Management of immune related adverse events (irAEs)

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Why are there immune related side effects?

- Oncological therapies have on-target and off-target effects.
- Off-targets could lead to important toxicity (febrile neutropenia, nausea, foot-hand-syndrome).
- In case of immune therapy, especially antibody based checkpoint blockade the side effects are mainly on-target, that is inhibition of the oncological target but in non-target « normal » tissue.
- The spectrum of side effects is markedly different from cytotoxics and small molecular tyrosine kinase inhibitors
- The symptoms should be quickly detected and treated as early as possible
- Blocking an ongoing pathological immune activation will not necessarily impact on treatment efficacy
- Explanation for most of the side effects is the focus of ongoing research projects
Side effects

Autoimmune:
1. Cutaneous
2. Gastrointestinal
3. Hepatic
4. Pulmonary
5. Endocrine
6. Rare: Neurological, pancreatic, renal, ocular

General:
1. Capillary leak syndrome
2. Cytokine release syndrome
3. Hemophagocytic lymphohistiocytosis

Infusion related reaction
Mechanisms
Definition:

Inhibitory pathways hardwired into the immune system that are crucial for maintaining self-tolerance and modulating the duration and amplitude of physiological immune responses in peripheral tissues in order to minimize collateral tissue damage.
CTLA-4 mechanism of action

Activation:
- CD28 binding to B7
- CTLA-4 not bound to B7

Inhibition:
- CTLA-4 binding to B7
- IPilimumab binding to CTLA-4

Dendritic Cell
Pathobiology of PD-L1 expression in cancer

1. Oncogenic origin

- Tumor cell
- Tumor antigen
- Oncogenic event

2. Induced by chronic inflammation

- Tumor cell
- STAT
- IFN-γ

- MHC-I
- TCR
- PD-L1
- PD-1

- CD8+ T cell

- Induced by chronic inflammation
PD-1/PD-L1 mechanism of action
## Treatment-Related Select AEs Reported in ≥10% of Patients

<table>
<thead>
<tr>
<th>Patients Reporting Event, %</th>
<th>NIVO + IPI (N=313)</th>
<th>NIVO (N=313)</th>
<th>IPI (N=311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3–4</td>
<td>Any Grade</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>59.1</td>
<td>5.8</td>
<td>41.9</td>
</tr>
<tr>
<td><strong>Pruritus</strong></td>
<td>33.2</td>
<td>1.9</td>
<td>18.8</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td>28.4</td>
<td>2.9</td>
<td>21.7</td>
</tr>
<tr>
<td><strong>Rash maculo-papular</strong></td>
<td>11.8</td>
<td>1.9</td>
<td>4.2</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>46.3</td>
<td>14.7</td>
<td>19.5</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>44.1</td>
<td>9.3</td>
<td>19.2</td>
</tr>
<tr>
<td><strong>Colitis</strong></td>
<td>11.8</td>
<td>7.7</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Hepatic</strong></td>
<td>30.0</td>
<td>18.8</td>
<td>6.4</td>
</tr>
<tr>
<td>Increase in alanine</td>
<td>17.6</td>
<td>8.3</td>
<td>3.8</td>
</tr>
<tr>
<td>aminotransferase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in aspartate</td>
<td>15.3</td>
<td>6.1</td>
<td>3.8</td>
</tr>
<tr>
<td>aminotransferase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td>30.0</td>
<td>4.8</td>
<td>14.4</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>15.0</td>
<td>0.3</td>
<td>8.6</td>
</tr>
</tbody>
</table>

- With immune modulatory agents, resolution rates for the majority of grade 3–4 select AEs were: 85-100% for NIVO + IPI, 50-100% for NIVO, and 83-100% for IPI
- As observed in prior studies, most endocrine events did not resolve
Time to Onset of Grade 3–4 Treatment-Related Select AEs

Circles represent medians; bars signify ranges
Cutaneous irAE
Cutaneous irAE

- Clinical presentations: maculopapular, papulopustular, acute febrile neutrophilic dermatosis (Sweet’s syndrome), follicular or urticarial dermatitis

- Severe irAEs: bullous phemphigoid, Stevens Johnson syndrome, toxic epidermic necrolysis (Lyell’s syndrome)

- Mucosal toxicity: lichenoid mucositis, oral mucositis, gingivitis, sicca syndrome-like

- Vitiligo

- Differential diagnoses: 1. Infections: Scabies, lice infection, or pics from insects 2. Central: liver disease (bilirubin), renal, paraneoplastic

- Examinations: dermal assessment, skin biopsy, kidney and liver function testing, tryptase and IgE.

