Society for Immunotherapy of Cancer

ADVANCES IN Cancer IMMUNOTHERAPY™

Toxicity Management

Jung-Min Song, CNS/RN

Cleveland Clinic Taussig cancer institute

AAEM AMERICAN ACADEMY OF EMERGENCY MEDICINE CHAMPION OF THE EMERGENCY PHYSICIAN

ACCC Association of Community Cancer Centers

HOPA Hematology/Oncology Pharmacy Association

Society for Immunotherapy of Cancer

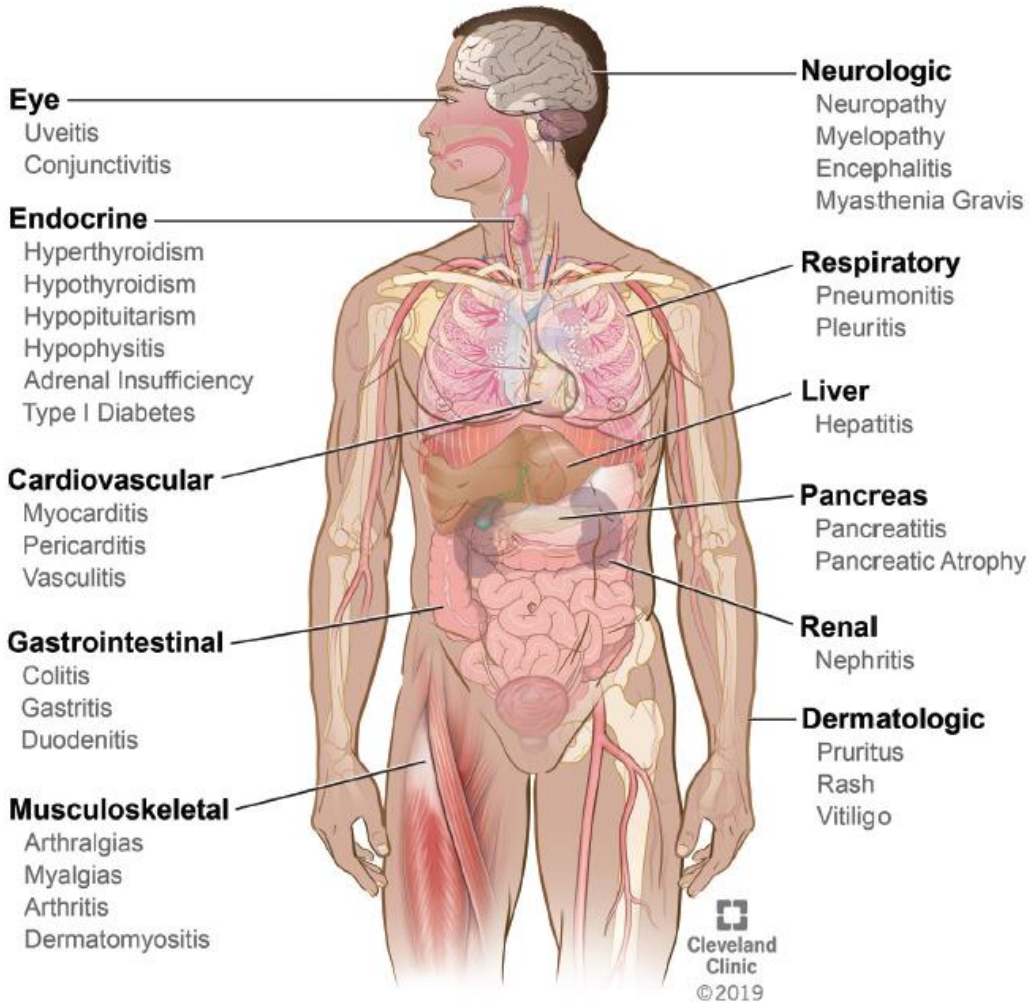
Disclosures

- I do not have any financial disclosures.
- I will be discussing non-FDA approved indications during my presentation.

Immune Related Adverse Events (irAEs)

- Each patient will develop different irAEs.
- Each irAE has different timing of onset.
- irAEs occur early and/or over prolonged period of time.
- First onset of irAEs can occur as long as 1 year after completion of treatment.
- Some irAEs can be permanent or life threatening.

irAEs by System



Common irAEs

- Colitis
- Hepatitis
- Pneumonitis
- Hypophysitis

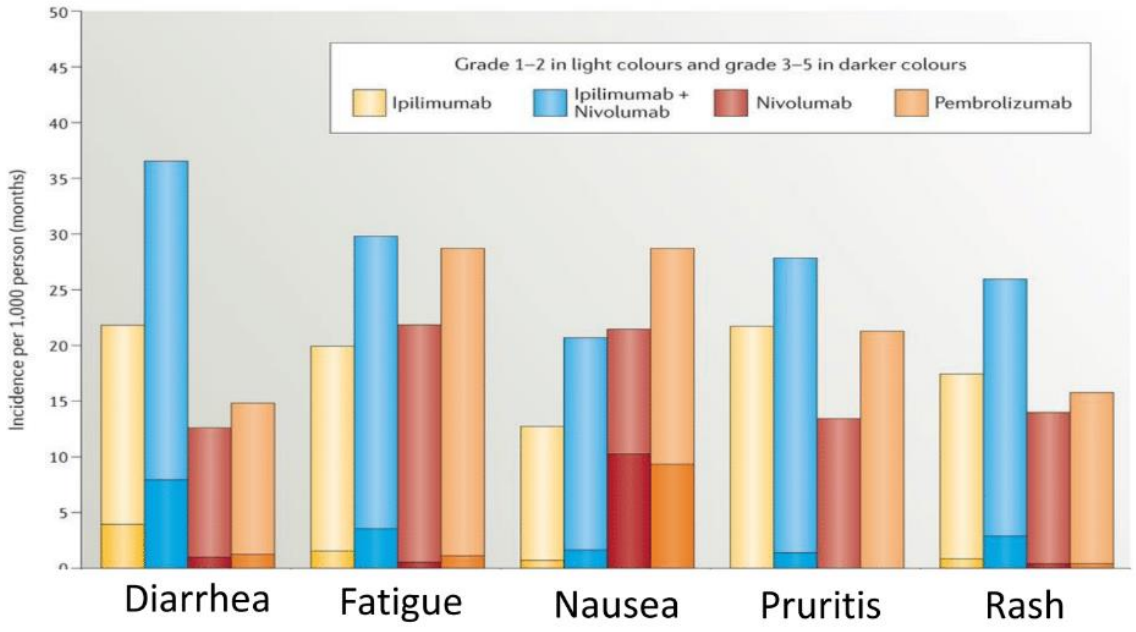
- Dermatitis
- Hypothyroidism
- Adrenal insufficiency
- Inflammatory arthritis

Rare irAEs

- Pancreatitis
- Duodenitis
- Nephritis
- Gastritis
- Myositis
- Rheumatoid arthritis
- Cytopenia
- Guillain-Barré syndrome

- Venous thromboembolism
- Uveitis, iritis
- Neuropathy
- DM type I
- Hyperthyroidism
- Pericarditis, vasculitis
- Myasthenia gravis
- Aseptic meningitis, encephalitis
- Bullous pemphigoid, Steven Johnson disease

