GUILD

Gastroenterology Updates
IBD • Liver Disease

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PSC: New Therapies and What is in the Pipeline

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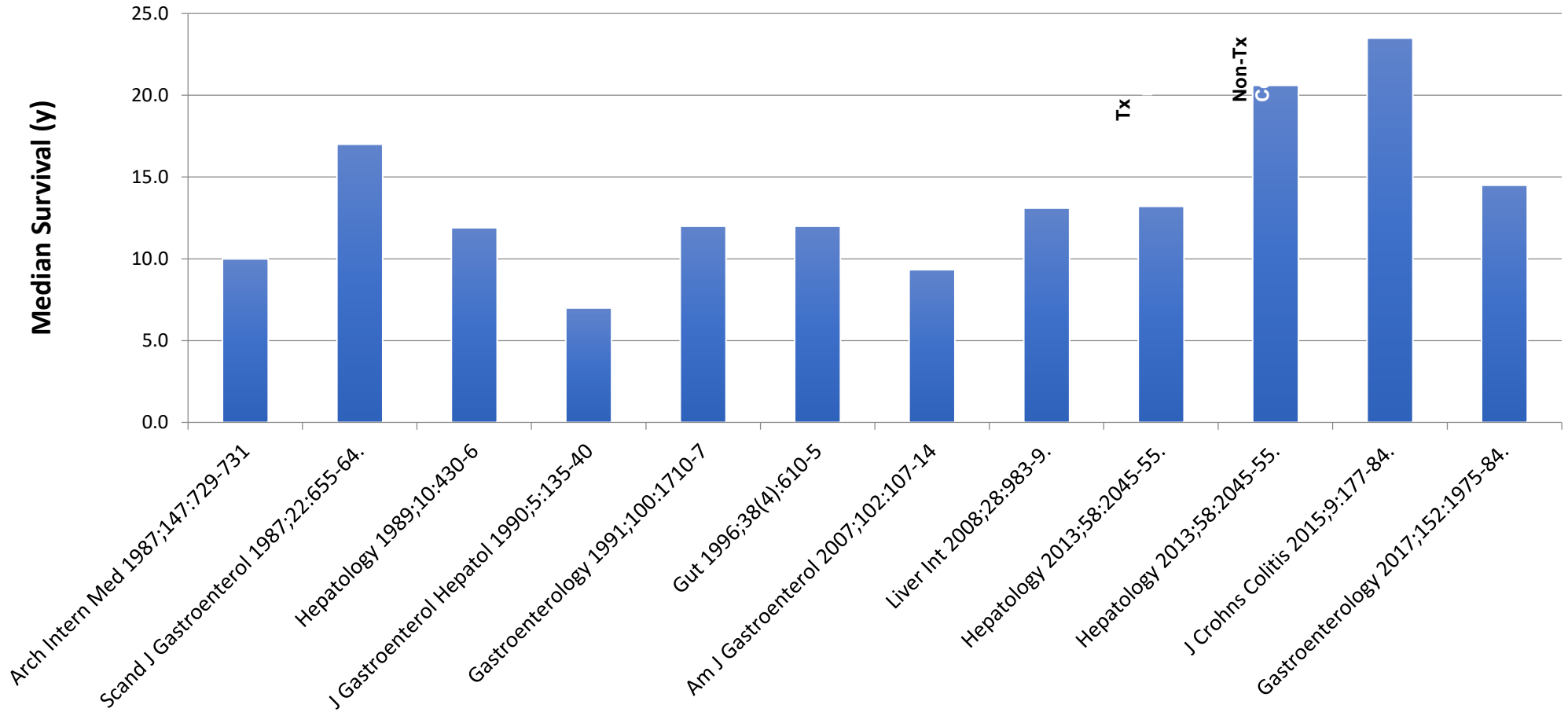
Disclosures

- Research:
  - Enanta, GSK, Gilead, HighTide, Genfit, Allergan, Novartis, Intercept, La Jolla, Conatus, Galectin, CymaBay, NGM Bio, Galectin,
- Consultant;
  - Genfit, HighTide, Gilead, Intercept, Enanta, Protagonist, La Jolla, Merck, Abbvie, Prometic, Corcept, Assembly BioSciences, Boeringer Ingelheim, IQVIA, Perspectum, WebMD, Callidtas
- Honoraria:
  - Gilead, Abbvie, Intercept,
- Royalties:
  - UpToDate

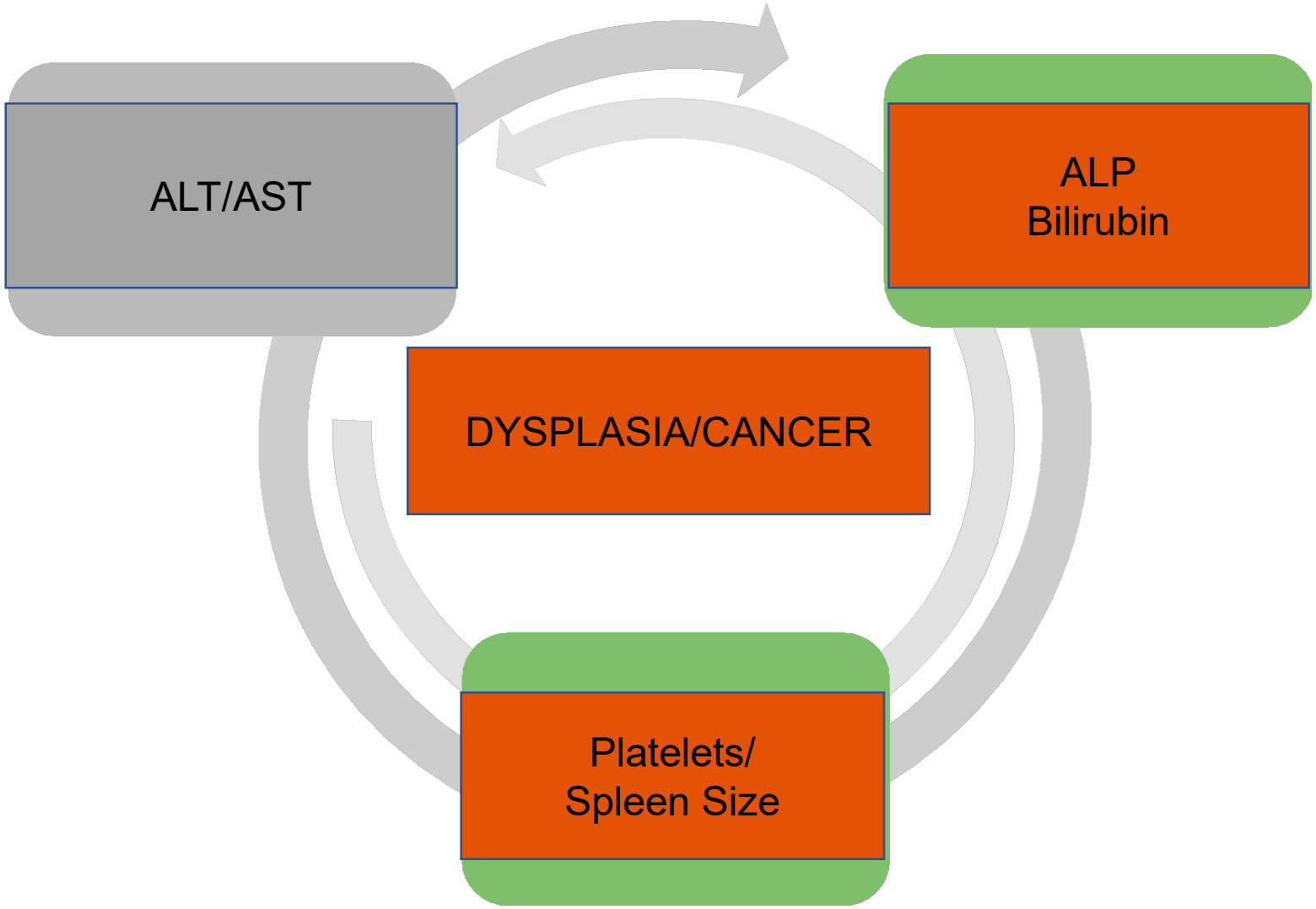
Treatment Considerations in PSC

- Assessment of stage and risk
- Noninvasive tools are limited
- Effect of IBD and risk of colon CA
- Risk of cholangitis, cholangiocarcinoma
  - May confound evaluation of efficacy and safety
- Limitations of liver biopsy
- Pathophysiology remains unclear
- No proven effective therapy

TRANSPLANT-FREE SURVIVAL IN PSC



The Cycle of Inflammation, Cholestasis, and Fibrosis



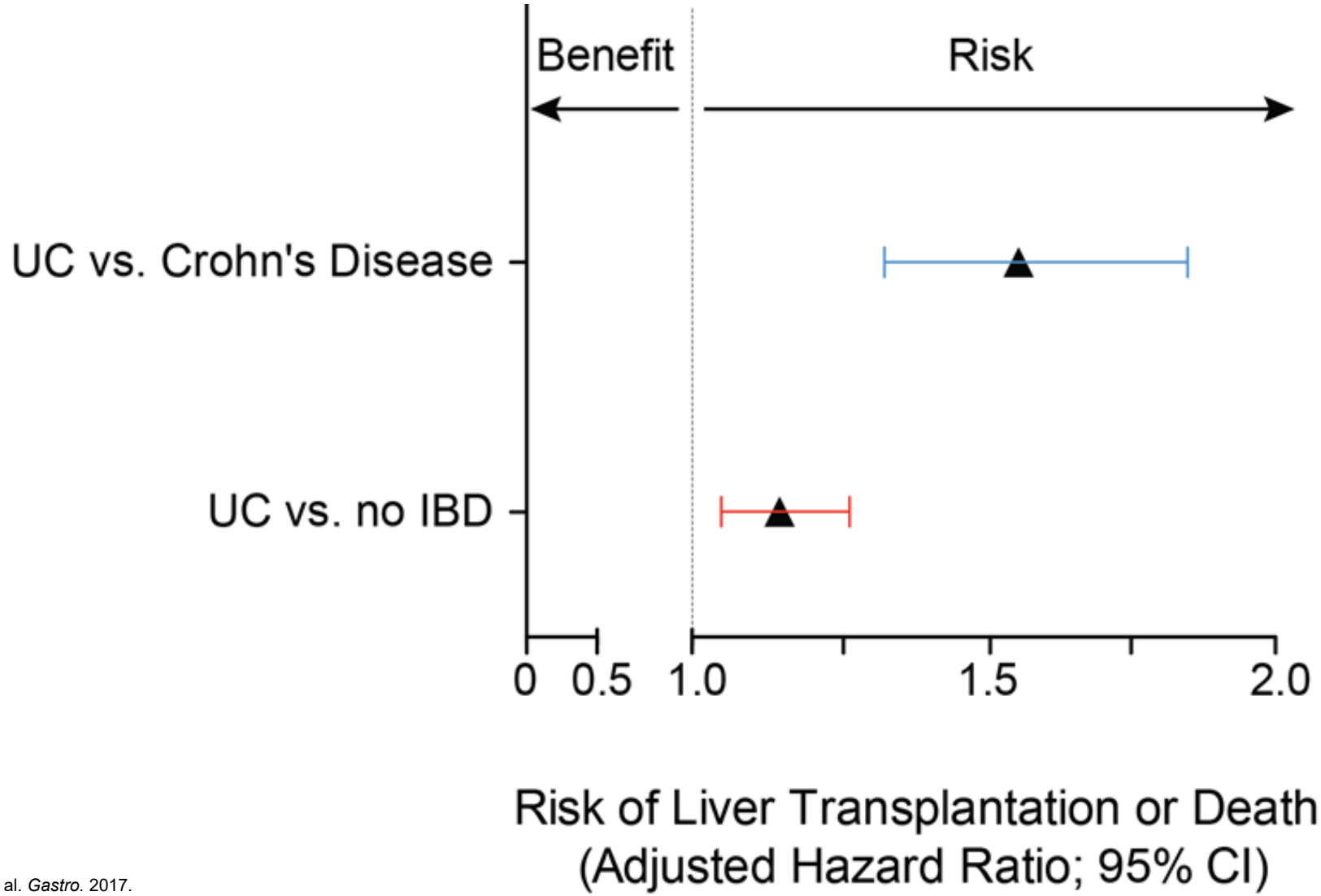
Current Licensed Therapies for PSC Remain Absent

Ursodeoxycholic Acid (UDCA) Established anti-cholestatic	New Generation Therapy
▲ Improves liver biochemistry	▲ Industry engagement
▼ No change in transplantation rates	▲ Multiple Phase 2 and now Phase 3 trials
▼ No survival benefit	▼ Unclear what end-points are meaningful
▼ Toxicity at 28-30mg/kg/day	▼ Reliance on liver biopsy
	▼ Cholangiocarcinoma not addressed

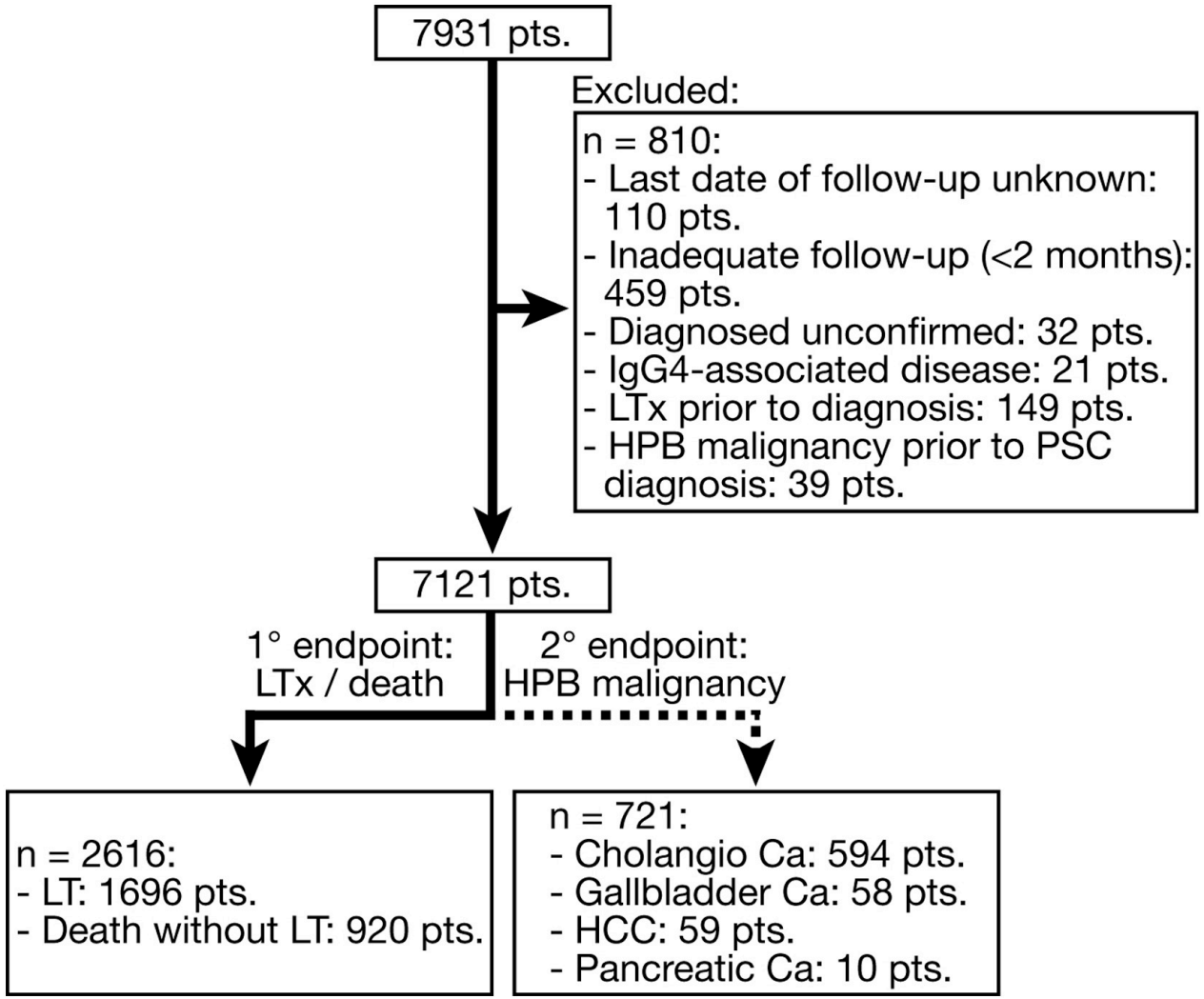
Ongoing need for:

Rational, targeted next-generation therapy
Improved efficacy
Better tolerance

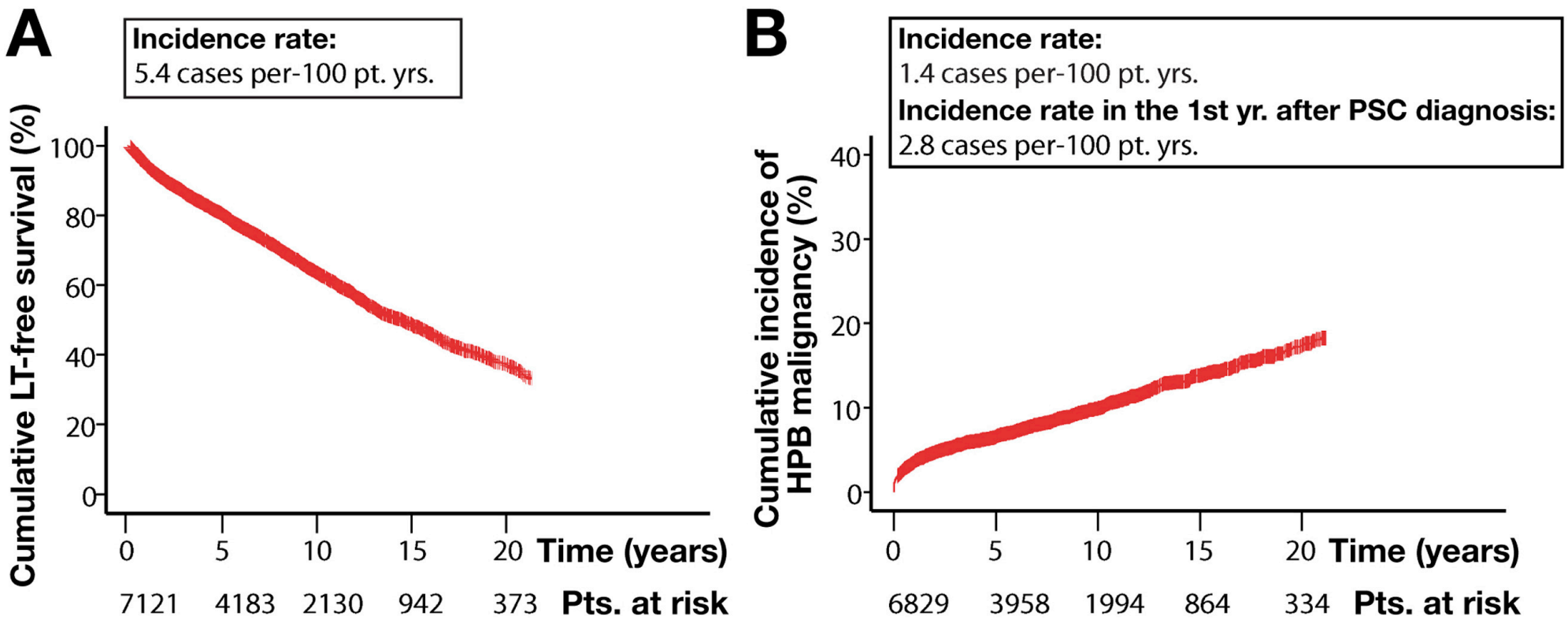
Pre-transplant Clinical Course Is Impacted by IBD Phenotype



Weismueller, Trivedi, et al. *Gastro.* 2017.

