Immunoterapia nel carcinoma mammario e ricerca clinica: risultati e nuovi orizzonti

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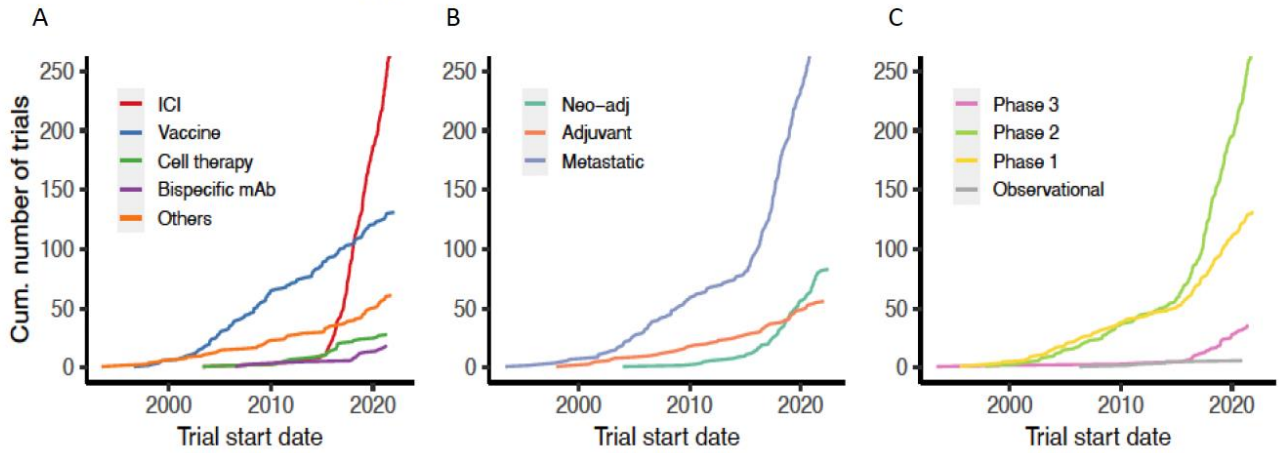
OUTLINE

- Immunotherapy in metastatic breast cancer : current treatment landscape
- Immune-based combination treatments: PARPi, ADC, VEGFi, other immuno-agents
- Biomarkers of immunotherapy benefit in metastatic breast cancer
- Future perspectives of Immunotherapy in metastatic breast cancer

IMMUNOTHERAPY DEVELOPMENT IN BREAST CANCER

Breast cancer immunotherapy trials



- Increasing number of trials investigating immunotherapeutic strategies in BC
- Both in advanced and early setting
- Shift of phase 1 towards phase 2 and 3 trials

BC subtype	Luminal A	Luminal B	HER2 - positive	Triple - negative
% of breast cancers	40%	20%	10-15%	10-15%
Receptors status	ER+PR+	ER+PR+/-	HER2+	ER-PR-HER2-
Proliferation				
Prognosis	Good			Poor
Treatment	Endocrine therapy		Anti-HER2 drugs	Chemotherapy / Immunotherapy

Summary of status of BC immunotherapy

Modality	Phase I	Phase II	Phase III	Approved?	Comment
CTLA-4	→			No	Minimal activity
PD-1/PD-L1	→	→	→	Yes	Survival benefit in early TNBC & in PD-L1+ metastatic TNBC
Therapeutic vaccines	→	→	X	No	Negative randomized studies, combinations critical
Prevention vaccines	→	→		No	Studies underway
T-cell agonists	→			No	Unlikely to offer single-agent activity in BC
Adoptive T cells	→			No	Initial CAR T cell studies underway

Adapted from *Robert H. Vonderheide et al. Clin Cancer Research 2017*

Summary of anti-PD-1/PD-L1 ICB

Setting	BC subtypes		
	TNBC	**Luminal**	**HER2**
Early	***Approved*** for Pembrolizumab (2021) with NAC (pCR and EFS benefit)	Increased pCR with ICB in phase III trials (Pembrolizumab, Nivolumab) ESMO 2023	No difference in pCR rate (IMpassion 50) Ongoing trials
Advanced	***Approved*** for Pembrolizumab (2020) in 1st line with chemo for pts with PD-L1 + tumors (OS benefit) Ongoing trials with ADC	Modest activity Ongoing trials with CDK4/6i	Modest activity (PD-L1+?) Ongoing trials
	Ongoing trials with iPARP in gBRCA mutant		

DESTINY-Breast07: Study Design

- Multicenter, randomized, open-label, 2-part modular phase Ib/II study; data presented from interim analysis of part 2 dose-expansion phase

Stratified by HR status, disease status, PD-L1 status

Previously untreated HER2+* advanced or metastatic BC with measurable disease; no or previously treated/stable brain mets; ≥12-mo DFI from adjuvant anti-HER2 therapy or CT; ECOG PS 0/1 (N = 125)

- T-DXd 5.4 mg/kg IV Q3W (n = 75)
- T-DXd 5.4 mg/kg IV Q3W + Pertuzumab 420 mg IV Q3W with 840-mg loading dose (n = 50)
- T-DXd + Durvalumab *(not presented)*

*IHC 3+ or IHC 2+/ISH+.

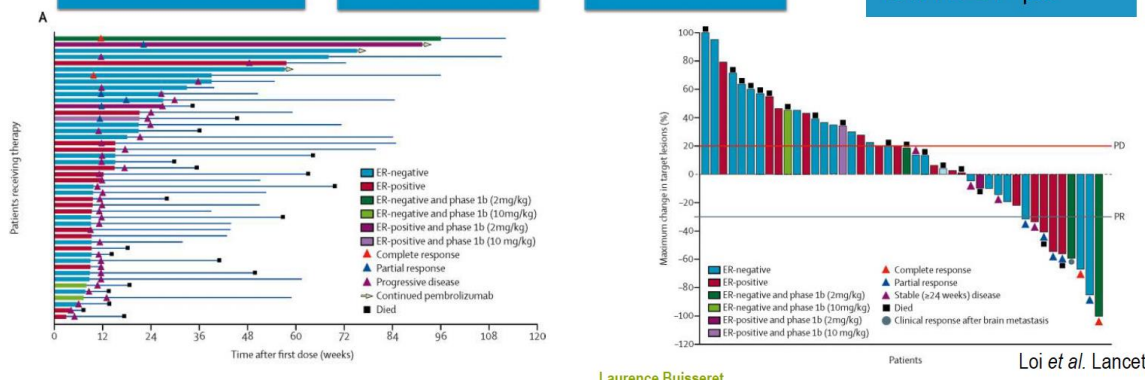
- **Primary endpoints:** safety and tolerability
- **Key secondary endpoints:** ORR, PFS per investigator (by RECIST v1.1), DoR

Andre. ASCO 2024. Abstr 1009. Slide credit: clinicaloptions.com

PANACEA trial – advanced disease

Advanced HER2+ BC Trastuzumab resistant Up to 3 lines previous anti-HER2 therapy → Confirmed PD-L1 expression on a metastatic lesion → Trastuzumab + MK3475 until progression Biopsy on progression

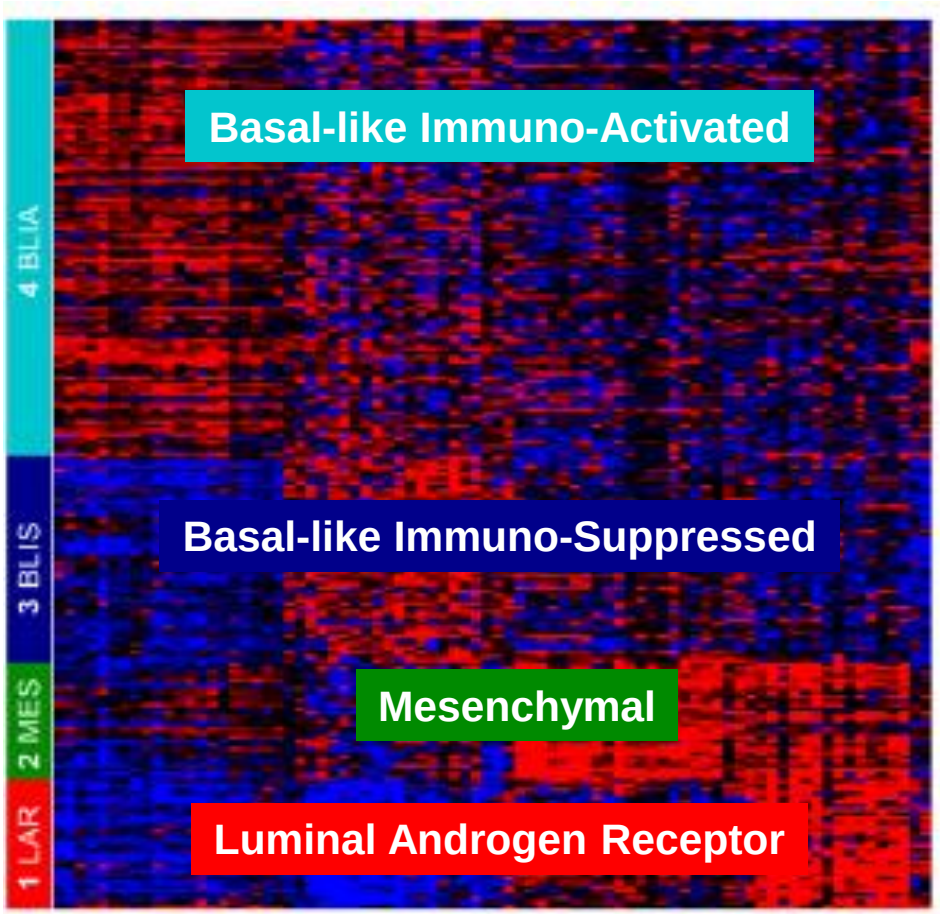
ORR :
0% PD-L1 neg pts
15% PD-L1+ pts



Loi *et al.* Lancet Oncol 2019

mTNBC: biology and heterogeneity

Molecular subtyping of TNBC



- Complex genomic profiles
- *TP53* mutations in >90%
- Higher frequency of HRD
- Higher pCR rates
- Majority of TNBCs

- Complex genomic profiles
- *TP53* mutations in >90%
- Lower TILs and lower pCR rates

- Lower genomic complexity
- Activation of the PI3K pathway
- Intermediate pCR rates

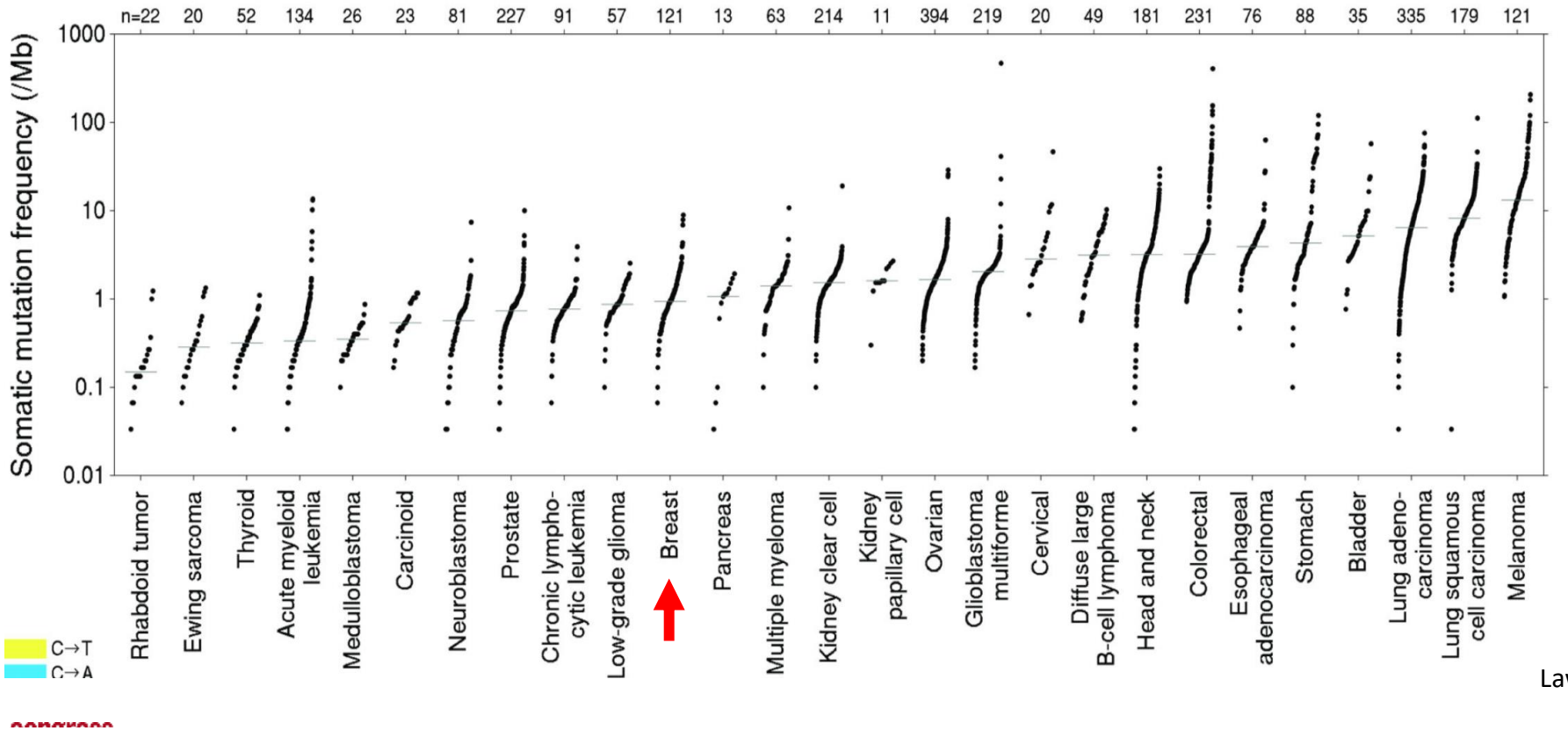
- Lower genomic complexity
- *PIK3CA, AKT1, NF1, GATA3* and *CDH1* mutations
- Lower TILs
- Lower pCR rates

Perou, Nature 2000; Lehmann, JCI 2011; Curtis, Nature 2012; Lehmann, PLoS ONE 2016; Jiang, Cancer Cell 2019

mTNBC: biology and heterogeneity

Immune microenvironment

Breast cancer is less immune activated than many other tumor types…



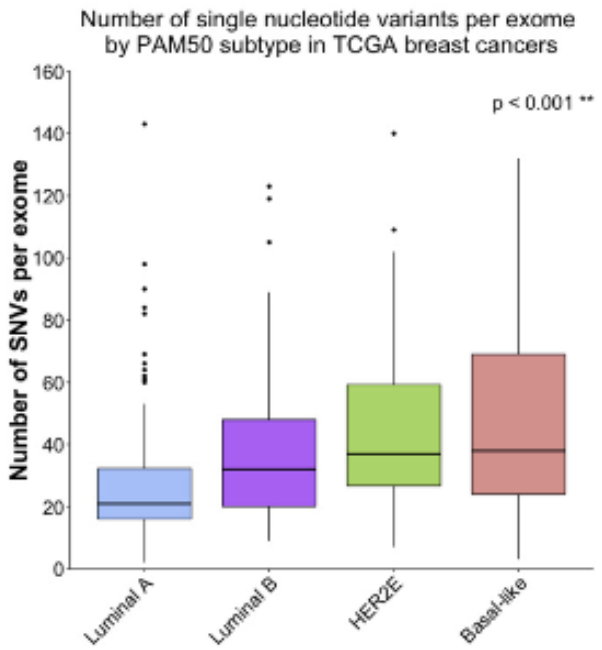
Lawrence et al, Nature 2013

mTNBC: biology and heterogeneity

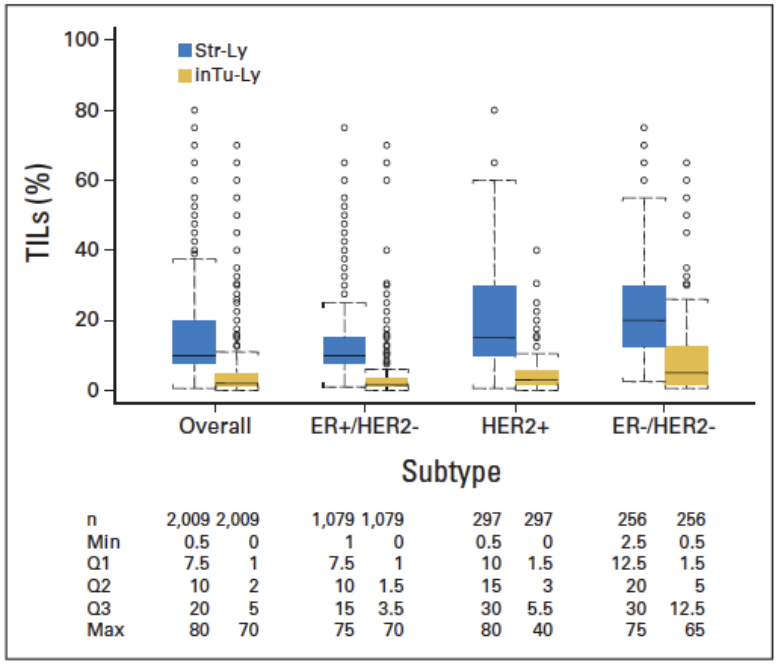
Immune microenvironment

…but, compared to the other breast cancer subtypes, triple-negative BC is characterized by higher:

