Association Between Histologic Indices and Ulcerative Colitis Activity Measures Among Patients in the HICKORY (Etrolizumab) Open-Label Induction Cohort

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Disclosures

- Consultant: AbbVie, Allergan, Amgen, Biogen, Bristol-Myers Squibb, Celgene, Celltrion, Ferring, Hospira, Gilead, Janssen, Lilly, MSD, Mundipharma, Mylan, Pfizer, Roche, Samsung Bioepis, Sandoz, Sofar, Takeda
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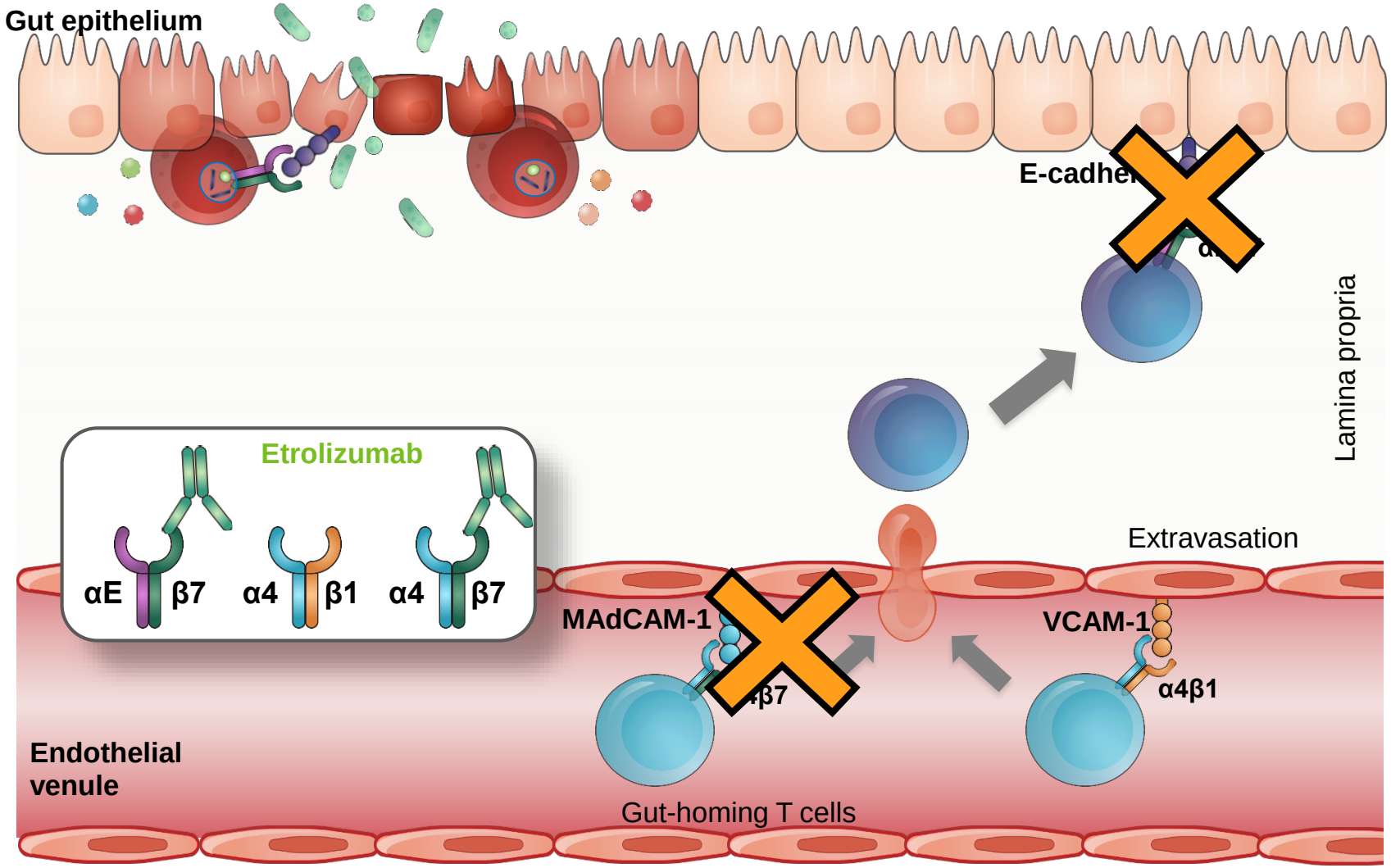
Introduction

