Immune Mechanisms in Breast Cancer

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Vienna Cancer Center

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Disclosure of Interest

Consultancies and Speaker's Honoraria:

Roche, Novartis, BMS, MSD, Imugene, Ariad, Pfizer, Merrimack / Shire, Merck KGaA, Fibrogen, AstraZeneca, Tesaro, Gilead, Servier, Eli Lilly, Amgen, Athenex

Financial support for research my Institution (CECOG):

BMS, MSD, Pfizer, AstraZeneca, Merrimack / Shire

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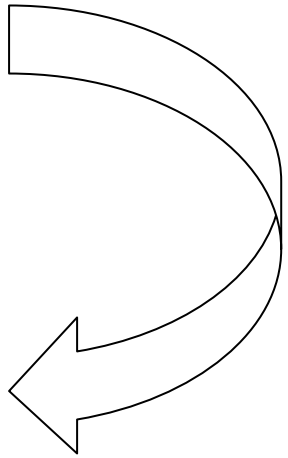
The Story is About Tolerance and the Maintenance of Physiologic Immune Responses.

Is Breast Cancer an Ideal Model for the Study of Efficacy of Immune Checkpoint Inhibitors?



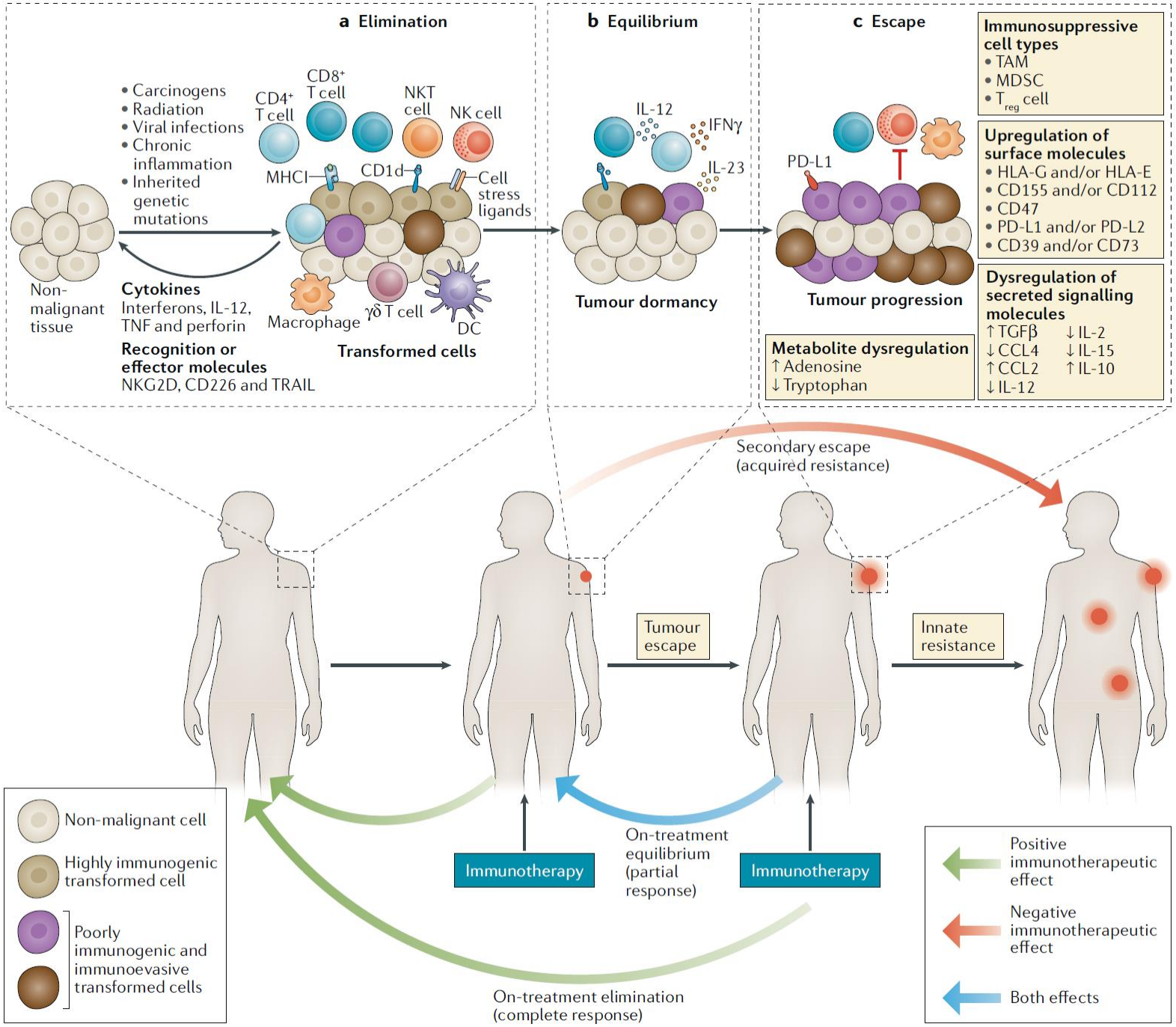
Cancer as Immunological Disease

Cancer comprises always failure of the immune system. Possible epitopes are hit by tolerance.

Cancer development and progression is accompanied by immune evolution.

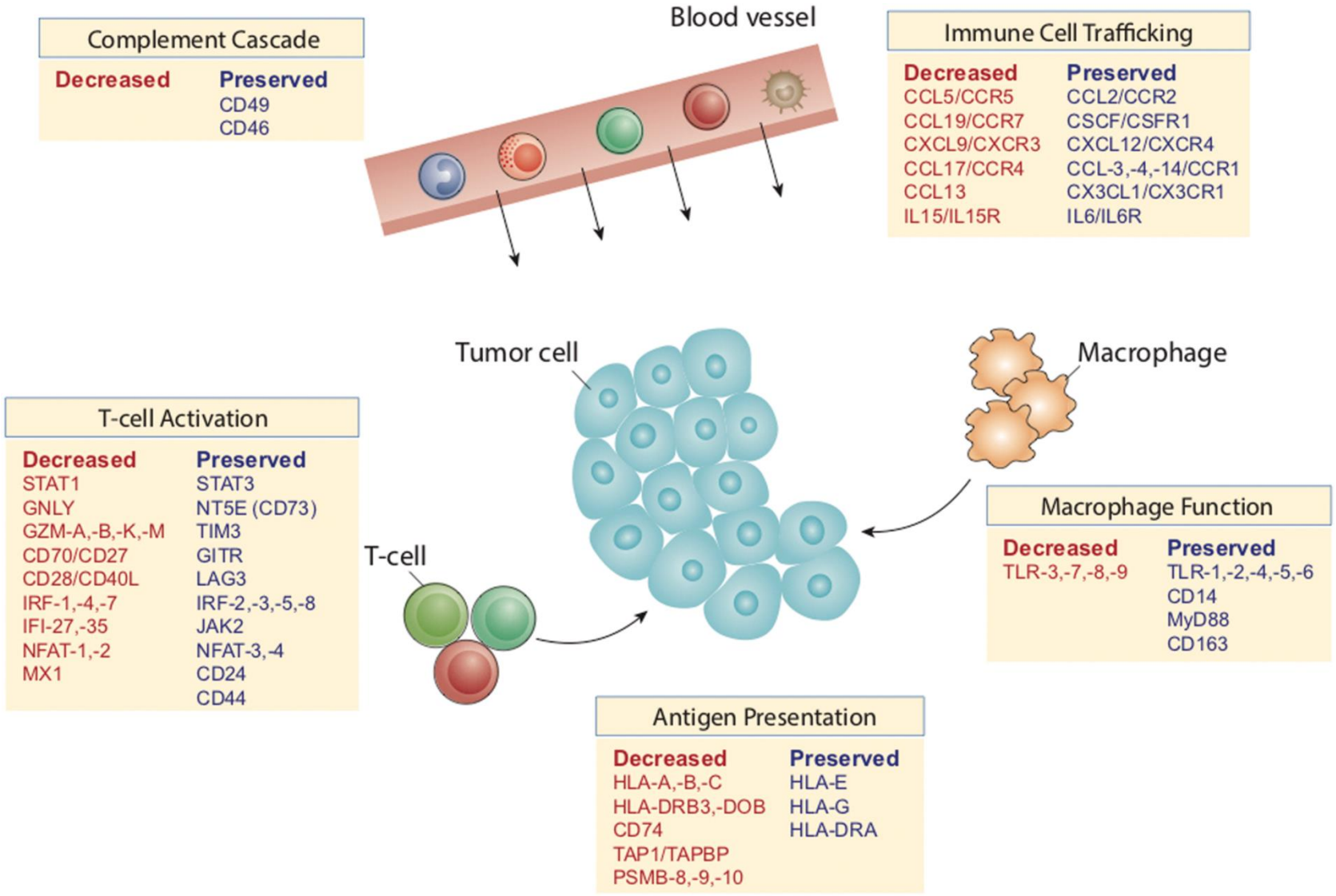
Most frequent cancer mutations and translocations are non immunogenic.

Every novel alteration leading to a changed protein is a chance for recognition by the immune system.



O'Donnell et al., Nat Rev Clin Oncol 2019

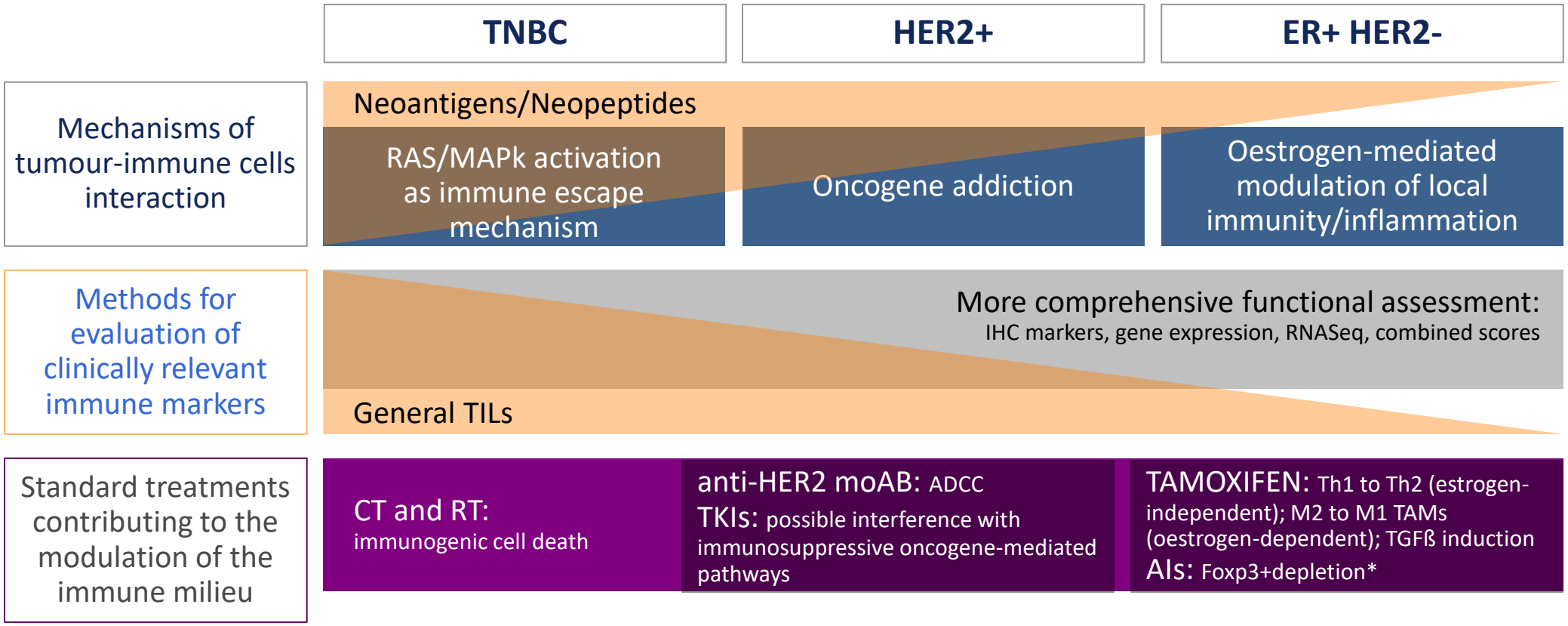
Immune Escape Mechanisms Observed in MBC



Annals of Oncology, Volume 29, Issue 11, 10 September 2018, Pages 2232–2239, https://doi.org/10.1093/annonc/mdy399

Immuno Oncology In Breast Cancer

Dieci MV, et al. *Cancer Treat Rev.* 2016;46:9–19. Figure reproduced from Dieci et al. 2016

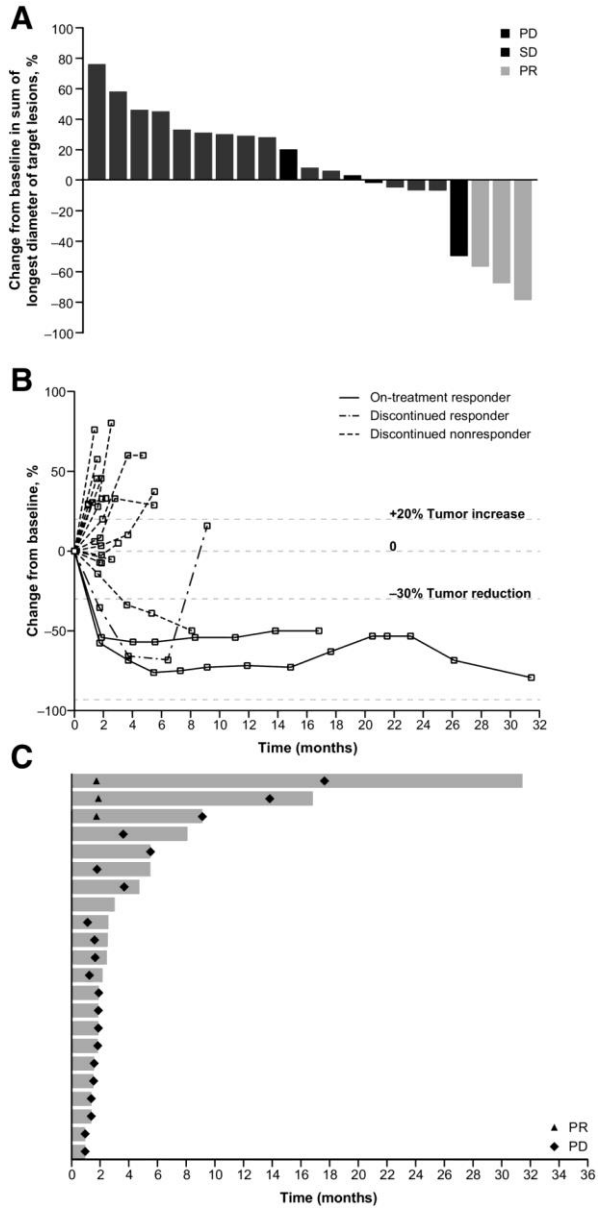


Interplay between the immune system and breast cancer might involve the modulation of the tumour microenvironment, endocrine factors, pro-inflammatory status and immune cells

Immunomodulation by Antiendocrine Treatment in ER+ BC

- **Tamoxifen and Fulvestrant: 2-3 Fold Increase in Tumor Antigens in vitro and in mice (R. Jaini et al., Oncotarget, 2017)**
- **Tamoxifen-Mediated Neutrophil Stimulation in vitro and in vivo (R. Corriden et al., Nat. Commun., 2015)**
- **Tamoxifen Reduces Numbers of Myeloid Derived Suppressor Cells, Increases Effector and Cytotoxic T Cells (N. Svoronos et al., Cancer Discov. 2017)**
- **Letrozole Reduces the Number of Tregs in Tumour Tissue Significantly Corresponding with Treatment Response (D. Generali et al., Clin Cancer Res., 2009)**

Keynote 028 Phase Ib Study: Pembrolizumab in ER+/Her- MBC (n = 22).



