GI Biopsies in the Era of Immunotherapy

(Immune Checkpoint Inhibitors)

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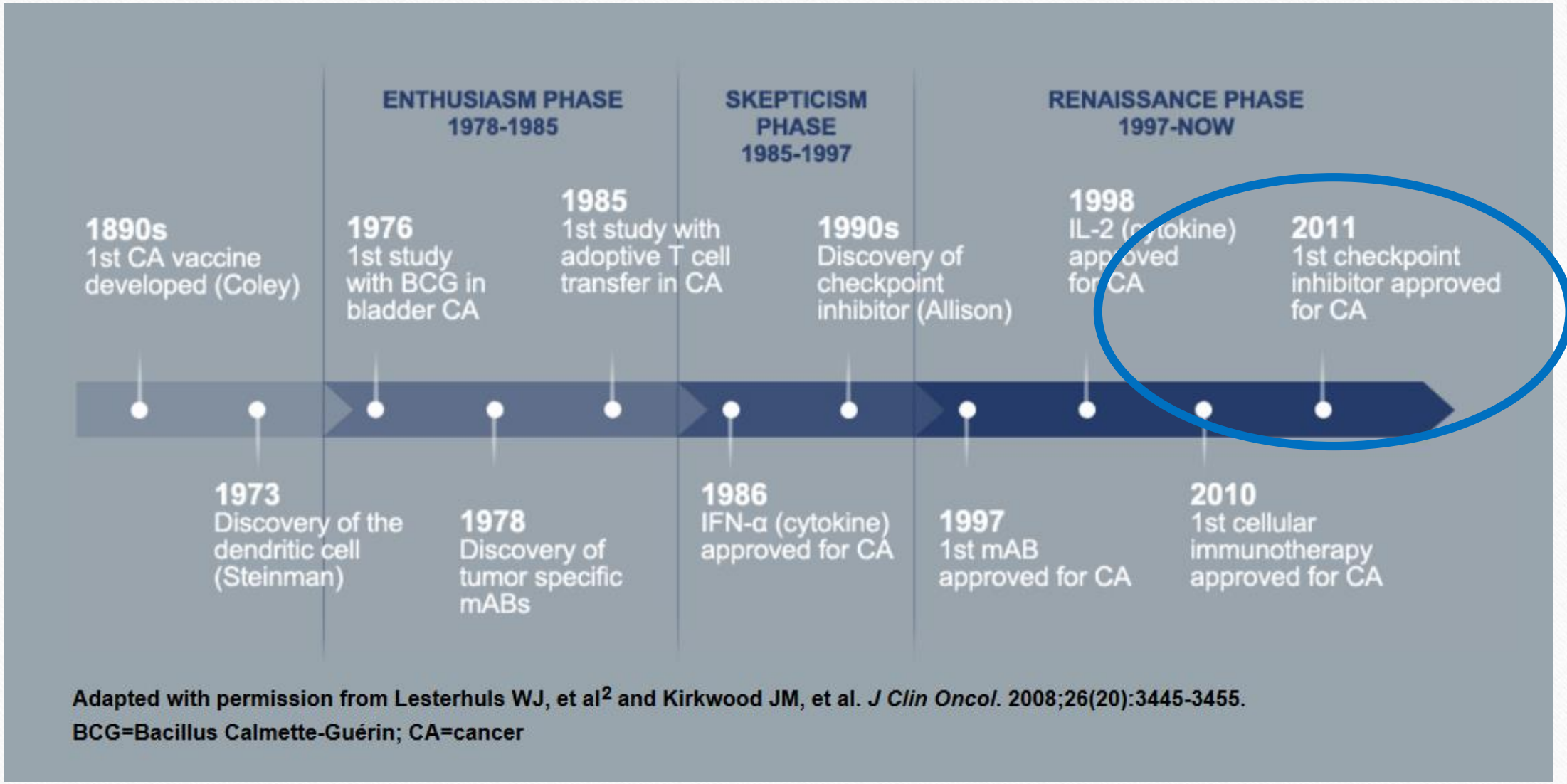
Digestive Disease Week (DDW); 6/3/2018

#DDW2018 #GIPath @USGIPS



Adapted with permission from Lesterhuls WJ, et al[2] and Kirkwood JM, et al. *J Clin Oncol.* 2008;26(20):3445-3455.

BCG=Bacillus Calmette-Guérin; CA=cancer

http://www.fightcancerwithimmunotherapy.com/

Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4 inhibitor)

ipilimumab

Programmed Cell Death Receptor-1 (anti-PD-1)

pembrolizumab

nivolumab

Programmed Death Ligand 1 (anti- PD-L1)

atezolizumab

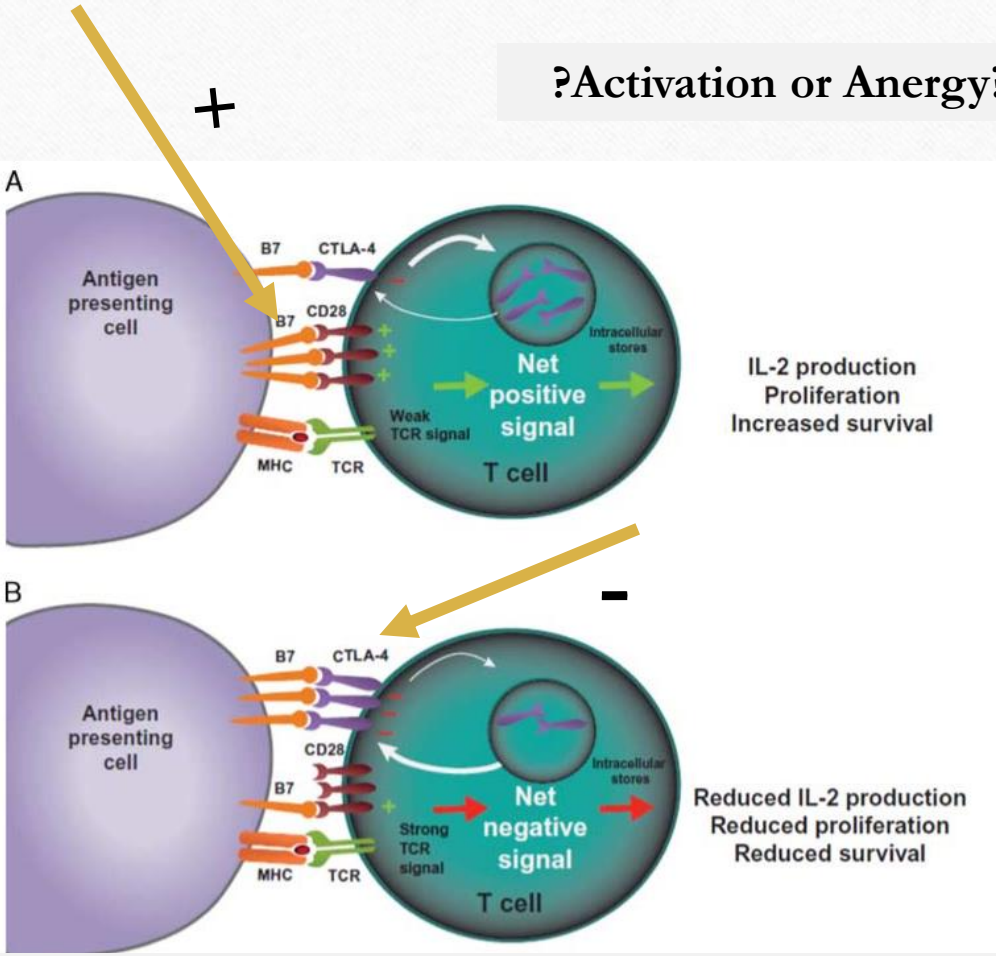
Immune Checkpoints
&
The Monoclonal Antibodies that Inhibit them

Immune Checkpoint CTLA-4

- Cytotoxic T lymphocyte associated antigen (CTLA-4) is upregulated after T cells are activated by signals from an APC occurring in secondary lymphoid tissue.

- CTLA-4 binds to B7, the main co-stimulatory molecule for T-cells, preventing T cell activation.

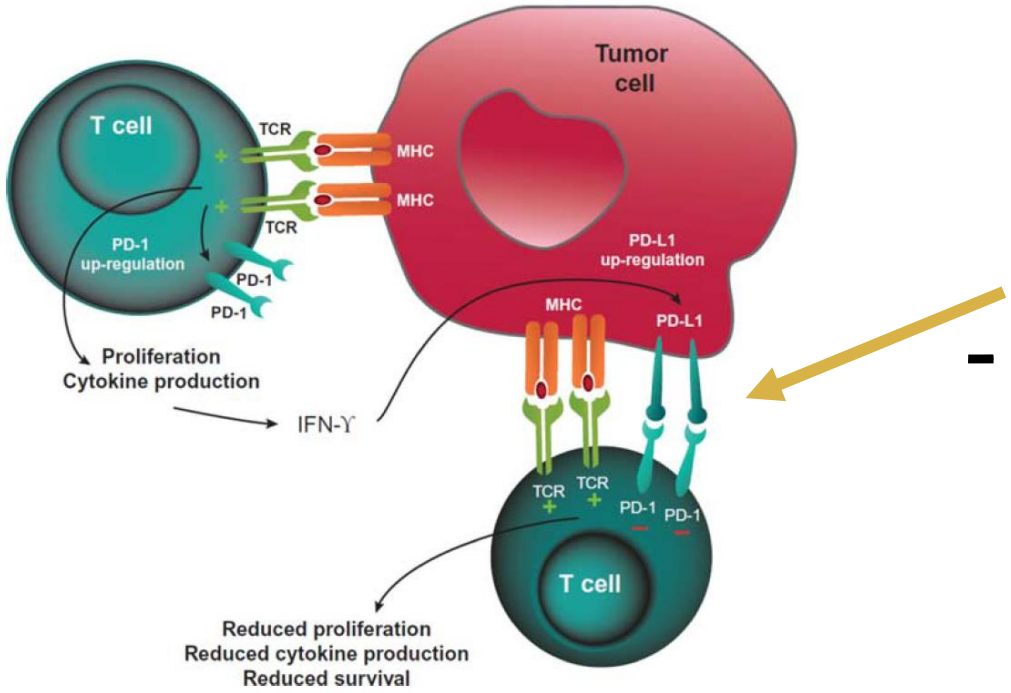
?Activation or Anergy?



