

2019 NEWS IN ONCOLOGY



Federica Miglietta

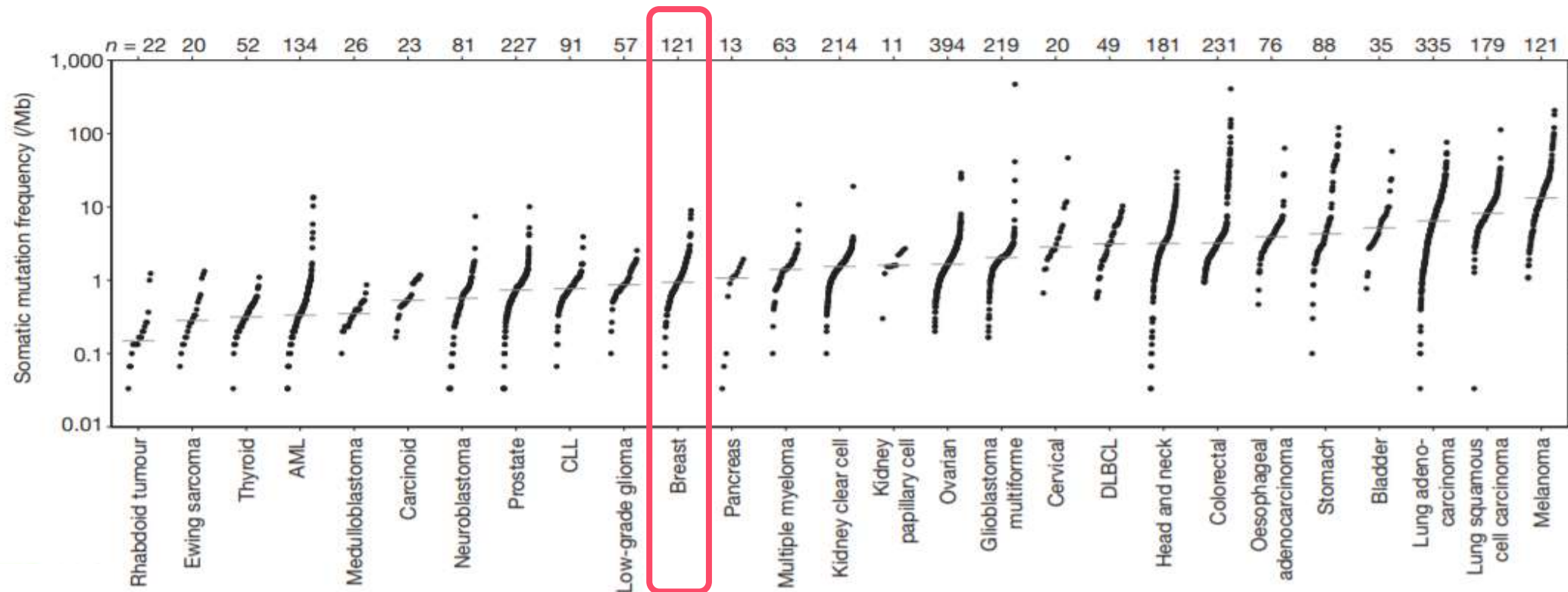
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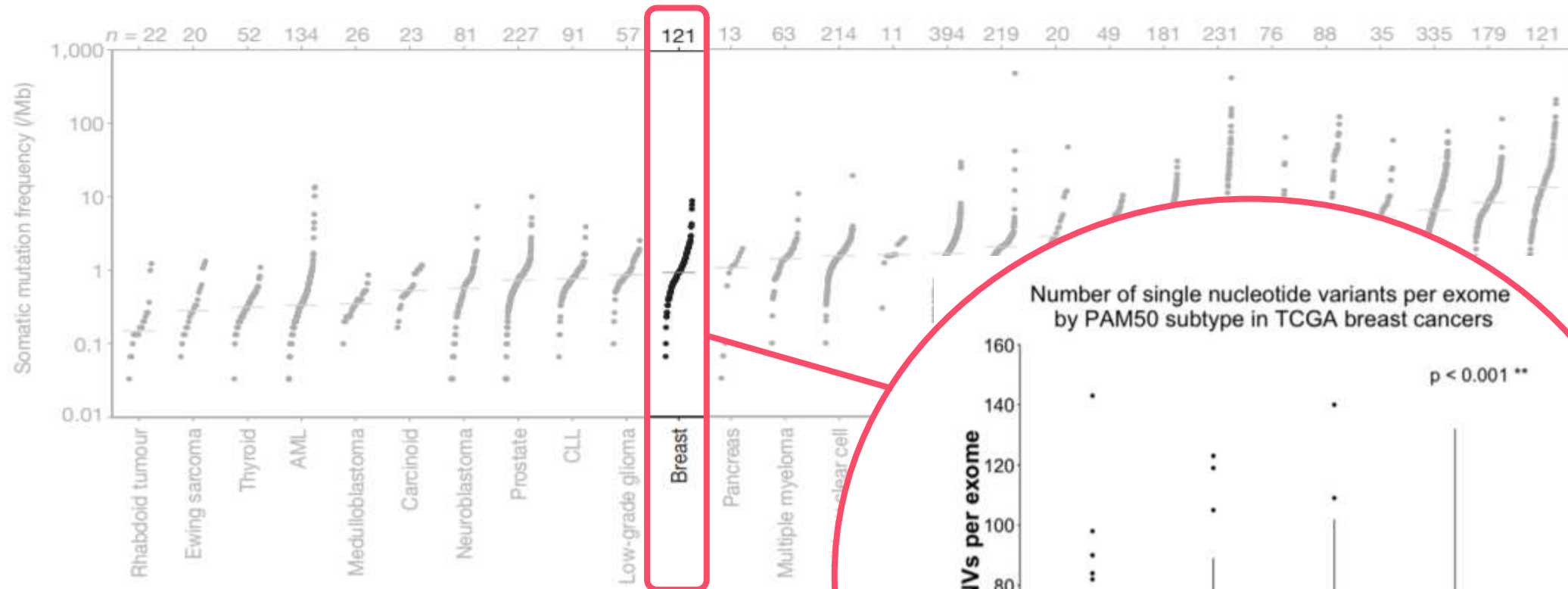
Agenda

- Rationale for immunotherapy in BC
- Immune-checkpoint inhibitors in monotherapy
- Combination strategies:
 - Chemotherapy
 - Targeted agents
- Open questions
 - Timing immunotherapy
 - Biomarkers
- Future perspectives

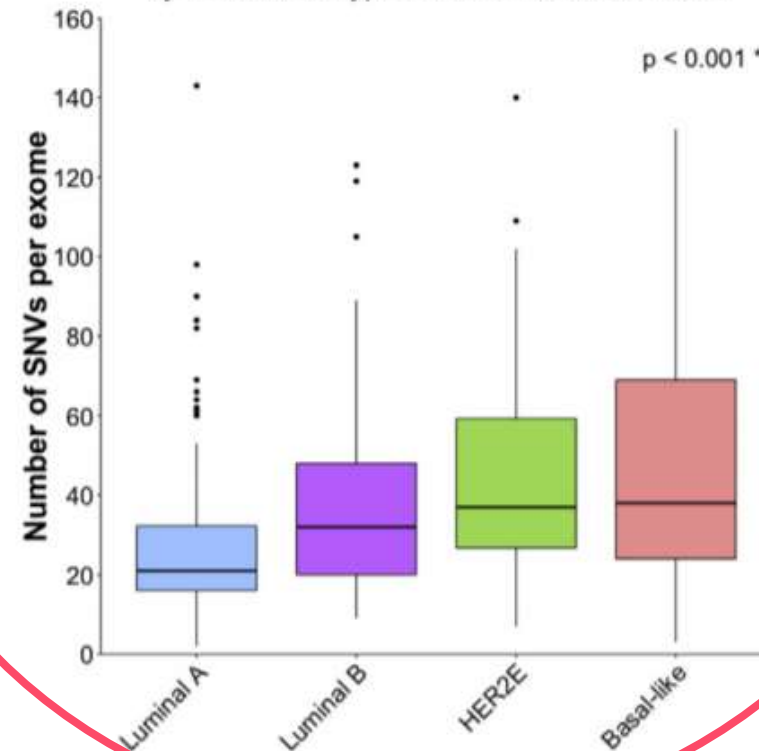
Breast Cancer (BC) immunogenicity



Mutational load



Number of single nucleotide variants per exome by PAM50 subtype in TCGA breast cancers



NEOANTIGENS

- **Quantity:** HER2+ and TN BC: show the greatest degree of immunogenicity
- **Quality:** more easily identified as non-self → more likely to induce antitumor immune response

Tumor-infiltrating lymphocytes (TILs)

Variation in incidence and magnitude of TILs according to BC subtypes

		Median %		
	N	None/ absent	Intermediate/ present	High (LPBC)
All	4161	16	89	11
TN	1640	15	80	20
HER2+	929	9	84	16
HR+	2410	20	94	6

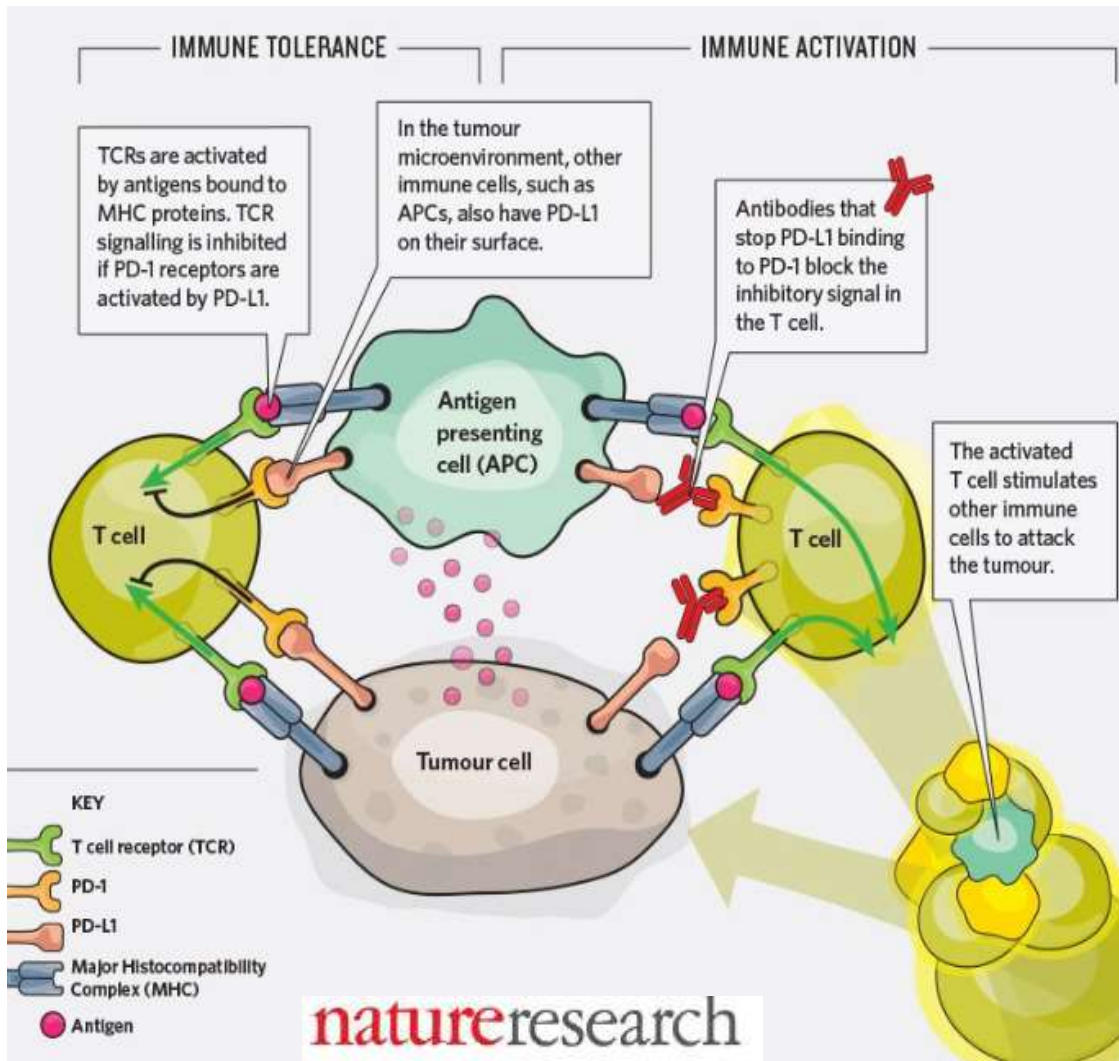
TILs a prognostic marker

- **TN**: robust linear relationship between increased TILs and improved survival
- **HER2+**: similar relationship, but caution in interpretation due to the confounding role of adjuvant trastuzumab
- **HR+HER2-**: no significant prognostic value

