Phase III Clinical Trials in Immunotherapy

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Disclosure Information

I have the following financial relationships to disclose:

Consultant for: Vaccinex, Celgene, Bristol Meyers Squibb, AstraZeneca, Amgen, Syndax, Molecuvax, eTHeRNA, Peregrine, Bayer, Gritstone, Medimmune, Abbvie, Replimune, Bristol-Myers Squibb, Roche, Genentech, Macrogenics

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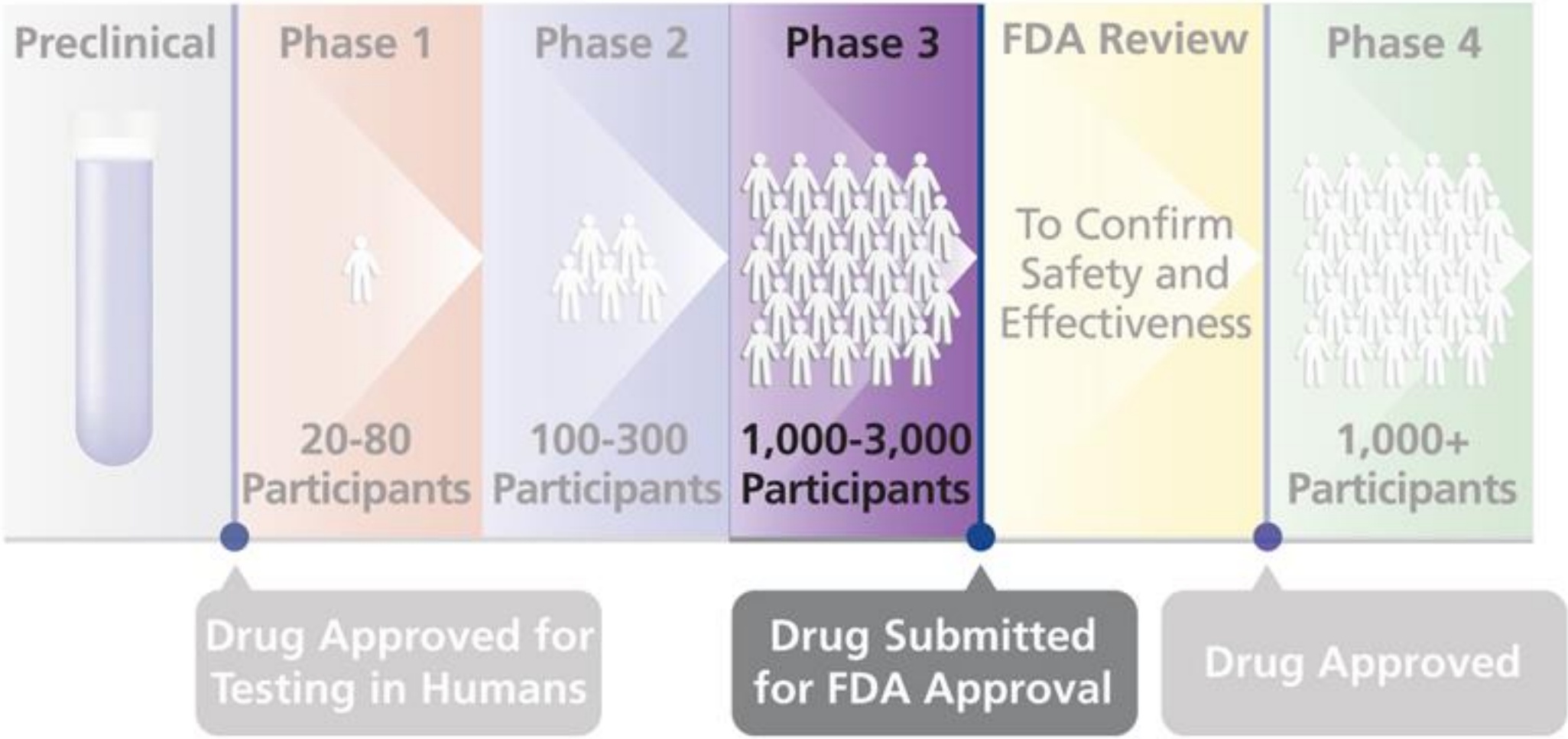
Under a licensing agreement between Aduro Biotech, and the Johns Hopkins University, the University and Dr. Emens are entitled to milestone payments and royalty on sales of a GM-CSF-secreting breast cancer vaccine. The terms of these arrangements are being managed by the Johns Hopkins University in accordance with its conflict of interest policies

I will discuss the following off-label use and/or investigational use:

Atezolizumab

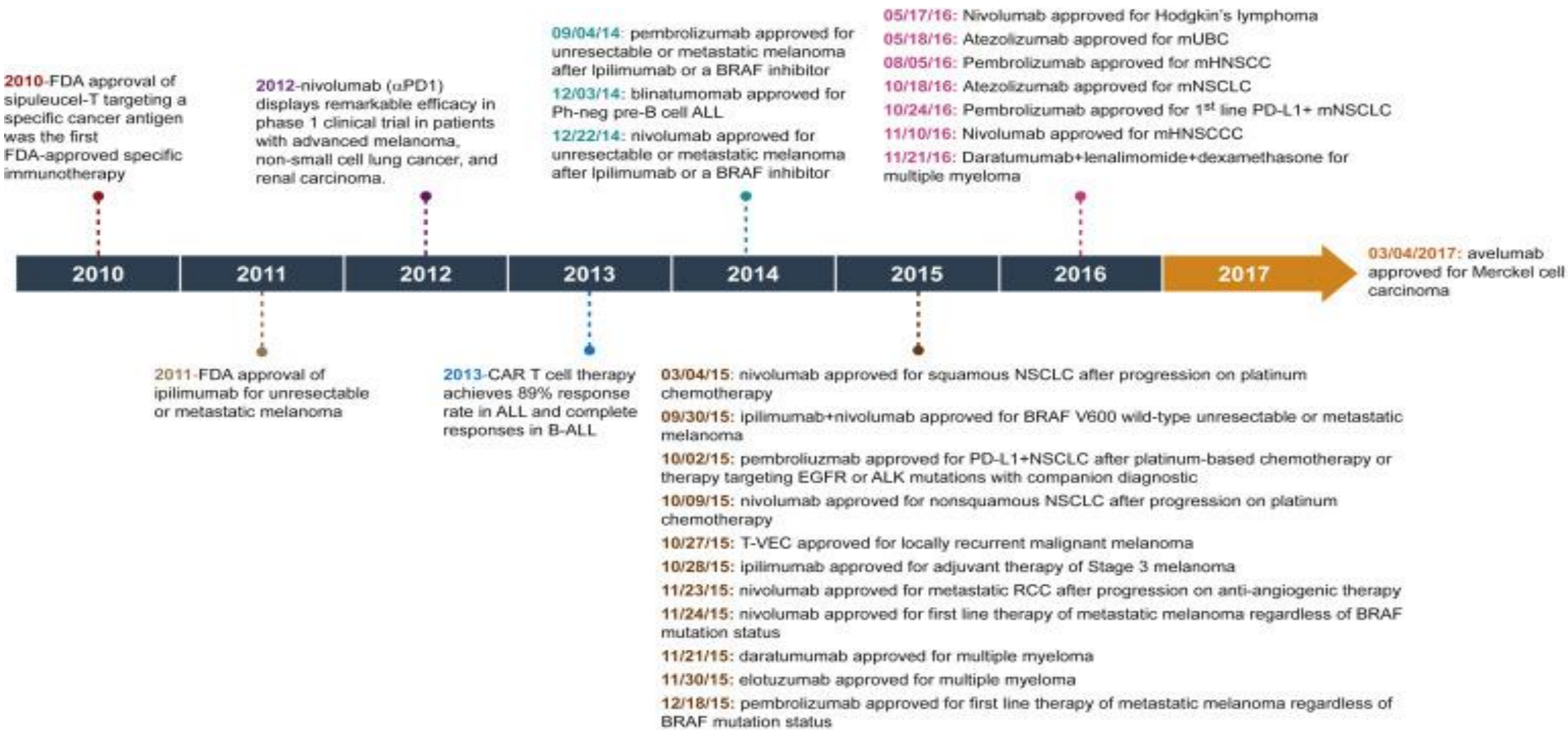
The Drug Development Continuum



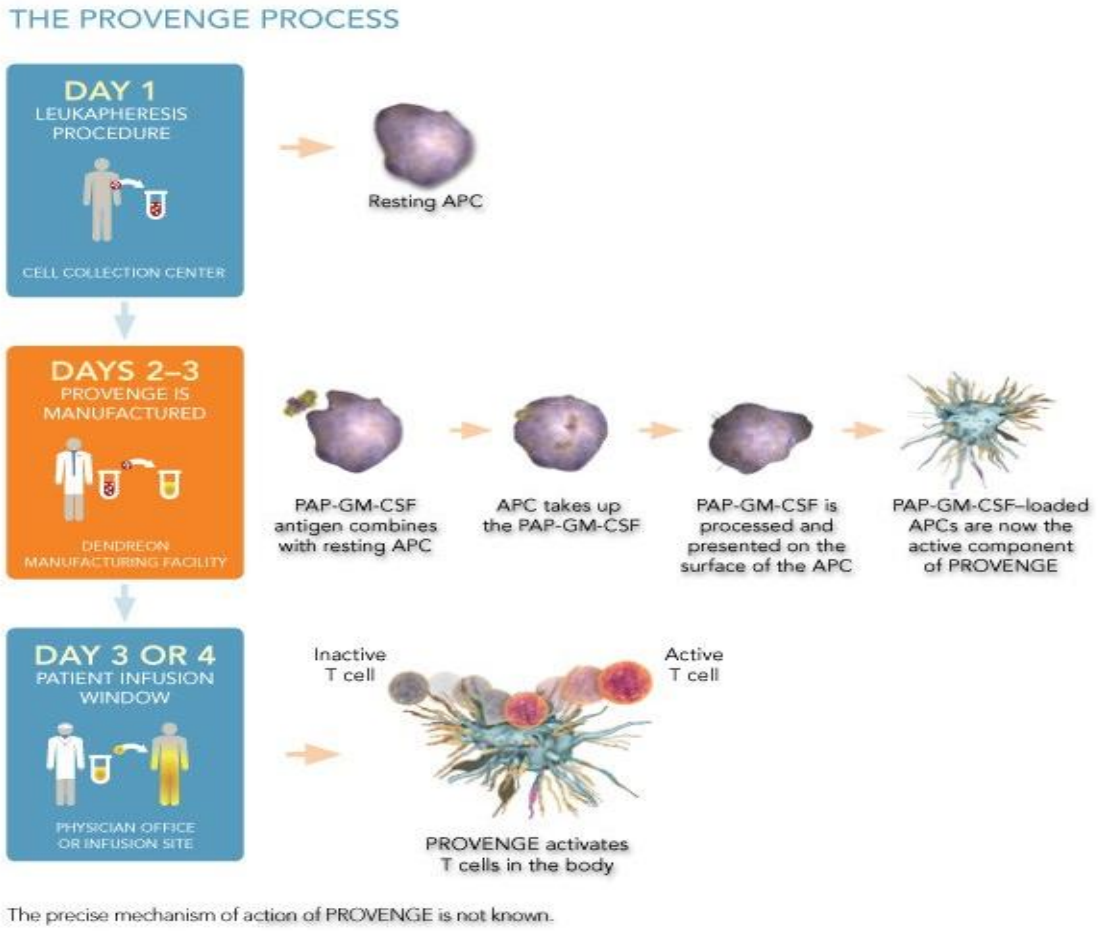
What is a Phase III Clinical Trial?

- confirms and expands on the safety and effectiveness data from Phase I and II trials
- compares a new drug or treatment regimen to the current standard of care for the disease or condition being studied
- evaluates the overall risks and benefits of the drug
- recruits a large group of carefully defined subjects with the disease or condition, typically ranging from 1000-3000 participants
- provides a data set for the FDA to review when considering a drug for approval

FDA Approvals in Immunotherapy 2010-2016



Placebo Controlled Phase III Trial of Sipuleucel-T in Patients with Metastatic, Asymptomatic Hormone-Refractory Prostate Cancer

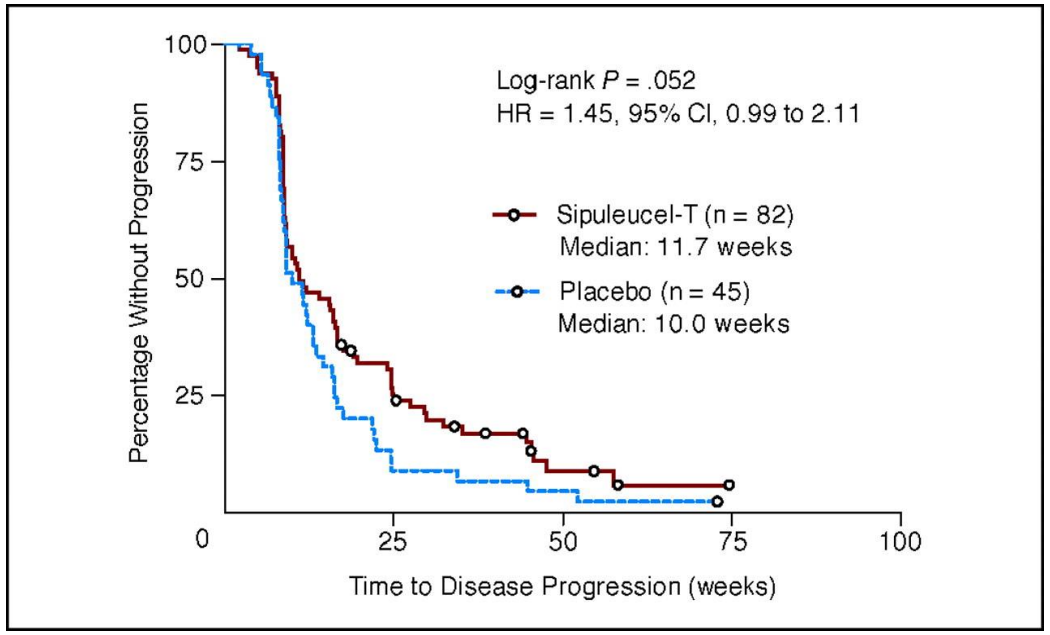


- n = 127
- randomized at 2:1 ratio
- 3 infusions of sipuleucel-T or placebo every 2 weeks
- placebo patients allowed to cross over at PD
- primary endpoint of TTP
- 36-month follow up for OS

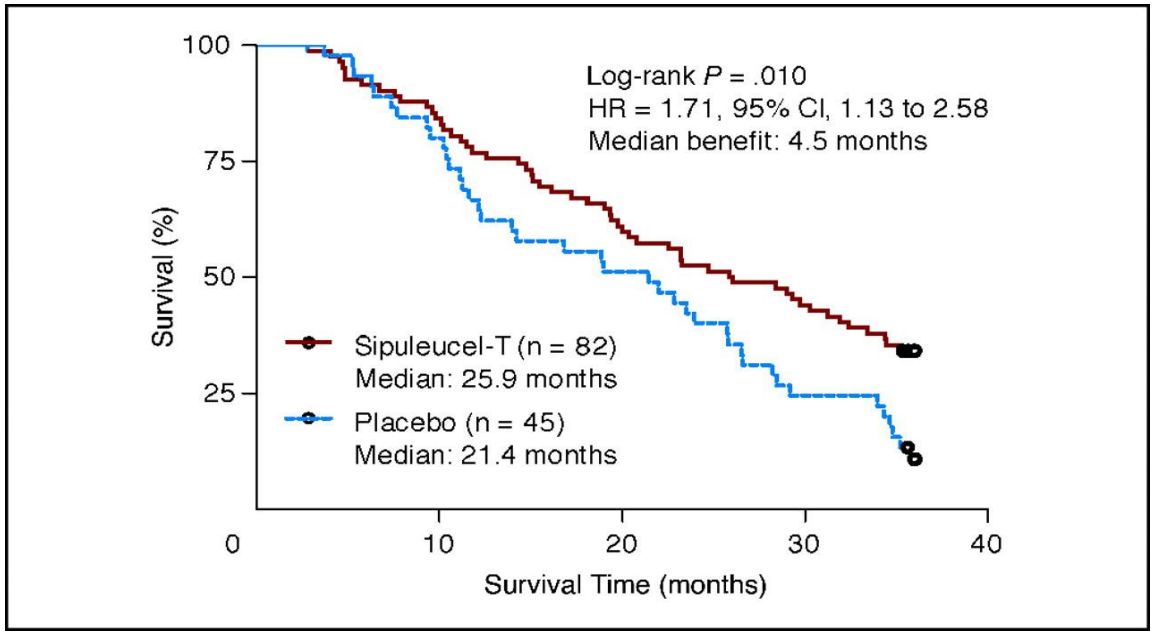
Small EJ et al J Clin Oncol 2006

Randomized, Placebo Controlled Phase III Trial of Sipuleucel-T in Patients with Metastatic, Asymptomatic Hormone-Refractory Prostate Cancer

Progression-Free Survival



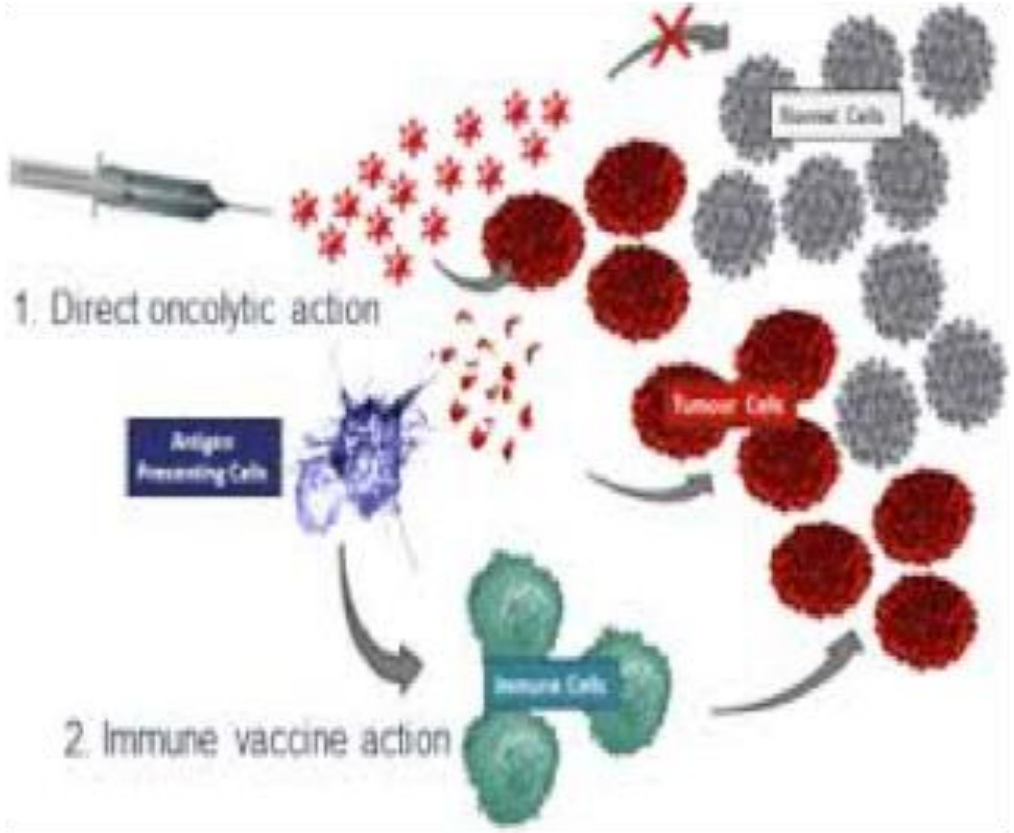
Overall Survival



median ratio of T cell stimulation pre-trt to 8W post-trt was 8X higher in Sipuleucel-T group: 16.9 v 1.99, p<0.001
adverse events: rigors, pyrexia, tremor, feeling cold