Symptoms with ICPI



Other symptoms to look for

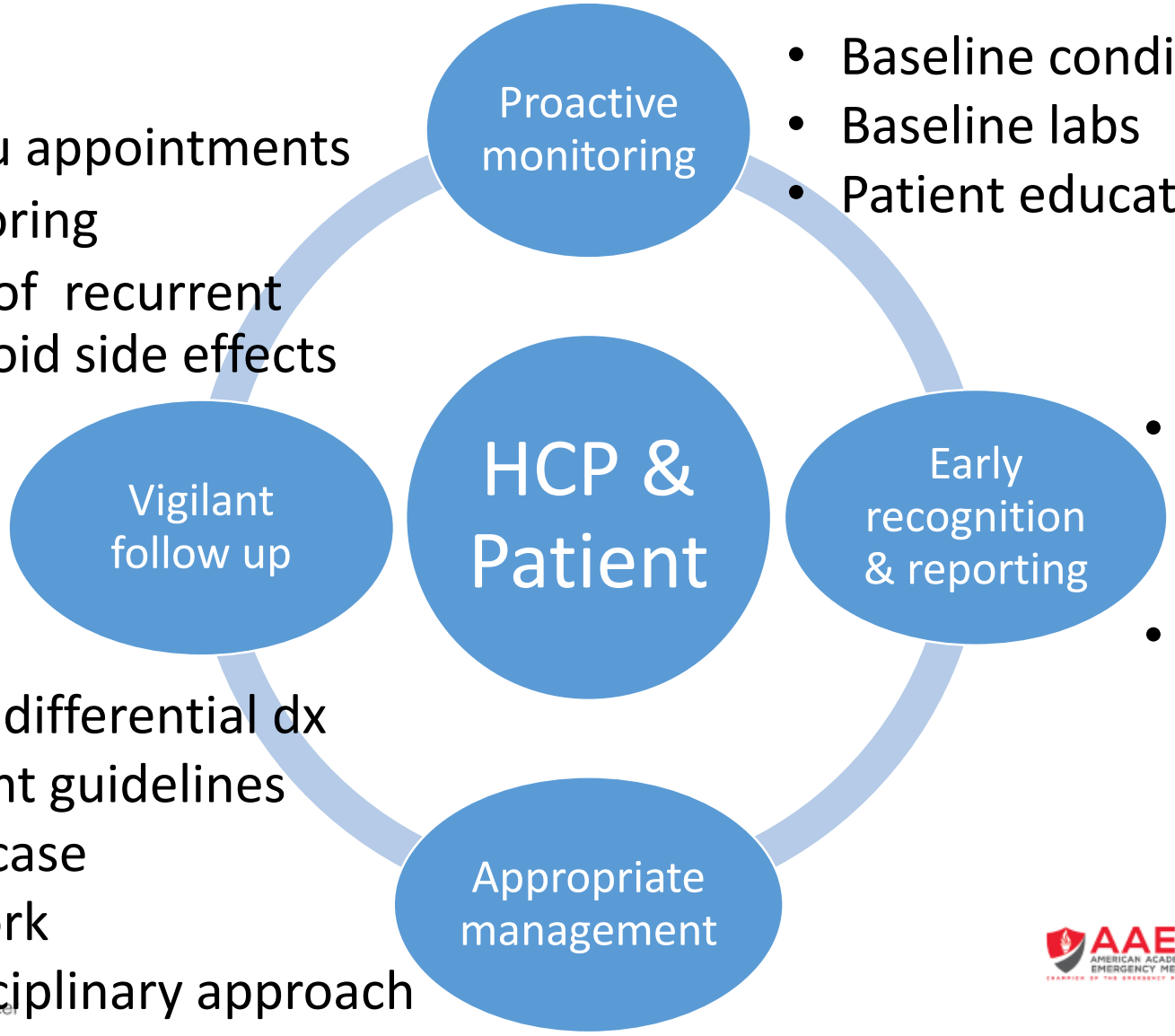
- Joint pain
- Dry mouth
- Dry eyes
- Fevers/chills
- Infusion reactions
- Hair loss

Boutros, *Nature Reviews Clinical Oncology*, 2016

irAE Crisis

- Adrenal insufficiency
- Hypophysitis
- DM I – DKA
- Misdiagnosed colitis
- Myocarditis

Principles of Management



- Baseline conditions
- Baseline labs
- Patient education

- Non-judgmental environment for patient to report irAEs
- Through assessment

- Rule out differential dx
- Treatment guidelines
- Case by case
- Team work
- Multidisciplinary approach

- Discharge f/u appointments
- Close monitoring
- Assessment of recurrent irAEs and steroid side effects

Labs/Tests for ICIP

Basic labs

- CBC with differential counts
- CMP
- TSH

At least baseline/Serially

- CK
- Troponin T
- ESR/CRP

Specializing testing

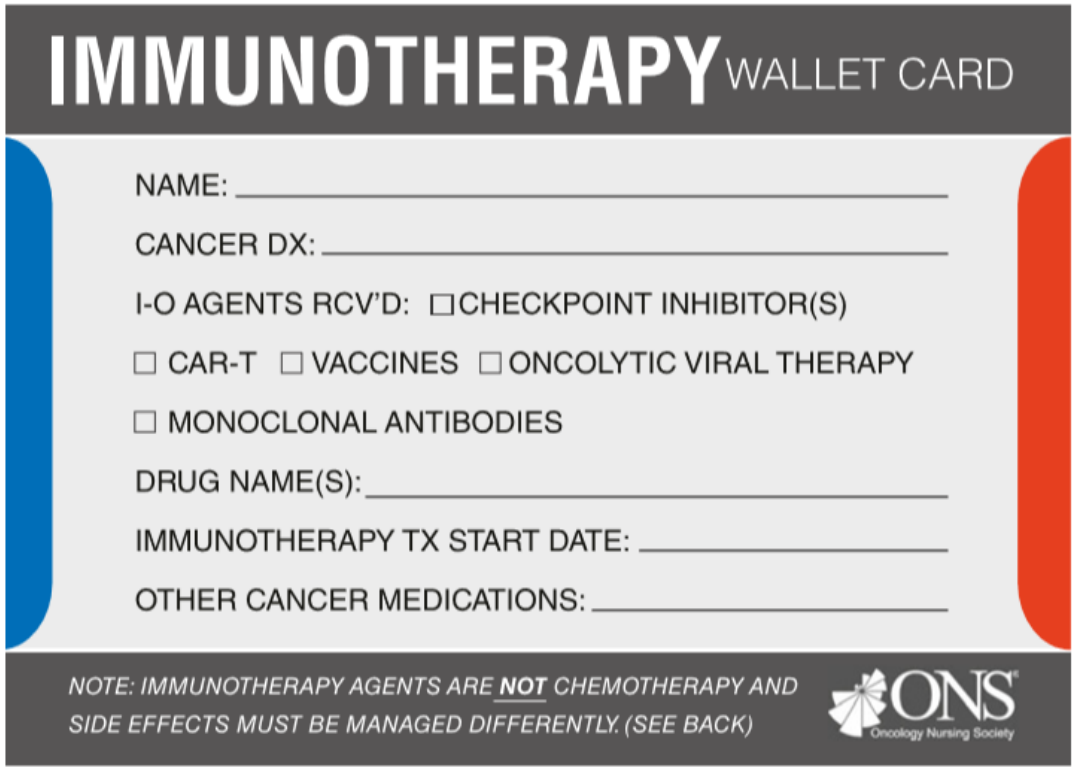
- Acute hepatitis panel, amylase, lipase
- Stool: c diff, stool culture, CMV, ova+parasite, fecal occult blood
- Imaging (CT, MRI, MRCP, US, etc.)
- Bronchoscopy
- EGD/Colonoscopy
- ECHO

