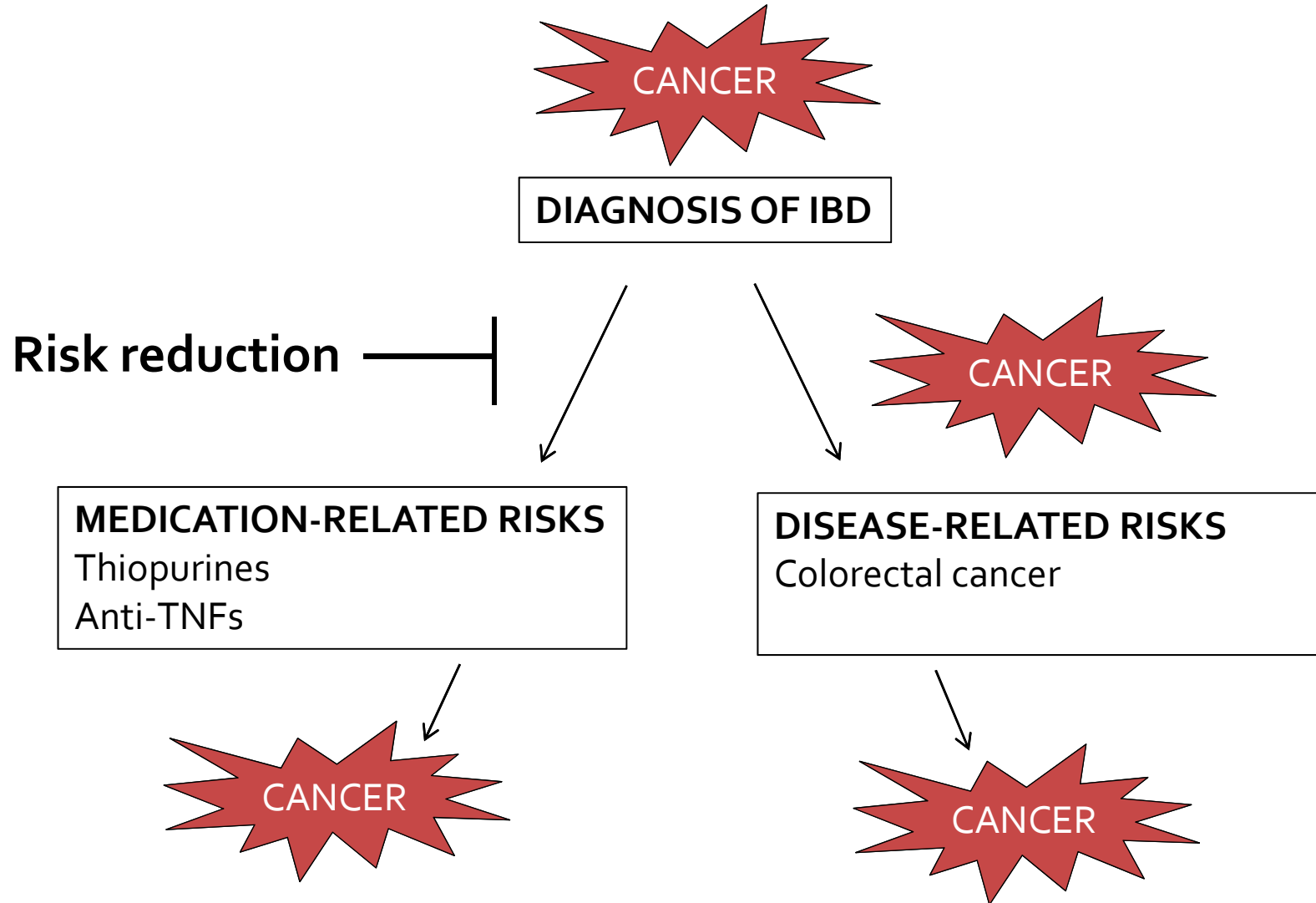


Management issues in the patient with cancer and IBD

Elisa Boden, MD
Virginia Mason Medical Center
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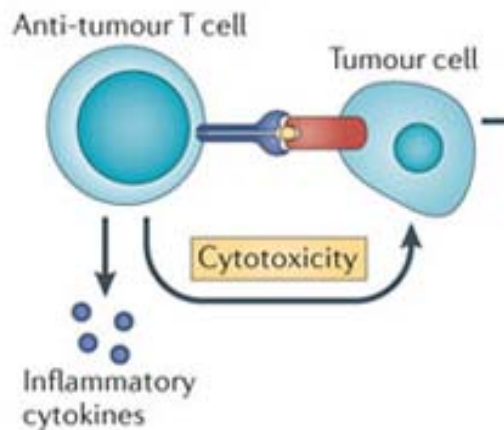


Cancer and IBD



How may immunosuppressant medications increase cancer risk?

