Advances in Cancer Immunotherapy™ – Recent AACR and Related Updates

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Disclosures

- None

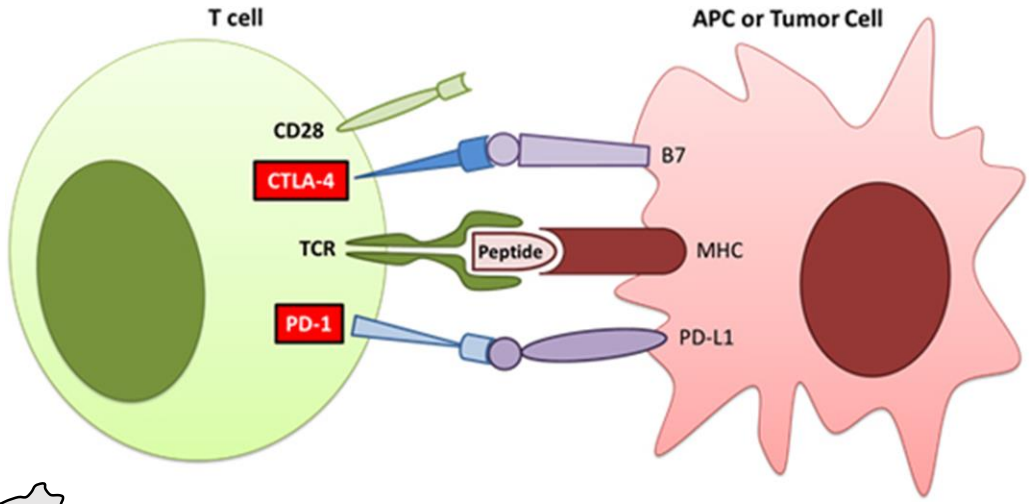
AACR Highlights

- Combination Therapies (using checkpoint blockade)
- CAR T cells
- Novel Targets
- Biomarkers
- Microbiome

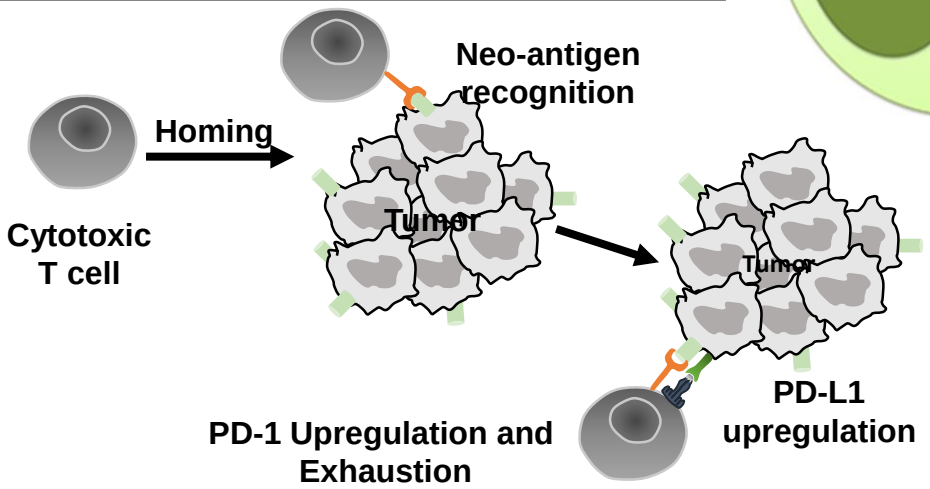
T-Cell Based Breakthroughs

- Checkpoint Blockade
  - CTLA-4
  - PD-1/ PD-L1
- CAR T-Cells

CTLA-4 Critical in T cell Priming

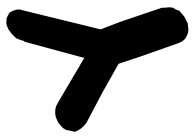


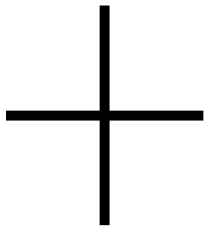
PD-1 Critical in T cell Exhaustion



Immune Checkpoint Therapy: What is Next?

Anti–PD-1/PD-L1

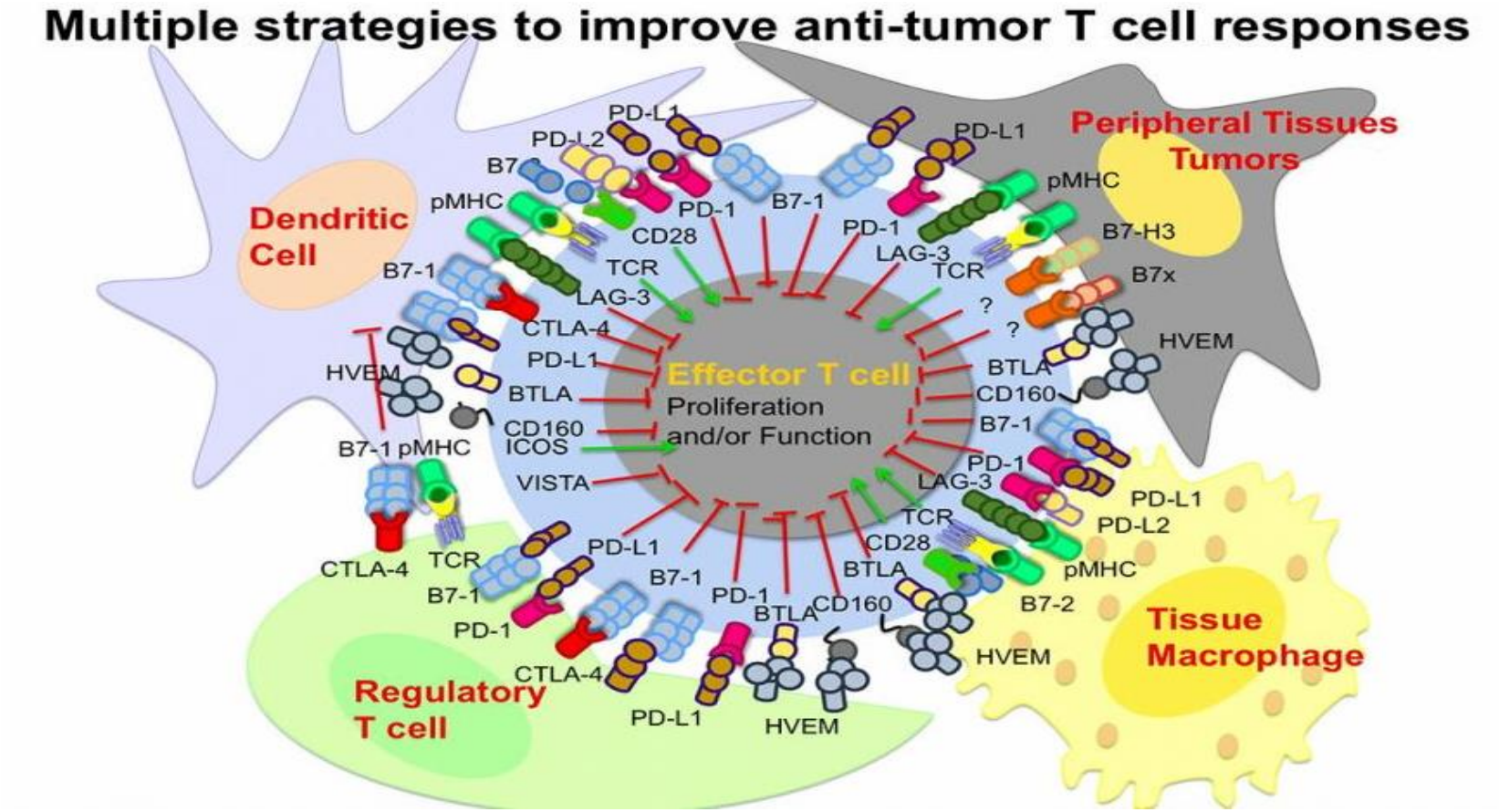




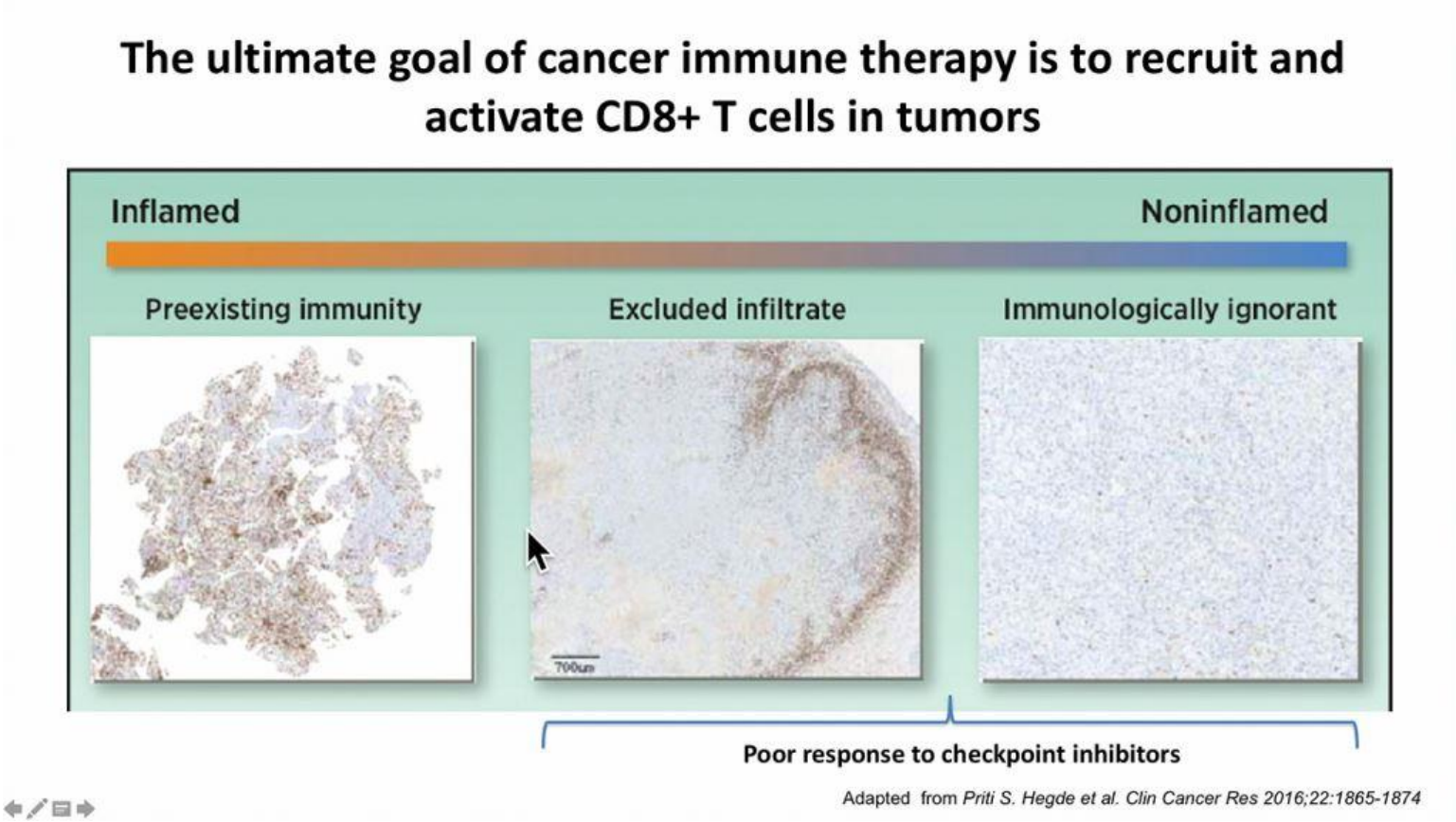
Your favorite treatment

The future of cancer therapy

The Complexity of Host-Tumor Immunoregulation



Tumor Microenvironment and Immune Surveillance



Galon et al., *Science*. 2006; 313 (5795): 1960–1964.

Dual-Checkpoint Blockade

- Effective in melanoma and lung cancer, but with significant toxicity

DART (Dual Anti-CTLA-4 and Anti-PD-1 Blockade in Rare Tumors)

- DART first NCI-sponsored basket study for rare tumors
- Ipilimumab/ nivolumab combination being tested in patients with 37 types of rare cancer
- Dr. Sandip Patel (UCSD) presented data on a cohort of 33 patients with neuroendocrine tumors

Patel SP et al: A phase II basket trial of dual anti–CTLA-4 and anti–PD-1 blockade in rare tumors (DART) S1609: The neuroendocrine cohort. 2019 AACR Annual Meeting. Abstract CT039.

DART for NET

- Rare tumors comprise 25% of US cancer diagnoses
- DART open at 800 sites
- Accrual in NET completed in 3 months
- Clinical trials in rare tumors are feasible

Patel SP et al: A phase II basket trial of dual anti–CTLA-4 and anti–PD-1 blockade in rare tumors (DART) S1609: The neuroendocrine cohort. 2019 AACR Annual Meeting. Abstract CT039.

DART for NET

- Prior studies of checkpoint inhibitor monotherapy showed response rates of ~5%
- Ipilimumab at 1 mg/kg given intravenously every 6 weeks plus nivolumab at 240 mg IV every 2 weeks
- No responses in low grade tumors (44% response rate in high grade vs. 0% low/ intermediate grade)

Age	**Median 60.5**
Sex	**41% Female 59% Male**
Objective Response	**25%**
6-month PFS	**31%**
Overall Survival	**11 months**
Grade 3 Toxicity	**Liver 9% (LFTs) Colitis 6%**

Dual Checkpoint Blockade for NET

- High grade extra-pulmonary NET behave like small cell lung cancer
- Checkpoint blockade has been approved for SCLC
- Dual agent checkpoint blockade shows evidence of activity in high grade NET
- Additional studies are underway

Patel SP et al: A phase II basket trial of dual anti–CTLA-4 and anti–PD-1 blockade in rare tumors (DART) S1609: The neuroendocrine cohort. 2019 AACR Annual Meeting. Abstract CT039.

Society for Immunotherapy of Cancer

3rd Line Pembro in SCLC

Pembrolizumab as Third-Line Option for Extensive-Stage Small Cell Lung Cancer

- Pooled analysis of KEYNOTE-028 (phase Ib) and KEYNOTE-158 (phase II) of pembrolizumab in patients with advanced SCLC
- Immunotherapy naïve patients
- ≥ 2 prior lines of systemic therapy
- 10 mg/kg Q2W (KN028) or 200 mg Q3W (KN158) for 2 y, disease progression, or intolerable toxicity
- Response assessed by RECIST

Chung HC, et al: Pembrolizumab after two or more lines of prior therapy in patients with advanced small-cell lung cancer. Abstract CT073.