TILs as a predictive marker

- increased TILs associated with higher rates of **pCR** (most HER2+ and TN BC pts) after neoadjuvant therapy

PD-L1 expression



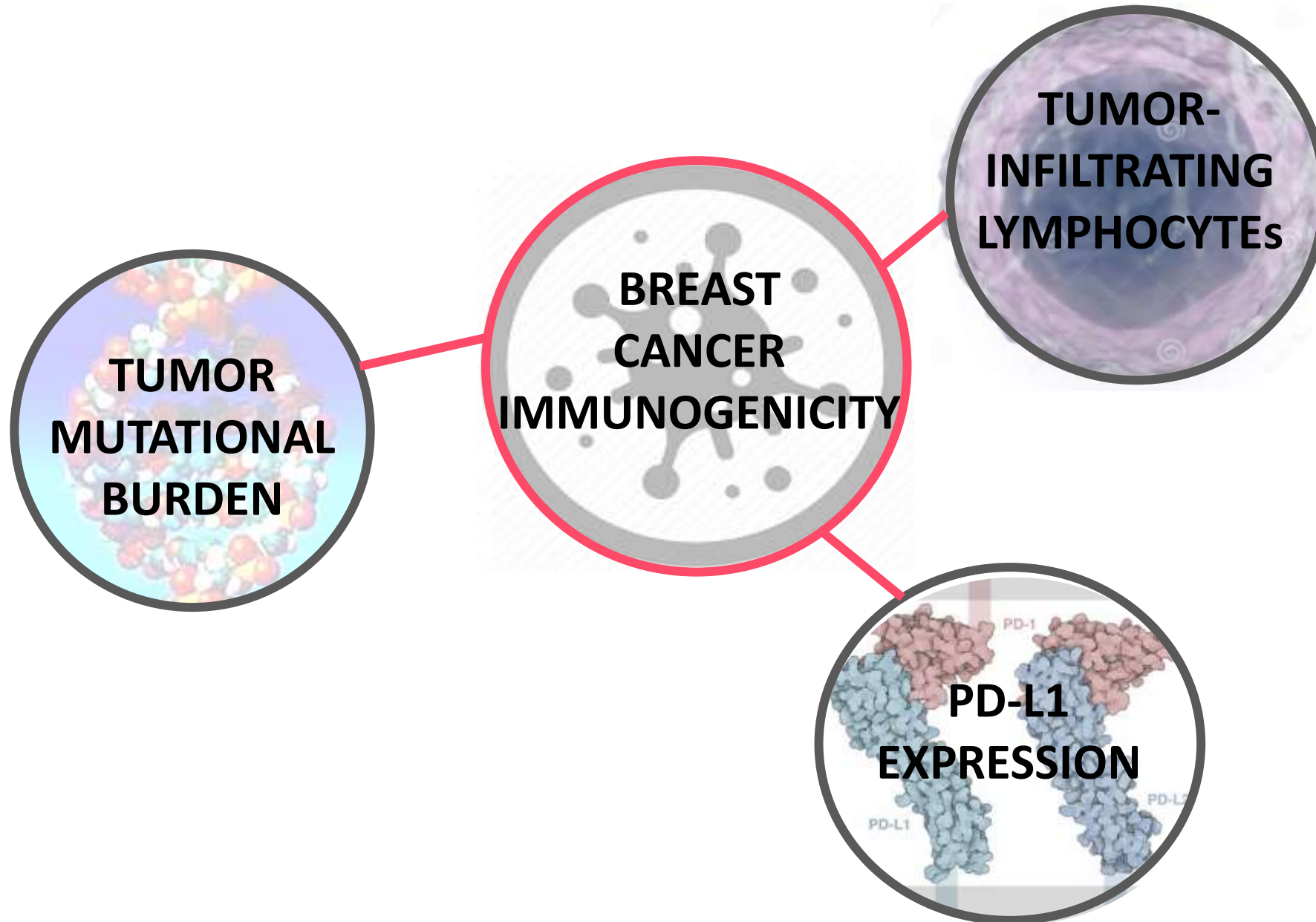
PD-L1 expression in BC

- 20-40% of all BCs
- Invasive disease > normal breast tissue/in situ carcinoma

PD-L1 according to BC subtype

- By IHC: TN > non-TN BC; in HER2+ controversial evidence, some data HER2+ > HER2-
- By intrinsic subtypes (PAM50): basal-like and HER2-enriched > Luminal

Rationale for immunotherapy in BC



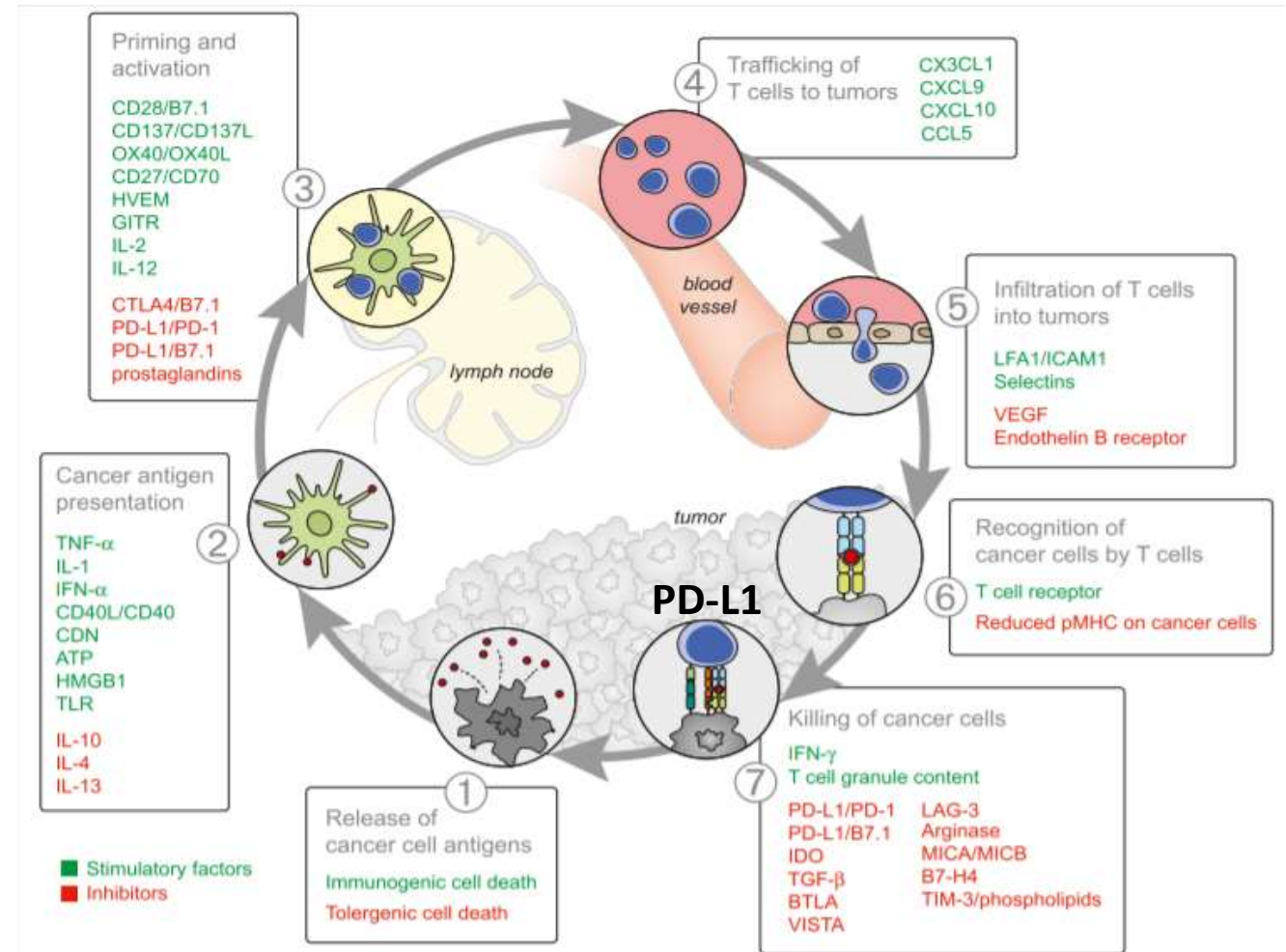
TRIPLE-NEGATIVE BC

Anti PD-L1/PD1 monotherapy: triple-negative BC

Key results from phase I/II trials

- Modest overall response rates (4.7 – 23.1%)
- Greater responses in 1° line (up to 24%)
- Responses in both PD-L1+ and PD-L1- patients
- Durable responses were observed

