Immuno-Oncology The 4th Pillar of Cancer Therapy:
How does it work and managing adverse events

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April 20, 2017

Presenter Disclosures

- I have receiving consulting fees and/or speaking honoraria from the following companies:
  - Bristol Myers Squibb
  - Roche
  - Merck
  - Novartis

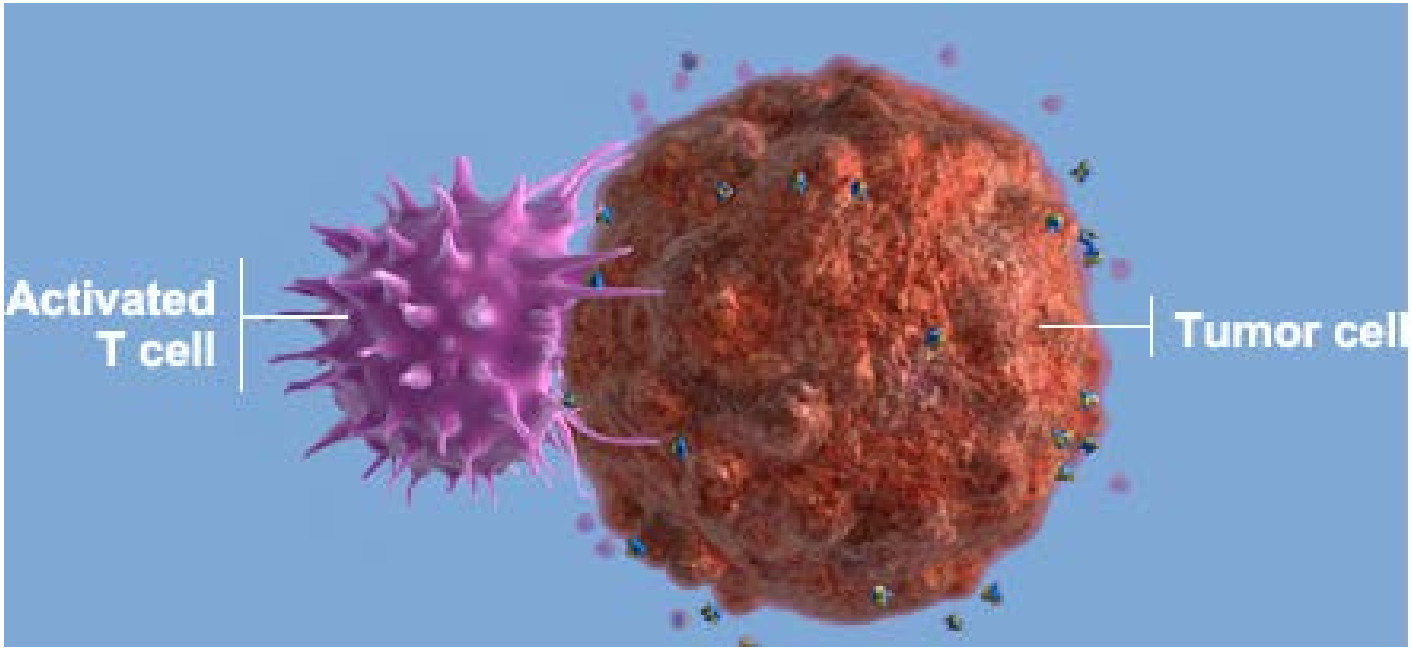
- I have received unrestricted educational grants or sponsorship for five multidisciplinary melanoma meetings in Victoria held between 2013-2015 from BMS, Roche, Merck, Novartis.

- Some slides were provided to me by Bristol Myers Squibb.

Overview

- Review how the immune system targets cancer.
- Review the mechanisms of action and efficacy of checkpoint inhibitors
  - CTLA4 antagonists
  - PD1 inhibitors
- Review the patterns of response to checkpoint inhibitors.
- Review the standard AE and how to manage them.

Immuno-Oncology
Helping Your Immune System Fight Cancer



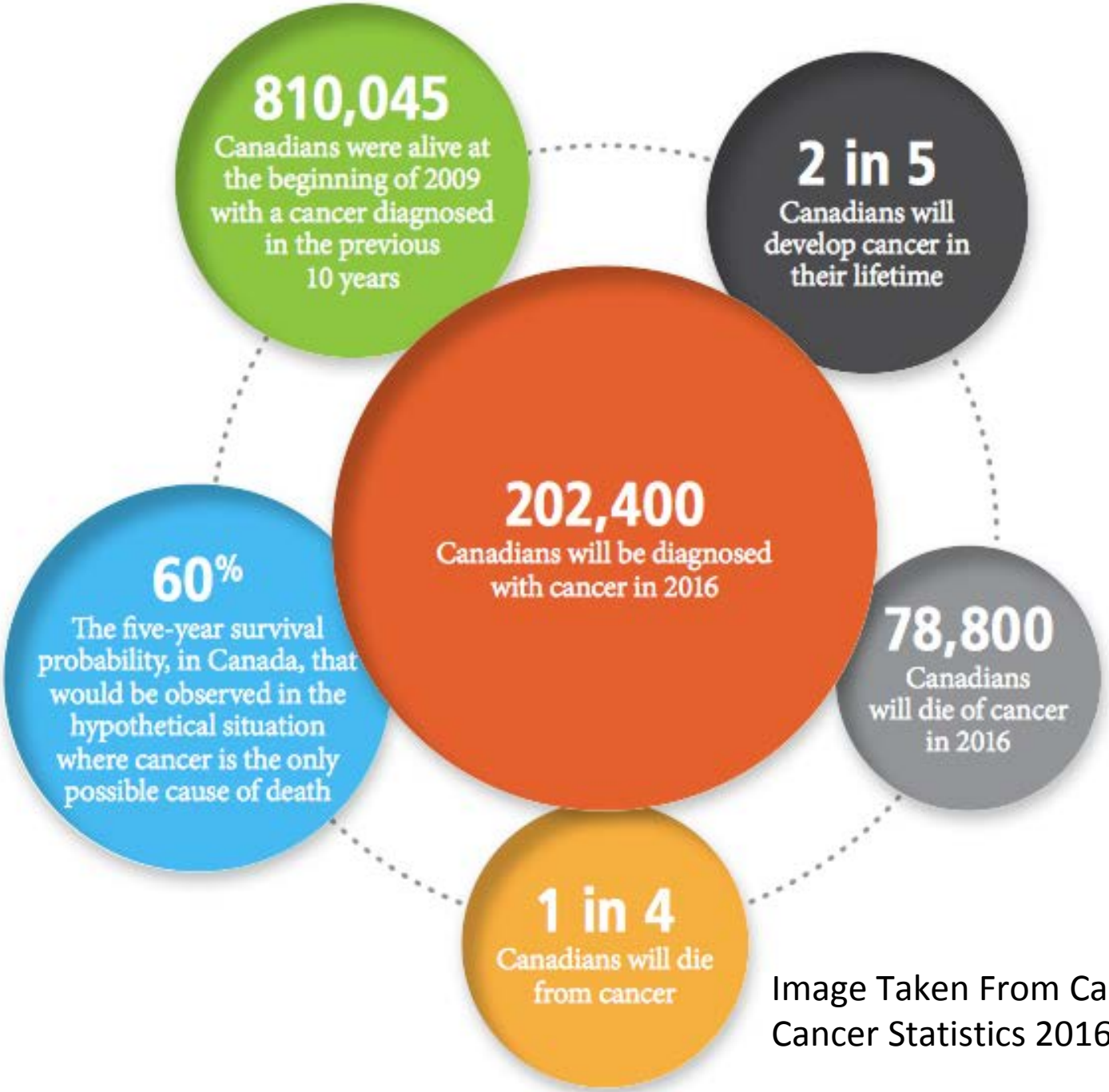
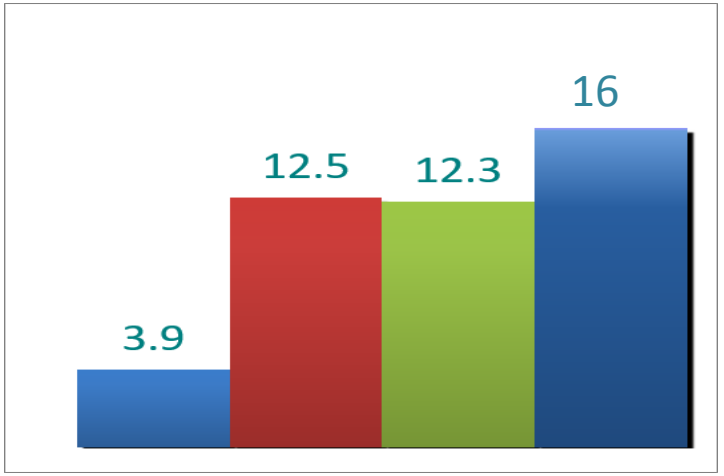


Image Taken From Canadian Cancer Statistics 2016

Long-term Survival Remains a Challenge in Some Advanced Cancers

- Five-year survival remains poor for many patients with metastatic solid tumours[1]
- There is a need for new treatments and therapeutic modalities for patients with advanced cancers[2]

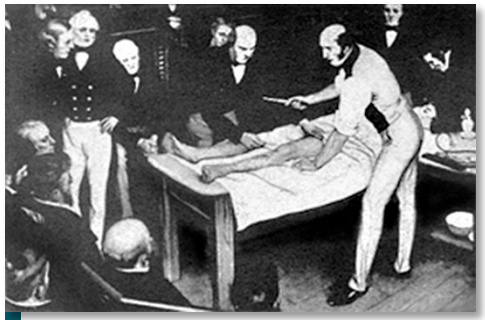
Five-year survival (%) 2010 data[1]



Immuno-oncology (I-O) therapies are being investigated in an attempt to fill the unmet need for improving clinical outcomes in advanced cancer

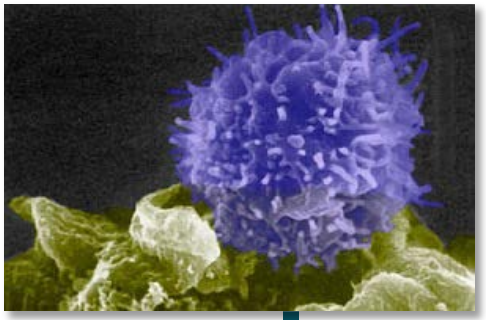
Surveillance, Epidemiology and End Results (SEER) Program. http://seer.cancer.gov (statistics for diagnosis years 2003 through 2009, with all patients followed through 2010); 2. Rosenberg SA. *Sci Transl Med*. 2012;4(127ps8):1-5. * including current immunotherapies. Rate was less than 5% prior to the introduction of immuno-oncology (Korn, *JCO*. 2008 Feb 1; 26(4)

Evolution of Cancer Therapy: Treatment Modalities



Surgery
1846

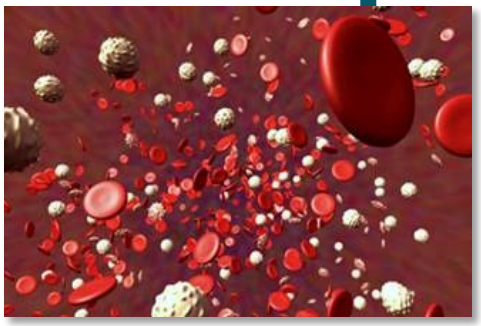
Chemotherapy
1946



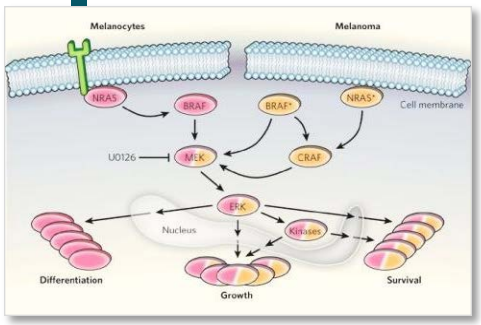
Immuno-oncology
Sipuleucel-T 2010
Ipilimumab 2011

Radiation Therapy
1901

Immunotherapy
Interferon-α 1995
Interleukin-2 1998



Targeted Therapy
1997

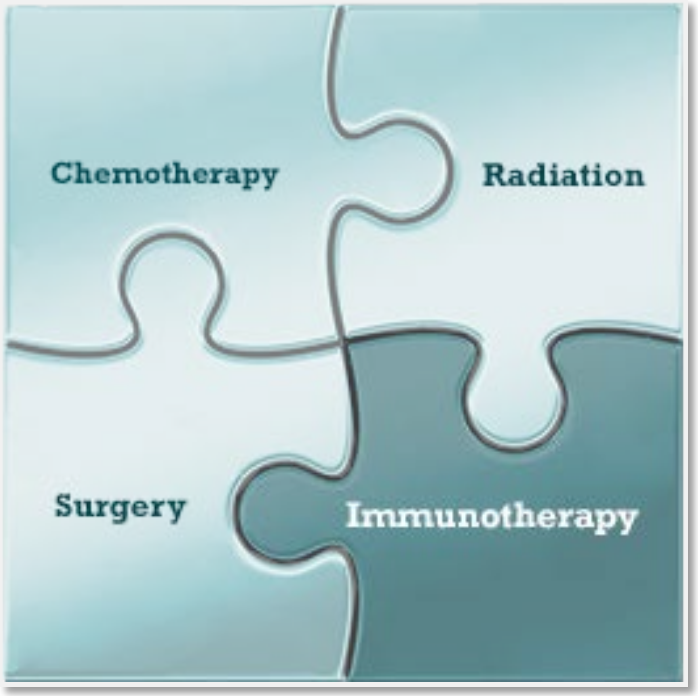


DeVita VT Jr, Chu E. *Cancer Res* 2008; 68(21):8643-53; The American Cancer Society. The History of Cancer. Available from: cancer.org/cancer/cancerbasics/thehistoryofcancer/; Finn OJ. *Ann Oncol* 2012; 23 Suppl 8:viii6-9; Mansh M. *Yale J Biol Med* 2011; 84(4):381-9; Kirkwood JM, *et al. CA Cancer J Clin* 2012; 62(5):309-35; National Cancer Institute (NCI) Cancer Drug Information: Vemurafenib. Available from: cancer.gov/cancertopics/druginfo/vemurafenib; NCI Cancer Drug Information: Dabrafenib. Available from: cancer.gov/cancertopics/druginfo/fda-dabrafenib; NCI Cancer Drug Information: Trametinib. Available from: cancer.gov/cancertopics/druginfo/fda-trametinib.

Immuno-oncology (I-O) Is an Emerging Therapeutic Modality

- Traditional therapies for advanced cancer targets the tumour and include[1,2]
  - Surgery, radiation and cytotoxic/targeted therapy
- Immunotherapy harnesses the body's own immune system to fight diseases[3]
- Immuno-oncology (I-O) uses immunotherapy to treat cancer.[1,2]

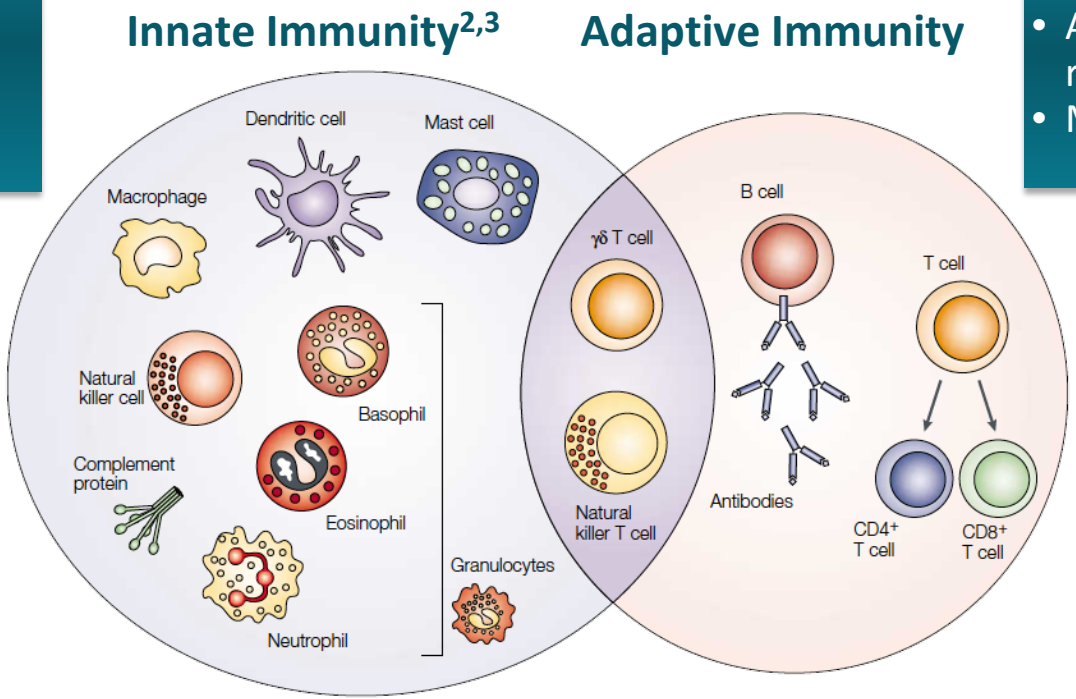
Pillars of Cancer Therapies



1. DeVita BT, Rosenberg SA. *N Engl J Med*. 2012;366:2207-2214; 2. Kirkwood JM, *et al*. *CA Cancer J Clin*. 2012;62:309-335;
3. Murphy JF. *Oncology*. 2010;4:67-80.