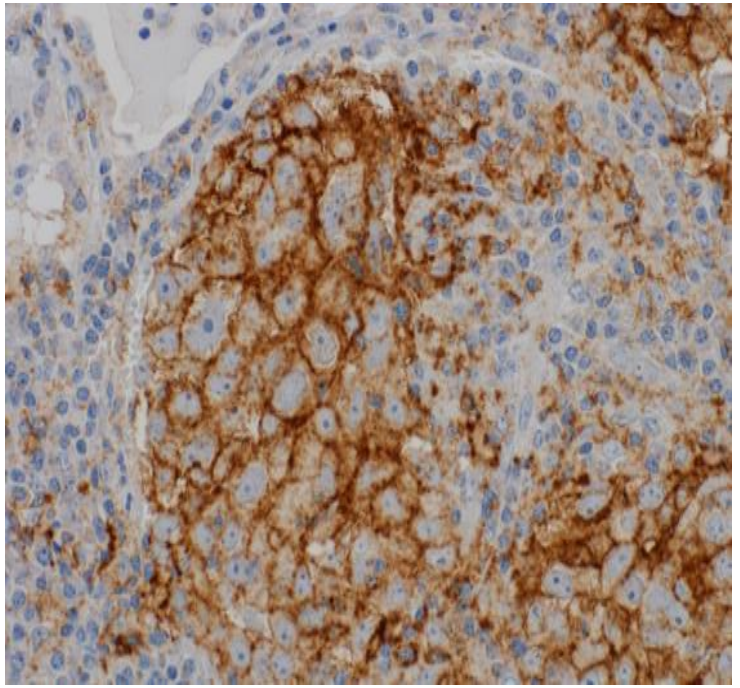
Tumor mutation burden



T-cell infiltration



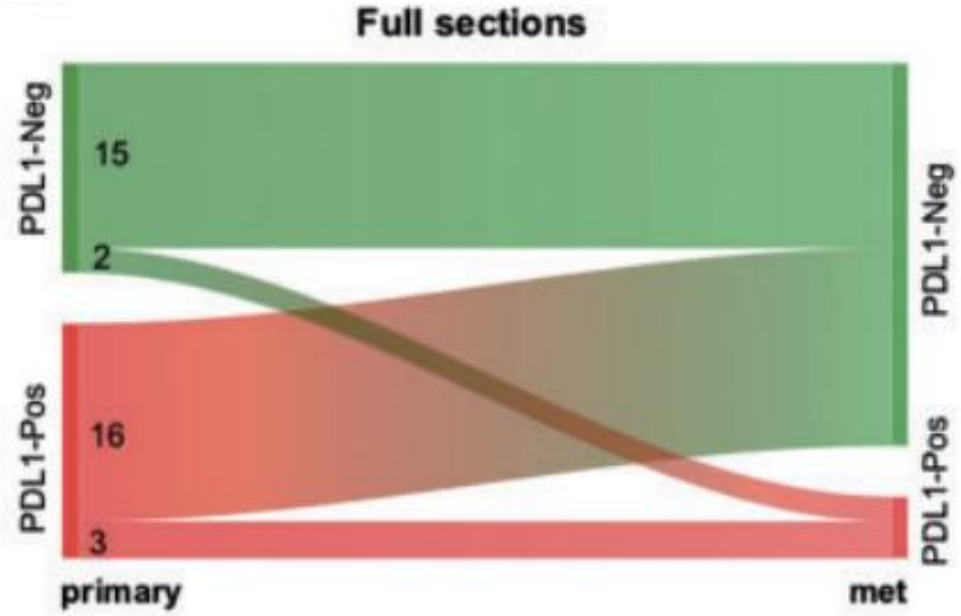
PD-L1 expression



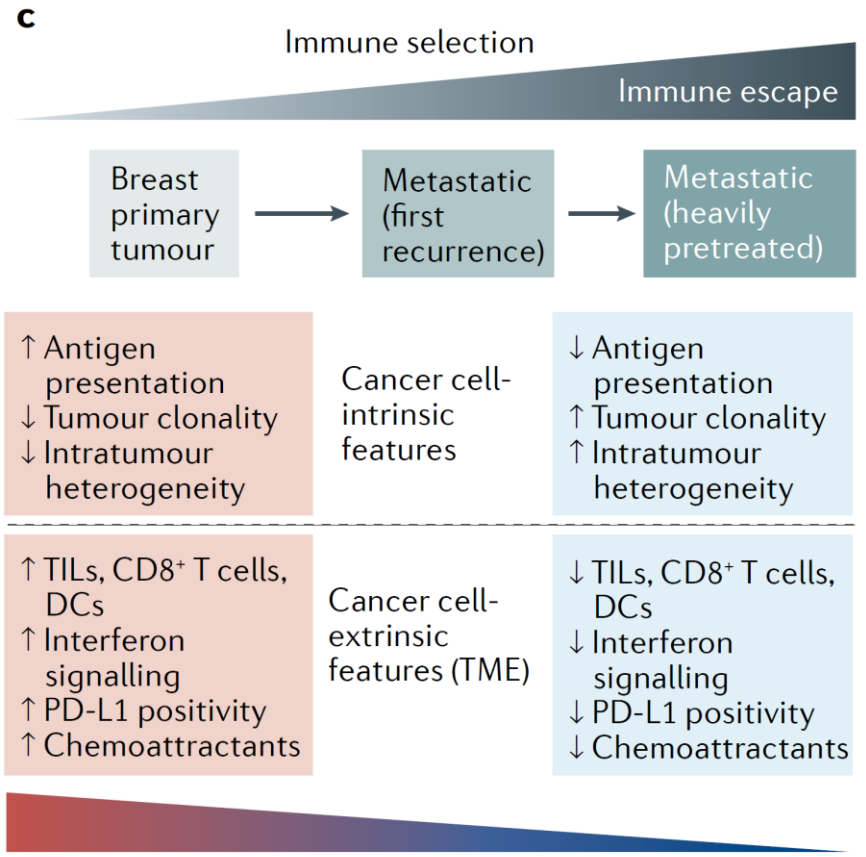
TCGA, Nature 2012; Luen, Breast 2016; Lehmann, J Clin Invest 2011; Cimino Matthews, Hum Pathol 2013; Loi, JCO 2013; Loi, Ann Oncol 2014; Chen and Mellman, Immunity 2013 ; Mittendorf, Cancer Immunol Res 2014

mTNBC: biology and heterogeneity

Immune activation decreases in metastatic disease compared to early disease

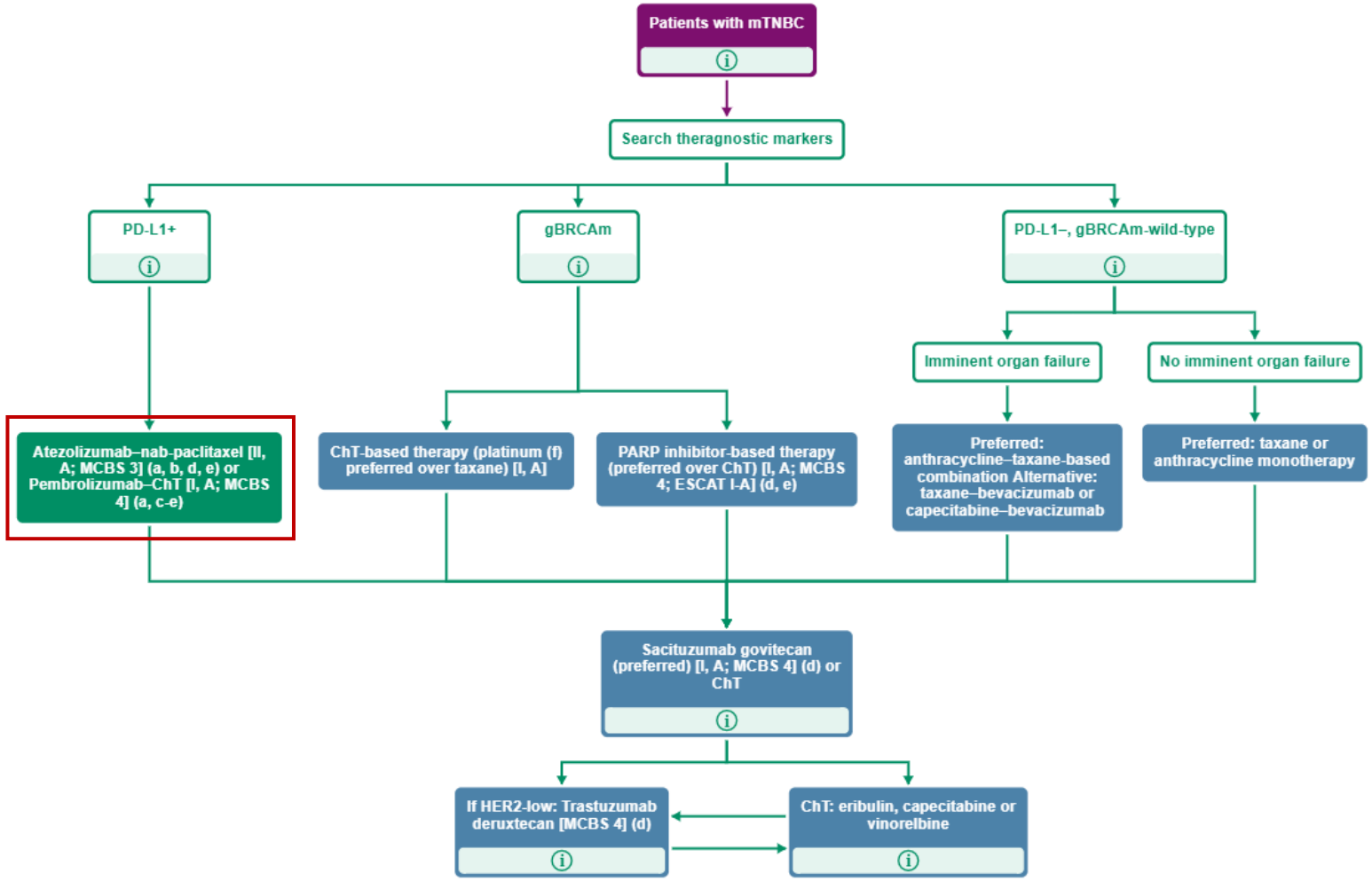


Szekely, Ann Oncol 2019



Bianchini G Nat Rev Clin Oncol 2022

Immunotherapy in metastatic triple-negative breast cancer



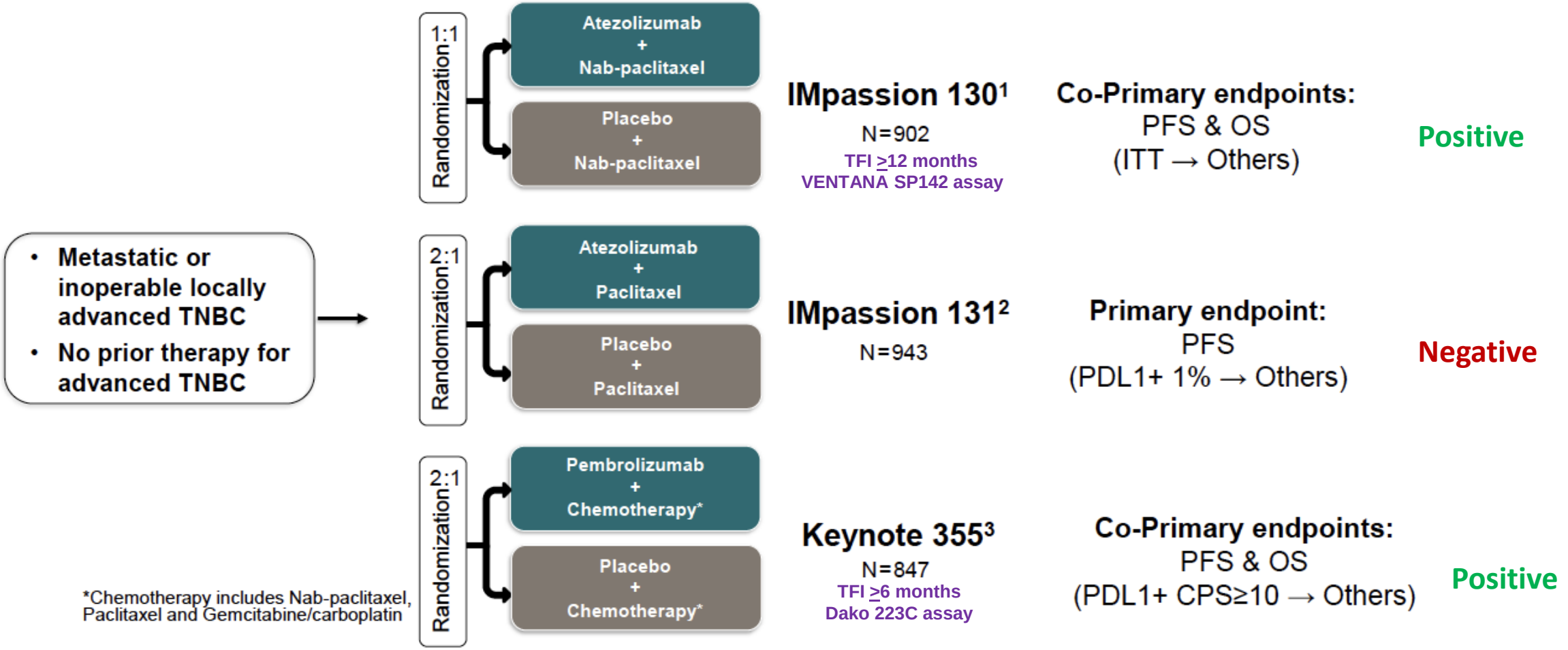
Curigliano, ESMO Living Guidelines 2023

Immunotherapy: First-Line Rx for mTNBC

	IMPASSION 131	IMPASSION 130	KEYNOTE 355
N (PD-L1+)	943 (292, 45%) ≥1%	902 (369, 41%) ≥1%	847 (332, 38%) CPS≥10
Randomization and Treatment	2:1 Paclitaxel 90 mg/m2 Atezolizumab	1:1 nab-Paclitaxel 100 mg/m2 Atezolizumab	2:1 Pac/nab/gem+carbo Pembrolizumab
de novo	28-30%	~37% (no chemo)	30%
Prior taxane	51-53%	51%	45%
PFS in PD-L1+	5.7 → 6 mo; HR 0.82 P=0.2	5 → 7.5 mo; HR 0.62 P<0.0001	5.6 → 9.7 mo; HR 0.65 P=0.0012 FDA approved 7/21
OS benefit	No	YES	YES

Miles et al, Ann Oncol 2021; Schmid et al, NEJM 2018 & Emens et al, Ann Oncol 2021; Cortes et al, Lancet 2020; Rugo et al, ESMO 2021

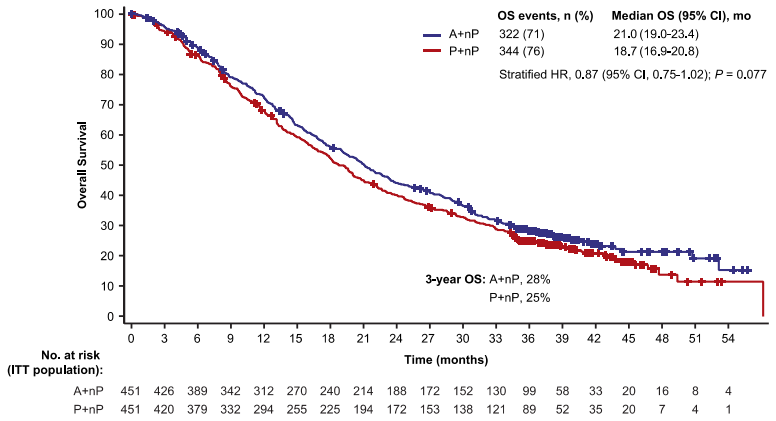
Randomized Phase III studies with chemotherapy plus PD-1/PD-L1 inhibitors in 1st line TNBC



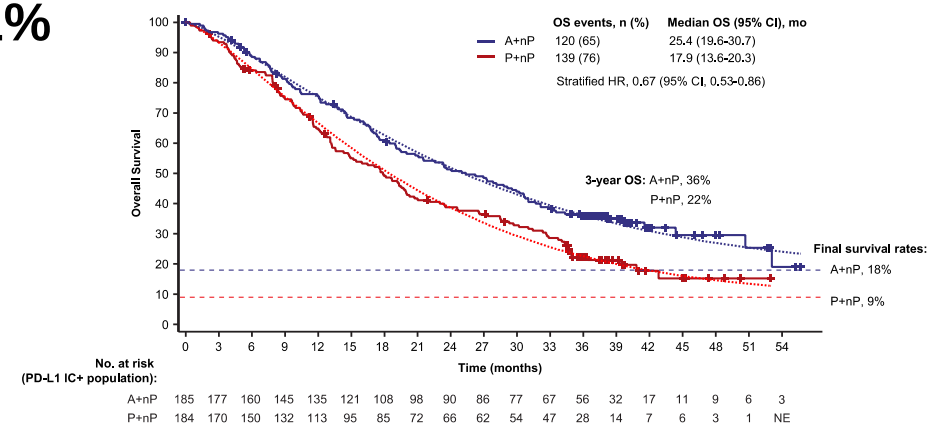
1. Schmid, NEJM 2018; 2. Miles, Ann Oncol 2021; 3. Cortes, Lancet 2020

