Managing Immunotherapy Toxicity: The Good, the Bad, and the Ugly

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DISCLOSURE

Relevant Financial Relationship(s)

Consultant- Bristol Myers Squibb Advisory Board (money paid to institution)

Consultant- Novartis Nurse Advisory Board

Consultant-Merck –Internal Training Program (money paid to institution)

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Objectives

Participants should be able to:

- Describe the mechanism of action of anti-CTLA-4 and anti PD-1 antibodies in cancer.
- List the frequency of the most common immune related adverse events (irAE's) experienced by patients undergoing cancer therapy with checkpoint blockade.
- Describe immunologic immune related adverse event (irAE) management and nursing's role in the management of patients on immunotherapy.

FDA approval timelines

- Ipilimumab (Yervoy™)
  - 3/28/2011- Advanced melanoma
  - 10/28/2015- Resected HR melanoma
- Pembrolizumab (Keytruda™)
  - 9/4/2014- Advanced melanoma
  - 10/2/2015- Advanced NSCLC
- Nivolumab (Opdivo™)
  - 12/22/2014- Advanced melanoma
  - 3/4/2015- Advanced NSCLC
  - 11/23/2015- Advanced RCC
  - 5/17/2016- Hodgkin's Lymphoma
- Ipi/Nivo
  - 10/1/2015- Advanced melanoma
- Atezolizumab (Tecentriq™)
  - 5/18/2016 – Advanced urothelial carcinoma

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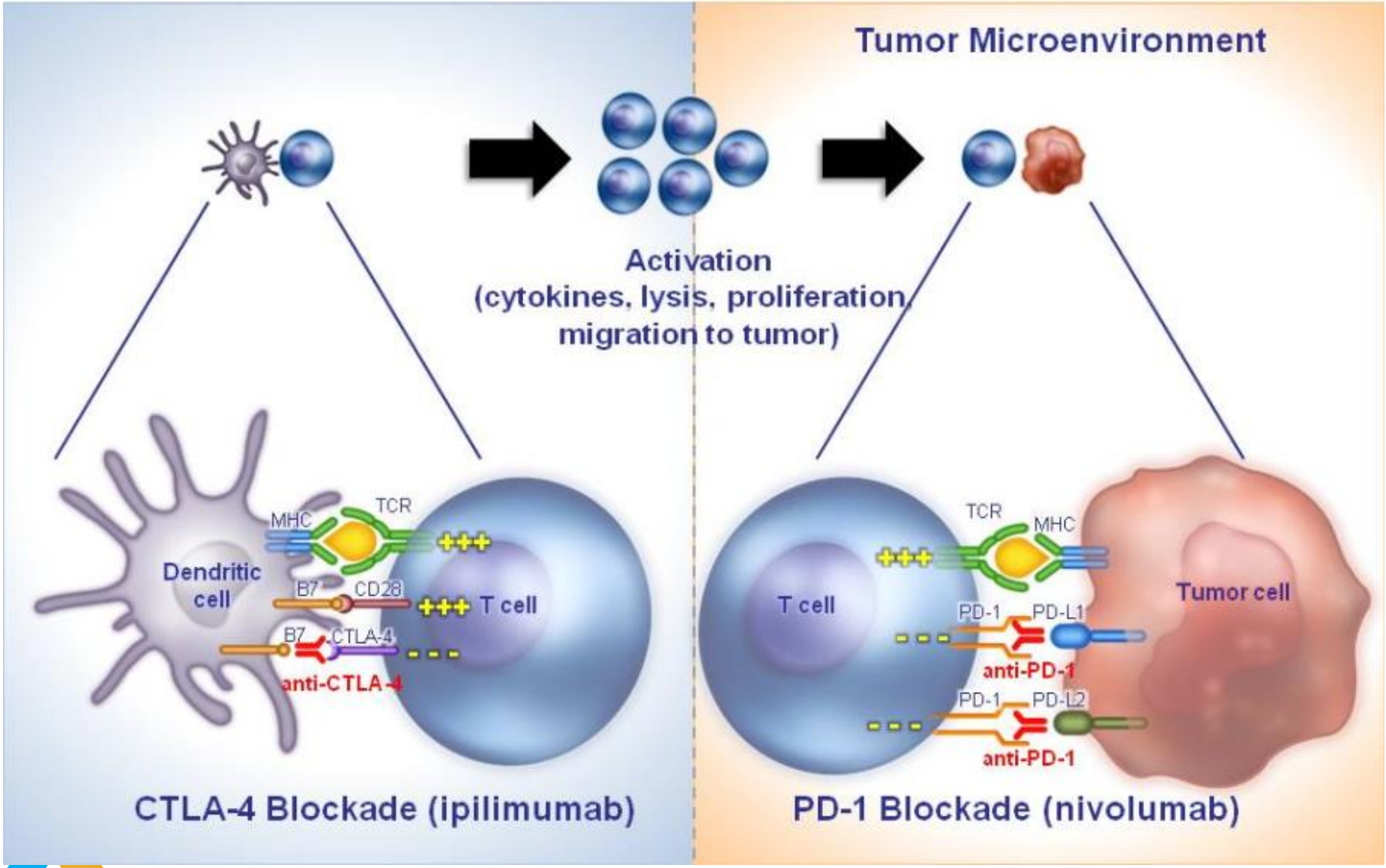
Blocking CTLA-4 and PD-1