Small EJ et al J Clin Oncol 2006

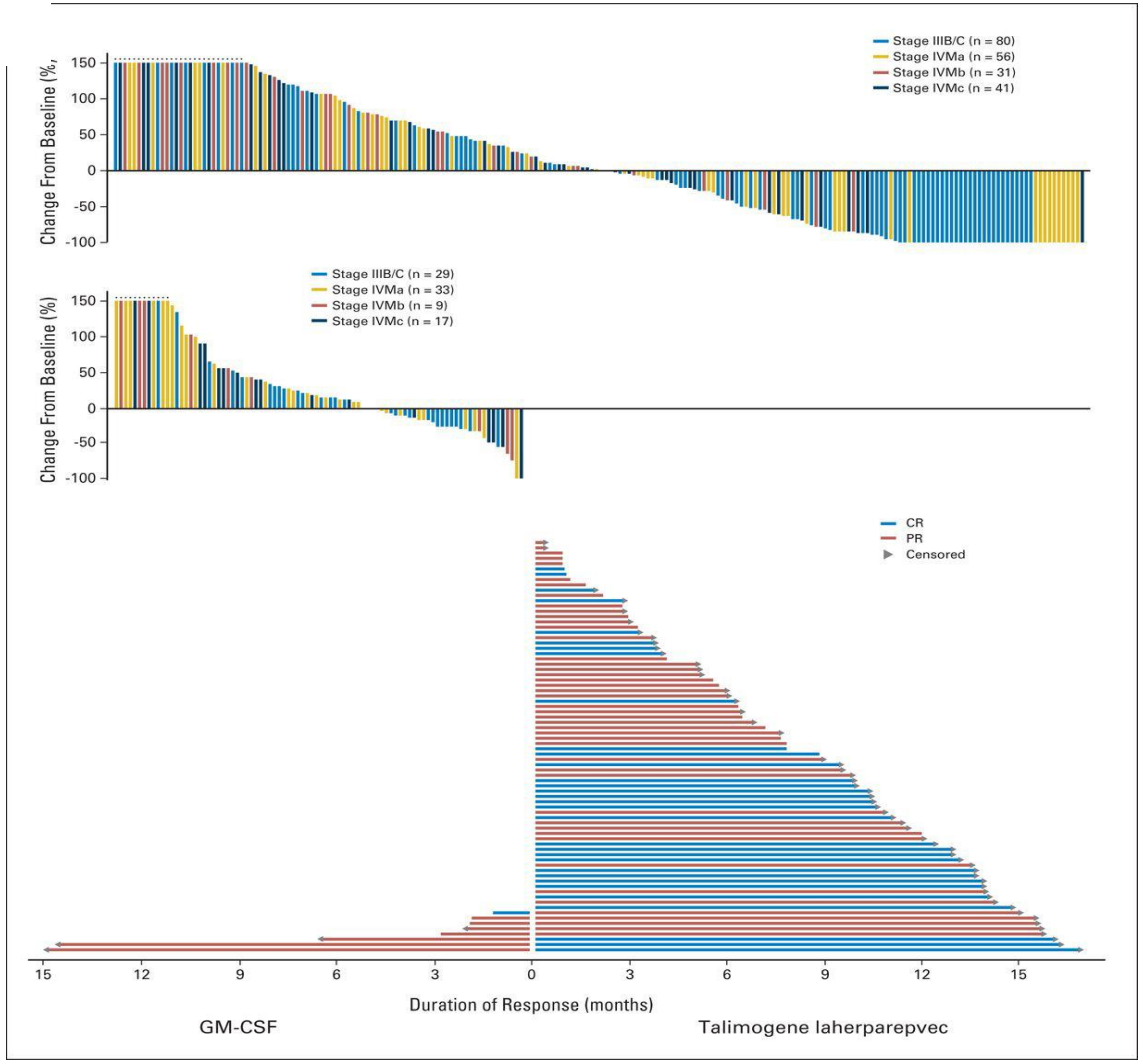
A Randomized, Open Label Phase III Trial of T-VEC: Talimogene Laherparepvec in Advanced Melanoma



Andtbacka RHI et al J Clin Oncol 2015

- unresected Stage 3B-4 melanoma
- randomized 2:1 to intralesional T-VEC or SQ GM-CSF
- primary endpoint was DRR: objective response beginning within 12 months of starting treatment and lasting 6 months or longer
- secondary endpoints were ORR and OS

A Randomized, Open Label Phase III Trial of T-VEC: Talimogene Laherparepvec in Advanced Melanoma



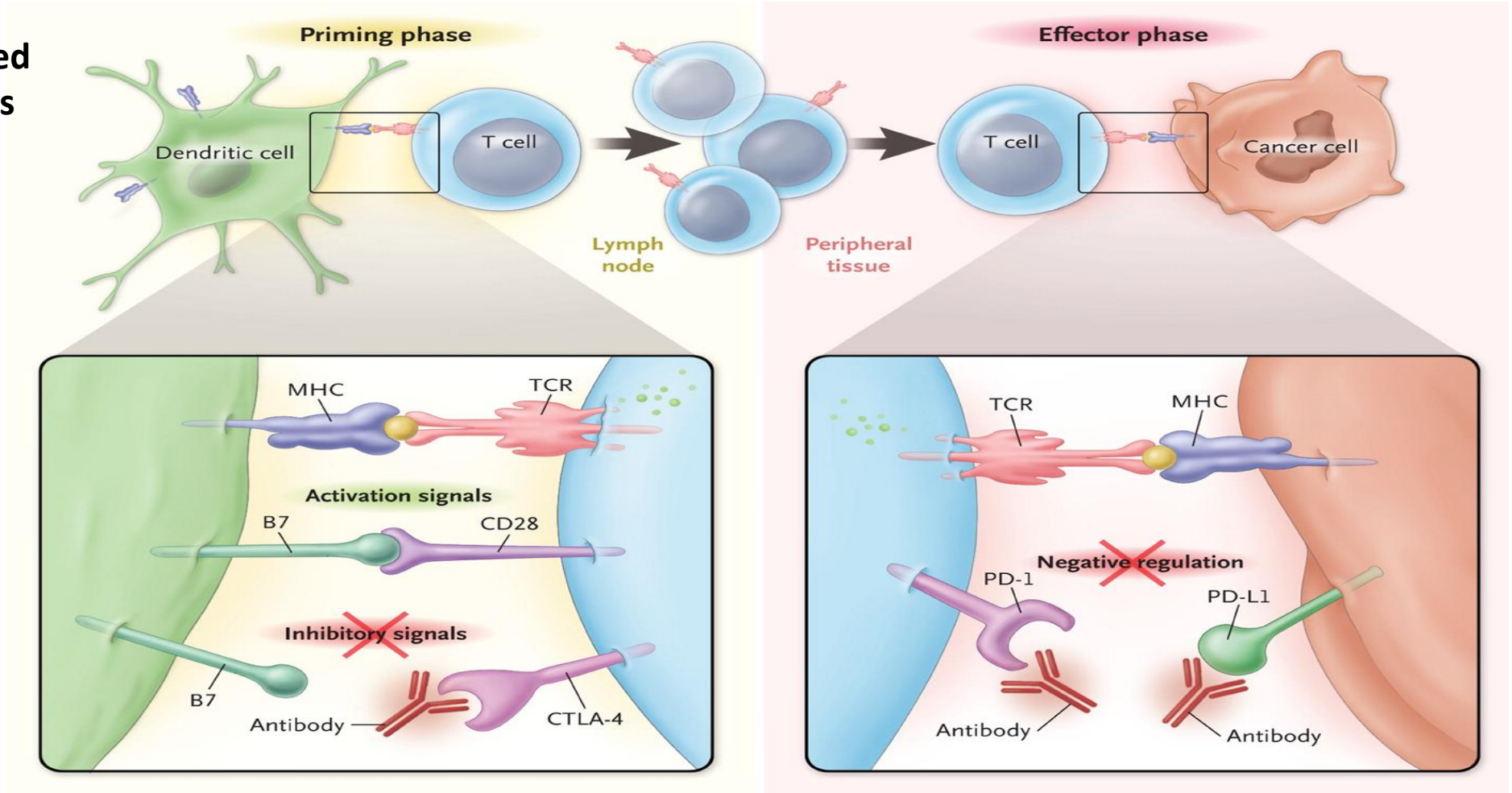
Andtbacka RHI et al J Clin Oncol 2015

Outcome	GM-CSF (N=141)	T-VEC (N= 295)	Treatment Difference (T-VEC – GM-CSF)
Durable Response Rate	2.1%	16.3%	14.1% $P < 0.0001^{*}$
Overall Response Rate	5.7%	26.4%	20.8% $P < 0.0001^{*}$
Progression Free Survival (modified)	2.9 months	8.2 months	HR=0.42 $P < 0.0001^{*}$
Overall Survival	18.9 months	23.3 months	HR=0.787 P = 0.051

Adverse events: chills, pyrexia, injection site pain, nausea, flu-like sx, fatigue

Immune Checkpoint Era

Toxicity:
immune related adverse events



Ipilimumab/Tremelimumab

pembrolizumab, nivolumab, atezolizumab, avelumab, durvalumab and many others

Ribas A NEJM 2012

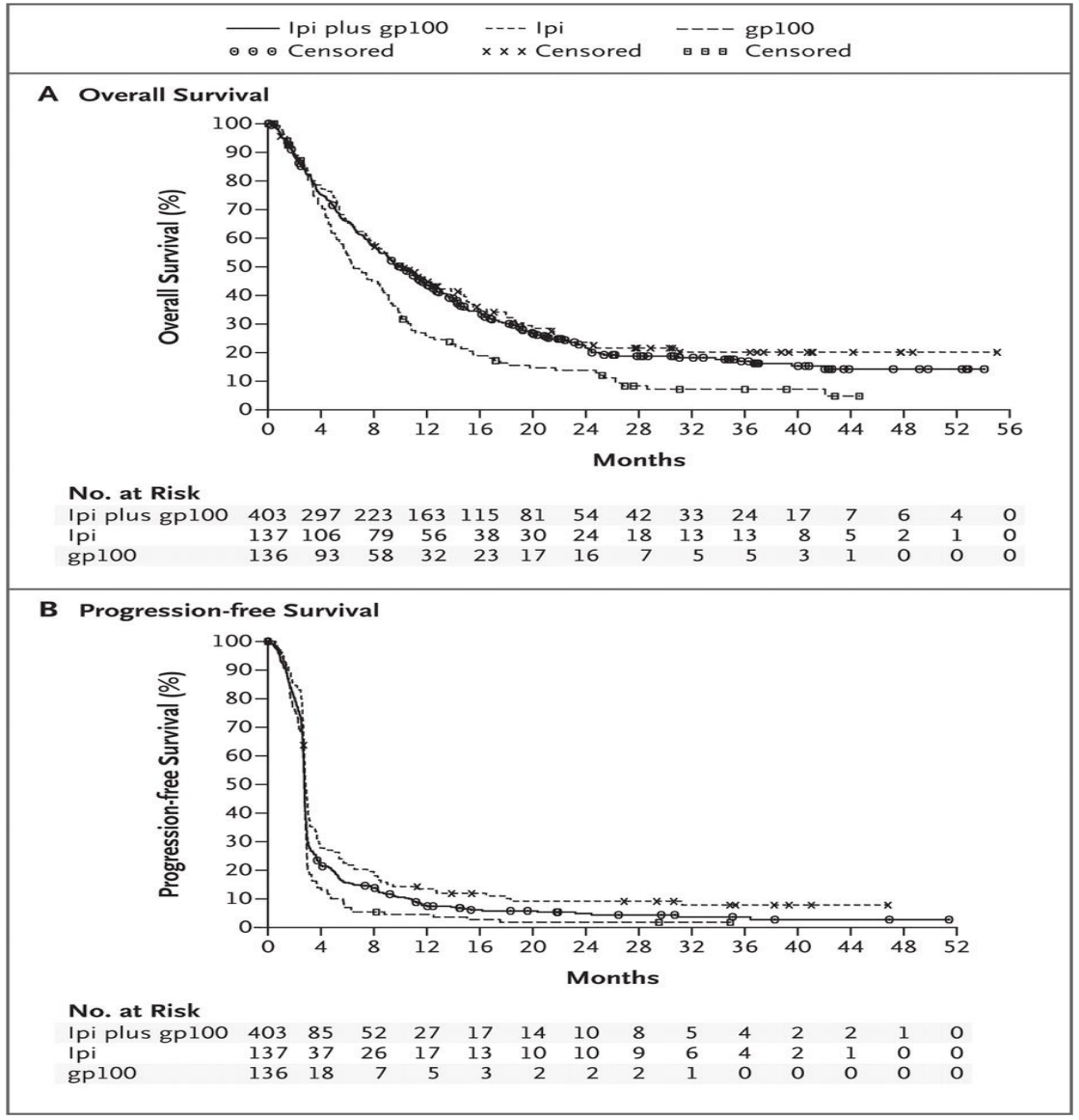
A Phase 3 Clinical Trial of Ipilimumab, gp100 peptide vaccine, or Both in Patients with Previously Treated Metastatic Melanoma

- median OS < 1 year if distant mets
- only approved therapy 1st line
- no accepted SOC except clinical trial
- gp100 thus was active control
- no randomized study had ever shown OS benefit

- n = 676
- HLA-A*0201
- randomized at 3:1:1 ratio
- ipi + gp100 v ipi v gp100
- ipi 3 mg/kg q 3w x 4 induction
- eligible patients could get re-induced
- primary endpoint OS

Hodi FS et al NEJM 2010

A Phase 3 Clinical Trial of Ipilimumab, gp100 Peptide Vaccine, or Both in Patients with Previously Treated Metastatic Melanoma



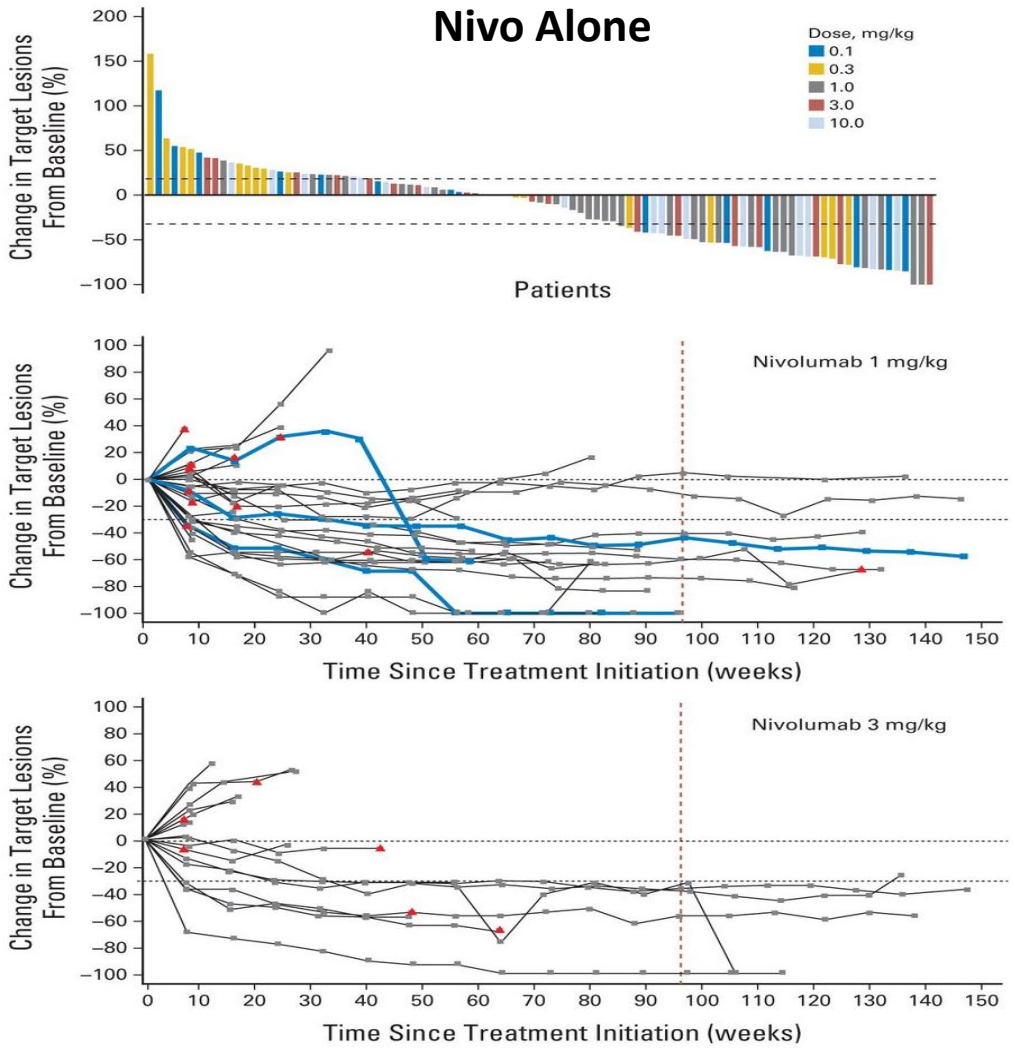
	Ipi	gp100	Ipi + gp100
mFU, mos	**27.8**	**17.2**	**21.0**
mOS, mos	**10.1**	**6.4**	**10.0**
mPFS, mos	**2.86**	**2.76**	**2.76**
12W PFS	**57.7%**	**48.5%**	**49.1%**

- Grade 3-4 irAEs in 10-15% ipi-treated patients and 3% gp100 alone-treated patients
- 14 deaths (2.1%) r/t study treatment, 7 associated with irAEs

Hodi FS et al NEJM 2010

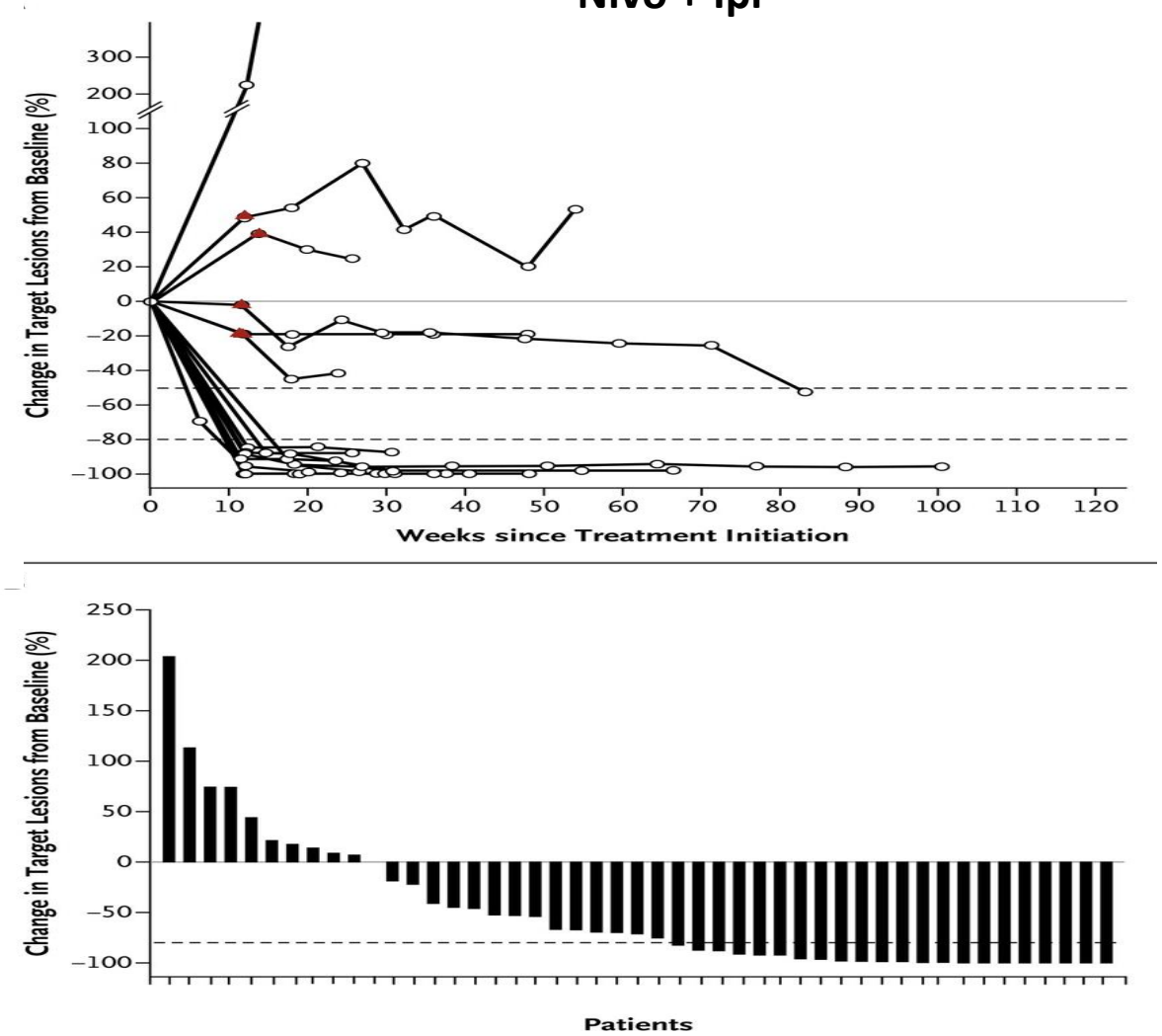
Activity of Nivo Alone or with Ipi in Advanced Cancers

