Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

Breast Cancer Immunotherapy: Early Data Across Agents

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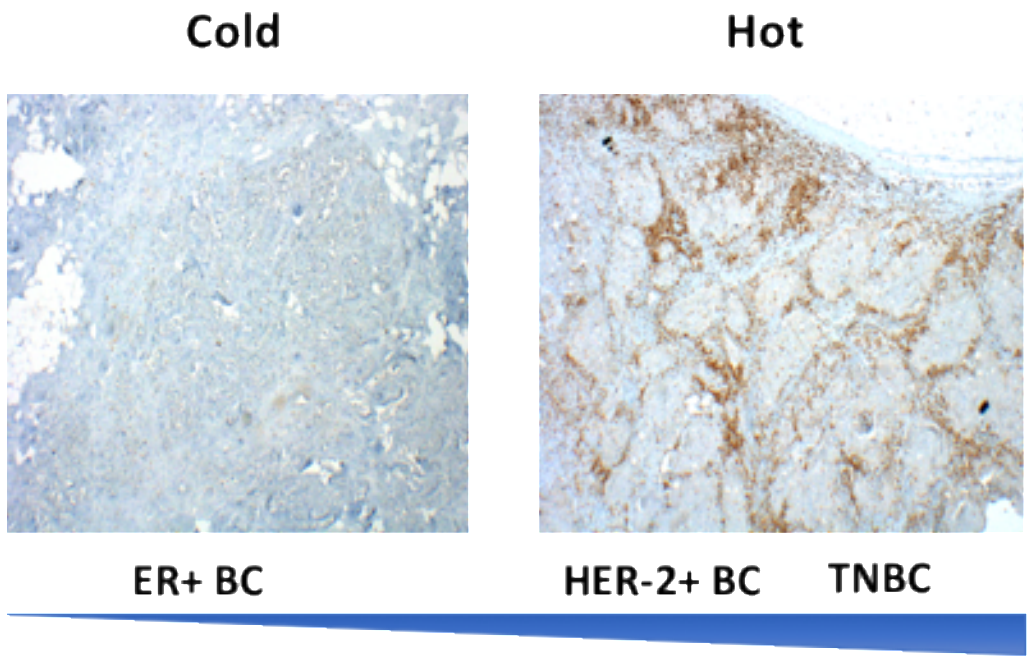
Conflict of Interest

Consulting Fees: Genentech, F Hoffman La Roche, Chugai, GCPR, Gilead, Immune Onc, Shionogi, Mersana

Contracted Research: Abbvie, Astrazeneca, Bolt Therapeutics, Bristol Myers Squibb, Compugen, Corvus, CytomX, EMD Serono, Genentech, F Hoffman La Roche, Immune Onc, Maxcyte, Merck, Next Cure, Silverback, Takeda, Tempest

Other (Grants): HeritX Incorporated, NSABP Foundation, Translational Breast Cancer Research Consortium, Breast Cancer Research Foundation, National Cancer Institute, Department of Defense, Johns Hopkins University, University of California San Francisco, Cornell University, Dana Farber Cancer Institute

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Cimino-Mathews A/Emens LA, unpublished images.

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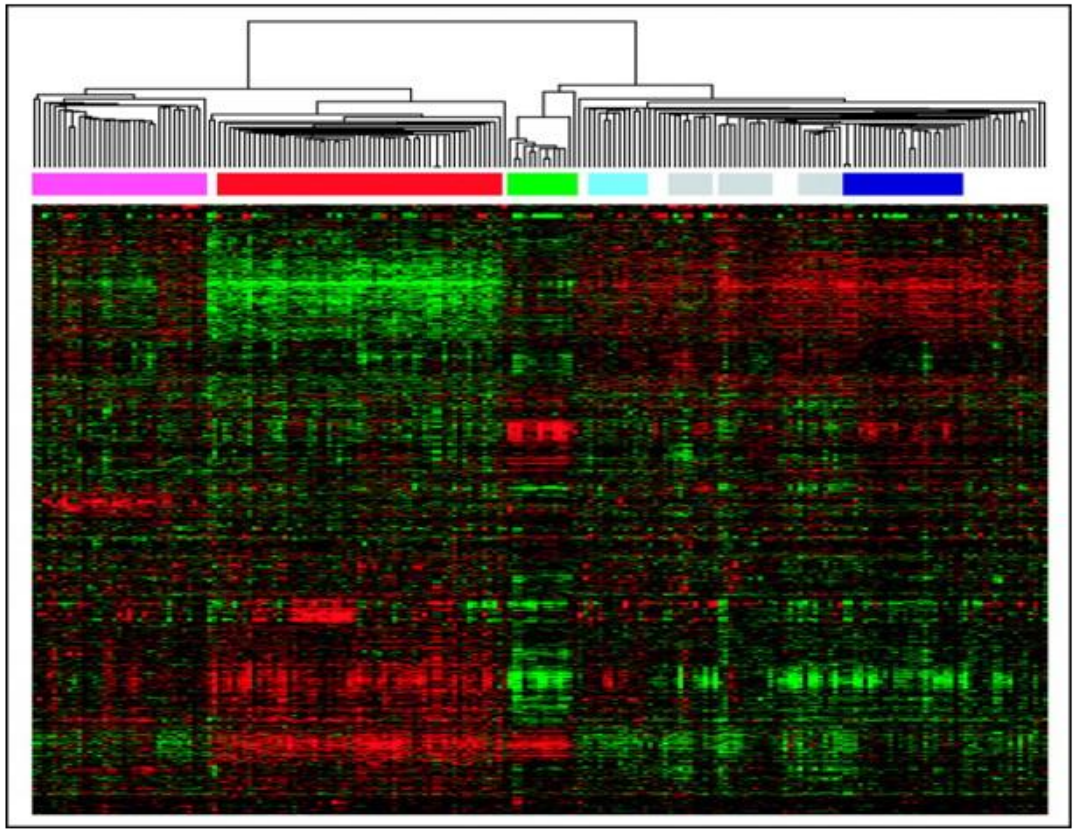
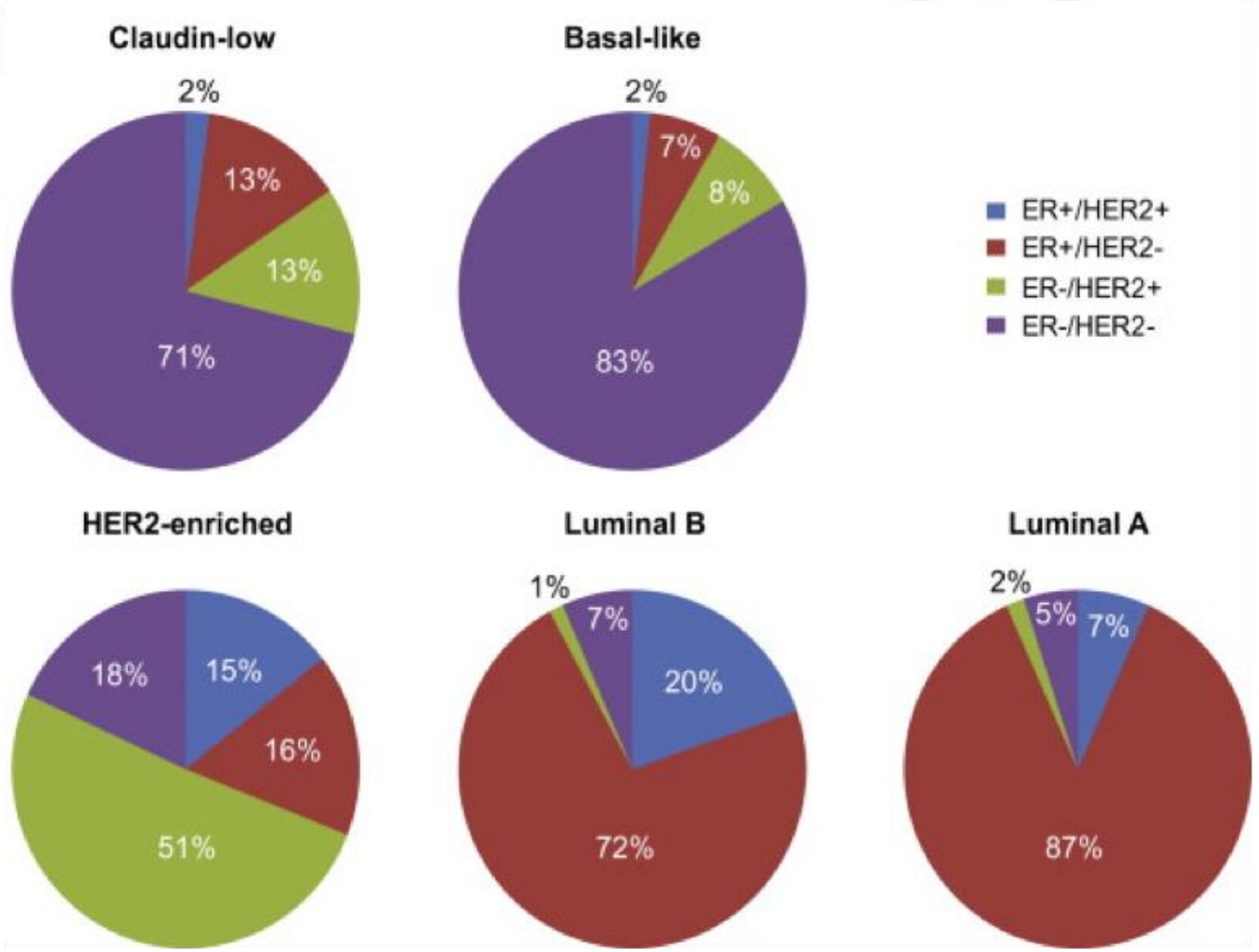
Clinical versus Intrinsic Breast Cancer Subtypes

Intrinsic Breast Cancer Subtypes



HER-2 Basal-like Luminal B Luminal A



Prat/Perou et al Molec Oncol 2011; 25: 5-23..

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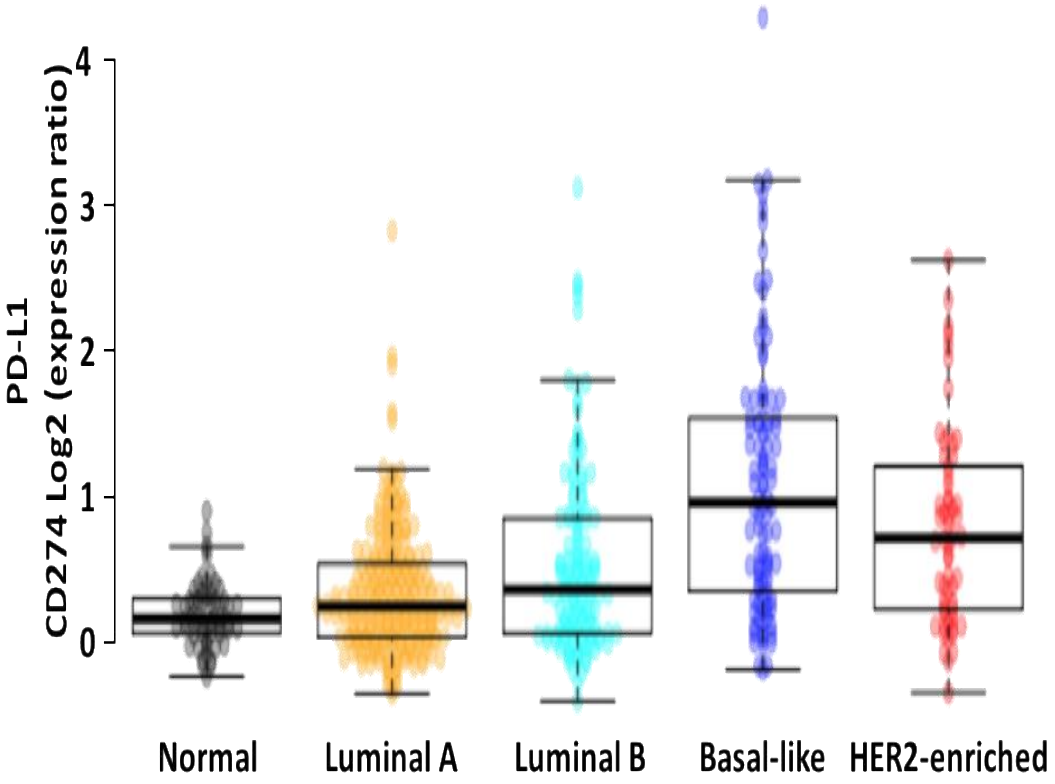
Immunologic Features of Breast Cancer Subtypes

Breast Cancer Subtype	Clinical Phenotype	Immunologic Phenotype
Luminal A	90% ER+ 89% PR+ 14% HER-2+	Lymphocyte predominant 2.9% Median stromal TILs 10% Median intratumoral TILs 1.5% **TILs at Dx not predictive**
Luminal B	98% ER+ 82% PR+ 24% HER-2+	
HER-2-enriched	38% ER+ 20% PR+ 72% HER-2+	Lymphocyte predominant 11.1% Median stromal TILs 15% Median intratumoral TILs 3% **TILs at Dx predictive of response**
Basal-like (includes 70-80% TNBC)	8% ER+ 7% PR+ 7% HER-2+	Lymphocyte predominant 10.6% Median stromal TILs 20% Median intratumoral TILs 5% **TILs at Dx predictive of response**

Kroemer G et al. Nature Med 2015 21: 1128-38.

