ICRO PROADVANCE NORTH ZONE 2023
19th & 20th August 2023

Advances in Immunotherapy of Breast Cancer

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Topics Covered

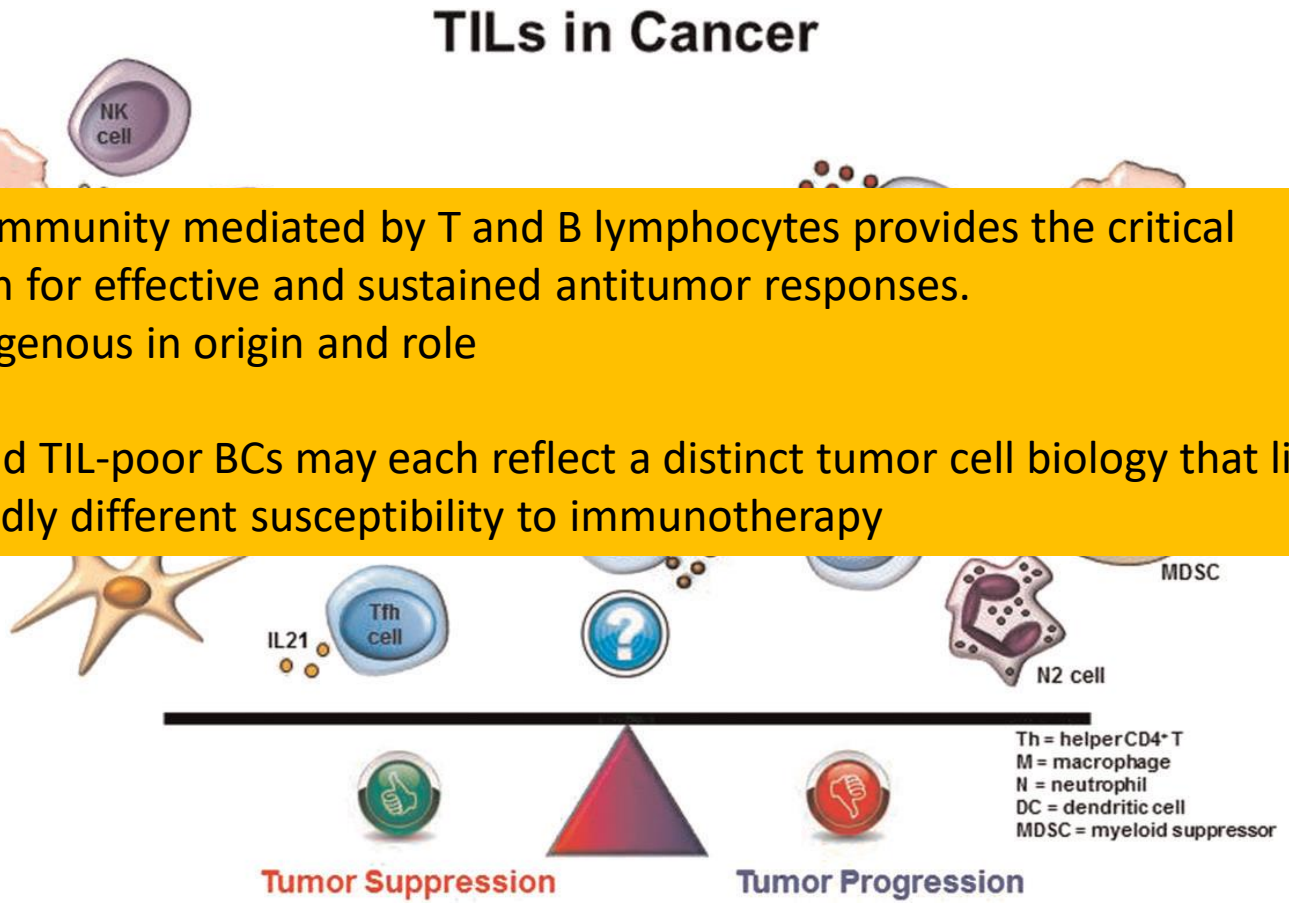
- Current understanding and Immune landscape in breast cancer: Biomarkers of immune response
- Evidence of use of immunotherapy in different molecular subtypes
- Advances in Combining Radiation and Immunotherapy

Immune landscape of breast tumors

- Early data: breast tumors were immunologically silent and that ICIs would not be an effective therapy

- Challenged by studies demonstrating high tumor-infiltrating lymphocytes (TILs) in aggressive subsets of breast cancers

Tumor Infiltrating Lymphocytes



Adaptive immunity mediated by T and B lymphocytes provides the critical foundation for effective and sustained antitumor responses.

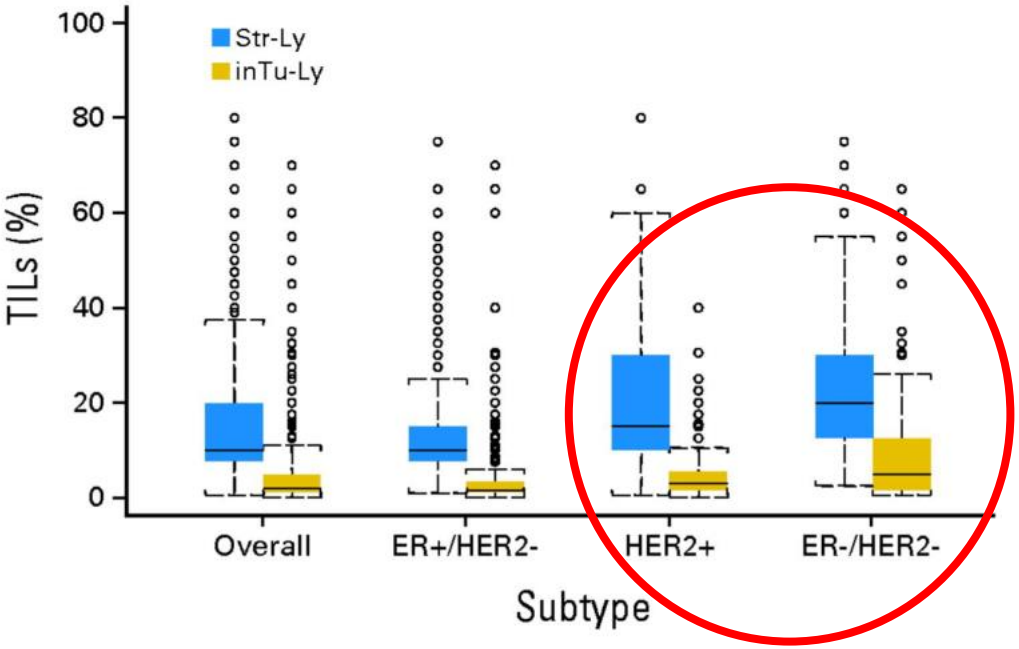
- Heterogenous in origin and role

TIL-rich and TIL-poor BCs may each reflect a distinct tumor cell biology that likely has markedly different susceptibility to immunotherapy

The cellular cross-talk between different leukocyte subsets and their predominant contribution to either pro- or antitumor activities

Salgado R, Ann Oncol. 2015 Feb;26(2):259-71.

Breast Cancer subtypes & TIL's



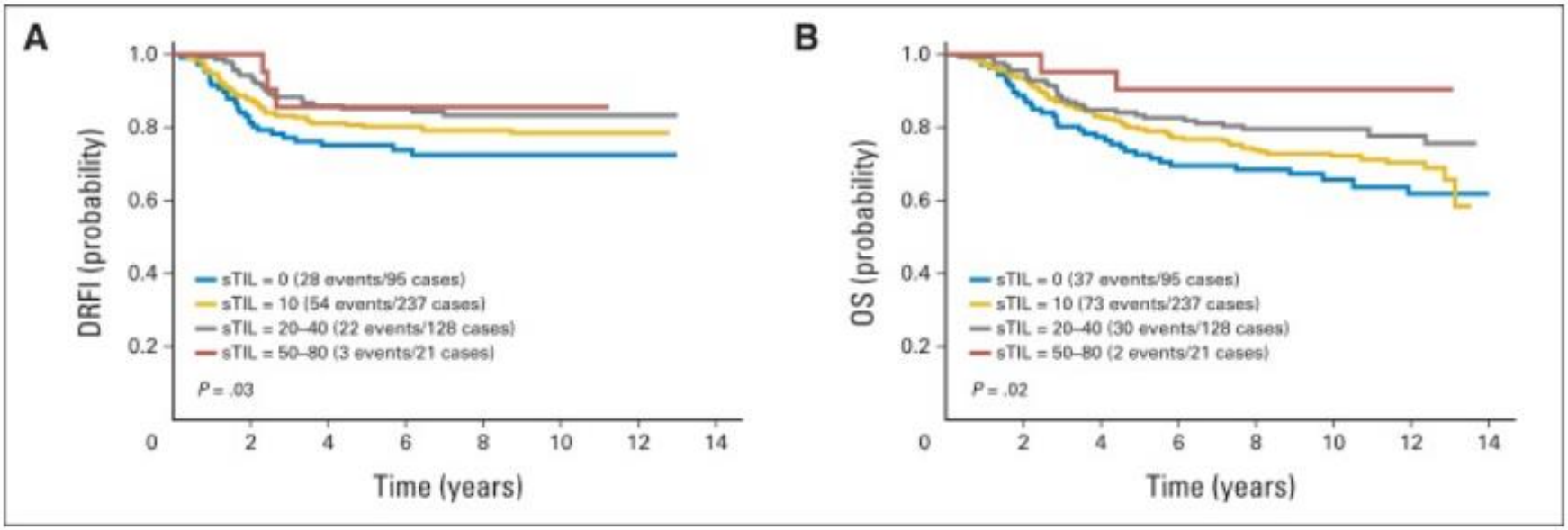
n	2,009	2,009	1,079	1,079	297	297	256	256
Min	0.5	0	1	0	0.5	0	2.5	0.5
Q1	7.5	1	7.5	1	10	1.5	12.5	1.5
Q2	10	2	10	1.5	15	3	20	5
Q3	20	5	15	3.5	30	5.5	30	12.5
Max	80	70	75	70	80	40	75	65

TILs are higher in ER-negative/HER2-negative and HER2-positive BC subgroups compared with the ER-positive/HER2-negative BC subgroups ($P < .001$).

Loi S, J Clin Oncol. 2013 Mar 1;31(7):860-7.

TIL &Prognostic implications:TNBC

ECOG 2197 and ECOG 1199, Phase III studies,480 patients

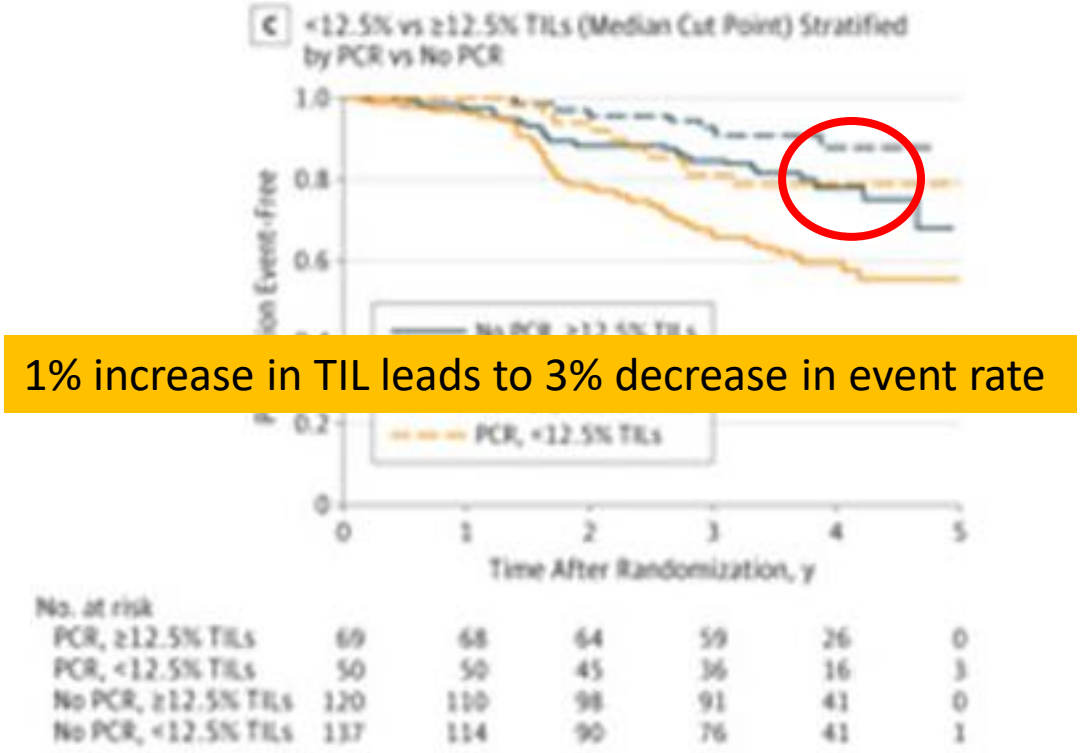


Kaplan-Meier curves of estimated (A) distant recurrence–free interval (DRFI) and (B) overall survival (OS) for all patients for sTILs (grouped as 0 [defined as 0% to 1%] *v* 10 [2% to 10%] *v* 20 to 40 [11% to 40%] *v* 50 to 80 [41% to 80%]);

Adams S, J Clin Oncol. 2014 Sep 20;32(27):2959-66.

