ICLIO
INSTITUTE FOR CLINICAL IMMUNO-ONCOLOGY

Immuno-Oncology Management Best Practices 2.0

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Objectives

- Review changing landscape of I-O
- Identify best practices in various domains of practice related to I-O
- Introduction of new concept – Palliative Care and I-O

New England Cancer Specialists

- The only private oncology practice in Maine
- Fourteen physicians; Eleven Nurse Practitioners and Physicians Assistants
- Three physical locations in southern Maine
- Come Home practice; OCM participant; OMH (CoC and NCQA) and QOPI certification
- Driven by quality, value, and innovation
- Dedicated physician to I-O (Best Practice)

I-O Clinical Education

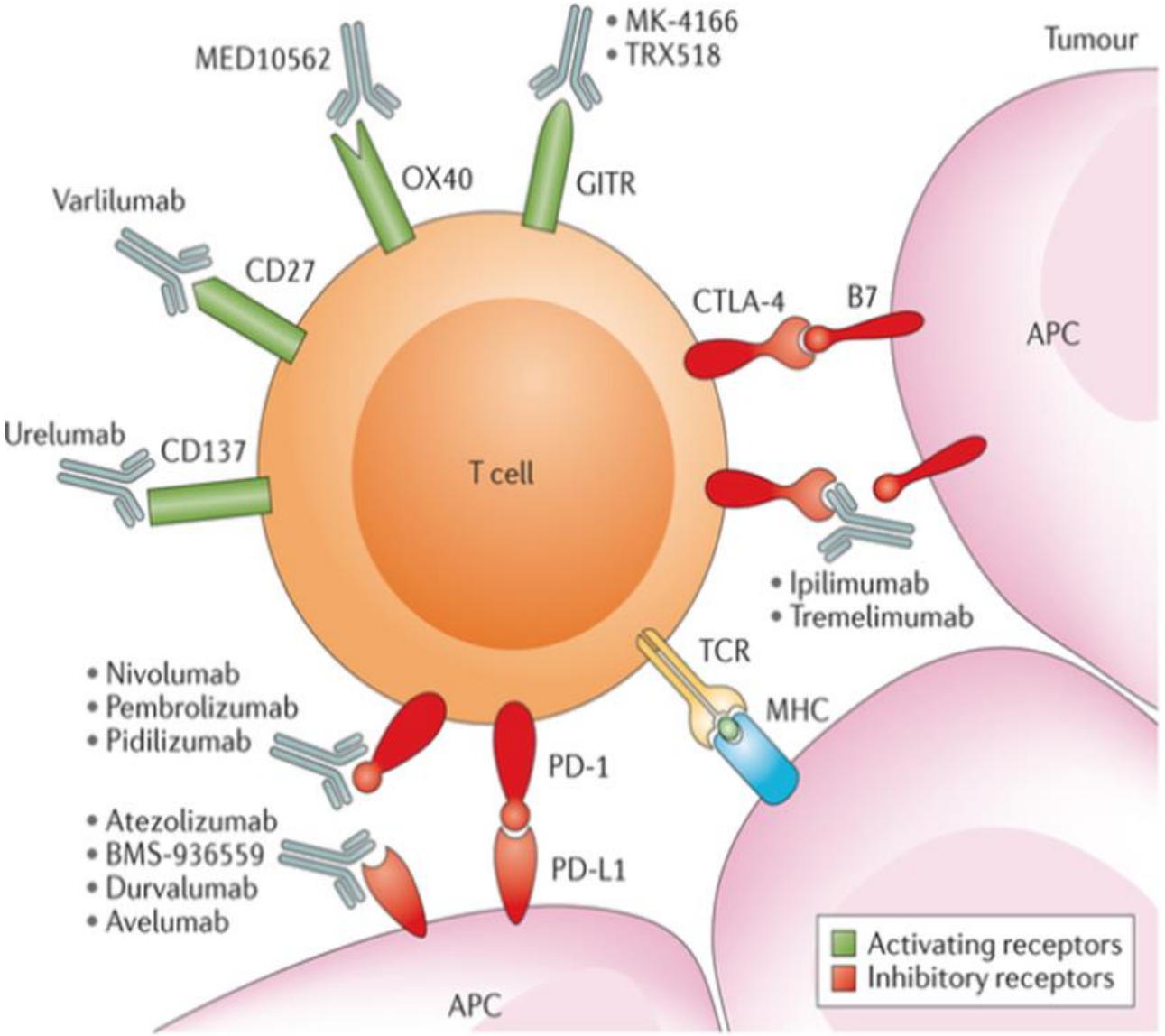
- Growing number of indications and products entering the market
- Dosing changes
  - Staff education, regimen updates, when to change to new dosing from previous dosing
- Regimens – best practices incorporate all necessary baseline and follow-up testing
- Adverse event tracking; development of I-O triage specificity, patient identifiers
- Management algorithms for I-O toxicity
- Emergence of combination therapies

