Primary sclerosing cholangitis: current and future medical approaches

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Faculty Disclosure

I herewith declare the following paid or unpaid consultancies, business interests or sources of honoraria payments, and anything else which could potentially be viewed as a conflict of interest:

Advisor

Abbvie, Albireo, Agomab, Boehringer Ingelheim, Chemomab, Falk, Gilead, Genfit, Hightide, Intercept, Ipsen, Jannsen, Mirum, Novartis, Pliant, ProQR, Rectify

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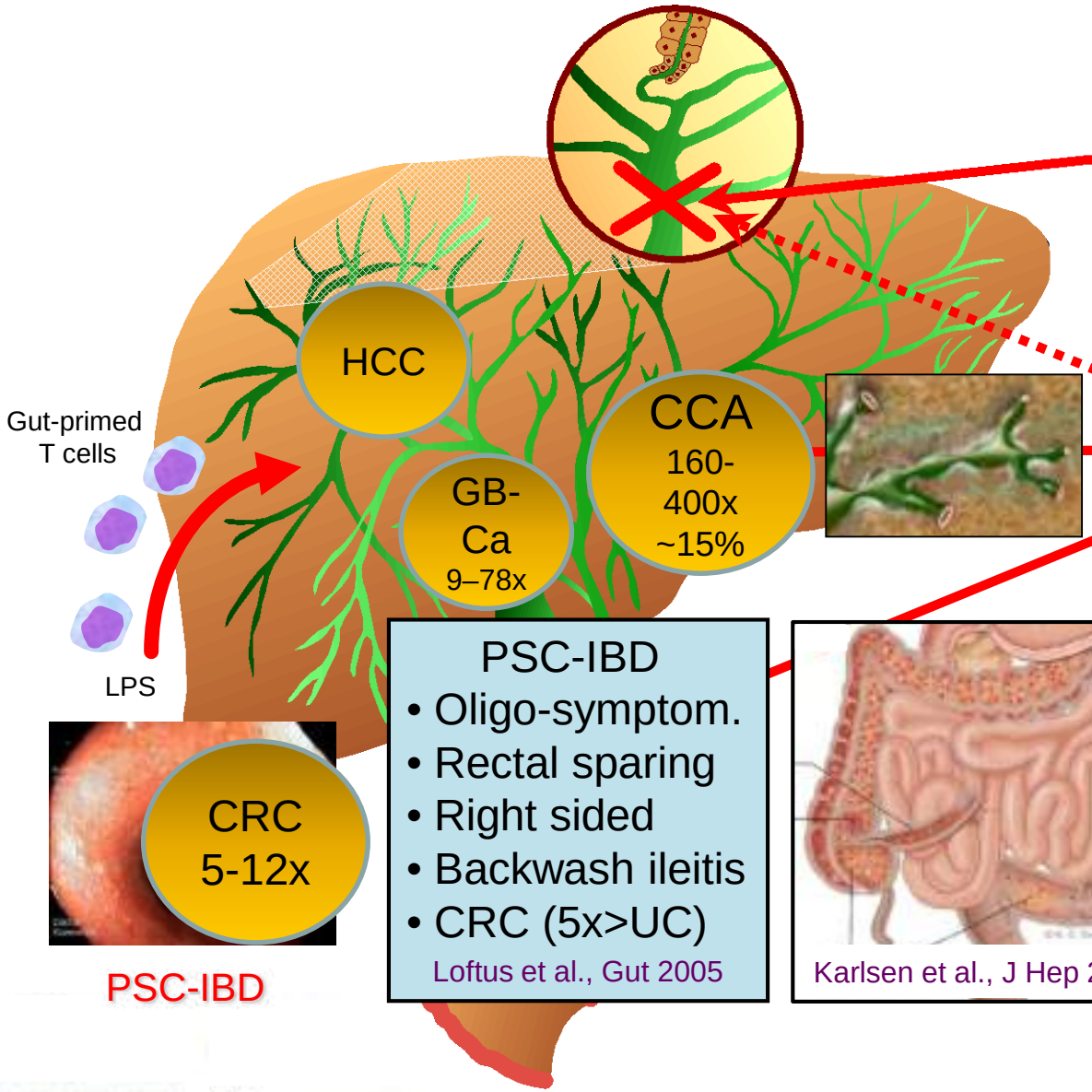
Property rights

Co-inventor (service invention) for patents on medical use of *nor*UDCA (filed by the Medical Universities of Graz and Vienna)

Biliary Diseases / Cholangiopathies: Clinical Challenges & Unmet Therapeutic Needs



Primary Biliary Cholangitis (PBC)

- Effective Rx: UDCA
- 1/3 NR: FXR, PPARs

Primary Sclerosing Cholangitis (PSC)

- No established drug Rx
  - UDCA controversial
- IBD ~ 70%
  - worse prognosis
- Malignancy risk
  - 44% of deaths

PSC-IBD

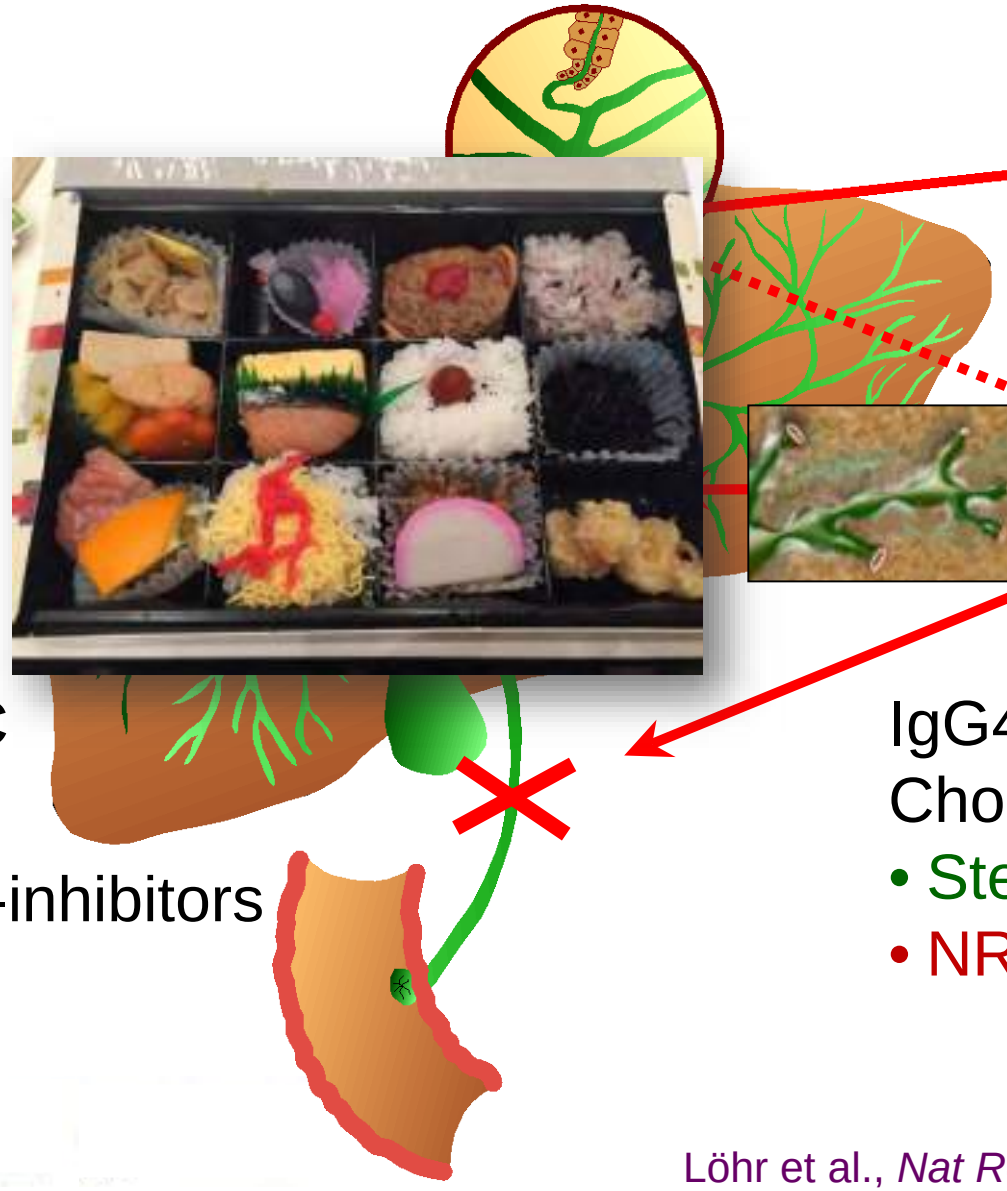
- Oligo-symptom.
- Rectal sparing
- Right sided
- Backwash ileitis
- CRC (5x>UC)

Loftus et al., Gut 2005

Karlsen et al., J Hep 2017

Reviews: Lazaridis & LaRusso, *N Engl J Med* 2016
Karlsen et al., *J Hepatol* 2017; Dyson et al., *Lancet* 2018

Biliary Diseases / Cholangiopathies: Clinical Challenges & Unmet Therapeutic Needs

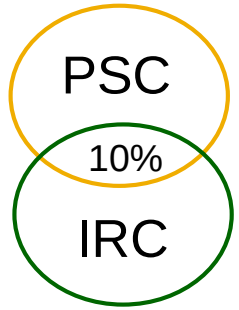


Primary Biliary Cholangitis (PBC)

Primary Sclerosing Cholangitis (PSC)

Secondary Sclerosing Cholangitis (SSC)

Identify potentially treatable causes



ABCB4 deficiency

Newer SSC Examples

Checkpoint-inhibitors
Ketamine
COVID-19

IgG4-related Cholangitis (IRC)

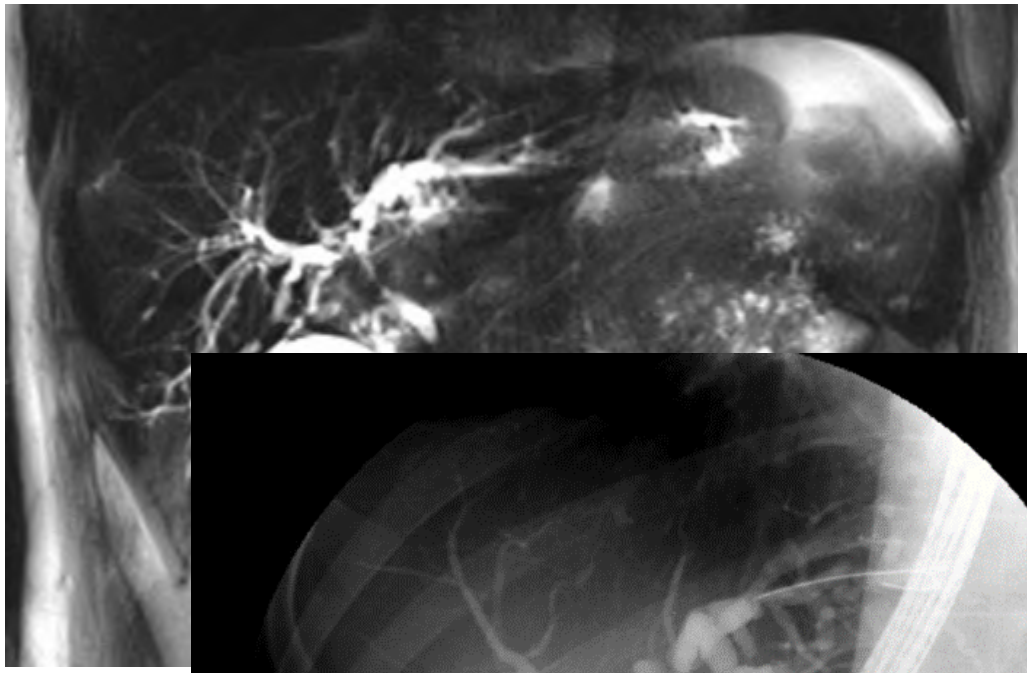
- Steroids + Aza
- NR: Rituximab

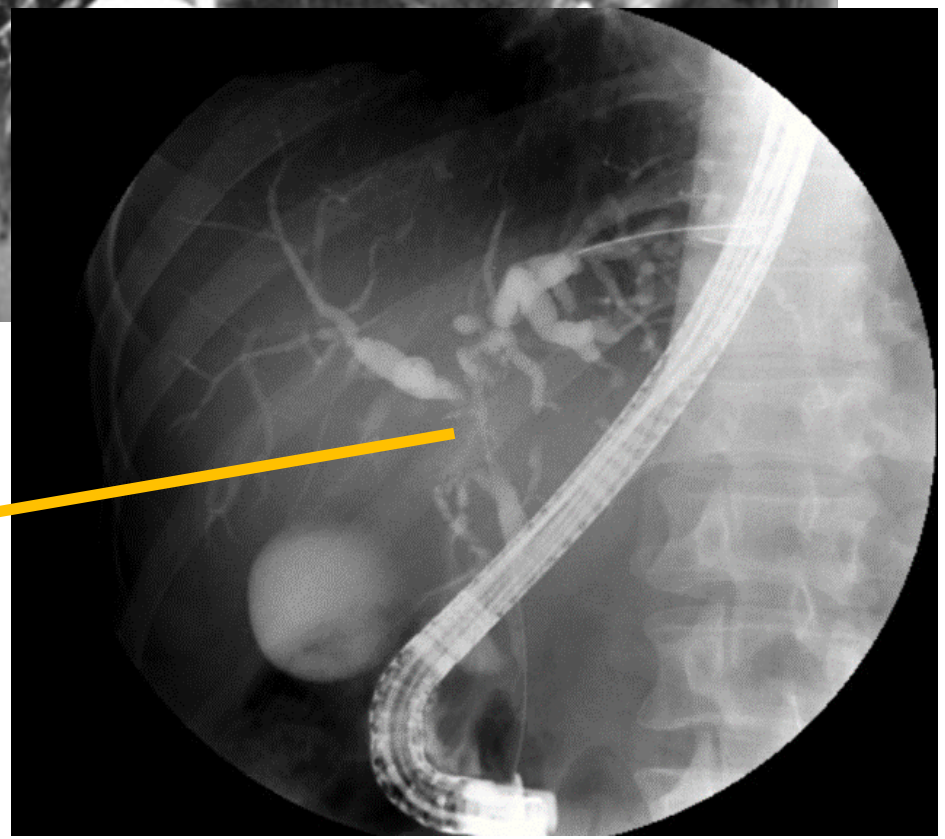
Reviews: Pötter-Lang et al., *Br J Radiol* 2021
Löhr et al., *Nat Rev Gastroenterol Hepatol* 2022; EASL CPG, *J Hepatol* 2022