TIL &Prognostic implications:Her2Neu3+

A Secondary Analysis of the NeoALTTO Trial



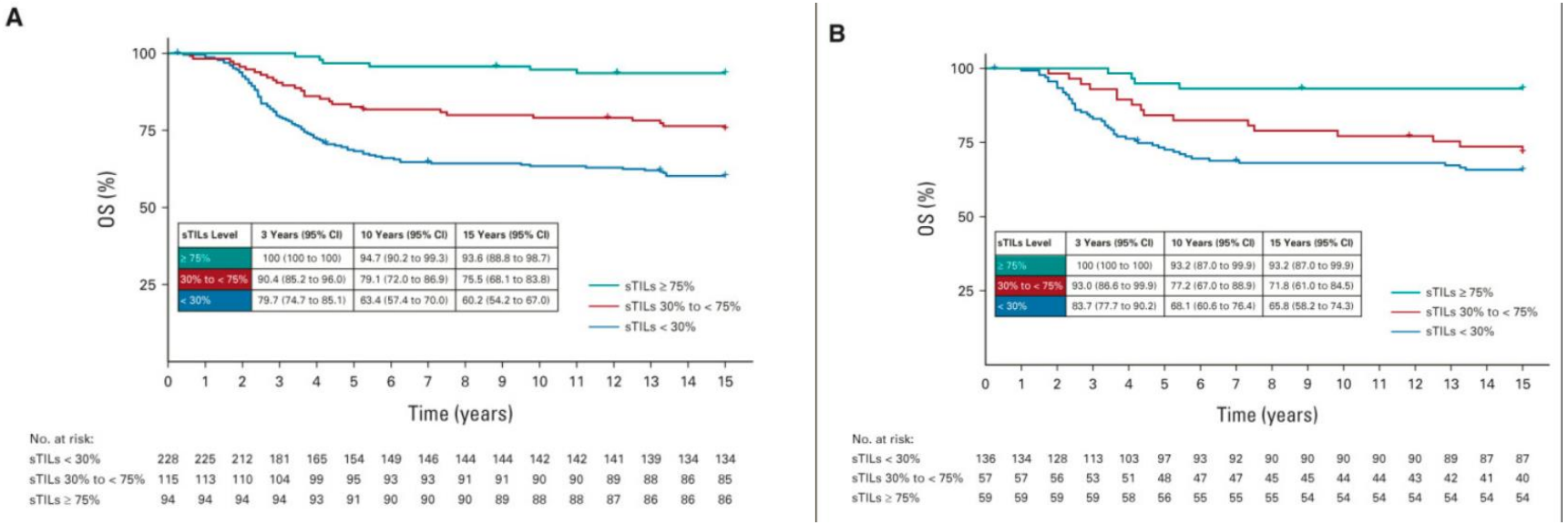
1% increase in TIL leads to 3% decrease in event rate

Higher Levels of Tumor-Infiltrating Lymphocytes (TILs) Result in Better Survival Outcomes and Provide Information Independently of Pathological Complete Response (pCR)

Salgado R, JAMA Oncol. 2015 Jul;1(4):448-54.

sTIL's: May aid in treatment de-escalation in early TNBC

young (< 40 years) patients with N0 TNBC with high sTILs (≥ 75%) have an excellent prognosis.

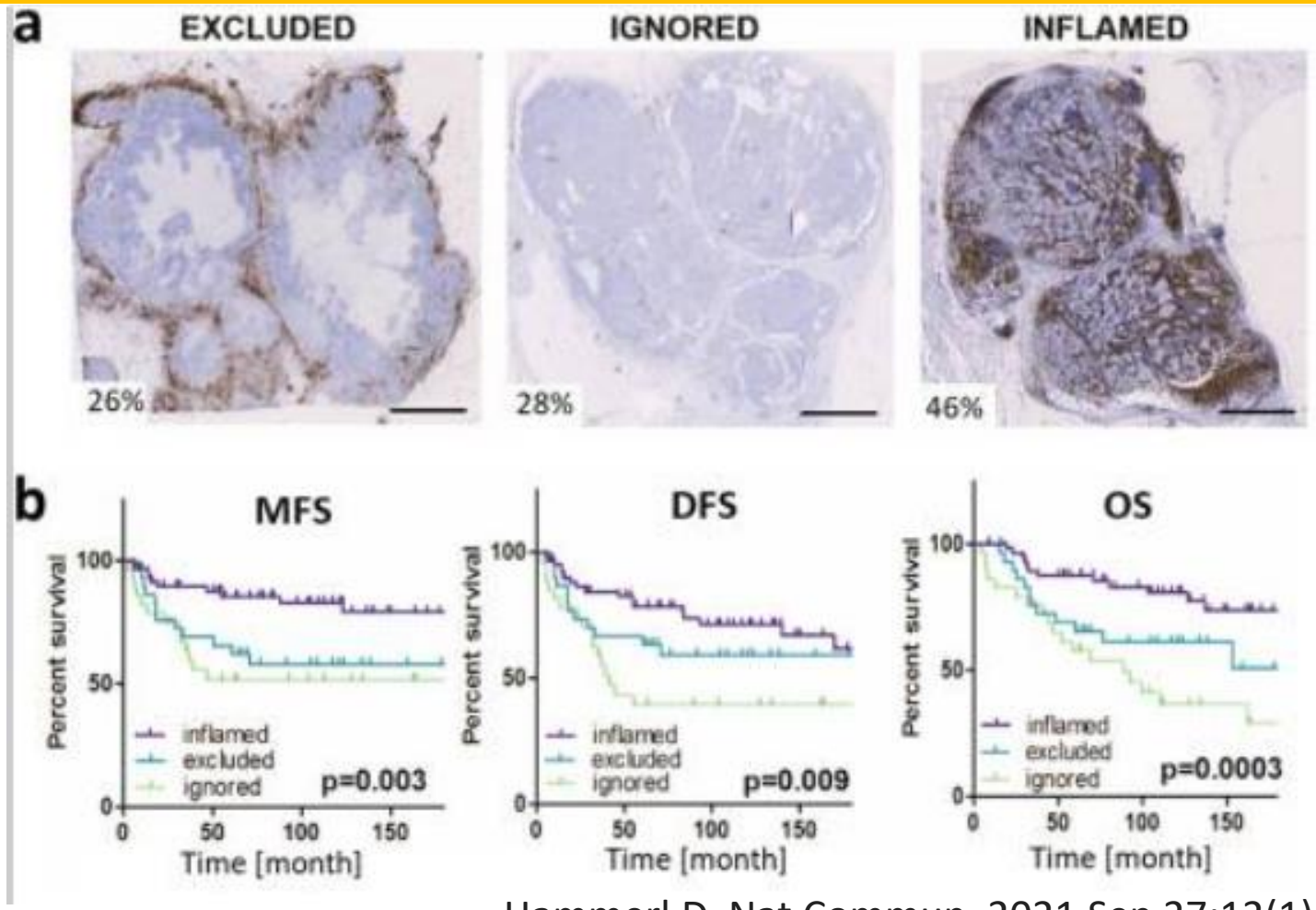


sTILsmay identify stage I TNBC patients with excellent prognosis in whom treatment deescalation/witheldstrategies may be pursued

de Jong VMT, J Clin Oncol. 2022 Jul 20;40(21):2361-2374.

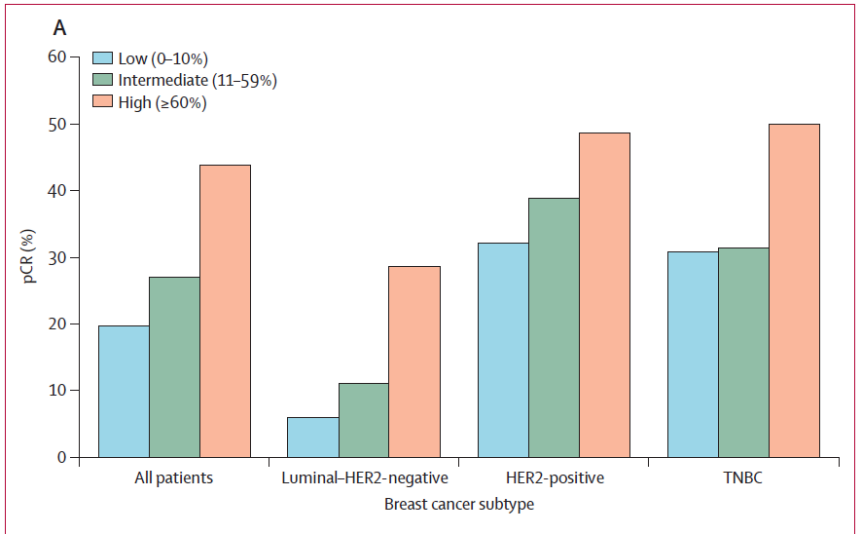
TIL´s–Spatial immune cell contextures: TNBC

to assess tumor-immune interactions in TNBCCD8+ T cells at border and centre

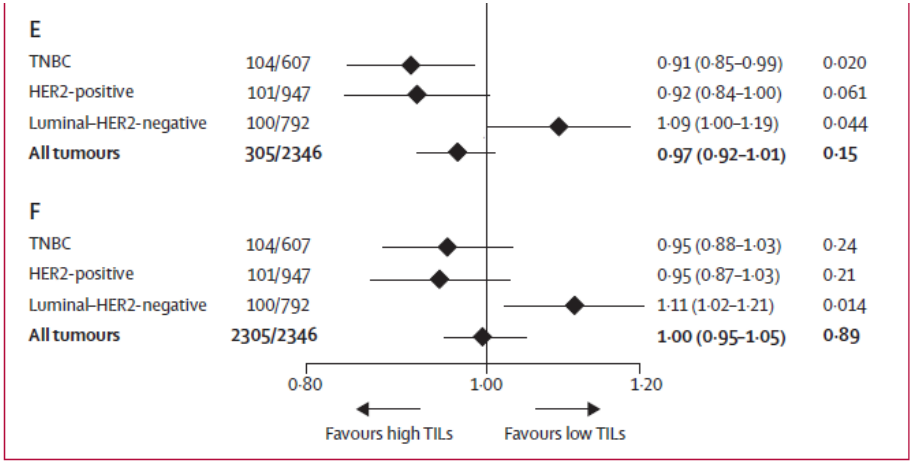


Hammerl D, Nat Commun. 2021 Sep 27;12(1):5668.

sTIL in ER+ve/Her2Neu-ve subtype



pCR in three predefined TIL groups in all breast cancer subtypes



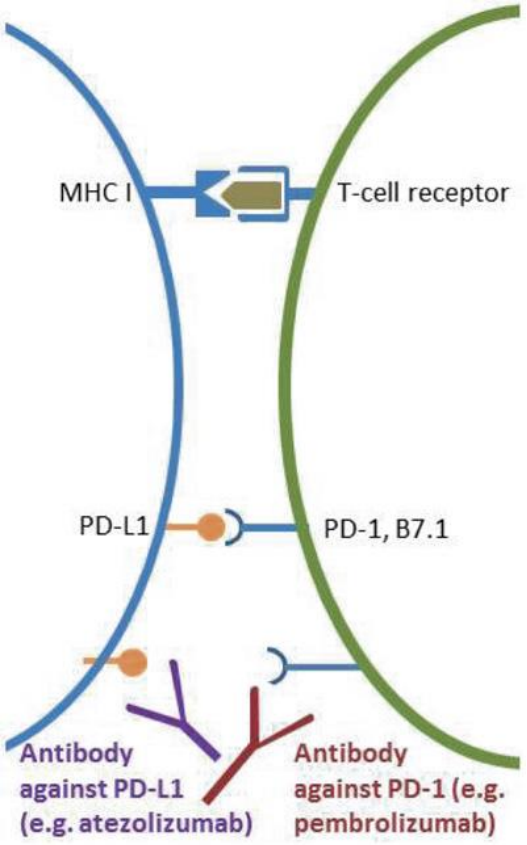
OS by multivariable analysis including all baseline parameters (E), and multivariable analysis including all baseline parameters and pCR (F).

