5th European Immunology Conference
Berlin, Germany July 21-23, 2016

Unmasking the masquerading cancer cells: have we made progress with the revival of immunotherapy?

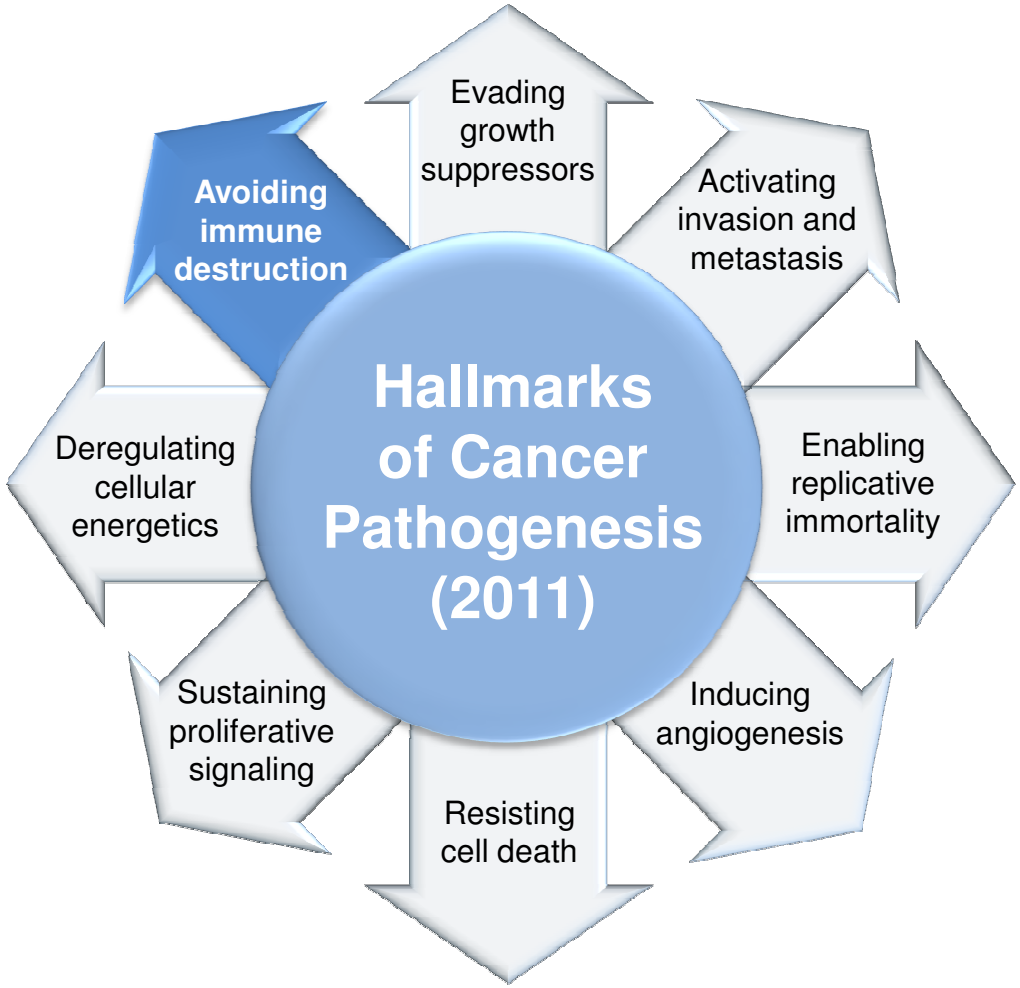
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dr_bhat2@yahoo.com
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Presentation outline

- Immune System's Role in Cancer
- Immunotherapy Landscape
- State of Immunotherapy
- Clinical Considerations of Immunotherapy
- Where are we and How far will we go?

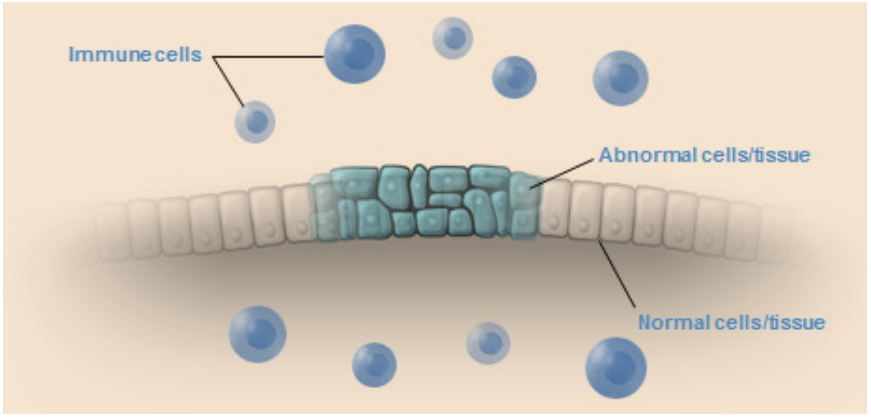
Immune Evasion Recognized as a Hallmark



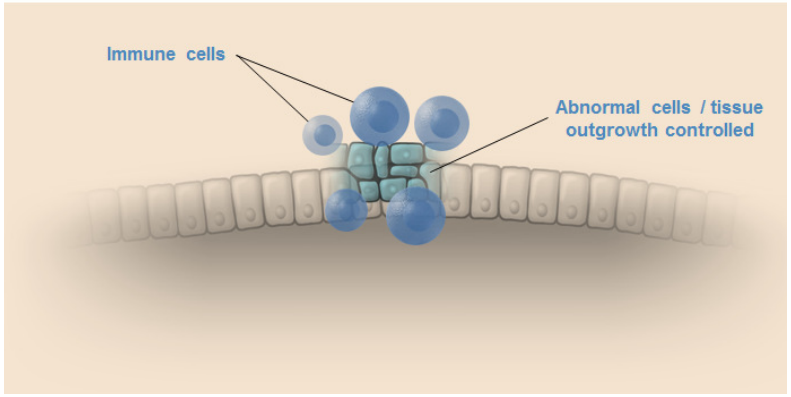
Hanahan D, Weinberg RA. *Cell*. 2011;144(5):646-674.

Dynamics Between Cancer and the Immune System

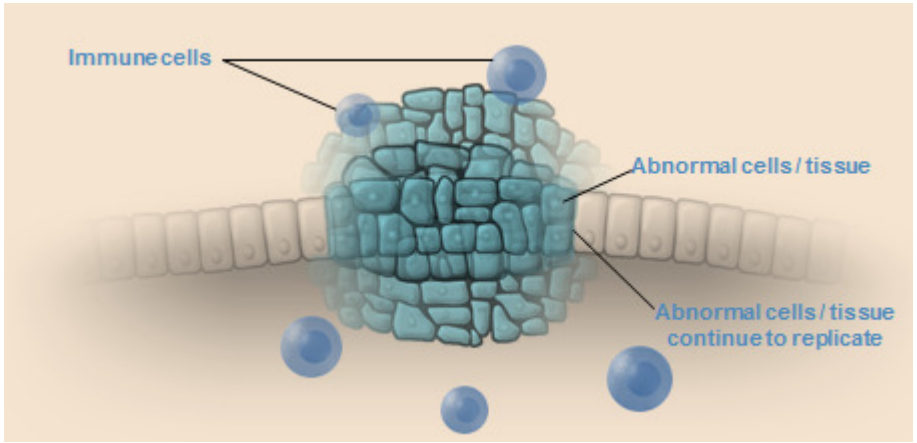
- The 3 E's



Elimination -Immune System Eradicates Cancer Cells



Equilibrium - Immune System Controls Cancer Cells



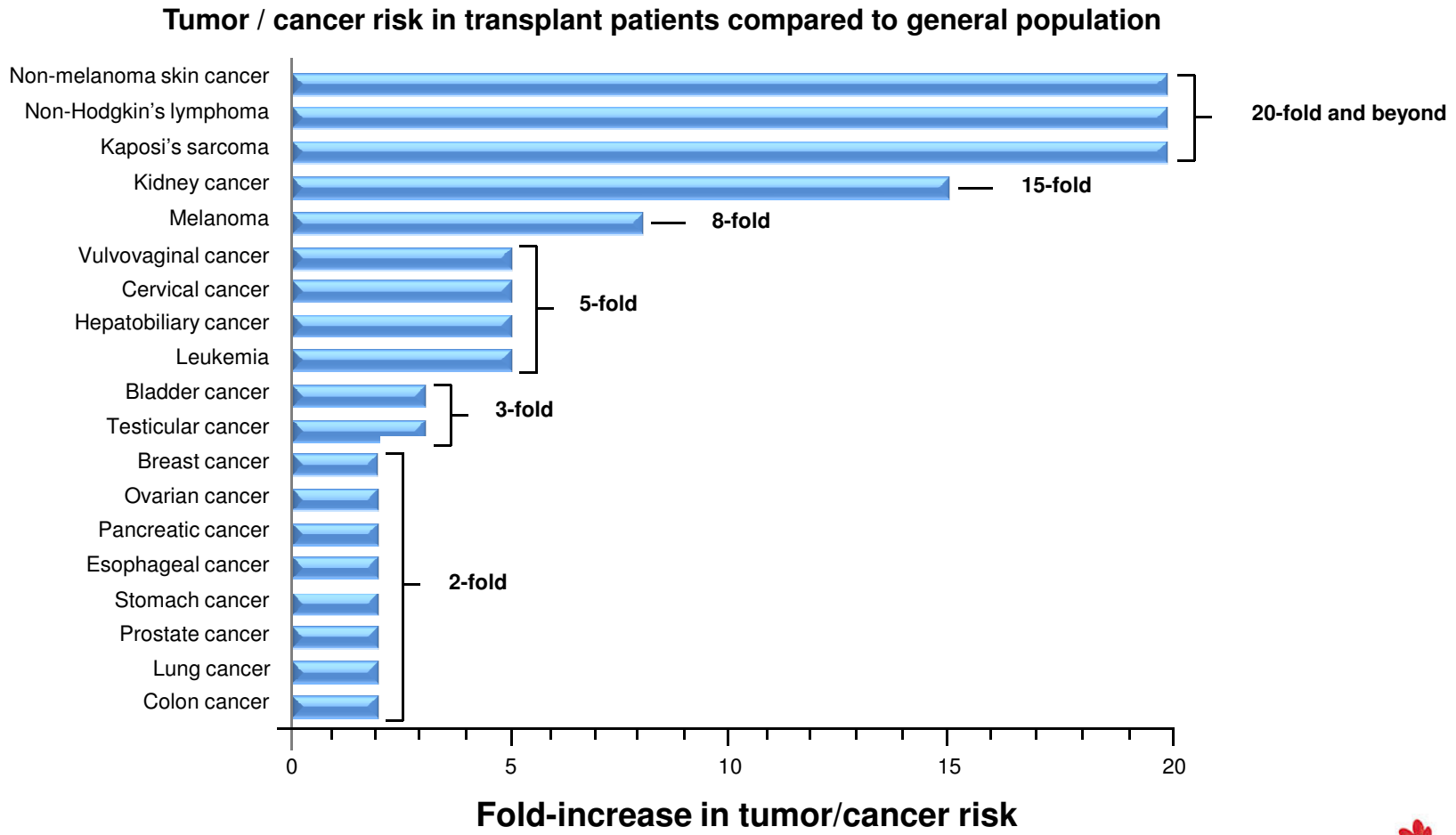
Escape - Cancer Cells Evade Immune System

Dunn GP, Schreiber RD, et al. *Nat Rev Immunol.* 2006;6(11):836-848.