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

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

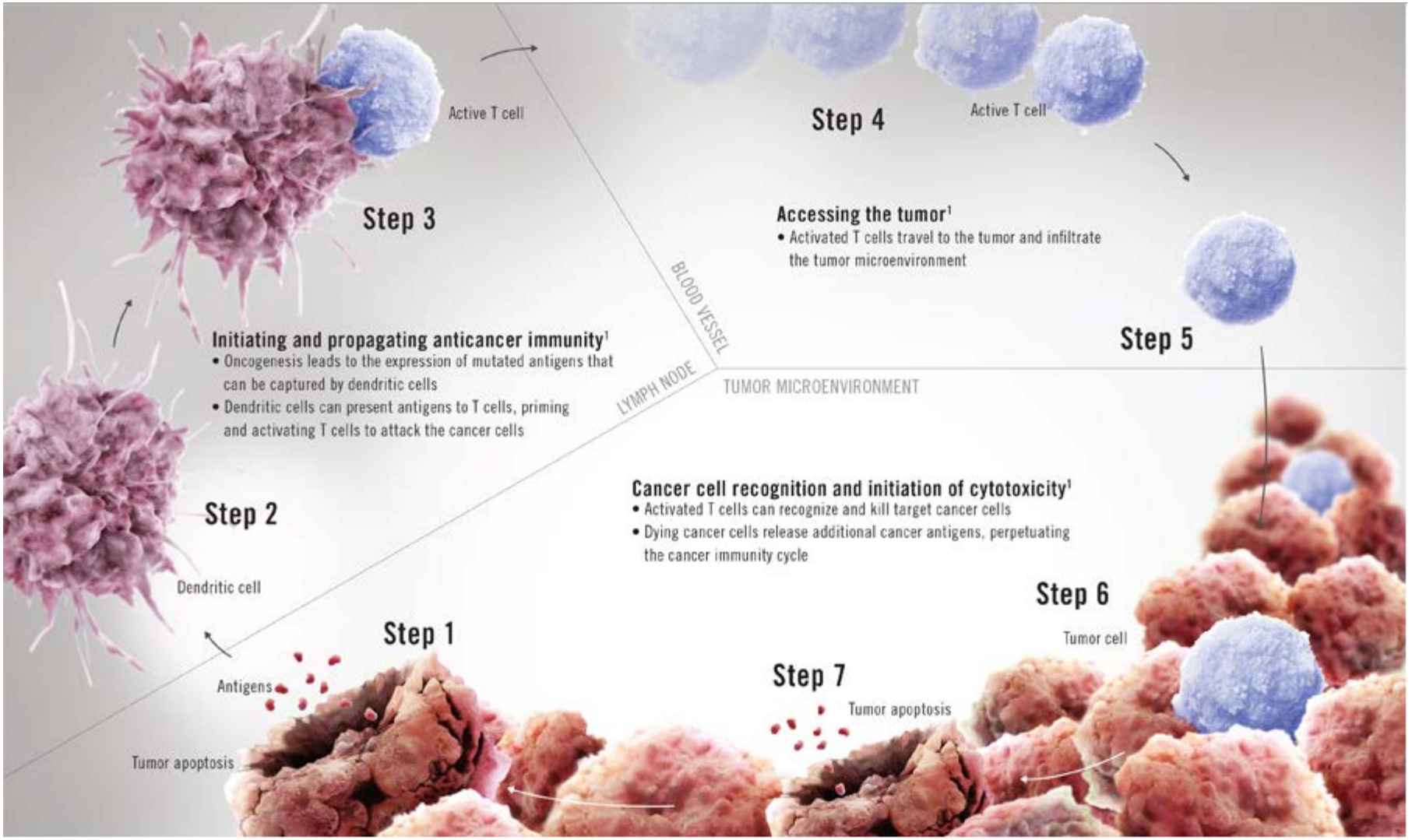


- Slow response
- Antigen-specific response
- Memory

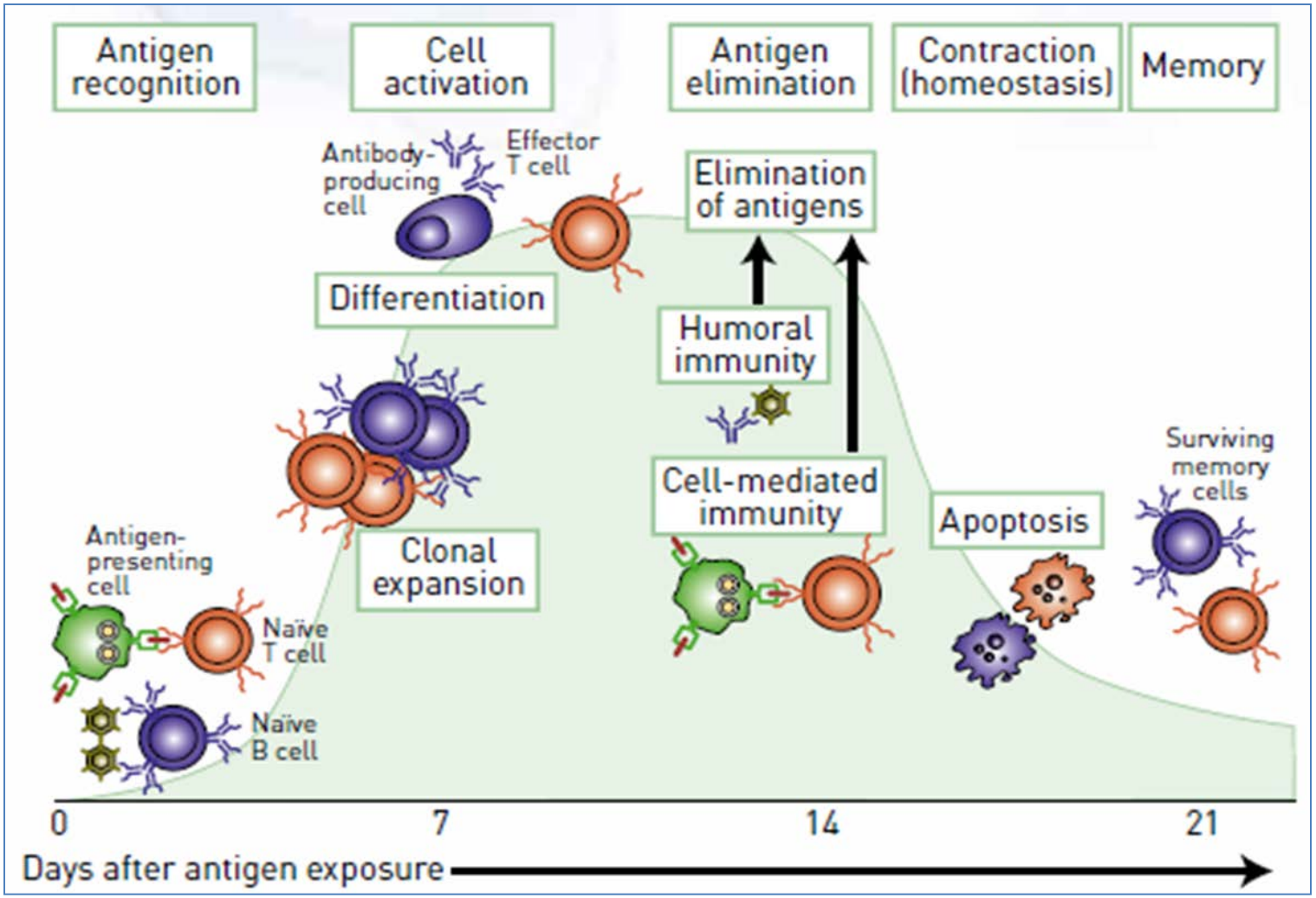
- External threats: viruses, parasites, protozoa, fungi, bacteria, toxins
- Internal threats: cancer

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, copyright 2004; 3. Vesely MD, *et al*. *Annu Rev Immunol*. 2011;29:235-271.

Activating T Cells Against Cancer



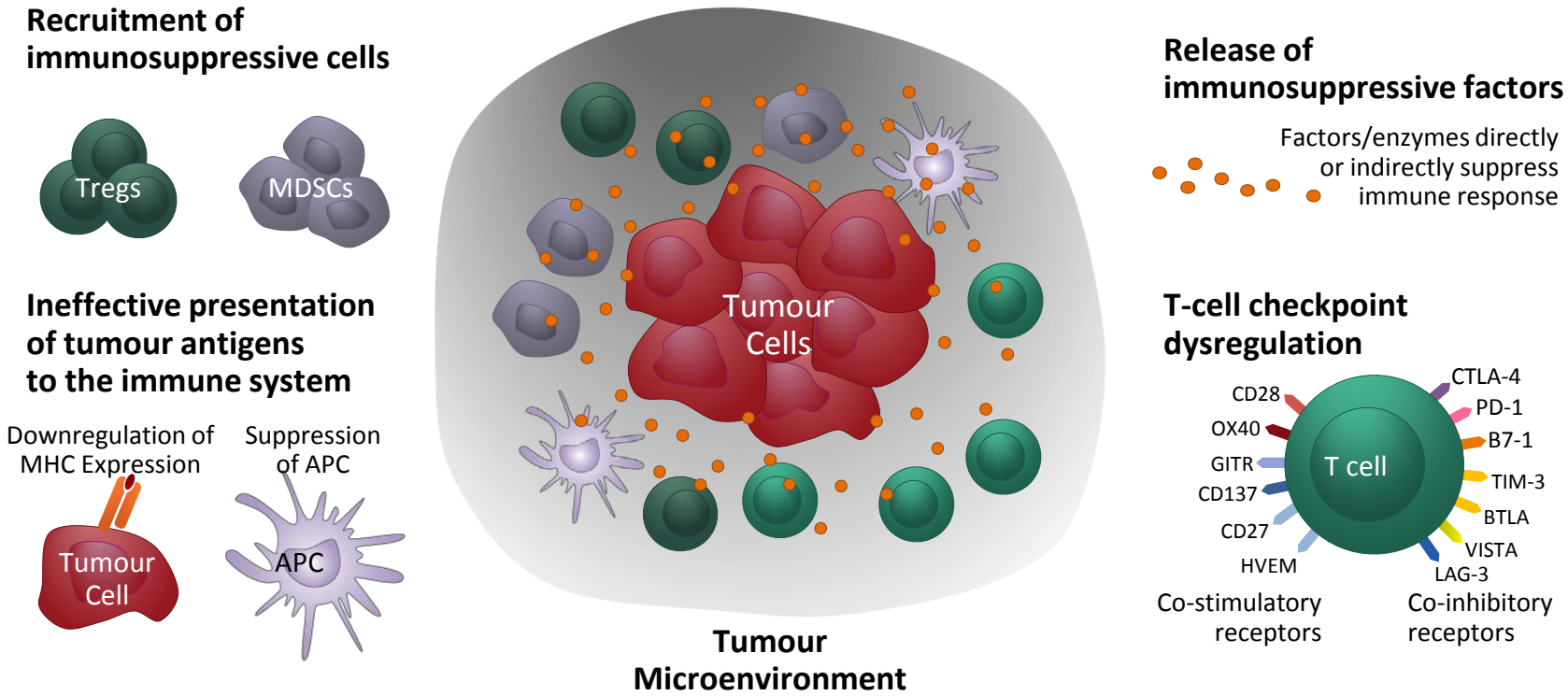
Adaptive Immune Response



Adapted from Abbas *et al. Cellular and Molecular Immunology*. 6th ed. Philadelphia, PA: Elsevier Saunders; 2010.

Immune Escape in Cancer

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

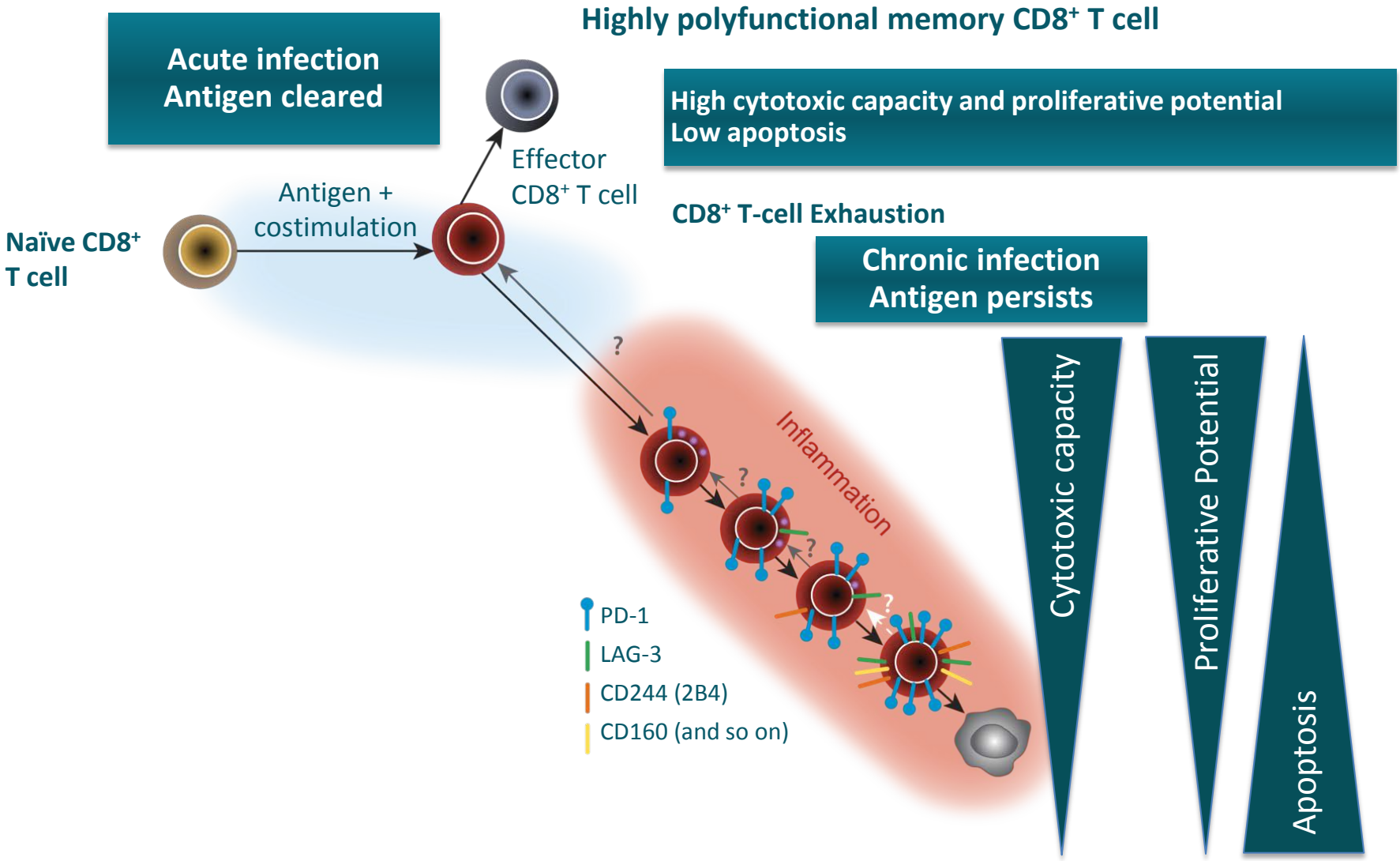


The mechanisms tumours use to escape the immune system provide a range of potential therapeutic targets for cancer

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

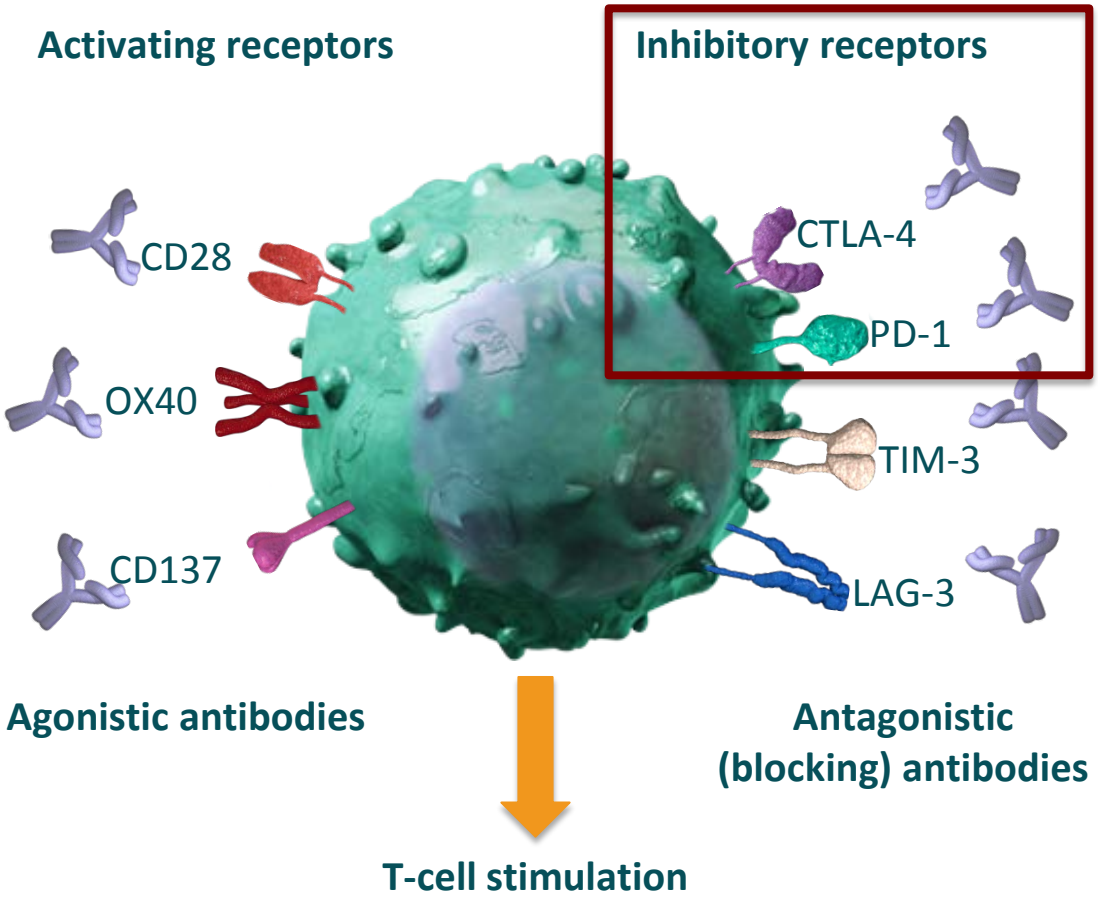
1. Bremnes RM *et al*. *J Thorac Oncol*. 2011;6:824-833. 2. Jadus MR *et al*. *Clin Dev Immunol*. 2012:160724.

CD8+ T-cell Exhaustion Due to Chronic Antigen Simulation: Model Based on Viral Infections



Modified from: Wherry *et al. Nat Immunol*. 2011;12(6):492-499.

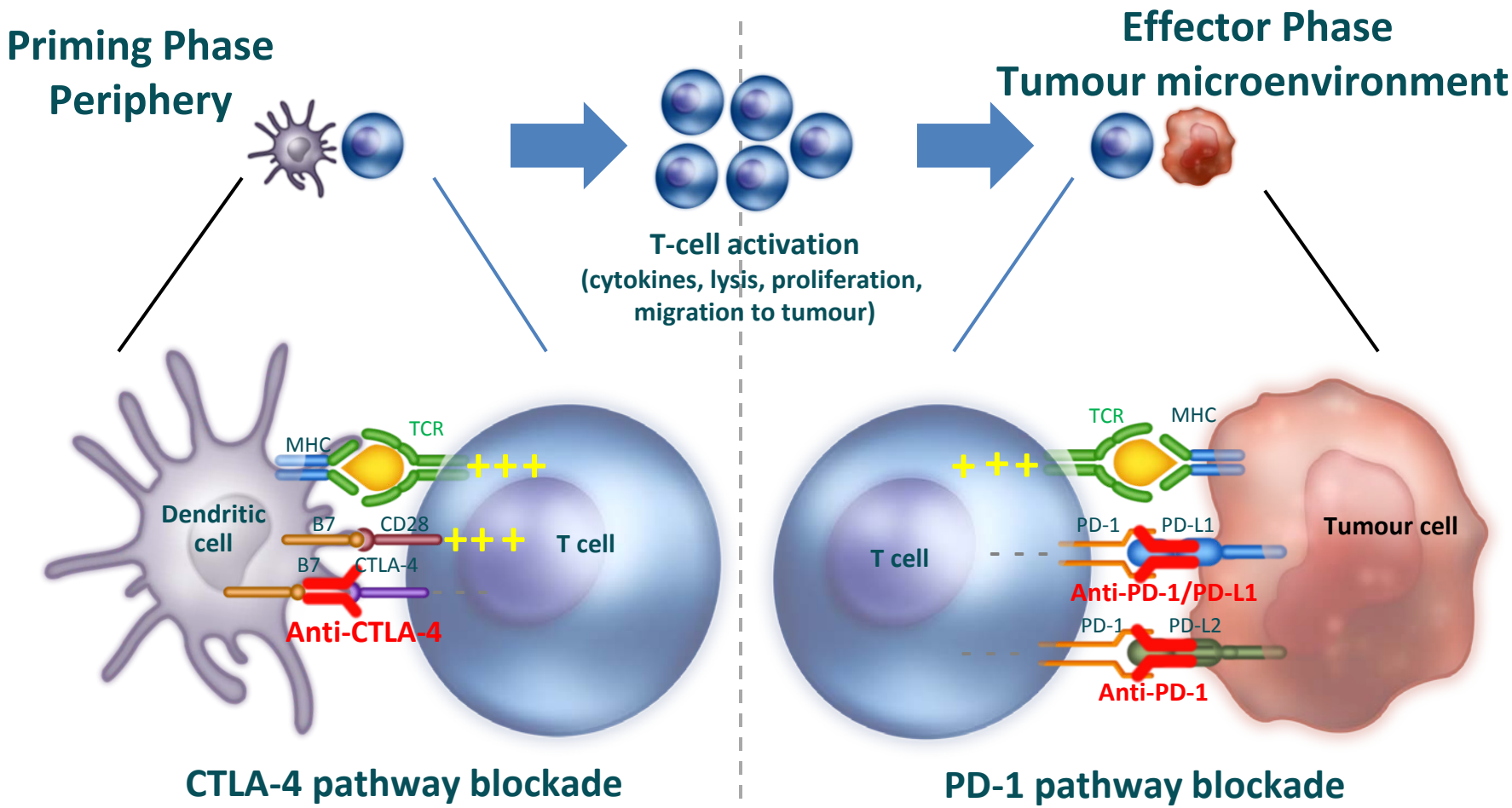
T-Cell Checkpoint Regulation is an Evolving Approach to Cancer Therapy



- 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.