- Cross-sectional analyses in UC have demonstrated at best a moderate association between histologic and clinical or endoscopic measures of disease activity[1,2]
- Some longitudinal studies in UC have suggested that histologic outcomes, such as the absence of neutrophilic inflammation, may be better predictors of long-term clinical outcomes than endoscopic measures[3-7]
- This post hoc analysis evaluates the correlation between histologic changes and established disease activity measures using data from the open-label induction cohort of the ongoing HICKORY Phase 3 study evaluating etrolizumab in aTNF-experienced patients with moderate to severe UC[8]

aTNF, anti–tumor necrosis factor; UC, ulcerative colitis.

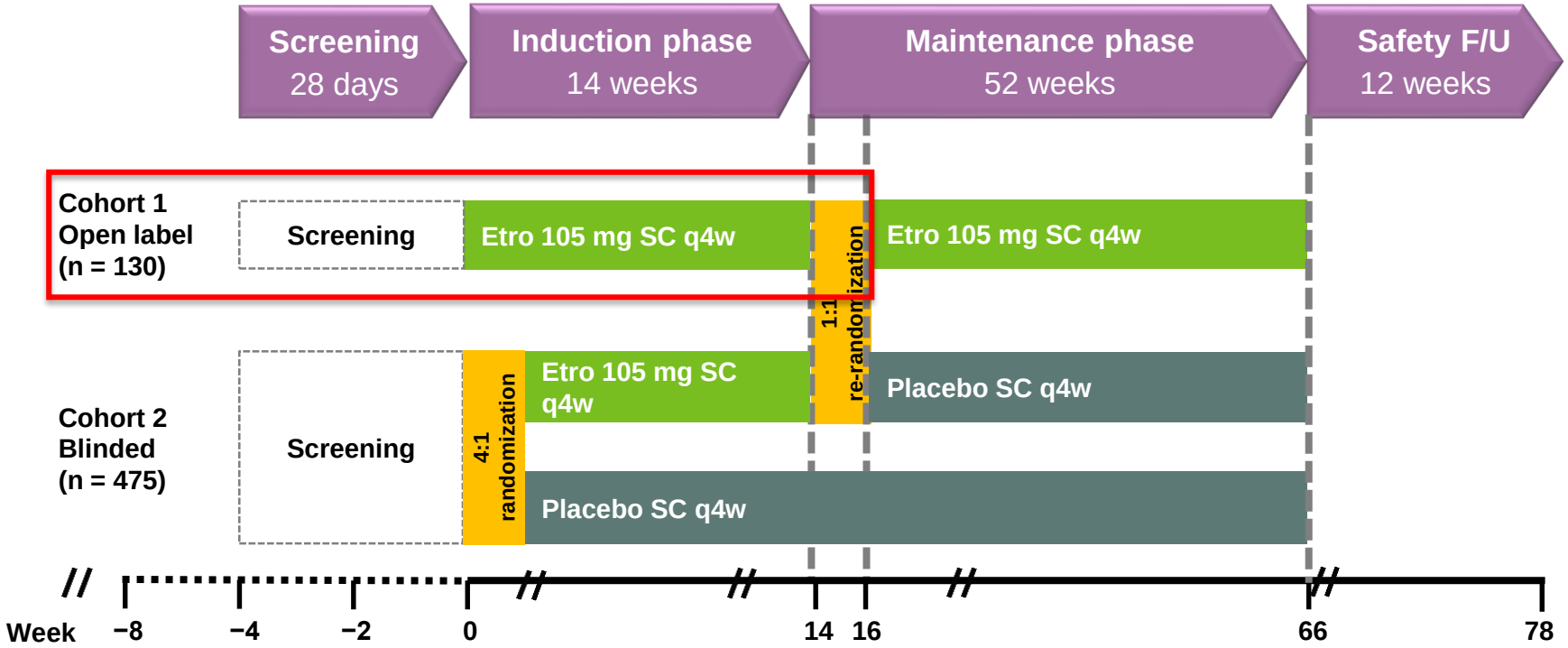
1. Lemmens B, et al. *Inflamm Bowel Dis*. 2013;19(6):1194-201. 2. Fluxa D, et al. *J Dig Dis*. 2017;18(11):634-41. 3. Bessissow T, et al. *Am J Gastroenterol*. 2012;107(11):1684-92. 4. Bryant RV, et al. *Gut*. 2016;65(3):408-14. 5. Christensen B, et al. *Clin Gastroenterol Hepatol*. 2017;15(10):1557-64. 6. Feagins LA, et al. *Inflamm Bowel Dis*. 2013;19(7):1477-82. 7. Zenlea T, et al. *Am J Gastroenterol*. 2016;111(5):685-90. 8. ClinicalTrials.gov, NCT02100696.

