3rd IBDHORIZONS UPDATES FOR APP

IBDH

King Street Ballroom, October 29, 202

OVERVIEW OF CURRENT IBD THERAPIES

IBDH

ARS QUESTION 1

Which medication has **a Boxed Warning:**

A. Vedolizumab
B. Ustekinumab
C. Risankizumab
D. Ozanimod
E. None of the above

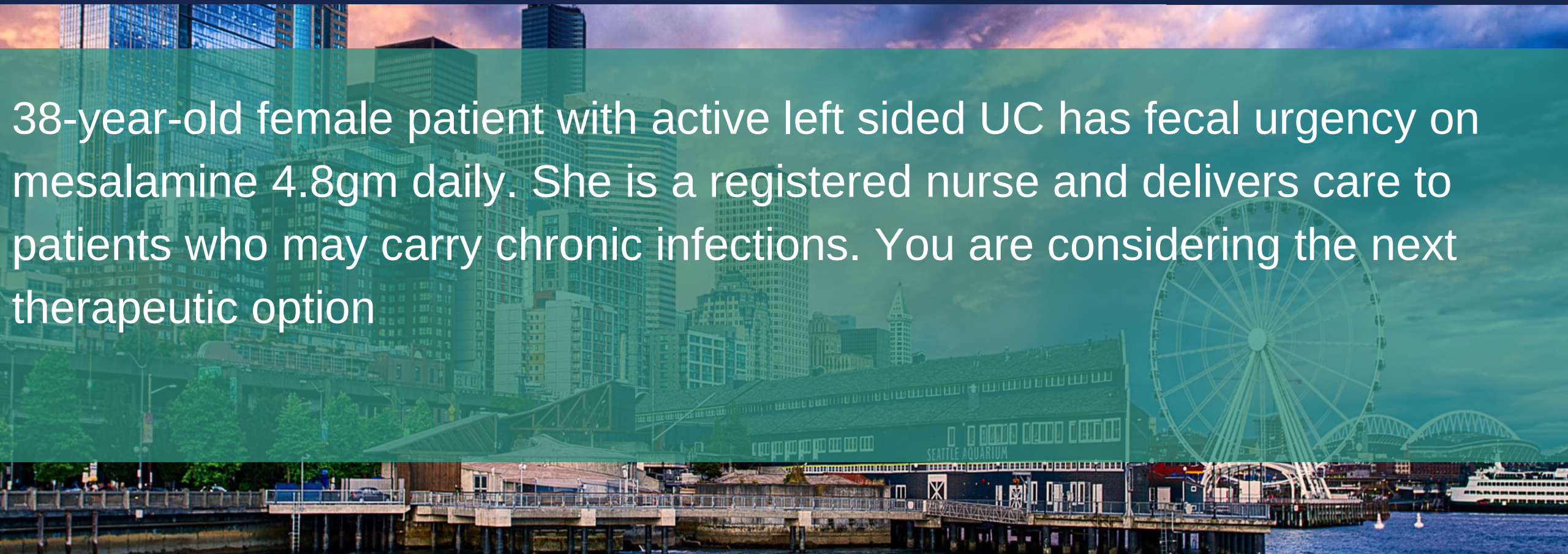
ARS QUESTION 2

Which statement is FALSE:

A. In head-to-head trial, Vedolizumab has shown superior remission rates compared to adalimumab in UC
B. Previous biologic failure is associated with lower response rates to ozanimod
C. Upadacitinib has **no** boxed warnings
D. In head-to-head trial, Ustekinumab showed similar efficacy to adalimumab in CD

CLINICAL CASE 4

IBDH



38-year-old female patient with active left sided UC has fecal urgency on mesalamine 4.8gm daily. She is a registered nurse and delivers care to patients who may carry chronic infections. You are considering the next therapeutic option

Overview of current IBD therapies

Jeffrey Jacobs, MD

JEFFREY JACOBS

Dr. Jeffrey Jacobs is a GI with a patient-centered and team-based approach to medical care while using the most up-to-date research to get the best outcome for his patients.
His clinical interests include integrating intestinal ultrasound (IUS) for the diagnosis and monitoring of patients with inflammatory bowel disease (IBD).
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IBDHORIZONS

DISCLOSURES

No relevant financial relationships to disclose

Drug class	Agent	Mode of delivery	Crohn's disease	Ulcerative colitis
Anti-TNFα	Infliximab	IV	FDA approved	FDA approved
	Adalimumab	SC	FDA approved	FDA approved
	Certolizumab	SC	FDA approved	
	Golimumab	SC		FDA approved
Anti-trafficking	Vedolizumab	IV	FDA approved	FDA approved
	~~Natalizumab~~	~~IV~~	~~FDA approved~~	
IL-12/23 inhibitor	Ustekinumab	IV, SC	FDA approved	FDA approved
IL-23 inhibitor	Risankizumab	IV, SC	FDA approved	
JAK inhibitor	Tofacitinib	PO		FDA approved
	Upadacitinib	PO		FDA approved
S1P receptor modulator	Ozanimod	PO		FDA approved

Case 1: A 44-year-old man with a history of CHF, DM2, and ulcerative proctosigmoiditis diagnosed 3 years ago had been maintained on 2.4 g po mesalamine. He develops rectal bleeding (75% of BMs) and diarrhea (8 BM/day with urgency), and colonoscopy shows Mayo 3 pancolitis.

What is your next step?

A. Prednisone
B. Increase mesalamine to 4.8 g/day
C. Start advanced therapy
D. All of the above

If you and the patient opt for advanced therapy, which medication do you recommend?

Case 2: A 23 yo M with ileal Crohn's disease with a history of ileocecal resection 4 years ago and has not been on therapy since. Colonoscopy shows multiple (>5) small and medium sized ulcers in the TI. What do you recommend?

