Immune Checkpoint Inhibitors in Metastatic Triple Negative Breast Cancer

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Disclosure of Interest

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

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BMS, MSD, Pfizer, AstraZeneca, Merrimack / Shire

COMPREHENSIVE
CANCER
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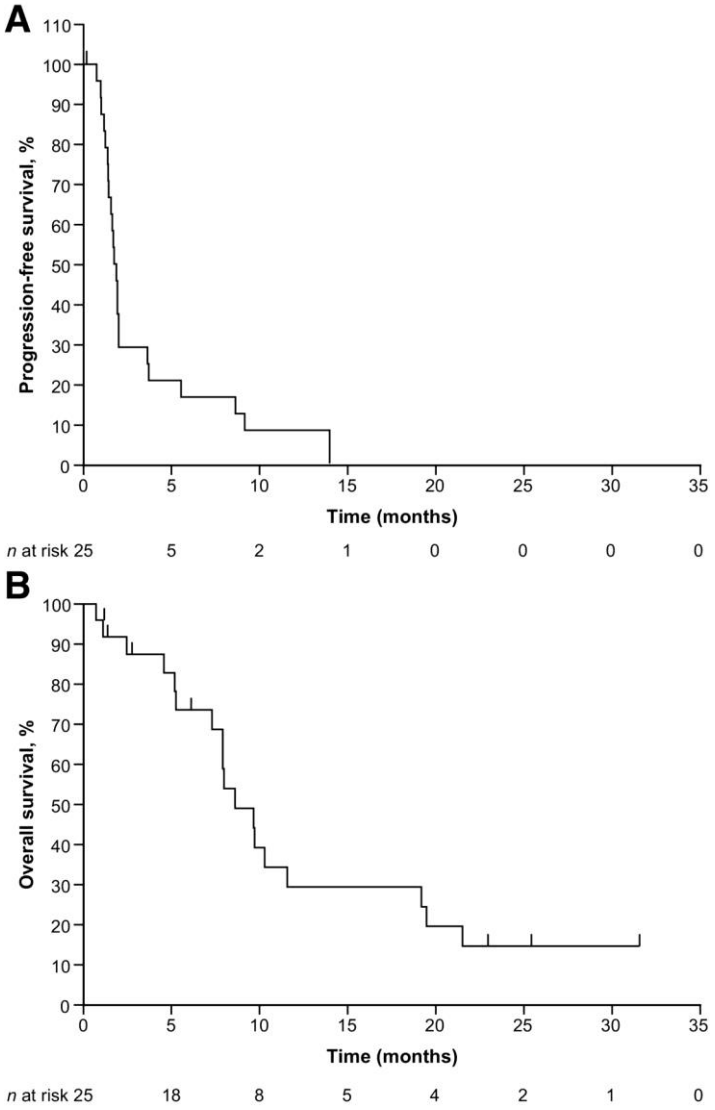
Keynote 028 Phase Ib Study: Pembrolizumab in ER+/Her- MBC (n = 22): PFS and OS



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

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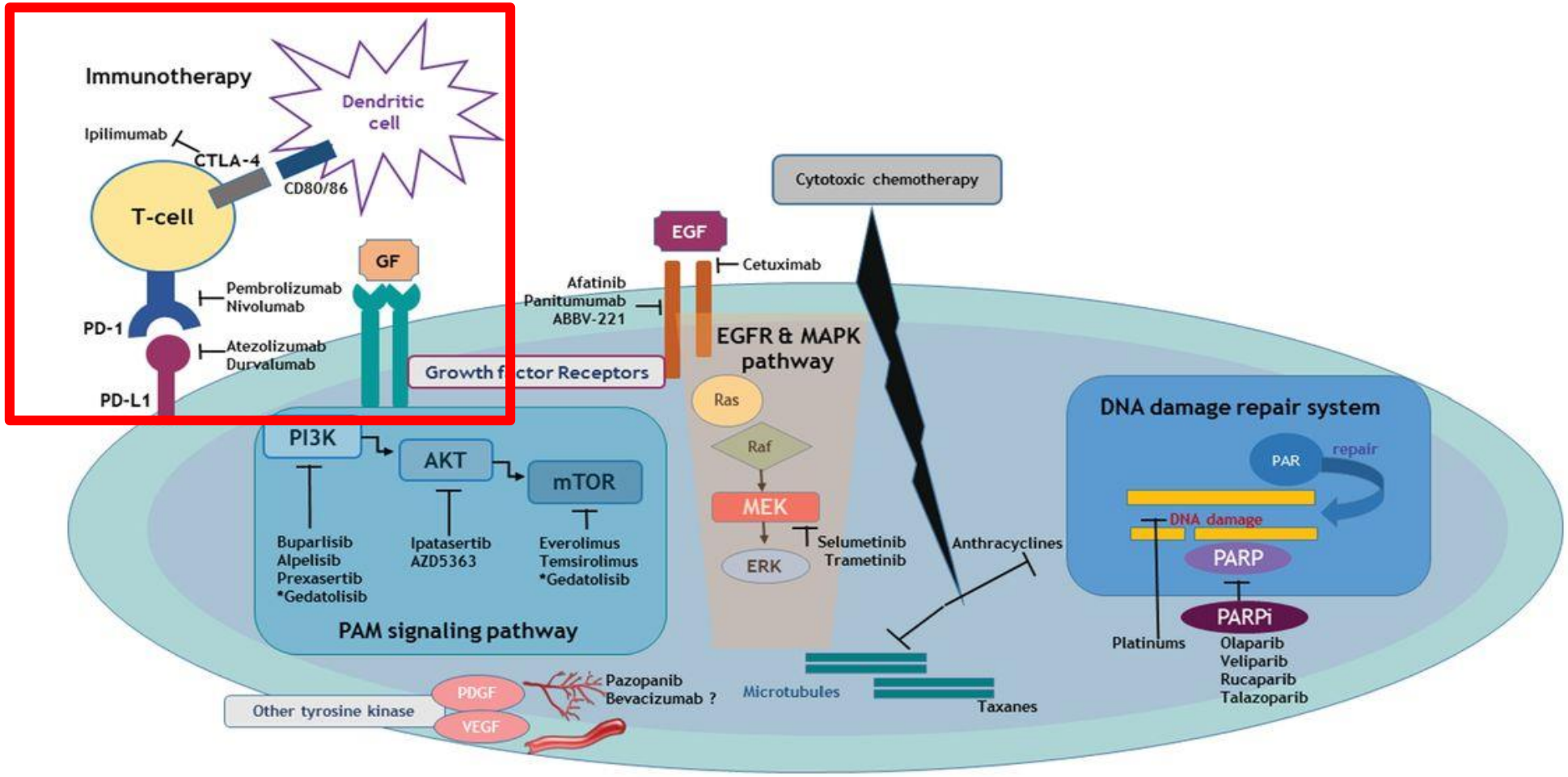
The Story is About Tolerance and the Maintenance of Physiologic Immune Responses.