Targeting the PD-1 Pathway in Breast Cancer



Microarray, TCGA Data

TNBC and HER-2$^+$ BC are high value targets for cancer immunotherapy:

- Higher rates of mutational complexity
- Presence of PD-1$^+$ and PD-L1$^+$ TIL
- Several potentially synergistic targeted therapies
  - Trastuzumab/Pertuzumab
  - TDM1, Sacituzumab
  - Bevacizumab (ex US)

ER+ breast cancers present the challenge of transforming tumors from cold to hot

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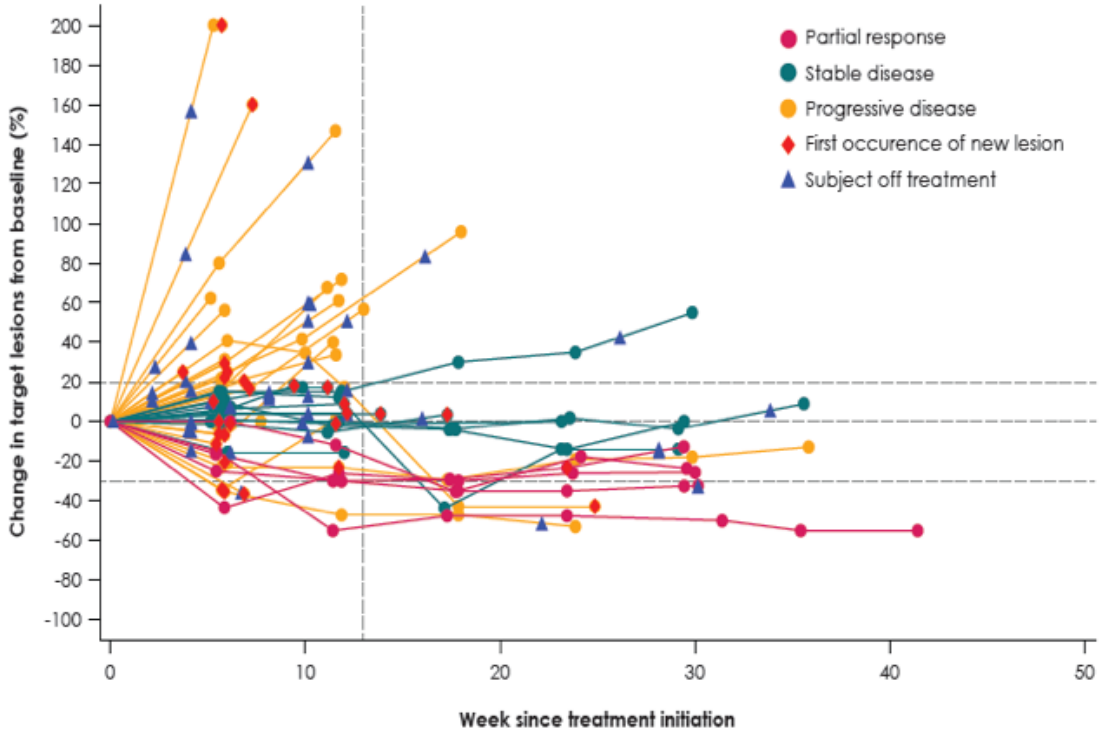
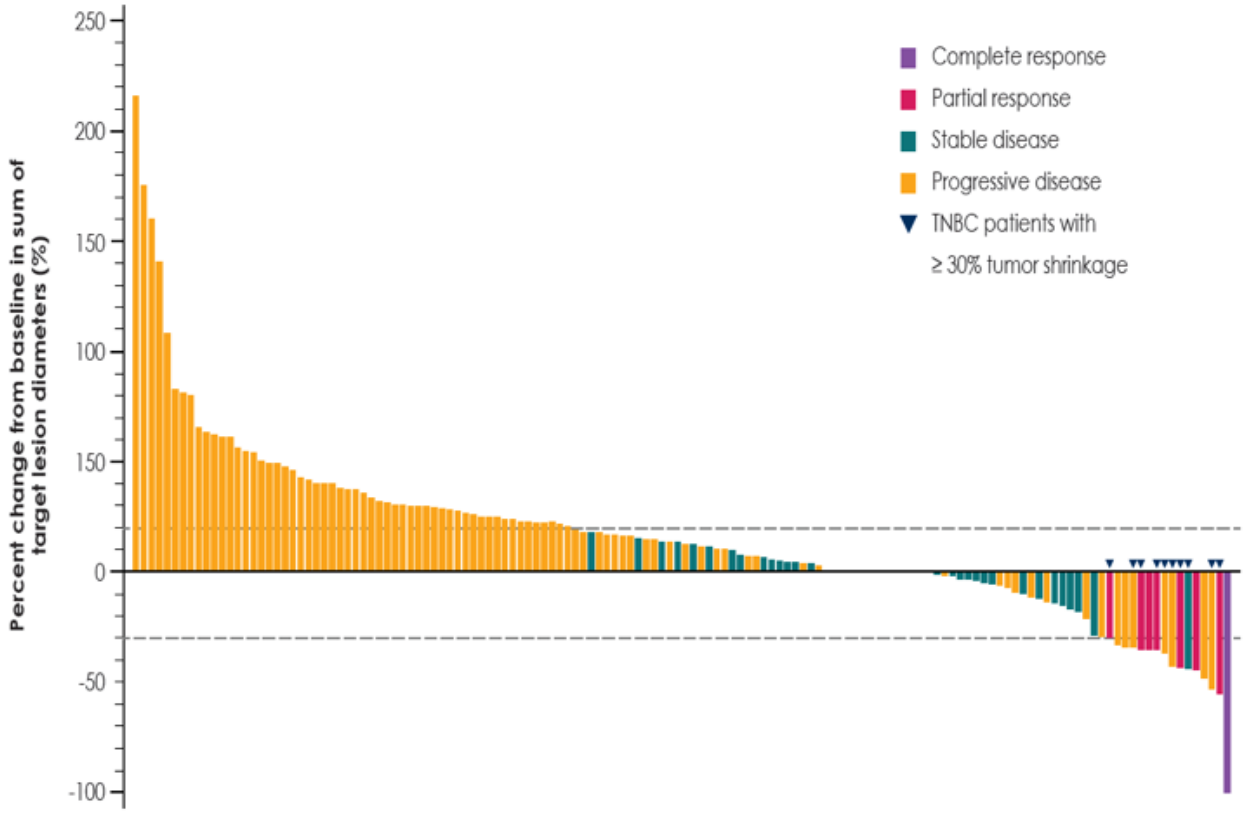
Avelumab Activity in Breast Cancer Patients





- 168 PD-L1 unselected patients/all BC subtypes
- ORR in breast cancer = 4.8%
- 1 CR, 7 PRs, 39 patients with SD; DCR = 28%

Dirix L et al SABCS 2015

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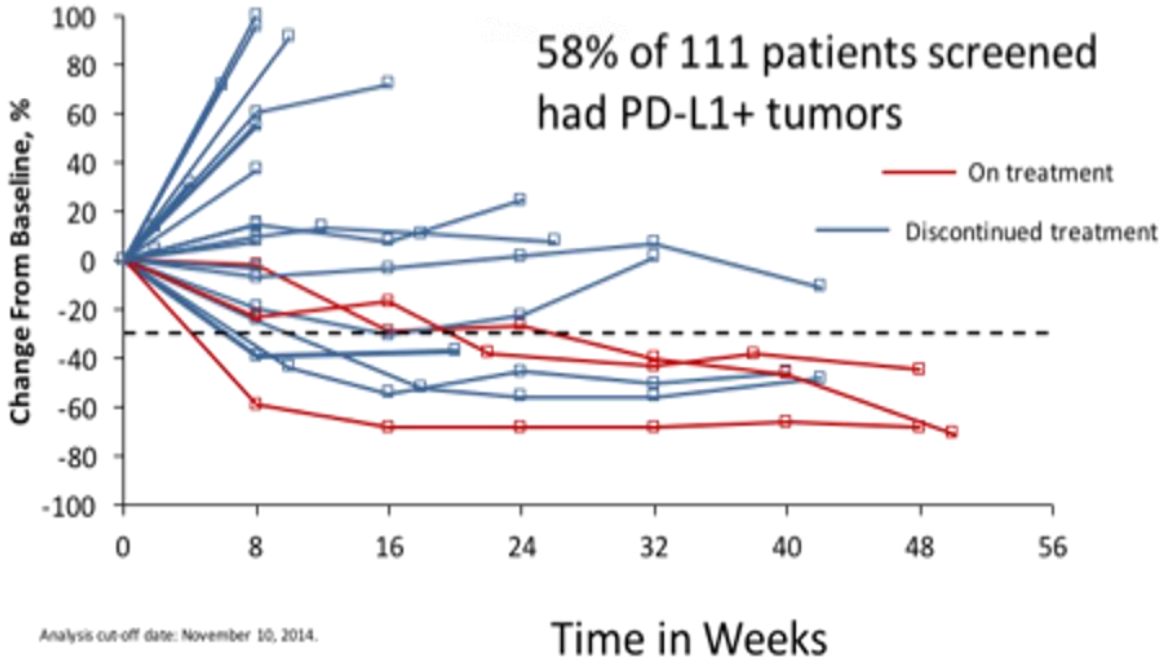
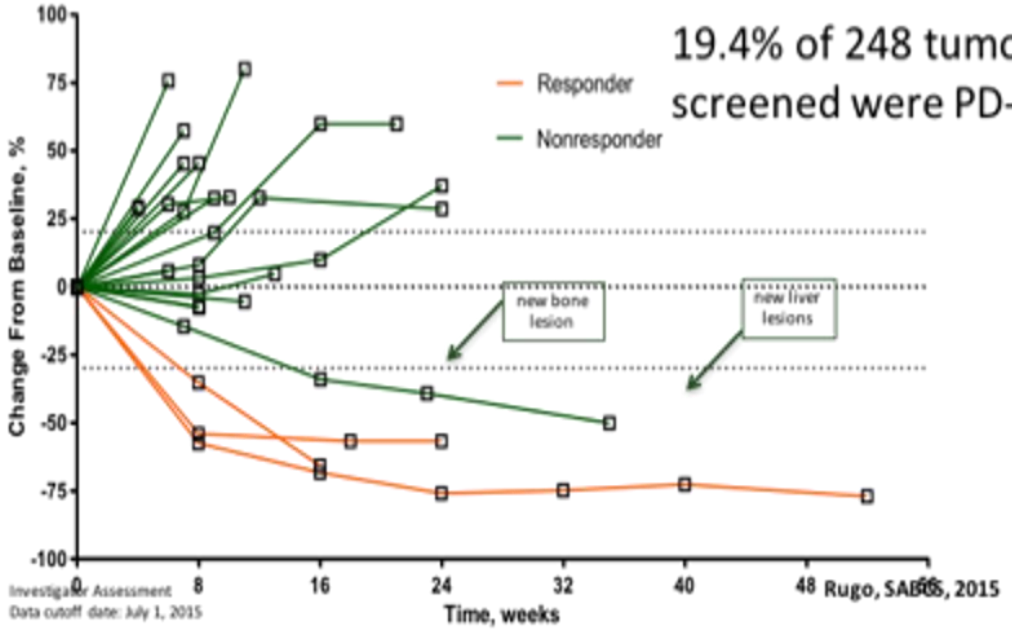
Pembrolizumab Activity in PD-L1+ TNBC and ER+ BC

- ORR: 18.5%; PFS rate at 24 weeks: 23.3% (n= 27)
- 1 CR, 4 PRs, 7 SD, 3 of 5 responses ongoing



- ORR: 12%; PFS rate at 24 weeks: 20% (n=20)
- No CRs, 3 PRs, evidence of pseudoprogression



Nanda R et al. JCO 2016;34:2460.
Rugo H et al. SABCS 2015.

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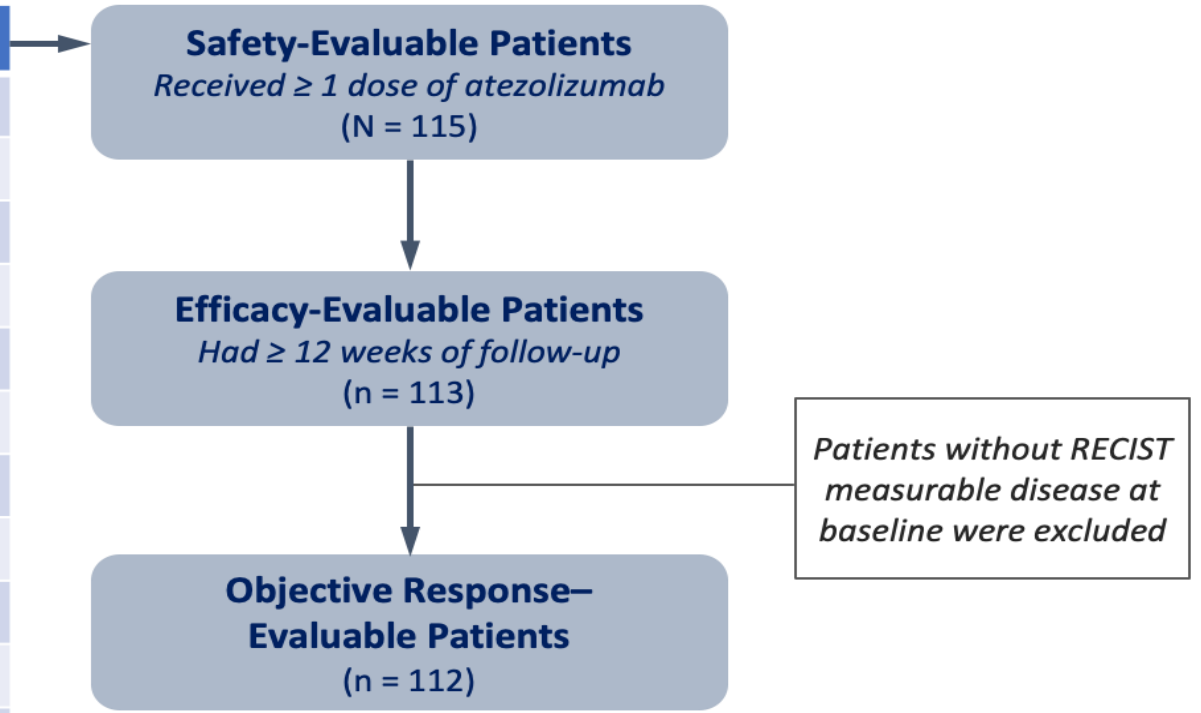
Atezolizumab Monotherapy in Metastatic TNBC: Patient Population

Baseline Characteristics	Patients (N = 115)
Median age (range)	53 y (29 to 82)
ECOG PS, 0 | 1 | 2	46% | 52% | 2%
Visceral metastatic sites[a]	65%
Bone metastatic sites[b]	30%
PD-L1 status on IC[c]	
IC0/1 (< 5%)	33%
IC2/3 (≥ 5%)	63%
Median prior systemic therapies (range)[d]	7 (0 to 21)
Anthracycline | taxane	85% | 94%
Platinum | bevacizumab	58% | 21%
Current line of therapy,[e] 1L | 2L | 3L+	17% | 24% | 58%



