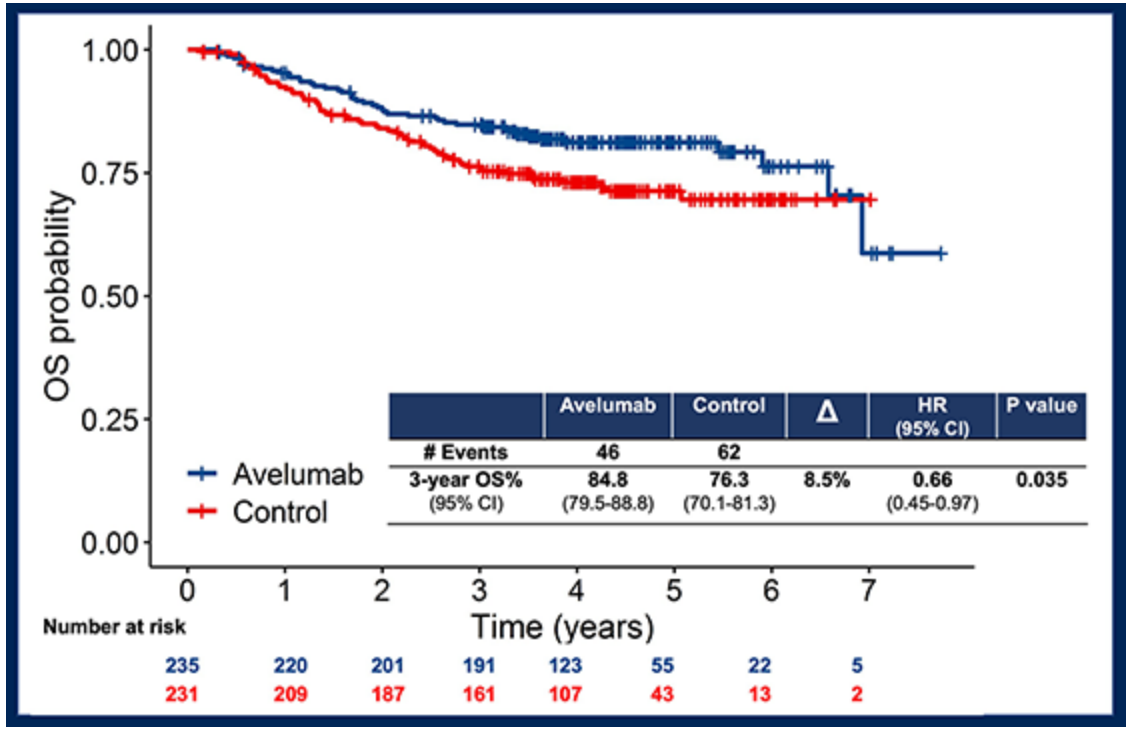


- **Primary endpoint:** iDFS in ITT
- **Secondary endpoints:** iDFS PD-L1 IC1/2/3, OS, RFI, distant RFI, safety, and health-related QoL