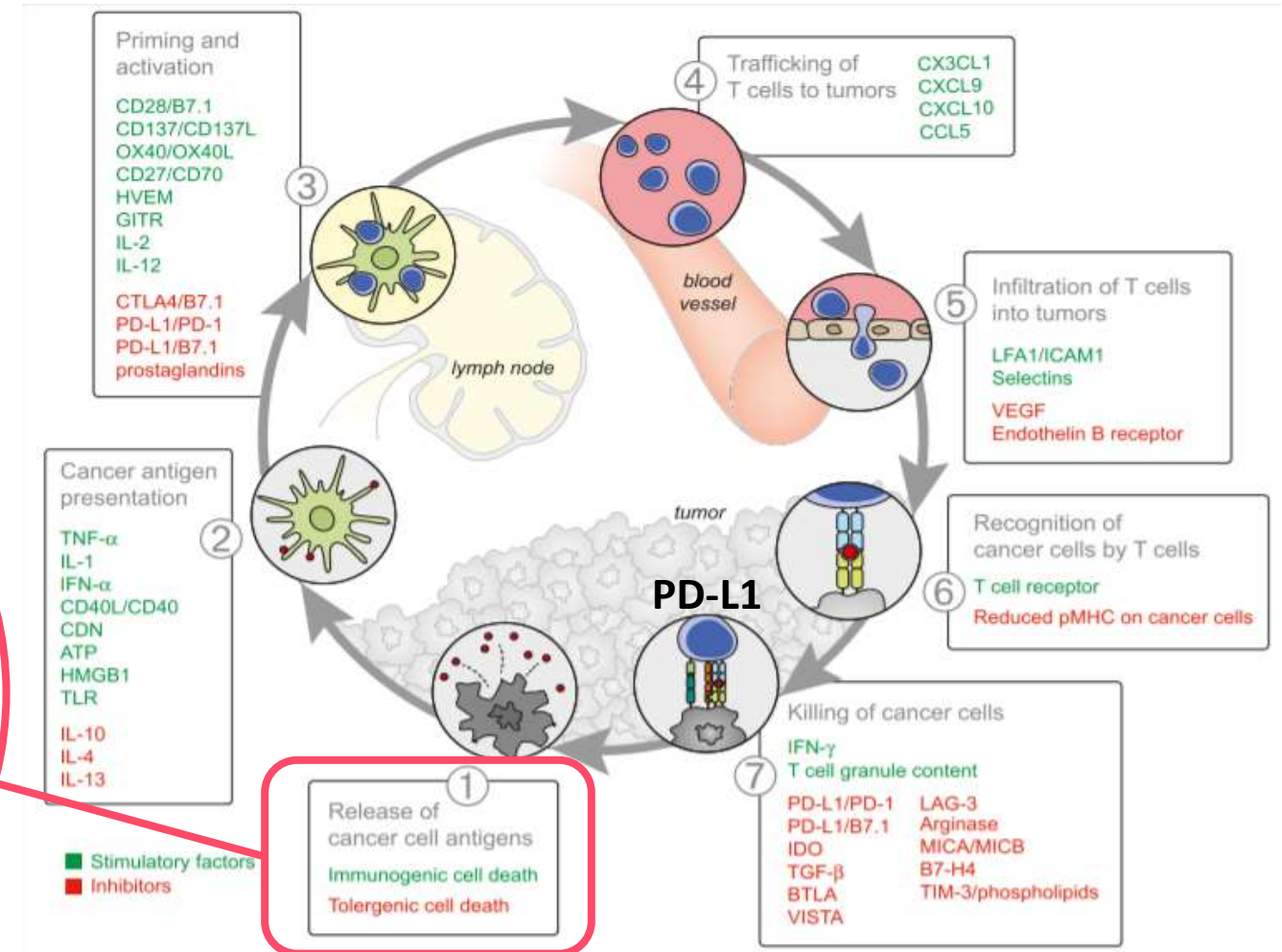
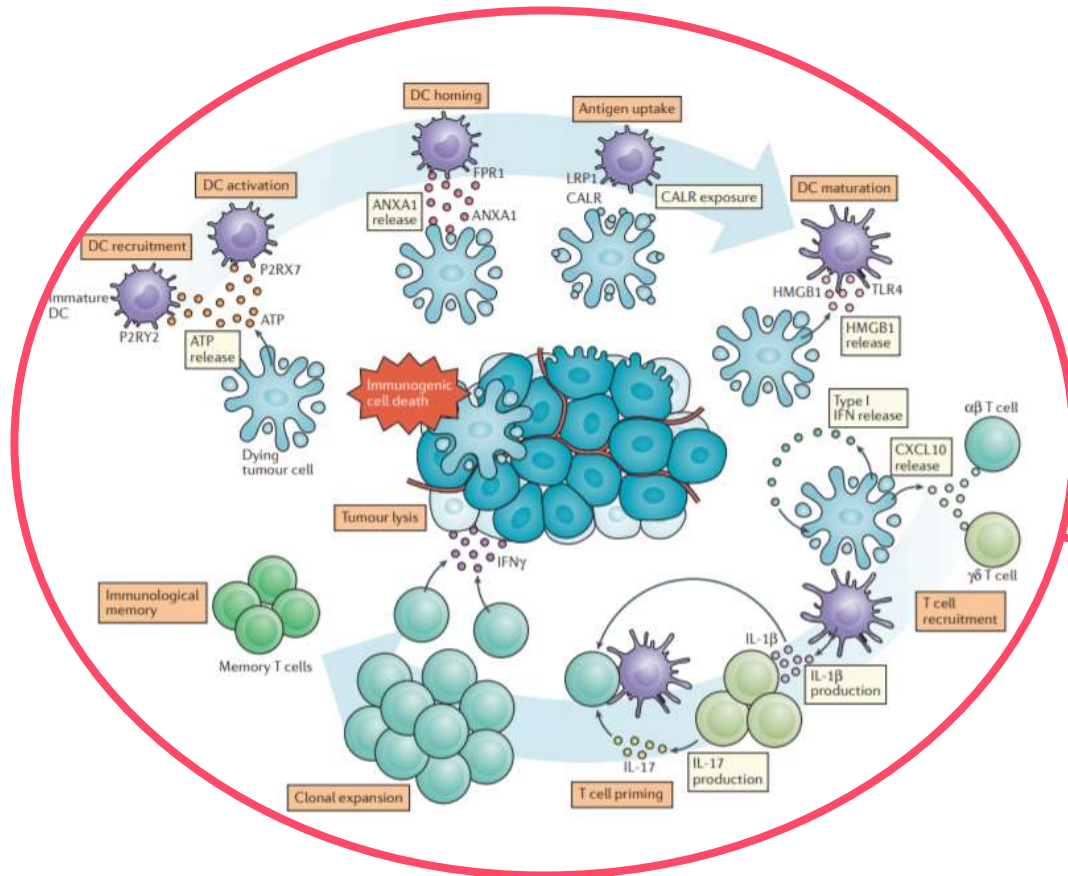
Enhancement of immunotherapy response



Combination with CHEMOTHERAPY

Chemotherapy induces IMMUNOGENIC CELL DEATH

- Anthracyclines
- Cyclophosphamide
- Microtubule-stabilizing agents



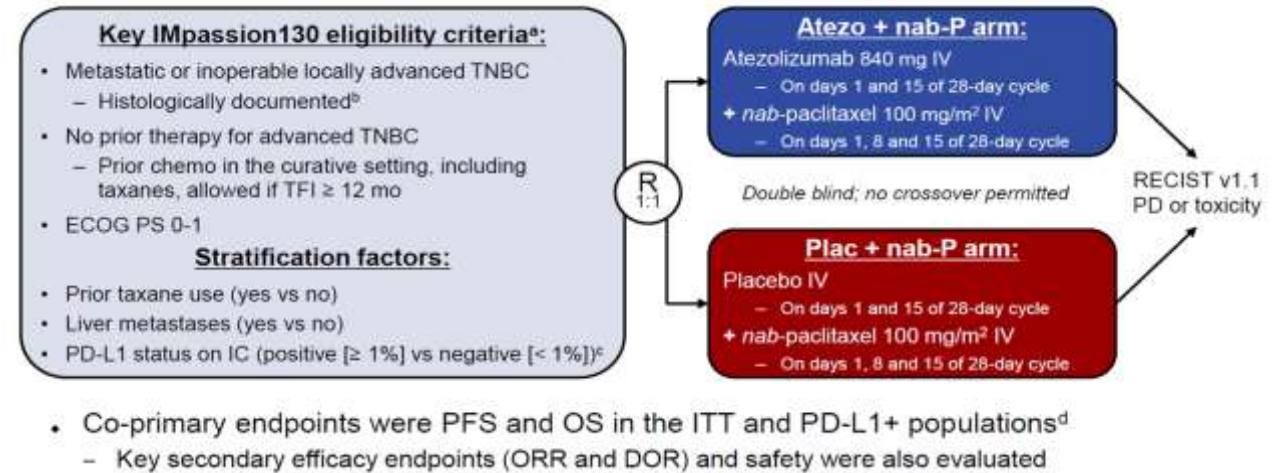
Combination with CHEMOTHERAPY: triple-negative BC

Early-phase trials of immune-checkpoint inhibitor + CT in MBC

Study (phase)	Treatment arms	Population	ORR	Survival (months)
Adams (Ib)	Atezolizumab + nab-paclitaxel (1st-3rd line)	PD-L1+ and PD-L1- (N=33)	39.4% First line: 53.8% Later lines: 30%	mPFS: 5.5 mOS: 14.7
Tolaney Enhance (Ib-II)	Pembrolizumab + eribulin mesylate 1st-3rd line)	PD-L1+ and PD-L1- (N=107)	26.4% First line: 29.2% Later lines: 22%	mPFS: 4.2 mOS: 17.7

Combination with CHEMOTHERAPY: triple-negative BC

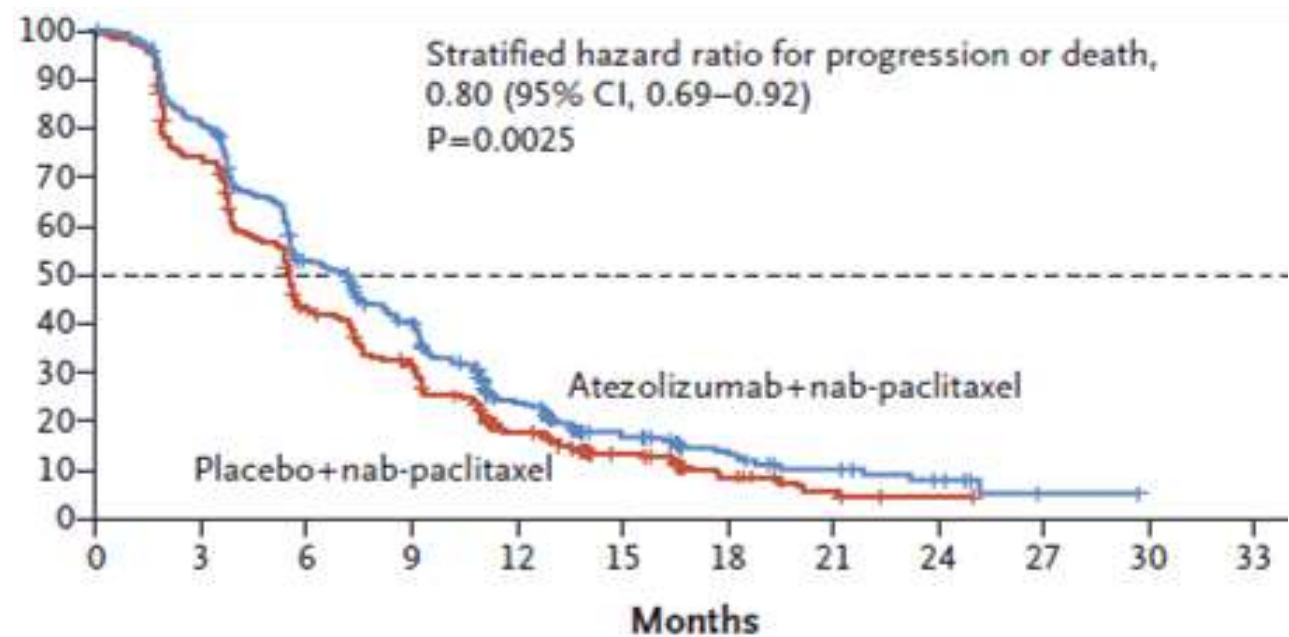
Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer



Combination with CHEMOTHERAPY: triple-negative BC

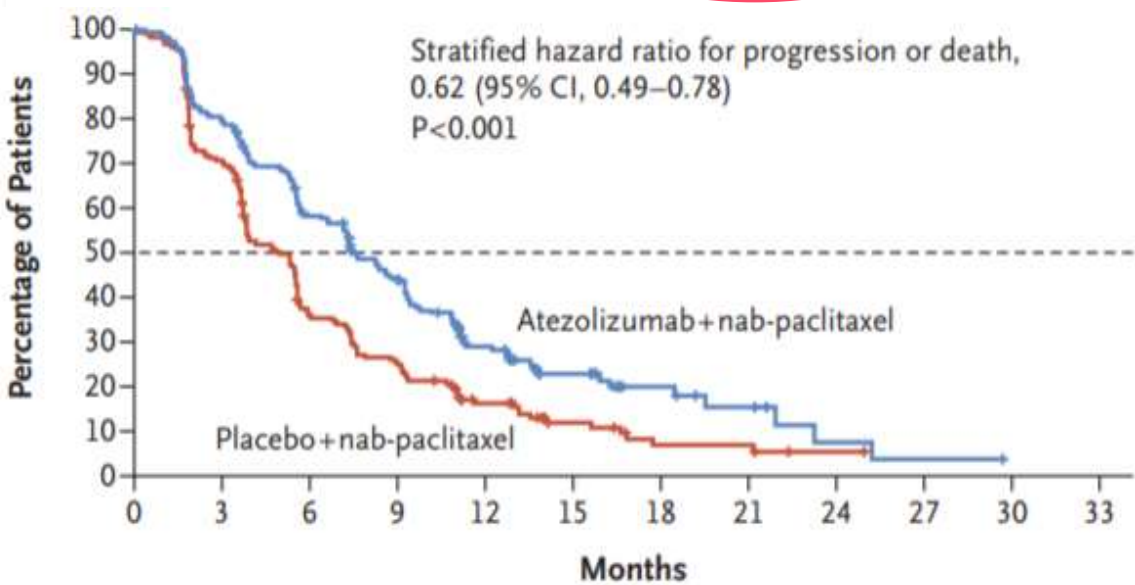
Atezolizumab and Nab-Paclitaxel
in Advanced Triple-Negative Breast Cancer

