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40 YEAR ANNIVERSARY
SAN ANTONIO BREAST CANCER SYMPOSIUM®

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Immunotherapy for Breast Cancer

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Disclosure(s)

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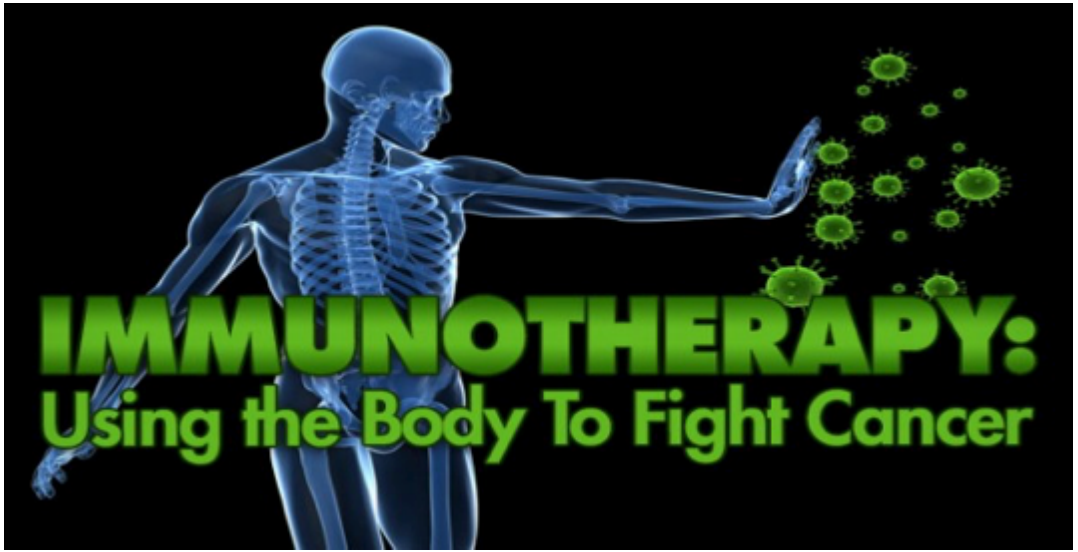
Speaker's Bureau:	**N/A**
Advisory Panel/ Consultant:	**N/A**
Co-founder/ Stockholder:	**N/A**
Employee (part time):	**N/A**

Immunotherapy for Breast Cancer



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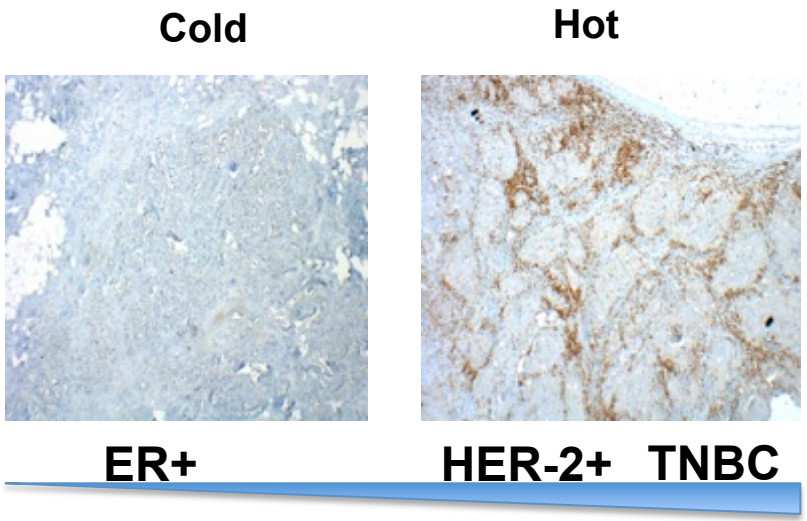
The Immune System and Breast Cancer



- Poor prognostic factors (ER^{neg}, PR^{neg}, high grade, LN^{+}) are associated with higher T cell infiltrates at diagnosis
- Higher numbers of $CD8^{+}$ TILs and a higher CD8+ T cell/FoxP3+ Treg ratio predict better clinical outcomes (cPR, DFS, OS), except for ER+ BC
- TNBC and HER-2+ breast cancers are high value targets for cancer immunotherapy
  - --No approved targeted therapies for TNBC
  - --Potentially synergistic targeted therapies in HER-2+ BC
- ER+ breast cancers present the challenge of transforming tumors from cold to hot

Gajewski TF Semin Oncol 2015 42: 663-71.
Herbst RS et al Nature 2014 515: 568-71.
Chen DS Mellman I Immunity 2013 39: 1-10.
Cimino-Mathews A/Emens LA, unpublished images.

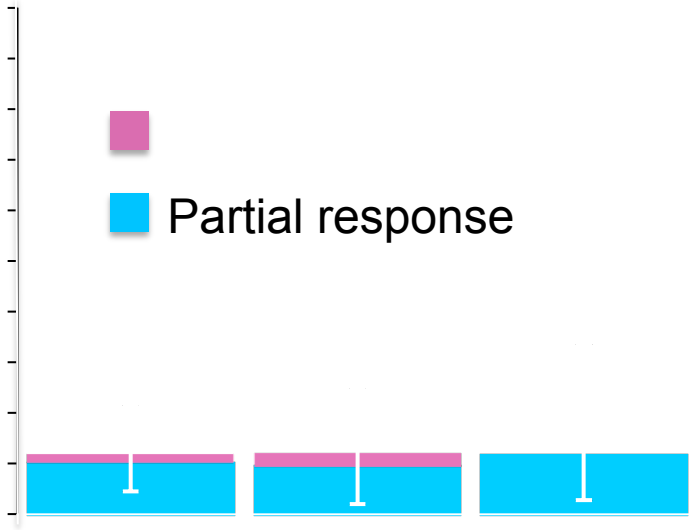
Overall Response Rates by PD-L1 Status: Initial Trials

Agent	Subtype	ORR	ORR (PD-L1+)
Pembrolizumab			
• Single agent (Keynote-012, n=27)	TNBC	18.5%	18.5%
• Single agent (Keynote-028, n=25)	ER+/HER2-	12.0%	12.0%
Atezolizumab			
• Single agent (n=21)	TNBC	19.0%	19.0%
• Phase Ib with nab-paclitaxel (n=32)	TNBC	41.7%	77.8%
Avelumab			
• Single agent (Javelin, n=168)	All ER+/HER2- HER2+ TNBC	4.8% 2.8% 3.8% 8.6%	33.3% (n=4/12) NR NR 44.4% (n=4/9)

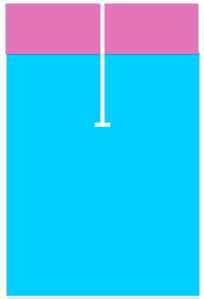
Studies used different antibodies and cutoffs for determining PD-L1 positivity

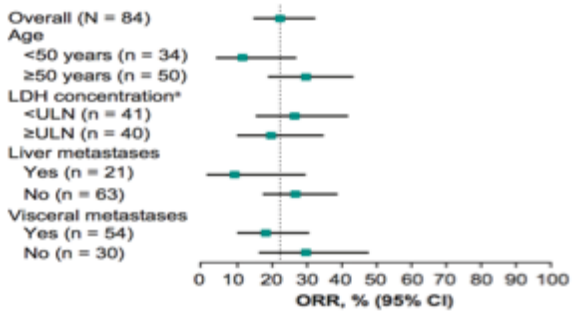
Nanda et al, JCO 2016, Emens et al, AACR 2015, Adams et al, ASCO 2016, Dirix et al, BCRT 2017, Rugo et al, SABCS 2015

Pembrolizumab Antitumor Activity in Previously Treated and Previously Untreated mTNBC



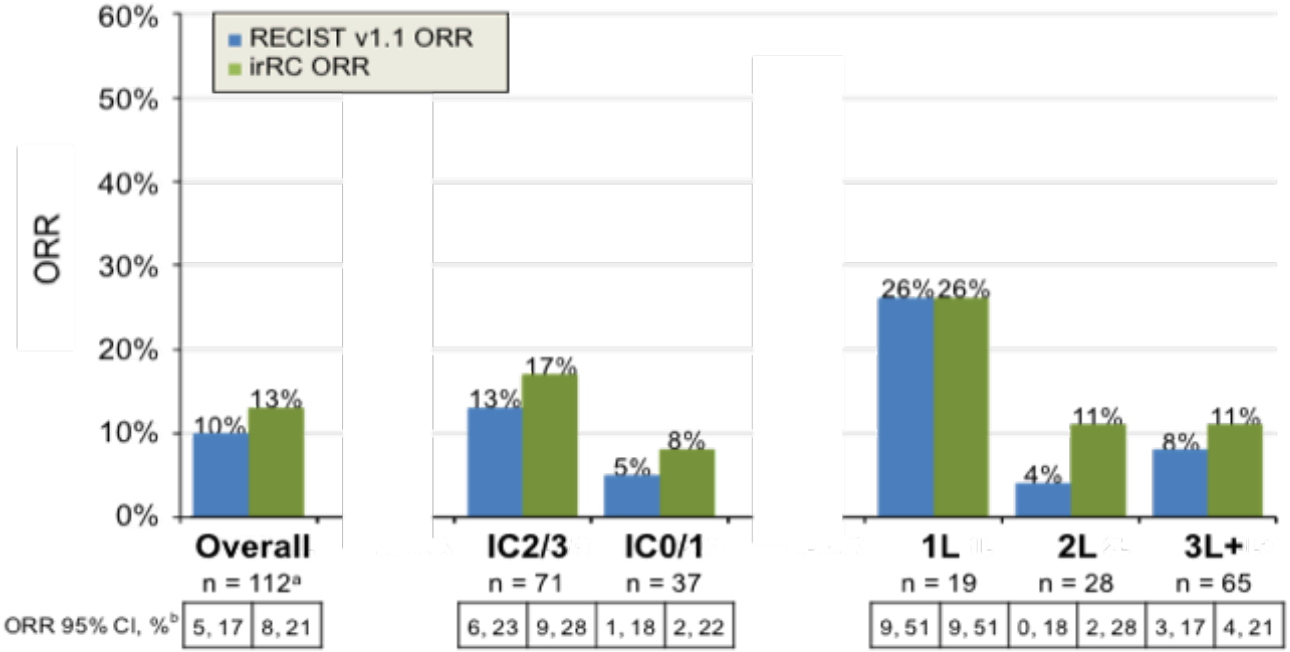
Time to response 2 mo (1.7-6.2)
DOR 10.4 mo (4.2-16.6+)





Adams et al, ASCO 2017 and SABCS 2017

TNBC Response Rates to Atezolizumab by Subgroup



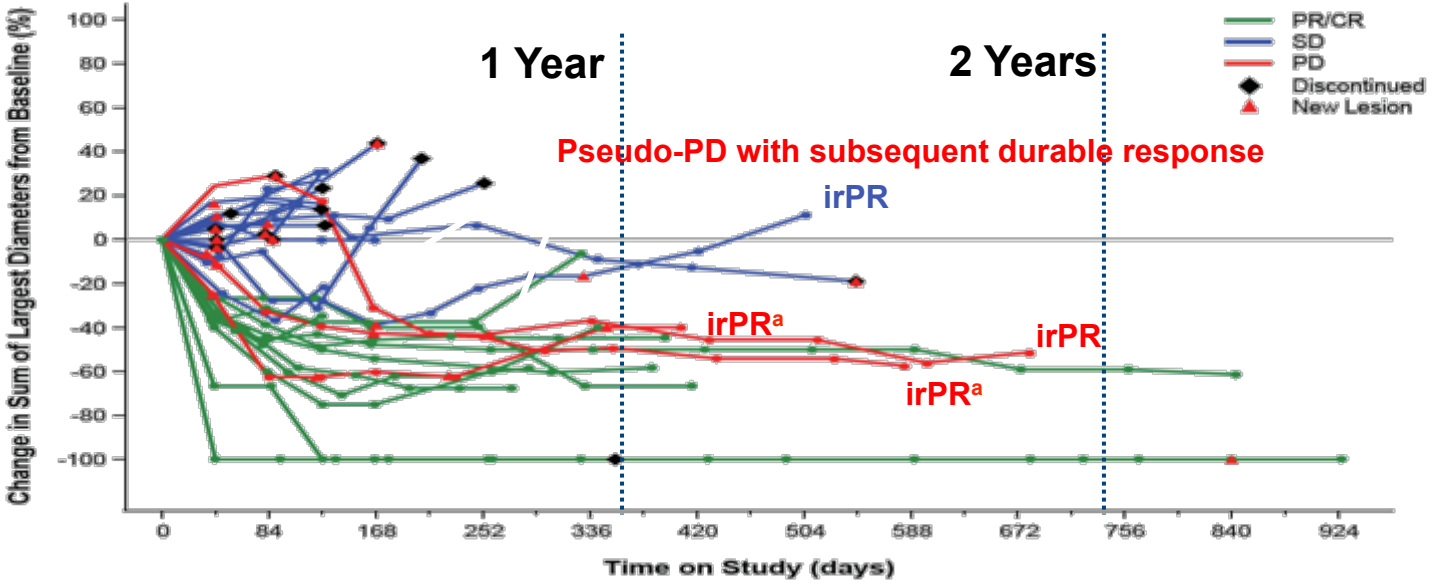
- Numerically higher ORRs were observed in IC2/3 and 1L subgroups
- irRC criteria captured non-classical responses to atezolizumab

[a] Objective response–evaluable patients. Four patients had unknown PD-L1 status. Confirmed, investigator-assessed responses are plotted. Patients with missing or unevaluable responses are included (16 per RECIST v1.1 and 23 per irRC). [b] ORR 95% CI was estimated using Clopper-Pearson method. Data cutoff: March 31, 2016.

