Recognizing and Managing the Toxicities of Treatment for Renal Cell Carcinoma

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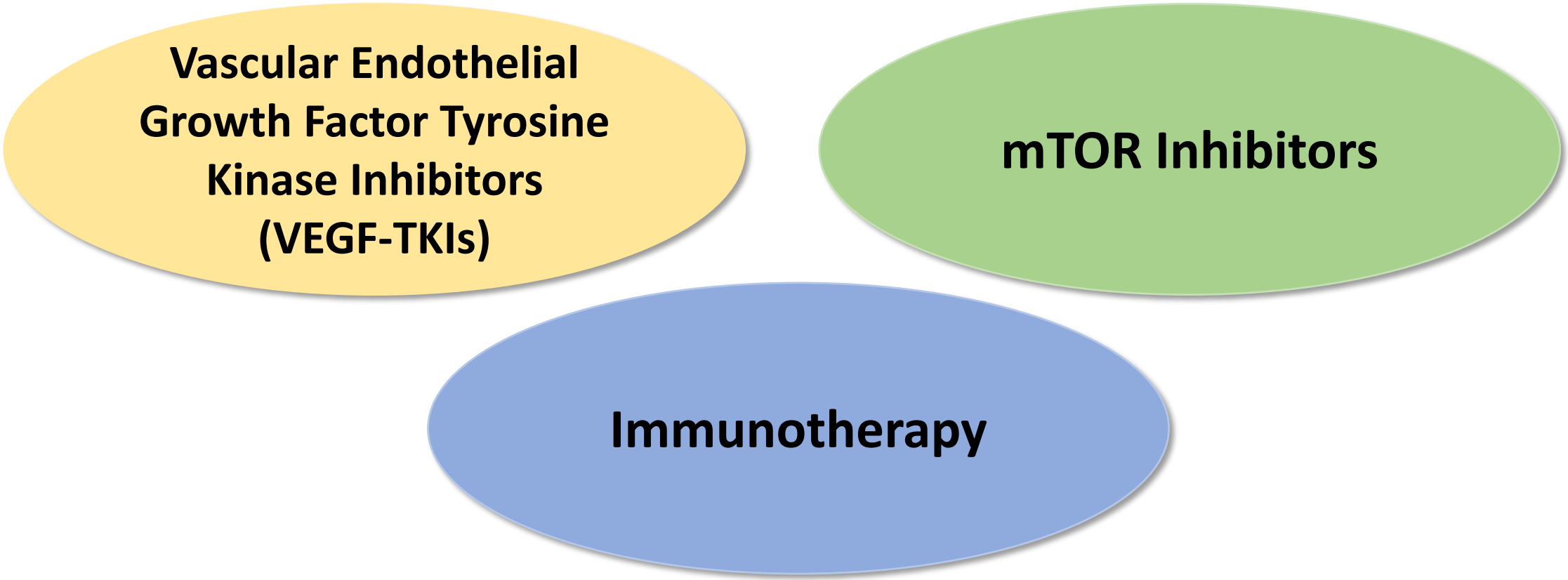
Classes of Therapy for Metastatic Renal Cell Carcinoma (RCC)



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Common Therapies for Metastatic RCC

- **VEGF-TKIs**
  - Sorafenib
  - Sunitinib
  - Pazopanib
  - Axitinib
  - Lenvatinib
  - Cabozantinib
- **Immunotherapies**
  - Nivolumab
  - Pembrolizumab
  - Ipilimumab
  - Avelumab
- **mTOR Inhibitors**
  - Everolimus
  - Temsirolimus

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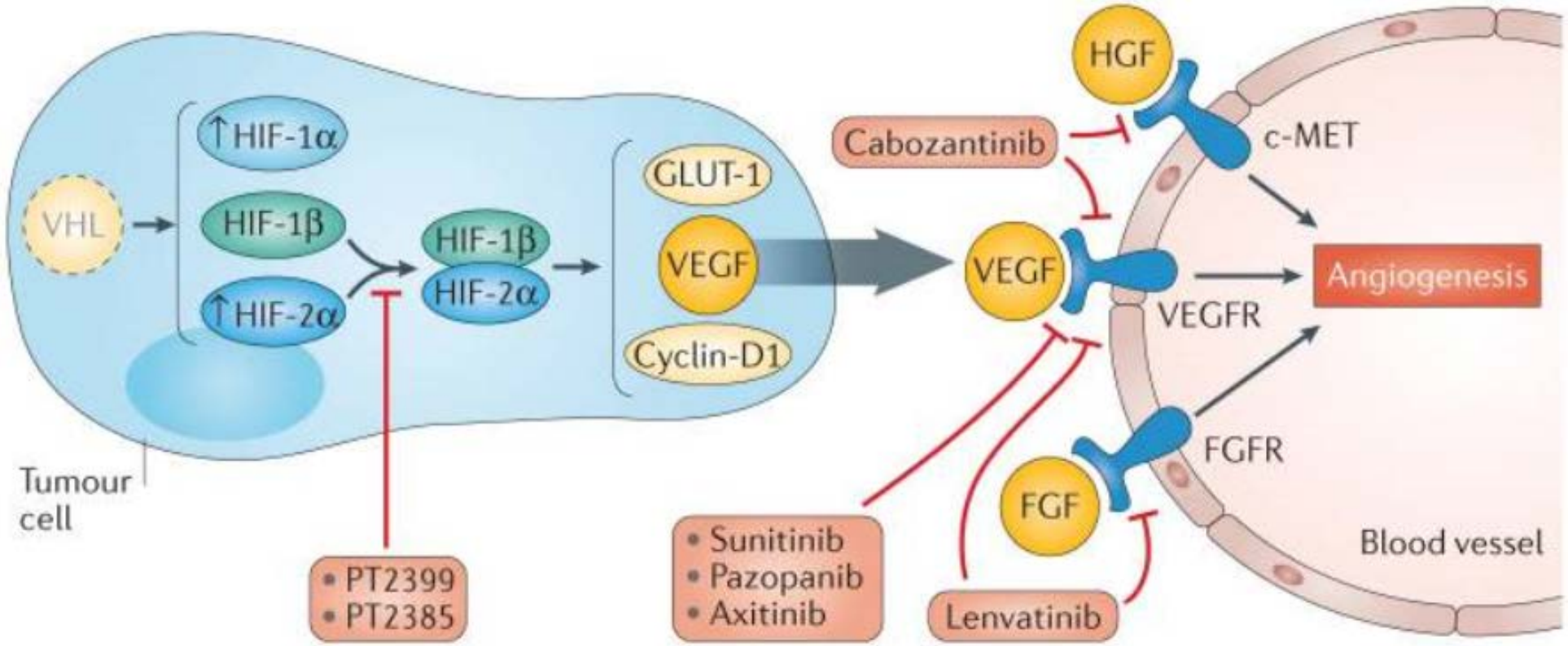
Mechanism of VEGF-TKIs



