Immunotherapy

The Dark Side

Presenters: Blair Einarson & Belynda Salter-Oliver

Presenter Disclosure

- **Faculty/Speaker: Belynda Salter-Oliver**
- **Relationships with financial sponsors:**
  - **None**

Presenter Disclosure

- **Faculty/Speaker: Blair Einarson**

- **Relationships with financial sponsors:**

  None to disclose

Mitigating Potential Bias

- Not Applicable

Equity Commitment

- In preparing for this presentation, we have considered the Health Equity Resource for Presenters provided by the conference planning committee.

- This was provided to help presenters reflect on how these topics and content can have good effects or bad effects on people or populations that are underserved.

Learning Objectives

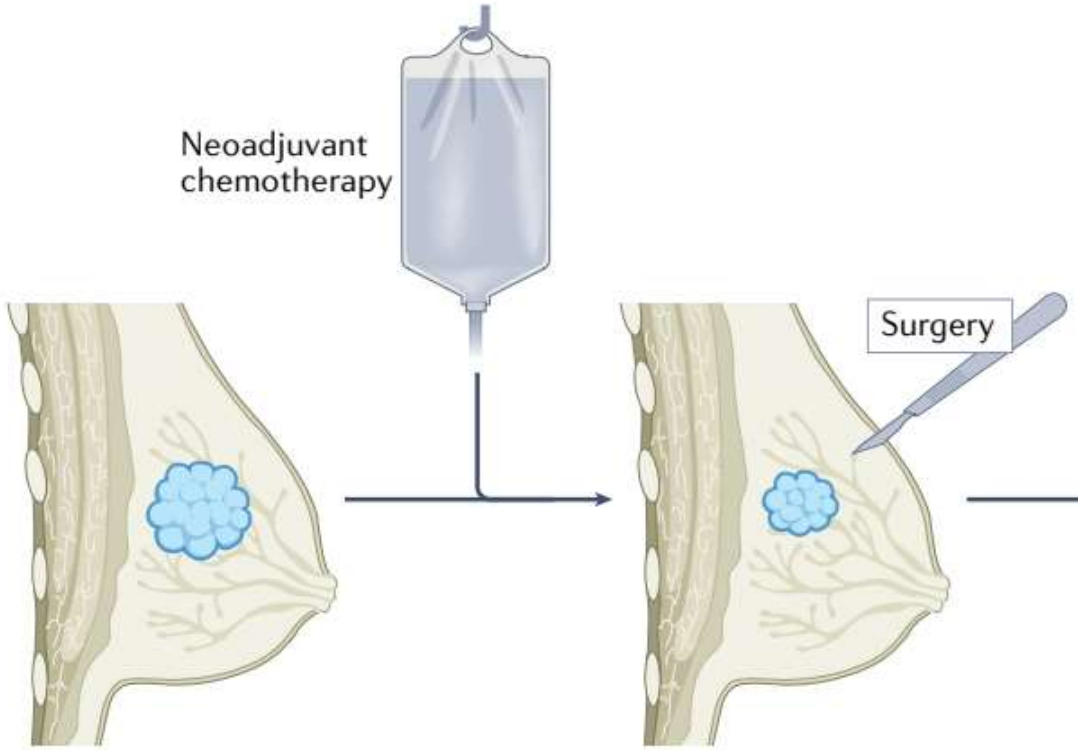
- List common immunotherapy agents
- List new immune checkpoint inhibitor treatment regimens and dosing schedules based on recent Health Canada approvals
- List the common side-effects associated with immunotherapy and their typical presentation
- Describe the treatment of the adverse events associated with immunotherapy

Health Canada approved immune checkpoint inhibitors

PD-1 inhibitors	PD-L1 inhibitors	CTLA-4 inhibitors
• nivolumab - 2015 • pembrolizumab - 2017 • cemiplimab - 2019 • dostarlimab - 2022	• atezolizumab - 2017 • durvalumab - 2017 • avelumab - 2017	• ipilimumab - 2012 • *tremelimumab* (not approved In Canada; FDA approval October 2022)*

Neoadjuvant Treatment

use of systemic therapy (such as chemotherapy, radiation therapy, hormonal therapy or a combination) *prior* to definitive curative surgery



Goal: Improve the rate of cure, improve patient survival

Neoadjuvant immune checkpoint inhibitor treatment

- The use of immune checkpoint inhibitors in the neoadjuvant setting is rapidly expanding
- currently being explored in over 100 clinical trials

Regimens include:
• monotherapy (PD-(L)1 inhibitor) • combination immune checkpoint inhibitors (PD-(L)1 inhibitor + CTLA-4 inhibitor) • immune checkpoint inhibitor in combination with chemotherapy

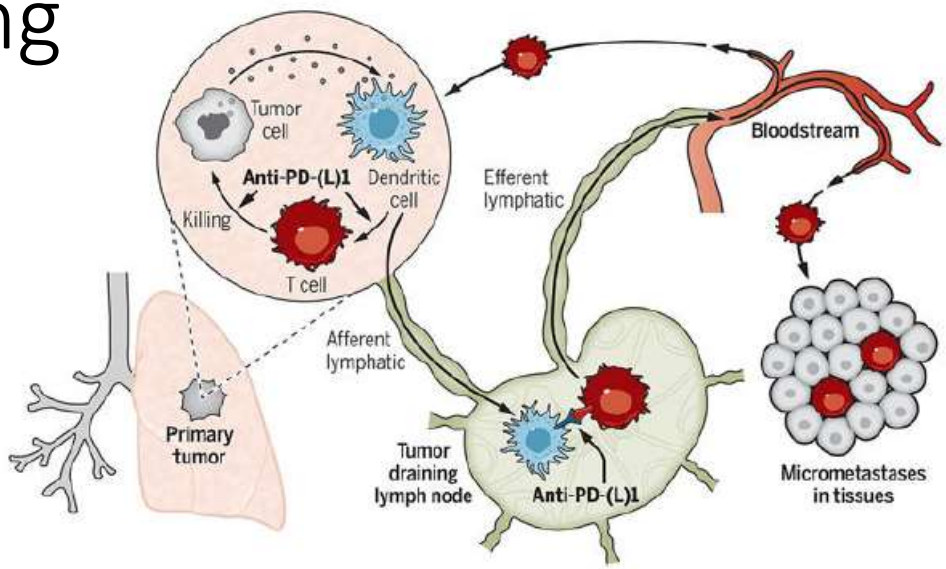
Proposed Mechanisms for ICI in the neoadjuvant setting

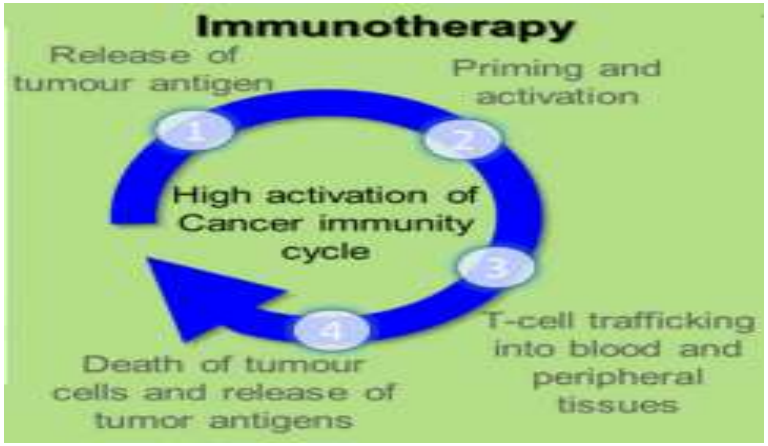
Enhance immune system against tumor antigens

Increase T cell priming by using high levels of tumor antigen found in the primary tumor before resection

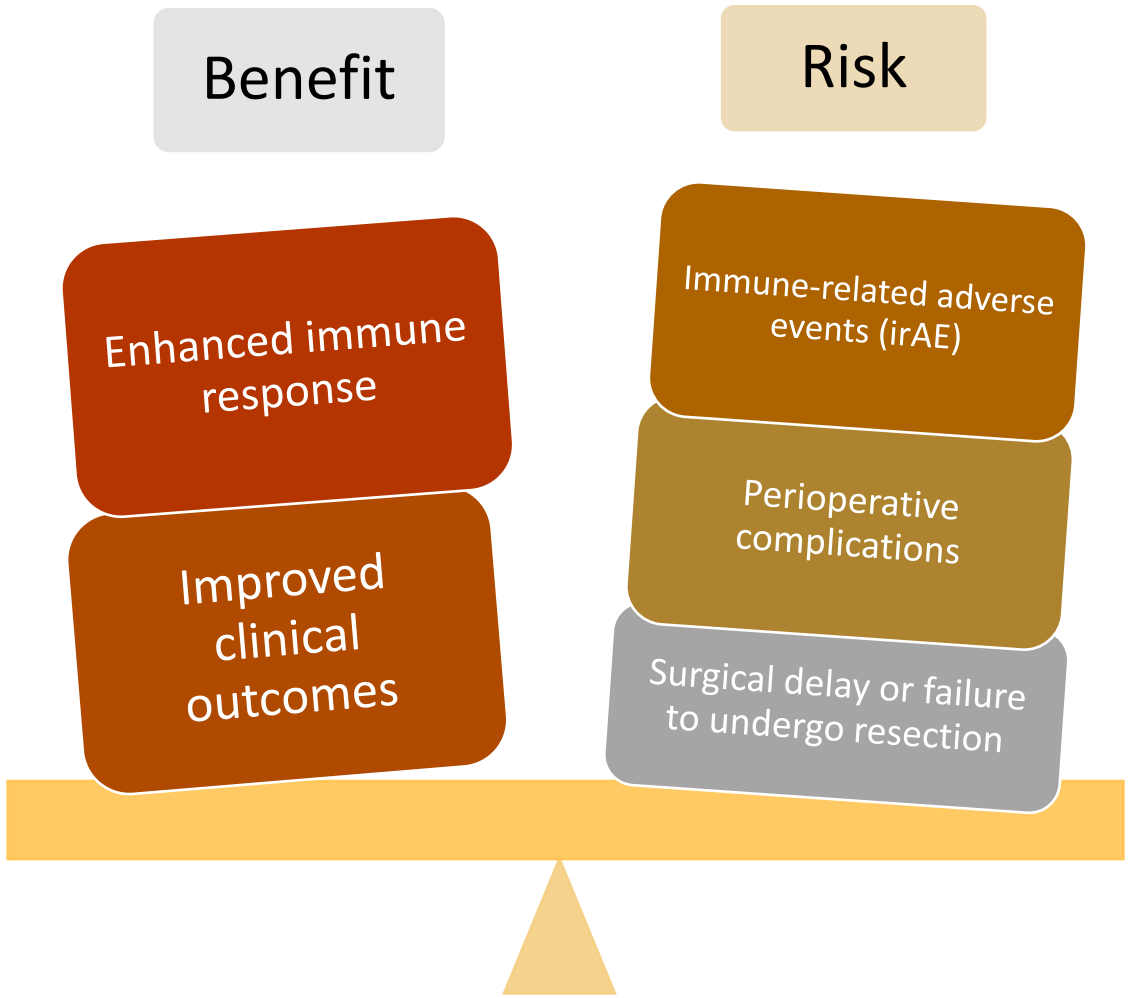
T cells are primed within the primary tumor via dendritic cells, as well as within tumor-draining lymph nodes

Activated T cells can reach micrometastases outside of primary tumor





Balance


Benefit
Risk
Enhanced immune response
Improved clinical outcomes
Immune-related adverse events (irAE)
Perioperative complications
Surgical delay or failure to undergo resection

Neoadjuvant Immunotherapy in Manitoba

- Currently no provincially funded indications in Manitoba
- Two Health Canada approved indications available through manufacturer access program for immune checkpoint inhibitors

Triple Negative Breast Cancer	pembrolizumab + BrighTNess, followed by adjuvant pembrolizumab • KeyNote522
Resectable Non Small Cell Lung Cancer	nivolumab + platinum doublet • CheckMate 816