3rd Line Pembro SCLC

- 64% had 2 prior lines of chemotherapy
- 36% had 3 or more prior lines of chemotherapy
- 57% had PD-L1 positive tumors

- Overall response rate was 19% (2% CR and 17% PR)
- 9/16 patients responded for > 18 months
- Median PFS was 2.0 months, and median OS was 7.7 months

Chung HC, et al: Pembrolizumab after two or more lines of prior therapy in patients with advanced small-cell lung cancer. Abstract CT073.

Society for Immunotherapy of Cancer

Immunotherapy in Breast Cancer

Analysis of immune cell infiltrates as predictors of response to pembrolizumab in the neoadjuvant I-SPY 2 TRIAL

- I-SPY 2 trial (NCT01042379) is an adaptive phase II randomized, controlled, multicenter trial for women with stage II/III breast cancer
- Assessing new treatments and identifying novel therapies in specific patient subgroups based on molecular characteristics
- The primary endpoint is pathologic complete response at the time of surgery

https://www.ispytrials.org/

Immune Infiltration in Breast Cancer

- Until recently, results of checkpoint immunotherapy in breast cancer have been disappointing

- Perception that breast cancers are immunologically "cold"

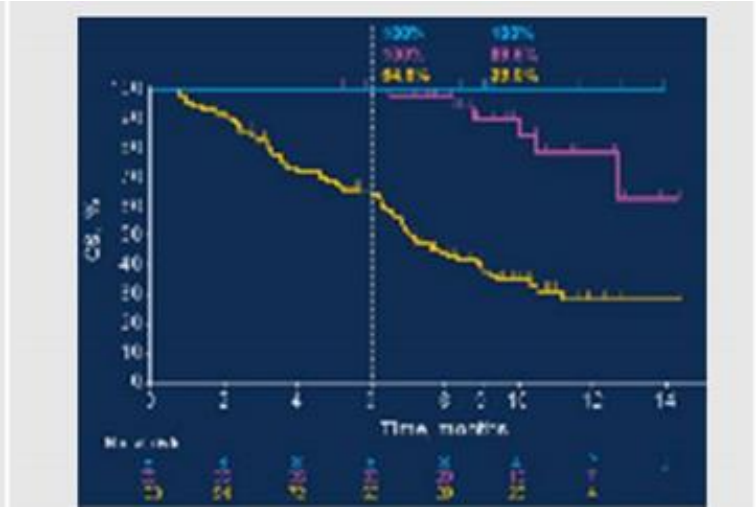
Loi S. et al., *J Clin Onc*. 2013; 31: 860 – 867.

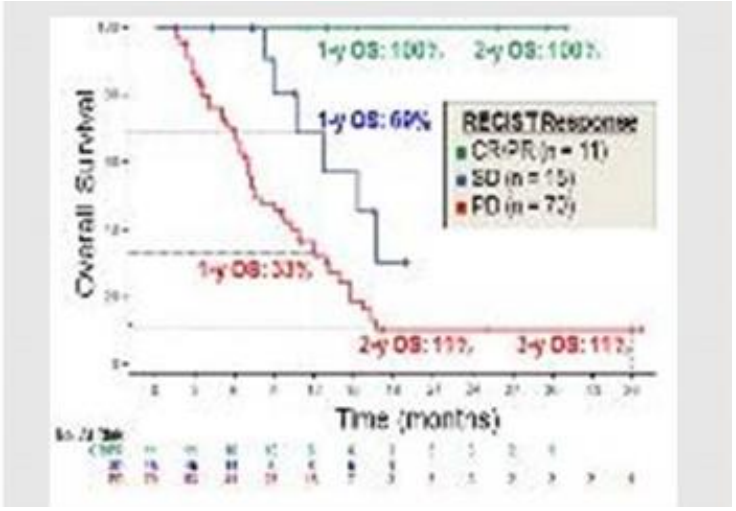
Checkpoint Blockade Monotherapy

(Adapted from Dr. Elizabeth Mittendorf)

	Pembrolizumab (n=254)	Atezolizumab (n=112)
Population	mTNBC	mTNBC
Overall ORR	4.7% (Cohort A; n=170)	10%
ORR in 1st line	23% (Cohort B; n=84)	26% (n=19)

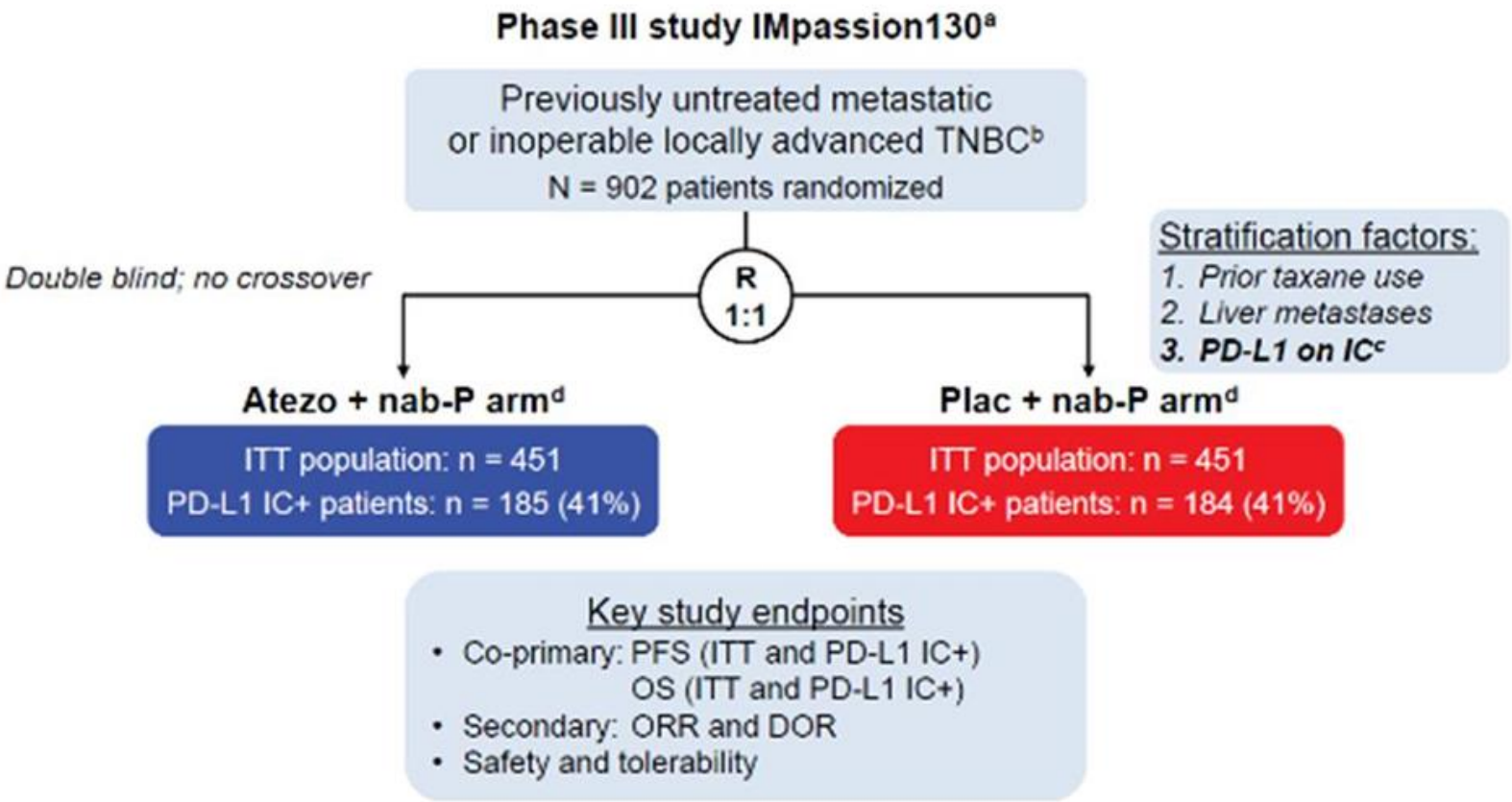
Survival in Responders





Adams S. et al., *Ann Oncol* 2019; 30: 397 – 404.
Schmid P. et al., AACR 2017, Abstract 2986.

Impassion 130



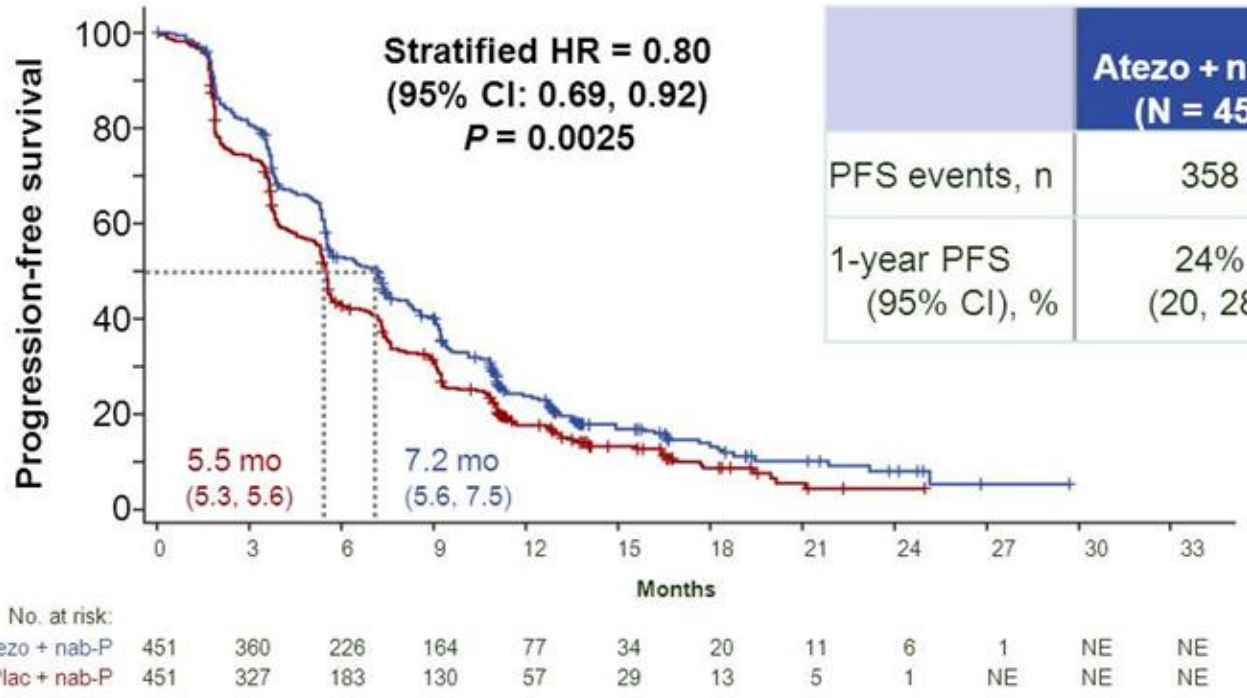
Schmid P. et al., *NEJM* 2018; 379(22):2108-2121.

Baseline Characteristics

	Atezo + nab-P (N = 451)	Placebo + nab-P (N = 451)
Age	55 (20 – 82)	56 (26 – 82)
Ethnicity	68.3% Caucasian	66.7% Caucasian
ECOG 0/1	99.8%	99.8%
Metastatic Disease	89.8%	90.7%
Previous Therapy		
Taxanes	51.2%	51.0%
Anthracyclines	53.9%	53.7%
PD-L1 Positive	41.0%	40.8%

Schmid P. et al., *NEJM* 2018; 379(22):2108-2121.

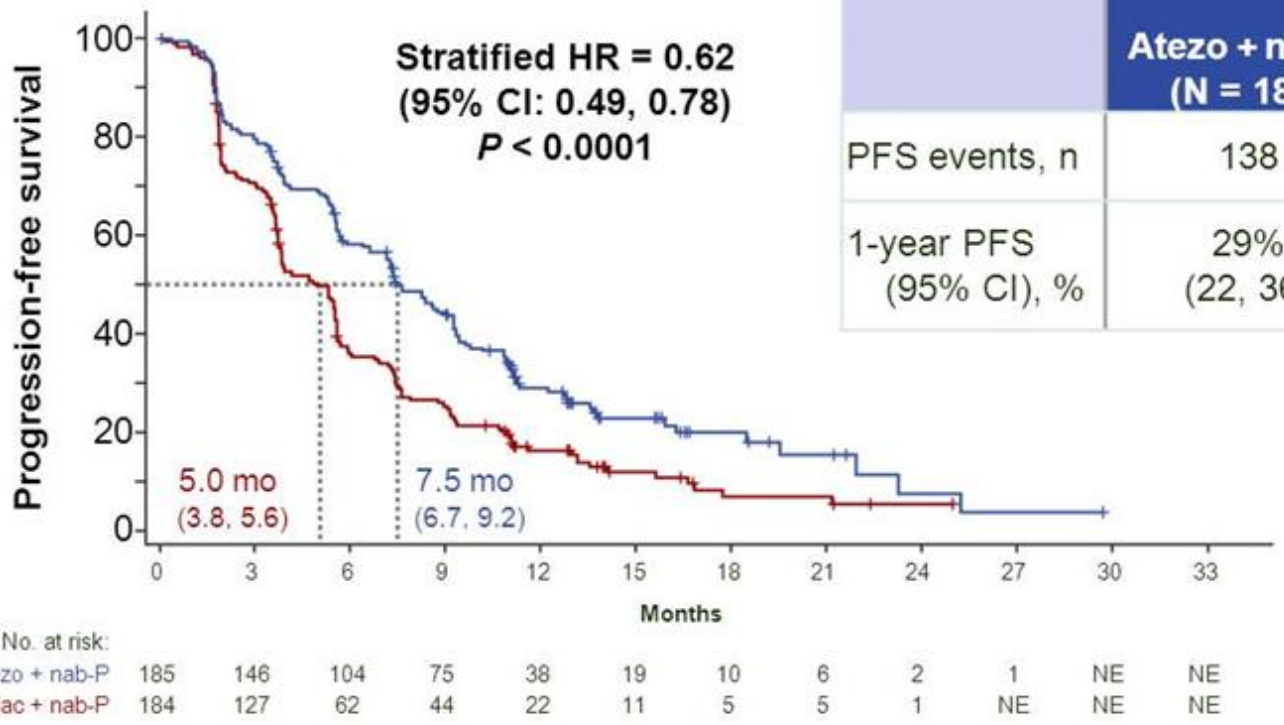
PFS – Intention to Treat



	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
PFS events, n	358	378
1-year PFS (95% CI), %	24% (20, 28)	18% (14, 21)

Schmid P. et al., *NEJM* 2018; 379(22):2108-2121.