- Rash is More frequent with pembrolizumab (39%) followed by nivolumab (34%) and ipiilimumab at 21%.

- Vitiligo 10% with pembrolizumab and 2% with ipiilimumab
# Cutaneous irAE

<table>
<thead>
<tr>
<th>Any immune-related event</th>
<th>221 (58.2)</th>
<th>37 (9.7)</th>
<th>2 (0.5)</th>
<th>80 (61.1)</th>
<th>16 (12.2)</th>
<th>3 (2.3)</th>
<th>42 (31.8)</th>
<th>4 (3.0)</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatologic</td>
<td>152 (40.0)</td>
<td>8 (2.1)</td>
<td>1 (0.3)</td>
<td>57 (43.5)</td>
<td>2 (1.5)</td>
<td>0</td>
<td>22 (16.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>67 (17.6)</td>
<td>1 (0.3)</td>
<td>0</td>
<td>32 (24.4)</td>
<td>0</td>
<td>0</td>
<td>14 (10.6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>67 (17.6)</td>
<td>5 (1.3)</td>
<td>0</td>
<td>25 (19.1)</td>
<td>1 (0.8)</td>
<td>0</td>
<td>6 (4.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>14 (3.7)</td>
<td>0</td>
<td>0</td>
<td>3 (2.3)</td>
<td>0</td>
<td>0</td>
<td>1 (0.8)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Cutaneous irAE

Anti-CTLA-4 / Skin Rash

Erythematous papilles, confluent plaques, predominantly in regions with fine skin

Eczema
Cutaneous irAE

Anti-CTLA-4 / Skin Rash
Cutaneous irAE

Anti-CTLA-4 / Pemphigoid bulleuse
Cutaneous irAE

Anti-CTLA-4 / Vitiligo

Lampe de Wood
Management of Cutaneous irAE
Management of Cutaneous irAE

**Grade**

1. Macules/papules covering <10% BSA*
   - Asymptomatic or with symptoms**

2. Macules/papules covering 10-30% BSA*
   - Asymptomatic or with symptoms**
   - Limiting self-care ADL**

3-4. Macules/papules covering >30% BSA*
   - Asymptomatic or with symptoms**
   - Severe/Life-threatening symptoms
   - Generalized exfoliative/ulcerated/bullous rash

**Investigations**

- Mucocutaneous clinical examination
- Serum testing for liver, kidney function, tryptase, IgE levels
- Consider dermatology consult
- Consider skin biopsy

**Management**

- Continue Immunotherapy
  - Topical corticosteroids (intermediate to high potency)
  - Oral antihistamines for pruritus
- Oral prednisone 1mg/kg/day or equivalent
- Oral antihistamines for pruritus
- Hold immunotherapy
  - Oral prednisone 1mg/kg/day or equivalent
  - Oral antihistamines for pruritus

**Follow-up**

- Repeat skin exam
- If develops symptoms, treat as higher grade
- If improves to ≤Grade 1, resume immunotherapy
  - After symptoms improve, taper steroids over ≥1 month
  - If rash does not improve after 12 weeks from last dose of therapy, discontinue immunotherapy
- If improves to ≤Grade 1, taper steroids over ≥1 month
  - If worsens in 48 hours, consider additional immunosuppression (infliximab, cyclophosphamide, mycophenolate mofetil) or supportive measures**
  - If not improvement ≥12 weeks from last dose of therapy, discontinue immunotherapy

*BSA = Body surface area, **Symptoms: As per CTCAE version 4.0. For example: pruritus, burning, tightness. **ADL = activities of daily living,