Co-PIs: Ignatiadis, McArthur, Saji

NCT03498716

A-BRAVE - randomized phase 3 trial of adjuvant avelumab in high-risk TNBC

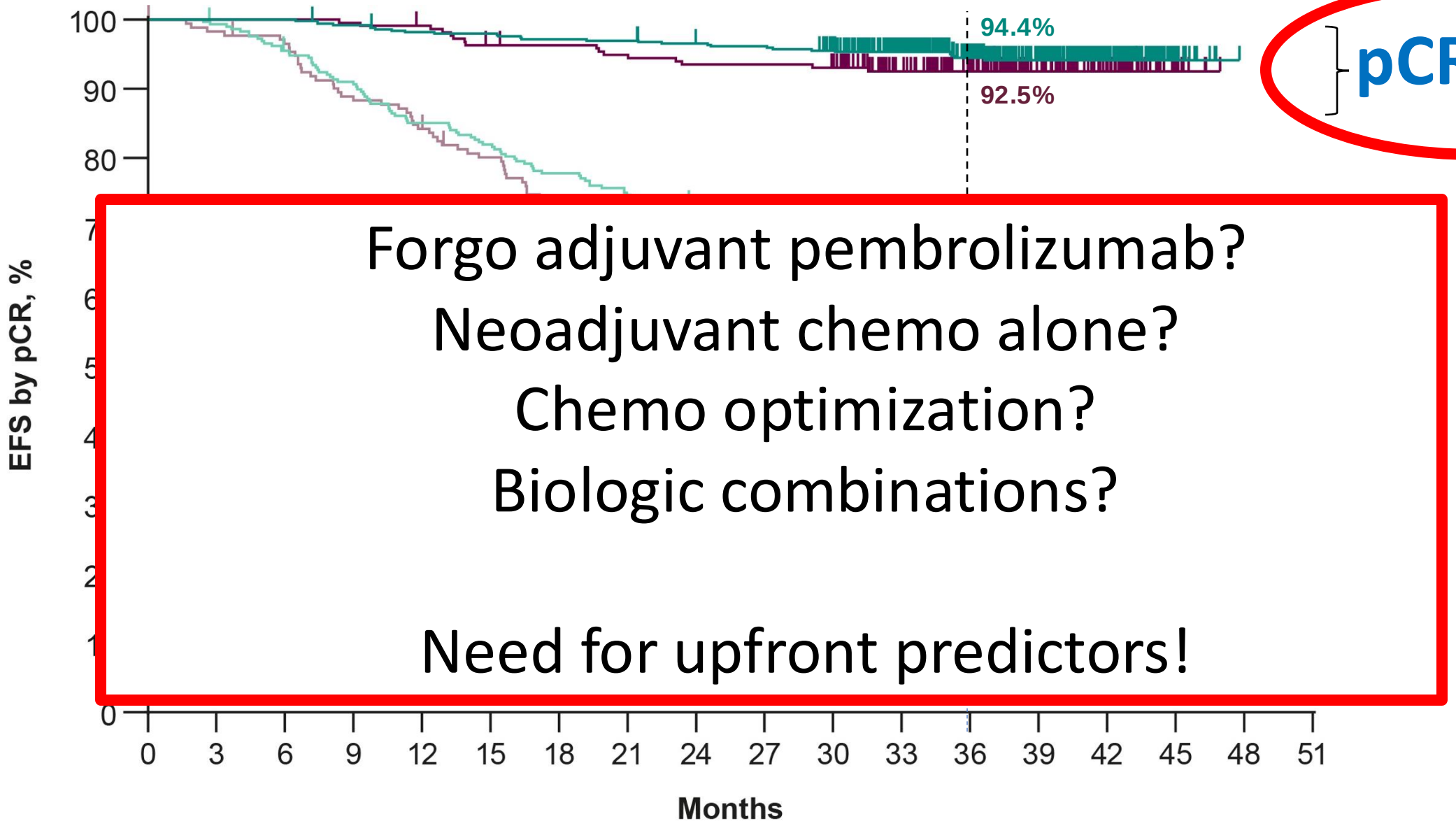


	Avelumab	Control	Δ	HR (95% CI)	P value
# Events	46	62			
3-year OS% (95% CI)	84.8 (79.5-88.8)	76.3 (70.1-81.3)	8.5%	0.66 (0.45-0.97)	0.035

These data may represent an option for patients treated with neoadjuvant chemotherapy alone (without pembrolizumab) and who have invasive residual disease at surgery, and may benefit from adjuvant pembrolizumab

https://meetings.asco.org/abstracts-presentations/232429

EFS by pCR



Forgo adjuvant pembrolizumab?

Neoadjuvant chemo alone?

Chemo optimization?

Biologic combinations?

Need for upfront predictors!

Schmid et al. ESMO Virtual Plenary. Abstract VP7-2021. Presented July 15, 2021.

Q#2: What is the optimal chemo partner for IO?

Paclitaxel		Nab-paclitaxel	
"Positive"	"Negative"	"Positive"	"Negative"
Keynote 522[1]	IMpassion131[2]	IMpassion130[3]	Neotrip[4]
ISPY2[5]		IMpassion031[6]	Geparnuevo[7]

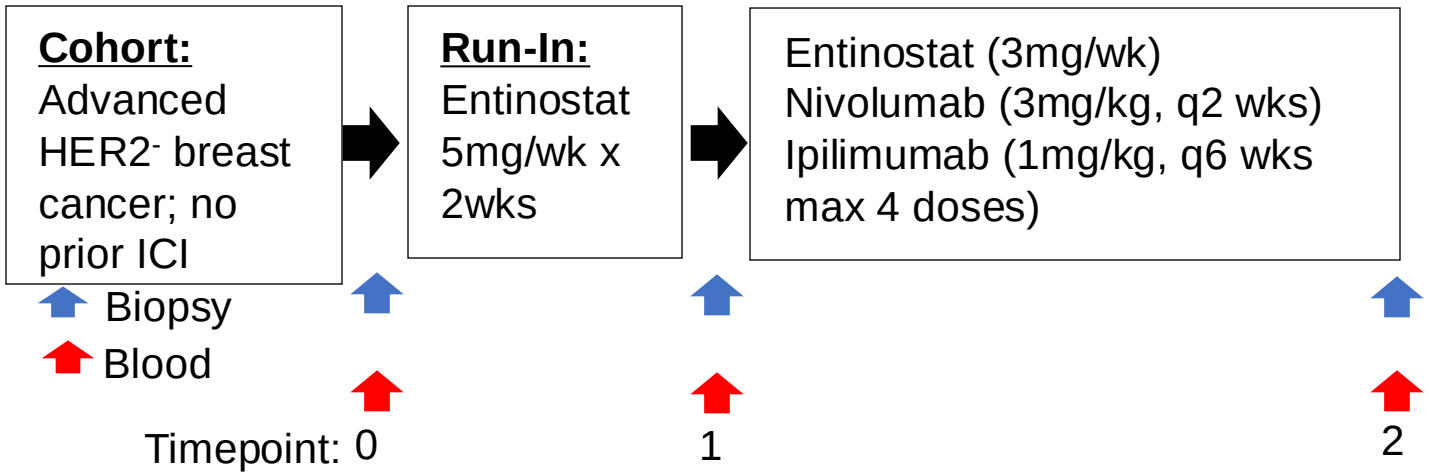
[1]Schmid et al. NEJM 2020. [2]Miles D et al. ESMO 2020. [3]Schmid et al. NEJM 2018 and Lancet Oncol 2020.

[4]Gianni SABCS 2019. [5]Nanda JAMA Oncol 2020. [6]Mittendorf et al. Lancet 2020. [7]Loibl Ann Oncol 2019.