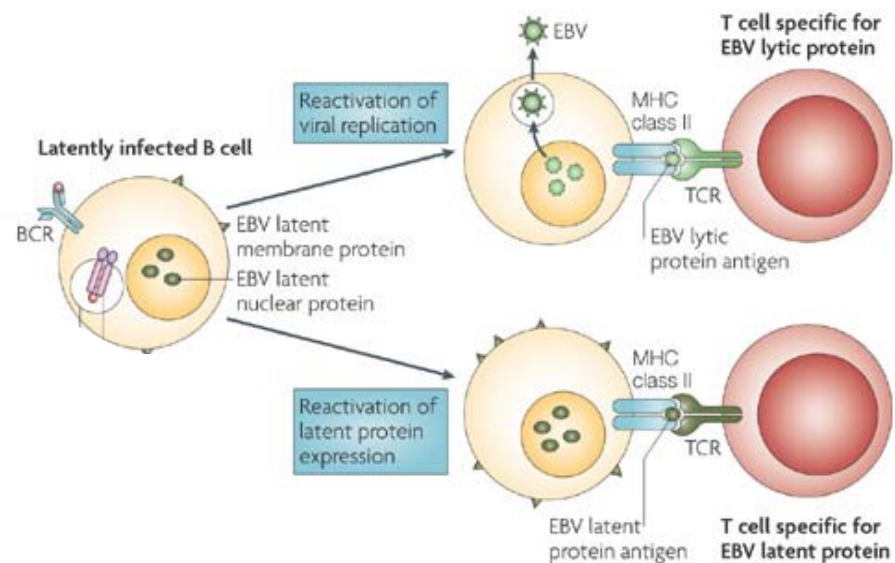
DECREASED IMMUNE SURVEILLANCE



DIRECT EFFECTS



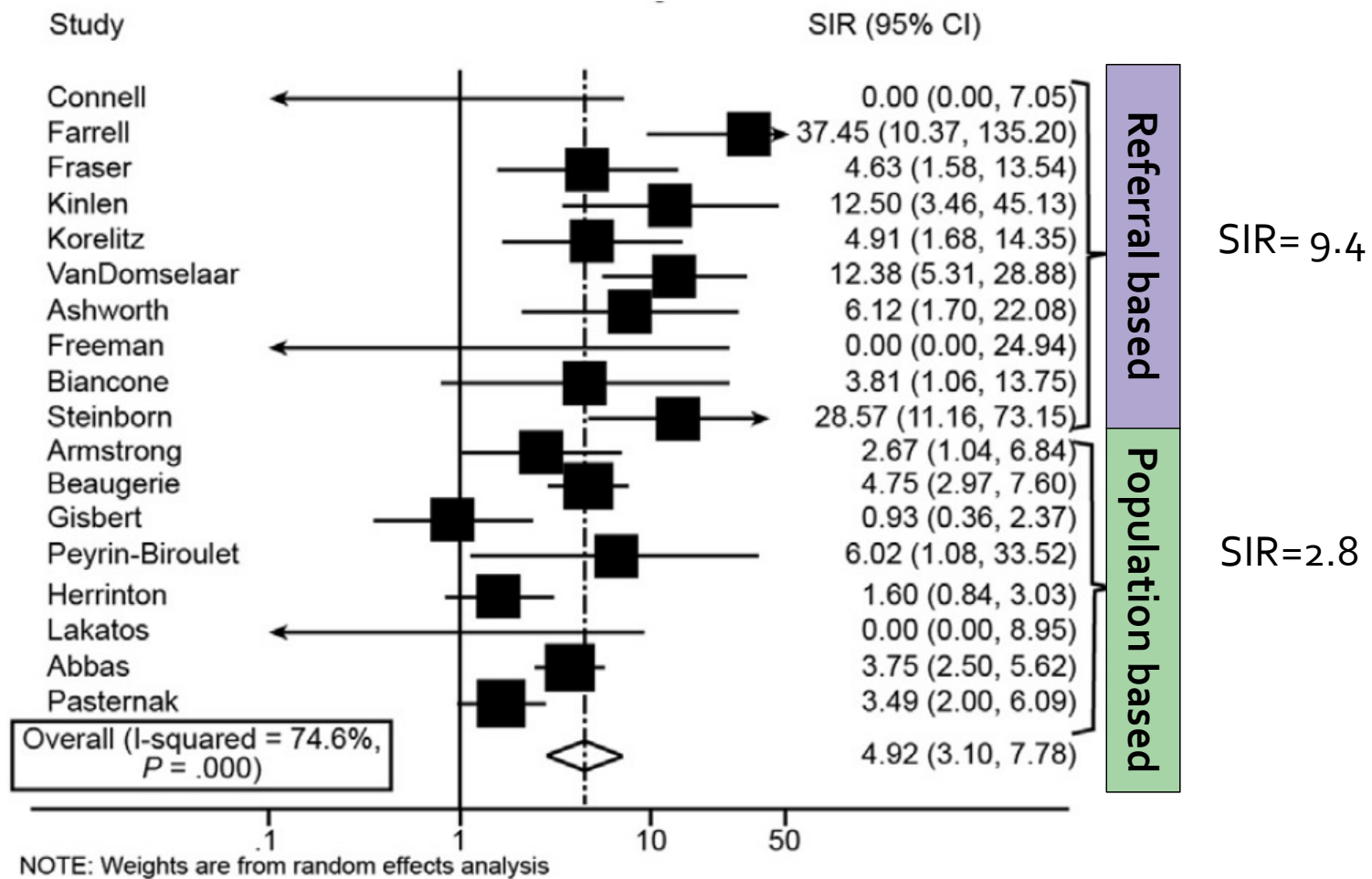
IMPAIRED CONTROL OF LATENT ONCOVIRUSES



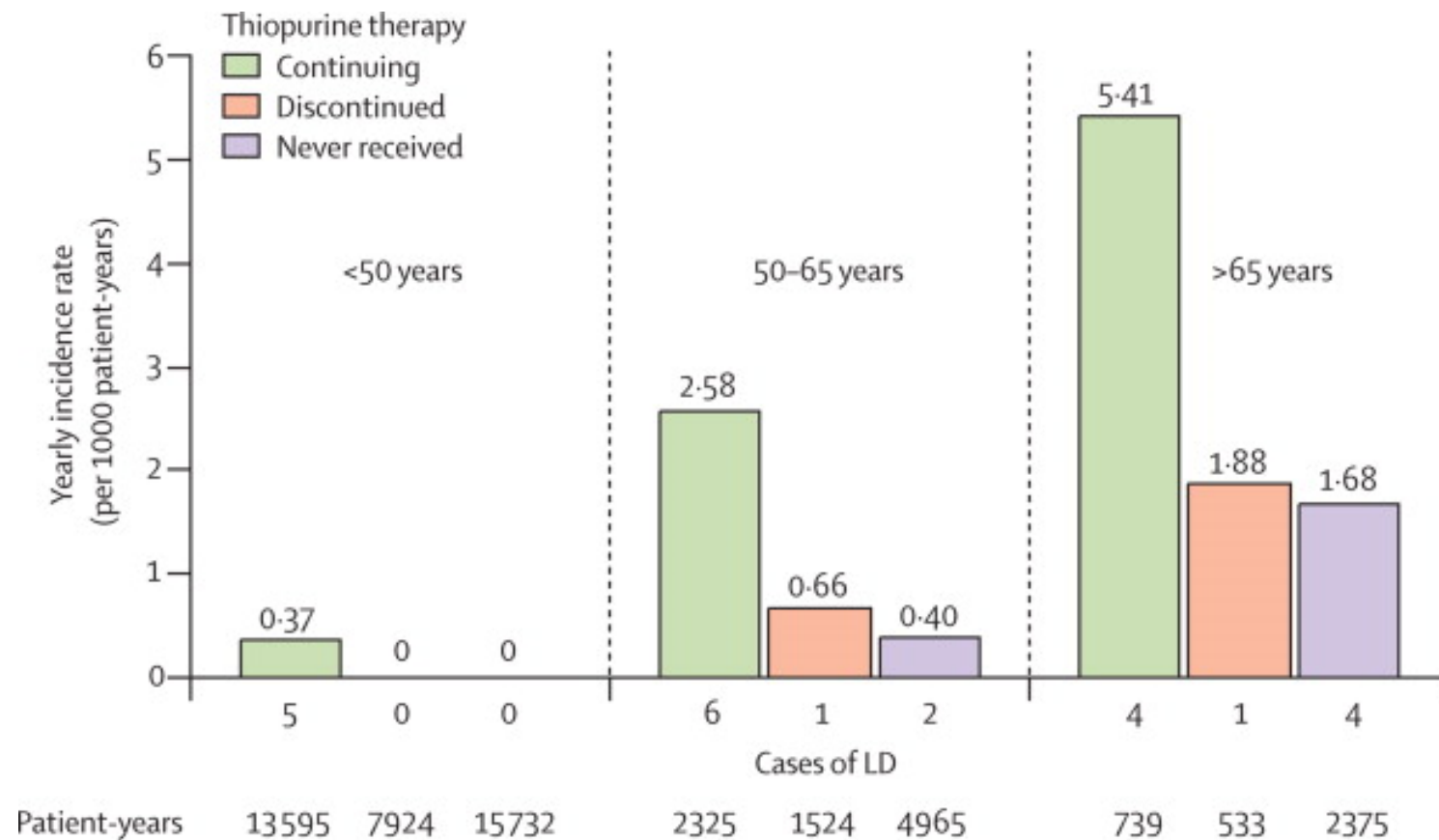
adapted from *Nat Rev Immunol*

Thiopurines

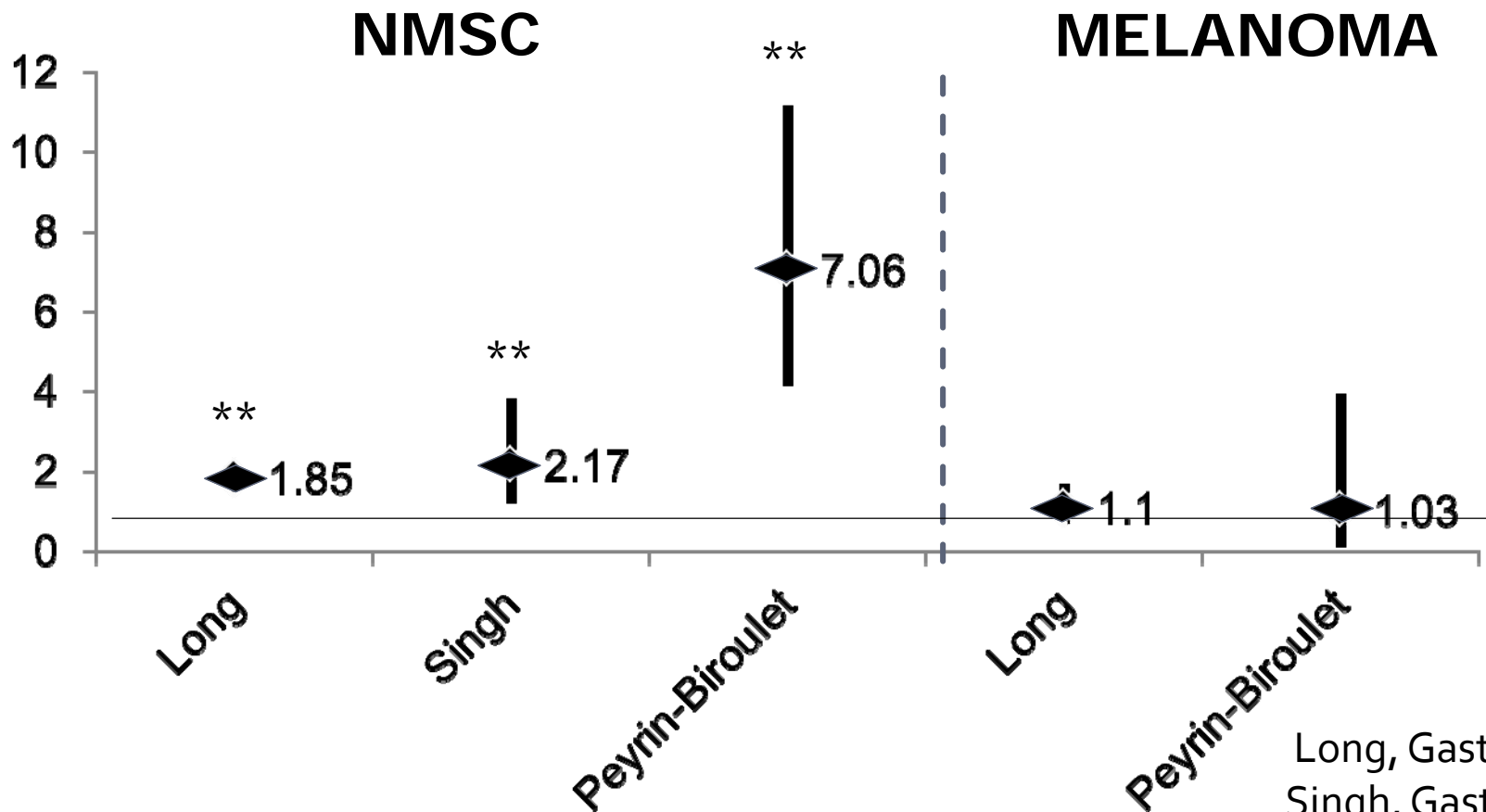
Meta-analysis of lymphoma risk with thiopurine use



Thiopurine use and lymphoma



Thiopurines and skin cancer in IBD