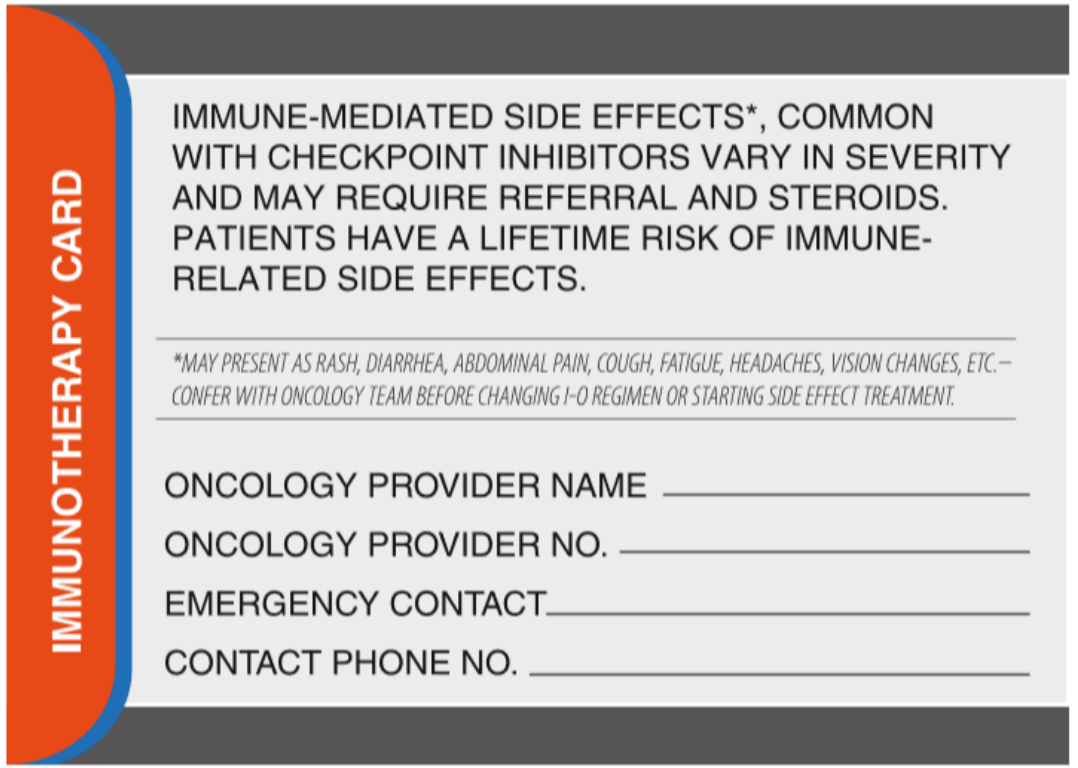
Nurse's Role in irAEs Management

- Face-to-face education during first treatment and ongoing
  - Teach patients mechanism of ICPi, irAEs, symptoms, toxicity management
  - Highlight the importance of reporting symptoms immediately
  - Give pertinent contact information.
  - Provide available resources, e.g. wallet card, handouts, 4th Angel program, Reflections, SW, nutrition, psych-oncology, art/music therapy etc.
- Follow-up call to check on patient's condition within 1 week of first tx
- First-line contact to assess changes in patient's condition and triage
- Close monitoring throughout treatment of irAEs
- Emotional support to patients and care givers

Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

Immunotherapy wallet card





AAEM American Academy of Emergency Medicine
ACCC Association of Community Cancer Centers
HOPA Hematology/Oncology Pharmacy Association
sitc Society for Immunotherapy of Cancer

irAE Guideline I

Annals of Oncology 28 (Supplement 4): iv119–iv142, 2017
doi:10.1093/annonc/mdx225

CLINICAL PRACTICE GUIDELINES

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

J. B. A. G. Haanen[1], F. Carbonnel[2], C. Robert[3], K. M. Kerr[4], S. Peters[5], J. Larkin[6] & K. Jordan[7], on behalf of the ESMO Guidelines Committee*

[1]Netherlands Cancer Institute, Division of Medical Oncology, Amsterdam, The Netherlands; [2]Department of Gastroenterology, Kremlin Bicêtre Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France; [3]Department of Medicine, Dermatology Unit, Gustave Roussy Cancer Campus, Villejuif, France; [4]Department of Pathology, Aberdeen University Medical School & Aberdeen Royal Infirmary, Aberdeen, UK; [5]Oncology Department, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland; [6]Royal Marsden Hospital NHS Foundation Trust, London, UK; [7]Department of Medicine V, Hematology, Oncology and Rheumatology, University Hospital of Heidelberg, Heidelberg, Germany

*Correspondence to: ESMO Guidelines Committee, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland. E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Committee: May 2017.

irAE Guideline II

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)
in partnership with the American Society of Clinical Oncology (ASCO)

Management of Immunotherapy-Related Toxicities

(Immune Checkpoint Inhibitor-Related Toxicities)

Version 1.2018 — February 14, 2018

NCCN.org

irAE Guideline III

VOLUME 36 · NUMBER 17 · JUNE 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline

Julie R. Brahmer, Christina Lacchetti, Bryan J. Schneider, Michael B. Atkins, Kelly J. Brassil, Jeffrey M. Caterino, Ian Chau, Marc S. Ernstoff, Jennifer M. Gardner, Pamela Ginex, Sigrun Hallmeyer, Jennifer Holter Chakrabarty, Natasha B. Leighl, Jennifer S. Mammen, David F. McDermott, Aung Naing, Loretta J. Nastoupil, Tanyanika Phillips, Laura D. Porter, Igor Puzanov, Cristina A. Reichner, Bianca D. Santomasso, Carole Seigel, Alexander Spira, Maria E. Suarez-Almazor, Yinghong Wang, Jeffrey S. Weber, Jedd D. Wolchok, and John A. Thompson in collaboration with the National Comprehensive Cancer Network

Common Terminology Criteria for Adverse Events (CTCAE) Ver. 5.0

Grade	Severity
1 Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2 Moderate	Minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL
3 Severe: medically significant but not immediately life-threatening	Hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
4 Life-threatening consequences	Urgent intervention indicated
5	Death related to AE

General corticosteroid management

Grade of irAE	Corticosteroid Management	Additional Notes
1	• Usually not indicated • Supportive care	• Delay/Continue immunotherapy
2	• Start oral **prednisone 0.5-1 mg/kg/day** • If IV required, start **methylprednisone 0.5-1 mg/kg/day** • If no improvement in 2-3 days, **increase dose** to 2 mg/kg/day • Once improved to ≤grade 1 AE, start **4-6 week steroid taper**	• **Hold immunotherapy** during corticosteroid use • **Continue immunotherapy** once resolved to ≤grade 1 and off corticosteroids • Start proton pump inhibitor with steroid for GI prophylaxis

Puzanov & Diab, JITC 2017.

