THE UNIVERSITY OF CHICAGO MEDICINE

Immunotherapy for Breast Cancer

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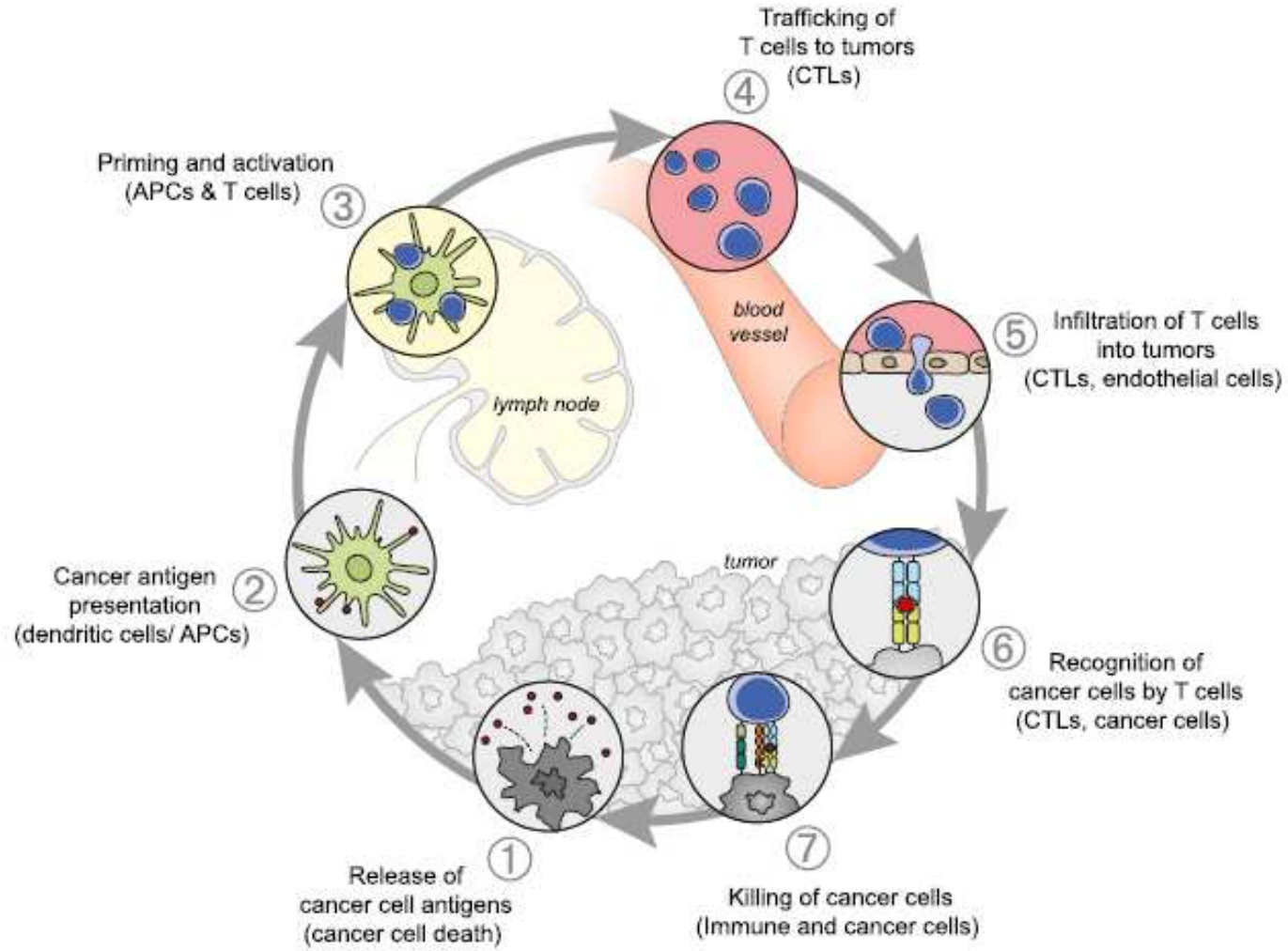
Disclosures