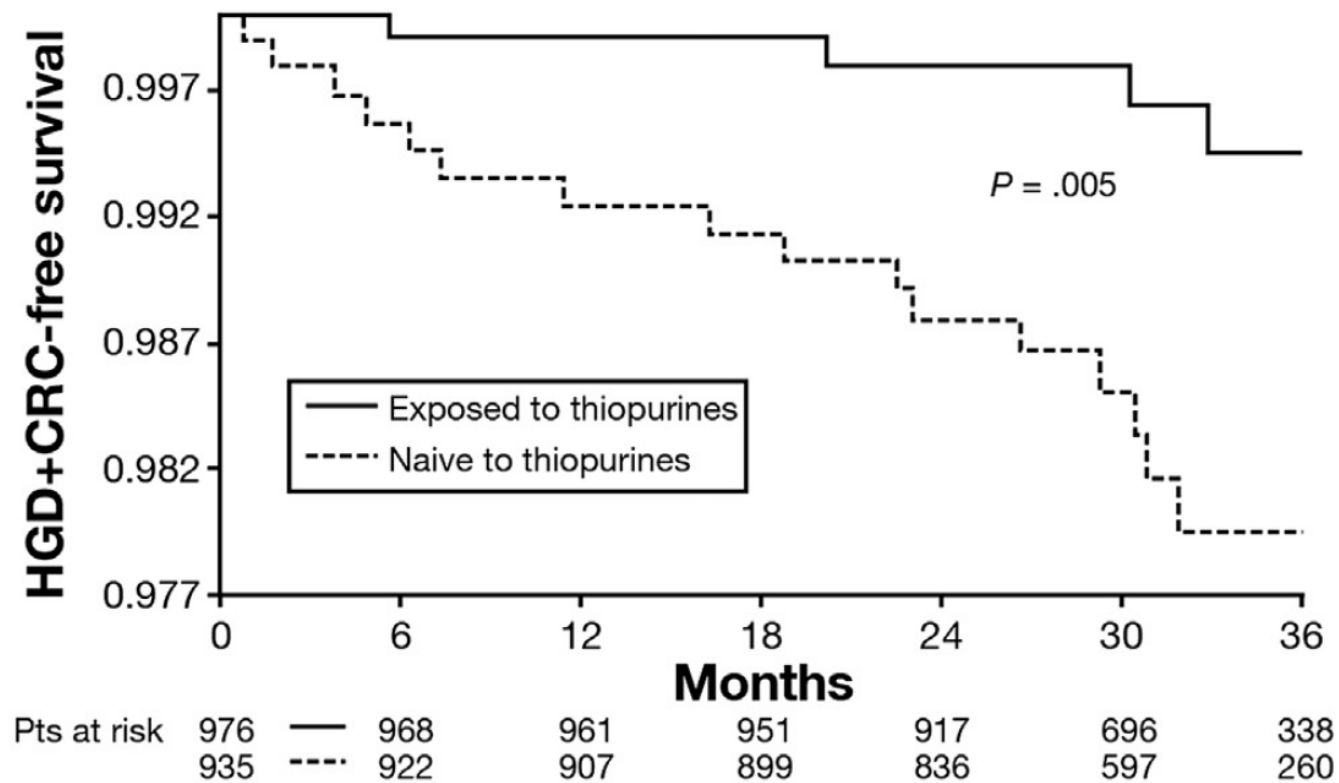


Long, Gastro, 2012
Singh, Gastro, 2011
Peyrin-Biroulet, Gastro, 2011
Peyrin-Biroulet, AJG, 2012

No consistent association between thiopurine use and solid tumors in IBD

Study	Type of study	Number of patients	Statistically significant
Pasternak 2013	Population-based, Denmark	5197	+ urinary tract
Armstrong 2010	Population-based, UK	1955	NO
Fraser 2002	Single center, UK	6262	NO
Connell 1994	Single center, UK	755	NO

