Cancer Immunotherapy Program

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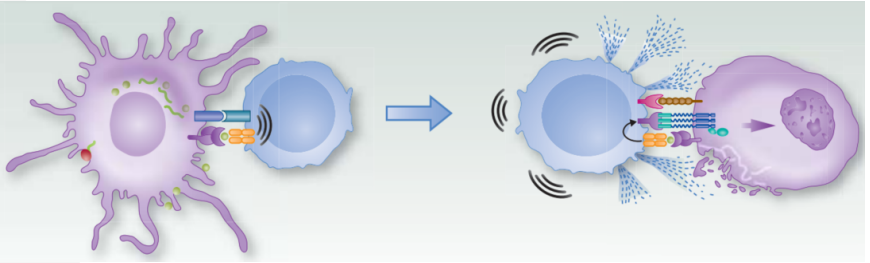


NIH NATIONAL CANCER INSTITUTE

I've always been a tumor immunologist!
I was in style, out of style, in style,
out of style, in style!
S.Harris

What Does “Immunotherapy” Encompass?

1. **Monoclonal Antibodies**
   — herceptin/rituximab/bevacizumab, etc.
   “targeted therapies”

2. **Cytokines**
   — IL-2, GM-CSF, IL-15

3. **Vaccines**
   — Sipuleucel-T, PROSTVAC, Stimuvax, GVAX

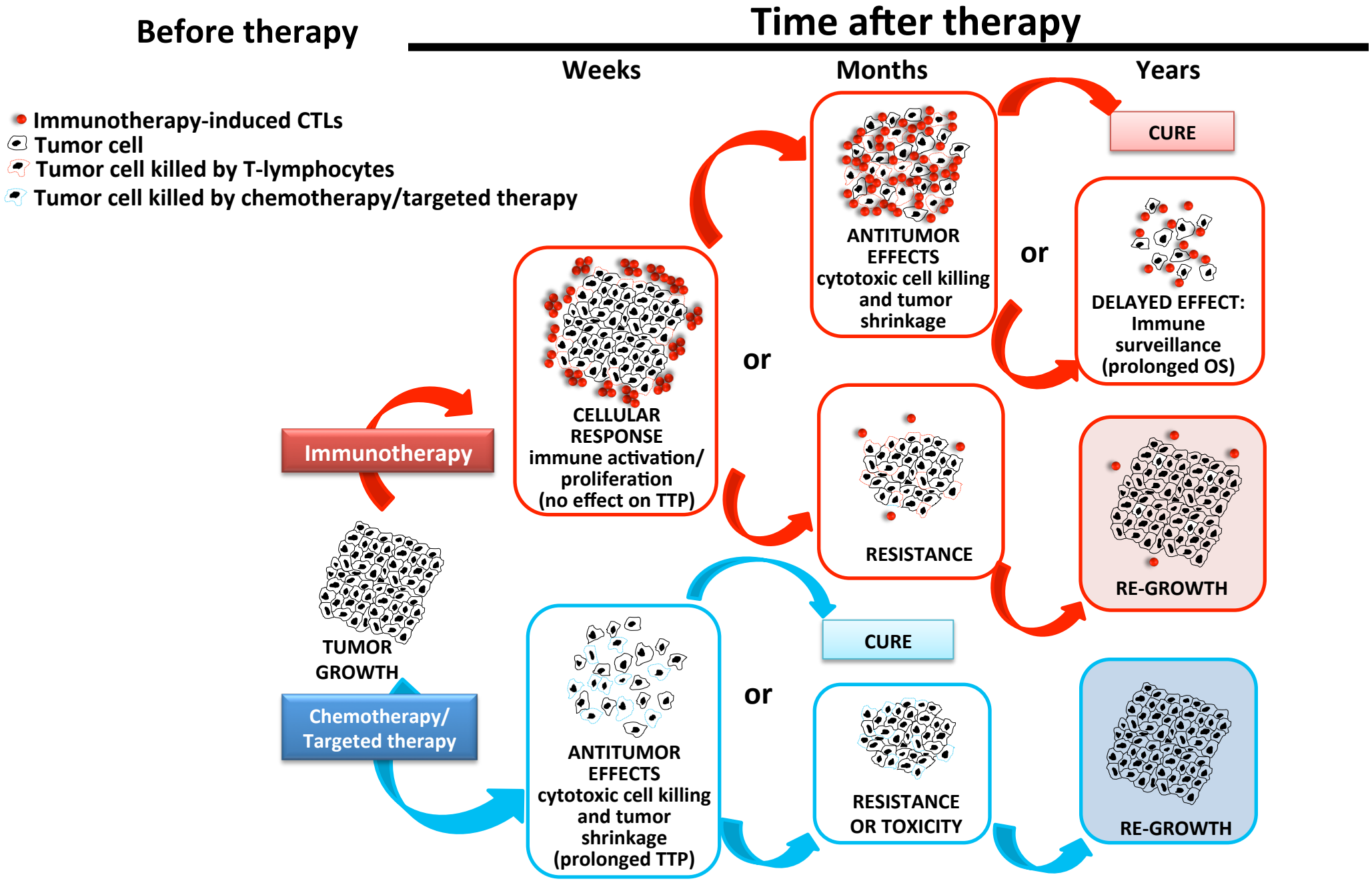
4. **Checkpoint Inhibitors**
   — Ipilimumab* (anti-CTLA-4), anti-PD1, anti-PD-L1

5. **Inhibitors of Immune Suppression**
   — anti-TGF-β, anti-IL8
   — anti-IDO (d-methyl-tryptophan, d-1-MT)

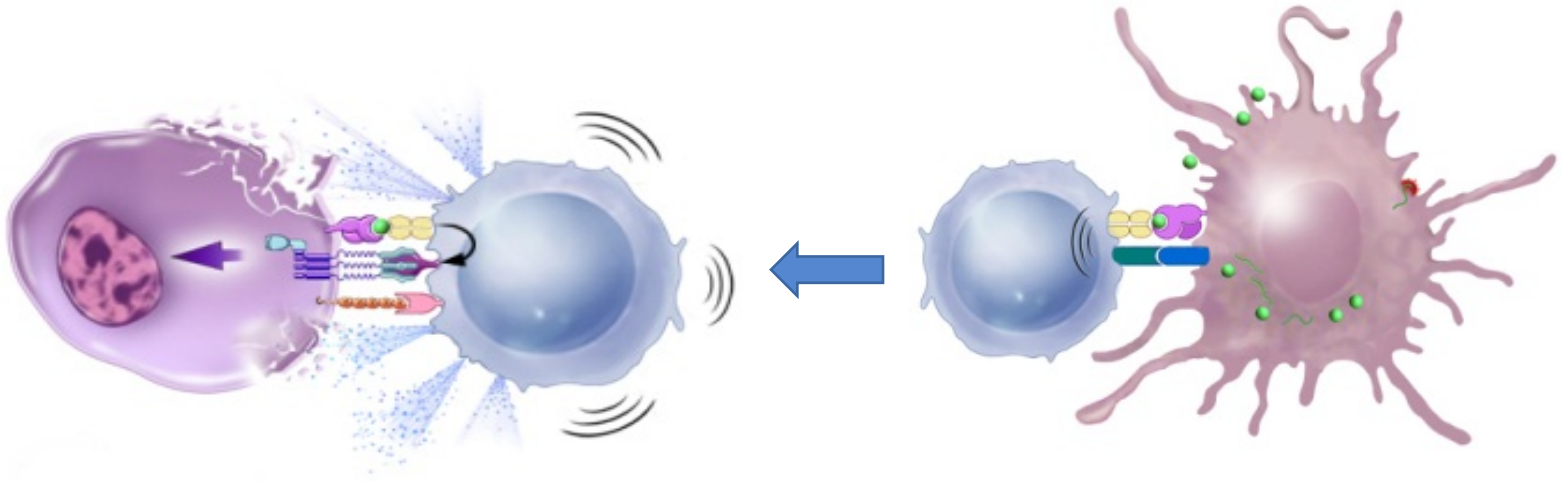
6. **Adoptive Transfer of Immune Cells**
   — LAK, TIL, Genetically modified T cells and NK cells

Conventional Therapy vs. Immunotherapy

	Conventional Therapy	Immunotherapy
Target	Tumor or its microenvironment	Immune system
Limitations	Toxicity	Requires adequate immune system function (tumor size, multiple prior therapies)
Tumor evolution/ new mutations	Resistance to therapy	Induction of new immunogenic targets via "antigen cascade" – enormous diversity of the immune system
Pharmacodynamics	Often immediate action	Delayed (may get better over time, e.g., booster vaccinations)
Memory response	No	Yes

