

Azathioprine for Induction and Maintenance of Remission in Crohn's Disease

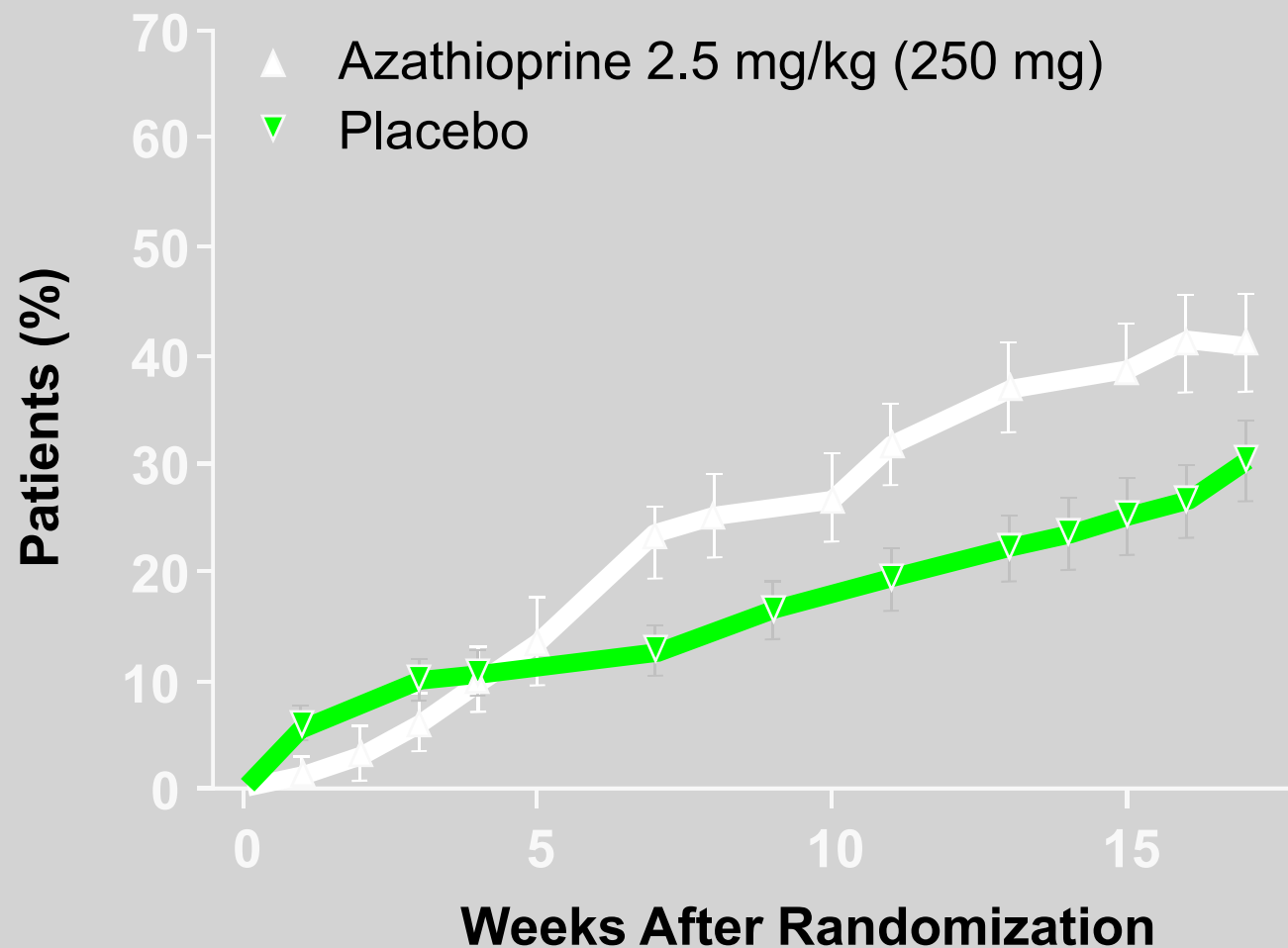


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Objectives

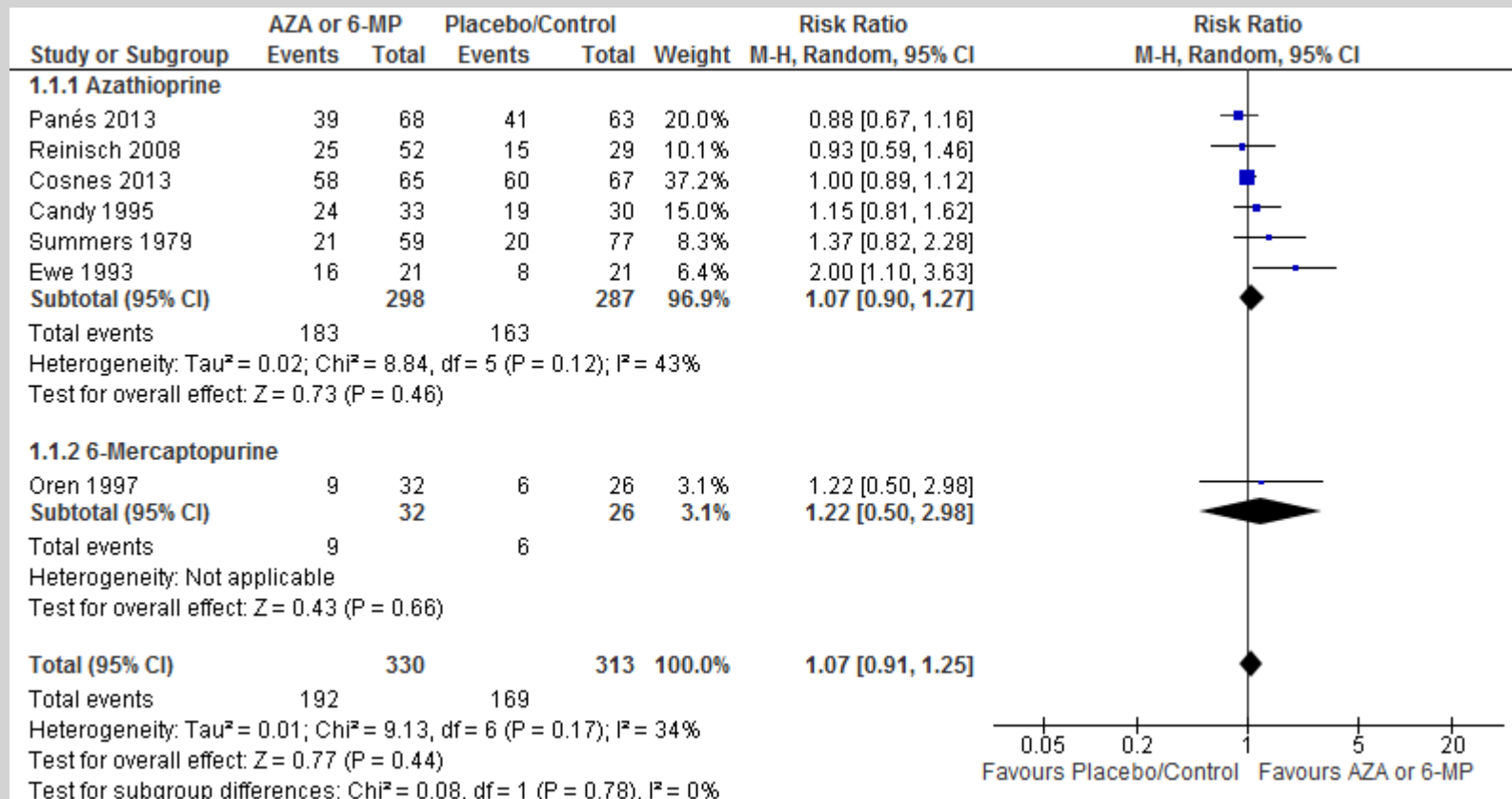
- Azathioprine as induction and maintenance therapy for CD and UC
- Results of AZTEC and GETAID trials
- To review the evidence for use of combination therapy with an immunosuppressive and an anti-TNF biologic in patients with IBD
- To review the evidence regarding adverse effects associated with azathioprine

NCCDS: Cumulative Remission During Therapy With Azathioprine for Active Crohn's Disease

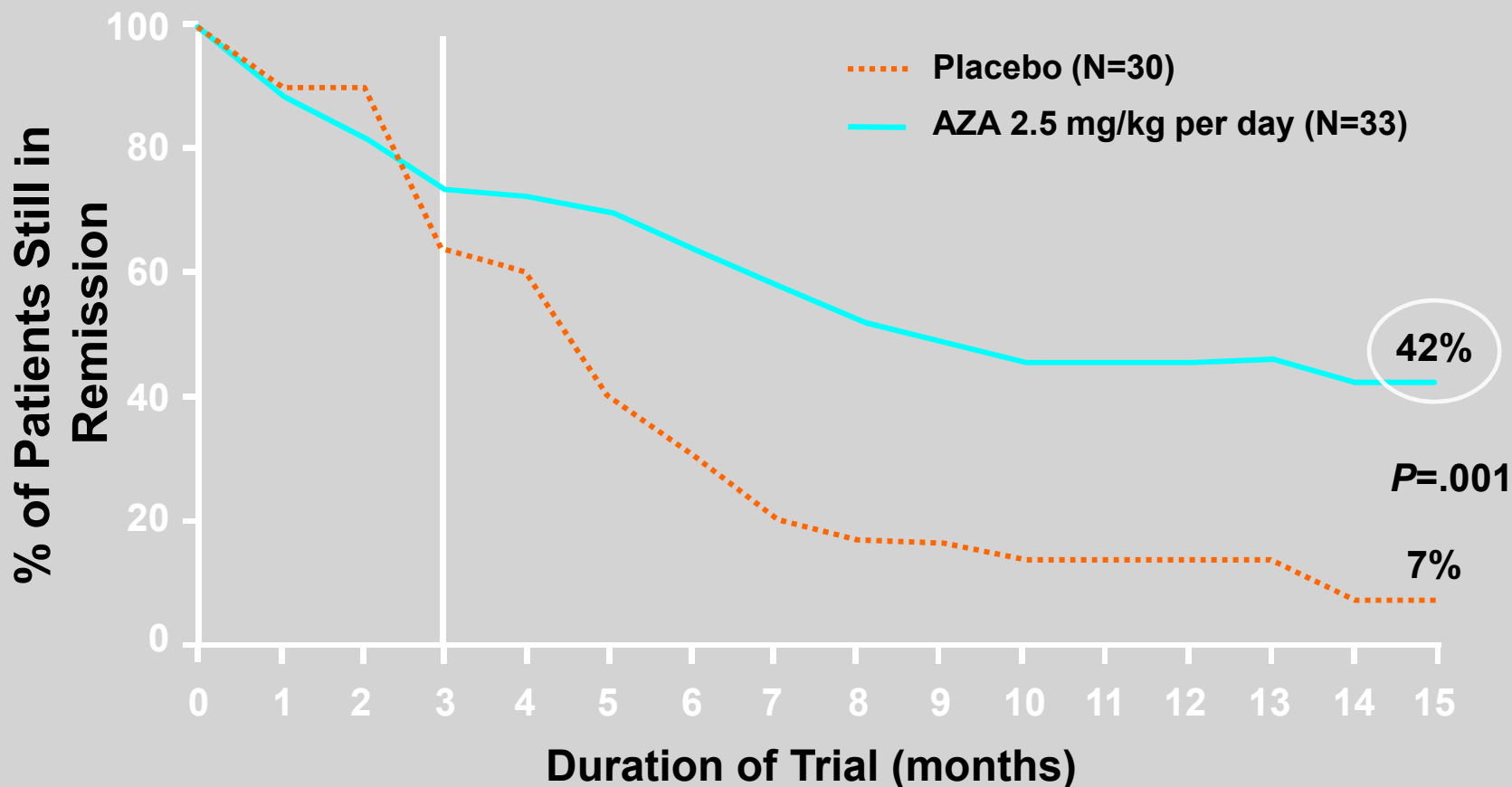


NCCDS = National Cooperative Crohn's Disease Study.
Summers. Gastroenterology. 1979