Triple Negative Breast Cancer

ORIGINAL ARTICLE

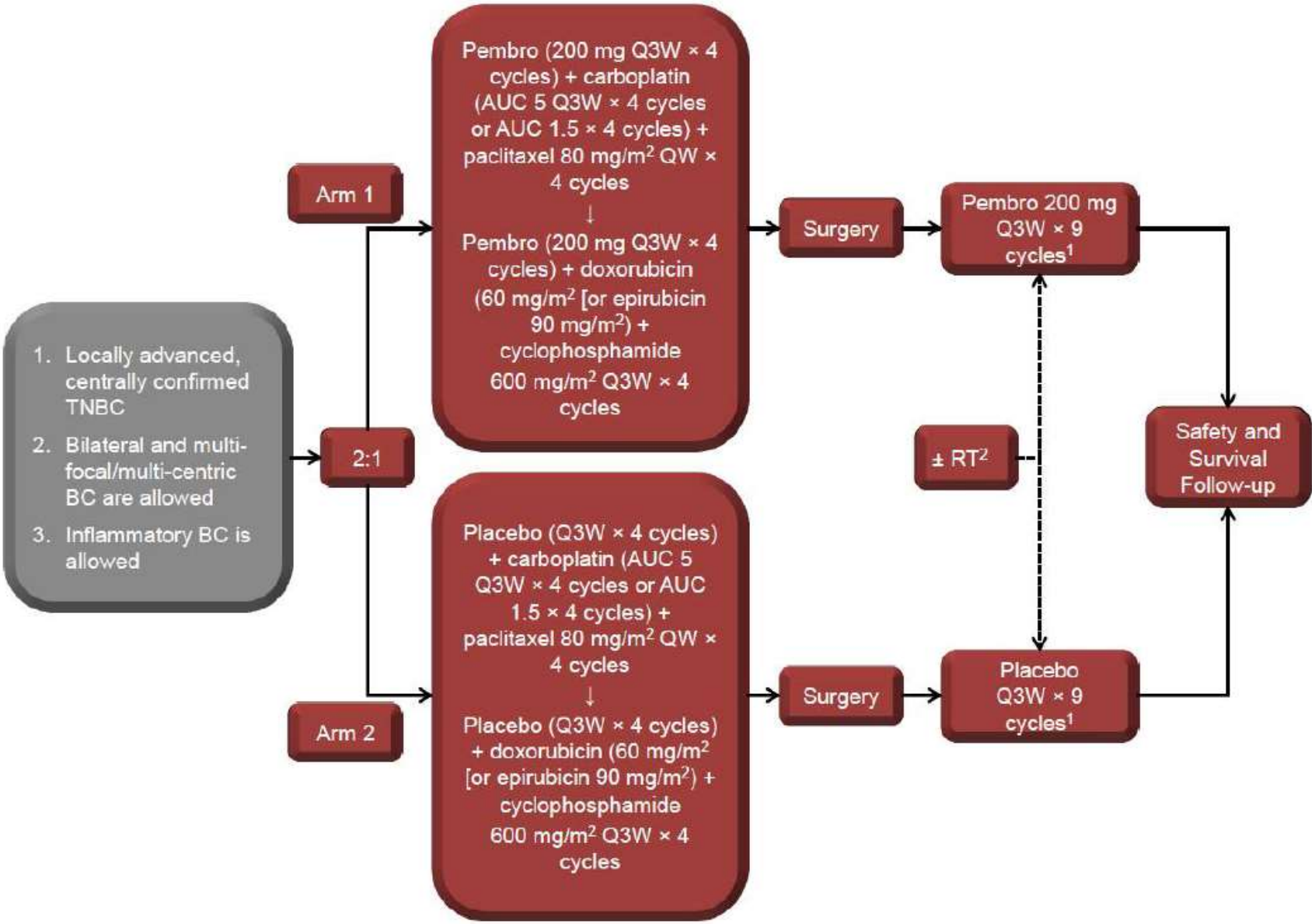
Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer

P. Schmid, J. Cortes, R. Dent, L. Pusztai, H. McArthur, S. Kümmel, J. Bergh, C. Denkert, Y.H. Park, R. Hui, N. Harbeck, M. Takahashi, M. Untch, P.A. Fasching, F. Cardoso, J. Andersen, D. Patt, M. Danso, M. Ferreira, M.-A. Mouret-Reynier, S.-A. Im, J.-H. Ahn, M. Gion, S. Baron-Hay, J.-F. Boileau, Y. Ding, K. Tryfonidis, G. Aktan, V. Karantza, and J. O'Shaughnessy, for the KEYNOTE-522 Investigators*

N Engl J Med 2022;386:556-67.

Keynote 522

- Phase III, double-blind, randomized controlled trial
- 1174 adults with previously untreated Stage II or Stage III breast cancer
- “Triple Negative”: ER/PR receptor negative, HER2 negative
- Randomized to receive pembrolizumab/placebo + neoadjuvant chemotherapy followed by definitive surgery
  - chemotherapy consisted of PACLitaxel + CARBOplatin x 4 cycles, followed by anthracycline + cyclophosphamide x 4
  surgery
- Following surgery, patients received adjuvant pembrolizumab/placebo to complete 1 year of treatment

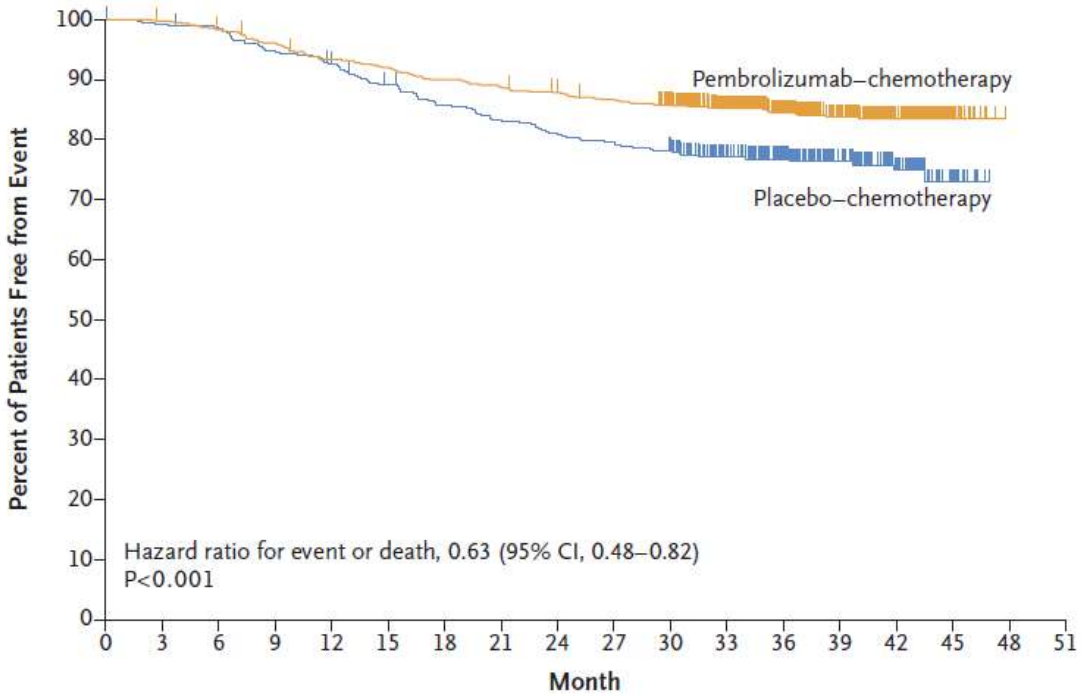

1. Locally advanced, centrally confirmed TNBC
2. Bilateral and multi-focal/multi-centric BC are allowed
3. Inflammatory BC is allowed
2:1
Arm 1
Pembro (200 mg Q3W × 4 cycles) + carboplatin (AUC 5 Q3W × 4 cycles or AUC 1.5 × 4 cycles) + paclitaxel 80 mg/m² QW × 4 cycles
↓
Pembro (200 mg Q3W × 4 cycles) + doxorubicin (60 mg/m² [or epirubicin 90 mg/m²) + cyclophosphamide 600 mg/m² Q3W × 4 cycles
Surgery
Pembro 200 mg Q3W × 9 cycles[1]
± RT[2]
Safety and Survival Follow-up
Arm 2
Placebo (Q3W × 4 cycles) + carboplatin (AUC 5 Q3W × 4 cycles or AUC 1.5 × 4 cycles) + paclitaxel 80 mg/m² QW × 4 cycles
↓
Placebo (Q3W × 4 cycles) + doxorubicin (60 mg/m² [or epirubicin 90 mg/m²) + cyclophosphamide 600 mg/m² Q3W × 4 cycles
Surgery
Placebo Q3W × 9 cycles[1]

Primary Endpoint: pcR

- Pathological Complete response (pcR)
  - Defined as no residual invasive cancer tissue in resected specimen and all sampled regional lymph nodes
    - Pathological stage ypT0-Tis yp N0

Primary Endpoint: EFS

- Event-Free Survival
  - disease progression that precluded surgery,
  - local or distant recurrence,
  - occurrence of a second primary cancer
  - Death from any cause

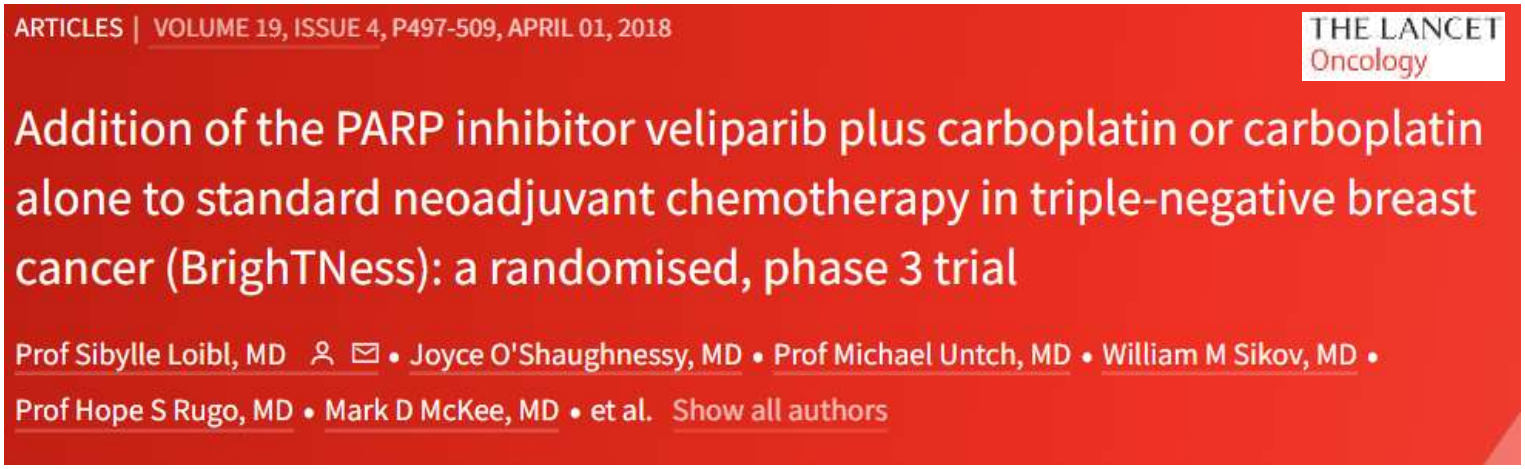


Estimated event-free survival at 36 mo	84.5%	76.8%

HR for event or death, 0.63; 95% CI, 0.48–0.82; P<0.001

Pembrolizumab + BrighTNess

- Treatment regimen adopted in Manitoba: pembrolizumab in combination with BrighTNess protocol chemotherapy



- BrighTNess regimen received provincial funding in March 2021

4 cycles of CARBOplatin q 3 weeks plus PACLitaxel weekly (21 day cycle)

4 cycles of dose dense AC – DOXOrubicin + cyclophosphamide (14 day cycle)

Pembrolizumab + BrighTNess

- Challenge: scheduling pembrolizumab q 21 days with q 14 day chemotherapy

- Extended dosing interval for pembrolizumab: every 42 day administration
  - allows for pembrolizumab treatment to align with chemotherapy treatment days

- Schedule can be quite confusing – pembrolizumab administered only on *specific cycles*
  - Cycles 1 and 3 during Phase 1 (CARBOplatin + PACLitaxel)
  - Cycles 1 and 4 during Phase 2 (dose dense AC)

Dosing Schema from RRO

	Phase 1 – Cycle 1 (21-day cycle)				Phase 1 – Cycle 2 (21-day cycle)				Phase 1 – Cycle 3 (21-day cycle)				Phase 1 – Cycle 4 (21-day cycle)			
	Day	1	8	15	Day	1	8	15	Day	1	8	15	Day	1	8	15
pembrolizumab																
PACLitaxel																
CARBOplatin																

	Phase 2 – Cycle 1 (14-day cycle)			Phase 2 – Cycle 2 (14-day cycle)			Phase 2 – Cycle 3 (14-day cycle)			Phase 2 – Cycle 4 (14-day cycle)			Phase 3 – Cycles 1 to 5 (42-day cycle)						
	Day	1	8	Day	1	8	Day	1	8	Day	1	8	Day	1	8	15	22	29	36
pembrolizumab																			
DOXOrubicin																			
cyclophosphamide																			

Key:

Indicates that *pembrolizumab* will be administered on this day

Indicates that *chemotherapy* will be administered on this day

Toxicity

- Over 80% of patients experienced at least one grade 3 or higher adverse event

Overlapping toxicity profile can make determination of the causative agent quite challenging