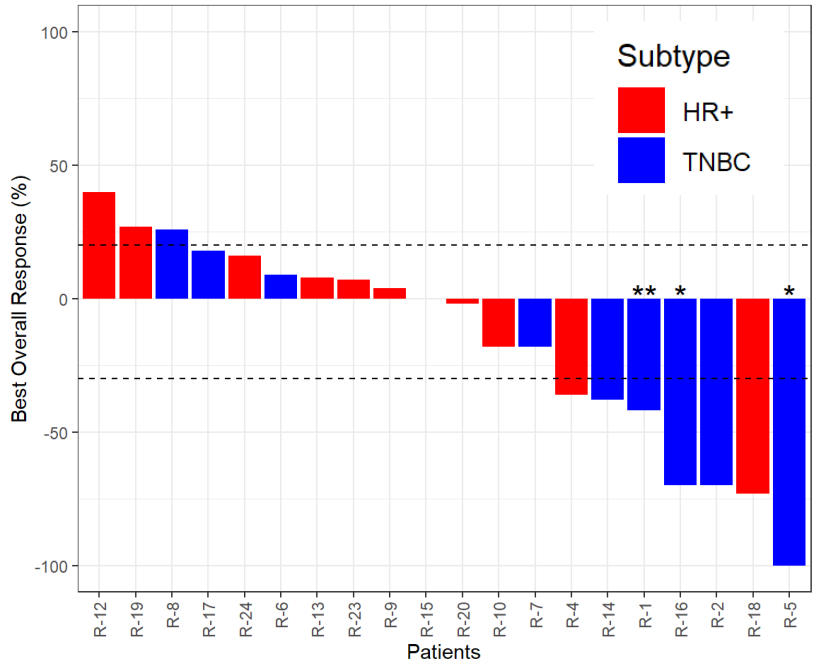
Q3: Is chemotherapy necessary for success of IO therapy in breast cancer?

Phase I: dose escalation cohort established RP2D and acceptable AEs

Roussos Torres et al. (CCR, 2021)



Characteristics	N = 24*
Age	
Median	55
Range	38-77
ECOG Performance Status	
0	6 (25%)
1	18 (75%)
Tumor type	
Hormone receptor-positive	12 (50%)
Triple-negative (TNBC)	12 (50%)
Median prior therapies	6.5 (1-13)
Patients with evaluable disease for objective response	20