General corticosteroid management

Grade of irAE	Corticosteroid Management	Additional Notes
3	• Start **prednisone 1-2 mg/kg/day** (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add **additional/alternative** immunosuppressant • Once improved to ≤ grade 1, start **4–6-week steroid taper** • Provide **supportive treatmen**t as needed	• **Hold immunotherapy**; if symptoms do not improve in 4–6 weeks, **discontinue immunotherapy** • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day) • Consultation
4	• Start **prednisone 1-2 mg/kg/day** (or equivalent dose of methylprednisolone) • If no improvement in 2–3 days, add additional/alternative immune suppressant, e.g., **infliximab** • Provide **supportive care** as needed	• **Discontinue immunotherapy** • Start proton pump inhibitor for GI prophylaxis • Add PCP prophylaxis if more than 3 weeks of immunosuppression expected (>30 mg prednisone or equivalent/day) • Consultation

Pazanov & Diab, JITC 2017.

Additional Immunosuppressive Treatments

Off - label use

Organ-specific interventions

- Hepatitis: budesonide, mycophenolate mofetil
- Colitis: infliximab
- RA: NSAID, hydroxychloroquine, infliximab, methotrexate
- Pancreatitis: rituximab
- Myocarditis: abatacept, alemtuzumab

Supportive Management

- Dermatitis – hydrocortisone topical cream, antihistamine
- Hypothyroidism - levothyroxine
- Adrenal insufficiency – hydrocortisone po
- Venous thromboembolism – anticoagulant
- Uveitis – steroid eye drops
- Inflammatory arthralgia – steroid injection

Case 1: 31yr F Metastatic Melanoma

Positive BRAF V600E mutation

Site of metastases**:** SQ on lower abdomen and breast, nodes, bone

Personal/family hx: no significant history

Oncology history:

- 2012 Melanoma of the left thigh: Stage IIIA (pT2N1a), Breslow 1.1mm. Clark IV, 1/25LN (0/24 CLND).
- 2013 One year of adjuvant interferon
- 3/2019 -5/19 ipilimumab and nivolumab x 3
- 7/2019 encorafenib 450 mg daily and binimetinib 45mg BID

Case 1: 31yr F Metastatic Melanoma

- Day 28, ED visit for fevers (100.4 ^{o}F), sweating, tachycardia (104-123)
- Day 31, ED visit for fevers, nausea, vomiting, loose stools x 4, palpitation

		Day 0	Day 23	Day 32	Day 34	Day 42	Day 63	Day 113
TSH	**0.400-5.55uU/mL**	**3.02**	**0.024**	**0.008**	**0.023**	**0.856**	**38.12**	**2.76**
Free T4	**0.9 - 1.7 mg/dL**						**0.5**	**1.2**
Free thyroxine	**0.76 - 1.46uU/dL**			**2.32**				
T3 total	**0.6 -1.8 ng/mL**			**1.9**				

How to Treat ir Thyroiditis?

Hyperthyroidism

G1: Asymptomatic or mild symptoms	Can continue ICPi with close follow-up and monitoring of TSH, FT4 every 2-3 weeks until it is clear whether there will be persistent hyperthyroidism (see below) or hypothyroidism (see 4.1.1)
G2: Moderate symptoms, able to perform ADL	Consider holding ICPi until symptoms return to baseline Consider endocrine consultation β-Blocker (eg, atenolol, propranolol) for symptomatic relief Hydration and supportive care Corticosteroids are not usually required to shorten duration For persistent hyperthyroidism (> 6 weeks) or clinical suspicion, work-up for Graves disease (TSI or TRAb) and consider thionamide (methimazole or PTU) Refer to endocrinology for Graves disease

Hypothyroidism

G1: TSH < 10 mIU/L and asymptomatic	Should continue ICPi with close follow-up and monitoring of TSH, FT4
G2: Moderate symptoms; able to perform ADL; TSH persistently > 10 mIU/L	May hold ICPi until symptoms resolve to baseline Consider endocrine consultation Prescribe thyroid hormone supplementation in symptomatic patients with any degree of TSH elevation or in asymptomatic patients with TSH levels that persist > 10 mIU/L (measured 4 weeks apart) Monitor TSH every 6-8 weeks while titrating hormone replacement to normal TSH FT4 can be used in the short term (2 weeks) to ensure adequacy of therapy in those with frank hypothyroidism where the FT4 was initially low Once adequately treated, should monitor thyroid function (at least TSH) every 6 weeks while on active ICPi therapy or as needed for symptoms to ensure appropriate replacement; repeat testing annually or as indicated by symptoms once stable

Brahmer, et al. Journal of Clinical Oncology, 2018

Immune Related Thyroiditis

		Day 0	Day 23	Day 32	Day 34	Day 42	Day 63	Day 113
TSH	0.400-5.55uU/mL	3.02	0.024	0.008	0.023	0.856	38.12	2.76
Free T4	0.9 - 1.7 mg/dL						0.5	1.2
Free thyroxine	0.76 - 1.46uU/dL			2.32				
T3 total	0.6 -1.8 ng/mL			1.9				

Propranolol 10mg TID

Levothyroxine 100 mcg

Case 1: 31yr F Metastatic Melanoma

- Day 82, ED visit for fevers/chills, vomiting x 1, abdominal pain, fevers
- Labs: AST/ALT: 425/518, total bilirubin 2.5
- US RUQ: thickening gall bladder

Day 83, IM admission note

Hospital

Metastatic malignant melanoma (HCC)

Current Assessment & Plan

Assessment: mets to SQ lower abdomen and breast, left EI node
Chemotherapy- ipilimumab and nivolumab s/p 3 cycles
PLAN:
-F/u with primary oncologist outpatient

*** (Principal) Fever**

Current Assessment & Plan

Assessment: 2/2 possible acalculous cholecystitis vs viral respiratory infection
No urinary symptoms.
Denies any headache, rash.
CXR negative for infection
PLAN:
-BI cx ordered (not obtained in ED prior to Zosyn)
-Continue Zosyn, HIDA scan and gen surg consult for gallbladder thickening
-MIVF
-Continue tessalon PRN cough

Thickening of wall of gallbladder

Current Assessment & Plan

Assessment: With associated transaminitis and hyperbili though relatively benign exam.
RUQ US no evidence of stones or fluid
PLAN:
-Gen surg consulted
-HIDA scan
-MIVF
-Continue Zosyn
-Morphine PRN pain
-Zofran PRN nausea

Hashimoto's disease

Current Assessment & Plan

Assessment: Followed by endocrinology
PLAN:
-Continue propanolol

Case 1: 31yr F Metastatic Melanoma

		Day 0	Day 61	Day 63	Day 71	Day 83	Day 84	Day 85
total bilirubin	0.2 - 1.3 mg/dL	0.3	0.4	0.4	0.3	2.5	1.7	1.3
AST	13-35 U/L	17	27	40	25	505	372	346
ALT	7 - 38 U/L	21	46	46	55	518	385	339
Alk phosphatase	34 - 123 U/L	68	148	156	143	425	466	544

Day 85, Discharge Note

Assessment/Plan

Active Problems:

1. Abdominal pain with finding of colitis, leukocytosis, fever, and sepsis
-- Sepsis protocol
-- IV Vancomycin and Zosyn
-- Monitor blood cultures
-- Monitor lactate
-- IV Zofran prn nausea
-- IV morphine prn pain
-- IV PPI
-- ID consult

2. Metastatic melanoma
-- Continue home medications (chemo)

3. Hypothyroidism/thyroiditis
-- Continue Synthroid
-- Check TSH

How to Treat Immune Related Hepatitis?

