Developing Novel Immunotherapeutic Cancer Treatments for Clinical Use

Oncology for Scientists
March 8th, 2016

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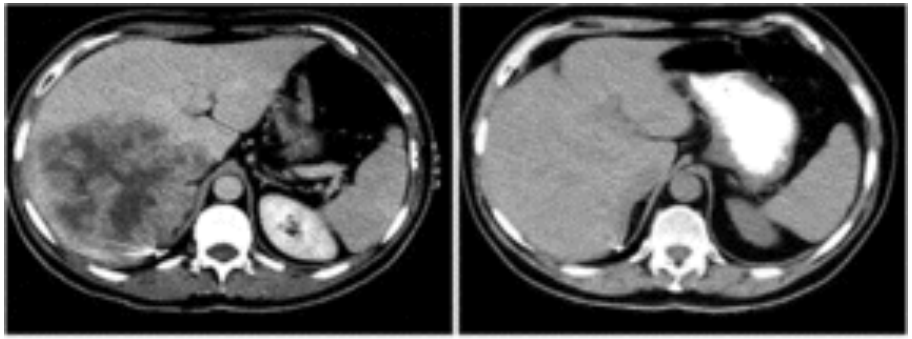
Disclosures

- Muhitch Laboratory Support:
  - Dendreon
  - Argos Therapeutics

Holy Grail of Tumor Immunity

Realized in 1987 in a subset of RCC and melanoma patients treated with HD IL-2

Rosenberg, S et al. *NEJM 1987*



Rosenberg, S. *J Immunol* 2014

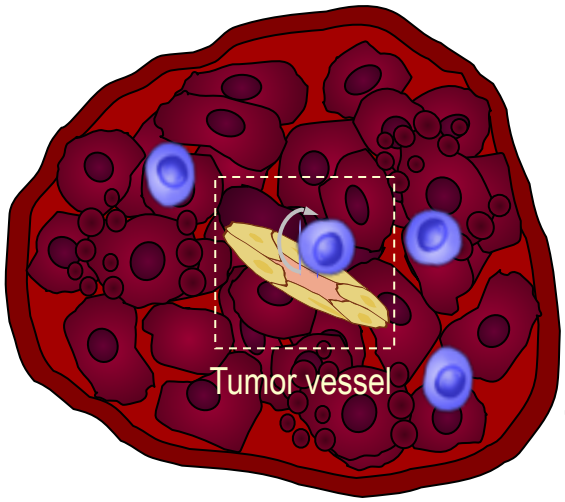
RCC and Melanoma are the most responsive to state-of-the-art (checkpoint blockade, DC, adoptive transfer) and traditional (IL-2) immunotherapy

Requirements for Effective Anti-Tumor Immune Responses

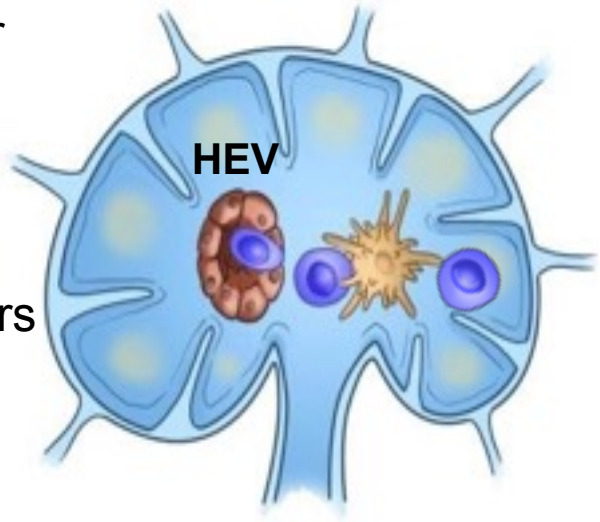
Tumor Ag
Soluble factors
Dendritic cells

Tumor

Draining Lymph Node



1. T cell recognition of tumor Ags presented by DC
2. T cell Activation
3. T cell infiltration into tumors
4. Lysis of tumor targets



Tumor cell destruction

CD8 effector T cells

T cell expansion

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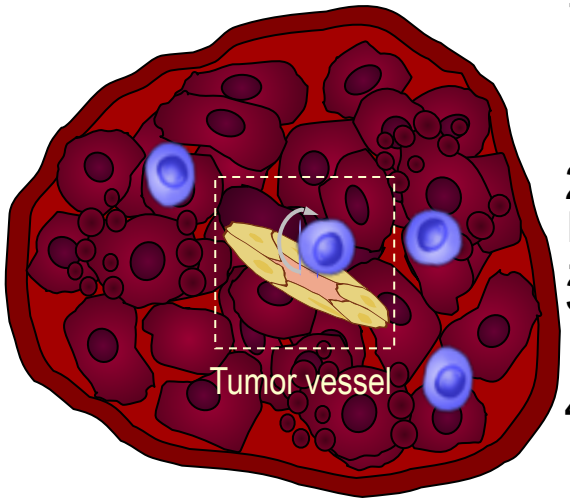

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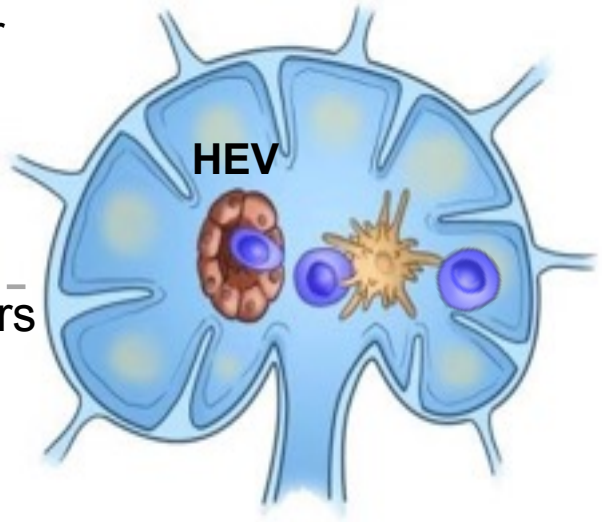

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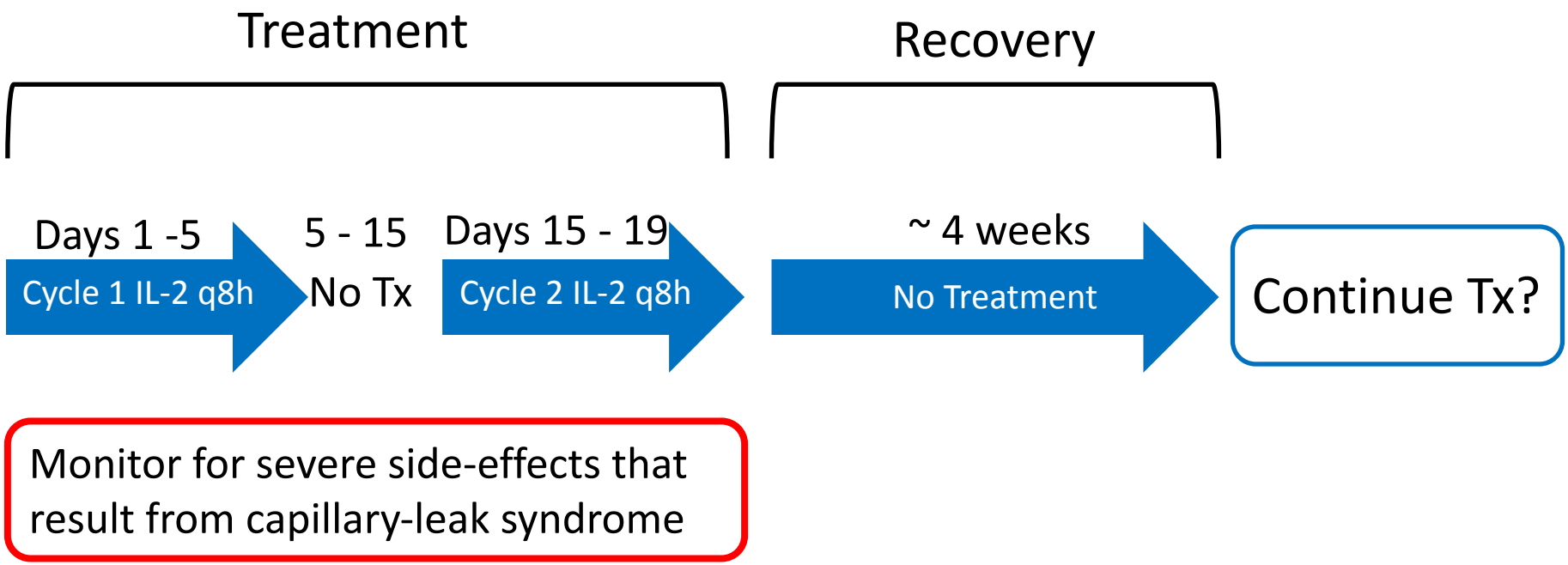
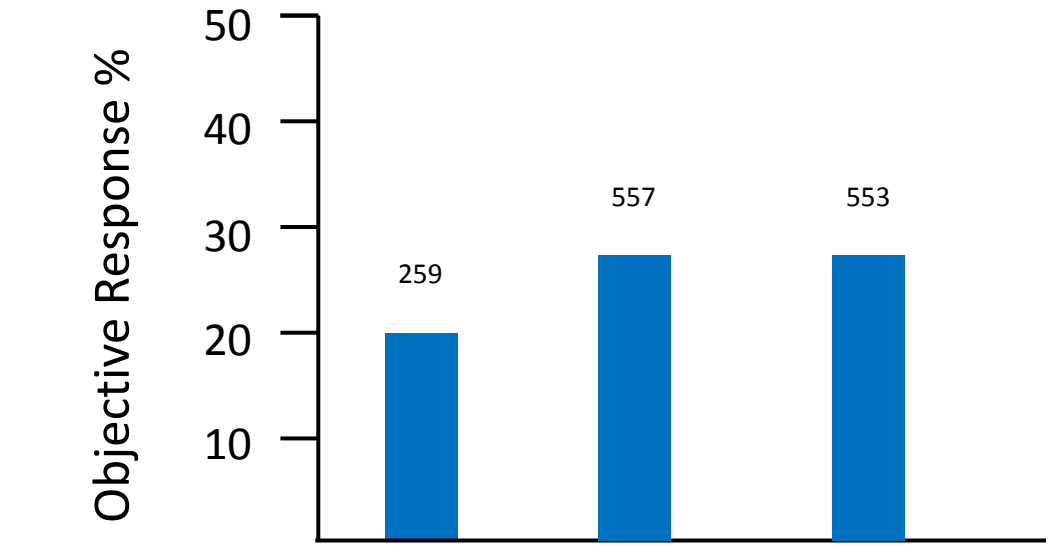
IL-2 Treatment Protocols