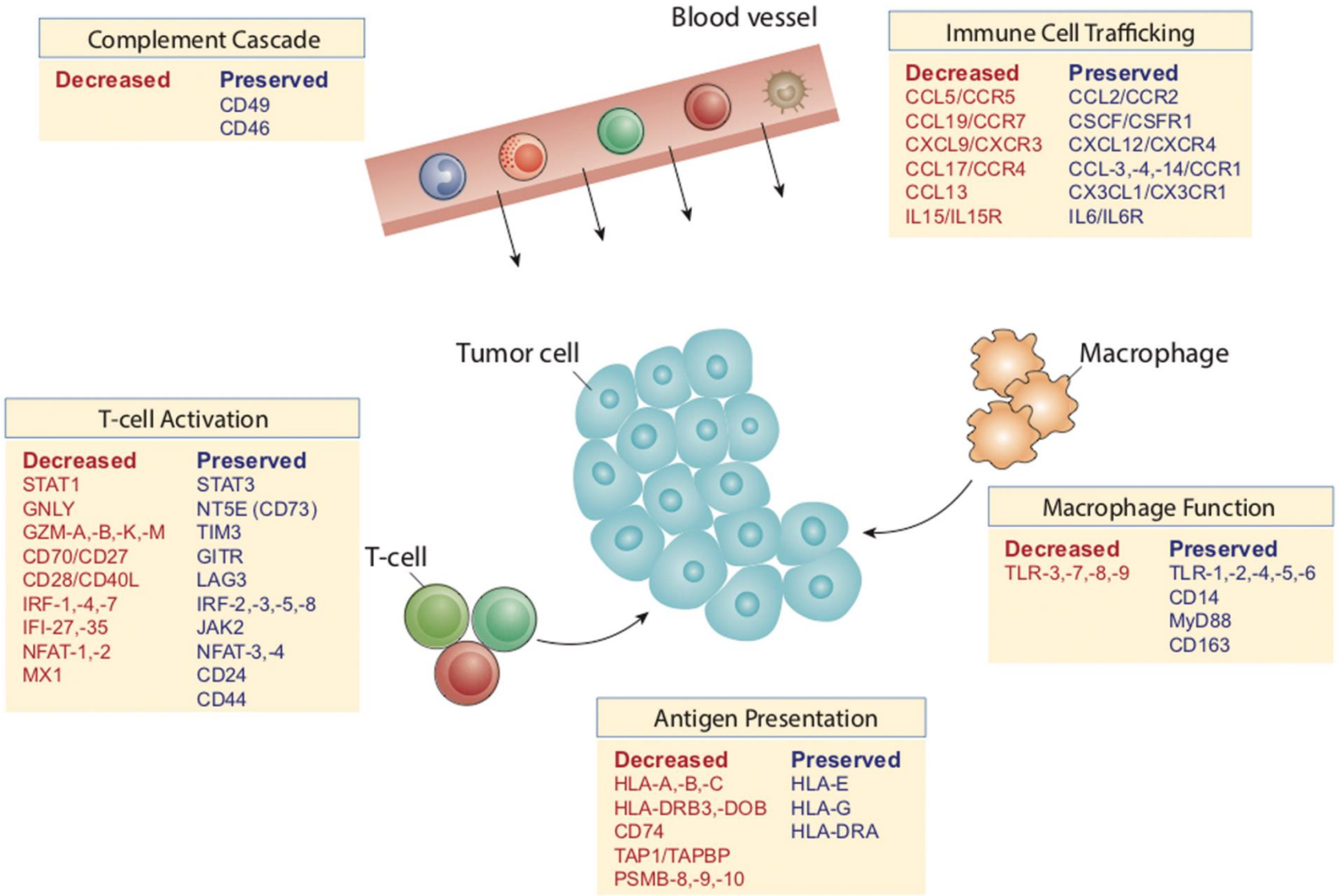
Is Breast Cancer an Ideal Model for the Study of Efficacy of Immune Checkpoint Inhibitors?

Signalling Pathways and Involved Entities that are Unravelling Experimental Therapeutic Targets for TNBC



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

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

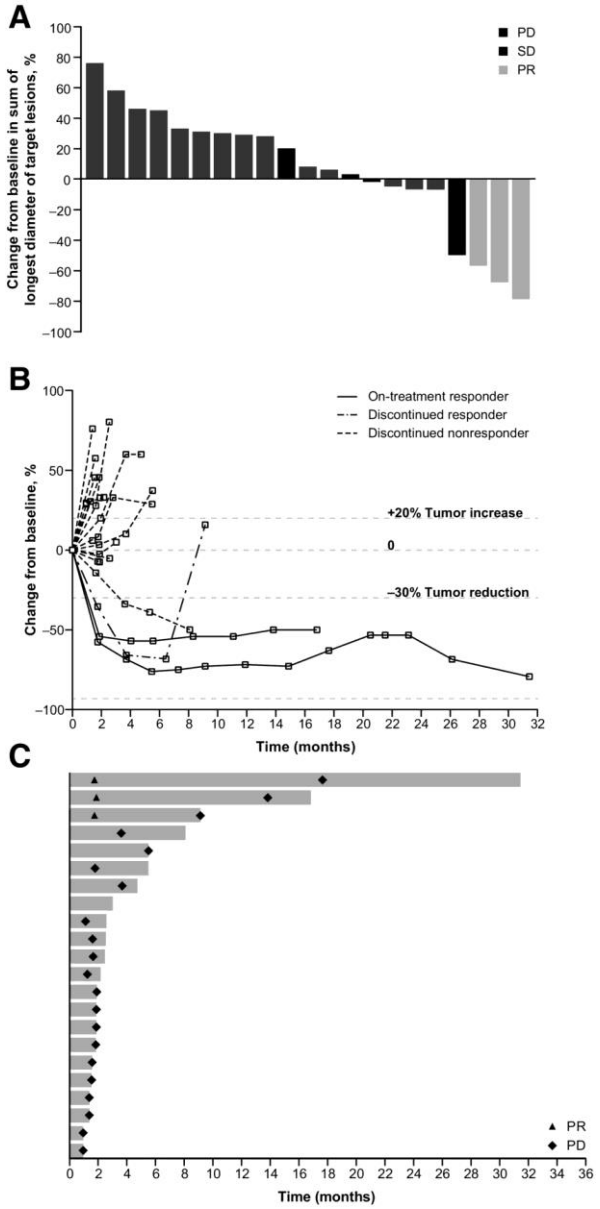
	TNBC	HER2+	ER+ HER2-
Mechanisms of tumour-immune cells interaction	Neoantigens/Neopeptides RAS/MAPk activation as immune escape mechanism	Oncogene addiction	Oestrogen-mediated modulation of local immunity/inflammation
Methods for evaluation of clinically relevant immune markers	More comprehensive functional assessment: IHC markers, gene expression, RNASeq, combined scores General TILs		
Standard treatments contributing to the modulation of the immune milieu	CT and RT: immunogenic cell death	anti-HER2 moAB: ADCC TKIs: possible interference with immunosuppressive oncogene-mediated pathways	TAMOXIFEN: Th1 to Th2 (estrogen-independent); M2 to M1 TAMs (oestrogen-dependent); TGFß induction AIs: Foxp3+depletion*

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

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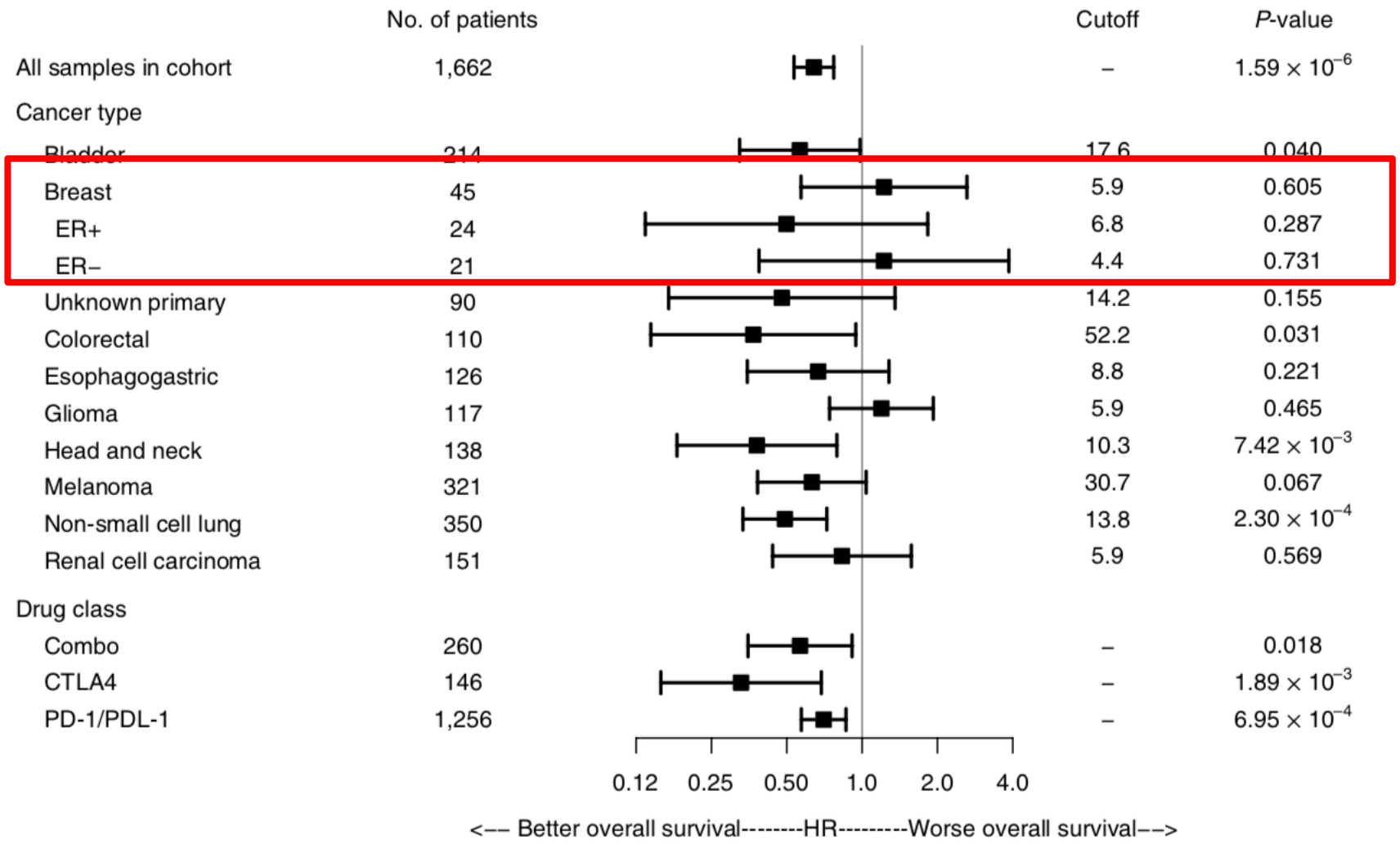
R. Cristescu et al., Science. 2018 Oct 12;362(6411). pii: eaar3593.
doi: 10.1126/science.aar3593