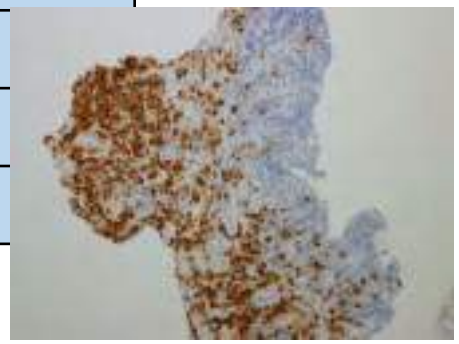
Surprises can & will happen

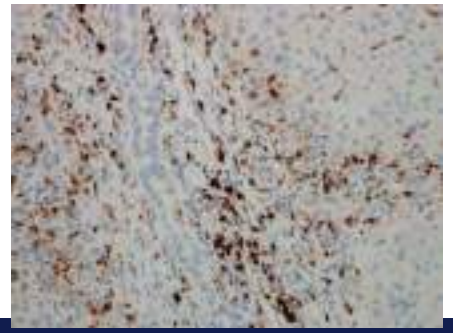
- 41 y/o, male, from Serbia
- Referral for unclear cholestasis

Bilirubin	0,74 mg/dl *(0,3-1,2)*
ALP	773 U/l *(40-130)*
GGT	679 U/l *(< 60)*
ASAT	124 U/l *(< 50)*
ALAT	188 U/l *(< 50)*





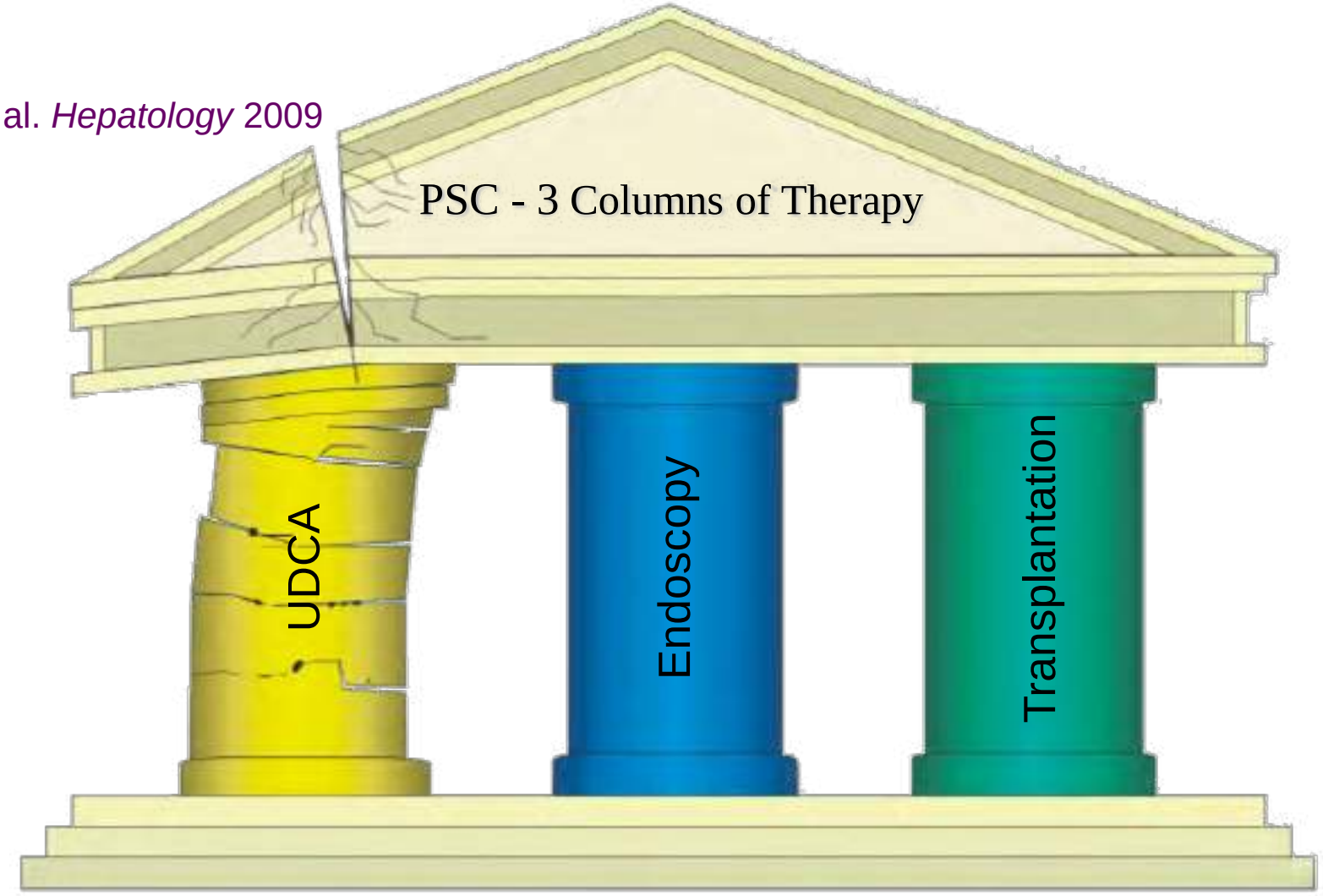




- Histological diagnosis of **Histocytosis X** (Langerin pos. IHC)

Pillars of PSC Therapy

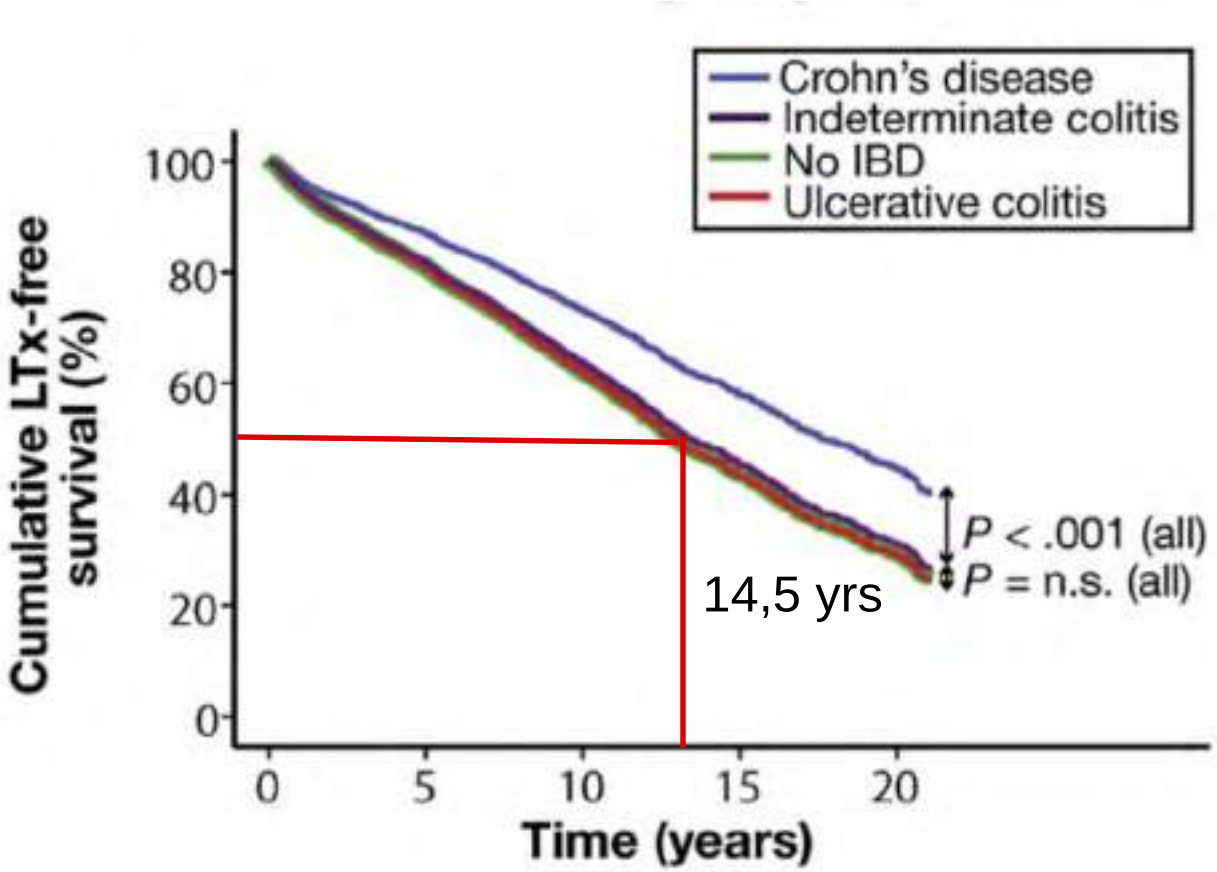
Lindor et al. *Hepatology* 2009



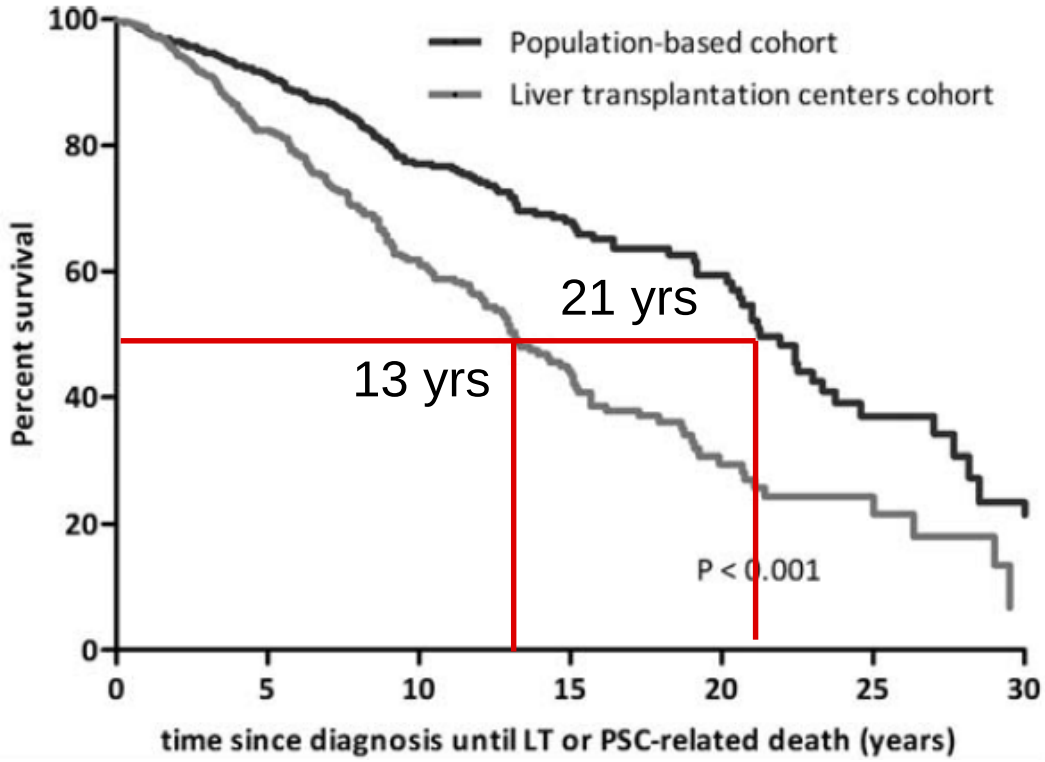
Slide courtesy Michael P. Manns

Real life data on prognosis in PSC

IPSSG (n=7121)