AZA/6-MP versus Placebo or Control Induction of Clinical Remission



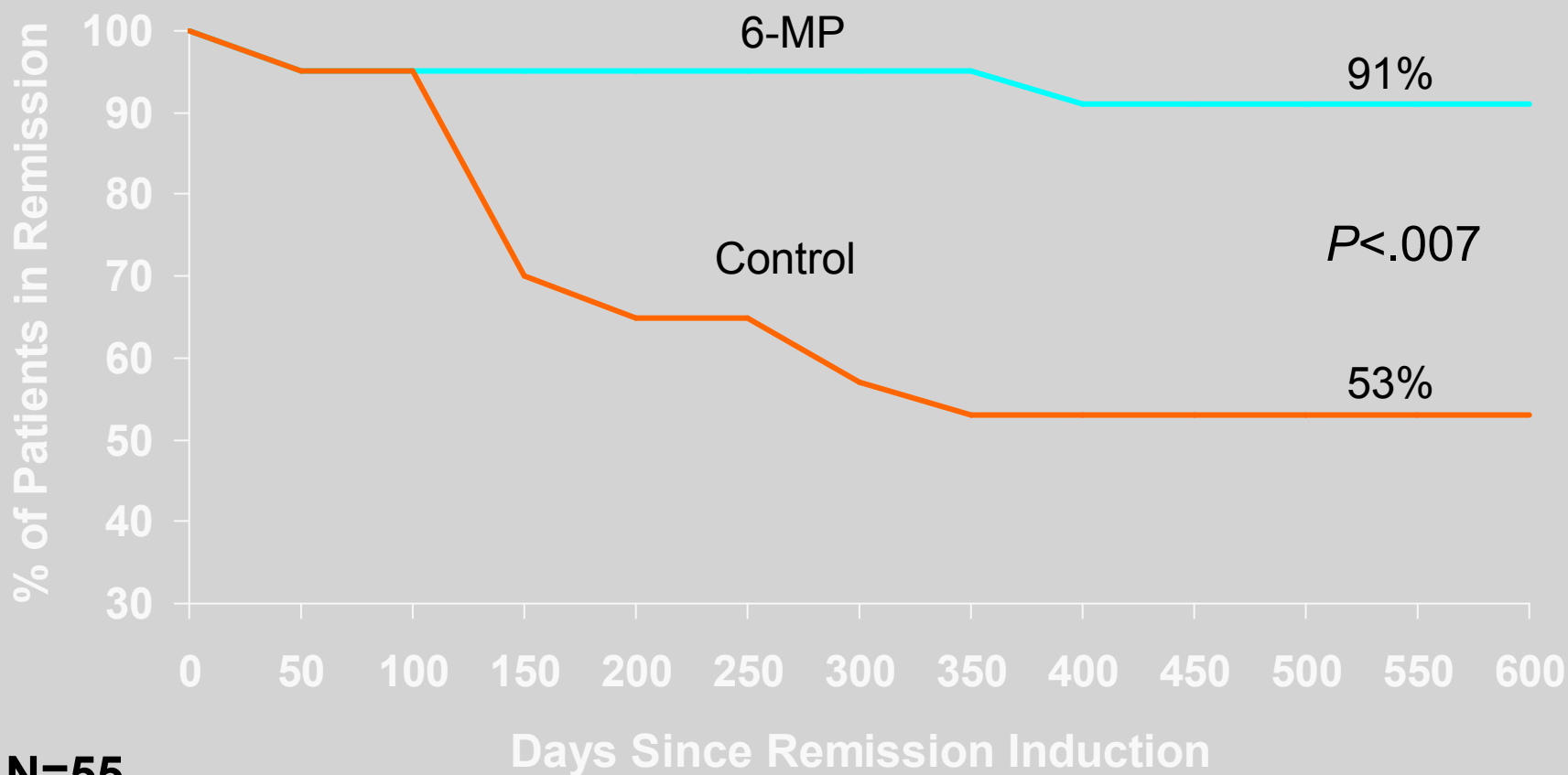
Efficacy of Azathioprine as Maintenance Therapy in Adults With Refractory Crohn's Disease



* Remission induced by prednisolone tapered over 12 wk

Reproduced with permission from Candy S et al. *Gut*. 1995;37:674.

6-Mercaptopurine for Maintenance of Remission in Moderate-to-Severe Pediatric Crohn's Disease



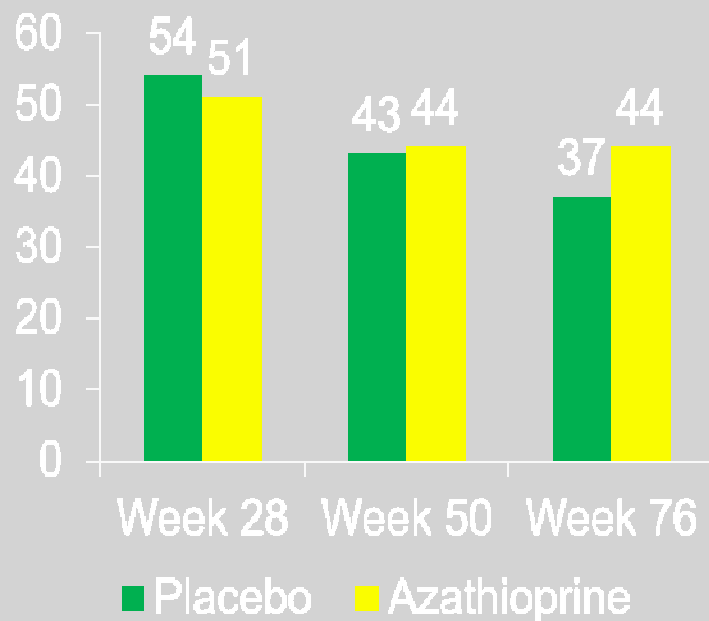
N=55

At baseline, patients received prednisone plus either 6-MP or placebo. Steroids were tapered after induction of remission.

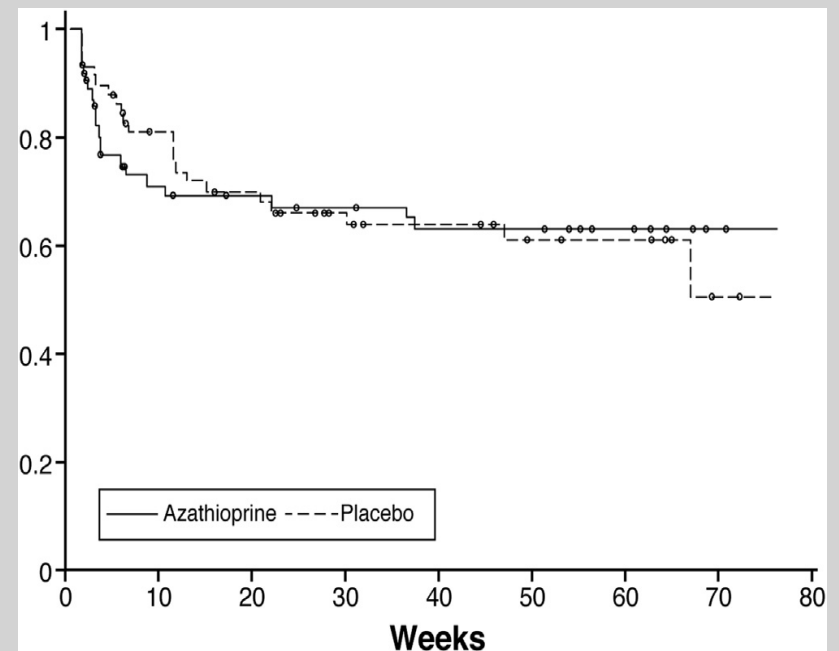
Markowitz J et al. *Gastroenterology*. 2000;119:895

Top Down Therapy With Azathioprine + Prednisone versus Prednisone in Adults with Newly Diagnosed Crohn's Disease