None

Agenda

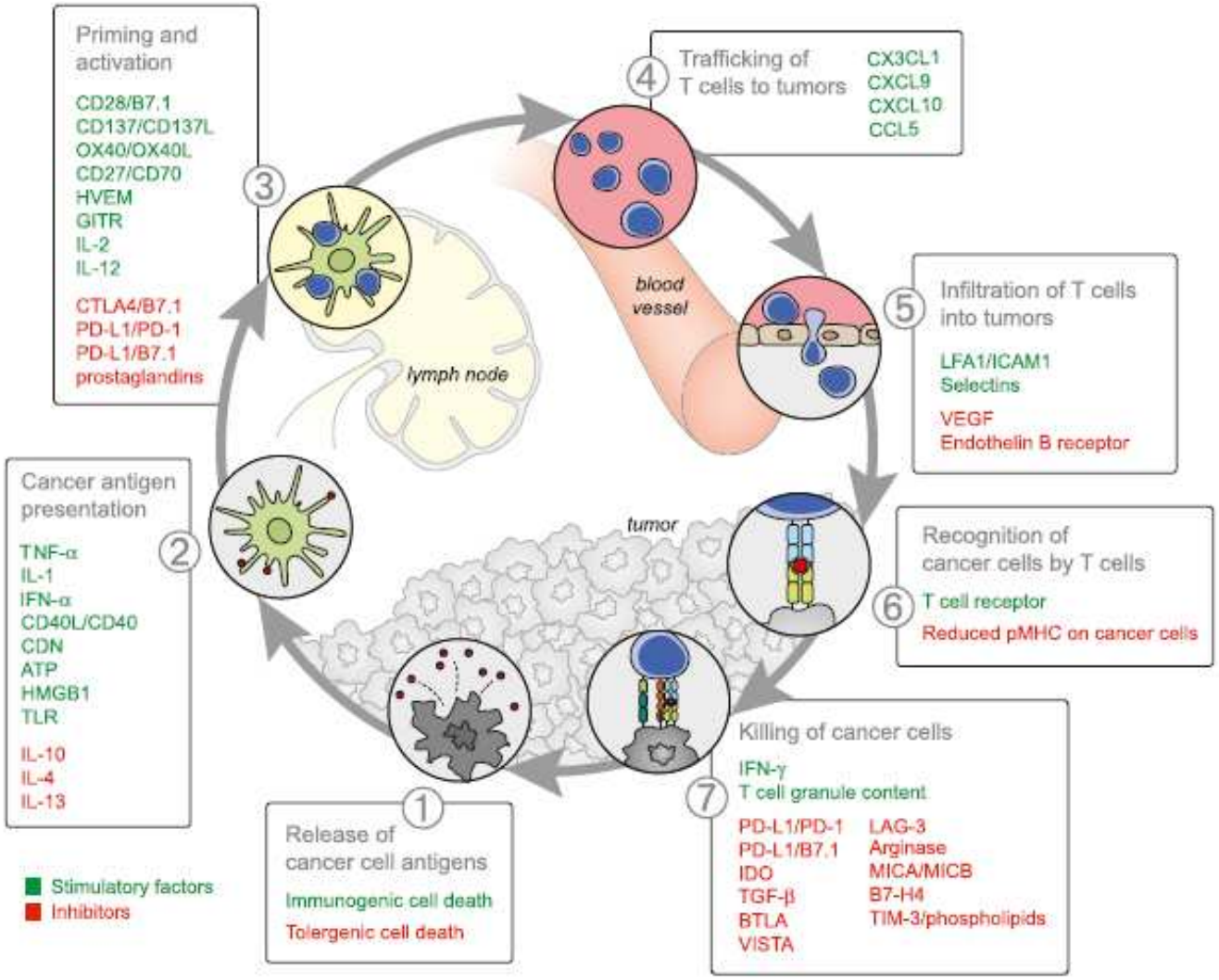
- Background/Rationale
- Clinical trials of immune checkpoint inhibitors in breast cancer to date
- Future opportunities/challenges

Cancer-Immunity Cycle



Chen and Mellmen, Immunity, 2013

Stimulatory and Inhibitory Factors



Chen and Mellmen, Immunity, 2013

Triple-Negative Breast Cancer (TNBC)

- As TNBCs are ER, PR, and HER2 negative, they do not benefit from targeted therapies
- They are associated with worse clinical outcomes
- Continue to represent an important clinical challenge
- There is great need to improve outcomes for patients with this aggressive for of breast cancer

Rationale for Immunotherapy in TNBC

- ER negative tumors have a higher density of tumor infiltrating lymphocytes (TILs) than their ER positive counterparts
- TNBCs have high PD-L1 expression, which can suppress T cell function
- Identification on gene expression profiling of a subset of TN tumors that are characterized by the elevated expression of genes involved in T cell function (immunomodulatory subtype)
- TNBCs are genomically unstable and have a high mutation rate, which can produce neoantigens that induce an immune response

Loi et al, Ann Onc 2014; Mittendorf et al, Cancer Immunol Res 2014;
Lehmann et al, JCI 2011; Wang et al, Nature 2014

Clinical Trials of Immune Checkpoint Inhibitors in Advanced Breast Cancer

- Pembrolizumab (MK-3475)
  - PD-1 inhibitor
- Atezolizumab (MPDL3280A)
  - PD-L1 inhibitor
- Investigating role of checkpoint inhibitor monotherapy in PD-L1 positive metastatic triple-negative breast cancer
  - Atezo trial expanded to include PD-L1 negative TNBCs
  - Studies including HER2 amplified and HR+ ongoing/planned
- Focused on safety/tolerability and preliminary investigation into efficacy

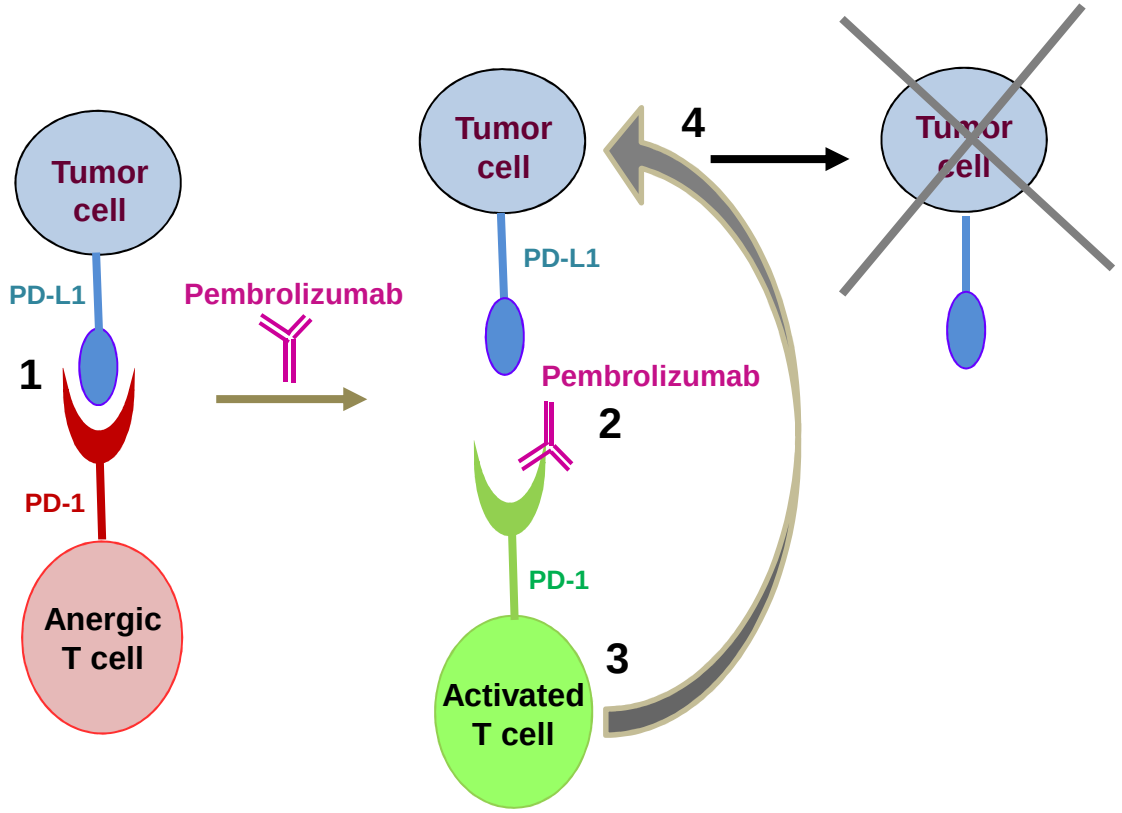
Targeting the Immune Checkpoint Pathway with Pembrolizumab, a humanized mAB of the IgG4/kappya isotype

