Post IASLC

Immunotherapy in the Real World-High Risk Population And Patient Support

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Consultant in Medical Oncology

MTE12 - IO in the Real World - High Risk Populations And Patient Support (Ticketed Session) (ID 822)

Type: **Meet the Expert Session** | Track: **Immunooncology** | Presentations: **2**

Moderators:

Coordinates: 9/25/2018, 07:00 - 08:00, Room 206 AC

+ **MTE12.01 - Is IO an Option for Patients with Contraindications (Auto-immune Disease, Pulmonary Fibrosis, HIV, Hepatitis, Transplant etc)**
  07:00 - 07:40 | Presenting Author(s): Andrew G Robinson

+ **MTE12.02 - How can we Minimize Toxicity for our High Risk Patients?**
  07:40 - 08:00 | Presenting Author(s): Massey Nematollahi

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Is Immune therapy an option for patients with contra-indications?

Pr. Andrew G. Robinson *(Staff Kingston General Hospital)*

Is Immune therapy the **best option** for this individual patient at this time?

Rationalization Oncology
“Clinical Trial Eligibility Only”

Desperation Oncology
“All patients should have IO before they die”

Review a systematic approach to making informed decisions with patients largely excluded from the pivotal clinical trials of immunotherapy and combinations.

Use that approach to lung cancer in patients with distinct clinical entities:

Chronic infection

AI(auto immune) disease

Organ transplant

1. What is the benefit and toxicity of this therapy compared to it's alternatives in the absence of contraindications for this patient?

Clinical trial Data
Prognostic Scores/predictive markers
Single Agent IO, Chemo/IO, Doublet IO

2. How may the underlying condition impact the benefit and toxicity?

Bcell/Tcell/Basic Science/Pathophysiology
Specialist (Disease) expertise
Patient Expertise
Critical Review of Literature/Case series/report
Disease > Drug > Cancer

3. How may concomitant medications impact the benefit and toxicity, what are the alternatives (if any) to these medications?

…

Pharmacist Expertise/ Patient Expertise

i.e. is a timely switch to another DMARD with less T-cell toxicity an option?

4. If this patient requires immune suppression for toxicity, are there special considerations or risks?

Hep B, TB - ? high dose steroids
Previous steroid psychosis etc.

infectious disease specialists (i.e. suppressive therapy)

5. Does the patient have the reserve to tolerate the expected or possible toxicities of the immunotherapy?

Clinical Experience; patient values

Beware of "grade creep" when translating clinical trials patients to real world patients with less reserve

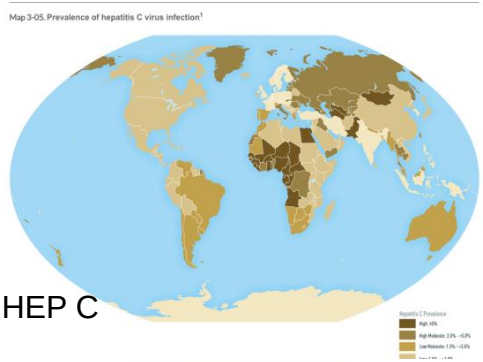
6: If I proceed with IO therapy, how do I monitor to intervene early if complications arise?

Specialist Help, laboratory medicine

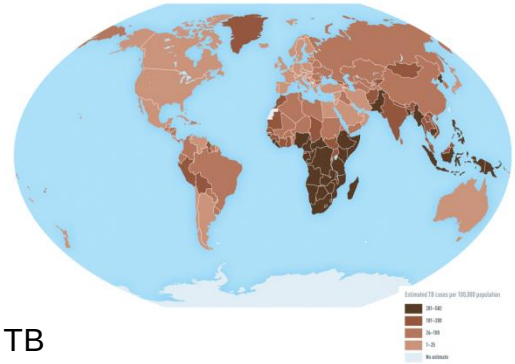
? what tests do I have timely access to that can detect AI flare/infection flare/rejection

INFECTIONS

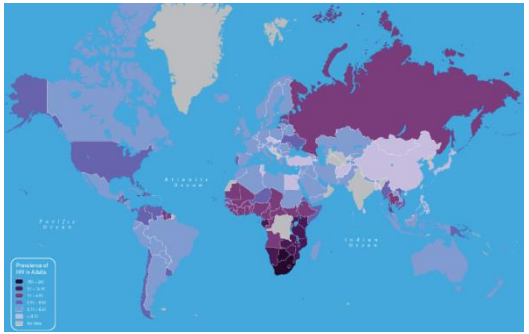
HIV
HEPATITIS B
HEPATITIS C
TUBERCULOSIS



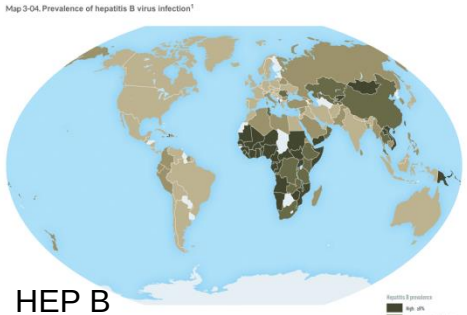
HEP C



TB



HIV



HEP B

HIV

acute infection, latency, HAART, immune reconstitution, AIDS

Trials and small Case series – Lung Cancer (10 patients), melanoma

Did disease affect efficacy? *3/7 responses (3/4 in high PD-L1)*

Did disease affect toxicity? *Only one patient was HAART naïve, but no evidence of reconstitution syndrome (IRIS)*

My approach – ***Pr. Andrew G. Robinson's***

- Manage with HIV team, use HAART
- Unlikely to be MORE toxic than chemotherapy in this population

HAART highly active antiretroviral therapy

Hepatitis C

Chronic Infection
Cirrhosis
Extra-Hepatic Manifestations (immune mediated)

Hepatitis C

No discernible effect on checkpoint efficacy, small numbers

Some evidence of anti-viral activity of PD-1 blockade, some evidence of hepatitis

My approach – ***Pr. Andrew G. Robinson's***

Refer to hepatologist.
Can treat before antivirals if needed.
Can use antivirals if flare.
Monitor liver function (?Monitor viral load), Monitor/consider extra-hepatic manifestations

Hepatitis B

Acute, Chronic, HBeAg positive, Immune Tolerance/Immune Clearance/Immune Escape etc.