Distinct distribution of immune cell types in the breast cancer subtypes.
The presence of T cells were not prognostic for survival, cell types linked to improved prognosis were B cells and myeloid dendritic cells

***Denkert C, Lancet Oncol* 2018: 19: 40–50**

PD-1/PD-L1 Targeting in Breast Cancer

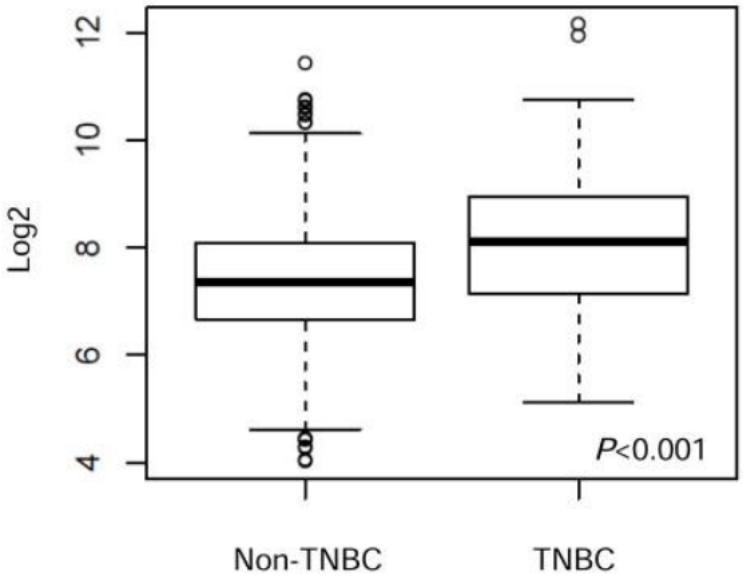
- PD-1/PD-L1 pathway is a major checkpoint pathway for immune responses
- PD-1 is an inhibitory immune checkpoint inhibitor which is expressed on the surface of T-cells, B-cells, natural killer T-cells, monocytes, and dendritic cells, but not resting T-cells
- PD-1 binds 2 ligands, PD-L1 (B7-H1) and PD-L2 (B7-DC).
- Activation of PD-1 by PD-L1 or -L2 induces downregulation of T-cell activity, reduced cytokine production, T-cell lysis, and induction of tolerance to antigens



Oncol Res Treat. 2017;40(5):294-297

PD-1/PD-L1 Targeting in Breast Cancer

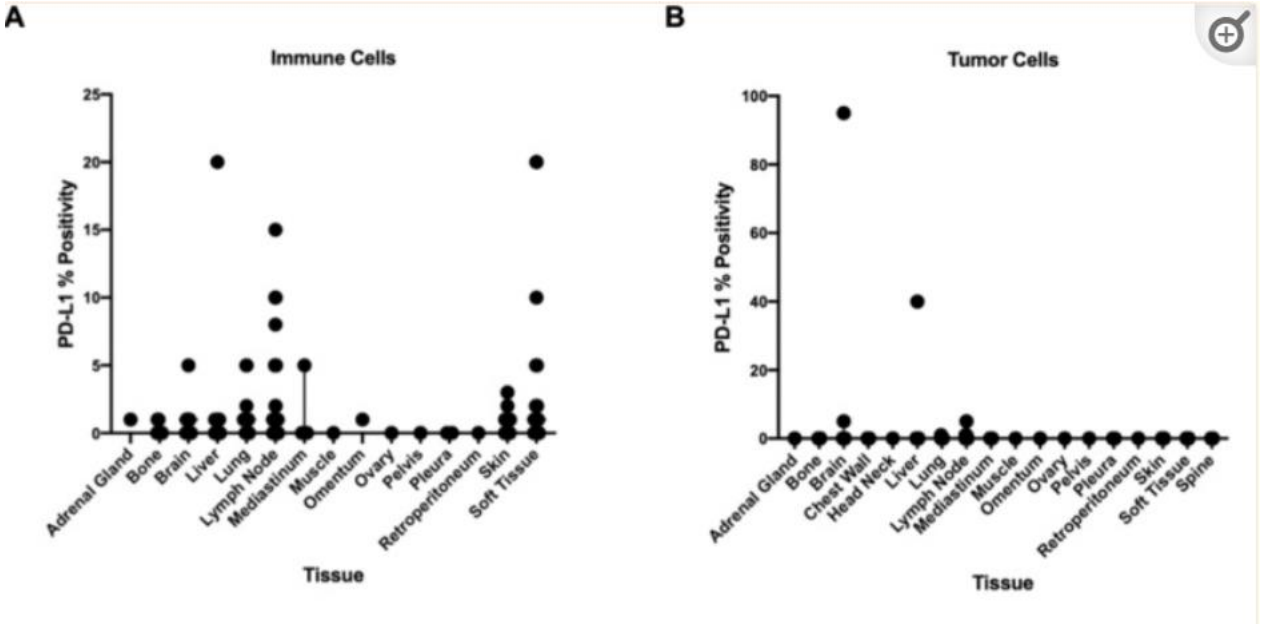
- PD-L1 is overexpressed in most breast cancers as compared to its expression in normal breast tissue
- PD-L1 expression in 45% of all breast cancers subtypes but higher in TNBC (40% -65%)
- PD-L1 overexpression has been associated with poor prognosis
- PD-L1 expression alone may not fully predict response to immunotherapy
- The lack of standardization and variable cutoffs also hamper development of this biomarker.



Santa-Maria CA, J Natl Compr Canc Netw. 2018 Oct;16(10):1259-1268.
Davey MG, Br J Surg. 2021 Jun 22;108(6):622-631.

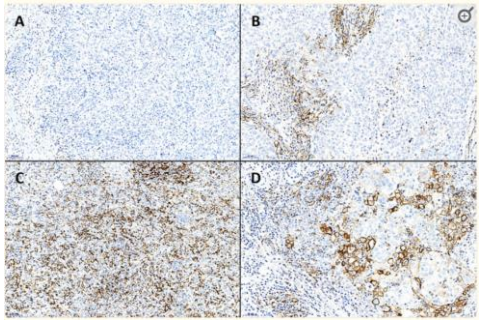
PD-1/PD-L1 Targeting in Breast Cancer

- Expression is restricted, in most cases, to immune cells showing a strong correlation with TIL density
- PD-L1 positivity varies by metastatic location with lower positivity rates in liver, skin and bone metastases



Rozenblit M, J Immunother Cancer. 2020 Nov;8(2):e001558.

Approved IHC tests for PDL1



Immune Cell Score (IC, atezolizumab)

The Ventana SP142 antibody evaluates tumor immune cells (IC)

Percentage of the area occupied by all PD-L1-positive immune cells (lymphocytes, dendritic cells, macrophages, and granulocytes) relative to the whole tumor area (neoplastic cells and tumor

IC >1%

Combined positive score (CPS, pembrolizumab)

Dako 22C3 antibody evaluates both tumor cells (TCs) and IC.

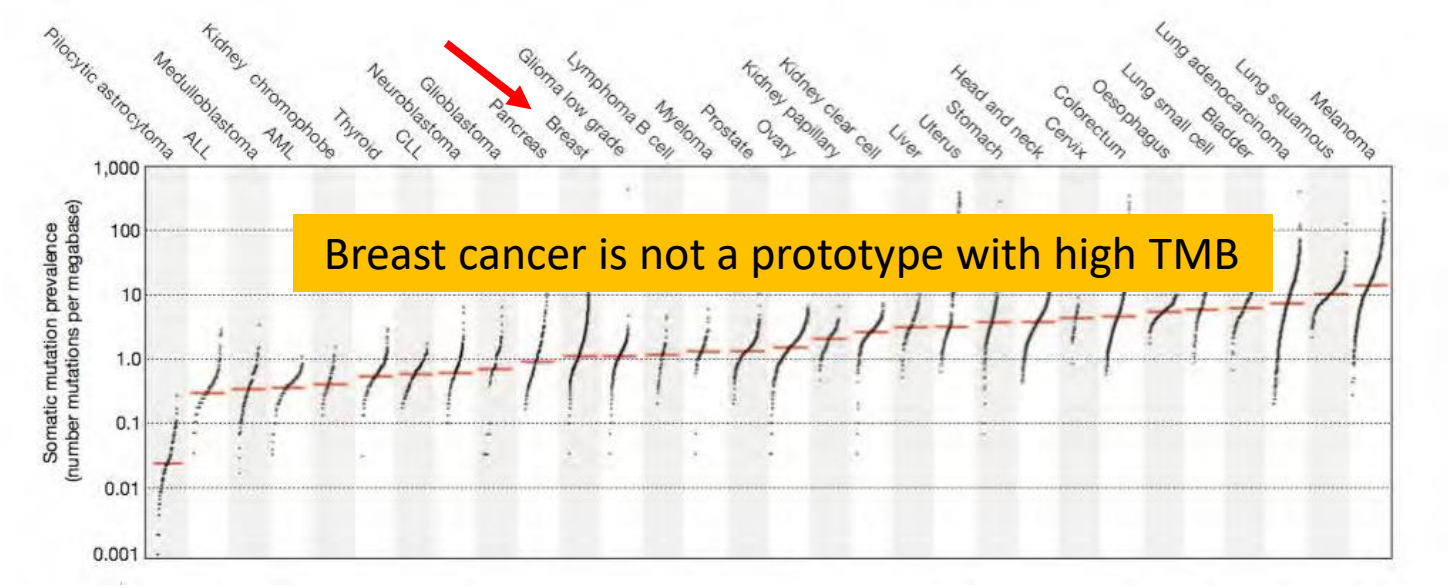
The number of PD-L1-positive tumor cells and PD-L1-positive immune cells is summarized, relative to the number of all vital tumor cells, and then multiplied by 100.

CPS is a score of >10

Erber R, Breast Care (Basel). 2020 Oct;15(5):481-490.

Tumor Mutational Burden

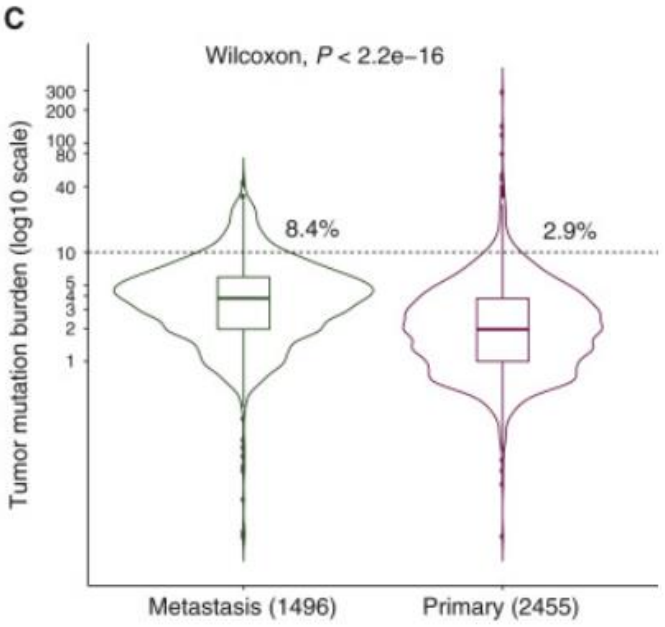
somatic mutations per megabase of the sequenced genome.
this is uncommon in breast cancer and primarily seen in lobular cancer



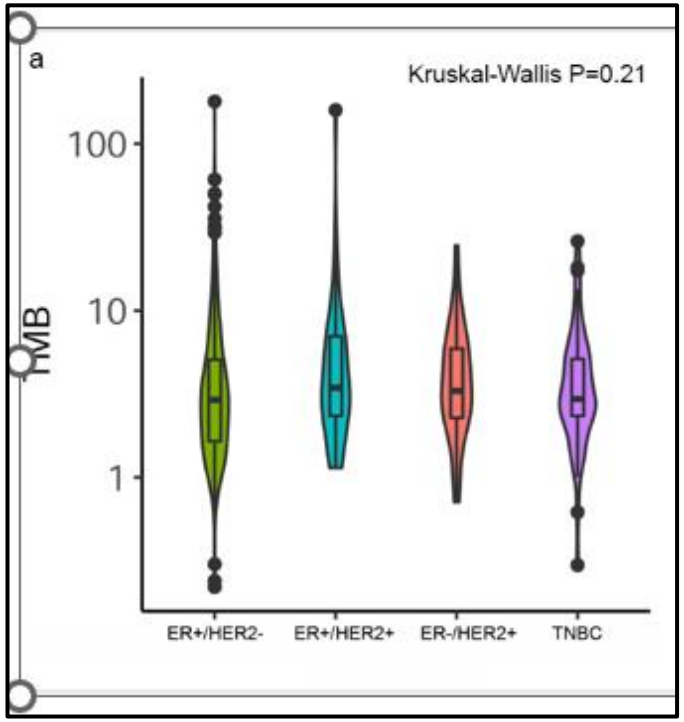
TMB is not prognostic in breast cancer in general
work is needed to establish the best TMB cutoff and the best immunotherapy regimen to be used in breast cancer