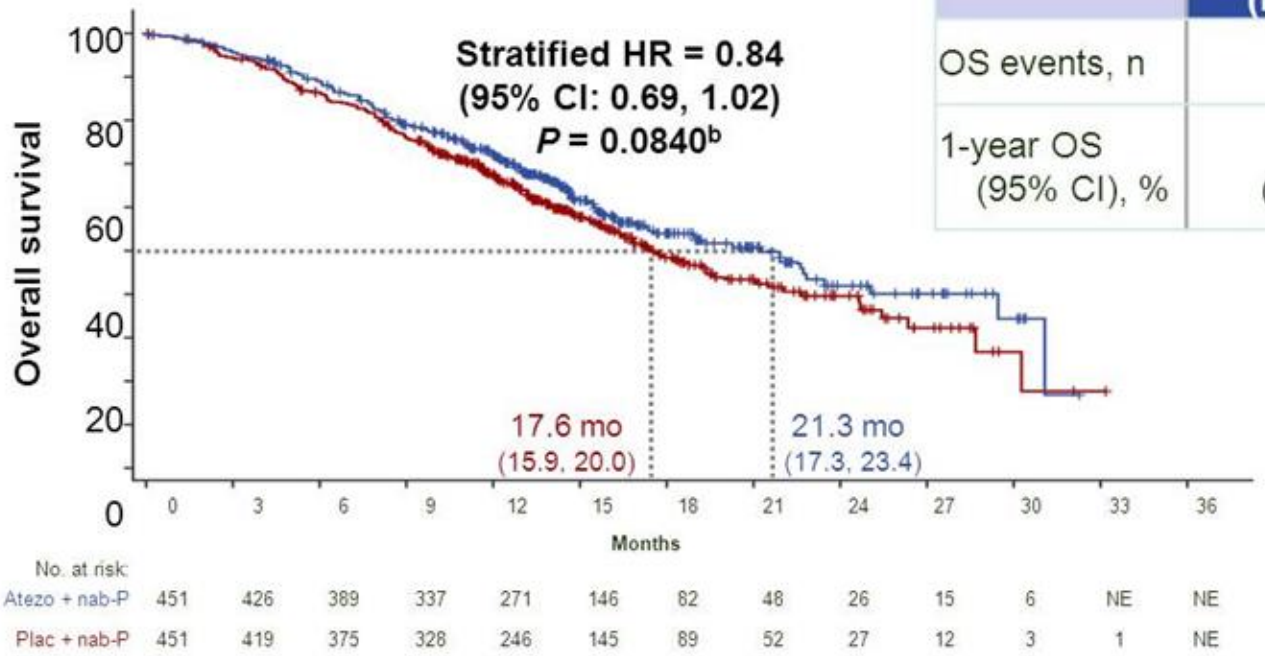
PFS – PD-L1+ Subgroup



	Atezo + nab-P (N = 185)	Plac + nab-P (N = 184)
PFS events, n	138	157
1-year PFS (95% CI), %	29% (22, 36)	16% (11, 22)

Schmid P. et al., *NEJM* 2018; 379(22):2108-2121.

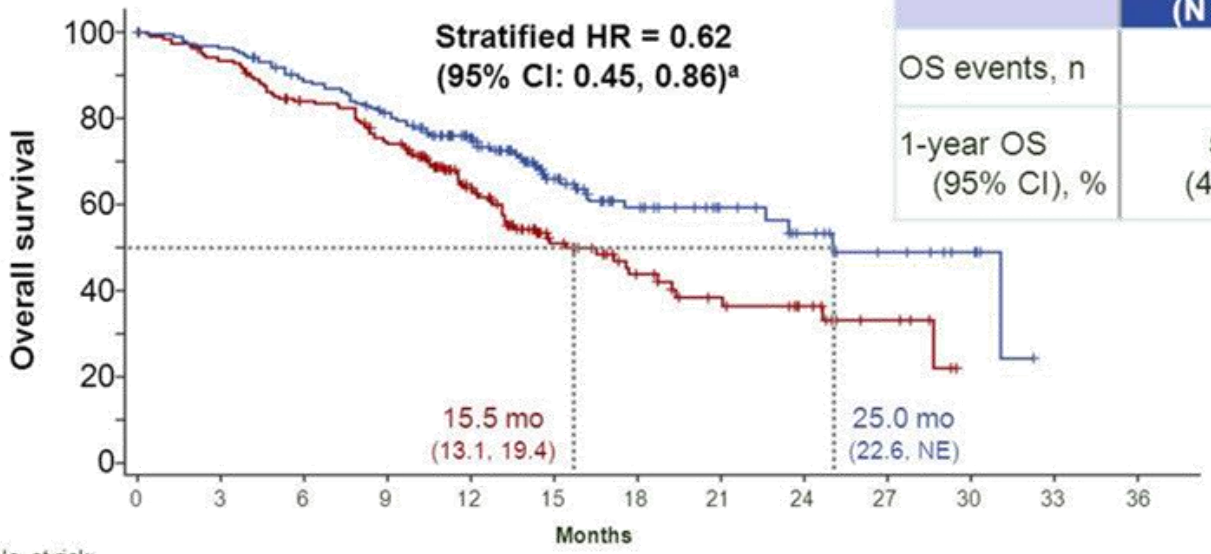
OS – Intention to Treat



	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
OS events, n	181	208
1-year OS (95% CI), %	42% (34, 50)	40% (33, 46)

Schmid P. et al., *NEJM* 2018; 379(22):2108-2121.

OS-PD-L1+ Subgroup



	Atezo + nab-P (N = 185)	Plac + nab-P (N = 184)
OS events, n	64	88
1-year OS (95% CI), %	54% (42, 65)	37% (26, 47)

- Because of hierarchical statistical analysis procedure, testing of OS in PD-L1+ subgroup was not conducted

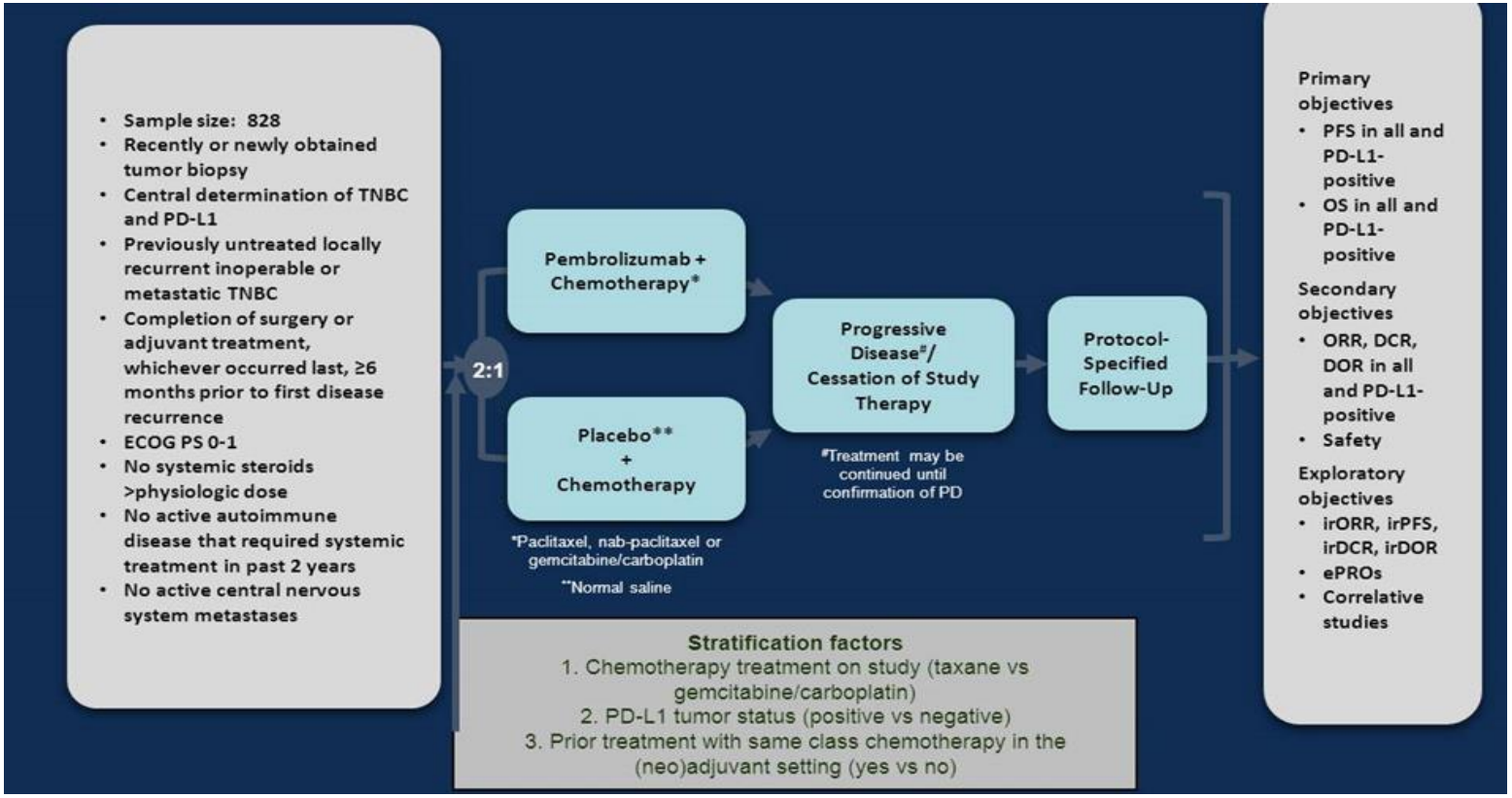
Schmid P. et al., *NEJM* 2018; 379(22):2108-2121.

Immunotherapy for Breast Cancer

- BRCA status likely significant
- Impact of other systemic agents (cyclophosphamide, steroids, antibiotics)
- Biomarkers of response/ resistance

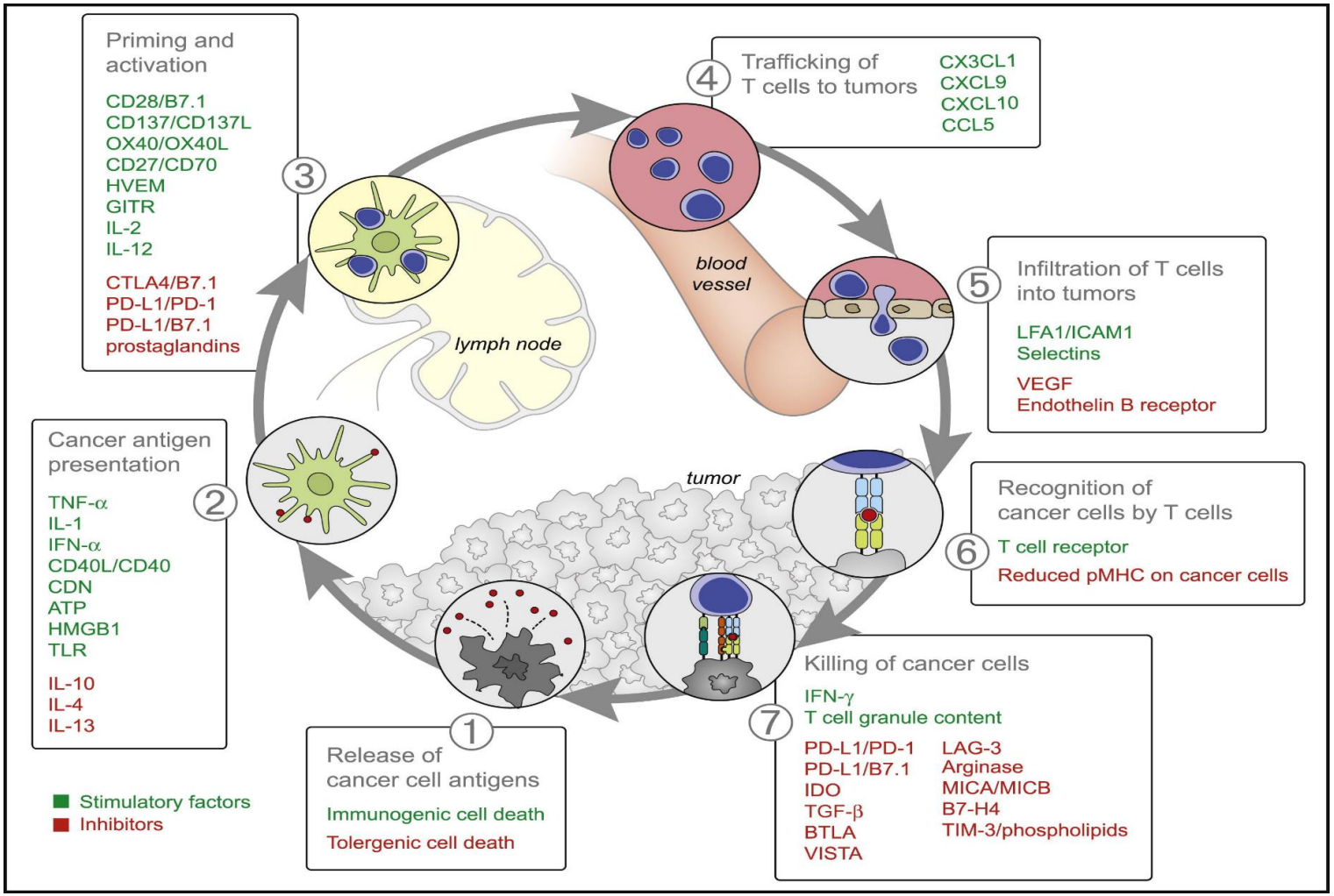
- PD-1/ PD-L1 inhibitor monotherapy not effective
- IMpassion 130 a positive study
- FDA approval for combination therapy with PD-L1+ in March 2019 contingent on a follow up Phase 3 study
- Other combination studies are ongoing

KEYNOTE - 355



Treatment	Sponsor	Setting	Study	Trial ID	Primary completion
Keytruda + chemo	Merck	1st-line	Keynote-355	NCT02819518	Dec 2019

Cancer-Immunity Cycle



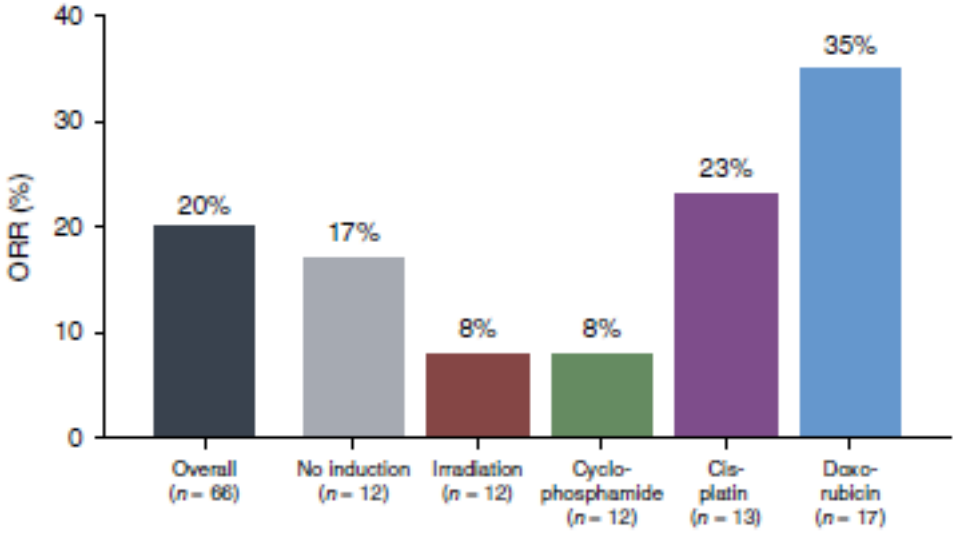
Chen and Mellman, *Immunity* 2013; 39:1 – 9.