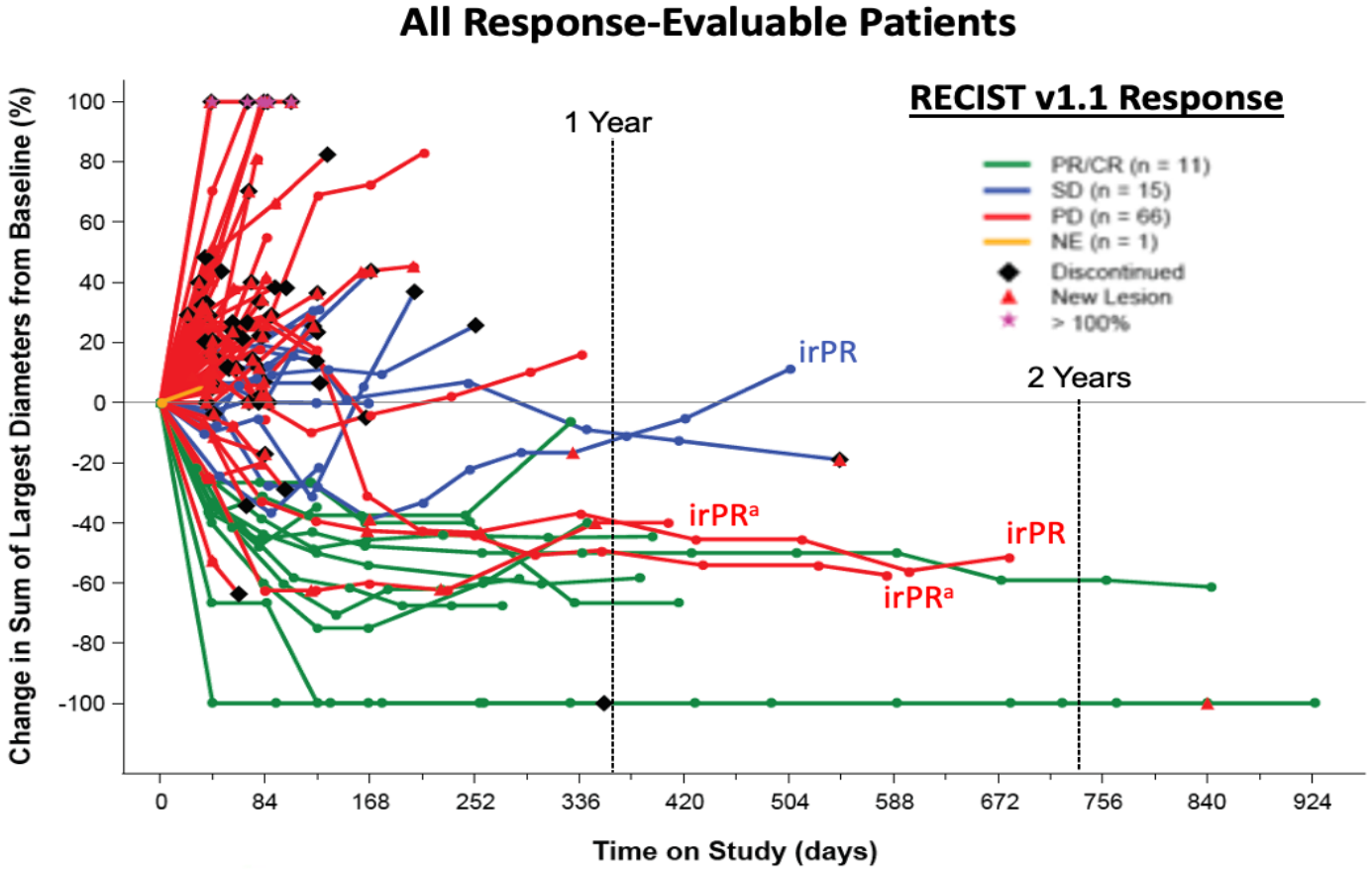
- Prior to receiving atezolizumab, most patients were heavily pretreated

- At data cutoff, median treatment duration was 2.1 mo (range, 0.0-36.6)
- Median of 4 cycles (range, 1-45)

1L, first line; 2L, second line; 3L, third line. [a] Includes lung, liver, adrenal and pelvis metastatic sites. [b] Includes bone and other sites. [c] Four patients (4%) had unknown IC status. [d] Refers to all treatment settings. [e] Refers to treatment in metastatic setting only.
Data cutoff: March 31, 2016

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

Classical and Atypical Responses in TNBC Patients Treated with Atezolizumab



- Clinical benefit was observed in some patients with RECIST v1.1 SD or PD status

Overall TNBC cohort

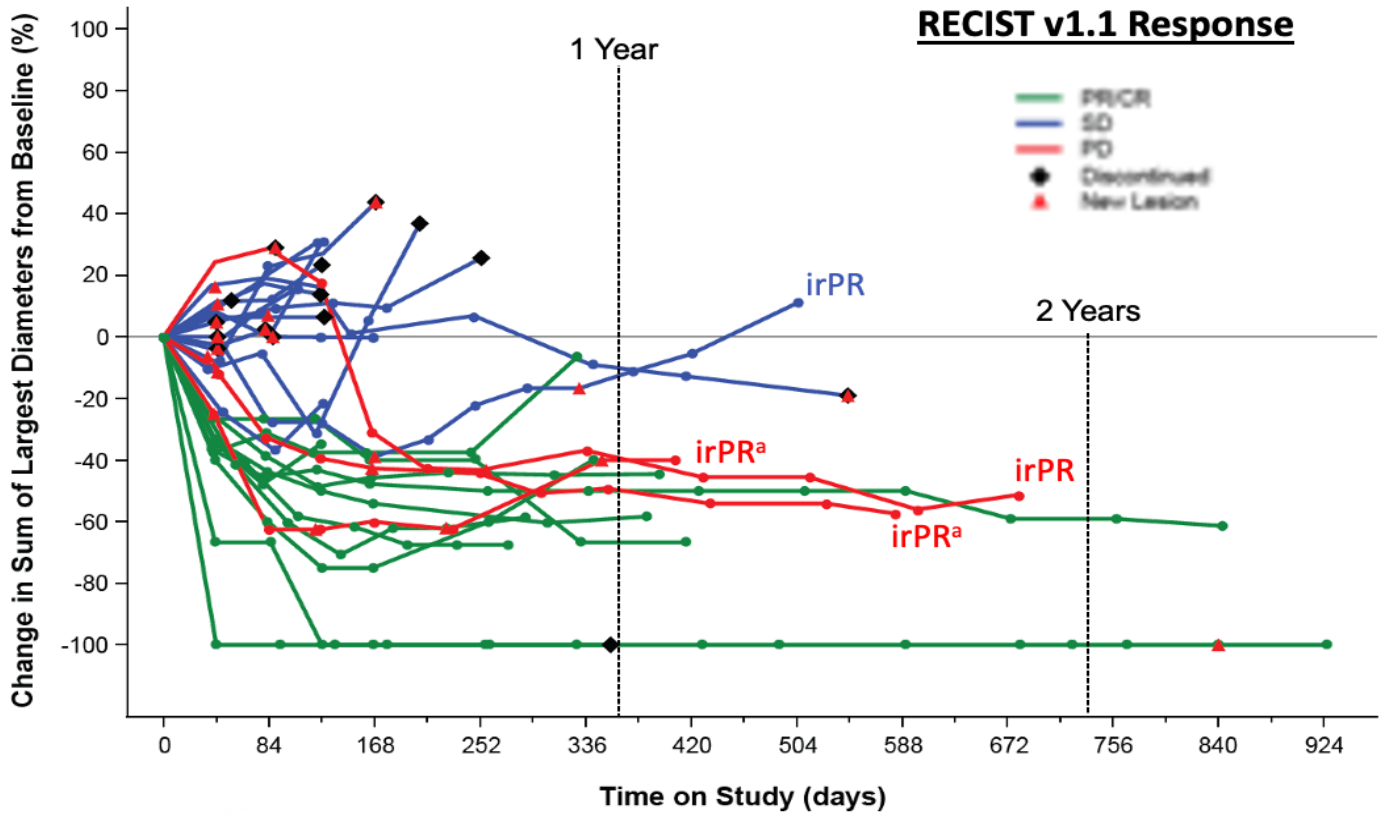
Criteria	Median DOR (range)	Median PFS (95% CI)
RECIST v1.1	21.1 mo (2.8 to 26.5+)	1.4 mo (1.3, 1.6)
irRC	21.1 mo (2.8 to 33.9+)	1.9 mo (1.4, 2.6)

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

irPR, PR per irRC; SLD, sum of target lesion longest diameter. [a] Re-treatment period not plotted.
Confirmed, investigator-assessed RECIST responses are included for patients with post-baseline tumor measurements.
Data cutoff: March 31, 2016

Classical and Atypical Responses in TNBC Patients Treated with Atezolizumab

Patients With RECIST v1.1 Response or Stable Disease or irRC Response



irPR, PR per irRC; SLD, sum of target lesion longest diameter. [a] Re-treatment period not plotted.
Confirmed, investigator-assessed RECIST responses are included for patients with post-baseline tumor measurements.
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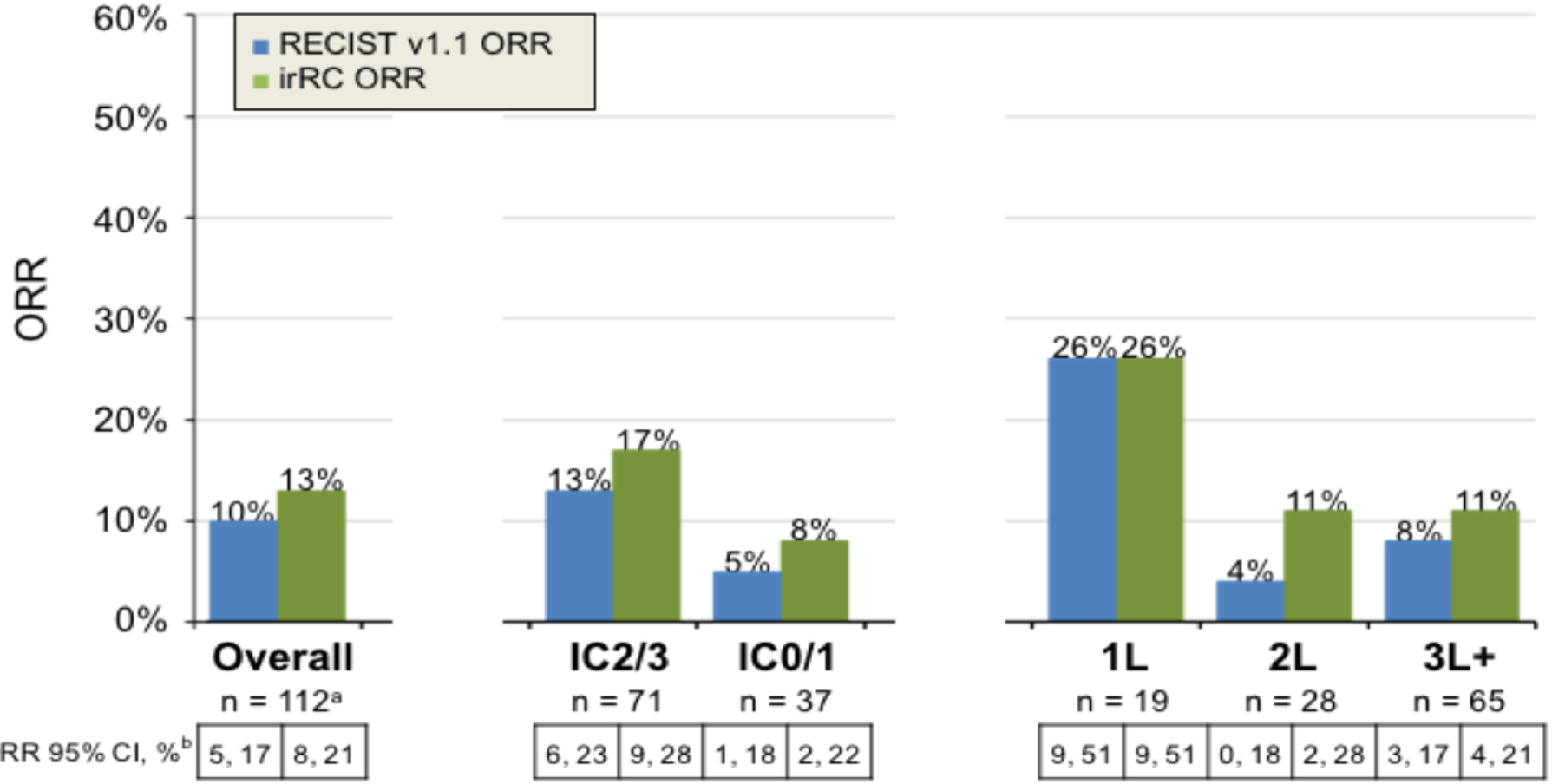
Schmid P, et al. AACR 2017
Phase Ia Atezolizumab in TNBC

TNBC Response Rates to Atezolizumab by Subgroup



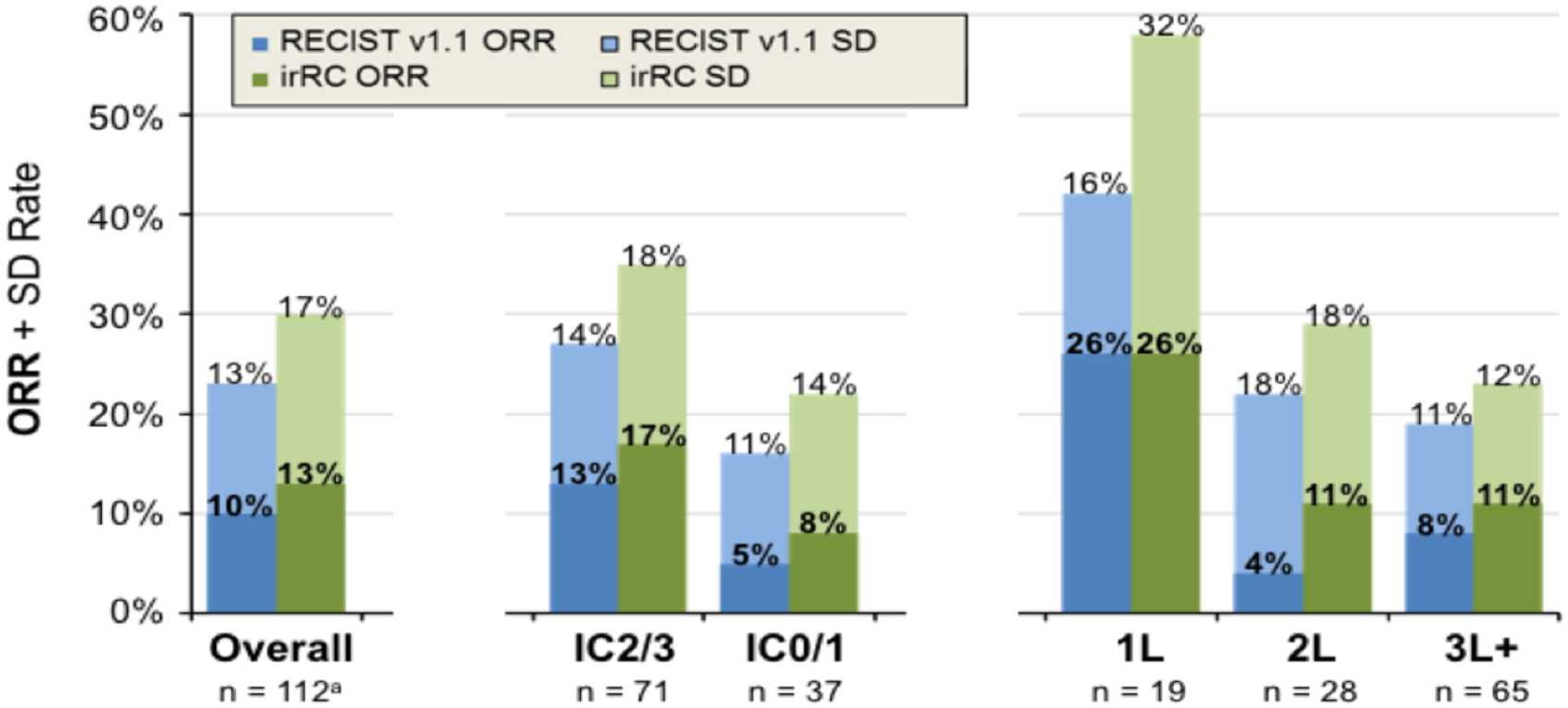
- Numerically higher ORRs were observed in IC2/3 and 1L subgroups
- irRC criteria captured non-classical responses to atezolizumab

[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.