- Pembrolizumab has extended dosing interval and potential for delayed onset of immune related adverse events
  - toxicity may not have temporal relationship with most recent cycle

Table 2. Adverse Events in the Combined Neoadjuvant and Adjuvant Phases (As-Treated Population).*

Event	Pembrolizumab–Chemotherapy (N=783)		Placebo–Chemotherapy (N=389)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any adverse event	777 (99.2)	645 (82.4)	389 (100)	306 (78.7)
Treatment-related adverse event†	774 (98.9)	604 (77.1)	388 (99.7)	285 (73.3)
Nausea	495 (63.2)	27 (3.4)	245 (63.0)	6 (1.5)
Alopecia	471 (60.2)	0	220 (56.6)	0
Anemia	429 (54.8)	141 (18.0)	215 (55.3)	58 (14.9)
Neutropenia	367 (46.9)	270 (34.5)	185 (47.6)	130 (33.4)
Fatigue	330 (42.1)	28 (3.6)	151 (38.8)	6 (1.5)
Diarrhea	238 (30.4)	20 (2.6)	98 (25.2)	5 (1.3)
Alanine aminotransferase increased	204 (26.1)	43 (5.5)	98 (25.2)	9 (2.3)
Vomiting	200 (25.5)	19 (2.4)	86 (22.1)	6 (1.5)
Asthenia	198 (25.3)	28 (3.6)	102 (26.2)	9 (2.3)
Rash	196 (25.0)	12 (1.5)	66 (17.0)	1 (0.3)
Constipation	188 (24.0)	0	85 (21.9)	0
Neutrophil count decreased	185 (23.6)	146 (18.6)	112 (28.8)	90 (23.1)
Aspartate aminotransferase increased	157 (20.1)	20 (2.6)	63 (16.2)	1 (0.3)
Peripheral neuropathy	154 (19.7)	15 (1.9)	84 (21.6)	4 (1.0)
Immune-mediated adverse event‡	262 (33.5)	101 (12.9)	44 (11.3)	4 (1.0)
Hypothyroidism	118 (15.1)	4 (0.5)	22 (5.7)	0
Severe skin reaction	45 (5.7)	37 (4.7)	4 (1.0)	1 (0.3)
Hyperthyroidism	41 (5.2)	2 (0.3)	7 (1.8)	0
Adrenal insufficiency	20 (2.6)	8 (1.0)	0	0
Pneumonitis	17 (2.2)	7 (0.9)	6 (1.5)	2 (0.5)
Thyroiditis	16 (2.0)	2 (0.3)	5 (1.3)	0
Hypophysitis	15 (1.9)	10 (1.3)	1 (0.3)	0

Infusion Related Reactions

PACLitaxel:

- approximately 4-10% (1-2% severe)

CARBOplatin

- Frequency increases after repeated administration. Significant increase after 6 doses (from < 1% to 6.5% and higher)

Immune checkpoint inhibitors

- Highest incidence with avelumab (25%)
- Pembrolizumab – Generally considered uncommon (less than 10%) but have been reported in clinical trials

Dermatologic Toxicity

Cutaneous reactions can be caused by both taxanes and immune checkpoint inhibitors

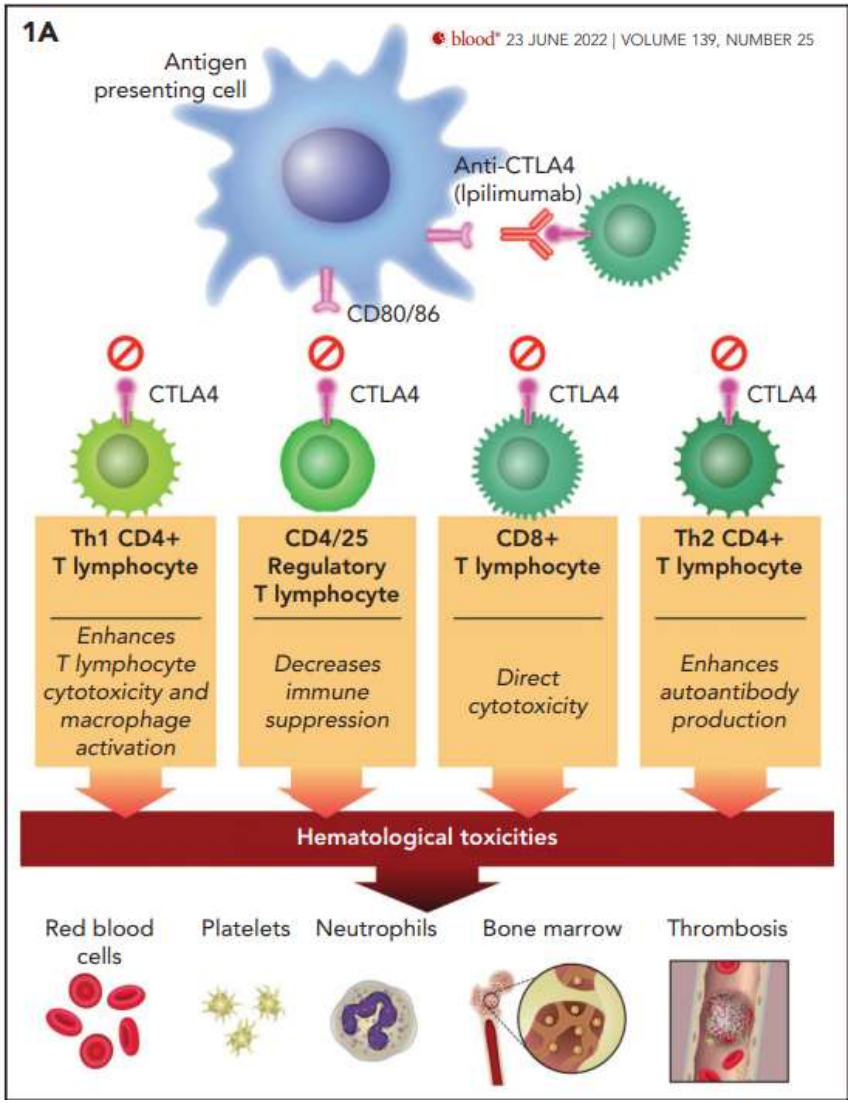
- Maculopapular reactions
- Pruritis
- alopecia
- Onycholysis
- Delayed infusion reactions

Hematologic toxicity

- Generally associated with cytotoxic chemotherapy

- Immune-related hematologic toxicity
  - Rare, but adverse events reported in literature include neutropenia, ITP, hemolytic anemia, Hemophagocytic lymphohistocytosis (HLH), cytopenia, thrombosis

  - 2019 study examined 5923 patients from 19 clinical trials, estimated the hematologic irAE rate to be 3.6% (all grades)



Pembro + BrighTNess takeaways

Complicated treatment schedule

Local experience has demonstrated higher than expected toxicity rates

Collaboration between health care teams is essential to optimize success of treatment

- Surgical oncology has requested morning cortisol and thyroid levels to be ordered prior to the end of Phase 2 to evaluate for preoperative endocrine abnormalities

Neoadjuvant treatment of NSCLC

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 26, 2022 VOL. 386 NO. 21

Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer

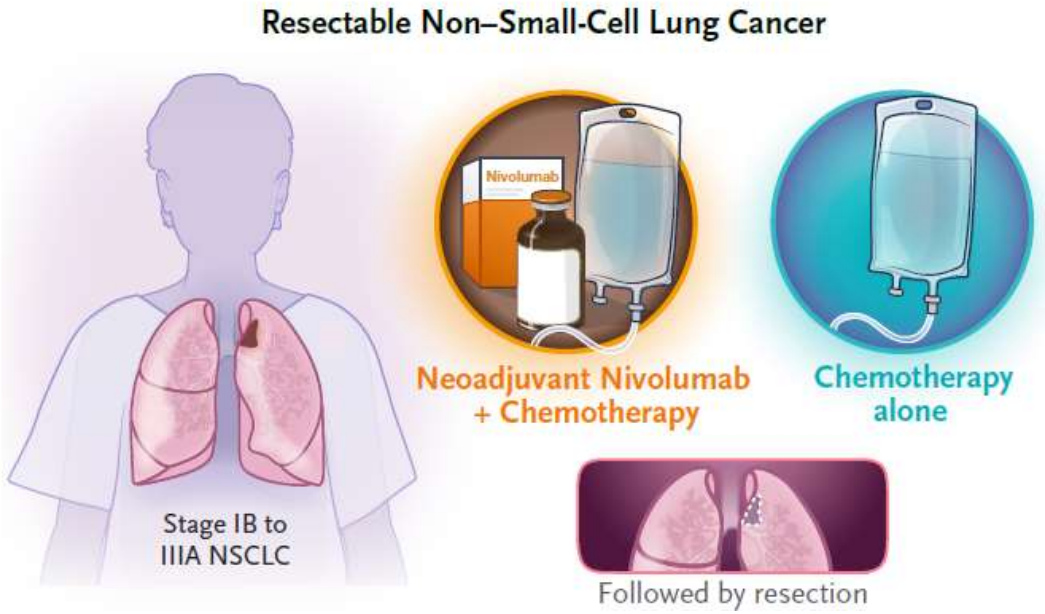
P.M. Forde, J. Spicer, S. Lu, M. Provencio, T. Mitsudomi, M.M. Awad, E. Felip, S.R. Broderick, J.R. Brahmer, S.J. Swanson, K. Kerr, C. Wang, T.-E. Ciuleanu, G.B. Saylors, F. Tanaka, H. Ito, K.-N. Chen, M. Liberman, E.E. Vokes, J.M. Taube, C. Dorange, J. Cai, J. Fiore, A. Jarkowski, D. Balli, M. Sausen, D. Pandya, C.Y. Calvet, and N. Girard, for the CheckMate 816 Investigators*

CheckMate 816

- Phase 3 randomized controlled trial
- Open label (no placebo)
- Stage IB to IIIA (7th edition AJCC; differences from current 8th edition)
  - Health Canada approval: Tumor ≥4 cm or node positive

- 358 patients were randomized to receive either:
  - nivolumab 360 mg every 3 weeks in combination with a platinum doublet for 3 cycles
  - Platinum doublet for 3 cycles,

