CancerCare Manitoba
COMMUNITY ONCOLOGY PROGRAM
Community Cancer Programs | Uniting Primary Care and Oncology

New kids on the block:
Immunotherapy in melanoma and GI Malignancies

Ralph P.W. Wong, MD FRCPC

"Cry 'Havoc!', and let slip the dogs of war"

Julius Caesar Act iii. Sc. 1

UPCON Primary Care Conference

Ralph P.W. Wong MD FRCPC

Disclosures

- **Faculty / Speaker's name: Ralph Wong**

- **Relationships with commercial interests:**
  - **Grants/Research Support: None**
  - **Speakers Bureau/Honoraria: None**
  - **Consulting Fees: None**
  - **Other: None**

Mitigating Potential Bias

- Not Applicable

Objectives

At the end of the presentation the learner will be able to:

1. To review the basic principles of how the immune system interacts with malignancy
2. To understand the concept of Checkpoint inhibition and it use in the management of GI malignancies and Melanoma

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"

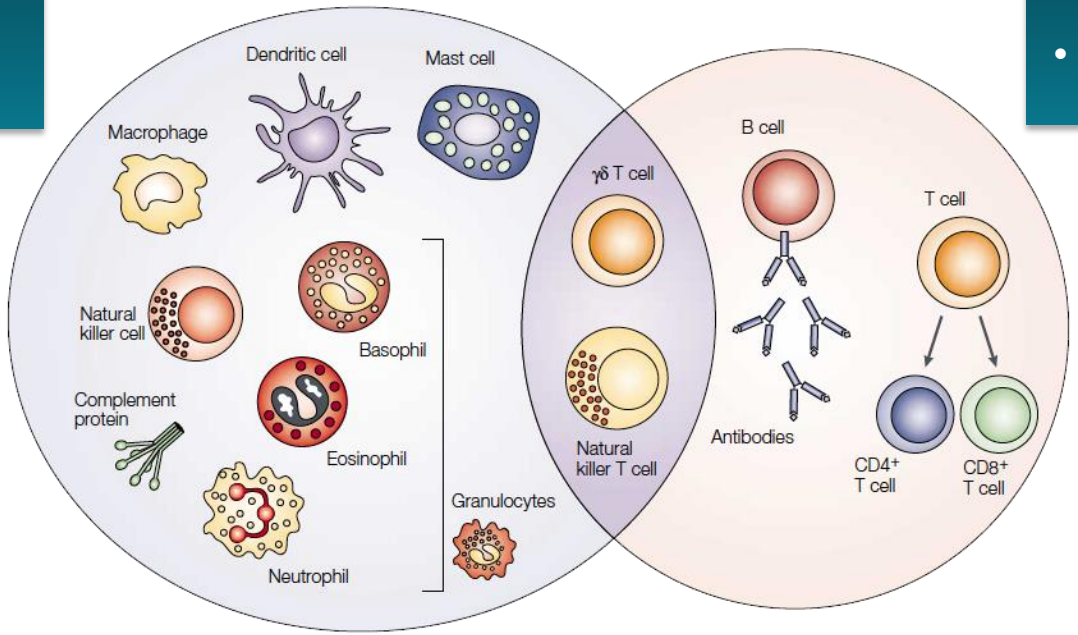
Couzin-Frankel J. Science 2013;342:1432-33

Immuno-Oncology

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

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

- Slow response
- Antigen-specific response
- Memory



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

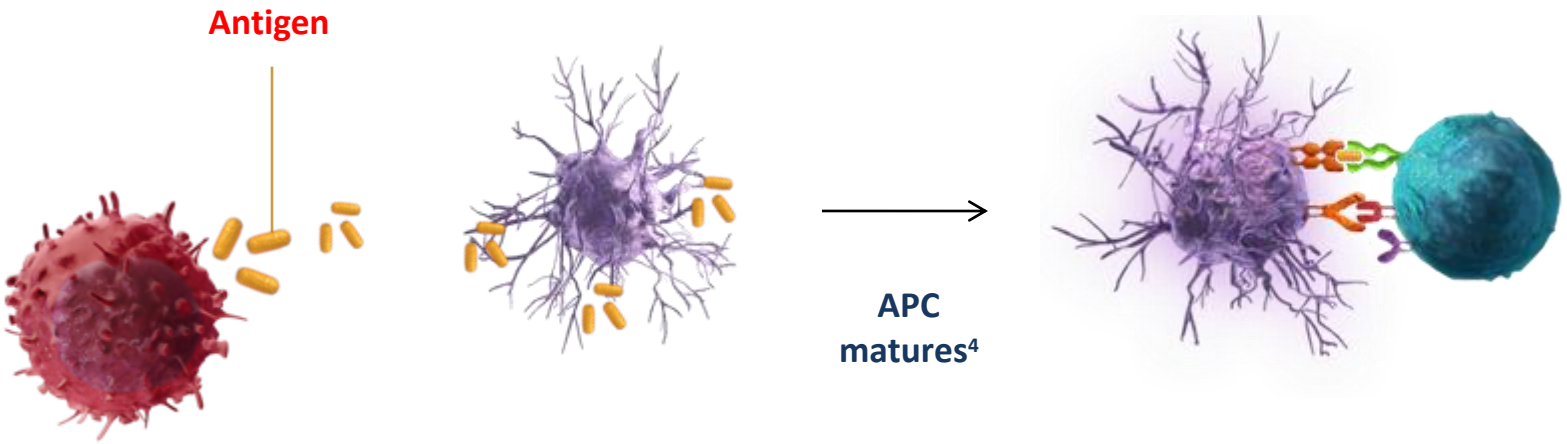
1. Abbas AK, *et al*. *Cellular and Molecular Immunology*. 7th ed. Philadelphia, PA: Elsevier Saunders; 2012.
2. Figure reprinted by permission from Macmillan Publishers Ltd: *Nature Reviews Cancer.* Dranoff G. *Nat Rev Cancer.* 2004;4:11-22. 3..Vesely MD, *et al*. *Annu Rev Immunol*. 2011;29:235-271.

CancerCare Manitoba
ActionCancerManitoba

T-cell Activation: Tumour-associated Antigens

2017 CANCER DAY FOR PRIMARY CARE

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



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

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

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
Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature*. 2011;480:480-489
P, Schumacher TNM. The cancer antigenome. *EMBO J*. 2013;32(2):194-203

2. Mellman I,
3. Heemskerk B, Kvistborg
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

Activated APC presents the tumour-associated antigen to the T cell along with a co-stimulatory signal[1]

Inactive T cell

Antigen

Co-stimulatory signal

Activates[1]

Activated T cell

T cells proliferate

Active, cytotoxic (killer) T cells

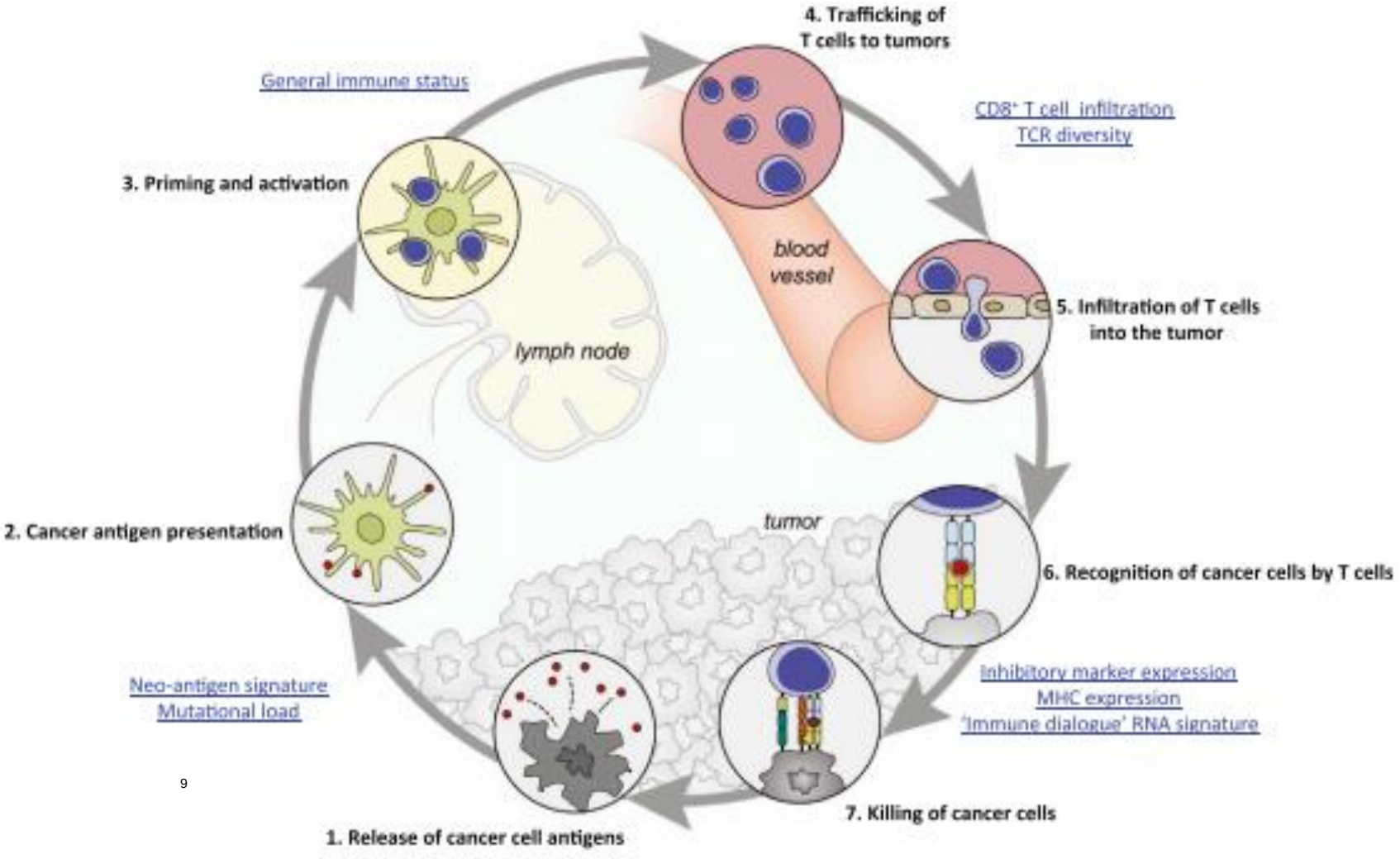
Antigen recognition

Tumour cell

Cytotoxic T cell induces *apoptosis* in tumour cell[1]

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 Cancer to Evade the 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:

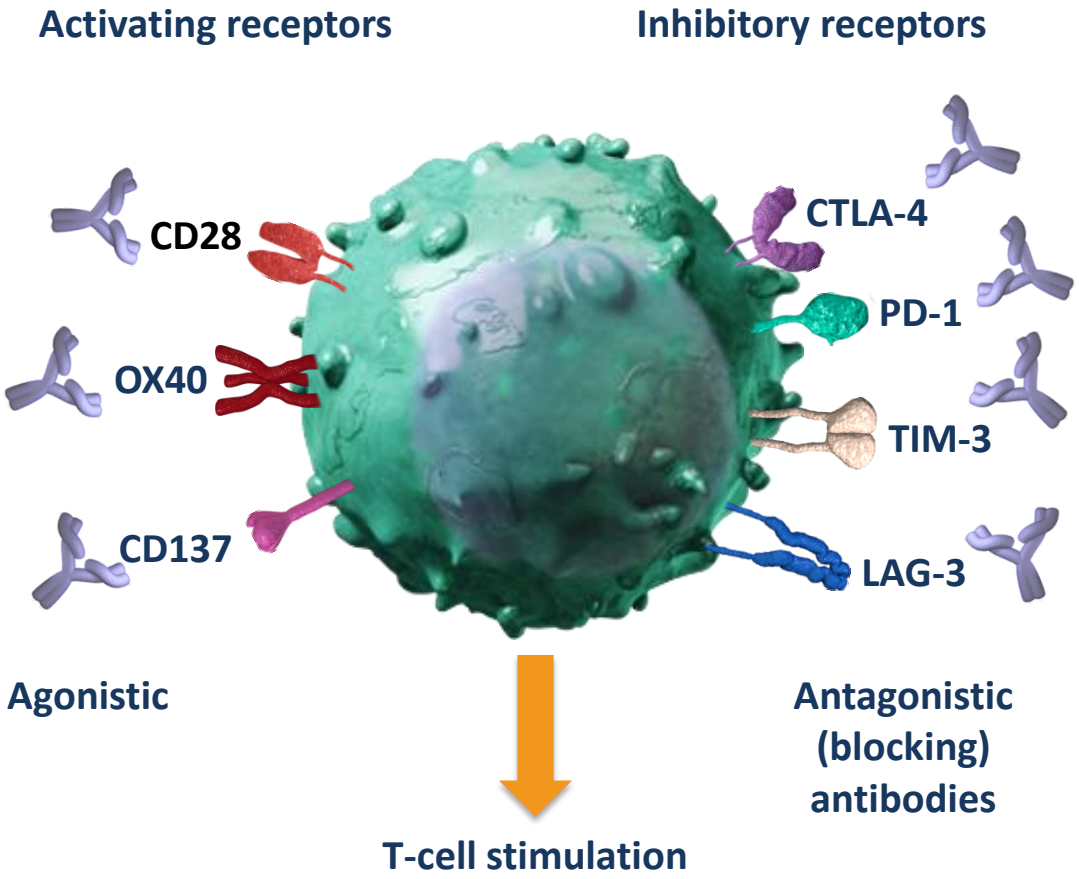
- **CD28**
- **CD40**
- **OX40**
- **CD137**
- **GITR**