Hope S. Rugo et al. Clin Cancer Res 2018;24:2804-2811

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Corner Stones of the Elimination of Tumour Cells

1. Recognizing tumour cells as „foreign“

high TMB, high MSI in any tumour

2. Inflammatory T cell environment

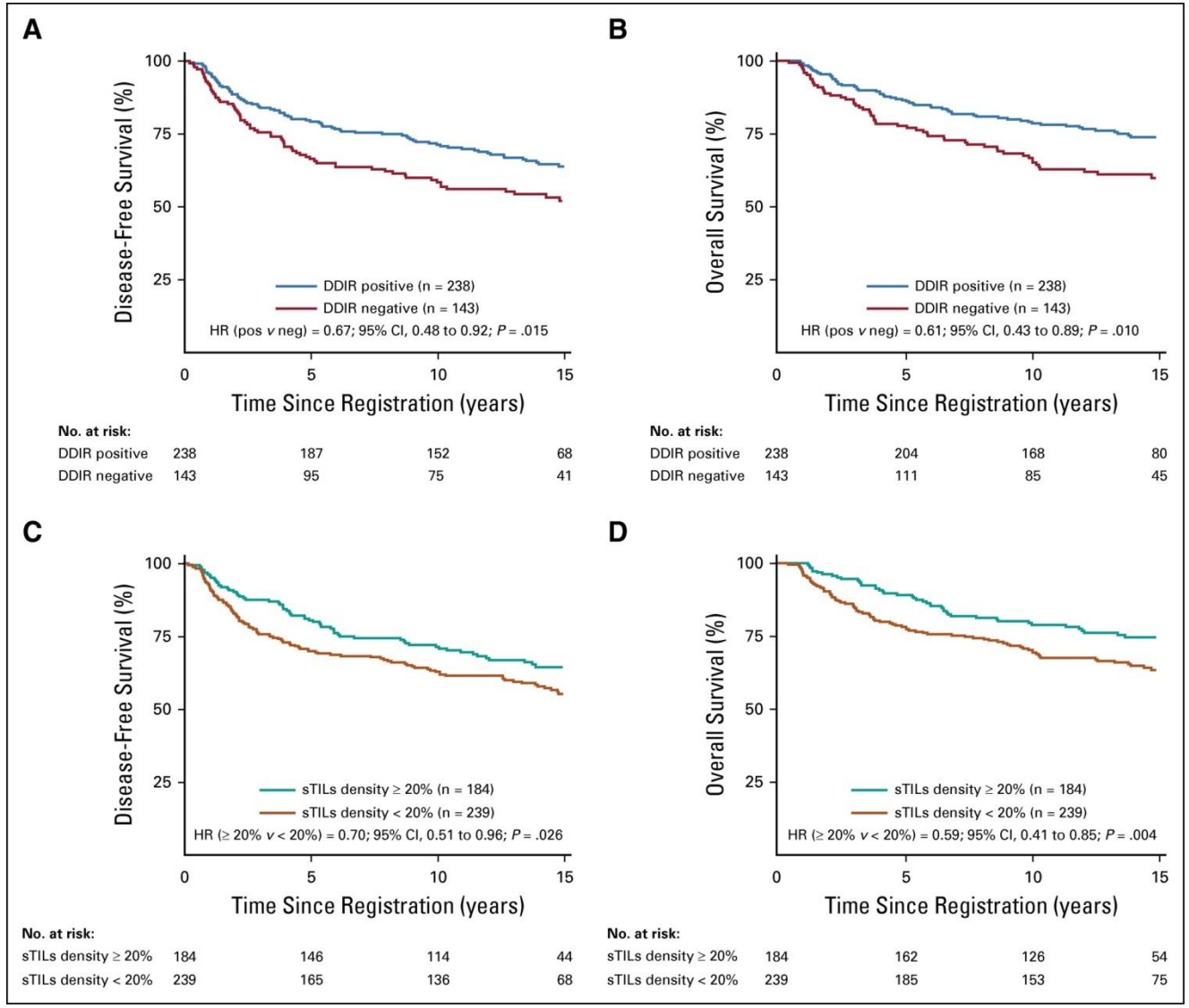
presence of effector cells, high interferon-gamma,

high PD-L1 expression

3. Microenvironmental Influence

R. Cristescu et al., Science. 2018 Oct 12;362(6411). pii: eaar3593.
doi: 10.1126/science.aar3593

DFS (A) and OS (B) by DNA Damage Immune Response Signature Status, and DFS (C) and OS (D) by Stromal Tumor-Infiltrating Lymphocyte Density in TNBC



P. Sharma et al., ; J. Clin. Oncol. 2019 DOI: https://doi.org/10.1200/JCO.19.00693

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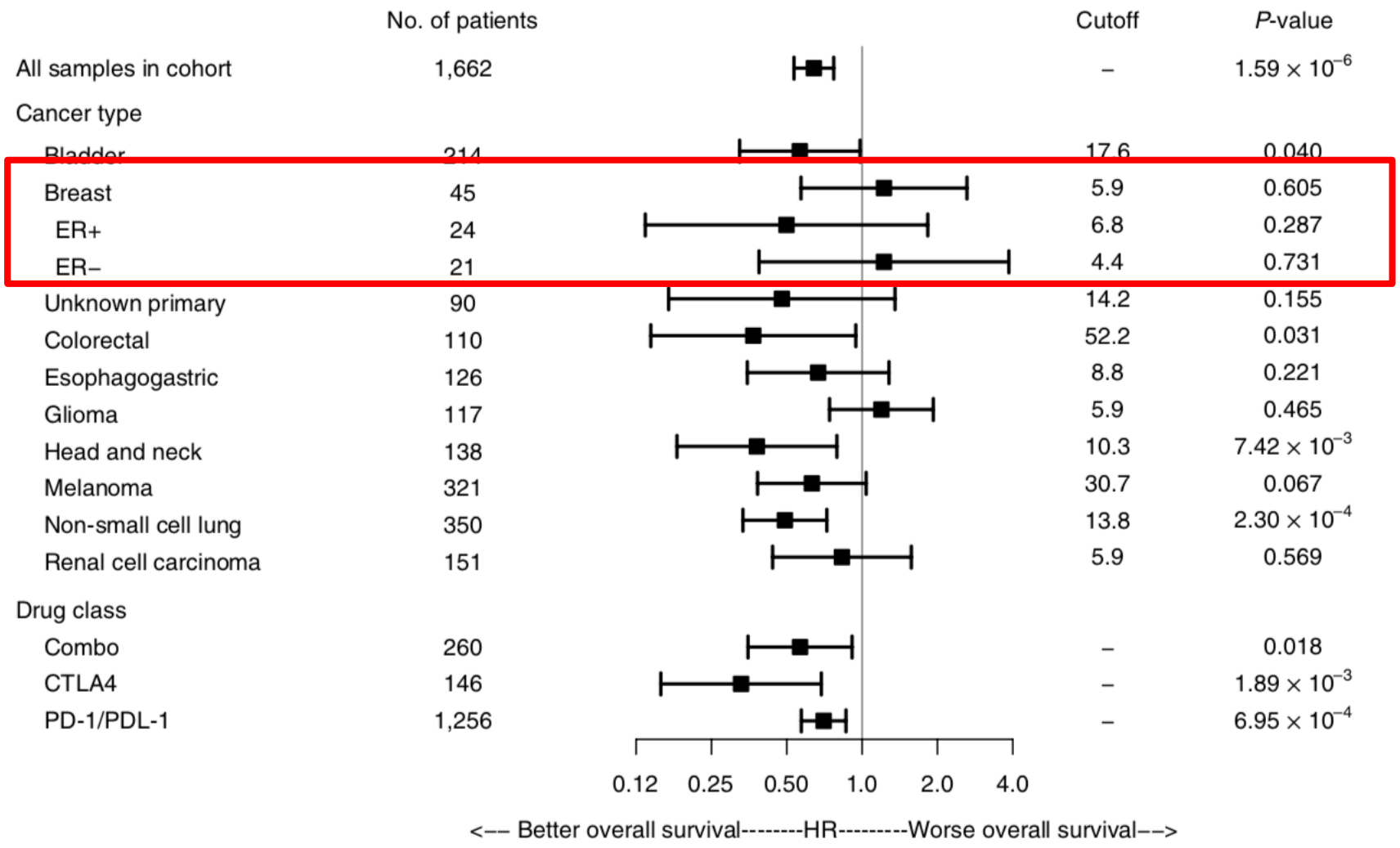
R. Cristescu et al., Science. 2018 Oct 12;362(6411). pii: eaar3593.
doi: 10.1126/science.aar3593

Effect of Nonsynonymous Mutational Load on OS of Various Cancers by ICPIs



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R.M. Samstein et al., Nature Genet.,;doi.org/10.1038/s41588-018-0312-8, 2019

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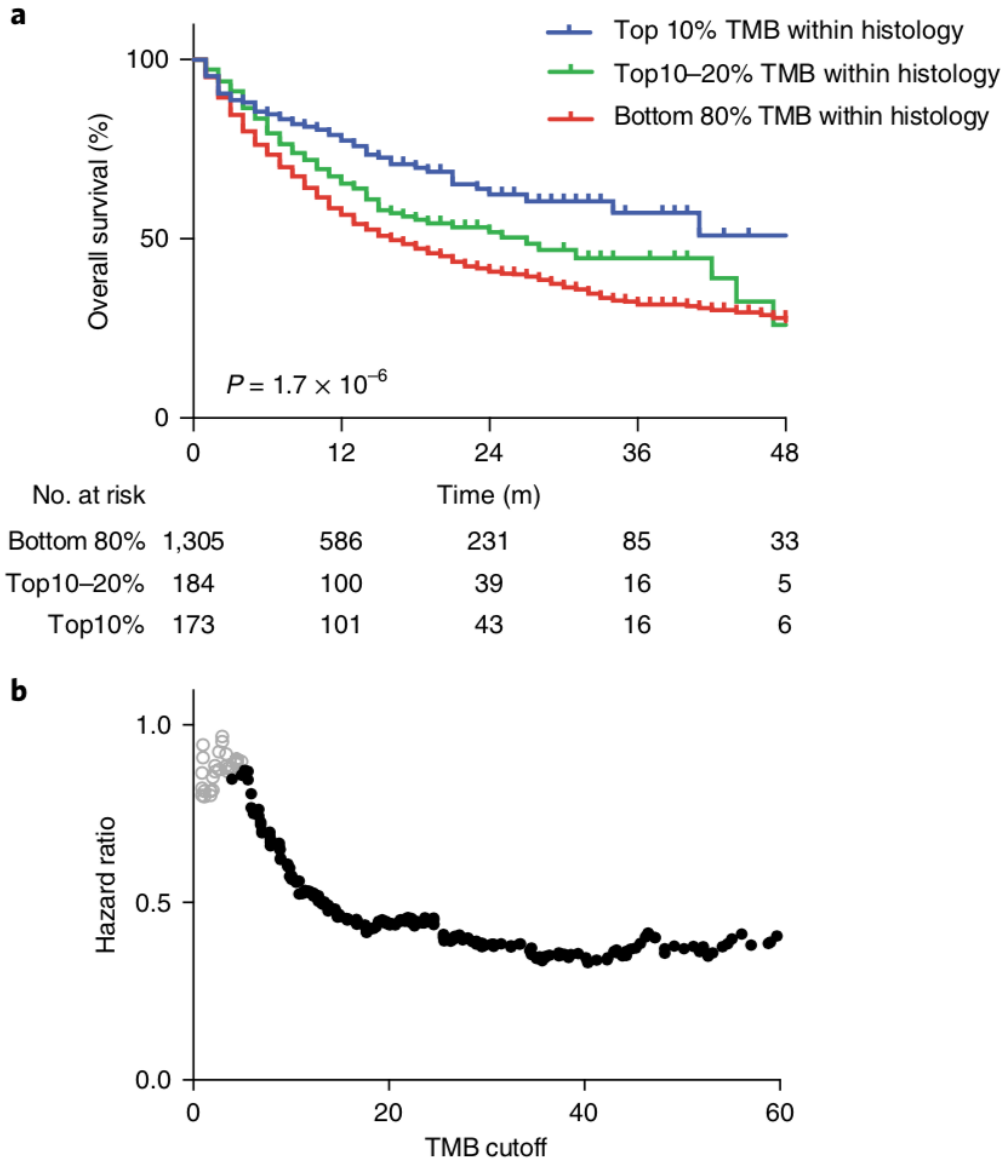
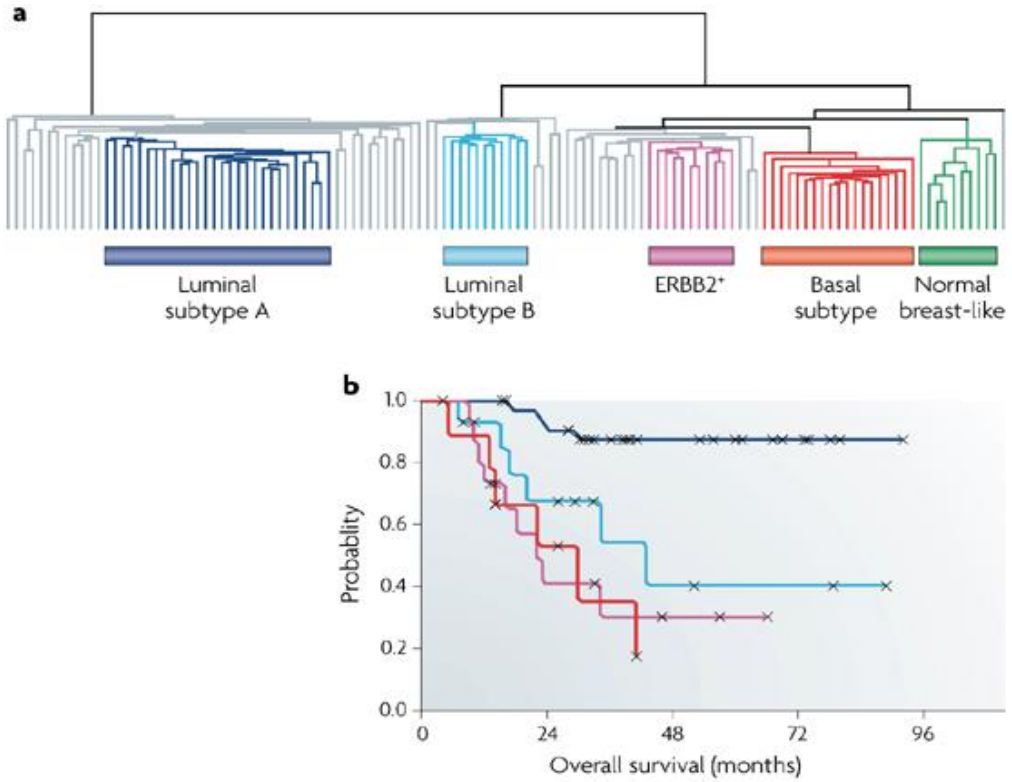
Effect of Mutational Load on OS after ICPI Treatment