Etrolizumab, an Anti-β7 Antibody, Blocks T Cell Trafficking and Retention



Adapted from Marsal J, Agace WW. *J Int Med*. 2012;272(5):411-429; Vermeire S et al. *Lancet*. 2014;384(9940):309-318.

HICKORY Is an Ongoing Phase 3 Study of Etrolizumab in Patients With Moderate-to-Severe UC Who Were aTNF Experienced



Previously reported preliminary results from the OLI cohort of HICKORY showed that etrolizumab was well tolerated and resulted in improvement in clinical, endoscopic, and histologic outcomes[1-4]

aTNF, anti–tumor necrosis factor α; F/U, follow-up; OLI, open-label induction; q4w, every 4 weeks; SC, subcutaneous; UC, ulcerative colitis.
ClinicalTrials.gov ID: NCT02100696.

1. Peyrin-Biroulet L, et al. Presented at United European Gastroenterology Week, 2017. LB02. 2. Peyrin-Biroulet L, et al. *J Crohns Colitis.* 2017;11(suppl 1):S6-7. 3. Peyrin-Biroulet L, et al. *Gastroenterology*. 2017;152(5):S603. 4. Rubin DT, et al. *Gastroenterology*. 2018;154(6):S1366.

Histologic Assessments[1]

- Biopsies were obtained at **baseline** and **week 14** using flexible sigmoidoscopy from the most inflamed colonic area within 20-40 cm from the anal verge