IMpassion130: Final overall survival

ITT

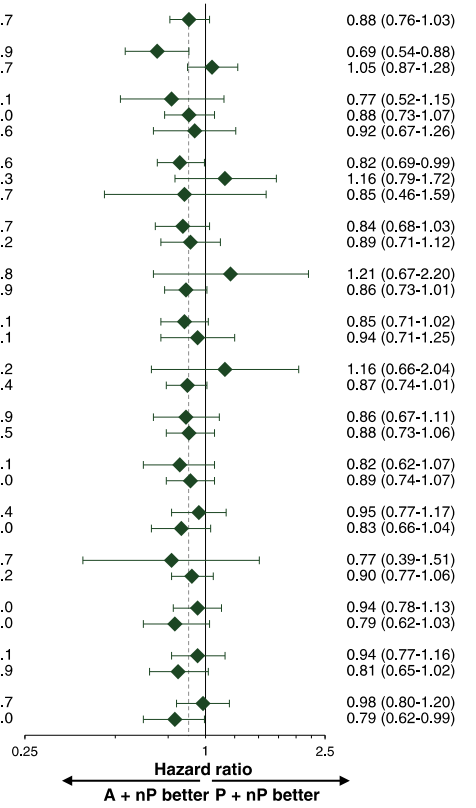


PD-L1 >1%



ITT

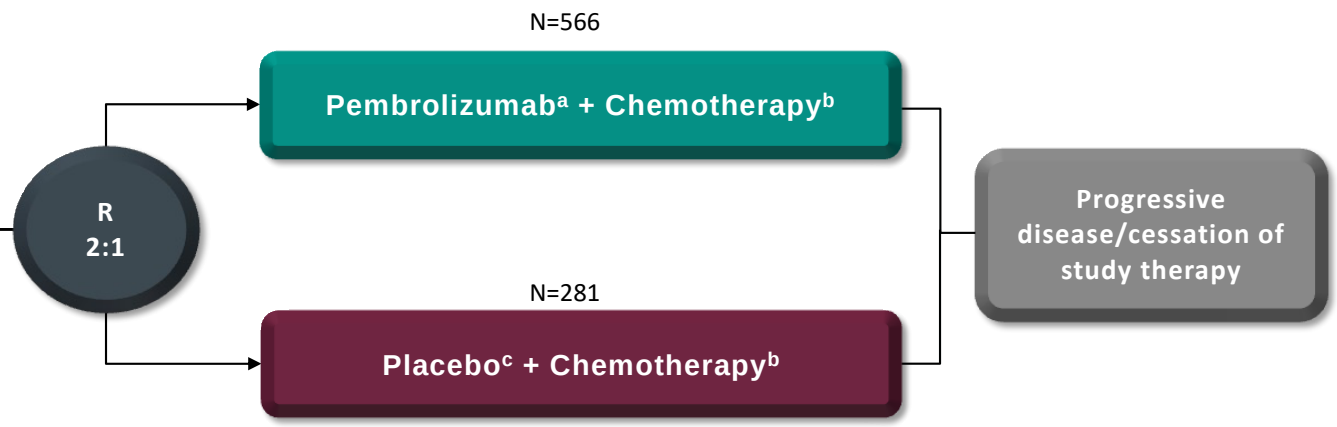
Baseline characteristic	A + nP Patients, *n*	A + nP Median OS, months	P + nP Patients, *n*	P + nP Median OS, months	HR (95% CI)
All	451	21.0	451	18.7	0.88 (0.76-1.03)
PD-L1 status					
Positive	185	25.4	184	17.9	0.69 (0.54-0.88)
Negative	266	19.7	267	19.7	1.05 (0.87-1.28)
Age, years					
18-40	63	16.8	51	13.1	0.77 (0.52-1.15)
41-64	284	21.1	285	20.0	0.88 (0.73-1.07)
≥65	104	22.6	115	19.6	0.92 (0.67-1.26)
Race[a]					
White	308	21.0	301	17.6	0.82 (0.69-0.99)
Asian	85	27.9	76	29.3	1.16 (0.79-1.72)
Black/African American	26	18.5	32	15.7	0.85 (0.46-1.59)
ECOG PS[a]					
0	256	25.0	270	22.7	0.84 (0.68-1.03)
1	193	16.3	179	13.2	0.89 (0.71-1.12)
Baseline disease status[a]					
Locally advanced	46	29.6	42	38.8	1.21 (0.67-2.20)
Metastatic	404	20.4	408	17.9	0.86 (0.73-1.01)
Number of metastatic sites[a]					
0-3	332	24.1	341	21.1	0.85 (0.71-1.02)
>3	118	12.7	108	12.1	0.94 (0.71-1.25)
Brain metastases					
Yes	30	14.3	31	16.2	1.16 (0.66-2.04)
No	421	21.6	420	19.4	0.87 (0.74-1.01)
Bone metastases					
Yes	145	17.1	141	14.9	0.86 (0.67-1.11)
No	306	22.6	310	20.5	0.88 (0.73-1.06)
Liver metastases					
Yes	126	14.0	118	12.1	0.82 (0.62-1.07)
No	325	23.7	333	22.0	0.89 (0.74-1.07)
Lung metastases					
Yes	227	17.8	242	17.4	0.95 (0.77-1.17)
No	224	23.7	209	20.0	0.83 (0.66-1.04)
Lymph node-only disease[a]					
Yes	33	34.4	23	34.7	0.77 (0.39-1.51)
No	417	20.3	426	18.2	0.90 (0.77-1.06)
Prior (neo) adjuvant chemotherapy					
Yes	284	21.4	286	20.0	0.94 (0.78-1.13)
No	167	20.8	165	16.0	0.79 (0.62-1.03)
Prior taxane treatment					
Yes	231	20.5	230	20.1	0.94 (0.77-1.16)
No	220	21.1	221	17.9	0.81 (0.65-1.02)
Prior anthracycline treatment					
Yes	243	20.2	242	19.7	0.98 (0.80-1.20)
No	208	22.0	209	18.0	0.79 (0.62-0.99)



Emens, Ann Oncol 2021

KEYNOTE-355:
Pembrolizumab + chemotherapy as first-line in mTNBC

Key Eligibility Criteria
- Age ≥18 years
- Central determination of TNBC and PD-L1 expression
- Previously untreated locally recurrent inoperable or metastatic TNBC
- Completion of treatment with curative intent ≥6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease



Stratification Factors:
- Chemotherapy on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor expression (CPS ≥1 vs CPS <1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

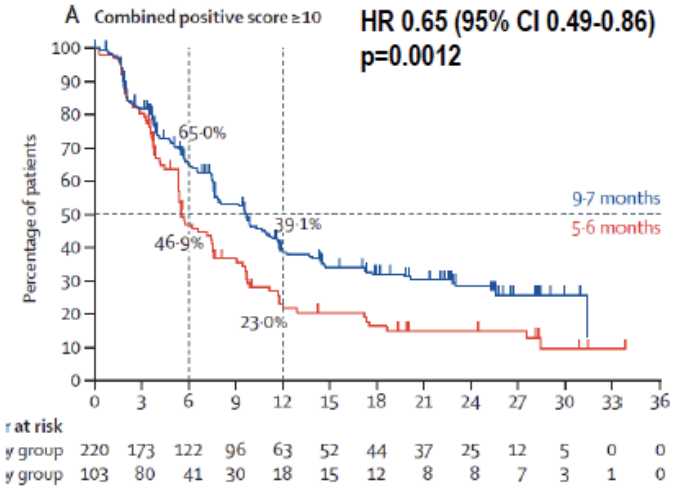
Endpoints:
- Primary: **PFS and OS in patients with PD-L1+ tumors (CPS ≥10 and CPS ≥1) and in the ITT population**
- Secondary: ORR, DOR, DCR, Safety in all treated patients

[a] Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 every 28 days
Paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 days
Gemcitabine 1000 mg/m^2/carboplatin AUC 2 on days 1 and 8 every 21 days

Cortes, ASCO 2020; Cortes, Lancet 2020

KEYNOTE-355: Progression-free survival

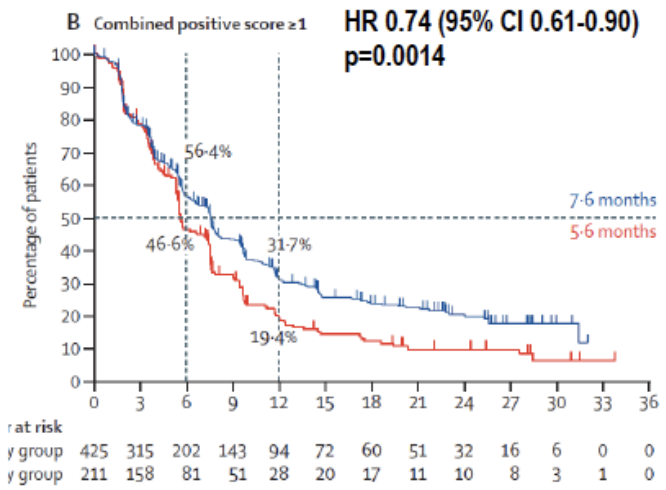
PD-L1 CPS ≥10



PFS superiority CPS ≥10
boundary α=0.00411

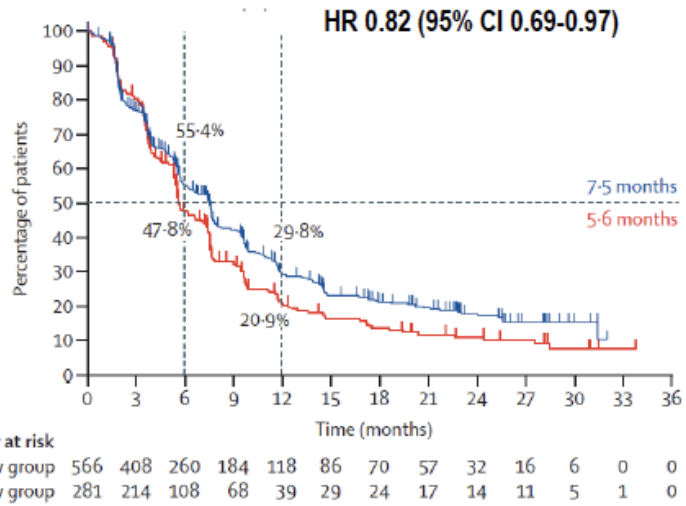
38% of pts

PD-L1 CPS ≥1



PFS superiority CPS ≥1
boundary α=0.00111 not met

ITT population

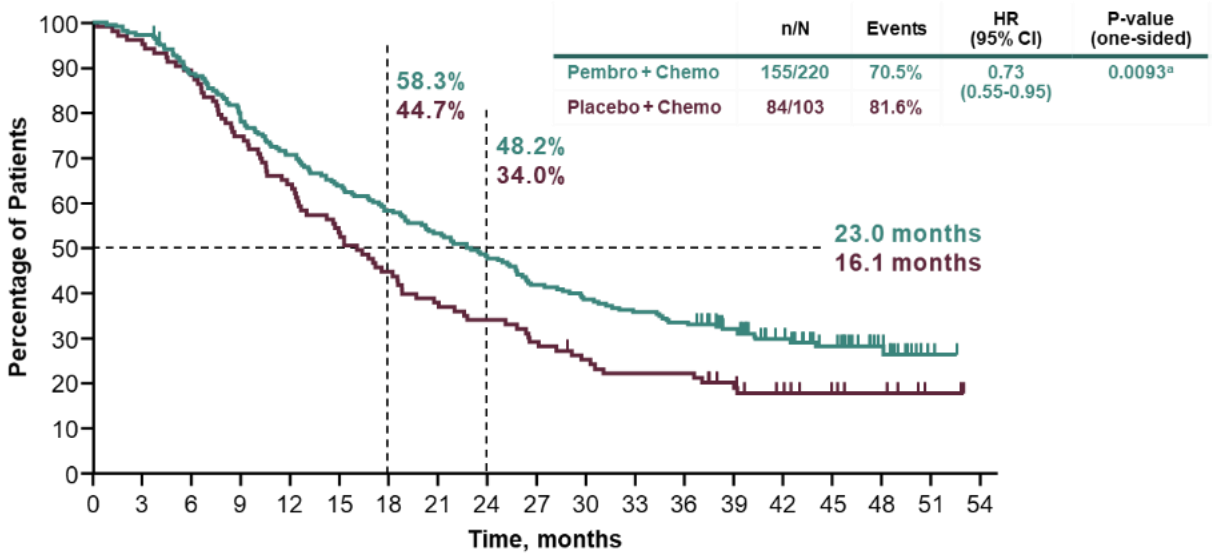


Significance not tested according to hierarchical statistical design

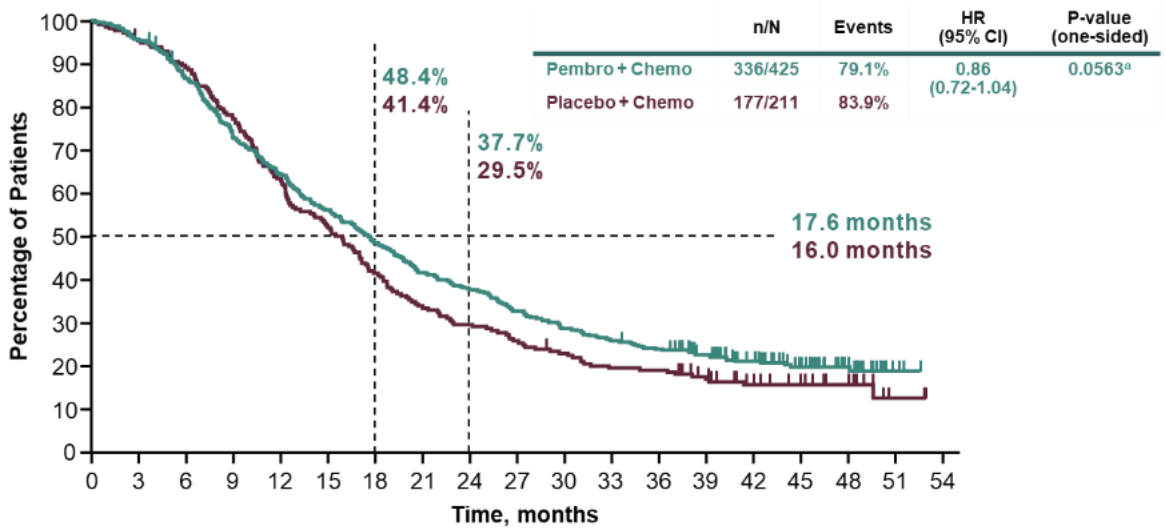
Cortes, ASCO 2020; Cortes, Lancet 2020

KEYNOTE-355: Overall survival

PD-L1 CPS ≥10



PD-L1 CPS ≥1



No significant difference in CPS ≥1 and ITT

- For pembrolizumab + chemotherapy in mTNBC, CPS ≥10 is the best cut-off to define those expected to benefit
- Pembrolizumab + chemotherapy is a new standard of care for the treatment of mTNBC with CPS≥10

Rugo, ESMO 2021; Cortes, NEJM 2022

KEYNOTE-355: Overall survival in subgroups CPS ≥10

Subgroup	N	Median OS (mo) Pembro + Chemo	Median OS (mo) Placebo + Chemo	Hazard Ratio for Death (95%)
Overall	323	23.0	16.1	0.73 (0.55 to 0.95)
Age (years)				
<65	257	21.8	16.8	0.78 (0.58 to 1.05)
≥65	66	28.3	12.6	0.51 (0.28 to 0.92)
Geographic region				
N America/EU/ANZ	212	23.5	15.2	0.72 (0.52 to 1.00)
Asia	56	26.7	17.4	0.44 (0.23 to 0.84)
Rest of world	55	18.0	22.0	1.07 (0.57 to 1.98)
ECOG PS				
0	196	26.4	19.8	0.70 (0.49 to 1.00)
1	127	17.7	10.6	0.70 (0.47 to 1.05)
On-study chemotherapy				
Nab-paclitaxel	99	29.8	18.4	0.63 (0.39 to 1.03)
Paclitaxel	44	28.6	8.5	0.34 (0.16 to 0.72)
Gemcitabine-Carboplatin	180	19.1	16.2	0.88 (0.61 to 1.25)
Prior same-class chemotherapy				
Yes	65	23.5	14.9	0.60 (0.32 to 1.09)
No	258	22.8	16.9	0.74 (0.55 to 1.00)
Prior (neo)adjuvant chemotherapy				
Yes	193	20.3	17.1	0.86 (0.61 to 1.22)
No	130	28.3	13.0	0.53 (0.34 to 0.80)
Disease-free interval				
de novo metastasis	104	26.4	12.5	0.54 (0.34 to 0.86)
<12 months	65	17.1	19.7	1.44 (0.73 to 2.82)
≥12 months	153	24.9	17.1	0.65 (0.45 to 0.96)
Number of metastatic sites				
<3	184	32.1	18.8	0.63 (0.43 to 0.91)
≥3	138	13.2	10.5	0.75 (0.51 to 1.10)

Rugo, ESMO 2021; Cortes, NEJM 2022

Immunotherapy in metastatic triple-negative breast cancer

Impassion 132: Study design

Double-blind placebo-controlled randomised phase 3 trial

- **Unresectable locally advanced/ metastatic TNBC**
- **Prior anthracycline and taxane for early TNBC**
- **Disease progression <12 months after last treatment with curative intent for early TNBC[a]**
- **No prior CT for advanced TNBC**
- **Known PD-L1 status (SP142)**

R 1:1

Carboplatin/gemcitabine or capecitabine[b] + atezolizumab 1200 mg q3w

Carboplatin/gemcitabine or capecitabine[b] + placebo q3w

Treatment continued until disease progression or unacceptable toxicity

Stratification factors:

- Visceral (lung and/or liver) metastases
- CT backbone
- PD-L1 status (during all-comer enrolment)

Primary endpoint:

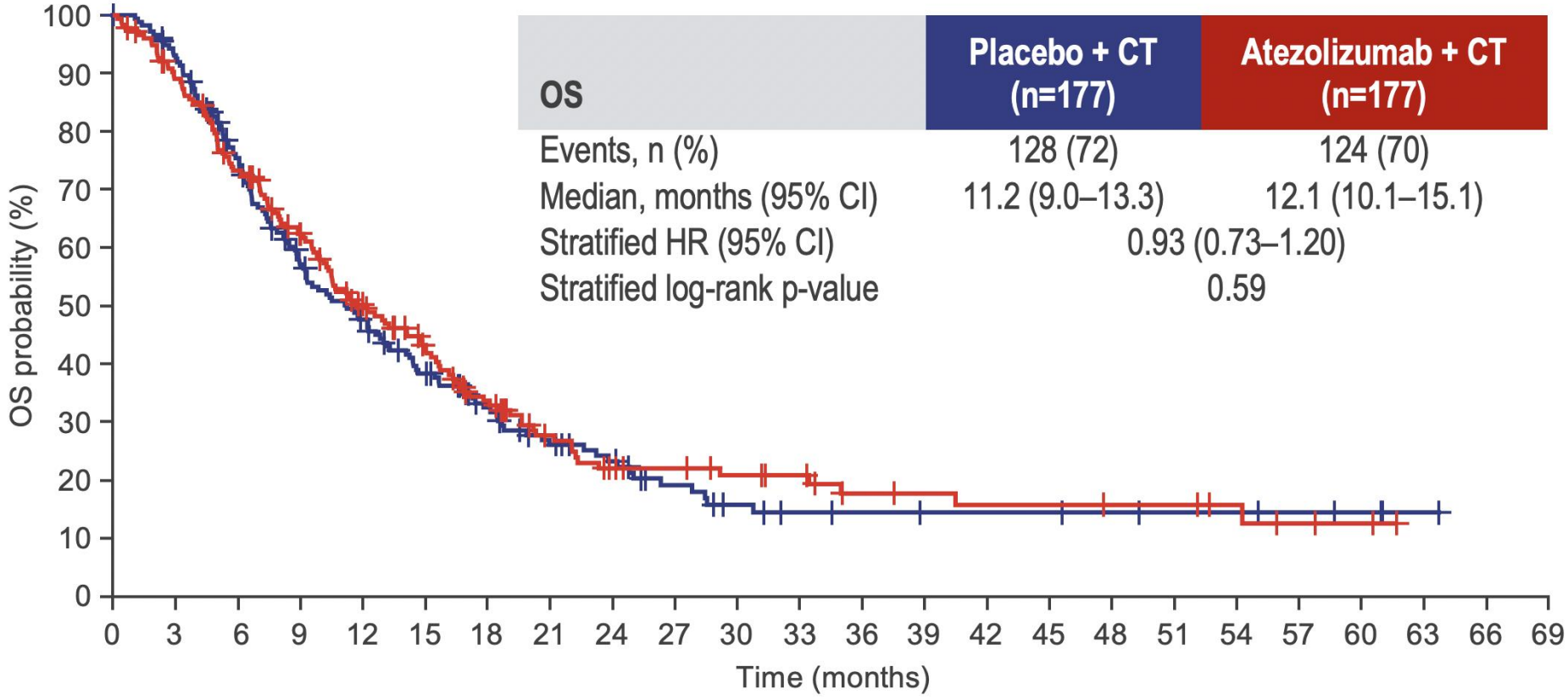
- OS (hierarchical testing: PD-L1+ TNBC[c] then, if positive, modified ITT population[d])

Dent, Ann Onc 2024

Immunotherapy in metastatic triple-negative breast cancer

Impassion 132: Overall Survival

No significant improvement in OS with atezolizumab (median F/U: 9.8 months)

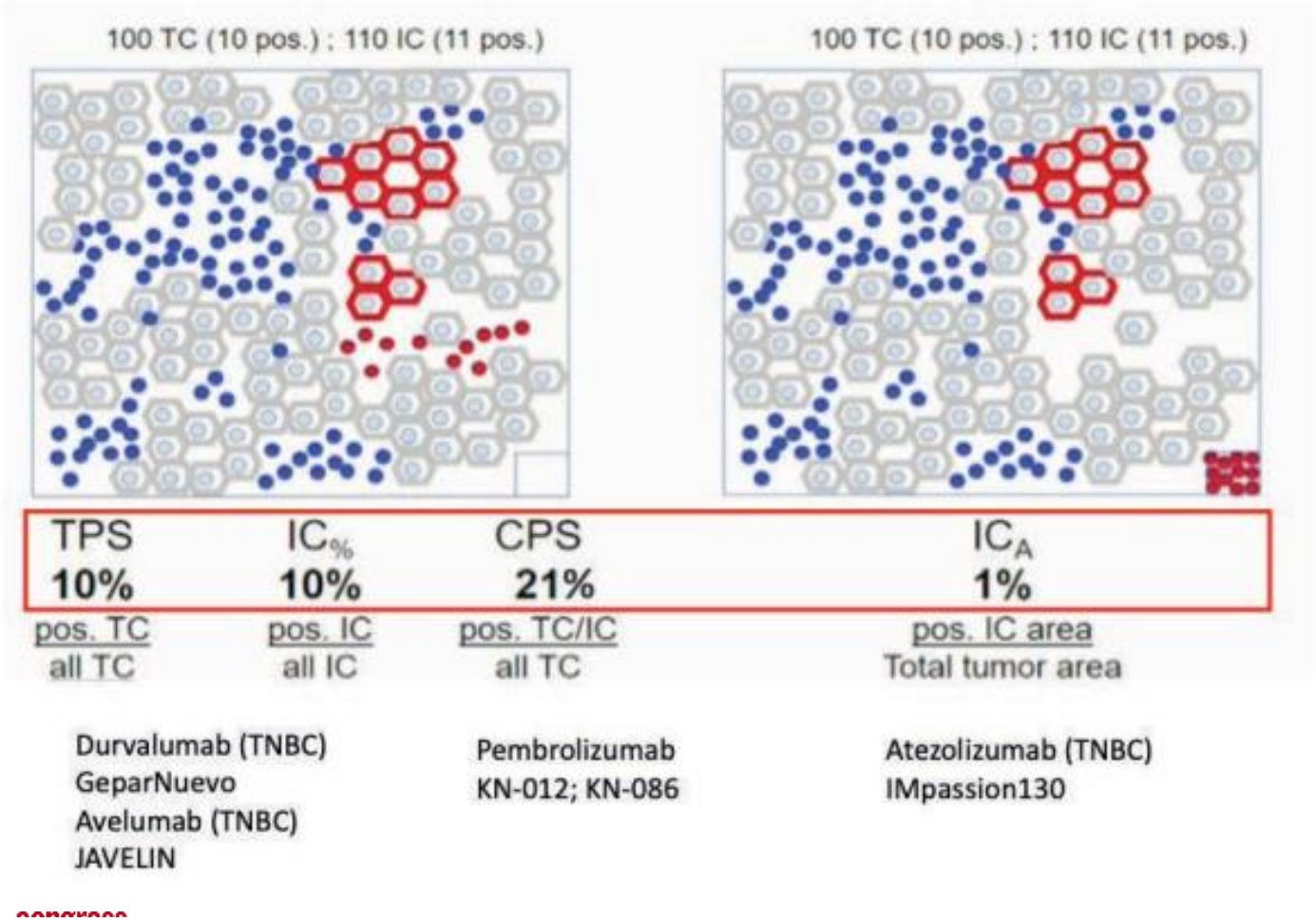


OS	Placebo + CT (n=177)	Atezolizumab + CT (n=177)
Events, n (%)	128 (72)	124 (70)
Median, months (95% CI)	11.2 (9.0–13.3)	12.1 (10.1–15.1)
Stratified HR (95% CI)	0.93 (0.73–1.20)	
Stratified log-rank p-value	0.59	

Dent, Ann Onc 2024

Immunotherapy in metastatic triple-negative breast cancer

Discordance across PD-L1 tests

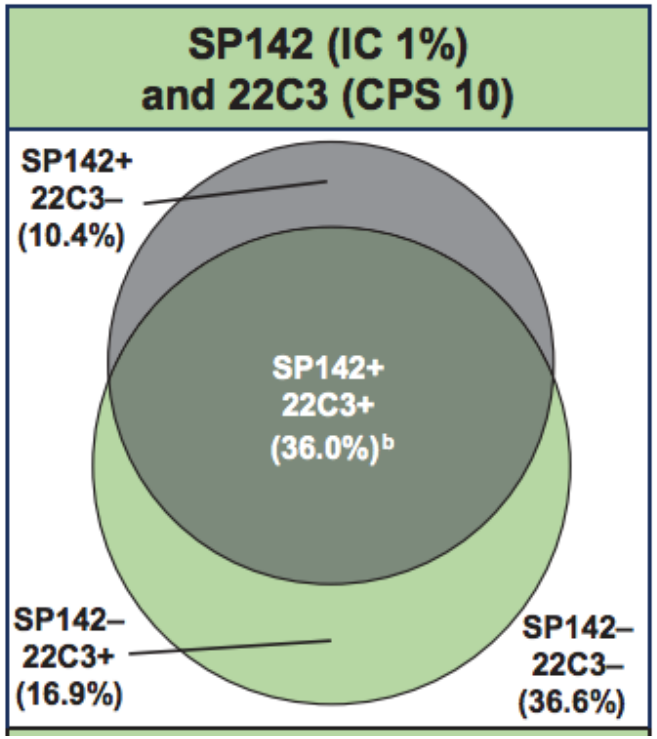


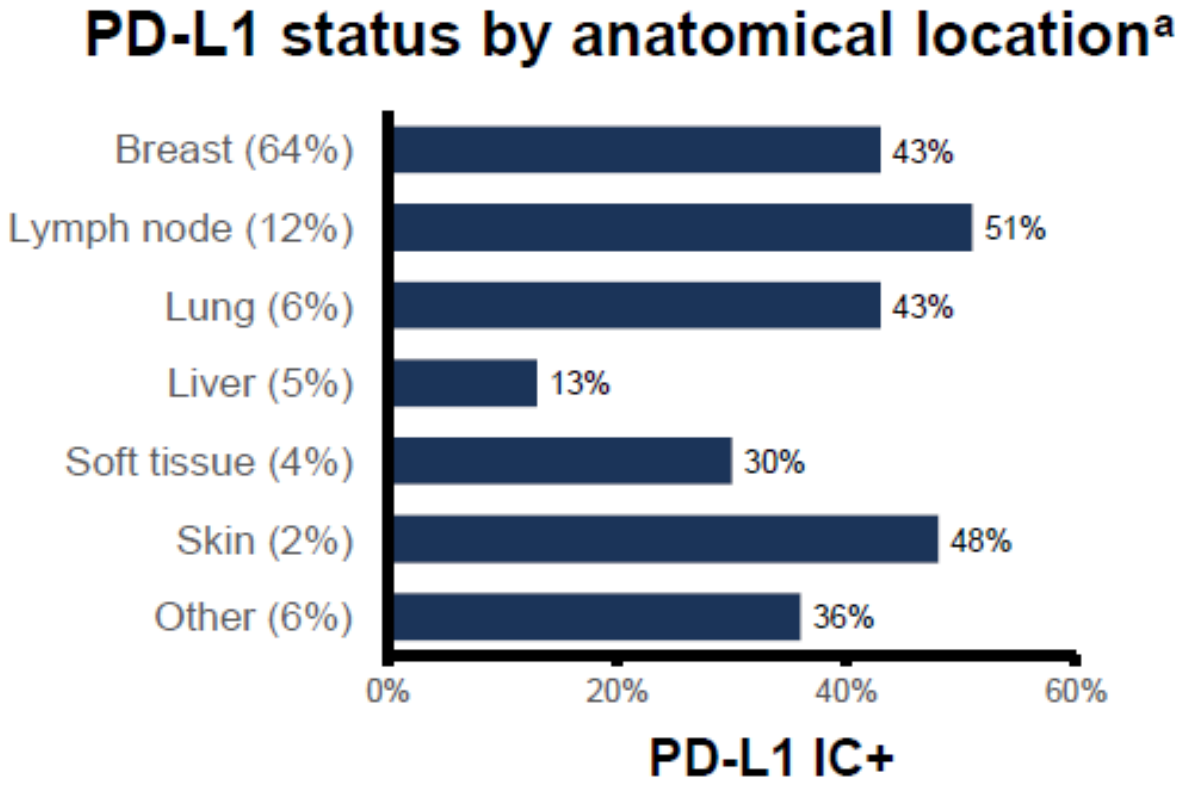
ASSESSMENT

TPS = Tumor proportion score = (pos TC/all TC)*100
CPS = Combined pos Score = ((posTC + posIC)/allTC)*100
IC% = Immun cell (proportion) score (pos IC/all IC)*100
ICA = Immun cell (area) score (pos IC area/tumor area)*100

Immunotherapy in metastatic triple-negative breast cancer

PD-L1 testing





27% of patients is PD-L1 «single-positive»

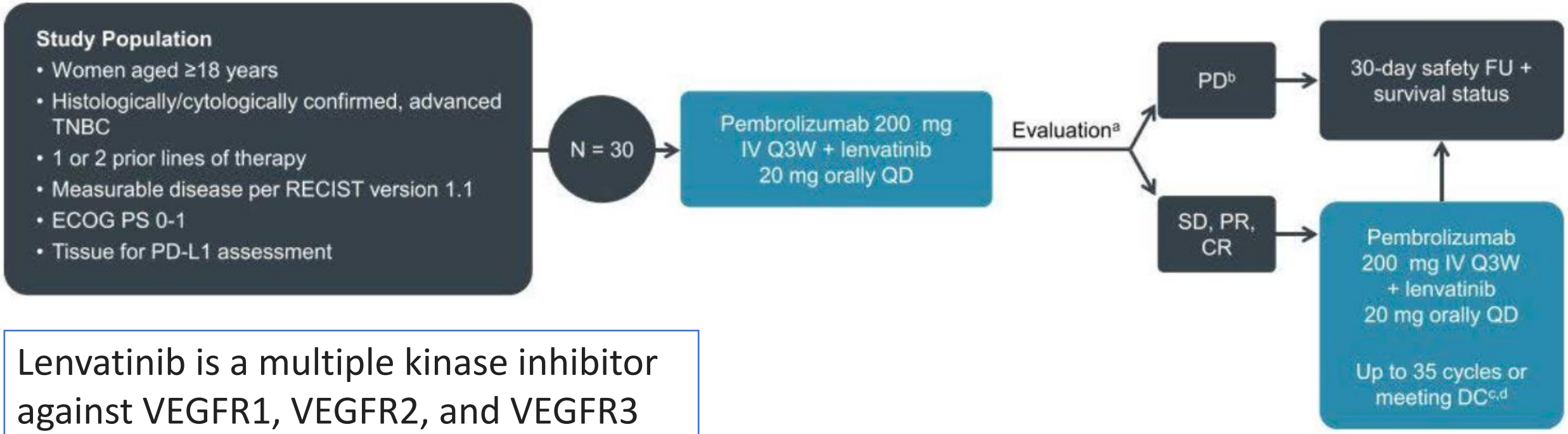
Consider both tests if both ICIs are available