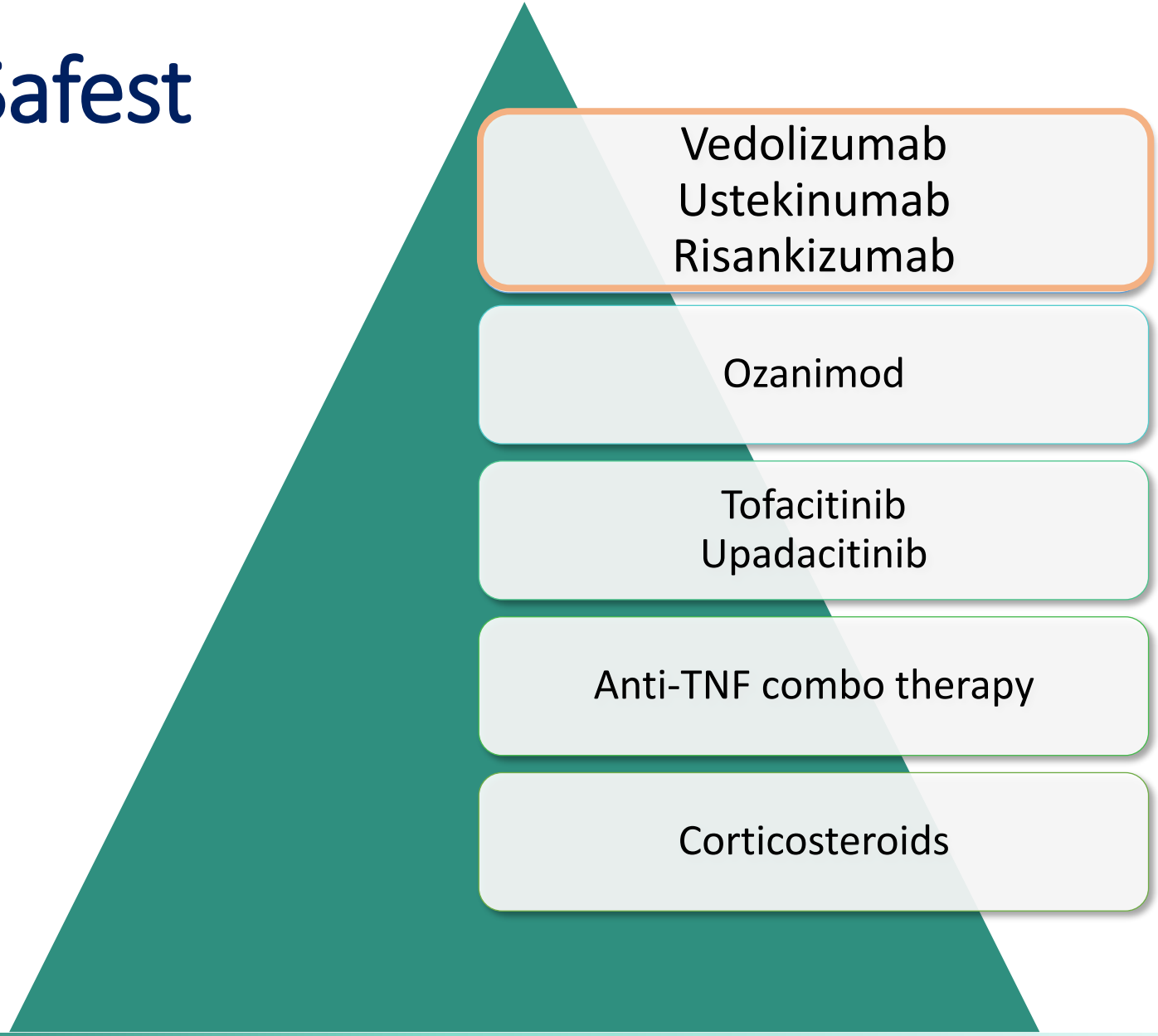
A. Mesalamine
B. Budesonide and monitor with a colonoscopy in 1 year.
C. Vedolizumab
D. Risankizumab

Mesalamine is effective for mild-moderate ulcerative colitis

- Standard dose po mesalamine (2-3 g/d) is effective for induction of remission of mild-moderate UC
- High dose mesalamine (>3 g/d) can be used initially or if response to standard dose is suboptimal
  - No benefit shown for high dose over standard dose mesalamine for maintenance of remission
- No benefit to continuing mesalamine once advanced therapy has been started
- Mesalamine has not been shown to be more effective than placebo for Crohn's disease either for induction of remission or mucosal healing
  - Sulfasalazine 3-6 g/d can be used for management of symptoms due to colonic Crohn's disease but has not been shown to induce mucosal healing

Ko et al. Gastro. 2019. Lichtenstein et al. AJG. 2018.

Safest


Vedolizumab
Ustekinumab
Risankizumab
Ozanimod
Tofacitinib
Upadacitinib
Anti-TNF combo therapy
Corticosteroids

Vedolizumab

- Low risk of infections and infusion reactions
- No known difference between ileal and colonic response
  - GEMINI-I/GEMINI-M: no difference between clinical remission rates in isolated ileal and colonic disease (21.2% vs. 22.4%)
  - VISIBLE2: SC vedolizumab clinical remission more likely in colonic (49%) than ileal disease (36%) at wk 52
  - Less known about endoscopic response in ileal vs colonic disease

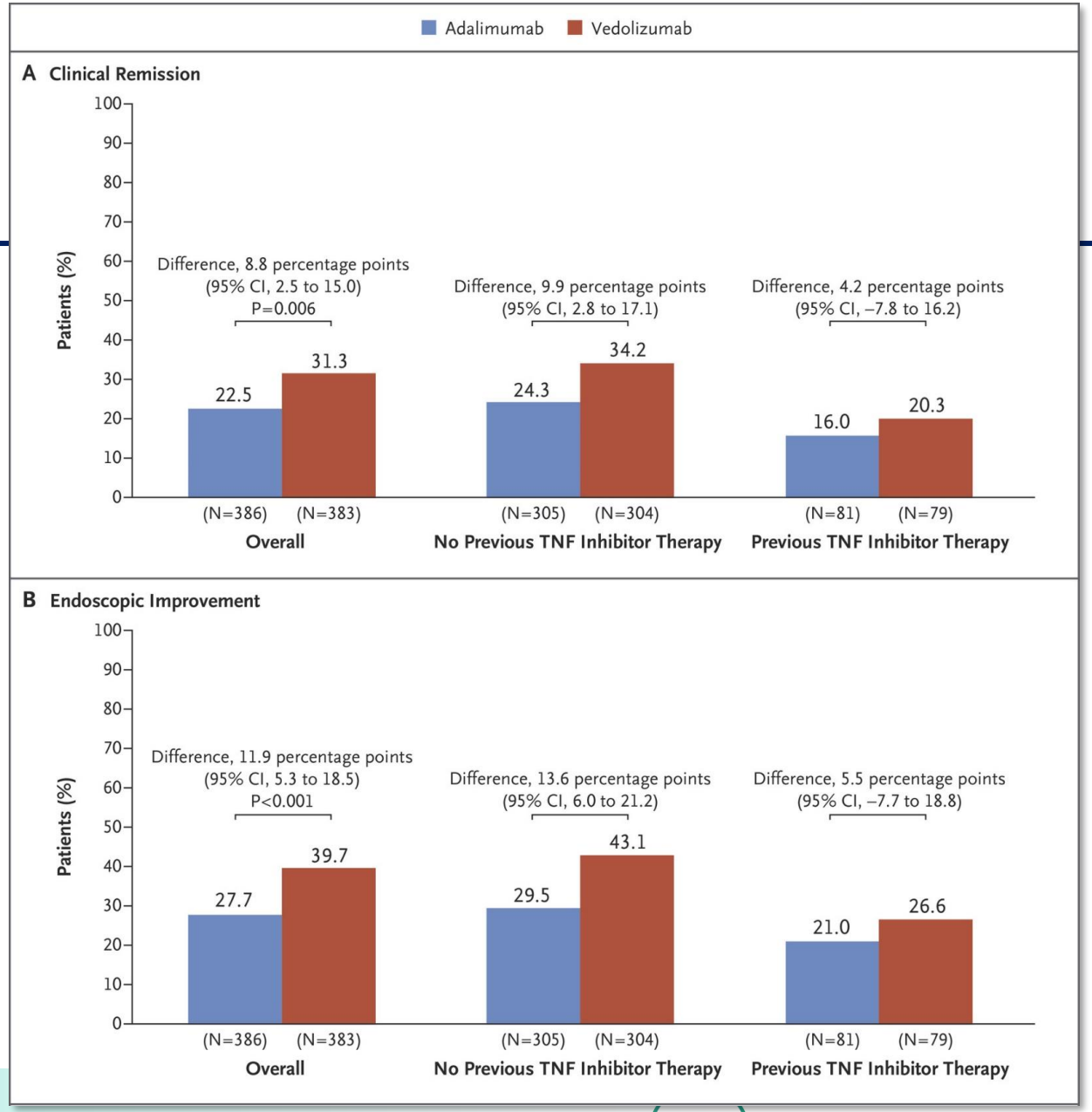
Incidence of gastrointestinal infections of special interest in patients with UC or CD