Lee and Motzer, Nature Reviews Nephrology, 2017.

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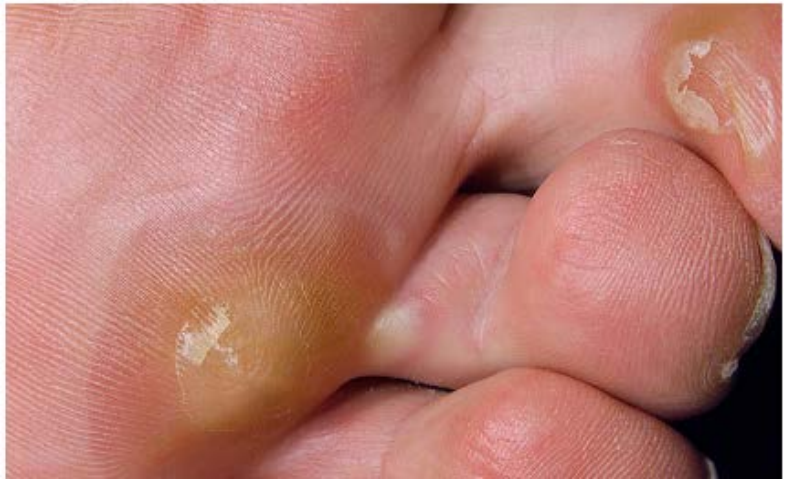
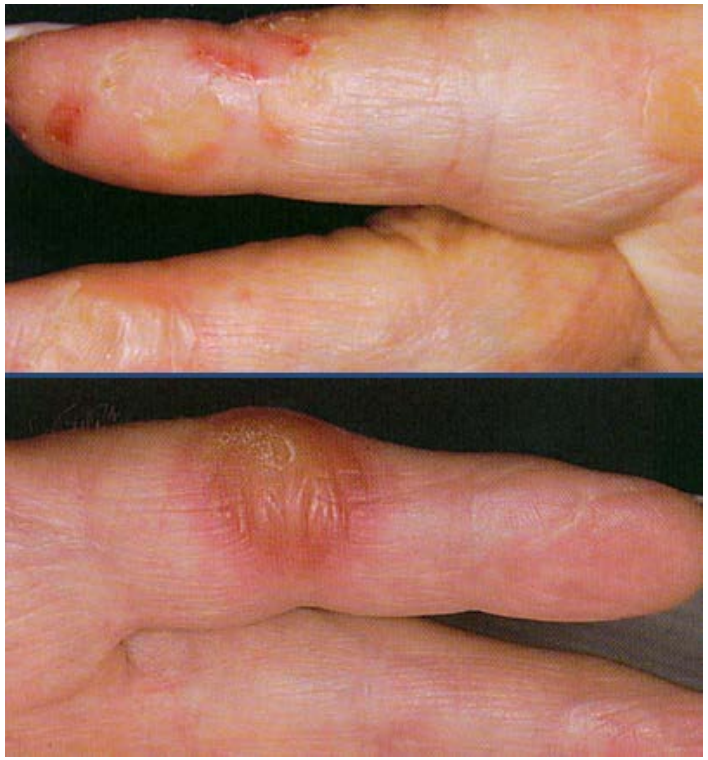
VEGF-TKI Toxicities

- **Skin:** Hand-foot syndrome, changes in hair or skin color
- **Oral:** Inflammation of the oral mucosa, taste changes, dry mouth
- **GI:** Diarrhea, nausea
- **Cardiovascular:** Hypertension, heart failure, heart attack, blood clots
- Delayed wound healing—must hold therapy for procedures
- Protein in the urine
- Bleeding
- Low blood counts
- Thyroid dysfunction
- Weight loss, decreased appetite
- Fatigue

Hand-Foot Syndrome

- Aka “palmar-plantar erythrodysesthesia”
- Symptoms:
  - Localized, tender lesions which often appear as blisters in areas of trauma or friction
  - Tingling, burning
  - Decreased tolerance to hot temperatures
  - Callus formation
- Often occurs within the first 2-4 weeks of therapy
- Occurs in 40% of patients receiving cabozantinib





Images from R. Motzer, MD

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Prevention is Key!