Thiopurine use and colorectal cancer

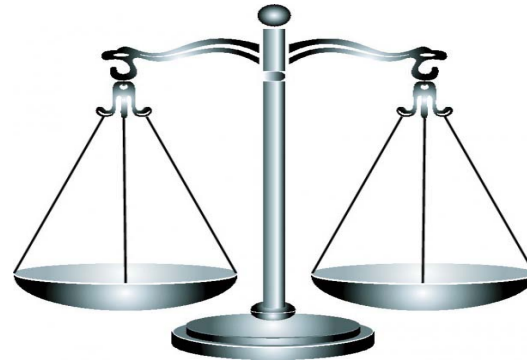


Mechanisms of thiopurine-induced carcinogenesis

Increased risk	Mechanism	Reversibility
EBV-related lymphoproliferative disorders	Cytotoxicity of NK/CTLs important for immunosurveillance of EBV infected B cells	Yes
?cervical dysplasia in HPV infected women	Reduced immunosurveillance	
AML, myelodysplastic syndromes	Selection of clones with DNA mismatch repair deficiency	No
Non- melanoma skin cancers	Enhance UVA-induced mutations in epithelial skin cells, reduces repair of UVA-induced DNA lesions, may cause mutations in PTCH (tumor suppressor gene)	No

Anti-TNFs

TNF-alpha



ANTI-ONCOGENIC

PRO-ONCOGENIC

- Recruitment of leukocytes important for immunosurveillance
- Stimulates apoptosis



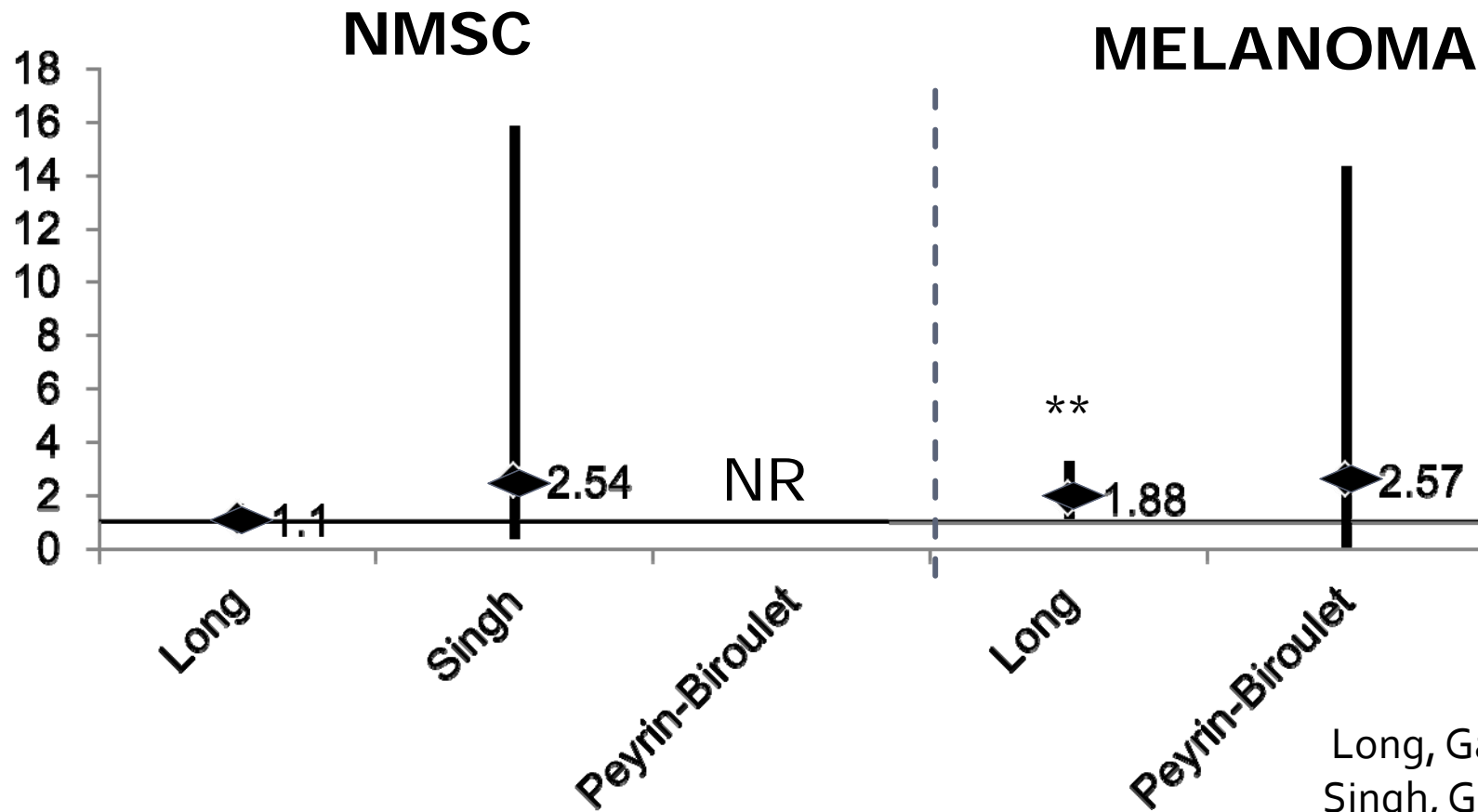
TNF α

- Secretion of pro-inflammatory cytokines and chemokines
- Vascular endothelial growth factor (VEGF)
- Metalloproteinase synthesis
- Cachexia

Meta-analysis of lymphoma risk in Crohn's disease

	NHL rate per 10,000	SIR	95% CI
SEER all ages	1.9	-	-
IM alone	3.6	-	-
Anti-TNF + IM vs SEER	6.1	3.23	1.5-6.9
Anti-TNF+ IM vs IM alone	6.1	1.7	0.5-7.1

Anti-TNFs and skin cancer in IBD



Long, Gastro, 2012
Singh, Gastro, 2011
Peyrin-Biroulet, Gastro, 2011
Peyrin-Biroulet, AJG, 2012

No clear association between anti-TNFs and solid tumors in IBD

Study	Type of study	Number of patients	Statistically significant
Anderson 2014	Population-based, Denmark	4553	NO
Williams 2014	Meta-analysis of clinical trials	7054	NO
Lichtenstein 2014	Cohort, US	6273	NO
Lichtenstein 2012	Meta-analysis of clinical trials	2385	NO
Fidder 2009	Single-center	1400	NO
Peyrin-Biroulet 2008	Meta-analysis of clinical trials	5356	NO

Summary: medication effect on development of malignancy in IBD

	Thiopurines	Anti-TNF	Methotrexate
Lymphoma	++	?	+/-
NMSC	++	--	--
Melanoma	--	+	--
Colorectal cancer	--	--	--
All cancers	--	--	--

Anti-integrin therapy?

Adapted from Beaugerie, *Dig Dis*, 2013

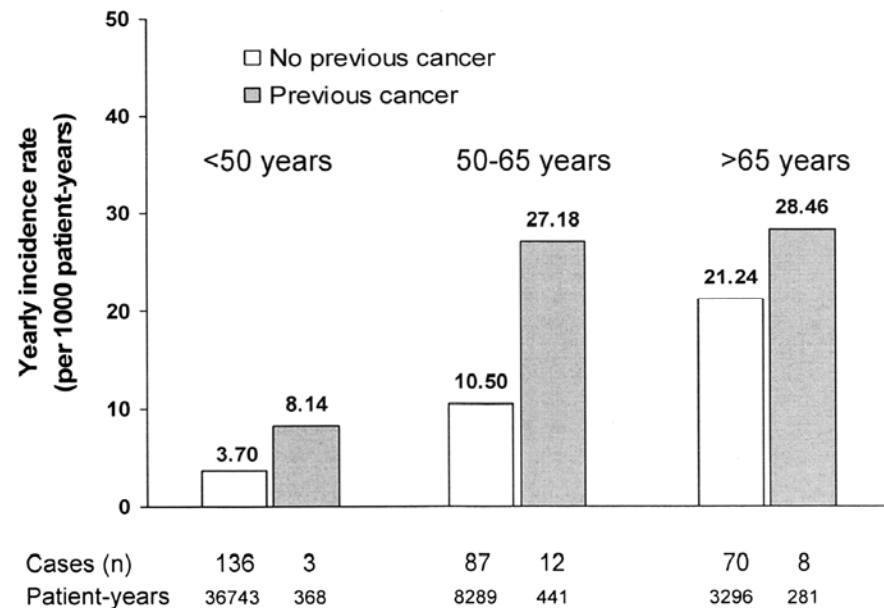
How can we limit risk of cancer in our patients?