	Ulcerative colitis (N = 894)		Crohn's disease (N = 1349)	
Parameter	**n (%)**	**Incidence/1000 person-years (95% CI)[a]**	**n (%)**	**Incidence/1000 person-years (95% CI)[a]**
Gastrointestinal infections of special interest	122 (13.6)	46.9 (38.3, 55.6)	162 (12.0)	46.1 (38.8, 53.4)
Abdominal and gastrointestinal infections (pathogen unspecified)[b]	92 (10.3)	34.9 (27.6, 42.3)	141 (10.5)	39.6 (32.9, 46.3)
Clostridium infections[c]	26 (2.9)	9.1 (5.6, 12.6)	21 (1.6)	5.4 (3.1, 7.8)
Campylobacter infections[d]	9 (1.0)	3.1 (1.1, 5.2)	8 (<1)	2.1 (0.6, 3.5)
Shigella infections[e]	0	0	1 (<1)	0.3 (0, 0.8)
Yersinia infections[f]	1 (<1)	0.3 (0, 1.0)	0	0
Bacterial infections (bacteria unspecified)[g]	0	0	1 (<1)	0.3 (0, 0.8)

Loftus, Jr. et al. AP&T. 2020. Atreya, Jr. et al. Curr Res Pharmacol Drug Discov. 2022.

Vedolizumab is superior to adalimumab in ulcerative colitis

- Higher rates of corticosteroid free remission in ADA treated patients
- Fewer overall and serious infections in VDZ treated
- More zoster in ADA treated patients
- More c. diff in VDZ treated patients



Sands, et al. NEJM. 2019.

IBDHorizons

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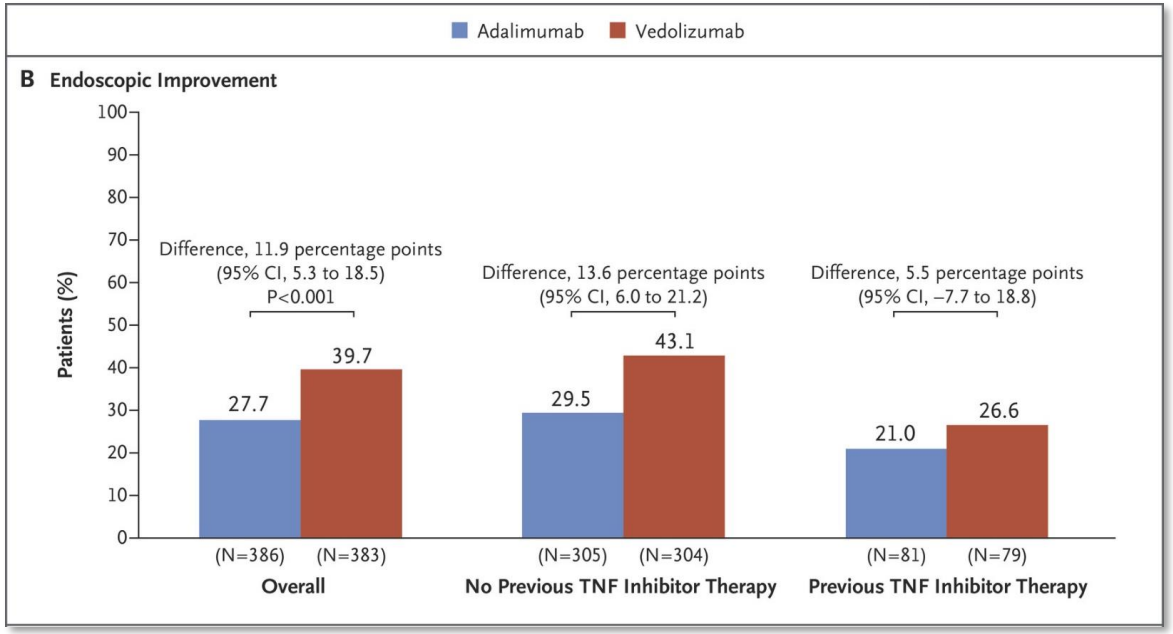
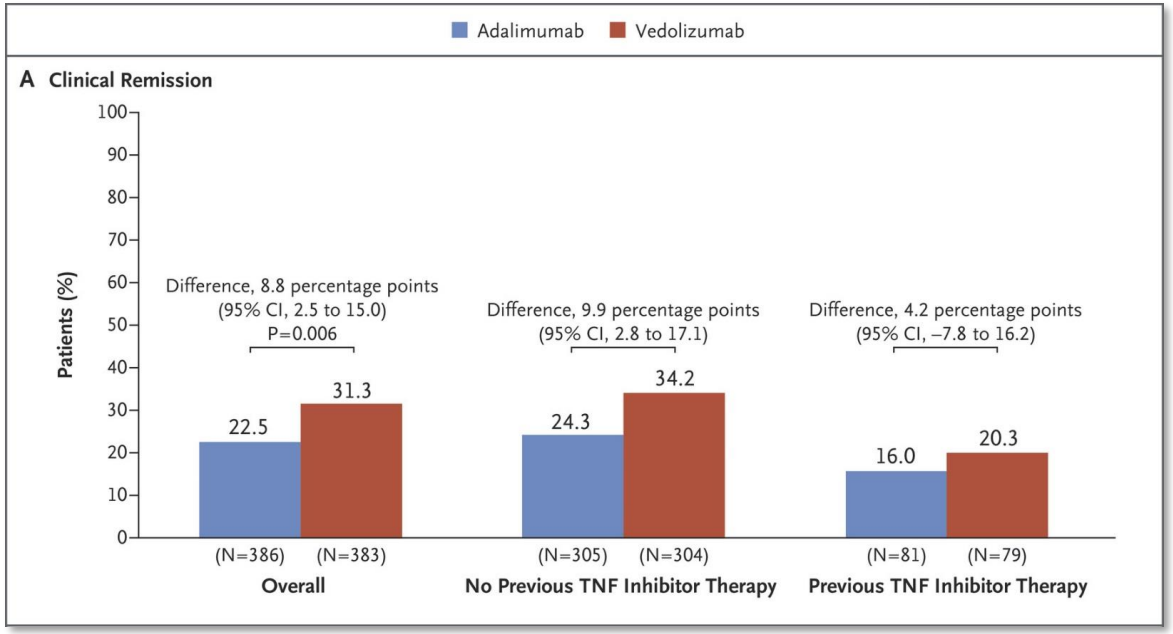


