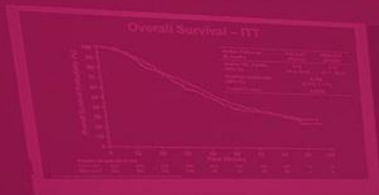
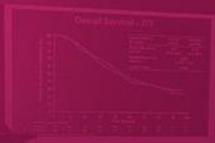


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REALIZAÇÃO



Future of Immunotherapy in Breast Cancer

Giampaolo Bianchini MD

Associate Professor - *Università Vita-Salute San Raffaele*
Head Breast Cancer Group
Head translational and clinical immunotherapy research
IRCCS Ospedale San Raffaele
Milan, Italy



UniSR
Università Vita-Salute
San Raffaele

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Instituto Projeto
cura.

Disclosures

Dr Bianchini has received honoraria for consultancy/advisory role/speaker fee from AstraZeneca, Daichii Sankyo, Eisai, Exact Science, Gilead, Eli Lilly, MSD, Novartis, Pfizer, Roche, Sanofi, Seagen, Menarini/Stemline and Agendia

Know where you have
been, where you are now
and where you want to be.

Jim Valvano

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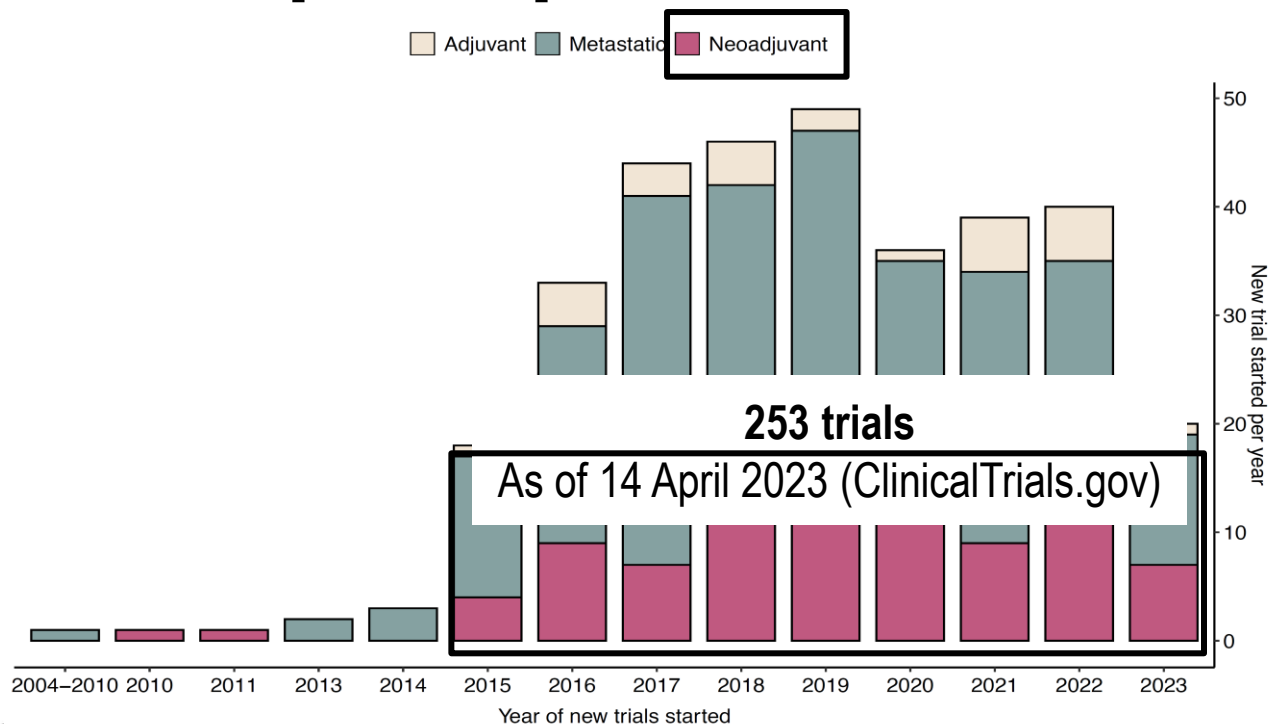
Immunotherapy in Breast Cancer

Past

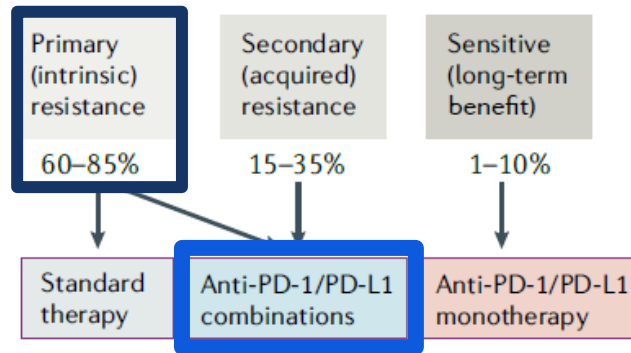
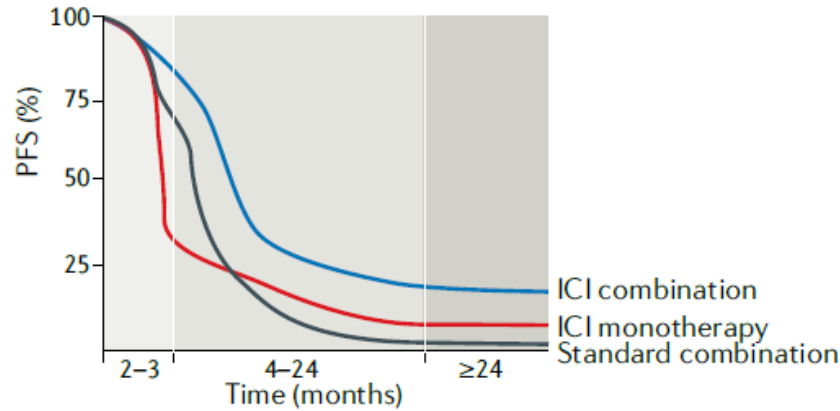
Present

Future

Completed, ongoing and planned trials of immunotherapies in patients with breast cancer



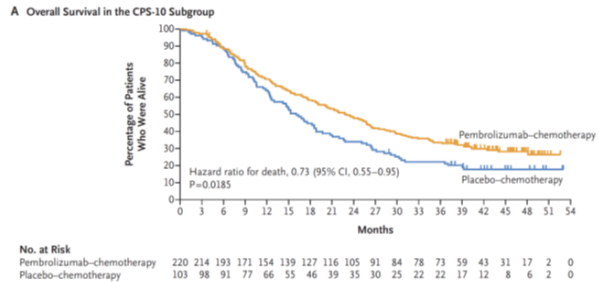
ICI monotherapy in (poorly selected) breast cancer patients is active, but it is not effective



Immunotherapy in advanced TNBC (only for “PD-L1” positive tumors)

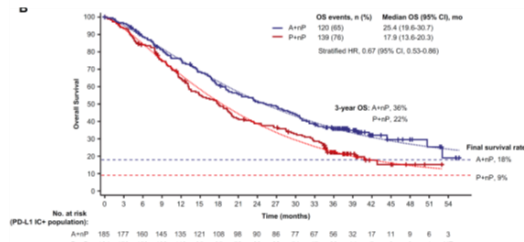
Advanced TNBC (1st line)
(only for “PD-L1” positive patients)

KEYNOTE 355
(CPS≥10, 22C3 Dako)



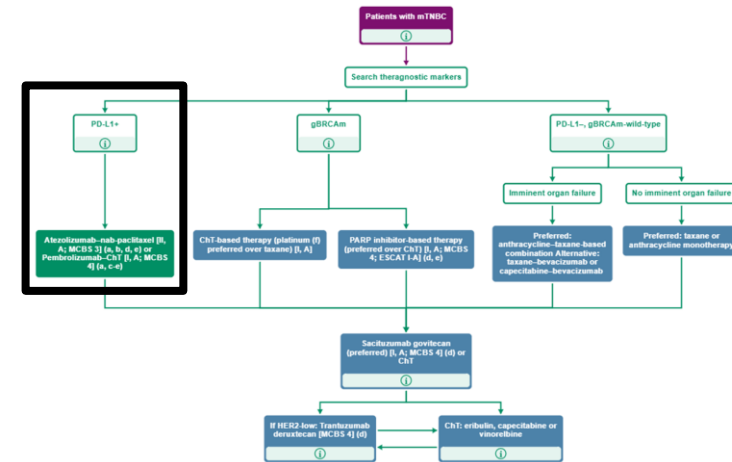
Cortes J NEJM 2022

IMpassion130
(IC≥1, SP142 Ventana)