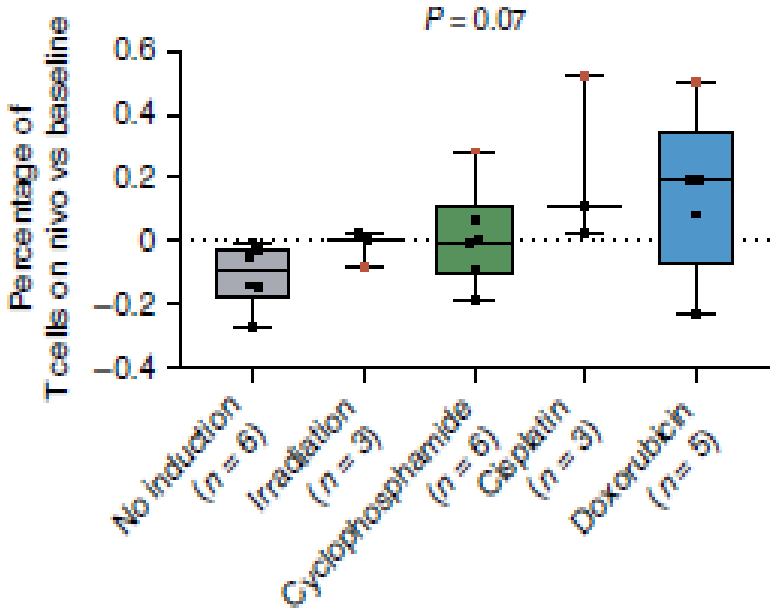
nature medicine

LETTERS

https://doi.org/10.1038/s41591-019-0432-4

Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial





Voorwerk L. et al., *Nat Med* 2019 May 13. Epub ahead of print

Immune cell infiltrates post pembrolizumab in the neoadjuvant I-SPY 2 TRIAL

- Pre-treatment biopsies analyzed for immune subsets by multispectral imaging (N = 54)
- Favorable immune infiltrates – expected
  - CD3+ T cells, CD8+ T cells, PD-1+ T cells
- Favorable immune infiltrates – unexpected
  - FoxP3+ Tregs
- Unfavorable immune infiltrates
- Tumor associated macrophages (TAMs)

Campbell M et al: Abstract CT003.

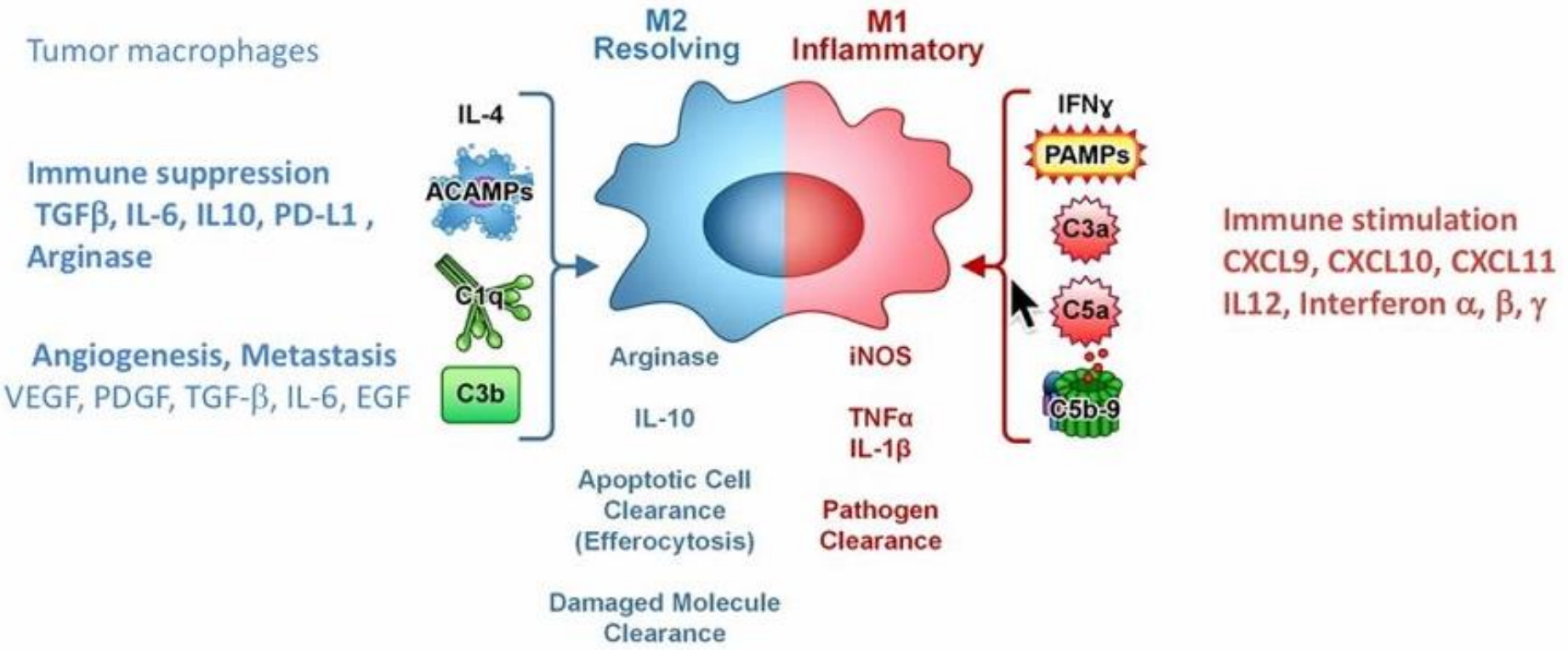
Poll Question

Which of the following immune cell infiltrates are not associated with favorable outcomes in pembrolizumab treatment of TNBC?

a. CD3+
b. FoxP3+
c. Tumor-associated macrophages (TAMs)
d. CD8+
e. PD-1+ T cells

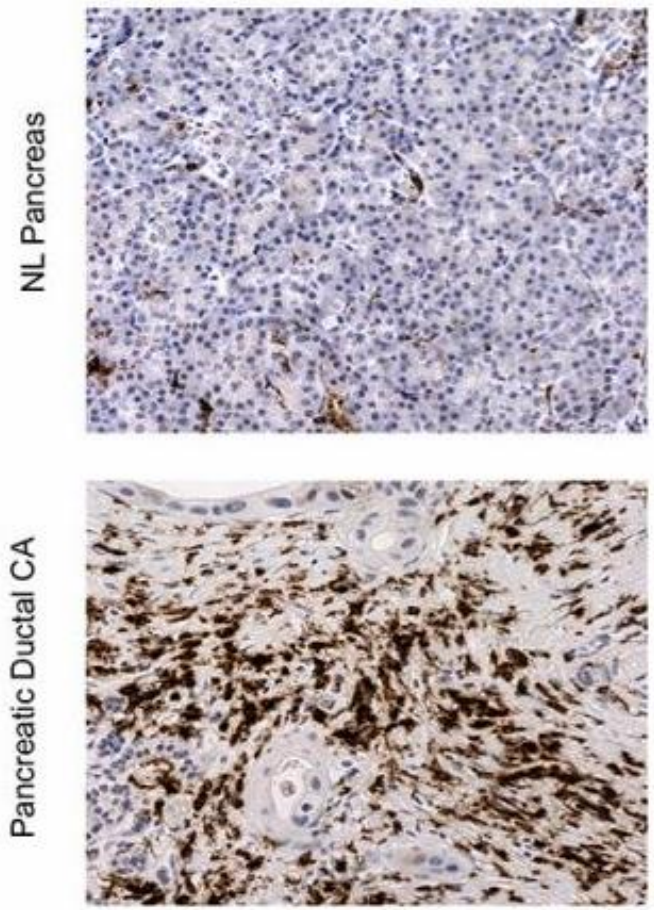
Novel Targets

Macrophages and the Adaptive Immune Response

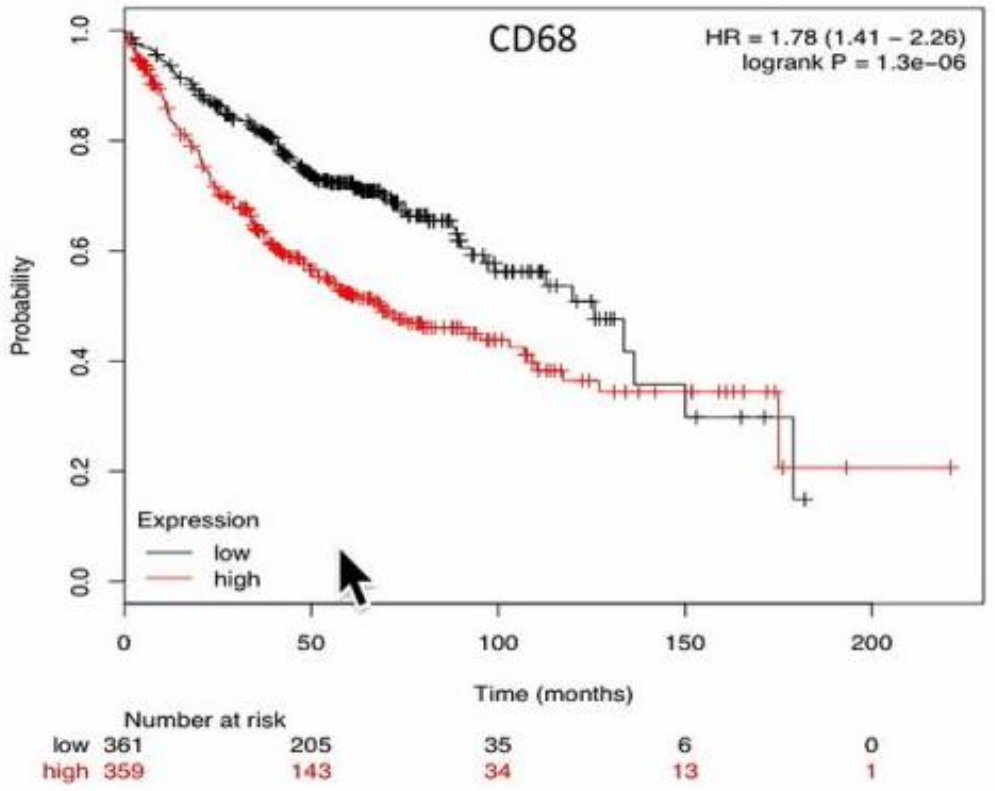


- Ilya Metchnikoff – “look for the macrophages”

TAMs Linked to Tumor Progression



30-60% CD68+ cells in tumor

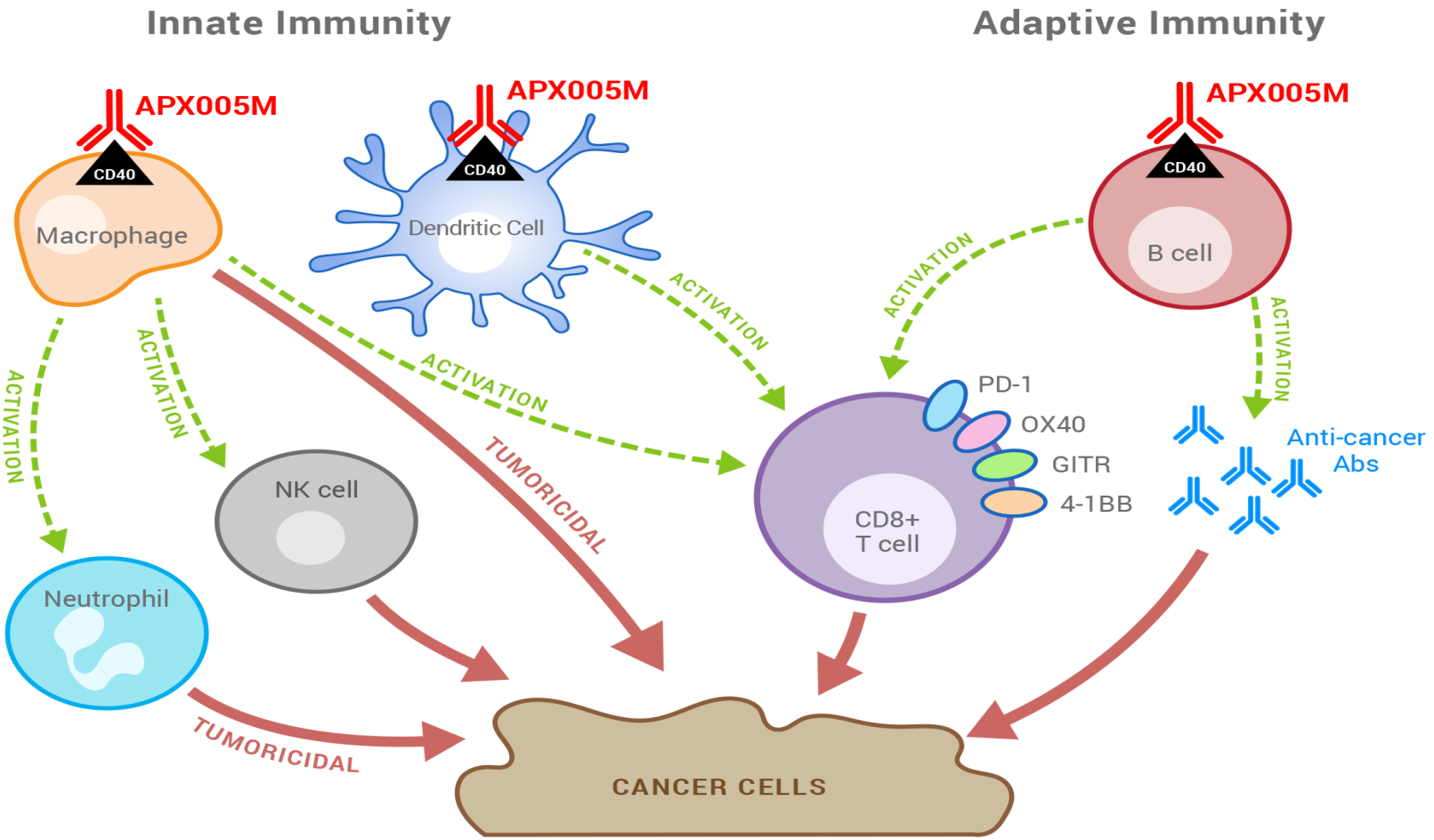


KM Plotter: Lanczky A, et al. **Breast Cancer Res Treat.** 2016;160(3):439-446.