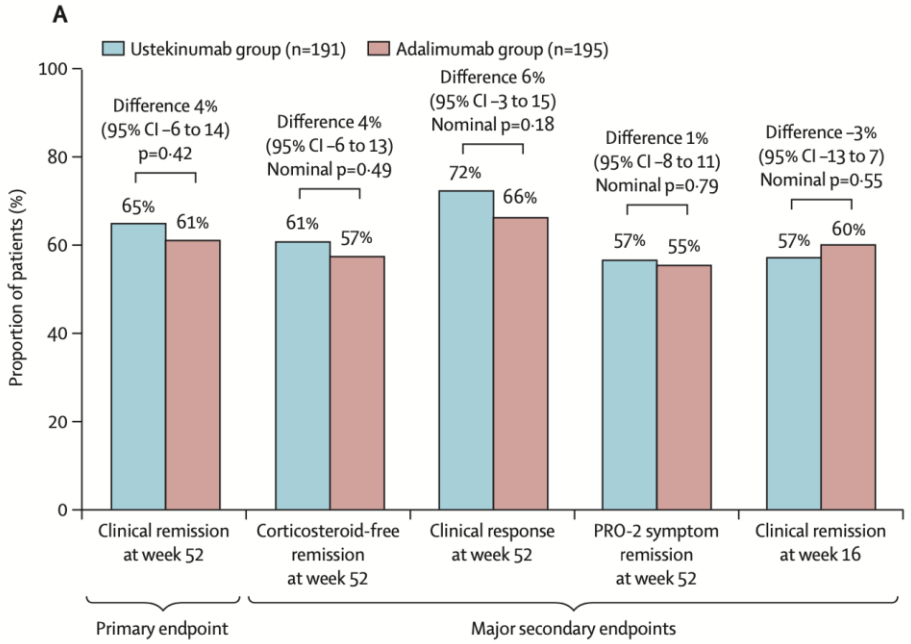


Sands, et al. NEJM. 2019.

IBDHorizons

Ustekinumab (CD and UC)

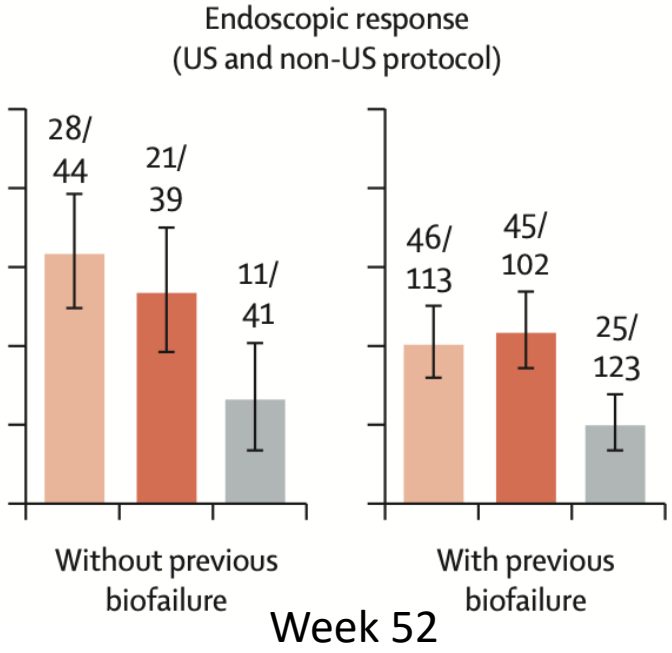
SEAVUE: no difference between ustekinumab and adalimumab in bio-naïve Crohn's disease



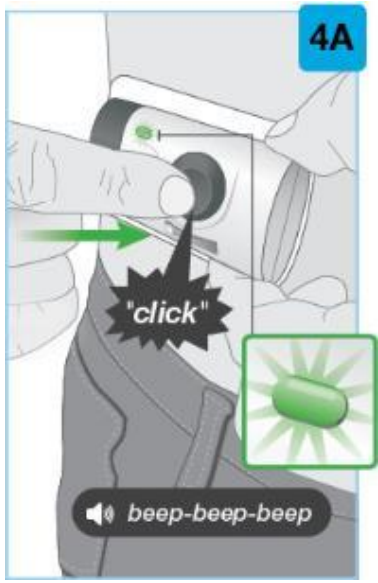
Sands, et al. Lancet. 2022.

Risankizumab (Crohn's disease)

600 mg IV weeks 0, 4, and 8, then SC 360 mg at week 12 and every 8 weeks thereafter via on-body injector

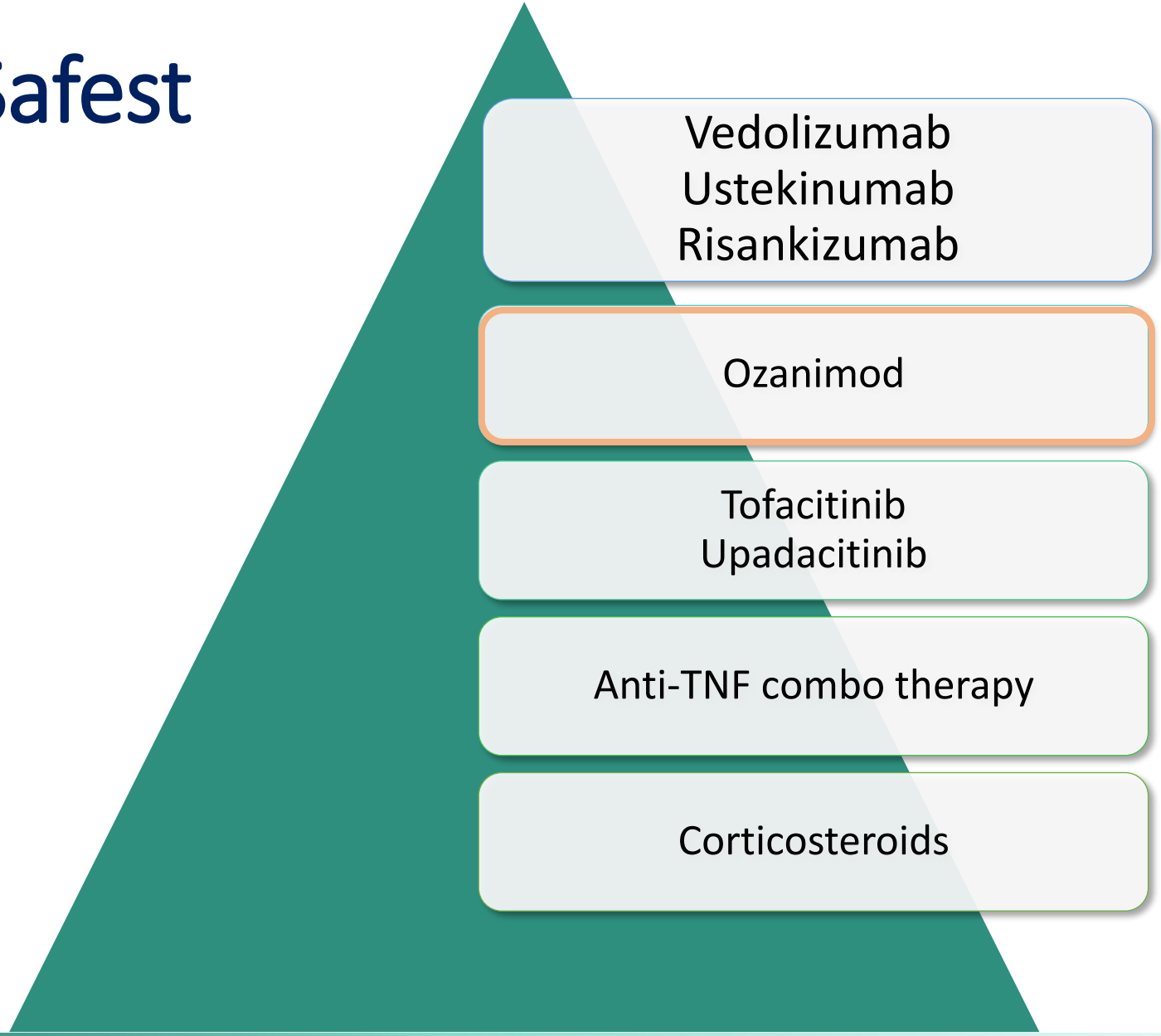


Ferante, et al. Lancet. 2022.