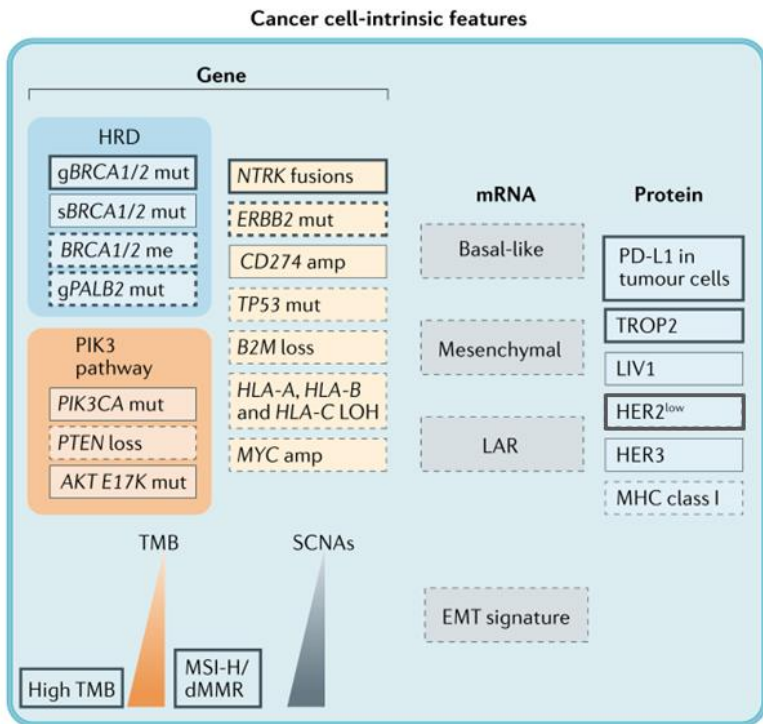
Emens LA Ann Oncol 2021

ESMO guidelines

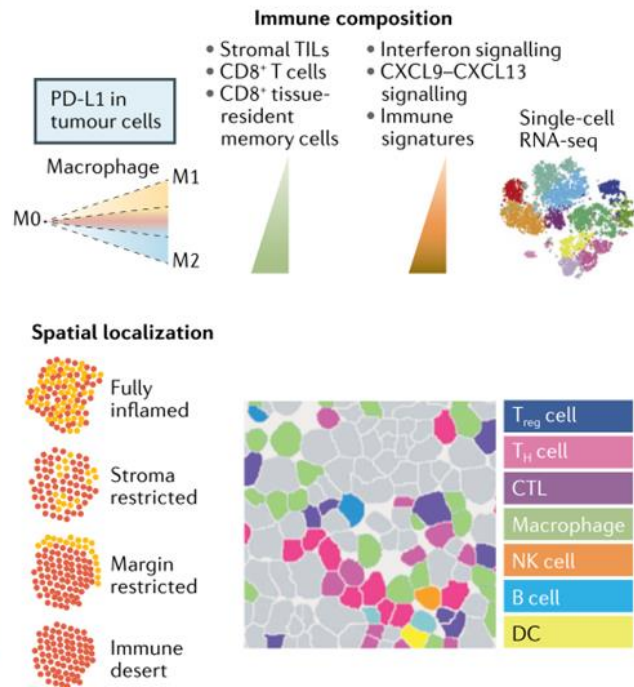


G Curigliano, Living Guidelines, ESMO Breast 2023

Breast cancer is an ecosystem resulting from the co-evolution of cancer-cell and the tumor microenvironment

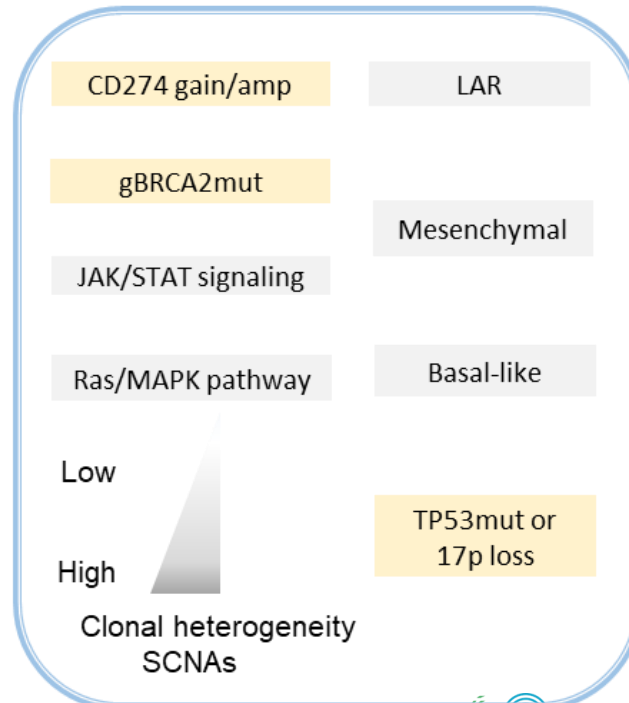


Cancer cell-extrinsic features (TME)

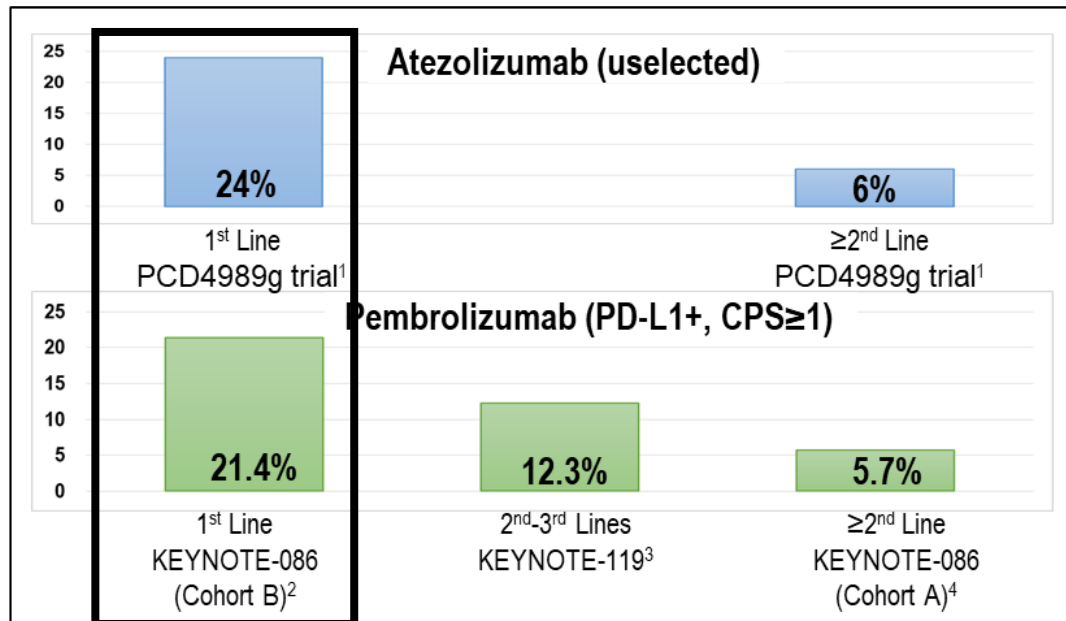
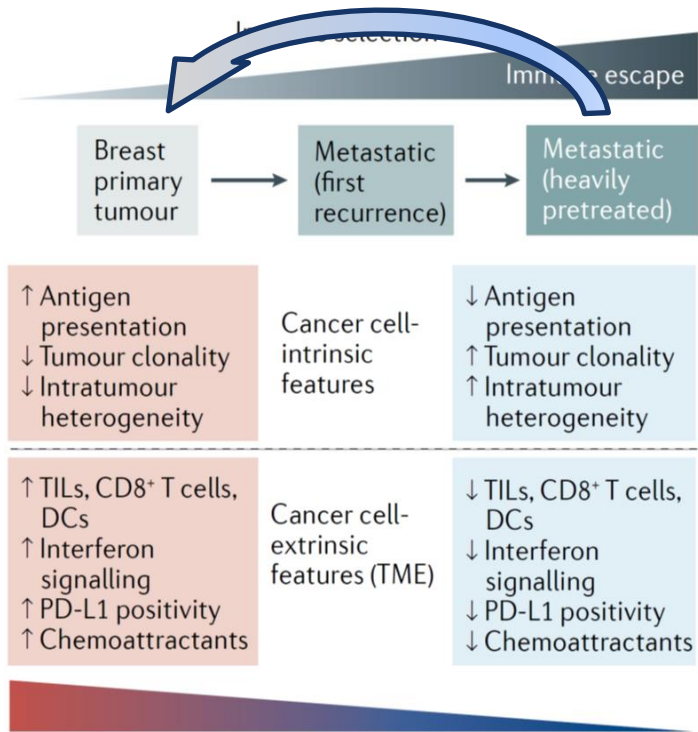


Tumor/immune co-evolution as integrated system

Cancer cell

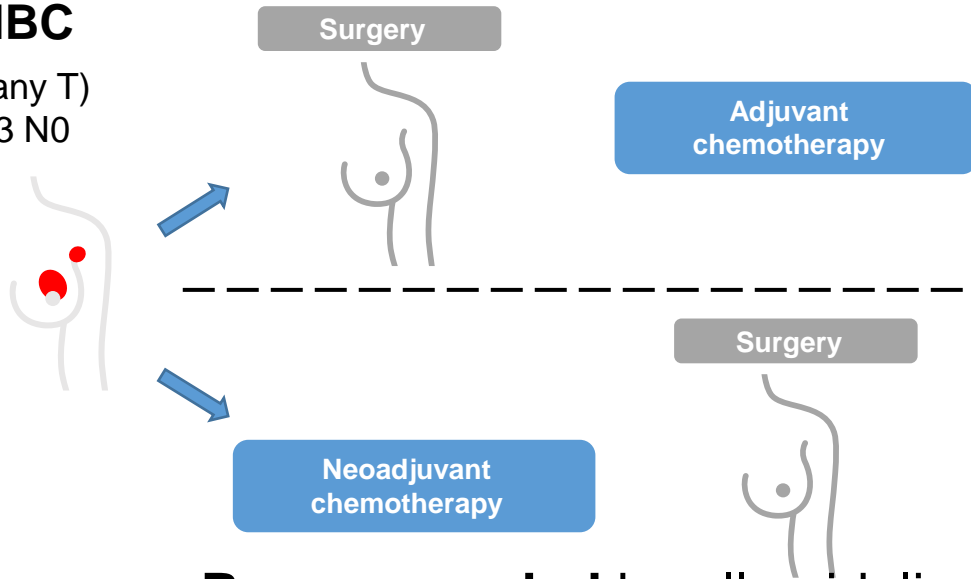


Implication of tumor/immune co-evolution



Neoadjuvant vs adjuvant chemotherapy: different approaches with similar results

TNBC
N+ (any T)
T2/T3 N0

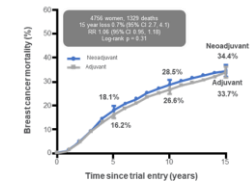


Recommended by all guidelines

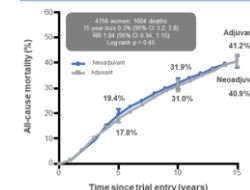
Same chemotherapy
Same chance to be cured