Romualdo Barroso-Sousa. Cancers 2023, 15(15), 3997

Tumor Mutational Burden



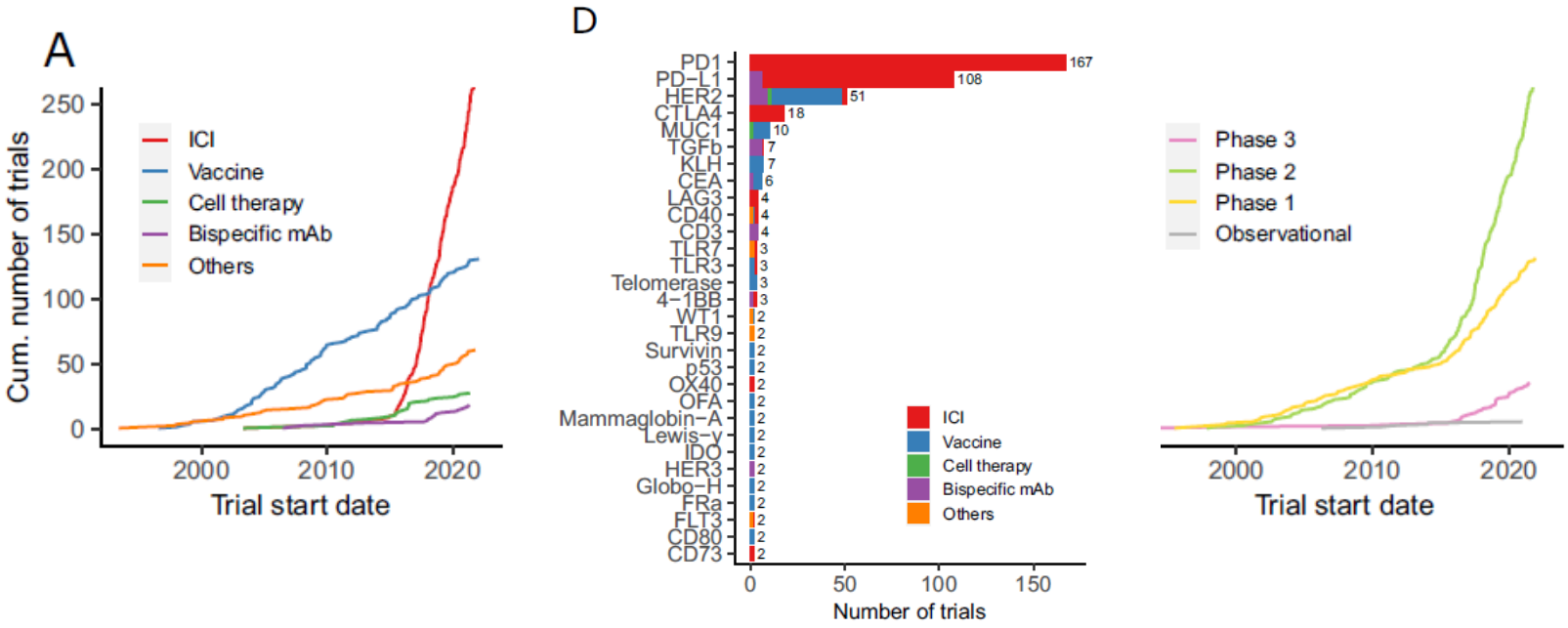
TMB according to primary vs metastasis



TMB according to subtypes

Barroso-Sousa R, Ann Oncol. 2020 Mar;31(3):387-394.
Angus L, Nat Genet. 2019 Oct;51(10):1450-1458.

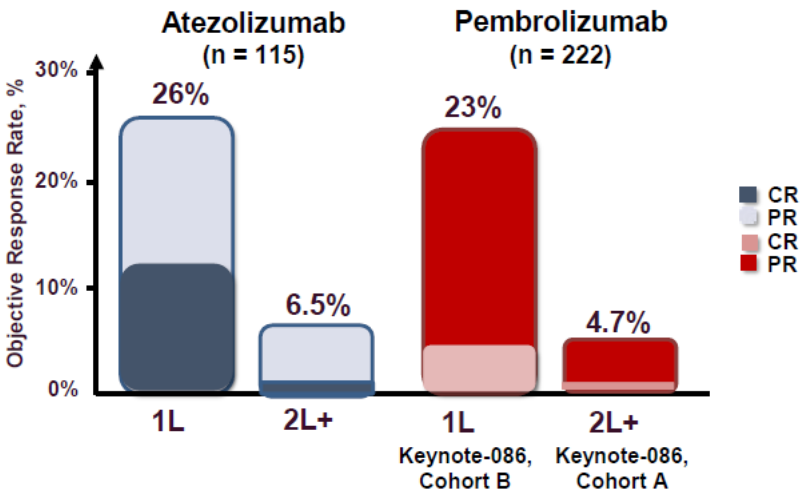
Immunotherapy trial landscape in breast cancer



Debien V, NPJ Breast Cancer. 2023 Feb 13;9(1):7.

Immunotherapy as monotherapy in metastatic tnbc

- KEYNOTE-012 and KEYNOTE-086 evaluated pembrolizumab monotherapy
  - higher rates of response when pembrolizumab was used in the first line
  - PD-L1–positive (PD-L11) disease



Median OS= 17.6-18 months
Median DOR= 10-4 to 21 months

Grade3/4 adverse= 9.5-11%

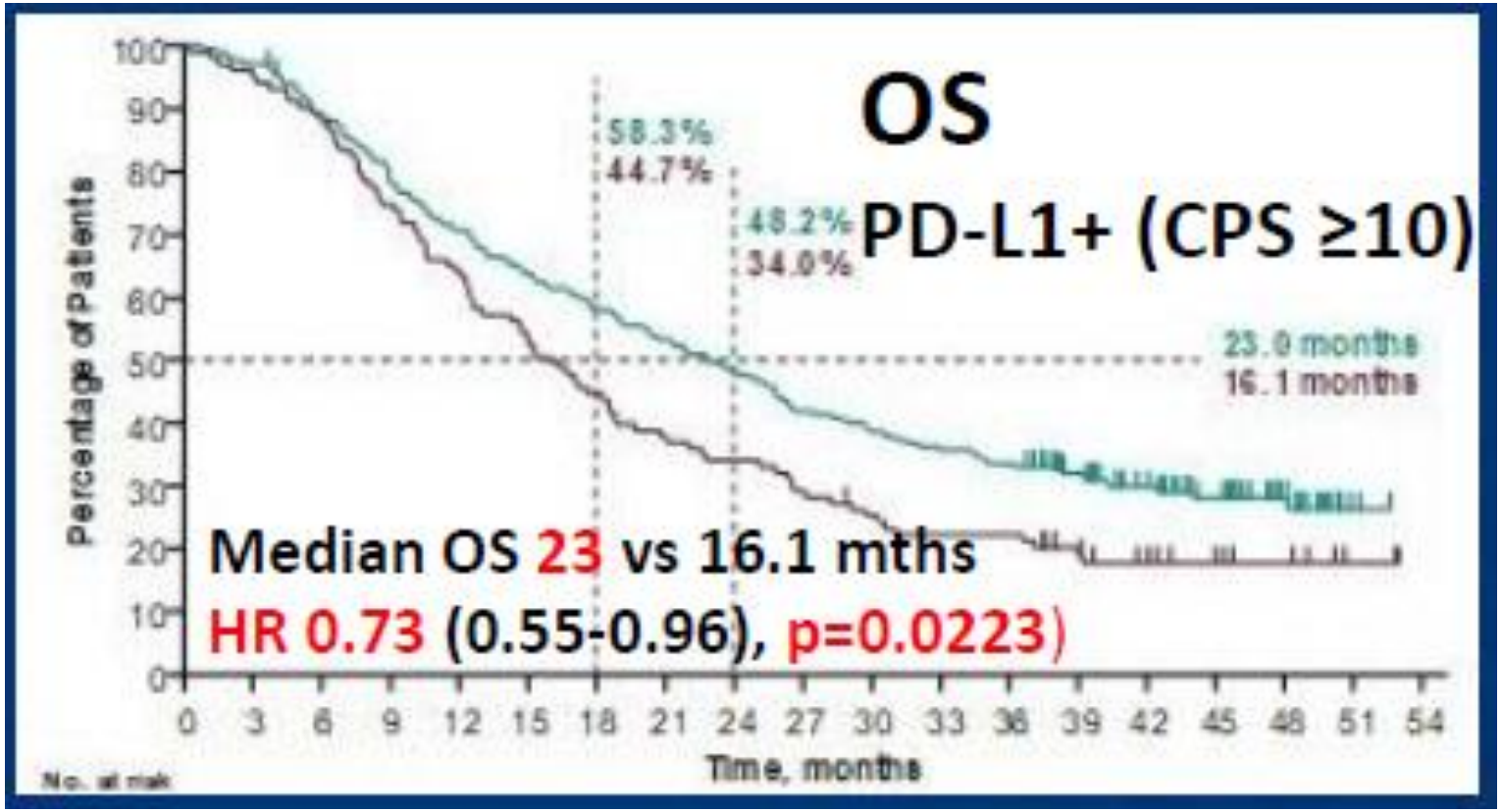
Emens LA, JAMA Oncol. 2019 Jan 1;5(1):74-82.
Adams S, Ann Oncol. 2019 Mar 1;30(3):405-411.
Adams S, Ann Oncol. 2019 Mar 1;30(3):397-404.

IMMUNOTHERAPY IN COMBINATION WITH CHEMOTHERAPY IN METASTATIC TNBC

Characteristic	IMpassion130	IMpassion131	KEYNOTE-355
No. of patients (PD-L1+)[a,b]	943 (292)	902 (369)	847 (323)
Random assignment	1:1	2:1	2:1
ICI therapy	Atezolizumab	Atezolizumab	Pembrolizumab
% with prior taxane therapy	51%	51%-53%	45%
Chemotherapy	Nab-paclitaxel	Paclitaxel	Paclitaxel Nab-paclitaxel Gemcitabine/carboplatin
PFS in ITT (placebo *v* ICI)	**5.5 *v* 7.2 months HR 0.79 (95% CI 0.69 to 0.91), *P* = .002**	5.6 *v* 5.7 months HR 0.86 (95% CI, 0.70 to 1.05)	5.6 *v* 7.5 months HR 0.82 (95% CI 0.69 to 0.97)[c]
PFS in PD-L1+	**5.3 *v* 7.5 months HR 0.63 (95% CI 0.5 to 0.8), *P* < .0001**	5.7 *v* 6 months HR 0.82 (95% CI 0.60 to 1.12), *P* = .2	**5.6 *v* 9.7 months HR 0.65 (95% CI 0.49 to 0.86), *P* = .0012**
OS in ITT	18.7 *v* 21.0 months HR 0.87 (95% CI 0.75 to 1.02), *P* = .077	22.8 *v* 19.8 months HR 1.12 (95% CI 0.88 to 1.43)	15.5 *v* 17.2 months HR 0.89 (95% CI 0.76 to 1.05)[c]
OS in PD-L1+	**17.9 *v* 25.4 months HR 0.67 (95% CI 0.53 to 0.86)[c]**	28.3 *v* 22.1 months HR 1.11 (95% CI 0.76 to 1.64)	**16.1 *v* 23.0 months HR 0.73 (95% CI 0.55 to 0.95), *P* = .0093**
% irAE (placebo *v* ICI)	41.8% *v* 57.3%[d]	53% *v* 62%[d]	6.4% *v* 26.5%

Jacob SL, JCO Oncol Pract. 2023 Apr;19(4):167-179.

Keynote 355: Biomarker



Benefit (OS) derived from Pembrolizumab related to PD-L1 expression

Cortes J, Lancet. 2020 Dec 5;396(10265):1817-1828.