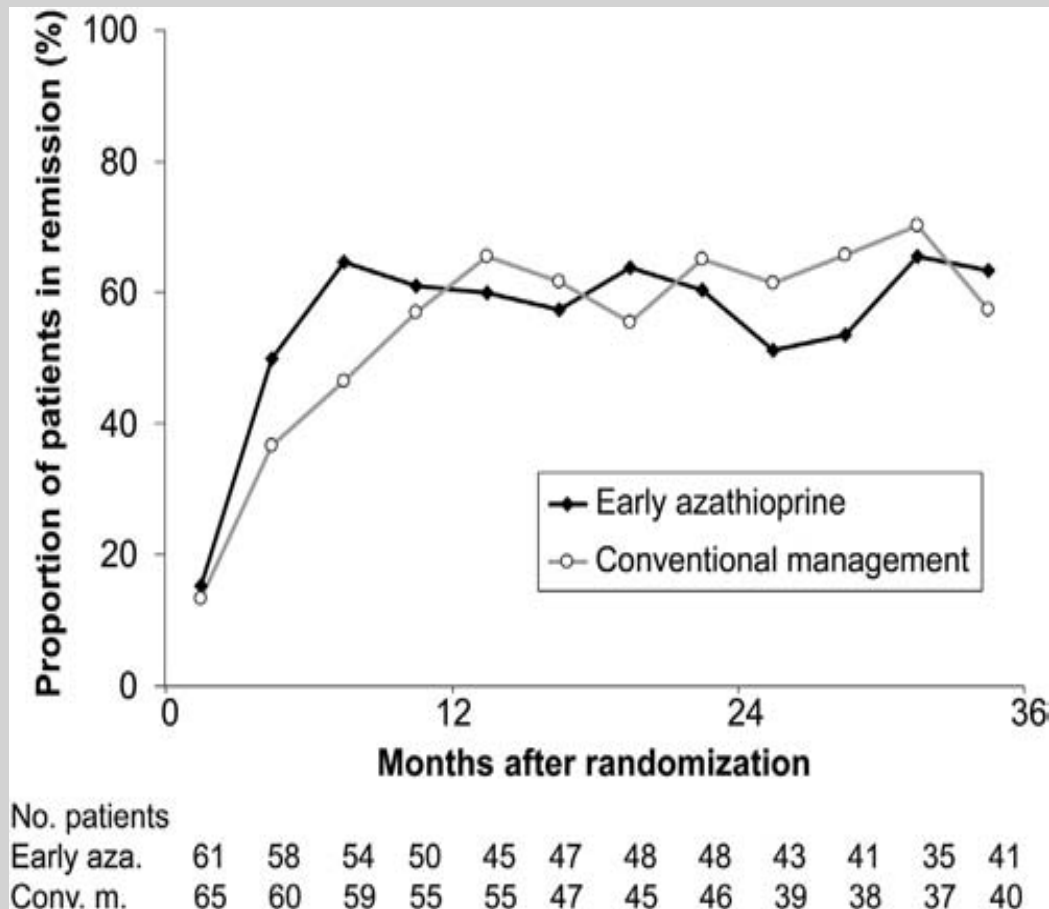
Sustained steroid free remission



Survival free of relapse

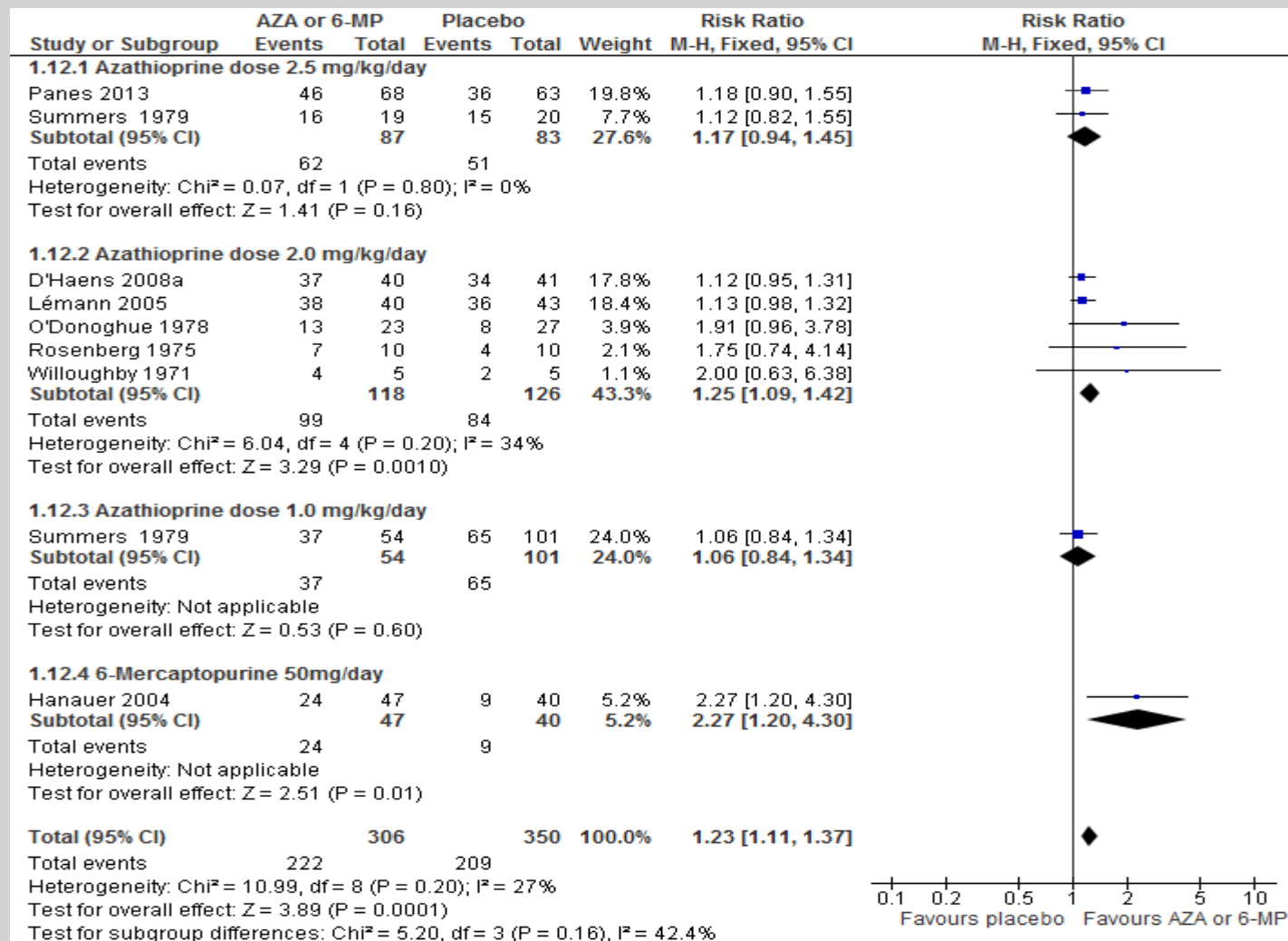


Top Down Therapy With Azathioprine + Prednisone versus Step Up Therapy with Prednisone and then Azathioprine in Adults with Newly Diagnosed Crohn's Disease