Buchbinder EI, A Desai. CTLA-4 and PD1 Pathways: Similarities, Differences, and Implications of Their Inhibition. *Am J Clin Oncol* 2016; 39:98-106.

Immune Checkpoint PD-1

- **Programmed Cell Death Receptor-1 (PD-1)** expression induced after effector T cells become activated in the microtumor environment.
- PD-1 inhibits T-cell activation through binding to its ligands, **Programmed Death Ligand 1 (PD-L1) and PD-L2** present on both tumor and normal cells.
- Chronic antigen exposure of cancer can lead to persistent CD8 PD-1 expression and anergy.



Antibody Blockade of CTLA-4 and PD-1 Comparison

	CTLA-4 Blockade	PD1-Blockade
Site of Action	Secondary Lymphoid Tissue	Tumor Microenviornment
Ligand	B7; expressed by professional APC	PDL1 & PDL2; more widely expressed
Cells Enhanced	CD4, CD8	CD8, NK Cells, B Cells
Side Effects	• Mouse knockouts cause a lethal AI response • Generally worse AE	• Mouse knockouts; less severe AI response • Less severe AE
Cancer Types Responsive	Melanoma, NSCLC	**Broader diversity of cancers** Melanoma, NSCLC, Solid tumors with MSI, RCC, SCC, Urothelial

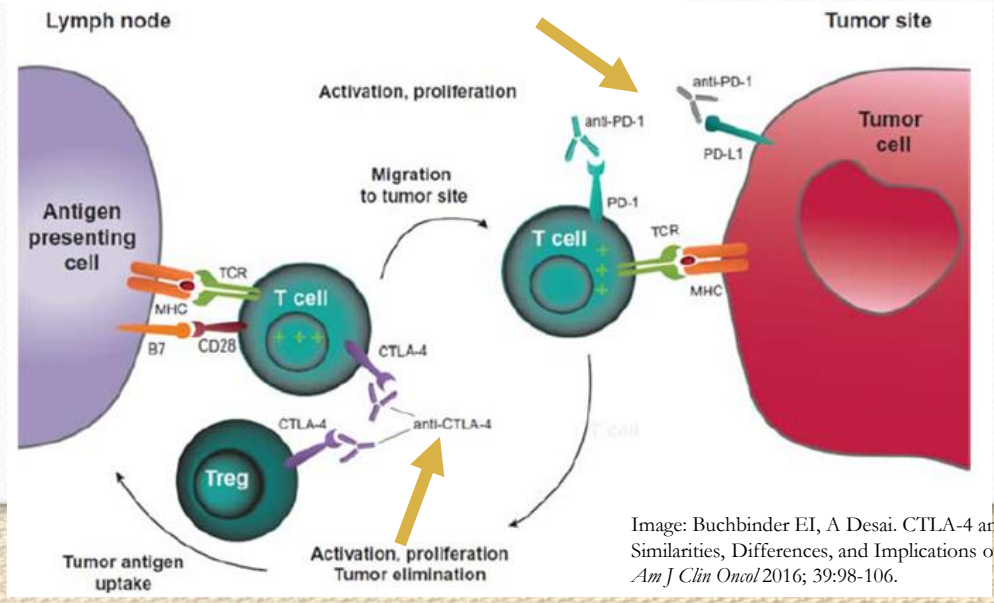


Image: Buchbinder EI, A Desai. CTLA-4 and PD1 Pathways: Similarities, Differences, and Implications of Their Inhibition. *Am J Clin Oncol* 2016; 39:98-106.

Successful Therapeutic Responses with Increased Overall Survival

Baseline (Day 0)

Week 12 (Day 84)

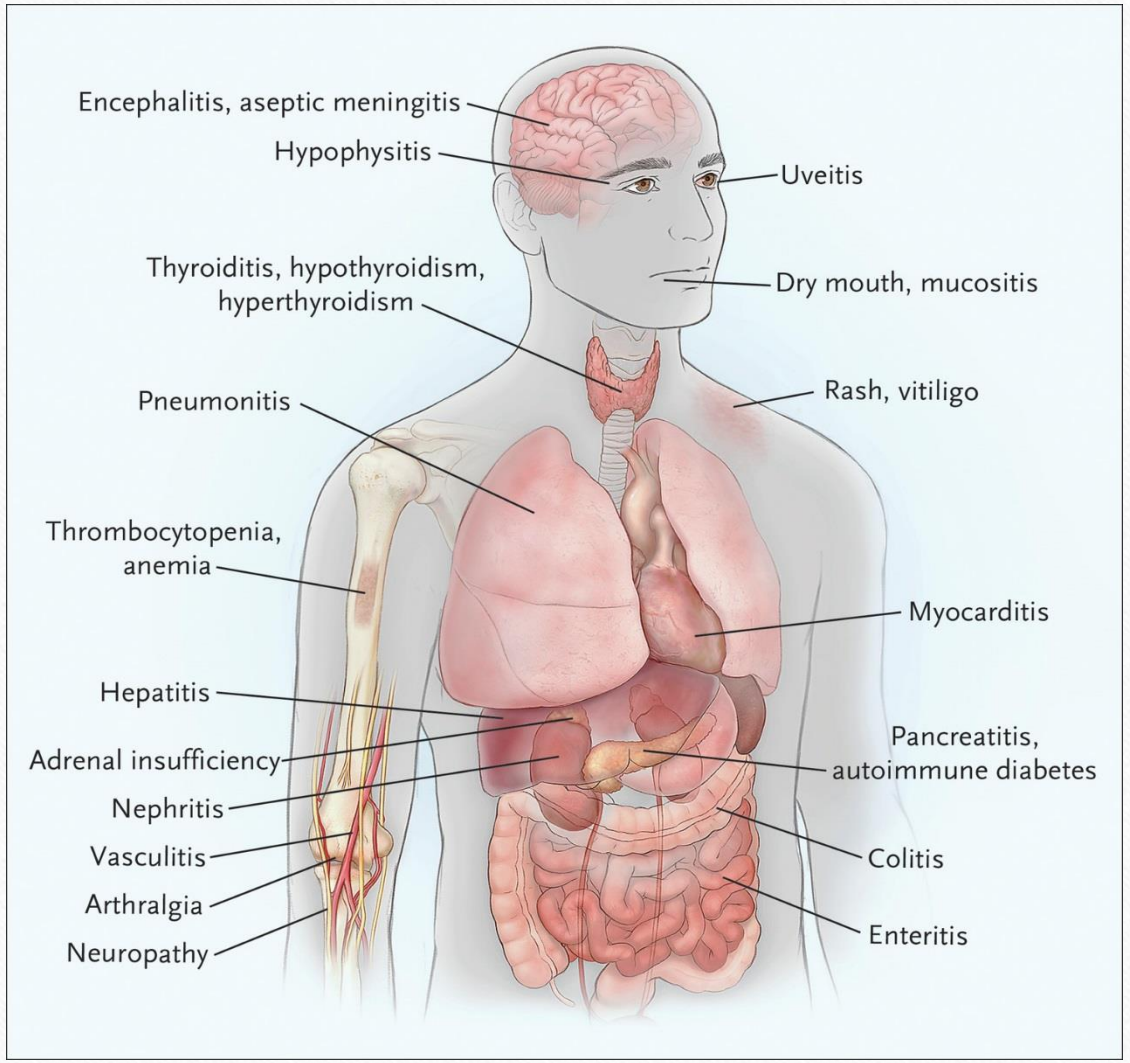
Week 16 (Day112)

Week 72 (Day 503)

The NEW ENGLAND JOURNAL of MEDICINE

Immune-Related Adverse Events (irAE)

- ✓ Immune checkpoint inhibitor therapy induces irAE in about 70% of patients
  - ✓ Can be seen after cessation of tx
- ✓ Important to recognize as irAE can cause life threating toxicity, and early recognition and treatment can prevent progression



Organs Affected by Immune Checkpoint Blockade

MA Postow et al. N Engl J Med 2018;378:158-168

Immune-Related Adverse Events (irAE)

Table 1
Immune-related adverse event rates associated with immune checkpoint inhibitors in advanced melanoma.