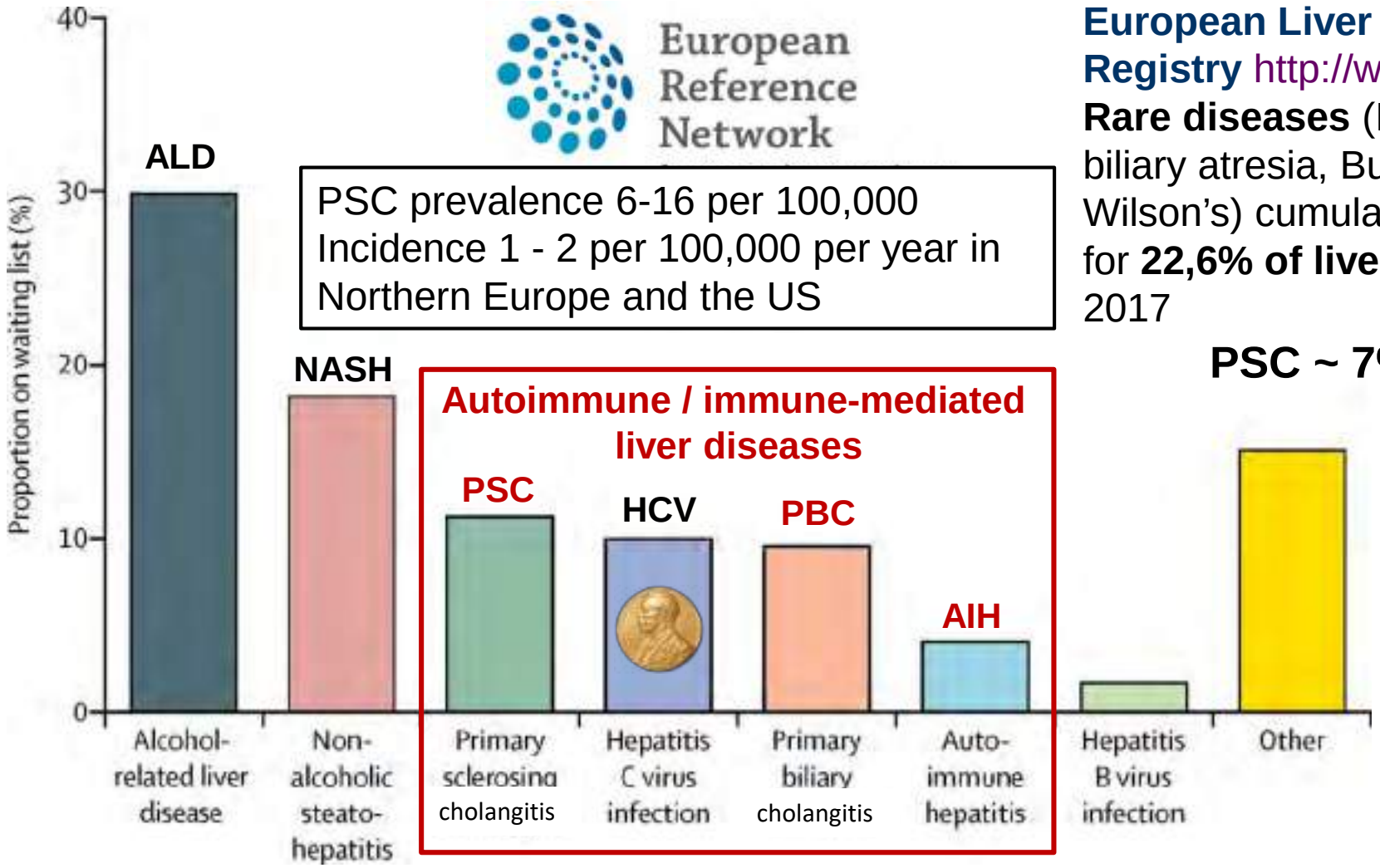
Netherlands (n=1012)



Weismüller et al., *Gastroenterology* 2017; 152: 1975-1984

Boonstra et al., *Hepatology* 2013; 58: 2045-55

Indications for liver transplantation in Europe



European Liver Transplant Registry http://www.eltr.org/
Rare diseases (PBC, PSC, AIH, biliary atresia, Budd–Chiari Wilson's) cumulatively accounted for **22,6% of liver transplants** in 2017

PSC ~ 7% in US

Williams et al., *Lancet* 2018

Indications for liver transplantation in PSC

EASL Clinical Practice Guidelines

Should

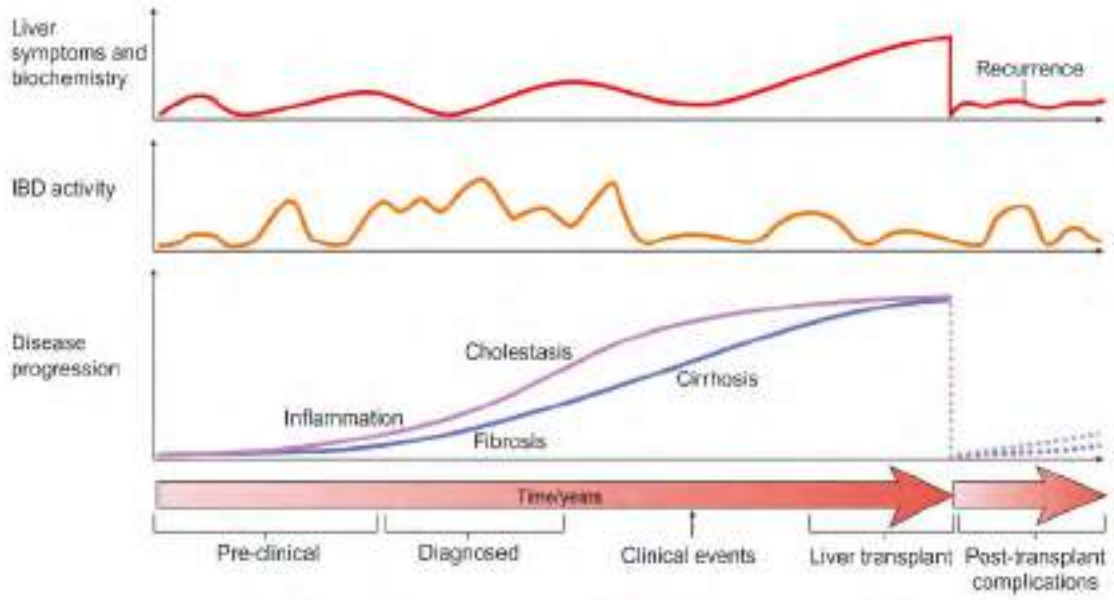
- **Decompensated cirrhosis or HCC according to standard guidelines**
  - Production of coagulation factors and serum proteins usually sustained for a long time
  - Complications of portal hypertension often occur late
- **Recurrent bacterial cholangitis and/or severe pruritus or jaundice despite endoscopic and pharmacological therapy**
  - Relevant (dominant) bile duct stenosis, progressing marasmus
  - Universally accepted definition of cholangitis lacking (LTx ind. - 17% Norway, 5% UK)
  - MELD exception points can be granted for recurrent cholangitis (controversial)

Can

- **High-grade biliary dysplasia (cytology or ductal histology)**
  - 20%(-60%) of the liver explants may show no signs of neoplasia
- **Early-stage pCCA in PSC within the context of clinical trials**
  - Highly selected cases with early-stage CCA < 3 cm (Mayo criteria), most often after neoadjuvant chemoradiation

EASL CPG, *J Hepatol* 2022

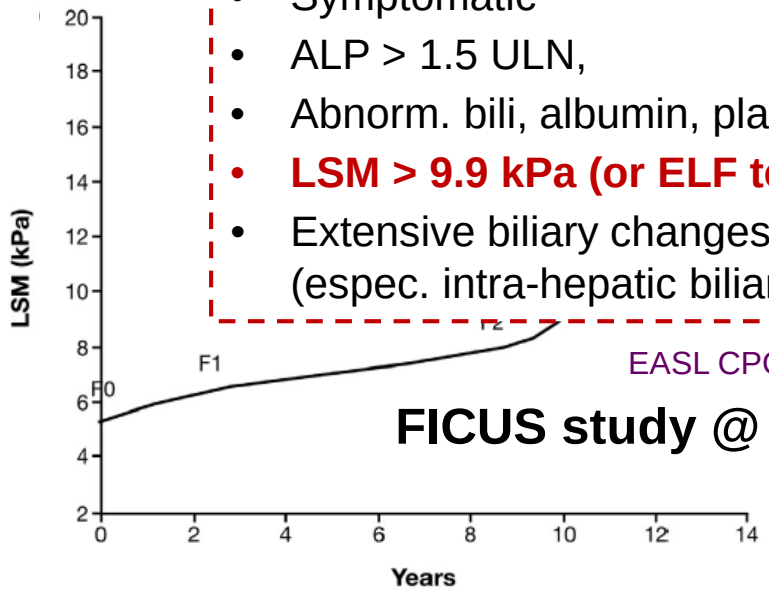
Disease course of PSC – role of fibrosis



Karlsen et al., *J Hepatol* 2017

"Significant risk" if any present:

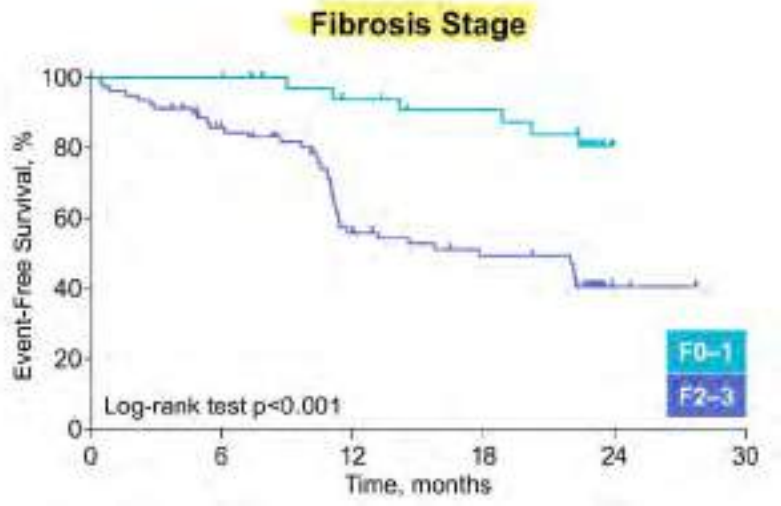
- Symptomatic
- ALP > 1.5 ULN,
- Abnorm. bili, albumin, platelets, or PT
- **LSM > 9.9 kPa (or ELF test > 10.6)**
- Extensive biliary changes (espec. intra-hepatic biliary dilatation)



EASL CPG, *J Hepatol* 2022

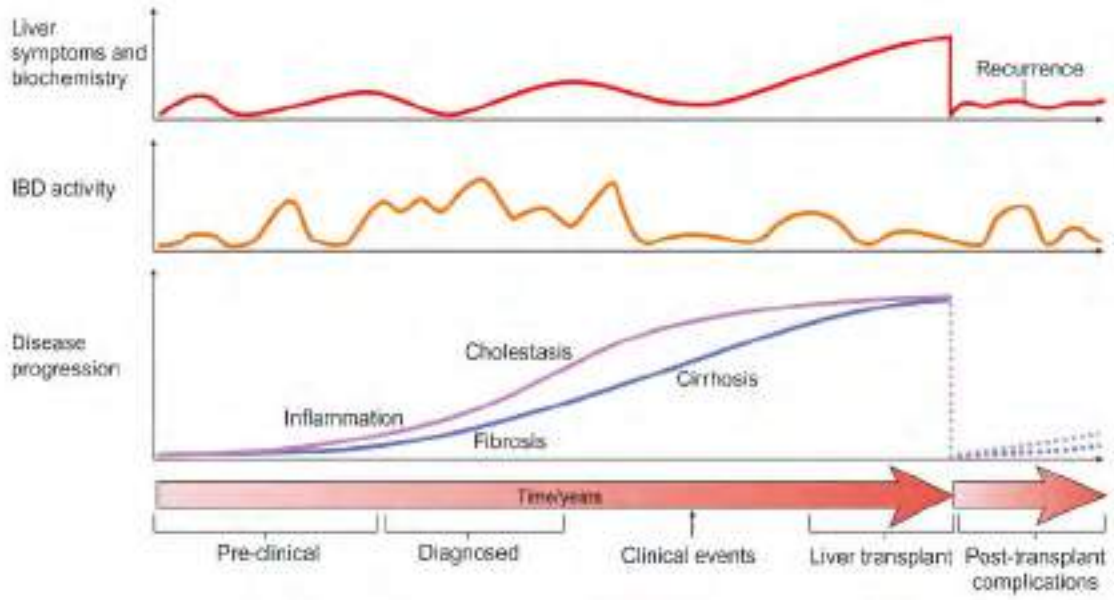
FICUS study @ EASL 2024

Corpechot et al., *Gastroenterology* 2014

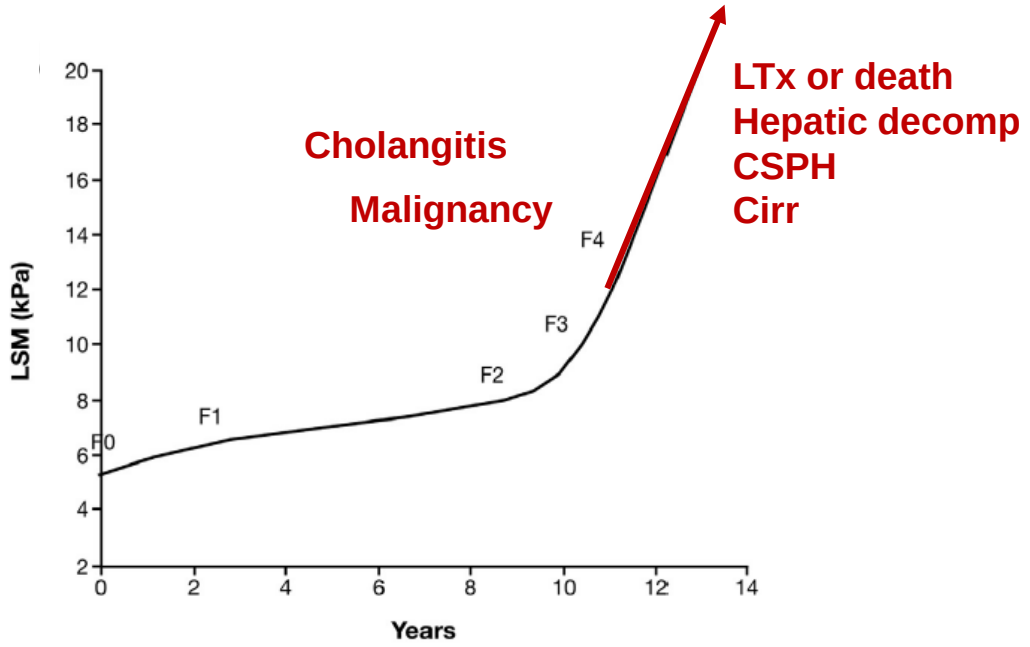


Trauner et al., *BMC Gastro* 2023

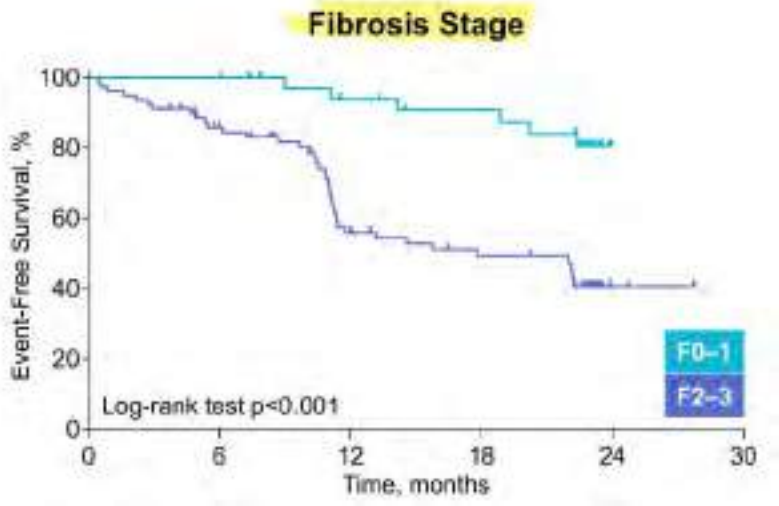
Disease course of PSC – role of fibrosis