1. Pembrolizumab binds to PD-1 on anergic T cells

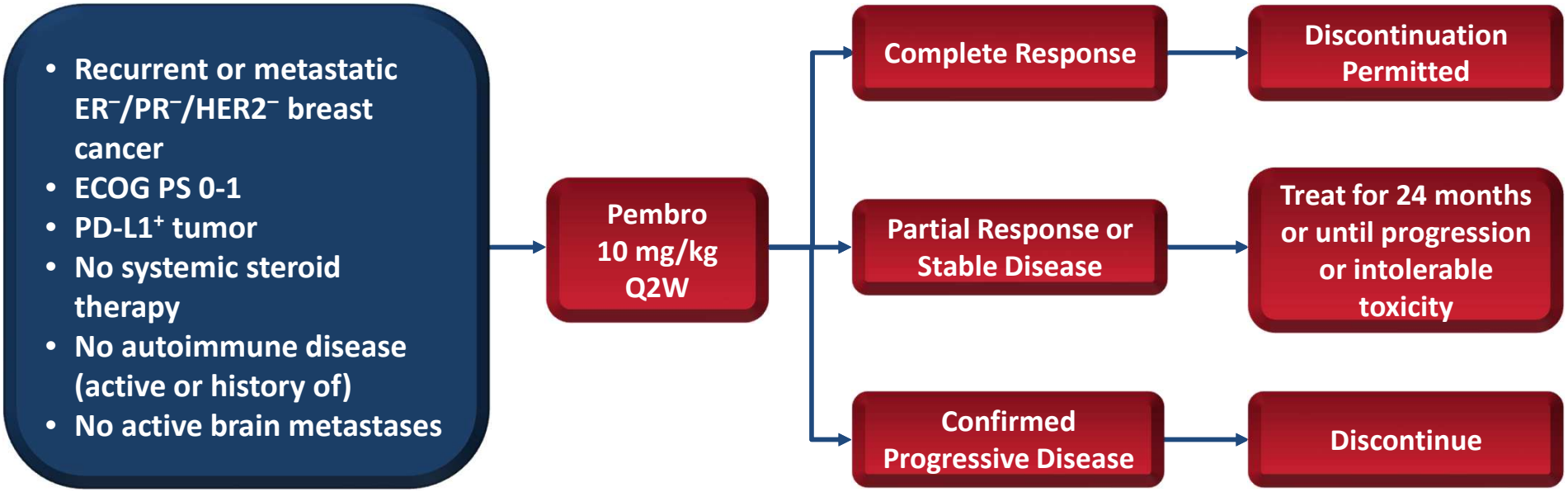
2. Pembrolizumab blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2

3. Pembrolizumab-bound T cells become activated

4. Activated T cells promote immune- mediated tumor cell death



KEYNOTE-012:
Triple-Negative Breast Cancer Cohort



- **PD-L1 positivity:** 53% of all patients screened had PD-L1-positive tumors (≥1% cells +)
- **Response assessment:** Performed every 8 weeks per RECIST v1.1

Nanda et al, SABCS 2014

Baseline Characteristics

Characteristic	N = 32
Age, mean (range), years	51.9 (29-72)
Female	32 (100.0%)
Race	
Black or African American	7 (21.9%)
White	25 (78.1%)
ECOG PS	
0	15 (46.9%)
1	16 (50.0%)
Unknown	1 (3.1%)
History of brain metastases	4 (12.5%)

Characteristic	N = 32
No. prior therapies for metastatic disease	
0	5 (15.6%)
1	6 (18.8%)
2	6 (18.8%)
3	5 (15.6%)
4	3 (9.4%)
≥5	7 (21.9%)
Previous neoadjuvant or adjuvant therapy	28 (87.5%)
Any previous chemotherapy	
Taxane	30 (93.8%)
Anthracycline	25 (78.1%)
Capecitabine	21 (65.6%)
Platinum	19 (59.3%)
Eribulin	7 (21.9%)

Treatment-Related Adverse Events With Incidence ≥5%

	N = 32	
	Any Grade	Grade 3-5
Arthralgia	6 (18.8%)	0 (0.0%)
Fatigue	6 (18.8%)	0 (0.0%)
Myalgia	5 (15.6%)	0 (0.0%)
Nausea	5 (15.6%)	0 (0.0%)
ALT increased	2 (6.3%)	0 (0.0%)
AST increased	2 (6.3%)	0 (0.0%)
Diarrhea	2 (6.3%)	0 (0.0%)
Erythema	2 (6.3%)	0 (0.0%)
Headache	2 (6.3%)	1 (3.1%)

- Adverse events of a potentially immune-mediated nature, regardless of attribution, included pruritus (n = 3; all grade 1-2), hepatitis (n = 1; grade 3), and hypothyroidism (n = 1; grade 2)

Summary of Treatment-Related AEs

	N = 32
Any grade	18 (56.3%)
Grade 3	4 (12.5%)
Grade 4	1 (3.1%)
Serious	3 (9.4%)
Resulted in death*	1 (3.1%)