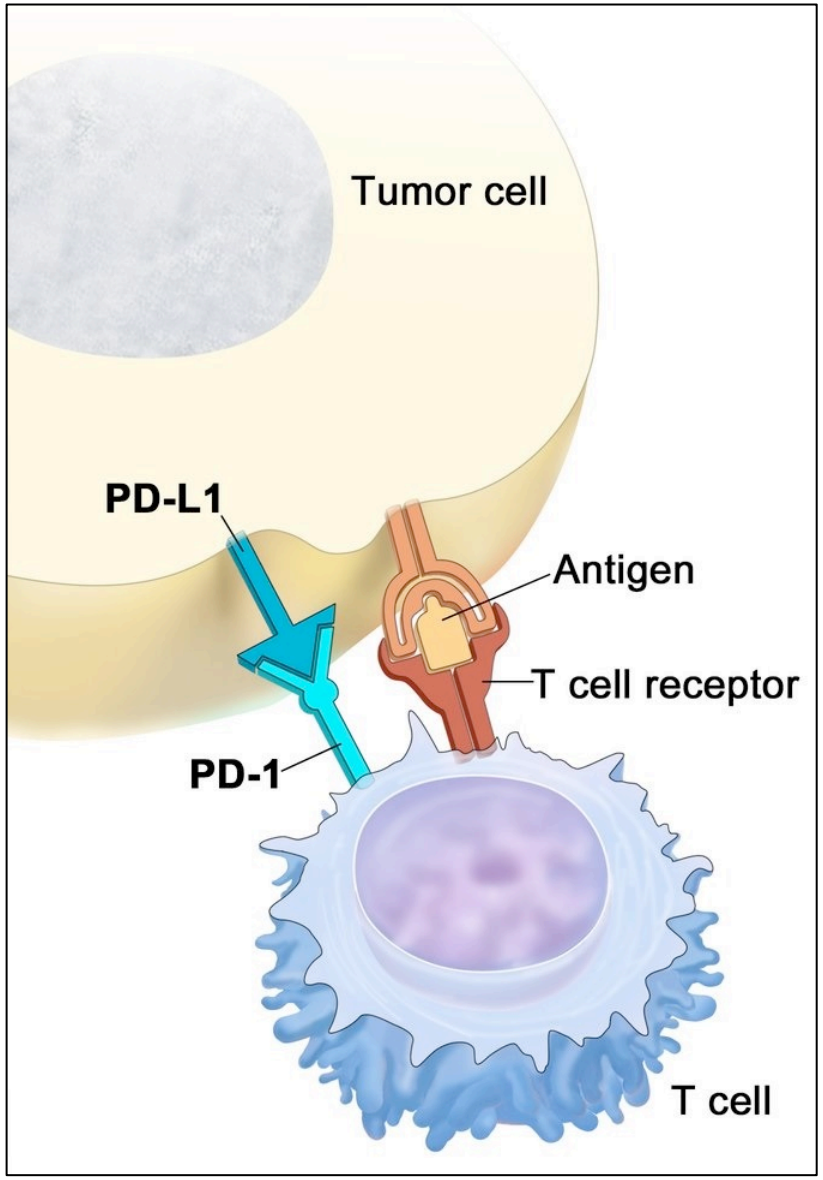

Before therapy
Time after therapy
Weeks
Months
Years
Immunotherapy-induced CTLs
Tumor cell
Tumor cell killed by T-lymphocytes
Tumor cell killed by chemotherapy/targeted therapy
Immunotherapy
TUMOR GROWTH
Chemotherapy/ Targeted therapy
CELLULAR RESPONSE immune activation/ proliferation (no effect on TTP)
ANTITUMOR EFFECTS cytotoxic cell killing and tumor shrinkage (prolonged TTP)
or
ANTITUMOR EFFECTS cytotoxic cell killing and tumor shrinkage
RESISTANCE
CURE
RESISTANCE OR TOXICITY
or
CURE
DELAYED EFFECT: Immune surveillance (prolonged OS)
RE-GROWTH
RE-GROWTH

Requirements for Effective Immunotherapy

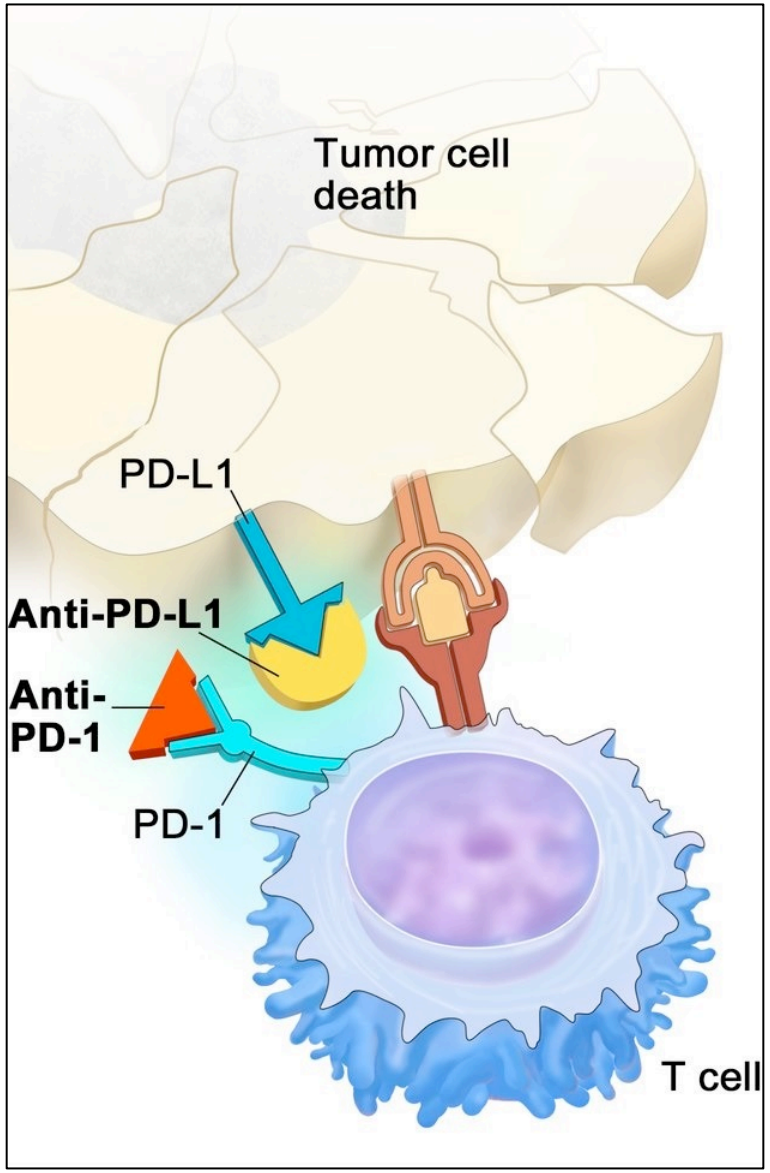


Effector Cells Functional within Tumor **Generate Immune Response**

PD-L1 Binds to PD-1 and Inhibits T-cell Killing of Tumor Cell



Blocking PD-L1 or PD-1 Allows T-cell Killing of Tumor Cell

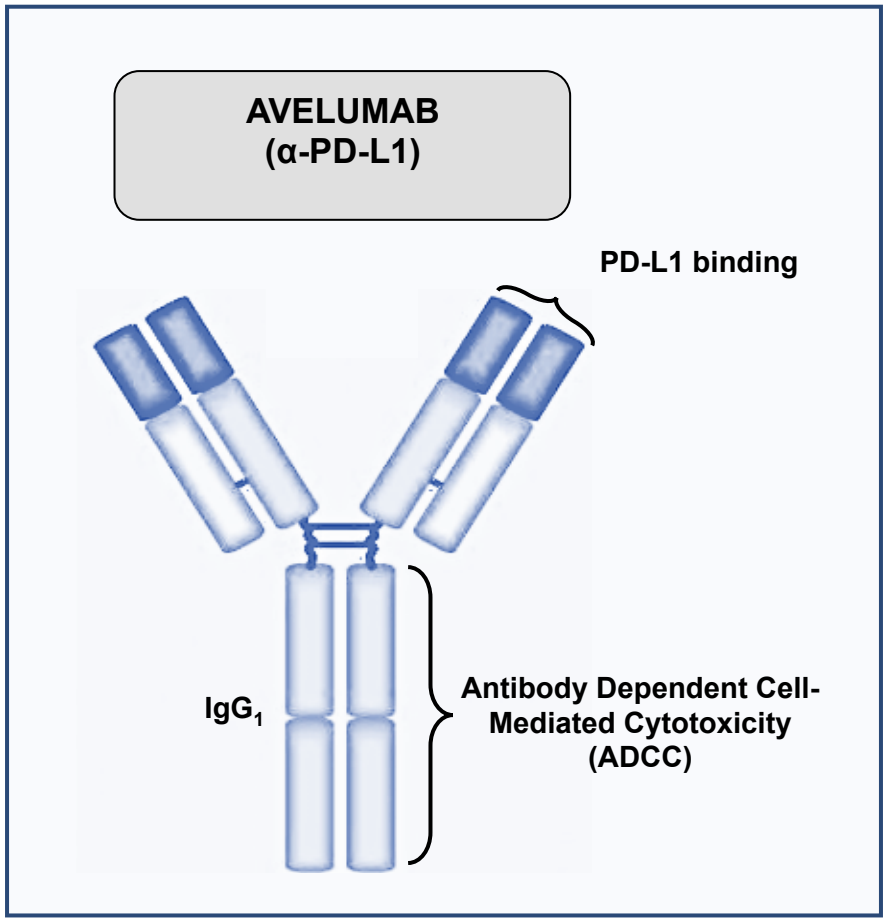


MSB0010718C (anti-PD-L1)

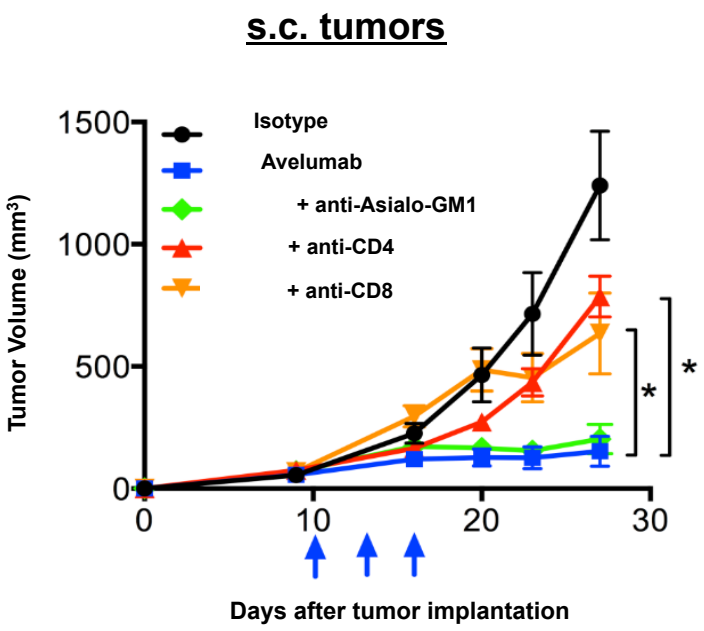
- Fully human monoclonal antibody targeting PD-L1, IgG1 isotype
  - PD-L1 on APC and tumor cells
  - Potentially lower risk of immune related adverse events than other immune checkpoint targets

- Two main mechanisms of action for exerting its anti-tumor effects:
  1. Blocking PD-L1 interaction with PD-1 or B7-1 by anti-PD-L1 can prevent T-cell immunosuppression from PD-L1^{+} tumors
  2. ADCC-mediated lysis of tumor cells expressing surface PD-L1