PFS ITT



ITT	Events/pts	mPFS, months (95%CI)	1yr PFS% (95%CI)
Atezo+Nab	358/451	7.2 (5.6-7.5)	23.7 (19.6-27.9)
Plac+Nab	378/451	5.5 (5.3-5.6)	17.7 (14.0-21.4)

PFS in PD-L1+



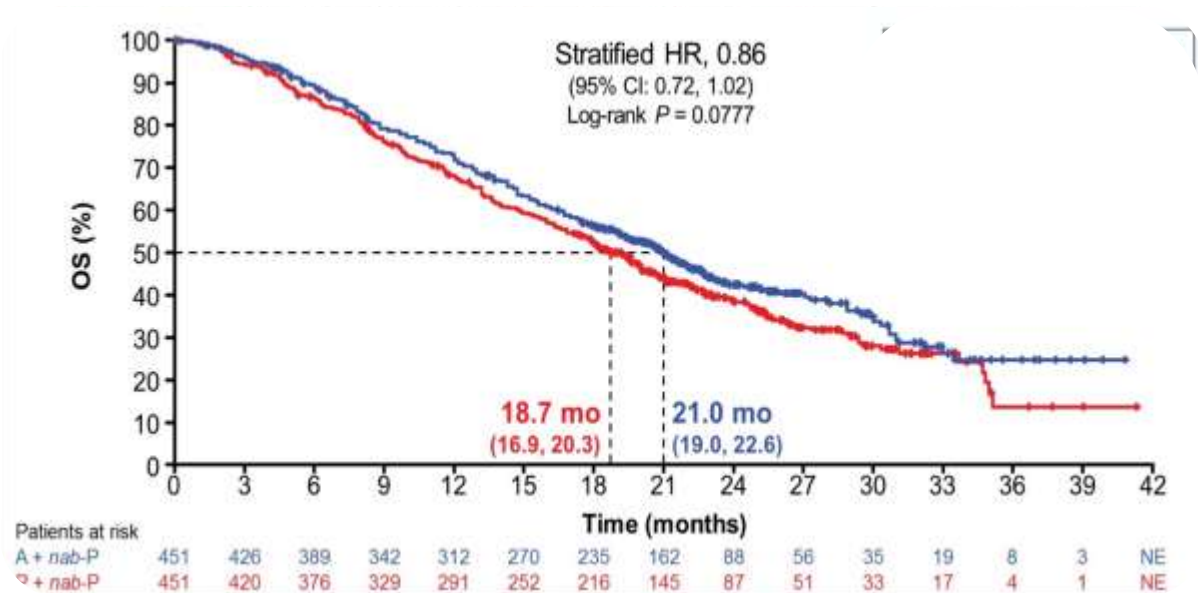
41% PD-L1+ (1% of
positively stained IC
over the total tumor area
– SP142)

PD-L1+	mPFS, months (95%CI)	1yr PFS% (95%CI)
Atezo+Nab	7.5 (6.7-9.2)	29.1%
Plac+Nab	5.0 (3.8-5.6)	16.4%

Combination with CHEMOTHERAPY: triple-negative BC

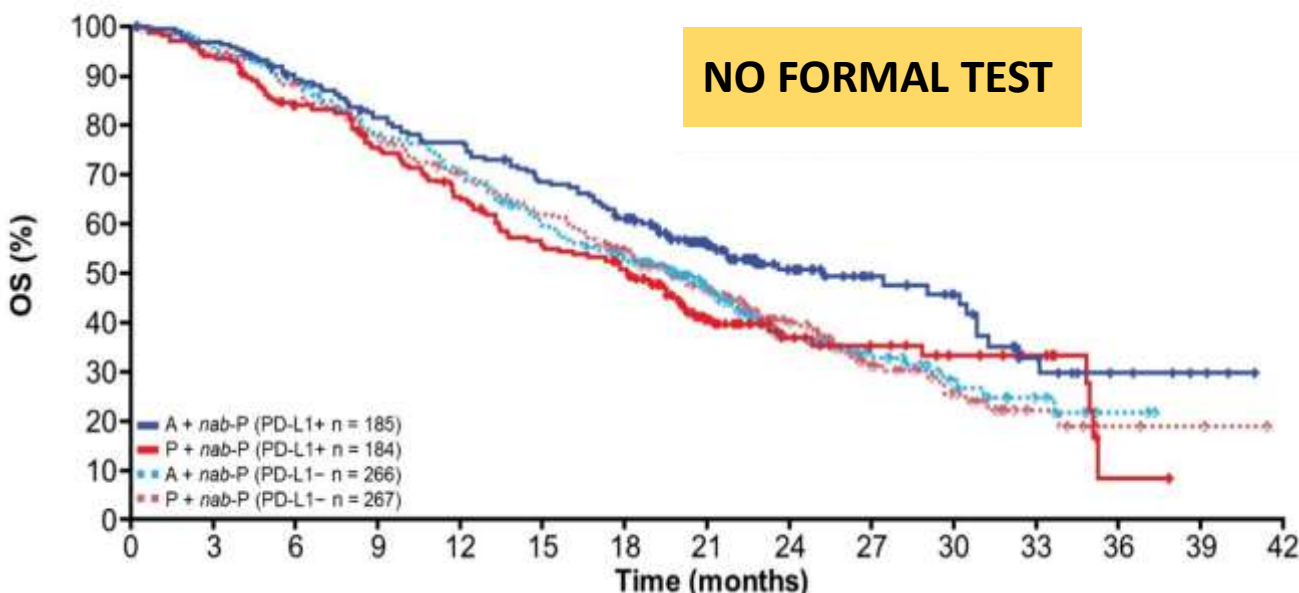
2° interim: 59% deaths in ITT population

OS ITT



ITT	mOS, months (95%CI)	2y OS (95%CI)
Atezo+Nab	18.7 (16.9-20.3)	42% (37-47)
Plac+Nab	21.0 (19.0-22.6)	39% (34-44)

OS by PD-L1 status



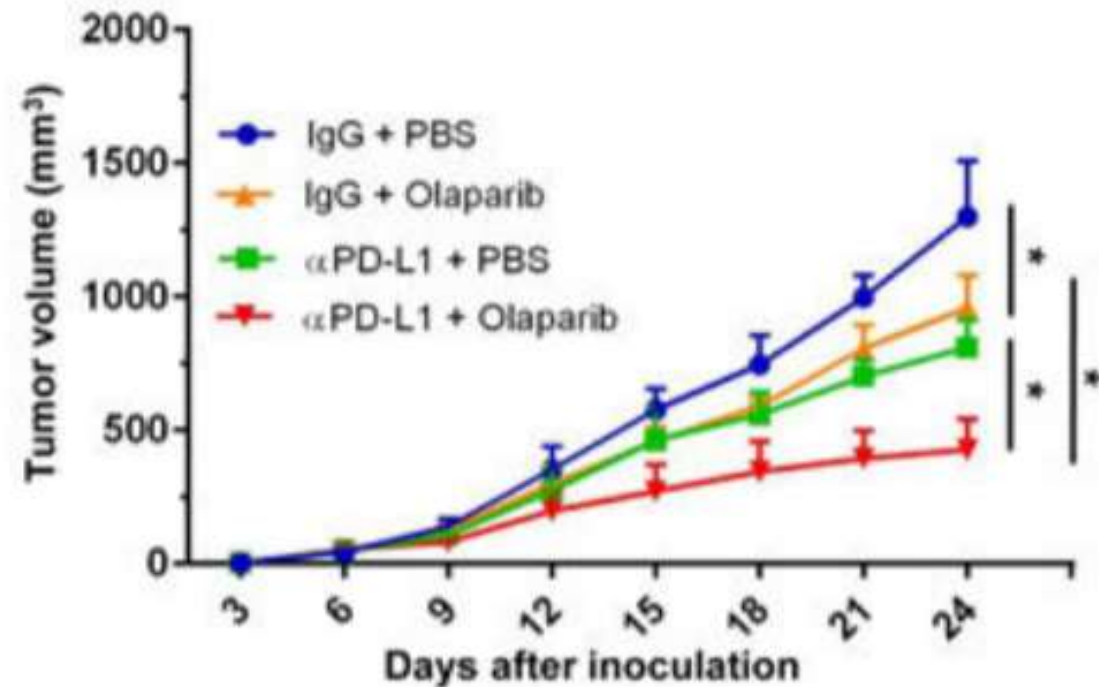
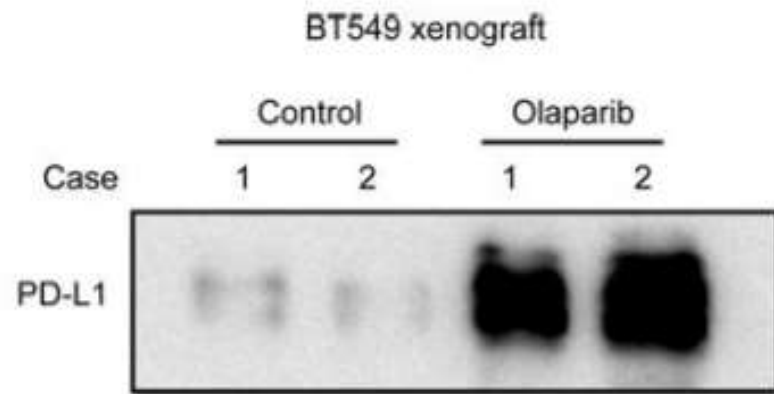
PD-L1+	mOS, months (95%CI)	HR (95%CI)
Atezo+Nab	25.0 (6.7-9.2)	0.71 (0.54-0.93)
Plac+Nab	18.0 (3.8-5.6)	

Combination with CHEMOTHERAPY: triple-negative BC

- Impassion130 trial in the first phase III trial reporting a benefit from immunotherapy for TN MBC
- Advantage in OS superior than in PFS
- Accelerated FDA/approval in US on March 8, 2019
 - FDA also approved the VENTANA PD-L1 (SP142) assay as a companion diagnostic device for selecting TNBC patients for atezolizumab

Combination with TARGETED-therapy: PARP-inhibitors

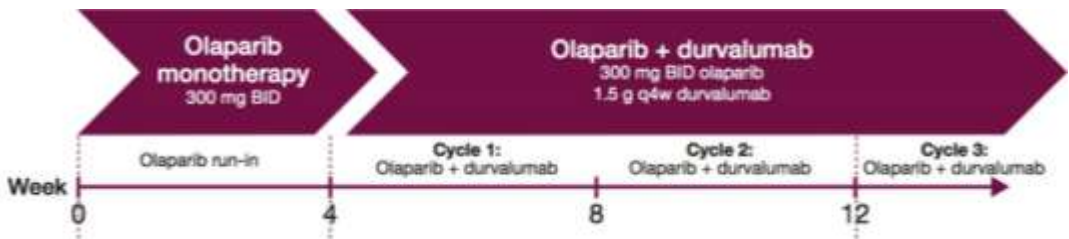
Rationale for combining PARP-inhibitors and immune-checkpoint inhibitors



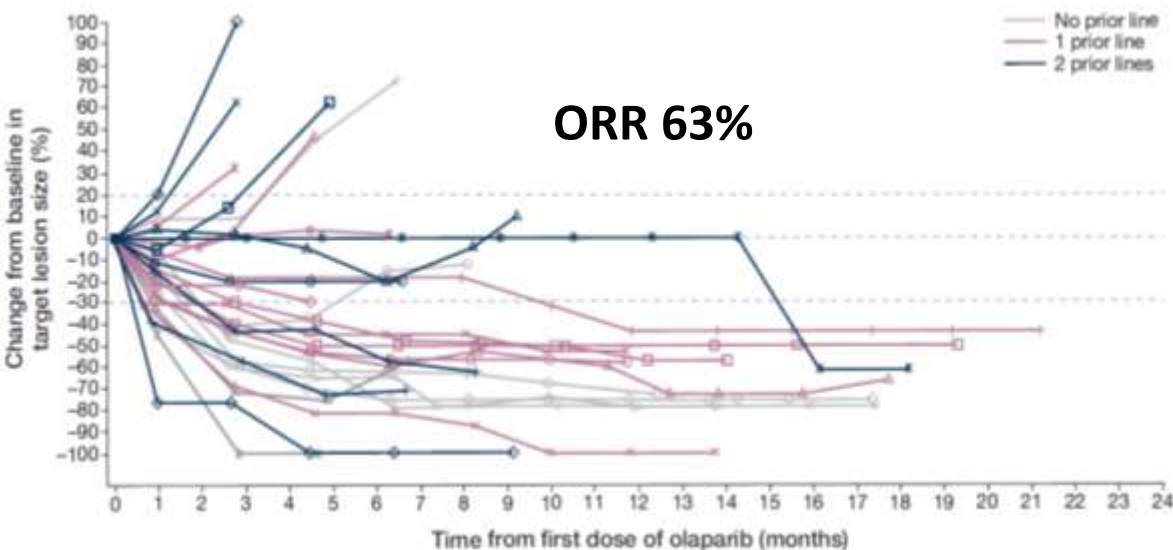
PARPi attenuated anticancer immunity via upregulation of PD-L1, and blockade of PD-L1 re-sensitized PARPi-treated cancer cells to T cell killing