Dynamics Between Cancer and the Immune System

Increased Incidence of Cancer in Immunocompromised Individuals

- Malignant tumors develop in individuals with compromised immune systems



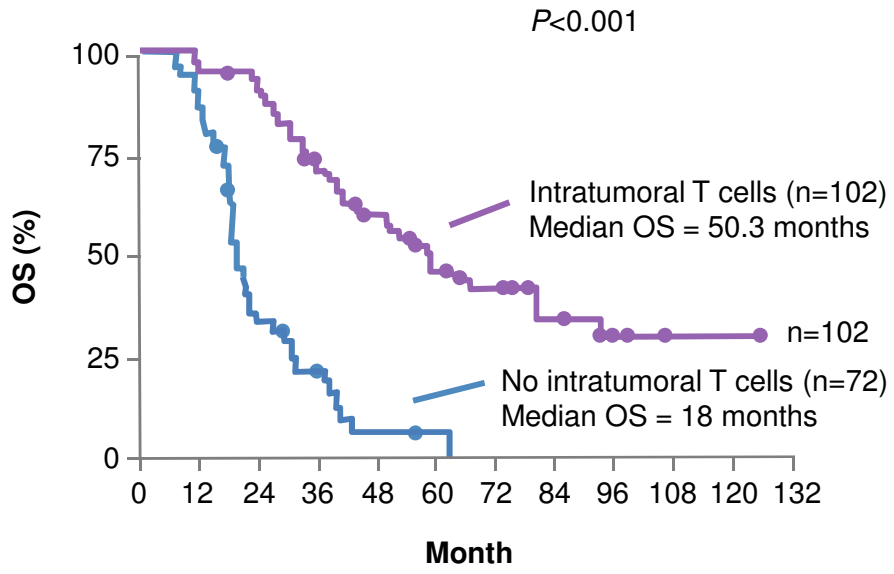
1. Kasiske BL, Wang C, et al. *Am J Transplant*. 2004;4(6):905-913.
2. Le Mire L, Wojnarowska F, et al. *Br J Dermatol*. 2006;154(3):472-477.
3. Herrero JI. *Liver Transpl*. 2009;15(suppl 2):S90-S94.
4. Abbas AK, Lichtman AH. *Basic Immunology*. 3rd ed. 2011.

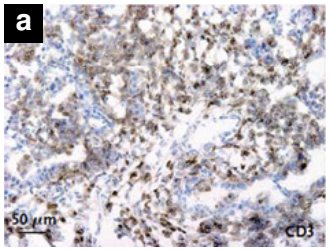
Dynamics Between Cancer and the Immune System

Immune Cells Within Tumors Predicts Overall Survival

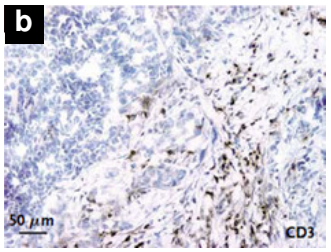
- T-cell infiltration within tumors is associated with overall survival (OS) in patients with different cancers

Kaplan-Meier Curve for OS in Advanced Ovarian Cancer[1]





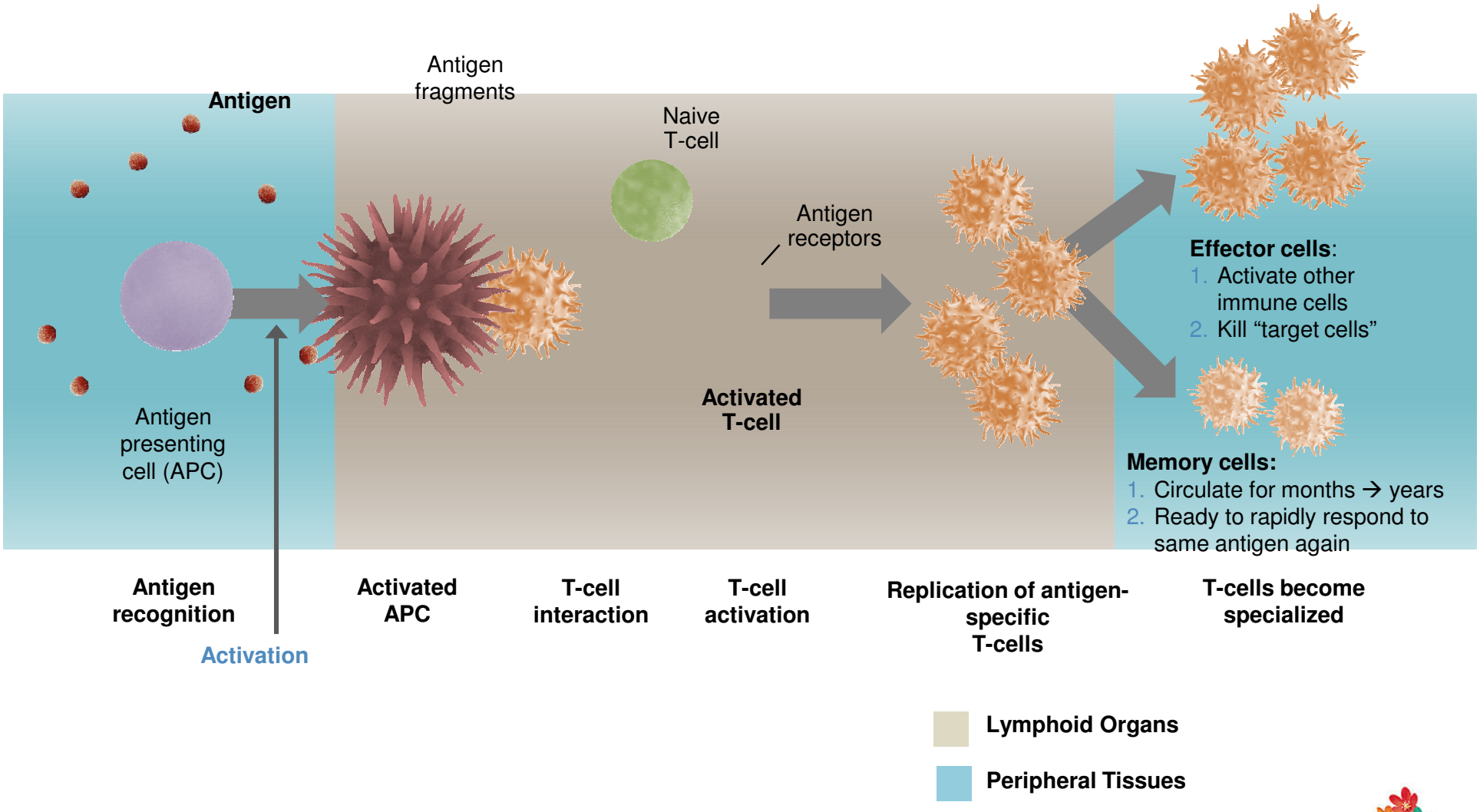
a) T cells infiltrating tumor cells



b) No intratumoral T cells detected: T cells restricted to tissue surrounding tumor

1. Zhang L, Coukos G, et al. *N Engl J Med.* 2003;348(3):203-213.
2. Galon J, Pagès F, et al. *Science.* 2006;313(5795):1960-1964.

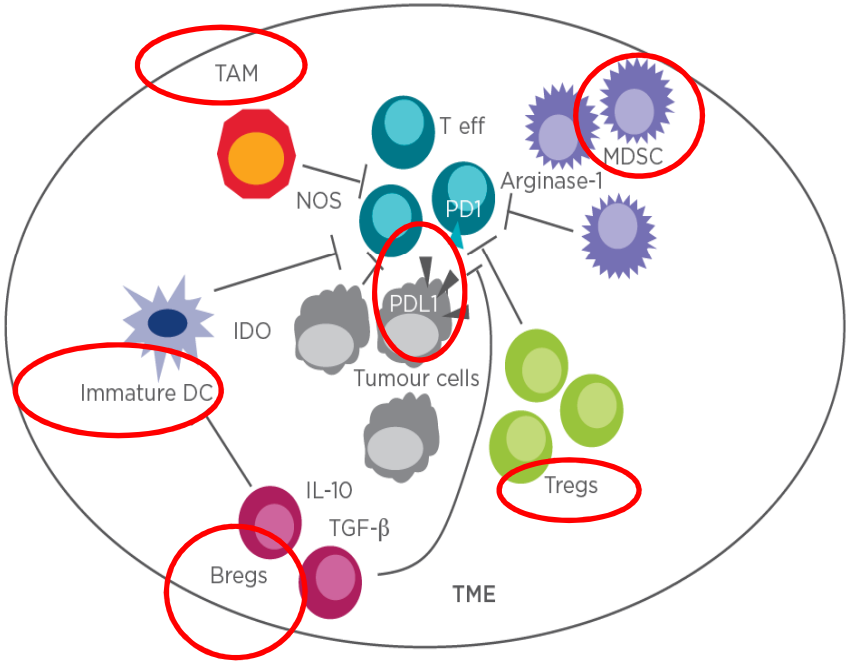
Initiation of Immune Response: Key Components



Abbas AK, Lichtman AH. *Basic Immunology*. 3rd ed. 2011.

Cancer immune escape mechanisms

Within the **tumour micro-environment (TME)** several mechanisms that help tumours to escape immune attack:



1. **regulatory B cells (Bregs)** produce immunosuppressant cytokines including interleukin (IL)-10 and transforming growth factor-beta (TGF-β);

2. **regulatory T cells (Tregs)** directly inhibit the function of effector T cells (Teff);

3. **myeloid derived suppressor cells** (MDSCs) suppress effector T cells through arginase-1;

4. **tumour-associated macrophages (TAM)** inhibit effector T cells through nitric oxide produced by NO synthase (NOS);

5. **immature dendritic cells (immature DC),** but also tumour cells highly express indoleamine 2,3-dioxygenase (IDO) leading to tryptophane deprivation, which inhibits effector T cell function.