Additional supportive measures = prophylactic antibiotics, management in the burns unit.
Management of Cutaneous irAE
Management of Cutaneous irAE

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Management of Cutaneous irAE

Prurit

1. Treatment: corticosteroids (anti-histamins are not effiaceouse)
2. Topical therapy: Class III-IV
3. Polidocanol 5% in cold cream
Care of Vitiligo

1. Could be sign of an immune response against melanoma

2. ASCO recommendation is protection against sun

3. Dermatological treatments are possible but limited
Colonic irAE

- Symptoms: 1. Diarrhea as increased stool frequency 2. colitis: abdominal pain, descending colon is the most common site

- Differential diagnoses: 1. infections including overt infections (bacterial, viral, fungal),

- Examinations: colonoscopy with biopsies for every grade 2 diarrhea or rectal bleeding, CT Imaging only if severe abdominal pain and/or peritonitis signs, persistent or > grade 2 diarrhea: Rule out infection. C. Difficile, stool cultures, parasites

- More frequent with CTLA4 blockade (5-8%), less with PD-1/PD-L1 blockade 1-3%.

- Pathology: neutrophilic and lymphocytic infiltration

- Severity: could lead to perforation
Colonic irAE: endoscopy showing deep ulcers
Colonic irAE: histological signs of colonic inflammation
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)**

**Grade 1**
- Diarrhea: <4 stools/day over baseline;
- Colitis: asymptomatic

**Management**
- Continue I-O therapy per protocol
- Symptomatic treatment

**Follow-up**
- Close monitoring for worsening symptoms.
- Educate patient to report worsening immediately if worsens:
  - Treat as Grade 2 or 3/4

**Grade 2**
- Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL
- Colitis: abdominal pain; blood in stool

**Management**
- Delay I-O therapy per protocol
- Symptomatic treatment

**Follow-up**
- 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 ≥224 hrs; interfering with ADL
- Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs
- G4: life-threatening, perforation

**Management**
- 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

**Follow-up**
- 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 irAE

- Symptoms: 1. Mostly asymptomatic especially if only transaminitis (autoimmune hepatitis), 2. Fever 3. Malaise 4. If bilirubin is also increased symptoms could be linked hyperbilirubinemia (drug induced liver injury, DILI = AST/ALT plus bilirubin increase)

- Differential diagnoses: 1. Infections including overt infections (bacterial, viral, fungal), 2. progressing liver metastases, 3. Vascular complications

- Examinations: US, CT scan /PET, laboratory tests, virology including rare viruses (EBV, CMV), biopsies (repeat if needed),

- More frequent with CTLA4 blockade (10%), less with PD-1/PD-L1 blockade 5%.

- Anti PD1/PD-L1 therapy of HCC results in increased hepatitis (20%)

- Nivolumab + pazopanib or sunitinib resulted in increased grade 3/4 irAE of 9 and 20 %.

- Pathology: panlobular hepatitis, perivenular infiltrates, or lymphocytic infiltrates around ducts

- Evolution: can evolve chronically
Pulmonary irAE

- Symptoms: shortness of breath, cough, fever, chest pain

- Differential diagnoses: 1. infections including overt infections (bacterial, viral, fungal pneumonia), 2. malignant lung infiltration 3. pulmonary embolism, 4. cardiac origin, 5. pericarditis

- Examinations: chest CT scan, bronchoscopy with bronchoalveolar lavage for lymphocytes, infections, lung function tests, cardiac US

- More frequent (~10%) with PD-1/PD-L1 therapy than with CTLA4 blockade

- Incidence could be higher when PD-1/PD-L1 blockade is combined with chemotherapies and targeted agents with known risk of pneumonitis

- In monotherapy of CTLA4 blockade pneumonitis were not described instead sarcoid-like granulomatous reactions and obstructive pneumonia were present

- More common in patients with lung cancer
Pulmonary irAE

Figure 3: Different Radiographic Patterns of Checkpoint Blockade-Associated Pneumonitis Seen on CT Scanning In a Single Patient Treated With Ipilimumab and Nivolumab—Pneumonitis secondary to ipilimumab is shown in the left-hand panel, and pneumonitis secondary to nivolumab is shown in the center and right-hand panels. Red arrows indicate areas of radiologic abnormality.

