Combination Strategy of Immunotherapy and Chemotherapy in mTNBC

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Sep 25th, 2021

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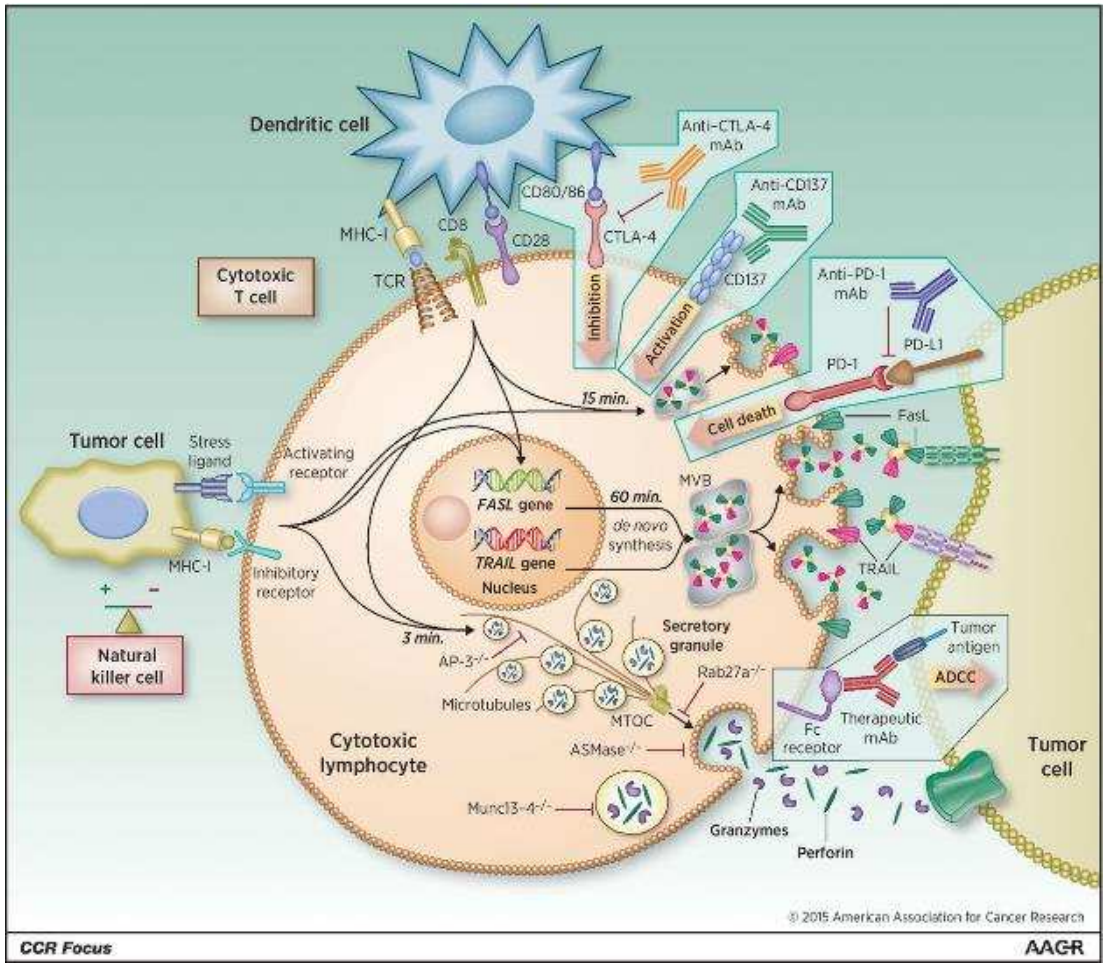
Outline

- Current pearls of immune checkpoint inhibition strategy in mTNBC
- Role of chemotherapy in IO-combination
- Controversy and future perspectives

Activation of the main effector mechanisms of cytotoxic lymphocytes.



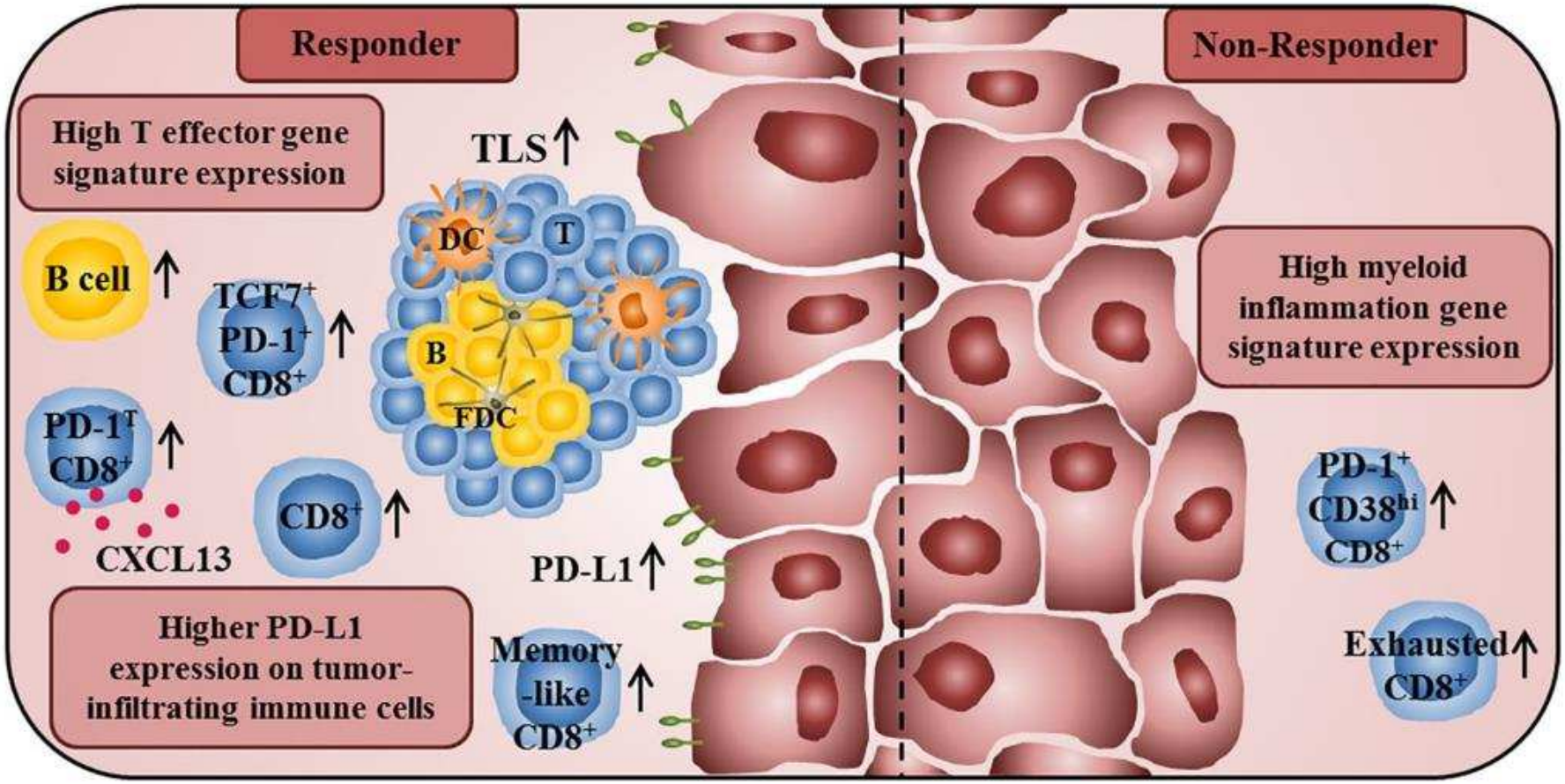
Luis Martínez-Lostao et al. Clin Cancer Res 2015;21:5047-5056

Clinical Cancer Research
AACR

Who is the true killer in PD1/PD-L1 immune checkpoint blockade?

Nature Medicine 2018;24, 994–1004
Front. Immunol 2020. 11:364.

Immune cell characteristics that may influence the clinical efficacy of anti-PD-1/PD-L1 therapy

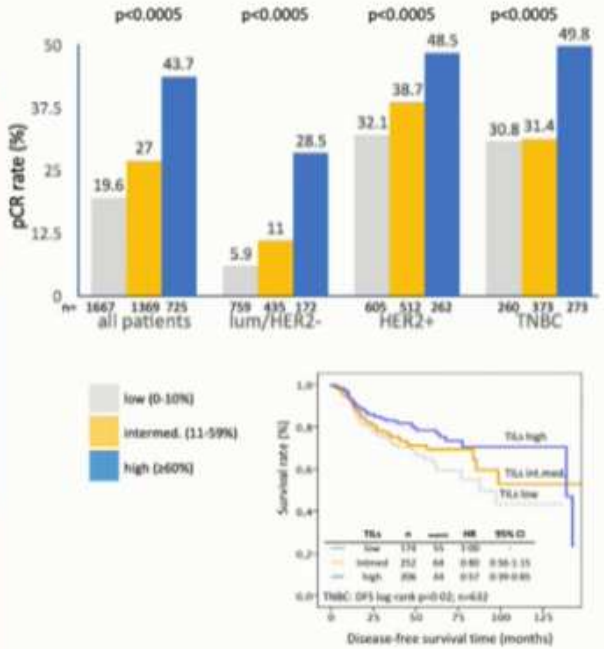


Front. Immunol 2020. 11:364.

TIL as immunogenic marker for TNBC

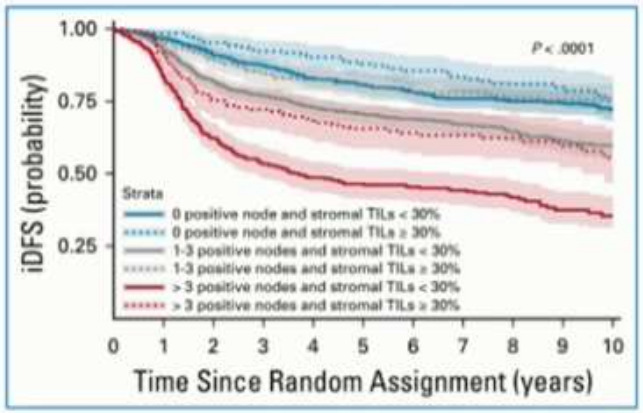
Tumor-infiltrating lymphocytes – update since 2017

Neoadjuvant
(n=3771, GBG trials)



Denkert et al, Lancet Oncol, 2018

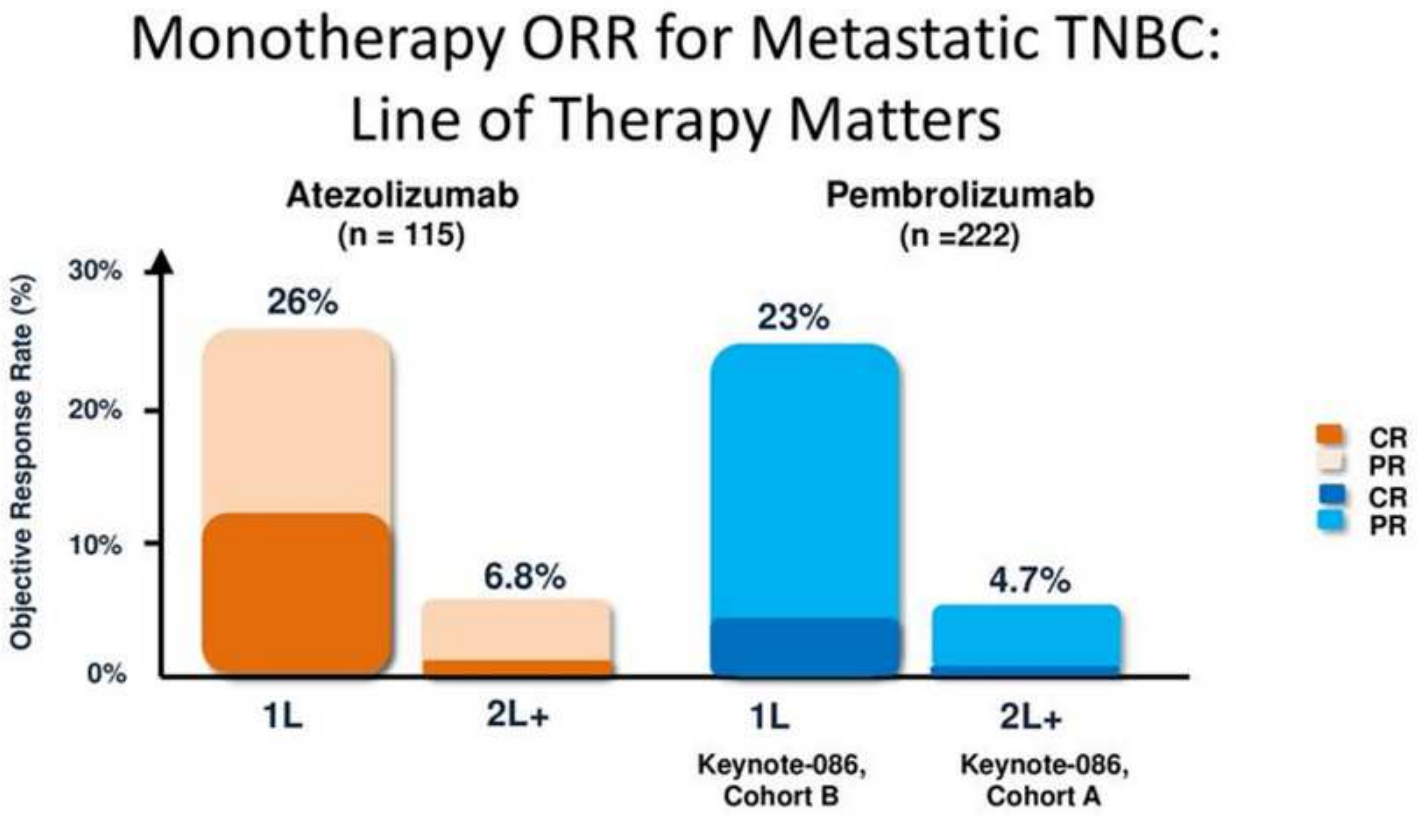
Adjuvant
(n=2148, TNBC)



„…our data suggest that this new biologic biomarker is ready for clinical use and could be implemented globally for patient prognostication and clinical trial stratification."

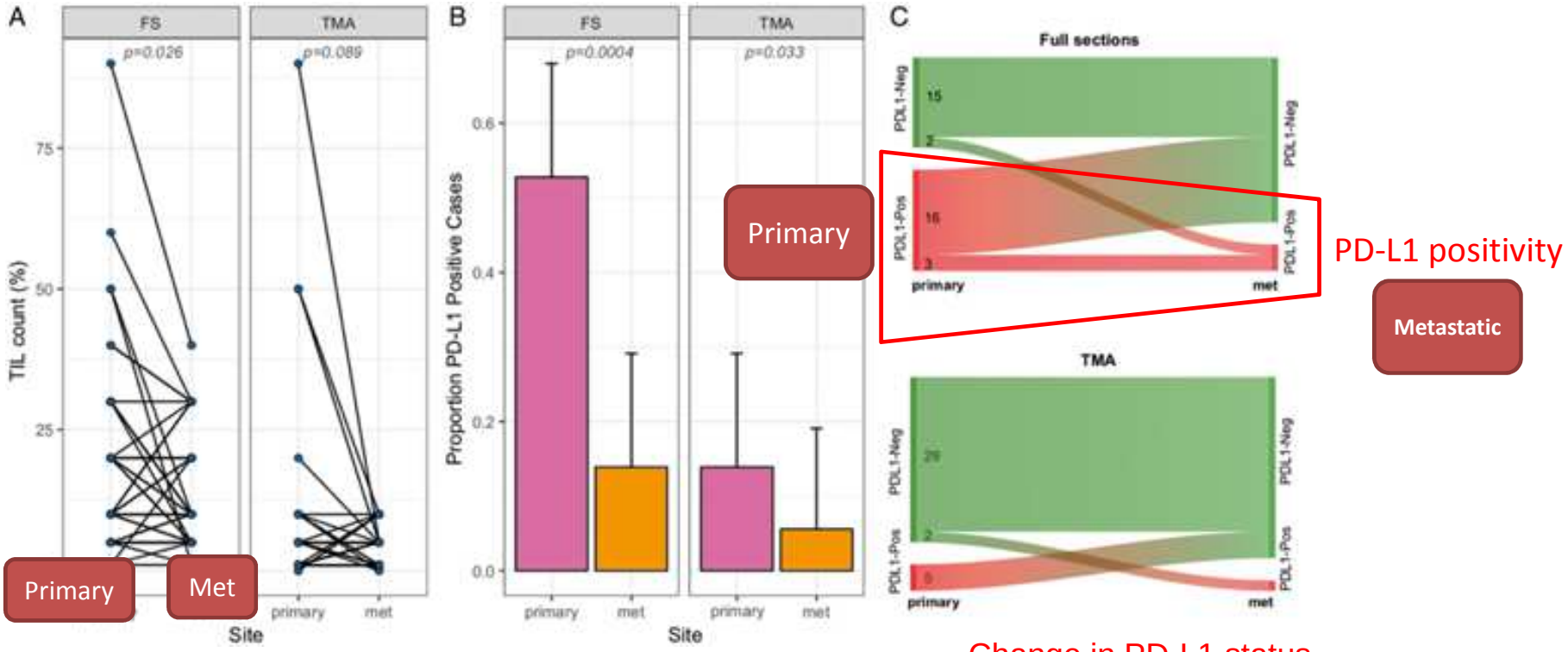
Loi et al, J Clin Oncol. 2019, Mar 1

Low response rate in >2+ Lines



Emens et al, JAMA Onc 2018; Adams et al, Ann Onc 2018

Immunologic Differences Between Primary and Metastatic Tumor Samples



Percent TIL counts in full sections and TMAs.

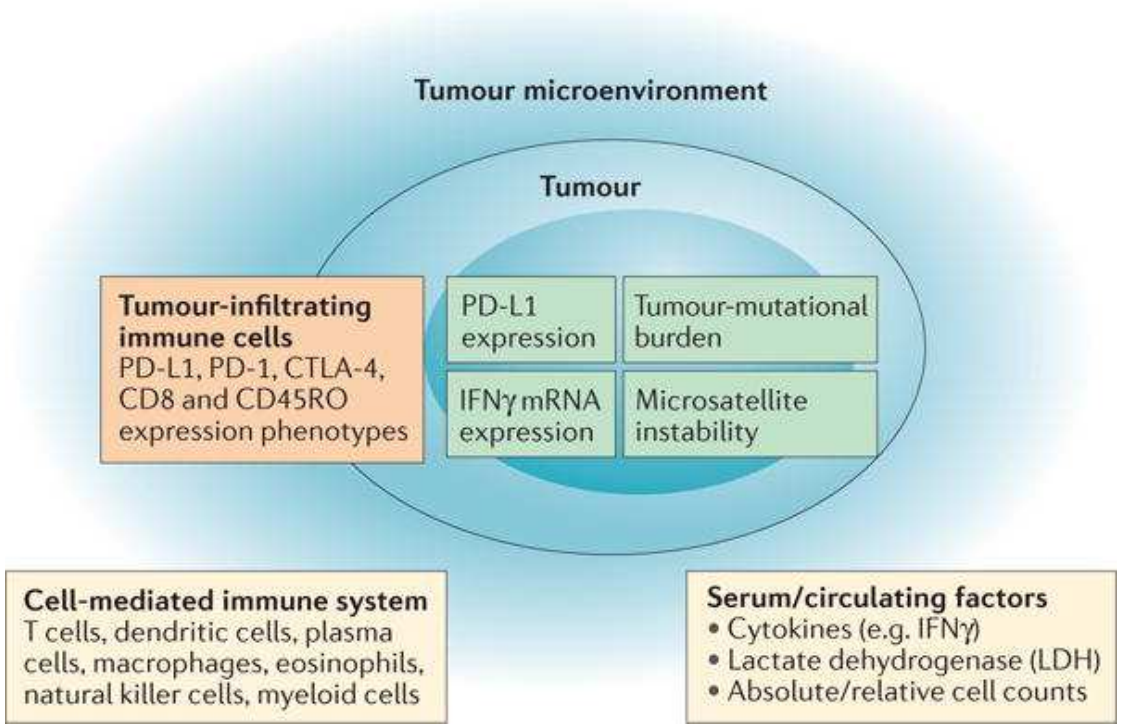
PD-L1 + rates (≥1% stromal or tumor cells)

PD-L1 IHC (E1L3N clone)

Change in PD-L1 status between the primary and metastatic cohorts.

