Northern California Society Clinical Gastroenterology
Best of DDW 2019
IBD

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July 13, 2019

Stopping 5ASA in CD Patients Does Not Increase Risk of Adverse Outcomes

- Methods
  - Analysis 2 national DB (Truven, Danish Registry)
  - 2960 US, 218 Denmark
  - Inclusion: 1 CD Code, anti-TNF 90 days, 5ASA at least 90 days prior to TNF
  - Adverse Event: New steroid use, hospitalization, surgery

- Results

Table 1: Multivariable Cox Regression Model

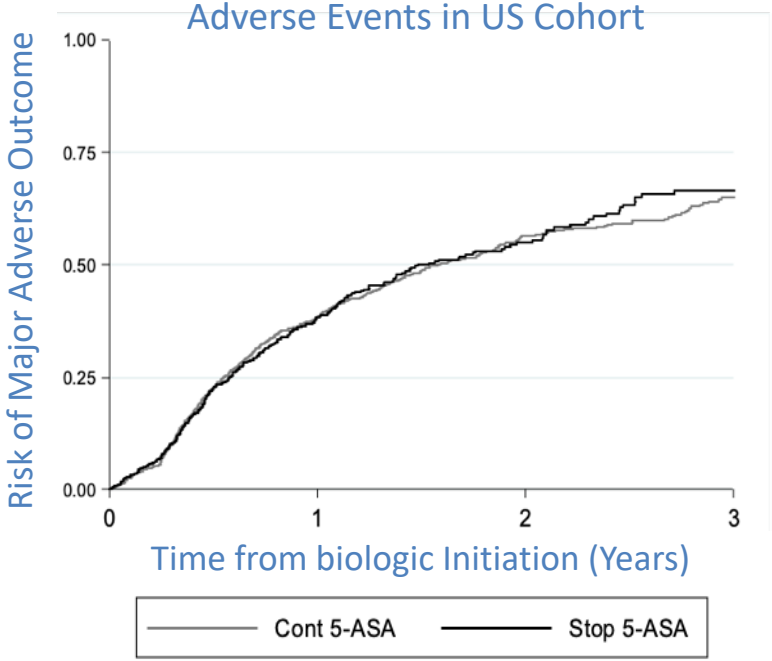
Discontinue versus Continue 5-ASA			
United States Cohort	**aHR***	**95% CI**	***P*-value**
New Steroid Use	0.87	0.74-1.03	0.12
Hospitalization	0.87	0.70-1.08	0.21
Surgery	0.79	0.49-1.29	0.35
Composite	0.89	0.77-1.03	0.13
Denmark Cohort	**aHR***	**95% CI**	***P*-value**
New Steroid Use	1.18	0.60-2.33	0.63
Hospitalization	2.06	1.01-4.20	0.05
Surgery	1.13	0.45-2.83	0.80
Composite	1.13	0.68-1.87	0.63

*Adjusted for age, sex, duration of 5-ASA treatment, and baseline health care utilization

Ungaro RC; Sa 110 DDW 2019

Stopping 5ASA in CD Patients Does Not Increase Risk of Adverse Outcomes

Figure 1: Cumulative Rates for Adverse Events in US Cohort



- Conclusion
  - In two national databases, stopping 5-ASA in CD patients starting anti-TNF therapy did not increase the risk of adverse clinical events

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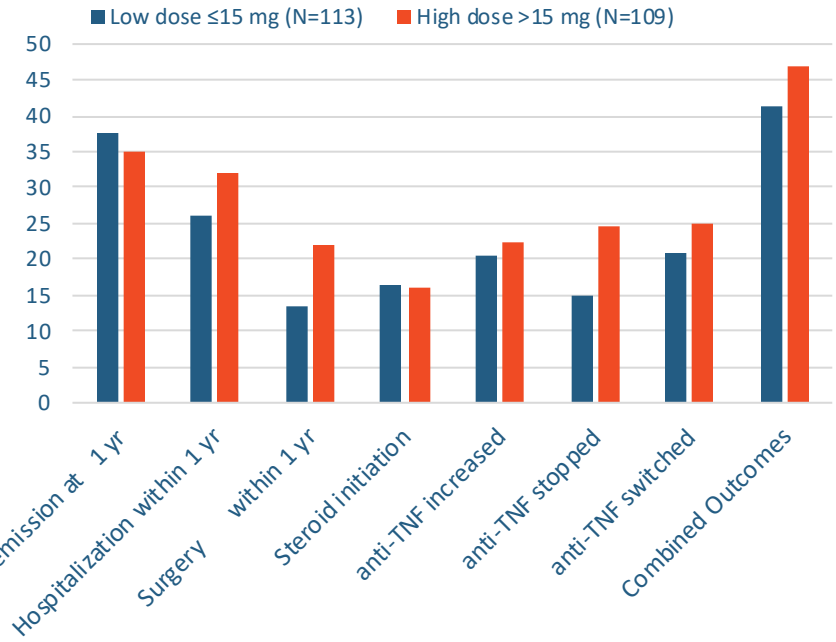
Low Dose Methotrexate is Equally Effective as High Dose in Combination with Anti-TNF's