PD1: programmed death receptor

Features of an Effective Immune Response

- **Specificity**- Ability of immune cells to identify and target a specific antigen
- **Trafficking**- Ability of activated immune system cells to migrate to particular antigens throughout the body
- **Adaptability**- Allows for a broader immune response (eg, immune response to additional antigens)
- **Target elimination-** Ability of immune cells to destroy their target (eg, cancer cells) Usually via induction of apoptosis
- **Durability** (immune memory)- Ability of immune system to recognize an antigen to which it has previously been exposed and provide long-lasting protection against it

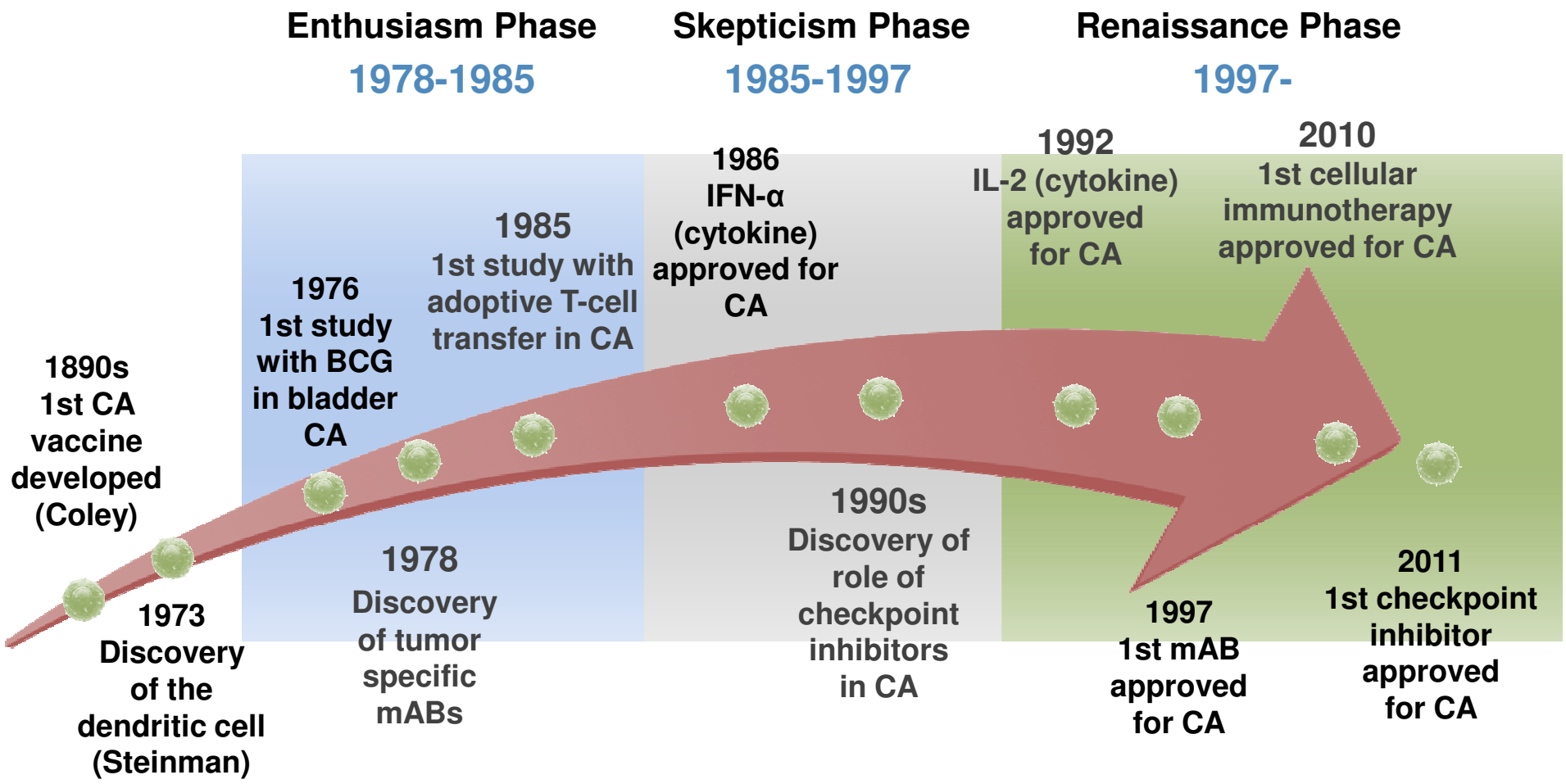
1. Abbas AK, Lichtman AH. *Basic Immunology*. 3rd ed. 2011.
2. Drake CG. *Nat Rev Immunol*. 2010;10(8);580-593.

Immunotherapy in Cancer

- Therapies that engage the immune system have been shown to improve patient survival in randomized, phase 3 cancer trials
- Immunotherapies (cytokines, checkpoint inhibitors, therapeutic vaccines, monoclonal antibodies) have been approved by the FDA to treat certain cancers

1. Robert C, Wolchok JD, et al. *N Engl J Med*. 2011;364(26):2517-2526.
2. Hodi FS, Urba WJ, et al. *N Engl J Med*. 2010;363(8):711-723.
3. Kantoff PW, Schellhammer PF, et al. *N Engl J Med*. 2010;363(5):411-422.
4. Mellman I, Dranoff G, et al. *Nature*. 2011;480 (7378): 480-489.

The timeline Immunotherapy

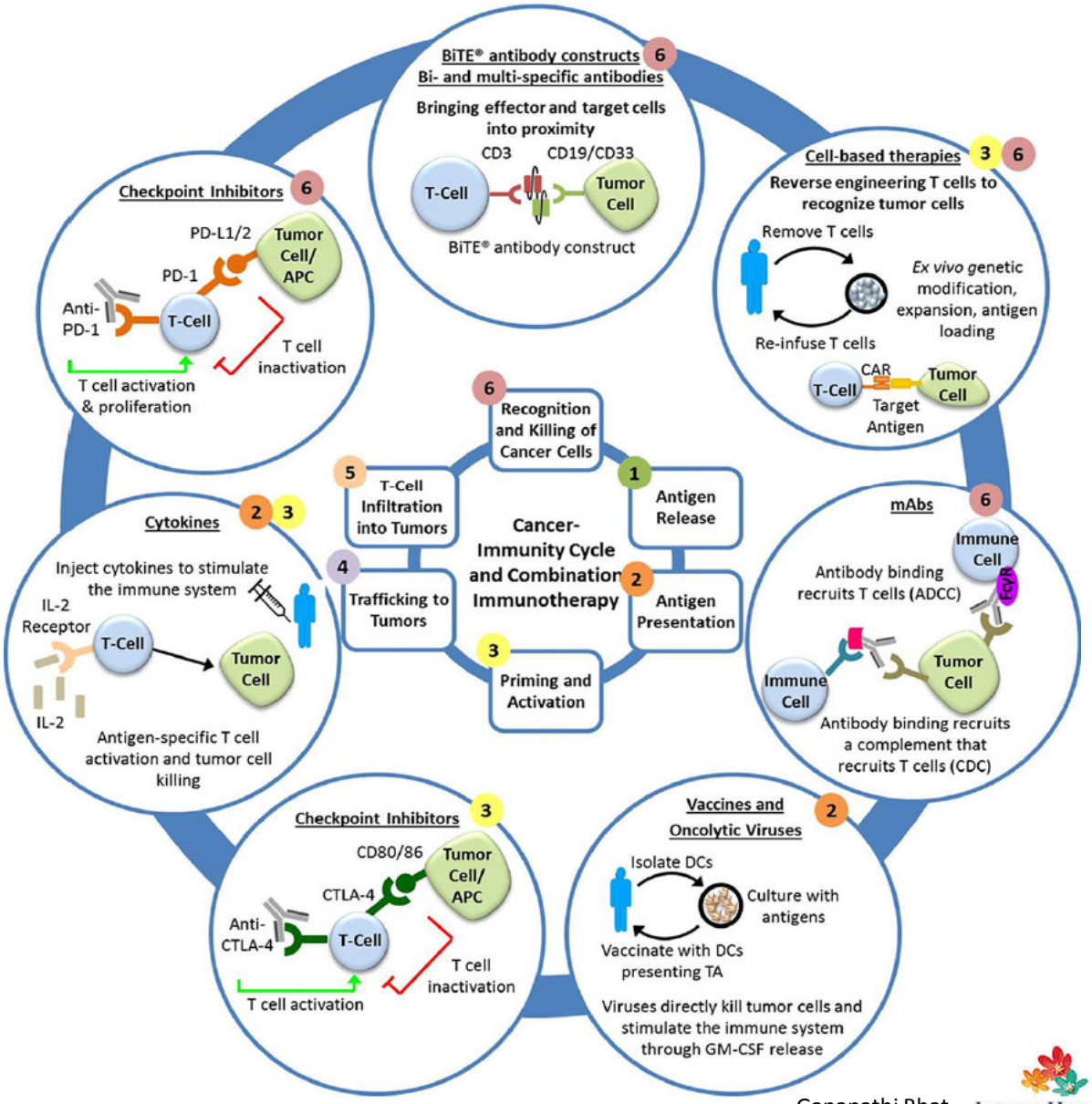


BCG, Bacille Calmette-Guerin; mABs, monoclonal antibodies; CA, cancer; IFN-α, interferon alpha; IL-2, interleukin-2

1. Kirkwood JM, Ferrone S, et al. *CA Cancer J Clin*. 2012;62(5):309-335.
2. Lesterhuis WJ, Punt CJ, et al. *Nat Rev Drug Discov*. 2011;10(8):591-600.
3. Krummel MF, Allison JP. *J Exp Med*. 1995;182(2):459-465.
4. Lotze M. In: *Cancer: Principles & Practice of Oncology*. 9th ed. 2011.
5. Leget GA, Czuczman MS. *Curr Opin Oncol*. 1998;10(6):548-551.

Intervention in the cancer-immunity cycle by immunotherapy agents

Overcoming resistance and restoring a functional immunesurveillance system requires leveraging multiple, complementary mechanisms of action and agents that acts in multiple phases of the cancer-immunity cycle **(numbers denote the phases at which each type of immunotherapy acts)**



Clin Transl Sci (2016) 9, 89–104; doi:10.1111/cts.12391

Immunotherapy: Gaining approval

- More than a dozen different immunotherapy agents have been approved, with the majority over the last decade
- Immunotherapy agents currently approved target >10 different cancer types

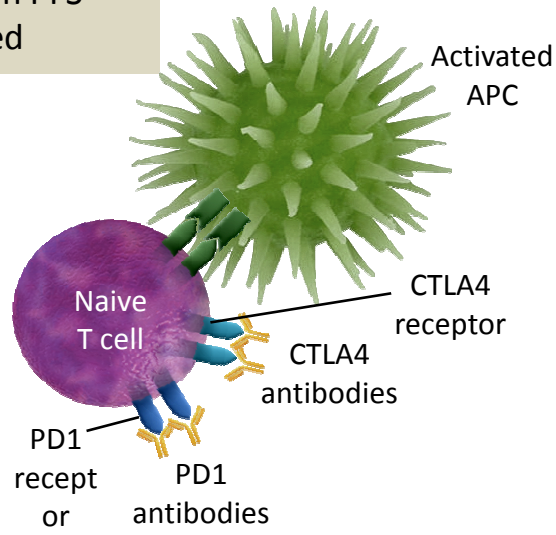
FDA-Approved Immunotherapies[a]	
Class	Approvals
Checkpoint inhibitor	2011
Therapeutic vaccine	2010
Monoclonal antibodies	1997, 1998, 2000, 2001, 2002, 2003, 2004, 2006, 2009
Cytokines	1986, 1992, 1995, 1998

[a]Not inclusive of all immunotherapy classes.