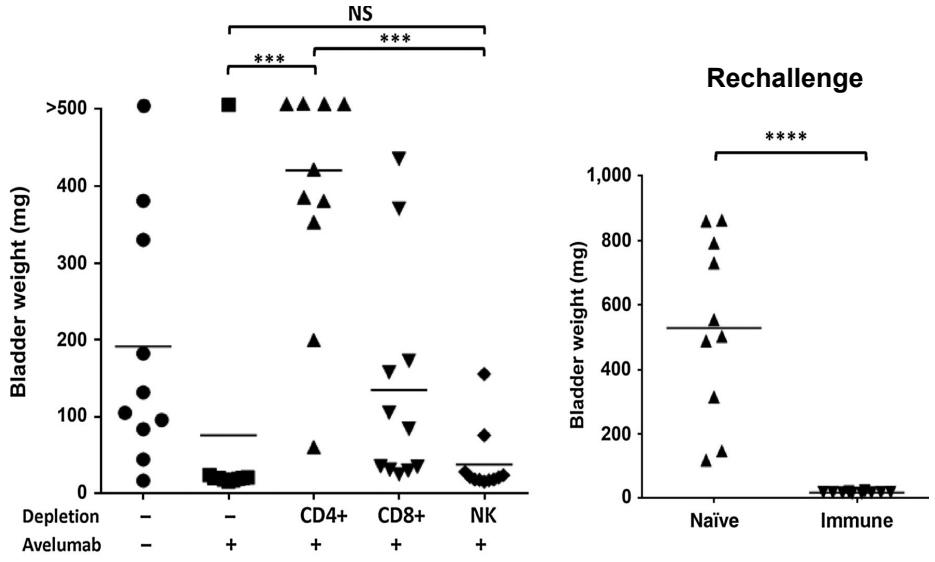
Dual Functionality of Avelumab



Anti-tumor Activity of Avelumab in Bladder Cancer Models

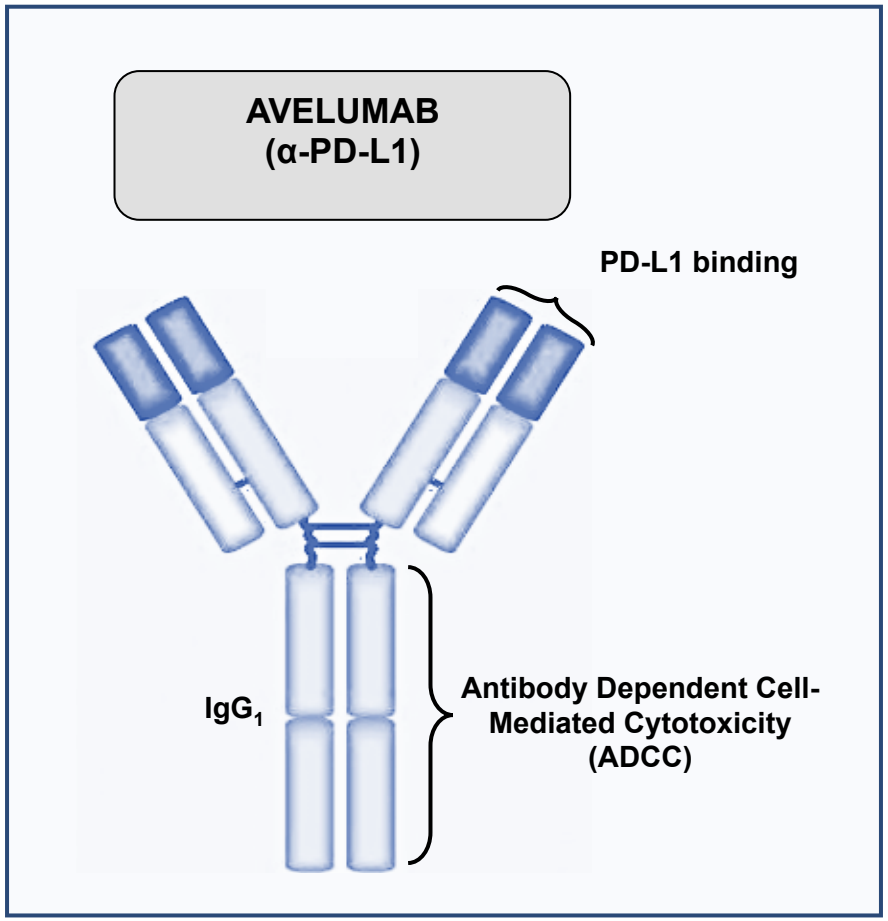


Fallon, Oncotarget. 2017; 8:20558-20571.

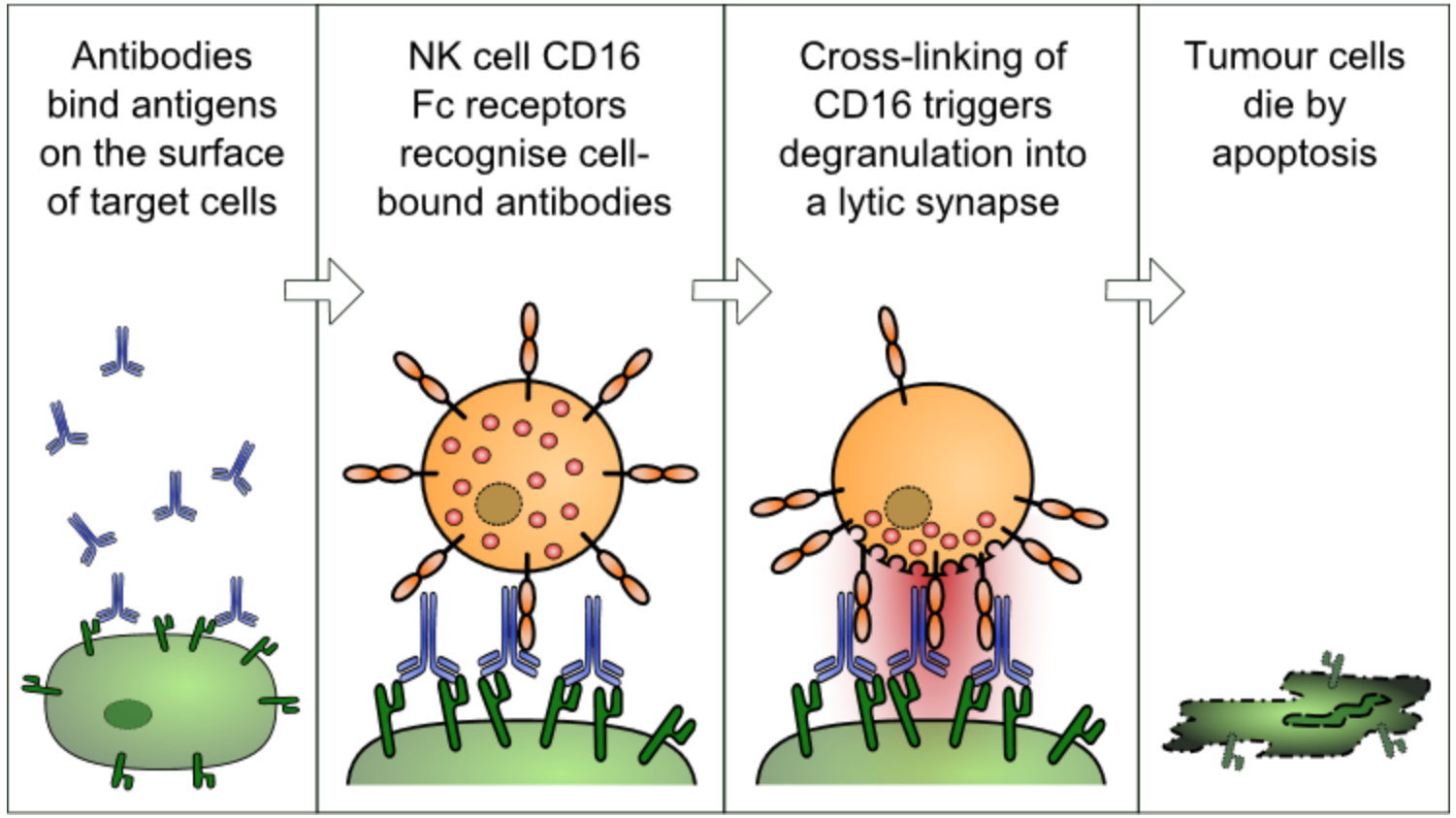


Vandeveer, Cancer Immunol Res 2016;4:452-462

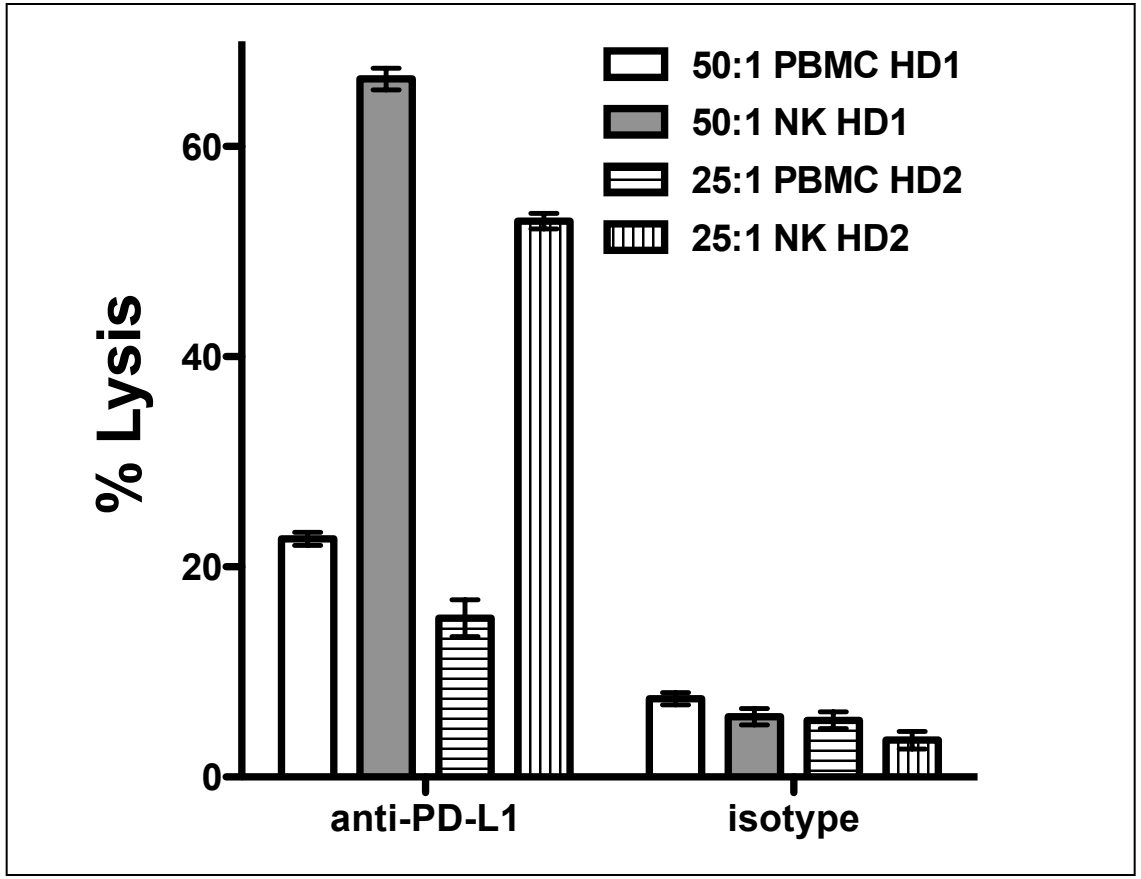
Dual Functionality of Avelumab



Antibody-dependent Cell-mediated Cytotoxicity (ADCC)