Safety Summary

- Updated safety information with 9 additional months of follow-up were consistent with the initial report

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
Patients reporting event, %	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related adverse event (AE)	95.8	56.5	84.0	19.8	85.9	27.0
Treatment-related AE leading to discontinuation	38.7	30.7	10.5	7.3	15.4	13.5
Treatment-related death*	0		0.3		0.3	

- 68.8% of patients who discontinued NIVO+IPI due to treatment-related AEs achieved a response

*One reported in the NIVO group (neutropenia) and one in the IPI group (colon perforation)

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Most Common Treatment-related Select AEs

	NIVO+IPI (N=313)		NIVO (N=313)		IPI (N=311)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Skin AEs, %	60.4	5.8	43.8	2.2	54.7	2.9
Rash	28.4	2.9	22.7	0.3	21.2	1.6
Pruritus	35.1	1.9	20.4	0.3	36.3	0.3
Gastrointestinal AEs, %	47.6	15.3	21.7	2.9	37.3	11.6
Diarrhea	45.4	9.6	20.8	2.2	33.8	6.1
Colitis	11.5	8.0	2.2	1.0	11.3	8.0
Endocrine AEs, %	32.3	5.8	15.7	1.6	11.6	2.6
Hypothyroidism	16.0	0.3	9.3	0	4.5	0
Hyperthyroidism	10.2	1.0	4.5	0	1.0	0
Hepatic AEs, %	31.6	19.8	7.3	2.6	7.4	1.6
Elevated ALT	17.9	8.6	3.8	1.0	3.9	1.6
Elevated AST	15.7	6.1	4.2	1.0	3.9	0.6
Pulmonary AEs, %	7.3	1.0	1.6	0.3	1.9	0.3
Pneumonitis	6.7	1.0	1.3	0.3	1.6	0.3
Renal AEs, %	6.4	1.9	1.0	0.3	2.6	0.3
Elevated creatinine	4.2	0.3	0.6	0.3	1.6	0

- Immune-modulating medicines were used to manage adverse events and led to resolution rates of immune mediated AEs in the vast majority (>85%) of patients

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Gastrointestinal

- Diarrhea/Colitis
  - Most commonly seen with Ipi-30%(10% grade 3/4), combo therapy-50% (20% grade 3/4)
  - Less common with anti-PD-1/anti-PD-L1 therapy alone- 18-20% (1-3% grade 3/4)
  - 1%- fatal bowel perforation (Ipi)
  - Median onset is 7.4 wks (1.6-13.4)