- Median time on pembrolizumab: 59.5 days (range, 1-383)
- Grade 3 treatment-related AEs were anemia, headache, aseptic meningitis, and pyrexia (n = 1 each)
- Grade 4 treatment-related AE was decreased blood fibrinogen (n = 1)

* The AE attributed to treatment that resulted in death was disseminated intravascular coagulation (DIC)

- This was the only treatment-related AE that led to discontinuation

Best Overall Response (RECIST v1.1, Central Review)

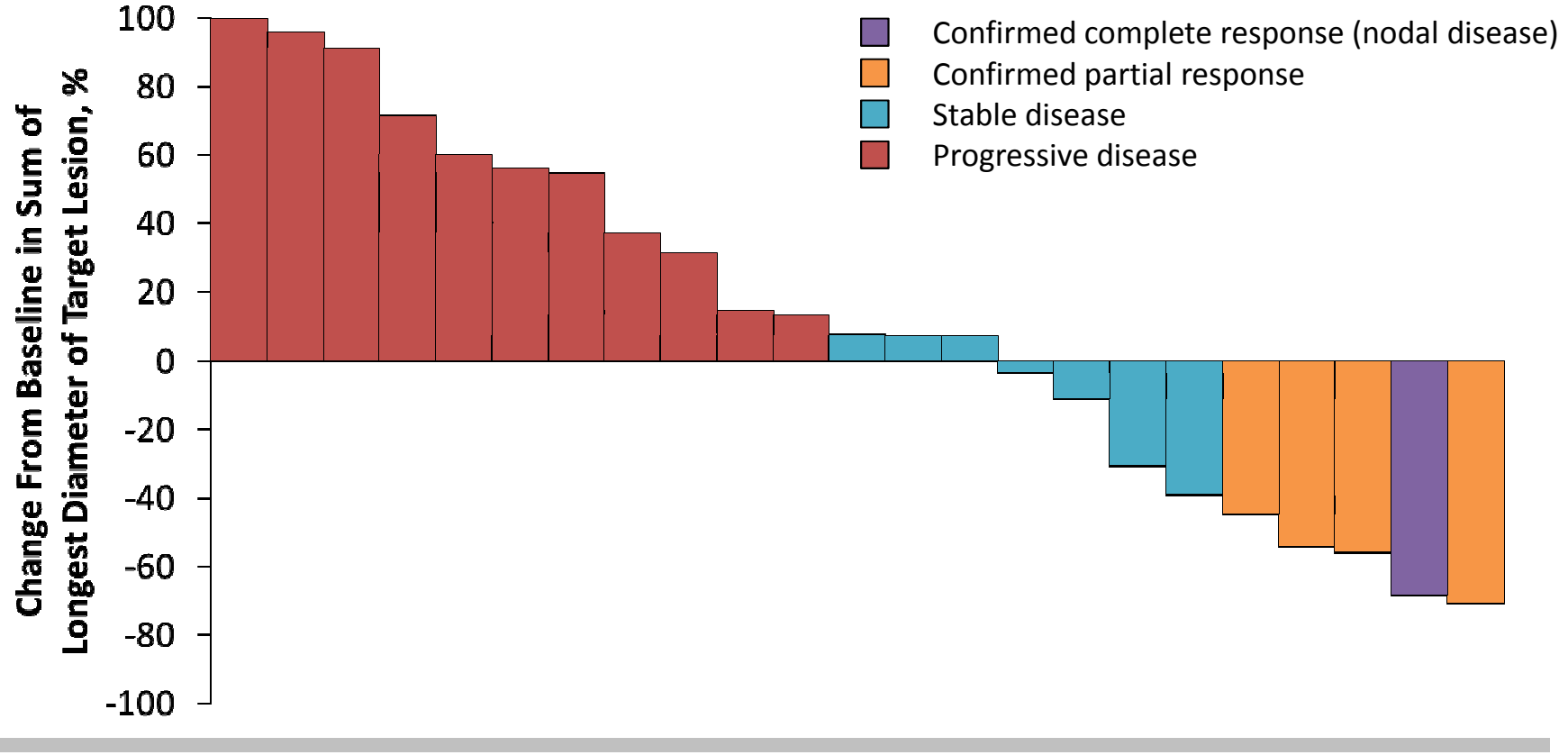
	Patients Evaluable for Response n = 27
Overall response rate	5 (18.5%)
Best overall response	
Complete response	1 (3.7%)
Partial response	4 (14.8%)
Stable disease	7 (25.9%)
Progressive disease	12 (44.4%)
No assessment	3 (11.1%)

Best Overall Response By Previous Therapy (RECIST v1.1, Central Review)

