Immunotherapy: ”Cry ’Havoc!’ and Let slip the dogs of war”

Cancer Day for Primary Care
May 10, 2019
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Medical Oncology Lead
St Boniface Site Director
CancerCare Manitoba

CancerCare MANITOBA

Objectives

- Explain the pathophysiology of the Immune System and Cancer
- Describe the relevance of Immuno-oncology in the Clinic

Conflicts of Interest

- Advisory Boards
  - BMS
  - Merck
- Clinical Trials
  - BMS
  - Merck
  - Roche
  - AstraZeneca

Breakthrough of the Year; Science 2013

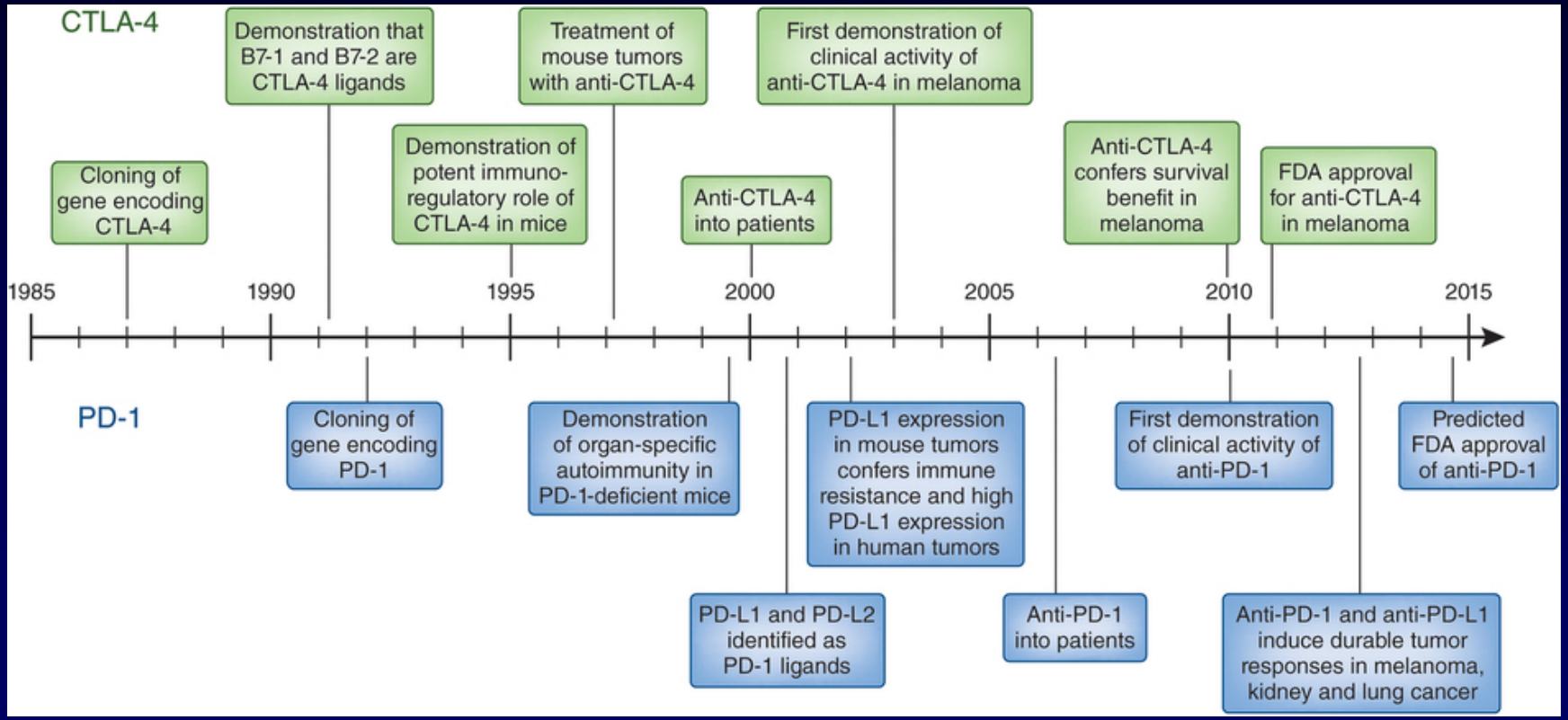
"This year marks a turning point in cancer, as long-sought efforts to unleash the immune system against tumours are paying off – even if the future remains a question mark"

Couzin-Frankel J. Science 2013;342:1432-33

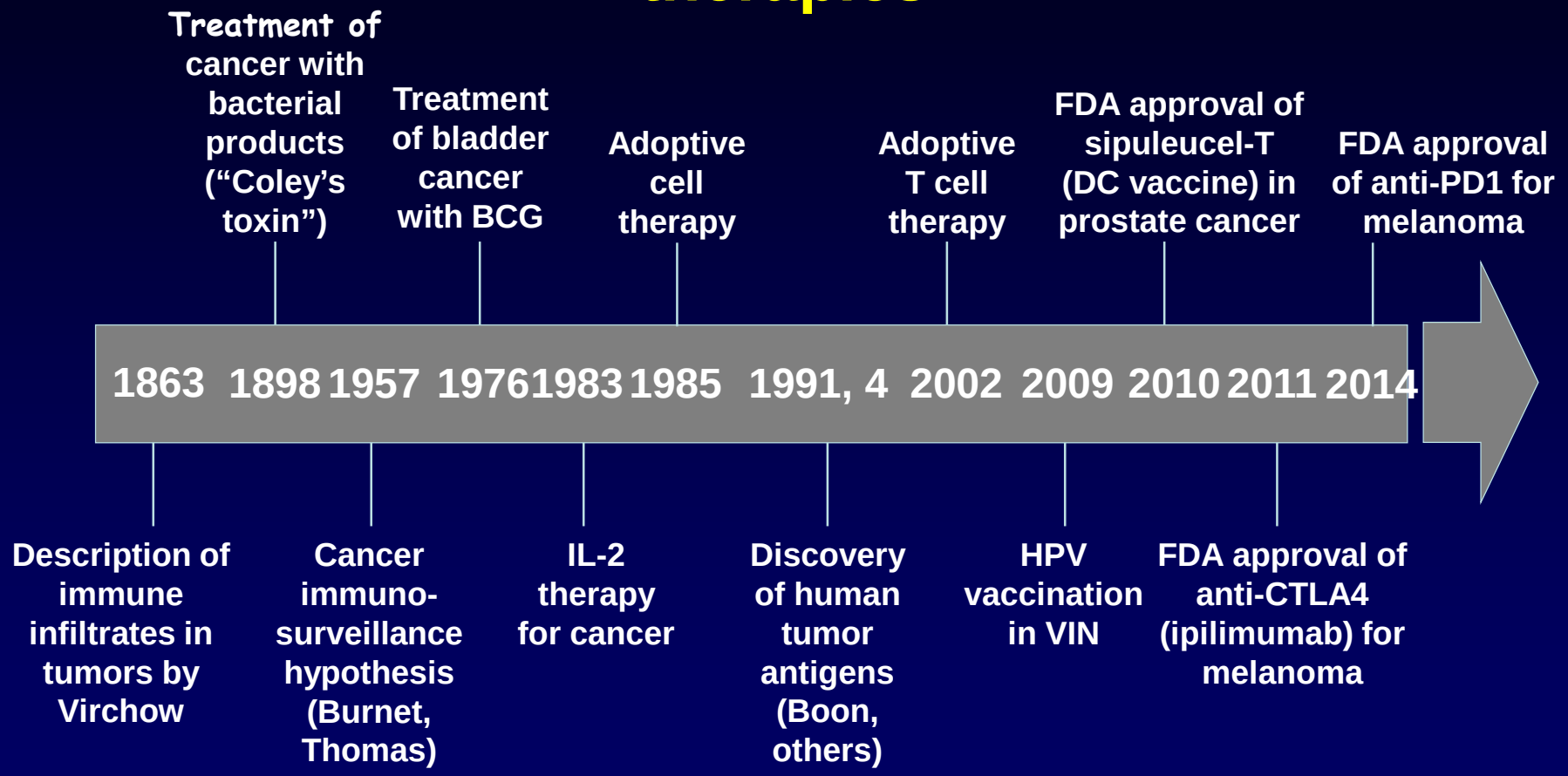
2018 Nobel Prize in Physiology or Medicine

James Allison

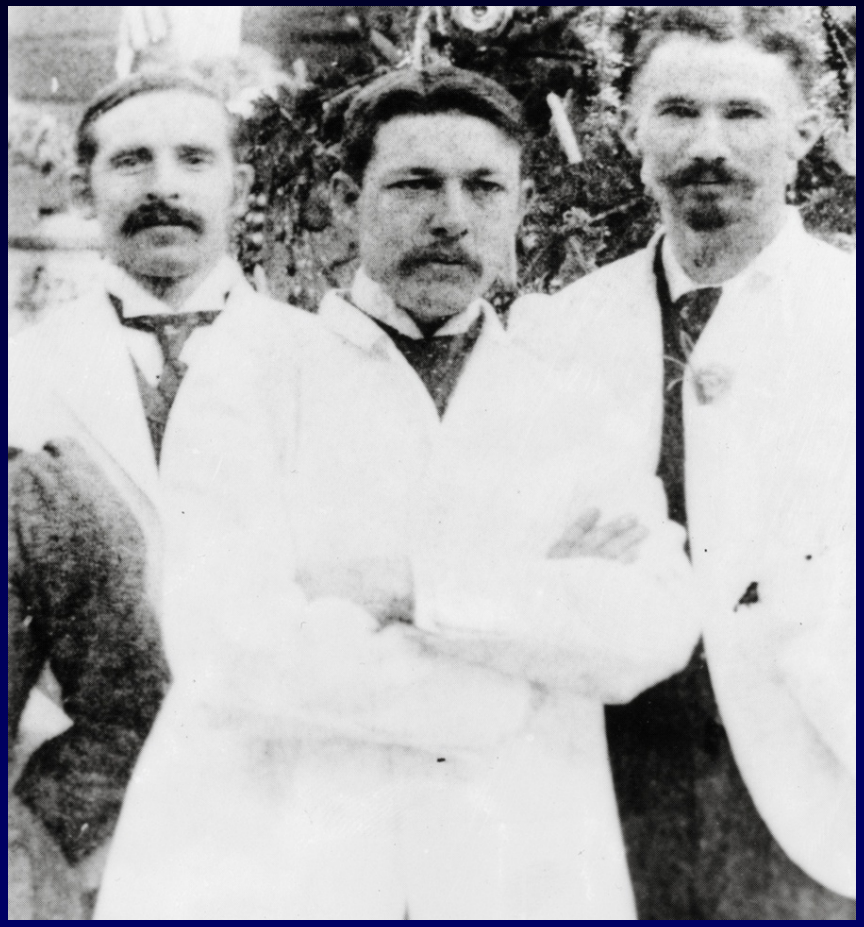
Tasuko Honjo


CTLA-4
Cloning of gene encoding CTLA-4
Demonstration that B7-1 and B7-2 are CTLA-4 ligands
Demonstration of potent immuno-regulatory role of CTLA-4 in mice
Treatment of mouse tumors with anti-CTLA-4
Anti-CTLA-4 into patients
First demonstration of clinical activity of anti-CTLA-4 in melanoma
Anti-CTLA-4 confers survival benefit in melanoma
FDA approval for anti-CTLA-4 in melanoma
1985
1990
1995
2000
2005
2010
2015
PD-1
Cloning of gene encoding PD-1
Demonstration of organ-specific autoimmunity in PD-1-deficient mice
PD-L1 and PD-L2 identified as PD-1 ligands
PD-L1 expression in mouse tumors confers immune resistance and high PD-L1 expression in human tumors
Anti-PD-1 into patients
First demonstration of clinical activity of anti-PD-1
Anti-PD-1 and anti-PD-L1 induce durable tumor responses in melanoma, kidney and lung cancer
Predicted FDA approval of anti-PD-1

The history of cancer immunotherapy: from empirical approaches to rational, science-based therapies



Ebers Papyrus c1550 BC



CONTRIBUTION TO THE KNOWLEDGE OF SARCOMA.[1]

By WILLIAM B. COLEY, M.D.,

OF NEW YORK.

I. A Case of Periosteal Round-Celled Sarcoma of the Metacarpal Bone; Amputation of the Forearm; General Dissemination in Four Weeks; Death Six Weeks Later.

II. The General Course and Prognosis of Sarcoma, Based Upon an Analysis of Ninety Unpublished Cases.

III. The Treatment of Sarcoma by Inoculation With Erysipelas, With a Report of Three Recent (Original) Cases.

I. THE patient a young lady, æt. 18, had been in perfect health from earliest childhood. The family history was likewise good with the exception of a remote tubercular tendency, and the fact that an ancestor, three generations before, had died of "cancer" of the lip, presumably epithelioma.