Comparison of Conventional Cytokine Therapy with Kinase Inhibitors for Treatment of Metastatic RCC

IL-2 has the greatest level of cytoxicity and patient management



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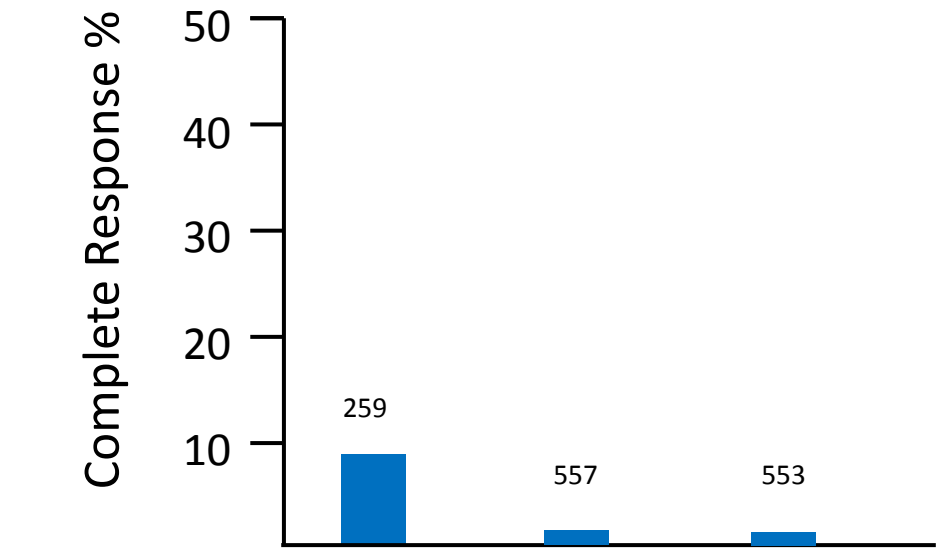


Removing a Tumor's Cloak of Invisibility: Overcoming Tumor Immunosuppression

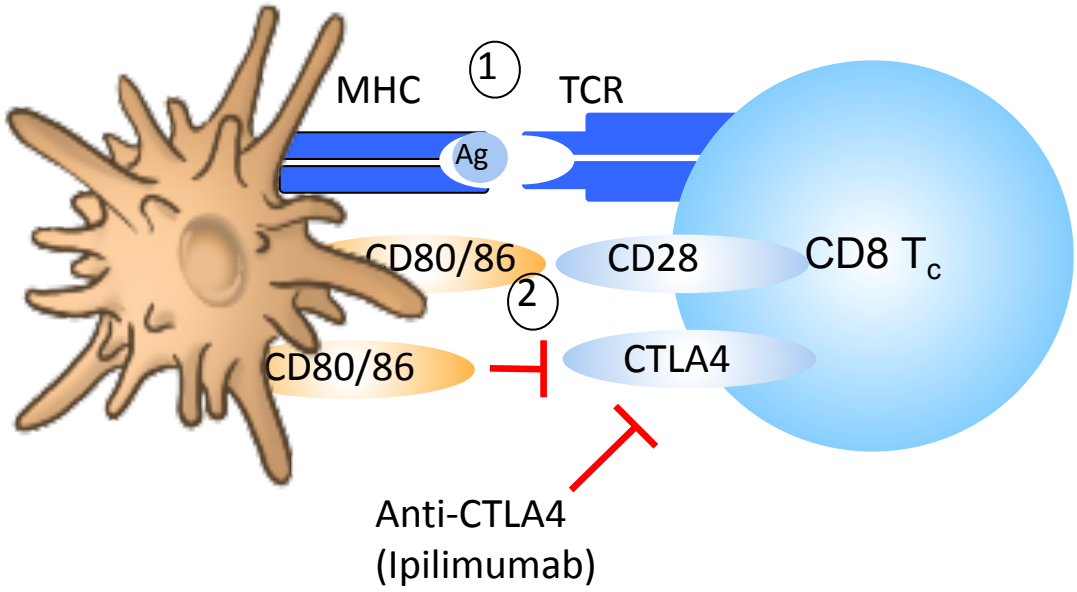
- Antibody immune-based therapeutics (3 of top 10 2013 experimental cancer drugs)
  - ✓ CTLA-4
    - Yervoy (Merck)
  - ✓ PD-1
    - Nivolumab (BMS-936558) (Bristol-Myers Squibb)
    - *Permbrolizumab née Lambrolizumab* (MK-3475)
  - ✓ PDL-1
    - *MPDL320A* (Roche, Genentech)

- Dendritic cell vaccinations

Improving T cell Activation Through CTLA-4 Inhibition

Yervoy (anti-CTLA-4, ipilimumab)

Bristol-Myers Squibb



Improving T cell Activation Through CTLA-4 Inhibition

Yervoy (anti-CTLA-4, ipilimumab)

Bristol-Myers Squibb

- Approved by FDA as first-line or second-line treatment for advanced melanoma.
- Blocks inhibitory signal for activated T cells.
- Enhances survival & durable responses (>2.5 y) in 15- 20% of patients.
- Response can be delayed.
- Associated with immune-mediated side effects.
  - Colitis
  - Dermatitis

Vanneman et al Nature Rev Canc 2012
Hodi et al NEJM 2010

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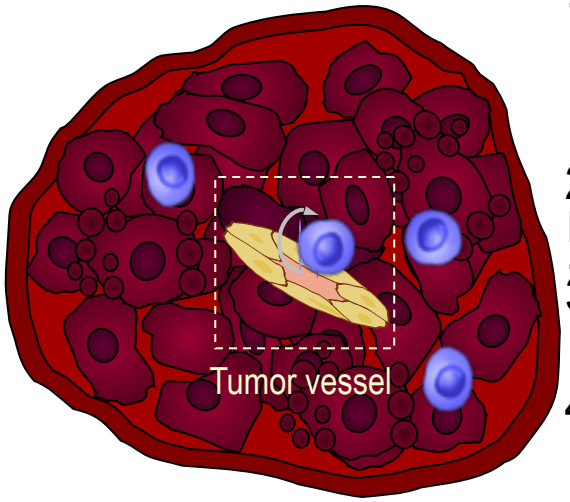