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



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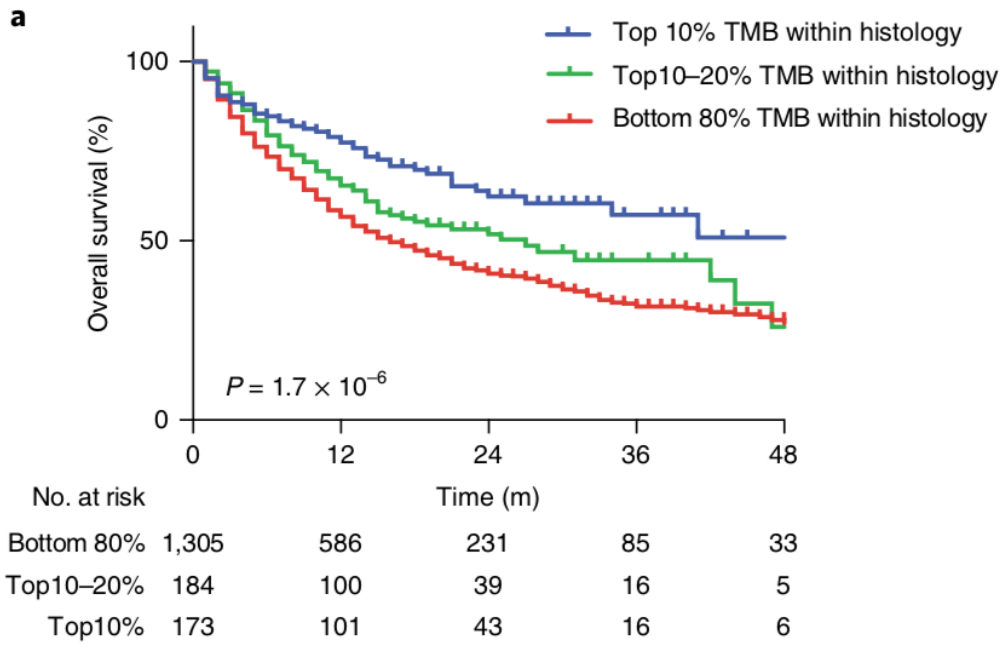
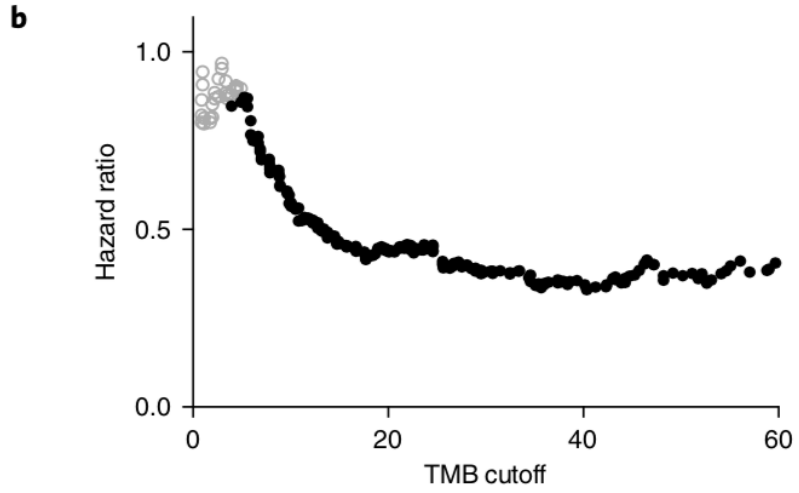
R.M. Samstein et al., Nature Genet.,;doi.org/10.1038/s41588-018-0312-8, 2019

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

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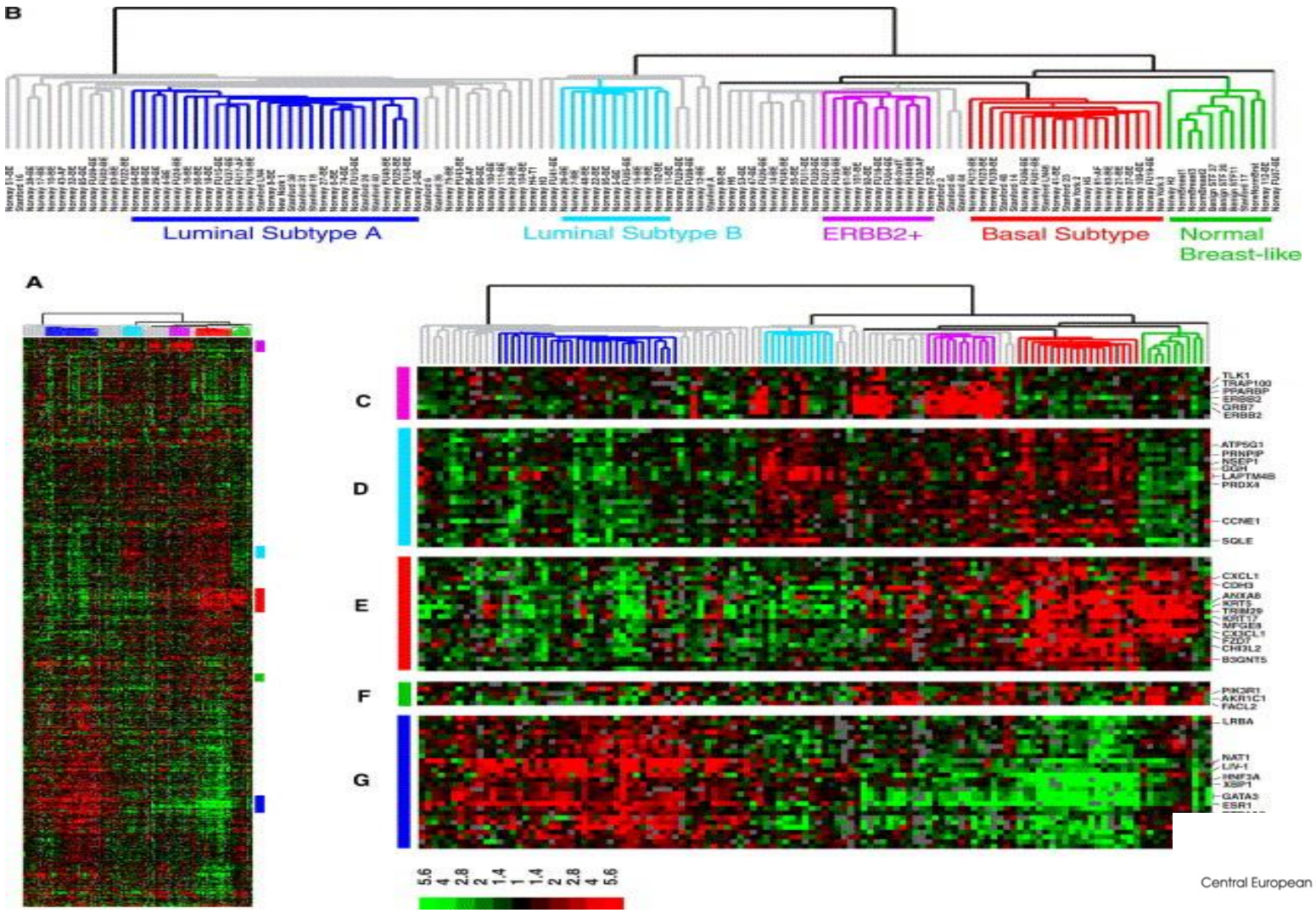
Molecular Mutations in Various Types of Breast Cancer