G3: Symptomatic liver dysfunction, fibrosis by biopsy, compensated cirrhosis, reactivation of chronic hepatitis (AST or ALT 5-20 × ULN and/or total bilirubin 3-10 × ULN)	Permanently discontinue ICPi Immediately start corticosteroid 1-2 mg/kg methylprednisolone or equivalent If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil or azathioprine (if using azathioprine should test for thiopurine methyltransferase deficiency) Laboratories at daily or every other day; consider inpatient monitoring for patients with AST/ALT > 8 × ULN and/or elevated TB 3 × ULN Increase frequency of monitoring to every 1-2 days Infliximab might not be the most appropriate treatment option in the situation of immune-mediated hepatitis given the potential risk of liver failure (Note: No clear evidence shows that the liver toxicity from infliximab from other studies); alternatives include non–TNF-α agents as systemic immunosuppressants If no improvement is achieved with corticosteroids or for patients on combination therapy with a novel agent, with standard chemotherapy, or with targeted therapy, refer to hepatologist for further pathologic evaluation of hepatitis Corticosteroid taper can be attempted around 4-6 weeks; re-escalate if needed; optimal duration unclear
G4: Decompensated liver function (eg, ascites, coagulopathy, encephalopathy, coma; AST or ALT > 20 × ULN and/or total bilirubin > 10 × ULN)	Permanently discontinue ICPi Administer 2 mg/kg/d methylprednisolone equivalents If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil Monitor laboratories daily; consider inpatient monitoring Avoid the use of infliximab in the situation of immune-mediated hepatitis Hepatology consult if no improvement was achieved with corticosteroid Corticosteroid taper can be attempted around 4-6 weeks when symptoms improve to G1 or less; re-escalate if needed; optimal duration unclear Consider transfer to tertiary care facility if necessary

Brahmer, et al. Journal of Clinical Oncology, 2018

Day 84, Oncology note

- Fever
  - Patient presented with abdominal pain and noted to be febrile
  - Continues to have intermittent fevers - last fever was 101.6F
  - 5/19 Blood cultures - NG < 2 days
  - 5/19 CXR - no acute process
  - 5/19 UCx insignificant colony of Enterococcus
  - Currently on Zosyn. Given 1 dose of Vancomycin on 5/20

  Plan:
  - Checking repeat cultures
  - Continue empiric Zosyn. Consider de-escalating antibiotics tomorrow if she remains afebrile
  - Monitor cultures and fever curve

- Metastatic malignant melanoma (H
  - Diagnosed 2012
  - Prior treatments: IFN
  - Current treatment: Ipilimumab/
  - Completed Cycle 3 5/7/2019
  - Had admission to Akron Gener admission
  - CMP improving on 5/20 labs

  Plan:
  - Current symptoms maybe immune-related toxicity (less likely, as they are now improving)
  - Monitor CMP. If LFT's continue to worsen, plan to start solumedrol 1mg/kg q24h for immune-related toxicity

- Thickening of wall of gallbladder
  - RUQ pain x 2 days (since Friday) - improving
  - U/S RUQ with gallbladder wall thickening
  - LFT's elevated on admission (AST/ALT 505/518, alkp 425,
  - HIDA shows *Normal gallbladder functional response/EF is not a typical scintigraphic finding of chronic cholecystitis. Clinical correlation is recommended. Patent cystic duct and CBD.*
  - MRCP shows *DIFFUSE, NONSPECIFIC GALLBLADDER WALL THICKENING. NO GALLBLADDER DILATION OR CHOLELITHIASIS. NO INTRA OR EXTRA HEPATIC BILIARY DUCTAL DILATION. NORMAL HEPATIC MORPHOLOGY WITHOUT LIVER MASS. NO HEPATIC STEATOSIS OR IRON DEPOSITION. BILATERAL RENAL MASSES SUSPICIOUS FOR NEOPLASM. THE LEFT RENAL MASS APPEARS NEW FROM 03/08/2019 PET/CT. DIFFERENTIAL INCLUDES METASTATIC DISEASE OR PRIMARY NEOPLASM.*

  Plan:
  - Per General Surgery - no signs of acute cholecystitis. Abdominal pain resolved and LFTs slowly trending down. General surgery will sign off, please call with questions or concerns. Appreciate recs
  - Continue Zosyn
  - Trend LFT's. Consider steroids if concern for autoimmune hepatitis 2/2 checkpoint inhibitors

Current symptoms maybe immune related toxicity (less likely, as they are not improving)

Monitor CMP. If LFTs continue to worsen, plan to start solumedrol 1mg/kg q 24h for ir toxicity

Immune Mediated Hepatitis

		Day 0	Day 61	Day 63	Day 71	Day 83	Day 84	Day 85	Day 92	Day 94	Day 98	Day 101	Day 103	Day 113
total bilirubin	0.2 - 1.3 mg/dL	0.3	0.4	0.4	0.3	2.5	1.7	1.3	1.1	1.2	1	0.8	0.7	0.3
AST	13-35 U/L	17	27	40	25	505	372	346	506	418	237	182	96	16
ALT	7 - 38 U/L	21	46	46	55	518	385	339	493	625	544	454	3.6	33
Alk phosphatase	34 - 123 U/L	68	148	156	143	425	466	544	279	418	237	189	176	102

Tapering plan

- After LFT is normal, tapering prednisone over 5 weeks
- After completion of prednisone, start tapering budesonide by 3mg biweekly

Prophylactic intervention for high dose steroid

Prednisone 60mg (>0.5mg/kg)
Budesonide 9mg daily

Case 1: 31yr F Metastatic Melanoma

- Day 147, ED visit for severe abdominal pain x 2 days, fatigue, constipation like feeling with loose stools, several vomiting, chills, fevers, tachycardia
- Baseline condition: once daily formed BM. Sometimes loose if nervous, lactulose sensitive

- 76 days after last ipilimumab + nivolumab
- 18 days after starting encorafenib (BRAFi)+ binimetinib (MEKi)

Case 1: 31yr F Metastatic Melanoma

- Labs: WBC 16.9, lipase 469, Lactic acid 3.6, Total bili 1.4, normal LFT, UA bacteremia
- CMV, EBV, enteric stool panel, c diff: Negative
- Pregnancy test: Negative
- KUB: Possible focal ileus at the left upper quadrant
- CT: There is now severe edematous wall thickening present throughout the ascending colon and hepatic flexure compatible with colitis.

Day 148, Oncology Note

Current Assessment & Plan

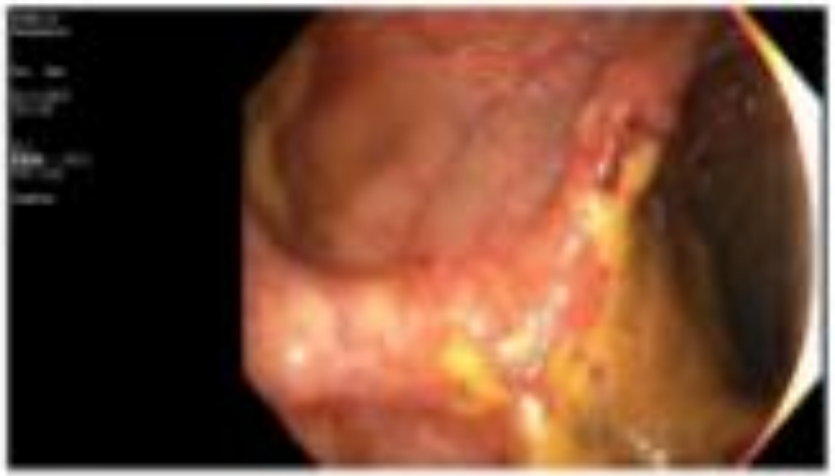
Assessment:

Presenting with persistent diffuse abdominal pain with CT evidence of colitis involving the ascending colon and hepatic flexure. Likely autoimmune colitis in the setting of chemotherapy. Also must rule-out infectious colitis. Patient received 2 days of vanc/zosyn at OSH. Received 1 dose of 120mg solumedrol at OSH.