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



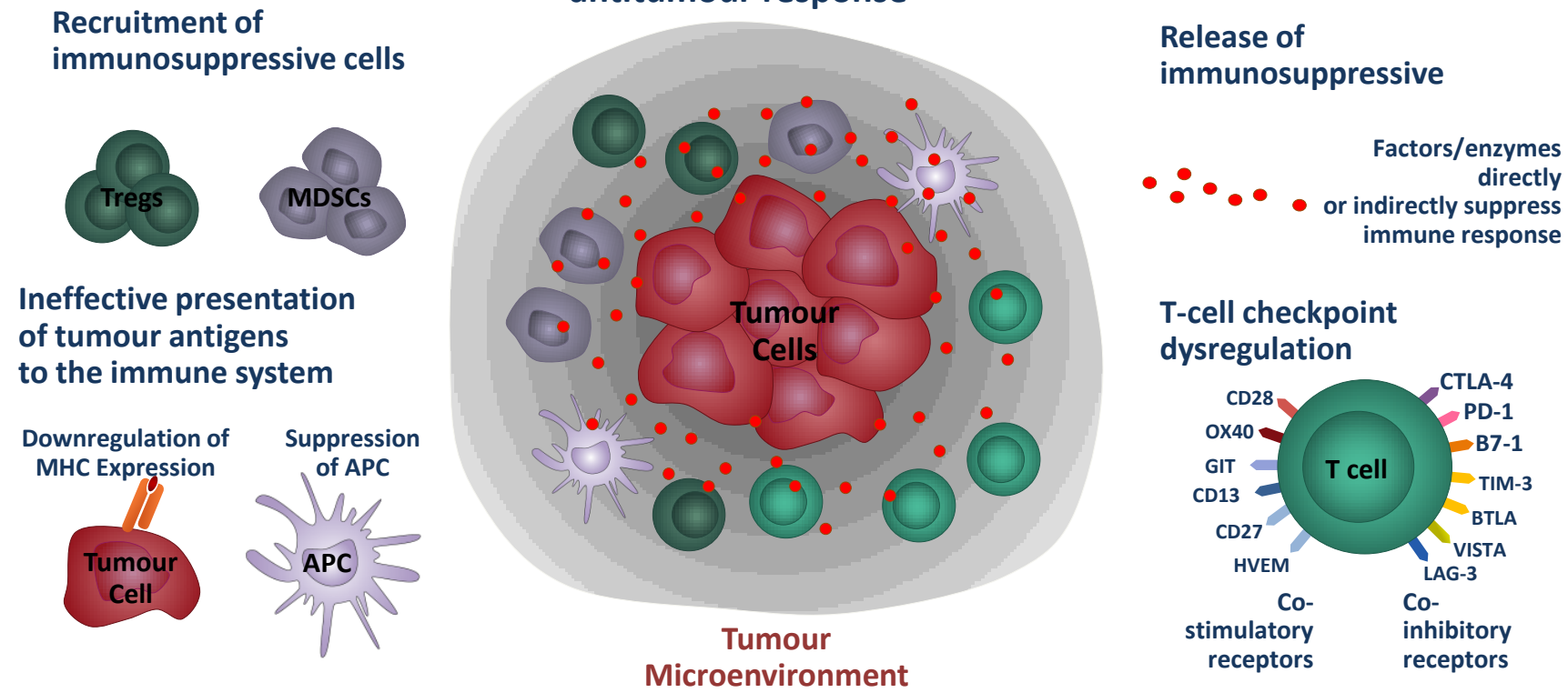
- **T-cell responses are regulated though a complex balance of inhibitory (“checkpoint”) and activating signals**
- **Tumours can dysregulate these pathways and consequently, the immune response**
- **Targeting these pathways is an evolving approach to cancer therapy**

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

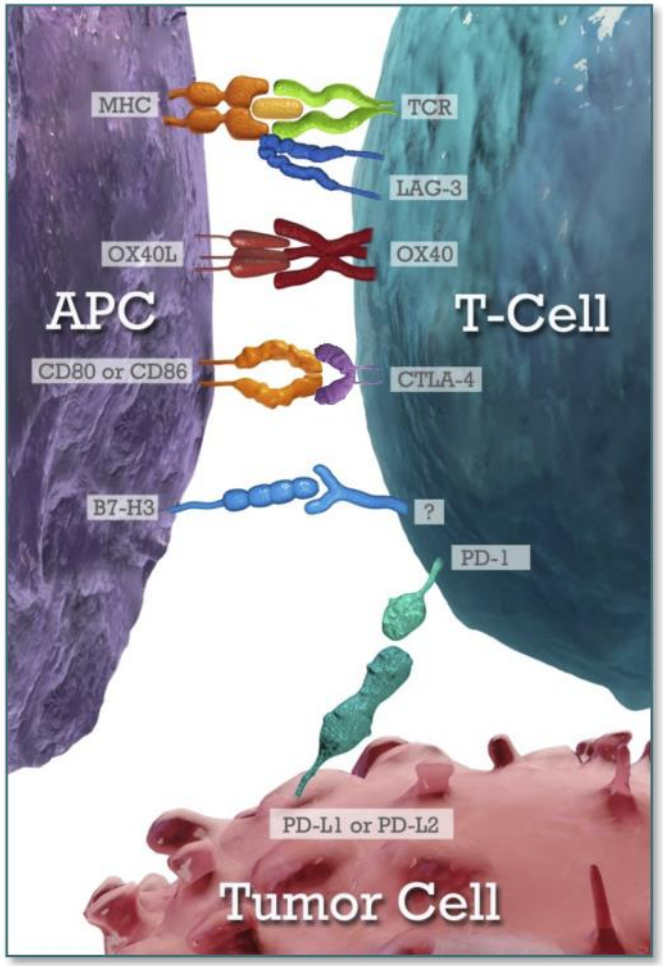
APC=antigen-presenting cell; MDSC=myeloid-derived suppressor cell; MHC=major histocompatibility complex; Treg=regulatory T cell.

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

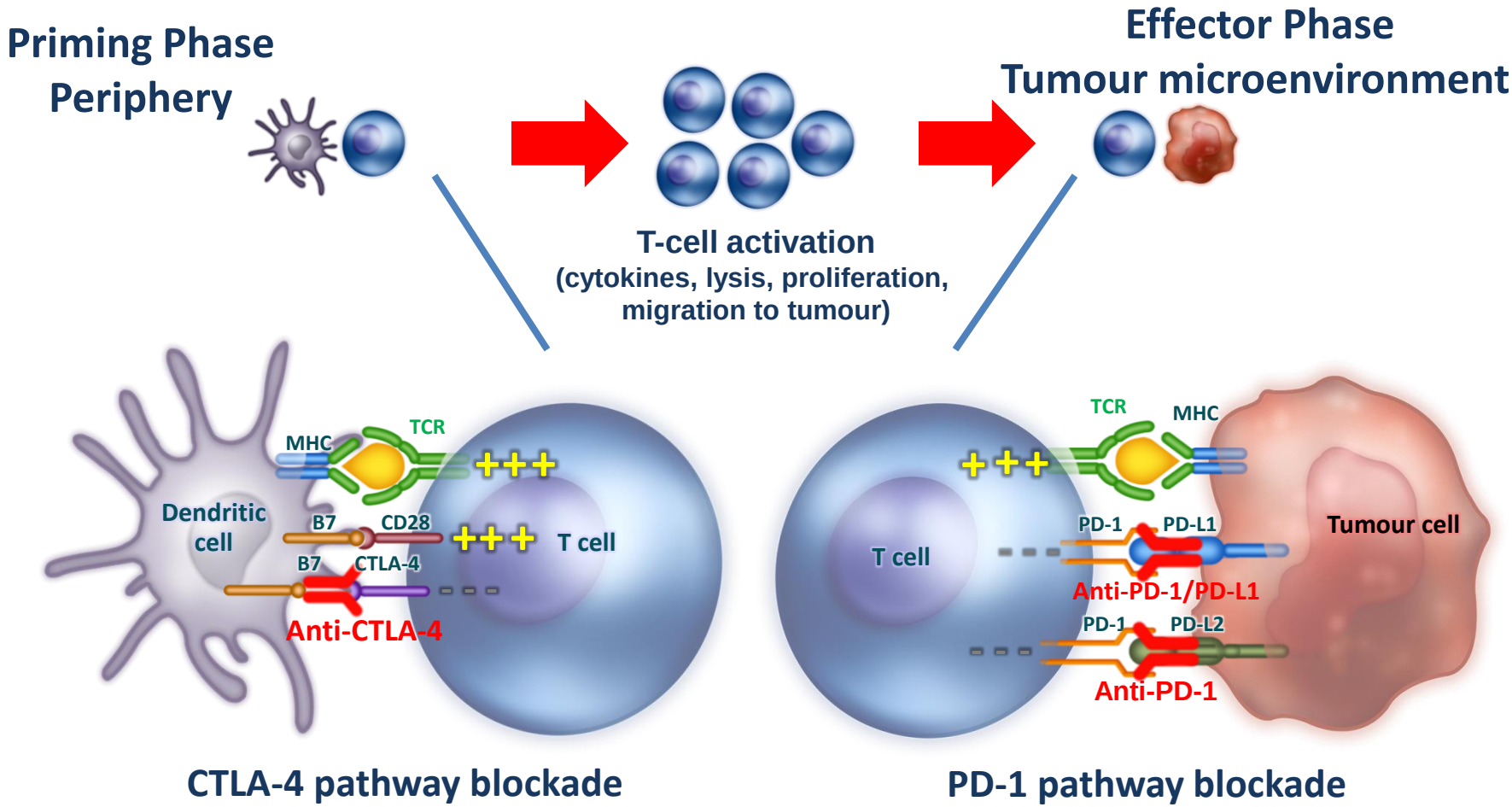


1. Baruah P, *et al*. *Immunobiology*. 2012;217(7):669-675; 2. Hemon P, *et al*. *J Immunol*. 2011,186:5173-5183;
3. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264; 4. Kirkwood JM, *et al*. *CA Cancer J Clin*. 2012;62:309-335;
5. Zang X, *et al*. *PNAS*. 2007;104(49):19458-19463; 6. Leitner J. *Eur J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

CancerCare Manitoba
ActionCancerManitoba

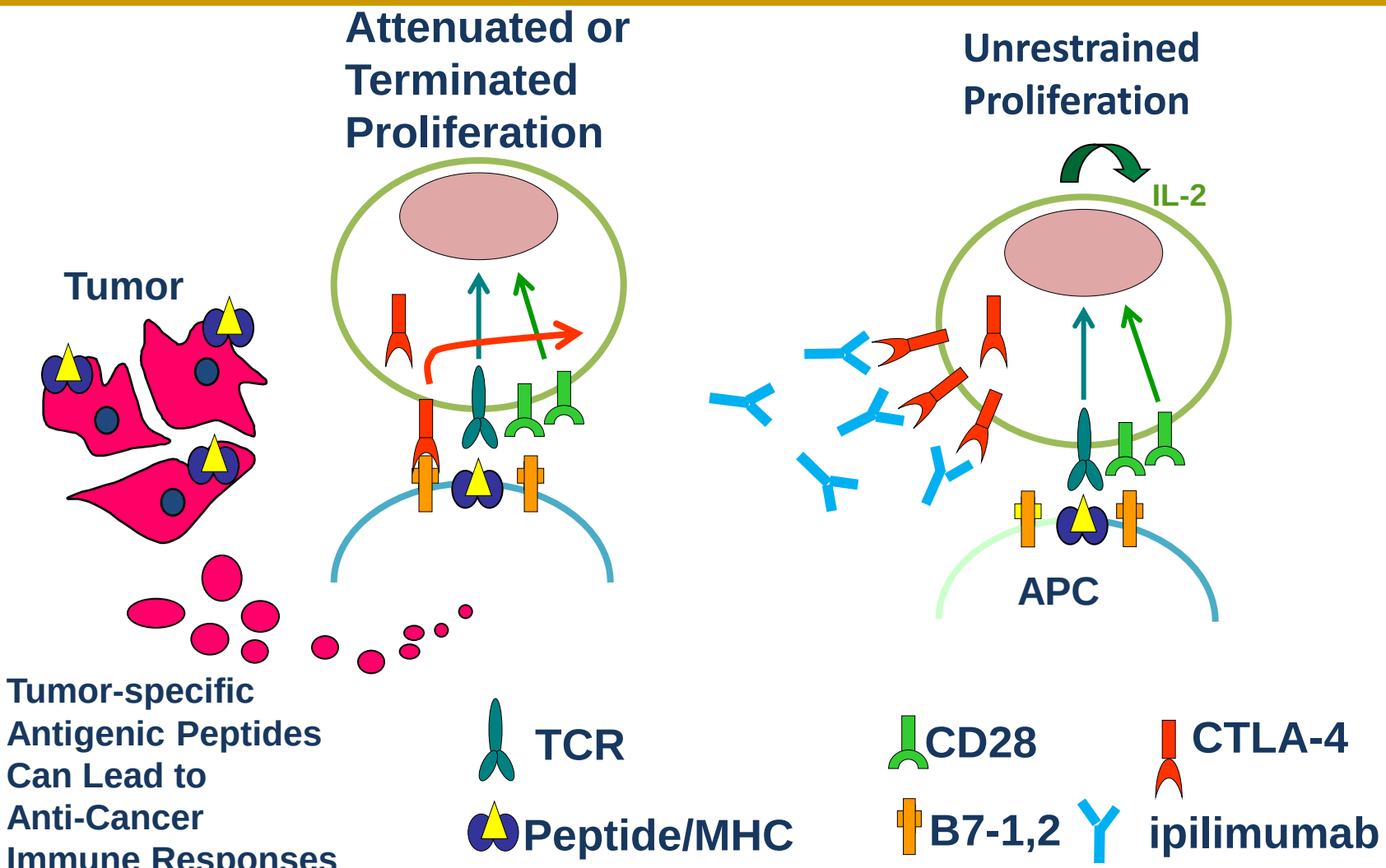
Immuno-oncology:
Blocking CTLA-4 and PD-1 Pathways with Monoclonal Antibodies

2017 CANCER DAY FOR PRIMARY CARE



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).