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

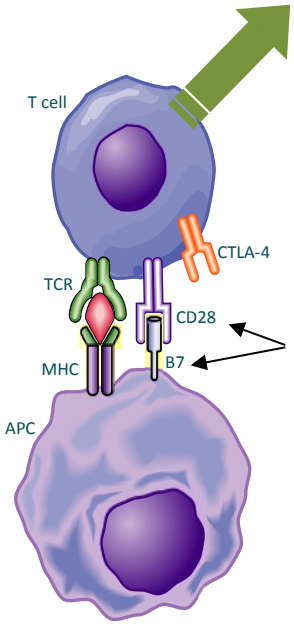


CTLA-4=cytotoxic T-lymphocyte antigen-4; PD-1=programmed cell death 1; PD-L1/2=PD ligand 1/2; TCR=T cell receptor.
Adapted from Wolchock J, *et al*. Oral presentation at ASCO 2013 (Abstract 9012).

Proof of Concept –
Efficacy of Checkpoint Blockade:
CTLA-4 and PD-1 Inhibition

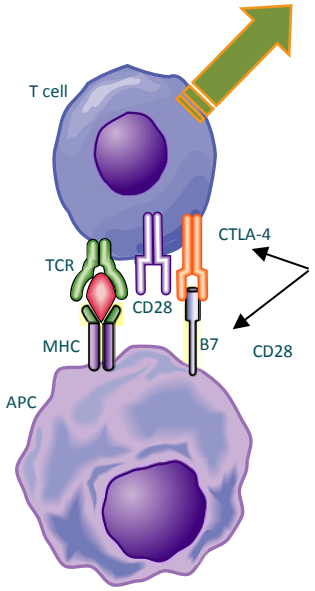
Novel Immune Therapy: Targeting the Natural T-cell Braking System from CTLA-4

T-cell activation



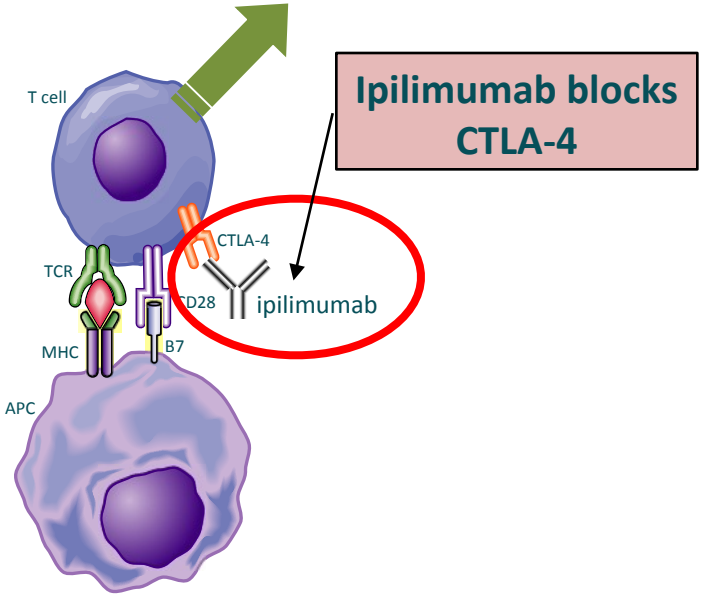
Antigen presentation and ligation of B7/CD28 co-activators results in T-cell activation

T-cell inhibition



In the activated T cell, CTLA-4 competes with CD28 and acts as the brakes on T-cell activation by binding to B7

T-cell activation and proliferation



By inhibiting CTLA-4, ipilimumab releases the natural braking system and restores T-cell activation, allowing T-cell proliferation to continue

B7: B7.1 (CD80) or B7.2 (CD86)

APC=antigen-presenting cell; CTLA-4=cytotoxic T-lymphocyte-associated antigen-4; MHC=major histocompatibility complex; TCR=T-cell receptor.
Adapted from Lebbé C, *et al*. *Ann Oncol* 2008; 19(suppl 8):viii289-viii311.

Past Treatments for Metastatic Melanoma

Treatment

Dacarbazine (DTIC)

- In large randomized trials, Response rate (RR) of <15%

Temozolomide

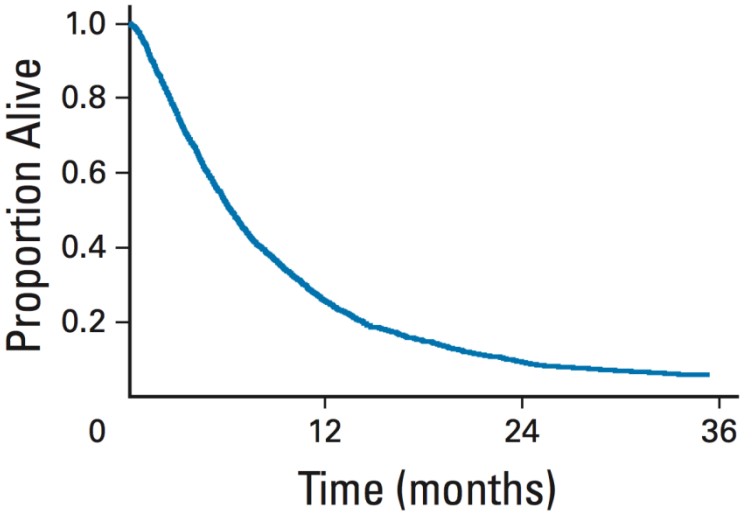
- Similar to DTIC

IL-2

- RR of 15-20%
- A minority are durable responses
- Highly toxic treatment

Survival[1]

- Median OS: 6.2 months
- One year OS: 25.5% (95% CI, 23.6% to 27.4%)

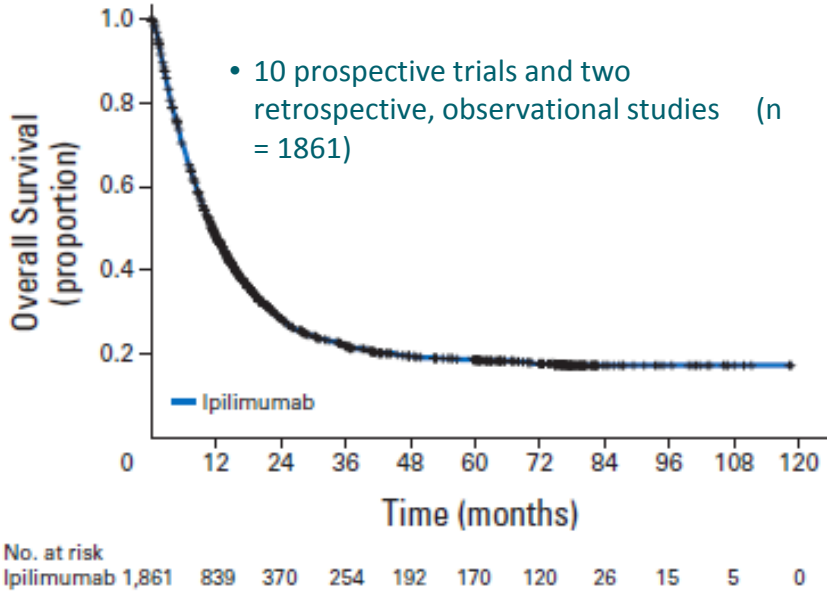


OS=overall survival.

1. Korn, JCO. 2008 Feb 1; 26(4)

Long-Term Survival with Ipilimumab in Melanoma

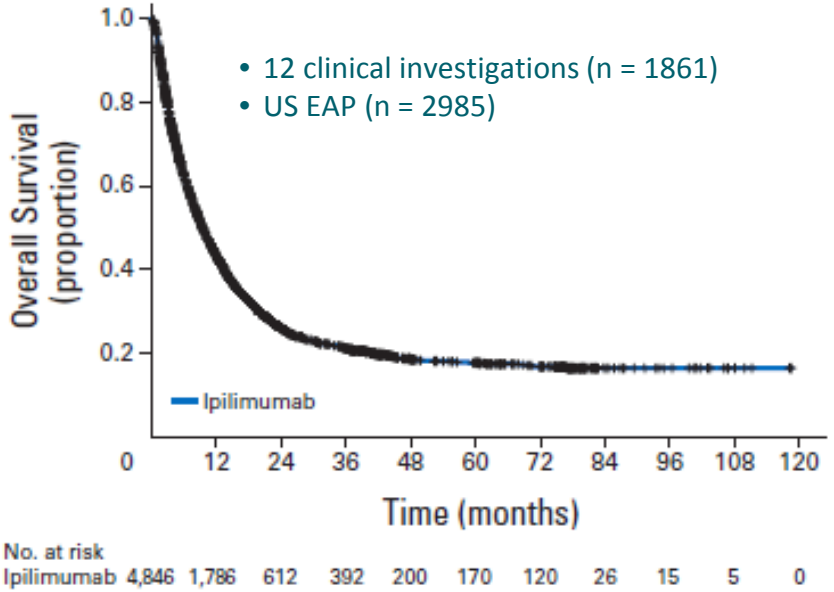
Pooled Analysis: Phase III and Phase II Trials



Median OS: 11.4 months
(95% CI, 10.7-12.1 months)

3-year survival rate: 22%
(95% CI, 20% to 24%)

Pooled Analysis: Phase III, Phase II Trials and EAP



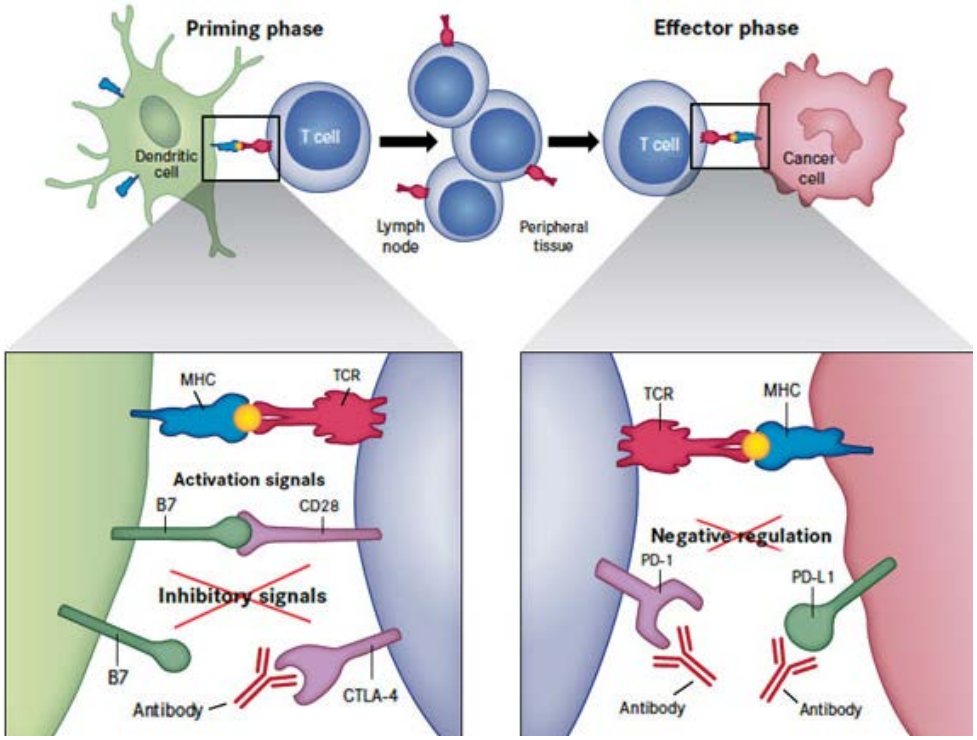
Median OS: 9.5 months
(95% CI, 9.0-10.0 months)

3-year survival rate: 21%
(95% CI, 20% to 22%)

Schadendorf D, *et al.* J Clin Oncol. 2015 Feb 9.

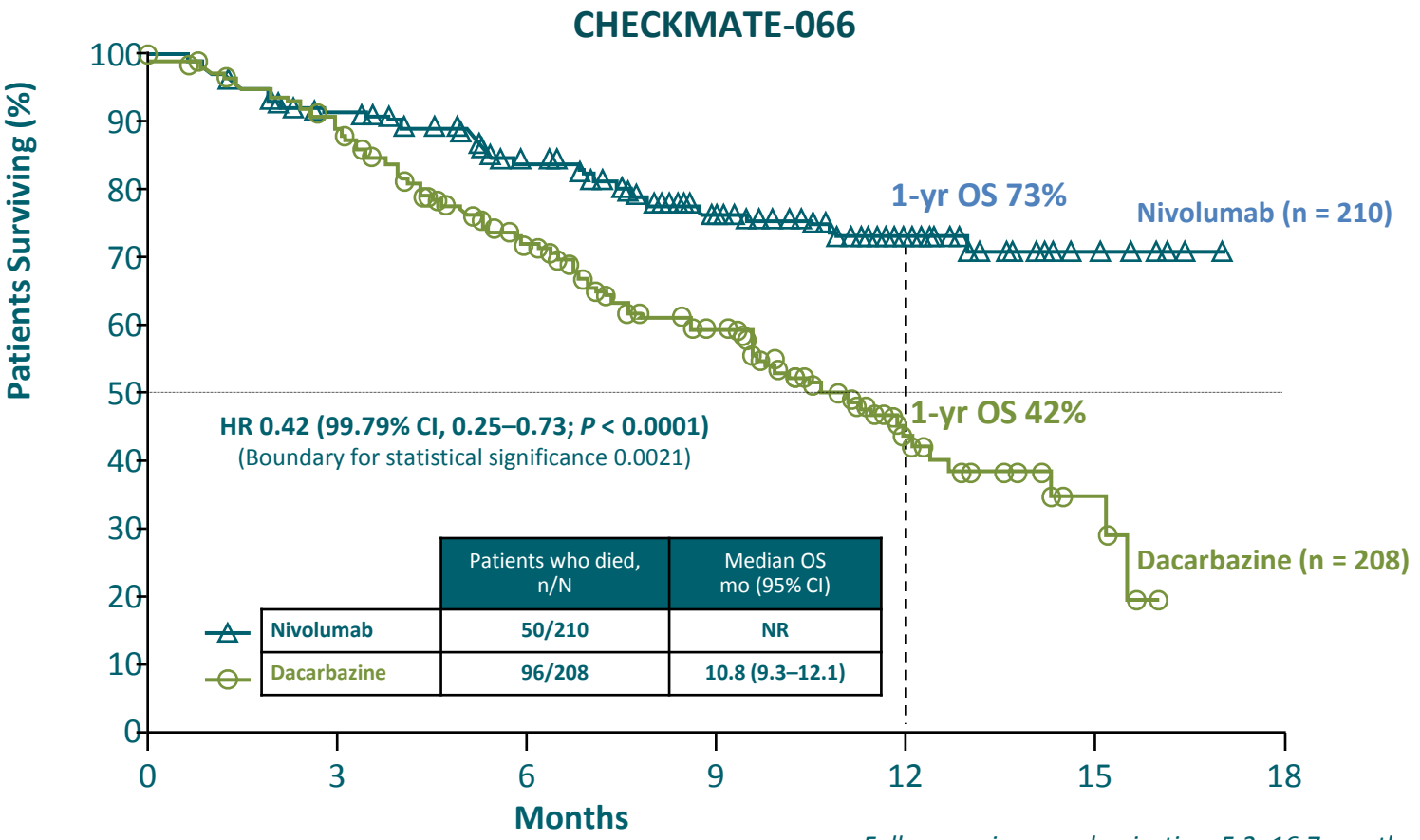
PD-1 and PD-L1 Antibodies

- 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

Nivolumab Improved Overall Survival vs. Dacarbazine in Melanoma



Follow-up since randomization: 5.2–16.7 months.

Patients at Risk

Nivolumab	210	185	150	105	45	8	0
Dacarbazine	208	177	123	82	22	3	0

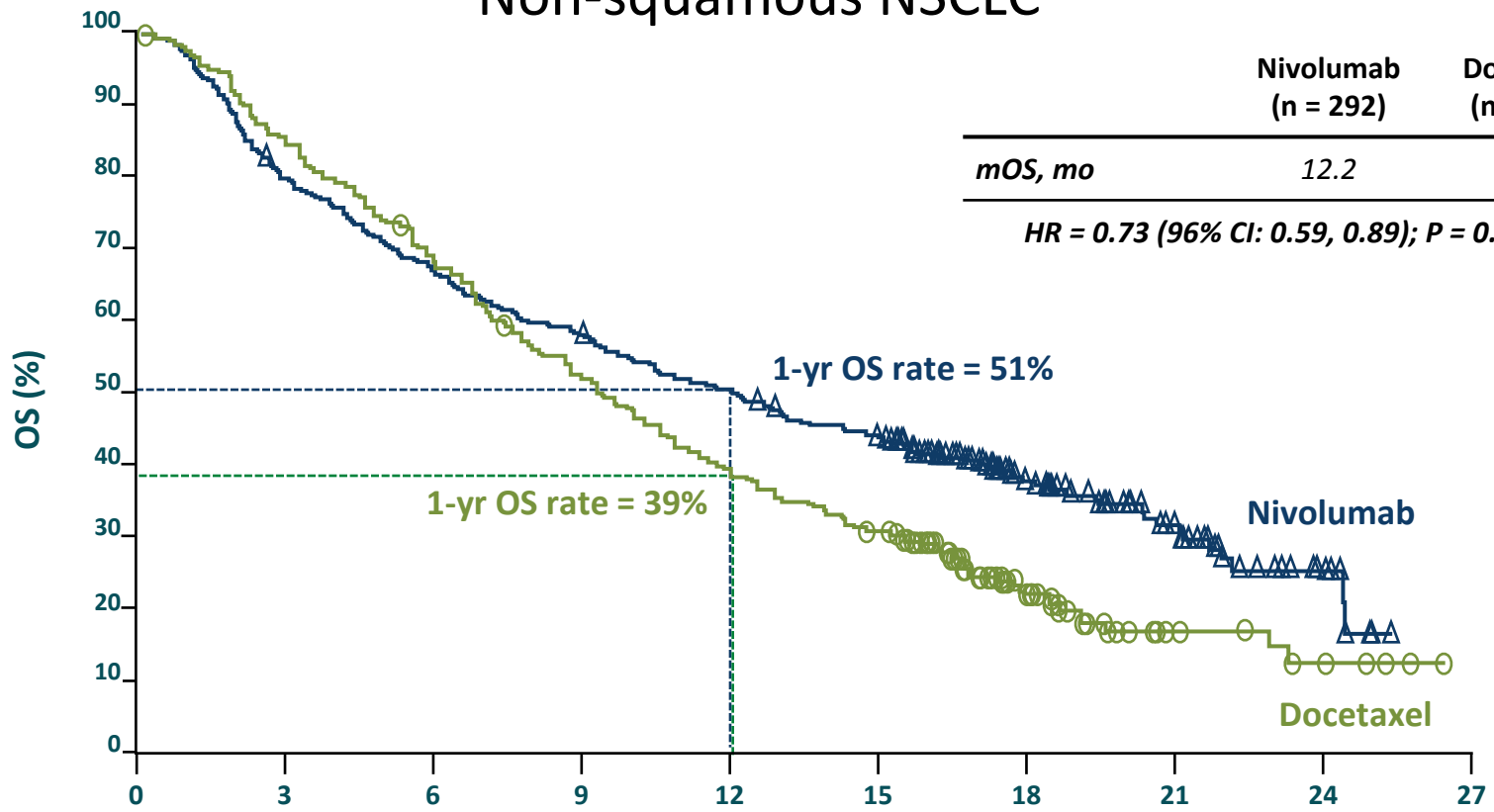
NR = not reached.
Based on 5 August 2014 database lock.