  followed by surgery



Platinum doublet options based on Histology

Squamous

- nivolumab + gemcitabine+ CISplatin
- nivolumab + gemcitabine + CARBOplatin

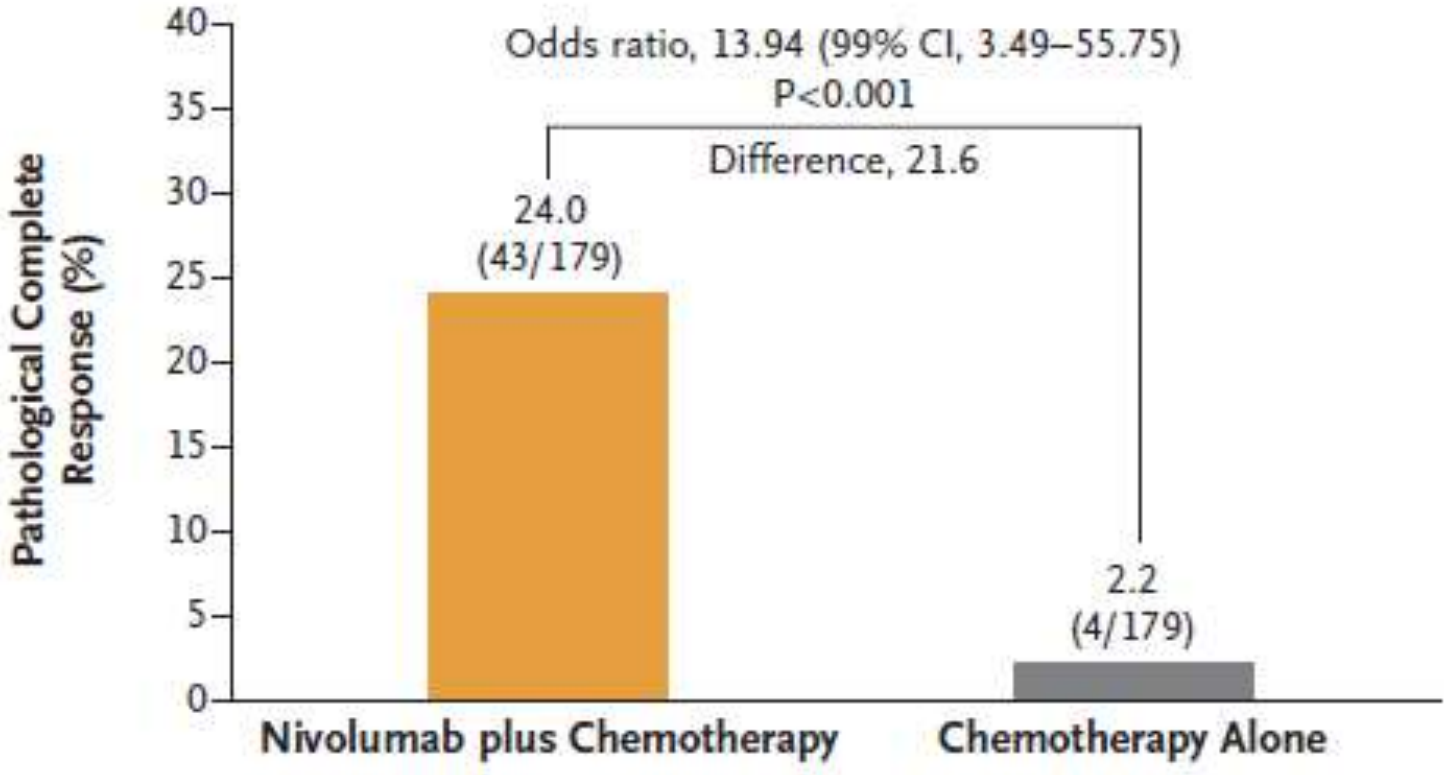
Non-Squamous

- nivolumab + PEMEtrexed + CISplatin
- nivolumab + PEMEtrexed + CARBOplatin

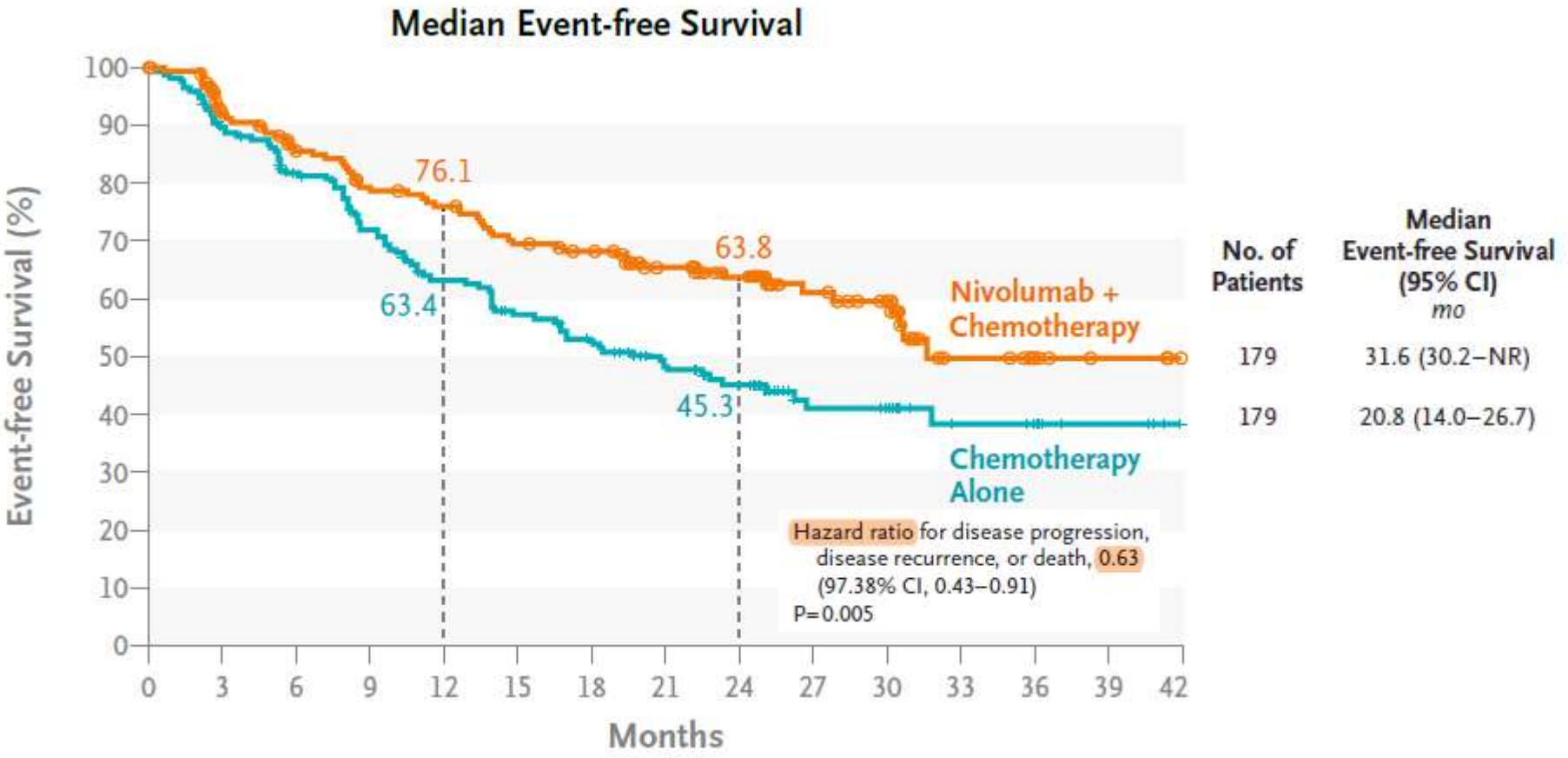
All Histologies

- nivolumab + PACLitaxel + CARBOplatin

Primary Endpoint: Pathological Complete Response (pCR)



Primary Endpoint: Event-Free Survival



Takeaways from CM816

Very new – access program opened in September 2022

- Only one patient enrolled as of November 2022, but expect more patients in the upcoming months

Only 3 cycles of immune checkpoint inhibitor therapy

- Patients can receive adjuvant chemotherapy after surgery if clinically appropriate, but nivolumab does not continue in the adjuvant setting

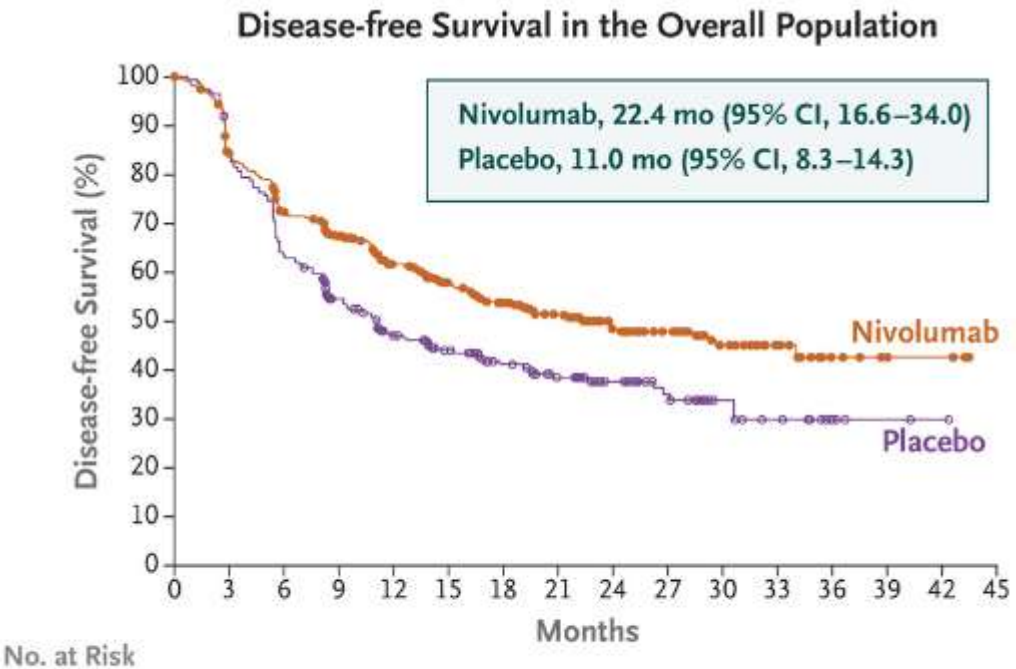
Control arm was neoadjuvant chemotherapy - not a standard of care in Manitoba

- More challenging to evaluate benefit of treatment

Adjuvant update

Esophageal cancer: Checkmate 577

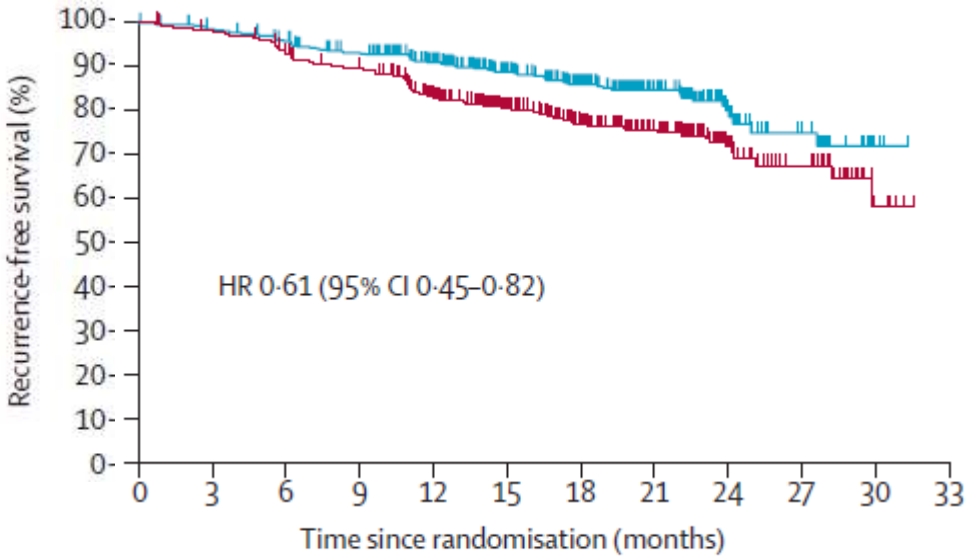
- Patients with completely resected (R0) esophageal or gastroesophageal cancer, received prior neoadjuvant chemoradiation and had residual disease
- 1 year of adjuvant nivolumab or placebo
- Dosing schedule: 3 mg/kg (max 240 mg) q 14 days for 8 doses (cycles 1 to 4, day 1 + 15) followed by 6 mg/kg (max 480 mg) q 28 days for 9 doses (cycles 5-13)
- Improved Disease-free Survival
- Provincially funded as of October 21, 2022 (previously prescribed through access program)



Adjuvant Update

Stage IIB/IIC melanoma: KeyNote 716

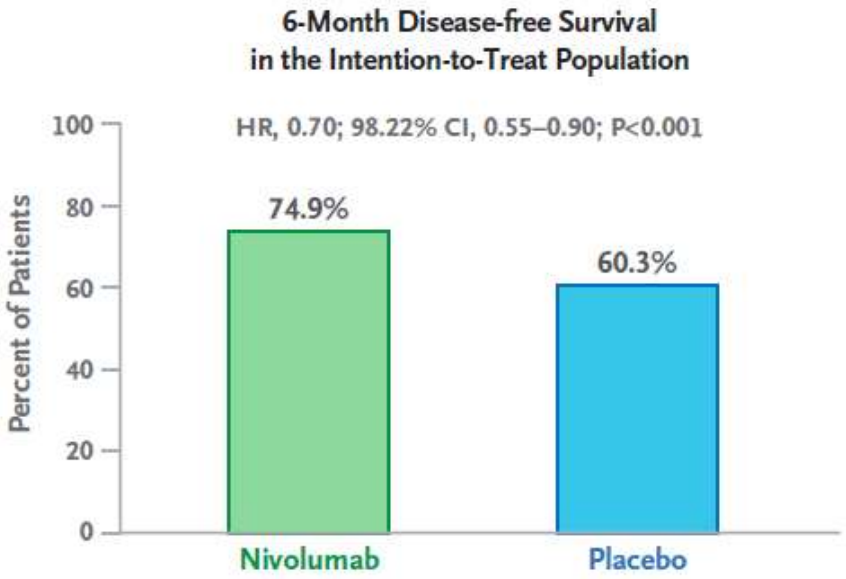
- Newly diagnosed, completely resected, high risk Stage IIB/IIC melanoma
- 1 year of adjuvant pembrolizumab 200 mg or placebo q 21 days
- Estimated recurrence free survival at 18 months: 86% with pembrolizumab, 77% with placebo
- Available through manufacturer access program