#LecnACI

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

TNBC Response Rates to Atezolizumab by Subgroup



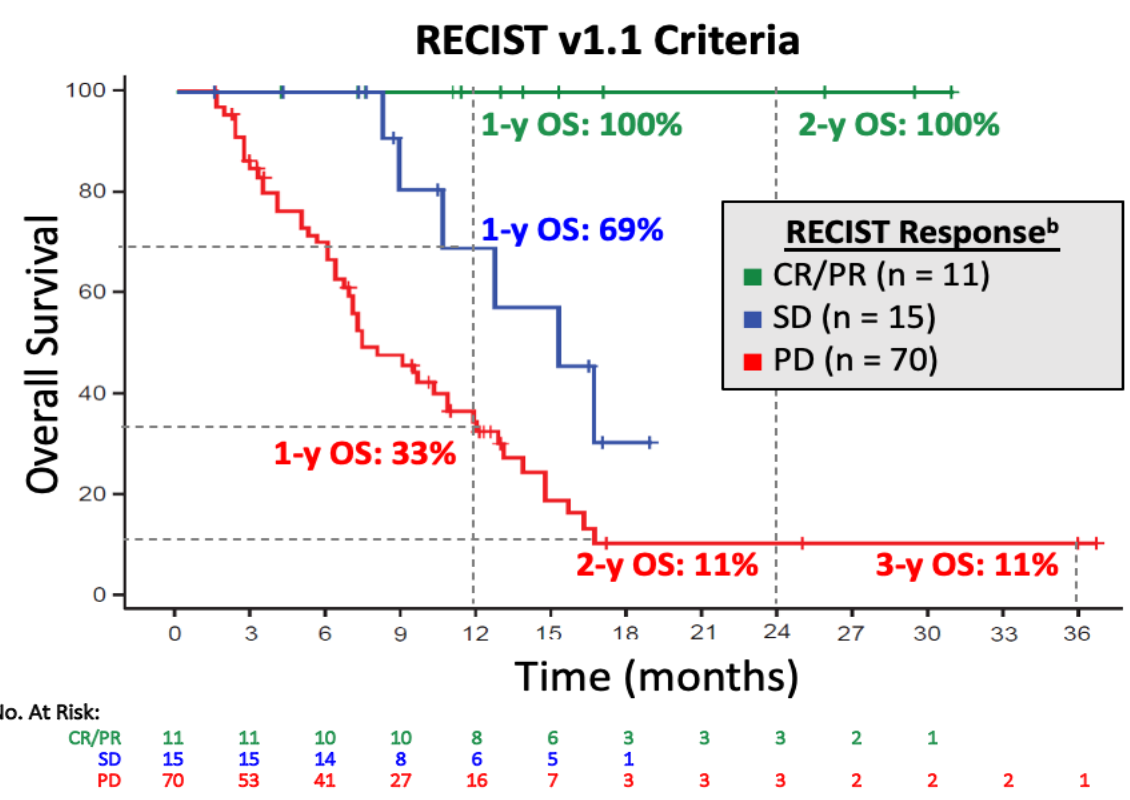
- Numerically higher ORRs were observed in IC2/3 and 1L subgroups
- irRC criteria captured non-classical responses to atezolizumab
- Best response of SD were also observed
  - DCR[b] per RECIST v1.1 was 23% in all patients
    - 27% in IC2/3 patients
    - 16% in IC0/1 patients

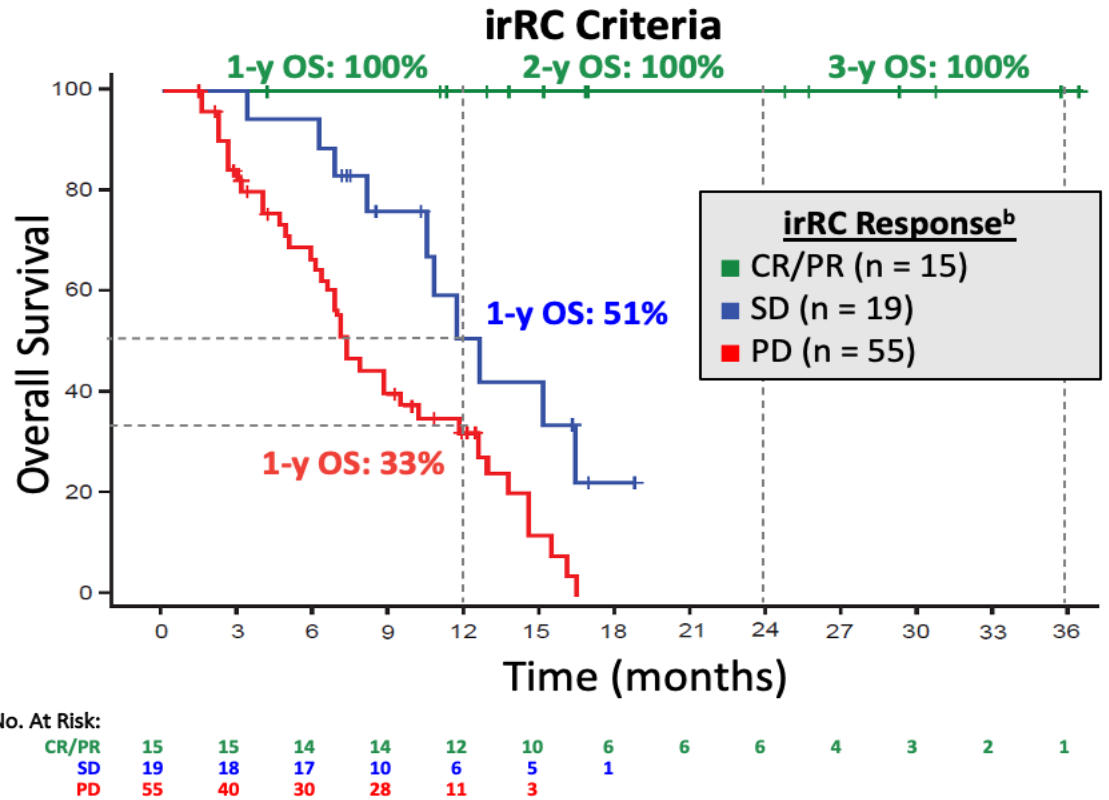
DCR, disease control rate. [a] Objective response–evaluable patients. Four patients had unknown PD-L1 status. [b] Defined as CR + PR + SD ≥ 3 months. Confirmed investigator-assessed responses are plotted. Patients with missing or unevaluable responses are included (16 per RECIST v1.1 and 23 per irRC). Data cutoff: March 31, 2016.

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

Overall Survival by Response Status

- Median OS was 9.3 mo (95% CI: 7.0, 12.6) in all patients[a]
  - Landmark OS rates (95% CI) were: 41% (31, 51) at 1 year, and 22% (12, 32) at both 2 and 3 years



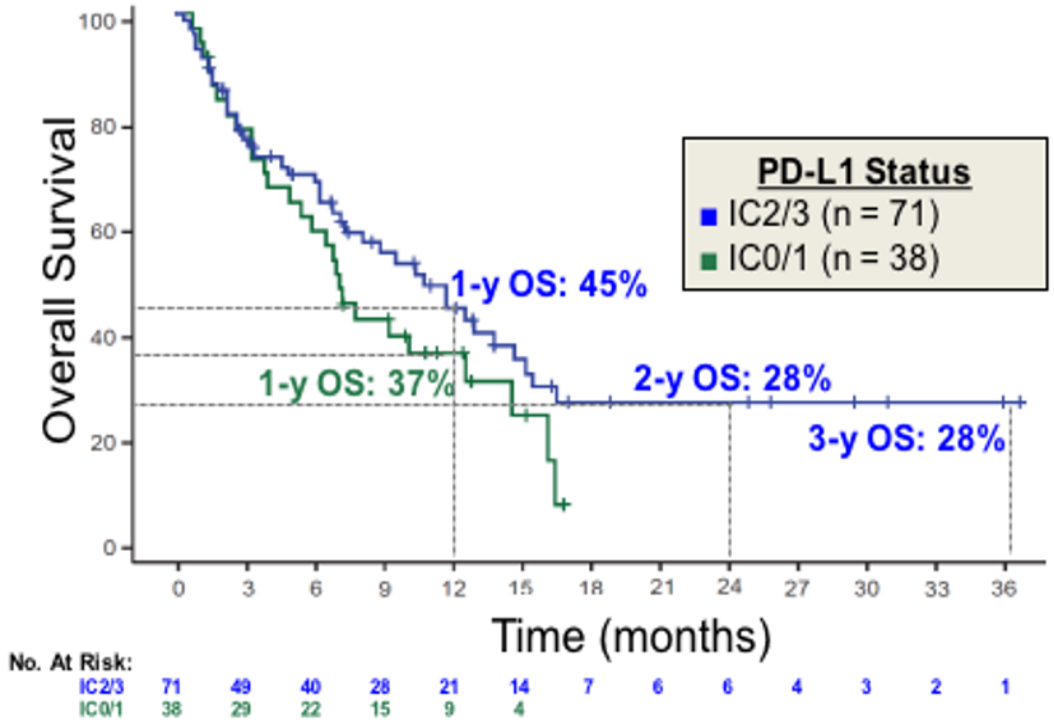


- Pseudo-progression was observed in patients with RECIST PD and long-term OS

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

[a] Median survival follow-up (range) was 15.2 mo (0.4+ to 36.7) in all patients, 17.0 mo (0.43+ to 36.7) in IC2/3 patients and 12.8 mo (0.8+ to 16.9) in IC0/1 patients. [b] Patients included in the Kaplan-Meier plots were alive for ≥ 6 weeks. Data cutoff: March 31, 2016.

Overall Survival with Atezolizumab by PD-L1 Status



	All Pts (n = 113)	PD-L1 Status[a] IC2/3 (n = 71)	PD-L1 Status[a] IC0/1 (n = 38)
mOS (95% CI)	9.3 mo (7.0, 12.6)	10.7 mo (7.2, 14.7)	7.1 mo (5.1, 12.6)

- Longer OS was observed in patients with higher PD-L1 IC status

[a] Four patients had unknown PD-L1 status. Median survival follow-up (range) was 15.2 mo (0.4+ to 36.7) in all patients, 17.0 mo (0.43+ to 36.7) in IC2/3 patients and 12.8 mo (0.8+ to 16.9) in IC0/1 patients. Data cutoff: March 31, 2016.

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Phase Ia Atezolizumab in TNBC