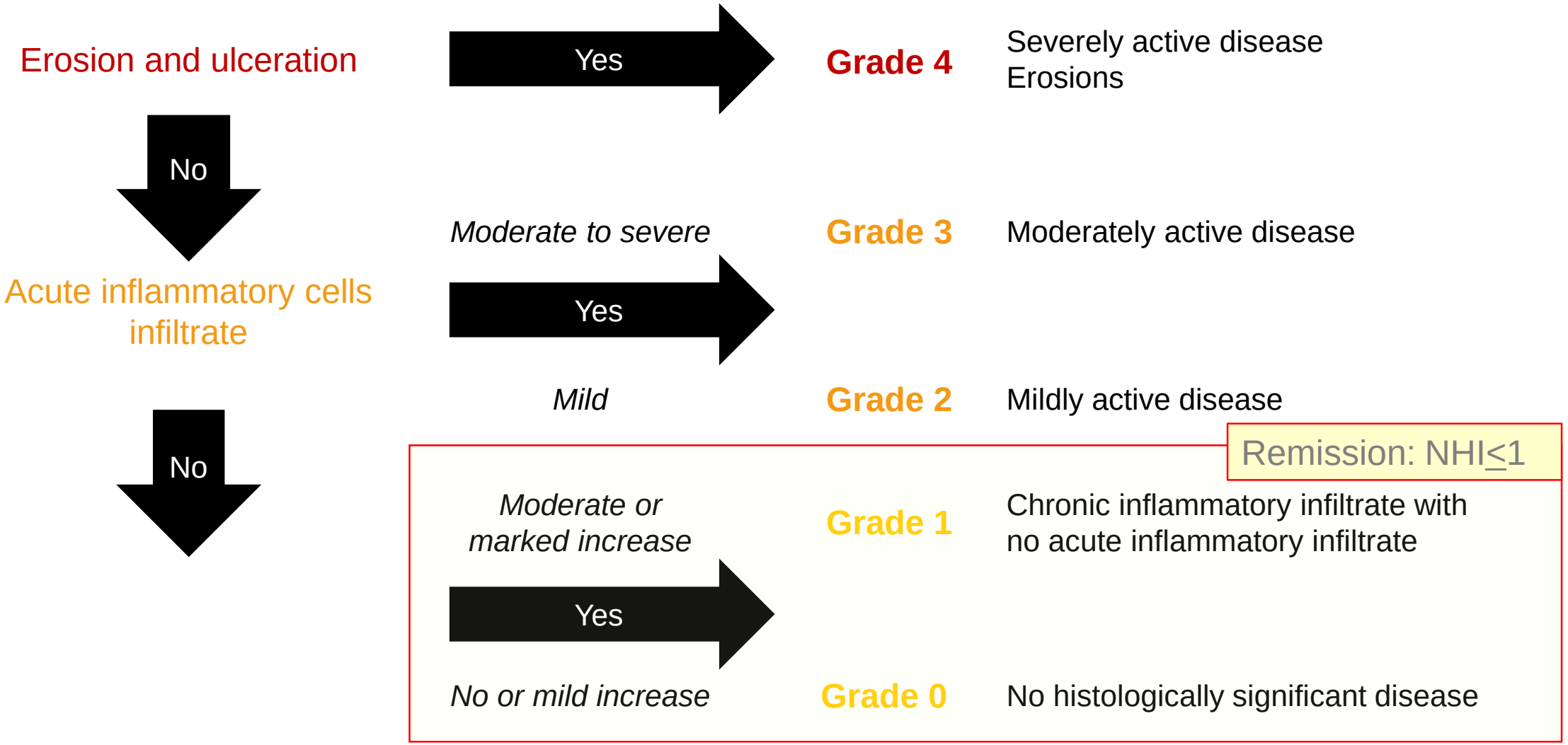
- The hematoxylin and eosin–stained biopsy slide images were scored by central reader using the NHI(Nancy histological Index) and RHI (Robarts histopathology index)

- Week 14 histologic outcomes were assessed for the presence or absence of neutrophils[a]
  - Neutrophilic resolution was defined as NHI ≤ 1 or as RHI ≤ 3 plus Geboes subgrades 2B.0/3.0

[a]Histologic disease activity in UC is marked by the presence of neutrophils within the crypt epithelium and the crypt lumen.[2]

1. Peyrin-Biroulet L, et al. Presented at 14th Congress of ECCO (European Crohn's and Colitis Organisation); March 6-9, 2019; Copenhagen, Denmark. P136. 2. Bryant RV, et al. *Gut*. 2016;65(3):408-14.

The Nancy Histologic Index



Marchal-Bressenot A et al. *Gut.* 2017;66(1):43-9.

The Robarts Histopathology Index

Remission: RHI score ≤ 3 and Geboes subgrades 2B.0 and 3.0.

Marker	Geboes subgrade	RHI Rating	RHI Multiplier
Chronic inflammatory infiltrate	1.0 No increase	0	1
	1.1 Mild but unequivocal increase	1	
	1.2 Moderate increase	2	
	1.3 Marked increase	3	
Lamina propria neutrophils	2B.0 None	0	2
	2B.1 Mild but unequivocal increase	1	
	2B.2 Moderate increase	2	
	2B.3 Marked increase	3	
Neutrophils in epithelium	3.0 None	0	3
	3.1 < 5% of crypts involved	1	
	3.2 < 50% of crypts involved	2	
	3.3 > 50% of crypts involved	3	
Erosion or ulceration	5.0 None	0	5
	5.1 Recovering epithelium with adjacent inflammation	1	
	5.2 Probably erosion, focally stripped	1	
	5.3 Unequivocal erosion	2	
	5.4 Ulcer or granulation tissue	3	
		RHI RANGE	0–33

RHI = 1 × (chronic inflammatory infiltrate) + 2 × (lamina propria neutrophils) + 3 × (neutrophils in epithelium) + 5 × (epithelial erosion or ulceration).
Mosli MH et al. *Gut.* 2017;66(1):50-8.