- Patient selection
- Screen for latent cancers
- Skin exams/ sunscreen
- Annual pap smears/HPV vaccine
- Colorectal cancer surveillance
- Smoking cessation
- Avoid radiation exposure

IBD in patients with a cancer history

- Recurrence: local, regional, metastatic
- New primary tumor of same organ
- Primary tumor of different organ

- Higher risk of developing a second malignancy than general population



Beaugerie, *Gut*, 2014

Risk of cancer recurrence after renal transplant

LOW

- Kidney (incidental)
- Lymphoma
- Testicle
- Cervix
- Thyroid

INTERMEDIATE

- Breast
- Uterine
- Colon
- Prostate

HIGH

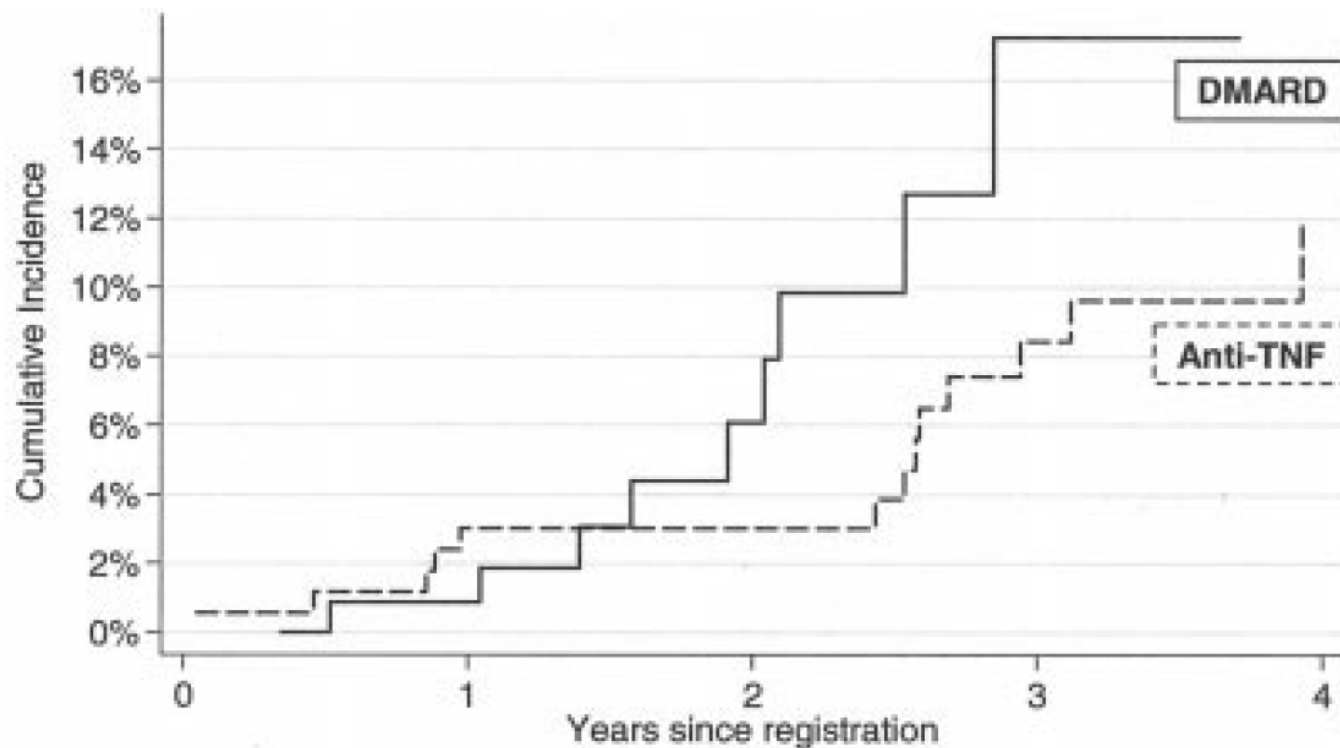
- Bladder
- Kidney (symptom)
- Sarcoma
- Melanoma
- NMSC
- Myeloma

**Overall recurrence rate 21%

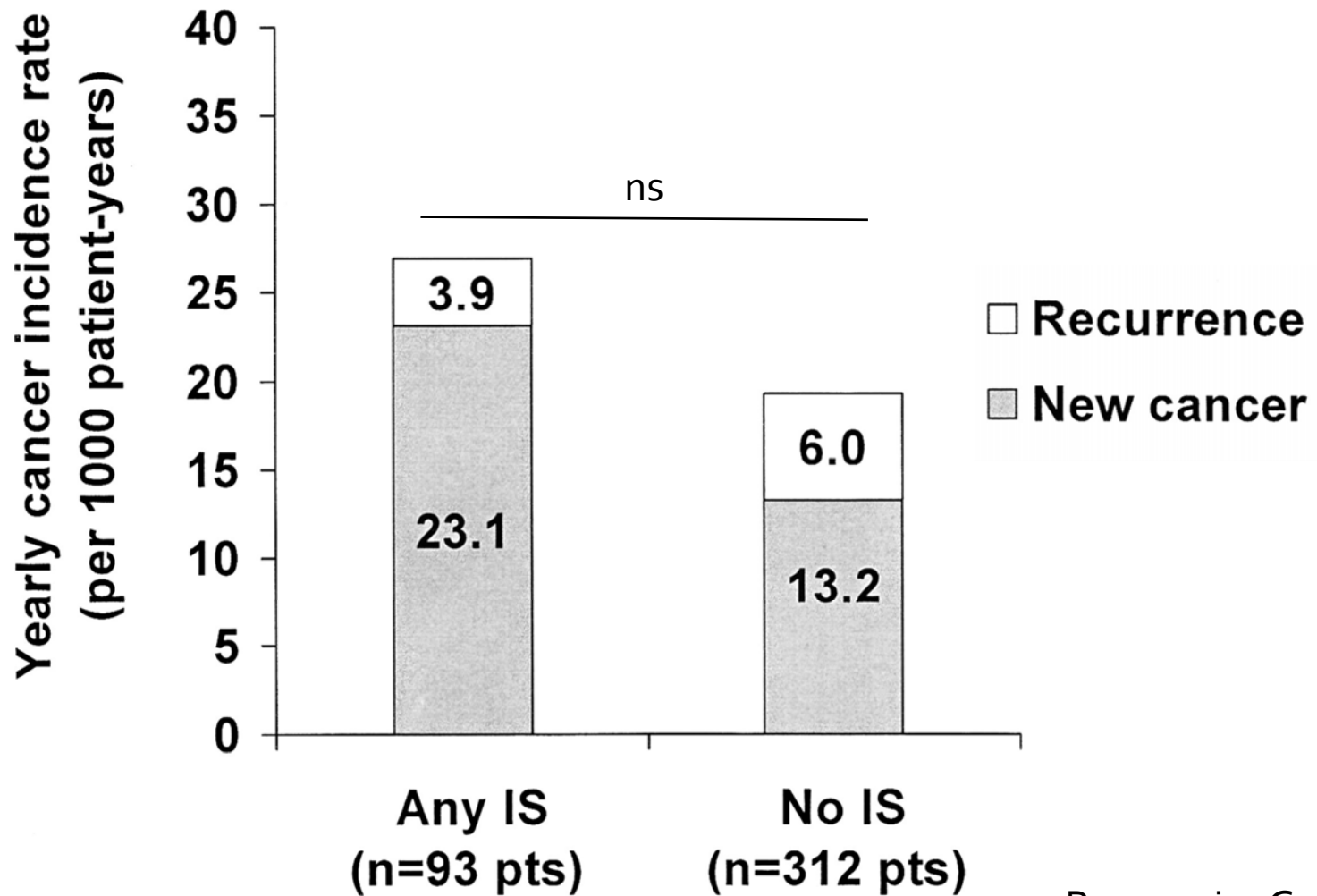
- 54% recurrences treated <2 years prior to transplant
- 33% recurrences treated 2-5 years
- 13% recurrences treated >5 years