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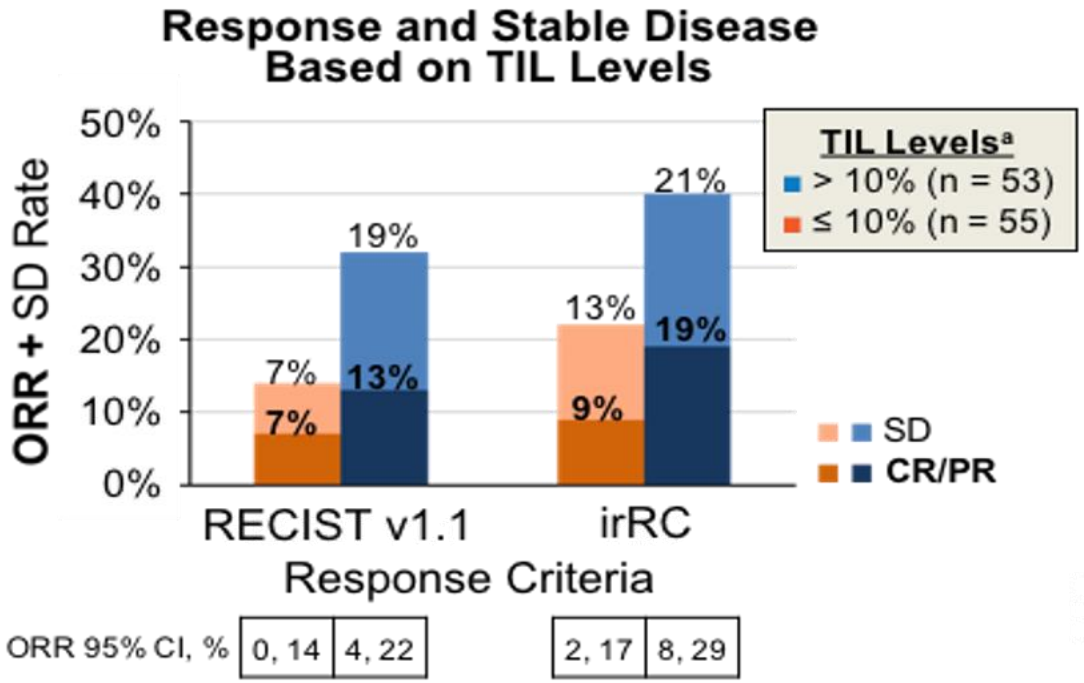
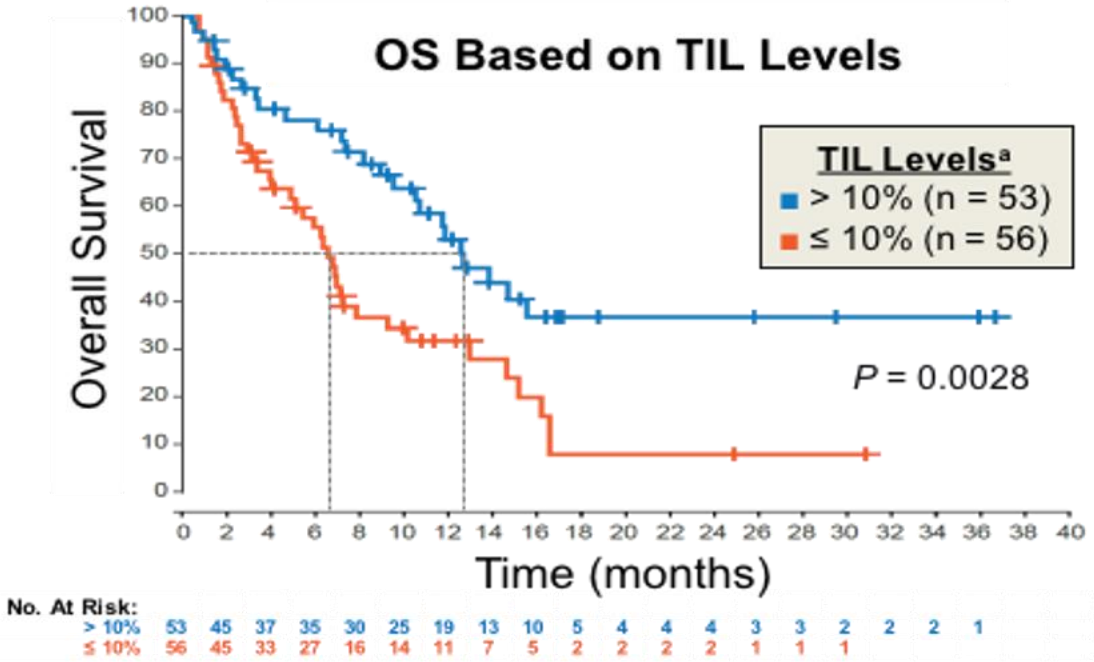
Association of Response and Survival with TILs

- Median TIL infiltration (% tumor area) in tumors from enrolled patients defined the cutoff used for analysis





- Higher ORR and longer OS were seen with higher baseline TIL infiltration
- Similar results were observed with CD8 infiltration

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

[a] Samples unevaluable for TIL assessments (6 per RECIST v1.1 and 5 per irRC) are not included. Objective response–evaluable population includes patients with unevaluable response assessments (16 per RECIST v1.1 and 23 per irRC). Log-rank (Mantel-Cox) *P* value is exploratory. Data cutoff: March 31, 2016.

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

KEYNOTE-086: Phase 2 Study of Pembrolizumab in Metastatic TNBC

Cohort A:
Previously Treated
PD-L1 Unselected

386 patients screened

170 patients enrolled/treated
- **105 PD-L1 positive (61.8%)**
- **64 PD-L1 negative (37.6%)**
- **1 PD-L1 unknown (0.6%)**

PD-L1 is an imperfect biomarker.
Context is important.

	Previously Treated Any PD-L1 Expression Cohort A			*First Line PD-L1 Selected*
	All (n=170)	**PD-L1+ (n=105)**	**PD-L1- (n=64)**	***PD-L1+ (n=52)***
ORR, %	**4.7%**	**4.8%**	**4.7%**	***23.1%***
DCR, %	**7.6%**	**9.5%**	**4.6%**	
CR, n	**1**	**1**	**0**	
PR, n	**7**	**4**	**3**	
SD, n	**35**	**22**	**112**	

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Adams S, ASCO 2017

PD-1/PD-L1 Blockade in Breast Cancer

Antibody	Target	Subtype	Patients	ORR
Avelumab	PD-L1	All	168	4.8%
		PD-L1+ All	12	33.3%
		TNBC	58	8.6%
		PD-L1+ TNBC	9	44.4%
Pembrolizumab	PD-1	PD-L1+ TNBC	20	18.5%
		PD-L1+ ER+HER-2-	21	12%
Atezolizumab	PD-L1	TNBC	112	10%
		PD-L1+ TNBC	71	13%

Dirix L et al SABCS 2015

Nanda R et al JCO 2016;34:2460
Rugo et al SABCS 2015

Emens LA et al AACR 2015
Schmid P et al AACR 2017

The Major Challenges of Breast Cancer Immunotherapy Today

- Subtype framework—well established but the lines are blurred
  - Clinical subtypes
  - Intrinsic subtypes
  - Immune profiles
- Shared antigens vs. neoantigens and the T cell repertoire
- Many standard therapies with significant efficacy
- Effects of drugs on the tumor *and* the immune system
- Matching patients to the most relevant combinations
- **Converting nonresponders to responders**

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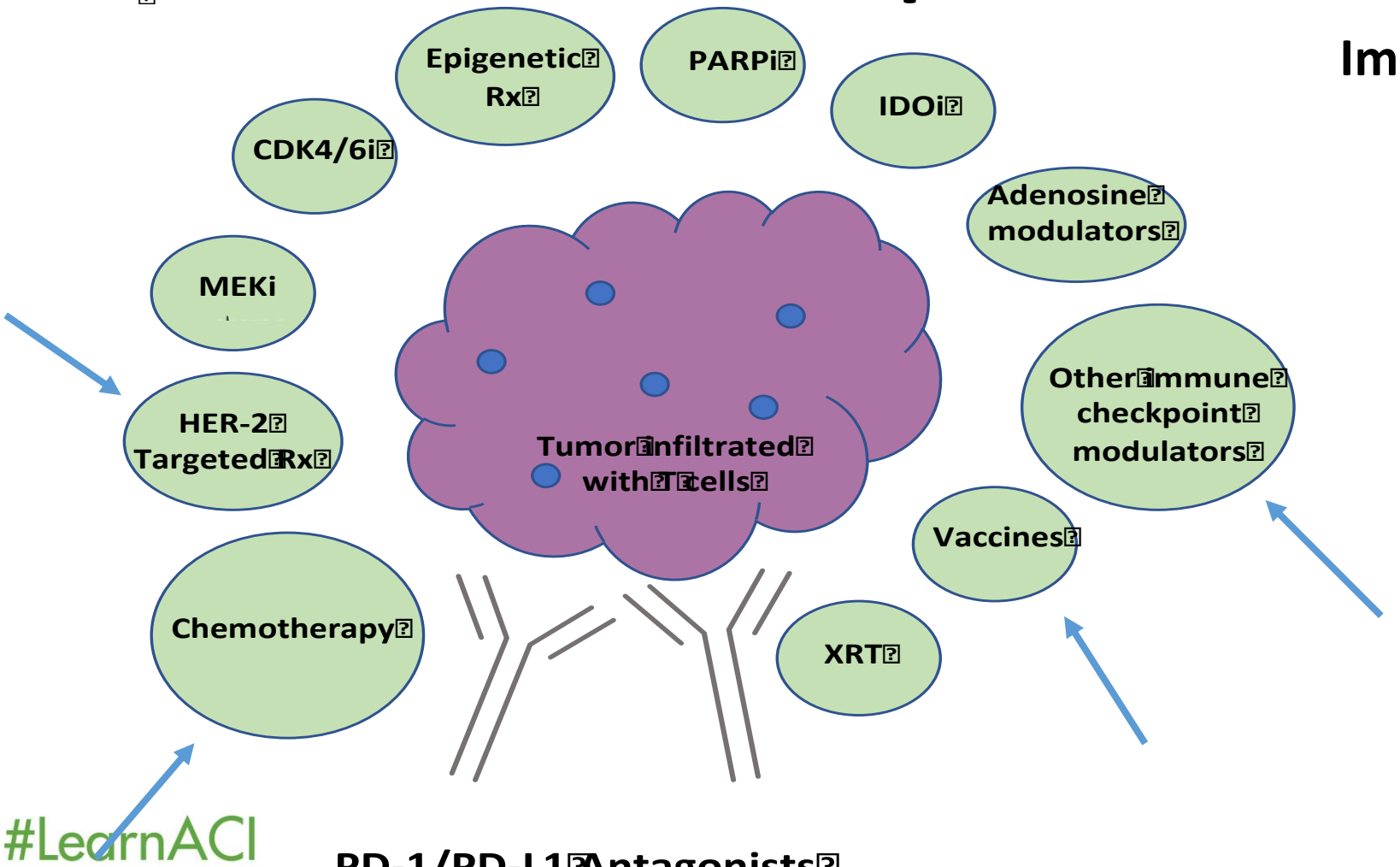
Selected Promising Combination Immunotherapies for Breast Cancer



Important Variables:

Drug

Dose

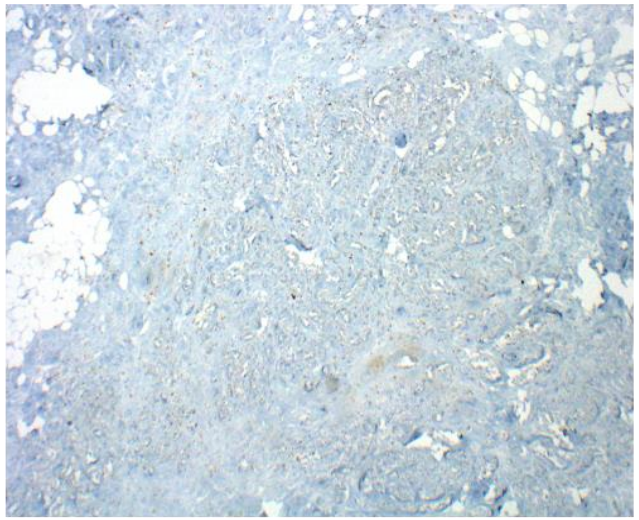
Sequence

Individualization to tumor
- **mutated vs. shared Ags**
- **immunoregulation**

One Framework for Personalizing Breast Cancer Immunotherapy

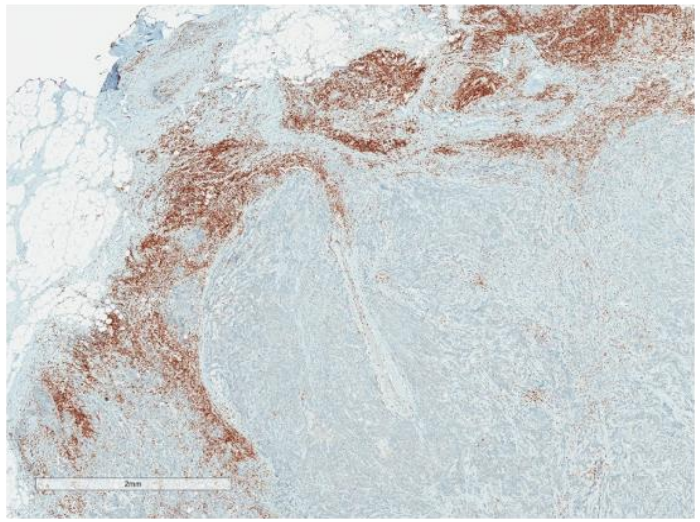
Patterns of T Cell Infiltration

Non-inflamed



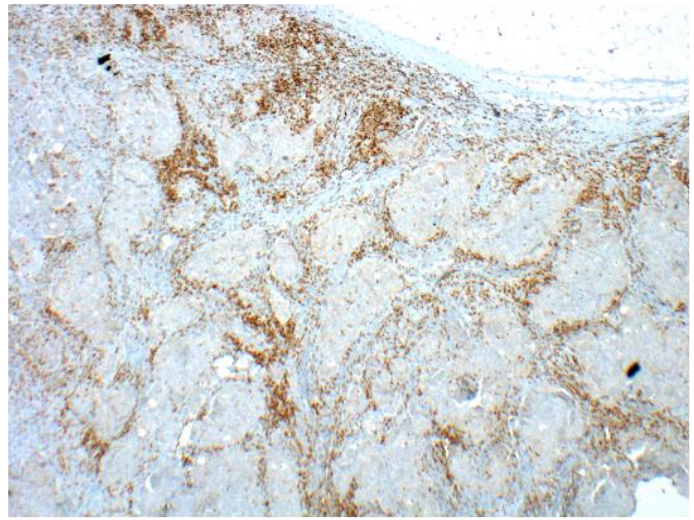
Chemotherapy, XRT
HER-2-directed antibodies
Vaccines, STING agonists