Baseline Characteristics of HICKORY OLI with NHI, RHI, and MCS-Evaluable Patients

Demographics and baseline characteristics were similar to the full OLI

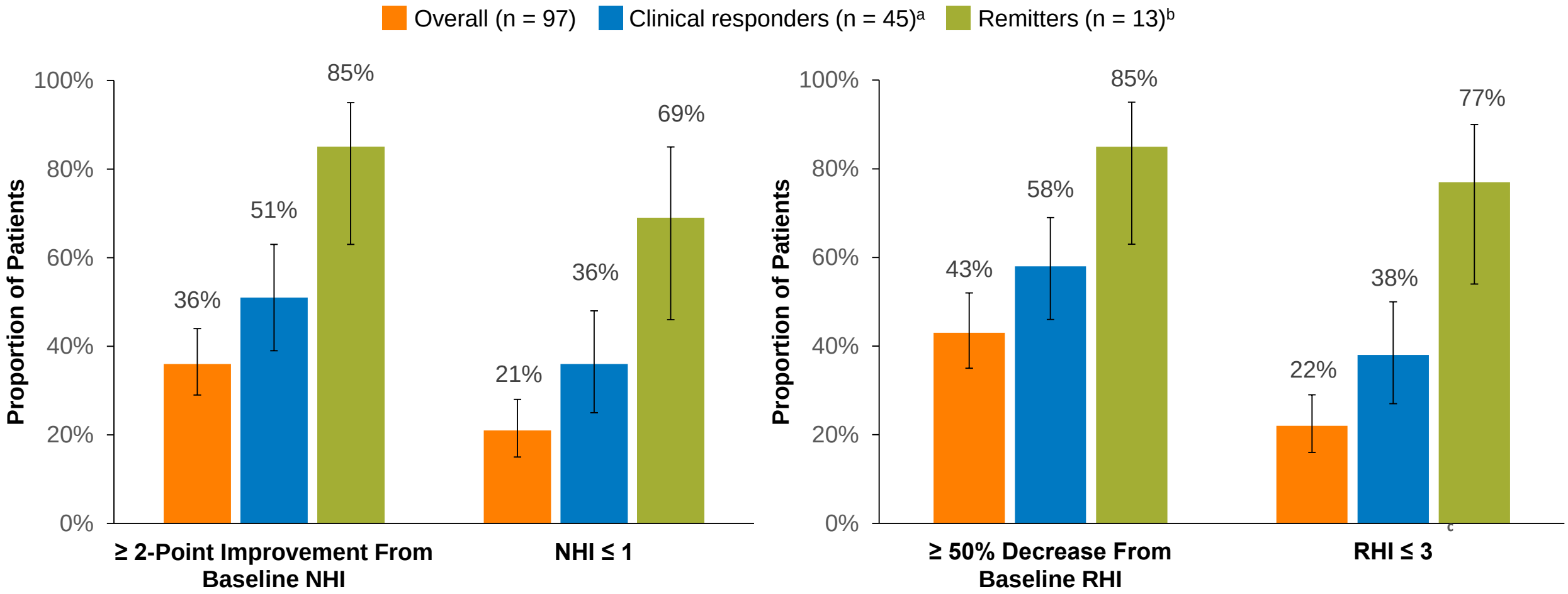
Baseline Demographics and Disease Characteristics	HICKORY OLI Patients with Evaluable NHI and RHI (n = 97)	HICKORY OLI Patients Full Cohort (n = 130)[1]
Age, median (range), years	40 (18–74)	37.5 (18–74)
Sex, male, %	61	60
Race, white, %	83	84
BMI, median (range), kg/m^2	25 (16–49)	25 (16–49)
UC duration, median (range), years	6.1 (1–40)	5.9 (0.6–40.1)
Extensive/pancolitis, %	43	51
CS use at baseline, %	49	49
IS use at baseline, %	36	35
MCS, mean (range)	9.3 (7–12)	9.3 (6–12)
ES, mean (range)	2.7 (2–3)	2.7 (2–3)
C-reactive protein, median (range), mg/L	6.9 (0.2–143.0)	6.7 (0.2–143.0)
Fecal calprotectin,[a] median (range), µg/mL	1,796 (167–23,603)	1,775 (108–23,603)
NHI, mean (range)	3.0 (2–4)	n/a
RHI, mean (range)	19.9 (5–33)	n/a