R.M. Samstein et al., Nature Genet.,;doi.org/10.1038/s41588-018-0312-8, 2019

Breast Cancer Subtypes, Surrogate Immunohistochemistry and Prognosis



Typical immunohistochemistry findings:

luminal A: strongly ER+, PR vary, HER2–, ki67 low

luminal B: weakly ER+, PR vary, HER2–/+, ki67 higher

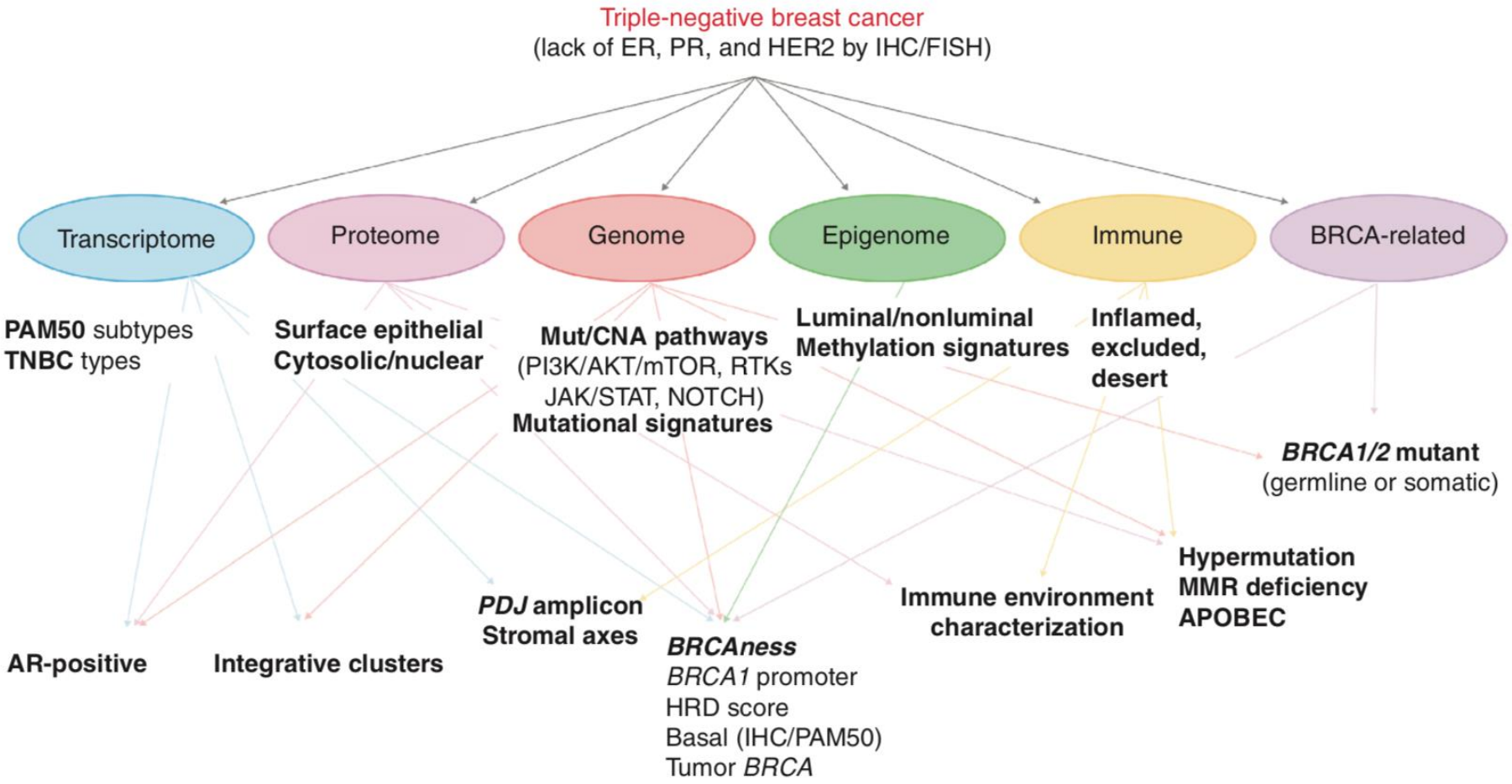
basal-like: ER–/PR–, HER2–: „triple negative"; ki67 high

HER2 amplified: ER/PR vary, HER2 positive, ki67 high

T. Sørliea et al., PNAS 2001

Heterogeneity of Triple Negative Breast Cancer

A.C. Garrido-Santo et al., Cancer Discov. Doi: 10.1158/2159-8290.CD-18-1177, 2019



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Gene Expressions in TNBC

Subtype Genes	Gene Expression Profile / High Expression of
Basal-like 1 (BL-1)	cell cycle progression, cell division, and DNA damage response pathways
Basal-like 2 (BL.2)	cell cycle progression, cell division and growth factor signalling
Immunomodulatory	immune processes and cell signaling
Mesenchymal	motility and extracellular matrix
Mesenchymal stem-like	motility, extracellular matrix, growth factor signalling (consistent with claudin-low)
Luminal androgen receptor	hormonally regulated pathways

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R. Cristescu et al., Science. 2018 Oct 12;362(6411). pii: eaar3593. doi: 10.1126/science.aar3593

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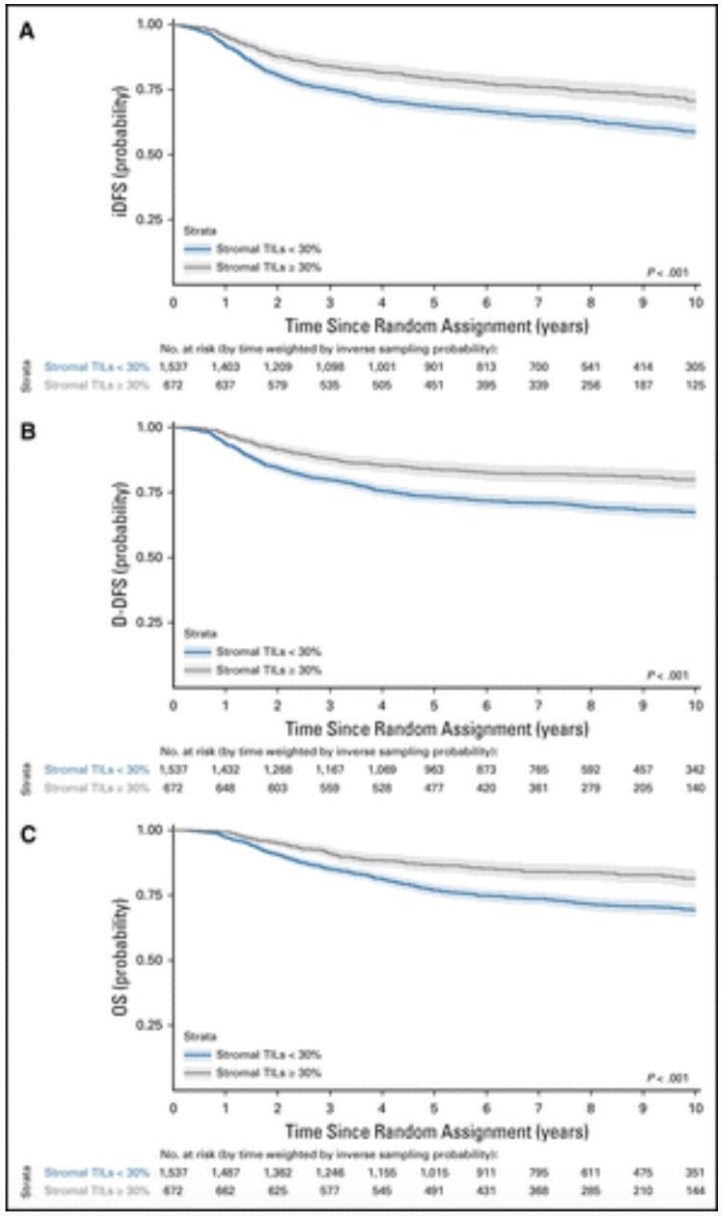
Triple Negative Breast Cancer: Prognostic Effect of Stromal TILs Dichotomized at </> 30%



DFS

Distant –DFS

OS

S. Loi et al., J Clin Oncol 37, 2019

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TNBC: Prognostic Effect of Stromal TILs Dichotomized at </> 30%

sTILs significantly lower with:

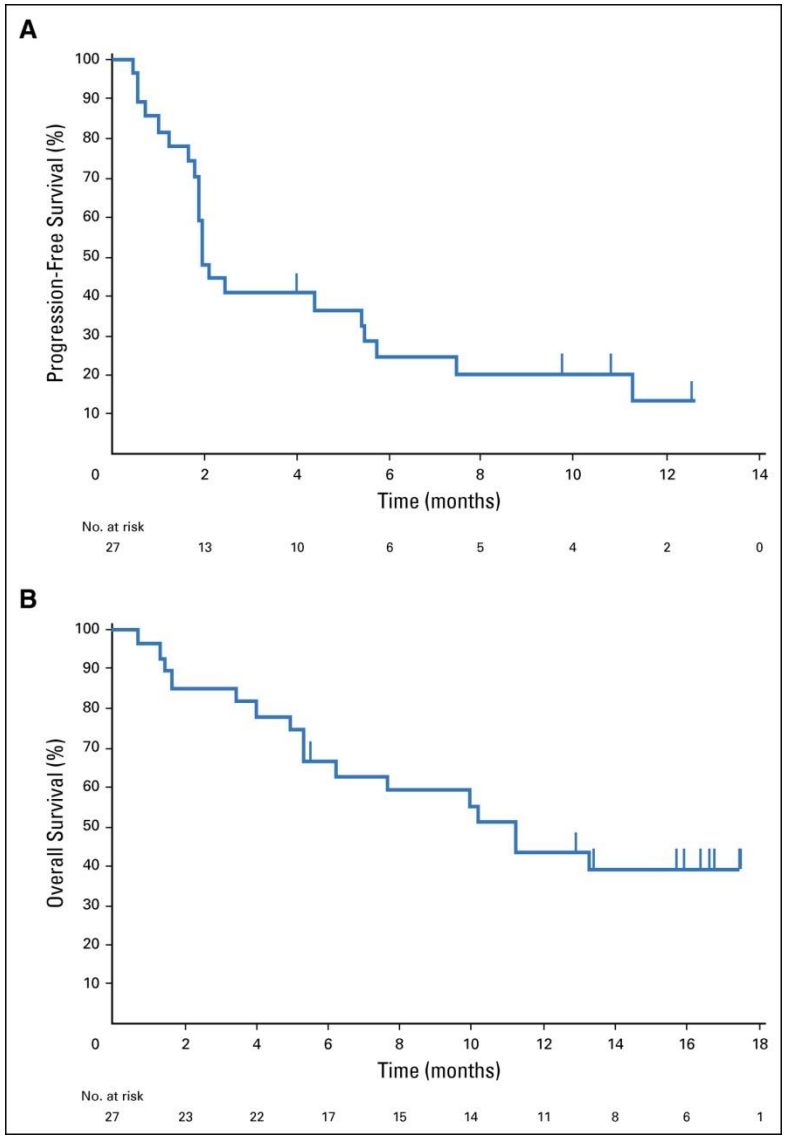
- *older age (p=001)*
- *larger tumour size (p=0.01)*
- *more nodal involvement (p=0.02)*
- *lower histologic grade (p=0.001)*

S. Loi et al., J Clin Oncol 37, 2019

Full Publications on Immune Checkpoint Inhibitors in MBC

	Study	*Population*
Monotherapy:		
TNBC	*Keynote 012 (Phase Ib)*	*heavily pretreated*
TNBC	*Keynote 086 (Phase II)*	*previously untreated*
	Keynote 028 (Phase Ib)	*ER+/Her−*
	NCT01375842 (Phase Ia)	*TNBC*
	JAVELIN (Phase Ib)	*all BC, unselected*
Combinations with Chemotherapy:		
	Eribulin + Pembrolizumab	*TNBC*
	Abraxane + Atezolizumab (IMpassion130)	*TNBC*

Keynote 012 Phase Ib Study of Pembrolizumab in Patients with Pretreated, PD-L1 Positive TNBC: PFS and OS



R Nanda et al., *J Clin Oncol* 2016; 34: 2460-2467.; DOI: 10.1200/JCO.2015.64.8931