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Prevention of Hand-Foot Syndrome

P: Always **p**edicure/remove calluses BEFORE treatment

O: Fatty **o**intments 3 times daily (fragrance- and alcohol-free moisturizers—urea cream 20-40%)

P: Use **p**atches on all areas of increased calluses

S: Use **s**hoes with **s**oft insoles

-Wear shoes that are not constrictive, thick socks

-For hands: thick cotton gloves

And, avoid exposure of hands and feet to hot water

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Management of Hand-Foot Syndrome

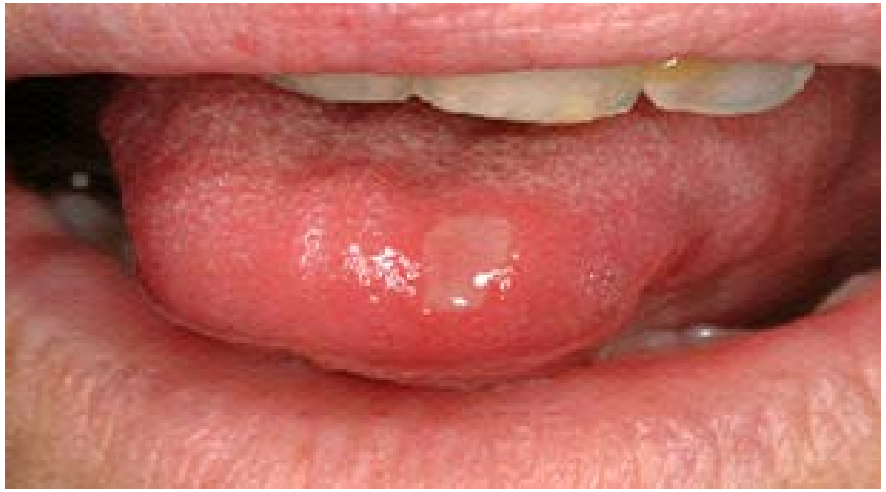
- **For mild symptoms:** Numbness, tingling, redness, or painless swelling not affecting daily activities
  - Liberal use of moisturizers
  - Reduce pressure to affected areas

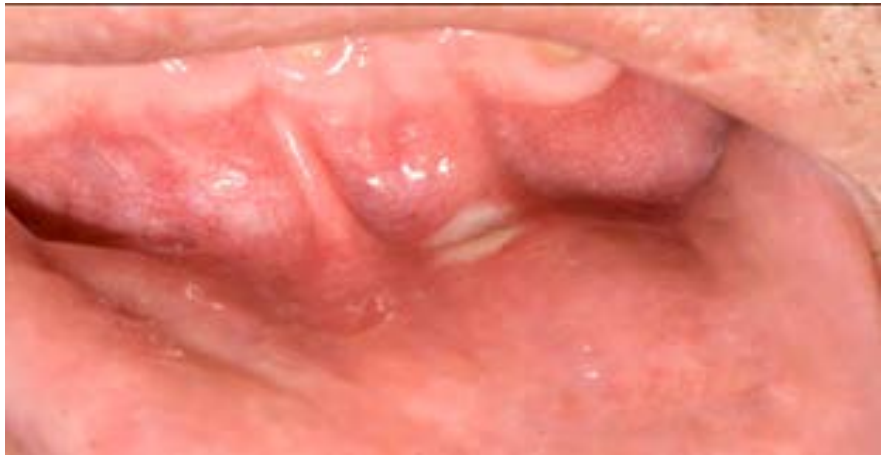
- **For moderate symptoms:** Painful redness and/or swelling affecting daily activities
  - Add topical corticosteroid (clobetasol 0.05% ointment twice daily)
  - For discomfort, topical 2% lidocaine, topical DMSO, gabapentin
  - May require temporary VEGF-TKI dose reduction

- **For severe symptoms**: Peeling, blistering, erosions, or severe pain causing inability to work or do daily activities
  - Discontinue treatment for at least one week (or until symptoms improve)
  - Resume treatment at dose reduction

Oral Toxicity

- Mucositis/stomatitis
  - Inflammation of oral mucous membranes
  - Often occurs 1 month after initiation of treatment
- Oral pain and sensitivity without ulcers
- Altered taste
- Dry mouth
- Most common with sunitinib and cabozantinib (up to 50%); least common with pazopanib or axitinib (~15%)
- Also a common toxicity with mTOR inhibitors
  - Can occur rapidly (<5 days)
  - Most often involves mucosa of the lips, lateral tongue, buccal mucosa and soft palate
  - Dose-effect relationship





Images from Carmen Jacobs, RN, OCN

Management of Oral Toxicity

- Mouthwash
  - Dexamethasone swish and spit 0.5mg twice daily
    - Do not swallow as this can impair VEGF-TKI absorption!
  - Topical analgesics: magic mouthwash (Lidocaine, Benadryl, Maalox), viscous lidocaine 2%, benzocaine
- Oral hygiene
- Avoid agents containing alcohol, hydrogen peroxide, and iodine
- Avoid spicy food
- Dose interruption and/or modification

Hypertension

- Up to 80% of patients develop high blood pressure (either de novo or worsening of pre-existing hypertension)
- Can develop within hours to days of starting treatment
- An acute rise in BP can precipitate acute end-organ complications:
  - Stroke, heart attack, heart failure, acute kidney injury
- Need to monitor closely
  - Home blood pressure cuff
- Requires treatment if BP≥140/90