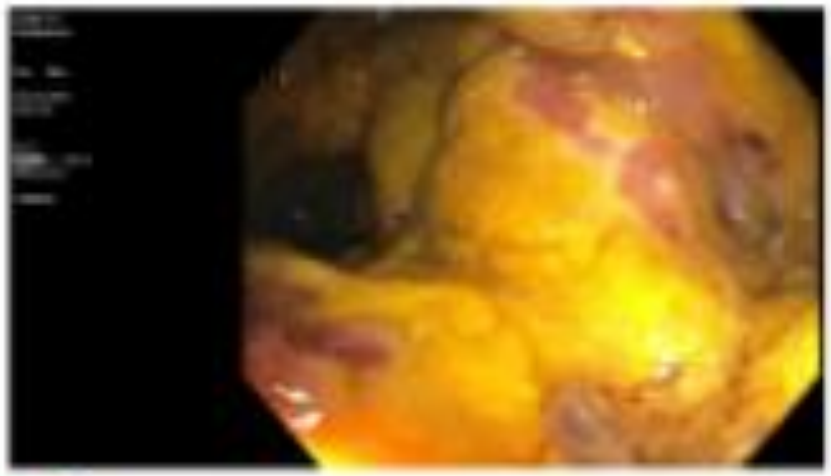
PLAN:

- 100mg solumedrol daily
- hold antibiotics with low threshold for reinitiating
- consult GI for consideration of colonoscopy to investigate etiology of colitis
- stool cultures and CMV testing
- continue home budesonide

Day 157, Colonoscopy



5 Hepatic Flexure



7 Ascending Colon

- Colonoscopy: Diffuse severe inflammation characterized by altered vascularity, erosions, friability, confluent ulcerations and deep ulcerations was found in the ascending colon.
- Biopsy: Active colitis in ascending and descending colon

How to Treat Immune Related Colitis?

Table 2. Management of GI irAEs in Patients Treated With ICPis

2.0 GI Toxicities
2.1 Colitis
Definition: A disorder characterized by inflammation of the colon
Diagnostic work-up
G2
Work-up of blood (CBC, comprehensive metabolic panel, TSH, ESR, CRP), stool (culture, *Clostridium difficile*, parasite, CMV or other viral etiology, ova and parasite) should be performed
Consider testing for lactoferrin (for patient stratification to determine who needs more urgent endoscopy) and calprotectin (to follow up on disease activity)
Screening laboratories (HIV, hepatitis A and B, and blood quantiferon for TB) to prepare patients to start infliximab should be routinely done in patients at high risk for those infections and appropriately selected patients based on infectious disease expert's evaluation
Imaging (eg, CT scan of abdomen and pelvis and GI endoscopy with biopsy) should be considered as there is evidence showing that the presence of ulceration in the colon can predict a corticosteroid-refractory course, which may require early infliximab
Consider repeating endoscopy for patients who do not respond to immunosuppressive agents; repeating endoscopy for disease monitoring can be considered when clinically indicated and when planning to resume therapy
G3-4
All the work-up listed for G2 (blood, stool, imaging, and scope with biopsy) should be completed immediately
Consider repeating endoscopy for patients who do not respond to immunosuppressive agents; repeating endoscopy for disease monitoring should only be considered when clinically indicated and when planning to resume ICPi

Brahmer, et al. Journal of Clinical Oncology, 2018

How to Treat Immune Related Colitis?

G3: Increase of seven or more stools per day over baseline, incontinence, hospitalization indicated, severe increase in ostomy output compared with baseline, limiting self-care ADL	Should consider permanently discontinuing CTLA-4 agents and may restart PD-1, PD-L1 agents if patient can recover to G1 or less. Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent) Consider hospitalization or outpatient facility for patients with dehydration or electrolyte imbalance If symptoms persist ≥ 3-5 days or recur after improvement, consider administering IV corticosteroid or noncorticosteroid (eg, infliximab) Consider colonoscopy in cases where patients have been on immunosuppression and may be at risk for opportunistic infections as an independent cause for diarrhea (ie, CMV colitis) and for those who are anti-TNF or corticosteroid refractory
G4: Life-threatening consequences; urgent intervention indicated	Permanently discontinue treatment Should admit patient when clinically indicated; patients managed as outpatients should be very closely monitored Administer 1-2 mg/kg/d methylprednisolone or equivalent until symptoms improve to G1, and then start taper over 4-6 weeks Consider early infliximab 5-10 mg/kg if symptoms refractory to corticosteroid within 2-3 days Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections

Brahmer, et al. Journal of Clinical Oncology, 2018

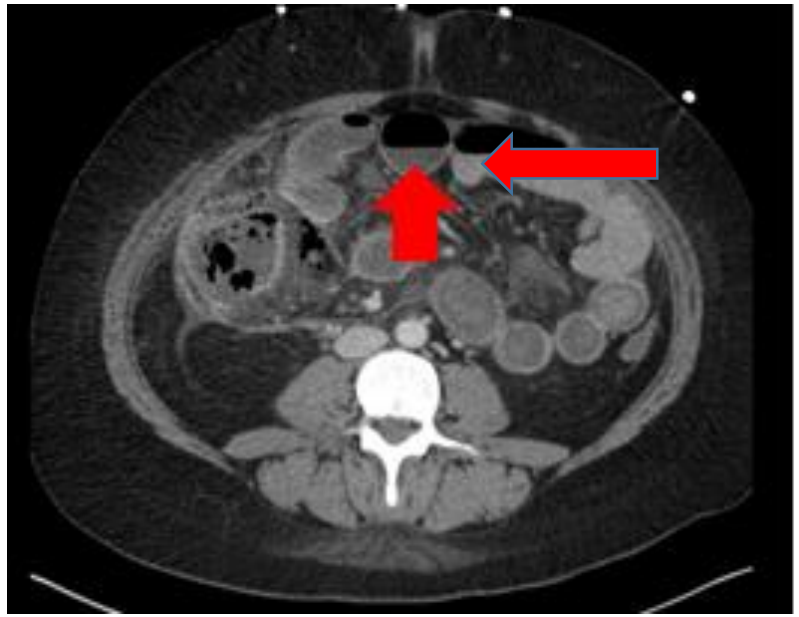
Case 1: 31yr F Metastatic Melanoma

- IV steroid 1.5mg/kg x 4 days, d/c'd home with oral steroid 1mg/kg

- Day 161, ED visit for severe abdominal pain, nausea, vomiting, abdominal distension, SOB
- Labs: WBC 21.87, Lactic acid 1.6, Lipase 128, CRP 15.7
- KUB: non specific pattern of proximal small bowel dilation

Day 161, CT abdomen

- PERFORATED ASCENDING COLITIS WITHOUT ASSOCIATED WALLED OFF COLLECTION.
  UPSTREAM DILATED SMALL BOWEL LOOPS CONSISTENT WITH ILEUS/PSEUDOOBSTRUCTION RELATED TO STASIS IN THE ASCENDING COLON