Adapted from Sorlie T *et al*. Proc Natl Acad S 2001;98(19):10869-10874



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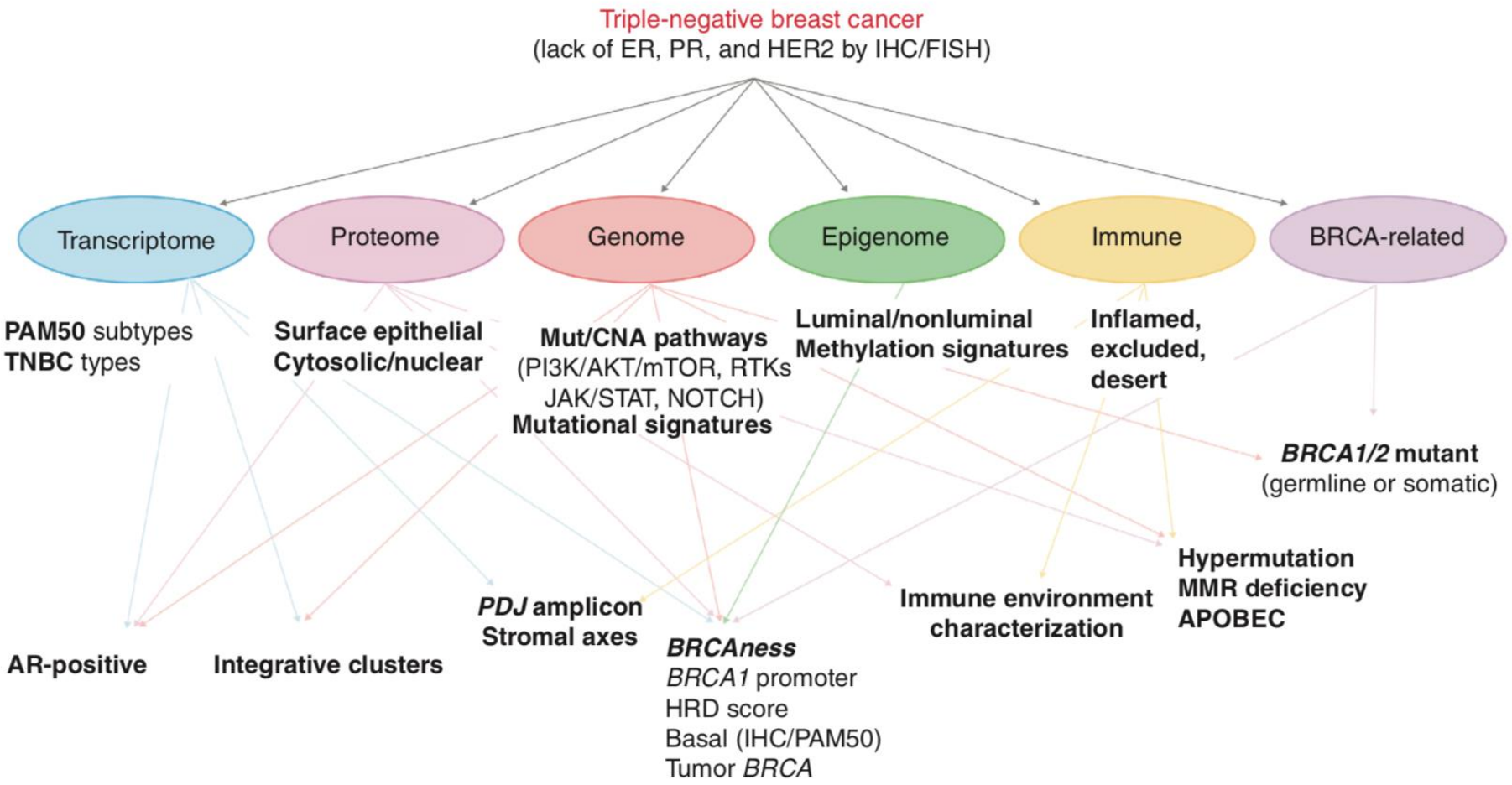
Heterogeneity of Triple Negative Breast Cancer

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



Gene Expressions in TNBC

Subtype	Gene Expression Profile / High Expression of Genes
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

Corner Stones of the Elimination of Tumour Cells

1. Recognizing tumour cells as „foreign“

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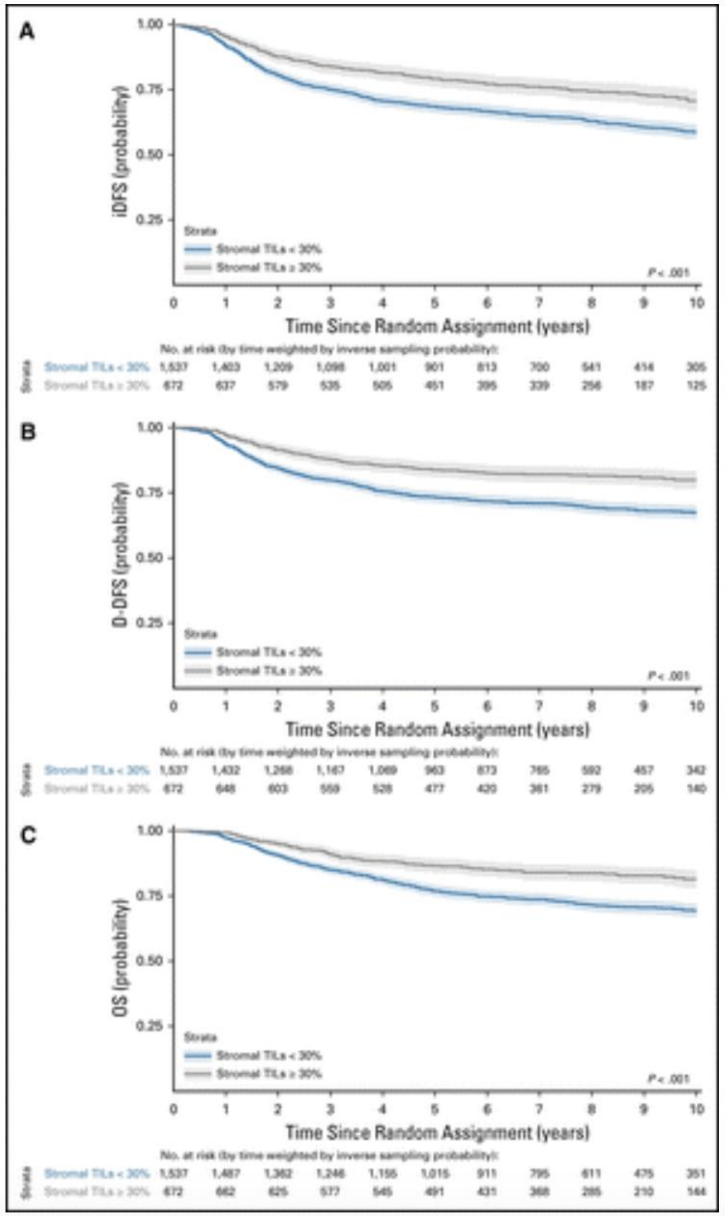
Triple Negative Breast Cancer: Prognostic Effect of Stromal TILs Dichotomized at </> 30%



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:

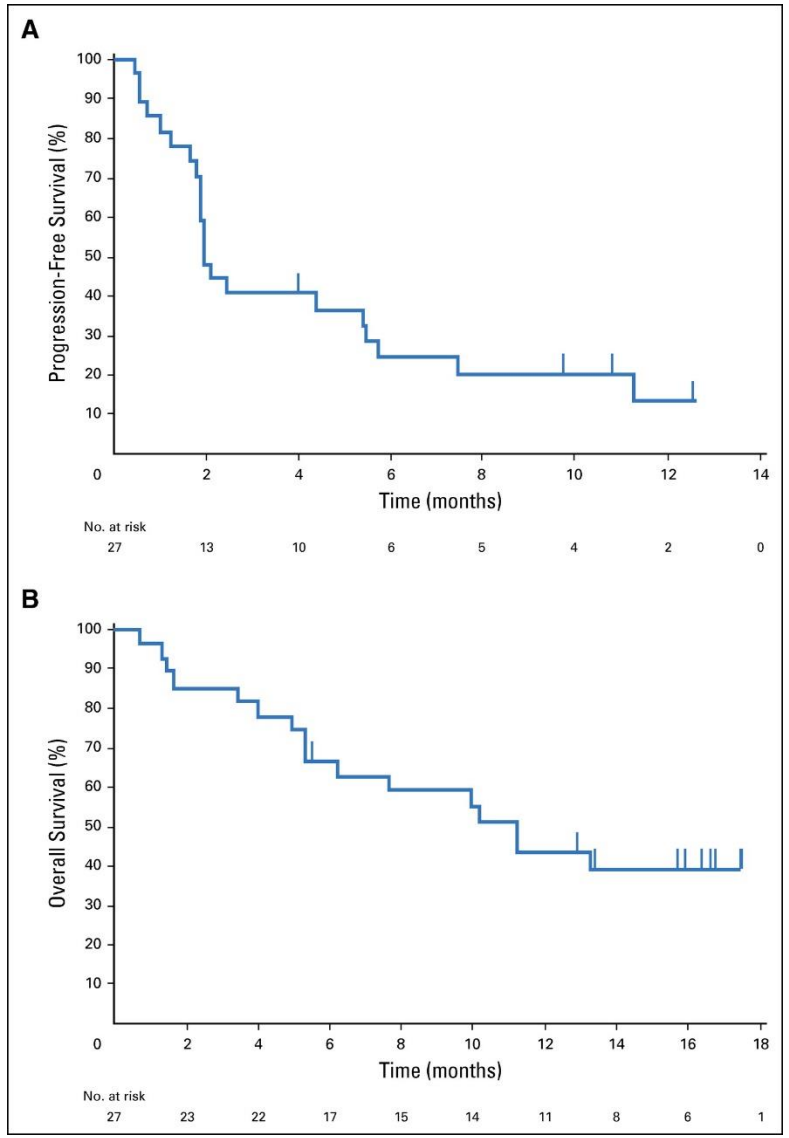
- **older age (p=001)**
- **larger tumour size (p=0.01)**
- **more nodal involvement (p=0.02)**
- **lower histologic grade (p=0.001)**