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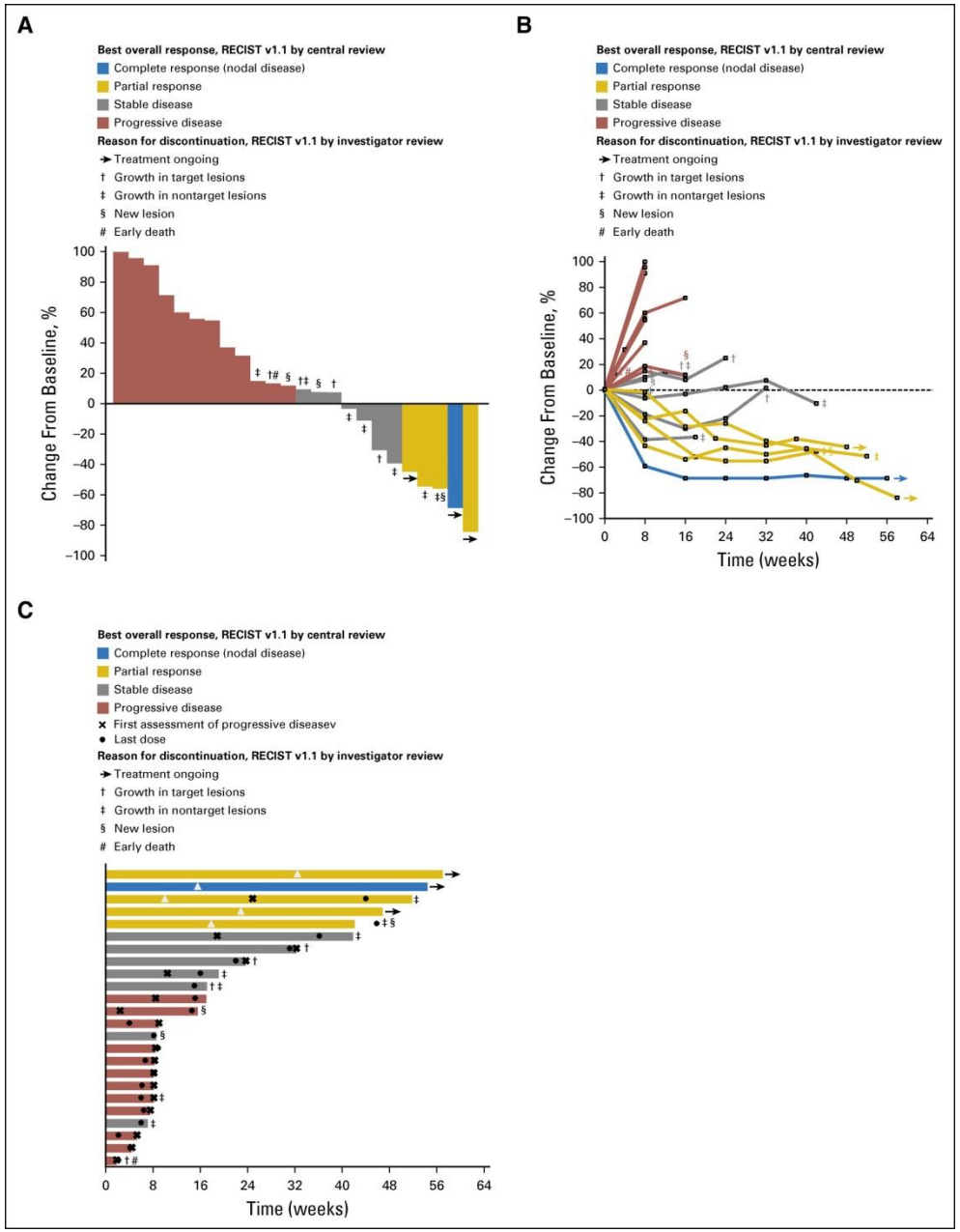
Keynote 012 Phase Ib Study: Responses



R Nanda et al., *J Clin Oncol* 2016; 34: 2460-2467.; DOI: 10.1200/JCO.2015.64.8931

Keynote 012 Phase Ib Study of Pembrolizumab in PD-L1 Positive TNBC

Response Type	Patients Evaluable for Response, N = 27*
Overall response rate, % (95% CI)	18.5 (6.3 to 38.1)
Best overall response, No. (%)	
Complete response†	1 (3.7)
Partial response†	4 (14.8)
Stable disease	7 (25.9)
Progressive disease	13 (48.1)
No assessment‡	2 (7.4)

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R Nanda et al., *J Clin Oncol* 2016; 34: 2460-2467.; DOI: 10.1200/JCO.2015.64.8931

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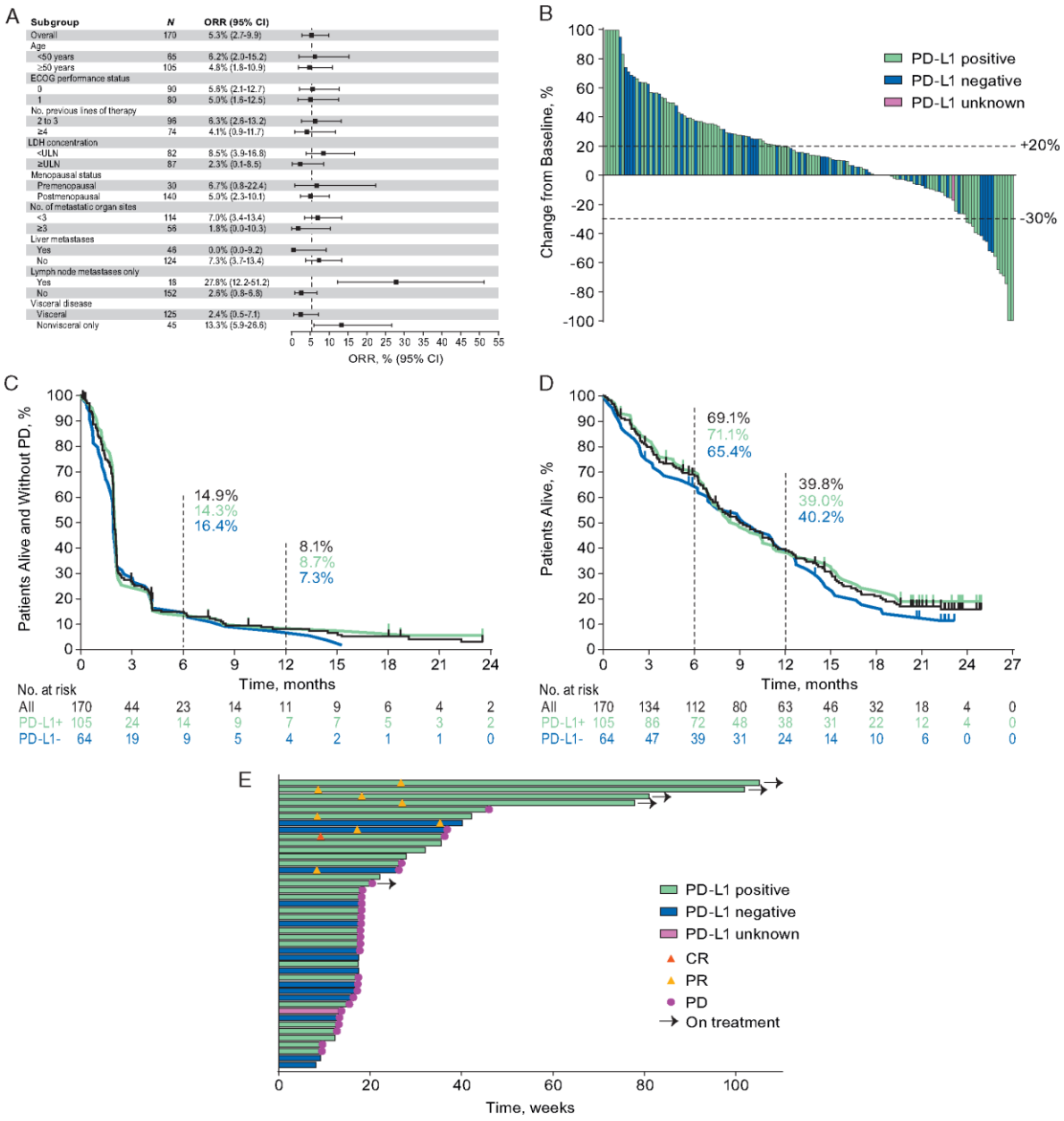
Pembrolizumab Previously Treated Metastatic TNBC: Keynote 086 Phase II Study

S. Adams et al., Ann. Oncol. 30: 397–404, 2019, https://doi.org/10.1093/annonc/mdy517

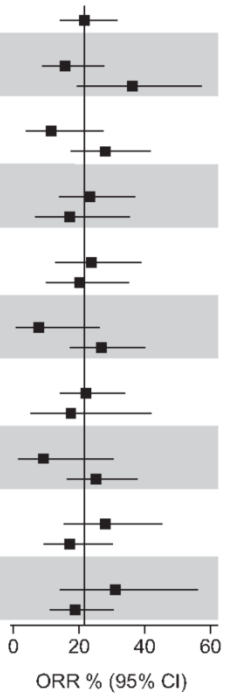


Pembrolizumab for Previously Untreated, PD-L1-positive, Metastatic TNBC: Phase II KEYNOTE-086 Study

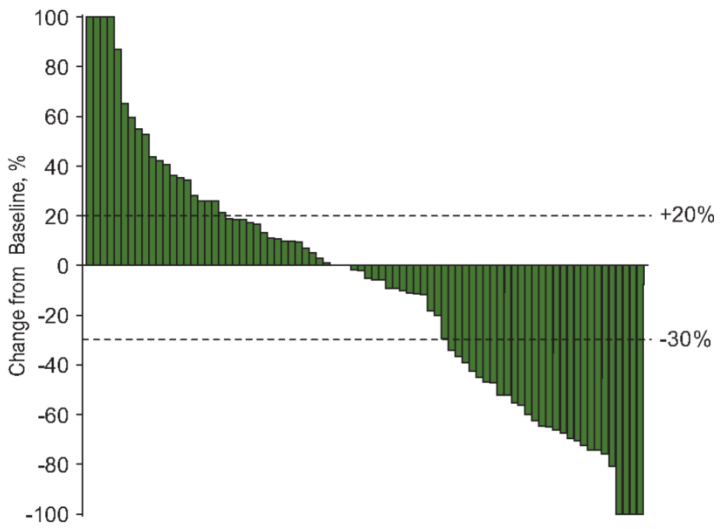
S. Adams et al., Ann Oncol. published online November 26, 2018. doi:10.1093/annonc/mdy518

A

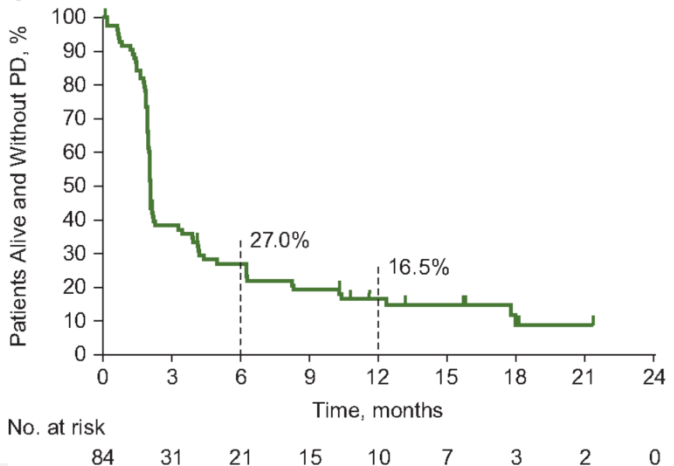
	N	ORR	95% CI
Overall	84	21.4	(13.9, 31.4)
Age group 1			
<65	62	16.1	(8.8, 27.4)
≥65	22	36.4	(19.6, 57.1)
Age group 2			
<50	34	11.8	(4.1 27.2)
≥50	50	28.0	(17.4, 41.8)
ECOG PS			
0	55	23.6	(14.2, 36.5)
1	29	17.2	(7.1, 35.0)
Lactate dehydrogenase			
LDH < ULN	42	23.8	(13.3, 38.7)
LDH ≥ ULN	40	20.0	(10.2, 35.0)
Menopausal status			
Premenopausal	25	8.0	(1.1, 26.1)
Postmenopausal	59	27.1	(17.4, 39.7)
No. of metastatic organ sites			
<3	67	22.4	(14.0, 33.8)
≥3	17	17.6	(5.4, 41.8)
Liver metastases			
Present	21	9.5	(1.4, 30.1)
Absent	63	25.4	(16.2, 37.4)
Visceral metastases			
Non-visceral only	32	28.1	(15.4, 45.5)
Visceral	52	17.3	(9.2, 30.0)
Lymph node metastases			
Lymph node metastases only	16	31.3	(13.9, 55.9)
Other	68	19.1	(11.4, 30.1)