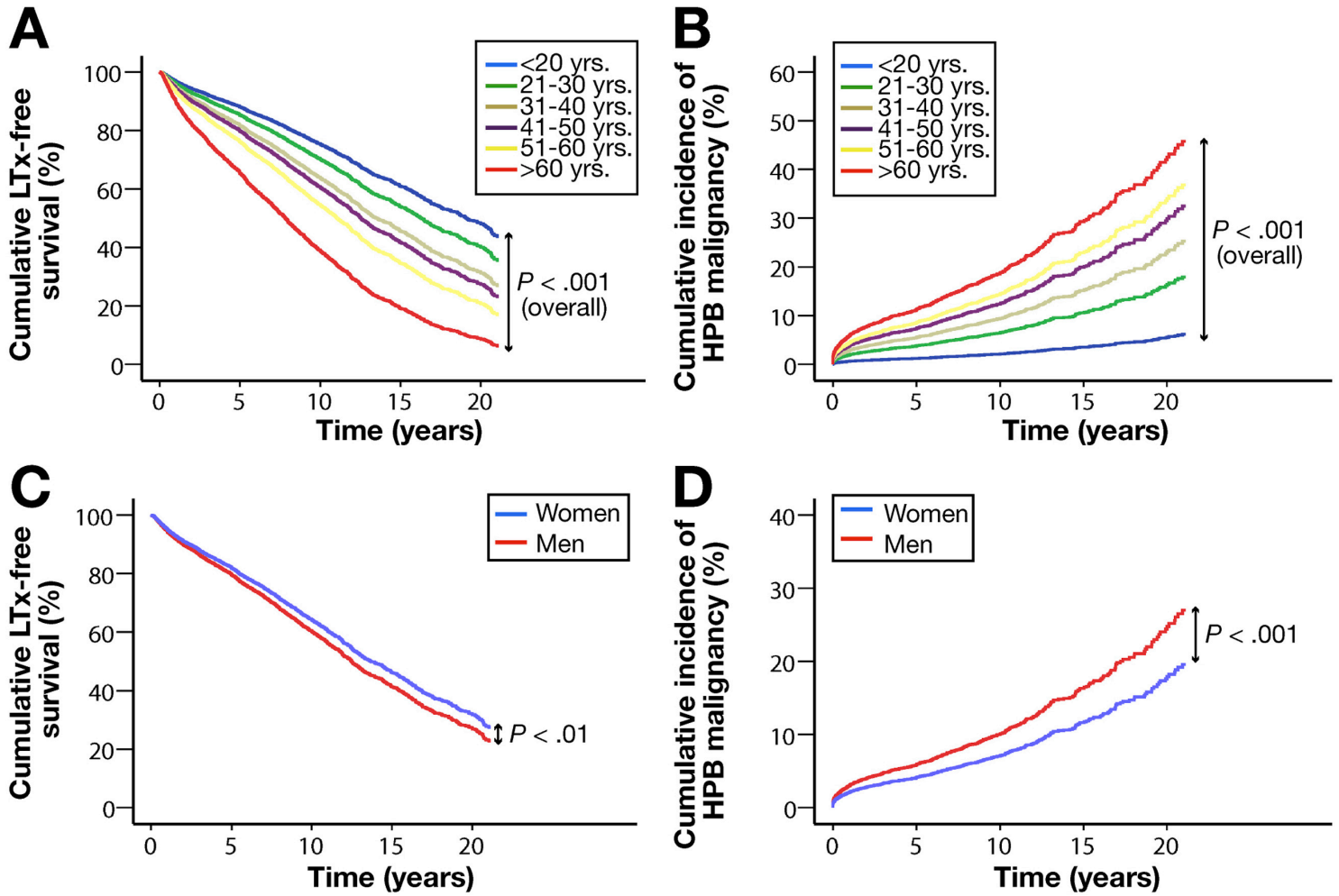


Gastroenterology 2017



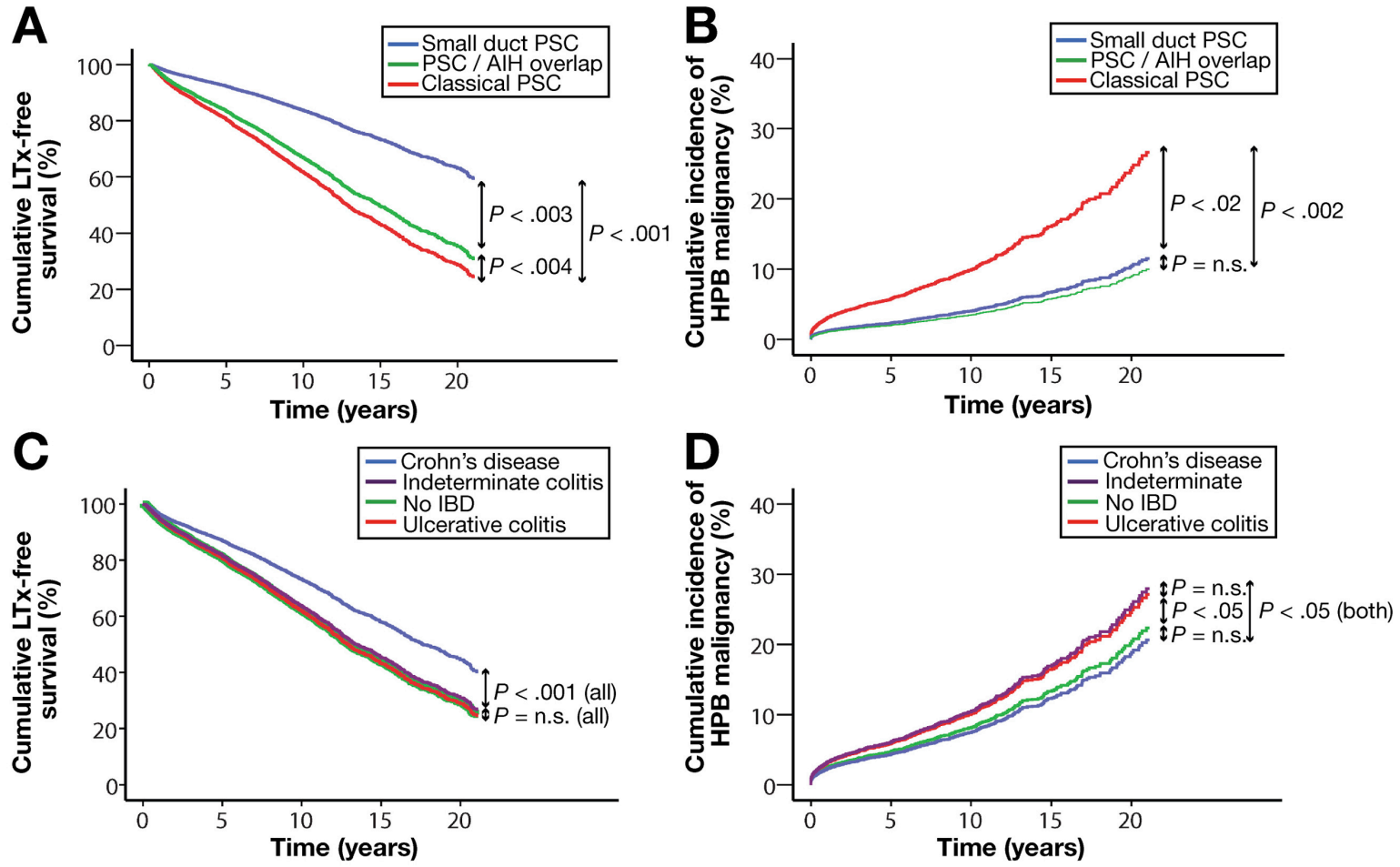
Gastroenterology 2017

Patient age and gender and clinical outcome



Gastroenterology 2017

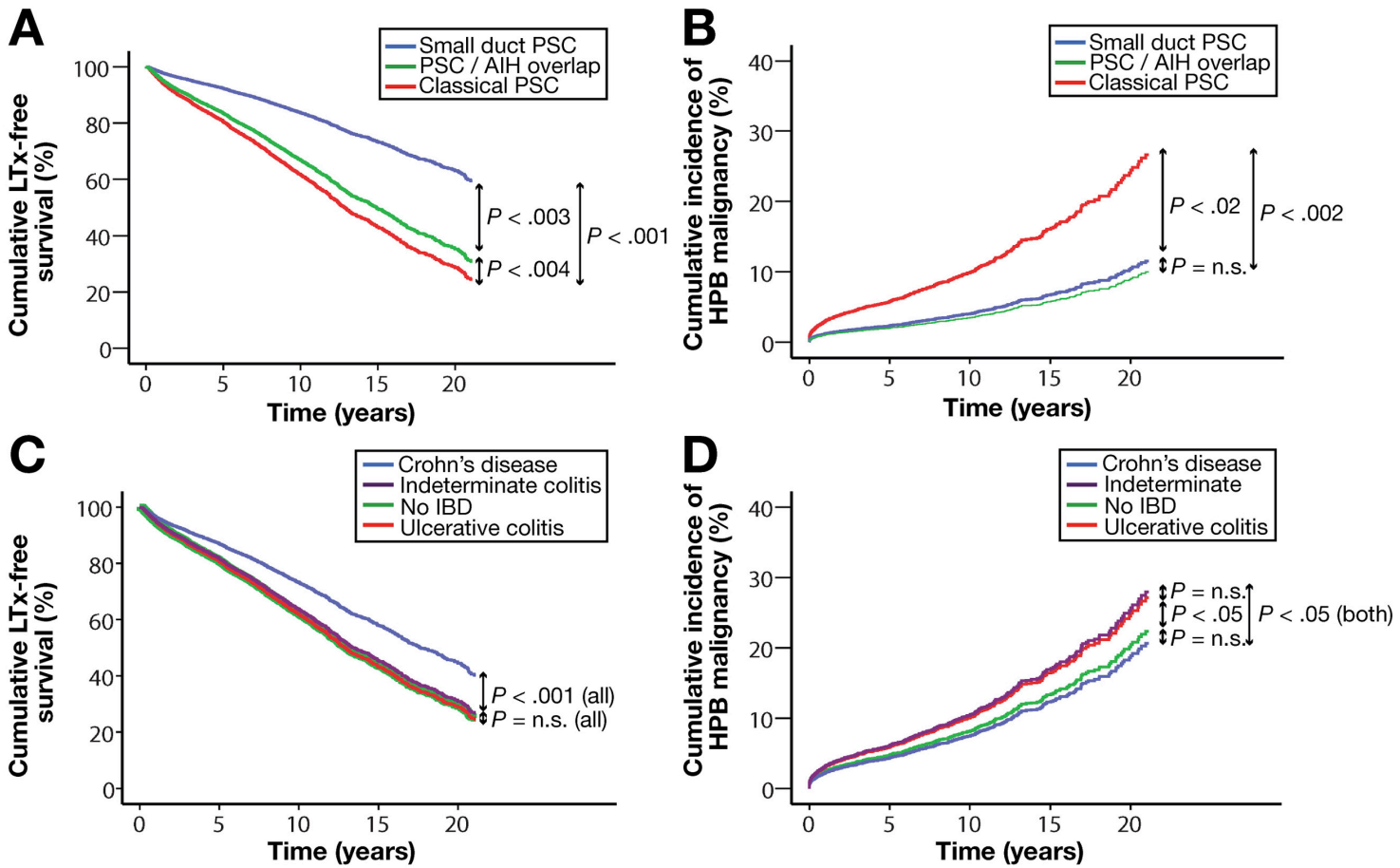
Cumulative Incidence of Clinical Events



38% of HPB Malignancies in first year after diagnosis

Gastroenterology 2017

Impact of variant PSC sub-phenotypes and IBD phenotypes on clinical outcome

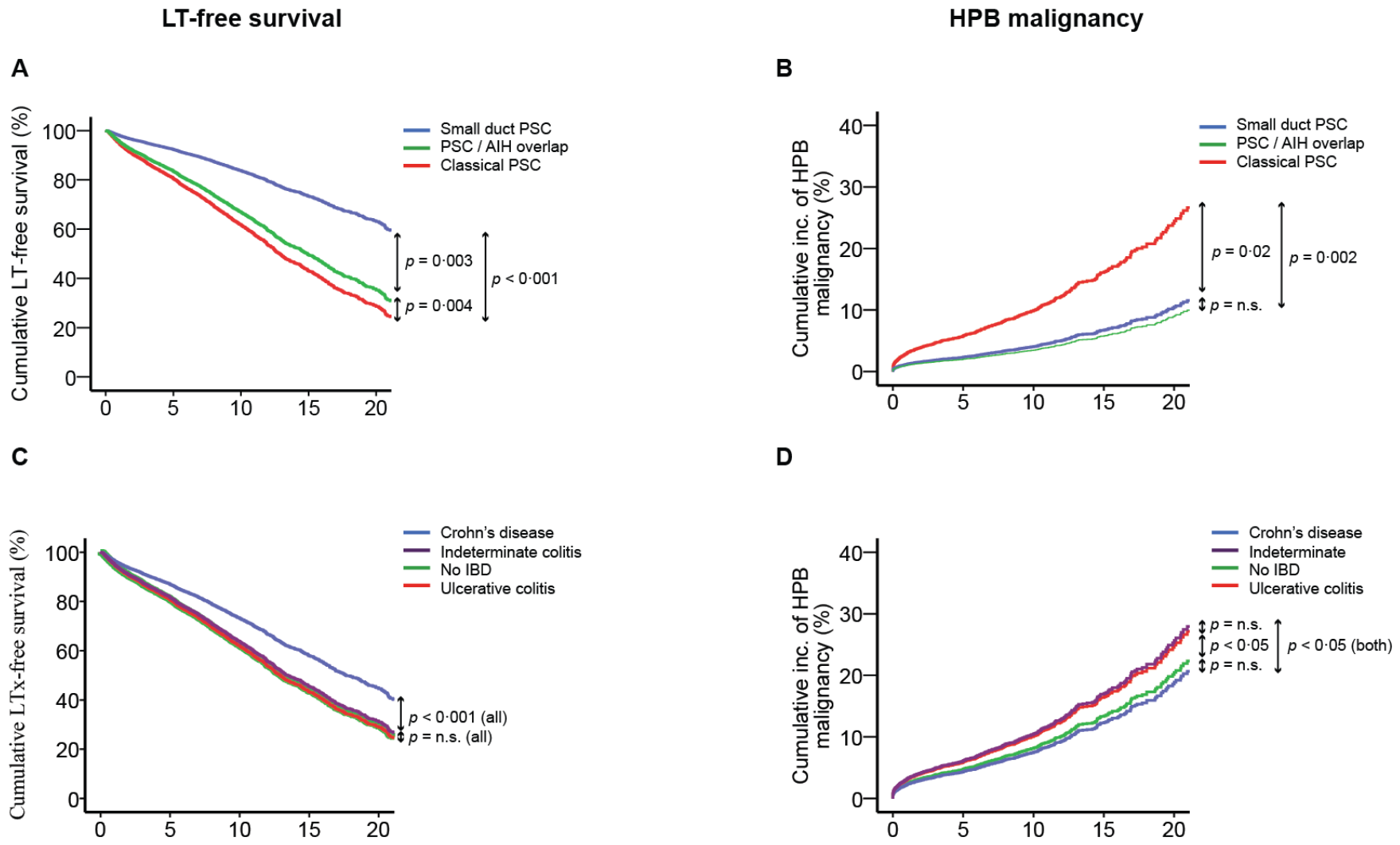


Gastroenterology 2017

Heterogeneity of Disease

Ductal phenotype

IBD phenotype



Weismueller, Trivedi, et al. *Gastro.* 2017.