IBDHorizons

Safest


Vedolizumab
Ustekinumab
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Anti-TNF combo therapy
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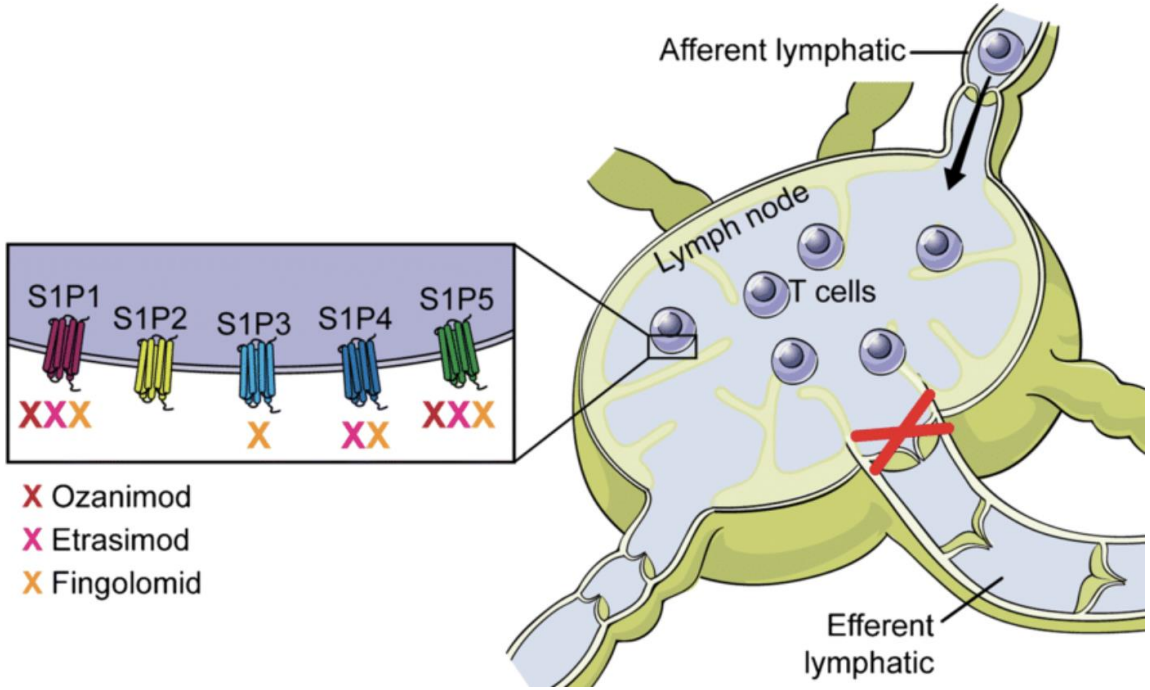
Ozanimod (ulcerative colitis)

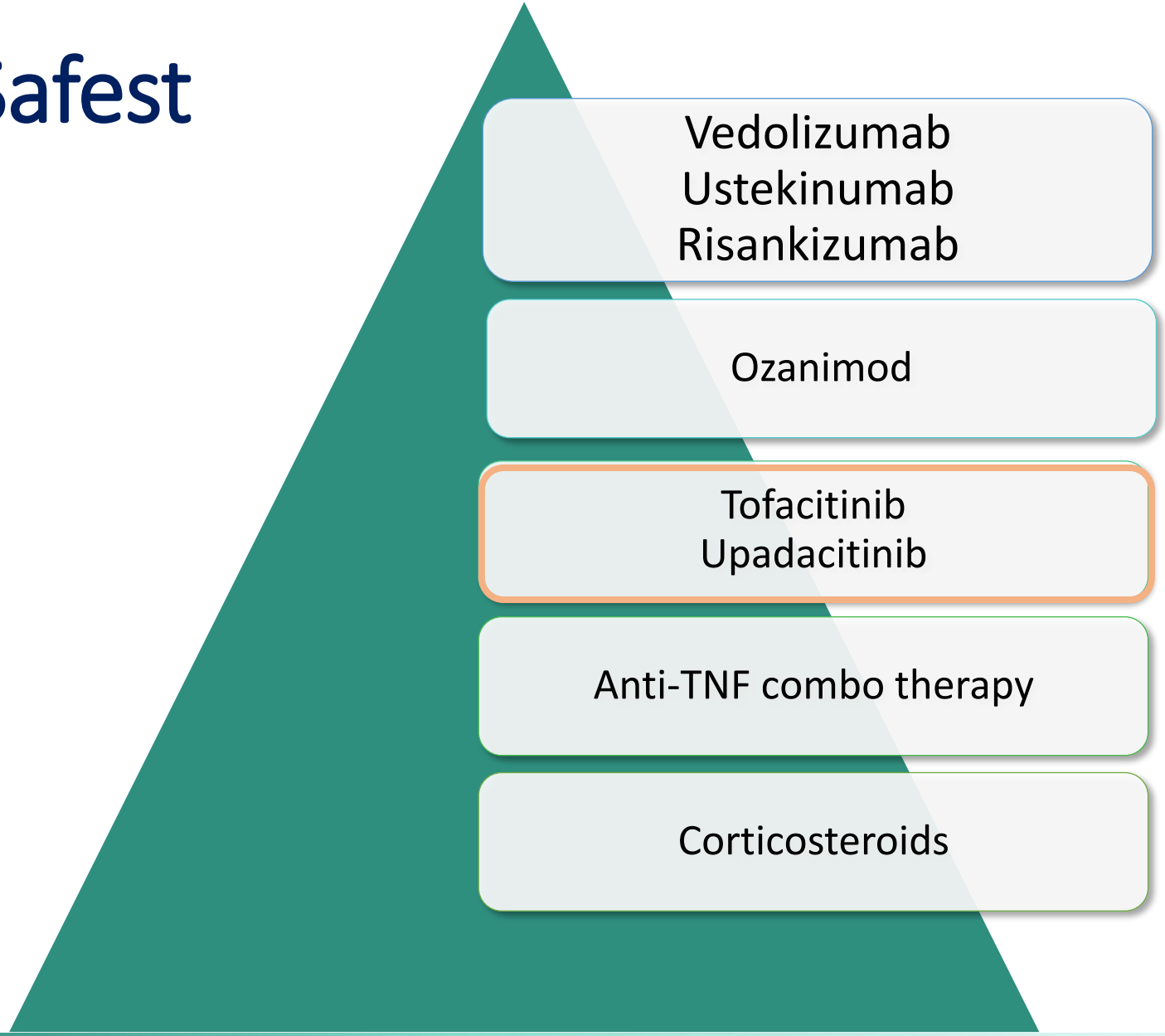
- S1P receptor modulator (S1P1 and S1P5) → blocks egress of the lymphocytes from lymphoid tissue
- Ozanimod more effective than placebo for all endpoints – clinical remission, endoscopic improvement, and mucosal healing
  - Most common adverse effects:
    - Reduction in lymphocyte count – decrease by a mean of 54% at week 10
      - ALC <200 occurred in 1.1%. Recovers with holding the medication.
    - Increase in LFTs
    - Macular edema (DM, uveitis)
    - Bradycardia
- Dose increase over 7 days then 1 mg per day po



Shukla T & Sands B. et al. Inflamm Bowel Dis. 2019.