Immunotherapy for Malignant Disease

- Monoclonal Abs
  - Targeting tumor cells
    - rituximab, alemtuzumab, ofatumumab, obinutuzumab, brentuximab, daratumumab, elotuzumab
  - Targeting angiogenesis
    - bevacizumab, ramucirumab
  - Targeting growth and differentiation
    - cetuximab, panitumumab, necitumumab, trastuzumab, pertuzumab, olartumab, denosumab
  - Antibody-drug conjugates
    - gemtuzumab ozogamicin, ado-trastuzumab emtansine
  - Targeting immune checkpoint inhibitors
    - ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab

Immune Checkpoint Inhibitors –

Where Do They Work?



Nature Reviews | Urology

Checkpoint Inhibitors

- **Melanoma** — **FDA approved indications**
- **Lung cancer**
- Classical Hodgkin's lymphoma
- Urothelial cancer
- Head & Neck SCC
- Renal cell cancer
- Merkel cell carcinoma

- MSI colon and other cancers — **Not yet but soon**
- Hepatocellular carcinoma
- Others…

- Adrenal cortical carcinoma — **Anecdotal but impressive**

I-O Pharmacy Considerations

- Addition of I-O agents is driving up on-hand inventory costs
- Refer to Dr. Ali McBride's webinar on Specialty Pharmacy: Managing Immunotherapy Access, Cost, and Patient Expectations
  - http://accc-iclio.org/events/1224-2/
- Vial optimization or batching – need to adhere to regulatory and state statutes but can save system and practice money
- Regimen optimization

I-O Financial Issues

- Ever increasing cost of new therapies
- Value-based assessments
  - Various stakeholders; methodologies; vetting of information; utilization
- Length of therapy in I-O and cost implications
  - Two years versus continue until progression
- Financial assessment demands on practices (OCM)
- Bundled payment strategies, little oncology experience or programs
- Financial Advocates (Best Practice) for prior authorization, off-label use, and drug acquisition
- Longevity of patient assistance
- Access

I-O Payer Landscape

- Depends on geographic market and payers
- No denials in Maine by any payer to date
- Future conversations with payers may evolve as class grows and data emerges
- ? Cost driving selection in the future

Common Terminology Criteria for Adverse Events (CTCAE)

