IMMUNOTHERAPY IN CANCER

WHAT DOES A FAMILY DOCTOR NEED TO KNOW?

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Physician Lead - Oncology Clinical Research Department

Northeastern Ontario Regional Systemic Therapy Lead

CONFLICTS OF INTEREST

- Paid Presenter – Ribbon Program – Treating Ovarian Cancer Sept. 2018 - **Novartis Pharmaceuticals**
- Paid Presenter– Journal Club – Sept. 2018 - **Astra Zeneca**
- Paid Presenter – Tissue sparing algorithm for metastatic NSCLC Feb. 2018 – **EMD Serono Oncology**
- Paid Presenter – Topics in Lung Cancer - Dec. 2017 - **Merck Oncology**
- Paid Presenter – Topics in Breast Cancer - May 2017 - **Merck Oncology**
- Consultant - Targeting BRCA-Mutated Solid Tumours: Ovarian Cancer Nov. 2017 - **FUSE Health**
- Advisory Board – Updates in Treating Prostate Cancer - Feb. 2016 **Astellas Oncology**

PHYSICIAN LEAD - ONCOLOGY CLINICAL RESEARCH DEPARTMENT

- **BREVITY –** June 2019 - present
- **CCTG ME.13 (STOP-GAP)** January 2019 - present
- **NRG-BR003** National Research Group June 2018 – Sept. 2019
- **ReACT TC2** May 2018 – present
- **CCTG MAC.20/A011401 -** November 2017 - present
- **COMPLEEMENT-1** May 2017 – present. **Novartis**
- **BI 1199.93** - June 2016 – present. **Boehringer Ingelheim**
- **BMS CA209451** –June 2016 – present. **Bristoll Myers Squibb**
- **DCARE** - June 2016 – Sept. 2019. **Amgen**
- **CCTG - MAC.4** June 2016 - present
- **CCTG - MA.32** June 2016 – present

OBJECTIVES/PLAN

- What IS immunotherapy?
  - Mechanism of action
- What immunotherapy ISN'T?
  - Not CAR-T, not cytotoxic chemotherapy
  - ?A 'miracle' drug for all cancer types
- Side effects – expected and unexpected
- **Practical questions – MD Inquiries**
  - Immunotherapy side effects and steroid use
  - Influenza vaccines
  - COVID-19 risk in patients on immunotherapy
  - COVID-19 vaccine

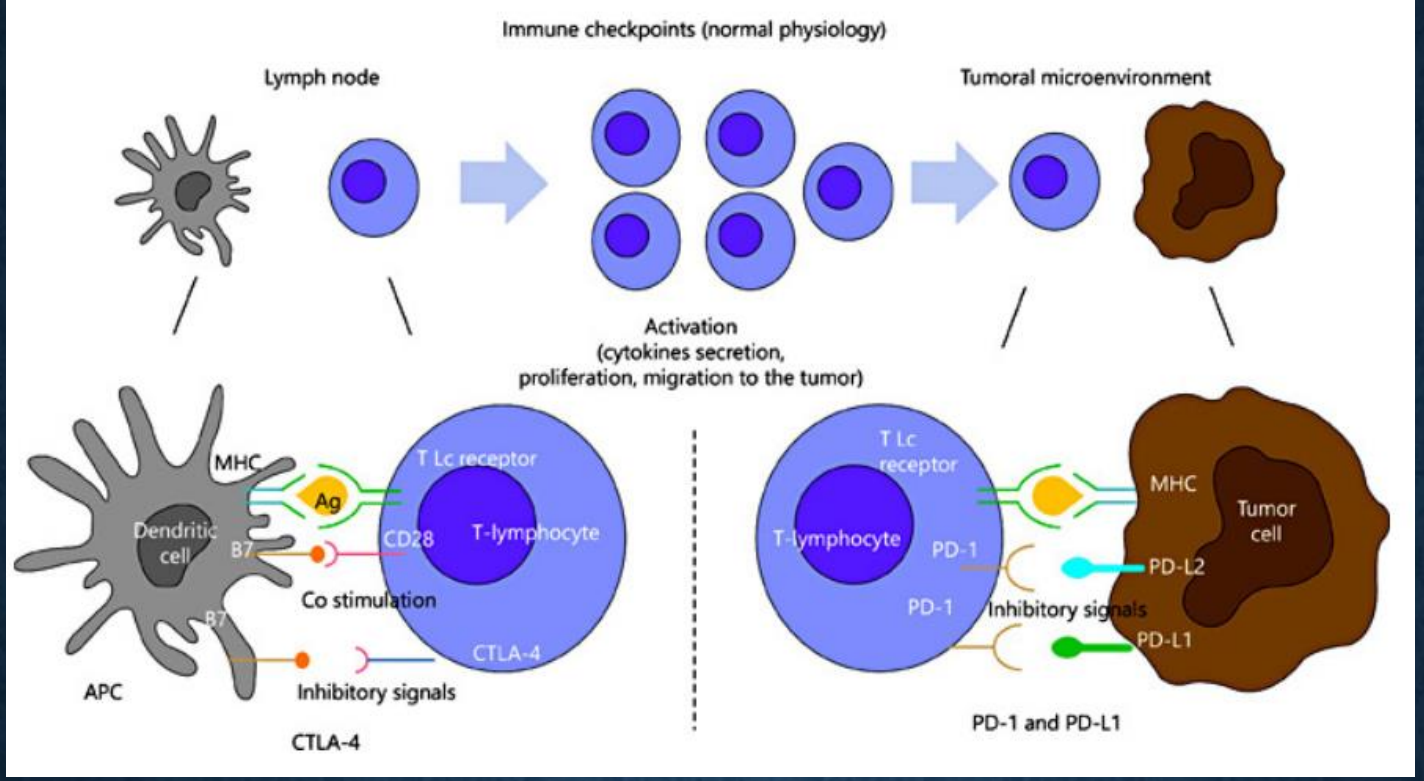
WHAT YOU REALLY NEED TO KNOW

1. Immunotherapy is not a set of miracle drugs. They have fewer S/E than traditional chemotherapy, but when side effects happen – they can be very serious.

2. Avoid prescribing steroids (it can 'turn off' immunotherapy) unless the patient is having a serious reaction. Then know where to find the best resources and employ steroids.

3. It's best to ensure your patient has approval from their treating oncologist before vaccinating (influenza, covid-19) but in almost all circumstances (except possibly one) – it appears safe to offer vaccines

CTLA-4 inhibitors
- Ipilimumab
- Tremelimumab



PD1/PDL1 inhibitors
- **PD1**
  - Nivolumab
  - Pembrolizumab
- **PDL1**
  - Atezolizumab
  - Durvalumab
  - Avelumab

CTLA-4 inhibitors prevent CTLA-4 from binding B7, leading to sustained activity of the T cell

Lifting the foot OFF of the BRAKES

PD1/PDL1 inhibitors bind the PD1 molecule, preventing interaction with PDL1/2 leading to continued T-cell stimulation