Adjuvant Update

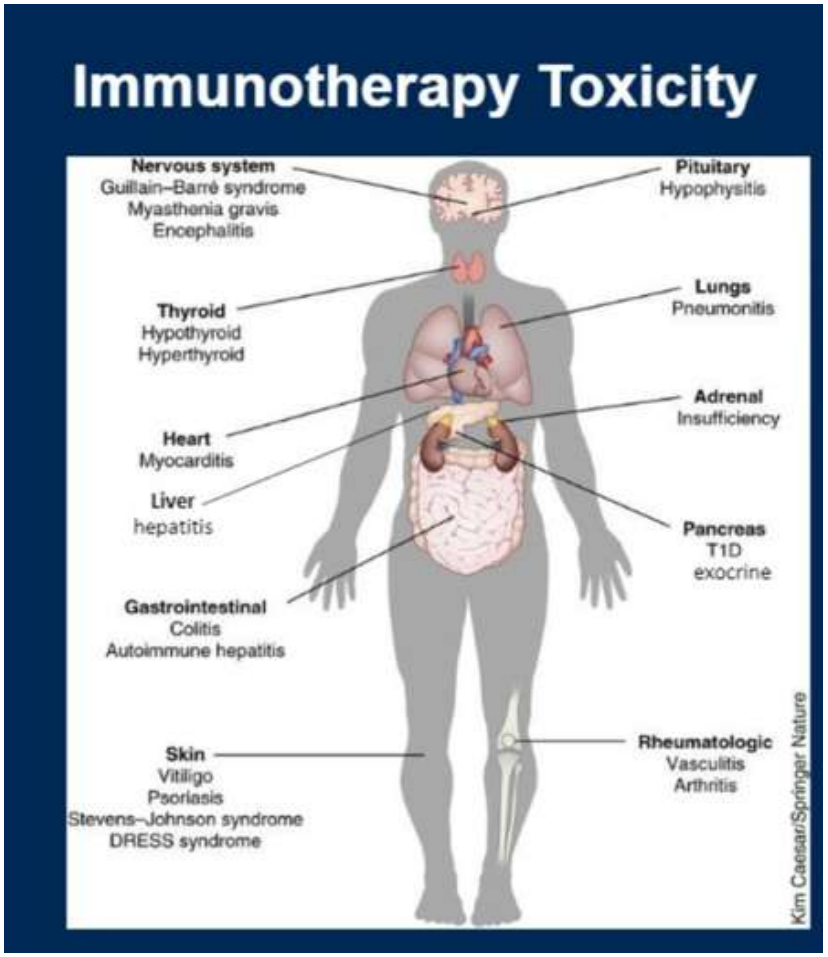
Urothelial Carcinoma: Checkmate 274

- Muscle invasive urothelial carcinoma at high risk of recurrence, after radical resection
- 1 year of nivolumab or placebo
- Improved Disease Free Survival
- Available through manufacturer access program



Disease-free Survival	Nivolumab	Placebo
Median disease-free survival in ITT sample	20.8 months (95% CI, 16.5–27.6)	10.8 months (95% CI, 8.3–13.9)

Immune Related Adverse Events



ASCO GU 2020: Challenging Clinical Scenarios in the Management of Renal Cell Carcinoma: Rechallenge with ICI Following Immune-Related Adverse Events (urotoday.com)

Case 1:

- Mr. DV is a 70 year old with unresectable adenocarcinoma of the colon on pembrolizumab every 3 weeks. He comes in prior to his 4th cycle.

PMH: Type 2 diabetes, HTN, BPH, OA

- Apart from the occasional headache he feels well. He uses a walker to get around, but has required one for the last couple of years.
- You review recent bloodwork

Case 1: Mr. DV

Labs:

CBC – unremarkable

Na 134 (N 135-147)

K 4.8 (N 3.5-5.1)

Cl 97 (N 97-106)

CO2 25 (N22-30)

Urea 6 (N 2.8-7.1)

Creat 94 (N 44-106)

TSH 0.25 (N 0.4-4.2)

Question 1

You note that his TSH is low at 0.25. What would you like to do next.

a) He's mildly hyperthyroid. As he's asymptomatic, I will wait and see what his repeat TSH is at the next visit.

b) He's hyperthyroid and should start treatment

c) I would like to know what his T4 is.

Case 1: Mr. DV

TSH - 0.25 (N 0.4-4.2)

T4 - 6 (N 9.7 -27.5)

T3 - 1.6 (N 3.7-6.9)

You also obtain:

Cortisol 485 (N am 140-690, pm 80-440)

ACTH 15.6 (N 0-10)

Question 2

On review of the TSH, T4 and T3 you diagnose him with

a) Hyperthyroidism
b) Hypothyroidism
c) I may need to review this with my friendly neighborhood endocrinolgist

Case 1: Mr. DV

- Given the low TSH along with a low T3 and T4 there is concern this represents a central hypothyroidsm.
- You speak with endocrinology. They state it is possible this is a central hypothyroidism, but it may also represent an evolving thyroiditis.
- Given his age, it is suggested that levothyroxine be started at 25 mcg daily and increased every 4 week by 25 mcg until T4 ~ 20.
- There is no evidence of primary or secondary adrenal insufficiency.

ENDOCRINE TOXICITY

- Symptoms to be vigilant for:
  - new headaches
  - visual changes
  - palpitations
  - diaphoresis
  - fatigue
  - myalgia
  - weight changes
  - dizziness
  - polydipsia &polyuria
  - hair loss
  - mood changes
  - Constipation
  - nausea/vomiting
  - abdominal pain
  - cold intolerance

ENDOCRINE TOXICITY

- Pembrolizumab – incidence based on monograph
  - Hypothyroid 8% all grades
  - Hyperthyroid 3.4% all grades
  - Adrenal insufficiency 0.8% all grades
  - Hypophysitis 0.6% all grades
  - Thyroiditis 0.3%
  - Type 1 DM 0.2%

  Safety Data for KEYTRUDA® (pembrolizumab) | HCP (keytrudahcp.com)

- TSH should be checked with each cycle. Test for other endocrine disorders based on symptoms.
- Once an endocrinopathy is diagnosed, most patients are going to require long term treatment.

ENDOCRINE TOXICITY
– PITUITARY HYPOPHYSITIS

- Inflammation of the pituitary
  - Can lead to adrenal insufficiency, hypothyroidism, diabetes insipidus and hypogonadism
- Work-up includes: ACTH, cortisol, TSH, T4, electrolytes. Also consider LH, FSH, testosterone (men), estrogen (females)
- Imaging of the brain with CT or MRI

ENDOCRINE TOXICITY - Treatment

- This depends on the specific diagnosis.
- Things to remember:
  - If both adrenal insufficiency and hypothyroidism are present, treat the adrenal dysfunction first before initiating treatment of the hypothyroidism. Thyroid hormones can increase clearance of the cortisol, thus causing even lower cortisol levels.
  - Don't forget about stress dosing in patients with adrenal insufficiency.
  - Often immunotherapy is held until the patient is stabilized.

Case 1: Mr. DV – 2 weeks later

- You receive a note that Mr. DV was in emergency. He presented with fatigue, generalized weakness, muscle cramping and felt short of breath with activity. His oral intake had been poor.
- He was noted to have a BP 96/67, HR 105, afebrile, O2 sat 100% on RA
- Physical exam was normal, EKG showed NSR and CXR was unremarkable. CBC and a chem 10 were normal.
- He was given fluids and sent home.

Case 1: Mr. DV

- Concerned, you call him. He reports he feels better since the fluids.
- He agrees to go to ER should his symptoms reoccur and you schedule a follow-up in the clinic early next week.

Case 1: Mr. DV – F/U 1 week later

- He comes in for his scheduled follow-up in a wheelchair as he can no longer ambulate independently. He states he has no energy and is generally weak. He has been getting muscle cramps. He has decreased oral intake.
- He is short of breath at rest and has developed a cough. He has noted significant edema to his lower extremities. He denies chest pain or palpitations
- He is not eating or drinking.
- He looks AWFUL!!

Case 1: Mr. DV – 1 week later

ON EXAMINATION

- BP 83/59, HR 103, O2 sat 100% Temp 36.8
- He appears unwell, slumped in his wheelchair, notably short of breath
- His heart sounds are normal, lungs are surprising clear. He is noted to have Gr 3 pitting edema bilaterally. Abdominal exam is normal.

Question 3

You realize that Mr. DV is going to require further work-up and likely admission to hospital. You are concerned this may represent:

a) Pneumonia or other infectious cause
b) PE
c) Pneumonitis related to his immunotherapy
d) CHF
e) All of the above

PNEUMONITIS

- Incidence of ~ 5% (higher in combination vs monotherapy
- Suspect in new or worsening cough, shortness of breath, hypoxia
- Differential diagnosis – PE, infectious, pleural effusion, CHF, COPD, radiation pneumonitis
- Work-up – physical exam, CXR, CT, consider viral studies for respiratory viruses, sputum culture
- Radiologic findings – ground-glass opacities, patchy nodular infiltrates, increased interstitial markings

Table 3. Management of Lung irAEs in Patients Treated With ICPis

3.0 Lung Toxicities	
3.1 Pneumonitis	
Definition: Focal or diffuse inflammation of the lung parenchyma (typically identified on CT imaging) No symptomatic, pathologic, or radiographic features are pathognomonic for pneumonitis	
Diagnostic work-up Should include the following: CXR, CT, pulse oximetry For G2 or higher, may include the following infectious work-up: nasal swab, sputum culture and sensitivity, blood culture and sensitivity, urine culture and sensitivity	
Grading	**Management**
G1: Asymptomatic, confined to one lobe of the lung or < 25% of lung parenchyma, clinical or diagnostic observations only	Hold ICPi with radiographic evidence of pneumonitis progression May offer one repeat CT in 3-4 weeks; in patients who have had baseline testing, may offer a repeat spirometry/DLCO in 3-4 weeks May resume ICPi with radiographic evidence of improvement or resolution. If no improvement, should treat as G2 Monitor patients weekly with history and physical examination and pulse oximetry; may also offer CXR
G2: Symptomatic, involves more than one lobe of the lung or 25%-50% of lung parenchyma, medical intervention indicated, limiting instrumental ADL	Hold ICPi until resolution to G1 or less Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks Consider bronchoscopy with BAL Consider empirical antibiotics Monitor every 3 days with history and physical examination and pulse oximetry, consider CXR; no clinical improvement after 48-72 hours of prednisone, treat as G3
G3: Severe symptoms, hospitalization required, involves all lung lobes or > 50% of lung parenchyma, limiting self-care ADL, oxygen indicated G4: Life-threatening respiratory compromise, urgent intervention indicated (intubation)	Permanently discontinue ICPi Empirical antibiotics; (methyl)prednisolone IV 1-2 mg/kg/d; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks Pulmonary and infectious disease consults if necessary Bronchoscopy with BAL ± transbronchial biopsy Patients should be hospitalized for further management
Additional considerations GI and *Pneumocystis* prophylaxis with PPI and Bactrim may be offered to patients on prolonged corticosteroid use (> 12 weeks), according to institutional guidelines[34-37] Consider calcium and vitamin D supplementation with prolonged corticosteroid use The role of prophylactic fluconazole with prolonged corticosteroid use (> 12 weeks) remains unclear, and physicians should proceed according to institutional guidelines[33] Bronchoscopy + biopsy; if clinical picture is consistent with pneumonitis, no need for biopsy	
All recommendations are expert consensus based, with benefits outweighing harms, and strength of recommendations are moderate.	

Abbreviations: ADL, activities of daily living; BAL, bronchoalveolar lavage; CT, computed tomography; CXR, chest x-ray; DLCO, diffusing capacity of lung for carbon monoxide; G, grade; ICPi, immune checkpoint inhibitor; irAE, immune-related adverse event; IV, intravenous; IVIG, intravenous immunoglobulin; PPI, proton pump inhibitor.