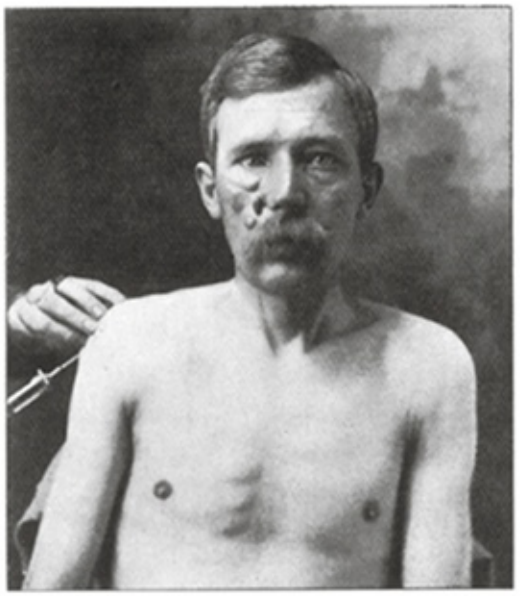
In the early part of July, 1890, she received a slight blow upon the back of the right hand. The hand became a little swollen and somewhat painful the first night. The next few days the pain became a trifle less and the swelling subsided, but did not entirely disappear. About a week later the swelling again began to increase very slowly, and the pain became more severe. She consulted a physician at the time of the injury, but there being no evidence of anything more than an ordinary bruise the usual local applications were applied.

August 12. The pain and swelling continuing, she again sought

[1]Read before the Surgical Section of the New York Academy of Medicine, April 27, 1891. (With a report of three cases treated since).

a

b



Immuno-Oncology

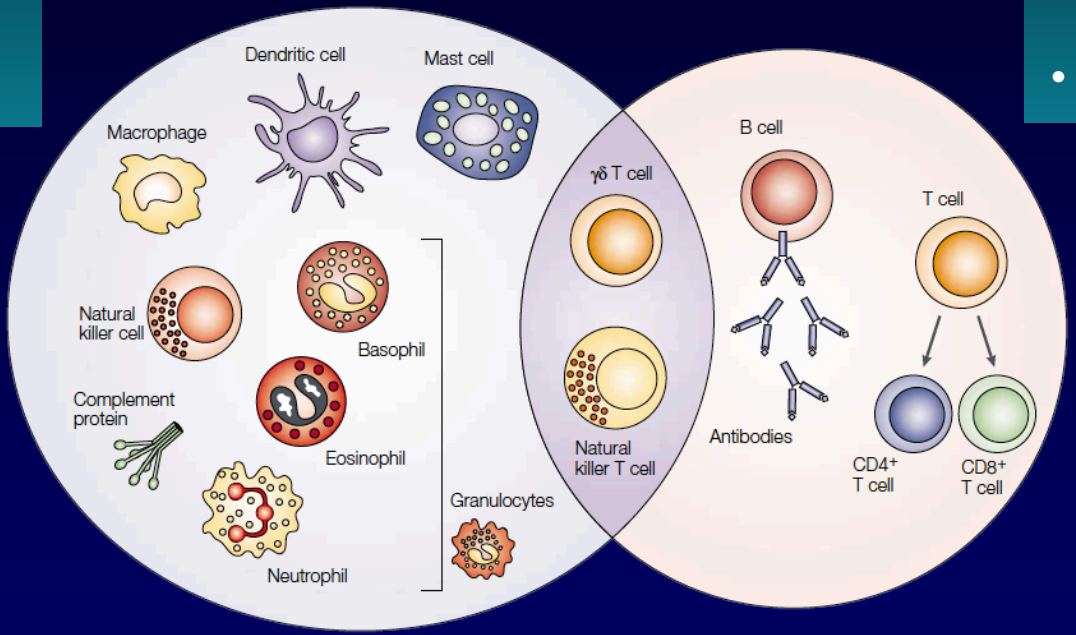
The Immune System is Comprised of Two "Arms": Innate and Adaptive[1]

- Immediate
- First line of immune defense
- Not antigen-specific response

Innate Immunity[2,3]

Adaptive Immunity

- Slow response
- Antigen-specific response
- Memory

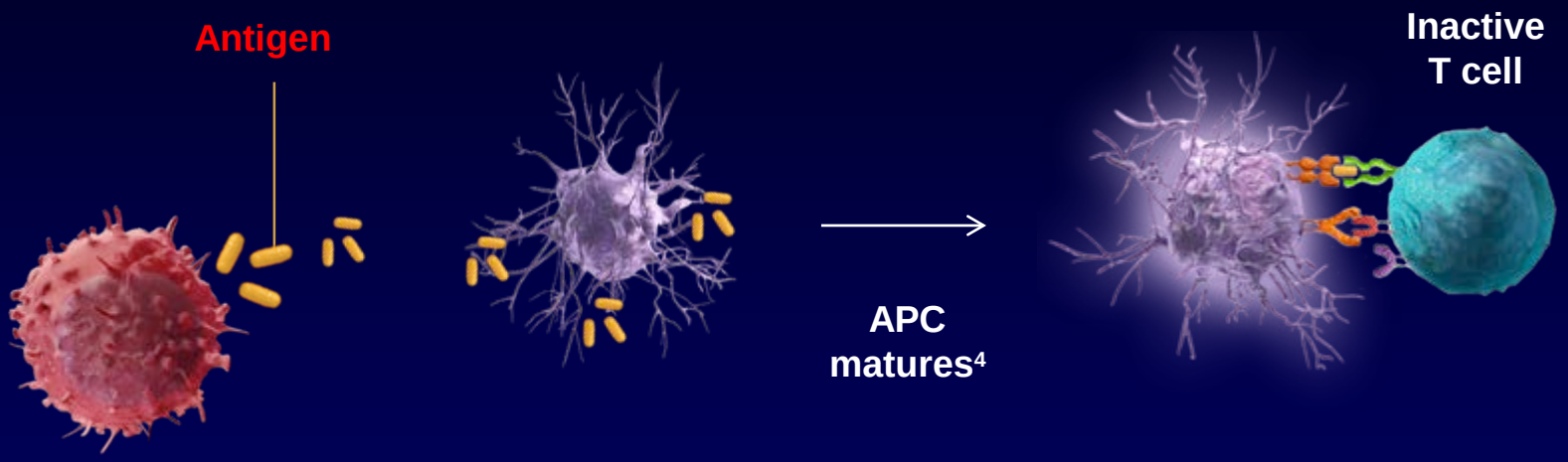


- External threats: viruses, parasites, protozoa, fungi, bacteria, toxins
- Internal threats: cancer

1. Abbas AK, *et al*. *Cellular and Molecular Immunology*. 7th ed. Philadelphia, PA: Elsevier Saunders; 2012.
2. Figure reprinted by permission from Macmillan Publishers Ltd: *Nature Reviews Cancer*. Dranoff G. *Nat Rev Cancer*. 2004;4:11-22.
3. Vesely MD, *et al*. *Annu Rev Immunol*. 2011;29:235-271.

T-cell Activation: Tumour-associated Antigens

Tumour-associated antigens can trigger a tumour-specific immune cell response:



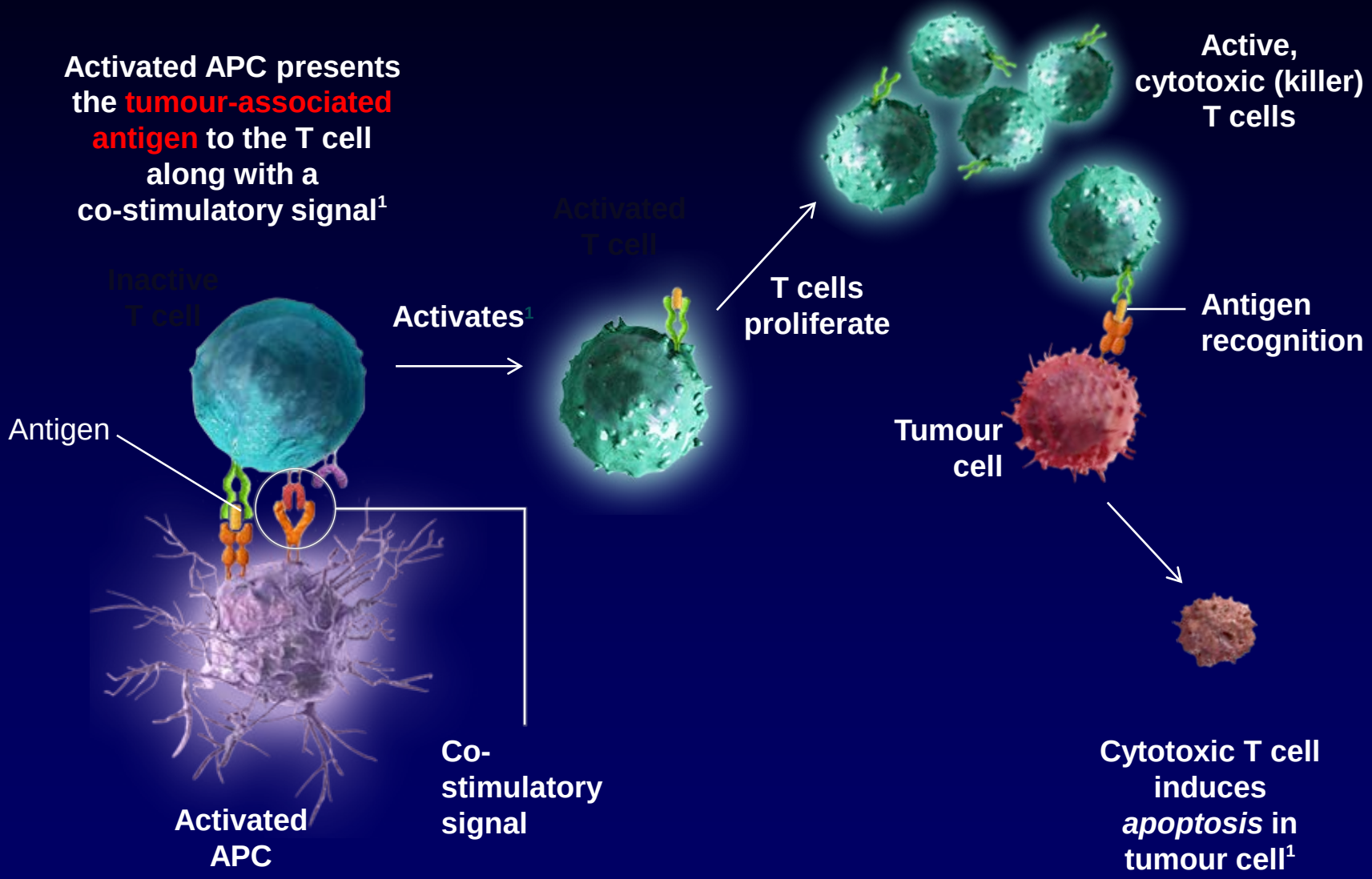
1
Tumours express a multitude of proteins, known as tumour-associated antigens[1,2,3,4]