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

Full Publications on Immune Checkpoint Inhibitors in MBC

	Study	Population
Monotherapy:	Keynote 012 (Phase Ib)	heavily pretreated TNBC
	Keynote 086 (Phase II)	previously untreated TNBC
	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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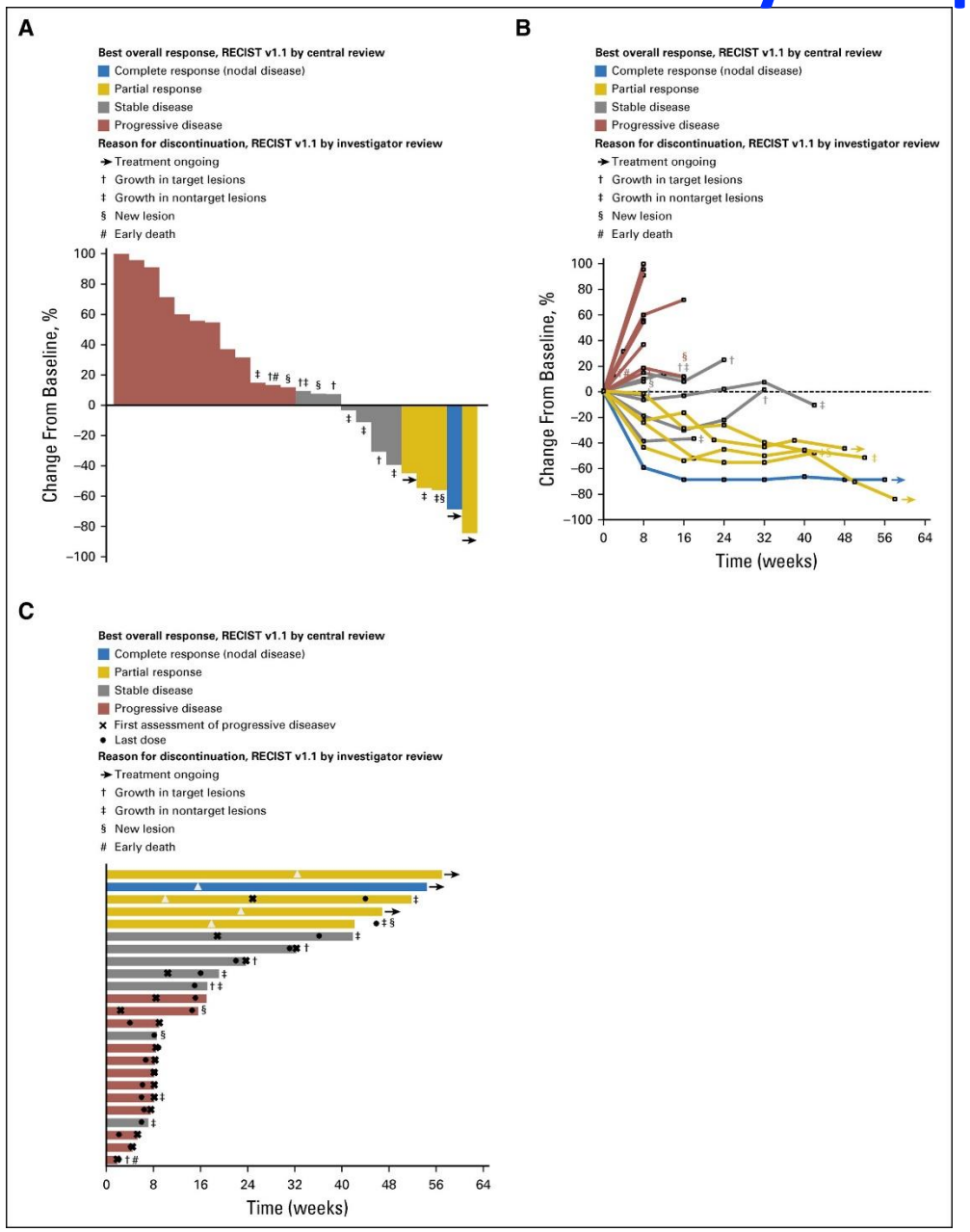
Keynote 012 Phase Ib Study: Responses



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

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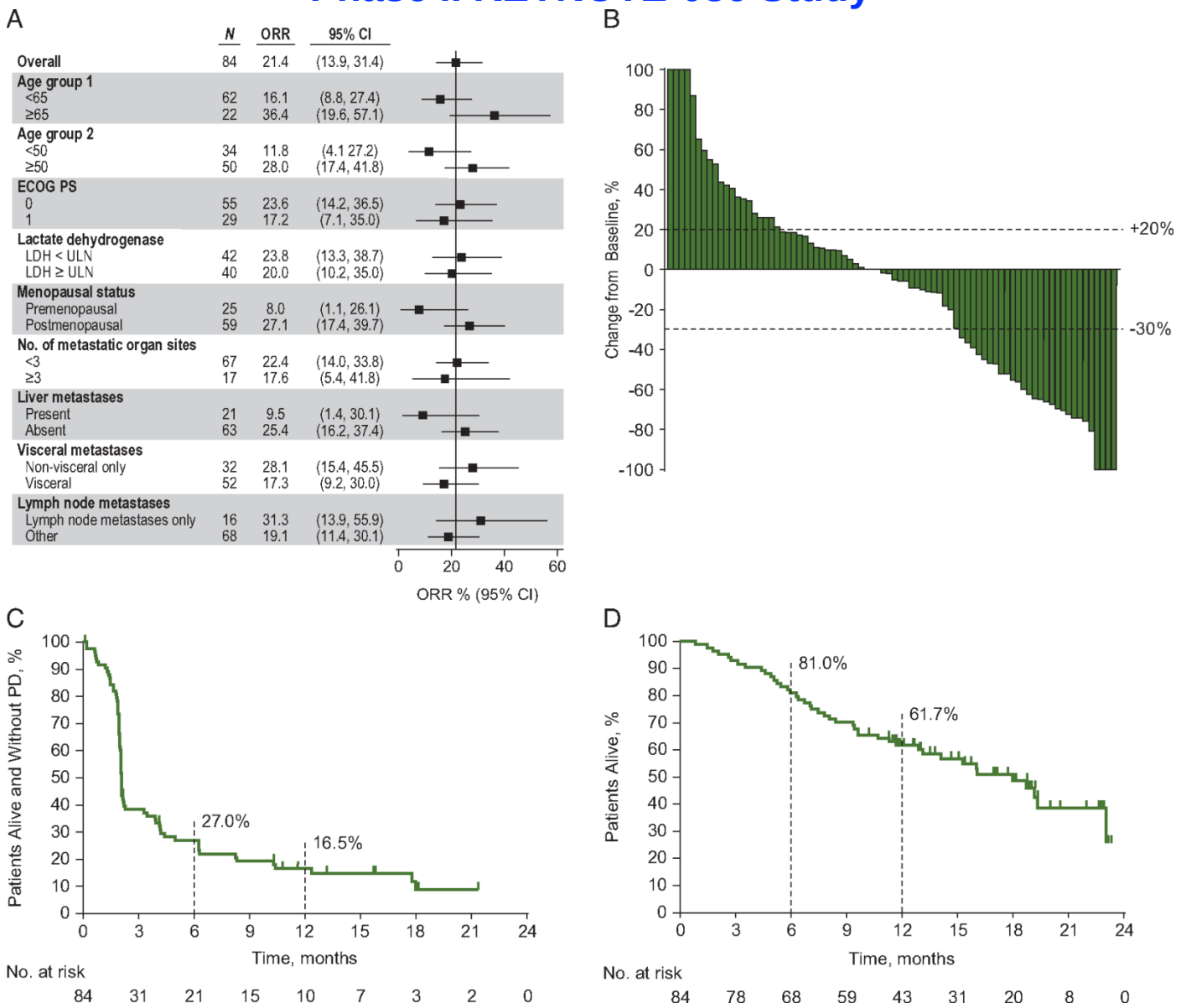
Pembrolizumab for Previously Untreated, PD-L1-positive, Metastatic TNBC: Phase II KEYNOTE-086 Study