CLTA-4 Monoclonal Antibodies

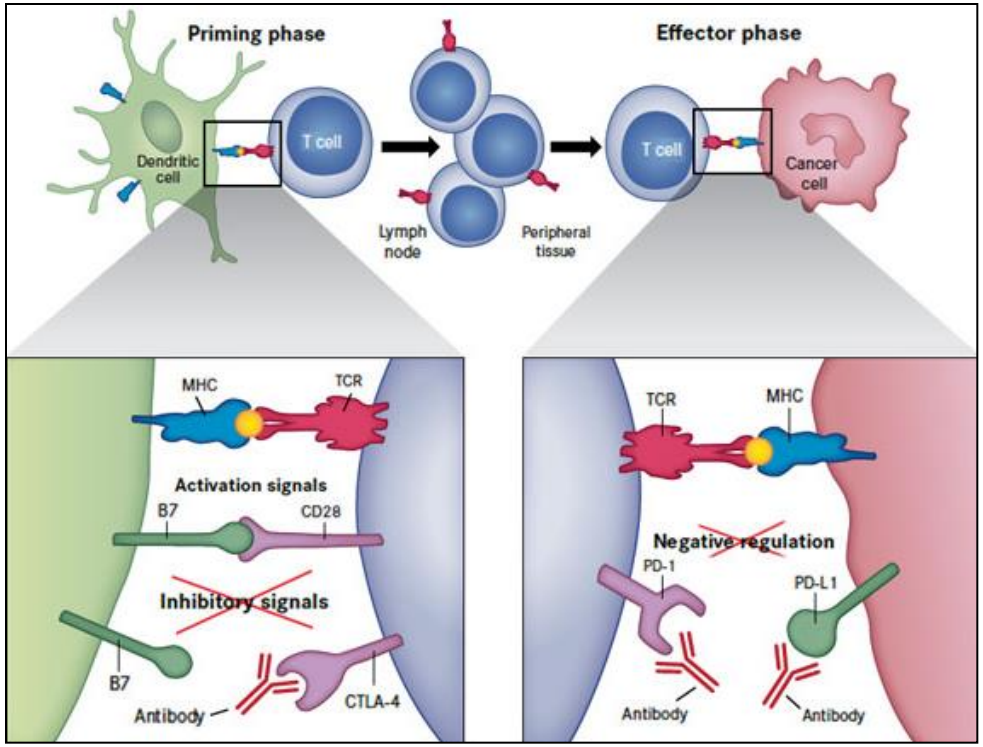


Adapted from Chambers CA, et al. *Annu Rev Immunol.* 2001;19:565-594.

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

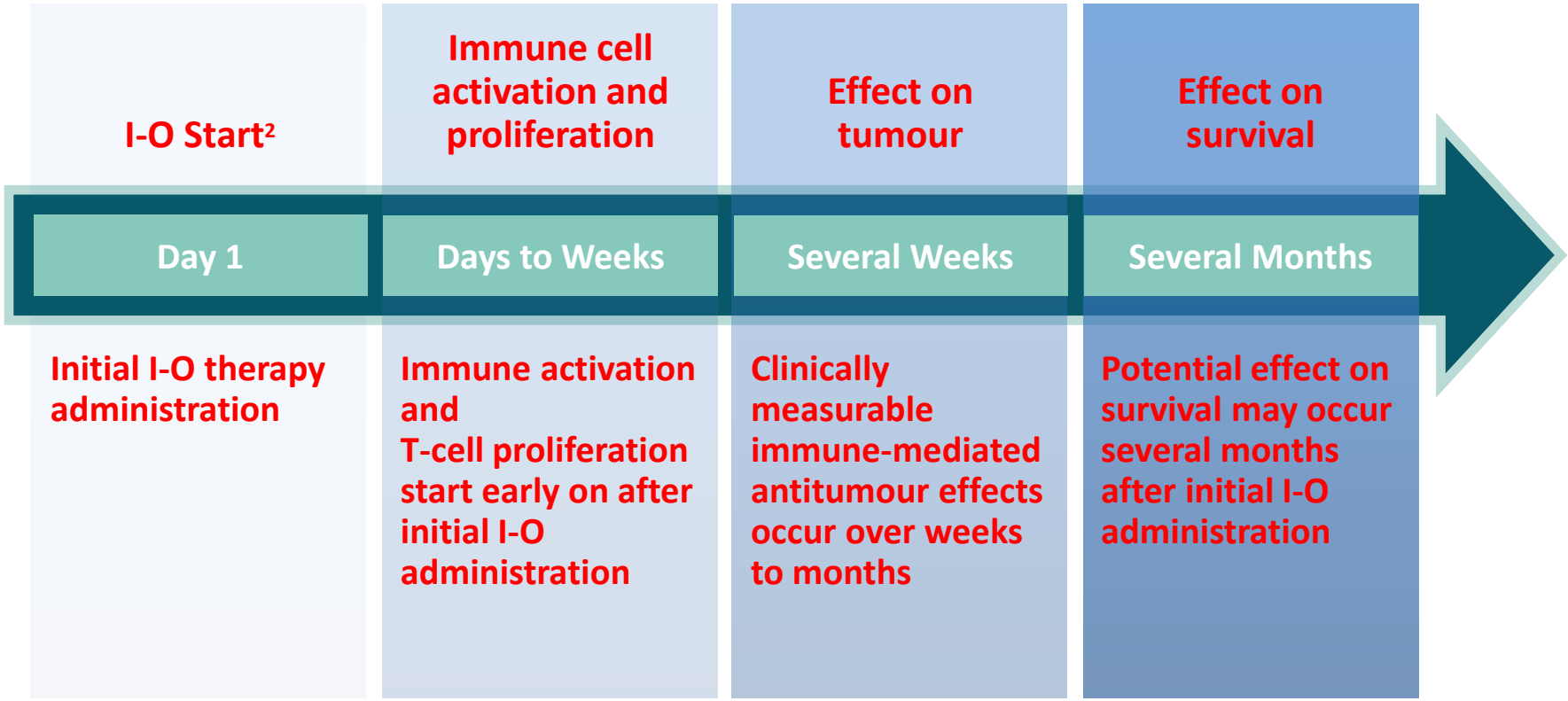


Adapted from *N Engl Med*. 2012;366(26):2517

Potential Clinical Response Patterns with I-O Therapeutic Approaches

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]



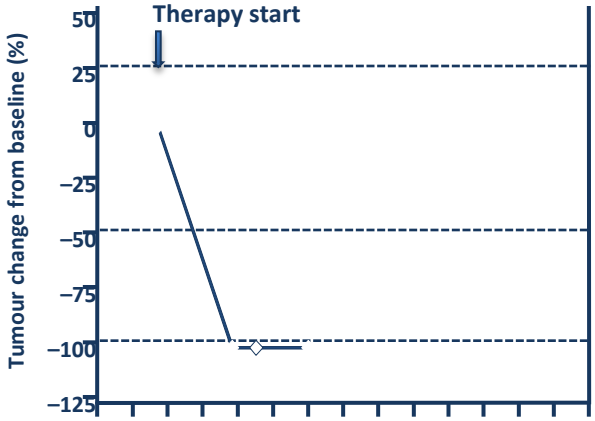
1. Hoos A, Britten CM. *OncoImmunology*. 2012;1:334-339;

2. Hoos A, *et al*. *J Natl Cancer Inst*. 2010;102:1388-1397.

Potential Tumour Response Patterns to Therapy

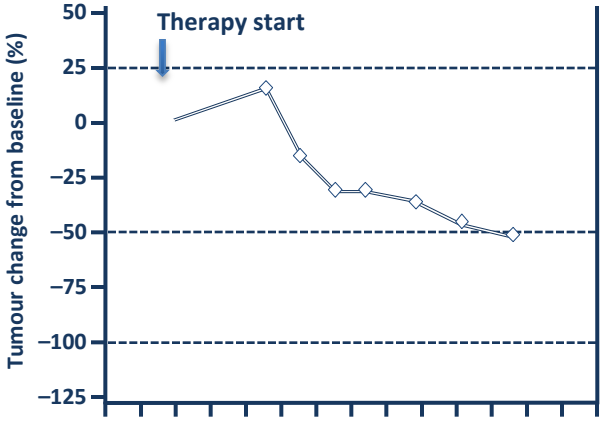
Response in baseline lesions typically seen with chemotherapy, but also I-O therapies and targeted therapies. Captured by existing RECIST and WHO criteria

"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)

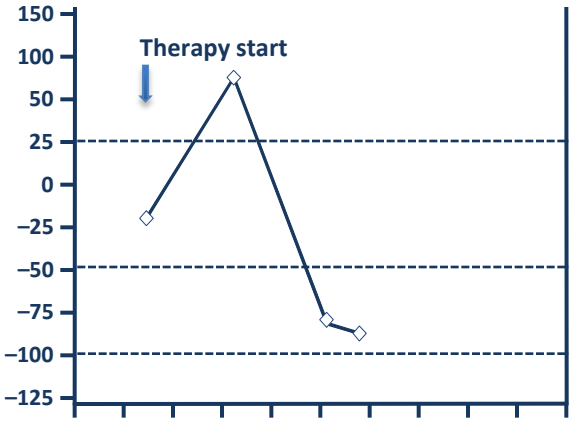
Graphs for illustrative purposes showing responses to ipilimumab in advanced melanoma



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.

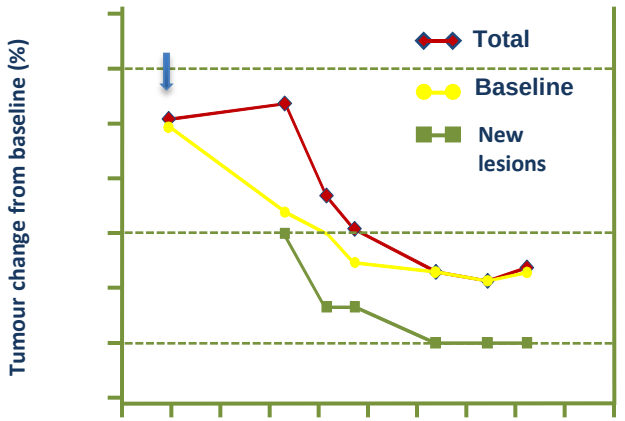
Potential Tumour Response Patterns to Therapy

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



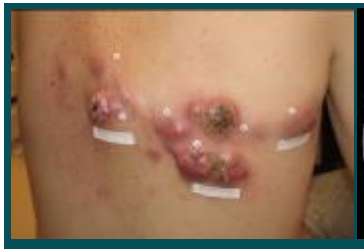
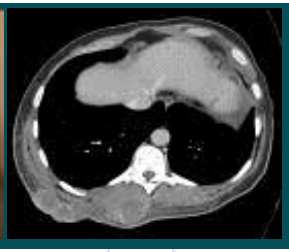
Some vaccines may not follow similar patterns of response as other I-O therapies

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

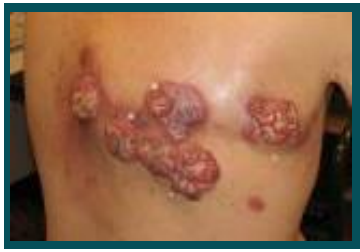
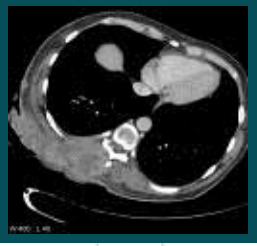


Adapted from Wolchok JD, *et al*. *Clin Cancer Res* 2009;15:7412–7420; Hoos A, *et al*. *Annals of Oncology* 2012;23(suppl 8): viii47–viii52.

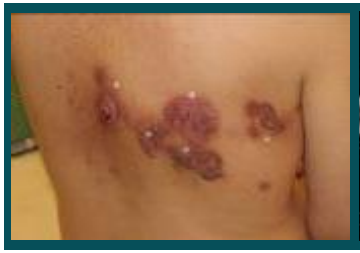
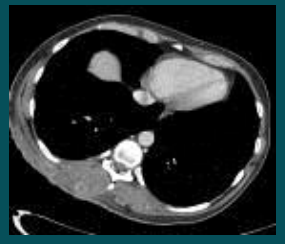
Example of Evolution of Response to CTLA-4 Inhibition

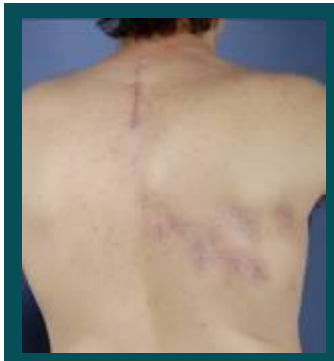
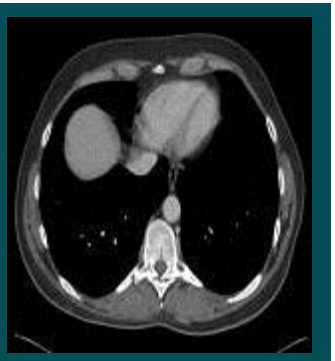
Screening

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-realted 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]

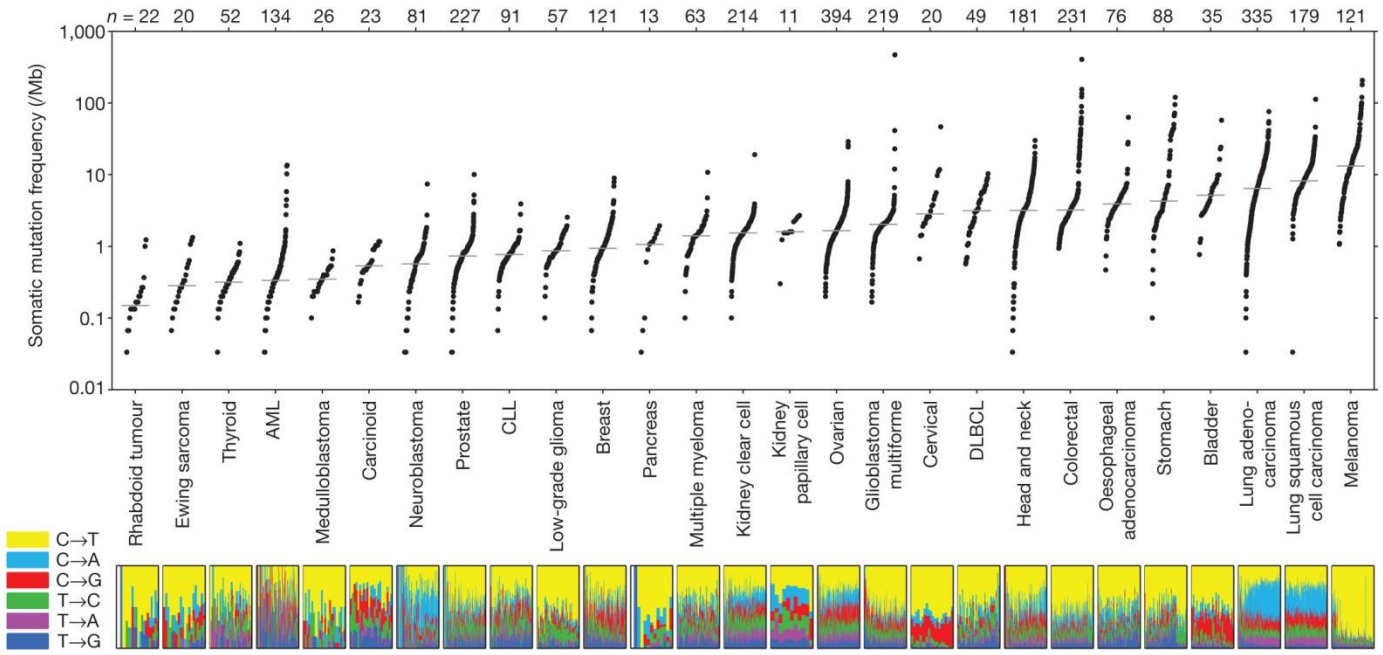
Considerations when evaluating true progression vs. pseudo-progression

	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/detailedguide/non-small-cell-lung-cancer-diagnosis.