Immunotherapy in Early-Stage TNBC

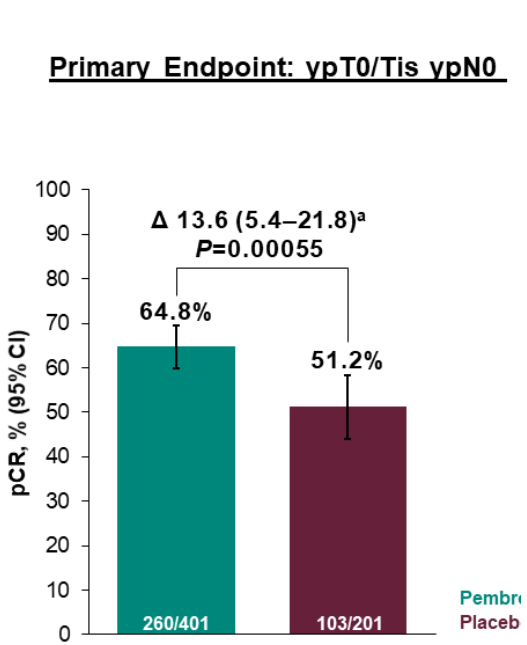
	I-SPY 2	GeparNUEVO	Neo-Trip
Phase	2	2	3
Number	250	174	280
Immune Therapy	Neoadj Pembro 4 cycles	Neoadj Durvalumab 5 cycles	Neoadj atezolizumab 8 cycles
Chemotherapy	Paclitaxel + AC	Nab-paclitaxel + EC	Nab-paclitaxel/carboplatin +adjuvant anthracycline
EFS/DFS/OS	**Not sig**	DFS 85.6% v 77.2%,p = 0.0398 OS 83.5% v 95.2%, p= .0108	Not reported
Adverse events	13.8% v 65.2%	95.1% v 96.7%	0.7% v 10.5%
p CR	22% v 60%	44.2% v 53.4% P =0.182	44.4% vs 48.6% P=0.48
Summary p CR improvement	Yes	No	No
EFS benefit	NR	Yes	NR

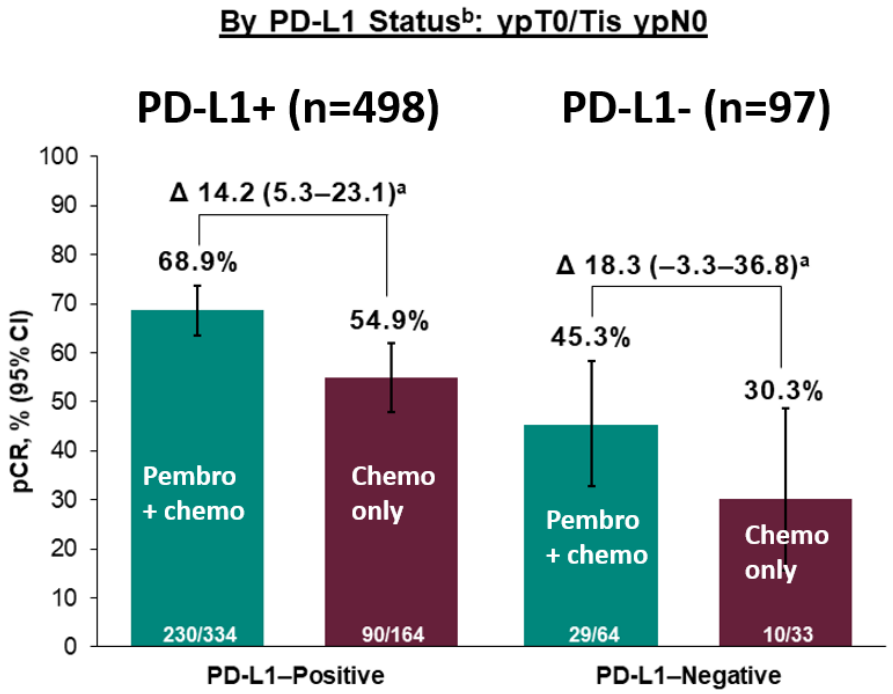
Immunotherapy in Early-Stage TNBC

	Key note-522	Impassion 031
Phase	3	3
Number	1174	333
Immune Therapy	Neoadjuvant=08 /adjuvant pembrolizumab=9 1 year	Neoadjuvant=10/adjuvant Atezolizumab=11 1 year
Chemotherapy	Paclitaxel/carboplatin+ AC	Nab-paclitaxel + AC
EFS/DFS/OS	76.8% v 84.5% P = .0003	Not reported
Adverse events	11.3% v 33.5%	60% v 70%[b]
p CR	51.2% v 63.8% p< .001	41.1% v 57.6% p = .0044
Summary p CR improvement	Yes	Yes
EFS benefit	Yes	NR

Keynote 522

PD-L1 expression **did not select** for patients who benefit from pembrolizumab
PD-L1+ tumors **more likely to achieve pCR**(with or without pembrolizumab)

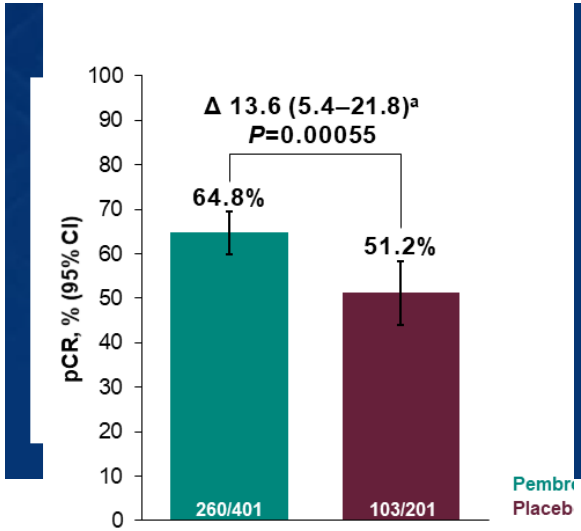


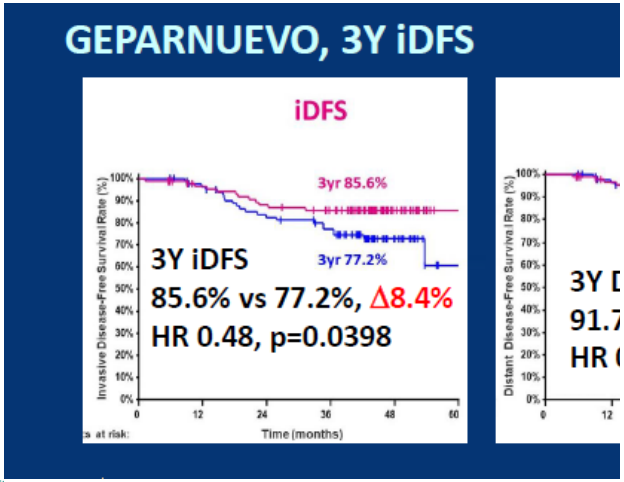


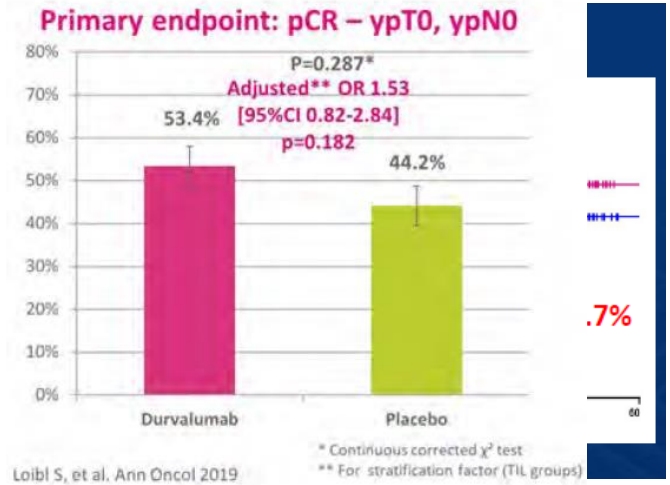
Schmid P, N Engl J Med. 2020 Feb 27;382(9):810-821.

P CR might not reliably predict OS/DFS

Primary Endpoint: ypT0/Tis ypN0







Schmid P, N Engl J Med. 2020 Feb 27;382(9):810-821
Loibl S, Ann Oncol. 2019 Aug 1;30(8):1279-1288.

Hormone receptor Positive Breast Cancer

- HR+ breast cancer is generally a more indolent breast cancer subtype with: Low PD-L1 expression
- Low numbers of TILs density
- HR+/HER2-cancers have lowest level of HLA class I expression compared to other subtypes1

KEYNOTE-028 (NCT02054806) study.

Median duration of response:12.0 months
Grade 3 adverse effects: 20%

	N = 25	95% CI
Overall response rate, *n* (%)	3 (12)	2.5–31.2
Clinical benefit rate[b], *n* (%)	5 (20)	6.8–40.7
Best overall response[c], *n* (%)		
CR	0 (0)	0.0–13.7
PR	3 (12)	2.5–31.2
SD	4 (16)	4.5–36.1
Progressive disease	15 (60)	38.7–78.9
No assessment[d]	3 (12)	2.5–31.2

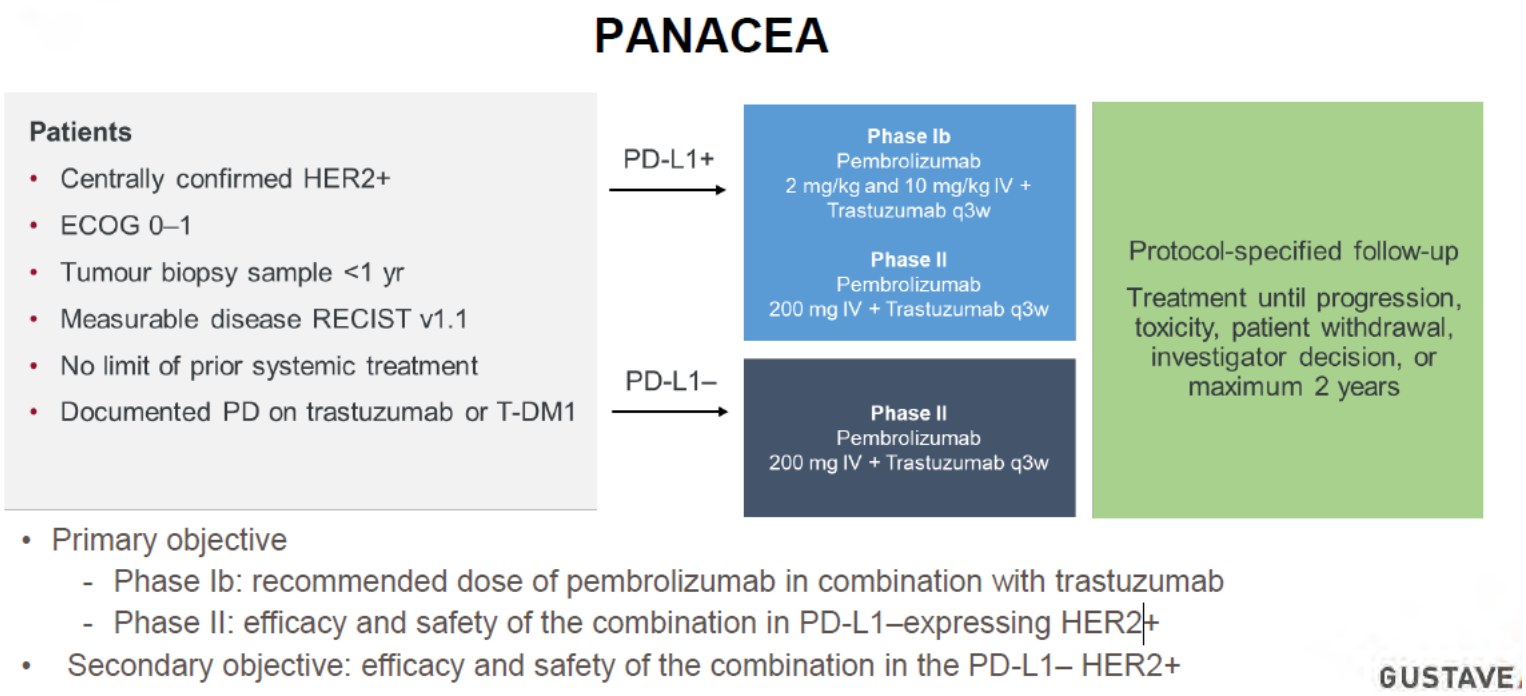
Rugo HS, Cancer. Clin Cancer Res. 2018 Jun 15;24(12):2804-2811.