Robert C *et al*. *N Engl J Med*. 2015 Jan 22;372(4):320-30

Nivolumab Demonstrated 51% 1-Year Overall Survival as 2nd-line Treatment for Non-squamous NSCLC

	Nivolumab (n = 292)	Docetaxel (n = 290)
mOS, mo	*12.2*	*9.4*

HR = 0.73 (96% CI: 0.59, 0.89); P = 0.0015



Number of Patients at Risk										
Nivolumab	292	232	194	169	146	123	62	32	9	0
Docetaxel	290	244	194	150	111	88	34	10	5	0

Symbols represent censored observations.

Paz-Arez L et a., Oral presentation. Presented at ASCO 2015.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 5, 2015 VOL. 373 NO. 19

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma

R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. Castellano, T.K. Choueiri, H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gauler, T. Ueda, Y. Tomita, F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud, J.S. Simon, L.-A. Xu, I.M. Waxman, and P. Sharma, for the CheckMate 025 Investigators*

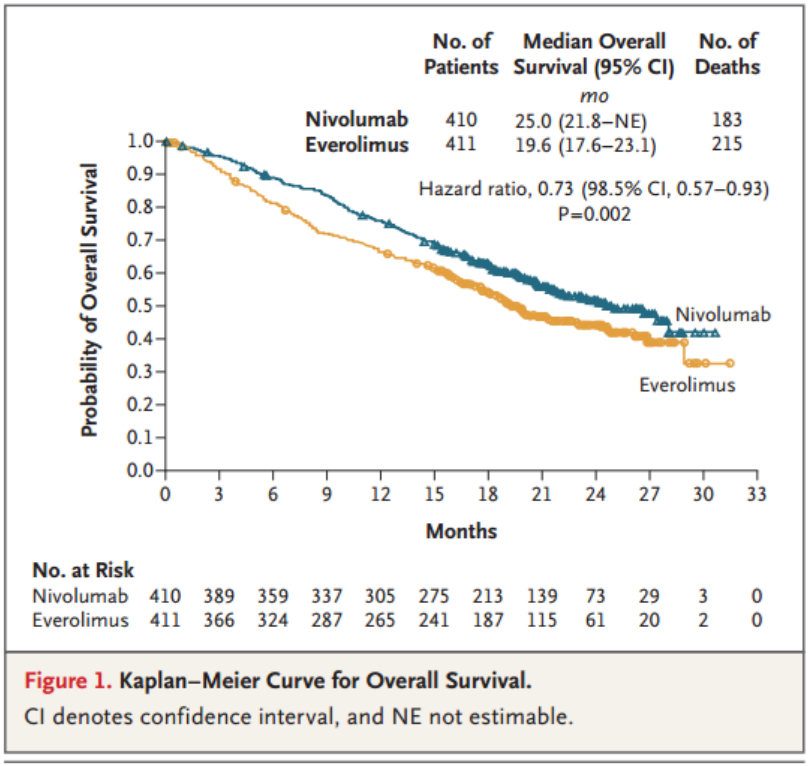


Figure 1. Kaplan–Meier Curve for Overall Survival.

CI denotes confidence interval, and NE not estimable.

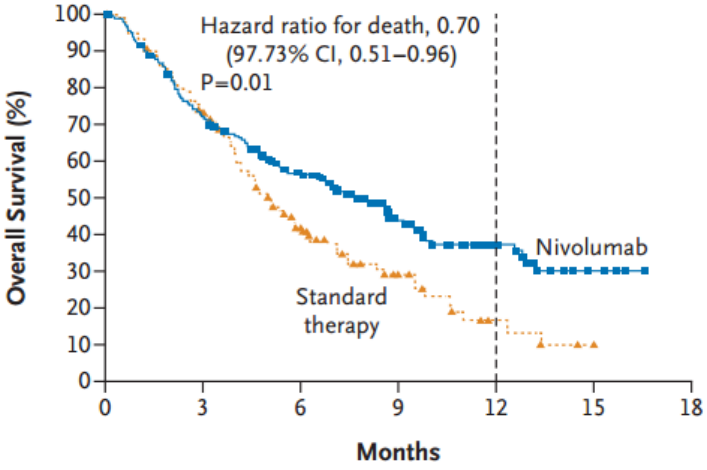
ORIGINAL ARTICLE

Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck

R.L. Ferris, G. Blumenschein, Jr., J. Fayette, J. Guigay, A.D. Colevas, L. Licitra, K. Harrington, S. Kasper, E.E. Vokes, C. Even, F. Worden, N.F. Saba, L.C. Iglesias Docampo, R. Haddad, T. Rordorf, N. Kiyota, M. Tahara, M. Monga, M. Lynch, W.J. Geese, J. Kopit, J.W. Shaw, and M.L. Gillison

A Overall Survival

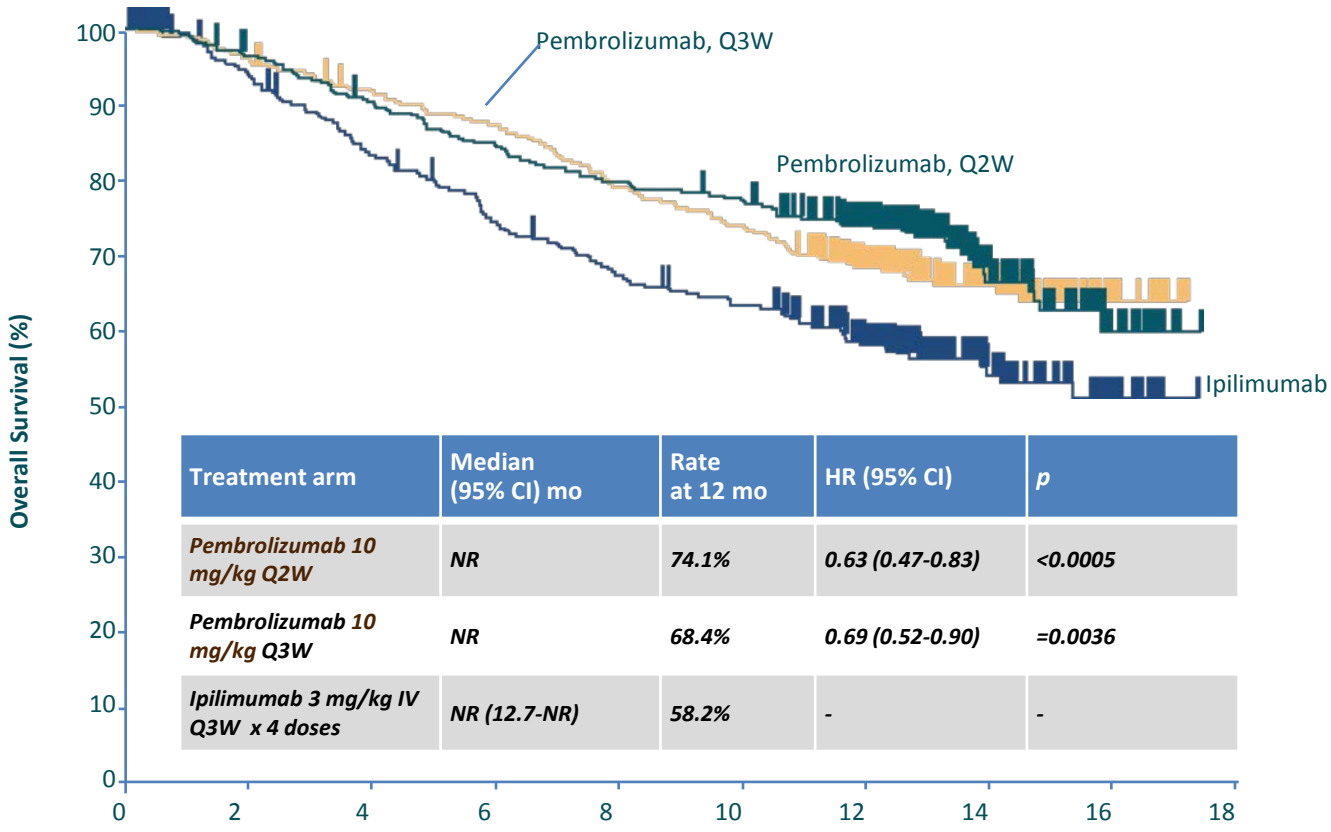
	No. of Patients	No. of Deaths	1–Yr Overall Survival Rate % (95% CI)	Median Overall Survival mo (95% CI)
Nivolumab	240	133	36.0 (28.5–43.4)	7.5 (5.5–9.1)
Standard Therapy	121	85	16.6 (8.6–26.8)	5.1 (4.0–6.0)



No. at Risk							
Nivolumab	240	167	109	52	24	7	0
Standard therapy	121	87	42	17	5	1	0

Pembrolizumab Showed Improved OS (RECIST v1.1) vs. Ipilimumab at the First Interim Analysis

B Overall Survival



Treatment arm	Median (95% CI) mo	Rate at 12 mo	HR (95% CI)	*p*
Pembrolizumab 10 mg/kg Q2W	*NR*	*74.1%*	*0.63 (0.47-0.83)*	*<0.0005*
Pembrolizumab 10 mg/kg Q3W	*NR*	*68.4%*	*0.69 (0.52-0.90)*	*=0.0036*
Ipilimumab 3 mg/kg IV Q3W x 4 doses	*NR (12.7-NR)*	*58.2%*	-	-

No. at Risk

Pembrolizumab, Q2W	279	266	248	233	219	212	177	67	19	0
Pembrolizumab, Q3W	277	266	251	238	215	202	158	71	18	0
Ipilimumab	278	242	212	188	169	157	117	51	17	0

NR= not reached

Robert C, *et al. N Engl J Med* 2015; Apr 19. [Epub ahead of print].

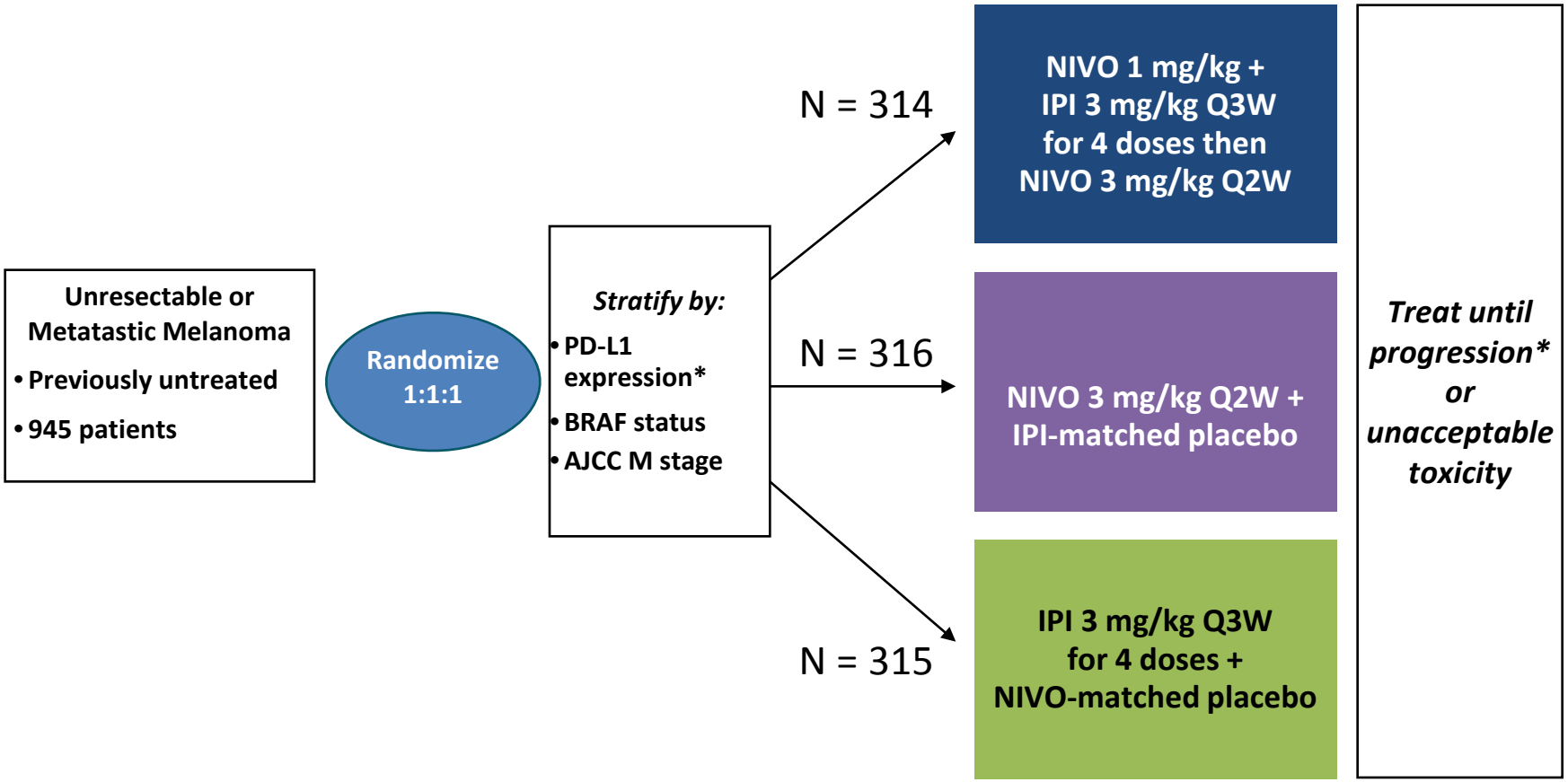
73-80% of Patients Experienced Treatment-related AEs with Pembrolizumab

	Pembrolizumab 10 mg/kg Q2W n = 279	Pembrolizumab 10 mg/kg Q3W n = 277	Ipilimumab 3 mg/kg x 4 doses n = 278
Days on therapy, mean (range)	*163.9 (1-336)*	*151.5 (1-332)*	*49.9 (1-92)*
No of doses, median (range)	*13 (1-20)*	*9 (1-16)*	*4[a] (1-4)*
>1 Treatment-related AE			
Any grade	*79.5%*	*72.9%*	*73%*
Grade 3-4	*13.3%*	*10.1%*	*19.9%*
Death	*0%*	*0%*	*0.4%*
Discontinuation	*4.0%*	*6.9%*	*9.4%*

[a] 56% of patients received all 4 ipilimumab doses

Robert C, *et al. Oral Presentation at AACR Conference Apr 2015*

Efficacy and Safety with Nivolumab Alone or Combined with Ipilimumab vs. Ipilimumab Alone in Treatment-naïve Patients: Study Design



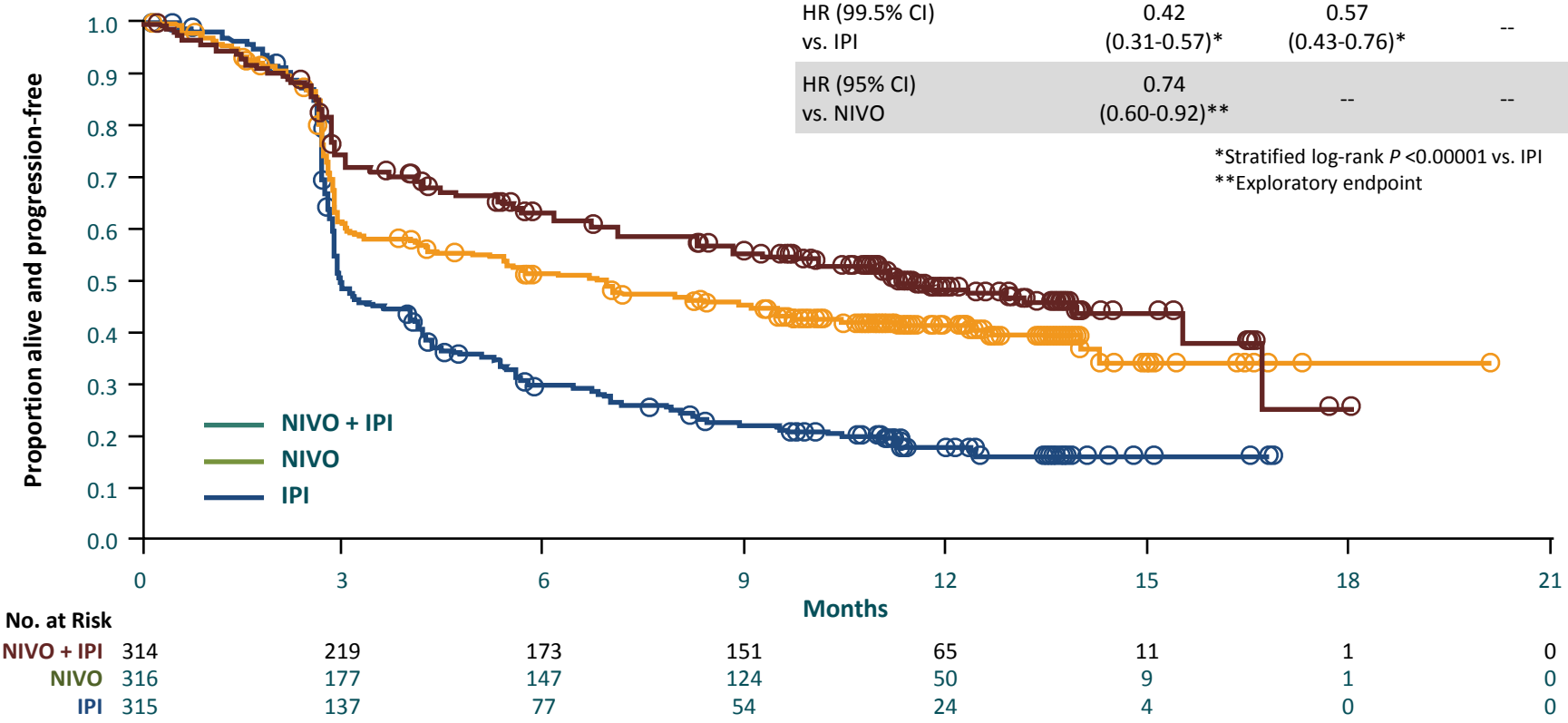
*This study was not powered to compare the combination Ipi + Nivo to Nivo alone
**Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.
***Patients could have been treated beyond progression under protocol-defined circumstances.