A: ORR

B: Change from baseline

C: PFS, N=84

D: OS

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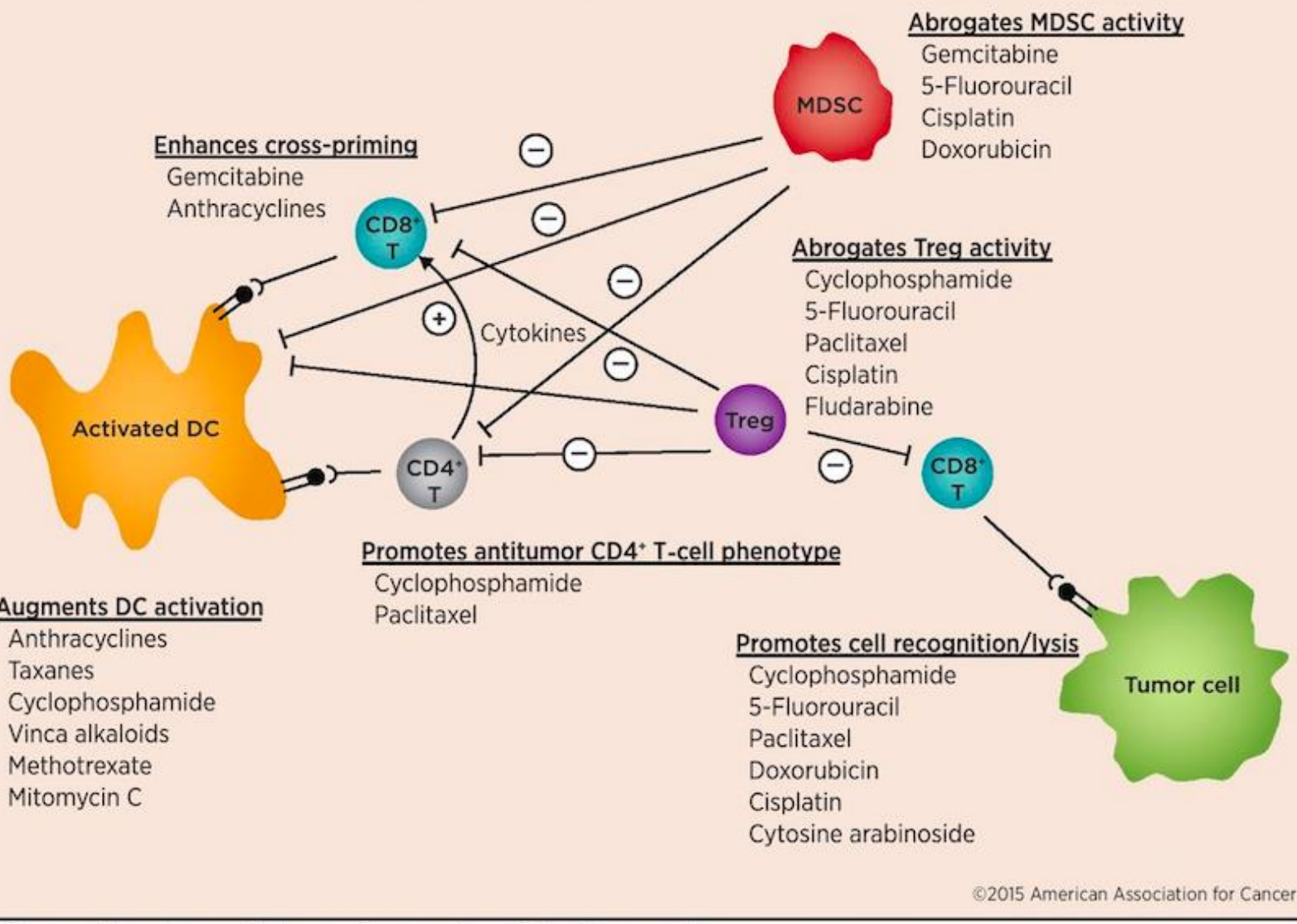
Long-Term Clinical Outcomes and Biomarker Analyses of Atezolimzumab Monotherapy in TNBC: A Phase I Study

	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



Cancer Immunology Research: Cancer Immunology at the Crossroads AACR

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GeparNUEVO Trial: Addition of Durvalumab to CT

Phase II, neoadjuvant, TNBC

WOO phase closed after amendment

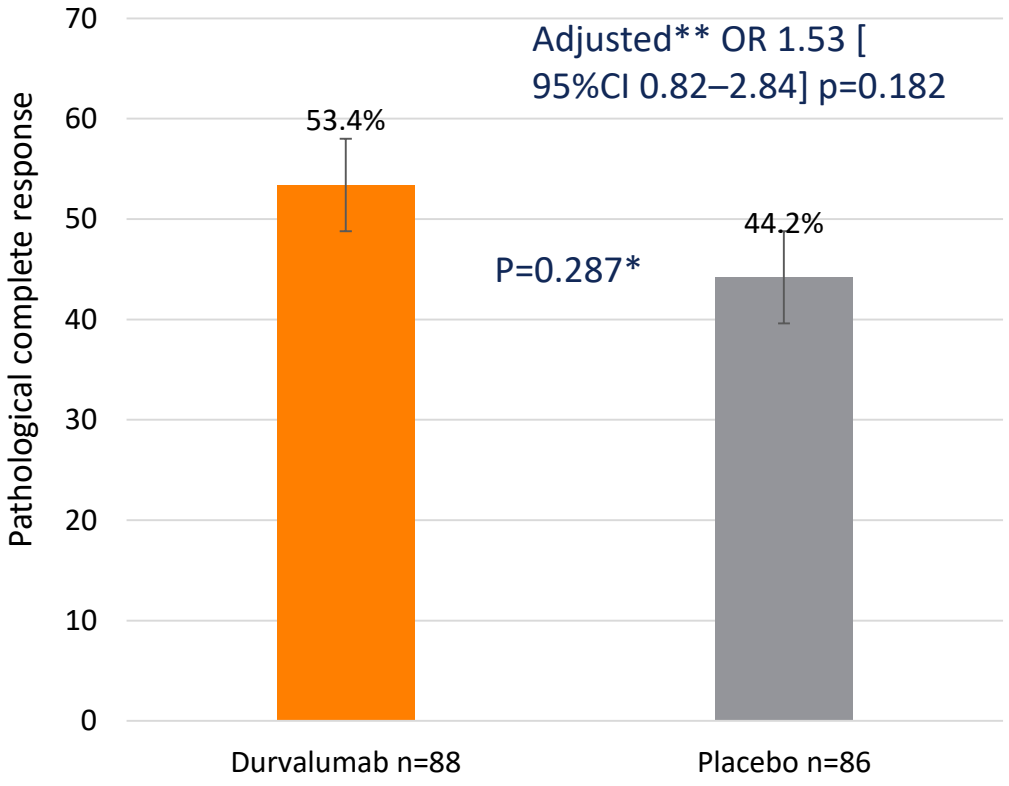
N=174, stratified by TILs (low/med/high)

Durvalumab or placebo for 2 weeks

Core biopsy

Durvalumab or placebo + nab-paclitaxel weekly for 12 weeks

Durvalumab or placebo + epirubicin cyclophosphamide for 4 courses



Neoadjuvant combination treatment with chemotherapy plus durvalumab yielded a high pCR rate in TNBC, although this was not significantly different from chemotherapy plus placebo

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Loibl S, et al. *J Clin Oncol.* 2018;36(15 Suppl): Abstract 104. Figure reproduced from Loibi et al. 2018.