	Pembrolizumab (2 mg/kg 2- and 3-weekly) [5]		Nivolumab (3 mg/kg 2-weekly) [7,8,10]		Ipilimumab (3 mg/kg 3-weekly) [5,10]		Ipilimumab + Nivolumab (3 mg/kg + 1 mg/kg every 3 weeks) [10]	
	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Diarrhoea (%)	14–17	1–3	11–19	0–2	23–33	3–6	44	9
Colitis (%)	2–4	1–3	1	<1	8–12	7–9	12	8
Hepatitis* (%)	1–2	1–2	3–6	2–3	1–7	0–2	30	19
Pruritus (%)	14	0	16–19	<1	25–35	<1	33	2
Rash (%)	13–15	0	9–22	<1	15–21	1–2	28	3
Vitiligo (%)	9–11	0	5–11	0	2–4	0	7	0
Pneumonitis (%)	<1	<1	1–2	<1	0–2	<1	6	1
Hypothyroidism (%)	9–10	<1	4–9	0	2–4	0	15	<1
Hyperthyroidism (%)	3–7	0	2–4	<1	1–2	<1	10	1
Hypophysitis (%)	<1	<1	<1	<1	2–4	2	8	2
Renal injury (%)	1	0	1	<1	<1	<1	NR	NR
Rheumatological (%)								
Myalgia	2–7	<1	4	0	2	<1	NR	NR
Arthralgia	9–12	<1	6–8	0	5	<1	11	<1
Arthritis	0–2	0		NR	0	0		NR
Myositis		0		NR	NR	NR		NR
Uveitis (%)	<1	0	NR	NR	0	0	NR	NR
Neurological (%)	1	0	1	NR	1	<1	NR	NR
Cardiac (%)	NR	1–2	0**	NR	NR	NR**	NR	NR
Fatigue (%)	19–21	0	34	0–1	15	1	35	4
Haematological (%)								
Anaemia	1–2	0	4	NR	<1	<1	NR	NR
Neutropenia	NR	NR	NR	0	0	0	NR	NR
Thrombocytopenia	NR	NR	NR	**0	NR	NR	NR	NR

NR = not reported
* Deemed to be any elevation of ALT or AST.
** G5 event.

- ✓ Median onset of diarrhea was 7 weeks
  - ✓ Wide interval range of 1 week to 6 months

Case Study:

- **April 2016** 69 year old woman with metastatic MSI-high colorectal cancer: AJCC pT4N0M1
- **May 2016** 6 cycles of FOLFOX; Progression of cancer on imaging
- **September 2016** began Pembrolizumab (anti-PD1)

November 2016:

Maculopapular rash over upper and lower extremities and pain and swelling of lips

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March 2017:
Last Treatment
(7 total cycles)

April 2017:
Diarrhea and abdominal pain. Referred to GI +Prednisone

Case Study:

- **April 2016** 69 year old woman with metastatic MSI-high colorectal cancer: AJCC pT4N0M1
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Elevated TSH/low T4; Started on levothyroxine

March 2017:
Last Treatment (7 total cycles)

April 2017:
Diarrhea and abdominal pain. Referred to GI +Prednisone

May 2017:
Endoscopic biopsies c/w immune checkpoint inhibitor colitis. Started on Infliximab.

Follow Up: **February 2018**; Lung nodules stable; No liver Mets

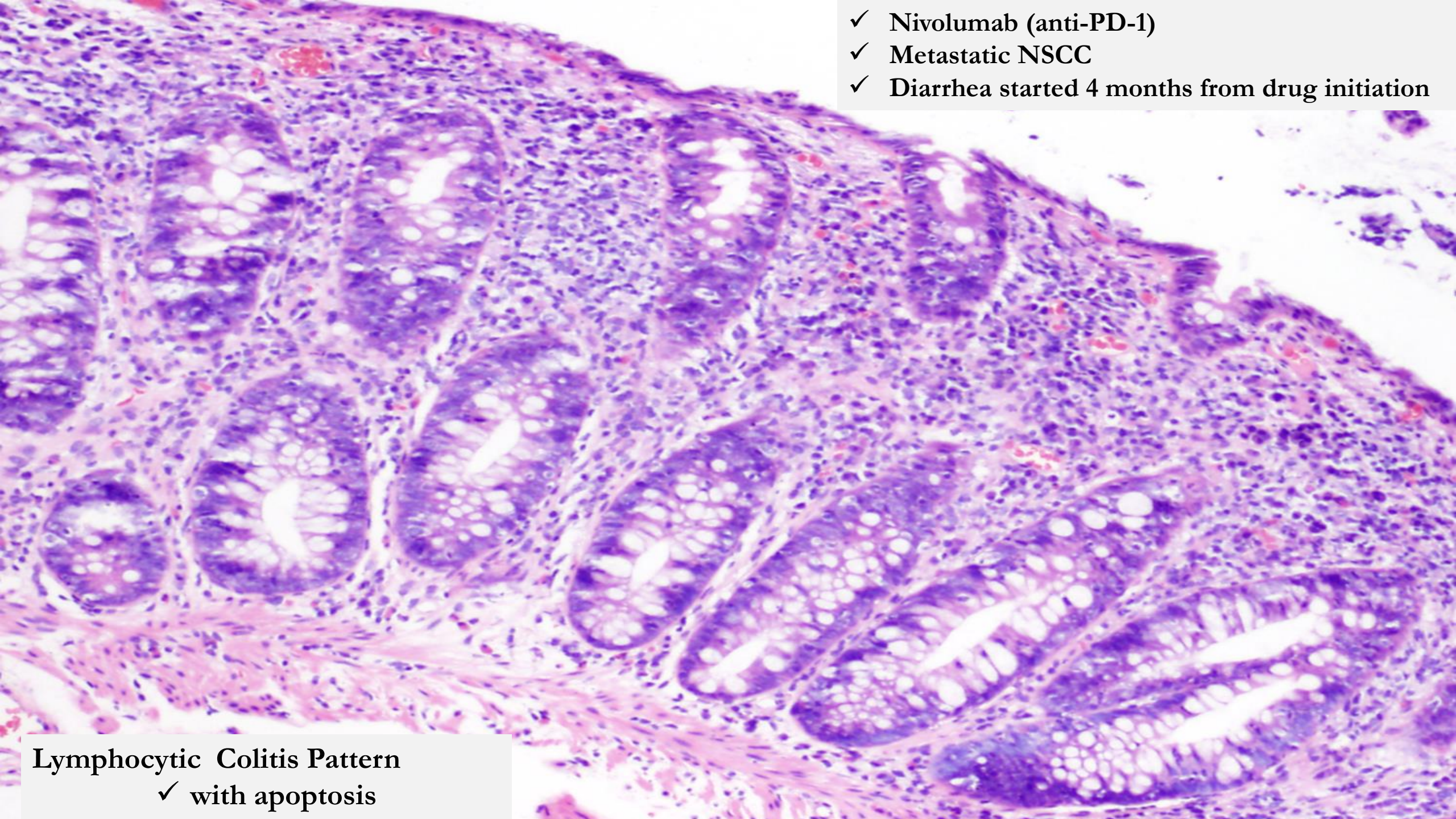
Immune Checkpoint Inhibitor Colitis

CTLA4 inhibitors (ipilimumab)	*Autoimmune-like* enterocolopathy: – Lymphoplasmocytic expansion of lamina propria – Increased apoptosis and intraepithelial lymphocytes – Cryptitis and crypt elongation – Lack of basal plasmocytosis
PD1 inhibitors (pembrolizumab and nivolumab)	– *Active colitis pattern* with increased apoptosis – *Lymphocytic colitis pattern* – Features of chronicity in recurrent cases – Ruptured granuloma

Assarzadegan N, Montgomery E, R Anders. Immune checkpoint inhibitor colitis: the flip side of the wonder drugs. *Virchows Arch*. 2018; 472:125-133.

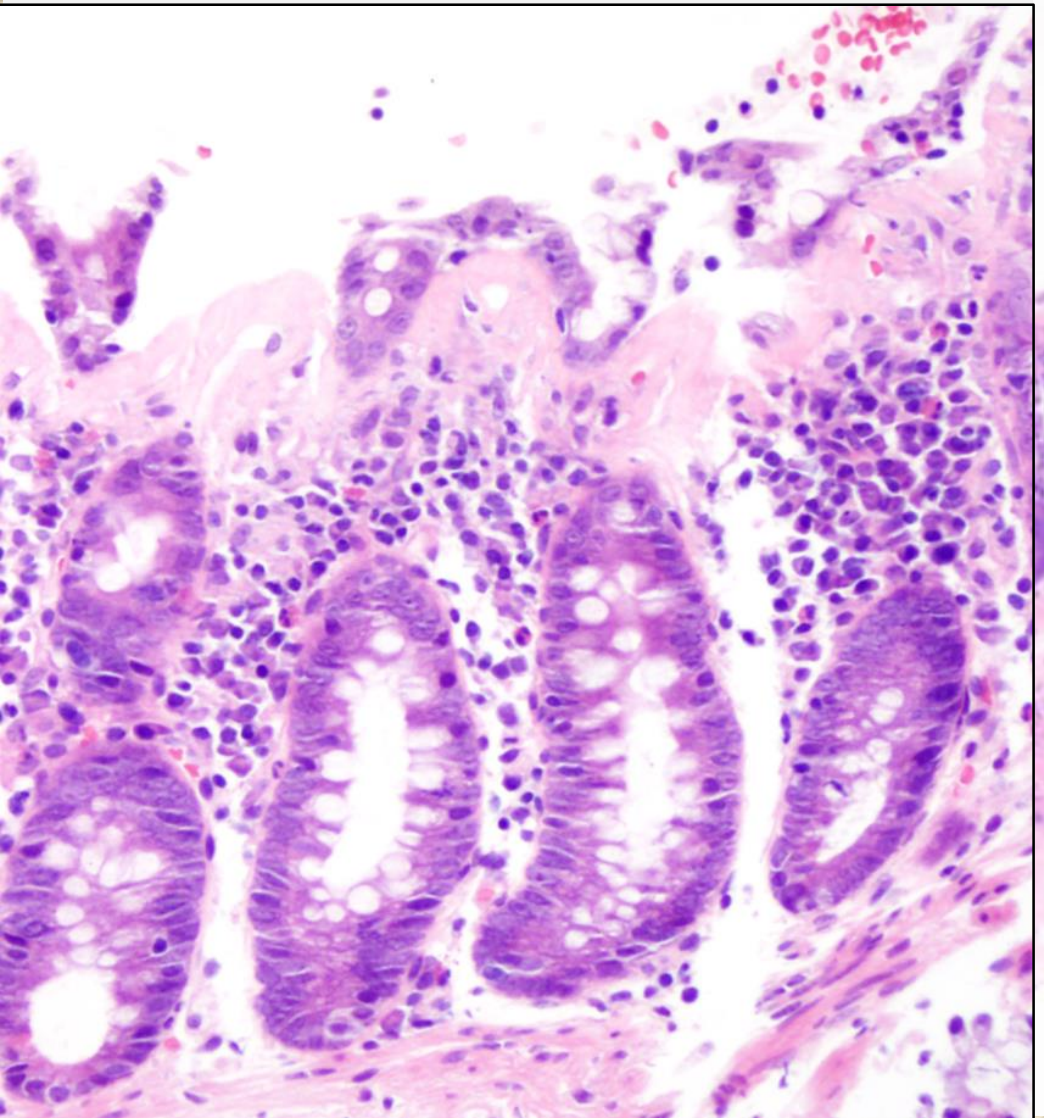
Differential Diagnosis

- ✓ Infectious Colitis (e.g. CMV)
- ✓ GVHD
- ✓ Ischemic Colitis
- ✓ Drugs other than immune checkpoint inhibitors (e.g. Mycophenolate)