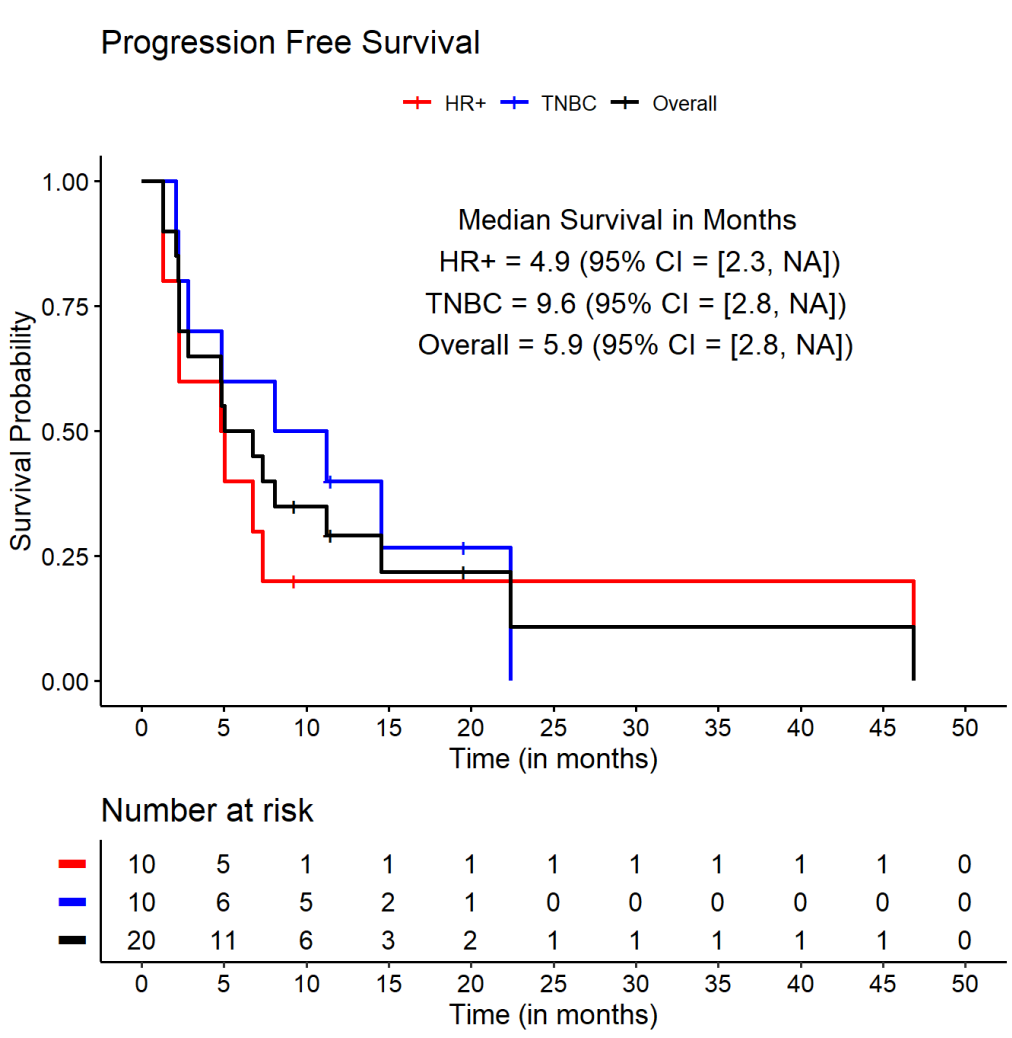


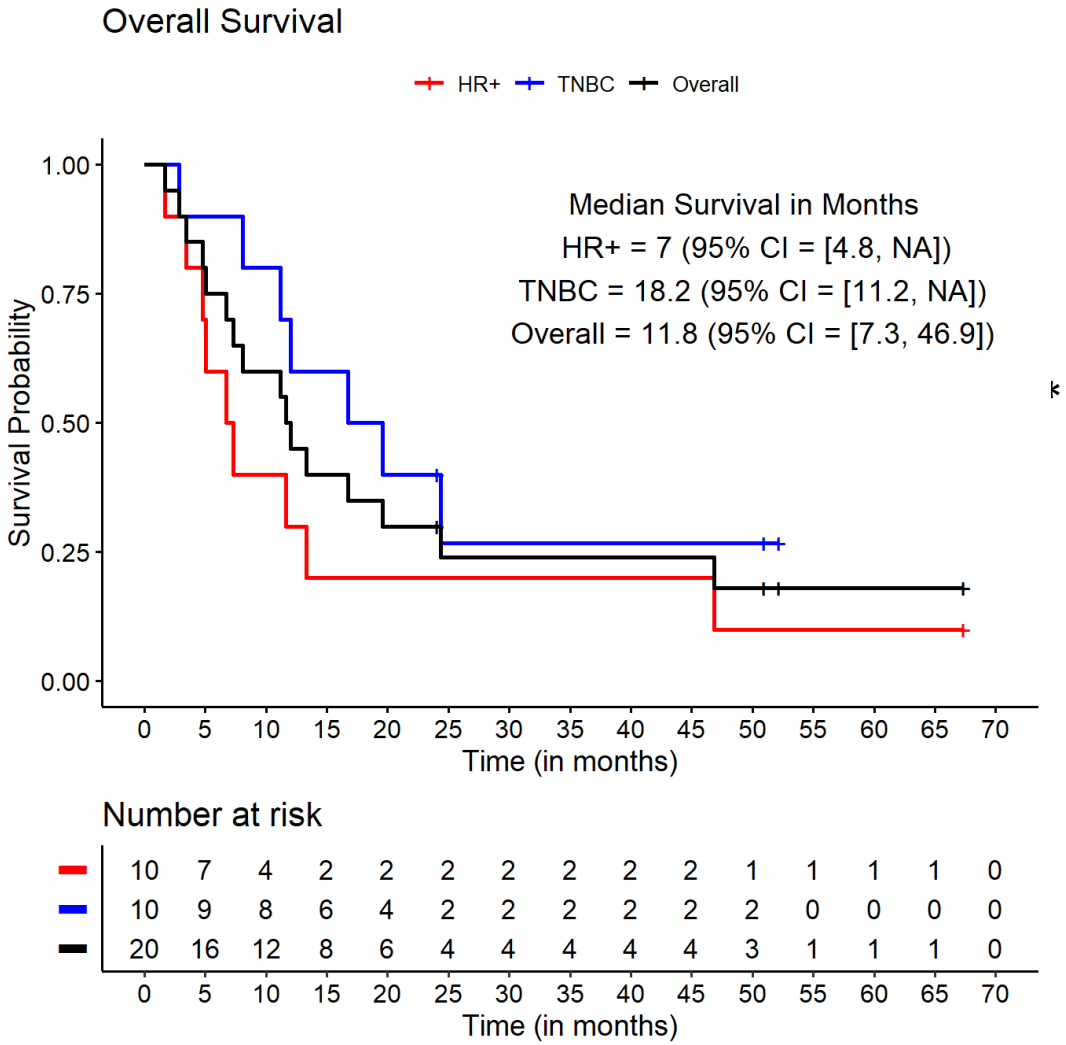
Phase Ib: dose Expansion cohort in advanced breast cancer demonstrates efficacy

- ORR 40% in TNBC (N= 4/10)
- ORR 10% in Hormone receptor positive (N=1/10)
- Clinical benefit rate at 24 weeks: 40% overall (N= 7/20)

Roussos Torres et al. (Nature Cancer 2/2024)

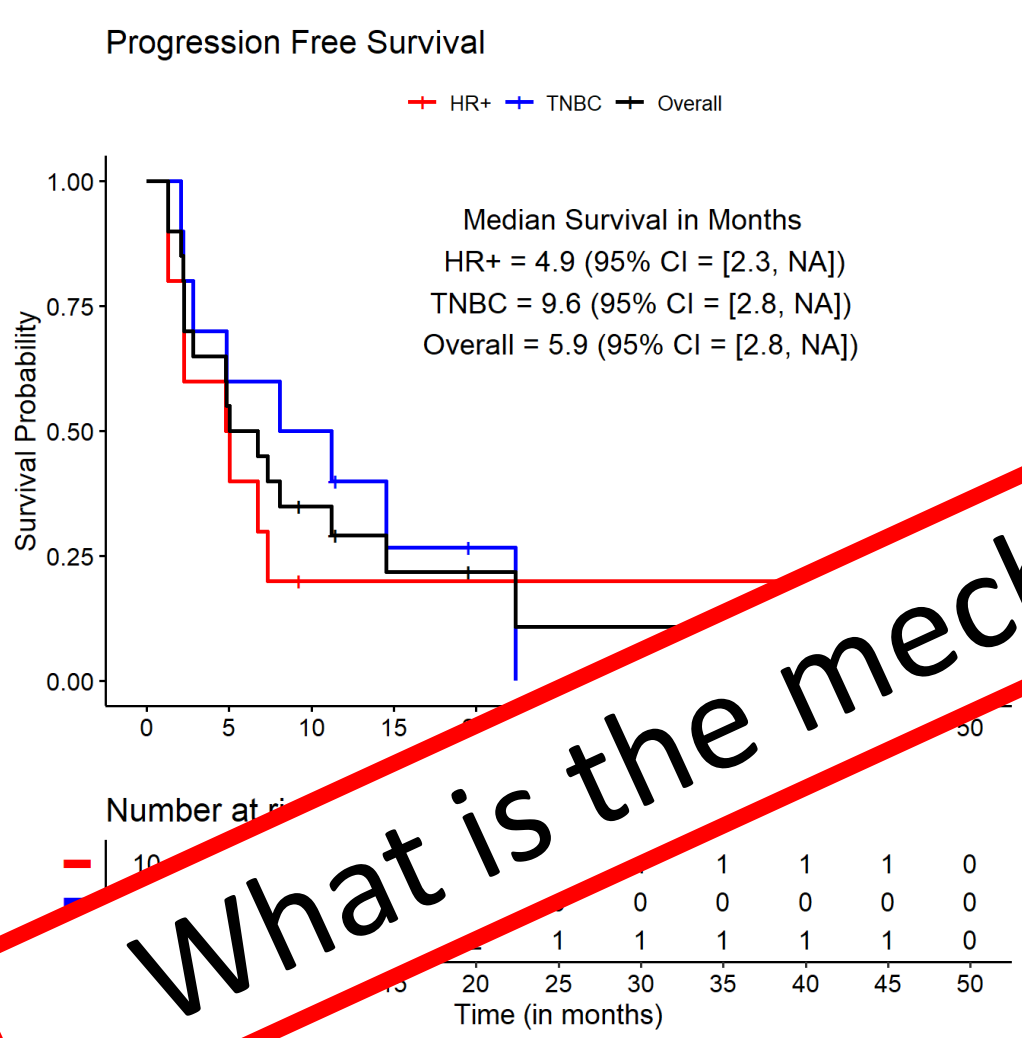
PFS/OS rivals that achieved with chemo/pembro in PD-L1+ TNBC Keynote 355