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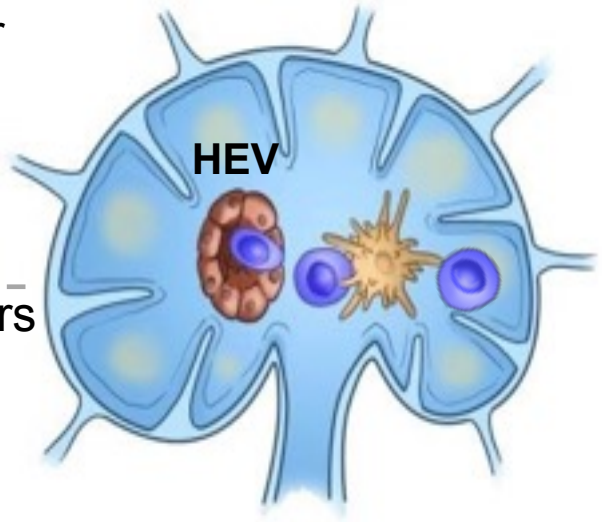
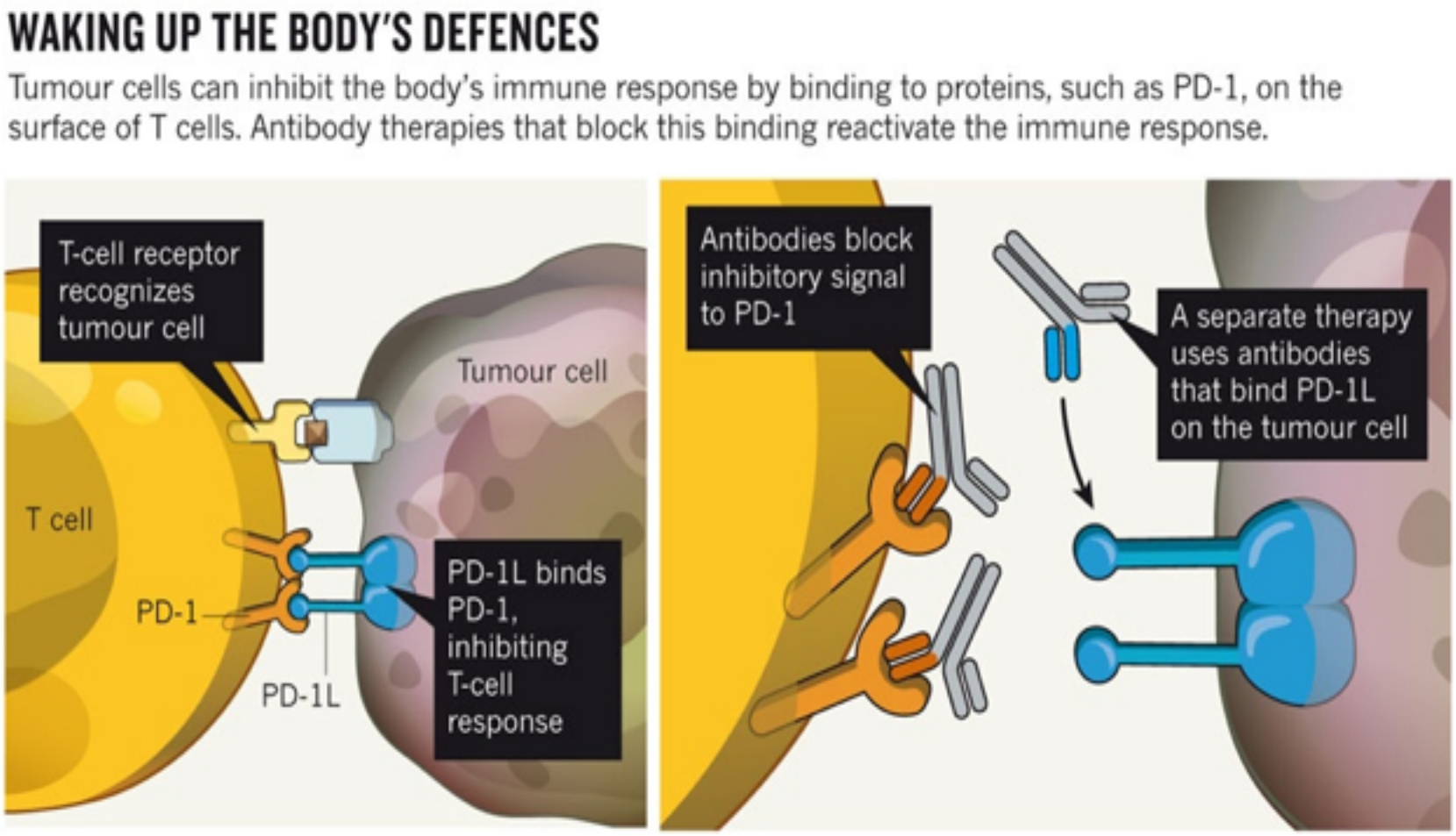


Tumor cell destruction

CD8 effector T cells

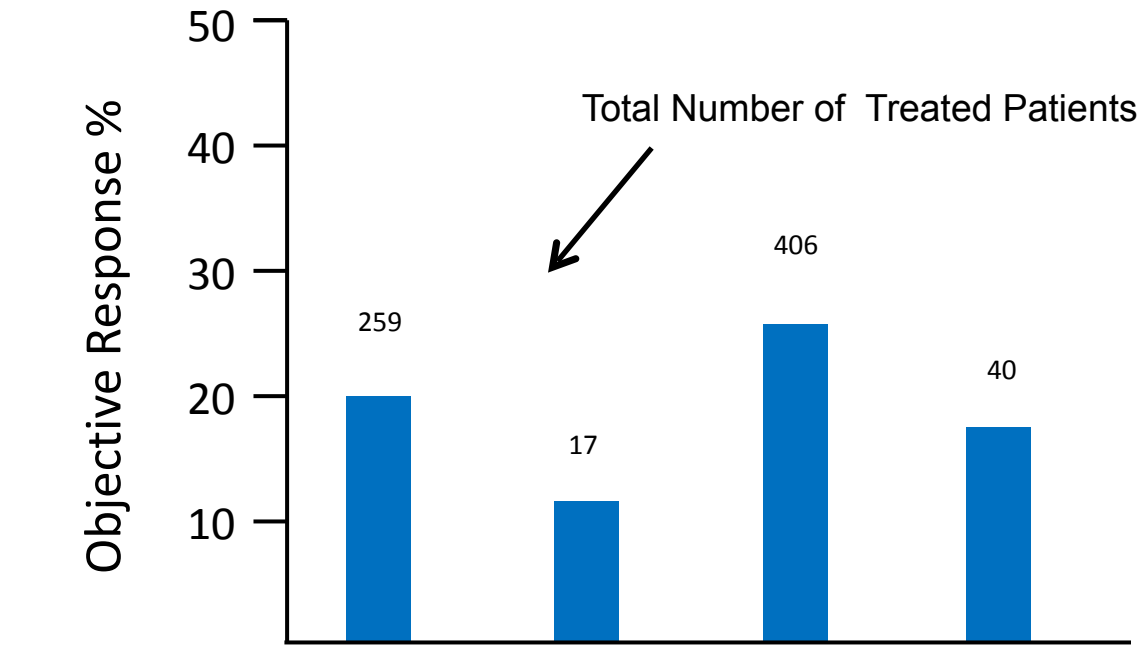
T cell expansion

Enhancing T cell Function within the Tumor Microenvironment through PD-1/PD-L1 Axis Blockade



Nature Medicine 18, 993 (2012)

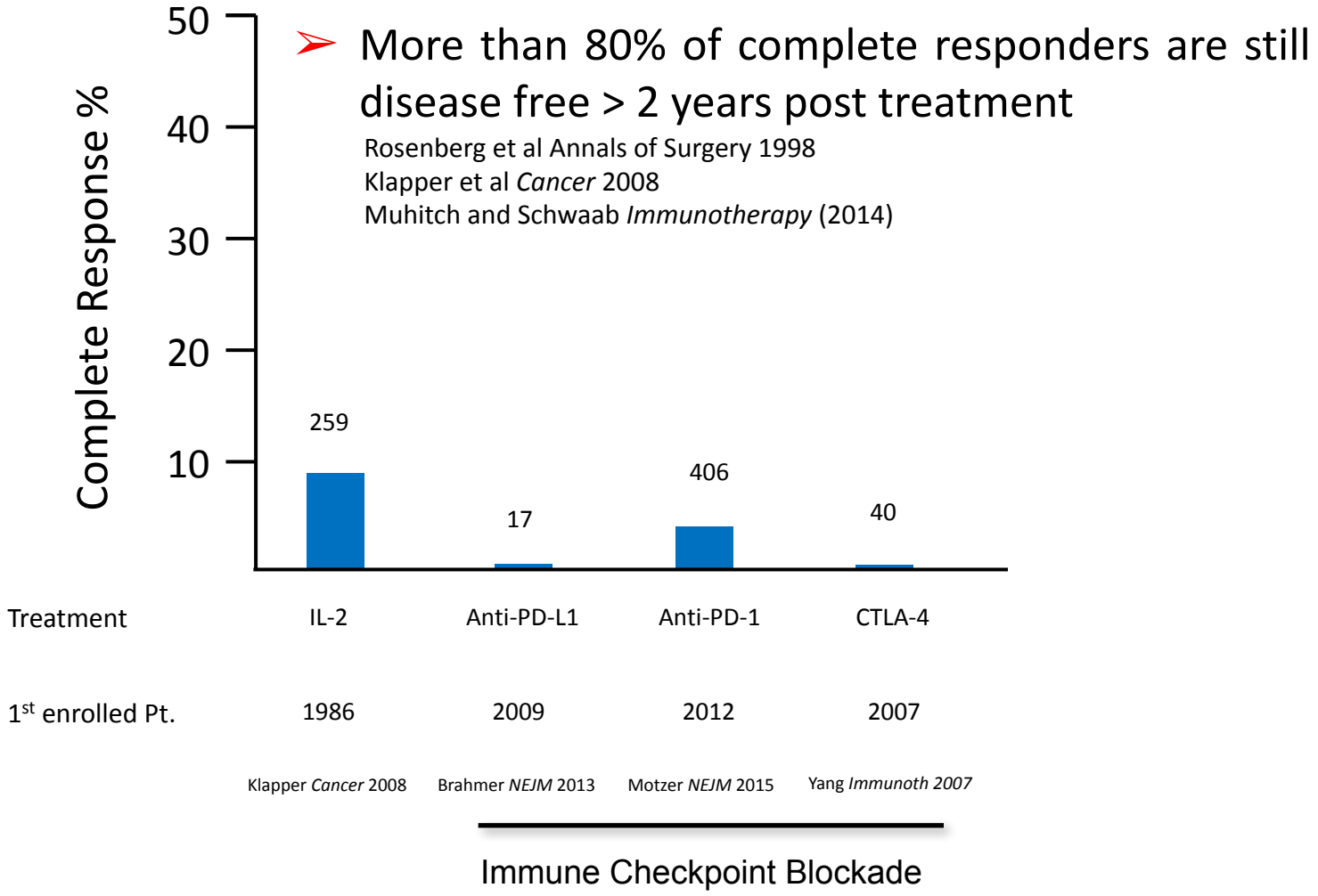
Comparison of Checkpoint Inhibitors for Treatment of Metastatic RCC