Szekely, et al (Pusztai), Ann Oncol 2018

Biomarkers for immune check point inhibitors (Concept and clinical validity)



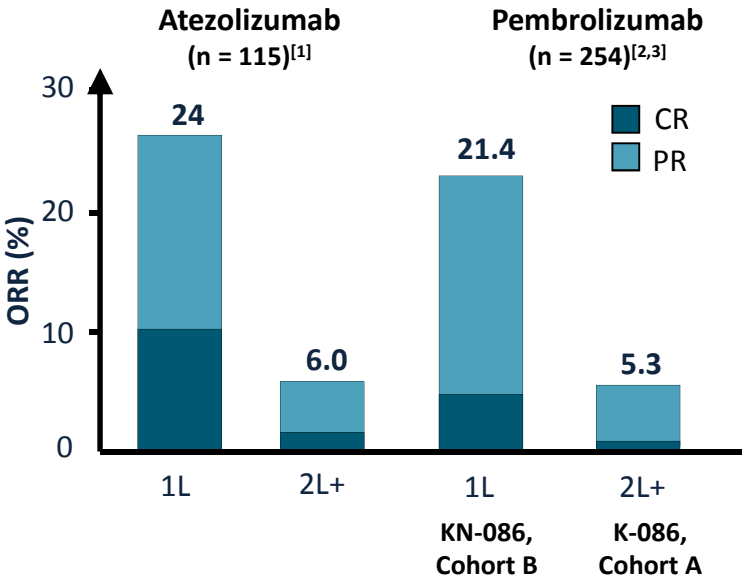
Nat Rev Clin Oncol. 2017 Nov;14(11):655-668

- Current practice (by 2021. Aug)
  - MSI (MSI-H)*
  - TMB (≥10 mutations/megabase)*
  - PD-L1 status (by IHC)
- Emerging and/or investigational
  - Microbiome (腸道微菌叢)
  - TILs
  - Neoantigen
  - Immune cell repertoire
  - Immune response gene signature

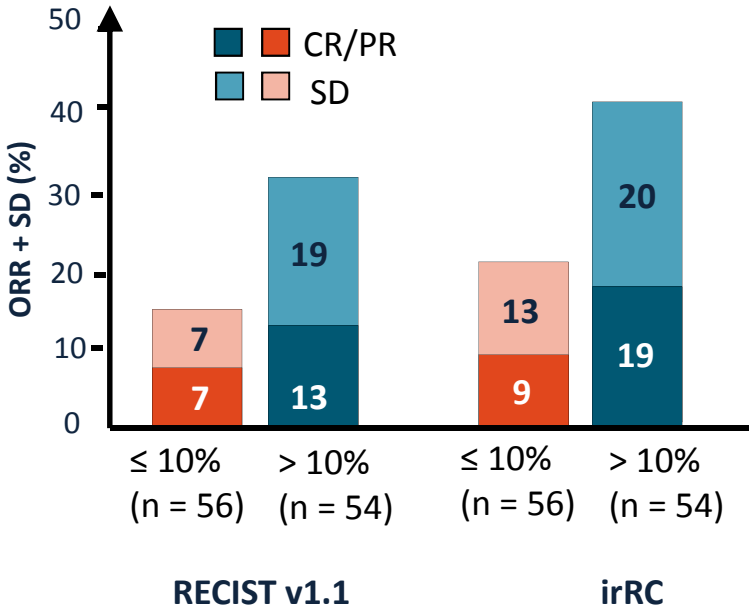
*approved for pembrolizumab only

Checkpoint Blockade: Enriching for Monotherapy Responders

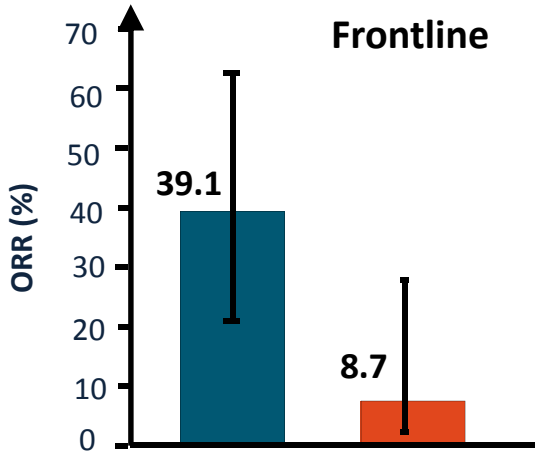
Line of Therapy



TILs[1]



Line, TILs, PD-L1+[4]



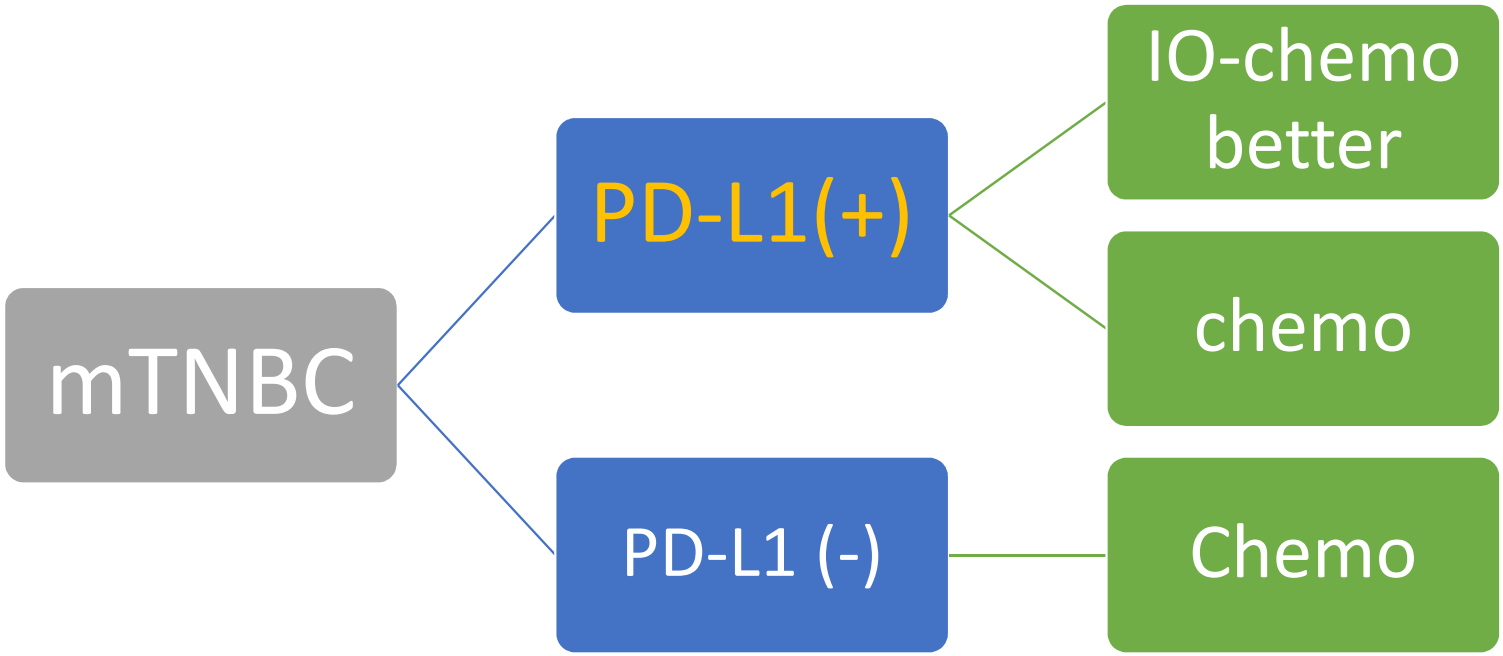
sTIL level	≥ 17.5%	< 17.5%
n	23	23
Responders	9	2
Ongoing responses	5	2

- Frontline therapy
- High level of TIL
- PD-L1+
- TMB

1. Emens. JAMA Onc. 2018;5:74. 2. Adams. Ann Onc. 2018;30:397. 3. Adams. Ann Onc. 2019;30:405. 4. Loi. ESMO 2017. Abstr LBA13.

Slide credit: clinicaloptions.com

Immunotherapy not likely one-size fit for all



IMpassion130 study design

Key IMpassion130 eligibility criteria[a]:

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

Stratification factors:

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

R 1:1

Atezo + nab-P arm:

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

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

Double blind; no crossover permitted

Plac + nab-P arm:

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

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

RECIST v1.1
PD or toxicity

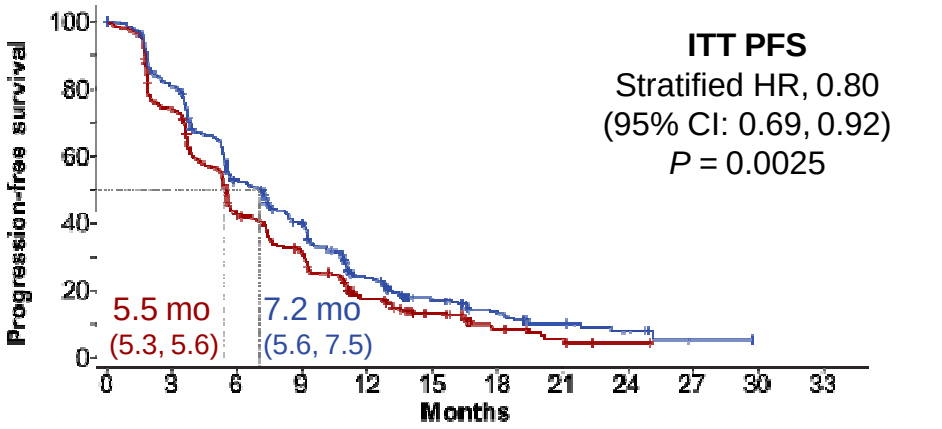
- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

IC, tumour-infiltrating immune cell; TFI, treatment-free interval. [a] ClinicalTrials.gov: NCT02425891. [b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). [d] Radiological endpoints were investigator assessed (per RECIST v1.1).

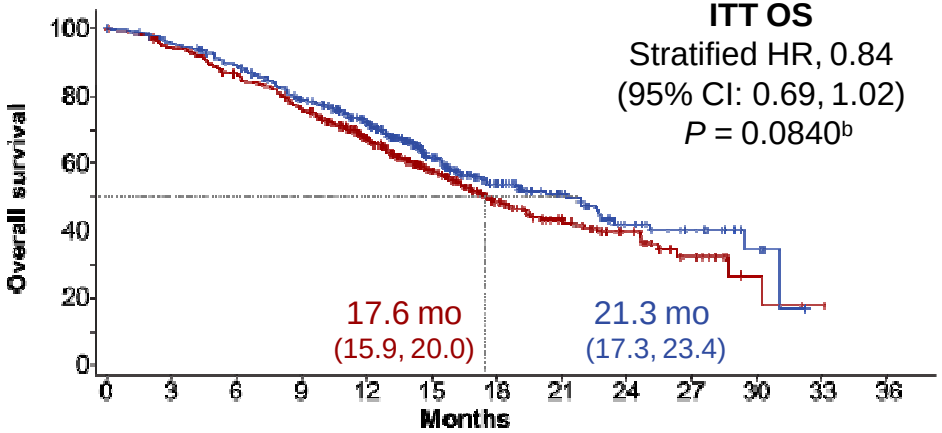
Schmid P, et al. IMpassion130 ESMO 2018 (LBA1_PR) http://bit.ly/2DMhayg

IMpassion130 primary analysis[1,2]: Clinically meaningful PFS and OS benefit in the PD-L1+ population

ITT population

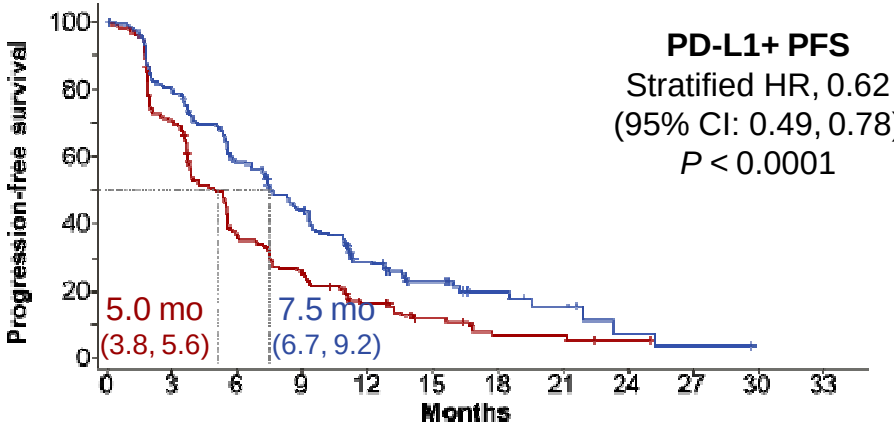


ITT PFS
Stratified HR, 0.80
(95% CI: 0.69, 0.92)
P = 0.0025

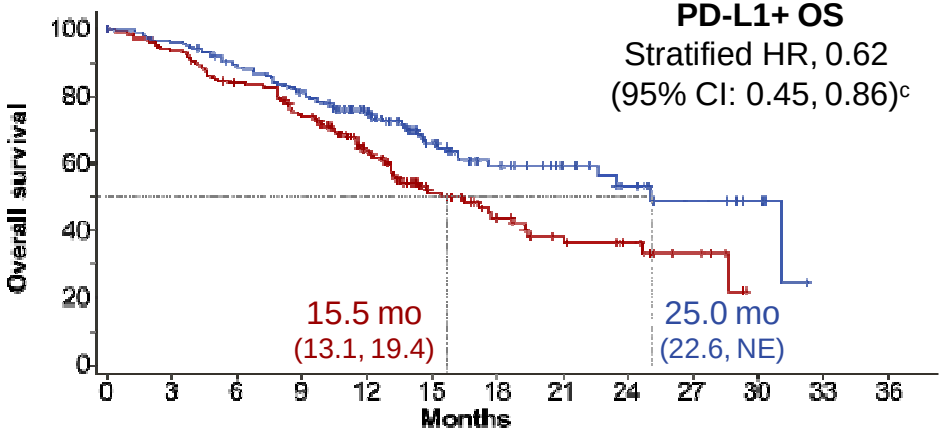


ITT OS
Stratified HR, 0.84
(95% CI: 0.69, 1.02)
P = 0.0840[b]

PD-L1+ population[a]



PD-L1+ PFS
Stratified HR, 0.62
(95% CI: 0.49, 0.78)
P < 0.0001



PD-L1+ OS
Stratified HR, 0.62
(95% CI: 0.45, 0.86)[c]

*Tecentriqis only approved for PD-L1 IC+ mTNBCpopulation in Taiwan.

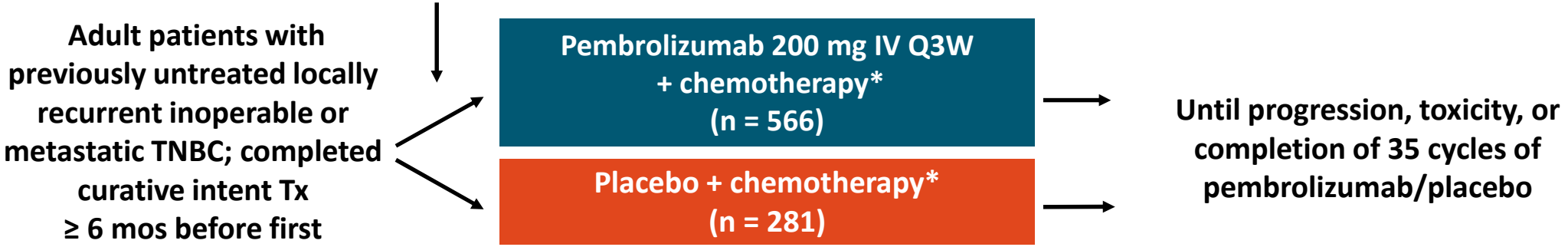
NE, not estimable.
Median follow-up (ITT): 12.9 months.
[a] PD-L1+: PD-L1 in ≥ 1% of IC. [b] Not significant. [c] Not formally tested per hierarchical study design.
1. Schmid *N Engl J Med* 2018. 2. Schmid ESMO 2018 [LBA1_PR].

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

KEYNOTE-355: Study Design

- Randomized, double-blind, multicenter phase III trial

Stratified by chemotherapy (taxane vs gem/carbo); PD-L1 tumor expression (CPS > 1 vs < 1); previous Tx with same class of chemotherapy for EBC (Y vs N)



*Investigator's choice of chemotherapy was permitted:

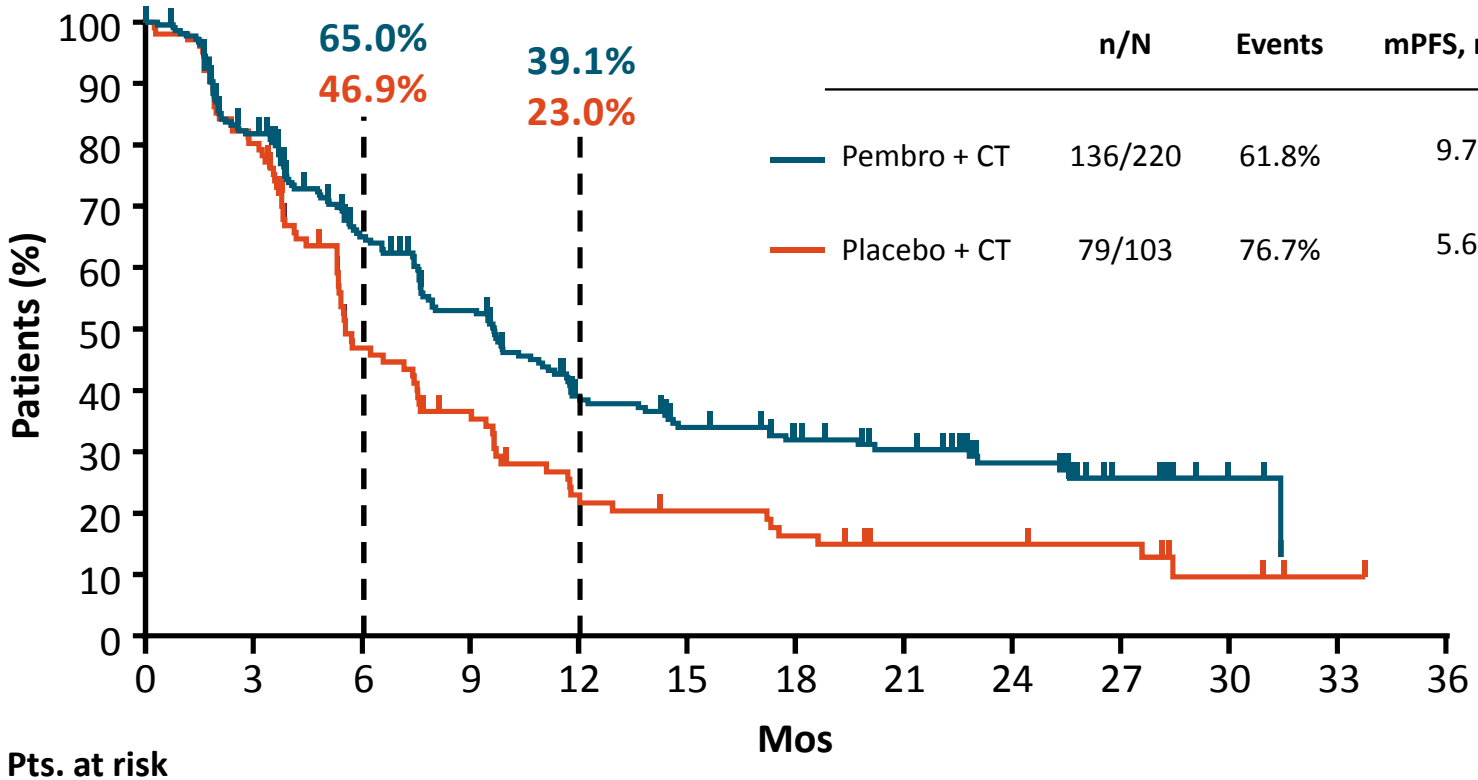
- Nab-paclitaxel 100 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle
- Paclitaxel 90 mg/m^2 IV on Days 1, 8, 15 of 28-day cycle
- Gem 1000 mg/m^2 + carbo AUC 2 on Days 1, 8 of 21-day cycle

- Primary endpoints: PFS and OS (PD-L1 CPS ≥ 10, PD-L1 CPS ≥ 1, and ITT)
- Secondary endpoints: ORR, DoR, DCR, safety

Cortes. ASCO 2020. Abstr 1000.

