New Immunotherapies: Management of Immune Related Adverse Events

Dr. Margaret Smith
General Practitioner in Oncology
Declaration of Conflict of Interest

Dr. Margaret Smith:
* None

Dr. Kerry Savage:
* Advisory Board Memberships: BMS, Merck, Seattle Genetics
* Grants/honorariums received: BMS, Merck, Seattle Genetics, Infinity
* Clinical trial participation within the past 2 years: BMS, Seattle Genetics
At the end of this workshop, participants will be able to:

- Describe the mechanism of action of the new immunotherapies: PD-1 and CTLA-4 Immune Checkpoint Inhibition currently approved and in use in BC
- Describe the difference between the new immunotherapies and targeted therapies for treatment of metastatic cancer.
- Identify and effectively carry out surveillance of immune-related adverse events (irAEs) and toxicities of these therapies
- Institute appropriate treatment and management of irAEs associated with these therapies
* Actual irAEs from VICC patient cases over the past year will be discussed.
* Approval and use of these therapies in British Columbia is new: we are essentially in a “Phase IV post marketing survey” with these agents
* We are all learning and gaining experience with these agents as they come in to use locally: Oncologists, GPO’s, support specialists: nephrologists, gastroenterology, endocrinology and more.
Which of the following are immune related adverse events associated with ipilimumab:

a) vitiligo  
b) colitis  
c) neuropathy  
d) pituitary failure  
e) lymphadenopathy  
f) all

Emergence of immune related adverse events from checkpoint inhibition may correlate with treatment response:

true  
false  
unknown at this time
Which of these tumors have current Canada Health Approval for use of Checkpoint Inhibition therapy:

a) melanoma
b) advanced stage ovarian/fallopian tube carcinoma
c) advanced renal clear cell carcinoma
d) pancreatic carcinoma
e) advanced non-small cell lung cancer
Which of the following are targeted therapies for melanoma:

a) ipilimumab  
b) vemurafenib  
c) nivolumab  
d) pertuzumab  
e) dabrafenib/trametinib
First Things First: Basic Immunology to Understand Checkpoint Inhibition

Thanks to various contributors for graphics on T Cell Immune Theory
* T cells are thought to play an important role in immune surveillance and tumor destruction.

* Immune response regulation is built into our T cell immune system to prevent “bystander tissue damage”

* Cytokines, T reg cells, and cosignalling molecules are some of the mechanisms that limit the strength and extent of the activated T cell’s immune response
Limiting the immune response prevents bystander tissue damage

Mechanisms are in place to prevent overactivation of the immune response

- Immune response termination prevents bystander tissue damage and the development of autoimmunity
  - Cytokines
  - Treg cell
  - Cosignalling molecules
Immune Escape in Cancer

Many tumours escape the immune response by creating an immunosuppressive microenvironment that prevents an effective antitumour response.

Recruitment of immunosuppressive cells
- Tregs
- MDSCs

Ineffective presentation of tumour antigens to the immune system
- Downregulation of MHC expression
- Suppression of APC

Release of immunosuppressive factors
- Factors/enzymes directly or indirectly suppress immune response

T-cell checkpoint dysregulation
- CTLA-4
- PD-1
- PDL-1
- TIM-3
- BTLA
- VISTA
- LAG-3
- Co-inhibitory receptors

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

How Do T-cells Recognize and Kill Tumour Cells?

Tumours express tumour-associated antigens\(^1,2\)

Antigen presenting cell (APC) captures tumour-associated antigens\(^2\)

APC presents the tumour-associated antigen to an inactive T-cell, along with a co-stimulatory signal\(^2\)

Inactive T-cell

T-cell becomes activated and binds to tumour cell

Cytotoxic T-cell

Cytotoxic T-cell induces tumour cell death by apoptosis\(^1,2\)

Co-stimulatory signal

Antigen

References:
Proper T-cell activation requires two signals

- To be properly activated, a T cell MUST receive two signals
  - Binding of an MHC-antigen complex to TCR
  - Binding of a second costimulatory signal
- This initiates intracellular signalling that activates the T cell, which may then kill infected or cancer cells or help support other immune functions

Image © 2012 from Janeway’s Immunobiology, Eighth Edition by Murphy. Adapted by permission of Garland Science/Taylor & Francis LLC.

APC=antigen-presenting cell; MHC=major histocompatibility complex; TCR=T-cell receptor
T cells are thought to play an important role in immunosurveillance and tumour destruction\textsuperscript{1,2}.

