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All You Need to Know about Immunotherapy Related Colitis

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Disclosures:

Consulting fees: AstraZeneca, Ferring, Gilead, Janssen, Teva

Research Grant: Janssen

I will be discussing the use of off-label medications during this presentation

Objectives:

10 things you should know about immune-related colitis

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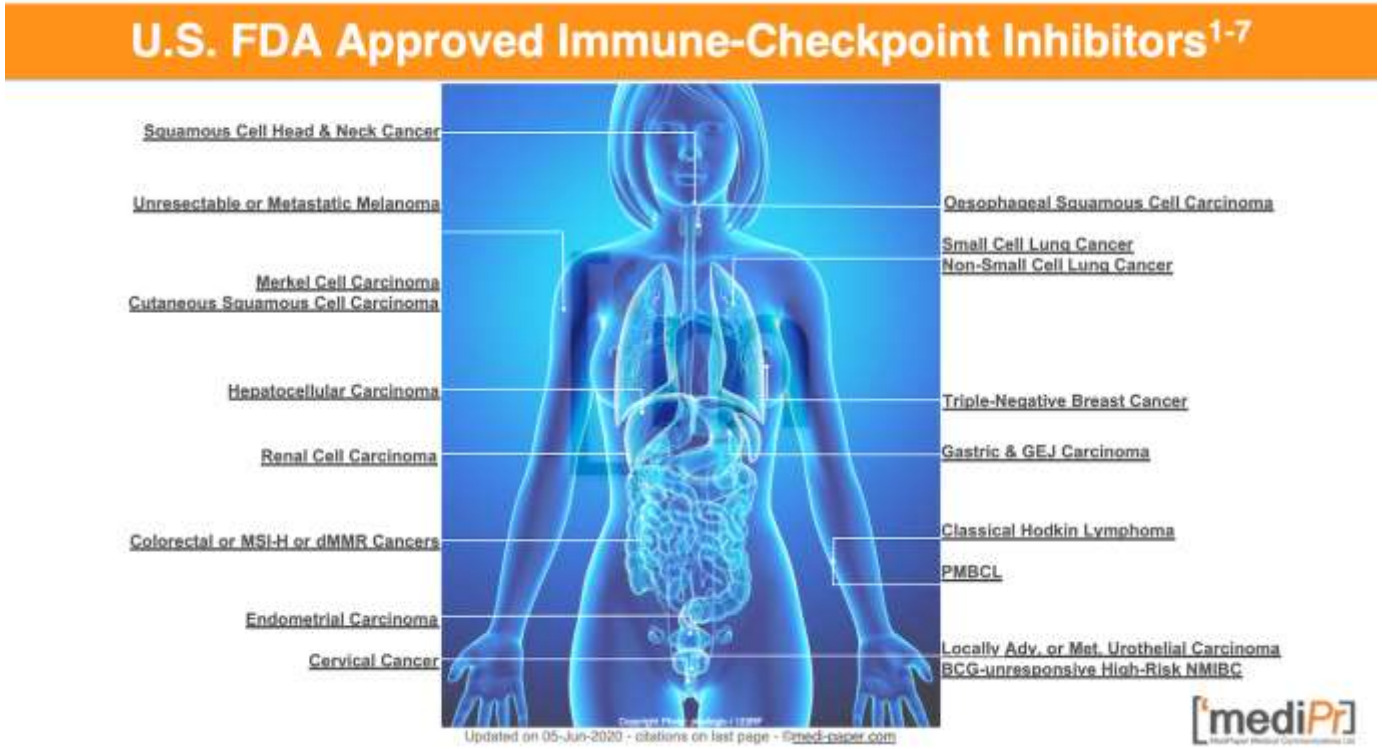
#1: ICIs are exploding across cancer landscape



CTLA-4

PD-1

PD-L1

Ipilimumab (2011)

Pembrolizumab
Nivolumab (2014)

Atezolizumab (2016)

Durvalumab
Avelumab (2017)

Cemiplimab (2018)

Tremelimumab
Dostarlimab (2022)

Retifanlimab
Toripalimab (2023)