adapted from Penn, *Transplantation*, 1993
Penn, *Ann Transplant*, 1997

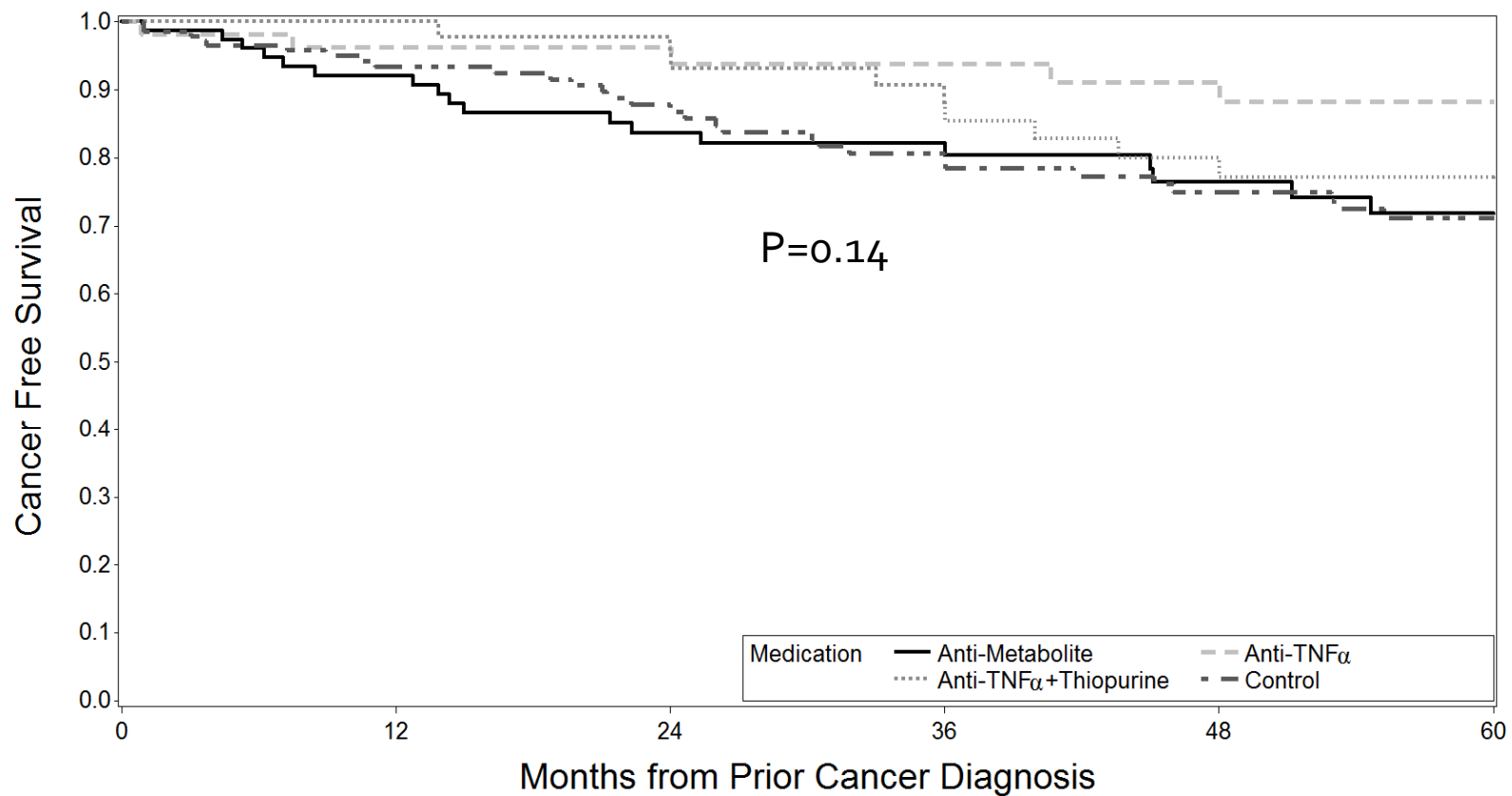
Risk of incident or recurrent cancer after anti-TNF therapy in RA