Her2+ve breast cancer

HER2+ breast cancer is generally characterized by:

- Greater numbers of TILs
- Significant rates of PD-L1 positivity
- Higher mutational rate

Immunotherapy in hormone receptor–negative, HER2+breast cancer

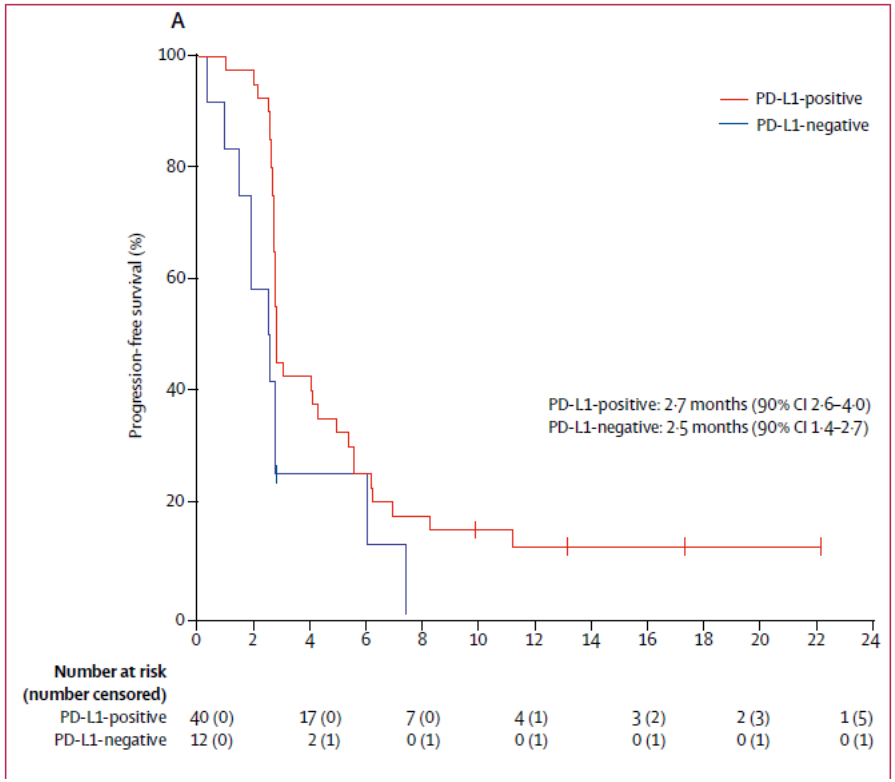


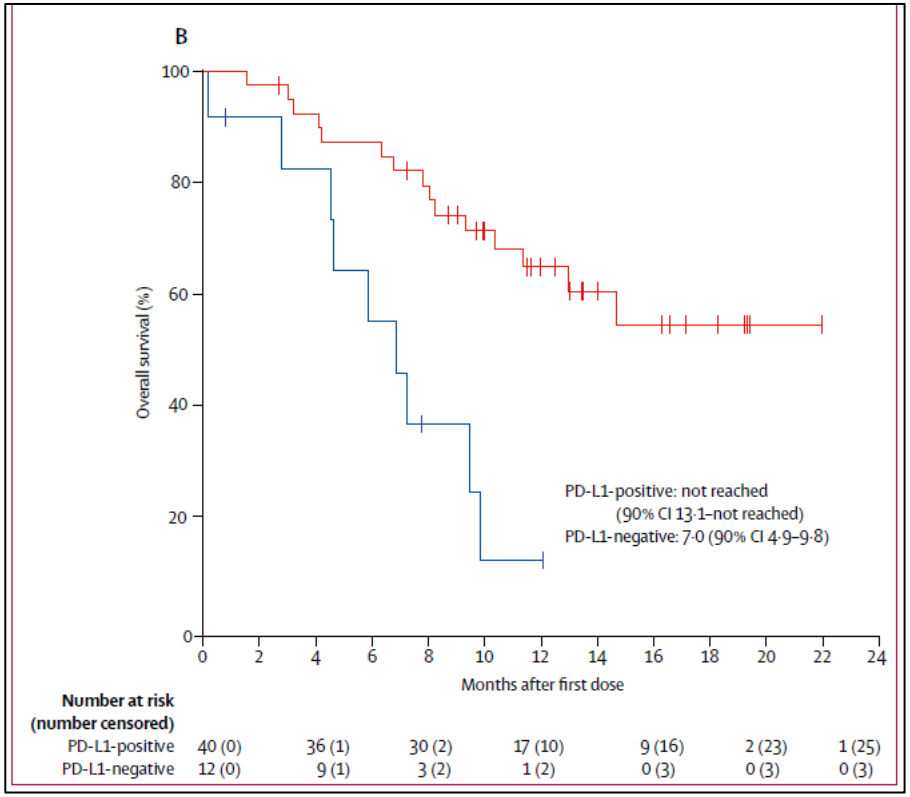
Ann Oncol. 2019 Aug 1;30(8):1279-1288.

HER+ve Breast Cancer Metastatic Setting

Overall response: 15.2%

Median duration of control:11 months

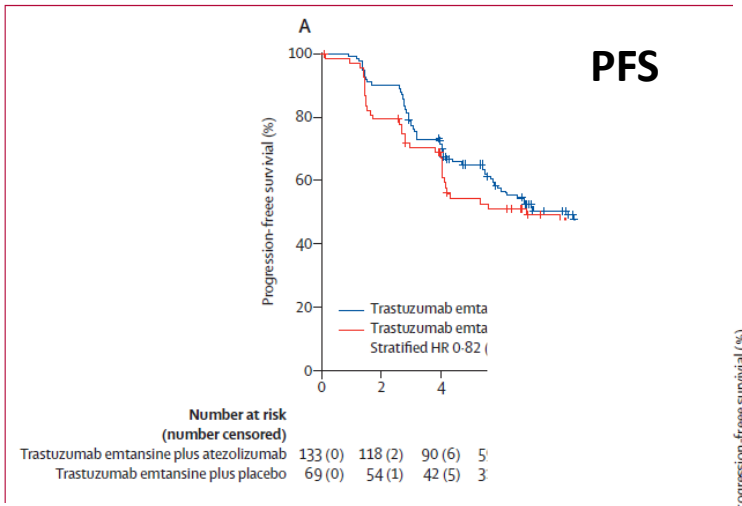




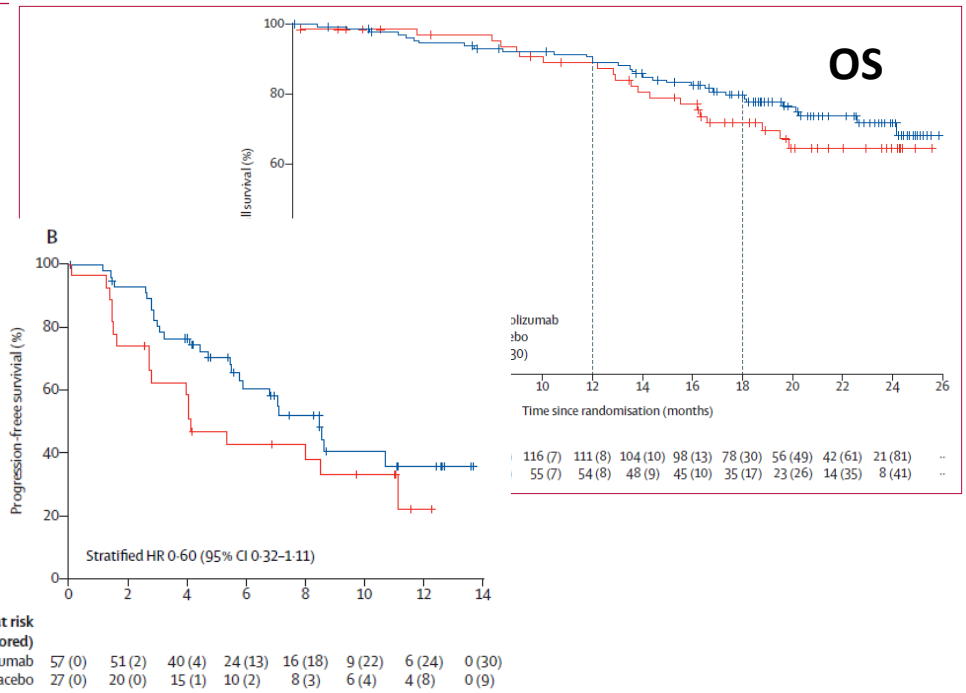
Ann Oncol. 2019 Aug 1;30(8):1279-1288.

HER+ve Breast Cancer Metastatic Setting : Atezolizumab+TDM1

(KATE2): a phase 2, multicentre, randomised, double-blind trial



PFS

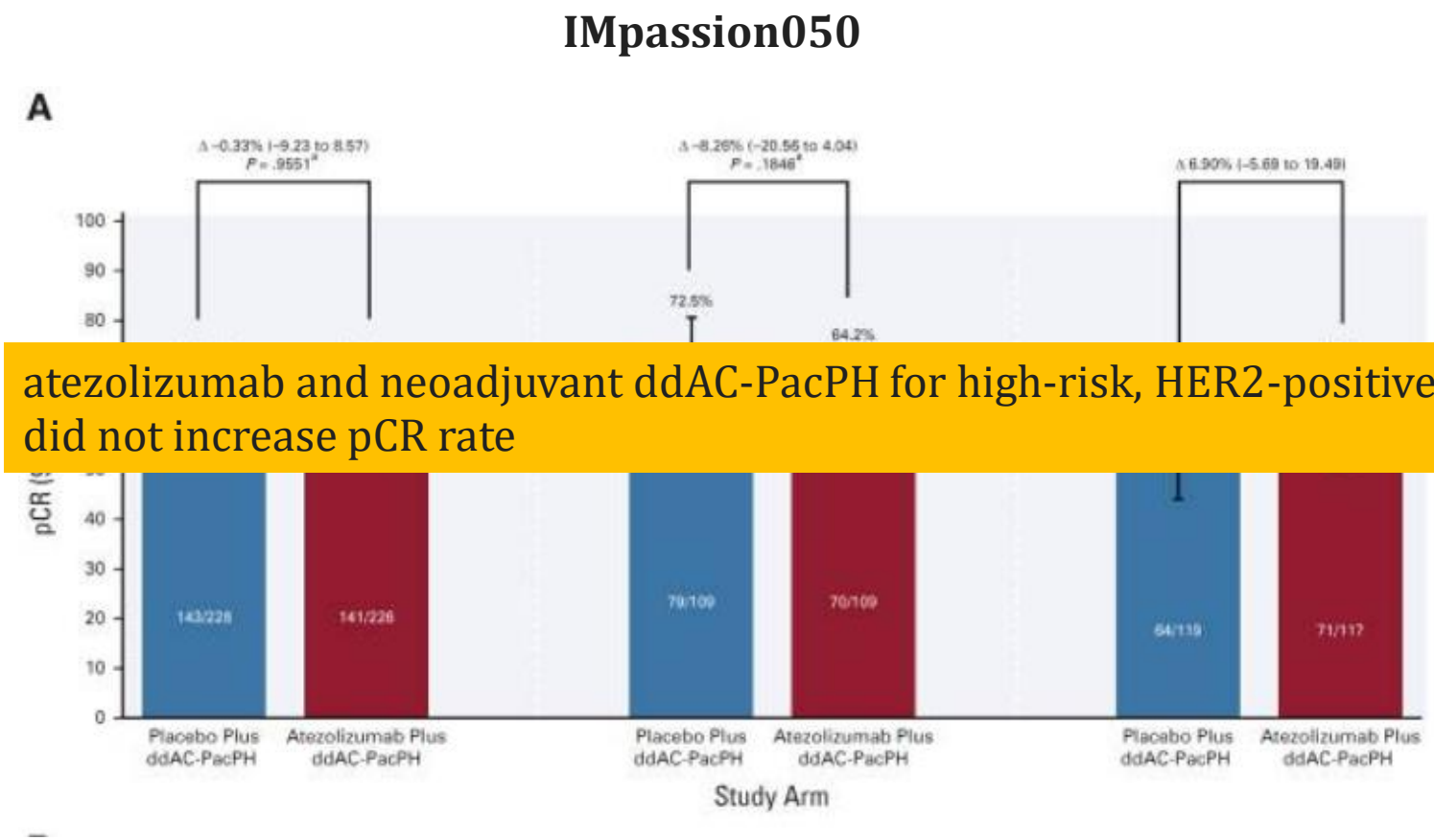


OS

Addition of atezolizumab to trastuzumab emtansine did not show a clinically meaningful improvement in progression-free survival and was associated with more adverse events.

Emens LA, Lancet Oncol. 2020 Oct;21(10):1283-1295.