✓ Nivolumab (anti-PD-1)
✓ Metastatic NSCC
✓ Diarrhea started 4 months from drug initiation
Lymphocytic Colitis Pattern
✓ with apoptosis

Collagenous Colitis Pattern

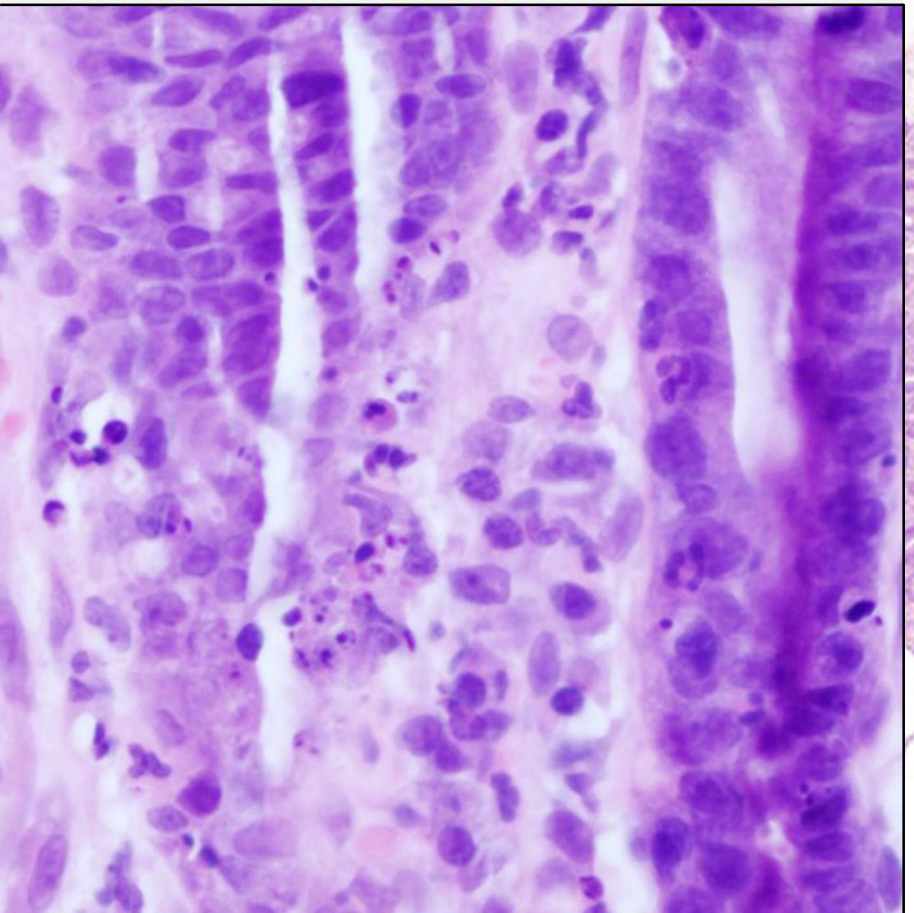
- ✓ Nivolumab (anti-PD-1)
- ✓ Metastatic NSCC
- ✓ Normal Endoscopy