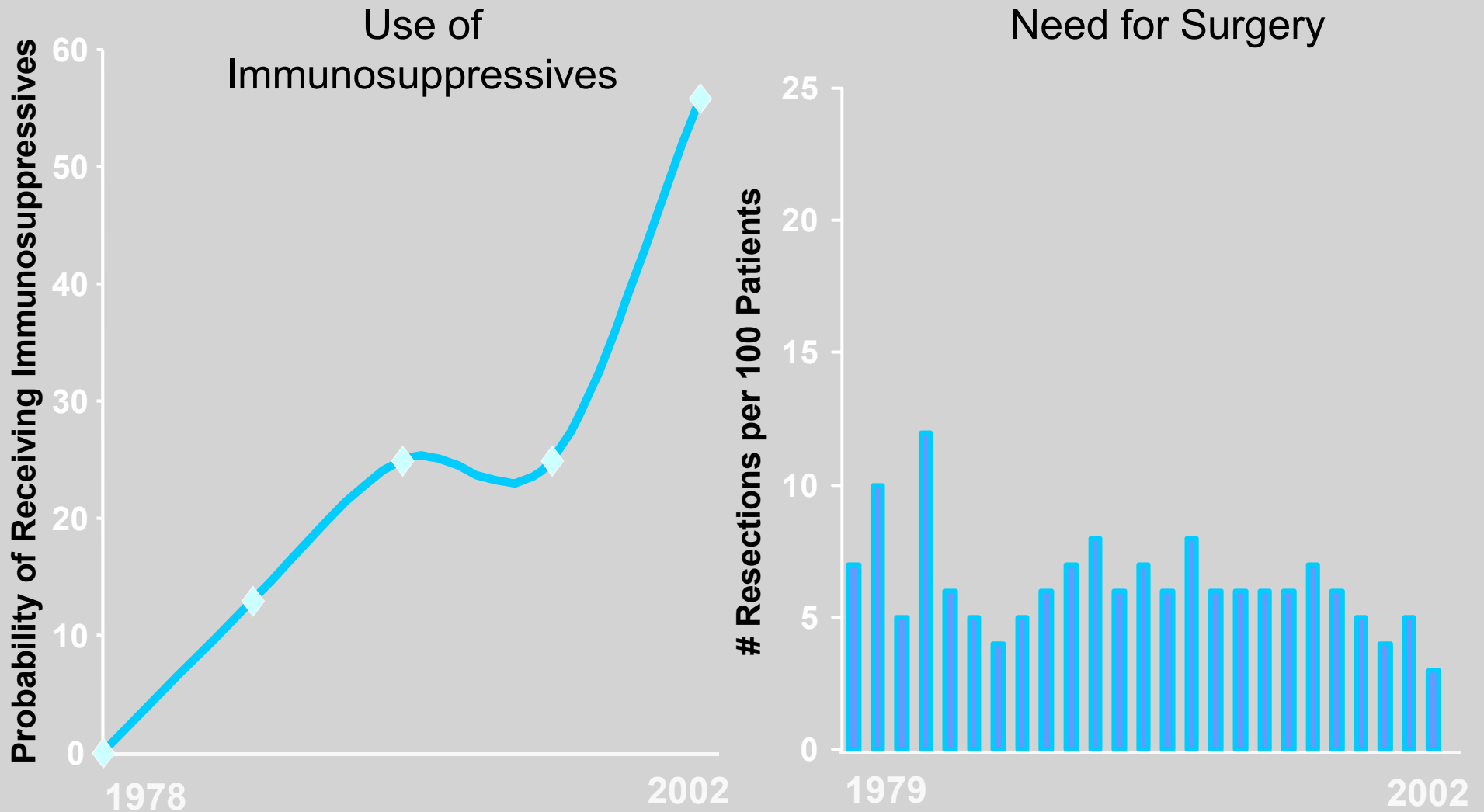


AZA/6-MP versus Placebo

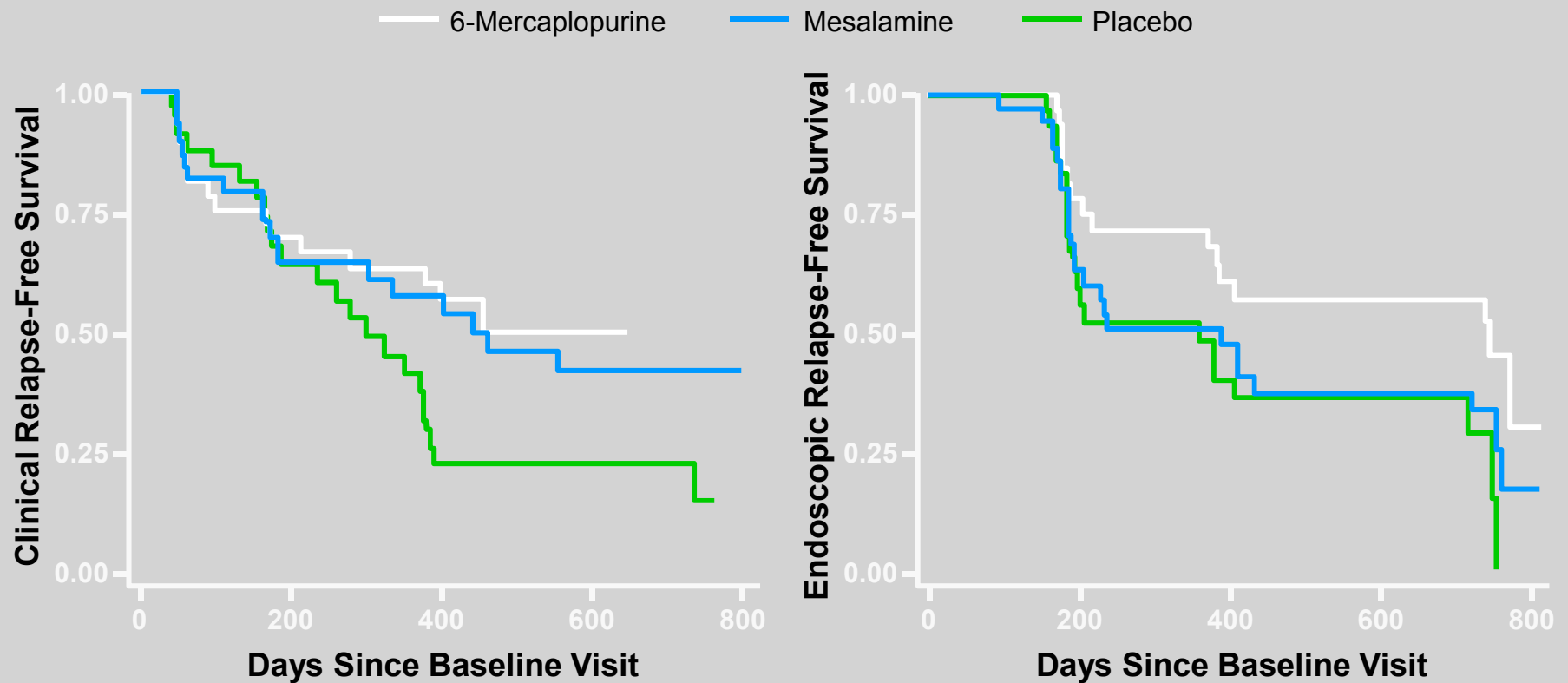
Outcome = Maintenance of Clinical Remission



Rate of Surgery for Crohn's Disease and the Use of Immunosuppressives in Paris Over 3 Decades

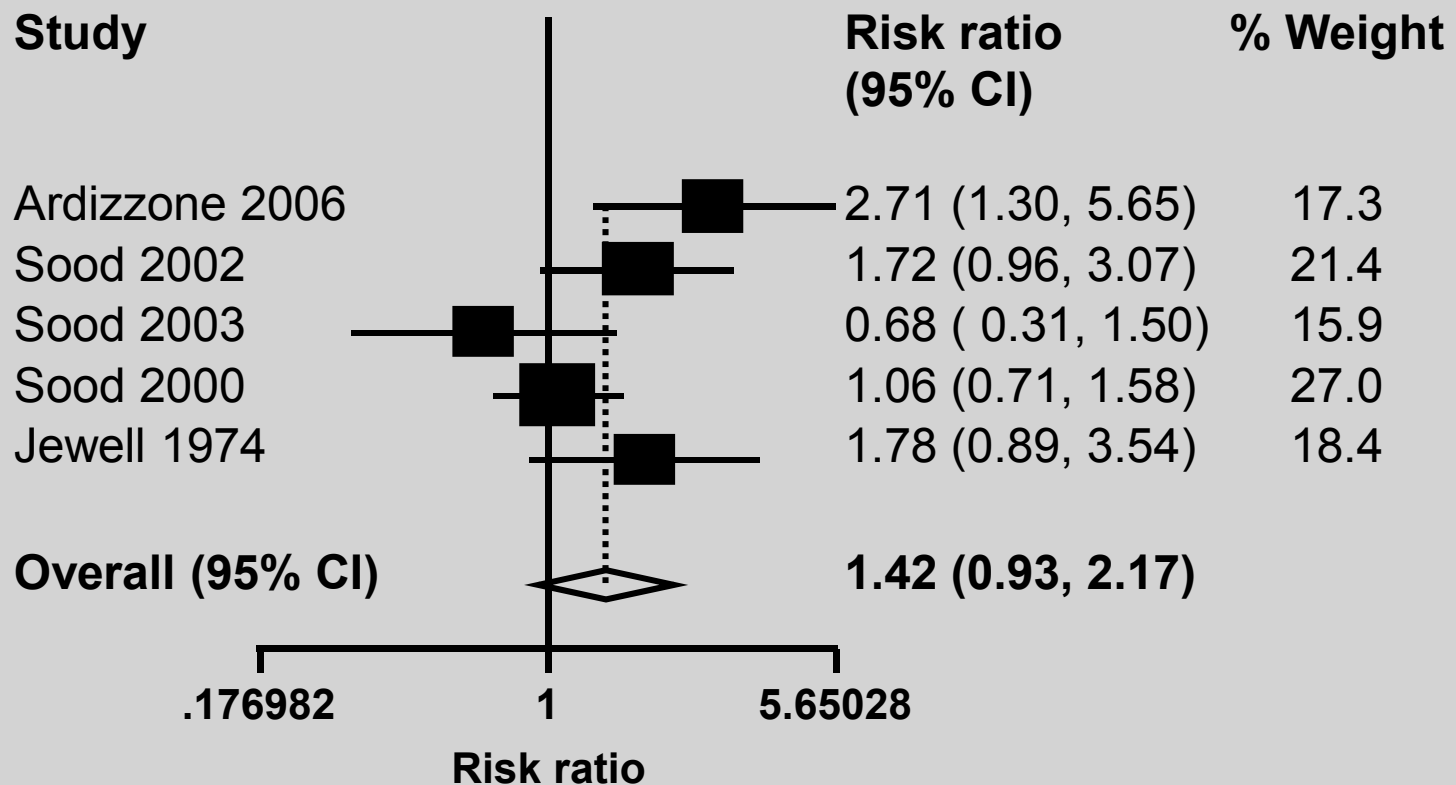


6-Mercaptopurine and Mesalamine for Prevention of Post-Operative Recurrence of Crohn's Disease



Estimate of Efficacy of AZA for Treatment Success in UC Patients: Meta-Analysis

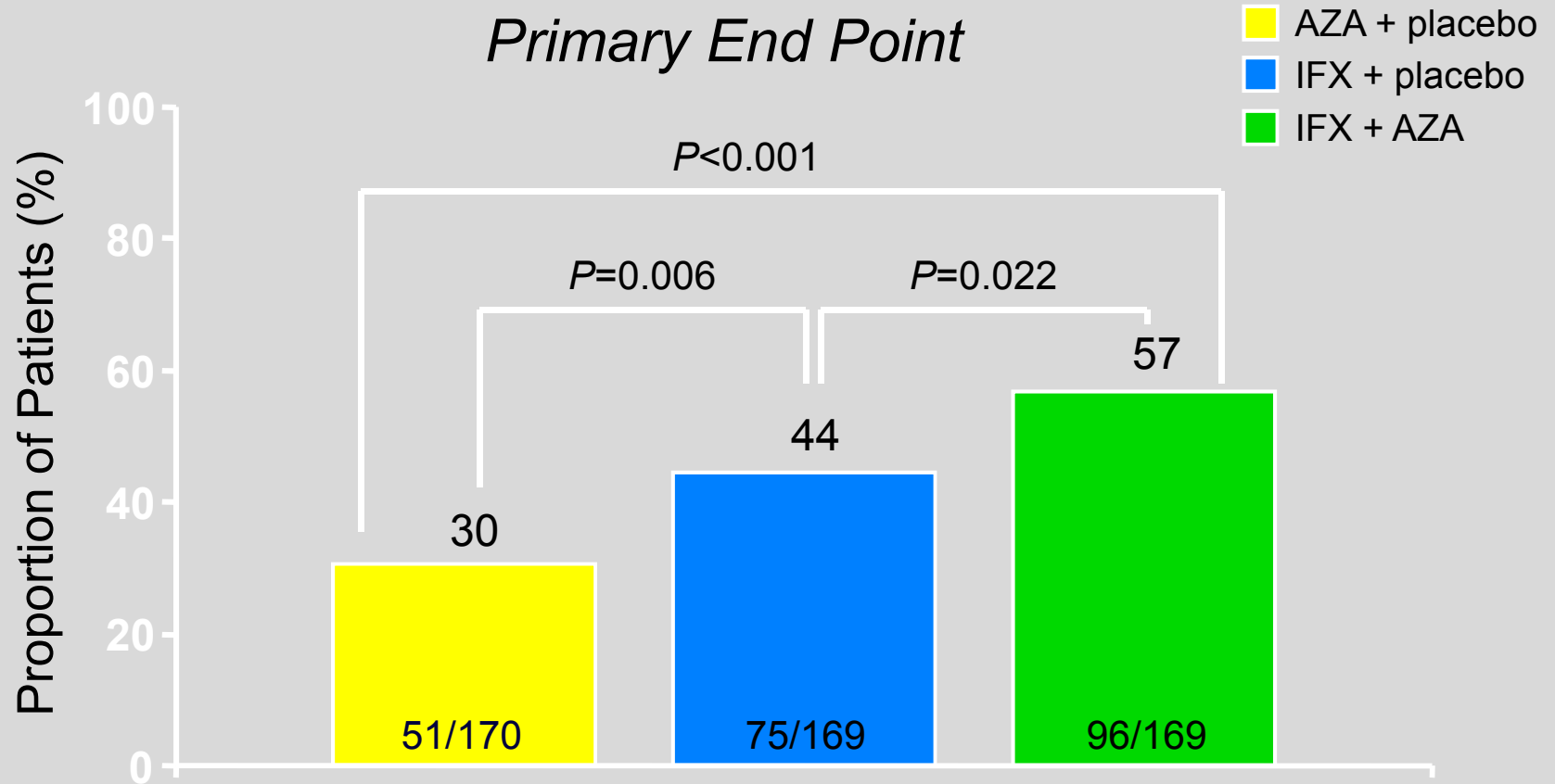
Pooled RR Estimate Across 5 Trials



What is the Evidence for Use of Combination Therapy with an Immunosuppressive and an Anti-TNF Biologic in Patients with IBD?