Reducing TAMs in the TME

Target	Compounds
CSF1R inhibitors	Pexidartinib PLX7486 Emactuzumab
PI3Kγ inhibitors	IPI-549
HDAC inhibitors	TMP195
CD40 (pleiotropic)	APX005M

CD40 Agonism



A Phase Ib study of APX005M with gemcitabine and nab-paclitaxel with or without nivolumab in untreated metastatic PDAC patients – CT004

- Monoclonal antibody targeting CD40
- CD40 a key member of the TNF receptor superfamily
- Expressed on APCs (monocytes, macrophages, and dendritic cells) as well as other immune and non-immune cells
- Critical in CD8 priming and CD4 help
- Reprograms Macs[1]

Beatty GL et al., *Science* 2011, 331.

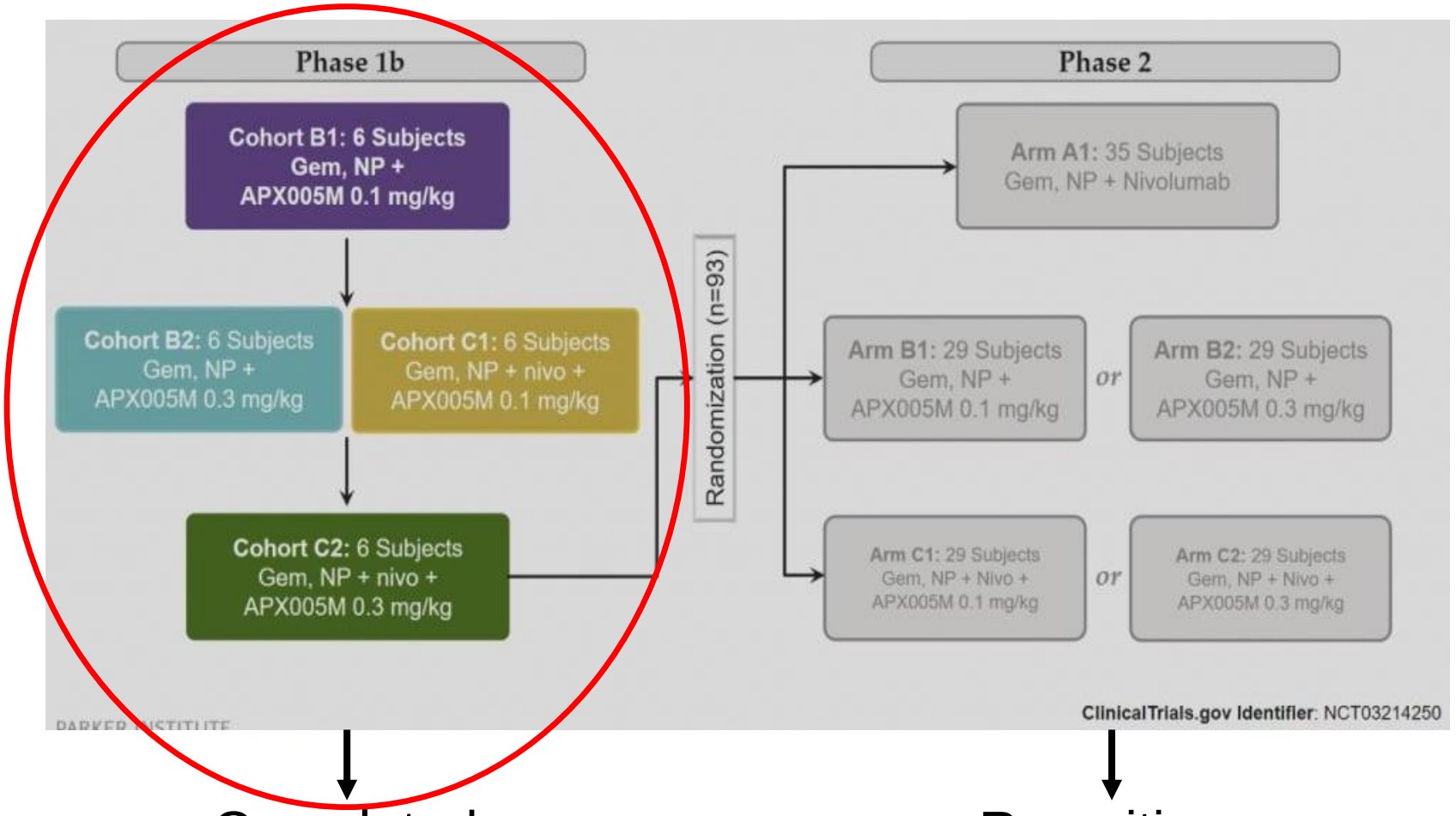
Phase Ib study of APX005M plus Chemo +/- Nivo in PDAC

- Previously untreated PDAC, N = 30
- 4 cohorts
- 24 patients were evaluable
- Median follow up 32 weeks

Cohort 1	Gemcitabine, Nab-Paclitaxel, APX005M 0.1 mg/kg
Cohort 2	Gemcitabine, Nab-Paclitaxel, APX005M 0.3 mg/kg
Cohort 3	Gemcitabine, Nab-Paclitaxel, APX005M 0.1 mg/kg Nivolumab
Cohort 4	Gemcitabine, Nab-Paclitaxel, APX005M 0.3 mg/kg Nivolumab

O'Hara M,… Vonderheide R – CT004

Study Design



Completed

Recruiting

O'Hara M,… Vonderheide R – CT004

Key Inclusion and Exclusion Criteria

Inclusion

- Metastatic pancreatic adenocarcinoma
- Measurable disease per RECIST 1.1
- Age ≥ 18
- ECOG status 0 or 1
- Baseline tissue mandatory
- Adequate hematologic, hepatic and renal function

Exclusion

- Previous systemic therapy in the metastatic setting
- Symptomatic CNS metastases
- Concurrent active invasive malignancy
- History of autoimmune disorders
- Concomitant use of immunosuppressive agent within 14 days of first dose

Results

Toxicity

54% AEs leading to discontinuation
42% treatment-related serious AEs
8% (N=2) grade 4/5 toxicity – sepsis/ neutropenia

Efficacy

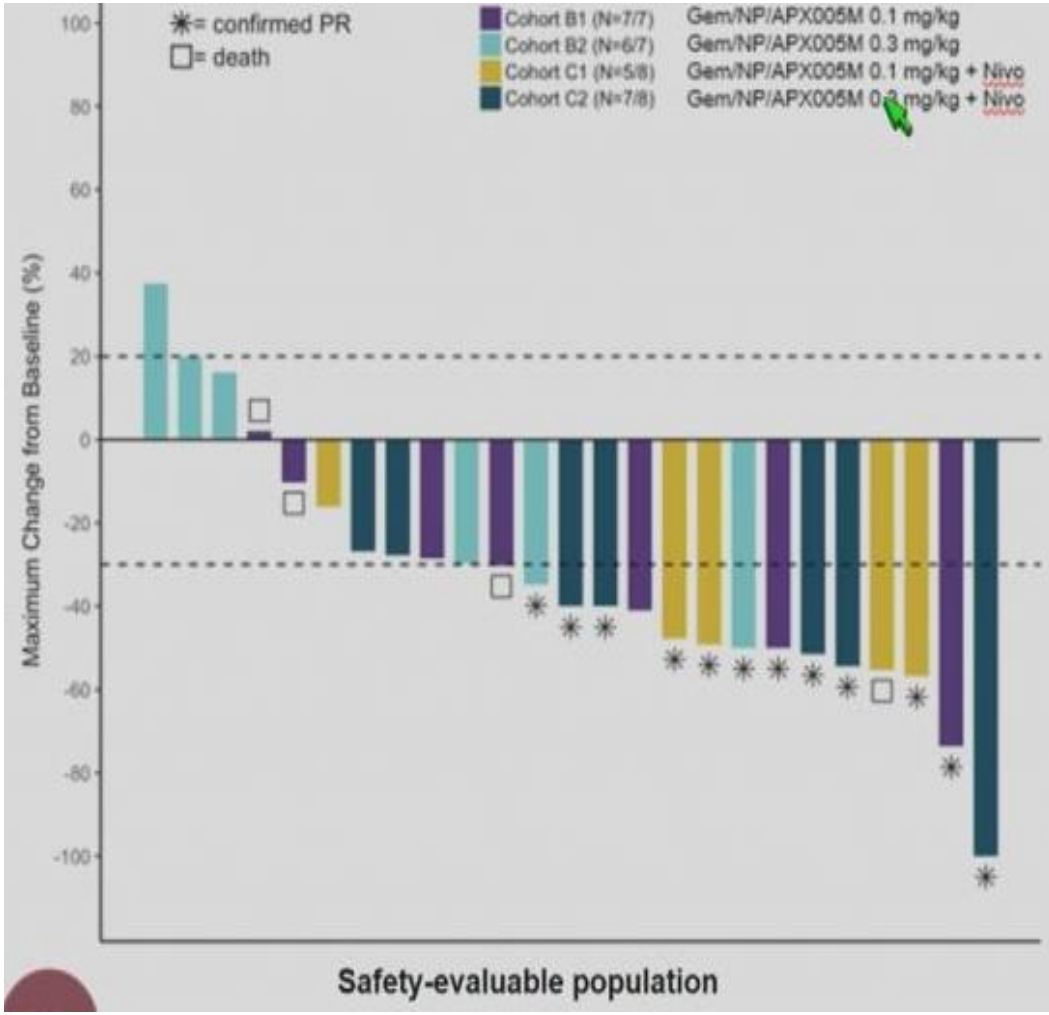
58% ORR (all partial)
92% clinical benefit rate (CR + PR + SD)

Immune Correlative Studies

- Low CD8 and high macrophages in baseline TME
- Decrease in circulating mutant KRAS DNA
- Remodeling of myeloid compartment in TME

O'Hara M,… Vonderheide R – CT004

Promising Anti-tumor Activity



	Total (N=24)
Complete Response (CR)	0
Partial Response (PR)	13 (54%)
Confirmed PR	11
Unconfirmed PR	2
Stable Disease (SD)	9 (38%)
Progressive Disease (PD)	1 (4%)
Not Evaluable / No Scan	1 (4%)
Early Death	1

- DLT-evaluable population (N=24): ORR = 54.2%
- Safety-evaluable population (N=30): ORR = 46.7%

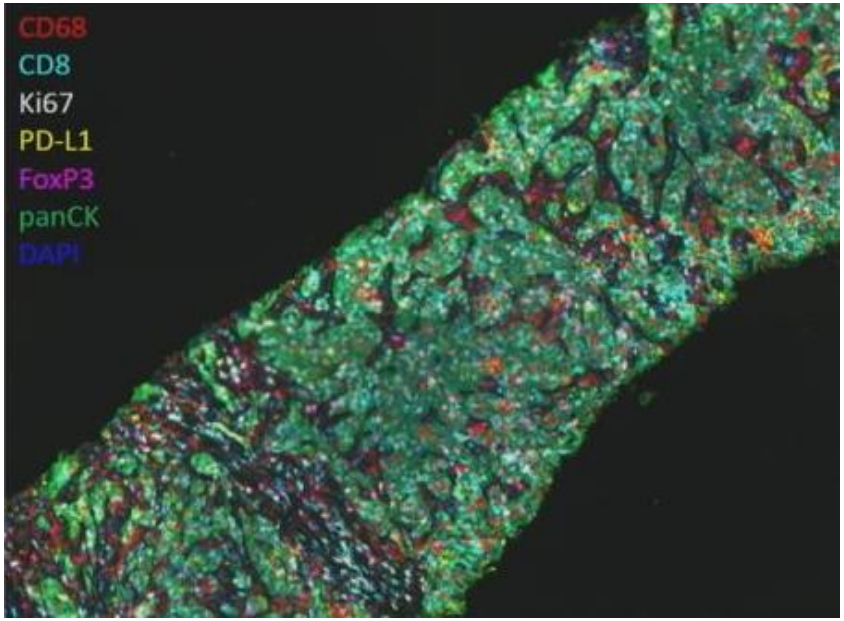
Grade 3 or 4 Treatment-Related AEs

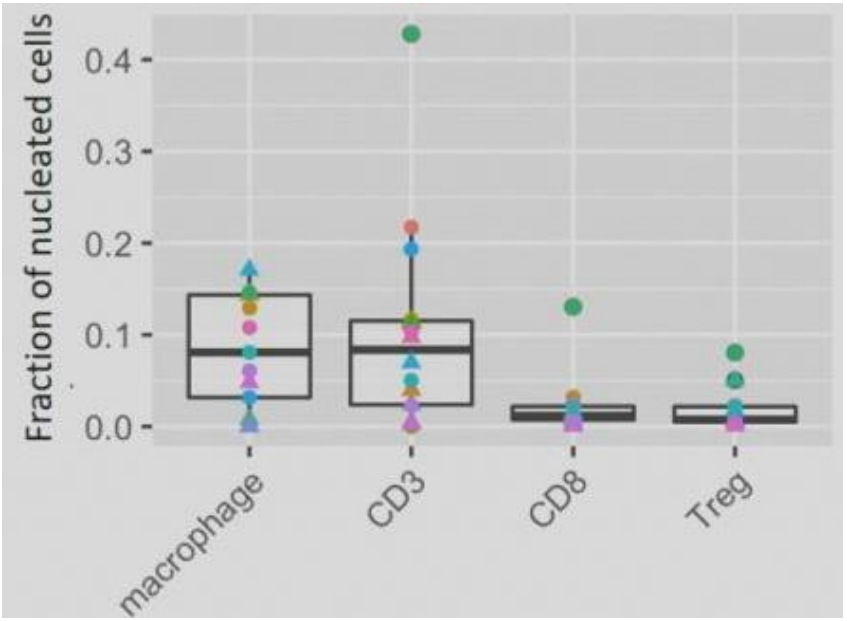
MedDRA Preferred Term	Cohort B1 Gem/NP/ APX005M 0.1 mg/kg (N=7)	Cohort B2 Gem/NP/ APX005M 0.3 mg/kg (N=7)	Cohort C1 Gem/NP/nivo/ APX005M 0.1 mg/kg (N=8)	Cohort C2 Gem/NP/nivo/ APX005M 0.3 mg/kg (N=8)	Total (N=30)
Lymphocyte count decreased	5 (71.4%)	6 (85.7%)	5 (62.5%)	4 (50.0%)	20 (66.7%)
Neutropenia	3 (42.9%)	5 (71.4%)	1 (12.5%)	3 (37.5%)	12 (40.0%)
Anemia	2 (28.6%)	3 (42.9%)	4 (50.0%)	1 (12.5%)	10 (33.3%)
Fatigue	3 (42.9%)	2 (28.6%)	3 (37.5%)	0	8 (26.7%)
Aspartate aminotransferase increased	0	4 (57.1%)	0	3 (37.5%)	7 (23.3%)
Leukopenia	0	4 (57.1%)	1 (12.5%)	1 (12.5%)	6 (20.0%)