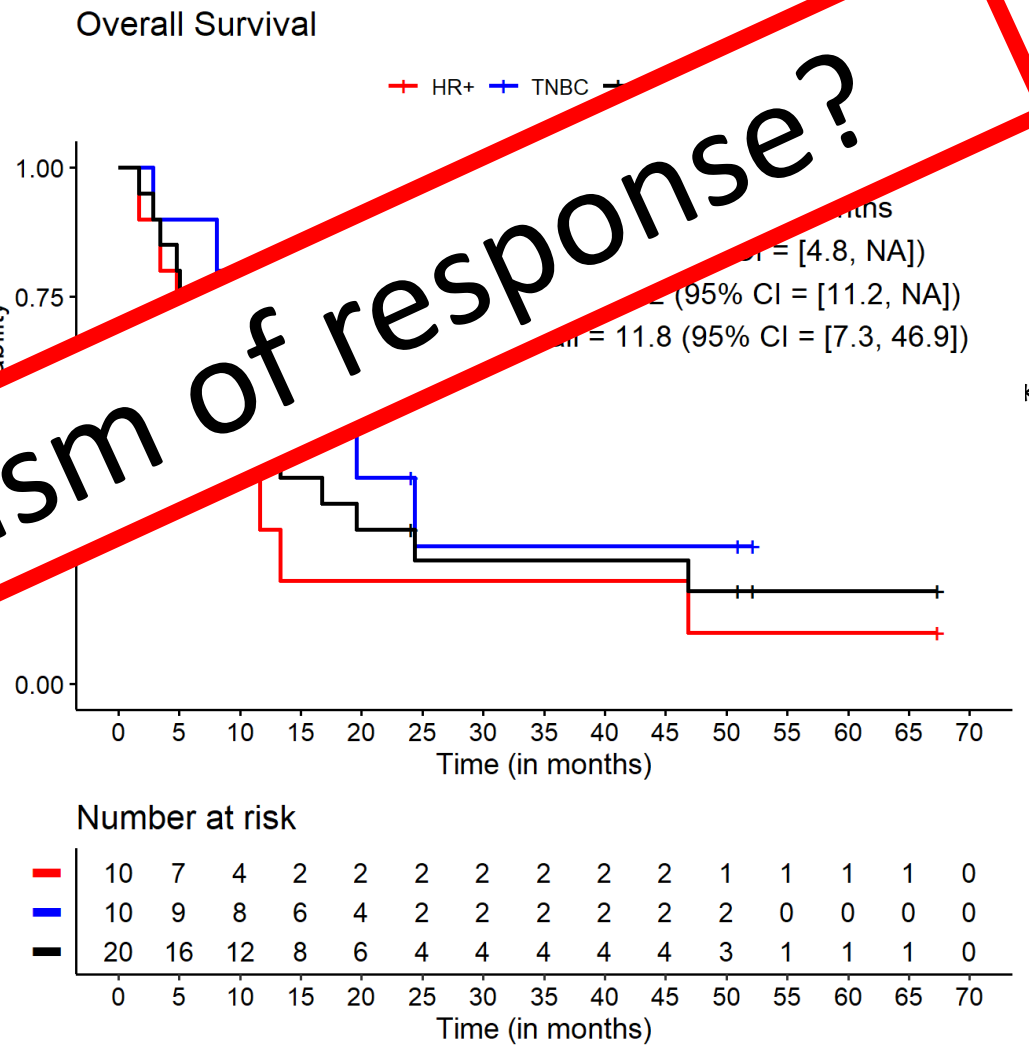




Response is not correlated with PD-L1 status, TMB or TIL infiltration

PFS/OS rivals that achieved with chemo/pembro in PD-L1+ TNBC Keynote 355



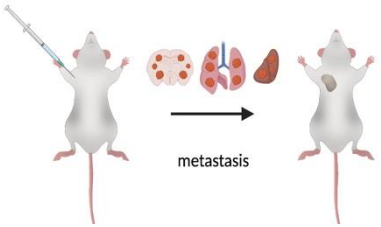


What is the mechanism of response?