Larkin J et al. *N Engl J Med*, May 2015. epub ahead of print.

PFS (Intent-to-Treat) was Improved with Nivo + Ipi vs. Either Alone

	NIVO + IPI (N = 314)	NIVO (N = 316)	IPI (N = 315)
Median PFS, months (95% CI)	11.5 (8.9-16.7)	6.9 (4.3-9.5)	2.9 (2.8-3.4)
HR (99.5% CI) vs. IPI	0.42 (0.31-0.57)*	0.57 (0.43-0.76)*	--
HR (95% CI) vs. NIVO	0.74 (0.60-0.92)**	--	--

*Stratified log-rank P <0.00001 vs. IPI
**Exploratory endpoint



No. at Risk								
NIVO + IPI	314	219	173	151	65	11	1	0
NIVO	316	177	147	124	50	9	1	0
IPI	315	137	77	54	24	4	0	0

Larkin J *et al. N Engl J M*ed, May 2015. epub ahead of print.

Safety Summary

Patients Reporting Event, %	NIVO + IPI (N = 313)		NIVO (N = 313)		IPI (N = 311)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.5	55.0	82.1	16.3	86.2	27.3
Treatment-related AE leading to discontinuation	36.4	29.4	7.7	5.1	14.8	13.2
Treatment-related death*	0		0.3		0.3	

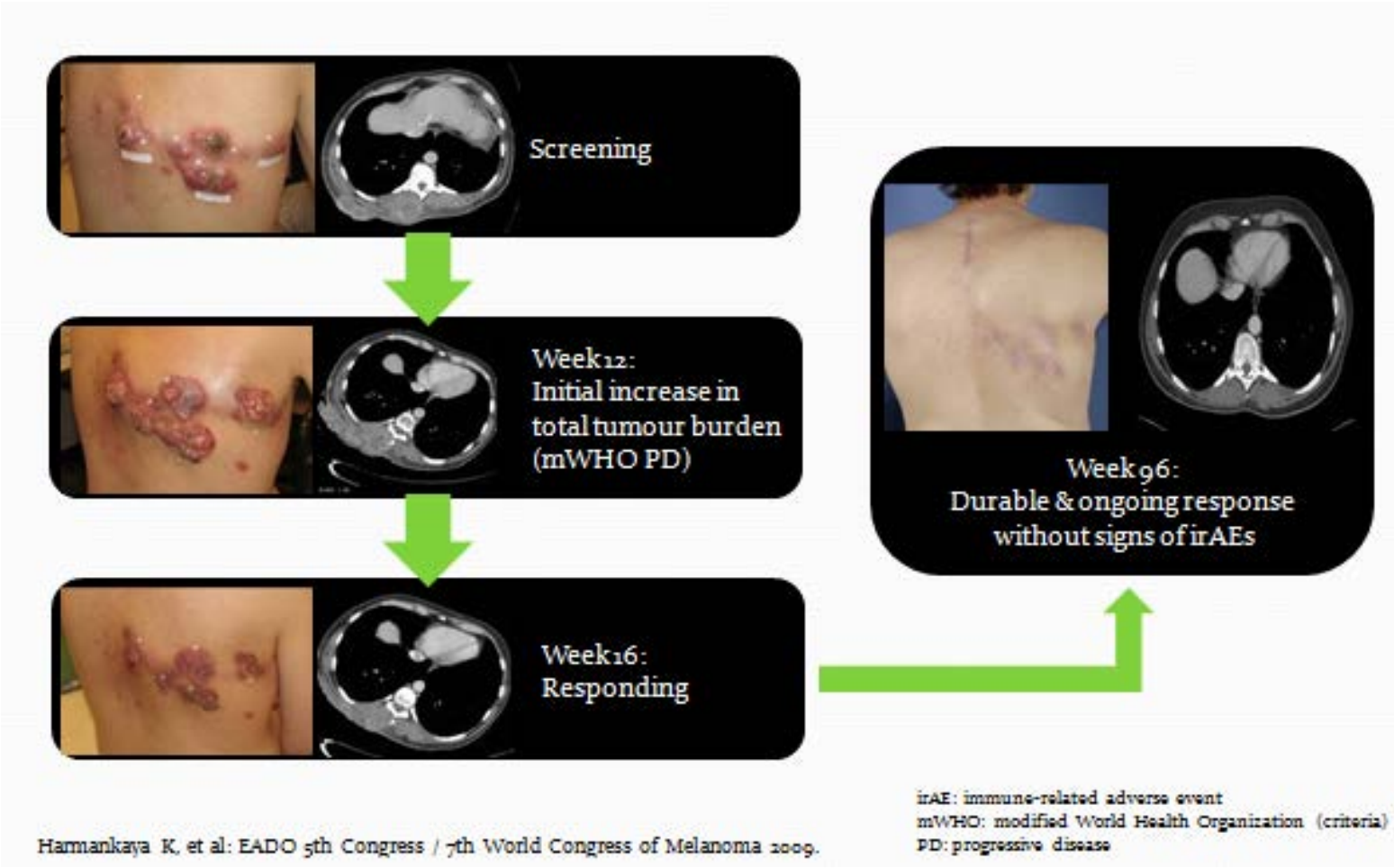
67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response.

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).

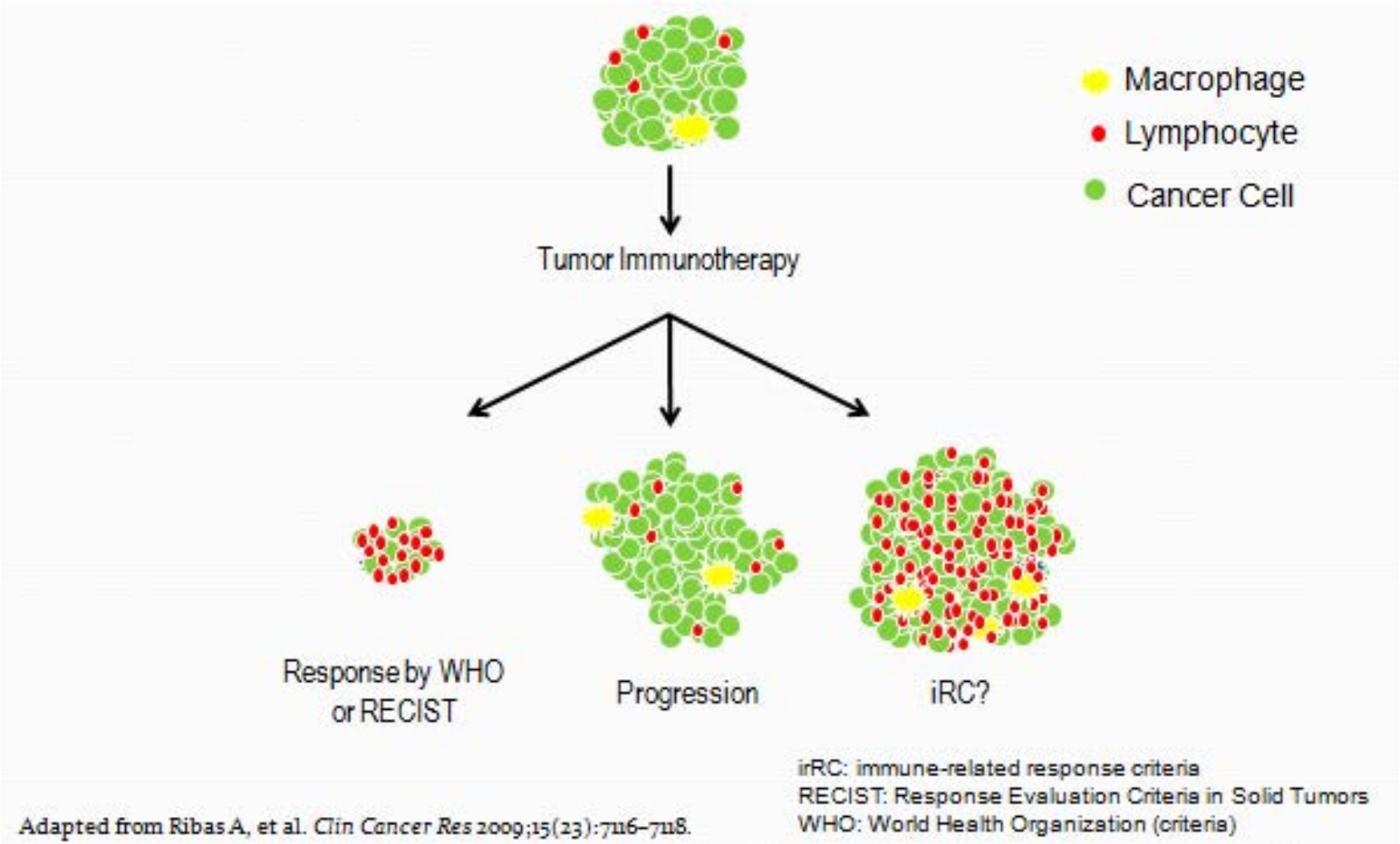
Larkin J *et al*. *N Engl J M*ed, May 2015. epub ahead of print.

Potential Clinical Response Patterns With I-O Therapeutic Approaches

Example of Evolution of Response to CTLA-4 Inhibitor



Immune Response Criteria for Tumour Immunotherapy?



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. Accessed September 30, 2013.

Key Principles of Managing Immune Mediate Adverse Events (irAE)

Systemic Oncology Therapies

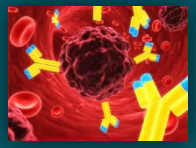
CHEMOTHERAPY

Target: rapidly dividing tumour and normal cells

Adverse events: diverse due to non-specific nature of therapy

TARGETED THERAPIES

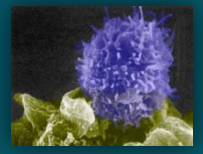
Target: specific molecules involved in tumour growth and progression



Adverse events: reflect targeted nature

I-O THERAPIES

Target: immune system



Adverse events: unique events can occur as a result of immune-system activity

Different spectrum of adverse events with each type of therapy

Although adverse events may have different etiologies, some adverse events with I-O may present like those with other therapies

Require different management strategies

American Cancer Society. *Treatment types* http://www.cancer.org/; Bristol-Myers Squibb. YERVOY™ (ipilimumab) prescribing information updated May 2013; Topalian SL, et al. *N Eng J Med* 2012;366(26):2443–2454 and oral presentation at ASCO 2013: *J Clin Oncol* 2013;31(15 suppl):abstract 3002; 3. Hamid O, et al. *N Eng J Med* 2013;369(2):134–144; 4. Dendreon. PROVENGE® (sipuleucel-T) prescribing information updated June 2011; Bristol-Myers Squibb. YERVOY (ipilimumab) Immune-related Adverse Reactions (IrAR) Management Guide and Online Tool at https://www.yervoy.co.uk/; Bristol-Myers Squibb. YERVOY (ipilimumab) SmPC updated July 2013, available at http://www.ema.europa.eu.

I-O Therapy May Induce Inflammation in Certain Organ Systems

I-O therapy–associated AEs target certain organ systems[1]

***Skin*[1-6]**

***Endocrine system*[2,4,6,7-10]**

***Liver*[2,6,11-12]**

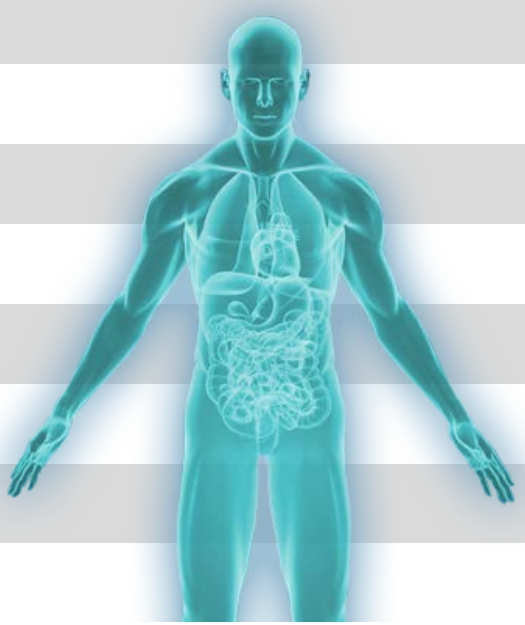
***Gastrointestinal tract*[2,6,9,13]**

***Nervous system*[6,10,14,15]**

***Eyes*[1,4,16-18]**

Respiratory system[1,5,6,10,15,19]

Hematopoietic cells[6,9,12,20-22]

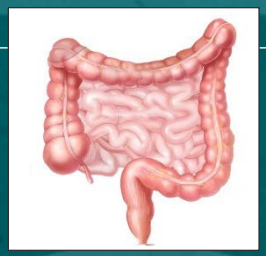


1. Amos SM, *et al. Blood.* 2011;118:499-509; 2. Phan GQ, *et al. PNAS.* 2003;100:8372-8377; 3. Rosenberg SA, White DE. *Immunother Emphasis Tumor Immunol.* 1996;19:81-84; 4. Chianese-Bullock KA, *et al. J Immunother.* 2005;28:412-419; 5. Harris J, *et al. Med Pediatr Oncol.* 1994;22:103-106; 6. Chow LQ. Am Soc Clin Oncol Educ Book. 2013:280-285; 7. Bendle GM, *et al. Nat Med.* 2010;16:565-570; 8. Soni N, *et al. Cancer Immunol Immunother.* 1996;43:59-62; 9. Ronnblom LE, *et al. Ann Intern Med.* 1991;115:178-183; 10. Fraenkel PG, *et al. J Immunother.* 2002;25:373-378; 11. Lamers CH, *et al. J Clin Oncol.* 2006;24:e20-e22; 12. Roskrow MA, *et al. Leuk Res.* 1999;23:549-557; 13. Parkhurst MR, *et al. Mol Ther.* 2011;19:620-626; 14. Pellkofer H, *et al. Brain.* 2004;127:1822-1830; 15. Smalley RV, *et al. Blood.* 1991;78:3133-3141; 16. Dudley ME, *et al. J Clin Oncol.* 2008;26:5233-5239; 17. Yeh S, *et al. Ophthalmology*. 2009;116:981-989; 18. Robinson MR, *et al. J Immunother*. 2004;27:478-479; 19. Morgan RA, *et al.* Mol *Ther.* 2010;18:843-851; 20. Kochenderfer JN, *et al. Blood.* 2010;116:4099-4102; 21. Lin TS, *et al. J Clin Oncol.* 2010;28:4500-4506; 22. Herishanu Y, *et al. Leuk Lymphoma.* 2003;44:2103-2108.

Organ Specific Immune-related Adverse Events

1 GI | 2 SKIN | 3 HEPATIC | 4 ENDOCRINE | 5 NEURO-LOGICAL | 6 PULMONARY | 7 RENAL

Incidence *	• ***All grades: 10-25%*** • ***Grades 3-4: 1-5%***
Symptoms	• ***Diarrhea*** • ***Stomach pain*** • ***Nausea/vomiting/pain*** • ***Blood in stool*** • ***Constipation*** • ***Abdominal cramping***
Assessment	• ***Number of BM/day*** • ***Presence of watery diarrhea*** • ***Blood or mucus in stool***
Management	• ***Most cases respond to symptomatic treatment or high-dose steroids with a long taper (over a month)*** • ***Infliximab is used in steroid-refractory cases*** • ***Consider GI consultation in patients with moderate to severe symptoms*** • ***In patients symptomatic for enterocolitis, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms***



*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)

If not vigilant, may result in more serious immune-related adverse events

BACK

Infliximab for the Management of I/O-Associated Colitis

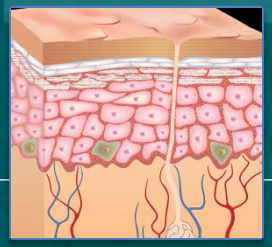
Dosing	**5 mg/kg IV induction regimen at 0, 2 and 6 weeks followed by 5 mg/kg IV every 8 weeks thereafter as required**
Contraindications	• **Severe infections (e.g., sepsis, abscesses, tuberculosis and opportunistic infections)** • **Moderate or severe (NYHA Class III/IV) congestive heart failure**
Most common adverse events	• **Infections** • **Allergic reactions** • **Infusion-related reactions**
Considerations for co-administration with other agents	• **Do not administer concurrently with another biologic (*e.g.*, abatacept, rituximab, tocilizumab)** • **Live vaccines should not be given concurrently (acetaminophen and antihistamines may be used to manage reactions).** • **Monitor the effects/concentration of drugs with a narrow therapeutic index metabolized through CYP450**

Adapted from Janssen Inc. Remicade Product Monograph, Date of Authorization: July 22, 2015.