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline | Journal of Clinical Oncology (ascopubs.org)

Case 1: Mr. DV – in hospital

- He is admitted to hospital
- CT chest – no PE, no evidence of pneumonitis
- CT abdomen – evidence of disease progression
- CT head - unremarkable
- EKG – normal
- ECHO – Normal EF > 60%

Case 1: Mr. DV – in hospital

WBC – 9.8

Hg – 99

Plt – 318

Na – 129

K – 3.6

Cl – 92

Creat -89

cor Ca 2.32

Phosphate 0.91

Mg 0.65

cortisol 68 (N am 140-690)

ACTH < 1

LH - 1.7 (N 1.5-15)

FSH – 1.7 (N 9.7-3.8)

testosterone < 0.1

Case 1: Mr. DV

- Results ACTH stimulation:

Cortisol: basal - 77

30 min - 136

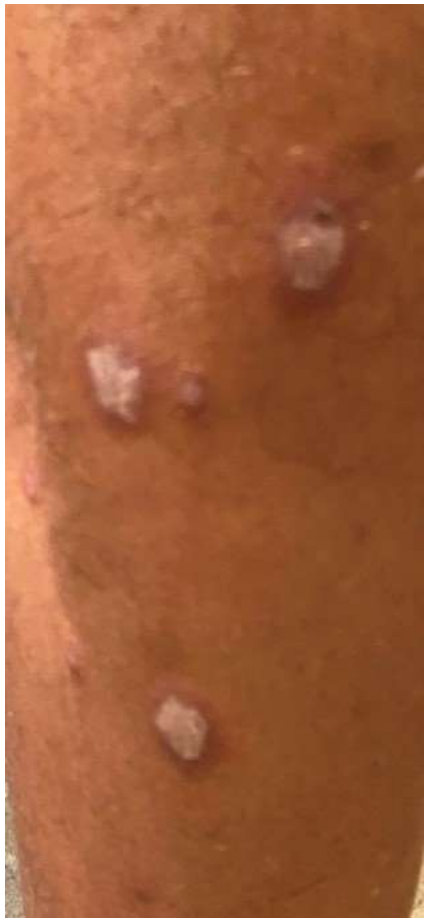
60 min - 189

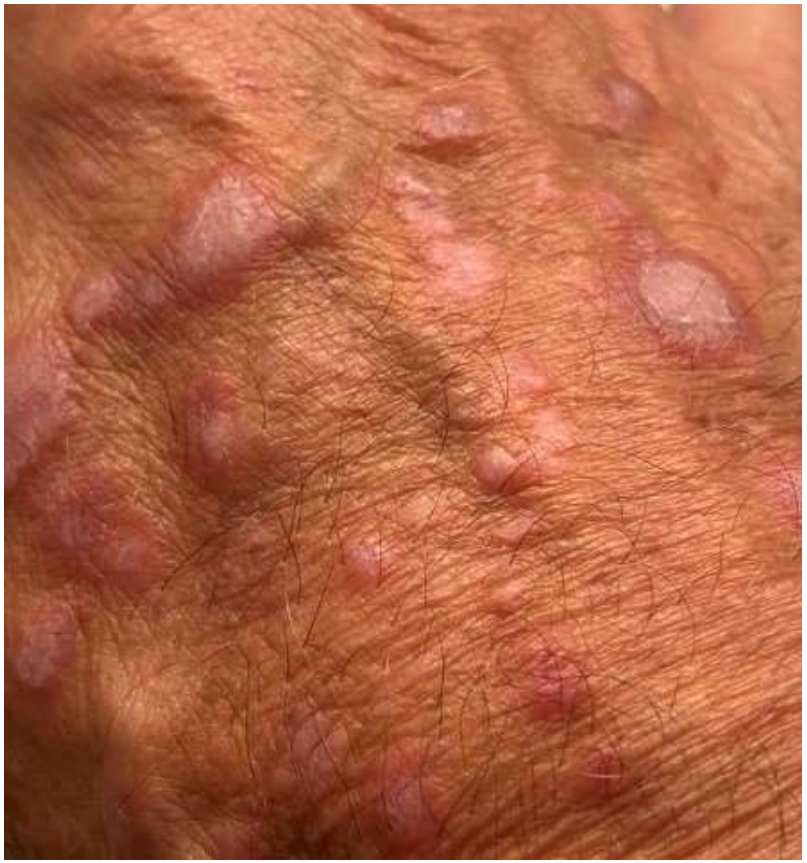
- He was started on prednisone 10 mg am and 5 mg pm as a stress dose. On discharge this was decreased to 5 mg am and 2.5 mg pm.
- You see him in follow-up after he is discharge and is feeling much better. Pembrolizumab is not reinitiated

Case 2 - Mr. LS

- 70 year old with metastatic urothelial carcinoma of the bladder who presents prior to cycle 12 of q 3 week pembrolizumab
- He has had this rash to his hands and feet for 2 months, but recently it has been getting worse.
- It is mildly itchy. He is using an OTC hydrocortisone, but finds it is not beneficial.
- He has a history of rosacea, but otherwise no other significant dermatological issues.

Case 2





Case 2 - Mr. LS

- You speak with dermatology and the differential they provide is

  Lichen planus

  Prurigo

  Hypertrophic lupus erythematous

  Lichen simplex chronicus

SKIN TOXICITY

- 30-50% of patients treated with immunotherapy
- **Inflammatory dermatitis**

- eczematous, psoriasiform, erythema multiforme, lichenoid, morbilliform

- assess for other causes such as infection, drug reaction, cutaneous metastases

- work-up is based on your physical exam. This may include culture, cbc, liver and renal function. Autoimmune work-up if underlying autoimmune condition is suspected.

- if the diagnosis is unclear a skin biopsy should be considered

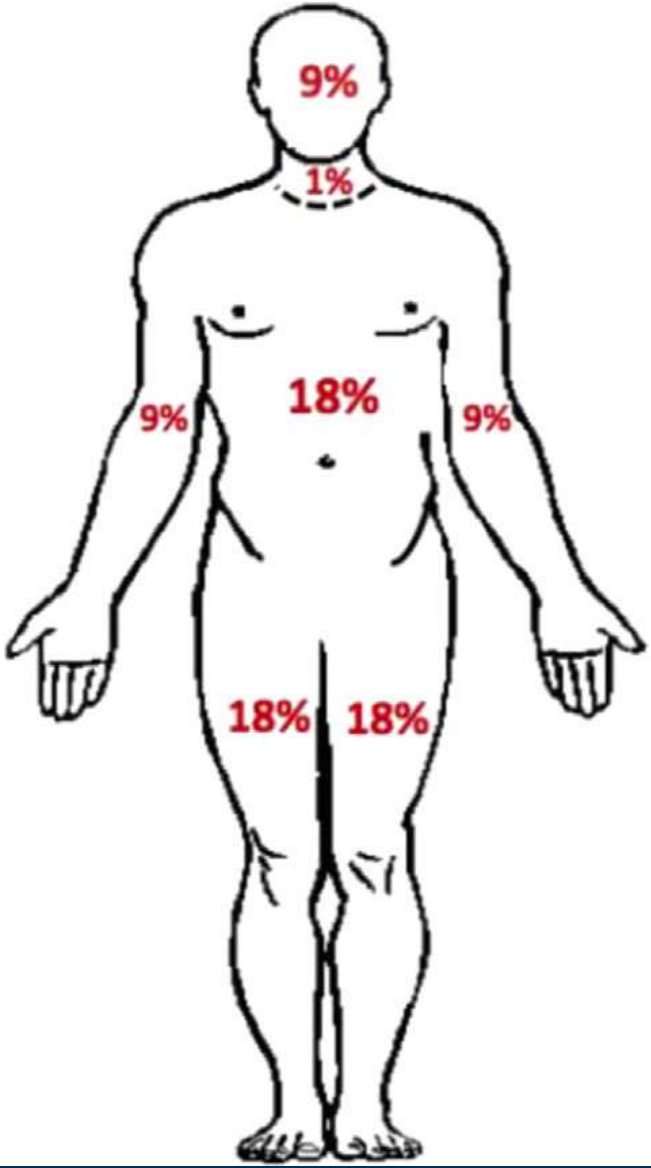
- monitor for progression to severe cutaneous adverse reaction (SJS, TEN, DRESS)

TABLE 1. Cutaneous Toxicities

1.1. Rash or Inflammatory Dermatitis

Workup and evaluation	
Pertinent history and physical examination including examination of the oral mucosa, assessment for blister formation, and assessment of BSA involved. Review full list of patient medications to rule out other drug-induced cause for photosensitivity. Rule out any other etiology of the skin problem, such as an infection, an effect of another drug, including prior or other recent cancer therapies, or a skin condition linked to another systemic disease or unrelated primary skin disorder. Recent or new complete blood count and comprehensive metabolic panel (if needed for skin differential diagnosis). Consider referral to dermatologist if autoimmune skin disease is suspected. Consider skin biopsy. Consider clinical monitoring with use of serial clinical photography.	
Grading (grading according to CTCAE criteria is a challenge for skin. Instead, severity may be based on BSA, tolerability, morbidity, and duration).	**Management**
G1: Rash covering < 10% BSA, which may or may not be associated with symptoms of pruritus or tenderness.	Continue ICPi. Treat with topical emollients and/or mild-moderate potency topical corticosteroids. Counsel patients to avoid skin irritants.
G2: Rash covering 10%-30% BSA with or without symptoms (eg, pruritus, burning, and tightness); limiting instrumental ADL; rash covering > 30% BSA with or without mild symptoms.	Consider holding ICPi and monitor weekly for improvement. If skin toxicity is not improved after 4 weeks, then regrade toxicity as grade 3. In addition, treat with topical emollients, oral antihistamines, and medium-to-high potency topical corticosteroids. Consider initiating prednisone (or equivalent) at dosing 0.5-1 mg/kg, tapering over 4 weeks. In patients with pruritis without rash, consider topical anti-itch remedies (eg, refrigerated menthol and pramoxine).
G3: Rash covering > 30% BSA with moderate or severe symptoms; limiting self-care ADL.	Hold ICPi therapy and consult with dermatology to determine appropriateness of resuming. Treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids. May also consider phototherapy to treat severe pruritus. Initiate oral prednisone or equivalent (1 mg/kg/d) tapering over at least 4 weeks. Once downgraded to ≤ G1 and prednisone (or equivalent) below 10 mg/d, clinicians may consider resuming ICPi therapy with close monitoring and follow-up with dermatology in certain cases such as psoriasis. In patients with pruritis without rash, may treat with gabapentin, pregabalin, aprepitant, or dupilumab.
G4: Severe consequences requiring hospitalization or urgent intervention indicated or life-threatening consequences.	Immediate hold ICPi May admit patient immediately with direct oncology involvement and with an urgent consult by dermatology. Systemic steroids: IV methylprednisolone (or equivalent) dosed at 1-2 mg/kg with slow tapering when the toxicity resolves. Monitor closely for progression to SCAR. Consider alternative antineoplastic therapy over resuming ICPis if the skin irAE does not resolve to ≤ G1. If ICPis are the patient's only option, consider restarting once these side effects have resolved to a G1 level with close dermatology follow-up.

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update | Journal of Clinical Oncology (ascopubs.org)


9%
1%
9%
18%
9%
18%
18%

Case 2 - Mr. LS

- A biopsy is done and pathology is consistent with lichen planus
- He is started on clobetasol 0.05% daily with resolution of his symptoms

Resources:

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY

Updated November 2021

Helpful appendix tables at the end of guideline

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update

J Clin Oncol 39:4073-4126. © 2021 by American Society of Clinical Oncology

TABLE 4. Endocrine Toxicities

4.1. Thyroid

4.1.1. Primary hypothyroidism

Workup and evaluation

- TSH, with the option of also including FT4, can be checked every 4-6 weeks as part of routine clinical monitoring for asymptomatic patients on ICPi therapy.
- TSH and FT4 should be used for case detection in symptomatic patients.
- Low TSH with a low FT4 is consistent with central hypothyroidism. Evaluate as per hypophysitis (see 4.3).
- Commonly develops after thyrotoxicosis phase of thyroiditis (4.1.2).

Grading	Management
G1: TSH > 4.5 and < 10 mIU/L and asymptomatic	Should continue ICPi with monitoring of TSH (option for FT4) every 4-6 weeks as part of routine care.
G2: Moderate symptoms, able to perform ADL. TSH persistently > 10 mIU/L	May continue or hold ICPi until symptoms resolve to baseline. Consider endocrine consultation for unusual clinical presentations, concern for central hypothyroidism, or difficulty titrating hormone therapy. Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist over 10 mIU/L (measured 4 weeks apart).[131,132] Monitor TSH every 6-8 weeks while titrating hormone replacement to goal of TSH within the reference range. FT4 can be used to help interpret ongoing abnormal TSH levels on therapy, as TSH may take longer to normalize. Once adequately treated, repeat testing every 6-12 months or as indicated for a change in symptoms.
G3-4: Severe symptoms, medically significant or life-threatening consequences, unable to perform ADL	Hold ICPi until symptoms resolve to baseline with appropriate supplementation Endocrine consultation to assist with rapid hormone replacement. Hospital admission for developing myxedema (bradycardia, hypothermia, and altered mental status). Inpatient endocrinology consultation can assist with IV levothyroxine dosing, steroids, and supportive care. If there is uncertainty about whether primary or central hypothyroidism is present, hydrocortisone should be given before thyroid hormone is initiated. Myxedema coma is a life-threatening emergency requiring admission and a high level of care. Thyroid supplementation and reassessment as in G2.

Additional considerations

- For patients without risk factors (ie, < 70 years old, not frail, and without cardiac disease or multiple comorbidities), full replacement can be estimated using ideal body weight for a dose of approximately 1.6 mcg/kg/d.
- For those older than age 70 years and/or frail patients with multiple comorbidities (including cardiac disease), consider titrating up from a lower starting dose of 25-50 µg.
- Elevated TSH can be seen in the recovery phase of thyroiditis. In asymptomatic patients with FT4 that remains in the reference range, it is an option to monitor before treating to determine whether there is recovery to normal within 3-4 weeks. Progression or development of symptoms should be treated as per G2.
- Development of a low TSH on therapy suggests overtreatment or recovery of thyroid function and dose should be reduced or discontinued with close follow-up.