Clinical Efficacy of Immuno-oncology Treatment

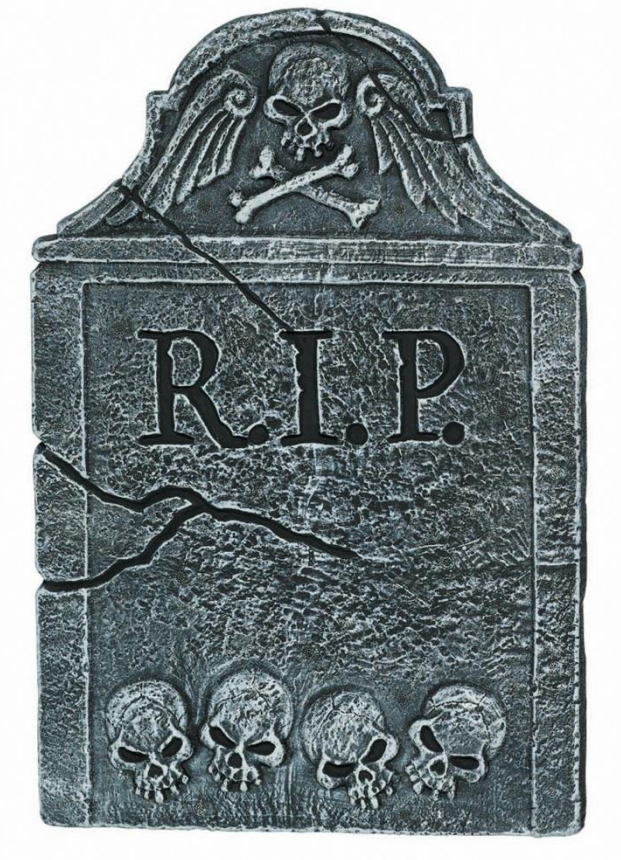
Somatic mutation frequencies observed in exomes from 3,083 tumour–normal pairs.



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

MS Lawrence *et al. Nature* 000, 1-5 (2013) doi:10.1038/nature12213

Melanoma

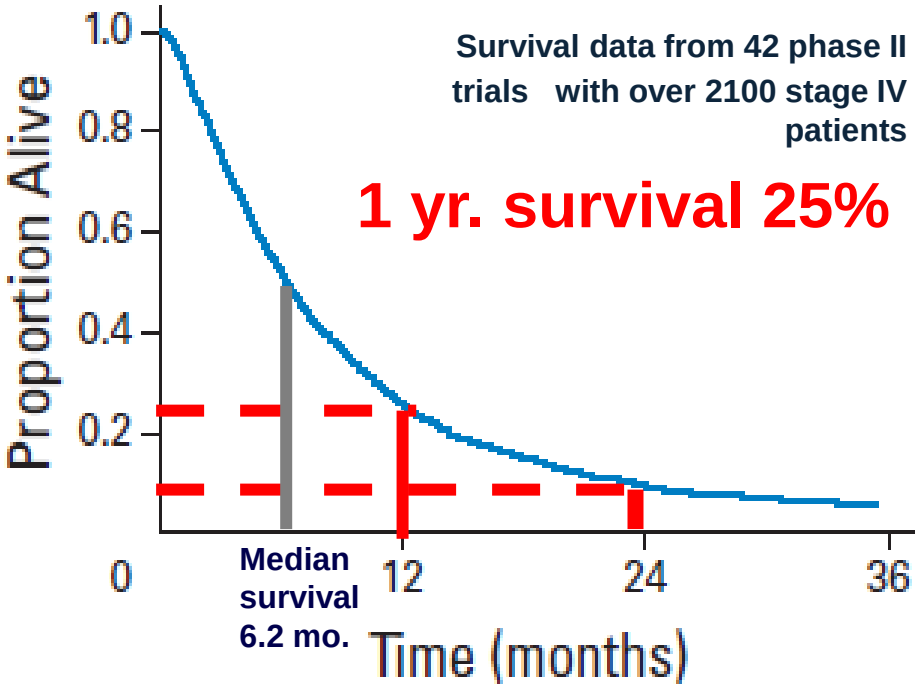


Chemotherapy (1976-2014)

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

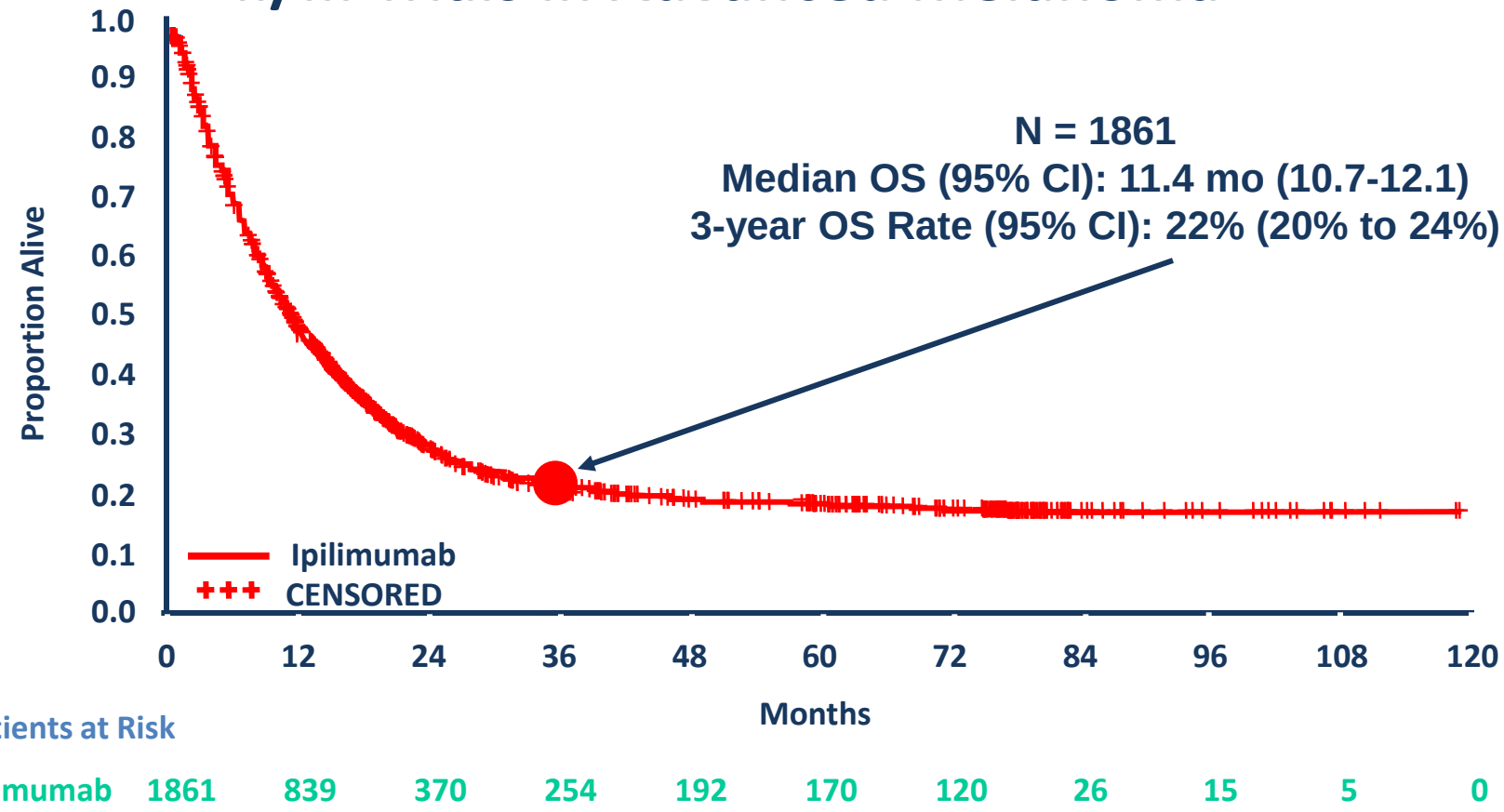
Median OS: 6.2 months

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



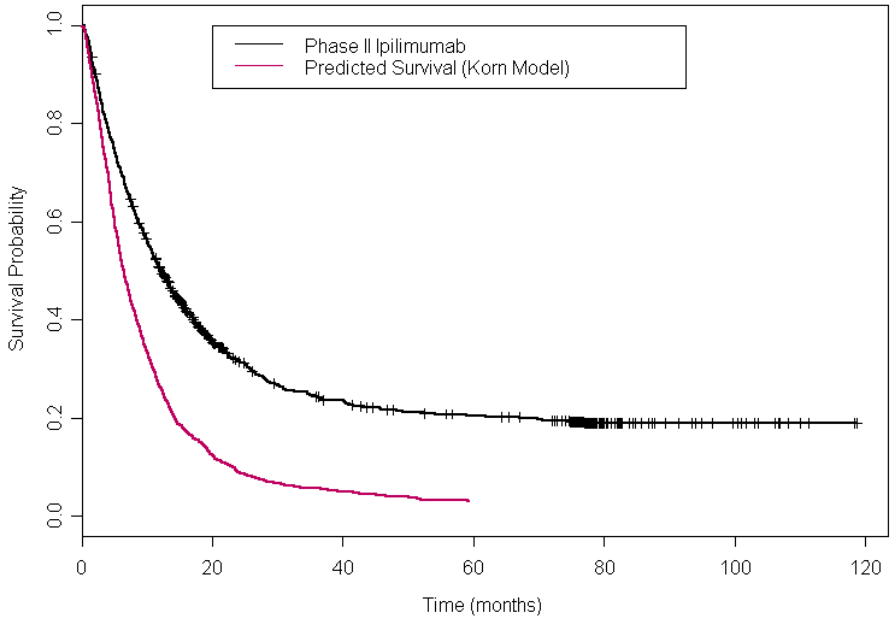
Korn EL, et al. *J Clin Oncol.* 2008;26(4):527-534.

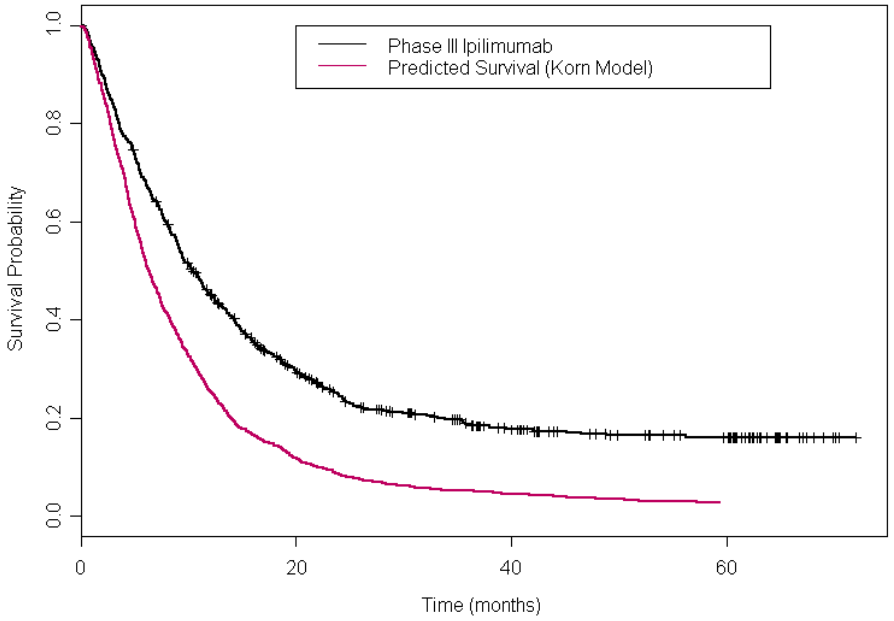
Ipilimumab: Pooled Survival Analysis from Phase II/III Trials in Advanced Melanoma



Schadendorf et al. J Clin Oncol 2015; 33(17):1889-1894.