Pulmonary irAE management

- Grade
  - Grade 1
    - Asymptomatic, radiologic changes only
  - Grade 2
    - Mild/moderate new symptoms
    - Microbiological assessment where necessary
    - Consider Pulmonary/Infectious Diseases Consults and Bronchoscopy
  - Grades 3-4
    - Severe/life-threatening new symptoms, worsening hypoxia

- Investigations
  - Radiologic imaging (High resolution CT chest)

- Management
  - Continue immunotherapy
    - Monitor for symptoms every 3 days
    - If persistent beyond 3 days, discontinue immunotherapy
    - After symptoms improve, taper steroids over ≥1 month
  - Withhold immunotherapy
    - Monitor for symptoms daily
    - Oral prednisone 1mg/kg/day or equivalent
    - If improves to ≤Grade 1 within 3 days of supportive care, resume immunotherapy at next dose
    - If persistent beyond 3 days, discontinue immunotherapy
  - Discontinue immunotherapy
    - Hospitalization
    - IV methylprednisolone 2-4mg/kg/day or equivalent
    - Prophylactic antibiotics

- Follow-up
  - Repeat CT every cycle
  - If develops symptoms, treat as higher grade
  - After symptoms improve to ≤Grade 1 or baseline, taper steroids over ≥6 weeks
  - If worsens in 48 hours consider additional immunosuppression (infliximab, cyclophosphamide, mycophenolate mofetil)
Endocrine irAE

- Symptoms: fatigue, headache, diagnosis can be challenging as symptoms could be non-specific

- Types of endocrinopathies: hypophysitis, hypothyroidism, hyperthyroidism, thyroiditis, primary adrenal insufficiency

- Differential diagnoses: 1. Disease progression, 2. brain metastases 3. pituitary metastases, 4. pituitary bleeding, 5. meningitis

- Examinations: Hormonal tests: TSH, free T4, LH, FSH, ACTH, cortisol, for pituitary gland: MRI, anti-thyroglobulin antibodies, anti-thyroid peroxidase antibodies

- Thyroid toxicities more frequent with PD-1/PD-L1 (10%) therapy than with CTLA4 (5%)

- Hypophysitis similar incidence between classes

- Complete recovery of gonadal axis has been reported in 57% of men and recovery of the thyroid axe in 37-50% of cases
Endocrine irAE
Endocrine irAE

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

Asymptomatic TSH elevation
- Continue I-O therapy per protocol
- If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include 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 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.
Rare irAEs

- **Neurological autoimmune disease:**
  1. more frequent with CTLA4 than with PD1/PDL1.
  2. PD1: cases of myasthenia gravis
  3. CTLA4: transverse myelitis, enteric neuropathy, aseptic meningitis, one case of Guillain-Barre syndrome
  4. Therapy: High dose corticoids, IV immunoglobulins, plasmapheresis

- **Pancreatitis**
  1. Asymptomatic increase of lipase and amylase with both CTLA4 and PD1/PDL1 therapies
  2. Amylase and lipase should not be checked routinely only in case of suspected pancreatitis

- **Renal toxicity**
  1. Interstitial nephritis could occur
  2. Pathological appearances so far only described for CTLA4 in form of lupus nephritis or granulomatous nephritis
  3. Asymptomatic gradual increase of creatinin, which responds well to steroids after exclusion of other causes of renal failure

- **Ocular toxicity**
  1. Uveitis with both classes of agents
  2. Generally treated with topical steroids
  3. Should receive systemic corticoids in case of grade 3/4 toxicity
What if steroids fail?