Rugo, JNCI 2021

Immunotherapy in metastatic triple-negative breast cancer

Immunotherapy and VEGF inhibition

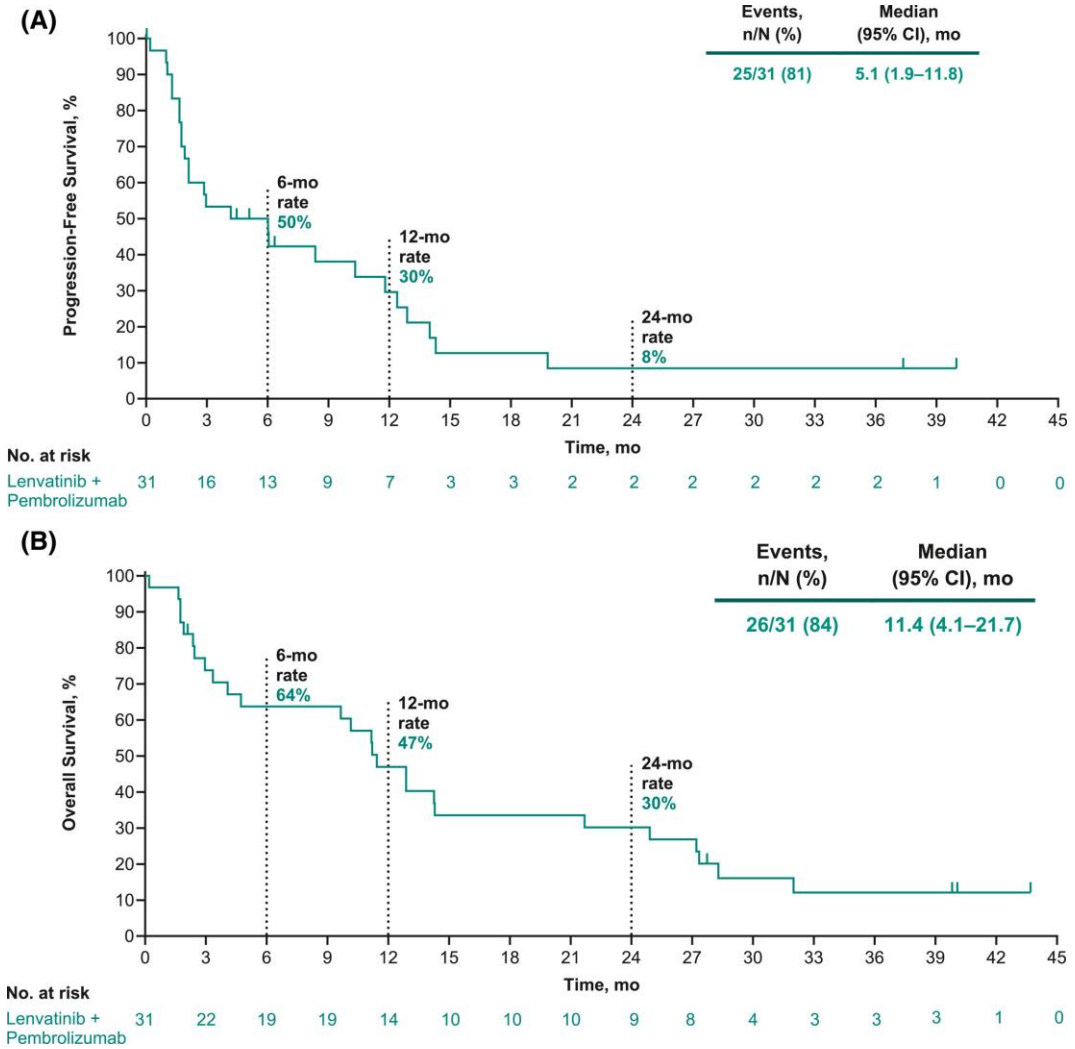
Figure 1. LEAP-005 Study Design



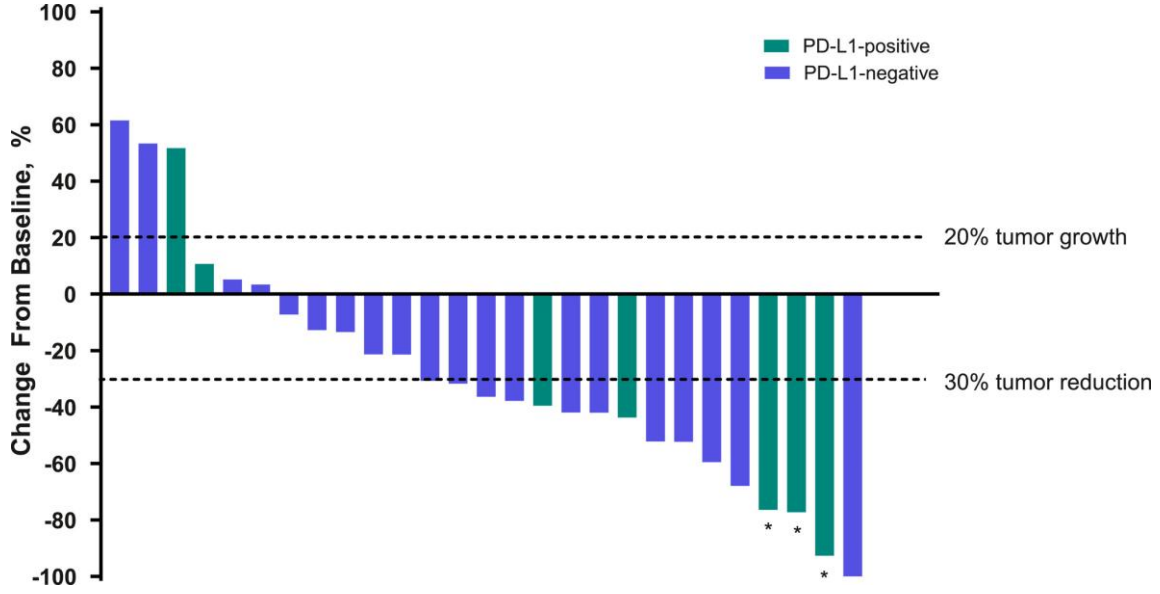
Lenvatinib is a multiple kinase inhibitor against VEGFR1, VEGFR2, and VEGFR3

Immunotherapy and VEGF inhibition

LEAP-005 study



	ITT	*PDL1+	PDL1-
ORR [95% CI], %	32 [17–51]	50 [16–84]	27 [11–50]

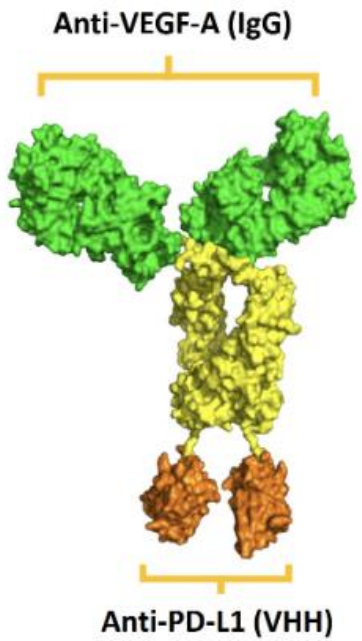


*CPS: PD-L1 IHC 22C3 pharmDx >/=10

Immunotherapy in metastatic triple-negative breast cancer

Immunotherapy and VEGF inhibition: **bispecific antibodies**

PM8002



Key Eligibility Criteria

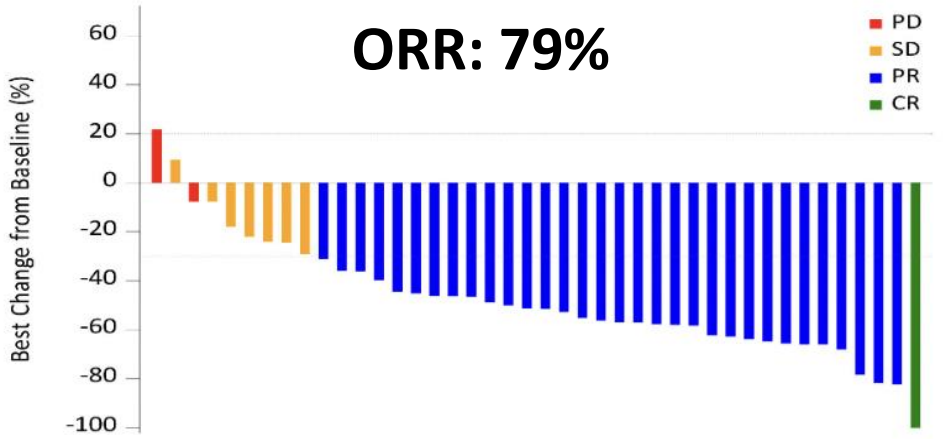
- Patients with locally advanced or metastatic TNBC who have not received prior systemic treatment for TNBC;
- Age ≥ 18 years;
- ECOG score 0-1;
- Adequate organ function.

Open label, Single arm study
PM8002+Nab-paclitaxel
PM8002 20mg/kg
- On days 1 and 15 of 28-day cycle
Nab-paclitaxel 100 mg/m²
- On days 1, 8 and 15 of 28-day cycle

Disease progression/ unacceptable toxicity

Primary endpoint: Objective Response Rate (ORR) assessed by investigators per RECIST1.1, the incidence and severity of Treatment-Related Adverse Events (TRAEs) graded according to NCI-CTCAE v5.0.
Secondary endpoint: Progression Free Survival(PFS), Disease Control Rate (DCR).

ORR: 79%



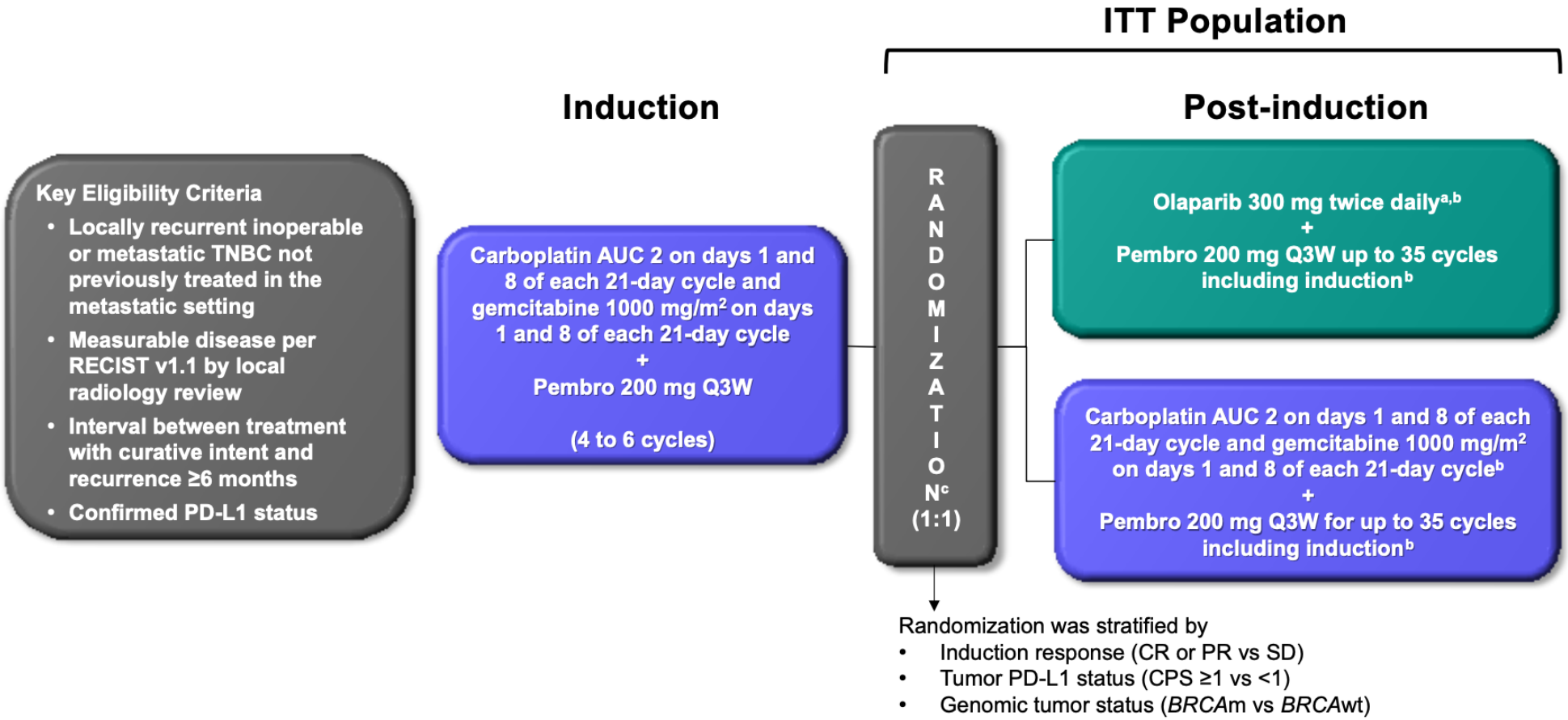
Conclusions

PM8002 combined with nab-paclitaxel showed encouraging antitumor activity regardless of PD-L1 status and good safety profile as a first-line therapy for TNBC patients.
This phase II study is still ongoing with near-term plans to enter phase III trials.

Wu, SABCS 2023

PARP inhibitors in metastatic triple-negative breast cancer

PARP inhibitors and immune-checkpoint inhibitors: KEYLYNK-009 study design



Primary Endpoint: **PFS**

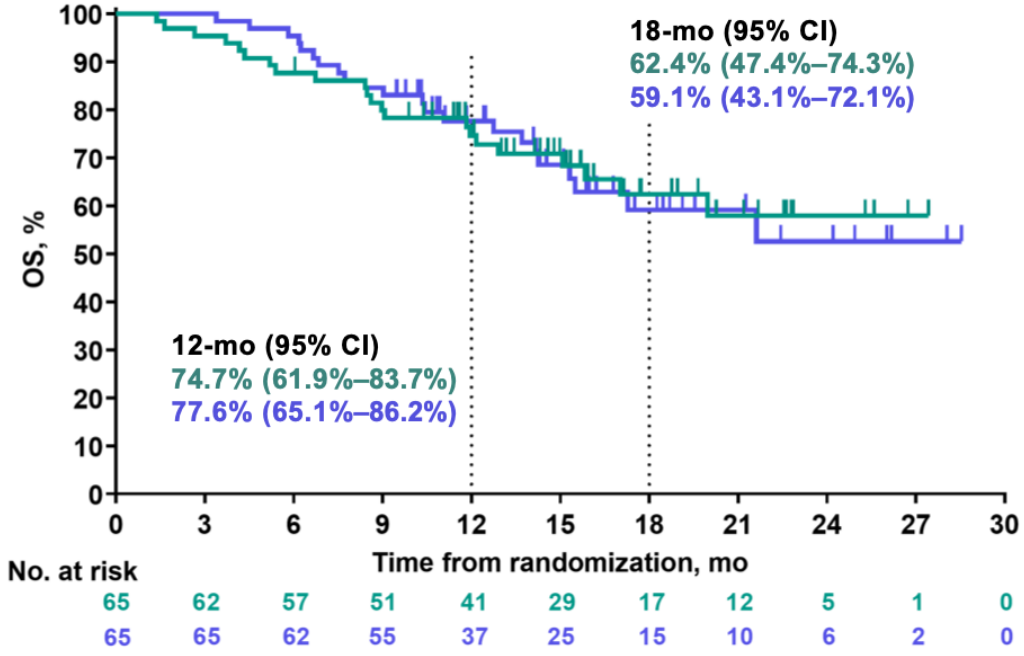
Rugo, SABCS 2023

PARP inhibitors in metastatic triple-negative breast cancer

KEYLYNK-009: estimates of OS according to PD-L1 CPS and t*BRCA*m

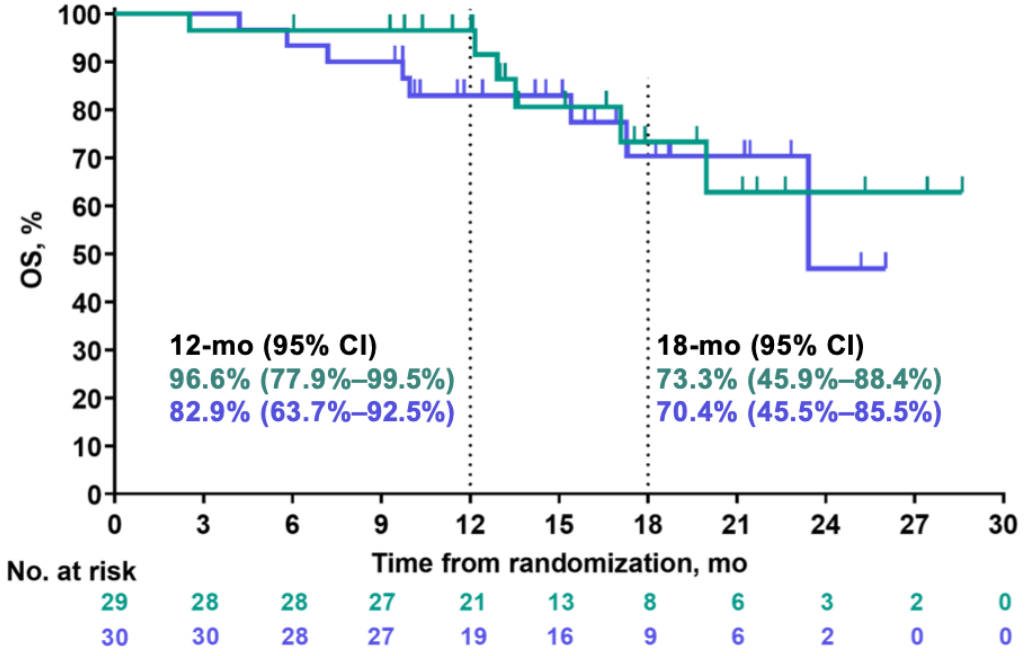
Tumor PD-L1 CPS ≥10 Population

	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)
Pembro + Olaparib	22 (33.8)	NR (17.0–NR)	0.97 (0.53–1.76)
Pembro + Chemo	22 (33.8)	NR (15.5–NR)	



t*BRCA*m Population

	Events, n (%)	Median, mo (95% CI)	HR[b] (95% CI)
Pembro + Olaparib	6 (20.7)	NR (17.1–NR)	0.81 (0.28–2.37)
Pembro + Chemo	8 (26.7)	23.4 (17.3–NR)	