Case 1: 31yr F Metastatic Melanoma

- Day 161, Exploratory laparotomy, right hemicolectomy with 30 cm of terminal ileum resection, abdominal washout, implantation of the transverse colon blind end in the subcutaneous fat, creation of an end ileostomy.
- Continue methylprednisolone 100mg IV x 10 days
- Day 171, Discharged home with prednisone 100mg po daily
- Day 178, Outpatient discharge f/u – tapering over 8 weeks

Case 1: 31yr F Metastatic Melanoma

- Multiple irAEs
- Early and delayed irAEs
- Appropriate managements

Case 2: 54yr M metastatic melanoma

BRAF mutation

Sites of metastases: bone, jejunum, liver, and lymph nodes

Personal Hx: severe white coat HTN, former tobacco

Oncology history

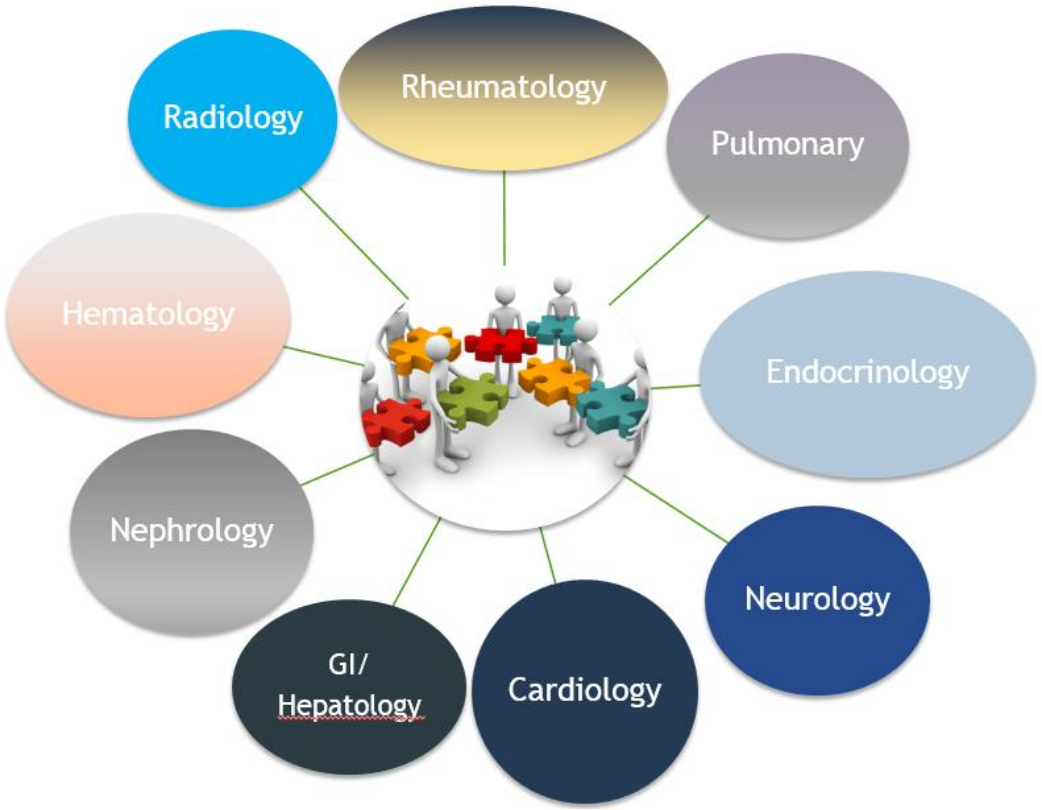
- 11/16 trial pembrolizumab +PEG – interferon
- 2/18 ipilimumab x 1 cycle
- 3/18 ipilimumab/nivolumab x 1 cycle
- 5/18-5/19: Nivo restarted 480mg
- 5/19 encorafenib 450 mg daily and binimetinib 45mg BID

Case 2: 54yr M metastatic melanoma

- Arthritis, Neuropathy, Colitis, Keratoconjunctivitis SICCA, Pansinusitis

- Management
- Multidisciplinary approach

Multidisciplinary team approach



Monthly irAEs tumor board

Cardiology - Dr. Rohit Moudgil/ Dr. Patrick Collier

Hepatology - Dr. Carlos Romero-Marrero

GI - Dr. Tavankhit Singh (fellow clinic), Donna Oliver(NP), Dr. Jessica Philpott

Rheumatology - Dr. Cassandra Calabrese/ Dr. Leonard Calabrese/ Dr. Mathilde Pioro

Dermatology - Dr. Josh Arbesman

Endocrinology -Dr. Leila Khan/ Dr Divya Yogi Morren

Neurology - Dr. Marisa McGinley/Dr John Morren

Nephrology –Dr. Georges Nakhoul / Dr. James Simon

Pulmonology – Dr. Manny Ribiero/ Dr. Aman Pande/ Dr. Kristen Highland

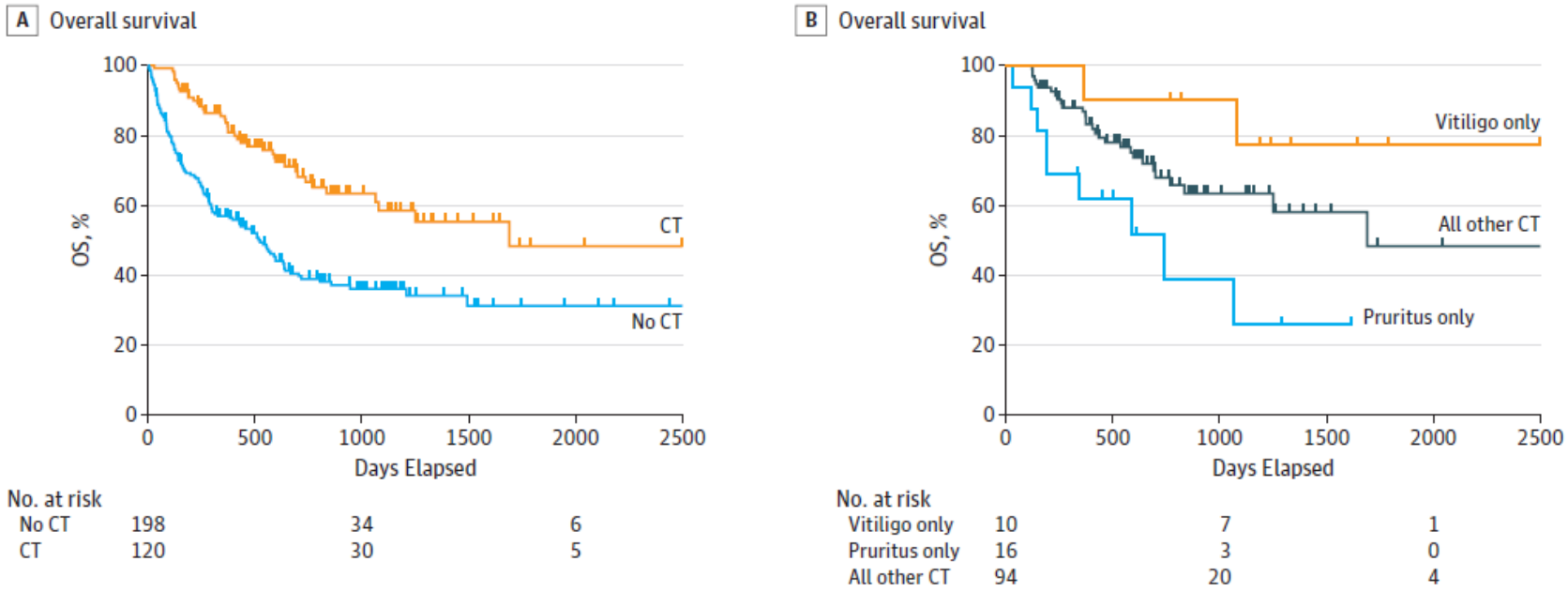
Hematology- Dr. Dana Angelini

Challenges to Manage irAEs

- Unique presentations with each individual
- Lack of understanding and awareness of irAEs in community and ER
- Unknown delayed irAEs after completion of ICPi
- Management of combination treatments, e.g. ICPi + targeted therapy, ICIi + chemotherapy
- New optional treatments evolving
- Management of long term steroid side effects
- Survivorship care plan for irAEs– f/u with oncologist vs PCP

irAEs as Prognostic Marker?