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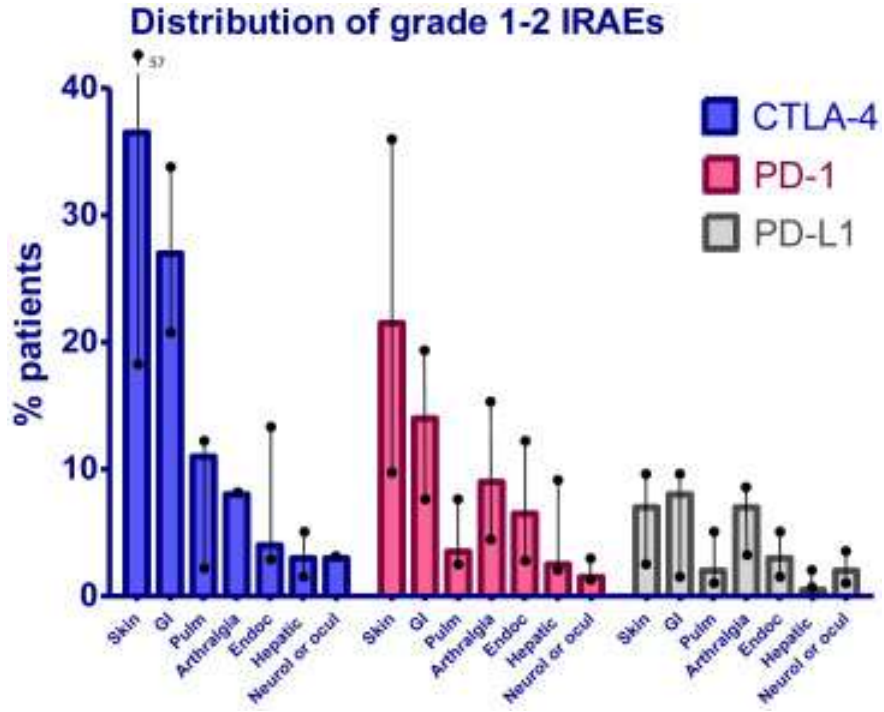
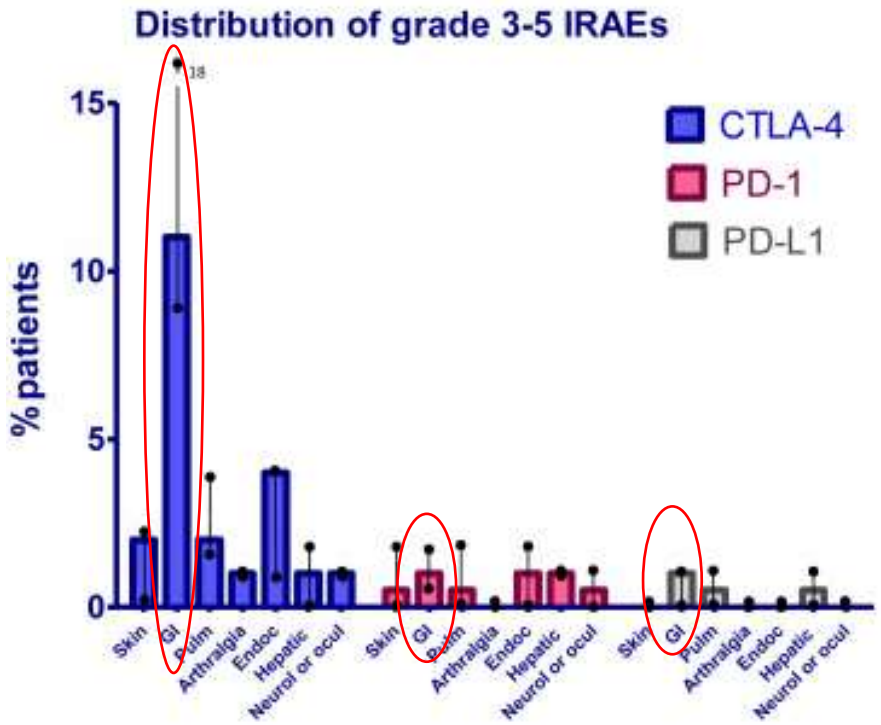
#2: GI toxicity is common and often severe

Epidemiology: an irAE occurs in up to 90% of patients treated with an anti-CTLA-4 antibody and 70% of patients treated with an anti-PD-1/PD-L1 antibody





Michot et al. Eur J Cancer 2016

#3: GI toxicity can be unpredictable: be aware!