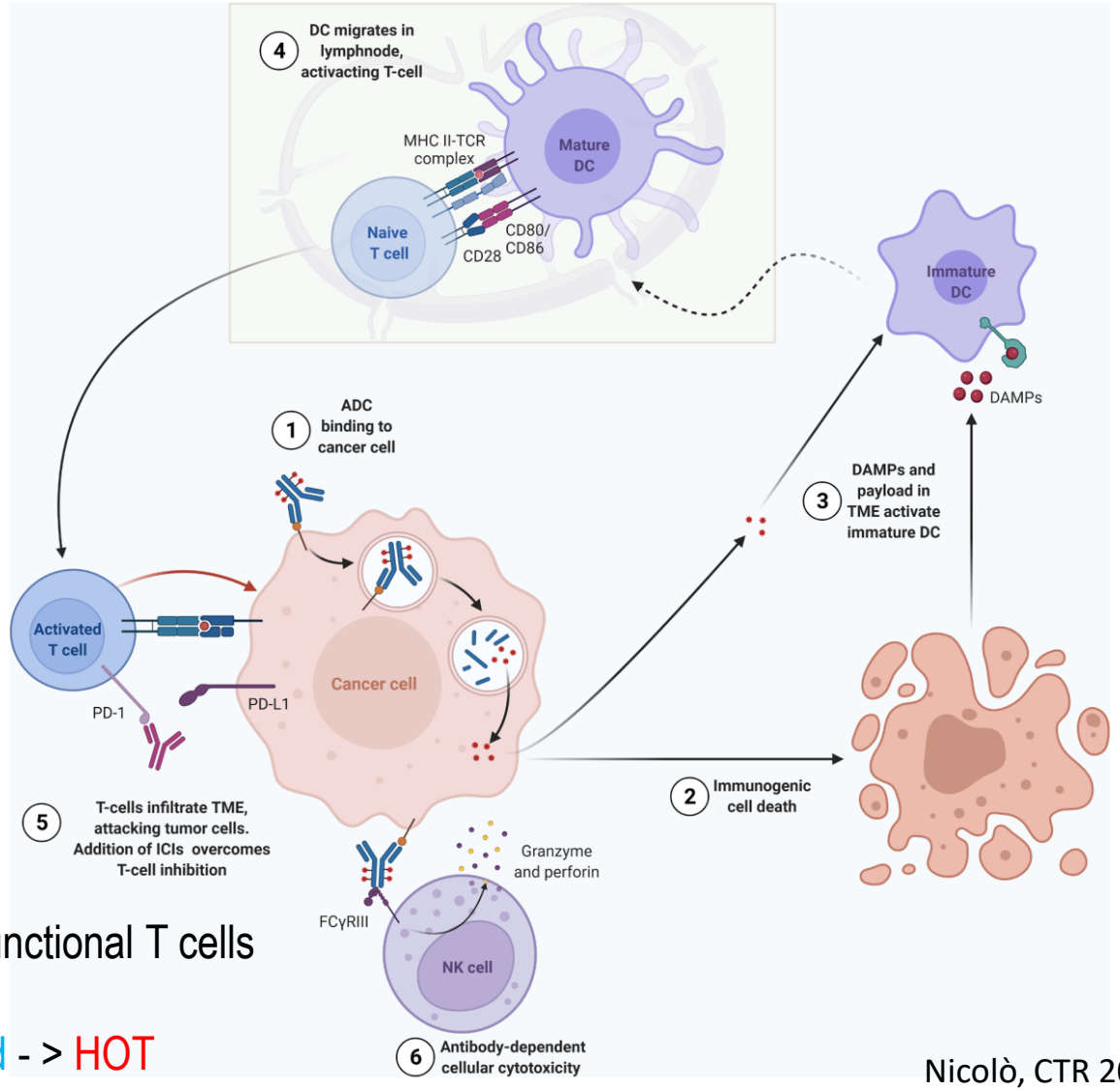


Rugo, SABCS 2023

ADCs in metastatic triple-negative breast cancer

Combining ADCs and immune-checkpoint inhibitors

- ADCs and ICIs demonstrated to improve the OS in patients with mTNBC
- The combination of ADCs and ICIs may have synergistic properties
- ADCs could transform a cold tumor microenvironment into a hot one



⇧ functional T cells

Cold - > HOT

Nicolò, CTR 2022

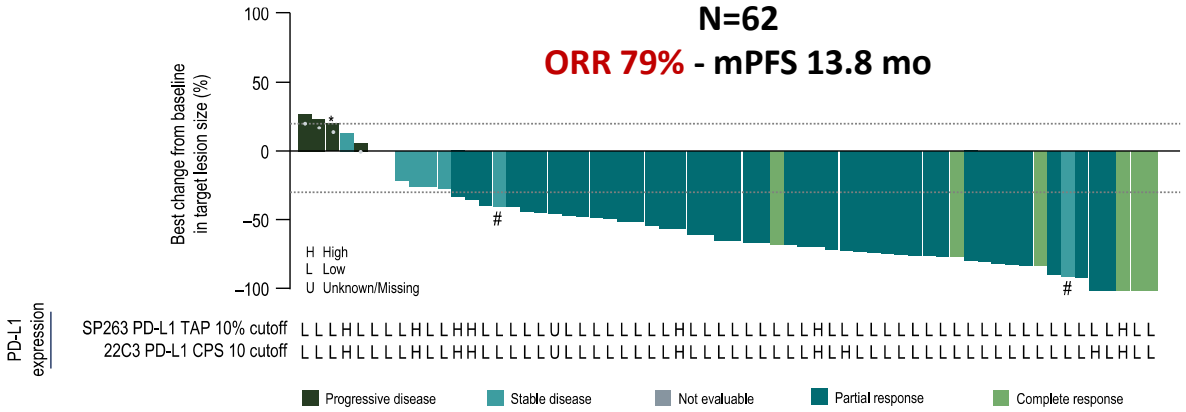
ADCs in metastatic triple-negative breast cancer

Combining ADCs and immune-checkpoint inhibitors

BEGONIA Trial
Dato-DXd + Durvalumab
in 1st line mTNBC

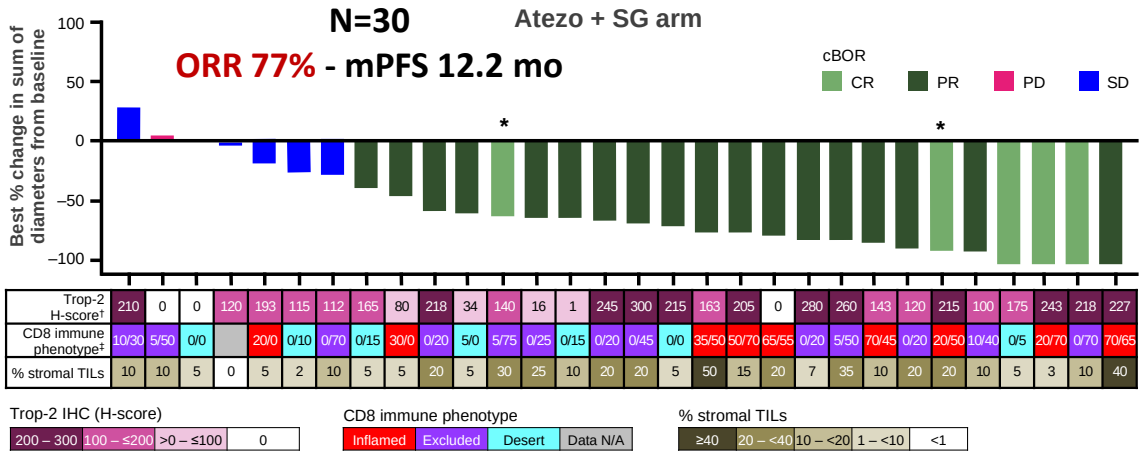
Median follow-up: 11.7 (range, 2–20) months

N=62
ORR 79% - mPFS 13.8 mo



Morpheus-PAN BC Trial
Sacituzumab Govitecan + Atezolizumab
in PD-L1+ 1st line mTNBC

N=30 Atezo + SG arm
ORR 77% - mPFS 12.2 mo



Antitumour responses were observed **regardless of PD-L1 expression** level as assessed by 2 separate PD-L1 assays and scoring methods

Schmid et al, ESMO 2023

Schmid et al, ESMO Breast 2024

Combining ADCs and ICI in metastatic breast cancer

SACI-IO TNBC: sacituzumab govitecan and pembrolizumab in 1° line PD-L1- mTNBC (ER<5%)

SACI-IO HR+: Study Schema

Metastatic or locally advanced unresectable breast cancer

- HR-positive (ER ≥ 1% or PR ≥ 1%), HER2-negative (IHC 0, 1+, or 2+/ ISH-)
- No restriction on PD-L1 status[a]
- ≥1 endocrine therapy for mBC or progression on or within 12 months of adjuvant endocrine therapy
- 0-1 prior chemotherapy for mBC
- No prior topoisomerase I-inhibitor ADC, irinotecan, or PD-1/-L1 inhibitor
- No known active brain metastases or leptomeningeal disease

Treatment continued until progression or unacceptable toxicity

N=110

R 1:1

Sacituzumab govitecan (SG)
10 mg/kg IV D1, D8 of every 21 days
+
Pembrolizumab
200 mg IV D1 of every 21 days

Sacituzumab govitecan (SG)
10 mg/kg IV D1, D8 of every 21 days

Baseline Research Biopsy | Cycle 2 Research Biopsy | Optional EOT Biopsy

Endpoints

Primary:
- PFS (ITT)

Secondary:
- PFS (PD-L1+)[b]
- OS (ITT, PD-L1+)
- ORR, DOR, TTOR, CBR (ITT, PD-L1+)
- Safety

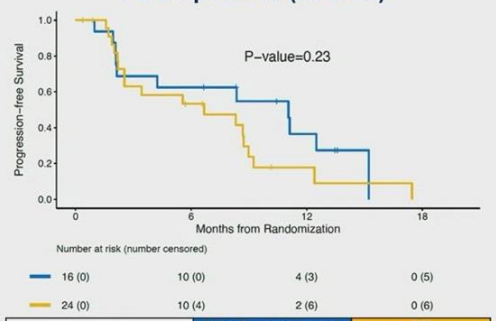
Exploratory:
- Correlative
- HRQoL

NCT04448886

Study activation date: 9/23/2020. Data cutoff for analysis: 3/9/2024.
[a] Protocol amendment activated in 1/2022 to allow participants with any PD-L1 status to enroll. [b] Central PD-L1 testing performed with PharmDx 22C3 assay. PD-L1-positive, combined positive score (CPS) ≥1. Note: There is no approved CDx with 22C3 for HR+/HER2- mBC.
Abbreviations: HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; ADC, antibody drug conjugate; ITT, intent-to-treat; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; DOR, duration of response; TTOR, time to objective response; CBR, clinical benefit rate; HRQoL, health-related quality of life.

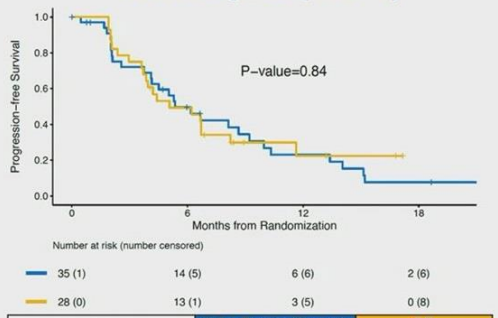
Progression-Free Survival by PD-L1 IHC status

PD-L1-positive (CPS ≥1)



Treatment Arm	SG + Pembrolizumab (N=16)	SG (N=24)
N PFS events	11	18
Median PFS, mo (95% CI)	**11.05** (2.14-NA)	**6.68** (2.53-9.24)
HR (95% CI)	**0.62** (0.29-1.36)	
p-value (logrank test)	0.23	

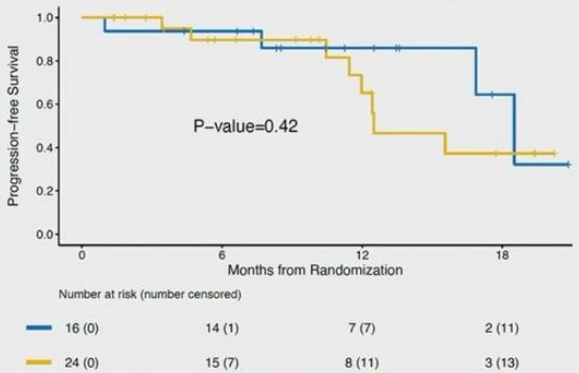
PD-L1-negative (CPS <1)



Treatment Arm	SG + Pembrolizumab (N=35)	SG (N=28)
N PFS events	27	20
Median PFS, mo (95% CI)	**5.36** (4.14-9.97)	**5.07** (3.85-NA)
HR (95% CI)	**1.06** (0.59-1.90)	
p-value (logrank test)	0.84	

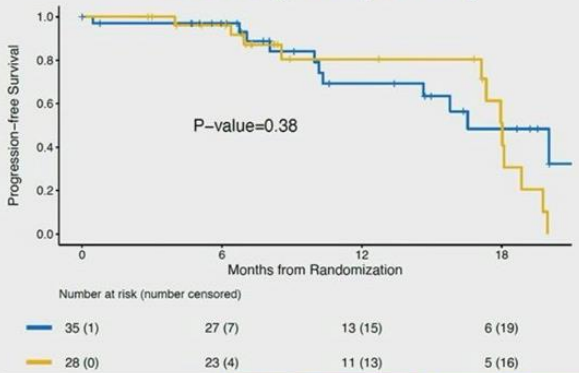
Overall Survival by PD-L1 IHC status

PD-L1-positive (CPS ≥1)



Treatment Arm	SG + Pembrolizumab (N=16)	SG (N=24)
N OS events	4	8
Median OS, mo (95% CI)	**18.52** (16.88-NA)	**12.50** (11.97-NA)
HR (95% CI)	**0.61** (0.18-2.04)	
p-value (logrank test)	0.42	

PD-L1-negative (CPS <1)



Treatment Arm	SG + Pembrolizumab (N=35)	SG (N=28)
N OS events	11	12
Median OS, mo (95% CI)	**16.55** (14.64-NA)	**18.03** (17.34-NA)
HR (95% CI)	**0.68** (0.29-1.59)	
p-value (logrank test)	0.38	

SYNERGY TRIAL

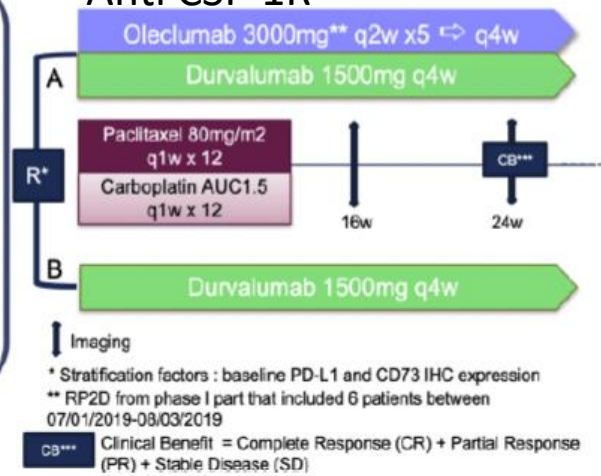
First-line treatment in advanced TNBC

Phase II : study design

Multicenter, open-label, randomized (1:1 ratio)

Anti CSF-1R

Key eligibility criteria:
- Female, ≥18yo
- Locally advanced or metastatic TNBC
- 1st Line
- ≥ 6mo since end of adjuvant treatment
- ECOG 0-1
- Adequate organ function
- Measurable disease per RECIST v1.1
- No prior treatment with checkpoint inhibitor
- No major auto-immune disease



* Stratification factors : baseline PD-L1 and CD73 IHC expression

** RP2D from phase I part that included 6 patients between 07/01/2019-08/03/2019

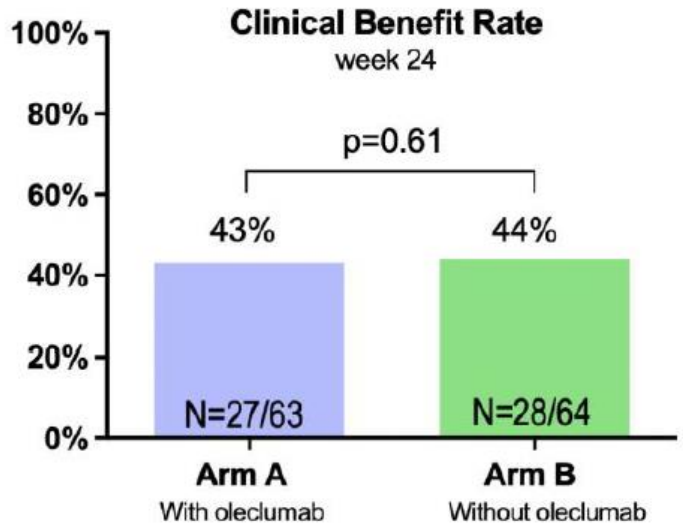
CB*** Clinical Benefit = Complete Response (CR) + Partial Response (PR) + Stable Disease (SD)

Primary endpoint:
- Clinical Benefit (CB) at week 24

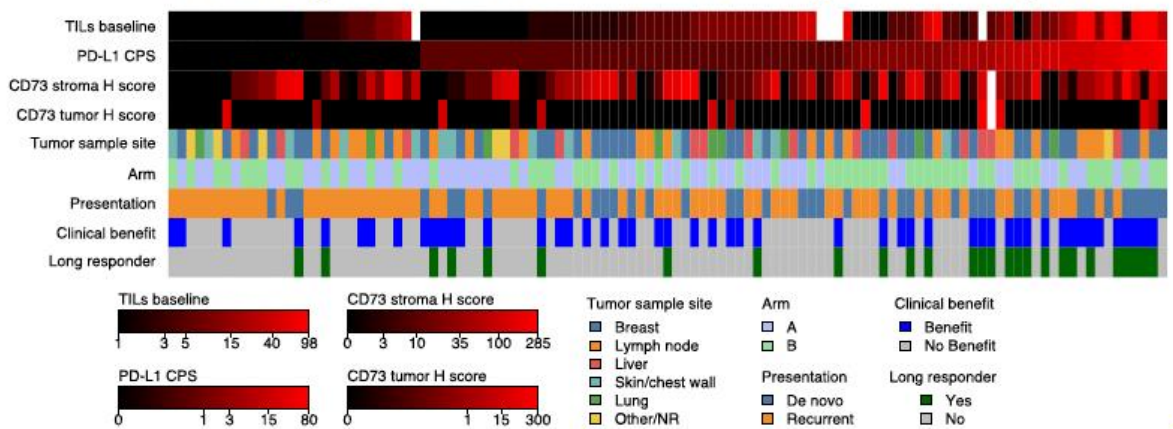
Secondary endpoints:
- OR
- DOR
- PFS
- OS
- CBR according to PD-L1 and CD73

Exploratory endpoints:
- Response RECIST v1.1 vs iRESIST v1.1
- PFS RECIST v1.1 vs iRESIST v1.1

OR: objective response; DOR: duration of response; PFS: progression free survival; OS: overall survival



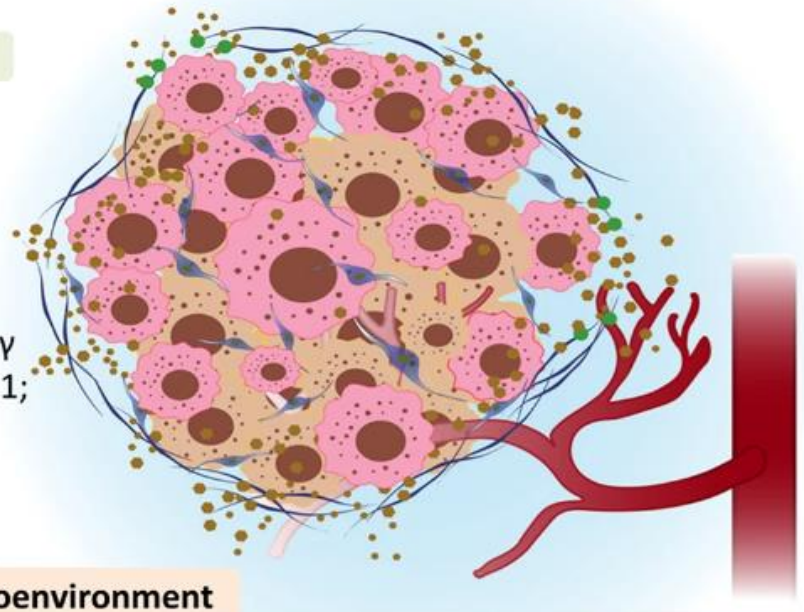
Heterogenous disease → heterogenous responses



URGENT need for effective biomarkers

Buisseret *et al*. Nature Com 2023

What biomarkers may predict immunotherapy benefit?