Schmid P, et al. AACR 2017
Phase Ia Atezolizumab in TNBC

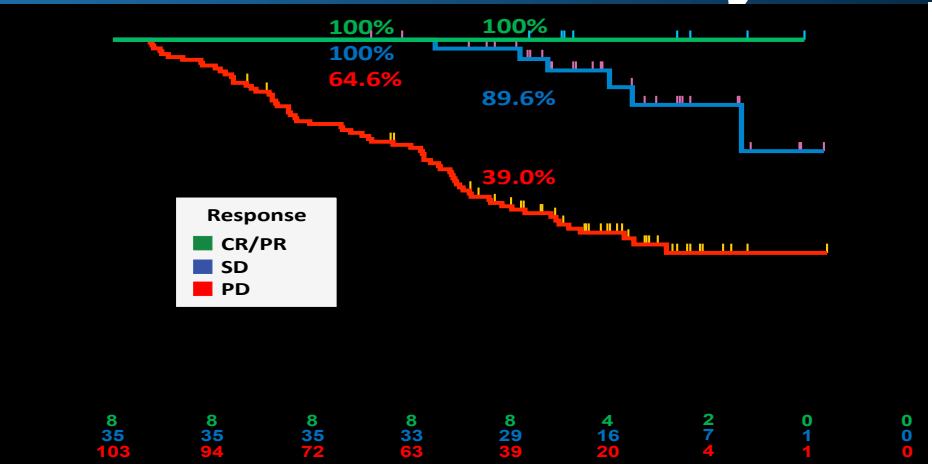
Activity after Pseudo-PD and Duration of Response

Patients With RECIST v1.1 Response or SD or irRC Response

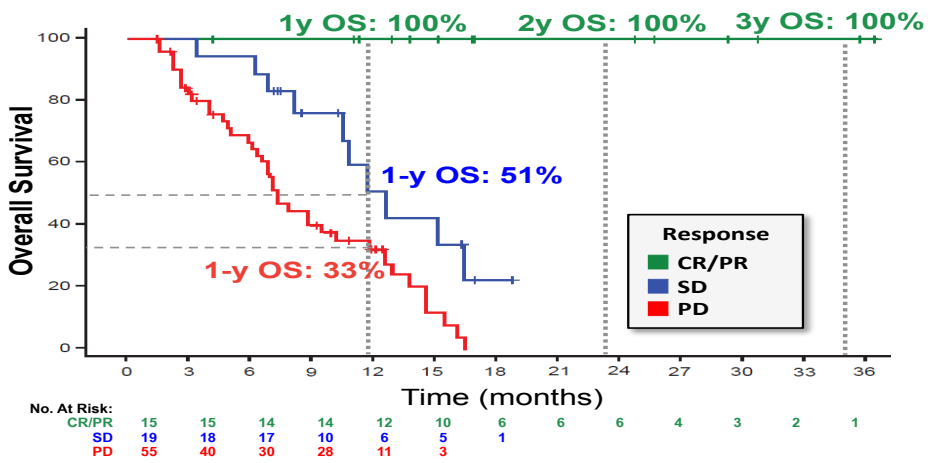


Schmid P, et al. AACR 2017

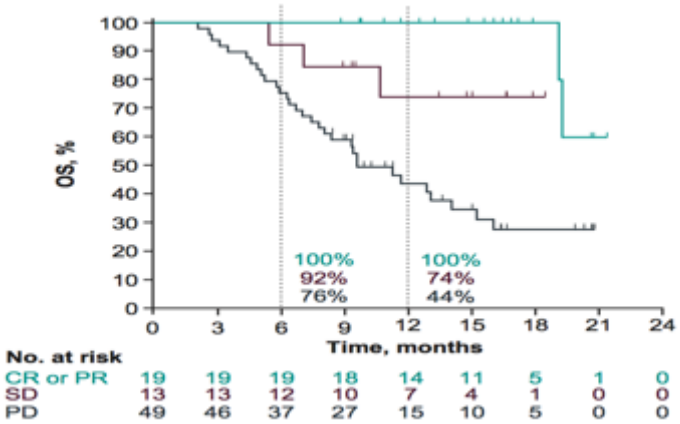
Overall Survival by Best Response



Pembrolizumab single agent in mTNBC ≥1L, PDL1+/-



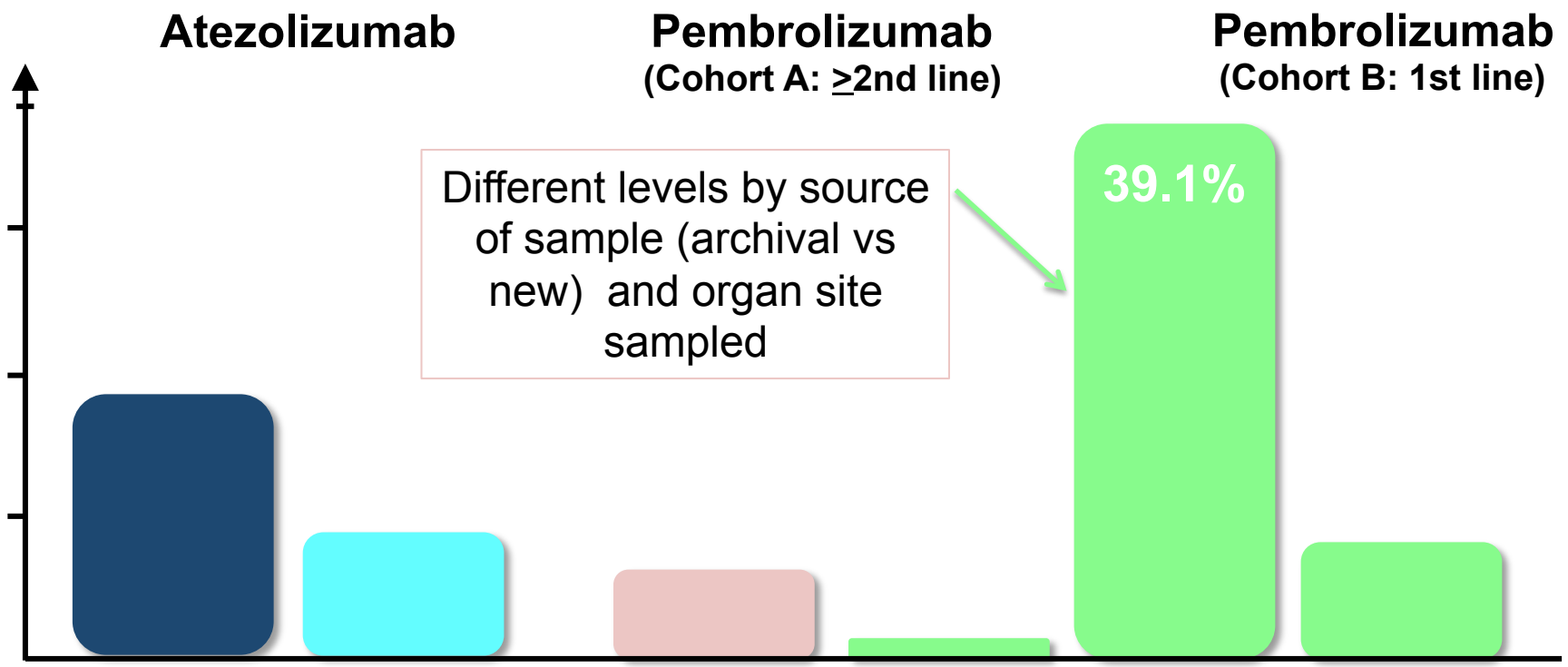
Atezolizumab single agent in mTNBC ≥1L, PDL1+/-



Pembrolizumab single agent in mTNBC 1L, PDL1+

Adams S, et al ASCO 2017 and SABCS 2017; Schmid P, et al. AACR 2017

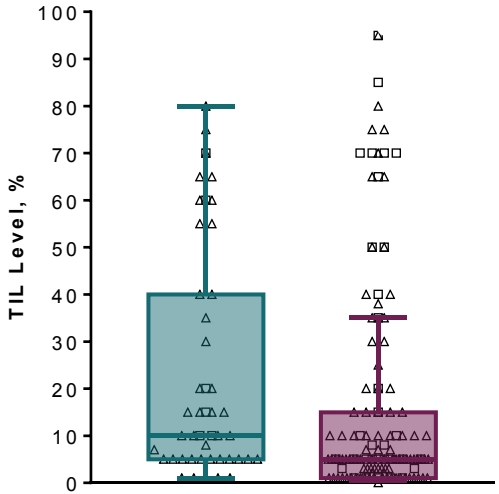
High sTILs are Associated with Improved Response Particularly in the First-Line Setting

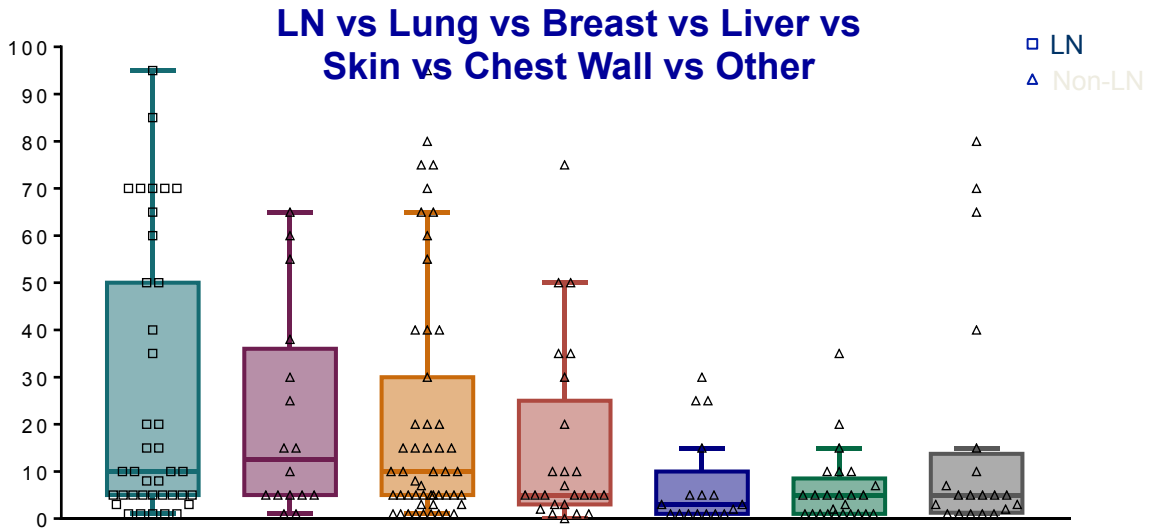


[1]</≥ Median

Schmid P, et al. AACR 2017; Adams S, et al ASCO 2017, Loi, ESMO 2017

sTIL Levels by Sample Type and Site: KN086



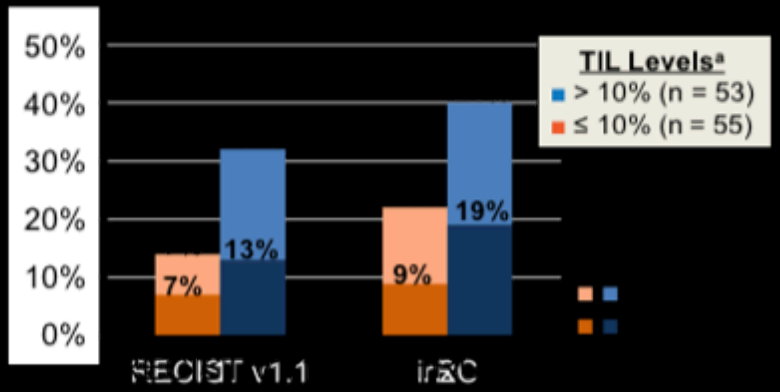


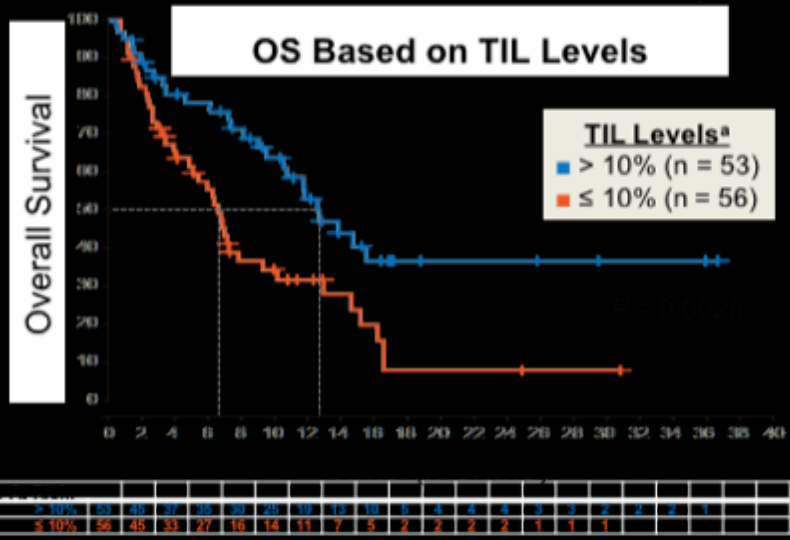
	Archival	New	LN	Lung	Breast	Liver	Skin	Chest Wall	Other
n	47	146	39	16	51	25	17	25	20
Median (IQR)	10% (5-40)	5% (1-15)	10% (5-50)	12.5% (5-36)	10% (5-30)	5% (3-25)	3% (1-10)	5% (1-8.5)	5% (1.25-13.75)
P	0.001[a]		0.003[b]						