- **Methods**
  - CD or UC patients on combination MTX and anti-TNF
  - Definition of MTX dosing
    - Low Dose (LD) <=15 mg/week
    - High dose (HD) >15 mg/week
- **Results**
  - 163 CD, 59 UC patients
  - Most common anti-TNF was IFX (36% HD, 40% LD)
  - No change in primary composite outcome at 1 year: Hospitalization, steroids, surgery, change biologic
  - 47%HD, 42% LD (p=0.18)
  - No difference in infections

Figure 1: Efficacy Outcomes



Borren NK; Su1862 DDW 2019

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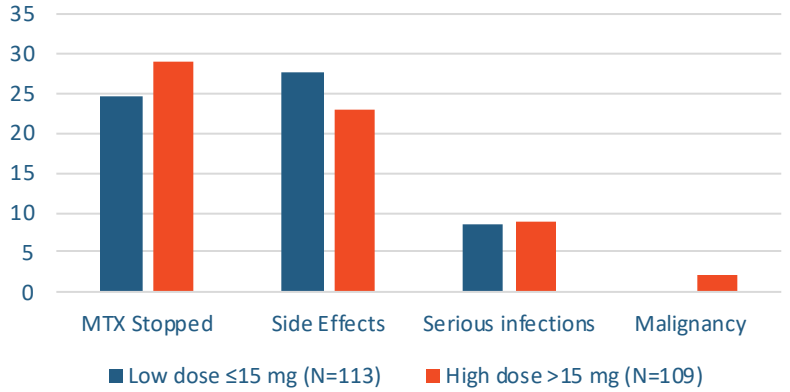
Figure 2: Safety Outcomes



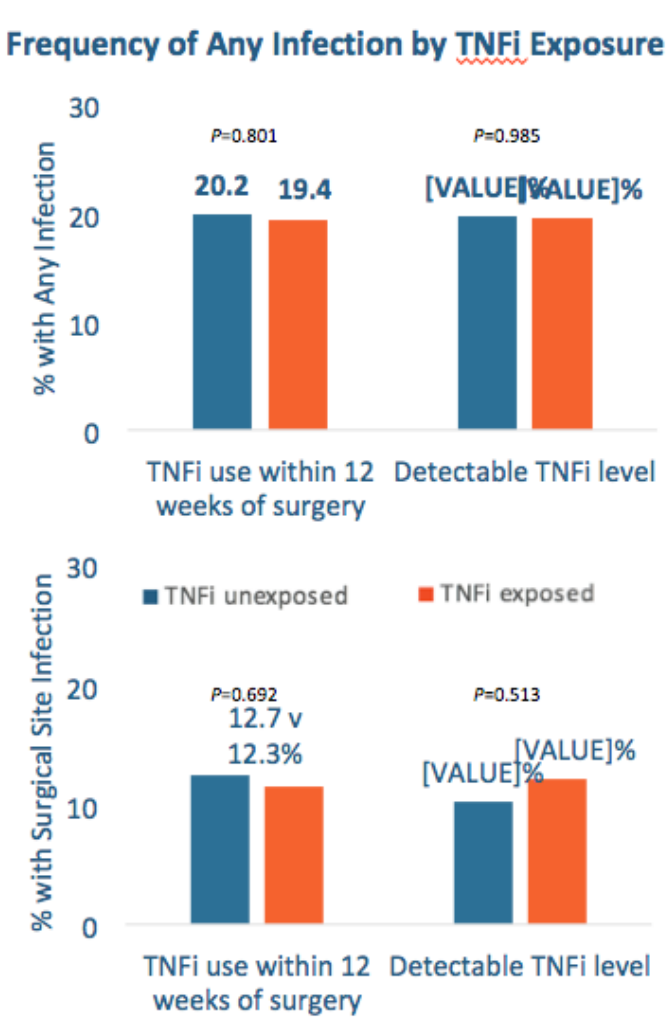
Conclusion:
Low dose MTX (≤ 15mg SQ weekly) was equally effective as high dose (> 15mg weekly) MTX when used along with anti-TNF therapy and may be sufficient for combination therapy in patients with IBD.