Slide credit: clinicaloptions.com

KEYNOTE-355: PFS in PD-L1 CPS ≥ 10 Population



	n/N	Events	mPFS, mos	HR (95% CI)	*P* value (one-sided)
Pembro + CT	136/220	61.8%	9.7	0.65 (0.49-0.86)	0.0012
Placebo + CT	79/103	76.7%	5.6		

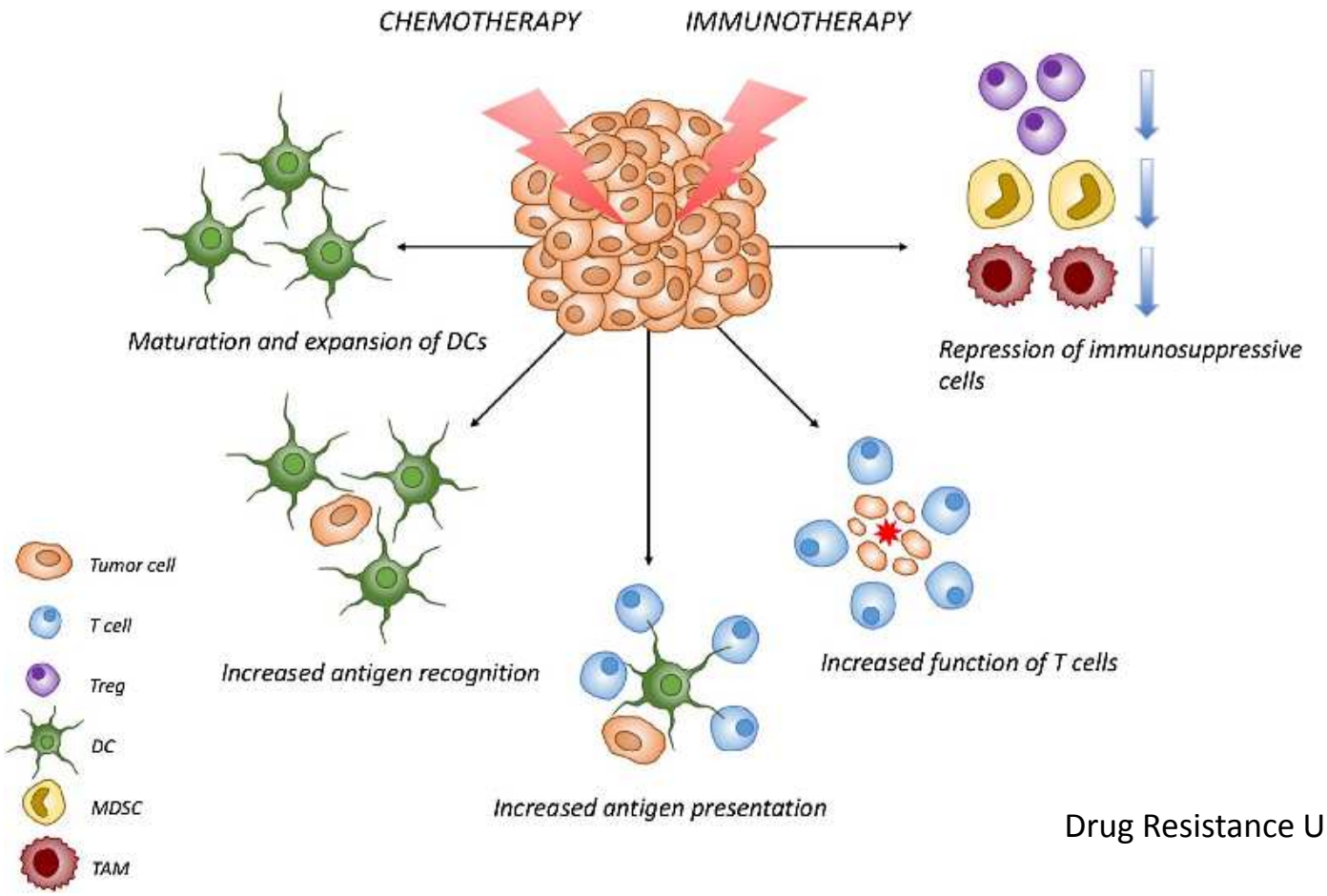
Pts. at risk

220	173	122	96	63	52	44	37	25	12	5	0	0
103	80	41	30	18	15	12	8	8	7	3	1	0

Cortes. ASCO 2020. Abstr 1000. Reproduced with permission.

Slide credit: clinicaloptions.com

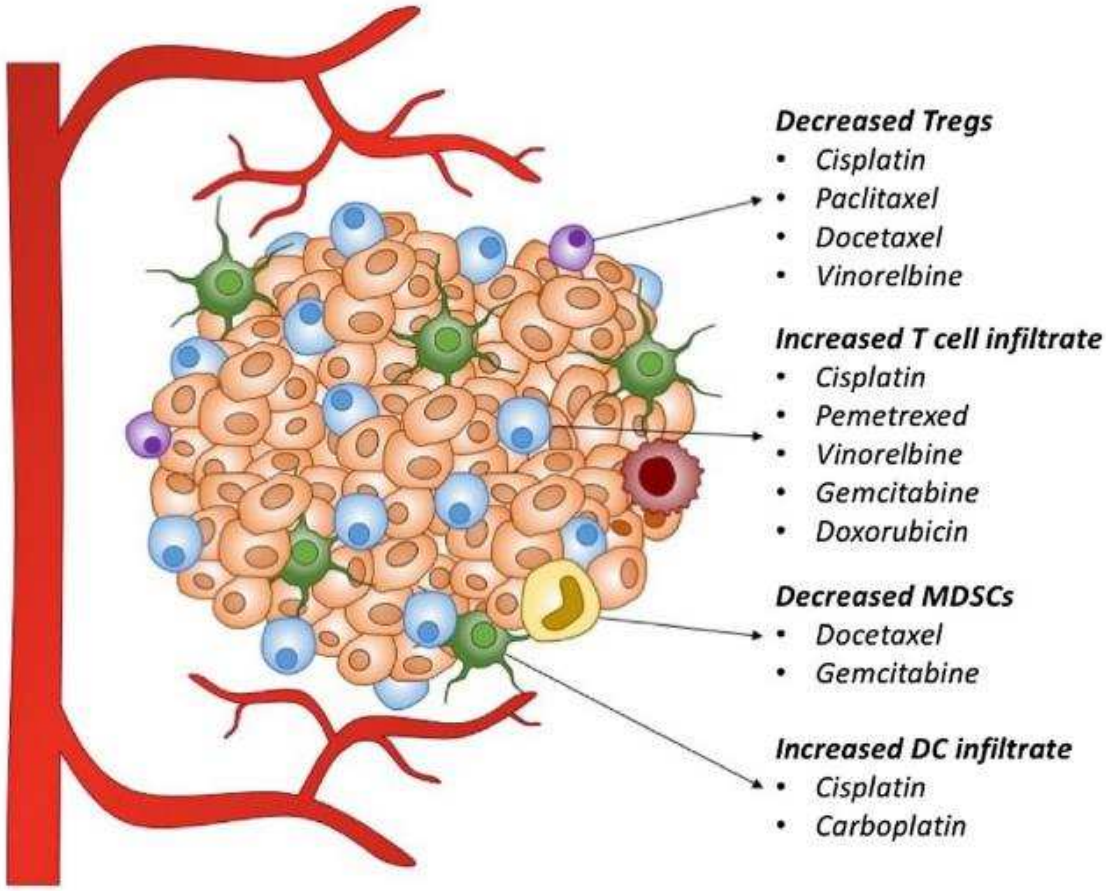
Molecular basis and rationale for combining immune checkpoint inhibitors with chemotherapy in cancer

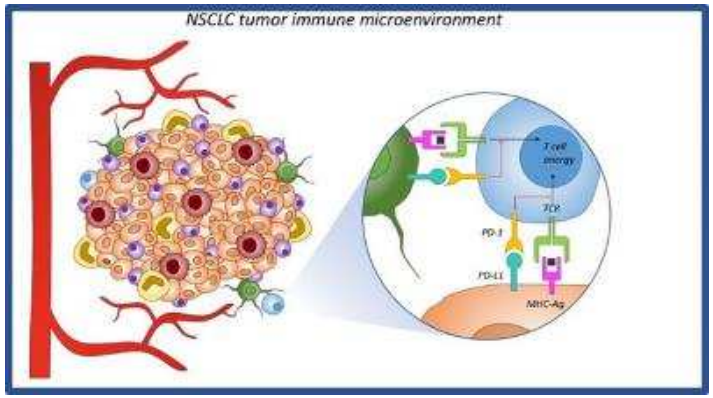


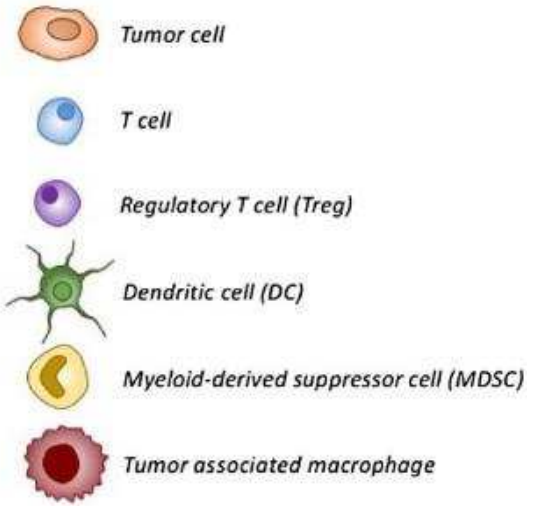
Drug Resistance Updates 46:100644

Chemotherapy-induced immune modulation in TME of NSCLC

Effects of chemotherapy on the structure of NSCLC tumor immune microenvironment

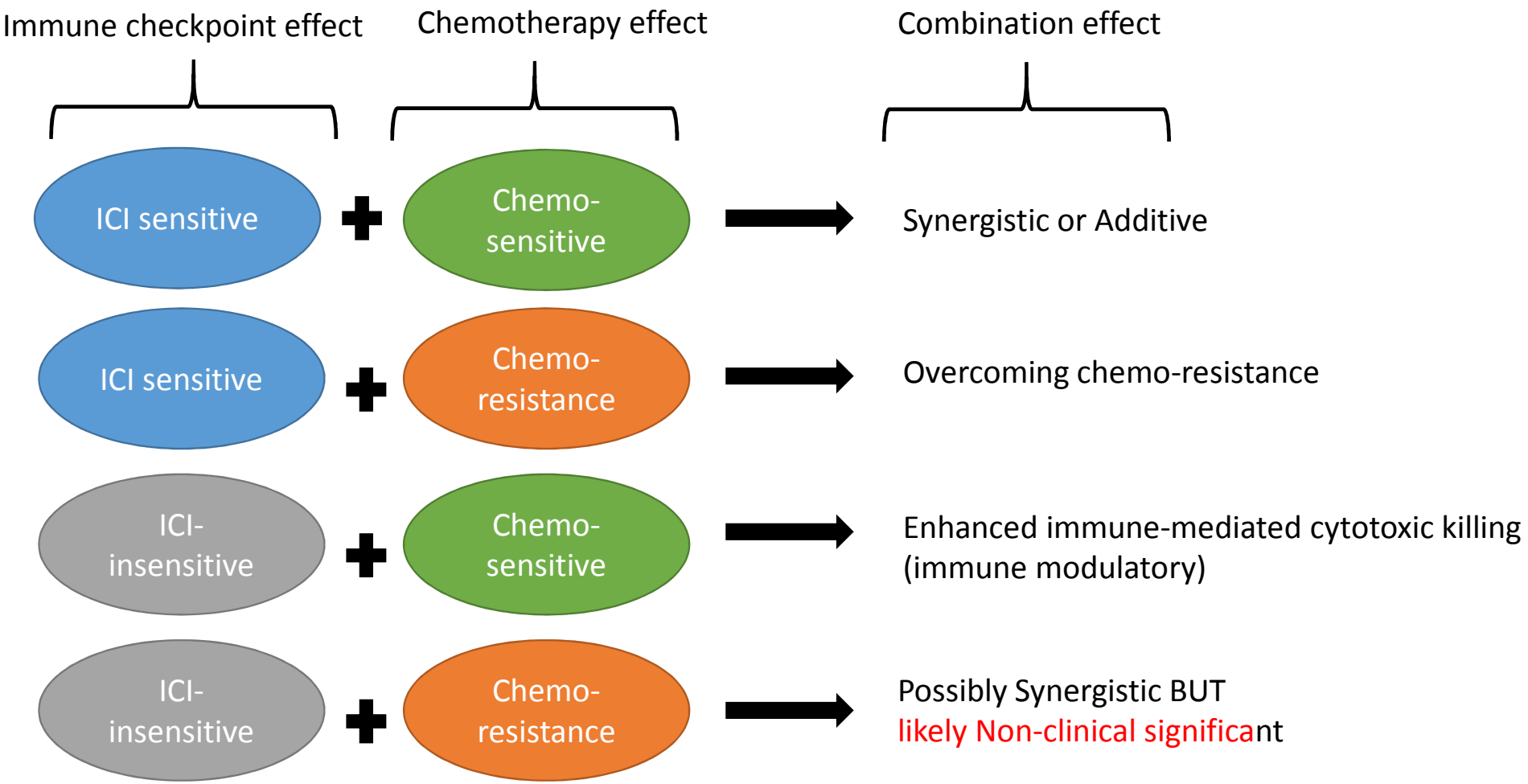






Drug Resistance Updates 46:100644

Theoretical combination strategy of chemo-immunotherapeutic regimens

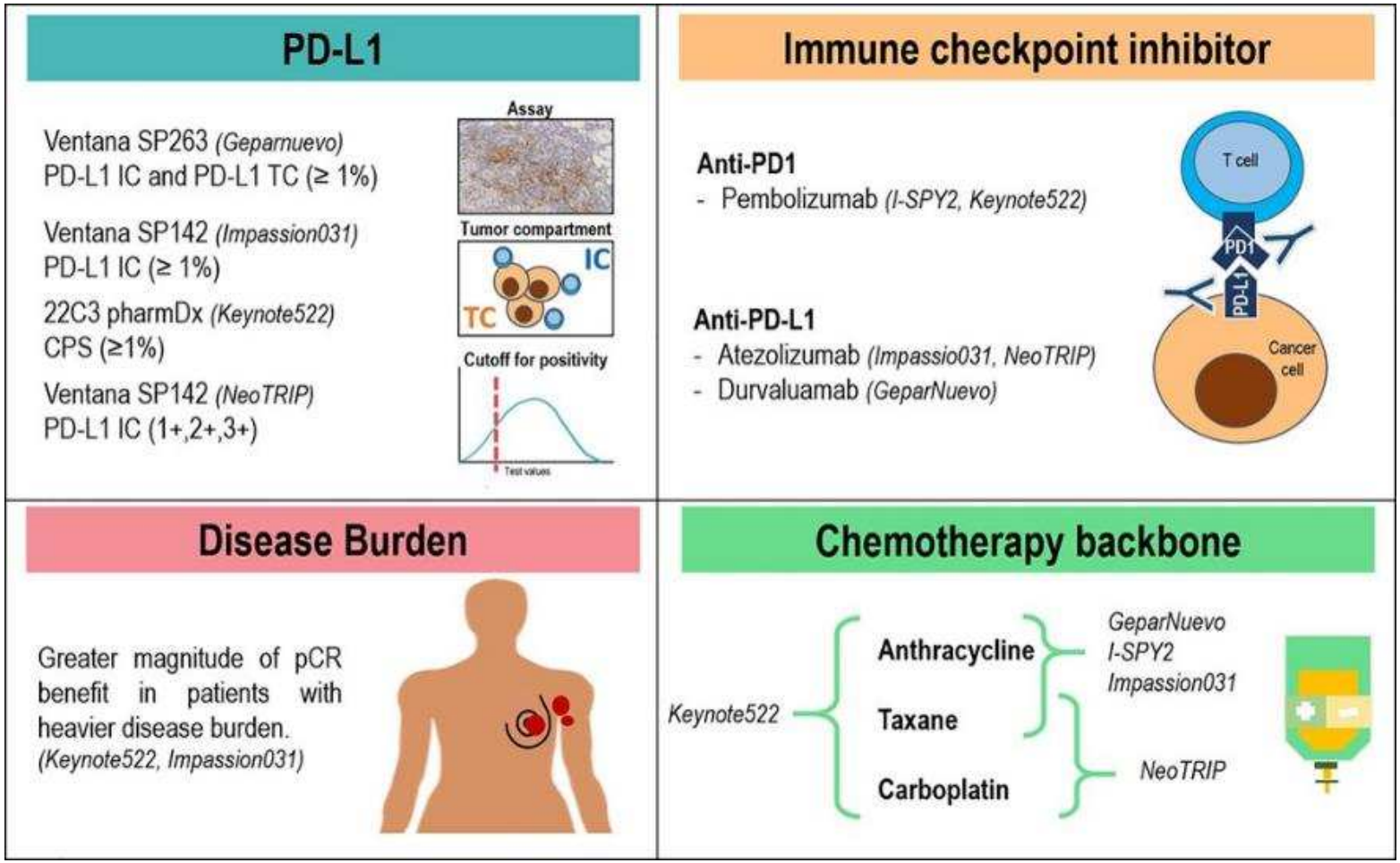


Neoadjuvant IO trials

	Trial	Population (n)	Drugs (n per arm)	pcR rates[a] % (95% CI)	p
aPD1	GeparOLA (non-comparative phase II)	HER2-negative (106; TN cohort, 77)	P-Cb-Placebo → AC P-O → EC P-Cb → EC	58 56.0 (43.4–68.0) 59.3 (41.7–75.2)	NA
aPD-L1	GeparNuevo (phase II, randomized)	TN (1 7 4) Window (induction ICI)	Durva[b] → Durva-NabP → Durva-EC Durva[b] → Placebo-NabP → Placebo-EC	53.4 (42.5–61.4) Window cohort: 61.0 44.2 (33.5–55.3) Window cohort: 41.4	1.45 (0.80–2.63), p = 0.224 Window cohort: 2.22 (1.06–4.64), p = 0.035
aPD1	Keynote-522 (phase III)	TN (6 0 2)	Pembro-NabP-Cb → A/E-C-Pembro Placebo-NabP-BC → A/E-C-Placebo	64.8 (59.9–69.5) 51.2 (44.1–58.3)	Estimated treatment difference: 13.6% (5.4–21.8, p > 0.001)
aPD-L1	NeoTRIP aPDL1 (phase III)	TN (2 8 0) No AC regimen	Atezo-NabP-Carboplatin NabP-Cb	43.5 (35.1–52.2) 40.8 (32.7–49.4)	1.11 (0.69–1.79), p = 0.66[c]
aPD-L1	Impassion 031 (phase III)	TN (3 3 3) No platinum regimen	Placebo-NabP → Placebo-AC Atezo-NabP → Atezo-AC	41.1 57.6	Delta pCR 16.5 (5.9–27.1), p = 0.0044
aPD1	I-SPY-2 (phase II adaptive randomized)	HER2- (205; TN cohort, 21)	Pembro-P → AC P → AC	TN: 60 (44–75) TN: 22 (13–30)	>99.9% predicitive probability of being superior to the control arm

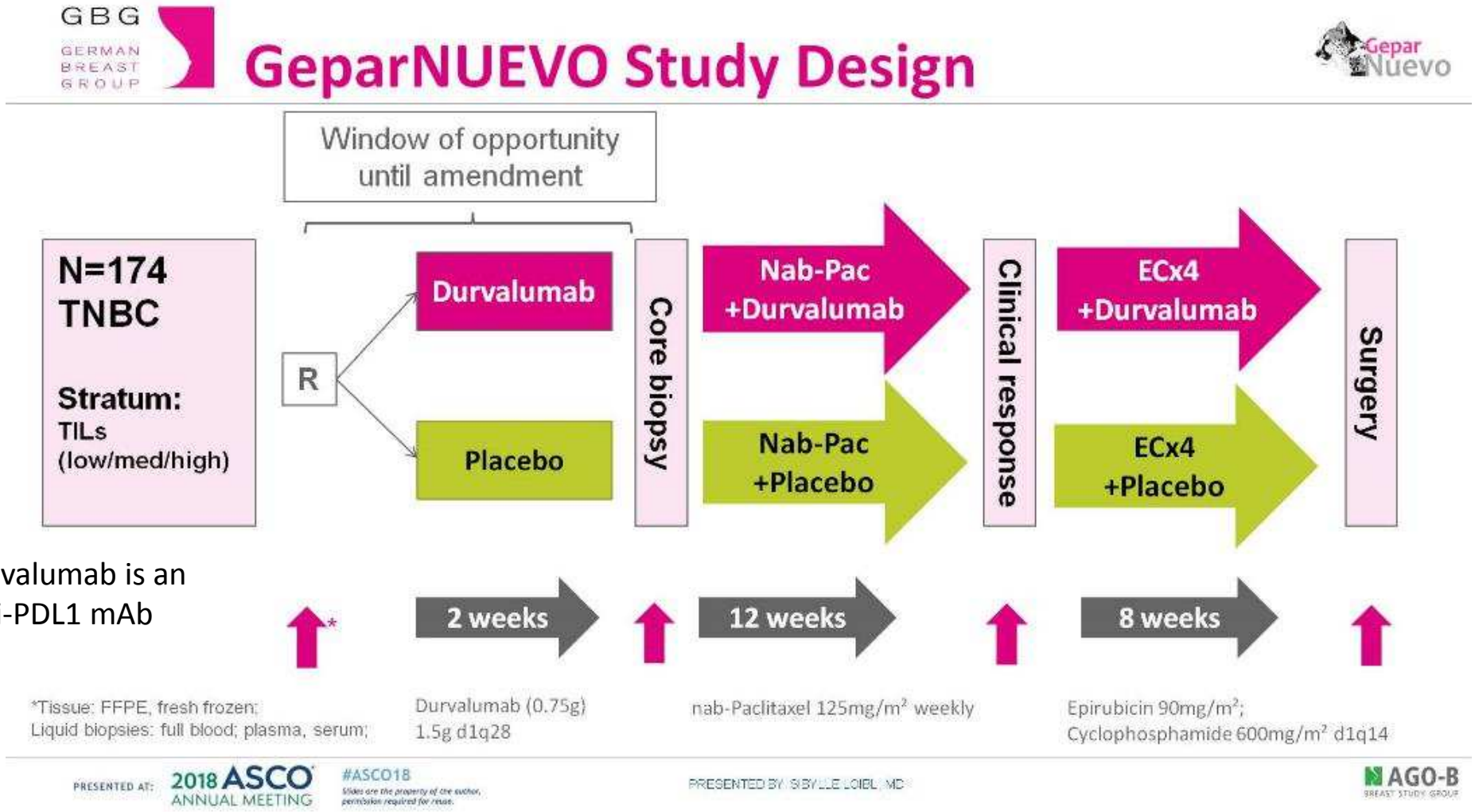
Cancer Treatment Reviews 98 (2021) 102222

Uncertainty of neoadjuvant IO approach in TNBC



Cancer Treatment Reviews 98 (2021) 102222

Priming Immune with ICI followed by chemotherapy combination?