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Dermatologic

- Rash/Pruritus
  - Most common reported irAE (40-50% monotherapy-up to 60% combo therapy)
  - Pruritus in absence of rash occurs approximately 10-30% of cases.
  - Reported cases of Stevens-Johnsons Syndrome or Toxic Epidermal Necrolysis (TENS)
- Vitiligo
  - 3% grade 1-2
  - 0% grade 3-5

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Hepatotoxicity

- Immune mediated hepatitis/elevated LFT's
  - 30% any grade in combo therapy (15% grade 3-4)
  - <10% in monotherapy
  - 0.2% hepatic failure
  - Can manifest as transaminitis, hyperbilirubinemia or both

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Endocrinopathies

- Hypothyroidism/hyperthyroidism common
- Incidence around 4-10% (mono) up to 20% (combo)
  - Usually presents in two phases:
    - Acute/inflammatory/painless thyroiditis associated thyrotoxicosis (↓TSH, ↑FT4 and/or T3)
    - Resolution to euthyroid or progress to overt hypothyroidism (TSH >10)
  - May present as lab abnormalities only (asymptomatic)
  - May be early indicator of other endocrinopathies (i.e hypophysitis)

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Endocrinopathies cont.

- PGA incidence
  - Likely underreported, and/or lumped in with other irAE's
- Hypophysitis
  - Clinically present with fatigue (the "run over by the truck" phenomenon) abrupt onset headache, possible visual changes/nausea/vomiting
  - Low or undetectable ACTH & AM cortisol levels
  - Enlarged pituitary on MRI (75%)
- Panhypopituitarism
- Adrenal Insufficiency
  - Primary-rare
  - Secondary- almost universal after hypophysitis

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Neuropathy

- Several cases of Guillain-Barre type syndrome have been reported
- Severe motor/sensory neuropathy
  - Unilateral or bilateral
- Incidence around 1%
- Can present late

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Hematologic

- Anemia (including hemolytic anemia)
- ITP/TTP
- Thrombocytopenia
- HUS
- DIC
- Exact incidence not known

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Additional irAE's

- Incidence rate of around1-2 %
- Most common with anti-PD-1 therapy
  - Pneumonitis (up to 6% in combo therapy)
  - Pancreatitis
  - Nephritis
  - Myocarditis
  - Pericarditis
  - Uveitis/Iritis
  - Diabetes

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Pneumonitis

- May present asymptomatically (only seen on scans)
- DOE, SOB at rest, orthopnea
- Dry nagging cough (deep in chest)
- Chest pain

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Pancreatitis/diabetes

- Often present with vague abdominal pain (postprandial)
- Extreme fatigue
- Nausea and vomiting
- Sudden unexplained weight loss
- Steatorrhea (oily, smelly stools)
- Polydipsia, polyuria

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Uveitis/iritis

- “Dry eyes”
- Pain, visual changes
- Floaters
- Field vision deficit

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Pretreatment Nursing Evaluation and Pertinent Education

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Gastrointestinal-Nursing Assessment

- # of baseline stools
- Stool consistency
- History of GI problems (i.e IBS, chronic constipation)

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Dermatologic- Nursing Assessment

- Skin integrity
- History of dermatitis, chronic rash
- Complete skin assessment for existing rash

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Neurologic-Baseline Nursing Assessment

- Has patient had prior neurotoxic chemotherapy?
- Pre-existing diabetes or diabetic neuropathy?
- Other history of neuropathy or neurologic condition?
- Existing brain mets?

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Endocrinopathies- Baseline Nursing Assessment

- History of thyroid disease (i.e primary hypothyroidism, Hashimoto's)
- Baseline history of headaches
- Baseline fatigue level

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Hematologic-Baseline Nursing Assessment

- Assess pre-treatment CBC
- Any history of hematologic disorder?
- Is patient a lymphoma patient?