(i) Tumor cells

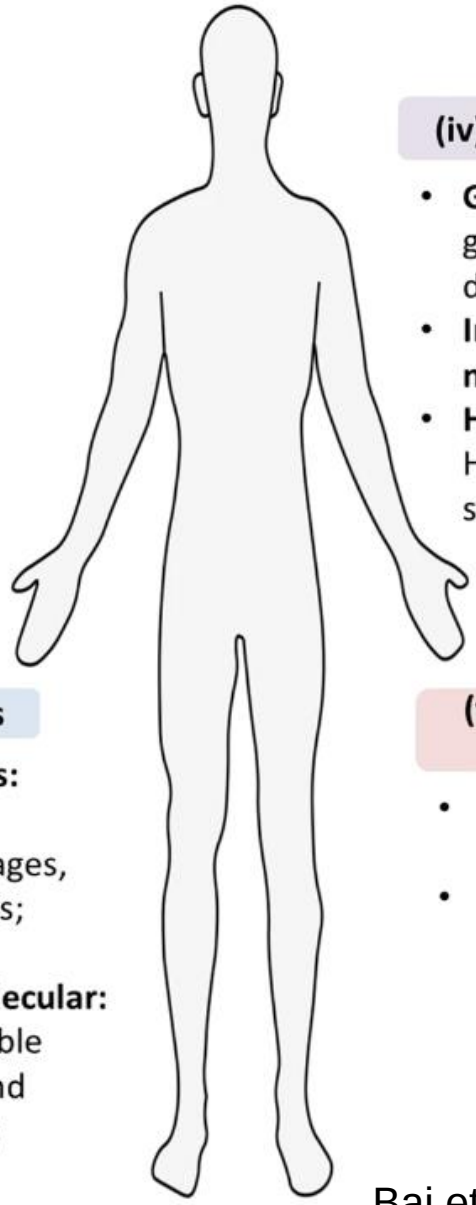
- **PD-L1 expression;**
- **TMB;**
- **DDR pathways:** dMMR/MSI;
- **Specific mutated gene pathways:** IFN-γ pathway, KRAS, STK11;
- **Neoantigen load;**

(ii) Tumor microenvironment

- **PD-L1 expression;**
- **Tumor-infiltrating immune cells:**
  Immune status of TME: immunologic classification, immunoscore;
  Immune cells with specific phenotypes: $CD39^+CD8^+$T, $CD4^+$T cells, $FOXP3^+$T cells, TAMs, myeloid cells, $NKp46^+$ cells;
  Diversity of immune repertoires: TIL richness and clonality, TCR clonality;

(iii) Circulating factors

- **Peripheral blood cells:** myelogenous cells, eosinophils, nacrophages, $CD4^+ICOS^+$T cells, CTCs;
- **ctDNA;**
- **Other circulating molecular:** exosomal PD-L1, soluble proteins, cytokines and inflammatory factors;



(iv) Host-related markers

- **General characteristics:** gender, age, body fat distribution;
- **Intestinal commensal microbiota;**
- **Host germline genetics:** HLA diversity and other specific mutations;

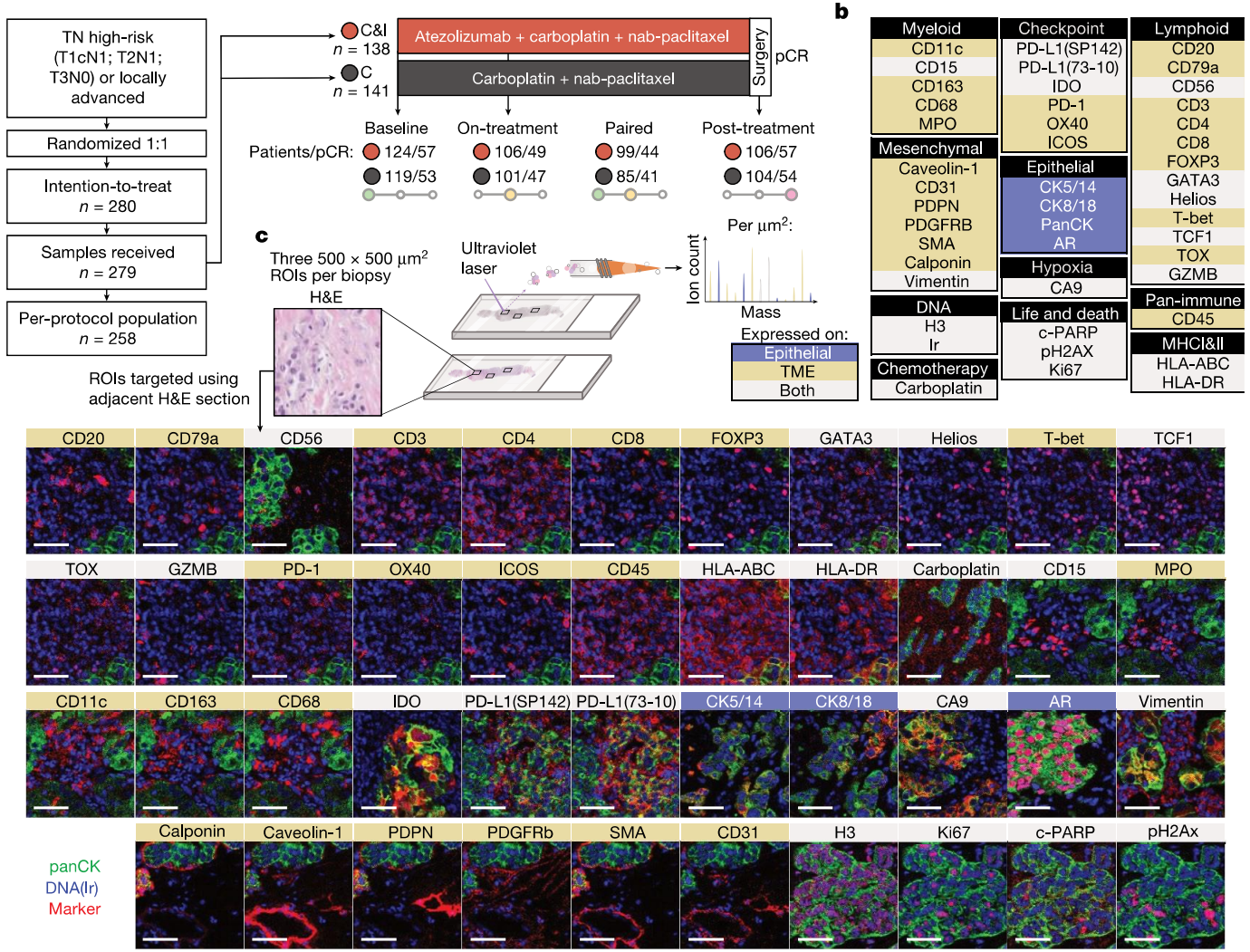
(v) Immune-related adverse events

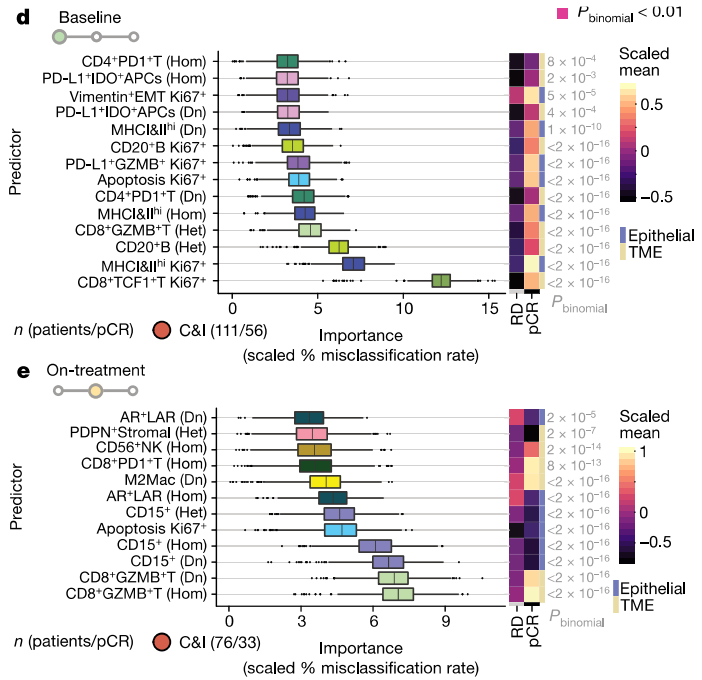
- **Endocrine irAEs:** thyroid dysfunction;
- **Skin irAEs:** vitiligo, pruritus, lichenoid toxicity;

Bai et. al. *Biomarker Research* 2020

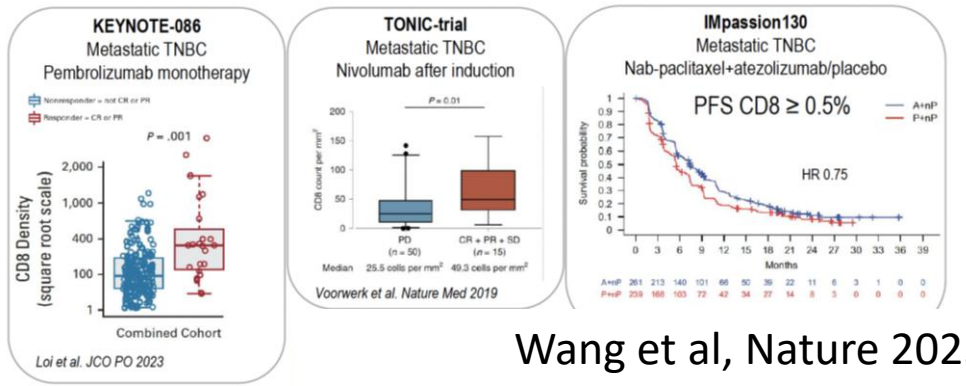
Spatial predictors of immunotherapy response in TNBC

CD8+TCF1+T cells and **MHCII+ cancer cells** are dominant predictors of response to ICI





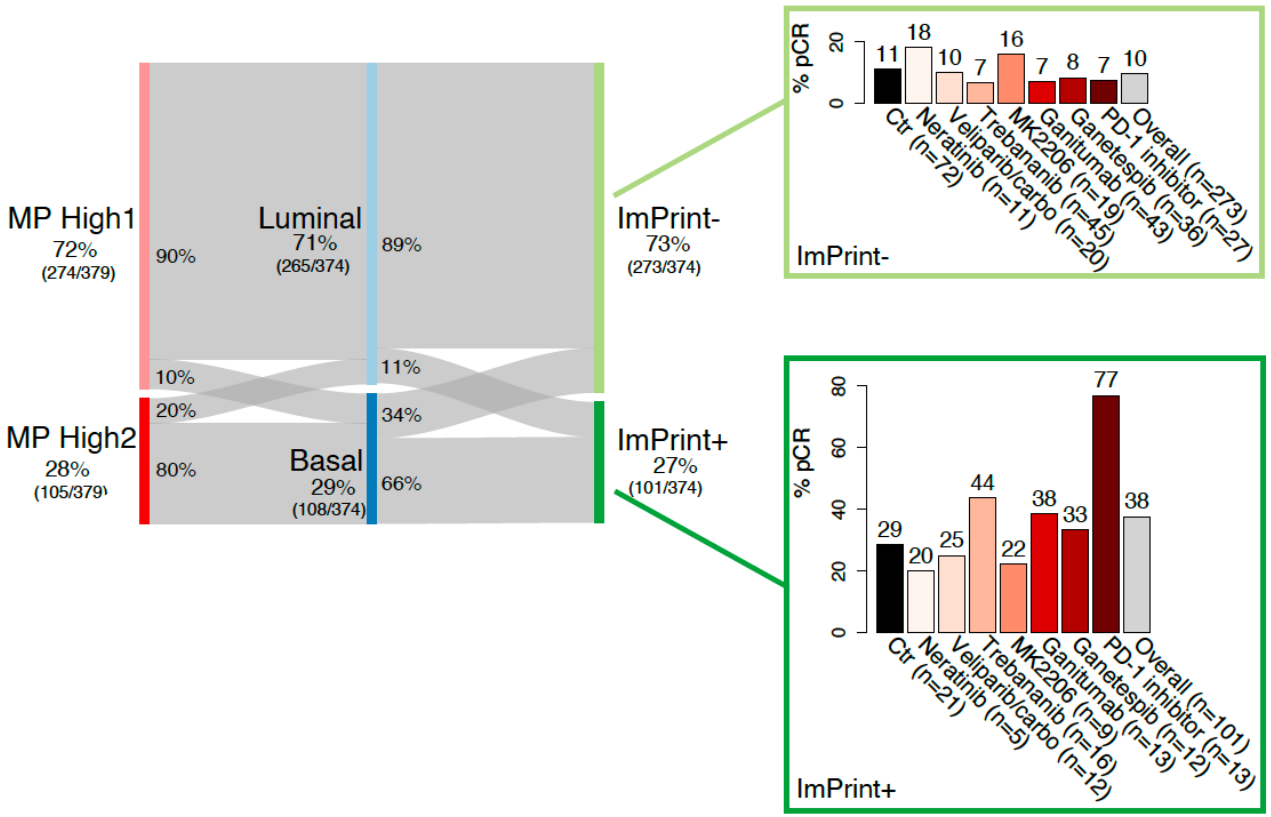
CD8 T CELL INFILTRATION



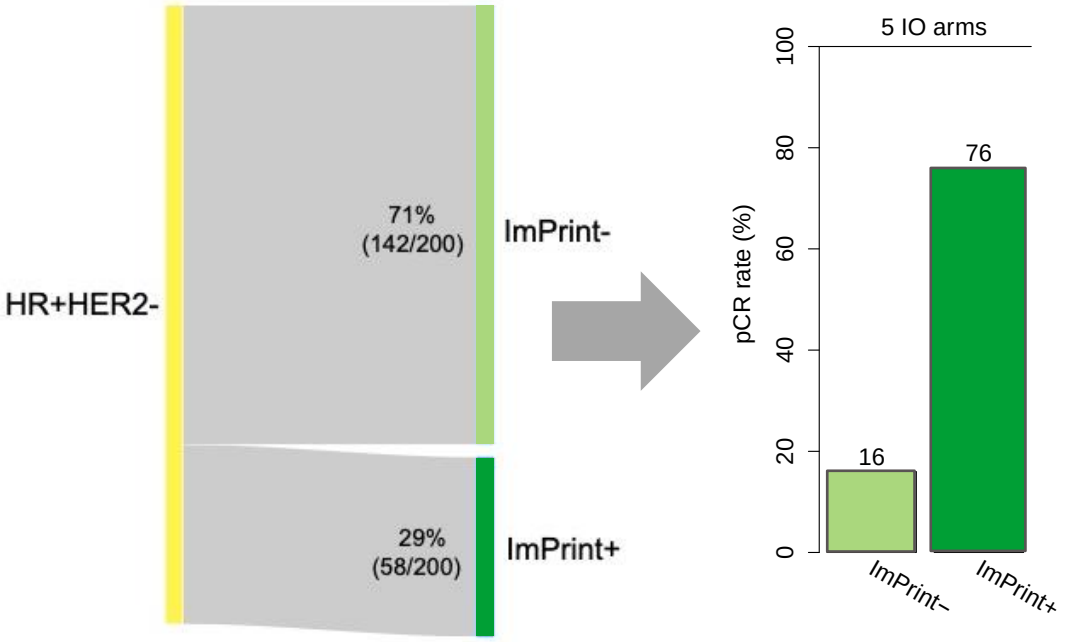
Wang et al, Nature 2023

ISPY2: Use of the ImPrint immune signature to predict IO response?