OS Relative to Historical Data

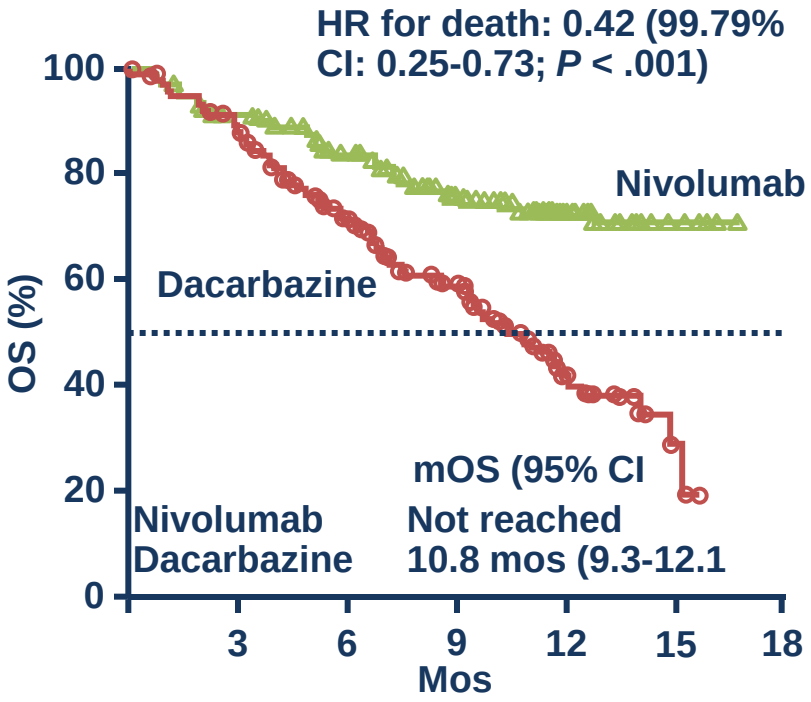




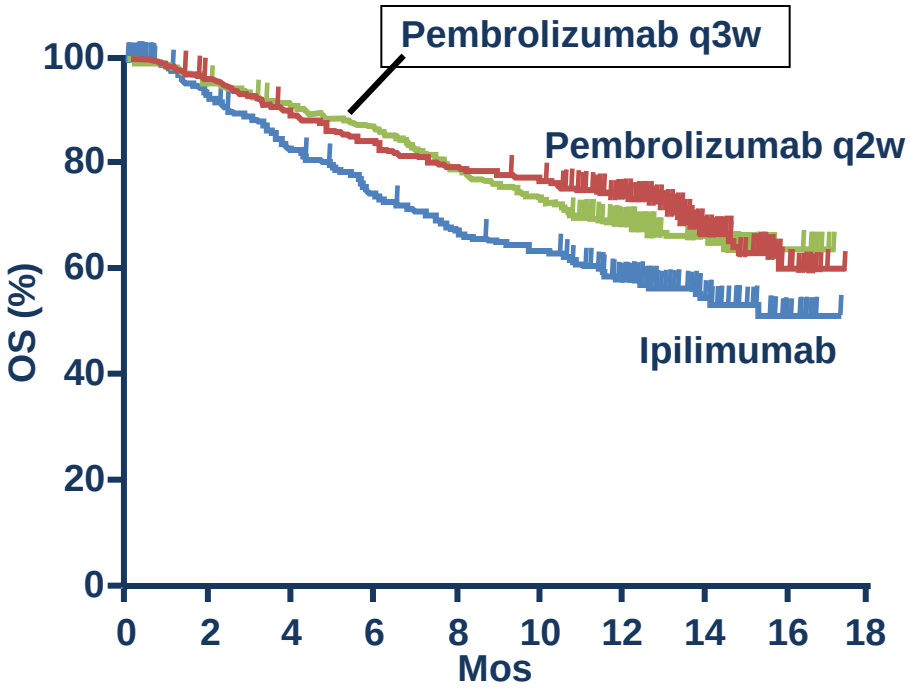
- **Historical controls**
  - **Phase II: 1278 patients in 42 cooperative group trials from 1975 to 2005**
  - **Phase III: 3739 patients in 10 trials from 1999 to 2011**

CHECKMATE 066 and KEYNOTE 006: Overall survival

Nivolumab vs DTIC in *BRAF*-negative, previously untreated melanoma[1]



Pembrolizumab vs Ipilimumab in Advanced Melanoma[2]



1. Robert C, et al. N Engl J Med. 2015;372:320-330.
2. Robert C, et al. N Engl J Med. 2015;372(28):2521-32.

CTLA 4/PD-1 combination

Case Presentation

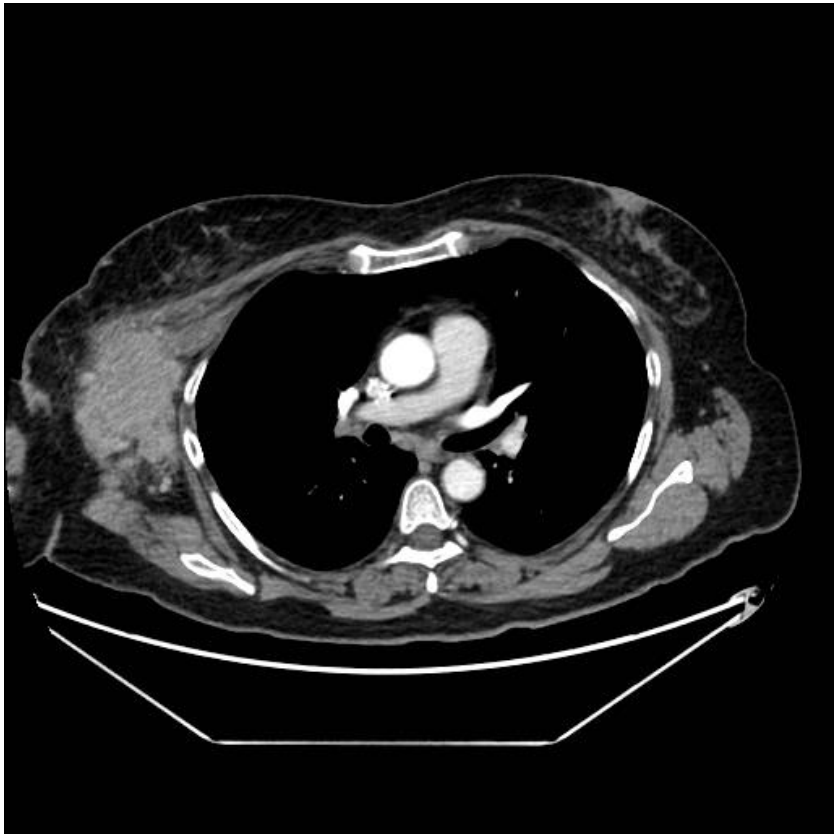
- 56 yr. old female 4.9 mm ulcerated (T4b, Nx M0) BRAF wild type, NRAS mutated melanoma right upper arm resected April 2016
- declined adjuvant interferon

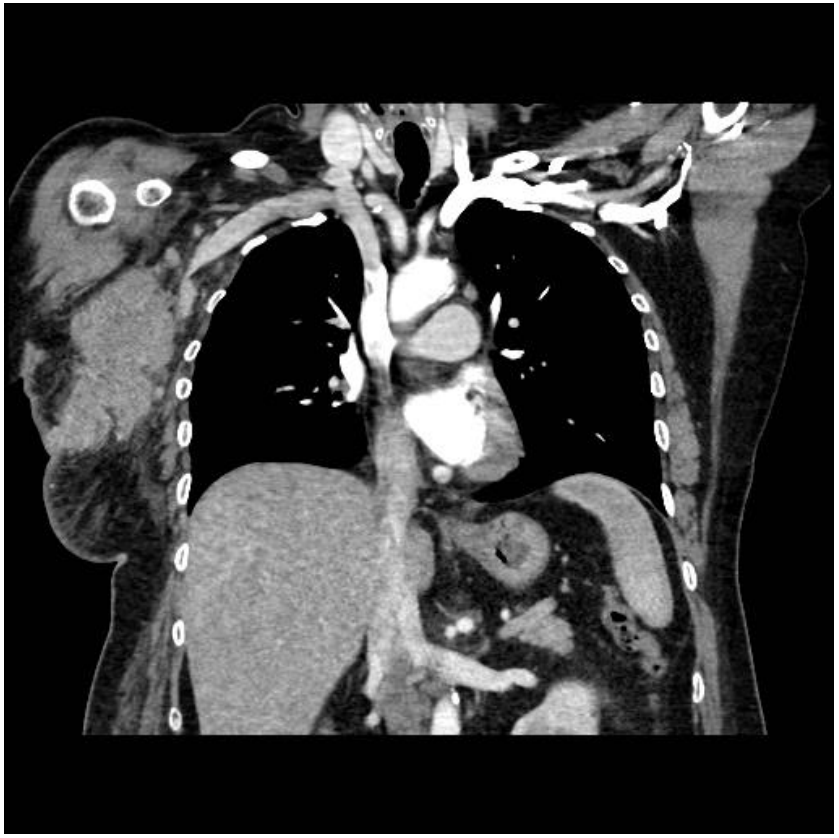
Case Presentation

- **October 2016, presents to clinic with increasingly severe axillary pain, hoarse voice**
- **Exam confirmed large mass in right axilla, right arm swelling and inability to abduct arm**
- **Pain syndrome consistent with brachial plexopathy**

Case Presentation

October 30, 2016



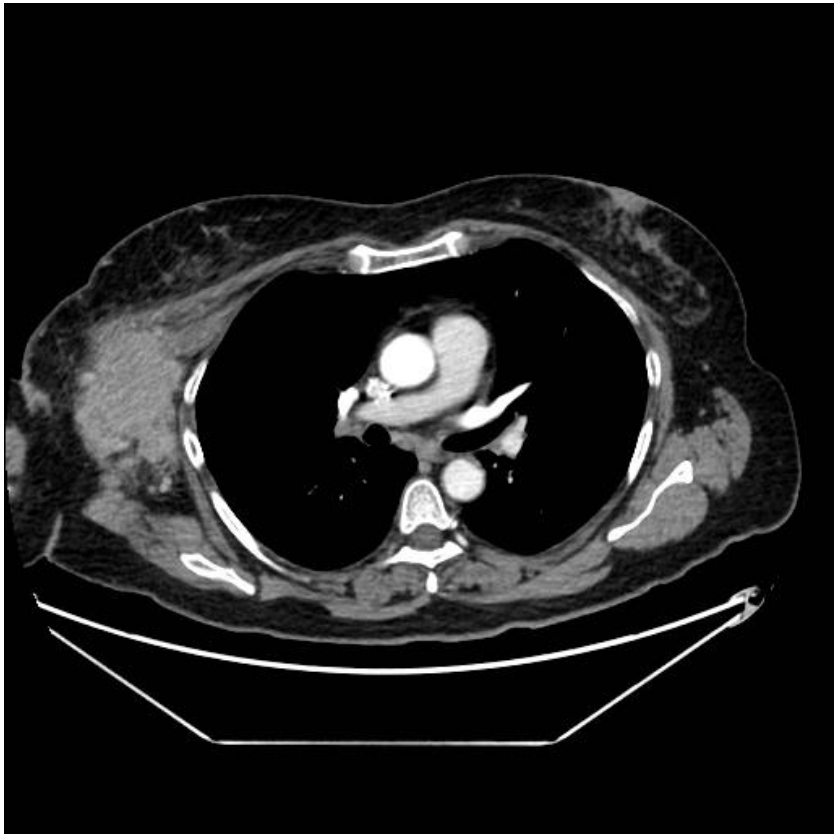


Case Presentation

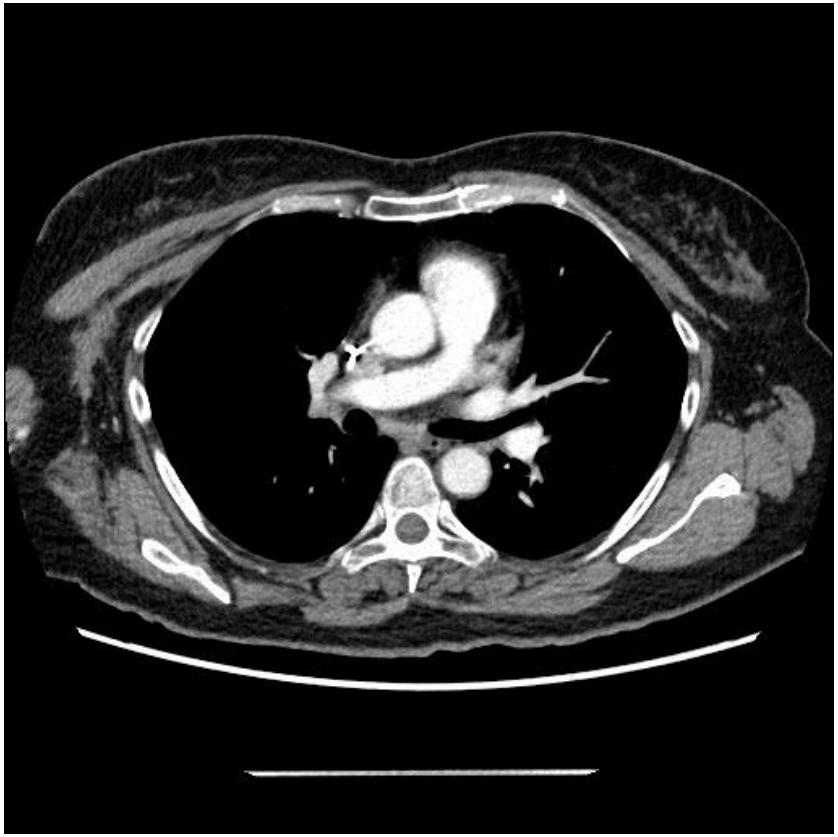
- Offered clinical trial with nivolumab/ipilimumab
- Commenced therapy November 24, 2016
- Noted decreased mass and pain after one cycle, hoarse voice resolved
- Developed Grade 1 rash after third cycle Jan 6, 2017

Case Presentation

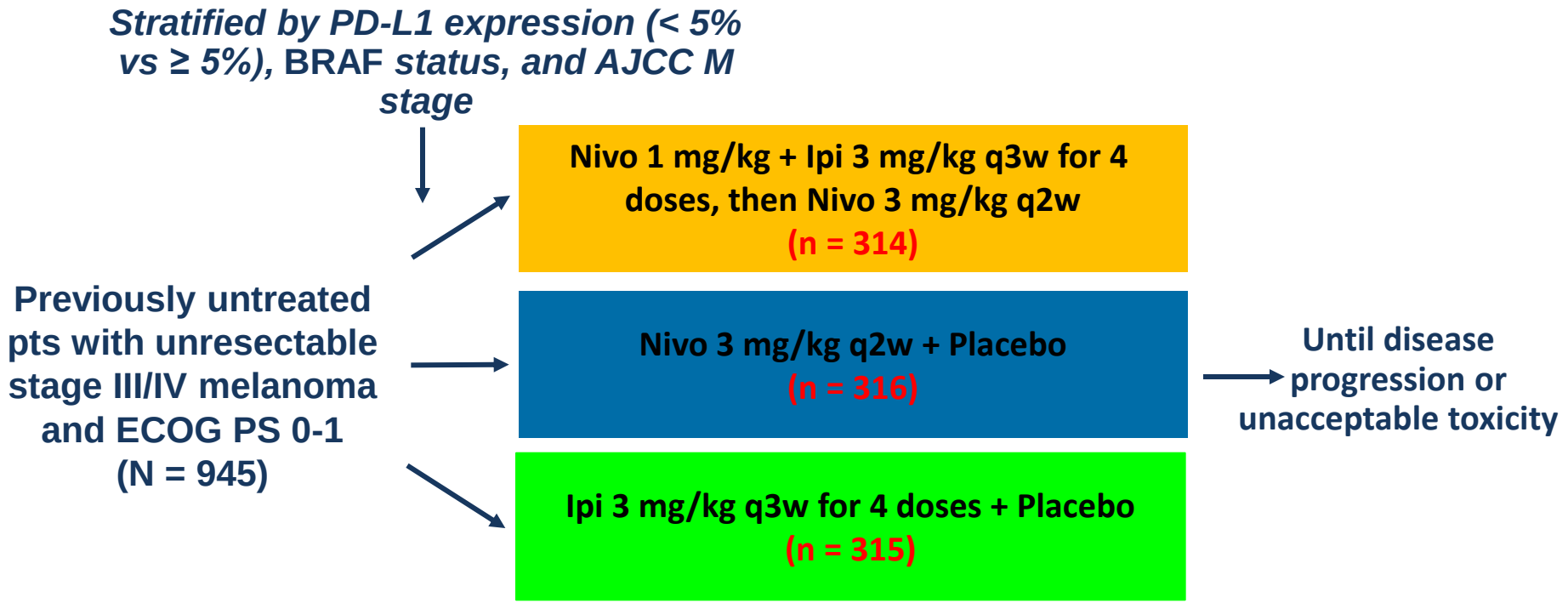
October 30, 2016



April 27, 2017



CHECKMATE 067: Phase III Trial of Nivolumab + Ipilimumab vs. Nivolumab vs. Ipilimumab for First-line Treatment of Melanoma



- Coprimary endpoints: PFS, OS
- Secondary endpoints: ORR, tumor PD-L1 expression and efficacy, safety

Larkin, et al. NEJM epub May 31, 2015.