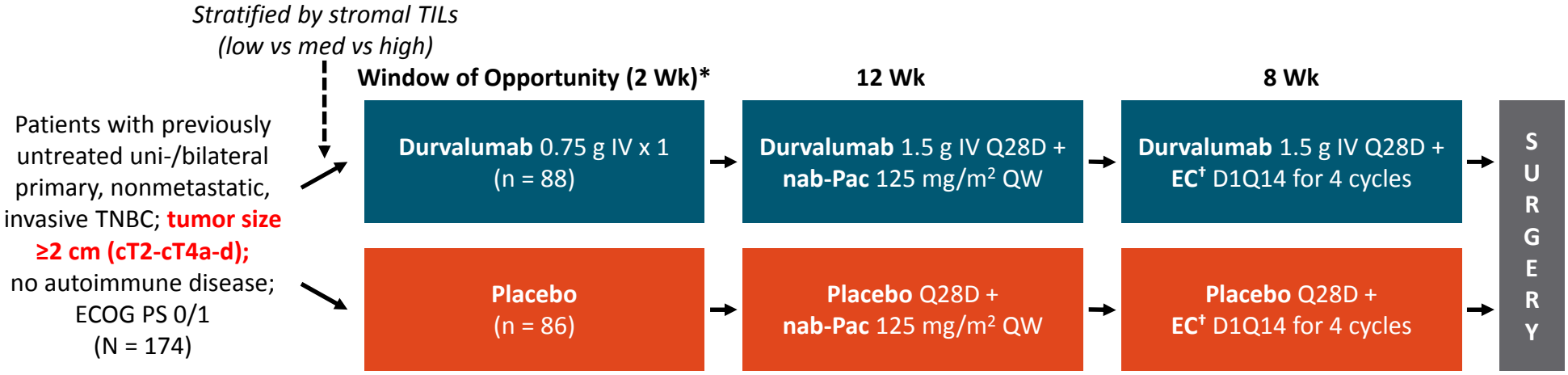


Durvalumab is an anti-PDL1 mAb

Presented By Sibylle Loibl at 2018 ASCO Annual Meeting

GeparNUEVO Survival Analysis: Study Design

- Randomized, double-blind phase II trial
  - Current analysis of long-term outcomes after median follow-up of 43.7 mo (range: 4.9-56.1)



***Window of opportunity closed after n = 117 enrolled due to IDMC concerns about delay in patients starting CT in placebo arm.** †Epirubicin 90 mg/m² + cyclophosphamide 600 mg/m².

- **Primary endpoint:**
  pCR (ypT0, ypN0) at surgery
- **Secondary endpoints:**
  invasive DFS, distant DFS, OS

Loibl. ASCO 2021. Abstr 506. Loibl. Ann Oncol. 2019;30:1279. NCT02685059.

Slide credit: clinicaloptions.com

GBG GERMAN BREAST GROUP

Primary Endpoint - pathological complete response
pCR – ypT0, ypN0

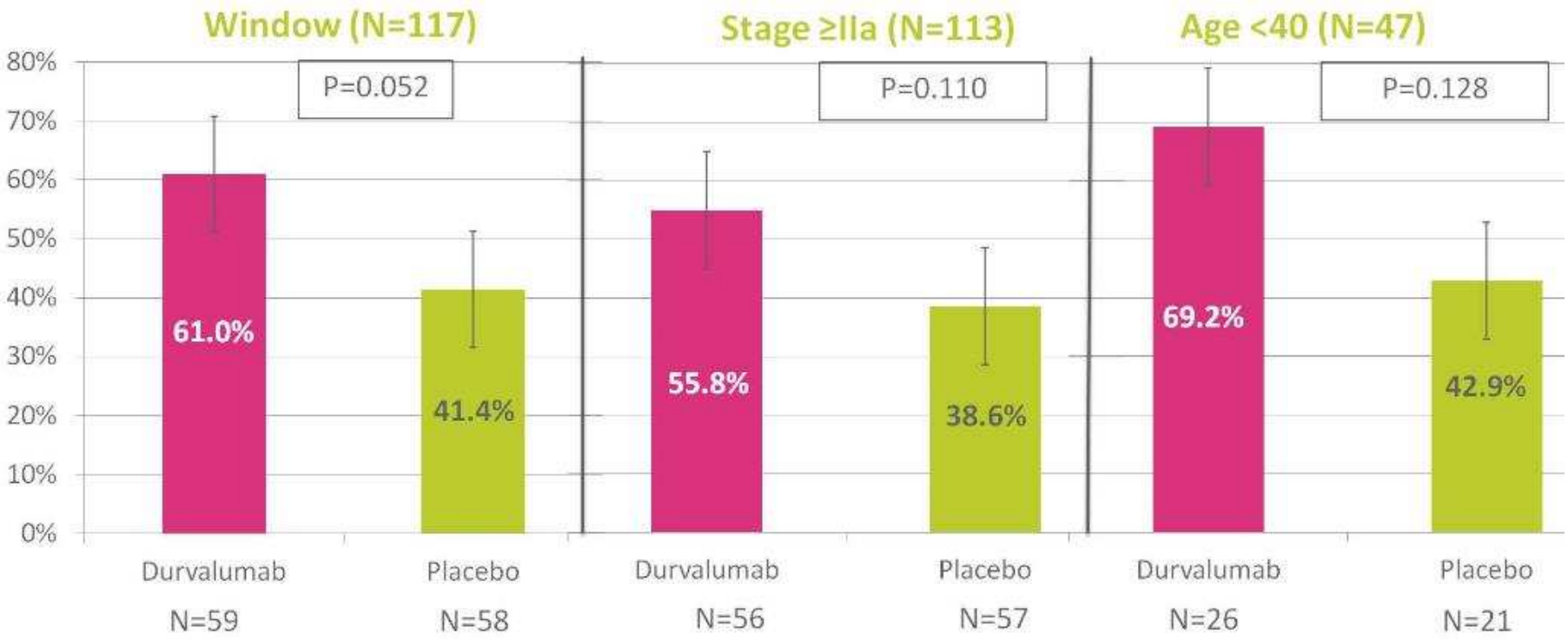
Gepar Nuevo

* Continuous corrected χ^2 test
** For stratification factor (TIL groups)

GBG GERMAN BREAST GROUP

Subgroup Analysis – pCR rates

Gepar Nuevo



PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

PRESENTED BY: SIBYLLE LOIBL, MD

AGO-B BREAST STUDY GROUP

GeparNUEVO Survival Analysis: iDFS

iDFS Outcome	Durvalumab (n = 88)		Placebo (n = 86)	
Events, n	12		22	
3-yr iDFS, %	85.6		77.2	
Stratified HR* (95% CI)	0.48 (0.24-0.97; *P* = .0398)			
By pCR status	**pCR (n = 47)**	**No pCR (n = 40)**	**pCR (n = 38)**	**No pCR (n = 48)**
Events, n	2	9	7	15
3-yr iDFS, %	95.5	76.3	86.1	69.7
Log-rank *P* value	.0071			

- iDFS benefit with durvalumab generally consistent across subgroups
  - Benefit potentially greater in those with PD-L1–positive† disease (*P* = .053 for durvalumab vs placebo)
- HR (95% CI) for pCR vs no pCR: 0.34 (0.16-0.73; log-rank *P* = .004)
- HR (95% CI) for durvalumab vs placebo: pCR, 0.22 (0.05-1.06; log-rank *P* = .038); no pCR, 0.67 (0.29-1.54; log-rank *P* = .346)

Loibl. ASCO 2021. Abstr 506.

*Stratified by stromal TILs. †Determined using Ventana SP263 antibody with cutoff of 1%.

GeparNUEVO Survival Analysis: OS

OS Outcome	Durvalumab (n = 88)		Placebo (n = 86)	
Events, n	4		15	
3-yr OS, %	95.2		83.5	
Stratified HR* (95% CI)	0.24 (0.08-0.72; *P* = .0108)			
By pCR status	**pCR (n = 47)**	**No pCR (n = 40)**	**pCR (n = 38)**	**No pCR (n = 48)**
Events, n	0	3	4	11
3-yr OS, %	100	92.0	88.9	78.8
Log-rank *P* value	.0023			

- HR (95% CI) for pCR vs no pCR: 0.27 (0.09-0.81; log-rank *P* = .012)
- HR (95% CI) for durvalumab vs placebo:
  - pCR: 0.00 (0.00-; log-rank *P* = .024)†
  - no pCR: 0.30 (0.08-1.09; log-rank *P* = .053)

Loibl. ASCO 2021. Abstr 506.

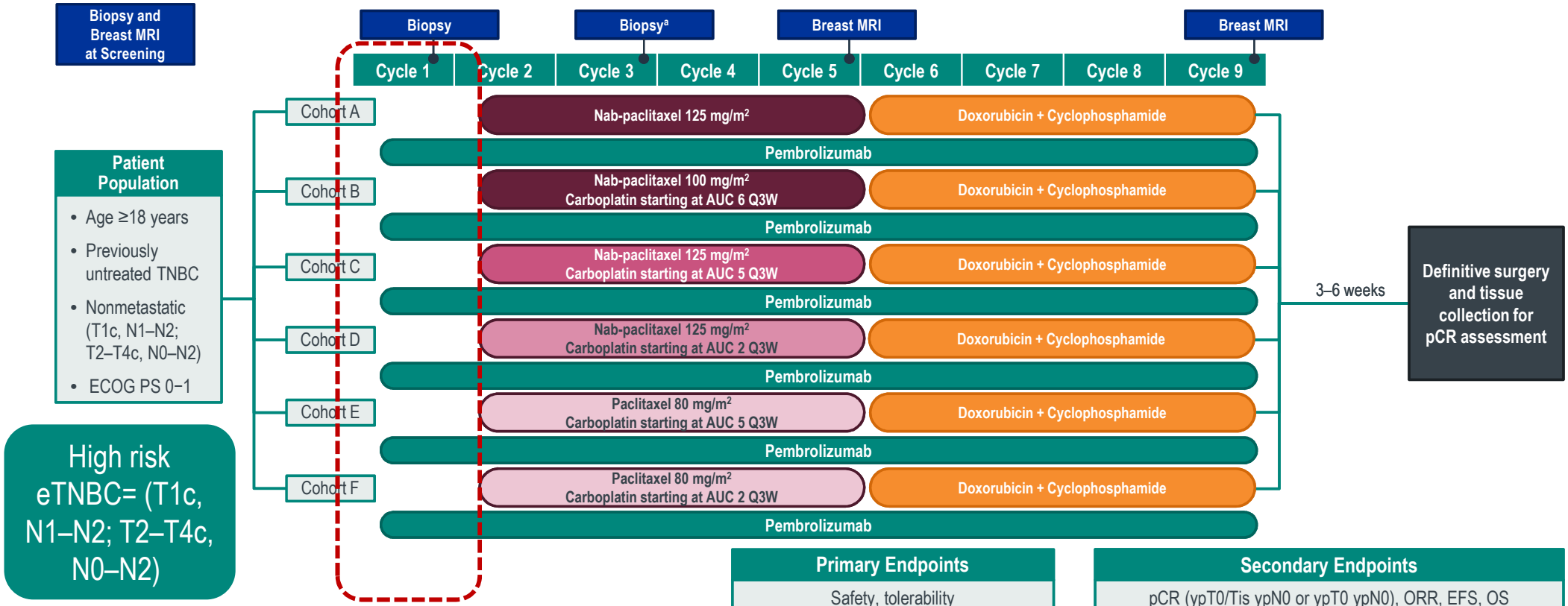
*Stratified by stromal TILs. †No events in durvalumab arm.

Slide credit: clinicaloptions.com

Priming Immune with ICI followed by chemotherapy combination?

Determining DLT of IO + chemo

KEYNOTE-173: Phase I Study of Pembrolizumab + Chemotherapy as Neoadjuvant Treatment in TNBC



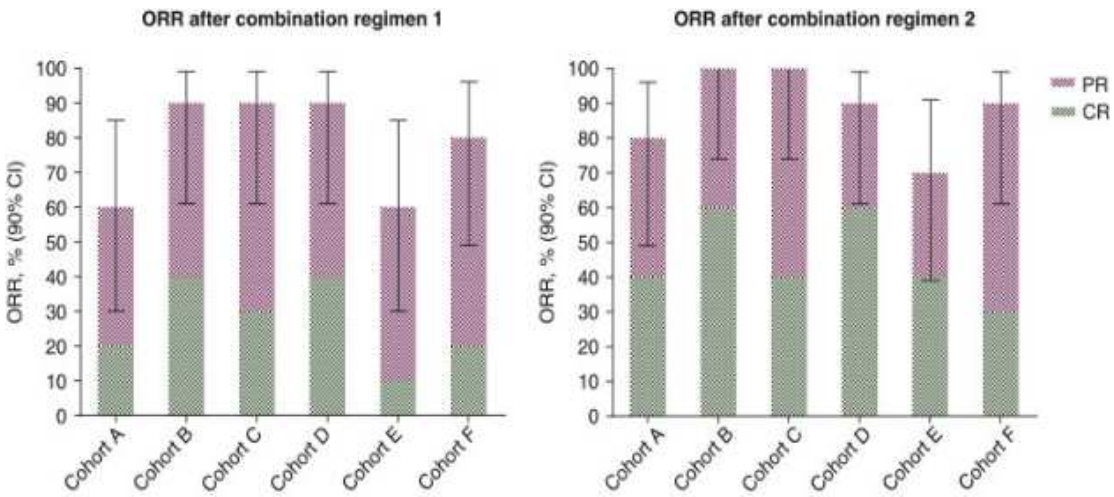
[a]Optional biopsy was performed between Days 15 and 21 of Cycle 3.

Nab-paclitaxel and paclitaxel were administered Days 1, 8, 15 Q3W. Pembrolizumab dose: pembrolizumab 200 mg Day 1 Q3W. Doxorubicin dose: 60 mg/m² Day 1 Q3W. Cyclophosphamide dose: 600 mg/m² Day 1 Q3W. All treatment administered IV.

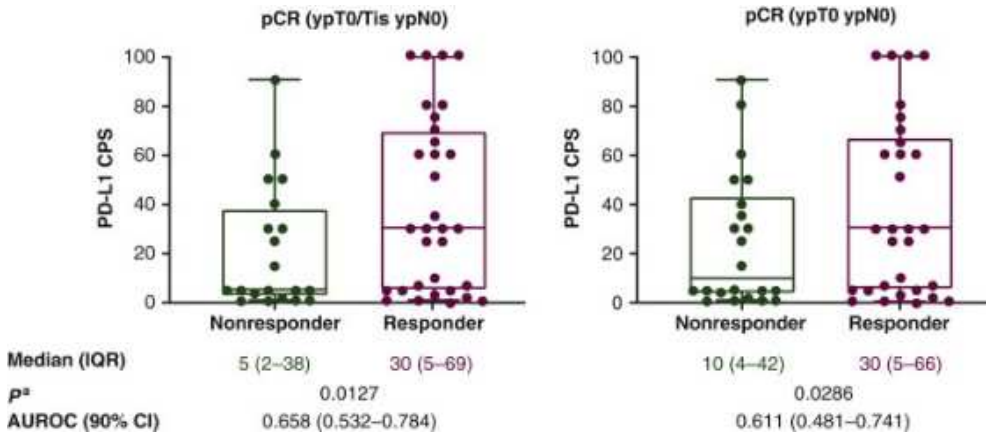
Schmid P et al. *Ann Oncol*. 2020;31(5):569–581.