irEC Diagnostic Pearls

- Timing is usually early (4-8 weeks from first dose)
  - **Hyperacute** (within days) or **delayed onset** (within 6 months after stopping) can occur
- CT can miss the diagnosis (NPV 43%)
- Fecal Calpro has good (86%) sensitivity
  - ↑ (465 vs 152) if ulceration present
- Flex sig is usually (>90%) sufficient for initial dx

Risk Factors for irEC:

- Type of ICI
  - CTLA-4: 30% (7% G3-4)
  - PD-(L)1: 12% (1% G3-4)
  - Combo: 37% (7% G3-4)
- Dose of ICI (at least for CTLA-4)
- PPI use
- Antibiotic use

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Soularue, Faleck et al. Gut 2018; Yin et al. Clin Genitourin Cancer 2022; Mohiuddin et al. JNCI 2021; Abu-Sbeih et al. JITC 2018; Garcia-Neuer et al. Cancer Imm Res 2017; Wright et al. APT 2019

#4: IBD patients can get ICIs but are at ↑ risk for flare

Multi-center study of 102 patients with UC/CD treated with ICI

- Cohort had mild IBD: only 22% on immunosuppressives, 85% had normal/mild endoscopic severity at most recent exam
- 42 (41%) developed GI flare, 21 (21%) G3-4 symptoms
  - Non-IBD control: 11%
- 4 (4%) spontaneous perforation
- ZERO GI-related mortality

➢My approach: optimize IBD control in advance, if possible:

✓ Mild: start/escalate 5-ASA

✓ Moderate-severe: start biologic

Abu-Sbeih, Faleck et al. JCO 2019

#5 Not all diarrhea is immune-related colitis

1. **Infectious enterocolitis**:
   a. **GI PCR**: 61/521 (12%) in MSK study of ICI patients with new onset diarrhea
      - More frequent G3-4 diarrhea but more often self-limited course not requiring steroids (23% vs. 45%)
   b. **C. difficile**: 111/605 (18%) PCR+ in MSK study
      - 76% responded to abx alone, 24% required immunosuppressives
2. **ICI-related exocrine pancreatic insufficiency (EPI)**
   - Rare cause, generally delayed onset (median 13mo)
   - 40% develop concomitant diabetes
3. **ICI-related upper GI toxicity**
   - Suspect if nausea, vomiting, anorexia, wt loss
4. **Concomitant Anti-Neoplastics**
   - Frequently on chemotherapy or tyrosine kinase inhibitors (TKI)

My approach:

- **GI PCR+:** Consider supportive mgmt ~7 days before escalating treatment
- **CDI+**: Treat CDI and then if no improvement after 48-72h start or escalate immunosuppressives
- **EPI+**: Treat with pancreas enzyme replacement, avoid steroids
- **Upper GI tox**: try PPI and/or open capsule budesonide
- **Concomitant TKI**: hold 3-5 days and reassess

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Magahis P…Faleck D, Oncologist 2024; Magahis P…Faleck D, *Manuscript under revision;* Satish…Faleck, Oncologist 2023; Magahis…Faleck, JITC 2024

#6 Endoscopic evaluation is important for diagnosis and prognosis

- **Diagnosis**: 15-30% of patients have alternative diagnoses
  - Tumor invasion / overflow, radiation enterocolitis, transient diarrhea
- **Prognosis**: endoscopic activity is better predictor than symptoms of disease trajectory
  - Microscopic Colitis
    - Budesonide often (~70%) effective for microscopic colitis
    - ICI can be quickly resumed while on concomitant budesonide
  - Severe Colitis
    - Generally (~80%) require biologic for durable control
    - ➢ Don't wait for them to fail steroids!

Hughes et al. JITC 2019; Foppen et al. ESMO Open 2018; Abu-Sbeih et al. JITC 2018
Ibraheim et al. APT 2020, Johnson et al. JITC 2018