Her2Neu +ve early breast cancer



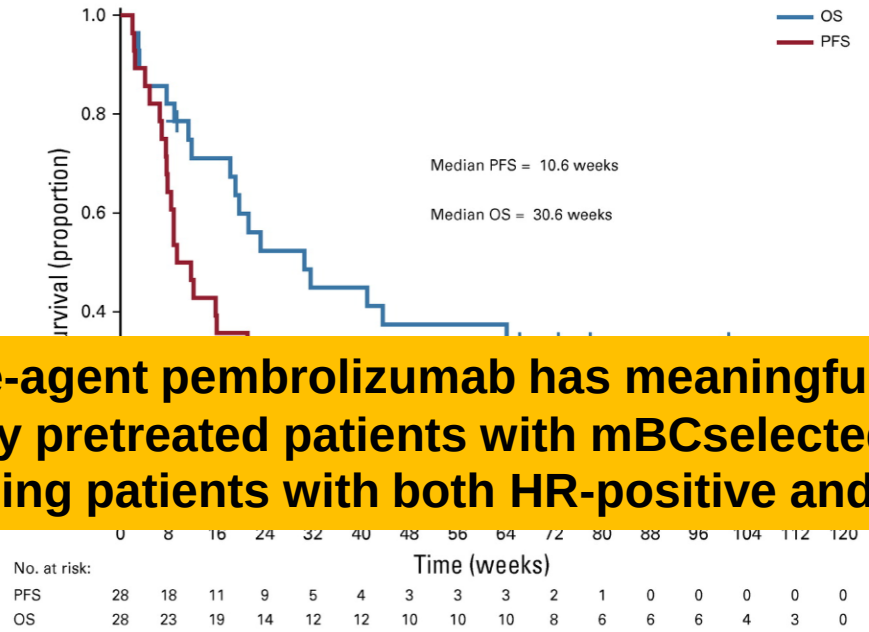
atezolizumab and neoadjuvant ddAC-PacPH for high-risk, HER2-positive EBC did not increase pCR rate

Huober J, J Clin Oncol. 2022 Sep 1;40(25):2946-2956.

Agonistic Indications: Tumors with high tumor mutational burden

TAPUR

Cohort of patients with Metastatic breast cancer (mBC) with high tumor mutational burden (HTMB) treated with pembrolizumab



TMB ranged from 9 to 37 Mut/Mb, with a median value of 13 Mut/Mb.

OR rate was 21%

Single-agent pembrolizumab has meaningful clinical activity in heavily pretreated patients with mBCselected for HTMB, including patients with both HR-positive and TNBC

Evidence of use of immunotherapy in different molecular subtypes: Conclusions

Role of immunotherapy in **TN breast cancer:**

- ICIs have demonstrated efficacy in combination with chemotherapy in the treatment of both early- and late-stage TNBC
- In metastatic TN breast cancer: likely benefit in patients with PD-L1 positive cancer
- In stage II-III TN breast cancer: efficacy independent of PD-L1 expression
- No validated biomarkers besides PD-L1 IHC for metastatic (but not localised) TNBC

Evidence of use of immunotherapy in different molecular subtypes: Conclusions

Role of immunotherapy in HR+ve breast cancer:

-low TIL infiltration and minimal response to ICB

-Immunosuppressive TME characterized by TAMs and low levels of tumor HLA-I expression, limits antitumor immune activity and may be the culprit for T cell and NK cell exclusion

Multiple ongoing studies in metastatic and neoadjuvant settings that may better define the role of IT in this setting

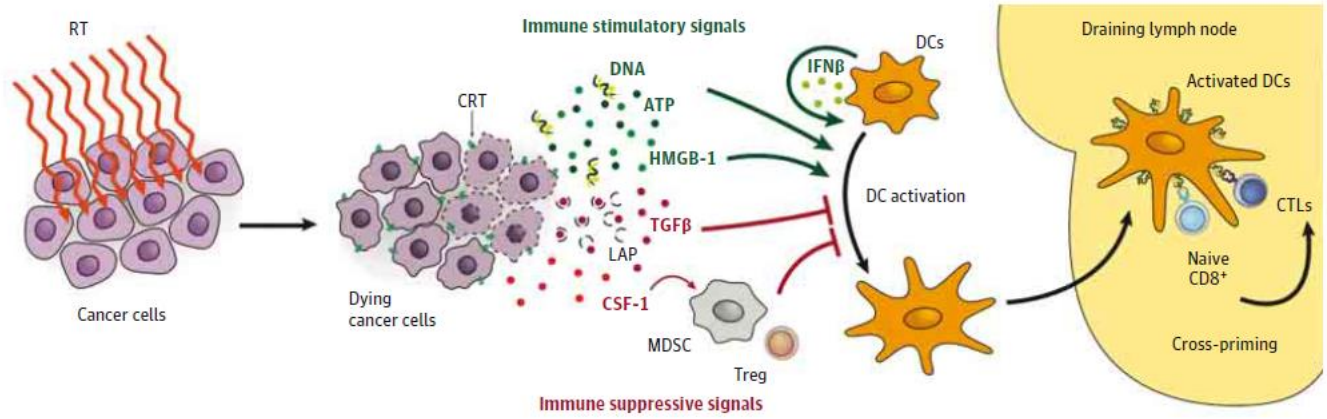
Role of immunotherapy in HER+vebreast cancer:

- Possible combination with anti-HER2, Role evolving

Immunotherapy combination with radiation in breast cancer

- The immune system has long been recognized for its role in RT- mediated tumor responses.
- Radiotherapy can induce antigen release, increasing the recruitment of antigen-presenting cells and stimulating T-cell responses

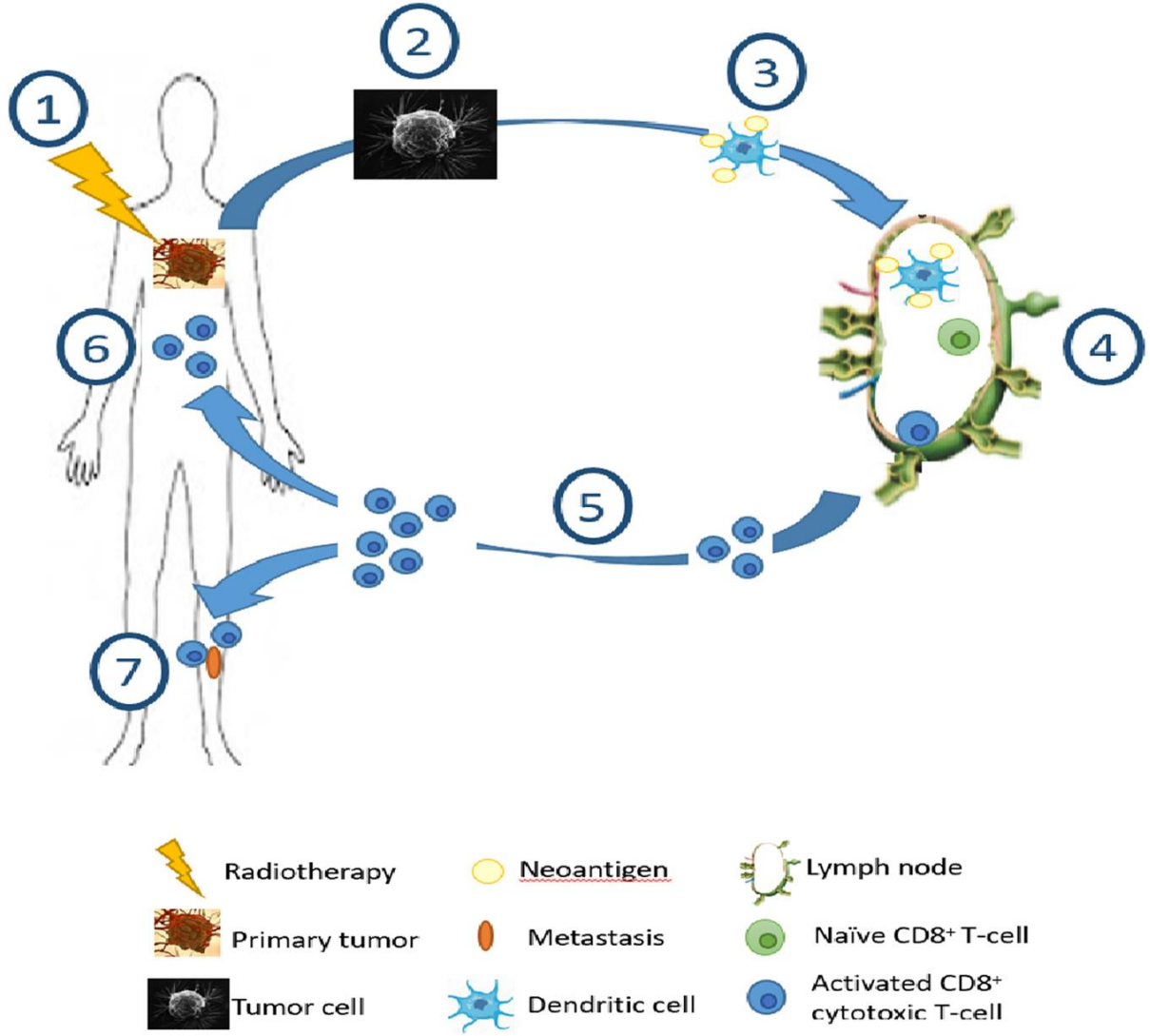
Figure 1. Generation of Antitumor T Cells by Radiation



- antitumor immune responses generated in the irradiated tumor may lead to systemic antitumor immunity, also known as the abscopal effect.
- have demonstrated that targeting various aspects of the immune system can augment antitumor immunity following RT.

Demaria S,JAMA Oncol. 2015 Dec;1(9):1325-32.

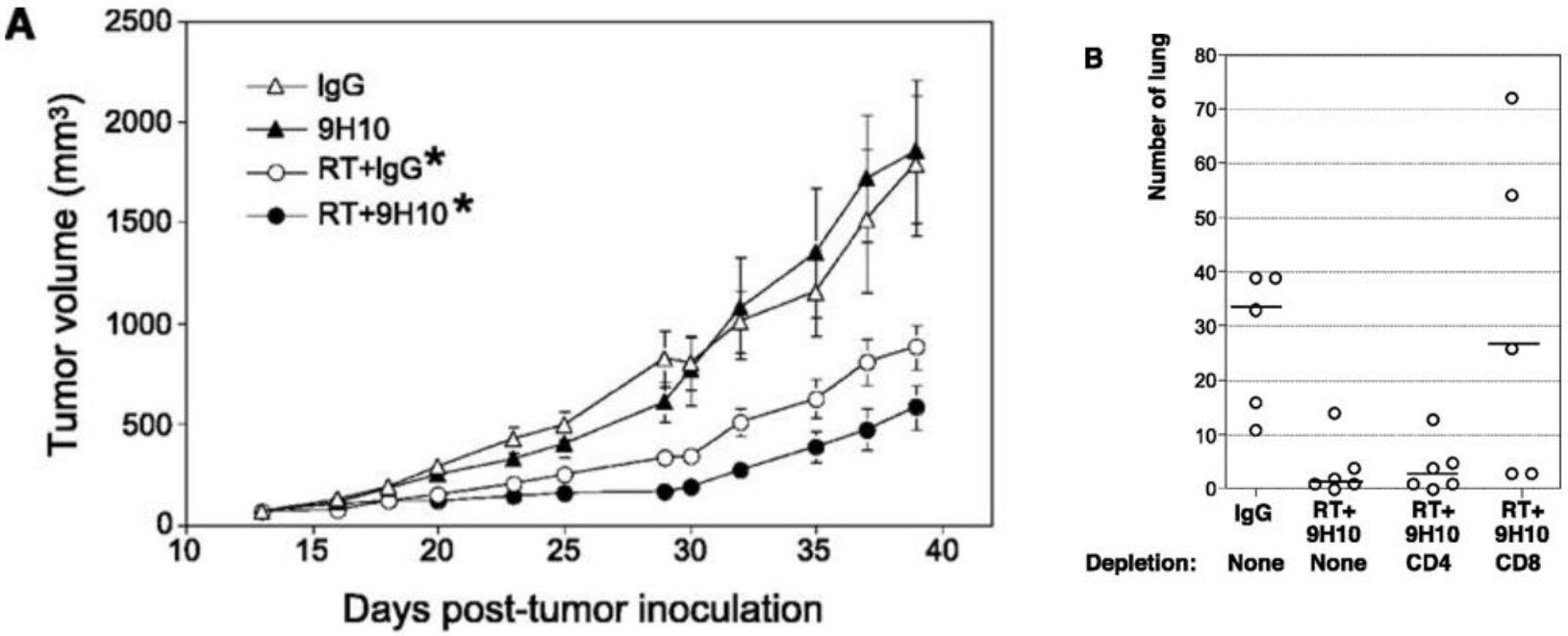
Primary response and abscopal effect



Preclinical Rationale for Combining RT and ICB

Early preclinical studies combining RT with ICB were performed in murine models of breast cancer and demonstrated synergy.