[a]Wilcoxon rank sum (one sided). [b]Kruskal-Wallis test (one sided). Red font indicates statistical significance.
Box = 25th and 75th percentiles; line = median; whiskers = 1.5×IQR.
Data cutoff date: Nov 10, 2016.

Loi et al, ESMO 2017

Association of Response and Survival with TILs





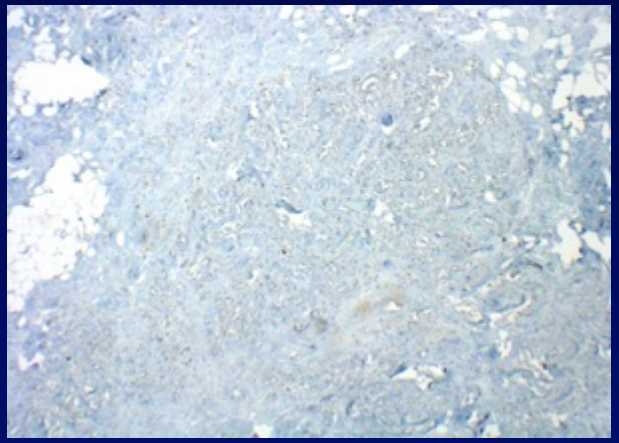
	≤ 10% TILs (n = 53)	> 10% TILs (n = 56)
mOS (95% CI)	6.6 mo (4.9, 10.2)	12.6 mo (10.5, NA)

Schmid P, et al. AACR 2017
Phase Ia Atezolizumab in TNBC

One Framework for Personalizing Breast Cancer Immunotherapy

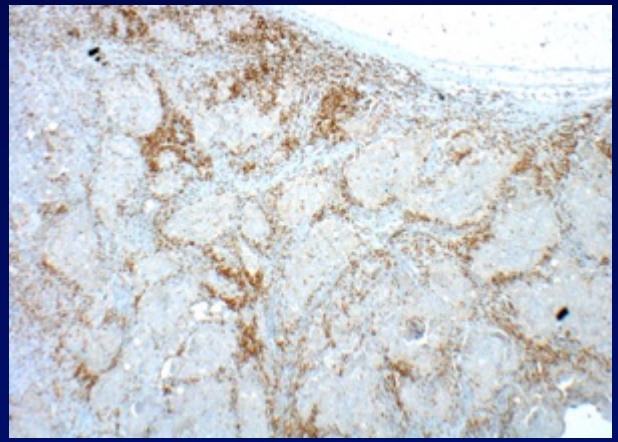
Patterns of T Cell Infiltration

Non-inflamed



Chemotherapy, XRT
HER-2-directed antibodies
Vaccines, STING agonists

Inflamed



Anti-PD-1/PD-L1
IDO inhibition

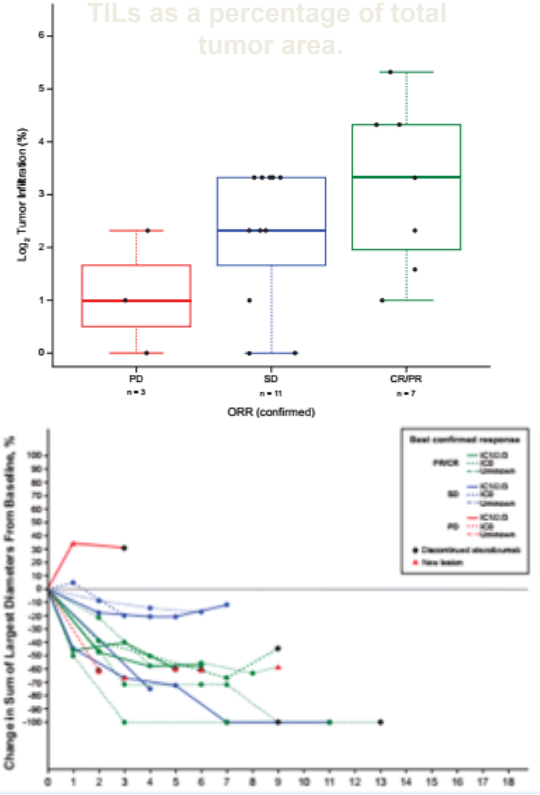
Gajewski TF Semin Oncol 2015 42: 663-71.; Herbst RS et al Nature 2014 515: 568-71.
Chen DS Mellman I Immunity 2013 39: 1-10.; Cimino-Mathews A/Emens LA, unpublished images.

Atezolizumab in Combination with nab-Paclitaxel in TNBC: Phase Ib Trial

Best Objective Response per RECIST v1.1 by line of therapy

- 32 pts evaluable for response
  - Median no. (range) of prior systemic cancer therapies: 5 (1-10)
  - Prior taxane use: 88%

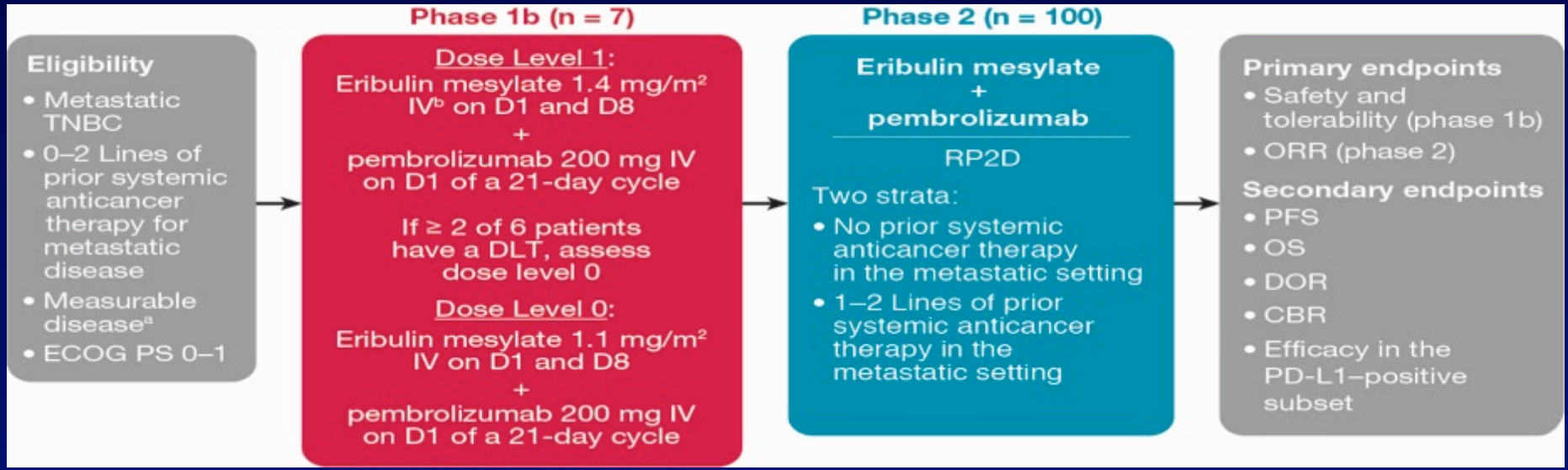
Best ORR	1L n = 13	2L n = 9[b]	3L+ n = 10[c]	All N = 32



- Responses seen regardless of PD-L1 tumor status
- Baseline levels TILs showed a trend with increased response

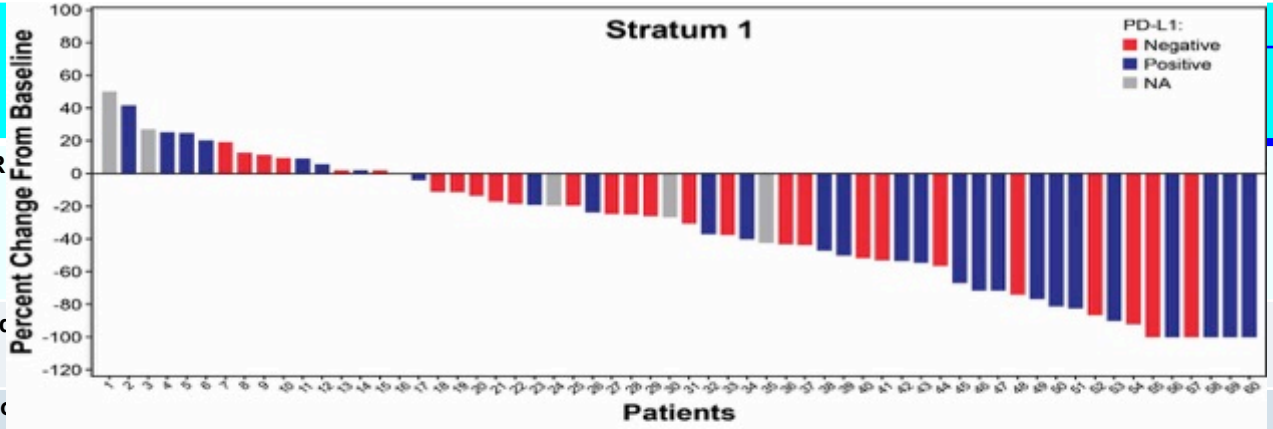
Adams, et al. ASCO 2016

Phase 1b/2 Study to Evaluate Eribulin Mesylate in Combination With Pembrolizumab in Patients With Metastatic Triple-negative Breast Cancer (ENHANCE 1)



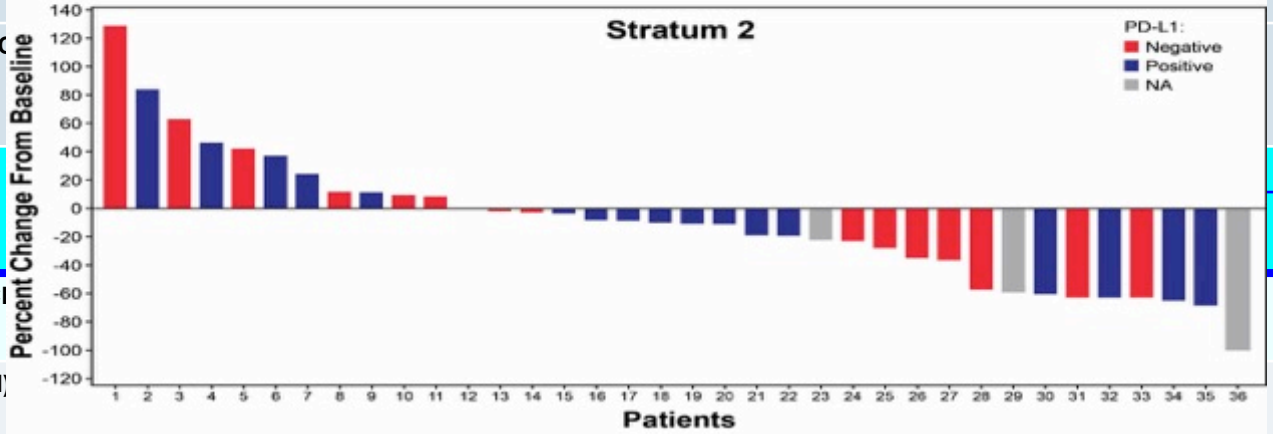
No DLTs in phase Ib

Tolaney et al, SABCS 2017



	Total (n = 106)
Objective Response Rate (CR (95% CI)	28 (26.4) (18.3–35.9)
CR, n (%)	3 (2.8)
PR, n (%)	25 (23.6)
CBR (CR + PR + durable SD [d	39 (36.8)