HCC (Clinical Trials); reports from endemic areas

Viral Load < 100 (inclusion criteria); all Chronic Hep B

Higher rates of hepatic dysfunction (10-30%)

Significant risk of reactivation if steroids/immunosuppression

My approach – ***Pr. Andrew G. Robinson***

test for Hepatitis B, treat with antivirals, treat with PD(L)-1

Tuberculosis

TB disease/Latent TB/hepatotoxic meds

Multiple case reports of activation during PD-1 treatment; incidence not known.

Risk of reactivation with immunosuppression, risk of exaggerated immune response.

Latent TB – Options –

treatment for LTB if time (3 months)
Single Agent IO +/- LTB treatment if needed

Active TB –

treat active TB
start IO ~3-4 wks after
prepare for hepatotoxicity

Chronic Infections

Unless profound immunosuppression, unlikely to impact efficacy; may impact toxicity.

Concomitant medications – Overlapping toxicity, unlikely to impact efficacy.

Risk of steroids/immunosuppressants – may be significant

Monitoring – Organ monitoring, viral monitoring

Auto-immune diseases (80-100)

Different patterns of relapse/etiology/organ/morbidity
Prevalence: ~ 10-15% (of lung cancer patients)

Largest Series –
56 lung cancer patients over 3 years at 5 large academic centers.
123 patients in 49 publications (all cancer)

Abdel-Wahab
all tumour types
both CTLA4 and PD(L)1

75% flare OR irAE OR both. 50% continued

No difference - active versus inactive disease.

immunosuppressive therapy = fewer adverse events

Corticosteroids worked; 16% required other suppressive

JCO Leonardi (Lung Cancer; PD(L)1) 55 patients

55% flare OR irAE OR both

20% on immunosuppressives at baseline

Predominantly rheumatoid, skin, endocrine (90%)

Symptomatic at baseline – 50% flare ORR 22%

Conclusions

In selected patients, PD-1 axis therapy may be safe.

Symptomatic at baseline (worse disease) = higher rate of worsening.

Patient with Rheumatoid Arthritis on Etanercept

There is a risk of flare of arthritis secondary to IO.
Life threatening iRAE's are rare (biology, weak evidence)
Etanercept may lower efficacy (unclear)
Consider change if feasible.
(biology/pharmacology, no evidence)
No significant increased risk with steroids
Reserve for toxicity may be impacted depending on severity.

Monitor – discuss with Rheumatologist

Patient with Relapsing/Remitting MS on Beta-IFN

- Small case reports in MS, no worsening.
- MS is T cell dependent at this stage (B cell later in evolution).
- Beta-IFN – not associated with OI's, works on T cells
- Steroids may worsen muscle weakness etc. may have less reserve.

- Self-monitor for symptoms, unclear role of biomarkers/MRI
- In context of lung cancer – if no other treatments available, and high chance of working, may be worth the risk but +++ care needed.

Pulmonary Fibrosis

Toxicity may increase. May be safe in some

POSTER P1.01-49. Komiya et al.
12 patients with IPF or Radiation Pneumonitis.
50% (6) had flare requiring steroids (1 death)
Not treated with immunosuppressants

Solid Organ Transplant (Ontario Data)

Lung Cancer 21% of cancer deaths

SMR 2

60% kidney; 23% liver; 9% heart; 8% lung

Standardized mortality ratios (SMR)

Solid Organ Transplant

PD1 axis , CTLA-4

Multiple Case Reports (<20)

Not everyone rejects, but reported rates high

multiple factors influence rejection(organ type, age of rejection, donor type/sex, immunosuppression etc.)

Solid Organ Transplant

Risk of toxicity – Yes (++high)

Immune Suppressants - ?Reduce (as in post-transplant lymphoproliferative)? Unclear

Risk of steroids, further immunosuppression.

?early and frequent monitoring.

Solid Organ Transplant

Renal – prepare for dialysis.

Discuss immunoreduction vs. continued immune suppression.

Hepatic/Cardiac/Pulmonary – Continue anti-rejection drugs, discuss risk.

Summary

Viral illnesses/Auto-immune Disease/Transplant

Literature is Sparse.

Individual Patient/Team Approach, but structured decision making.

Assess benefit (trials, predictive markers, prognostic markers)

Effect of Disease on Response or Toxicity (biology, experts, case reports)

Effect of Medications on Response/Toxicity (pharmacology, experts, biology, case reports)

Plan for/Assess Risk of additional immune suppression.

Assess reserve to handle toxicity (underlying organ function/ “protoplasm”)

Individualize monitoring plan if needed.

How can we Minimize Toxicity on our High Risk Patients?

Massey Nematollahi
IO Clinical Nurse Specialist
Brampton Hospital

Immunotherapy

- Significant impact in patient's outcomes
- Durable tumor responses
- Severe irAE's in some cases
- Rapid broadening

Introduction

CIOSK COMMUNITY IMMUNO-ONCOLOGY SUPPORT KIT

- Early recognition of symptoms and frequent monitoring is key to irAE management[1]
- Patients need to be their own advocates[1]
- Patient education and materials are needed to assist in irAE[1-3]:
  - Recognition
  - Management
  - Monitoring

irAE, immune-related adverse event.

1. Fecher LA, et al. The Oncologist. 2013;18:733-743.
2. Brigden M, Humphreys M and Imbulgoda A. Oncology Exchange. 2016;15(3):10-14.
3. Champiat S, et al. Ann Oncol. 2016;27(4):559-574.