Treatment	IL-2	Anti-PD-L1	Anti-PD-1	CTLA-4
1st enrolled Pt.	1986	2009	2012	2007
	Klapper *Cancer* 2008	Brahmer *NEJM* 2013	Motzer *NEJM* 2015	Yang *Immunoth 2007*

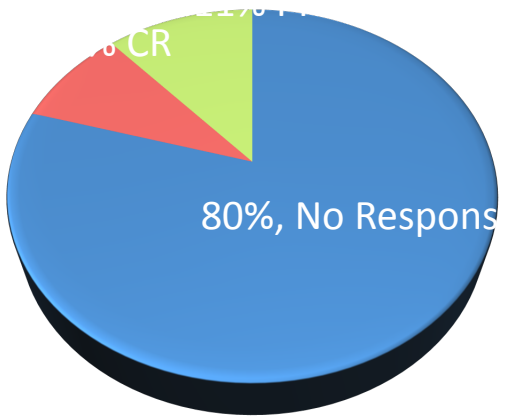
Immune Checkpoint Blockade

Comparison of Immunotherapy and Tyrosine Kinase Inhibitors for Treatment of Metastatic RCC



Improving Immunotherapy Through Combinatorial Approaches and Patient Selection

- How can immune-based treatments be improved to obtain > 20 - 30% response?
- Can responding patients be identified prior to therapy?



Multiple Obstacles Must be Overcome for Effective Anti-Tumor Immunity

Targeted by anti-CTLA-4

* Targeted by anti-PD-1/PD-L1

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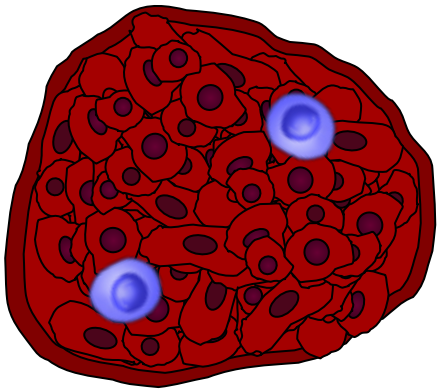
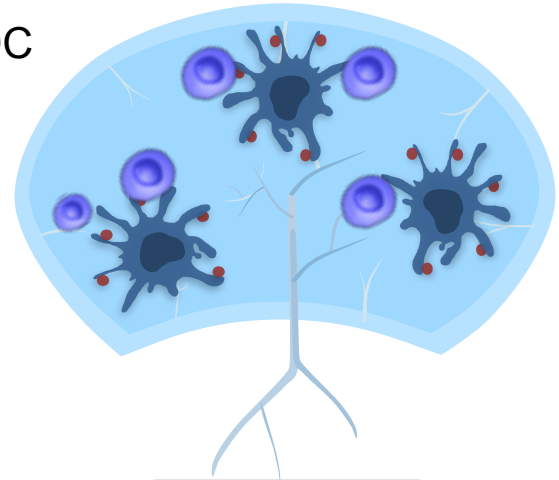
Tumor



Draining Lymph Node



1. T cell recognition of tumor antigens (Ag) presented by DC
2. T cell Activation#
3. T cell infiltration into lymph nodes & tumors
4. Lysis of Ag^+ tumor targets*

Tumor cell destruction

T cell expansion

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Improved Responses To Combined Immune Checkpoint Blockade Treatment (CTLA-4 + PD-1) in Melanoma

Table 3. Clinical Activity in Patients Who Received the Concurrent Regimen.

Cohort No.	Dose	Patients with a Response*	Response				Stable Disease for ≥24 Wk	Immune-Related Stable Disease for ≥24 Wk†	Objective-Response Rate (95% CI)‡	Aggregate Clinical-Activity Rate (95% CI)§	≥80% Tumor Reduction at 12 Wk
			Complete	Partial	Unconfirmed Partial¶	Immune-Related Partial†					
	mg/kg		no.						%		no. (%)
1	Nivolumab, 0.3; ipilimumab, 3	14	1	2	0	2	2	0	21 (5–51)	50 (23–77)	4 (29)
2	Nivolumab, 1; ipilimumab, 3	17	3	6	0	0	0	2	53 (28–77)	65 (38–86)	7 (41)‖
2a	Nivolumab, 3; ipilimumab, 1	15	1	5	2	1	2	0	40 (16–68)	73 (45–92)	5 (33)
3	Nivolumab, 3; ipilimumab, 3	6	0	3	0	1	0	1	50 (12–88)	83 (36–100)	0
All	—	52	5	16	2	4	4	3	40 (27–55)	65 (51–78)	16 (31)

* Data are for patients who had a response that could be evaluated, defined as patients who received at least one dose of study therapy, had measurable disease at baseline, and had one of the following: at least one tumor evaluation during treatment, clinical progression of disease, or death before the first tumor evaluation during treatment.

† Data include patients who had a reduction in the target tumor lesion in the presence of new lesions, which was consistent with an immune-related partial response or stable disease.[11]

‡ The objective-response rate was calculated as the number of patients with either a complete response or a partial response, divided by the number of patients with a response that could be evaluated, times 100. Unconfirmed or immune-related responses were not included in this calculation. Confidence intervals (CIs) were estimated by the Clopper–Pearson method.

§ The aggregate clinical-activity rate was calculated as the number of patients with a complete response, a partial response, an unconfirmed complete response, an unconfirmed partial response, an immune-related partial response, stable disease for at least 24 weeks, or immune-related stable disease for at least 24 weeks, divided by the number of patients with a response that could be evaluated, times 100.

¶ Data include patients who had a partial response after one tumor assessment but did not have sufficient follow-up time for confirmation of the initial partial response.

‖ Two additional patients in cohort 2 had tumor reduction of 80% or more at their first scheduled assessment, which was conducted after week 12.