TABLE A3. Commonly Conducted Testing at Baseline Before Immune Checkpoint Inhibitor Therapy[a]

Baseline Testing
Clinical
Physical examination including PS, weight, BMI, heart rate and BP, and SPO2
Comprehensive history including autoimmune, organ-specific disease, endocrinopathy, neuropathy, and infectious disease
Comprehensive systems review should be performed with specific attention to bowel habits, respiratory symptoms, skin rash, arthralgias, and neurologic symptoms.
Laboratory
Complete CBC plus DIFF
Complete metabolic panel that may include serum electrolytes (Na, K, Ca, and CO2), liver function (AST, ALT, ALKP, and GGT), creatinine, CK, total bilirubin, and glucose
TSH, free T4
Imaging or other testing
Chest X-ray
CT
ECG

Abbreviations: ALKP, alkaline phosphatase; BMI, body mass index; BP, blood pressure; CK, creatine kinase; CT, computed tomography; DIFF, differential test; GGT, gamma-glutamyl transferase; PS, performance status; TSH, thyroid-stimulating hormone.

[a]Other testing may also be necessary, based on patient's history and pre-existing comorbidities and/or risk factors.

TABLE A4. Commonly Conducted Testing During irAE Management With Steroids[a]

Testing During irAE Management with Steroids
Clinical
Physical examination including blood pressure, weight, heart rate, and SPO2
Assess for presence of infection including oral Candida
Screen for classic symptoms of hyperglycemia or diabetes: polyuria, polydipsia, and weight loss
Eye examination, including assessment of increased intraocular pressure with therapy > 6 weeks
Laboratory
Complete CBC plus DIFF
Complete metabolic panel that may include serum electrolytes (Na, K, Ca, and CO2), liver function (AST, ALT, ALKP, and GGT), creatinine, CK, total bilirubin, and glucose
Imaging
Bone mineral density (during prolonged therapy)

Abbreviations: ALKP, alkaline phosphatase; CK, creatine kinase; DIFF, differential test; GGT, gamma-glutamyl transferase; irAE, immune-related adverse event.

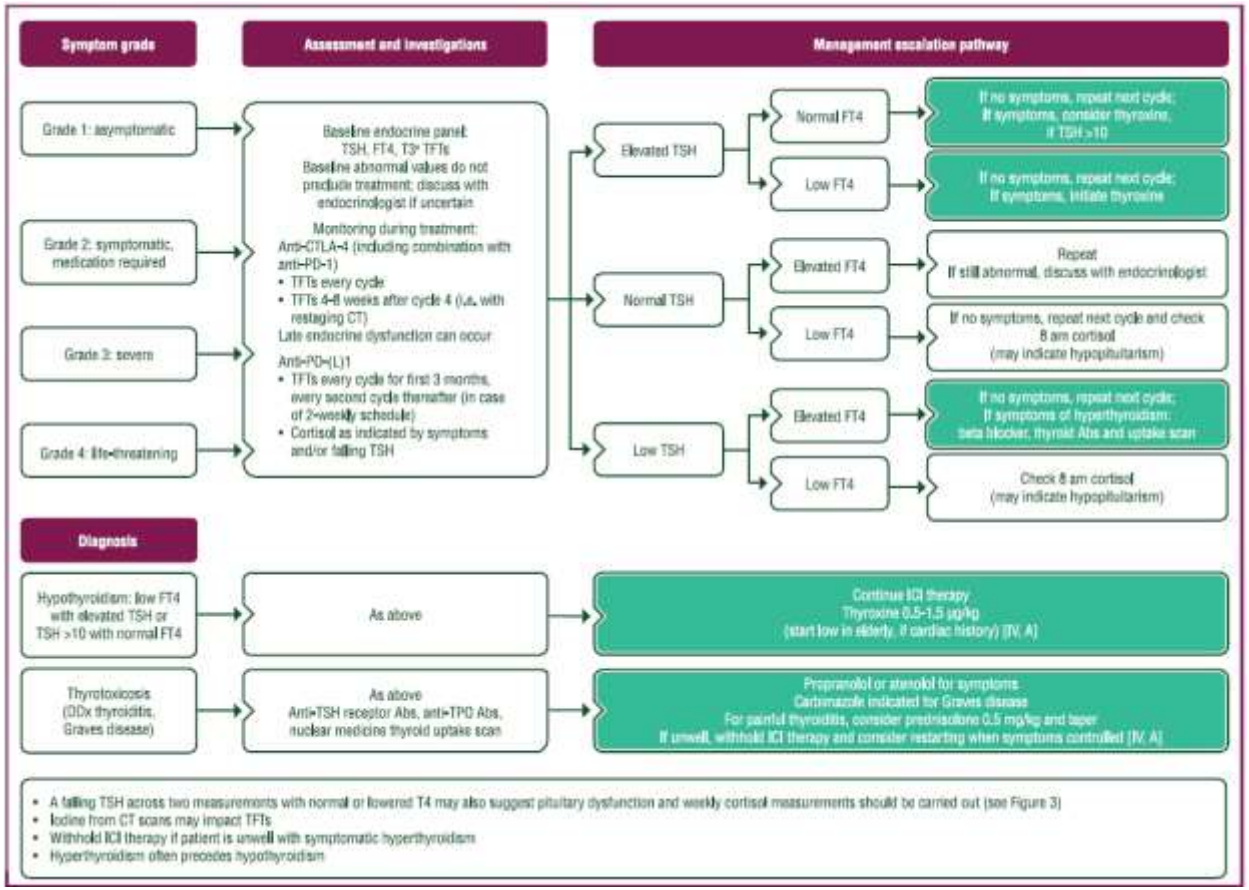
[a]Other testing may also be necessary, based on patient's history and pre-existing comorbidities and/or risk factors.

Resources: ESMO

updated October 2022

Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

ANNALS OF ONCOLOGY



Resources:

Updated June 2021

comprehensive recommendations

No visual tables/chart

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events

Brahmer JR, *et al. J Immunother Cancer* 2021;**9**:e002435.

Hypothyroidism and hyperthyroidism

Hypothyroidism and hyperthyroidism are frequently asymptomatic or exhibit ambiguous symptoms, necessitating routine monitoring of parameters such as TSH and total T3/fT4 levels.[222–224] Hypothyroidism is the more common of the two toxicities, occurring in about 8% of patients receiving anti-PD-(L)1 therapy, 3% of patients receiving anti-CTLA-4 therapy, and 15% of patients receiving combination ICI therapy. Grade ≥3 hypothyroidism is rare, occurring in roughly 0%–2% of patients receiving combination ICI therapies.[4] The standard of care for the treatment of hypothyroidism is levothyroxine.[225]

Hyperthyroidism occurs less frequently, in 5% of patients treated with anti-PD-(L)1 inhibitors and 4% of patients treated with anti-CTLA-4 inhibitors.[4] Rarely, ICI therapy may lead to Graves' disease.[226] Symptoms of elevated thyroid hormone may also appear transiently and evolve into hypothyroidism[215] as a result of patients experiencing thyrotoxicosis during the course of thyroiditis, due to the destruction of thyroid follicles and necrosis.[227] Hypothyroidism frequently occurs following this transient hyperthyroidism, as a sequela of ongoing thyroiditis—roughly 90% of patients who develop thyrotoxicosis do not recover full thyroid function, requiring long-term levothyroxine replacement. The median time to thyrotoxicosis is 5 weeks, and the median time to hypothyroidism is 10 weeks.[215]

Hypothyroidism and hyperthyroidism

- Thyroid function (TSH, fT4) should be tested every 4–6 weeks during ICI treatment, and should continue to be tested every 6–12 months following the conclusion of ICI treatment.
- Patients with elevated TSH and normal fT4 should receive repeat TSH and fT4 testing routinely, and if this pattern persists without hypothyroidism symptoms then levothyroxine treatment should be considered. Levothyroxine should be administered to patients with hypothyroidism at 1.5–1.6 µg/kg/day for young, healthy patients, and should be administered at 25 or 50 µg/day for patients >65 years of age or with heart disease.
- Patients with symptoms of hypothyroidism and/or with elevated TSH and low fT4 should be tested for morning cortisol to identify possible concurrent adrenal insufficiency.
- Patients with low TSH and normal fT4 should receive repeat TSH and fT4 testing routinely, and if symptoms of hyperthyroidism or high fT4 develop patients should be treated with beta-blockers. Patients with asthma or chronic obstructive pulmonary disease should be treated with cardioselective beta-blockers such as atenolol or metoprolol.
- Patients with persistently low TSH and high fT4 should be evaluated for hyperthyroidism and Graves' disease etiology.

Resources:

SCIMMUNE protocol – revised February 2022

Toxicity grading chart

BC Cancer Protocol Summary for Management of Immune-Mediated Adverse Reactions to Checkpoint Inhibitor Immunotherapy

Protocol Code *SCIMMUNE*

Endocrine: Hypothyroidism

Monitoring

Extreme tiredness, weight gain, mood or behaviour changes (e.g., decreased libido, confusion, forgetfulness), dizziness or fainting, hair loss, feeling cold, constipation, hoarseness

Grade 1 (Asymptomatic TSH elevation or mild symptoms)	• Physician notified and collaborative symptom management initiated • **Continue checkpoint inhibitors** • If TSH greater than 2 x ULN, or consistently out of range in 2 subsequent measurements: include free T4 at subsequent cycles as clinically indicated	

Grade 2 (Symptomatic TSH elevation, moderate symptoms)	• Physician notified and collaborative symptom management initiated
	• **Consider withholding checkpoint inhibitors**
	• Endocrinology consultation
	• Initiate/adjust thyroid hormone replacement therapy (e.g., levothyroxine):
	  ○ Usual: 1 to 1.8 mcg/kg/day PO
	  ○ Elderly or cardiac disease: start with 12.5 to 25 mcg/day PO, then slowly titrate up
		Continue standard monitoring

Grade 3 or 4 (Severe or potentially life threatening symptoms of TSH elevation, limiting self-care ADLs)	• Physician notified and collaborative symptom management initiated
	• **Withhold checkpoint inhibitors**
	• Endocrinology consultation (urgent if myxedema coma)
	• Initiate/adjust thyroid hormone replacement (see above)
	• If myxedema coma:
	  ○ ICU admission
	  ○ Hydrocortisone 100 mg q8h IV until adrenal insufficiency ruled out
		Continue standard monitoring

Grading System of Immune-Related Adverse Events Associated with Checkpoint Immunotherapy