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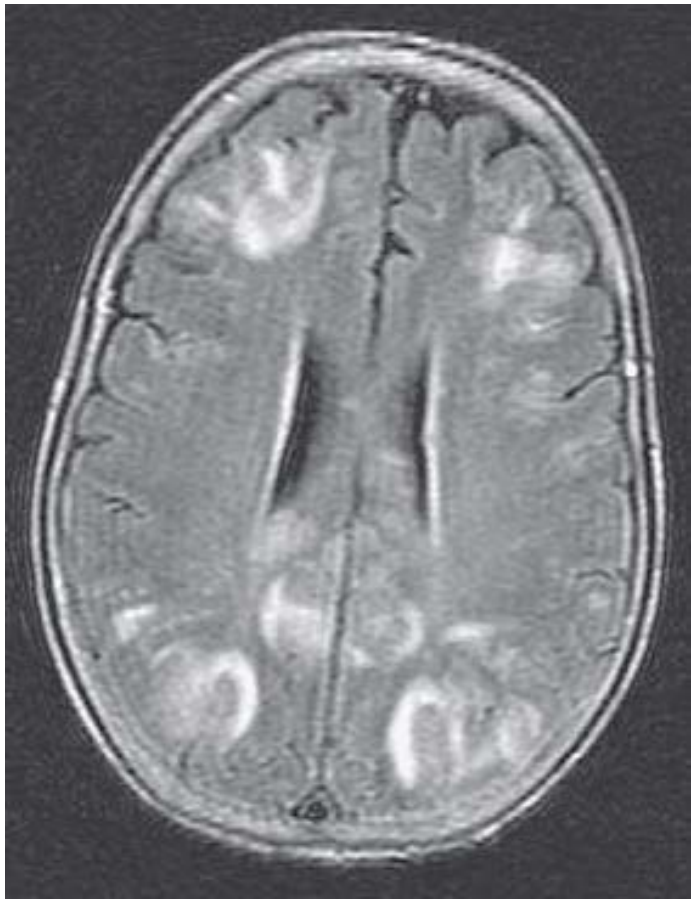
Posterior Leukoencephalopathy

- A rare complication of hypertension + VEGF TKI therapy
- Insidious onset of headache, confusion, decreased level of consciousness, visual changes, seizures with associated characteristic neuroimaging findings
- Contact your primary oncology team immediately
  - Requires emergency management



NEJM Vol 354:980-982

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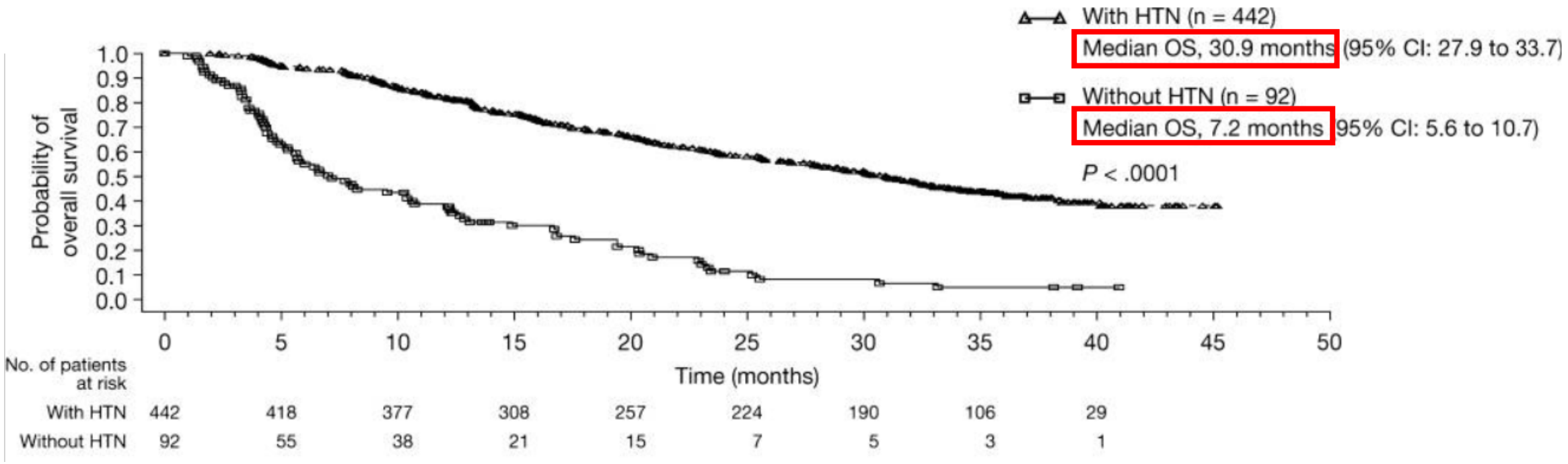
Hypertension as a Biomarker



Rini et al. JNCI 2011

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Management of Other Toxicities