Borren NK; Su1862 DDW 2019

Anti-TNF therapy not associated with post-operative infection (PUCCINI)

- **Methods**
  - Prospective trial (2014-2017) at 17 US Centers
  - IBD Patients undergoing intra-abdominal surgery
  - Exposed to anti-TNF within 12 weeks or detectable levels preoperatively
  - Look at risk factors for 30-day infections (patient interview and chart abstraction)
- **Results**
  - 955 patients underwent surgery (ileocolonic resection 43%, segmental resection 18%, subtotal colectomy 18%)
  - 382/955 (40%) preop TNF exposure
  - 223/322 (70%) with detectable TNF level

Cohen BL; Su 415a DDW 2019 IMIBD Plenary



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- **Conclusion**
  - Pre-op use of anti-TNF drugs, as determined by history or by drug levels, was not an independent risk factor for post-op infections in a large prospective multi-center cohort.

Cohen BL; Su 415a DDW 2019 IMIBD Plenary

VARSITY trial: vedolizumab shows superior efficacy over adalimumab for Moderate to Severe UC

- **Methods**
  - Head to head trial
  - Phase 3, RCT, double blind
  - Adult patients with moderate-severe UC (Mayo 6-12); endoscopic subscore>=2
  - 25% restriction to prior anti-TNF therapy (only 1 prior allowed)

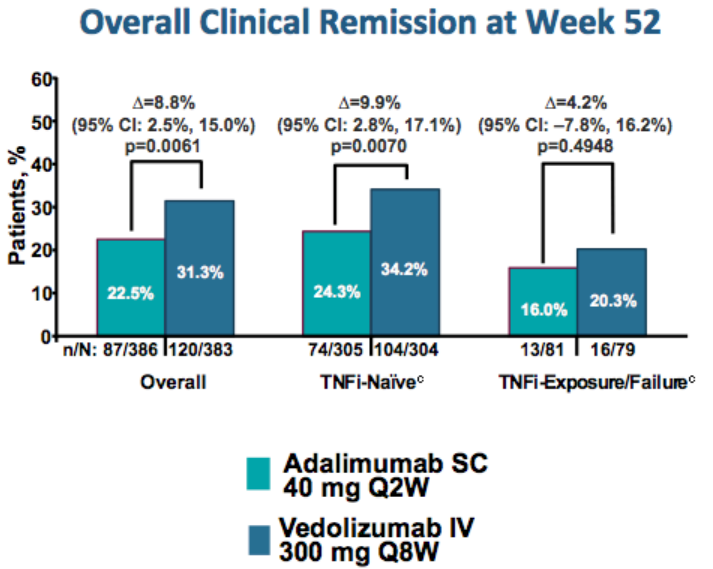
VDZ IV / PBO INJ (n=383)

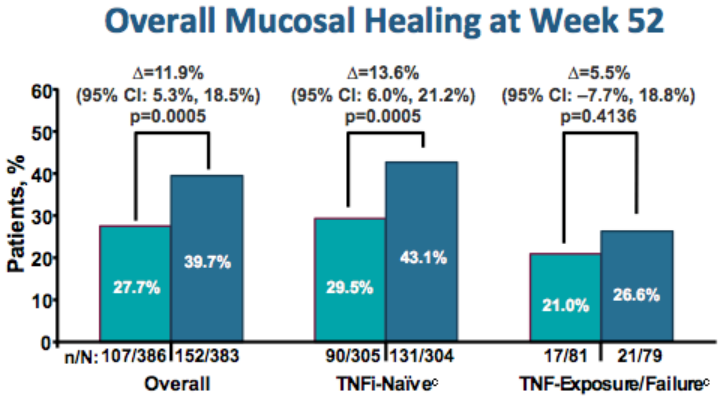
PBO IV / ADA INJ (n=386)