WCLC 2018

Community Oncology Setting

CIOSK COMMUNITY IMMUNO-ONCOLOGY SUPPORT KIT

- May not have access to the variety of sub-specialists as those in highly-populated, academic centres
- First point of contact for cancer patients experiencing complications are often:
  - General practitioners, hospitalists, emergency room staff or pharmacists
- To minimize complications from immuno-oncology therapies, centres need a:
  - Proactive approach
  - Comprehensive management process

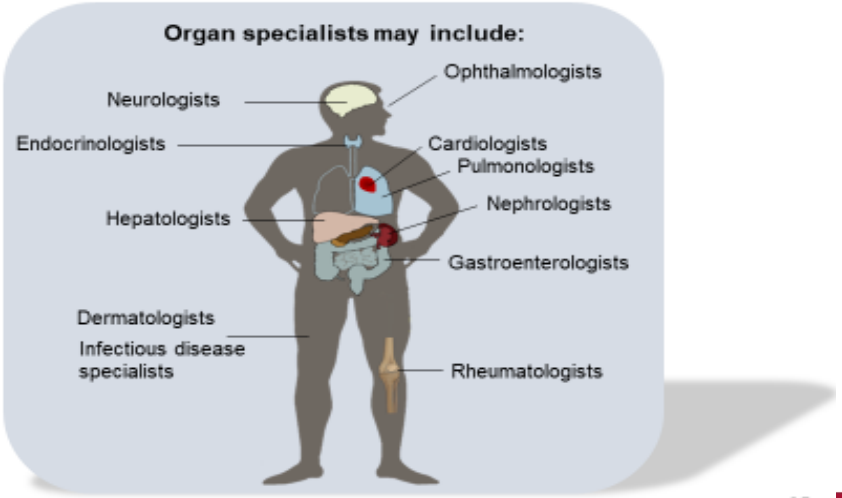
Brigden M, Humphreys M and Imbulgoda A. Oncology Exchange. 2016;15(3):10-14.

Multidisciplinary Care for irAEs

CIOSK COMMUNITY IMMUNO-ONCOLOGY SUPPORT KIT

- Specific and urgent nature of irAE management requires coordination with various healthcare teams[1,2]
- Grade >1 toxicities often require sub-specialist expertise[1]
- Sub-specialist referral is important to help optimize patient care[1,2]

- May need to define and seek support of local organ specialists[1]



irAE, immune-related, adverse event.

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2. Fecher LA, et al. The Oncologist. 2013;18:733-743.

Generating a standardized, reproducible, and safe implementation of immunotherapy in our high risk population

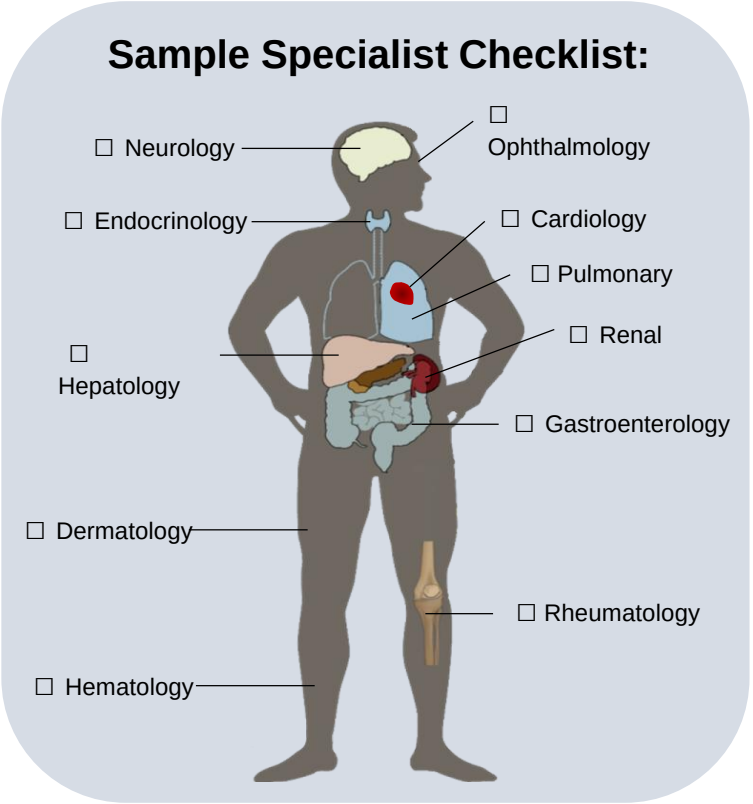
FIRST IMMUNOTHERAPY CLINIC IN CANADA

Checklist for IO therapy program initiation

- ❑ General education program for all cancer centre clinic staff regarding IO agents
- ❑ Copies of irAEs treatment algorithms developed/distributed
  - ❑ Educate all staff interacting with patients
- ❑ Follow-up process and single-most responsible individual identified (eg, oncology nurse)
  - ❑ Blood count checking protocol
  - ❑ Protocol for grade ≥2 irAE immediate follow-up
  - ❑ Back-up person identified
- ❑ Monthly healthcare team conferences scheduled on status of each patient on IO agents
- ❑ Educational program for ER physicians, pharmacists, hospitalists, internists planned/ undertaken
- ❑ Back-up community consultants for each major irAE identified and informed
- ❑ Patient educator clearly identified
- ❑ Patient education process developed
  - ❑ Should be performed by single, consistent individual
  - ❑ Periodic reinforcement re-education process
- ❑ Patient education materials available for use
  - ❑ Patient handouts, classes, and training videos
  - ❑ Patient wallet card or drug ID