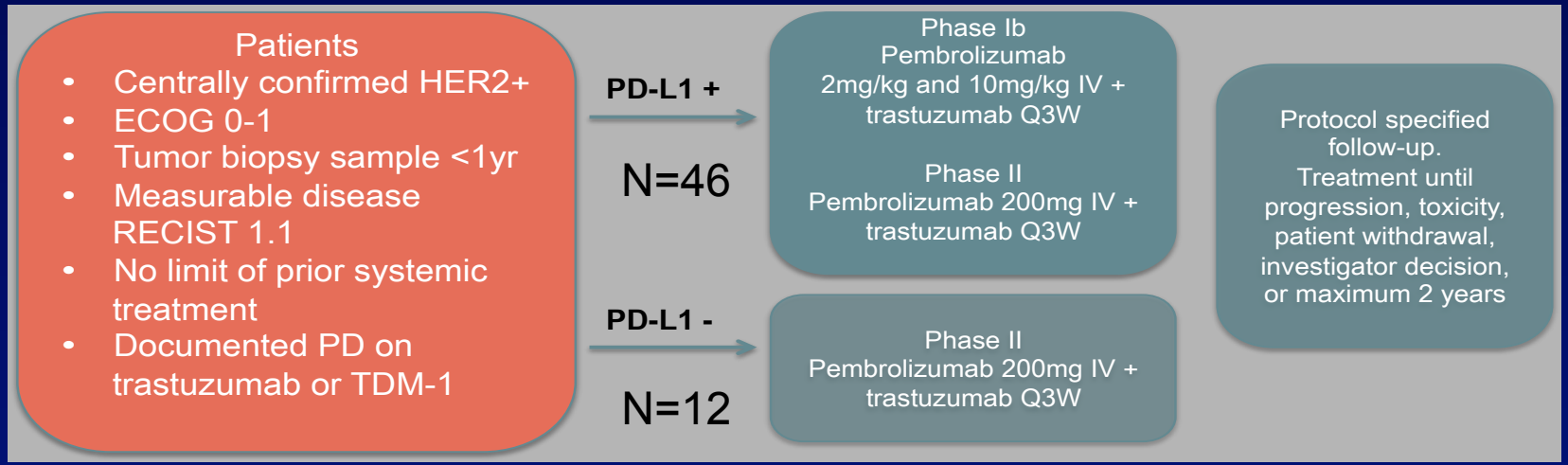
	Total (n = 28)
Patients With Objective Respo	
DOR (months), median (95% C	8.3 (6.5–12.9)
DOR > 6 months, n (%)	15 (53.6)
DOR > 12 months, n (%)	4 (14.3)



	Total (N = 107)
PFS (months), median (95%CI	4.2 (4.1–5.6)
PD/death, n (%)	77 (72.0)
OS (months), median (95% CI	17.7 (13.7–NE)
Death, n (%)	42 (39.3)

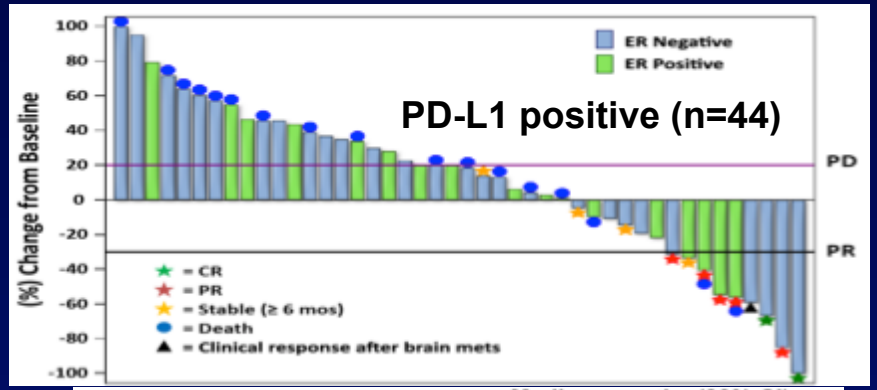
Panacea: Phase Ib/II Trial of Pembrolizumab and Trastuzumab

- HER2-positive breast cancer has high levels of T cell infiltration
- Preclinical studies suggest immune-mediated mechanisms of trastuzumab resistance can be overcome with CPI

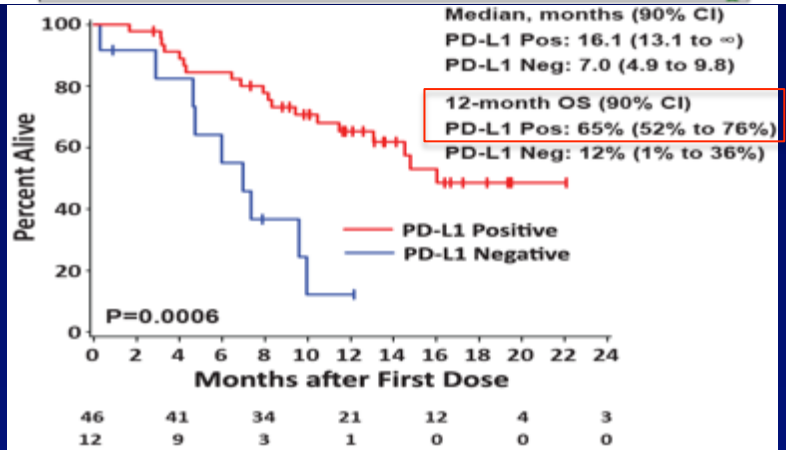


Loi et al, SABCS 2017

	PD-L1 Positive Phase Ib, n=6	PD-L1 Positive Phase II, n=40	PD-L1 Negative Phase II, n=12
ORR n (%) [90%CI]	1 (17%) [1-58]	6 (15%) [7-29]	0 (0%) [0-18]

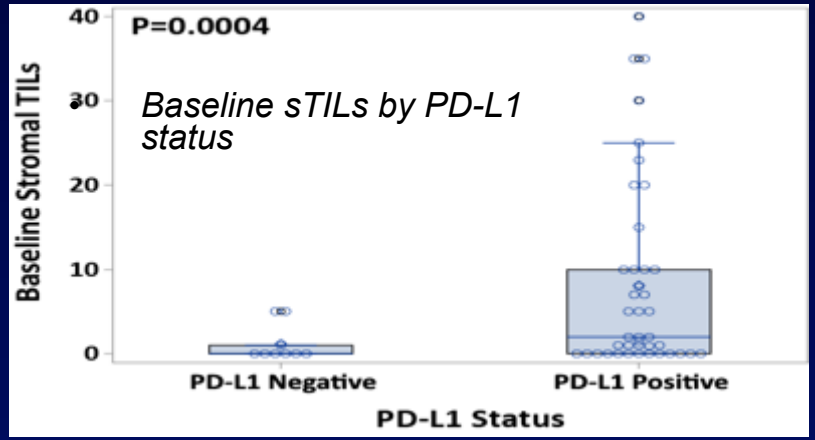


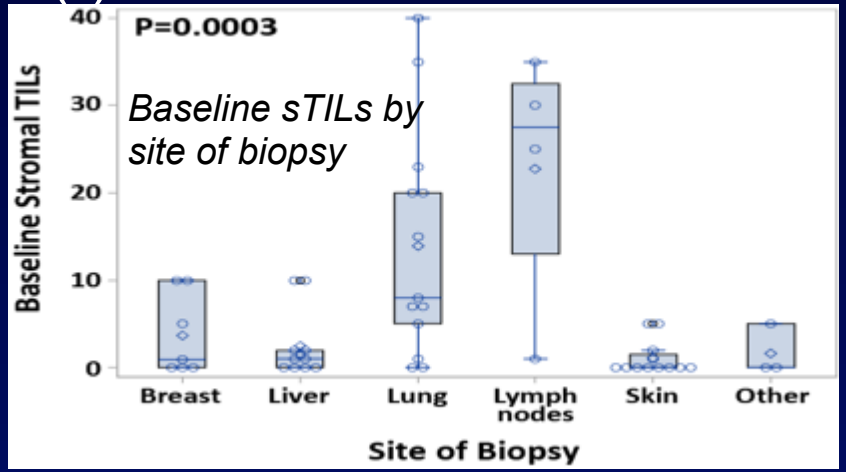
OS

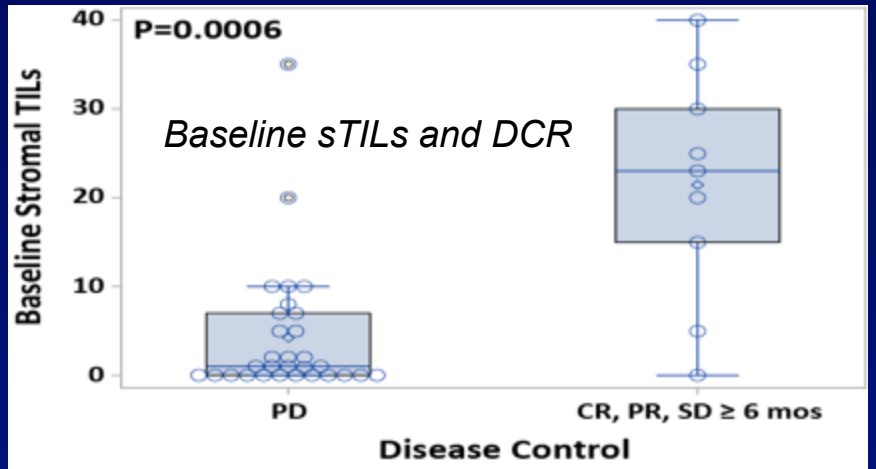


- Median duration of disease control: 11.1 months (90% CI: 6.2 -∞)
- Mean DoR: 10 months (90% CI: 2.7-23.1)
- Five patients (10.8%) continue with no progression at time of reporting

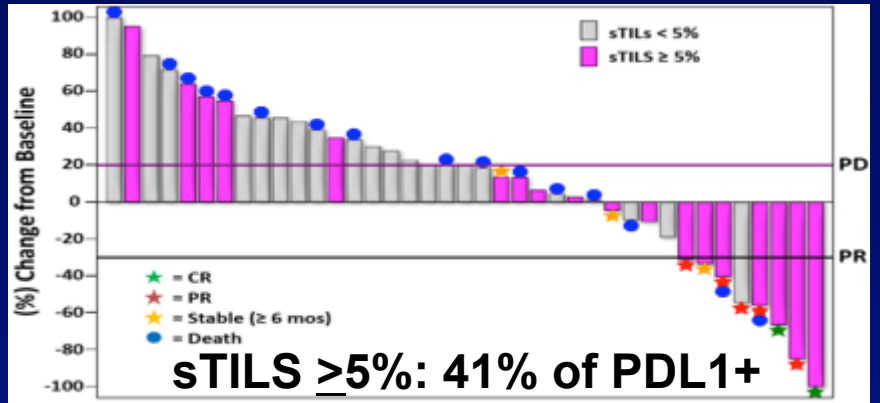
- Median PFS 2.7(+) vs 2.5 mo(-)