1. Mellman I, Dranoff G, et al. *Nature*. 2011;480(7378):480-489.
2. Kirkwood JM, Ferrone S, et al. *CA Cancer J Clin*. 2012;62(5):309-335.
3. Lotze M. In: *Cancer: Principles & Practice of Oncology.* 9th ed. 2011.
4. Sondak VK, Hauschild A, et al. In: *Cancer: Principles & Practice of Oncology.* 9th ed. 2011.
5. Robinson MK, Weiner LM, et al. In: *Cancer: Principles & Practice of Oncology.* 9th ed. 2011.

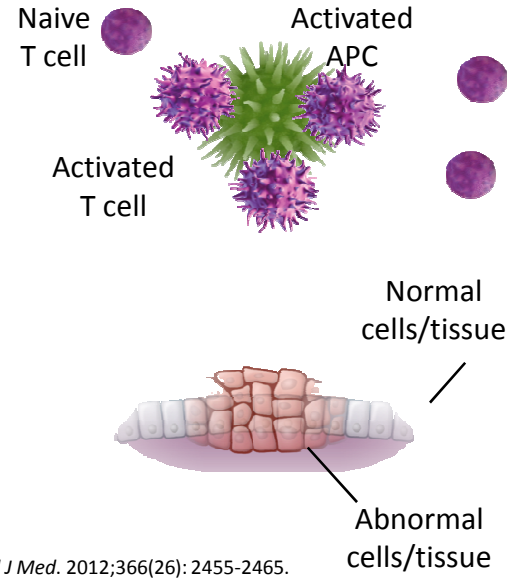
Checkpoint Inhibitors

- **Mechanism of action**
  - Block immune checkpoints that regulate T cell activation/function
- **Examples**
  - CTLA-4 and PD1
- **Efficacy**
  - Extends overall survival in certain metastatic diseases
  - A significant effect on PFS not consistently observed



Therapeutic Cancer Vaccines

- **Mechanism of action**
  - Activation of T cells to seek out and destroy target cancer cells
- **Efficacy**
  - Extended overall survival in certain metastatic diseases without an effect on PFS



CTLA-4, cytotoxic T lymphocyte-associated antigen 4; PD1, programmed cell death protein 1

1. Pardoll D. *Nat Rev Cancer*. 2012;12(4):252-264.
2. Sharma P, Allison JP, et al. *Nat Rev Cancer*. 2011;11(11):805-812.
3. Hodi FS, Urba WJ, et al. *N Engl J Med*. 2010;363(8):711-723.
4. Robert C, Wolchok JD, et al. *N Engl J Med*. 2011;364(26):2517-2526.
5. Brahmer JR, Wigginton JM, et al. *N Engl J Med*. 2012;366(26): 2455-2465.
6. Topalian SL, Sznol M, et al. *N Engl J Med*. 2012;366(26): 2443-2454.
7. Drake CG. Nat Rev Immunol. 2010;10(8):580-593.
8. Kantoff PW, Schellhammer PF, et al. N Engl J Med. 2010;363(5):411-422.
9. Kantoff PW, Godfrey WR, et al. J Clin Oncol. 2010;28(7):1099-1105.

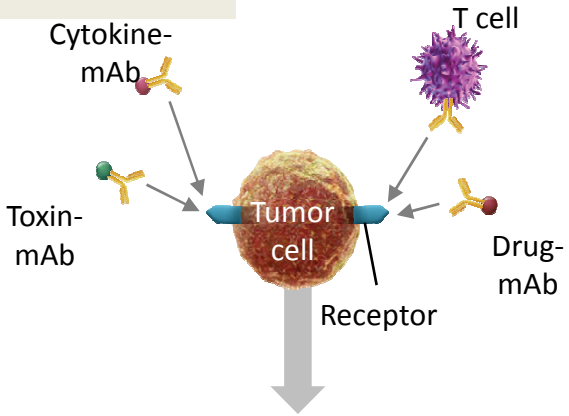
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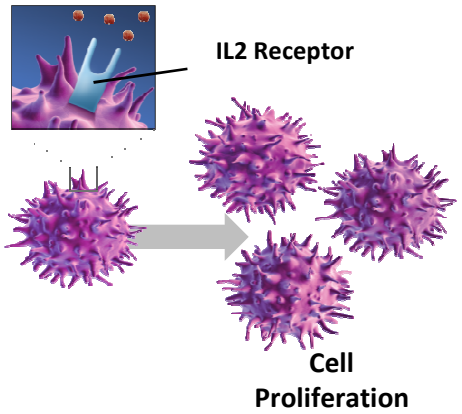
Monoclonal Antibodies (mABs)

- **Mechanism of action**
  - Differs between agents
  - Bind to their specific target antigen ultimately causing cell death
- **Efficacy**
  - Improved overall and progression-free survival (PFS) in randomized, phase 3 clinical trials in breast cancer, colorectal cancer, leukemia, and head and neck cancer

Cytokines

- **Mechanism of action**
  - Interleukin-2 (IL-2) stimulates T-cell proliferation
- **Examples**
  - Interleukins, interferons
- **Efficacy**
  - High dose IL-2 administration resulted in long term disease-free survival in patients with melanoma and renal cell carcinoma





1. Cheson BD, Leonard JP. *N Engl J Med*. 2008;359(6):613-626.
2. Weiner LM, Wang S. *Nat Rev Immunol*. 2010;10(5):317-327.
3. Slamon DJ, Norton L, et al. *N Engl J Med*. 2001;344(11):783-792.
4. Curran D, Bonner JA, et al. *J Clin Oncol*. 2007;25(16):2191-2197.
5. Vermorken JB, Hitt R, et al. *N Engl J Med*. 2008;359(11):1116-1127.
6. Jonker DJ, Moore MJ, et al. *N Engl J Med*. 2007;357(20):2040-2048.
7. Robak T, Moiseev SI, et al. *J Clin Oncol*. 2010;28(10):1756-1765.
8. Bachmann MF, Oxenius A. EMBO Rep. 2007;8(12):1142-1148.
9. Lotze M. In: Cancer: Principles & Practice of Oncology. 9th ed. 2011.

Classes of immunotherapy agents in oncology

Active Immunotherapies	
Classes	***Examples***
Cancer vaccines	Sipuleucel-T
Cytokines	Interleukin-2, interferon-α
Immunomodulatory mAbs	Nivolumab, ipilimumab, pembrolizumab
Passive immunotherapies	
Classes	***Examples***
Cell-based therapies	Adoptive T-cell therapy (e.g., TIL, TCR, CAR-T)
Oncolytic viruses	T-Vec
Bi- and multispecific antibodies	Blinatumomab
Tumor-targeting mAbs	Rituximab

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Selected list of combination immunotherapies in clinical development

Immunotherapy + Immunotherapy			
Combination therapy	*Mechanisms of action*	*Phase*	*Indication*
Nivolumab + ipilimumab	Anti-PD1 + anti-CTLA-4	I/II	Gastric, TNBC, PA, SCLC, Bladder, Ovarian
		II/III	Melanoma, RCC
		III	SCLC, GBM, NSCLC
Nivolumab + BMS-986016	Anti-PD1 + anti-LAG3	I	Solid tumors
Nivolumab + viagenpumatucel-L	Anti-PD1 + vaccine	I	NSCLC
Nivolumab + urelumab	Anti-PD1 + anti-4-1BB	I/II	Solid tumors, B-cell NHL
Atezolizumab + MOXR0916	Anti-PDL1 + anti-OX40	I	Solid tumors
Atezolizumab + varlilumab	Anti-PDL1 + anti-CD27	II	RCC
Atezolizumab + GDC-0919	Anti-PDL1 + IDO inhibitor	I	Solid tumors
Epacadostat + atezolizumab, durvalumab, or pembrolizumab	IDO inhibitor + anti-PDL1 or anti-PD1	I/II	Solid tumors
Pembrolizumab + T-Vec	Anti-PD1 + vaccine	III	Melanoma
Durvalumab + tremelimumab	Anti-PDL1 + anti-CTLA-4	I/II	Melanoma
		I/II/III	SCCHN
		II	Mesothelioma, UBC, TNBC, PA
		III	NSCLC, Bladder
Pidilizumab + dendritic cell/RCC fusion cell vaccine	Anti-PD1 + vaccine	II	RCC

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Selected list of combination immunotherapies in clinical development

Immunotherapy + Targeted Therapy

Combination therapy	*Mechanisms of action*	*Phase*	*Indication*
Atezolizumab + bevacizumab	Anti-PDL1 + anti-VEGF	II/III	RCC
Atezolizumab + cobimetinib	Anti-PDL1 + MEK inhibitor	I	Solid tumors
Atezolizumab + vemurafenib	Anti-PDL1 + BRAF inhibitor	I	Melanoma
Atezolizumab + erlotinib or alectinib	Anti-PDL1 + EGFR or ALK inhibitor	I	NSCLC
Nivolumab + bevacizumab	Anti-PD1 + anti-VEGF	II	RCC
Pembrolizumab + pazopanib	Anti-PD1 + tyrosine kinase inhibitor	I	RCC
Pembrolizumab + dabrafenib + trametinib	Anti-PD1 + BRAF inhibitor + MEK inhibitor	I/II	Melanoma
Durvalumab + dabrafenib + trametinib	Anti-PDL1 + BRAF inhibitor + MEK inhibitor	I/II	Melanoma
Nivolumab + sunitinib, pazopanib, or ipilimumab	Anti-PD1 + RTK inhibitor, RTK inhibitor,	I	RCC