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Additional Baseline Nursing Assessments

- Any pulmonary conditions (i.e asthma, COPD)?
- Any pre-existing cardiac conditions? Received any other cardiotoxic drugs?
- History of renal issues? Assess baseline creatinine.
- History of dry eyes, cataracts, other ocular issues?
- History of pancreatitis?
- History or predisposition for diabetes?

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Additional Pretreatment Labs/Evaluation

- PE, CBC w/differential, CMP, LFT's , TSH (FT4 if abnormal)
- Assess for any history of autoimmune disorder or history of/risk for diabetes
- Assess medications for current steroid use, or thyroid replacement
- Assure provider has given patient prescription for steroids
  - Patients should have this filled
  - Instruct not to use unless under direction of provider.
- **Assure patient has emergency phone numbers**

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Ongoing Assessments (prior to subsequent cycles)

- PE, repeat baseline labs
- Skin assessment (rash, pruritus, vitiligo)
- Bowel assessments (quantity, quality, hematochezia)
- Fatigue (assess 0-10)
- Abdominal pain (cramping, bloating)
- Respiratory status (DOE, orthopnea, dry nagging cough in absence of fever)
- Neurologic status (numbness, tingling, weakness)
- Eye discomfort (dryness, pain in the eye)
- Headache (sudden onset, unrelenting)

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MAYO CLINIC

Principles of irAE Management

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STEROIDS-STEROIDS-STEROIDS

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MANAGEMENT OF DIARRHEA/COLITIS

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Management of diarrhea/colitis

- Assess the following:
  - # of stools over baseline
  - Red flags:
    - Abdominal pain
    - Blood or mucus in stool
    - Fever
    - If any of the above-pt needs to be ruled out for bowel perforation
  - Rule out any infectious etiology
    - Don't hold steroids while awaiting results

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Management of diarrhea/colitis cont.

- Grade 1 (<4 stools above baseline)
  - BRAT diet
  - Avoid anti-diarrheals
  - Increase fluid intake
  - Instruct patients to report any of the following:
    - Increase in #
    - Bloody stools
    - Abdominal pain
- Contact patient weekly between treatments

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Management of diarrhea/colitis cont.

- Grade 2 (4-6 stools over baseline)
- Grade 3 and above (>7 stools over baseline)
  - Everything from grade 1
  - Steroids
  - Patients need to be called twice weekly until resolved to <or= grade 1
  - Patients at risk for dehydration (may need hospitalization).

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Management of diarrhea/colitis cont.

- Once patients have improvement of symptoms to grade 0 or 1-taper of steroids should occur over at least 1 month
  - **Beware of rebound diarrhea!**
- If patients have been started on budesonide in addition to systemic steroids, start tapering the prednisone **FIRST**.
- **Do NOT administer antidiarrheals in patients with ≥ Grade 2 diarrhea as this may cause toxic megacolon and/or perforation.**

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MANAGEMENT OF RASH/PRURITUS

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Management of Rash/Pruritis

- Assess the following:
  - Percentage BSA of rash/pruritis
  - Any blistering/skin peeling?
  - Any fever?
  - Any lesions in oral mucosa/anogenital area?
- Instruct patient to report:
  - Any of the above
  - Worsening of rash/pruritis

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• Management of Rash/Pruritis cont.

- Contact patients 1-2 times weekly between treatments
- Assess compliance with topical medications/oral steroids/antihistamines
- Have patients avoid hot showers, excessive drying, etc.
- Encourage photoprotection in those with vitiligo