- Combination therapy
 - More effective in prospective randomized trials
 - Reduces rates of antibody formation
 - Results in higher blood concentrations of the biologic
 - Similar side effect profile to monotherapy

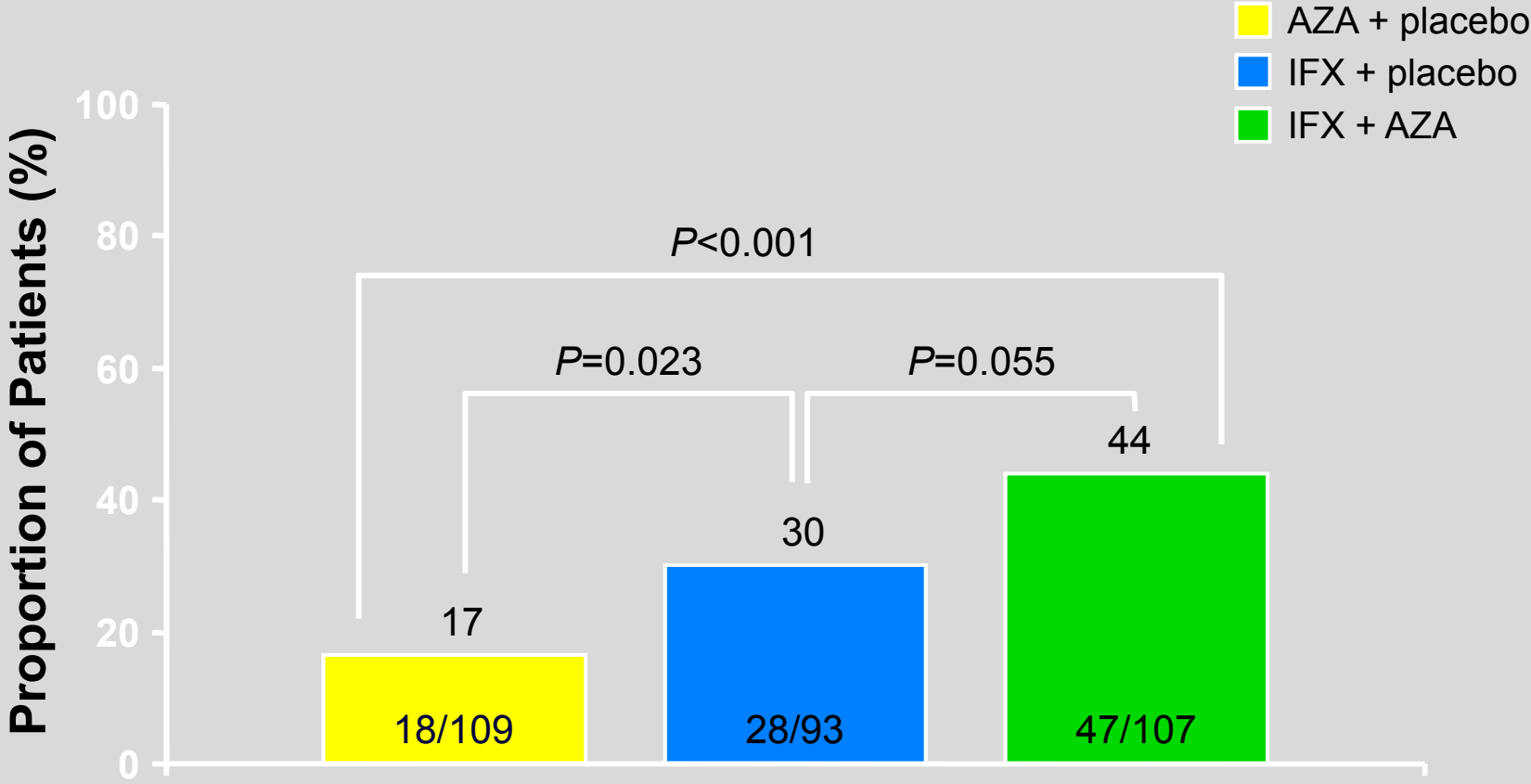
SONIC: Clinical Remission without Corticosteroids at Week 26



IFX, infliximab

Colombel JF, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med.* 2010 Apr 15;362(15):1383-1395. © 2010 Massachusetts Medical Society. All rights reserved.

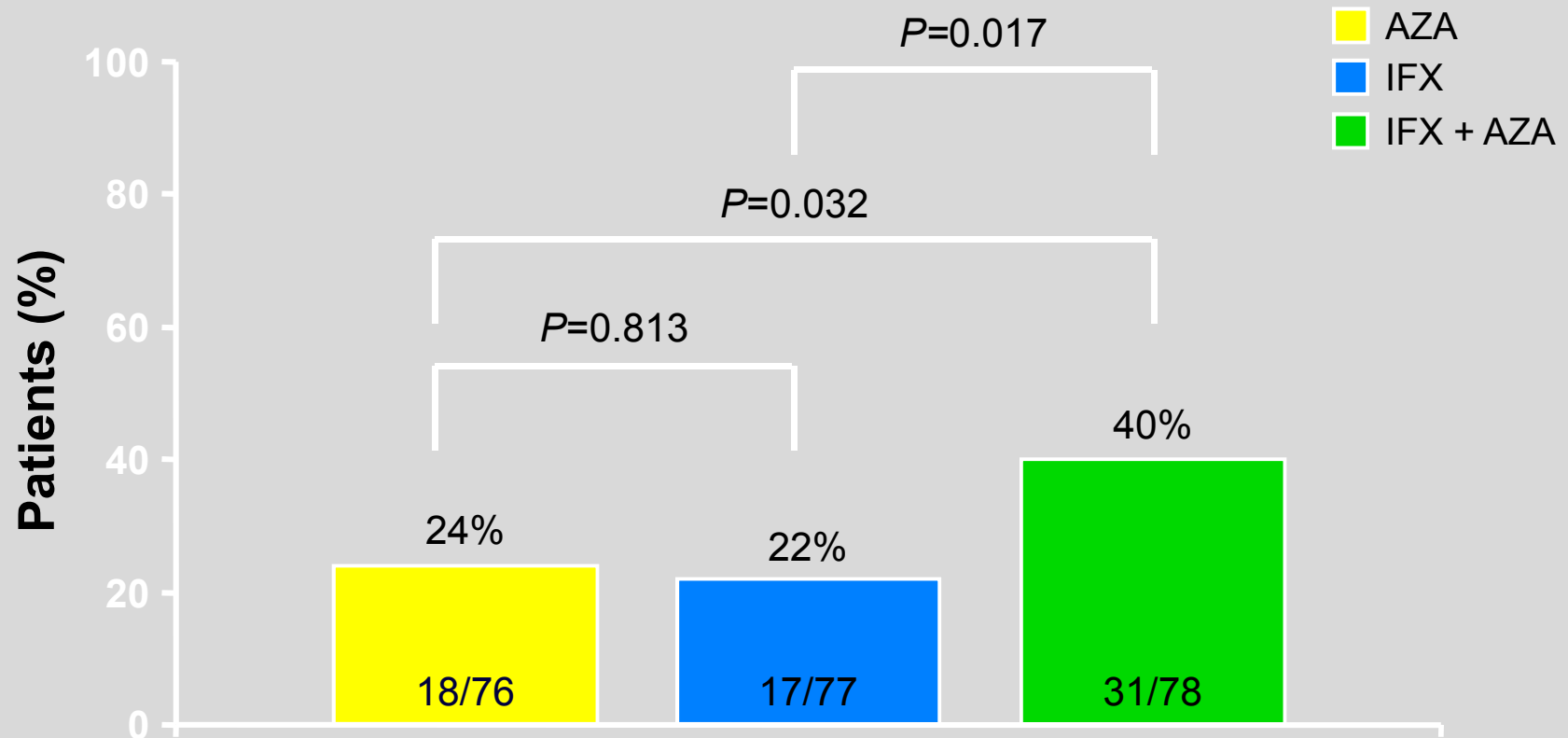
SONIC: Mucosal Healing at Week 26



Colombel JF, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med.* 2010 Apr 15;362(15):1383-1395. © 2010 Massachusetts Medical Society. All rights reserved.

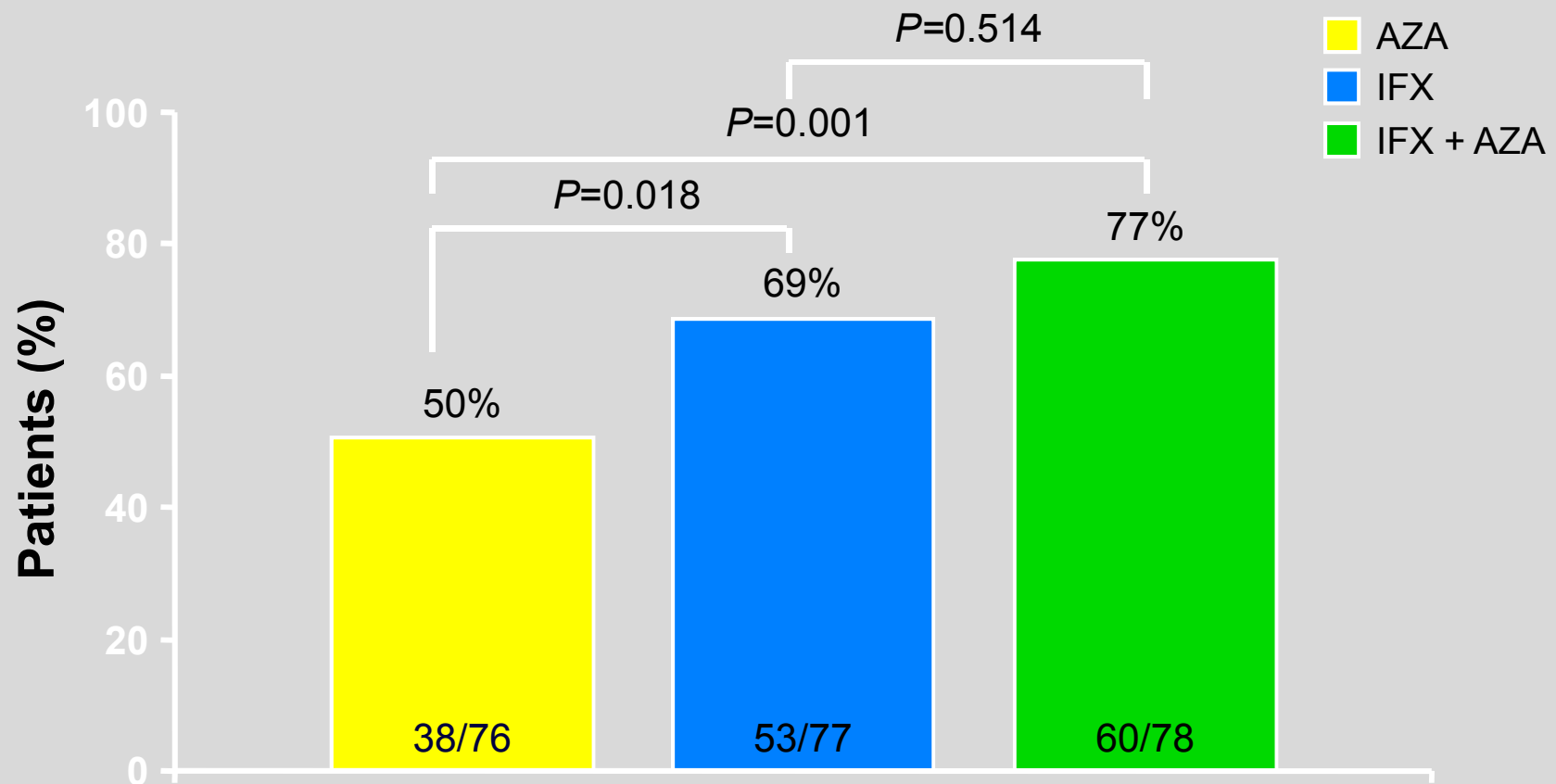
Infliximab, Azathioprine, or Infliximab + Azathioprine for Treatment of Moderate to Severe UC: UC SUCCESS Trial