Exploratory biomarker

pCR increased after regimen 2
(AC regimen, cycle 6-9)



PD-L1 CPS correlates with pCR

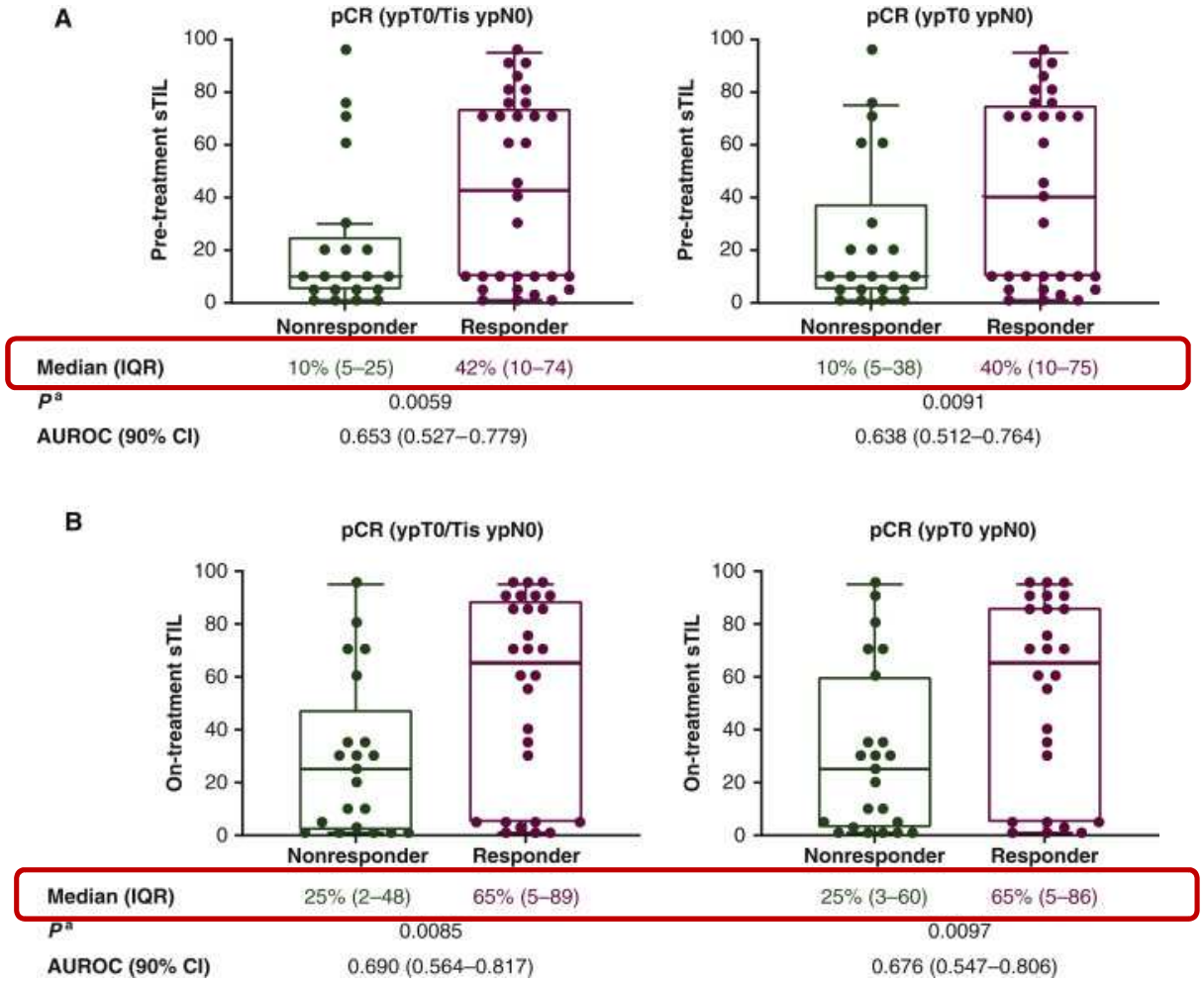


Schmid P et al. Ann Oncol. 2020;31(5):569–581

Stromal TILs are effectors/biomarkers

Pretreatment TILs

On-treatment TILs
(after 1 dose Pembro, at end of Cycle 1)



On-target effect of pembrolizumab

KEYNOTE-173 Safety
Grade ≥3 TRAEs

Two chemotherapy regimens met the RP2D threshold: nab-paclitaxel 125 mg/m^2 qw; paclitaxel 80 mg/m^2 qw + carboplatin AUC5 q3w.

n (%)	Cohort A Pembrolizumab + (Nab-pac→AC)[a] N=10	Cohort B Pembrolizumab + (Nab-pac + Carbo AUC 6→AC)[b] N=10	Cohort C Pembrolizumab + (Nab-pac + Carbo AUC 5→AC)[c] N=10	Cohort D Pembrolizumab + (Nab-pac + Carbo AUC 2→AC)[d] N=10	Cohort E Pembrolizumab + (Pac + Carbo AUC 5→AC)[e] N=10	Cohort F Pembrolizumab + (Pac + Carbo AUC 2→AC)[f] N=10	Total N=60
Any	8 (80)	10 (100)	9 (90)	10 (100)	7 (70)	10 (100)	54 (90)
Neutropenia	5 (50)	8 (80)	9 (90)	10 (100)	6 (60)	8 (80)	44 (73)
Febrile neutropenia	1 (10)	2 (20)	4 (40)	5 (50)	0	1 (10)	13 (22)
Anemia	0	1 (10)	3 (30)	3 (30)	2 (20)	3 (30)	12 (20)
Thrombocytopenia	0	2 (20)	0	2 (20)	0	1 (10)	5 (8)
Vomiting	1 (10)	1 (10)	1 (10)	0	1 (10)	0	4 (7)
WBC decreased	0	0	1 (10)	2 (20)	1 (10)	0	4 (7)
ALT increased	1 (10)	0	0	1 (10)	0	1 (10)	3 (5)
Fatigue	1 (10)	0	0	0	1 (10)	1 (10)	3 (5)
Nausea	3 (30)	0	0	0	0	0	3 (5)

Data cutoff date: 31 May 2018.
AC = Doxorubicin 60 mg/m^2 IV Day 1 Q3W + cyclophosphamide 600 mg/m^2 IV Day 1 Q3W.
Pembrolizumab dose = pembrolizumab 200 mg IV Q3W.

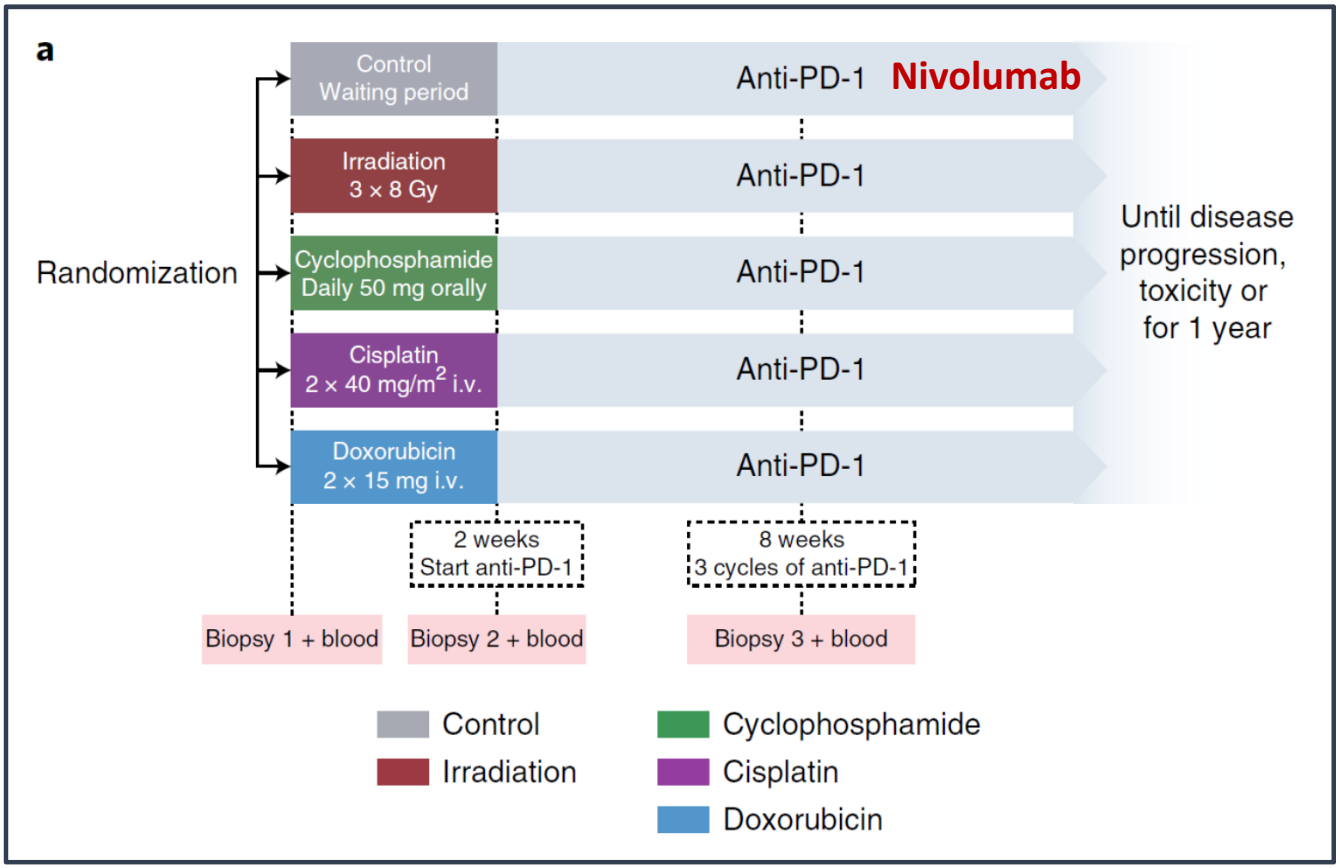
Cohort A: pembrolizumab + (Nab-paclitaxel 125 mg/m^2 IV Days 1, 8, 15 Q3W → AC); Cohort B: pembrolizumab + (Nab-paclitaxel 100 mg/m^2 IV Days 1, 8, 15 Q3W + Carboplatin starting at AUC 6 IV Day 1 Q3W → AC); Cohort C: pembrolizumab + (Nab-paclitaxel 125 mg/m^2 IV Days 1, 8, 15 Q3W + Carboplatin starting at AUC 5 IV Day 1 Q3W → AC); Cohort D: pembrolizumab + (Nab-paclitaxel 125 mg/m^2 IV Days 1, 8, 15 Q3W + Carboplatin starting at AUC 2 IV Days 1, 8, 15 Q3W → AC); Cohort E: pembrolizumab + (Paclitaxel 80 mg/m^2 IV Days 1, 8, 15 Q3W + Carboplatin starting at AUC 5 IV Day 1 Q3W → AC); Cohort F: pembrolizumab + (Paclitaxel 80 mg/m^2 IV Days 1, 8, 15 Q3W + Carboplatin starting at AUC 2 IV Days 1, 8, 15 Q3W → AC).

Schmid P et al. *Ann Oncol*. 2020;31(5):569–581 (Supplement).

Induction chemotherapy followed by ICI?
(immune induction by chemotherapy)

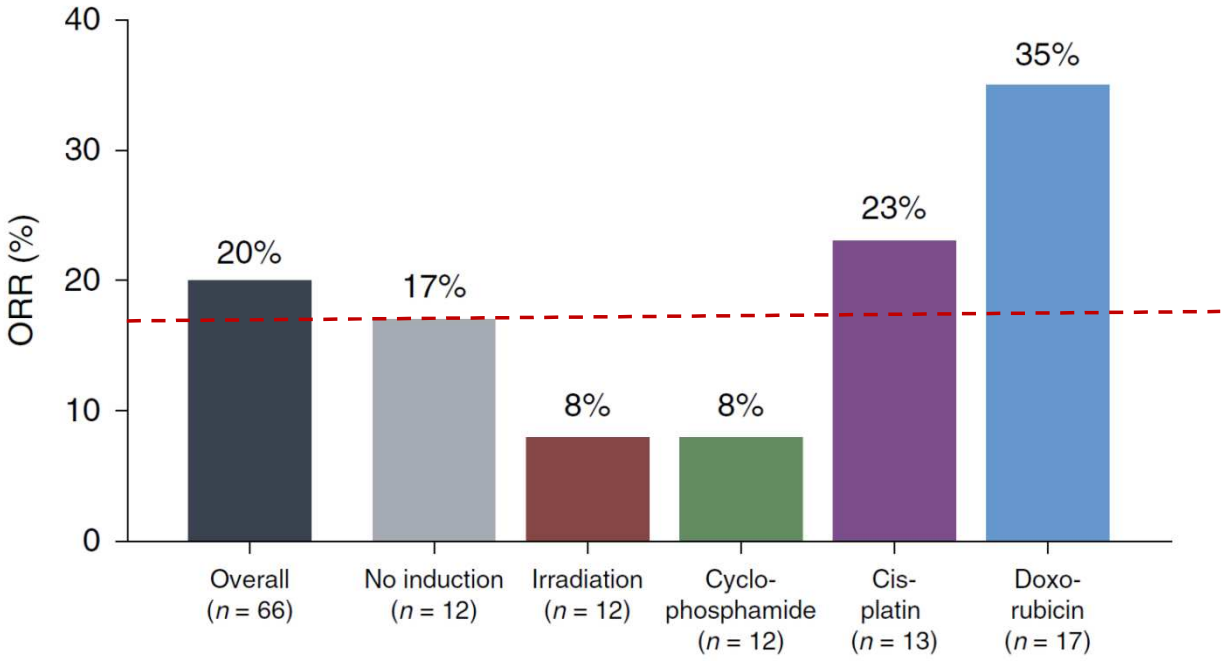
Median age, years (range)	**51 (29–70)**
Germline BRCA1/2 , n (%)	
Mutation	6 (9%)
Wild type	50 (71%)
Unknown	14 (20%)
Number of previous therapies for metastatic disease, n (%)	
0	17 (24%)
1	34 (49%)
2–3	19 (27%)
Previous chemotherapy exposure, n (%)	
Taxane	64 (91%)
Anthracycline	60 (86%)
Platinum	42 (60%)
Capecitabine	34 (49%)
PD-L1 expression on tumor cells, n (%) (DAKO 22C3 clone)	
Not available	**5 (7%)**
≥1% on tumor cells	**44 (63%)**
≥5% on tumor cells	**23 (33%)**

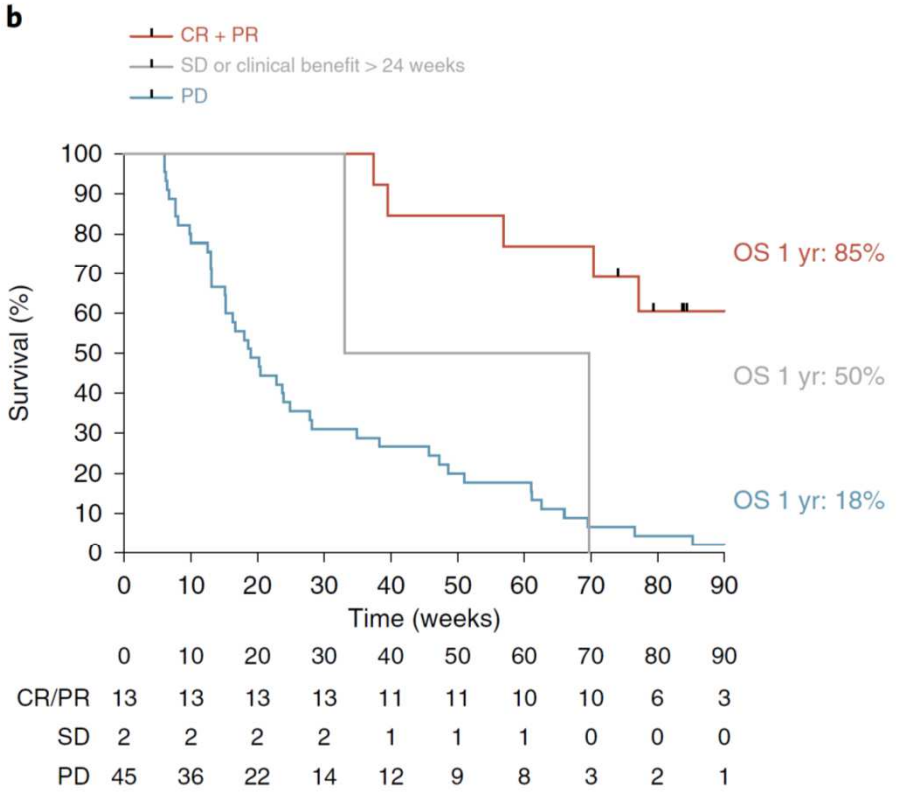
These are relatively low inflammable tumors



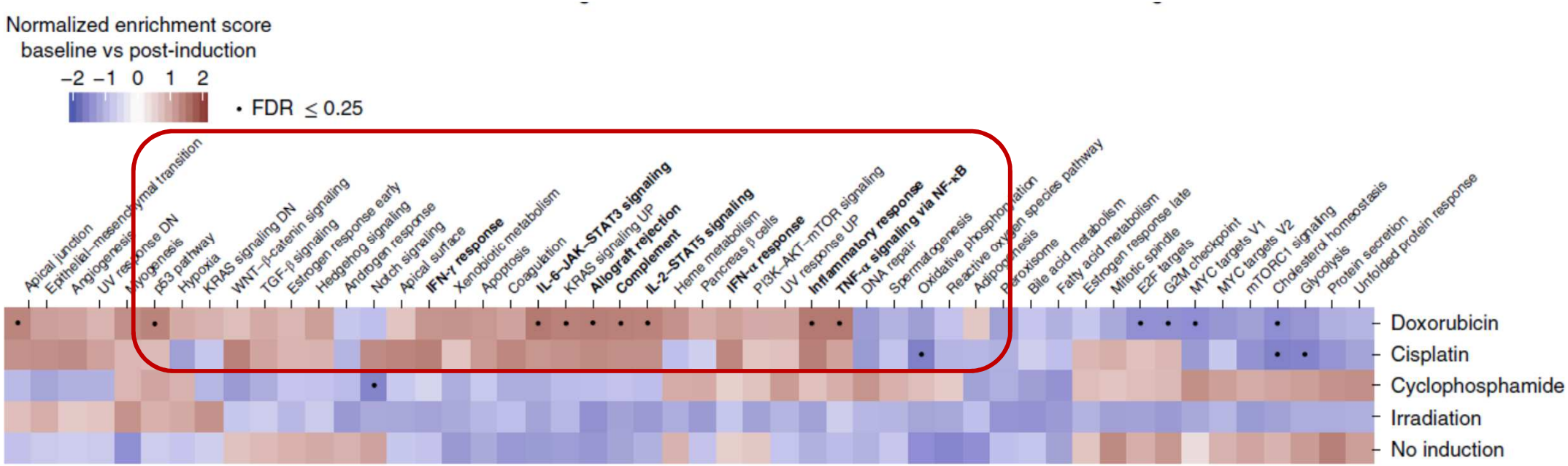
Nature Medicine vol 25, pages 920–928 (2019)

Short-term doxorubicin and cisplatin may increase the likelihood of response to PD-1 blockade in TNBC





Short-term doxorubicin and cisplatin may induce a more favorable tumor microenvironment



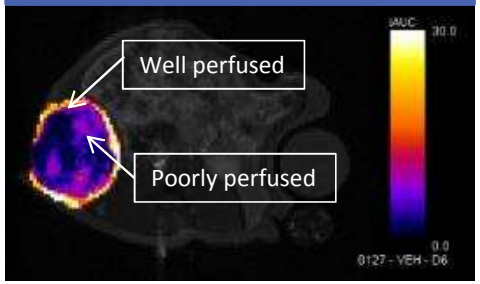
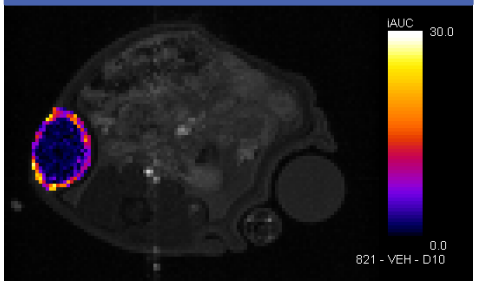
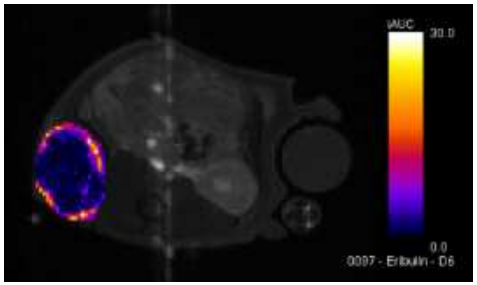
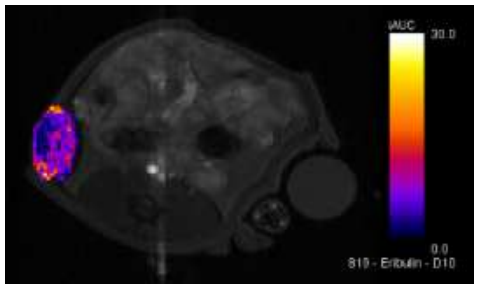
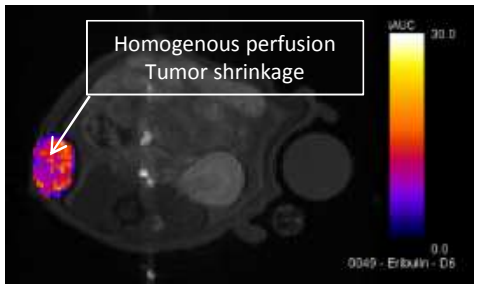
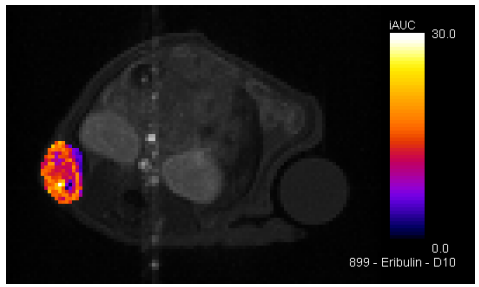
Eribulin's Mechanisms of Action

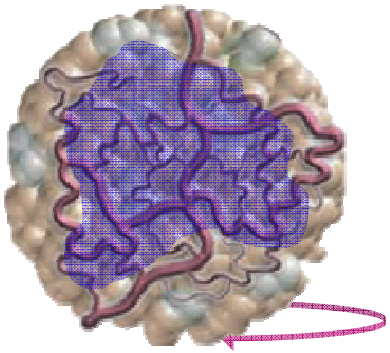
1. Tubulin-based Antimitotic Effects

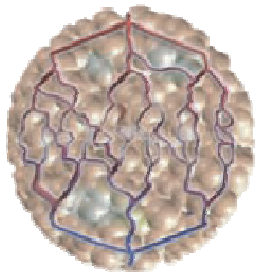
2. Complex Non-Mitotic Effects on Tumor Biology
   1. Reversal of Epithelial-Mesenchymal Transition (EMT)
   2. Tumor Vasculature Remodeling
   3. Decreased Capacity for Migration and Invasion

The Novel MOA of Eribulin :

Following Eribulin Treatment, Perfusion Becomes Uniform Throughout the Tumor Core and Rim

	MX-1 xenograft in nude rats (Day 6)	MDA-MB-231 xenograft in nude rats (Day 10)
Vehicle		
Eribulin mesylate 0.1 mg/kg		
Eribulin mesylate 0.3 mg/kg		





Funahashi Y, Okamoto K, et al. 2014.