Proving It Works…

IPSCSG statement 2

Alkaline phosphatase is widely recognized as a clinical measure of cholestasis. Currently, albeit not formally validated, it is regarded as a potential surrogate outcome parameter *[EL 4, RG D]*

In early phase studies bloods alone are ok to show a drug may work

IPSCSG statement 4

Liver histology has the potential to be a robust surrogate endpoint for clinical trials in PSC *[EL2b, RG B]*

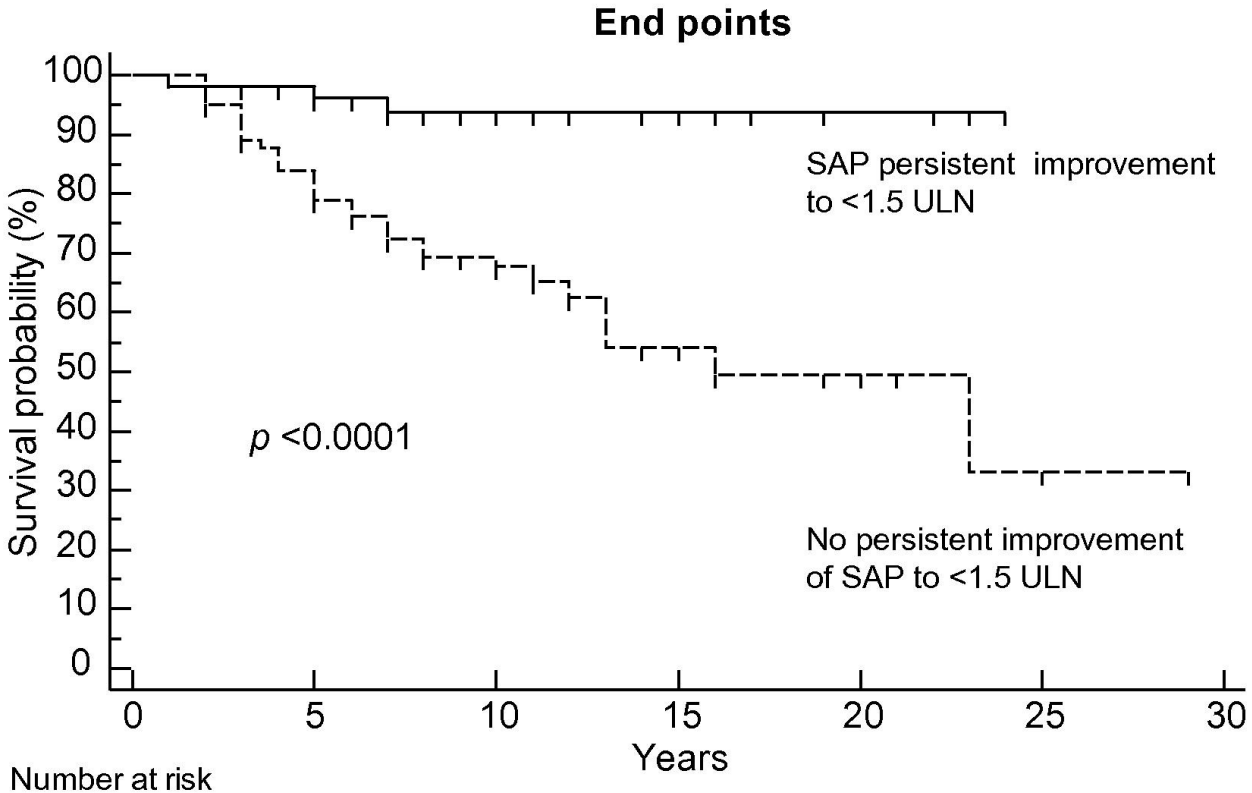
Liver biopsy is likely solid evidence a treatment works

IPSCSG statement 5

In the absence of a convincing single surrogate endpoint combining multiple endpoints is considered advisable and should be explored further *[EL 5, RG D]*

The next drug will probably be shown to work by looking at a combination of bloods, scans, and maybe biopsies

Survival in PSC and Serum ALP Values



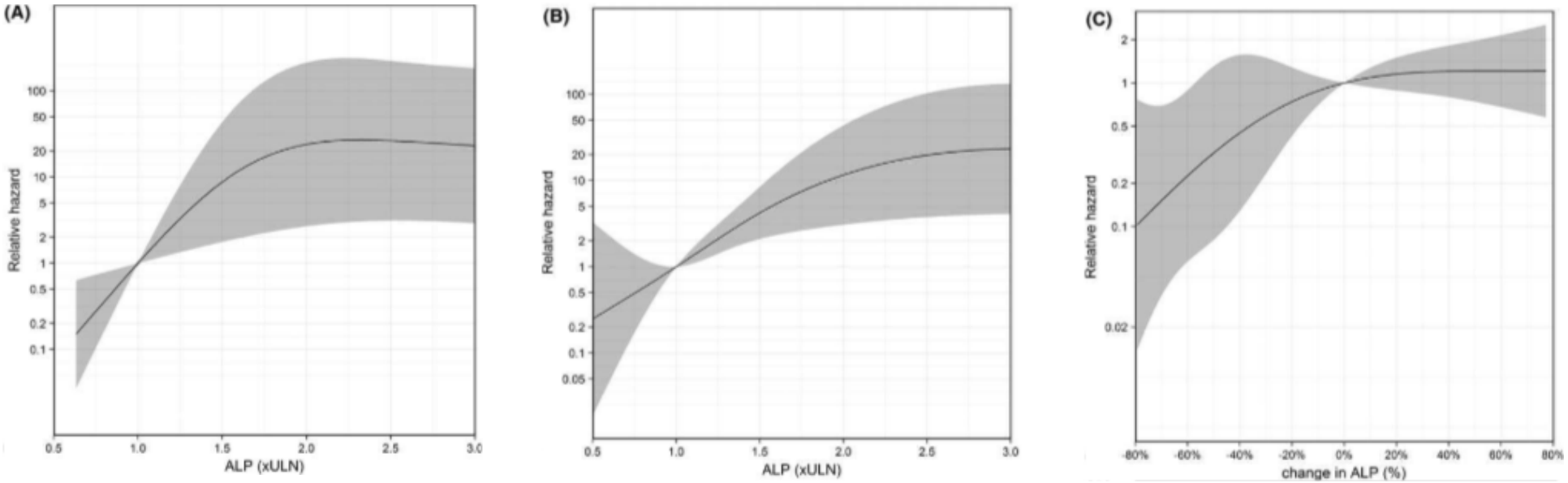
Number at risk

Group: No SAP improvement to <1.5 ULN	84	60	29	12	4	1	0
Group: SAP improvement to <1.5 ULN	55	46	22	12	5	0	0

Journal of Hepatology. 2013; 58:329-334.

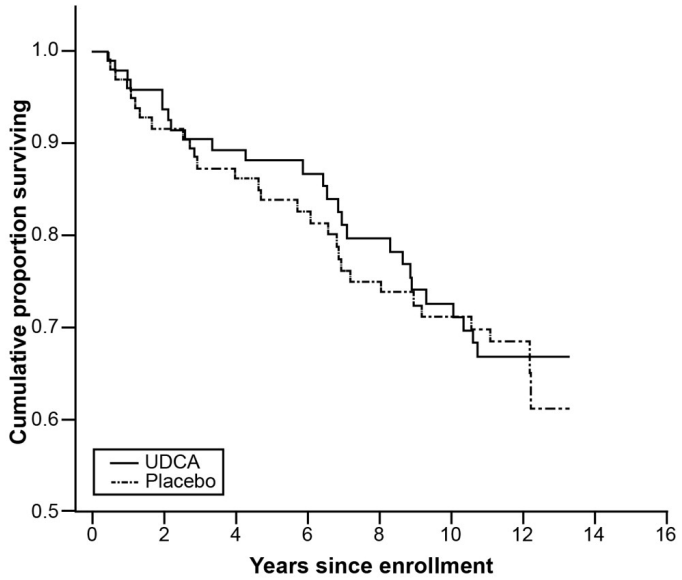
Potential Biomarkers – ALP

- Retrospective study, 366 patients with PSC were followed for a median of 100 months (67,150)
  - 66 (18%) had an outcome of PSC-related death or liver transplant
- Hazard ratio increased with increasing ALP in a range from 0.5-2.5x ULN at both T0 (Fig A) and T1 (Fig B), and patients with a reduction in ALP from T0 to T1 also had a reduction in hazard ratio (Fig C)
- In this cohort of patients the optimal cutoff was found to be ALP <1.3x ULN



de Vries EMG, et al. *Liver Int*. 2016;36:1867-1875.

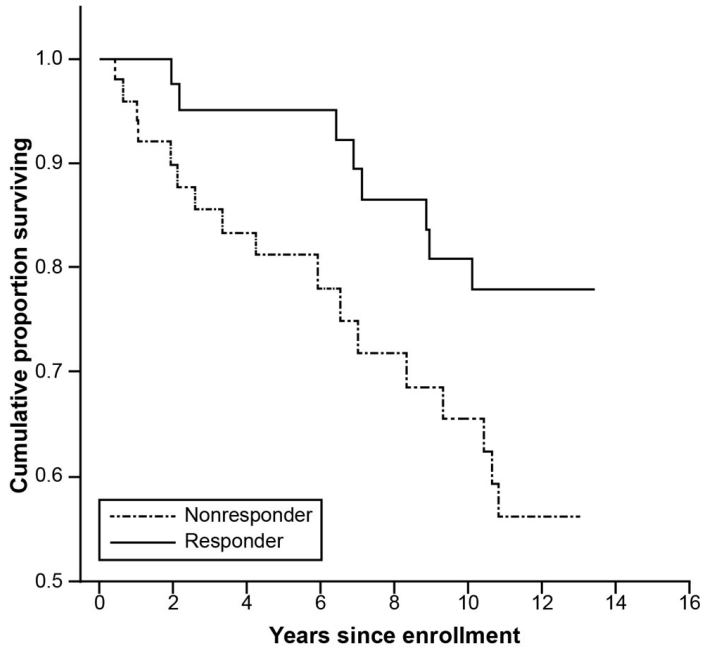
Association Between Reduced Values of ALP and Survival Times of Patients With Primary Sclerosing Cholangitis



Numbers at risk

Years	0	2.5	5	7.5	10	12.5
UDCA	97	84	78	56	51	20
Placebo	101	84	72	59	56	19

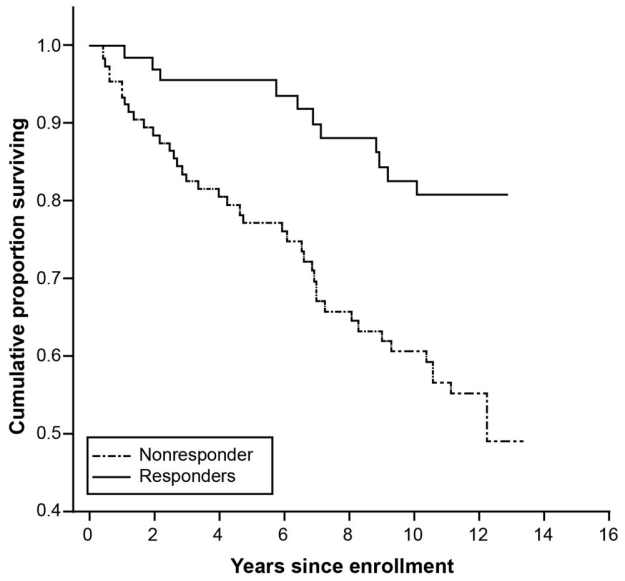
198 patients enrolled in the 5-year Scandinavian UDCA trial in 1996 randomized to UDCA vs placebo with extended follow-up



Numbers at risk

Years	0	2.5	5	7.5	10
Responder	43	40	34	24	23
Nonresponder	51	45	35	19	15

UDCA-treated patients with a biochemical response (ie, normal or ≥40% reduction in ALP after 1 year in the trial) vs nonresponders



Numbers at risk

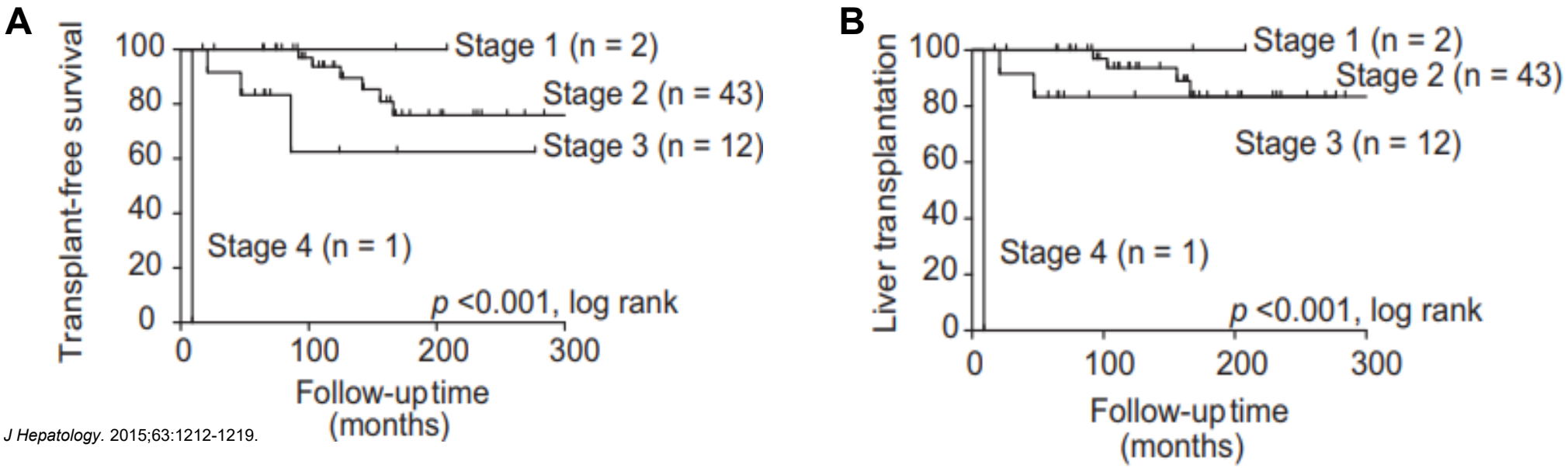
Years	0	2.5	5	7.5	10	12.5
Responders	79	72	69	56	53	17
Nonresponders	116	93	78	56	52	21

Biochemical responders vs nonresponders, regardless of treatment with UDCA (P=0.0001, log-rank test)

Clinical Gastroenterology and Hepatology. 2013;11(7):841-846.

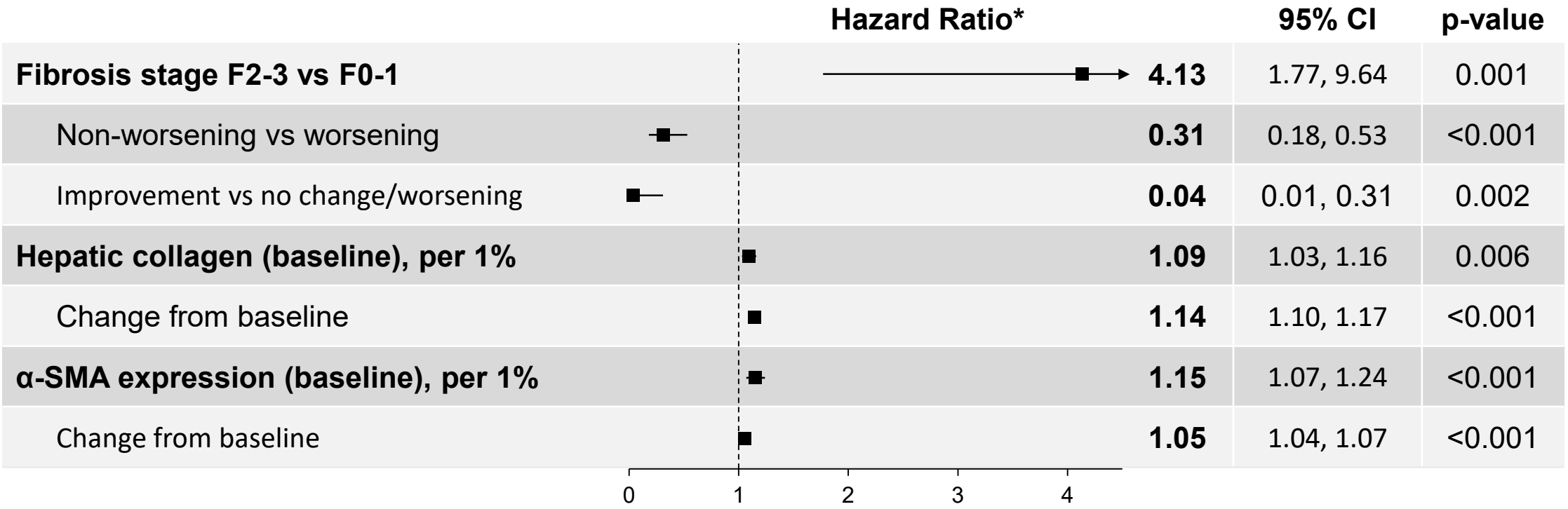
Liver Histology and PSC Outcome

- 4 observational publications with long-term follow-up comprising 826 cases demonstrated that Ludwig stage was independently associated with death/Ltx
- de Vries et al. assessed the prognostic value of Ludwig, Ishak, and Nakanuma scoring systems in 64 patients with PSC with a median follow-up of 112 months
  - Outcomes included PSC-related death, PSC-related malignancies, LTx and cirrhosis-related symptoms
  - In univariate analysis, Ishak, Nakanuma, and Ludwig stage all associated with transplant-free survival and time to liver transplant but not cirrhosis-related symptoms (Nakanuma KM shown below)
  - Nakanuma staging had a larger hazard ratio than Ishak/Ludwig



de Vries EMG, et al. *J Hepatology*. 2015;63:1212-1219.