Pressing on the ACCELERATOR

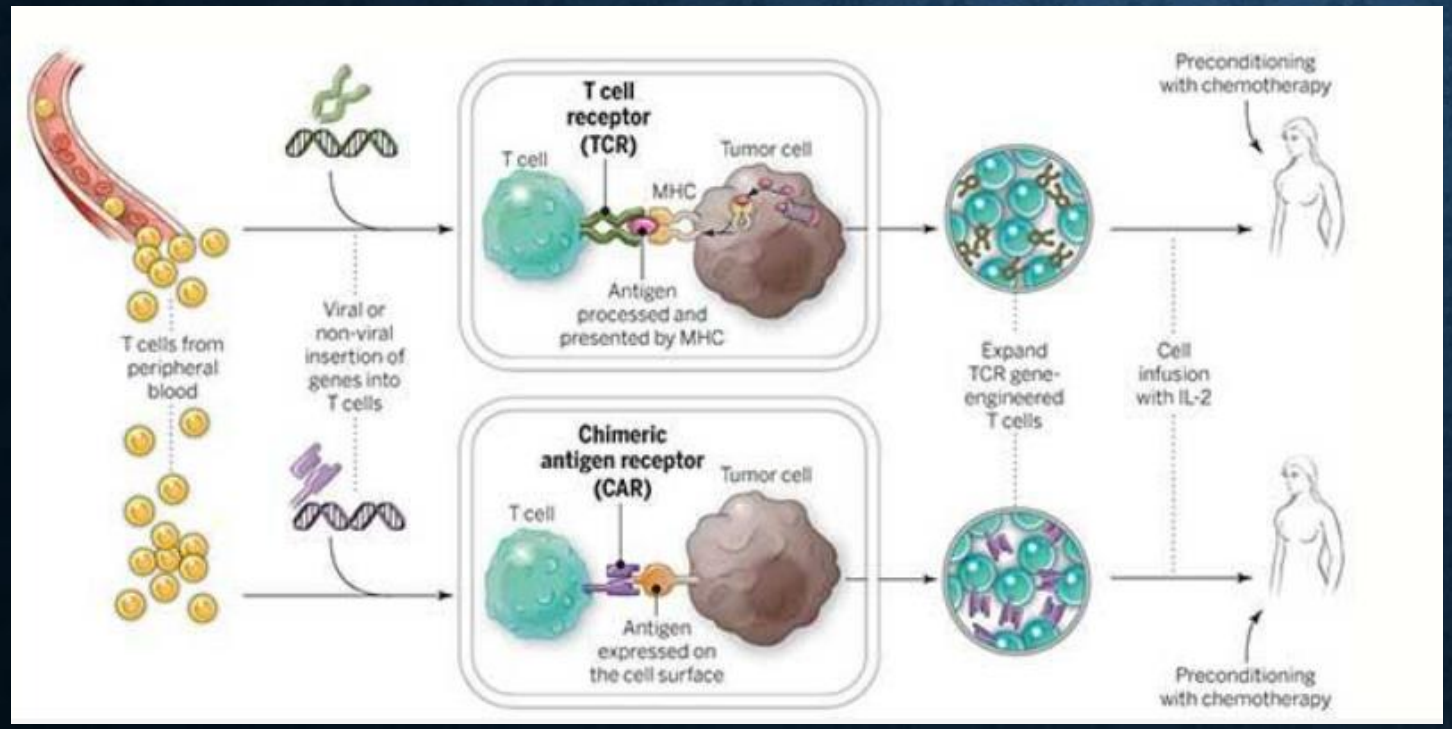
Wanchoo et al. Adverse Renal Effects of Immune Checkpoint Inhibitors: A Narrative Review. Am J Nephrol 2017;45:160-169. doi: 10.1159/000455014

EFFECTIVELY UNLEASHING THE IMMUNE SYSTEM*

*The hounds have little focus. The immune system can attack anything it deems ‘foreign’ in this agitated state

IMMUNOTHERAPY IS NOT CAR-T*

- *At least for the purposes of this talk
- Currently approved for selected lymphomas and leukemia



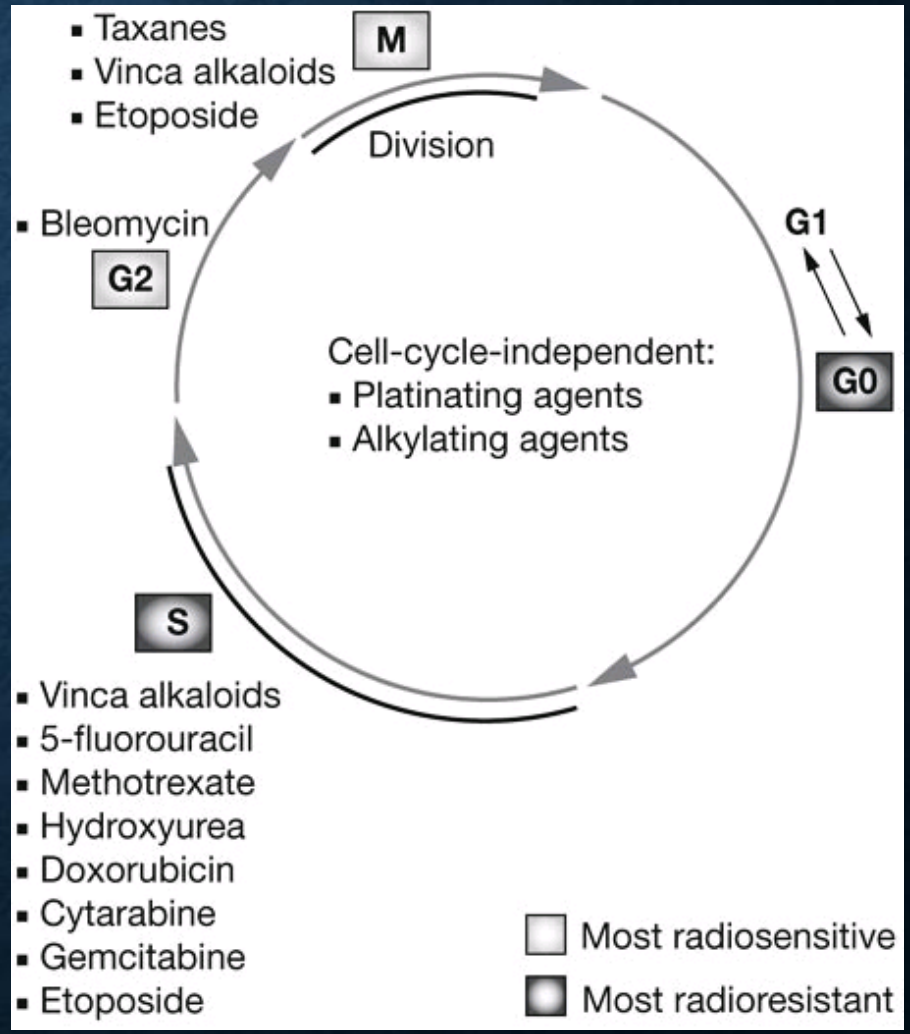
https://www.cancer.gov/about-cancer/treatment/research/car-t-cells

- Patient's own T cells are collected
- T cells are modified with proteins used to recognize malignant cells
- T cells re-infused into patient to proliferate and destroy cancer 'targets'

IMMUNOTHERAPY IS NOT TRADITIONAL CHEMOTHERAPY

- Traditional chemotherapy (cytotoxic chemo) acts directly on cancer cells to inhibit tumor growth or cause death
  - Usually by interrupting DNA synthesis, replication, and repair or inhibiting cell division

Both tumor cells and normally dividing cells are affected



Hanna et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *Journal of Clinical Oncology*. 22(9):1589–1597.

ESSENTIALLY…YOU'RE SENDING OUT 'DOGS TO SEARCH AND DESTROY'

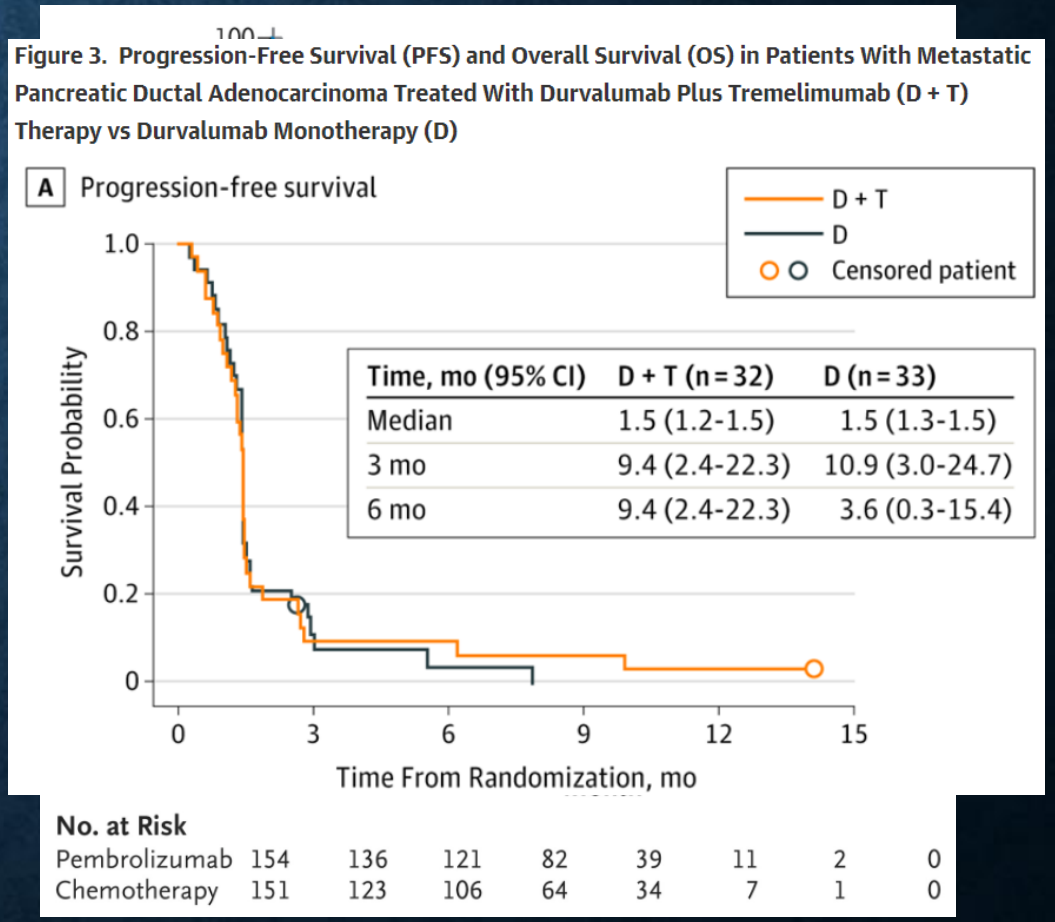
- **CAR-T:** Give the dogs the scent of the person/persons we are targeting. Maximizes chances of sparing innocent bystanders and focuses our dogs.