Wolchok JD et al. N Engl J Med 2013;369:122-133

Boosting Tumor Immune Responses

- Antibody immune-based therapeutics (3 of top 10 experimental cancer drugs)
  - ✓ CTLA-4
    - Yervoy (Merck)
  - ✓ PD-1
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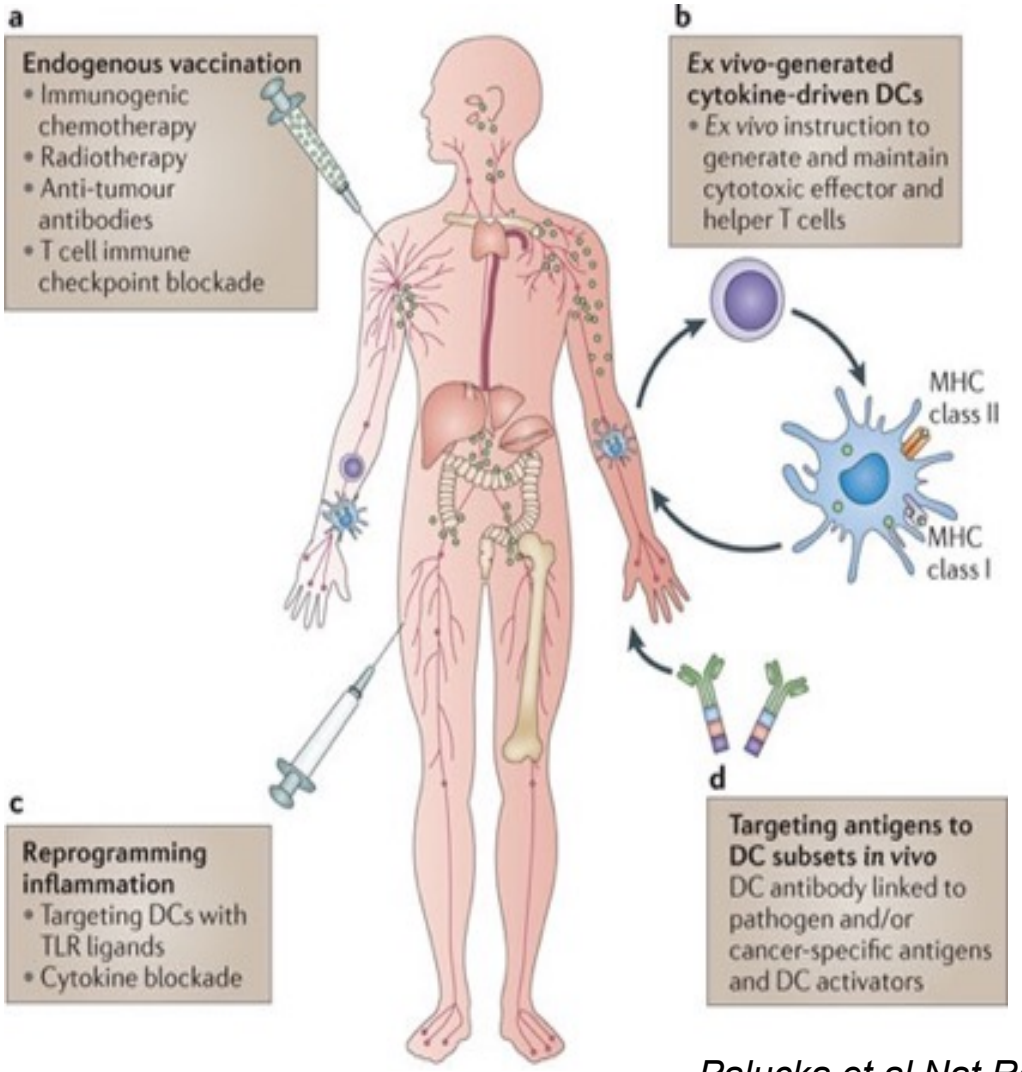
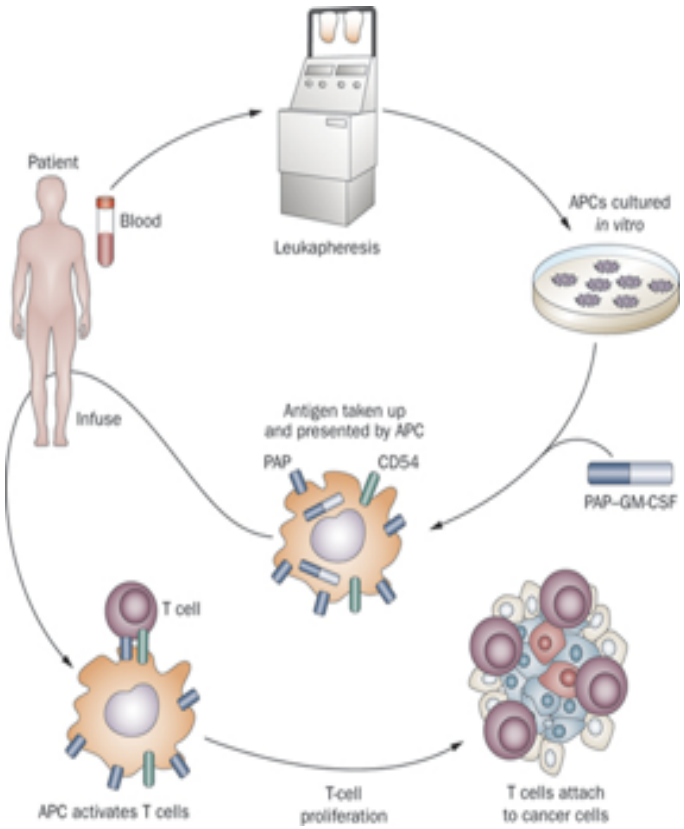
- Dendritic cell vaccinations

Dendritic Cell Vaccinations: Orchestrating Immune Responses from the Battleground



Palucka et al Nat Rev Cancer 2012

Sipuleucel-T

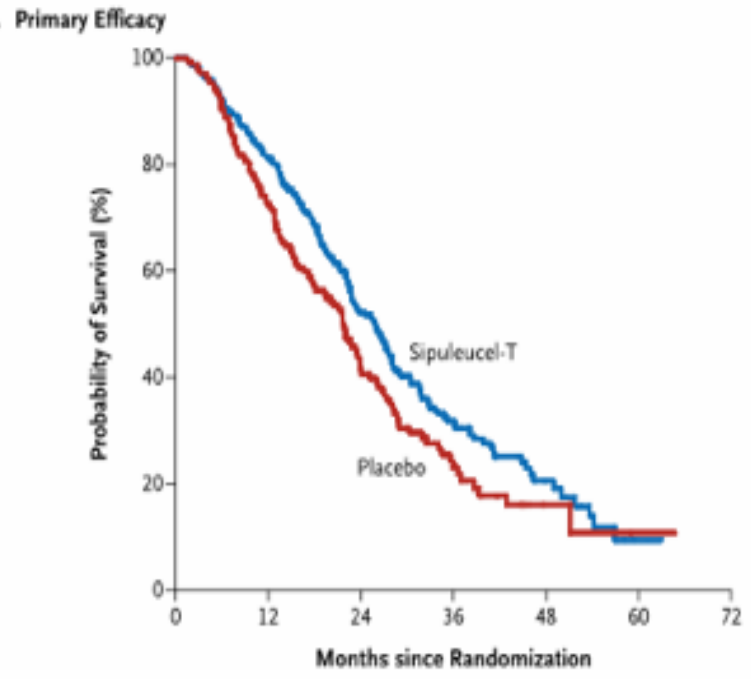


- **FDA approved** for treatment of metastatic castrate resistant prostate cancer
- Induces antibody and T cell responses against **a single antigen**
- Overall 4 month prolonged median survival benefit
- Few objective biological responses

Kantoff et al. N Engl J Med. 2010

Di Lorenzo Nature Reviews Clinical Oncology 2011

Sipuleucel-T



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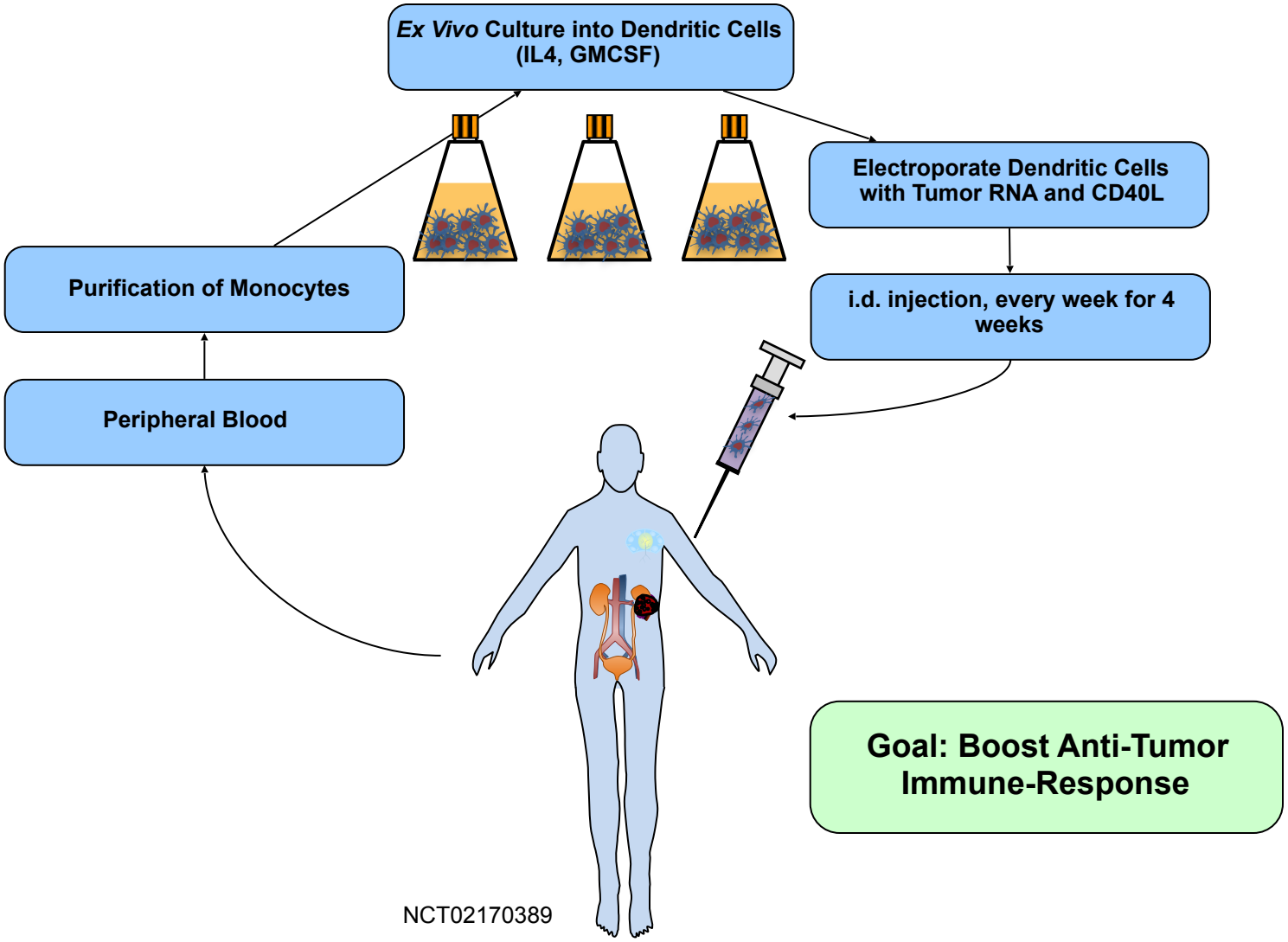
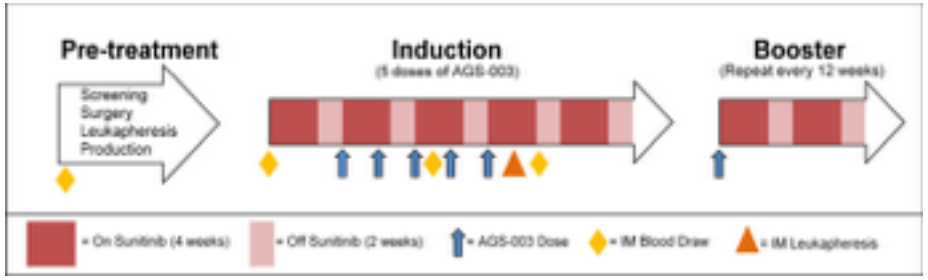
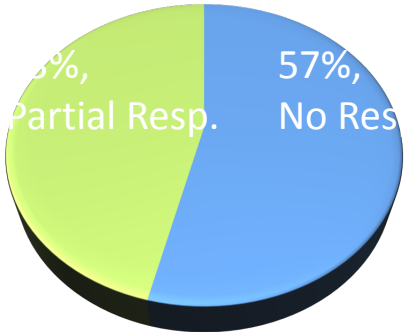
State-of-the-art Dendritic Cell Vaccination Utilizing Tumor RNA and Costimulation Signals (AGS-003)