Immune-Excluded



Bevacizumab
Chemokine Modulators

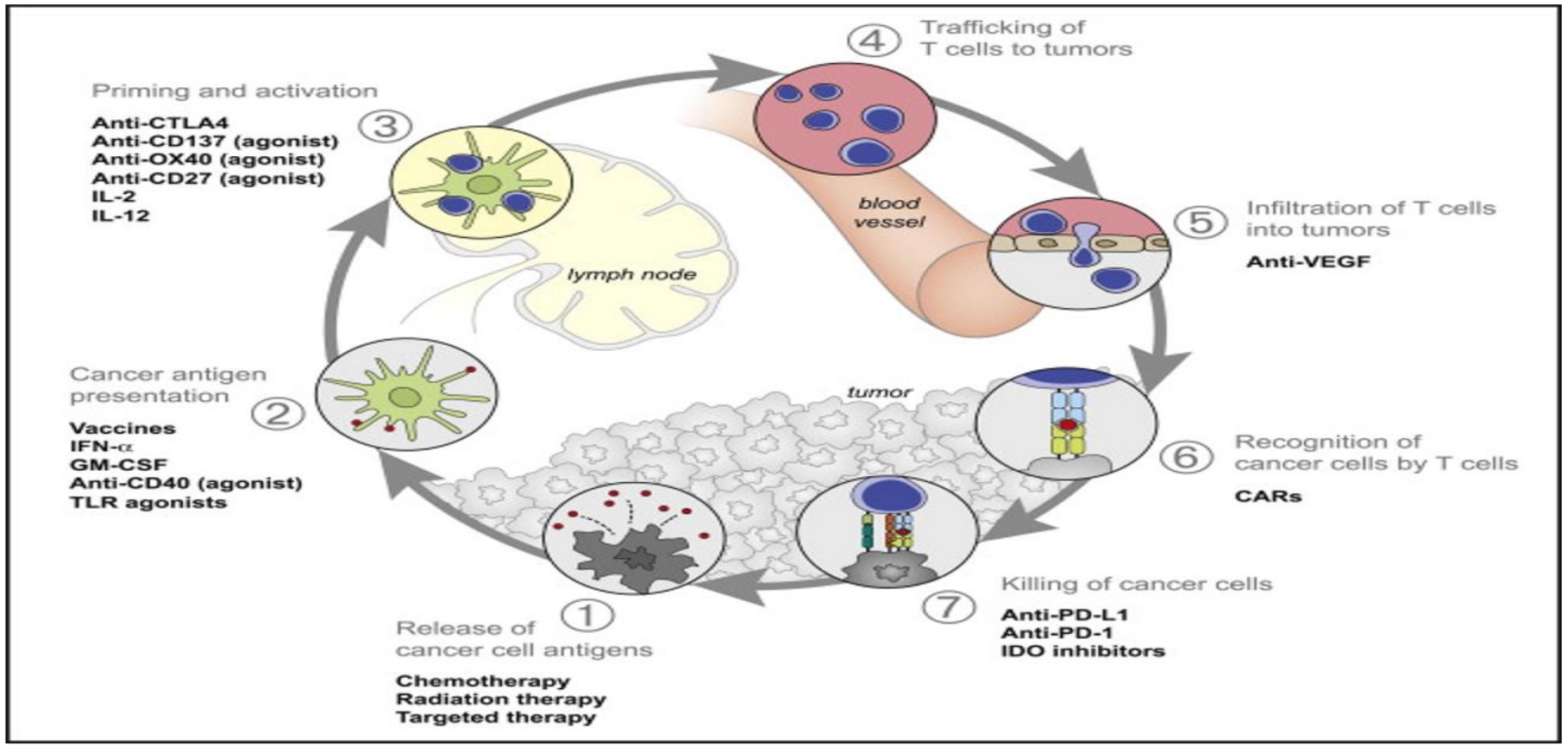
Inflamed



Anti-PD-1/PD-L1
IDO inhibition
A2AR 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.

Mechanism-Driven Cancer Immunotherapy Combinations



Chen DS and Mellman I. Immunity 39:1-10, 2013

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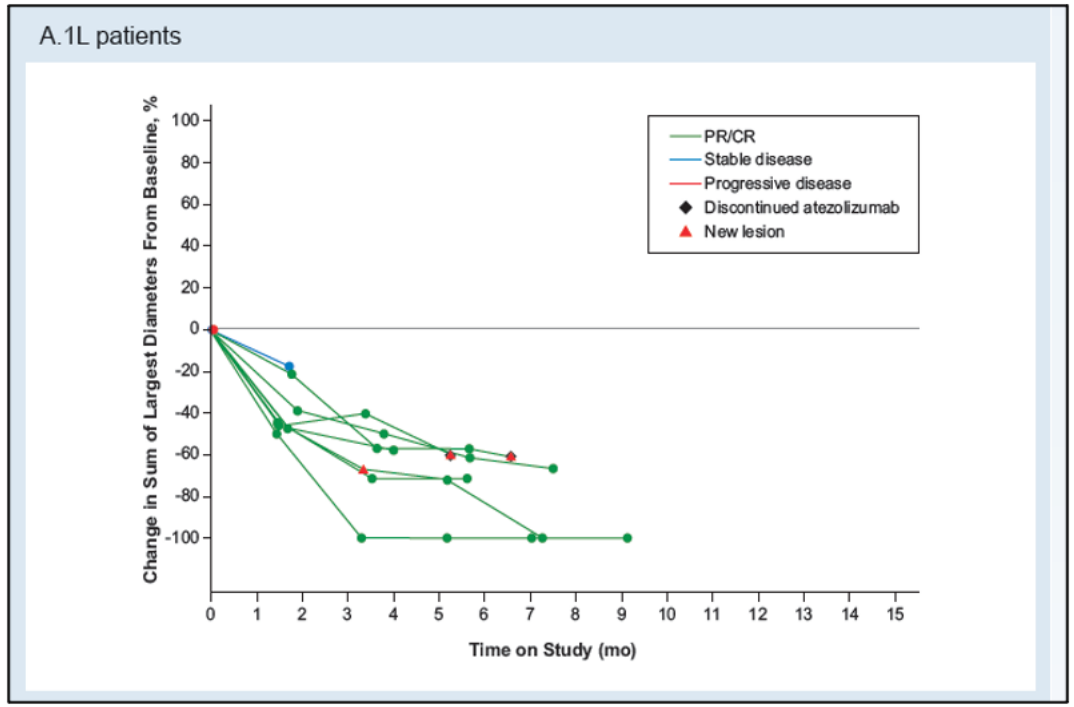
Atezolizumab and Nab-Paclitaxel Have Activity in mTNBC

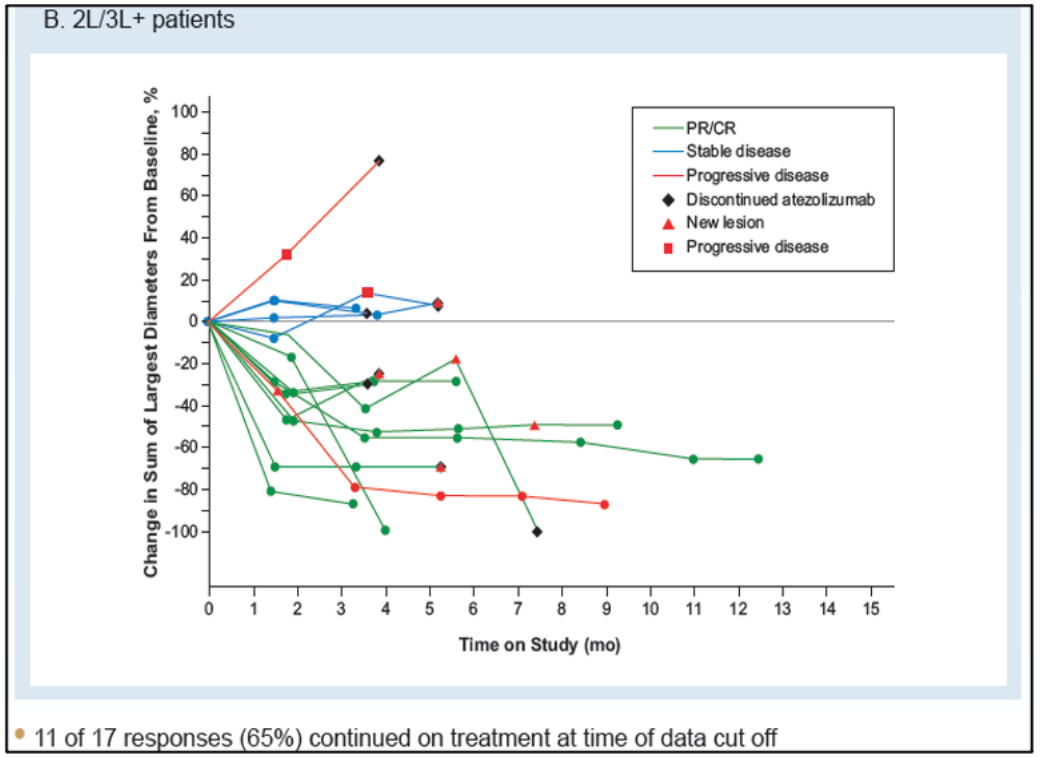
Change in Tumor Burden Over Time with Line of Therapy

- PD-L1 unselected patients
- Atezolizumab 840 mg every 2W; Nab-paclitaxel 100 mg/m^2 weekly
- Confirmed ORR = 41.7%; 3 pseudoprogressors

n = 9 (ORR ~ 67%)



n = 15 (ORR ~ 25-28%)



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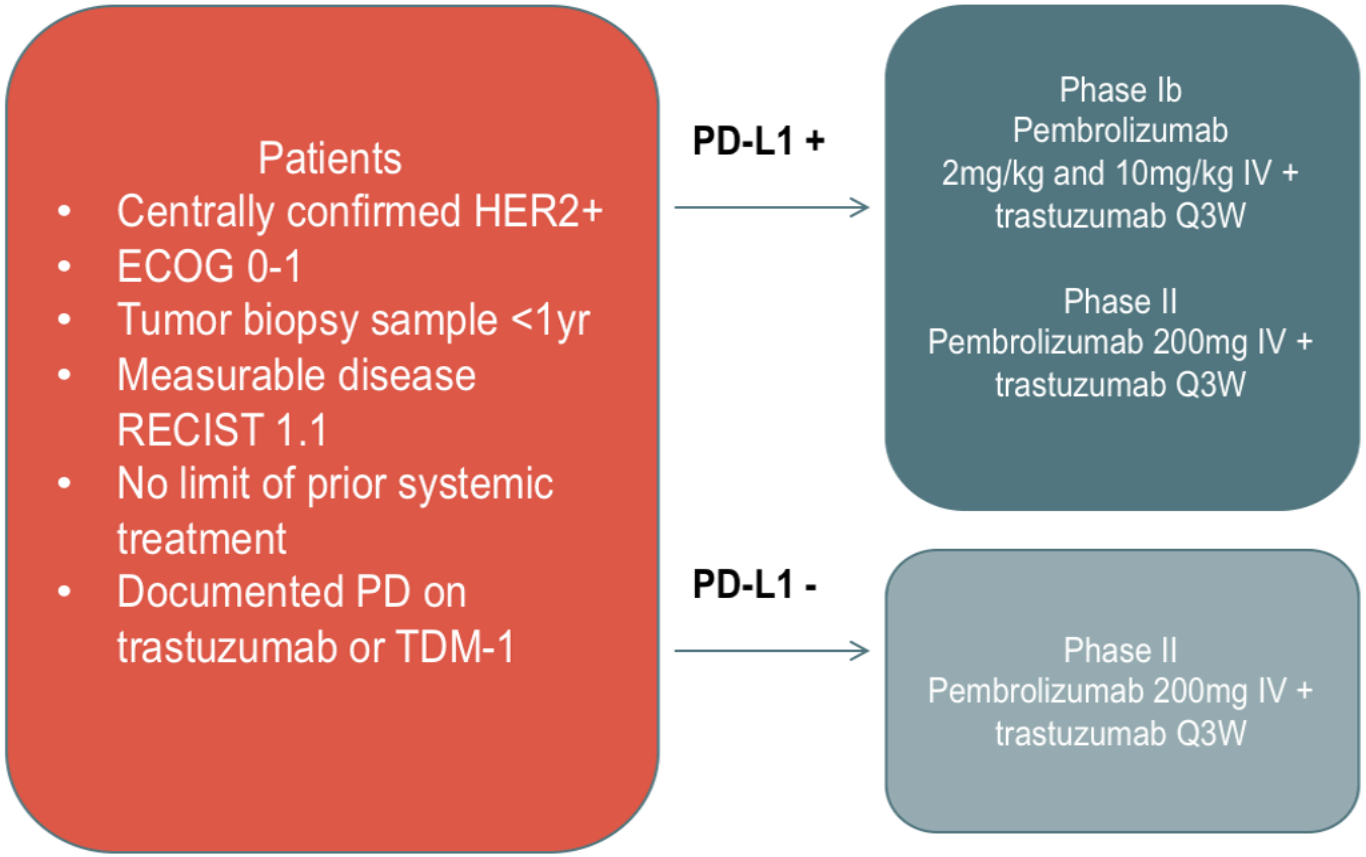
Adams S, et al SABCS 2015

PANACEA: A Phase 1b/2 Trial of Pembrolizumab and Trastuzumab in Patients with Trastuzumab^{R} Metastatic HER-2+ Breast Cancer



- Determine RP2D of pembrolizumab in combination wit trastuzumab
- Evaluate safety and efficacy in PD-L1+ and PD-L1- HER-2+ breast cancer progressing on trastuzumab-based therapy
- Explore the possible association of sTILs with efficacy

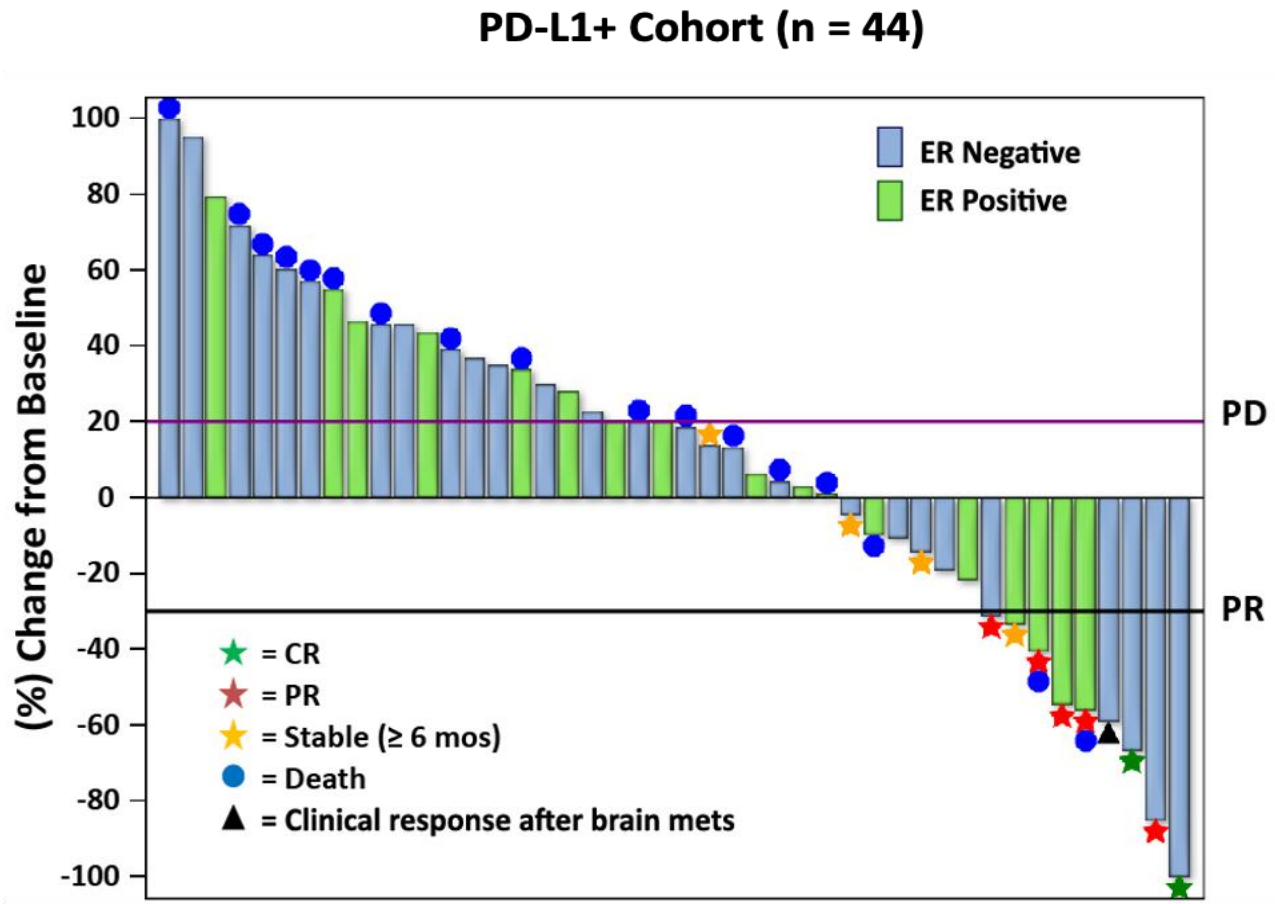
Treat to PD, toxicity, withdrawal, or max 2 years.