Risk of cancer in IBD patients with cancer history treated with IS

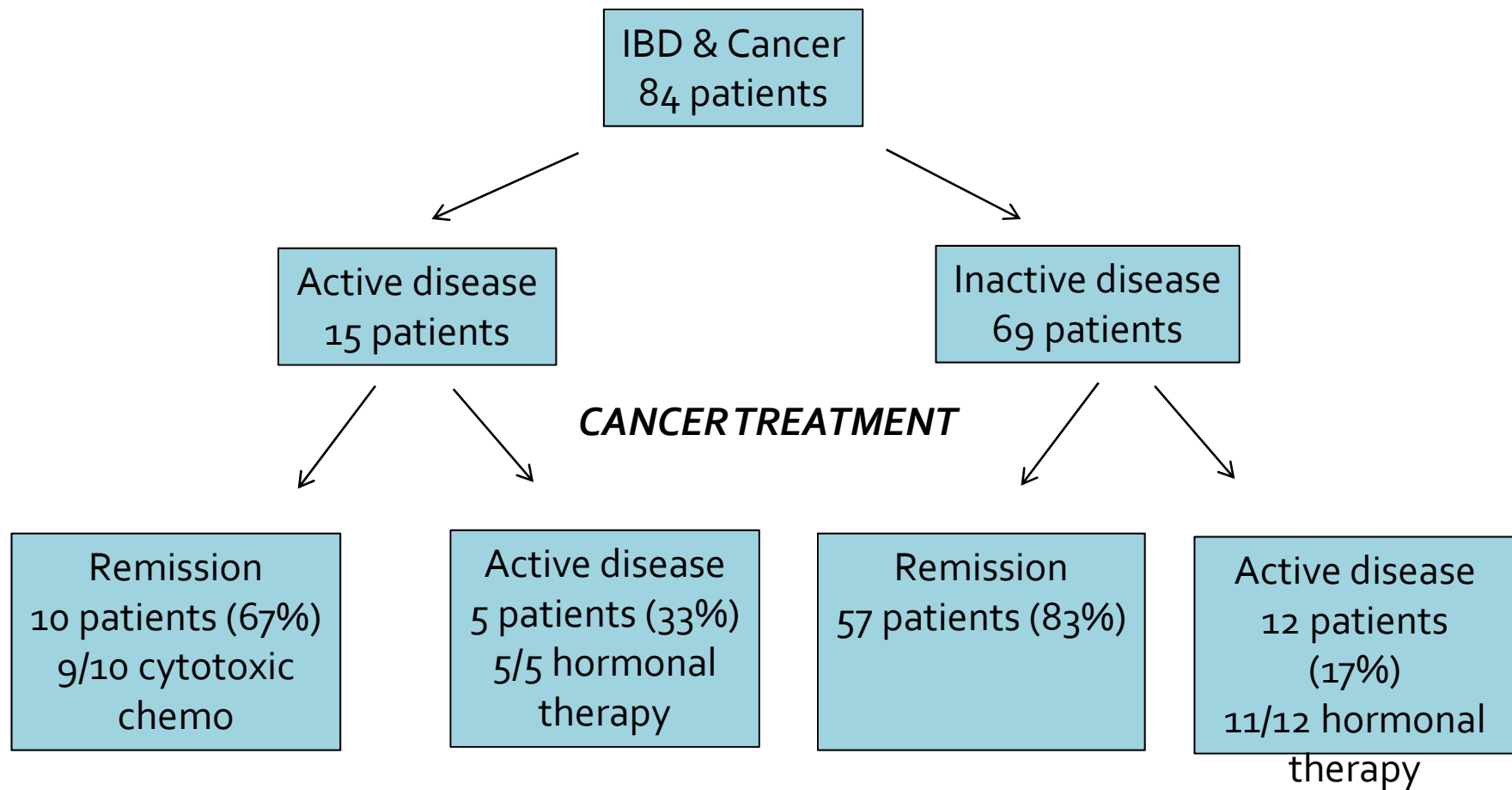


Risk of incident cancer in IBD patients with history of cancer



Log rank test: p = 0.1415

How does a cancer diagnosis affect the course of IBD?



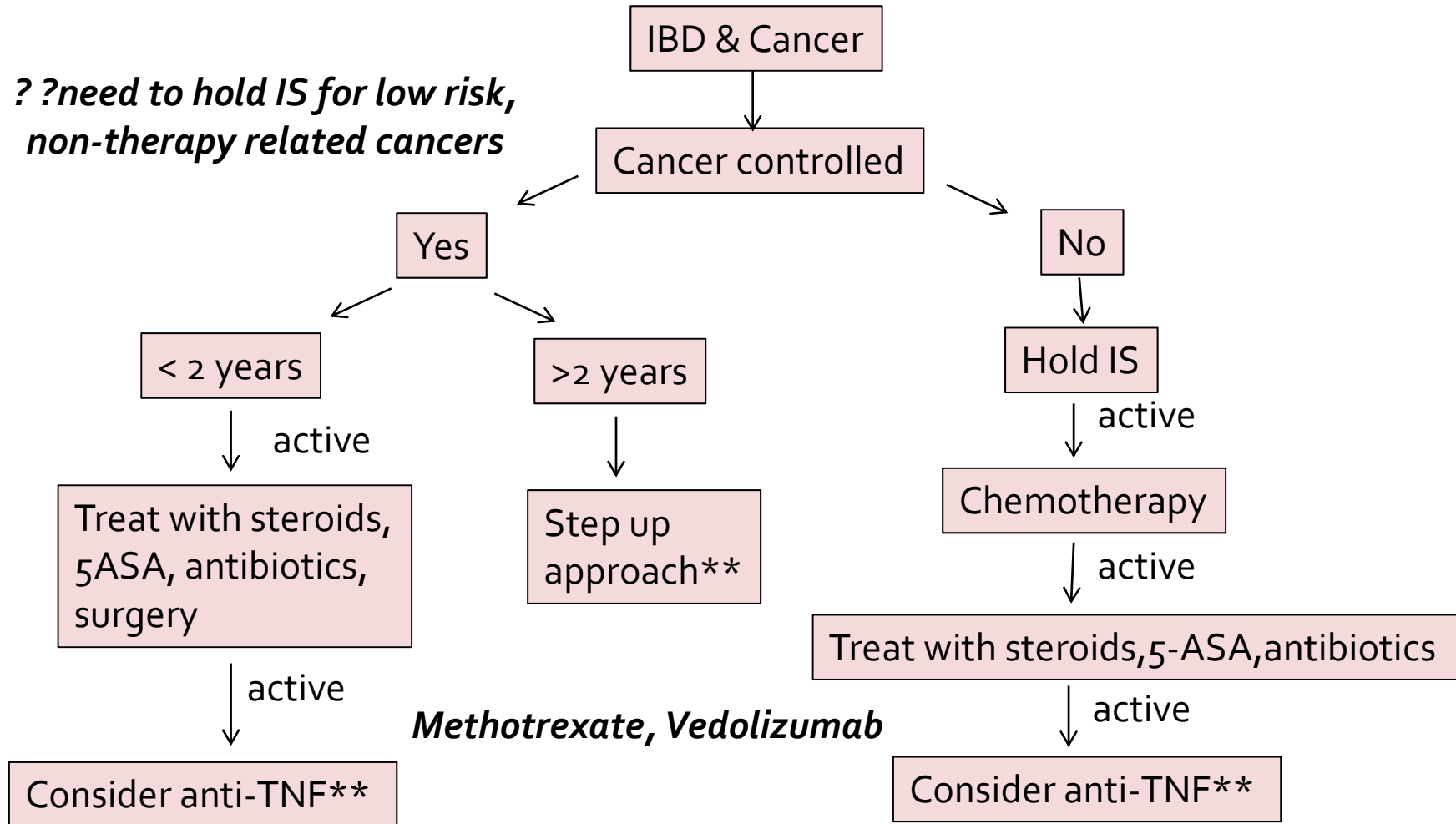
**Hormonal therapy associated with active disease

Axelrad, *CGH*, 2012

How do we translate data into clinical practice?

- Limited and flawed data available
- Lack of recommendations or guidelines from major societies
- Fear of malpractice liability
- Individualized multidisciplinary decision-making (gastroenterologist, oncologist and patient)
 - Type and stage of cancer, risk of recurrence, adequacy of treatment
 - Relationship of cancer to IBD therapy
 - Risks of complication and detriment to quality of life associated with IBD activity

Approach to patient with cancer and IBD

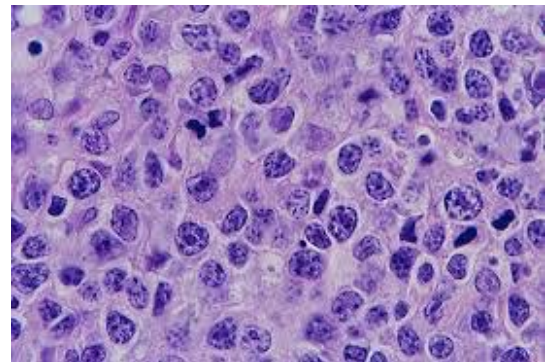


**avoid meds associated with risk of prior cancer

adapted from Bernheim, Gut, 2013

Case 1: Lymphoma

- 21 year old woman with UC
- Presented 1 year ago with severe bloody diarrhea, hospitalized and started on Infliximab/Azathioprine
- Symptoms in remission with recent colonoscopy showing pan-inactive colitis
- Presents to the office with night sweats and low-grade temps
- Exam reveals unilateral occipital adenopathy
- Excisional biopsy: large follicular B cell lymphoma, EBV⁺