2
Antigen presenting cell (APC) captures tumour-associated antigens[2]

3
Activated APC can interact with T cells[4]

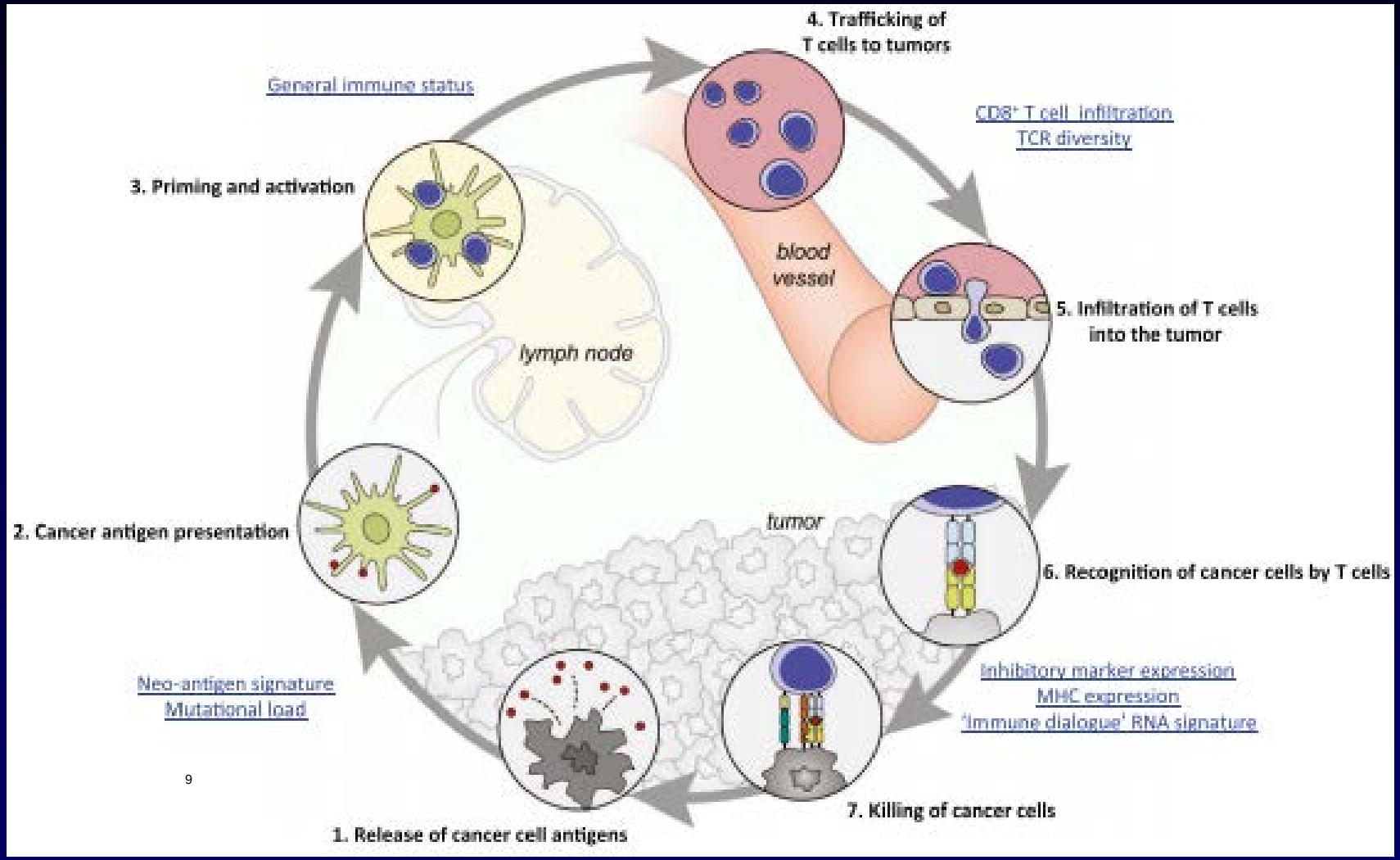
1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;11:252-264
2. Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature*. 2011;480:480-489
3. Heemskerk B, Kvistborg P, Schumacher TNM. The cancer antigenome. *EMBO J*. 2013;32(2):194-203
4. Boudreau JE, Bonehill A, Thielemans K, Wan Y. Engineering dendritic cells to enhance cancer immunotherapy. *Mol Ther*. 2011;19(5);841-8

T-cell Activation: Cytotoxic T cells



1. Janeway CA, *et al*. Immunobiology: The Immune System in Health and Disease. 6th ed. New York, NY: Garland Science; 2004

The Cancer – Immunity Cycle



1.Schumacher TN et al. *Cancer Cell* 2015;27:12-4
2.Chen DS, Mellman I. *Immunity* 2013;39:1-10

Mechanisms for Regulation of the Adaptive Immune System

Immune System Pathways

- **Normal conditions:**
  - **There are a number of immune activation and inhibition pathways that modulate the immune response and protect healthy tissues from collateral damage[1,7]**
- **Tumour evasion of the immune system may be associated with an imbalance in immune activation and inhibition.[1-5]**

Tumours may *down-regulate co-stimulatory pathways.*[2-3]
Co-stimulatory receptors include:

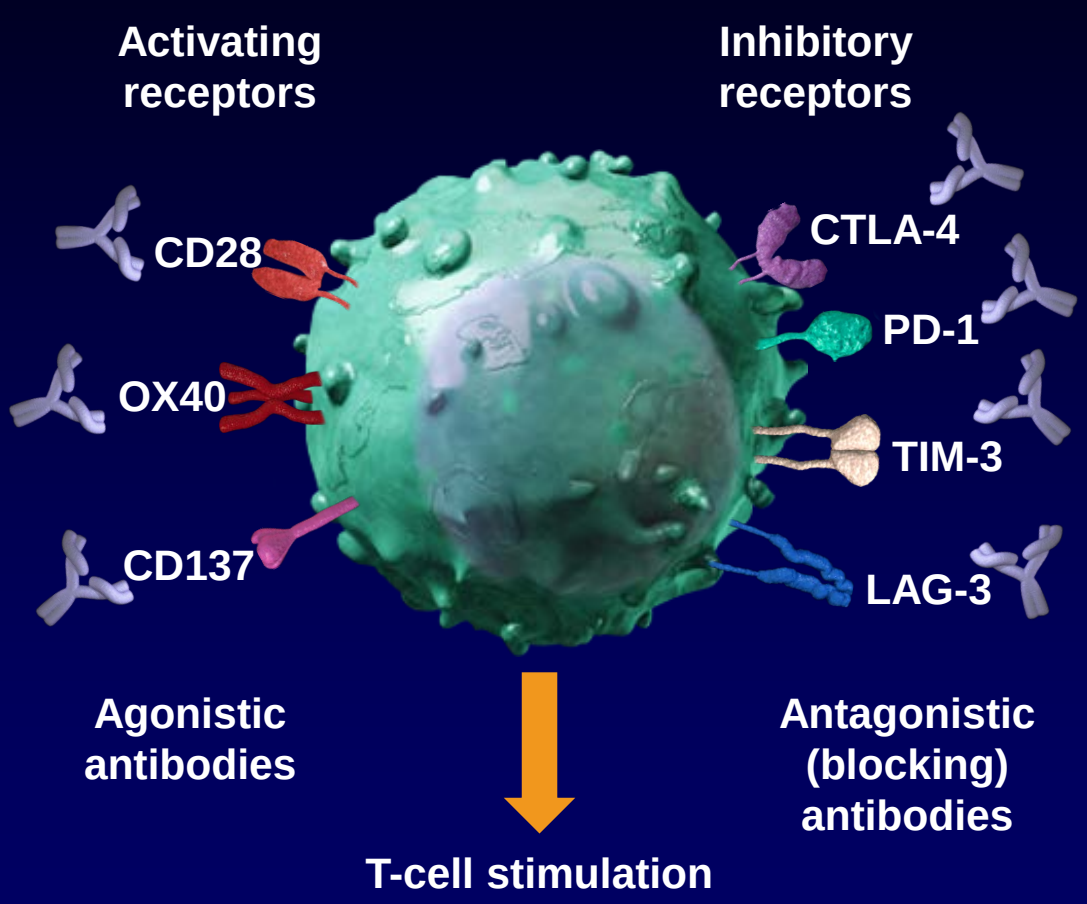
- **CD28**
- **CD40**
- **OX40**
- **CD137**
- **GITR**

Tumours may *up-regulate immune checkpoints* (inhibitory signaling pathways).[2,3,5,6] Checkpoint pathway molecules include:

- **LAG-3**
- **CTLA-4**
- **B7-H3**
- **PD-1**
- **TIM-3**

1. Baruah P, *et al*. *Immunobiology*. 2012;217(7):669-675 2. Hemon P, *et al*. *J Immunol*. 2011,186:5173-5183 3. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264 4. Kirkwood JM, *et al*. CA *Cancer J Clin*. 2012;62:309-335 5. Zang X, *et al*. *PNAS*. 2007;104(49):19458-19463 6. Leitner J. *Eur J Immunol*. 2009;39:1754-1764. 7. Janeway CA, *et al*. Immunobiology: The Immune System in Health and Disease. 6th ed. New York, NY: Garland Science; 2004

T-cell Checkpoint Regulation



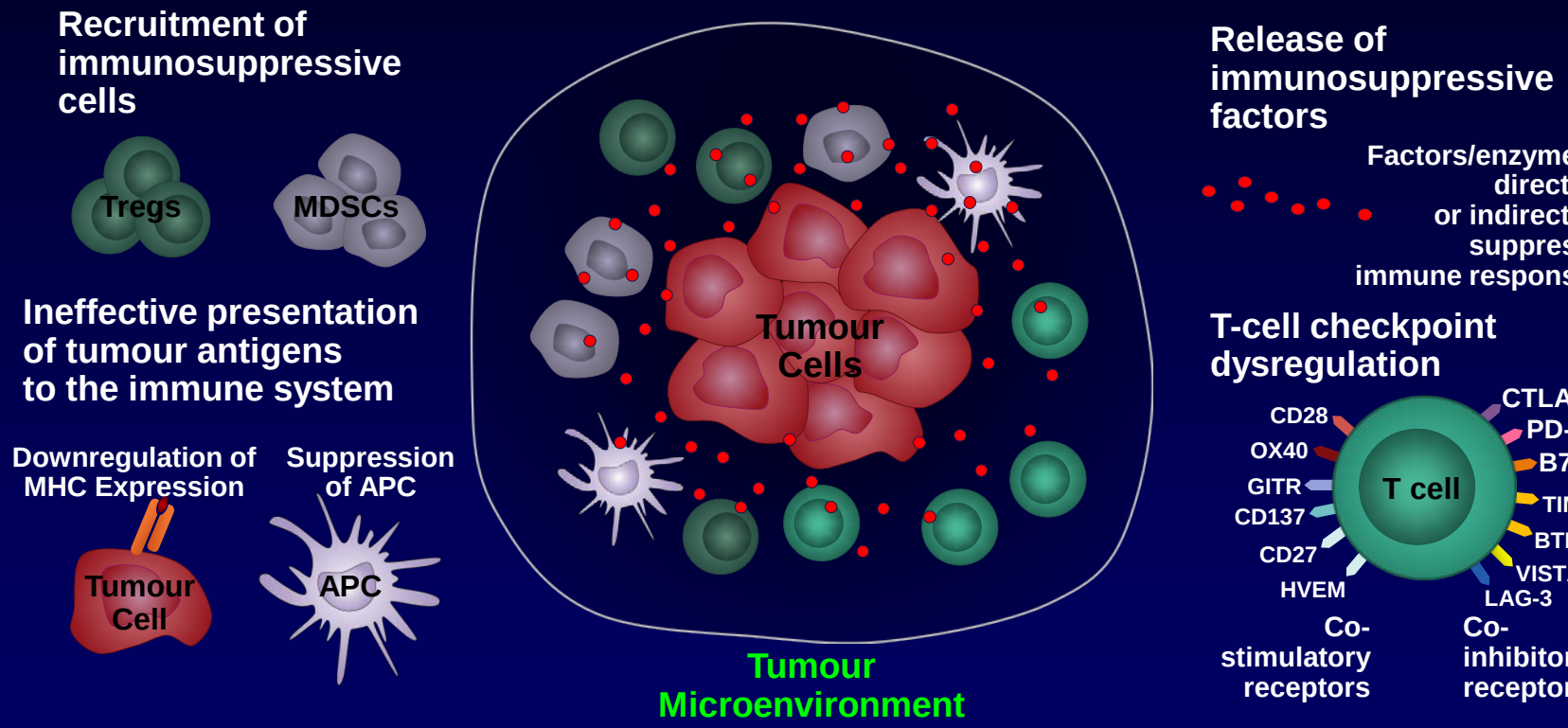
- T-cell responses are regulated though a complex balance of inhibitory (“checkpoint”) and activating signals
- Tumours can dysregulate these pathways and consequently, the immune response
- Targeting these pathways is an evolving approach to cancer therapy

Adapted from Mellman I, *et al*. *Nature* 2011; 480(7378):480-9; Pardoll DM. *Nat Rev Cancer* 2012; 12(4):252-64.

Mechanisms for Cancer to Evade the Immune System

Immune Escape in Cancer

Many tumours escape the immune response by creating an immunosuppressive microenvironment that prevents an effective antitumour response[1,2]



The mechanisms tumours use to escape the immune system provide a range of potential therapeutic targets for cancer

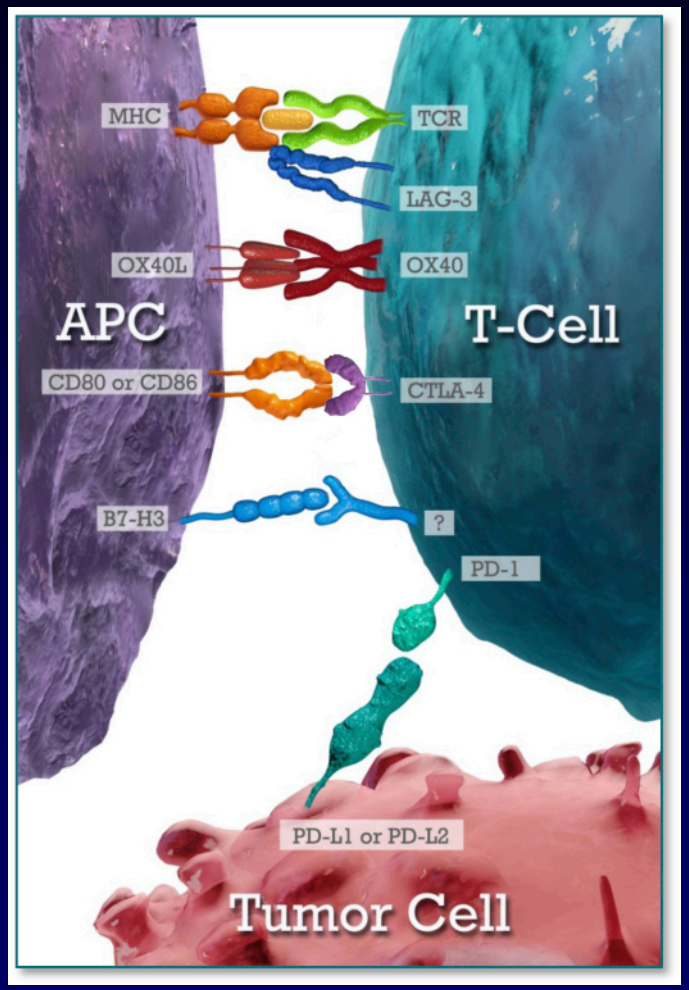
APC=antigen-presenting cell; MDSC=myeloid-derived suppressor cell; MHC=major histocompatibility complex; Treg=regulatory T cell.