**standard dosing*

**no dose escalation permitted*

Sands B; Su 416a DDW 2019 IMIBD Plenary





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- **Results**
  - VDZ>ADA
    - Clinical remission: (31.3 v 22.5%, p=0.006)
    - Mucosal healing (Mayo subscore <=1) 39.7% vs 27.7%, p=0.0005
    - Benefit in TNF naïve
  - ADA=VDZ
    - Steroid free remission (trend favor ADA)
    - Adverse events (62.7% vs 69.2%)

- **Conclusion**
  - Vedolizumab superior to adalimumab in clinical and endoscopic efficacy
  - Both safe and well tolerated

Ustekinumab IV Reinduction for Crohn's Patients with Partial Response or Loss of Response

METHODS

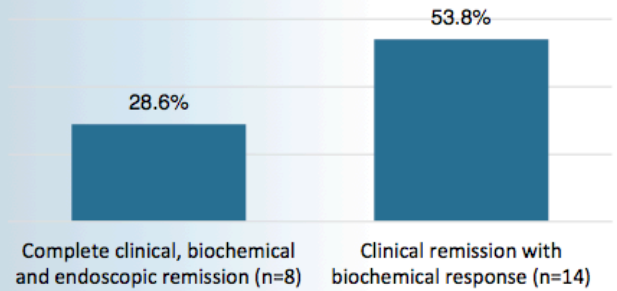
- Multi-center retrospective cohort study
- 28 adult CD patients with prior anti-TNF failure, experiencing clinical or endoscopic LOR or partial response to UST maintenance

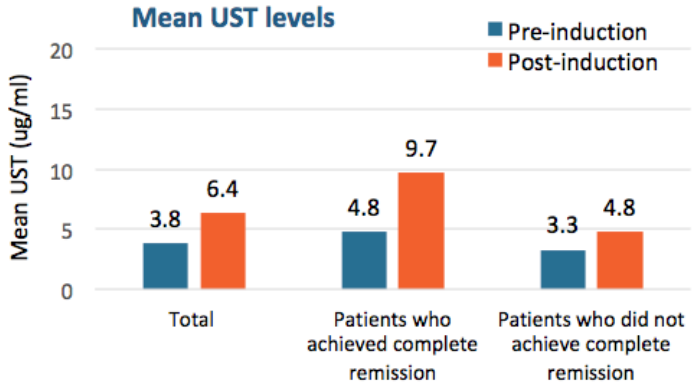
Initial UST induction (IV/SC) → Maintenance UST q 8 or q 4 weeks → **UST IV reinduction for LOR/ partial response** → Clinical, biochemical and/or endoscopic follow up

Median 18.5 months (IQR: 13.0-34.8)

Median 14 weeks (IQR: 13-17) from reinduction to follow-up

Results





CONCLUSION

- **Ustekinumab IV reinduction can be used safely to induce clinical remission and endoscopic response in patients with active Crohn's disease with partial response or loss of response**

UST, ustekinumab; LOR, loss of response.
Heron V, et al. presented at DDW May 2019. Mo1895.

Escalation of Ustekinumab Dosing is Associated with Recapture of Response

Methods:

- Prospective study of 35 CD patients experiencing either a partial response or a secondary LOR to UST
- Reassessed for complete remission after optimization

Results:

- **Optimization in CD patients with a LOR → recapture of response in 69% of patients (Table 1)**
- Mean UST concentration (assessed using liquid phase assay) was higher at baseline & post-treatment in those achieving complete remission (Table 2)
- Baseline fecal calprotectin lower in patients who achieved complete remission vs. those who did not (414 vs 993 ug/g, *P*=0.03).