Organ Specific Immune-related Adverse Events

1 GI | **2 SKIN** | 3 HEPATIC | 4 ENDOCRINE | 5 NEURO-LOGICAL | 6 PULMONARY | 7 RENAL

Incidence*	• ***All grades: 7-25%*** • ***Grades 3-4: 1<1%*** ***Most cases are grade 1-2***
Symptoms / Assessment	• ***Itchiness*** • ***Redness*** • ***Presence of rash or pruritus*** • ***Peeling*** • ***Skin excoriations***
Management	***Most cases are grade 1/2 and treatable with:*** • ***Symptomatic therapy (e.g., antihistamines), and*** • ***Topical therapy (e.g., moisturizing creams and topical steroids)*** • ***Generally reversible*** • ***Important to evaluate and identify alternative etiologies not attributable to I-O therapy (e.g., viral/bacterial infection)*** • ***Do not administer I-O therapy if moderate-to-severe rash is present***



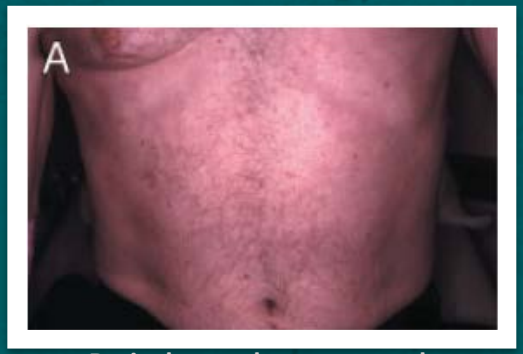
*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)

If not vigilant, may result in more serious immune-related adverse events

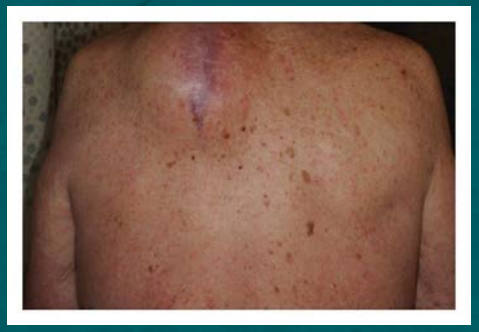
Skin/Dermatologic Adverse Events of I-O Therapy

1 GI | 2 SKIN | 3 HEPATIC | 4 ENDOCRINE | 5 NEURO-LOGICAL | 6 PULMONARY | 7 RENAL

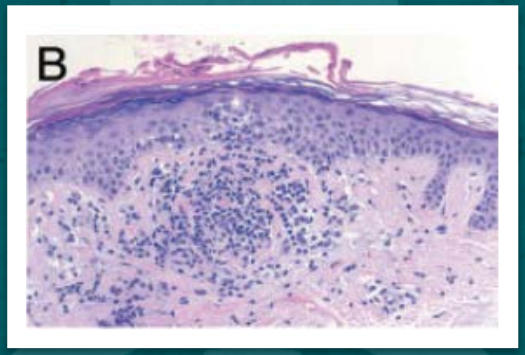
Example of ipilimumab-associated rash in a patient with advanced melanoma



Reticular erythematous rash

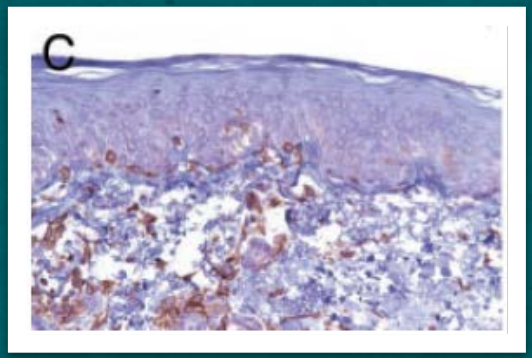


Immune-related maculopapular rash in a patient receiving ipilimumab

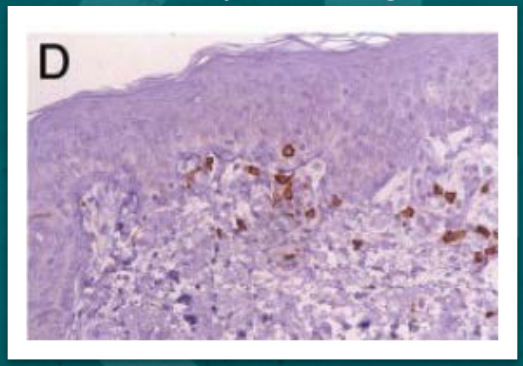


Perivascular lymphocyte infiltrate extending into epidermis. Magnification: x125

Ipilimumab-stimulated melanocyte immune recognition



CD4+ T cells apposed to dying melanocytes. Magnification: x250



CD8+ T cells apposed to dying melanocytes. Magnification: x250

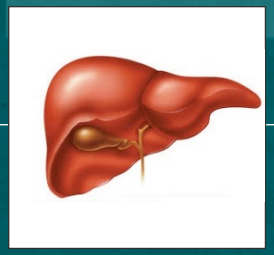
Hodi FS, et al. *Proc Natl Acad Sci USA* 2003;100:4712.
Tarhini et al. *Scientifica*. 2013, 19

BACK

Organ Specific Immune-related Adverse Events

1 GI | 2 SKIN | **3 HEPATIC** | 4 ENDOCRINE | 5 NEURO-LOGICAL | 6 PULMONARY | 7 RENAL

Incidence*	• ***All grades: 6.4-7.1%*** • ***Grades 3-4: 1.6-2.6%***
Symptoms	• ***Jaundice*** • ***Tiredness*** • ***Nausea, vomiting*** • ***Abdominal pain***
Assessment	• ***Liver function tests before each dose of I-O agents***
Management	• ***Delay I-O therapy if grade2, discontinue if grade 3-4*** • ***Increase frequency of monitoring*** • ***Consider IV steroids if grade 3-4*** • ***Add prophylactic antibiotics for opportunistic infections*** • ***Consult gastroenterologist***



ALT: alanine aminotransferase
AST: aspartate aminotransferase
irAE: immune-related adverse event
LFT: liver function test

*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)

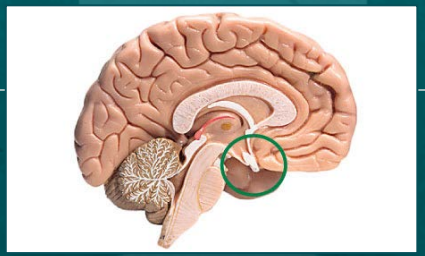
If not vigilant, may result in more serious immune-related adverse events

BACK

Organ Specific Immune-related Adverse Events

1 GI | 2 SKIN | 3 HEPATIC | **4 ENDOCRINE** | 5 NEURO-LOGICAL | 6 PULMONARY | 7 RENAL

Incidence*	• ***All grades: 10.9-14.4%*** • ***Grades 3-4: 0.6-2.3%***
Symptoms	• ***Headaches*** • ***Visual changes*** • ***Fever*** • ***Fatigue/weakness*** • ***Mental status changes, confusion*** • ***Hypotension*** • ***Abdominal pain and/or unusual bowel habits***
Assessment	• ***Monitor patients for signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism***
Management	• ***Delay I-O therapy if grade 2, discontinue if grade 3-4*** • ***Consider IV steroids if grade 3-4*** • ***Monitor thyroid function tests and clinical chemistries at the start of treatment, before each dose, and as clinically indicated based on symptoms.***



*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)

If not vigilant, may result in more serious immune-related adverse events

BACK

Organ Specific Immune-related Adverse Events

1 GI | 2 SKIN | 3 HEPATIC | 4 ENDOCRINE | **5 NEURO-LOGICAL** | 6 PULMONARY | 7 RENAL

Incidence*	• ***Grades 3-4: 0-0.4%***
Symptoms	• ***Sensory or motor neuropathy*** • ***Muscle weakness*** • ***Fatigue*** • ***Difficulty waking up***
Assessment	• ***Monitor signs and symptoms indicative of motor or sensory neuropathy such as:*** • ***Unilateral or bilateral weakness*** • ***Sensory alterations*** • ***Paresthesia***
Management	• ***Consider IV steroids***

*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)

If not vigilant, may result in more serious immune-related adverse events

BACK

Organ Specific Immune-related Adverse Events

1 GI | 2 SKIN | 3 HEPATIC | 4 ENDOCRINE | 5 NEURO-LOGICAL | **6 PULMONARY** | 7 RENAL

Incidence*	• ***All grades: 2%*** • ***Grades 3-4: <1%***
Risk factors	• ***No underlying factor identified to date*** • ***No apparent relationship to tumor type***
Symptoms	• ***Cough, SOB/Dyspnea (rest or exertion), fever*** • ***Asymptomatic radiographic changes***
Assessment	• ***Pulse oximetry (rest and exertion)*** • ***CXR and/or CT***
Management	• ***Delay I-O therapy dosing*** • ***Corticosteroids*** • ***if not improving in 48 hrs or worsening, add immunosuppressants (e.g., infliximab, cyclophosphamide, IVIG, or mycophenolate mofetil)***

*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)

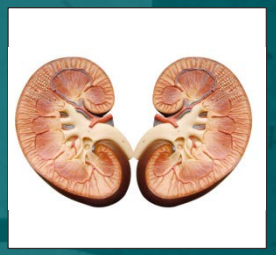
If not vigilant, may result in more serious immune-related adverse events

BACK

Organ Specific Immune-related Adverse Events

1 GI | 2 SKIN | 3 HEPATIC | 4 ENDOCRINE | 5 NEURO-LOGICAL | 6 PULMONARY | **7 RENAL**

Incidence*	• ***< 1% of subjects treated with nivolumab or pembrolizumab monotherapy have experienced a related SAE of acute renal failure*** • ***Case reports of renal dysfunction associated with ipilimumab have also been reported***
Onset	• ***Most commonly present with elevations in serum creatinine***
Management	• ***Steroids generally lead to clinical improvement/resolution***
Renal biopsy	• ***May help distinguish inflammatory versus non-inflammatory etiologies***



*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)
SAE= serious adverse event

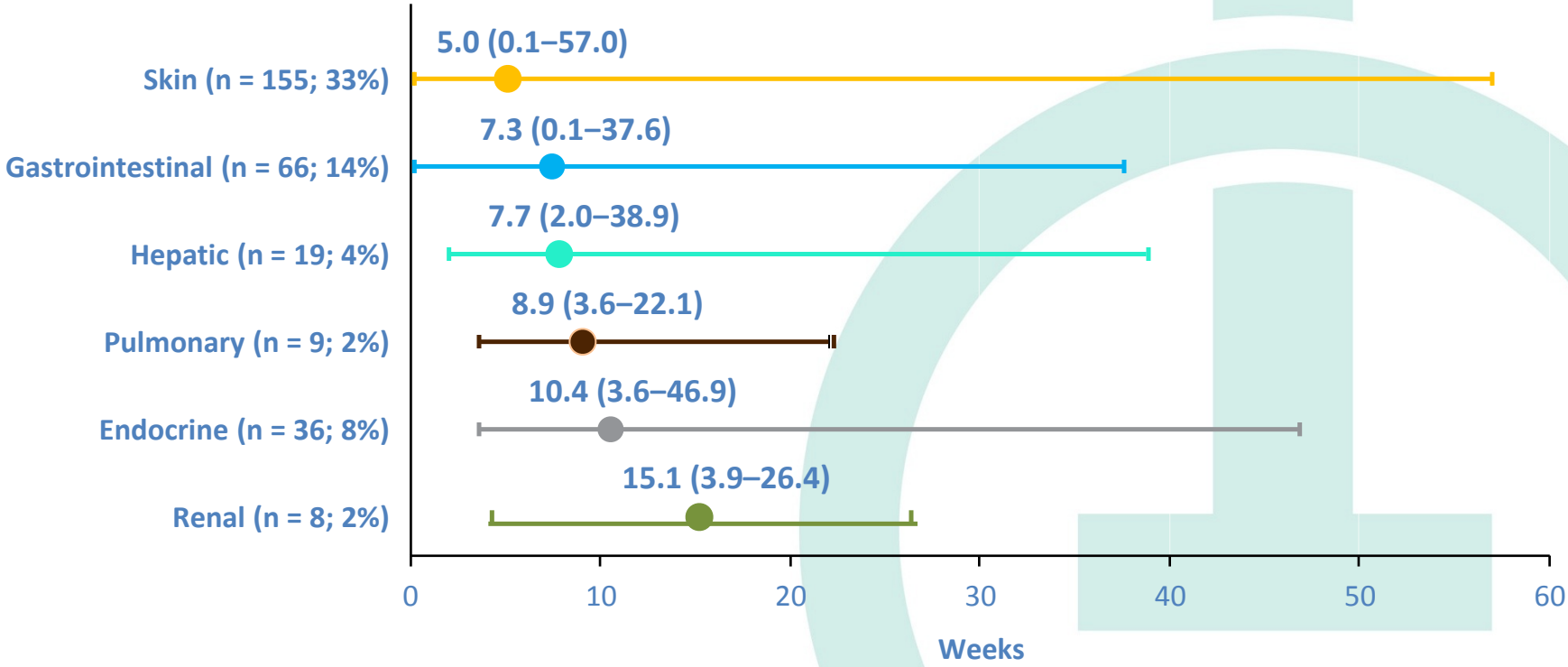
If not vigilant, may result in more serious immune-related adverse events

BACK

Kinetics of irAEs: Example for Nivolumab

Time to onset of select treatment-related AEs (any grade; n = 474)

Median time to onset for treatment-related select AEs ranged from 5.0 weeks for skin AEs to 15.1 weeks for renal AEs



Circles represent median; bars signify ranges. The kinetics of AEs presented on the slide are for melanoma but may not reflect the kinetics of AEs in other tumor types.
Weber JS, et al. Presentation at ASCO 2015.

Stepwise Approach to Using I-O Agents in Clinic

1 BASELINE ASSESSMENT | 2 EDUCATION | 3 MONITORING | 4 EARLY RECOGNITION | 5 irAE Management

- Medical History
  - Specific questions on organ function which may be affected by immune related adverse reactions, for example:
    - Shortness of breath on exertion?
    - Rash?
    - Bowel function?
    - Previous history of autoimmune disease?
- Physical examination
  - Vital signs (with oximetry when clinically indicated), physical exam, weight, other significant findings
- Laboratory investigations
  - CBC, biochemistry, renal function, LFT, TSH, other endocrine function evaluation when appropriate

Stepwise Approach to Using I-O Agents in Clinic

1 BASELINE ASSESSMENT | **2 EDUCATION** | 3 MONITORING | 4 EARLY RECOGNITION | 5 irAE Management

1. Patient education*
2. Multidisciplinary team (nurse, pharmacist, emergency, etc.)
3. Involve specialists
    - Gastroenterologist
    - Endocrinologist
    - Dermatologist
    - Pulmonologist
    - Ophthalmologist
    - Etc.

*Patient tools are available

Stepwise Approach to Using I-O Agents in Clinic

1 BASELINE ASSESSMENT | 2 EDUCATION | **3 MONITORING** | 4 EARLY RECOGNITION | 5 IiAE Management

- Initiate treatment according to prescribing Product Monograph
- Careful ongoing clinical assessment is necessary for early identification of irAEs
- irAEs can be severe or life-threatening if not identified early
- irAEs can occur any time
- Keep in mind that toxicity does not equal response
- Early recognition is key
- Consider all symptoms and signs as potential irAE
- Refer to organ-specific algorithms for the management of irAEs

Stepwise Approach to Using I-O Agents in Clinic

1 BASELINE ASSESSMENT | 2 EDUCATION | 3 MONITORING | 4 EARLY RECOGNITION | 5 irAE MANAGEMENT

The majority of immune-related AEs are manageable and reversible with drug interruption ± corticosteroid.

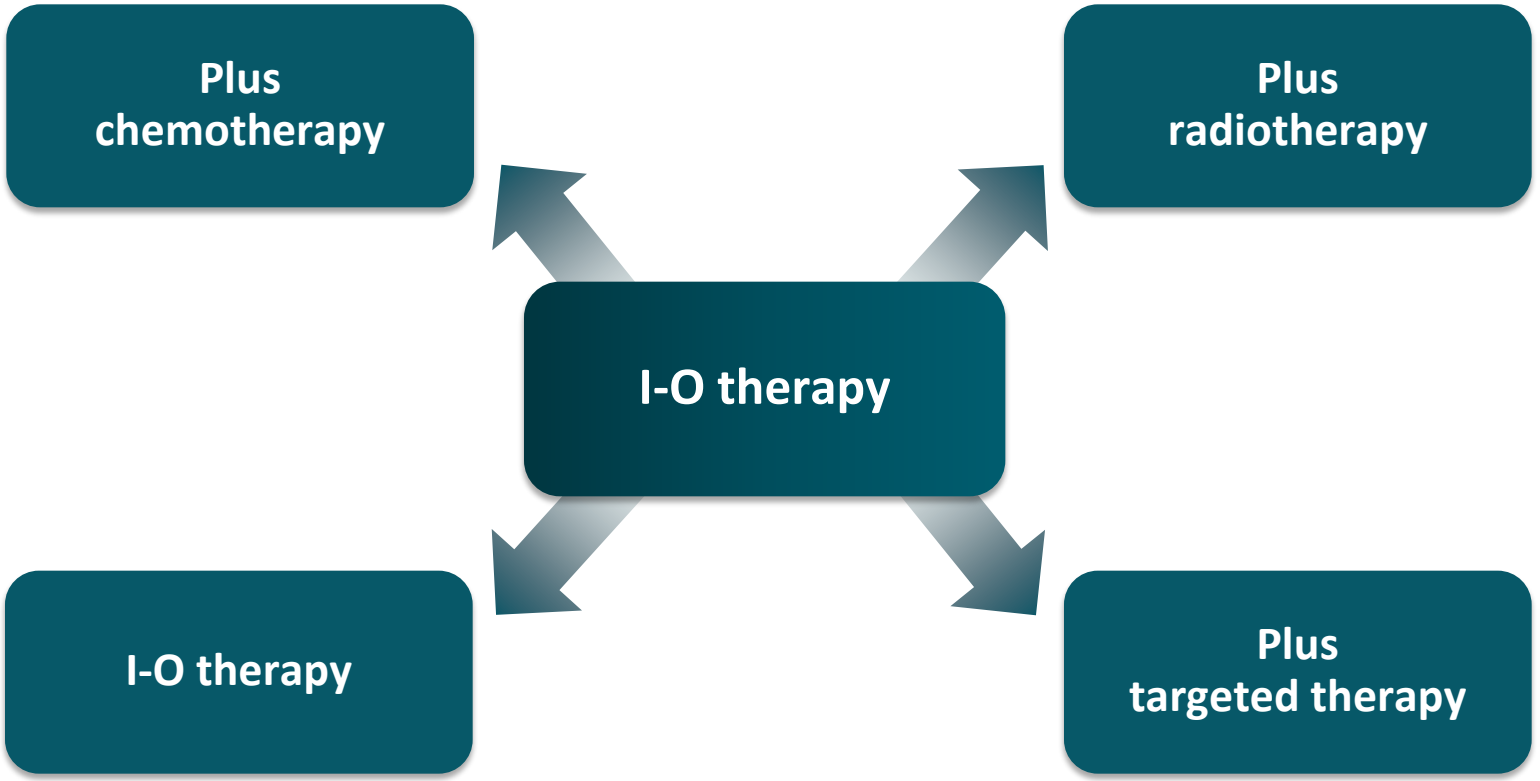
Steroid taper is generally required over at least one month.

Grade	Management	Continue the drug?
Low (gr 1)	Monitor closely	Continue (except for pneumonitis consider delay)
Moderate (gr 2)	Symptomatic management Monitor closely Oral corticosteriods	Delay the dose Resume IO drug when AEs resolve to grade ≤ 1 or baseline
High (gr 3-4)	Administer high dose IV Corticosteroids Symptomatic management Monitor closely Involve specialist consultant*	Discontinue I-O Drug permanently (Delay in some situations)

* In the event of grade 3 or 4 toxicity for practitioners in non-tertiary centres, consult with an oncologist or consider transfer to a tertiary centre

I-O Therapies have the Potential to be Used as Monotherapy or Part of Combination Regimens

I-O research and development will continue to inform future strategies, including new targets and rationale for drug combinations and sequencing.



1. Drake CG. *Ann Oncol*. 2012;23(suppl 8):viii41–viii46; 2. Ribas A, *et al. Curr Opin Immunol*. 2013:25:291–296.

Stepwise Approach to Using I-O Agents in Clinic

1 BASELINE ASSESSMENT | 2 EDUCATION | 3 MONITORING | 4 EARLY RECOGNITION | 5 irAE MANAGEMENT

Re-challenging with Immune Checkpoint Inhibitors after irAEs:

- irAEs can be re-challenged with immune checkpoint inhibitors once ≤ grade 1
- irAEs should NOT be re-challenged in grade 3-4 with the exception of son situations (e.g., skin, perhaps diarrhea)

Key Considerations on Management of Immune-related Events

Result from enhanced or excessive immune activity

Early diagnosis and appropriate management is essential

Health care team and patient education for early recognition

Can be severe or life-threatening, may involve various organs

Delayed irAE may occur

Multidisciplinary team approach is required for optimal management

Unless an alternate etiology has been identified, consider all symptoms and signs as potential irAE

Systemic high-dose corticosteroids* may be required for severe events

*with or without additional immunosuppressive therapy

Bristol-Myers Squibb. YERVOY (ipilimumab) Immune-related Adverse Reactions (IrAR) Management Guide and online Tool at https://www.yervoy.co.uk/;
Bristol-Myers Squibb. YERVOY (ipilimumab) SmPC updated July 2013, available at http://www.ema.europa.eu.

www.opdivo.ca

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OPDIVO (nivolumab)

AVAILABLE FOR 3 TUMOUR TYPES

OPDIVO®, indicated for the treatment of:

- patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for OPDIVO please refer to Health Canada's Notice of Compliance with conditions – drug products web site.

OPDIVO, indicated for the treatment of:

- unresectable or metastatic BRAF V600 wild-type melanoma in previously untreated adults
- adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving OPDIVO
- adult patients with advanced or metastatic renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy

have been issued marketing authorization without conditions.