1. Bremnes RM *et al*. *J Thorac Oncol*. 2011;6:824-833.
2. Jadus MR *et al*. *Clin Dev Immunol*. 2012:160724.

CHECKPOINT INHIBITION AS A WAY TO AWAKEN THE IMMUNE SYSTEM

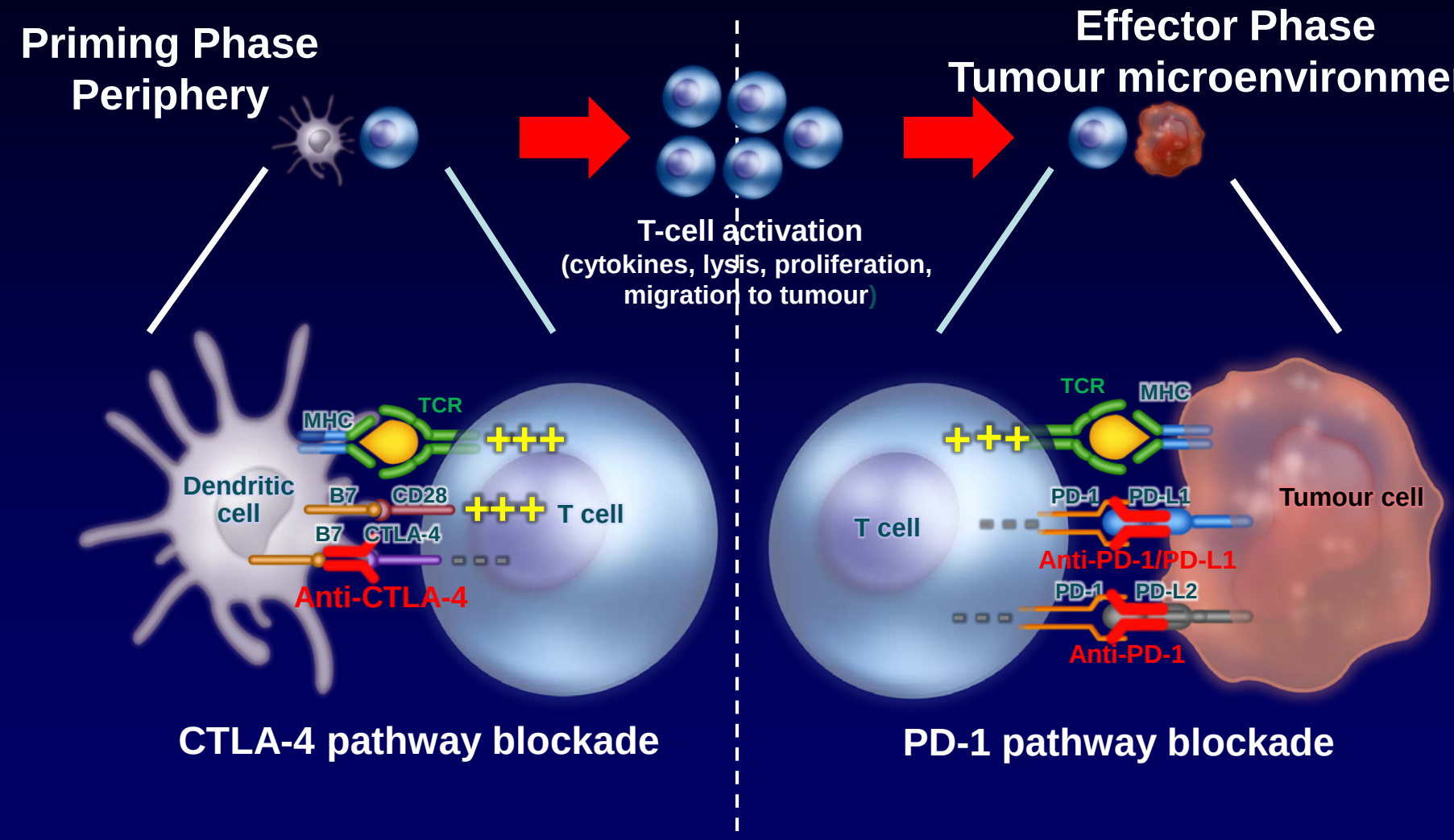
Multiple Potential I-O Targets to Activate the Immune System

- Antitumour response is a net balance of complex inhibitory and stimulatory interactions between APC, T cell, and tumour[1-6]
- Multiple potential I-O targets, such as:
  - T-cell co-stimulatory receptors
  - T-cell checkpoint/inhibitory receptors
  - APC
  - Microenvironment
- Modulation of these targets by I-O therapies may activate the immune system to eliminate the tumour



1. Baruah P, *et al*. *Immunobiology*. 2012;217(7):669-675; 2. Hemon P, *et al*. *J Immunol*. 2011,186:5173-5183; 3. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264; 4. Kirkwood JM, *et al*. *CA Cancer J Clin*. 2012;62:309-335; 5. Zang X, *et al*. *PNAS*. 2007;104(49):19458-19463; 6. Leitner J. *Eur J Immunol*. 2009;39:1754-1764.

Immuno-oncology: Blocking CTLA-4 and PD-1 Pathways with Monoclonal Antibodies

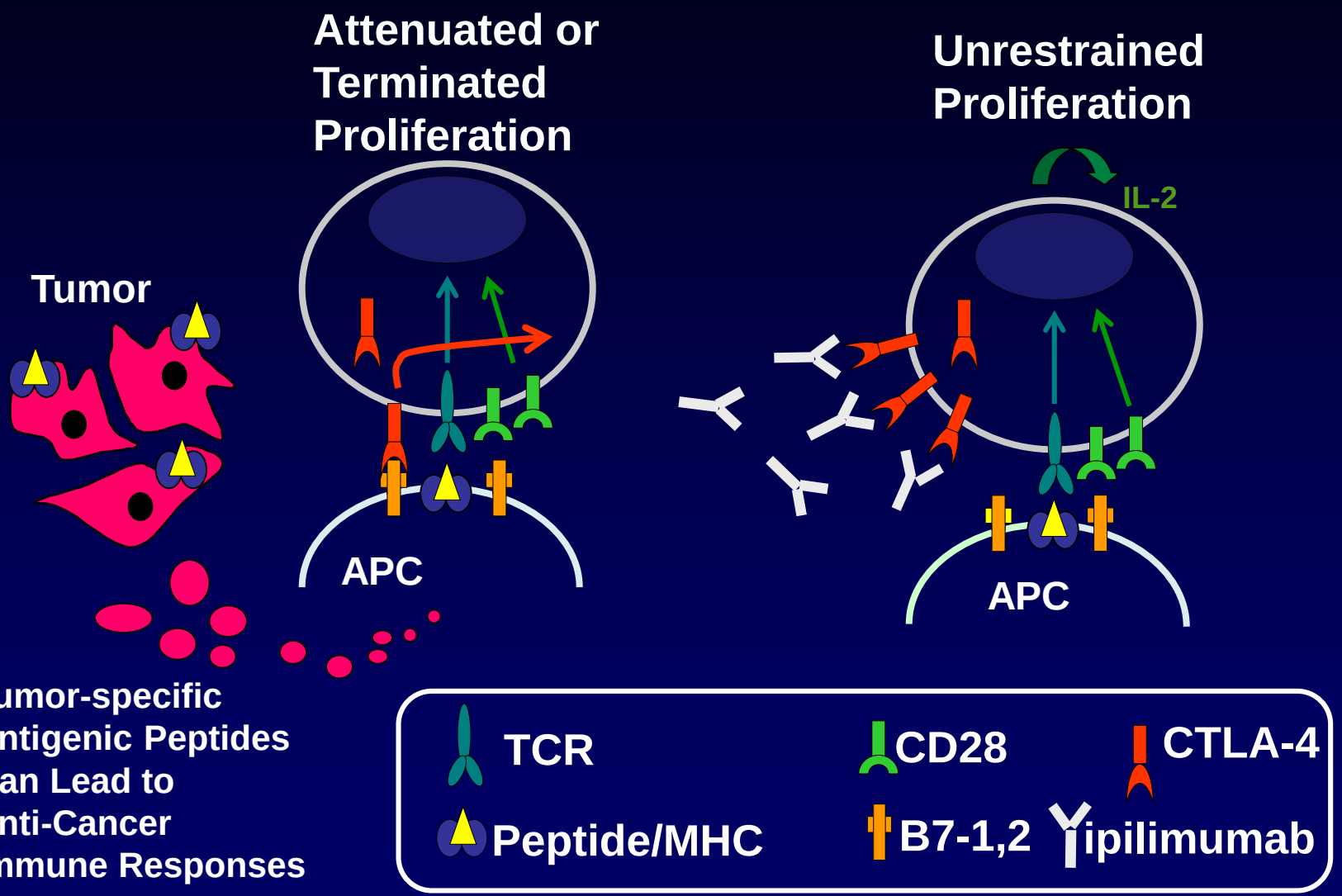


CTLA-4=cytotoxic T-lymphocyte antigen-4; PD-1=programmed cell death 1; PD-L1/2=PD ligand 1/2; TCR=T cell receptor.

Adapted from Wolchock J, *et al*. Oral presentation at ASCO 2013 (Abstract 9012).

CTLA-4 Monoclonal Antibodies

CTLA-4: Mechanism of Action (MoA)

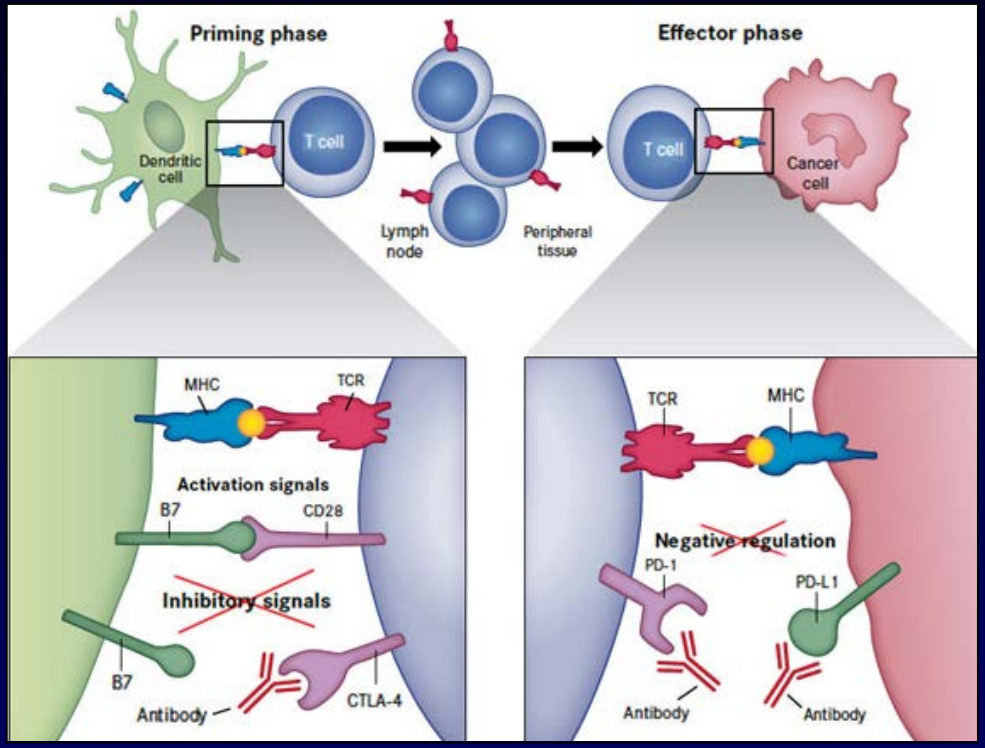


Adapted from Chambers CA, et al. *Annu Rev Immunol.* 2001;19:565-594.