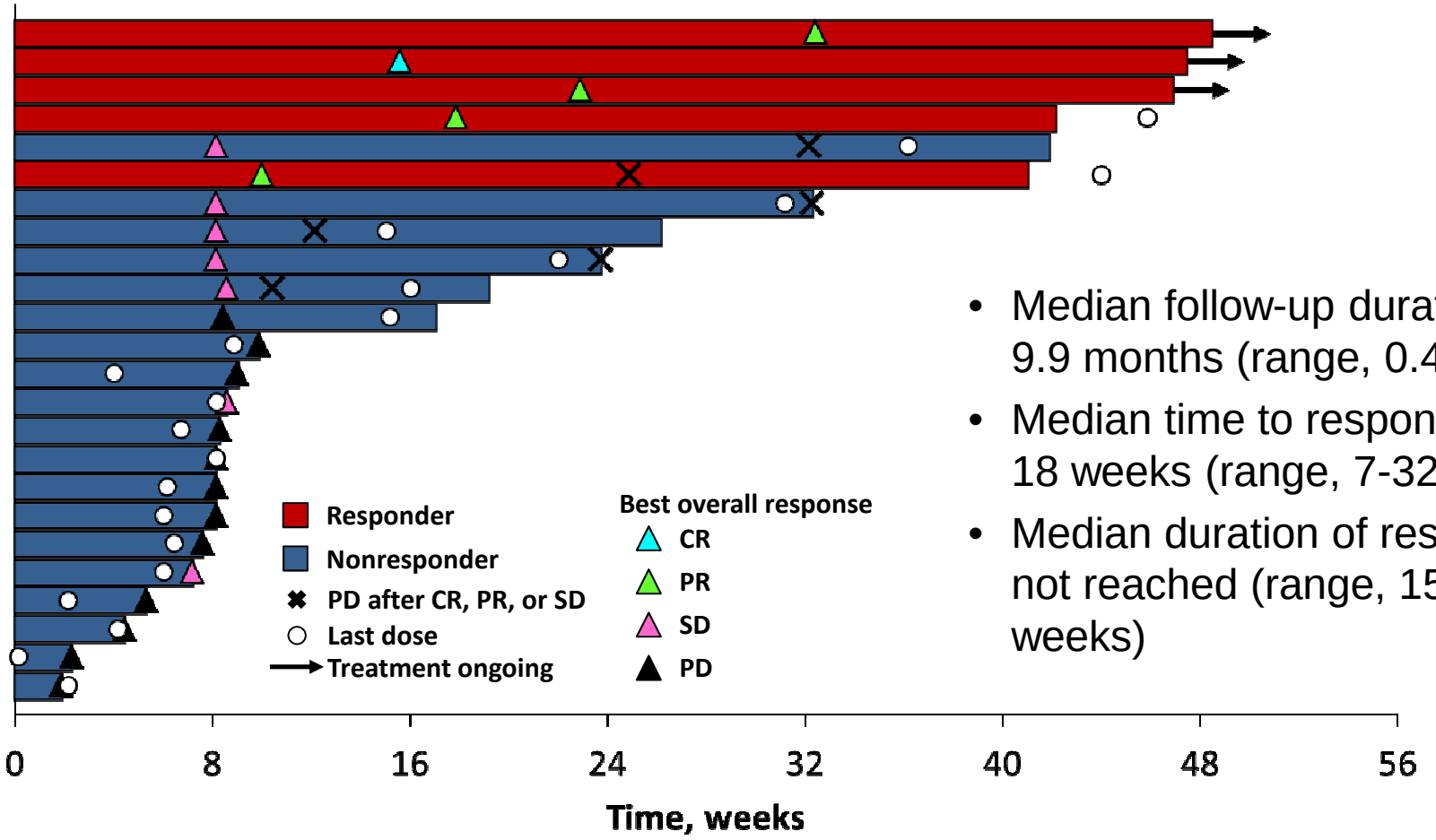
	Evaluable Patients N = 27[a]	CR or PR[b]	SD	PD or No Assessment[c]
Neoadjuvant or adjuvant	24	4 (16.7%)	7 (29.2%)	13 (54.2%)
No. of lines for metastatic disease				
0	4	0 (0.0%)	1 (25.0%)	3 (75.0%)
1	4	1 (25.0%)	1 (25.0%)	2 (50.0%)
2	6	0 (0.0%)	2 (33.3%)	4 (66.7%)
3	4	1 (25.0%)	1 (25.0%)	2 (50.0%)
4	3	1 (33.3%)	0 (0.0%)	2 (66.7%)
≥5	6	2 (33.3%)	2 (33.3%)	2 (33.3%)

- Previous therapy among the 5 patients with CR or PR
  - Capecitabine: 5 (100.0%)
  - Taxane: 5 (100.0%)
  - Anthracycline: 4 (80.0%)
  - Platinum: 3 (60.0%)
  - Eribulin: 1 (20.0%)

Maximum Percentage Change From Baseline in Target Lesions (RECIST v1.1, Central Review)