Product Monograph

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Patient Assistance Program Form

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Healthcare Professional Adverse Reaction Management Guide

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Consult the Product Monograph at http://www.bmscanada.ca/static/products/en/pm_pdf/OPDIVO_EN_PM.pdf for contraindications, warnings, precautions, adverse reactions, interactions, dosing, and conditions of clinical use. The Product Monograph is also available through our medical department. Call us at 1-800-463-6267.

Immune-Oncology

Bristol-Myers Squibb

Pr OPDIVO™ (nivolumab)

Immune-Mediated Adverse Reaction Management Guide

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- adult patients with advanced or metastatic renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy

have been issued marketing authorization without conditions.

Important safety information This guide is intended to provide information about the management of the important identified risks of prescribing OPDIVO for melanoma, NSCLC and RCC including immune-mediated endocrinopathies, gastrointestinal, hepatic, pulmonary, renal, rash, neurological and other adverse reactions, as well as infusion reactions.

All patients receiving treatment with OPDIVO must be given a Patient Alert Card to educate them about the symptoms of immune-mediated adverse reactions and the need to report them to their treating doctor immediately. Treating doctors should also advise their patients to keep the Patient Alert Card with them at all times and show it to any healthcare professional who may treat them.

For more information, please refer to OPDIVO Product Monograph available at Bristol-Myers Squibb Canada website at: http://www.bmscanada.ca

Explore the Following Sections to Learn More About Managing Immune-Mediated Adverse Reactions:

What is OPDIVO?

OPDIVO® (nivolumab) is a medicine that helps the immune system to attack and destroy cancer cells.

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T-cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumours and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.

Common adverse reactions

Melanoma

- In patients who received 3 mg/kg OPDIVO monotherapy in studies CA209066 and CA209037, the most frequently reported adverse reactions (occurring at ≥15%) were fatigue, nausea, diarrhea, pruritus and rash.[1,2]

NSCLC

- In patients who received 3 mg/kg OPDIVO monotherapy in studies CA209017 and CA209057, the most frequently reported adverse drug reactions (occurring in ≥10%) were fatigue, nausea, rash and decreased appetite.[4,5]
- In patients who received 3 mg/kg OPDIVO monotherapy in study CA209063, the most frequently reported adverse drug reactions (occurring in ≥10%) were fatigue, decreased appetite, nausea, diarrhea and rash.[6]

RCC

- In patients who received 3 mg/kg OPDIVO monotherapy in study CA209025, the most frequently reported adverse drug reactions (occurring in ≥10%) were fatigue, nausea, diarrhea, rash, pruritus and decreased appetite.[7]

Recognize and Manage Adverse Reactions Associated With Therapy

OPDIVO (nivolumab) is associated with immune-mediated adverse reactions.

- Early identification of adverse reactions and intervention are an important part of the safe use of OPDIVO.
- Patients should be monitored continuously as an adverse reaction with OPDIVO may occur at any time during OPDIVO therapy. Adverse reactions are sometimes delayed and may develop weeks or months after the last dose of OPDIVO.

If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1-month duration should be initiated upon improvement.

- Rapid tapering may lead to worsening of the adverse reaction.
- Non-corticosteroid immunosuppressive medications should be added if there is worsening or no improvement despite corticosteroid use.
- Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive medications.

Do not resume OPDIVO while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive medications.

Permanently discontinue treatment with OPDIVO for:

- Any Grade 4 immune-mediated adverse reactions;
- Grade 3 or 4 infusion reaction;
- Grade 3 hypophysitis, Grade 3 adrenal insufficiency, Grade 3 pneumonitis, Grade 3 serum creatinine elevation, Grade 3 aspartate aminotransferase (AST), alanine aminotransferase (ALT) or total bilirubin elevations;
- Any Grade 3 immune-mediated adverse reactions that persist despite treatment modifications;
- Any Grade 3 immune-mediated adverse reactions that recur;
- Any Grade 2 or 3 immune-mediated adverse reactions that persist despite treatment modifications;
- Any immune-mediated encephalitis;
- Inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day.

Immune-Mediated Endocrinopathies

Data for the following immune-mediated adverse reactions are based on patients who received nivolumab 3 mg/kg monotherapy in clinical studies across tumour types (melanoma, NSCLC and RCC), and includes the melanoma indication based on studies CA209066, CA209037, CA209067, CA209017, CA209057, CA209063 and CA209025, approved with conditions. Although the rates of immune-mediated adverse reactions were generally similar across tumour types, hepatic and renal adverse reactions occurred most commonly in RCC (11.3% and 6.9%, respectively); gastrointestinal and skin adverse reactions occurred most commonly in melanoma (17.7% and 38.4%, respectively); and pulmonary reactions, specifically pneumonitis occurred most commonly in RCC and NSCLC (3.9% and 3.6%, respectively).[1-7]

- Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, diabetes mellitus and diabetic ketoacidosis, have been observed with OPDIVO (nivolumab) treatment.
- Monitor patients for signs and symptoms of endocrinopathies (see below).
- In patients treated with nivolumab monotherapy, the incidence of thyroid disorders, including hypothyroidism or hyperthyroidism, was 8.6% (149/1728). The majority of cases were Grade 1 or 2 in severity reported in 3.6% (62/1728) and 4.9% (85/1728) of patients, respectively. Grade 3 thyroid disorders were reported in 0.1% (2/1728) of patients. Hypophysitis (one Grade 1; one Grade 2; and three Grade 3), adrenal insufficiency (one Grade 1; five Grade 2; and four Grade 3), diabetes mellitus (one Grade 2) and diabetic ketoacidosis (two Grade 3) were reported. No Grade 4 or 5 cases were reported in these studies.

Endocrinopathies

Signs and symptoms

- Fatigue
- Weight change
- Headache
- Mental status change
- Abdominal pain
- Increased frequency of bowel movements
- Hypotension
- Visual disturbances
- Thirst
- Need to urinate more often
- Increased appetite with a loss of weight
- Feeling weak, sleepy, irritable or forgetful
- Dizziness or fainting
- Other non-specific symptoms

If signs or symptoms are present, complete endocrine function evaluation.

Unresectable or Metastatic Melanoma, Metastatic NSCLC and Metastatic RCC (monotherapy):

Median time to onset:	Median time to resolution:	Cases resolved:
2.8 months (range: 0.4-14.0)	66.6 weeks (range: 0.4-96.1+)	74 patients (45.0%)

Managing Immune-Mediated Endocrinopathies

Monitor patients for signs and symptoms of endocrinopathy such as fatigue, weight change or headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease, changes in blood glucose levels and thyroid function.

Symptomatic Hypothyroidism and Symptomatic Hyperthyroidism:

		For Symptomatic Hypothyroidism	For Symptomatic Hyperthyroidism
Nivolumab (treatment) modification	Withhold OPDIVO until symptoms resolve	Grade 2 (moderate) Grade 3 (severe)	Grade 2 (moderate) Grade 3 (severe)
	Permanently discontinue OPDIVO	Grade 4 (for life-threatening situations)	Grade 4 (for life-threatening situations)
Hormone replacement		Initiate thyroid hormone replacement	Initiate anti-thyroid therapy
Steroids			Consider initiating corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalents for severe symptoms
Monitoring	Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilized		

Follow-up

Grade 2 or 3
Upon improvement, treatment may be resumed after corticosteroid taper, if needed

APPENDIX: Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 GRADING DEFINITIONS

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
General	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.*	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.**	Life-threatening consequences; urgent intervention indicated.	Death related to AE.

Endocrine Disorders	**Grade**		
Adverse Event	**2**	**3**	**4**
Adrenal insufficiency	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Hyperglycemia	Fasting glucose value >160-250 mg/dL; Fasting glucose value >8.9-13.9 mmol/L	>250-500 mg/dL; >13.9-27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Hypothyroidism	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Hyperthyroidism	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated

Gastrointestinal Disorders	**Grade**		
Adverse Event	**2**	**3**	**4**
Colitis	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated
Diarrhea	Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated

Hepatic Disorders	**Grade**		
Adverse Event	**2**	**3**	**4**
Alanine aminotransferase (ALT) increased	>3.0-5.0 x ULN	>5.0-20.0 x ULN	>20.0 x ULN
Aspartate aminotransferase (AST) increased	>3.0-5.0 x ULN	>5.0-20.0 x ULN	>20.0 x ULN
Blood bilirubin (TBIL) increased	>1.5-3.0 x ULN	>3.0-10.0 x ULN	>10.0 x ULN

Pulmonary Disorders	Grade		
Adverse Event	**2**	**3**	**4**
Pneumonitis	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)

Renal Disorders	Grade		
Adverse Event	**2**	**3**	**4**
Creatinine increased	>1.5-3.0 x baseline; >1.5-3.0 x ULN	>3.0 baseline; >3.0-6.0 x ULN	>6.0 x ULN

Skin Disorders	Grade		
Adverse Event	**2**	**3**	**4**
Rash acneiform	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences
Rash maculo-papular	Macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADL	-
Toxic epidermal necrolysis	-	-	Skin sloughing covering ≥30% BSA with associated symptoms (e.g., erythema, purpura or epidermal detachment)

Neurological Disorders	Grade		
Adverse Event	**2**	**3**	**4**
Encephalitis infection	-	IV antibiotic, antifungal or antiviral intervention indicated; severe changes in mental status; self-limited seizure activity; focal neurologic abnormalities	Life-threatening consequences; urgent intervention indicated
Encephalopathy	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

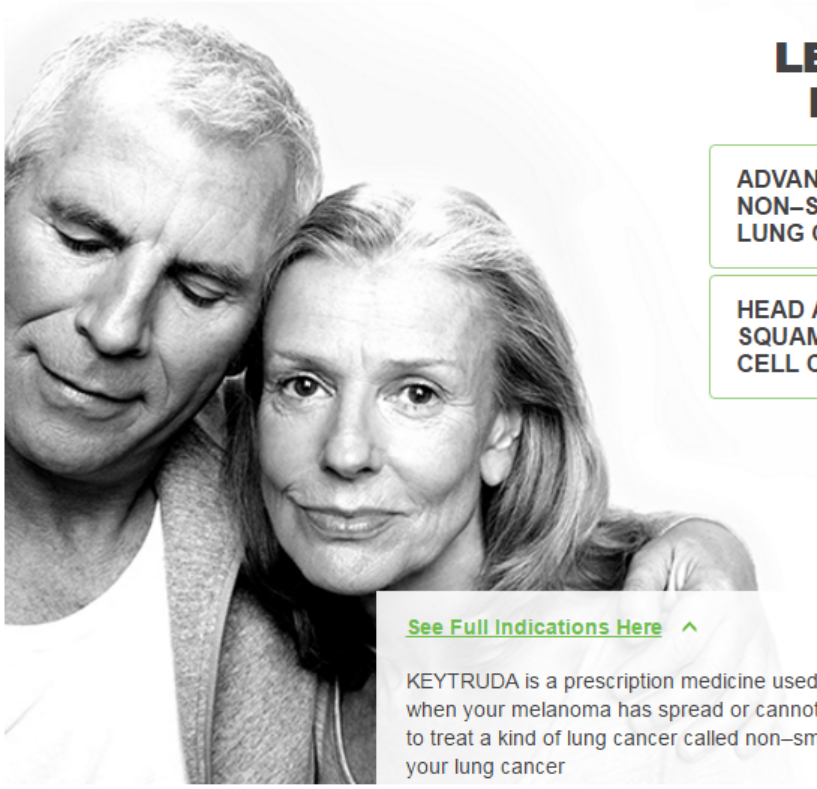
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

www.keytruda.com

KEYTRUDA (pembrolizumab) Injection 100 mg

IMPORTANT RISK INFORMATION | MEDICATION GUIDE | PRESCRIBING INFORMATION | SELECT CANCER TYPE

Financial Assistance | Patient Support | Get Updates | For Health Care Professionals



LEARN HOW KEYTRUDA CAN HELP FIGHT YOUR CANCER.

- ADVANCED NON–SMALL CELL LUNG CANCER
- ADVANCED MELANOMA
- HEAD AND NECK SQUAMOUS CELL CANCER
- TRU STORIES — Hear from real patients
- Watch TV commercial

IT'S TRU. KEYTRUDA.

See Full Indications Here

KEYTRUDA is a prescription medicine used to treat a kind of skin cancer called melanoma. It may be used when your melanoma has spread or cannot be removed by surgery (advanced melanoma). It also is used to treat a kind of lung cancer called non–small cell lung cancer (NSCLC). KEYTRUDA may be used when your lung cancer

- has spread (advanced NSCLC) **and,**
- tests positive for "PD-L1"* **and,**
  - you have not received chemotherapy to treat your advanced NSCLC and your tumor does not have an abnormal "EGFR" or "ALK" gene* **or**
  - you have received chemotherapy that contains platinum to treat your advanced NSCLC, and it did not work or is no longer working **and**
  - if your tumor has an abnormal "EGFR" or "ALK" gene,* you have also received an EGFR or ALK inhibitor medicine and it did not work or is no longer working.

It also is used to treat a kind of cancer called head and neck squamous cell cancer (HNSCC). KEYTRUDA may be used when your HNSCC has returned or spread (advanced HNSCC) **and** you have received chemotherapy that contains platinum to treat your advanced HNSCC, and it did not work or is no longer

KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma.

EFFICACY
LEARN ABOUT OVERALL SURVIVAL AND OTHER EFFICACY DATA

SAFETY
LEARN ABOUT SAFETY PROFILE

ACCESS & SUPPORT
LEARN ABOUT SUPPORT PROGRAMS

KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma.

SELECTED SAFETY INFORMATION

- KEYTRUDA can cause immune-mediated pneumonitis, including fatal cases. Pneumonitis occurred in 94 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 1 (0.8%), 2 (1.3%), 3 (0.9%), 4 (0.3%), and 5 (0.1%) pneumonitis, and occurred more frequently in patients with a history of prior thoracic radiation (6.9%) compared to those without (2.9%). Monitor patients for signs and symptoms of pneumonitis. Evaluate suspected pneumonitis with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 or recurrent Grade 2 pneumonitis.

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Our Key Products

PART III: CONSUMER INFORMATION

PrYERVOY™
(ipilimumab)

DOWNLOAD THE PRODUCT MONOGRAPH

This leaflet is part III of a three-part "Product Monograph" published when YERVOY (ipilimumab) was approved for sale in Canada and is designed specifically for Consumers.

This leaflet is a summary and will not tell you everything about YERVOY. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

YERVOY (ipilimumab) is a prescription medicine used to treat melanoma (a kind of skin cancer) that has spread or cannot be removed by surgery. It is for the treatment of melanoma in adults.

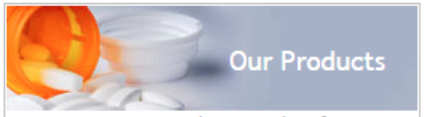
It is not known if YERVOY is safe and effective in children less than 18 years of age.

What it does:

YERVOY helps your immune system attack and destroy cancer cells by your immune cells.

Our Products

- Our Key Products
  - Abilify®
  - Daklinza™
  - Eliquis®
  - Evotaz™
  - Opdivo®
  - Orencia®
  - Reyataz®
  - Sprycel®
  - Sunvepra™
  - Sustiva®
  - Yervoy™
- Product Information
- Public Notices



Browse our product section for more information on any of our medicines

CASES

Case 1: Melanoma
Skin – anti-CTLA-4

1 INITIAL PRESENTATION | 2 TREATMENT | 3 ADVERSE EVENT | 4 irAE MANAGEMENT | 5 OUTCOMES & CONCLUSIONS | 6 TREATMENT ALGORITHM

- 57-year-old woman presented with a mole on left upper back
- Surgical pathology -T2b, N1a - 2.5mm, clark IV, 8mitosis/mm2
- 1 of 3 sentinel lymph node positive
- Healthy otherwise
- CT showed several small pulmonary nodules, suspicious for metastatic disease

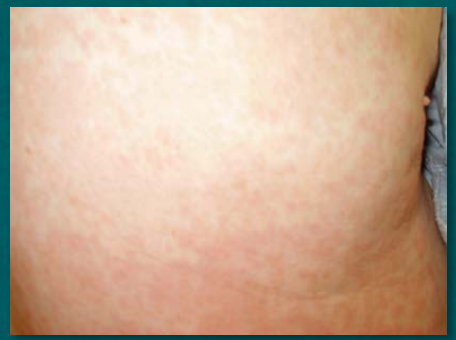
Case 1: Melanoma
Skin – anti-CTLA-4

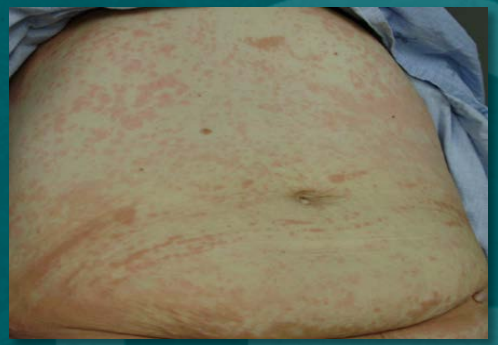
Case 1: Melanoma
Skin – anti-CTLA-4

1 INITIAL PRESENTATION | 2 TREATMENT | 3 ADVERSE EVENT | 4 irAE MANAGEMENT | 5 OUTCOMES & CONCLUSIONS | 6 TREATMENT ALGORITHM

2 weeks post cycle 1

Diffuse maculopapular skin rash >30% BSA (grade 3)





Grading the Rash

Skin Disorders	Grade		
Adverse Event	**2**	**3**	**4**
Rash acneiform	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences
Rash maculo-papular	Macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADL	-
Toxic epidermal necrolysis	-	-	Skin sloughing covering ≥30% BSA with associated symptoms (e.g., erythema, purpura or epidermal detachment)

Skin Adverse Event Management Algorithm

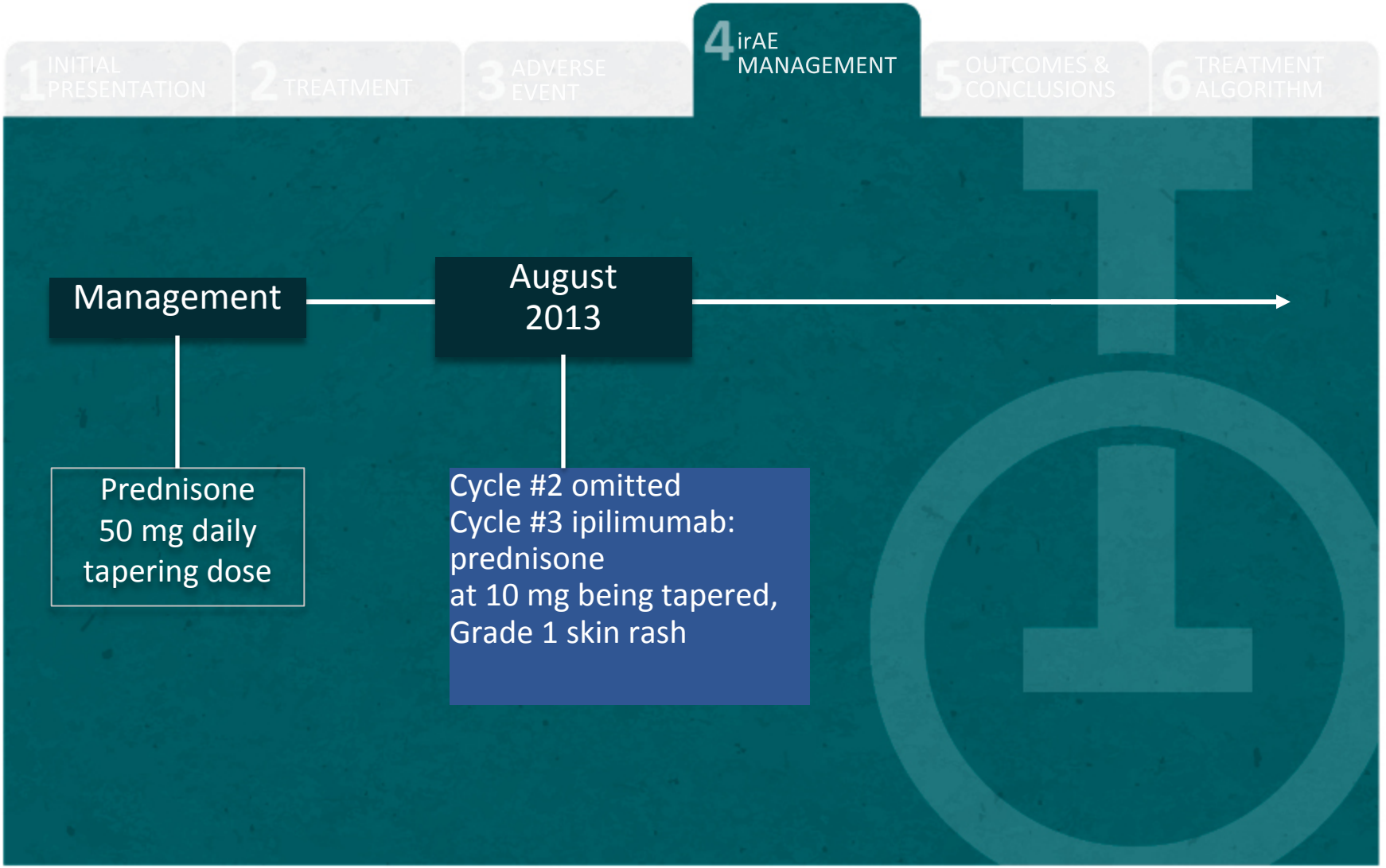
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Rash (NCI CTCAE v4)	Management	Follow-up
Grade 1-2 Covering ≤ 30% BSA*	• Symptomatic therapy (e.g. antihistamines, topical steroids) • Continue I-O therapy	If persists > 1-2 weeks or recurs: • Consider skin biopsy • Delay I-O therapy • Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy If worsens: • Treat as Grade 3-4
Grade 3-4 Covering >30% BSA; Life threatening consequences*	• Delay or discontinue I-O therapy • Consider skin biopsy • Dermatology consult • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent	If improves to Grade 1: • Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections • Resume I-O therapy

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

* Refer to NCI CTCAE v4 for term-specific grading criteria.