Karlsen et al., *J Hepatol* 2017



Corpechot et al., *Gastroenterology* 2014



Trauner et al., *BMC Gastro* 2023

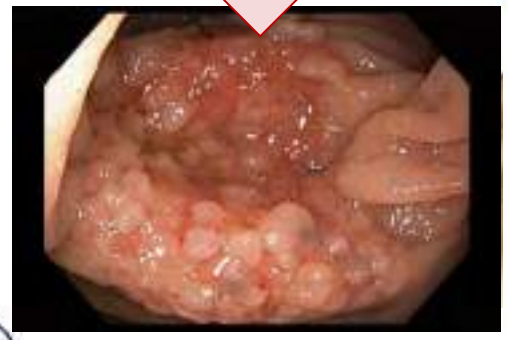
Cancer risk in PSC

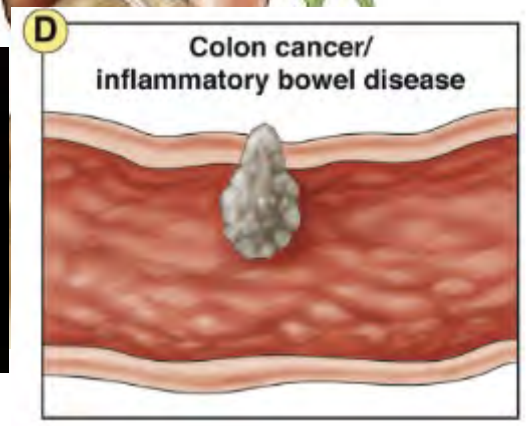
44% of deaths in PSC are due to cancer

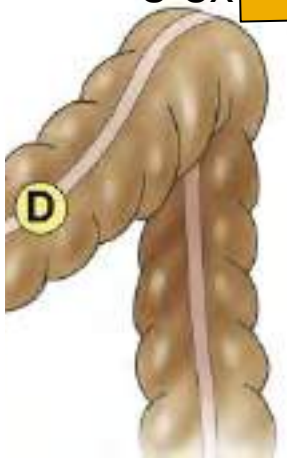
Bergquist et al., *J Hepatol* 2002; 36: 321–27

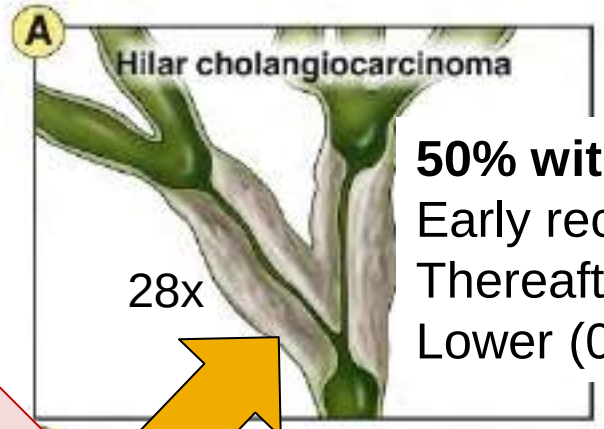
Surveillance (EASL & AASLD CPG):
MRI/MRCP and/or **US** (incl GB) every 12 mo
- US every 6 mo for cirr. (HCC)

Colonoscopy every 12 (-24) mo
- recall after 5 yrs for those without IBD



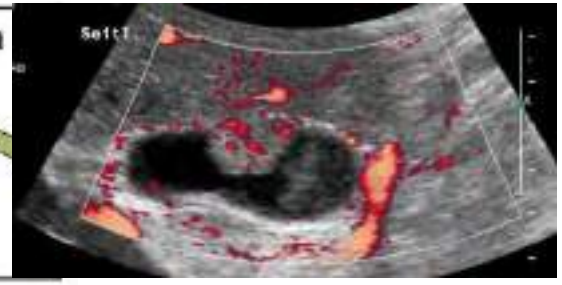






IBD

3-5x



50% within first 4-12 mo
Early recall after diagnosis?
Thereafter 1,5%/year
Lower (0.5%) in recent studies

Rizivi et al., *Clin Gastroenterol Hepatol* 2015; 13: 2152-65

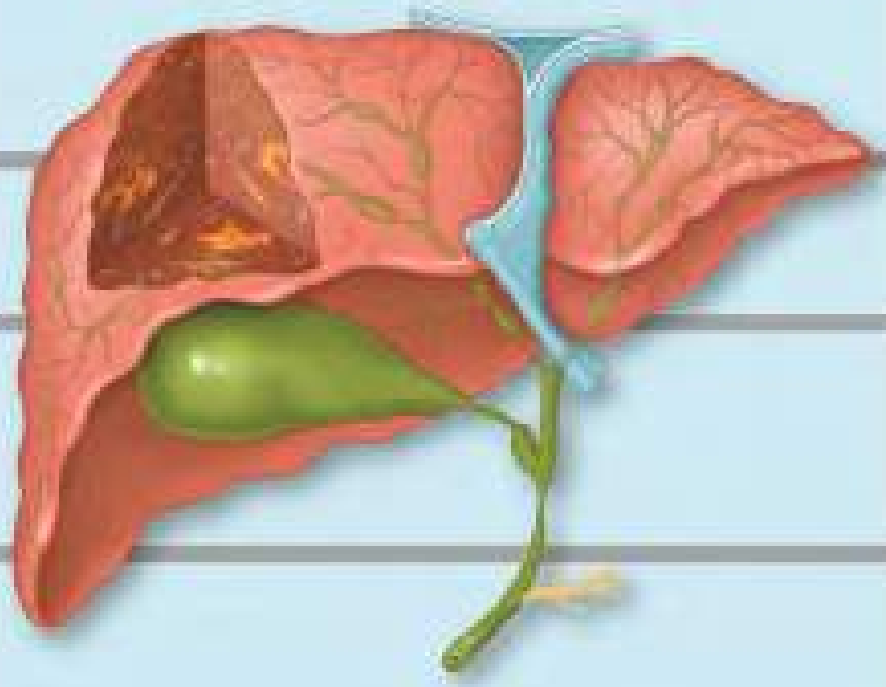
Therapeutic landscape in PSC

Therapy of PSC – Today‘s standard

- No approved / established medical therapy of PSC
- **UDCA** at doses of 15-20 mg/kg/d can be given (AASLD:13-23mg/kg/d)
  - Serum liver tests ↓, colorectal dysplasia ⇣?; so far no proven survival benefit (Japan?)
  - UDCA at doses of 28-30 mg/kg/d is harmful and should be avoided

EASL CPG on SC *J Hepatol* 2022, AASLD CPG on PSC and CCC *Hepatology* 2022

Emerging Treatment Options for PSC - Overview
Candidates for Recent & Ongoing Clinical Trials

Treatment	Biliary strictures and cholestasis	ALP signal
Bile-acid based therapy and PPARs • UDCA • *nor*UDCA • FXR and FGF19 analogues • Bezafibrate and fenofibrate • IBAT inhibitors (no ALP signal)		✓
Microbiota-based therapy • Antibiotics (e.g. vancomycin) • Fecal transplantation, bacteriophages		✓
Immune-modulation therapy • Glucocorticoids and azathioprine • Calcineurin-inhibitors and MMF • Anti-TNFα • Vedolizumab • Simtuzumab (i.e. anti-fibrotic)		✗

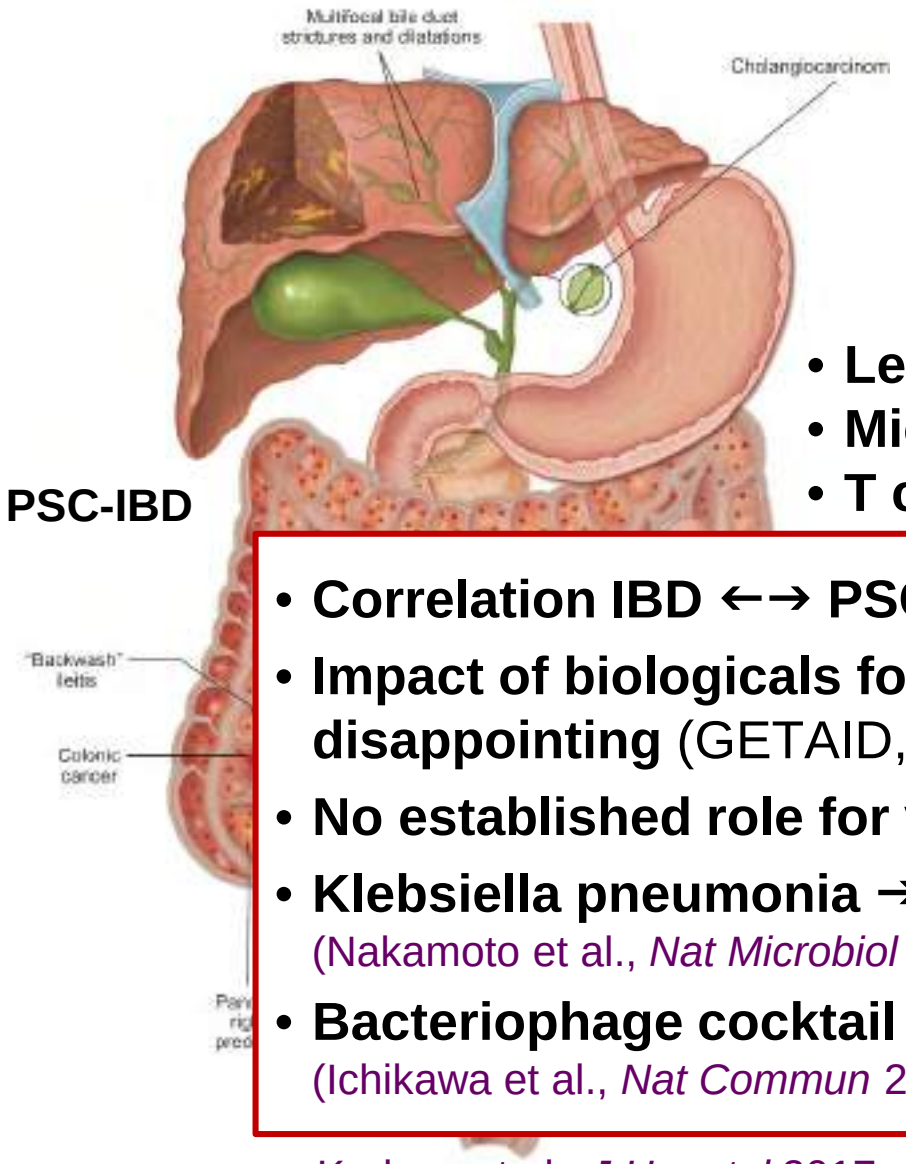
Pruritus

Cenicriviroc, **Tofa?**

Earlier diagnosis (before sclerosis)

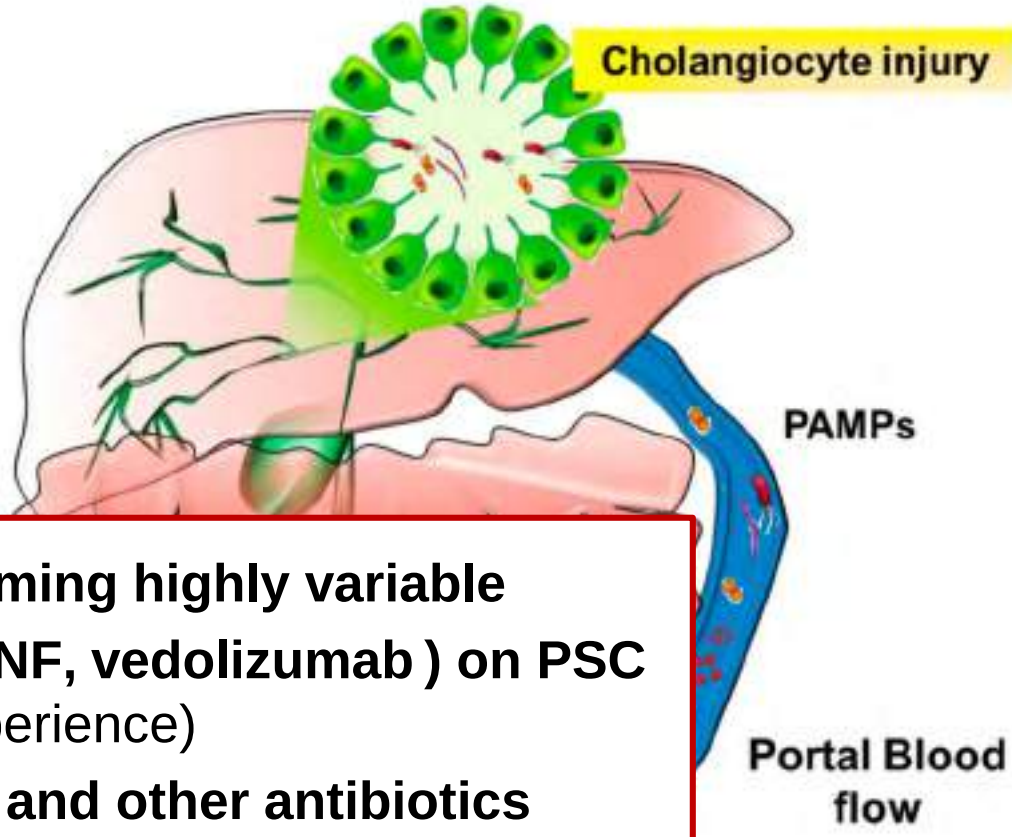
Modified after: Vesterhus & Karlsen, *J Gastroenterol* 2020; 55: 588–614