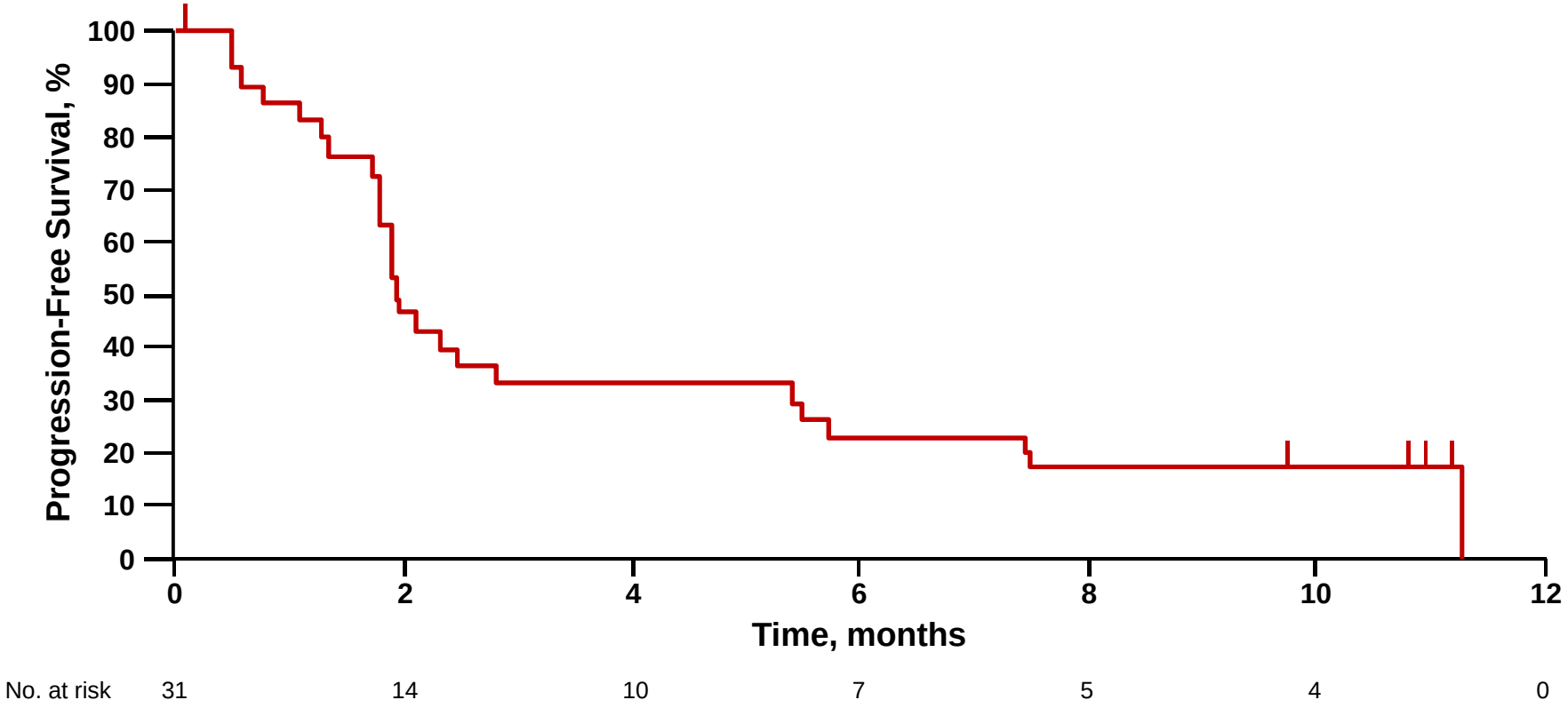


Time to and Durability of Response (RECIST v1.1, Central Review)



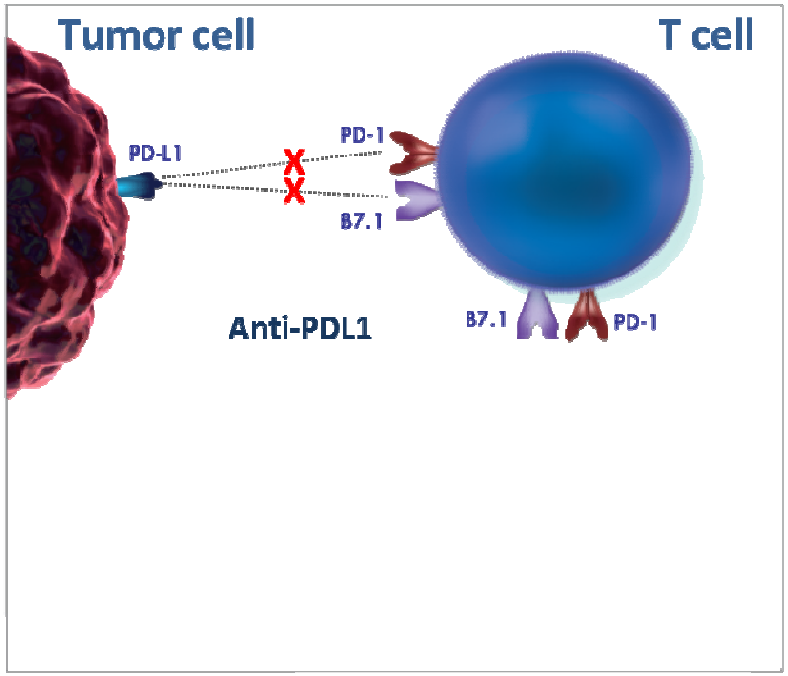
- Median follow-up duration: 9.9 months (range, 0.4-15.1)
- Median time to response: 18 weeks (range, 7-32)
- Median duration of response not reached (range, 15 to 40+ weeks)

Kaplan-Meier Estimate of PFS (RECIST v1.1, Central Review)

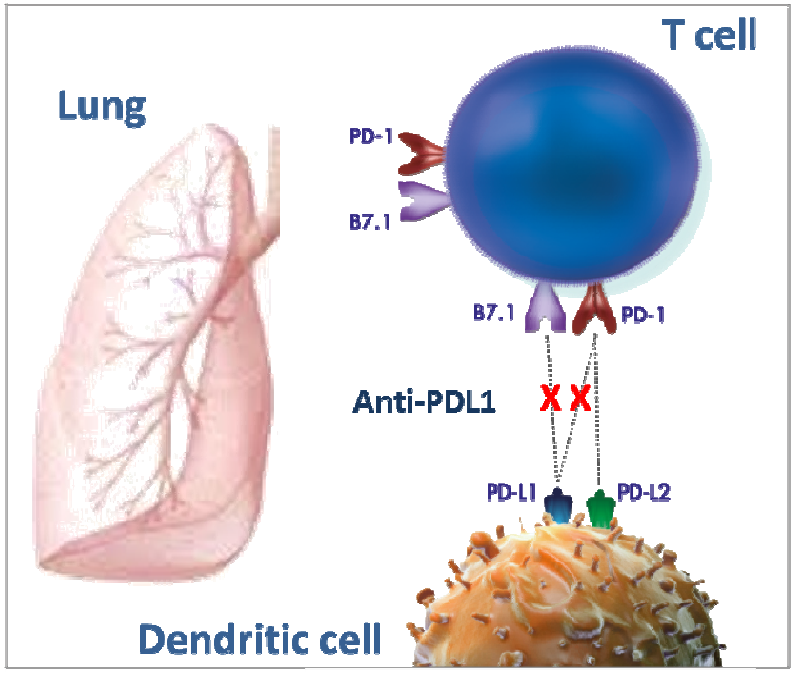


- Median PFS: 1.9 months (95% CI, 1.7-5.4)
- PFS rate at 6 months: 23.3%

Atezolizumab (MPDL3280A) Is an Engineered Anti-PDL1 Antibody That Inhibits the Binding of PD-L1 to PD-1 and B7.1 (CD80)