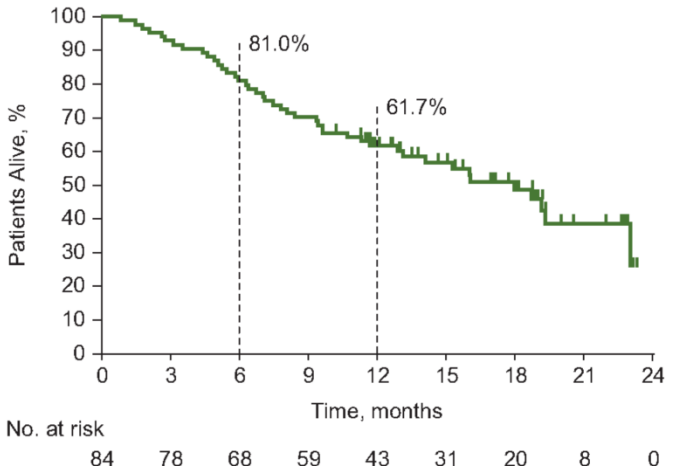
B



C



D



A: ORR

B: Change from baseline

C: PFS, N=84

D: OS

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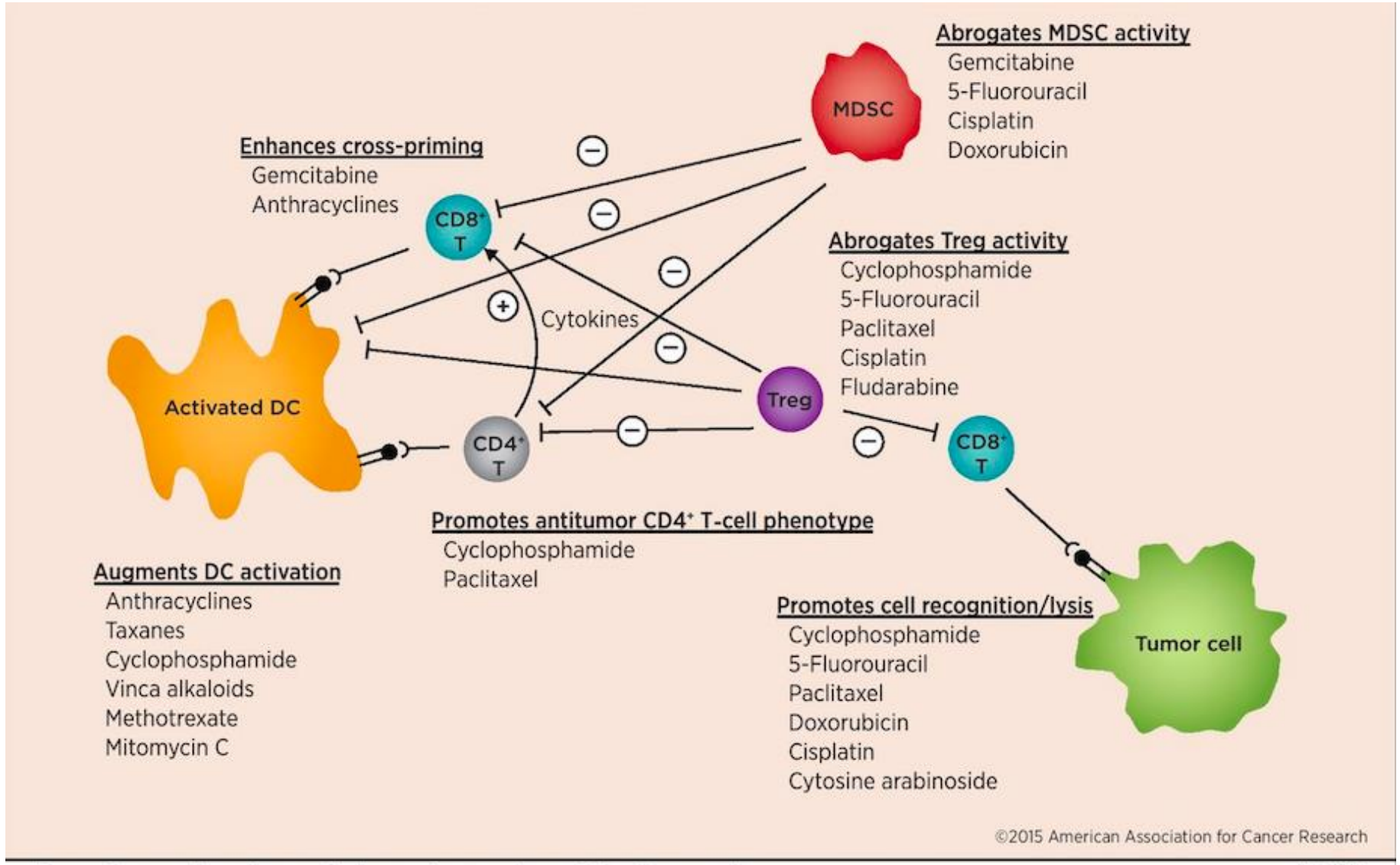
Long-Term Clinical Outcomes and Biomarker Analyses of Atezolimzumab Monotherapy in TNBC: A Phase I Study

	ORR	OS (median)
PD-L1 >1% (iCS, n=91)	12%	10.1 mos.
PD-L1 <1% (iCS, n=21)	0%	6.0 mos.

L.A. Emens et al., JAMA Oncol. Doi: 10.1001/jamaoncol.2018.4224, 2018

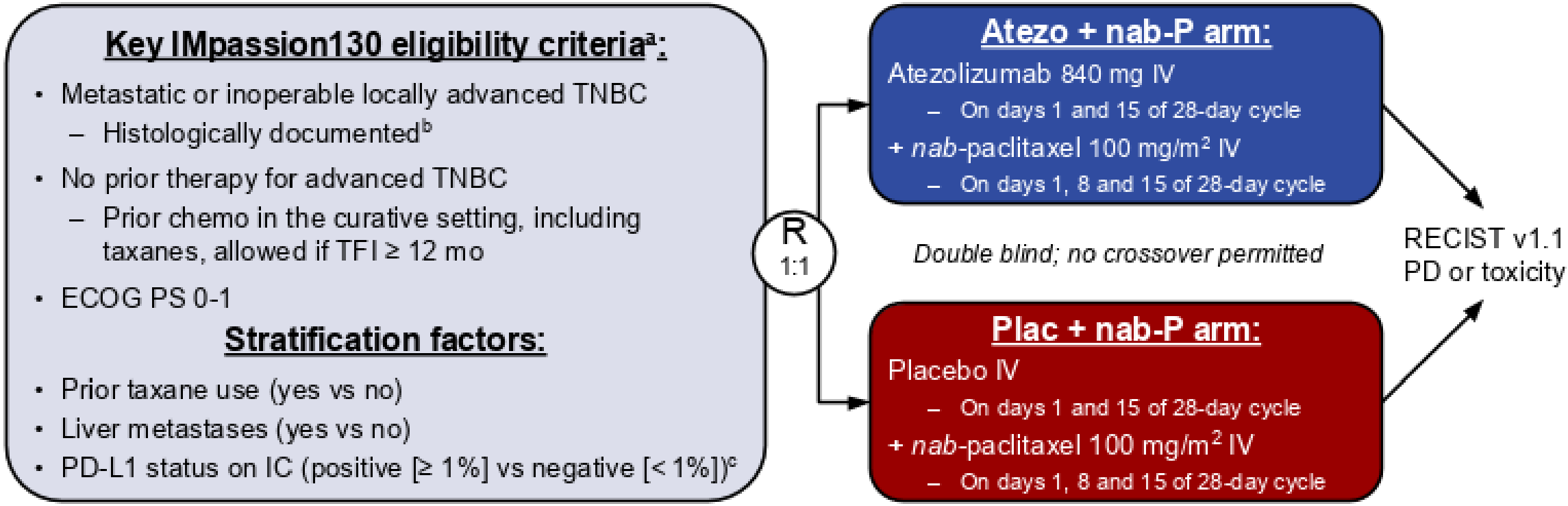
Chemotherapy Modulates Tumor Immunity apart from Immunogenic Cell Death

L.A. Emens, G. Middleton: Cancer Immunol. Res. 2015



Triple Negative Breast Cancer (TNBC): IMpassion 130

P. Schmid et al., N. Engl. J. Med. 379: 2108, 2018



- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

IC, tumour-infiltrating immune cell; TFI, treatment-free interval. [a] ClinicalTrials.gov: NCT02425891. [b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). [d] Radiological endpoints were investigator assessed (per RECIST v1.1).

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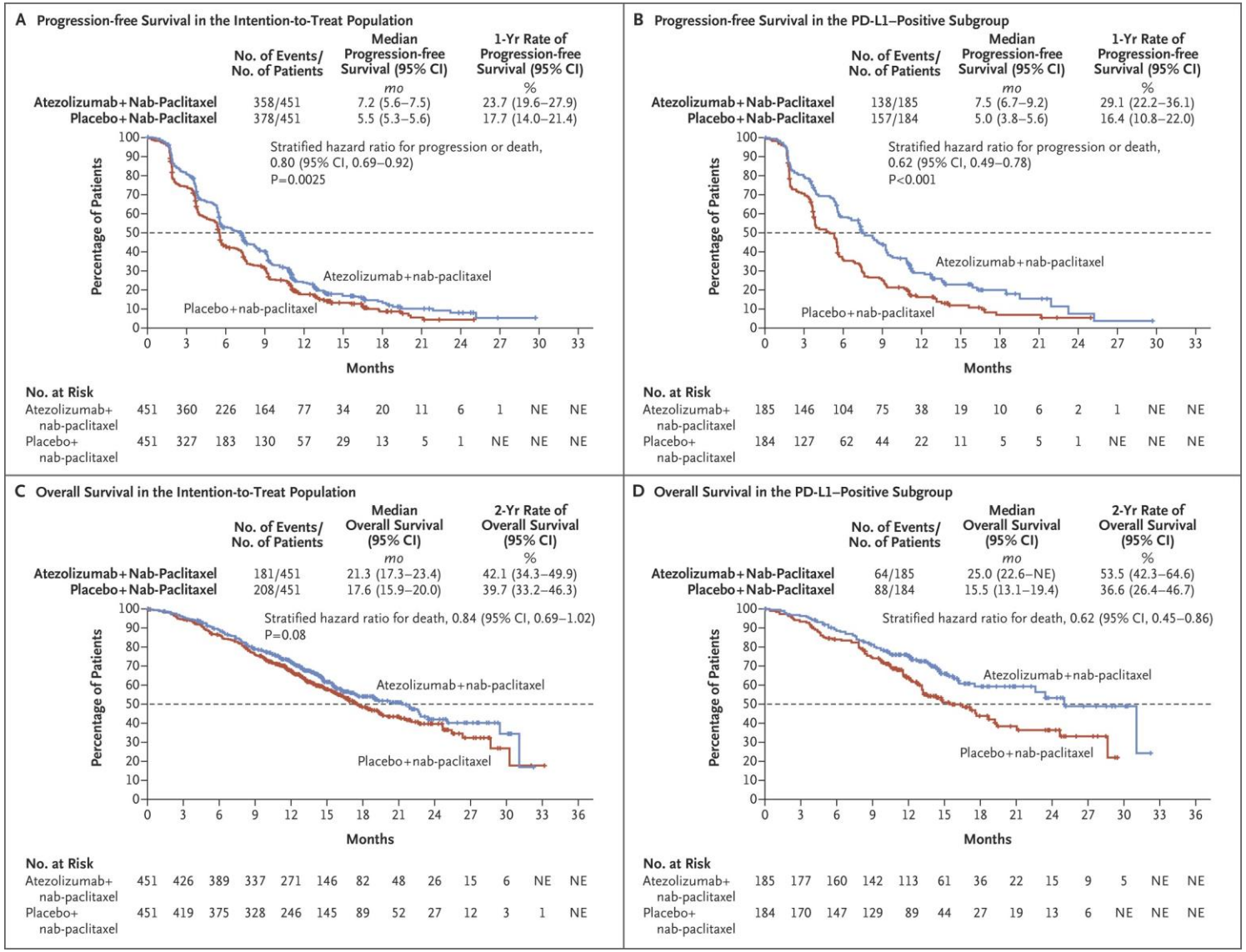
IMpassion130: Progression-Free and Overall Survival.



P. Schmid et al., N. Engl. J. Med. 379: 2108, 2018

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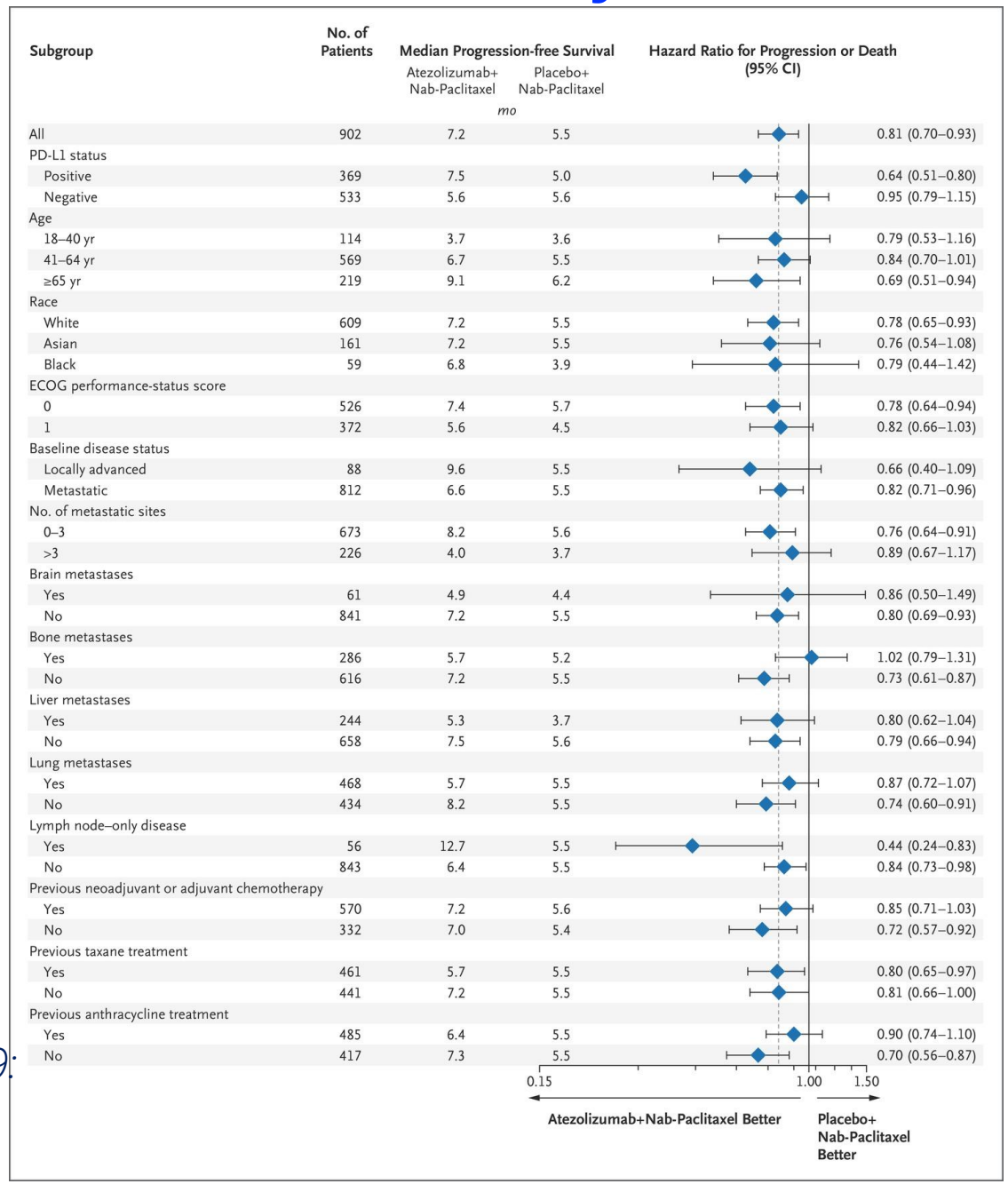
IMpassion 130: Forest-Plot Analyses of PFS in Subgroups.