Table 1: Treatment Intervention & Outcomes

Treatment: N (%)	Complete Remission N (%)	Response N (%)	No response N (%)
No change: 4 (11)	3 (75)	1 (25)	0 (0)
Q8 to Q4 Weeks: 22 (58)	10 (45)	7 (31)	5 (23)
IV/SQ Reinduction: 7 (18)	1 (14)	2 (29)	4 (57)
+IMM: 3 (8)	0 (0)	1 (33)	2 (67)
Changed out of class: 2 (5)	0 (0)	1 (50)	1 (50)

Table 2: UST Concentrations

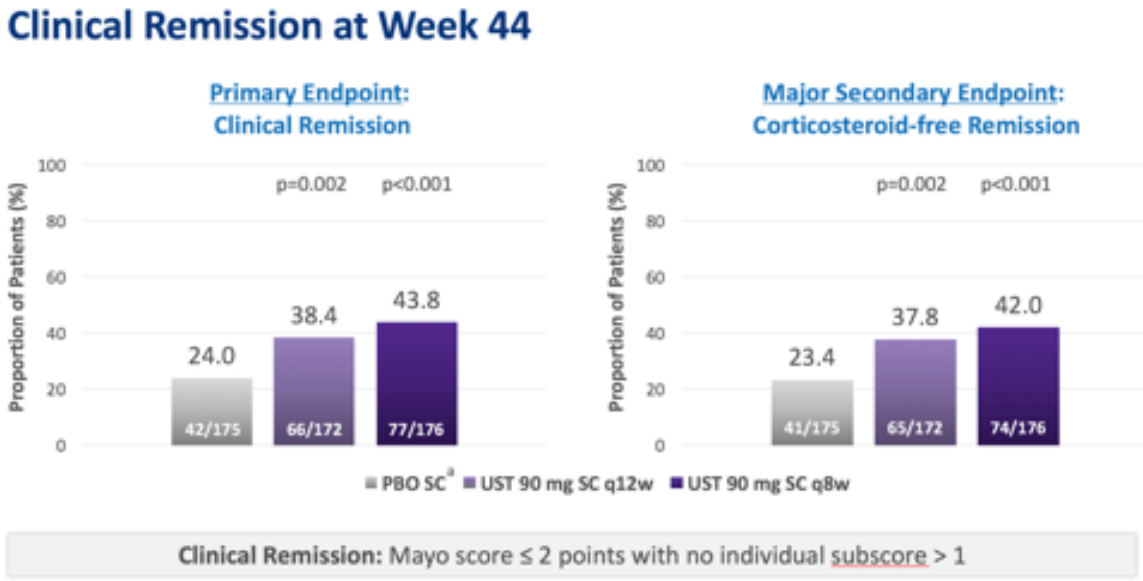
Complete Remission after Optimization?	Mean Baseline UST ug/ml (N)	Mean Post-Tx UST ug/ml (N)
Yes	7.61 (10)	13.04 (8)
No	4.01 (19)	8.57 (14)
P-Value	0.01	0.03

Heron V et al. Presented at DDW. May 2019. Abstract Tu1825.

IMM, immunomodulator; UST, ustekinumab; LOR, loss of response

Ustekinumab is effective and safe as maintenance therapy for UC

- **Methods**
  - Responders from induction study (6mg/kg IV, 130 mg IV, PBO) rerandomized
  - UST 90 mg sc q 8 w vs q12w vs PBO
  - 51% failed prior biologic



Sands B; Tu 833 DDW 2019

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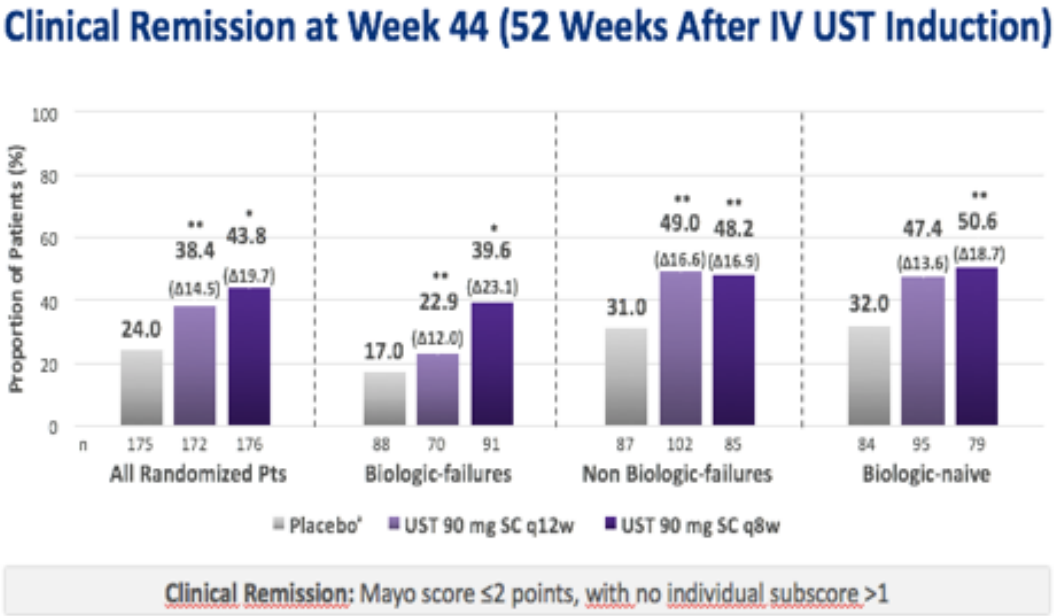