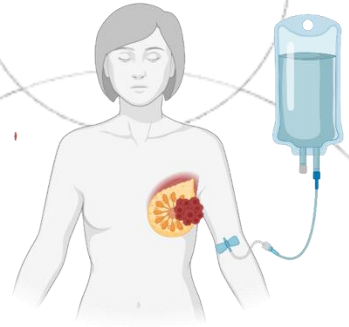
Response is not correlated with PD-L1 status, TMB or TIL infiltration

Translational research approach in Roussos Torres lab

…from mice to men (with some math) and back



MICE

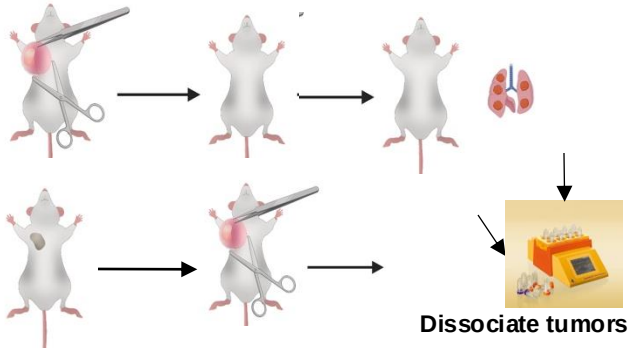


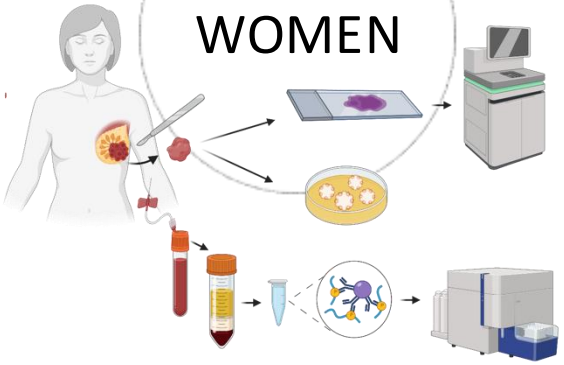
WOMEN

$$f(x_j(t), x_j(t-\tau)) = \begin{bmatrix} \alpha_1 x_T(t) \log\left(\frac{\eta}{x_T(t)}\right) - \beta_1 x_T(t) x_{NK}(t) - \beta_2 x_T(t) x_{CTL}(t) - \zeta_1 x_T(t) & (3a) \\ \alpha_2 + \alpha_3 \frac{x_T(t-\tau)}{\gamma_1 + x_T(t-\tau)} - \zeta_2 x_{MDSC}(t) & (3b) \\ \alpha_4 + \alpha_5 \frac{x_T(t)^2}{\gamma_2 + x_T(t)^2} - \beta_3 x_{MDSC}(t) x_{NK}(t) - \zeta_3 x_{NK}(t) & (3c) \\ \alpha_6 x_T(t) x_{NK}(t) + \alpha_7 \frac{x_T(t)^2}{\gamma_3 + x_T(t)^2} - \beta_4 x_{MDSC}(t) x_{CTL}(t) - \zeta_4 x_{CTL}(t) & (3d) \end{bmatrix}$$