- No grade 3/4 cytokine release syndrome was noted

O'Hara M,… Vonderheide R – CT004

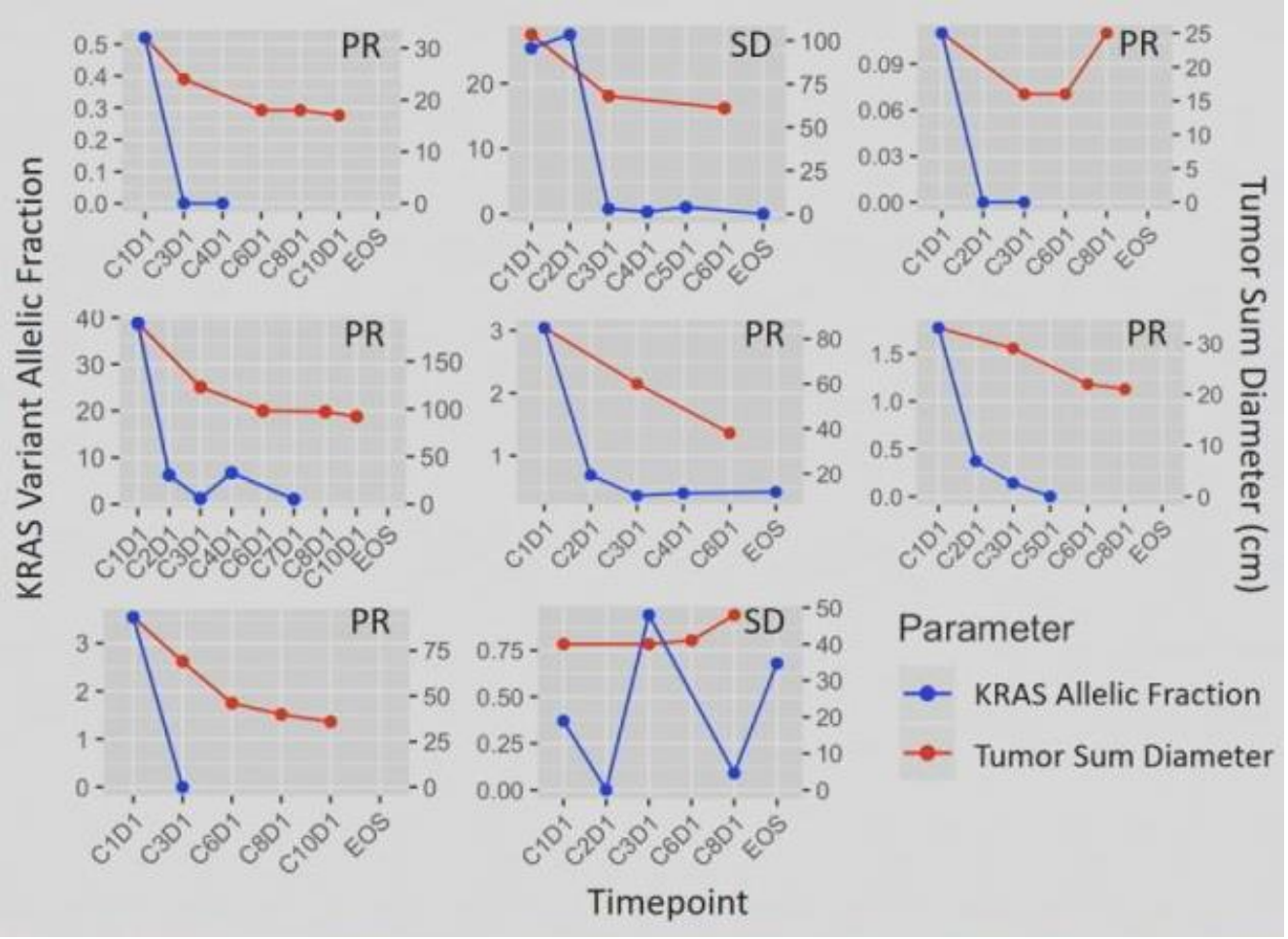
Immune Profiling





O'Hara M,… Vonderheide R – CT004

Circulating Tumor DNA

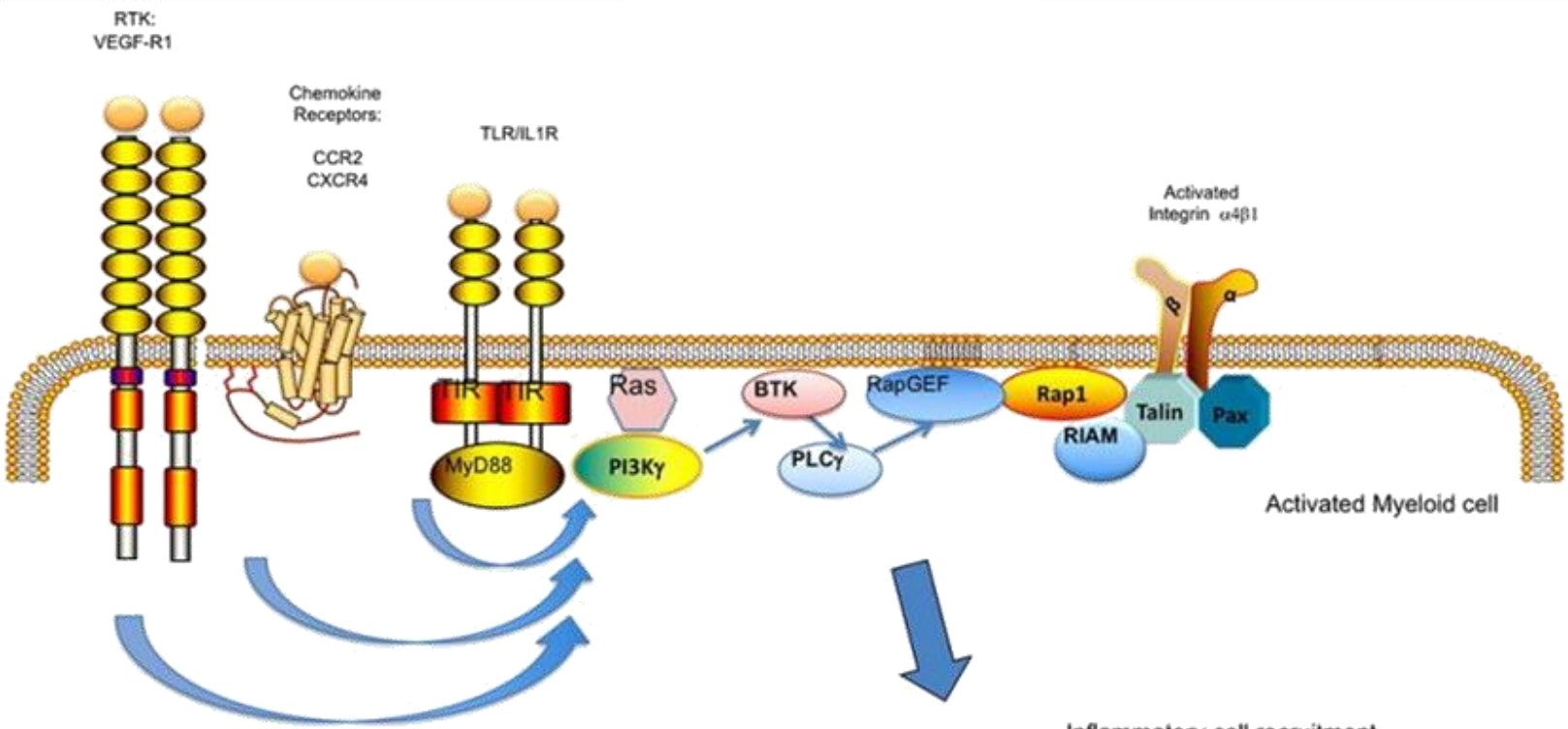


O'Hara M,… Vonderheide R – CT004

Summary Points

- Phase I trial, so results should be taken in context
- Combination of chemotherapy and immunotherapy
  - Better in treatment-naive setting
  - Allows more time for induction of immune responses
- Risk of toxicity with multiple agents
- Rationale for induction chemotherapy with immunotherapy
  - Immunogenic cell death may sensitize to immunotherapy
  - Chemotherapy can be reintroduced on disease progression

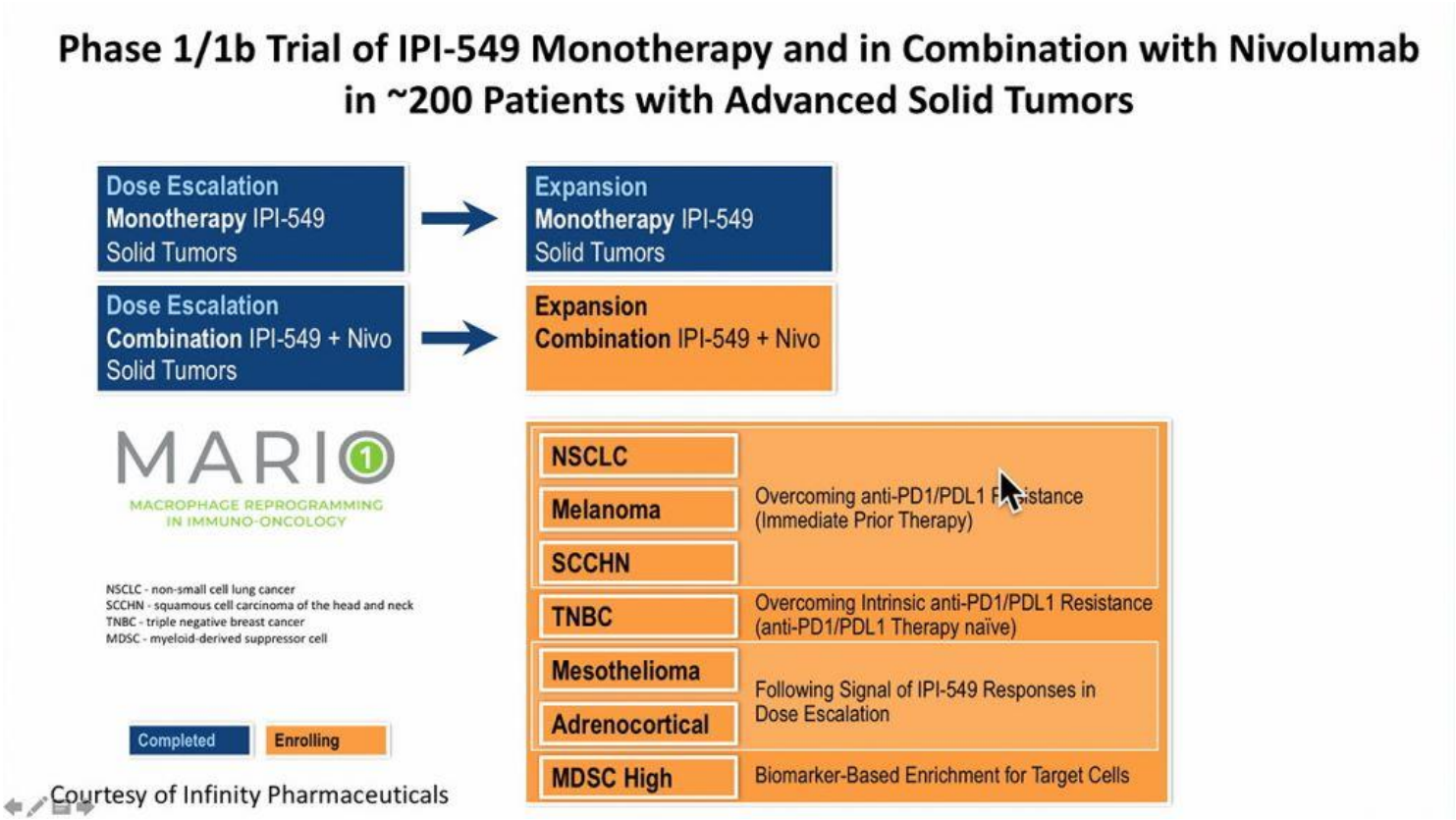
Other TAM Targeting Agents



Schmid et al 2011, *Cancer Cell*
Schmid et al 2011 *Cancer Research*
Schmid et al 2013 *PLoS One*
Schmid et al 2013 Vasc Cell
Gunderson, Kaneda et al 2016 *Cancer Discovery*
Kaneda et al 2016 Cancer Discovery
Foubert et al 2017 Canc. Immun. Res.