Fatigue

- Light exercise
- Short naps
- Dose modification, including night time dosing

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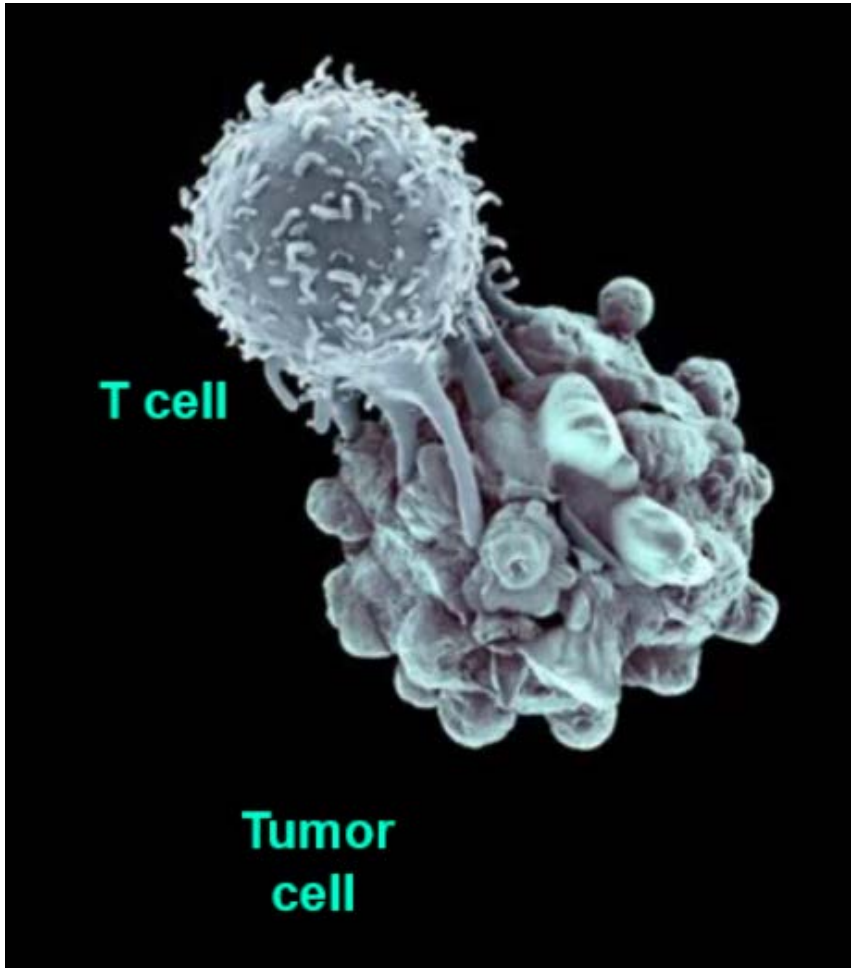
Mechanism of immune checkpoint blockade



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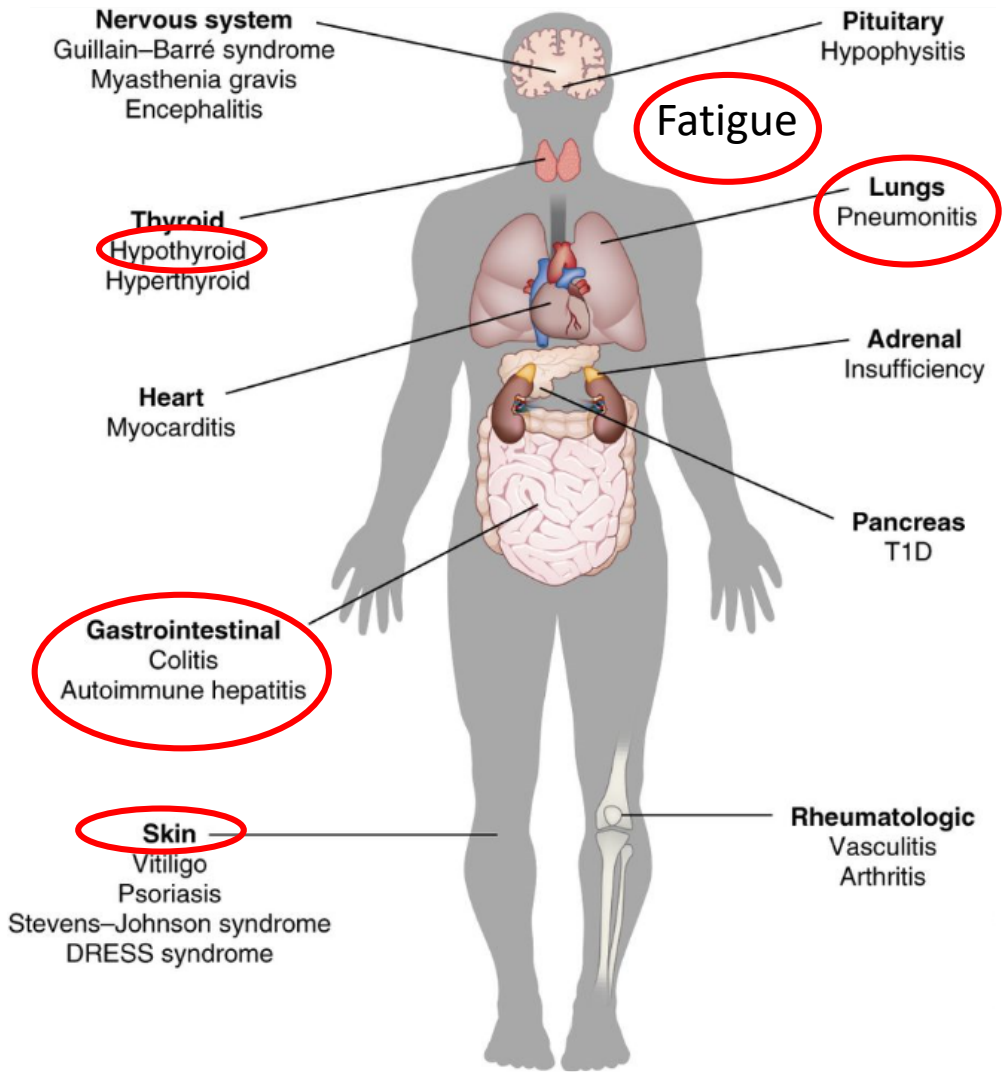
Immunotherapy Toxicities



- Uncommon, but may be severe and life threatening
- Time-limited and reversible
- Highly steroid responsive