Anti-PD-1/L1

PD-1 and PD-L1 Antibodies

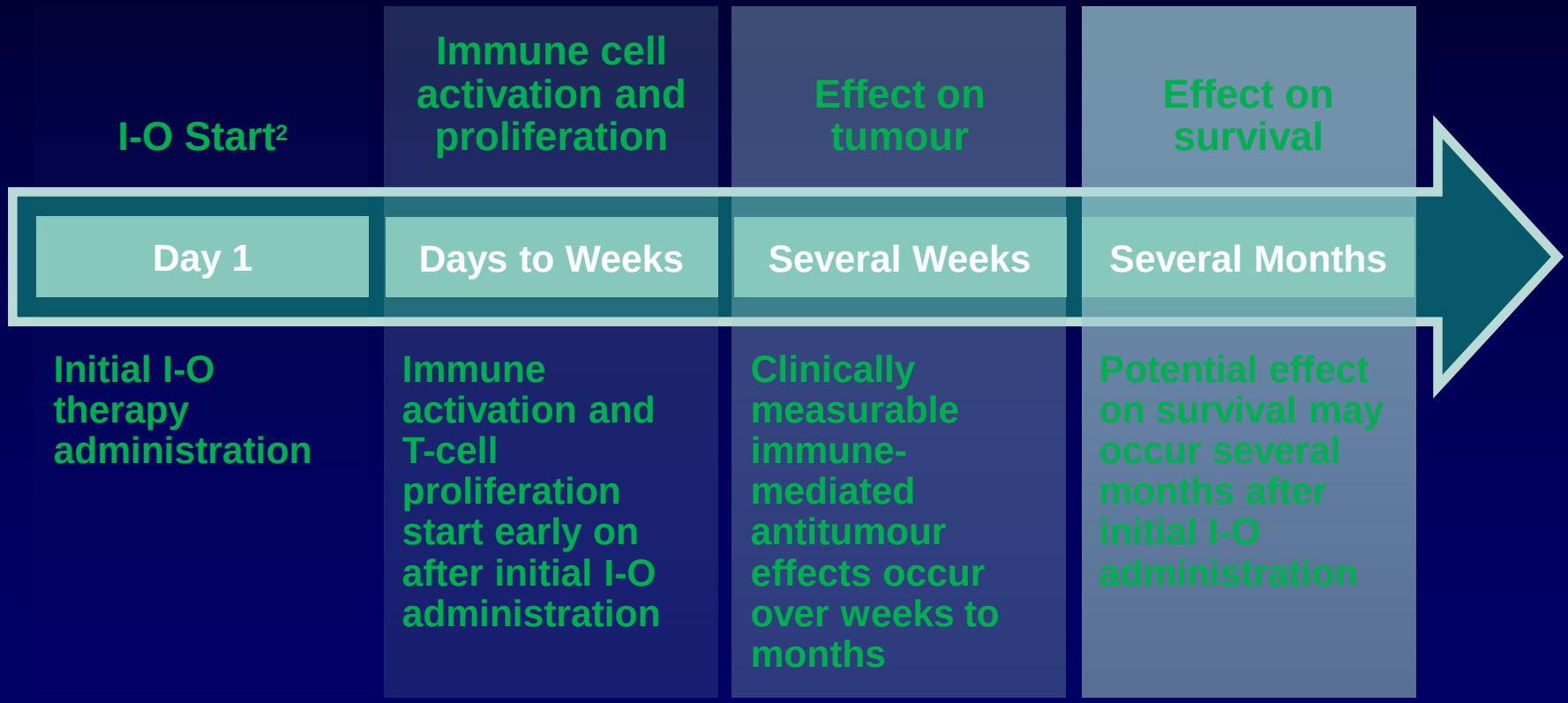
- PD-1 – inhibitory receptor found on activated lymphocytes and monocytes and is associated with tumour immune escape
- Binds with PD-L1 on tumour cells
- Interaction between PD-1 and PD-L1 suppresses the cytotoxic T-cell response



Adapted from *N Engl Med*. 2012;366(26):2517

Response to I-O Therapy is a Multi-step Process that May Impact Response Kinetics

Therapies that affect the immune system may not induce a measurable impact on tumour growth immediately after administration[1]

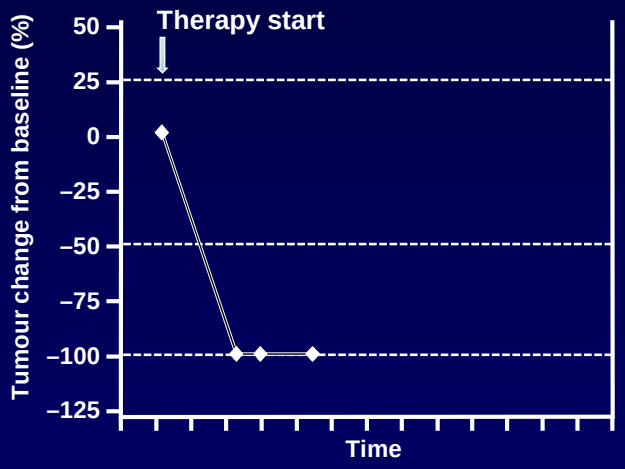


1. Hoos A, Britten CM. *OncoImmunology*. 2012;1:334-339;
2. Hoos A, *et al*. *J Natl Cancer Inst*. 2010;102:1388-1397.

Potential Tumour Response Patterns to Therapy

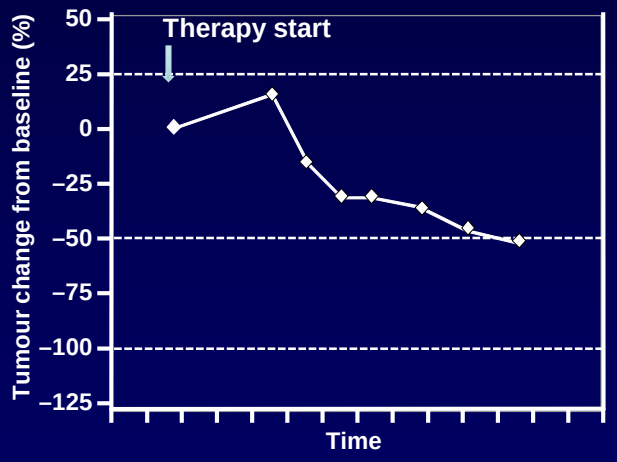
Response in baseline lesions typically seen with chemotherapy, but also I-O therapies and targeted therapies. Captured by existing RECIST and WHO criteria

"Stable disease": Slow, steady decline in tumour volume seen with chemotherapy, targeted and I-O therapies. Captured by existing RECIST and WHO criteria



Thresholds for response or progressive disease (RECIST)

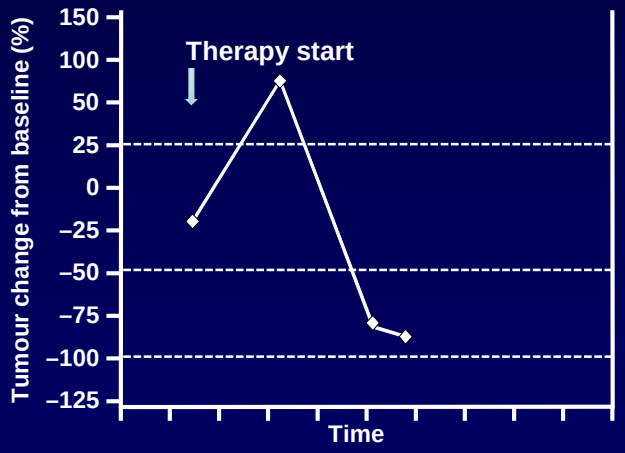
Graphs for illustrative purposes showing responses to ipilimumab in advanced melanoma



Adapted from Wolchok JD, *et al*. *Clin Cancer Res* 2009;15:7412–7420; Hoos A, *et al*. *Annals of Oncology* 2012;23(suppl 8): viii47–viii52.

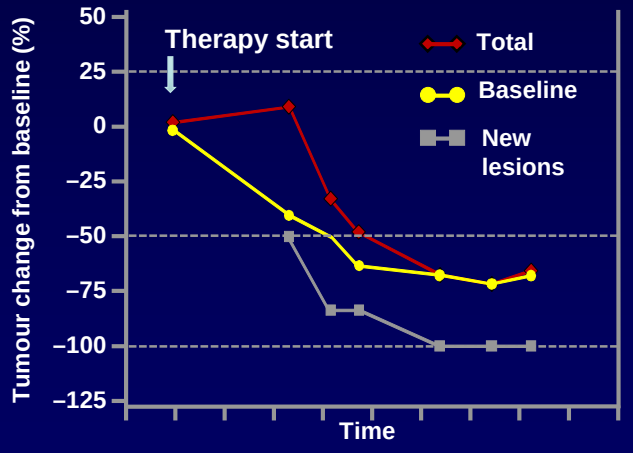
Potential Tumour Response Patterns to Therapy

Response after initial increase in tumour volume; novel and specific to I-O therapy RECIST or WHO criteria may not be appropriate to assess



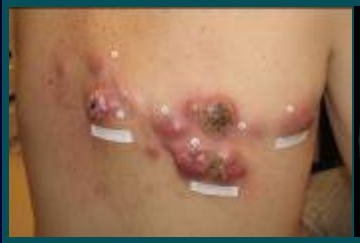
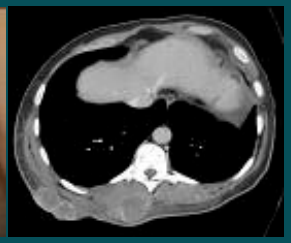
Some vaccines may not follow similar patterns of response as other I-O therapies

Reduction in tumour burden after appearance of new lesions; novel and specific to I-O therapy, RECIST or WHO criteria may not be appropriate to assess

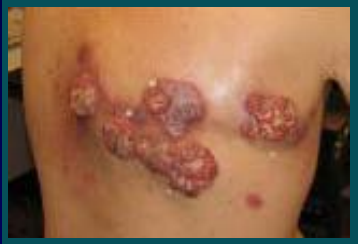
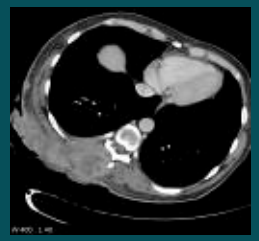


Adapted from Wolchok JD, *et al*. *Clin Cancer Res* 2009;15:7412–7420; Hoos A, *et al*. *Annals of Oncology* 2012;23(suppl 8): viii47–viii52.

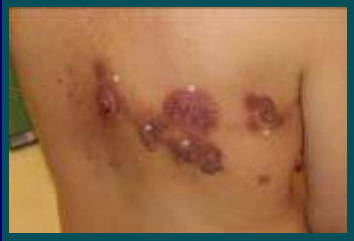
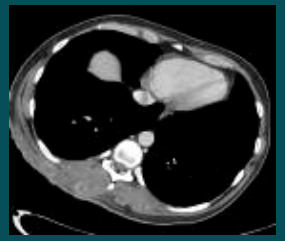
Example of Evolution of Response to CTLA-4 Inhibition

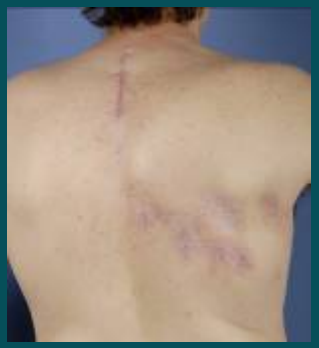
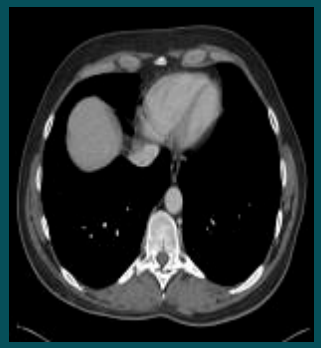
Screening

Week 12:
Initial increase in total tumour burden (mWHO PD)

Week 16:
Responding

Week 96:
Durable and ongoing response without signs of irAEs

irAE = immune-related adverse events

Harmankaya K, *et al.* Presented at the World Meeting of Interdisciplinary Melanoma/Skin Cancer Centers: November 19 - 21, 2009; Berlin, Germany.