Nivo Alone



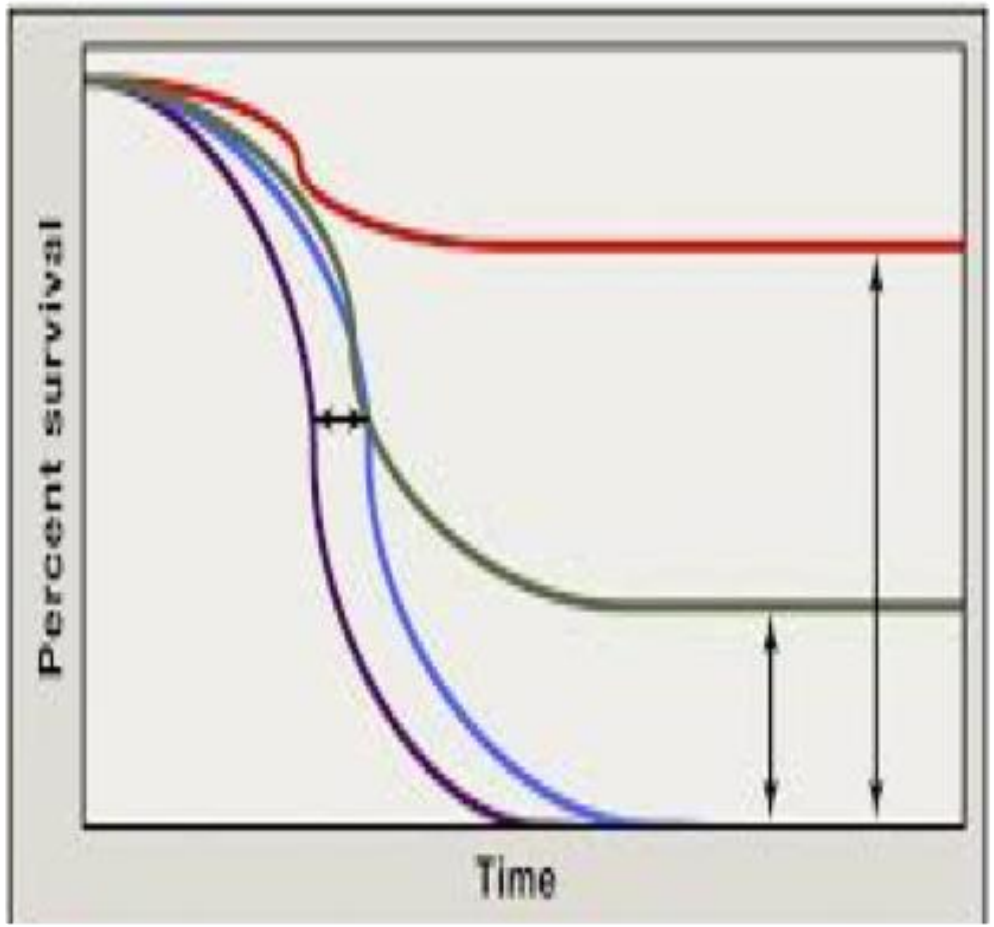
Topalian SL et al J Clin Oncol 2014

Nivo + Ipi

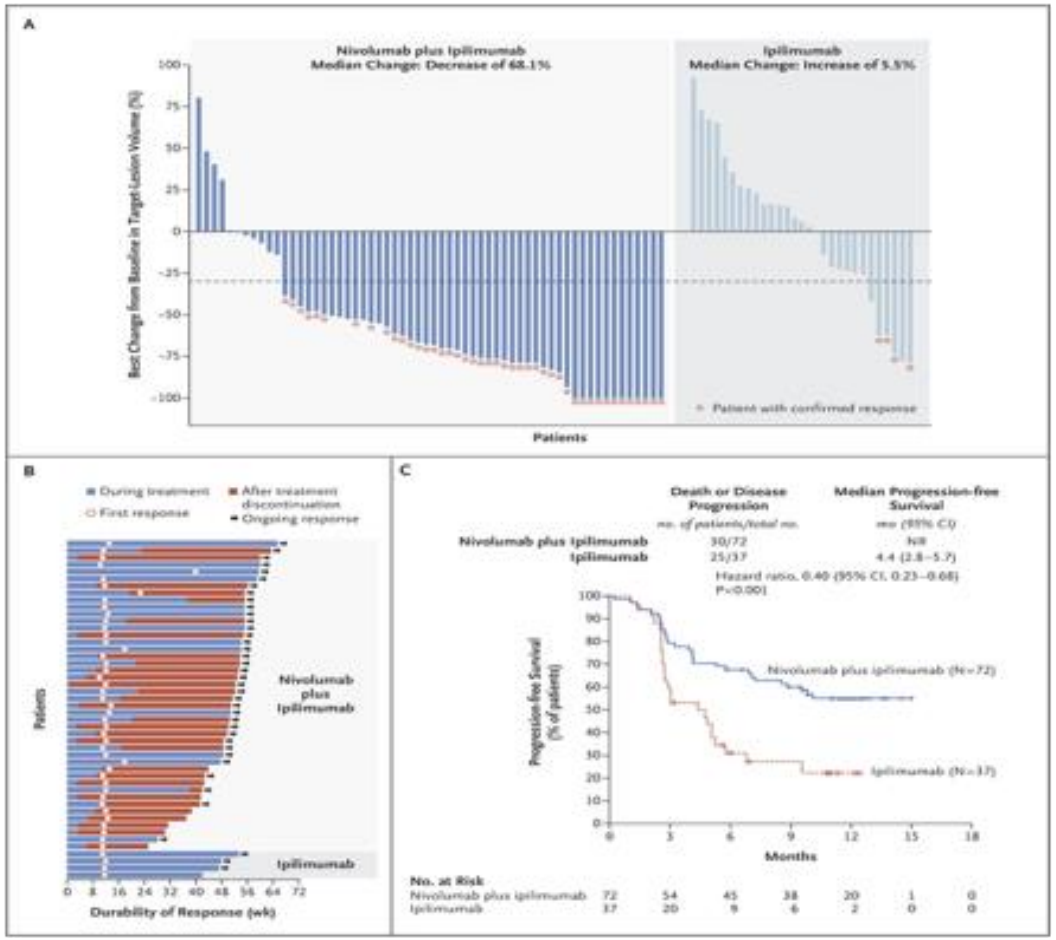


Wolchok JD et al NEJM 2015

Raising the Tail of the Curve with Immunotherapy Combinations



Sharma P and Allison JP: Cell 161: 205-214, 2015.



Postow MA et al: NEJM 372: 2006-2017, 2015.

Considerations for Phase III Clinical Trial Designs Unique to Immunotherapy

- durability of response and impact on overall survival dominates, with limited impact on ORR or PFS
- patients with disease progression by standard RECIST criteria may derive clinical benefit, with initial apparent progression followed by response—lead to development of irRECIST and iRECIST
- atypical response patterns may occur, with pseudoprogression, hyperprogression, and late responses possible
- side effect profile is distinct from standard cancer therapies
- targets a broad range of tumor types
- biomarker considerations may be complex

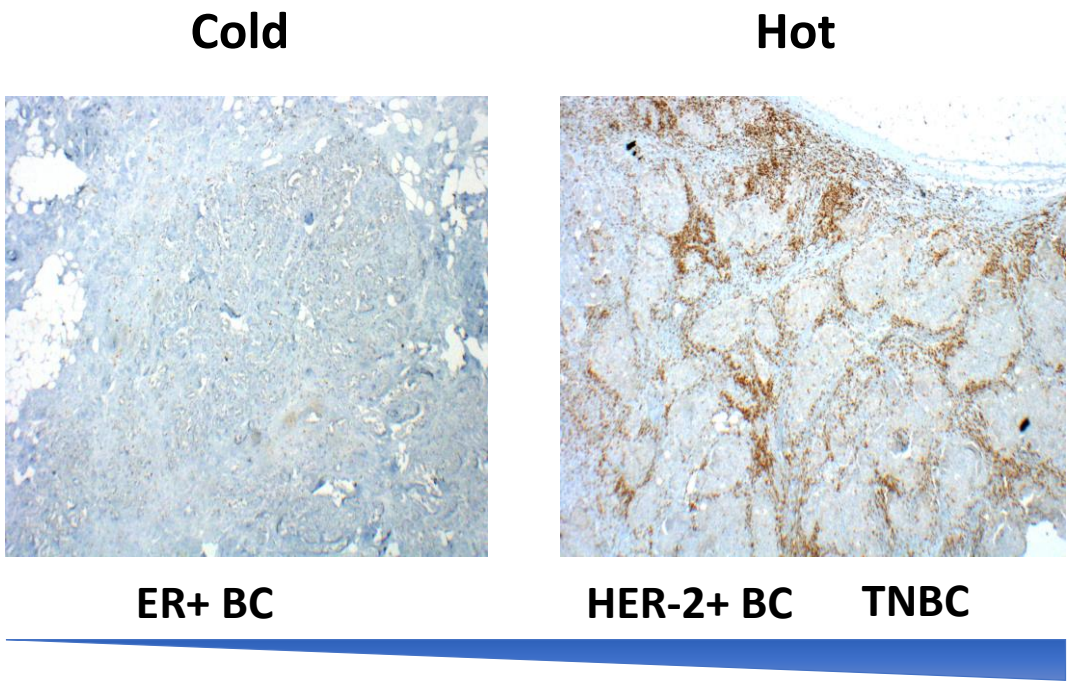
Three Pressing Challenges for the Field

1. Deepening Responses to SA Immunotherapy

2. Converting Non-Responders to Responders

3. Personalizing Immunotherapy

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

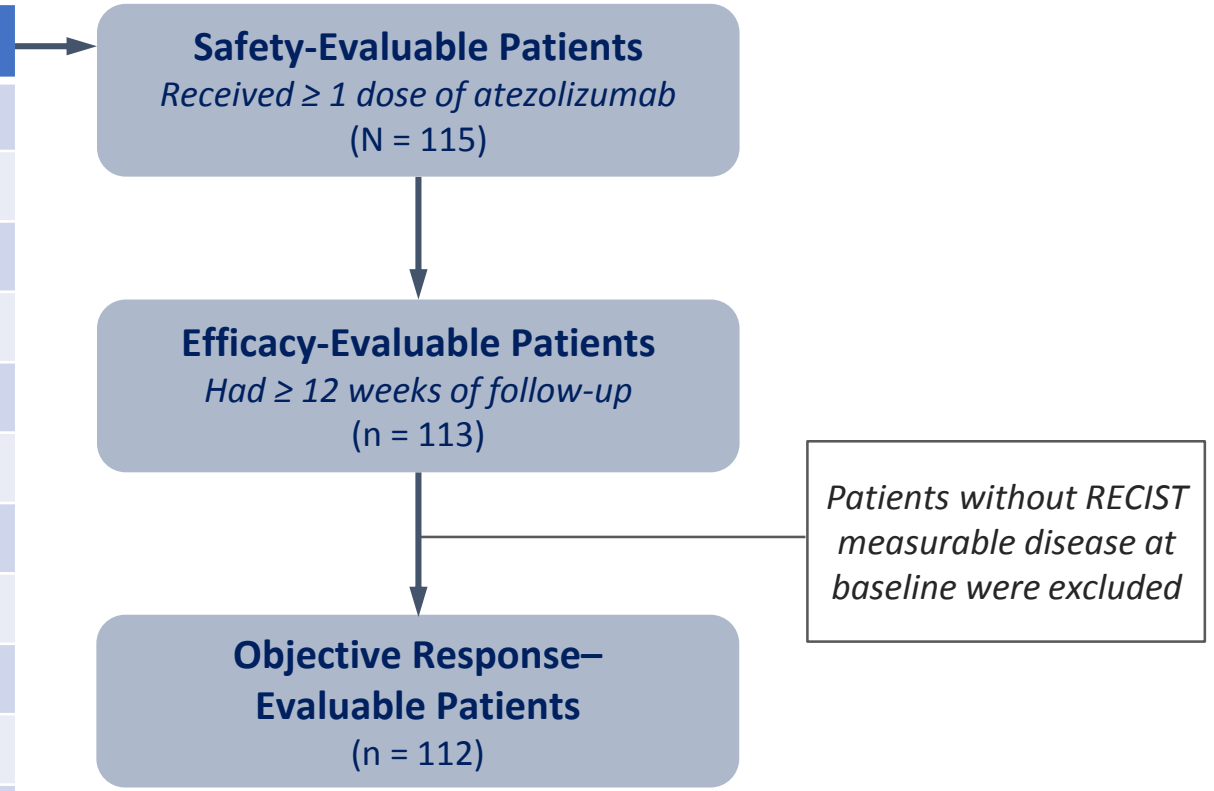
- TNBC and HER-2+ breast cancers are high value targets for cancer immunotherapy
  --Few approved targeted therapies for TNBC
  --Potentially synergistic targeted therapies in HER-2+ BC (trastuzumab, TDM-10)

- 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.

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%



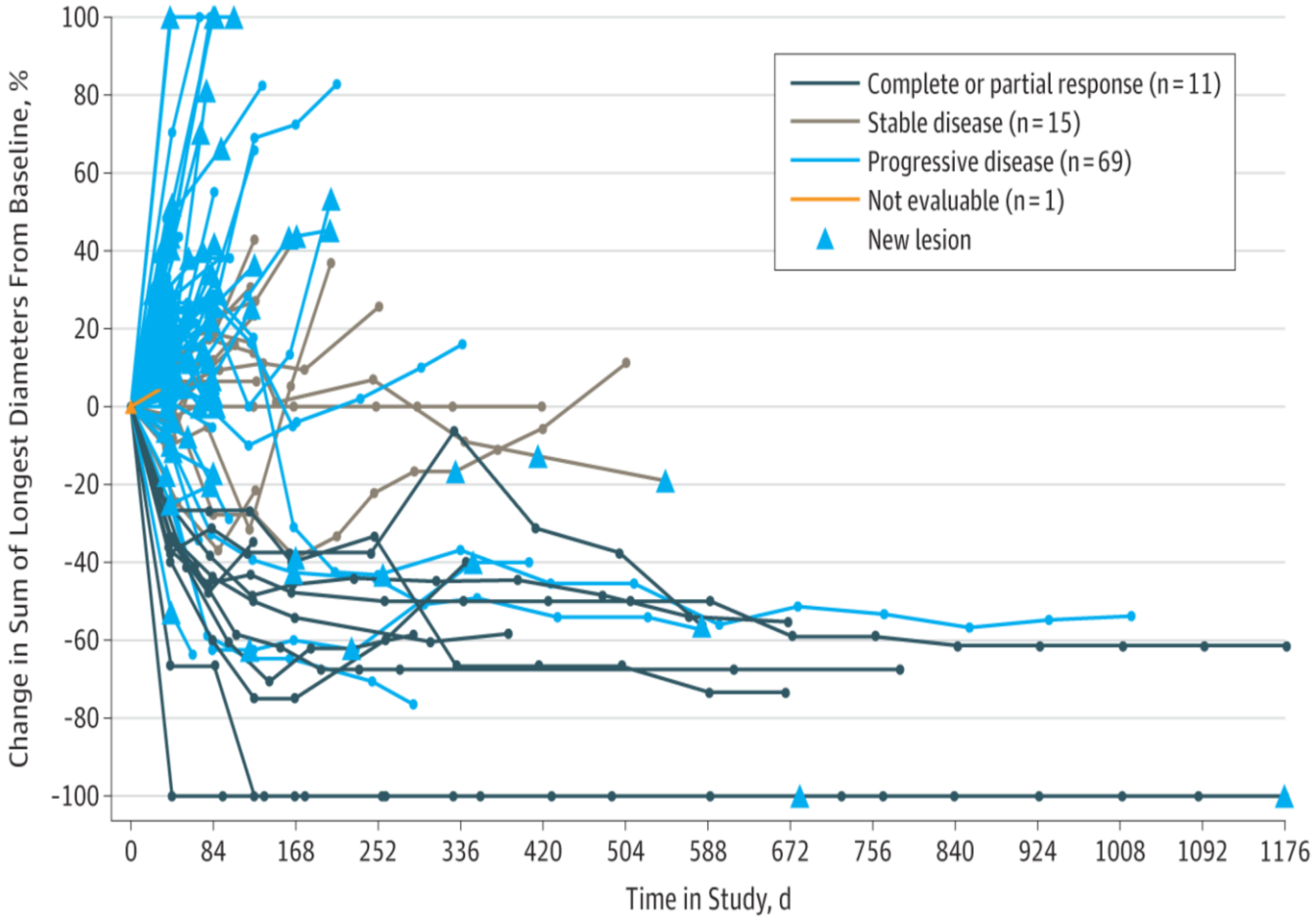
- Prior to receiving atezolizumab, most patients were heavily pretreated

- 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.

Emens LA et al JAMA Oncol 2018

Atezolizumab Monotherapy in Metastatic TNBC



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 mo (3 to 38+)	1.4 mo (1.3, 1.6)
irRC	25 mo (3 to 42+)	1.9 mo (1.4, 2.6)

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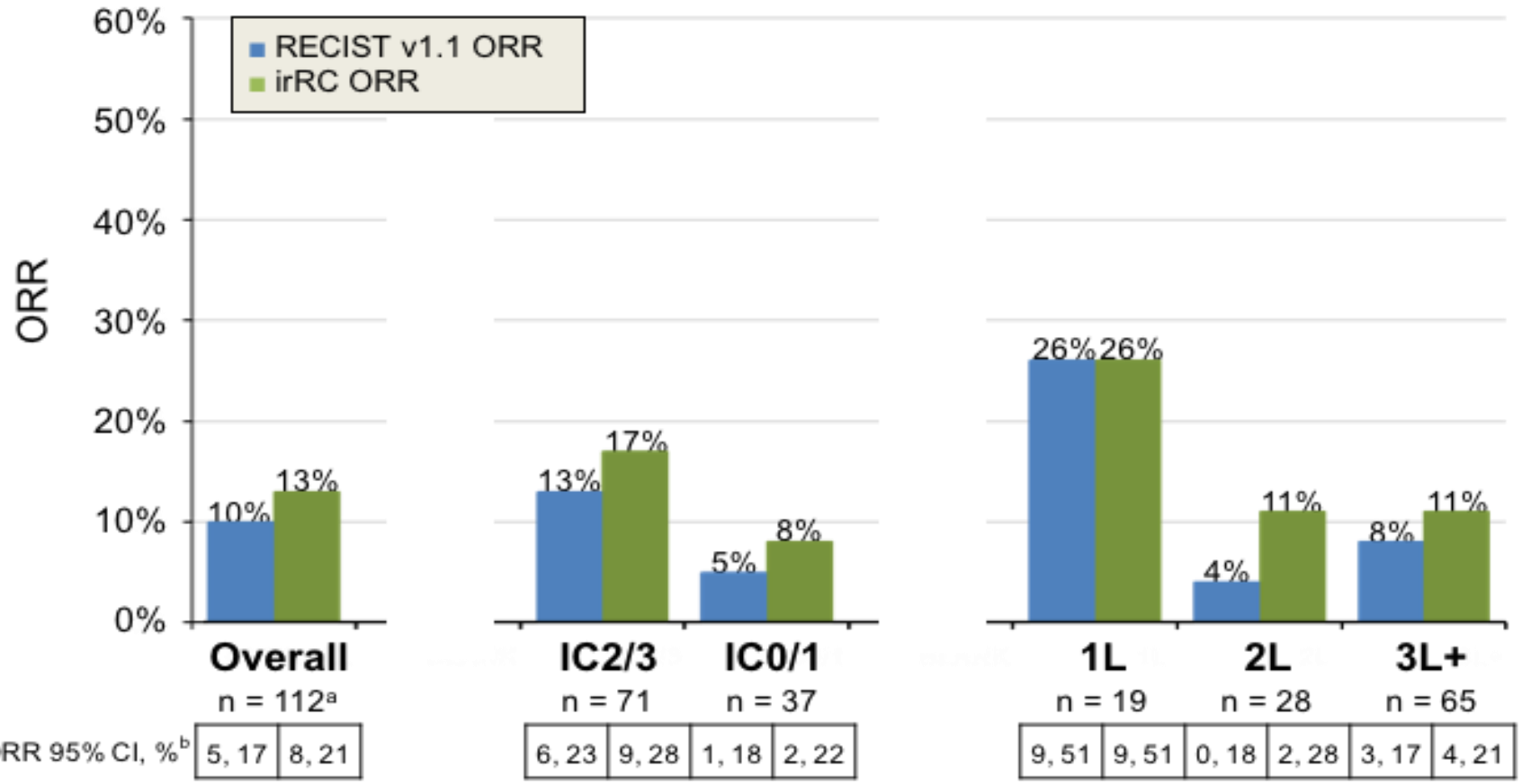
TNBC Response Rates to Atezolizumab by Subgroup



- 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.