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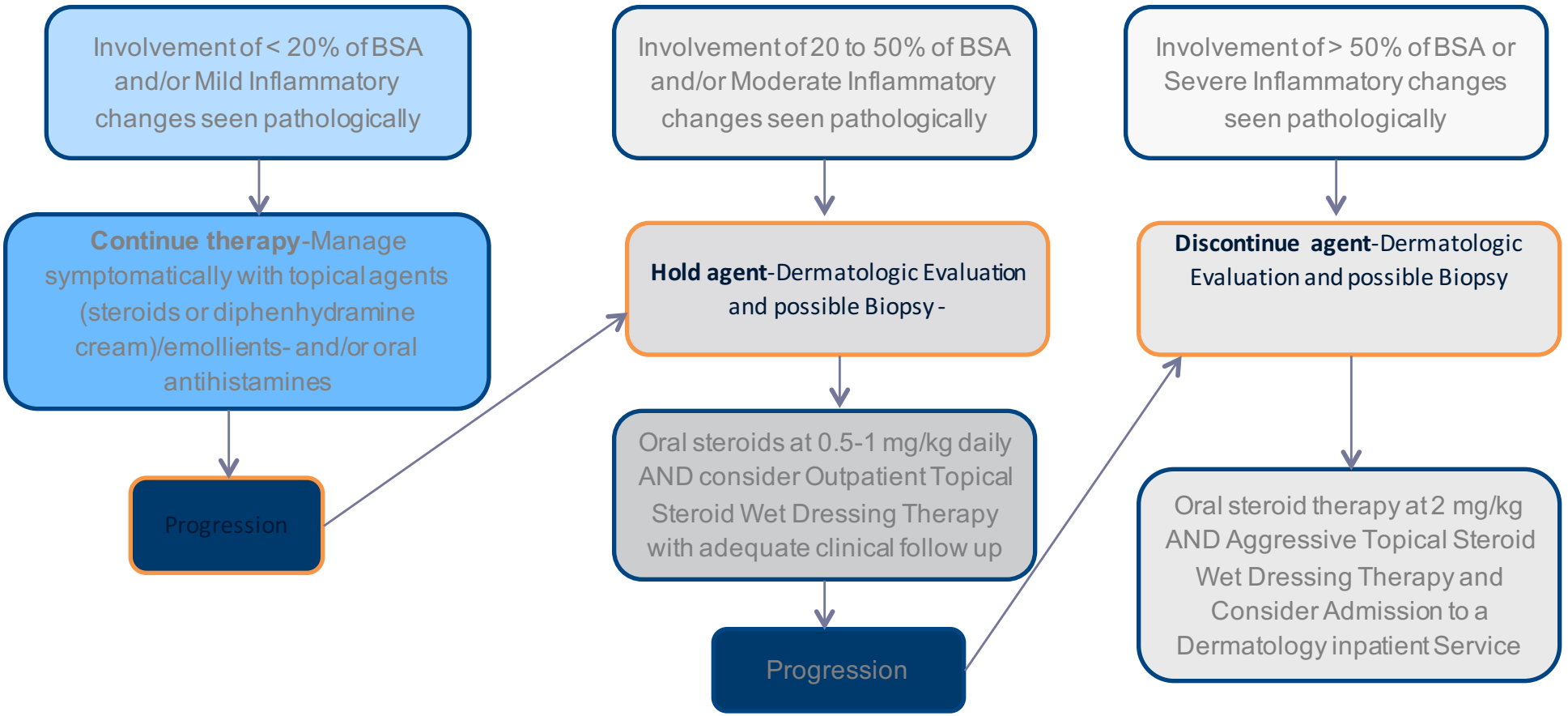

Algorithm for Dermatologic (rash and/or pruritus) irAE's from checkpoint inhibitor therapy

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Kottschade, L et. al- *Melanoma Research 2016*

MANAGEMENT OF ENDOCRINOPATHIES

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Thyroid disorders (hypo/hyperthyroidism)

- Assess for the following
  - Fatigue (both)
  - Hair loss (hypo)
  - Weight gain (hypo)- Weight loss (hyper)
  - Palpitations (hyper)
  - Sweating (hyper)
  - Nervousness/irritability/tremor (hyper)
  - Cold intolerance (hypo) heat intolerance (hyper)
  - Tightness of clothing around neck (both)

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Thyroid Disorders cont.