Combination with TARGETED-therapy: PARP-inhibitors

MEDIOLA phase II basket trial (HER2- MBC N=30)



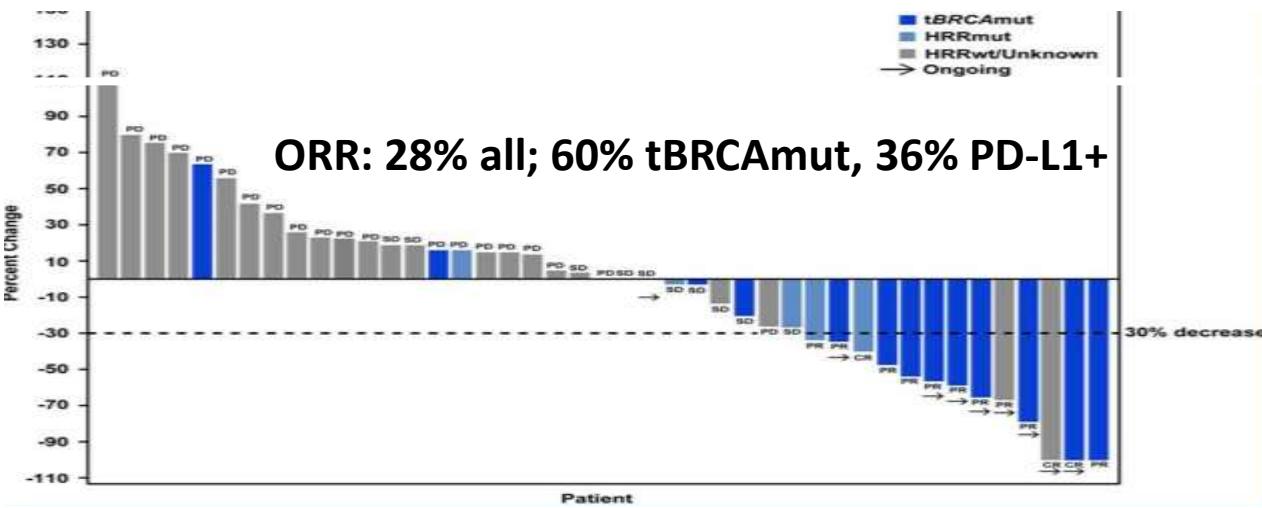
30% 1st line
43% prior platinum
43% HR+, 57% TN
50% BRCA1



TOPACIO phase I/II trial (TN MBC N=46)

Niraparib + Pembrolizumab

35% 1st line
38% prior platinum



HORMONE-RECEPTOR+ BC

Combination with TARGETED-therapy: CDK 4/6 inhibitors

Immune system in HR+ BC

	TNBC	HER2+	HR+/HER2-
Mechanisms of tumor-immune cells interaction	Neoantigens/Neopeptides		
	RAS/MAPk activation as immune escape mechanism [97]	Oncogene addiction	Estrogen-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 (estrogen-dependent); TGFβ induction AIs: Foxp3+ depletion*

CDK4/6 INHIBITOR-mediated enhancement of anti-tumor immunity

- Activation of tumor cell expression of endogenous retroviral elements
- ↓
- Increase in intracellular levels of double-strand RNA
- ↓
- stimulation of IFN type III production
- ↓
- Enhancement of tumor antigen presentation
- Suppression of regulatory T cell proliferation

Combination with TARGETED-therapy: : CDK 4/6 inhibitors

JPCE phase Ib trial (HR+HER2- MBC N=28)

Abemaciclib + Pembrolizumab

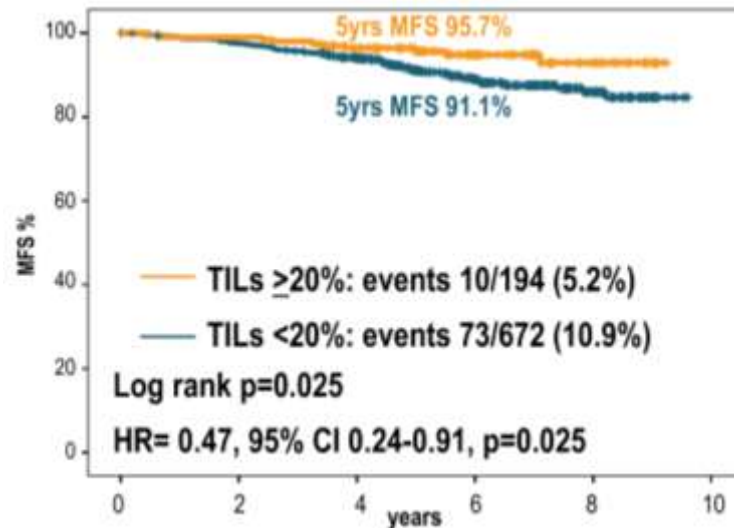
- Generally manageable safety profile
 - single-agent toxicity profiles not exacerbated
- ORR: 14.3%
- Rate of stable disease at 16 weeks: 60%

HER2+ BC

Combination with TARGETED-therapy: anti-HER2 therapy

TILs are prognostic for HER2+ BC treated with adjuvant CT and anti-HER2

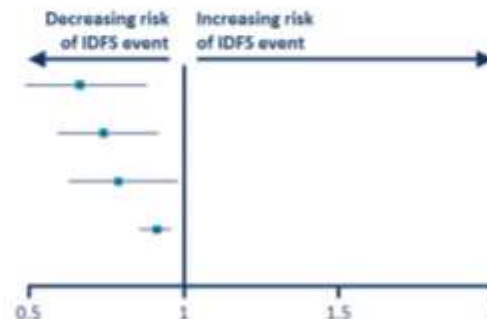
ShortHER trial



Aphinity trial

Prognostic analysis (arms pooled)

Biomarker	Patients, n	HR (95% CI)	p-value
TILs >75% percentile	4313	0.66 (0.49, 0.88)	0.005
TILs >50% percentile	4313	0.74 (0.59, 0.92)	0.006
TILs >25% percentile	4313	0.78 (0.63, 0.98)	0.03
TILs continuous	4313	0.91 (0.86, 0.96)	0.001



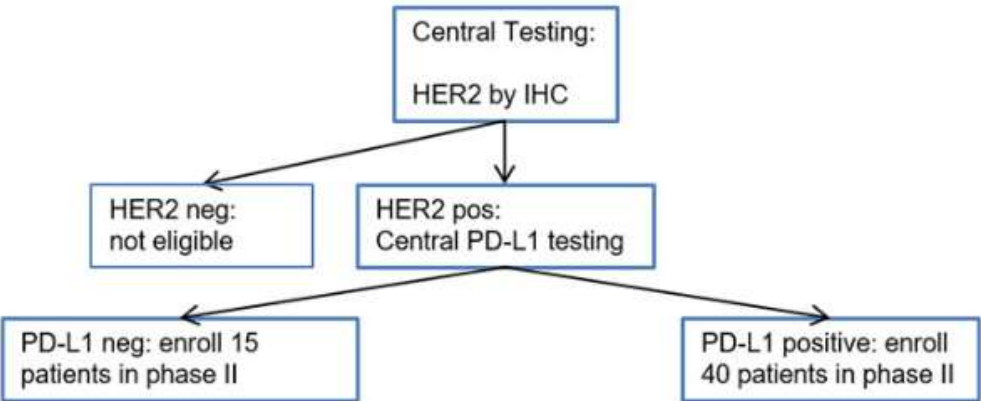
TRASTUZUMAB-mediated enhancement of anti-tumor immunity

- antibody-dependent cell-mediated cytotoxicity: ADCC
↓
promotion of antigen cross-presentation
↓
stimulation of antiHER2 CD8+ T cells
- Increase in anti-HER2 CD4+ T-cells
- Increase in anti-HER2 antibody responses

Combination with TARGETED-therapy : anti-HER2 therapy

Pembrolizumab plus trastuzumab in trastuzumab-resistant, advanced, HER2-positive breast cancer (PANACEA):
a single-arm, multicentre, phase 1b-2 trial

Screening: unresectable locoregional or metastatic breast cancer overexpressing HER2
→ Submit **an FFPE block from** core biopsy for central testing