BMI, body mass index; CS, corticosteroid; ES, endoscopic score; IS, immunosuppressant; SD, standard deviation.

[a]12 patients had missing fecal calprotectin data at baseline.

1. Peyrin-Biroulet L, et al. *United European Gastroenterology Week,* 2017. LB02.

HICKORY OLI: NHI- and RHI-Based Outcome Rates at Week 14



MCS, Mayo Clinic score; NHI, Nancy histological index; OLI, open-label induction; RB, rectal bleeding score; RHI, Robarts histopathology index.
Bars correspond to 90% confidence intervals for the rates shown.
[a]Clinical response was defined as a ≥ 3-point and 30% reduction of MCS from baseline and ≥ 1-point decrease in RB or RB ≤ 1 (based on integer 3-day maximum RB).
[b]Remission was defined as a MCS ≤ 2, with individual subscores ≤ 1 and an RB subscore of 0.
[c]RHI ≤ 3 and Geboes subgrades 2B.0 and 3.0.
Rubin DT, et al. *Gastroenterology.* 2018;154(6):S1366. Presented at DDW (Digestive Disease Week) 2018; Washington, DC, USA. Poster # Tu2006.

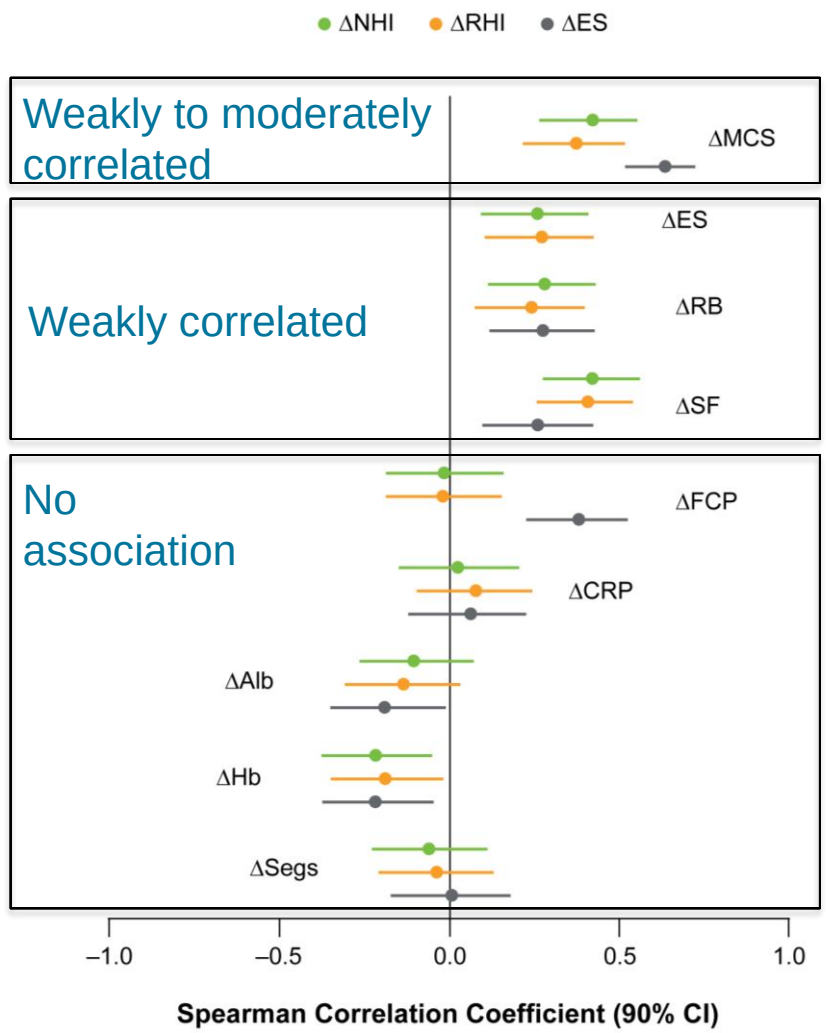
Patients Treated With Etrolizumab Demonstrated Improved Histologic, Endoscopic, and Symptomatic Outcomes