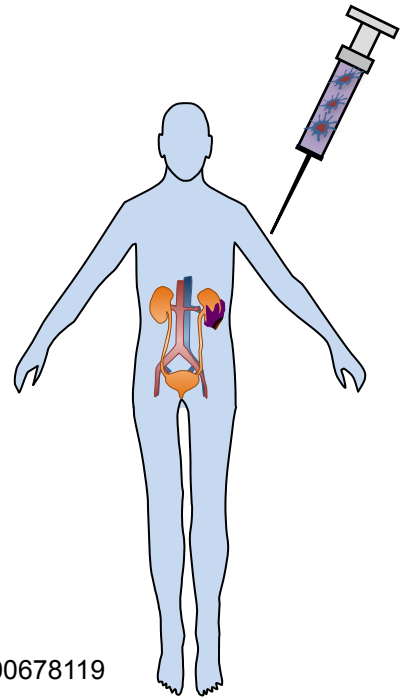
Dendritic Cell Vaccination (AGS-003) Combined with Sunitinib Treatment Extends Long-Term Survival in mRCC



Amin et al Journal for ImmunoTherapy of Cancer 2015

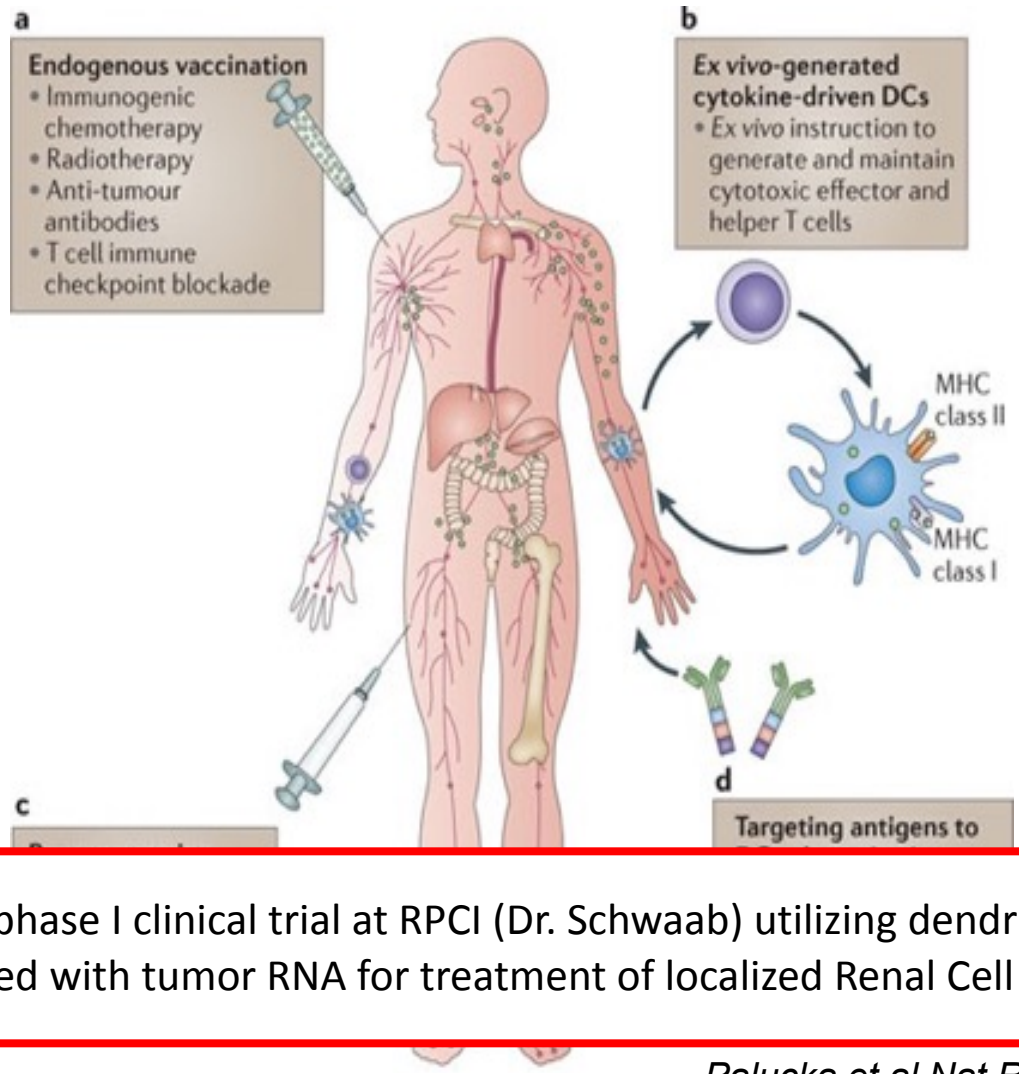


Median OS from registration 30.2 months for all patients



NCT00678119

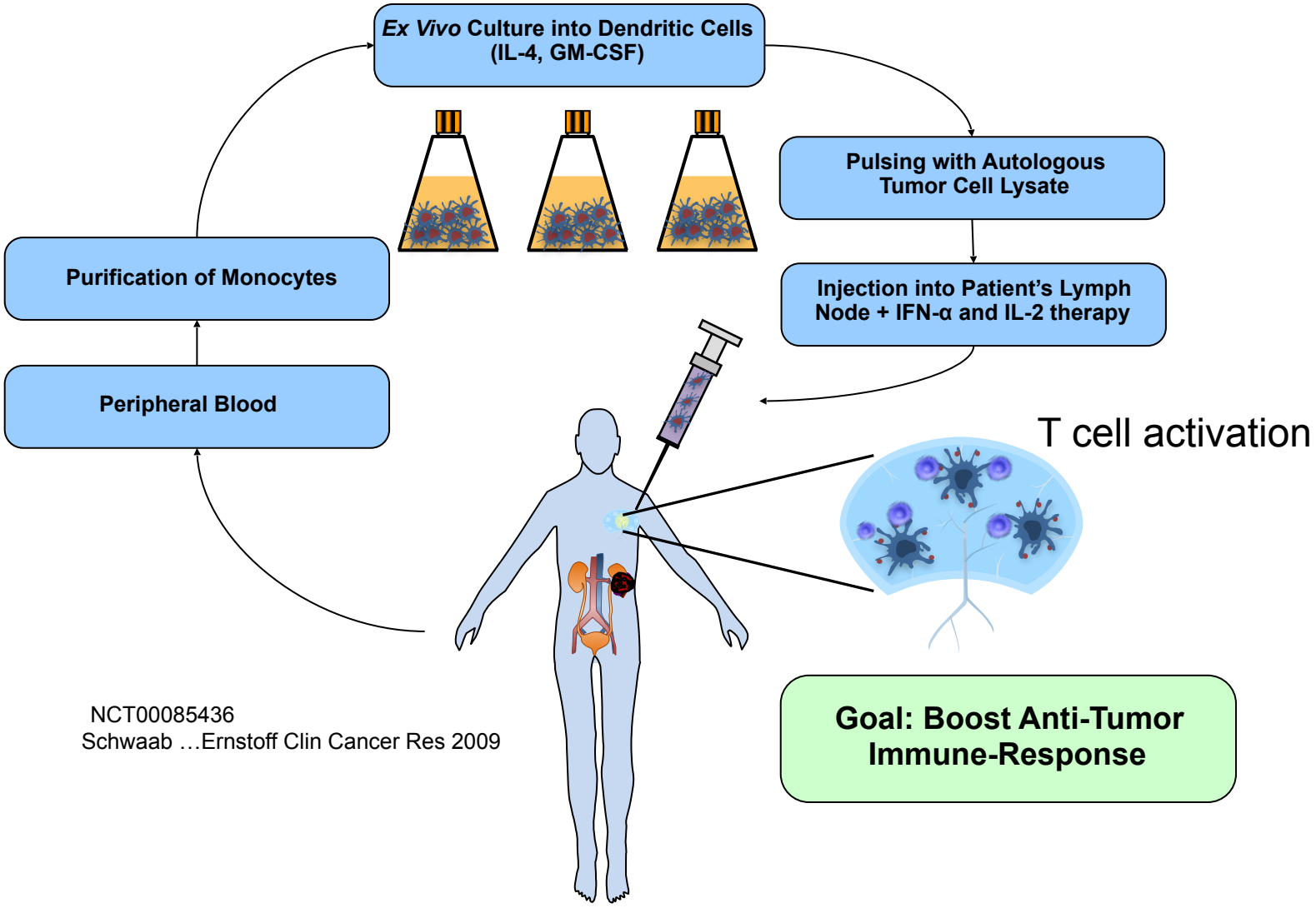
Dendritic Cell Vaccinations: Orchestrating Immune Responses from the Battleground



Ongoing phase I clinical trial at RPCI (Dr. Schwaab) utilizing dendritic cells electroporated with tumor RNA for treatment of localized Renal Cell Carcinoma

Palucka et al Nat Rev Cancer 2012

Combining Cytokine and Dendritic Cell Vaccination to Improve Patient Responses



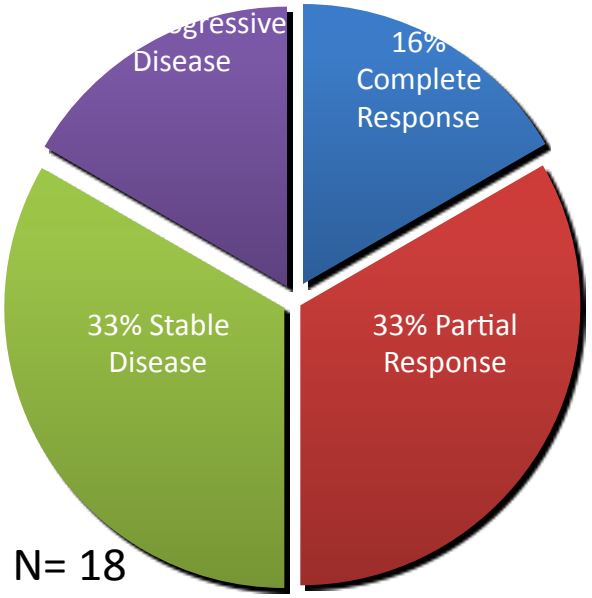
NCT00085436
Schwaab …Ernstoff Clin Cancer Res 2009

Heterogeneous Patient Responses to DC Vaccination

Clinical and Immunologic Effects of Intranodal Autologous Tumor Lysate-Dendritic Cell Vaccine with Aldesleukin (Interleukin 2) and IFN-α2a Therapy in Metastatic Renal Cell Carcinoma Patients