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Triple Negative Breast Cancer (TNBC): IMpassion 130

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

Key IMpassion130 eligibility criteria[a]:

- Metastatic or inoperable locally advanced TNBC
  - Histologically documented[b]
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

Stratification factors:

- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])[c]

R 1:1

Atezo + nab-P arm:

Atezolizumab 840 mg IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m^2 IV
- On days 1, 8 and 15 of 28-day cycle

Double blind; no crossover permitted

Plac + nab-P arm:

Placebo IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m^2 IV
- On days 1, 8 and 15 of 28-day cycle

RECIST v1.1
PD or toxicity

- 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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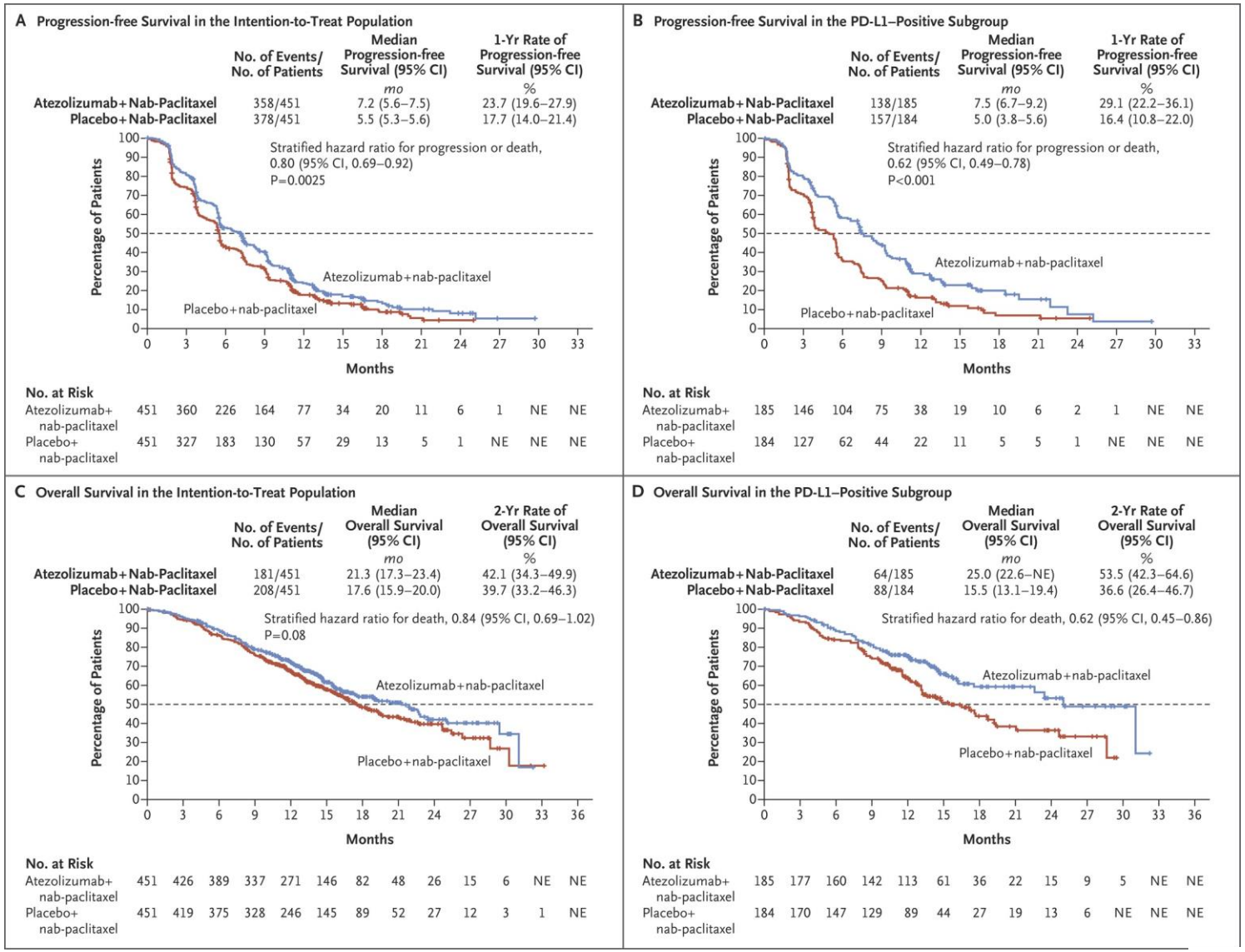
IMpassion130: Progression-Free and Overall Survival.



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

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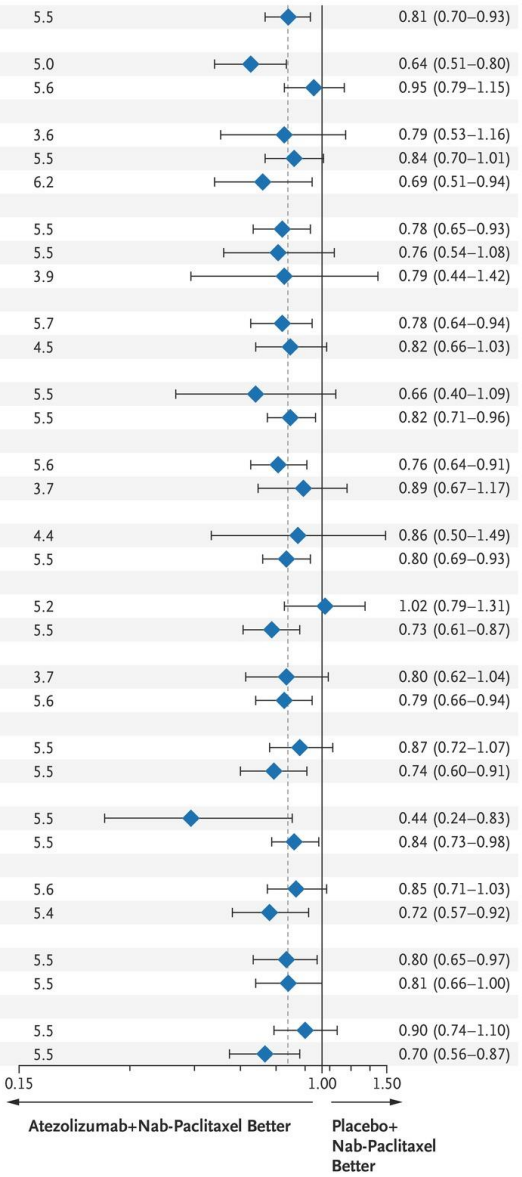
IMpassion 130: Forest-Plot Analyses of PFS in Subgroups.

Subgroup	No. of Patients	Median Progression-free Survival: Atezolizumab+ Nab-Paclitaxel (mo)	Median Progression-free Survival: Placebo+ Nab-Paclitaxel (mo)	Hazard Ratio for Progression or Death (95% CI)
All	902	7.2	5.5	0.81 (0.70–0.93)
PD-L1 status				
Positive	369	7.5	5.0	0.64 (0.51–0.80)
Negative	533	5.6	5.6	0.95 (0.79–1.15)
Age				
18–40 yr	114	3.7	3.6	0.79 (0.53–1.16)
41–64 yr	569	6.7	5.5	0.84 (0.70–1.01)
≥65 yr	219	9.1	6.2	0.69 (0.51–0.94)
Race				
White	609	7.2	5.5	0.78 (0.65–0.93)
Asian	161	7.2	5.5	0.76 (0.54–1.08)
Black	59	6.8	3.9	0.79 (0.44–1.42)
ECOG performance-status score				
0	526	7.4	5.7	0.78 (0.64–0.94)
1	372	5.6	4.5	0.82 (0.66–1.03)
Baseline disease status				
Locally advanced	88	9.6	5.5	0.66 (0.40–1.09)
Metastatic	812	6.6	5.5	0.82 (0.71–0.96)
No. of metastatic sites				
0–3	673	8.2	5.6	0.76 (0.64–0.91)
>3	226	4.0	3.7	0.89 (0.67–1.17)
Brain metastases				
Yes	61	4.9	4.4	0.86 (0.50–1.49)
No	841	7.2	5.5	0.80 (0.69–0.93)
Bone metastases				
Yes	286	5.7	5.2	1.02 (0.79–1.31)
No	616	7.2	5.5	0.73 (0.61–0.87)
Liver metastases				
Yes	244	5.3	3.7	0.80 (0.62–1.04)
No	658	7.5	5.6	0.79 (0.66–0.94)
Lung metastases				
Yes	468	5.7	5.5	0.87 (0.72–1.07)
No	434	8.2	5.5	0.74 (0.60–0.91)
Lymph node–only disease				
Yes	56	12.7	5.5	0.44 (0.24–0.83)
No	843	6.4	5.5	0.84 (0.73–0.98)
Previous neoadjuvant or adjuvant chemotherapy				
Yes	570	7.2	5.6	0.85 (0.71–1.03)
No	332	7.0	5.4	0.72 (0.57–0.92)
Previous taxane treatment				
Yes	461	5.7	5.5	0.80 (0.65–0.97)
No	441	7.2	5.5	0.81 (0.66–1.00)
Previous anthracycline treatment				
Yes	485	6.4	5.5	0.90 (0.74–1.10)
No	417	7.3	5.5	0.70 (0.56–0.87)



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

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IMpassion130: Key Adverse Events.