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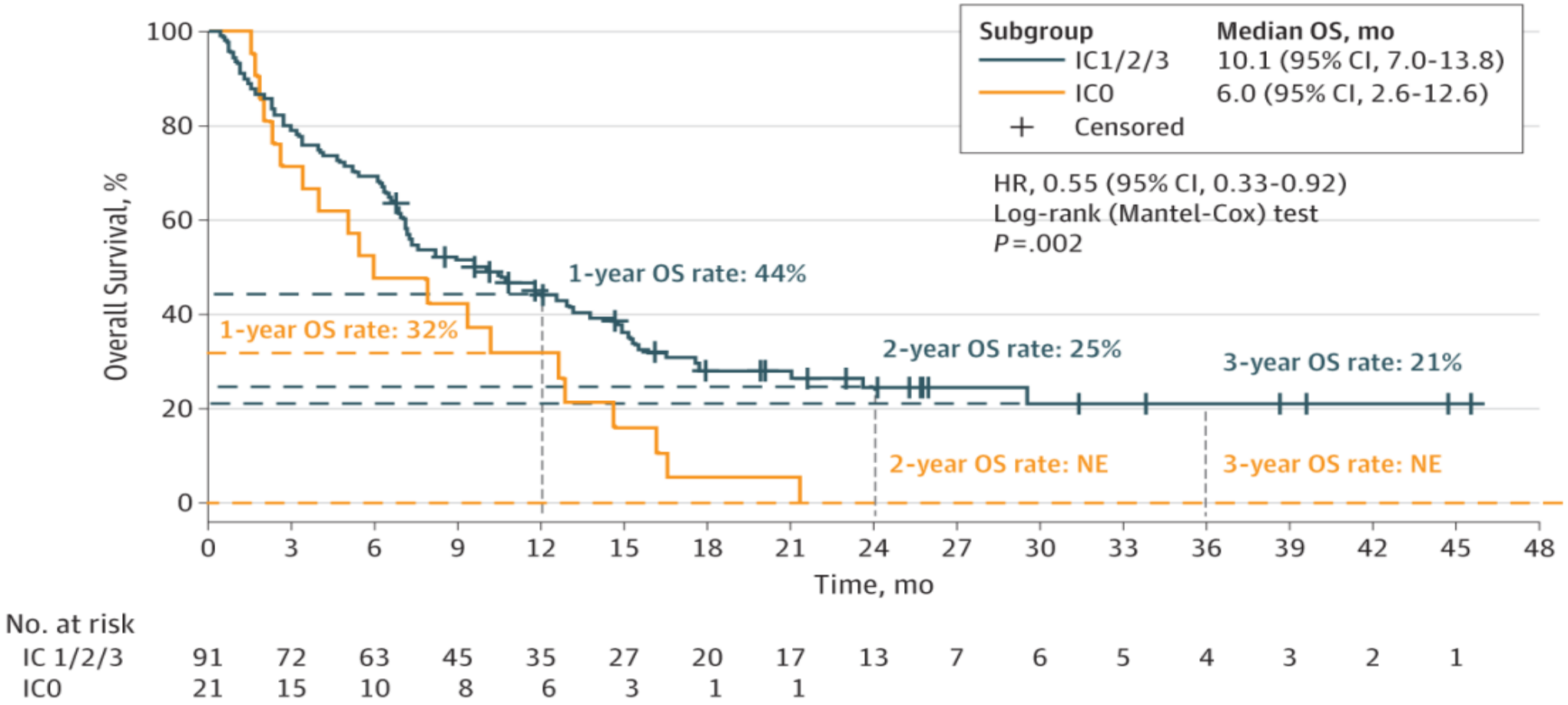
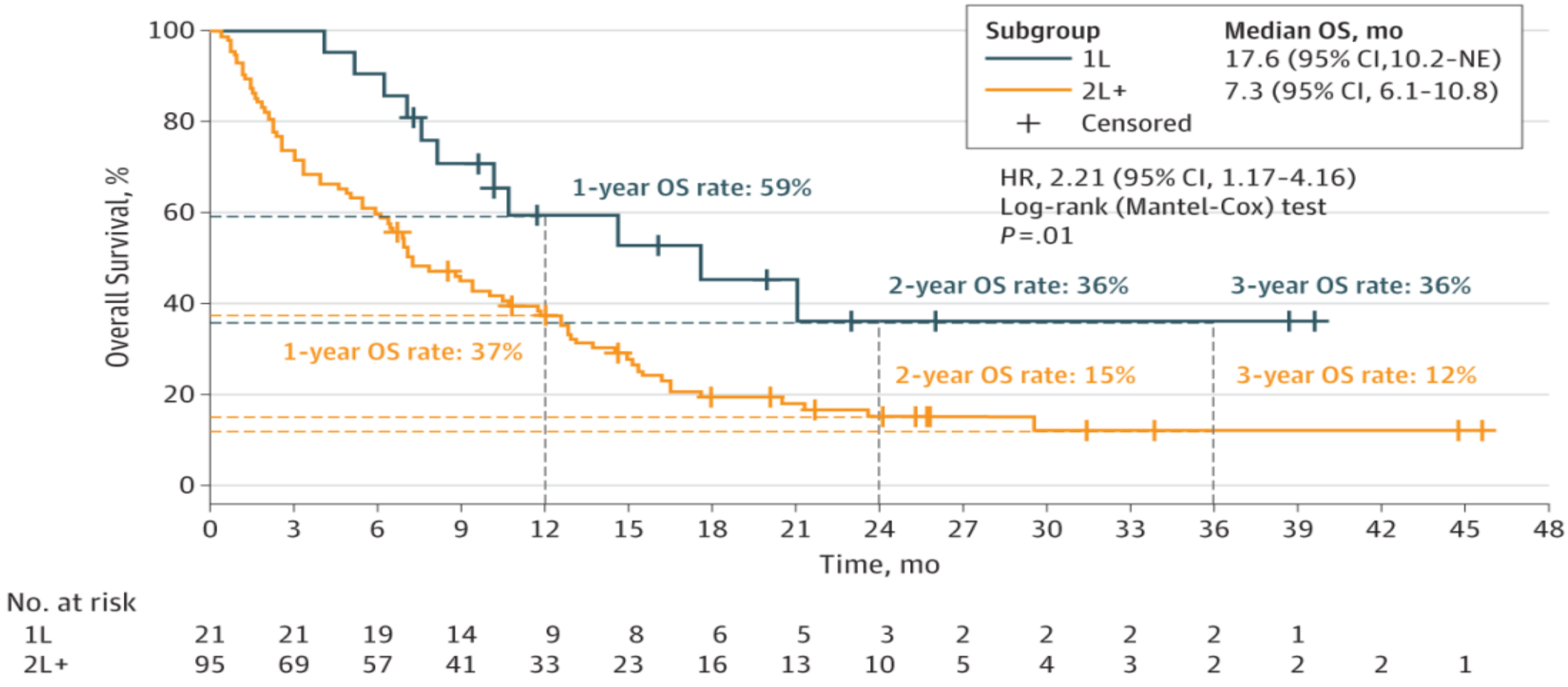
Atezolizumab Monotherapy and Overall Survival of TNBC Patients by PD-L1 Subgroup



Emens LA et al JAMA Oncol 2018

Atezolizumab Monotherapy and Overall Survival of TNBC Patients: Line of Treatment



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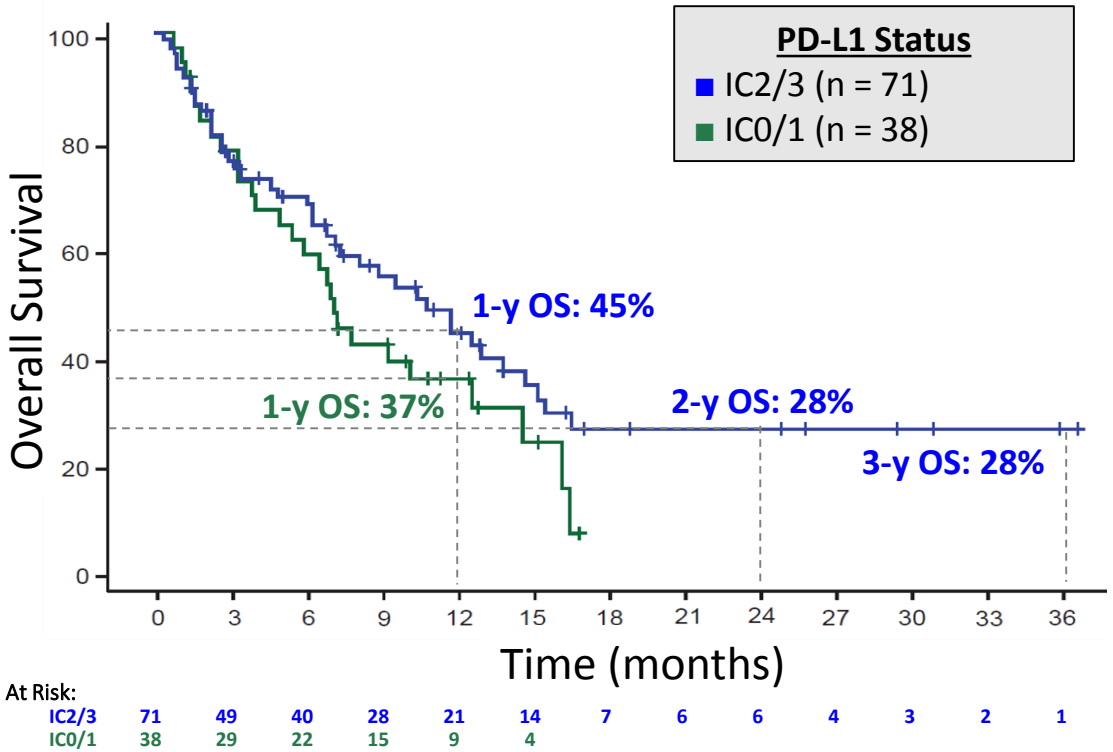
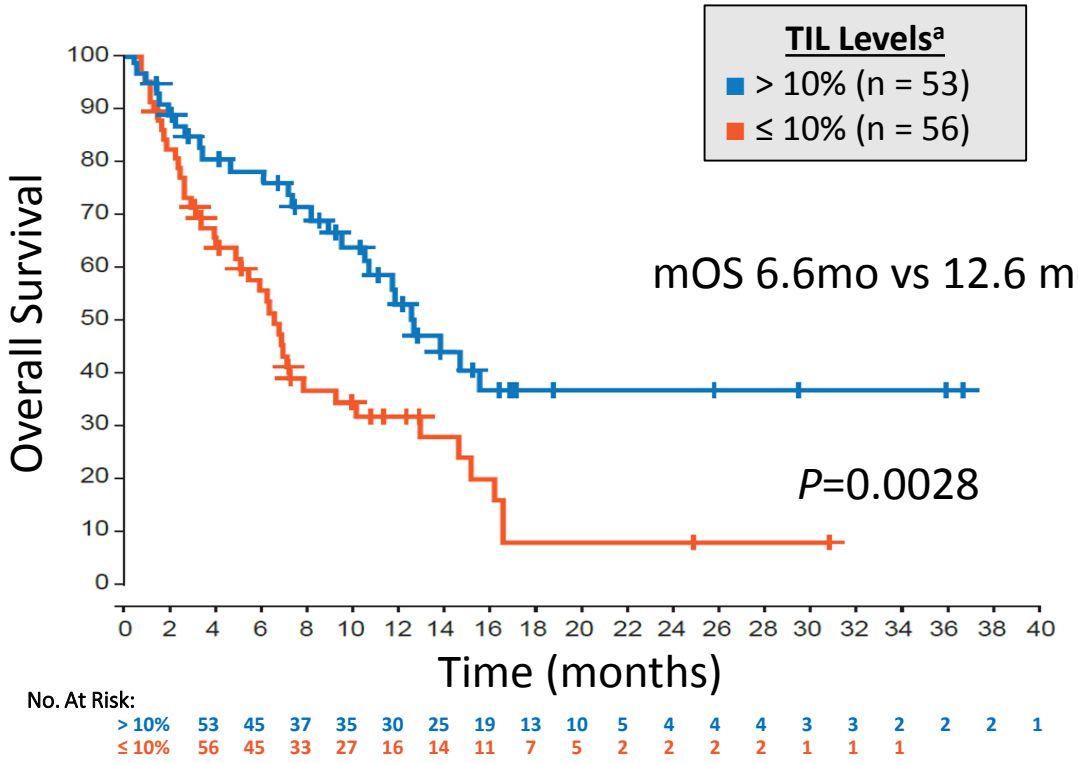
Overall Survival by PD-L1 and TIL Status

OS Based on PD-L1 Status



OS Based on TIL 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. Median TIL level based on median TIL. [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.

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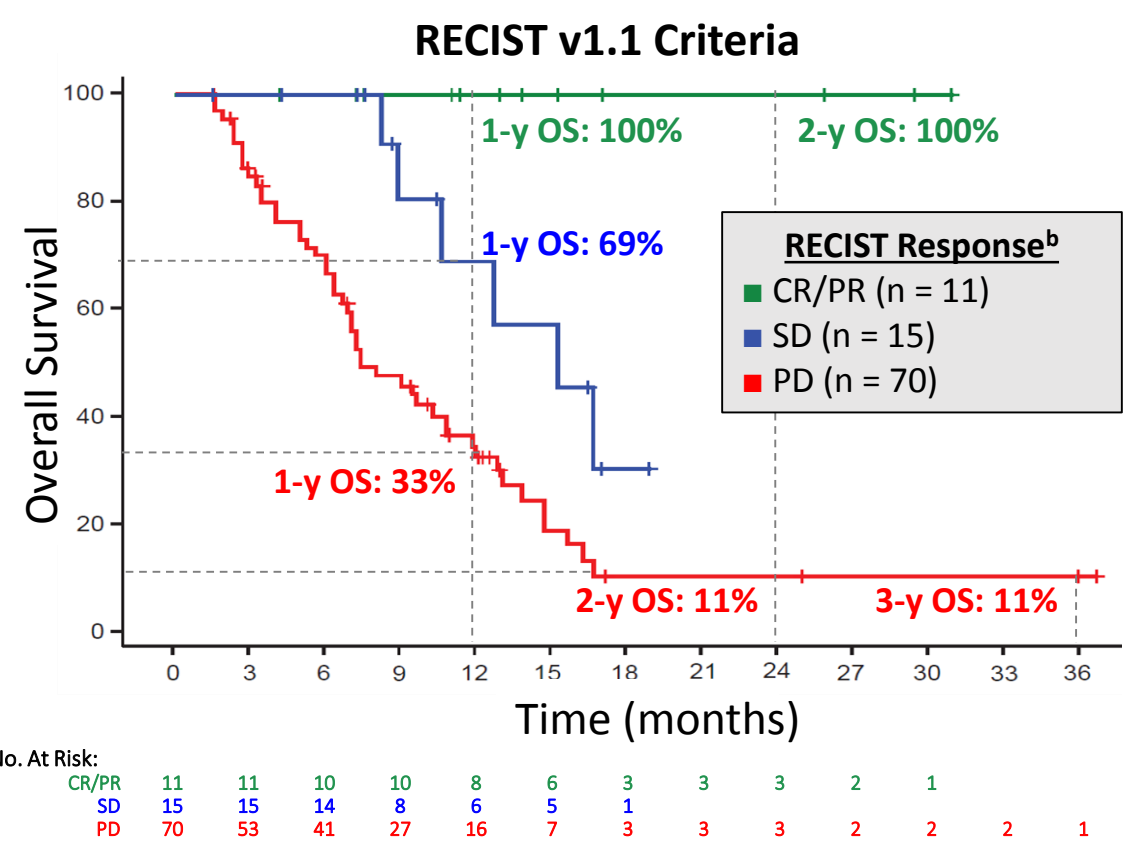
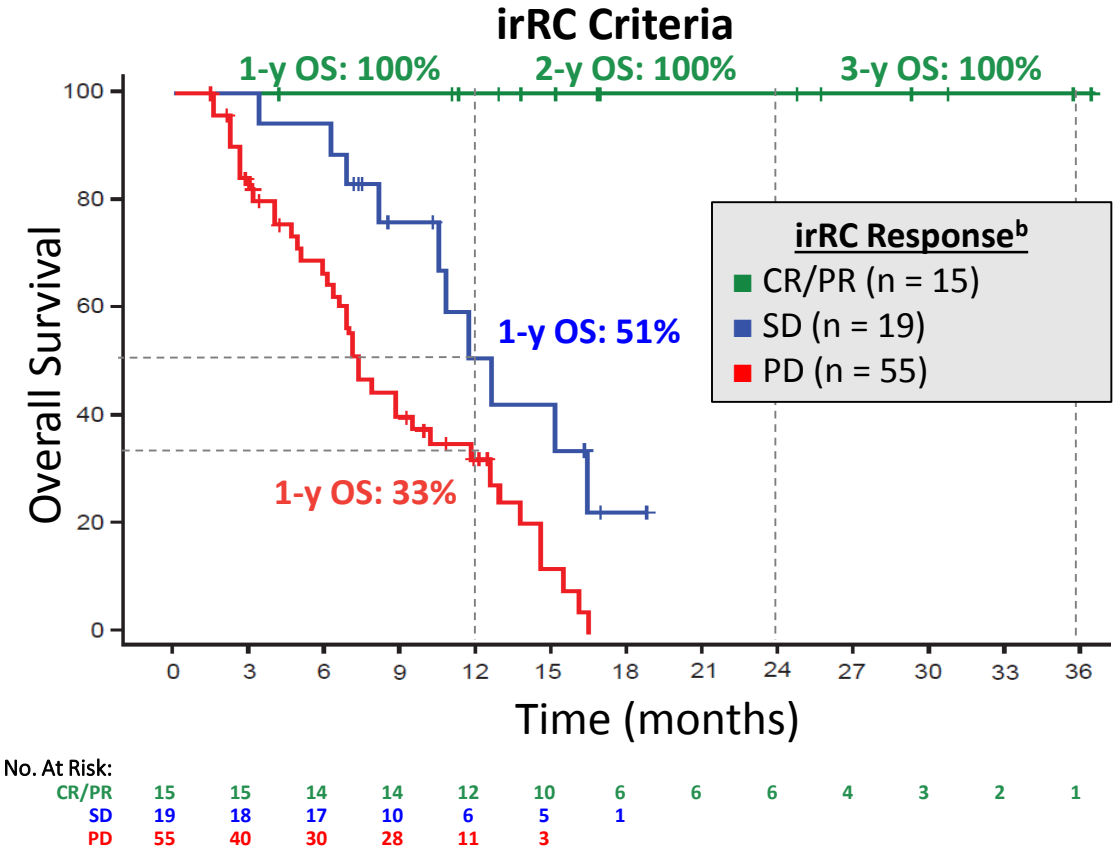
Overall Survival by Response Status (RECIST v1.1 and irRC)

- 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

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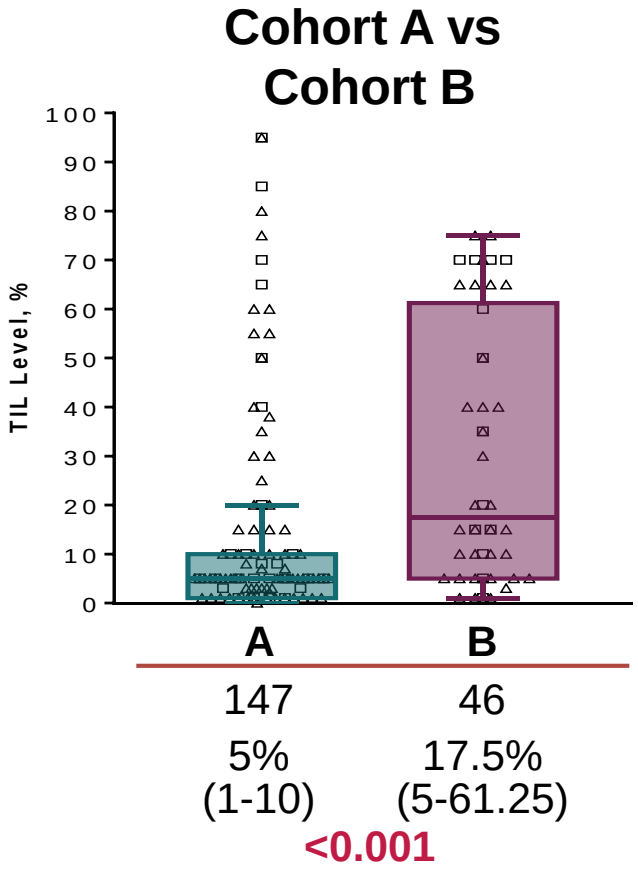
[a] Median survival follow-up (range) was 15.2 mo (0.4+ to 36.7) in all patients, 17.0 mo (0.43+ to 36.7) in IC2/3 patients and 12.8 mo (0.8+ to 16.9) in IC0/1 patients. [b] Patients included in the Kaplan-Meier plots were alive for ≥ 6 weeks. Data cutoff: March 31, 2016.