Thomas Schwaab, Adrian Schwarzer, Benita Wolf, et al.

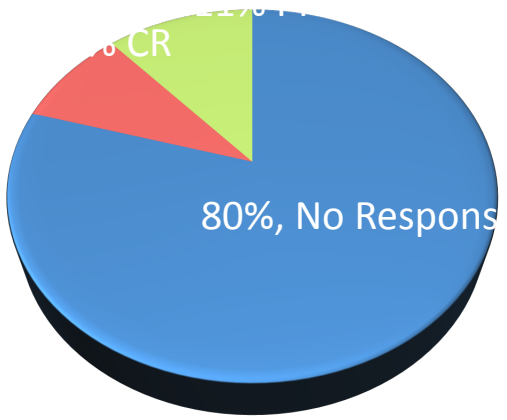
Clin Cancer Res 2009



Complete Response	Disappearance of all measurable tumors for more than 4 weeks
Partial Response	>30% tumor size reduction of all lesions
Stable Disease	<30% tumor size reduction and <20% tumor size increase
Progressive Disease:	>20% tumor size increase or appearance of new lesions

Improving Dendritic Cell Vaccines Through Combinatorial Approaches and Patient Selection

- How can immune-based treatments be improved to obtain > 20 - 30% response?
  - ✓ Improve and combine immune-based treatments:
    - Dendritic Cell Vaccination + IL-2
    - Anti-CTLA-4 + anti-PD-1
- Can responding patients be identified prior to therapy?



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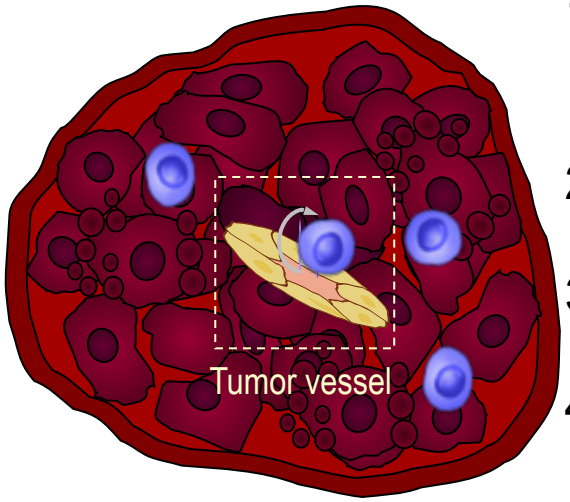

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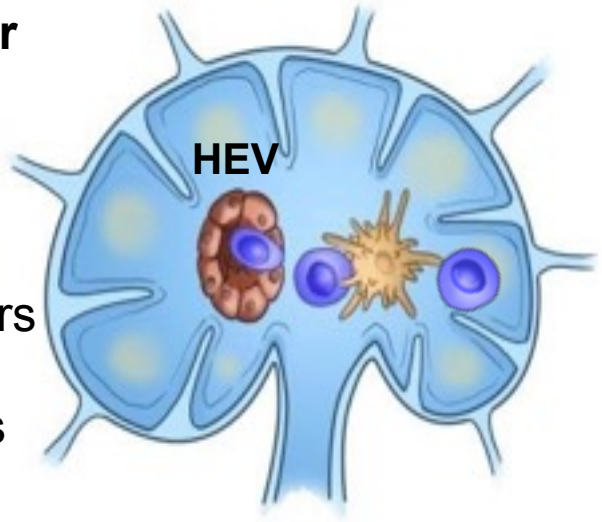
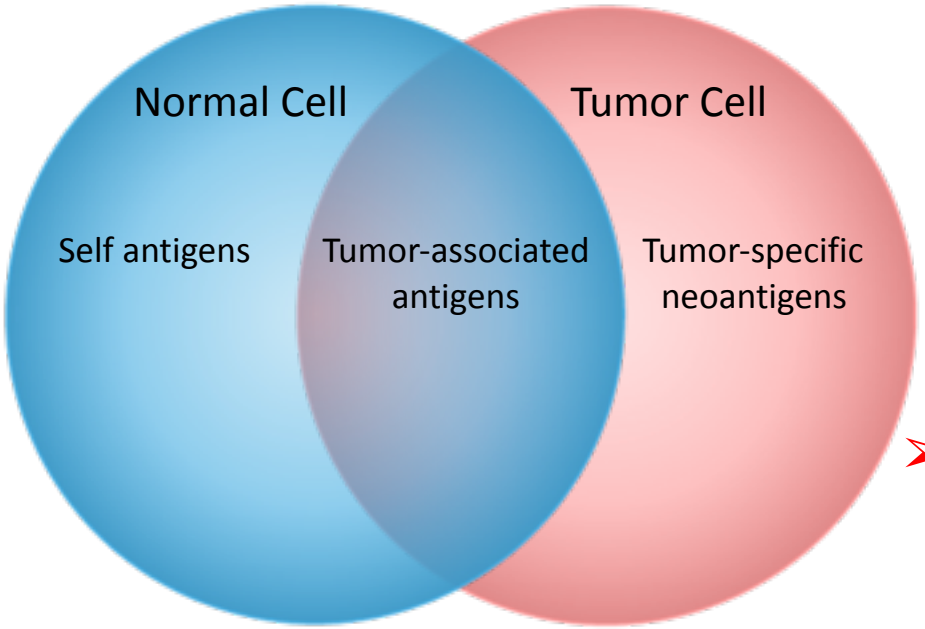