Associations Between Histologic Features on Disease Progression



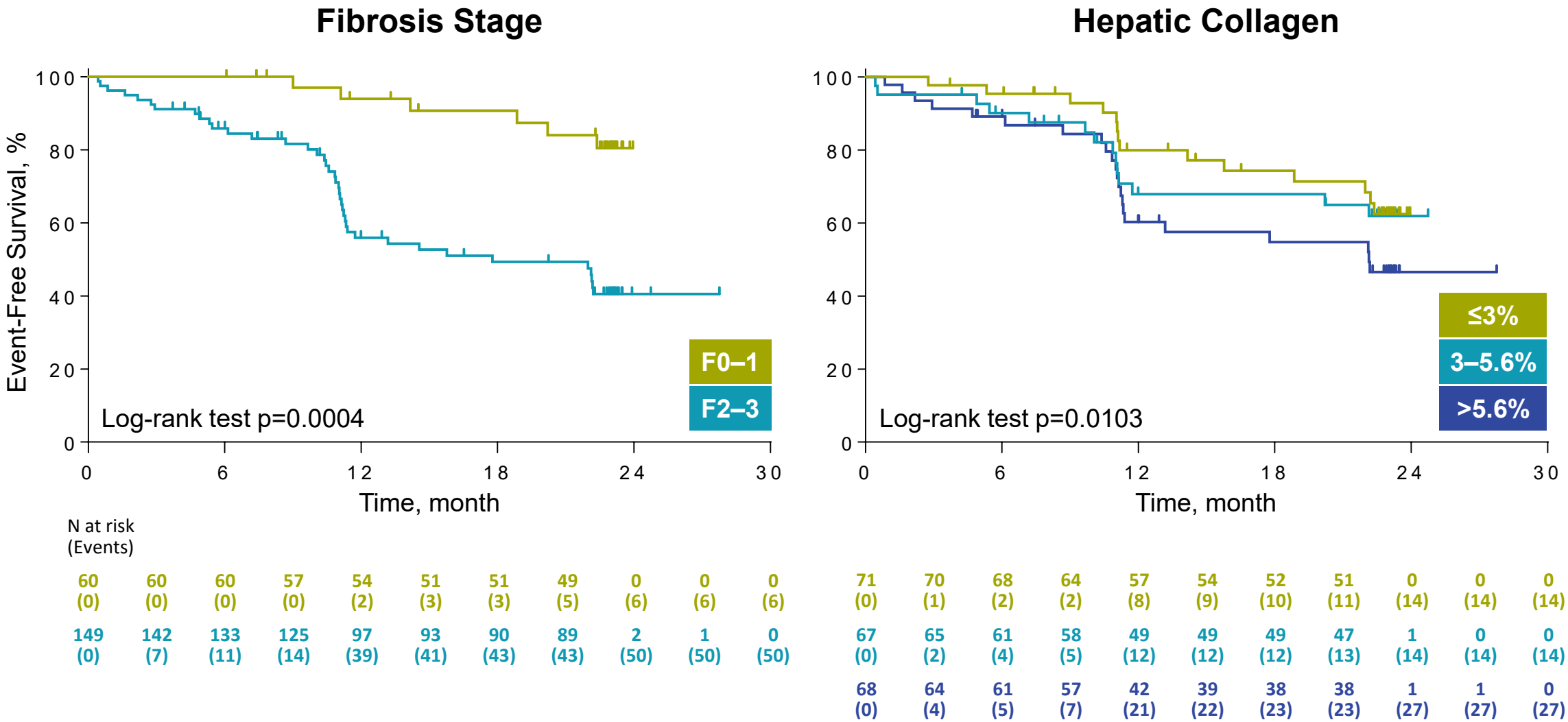
	Hazard Ratio*	95% CI	p-value
Fibrosis stage F2-3 vs F0-1	**4.13**	1.77, 9.64	0.001
Non-worsening vs worsening	**0.31**	0.18, 0.53	<0.001
Improvement vs no change/worsening	**0.04**	0.01, 0.31	0.002
Hepatic collagen (baseline), per 1%	**1.09**	1.03, 1.16	0.006
Change from baseline	**1.14**	1.10, 1.17	<0.001
α-SMA expression (baseline), per 1%	**1.15**	1.07, 1.24	<0.001
Change from baseline	**1.05**	1.04, 1.07	<0.001

- Increased risk of events associated with:
  - More severe fibrosis at baseline (F2-3; greater collagen and α-SMA expression)
  - Worsening of fibrosis (by Ishak stage, collagen content, α-SMA)

Separate multivariate models run with baseline and change from baseline for each variable.
Hazard ratios for changes from baseline adjusted for baseline value.

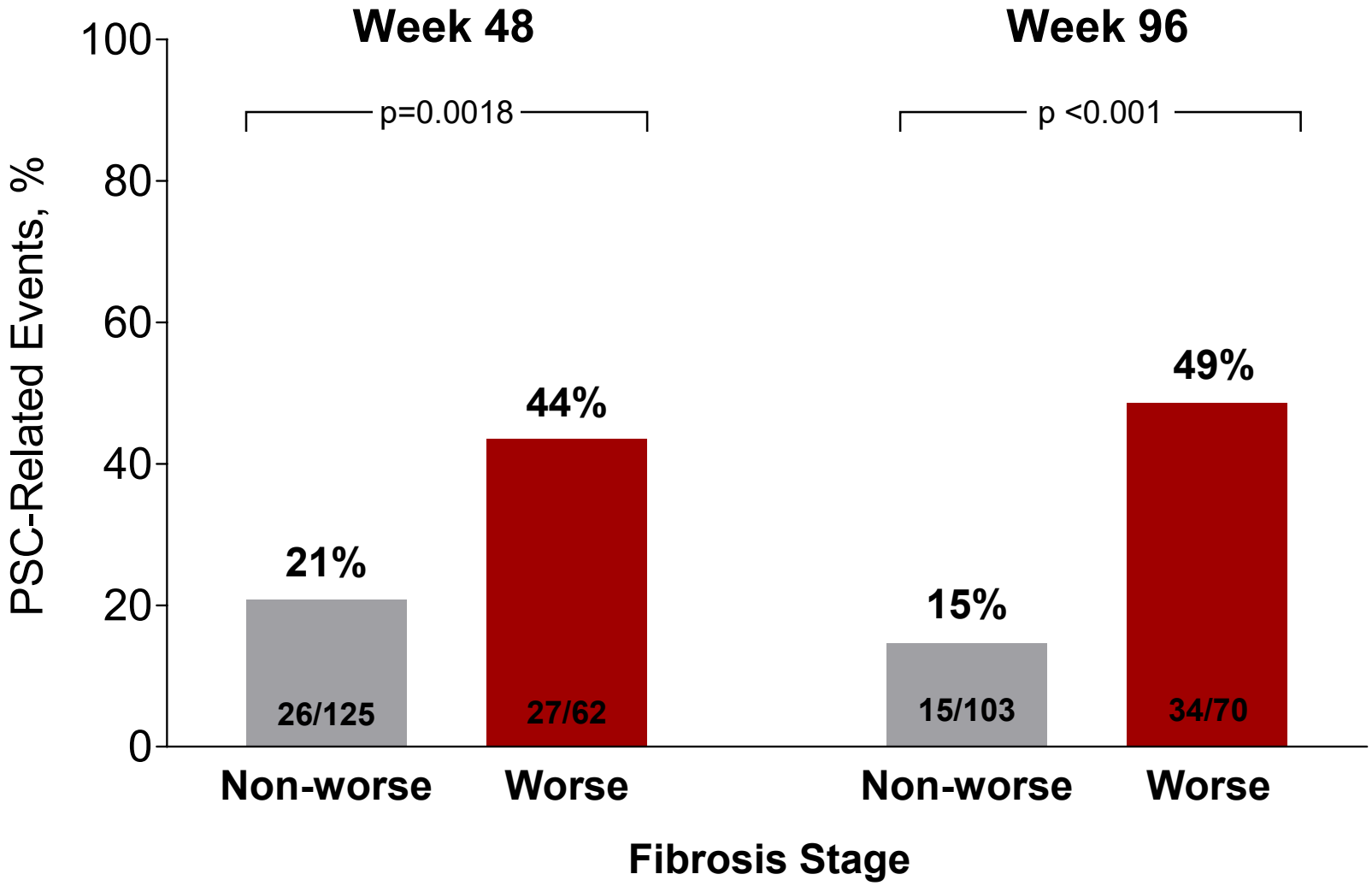
Bowlus et al.

F2-3 Fibrosis and Greater Hepatic Collagen Associated With Increased Risk of Disease Progression



Bowlus et al.

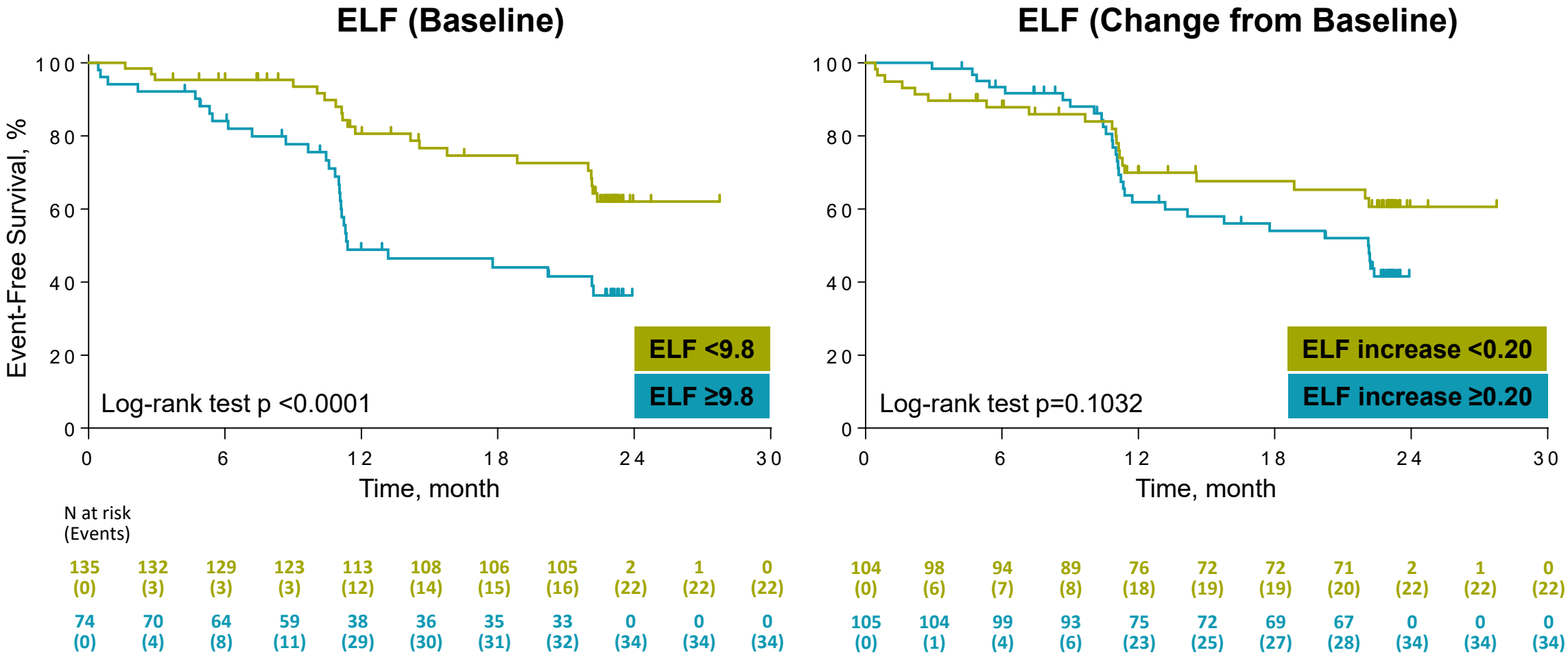
Non-Worsening of Fibrosis Is Associated With a Reduced Incidence of Disease Progression



P-values by Fisher's exact test.

Bowlus et al.

Association Between ELF and Disease Progression in SIM Study



N at risk
(Events)

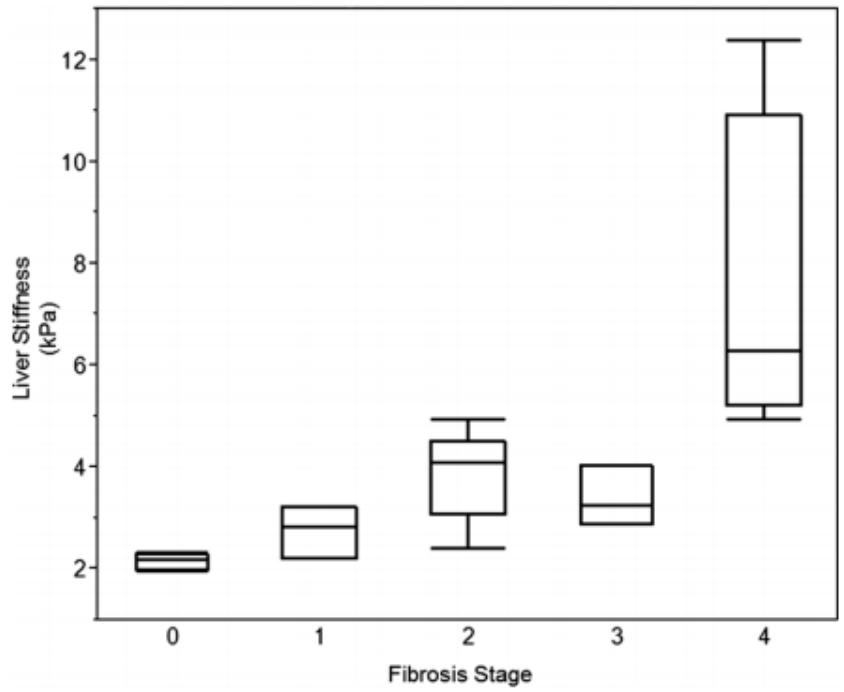
135 (0)	132 (3)	129 (3)	123 (3)	113 (12)	108 (14)	106 (15)	105 (16)	2 (22)	1 (22)	0 (22)
74 (0)	70 (4)	64 (8)	59 (11)	38 (29)	36 (30)	35 (31)	33 (32)	0 (34)	0 (34)	0 (34)

104 (0)	98 (6)	94 (7)	89 (8)	76 (18)	72 (19)	72 (19)	71 (20)	2 (22)	1 (22)	0 (22)
105 (0)	104 (1)	99 (4)	93 (6)	75 (23)	72 (25)	69 (27)	67 (28)	0 (34)	0 (34)	0 (34)

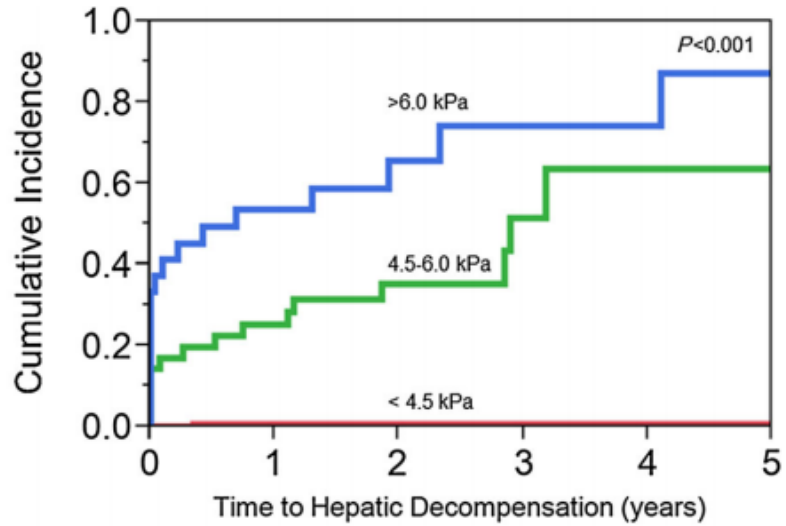
Bowlus et al.

MRE

A



B



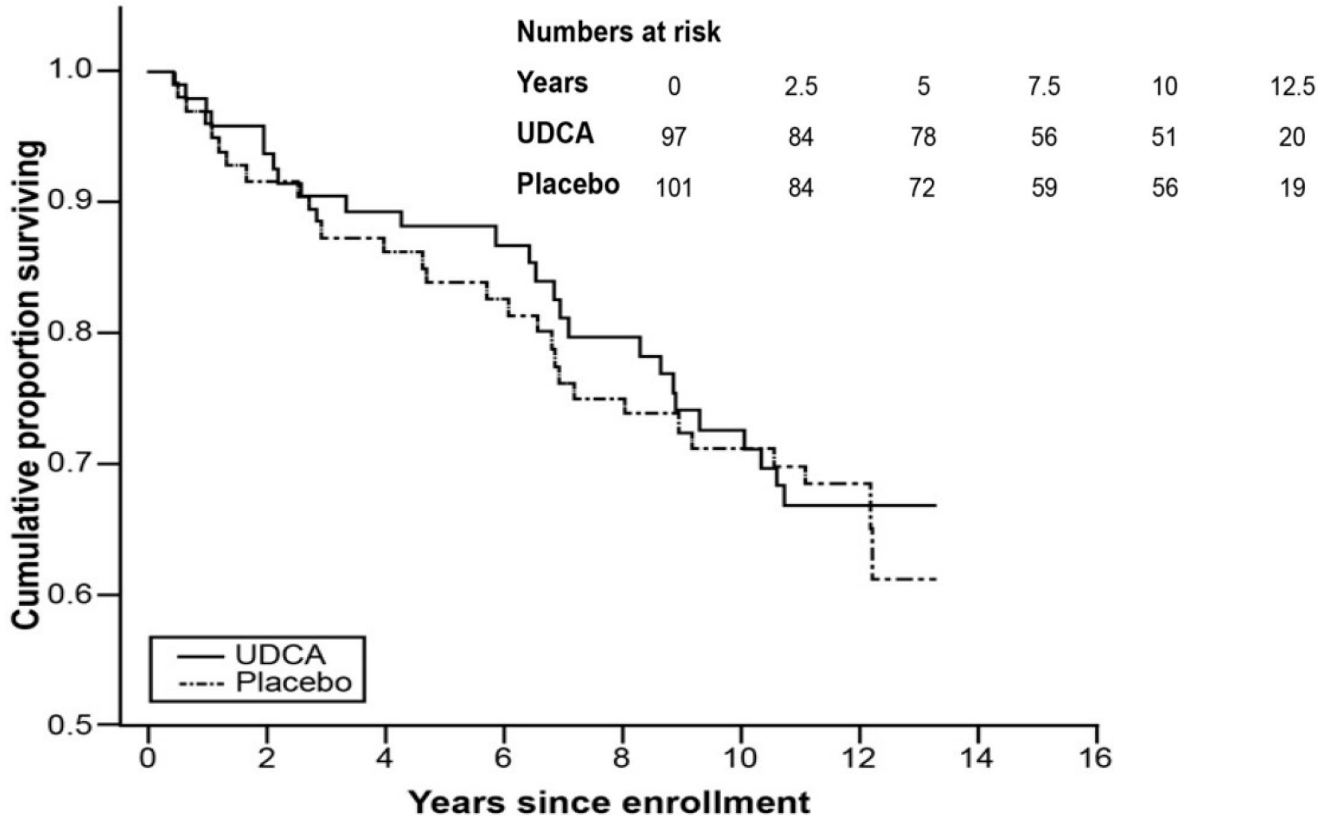
Number at Risk:						
>6.0 kPa	27	11	6	3	3	2
4.5-6.0 kPa	42	26	18	6	3	2
<4.5 kPa	197	163	107	45	24	17

- Only 20 patients had biopsy info (F0, n=4; F1, n=3; F2, n=6; F3, n=3; F4, n=4); however, liver stiffness was still found to be strongly correlated with fibrosis stage (R=0.84, P<0.001, Fig A)
- Patients who had baseline liver stiffness >4.5 kPa had significantly increased risk of hepatic decompensation (Fig B)
- These results require further validation (this is the only paper on MRE in PSC)
- MRE has high cost/limited availability but may be more accurate than TE and can be combined with MRCP in a single visit for more

Eaton JE, et al. *Journal of Gastroenterology and Hepatology*.2016;31:1184-1190.