Immunotherapy + Chemotherapy

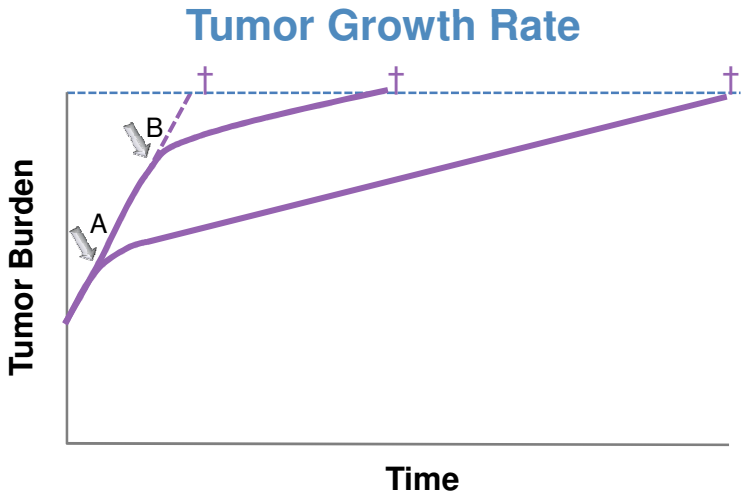
Combination therapy	*Mechanisms of action*	*Phase*	*Indication*
Nivolumab + platinum doublet chemo[a]	Anti-PD1 + chemotherapy	III	NSCLC
Pembrolizumab + cisplatin	Anti-PD1 + chemotherapy	III	Gastric
Pidilizumab + lenalidomide	Anti-PD1 + chemotherapy	I/II	Multiple myleloma
Pidilizumab + sipuleucel-T + cyclophosphamide	Anti-PD1 + vaccine + chemotherapy	II	Prostate
Atezolizumab + carboplatin/paclitaxel +/– bevacizumab	Anti-PDL1 + chemotherapy +/– anti-VEGF	III	NSCLC

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Immunotherapy: Treatment Considerations

- Relative efficacy of immunotherapy may be greater with lower tumor burden
- Patient given immunotherapy earlier in disease course might have a better outcome

- Standard practice in oncology is the use of combination agents with different mechanisms of action
  - Chemotherapy and mABs
  - Radiation and chemotherapy
  - Multiple chemotherapy regimens
- Immunotherapy **offers potential for synergy with other therapies**



--- Expected clinical outcome if no treatment is provided

† Death

A Patient given a vaccine earlier

B Patient given a vaccine later

1. Kirkwood JM, Ferrone S, et al. *CA Cancer J Clin.* 2012;62(5):309-335.
2. Drake CG. *Nat Rev Immunol.* 2010;10(8):580-593.
3. Gulley JL, Drake CG. *Clin Cancer Res.* 2011;17(12):3884-3891.

1. Vermorken JB, Hitt R, et al. *N Engl J Med.* 2008;359(11):1116-1127.
2. Slamon DJ, Norton L, et al. *N Engl J Med.* 2001;344(11):783-792.
3. Gulley JL, Drake CG. *Clin Cancer Res.* 2011;17(12):3884-3891.
4. Drake CG, Adler AJ, et al. Cancer Cell. 2005;7(3):239-249.
5. Mercader M, Kwon ED, et al. Proc Natl Acad Sci USA. 2001;98(25):14565-14570.
6. Aragon-Ching JB, Gulley JL, et al. Front Biosci. 2007;12:4957-4971.

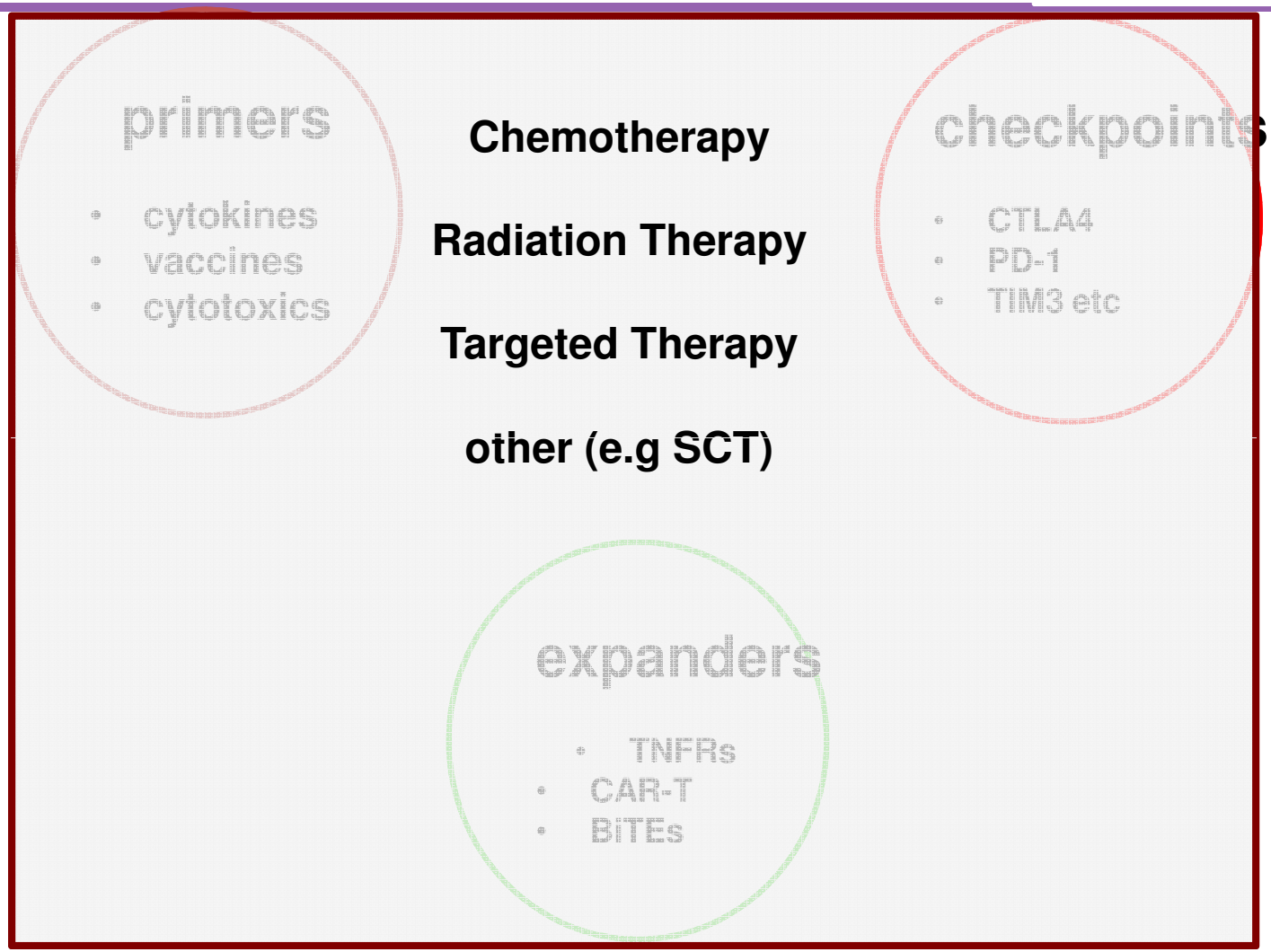
Immunotherapy: Increasing research interest

- Rapid increase in immunotherapy clinical research
  - Doubling of abstracts at major conferences from 2009 to 2012
  - Approximately 800 clinical trials in various phases ongoing
    - eg, breast, colon, head and neck, kidney
- Trials utilize agents alone and in combination with conventional therapies



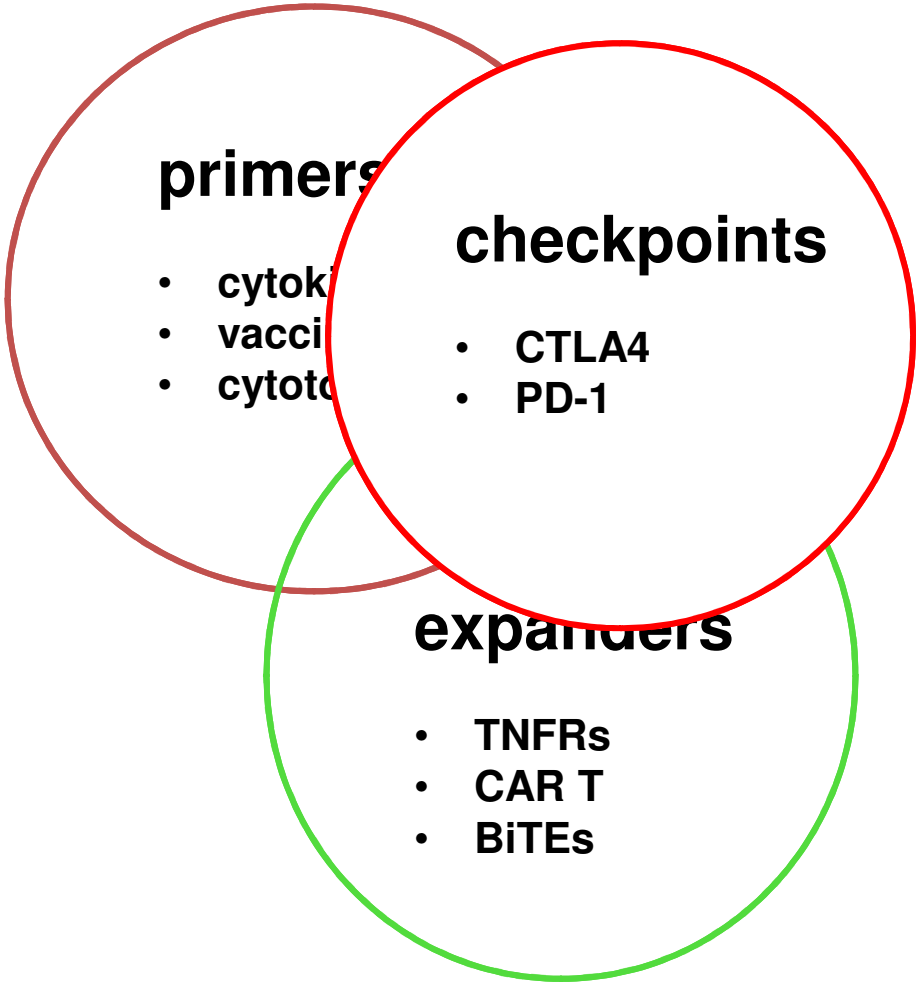
SeekingAlpha.com. http://seekingalpha.com/article/667581-immunotherapy-comes-of-age-at-asco-2012. Accessed January 4, 2013.
ClinicalTrials.gov. http://clinicaltrials.gov/. Accessed January 4, 2013.