EBCTCG Meta-analysis

Breast cancer mortality



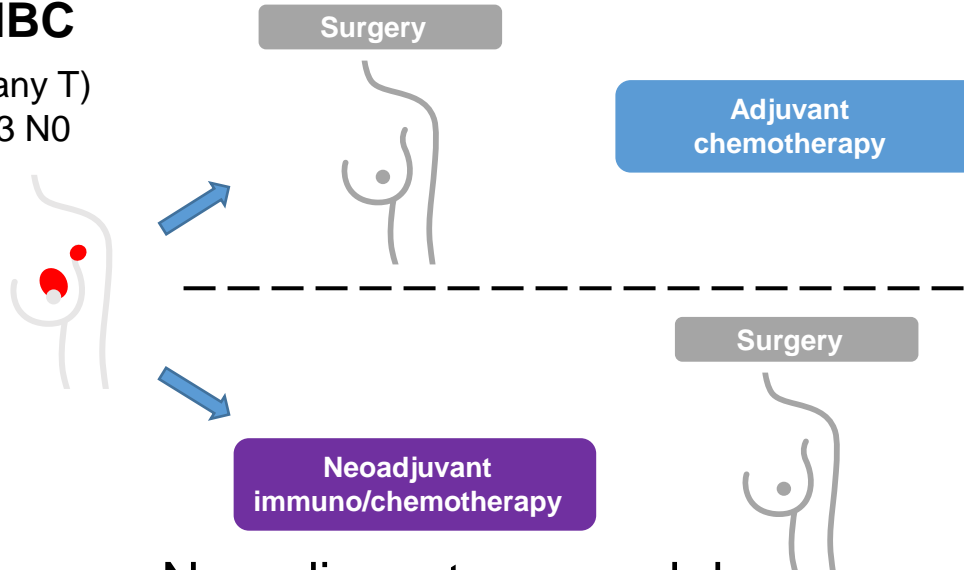
All-cause mortality



Neoadjuvant immunotherapy: different therapies with different results

TNBC

N+ (any T)
T2/T3 N0

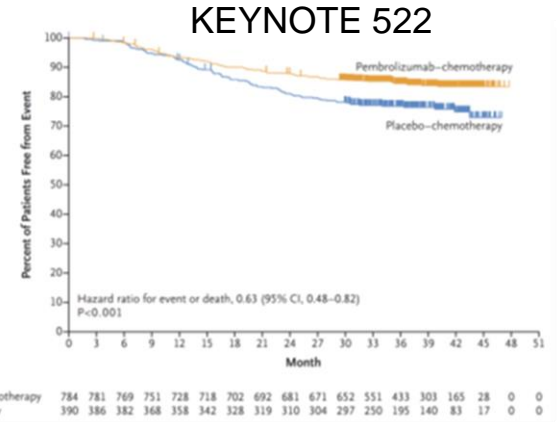
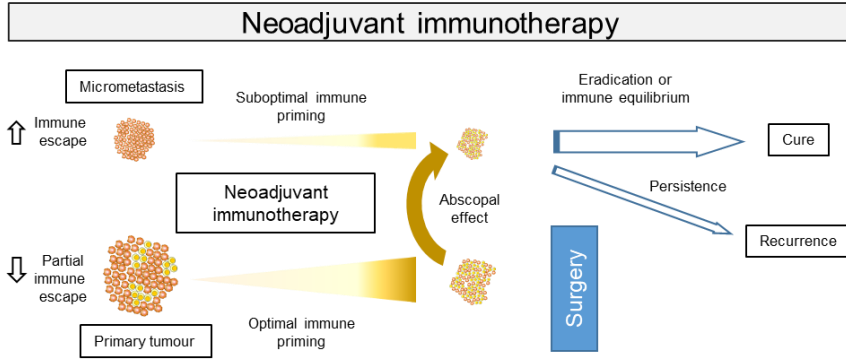


DETRIMENTAL

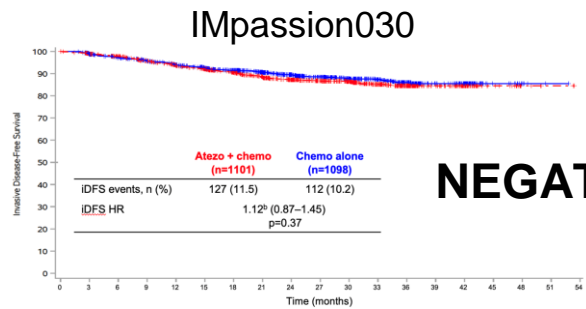
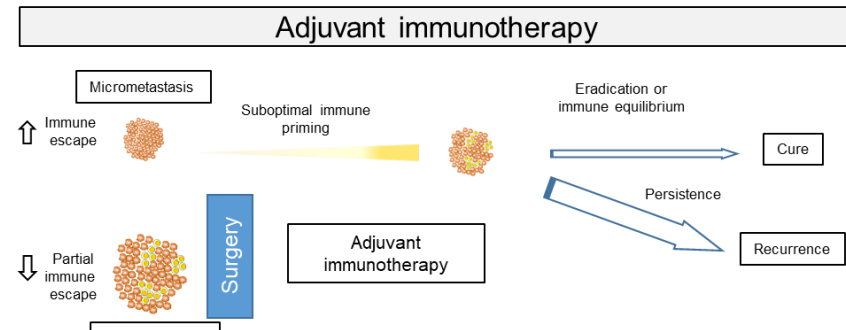
Different therapies
Different chance to be cured

Neoadjuvant approach become **mandatory**
(unless immunotherapy is not indicated or recommended)

Neoadjuvant vs adjuvant immunotherapy



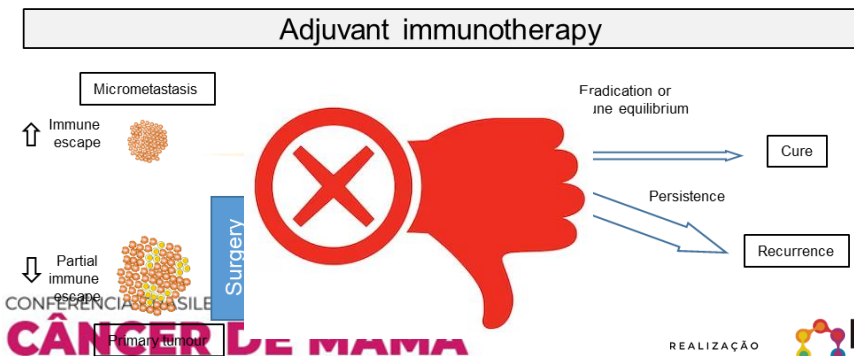
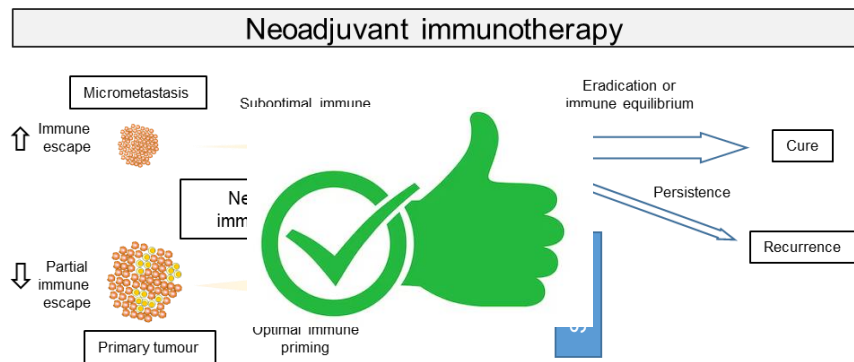
Schmid P NEJM 2022



NEGATIVE

Neoadjuvant vs adjuvant immunotherapy in advanced melanoma

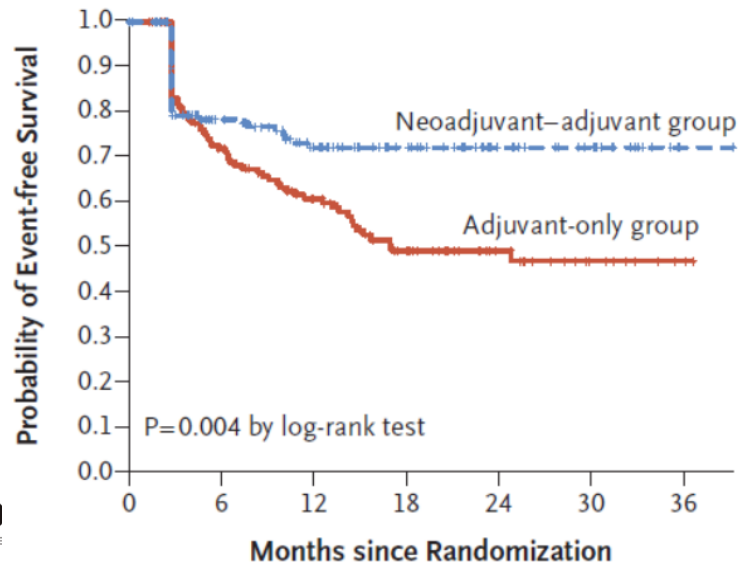
The NEW ENGLAND JOURNAL of MEDICINE



ORIGINAL ARTICLE

Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

S.P. Patel, M. Othus, Y. Chen, G.P. Wright, Jr., K.J. Yost, J.R. Hynstrom,



Immunotherapy in Breast Cancer

Past

Present

Future

Landscape of anti-PD-1/anti-PD-L1 combination strategies IN TNBC

Radiotherapy and cryoablation

Stereotactic Ablative Body Radiosurgery
Brain radiotherapy or Stereotactic IORT
Cryoablation
Microwave ablation
High intensity focused ultrasound

Immunotherapies

Intra-lesional GM-CSF and imiquimod
Tavokinogene telseplasmid
Talimogene laherparepvec (T-VEC)
Adenoviral-mediated IL-12
Intratumorally Injected Autologous DC

Antiangiogenic

Bevacizumab
Lenvatinib
Apatinib
Cabozantinib
Anlotinib
Ab anti-VEGFR-2
Surufatinib

Molecular target therapies

MEK inhibitors
AKT inhibitors
Histone deacetylase inhibitor
Hypomethylating agent
JAK inhibitor
AXL kinase inhibitor
Antiprogesterin
Selective Androgen Receptor Modulator
Androgen receptor inhibitor
Multi-TKIs
MET-inhibitor
PLK4 inhibitor
Proto Pump Inhibitor (PPI)
Proteasome inhibitor
CDK inhibitors (palbociclib, dinaciclib)
PI3K inhibitors
Angiotensin II receptor blocker
Anti EGFR
BET inhibitor
ATR kinase inhibitor