Pseudo-progression: Inflammation Causes Swelling, May Appear as Tumour Growth or New Lesions Upon Imaging[1]

Considerations when evaluating true progression vs. pseudo-progression

	May indicate progression	May indicate pseudo-progression
Performance status	Deterioration of performance	Remains stable or improves
Systemic symptoms	Worsen	May or may not improve
Symptoms of tumour enlargement	Present	May or may not be present
Tumour burden Baseline New lesions	Increase Appear and increase in size	Increase followed by response Appear then remain stable and/or subsequently respond
Biopsy may reveal	Evidence of tumour growth	Evidence of T-cell infiltration

1. Wolchok JD, *et al. Clin Cancer Res*. 2009;15:7412-7420; 2. Topalian SL, *et al. N Engl J Med*. 2012;366:2443-2354;
3. Eisenhauer EA, *et al. Eur J Cancer*. 2009;45:228-247; 4. Chow LQ. Am Soc Clin Oncol Educ Book. 2013:280-285;
5. American Cancer Society. Lung Cancer. http://www.cancer.org/cancer/lungcancer-non-smallcell/detailed guide/non-small-cell-lung-cancer-diagnosis.

Measurement of Response

Table 1. Comparison of imRECIST With RECIST v1.1 and irRC

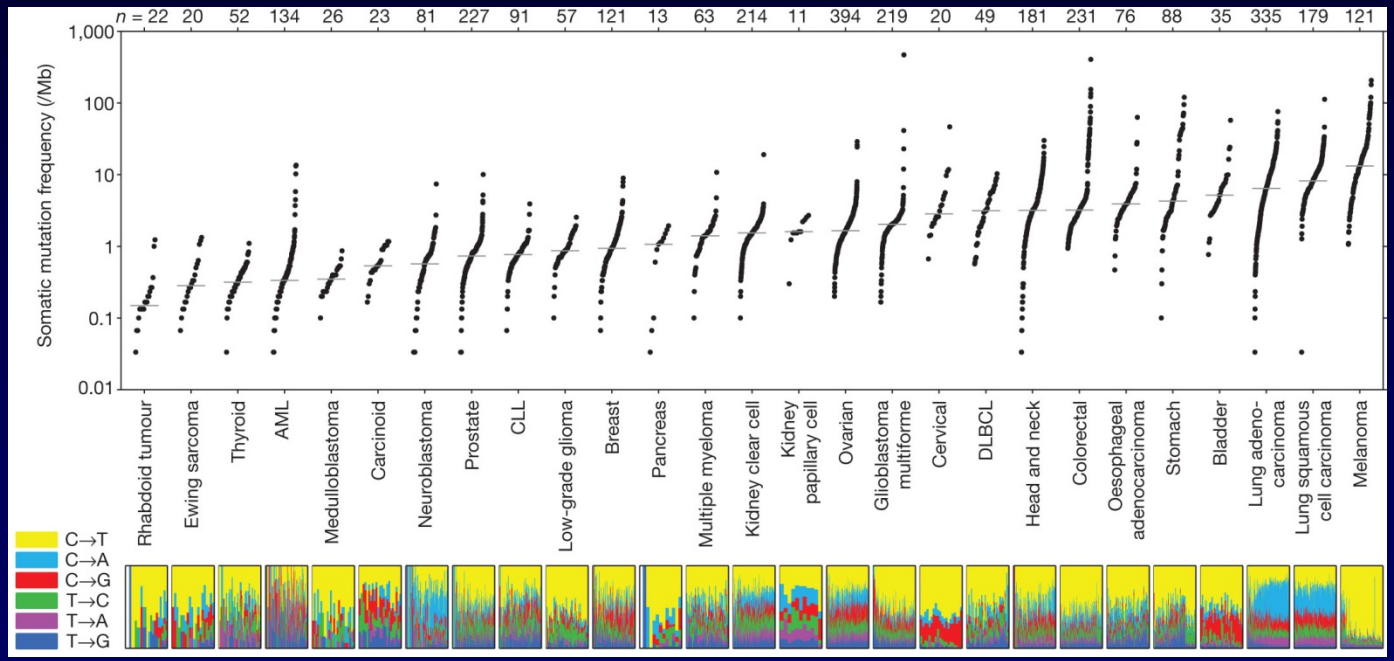
Criterion	RECIST v1.1	irRC[6]	imRECIST*
Tumor burden	Unidimensional Up to five target lesions/two per organ	Bidimensional per WHO Up to 10 target lesions/ five per organ	Unidimensional, with other target lesion criteria (number, measurability) per RECIST v1.1
New lesions	Always represent PD	New lesions do not categorically define PD Measurable new lesions incorporated into the total tumor burden Nonmeasurable new lesions preclude CR	
Nontarget lesions	Can contribute to defining CR or PD (unequivocal progression)	Nontarget progression does not define PD Can only contribute to defining CR (complete disappearance required)	
PD	≥ 20% increase in the SLD (RECIST) and ≥ 5 mm increase compared with nadir, unequivocal progression in nontarget lesions, and/or appearance of new lesions	Determined only on the basis of measurable disease	
		Negated by subsequent non-PD assessment ≥ 4 weeks from the date first documented (lack of confirmation)	
		≥ 25% increase in the SLD compared with baseline/ nadir	≥ 20% increase in SLD (RECIST) compared with baseline/nadir
	Confirmation of PD not required	Best response may occur before confirmed PD	Best response may occur after any number of PD assessments

Abbreviations: CR, complete response; imRECIST, immune-modified RECIST; irRC, immune-related response criteria; PD, progressive disease; RECIST, Response Evaluation Criteria In Solid Tumors; SLD, sum of longest diameters.
*imRECIST follows RECIST v1.1 conventions unless otherwise stated.

Hodi et al. JCO 2018;36:850-858.

Impact of Immunotherapy in the clinic

Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs



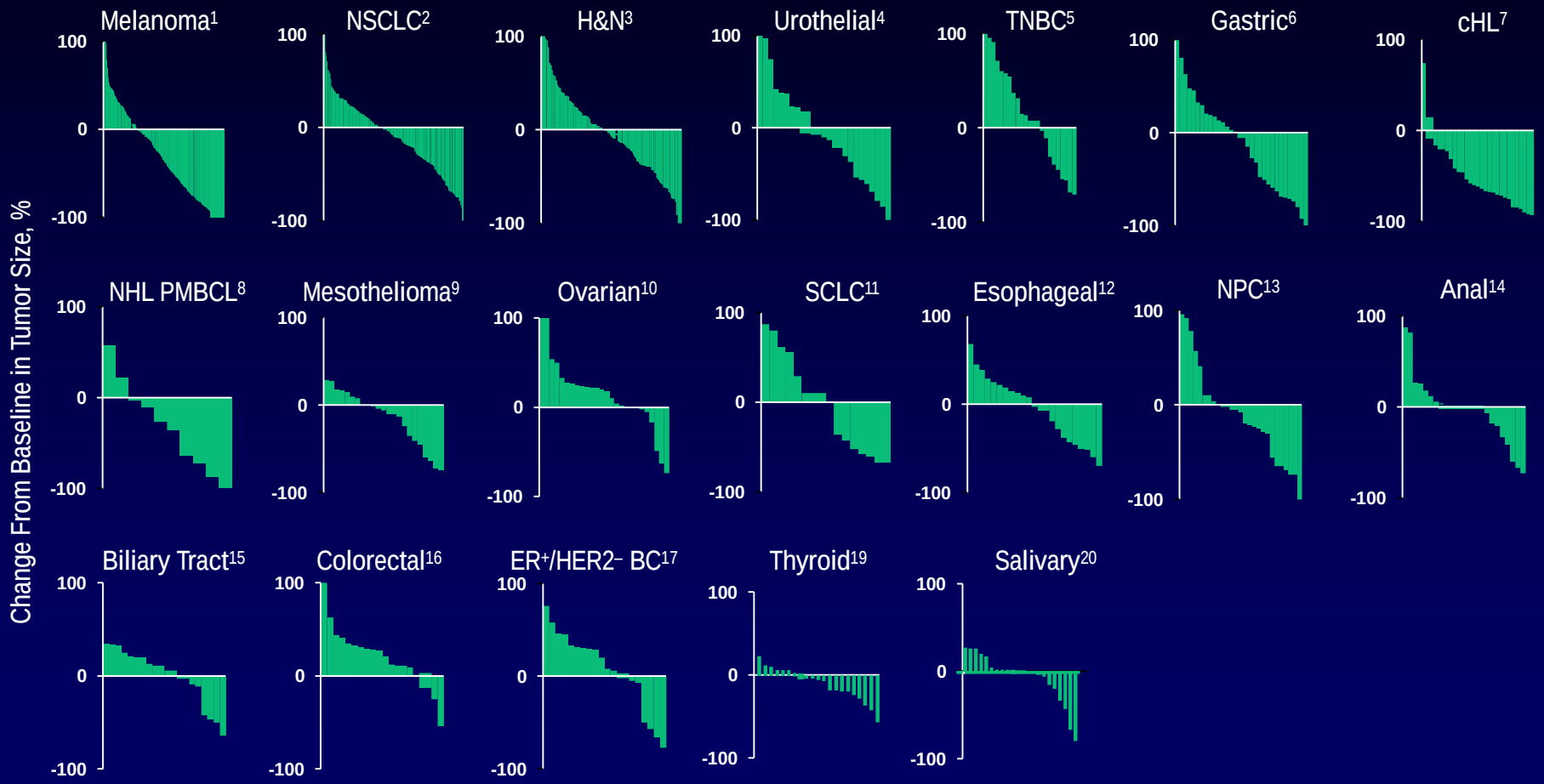
Mutational heterogeneity in cancer-altered proteins contain neoepitopes for immune recognition

MS Lawrence et al. Nature 2013 ;499(7457):214-218.

- **Currently approved/access to in Manitoba;**
  - **Adjuvant and metastatic melanoma**
  - **Adjuvant Stage III and metastatic 1st and 2nd line NSCLC**
  - **Metastatic 1st line and beyond Renal Cancer**
  - **Metastatic urothelial cancer**
  - **2nd line SCC of the Head and Neck**
  - **Merkel Cell Carcinoma**
  - **Relapsed Hodgkin's Disease**

- **Coming up in the next six months;**
  - **TNBC 1st line**
  - **Metastatic SCC lung**
  - **Metastatic SCLC**
  - **Metastatic SCC skin**

Pembrolizumab Activity

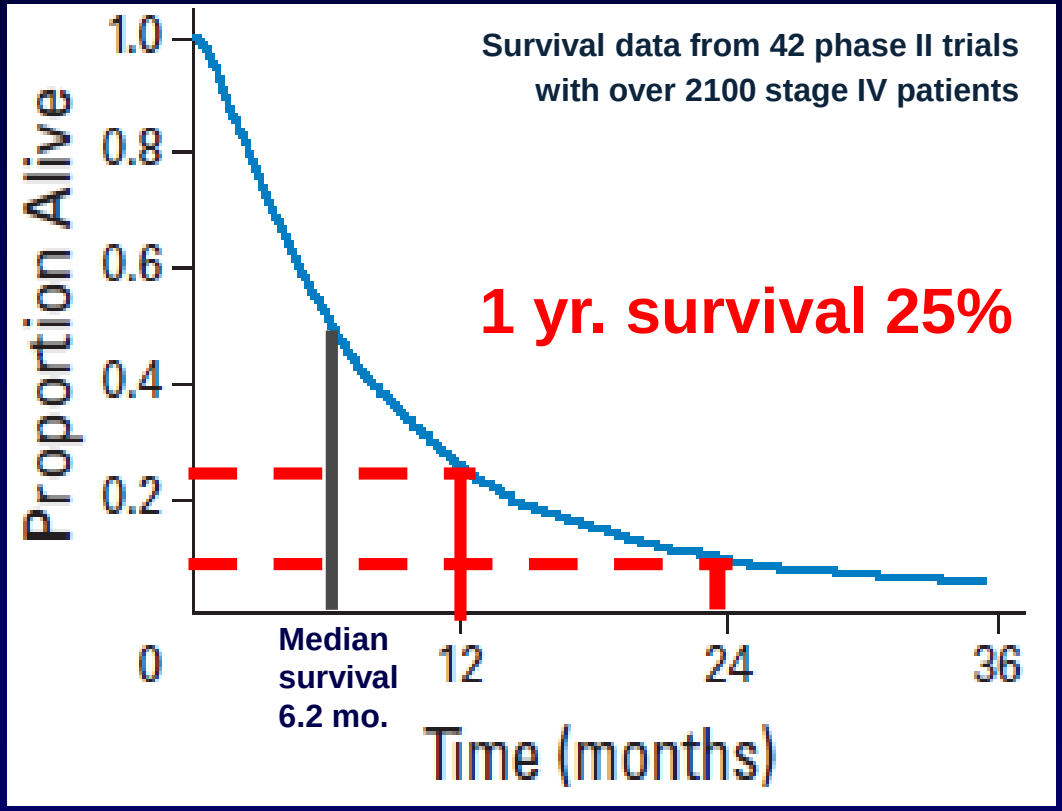


1. Daud A et al. ASCO 2015; 2. Garon EB et al. ESMO 2014; 3. Seiwert T et al. ASCO 2015; 4. Plimack E et al. ASCO 2015; 5. Nanda R et al. SABCS 2014; 6. Bang YJ et al. ASCO 2015 ; 7. Moskowitz C et al. ASH 2014; 8. Zinzani PL et al. ASH 2015; 9. Alley EA et al. AACR 2015; 10. Varga A et al. ASCO 2015; 11. Ott PA et al. 2015 ASCO; 12. Doi T et al. ASCO 2015; 13. Hsu C et al. ECC 2015; 14. Ott PA et al. ECC 2015; 15. Bang Y-J et al. ECC 2015; 16. O'Neil B et al. ECC 2015; 17. Rugo HS et al. SABCS 2015; 18. Frenel JS et al. ASCO 2016; 19. Mehnert JM et al. ASCO 2016; 20. Cohen R et al. ASCO 2016.