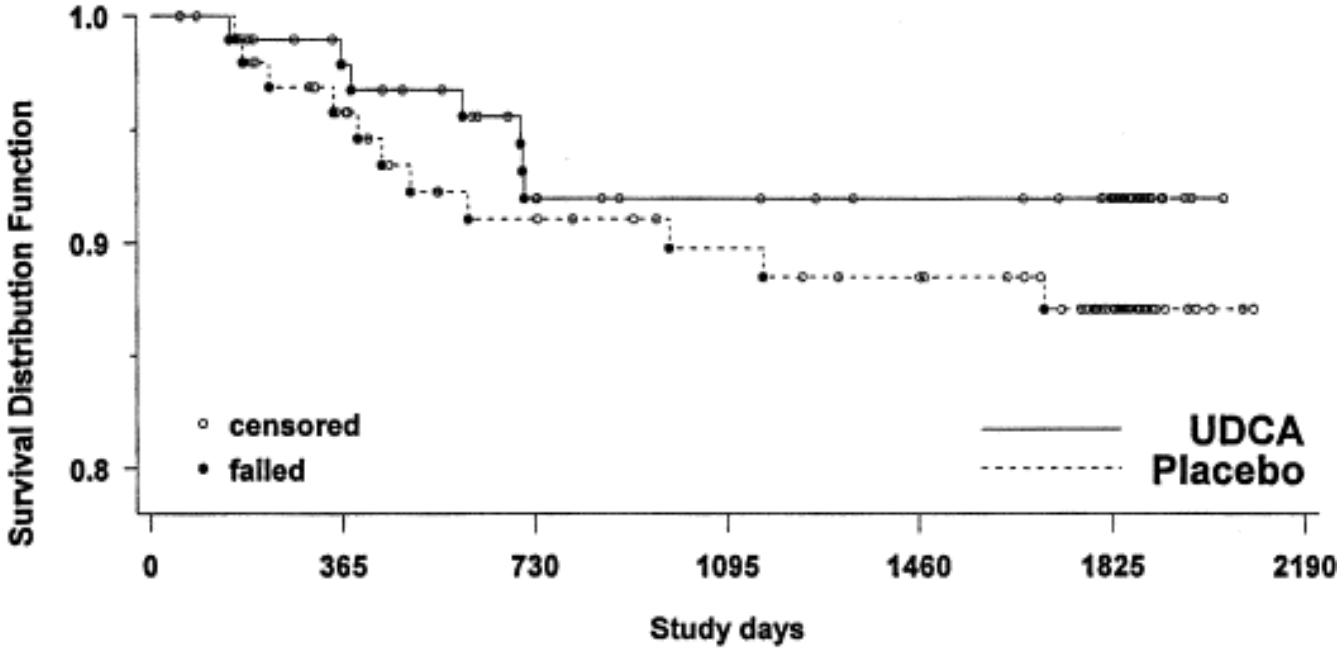
Ursodiol in PSC

Kaplan-Meier Survival Curve of 198 PSC Patients Enrolled in a 5 year UDCA Trial



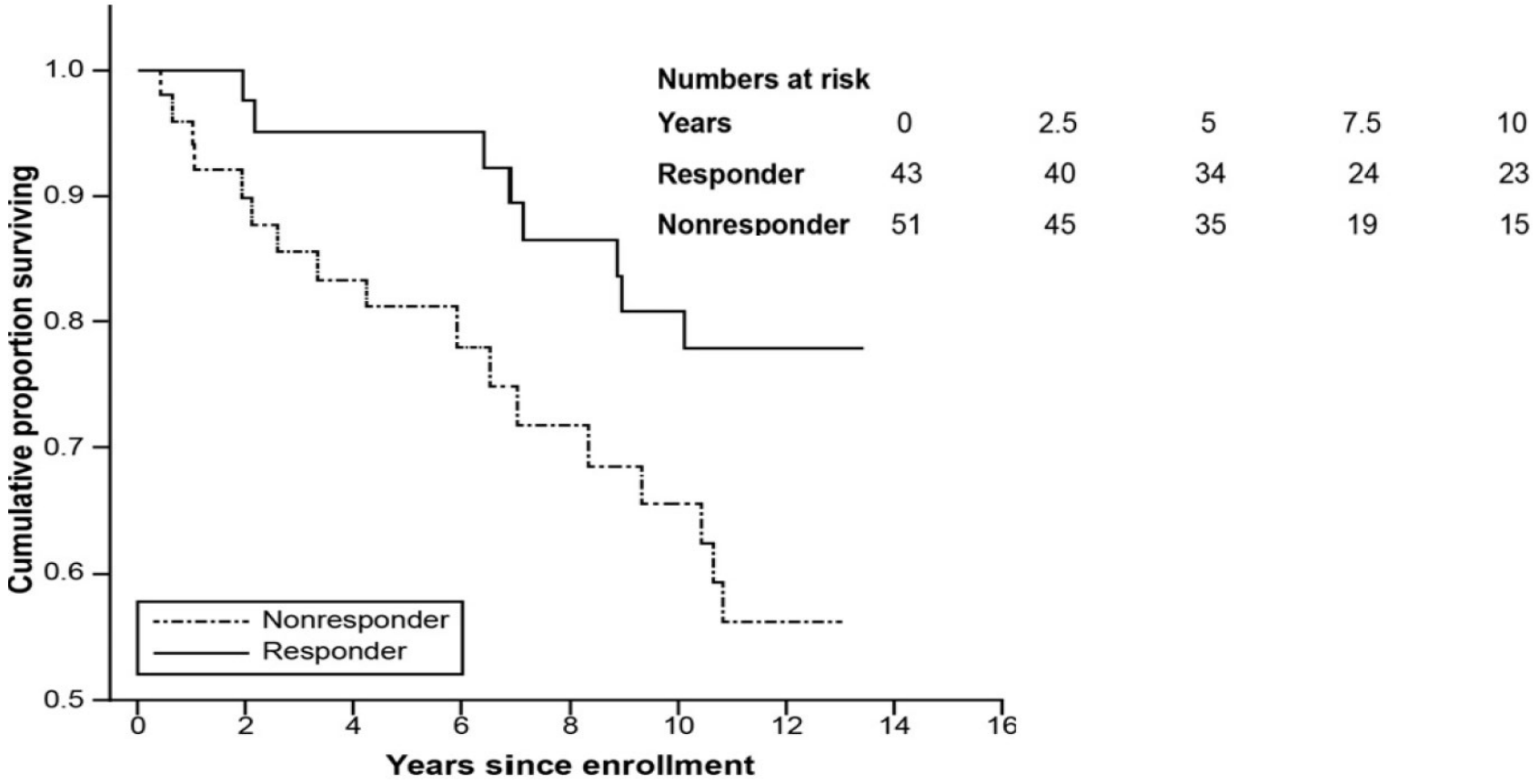
Lindstrom L, Hultcrantz R, Boberg KM,, et al. Assoc. btwen reduced levels of ALK and Survival Times of Patients with PSC. Clin Gastro Hep. 2013;11(7):841-846.

Intermediate Dose UDCA in PSC



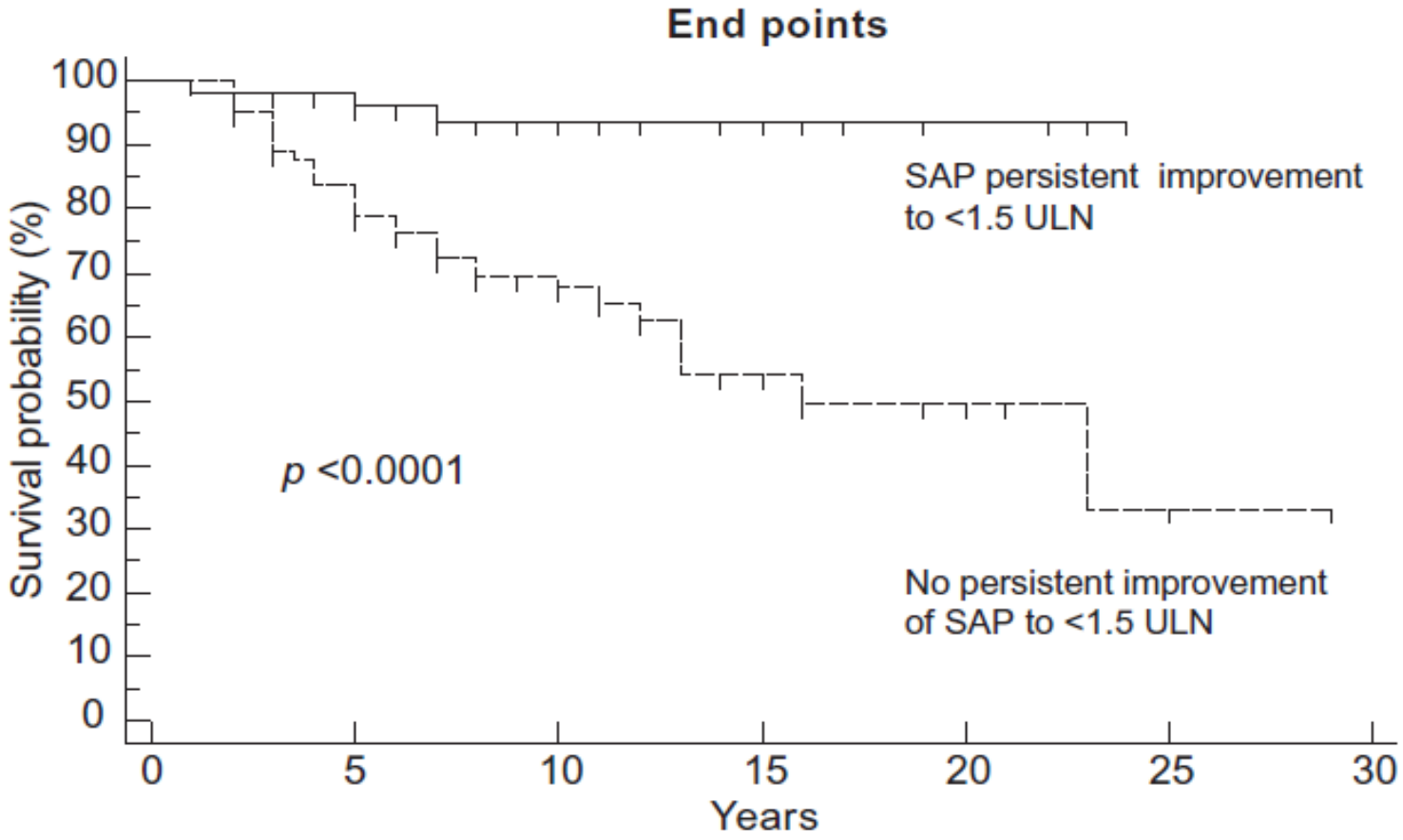
Gastroenterology 2005 129, 1464-1472

Kaplan-Meier Analysis of Endpoint Free Survival in UDCA Treated Patients with PSC



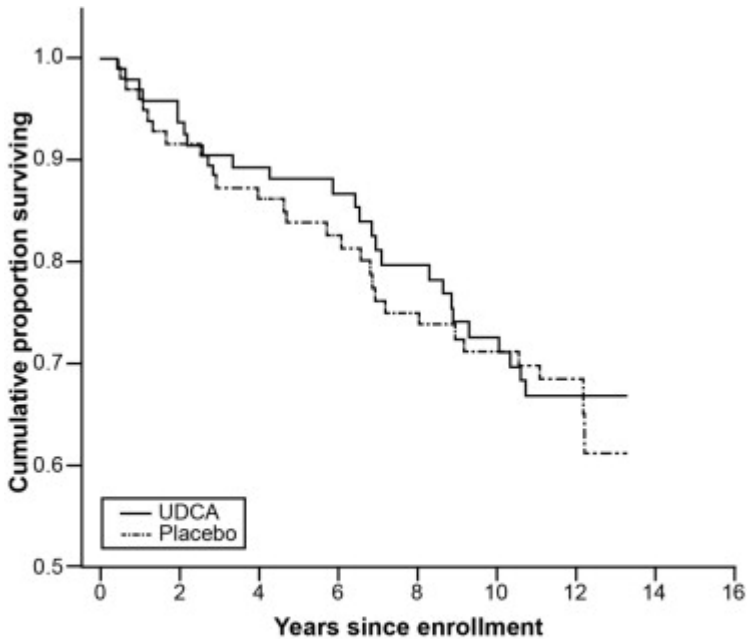
Lindstrom L, Hultcrantz R, Boberg KM,, et al. Assoc. btwen reduced levels of ALK and Survival Times of Patients with PSC. Clin Gastro Hep. 2013;11(7):841-846.

ALP Levels <1.5x ULN Associated With Improved Survival



Adapted from Al Mamari S, et al. *J Hepatol*. 2013;58(2):329-334.

Survival in Patients Treated With Ursodeoxycholic Acid vs Placebo
(*P* = .774, log-rank).



Numbers at risk

Years	0	2.5	5	7.5	10	12.5
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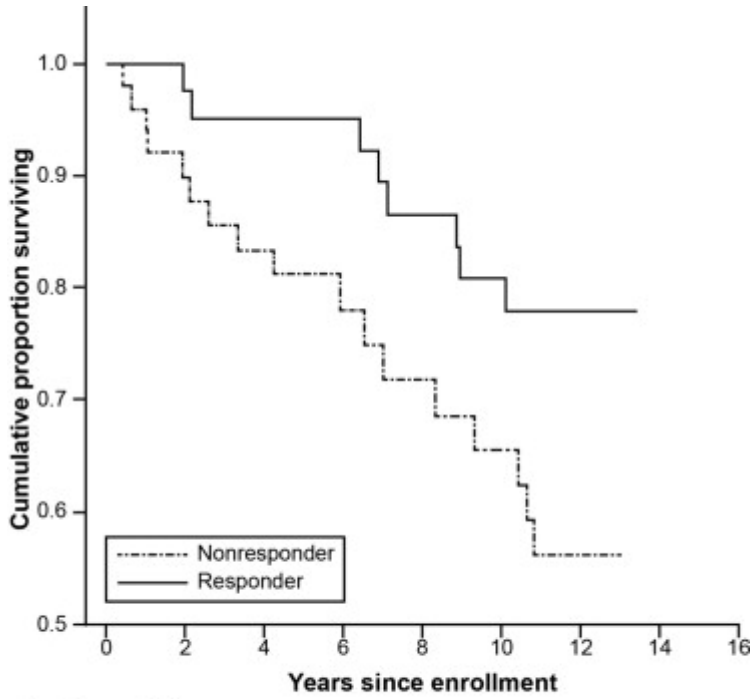
Placebo	101	84	72	59	56	19

Survival in Biochemical Responders vs Nonresponders



Numbers at risk

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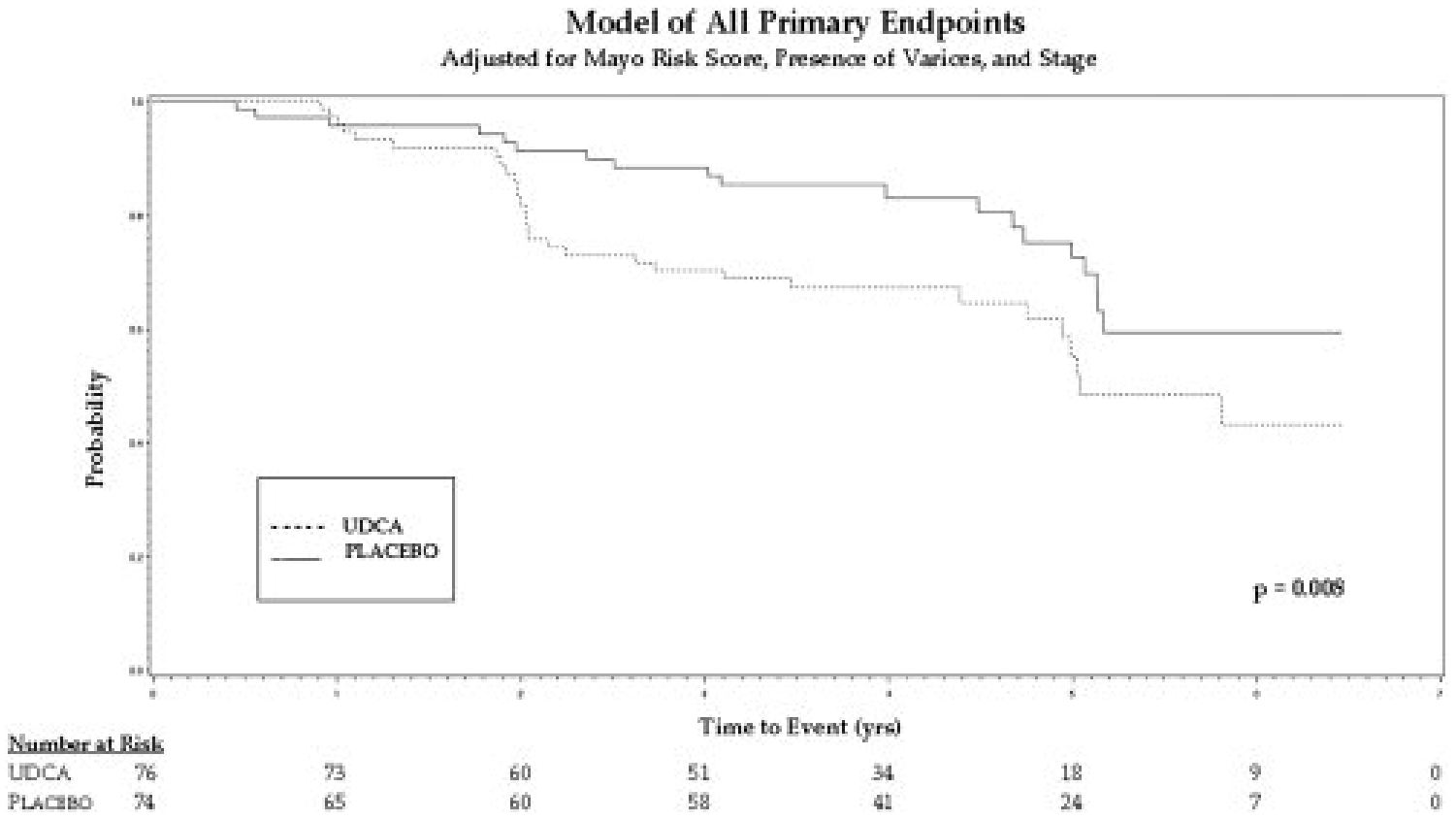
Responder	43	40	34	24	23
Nonresponder	51	45	35	19	15