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- **Conclusion**
  - UST 90 mg q8w and q12 sc maintenance therapy
    - Superior to PBO clinical remission, endoscopic and clinical improvement
    - Achieved steroid free remission
    - Effective in biologic failures

Sands B; Tu 833 DDW 2019

New therapies

Molecule	Mechanism	Disease	Phase	Notes
Mirikizumab	Anti-IL23	CD/UC	2	IV (induction), sc
TD-1473	JAK inhibitor	UC	1	po, gut selective
Upadacitinib	JAK1 inhibitor	UC	2	po
Etrasimod	S1P1 inhibitor	UC	2	po

Sands B; 1004 DDW 2019
Peyrin-Biroulet 1006 DDW 2019
Panaccione R 799 DDW 2019
Sandborn W 801 DDW 2019

Risk of Venous Thromboembolism in RA with Tofacitinib – New EMA Warning

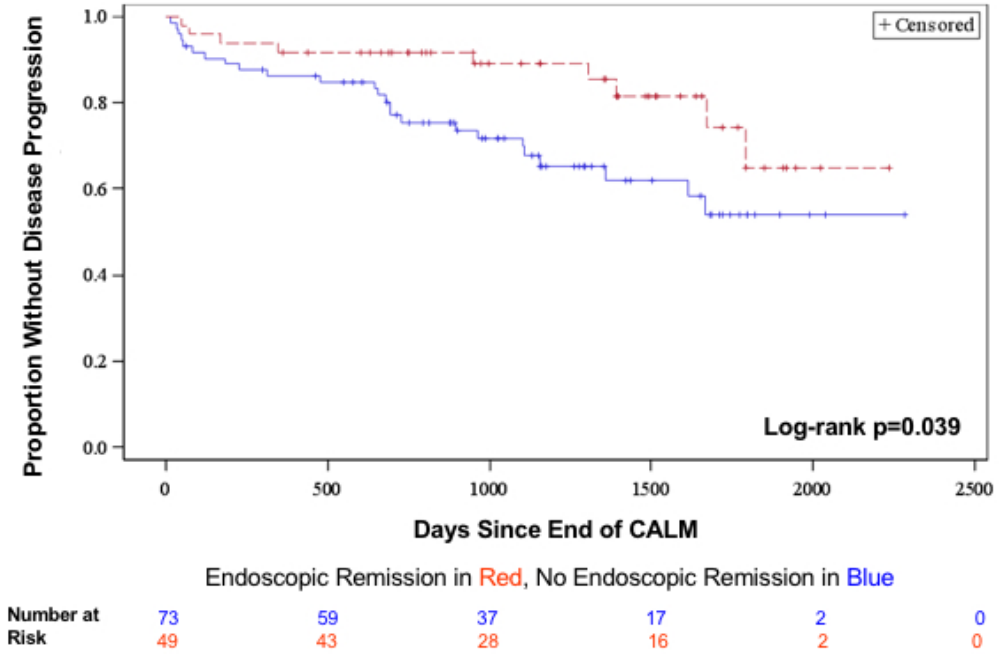
- **RA: 1133 Study – ongoing, open label, study on safety of tofacitinib vs. TNFi designed to assess risk of cardiovascular events**
  - Patients >50 years old with at least one CV risk factor
  - Stable background Methotrexate