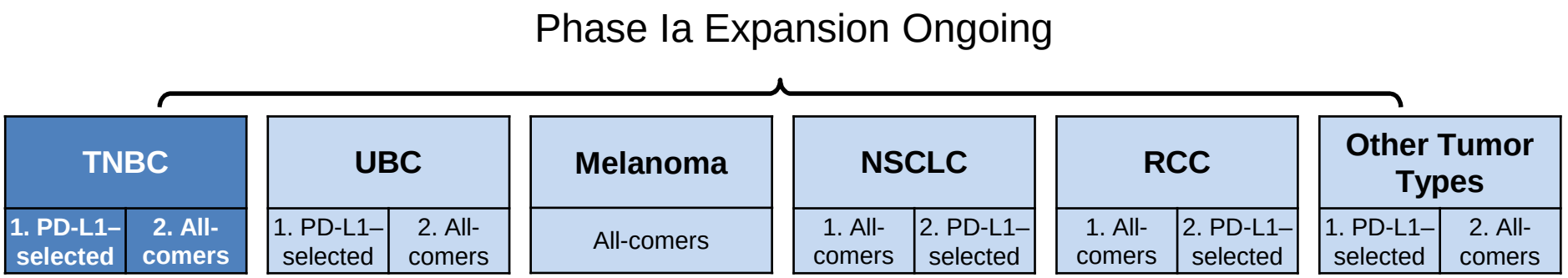
- Inhibiting PD-L1/PD-1 and PD-L1/B7.1 interactions can restore antitumor T-cell activity and enhance T-cell priming



- MPDL3280A leaves the PD-L2/PD-1 interaction intact, maintaining immune homeostasis and potentially preventing autoimmunity

Emens et al, AACR 2015

Atezolizumab: Phase Ia Trial Schema



MPDL3280A doses: IV q3w 15 mg/kg, 20 mg/kg or 1200 mg

Key eligibility criteria: measurable disease per RECIST v1.1 and ECOG PS 0 or 1

- **TNBC cohort objective:** to explore the safety, efficacy and biomarkers of MPDL3280A in women with metastatic TNBC in an ongoing Phase Ia trial in solid tumors
- The TNBC cohort originally enrolled PD-L1–selected patients and then all-comers
- PD-L1 expression was centrally on tumor-infiltrating immune cells (IC) determined using the SP142 antibody assay (≥ 5% cutoff for positivity)

Modified from Emens et al, AACR 2015

Atezolizumab: TNBC Baseline Characteristics

Safety-evaluable population (N = 54) with TNBC in Phase Ia expansion

Characteristic	IC2/3 and IC0/1 patients
Median age (range), y	53 (29-82)
ECOG PS 0/1, %	48%/50%
Metastases	
Visceral, %	70%
Bone, %	24%
Prior systemic therapy	
Anthracycline, %	85%
Taxane, %	74%
Platinum-based chemotherapy, %	57%
Cisplatin, %	17%
Carboplatin, %	44%
Exposure to ≥ 4 systemic therapies, %	89%

- Approximately 69% of patients were IC2/3 (≥5% of IC positive for PD-L1)

Emens et al, AACR 2015

Atezolizumab: Treatment-Related Adverse Events

Safety-evaluable population (N = 54) with TNBC in Phase Ia expansion

- 63% of patients experienced a treatment-related AE, of which most were Grade 1-2
- 11% of patients experienced a treatment-related Grade 3 AE
- Two deaths, assessed as related by the investigator, currently under investigation
- Median duration of safety follow-up was 9 wk (range, 2 to 87 wk)
- Median duration of treatment was 6 wk (range, 0 to 85 wk)

Treatment-Related Adverse Event	All-Grade in ≥ 3 Patients n (%)	Grade 3-4 n (%)
Fatigue	8 (15%)	0
Nausea	8 (15%)	1 (2%)
Pyrexia	8 (15%)	0
Asthenia	6 (11%)	0
Decreased appetite	6 (11%)	0
Diarrhea	5 (9%)	0
Headache	4 (7%)	0
Pruritus	4 (7%)	0
Vomiting	4 (7%)	1 (2%)
Anemia	3 (6%)	1 (2%)
Influenza-like illness	3 (6%)	0
Neutropenia	3 (6%)	1 (2%)
Pain	3 (6%)	0
Rash	3 (6%)	0

Emens et al, AACR 2015

Atezolizumab: Summary of Efficacy

Efficacy-evaluable patients (n = 21) with TNBC in Phase Ia expansion

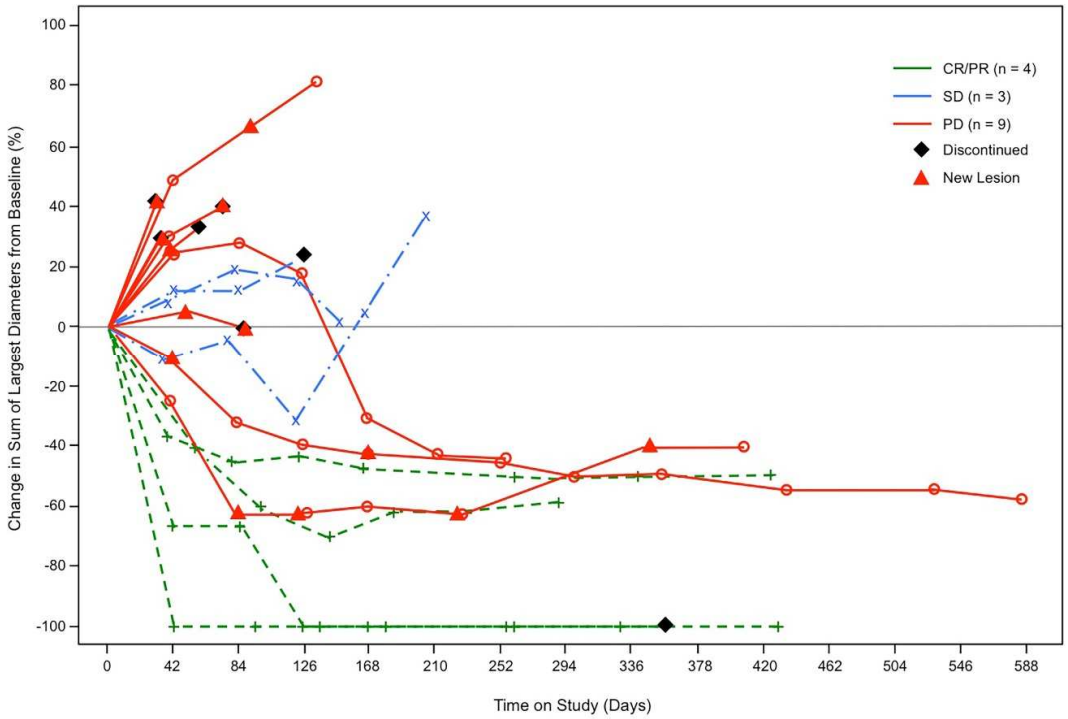
IC2/3 patients, n	ORR (95% CI)	24-Week PFS (95% CI)
21	19% (5-42)	27% (7-47)