Antiangiogenic

Local therapy

Fasting-like approach

Anti-PD-1
Anti-PD-L1

Chemotherapy

Targeted therapy

Immunotherapy

Chemotherapy

Paclitaxel
Nab-paclitaxel
Docetaxel
Teseaxel
Doxorubicin
Epirubicin
Pegylated liposomal doxorubicin
Pegylated liposomal irinotecan
Cyclophosphamide
Cisplatin
Carboplatin
Eribulin mesylate
Capecitabine
Gemcitabine
Fluorouracil
Dacarbicine

PARP inhibitors

Olaparib
Talazoparib
Veliparib
Fluzoparib
Niraparib

Antibody drug conjugates

Sacituzumab govitecan
Ladiratumab vedotin
Trastuzumab deruxtecan
Datopotamab deruxtecan
Anti-CD166 (Probody drug conjugate)

T-cell targeted immunomodulator

Anti-CTLA4
Anti-LAG3
Anti-TIGIT
Anti-CD137 agonistic antibody
Anti-OX40 agonistic antibody
Anti-CD40 agonistic antibody

Cancer vaccine

Autologous whole cell cancer
Multi-peptide therapeutic cancer
Neoantigen personalized
Genetically engineered whole-cell
Modified Ankara–Bavarian Nordic
Other vaccines

Adoptive T cell therapy

Immunomodulators

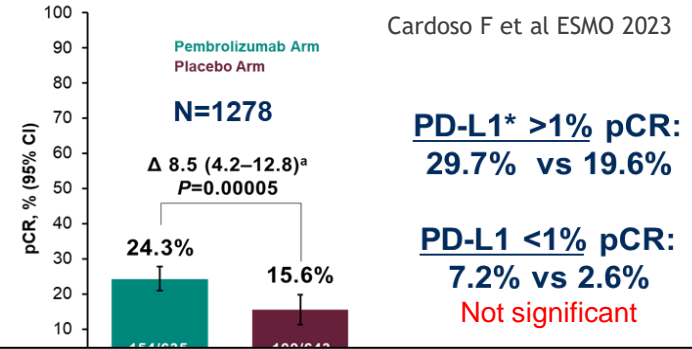
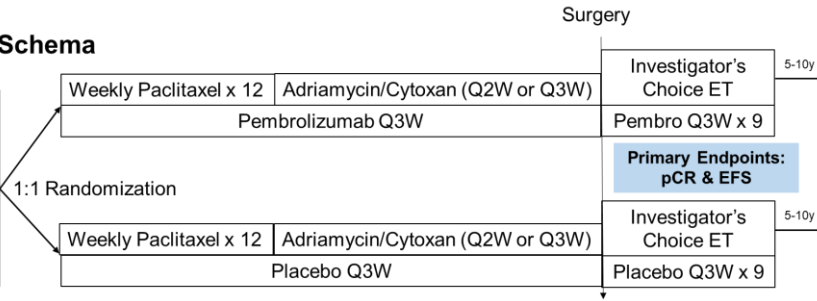
Acetylsalicylic acid
COX2 inhibitor
Recombinant interferon alfa-2b
Activating the TLR-3 receptors
Anti-CD73
A2aR antagonist
CSF-1R inhibitors
Long-acting interleukin-7
Anti-TGFb
L-NMMA (pan-NOS inhibitor)
Oncolytic reovirus
Ab anti-IL-1 beta
Poly-ICLC
Anti-IL-6 receptor
Soluble LAG-3 fusion protein
Recombinant human hematopoietic cytokine
CXCR4 inhibitor

Neoadjuvant pembrolizumab and nivolumab in grade 3 ER+/HER2-breast cancers

KEYNOTE-756 Schema

HR+ HER2- Invasive Ductal Carcinoma

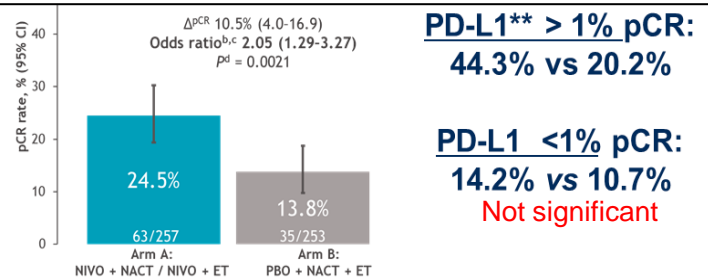
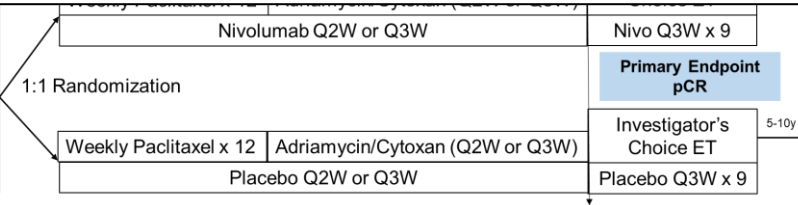
T1c-T2, cN1-cN2
OR
T3-T4, cN0-cN2
AND
Grade 3



Some promising results also in HER2-positive breast cancer (e.g KATE-2, APTneo)

HR+ HER2- invasive breast cancer

T1c-T2/cN1-cN2
OR
T3-T4, or cN0-cN2
AND
grade 3 or grade 2 with ER 1-10%



* 22C3 CPS score (75% of cases were positive)

** SP142 (34% of cases were positive)

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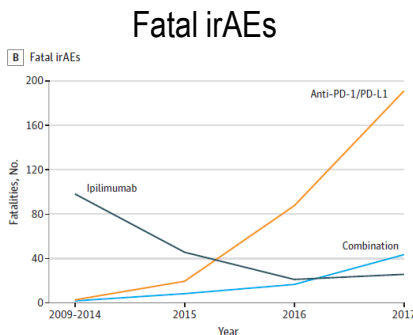
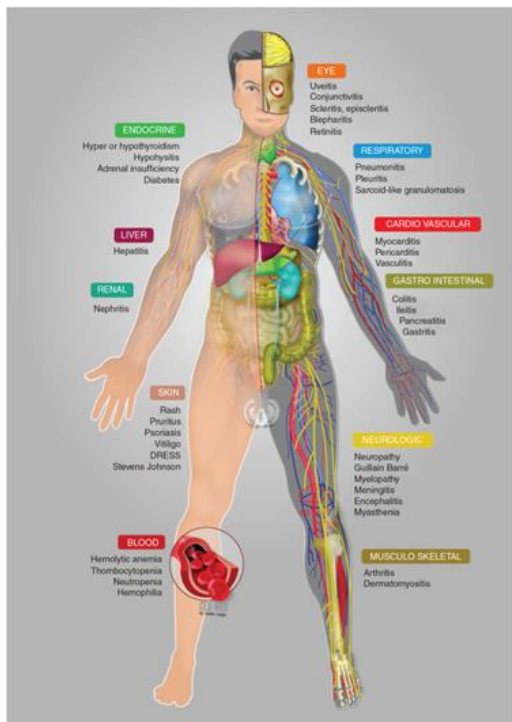
Landscape of anti-PD-1/anti-PD-L1 combinations in HER2-positive and ER+/HER2- Breast Cancer

HER2-positive

HR-positive/HER2-negative

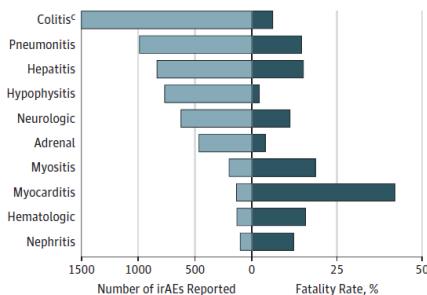


The Achilles' heel of immunotherapy and immunotherapy combinations



Fatal irAEs: rare but real

Cases and fatality rates



Combination trials with PD-1/PD-L1 inhibitors explosion: do we follow a rationale?

“Too many of the combinations we see in the clinic are being conducted with noses held or eyes closed,” says Ira Mellman, vice-president of cancer immunology at Genentech. “We just don’t know enough about the basic mechanisms.”

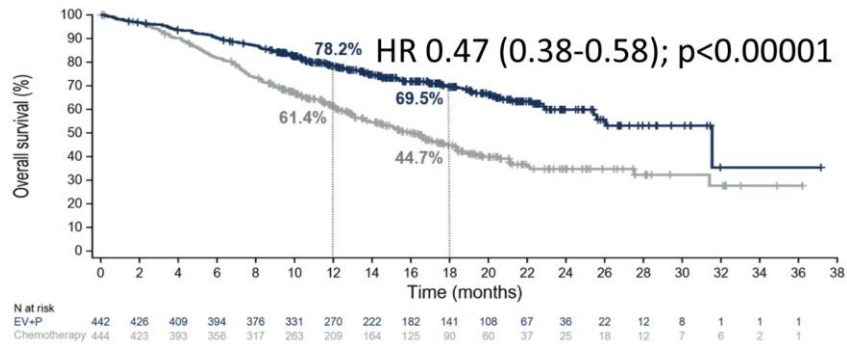
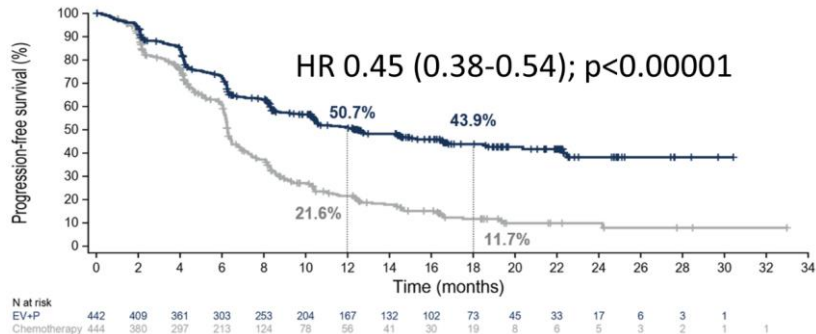
Weitraub K Nature 2017

“Many seem to be tried simply because they are possible to do or the agents are available”