MHC = major histocompatibility complex.
There are many potential sites for checkpoint receptor inhibition.
Tumour Immune suppression

Tumour cells can escape from immune system destruction through many mechanisms, including the expression of immune suppressive molecules on their cell surface.

Tumour Cells

PD-L1

Tumour Antigen

Tumour Cells
Tumour cells can escape from immune system destruction through many mechanisms, including the expression of immune suppressive molecules on their cell surface.

1. Activated T-cells
   - Activated T-cells go to tumour site
   - Able to recognize and destroy tumour cells
   - Have PD-1 on their surface

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PD-1
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2. PD-1 on T-cells binds to PD-L1 on tumour cells
Tumour Immunosuppression

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2. PD-1 on T-cells binds to PD-L1 on tumour cells

3. T-cells are “inactivated” = Immunosuppression
How Does Anti-PD-1/PD-L1 Therapy Work?

Anti-PD-1 or anti-PD-L1 antibody therapy blocks the interaction between PD-1 and PD-L1.
CTLA-4 regulation occurs centrally in the lymph node where there is initial response to the tumor antigen. PD-1 regulation and response occurs in the peripheral tissues where it binds to PD-1 ligand, which is overexpressed on some tumor cells.
CTLA4 and PD-1 are immune checkpoint inhibitors

Immune checkpoint inhibitors maintain self-tolerance and modulate the duration and amplitude of immune responses

**Major Role**

**CTLA4** regulates initial response to antigen.

**PD-1** regulates response in tissues.

CTLA4: cytotoxic T-lymphocyte-associated antigen 4; DC: dendritic cell; MHC: major histocompatibility complex; PD-1: programmed cell death protein-1; TCR: t-cell receptor.
Examples of targeted therapy receptors:

- BRAF (vemurafenib)
- VEGF (bevacizumab)
- HER2 (trastuzumab)
- PDGFR (sorafenib, sunitinib)
- KRAS (panitumumab)
Why all the interest in Checkpoint Inhibitor Immune Therapies?

They bring new hope of effective treatments in tumor sites that previously had little or no success with systemic therapies.
Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

Ph 3 previously treated

- IPI
- IPI + GP100
- GP100

IPI 3mg/kg Q3 weeks x 4 doses – 12 week treatment course

ORR 10% and PFS was similar – 2.7 m

Improved OS IPI arms median 10 m vs 6.4 m
First study to shown OS benefit with any therapy in metastatic melanoma

Hodi NEJM
August 2010
NEJM May 21, 2015 Michael A Postow et al  Untreated Melanoma

**Graph C:**

- **Death or Disease Progression**
  - Nivolumab plus Ipilimumab: 30/72, 25/37
  - Ipilimumab: not reported (NR)

- **Median Progression-free Survival**
  - Nivolumab plus Ipilimumab: 4.4 (2.8–5.7) months (95% CI)
  - Ipilimumab: not reported

- Hazard ratio: 0.40 (95% CI, 0.23–0.68)
- P-value: <0.001

**Progression-free Survival (%) of patients**
- Nivolumab plus Ipilimumab (N=72)
- Ipilimumab (N=37)

**No. at Risk**
- Nivolumab plus Ipilimumab: 72, 54, 45, 38, 20, 1
- Ipilimumab: 37, 20, 9, 6, 2

**Months**
- 0, 3, 6, 9, 12, 15, 18
Figure 1. Kaplan–Meier Curve for Overall Survival.
CI denotes confidence interval, and NE not estimable.
Nivolumab
CheckMate 017: PFS in advanced non small cell lung cancer  
Brahmer et al, NEJM May 21, 2015

CI: confidence interval; HR: hazard ratio; PFS: progression-free survival.
Pembrolizumab in NSCLC

KEYNOTE-010: OS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS, months (95% CI)</th>
<th>HR vs. docetaxel</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 2 mg/kg</td>
<td>10.4 (9.4-11.9)</td>
<td>0.71 (0.58-0.88);</td>
<td>0.0008</td>
</tr>
<tr>
<td>Pembro 10 mg/kg</td>
<td>12.7 (10.0-17.3)</td>
<td>0.61 (0.49-0.75);</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>8.5 (7.5-9.8)</td>
<td></td>
<td></td>
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</tbody>
</table>

HR: hazard ratio; CI: confidence interval.