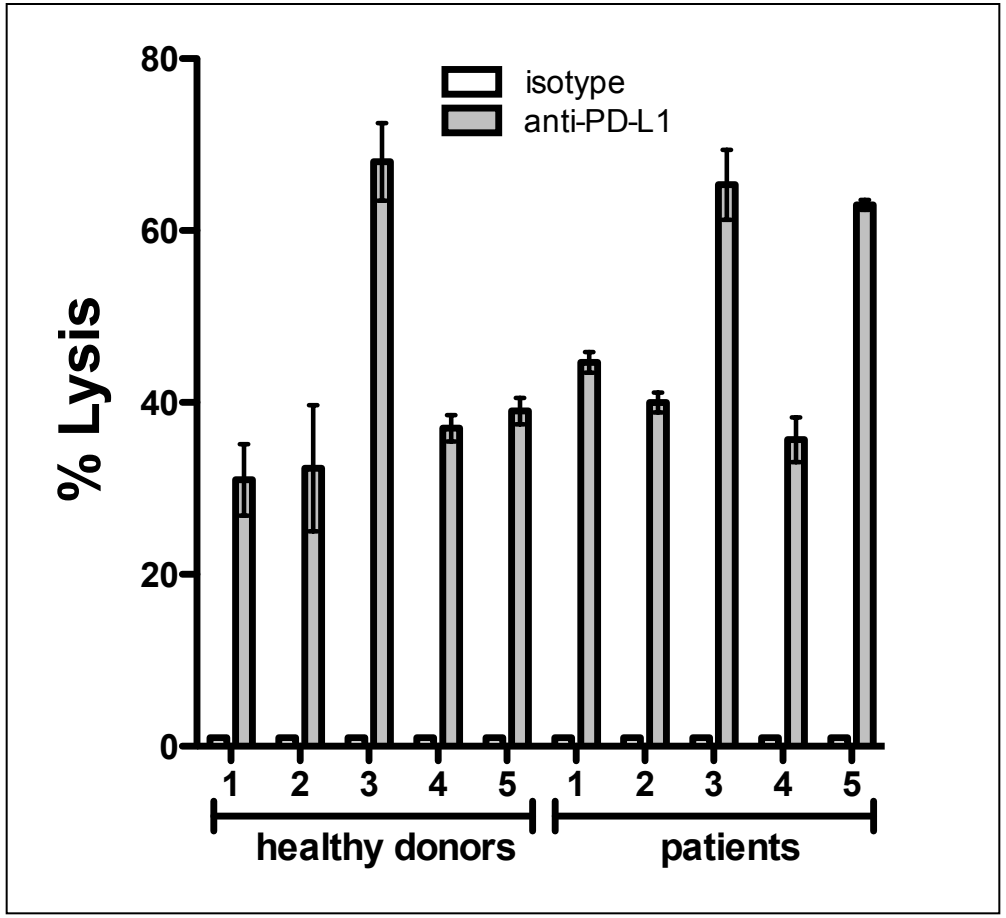


Purified NK Cells Are Efficient Effectors of ADCC Mediated by anti-PDL1 Avelumab



NK cells were purified from PBMC from 2 healthy donors (HD).
Human lung cancer cell line as target.

Purified NK Cells from Cancer Patients Mediate ADCC Induced by Avelumab as Effectively as Those Isolated from Healthy Donors



Isolated NK cells from 5 healthy donors and 5 lung cancer patients were used in *in vitro* ADCC assays against the H441 human lung cancer cell line.

Immunophenotyping: Changes post- vs. pre-immunotherapy
Flow-cytometry analysis of PBMC immune subsets: 30 markers, 123 subsets

Subsets analyzed: 9 standard immune cell subsets, and 118 additional subsets relating to maturation/function

1. CD4: Helper T lymphocytes (32 subsets)
2. CD8: Cytotoxic T lymphocytes (29 subsets)
   - Markers of PD-1 pathway and T cell activation (in CD4 and CD8):
     - EOMES: activation
     - TCR-αβ: activation
     - Tbet: activation
     - BATF: activation/exhaustion
   - Maturation status of T lymphocytes (in CD4 and CD8):
     - Naïve: $CD45RA^{+}$ $CCR7^{+}$
     - Central Memory: $CD45RA^{-}$ $CCR7^{+}$
     - Effector Memory: $CD45RA^{-}$ $CCR7^{-}$
     - Terminal (EMRA): $CD45RA^{+}$ $CCR7^{-}$
   - T lymphocyte markers (in CD4 and CD8):
     - CTLA-4: inhibition
     - PD-1: activation/inhibition
     - PD-L1: activation/cross-inhibition
     - TIM-3: inhibition
     - ICOS: activation (only on CD4)
3. Tregs: Regulatory T lymphocytes ($CD4^{+}$ $CD25^{+}$ $FoxP3^{+}$ $CD127^{-}$) (7 subsets)
   - CD45RA: Tregs highly expandable *in vitro*
   - CTLA-4: Treg suppression
   - CD49d: "contaminating" effector lymphocytes (non-Tregs)
   - ICOS: Treg suppression
   - PD-1: activation/inhibition
   - PD-L1: cross-inhibition
4. B lymphocytes: $CD19^{+}$ (5 subsets)
   - CTLA-4: inhibition
   - TIM-3: inhibition
   - PD-1: activation/inhibition
   - PD-L1: cross-inhibition
5. NK: Natural killer cells ($CD56^{+}$ $CD3^{-}$) (20 subsets)
   - $CD16^{+}$ $CD56^{br}$: Functional intermediate, lytic and cytokine production
   - $CD16^{+}$ $CD56^{dim}$: Mature NK, cytokine production
   - $CD16^{-}$ $CD56^{br}$: Immature, abundant in human placenta
   - $CD16^{-}$ $CD56^{dim}$: non-lytic, non-cytokine production
   - TIM-3: activation
   - PD-1: activation/inhibition
   - PD-L1: cross-inhibition
6. NK-T: $CD56^{+}$ $CD3^{+}$ (4 subsets)
   - TIM-3: activation
   - PD-1: activation/inhibition
   - PD-L1: cross-inhibition
7. cDCs (Conventional DCs): $CD3^{-}CD56^{-}CD1c^{+}CD303^{-}$ (5 subsets)
8. pDCs (plasmacytoid DCs): $CD3^{-}CD56^{-}CD1c^{-}CD303^{+}$ (5 subsets)
   - Markers of DC activation
     - CD83: activation
     - TIM-3: inhibition
     - PD-1: activation/inhibition
     - PD-L1: cross-inhibition
9. MDSCs: Myeloid-derived suppressor cells ($CD11b^{+}$ $HLA\text{-}DR^{low/-}$ $CD33^{+}$) (20 subsets)
   - CD14: Common Myeloid Marker (high in monocytes, dim in granulocytes)
   - CD15: Granulocyte marker
   - CD16: most immature monocytic MDSCs
   - PD-1: activation/inhibition
   - PD-L1: cross-inhibition

PD-1 in Standard Subsets:
No significant changes at any time point tested compared to pre

Subset	Pre N=19	Day 15 N=19	Holm adjusted p
PD-1+ CD4	4.4	4.2	0.9999
PD-1+ CD8	1.3	1.5	0.9999
PD-1+ Treg	0.12	0.16	0.0705
PD-1+ NK	0.01	0.01	0.9999
PD-1+ NK-T	0.03	0.04	0.5457
PD-1+ B cells	0.4	0.3	0.9999
PD-1+ cDC	<0.01	<0.01	n/a
PD-1+ pDC	<0.01	<0.01	n/a
PD-1+ MDSC	0.6	0.5	0.9999