Figure. Comparisons of Overall Survival Using Log-Rank Testing



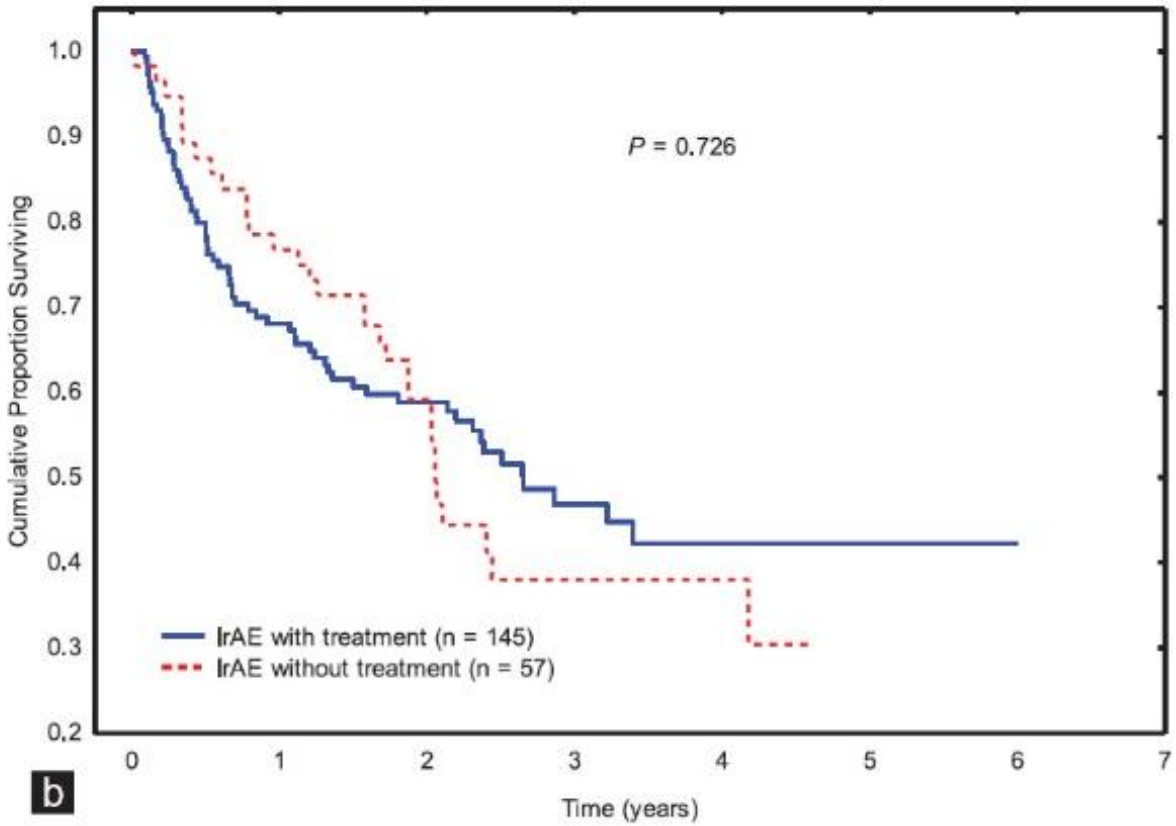
Quach, JAMA Oncology, 2019

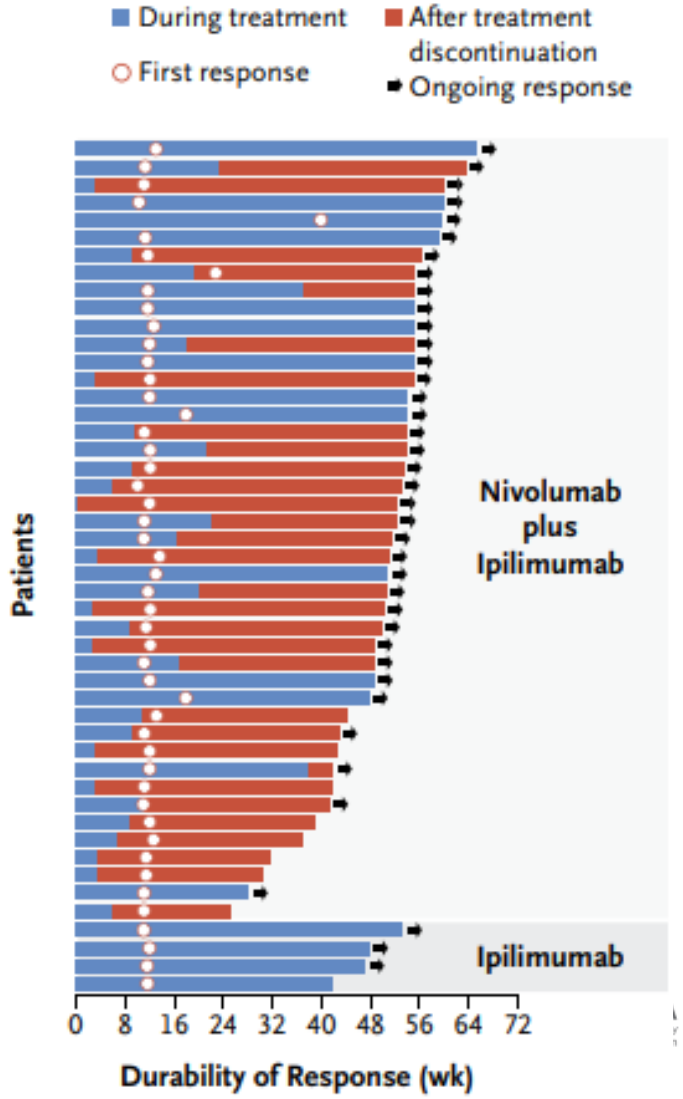
Impact of Toxicity Management on Treatment Outcomes

While still under debate,

the administration of immunosuppressive treatments for irAE management does not seem to impact cancer control.

Impact of Toxicity Management on Treatment Outcomes





Abu-Sbeih, J Immunoth Prec Oncol 2018
Pastow, The New England Journal of Medicine 2015

sitc Society for Immunotherapy of Cancer
ADVANCES IN Cancer IMMUNOTHERAPY™

Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma

M. H. Pollack[1,2†], A. Betof[3†], H. Dearden[4], K. Rapazzo[5,6], I. Valentine[7], A. S. Brohl[7], K. K. Ancell[5,6], G. V. Long[4,8,9], A. M. Menzies[4,8,9], Z. Eroglu[7], D. B. Johnson[5,6*,†] & A. N. Shoushtari[3†]