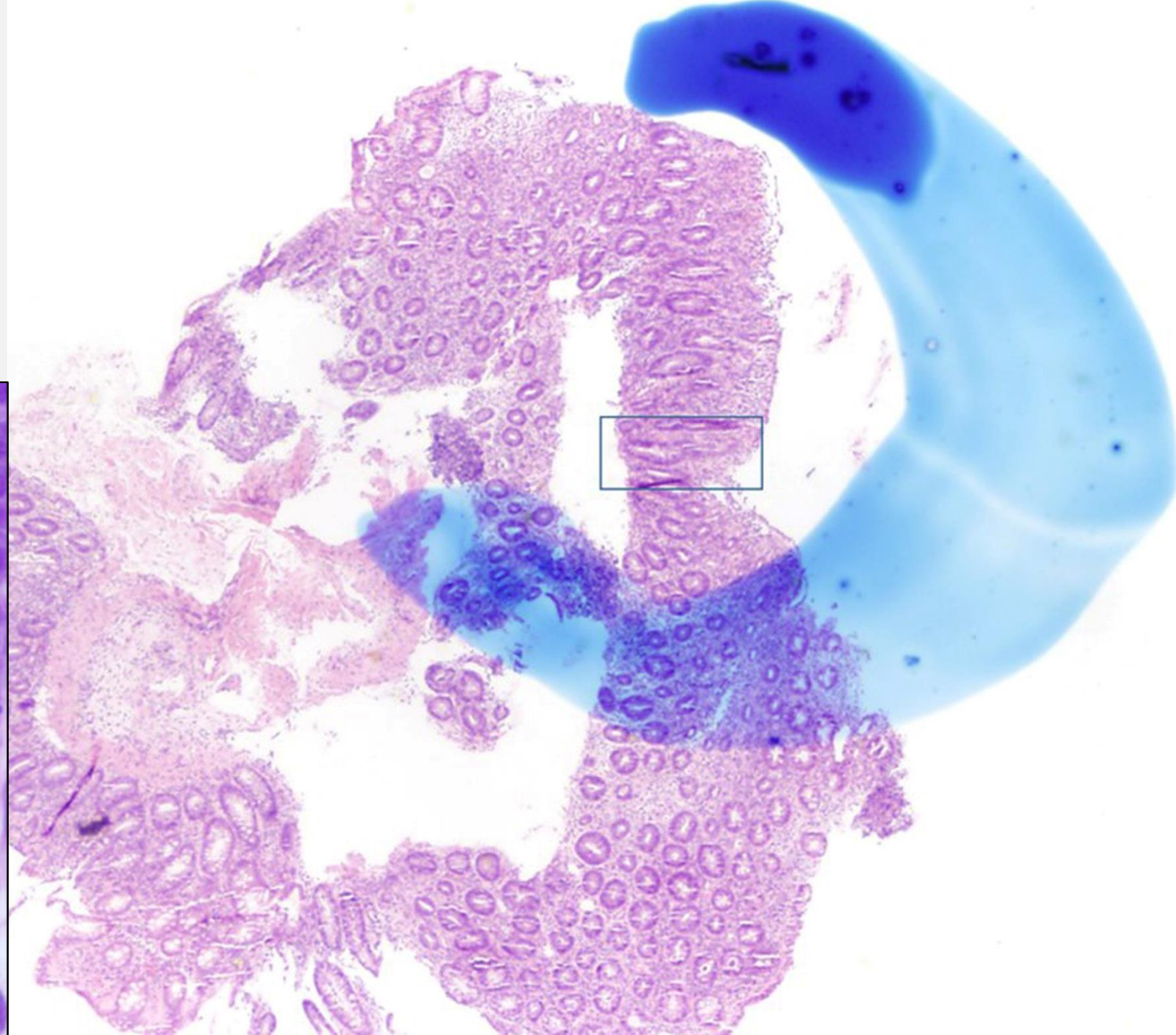


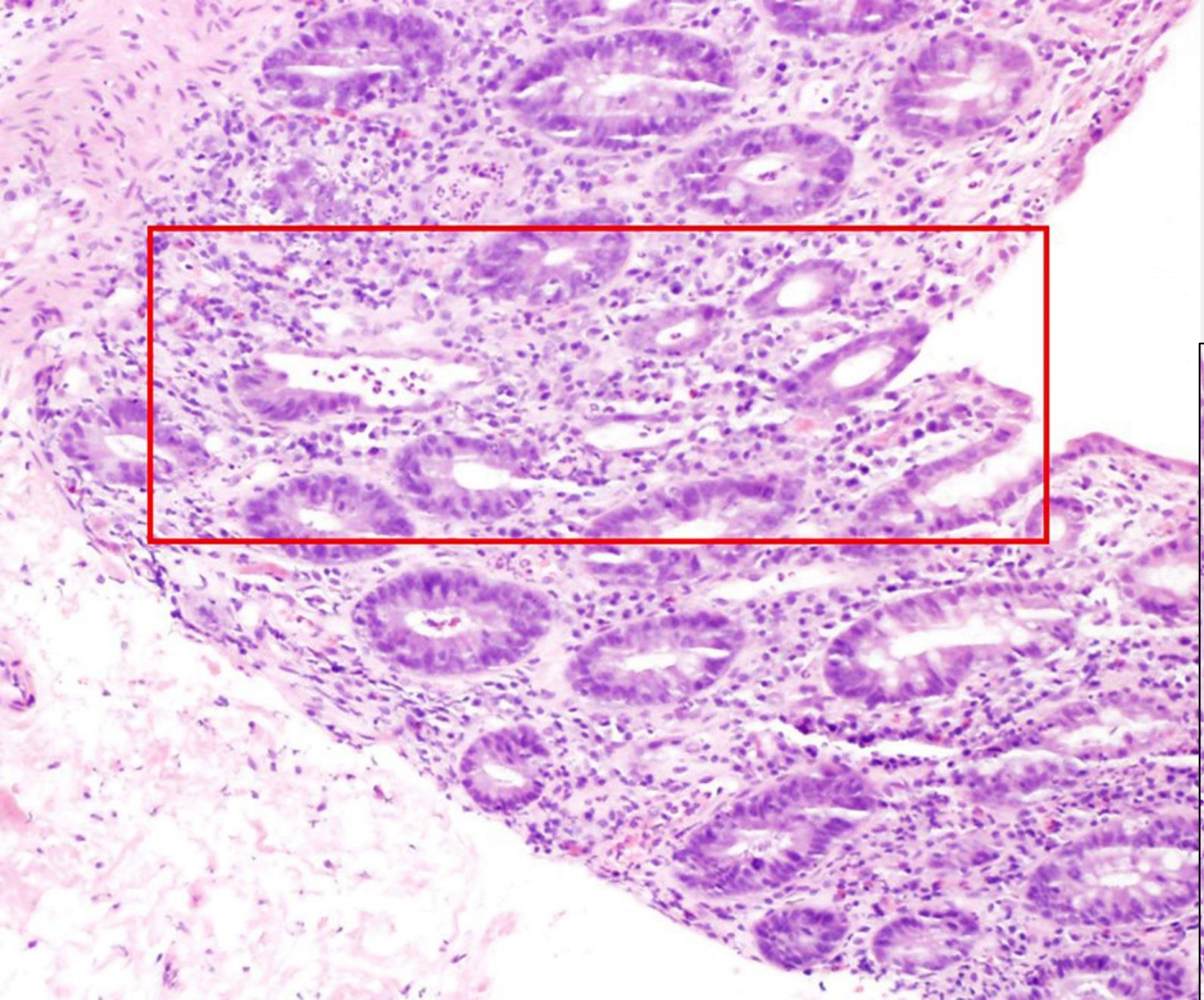
- ✓ Pembrolizumab (anti PD-1)
- ✓ Metastatic MSI CRC
- ✓ Colitis s/p treatment cessation

- ➢ Changes resembling ischemic colitis

- ➢ With marked apoptosis



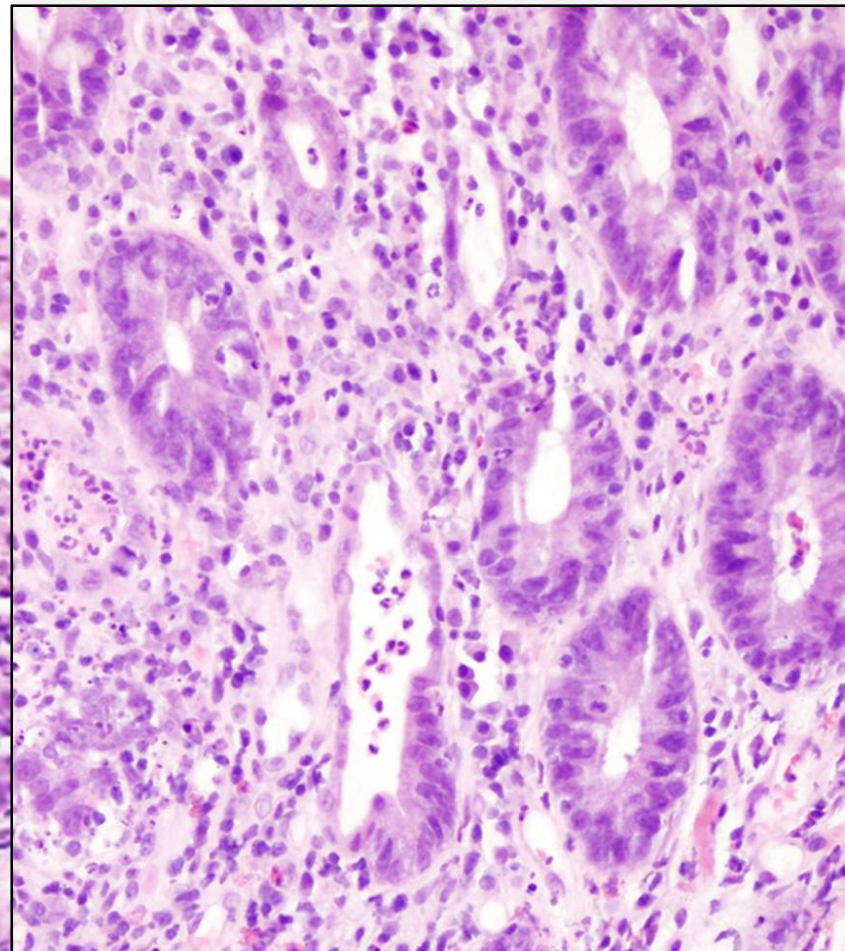




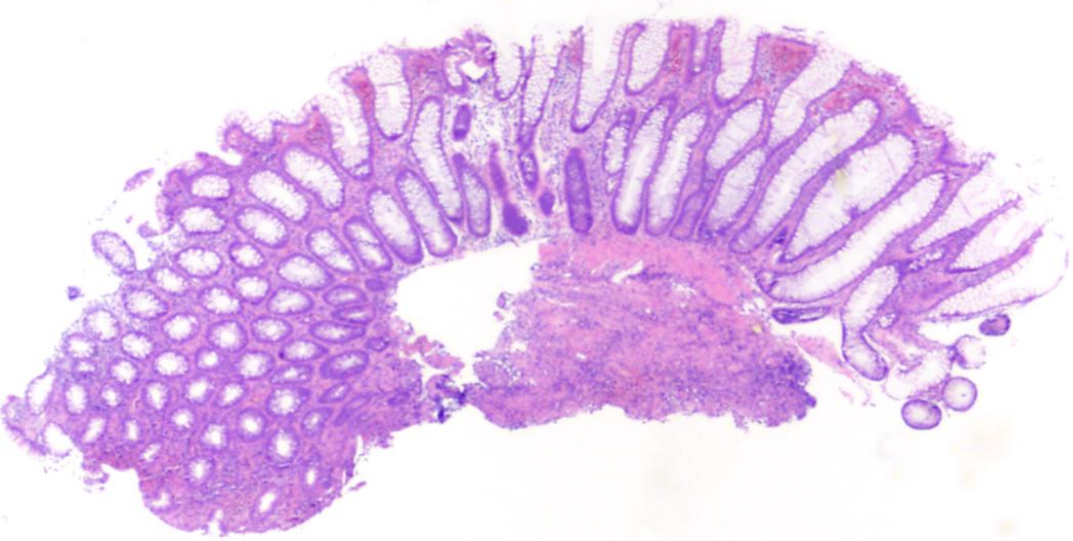
- ✓ Pembrolizumab (anti PD-1)
- ✓ Metastatic MSI CRC
- ✓ Colitis s/p treatment cessation