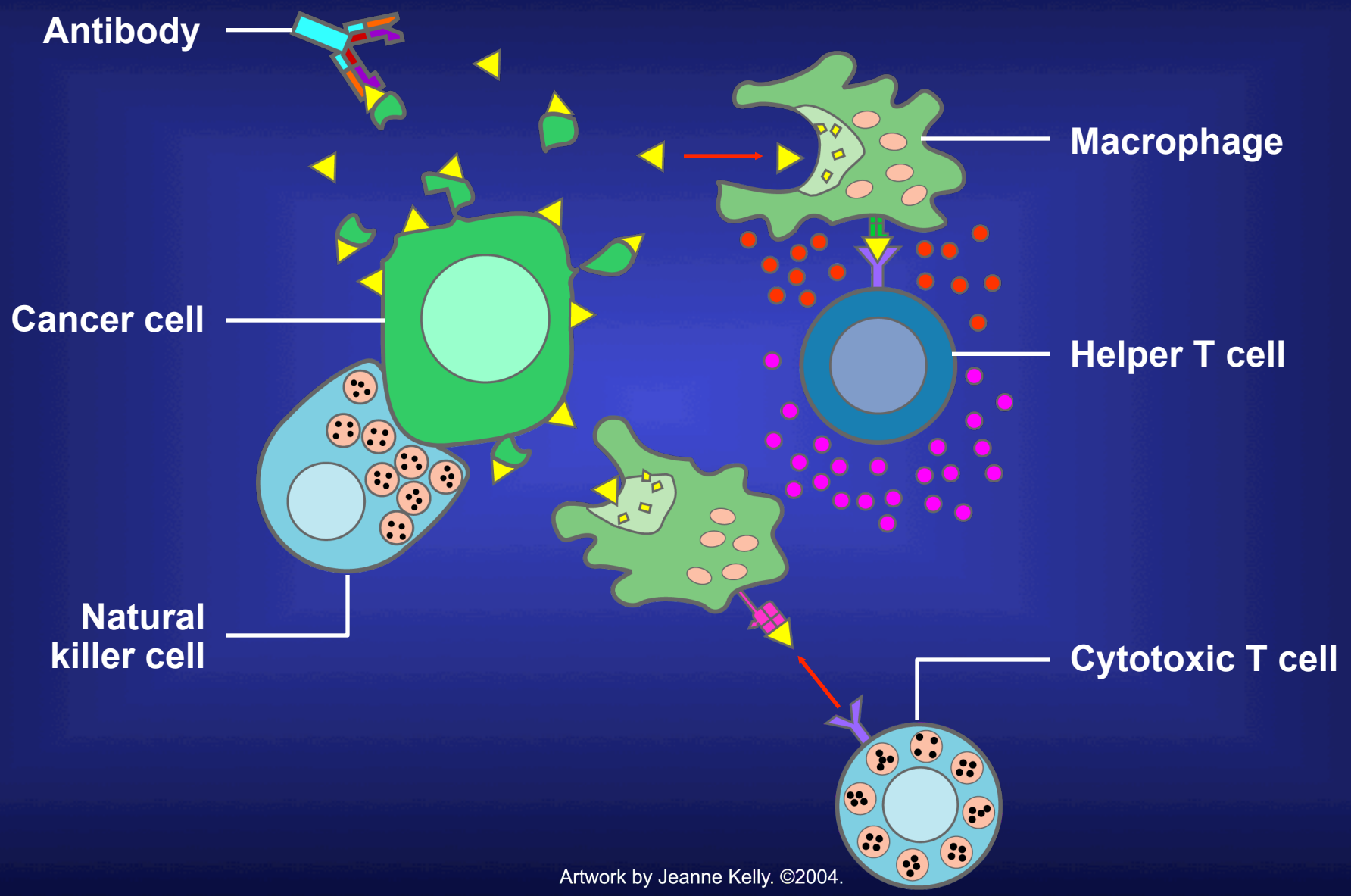
Subset	Pre N=14	Day 43 N=14	Holm adjusted p
PD-1+ CD4	4.1	4.5	0.9999
PD-1+ CD8	1.3	1.3	0.9999
PD-1+ Treg	0.13	0.16	0.5200
PD-1+ NK	0.02	0.01	0.8112
PD-1+ NK-T	0.02	0.03	0.8526
PD-1+ B cells	0.5	0.5	0.9999
PD-1+ cDC	<0.01	<0.01	n/a
PD-1+ pDC	<0.01	<0.01	n/a
PD-1+ MDSC	0.6	0.6	0.9999

Subset	Pre N=16	Day 127 N=16	Holm adjusted p
PD-1+ CD4	3.3	3.1	0.9999
PD-1+ CD8	1.2	1.1	0.9999
PD-1+ Treg	0.07	0.08	0.9999
PD-1+ NK	0.02	0.02	0.9999
PD-1+ NK-T	0.03	0.02	0.3891
PD-1+ B cells	0.4	0.4	0.9999
PD-1+ cDC	<0.01	<0.01	n/a
PD-1+ pDC	0.02	0.03	0.1005
PD-1+ MDSC	0.7	0.8	0.6664

Values indicate median % of PBMC

Significant change: P<0.05 based on Wilcoxon matched-pairs signed rank test with holm adjustment made for number of subsets within each standard subset with frequency above 0.01% of PBMC (n= 9 for standard subsets, 31 for CD4, 25 for CD8, 5 for Treg, 14 for NK, 3 for NK-T, 4 for B cells, 2 for cDC, 3 for pDC, 15 for MDSC)

Immunity and Cancer



Artwork by Jeanne Kelly. ©2004.

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Multifactoral Approach to Cancer Immunotherapy

I. **Generation of an Effective Immune Response**

- Vaccine: TAA, neoantigens
- Immunocytokine: IL-15 superagonist (ALT-803)
- IDOi: enhance DC function

II. **Maintenance of an Effective Immune Response at the Tumor Site/ Reduction of Immunosuppressive Entities**

- anti-PD-L1 (avelumab)
- anti-PD-L1/TGFβR2 (M7824)
- Immunocytokine: NHS-IL12
- Agonist MAbs to GITR, OX40, 41BB
- IDOi
- anti-PD-L1/IL15-FP (FP-809)

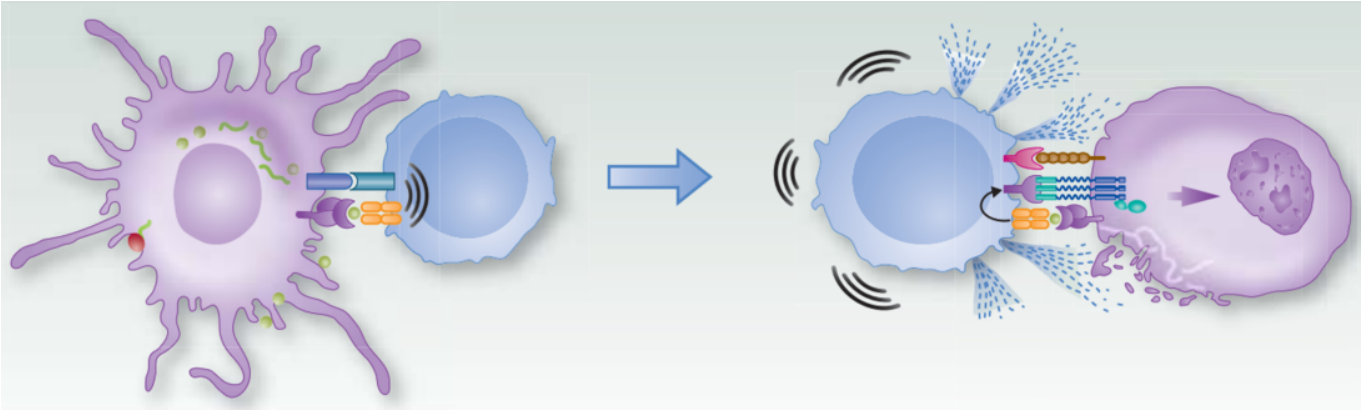
III. **Modification of the Tumor/Tumor Microenvironment to Enhance Immune-mediated Effectiveness**

- Immunogenic tumor cell death
- Immunogenic modulation of tumor phenotype
- anti-PD-L1/TGFβR2 (M7824)
- IL-8R antagonist