Loi S et al SABCS 2017

PANACEA: A Phase 1b/2 Trial of Pembrolizumab and Trastuzumab in Patients with Trastuzumab^{R} Metastatic HER-2+ Breast Cancer

Response Rates by RECISTv1.1

	PD-L1+ (n = 46)	PD-L1- (n = 12)
ORR	15.2% (7/46)	0
DCR	24% (11/46)	0
CR	2	-
PR	5	-
SD	7	2



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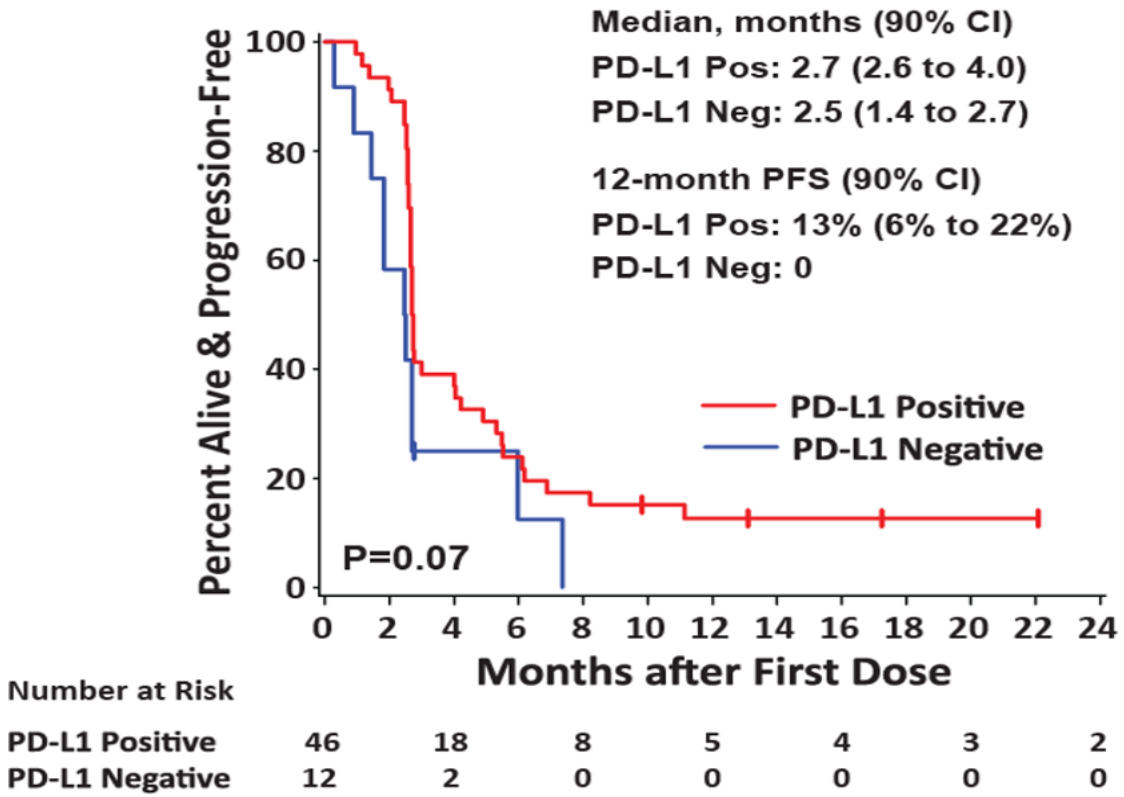
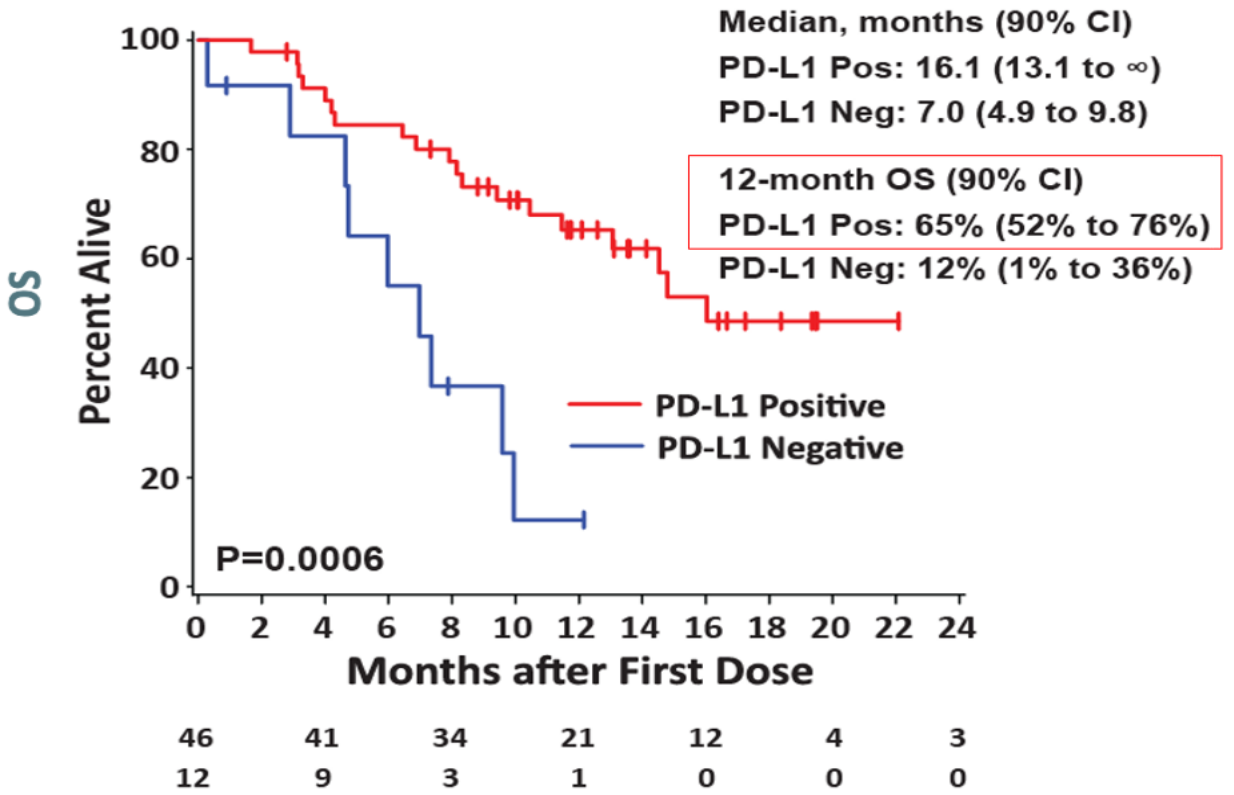
Loi S et al SABCS 2017

PANACEA: A Phase 1b/2 Trial of Pembrolizumab and Trastuzumab in Patients with Trastuzumab^{R} Metastatic HER-2+ Breast Cancer





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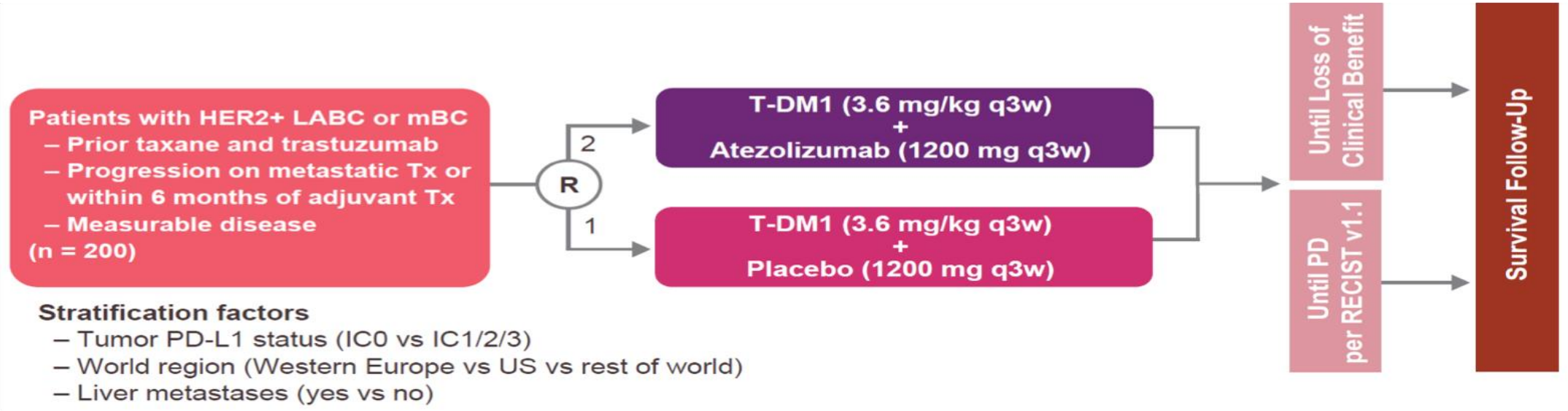
KATE2: A randomized Phase II study of atezolizumab + trastuzumab emtansine (T-DM1) vs placebo + T-DM1 in previously treated HER2+ advanced breast cancer



Primary endpoint
- Investigator-assessed PFS per RECIST v1.1 (ITT)

Secondary endpoints
- OS, ORR, DOR (ITT)

Exploratory endpoints
- PFS in the PD-L1+ (PD-L1 IC ≥ 1%) subgroup
- Efficacy in subgroups defined by immune-related (tumor-infiltrating lymphocytes and CD8 IHC expression) and HER2-related biomarkers

Safety endpoints
- AEs, SAEs, AEs leading to death, study discontinuation, or dose reduction and interruption

Emens LA et al SABCS 2018

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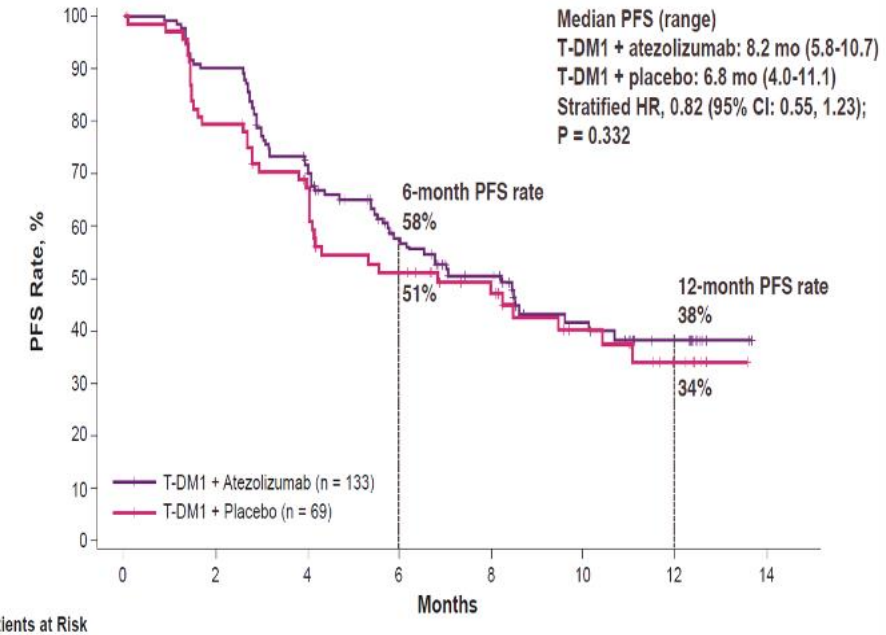
IC, tumor-infiltrating immune cells; LABC, locally advanced breast cancer; mBC, metastatic breast cancer; q3w, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; Tx, treatment.

KATE2: PFS in ITT and PD-L1 IC+ Populations

Primary Endpoint PFS in ITT Patients



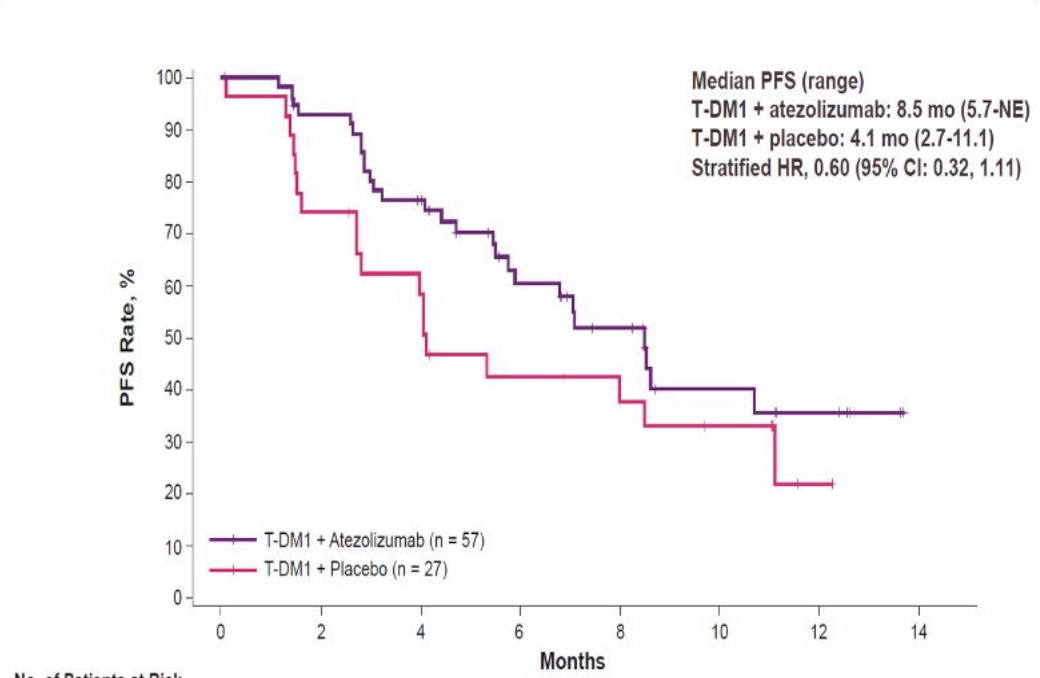
No. of Patients at Risk

T-DM1 + Atezolizumab	133	131	118	100	90	74	59	46	42	26	25	21	15	3
T-DM1 + Placebo	69	66	54	46	42	33	31	25	23	18	15	14	7	1

Data cutoff: 11 December 2017. Patients with PFS events: T-DM1 + atezolizumab, 68 (51%); T-DM1 + placebo, 39 (57%).