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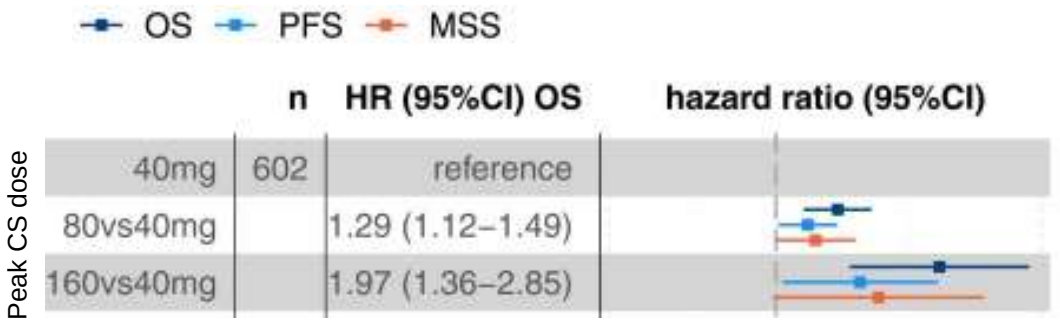
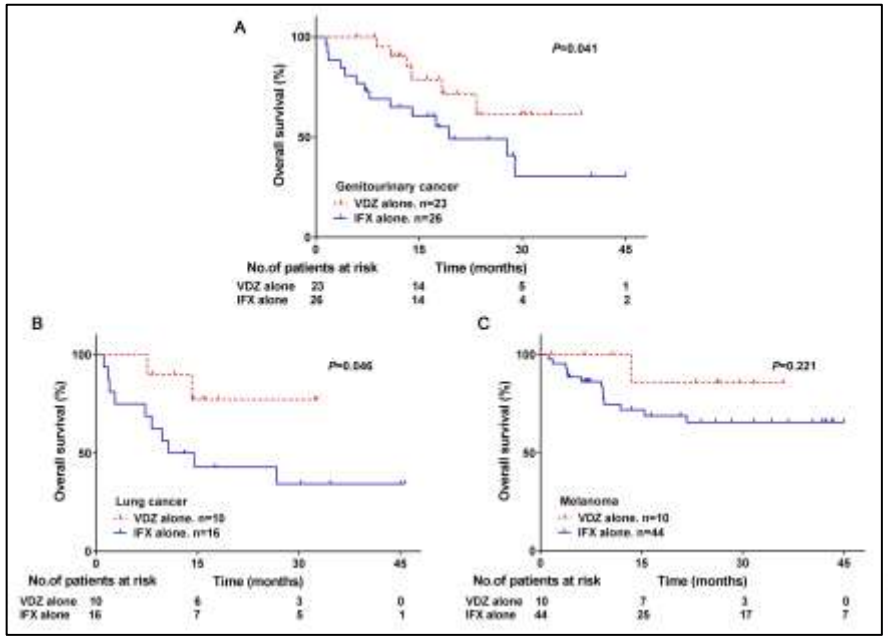
#7 Systemic immunosuppression is *not* benign

- High dose systemic steroids, especially early on during ICI, may impair anti-tumor response and are associated with **<u>impaired overall survival</u>**
- Impact of other immunosuppressants is less clear
  - **Anti-TNF**: mixed data, steroid backbone is a major confounder
    - Conflicting data on IFX/steroids vs steroids alone and impact on PFS/OS
    - Anti-TNF vs MTX for irArthritis: IFX worked faster but had worse PFS
  - **Vedolizumab**: retrospective data suggest it has better survival compared to IFX for irColitis





Faje et al. Cancer 2018; Syed et al. Cancers 2024; Verheijden et al. EJC 2024; Zou, Faleck et al. JITC 2021

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#8 Steroid-reducing approaches are key

- **Enteric steroids are effective for mild-moderate colitis**
  - 52/69 (75%) pts treated with budesonide for median G3 diarrhea responded; minimal side effects
- **Biologic therapies are effective for moderate-severe colitis**

	Infliximab	Vedolizumab	Ustekinumab
Mechanism	Anti-TNF-α	Anti-integrin (α4β7)	Anti-IL12/23
Dose	5 (to 10) mg/kg IV at 0/2/6 weeks	300mg IV at 0/2/6 weeks	~6mg/kg IV x1 -> 90mg SQ q8weeks
Efficacy in steroid-refractory irColitis	**~90% response**	**~90% response** (~70% if prior IFX failure)	80+% response **68% remission (highly refractory pts)**
Pros	**Rapid onset** Most experience	Excellent safety **Less likely to interfere with anti-tumor effect**	Excellent safety Convenient
Cons	Infection risk ?Impact on anti-tumor effect	Slower onset	Less experience ?onset rate ?IL-12 and tumor control
Additional Considerations	Consider avoiding if high risk for immunosuppression or concomitant hepatitis	Consider avoiding if GI cancer or GI metastases	Consider **if dermatologic involvement** and/or contraindication to anti-TNF

Machado et al. Cancers 2024; Zou, Faleck et al. JITC 2021; Johnson et al. JITC 2018; Abu-Sbeih et al. JITC 2018; Harris, Faleck et al. Oncologist 2022; Ibraheim et al. APT 2020; Thomas, Faleck et al. AJG 2023

#8 Steroid-reducing approaches are key cont.