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



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

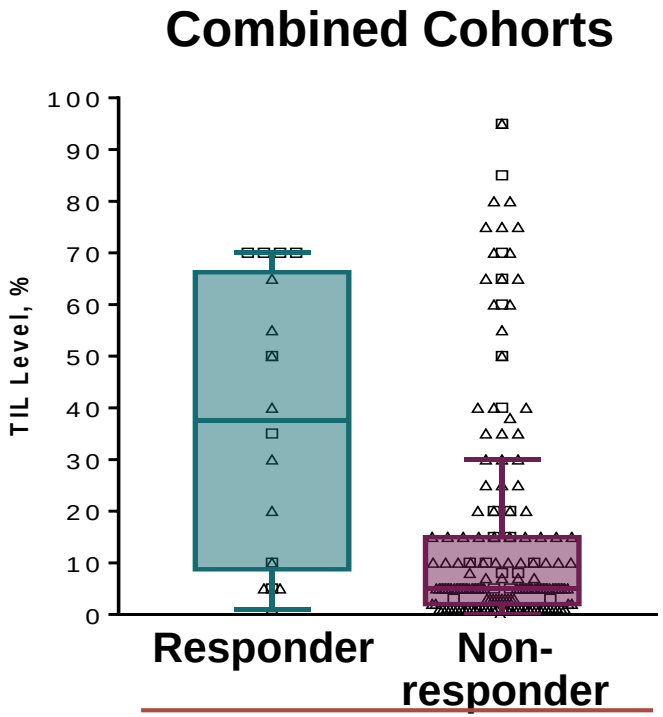
Adams S et al ASCO 2017, SABCS 2017

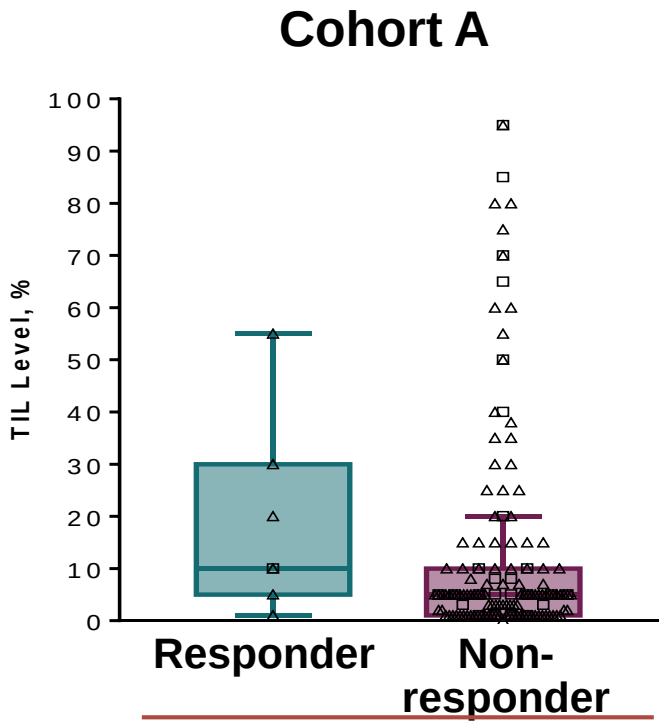
	Previously Treated Any PD-L1 Expression Cohort A			*First Line PD-L1+ Cohort B*
	All* (n=170)	**PD-L1+ (n=105)**	**PD-L1- (n=64)**	***PD-L1+ (n=52)***
ORR, %	**4.7%**	**4.8%**	**4.7%**	***23.1%***
DCR, %	**7.6%**	**9.5%**	**4.6%**	
CR, n	**1**	**1**	**0**	
PR, n	**7**	**4**	**3**	
SD, n	**35**	**22**	**12**	

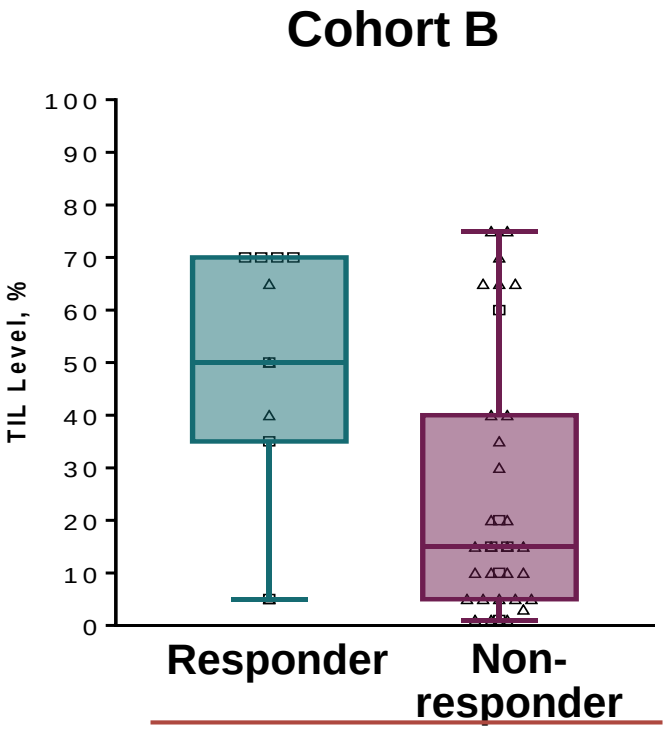
*1 patient was PD-L1 unknown

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

sTILs are an imperfect biomarker. Context is important.







	Combined Cohorts		Cohort A		Cohort B	
	Responder	Non-responder	Responder	Non-responder	Responder	Non-responder
n	18	175	7	140	11	35
Median (IQR)	37.5% (8.75-66.25)	5% (2-15)	10% (5-30)	5% (1-10)	50% (35-70)	15% (5-40)
P[a]	<0.001		0.062		0.009	

Loi S et al ESMO 2017

Three Pressing Challenges for the Field

1. Deepening Responses to SA Immunotherapy

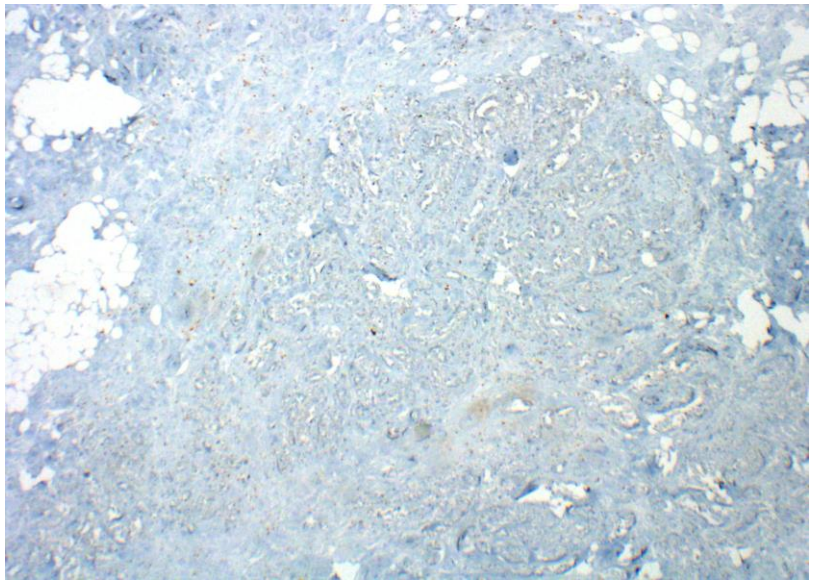
2. Converting Non-Responders to Responders

3. Personalizing Immunotherapy

One Framework for Personalizing Breast Cancer Immunotherapy

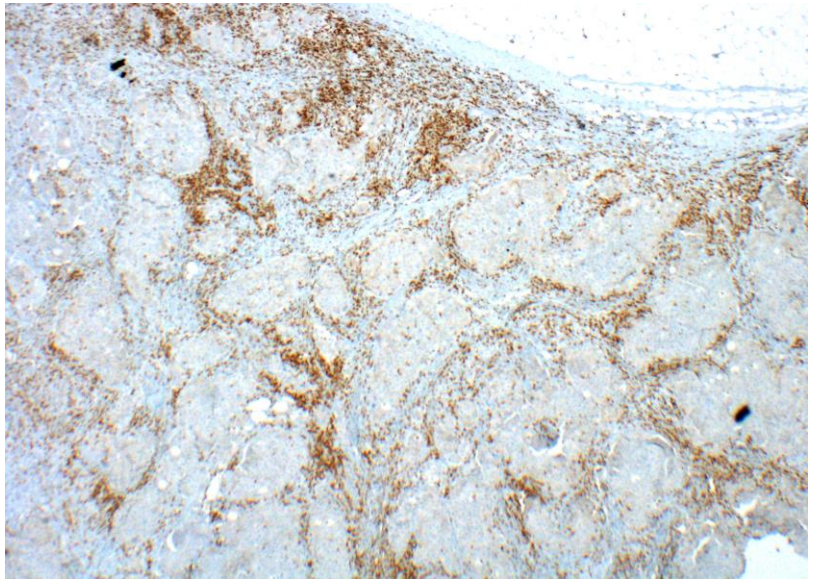
Patterns of T Cell Infiltration

Non-inflamed



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

Inflamed



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

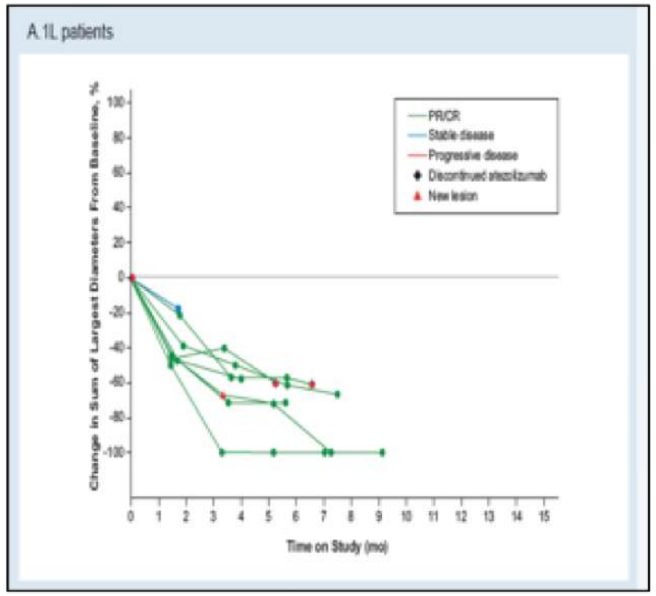
Combination of PD-1/PD-L1 Blockade with Standard Chemotherapy in TNBC

Atezolizumab with Nab-Paclitaxel

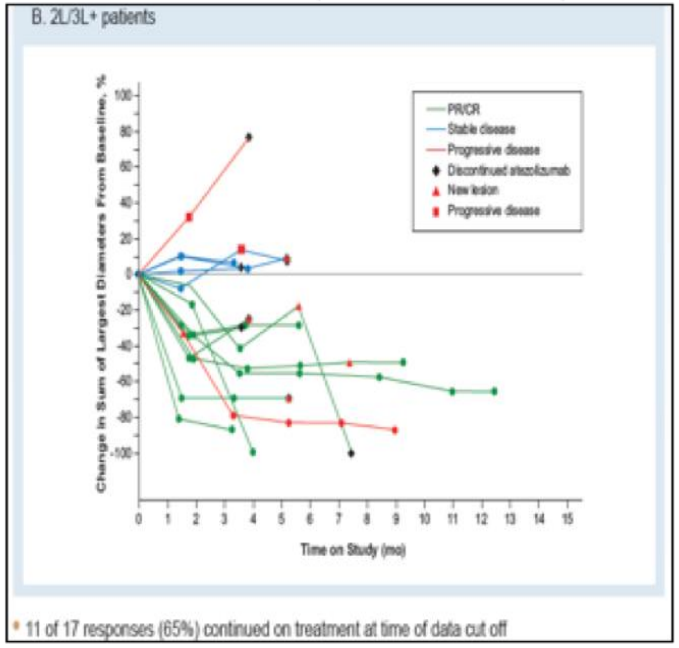
Changes in Tumor Burden Over Time with Line of Therapy

- PD-1 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%)



Taxane+Atezolizumab (ORR 41.7%)

N = 24

--antigen release
--signal through TLR-4
--augment DC activity and Ag presentation

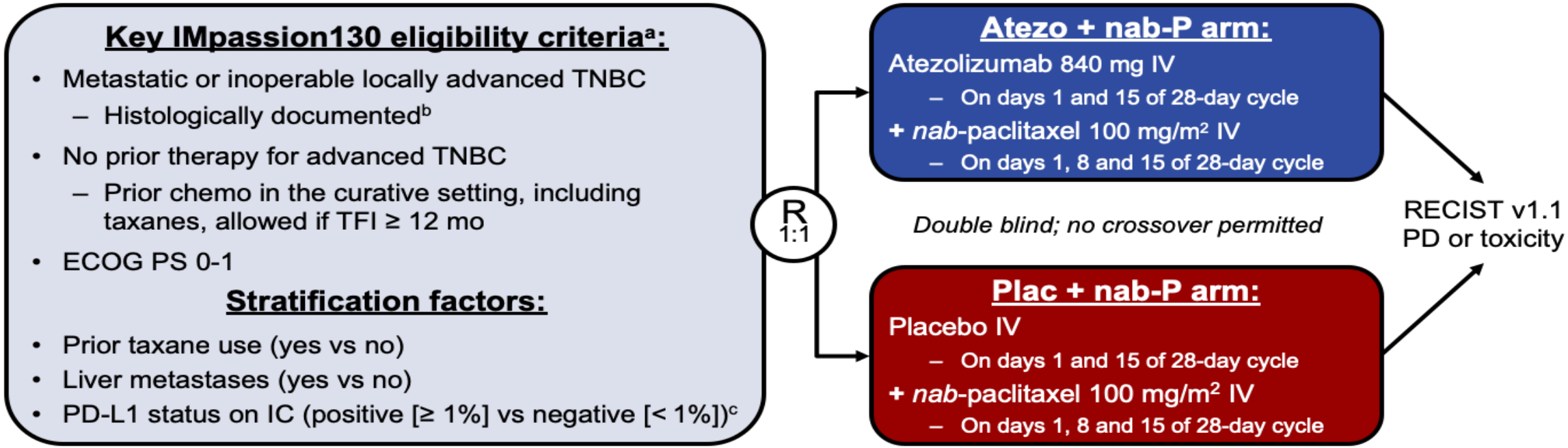
Eribulin+Pembrolizumab (ORR 26.4%)
(29.2% ORR 1st line, 22% 2nd/3rd line)

N = 107 (66/41)

--antigen release
--decreases Tregs
--decreases M2 macrophages

Adams S et al JAMA Oncol 2018
Tolaney S SABCS 2016, 2017

IMpassion130: A global, randomised, double-blind, Phase III study of atezolizumab + *nab*-paclitaxel vs placebo + *nab*-paclitaxel in treatment-naive locally advanced or metastatic triple-negative breast cancer



- 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).

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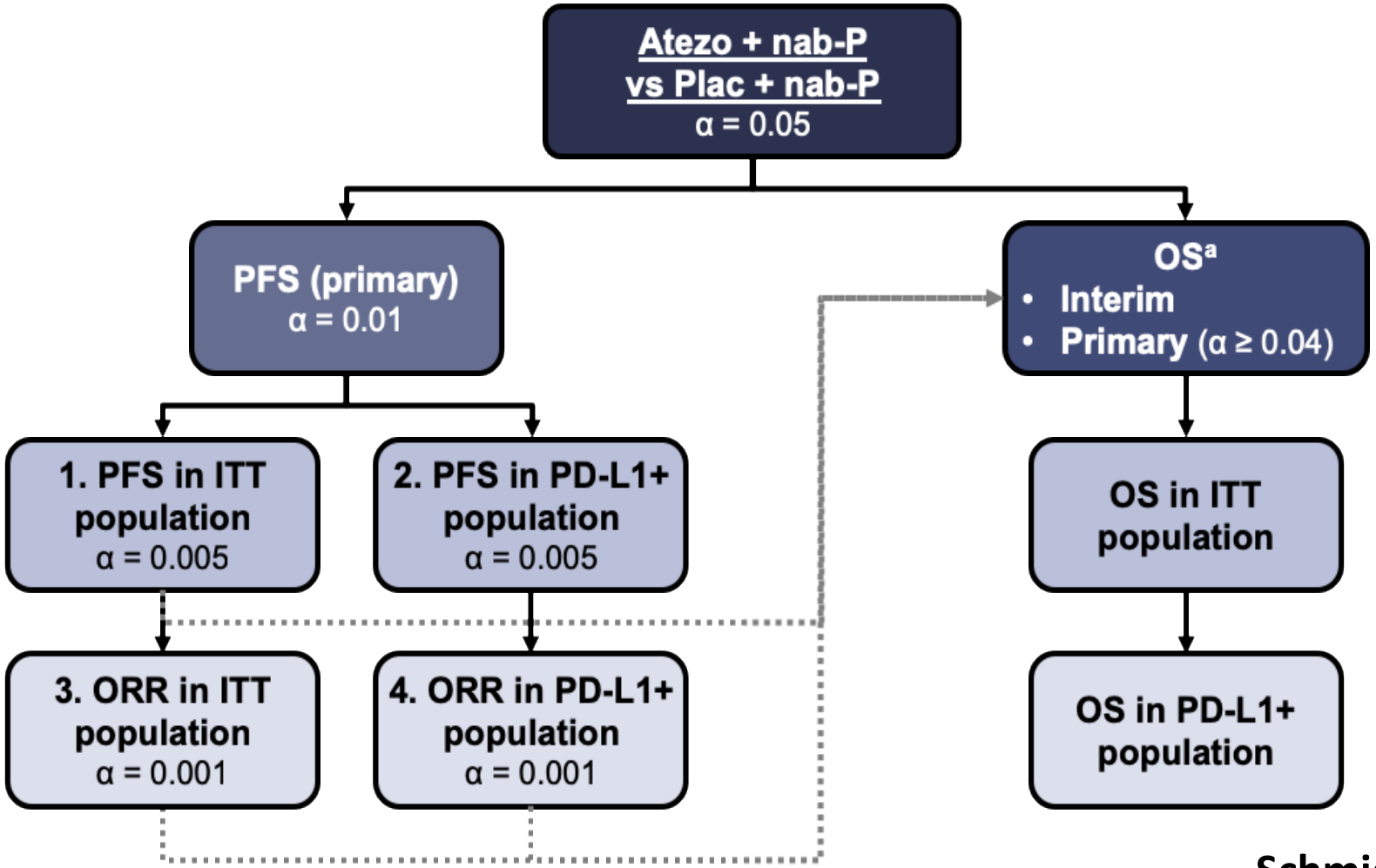
IMpassion130 statistical testing



- Primary PFS analysis (PFS tested in ITT and PD-L1+ populations)
- First interim OS analysis (OS tested in ITT population, then, if significant, in PD-L1+ population)

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[a] α recycled if PFS/ORR testing is significant. Hazard ratio (HR)/*P* value–stopping boundaries are dependent on the OS analysis timing.

IMpassion130 baseline characteristics

Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Median age (range), y	55 (20-82)	56 (26-86)
Female, n (%)	448 (99%)	450 (100%)
Race, n (%)[a]		
White	308 (68%)	301 (67%)
Asian	85 (19%)	76 (17%)
Black/African American	26 (6%)	33 (7%)
Other/multiple	20 (4%)	26 (6%)
ECOG PS, n (%)[b,c]		
0	256 (57%)	270 (60%)
1	193 (43%)	179 (40%)
Prior (neo)adjuvant treatment, n (%)	284 (63%)	286 (63%)
Prior taxane	231 (51%)	230 (51%)
Prior anthracycline	243 (54%)	242 (54%)

Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Metastatic disease, n (%)	404 (90%)	408 (91%)
No. of sites, n (%)[d]		
0-3	332 (74%)	341 (76%)
≥ 4	118 (26%)	108 (24%)
Site of metastatic disease, n (%)		
Lung	226 (50%)	242 (54%)
Bone	145 (32%)	141 (31%)
Liver	126 (28%)	118 (26%)
Brain	30 (7%)	31 (7%)
Lymph node only[d]	33 (7%)	23 (5%)
PD-L1+ (IC), n (%)	185 (41%)	184 (41%)

Data cutoff: 17 April 2018. [a] Race was unknown in 12 patients in the Atezo + nab-P arm and 15 in the Plac + nab-P arm. [b] Of n = 450 in each arm. [c] ECOG PS before start of treatment was 2 in 1 patient per arm. [d] Of n = 450 in the Atezo + nab-P arm and n = 449 in the Plac + nab-P arm arm.