Kaiser C Science 2018

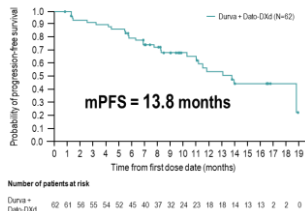
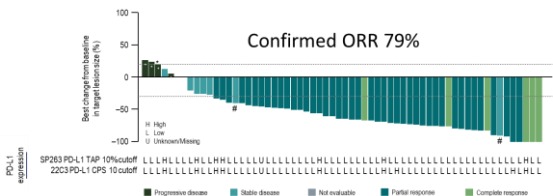
Synerigstic effect of ADC - ICIs combination

Enfortunab Vendotin + Pembro (mUC)

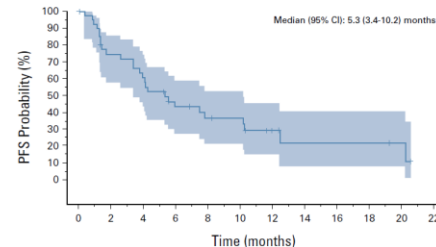
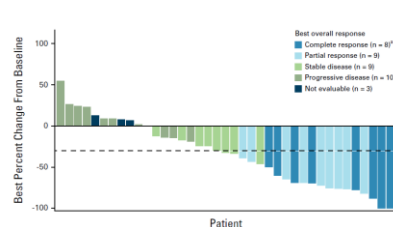


Powles T ESMO 2023; Powles T NEJM 2023

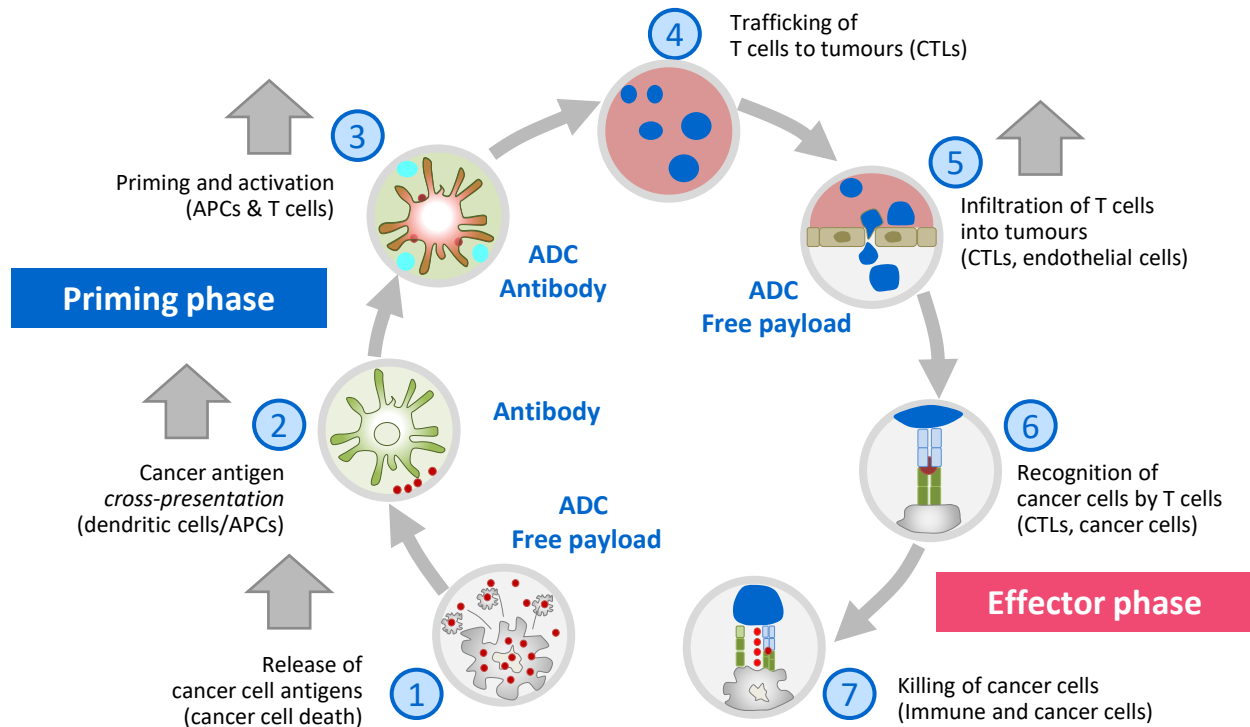
Datopotamab Deruxtecan + Durva (mTNBC)



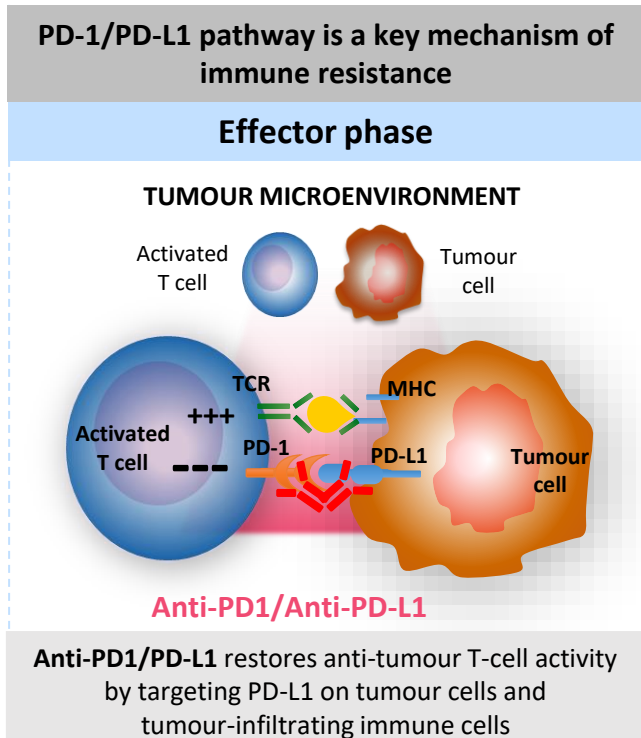
Sacituzumab Govitecan + Pembro (mUC)



Very strong rationale for ICI/ADCs combinations



APC, antigen-presenting cell; CTL, cytotoxic T lymphocyte;
PD-1, programmed cell death-1; PD-L1, programmed death-ligand 1.



Chen DS & Mellman I. *Immunity* 2013; Bianchini G & Gianni L. *Lancet Oncol* 2014; Herbst RS, et al. *Nature* 2014

What about re-challenge with ICI?

High Risk
TNBC



CT +
Pembro

Surgery (RD)

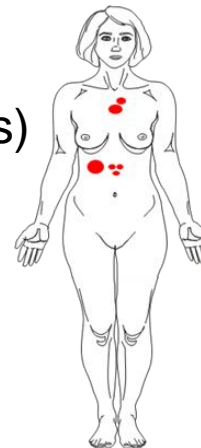


Pembro

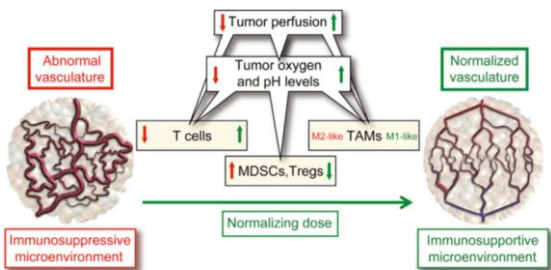
(more than 6-12 months)



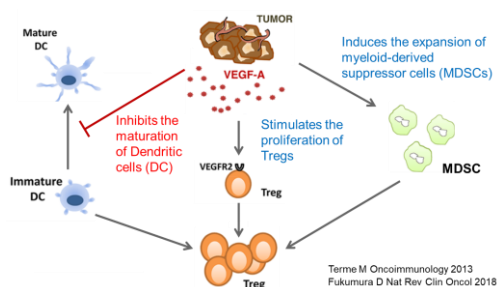
Re-challenge
with ICIs?



Immune escape associated with angiogenesis, hypoxia and EMT



Rakesh KJ Cancer Cell 2014

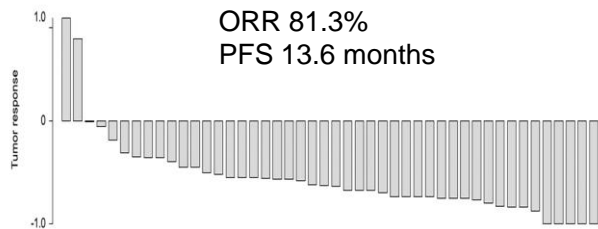


Terrie M Oncimmunology 2013
Fukumura D Nat Rev Clin Oncol 2018

Targeting mechanism
of “immune resistance”

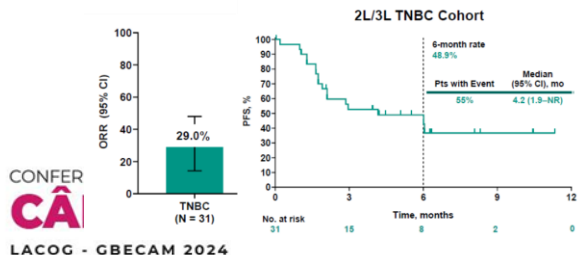
Antiangiogenic and ICI in metastatic TNBC

FUTURE-C-Plus (Camrelizumab, Famitinib and Nab-Paclitaxel)



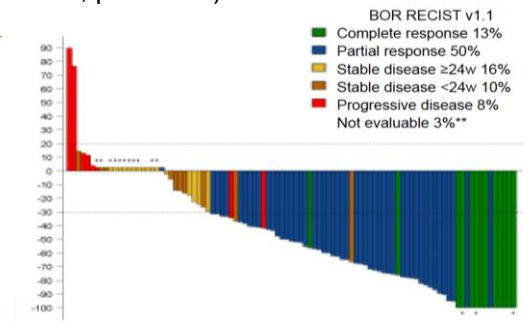
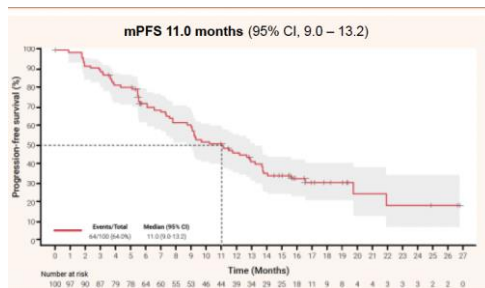
Wu SY Molecular cancer 2022; Chen L Clin Cancer Res 2022