Primary End Point: Steroid-Free Remission at Week 16



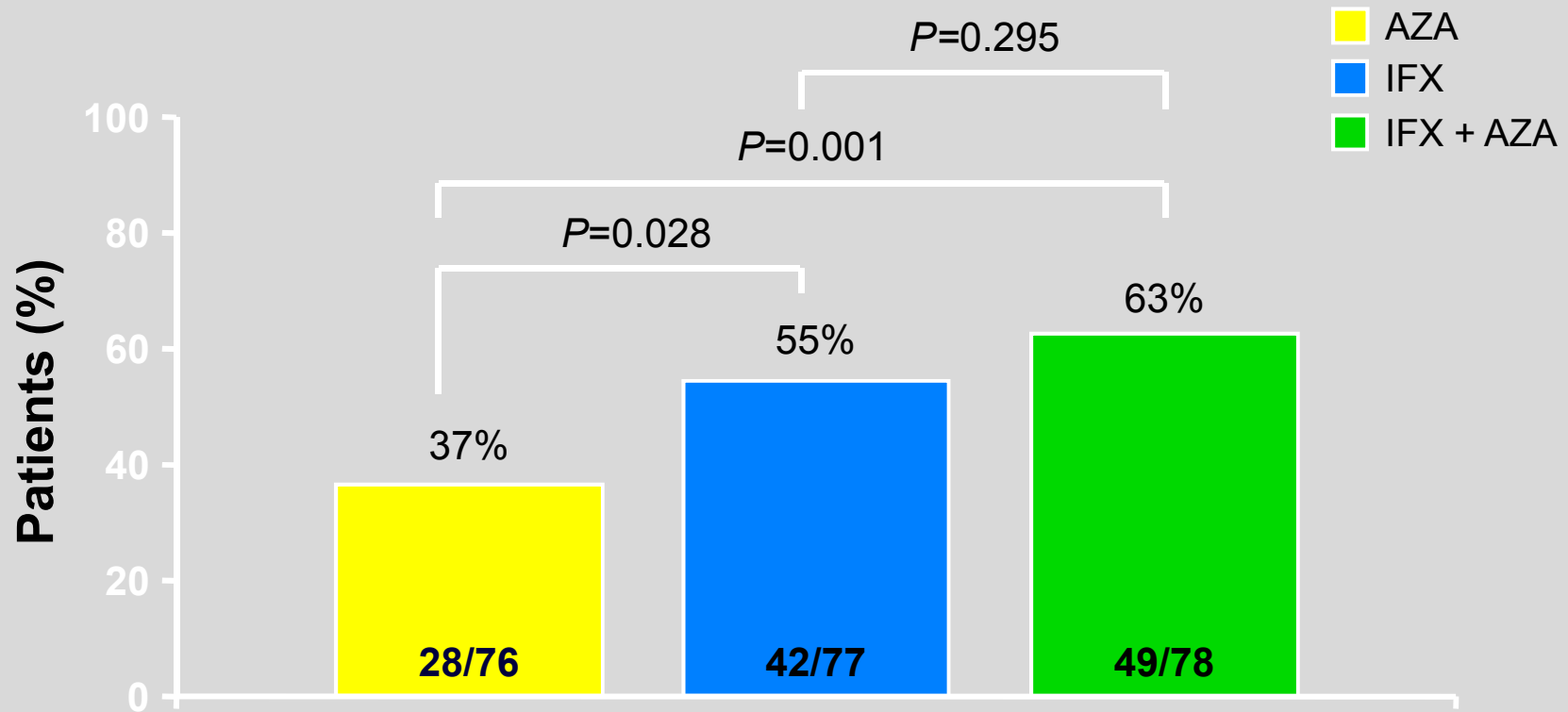
Infliximab, Azathioprine, or Infliximab + Azathioprine for Treatment of Moderate to Severe UC: UC SUCCESS Trial

Major Secondary End Point: Response at Week 16

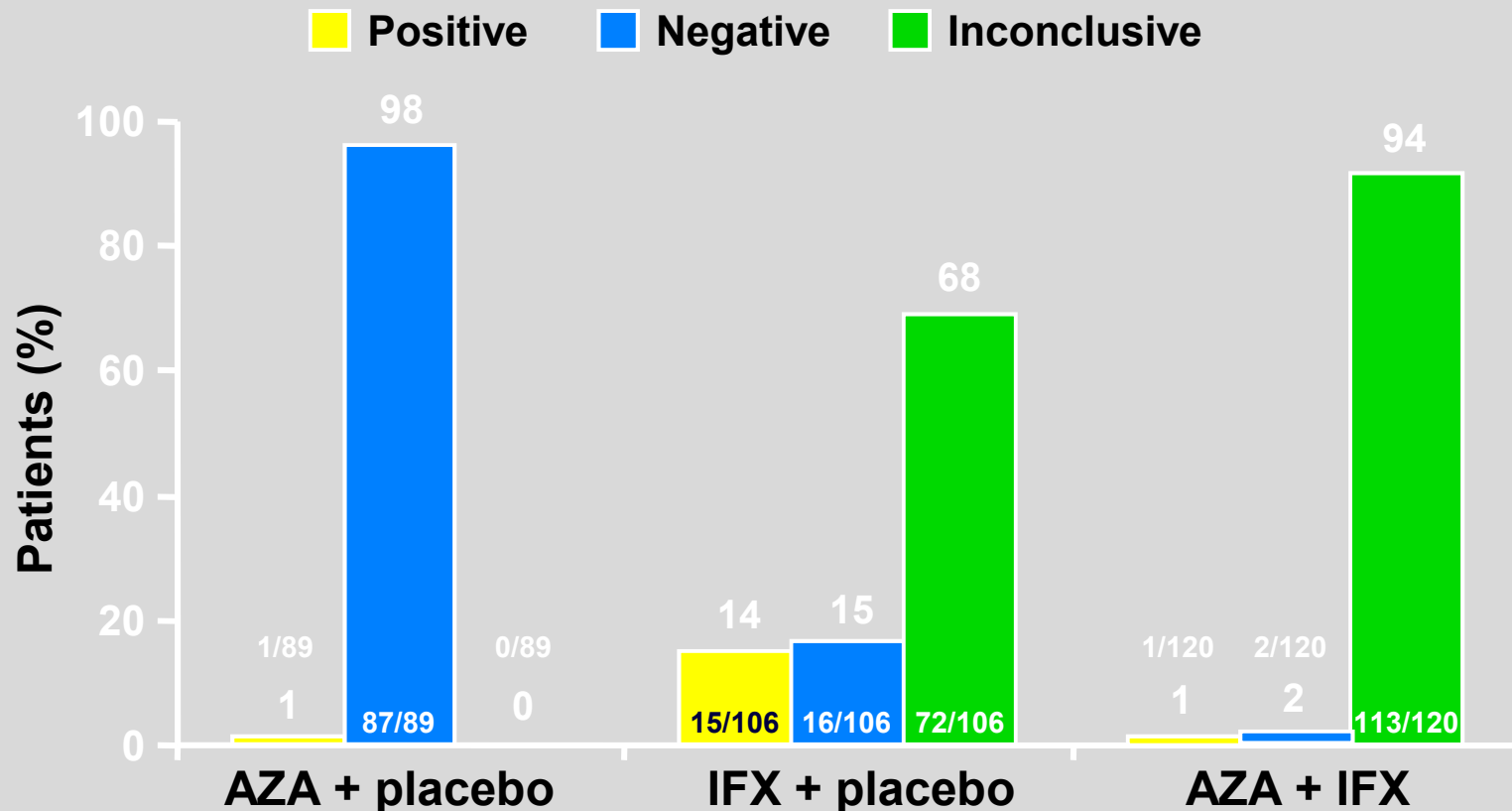


Infliximab, Azathioprine, or Infliximab + Azathioprine for Treatment of Moderate to Severe UC: UC SUCCESS Trial