Clin Gastroenterol Hepatol. 2013;11:841-6

High-Dose UDCA (28-30 mg/kg) vs Placebo for PSC



Hepatology 2009; 50:808–814

High-dose Urso for PSC Results

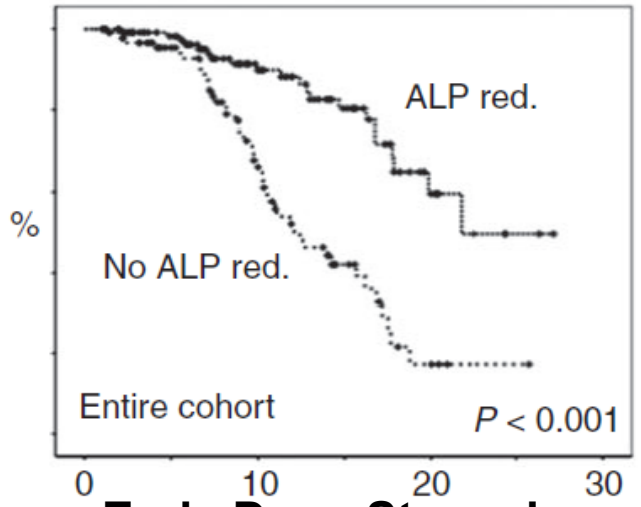
Primary Endpoints

Primary Endpoints	UDCA	Placebo
Death	5	3
Liver Transplant	11	5
Minimal Listing Criteria for Liver Transplant	13	10
Development of Cirrhosis	6	4
Esophageal and/or Gastric Varices	15	5
Cholangiocarcinoma	2	2
Total Endpoints	52	29

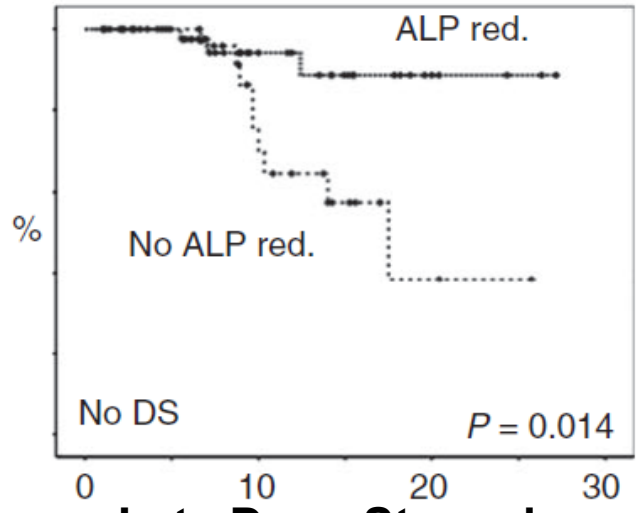
Lindor KD, Kowdley KV, Luketic VA, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. Hepatology 2009;50(3):808-14

Lower ALP Associated With Survival in Presence/Absence of Dominant Stenosis

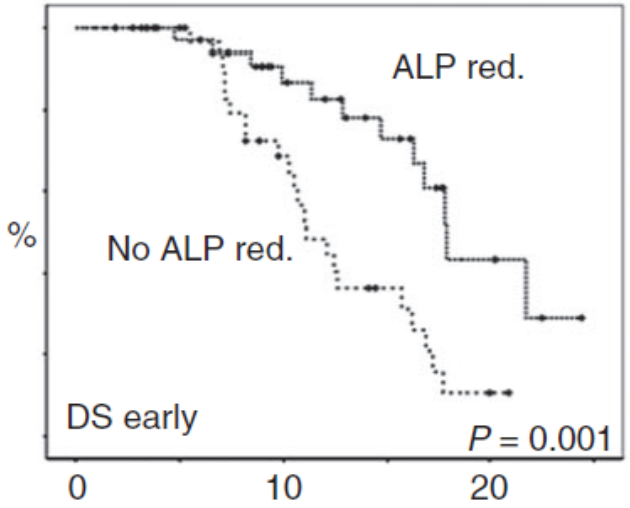
Overall



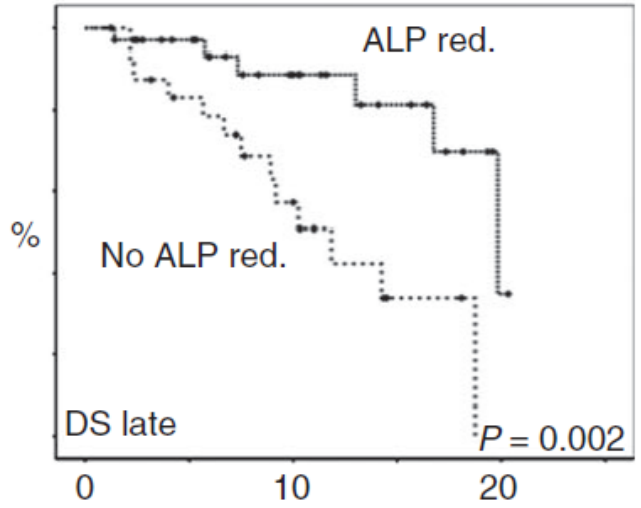
No Dom. Stenosis



Early Dom. Stenosis

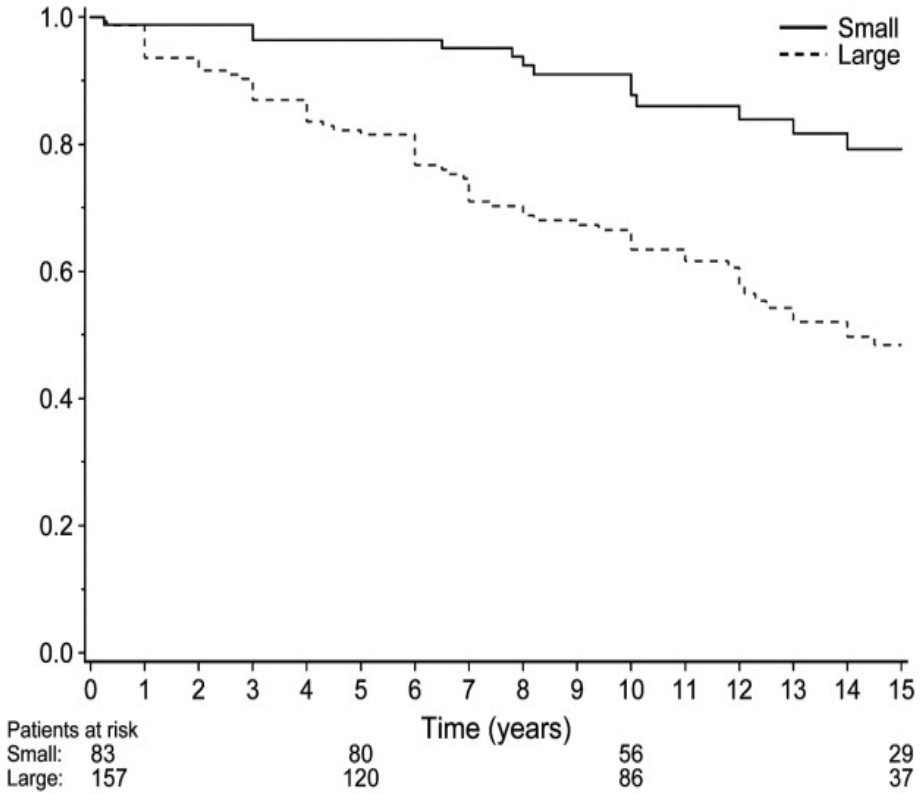


Late Dom. Stenosis



Rupp C, et al. *Aliment Pharmacol Ther*. 2014;40(11-12):1292-1301.

Survival in PSC Small Duct vs. Large



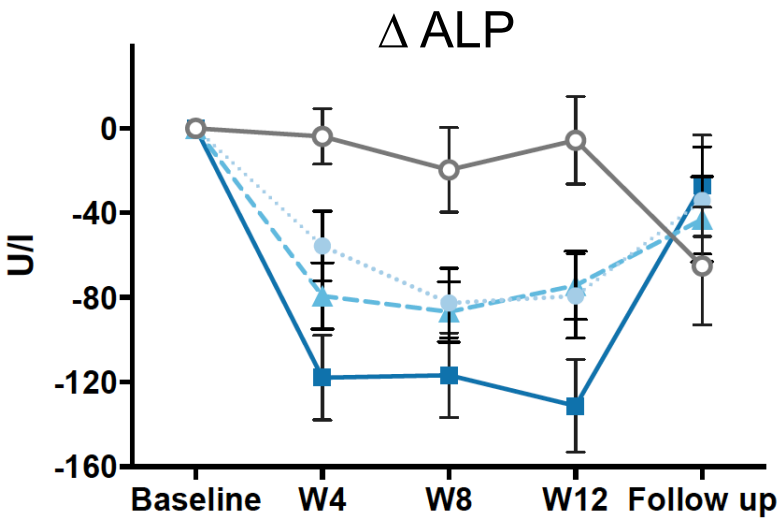
Bjornsson E, Olsson R, Berqquist A, et al. The Natural History of Small-Duct Primary Sclerosing Cholangitis. Gastroenterology 2008;134(4):975-80

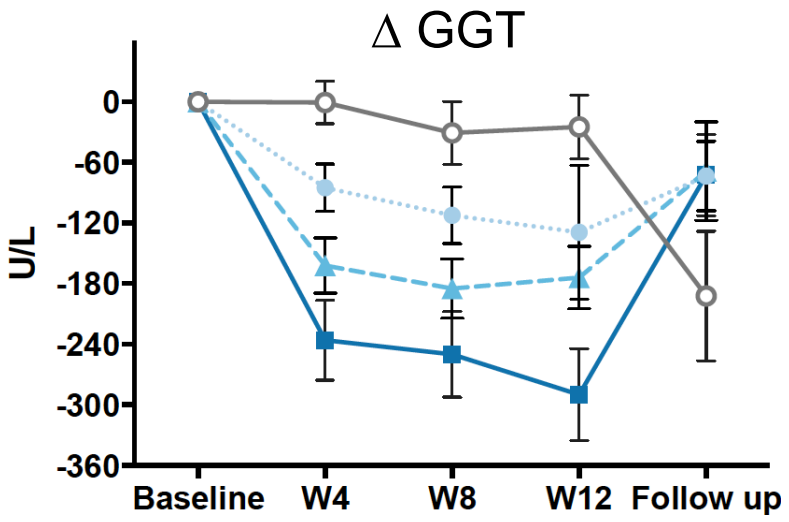
IgG4 ASSOCIATED CHOLANGITIS

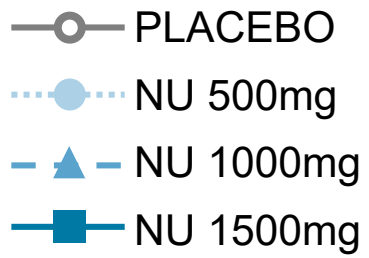
IgG4-related disease is a systemic disease characterized
by extensive IgG4-positive plasma cells and
T-lymphocyte infiltration of various organs.

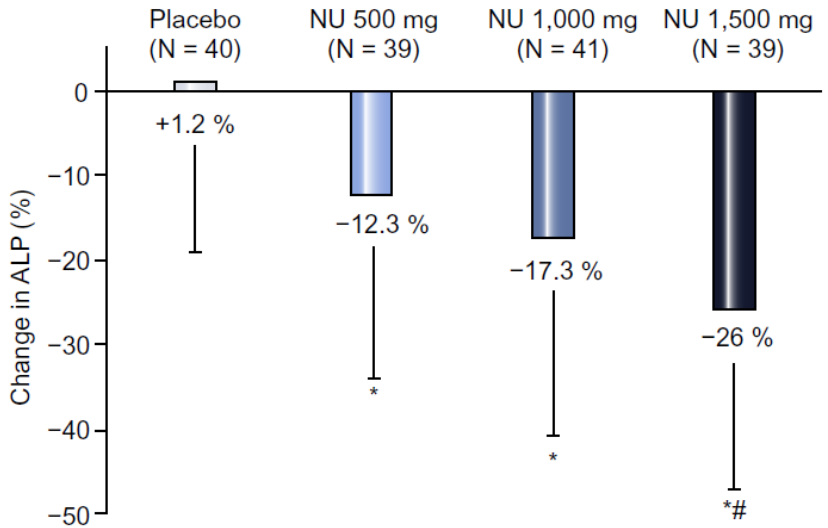
Organ	Name	Mimics
Pancreas	Autoimmune Pancreatitis (AIP)	Pancreatic Cancer
Bile Ducts	IgG4-associated Cholangitis (IAC)	PSC Cholangiocarcinoma

*nor*UDCA Improves Cholestasis in PSC: Results of a European Multicenter Phase II RCT (NUC-3)









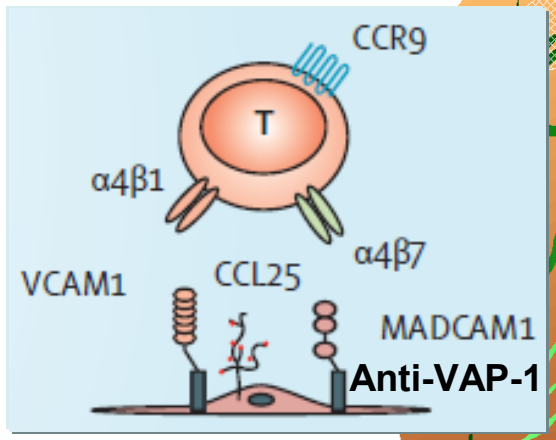
- *nor*UDCA resulted in a significant reduction of serum ALP within 12 weeks of treatment compared to placebo; n=161
- The effect occurred in a dose-dependent manner with the highest effect at 1500 mg/d - indep. of prev. UDCA response
- Safety profile of *nor*UDCA did not differ from placebo
- Phase III initiated (NUC-5): long-term treatment over 96 wks (DBE 192 wks); biochemical, histological & clinical endpoints; n=300

Fickert et al., *J Hepatol* 2017; 67: 549-558

Novel Therapeutic Strategies in PSC
Currently Tested in Clinical Trials - Overview

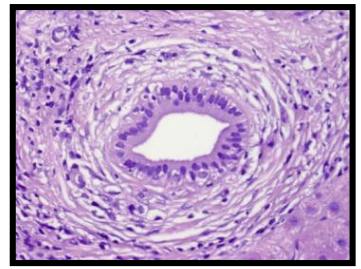
Cenicriviroc

Etrolizumab
Vedolizumab



Lancet 2013;382:1590

norUDCA

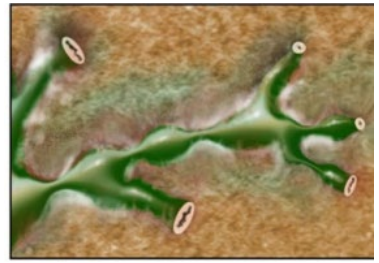


Small Duct PSC

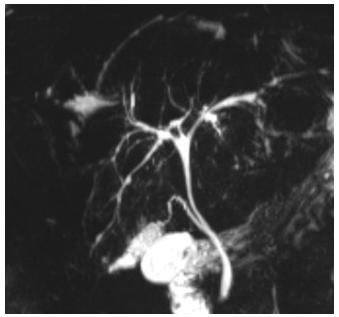
Obliterative fibrosis of bile ducts

PPAR FXR RAR

Simtuzumab

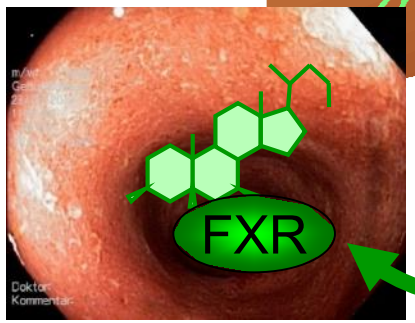


www.mayoclinic.org



Large Duct PSC

Antibiotics
(Vancomycin,
Minocyclin,
Metronidazol)



Colitis (~75%)

FXR

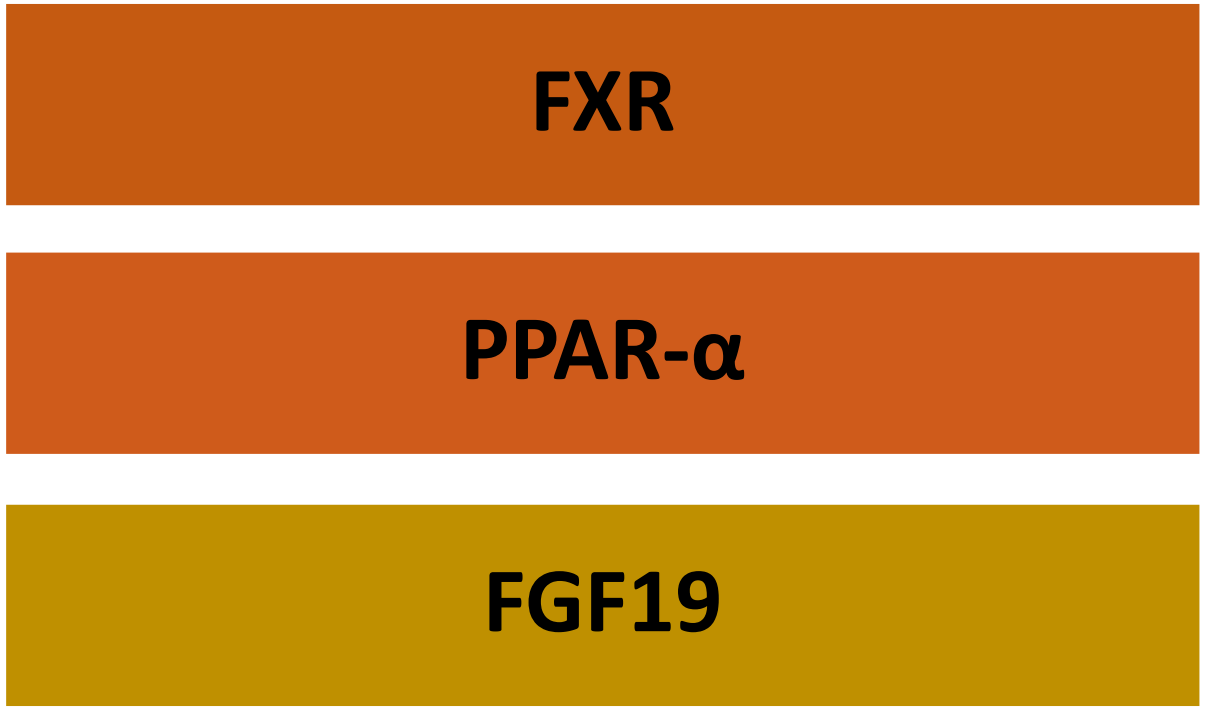
FMT?