- **EMA warning:**
  - Patients on **tofacitinib 10 mg twice daily exhibited higher rates of VTE/PE** compared to TNFi (5 times higher)
  - Recommendation that patients at high risk for VTE/PE (heart failure, cancer, inherited blood clotting disorders, history of VTE/PE, combined hormonal contraceptives, receiving HRT, undergoing major surgery) not receive 10 mg BID dose
  - This was **not seen with 5 mg BID dose**
  - Not described in IBD patients, who are generally younger and with less comorbidities

VTE, venous thromboembolism; PE, pulmonary embolism; CV, cardiovascular; TNFi, TNF inhibitor; HRT, hormone replacement therapy

CALM study follow-up: Crohn's Patients in Early Endoscopic Remission Have Less Progression

- **Methods**
  - 122 patients were stratified by outcomes of CALM study at 1 year
    - Clinical Remission
    - Endoscopic Remission
    - Deep Remission
  - Follow-up after the trial
  - Primary outcome (after trial)
    - New stricture
    - Fistula
    - Hospitalization
    - Surgery



Ungaro R; 1812 DDW 2019

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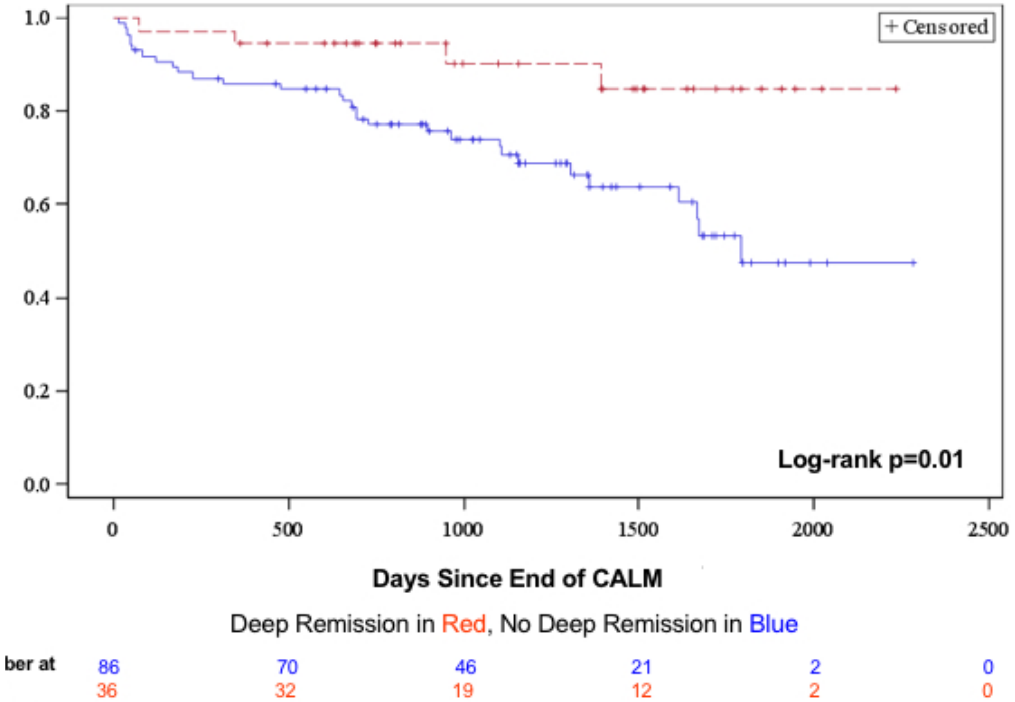

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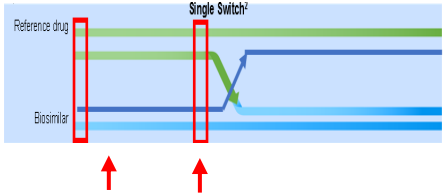
- **Conclusion**
  - Early CD patients who achieve endoscopic or deep remission after 1 year of intensive treatment are significantly less likely to have disease progression over a median of 3 years