Role of gut-liver axis in pathogenesis of PSC



PSC-IBD

- **Leaky gut**
- **Microbiome**
- **T cell homing**

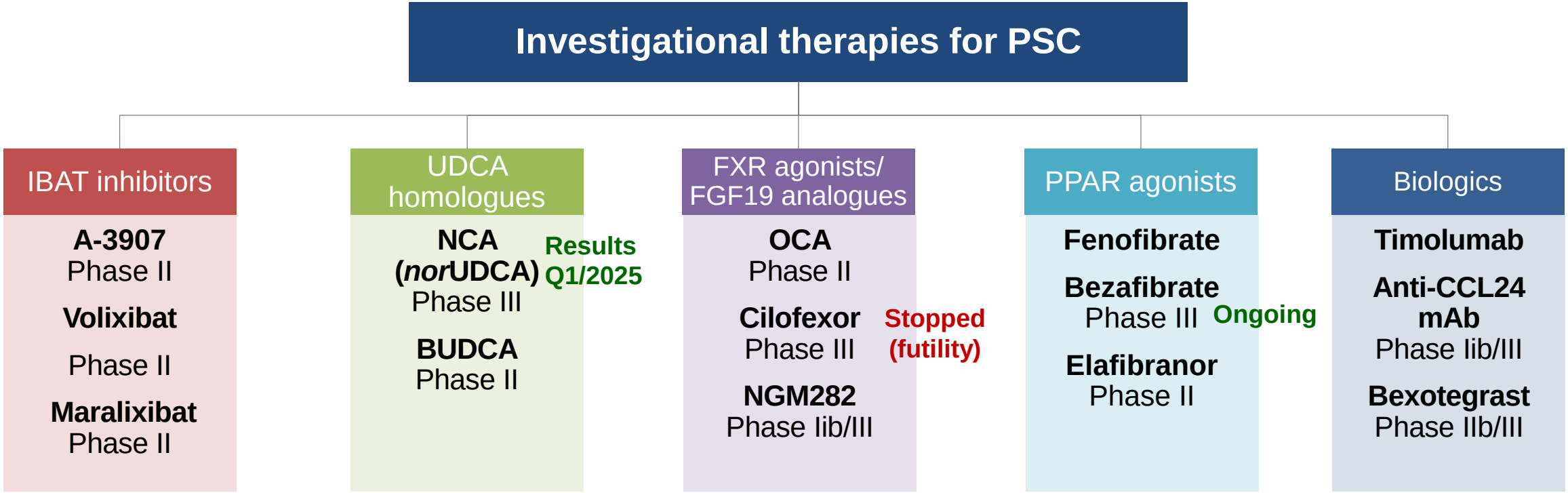


- **Correlation IBD ←→ PSC activity / timing highly variable**
- **Impact of biologicals for IBD (anti-TNF, vedolizumab) on PSC disappointing** (GETAID, IPSCSG experience)
- **No established role for vancomycin and other antibiotics**
- **Klebsiella pneumonia → T_H17-mediated hepatobiliary injury** (Nakamoto et al., *Nat Microbiol* 2019)
- **Bacteriophage cocktail attenuates experimental PSC** (Ichikawa et al., *Nat Commun* 2023)

Karlsen et al., *J Hepatol* 2017
Hov & Karlsen, *Nat Rev Gastroenterol Hepatol* 2023

Giordano et al., *Int J Mol Sci* 2018

Emerging Treatment Options for PSC - Overview
Candidates for Recent & Ongoing Clinical Trials



Modified after: Slide courtesy Chris Bowlus 2024

Topline results of recent phase 2 studies in PSC

	Drug (target)	ALP	Fibrosis	C4	FGF19	Pruritus	
Phase 3 stopped	**Obeticholic acid** (FXR) [1]	**reduced** (-25-30%)	unchanged	reduced	increased	**worsened**	
	Cilofexor [2] (FXR)	**reduced** (-21%)	(reduced NITs)	(reduced)	(increased)	unchanged	
	Aldafermin [3] (FGF19)	unchanged	**reduced NITs**	reduced	n.d.	unchanged	Phase 2b/3?
	Elafibranor [4] (PPARα/δ)	reduced (-45%)	stabilized NITs	n.d.	n.d.	**improved**	
Phase 3 completed	**NCA (*nor*UDCA)** [5]	**reduced** (-26%)	n.d.	n.d.	n.d.	unchanged	
	Cenicriviroc [6] (CCR2/5)	unchanged (-18% n.s.)	unchanged NITs	n.d.	n.d.	unchanged	
	Simtuzumab [7] (LOXL2)	unchanged	unchanged Ishak score	n.d.	n.d.	unchanged	
	Bexotegrast [8] ($\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrin/TGFβ)	reduced	stabilized NITs	n.d.	n.d.	reduced (vs PBO)	Phase 2b/3?
	Nebokitug [9] (CCL24)	unchanged (-2,5%)	**reduced NITs**	n.d.	n.d.	**improved**	Phase 2b/3 announced

1: Kowdley et al., *J Hepatol* 2020; 2: Trauner et al., *Hepatology* 2019 & *Clin Gastro Hep* 2022; 3: Hirschfield et al., *J Hepatol* 2019; 4: Levy et al., J Hepatol 2025; 5:Fickert et al., *J Hepatol* 2017; 6: Eksteen et al., *Hepatol Commun* 2020; 7: Muir et al., *Hepatology* 2019; 8: Kowdley et al., AASLD 2024; 9: Bowlus et al., AALSD 2024

A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of cilofexor in patients with non-cirrhotic PSC

Adults with large duct PSC and liver fibrosis stage F0–F3* (N=419)†

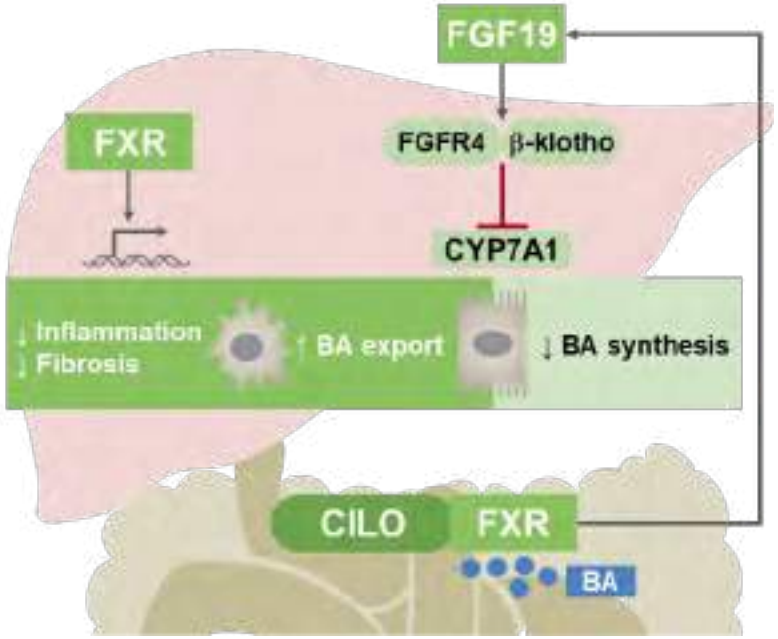
R 2:1

CILO 100 mg orally QD (n=277)

PBO (n=139)

Primary endpoint: Proportion of patients with progression of liver fibrosis‡ at Week 96

Pre-planned interim futility analysis§: Performed after 160 randomized patients received study drug and either completed Week 96 or had an early termination visit

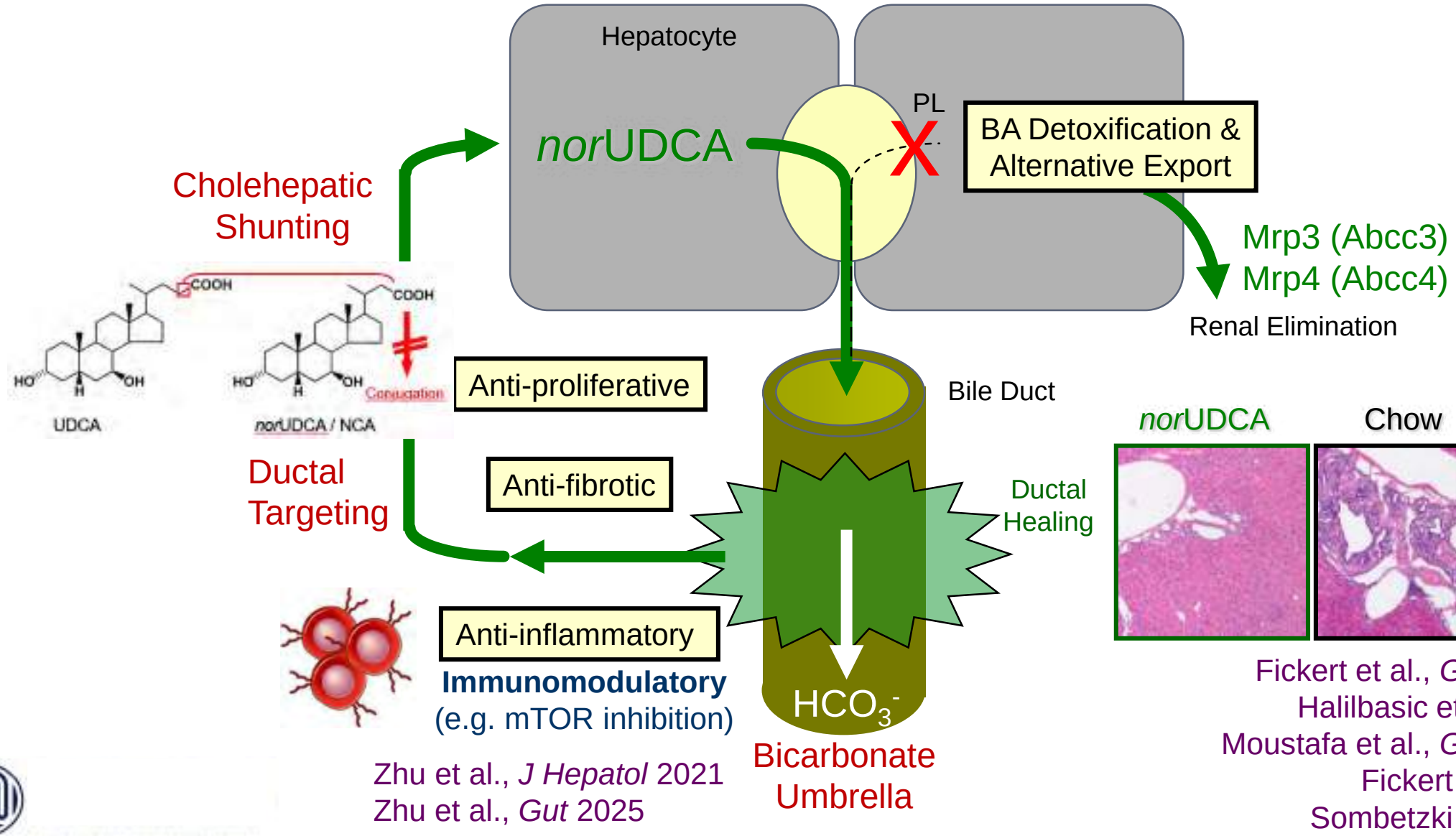


- **Phase 3 trial (PRIMIS) was terminated** early because the interim futility analysis showed that the estimated probability of meeting the primary endpoint was 6.8%
- At week 96, the proportion of patients with a **≥ 1-stage increase in fibrosis** (Ludwig stage) was **30.8%** in the CILO group compared with **32.8%** in the placebo group

*Ludwig stage. †Three participants were removed due to a randomization error. ‡≥1-stage increase in fibrosis score. §Early trial termination was considered if the likelihood (based on predictive power approach) of meeting its primary endpoint (if continued) was ≤10%