ATTRACTINIB trial (Atezolizumab, bevacizumab, paclitaxel)



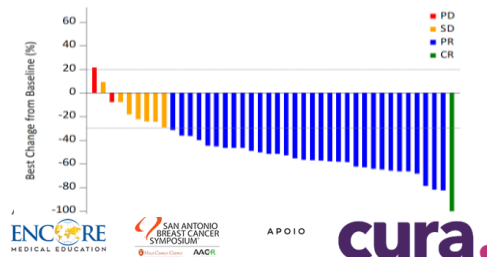
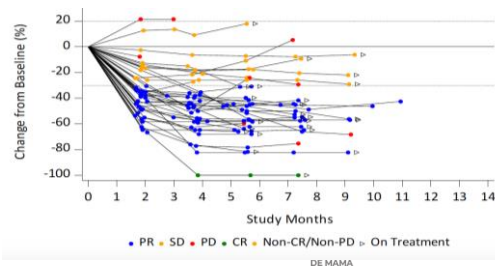
Lwin Z ESMO 2020

ATTRACTINIB trial (Atezolizumab, bevacizumab, paclitaxel)



Gion M SABCS 2023

PM8002 (anti-PD-L1 x VEGF-A Bispecific Ab) and nab-paclitaxel



Wu JSABCS 2023

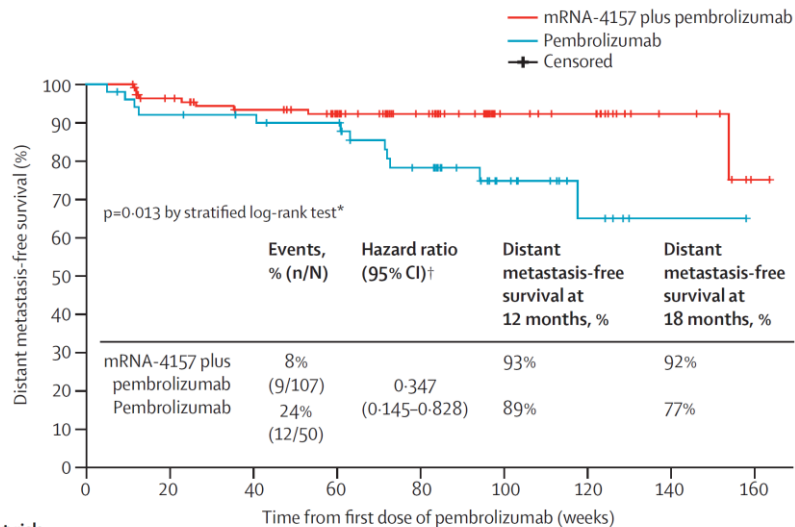
Emerging combination strategies in immuno-oncology

Personalised mRNA therapeutic VACCINE

KEYNOTE-942

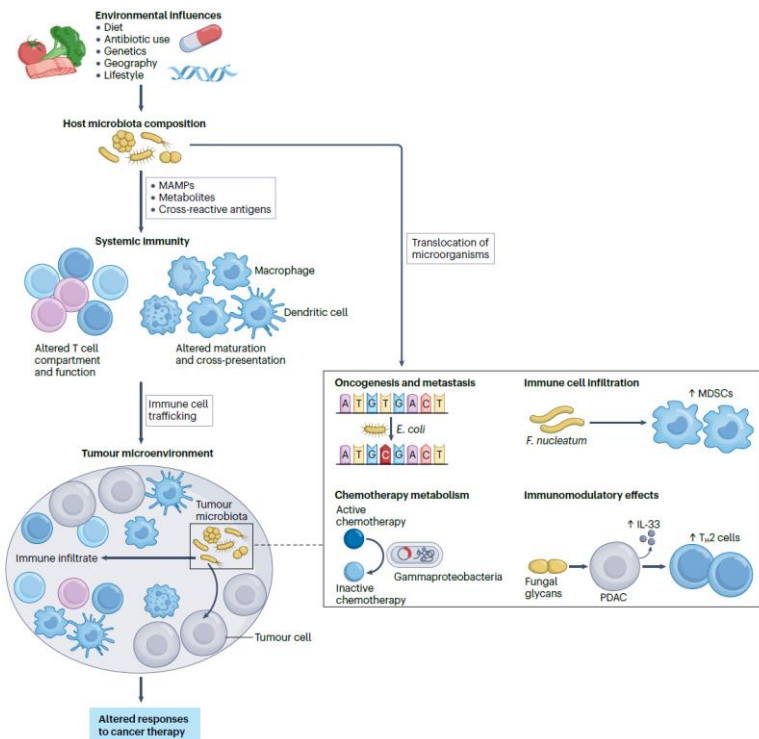
mRNA-4157 vaccine

It is a **personalised mRNA therapeutic created on demand** and encoding up to 34 neoantigens present in each patient's tumour



	0	20	40	60	80	100	120	140	160
Number at risk									
mRNA-4157 plus pembrolizumab	107 (0)	94 (9)	86 (14)	73 (26)	49 (50)	23 (76)	20 (79)	8 (91)	1 (97)
Pembrolizumab	50 (0)	43 (3)	41 (5)	39 (6)	29 (11)	14 (25)	6 (32)	1 (37)	0 (38)

Fecal microbiota transplantation

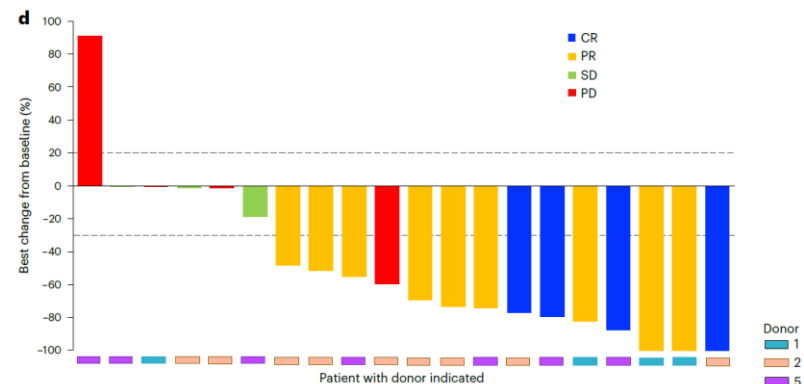


nature medicine

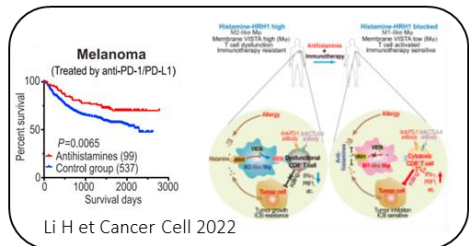
Article

<https://doi.org/10.1038/s41591-023-02453-x>

Fecal microbiota transplantation plus anti-PD-1 immunotherapy in advanced melanoma: a phase I trial



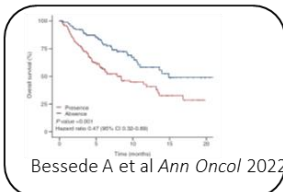
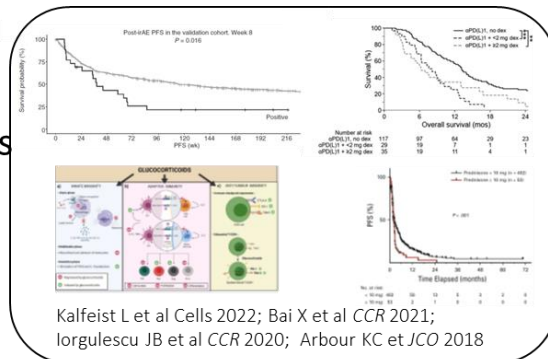
Unintended and under-recognized IMMUNE-MODULATORS



H1-antihistamine



Corticosteroids



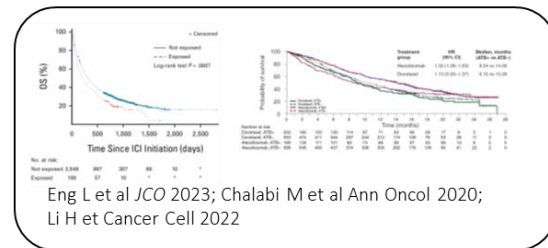
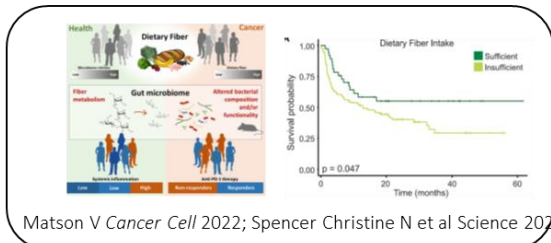
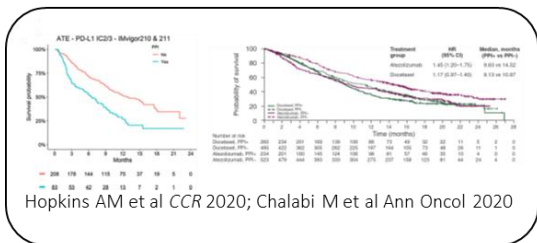
Acetaminophen