My approach:

Microscopic Colitis or Mild Colitis with G1-2 Symptoms	• Start budesonide • Vedolizumab if inadequate response
Moderate - Severe Colitis or Mild- Moderate Colitis with G3 symptoms	• Budesonide or short course prednisone (if needed) • Start biologic: a) Favor vedolizumab for most b) Prefer infliximab if multi-system irAE, severe endoscopy, need for rapid response w/o steroids, ? GI cancers
Severe Colitis + G3-4 Symptoms	• IV steroids + infliximab

Faleck et al. JCO 2023

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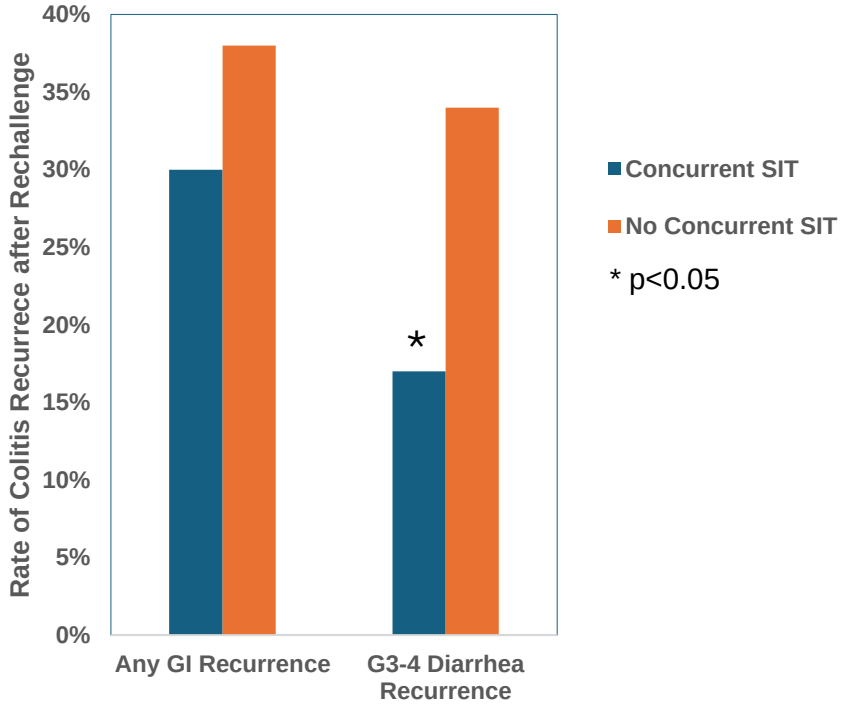
#9 ICI rechallenge after colitis is feasible and GI-directed therapy can help

- **Colitis relapse risk**: dependent on specific agents, but ~30-40%
- **Colitis-directed therapies can mitigate risk**
  - ***Budesonide*** continuation for patients who responded
    - Can taper to lowest effective dose for maintenance
  - ***Biologic*** continuation for patients who responded
    - Can often synchronize with ICI therapy