Treatment-Related AEs Associated With Nivolumab/Ipilimumab combination

Select Treatment-Related AEs, %	Nivo + Ipi (n = 313)		Nivo (n = 313)		Ipi (n = 311)	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Any reported AE	96	55	82	16	86	27
Leading to discontinuation	36	29	8	5	15	13
Skin	59	6	42	2	54	3
▪ Pruritus	33	2	19	0	35	< 1
▪ Rash	28	3	22	< 1	21	2
▪ Maculopapular rash	12	2	4	< 1	12	< 1
Gastrointestinal	46	15	20	2	37	12
▪ Diarrhea	44	9	19	2	33	6
▪ Colitis	12	8	1	< 1	12	9
Hepatic	30	19	6	3	7	2
▪ ALT increase	18	8	4	1	4	2
▪ AST increase	15	6	4	1	4	< 1
Endocrine	30	5	14	< 1	11	2
▪ Hypothyroidism	15	< 1	9	0	4	0

Updated Response To Treatment

	NIVO+IPI (N=314)	NIVO (N=316)	IPI (N=315)
ORR, % (95% CI)*	58.9 (53.3–64.4)	44.6 (39.1–50.3)	19.0 (14.9–23.8)
Best overall response — %			
Complete response	17.2	14.9	4.4
Partial response	41.7	29.7	14.6
Stable disease	11.5	9.8	21.3
Progressive disease	23.6	38.6	51.1
Unknown	6.1	7.0	8.6
Median duration of response, months (95% CI)	NR (NR–NR)	31.1 (31.1–NR)	18.2 (8.3–NR)

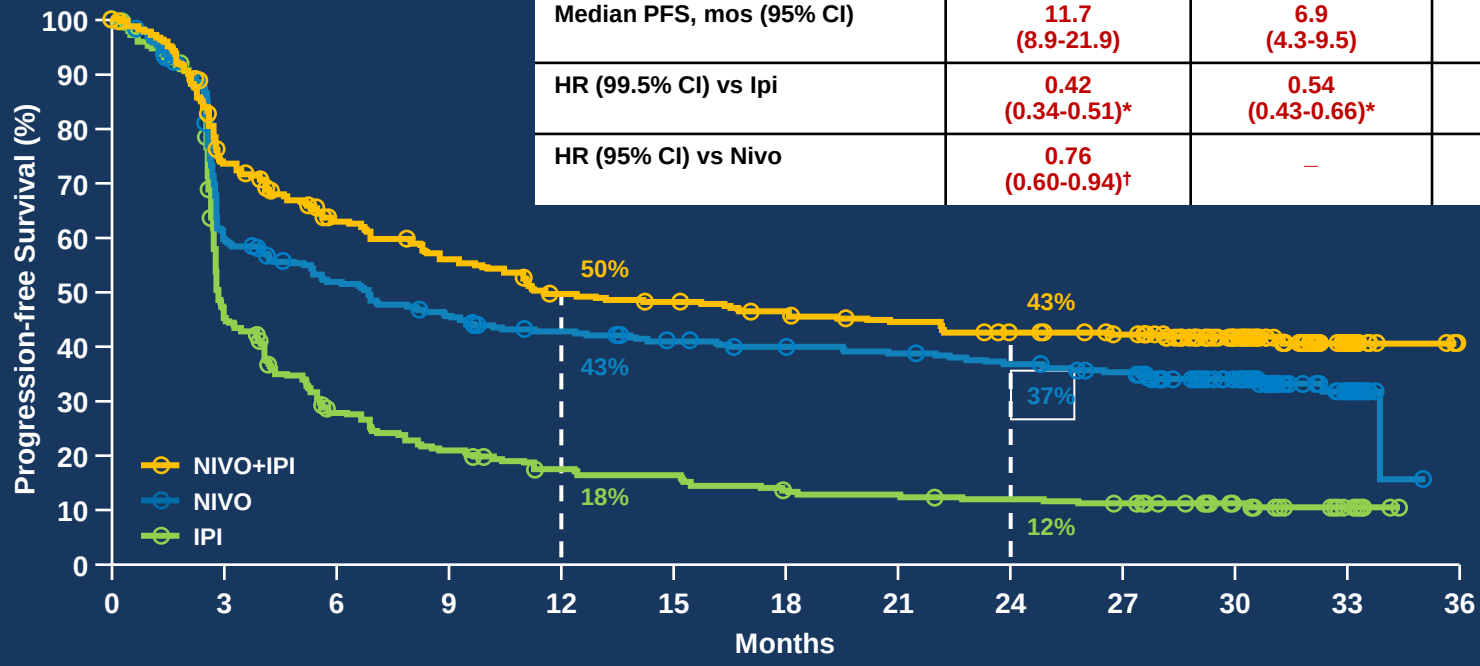
*By RECIST v1.1; NR = not reached.

- At the 18-month DBL, the CR rate for NIVO+IPI, NIVO and IPI was 12.1%, 9.8% and 2.2%, respectively

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

Updated Progression-Free Survival

	Nivo + Ipi (n = 314)	Nivo (n = 316)	Ipi (n = 315)
Median PFS, mos (95% CI)	11.7 (8.9-21.9)	6.9 (4.3-9.5)	2.9 (2.8-3.2)
HR (99.5% CI) vs Ipi	0.42 (0.34-0.51)*	0.54 (0.43-0.66)*	–
HR (95% CI) vs Nivo	0.76 (0.60-0.94)†	–	–



Patients at risk:

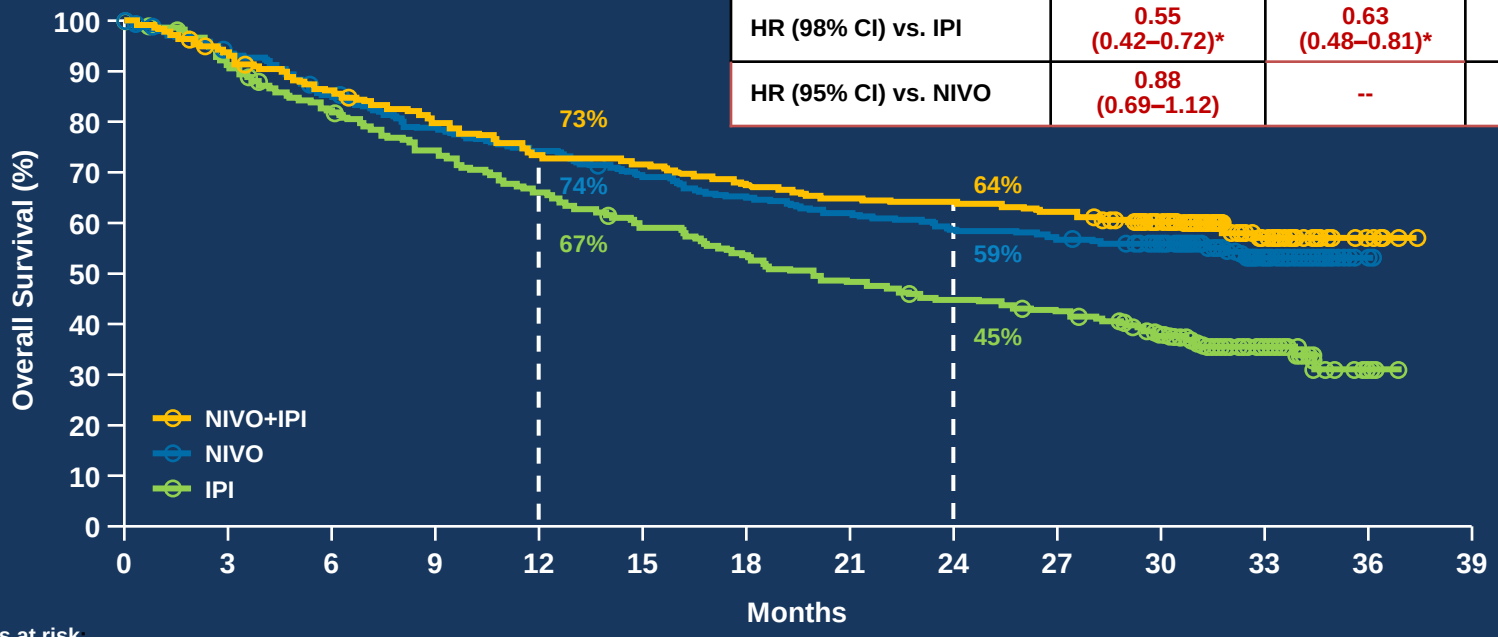
NIVO+ IPI	314	218	176	156	137	132	125	118	110	104	71	16	0
NIVO	316	178	151	132	120	112	107	103	97	88	62	16	0
IPI	315	136	77	58	46	43	35	33	30	27	16	5	0

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

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

GI Malignancies

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

Le et al NEJM 2015; 372(26): 2509-2520.

PD-1 Blockade in MMR-Deficient Tumors: Patient Population

Baseline Characteristics	MMR-Deficient CRC (n = 13)	MMR-Proficient CRC (n = 25)	MMR-Deficient Other Tumors (n = 10)
Median age, yrs	46	62	59
Diagnosis, %			
▪CRC	100	100	0
▪Ampullary/biliary	0	0	40
▪Endometrial	0	0	20
▪Small bowel	0	0	20
▪Prostate	0	0	10
▪Gastric	0	0	10
≥ 2 prior therapies, %	100	100	90
Lynch syndrome, %	85	0	40

Le et al NEJM 2015; 372(26): 2509-2520.

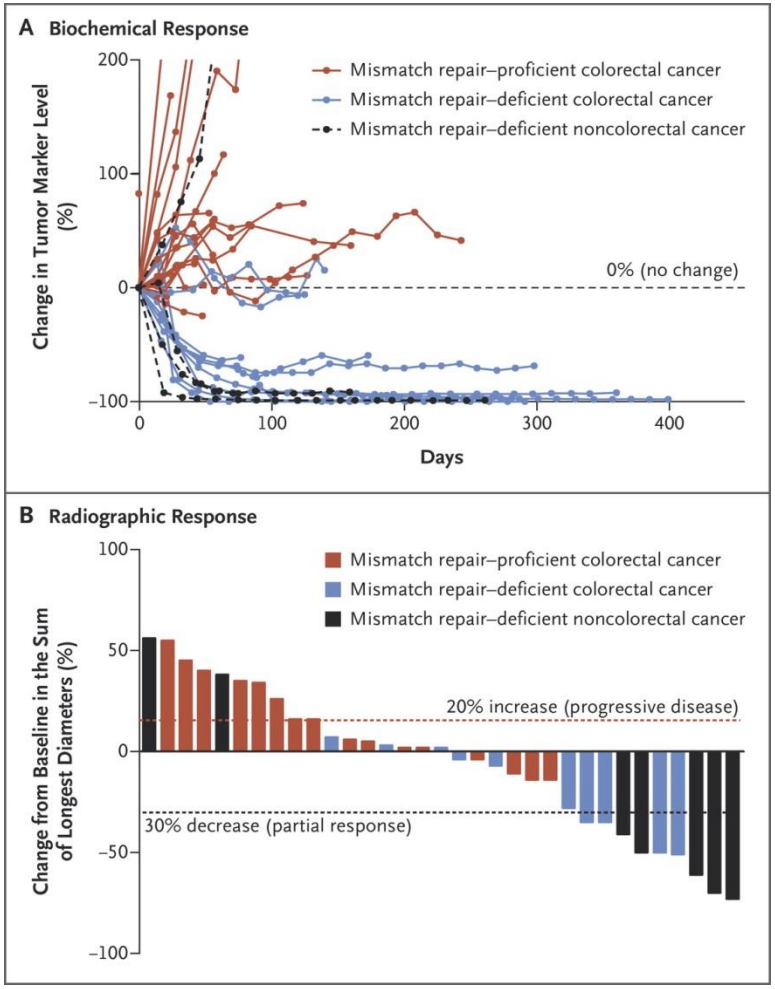
PD-1 Blockade in MMR-Deficient Tumors: Efficacy

Efficacy Outcome (RECIST), %	MMR-Deficient CRC (n = 13)	MMR-Proficient CRC (n = 25)	MMR-Deficient Other tumors (n = 10)
ORR	62	0	60
Disease control rate	92	16	70

- To date, responses > 1 yr. observed, and 13 or 14 responding pts continue to maintain response
- Other efficacy outcomes in MMR-deficient vs MMR-proficient tumors
  - Median PFS: not yet reached vs 2.3 mos
  - Median OS: not yet reached vs 5 mos
- Biochemical response (eg, CEA, CA-19) declined early with treatment in pts with MMR-deficient cancers and correlated with ORR, PFS, OS

Le et al NEJM 2015; 372(26): 2509-2520.

Clinical Responses to Pembrolizumab Treatment.