- **Immunotherapy:** Give dogs the scent of 'vanilla'. Any person wearing vanilla (even if this is the favoured scent of our targets) will be killed. Raises the significant possibility of endangering innocent bystanders although causes less mayhem than below.

- **Chemotherapy:** Give them no scent and let them loose. Dogs will chase after and kill without discrimination

IS IMMUNOTHERAPY A MIRACLE CURE?

- In selected patients – it works better than chemotherapy (e.g. 1st line NSCLC, PDL≥50%)
- Known to be effective in MANY disease sites:
  - Melanoma, RCC, NSCLC, SCLC, TNBC, HL, H&N, bladder ca, Merkel cell ca etc.
- Works less well for other disease sites
  - E.g. Pancreatic ca

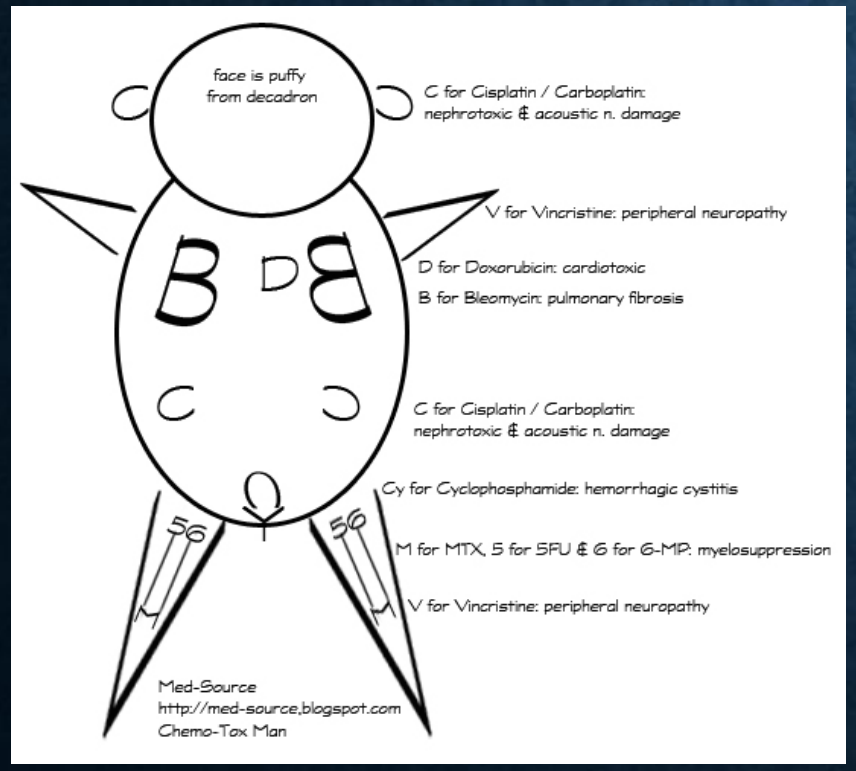


Reck et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. N Engl J Med 2016; 375:1823-1833

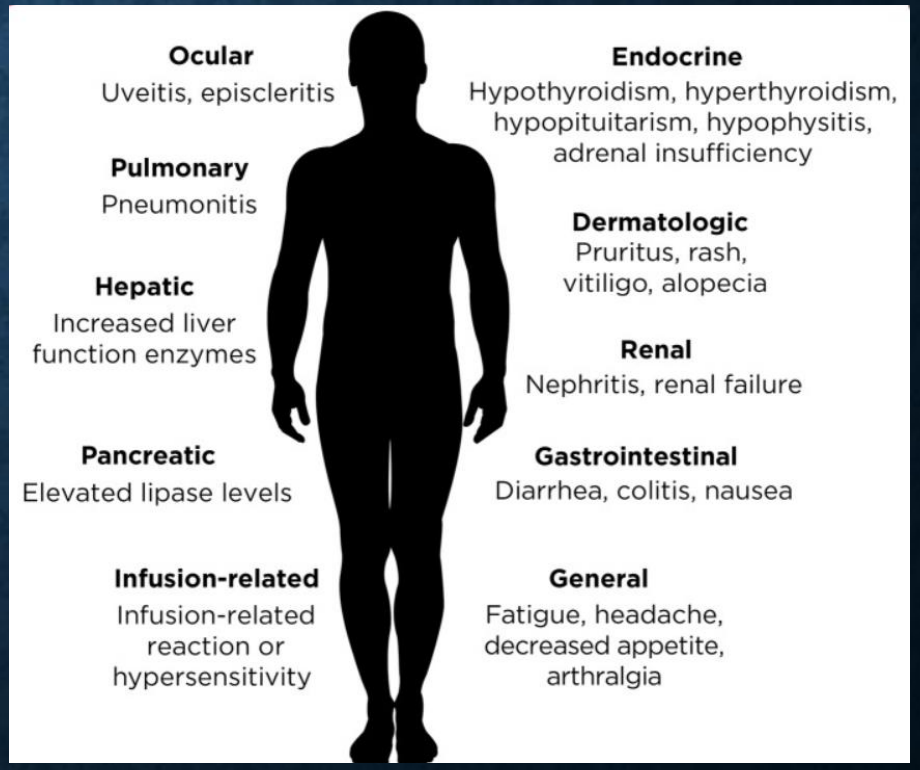
O'Reilly et al.. Durvalumab With or Without Tremelimumab for Patients With Metastatic Pancreatic Ductal Adenocarcinoma: A Phase 2 Randomized Clinical Trial. *JAMA Oncol.* 2019;5(10):1431–1438.

DIFFERENT EFFICACY, SAME SIDE EFFECTS?

Cytotoxic Chemotherapy

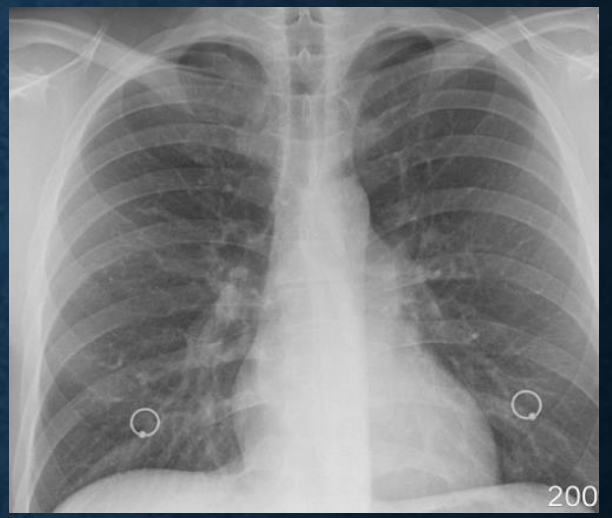


Immunotherapy "ITIS"



Kreamer KM. Immune Checkpoint Blockade: A New Paradigm in Treating Advanced Cancer. *J Adv Pract Oncol*. 2014;5(6):418-431.