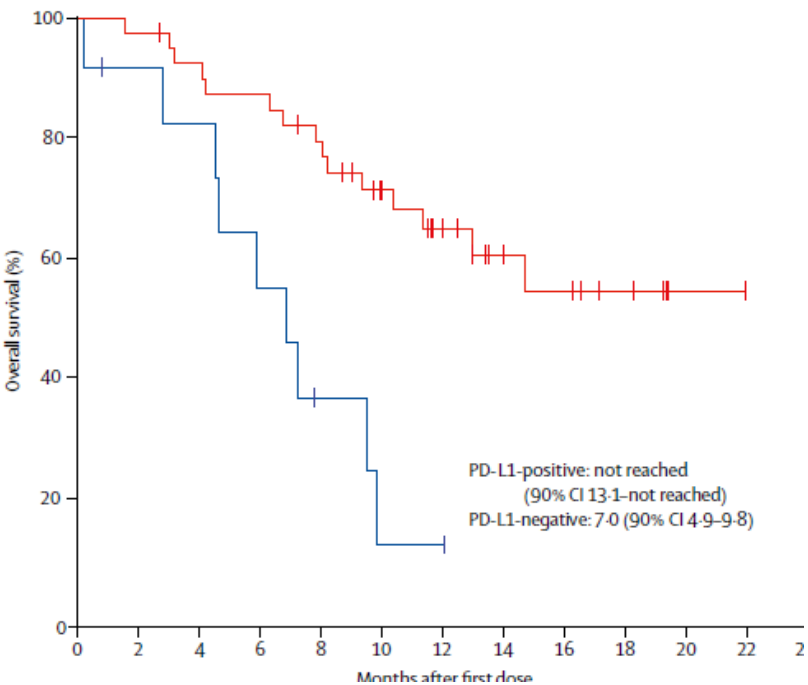


Phase 1b: dose finding for MK-3475 in 3+3 design — Phase II 200mg

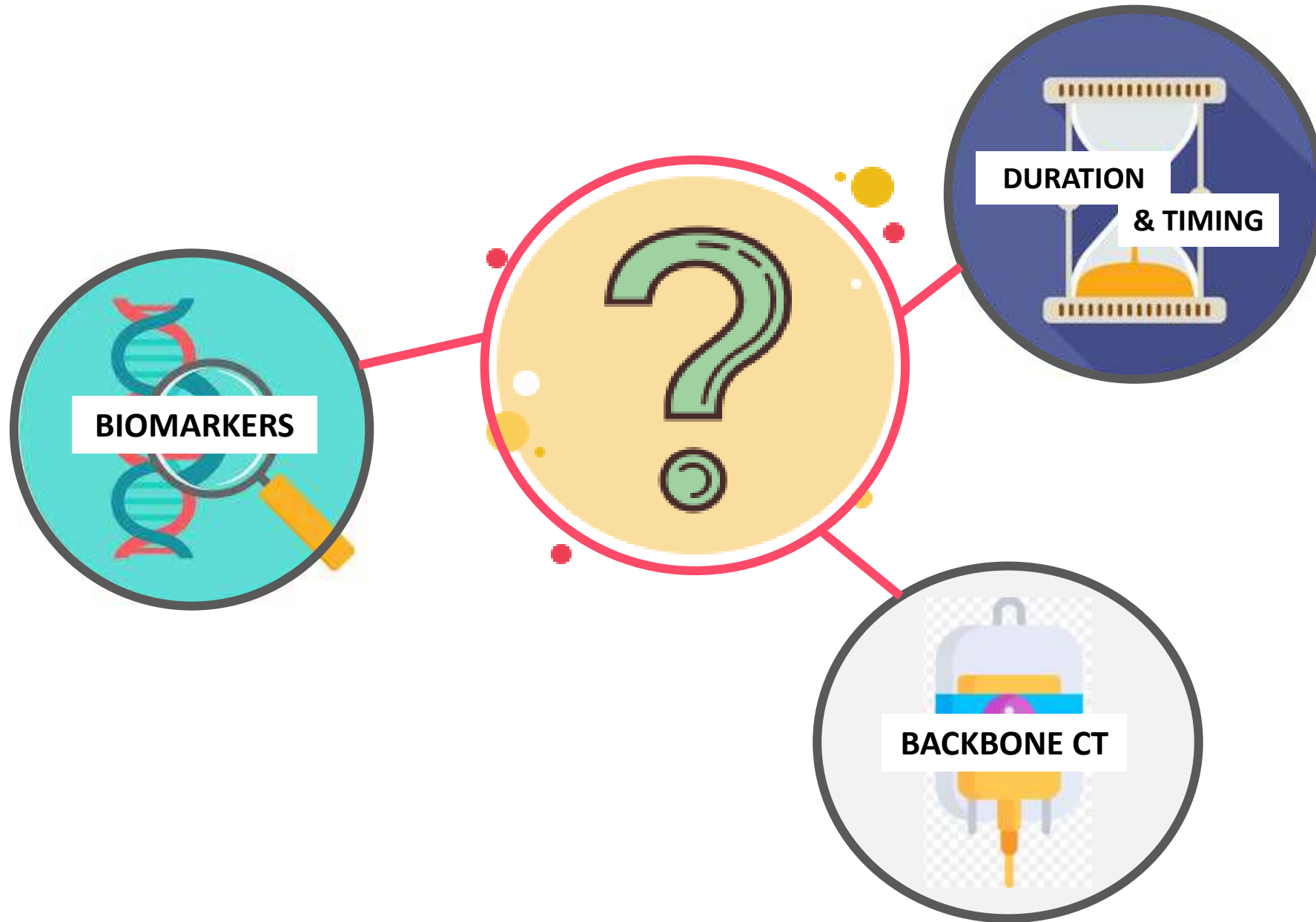
Treatment in 3 week cycles:	1	2	3	4	5 etc..... PD
T : trastuzumab 6mg/kg	T	T	T	T	T
M : MK-3475 200mg	M	M	M	M	M

Phase 2 → N=52

PD-L1 status	ORR
PD-L1+	15.2%
PD-L1-	0%



Open questions

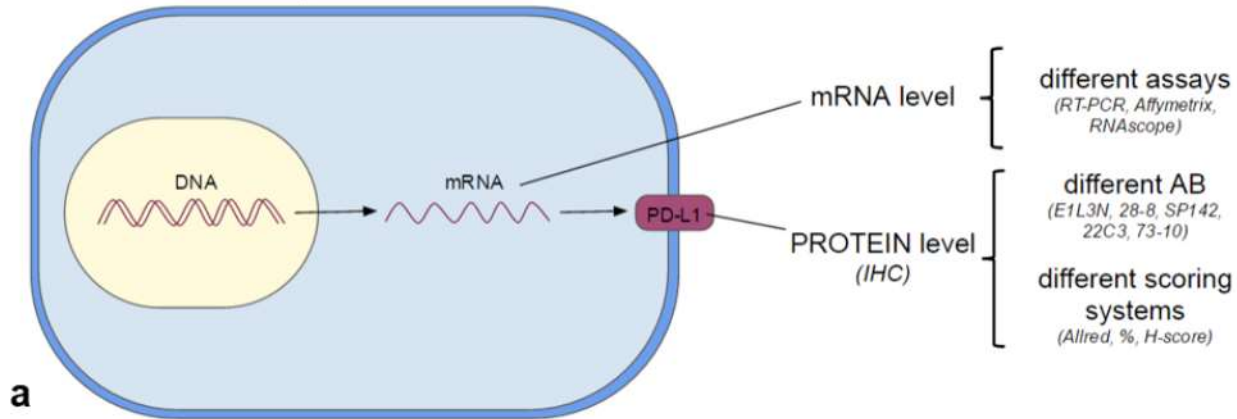


Biomarkers: PD-L1				
Study	Population	Treatment	PD-L1	Main finding
Nanda 2016 Keynote-012 (phase Ib)	111 (TN MBC) PDL1 positive	Pembrolizumab (ORR)	protein (prototype IHC assay: clone 22C3)	Increased ORR with increasing expression of PD-L1
Schmid 2017 (expansion cohort phase Ia study)	112 (TN MBC) initially limited to PDL1 positive, then opened also to PDL1 negative	Atezolizumab (ORR)	protein (IHC: clone SP142)	ORR for PDL1 2/3 vs PDL1 0/1 17% vs 8%
Dirix 2017 Javelin (expansion cohort phase I trial)	168 (MBC) regardless PDL1 status	Avelumab (ORR)	protein (IHC: clone 73-10)	TC PDL1: no efficacy trends in subgroups defined by PD-L1 expression in tumor cells at different thresholds
				IC PDL1: ORR for PD-L1+ vs PD-L1– 16.7% vs 1.6% in the overall group, and 22.2% vs 2.6% in TNBC
Loi 2017 Keynote 086 (phase II)	193 (TN MBC) cohort A: regardless PDL1 status cohort B: PDL1 positive	Pembrolizumab (ORR)	protein (IHC: clone 22C3)	No efficacy trends according to PDL1 status
Tolaney 2017 Keynote 150-Enhance 1 (phase Ib/II)	106 (TN MBC) regardless PDL1 status	Pembrolizumab + eribulin (ORR)	protein (IHC: clone 22C3)	No association between response and PDL1 status
Loi 2018 Panacea (phase Ib/II)	58 (HER2+ MBC) phase Ib: PDL1 positive phase II: regardless PDL1 status	Pembrolizumab + Trastuzumab (ORR)	protein (IHC: clone 22C3)	ORR for PDL1+ vs PDL1-: 15.2% vs 0% 1y-OS for PDL1+ vs PDL1-: 65% vs 12%
Adams 2016; Pohlmann 2018 (phase Ib; 2-years update)	32 (TN MBC) regardless PDL1 status	Atezolizumab + nab-paclitaxel(ORR)	protein (IHC: clone SP142)	ORR for PDL1+ (PDL1 1/2/3) vs PDL1- (PDL1 0): 42% vs 33% Secondary endpoints: longer PFS and OS with higher PDL1
Schmid 2018 Impassion130 (phase III)	902 (mTNBC) regardless PDL1 status (PDL1 status was a stratification factor)	nab-paclitaxel + atezolizumab /placebo (PFS, OS)	protein (IHC: clone SP142)	PFS for PDL1+ in control vs experimental arm: 7.5 vs 5.0 months OS for PDL1+ in control vs experimental arm: 55 vs 15.5 months
Adapted from Miglietta The Oncologist 2019 – in press				

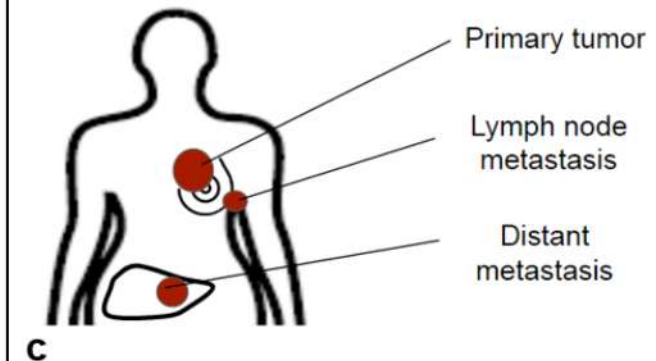
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Loi 2017 Keynote 086 (phase II)	<div> FDA approved the VENTANA PD-L1 (SP142) assay as a companion diagnostic device for selecting TNBC patients for atezolizumab </div>			in the overall group, and
Tolaney 2017 Keynote 150-Enhance 1 (phase Ib/II-interim analysis)				
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Biomarkers: PD-L1