Immune modulation does not exist in a vaccuum



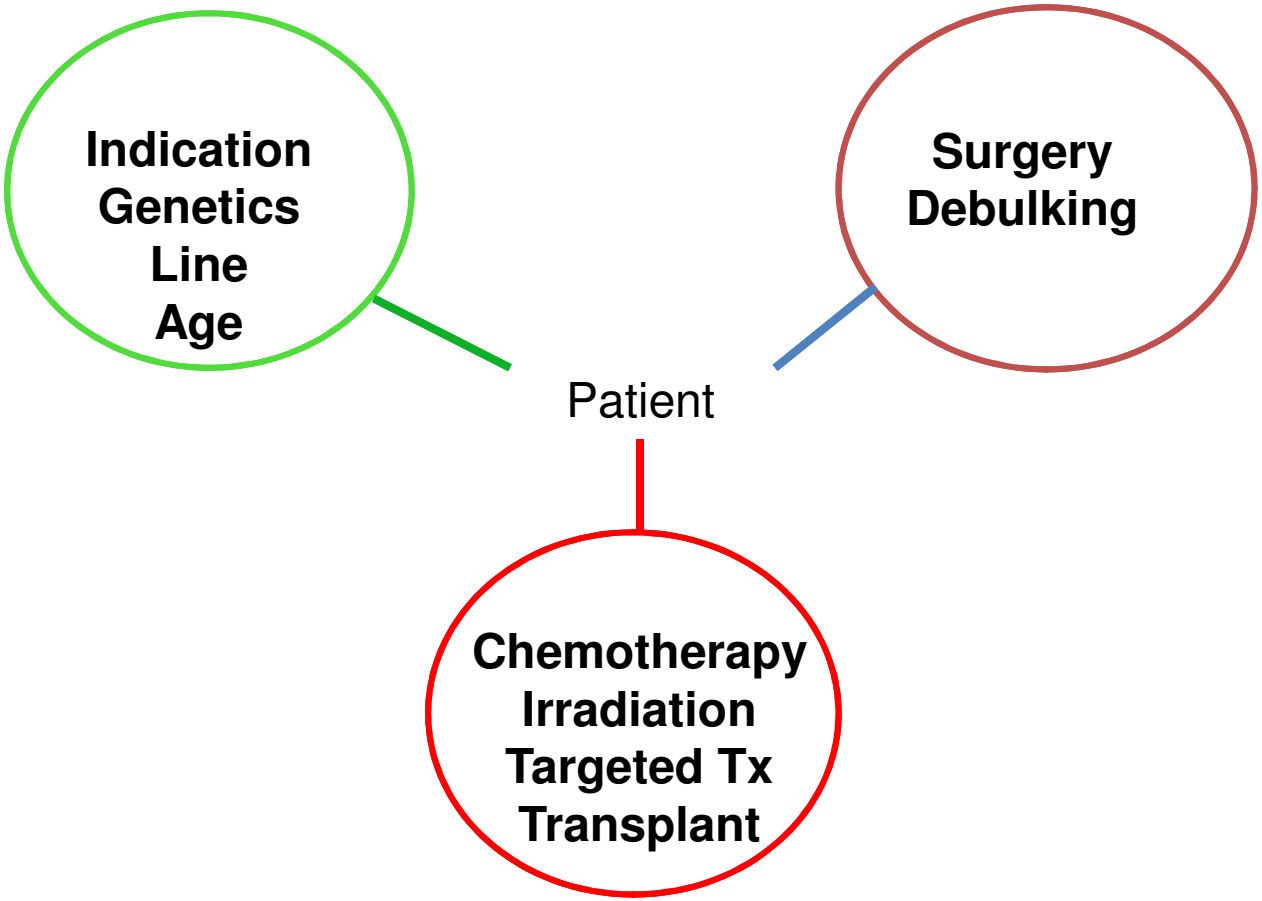
Such complexity offers significant challenge, but also opportunity, for new drugs to have a positive impact

Checkpoints Dominate....



- **Inhibition appears to be dominant over activation**
  - Preclinical models support this view
  - Early clinical data support this view, e.g. monotherapeutic activity of TNFR agonists is low
  - Even CAR T cells can be shut down by immune checkpoint expression
- The impact of removing constraints on NK cell activity and on immuno-suppression imposed by stromal cells is not known

Considering a patient



Efficacy/Tolerability: where we are headed depends on the indication

- Hematologists have been excited about the "post-chemo" era.
- Why? **Ibrutinib, rituxumab, idelalisib, revlimid** etc ...

- Solid tumor oncologists already know from targeted therapies that some of their patients can be cured (e.g. targeted therapies & antibodies in breast cancer) – **anticipating better cure rates with IO**

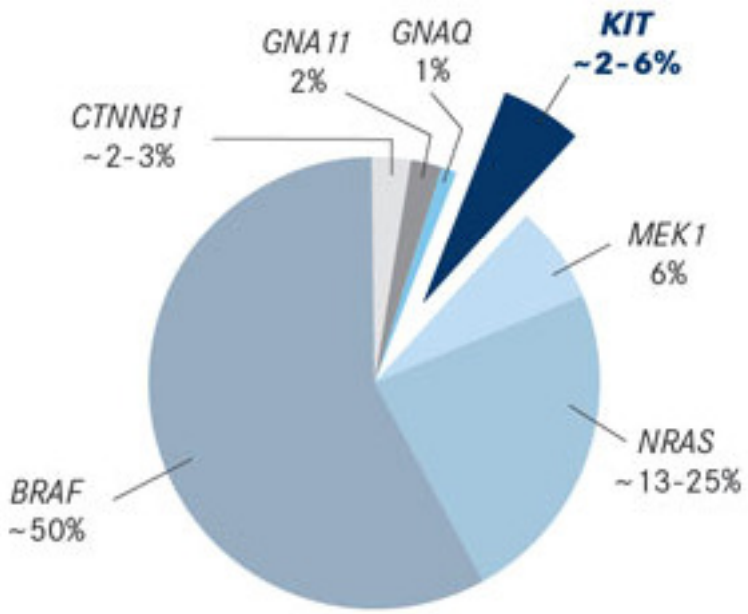
  - Oncologists in general are seeing success where for decades there has been only abject failure (NSCLC, H&N, bladder, etc)

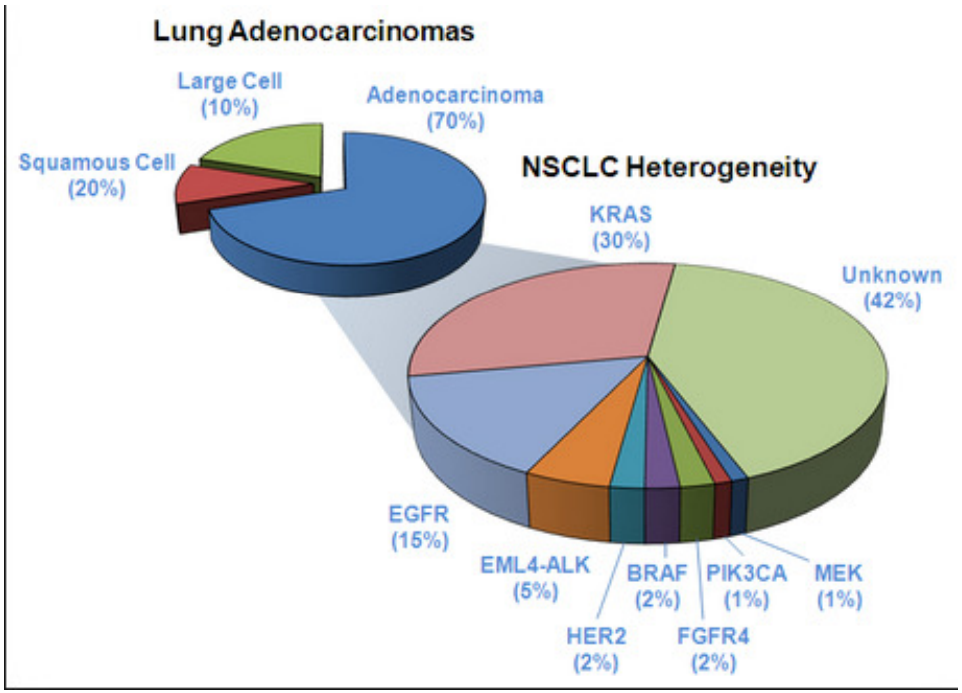
  - All oncologists recognize the **importance of being able to treat their elderly patients**

- ***In this landscape, the efficacy/tolerability profile can be differentiating***

Complex indications, complex patients

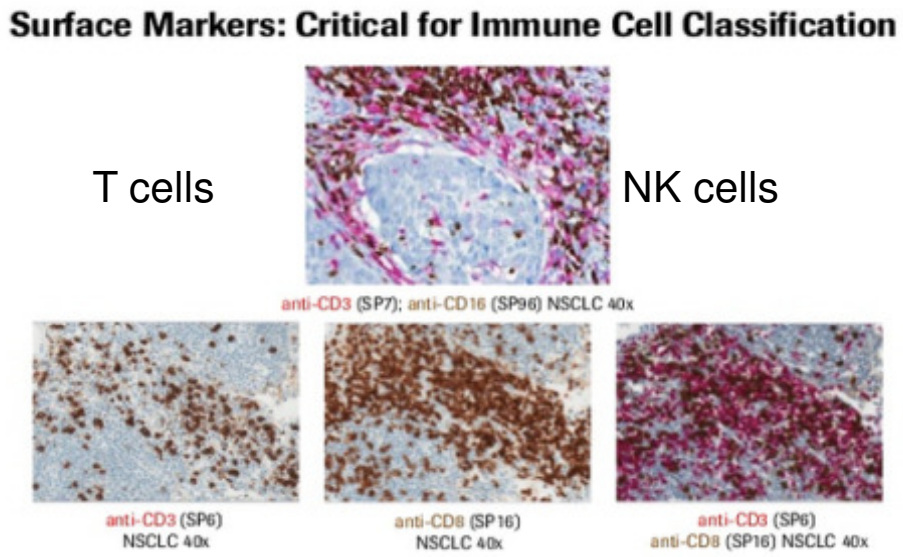
Driver mutations in metastatic melanoma and in lung cancers