The NEW ENGLAND JOURNAL of MEDICINE

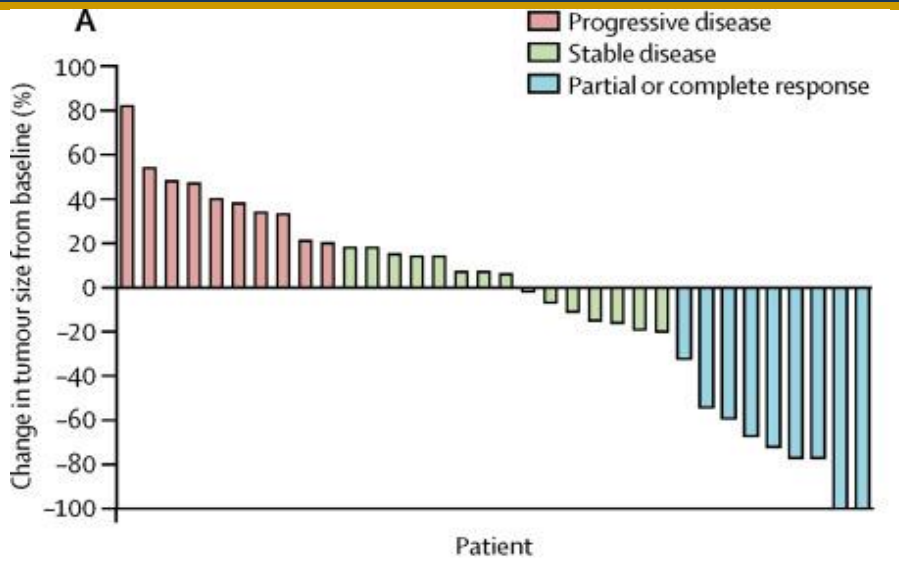
Le et al NEJM 2015; 372(26): 2509-2520.

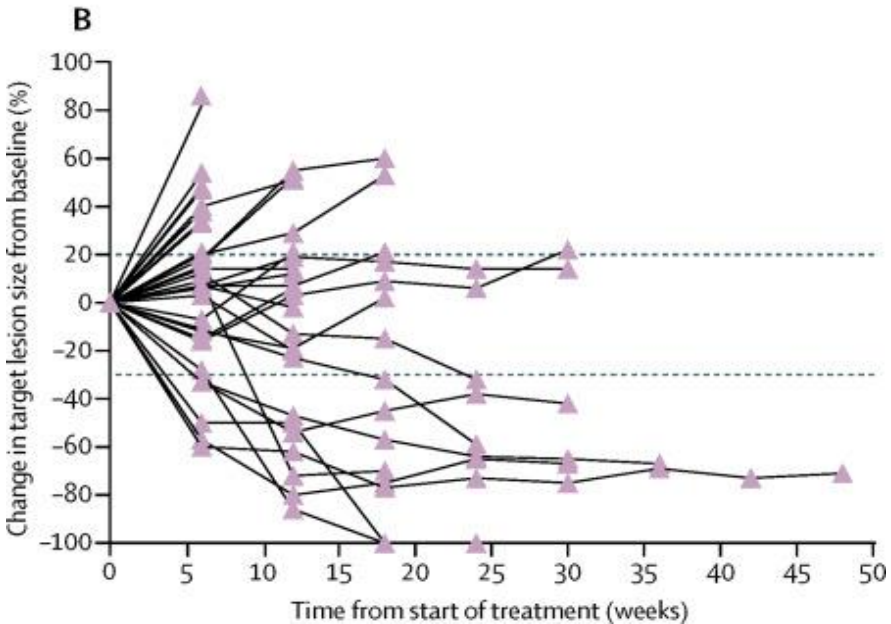
Anal cancer

Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study

Van K Morris, Mohamed E Salem, Halla Nimeiri, Syma Iqbal, Preet Singh, Kristen Ciombor, Blase Polite, Dustin Deming, Emily Chan, James L Wade, Lianchun Xiao, Tanios Bekaii-Saab, Luis Vence, Jorge Blando, Armeen Mahvash, Wai Chin Foo, Chimela Ohaji, Manolo Pasia, Gail Bland, Aki Ohinata, Jane Rogers, Amir Mehdizadeh, Kimberly Banks, Richard Lanman, Robert A Wolff, Howard Streicher, James Allison, Padmanee Sharma, Cathy Eng

Morris et al. Lancet Oncol epub Feb 2017

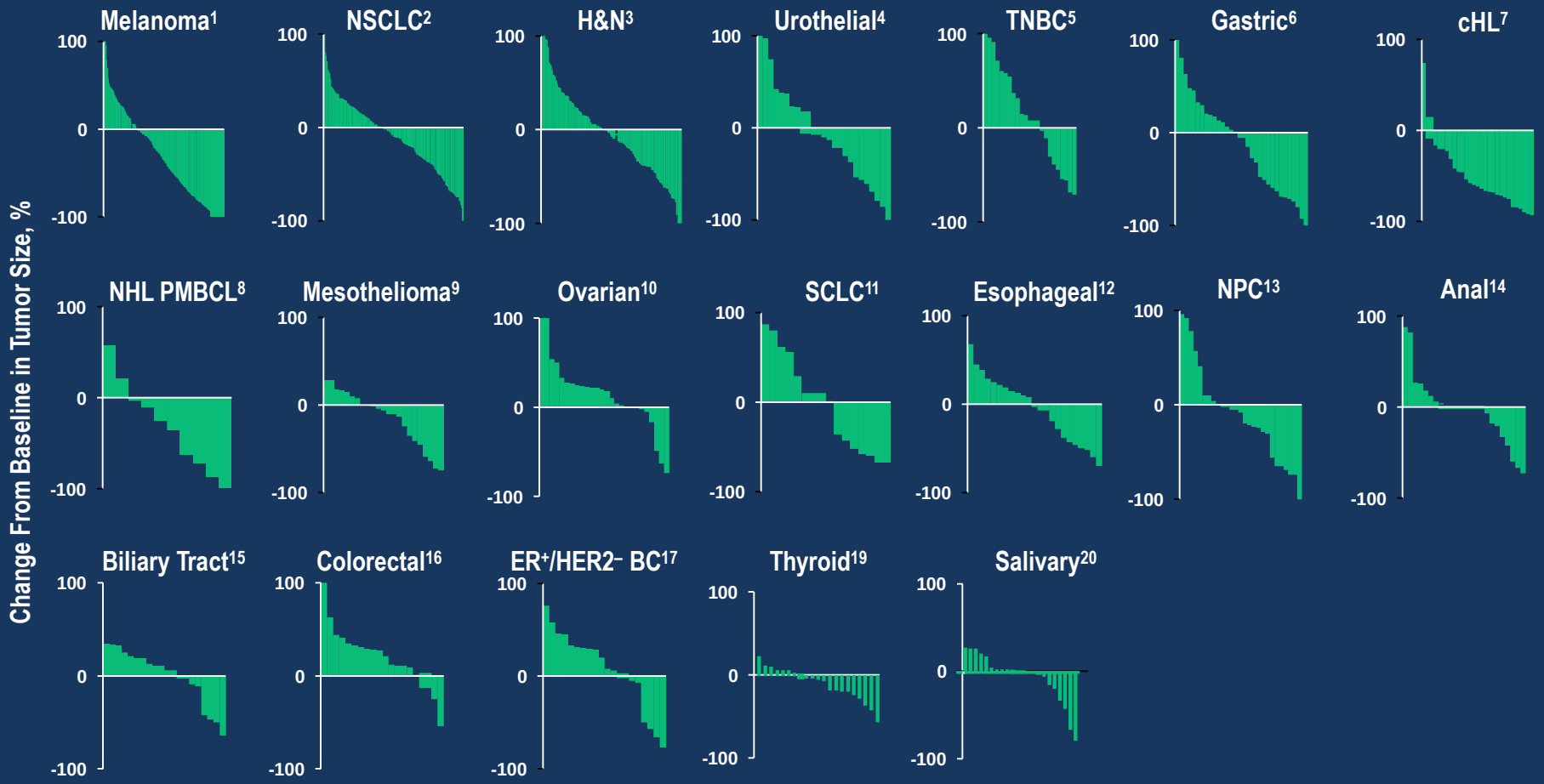

A
Progressive disease
Stable disease
Partial or complete response
Change in tumour size from baseline (%)
100
80
60
40
20
0
−20
−40
−60
−80
−100
Patient


B
Change in target lesion size from baseline (%)
100
80
60
40
20
0
−20
−40
−60
−80
−100
0
5
10
15
20
25
30
35
40
45
50
Time from start of treatment (weeks)

CancerCare Manitoba
ActionCancerManitoba

Pembrolizumab Activity

2017 CANCER DAY FOR PRIMARY CARE



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.

- **Phase III trials are underway in gastric cancer and hepatoma where PD-1 inhibition has shown activity**
- **Stay tuned……**

CancerCare Manitoba
ActionCancerManitoba

FDA Approvals

2017 CANCER DAY FOR PRIMARY CARE

	Nivolumab/ ipilimumab	Nivolumab	Pembrolizumab	Atezolizumab	Avelumab
Melanoma	Oct 2015	Dec 2014	Sept 2014		
NSCLC 1st line			Oct 2016 PD-L1 +ve		
NSCLC 2nd line		Oct 2015	Oct 2015 PD-L1 +ve	Oct 2016	
Renal Cancer 2nd line		Nov 2015			
Hodgkins' (Refractory)		May 2016			
SCCHN 2nd line		Nov 2016	Aug 2016		
Bladder Ca 2nd line		Feb 2017		May 2016	
Merkel Cell ≥ 1st line					March 2017

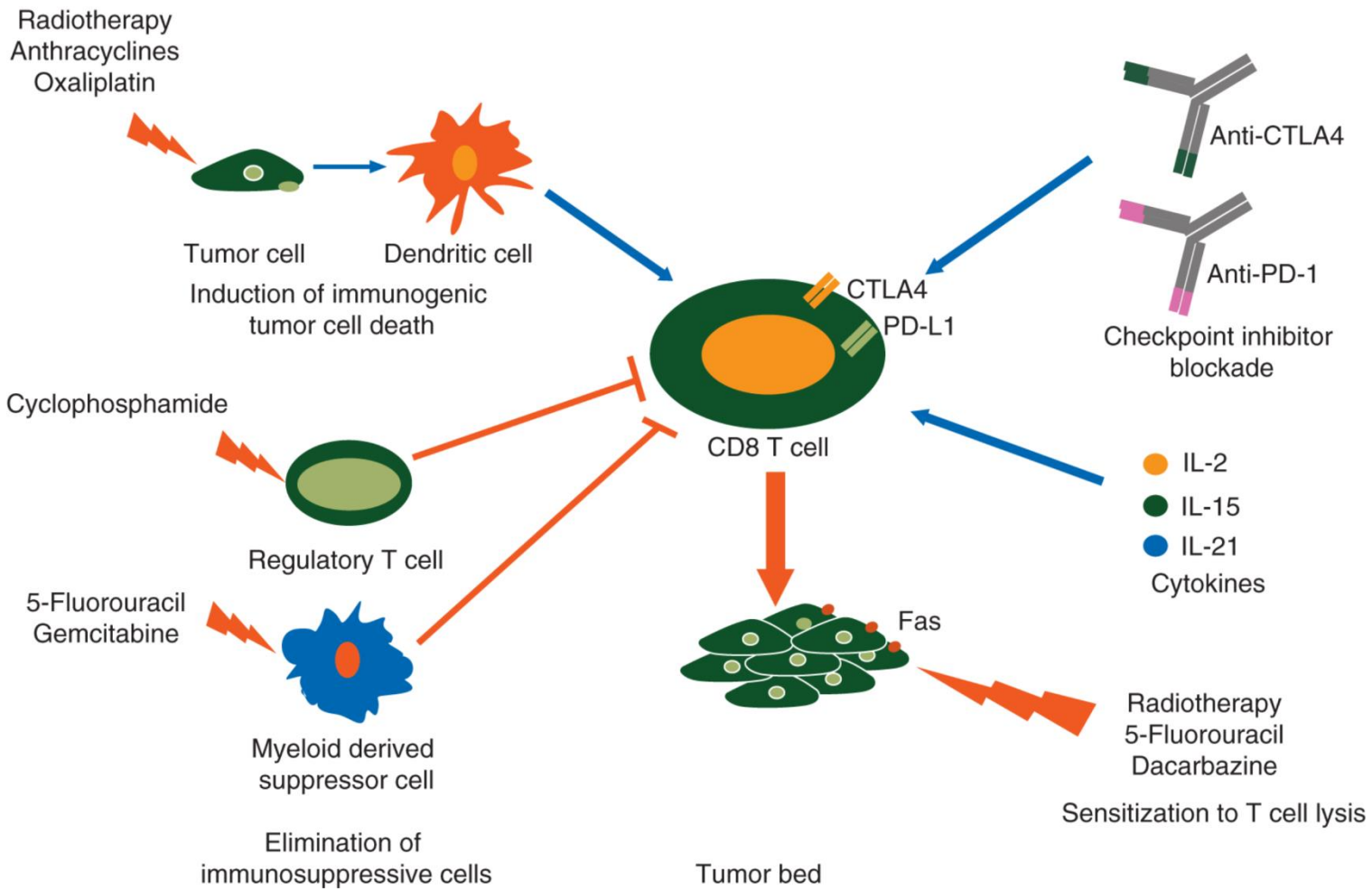
Health Canada Approvals

- **Melanoma (1st and 2nd line)**
  - **Nivolumab/ipilimumab**
  - **Nivolumab**
  - **Pembrolizumab**
- **Lung Cancer (2nd line)**
  - **Nivolumab**
  - **Pembrolizumab (PD-L1 +ve)**
- **Renal Cancer (2nd line)**
  - **Nivolumab**