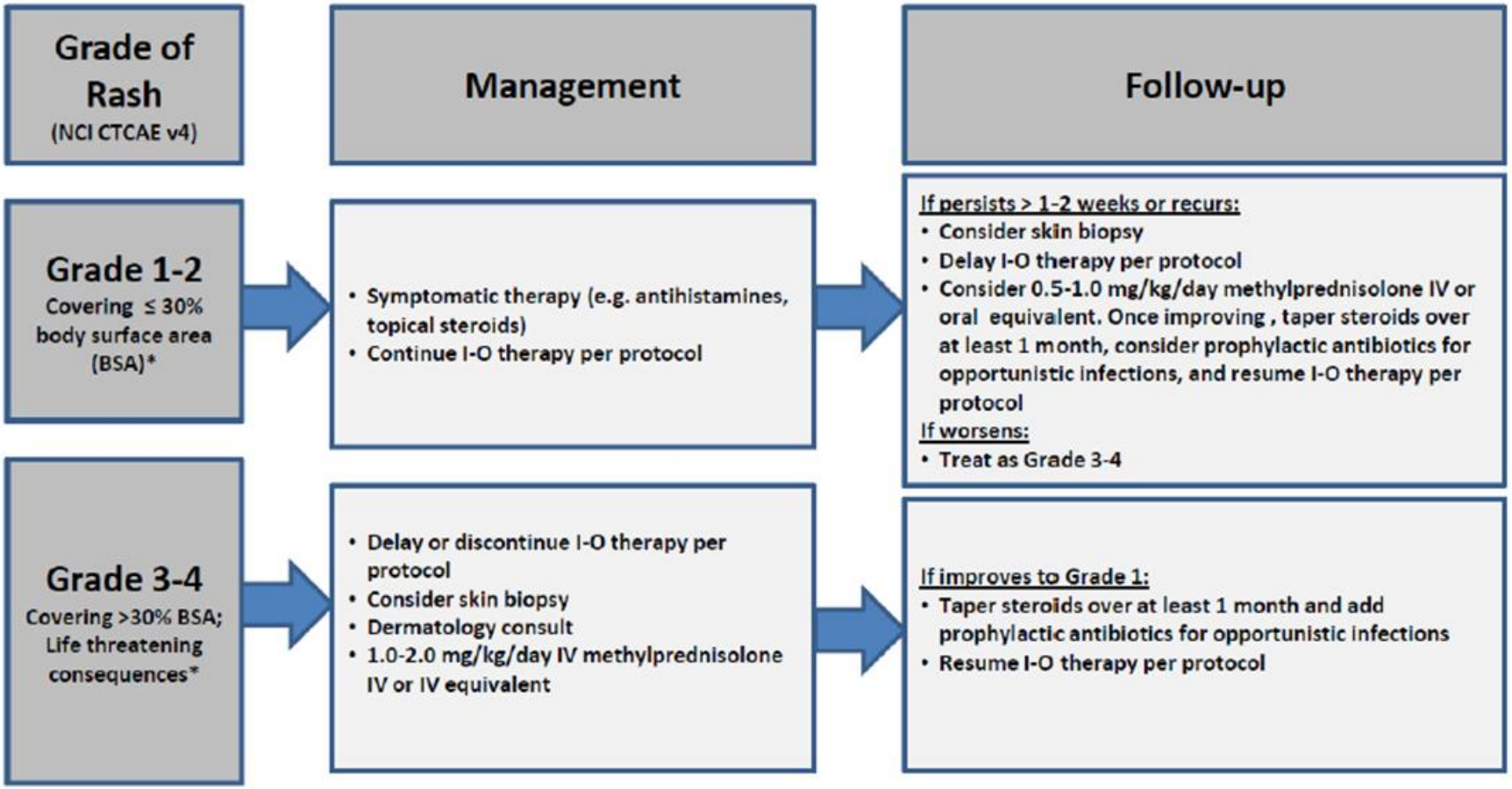
Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

Skin Adverse Event Management Algorithm

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



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade (G) 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hours (hrs); not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with activities of daily living (ADL) Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

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

Hepatic Adverse Event Management Algorithm

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

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin (T. bili) > ULN - 1.5 x ULN	• Continue I-O therapy per protocol	• Continue liver function tests (LFT) monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN and /or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 gram (g) twice daily (BID) • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

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

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and Infectious Disease (ID) consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression (e.g. infliximab, cyclophosphamide, intravenous immunoglobulin (IVIG), or mycophenolate mofetil)

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

Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue immuno-oncology (I-O) therapy.
Consider visual field testing, endocrinology consultation, and imaging.

Asymptomatic thyroid stimulating hormone (TSH) elevation

- Continue I-O therapy per protocol
- If TSH < 0.5 x lower limit of normal (LLN), or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include free thyroxine (fT4) at subsequent cycles as clinically indicated; consider endocrinology consult

Symptomatic endocrinopathy

- Evaluate endocrine function
- Consider pituitary scan

Symptomatic with abnormal lab/pituitary scan:
- Delay I-O therapy per protocol
- 1-2 mg/kg/day methylprednisolone IV or by mouth (PO) equivalent
- Initiate appropriate hormone therapy

No abnormal lab/pituitary MRI scan but symptoms persist:
- Repeat labs in 1-3 weeks /MRI in 1 month

If improves (with or without hormone replacement):
- Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections
- Resume I-O therapy per protocol
- Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component

Suspicion of adrenal crisis (*e.g.* severe dehydration, hypotension, shock out of proportion to current illness

- Delay or discontinue I-O therapy per protocol
- Rule out sepsis
- Stress dose of IV steroids with mineralocorticoid activity
- IV fluids
- Consult endocrinologist
- If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy

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

Renal Adverse Event Management Algorithm

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

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > upper limit of normal (ULN) and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline</u>: •Resume routine creatinine monitoring per protocol <u>If worsens:</u> •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy	<u>If returns to Grade 1:</u> •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	<u>If returns to Grade 1</u> : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