P. Schmid et al., N. Engl. J. Med. 379: 2108, 2018

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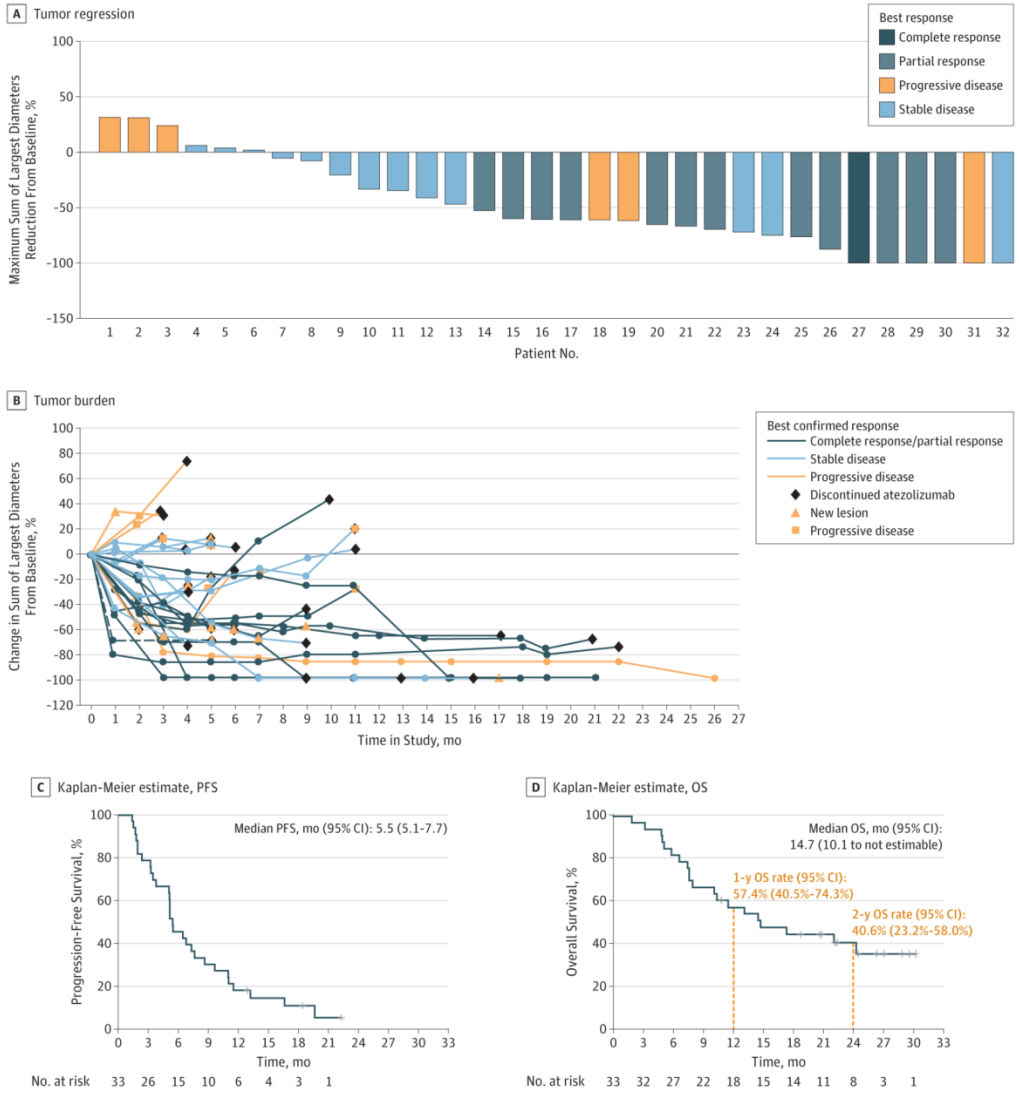
Atezolizumab plus nab-Paclitaxel in the Treatment of Metastatic TNBC with 2-Year Survival Follow-up: A Phase Ib Clinical Trial



JAMA Oncol. 2019;5(3):334-342. doi:10.1001/jamaoncol.2018.5152

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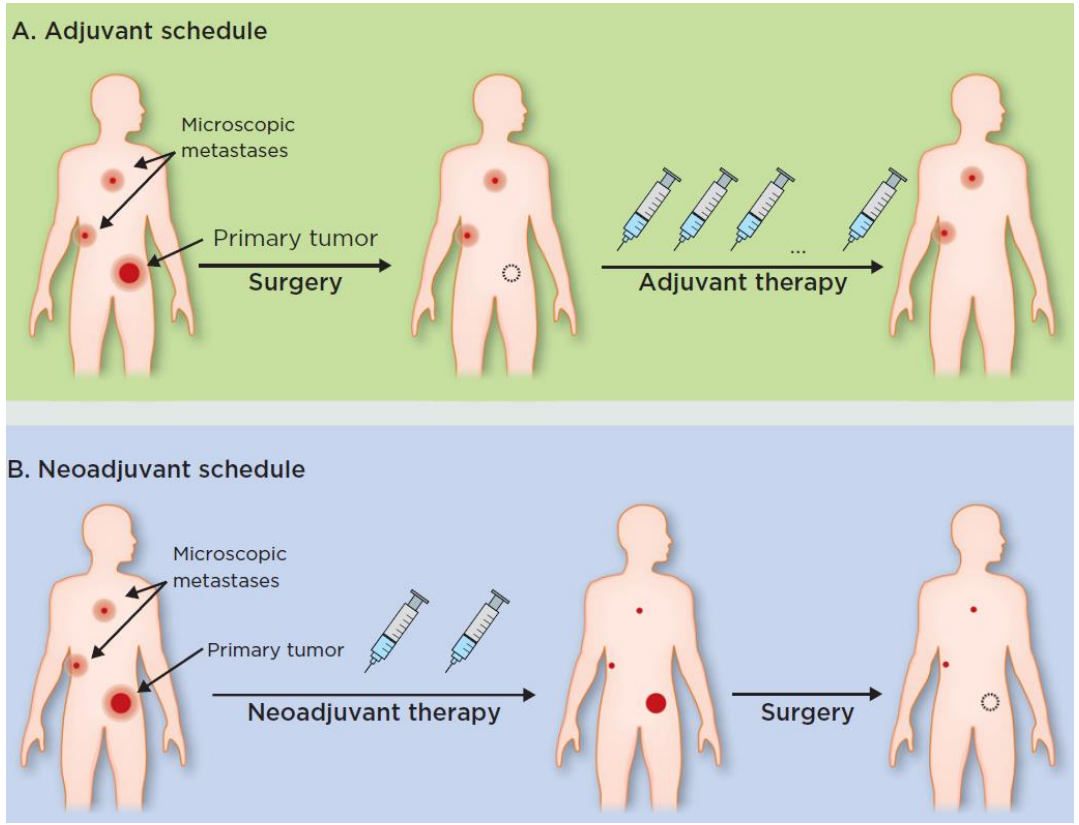
Neoadjuvant Treatment Approaches: Advantages

O'Donnel et al., Clin Cancer Res 2019



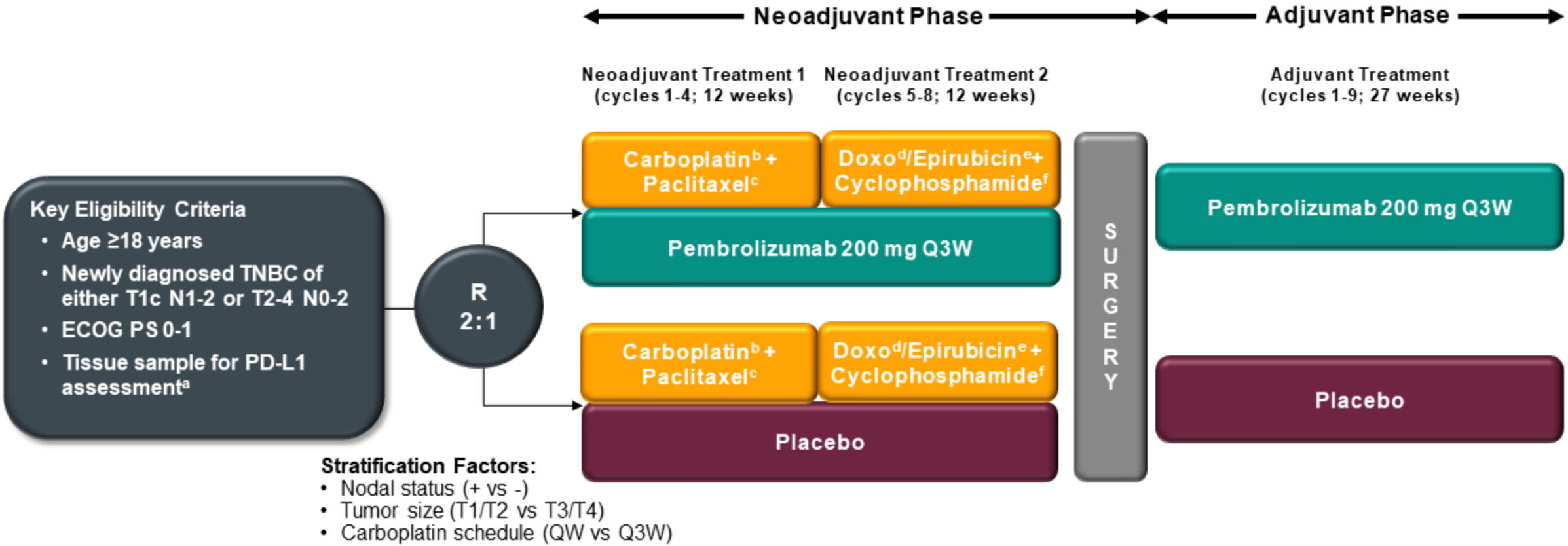
General

- **Reduction of tumor burden to allow improved surgery**
- **Material to determine on-treatment therapy response**
- **Pathological response data to allow prediction of relapse-free survival**

Immunotherapy

- **The induced anticancer immune response should be supported by enhanced neoantigen load**
- **Presence of additional (exhausted) tumor-resident T-cell clones**

KEYNOTE-522 Study Design (NCT03036488)

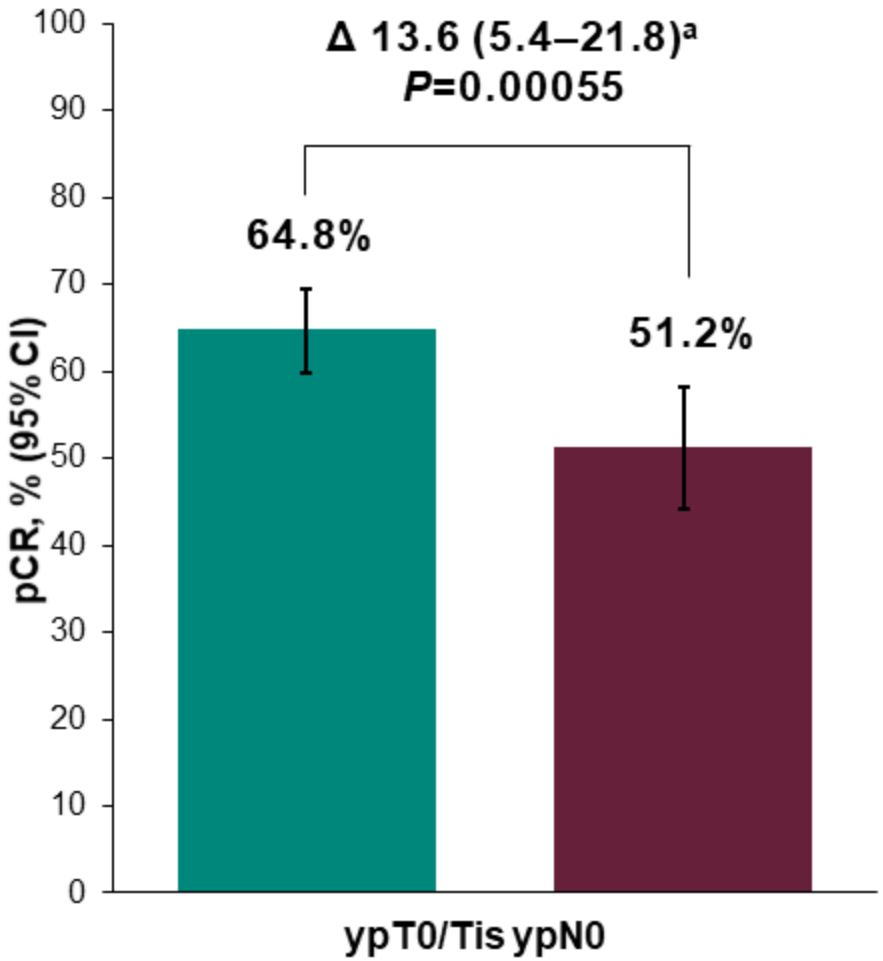


Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 QW.
[c]Paclitaxel dose was 80 mg/m^2 QW.
[d]Doxorubicin dose was 60 mg/m^2 Q3W.
[e]Epirubicin dose was 90 mg/m^2 Q3W.
[f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