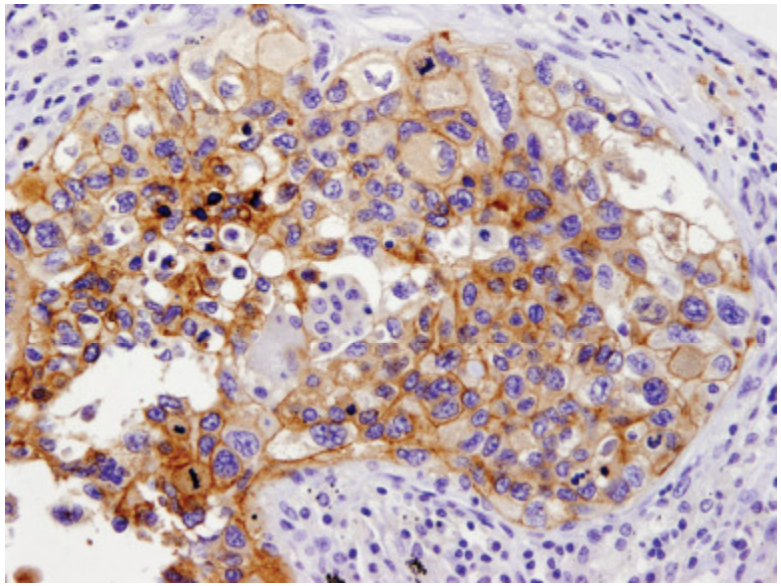




Complex indications, complex patients

Expression of lymphocyte markers and PD-L1 in NSCLC





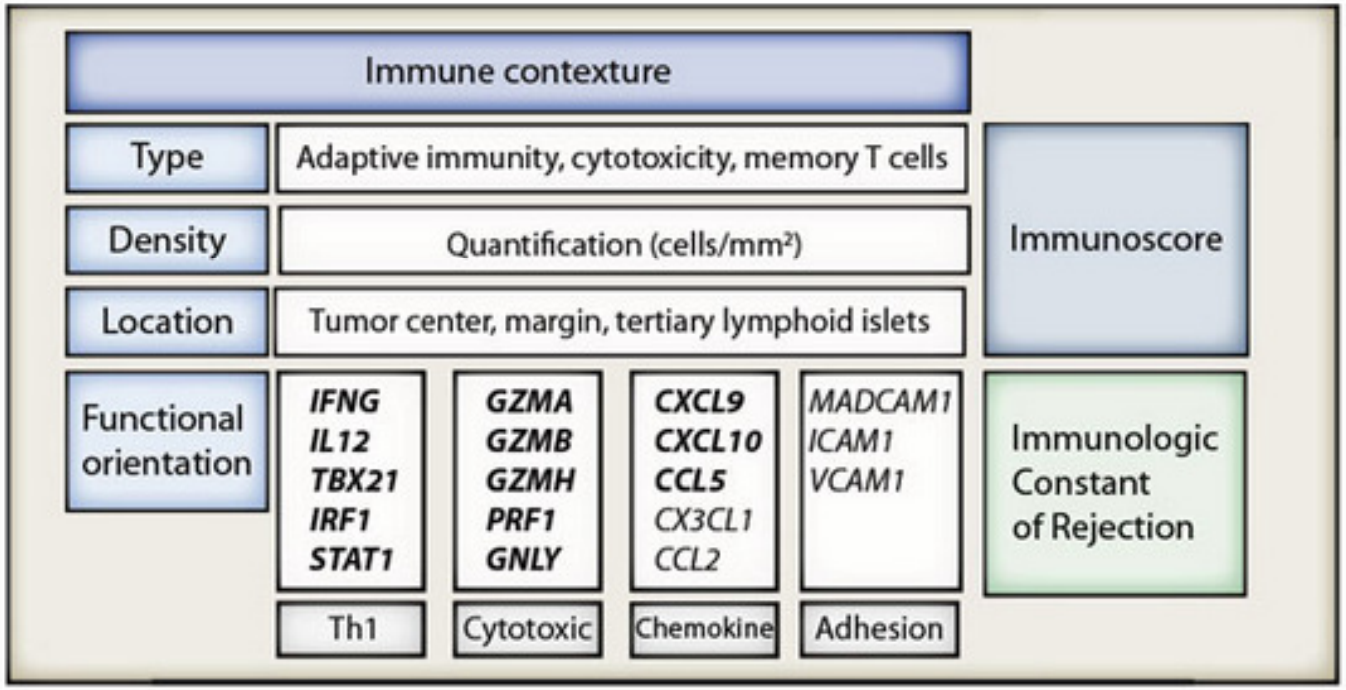
CD3+/CD8+ T cells

but this picture is highly variable

- degree of infiltration (starting at none)
- geography of infiltration (marginal, interstitial, stromal, excluded)
- functionality of infiltrates (PD-1, TIM-3, LAG3)

Complex indications, complex patients

Figure. A Model for Evaluating Immune Status

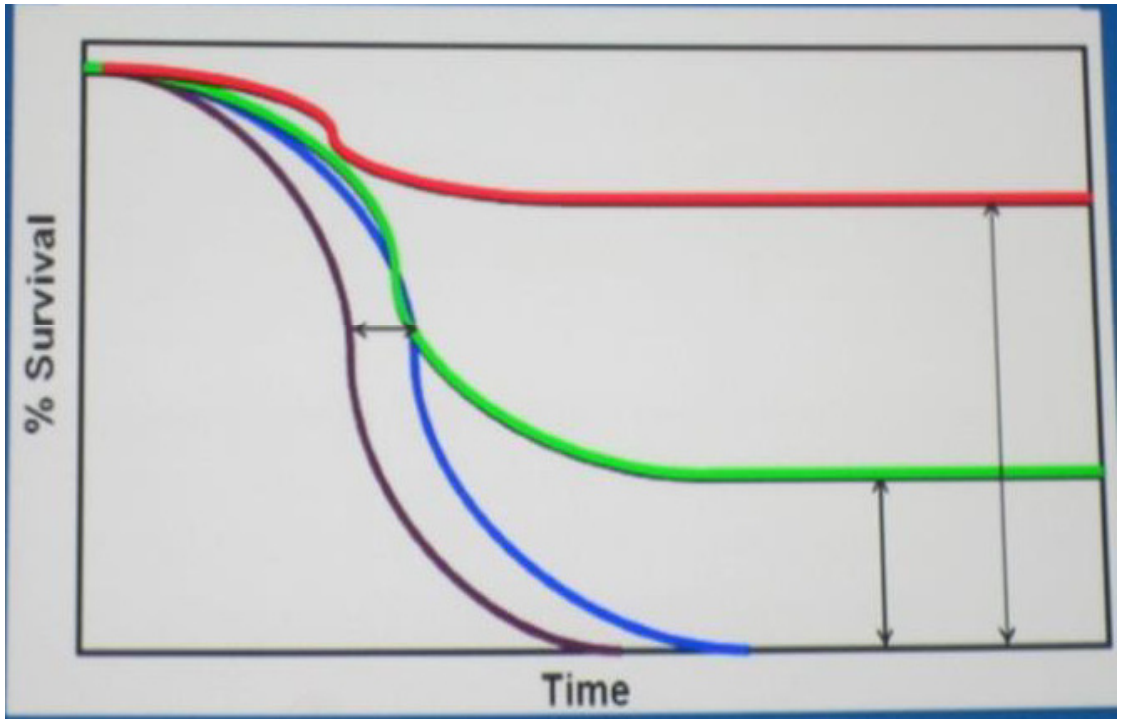


CD3+
CD8+

The immune status of a tumor can be assessed and stratified using three key measures (above): (1) the immune contexture; (2) an Immunoscore; and (3) an immunologic constant of rejection, according to an international task force working on standards for translating immunotherapy into clinical practice. The genes listed have been identified as those whose alterations are more likely to play an underlying role in biologic processes that may predict responses to immunotherapy.

Galon et al 2013. Immunity 39: 11-26

Assessing the benefit with immunotherapy



- **Combinations of traditional and immunotherapies** could combat the **initial drop in survival while also providing the long-term response** (**red**)

- Immunotherapies may show similar survival kinetics to traditional therapies as an immune response develops, but could **provide a much longer survival benefit for a subset of patients** (**long green tail**).

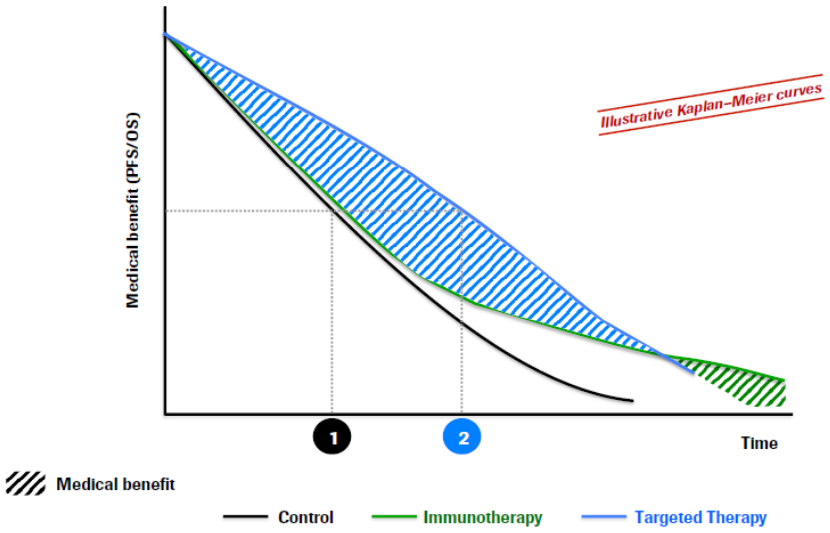
- Idealized characteristics of **traditional** (**blue**) and **immunotherapies** (**green**).

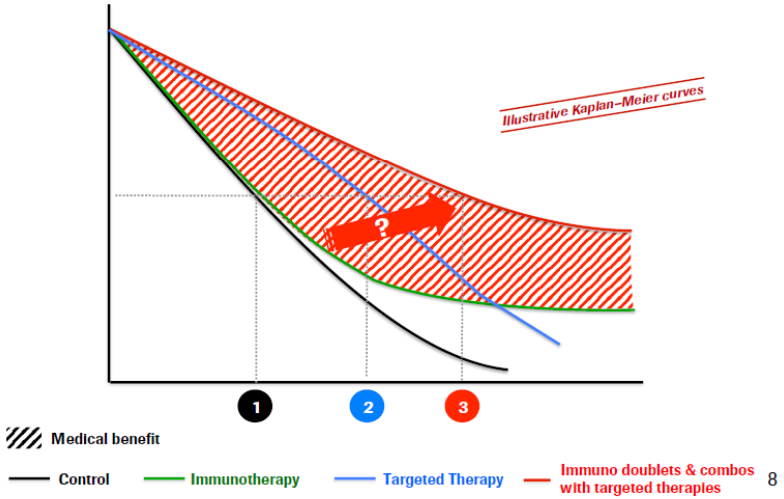
Adapted from Perlmutter, AACR 2014

Clinical considerations

Monotherapy
one cancer type, few patients

Combinations, broader use
Better patient selection?





Where are we and How far will we go?

Challenges: Developing them to the point of clinical utility

Immunotherapy drugs are highly effective, but not in everyone

What clinical data are needed in order to move agents and combinations to clinical practice?

What dosing schedules will determine efficacious response? And alternatively have favourable toxicity?

What is a standard criteria to measure response and prognosticate disease?

What will be the cost impact of these very expensive agents?