- Contraindicated if stroke, TIA, MI, unstable angina in last 6 mos, class III/IV CHF, or heart block w/o pacemaker
- Obtain pre-treatment CBC, LFTs, ECG, and eye exam if hx of uveitis or DM

Safest


Vedolizumab
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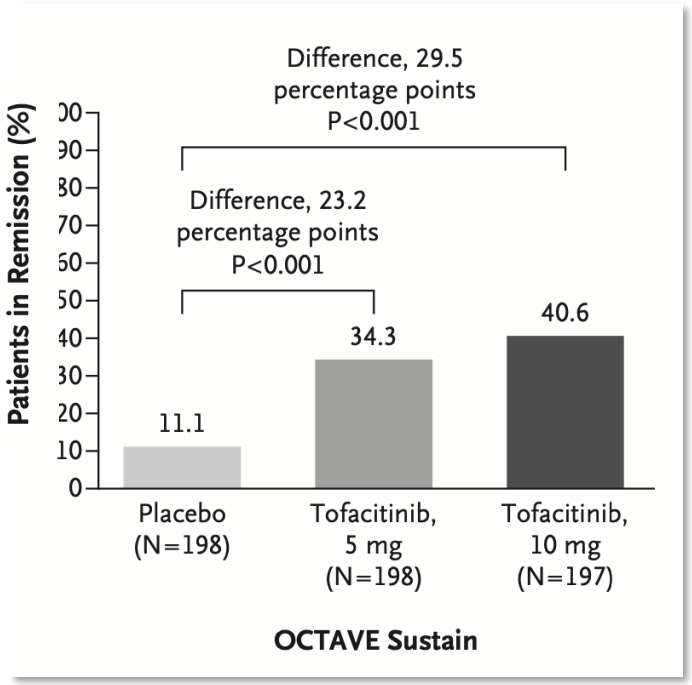
Tofacitinib (UC)

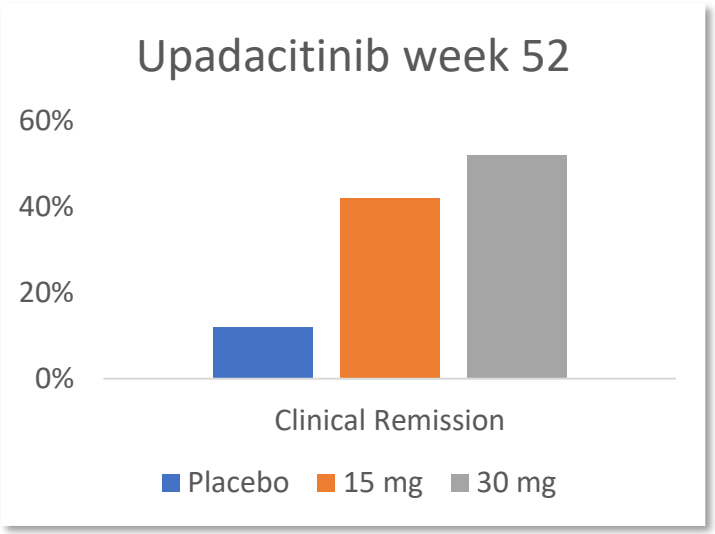
- Pan-JAK inhibitor
- 10 mg BID IR x8-16 weeks, then 5 mg BID



There is no clinically meaningful effect of age, sex, body weight, or disease severity at baseline (i.e., baseline albumin level and Mayo score) on average plasma JAK inhibitor concentration

Upadacitinib (UC)

- JAK1 inhibitor
  - 60-fold selective JAK1 over JAK2
  - 100-fold selective JAK1 over JAK3
  - Less NK cell depletion than tofa
- 45 mg qd for 8 weeks, then 30 mg or 15 mg daily maintenance
  - 30 mg for refractory, severe, extensive disease



Sandborn, et al. NEJM. 2017.
Danese, et al. Lancet. 2022.
Parmentier, et al. BMC Rheum. 2018.

IBDHorizons

JAK inhibitors: safety

- Infection (herpes zoster) [5 mg < 10 mg]
- Acne (JAKne)
- CPK elevation
- Dyslipidemia
- Laboratory abnormalities (leukopenia, increased LFTs)
- Require TNF failure or intolerance first

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE), AND THROMBOSIS

See full prescribing information for complete boxed warning.

- **Increased risk of serious bacterial, fungal, viral, and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Interrupt treatment with XELJANZ/XELJANZ XR/XELJANZ Oral Solution if serious infection occurs until the infection is controlled. Test for latent TB before and during therapy; treat latent TB prior to use. Monitor all patients for active TB during treatment, even patients with initial negative latent TB test. (5.1)**
- **Higher rate of all-cause mortality, including sudden cardiovascular death with XELJANZ vs. TNF blockers in rheumatoid arthritis (RA) patients. (5.2)**
- **Malignancies have occurred in patients treated with XELJANZ. Higher rate of lymphomas and lung cancers with XELJANZ vs. TNF blockers in RA patients. (5.3)**
- **Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) with XELJANZ vs. TNF blockers in RA patients. (5.4)**
- **Thrombosis has occurred in patients treated with XELJANZ. Increased incidence of pulmonary embolism, venous and arterial thrombosis with XELJANZ vs. TNF blockers in RA patients. (5.5)**

Ulcerative colitis risk: post-hoc analysis of OCTAVE induction and maintenance trials plus open label extension (OLE) study:

- Placebo:
  - 1 DVT and 1 PE in induction trial
  - 1 DVT and 1 PE in maintenance trial
- Tofacitinib:
  - 0 DVT or PE in induction or maintenance trials
  - 1 DVT and 4 PE in OLE study, all on 10 mg BID
    - One patient had DVT after a long-haul flight and leg infection from a motorbike accident
    - One had a history of prior DVT and PE and was not on anticoagulation, had mild disease activity
    - One had metastatic cholangiocarcinoma
    - One was obese and on OCPs
    - One was 57 with a history of stroke, hypertension, HLD, overweight, and a former smoker with mild disease activity