IMMUNE RELATED ADVERSE EVENTS



- Fatigue - 16-24%, usually mild
- Rash – early, maculopapular rash, vitiligo
- Pruritus
- Diarrhea/Colitis – Grade ¾ colitis 1-2%
- Hepatotoxicity – rare but increased rates with combination immunotherapy
- Endocrinopathies – hypophysitis, autoimmune thyroid disease, adrenal insufficiency
- Pneumonitis - ~3%

Naidoo et al Ann Oncol 2015;26(12)2315

DIFFERENT EFFICACY SAME CHANCE OF DEVELOPING SIDE EFFECTS?

and treatment-related adverse events of any grade were less frequent (occurring in 73.4% vs. 90.0% of patients), as were grade 3, 4, or 5 treatment-related adverse events (26.6% vs. 53.3%).

- Chemotherapy vs single agent PD1/PDL1 inhibitor – immunotherapy with 50% of the severe adverse events

- Varies GREATLY with respect to DUAL immunotherapy (+ipilimumab or tremelimumab), baseline autoimmune condition etc.

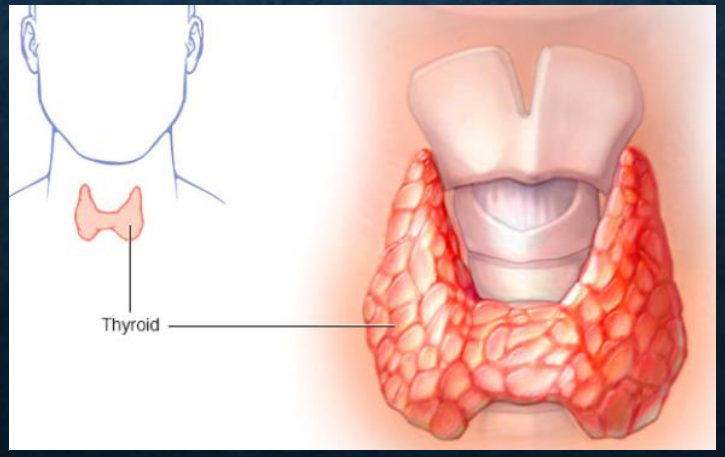
Table 3. Adverse Events in the As-Treated Population.*

Adverse Event	Pembrolizumab Group (N=154)		Chemotherapy Group (N=150)	
	Any Grade	Grade 3, 4, or 5	Any Grade	Grade 3, 4, or 5
	number of patients (percent)			
Treatment-related†				
Any	113 (73.4)	41 (26.6)	135 (90.0)	80 (53.3)
Serious	33 (21.4)	29 (18.8)	31 (20.7)	29 (19.3)
Led to discontinuation	11 (7.1)	8 (5.2)	16 (10.7)	9 (6.0)
Led to death	1 (0.6)	1 (0.6)	3 (2.0)	3 (2.0)
Occurred in ≥10% of patients in either group‡				
Nausea	15 (9.7)	0	65 (43.3)	3 (2.0)
Anemia	8 (5.2)	3 (1.9)	66 (44.0)	29 (19.3)
Fatigue	16 (10.4)	2 (1.3)	43 (28.7)	5 (3.3)
Decreased appetite	14 (9.1)	0	39 (26.0)	4 (2.7)
Diarrhea	22 (14.3)	6 (3.9)	20 (13.3)	2 (1.3)
Neutropenia	1 (0.6)	0	34 (22.7)	20 (13.3)
Vomiting	4 (2.6)	1 (0.6)	30 (20.0)	1 (0.7)
Pyrexia	16 (10.4)	0	8 (5.3)	0
Constipation	6 (3.9)	0	17 (11.3)	0
Stomatitis	4 (2.6)	0	18 (12.0)	2 (1.3)
Decreased neutrophil count	0	0	20 (13.3)	6 (4.0)
Increased blood creatinine level	3 (1.9)	0	15 (10.0)	1 (0.7)
Decreased platelet count	0	0	18 (12.0)	9 (6.0)
Thrombocytopenia	0	0	17 (11.3)	8 (5.3)
Decreased white-cell count	1 (0.6)	0	16 (10.7)	3 (2.0)
Dysgeusia	1 (0.6)	0	15 (10.0)	0
Immune-mediated§				
Any	45 (29.2)	15 (9.7)	7 (4.7)	1 (0.7)
Hypothyroidism	14 (9.1)	0	2 (1.3)	0
Hyperthyroidism	12 (7.8)	0	2 (1.3)	0
Pneumonitis	9 (5.8)	4 (2.6)	1 (0.7)	1 (0.7)

Reck et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. N Engl J Med 2016; 375:1823-1833

FAMILY MD INQUIRY #1

- "Hi Lacey,
  - Our mutual patient Mrs. S has stage IV Melanoma and is receiving immunotherapy from your team
  - I've noticed her TSH is 18 (elevated).
  - I was wondering if I should start her on thyroid replacement?"



ENDOCRINOPATHIES AND IMMUNOTHERAPY

- Overall incidence of clinically significant endocrinopathies is approximately 10% in patients on immunotherapy

- Thyroiditis can present with transient hyperthyroidism (low TSH and high free T4) which can be followed by more longstanding hypothyroidism (high TSH and low free T4).

- Risk of hypothyroidism on single agent immunotherapy (ipilimumab 4%, pembrolizumab/nivolumab 7%) and dual agent immunotherapy (13%)

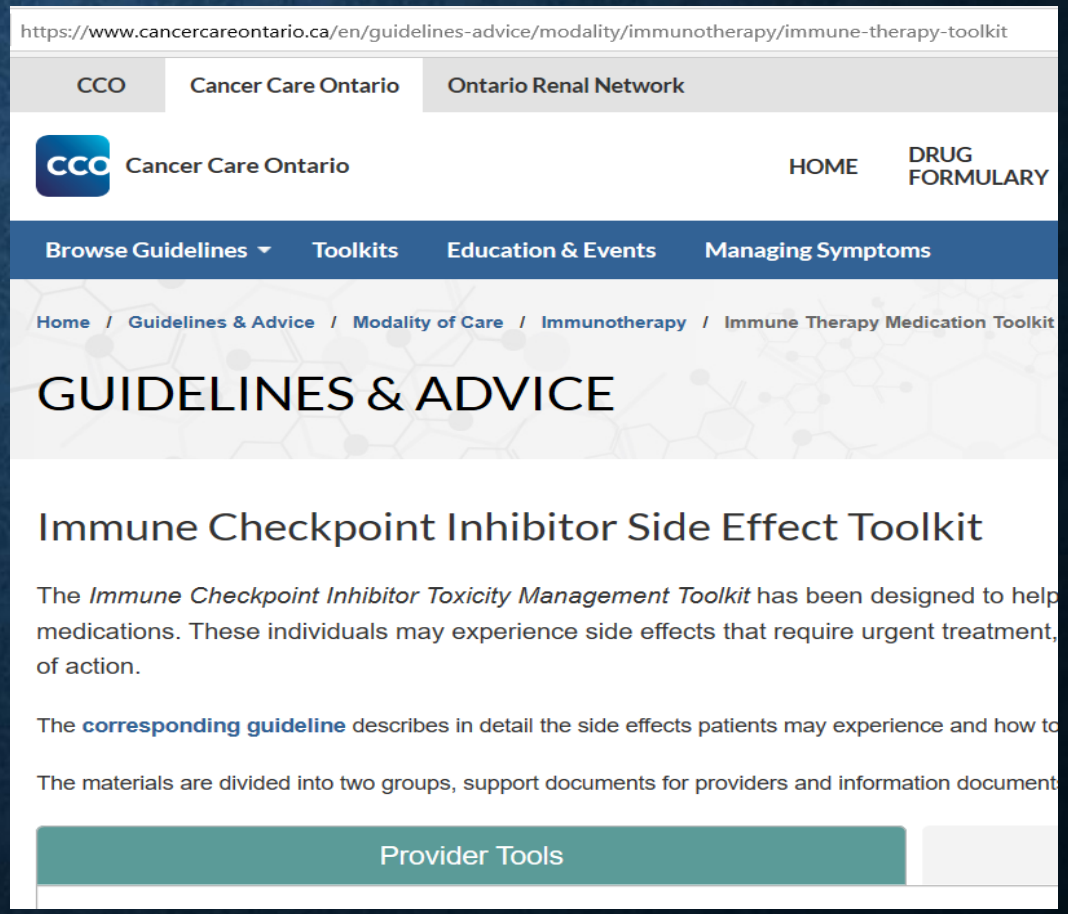
Barroso-Sousa R et al. JAMA Oncology. Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-analysis. 2018;4(2):173.