- Responses included 2 CRs (1 IC3 and 1 IC2) and 2 PRs (IC2)
  - 3 of 4 responses were ongoing
- 3 patients recorded as PD appeared to experience pseudoprogression, with durable shrinkage of target and new lesions

Emens et al, AACR 2015

Atezolizumab: Tumor Burden Over Time

Efficacy-evaluable population with TNBC



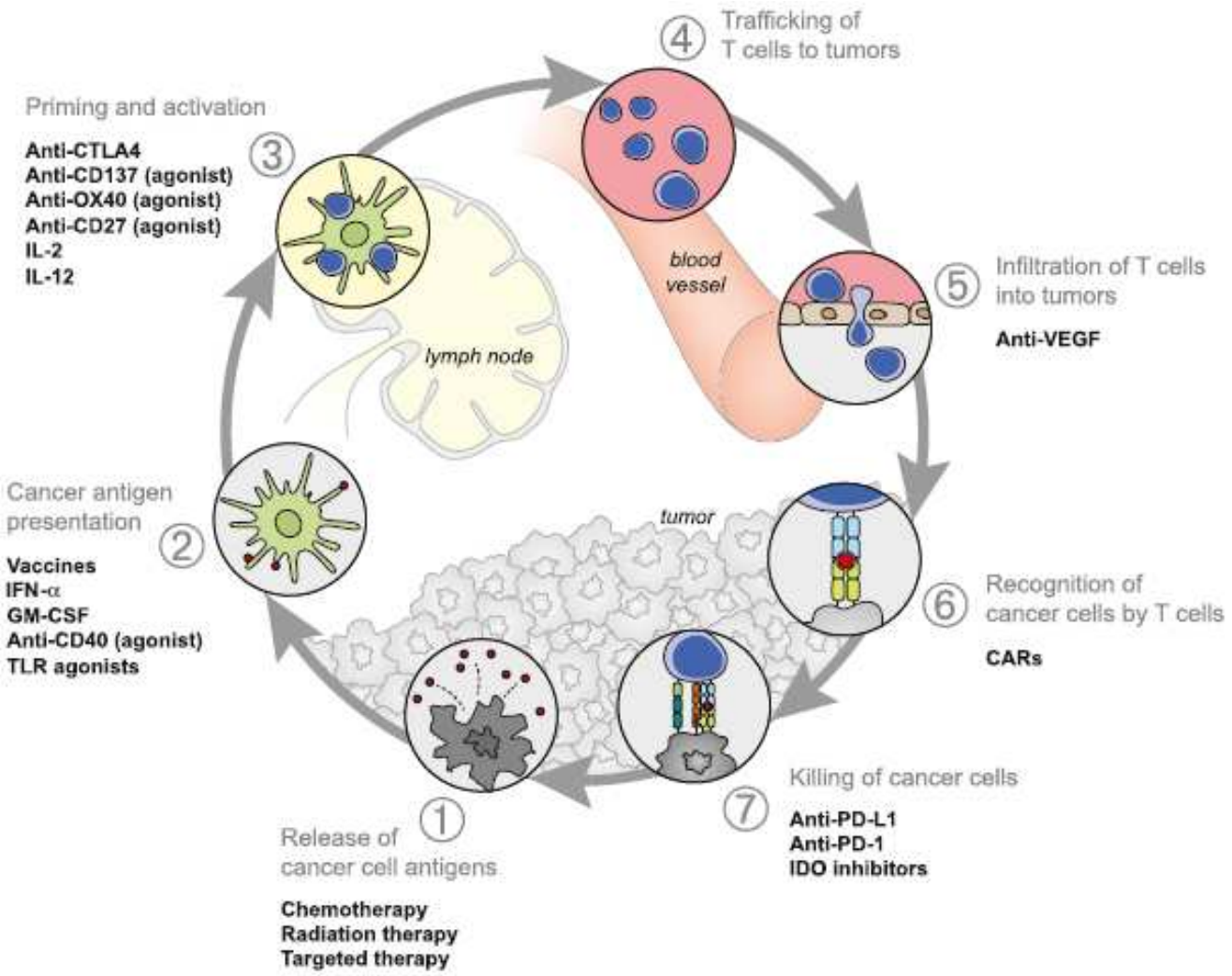
- Median duration of response has not yet been reached (range: 18 to 56+ wks)
- Median duration of survival follow-up is 40 wks (range: 2+ to 85+ wks)

Emens et al, AACR 2015

Summary: Immune Checkpoint Inhibition in TNBC

- Blockade of PD-1 or PD-L1 is associated with a response rate of ~20%
  - Somewhat lower than RR in melanoma (30-40% range)
  - Similar to monotherapy responses in other solid tumors
- Responses are durable
- Immune checkpoint inhibitors are safe and tolerable; majority of side effects are mild and easily managed
- Future work is aimed and building on these promising monotherapy responses

Therapy Options to Modulate Immunity



Chen and Mellmen, Immunity, 2013

Summary: Immunotherapy and Cancer

- Immunotherapy appears to benefit a subset of patients with TNBC
- Tumors evolve to avoid the immune response in different ways and at different steps of the cancer-immunity cycle
  - Immune checkpoint-induced T-cell anergy
- Combination therapies are being investigated
  - Be aware of additive toxicity
- Identification of what is limiting effective immunity in any individual tumor will allow for the greatest anticancer activity while limiting unrestrained autoimmune inflammatory responses

Thank You!

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