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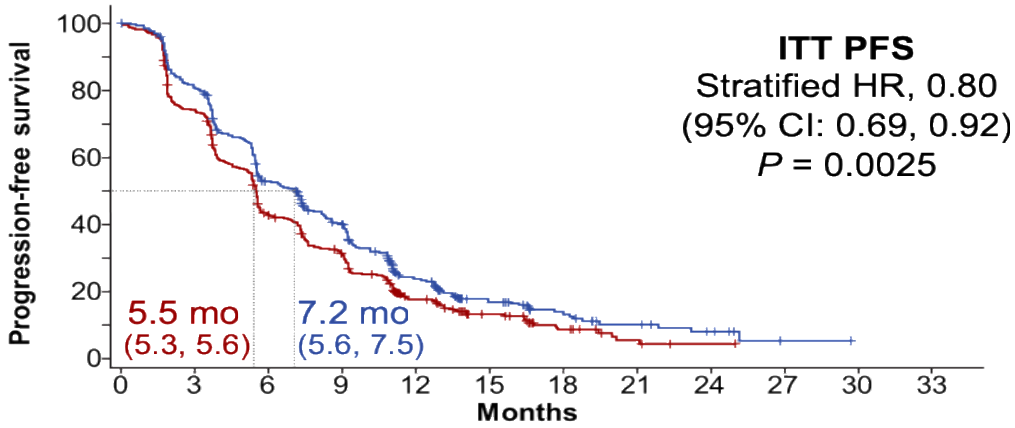
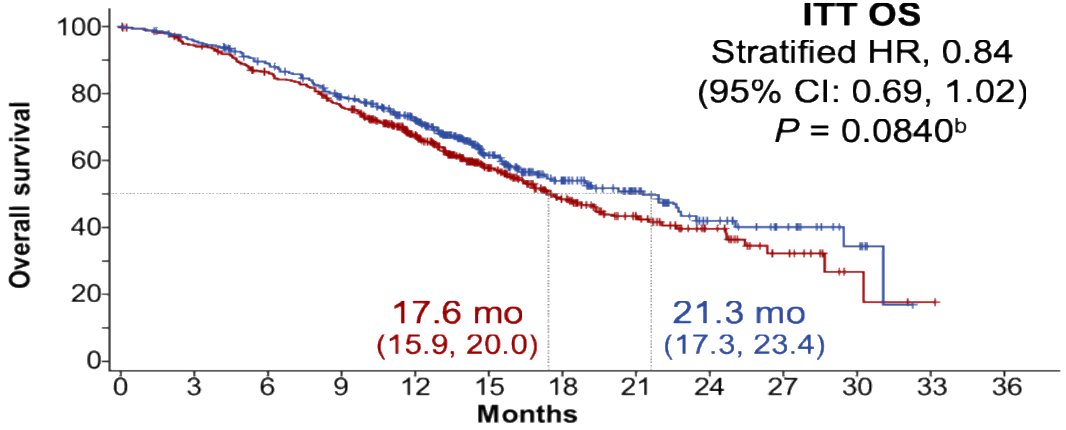
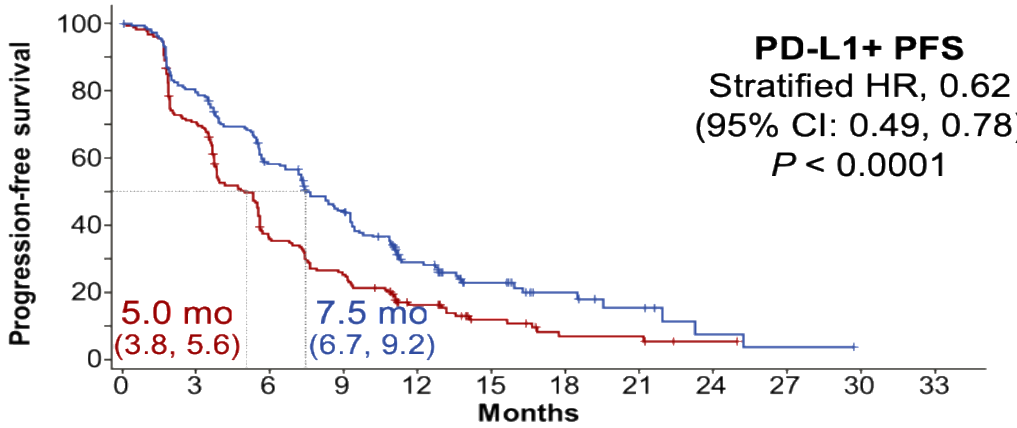
Atezolizumab + Nab-Paclitaxel: Clinically Meaningful Efficacy in PD-L1+ Patients

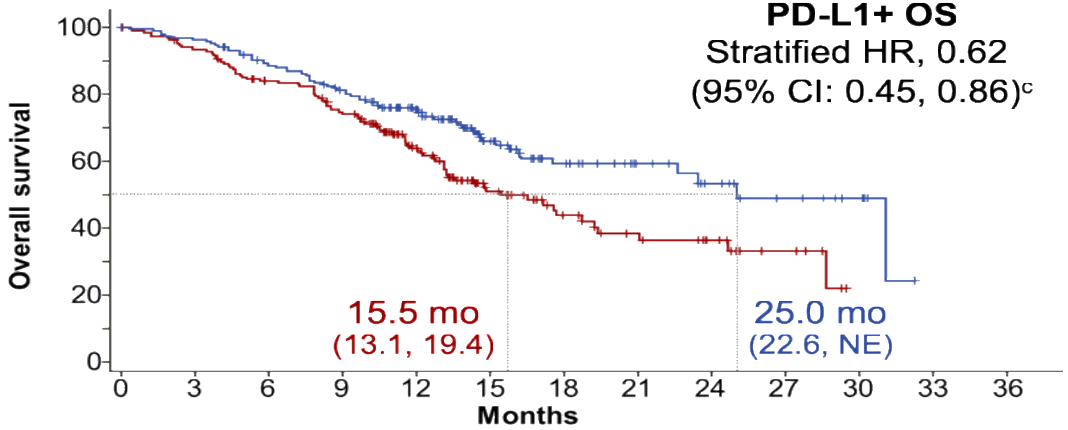
ITT population





PD-L1+ population[a]





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].

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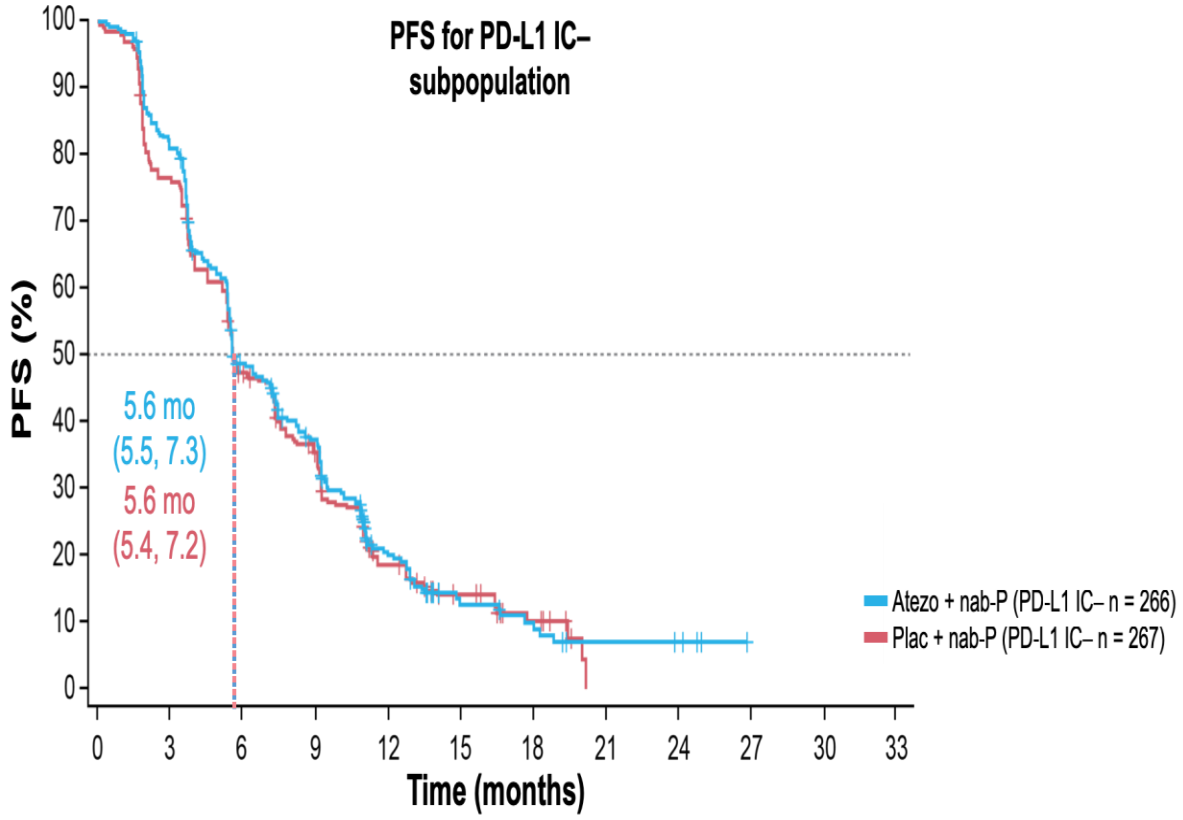
No Benefit for Atezolizumab + Nab-Paclitaxel in PD-L1- Patients



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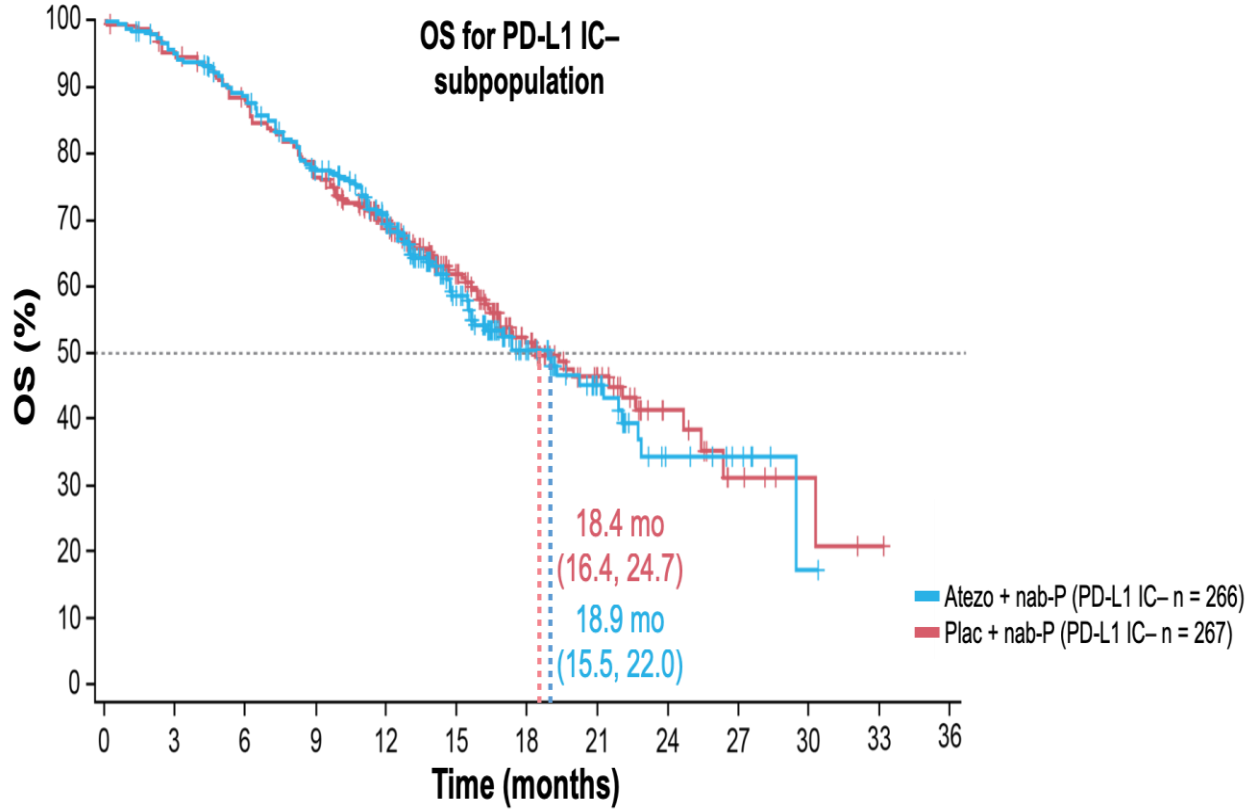

- A trend toward association between PD-L1 IC positivity and poor prognosis was observed but was not statistically significant
- PD-L1 IC positivity was predictive of PFS and OS benefit with atezolizumab + *nab*-paclitaxel

Median PFS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All *P* values except for PD-L1 IC+ PFS are nominal *P* values. Data cutoff: April 17, 2018.

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Median OS durations (and 95% CIs) are indicated on the plot. Stratified HRs are shown. All *P* values are nominal. Data cutoff: April 17, 2018.

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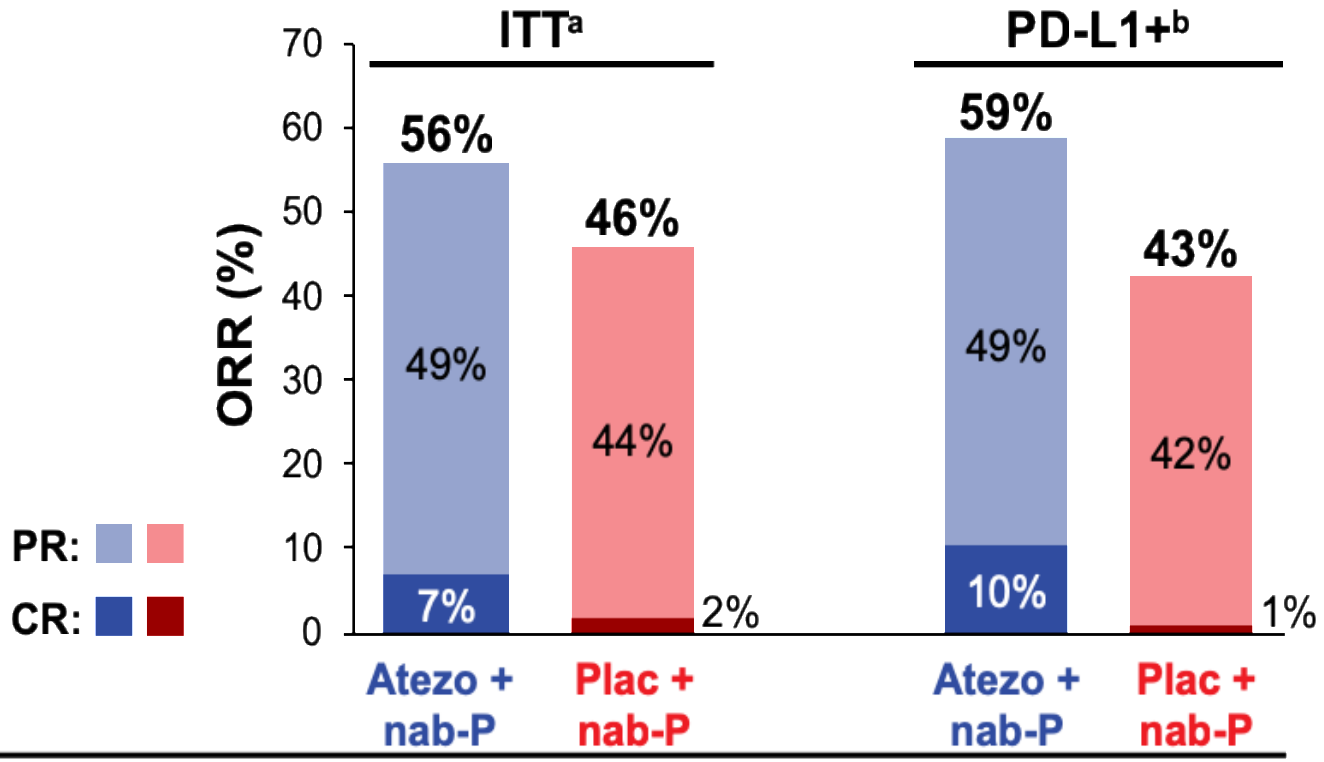
Secondary efficacy endpoints



	ITT[a]		PD-L1+[b]	
	Atezo + nab-P	Plac + nab-P	Atezo + nab-P	Plac + nab-P
DOR, median (95% CI), mo	7.4 (6.9, 9.0)	5.6 (5.5, 6.9)	8.5 (7.3, 9.7)	5.5 (3.7, 7.1)
No. of ongoing responses, n (%)[c]	78 (31%)	52 (25%)	39 (36%)	19 (24%)

- Numerically higher and more durable responses were seen in the Atezo + nab-P arm
  - Differences were not significant based on α level = 0.1% (ITT: *P* = 0.0021; PD-L1+: *P* = 0.0016)
- The CR rate was higher in the Atezo + nab-P arm vs the Plac + nab-P arm
  - ITT population: 7% vs 2%
  - PD-L1+ patients: 10% vs 1%

Data cutoff: 17 April 2018. Objective response–evaluable patients: [a] 450 in Atezo + nab-P arm and 449 in Plac + nab-P arm. [b] 185 in Atezo + nab-P arm and 183 in Plac + nab-P arm. [c] No death or PD.

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Exposure and dose intensity

	nab-P Exposure		Atezo or Plac Exposure	
	Atezo + nab-P (n = 452)	Plac + nab-P (n = 438)	Atezo + nab-P (n = 452)[a]	Plac + nab-P (n = 438)
Treatment duration, weeks				
Median (range)	22.1 (0-137)	21.8 (0-103)	24.1 (0-139)	22.1 (0-109)
Patients with indicated treatment duration, n (%)				
≤ 16 weeks	361 (80%)	316 (72%)	355 (79%)	316 (72%)
≤ 6 months	315 (70%)	257 (59%)	311 (69%)	259 (59%)
≤ 12 months	100 (22%)	75 (17%)	138 (31%)	108 (25%)
≤ 18 months	53 (12%)	44 (10%)	89 (20%)	63 (14%)
> 18 months	12 (3%)	7 (2%)	25 (6%)	15 (3%)
Dose intensity, %				
Mean (SD)	87.7 (18%)	90.4 (15%)	95.8 (10%)	NE
No. of cycles				
Median (range)	6.0 (1-34)	6.0 (1-26)	7.0 (1-35)	6.0 (1-28)

- A higher proportion of patients in the Atezo + nab-P arm compared with the Plac + nab-P arm received nab-P for at least 6 months (70% vs 59%) and at least 12 months (22% vs 17%)
- Atezo did not compromise the dose intensity of *nab*-P

Safety evaluable population. Data cutoff: 17 April 2018. [a] Excludes placebo exposure for 13 patients in the Atezo + nab-P arm.

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Most common AEs regardless of attribution

AEs in ≥ 20% (all grade) or ≥ 3% (grade 3-4) of patients in either arm, n (%)	Atezo + nab-P (n = 452)		Plac + nab-P (n = 438)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Alopecia	255 (56%)	3 (1%)	252 (58%)	1 (< 1%)
Fatigue	211 (47%)	18 (4%)	196 (45%)	15 (3%)
Nausea[a]	**208 (46%)**	**5 (1%)**	**167 (38%)**	**8 (2%)**
Diarrhoea	147 (33%)	6 (1%)	150 (34%)	9 (2%)
Anaemia	125 (28%)	13 (3%)	115 (26%)	13 (3%)
Constipation	113 (25%)	3 (1%)	108 (25%)	1 (< 1%)
Cough[a]	**112 (25%)**	**0**	**83 (19%)**	**0**
Headache	105 (23%)	2 (< 1%)	96 (22%)	4 (1%)
Neuropathy peripheral	98 (22%)	**25 (6%)**	97 (22%)	**12 (3%)**
Neutropaenia[a]	**94 (21%)**	**37 (8%)**	**67 (15%)**	**36 (8%)**
Decreased appetite	91 (20%)	3 (1%)	79 (18%)	3 (1%)
Neutrophil count decreased	57 (13%)	21 (5%)	48 (11%)	15 (3%)
Hypertension	22 (5%)	4 (1%)	24 (5%)	11 (3%)

- The most common AEs were generally similar between arms
- Most common Grade 3-4 AEs: neutropaenia, decreased neutrophil count, peripheral neuropathy, fatigue, anaemia
  - Grade 3-4 AEs ≥ 2% higher in the Atezo + nab-P arm included peripheral neuropathy (6% vs 3%)

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Data cutoff: 17 April 2018. [a] AEs with ≥ 5% higher incidence in the A + nab-P arm vs P + nab-P arm; others include pyrexia and hypothyroidism (not shown in the table because overall frequency was < 20%).

Most common serious AEs

SAEs occurring in ≥ 1% of patients in either arm (regardless of attribution)

SAE, n (%)	Atezo + nab-P (n = 452)		Plac + nab-P (n = 438)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All	103 (23%)	78 (17%)[a]	80 (18%)	56 (13%)[b]
Pneumonia	10 (2%)	8 (2%)[c]	5 (1%)	0
Urinary tract infection	5 (1%)	2 (< 1%)	0	0
Dyspnoea	5 (1%)	3 (1%)	2 (< 1%)	2 (< 1%)
Pyrexia	5 (1%)	3 (1%)	3 (1%)	0

- A higher proportion of patients in the Atezo + nab-P arm than in the Plac + nab-P arm reported SAEs (23% vs 18%)
- No SAE was reported with a ≥ 2% difference between treatment arms

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SAE, serious adverse event. Data cutoff: 17 April 2018. [a] Six Grade 5 events occurred. [b] Three Grade 5 events occurred. [c] One Grade 5 event occurred.

AESIs suggestive of potential immune-related aetiology

AESI, n (%)[a]	Atezo + nab-P (n = 452)		Plac + nab-P (n = 438)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All	259 (57%)	34 (8%)	183 (42%)	19 (4%)
Important AESIs				
Hepatitis (all)	69 (15%)	23 (5%)	62 (14%)	13 (3%)
Hepatitis (diagnosis)	10 (2%)	6 (1%)	7 (2%)	1 (< 1%)
Hepatitis (lab abnormalities)	62 (14%)	17 (4%)	58 (13%)	12 (3%)
Hypothyroidism	78 (17%)	0	19 (4%)	0
Hyperthyroidism	20 (4%)	1 (< 1%)	6 (1%)	0
Pneumonitis	14 (3%)	1 (< 1%)	1 (< 1%)	0
Meningoencephalitis[b]	5 (1%)	0	2 (< 1%)	0
Colitis	5 (1%)	1 (< 1%)	3 (1%)	1 (< 1%)
Adrenal insufficiency	4 (1%)	1 (< 1%)	0	0
Pancreatitis	2 (< 1%)	1 (< 1%)	0	0
Diabetes mellitus	1 (< 1%)	1 (< 1%)	2 (< 1%)	1 (< 1%)
Nephritis	1 (< 1%)	0	0	0
Other AESIs[c]				
Rash	154 (34%)	4 (1%)	114 (26%)	2 (< 1%)
Infusion-related reactions	5 (1%)	0	5 (1%)	0

- 1 grade 5 AESI per arm (both treatment related):
  - Atezo + nab-P: autoimmune hepatitis
  - Plac + nab-P: hepatic failure
- All hypothyroidism AESIs were grade 1-2; none led to discontinuation
  - Atezo + nab-P: 17%
  - Plac + nab-P: 4%
- Pneumonitis was infrequent with only 1 grade 3-4 event in the Atezo + nab-P arm
  - Atezo + nab-P: 3%
  - Plac + nab-P: < 1%
- Hepatitis rates were balanced

AESI, adverse event of special interest. Data cutoff: 17 April 2018. [a] Baskets of preferred terms according to medical concepts. [b] All events of photophobia.
[c] Includes all AESIs occurring in ≥ 1% of patients in either arm.