Challenges: Developing them to the point of clinical utility

Development of resistant disease and disease progression on or after therapy

PK and PD paradigms remain inadequate to guide the selection of doses and schedules, both starting and recommended Phase 2 for immunotherapies

When combining an immunotherapy with another treatment modality, it is important to determine the optimal dose, schedule, sequence and tumor mutational heterogeneity.

trAEs appear to increase in rate and severity with cancer immunotherapy combinations; depending on the combination partner, alterations in the toxicity profile are also possible.

Adoption of immunodynamic endpoints that are clinically meaningful to allow the selection of the most effective front-line agents or combinations, or second-line immune agents if and when immunotherapy fails.

Journal for ImmunoTherapy of Cancer20164:15.DOI: 10.1186/s40425-016-0118-0

Immunoprognostic and Immunotherapeutic Areas

Prognostic	
	Immunoscore
Therapeutic	
	Conventional Therapies
	Chemotherapy
	Radiation therapy
ITAs - Passive	
	Cellular Therapy
	Adoptive T and NK cells
	CAR T cells
ITAs - Active & Specific	
	Monoclonal Antibodies
	Tumor-targeting
	Immune-targeting, including checkpoint inhibitors
	Vaccines
	In situ Vaccines
	Cell-based Vaccines
	Dendritic cell–based Vaccines
	Non–cell-based Vaccines
ITAs - Active & Nonspecific	
	Cytokines
	IDO Inhibitors

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Challenges: Developing them to the point of clinical utility

The **safety profile is based on the mechanism of action**, and although adverse events can occur in any organ, the most commonly affected organs are gastrointestinal (diarrhea), dermatologic (rash, itchiness), hepatic (usually clinically asymptomatic elevation in transaminases), and endocrinopathies.

Most adverse events are low grade in severity and manageable, but if not properly managed, symptoms can worsen, possibly to the point of irreversibility and/or the necessity to discontinue treatment.

There is **no standard approach to identifying immune related adverse events**, but any inflammatory event should be taken seriously and the use of steroids should be considered.

Most adverse events, such as fatigue, headache, abdominal pain, colitis, and itchiness, can't be identified on physical exam and the treating **physician has to rely on the patient to make him/her aware of any new symptom or worsening of existing symptoms**

Comparative tox profiles - monotherapy

Table 2 Selected Adverse Events

Agent, Patients (N), and Study [Reference]	Nivolumab N = 296[7]		Pembrolizumab N = 135[65]		MPDL3280A N = 171[a][49]		BMS-936559 N = 207[17]		MEDI4736 10 mg/kg q2wk N = 346[19]		MSB-0010718C N = 28[67]	Ipilimumab N = 131[68]	
Adverse Event	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Gr 3/4	Any Gr	Any Gr	Gr 3/4
Pneumonitis	3%	1%	4%	0%	NR	0%	NR	NR	1%	0%	NR	NR	NR
Diarrhea	11%	1%	20%	1%	26%	1%	9%	0%	5%	0%	10.7%	32.8%	5.3%
Colitis	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	7.6%	5.3%
Rash	12%	0%	21%	2%	18%	1%	7%	0%	0%	< 1%	NR	19.1%	0.8%
Pruritus	9%	< 1%	21%	1%	NR	NR	6%	0%	0%	< 1%	NR	24.4%	0%
Vitiligo	3%	0%	9%	0%	NR	NR	2%	0%	NR	NR	NR	2.3%	0%
ALT elevation	4%	1%	8%	0%	NR	3%	1%	0%	4%	1%	NR	1.5%	0%
AST elevation	3%	1%	10%	1%	NR	NR	NR	NR	4%	1%	10.7%	0.8%	0%
Infusion reaction/hyper-sensitivity	3%	< 1%	NR	NR	NR	NR	11%	< 1%	NR	NR	NR	NR	NR
Fatigue	NR	NR	30%	1%	43%	4%	NR	NR	13%	1%	35.7%	42%	6.9%
Hyperthyroidism/ hypothyroidism	3%	< 1%	8%	1%	NR	NR	3%	0%	3%	< 1%	NR	1.5%	0%

[a]Regardless of attribution.

ALT = alanine transaminase; AST = aspartate transaminase; Gr = grade; NR = not reported.

Kim and Eder 2014 Oncology

Tox profiles – combotherapy ipi/nivo

Table 2. Highest Grade of Selected Treatment-Related Adverse Events That Occurred in at Least One of the Patients Who Received the Concurrent Regimen.*

Event	All Patients in Concurrent-Regimen Group (N=53)	
	All Grades	Grade 3 or 4
Pneumonitis	3 (6)	1 (2)
Endocrinopathy	7 (13)	1 (2)
Hypothyroidism	2 (4)	0
Hypophysitis	2 (4)	1 (2)
Thyroiditis	3 (6)	0
Adrenal insufficiency	2 (4)	0
Hyperthyroidism	2 (4)†	0
Thyroid-function results abnormal	1 (2)	0
Hepatic disorder	12 (23)	8 (15)
Aspartate aminotransferase increased	11 (21)	7 (13)
Alanine aminotransferase increased	11 (21)	6 (11)
Gastrointestinal disorder	20 (38)	5 (9)
Diarrhea	18 (34)	3 (6)
Colitis	5 (9)	2 (4)
Renal disorder	3 (6)	3 (6)
Blood creatinine increased	3 (6)	3 (6)
Acute renal failure	2 (4)	2 (4)
Renal failure	1 (2)	1 (2)
Tubulointerstitial nephritis	1 (2)	0
Skin disorder	37 (70)	2 (4)
Rash	29 (55)	2 (4)
Pruritus	25 (47)	0
Urticaria	1 (2)	0
Blister	1 (2)	0
Infusion-related reaction	1 (2)	0

- 21% of patients terminated treatment due to toxicity
- toxicity is associated with positive clinical response
- oncologists: the GI tox is **very difficult and limits use**

Kim and Eder 2014 Oncology

Challenges: Developing them to the point of clinical utility

While checkpoint blockade drugs currently focus on blocking two checkpoint mechanisms, others have been identified by research, as well as molecules that stimulate immune response.

Tumor mutational load has been shown to correlate with clinical response to checkpoint blockade in human cancers. Somatic neoepitopes were associated with a prolonged benefit in responders to aCTLA4 treatment in melanoma.

Immunotherapy can work for cancer patients; in a few cases it already does, but response patterns are different from traditional therapy. For example, the time to an antitumor response can be longer.

Often, a clinical response is apparent only after a period of "pseudoprogression," when immune cell infiltration can manifest as new lesions or growth of existing ones.

Journal for ImmunoTherapy of Cancer20164:15.DOI: 10.1186/s40425-016-0118-0

Challenges: Developing them to the point of clinical utility

- The cost of these **agents is staggering—higher than any previous class of cancer treatment**
- Therefore, payers are **seeking better evidence** that patients will clearly benefit, which brings the issue back to identifying biomarkers and their potential for **predicting success.**

Immuno-Oncology- What's Next

- what we want in specific indications:
  - better response rates
  - more durable responses
  - better tolerability
- because we are addressing new benchmarks clinical practice is evolving quickly
- for preclinical and early clinical programs a critical exercise is to look ahead in an effort to anticipate unmet need in a rapidly changing environment

Summary

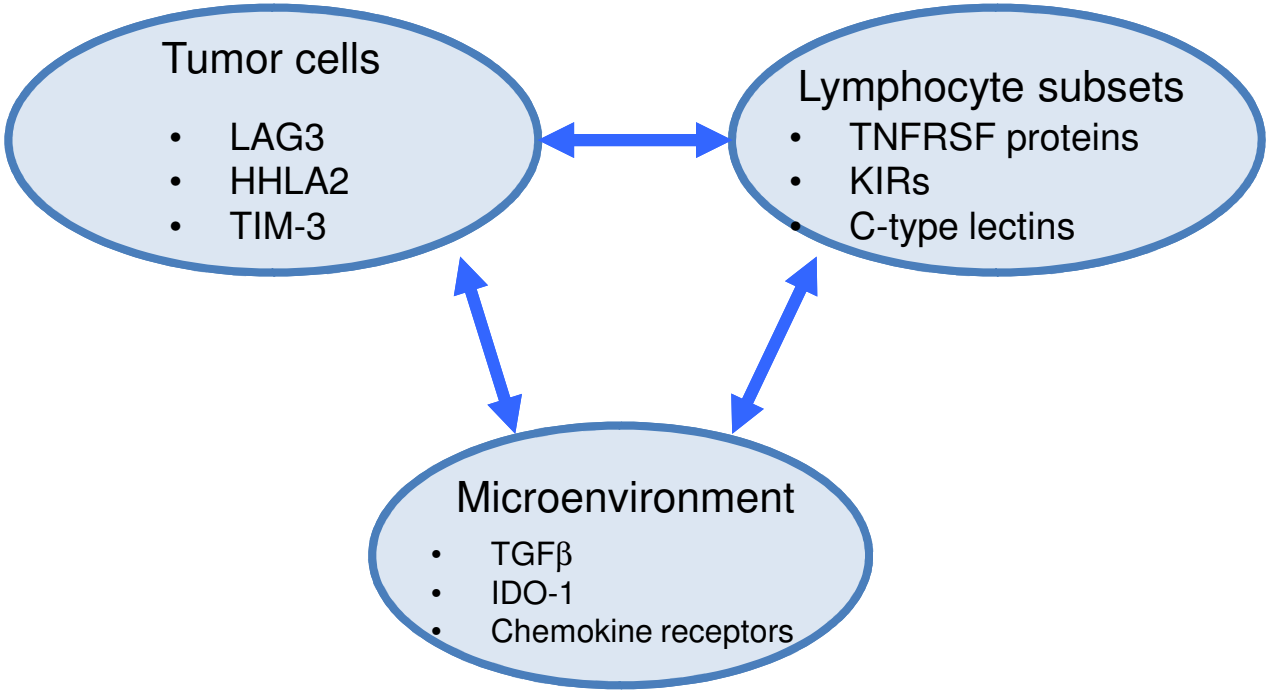
- The immune system plays a critical role in controlling cancer
- Key features of an effective immune response include
  - Specificity
  - Adaptability
  - Durability (immune memory)
- Future clinical considerations
  - May elicit better immune system response if used earlier in disease
  - Potential for **durable clinical effects** and **synergy with subsequent therapies**

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5th European Immunology Conference

Berlin, Germany July 21-23, 2016





NK cells: the next wave of immune-modulators

To watch out

- **KIRs**
- **LIRs (ILTs)**
- **Siglecs**
- **The PVR/nectin family (TIGIT)**
- **C-Type lectins**

Moving ahead

- The optimal efficacy/tolerability paradigm will impact more and more indications as therapeutics are successful
- Niche indications with high unmet need allow access to this remarkably competitive landscape
- Novel interrogation points to drive differentiation:
  - **T cells: effectors *and* Tregs**
  - **NK cells**
  - **The tumor microenvironment**
  - **The tumor itself**



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