Trauner M, et al. EASL 2023; LBO-03

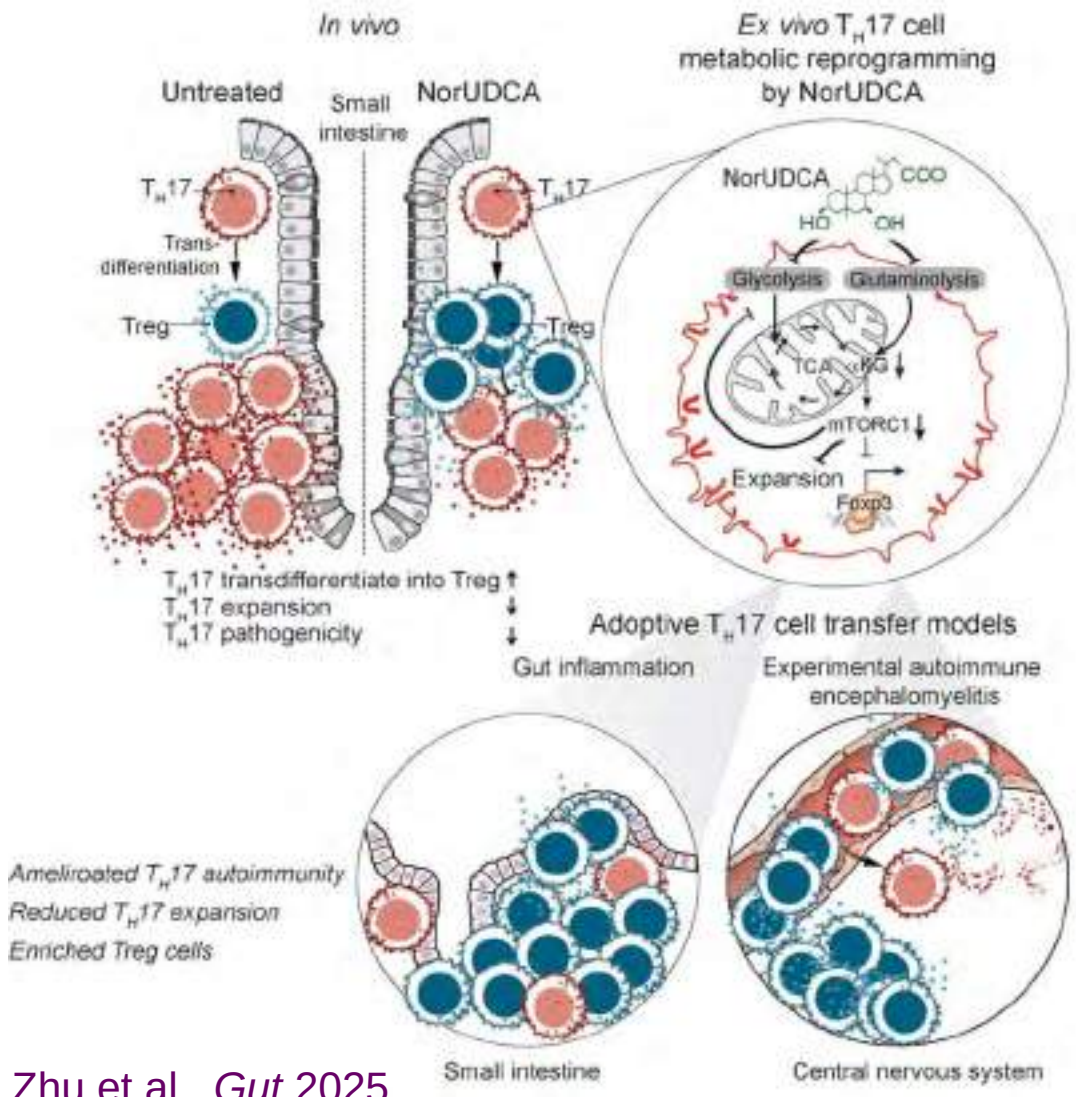
*nor*UDCA / norucholic acid (NCA): Mechanisms of Action in *Mdr2 (Abcb4)*$^{-/-}$ Model of Sclerosing Cholangitis

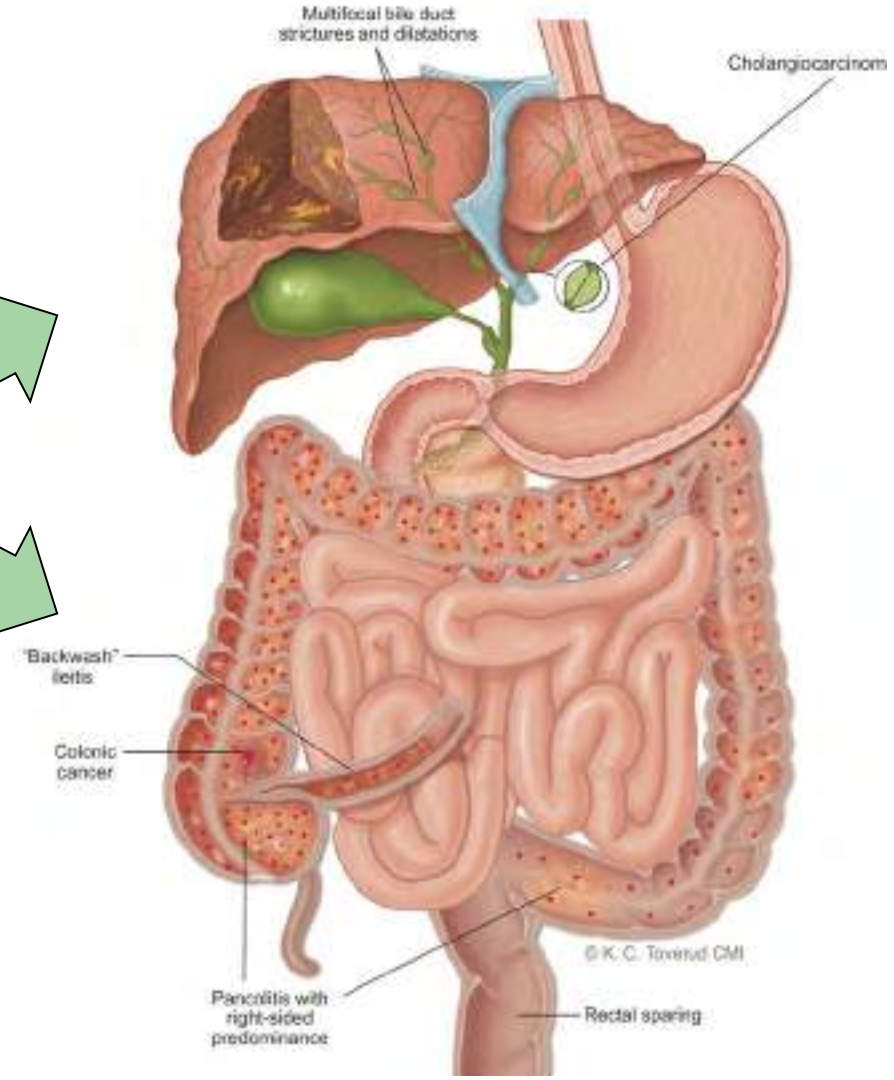


Zhu et al., *J Hepatol* 2021
Zhu et al., *Gut* 2025

Fickert et al., *Gastroenterology* 2006
Halilbasic et al., *Hepatology* 2009
Moustafa et al., *Gastroenterology* 2012
Fickert et al., *J Hepatol* 2013
Sombetzki et al., *J Hepatol* 2015

*nor*UDCA / NCA regulates metabolism and signaling pathways that support T_H17 transdifferentiation into Treg cells





Zhu et al., *Gut* 2025

Karlsen et al., *J Hepatol* 2017

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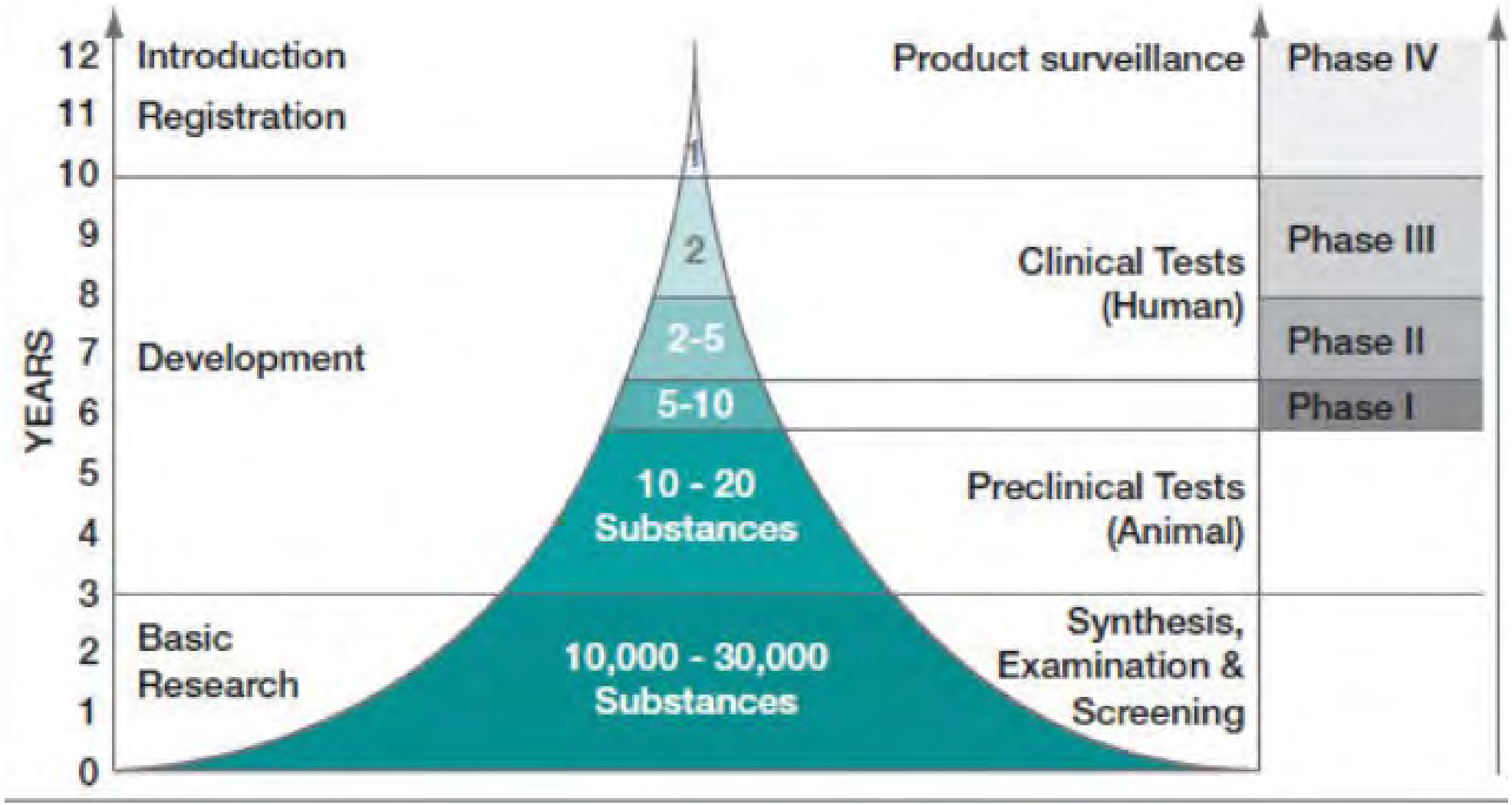
Norucholic acid for the treatment of primary sclerosing cholangitis: 96-week analysis of a pivotal phase 3 trial

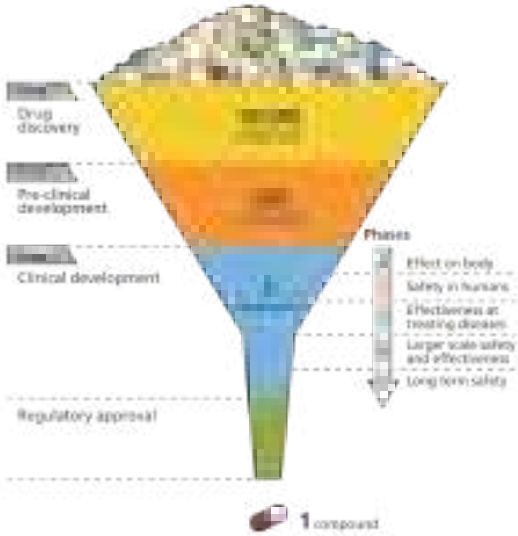
Michael Trauner[1], Palak J. Trivedi[2], Gerald Denk[3], Martti Färkkilä[4], Peter Schirmacher[5], Stefan G. Hübscher[6], Michael Dill[7], Gerda E. Villadsen[8], Christoph P. Berg[9], Kristin K. Jørgensen[10, 11], Marcel Vetter[12], Münevver Demir[13], Andreas E. Kremer[14], Christoph Schramm[15], Christian Strassburg[16], Heike Bantel[17], Tobias Böttler[18], Ulrich Beuers[19], Alexandre Louvet[20], Emina Halilbasic[1], Michael Stiess[21], Markus Proels[21], Ralph Mueller[21], Peter Fickert[22], Michael P. Manns[17, 23]

on behalf of the European PSC-NCA study group

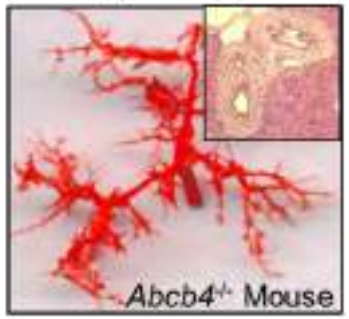
[1]Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University of Vienna, Vienna, Austria, [2]NIHR Birmingham Biomedical Research Centre, University of Birmingham, Birmingham, United Kingdom, [3]Department of Medicine II, University Hospital LMU, Munich, Germany, [4]Department of Gastroenterology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, [5]Institute of Pathology, University Hospital Heidelberg, Heidelberg University, Heidelberg, Germany, [6]School of Infection, Inflammation and Immunology, University of Birmingham, Birmingham, United Kingdom, [7]Department of Gastroenterology, Hepatology, Infectious Diseases and Intoxications, Heidelberg University Hospital, Heidelberg, Germany, [8]Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark, [9]Department of Gastroenterology, Hepatology and Infectiology, University Hospital Tübingen, Tübingen, Germany, [10]Norwegian PSC Research Center, Department of Transplantation Medicine, Clinic of Surgery and Specialized Medicine, Oslo University Hospital Rikshospitalet, Oslo, Norway, [11]Department of Gastroenterology, Akershus University Hospital, Akershus, Norway, [12]Department of Medicine 1, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany, [13]Department of Hepatology and Gastroenterology, Charité Universitätsmedizin Berlin, Berlin, Germany, [14]Department of Gastroenterology and Hepatology, University Hospital Zürich, University of Zürich, Zürich, Switzerland, [15]Department of Medicine and Martin Zeitz Centre for Rare Diseases, University Medical Centre Hamburg-Eppendorf, Hamburg, Germany, [16]Department of Internal Medicine I, University Hospital Bonn, Bonn, Germany, [17]Department of Gastroenterology, Hepatology, Infectious Diseases and Endocrinology, Hannover Medical School, Hannover, Germany, [18]Department of Medicine II, University Hospital Freiburg, Freiburg, Germany, [19]Department of Gastroenterology and Hepatology, Amsterdam UMC, Locatie AMC, Amsterdam, Netherlands, [20]Services des maladies de l'appareil digestif, CHRU de Lille, Lille, France, [21]Dr. Falk Pharma GmbH, Freiburg, Germany, [22]Department of Medicine, Medical University of Graz, Graz, Austria, [23]Center for Individualized Infection Medicine (CiiM), Hannover, Germany