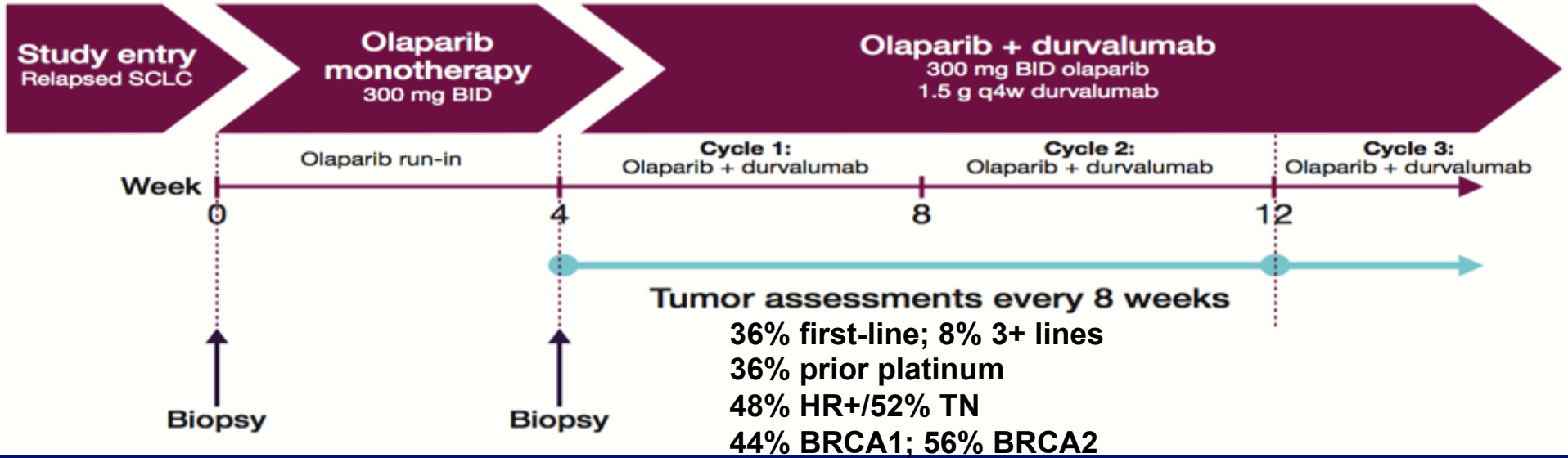


sTILs ≥ 5% as Potential Predictive Marker: PD-L1 Positive Cohort



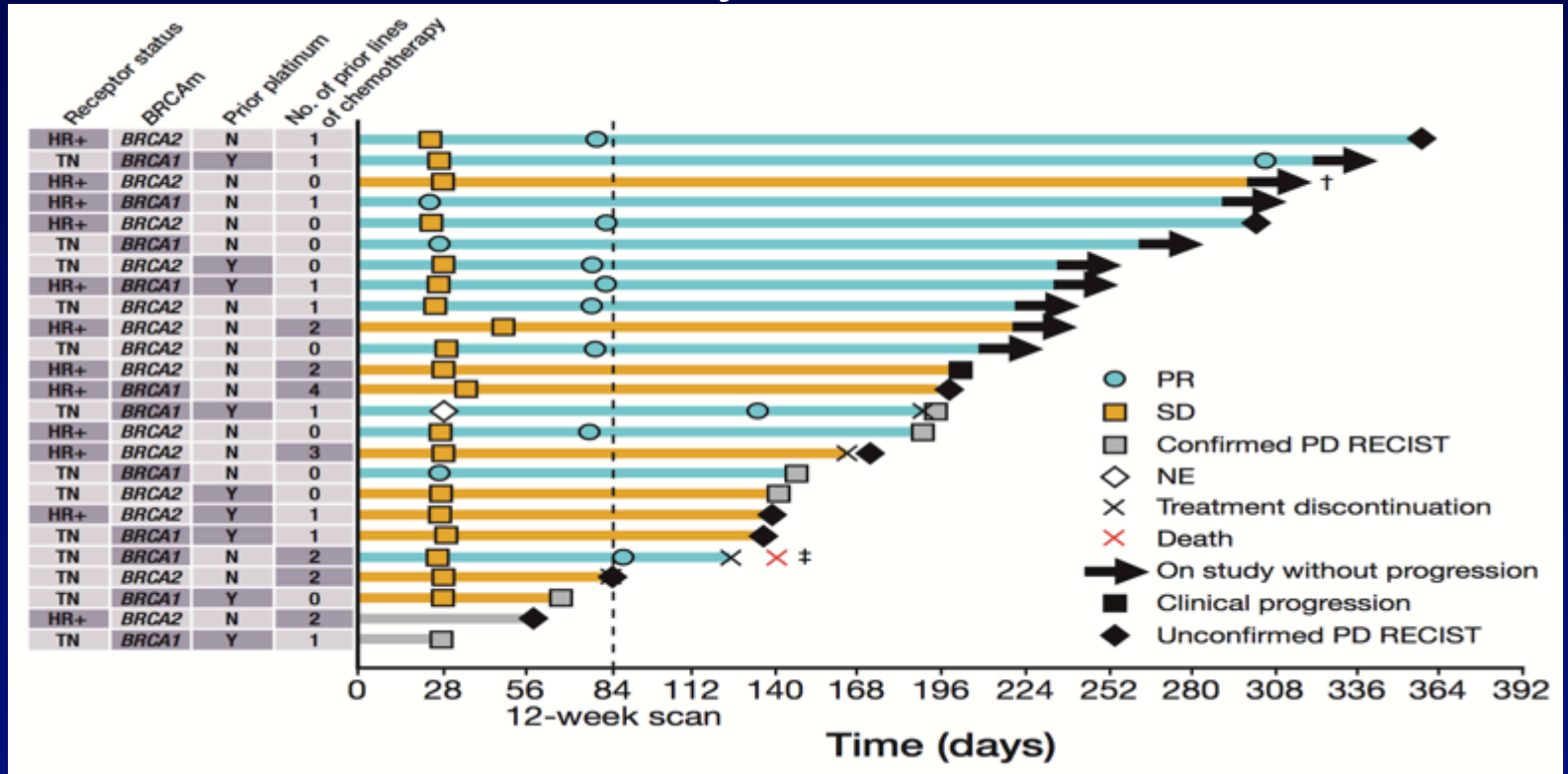
MEDIOLA: Open-label, Multitumor, Phase II Basket Study of Olaparib and Durvalumab: Results in Germline *BRCA*-mutated HER2neg MBC

- Rationale: DNA damage has the potential to modify tumor immunogenicity; PARP inhibition upregulates PD-L1 expression
- 34 pts enrolled, 25 pts included here



Domcheck et al, SABCS 2017

- 12/25 (48%) had disease control at 28 weeks
- Unconfirmed ORR 52% (13/25) (comp to 60% in Olympiad)
- Median DOR/PFS/OS not yet reached



Immune Checkpoint Inhibitors in ER+ Disease

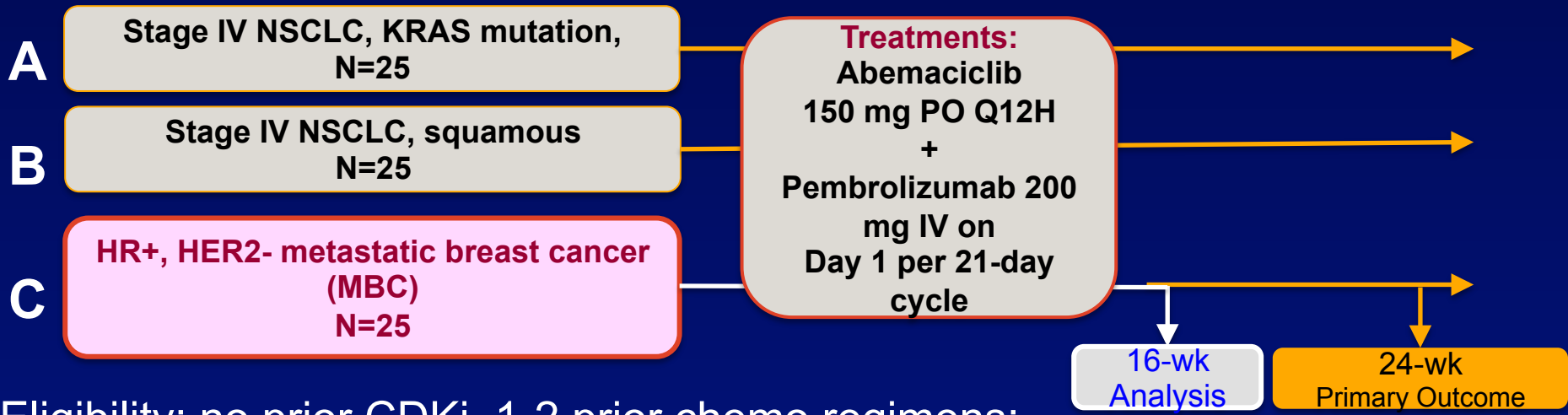
	Pembrolizumab (n = 25)	Avelumab (n=72)
Target	PD-1	PD-L1
Tumor PD-L1	≥1%	>10% hot spots (2/56)
ORR	12%	2.8% (All)
SD	16%	

- Need for immune agonists to stimulate host immune response
- Understand subtype differential response

Rugo et al. SABCS 2015 , Dirix et al BCRT 2017

Phase 1b Study of Abemaciclib plus Pembrolizumab for HR+ HER2- MBC

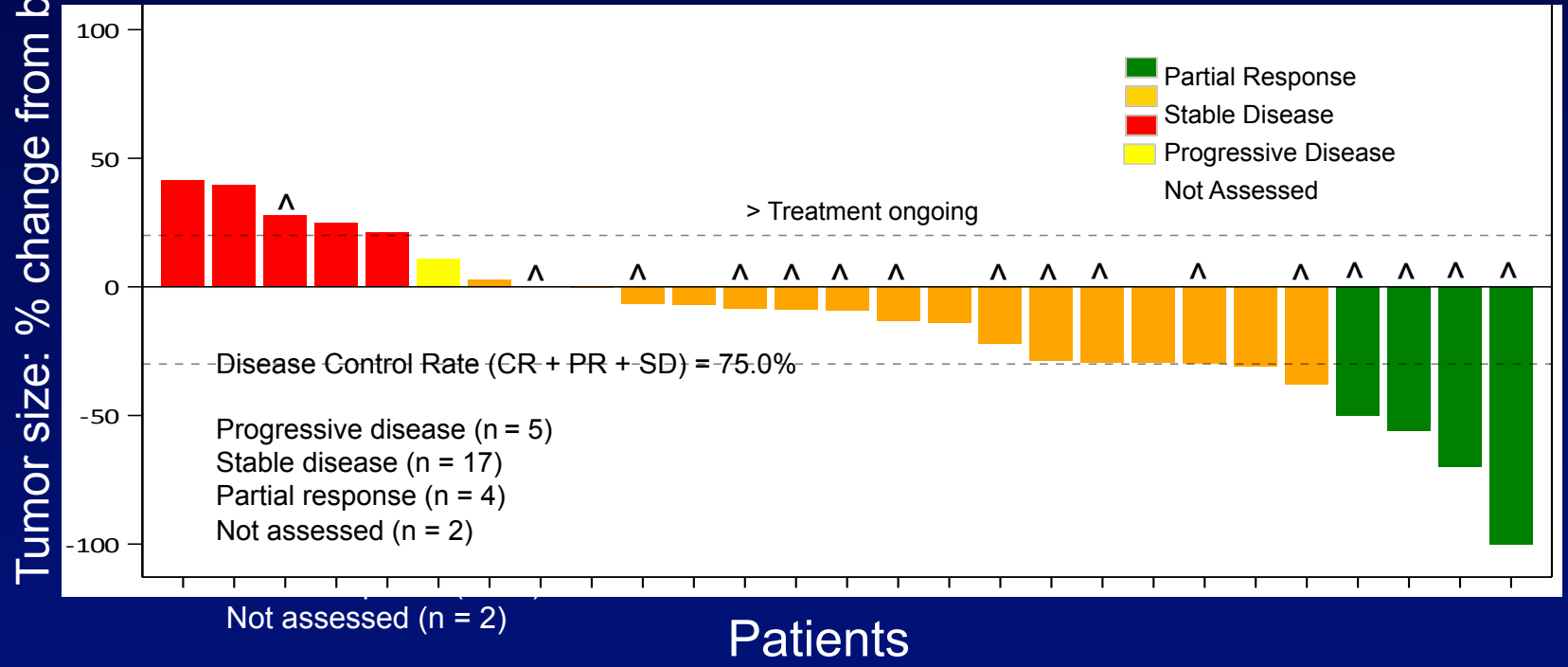
- Abemaciclib induces synergistic immune activation and anti-tumor efficacy in combination with PD-L1 blockade (Goel et al, Nature 2017)