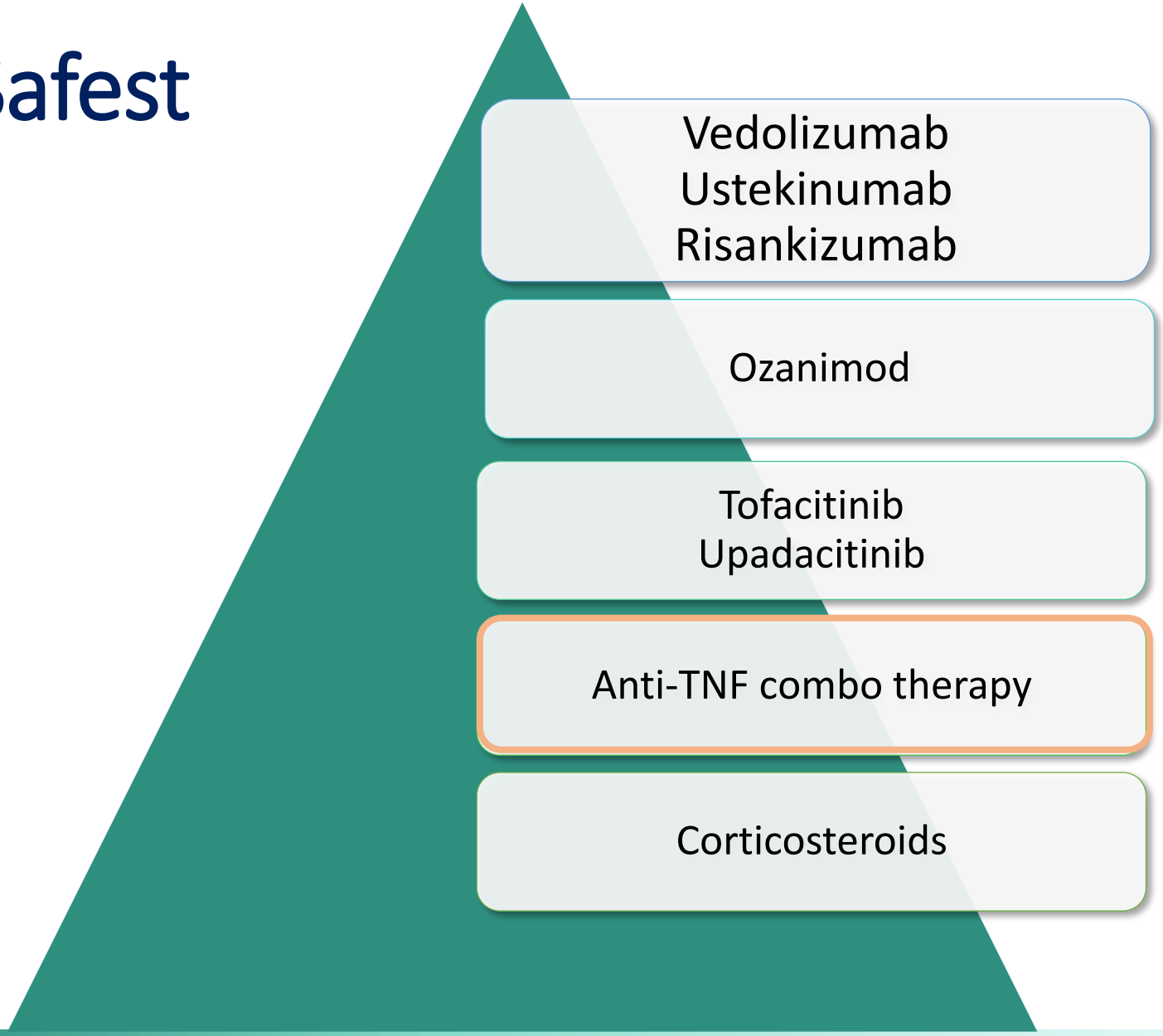
Baseline VTE risk high in UC:

- Severe disease
- Hospitalization
- Increasing age
- Corticosteroid use

Sandborn, et al. *AP&T.* July 2019.

IBDHorizons

Safest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Anti-TNFα

Safety considerations

- Infection (tuberculosis, HBV, pneumonia, herpes zoster)
- Malignancy (lymphoma, skin cancer)
- Injection/infusion reactions
- Avoid use in heart failure or demyelinating conditions
- Pancreatitis (azathioprine)
- Myelosuppression (azathioprine)

Advantages

- Fast onset (infliximab)
- Weight based (infliximab)
- Biosimilar available
- Best studied in pregnancy
- Use in many other non-IBD conditions

Drug class	Agent	Mode of delivery	Crohn's disease	Ulcerative colitis	Other conditions
Anti-TNFα	Infliximab	IV	FDA approved	FDA approved	Ankylosing spondylitis
	Adalimumab	SC	FDA approved	FDA approved	Psoriasis/psoriatic arthritis
	Certolizumab	SC	FDA approved		Rheumatoid arthritis
	Golimumab	SC		FDA approved	Sarcoidosis
					Hidradenitis
Anti-trafficking	Vedolizumab	IV	FDA approved	FDA approved	
	~~Natalizumab~~	~~IV~~	~~FDA approved~~		
IL-12/23 inhibitor	Ustekinumab	IV, SC	FDA approved	FDA approved	Psoriasis/psoriatic arthritis
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	Upadacitinib	PO		FDA approved	Psoriasis/psoriatic arthritis
					COVID-19
					Rheumatoid arthritis
					Atopic dermatitis
S1P receptor modulator	Ozanimod	PO		FDA approved	Multiple sclerosis

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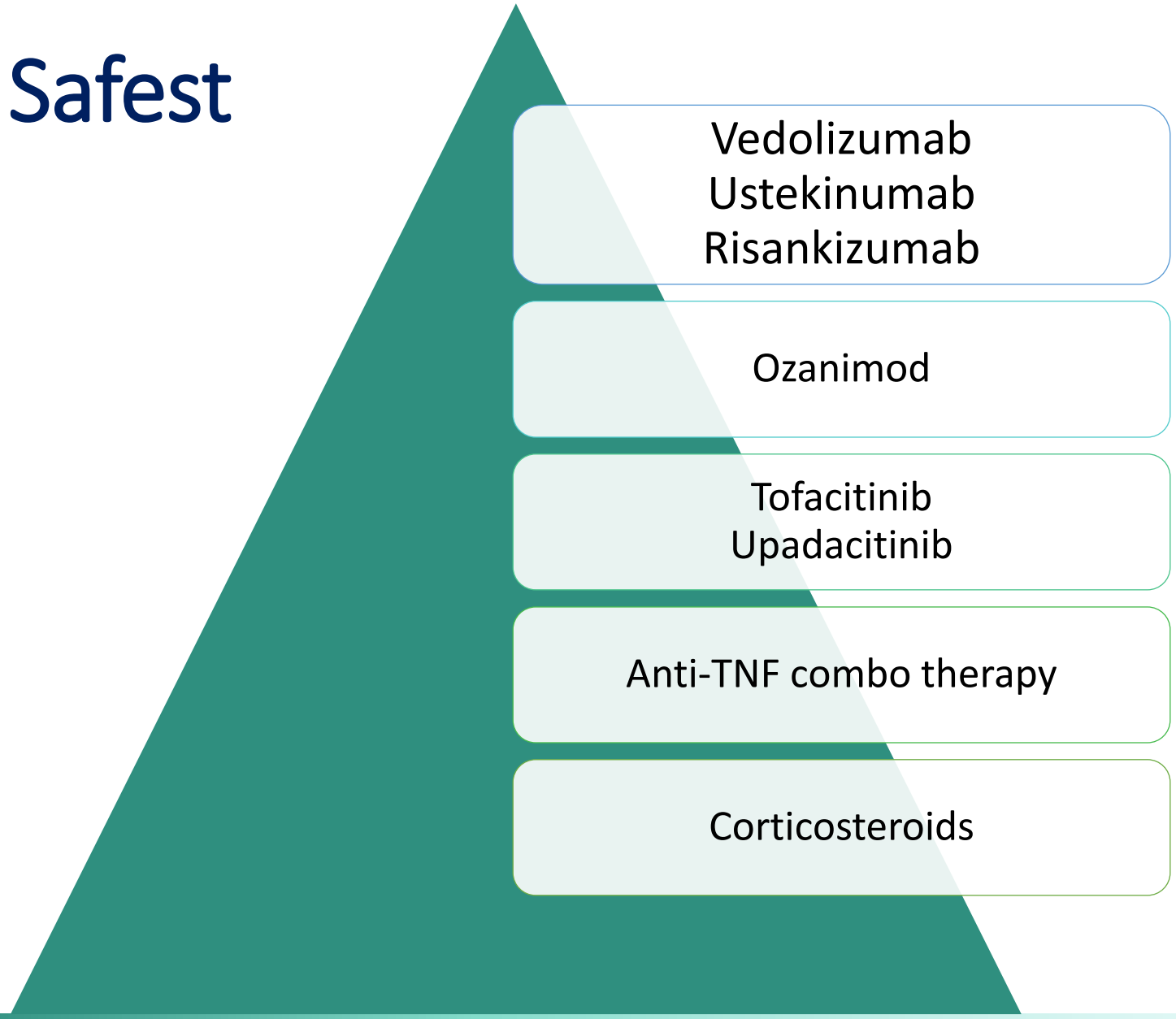