- Combining RT with an anti-CTLA-4 antibody significantly delayed metastases and improved survival in a breast cancer model.
- this synergy was augmented by administering short courses of fractionated RT and by administering anti-CTLA-4 prior to RT



Demaria S,Clin Cancer Res (2005) 11 (2): 728–734.

Clinical Rationale for RT with ICB in Breast Cancer

Trial	Voorwerk et al TONIC	Ho etal	Barroso-Sousa et al
Phase	2	2	2
N	12	17	8
Tumor Type	mTNBC	mTNBC	HR + /HER2 –mBC
Intervention	Sequential RT (24 Gy in 3 fractions) and atezolizumab	Concurrent RT (24 Gy in 3 fractions) and pembrolizumab	Pembrolizumab prior (2-7 days) to RT (20 Gy in 5 fractions)
Overall Response Rate	12%	17.6%	0%
Toxicity (Grd3-5)	5	4	1

Ongoing Trials of RT and ICB in Metastatic Breast Cancer

Table 2 Combination Radiotherapy and Immune Checkpoint Blockade Clinical Trials in Metastatic Breast Cancer

NCT Number	Phase	N	Status	Tumor Type	Intervention	Sponsor
NCT03004183	2	57	Recruiting	mTNBC or mNSCLC	ADV/HSV-tk + valacyclovir + pembrolizumab + SBRT (30 Gy in 5 fractions)	Houston Methodist Cancer Center
NCT03449238	1/2	41	Recruiting	mBC with brain metastases	Pembrolizumab + SRS	Weill Cornell College of Cornell University
NCT03464942	2	52	Recruiting	mTNBC	Atezolizumab + SBRT (20 Gy in 1 fraction or 24 Gy in 3 fractions)	Peter MacCallum Cancer Centre, Australia; Trans Tasman Radiation Oncology Group, TROG
NCT03524170	1	20	Recruiting	$HR^+/HER2^-$ mBC	M7824 (Anti-PD-L1/TGFβ Trap) + RT	MD Anderson Cancer Center
NCT03789097	1/2	56	Recruiting	Multiple tumor types, including mBC	Pembrolizumab + CDX-301 (Flt3 ligand) + RT + Poly-ICLC (TLR3 agonist)	Icahn School of Medicine at Mount Sinai

Nguyen AT, Clin Breast Cancer. 2021 Apr;21(2):143-152.

Efficacy in the preoperative setting

Phase1/2 trial of 50 patients TNBC with early breast cancer

- Pre-operative pembro (200mg IV)
- 3 weeks later: pembro (200mg IV) plus RT (24 Gy/3 fractions) to the primary breast tumor
- 3-5 weeks later: by standard-of-care (SOC) neoadjuvant chemotherapy
- Ommision of boost in adjuvant RT

- **Interim analysis of 20 patients: 60% p CR , no grade 3 toxicity**

Mc Arthur et al,Cancer Res (2020) 80 (4_Supplement): P3-09-09.

Current evidence and areas of contention : Dose fractionation & volumes

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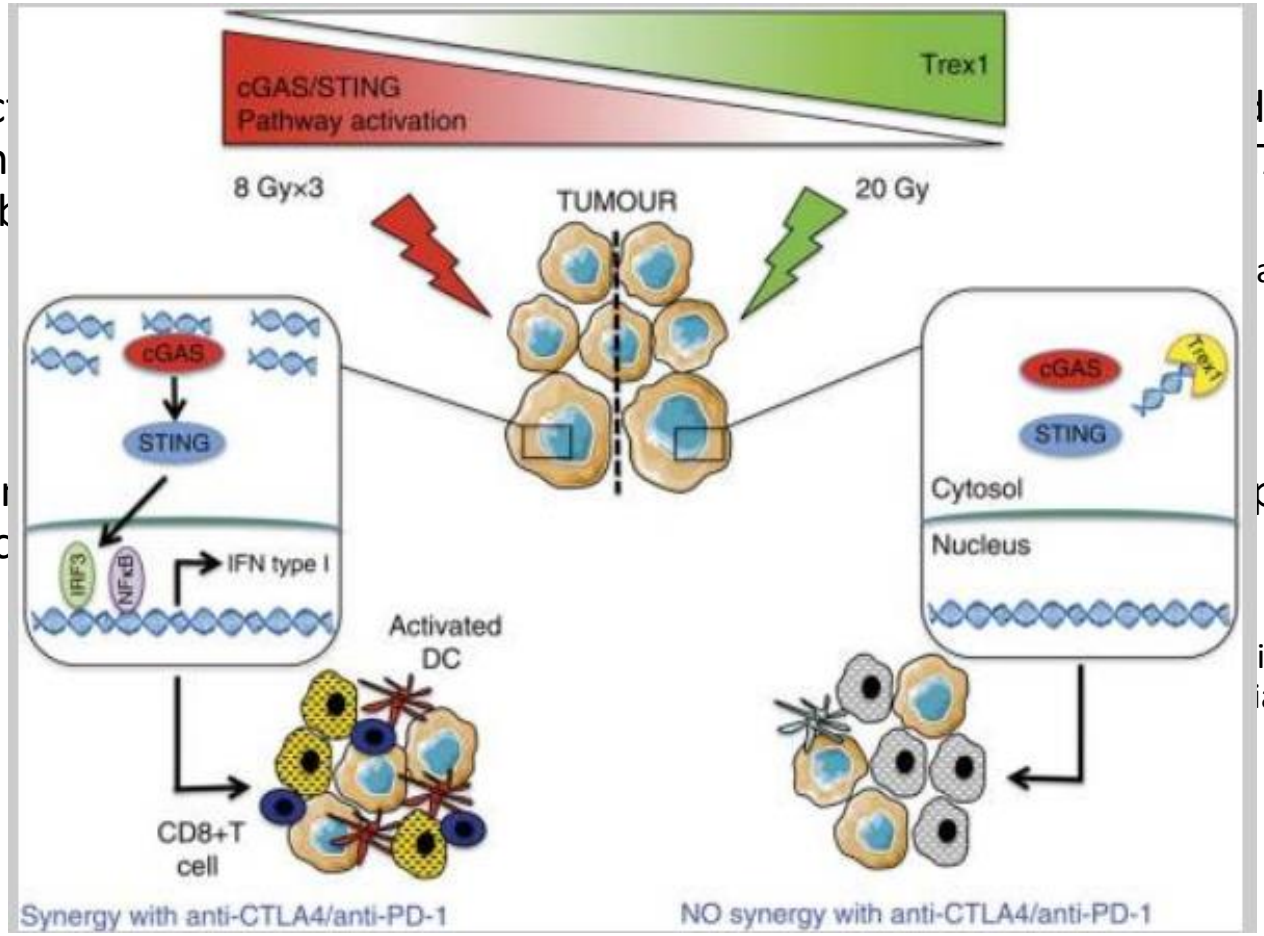

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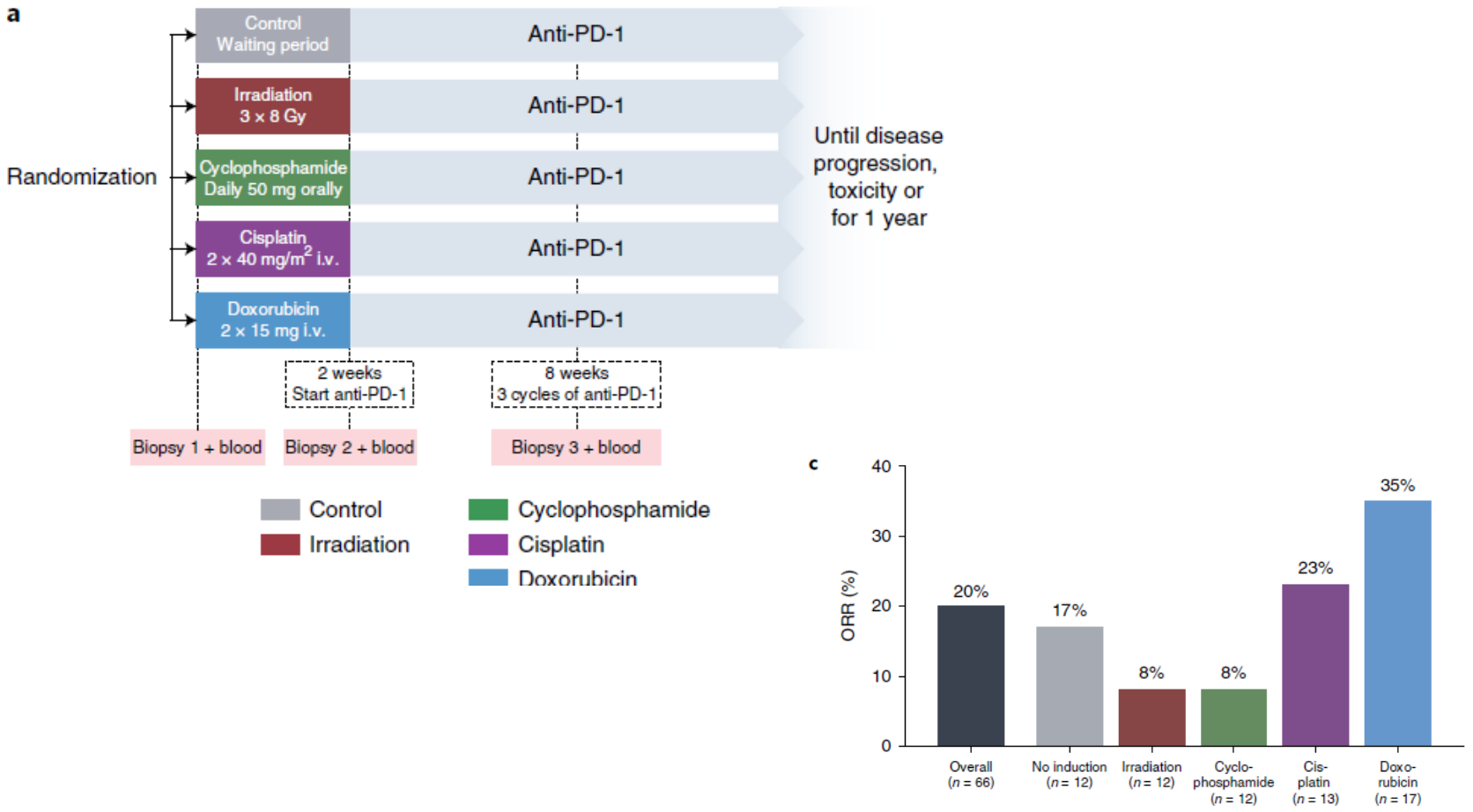
Vanpouille-Box C, Nat Commun. 2017 Jun 9;8:15618.

RT for abscopal effects

- No clear dose response trend to RT.
- Neither very low doses of radiation nor stimulated objective responses in nonirradiated lesions
- No dose of radiation will reliably elicit an abscopal response when combined with therapies targeting the CTLA-4 or PD-1/L1axis.
- Alternatively, radiation clearly exerts strong anti-tumor and immunologic effects locally.
- Irradiate1-2 lesions with high dose ablative RT and then irradiate remaining lesions with lowdose RT, an approach that proponent term“Radscopal”therapy.

Fitzgerald KJ ,Semin Radiat Oncol. 2023 Jul;33(3):327-335.

Immune induction strategies in metastatic triple-negative breast cancer



Voorwerk L, Nat Med. 2019 Jun;25(6):920-928.

RT- IT timing: The optimal RT-IT timing remains to be established

- Radiation-enhancement factor for IT ranged from 1.7 to 9.1, which was much higher than e.g. for cisplatin (1.1), thus supporting use of combined RT and IT in the clinical setting

- Combining RT (5×6 Gy) concurrently with pembrolizumab seemed promising (Ho et al., 2020b). IT should be given concurrently or ≤ 7 days after SBRT

- Bearing in mind the potential for overall toxicity and persistent immunological interactions, day+ 2 after SBRT appeared optimal according to vascular permeability and preclinical outcome studies.

- In summary, data on optimal timing are conflicting and translational research is required to unravel underlying biological mechanisms

Aristei C, Crit Rev Oncol Hematol. 2023 Jul;187:104035.

Advances in Combining Radiation and Immunotherapy :Several challenges need to be resolved

- The selection of patients with breast cancer likely to benefit from the immunotherapy–radiotherapy combination remains a challenge
- Secondly, the timing of RT relative to immunotherapy administration is quite heterogeneous.
- No clear RT dose has emerged as a clear winner for stimulating an abscopal effect.
- Future trials will likely focus on delivering radiation to most or all sites of gross disease.

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