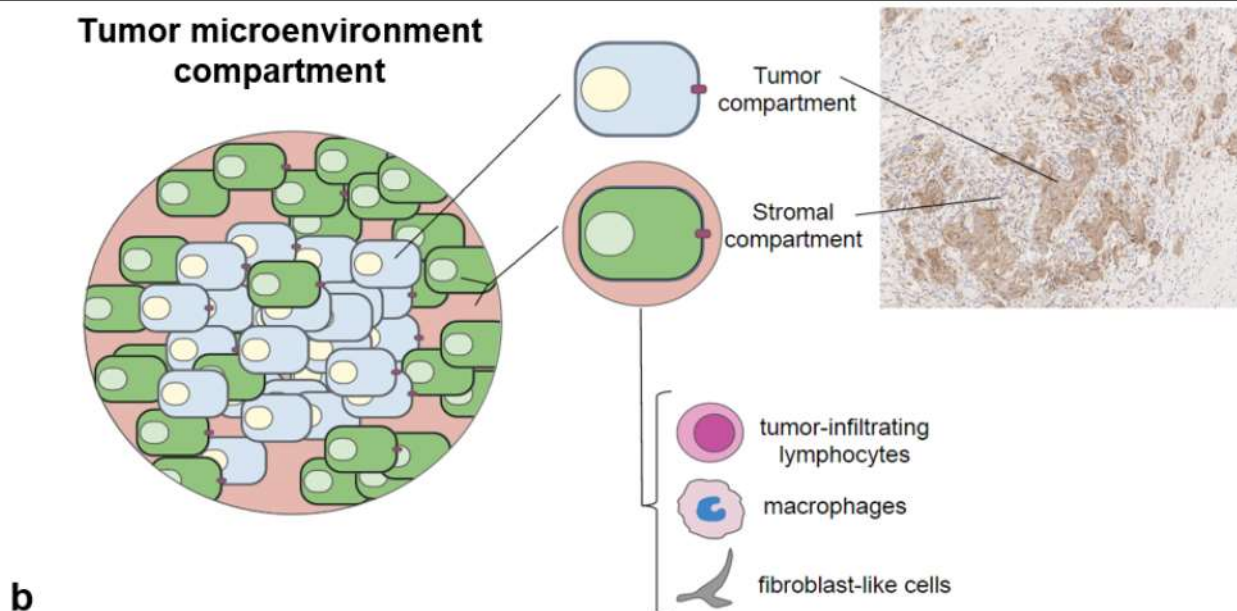
Level of the analysis



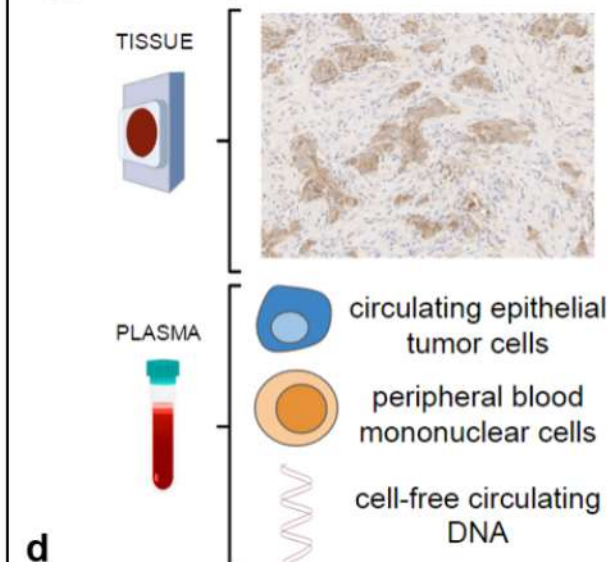
Temporal and spatial heterogeneity



Tumor microenvironment compartment

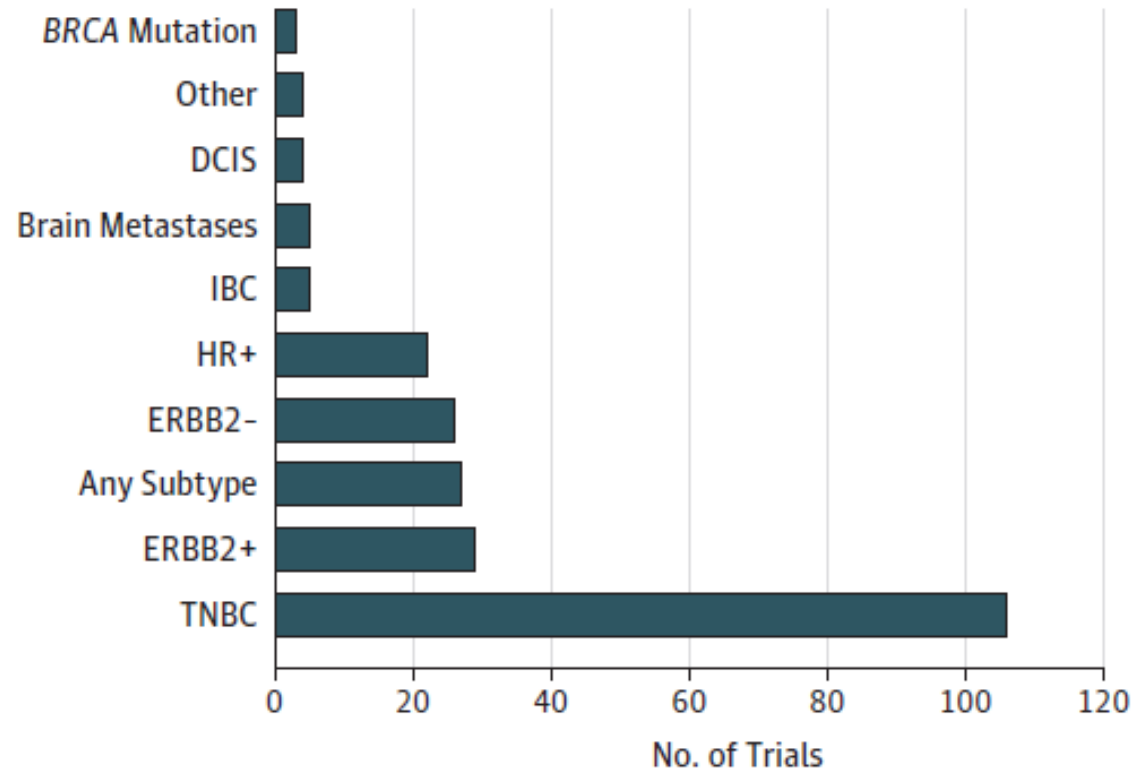


Type of sample

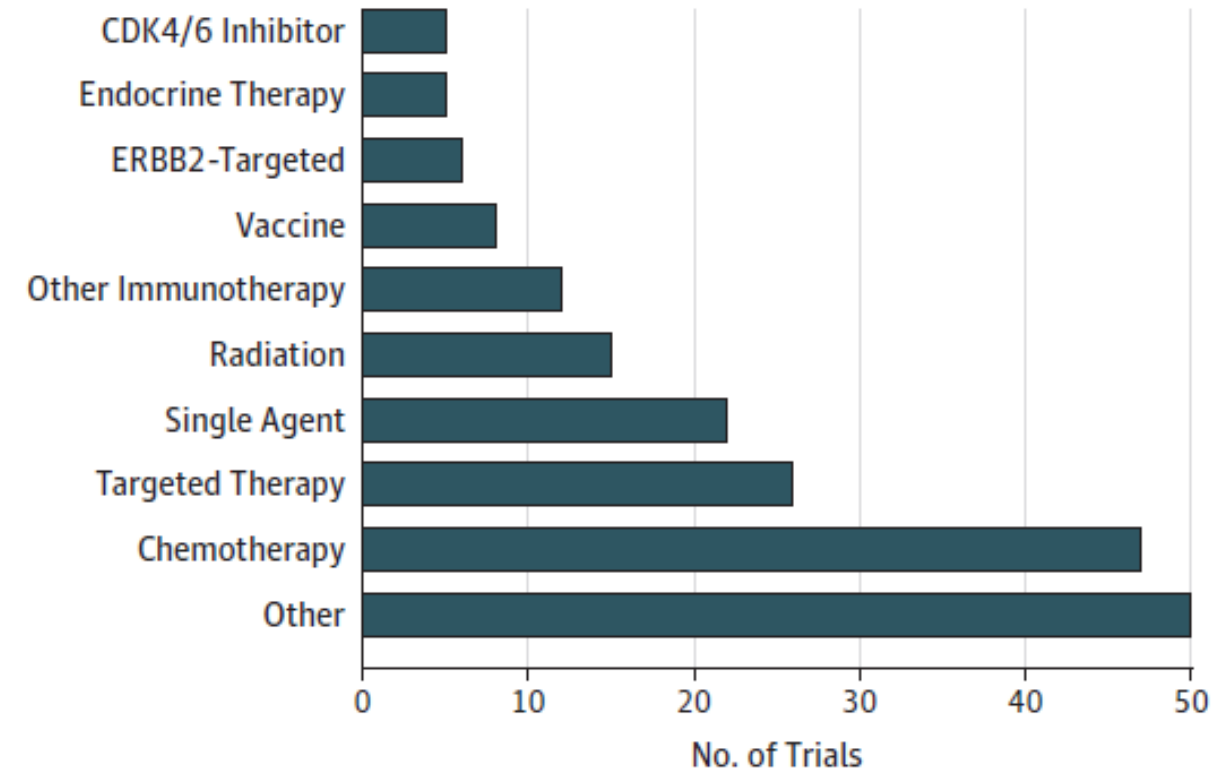


Future perspective: ongoing trials

A Subtypes of breast cancer studied



B Immune-checkpoint blockade studies



Future perspective

**HIGH RISK PRIMARY TNBC PTS
WHO COMPLETED
TREATMENT WITH CURATIVE
INTENT INCLUDING SURGERY,
CHEMOTHERAPY AND
RADIOTHERAPY (if indicated)**

Stratum A: Adjuvant
Stratum B: Post-neoadjuvant

Randomization 1:1 balanced for
adjuvant and post-neoadjuvant
patients.

Co-primary endpoints: 1. DFS in all-comers; 2. DFS in
PD-L1+ patients

Secondary endpoints: OS, Safety, Biomarkers

n=335 (for the 1st co-primary endpoint)

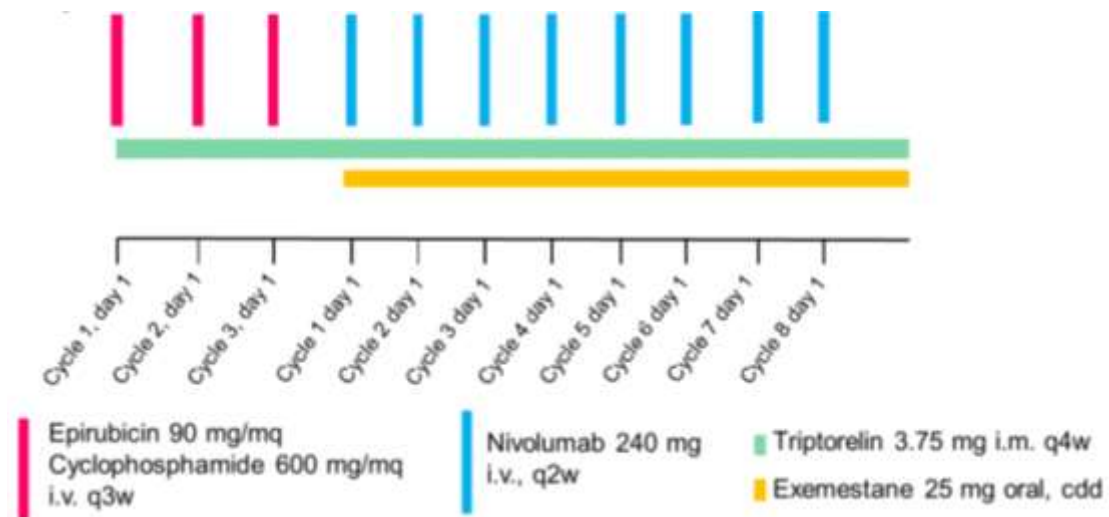


Sponsor: University of Padova
PI: P.Conte
Financial Support: BMS

Observation

**Avelumab
for 1 year**

**ENGAGING THE IMMUNE SYSTEM TO IMPROVE
THE EFFICACY OF
NEOADJUVANT CHEMO-ENDOCRINE THERAPY
FOR PREMENOPAUSAL LUMINAL B BREAST
CANCER PATIENTS.**



**-Luminal B (HR+/HER2-, G3
or Ki67 >20%)
-premenopausal
-stage II-IIIa BC patients**

Population: n=48
Primary endpoint: pCR
Secondary endpoints: OR, molecular
response (Ki67), PEPI score, conservative
surgery rate, safety, biomarkers

**FIRST SIMON'S STEP ACCOMPLISHED (AT
LEAST 3 pCR IN FIRST 18 ENROLLED PTS)**

Take home messages

- Rationale for immunotherapy in BC despite not traditionally considered immunogenic
- Combination with CHEMOTHERAPY
 - promising results in TN BC (Impassion130 phase III trial)
 - FDA-approval of atezolizumab+nab-paclitaxel
- Combination with TARGETED AGENTS
 - HER2- BC
 - HER2+ BC
 - HR+ BC
- Open questions
 - Timing immunotherapy
 - Biomarkers

Grazie!



Back up slides

Anti PD-L1/PD1 monotherapy: triple-negative BC

Study (phase)	Anti-PD1/PD-L1 agent	Population	ORR	Survival (months)
Nanda Keynote 012 (Ib)	Pembrolizumab	PD-L1+ (N=27)	18.5%	mPFS: 1.9 mOS: 11.2
Emens (Ia)	Atezolizumab	PD-L1+, subsequent amendment to include PD-L1- (N=115)	10% 1st line: 24% Later lines: 6%	mPFS: 1.4 mOS: 8.9
Dirix Javelin (Ib)	Avelumab (1st to 4th line)	PD-L1+ and PD-L1- (N=58)	5.2%	NA
Adams Keynote-086 (II) Cohort A	Pembrolizumab (≥2nd line)	PD-L1+ and PD-L1- (N=170)	4.7%	mPFS: 2 mOS: 8.9
Adams Keynote-086 (II) Cohort B	Pembrolizumab (1st line)	PD-L1+ (N=84)	23.1%	mPFS: 2.1

Higher ORR in FIRST-line therapy

Anti PD-L1/PD1 monotherapy: non-TN BC

Study (phase)	Anti-PD1/PD-L1 agent	Population	ORR	Survival (months)
Dirix Javelin (Ib)	Avelumab (1st to 4th line)	PD-L1+ and PD-L1- (HER2+=26 HR+HER2-=72)	HER2+: 0% HR+HER2-: 2.8%	NA
Rugo Keynote-028 (Ib)	Pembrolizumab (prior CT or ET allowed)	PD-L1+ (N=25)	HR+: 12%	mPFS: 1.8 mOS: 8.6