MATH

MICE

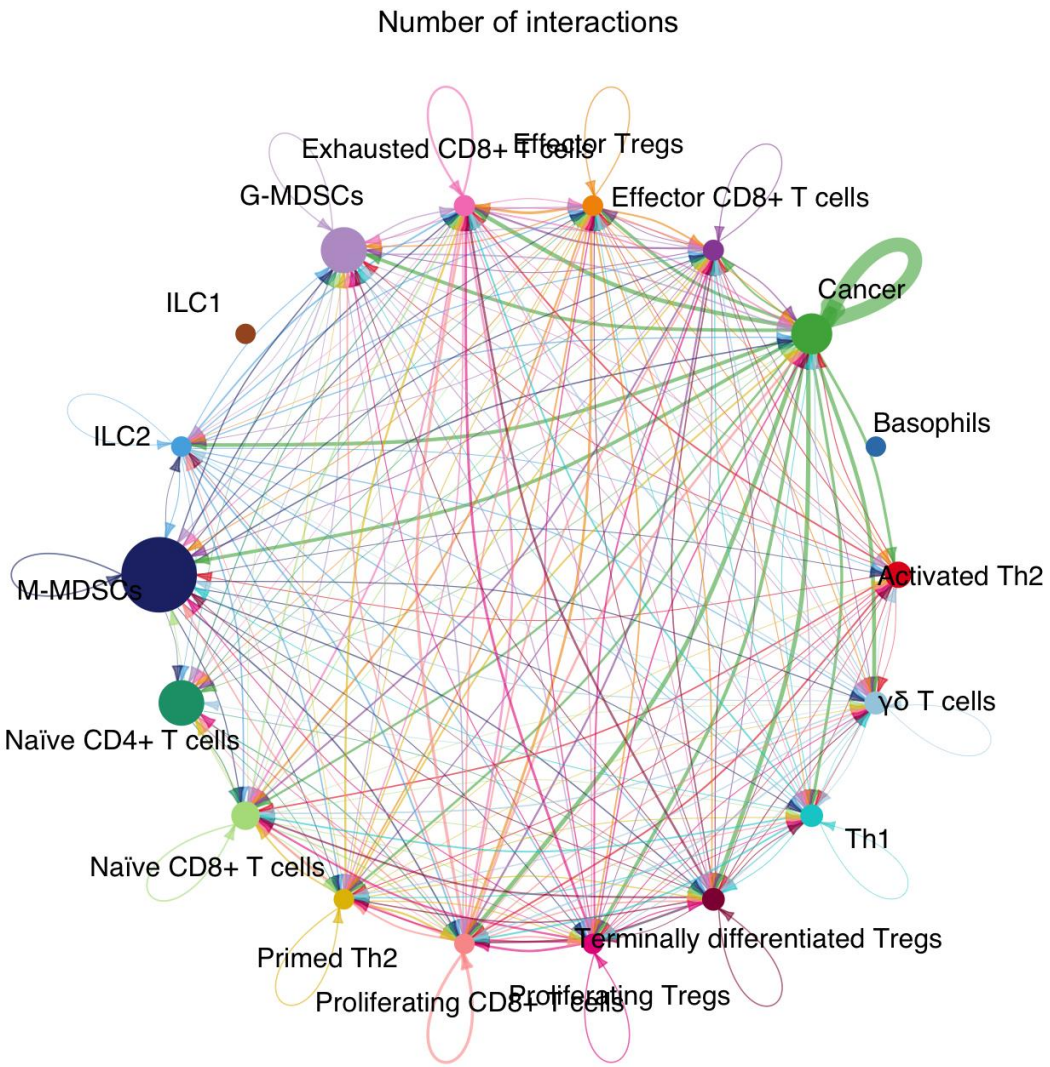


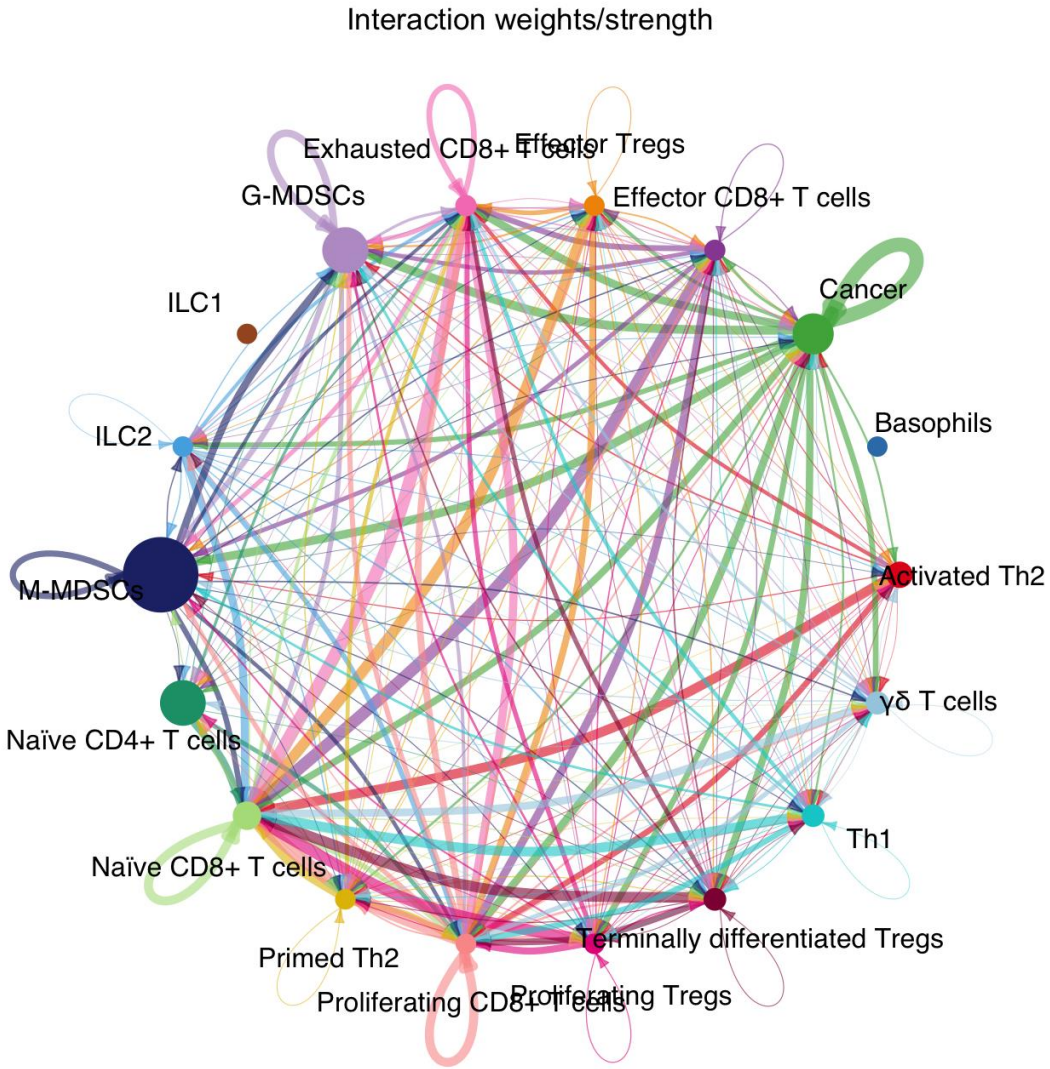


WOMEN

Investigations of immune suppression in breast cancer

MICE: How do change in immune cells by treatment effect cellular interactions?

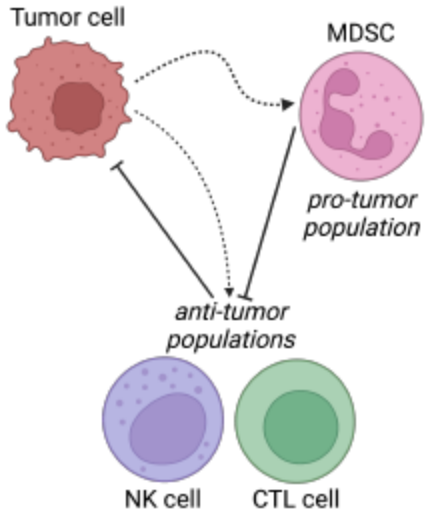




…ligand/Receptor interactions by CellChat

MATH:

Mathematical modeling can account for how MDSC suppression affects metastatic disease progression