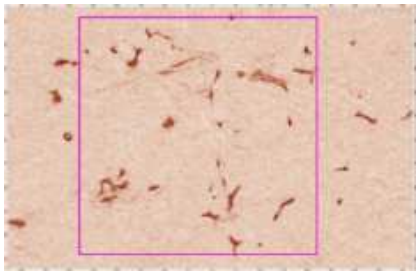
The Novel MOA of Eribulin :

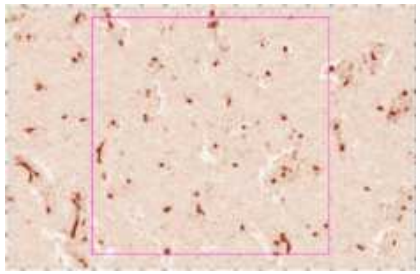
One Dose of Eribulin Induces Small Capillaries, Increases Perfusion and Eliminates Hypoxia

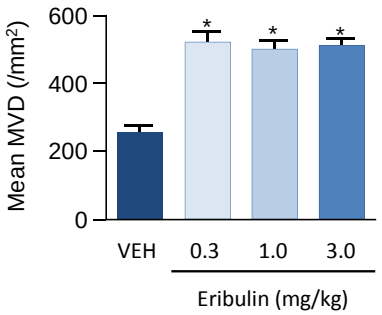
CD31 staining for endothelial cells

Vehicle

Eribulin, 3 mg/kg



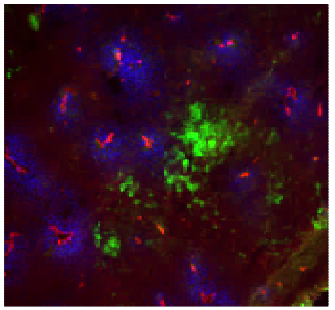


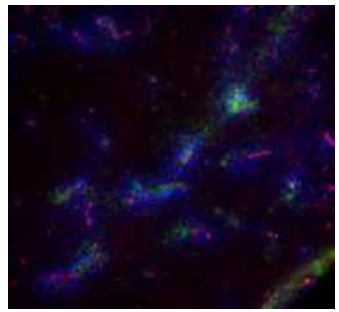


Staining for perfusion and hypoxia

Vehicle

Eribulin,1mg/kg





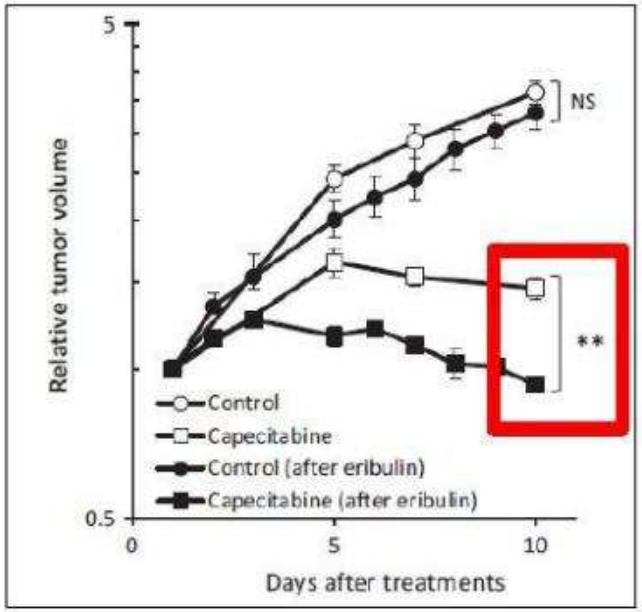
CD31:Endothelial cell marker
Hoechst: Perfusion marker
CA9:Hypoxia marker

MDA-MB-231 human breast cancer xenografts in nude mice

Funahashi et al., 2014

Enhanced Activity of Subsequently-Delivered Drugs
After Eribulin Treatment: Capecitabine

Human breast MDA-MB-231 tumor xenograft models in nude mice

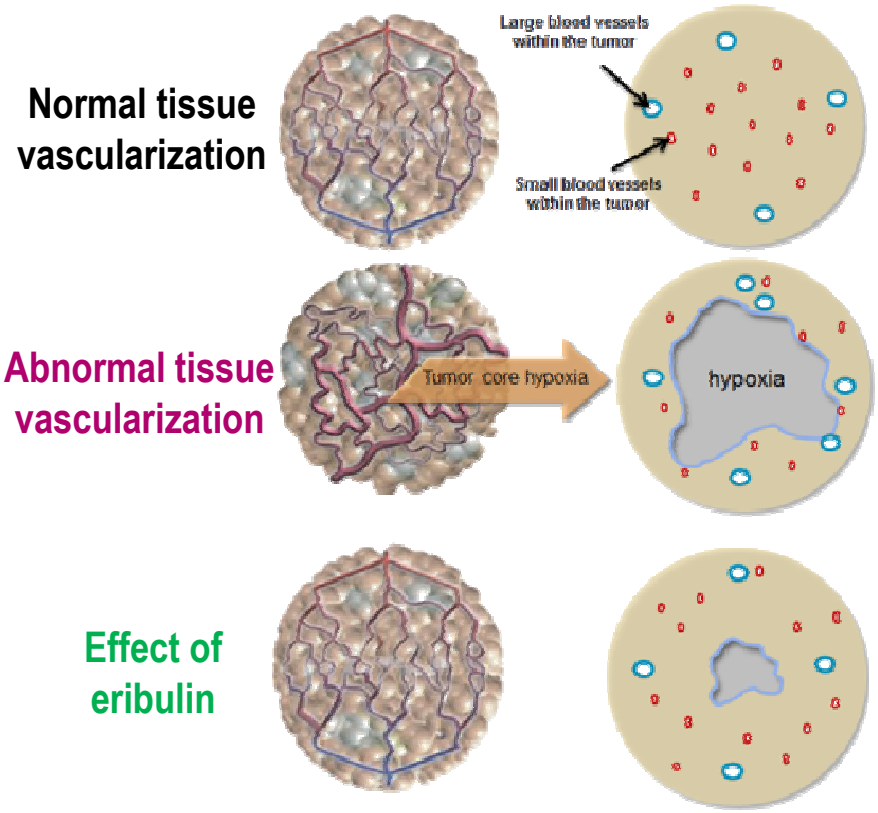


Funahashi et al., 2014

The Novel MOA of Eribulin :

Eribulin May Decrease Tumor Size and Inhibit Further Metastasis by Inducing Changes in Tumor Vasculature

Internal tumor environment



Poor tumor perfusion with hypoxia

Abnormal vascular network

- ▶ Dysfunctional blood vessels
- ▶ Poor perfusion
- ▶ Poor drug delivery

Large hypoxic region

Potential for metastasis

Eribulin-induced vascular remodeling

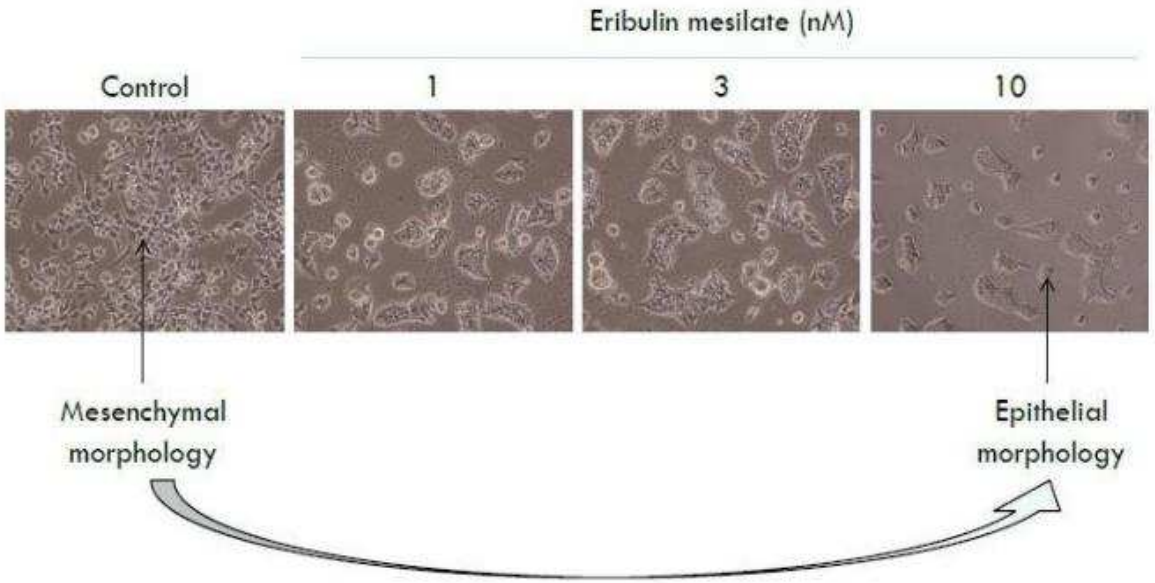
- ▶ Small vessels ↑
- ▶ Perfusion ↑
- ▶ Drug delivery ↑

Hypoxic region ↓

Tumor volume ↓

Metastasis ↓

Eribulin Induces Epithelial Morphology in Surviving Breast Cancer Cells *In Vitro*



MX-1 human breast cancer cells, 1 week treatment

Yoshida et al., AACR-NCI-EORTC meeting, 2013

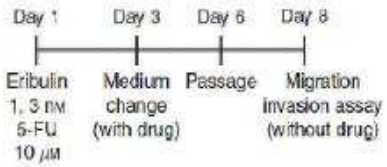
Eribulin Causes Reversal of EMT: mRNA Expression

mRNA levels in MX-1, MDA-MB-157, and Hs578T human breast cancer cells *in vitro* (1-3 nM, 7 days)

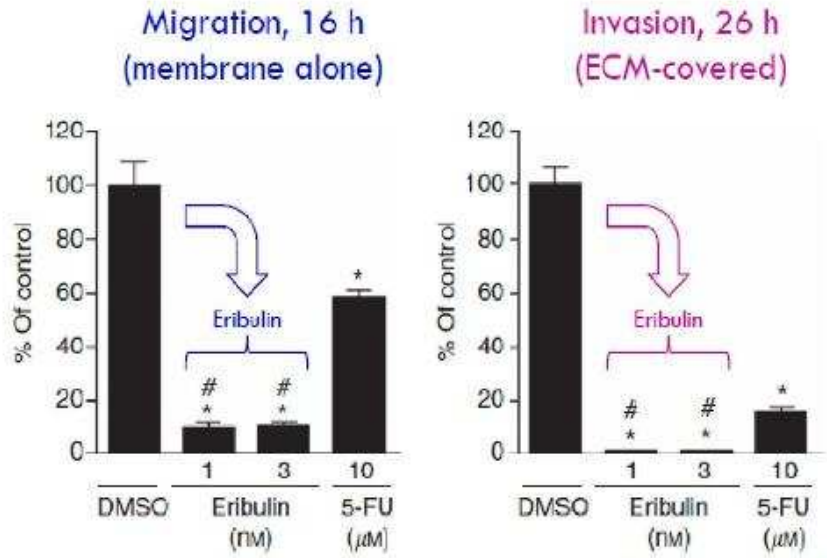
Human EMT/MET Genes		Upregulated (↑) or downregulated (↓) by eribulin
Epithelial markers	CDH1	↑
	KRT18	↑
Mesenchymal markers	CDH2*	↓
	SNAI2	↓
	TWIST1	↓
	VIM*	↓
	ZEB1*	↓
	ZEB2	↓

* No effect of eribulin on CDH2, VIM, and ZEB1 in MDA-MB-157 cells

Eribulin Decreases In Vitro Migration and Invasion

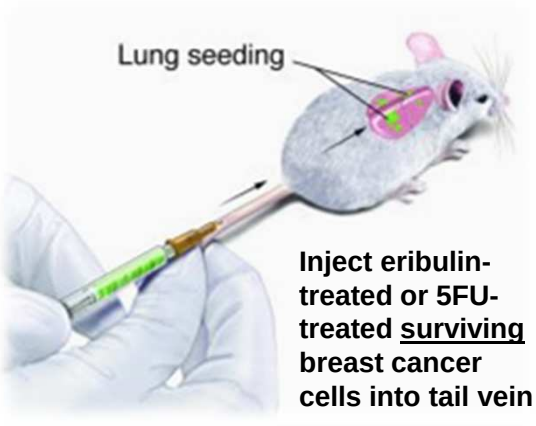


MX-1 human breast cancer cells *in vitro*



Yoshida et al., 2014

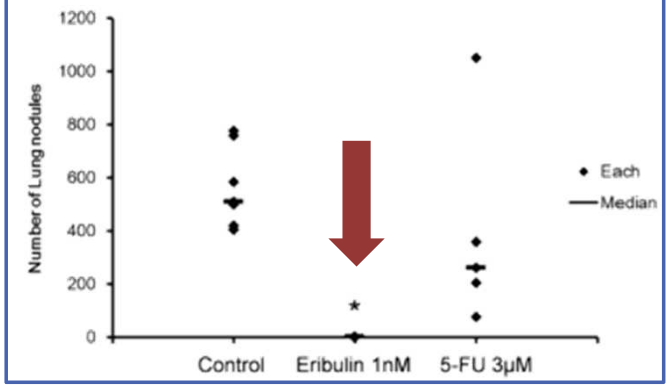
Eribulin Suppresses Experimental Metastasis In Vivo



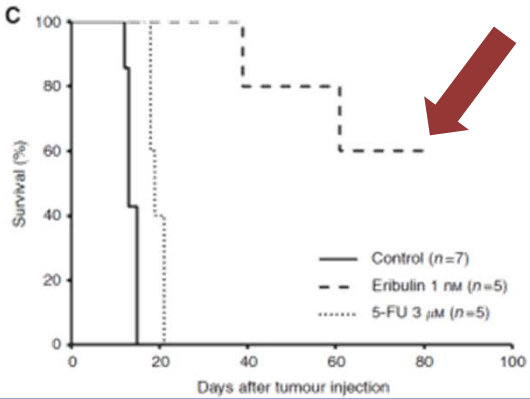
Inject eribulin-treated or 5FU-treated <u>surviving</u> breast cancer cells into tail vein

Representative lung images (Day15)

Number of lung nodules

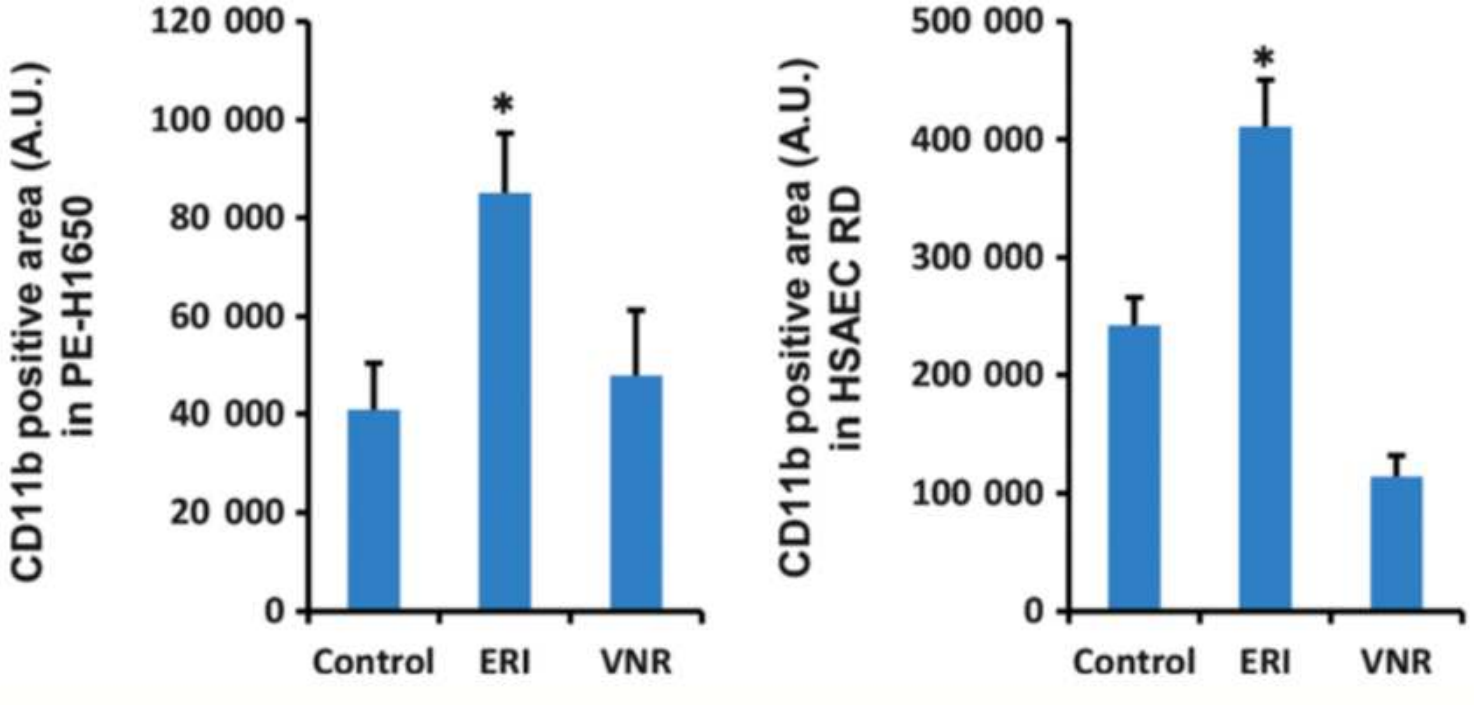


Survival of mice



Yoshida et al., 2014

Modulation of TME by eribulin



CD11b is immune activating marker*

Ito et al, Cancer Science 2017
Nature Communications* **v9: 5379 (2018)

Eribulin-responsive tumors showed improved anti-tumor immune response

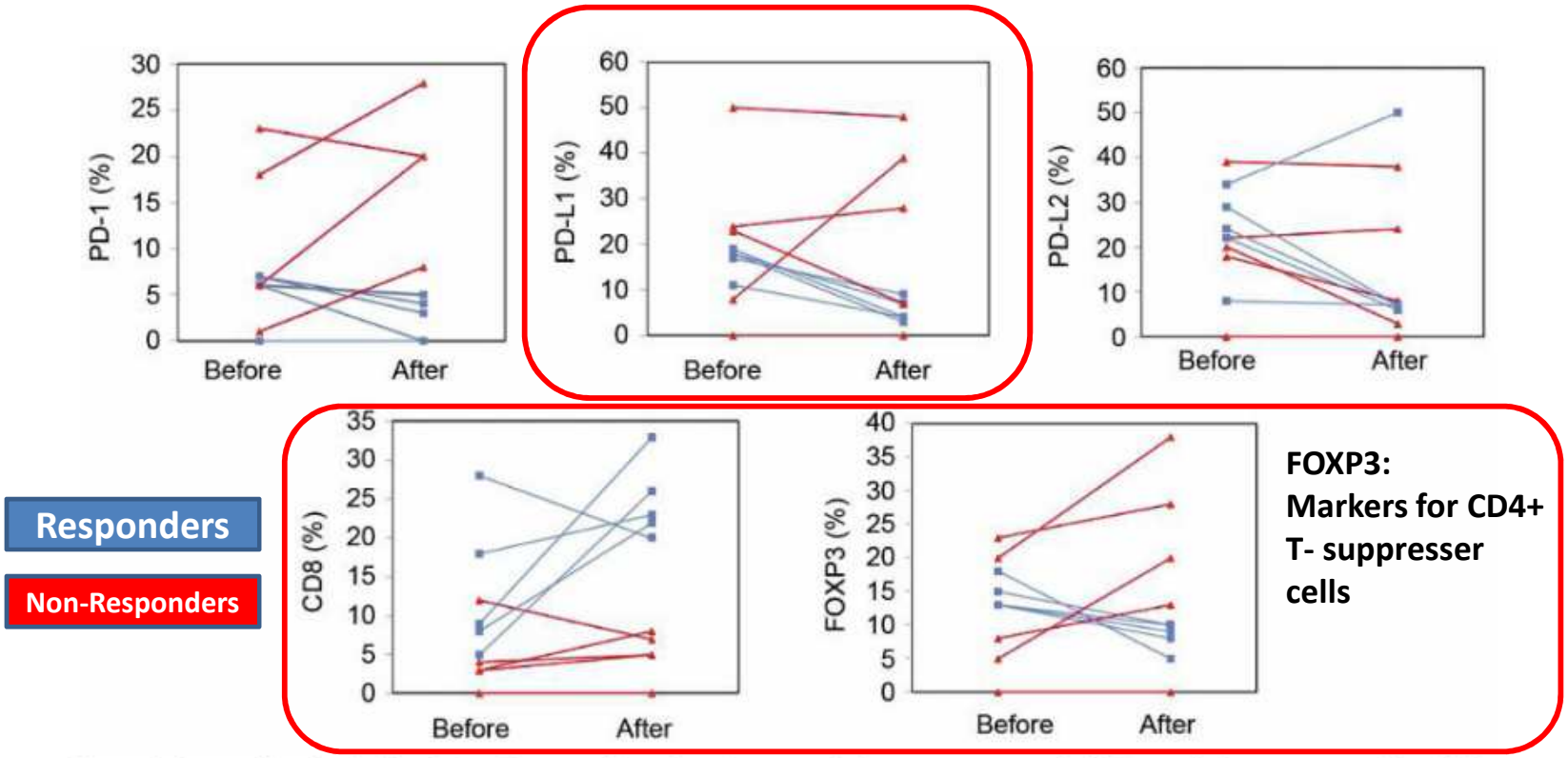


Figure 2. *Immunohistochemical analysis of immune biomarkers in metastatic breast cancer samples before and after treatment with eribulin (evaluable patients, n=10). % refers to the percentage of positive cells. The blue squares/lines show the results for responders and the red triangles/lines show the results for non-responders. PD-1: Programmed death 1; PD-L: programmed death ligand; FOXP3: forkhead box P3.*

Goto W et al. Anticancer Res. 2018; 38(5):2929-2938.