Management of immunosuppression

LIQUID TUMORS	Lymphoma	HSTCL
Thiopurine	STOP Do not restart	STOP Do not restart
Anti-TNF	STOP After treated and good prognosis: avoid if possible ? Future risk of monotherapy	STOP Do not restart

- She is in deep remission, stop TP and anti-TNF
- CHOP-R chemotherapy
- If future flare consider: step up: steroid/5-ASA, Vedolizumab, ileoanal pouch anastomosis

Case 2: skin cancer

- 54 year old man with Crohn's
- Long segment of jejunoileitis with stricturing phenotype
- 2 small bowel resections
- Developed antibodies to IFX and Adalimumab, now on Certolizumab+ 6MP x 3 years
- Intermittent obstructions, but otherwise minimal symptoms
- On physical exam, has lesion on back



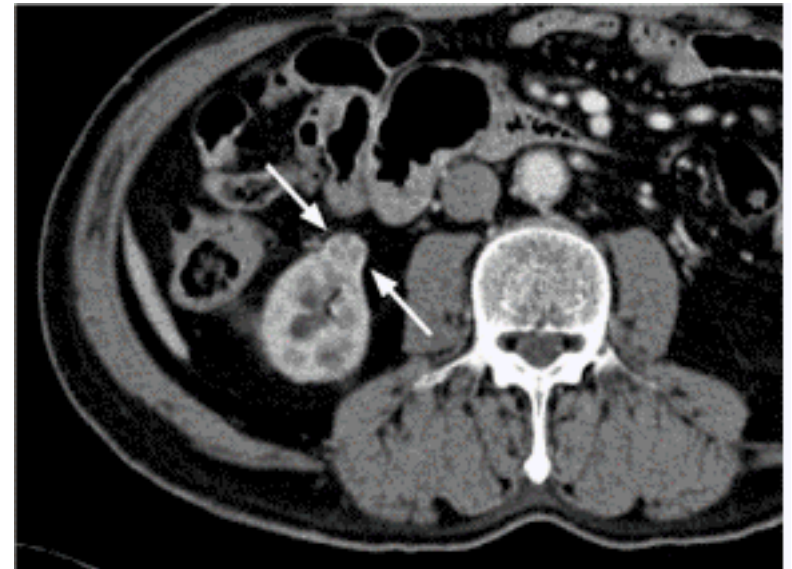
Management of immunosuppression

SKIN CANCER	Non-melanoma	Melanoma
Thiopurine	STOP if multiple, need for disfiguring surgery, aggressive phenotype Close DERM monitoring	STOP Avoid for at least 2 years from time treated Close DERM monitoring
Anti-TNF	Continue Close DERM monitoring	STOP Do not restart Close DERM monitoring

- High risk patient for significant damage from active disease, so medications both continued
- If multiple or more aggressive, stop thiopurine only
- Local control of basal cell carcinoma
- Close coordination with Dermatology and regular follow up

Case 3: incidental RCC

- 40 year old man with Crohn's colitis and perianal disease
- Minimal symptoms and fistula closure on Infliximab/Azathioprine x 1 year
- Seen in ED for symptoms of kidney stone and CT KUB shows an incidental small renal mass
- Biopsy is RCC and undergoes resection of stage 1 RCC



Management of immunosuppression

SOLID TUMORS	Low risk of recurrence, Early stage, Resected for cure	Medium-high risk of recurrence Later stage Undergoing cytotoxic chemo
Thiopurine	weigh risk of disease complication against risk of tumor recurrence	STOP : avoid for 2 years if possible, but may be OK to restart other options fail
Anti-TNF	weigh risk of disease complication against risk of tumor recurrence	STOP : avoid for 2 years if possible, but may be OK to restart if other options fail

- Multidisciplinary discussion with oncology, urology, patient
- Low risk of RCC recurrence and patient wished to continue
- Stopped AZA, continued IFX
- Close monitoring by CT scan , urology

Summary

- Disease and medications predispose IBD patients to development of cancers
- Thiopurines and anti-TNFs are associated with increased risk of lymphomas, skin cancers
- Immunosuppression may increase risk of cancer recurrence or new cancer
- Limited data on anti-TNF and thiopurine therapy in patients with a previous history of cancer are reassuring, but may underestimate risk
- A multidisciplinary individualized approach should be taken for patients with IBD and cancer, weighing the risks and benefits of disease control and cancer risk

Thank you

elisa.boden@vmmc.org



Baseline patient characteristics

	Anti-TNF N=55	Anti-TNF + IMM N=51	IMM N=78	Control N=149
Prior cancer category				
Gastrointestinal	9 (16%)	9 (18%)	13 (17%)	44 (30%)
Hematologic	1 (2%)	7 (14%)	4 (5%)	18 (12%)
Dermatologic	14 (25%)	20 (39%)	19 (25%)	16 (11%)
Solid	31 (56%)	15 (29%)	42 (53%)	71 (47%)
Prior cancer risk type				
High	16 (29%)	22 (43%)	22 (28%)	24 (16%)
Intermediate	15 (27%)	9 (18%)	35 (45%)	57 (38%)
Low	10 (18%)	6 (12%)	8 (10%)	25 (16%)
Undetermined	14 (26%)	14 (27%)	13 (17%)	44 (30%)
Stage of prior cancer				
1	36 (66%)	32 (63%)	52 (67%)	57 (38%)
2	9 (17%)	5 (10%)	6 (8%)	14 (9%)
3	3 (5%)	1 (2%)	4 (5%)	19 (13%)
4	4 (7%)	1 (2%)	5 (6%)	9 (6%)
Unknown	3 (5%)	12 (23%)	11 (14%)	50 (34%)

Results

	Anti-TNFα n= 55 (15.3%)	Anti-TNFα + Antimetabolite n= 51 (15.3%)	Antimetabolite n=78 (23.4%)	Control n=149 (44.7%)	P-value
Incident malignancy	<u>7 (13%)</u>	<u>15 (29%)</u>	<u>22 (28%)</u>	<u>46 (31%)</u>	
New	1 (14%)	5 (33%)	13 (59%)	25 (54%)	
Recurrent	6 (86%)	6 (40%)	7 (32%)	19 (41%)	
New and Recurrent	0 (0%)	4 (27%)	2 (9%)	2 (5%)	0.0712
Incident cancer category					
Gastrointestinal	0 (0%)	4 (24%)	5 (18%)	10 (20%)	
Hematologic	0 (0%)	1 (6%)	1 (4%)	1 (2%)	
Skin	3 (43%)	6 (35%)	10 (37%)	11 (23%)	
Solid	4 (57%)	6 (35%)	11 (41%)	27 (55%)	0.6165
Incident cancer risk type					
High	5 (72%)	7 (54%)	7 (35%)	17 (39%)	
Intermediate	0 (0%)	4 (31%)	5 (25%)	10 (23%)	
Low	1 (14%)	0 (0%)	1 (5%)	2 (4%)	
Undetermined	1 (14%)	2 (15%)	7 (35%)	15 (34%)	0.6143
Incident cancer rate per 100 person-years	2.46 per 285 person-years	3.63 per 414 person-years	5.75 per 383 person-years	5.4 per 852 person-years	

Hepatosplenic T Cell Lymphoma

- 41 cases from FDA AERS among patients with IBD
 - Thiopurine alone 17
 - Anti-TNF alone 1
 - Combination therapy 23
- Characteristics
 - Median age 22.5 (12 – 58)
 - 93% male
 - Median time since initiation of thiopurines ~6 years