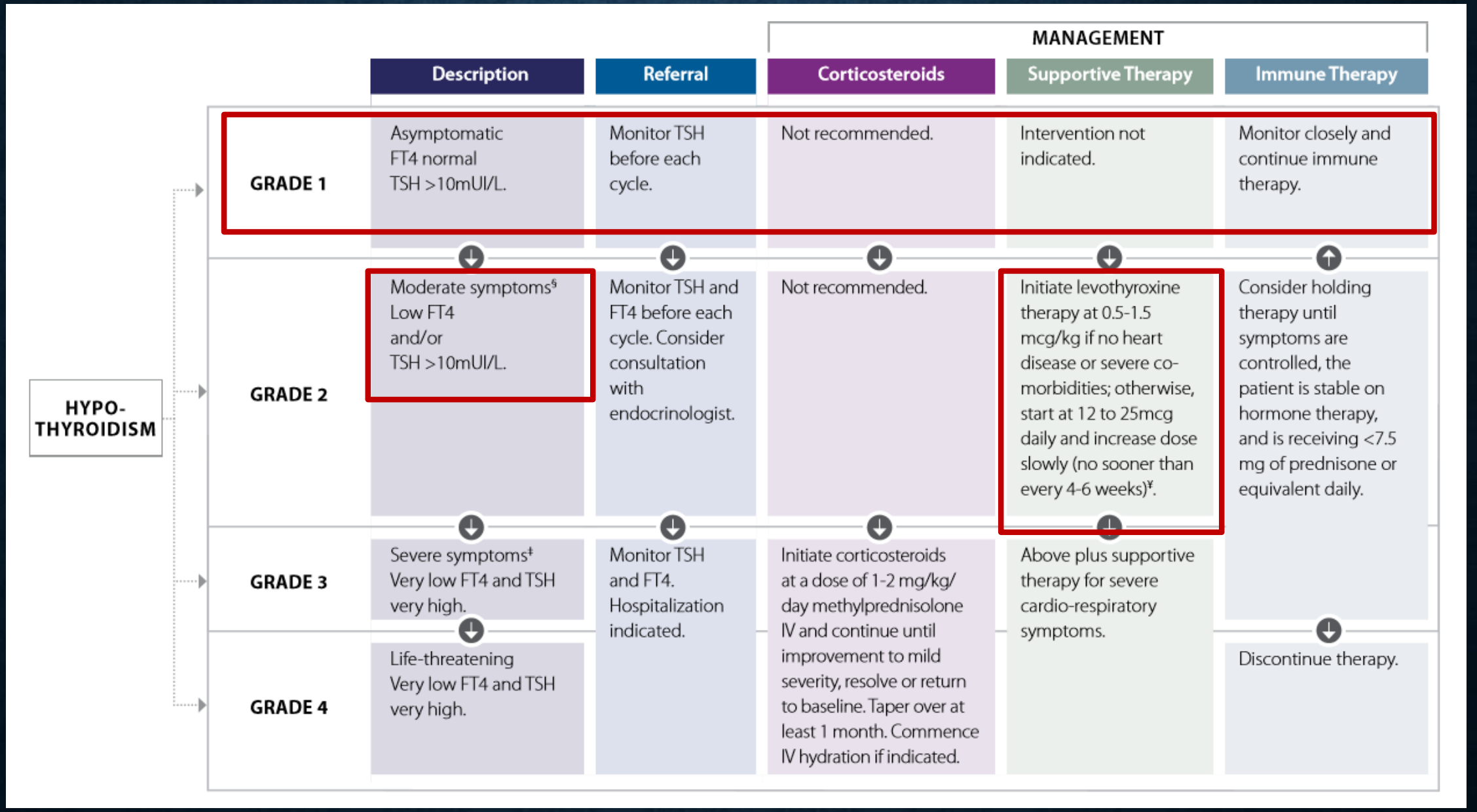
FAMILY MD INQUIRY #1

- T4 is 4
- Patient is fatigued (moderate) with bowel changes
- What should we do?

IMMUNE-RELATED SIDE EFFECTS BEST ADVICE FOR TREATMENT?

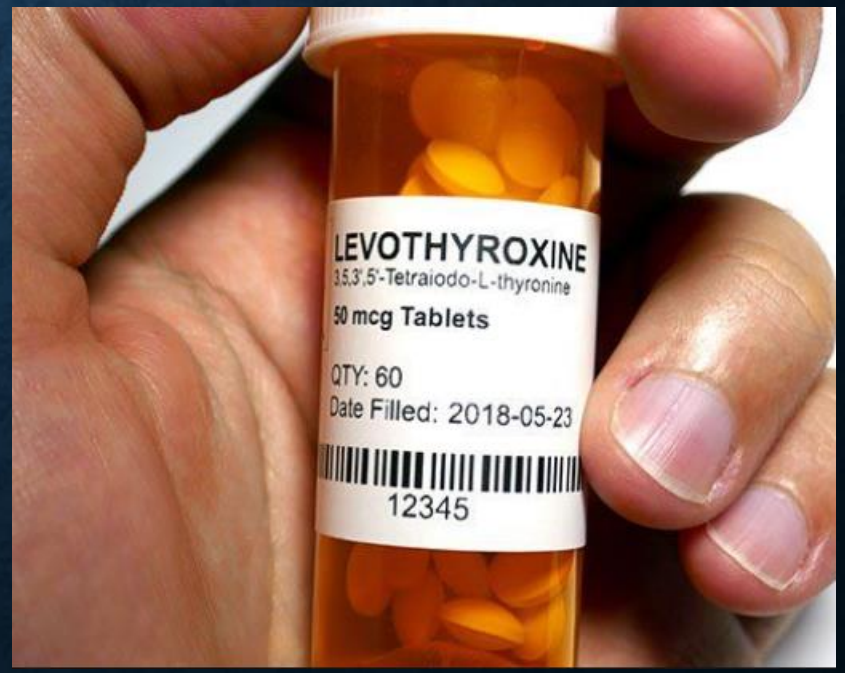
- Uptodate?
- Cancer Care Ontario – Immune Checkpoint Inhibitor Side Effect Toolkit




MANAGEMENT
Description
Referral
Corticosteroids
Supportive Therapy
Immune Therapy
HYPO-THYROIDISM
GRADE 1
Asymptomatic
FT4 normal
TSH >10mUI/L.
Monitor TSH before each cycle.
Not recommended.
Intervention not indicated.
Monitor closely and continue immune therapy.
GRADE 2
Moderate symptoms§
Low FT4
and/or
TSH >10mUI/L.
Monitor TSH and FT4 before each cycle. Consider consultation with endocrinologist.
Not recommended.
Initiate levothyroxine therapy at 0.5-1.5 mcg/kg if no heart disease or severe co-morbidities; otherwise, start at 12 to 25mcg daily and increase dose slowly (no sooner than every 4-6 weeks)¥.
Consider holding therapy until symptoms are controlled, the patient is stable on hormone therapy, and is receiving <7.5 mg of prednisone or equivalent daily.
GRADE 3
Severe symptoms‡
Very low FT4 and TSH very high.
Monitor TSH and FT4. Hospitalization indicated.
Initiate corticosteroids at a dose of 1-2 mg/kg/day methylprednisolone IV and continue until improvement to mild severity, resolve or return to baseline. Taper over at least 1 month. Commence IV hydration if indicated.
Above plus supportive therapy for severe cardio-respiratory symptoms.
GRADE 4
Life-threatening
Very low FT4 and TSH very high.
Discontinue therapy.