Pembrolizumab Antitumor Activity

Melanoma (N=655) KEYNOTE-001

NSCLC (N=262) KEYNOTE-001

H&N (N=132) KEYNOTE-012

Urothelial (N=33) KEYNOTE-012

Gastric (N=39) KEYNOTE-012

TNBC (N=32) KEYNOTE-012

cHL (N=29) KEYNOTE-013

Mesothelioma (N=25) KEYNOTE-028

Ovarian (N=26) KEYNOTE-028

SCLC (N=20) KEYNOTE-028

Esophageal (N=23) KEYNOTE-028

cHL = classical Hodgkin's lymphoma; H&N = head and neck; NSCLC = non-small cell lung cancer; TNBC = triple-negative breast cancer.

<table>
<thead>
<tr>
<th>Target</th>
<th>Antibody</th>
<th>Developmental Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1</td>
<td>Nivolumab</td>
<td>Phase III: multiple tumours&lt;br&gt;Health Canada approved: melanoma, advanced RCC and NSCLC&lt;br&gt;FDA approved: melanoma, NSCLC, advanced RCC, and cHL</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>Phase III: multiple tumours&lt;br&gt;Health Canada approved: melanoma and NSCLC&lt;br&gt;FDA approved: melanoma and NSCLC</td>
</tr>
<tr>
<td>PD-L1</td>
<td>Atezolizumab</td>
<td>Phase I/II: multiple tumours; Phase III: bladder, NSCLC&lt;br&gt;FDA “breakthrough” status in lung cancer&lt;br&gt;FDA approved: urothelial carcinoma</td>
</tr>
<tr>
<td></td>
<td>Avelumab</td>
<td>Phase I: multiple tumours, Phase III: NSCLC&lt;br&gt;FDA “breakthrough” status in MCC</td>
</tr>
<tr>
<td></td>
<td>Durvalumab</td>
<td>Phase I/II: multiple tumours&lt;br&gt;Phase III: NSCLC, HNSCC, bladder&lt;br&gt;FDA “breakthrough” status in urothelial carcinoma</td>
</tr>
</tbody>
</table>

While immune checkpoint inhibition has resulted in anti-tumour responses, toxicities in the form of autoimmune breakthrough or immune-related adverse events (irAEs) have also been reported.

- Even seemingly unimportant symptoms can escalate, causing serious life threatening complications if left unmanaged

- Close and careful patient monitoring is critical

- Most irAEs are mild to moderate in severity and can be medically managed using corticosteroids
Immune-related (IR) adverse events (AEs) with immunotherapies

Skin
- Skin rash or pruritus

Lung
- Pneumonitis

Renal

Gastrointestinal
- Colitis
- Pancreatitis
- IBD (general)

Hepatic

Endocrine
- Hyperthyroidism
- Hypothyroidism
- Adrenal insufficiency
- Hypophysitis

You need to be a good general internist and ever vigilant managing patients on checkpoint inhibitors

Ipilimumab
Kinetics of immune-related Adverse Events (irAEs)

Pooled analysis of patients with melanoma and treated with ipilimumab

- Approximately 60% of patients experienced irAEs of any grade
  - Approximately 15% were grade 3–4 events
- Manageable according to protocol treatment guidelines including careful monitoring and early corticosteroid use

Nivolumab
Kinetics of onset and resolution of select treatment-related AEs (any grade)

A. Most common select AEs (≥10%)

- Skin
- Gastrointestinal

B. Less common select AEs (<10%)

- Endocrine
- Hepatic
- Pulmonary
- Renal

The beginning and end of each curve represent the median time to onset and median time to resolution, respectively. Each peak reflects the incidence of the AE.

For patients with Grade 1 (mild) toxicity, proceed with caution, surveillance.

For Grade 2 (moderate) irAE toxicity: withhold the checkpoint inhibitor until symptoms resolve, or toxicity is grade 1 or less. Corticosteroids should be started (prednisone 1 mg/kg/day) if grade 2 symptoms persist beyond than 1 week.