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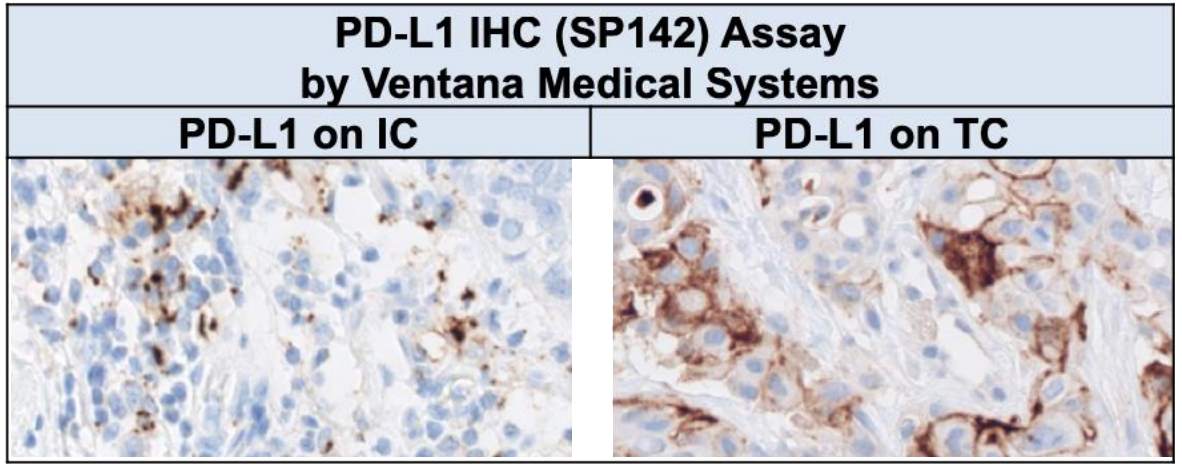
IMpassion130 Biomarker Analyses

- Pre-existing immune biology, including PD-L1 expression on TC, CD8+ T cells and stromal TILs, has also been associated with clinical benefit from anti–PD-L1/PD-1[1,2]
- In this exploratory analysis, we sought to evaluate whether this immune biology and *BRCA1/2* mutation status were associated with clinical benefit from atezolizumab + *nab*-paclitaxel
- Biomarkers were centrally analyzed in pre-treatment biopsies
  - PD-L1 on IC and TC by VENTANA SP142 IHC assay[a]
  - Intratumoral CD8+ T cells by IHC (Dako clone C8/144B) and stromal TILs by H&E[b]
  - *BRCA1/2* mutation status by FoundationOne assay



H&E, hematoxylin and eosin staining; IHC, immunohistochemistry.
[a] PD-L1 scoring: IC0: < 1%; IC1: ≥ 1% and < 5%; IC2: ≥ 5% and < 10%; IC3: ≥ 10%; TC–: < 1% PD-L1 on tumor cells; TC+: ≥ 1% PD-L1 on tumor cells.
[b] Pre-specified cutoffs for CD8 IHC and stromal TILs are based on references 1 and 2.
1. Adams *JAMA Oncol* 2018. 2. Denkert *Lancet Oncol* 2018.

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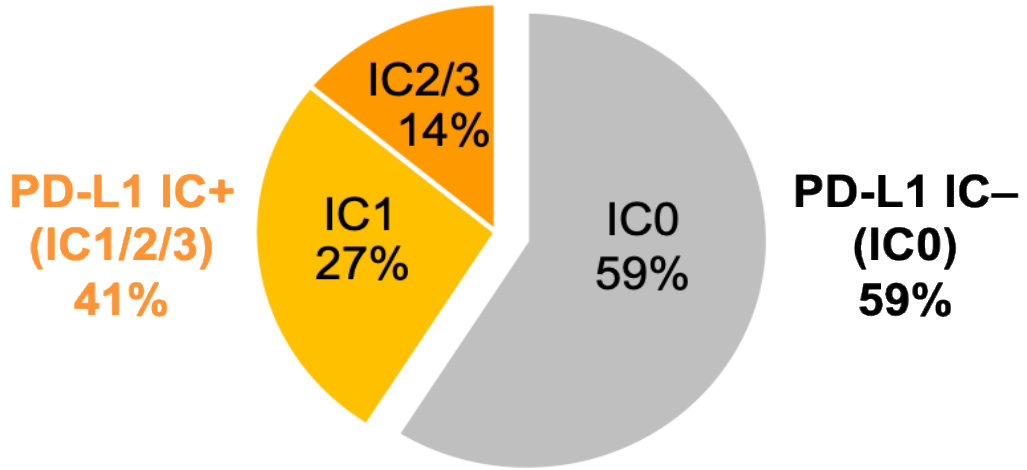
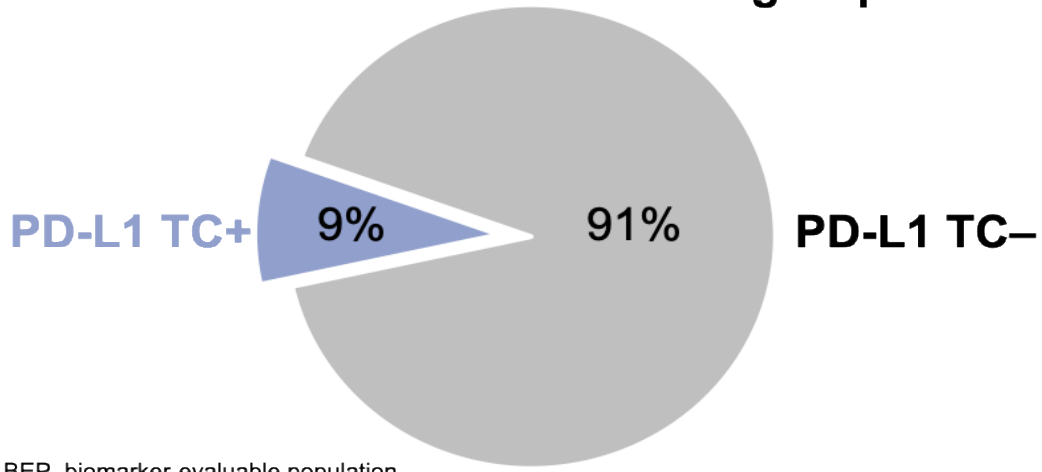
PD-L1 is Expressed Primarily on Tumor Infiltrating Immune Cells in mTNBC

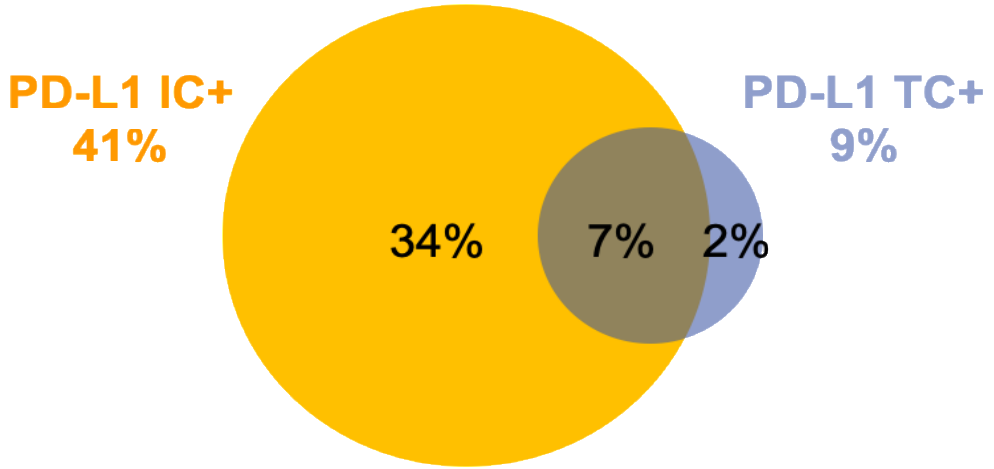
Prevalence of PD-L1 IC subgroups



Prevalence of PD-L1 TC subgroups



The majority of patients with expression of PD-L1 on TC are included within the PD-L1 IC+ population



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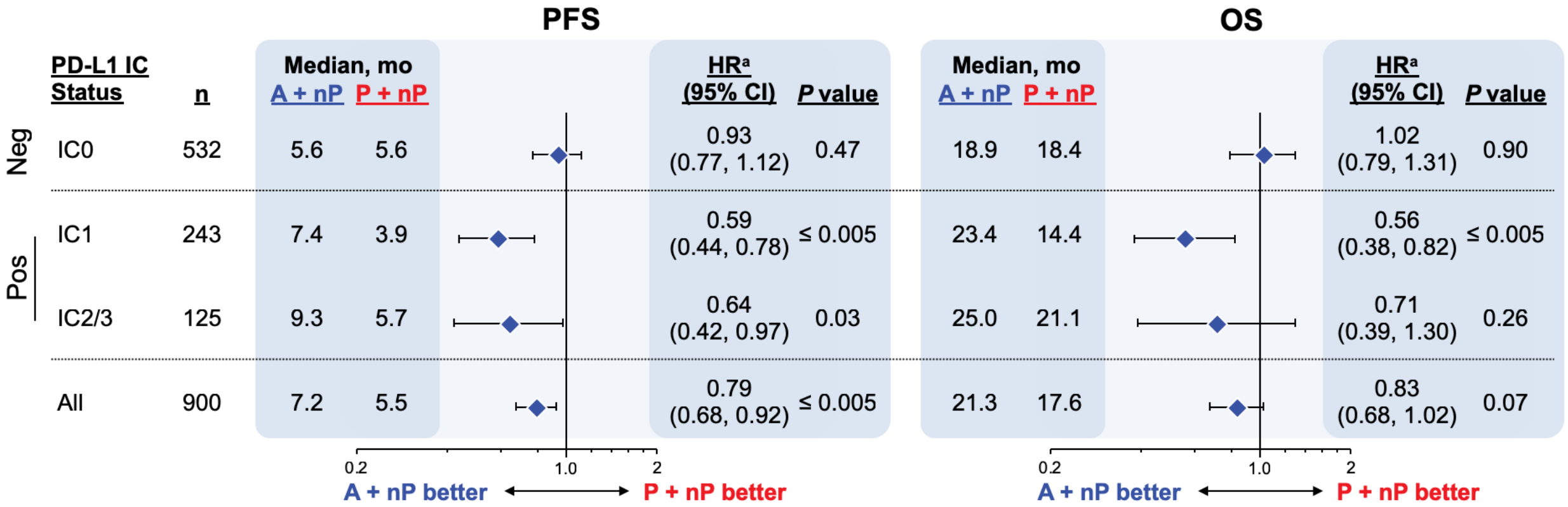
BEP, biomarker-evaluable population.
BEP (TC): n = 900. PD-L1 scoring: IC0: < 1%; IC1: ≥ 1% and < 5%; IC2: ≥ 5% and < 10%; IC3: ≥ 10%; TC–: < 1% PD-L1 on tumor cells; TC+: ≥ 1% PD-L1 on tumor cells.

Consistent Clinical Benefit for Atezolizumab + Nab-Paclitaxel was Observed Across All PD-L1 IC Subgroups



[a] Adjusted for prior taxane treatment and liver metastases.
A multivariate analysis was performed to account for imbalances in baseline characteristics between PD-L1 IC–expressing subgroups (IC1, IC2 and IC3).
IC0: < 1% PD-L1; IC1: ≥ 1% and < 5% PD-L1; IC2/3: ≥ 5% PD-L1. All *P* values are nominal. Data cutoff: April 17, 2018.

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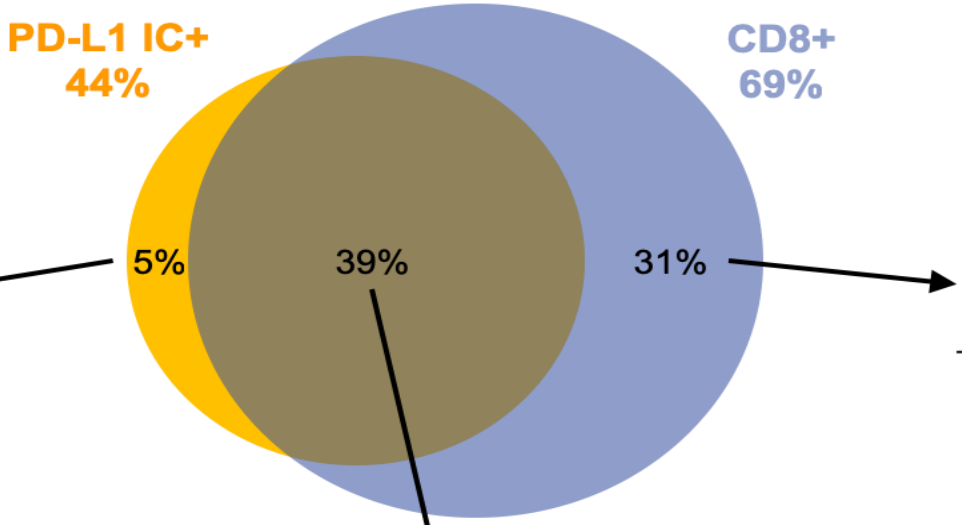
CD8+ T Cells Predict Clinical Benefit Only in PD-L1 IC+ Patients



CD8–/PD-L1 IC+ (n = 37)

	HR (95% CI)	*P* Value
PFS	0.33 (0.13, 0.87)	0.03
OS	0.25 (0.06, 1.02)	0.05

CD8+/PD-L1 IC+ (n = 280)

	HR (95% CI)	*P* Value
PFS	0.61 (0.46, 0.80)	≤ 0.005
OS	0.55 (0.38, 0.80)	≤ 0.005

CD8+/PD-L1 IC– (n = 220)

	HR (95% CI)	*P* Value
PFS	0.89 (0.66, 1.20)	0.45
OS	0.77 (0.50, 1.17)	0.21

- PD-L1 IC+ are enriched in CD8+ ($P < 0.0001$) and CD8+ are enriched in PD-L1 IC+ ($P < 0.0001$)[a]
- ***Patients with CD8+ tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+***

BEP (CD8): n = 720. A CD8+ cutoff of 0.5% was selected based on Phase Ib study in TNBC (Adams *JAMA Oncol* 2018). All *P* values are nominal.
[a] Data derived from contingency table with Fisher exact tests.

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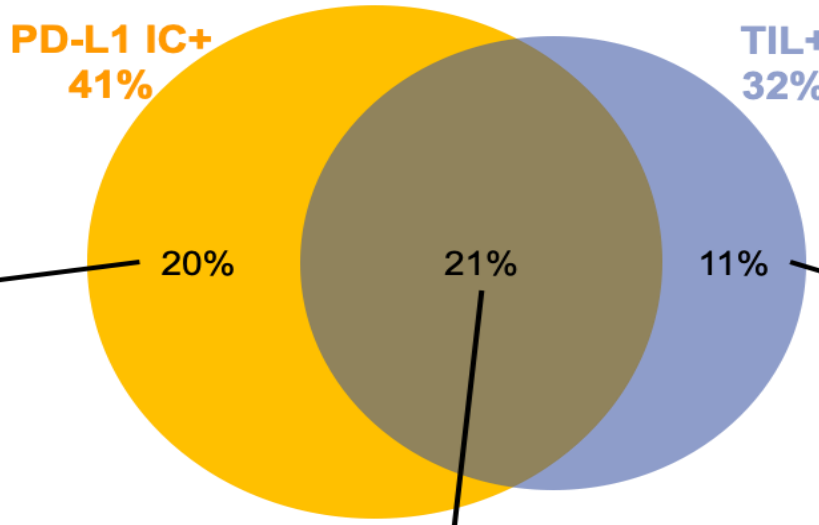
Stromal TILs Predict Clinical Benefit Only in PD-L1 IC+ Patients



TIL–/PD-L1 IC+ (n = 176)

	HR (95% CI)	*P* Value
PFS	0.74 (0.54, 1.03)	0.07
OS	0.65 (0.41, 1.02)	0.06

TIL+/PD-L1 IC+ (n = 190)

	HR (95% CI)	*P* Value
PFS	0.53 (0.38, 0.74)	≤ 0.005
OS	0.57 (0.35, 0.92)	0.02

TIL+/PD-L1 IC– (n = 94)

	HR (95% CI)	*P* Value
PFS	0.99 (0.62, 1.57)	0.97
OS	1.53 (0.76, 3.08)	0.24

- TIL+ were enriched for PD-L1 IC+ ($P < 0.0001$) but PD-L1 IC+ were not enriched for TIL+ (P = ns)[a]
- ***Patients with TIL+ tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+***

BEP (TILs): n = 893. Cutoff of 10% was used to distinguish low vs intermediate/high levels of TILs (Denkert *Lancet Oncol* 2018). All *P* values are nominal.
[a] Data derived from contingency table with Fisher exact tests.

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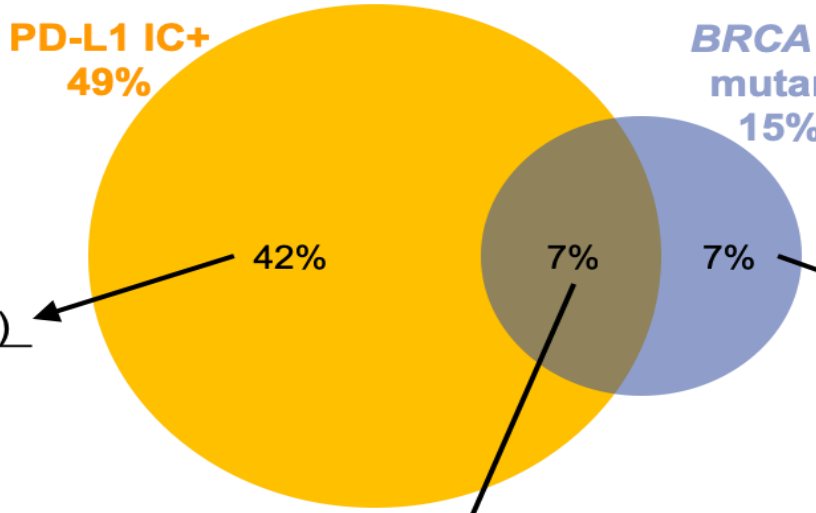
Clinical Benefit Derived by PD-L1 IC+ Patients is Independent of Their BRCA 1/2 Mutation Status



***BRCA1/2* non-mut/PD-L1 IC+** (n = 257)

	HR (95% CI)	*P* Value
PFS	0.63 (0.48, 0.83)	≤ 0.005
OS	0.62 (0.43, 0.91)	0.01

***BRCA1/2* mut/PD-L1 IC+** (n = 45)

	HR (95% CI)	*P* Value
PFS	0.45 (0.21, 0.96)	0.04
OS	0.87 (0.26, 2.85)	0.82

***BRCA1/2* mut/PD-L1 IC–** (n = 44)

	HR (95% CI)	*P* Value
PFS	0.77 (0.37, 1.61)	0.49
OS	0.85 (0.29, 2.43)	0.76

- *BRCA1/2* mutants and PD-L1 IC+ are independent from each other (*P* = ns)[a]
- ***Patients with BRCA1/2-mutant tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+[b]***

BEP (BRCA1/2): n = 612. Per FoundationOne *BRCA1/2* testing, *BRCA1/2* mutant: known and likely mutations. All *P* values are nominal.
[a] Data derived from contingency table with Fisher exact tests. [b] Data interpretation limited by small number of *BRCA1/2*-mutant patients.