Eribulin unique non-mitotic effects Summary (vs anti-mitotic comparators)

Effects	Taxane	Vinorelbine	Eribulin
Anti-angiogenesis	Yes, metronomic	Yes, metronomic	Yes, at therapeutic dose
Anti-tumor immunity	Docetaxel more prominent than Paclitaxel in peripheral immunomodulating effects.	Complex; Vinorelbine < Eribulin in terms of intra-tumor CD11b(+) cells	Yes, enhanced CD11b(+) immune cells infiltrates & overall improved anti-tumor immunity
Anti-EMT	Unclear; EMT phenotype is associated with taxane-resistant	No, may induce EMT through endoreticulum stress	Yes, reversal of EMT, and suppresses migration/invasion in vitro/in vivo

Eribulin in combination with I/O in triple negative breast cancer

Abstract No. 1015

A Phase 1b/2 Study of Eribulin Plus Pembrolizumab in Metastatic Triple-Negative Breast Cancer (ENHANCE 1)

Sara M. Tolaney[1], Kevin Kalinsky[2], Virginia G. Kaklamani[3], David R. D'Adamo[4], Gursel Aktan[5], Michaela L. Tsai[6], Ruth M. O'Regan[7], Peter A. Kaufman[8], Sharon T. Wilks[9], Eleni Andreopoulou[10], Debra A. Patt[11], Yuan Yuan[12], Grace Wang[13], Dongyuan Xing[4], Ella Kleynerman[4], Vassiliki Karantza[5], Sami Diab[14]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Columbia University Irving Medical Center, New York, NY, USA; [3]University of Texas Health Science Center, San Antonio, TX, USA; [4]Eisai Inc., Woodcliff Lake, NJ, USA; [5]Merck & Co., Inc., Kenilworth, NJ, USA; [6]Minnesota Oncology Hematology, Minneapolis, MN, USA; [7]University of Wisconsin Carbone Cancer Center, Madison, WI, USA; [8]University of Vermont Medical Center, the UVM Cancer Center, and the Larner College of Medicine at the University of Vermont, Burlington, VT, USA; [9]Texas Oncology, San Antonio, TX, USA; [10]Weill Cornell Medicine, New York, NY, USA; [11]Texas Oncology, Austin, TX, USA; [12]City of Hope National Medical Center, Duarte, CA, USA; [13]Miami Cancer Institute-Baptist Health South Florida, Miami, FL, USA; [14]Rocky Mountain Cancer Centers, Aurora, CO, USA

Poster presented at the: American Society of Clinical Oncology annual meeting; May 29-31, 2020; virtual format

ASCO: 2020

Paper: 2021

Published OnlineFirst March 16, 2021; DOI: 10.1158/1078-0432.CCR-20-4726

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: IMMUNOTHERAPY

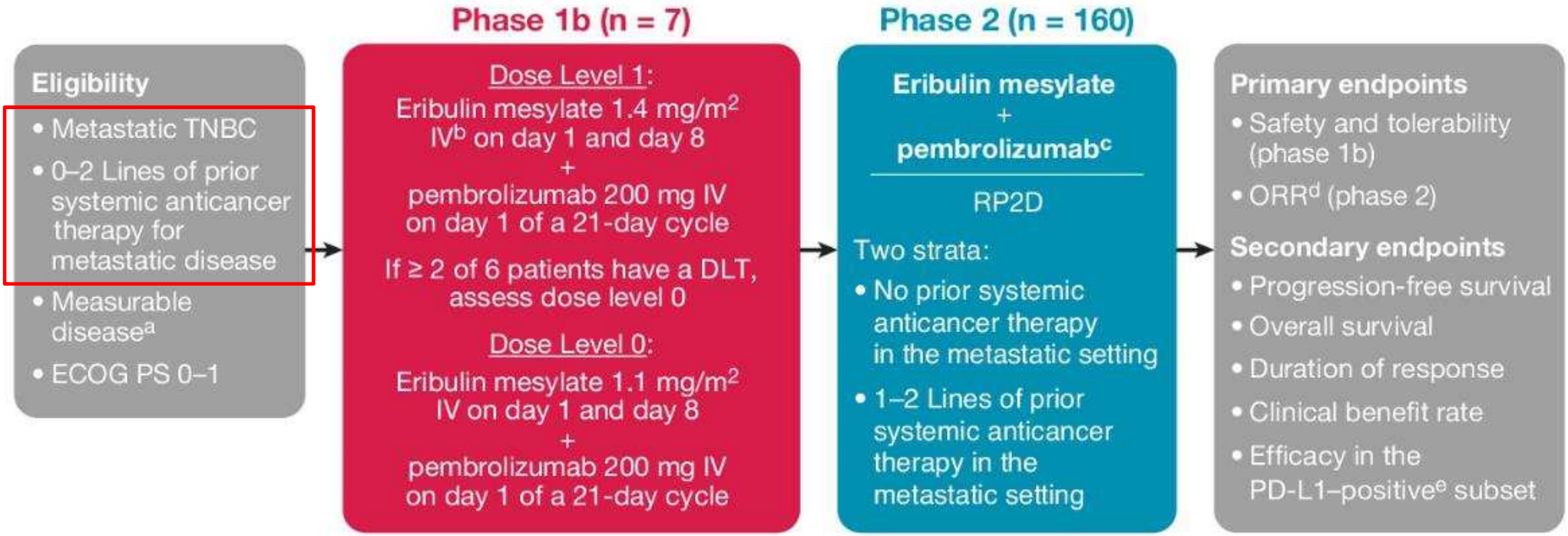
Eribulin Plus Pembrolizumab in Patients with Metastatic Triple-Negative Breast Cancer (ENHANCE 1): A Phase Ib/II Study AC

Sara M. Tolaney[1], Kevin Kalinsky[2], Virginia G. Kaklamani[3], David R. D'Adamo[4], Gursel Aktan[5], Michaela L. Tsai[6], Ruth M. O'Regan[7], Peter A. Kaufman[8], Sharon T. Wilks[9], Eleni Andreopoulou[10], Debra A. Patt[11], Yuan Yuan[12], Grace Wang[13], Claudio Savulsky[4], Dongyuan Xing[14], Ella Kleynerman[4], Vassiliki Karantza[5], and Sami Diab[15]

Tolaney, S. M., et al., (2021). Clin Cancer Res.; DOI: 10.1158/1078-0432.CCR-20-4726

Study design

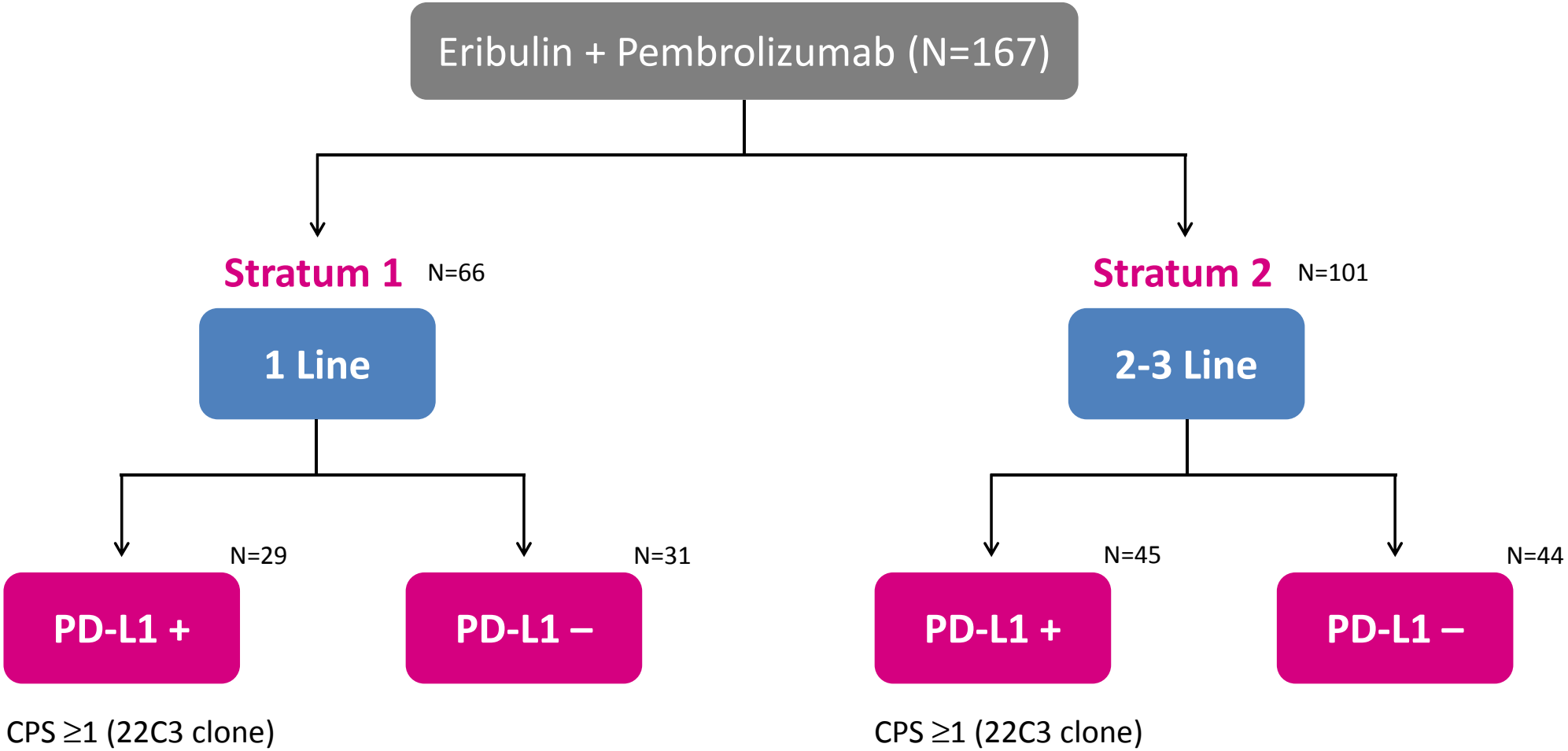
Open-label, single arm, Phase 1b/2 study



DLT: dose-limiting toxicity
RP2D: recommended phase 2 dose

Tolaney, S. M., et al., (2021). Clin Cancer Res.; DOI: 10.1158/1078-0432.CCR-20-4726

Study design: patient disposition



Tolaney, S. M., et al., (2021). Clin Cancer Res.; DOI: 10.1158/1078-0432.CCR-20-4726

Patient baseline characteristics

Table 1. Baseline Characteristics

Parameter	Eribulin Plus Pembrolizumab (N = 167)		
	Phase 1b (n = 7)	Phase 2 (n = 160)	Total (N = 167)
Median age, years (range)	54 (44–65)	56 (32–88)	56 (32–88)
Sex, female, n (%)	7 (100)	160 (100)	167 (100)
Race, n (%)			
White	7 (100)	134 (83.8)	141 (84.4)
Black or African American	0	19 (11.9)	19 (11.4)
Asian	0	1 (0.6)	1 (0.6)
Other	0	6 (3.8)	6 (3.6)
ECOG PS, n (%)			
0	4 (57.1)	102 (63.8)	106 (63.5)
1	3 (42.9)	57 (35.6)	60 (35.9)
2	0	1 (0.6)	1 (0.6)
PD-L1–expression status[a], n (%)			
Negative	2 (28.6)	73 (45.6)	75 (44.9)
Positive	3 (42.9)	71 (44.4)	74 (44.3)
Not available	2 (28.6)	16 (10.0)	18 (10.8)
Phase 2 enrollment strata, n (%)			
Stratum 1[b]	3 (42.9)	63 (39.4)	66 (39.5)
Stratum 2[c]	4 (57.1)	97 (60.6)	101 (60.5)

[a]PD-L1 status is positive if CPS ≥ 1 and negative if CPS < 1. [b]No prior systemic anticancer therapy for metastatic disease. [c]1–2 Prior systemic anticancer therapies for metastatic disease.

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death-ligand 1.

Tolaney, S. M., et al., (2021). Clin Cancer Res.; DOI: 10.1158/1078-0432.CCR-20-4726

Tumor responses overall, and by prior systemic anticancer therapy strata

	mPFS	mOS	ORR (%)	mDOR (mo)
Overall	4.1	16.1	23.4	8.3

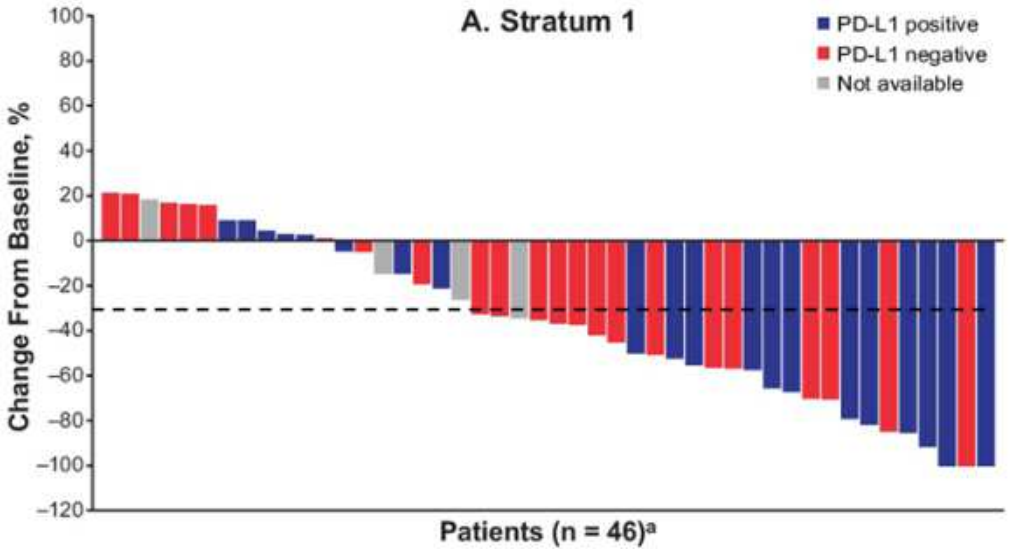
		mPFS	mOS	ORR (%)	mDOR (mo)
1 L	**Stratum 1**	4.2	17.4	25.8	9.0
2-3 L	**Stratum 2**	4.1	15.5	21.8	8.6

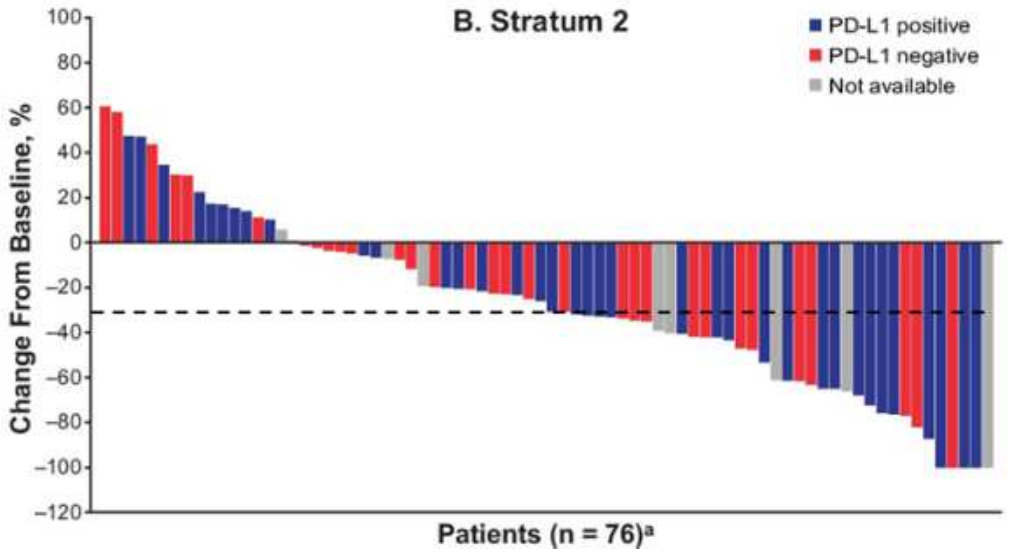
DOR: duration of response

Tolaney, S. M., et al., (2021). Clin Cancer Res.; DOI: 10.1158/1078-0432.CCR-20-4726

Most patients showed a decrease in target lesion size

	mPFS	mOS	ORR (%)
PD-L1 +	4.2	16.3	28.4
PD-L1 –	3.9	15.2	17.3





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Tumor responses stratified by both prior systemic anticancer therapy strata and PD-L1–expression status

	1 L		2-3 L	
Eribulin + pembrolizumab (*n* = 149)[a]	**PD-L1^{+} Stratum 1 (*n* = 29)**	**PD-L1^{-} Stratum 1 (*n* = 31)**	**PD-L1^{+} Stratum 2 (*n* = 45)**	**PD-L1^{-} Stratum 2 (*n* = 44)**
ORR[b], %	34.5	16.1	24.4	18.2
95% CI[b]	17.9–54.3	5.5–33.7	12.9–39.5	8.2–32.7
mOS[c], months	21.0	15.2	14.0	15.5
95% CI	8.3–29.0	12.8–19.4	11.0–19.4	12.4–18.7
mPFS[c], months	6.1	3.5	4.1	3.9
95% CI	4.1–10.2	2.0–4.2	2.1–4.8	2.3–6.3
mDOR[c,d] months	8.3	15.2	8.2	8.6
95% CI	3.2–NE	6.5–22.2	5.1–25.1	3.5–13.2