Clinical drug discovery pyramid / funnel





Sclerosing cholangitis model



Fickert et al., *Gastro* 2002
Fickert et al., *Gastro* 2004

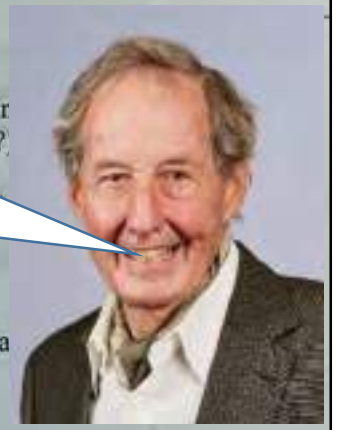
Sun et al., *Acta Pharmaceutica Sinica B* 2022

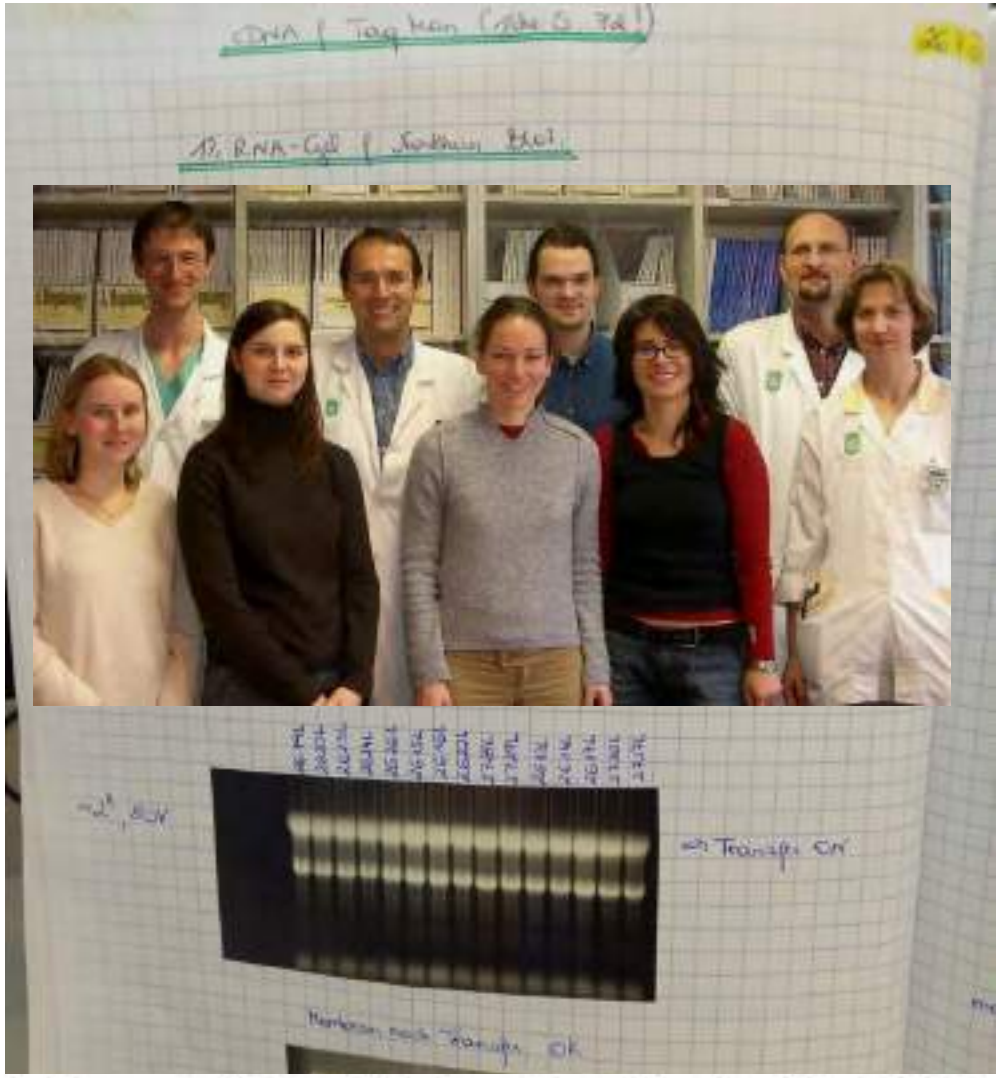
- Falls GSH denit. Vermindert: Mechanismus (Mrp2 Lokalisation) cohibelling DPPIV, radixin etc.
- Charakterisierung der Fibrogenese (samples bei Schuppan, Analyse pending)
- Ntcp, SHP Northern 8 w, n=3
- NORs and HNFs (falls RNA vermindert, dürfte it Lit nicht der Fall sein, aber wir zählen schon die Ameisenlaster... Antwort: RNA vermindert!!!!)
- ANCA etablieren
- TGFb1 in situ pending
- Dominant strictures (Epithelprotif.?)
- CHIP 2 und 8 w: Resultate pending
- TGFb in situ Hybridisierung
- LJ34, Keratin 8/18 ISH (onset of bile duct stress/injury???)
- Gallengangs-Phänotyp Weibchen

6. Mdr2-/- Folgeprojekte: Therapeutische Intervention
Ersteller/Hauptverantwortlicher: Peter

- Aktuell (si
- Zukunft:
  - Oxid Stress
  - Antifibrose-Strategien (Kollab mit Schuppan) mit Fra
    abgesprochen (Fokus auf TIMP)
  - Anti-oxid. Stress
  - PARP Inhibition?
  - Non-choleretic doses of UDCA bereits der schwangeren „Mutter" geben, check ob in Muttermilch (Z Gastroenterol. 1996 Mar;34(3):188-91: When the patient's breast milk was analyzed by high pressure liquid chromatography, cholic acid, deoxycholic acid and lithocholic acid, but not UDCA were detected in trace amount)
  - Nor-UDCA (noch besseres bile duct targeting)
  - Sulindac (COX inhibition targeted to the bile duct epithelium)
  - Heterozygotes +/- Challenge mit Noxe
  - FVBN Genotyp (more injury?) Frank Lammert
  - Caspase Inhibitoren (lt. Alan excreted into bile)

Try *nor*UDCA!





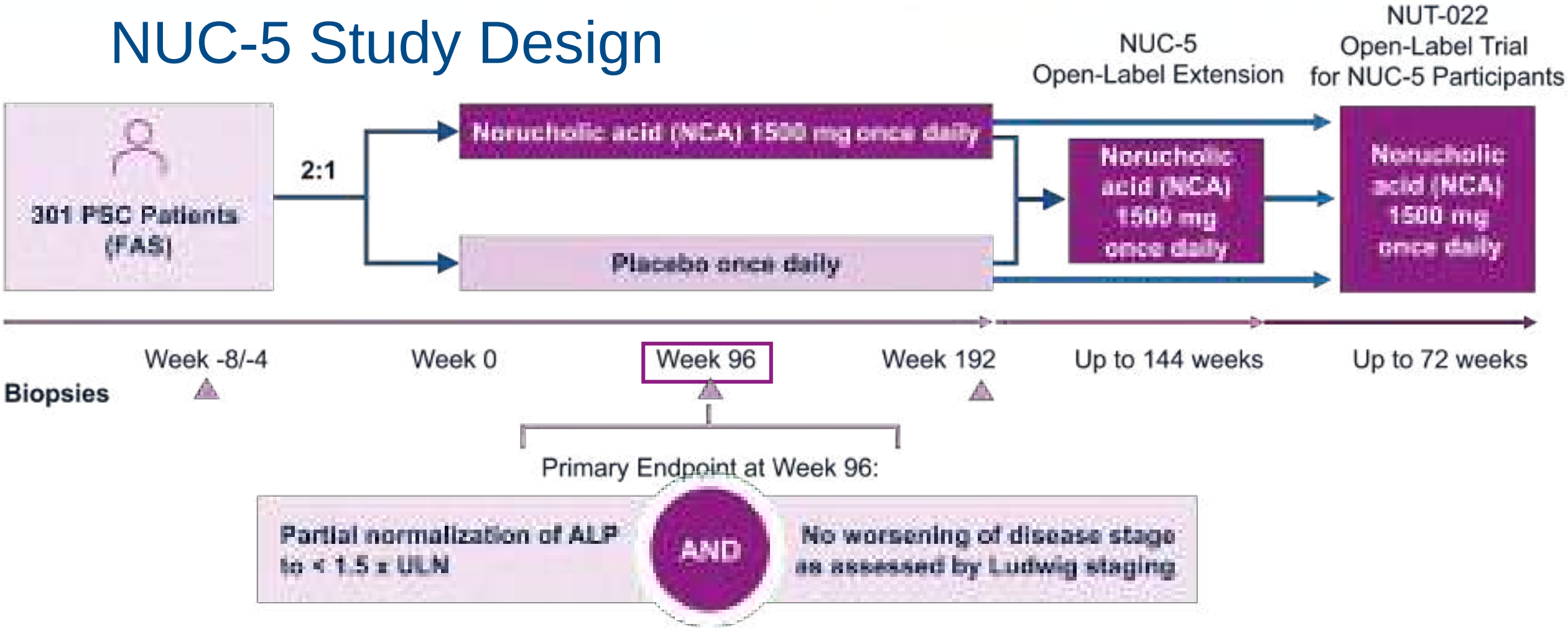
Sulindac Is Excreted Into Bile by a Canalicular Bile Salt Pump and Undergoes a Cholehepatic Circulation in Rats

GASTROENTEROLOGY 1999;117:962–971

ULRICH BOLDER,* NHAN V. TRANG,* LEE R. HAGEY,* CLAUDIO D. SCHTEINGART,* HUONG–THU TON–NU,* CAROLINA CERRÈ,* RONALD P. J. OUDE ELFERINK,‡ and ALAN F. HOFMANN*

*Division of Gastroenterology, Department of Medicine, University of California, San Diego, California; and ‡Department of Gastroenterology, Academisch Ziekenhuis, Amsterdam, The Netherlands

NUC-5 Study Design

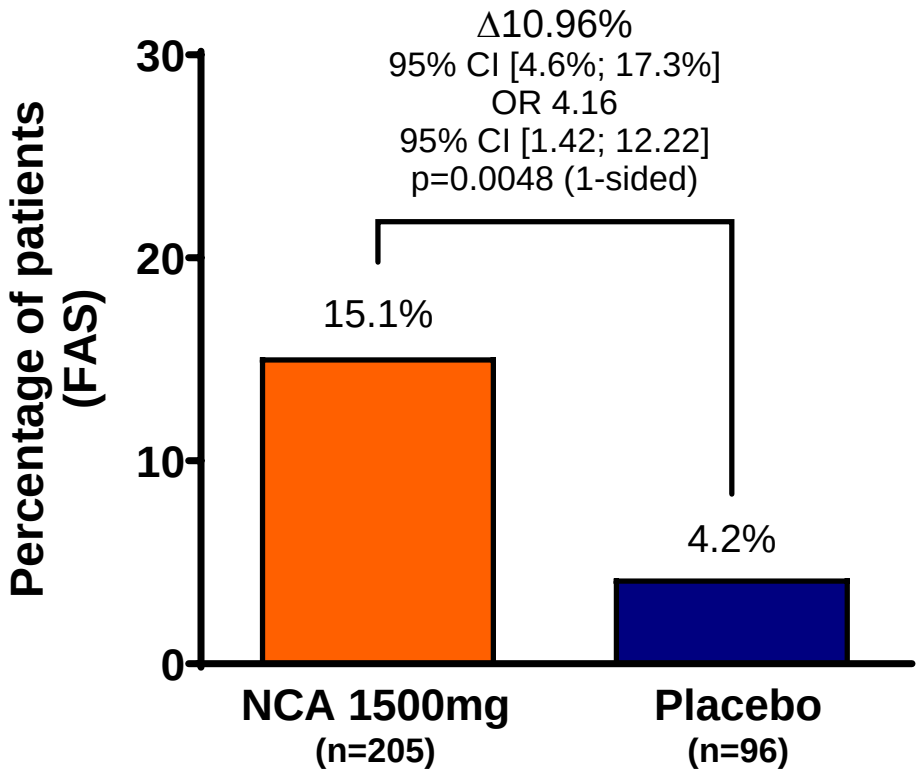


Patients were stratified by concomitant use of ursodeoxycholic acid (UDCA)

ALP: Alkaline phosphatase, FAS: Full Analysis Set, NCA: Norucholic acid, PSC: Primary sclerosing cholangitis, UDCA: ursodeoxycholic acid

Results: Combined Primary Endpoint

Partial normalization of ALP to <1.5 x ULN and no worsening of Ludwig stage

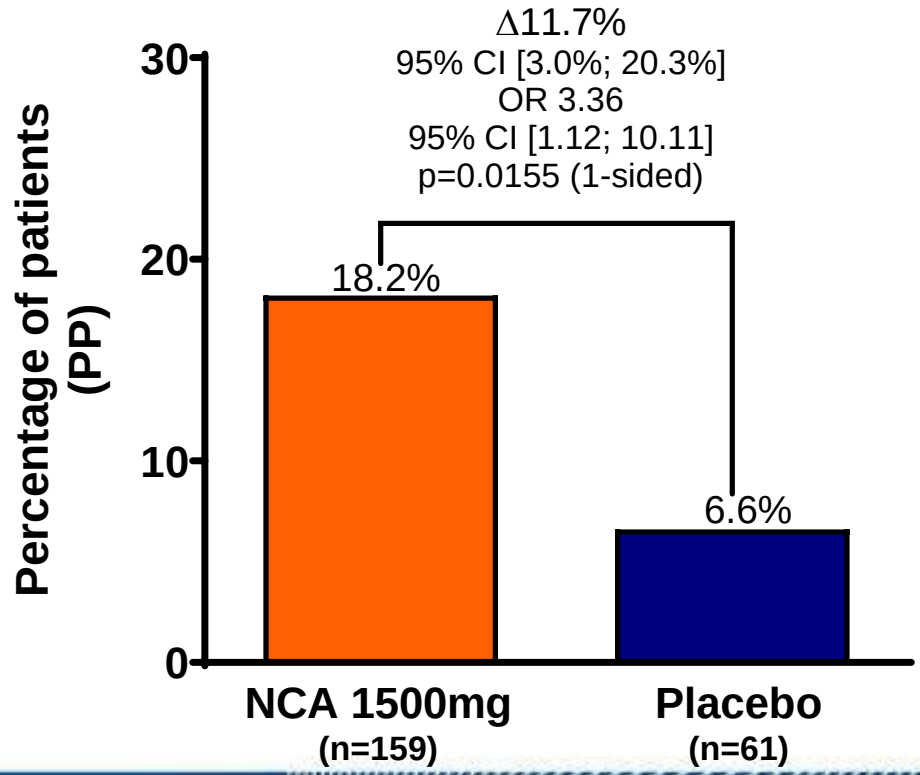


- NCA was significantly superior to placebo in the combined primary endpoint
- Patients without second biopsy were evaluated as non-responders