Secondary End Point: Mucosal Healing at Week 16

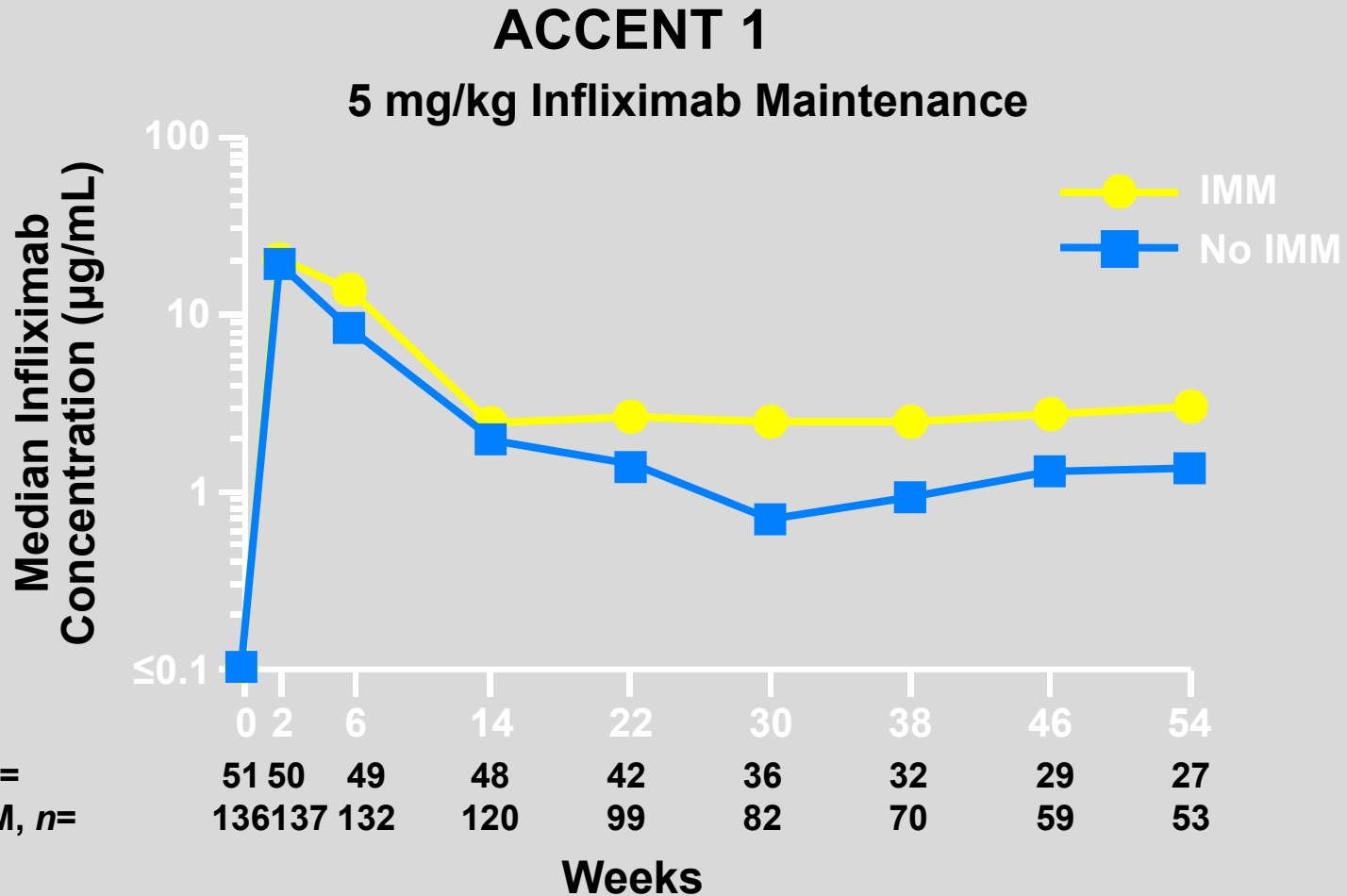


SONIC: Immunogenicity Results at Week 30*



*Patients who had 1 or more PK samples obtained after their first study agent administration were included in the analysis. PK data at Wk 30 was not available for 1 patient treated with AZA + placebo, 3 patients treated with IFX + placebo, and 4 patients treated with AZA + IFX.

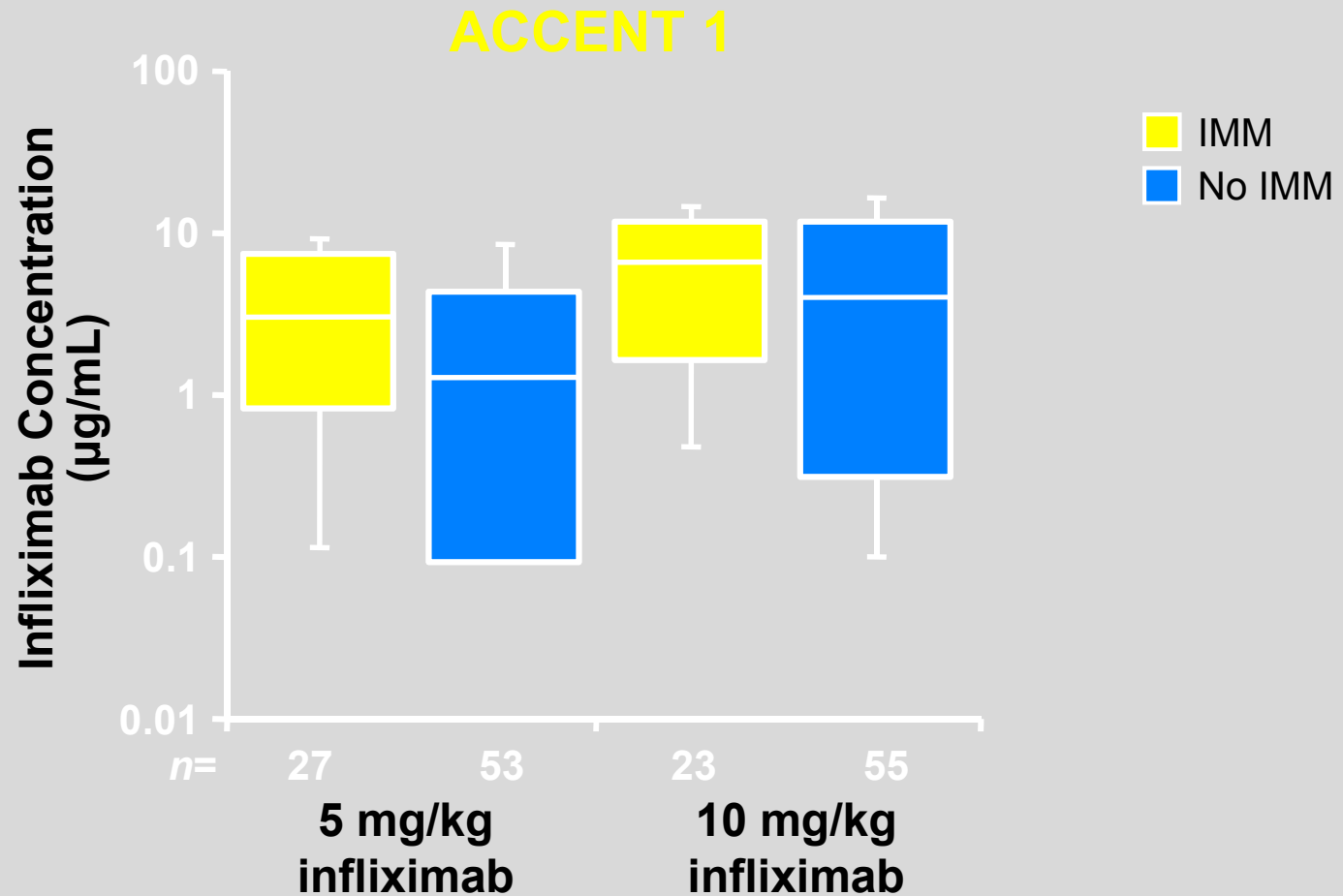
ACCENT 1 IFX in Crohn's Disease: Median Serum IFX Trough Concentrations Over Time Stratified by Immunosuppressive Therapy



IMM, immunomodulator

Lichtenstein GR, et al. Clinical trial: benefits and risks of immunomodulators and maintenance infliximab for IBD-subgroup analyses across four randomized trials. *Aliment Pharmacol Ther.* 2009 Aug;30(3):210-226. With permission from John Wiley and Sons.

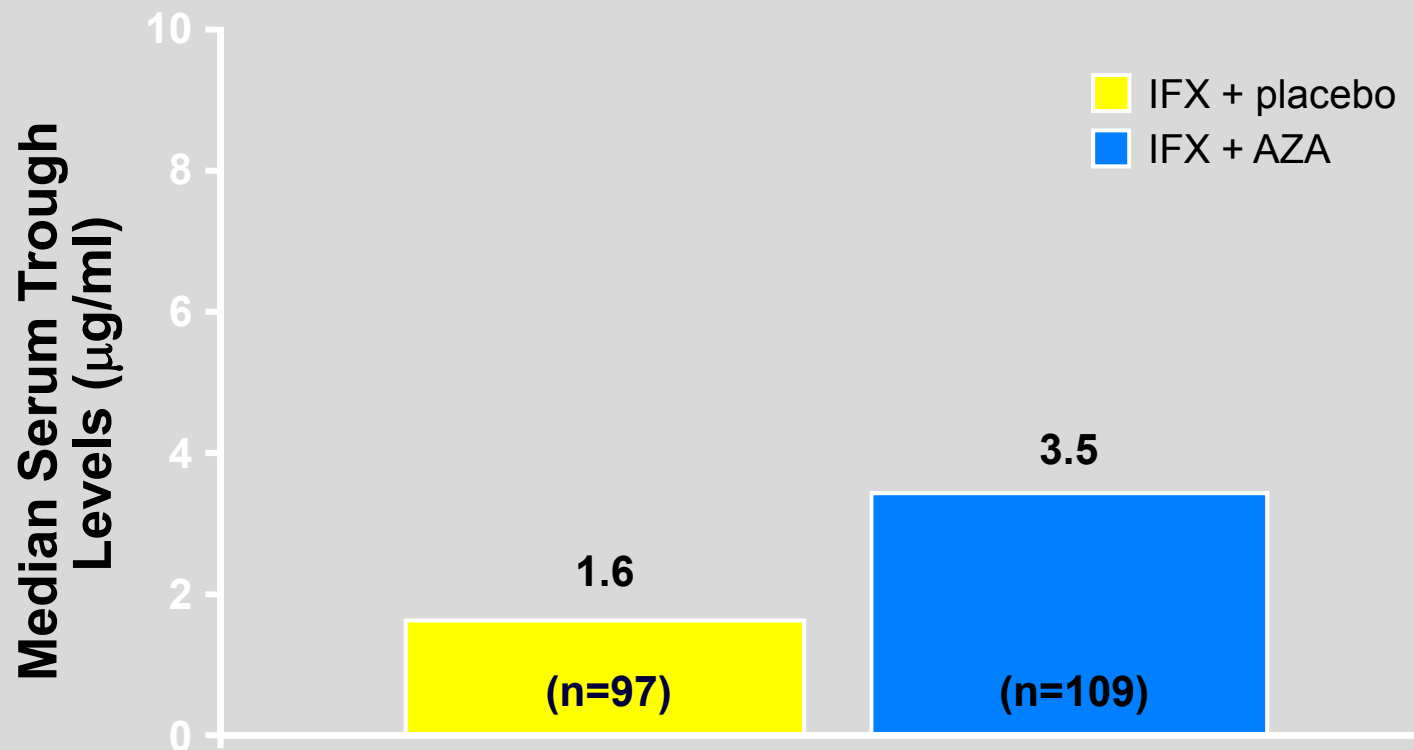
ACCENT 1 IFX in Crohn's Disease: Serum IFX Trough Concentration at the Last Clinical Visit Stratified by Immunosuppressive Therapy



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SONIC: IFX Trough Levels at Week 30*