For Grade 3 or 4 irAE toxicity (severe to life threatening): Permanently discontinue the Checkpoint inhibitor. High dose corticosteroids until symptoms subside to grade 1 or less, then begin a slow steroid taper over at least 1 month.
Pseudo-progression – A Clinical Challenge with Immune therapies

- Historically, significant tumour growth (i.e., by RECIST or WHO criteria) would be classified as treatment failure
- However, some patients on immunotherapies appear to have progressive disease after starting treatment
  - Tumour appears larger on initial CT scans
  - Increased tumour size actually due to infiltration of immune cells or necrosis → is followed by decreased tumour burden
- Continue to treat through this “pseudo-progression”, and reassess one month later
- Each patient must be monitored carefully on an individual basis with repeat assessments
  - Some patients may have true progressive disease and may consider alternate treatment options

CT: computed tomography.
Chiou and Burotto. JCO. 2015;33:3541-3.
Checkpoint Inhibitor therapy is expensive!

- Ipilimumab: about C$100,000 for the 4 treatments
- Nivolumab: estimated C$14,526 per 28 days (final Canadian price pending)
- Pembrolizumab: estimated C$8,213 per 28-days (2 mg/kg Q3W)

- Docetaxel: approximately $583 per 28 day course
- Erlotinib: $2240 per 28 day cycle
Let’s get to some actual cases of immune related adverse events from the Vancouver Island Cancer Clinic in the past year.
Ms. GV: 59 year old woman diagnosed with Stage IV non-small cell lung cancer; dominant mass RUL to LUL, R hilum, mediastinal lymphadenopathy June 2013.

- EGFR and ALK untested due to insufficient tissue, diagnosis on FNA of RUL mass

- 2013 progression after 2 cycles of pemetrexed and cisplatin, then further progression after 4 cycles of erlotnib. Feb 2014 Radiation therapy to RUL mass, then second course radiation to R mainstem bronchus due to disease progression causing partial obstruction Sept 2014, with improvement of symptoms of dyspnea and pain.
July 2015 CT confirms progression compression of R mainstem bronchus, infiltration into R hilum and mediastinum. Increasing pulmonary metastases, but no distant metastases. GV remains active, but dyspneic on exertion. Pain control satisfactory on long and short acting hydromorphone, with minimal breakthrough doses. Stable appetite, and weight. ECOG 1.

PE shows only a low pitched inspiratory rhonchus through all lung fields. JVP and cardiac exam normal. Rest of exam unremarkable. No clinical evidence of infection.

Full baseline labs unremarkable except WBC 19 and neutrophils 18
Would you offer the new PD-1 Inhibitor nivolumab to this patient?

Full disclosure to the patient of the possible toxicities, with a less than 5% risk of severe and life threatening immune mediated toxicity, including colitis, hepatitis, hyper/hypothyroidism, nephritis, and pneumonitis.

Ms. GV agrees to treatment with nivolumab, receiving the first dose Sept 16, 2015 at 10 am.
Ms GV, 59, non-small cell lung cancer

Ms GV presents to ER early hours of Sept 17 with hourly diarrhea, and dyspnea. VS: afebrile, HR 130, RR 28, O2 sat 92% on 10 L O2, BP not hypotensive

WHAT DRUGS would you advise the emergency room physician to administer?

* Hydrocortisone 100 mg IV was given in ambulance on transit to hospital
* Methylprednisolone 100 mg IV in ER. Piperacillin/tazobactram started in ER. Supportive nebulizers, oxygen.
Ms. GV, 59

- Chest X ray reports new consolidation of the lingula, a new consolidative mass over the left hilum consistent with pneumonitis, pulmonary vasculature is obscured, consistent with edema.
- Supportive care is given.
- There is respiratory deterioration over the course of the day, and VG dies late on Sept 18, 2016 of respiratory failure.
Mr. RE, 66, longstanding metastatic renal cell carcinoma, previous therapies included sunitinib, everolimus as part of Checkmate-25 study, and axitinib.

Started on nivolumab as per Checkmate-25 study.

Received 6 cycles without complication, and with documented response

Pre cycle 7 labwork: am cortisol 15 (170-650), Na 123, K 5.0, TSH normal

Previous month’s am cortisol 722 (170-650)

Not on exogenous steroids

No orthostatic symptoms, mild nausea and fatigue, no vomiting, no diarrhea

WHAT WOULD YOU DO?
RE, 66, renal cell cancer

- 1. Hold further nivolumab
- 2. Start high dose steroids with prednisone 1mg/kg/day
- 3. Urgent MRI of the pituitary gland
- 4. Referral to endocrinology
- 5. Counsel patient 50% chance of recovery, and 50% chance of life long replacement therapy.