- ➢ Active cryptitis

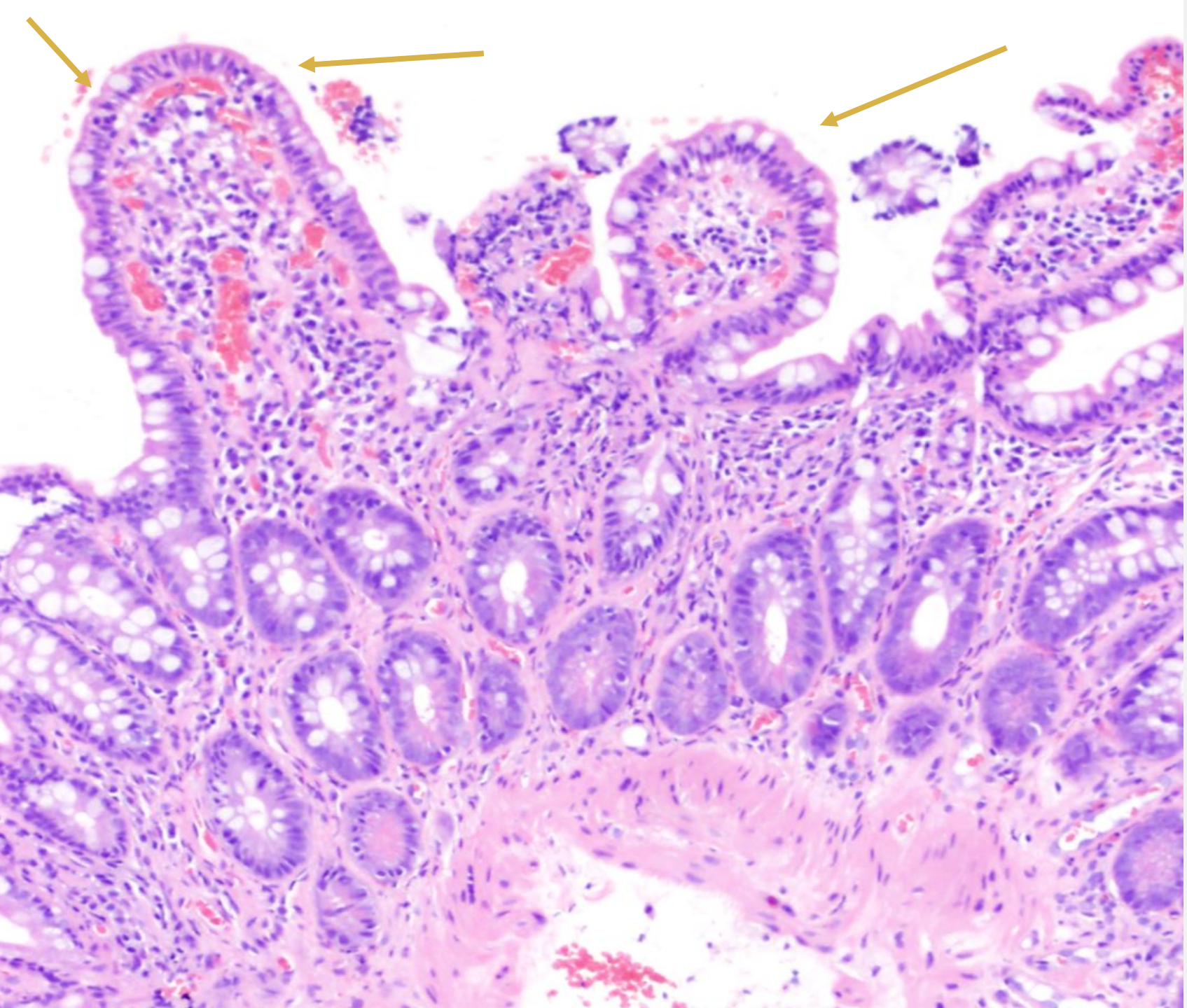
- ➢ With crypt atrophy/dropout



- Recurrent immune checkpoint inhibitor colitis
- Active Colitis with features of chronicity



- ✓ Metastatic Melanoma
- ✓ Ipilimumab (CTLA-4)
- ✓ Skin rash & Grade II diarrhea 4 wks. Tx
- ✓ Transitioned to Pembrolizumab (anti-PD-1)
- ✓ Recurrent colitis requiring infliximab



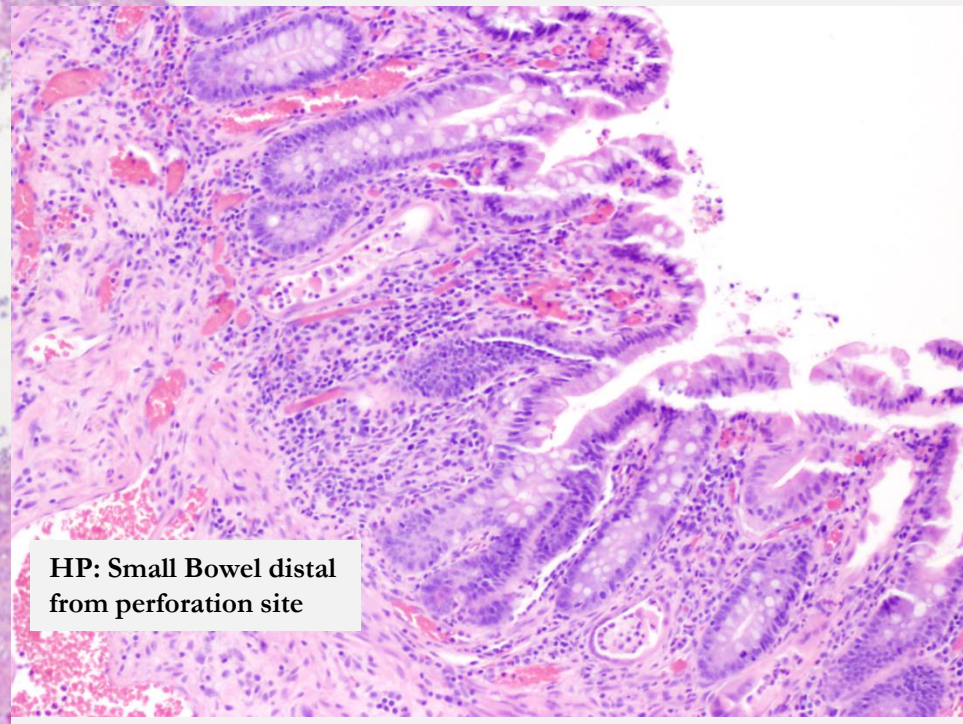
- ✓ Nivolumab (Anti-PD-1)
- ✓ SCC of unknown primary
- ✓ Pt Lower GI Biopsy Series: Lymphocytic colitis pattern immune checkpoint inhibitor colitis with apoptosis
- ✓ IgA tTG normal range

UPPER GI INVOLVEMENT

Terminal Ileum Biopsy

- ➢ Villous blunting
- ➢ Lymphoplasmocytic expansion of LP
- ➢ Intraepithelial lymphocytes

- ✓ Ipilimumab (CTLA-4)
- ✓ Metastatic Melanoma
- ✓ Diarrhea & Weight Loss
  - ✓ + Steroids
- ✓ Acute abdomen
  - ✓ Resection SB perforation



HP: Small Bowel distal from perforation site

** Deaths from intestinal perforation secondary to Ipilimumab have occurred in 1% of patients

* Urgent clinical assessment & management required in moderate to severe cases of diarrhea

Immune Checkpoint Inhibitor Colitis

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ENDOSCOPY FINDINGS:

<u>Significant range of findings:</u>

Normal
Mild to diffuse mucosa erythema
Diffuse to patchy erosion with active colitis
Ulcerations
Disappearance of vascular pattern
Pseudomembranous colitis