Tumor cell destruction

CD8 effector T cells

T cell expansion

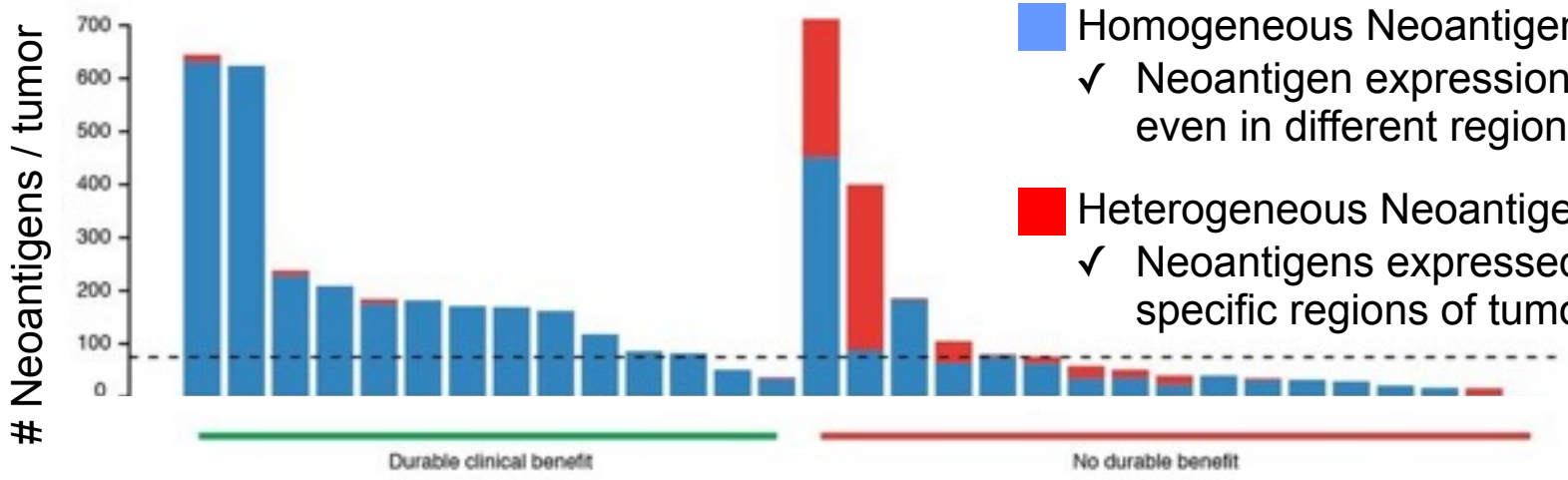
Immunogenic Antigens Represent Key Targets for Effector T cells



- Tumor-associated antigens
  - ✓ Increased expression in tumors with restricted expression in normal tissues
  - ✓ Shared expression, can be expressed in multiple tumor types as well as amongst multiple patients
  - ✓ Allows for broad treatment protocols that target tumor-associated antigens

- Neoantigens
  - ✓ Originate from mutations in the tumor microenvironment
  - ✓ Rarely shared/ expressed in different patients or tumor types
  - ✓ Likely to be more immunogenic due to higher frequency of circulating neoantigen-specific T cells

Neoantigen Expression in Non-small Cell Lung Cancer (NSCLC) Identifies Patients with a Clinical Benefit from PD-1 Treatment



Homogeneous Neoantigen Expression

✓ Neoantigen expression is consistent even in different regions of tumor

Heterogeneous Neoantigen Expression

✓ Neoantigens expressed only in specific regions of tumors

Adapted from McGranahan…Swanton et al. *Science 2016*

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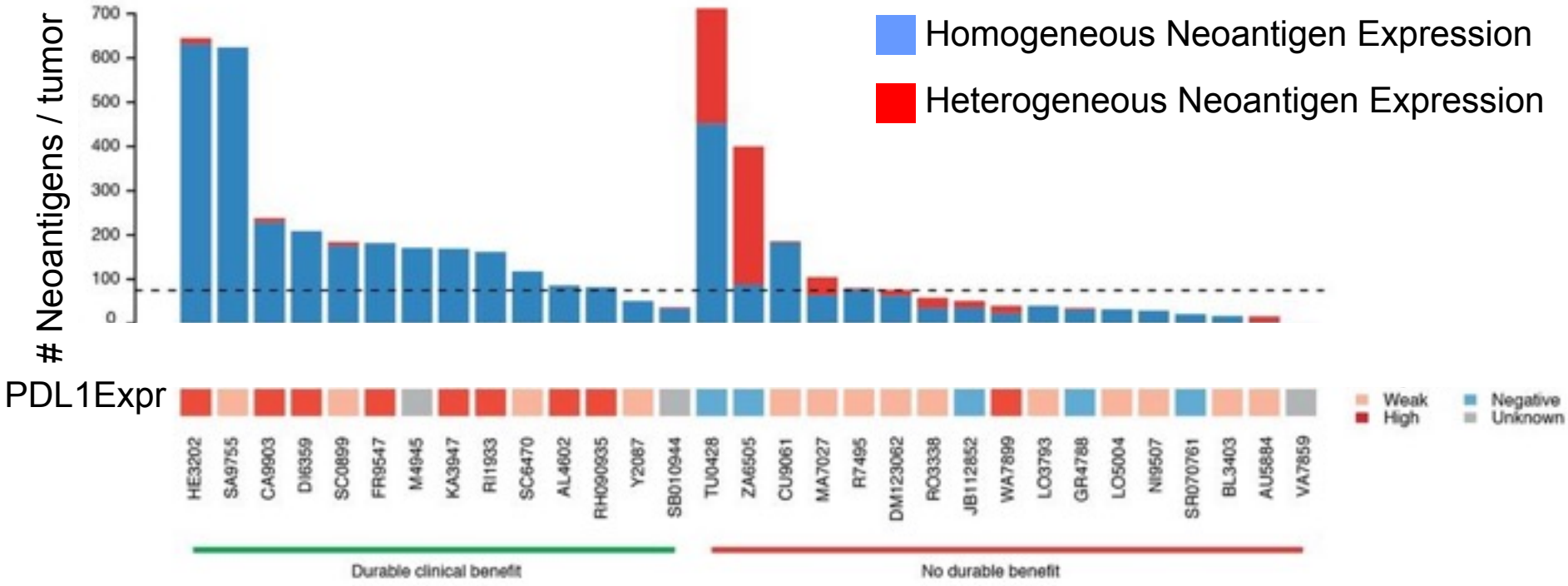
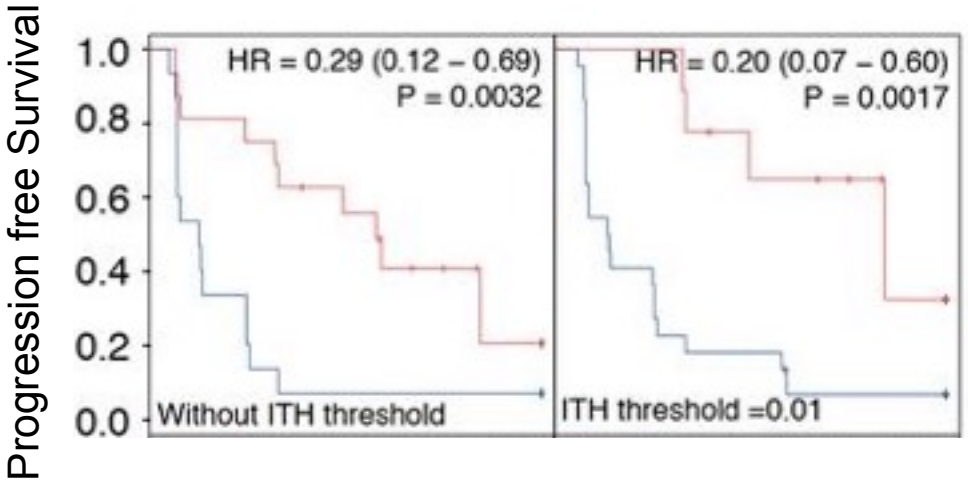


Adapted from McGranahan…Swanton et al. *Science 2016*

Clonal Neoantigen Expression in Tumors Identifies Patients with a Clinical Benefit from PD-1 Treatment



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- How can immune-based treatments be improved to obtain > 20 - 30% response?
  - ✓ Improve and combine immune-based treatments (IL-2, Intralymphatic injections) to attack multiple targets
- Can responding patients be identified prior to therapy?
  - ✓ Increased neoantigens identify patients likely to respond to checkpoint blockade