June et al. Nature Medicine 2017

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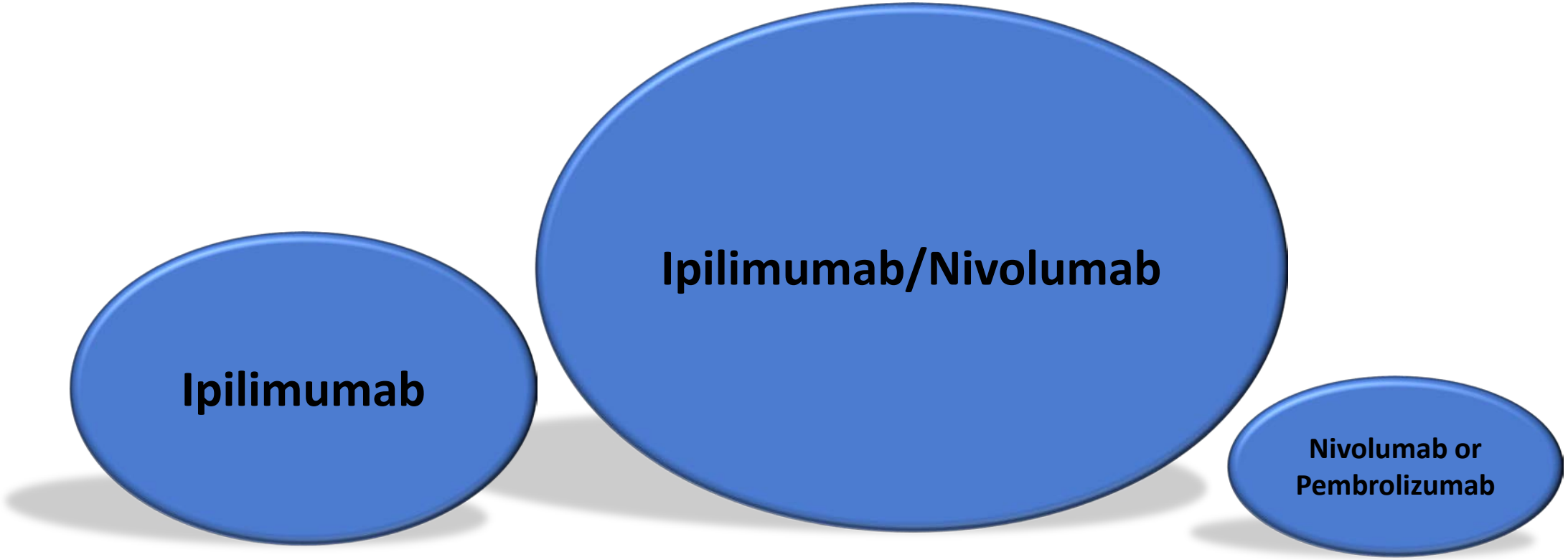
Risk of Toxicity



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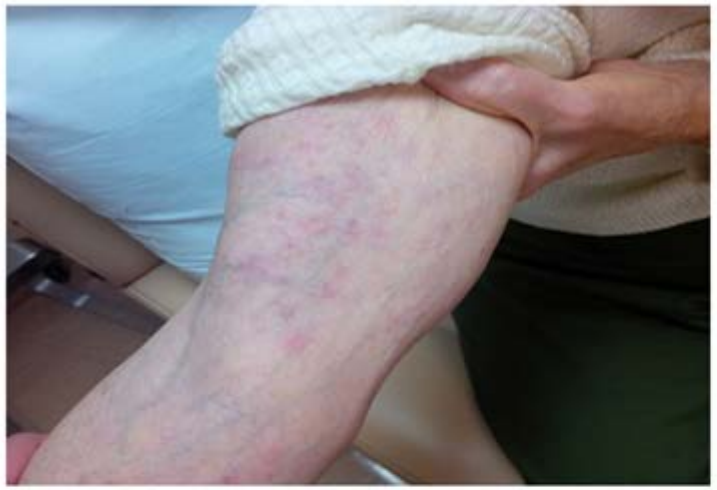
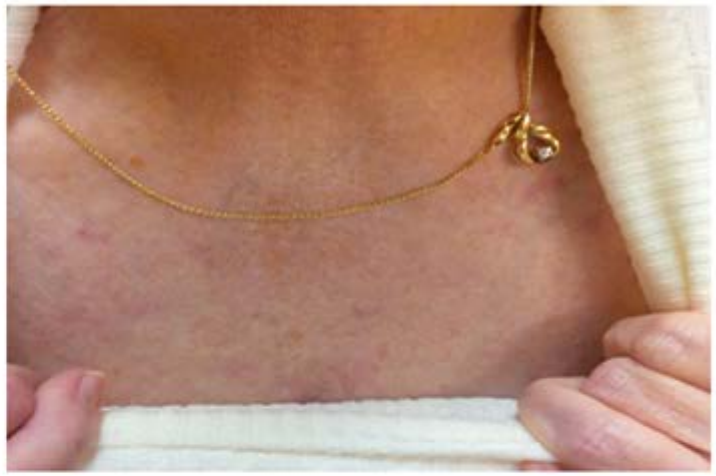
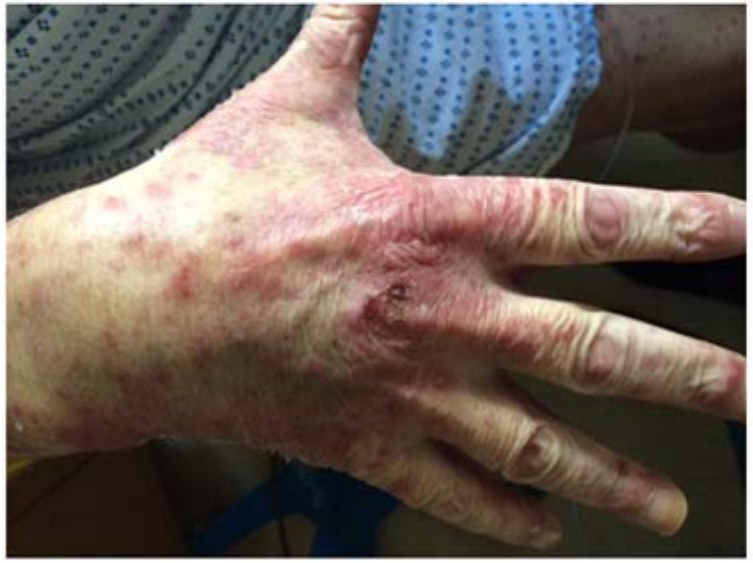
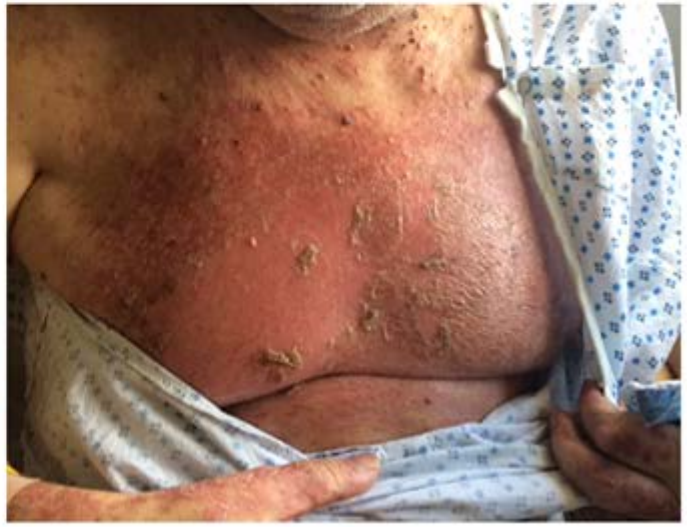
Rash