IV. **Adaptive Clinical Trial Designs Encompassing I, II, and III**

LTIB / GMB

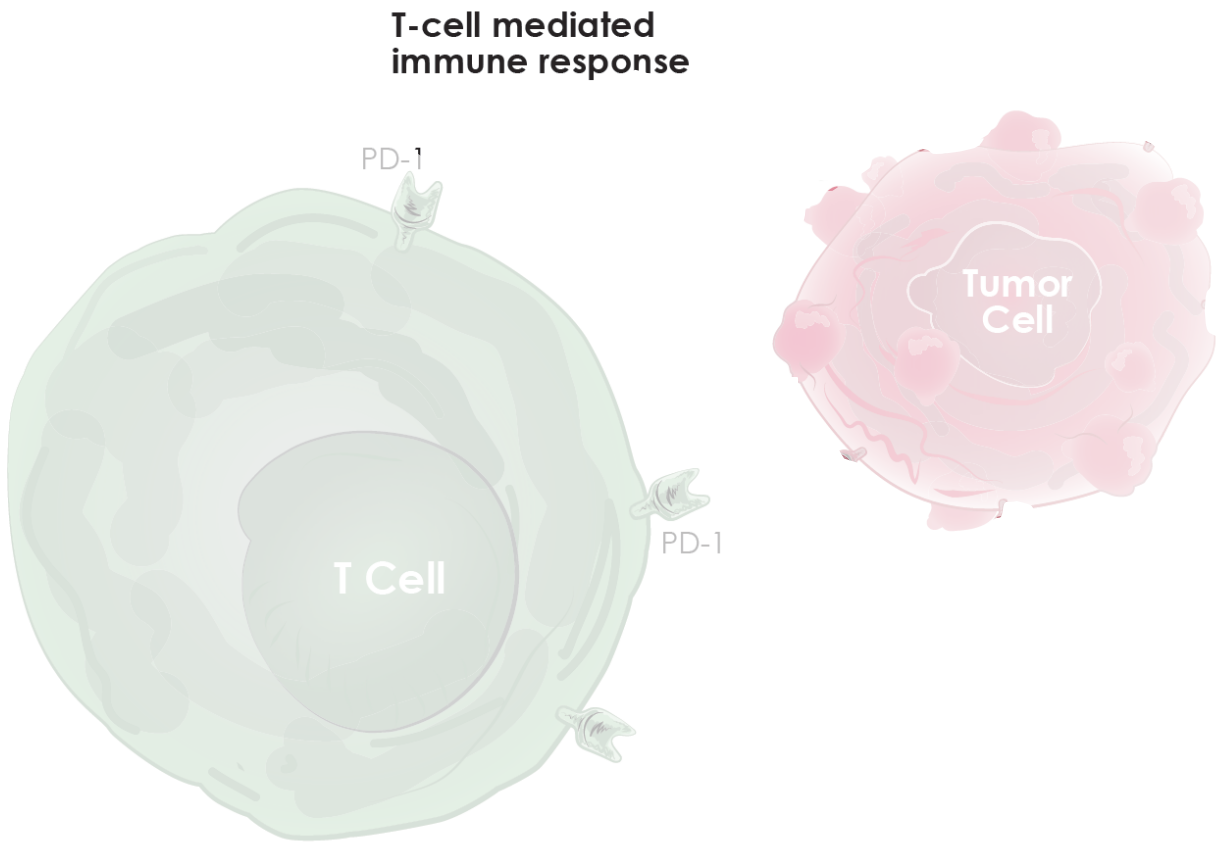
Cancer Immunotherapy Program



Better Science, Better Treatments, Better Future

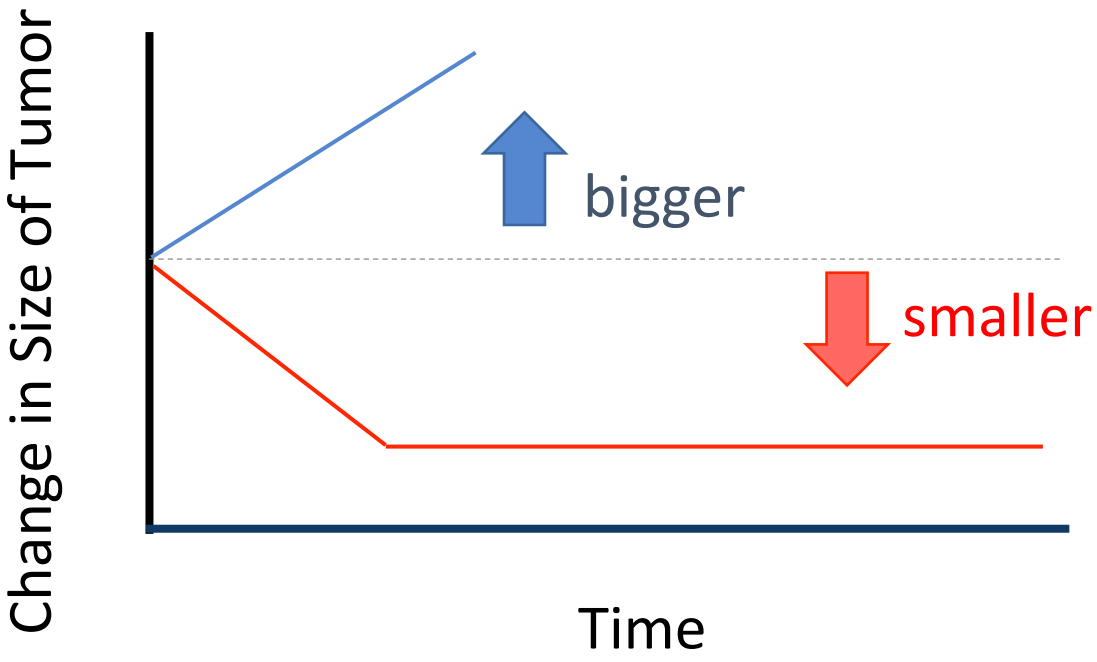
FIRST IN
HUMAN

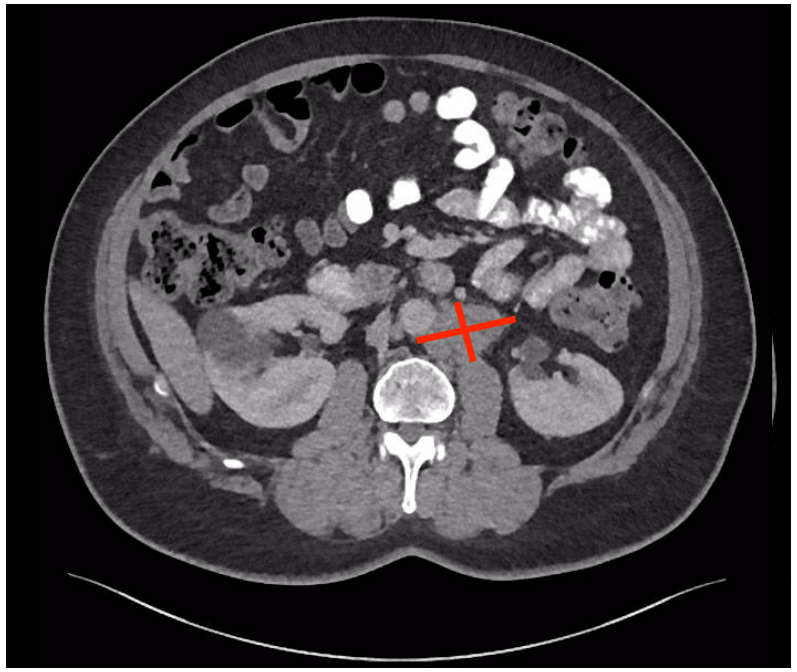
Importance of PD-1/PD-L1 blockade

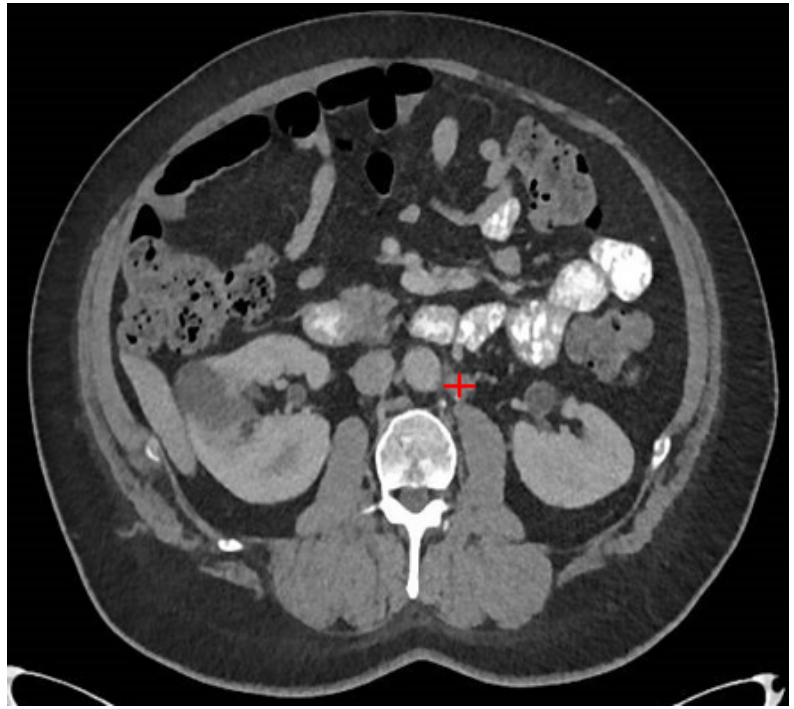


NIH. News Headlines: https://ccr.cancer.gov/news/article/investigators-lead-first-human-trials-of-new-immunotherapy-drug (accessed August 2017)

Spider Plot

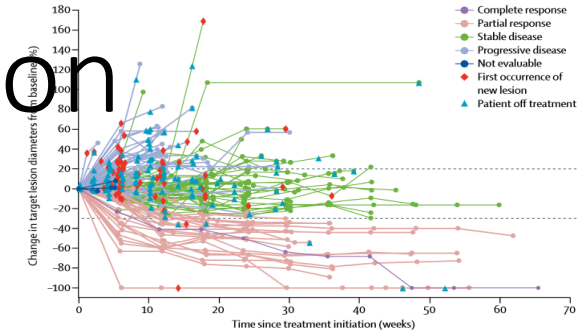




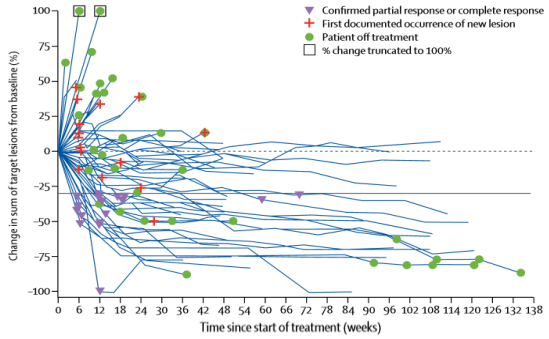


PD-1/PD-L1 inhibition

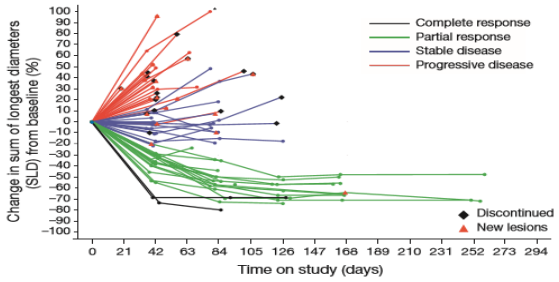
Rapid, deep, durable responses
Across a wide range of tumours
Seen in a subset of patients



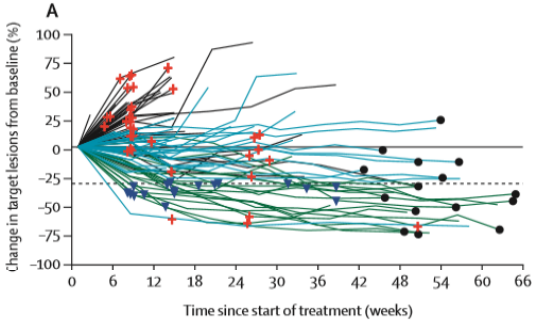
NSCLC: avelumab
Gulley JL et al. Lancet Oncol 2017



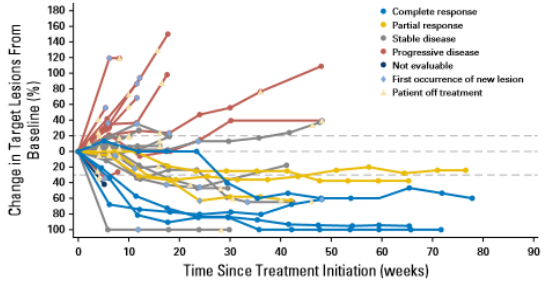
MSI hi CRC: nivolumab
Overman MJ et al. Lancet Oncol 2017



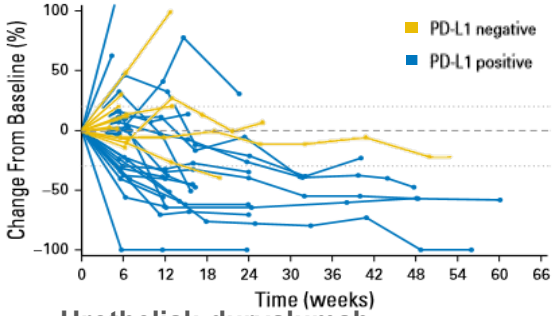
Urothelial: atezolizumab
Powles T et al. Nature 2014



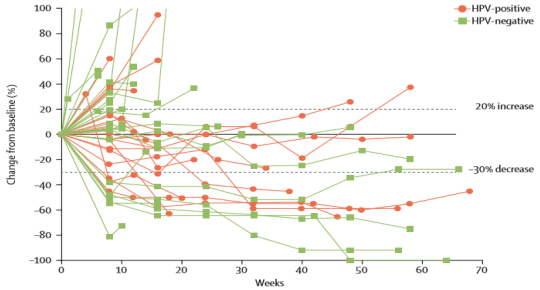
NSCLC (squamous only): nivolumab
Rizvi NA et al. Lancet Oncol 2015