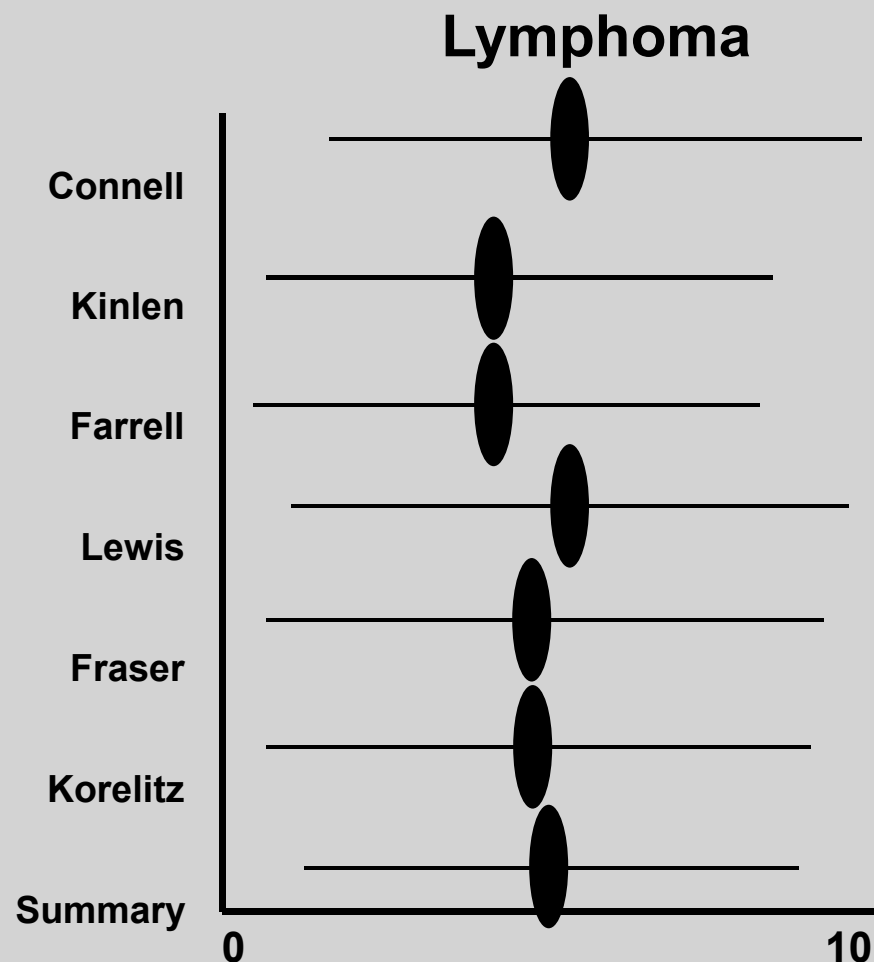
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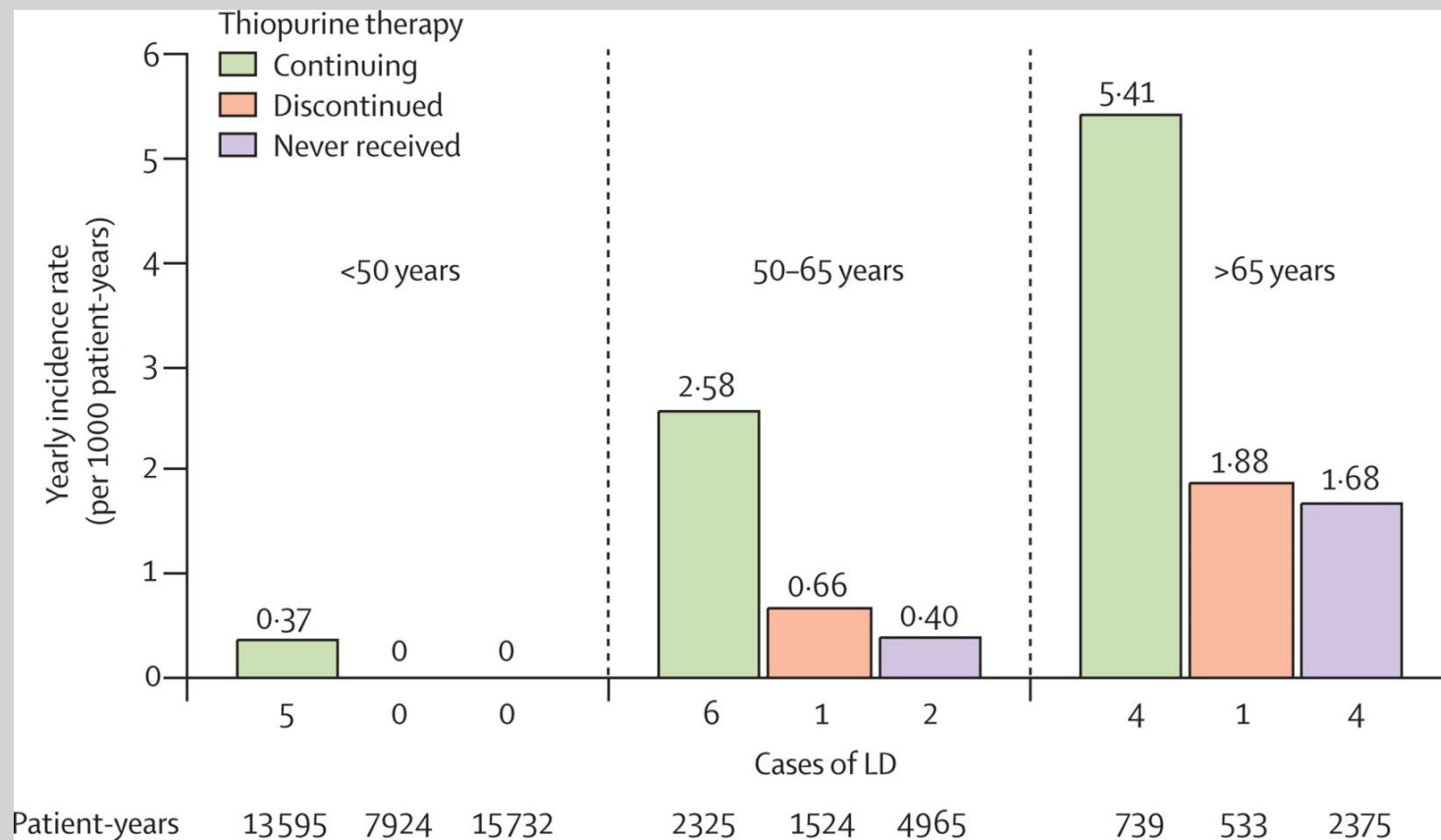
Adverse Events with Azathioprine

Toxicity of Azathioprine and 6-Mercaptopurine in Inflammatory Bowel Disease

- **Overall toxicity** 15%
 - Pancreatitis 3.3%
 - Bone marrow depression 2%
 - Allergic reactions 2%
 - Drug hepatitis 0.3%
 - Infectious complications 7.4%
 - Malignant neoplasm 3.1%
- **Lymphoma**
 - Meta-analysis of 6 studies showed that AZA/6MP treatment is associated with 4-fold increase (SIR = 4.2 [95% CI = 2.1–7.5]) in risk of EBV-positive lymphoma



CESAME: Incidence rates of lymphoproliferative disorders according to azathioprine exposure grouped by age at entry in the cohort



Risk of NH Lymphoma with anti-TNF + IM treatment for Crohn's Disease

Meta-analysis Results

- 8905 patients representing 20,602 pt-years of exposure
- 13 Non-Hodgkin's lymphomas → **6.1 per 10,000 pt-years**
- Mean age 52, 62% male
- 10/13 exposed to IM* (really a study of combo Rx)

	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

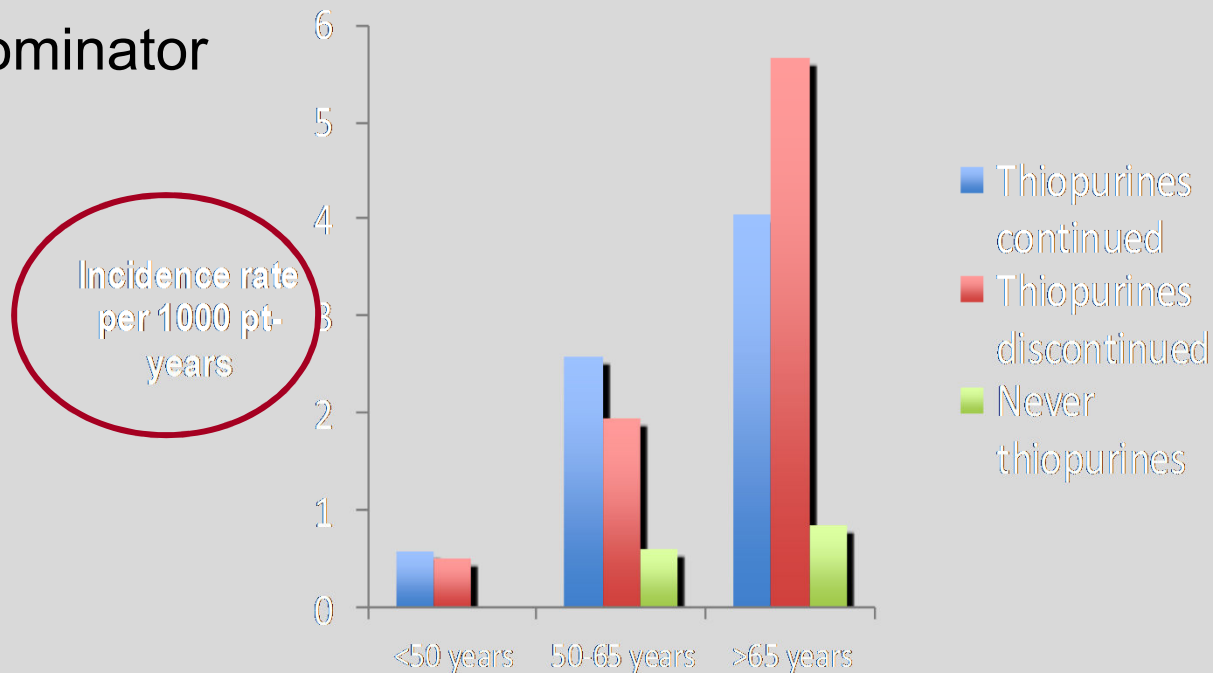
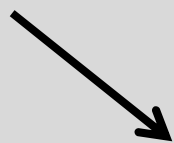


*not reported in 2

Risk of Skin Cancer Associated with Thiopurines (CESAME)

- 19,486 IBD patients
- 32 cases of skin cancer (20 basal cell, 12 squamous)

Look at denominator



SONIC: Summary of Adverse Events Through Week 50

All Randomized Patients

	AZA + placebo (n=161)	IFX + placebo (n=163)	IFX + AZA (n=179)
Pts with ≥ 1 AE, n (%)	144 (89.4%)	145 (89.0%)	161 (89.9%)
Pts with ≥ 1 SAE, n (%)	43 (26.7%)	39 (23.9%)	27 (15.1%)
Serious infections	9 (5.6%)	8 (4.9%)	7 (3.9%)

Tuberculosis: 1 patient treated with infliximab and azathioprine

Colon cancer: 2 patients treated with azathioprine monotherapy

Death: postcolectomy, in a patient treated with azathioprine monotherapy

Conclusions

- Azathioprine monotherapy is not effective for induction, it may be modestly effective for maintenance of steroid induced remission in patients with established Crohn's disease
- Combination therapy is more effective than azathioprine or anti-TNF monotherapy for steroid-free remission and mucosal healing
- Combination therapy results in lower immunogenicity and higher anti-TNF antibody blood concentrations
- Monotherapy and combination therapy have similar rates of serious infection when considering the combined rates of BOTH disease related infections and opportunistic infections

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