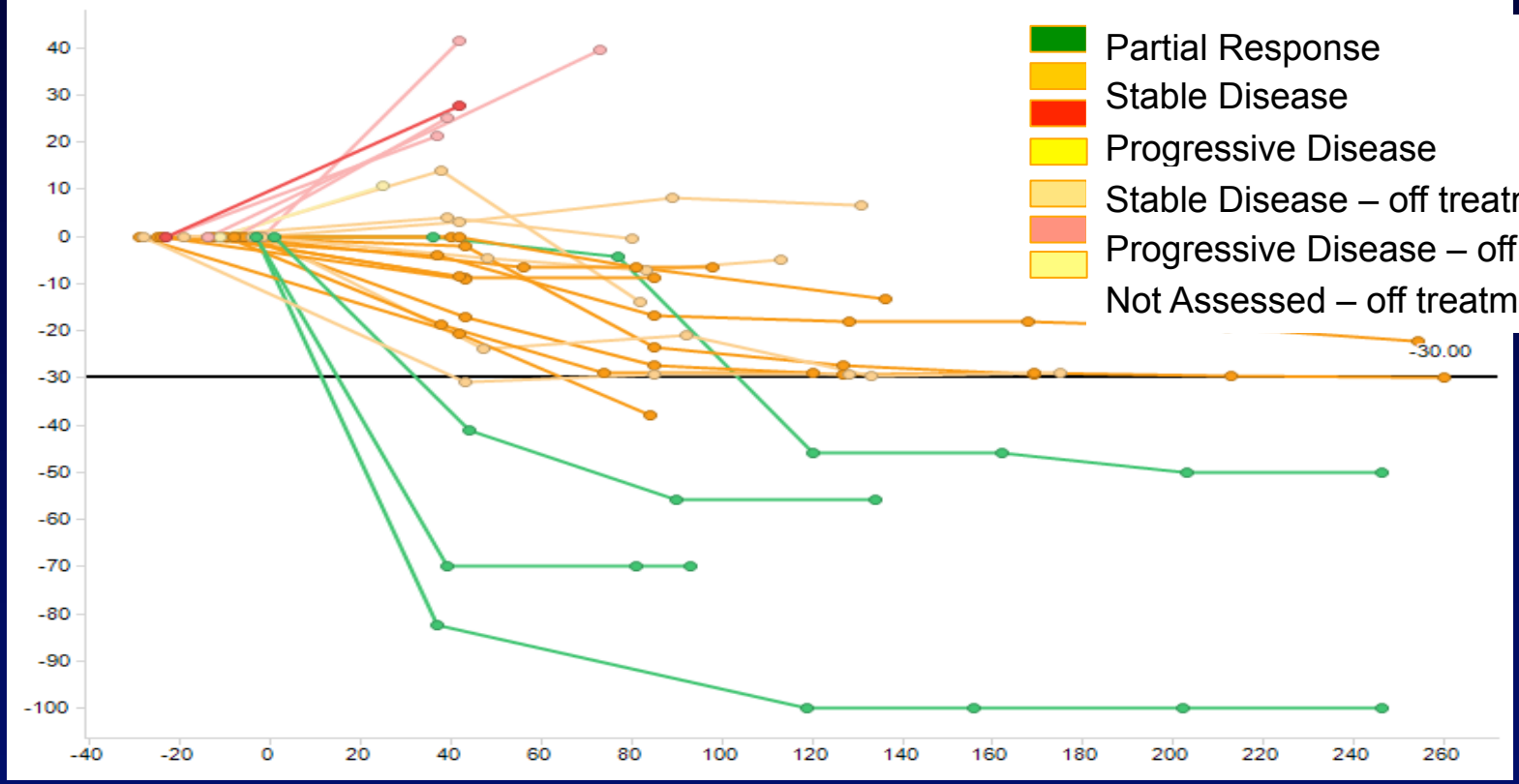


Eligibility: no prior CDKi, 1-2 prior chemo regimens; measurable disease , no h/0 brain mets

Rugo et al, SABCS 2017

Investigator Assessed Response	N=28
Confirmed Objective Response Rate (ORR = CR + PR) (95% CI)	**14.3% (1.3-27.2)**
CR	**0%**
PR (confirmed)	**14.3%**





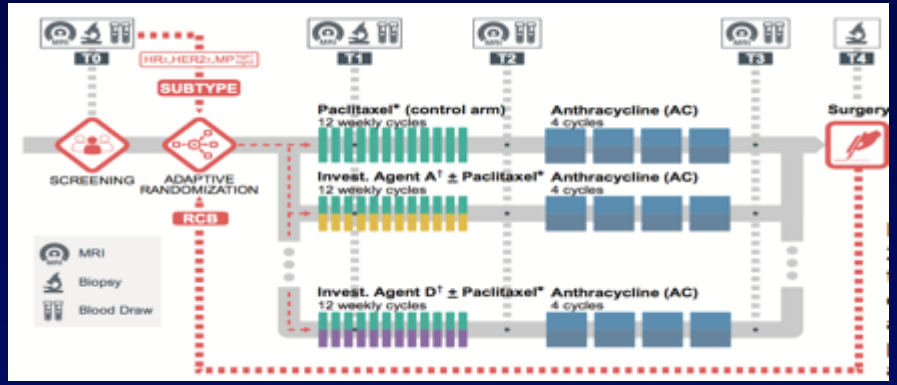
- Monarch 1: 200 mg BID abemaciclib
- ORR: 6.8% at 16 weeks; 19.7% at final analysis (12 months after last patient entered study)
- Median time to response 3.7 months

PD-L1 and TIL testing pending

TEAE of Clinical Interest

Investigator-assessed TEAE[a] (N=28)	All Grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grades 4-5 n (%)
Colitis	1 (3.6)	1 (3.6)	0	0	0
Diarrhea	22 (78.6)	11 (39.3)	9 (32.1)	2 (7.1)	0
Hypothyroidism	1 (3.6)	0	1 (3.6)	0	0
Hyperglycemia	1 (3.6)	0	0	1 (3.6)	0
Hyperthyroidism	None reported	0	0	0	0
Infusion-related reaction	None Reported	0	0	0	0
Pneumonitis	1 (3.6)	0	1 (3.6)	0	0
Acute Kidney Injury (Renal failure)	2 (7.1)	0	2 (7.1)	0	0
Rash	3 (10.7)	1 (3.6)	2 (7.1)	0	0
Dermatitis acneiform	2 (7.1)	1 (3.6)	1 (3.6)	0	0
Pruritus	7 (25.0)	5 (17.9)	2 (7.1)	0	0

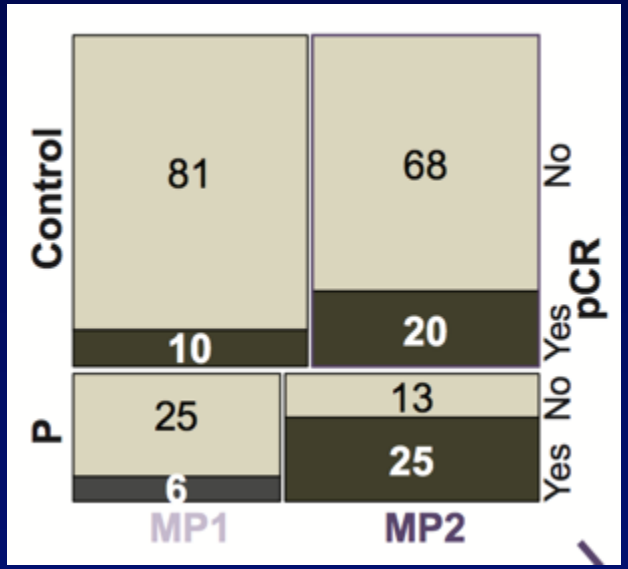
I-SPY 2 Neoadjuvant Trial: Increased Estimated pCR with Pembrolizumab

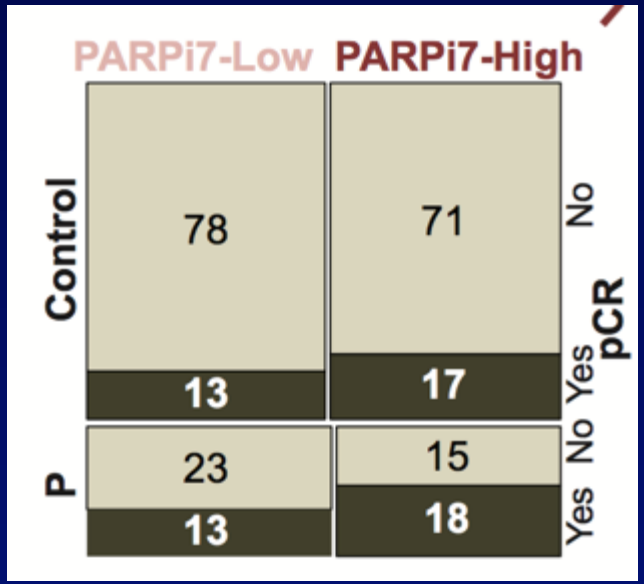


Signature	Estimated pCR Rate (95% Probability Interval)		Probability Pembro Superior to Control	Predictive Probability of Success in Phase 3
	Pembro	Control		
HER2-	**0.44** (0.33 – 0.55)	**0.17** (0.11 – 0.23)	>0.999	**0.985**
HR-HER2-	**0.60** (0.44 – 0.75)	**0.22** (0.13 – 0.30)	>0.999	**0.996**
HR+HER2-	**0.30** (0.17 – 0.43)	**0.13** (0.07 – 0.19)	0.996	**0.834**

Nanda et al, ASCO 2017

Analysis of DNA Repair Deficiency Biomarkers as Predictors of Response to the PD1 Inhibitor Pembrolizumab in I-SPY 2

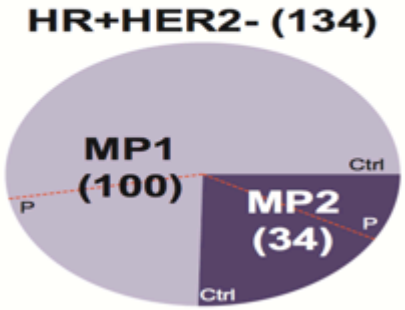


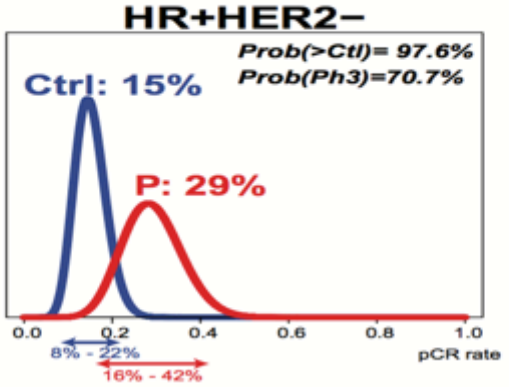


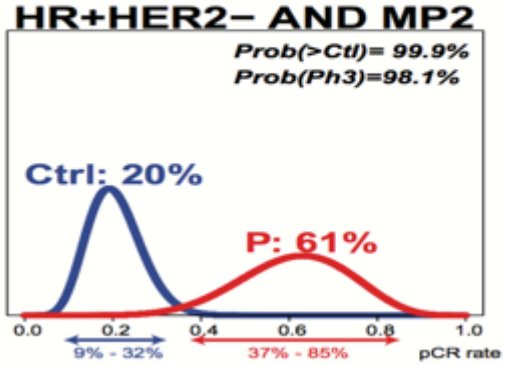
Combining MP2 and PARPi7 did not improve performance over MP2 as a single biomarker

Yau et al, SABCS 2017

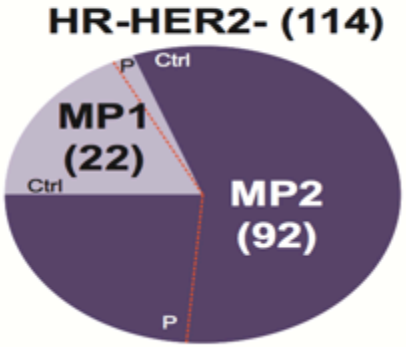
Although only ~30% of HR+HER2- patients were MP2, their estimated pCR rate in the P arm is 61%, compared to 29% in unselected HR+/HER2- patients.

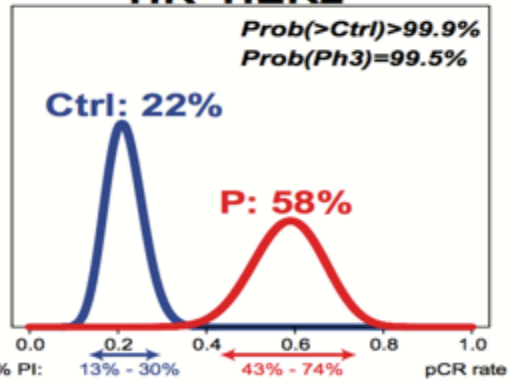


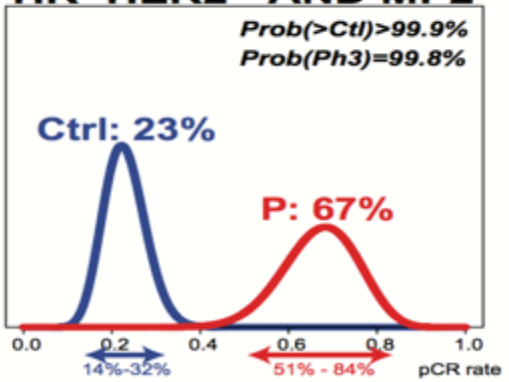




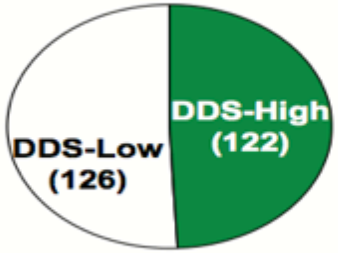
81% of HR-HER2- patients are MP2; and TN/MP2 patients have an estimated pCR rate of 67% in the P arm.