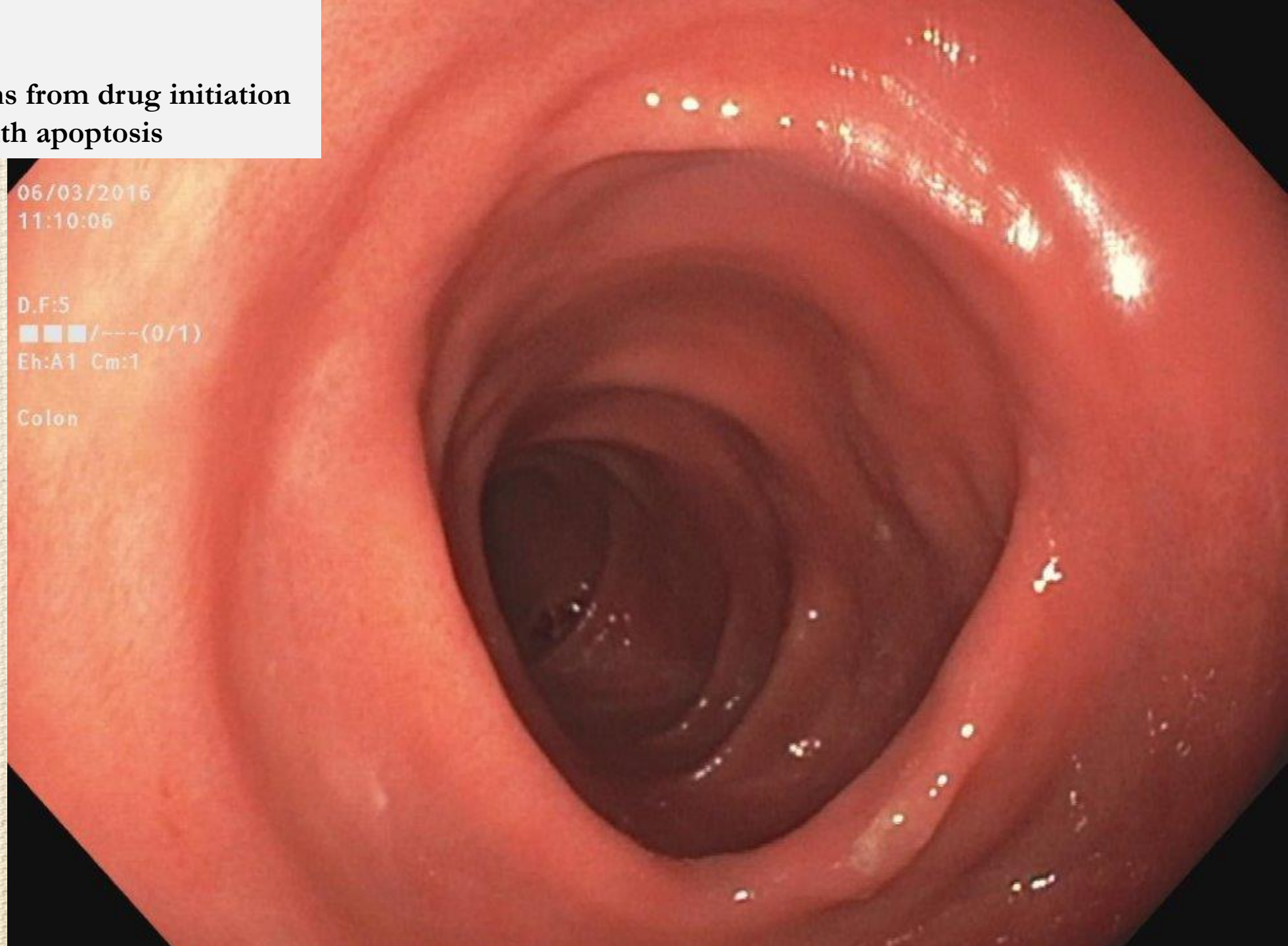
Assarzadegan et al 2017

Chen et al 2017

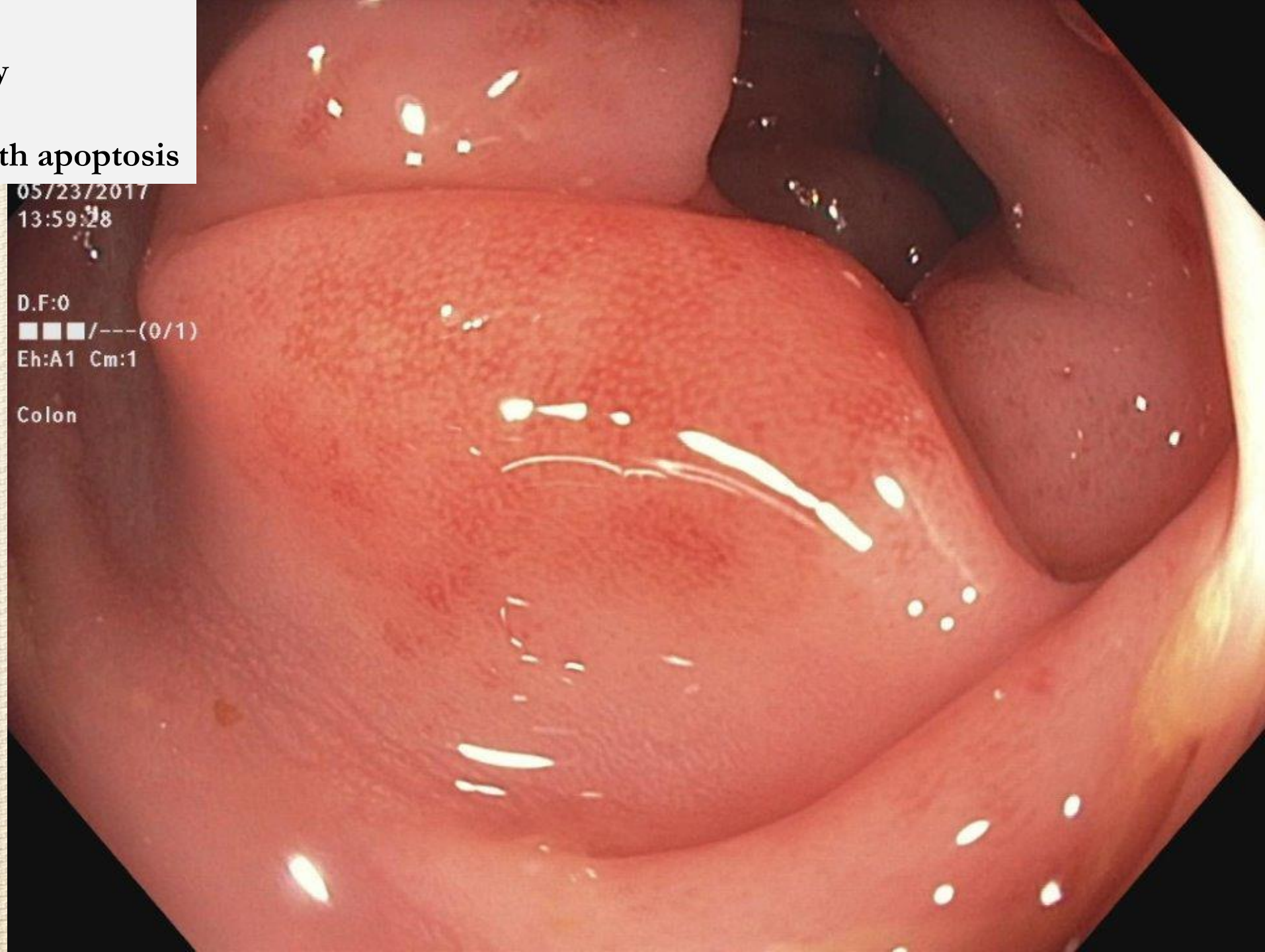
Gonzelez et al 2017

Prieux-Klotz et al 2017

- ✓ Nivolumab (anti-PD-1)
- ✓ Metastatic NSCC
- ✓ Diarrhea started 4 months from drug initiation
- ✓ Histology: LC pattern with apoptosis



- ✓ Nivolumab (Anti-PD-1)
- ✓ SCC of unknown primary
- ✓ New onset diarrhea
- ✓ Histology: LC pattern with apoptosis



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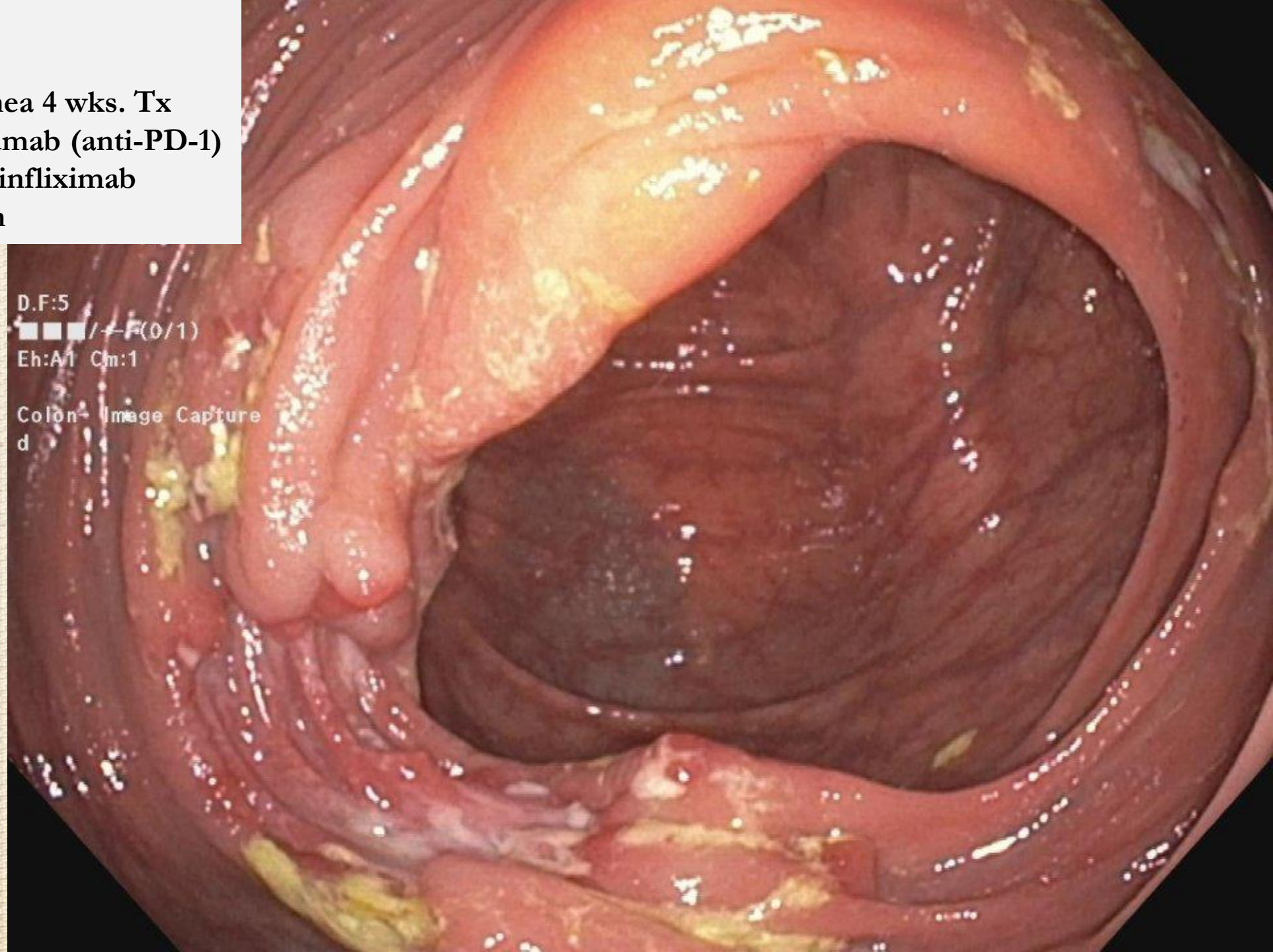