Case 1: Melanoma
Skin – anti-CTLA-4



Case 1: Melanoma
Skin – anti-CTLA-4

1 INITIAL PRESENTATION | 2 TREATMENT | 3 ADVERSE EVENT | 4 irAE MANAGEMENT | **5 OUTCOMES & CONCLUSIONS** | 6 TREATMENT ALGORITHM

Sept 2013

Received Cycle #4 ipilimumab

Off prednisone treatment

No further skin issues

Case 2: Melanoma
Endo – anti-PD-1

1 INITIAL PRESENTATION | 2 TREATMENT | 3 ADVERSE EVENT | 4 irAE MANAGEMENT | 5 OUTCOMES & CONCLUSIONS | 6 TREATMENT ALGORITHM

- 54-year-old male
- Metastatic melanoma to lungs
- Asymptomatic from lung metastases, ECOG 0
- PMHx: atrial fibrillation 1 year ago
- Medications: ASA 81 mg po OD

Randomized to pembrolizumab q2w on a clinical trial

Case 2: Melanoma
Endo – anti-PD-1

Jan 13, 2014

First dose of pembrolizumab

Thyroid function at start of PD1 was normal
TSH = 2.42 (0.5-5.0)
Free T4 = 15 (10-22)
T3 = 1.3 (1.2-3.2)
Tolerated PD1 well, exception grade 1 fatigue

February 24, 2014

4th treatment visit
Informed that he was discharged from ER in community for atrial fibrillation which required cardioversion
Started on β-blocker

Case 2: Melanoma
Endo – anti-PD-1

February 24, 2014

4th treatment visit
Informed that he was discharged from ER in community for atrial fibrillation which required cardioversion
Started on ®-blocker

TSH < 0.02 (0.5-5.0)
T4 = 22 (10-22)
T3 = 2.4 (1.2-3.2)

Endocrine Disorders	Grade		
Adverse Event	**2**	**3**	**4**
Adrenal insufficiency	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Hyperglycemia	Fasting glucose value >160-250 mg/dL; Fasting glucose value >8.9-13.9 mmol/L	>250-500 mg/dL; >13.9-27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Hypothyroidism	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Hyperthyroidism	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated

Managing Immune-Mediated Endocrinopathies

Monitor patients for signs and symptoms of endocrinopathy such as fatigue, weight change or headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease, changes in blood glucose levels and thyroid function.

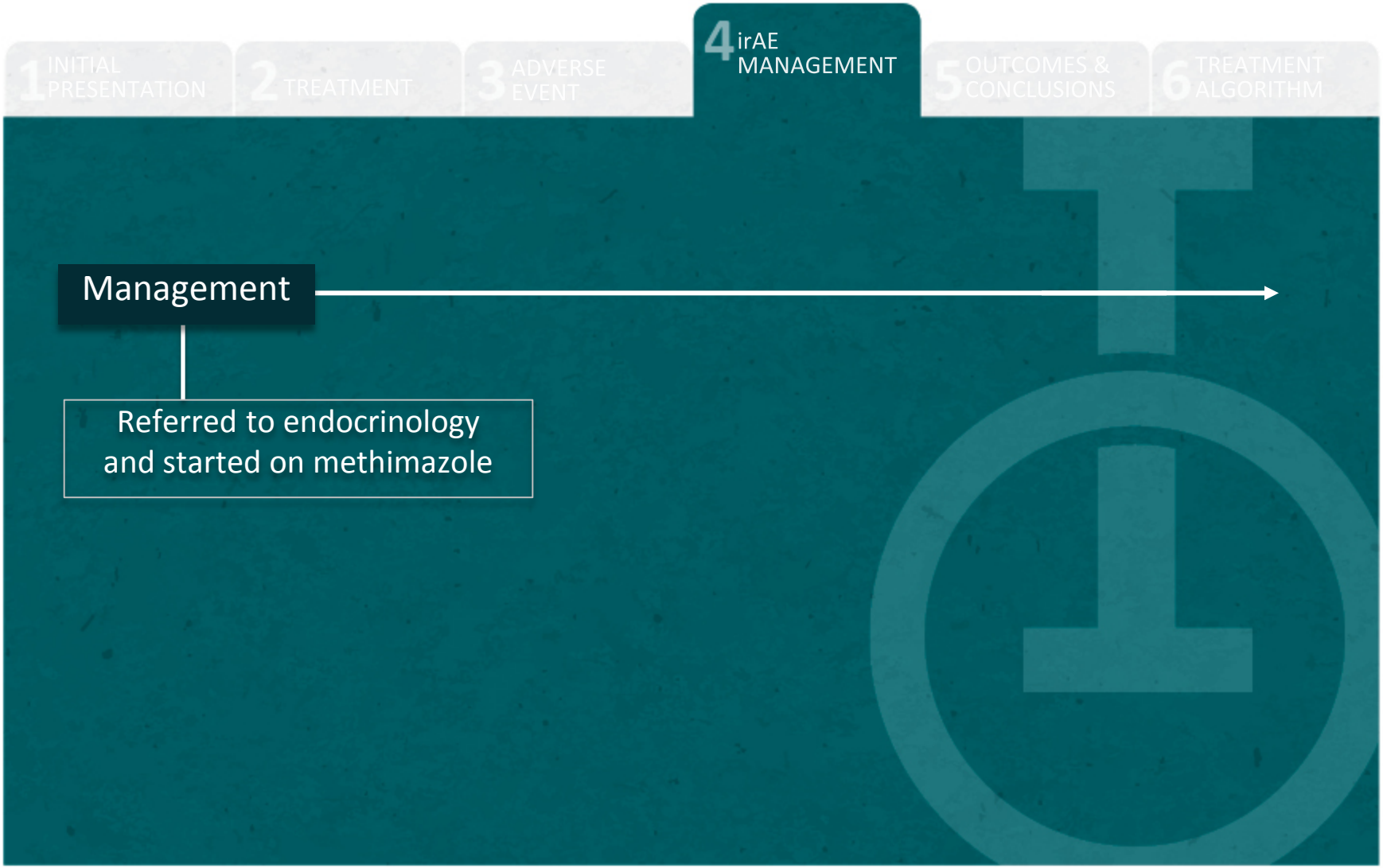
Symptomatic Hypothyroidism and Symptomatic Hyperthyroidism:

		For Symptomatic Hypothyroidism	For Symptomatic Hyperthyroidism
Nivolumab (treatment) modification	Withhold OPDIVO until symptoms resolve	Grade 2 (moderate) Grade 3 (severe)	Grade 2 (moderate) Grade 3 (severe)
	Permanently discontinue OPDIVO	Grade 4 (for life-threatening situations)	Grade 4 (for life-threatening situations)
Hormone replacement		Initiate thyroid hormone replacement	Initiate anti-thyroid therapy
Steroids			Consider initiating corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalents for severe symptoms
Monitoring	Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilized		

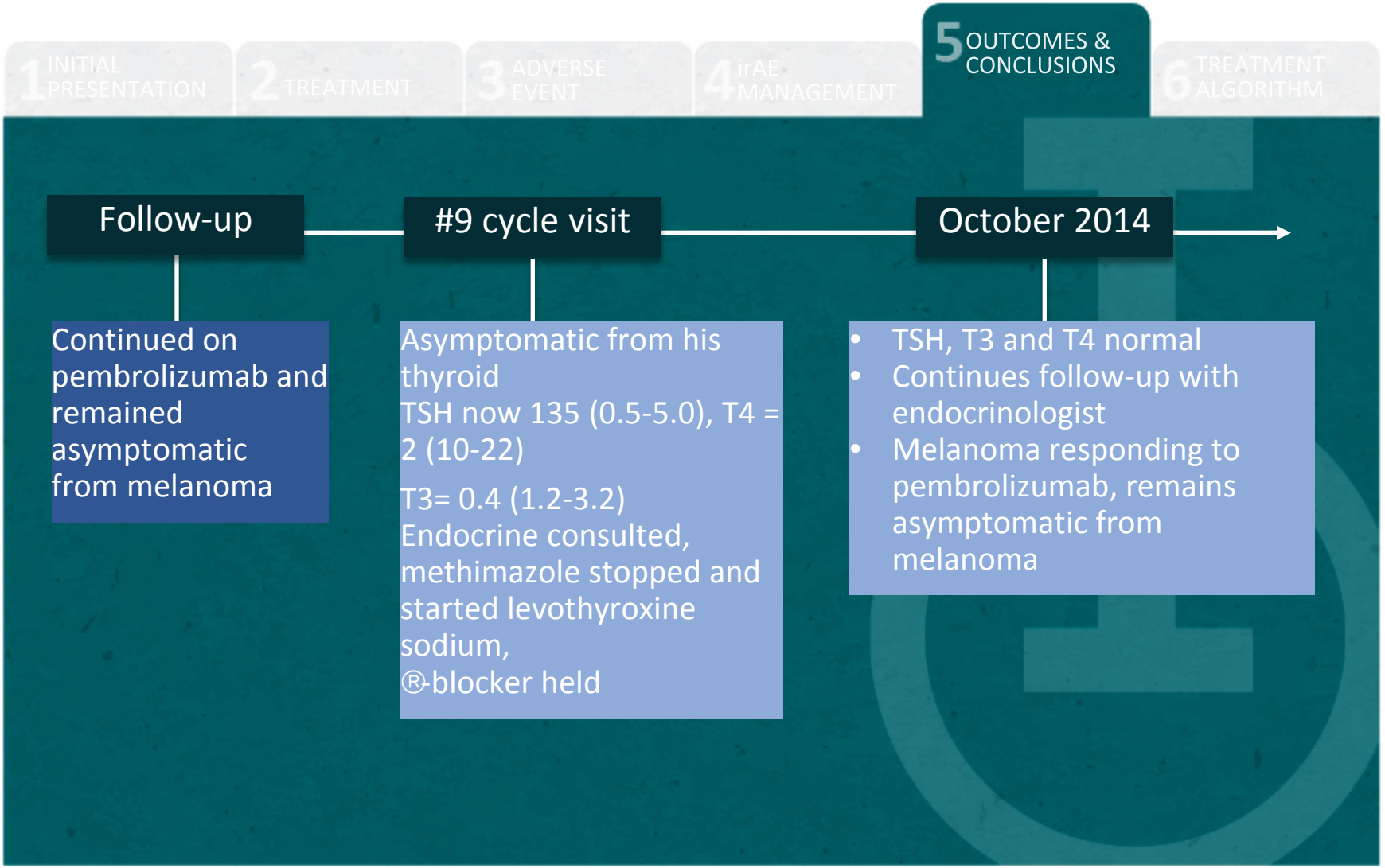
Follow-up

Grade 2 or 3
Upon improvement, treatment may be resumed after corticosteroid taper, if needed

Case 2: Melanoma
Endo – anti-PD-1



Case 2: Melanoma
Endo – anti-PD-1



Case 3: Melanoma

1 INITIAL PRESENTATION | 2 TREATMENT | 3 ADVERSE EVENT | 4 irAE MANAGEMENT | 5 OUTCOMES & CONCLUSIONS | 6 TREATMENT ALGORITHM

- 78-year-old male
- T4bN2a acral lenitiginous melanoma right toe 2008. BRAF WT.
- In transit mets to leg 2011 treated with limb perfusion and later surgery
- Relapse to base of tongue and cervical nodes
- Coughing up blood but ECOG 1.
- PMHx: HTN, acid reflux
- Medications: HCTZ, perinopril, tamsulosin, ranitidine.
- Started nivolumab by Access to Hope program

Case 3: Melanoma
Renal – anti-PD-1

Mar 21, 2016

First dose of nivolumab

- Hgb 134, Cr 111. All other labs normal.
- Tolerated PD1 well, exception mild headache x 1 day

May 2, 2016

- 5th treatment visit
- He had mild diarrhea 1-2 loose stool daily.
- Lost 6 lbs.
- 4/10 chest pain x 1 week.
- Just had CT – no pneumonitis.
- ECG normal.
- Troponin 30.
- ECHO negative for pericarditis
- Cr 114.
- Cancelled treatment to work up.

Case 3: Melanoma Renal – anti-PD-1

1 INITIAL PRESENTATION | 2 TREATMENT | 3 ADVERSE EVENT | 4 irAE MANAGEMENT | 5 OUTCOMES & CONCLUSIONS | 6 TREATMENT ALGORITHM

May 16, 2016

- 5th treatment visit
- Mild flu like symptoms but not unwell.
- Cr 338, BUN 16
- Admitted to hospital for presumed nephritis.

Grading Toxicity

Renal Disorders	Grade		
Adverse Event	**2**	**3**	**4**
Creatinine increased	>1.5-3.0 x baseline; >1.5-3.0 x ULN	>3.0 baseline; >3.0-6.0 x ULN	>6.0 x ULN

Managing Immune-Mediated Renal Adverse Reactions

Monitor patients for signs and symptoms of nephrotoxicity, including asymptomatic increase in serum creatinine and rule out disease-related etiologies.

Grade of serum creatinine elevation (NCI-CTCAE v4)	**Grade 2 serum creatinine elevation**	**Grade 3 or 4 serum creatinine elevation**
OPDIVO treatment and monitoring	Withhold OPDIVO until creatinine returns to baseline and management with corticosteroids is complete	Permanently discontinue OPDIVO
Steroids	Initiate corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents	Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents

NCI-CTCAE v4 – National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0

Follow-up

Grade 2 or 3 serum creatinine elevation
Upon improvement resume OPDIVO after corticosteroid taper
If worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day methylprednisolone equivalents and permanently discontinue OPDIVO

Case 3: Melanoma Renal – anti-PD-1

1 INITIAL PRESENTATION | 2 TREATMENT | 3 ADVERSE EVENT | 4 irAE MANAGEMENT | 5 OUTCOMES & CONCLUSIONS | 6 TREATMENT ALGORITHM

May 16, 2016

- 5th treatment visit
- Mild flu like symptoms but not unwell.
- Cr 338, BUN 16
- Admitted to hospital for presumed nephritis.
- Troponin was 61 (likely related to renal dysfunction)

- Started on prednisone 1 mg/kg
- Nephrology consulted
- Renal biopsy shows nephritis.
- May 19 Cr 286
- May 20 Cr 239
- Discharged on May 20th on prednisone 100 mg po daily + septra prophylaxis.

Case 3: Melanoma Renal – anti-PD-1

1 INITIAL PRESENTATION | 2 TREATMENT | 3 ADVERSE EVENT | 4 irAE MANAGEMENT | **5 OUTCOMES & CONCLUSIONS** | 6 TREATMENT ALGORITHM

May 25, 2016

- May 25 Cr 174.
- Seen in ER May 25th with blood in stool.
- Colonoscopy.
- Found to be a diverticular bleed.
- Seen May 30th in clinic Cr was 154
- June 13th Cr 123, started steroid taper.

July 26, 2016

- Down to 5 mg po bid prednisone.
- Cr 103.
- No longer coughing up blood.
- Leg edema due to prednisone.
- Did not restart therapy.

Aug 25, 2017

- CT shows progression in the liver.
- PDI resumed but switched to pembrolizumab as it was covered at BCCA .

Case 3: Melanoma Renal – anti-PD-1

1 INITIAL PRESENTATION | 2 TREATMENT | 3 ADVERSE EVENT | 4 irAE MANAGEMENT | 5 OUTCOMES & CONCLUSIONS | 6 TREATMENT ALGORITHM

Nov 9 2016

- Developed unrelated leg infection (maybe osteomyelitis) after picking a callus.
- Pembrolizumab held.

Nov 30, 2016

- Cr 169
- CRP14
- On antibiotics.

Dec 19, 2016

- ALT 385, AST 286 (normal in Nov).
- CRP 106
- Bad rash on new antibiotic.
- Stopped antibiotic.
- Had not had anti-PDI since mid October.

Case 3: Melanoma Renal – anti-PD-1

1 INITIAL PRESENTATION | 2 TREATMENT | 3 ADVERSE EVENT | 4 irAE MANAGEMENT | 5 OUTCOMES & CONCLUSIONS | 6 TREATMENT ALGORITHM

Dec 29, 2016

- ALT 529 AST 526
- CRP 41
- LDH 531
- Cr 151
- Started on high dose steroids 100 mg po daily prednisone for presumed auto-immune hepatitis, maybe initiated by antibiotic reaction.
- Labs 3x weekly.
- Liver lesions were stable on CT

Jan 11, 2017

- ALT 60, AST 28
- Cr 122
- On steroid taper.
- No more PDI.
- Will observe for now as clinically stable.

SUMMARY

- Immuno-oncology is a new corner stone of cancer therapy and is resulting in significant benefit in many cancers.
- Immunoncology agents have a new spectrum of adverse events, predominantly autoimmune in nature.
- Most of the immune-associated AEs are manageable with early recognition and treatment
- Optimal management of irAEs should involve multidisciplinary care team
- Remain vigilant throughout and after treatment
  - Educate and encourage patients to monitor for and report symptoms of immune-associated AEs
- Follow management guidelines for immune-associated AEs to give patients the best chance of therapeutic success