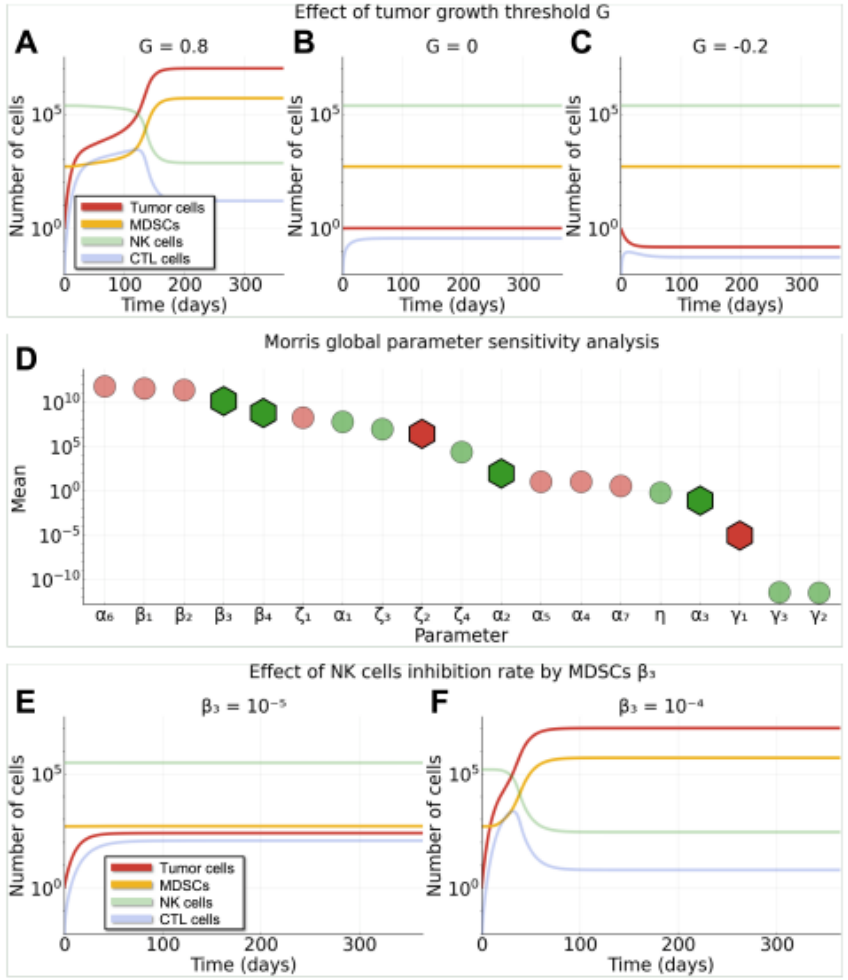


$$f(x_j(t), x_j(t-\tau)) = \begin{bmatrix} \alpha_1 x_T(t) \log\left(\frac{\eta}{x_T(t)}\right) - \beta_1 x_T(t) x_{NK}(t) - \beta_2 x_T(t) x_{CTL}(t) - \zeta_1 x_T(t) & (3a) \\ \alpha_2 + \alpha_3 \frac{x_T(t-\tau)}{\gamma_1 + x_T(t-\tau)} - \zeta_2 x_{MDSC}(t) & (3b) \\ \alpha_4 + \alpha_5 \frac{x_T(t)^2}{\gamma_2 + x_T(t)^2} - \beta_3 x_{MDSC}(t) x_{NK}(t) - \zeta_3 x_{NK}(t) & (3c) \\ \alpha_6 x_T(t) x_{NK}(t) + \alpha_7 \frac{x_T(t)^2}{\gamma_3 + x_T(t)^2} - \beta_4 x_{MDSC}(t) x_{CTL}(t) - \zeta_4 x_{CTL}(t) & (3d) \end{bmatrix},$$

$$\hat{x}_{MDSC} = \frac{\alpha_2(\hat{x}_T + \gamma_1) + \alpha_3 \hat{x}_T}{\zeta_2(\hat{x}_T + \gamma_1)}, \quad (6a)$$

$$\hat{x}_{NK} = \frac{\zeta_2(\hat{x}_T + \gamma_1)\left(\alpha_4\left(\hat{x}_T^2 + \gamma_2\right) + \alpha_5 \hat{x}_T^2\right)}{\left(\hat{x}_T^2 + \gamma_2\right)\left(\alpha_2\beta_3(\hat{x}_T + \gamma_1) + \alpha_3\beta_3\hat{x}_T + \zeta_2\zeta_3(\hat{x}_T + \gamma_1)\right)}, \quad (6b)$$

$$\hat{x}_{CTL} = \frac{\zeta_2 \hat{x}_T(\gamma_1 + \hat{x}_T)h_1}{\left(\gamma_2 + \hat{x}_T^2\right)\left(\gamma_3 + \hat{x}_T^2\right)h_2}, \quad (6c)$$



Kreger et al. (2023 CIR)

https://doi.org/10.1101/2022.06.15.496246

IV. Overall summary and conclusions

- Clearly there is activity of ICI in some patients, some (albeit few) can experience durable disease control
- Pembrolizumab + chemotherapy is approved for use in patients with TNBC
  - Neoadjuvant/ Adjuvant in combination with chemotherapy no PD-L1 testing needed
  - Metastatic patients with CPS score >10 (PD-L1 positive required)
- Considerations under investigation
  - What is most efficacious neoadjuvant vs. adjuvant checkpoint?
  - Non-traditional chemo approach used in trials (non-ddAC, +carbo, -capecitabine for RD), what is best chemo partner?
- Future directions: identify those likely to respond + develop rationale combinations and novel approaches
- Hormone receptor-positive/human epidermal growth factor receptor 2-negative BC (HR+/HER2− BC), HER2+ BC, and mTNBC in later lines of therapy, evidence is lacking to support the use of immunotherapy.

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