Local healthcare professionals Directory

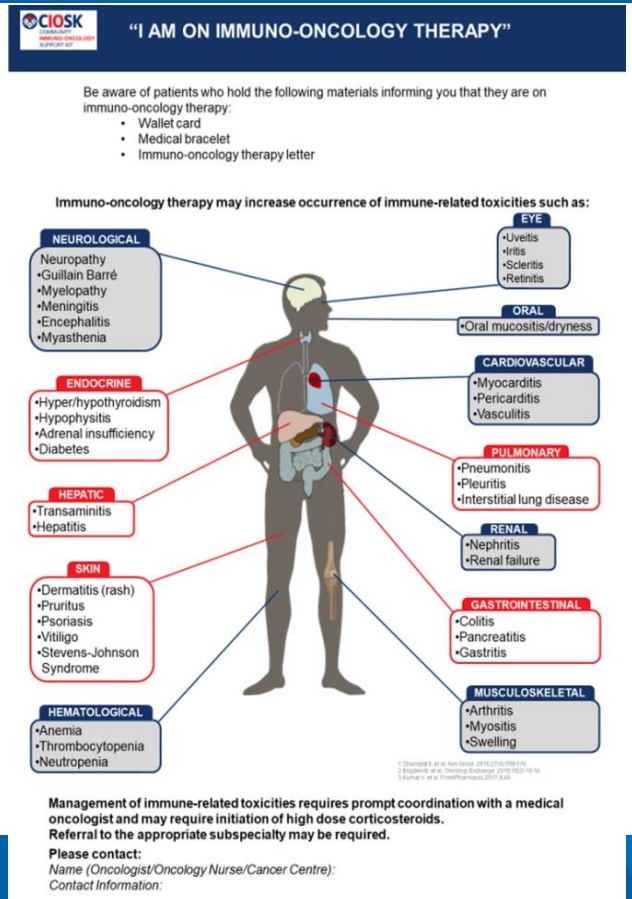
- Designate local sub-specialists who will be involved with irAE management
- Develop local sub-specialty contact card/HCP directory



HCP, healthcare professionals; irAE, immune-related adverse event.

1. Brigden M, Humphreys M and Imbulgoda A. Oncology Exchange. 2016;15(3):10-14.
2. Fecher LA, et al. The Oncologist. 2013;18:733-743.

irAE Postings in Clinics and ERs



Baseline visit
Baseline IO Panel
Language specific education

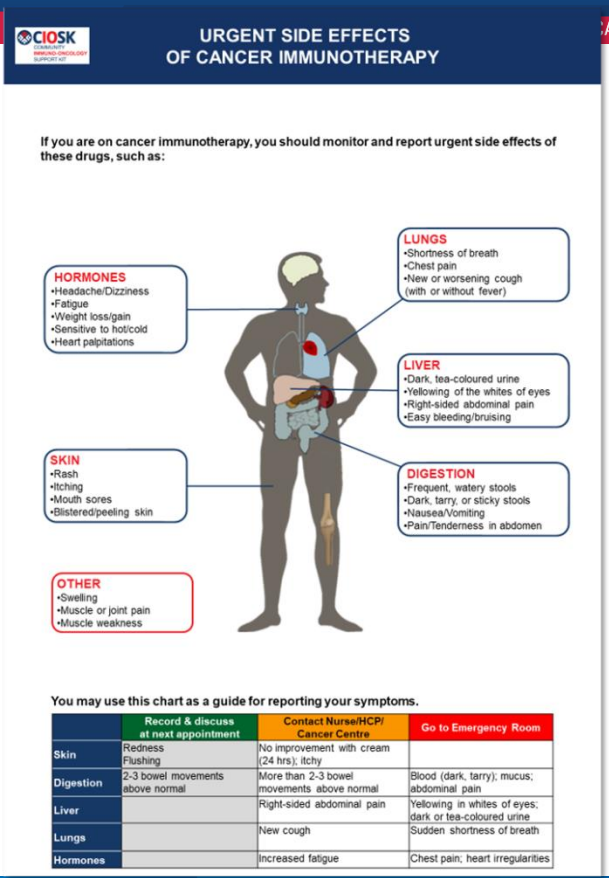
All patients that are offered I-O are enrolled in the immunotherapy clinic.

Standardize biochemical monitoring

Proactive reporting of irAE

Pathways for irAE management

Patient teaching and handouts



CIOSK COMMUNITY IMMUNO-ONCOLOGY SUPPORT KIT

URGENT SIDE EFFECTS OF CANCER IMMUNOTHERAPY

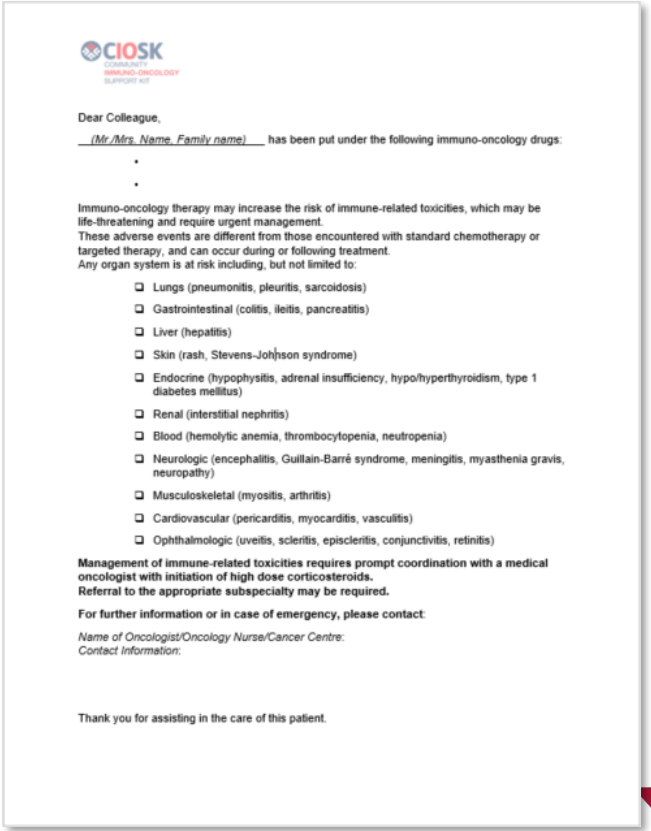
If you are on cancer immunotherapy, you should monitor and report urgent side effects of these drugs, such as:

You may use this chart as a guide for reporting your symptoms.

	Record & discuss at next appointment	Contact Nurse/HCP/ Cancer Centre	Go to Emergency Room
Skin	Redness Flushing	No improvement with cream (24 hrs); itchy	
Digestion	2-3 bowel movements above normal	More than 2-3 bowel movements above normal	Blood (dark, tarry); mucus; abdominal pain
Liver		Right-sided abdominal pain	Yellowing in whites of eyes; dark or tea-coloured urine
Lungs		New cough	Sudden shortness of breath
Hormones		Increased fatigue	Chest pain; heart irregularities

Adapted from Champiat S, et al. Ann Oncol. 2016;27(4):559-574.