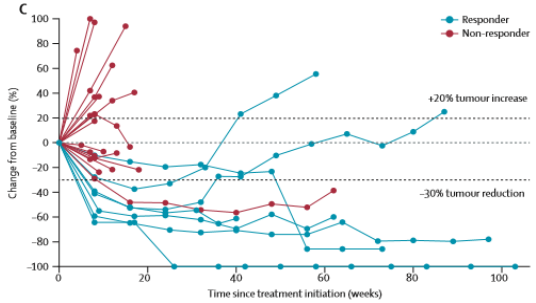
Urothelial: avelumab
Apolo AB et al. J Clin Oncol 2017



Urothelial: durvalumab
Massard C et al. JCO 2016

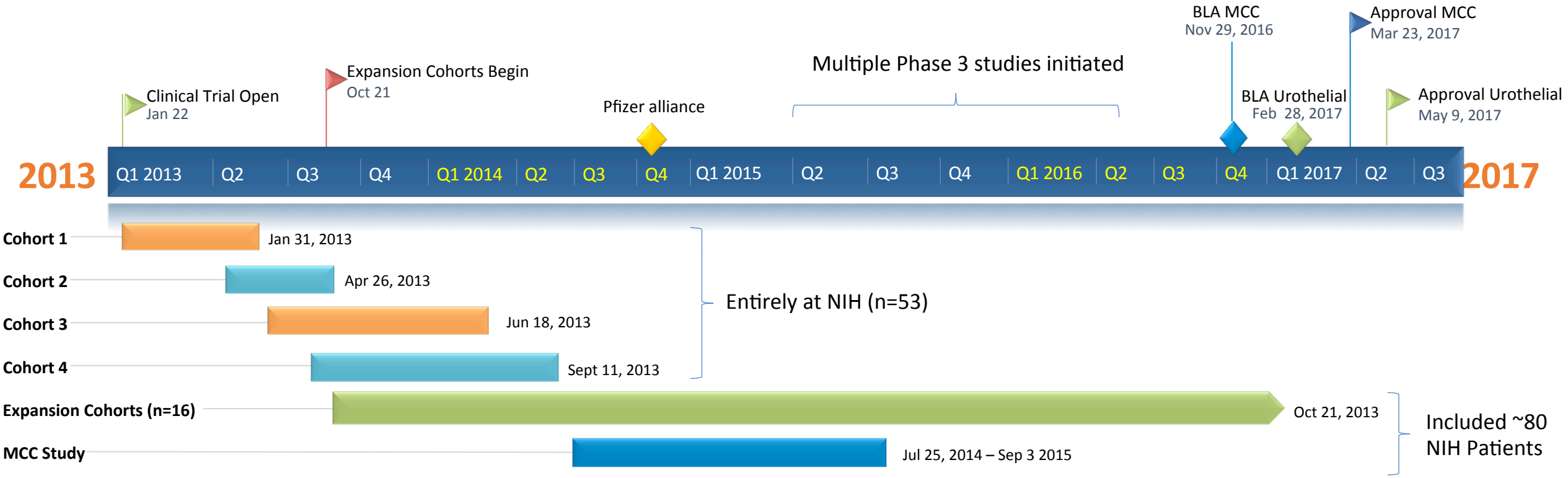


HNSCC: pembrolizumab
Seiwert TY et al. Lancet Oncol 2016



Urothelial: pembrolizumab
Plimack ER P et al. Lancet Oncol 2017

Avelumab Clinical Trial Timeline



Bavencio

Time from first patient enrolled to approval 4 yr, 1 month, 21 days

Because of CRADA, study started at NIH and recommended Phase 2 dose established prior to any outside contract finalized

Also allowed in-depth cutting edge analysis of immune cell subsets at NIH

Led to first agent ever approved for MCC

Treatment-related TEAEs

Event*, n (%) (n=600)	Most common any TEAE, all grades	Treatment-related TEAEs, all grades	Any TEAEs, grade ≥3	Treatment-related TEAEs, grade ≥3
Any event	559 (93.2)	405 (67.5)	266 (44.3)	68 (11.3)
Fatigue	175 (29.2)	110 (18.3)	7 (1.2)	5 (0.8)
Infusion-related reaction	83 (13.8)	81 (13.5)	5 (0.8)	5 (0.8)
Nausea	146(24.3)	68 (11.3)	6 (1.0)	1 (0.2)
Chills	61 (10.2)	44 (7.3)	0	0
Diarrhea	87 (14.5)	38 (6.3)	3 (0.5)	0
Pyrexia	64 (10.7)	35 (5.8)	1 (0.2)	0
Decreased appetite	91 (15.2)	33 (5.5)	1 (0.2)	1 (0.2)
Vomiting	95 (15.8)	30 (5.0)	10 (1.7)	2 (0.3)
Anemia	76 (12.7)	16 (2.7)	30 (5.0)	7 (1.2)

*Based on incidence criteria of ≥5% for treatment-related TEAEs and >1% for treatment-related grade ≥3 TEAEs

irAEs

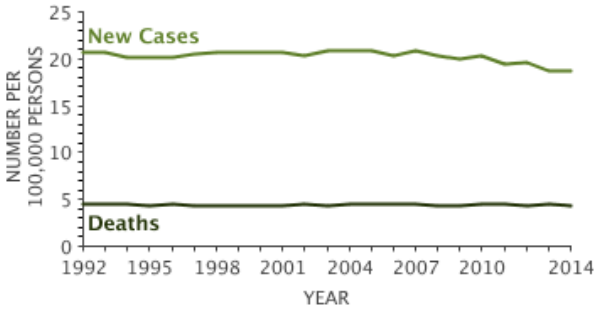
- AEs that were potentially immune-related were observed in 11.0% (66/600) of patients, with the most common being hypothyroidism

Events, n (%)	Immune-related AEs, n (%) (n=600)
Any event	66 (11.0)
Hypothyroidism	25 (4.2)
Arthritis	7 (1.2)
Pneumonitis	7 (1.2)

- Only IRR led to ≥1% of discontinuation events (n=12; 2.0%)

Bladder Cancer

Estimated New Cases in 2017	79,030
% of All New Cancer Cases	4.7%
Estimated Deaths in 2017	16,870
% of All Cancer Deaths	2.8%

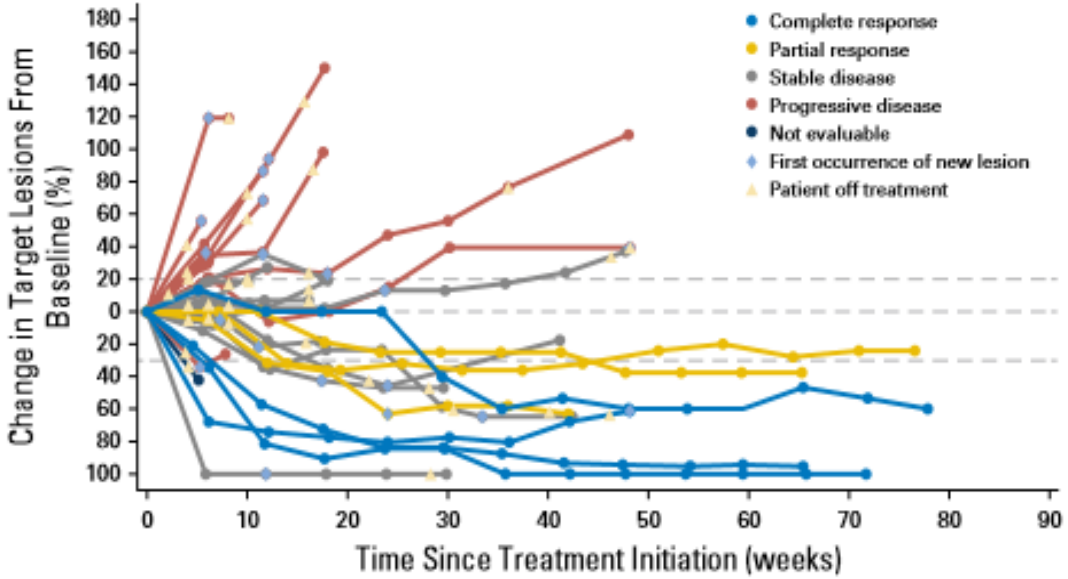


Percent Surviving 5 Years

77.3%

2007–2013

Urothelial (n = 44 → 249)



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ORIGINAL REPORT

Avelumab, an Anti–Programmed Death-Ligand 1 Antibody, In Patients With Refractory Metastatic Urothelial Carcinoma: Results From a Multicenter, Phase Ib Study

Andrea B. Apolo, Jeffrey R. Infante, Ani Balmanoukian, Manish R. Patel, Ding Wang, Karen Kelly, Anthony E. Mega, Carolyn D. Britten, Alain Ravaud, Alain C. Mita, Howard Safran, Thomas E. Stinchcombe, Marko Srdanov, Arnold B. Gelb, Michael Schlichting, Kevin Chin, and James L. Gulley

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ABSTRACT

Purpose
We assessed the safety and antitumor activity of avelumab, a fully human anti–programmed death-ligand 1 (PD-L1) IgG1 antibody, in patients with refractory metastatic urothelial carcinoma.

Methods
In this phase Ib, multicenter, expansion cohort, patients with urothelial carcinoma progressing after platinum-based chemotherapy and unselected for PD-L1 expression received avelumab 10 mg/kg intravenously every 2 weeks. The primary objectives were safety and tolerability. Secondary objectives included confirmed objective response rate (Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1), progression-free survival, overall survival (OS), and PD-L1–associated clinical activity. PD-L1 positivity was defined as expression by immunohistochemistry on ≥ 5% of tumor cells.

Results
Forty-four patients were treated with avelumab and followed for a median of 16.5 months (interquartile range, 15.8 to 16.7 months). The data cutoff was March 19, 2016. The most frequent treatment-related adverse events of any grade were fatigue/asthenia (31.8%), infusion-related reaction (20.5%), and nausea (11.4%). Grades 3 to 4 treatment-related adverse events occurred in three patients (6.8%) and included asthenia, AST elevation, creatine phosphokinase elevation, and decreased appetite. The confirmed objective response rate by independent central review was 18.2% (95% CI, 8.2% to 32.7%; five complete responses and three partial responses). The median duration of response was not reached (95% CI, 12.1 weeks to not estimable), and responses were ongoing in six patients (75.0%), including four of five complete responses. Seven of eight responding patients had PD-L1–positive tumors. The median progression-free survival was 11.6 weeks (95% CI, 6.1 to 17.4 weeks); the median OS was 13.7 months (95% CI, 8.5 months to not estimable), with a 12-month OS rate of 54.3% (95% CI, 37.9% to 68.1%).