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Summary of IMpassion130 Results

- In the Phase III IMpassion130 study, PD-L1 expression on IC is a predictive biomarker for selecting patients who clinically benefit from first-line atezolizumab + *nab*-paclitaxel treatment for mTNBC
  - PFS and OS benefit was observed in patients with a PD-L1 IC of ≥ 1% (by VENTANA SP142 IHC assay)
  - A treatment effect was not seen for adding atezolizumab to chemotherapy in the PD-L1–negative subgroup
- PD-L1 expression on TC did not provide additional information beyond PD-L1 IC status
  - Prevalence of tumor-cell PD-L1 expression was low, and the majority of these tumors were also PD-L1 IC+
- PD-L1 IC expression was the best predictor of clinical benefit as the patient subgroups with tumor-infiltrating immune cells (stromal TILs+) or cytotoxic T cells (CD8+) derived clinical benefit with atezolizumab + *nab*-paclitaxel if their tumors were also PD-L1 IC+
- PFS and OS results were consistent regardless of *BRCA1/2* mutation status
- Patients with newly diagnosed metastatic and unresectable locally advanced TNBC should be routinely tested for PD-L1 IC status to determine whether they might benefit from atezolizumab + *nab*-paclitaxel

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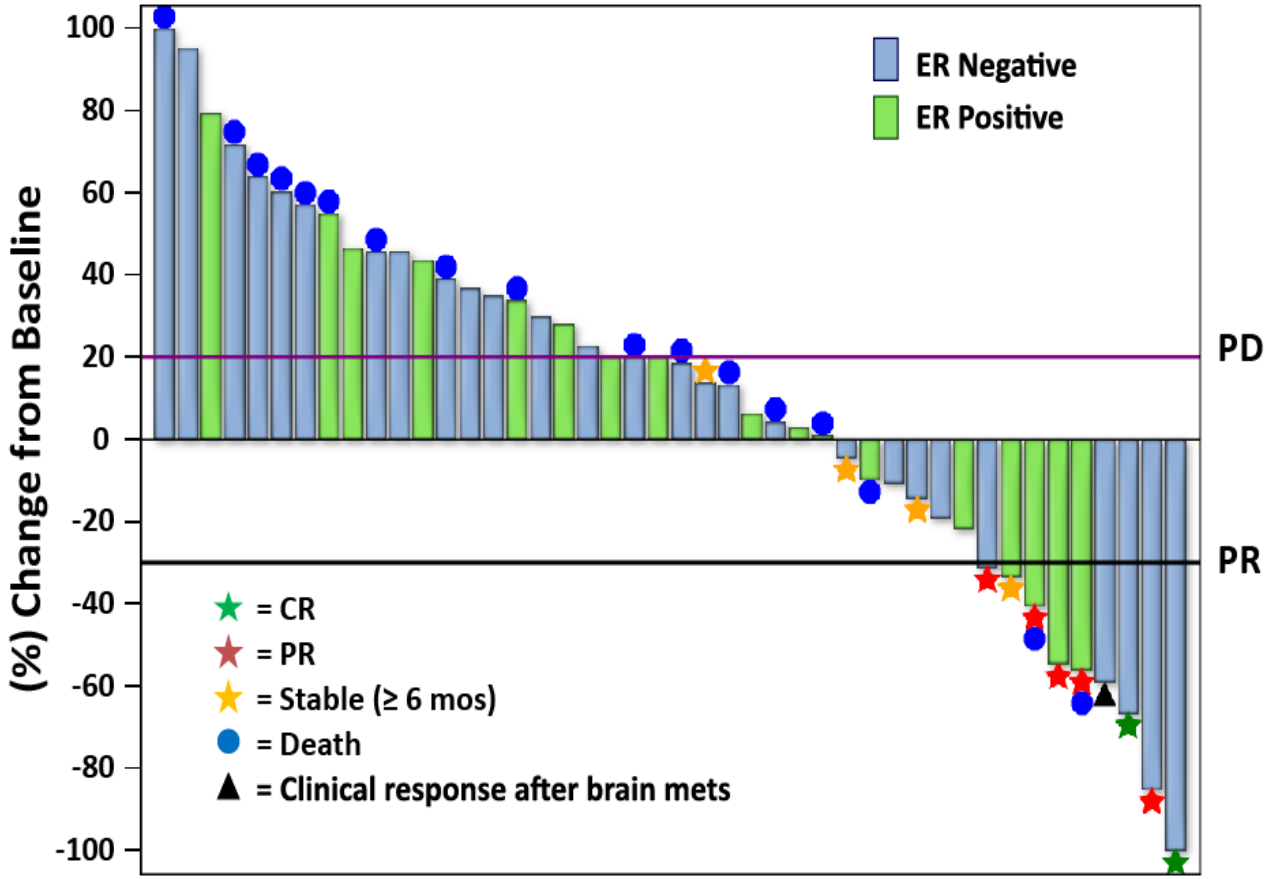
PANACEA: A Phase 1b/2 Trial of Pembrolizumab and Trastuzumab in Patients with Trastuzumab^{R} Metastatic HER-2+ Breast Cancer

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

PD-L1+ Cohort (n = 44)



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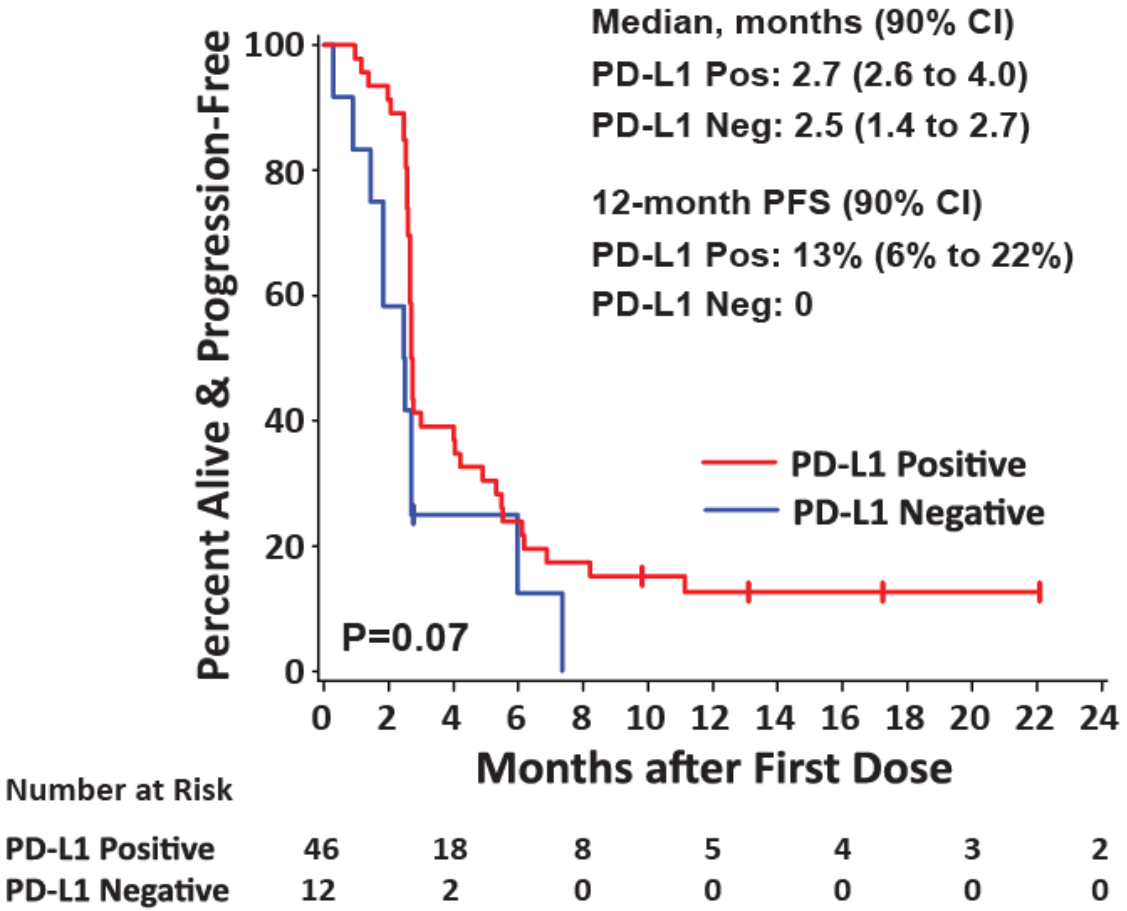
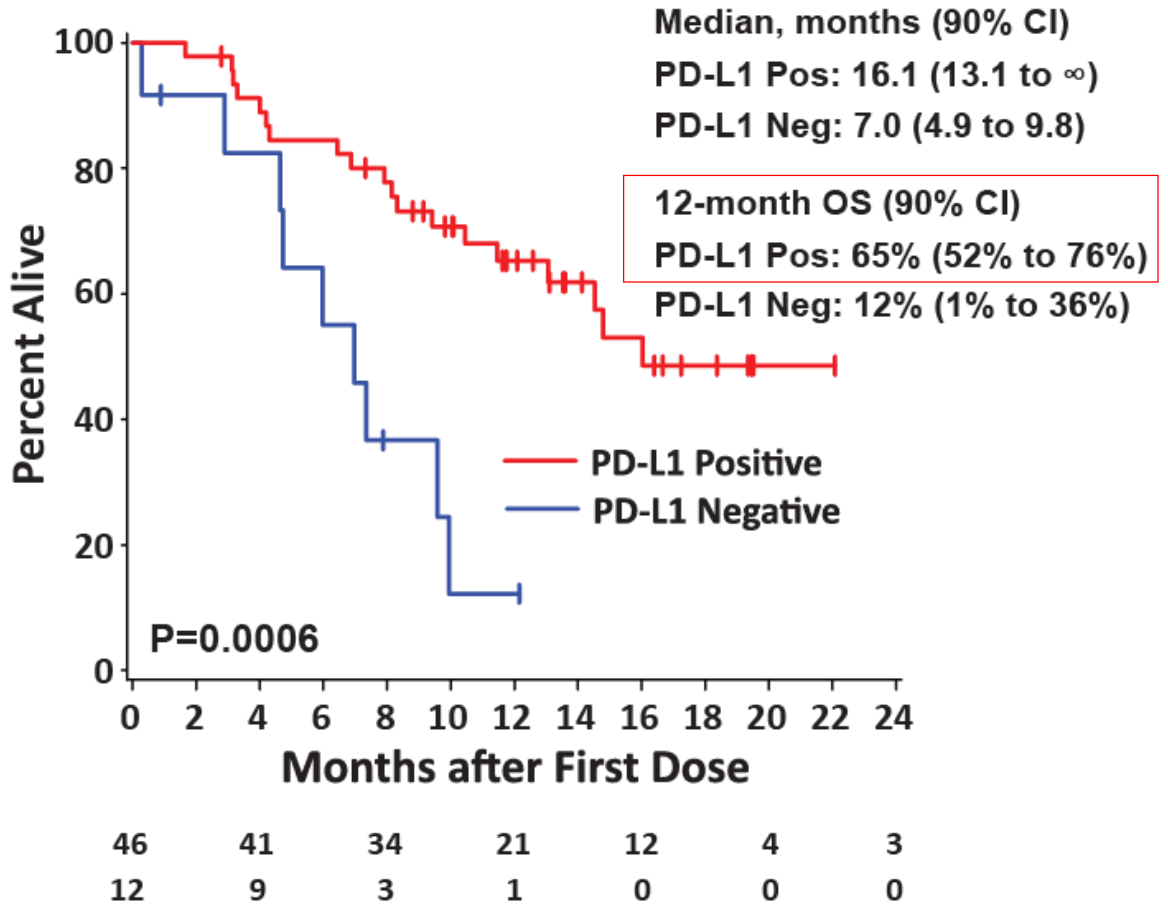
PANACEA: A Phase 1b/2 Trial of Pembrolizumab and Trastuzumab in Patients with Trastuzumab^{R} Metastatic HER-2+ Breast Cancer



OS



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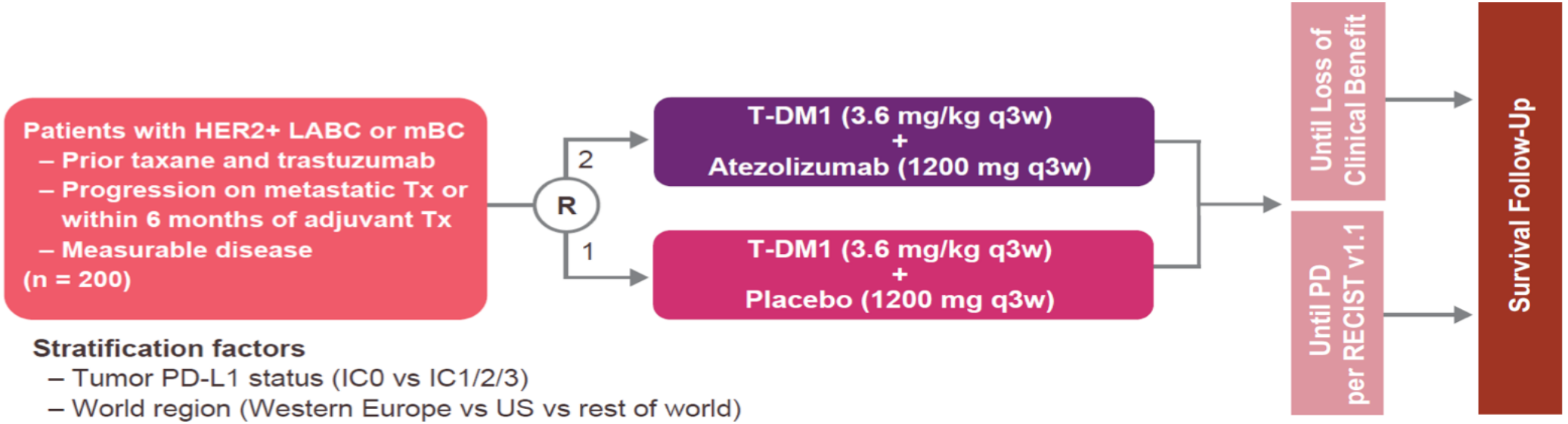
KATE2: A randomized Phase II study of atezolizumab + trastuzumab emtansine (T-DM1) vs placebo + T-DM1 in previously treated HER2+ advanced breast cancer



Stratification factors
- Tumor PD-L1 status (IC0 vs IC1/2/3)
- World region (Western Europe vs US vs rest of world)
- Liver metastases (yes vs no)

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

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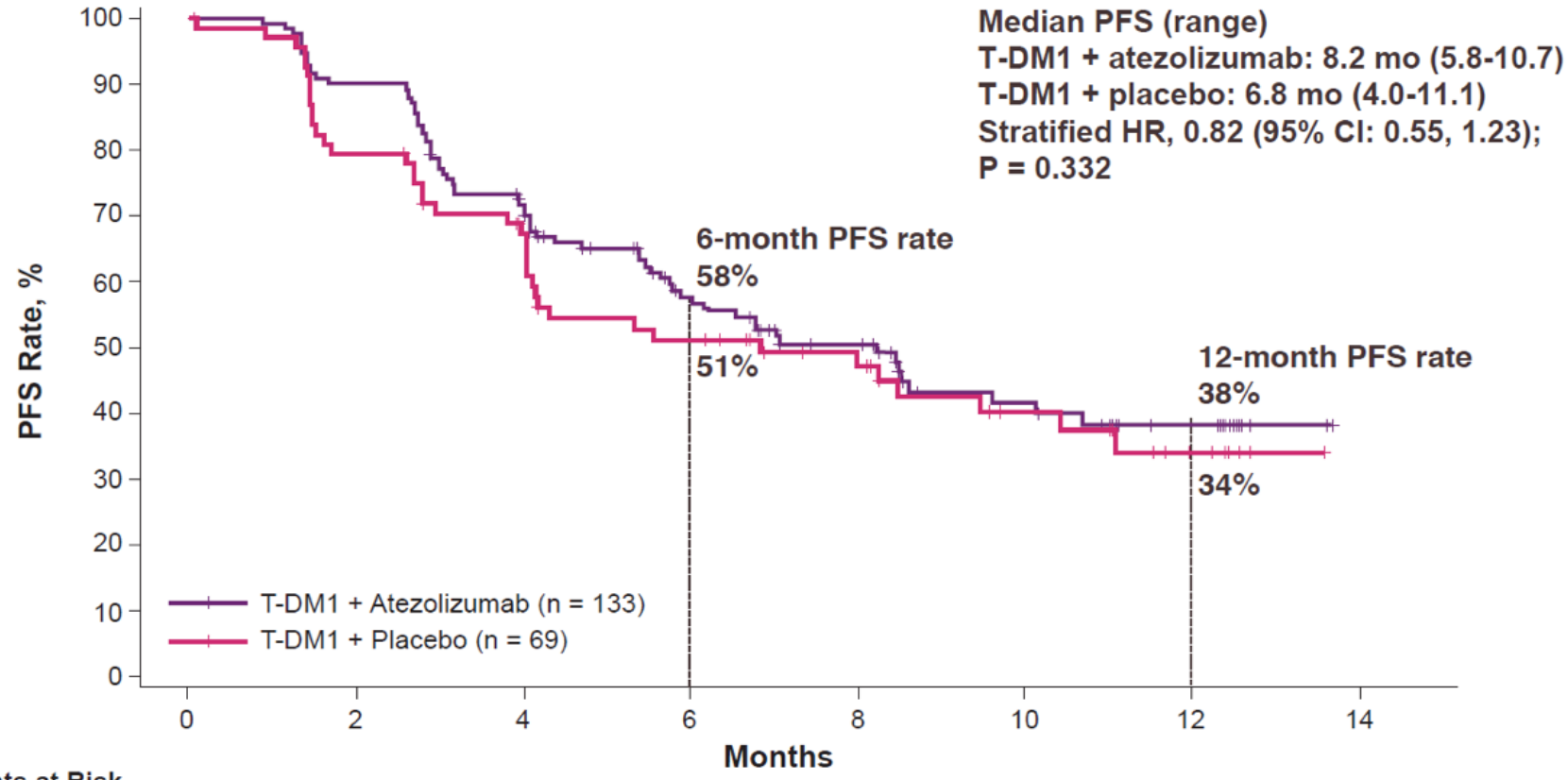
IC, tumor-infiltrating immune cells; LABC, locally advanced breast cancer; mBC, metastatic breast cancer; q3w, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; Tx, treatment.

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%).

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

Secondary Endpoint: ORR in ITT Patients

	T-DM1 + Atezolizumab (n = 132)[a]	T-DM1 + Placebo (n = 69)
ORR, %	45.5	43.5
CR, %	6.1	7.2
PR, %	39.4	36.2
SD, %	37.9	29.0
PD, %	16.7	26.1

PD, progressive disease; PR, partial response; SD, stable disease.
Data cutoff: 11 December 2017.
[a] Only 132 patients were evaluable for ORR (ie, had measurable disease at baseline).

- ORR and complete response (CR) rates in the ITT population were similar between arms
- OS data were not mature with 21 events (10%) in total. Median DOR was not reached

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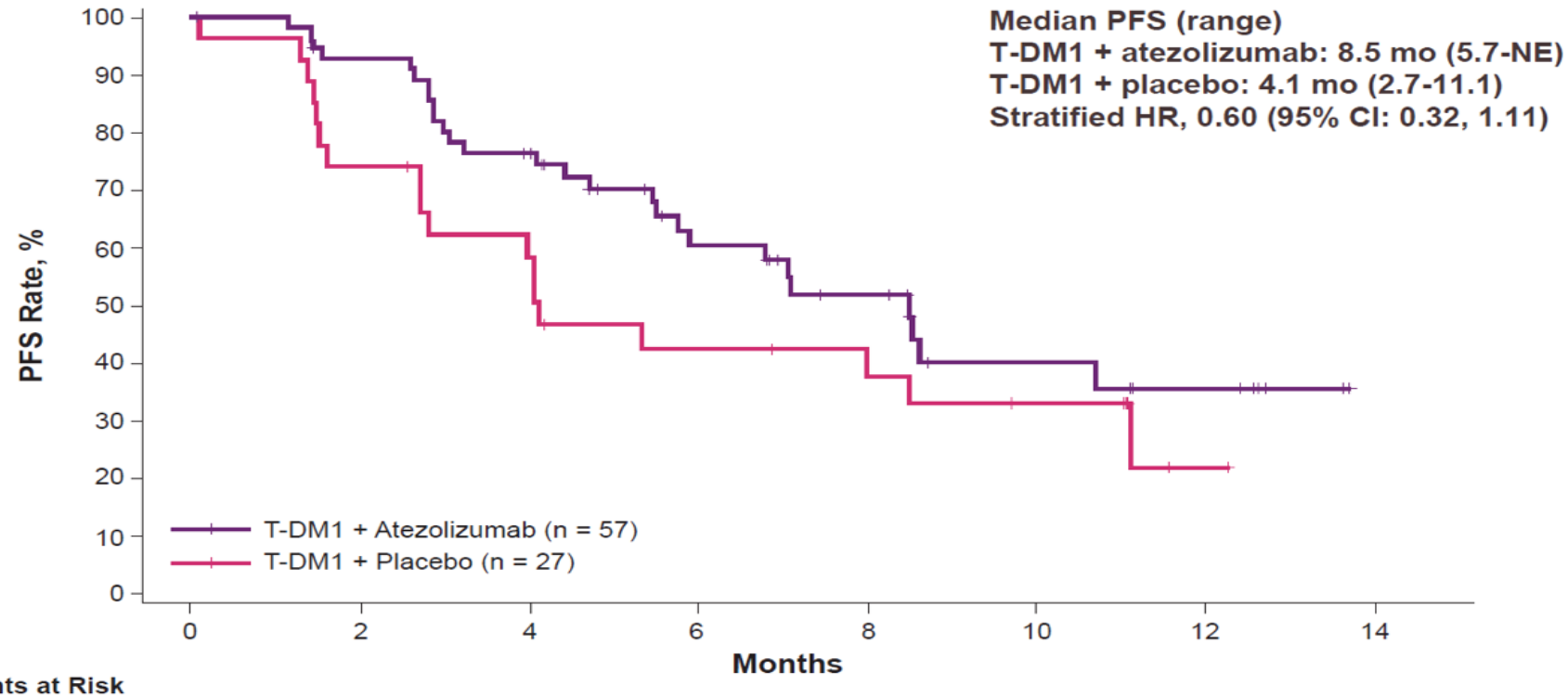
Primary Endpoint PFS in PD-L1+ Patients



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

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Conclusions

- Breast cancer can be immunogenic, most breast tumors are not
- Standard cancer therapies can be safely combined with immunotherapy, and may augment clinical efficacy
- Atezolizumab combined with nab—paclitaxel is well-tolerated in advanced mTNBC
- Atezolizumab plus nab-paclitaxel confers a PFS and OS benefit in PD-L1+ mTNBC patients, and is a new standard of care for first-line therapy
- Adding Atezolizumab to trastuzumab or T-DM1 is safe and may confer clinical benefit in advanced HER-2+ breast cancer
- PD-L1 is emerging as a reliable predictive biomarker in metastatic breast cancer
- We need to do smart trials that both prioritize the most promising immunotherapy combinations for testing in patients, and elucidate immunologic mechanisms of response and resistance in patients

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