- Monitor patient compliance with medication
- Continue to reassess symptoms (may fluctuate with continued treatment)
- Instruct patients in proper method for taking thyroid replacement
  - Assess for concomitant medications
    - Iron, Antacids, calcium supplements
  - Take in am 1 hour prior to food or other medications

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Pituitary/Adrenal dysfunction

- Assess for the following:
  - Fatigue
  - Nausea/vomiting
  - Unrelenting headache
  - Weakness
  - Dizziness
  - Visual changes
  - Electrolytes (low NA- High K, low glucose- primary- may be normal in secondary)

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Pituitary/Adrenal Dysfunction cont.

- Primary Adrenal Insufficiency-**medical emergency**
- Secondary adrenal insufficiency (pituitary failure)
  - Instruct patients on the following:
    - Taking steroids as directed
    - Need for lifelong steroid replacement
    - “sick day” steroids
    - Stress dose steroids (prior to surgery, etc)
    - Medic alert bracelet
    - Long term sequelae of steroid use

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PNEUMONITIS

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Management of Pneumonitis

- Assess the following:
  - DOE, orthopnea, any SOB at rest
  - Dry nagging cough (especially in absence of infectious symptoms)
  - Chest pain
  - Pulse ox prior to treatments (random spot checks)
  - Respiratory rate
  - Compliance with prior COPD/Asthma medications

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Management of Pneumonitis cont.

- Instruct patients on the following:
  - The need to report any difficulty breathing, cough, chest pain
  - Compliance with steroids (oral and inhaled)

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Principles of steroid management

- DO NOT use Medrol Dose paks
- Once irAE is resolved to grade 1 or baseline, taper steroids over at least one month.
- Closely monitor diabetics (or those at risk) for changes in glucose levels
- Be mindful of patients on long term steroid therapy and possibility of secondary infections, difficulty wound healing, GERD, etc.

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Important take home points

- Up front education-empower pts
- Frequent assessments
- Don’t be afraid to use steroids
- Beware of rebound symptoms (GI, rash)-need to taper steroids slowly.

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Case Study #1

- 39 yo. Female-
- Receiving Ipilimumab/Nivolumab for metastatic melanoma
- After cycle #3 she calls with diarrhea-3 stools in 24 hours. Watery, no fever, no hematochezia

- What would you do?

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- 1. Tell her she “likely picked up a bug” and it will go away in a few days
- 2. Tell her to take Imodium and call if it gets worse
- 3. Discuss the BRAT diet, keeping well hydrated, get stool studies, check in with her weekly, and instruct to call if worse
- 4. Tell her to go to the ER

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- Patient calls back 4 days later and now has 12 stools in a 24 hour period, is lightheaded and dizzy and has noticed some blood in her stool, with abdominal pain.

- What would you do?

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- 1. Tell her to start taking 60 mg of prednisone (1 mg/kg).
- 2. Have her come to the clinic for fluids
- 3. Instruct her to report to the nearest ER.
- 4. Get stool studies and you'll call her once those results are available, but for now to keep hydrated and use a liquid diet.

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Case Study #2

- 60 y.o male on adjuvant ipilimumab for high risk resected melanoma.
- Patient has had 3 cycles of induction therapy and present to clinic for his 4th induction cycle with the following symptoms:
  - Moderate fatigue and a pruritic rash that covers 30-40% of his body.
  - Labs show moderately elevated LFT's (approximately 3x ULN)

What would you do?

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- 1. Have him use OTC hydrocortisone cream, rest and call you if the rash gets worse. Proceed with next dose of therapy.
- 2. Hold therapy and start prednisone at 1 mg/kg daily-recheck LFT's in 1 week
- 3. Tell patient to take zyrtec 10 daily & Benadryl 25 mg every 6 hr prn and avoid hot showers. Manage fatigue symptomatically. Give next dose of Ipi.

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Questions?

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THANK-YOU!

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