IPI-549 – PI3Kγ inhibitor

Late-Breaking Presentation at SITC 33rd Annual Meeting - 2018

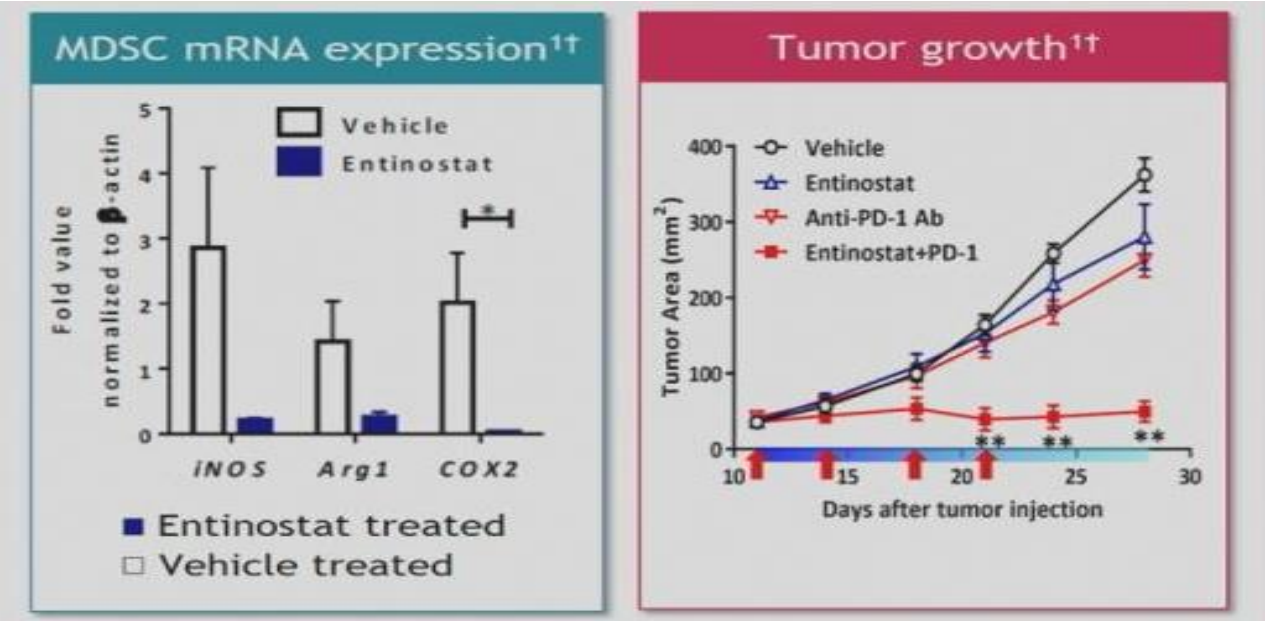


- Accrual ongoing, but only 2/27 (7%) PR to date

sitc
Society for Immunotherapy of Cancer

HDAC Inhibitor Plus Pembro In Melanoma After Progression on Checkpoint Blockade

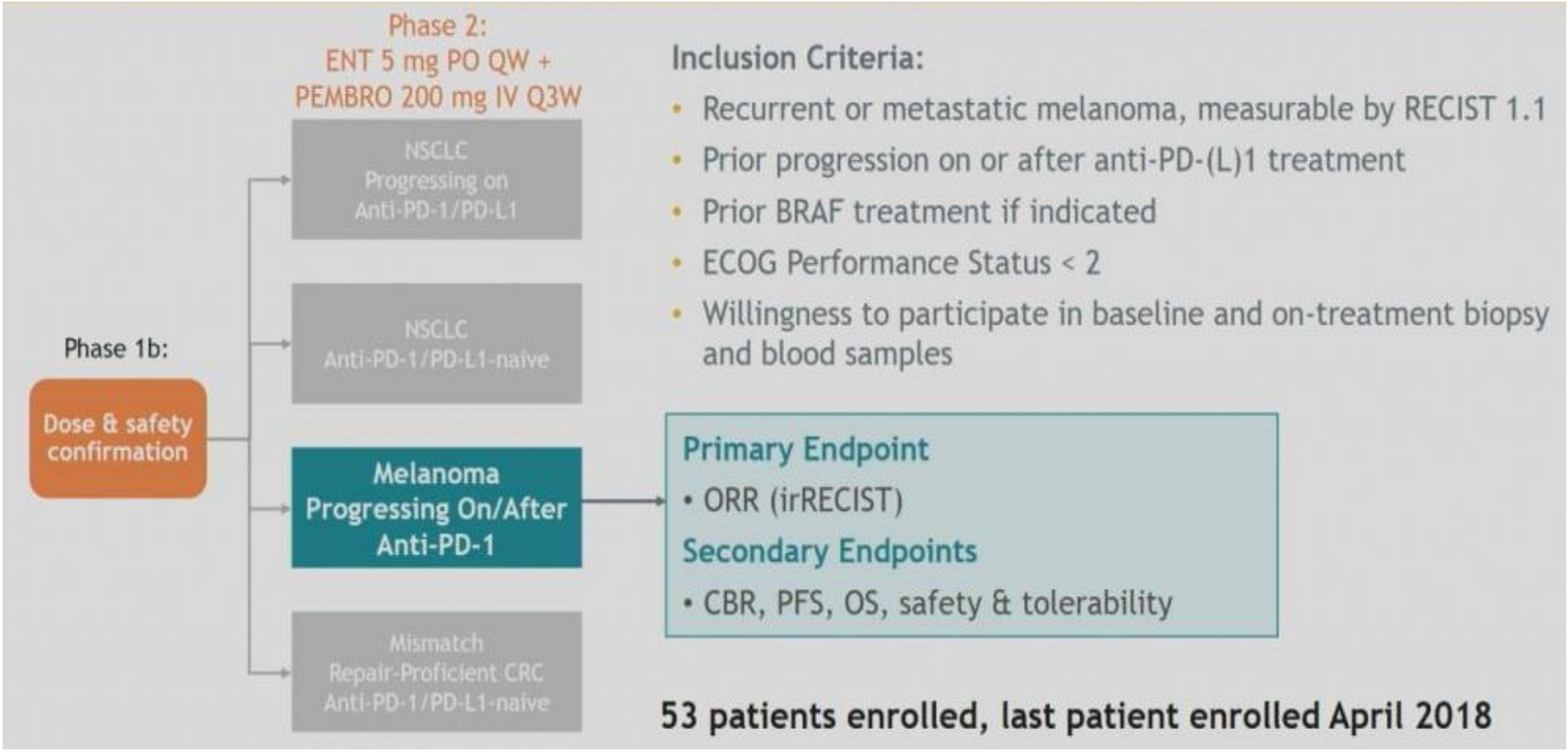
ENCORE-601 Study



- Entinostat is oral class I selective HDAC inhibitor
- Entinostat inhibits MDSCs
- Synergy with PD-1 inhibition in pre-clinical models

RJ Sullivan et al., – CT072

ENCORE-601 Study



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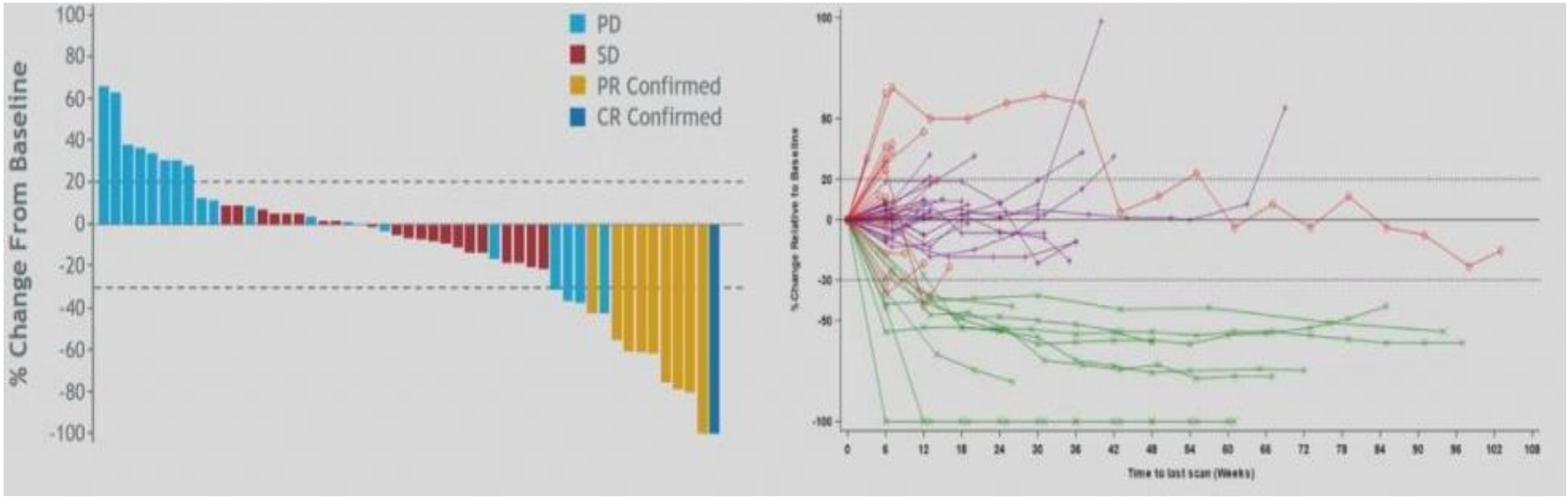
Clinical Outcomes Entinostat + Pembro in Melanoma



- 10 confirmed responses (1 CR, 9 PRs)
- ORR 19% (95% CI: 9 – 32%)
- Median duration of response 13 months
- 9 patients with SD x > 6 months
- 36% CBR

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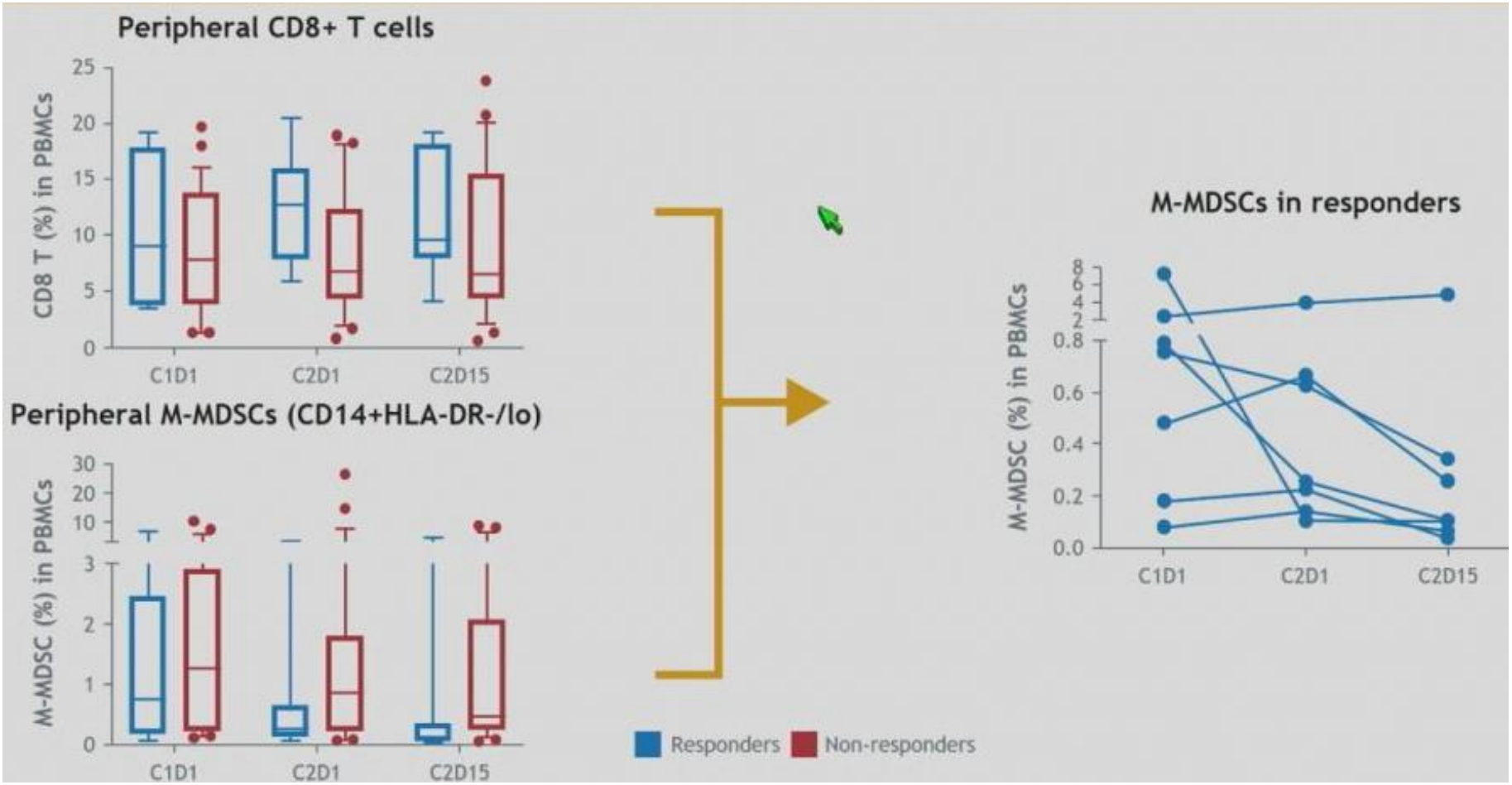
Circulating Immune Biomarkers