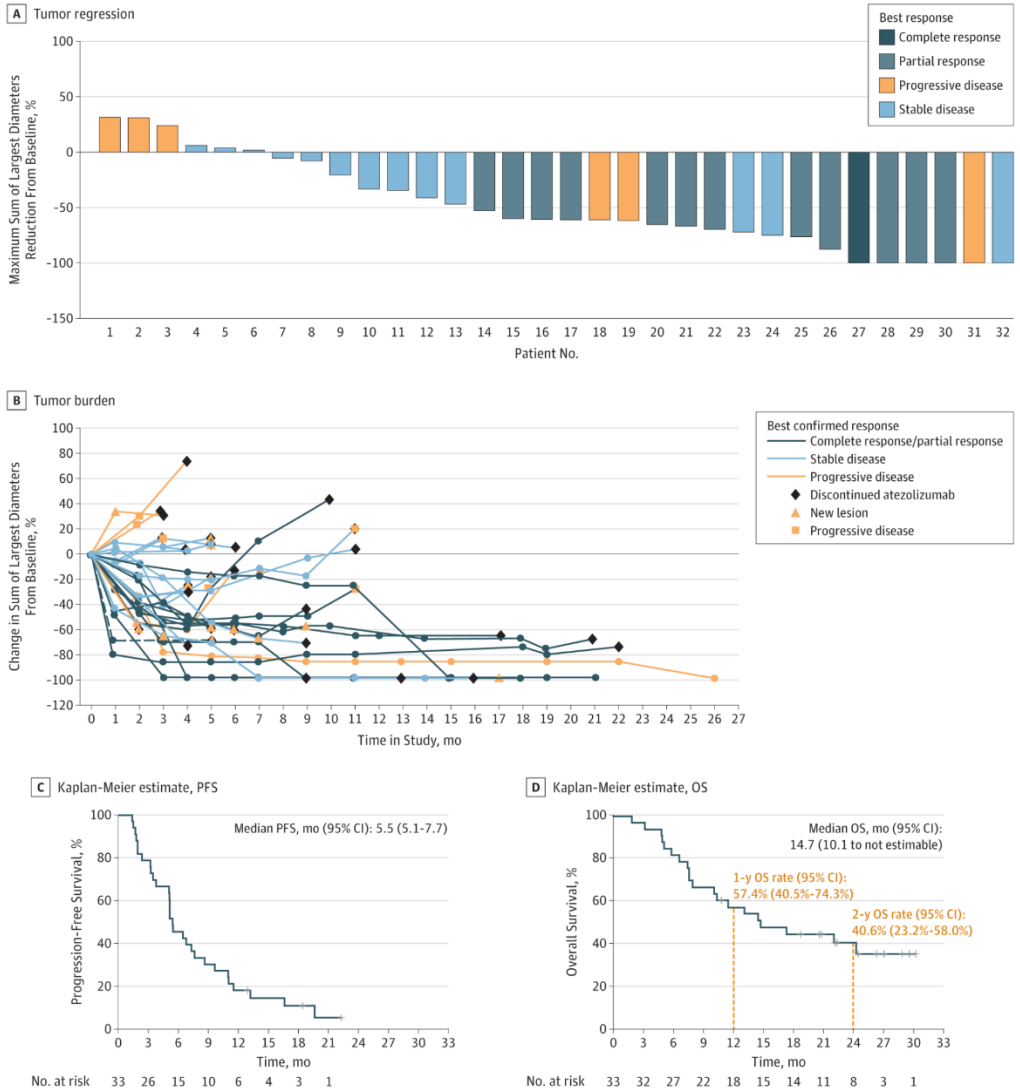
Table 3. Key Adverse Events.*

Event	Atezolizumab + Nab-Paclitaxel (N=452)		Placebo + Nab-Paclitaxel (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)			
Alopecia	255 (56.4)	3 (0.7)	252 (57.5)	1 (0.2)
Nausea	208 (46.0)	5 (1.1)	167 (38.1)	8 (1.8)
Cough	112 (24.8)	0	83 (18.9)	0
Peripheral neuropathy	98 (21.7)	25 (5.5)	97 (22.1)	12 (2.7)
Neutropenia	94 (20.8)	37 (8.2)	67 (15.3)	36 (8.2)
Pyrexia	85 (18.8)	3 (0.7)	47 (10.7)	0
Hypothyroidism	62 (13.7)	0	15 (3.4)	0

* Shown are the single most frequent adverse event of any grade, adverse events of any grade for which the rates differed by at least 5 percentage points between groups, and adverse events of grade 3 or 4 for which the rates differed by at least 2 percentage points between groups.

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

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



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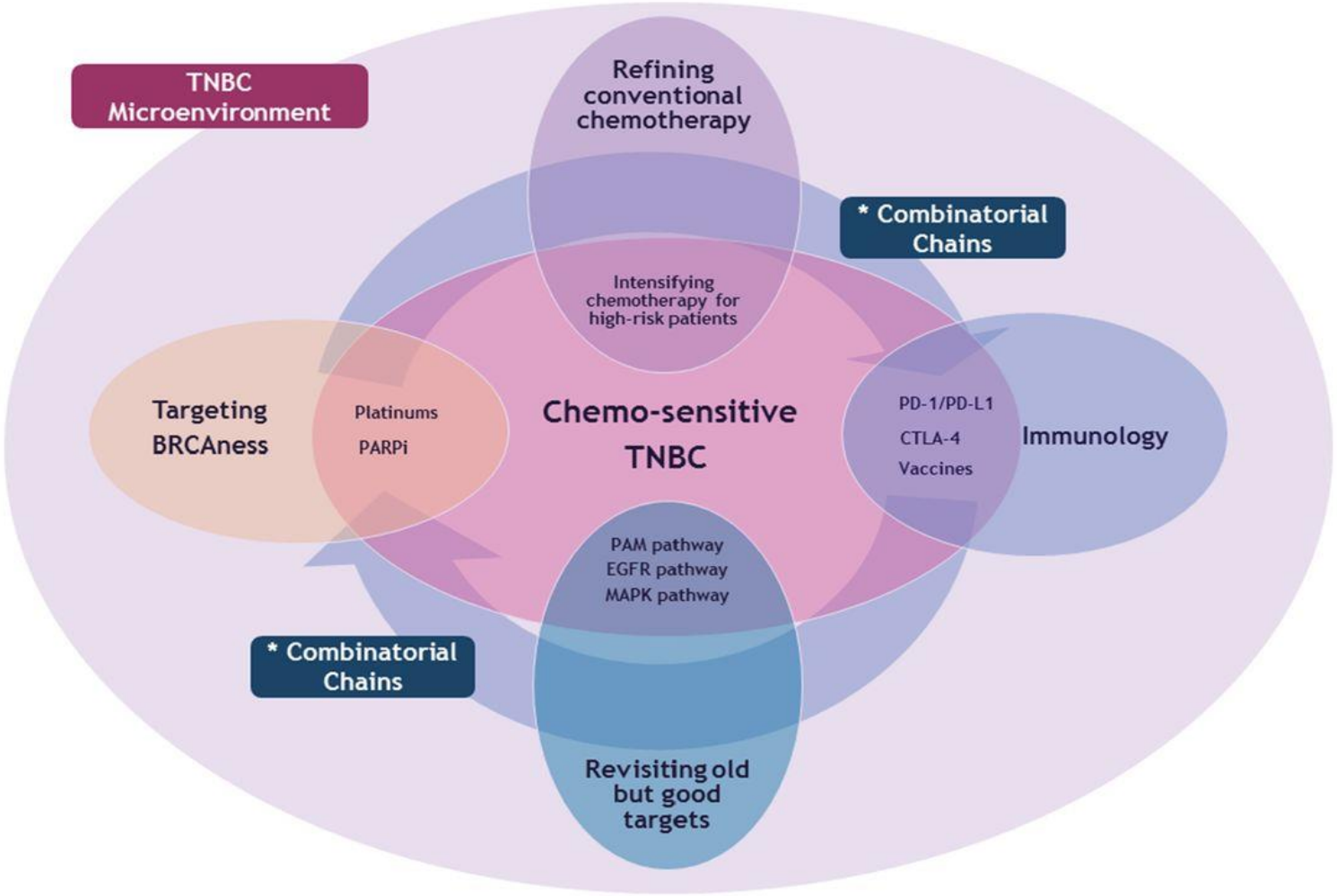
JAMA Oncol. 2019;5(3):334-342. doi:10.1001/jamaoncol.2018.5152

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



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

ESMO Open
Cancer Horizons

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Immune Checkpoint Inhibitor Treatment of MBC: 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.
- 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.