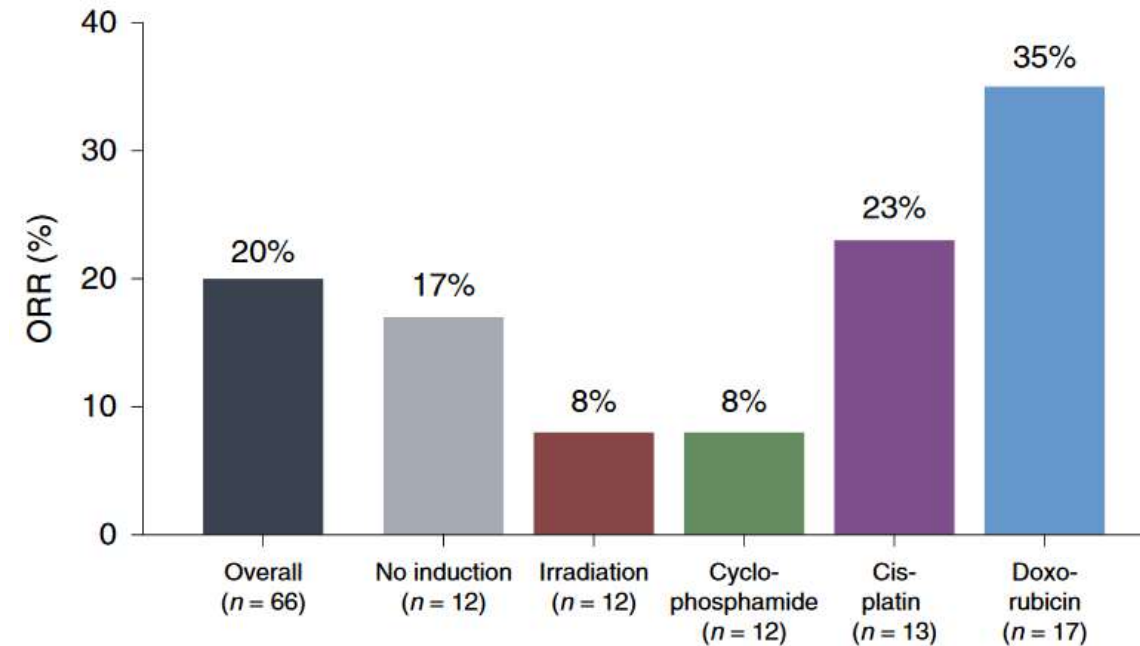
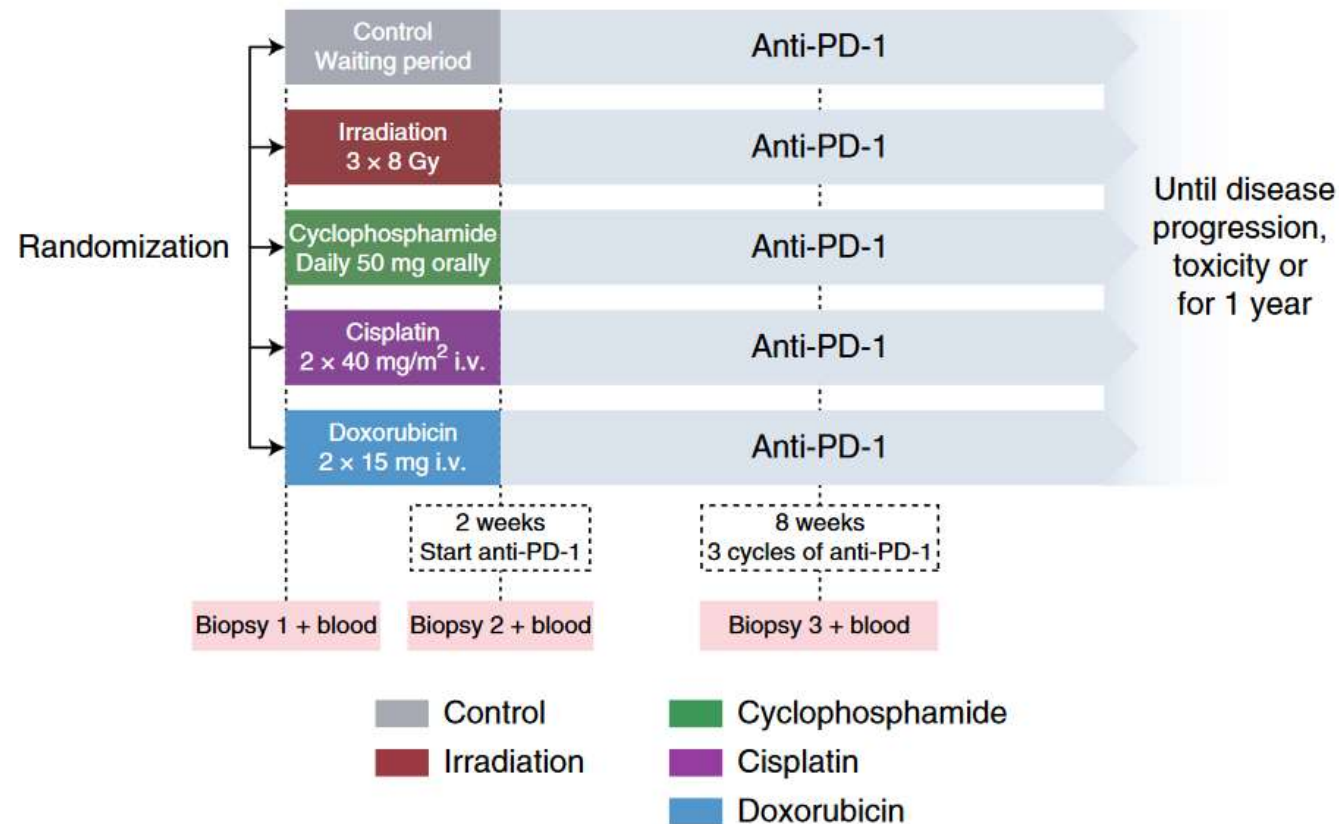
OPERABLE setting

Study (phase)	Treatment arms	Population	pCR
Nanda* 2017 ISPY-2 (II)	Paclitaxel +/- Pembrolizumab → AC	HER2- (N=69 vs 180 controls) TN: 29; HR+: 40	TN: 60% vs 20% HR+: 34% vs 13%
Loibl 2018 GeparNuevo (II)	Durvalumab or placebo + nab- paclitaxel → EC	TN (N=174)	53.4% vs 44.2% (p=NS)
Schmid 2019 Keynote-173 (Ib)	Pembrolizumab + CT (several regimens)	TN (N=20)	60%

* Increased incidence of adrenal insufficiency with pembrolizumab

INDUCTION strategies

TONIC phase II study (TN MBC N=66)

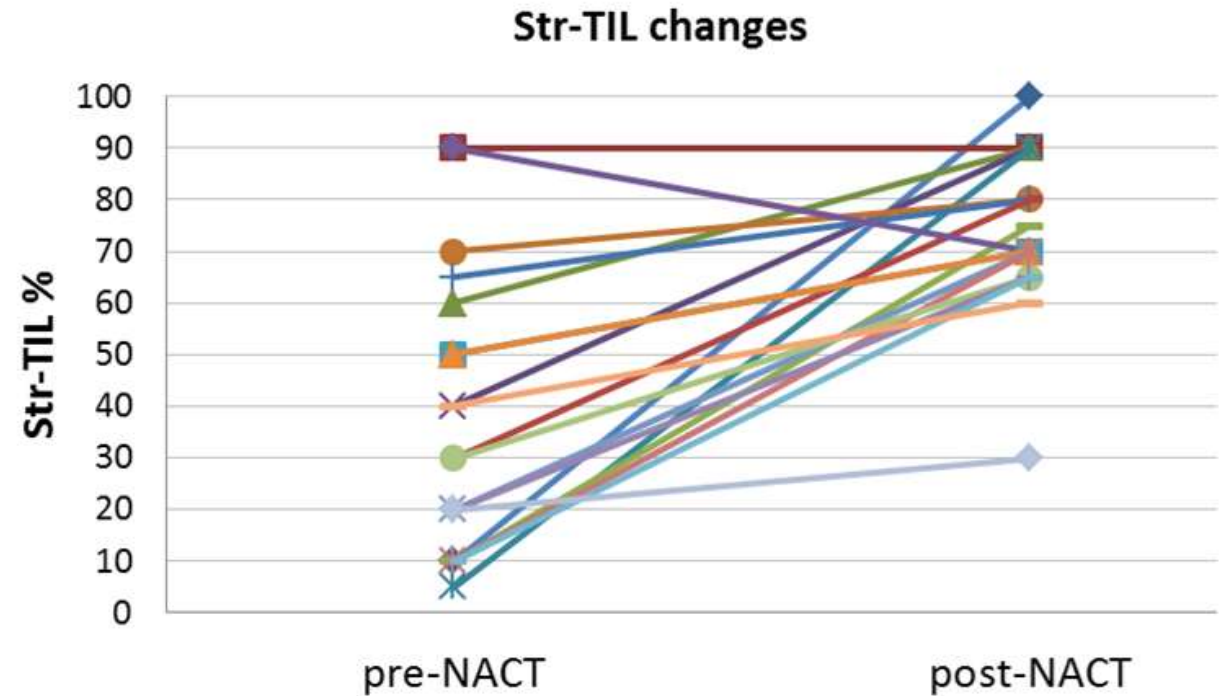
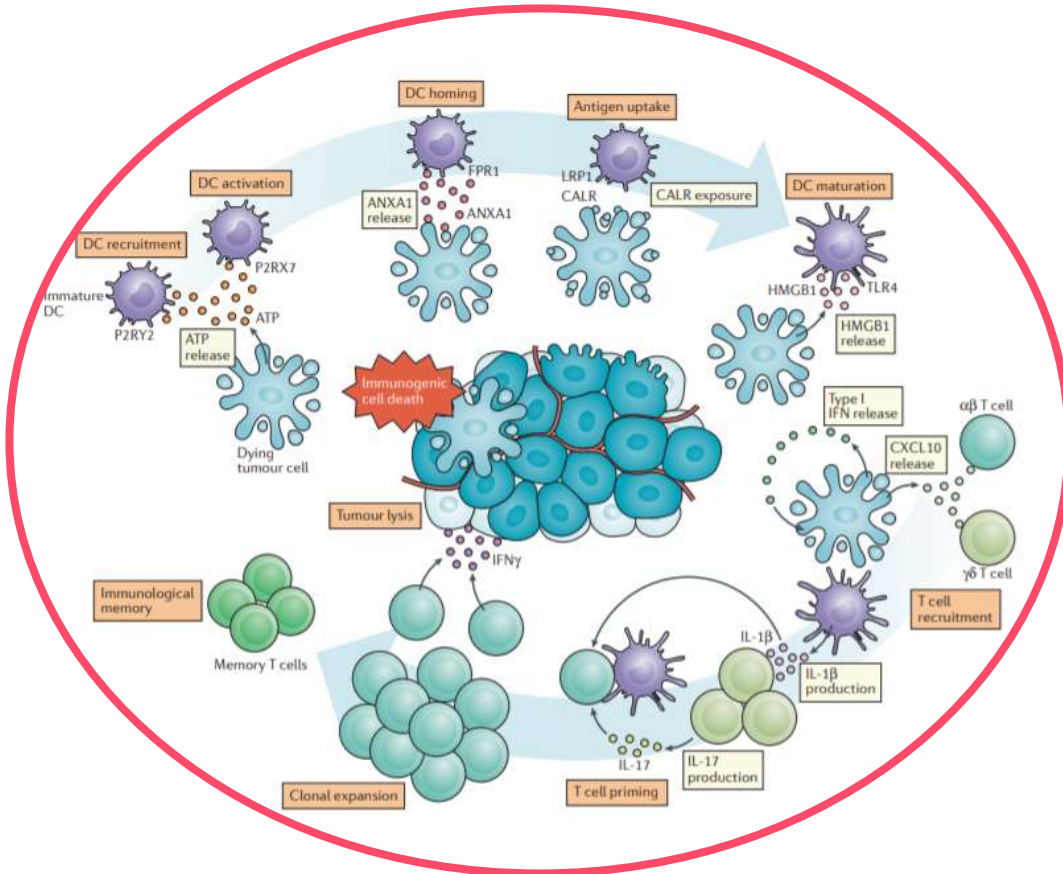


The doxorubicin cohort as an «immune induction» will be expanded in the stage II of the

Combination with CHEMOTHERAPY

Chemotherapy induces IMMUNOGENIC CELL DEATH

- Anthracyclines
- Cyclophosphamide
- Microtubule-stabilizing agents



Chemotherapy can induce lymphocytes
activation and attraction
→ boosts immunogenicity of the tumor