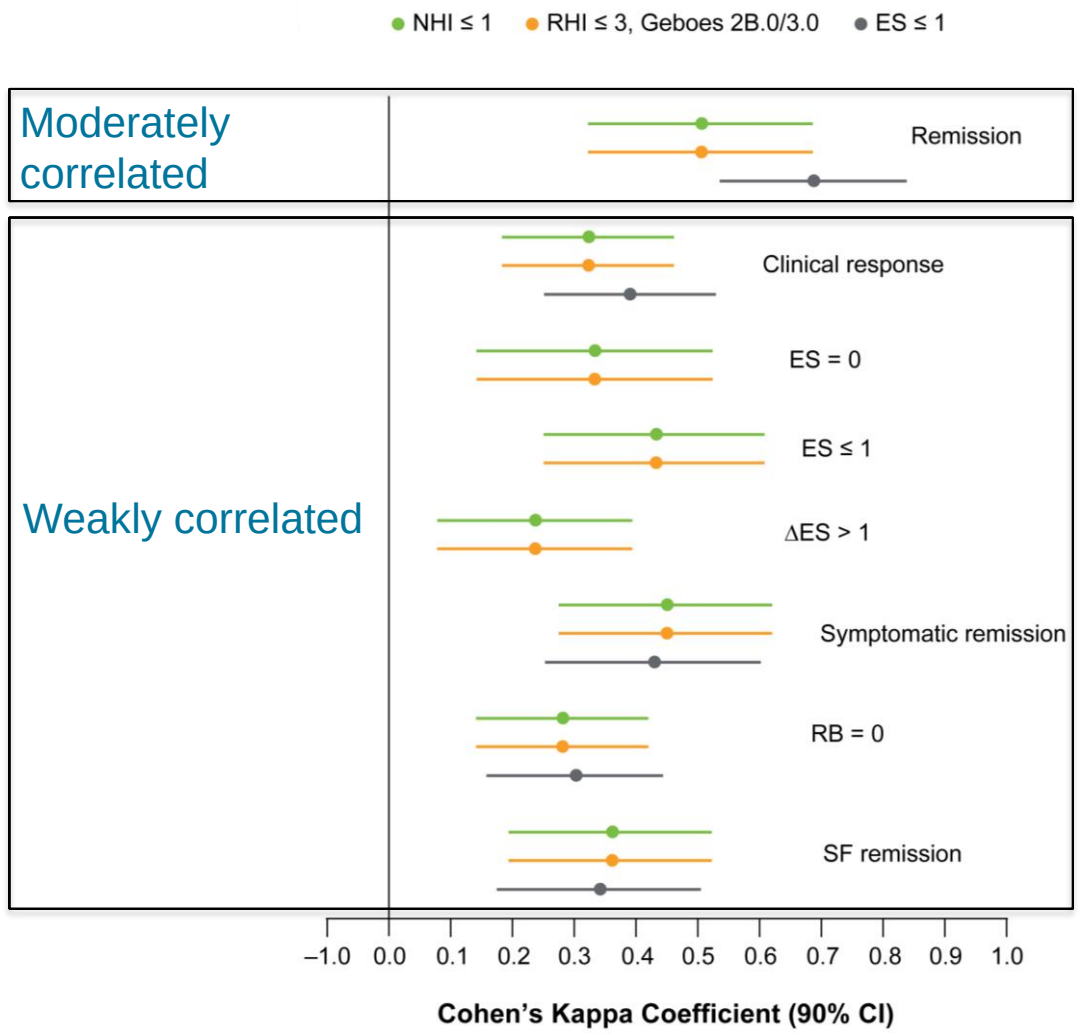
		Endoscopic Outcomes				Symptomatic Outcomes	
		Endoscopic Remission (ES = 0)		Endoscopic Improvement (ES ≤ 1)		Symptomatic Remission	
Histologic outcomes	n (%)	Not Achieved n (%)	Achieved n (%)	Not Achieved n (%)	Achieved n (%)	Not Achieved n (%)	Achieved n (%)
N (%)	97 (100)	89 (92)	8 (8)	75 (77)	22 (23)	65 (67)	32 (33)
NHI ≤ 1	21 (22)	15 (17)	**6 (75)**	9 (12)	**12 (55)**	7 (11)	14 (44)
RHI ≤ 3, Geboes 2B.0, 3.0	21 (22)	15 (17)	**6 (75)**	9 (12)	**12 (55)**	7 (11)	14 (44)