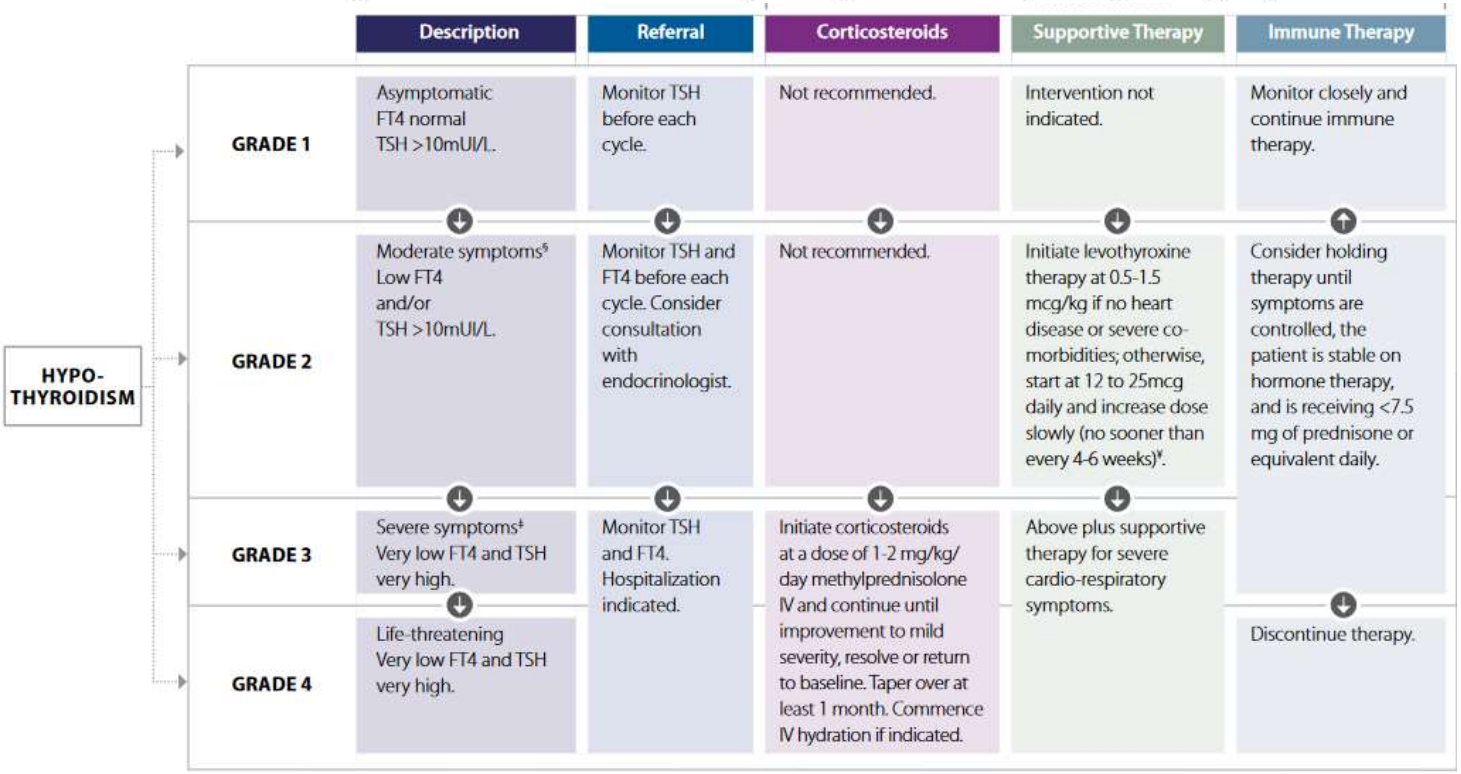
Immune-Related Adverse Events	Grade 1	Grade 2	Grade 3	Grade 4
Pneumonitis	Asymptomatic, radiographic changes only	Mild to moderate symptoms, worsens from baseline	Severe symptoms, respiratory compromise requiring oxygen	Potentially life-threatening symptoms, respiratory compromise requiring oxygen and/or urgent intervention
Enterocolitis	Diarrhea of less than 4 stools per day over baseline; asymptomatic colitis	Diarrhea of 4 to 6 stools per day over baseline, limiting instrumental ADL, abdominal pain, mucus or blood in stool.	Diarrhea of 7 or more stools per day over baseline, incontinence, ileus, fever, limiting self-care ADLs; colitis with severe abdominal pain, hospitalization indicated	life-threatening colitis, perforation
Hepatitis		ALT (or AST) 3 to 5 X ULN or Total bilirubin 1.5 to 3 X ULN	ALT (or AST) more than 5 X ULN or Total bilirubin more than 3 X ULN	ALT (or AST) increases ≥50% baseline and lasts ≥1 week in patients with liver metastasis who begin treatment with Grade 2 elevation of ALT (or AST)
Nephritis	Creatinine >1 - 1.5 x ULN	Creatinine >1.5 - 3.0 x ULN	Creatinine >3.0 - 6.0 x ULN	Creatinine >6.0 x ULN, life-threatening consequences, dialysis indicated
Hypothyroidism	Asymptomatic TSH elevation or mild symptoms	Symptomatic TSH elevation, moderate symptoms	Severe symptoms of TSH elevation	Potentially life threatening symptoms of TSH elevation
Hyperthyroidism	Asymptomatic or mild symptoms of TSH suppression	Moderate symptoms of TSH suppression	Severe symptoms of TSH suppression	Potentially life threatening symptoms of TSH suppression
Hypophysitis	Asymptomatic or mild symptoms	Moderate symptoms	Severe symptoms	Life-threatening symptoms
Adrenal Insufficiency	Asymptomatic or mild symptoms	Moderate symptoms	Suspicion of adrenal crisis (e.g., severe dehydration, hypotension, shock out of	

Immune-Related Adverse Events	Grade 1	Grade 2	Grade 3	Grade 4
Skin Toxicities	Rash covering 30% of skin surface or less, with or without associated symptoms (pruritus, etc.)		Rash covering more than 30% of skin surface, moderate to severe symptoms, limiting self-care ADL, life-threatening	
Neurologic Toxicities	Mild motor and/or sensory neuropathy, no interference with ADL	Moderate symptoms, limiting instrumental ADL	Limiting self-care ADL Severe motor or sensory neuropathy, (e.g., Guillain-Barré syndrome, myasthenia gravis, encephalitis, aseptic meningitis, transverse myelitis)	

Resources: Cancer Care Ontario

FIGURE 3
Management of Immune-Related Hypothyroidism[4,6,10,14,21]

Background: Around 5-10% of patients receiving CLTA-4 and anti-PD-1/PD-L1 antibodies are likely to develop an endocrine adverse event of any grade. Hypothyroidism was reported in approximately 2% of patients treated with ipilimumab, and 8.3% of patients treated with PD-1 inhibitors. Time of onset for hypothyroidism ranged from 0.7 weeks to 19 months. Hypothyroidism is diagnosed if TSH level is increased with a low free T4 level. When thyroid replacement is given, dose adjustments should occur no sooner than 4-6 weeks. An endocrinologist should be consulted with the exception of grade 1 or uncomplicated grade 2 hypothyroidism.



Resources:

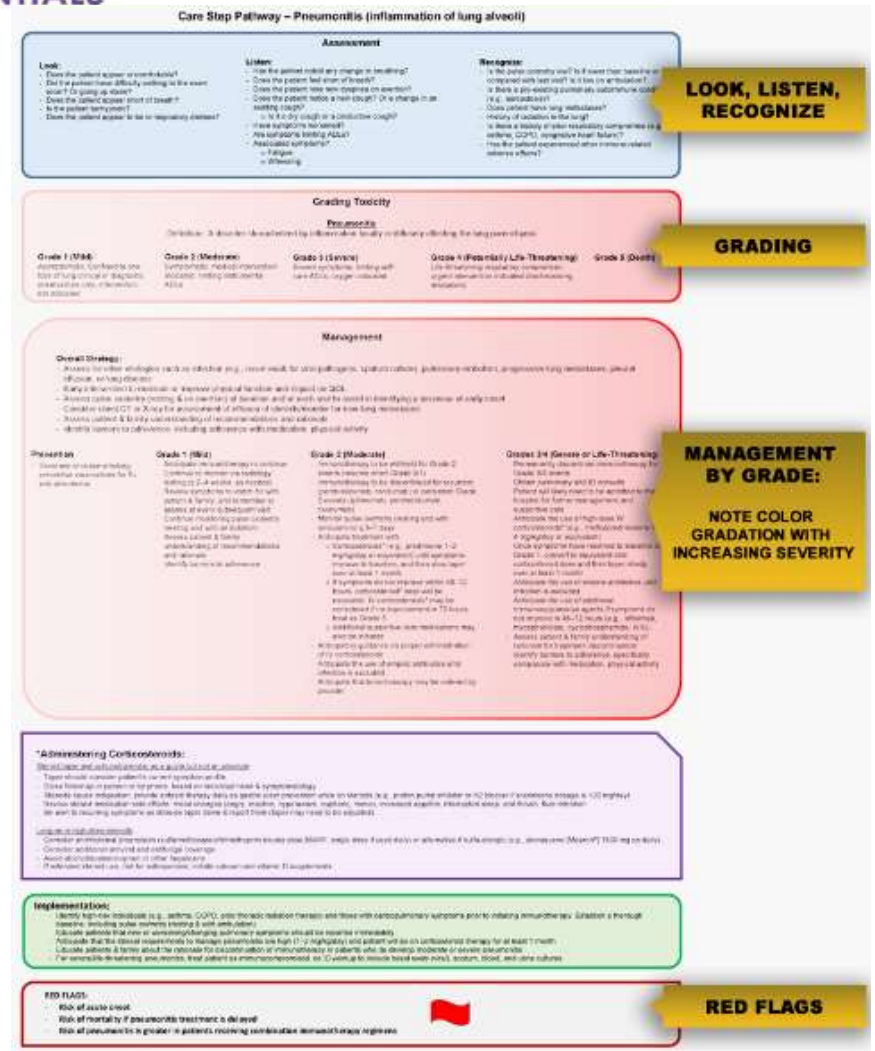
AIM WITH IMMUNOTHERAPY FOUNDATION | IMMUNO-ONCOLOGY ESSENTIALS

https://aimwithimmunotherapy.org/

Regional Content Customized for Canada

This page contains IO Essentials resources that have been customized for use by the Canadian healthcare professional.

- **Skin Toxicities** – View Online
- **Gastrointestinal Toxicities** (Diarrhea and Colitis)
- **Thyroiditis** – View Online
- **Hepatitis** – View Online
- **Hypophysitis** – View Online
- **Adrenal Insufficiency, primary** – View Online
- **Diabetes** – View Online
- **Pneumonitis** – View Online
- **Arthralgia/Arthritis** – View Online
- **Mucositis/Xerostomia** – View Online
- **Neuropathy** – View Online
- **Nephritis** – View Online



Take Home Messages

- Neoadjuvant immune checkpoint inhibitor therapy is a rapidly developing field
  - requires collaboration with multiple health care teams
  - Toxicity diagnosis and management is important to ensure patients can undergo surgery in a timely matter
- Immune related toxicities can affect multiple organ systems.
- Have a high level of suspicion that any new symptoms are treatment related.

References

1. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. *N Engl J Med*. 2020;382(9):810-821. doi:10.1056/NEJMoa1910549
2. Schmid P, Cortes J, Dent R, et al. Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer. *N Engl J Med*. 2022;386(6):556-567. doi:10.1056/NEJMoa2112651
3. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. *N Engl J Med*. 2022;386(21):1973-1985. doi:10.1056/NEJMoa2202170
4. Topalian SL, Taube JM, Pardoll DM. Neoadjuvant checkpoint blockade for cancer immunotherapy. Science. 2020;367(6477):eaax0182. doi:10.1126/science.aax0182
5. Byrd DR, Brierley JD, Baker TP, Sullivan DC, Gress DM. Current and future cancer staging after neoadjuvant treatment for solid tumors. CA Cancer J Clin. 2021;71(2):140-148. doi:10.3322/caac.21640
6. Haine AI, Notenboom CMAW, Tan LVP, Ruiter R, van der Deure WM. Ranitidine and the incidence of hypersensitivity reactions to paclitaxel: A retrospective cohort study. Pharmacol Res Perspect. 2022;10(4):e00985. doi:10.1002/prp2.985
7. Tai YH, Tai YJ, Hsu HC, et al. Risk Factors of Hypersensitivity to Carboplatin in Patients with Gynecologic Malignancies. Front Pharmacol. 2017;8:800. Published 2017 Nov 6. doi:10.3389/fphar.2017.00800
8. Schneider BJ, Naidoo J, Santomasso BD, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update [published correction appears in J Clin Oncol. 2022 Jan 20;40(3):315]. J Clin Oncol. 2021;39(36):4073-4126. doi:10.1200/JCO.21.01440
9. Aoyama Y, Ueda T, Kuradome Y, et al. Hypersensitivity Reaction to Carboplatin in Gynecologic Cancer: A Case Report and a Review of the Literature. J UOEH. 2021;43(1):81-86. doi:10.7888/juoeh.43.81
10. Michot JM, Lazarovici J, Tieu A, et al. Haematological immune-related adverse events with immune checkpoint inhibitors, how to manage?. Eur J Cancer. 2019;122:72-90. doi:10.1016/j.ejca.2019.07.014
11. Kroll MH, Rojas-Hernandez C, Yee C. Hematologic complications of immune checkpoint inhibitors. Blood. 2022;139(25):3594-3604. doi:10.1182/blood.2020009016
12. Davis EJ, Salem JE, Young A, et al. Hematologic Complications of Immune Checkpoint Inhibitors. Oncologist. 2019;24(5):584-588. doi:10.1634/theoncologist.2018-0574
13. Cercek A, Lumish M, Sinopoli J, et al. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. N Engl J Med. 2022;386(25):2363-2376. doi:10.1056/NEJMoa2201445
14. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. N Engl J Med. 2021;384(13):1191-1203. doi:10.1056/NEJMoa2032125
15. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma [published correction appears in N Engl J Med. 2021 Aug 26;385(9):864]. N Engl J Med. 2021;384(22):2102-2114. doi:10.1056/NEJMoa2034442
16. Luke JJ, Rutkowski P, Queirolo P, et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial. Lancet. 2022;399(10336):1718-1729. doi:10.1016/S0140-6736(22)00562-1
17. DOI: 10.1200/JCO.21.01440 Journal of Clinical Oncology 39, no. 36 (December 20, 2021) 4073-4126.
18. https://doi.org/10.1016/j.annonc.2022.10.001
19. Brahmer JR, Abu-Sbeih H, Ascierto PA, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer. 2021;9(6):e002435. doi:10.1136/jitc-2021-002435
20. van den Ende T, Menting SP, Ambarus CA, van Oijen MGH, van Laarhoven HWM. Cutaneous Toxicity After Chemoradiotherapy and PD-L1 Inhibition in Two Patients with Esophageal Adenocarcinoma: More than Meets the Eye. Oncologist. 2019;24(4):e149-e153. doi:10.1634/theoncologist.2018-0674
21. Soh J, Hamada A, Fujino T, Mitsudomi T. Perioperative Therapy for Non-Small Cell Lung Cancer with Immune Checkpoint Inhibitors. Cancers. 2021; 13(16):4035. https://doi.org/10.3390/cancers13164035