Microbiota (Dysbiosis)

Reviews: Hirschfield et al., *Lancet* 2013
Halilbasic et al., *Dig Dis* 2015
Ali et al., *Intract Rare Dis Res* 2015
Karlsen et al., *J Hepatol* 2017

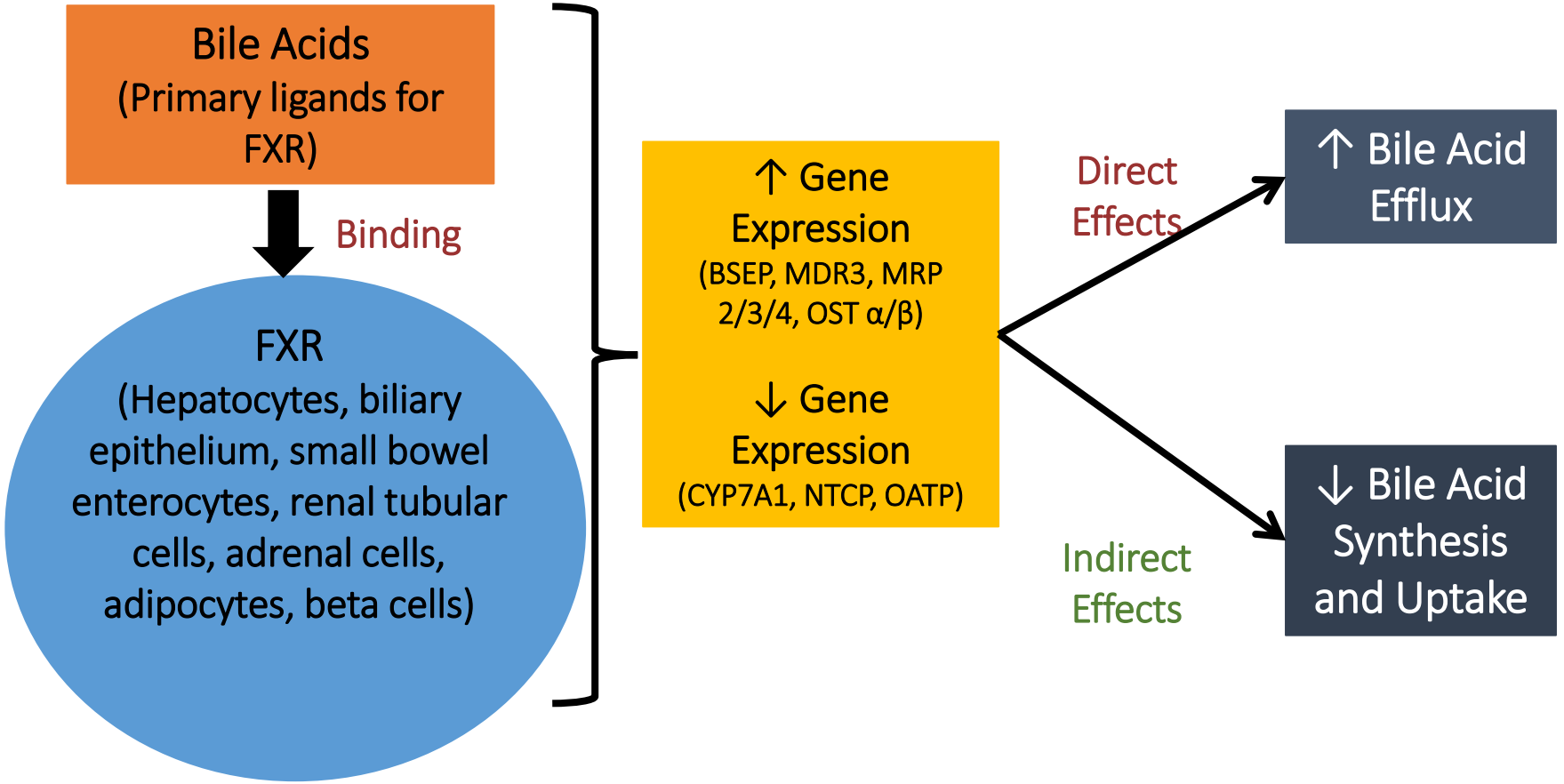
Courtesy of Dr. Michael Trauner

PBC Investigational Targets



Abbreviations: FGF, fibroblast growth factor; FXR, farnesoid X receptor; PBC, primary biliary cirrhosis; PPAR, peroxisome proliferator-activated receptor.

Farnesoid X Receptor Signaling



Abbreviations: BSEP, bile salt export pump; FXR, farnesoid X receptor; MRP 2/3/4, multidrug resistant protein 2/3/4; NTCP, sodium/taurocholate cotransporting polypeptide; OATP, organic anion transporting polypeptide; OST α/β, organic soluble transporter α/β.

Neuschwander-Tetri BA. *Curr Gastroenterol Rep.* 2012;14:55-62.

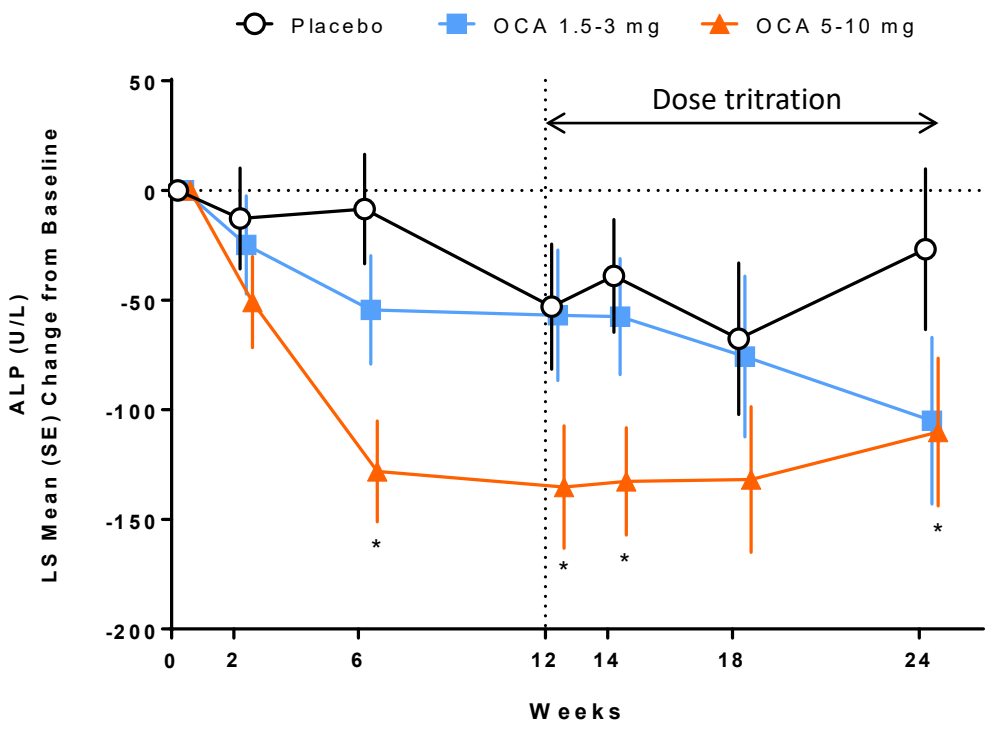
Bile Acid Receptor Signaling & Transport-based Drug Strategies in PSC

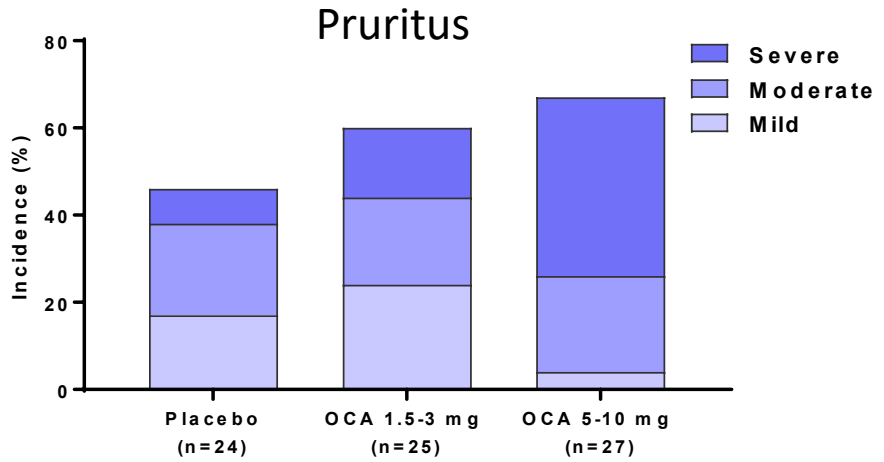
Drug (Target)	Phase	Outcome Parameters	ClinicalTrials.gov
OCA (FXR)	II RCT N=76 AESOP	Safety (pruritus) Reduction in ALP	NCT02177136 Completed Has results [1]
GS-9674 (FXR)	II RCT N=52	Safety & efficacy 12 wks + 96 wks OLE	NCT02943460 Fully recruited
NGM282 (FGFR/β-klotho)	II RCT N=62	Biochemistry (ALP, AST @ 12 wks)	NCT02704364 Completed
LUM001/Lopixibat (ASBT)	II Open Lbl N=27 CAMEO	Safety Reduction in SBA & pruritus No change in ALP (14 wks)	NCT02061540 Completed Has results [2]

1: Kowdley et al., AASLD 2017 LB-2 (Hepatology 2017, 66 (Suppl.1): 1254A)
2: Clinicaltrials.gov/ct2/show/results/NCT02061540

Courtesy of Dr. Michael Trauner

The AESOP Trial: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of OCA in Patients with PSC



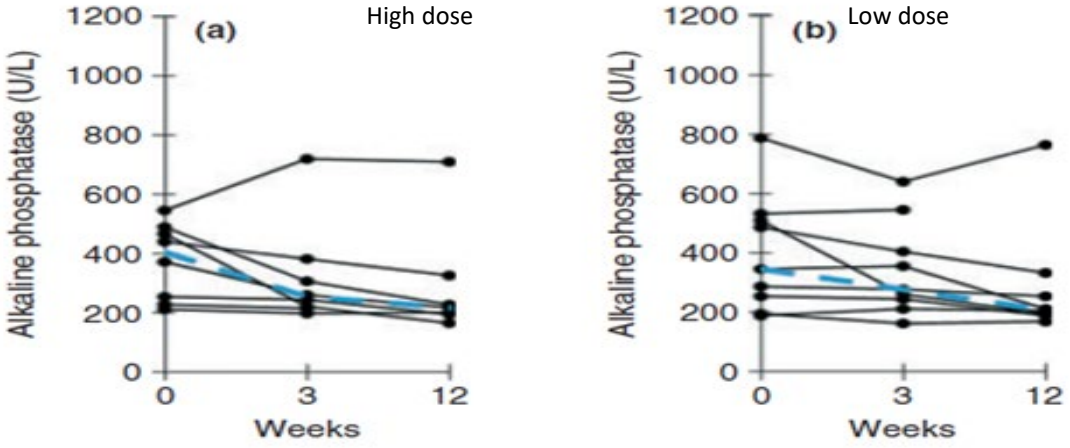


- OCA resulted in a significant reduction of serum ALP within 24 weeks of treatment compared to placebo; n=76
- The effect occurred in a dose-dependent manner, regardless of UDCA use (stable UDCA dose for 3 months required)
- Pruritus most common AE (increased with dose, few discontinuations n=4), no unexpected safety findings
- Findings warrant further investigation (OLE ongoing – 2 yrs)

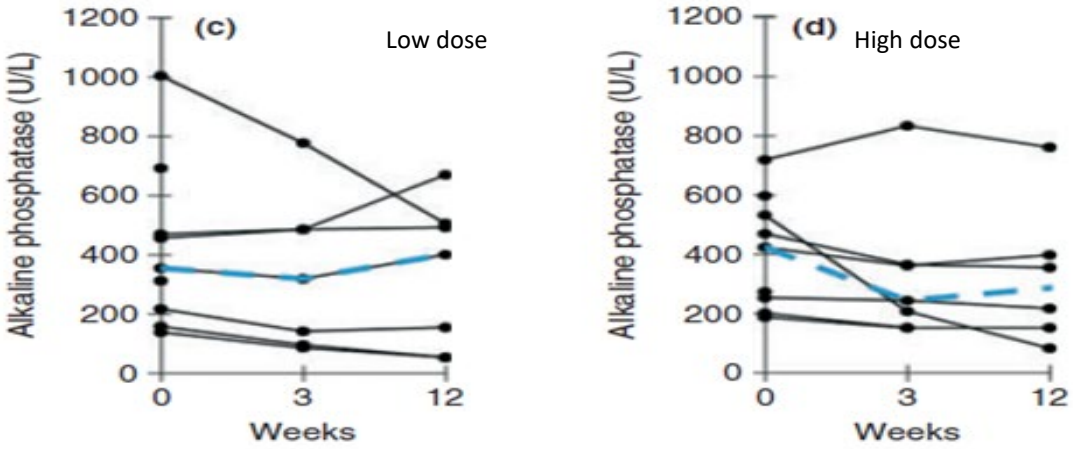
Kowdley et al., AASLD 2017 LB-2 (Hepatology 2017, 66 (Suppl.1): 1254A)

Vancomycin & Metronidazole in PSC

VANCOMYCIN



METRONIDAZOLE

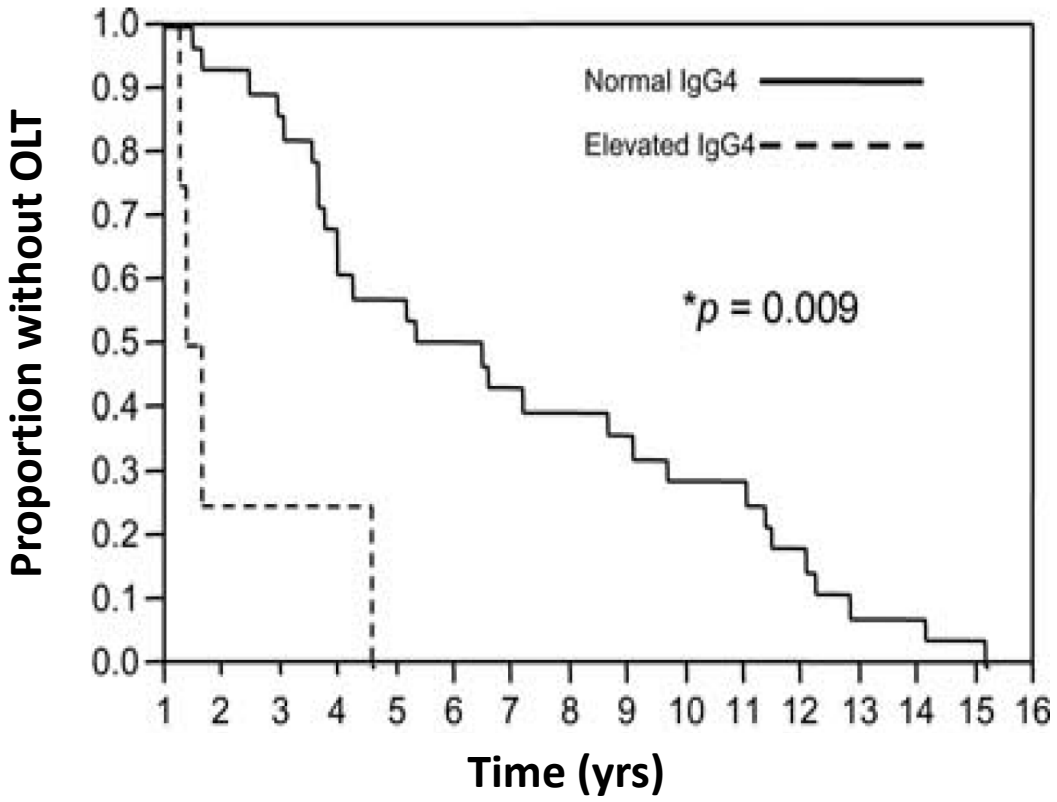


Tabibian JH, Weeding E, Jorgensen RA, et al. Randomized clinical trial: vancomycin or metronidazole in patients with primary sclerosing cholangitis – a pilot study. Aliment Pharmacol Ther. 2013; 37(6): 604-12.