Definitive pCR Analysis



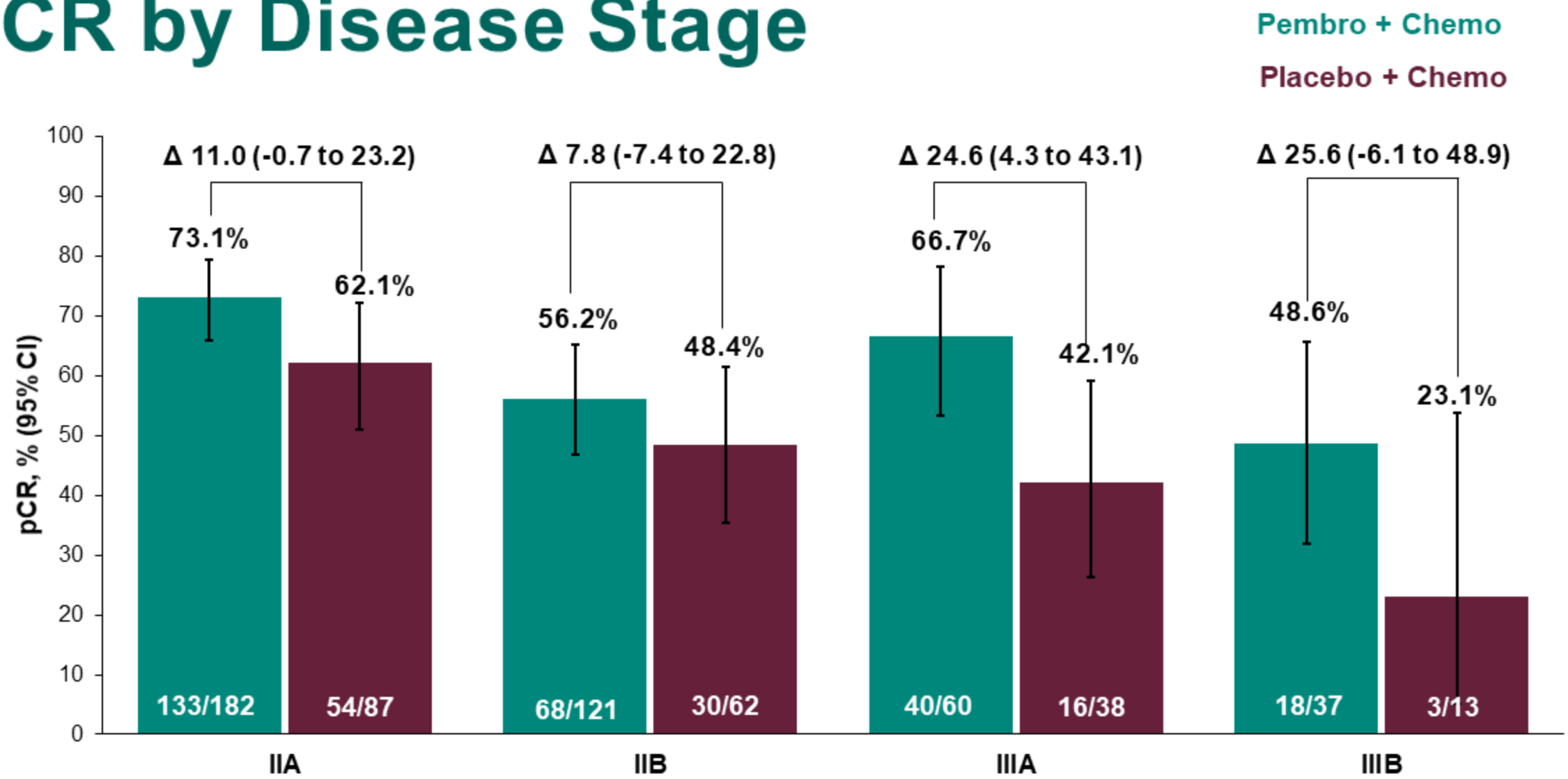
- Definitive pCR analysis to test primary hypothesis of pCR based on prespecified first 602 patients (pre-calculated P value boundary for significance of 0.003)
- Consistent benefit seen with pCR defined as ypT0 ypN0 and ypT0/Tis

Placebo + Chemo

Pembro + Chemo

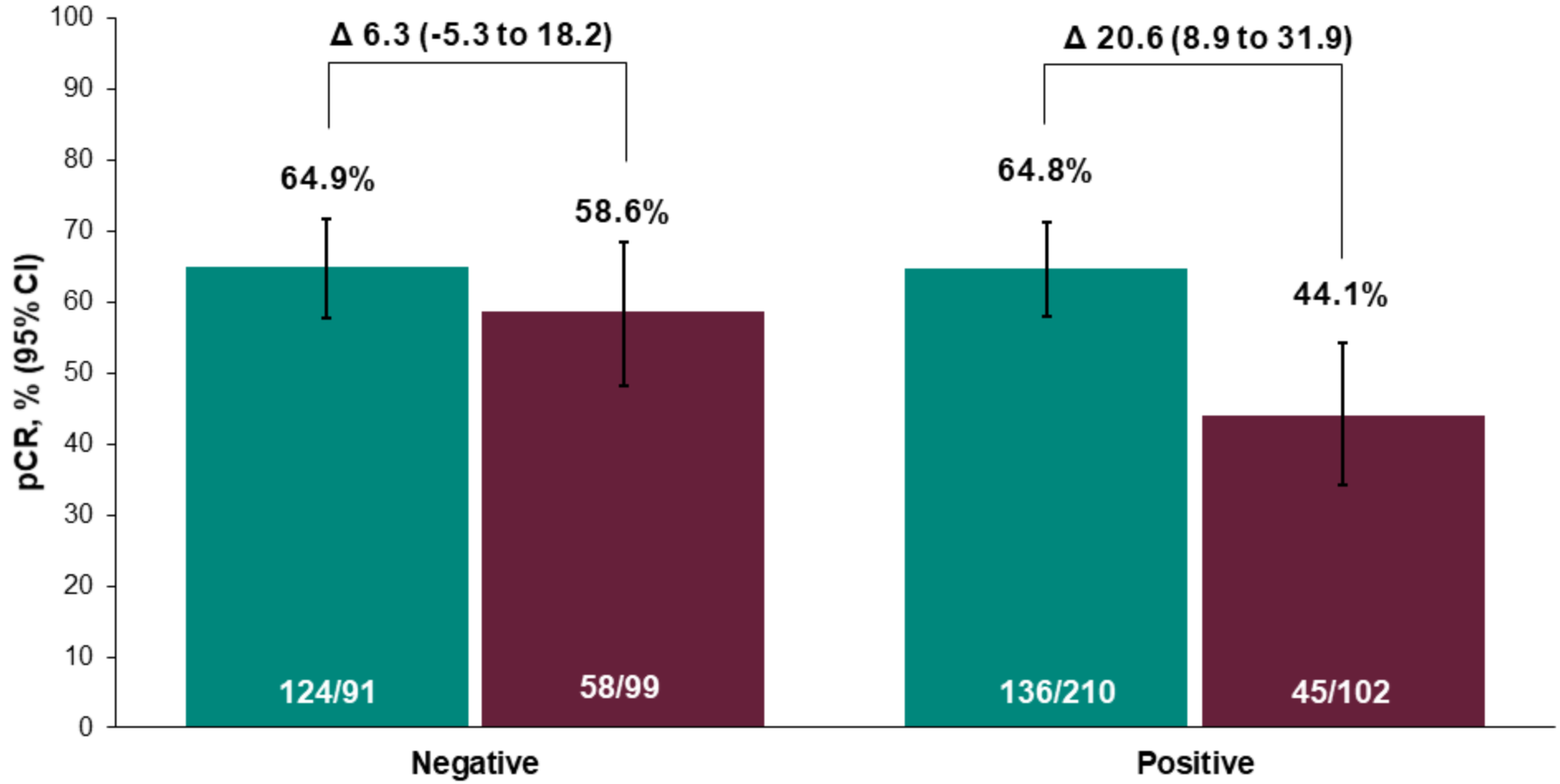
[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. Data cutoff date: September 24, 2018.

pCR by Disease Stage



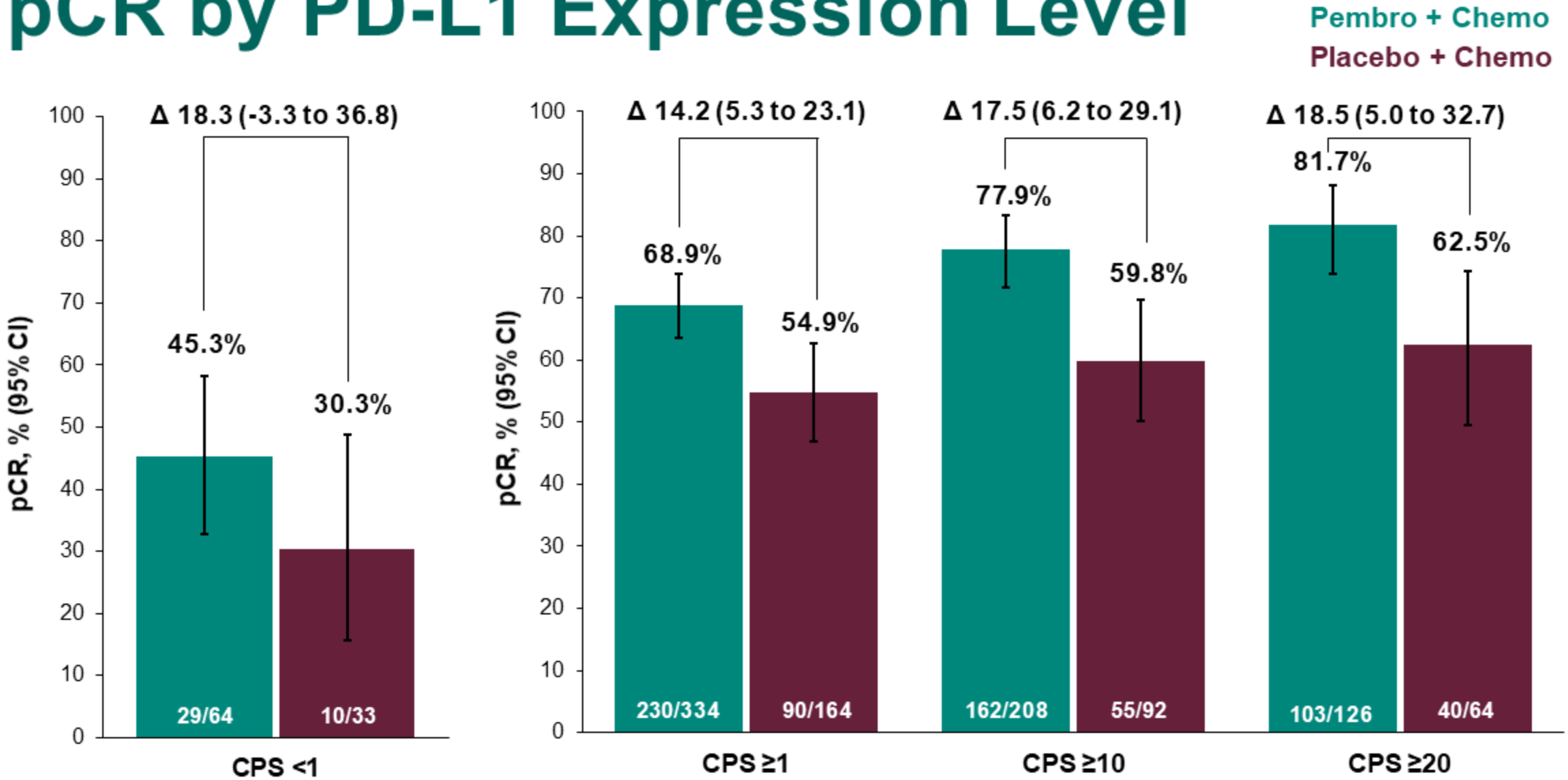
Post-hoc analysis. Estimated treatment difference based on unstratified Miettinen & Nurminen method. Data cutoff date: September 24, 2018.

pCR by Lymph Node Involvement



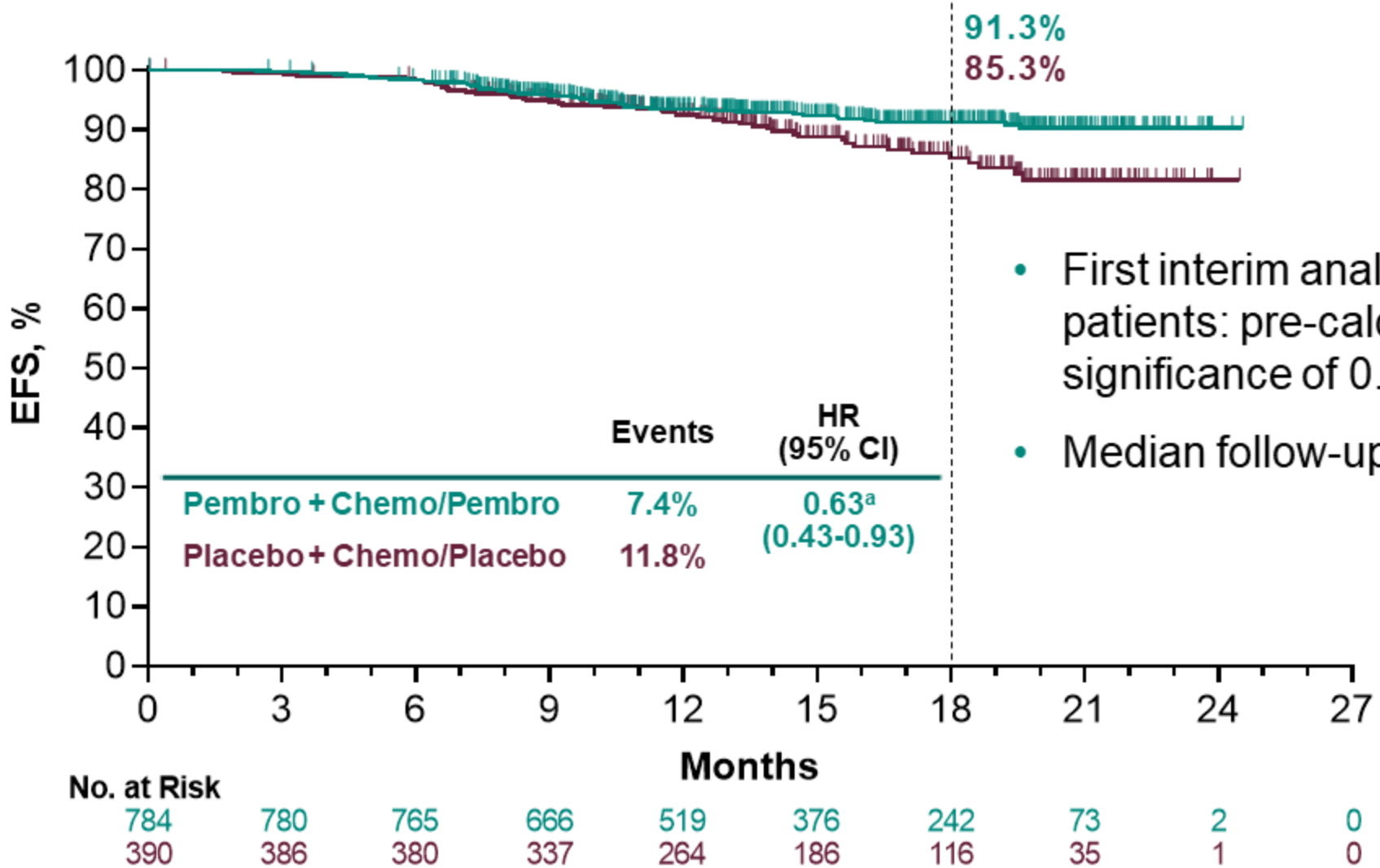
Pre-specified analysis. Lymph node involvement was determined by the study investigator by physical exam, sonography/MRI and/or biopsy. Estimated treatment difference based on unstratified Miettinen & Nurminen method. Data cutoff date: September 24, 2018.

pCR by PD-L1 Expression Level



Pre-specified analysis. PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using 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. Estimated treatment difference based on Miettinen & Nurminen method stratified by nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4) and choice of carboplatin (Q3W vs QW). Data cutoff date: September 24, 2018.