Immuno-Oncology Therapy Letter



CIOSK COMMUNITY IMMUNO-ONCOLOGY SUPPORT KIT

Dear Colleague,

(Mr./Mrs. Name, Family name) has been put under the following immuno-oncology drugs:

•

•

Immuno-oncology therapy may increase the risk of immune-related toxicities, which may be life-threatening and require urgent management.
These adverse events are different from those encountered with standard chemotherapy or targeted therapy, and can occur during or following treatment.
Any organ system is at risk including, but not limited to:

- ❑ Lungs (pneumonitis, pleuritis, sarcoidosis)
- ❑ Gastrointestinal (colitis, ileitis, pancreatitis)
- ❑ Liver (hepatitis)
- ❑ Skin (rash, Stevens-Johnson syndrome)
- ❑ Endocrine (hypophysitis, adrenal insufficiency, hypo/hyperthyroidism, type 1 diabetes mellitus)
- ❑ Renal (interstitial nephritis)
- ❑ Blood (hemolytic anemia, thrombocytopenia, neutropenia)
- ❑ Neurologic (encephalitis, Guillain-Barré syndrome, meningitis, myasthenia gravis, neuropathy)
- ❑ Musculoskeletal (myositis, arthritis)
- ❑ Cardiovascular (pericarditis, myocarditis, vasculitis)
- ❑ Ophthalmologic (uveitis, scleritis, episcleritis, conjunctivitis, retinitis)

Management of immune-related toxicities requires prompt coordination with a medical oncologist with initiation of high dose corticosteroids.
Referral to the appropriate subspecialty may be required.

For further information or in case of emergency, please contact:

Name of Oncologist/Oncology Nurse/Cancer Centre:
Contact Information:

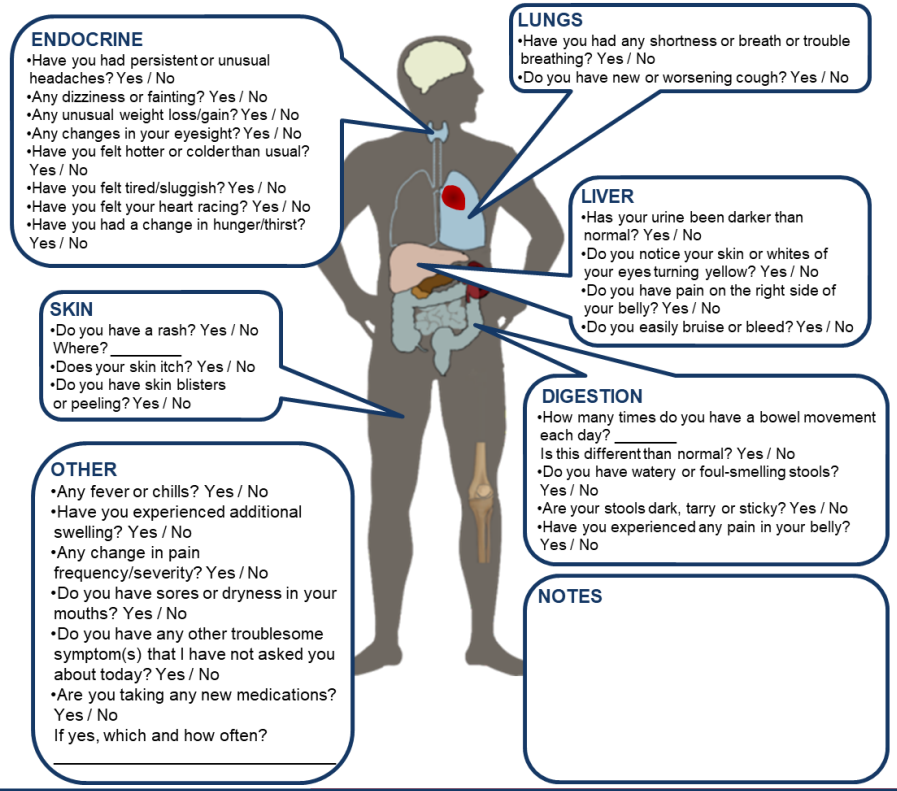
Thank you for assisting in the care of this patient.

Patient Call-Back Questionnaire

This checklist is intended for healthcare professionals to use prior to dosing each patient and at any follow-up visit or call with the patient to identify some signs and symptoms associated with adverse reactions related to immuno-oncology therapy. Adverse reactions from immuno-oncology therapies may differ from those observed with chemotherapy and targeted therapy and may require immunosuppression. Early identification of adverse reactions and intervention are important for the safe use of immuno-oncology therapies.

Please note: this checklist is not meant to be all-inclusive.

If the patient responds "Yes" to any of these questions, consult the patient's oncologist before administering further immuno-oncology treatment.



Adapted from BC Cancer Agency: Patient Monitoring Checklist

Patient Wallet Cards and ID Bracelets

CIOSK COMMUNITY IMMUNO-ONCOLOGY SUPPORT KIT

Name, Family name: _____
Immuno-oncology therapy drug(s): _____
I am currently receiving immuno-oncology therapy, which may increase the risk of occurrence of immune-related side effects, such as:

- Pneumonitis (inflammation of the lungs)
- Colitis (inflammation of the gut)
- Hepatitis (inflammation of the liver)
- Nephritis (inflammation of the kidneys)
- Endocrinopathy: hypophysitis, thyroid dysfunction, diabetes, adrenal insufficiency (inflammation of the hormone producing organs)
- Cutaneous rash (inflammation of the skin)

Other immune-related events may also occur (ie, cardiovascular, neurologic, hematologic, ophthalmologic, rheumatologic).
The management of these immune-related adverse events is specific and sometimes urgent. It absolutely requires coordination with the health care team that has prescribed the treatment:
Prescriber ID and contact information (reported at the back of this card)

I am receiving immuno-oncology (IO) therapy.