- Steroids work in most (>99%) of cases. Choose the right dose and start early
- In case steroids fail key is to understand the potential reasons. Talk to a team of experts including: immunologists, organ specialist, infectious disease, clinical pharmacologist

- Colitis: 1st choice is anti-TNF alfa infliximab 5 mg/kg IV, should be given up to max 3 days with lack of improvement, could be repeated every two weeks, exclude infections
- Hepatitis: Infliximab cannot be given since hepatotoxic
- Other options:
  1. Mycophenolat mofetil, (CELLCEPT)
  2. Tacrolimus
  3. Cyclophosphamide
  4. IVIG
  5. Anti-thymocyte globulin
1. Rare side effect linked to IL2
2. Inflammation of capillaries resulting in separation of the endothelial cells allowing leakage of liquid
3. Symptoms and findings: hypotension, peripheral oedema, hypoalbuminemia, hemoconcentration, weight gain, flu like symptoms, diarrhea, thirst and lightheadedness with sign of cerebral oedema, compartment syndrome, oligo-anuria
4. Resembles sepsis, and fever can also be present hence DD is difficult
5. If detected early good response to steroids
6. If left undetected, high rate of mortality due to Multi-organ failure
Hypotension

- Treatment to be based on drop of blood pressure and weight gain:
- Delay administration if hypotension consistent with VLS.
- Minimized fluid resuscitation to avoid fluid overload.
- Minimize crystalloid solutions (e.g., saline).
- Vasopressor support (e.g., phenylephrine) is indicated to stabilize blood pressure.
- Administer colloidal solutions (e.g., albumin) if clinically significant and persistent systolic blood pressure drop and patient is symptomatic, or urine output declines.
# Pulmonary congestion and oliguria

<table>
<thead>
<tr>
<th>Pulmonary congestion</th>
<th>Oliguria, rising serum creatinine level</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Provide diuretic and/or IV albumin treatment in case of hypoalbuminemia as appropriate</td>
<td></td>
</tr>
<tr>
<td>• Progressive shortness of breath may require in addition endotracheal intubation or drainage of a pleural effusion.</td>
<td></td>
</tr>
<tr>
<td>• Delay administration if Grade 3 urine output (&lt;10ml/hr)</td>
<td></td>
</tr>
<tr>
<td>• Use fluids judiciously if increase in urine output is required.</td>
<td></td>
</tr>
<tr>
<td>• Use dopamine if patient is unresponsive to or unable to tolerate fluids.</td>
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</tr>
<tr>
<td>Laboratory abnormalities</td>
<td></td>
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<tr>
<td>--------------------------</td>
<td></td>
</tr>
<tr>
<td>Electrolytes and minerals: frequently require correction.</td>
<td></td>
</tr>
<tr>
<td>Anemia and thrombocytopenia: may require transfusion.</td>
<td></td>
</tr>
<tr>
<td>Transient cholestasis should be monitored until resolution.</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic elevations in cardiac isoenzymes may represent risk for myocarditis and should be further monitored before next administration</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism: may require hormone replacement</td>
<td></td>
</tr>
</tbody>
</table>
Cytokine release syndrome/cytokine storm

1. Caused by direct activation of T cells
2. Happens with anti-T cell antibody therapies: ATG, OKT3, TGN1412, also with rituximab, T cell therapies (TILs or CAR-T cells)
3. Similar to severe infection with, high fever, hypotension, rigors, pulmonary edema, multi-organ failure
4. Exclude infectious diseases
Hemophagocytic lymphohistiocytosis

1. Hyperinflammation due to uncontrolled proliferation of lymphocytes and macrophages and release of cytokines

2. Signs and symptoms: fever, hepato-splenomegaly, lymphadenomegaly, jaundice, rash

3. Findings: pancytopenia, hemophagocytosis on blood film, elevated liver enzymes, normal albumin, CRP and ferritin are highly increased, low fibrinogen and high D-Dimers, increased sphingomyelinase, bone marrow biopsy shows hystiocytosis

4. Treatment: optimized for the individual patient and includes: corticosteroids, etoposide, cyclosporin, IVIG, other chemotherapies: methotrexate, vincristine

5. Overall mortality of 50%
Take home messages

1. Always look for side effects
2. Treat early proactively even grade 2 toxicity
3. Do not fear of negative impact no outcome
4. Adapt the therapy to the individual (if grade 4 toxicity with no change in 48 hours do not wait until 72 hours)
5. More combinations potentially more side effects
6. Education of non-oncologists in collaborations

Readings:

Thank you!