- The study did not demonstrate a meaningful PFS benefit from the addition of atezolizumab to T-DM1 in the ITT population

Primary Endpoint PFS in PD-L1+ Patients



No. of Patients at Risk

T-DM1 + Atezolizumab	57	56	51	44	40	31	24	19	16	9	9	8	6	2
T-DM1 + Placebo	27	26	20	16	15	11	10	9	8	7	6	6	1	

NE, not estimable.

- PFS in the PD-L1+ subgroup numerically favored atezolizumab + T-DM1 vs atezolizumab + placebo (HR, 0.60 [95% CI: 0.32, 1.11])
- The magnitude of the benefit is uncertain given the limited number of patients and the corresponding wide confidence interval of the hazard ratio
- One-year OS rate was numerically higher with the addition of atezolizumab in PD-L1 IC+ subgroup

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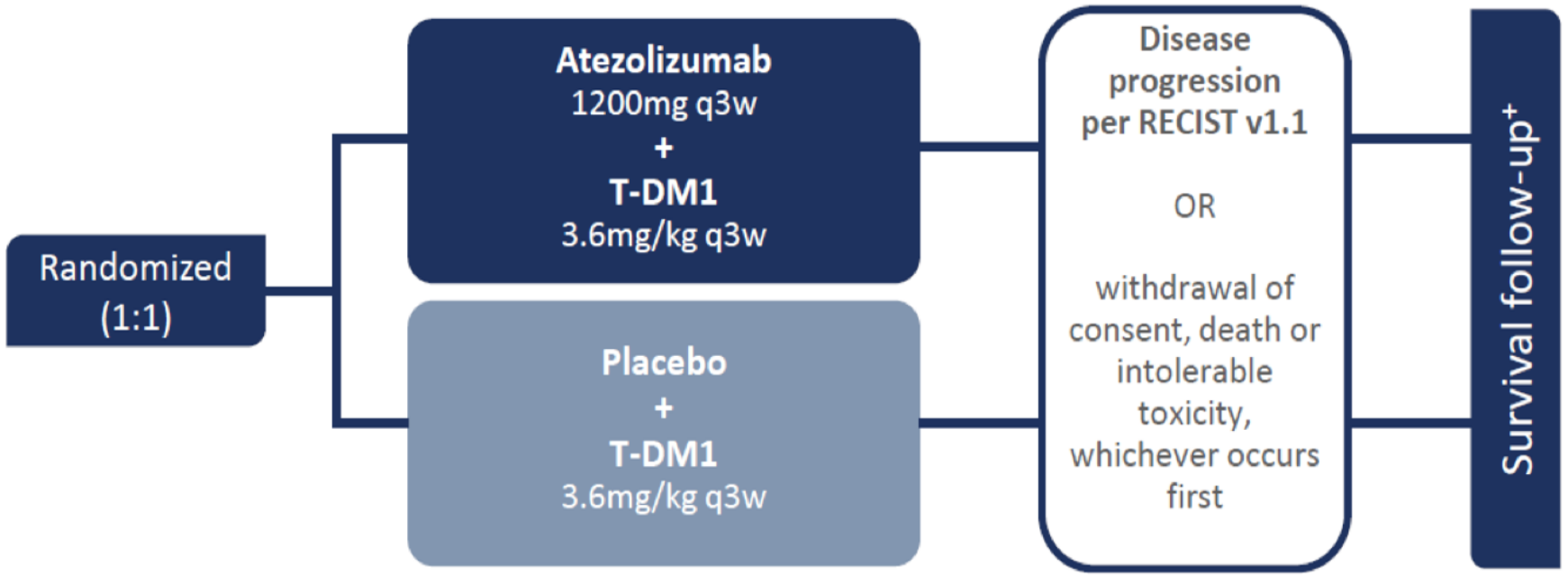
KATE 3 study

HER2+ and PD-L1+ LABC or MBC* (N = 350)

- prior trastuzumab-(+/-pertuzumab) and taxane based therapy
- Progression on metastatic treatment or within 6 months of adjuvant treatment



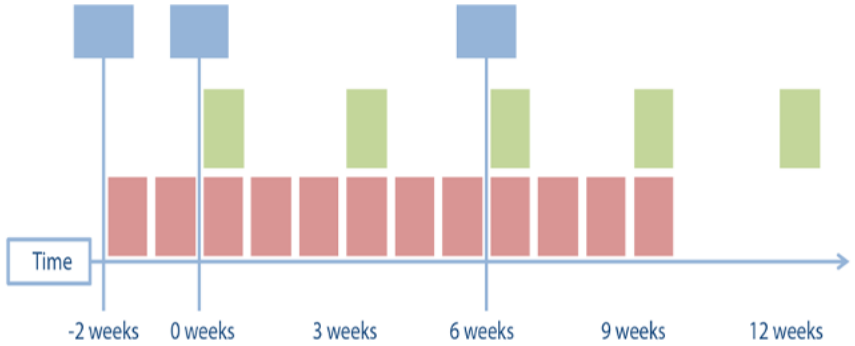
- **Co-Primary Endpoint:** PFS by investigator assessment using RECIST v1.1 and OS
- **Secondary Endpoint:** ORR, DOR, PFS by independent central review, PFS and OS in patients with baseline brain metastases, CNS PFS, QoL

*HER2 and PD-L1 positivity determined by central laboratory. +Patients will be followed for survival status and new anti-cancer therapy every 3 months until death, loss to follow-up, withdrawal of consent, or study termination.

LABC, locally advanced breast cancer; MBC, metastatic breast cancer; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; DOR, duration of response; CNS, central nervous system; QoL, quality of life

GELATO Trial: Clinical Benefit in Lobular Cancer

GELATO-trial design (NCT03147040)



Biopsy metastatic lesion + blood sampling

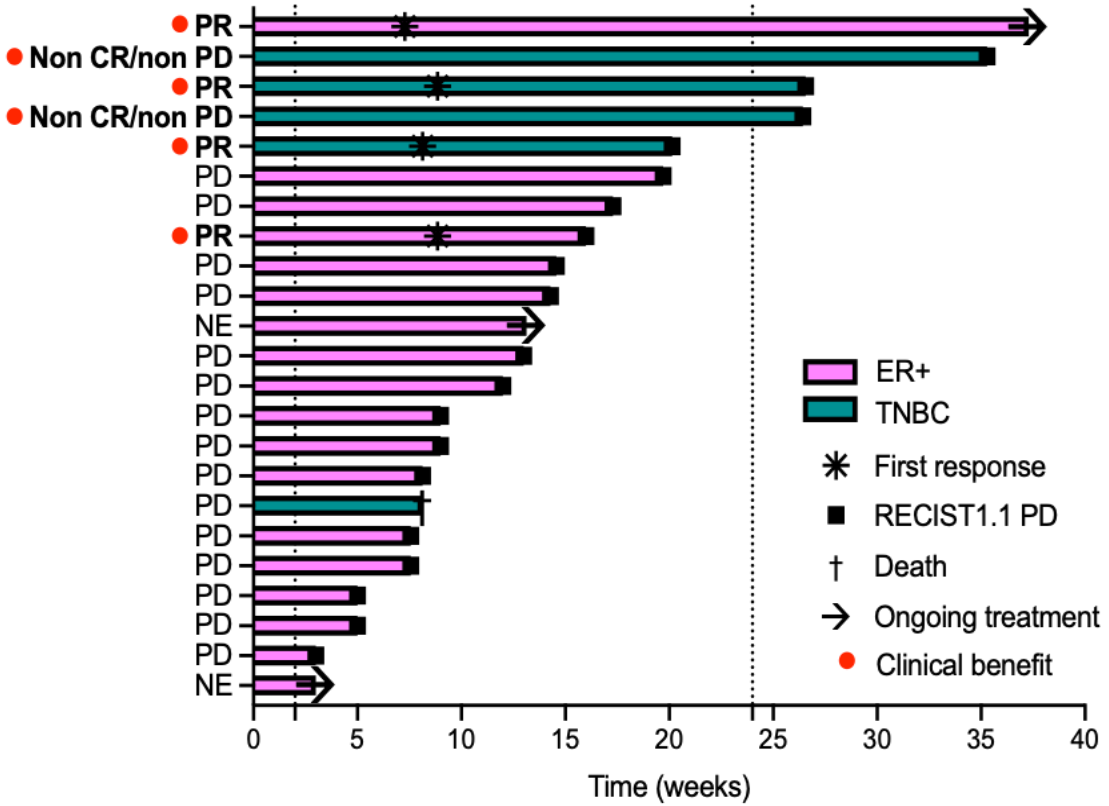
Carboplatin, AUC 1.5

Atezolizumab, 1200 mg

Simon's two-stage design:
n=22 in stage 1
At least 3 patients need to be progression-free at 6 months

Main inclusion criteria

- Metastatic ILC with negative or aberrant E-cadherin
- ER+ disease: endocrine treatment resistant
- Max. 2 lines of palliative chemotherapy
- LDH < 2 ULN



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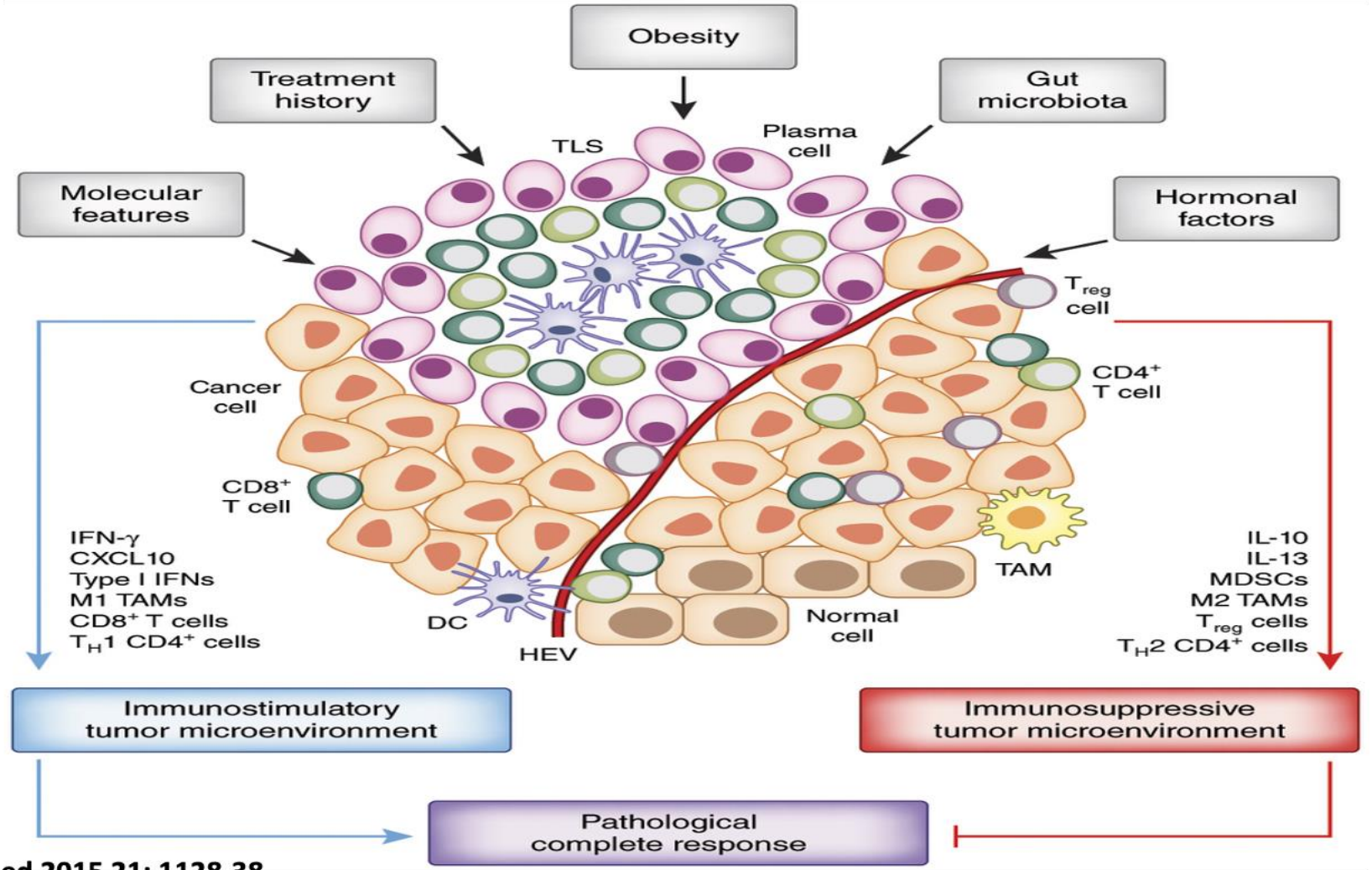
Voorwerk et al. LBA3 ESMO Breast Cancer 2021

Host Factors May Influence the Response to Breast Cancer Immunotherapy



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Kroemer G et al. Nature Med 2015 21: 1128-38.

Conclusions

- Breast cancer can be immunogenic, most breast tumors are not
- Multiple layers of regulation within the TME shut down tumor immunity
- Standard cancer therapies can augment the activity of immunotherapies
- The future is in combination immunotherapies which should have synergistic clinical activity but may come at a toxicity cost
- We need to do smart trials elucidating immunologic mechanisms of response and resistance in patients