Please contact my oncologist immediately before treatment.

My Name:
IO Drug:
Oncologist:
Contact**:**

Adapted from Champiat S, et al. Ann Oncol. 2016;27(4):559-574.

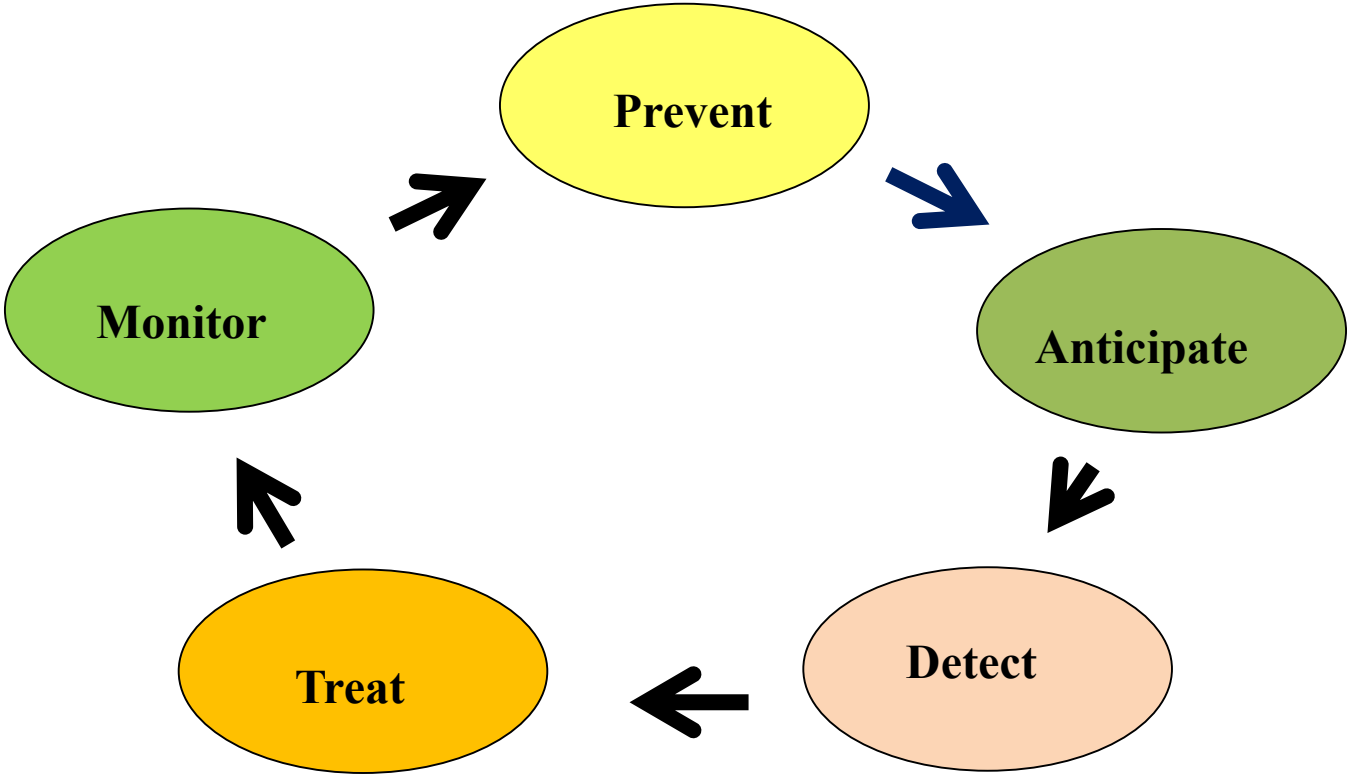
https://ciosktraining.net/
www.lungcancercanada.ca

Key Takeaways

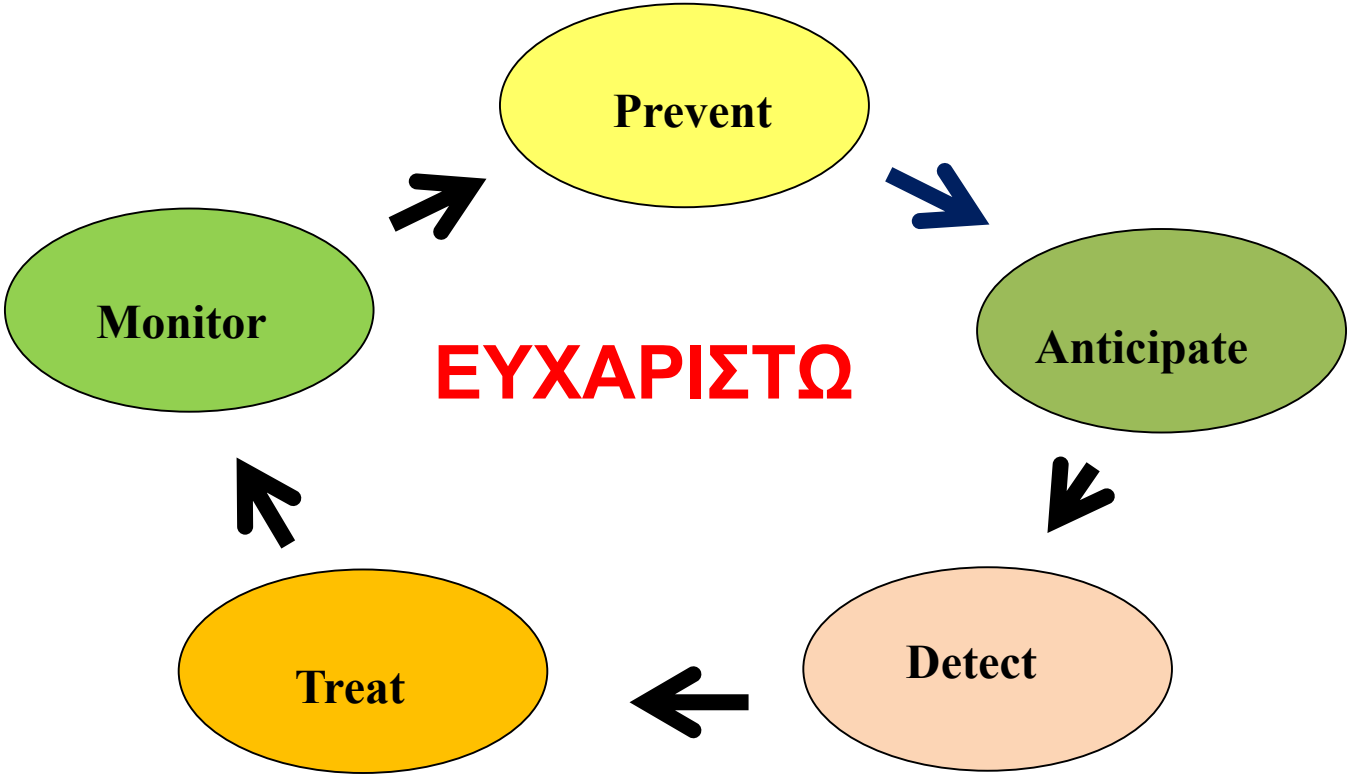
- Management toxicities on high risk population requires a multidisciplinary team to optimize patient care[1,2]
- Local sub-specialists should be consulted as soon as the diagnosis and treatment of irAEs become difficult[1]
- Comprehensive management process can minimize complications from IO therapies Includes: patient/HCP education, follow-up plan, and clear delineation of responsibilities[1]
- Key component to process: patients should be contacted on a regular basis[3]