Symptomatic remission: RB = 0 and either SF = 0 or SF remission
RB remission: RB = 0
SF remission: reduction in SF ≥ 1 and SF ≤ 1
Clinical remission: MCS ≤ 2, and remaining individual subscores ≤ 1.

ES, endoscopic score; NHI, Nancy histological index; RHI, Robarts histopathology index.
Peyrin-Biroulet L, et al. Presented at 14th Congress of ECCO (European Crohn's and Colitis Organisation); March 6-9, 2019; Copenhagen, Denmark. P136.

Weak to No Agreement Between Changes in Histologic Scores and Changes in Laboratory Results or Symptoms Was Seen at Week 14





Δ, change from baseline to week 14; Alb, albumin; CRP, C-reactive protein; ES, endoscopic score; FCP, fecal calprotectin; Hb, hemoglobin; MCS, Mayo Clinic score; NHI, Nancy histological index; RB, rectal bleeding score; RHI, Robarts histopathology index; Segs, segmented neutrophils; SF, stool frequency.
Remission = MCS ≤ 2, RB = 0, remaining individual subscores ≤ 1; clinical response = ΔMCS ≥ max (3, 0.3 baseline MCS) and either ΔRB ≥ 1 or RB ≤ 1; symptomatic remission = RB = 0 and either SF = 0 or SF remission; SF remission = ΔSF ≥ 1 and SF ≤ 1.
Peyrin-Biroulet L, et al. Presented at 14th Congress of ECCO (European Crohn's and Colitis Organisation); March 6-9, 2019; Copenhagen, Denmark. P136.

Conclusions

- Consistent with previous observational studies, correlation between histologic and endoscopic scores at week 14 was weak to moderate[1-3]
- Etrolizumab-treated patients with active histology at baseline experienced an improvement in histologic disease activity by week 14[4]
  - At week 14, 55% and 75% of patients who achieved endoscopic improvement and endoscopic remission, respectively, achieved neutrophilic resolution based on either NHI or RHI/Geboes

NHI, Nancy histological index; RHI, Robarts histopathology index.

1. Lemmens B, et al. *Inflamm Bowel Dis.* 2013;19(6):1194-201. 2. Bryant RV, et al. *Gut.* 2016;65(3):408-14. 3. Christensen B, et al. *Clin Gastroenterol Hepatol.* 2017;15(10):1557-64.
4. Peyrin-Biroulet L, et al. Presented at 14th Congress of ECCO (European Crohn's and Colitis Organisation); March 6–9, 2019; Copenhagen, Denmark. P136.