Unanswered questions

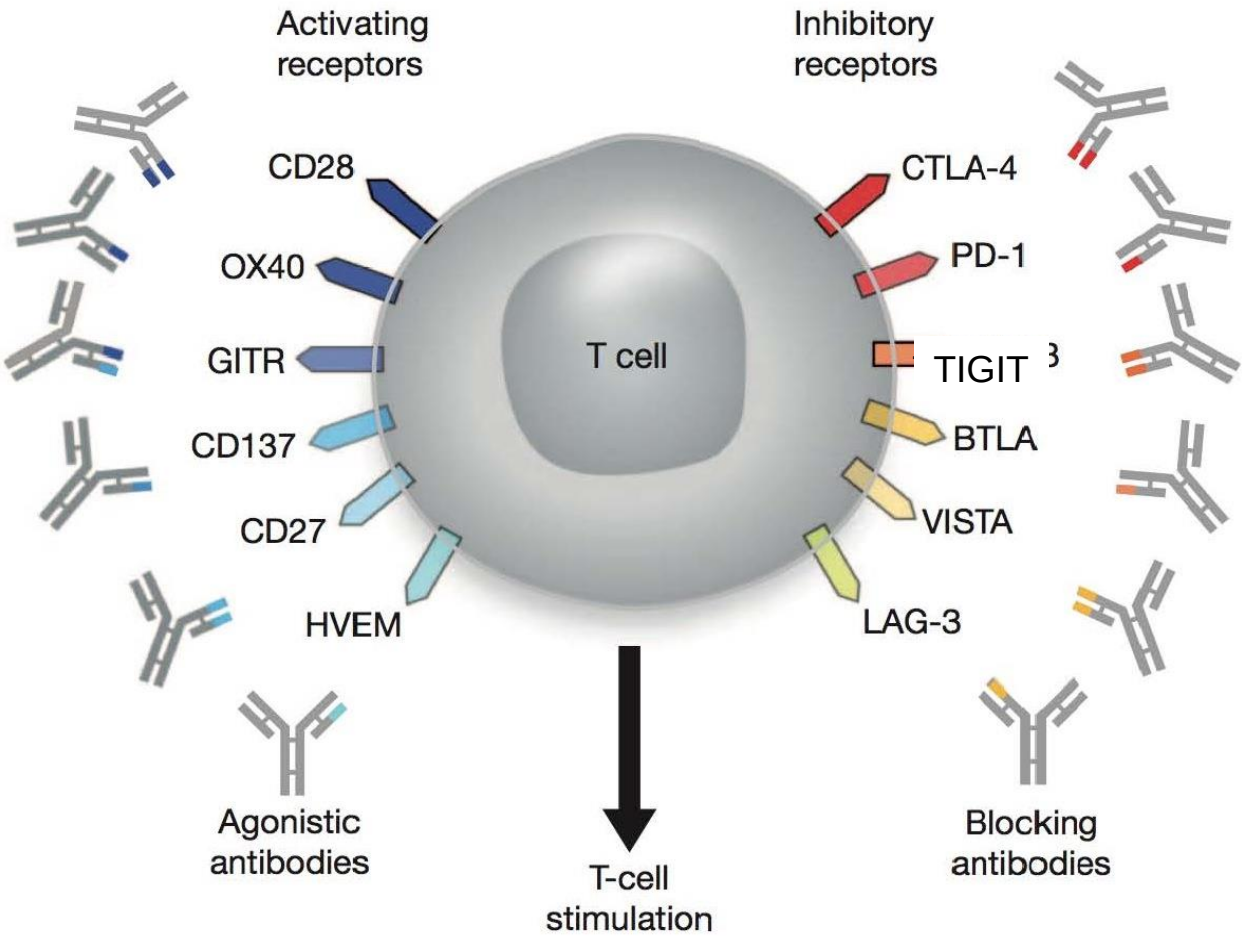
Quo Vadis?

Combining anticancer agents with Immunotherapy



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

The landscape of T cell activating and inhibitory receptors



Turning a "cold" tumour "hot"; Colon cancer

- **Open-label phase Ib dose escalation and expansion study**

3 + 3 Dose Escalation

Pts with chemo-refractory solid tumors, ECOG PS 0-1, measurable disease per RECIST v1.1 → **Cobimetinib* 20,† 40, or 60‡ mg PO QD + Atezolizumab 800 mg IV Q2W**

Dosed in cycles of 21 days on/7 days off.
†1 *KRAS* mutant pt, 1 *KRAS* WT pt.
‡1 *KRAS* mutant pt.

- **Dose-escalation: 3 mCRC pts (2 *KRAS* mutant, 1 *KRAS* WT); 28-day DLT window for MTD determination**
- **Dose-expansion: 20 mCRC pts (all *KRAS* mutant); other cohorts included NSCLC, metastatic melanoma, solid tumors serial biopsy**
- **Primary objectives: safety, clinical activity**

Bendell J, et al. ASCO 2016. Abstract 3502.

Efficacy

- Response/tumor volume reduction not associated with PD-L1 status
- 4 pts had PRs, 3 of which were mismatch repair proficient (1 not evaluable)
- Median time to first response: 3.7 mos (range: 1.8 to 4.1)
- Median DOR: NR (range: 5.4 to 11.1 mos)
  - 2 pts with ongoing responses
- Increased intratumoral CD8 T-cell infiltration over BL in the mCRC cohort

Outcome	*KRAS*-Mutant CRC (n = 20)	All CRC (n=23)
ORR, %	20	17
▪PR	20	17
▪SD	20	22
▪PD	50	52
▪NE	10	9
PFS		
▪Median, mos (95% CI)	2.3 (1.8-9.5)	2.3 (1.8-9.5)
▪6-mo, % (95% CI)	39 (0.16-0.61)	35(0.14-0.56)
OS		
▪Median, mos (95% CI)	NE (6.5-NE)	NE(6.5-NE)
▪6-mo, % (95% CI)	77 (0.57-0.97)	72(0.52-0.93)

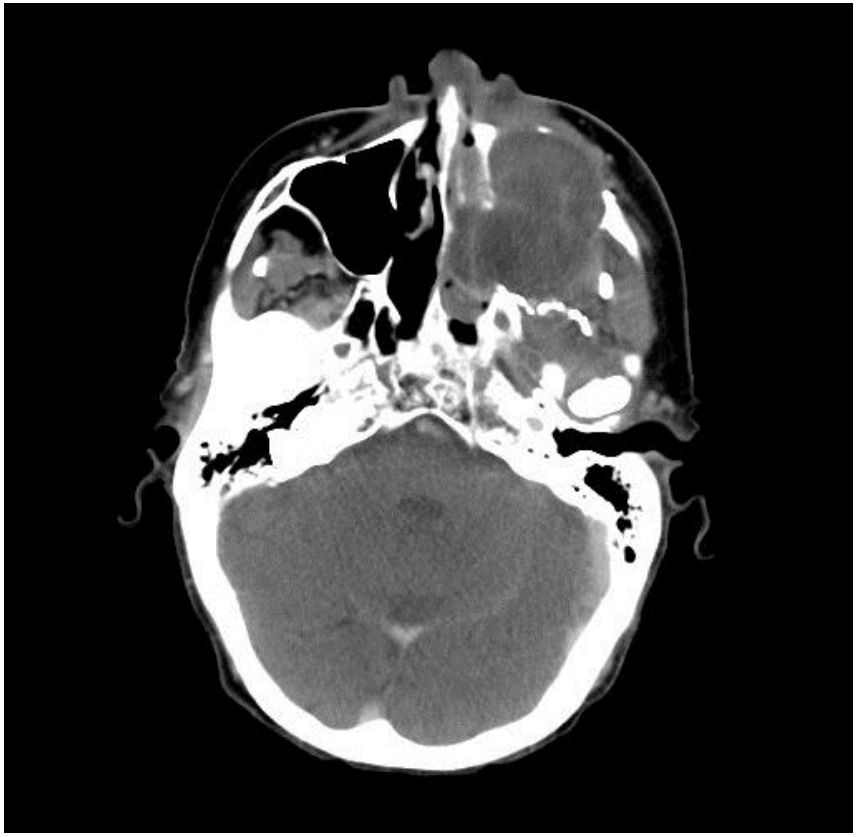
Bendell J, et al. ASCO 2016. Abstract 3502

Issues

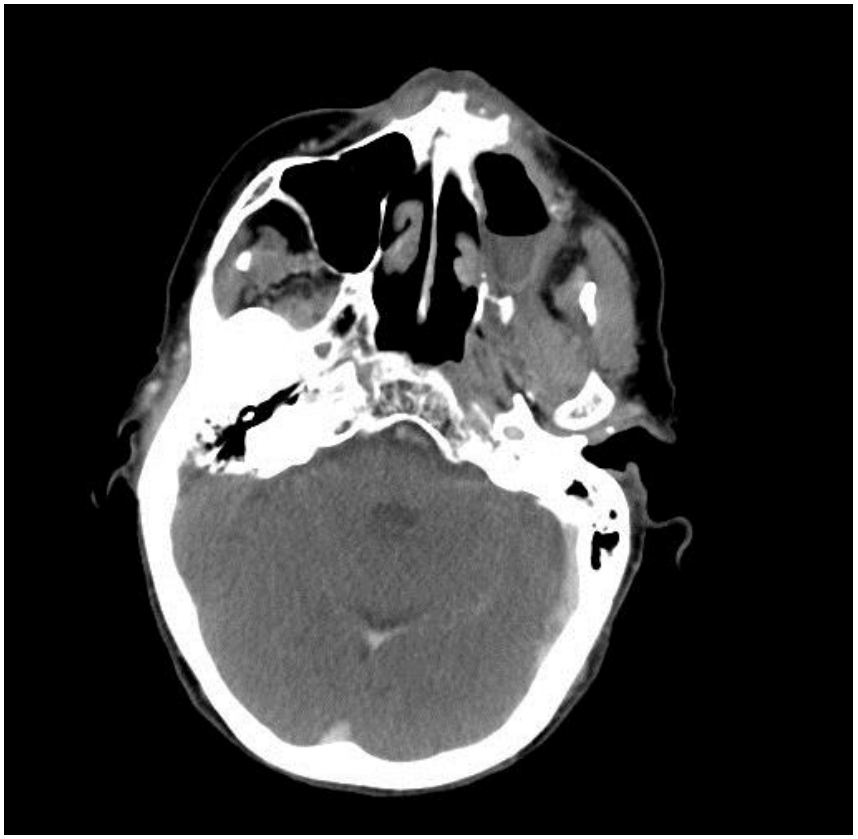

THE CARTER CENTER

Case Presentation

Oct 22, 2015

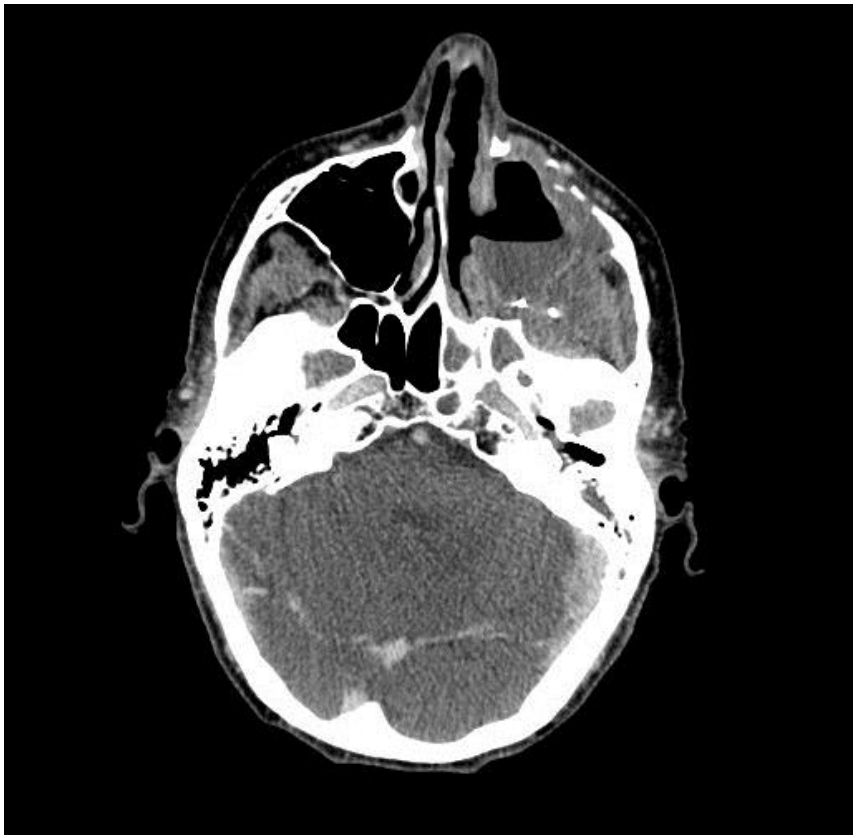


December 30, 2015

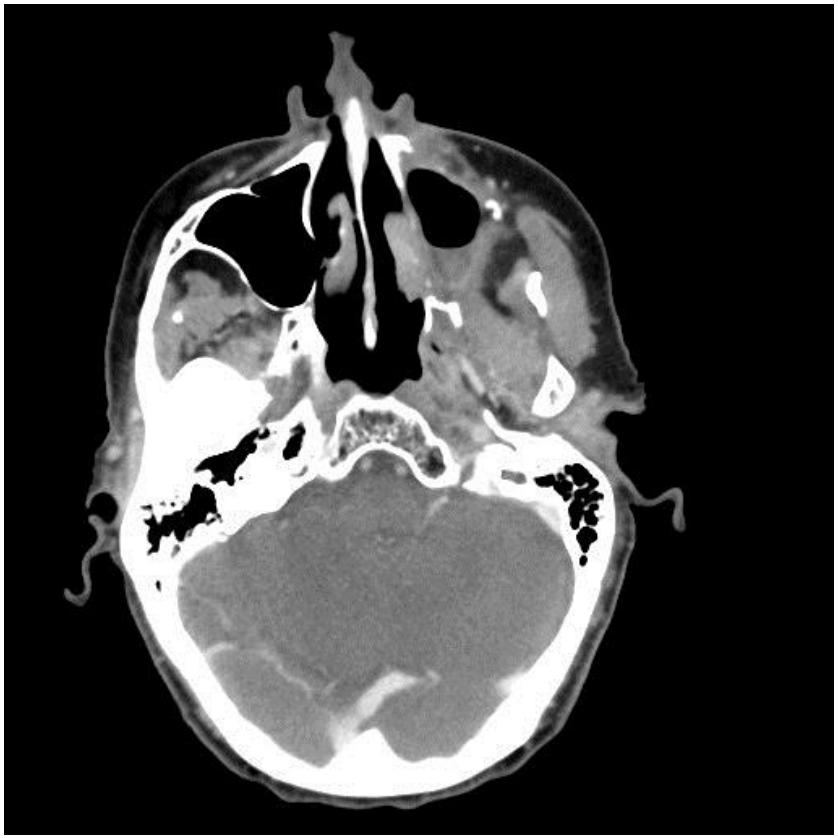


Case Presentation

May 26, 2016



February 8, 2017



The NEW "Tsunami"

Conclusion

- This is an exciting time to be in Medical Oncology
- The new I-O drugs are changing the way we look at managing patient with advanced cancer
- Previously untreatable Stage IV melanoma patients are now experiencing long term survival

Conclusion

- **Checkpoint inhibitors have yet to have a defined role in GI malignancies but would expect that to change in the near future especially for SCC anus**
  - **Phase III trial underway in gastric cancer and hepatoma**

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

PRESCRIPTIONS

**"This is one of those new miracle drugs.
If you can afford it, it's a miracle."**

CancerCare Manitoba
UNITING PRIMARY CARE AND ONCOLOGY

CancerCare Manitoba
COMMUNITY ONCOLOGY PROGRAM

QUESTIONS?