Abu-Sbeih et al. JCO 2019; Badran, Faleck et al. JITC 2023

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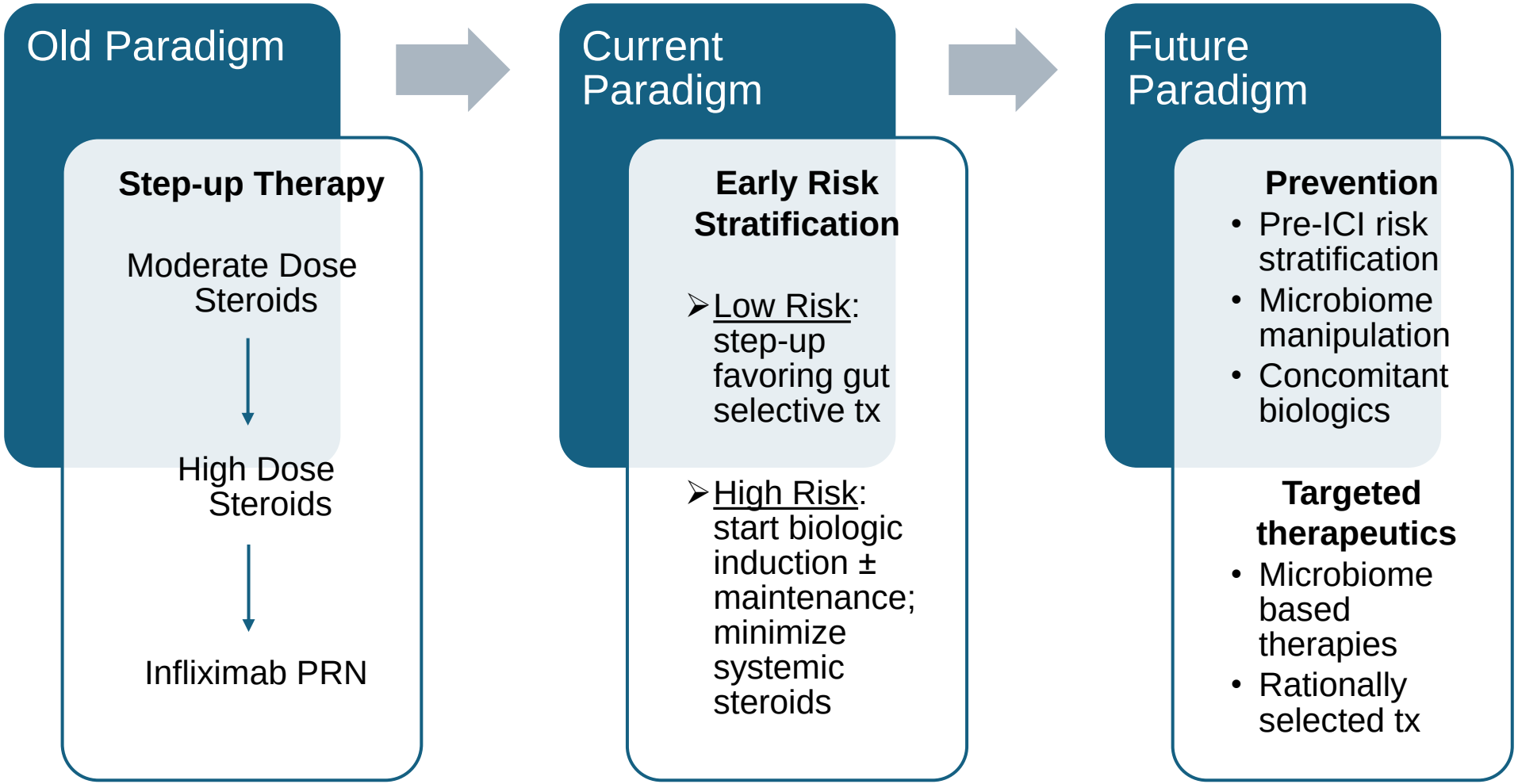
#10 Novel treatments & paradigms are emerging



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#10 Novel Treatments: the future is near…

1) Fecal Microbiota Transplantation

- 2018– 2023: > 20 cases published (MDACC, MSK) of patients treated with FMT salvage for refractory irEC with ~80% response rate
- 2024+: ongoing studies at MDACC of FMT for both first-line and salvage

2) Live Biotherapeutics

- *A Single-arm, Open-label, Phase 1 Study to Assess Safety and Preliminary Efficacy of Cultivated Multi-Strain Live Bacterial Therapeutic SER-155 for First-Line Treatment of Immunotherapy-Related Enterocolitis (*MSK investigator-initiated trial (PI: Faleck), **launch anticipated 12/2024)**

> ***SER-155*** *is a rationally designed, cultivated, set of 16 live human-commensal bacterial strains encapsulated for oral use*
>
> - **Restoration of epithelial barrier integrity**
> - **Reduction in GI inflammation**
> - **Colonization resistance against Enterobacteriaceae**

Wang et al. Nat Med 2018; Elkrief, Faleck et al. CIR 2024; Halsey et al Sci Trans Med 2023

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- Neil Shah, MD (GU Onc)
- Jonathan Peled, MD, PhD (BMT)
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