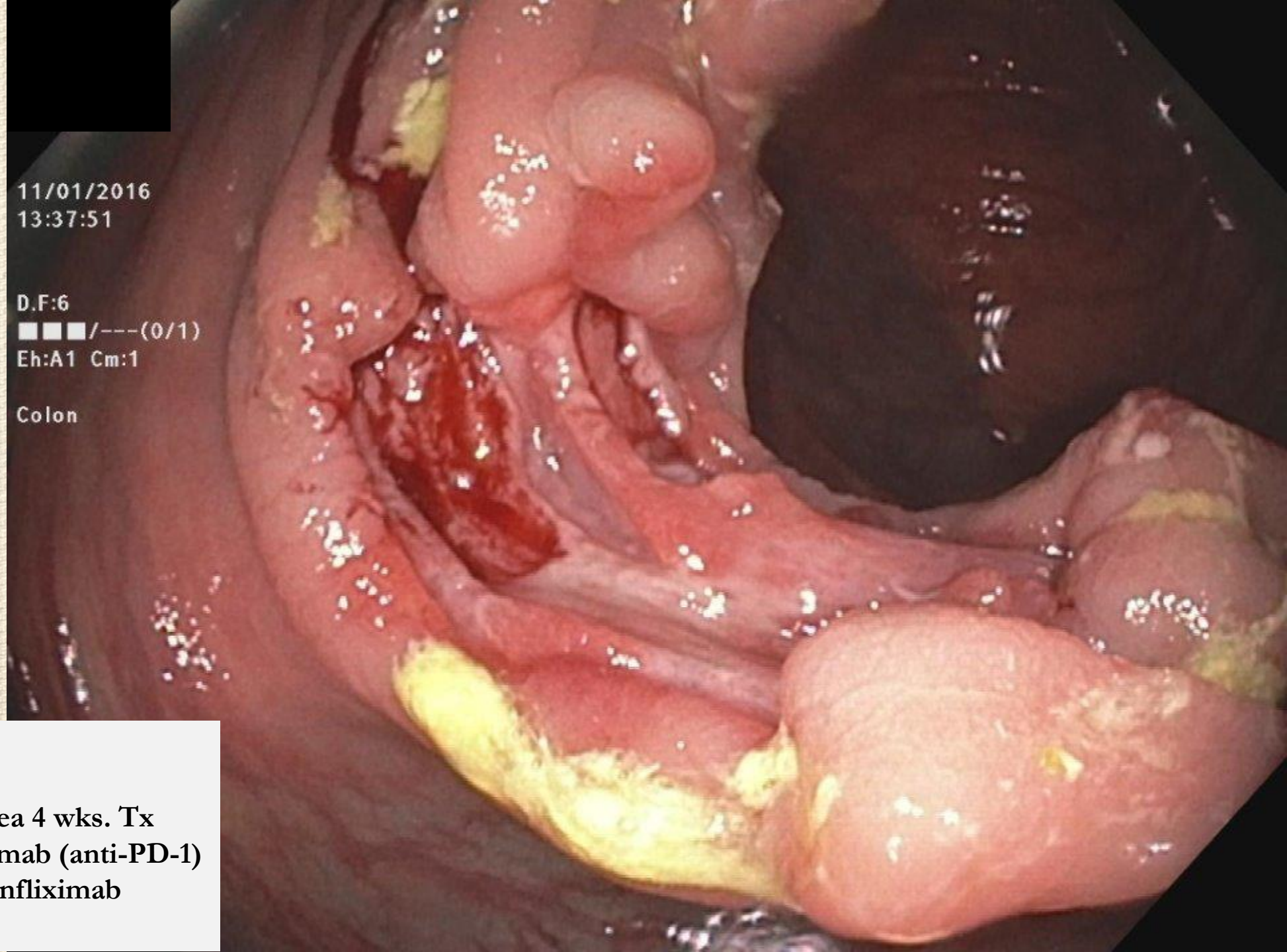

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Table 4
Management of immune-related diarrhoea, colitis and hepatitis.

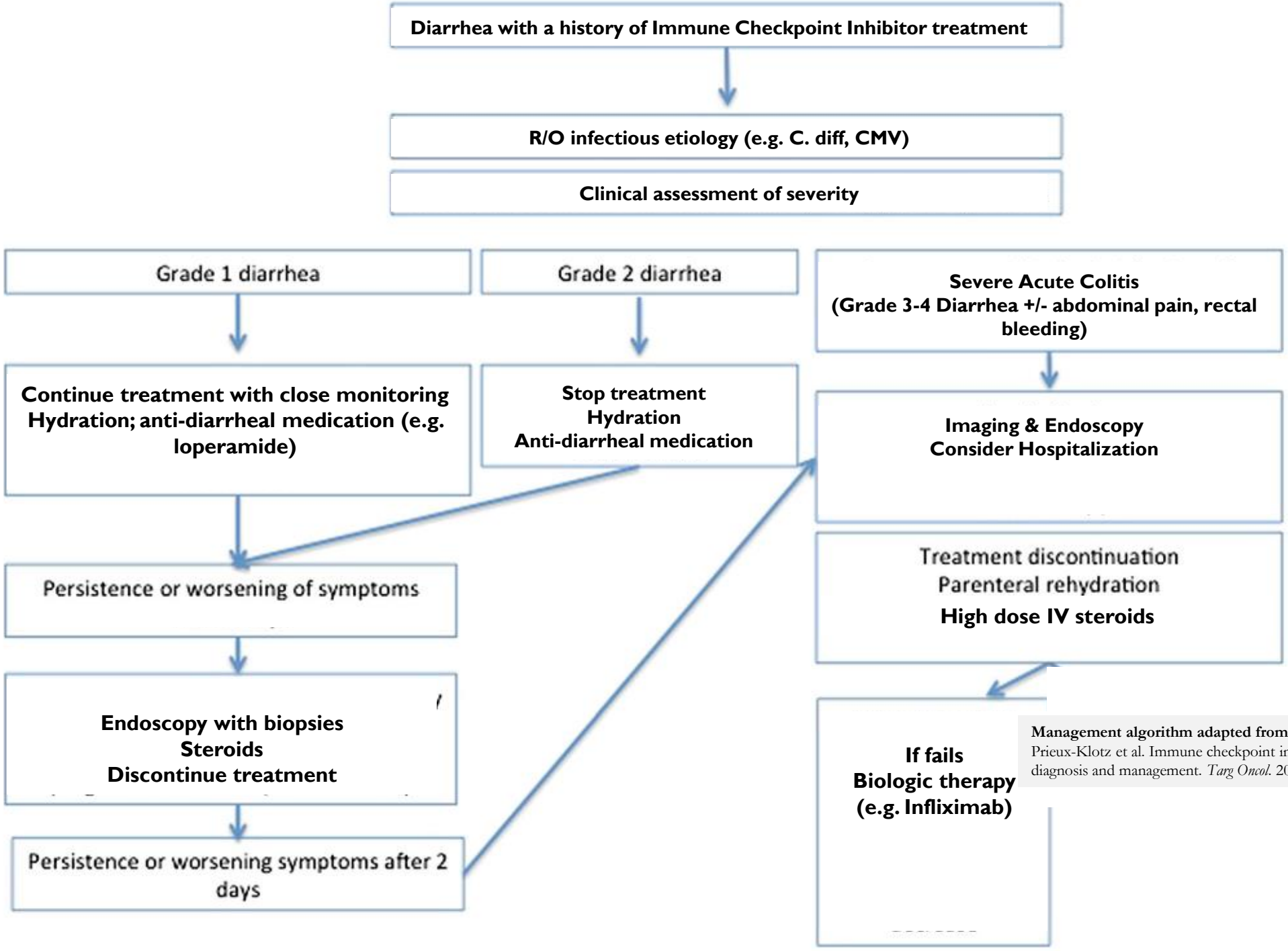
	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)	Grade 4 (life threatening)
Diarrhoea and Enterocolitis	*<4 bowel actions per day over baseline; mild:* supportive measures such as increasing oral fluid, anti-motility agents such as loperamide	*4–6 bowel actions per day over baseline; moderate:* withhold ICPI. As per Grade 1 if patient is well. If no improvement in 5 days, or if worsening of symptoms, commence steroids at a dose of 0.5–1 mg/kg per day of prednisolone (or IV equivalent) and continue until symptoms improve to G1. If no improvement occurs, manage as per G3. Steroids can be tapered over 2–4 weeks. Sigmoidoscopy and biopsy can be considered and may assist in determining the duration of steroid taper based on the macroscopic and microscopic inflammation evident	*⩾7 bowel actions per day over baseline; severe symptoms:* admit patient to hospital for intravenous hydration and clinical observation as appropriate. Commence steroids at 1–2 mg/kg prednisolone or IV equivalent. If no improvement in 2–3 days, commence infliximab 5 mg/kg and continue steroids. Infliximab is contraindicated in patients with sepsis or a perforation. Sigmoidoscopy and biopsy recommended to exclude other causes. Once symptoms resolve to G1, taper steroids over minimum 1 month (up to 3 months for severe cases). Infliximab may be re-administered at 2 and 6 weeks if symptoms persist or recur. Dietician input recommended	*Life threatening consequences, urgent intervention indicated:* management as per G3. Involve gastroenterologist and surgeon in management. Permanently discontinue ICPI

Common Terminology Criteria for Adverse Events (CTCAE)

- Descriptive lexicon of terms and adverse event severity
- Developed by the National Cancer Institute (NCI) at the NIH
- Goal of standardizing AE reporting across medical specialties

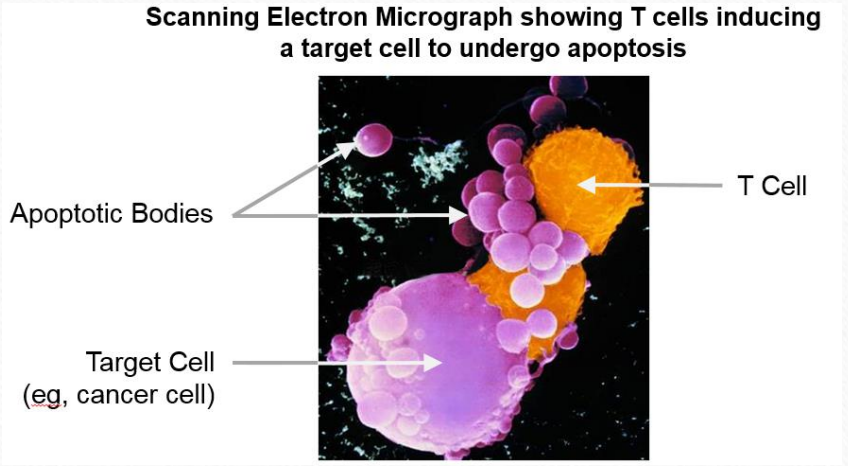
Puzanov et al. Journal for ImmunoTherapy of Cancer (2017) 5:95

SERVICES., U.S.D.O.H.A.H., Common Terminology Criteria for Adverse Events(CTCAE) Version 4.03. 2010.
https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_



Management algorithm adapted from:
Prieux-Klotz et al. Immune checkpoint inhibitor-induced colitis: diagnosis and management. *Targ Oncol.* 2017; 12: 301-308.

Take Home Points



- ✓ **Excellent communication = Excellent patient care**
- ✓ **Histologic features of ICI colitis are described but non-specific and evolving**
  - ✓ **Rule out other entities or concomitant entities**
  - ✓ **Apoptosis**
- ✓ **Early recognition/intervention essential**
- ✓ **Excellent multidisciplinary/interdisciplinary communication = Excellent patient care**