HCP, healthcare professionals; irAE, immune-related adverse event.

1. Champiat S, et al. Ann Oncol. 2016;27(4):559-574.
2. Fecher LA, et al. The Oncologist. 2013;18:733-743.
3. Brigden M, Humphreys M and Imbulgoda A. Oncology Exchange. 2016;15(3):10-14.

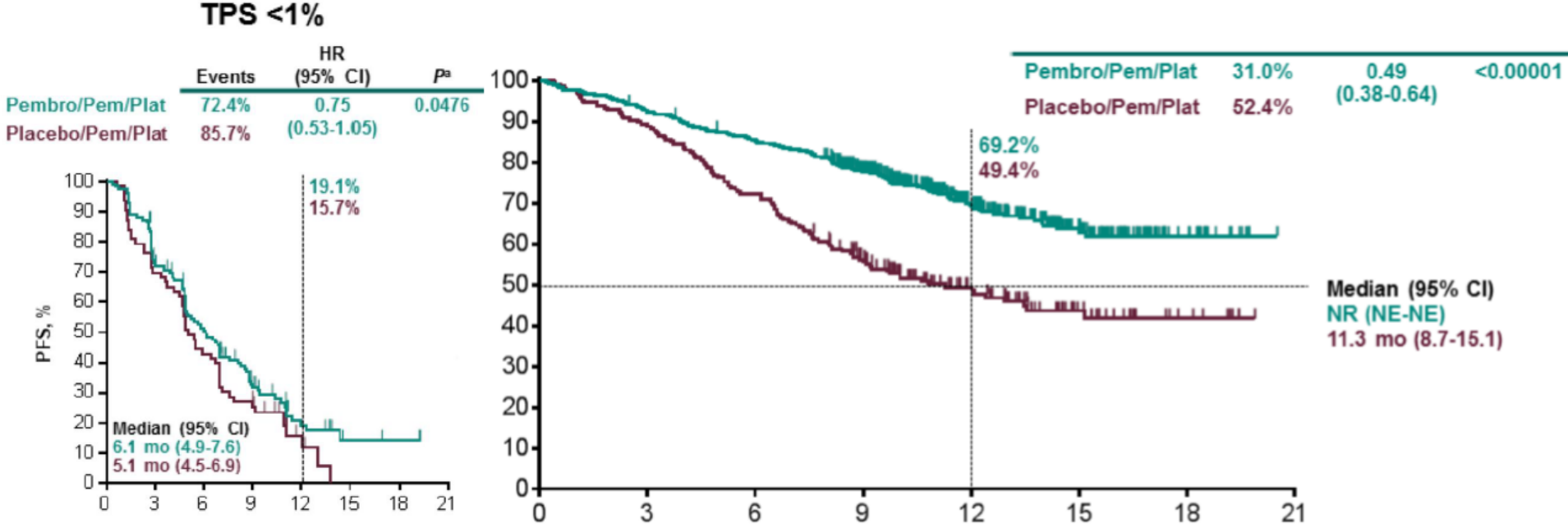


Champiat et al Annals of Oncology 2015



Champiat et al Annals of Oncology 2015

Platinum/pemetrexed/pembrolizumab is superior to platinum/pemetrexed irrespective of PD-L1 KEYNOTE-189



Co-primary endpoints PFS/OS

Gandhi, AACR 2018

Χημειοθεραπεία μόνο σε ασθενείς με PDL-1>50%

- ✓ Response: 19-32%
- ✓ Median PFS: 4.0 – 5.0 months
- ✓ Median OS: 7.9 – 9.9 months
- ✓ 1-year OS rate: 33 – 43%

Kelly K et al, J Clin Oncol 2001; 19: 3210-8, Scagliotti GV et al, J Clin Oncol 2002; 20: 4285-91, Schiller J et al, NEJM 2002; 346: 92-8; Scagliotti GV, J Thorac Oncol 2011; 6: 64-70; Soria JC, Ann Oncol 2013; 24: 20-30

Ανοσοθεραπεία μόνο σε ασθενείς με PDL-1>50%

Response: 48%

Median PFS:10.3

Median OS: 30months

1 year OS rate:70%

Reck M, et al. *N Engl J Med* 2016; DOI: 10.1056/NEJMoa1606774; 2. Reck M, *et al*. ESMO 2016

Χημειοθεραπεία μόνο

- ✓ Response: 19-32%
- ✓ Median PFS: 4.0 – 5.0 months
- ✓ Median OS: 7.9 – 9.9 months
- ✓ 1-year OS rate: 33 – 43%