Landmark Meta-analysis: Overall Survival (OS) in Metastatic Stage IV Melanoma

Median OS: 6.2 months

- 25.5% alive at 1 year
- Only ~10% alive at 24 months

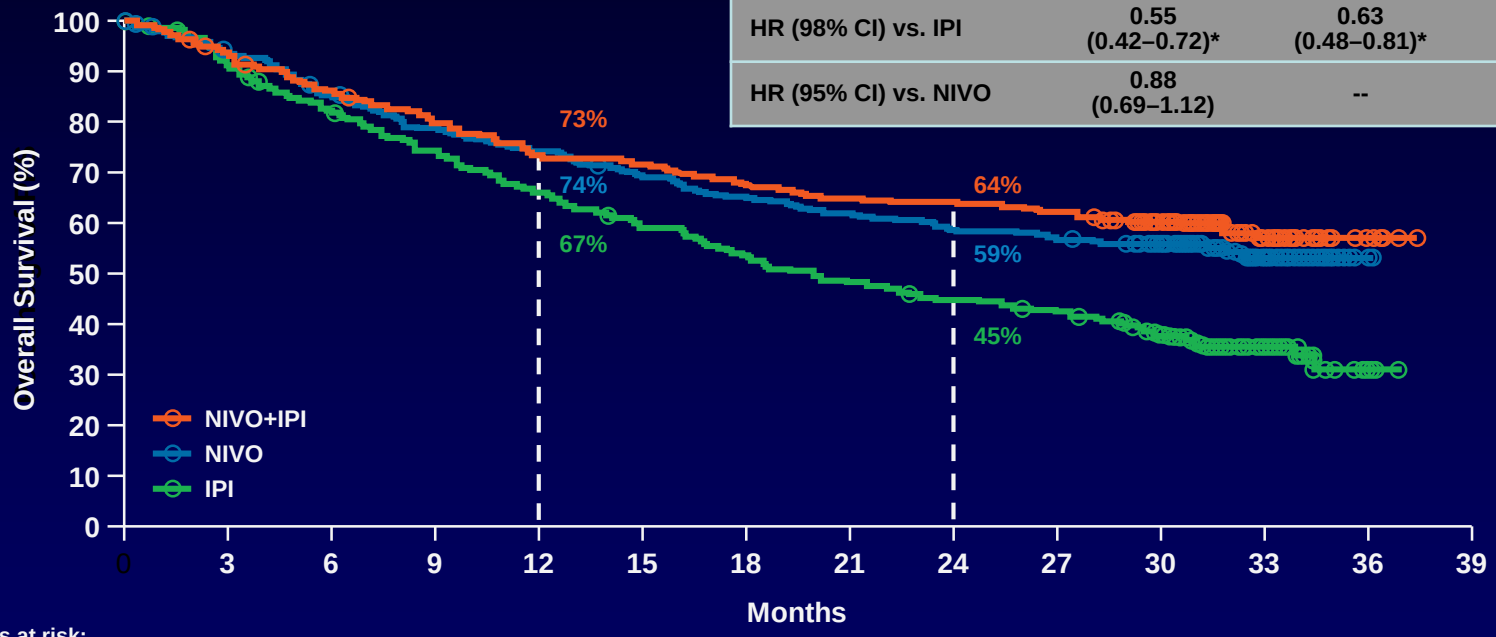


Korn EL, et al. *J Clin Oncol.* 2008;26(4):527-534.

Overall Survival

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
Median OS, mo (95% CI)	NR	NR (29.1–NR)	20.0 (17.1–24.6)
HR (98% CI) vs. IPI	0.55 (0.42–0.72)*	0.63 (0.48–0.81)*	--
HR (95% CI) vs. NIVO	0.88 (0.69–1.12)	--	--

*P<0.0001



Patients at risk:

NIVO+IPI	314	292	265	247	226	221	209	200	198	192	170	49	7	0
NIVO	316	292	265	244	230	213	201	191	181	175	157	55	3	0
IPI	315	285	254	228	205	182	164	149	136	129	104	34	4	0

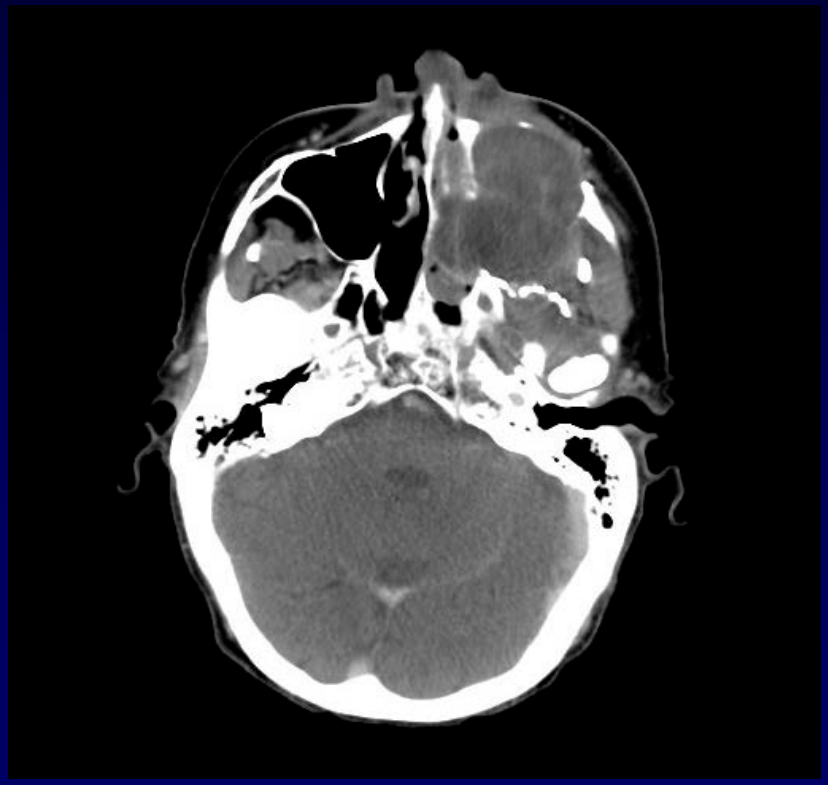
Database lock: Sept 13, 2016, minimum f/u of 28 months

Wolchuk et al. NEJM 2017; 377:1345-1356.