HR+/HER2- (n=379)
8 arms, including one IO arm



HR+/HER2- (n=200)
5 IO arms



29% ImPrint+ in HR+HER2-

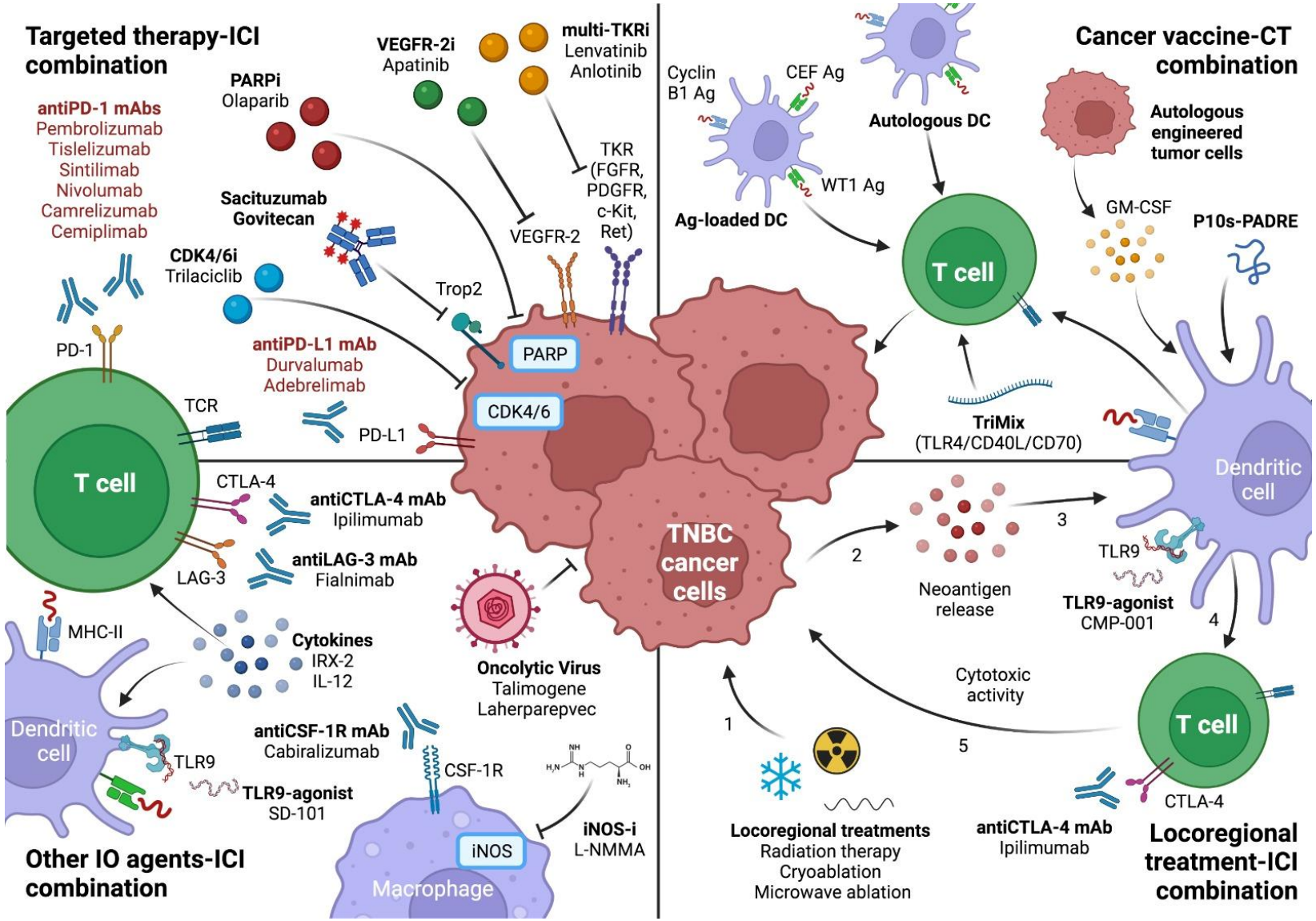
- 76% pCR in ImPrint+
- 16% pCR in ImPrint-

Huppert et. al. ASCO 2022

Wolfe, Yau et. al. ASCO 2023

Immunotherapy in metastatic breast cancer

… and future perspectives

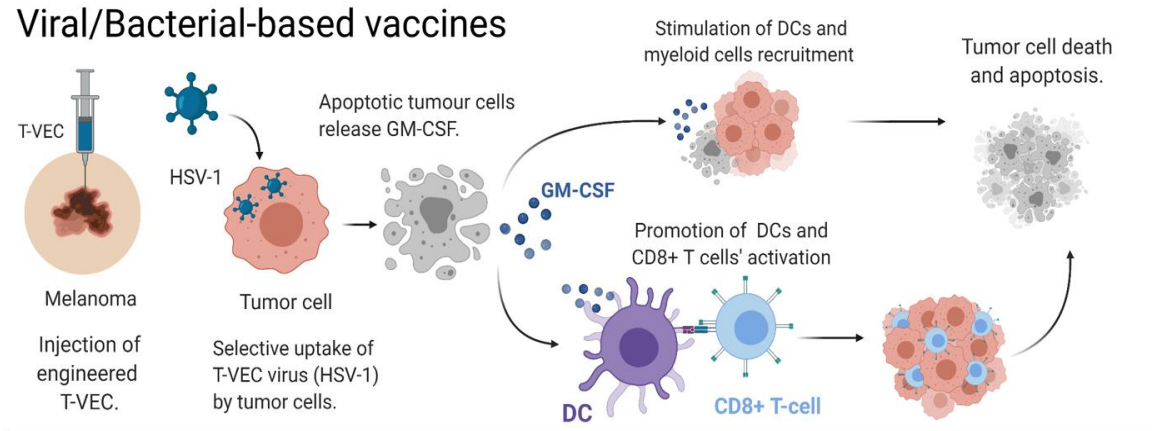


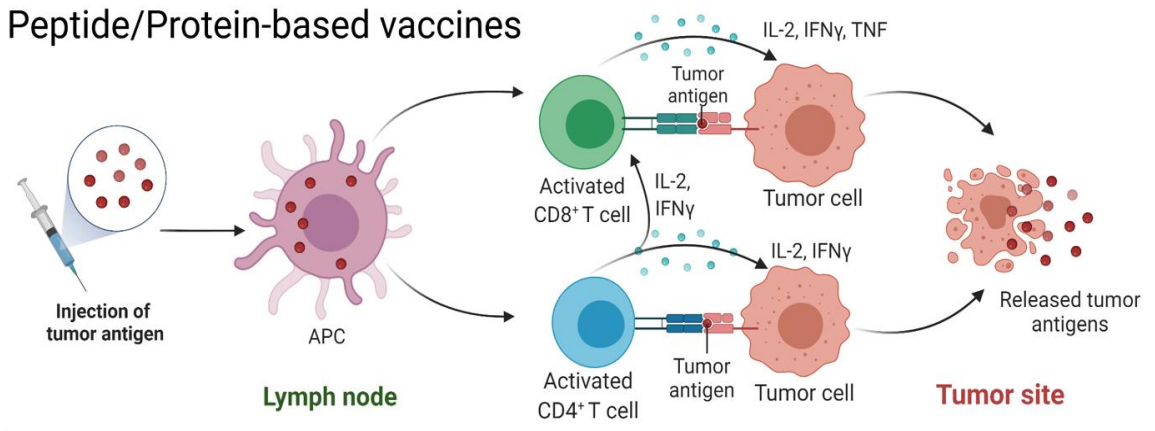
Personalised bispecific antibodies

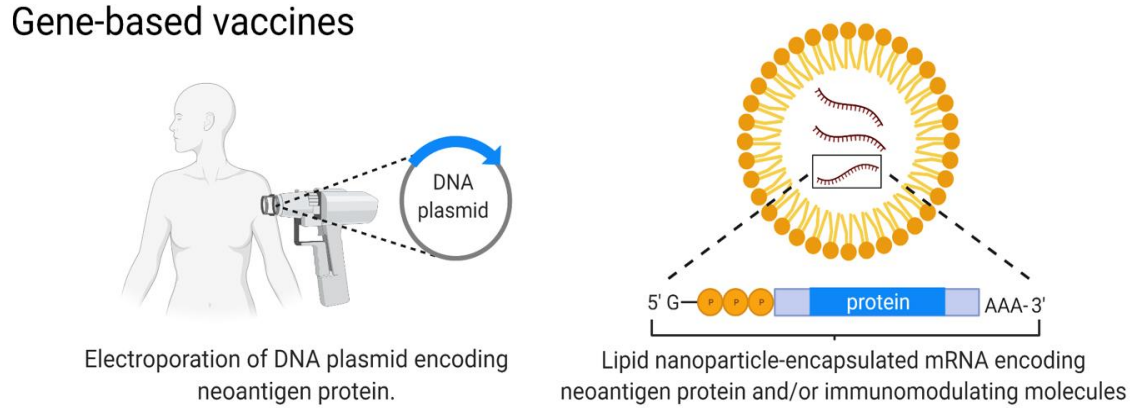
PROTAC e.g TP53mu

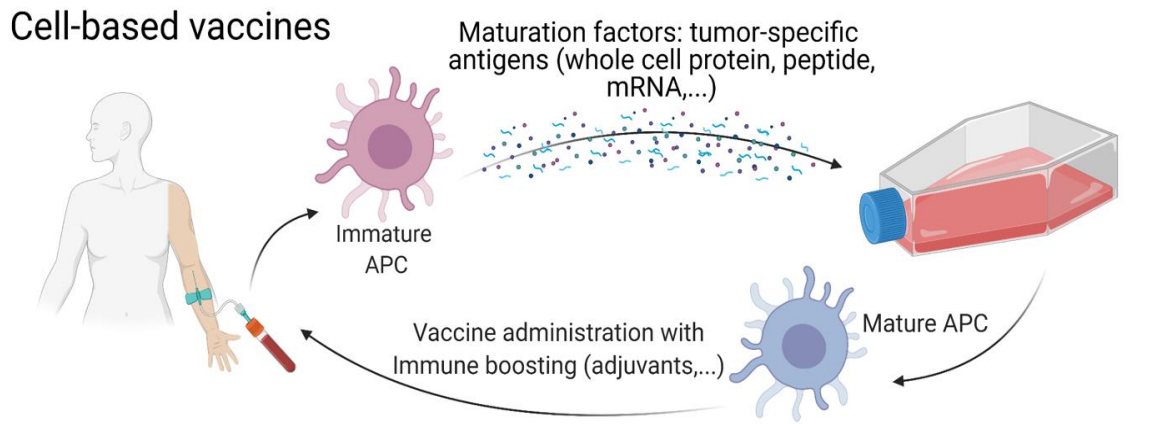
Immunotherapy in metastatic breast cancer

… and future perspectives







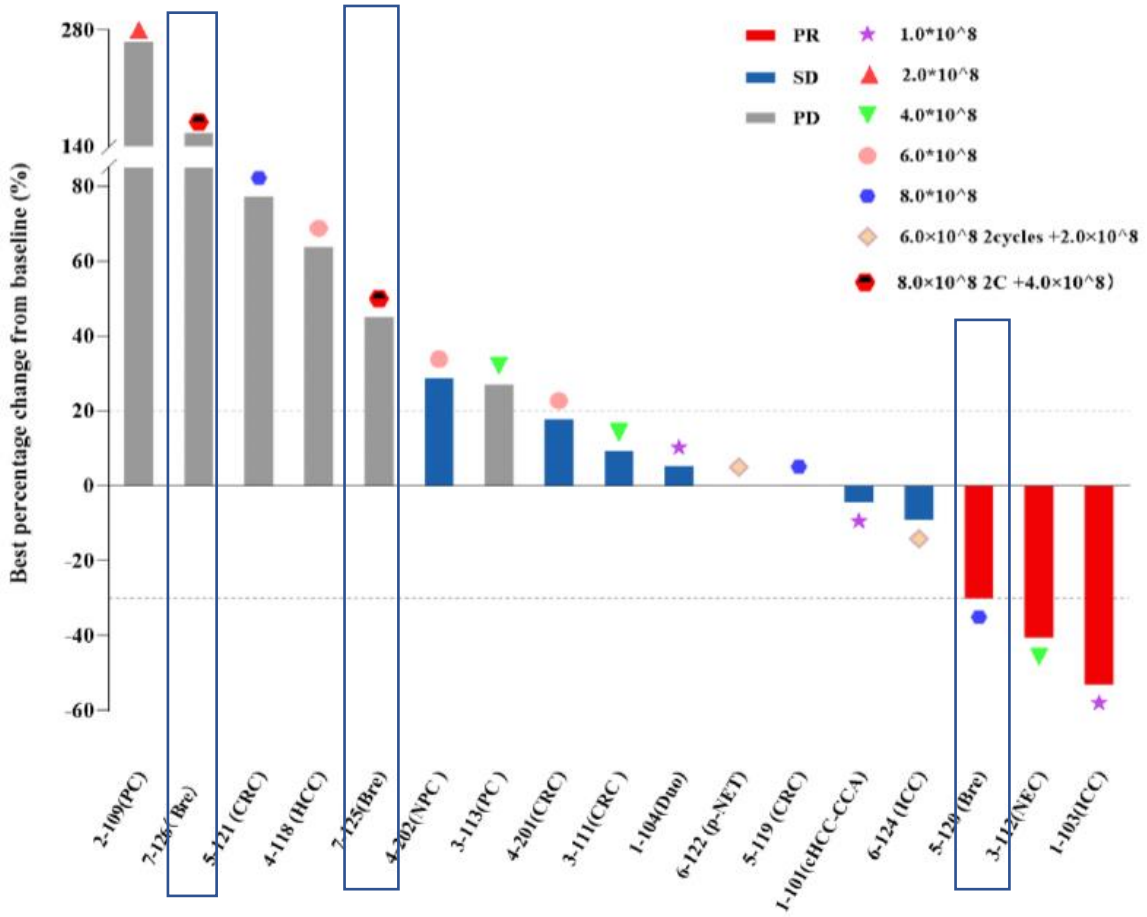


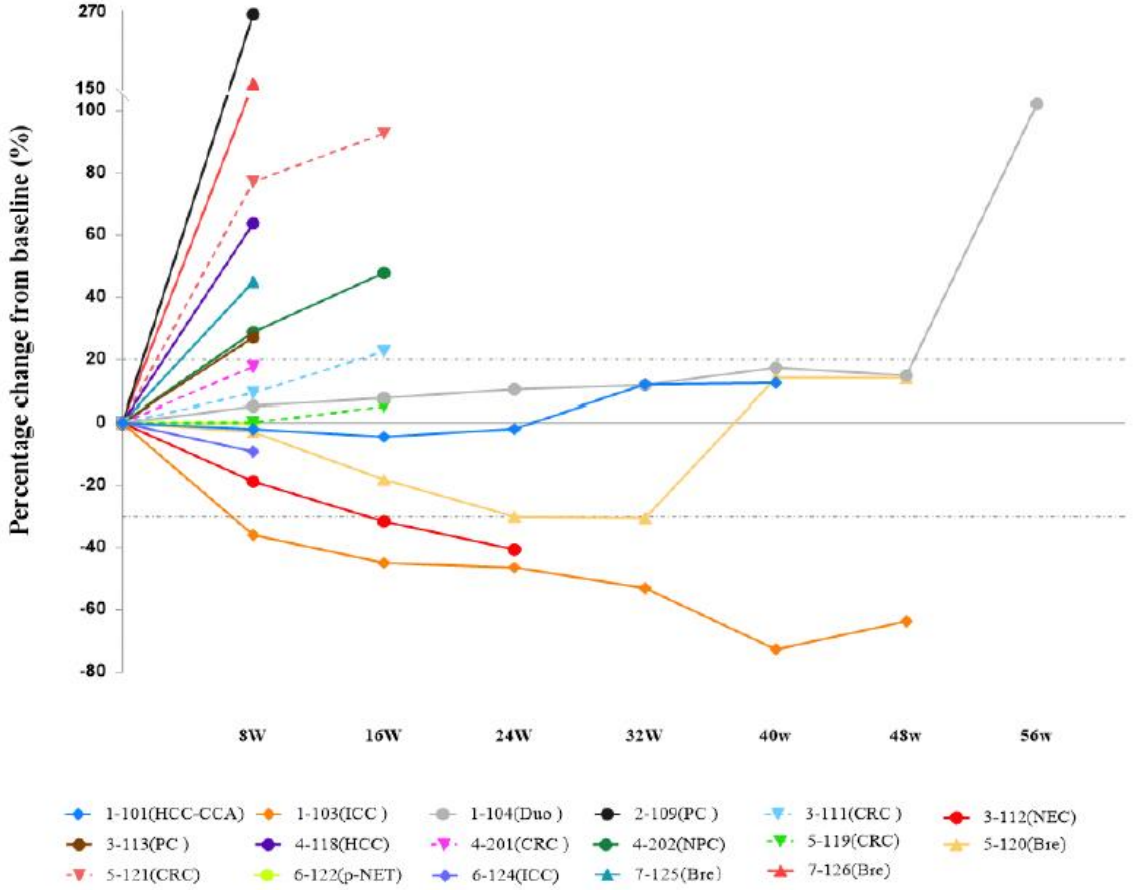
Corti, EJC 2022; Antonarelli, Ann Onc 2021

Giuseppe Curigliano, MD PhD

Promising Antitumor Efficacy of VG201-C101 Study

modified oncolytic HSV viral gBprotein





(N=17,Data cut-off: 2024-08-8)

Key points immunotherapy in mTNBC

- PD-L1 status: what, when, how?
- Future development:
  - Biomarkers beyond PD-L1: TILs, basal-like immune activated, immune phenotype, CD8+, CD274 gain/amplification
  - How to integrate redundant/overlapping biomarkers
  - Timing of chemotherapy, combinations with PARP inhibitors and novel ADCs
  - Early relapsers need more effective options

- Can we rechallenge immunotherapy in the first-line metastatic setting after (neo)adjuvant chemo-immunotherapy?
- Should patients with ER-low/HER2-negative disease be offered Immunotherapy?
- What is the optimal duration of chemotherapy in combination with immunotherapy in metastatic breast cancer?
- Should immunotherapy be continued until progression in metastatic breast cancer that is responding to therapy?

Thank you!

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