- FOLLOW UP appointment:
  - MRI shows normal pituitary, no evidence of hypophysitis
  - Slow taper of prednisone underway
  - Endocrinologist recommends transition to Cortef po (hydrocortisone) 20 mg am and 10 mg pm
RE, 66, renal cell cancer

* No evidence of any other irAE’s
* RE completes prednisone taper, and feels well (back to baseline performance) on maintenance Cortef. Labs, physical exam are WNL, CT shows stable metastatic disease
* Endocrinology follows him, he does not currently need Florinef (no postural hypotension). Pt knows about “stress dosing” of Cortef. Pre-existing hypothyroidism, on replacement, initial ACTH not helpful, as immediately placed on high dose steroids, LH, FSH, prolactin, testosterone levels checked and normal. Follow up ACTH remains <1 suggesting central cause for adrenal failure
* WOULD YOU RESTART NIVOLUMAB?
* Current status (late August, 2016)
* RE has completed 15 cycles of nivolumab. He remains clinically well on replacement Cortef, his only other noted irAE is mild pruritis and rash, non progressive. Physical exam WNL. Most recent CT shows stable to possible slight reduction in metastatic disease
Ms LH, 59, BRAF wild type, widespread metastatic melanoma. She has a remote history of ulcerative proctitis, quiescent for 15 years, and not requiring therapy.

LH was offered first line ipilimumab for incurable disease. She was fully counselled about 60% risk of irAE, and 10 to 15% risk of severe or life threatening toxicity, including 2% mortality risk.

Ipilimumab is given every 3 weeks for 4 cycles, which completes treatment.
* Started on ipilimumab immune therapy

* With cycle 1, she had Grade 1 diarrhea: maximum 4 watery bm/24 hrs for 4 days then 3 watery bm/24 hr, all non-bloody, on regular Imodium with each watery bm. No fever. Cramping only prior to bm. Felt mildly faint after one bm. VS normal. No other irAE. Subcutaneous, and dermal lesions were larger (pseudoprogression) Labs, and PE normal
Cycle 2, 8 days in, new onset bloody diarrhea, up to 9 episodes /24 hr, nocturnal diarrhea, continent. Contacted the medical oncologist on call and started immediately on prednisone 1 mg/kg/day po. Able to keep oral fluid intake adequate.

What recommendations would you make now to this patient with what is rated grade 2 diarrhea?
LH, 59, metastatic melanoma

- Continue prednisone 1mg/kg/24hr for 2 weeks, then a slow taper over 4 weeks, (down by 5mg/day every 2 weeks) until assessed by gastroenterology.
- Urgent outpatient referral to gastroenterology.
- Patient instructed to go to ER if fever, abdominal pain, worsening diarrhea.
- Would you stop further ipilimumab?
Plan: no further ipilimumab.

When recovered, and with gastroenterology blessing, could consider PD-1 inhibitor therapy with nivolumab.

Close monitoring is instituted as an outpatient.

Further Course: bloody diarrhea continues for 4 weeks despite continued high dose prednisone.

Patient admitted to RJH for assessment and treatment, October 12, 2015
GI Consult: “patient was placed on a new sophisticated therapy for melanoma. Shortly after that, she developed inflammatory bowel disease. High dose steroid have not improved her symptoms. Dr. Z (colleague gastroenterologist) has reviewed the literature, and the next step is Remicade (infliximab) at standard dosing regimen via infusion. Approval for Remicade was obtained, the first dose was given, steroid bridging was continued. Usually we can tell within 7 days if there is a clear benefit to Remicade. If there is no benefit in 7 days, a second course would be arranged.”
No response to Remicade was observed.

Surgery was consulted, and LH underwent a total colectomy on October 27, 2015.

Relatively uncomplicated recovery and discharge.

January 4, 2016 progressive symptomatic melanoma.

Would you offer alternate immune therapy with a PD-1 inhibitor?
Baseline labs within parameters.

LH received her first infusion of nivolumab on January 5, 2017.

A second cycle was given January 19, 2016. After this, bloody mucus from the rectal stump occurred. Emesis occurred. Steroids reinstituted. Further immune therapy abandoned.

LH died of metastatic melanoma.
Postow M, Wolchok J. Toxicities associated with checkpoint inhibitor immunotherapy. In: 2015 UpToDate®; Ross, Michael E. (Ed); Waltham, Massachusetts: UpToDate®; Available at www.uptodate.com; updated 6 Jan 2016;


Choi JM. How to recognize and manage ipilimumab-induced dermatologic adverse events. The ASCO Post 2013;4(16).

The End

Thanks for your Attention and Participation!