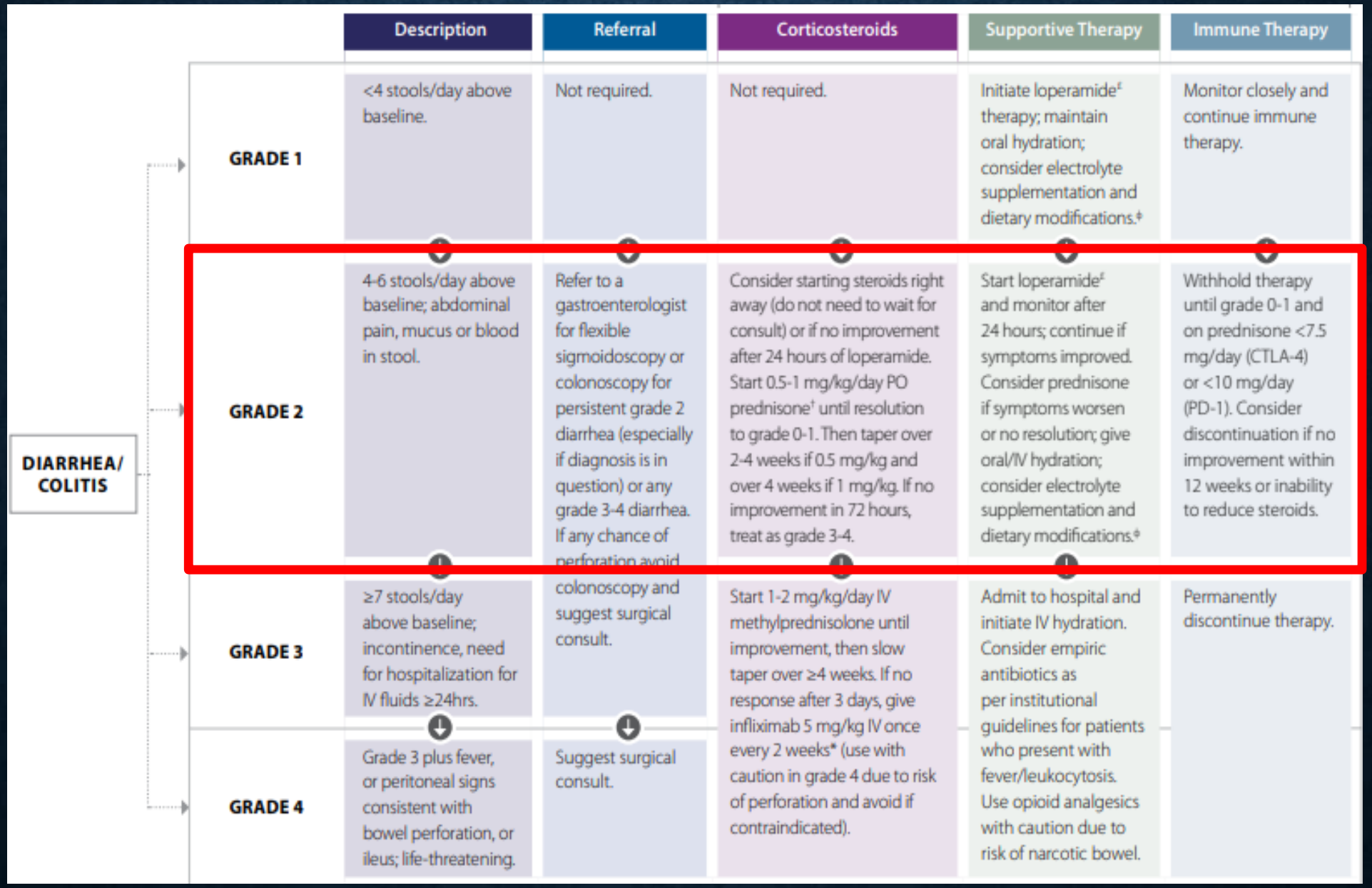
FAMILY MD INQUIRY #1

- Patient had cardiac risk factors, elderly
- Family MD started levothyroxine 25mcg po daily
- We monitored TSH/T4 with each cycle



FAMILY MD INQUIRY #2

- “Hi Lacey,
  - Our mutual patient Mr. P has stage III NSCLC and is receiving maintenance immunotherapy from your team
  - He came into the emergency department on Friday night with diarrhea (5 loose stools/day) and was slightly dehydrated.
  - We ordered a C.diff test that was negative and sent him home with Imodium post hydration.
  - I wanted you to be aware”


DIARRHEA/ COLITIS
Description
Referral
Corticosteroids
Supportive Therapy
Immune Therapy
GRADE 1
<4 stools/day above baseline.
Not required.
Not required.
Initiate loperamide[£] therapy; maintain oral hydration; consider electrolyte supplementation and dietary modifications.[ϕ]
Monitor closely and continue immune therapy.
GRADE 2
4-6 stools/day above baseline; abdominal pain, mucus or blood in stool.
Refer to a gastroenterologist for flexible sigmoidoscopy or colonoscopy for persistent grade 2 diarrhea (especially if diagnosis is in question) or any grade 3-4 diarrhea. If any chance of perforation avoid
Consider starting steroids right away (do not need to wait for consult) or if no improvement after 24 hours of loperamide. Start 0.5-1 mg/kg/day PO prednisone[†] until resolution to grade 0-1. Then taper over 2-4 weeks if 0.5 mg/kg and over 4 weeks if 1 mg/kg. If no improvement in 72 hours, treat as grade 3-4.
Start loperamide[£] and monitor after 24 hours; continue if symptoms improved. Consider prednisone if symptoms worsen or no resolution; give oral/IV hydration; consider electrolyte supplementation and dietary modifications.[ϕ]
Withhold therapy until grade 0-1 and on prednisone <7.5 mg/day (CTLA-4) or <10 mg/day (PD-1). Consider discontinuation if no improvement within 12 weeks or inability to reduce steroids.
GRADE 3
≥7 stools/day above baseline; incontinence, need for hospitalization for IV fluids ≥24hrs.
colonoscopy and suggest surgical consult.
Start 1-2 mg/kg/day IV methylprednisolone until improvement, then slow taper over ≥4 weeks. If no response after 3 days, give infliximab 5 mg/kg IV once every 2 weeks* (use with caution in grade 4 due to risk of perforation and avoid if contraindicated).
Admit to hospital and initiate IV hydration. Consider empiric antibiotics as per institutional guidelines for patients who present with fever/leukocytosis. Use opioid analgesics with caution due to risk of narcotic bowel.
Permanently discontinue therapy.
GRADE 4
Grade 3 plus fever, or peritoneal signs consistent with bowel perforation, or ileus; life-threatening.
Suggest surgical consult.

FAMILY MD INQUIRY #2

- Patient was contacted MONDAY – diarrhea resolved, drinking well.
- With next cycle of immunotherapy – diarrhea ++ (6/day), hematochezia, abdominal pain
- Diagnosed with immunotherapy-induced colitis
  - Prednisone started 1mg/kg/day with improvement, tapered over 4 weeks
  - Immunotherapy held until taper of prednisone, re-started safely

STEROIDS WITH IMMUNOTHERAPY

- **Suppress the immune system**
  - 'At higher doses - rapid depletion of most circulating T cells
  - De-activate' Immunotherapy

- **Act as 'antidote'**
  - Pneumonitis treatment: Steroids
  - Colitis treatment: Steroids
  - *If not urgent – always ASK!

Early Use of Systemic Corticosteroids in Patients with Advanced NSCLC Treated with Nivolumab

Susan C. Scott, MD, Nathan A. Pennell, MD, PhD*
Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio

Results

In all, 66 patients (31%) received concurrent systemic corticosteroids during nivolumab therapy. The most common indications included sequelae from active or treated brain metastases (27%) and chronic obstructive pulmonary disease or other respiratory disease (21%). For patients with early exposure to steroids (within the first 30 days of nivolumab therapy) (12% [n=25]), the median number of nivolumab cycles was 2, compared with five cycles in patients who were not exposed to corticosteroids ($p = 0.002$). The median overall survival time for patients who received steroids during the first 30 days was 4.3 months, compared with 11 months for patients who did not receive steroids (hazard ratio for death = 2.30, 95% confidence interval: CI 1.27–4.16, $p = 0.006$ in multivariate analysis).