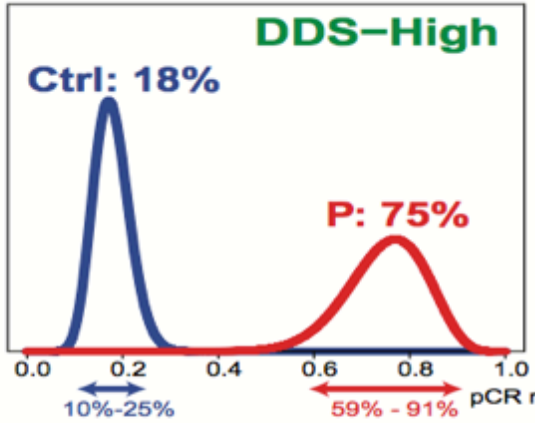


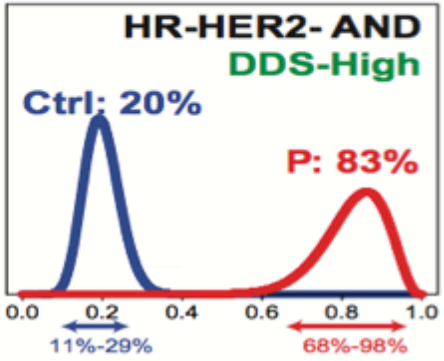


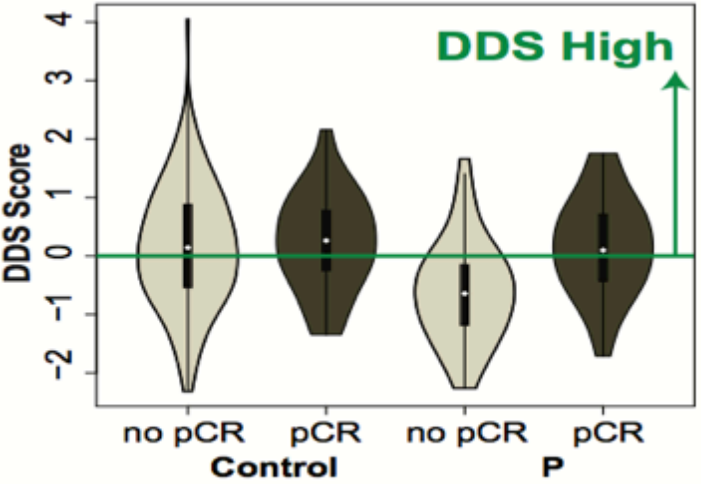


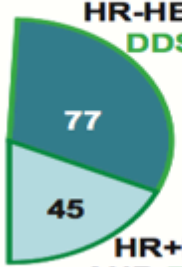
When dichotomized to optimize the biomarker x treatment interaction, the estimated pCR rate is 75% in P vs 18% in control, in the DDS-High subset.

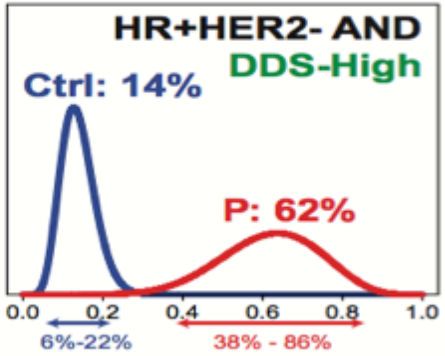












Evaluation of markers of DNA repair pathway signatures

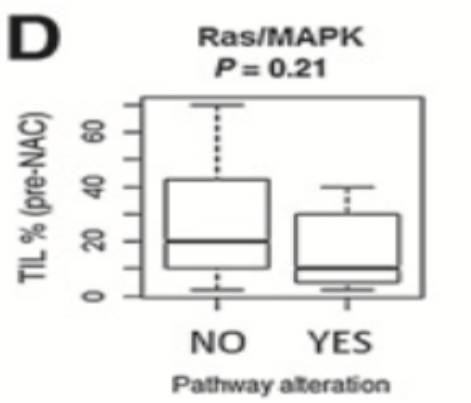
DDS: DNA Damage Sensing

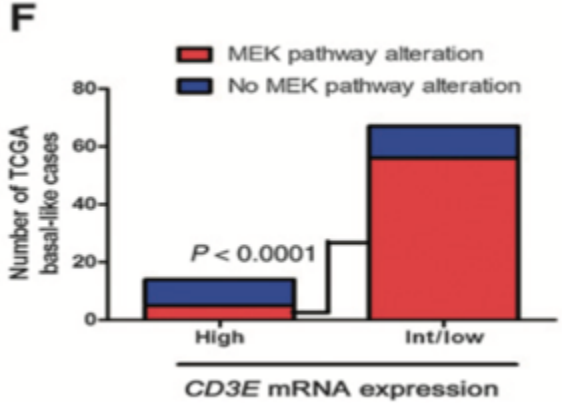
Ongoing Trials (examples)

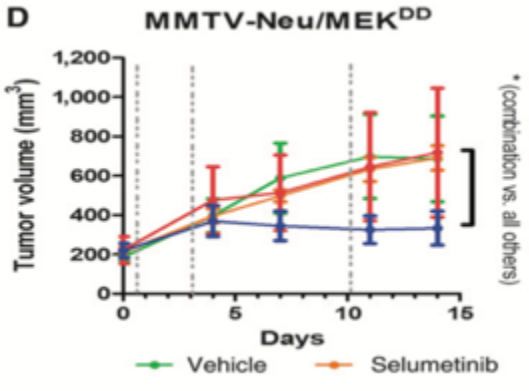
- Metastatic disease (all comers)
  - First line
    - Atezo + nab-paclitaxel (IMPASSION; completed accrual)
    - Pembro + gem/carbo vs paclitaxel/nab-P
    - Atezo + paclitaxel/gem+carbo
- Neoadjuvant therapy
  - 2 Phase III trials ongoing
  - ISPY 2: Drop AC in responders
- Adjuvant therapy
  - Post- neoadjuvant SWOG study
  - Phase III adjuvant
- Additional combinations
  - With alternate chemotherapy
  - With PARP inhibitors, targeted agents (MEK, etc)
  - In ER+ disease: with CDK 4/6 inhibitors, HDAC inhibitors
  - With radiation
  - In HER2+ disease

New Directions: Example

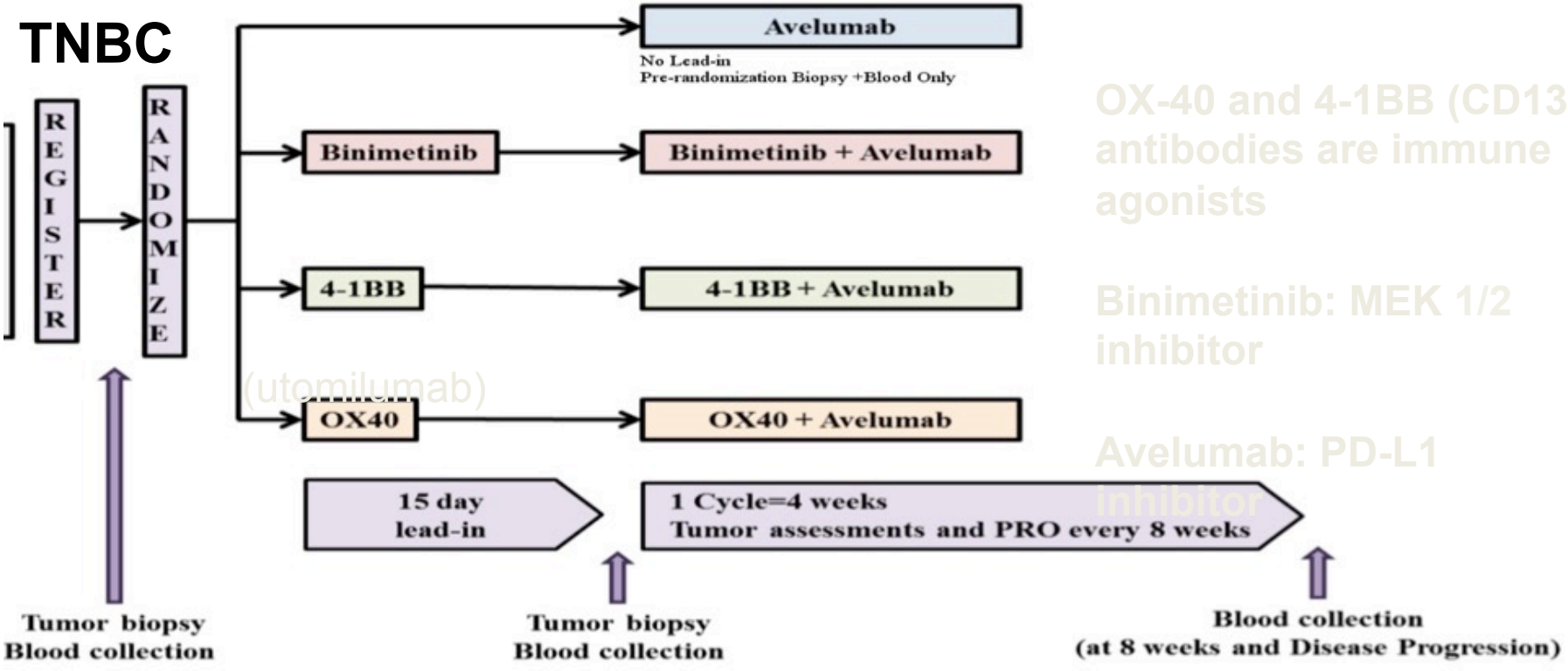
- Combination immunotherapy
  - Combine PD-L1 or PD-1 inhibitors with immune agonists, or agents targeted to related pathways
  - For example:
    - 'Tumor cell-autonomous' pathways that may promote host antitumor immune evasion
    - Therapeutic cooperation between MEK and PD-1/PD-L1 immune checkpoint inhibitors (Loi et al, Clin Cancer Res 2016, Dushyanthen et al (Loi), Nature Comm 2017)







INCITE (TBCRC047): UCSF/Vanderbilt/UNC Multi-Center Immunotherapy PCRF Funded Trial



(utomilumab)

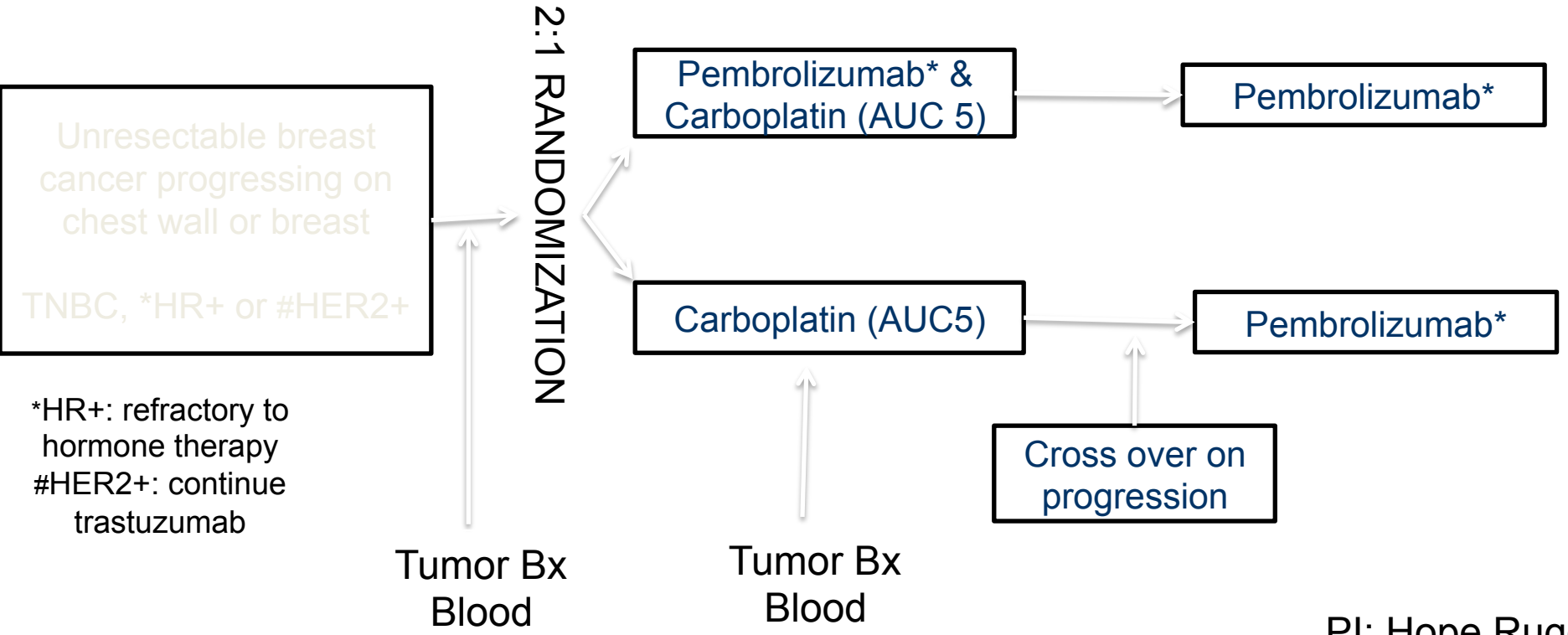
OX-40 and 4-1BB (CD137) antibodies are immune agonists