Proton pump inhibitors Dietary change

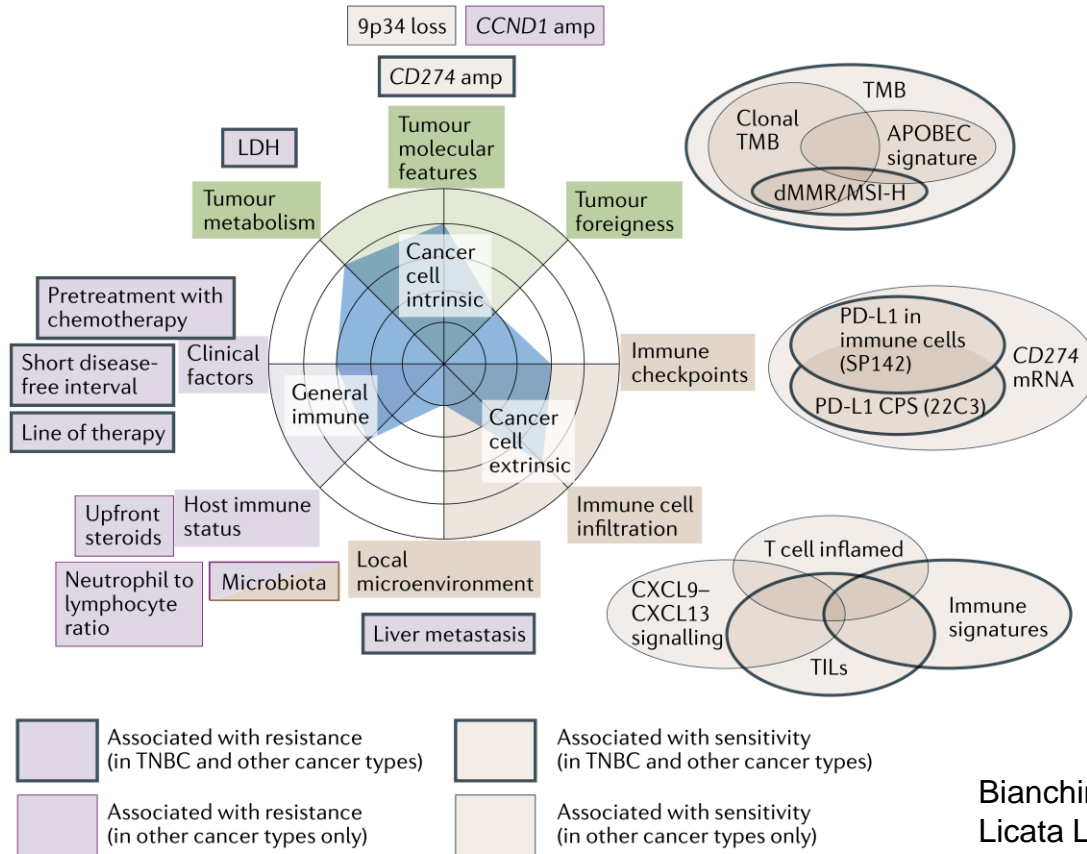


Antibiotics



Urgent need Precision Immunology

Urgent need for precision immunology: tailoring immunotherapy on individual cancer immunogram



Bianchini G Nat Rev Clin Oncol 2022
Licata L The Breast 2023

NeoTRIP trial results (NCT02620280), sample collection and imaging mass cytometry (IMC) assessment

TN high-risk
(T1cN1; T2N1;
T3N0) or locally advanced

R

Carboplatin + *nab*-paclitaxel

Carboplatin + *nab*-paclitaxel + Atezolizumab

Surgery

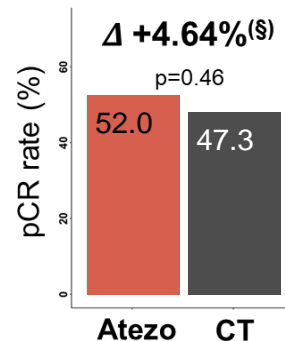
280 patients
(Intention-to-treat)

258 patients
(Per-protocol-population)

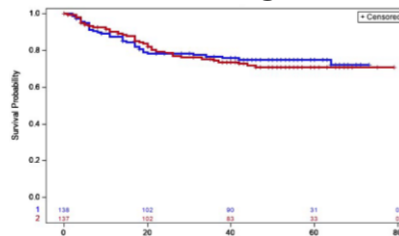
Baseline
(Pre-treatment)
100 %

Day 1
Cycle 2
87.7 %

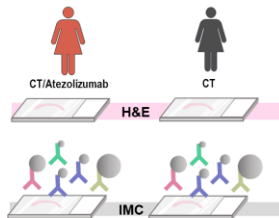
Surgery
88.8 %



EFS



Gianni L ESMO 2023



Checkpoint	Lymphoid	Epithelial	Life & Death
PD-L1 (SP142)	CD56	CK5/14	c-PARP
PD-L1 (73-10)	CD20	CK8/18	pH2AX
IDO	CD79a	PanCK	Ki67
PD-1	CD3	Heterogeneity	DNA
OX40	CD4	AR	H3
ICOS	CD8	GATA3	Ir
Myeloid	FOXP3	CD15	
CD11c	GATA3	Mesenchymal	
CD15	Helios	Caveolin-1	
CD163	T-bet	CD31	
CD68	TCF	PDPM	
MPO	TOX	PDGFRB	
MHC I&II	GZMB	SMA	
HLA-ABC	Pan-immune	Vimentin	
HLA-DR	CD45	Calponin	



Carboplatin (AUC2) + *nab*-paclitaxel (125 mg/m²) weekly for 2 wks every 3; 8 cy; Atezolizumab (1200 mg) day 1 every 3 wks for 8 cycles

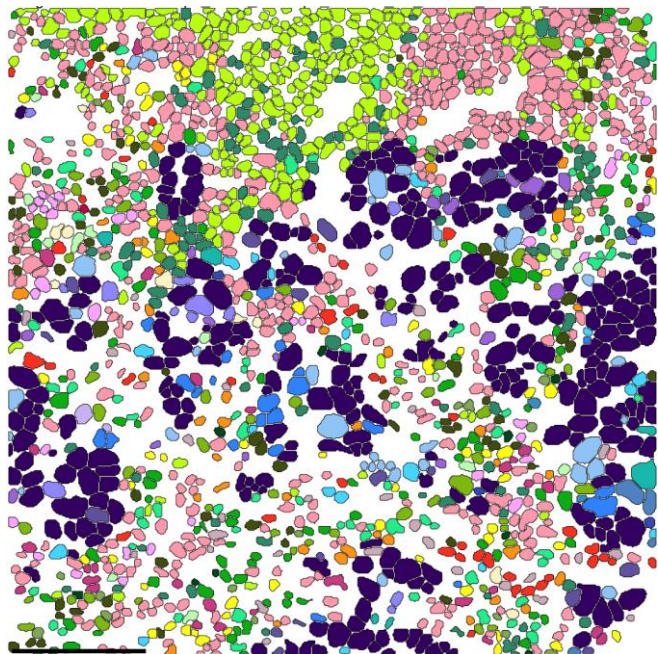
(S) Results in the Per-Protocol-Population (Bianchini G ESMO 2020 LBA13, Bianchini ESMO 2021 LBA11)

IMC: Imaging Mass Cytometry; PPP: Per-protocol-population (patients evaluable for pCR)

Bianchini G SABCS 2021; Gianni L Ann Oncol 2022; Wang XQ Nature 2023

Single-cell information with spatial resolution

Cell phenotypes



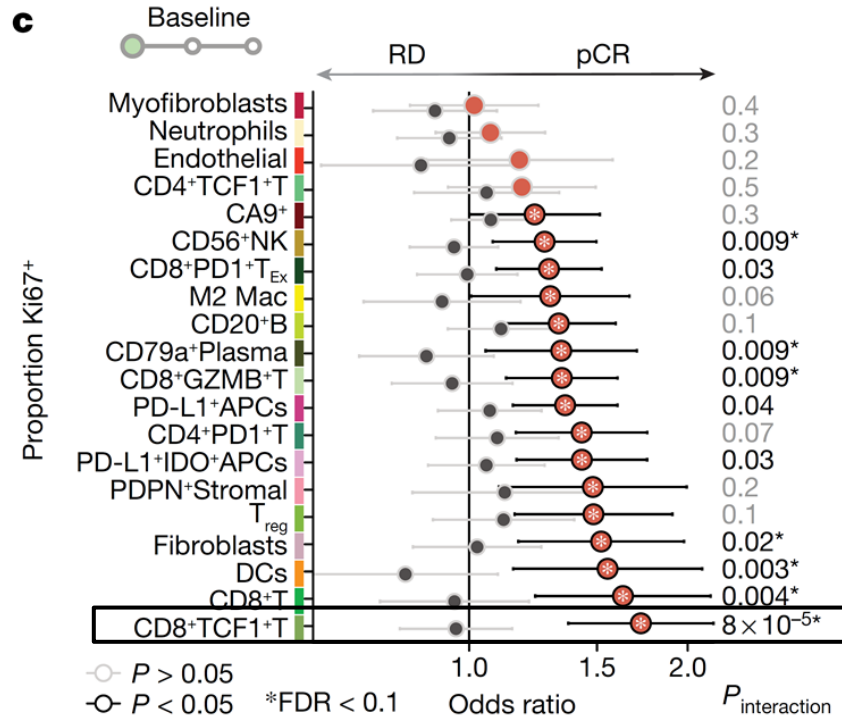
Epithelial

CK8/18 ^{med}
CK ^{lo} GATA3 ⁺
panCK ^{med}
Basal
Vimentin ⁺ EMT
CD15 ⁺
pH2AX ⁺ DSB
Apoptosis
MHC I&II ^{hi}
PD-L1 ⁺ IDO ⁺
PD-L1 ⁺ GZMB ⁺
TCF1 ⁺

TME

CD8 ⁺ T
CD8 ⁺ GZMB ⁺ T
CD8 ⁺ TCF1 ⁺ T
CD8 ⁺ PD1 ⁺ T _{Ex}
CD4 ⁺ TCF1 ⁺ T
CD4 ⁺ PD1 ⁺ T
Treg
CD20 ⁺ B
CD79a ⁺ Plasma
CD56 ⁺ NK
M2 Mac
DCs
Neutrophils
PD-L1 ⁺ APCs
PD-L1 ⁺ IDO ⁺ APCs
Endothelial
Fibroblasts
Myofibroblasts
PDPN ⁺ Stromal