Immunosuppressive and Other Agents

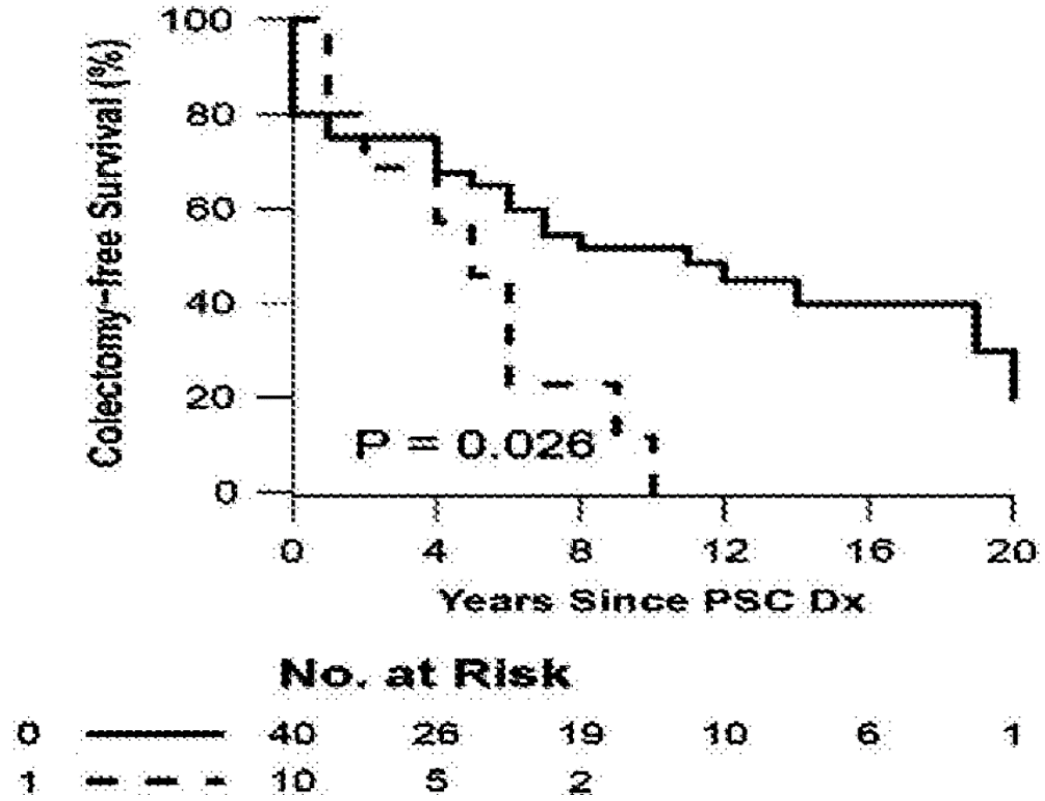
- Azathioprine
- Budesonide
- Docosahexaenoic acid
- Methotrexate
- Metronidazole
- Minocycline
- Mycophenolate mofetil
- Nicotine
- Pentoxifylline
- Pirfenodone
- Prednisolone
- Tacrolimus
- Vancomycin

Natural History “PSC” & IgG4



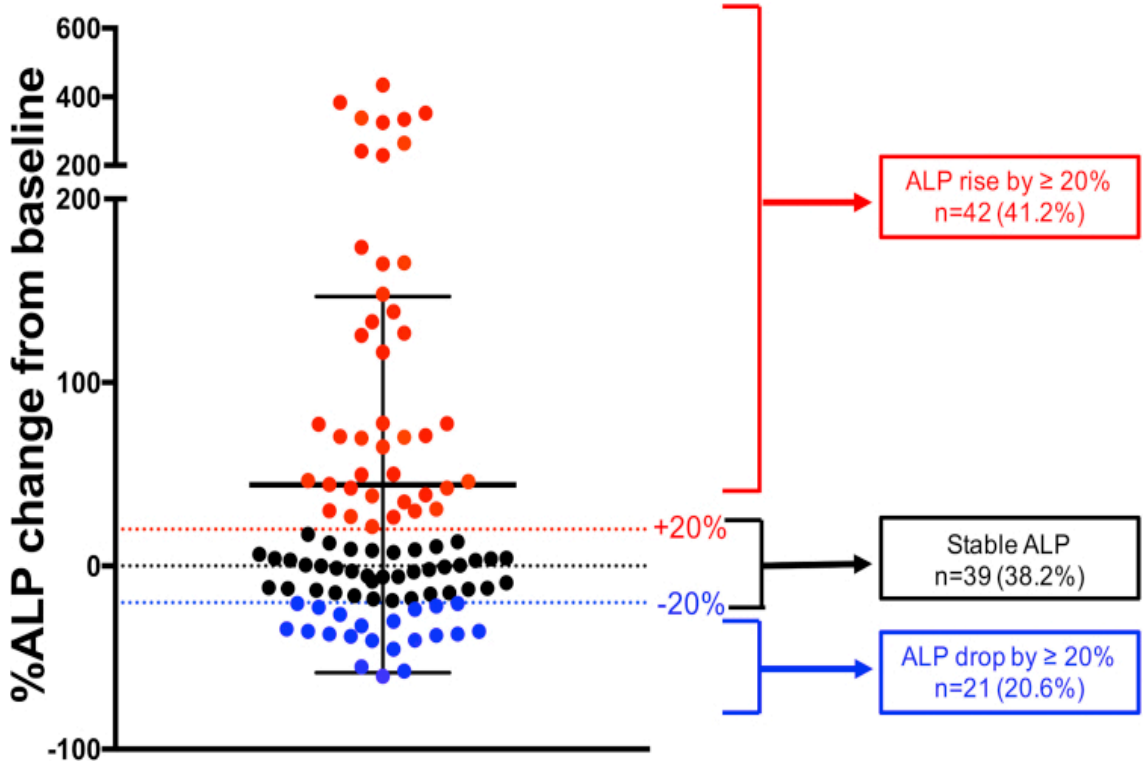
Mendes F, Jorgensen R, Keach J, et al. Elevated Serum IgG4 Concentration in Patients with Primary Sclerosing Cholangitis. Am J Gastroenterol 2006;101:2070-75

Elevated IgG4 level is associated with reduced colectomy-free survival in patients with PSC/UC

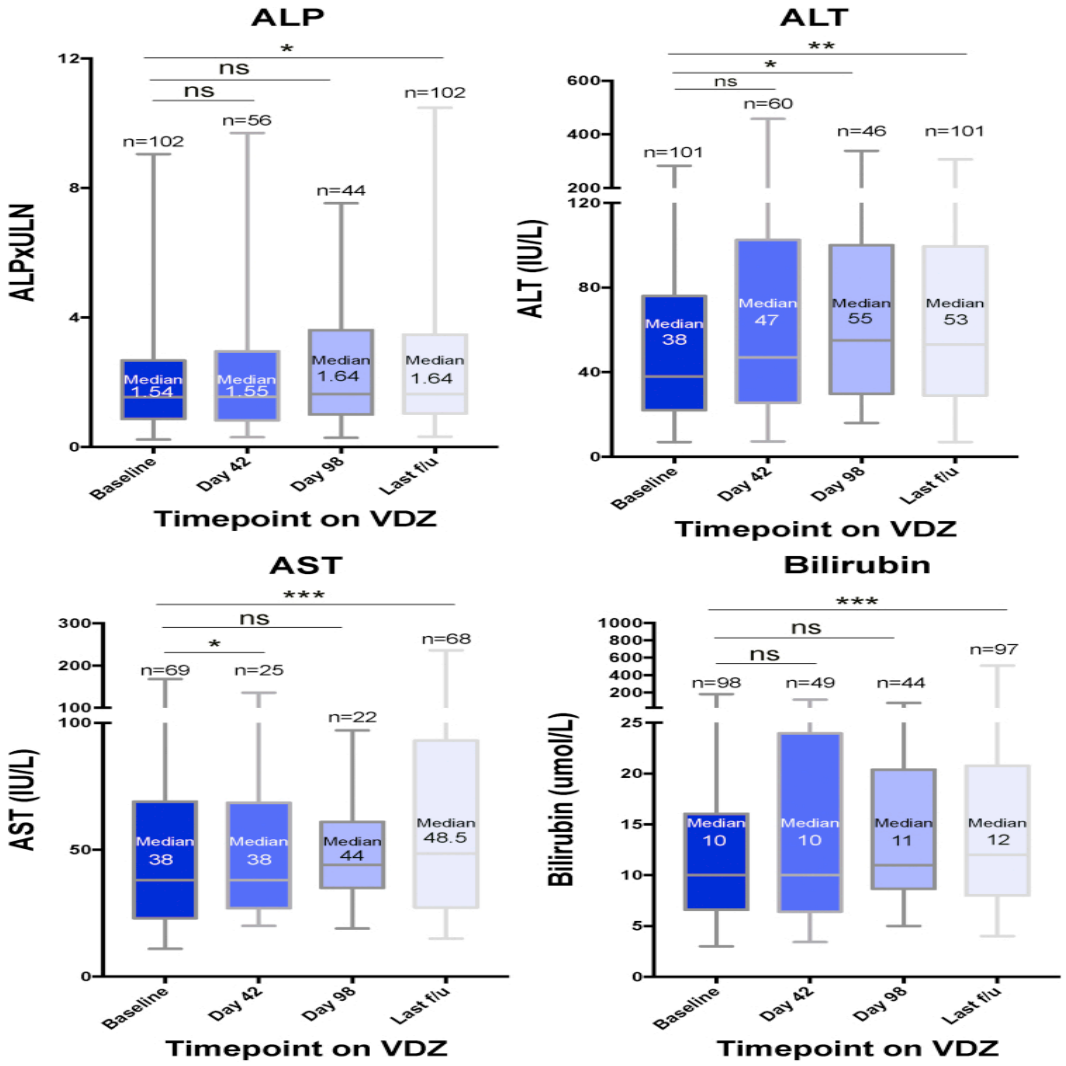


Navaneethan U, Venkatesh PGK, Choudhary M, et al. Elevated immunoglobulin G4 level is associated with reduced colectomy-free survival in patients with primary sclerosing cholangitis and ulcerative colitis. Journal of Crohn's and Colitis. 2013; 7: e35 –e41.

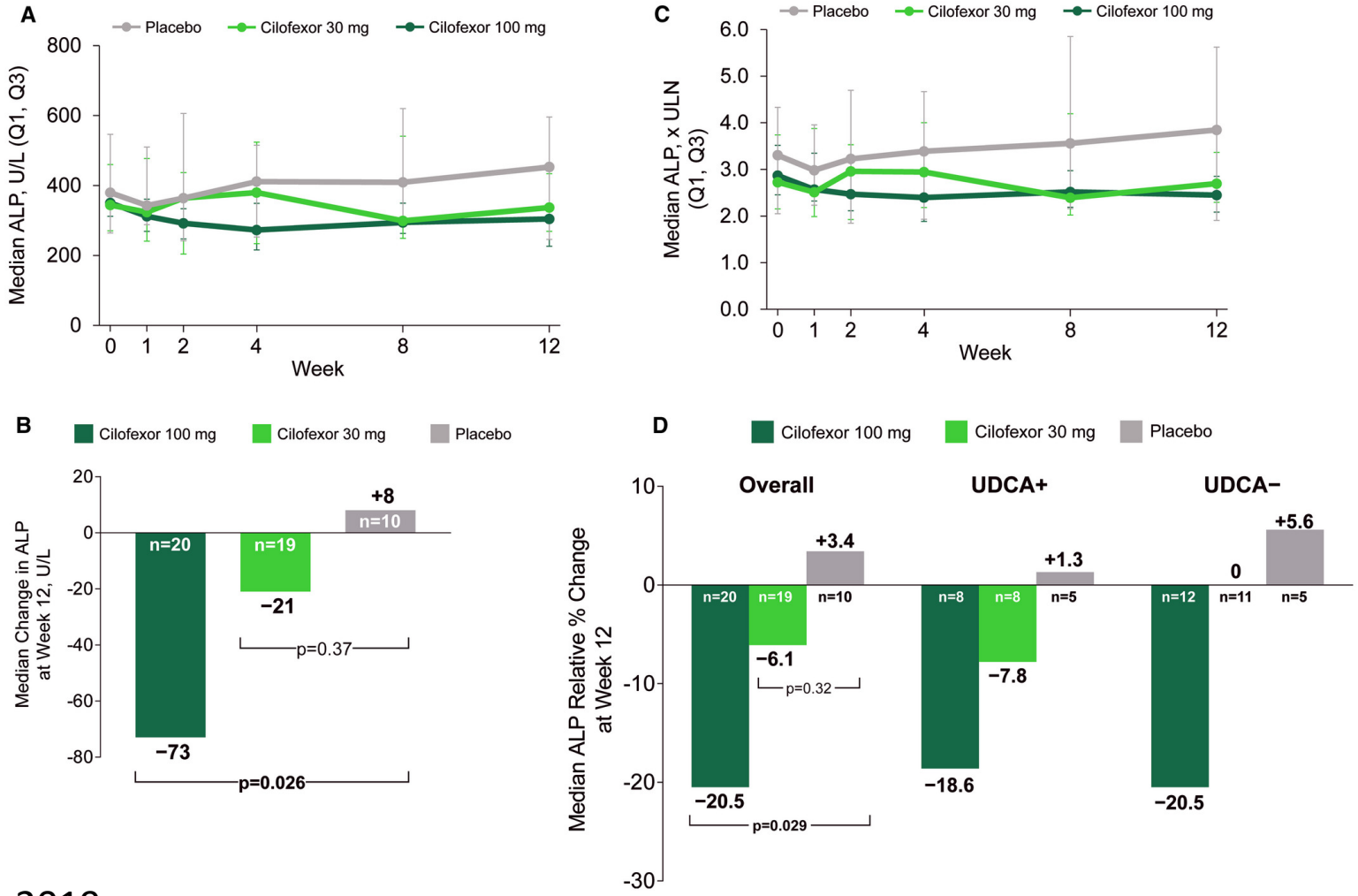
Effects of Vedolizumab in Patients With Primary Sclerosing Cholangitis and Inflammatory Bowel Diseases



CGH 2020



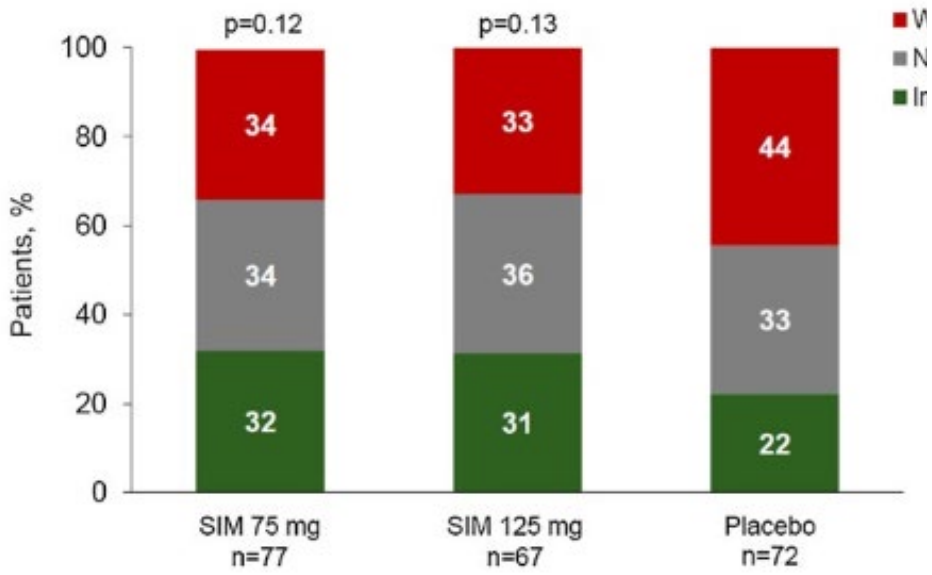
Cilofexor Improves Markers of Cholestasis and Liver Injury in Primary Sclerosing Cholangitis



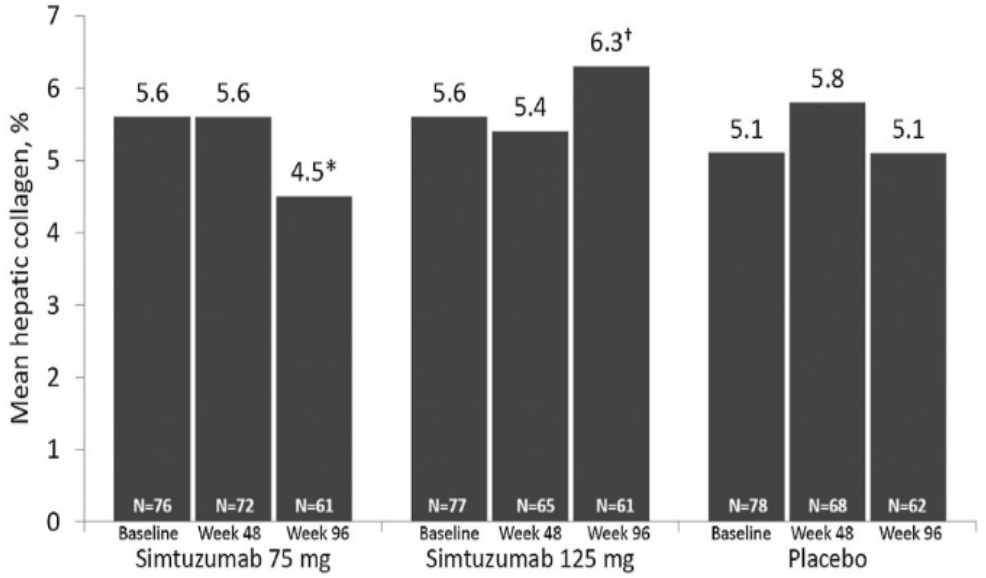
Hepatology 2019

Effect of Simtuzumab on Fibrosis in PSC

Ishak Fibrosis Stage



Hepatic Collagen Content



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PSC: Conclusions

- Pathogenesis complex
- Standard dose UDCA ineffective
- High-Dose (28-30 mg/kg) contraindicated
- Alkaline Phosphatase may be a biomarker
- Nonabsorbable antibiotics inconclusive
- Immunosuppression ineffective
- Combination therapies may be needed
- Personalized medicine may bring hope