Binimetinib: MEK 1/2 inhibitor

Avelumab: PD-L1 inhibitor

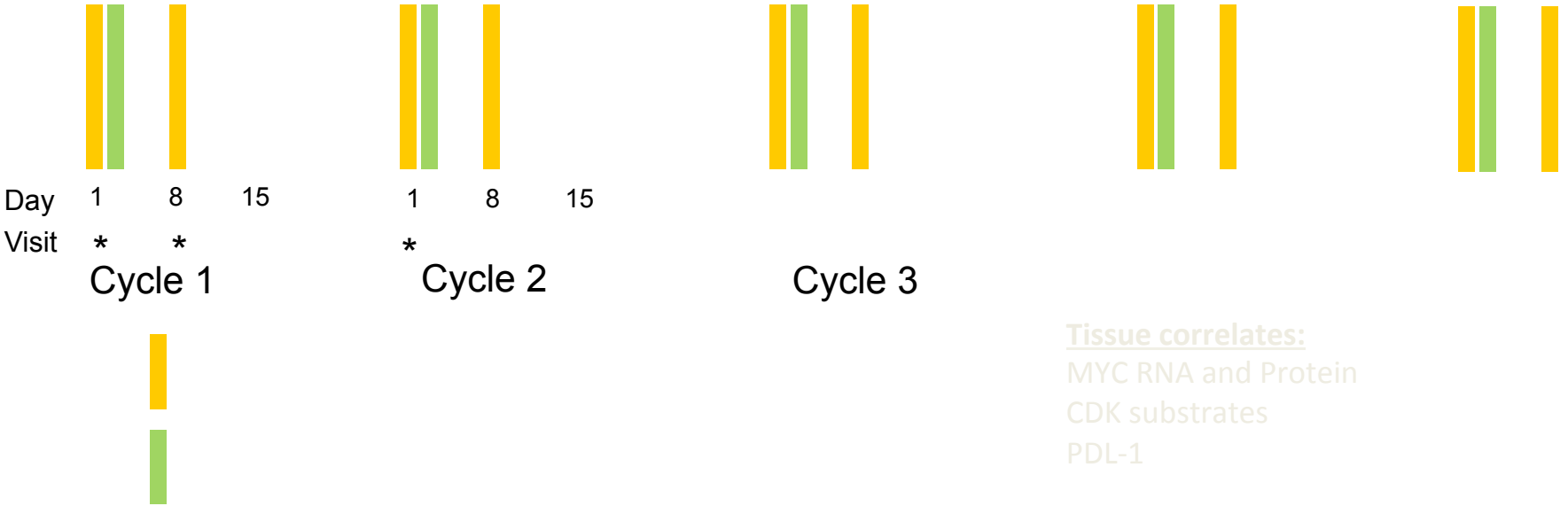
PI: Hope Rugo

TBCRC 044: Immunotherapy for Refractory Chest Wall Disease



PI: Hope Rugo

Phase 1b trial of Dinaciclib (CDKi) and Pe
in Advanced Breast Cancer

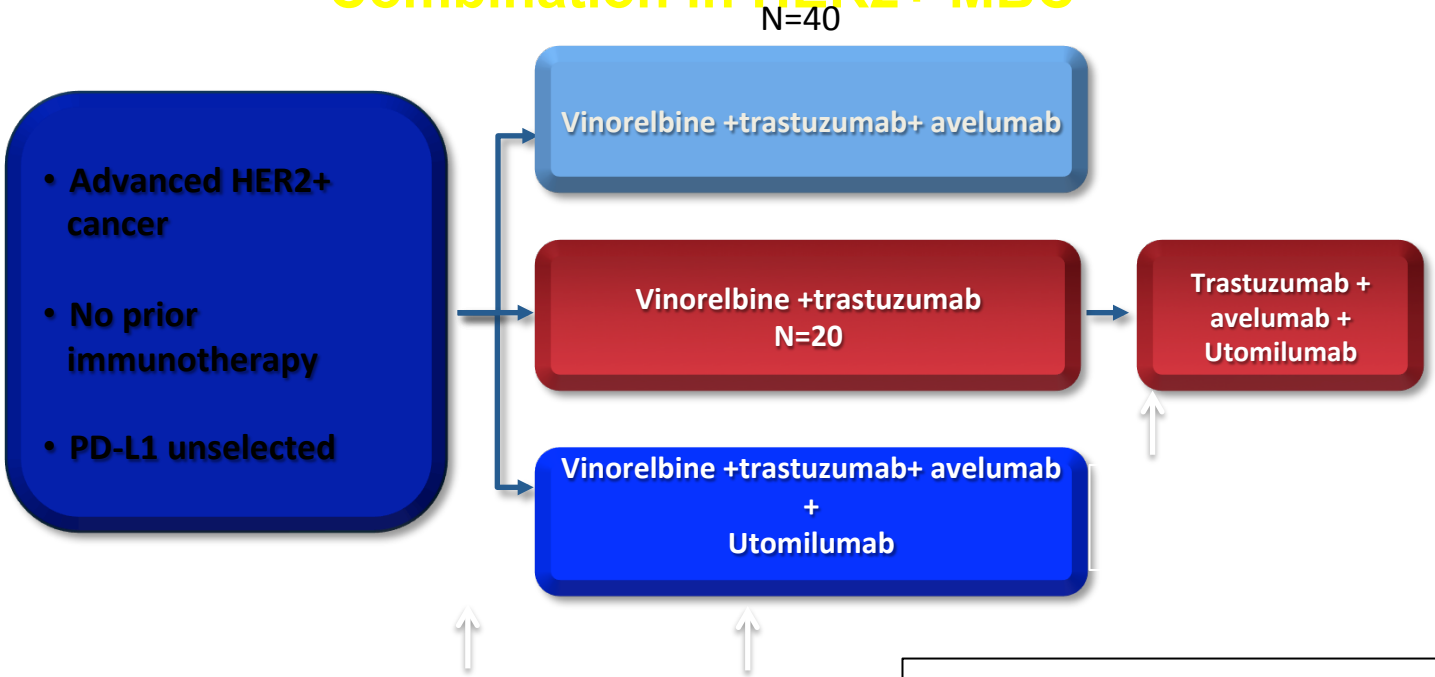


Tissue correlates:
MYC RNA and Protein
CDK substrates
PDL-1

Blood correlates:
T cell subsets

PI: Jo Chien

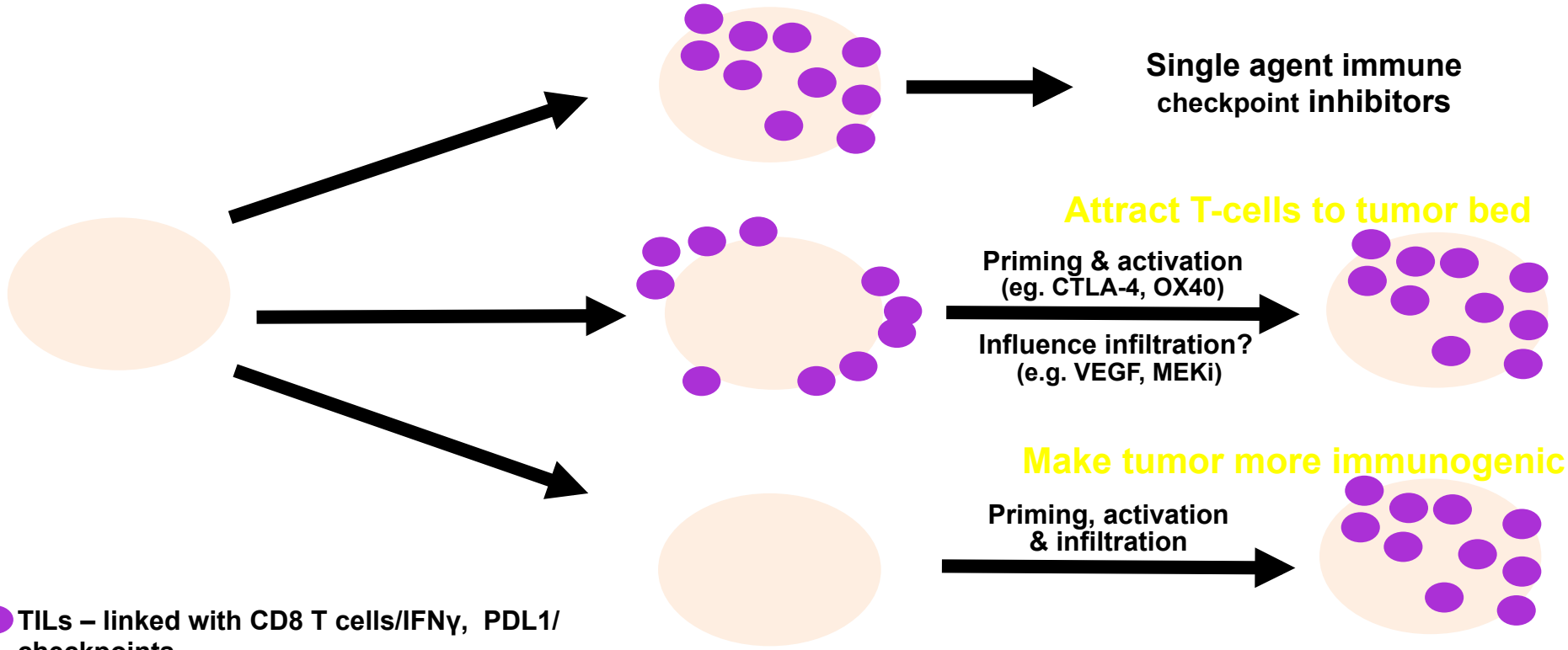
AVIATOR (TBCRC 045)
Additionof a 4-1BB Agonist to a Trastuzumab/anti-PD-L1 Combination in HER2+ MBC



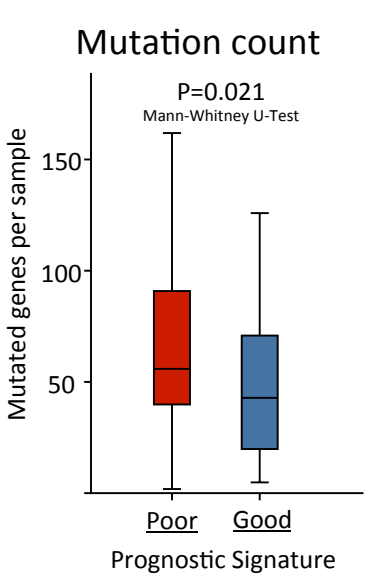
PI: Ian Krop

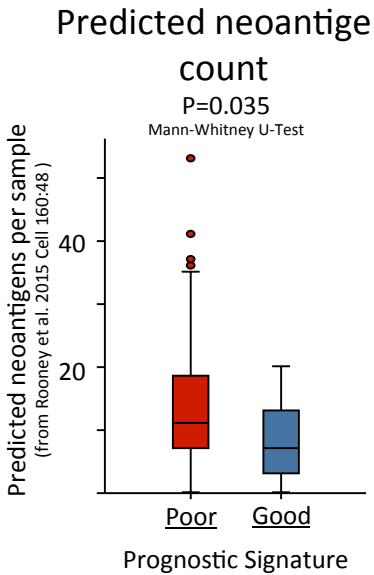
Tailoring Immunotherapy to Tumor Biology: Personalized Immunotherapy?

Immunologically



Immune Sculpting of the TNBC Genome: Good prognosis (i.e. immune rich/low inflammation) TNBC has





Tumor type	immune rich TNBC	immune poor TNBC
Prognosis	**good**	**poor**
Mutation load	**low**	**high**
Neoantigen load	**low**	**high**
Clonal heterogeneity	**low**	**high**
Negative association of heterogeneity and T-cell presence	**strong**	**weak**
Potential state of immuno editing hypothesis	equilibrium phase with pruning of clonal diversity	lack of immunogenicity / immune escape, clonal diversification

No correlation with mutational load and TIL infiltration

Hypothesis: Genomic instability is important to activate the immune response; increasing genomic complexity suppresses the immune response