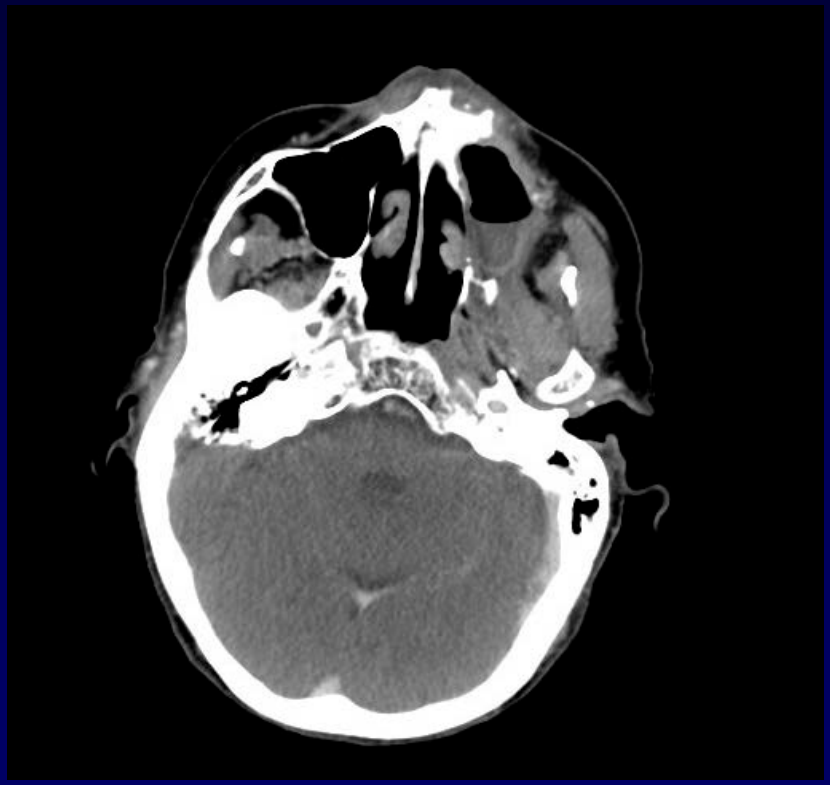

THE CARTER CENTER

Case Presentation

Oct 22, 2015

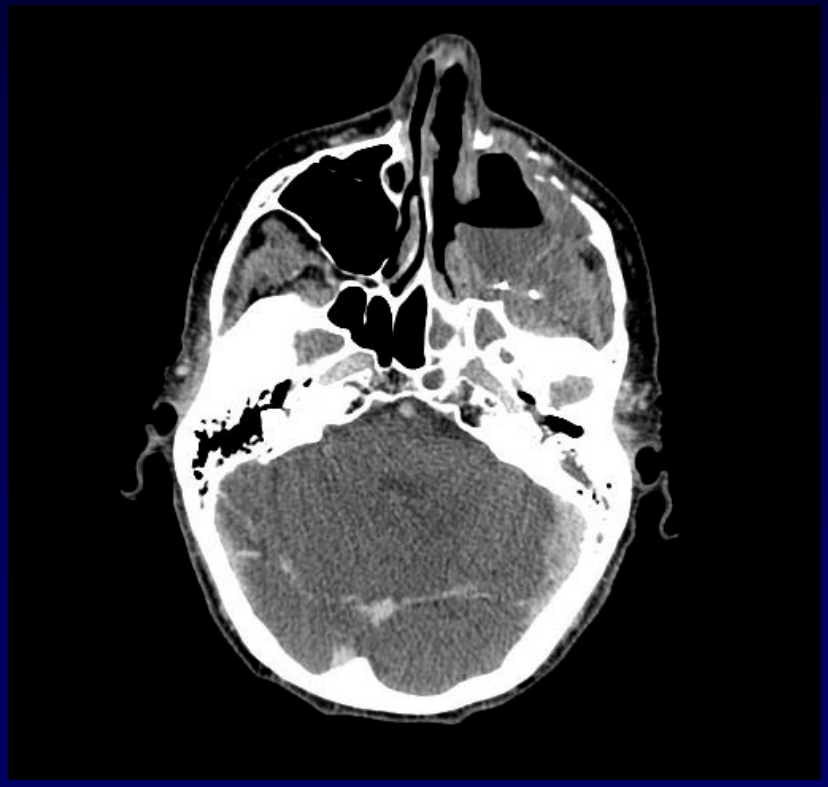


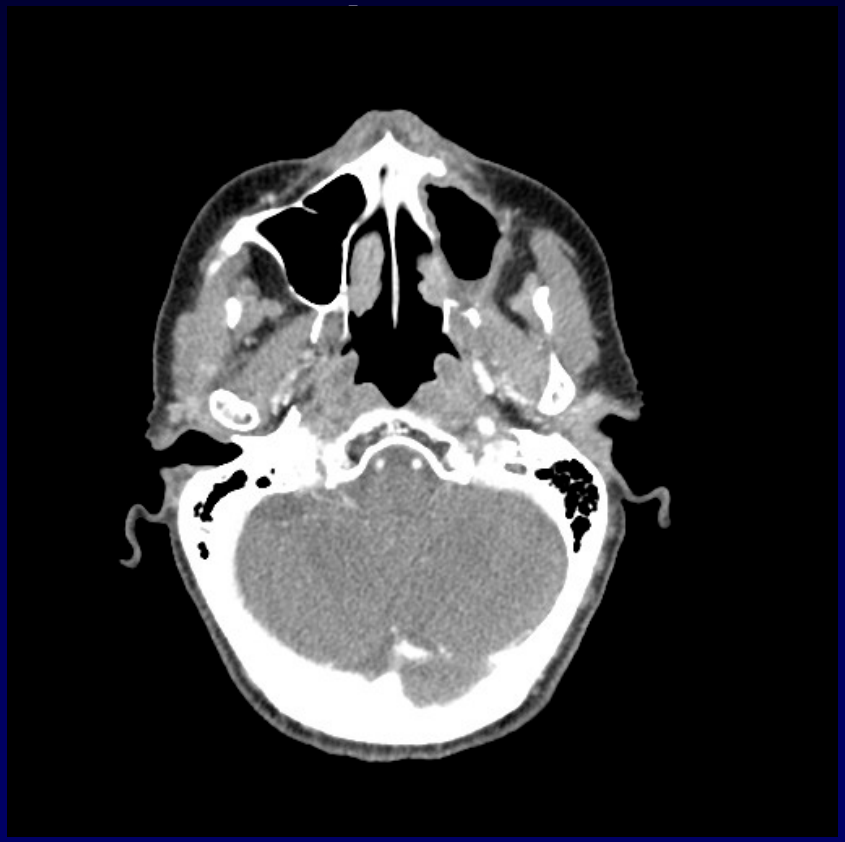
December 30, 2015



Case Presentation

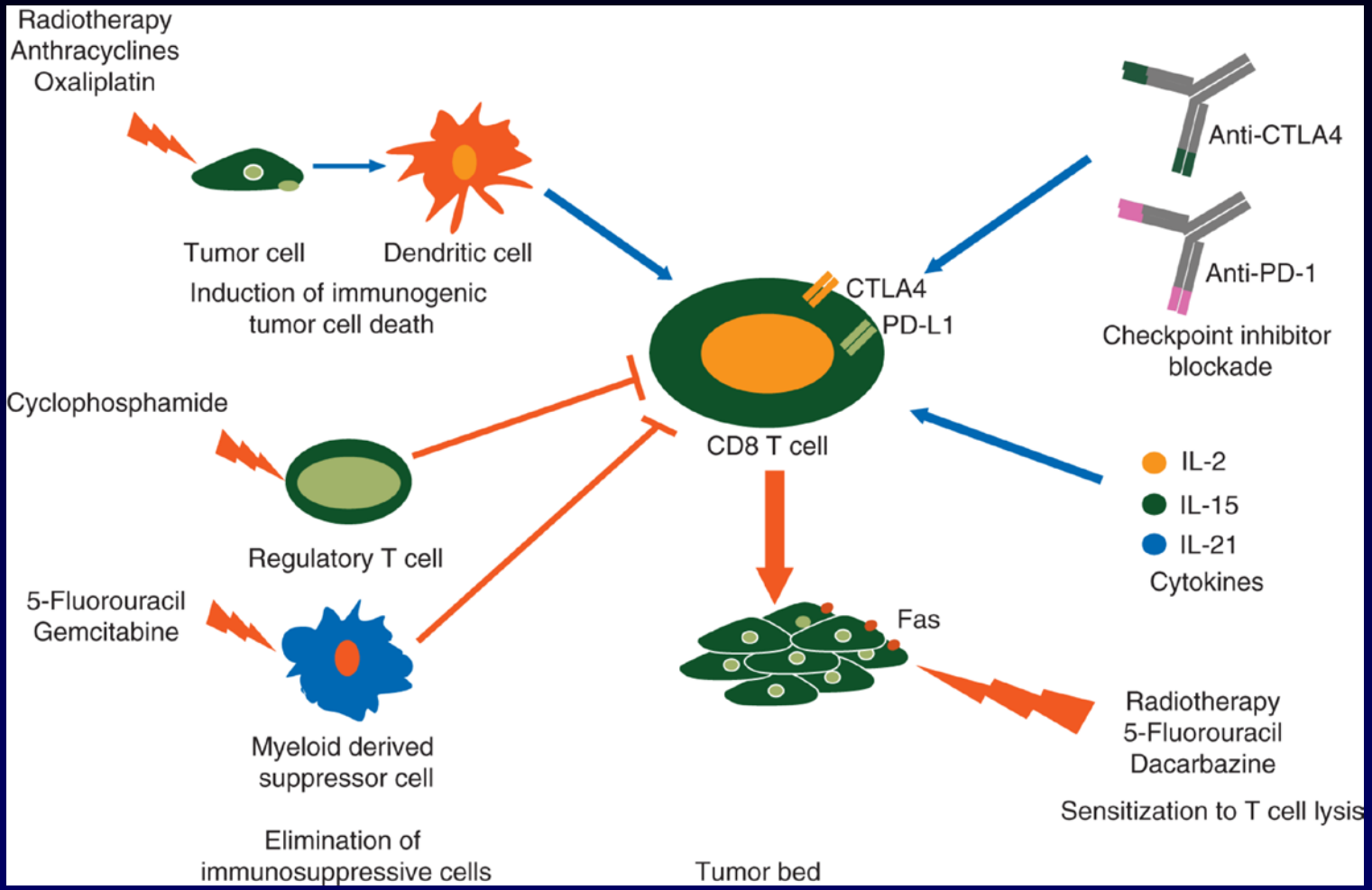
May 26, 2016





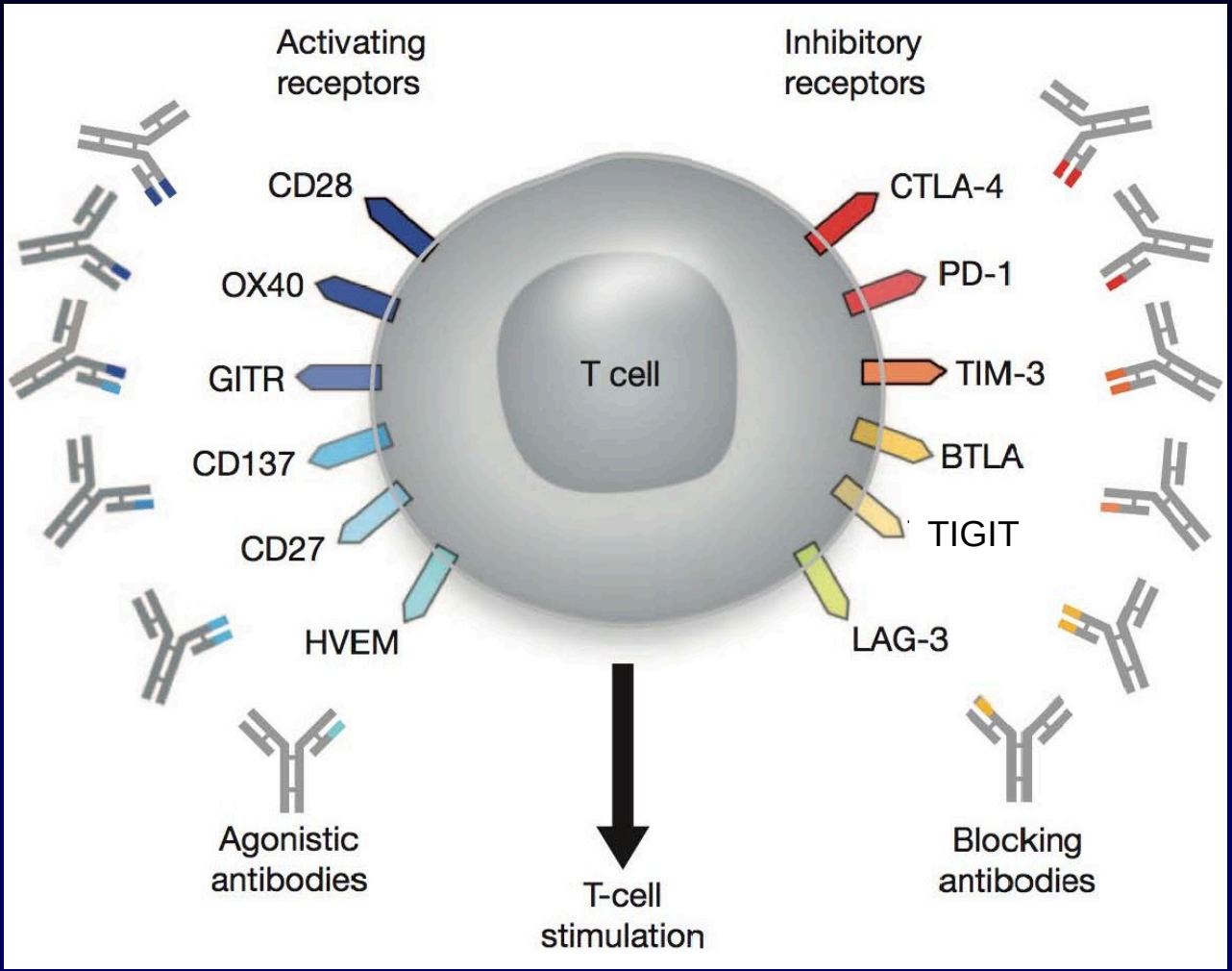
Quo Vadis?

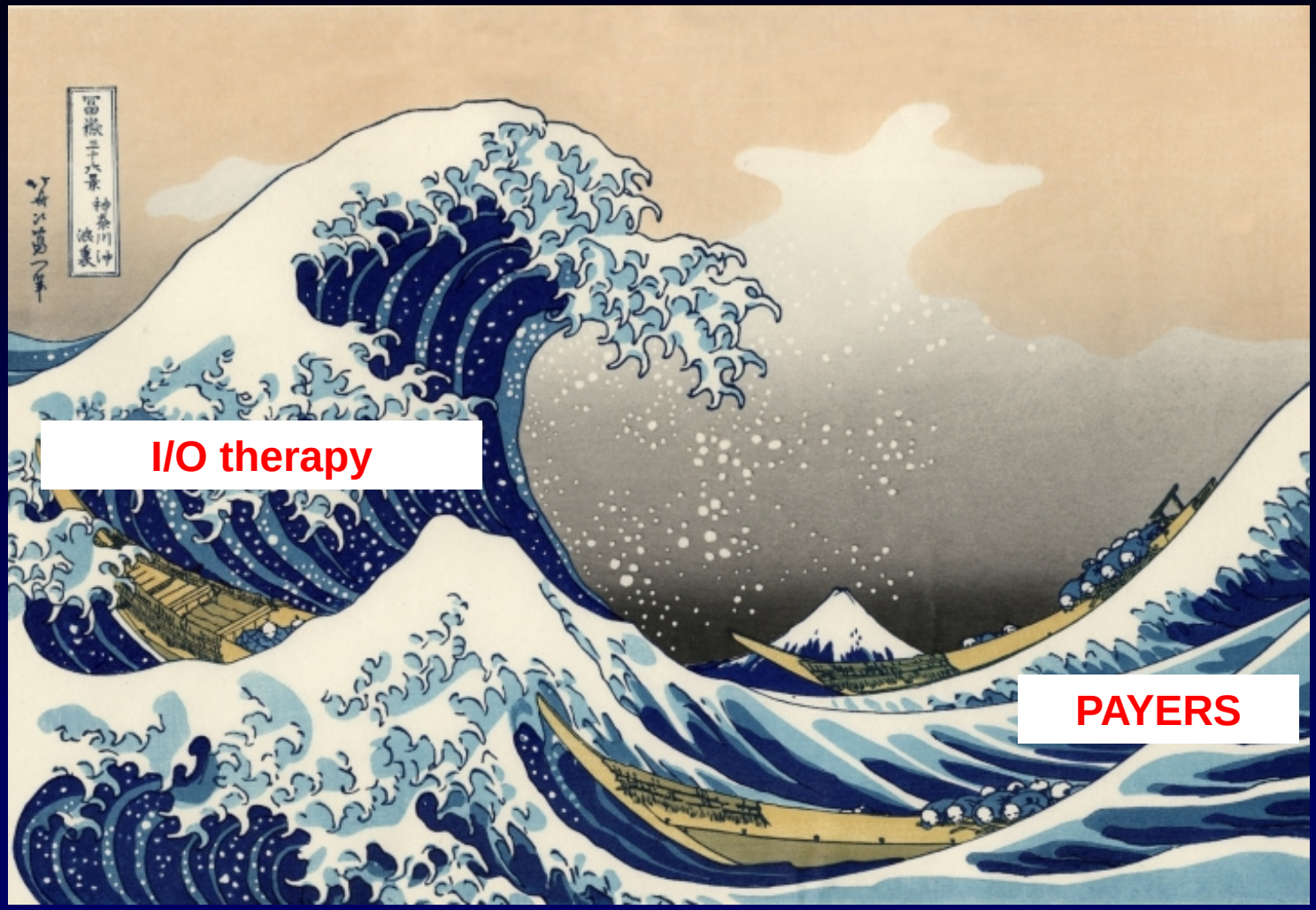
Combining anticancer agents with Immunotherapy



Apetoh et al Ann Oncol. 2015;26(9):1813-1823.

The landscape of T cell activating and inhibitory receptors





The NEW “Tsunami”

Conclusion

- This is an exciting time to be in Medical Oncology/Hematology
- The new I-O drugs are changing the way we look at managing patient with advanced cancer
- In one previously untreatable malignancy long term survival are now being seen routinely

- **We have only scratched the surface of what the immune system can potentially be harnessed to do in treating cancer patients**