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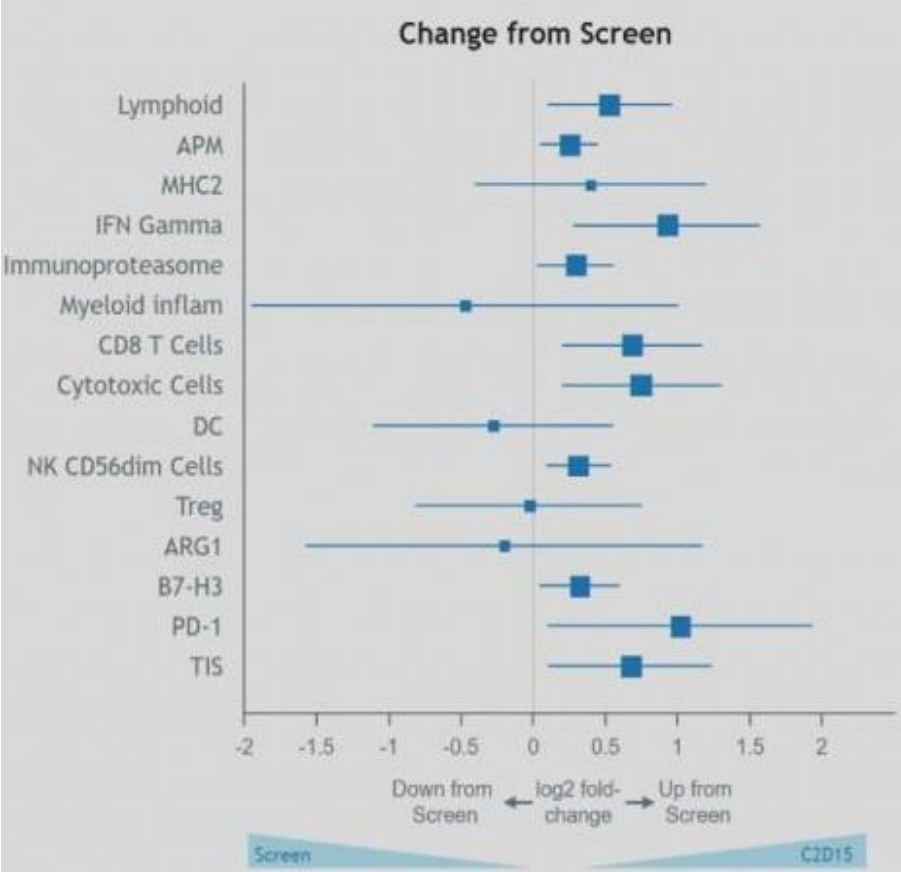
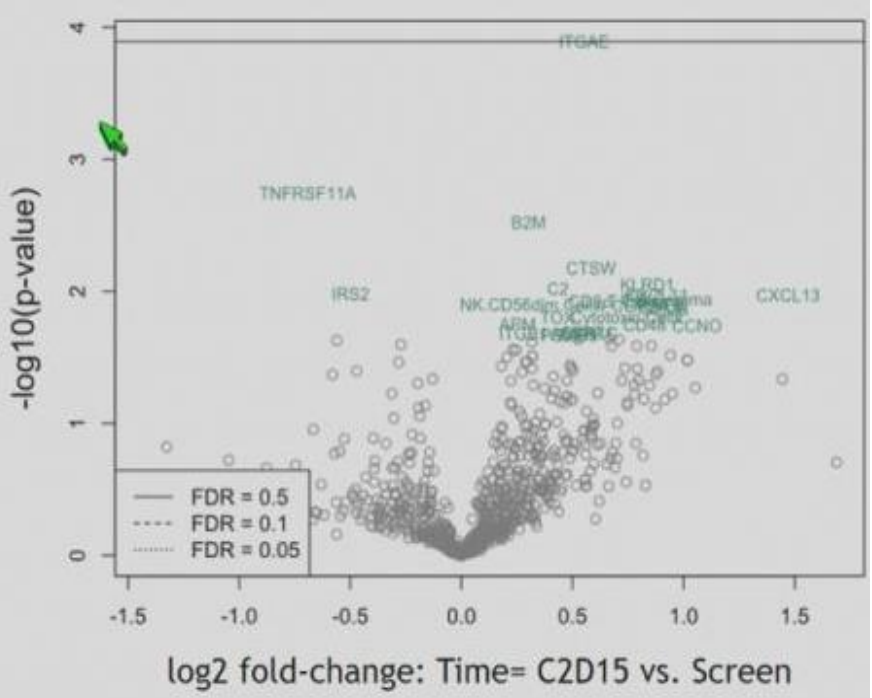
Immune Signatures Following Treatment





Nanostring analysis on tumor tissue post treatment (N = 7)

RJ Sullivan et al., – CT072

Summary

- Entinostat + Pembro showed encouraging activity in patients with progressive melanoma after single/ dual checkpoint blockade
- Toxicity primarily related to HDAC inhibition (nausea, fatigue, diarrhea)
- Preliminary predictors of response:
  - Reduction in circulating MDSCs
  - Baseline and tumor-specific increases in inflammatory pathways

CAR-T Cells

HER2-Targeted CAR T Cells in Sarcomas

- HER2 expressed in ~ 40% of osteosarcomas
- Limited success with HER2-directed therapies in sarcomas

Navai SA et al. Administration of HER2-CAR T cells after lymphodepletion safely improves T cell expansion and induces clinical responses in patients with advanced sarcomas. 2019 AACR Annual Meeting. Abstract LB-147. Presented April 1, 2019.

- Phase I trial 10 heavily-preated sarcoma patients
- 3 infusions of HER2-directed CARs after lymphodepletion with fludarabine +/- cyclophosphamide

HER2-Targeted CAR T Cells in Sarcomas

- 1 x 10^8 cells/ m2
- All patients developed lymphopenia and neutropenia
- 8/11 developed grade 1-II CRS
- T cells expanded in 9/11 patients
- TCR sequencing showed clonal expansion in 1 CR patient

Age	**4 – 54**
Histology	**5 Osteosarcoma** **3 Rhabdomyosarcoma** **1 Ewing's** **1 Synovial Sarcoma**
Best Response	**2 CR** **3 SD** **5 PD**
CAR T detection	**qPCR 10/10**

Navai SA et al. Abstract LB-147.

Society for Immunotherapy of Cancer

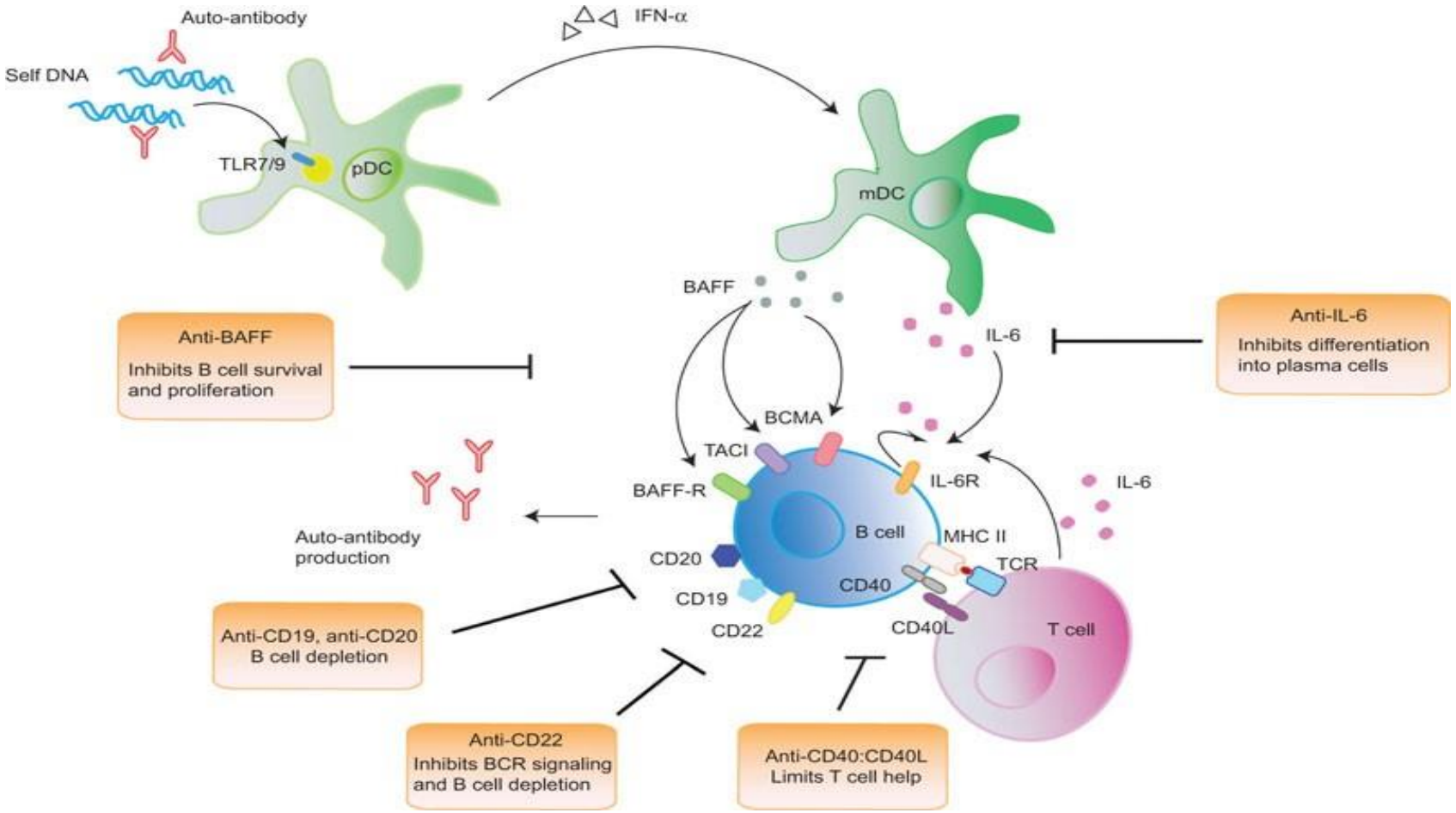
CAR-T Cells for Multiple Myeloma

Anti-BCMA CAR T-Cell Therapy in Relapsed or Refractory Multiple Myeloma

- Despite advances in systemic therapies, MM remains incurable
- B-cell maturation antigen (BCMA) is member of TNF superfamily and is primarily expressed on malignant and normal plasma cells as well as some mature B cells
- Bb2121 are autologous T cells with 2nd generation CAR incorporating anti-BCMA single-chain variable fragment with CD137 (4-1BB) and CD3-zeta domains

Raje et al., *N Engl J Med* 2019; 380:1726-1737

Survival and Differentiation of B Cells into Antibody-Producing Plasma Cells



Anti-BCMA CAR T-Cell Therapy in Relapsed or Refractory Multiple Myeloma

- 6 of 15 complete responders did relapse
- Median PFS was 11.8 months
- CAR-T expansion associated with response
- CAR T cells persisted up to 1 year

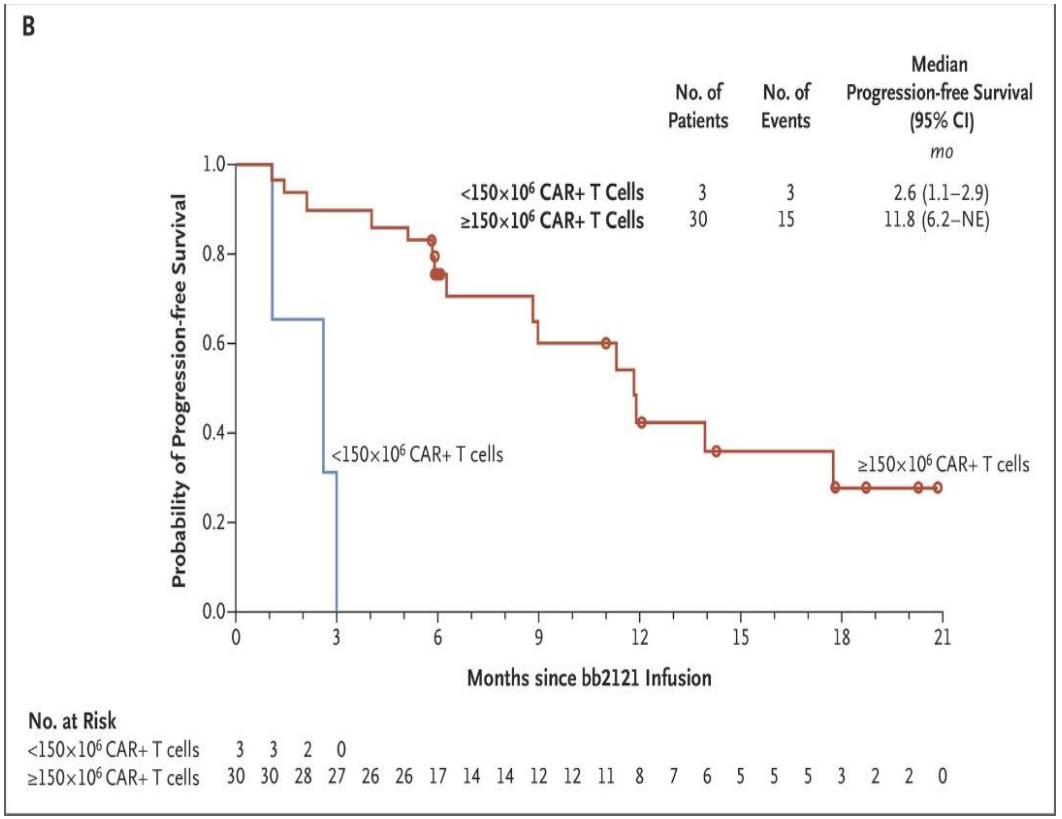
Age	**60 (37 – 75)**
Best Response	**15 CR (45%)** **13 PR (40%)**
Duration of Response	**Median 10.9 months**
Grade 3 Toxicity – Any	**97%**
Grade 3 Hematologic Toxicity	**85%**
CRS	**25 (76%)** **Grade 3 = 2 (6%)**
Neurological Toxicity	**14 (42%)** **Grade 4 = 1 (3%)**

Raje et al., *N Engl J Med* 2019; 380:1726-1737

Predictors of Response Anti-BCMA CARs

- Small sample size
- No statistical predictors of objective response
- Trend for superior responses in:
  - Low risk cytogenetics
  - Positive CRS syndrome
  - > 150 x 10^6 cells infused
  - In vivo CAR T expansion

Amount of Infused CAR-T Cells



Raje et al., *N Engl J Med* 2019; 380:1726-1737

Summary of Anti-BCMA CARs

- Heavily pre-treated population with evidence for anti-tumor activity
- Unlike anti-CD19 CARs, most responses don't persist
- Toxicity remains prevalent
- Data emphasize need for ongoing translational research to improve both efficacy and safety of novel CAR T cell therapies

Society for Immunotherapy of Cancer

CAR-T Cells for Mesothelioma

Phase I Clinical Trial

- Mesothelin-directed CAR T cells
- Direct injections into the pleural cavity in 21 patients with malignant pleural disease
- 14 patients also received anti-PD1 checkpoint blockade
- 2 CR (based on PET), 5 PR, and 4 SD

Poll Question

Which of the following is not a common side effect of CAR-T therapy?

a. Lymphopenia
b. Cytokine Release Syndrome (CRS)
c. Neutropenia
d. Neurologic Toxicity
e. Dermatologic Toxicity

Summary AACR Highlights

- Glass half-full
  - Durable responses are possible
- Glass half-empty
  - Majority of patients do not respond
- T cell-based treatments remain the focal point of immuno-oncology
- Novel combinations and overcoming resistance remain focal point of PD-1/ PD-L1 based therapies
- Novel targets, homing, and avoiding off-tumor effects are critical areas in CAR T-cell approaches