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

Neurological Adverse Event Management Algorithm

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

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

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

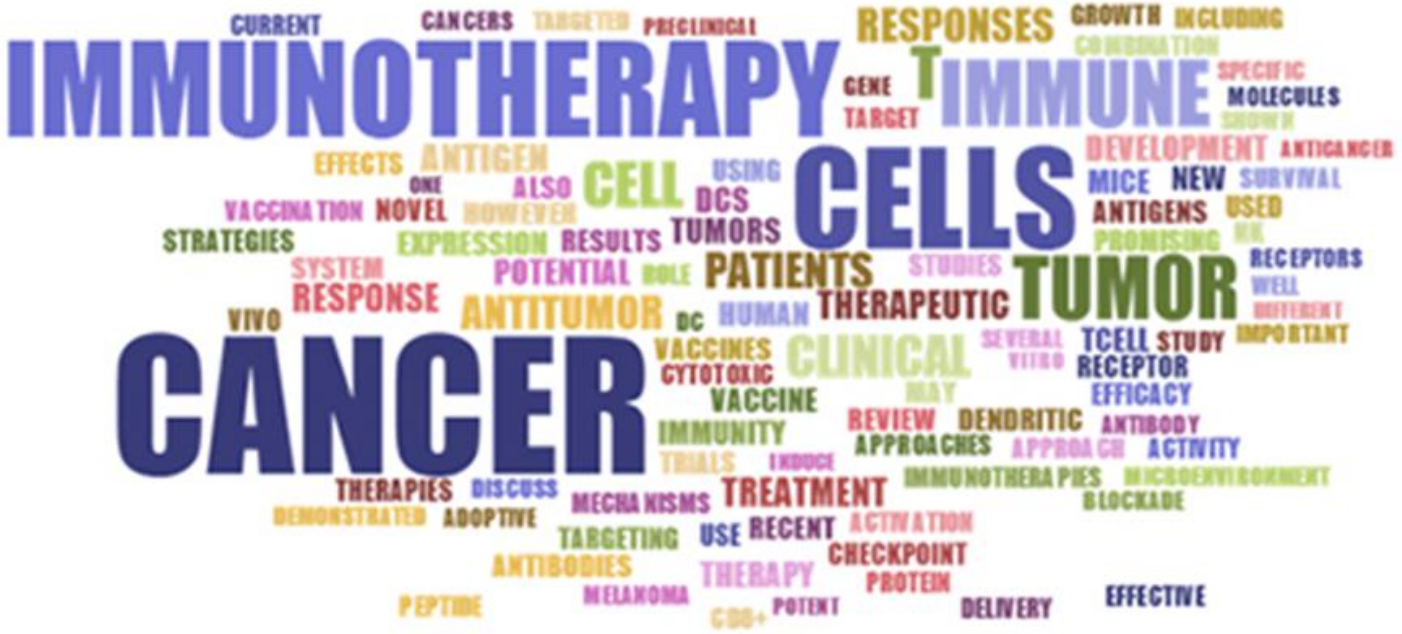
Laboratory and Testing

- Capability for all baseline and ongoing laboratory testing
- Coordination of appropriate testing prior to treatment with immunotherapy
- PD-L1 testing – reflex testing a best practice

Immunotherapy for malignant disease:

The “natural” approach to cancer treatment

What better way to distinguish the bad cells from the good?



Immunotherapy and Palliative Care

- Why now?
  - Immunotherapy = now a mainstream event
    - Target population growing more than exponentially
  - Immunotherapy goal = durable disease control
    - Already achieved in melanoma, renal, others very likely
  - Immunotherapy toxicity = a new paradigm is essential
    - Does not resolve with stopping treatment
      - Must be actively treated
    - Does not resemble toxicity of chemotherapy
      - Must be carefully assessed

Immunotherapy and Palliative Care

- Why now?
  - Immunotherapy of cancer is now a mainstream event
    - Target population growing more than exponentially
      - IFN – HCL, KS, melanoma, NHL
      - IL-2 – renal, melanoma
      - Anti-CTLA-4 – advanced and adjuvant melanoma
      - Anti-PD-1 – melanoma, NSC lung, renal, Hodgkin's, H+N, urothelial
      - Anti-PD-L1 – urothelial, NSC lung, Merkel cell
      - Others coming – both targets and tumor types
        - » OX40, CD39, KIR, CD94, MICA/B, CD73, TLR3, VISTA
        - » breast, colon, prostate, HCC, hematologic malignancies…

Immunotherapy and Palliative Care

- Main points:
  - Goals of treatment = durable disease control/remission
  - Toxicities = adverse immune reactions [autoimmunity]
  - Rapidly evolving and complex landscape

Summary

- I-O landscape is changing rapidly with many new agents in development for multiple disease states
- Financial impact on payers, patients, and providers
- Increased educational demands for all providers
- Palliative care will have a role in integrating with primary care teams to manage patients on I-O

Questions?

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Thank you for participating in the ICLIO e-Course. Presentation slides and archived recording will be available at accc-iclio.org.

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