Association between proliferation fraction of immune cell phenotypes

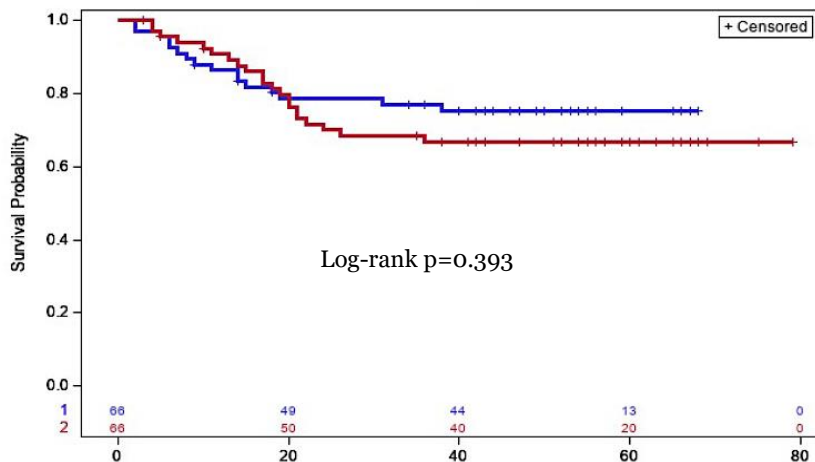


Arm (patients/pCR) ● C (111/53) ● C&I (113/56)

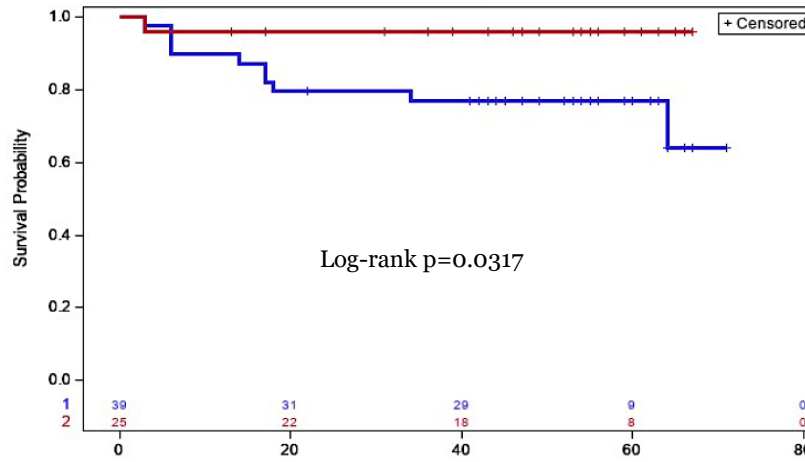
High CD8+TCF1+Ki67+ density linked to increased EFS by atezolizumab/CT combination

Exploratory analysis

CD8+TCF1+Ki67+ low



CD8+TCF1+Ki67+ high

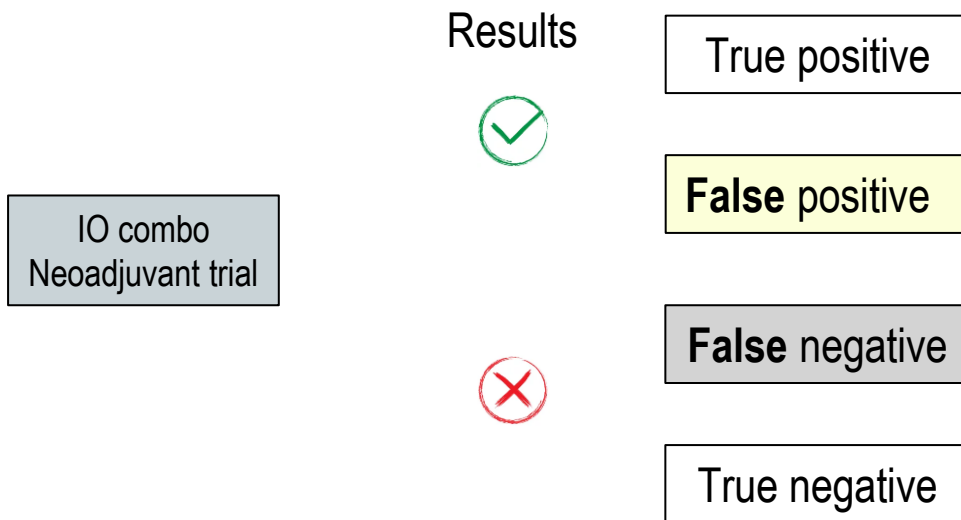


Test for interaction p = 0.046

Note: analysis by tertiles low (low and intermediate tertiles) and high (higher tertile)

Urgent need for new surrogate markers

Hurdle in immunotherapy drug development: high rate of false positive/negative results



surrogate endpoints developed for chemo/target therapy inadequate and misleading for immuno-oncology

Surrogate endpoints (pCR, ORR, PFS) developed for chemotherapy/targeted therapy are inadequate and misleading for Immuno-Oncology

KEYNOTE-522 (TNBC)

ITT population	ITT population
<i>modest</i>	<i>meaningful</i>
Δ 7.5% pCR	Δ EFS, DDFS
Schmid P NEJM 2020; Schmid P NEJM 2022	

GEPARNUEVO (TNBC)

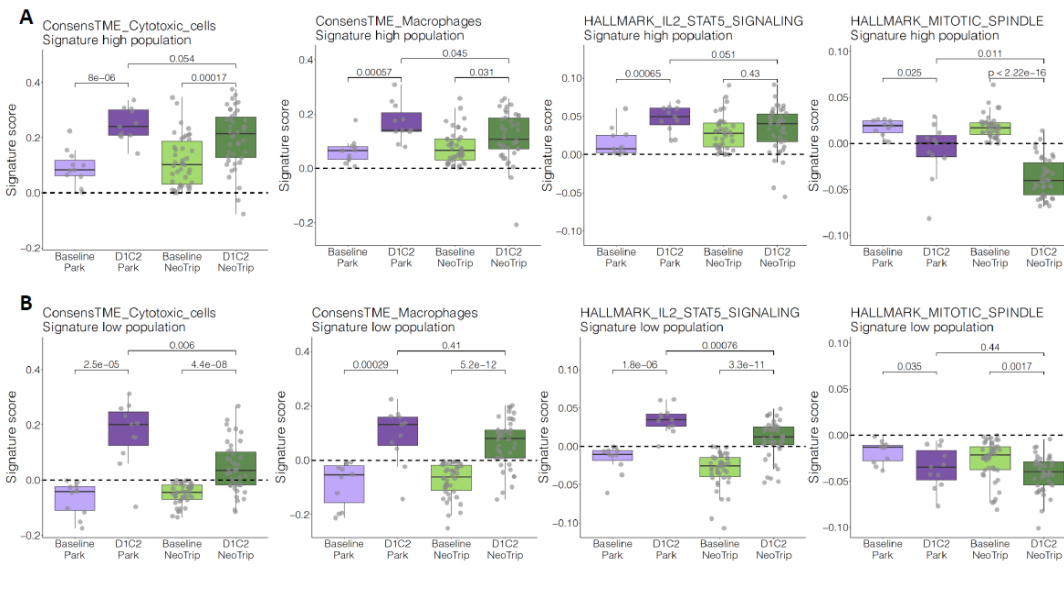
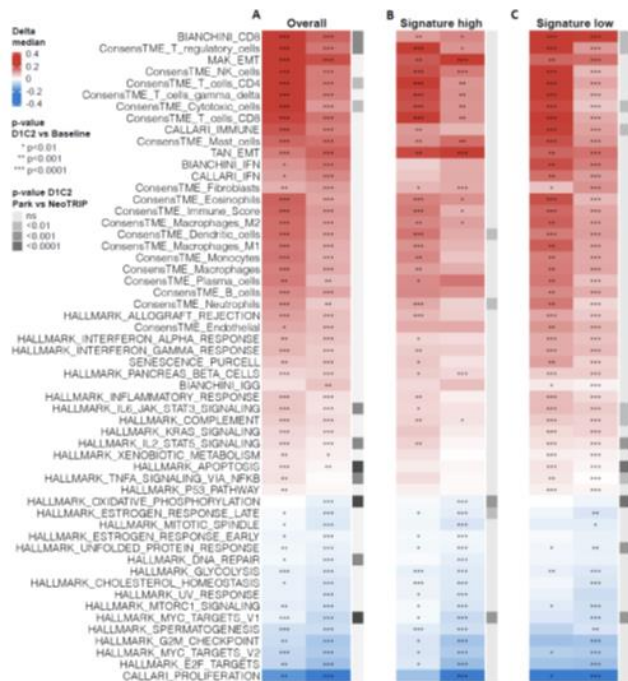
ITT population	ITT population
<i>ns</i>	<i>promising</i>
Δ 9.2% pCR	Δ EFS, DDFS
Loibl S Ann Oncol 2019; Loibl S Ann Oncol 2022	

Is pCR rate really informative?

Urgent need to define “biological surrogate markers” (TCR clonality, immune modulation, ctDNA dynamic) to directly assess an effective immune engagement

Genomics is static; the immune system is dynamic

Anthracycline elicit a stronger immunomodulatory effect in “immune low” (PD-L1 neg) tumors



Possible benefit from atezolizumab combined to anthracyclines in PD-L1 neg aTNBC

nature medicine



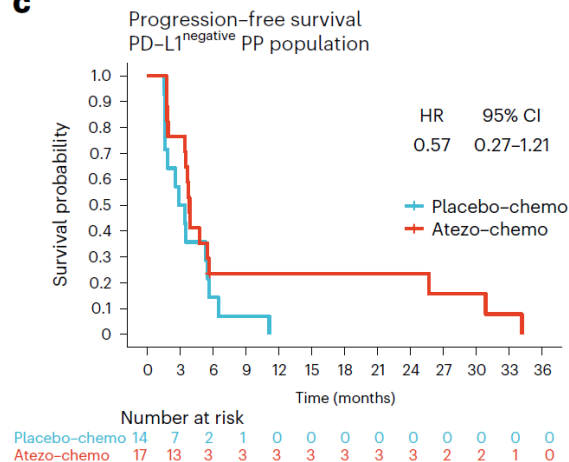
Article

<https://doi.org/10.1038/s41591-022-02126-1>

Atezolizumab plus anthracycline-based chemotherapy in metastatic triple-negative breast cancer: the randomized, double-blind phase 2b ALICE trial

PD-L1 status				
Positive	21	10		0.63 (0.28 – 1.43)
Negative	19	17		0.55 (0.27 – 1.14)

c



What's on the horizon of immunotherapy for BC?

The best is yet to come