Χημειοθεραπεία μαζί με ανοσοθεραπεία

Response: 47.6%

Median PFS: 8.8 months

Median OS:NR

1 year OS rate: 69.2%

Kelly K et al, J Clin Oncol 2001; 19: 3210-8, Scagliotti GV et al, J Clin Oncol 2002; 20: 4285-91, Schiller J et al, NEJM 2002; 346: 92-8; Scagliotti GV, J Thorac Oncol 2011; 6: 64-70; Soria JC, Ann Oncol 2013; 24: 20-30

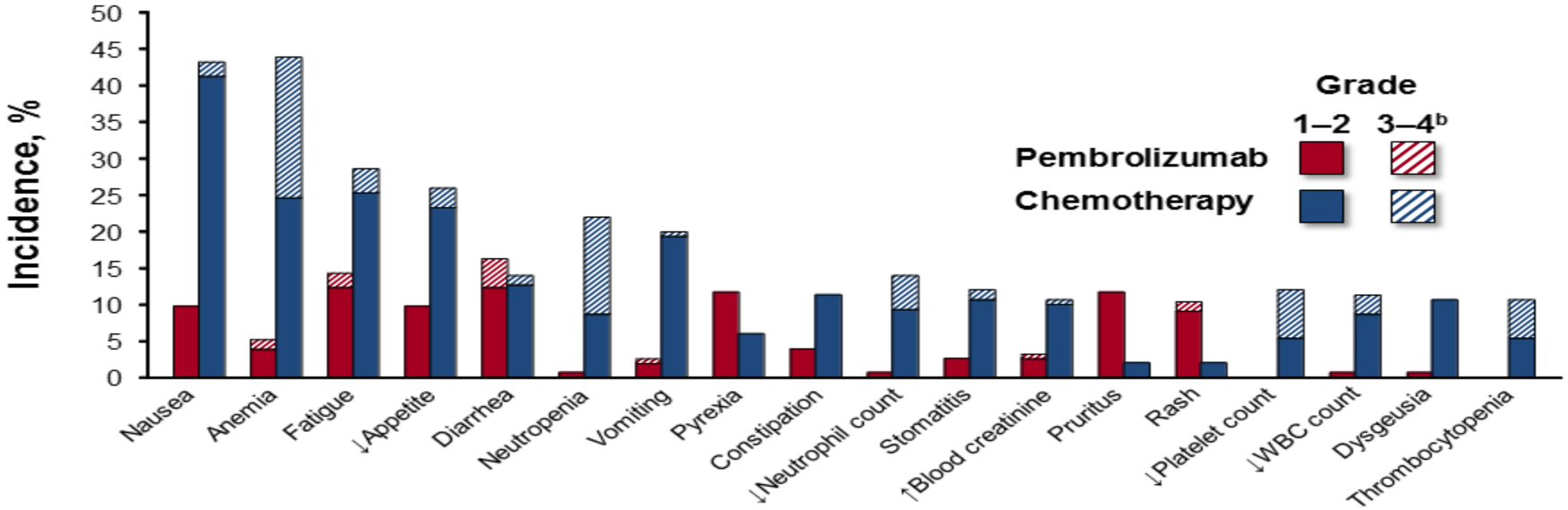
Adverse Event Summary[a]

	Pembrolizumab N = 154	Chemotherapy N = 150
Median (range) treatment duration with initially assigned therapy, mo	7.9 (0.03–28.8)	3.5 (0.03–30.5)
Treatment-related adverse events, n (%)	118 (76.6)	135 (90.0)
Grade 3–5	48 (31.2)	80 (53.3)
Serious	35 (22.7)	31 (20.7)
Led to discontinuation	21 (13.6)	16 (10.7)
Led to death	2 (1.3)	3 (2.0)
Immune-mediated adverse events,[b] n (%)	52 (33.8)	8 (5.3)
Grade 3–5	21 (13.6)	1 (0.7)
Led to death	1 (0.6)	0

[a]During treatment with the initially assigned therapy.
[b]Irrespective of attribution to treatment by the investigator.
Data cutoff: July 10, 2017.

Brahmer WCLC 2017

Treatment-Related Adverse Events[a]
(≥10% in Either Treatment Arm)



[a]During treatment with the initially assigned therapy.
[b]Two grade 5 treatment-related adverse events occurred in the pembrolizumab arm (pneumonitis, sudden death) and 3 in the chemotherapy arm (death, pulmonary sepsis, pulmonary alveolar hemorrhage). Data cutoff: July 10, 2017.

	Phase 1 Immune tolerance	Phase 2 Immune clearance	Phase 3 Immune control	Phase 4 Immune escape
Serology	HBeAg positive HBeAb negative	HBeAg positive HBeAb negative	HBeAg negative HBeAb positive	HBeAg negative HBeAb positive
ALT (IU/mL)	Persistently normal	Persistently or intermittently abnormal	Persistently normal	Persistently or intermittently abnormal

Checkpoint inhibitor therapy for cancer in solid organ transplantation recipients: an institutional experience and a systematic review of the literature Journal for ImmunoTherapy of Cancer April 201
Noha Abdel-Wahab,

ResultsThirty-nine patients with allograft transplantation were identified. The median age was 63 years (range 14–79 years), 74% were male, 62% had metastatic melanoma, 77% received anti-PD-1 agents, and 59% had prior renal transplantation, 28% hepatic transplantation, and 13% cardiac transplantation. Median time to CPI initiation after SOT was 9 years (range 0.92–32 years).

Allograft rejection occurred in **41% of patients** (11/23 renal, 4/11 hepatic, and 1/5 cardiac transplantations), at similar rates for anti-CTLA-4 and anti-PD-1 therapy. The median time to rejection was 21 days (95% confidence interval 19.3–22.8 days). There were no associations between time since SOT and frequency, timing, or type of rejection. Overall, 31% of patients permanently discontinued CPIs because of allograft rejection. Graft loss occurred in 81%, and death was reported in 46%. Of the 12 patients with transplantation biopsies, nine (75%) had acute rejection, and five of these rejections were T cell-mediated. In melanoma patients, 36% responded to CPIs.