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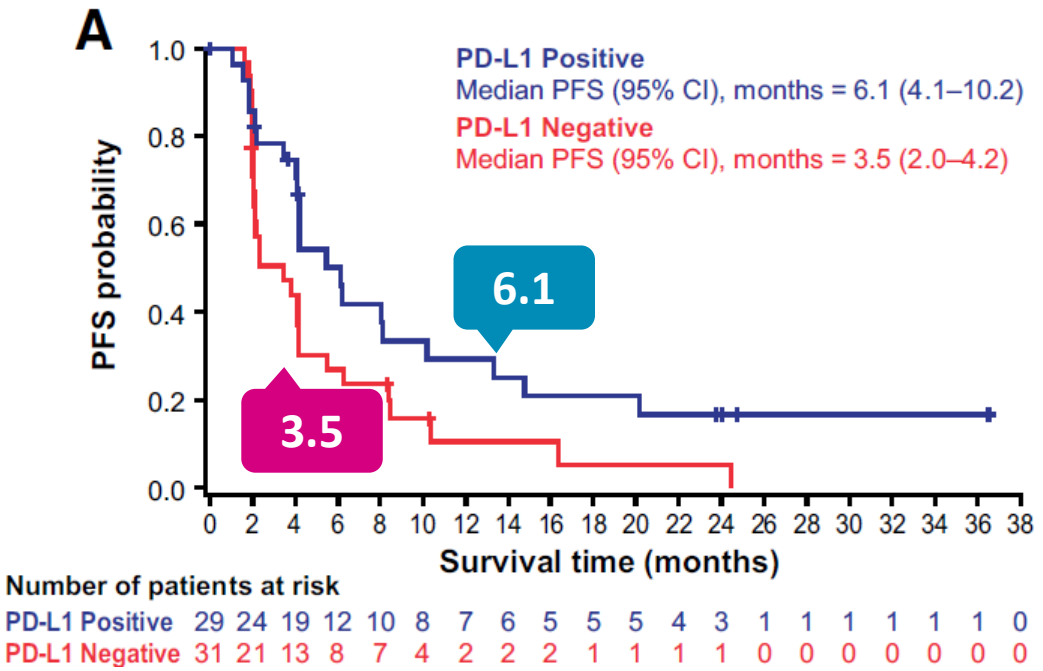
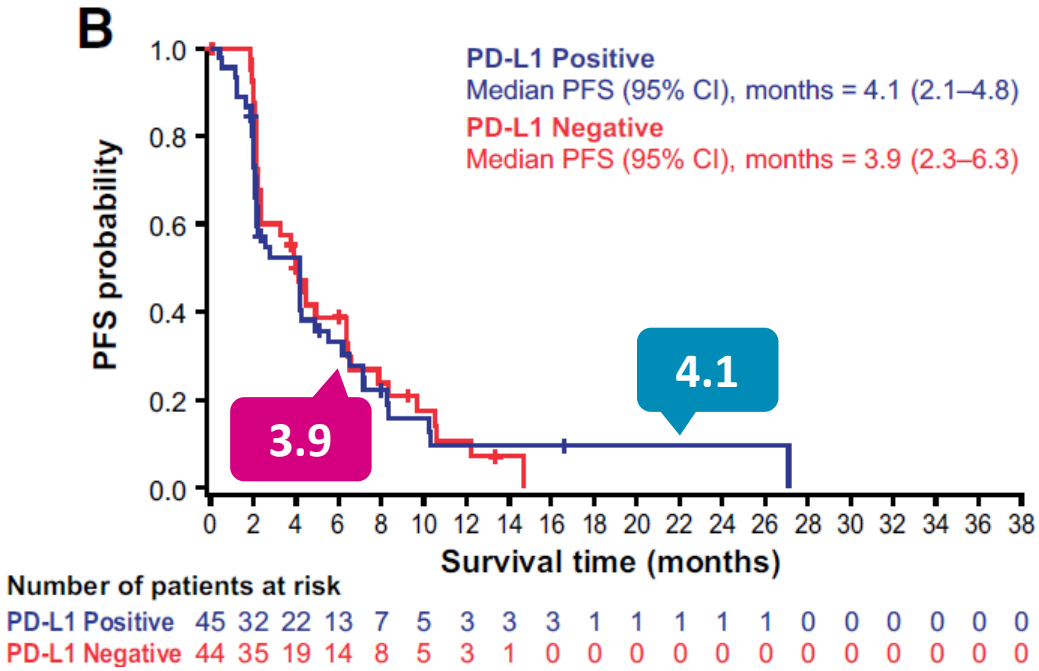
mPFS in stratum1 and stratum 2

Stratum 1 **1 Line**



Stratum 2 **2-3 Line**



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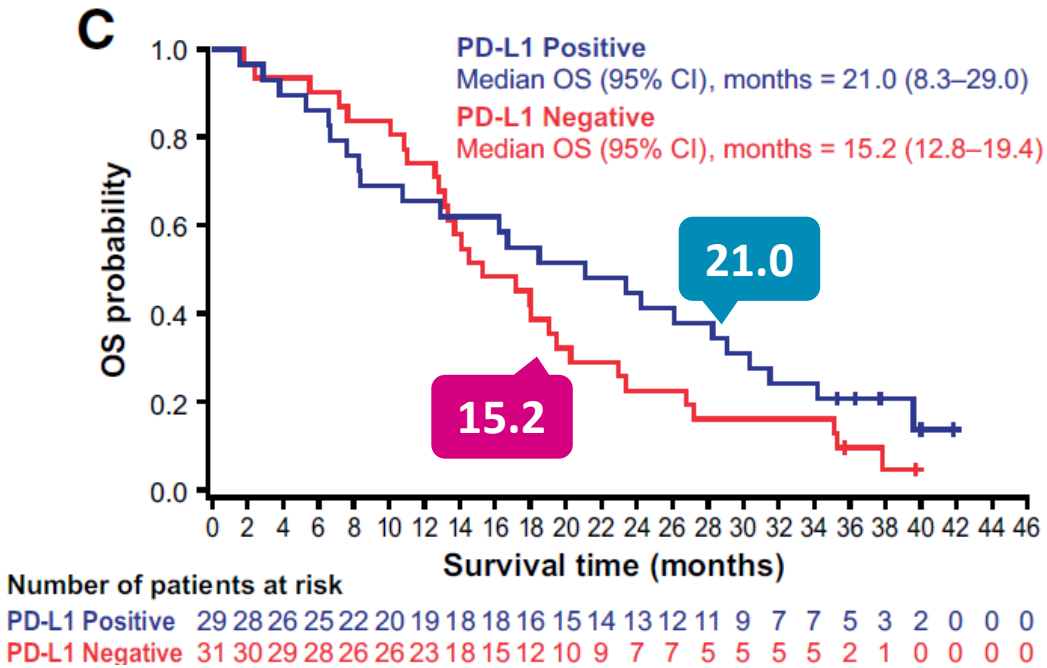
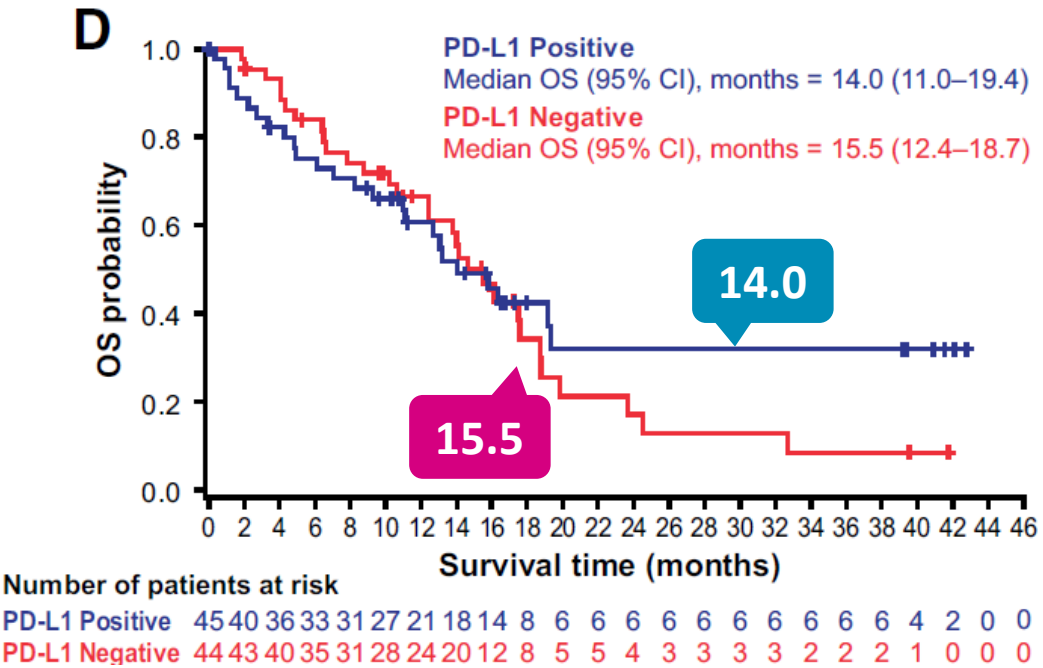
mOS in stratum1 and stratum 2

Stratum 1 **1 Line**



Stratum 2 **2-3 Line**



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Summary of TEAEs that occurred in ≥ 10% of patients

Table 2. Summary of TEAEs that occurred in ≥ 10% of patients.

Preferred term, *n* (%)	Eribulin + pembrolizumab (*N* = 167)	
	Any grade	Grade 3 or 4
Fatigue	110 (65.9)	12 (7.2)
Nausea	96 (57.5)	4 (2.4)
Peripheral sensory neuropathy	69 (41.3)	12 (7.2)
Alopecia	66 (39.5)	0
Constipation	61 (36.5)	2 (1.2)
Neutropenia	60 (35.9)	44 (26.3)
Cough	54 (32.3)	0
Pyrexia	53 (31.7)	1 (0.6)
Decreased appetite	52 (31.1)	3 (1.8)
Diarrhea	51 (30.5)	6 (3.6)
Anemia	47 (28.1)	10 (6.0)
Arthralgia	46 (27.5)	2 (1.2)
Vomiting	45 (26.9)	3 (1.8)
Weight decreased	41 (24.6)	3 (1.8)
Headache	41 (24.6)	0
Dyspnea	41 (24.6)	5 (3.0)
Stomatitis	32 (19.2)	4 (2.4)
Rash	31 (18.6)	2 (1.2)
Hypothyroidism	30 (18.0)	0
Aspartate aminotransferase increased	30 (18.0)	6 (3.6)
Dehydration	28 (16.8)	2 (1.2)
Hypokalemia	28 (16.8)	9 (5.4)
Urinary tract infection	27 (16.2)	0
Dizziness	27 (16.2)	0

Preferred term, *n* (%)	Eribulin + pembrolizumab (*N* = 167)	
	Any grade	Grade 3 or 4
Dry mouth	26 (15.6)	0
Alanine aminotransferase increased	26 (15.6)	4 (2.4)
Pain in extremity	25 (15.0)	4 (2.4)
Abdominal pain	24 (14.4)	2 (1.2)
Back pain	24 (14.4)	4 (2.4)
Insomnia	22 (13.2)	0
Dyspepsia	21 (12.6)	0
Neutrophil count decreased	21 (12.6)	13 (7.8)
Pruritus	21 (12.6)	1 (0.6)
Hot flush	21 (12.6)	0
Musculoskeletal pain	20 (12.0)	1 (0.6)
Myalgia	20 (12.0)	2 (1.2)
White blood cell count decreased	19 (11.4)	9 (5.4)
Chills	18 (10.8)	0
Hyponatremia	18 (10.8)	9 (5.4)
Nasal congestion	18 (10.8)	0
Pneumonitis	18 (10.8)	4 (2.4)
Rash maculopapular	18 (10.8)	3 (1.8)
Hypomagnesemia	17 (10.2)	0
Upper respiratory tract infection	16 (9.6)	0

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Treatment-emergent adverse events (TEAE)

TEAEs	Eribulin + Pembro
Fatigue (%)	65.9
Nausea (%)	57.5
PN-sensory (%)	41.3
Alopecia (%)	39.5
Constipation (%)	36.5

Immuno-related TEAEs	For Pembro
Hypothyroidism (%)	18 .0
Pneumonitis (%)	10.8
Hyperthyroidism (%)	7.8
Infusion-related reaction (%)	3.0

No dose-limiting toxicities observed

No deaths were considered treatment related

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Efficacy outcomes: prior systemic anticancer therapy and tumor PD-L1-expression status using a CPS cutoff of 1 or 10

Parameter	Eribulin + Pembrolizumab, Stratum 1 (n = 66)			
Stratum 1 (1 L)	n = 60[a]		n = 60[a]	
	PD-L1+	PD-L1−	PD-L1+	PD-L1−
	CPS ≥ 1 (n = 29)	CPS < 1 (n = 31)	CPS ≥ 10 (n = 13)	CPS < 10 (n = 47)
ORR[b,c], n (%) 95% CI	10 (34.5) 17.9–54.3	5 (16.1) 5.5–33.7	4 (30.8) 9.1–61.4	11 (23.4) 12.3–38.0
CR, n (%)	4 (13.8)	0	2 (15.4)	2 (4.3)
PR, n (%)	6 (20.7)	5 (16.1)	2 (15.4)	9 (19.1)
CBR[d], n (%) 95% CI	14 (48.3) 29.4–67.5	8 (25.8) 11.9–44.6	6 (46.2) 19.2–74.9	16 (34.0) 20.9–49.3
mDOR[e,f], months 95% CI	8.3 3.2–NE	15.2 6.5–22.2	NE 4.2–NE	8.1 3.2–22.2
mPFS[e], months 95% CI	6.1 4.1–10.2	3.5 2.0–4.2	6.1 3.5–14.8	4.1 2.1–5.5
mOS[e], months 95% CI	21.0 8.3–29.0	15.2 12.8–19.4	21.0 7.6–39.6	17.1 13.3–20.2
mFollow-up, months 95% CI	38.9 35.3–41.9	39.8 35.7–39.8	38.2 35.3–40.0	39.8 35.7–41.9

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Efficacy outcomes: prior systemic anticancer therapy and tumor PD-L1-expression status using a CPS cutoff of 1 or 10

Parameter **Stratum 2 (2-3 L)**	Eribulin + Pembrolizumab, Stratum 2 (n = 101)			
	n = 89[a]		n = 89[a]	
	PD-L1+	PD-L1−	PD-L1+	PD-L1−
	CPS ≥ 1 (n = 45)	CPS < 1 (n = 44)	CPS ≥ 10 (n = 21)	CPS < 10 (n = 68)
ORR[b,c], n (%) **95% CI[d]**	11 (24.4) 12.9–39.5	8 (18.2) 8.2–32.7	5 (23.8) 8.2–47.2	14 (20.6) 11.7–32.1
CR, n (%)	2 (4.4)	0	0	2 (2.9)
PR, n (%)	9 (20.0)	8 (18.2)	5 (23.8)	12 (17.6)
CBR[d], n (%) **95% CI**	13 (28.9) 16.4–44.3	13 (29.5) 16.8–45.2	6 (28.6) 11.3–52.2	20 (29.4) 19.0–41.7
mDOR[e,f], months **95% CI**	8.2 5.1–25.1	8.6 3.5–13.2	7.2 5.1–NE	8.3 4.3–25.1
mPFS[e], months **95% CI**	4.1 2.1–4.8	3.9 2.3–6.3	4.2 2.1–6.1	3.9 2.2–4.9
mOS[e], months **95% CI**	14.0 11.0–19.4	15.5 12.4–18.7	19.4 8.2–NE	14.1 11.1–17.5
mFollow-up, months **95% CI**	17.3 15.7–39.4	39.6 15.4–41.8	17.3 11.3–41.6	18.0 15.9–40.9

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Summary

- Eribulin + pembrolizumab was generally well tolerated and showed promising antitumor activity in mTNBC
- While the activity appeared enhanced in patients with PD-L1+ tumors, this combination also demonstrated promising antitumor activity in PD-L1(-) tumors
- These results support further clinical development of eribulin plus pembrolizumab as a potential antitumor strategy for patients with mTNBC

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Thank you !


For Discussion

Backup slides

Summary of tumor responses overall, and by prior systemic anticancer therapy strata

Parameter	1 L Stratum 1 (*n* = 66)	2-3 L Stratum 2 (*n* = 101)	Total (*N* = 167)
ORR[a], *n* (%)	17 (25.8)	22 (21.8)	39 (23.4)
95% CI[b]	15.8–38.0	14.2–31.1	17.2–30.5
CR, *n* (%)	5 (7.6)	3 (3.0)	8 (4.8)
PR, *n* (%)	12 (18.2)	19 (18.8)	31 (18.6)
SD, *n* (%)	24 (36.4)	29 (28.7)	53 (31.7)
mOS, months	17.4	15.5	16.1
95% CI[c]	13.2–21.0	12.5–18.7	13.3–18.5
mPFS, months	4.2	4.1	4.1
95% CI[c]	3.5–5.5	2.3–4.4	3.5–4.2
mDOR[c,d], months	9.0	8.6	8.3
95% CI	6.2–22.2	6.2–25.1	6.5–22.2

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Summary of efficacy outcomes

	mPFS	mOS	ORR (%)	mDOR (mo)
Overall	4.1	16.1	23.4	8.3

Table 2. Efficacy Outcomes by Prior Lines of Systemic Anticancer Therapy (Stratum) and PD-L1 Tumor-Expression Status as Assessed by IIR and RECIST v1.1

	Eribulin Plus Pembrolizumab (N = 167)			
Outcome	**Stratum 1 (n = 66)[a]**		**Stratum 2 (n = 101)[b]**	
ORR, n (%) (95% CI)[c]	17 (25.8) (15.8–38.0)		22 (21.8) (14.2–31.1)	
	(n = 149)[d]			
	Stratum 1 PD-L1 Positive (n = 29)	**Stratum 1 PD-L1 Negative (n = 31)**	**Stratum 2 PD-L1 Positive (n = 45)**	**Stratum 2 PD-L1 Negative (n = 44)**
ORR, n (%) (95% CI)[c]	10 (34.5) (17.9–54.3)	5 (16.1) (5.5–33.7)	11 (24.4) (12.9–39.5)	8 (18.2) (8.2–32.7)
mPFS, months (95% CI)[e]	4.2 (3.5–5.5)		4.1 (2.3–4.4)	
	6.1 (4.1–10.2)	3.5 (2.0–4.2)	4.1 (2.1–4.8)	3.9 (2.3–6.3)
mOS, months (95% CI)[e]	17.4 (13.2–21.0)		15.5 (12.5–18.7)	
	21.0 (8.3–29.0)	15.2 (12.8–19.4)	14.0 (11.0–19.4)	15.5 (12.4–18.7)
mDOR[f], months (95% CI)[e]	9.0 (6.2–22.2)		8.6 (6.2–25.1)	
	8.3 (3.2–NE)	15.2 (6.5–22.2)	8.2 (5.1–25.1)	8.6 (3.5–13.2)

1 L

2-3 L

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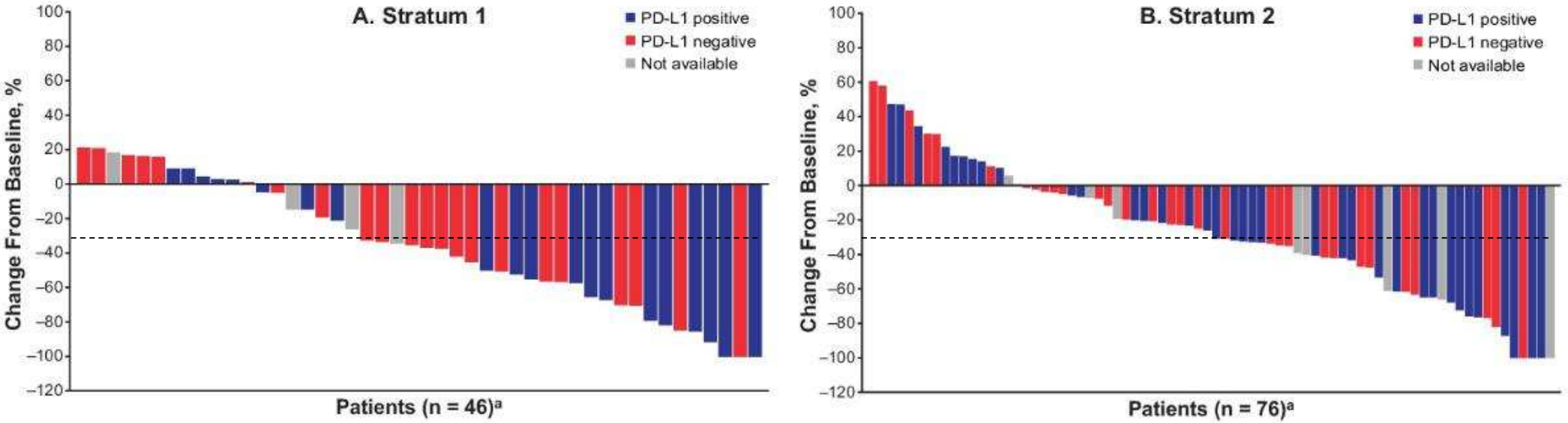
Waterfall Plots of maximum tumor changes from baseline

Most patients experienced a reduction of tumor size

Figure 2. Percent Change in Total Sum of Target Lesion Diameters From Baseline to Postbaseline Nadir per RECIST v1.1 by Independent Imaging Review in Stratum 1 (A) and Stratum 2 (B) (Evaluable Analysis Set)



[a]This analysis included evaluable patients with both baseline and at least 1 postbaseline target lesion assessment.
Stratum 1: No prior systemic anticancer therapy for metastatic disease.
Stratum 2: 1–2 Prior systemic anticancer therapies for metastatic disease.
PD-L1, programmed death-ligand 1; RECIST v1.1, Response Evaluation Criteria In Solid Tumors version 1.1.

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