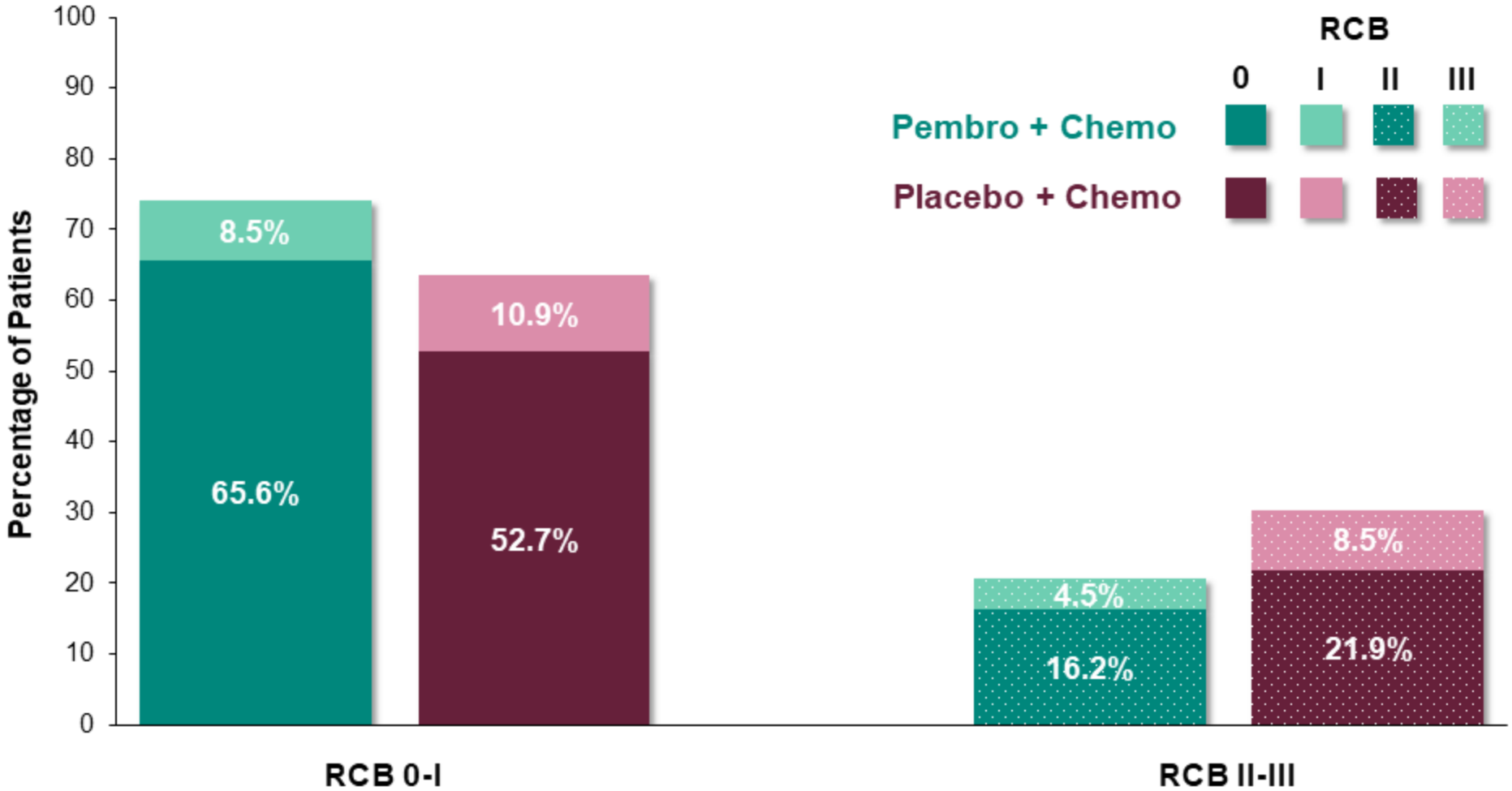
First Pre-planned Interim Analysis for EFS



- First interim analysis of EFS based on 1174 patients: pre-calculated P value boundary for significance of 0.000051 (HR <0.4)
- Median follow-up, 15.5 months

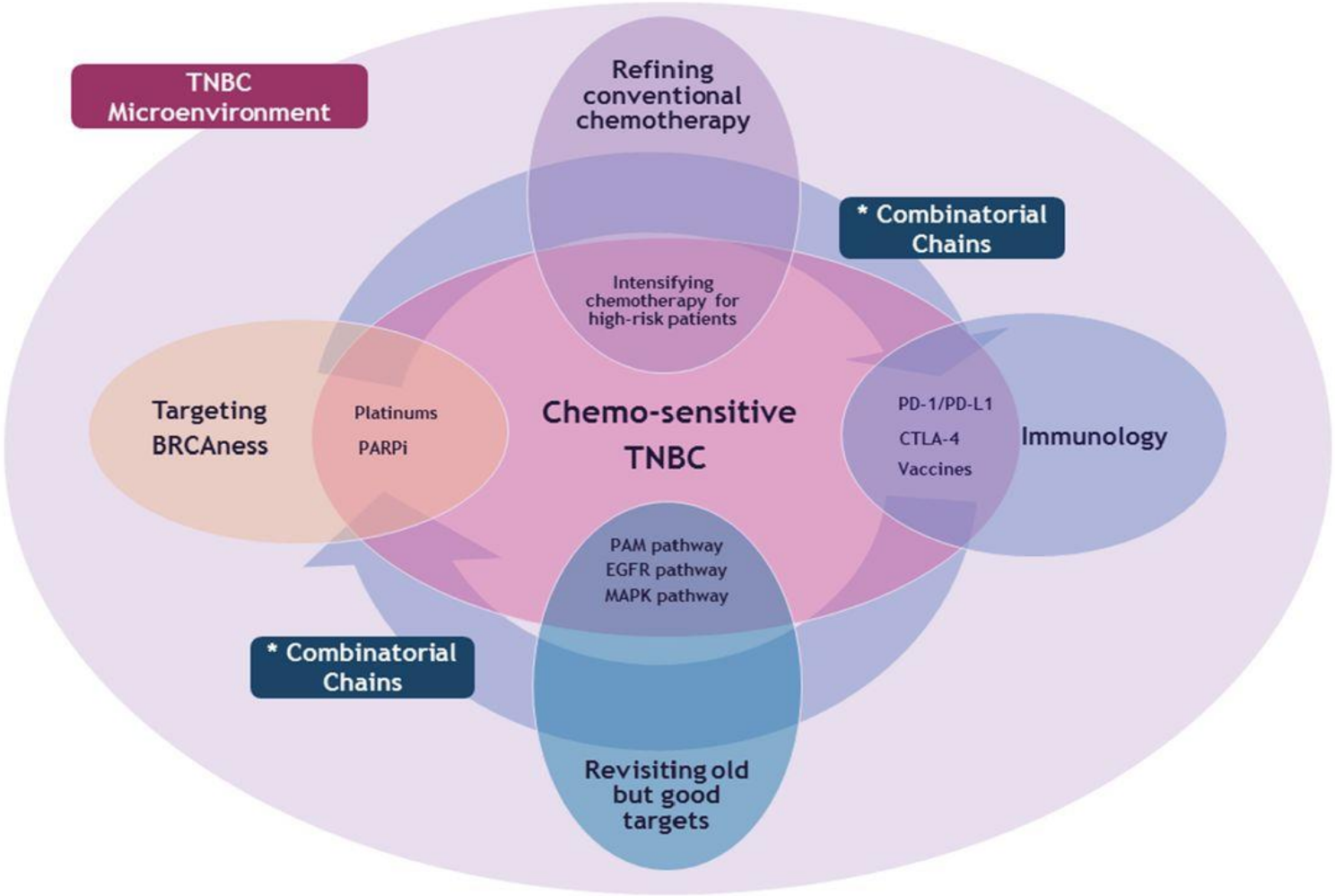
[a]Pre-specified P value boundary of 0.000051 not reached at this analysis (the first interim analysis of EFS). Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff April 24, 2019.

Residual Cancer Burden



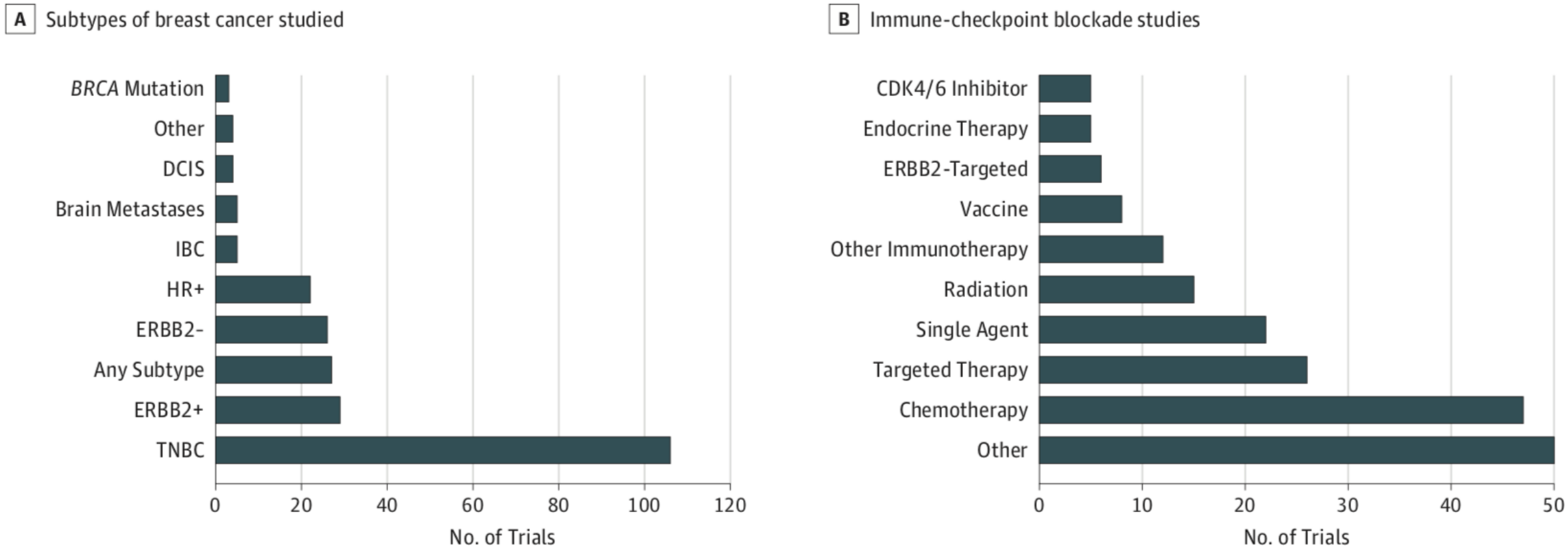
Data cutoff date: April 24, 2019.

Therapeutic Strategies in Patients with TNBC Based on its Chemosensitivity and Immune-Molecular Heterogeneity



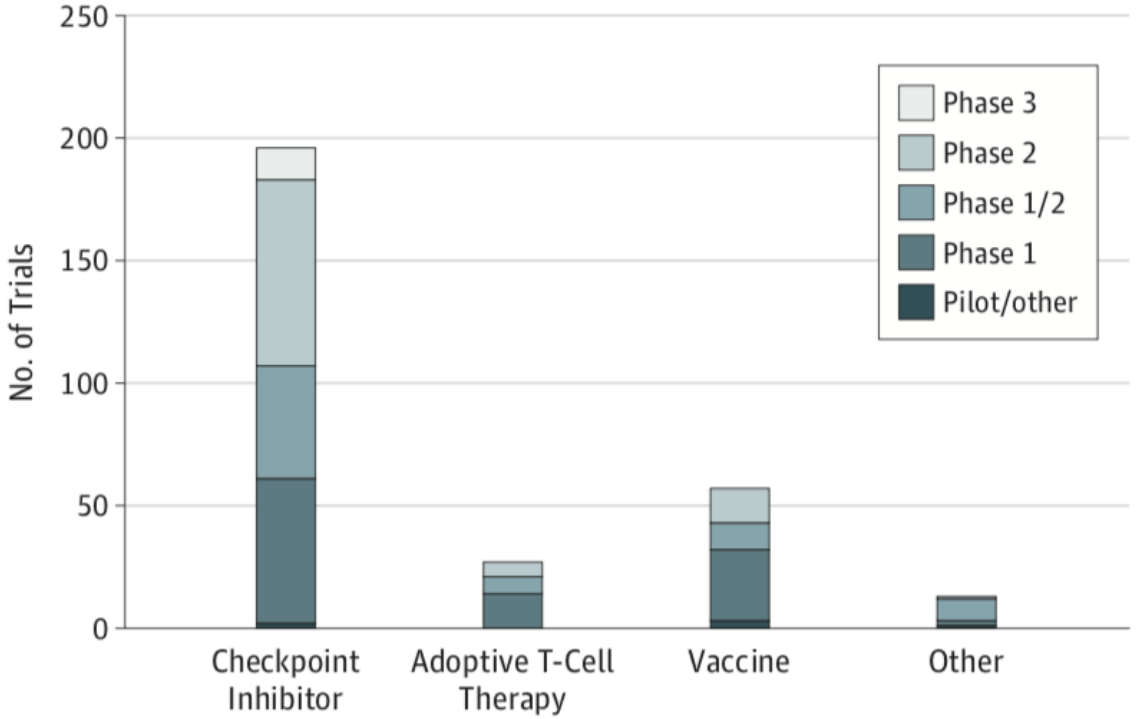
Ji Hyun Park et al. ESMO Open 2018;3:e000357

Breast Cancer Immunotherapy Trials 2020



S. Adams et al., JAMA Oncol. 5: 1205, 2019

Breast Cancer Immunotherapy Trials by Type of Immunotherapeutic Agent and by Study Phase



No. of trials	Checkpoint Inhibitor	Adoptive T-Cell Therapy	Vaccine	Other
Phase 3	13	0	0	0
Phase 2	76	6	14	1
Phase 1/2	46	7	11	9
Phase 1	59	14	29	2
Pilot/other	2	0	3	1

S. Adams et al., JAMA Oncol. 5: 1205, 2019

Immune Mechanisms in Breast Cancer: Conclusions

- *In a series of phase Ib and II trials, monotherapy with immune checkpoint inhibition has suggested efficacy in MBC of various characteristics and disease types, particularly when PD-L1 is expressed in triple-negative cancers and anti-PD-L1 treatment used early in the treatment sequence.*
- *The Impassion130 study is the first randomized trial which has further elaborated on the concept in advanced TNBC proving the previously acquired assumptions. Atezolizumab plus nab-Paclitaxel should be treatment of choice in PD-L1 positive advanced TNBC.*
- *In analogy, the KN-522 trial has established a new treatment standard for neoadjuvant therapy of TNBC with Pembrolizumab constituting the ICPI backbone.*