Ungaro R; 1812 DDW 2019

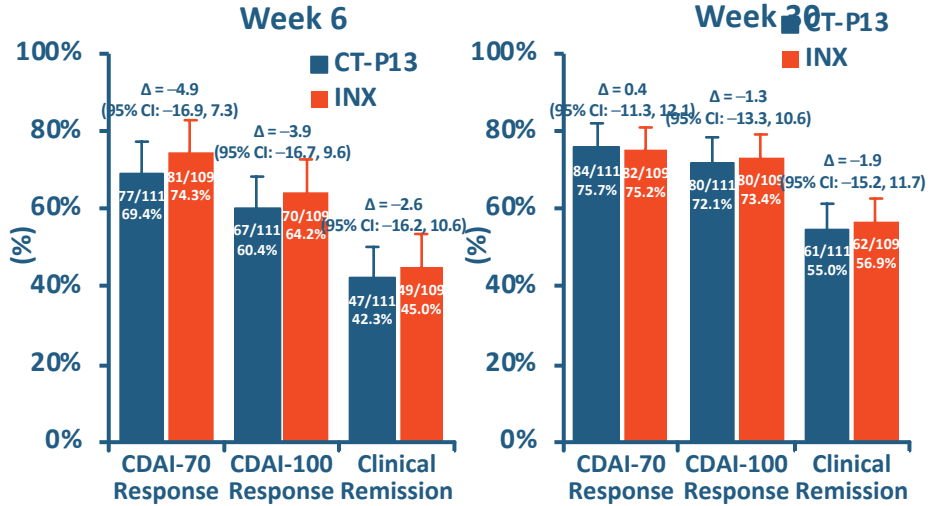
The Efficacy and Safety of CT-P13 Is Similar to Originator Infliximab in CD: Randomized Controlled Trial

- Methods
  - Randomized, double-blind, moderate to severe CD to CT-P13 or originator
  - Multicenter, multinational
  - CDAI-70, 100, remission at week 6. Non inferiority
- Results: 220 pts, 214 completed 6 weeks



Wk 6 (induction) Wk 30 (maintenance)

Efficacy: Clinical Response and Remission (ITT)

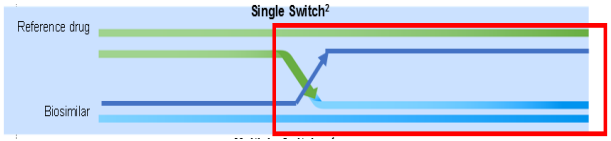


- No difference in FCP/CRP at week 6 and later
- No difference in adverse events
- No difference in drug level or ATI

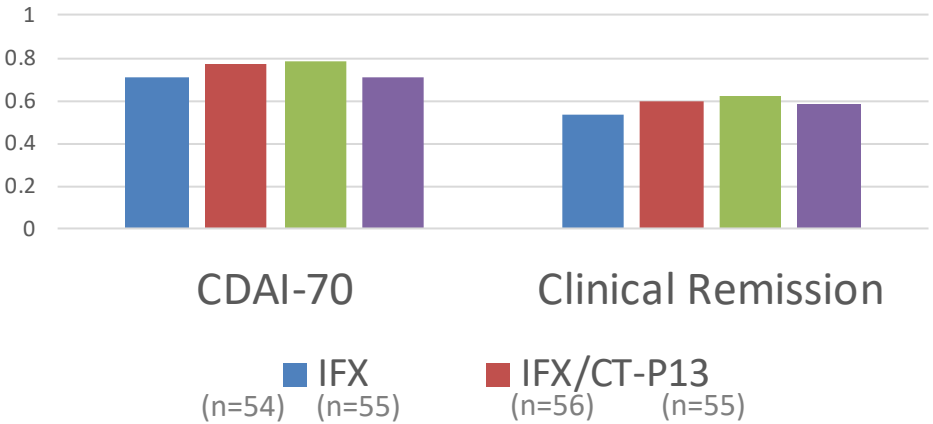
Kim et al. Lancet 2019.

Phase 3 RCT Comparing CT-P13 with Innovator IFX in Active CD-1 year maintenance and switching results

- Methods
  - At week 30, patients randomized to stay on treatment, switch CT-P13→IFX, siwthch IFX→CT-P13
  - CDAI-70, remission, SIBDQ, adverse events, immunogenicity at week 54 (6 months after switch)
- Results: of original 220 pts, 166 completed study at week 54



Week 54 Outcomes (24 weeks after switch)



- No difference IBDQ
- No difference adverse events
- No difference infusion reactions (1.8% CT-P13→IFX; 0% CT-P13→IFX

Kim et al. Lancet 2019.

- Kim et al. Phase 3 Randomized Control Trial to Compare Biosimilar Infliximab (CT-P13) with Innovator Infliximab in Patients with Active Crohn's Disease: 1 year maintenance and switching results