First line for most patients

First line if patient prefers an oral option (UC)

Severe UC, if failed TNF inhibitor

Severe disease or if hospitalized (IFX)

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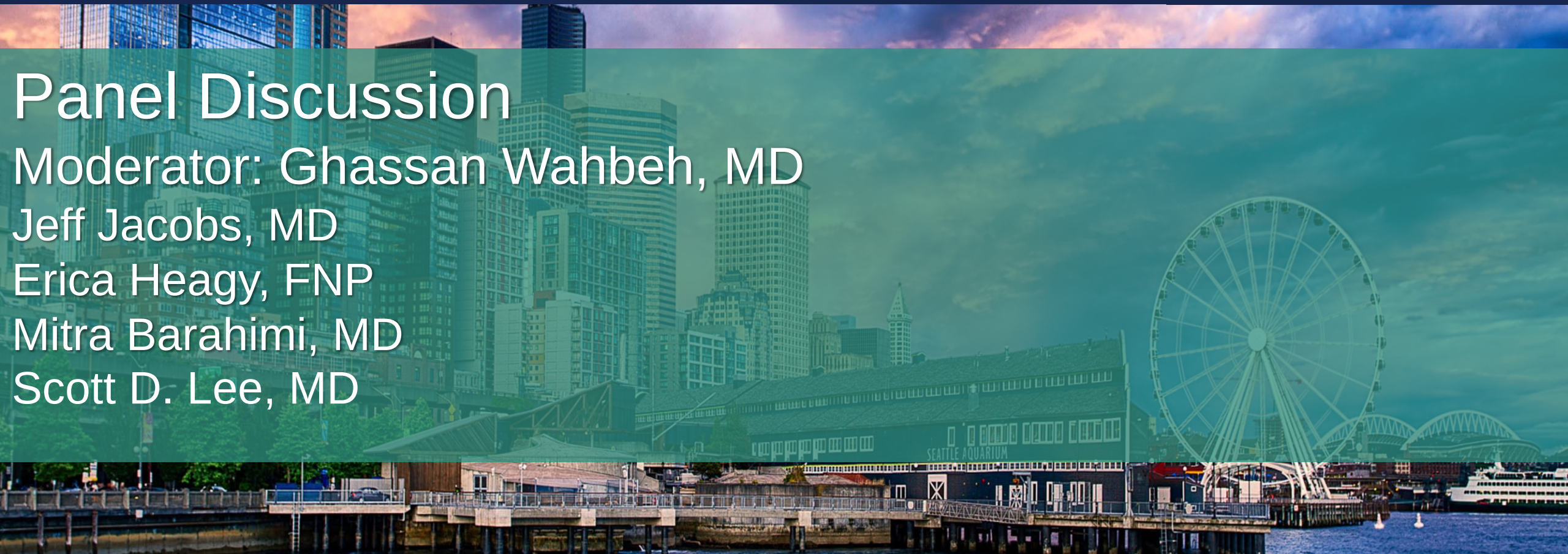
IBDHORIZONS

PANEL DISCUSSION

IBDH



Panel Discussion

Moderator: Ghassan Wahbeh, MD

Jeff Jacobs, MD

Erica Heagy, FNP

Mitra Barahimi, MD

Scott D. Lee, MD

CLINICAL CASE 4

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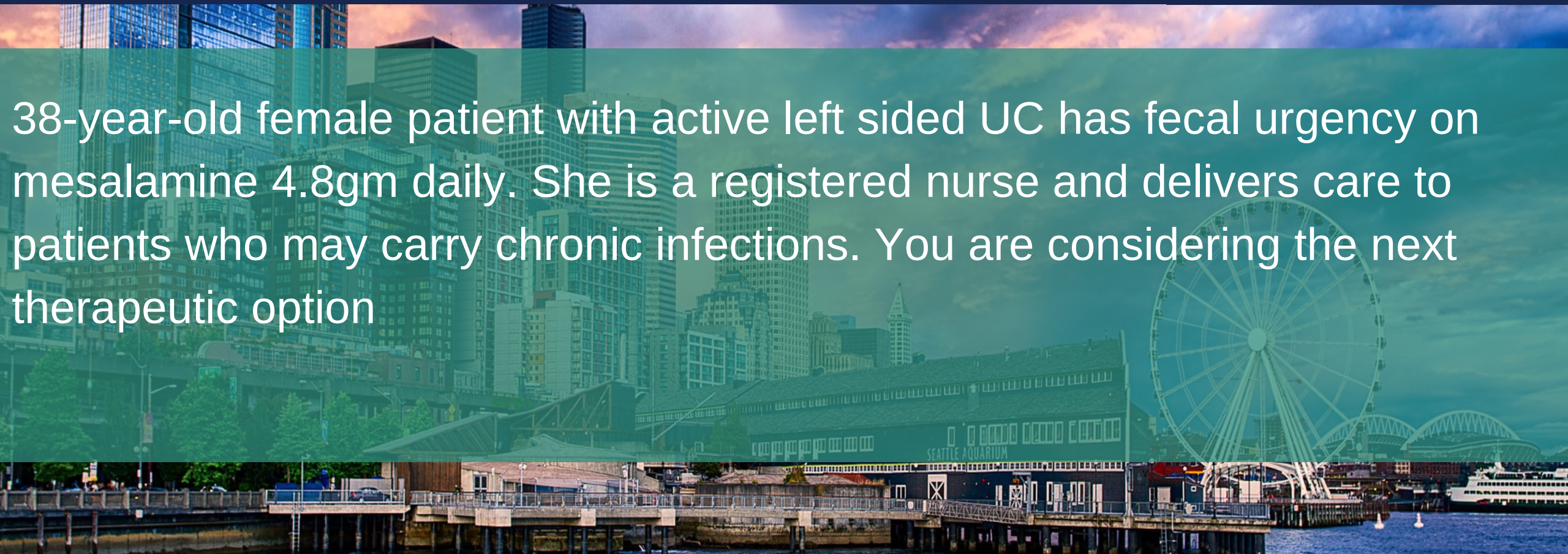

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B. Previous biologic failure is associated with lower response rates to ozanimod
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