- OS if steroid use: 4.3 months
- OS if NO steroid use: 11 months

IN SUMMARY

- If you give steroids to a patient on immunotherapy:
  - Give them with intention to treat something potentially life-threatening
  - Make the immunotherapy-prescriber aware

FAMILY MD INQUIRY #3

- "Hi Lacey,
  - Our mutual patient Mrs. V has stage IV Renal cell carcinoma and is receiving single-agent immunotherapy from your team
  - She's called about the flu shot. Can I administer it safely? Anything I should know before proceeding?"

FLU VACCINE: THE BASICS

- Cancer patients: higher risk for developing flu-related complications
- Response to flu vaccine is muted in chemotherapy patients (importance re: timing)
- Patients on immunotherapy: will mount robust T-cell response
  - **Theoretical risk: Vaccine increases immune-mediated AEs**

CAN WE GIVE THIS PATIENT THE FLU SHOT?

SUBJECT: KEYTRUDA® (pembrolizumab) – Use with vaccines

Patients enrolled in the registration trials of KEYTRUDA for melanoma and non-small cell lung cancer were allowed to receive inactivated vaccines. Seasonal influenza vaccines for injection are generally killed virus vaccines and were allowed during the registration trials; however, intranasal influenza vaccines are live attenuated vaccines and were not permitted. Live vaccines were prohibited within 30 days prior to the first dose of trial treatment and while participating in the trial. (2)

FLU SHOT AND COMBO THERAPY

A BMS safety database review revealed 4 patients who had received concomitant influenza vaccine prior to or during treatment with nivolumab plus ipilimumab (nivo + ipi) regimen reported serious adverse events.[1]

- Three melanoma patients had fatal events of myocarditis and co-occurrence of myositis (n=1), and rhabdomyolysis (n=2), respectively.
- One patient with renal cell carcinoma (RCC) had life-threatening rhabdomyolysis that subsequently resolved.

No signal with regards to the association between events of myositis and myocarditis and influenza vaccination while receiving nivolumab or the nivo+ipi regimen have been established.

Individual benefit-risk decision for influenza vaccination should be made by treating physicians.

Analysis and recommendation are not generalizable to all vaccines.

THE STORY LAST YEAR

- If on SINGLE-agent immunotherapy (PDL1/PD1 inhibitor): Yes to killed vaccine (any time)

- If on CTLA4 inhibitor or combination CTLA4-inhibitor + PDL1/PD1 inhibitor:
  - E.g. Nivolumab + ipilimumab or ipilimumab alone
- No. Possible very LOW risk of MYOCARDITIS (that can lead to death)

GUIDELINE RECOMMENDATIONS

National Comprehensive Cancer Network®

Vaccines that are inactivated or killed preparations are permissible during a course of immunotherapy. Due to the lack of clarity regarding live vaccine use, it is not recommended during ICI therapy.[1]

Alberta Health Services

Given the lack of safety information and the potential risk of a significant immune response, patients treated with CTLA-4 inhibitors (e.g., ipilimumab) alone or in combination with other anti-cancer agents and those who have discontinued treatment inhibitors in the past six months should not receive the influenza vaccine.[2]

Cancer Care Ontario

Given the current lack of evidence, patients on immune checkpoint inhibitors should avoid live vaccines. Literature around the use of inactivated vaccines is evolving. One small study reported an increased risk of irAEs with the inactivated influenza vaccine, whereas another study showed no difference. All vaccinations should be considered only after careful assessment of the risks vs. benefits.[3]

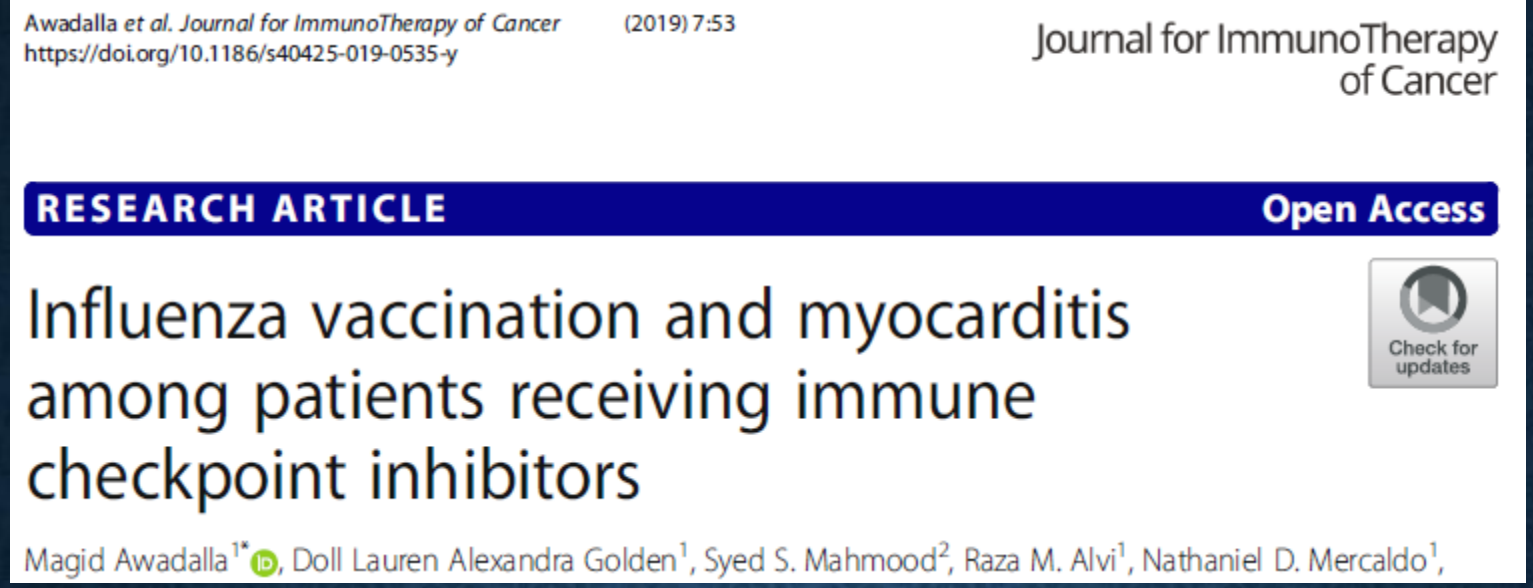
BC Cancer

Patients on PD-1/PD-L1 inhibitor monotherapy can be given at any time during therapy.

Patients on CTLA-4 inhibitor, alone or in combination should **NOT** receive any vaccine within 6-8 weeks of starting treatment or within 6-8 weeks of last dose.

For patients on maintenance nivolumab following combination therapy, discuss timing of vaccination with physician.[4]

1. NCCN Guidelines Version 2.2019. Management of Immune Checkpoint Inhibitor-Related Toxicities. 2. Alberta Health Services. Influenza Immunization for Adult and Pediatric Patients Undergoing Cancer Treatment. Clinical Practice Guideline SUPP-002 – Version 12. October 2020. 3. Cancer Care Ontario. Immune Checkpoint Inhibitor Toxicity Management. Clinical Practice Guideline. Version 1. March 2018. 4. BC Cancer Provincial Systemic Therapy Committee. Influenza Vaccine Guidelines. Revised by Dr Kerry Savage, BC Cancer Melanoma Group on 11 October 2018.