- Most common immune-related toxicity
- For mild symptoms:
  - Topical corticosteroids
    - Clobetasol propionate, betamethasone diproprionate for body
    - Hydrocortisone, aclometasone desonide for face
  - Oral anti-histamines
    - Non-sedating: Claritin, Zyrtec
    - Sedating: Hydroxyzine or Benadryl at bedtime
- Severe rashes may require oral steroids and holding therapy









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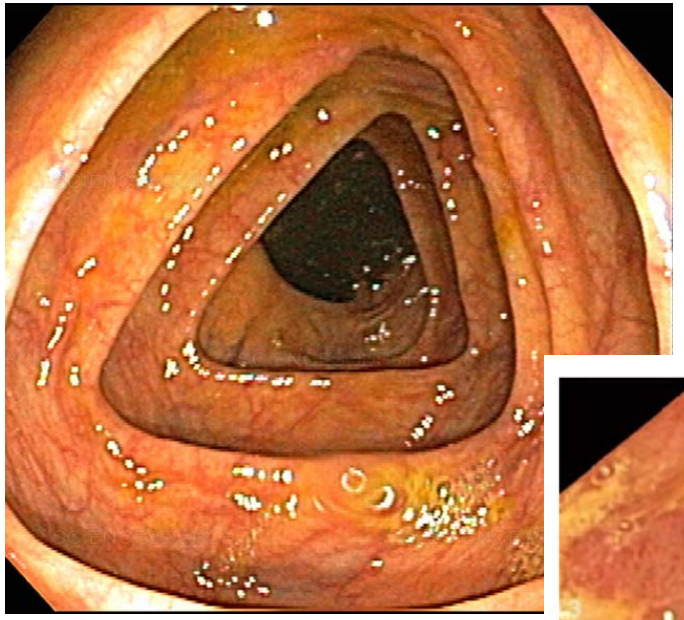
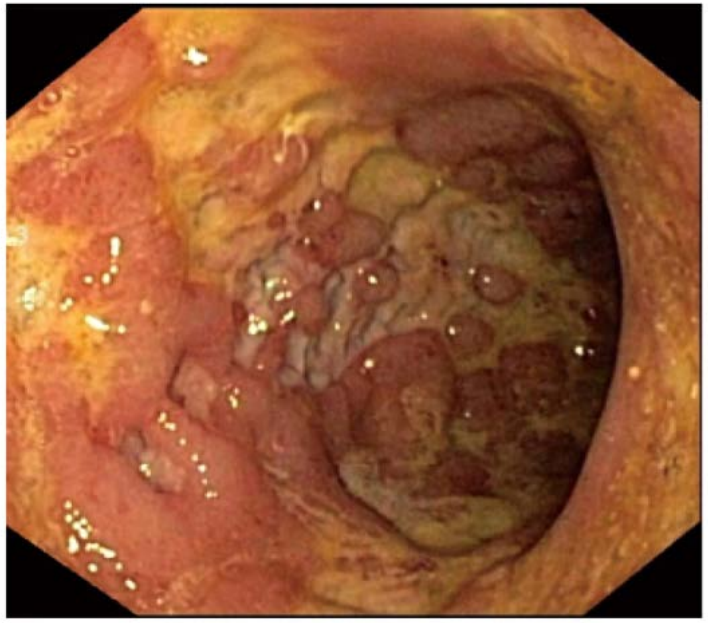
Colitis (Inflammation of the Colon)

- Symptoms
  - Diarrhea
  - Abdominal pain/cramping
  - Blood or mucous in stool

- Immediately report changes in bowel movements





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Management of Colitis

- Rule out other causes (i.e. c.difficile infection)
- **Mild (Bowel movement <4x above baseline)**
  - Supportive care (fluids, bland diet, Imodium)
- **Moderate (4-6x above baseline)**
  - Hold treatment, consider steroids
  - Consider colonoscopy
- **Severe (>7x above baseline or other complications)**
  - Permanently discontinue treatment, start steroids
  - Hospitalization may be warranted
  - If no improvement even with IV steroids, consider infliximab