Conclusion
Avelumab was well tolerated and associated with durable responses and prolonged survival in patients with refractory metastatic UC.

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INTRODUCTION

Urothelial carcinoma of the bladder is a leading cause of cancer deaths worldwide, with an estimated 429,800 new cases reported in 2012.[1] Patients with metastatic urothelial carcinoma are typically treated with cisplatin-based combination chemotherapy in the first-line setting, with a median overall survival (OS) of 14 to 15 months.[2,3] Prognostic factors associated with shorter OS include poor performance status, visceral metastasis, and low albumin or hemoglobin level.[4] Second-line chemotherapies, such as paclitaxel, pemetrexed, docetaxel, and vinflunine, have limited efficacy, with median survival of approximately 7 months.[5-8]

Immunotherapy with immune checkpoint inhibitors, particularly agents targeting the programmed death-ligand 1/programmed death-1 (PD-L1/PD-1) axis, has improved treatment outcomes in several tumor types.[9] Immunotherapy

ASSOCIATED CONTENT

See accompanying Oncology Grand Rounds on page 2109

Data Supplement
DOI: https://doi.org/10.1200/JCO.2016.71.6795

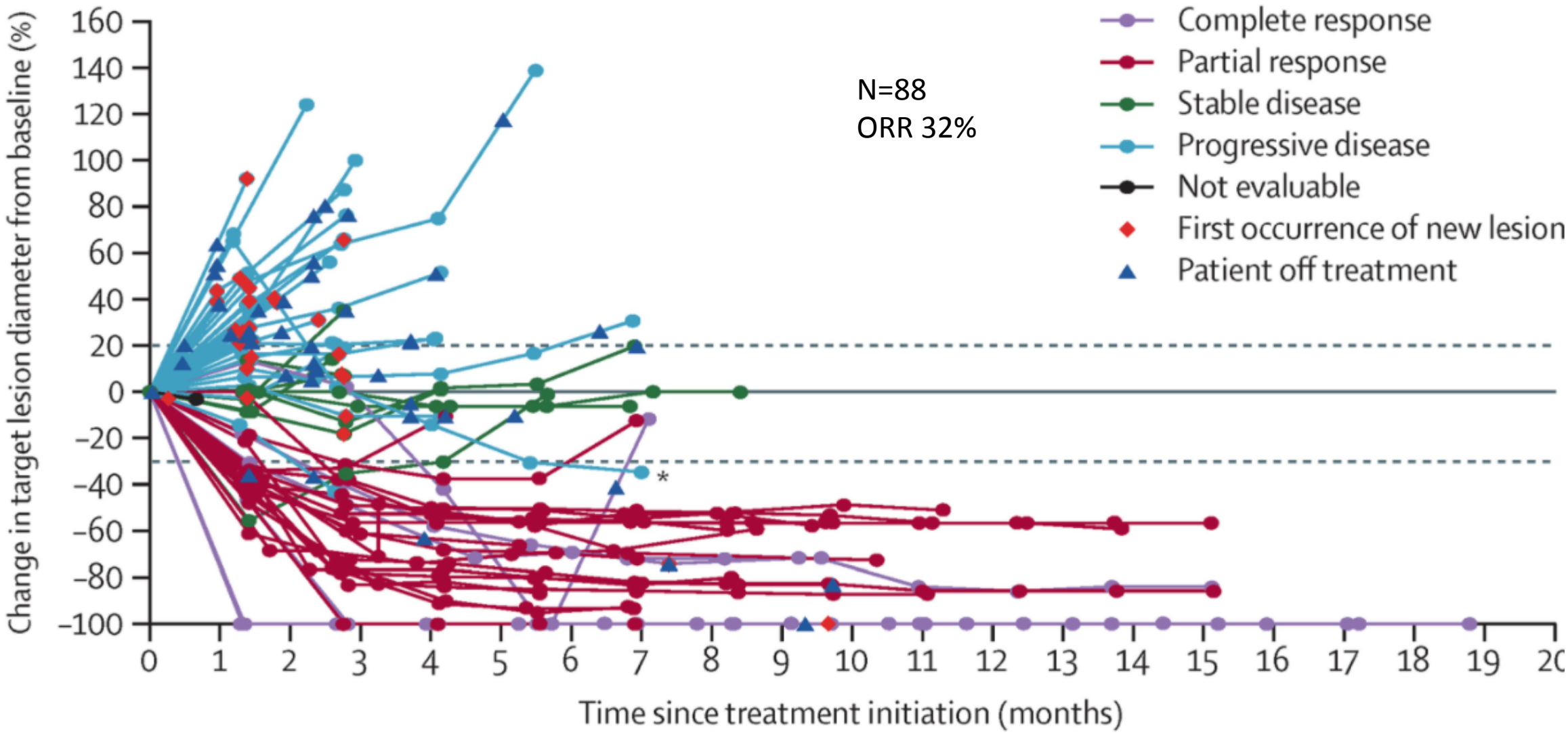
DOI: https://doi.org/10.1200/JCO.2016.71.6795

Merkel Cell

- Rare tumor (about 1,600 new cases a year in US)
- Sun exposed areas
  - Associated with MC virus or sun damage (mutations)
  - Typically has underlying immune recognition

Isaac Brownell, MD PhD

Merkel Cell



NIH NATIONAL CANCER INSTITUTE

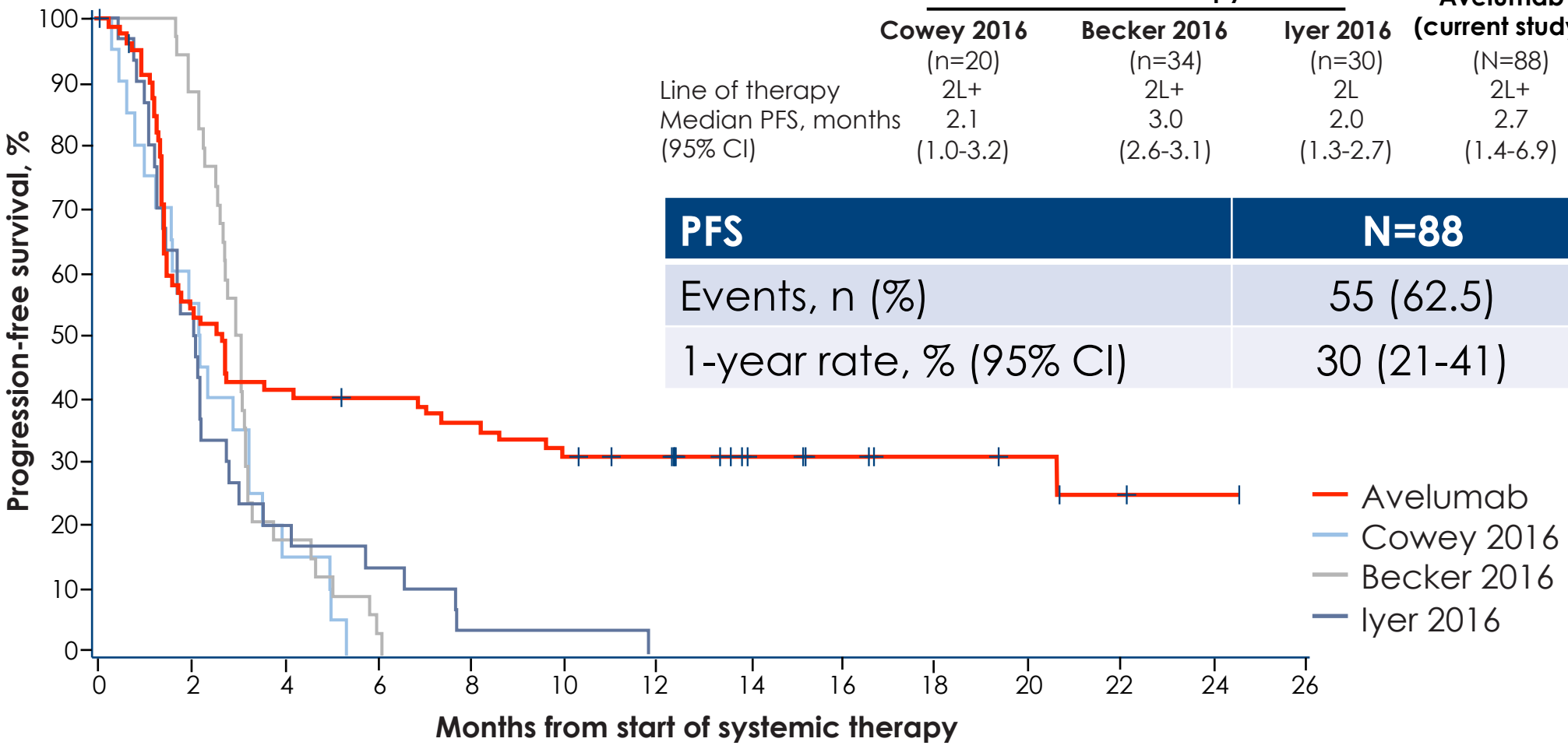
Kaufman et al, Lancet Oncology 201

PFS at ≥1 year of follow-up*

PFS with 2L+ treatment in distant mMCC[1-3]

	Chemotherapy			Avelumab (current study)
	Cowey 2016 (n=20)	**Becker 2016** (n=34)	**Iyer 2016** (n=30)	(N=88)
Line of therapy	2L+	2L+	2L	2L+
Median PFS, months (95% CI)	2.1 (1.0-3.2)	3.0 (2.6-3.1)	2.0 (1.3-2.7)	2.7 (1.4-6.9)

PFS	N=88
Events, n (%)	55 (62.5)
1-year rate, % (95% CI)	30 (21-41)



Number at risk 88 43 32 30 27 24 21 11 8 6 5 2 1 0

2L+, second line or later

* This figure is for illustrative purposes only and is not a direct head-to-head comparison.

1. Cowey CL, et al. Value Health. 2016;19(7):Abstract A717. 2. Becker J, et al. Ann Oncol. 2016;27(Suppl):Abstract 1154P. 3. Iyer JG, et al. Cancer Med. 2016;5(9):2294-301.

MCC patient

baseline

3 months

MCC patient

baseline

4 months

Cure from Within