Awadalla et al. Journal for ImmunoTherapy of Cancer (2019) 7:53
https://doi.org/10.1186/s40425-019-0535-y

Journal for ImmunoTherapy of Cancer

RESEARCH ARTICLE Open Access

Influenza vaccination and myocarditis among patients receiving immune checkpoint inhibitors

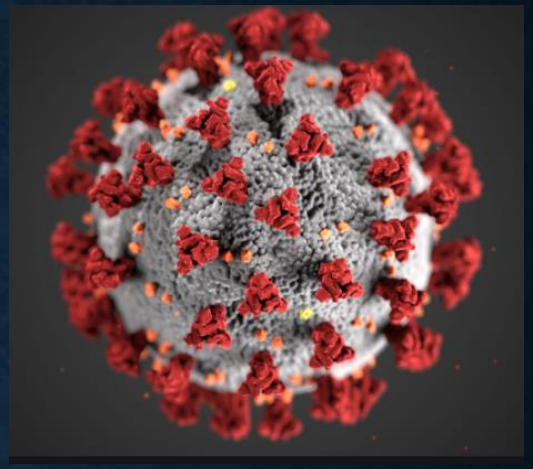
Magid Awadalla[1*], Doll Lauren Alexandra Golden[1], Syed S. Mahmood[2], Raza M. Alvi[1], Nathaniel D. Mercaldo[1],

- Case-control study of patients on immunotherapy who developed MYOCARDITIS (101 cases) compared to controls without myocarditis
- Flu vaccine given in 25% of myocarditis cases vs. 40% of non-myocarditis controls ($p = 0.01$)
- ***Among myocarditis cases – if you received FLU vaccine – lower rate of cardiogenic shock/cardiac arrest/complete heart block or death (24% vs. 59%)

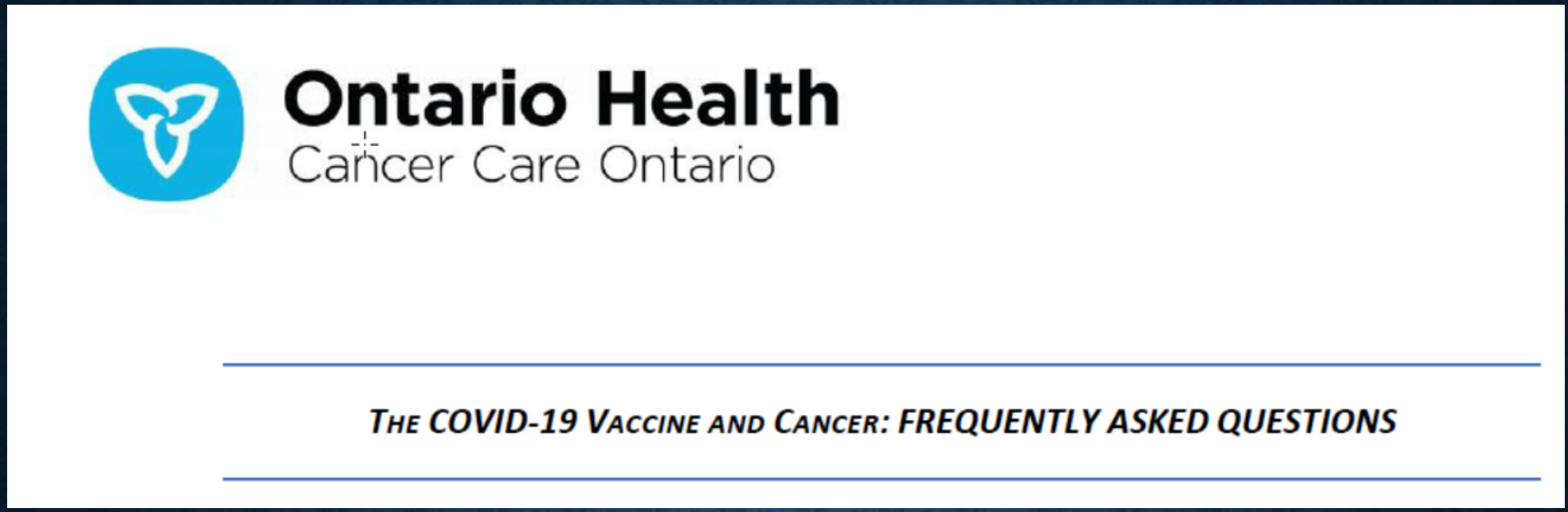
THE STORY THIS YEAR

- Do NOT use live vaccine (nasal). Yes to killed vaccine for (ALMOST all)
- If on SINGLE-agent immunotherapy (PDL1/PD1 inhibitor): Yes to killed vaccine (any time).
- If on CTLA4 inhibitor or combination CTLA4-inhibitor + PDL1/PD1 inhibitor): No. Very LOW risk of MYOCARDITIS (that can lead to death)
  - ***?Perhaps next year – FLU vaccine in ALL patients (even dual-immunotherapy***)

FAMILY MD INQUIRY #4



- “Hi Lacey,
  - Our mutual patient Mr. A has stage IV NSCLC and is receiving single-agent immunotherapy from your team
  - He’s called to ask about his risk of morbidity should he contract COVID-19 and about whether he can take the vaccine if it becomes rapidly available



- This advice is based on the best available evidence at this time. Guidance will be updated as more real-world evidence becomes available.
  - This information is referring specifically to the MODERNA, PFIZER, AstraZeneca and Johnson & Johnson vaccines
  - It is current as of March 8th, 2021

WHICH OF OUR PATIENTS ARE AT RISK?

Cancer patients have a higher risk of contracting COVID-19 and some cancer patients are at higher risk for poorer outcomes with the infection. The following patients are at a higher risk:

- Patients with **hematological cancers**
- Patients with **lung cancer**
- Patients who were **diagnosed with cancer within the last year**
- Patients who are on (or recently completed (within **the last 6 months**)) **immune checkpoint inhibitors**
- **Patients who have had a stem cell transplant within the last 6 months,** and
- Patients on or for whom the plan is to begin **active systemic treatment that has any risk of neutropenia** (i.e. chemotherapy, monoclonal antibodies, targeted therapies)

COVID-19 VACCINE

- The safety of COVID-19 vaccines in cancer patients has yet to be studied

- Prior experience with other protein-based or inactivated vaccines have not reported unique or major side effects in immunocompromised patients (e.g. flu vaccine)

COVID-19 VACCINE

- Immune checkpoint inhibitors (ICI):
  - Many trials using ICI do not allow vaccinations due to a concern of increased autoimmune events. However, recent evidence suggests that patients receiving ICI therapy may not experience an increase in immune-related adverse events when they receive inactivated influenza vaccine within 2 months of treatment.[9,10]
  - For patients receiving a combination of ICI, the risk of increased autoimmune events is uncertain and should be weighed against the definite risk of a patient potentially contracting COVID. Experience with vaccinations in this population is mostly with the influenza vaccine and more data will need to be collected before any further recommendations can be made.

In summary:

- Follow the same considerations as we do for the flu vaccine until we know more
- Single-agent immunotherapy with PD1/PDL1 inhibitors is potentially safe
- Dual-agent (PD1/PDL1 + CTLA4 inhibitor) safety is less certain
- Always review with primary oncologist before proceeding to review risks and benefits

Is the patient at a higher risk of ALLERGIC REACTION if they take the COVID-19 vaccine?

- PEG (polyethylene glycol) is a drug delivery vehicle used in both vaccines.
- Patients who have had an ANAPHYLACTIC reaction to a cancer therapy that contains PEG should take caution and discussion with oncologist/review of the nature and severity of the reaction is indicated.
- These therapies include:
  - Pegfilgrastim (e.g. Neulasta ® and others) , PEG-liposomal doxorubicin (Caelyx®), PEGaspargase (Oncaspar®), PEG-liposomal irinotecan (Onivyde®)
- Patients who have had an ANAPHYLACTIC reaction to the following cancer therapies should also take caution (cross reactivity between the contained polysorbate and PEG allergy) and discussion with oncologist/pharmacy team with review of the nature and severity of the reaction is indicated. These therapies include:
  - Cabazitaxel, Docetaxel, Paclitaxel, Etoposide, Fosaprepitant (IV), Rituximab

SOME CONSIDERATIONS

- Vaccine associated LYMPHADENOPATHY have been described
- During active chemotherapy treatment, both doses of the vaccine should be administered within a few days prior to next chemotherapy cycle, if possible
- Immunization in patients receiving chemotherapy when blood counts are low, is discouraged although not contraindicated
- Caution patient: If they develop post-vaccine fever, follow febrile neutropenia protocol and present to emergency department if sustained above 38.0°C for 1h or above 38.3°C on one occasion

WHAT YOU REALLY NEED TO KNOW

1. Immunotherapy is not a set of miracle drugs. They have fewer S/E than traditional chemotherapy, but when side effects happen – they can be very serious.

2. Avoid prescribing steroids (it can 'turn off' immunotherapy) unless the patient is having a serious reaction. Then know where to find the best resources and employ steroids.

3. It's best to ensure your patient has approval from their treating oncologist before vaccinating (influenza, covid-19) but in almost all circumstances (except possibly one – dual agent PD1/PDL1 + CTLA4 inhibitor) – it appears safe to offer vaccines

QUESTIONS

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