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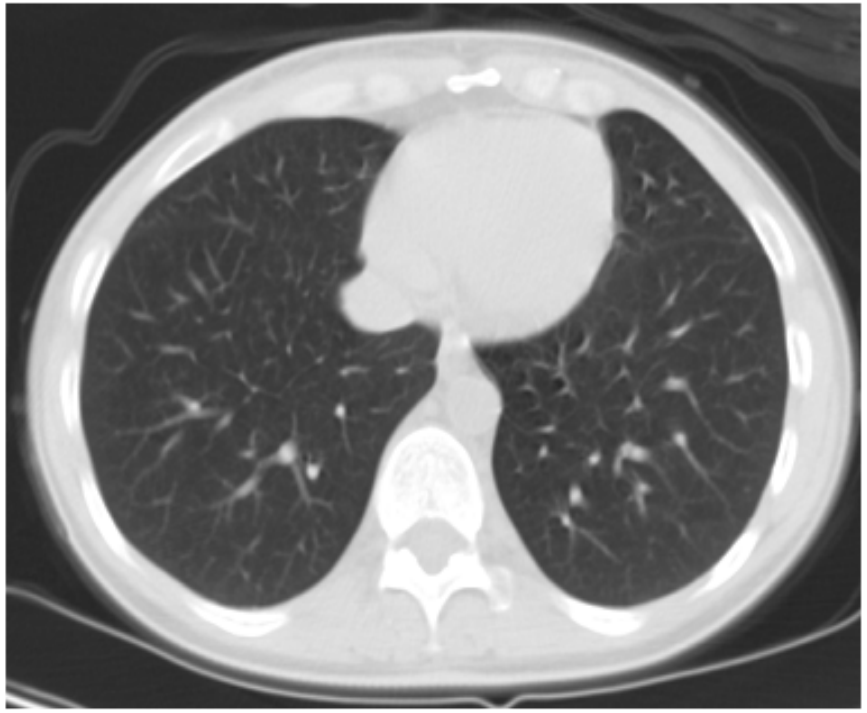
Pneumonitis (Inflammation of the Lungs)

- Symptoms: Cough, shortness of breath, low O2
- Also can occur with mTOR inhibitors



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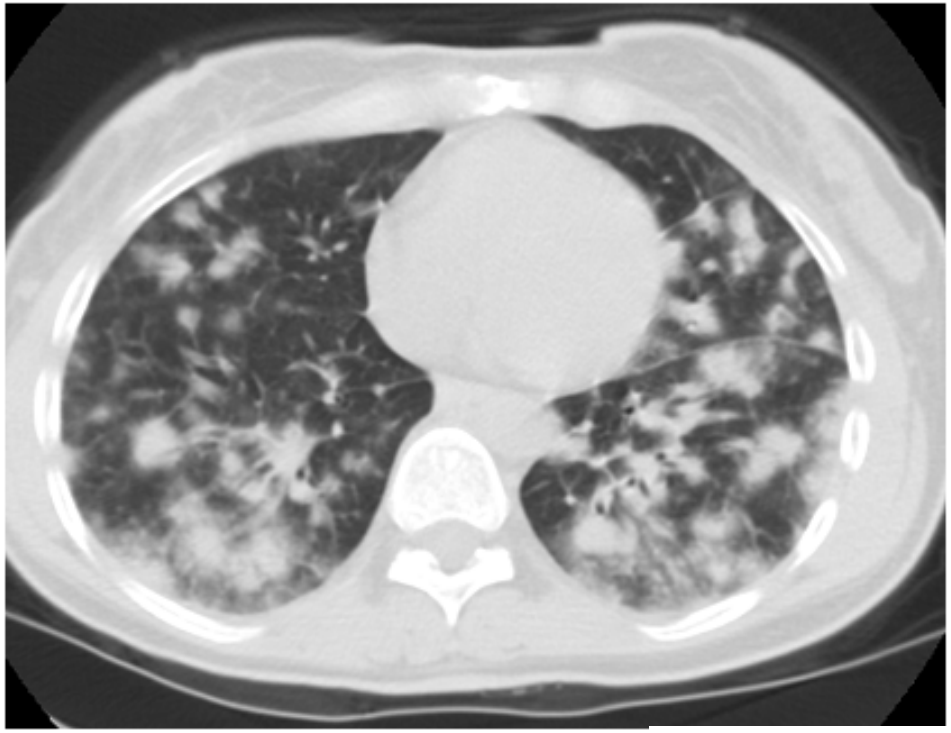

3/30/2011

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Management of Pneumonitis

- **Asymptomatic**
  - Can continue treatment with close observation vs hold therapy for 2-4 weeks

- **Symptomatic**
  - Hold treatment, start steroids
  - If severe symptoms or low O2:
    - Hospitalization, steroids, consideration of bronchoscopy

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mTOR Inhibitor Toxicities

- Fatigue
- Mucositis
- Low blood counts
- Nausea, vomiting, diarrhea
- Swelling
- Poor wound healing
- Inflammation of the lungs
- Elevated blood sugar
- Elevated cholesterol

Elevated Blood Sugar and Cholesterol

- Affects up to 70% of patients
- Requires intervention if ≥ grade 2
- Baseline lipid profile and continued monitoring necessary
- Very high triglycerides (≥ 500 mg/dl) require prompt treatment with fibrates (pancreatitis risk)

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Summary

- Treatment with VEGF-TKIs, immune checkpoint blockade, and mTOR inhibitors requires close monitoring for the development of toxicities
- VEGF-TKIs and mTOR inhibitors can produce a range of severe effects warranting aggressive supportive care and sometimes dose interruptions or treatment holidays
- Immune checkpoint blockade can cause unique immune-related side effects, which are often steroid-responsive, but in rare cases can be life-threatening
- Always contact your primary oncology team with any new symptoms

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Thank you!

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