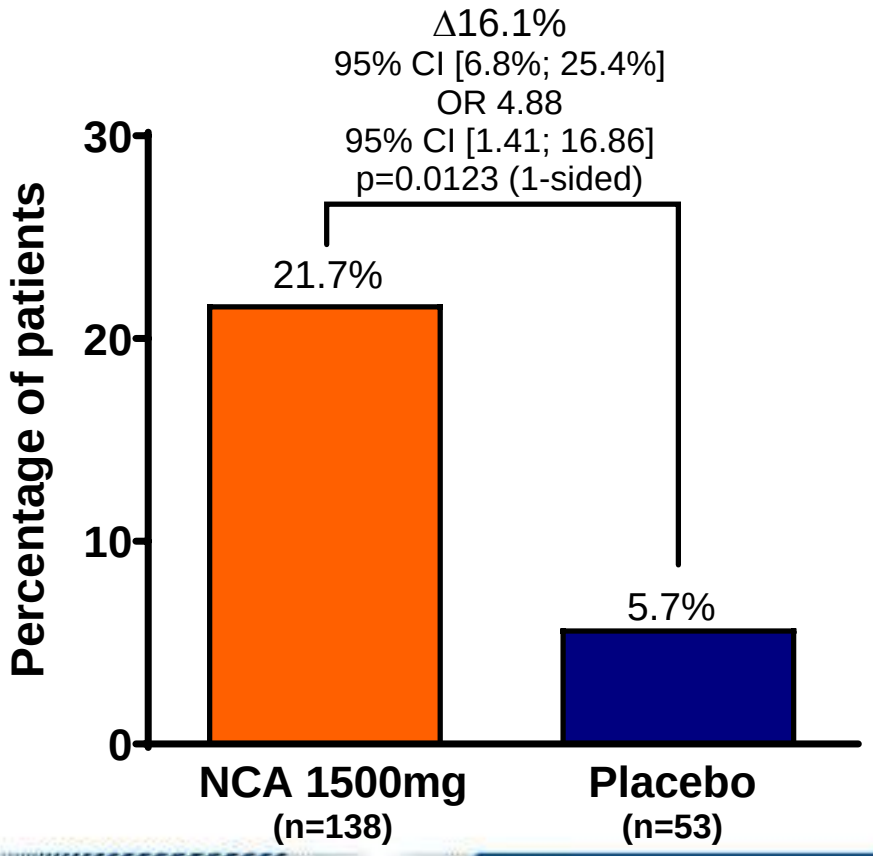
Combined Primary Endpoint

Partial normalization of ALP to <1.5 x ULN and no worsening of Ludwig stage

Per-protocol analysis

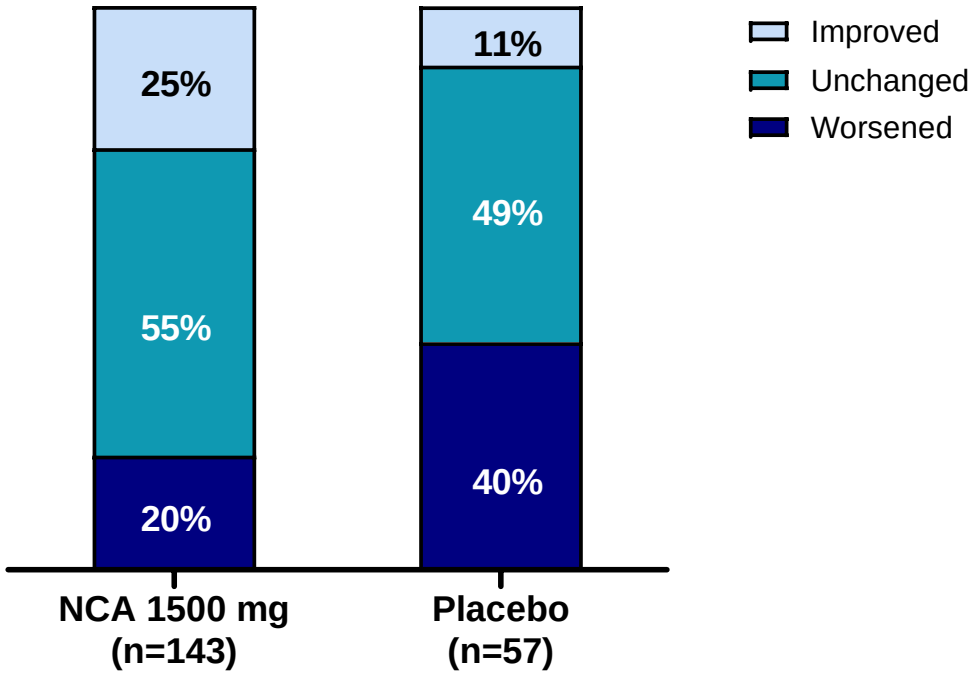


Patients with no missing values



Changes in Histology: Paired Biopsies

Changes in Ludwig stage (percentage of patients)



Improvement ≥1 Ludwig stage
NCA vs. placebo
25.2% vs 10.5%
p = 0.0217
(Fisher exact 2-sided)

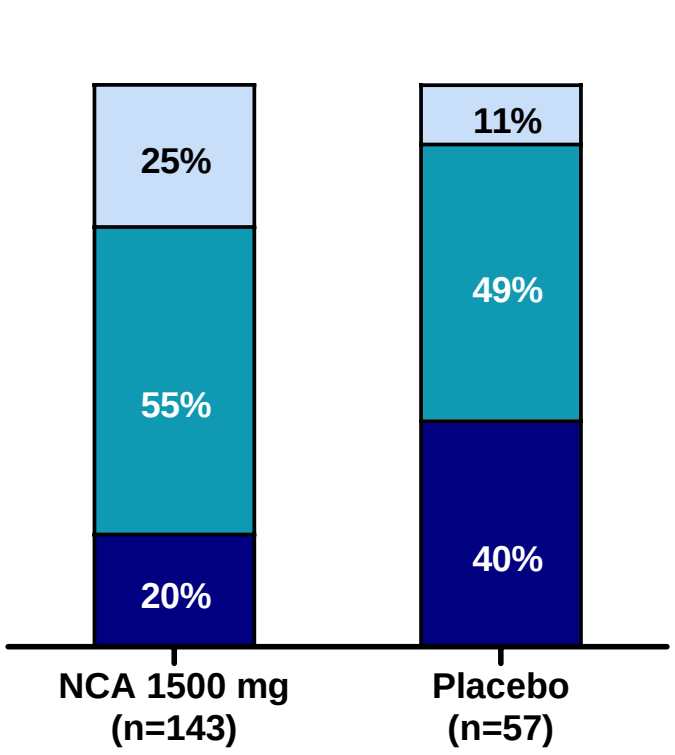
Worsening ≥ 1 Ludwig stage
NCA vs. placebo
20.3% vs 40.4%
p = 0.0069
(Fisher exact 2-sided)

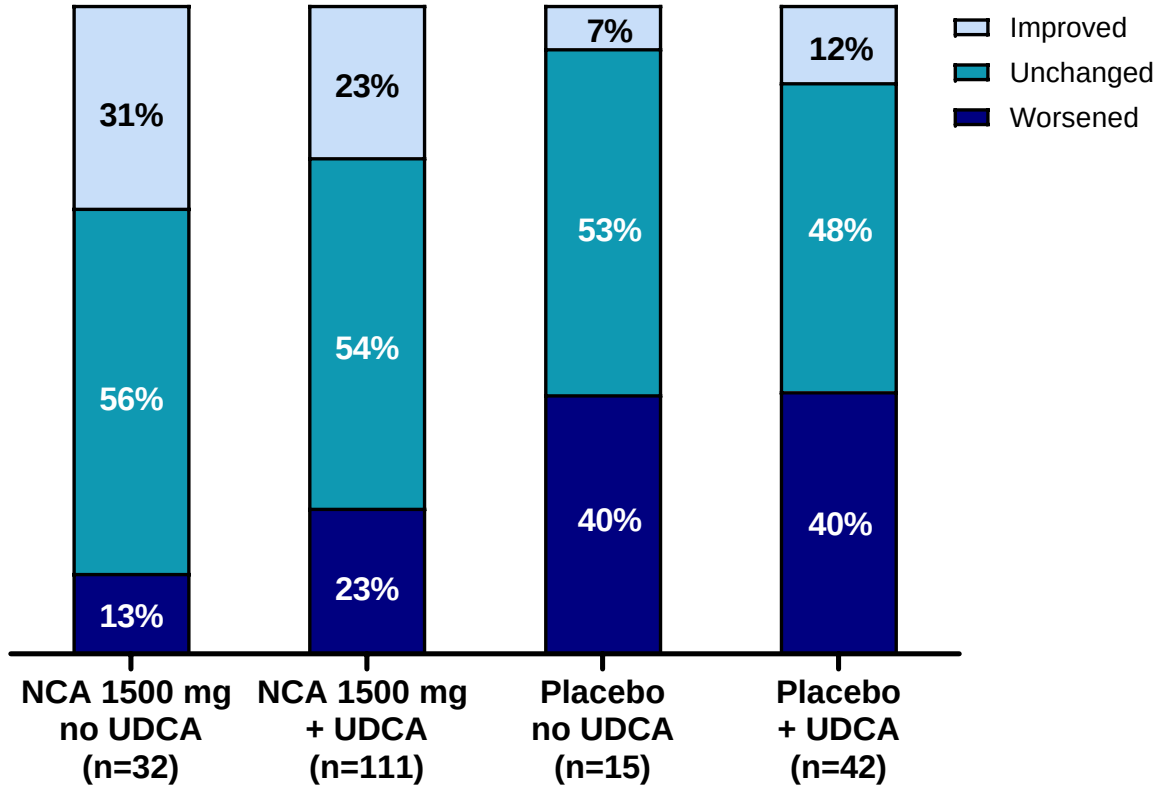
Progression to cirrhosis (Ludwig stage 4)
NCA vs. placebo
5.9% vs 10.7%

More improvement AND less worsening of histological disease stages with NCA vs. placebo

Changes in Histology: Paired Biopsies

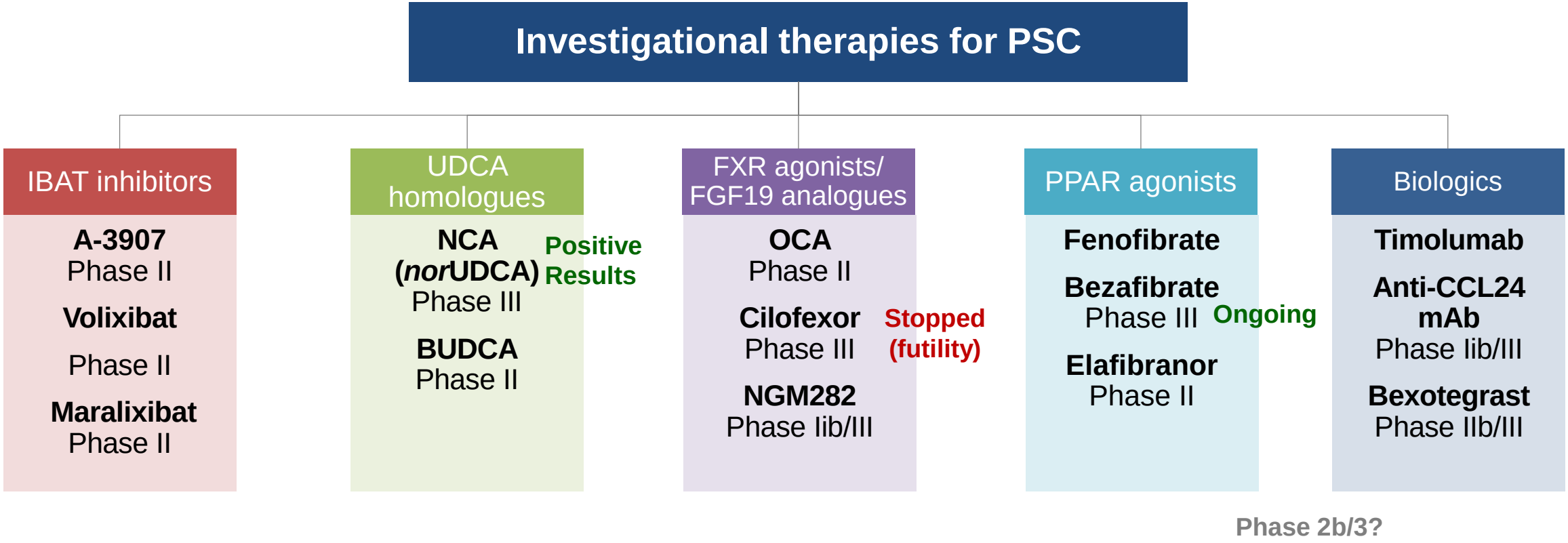
Changes in Ludwig stage (percentage of patients)





More improvement AND less worsening of histological disease stages with NCA vs. placebo

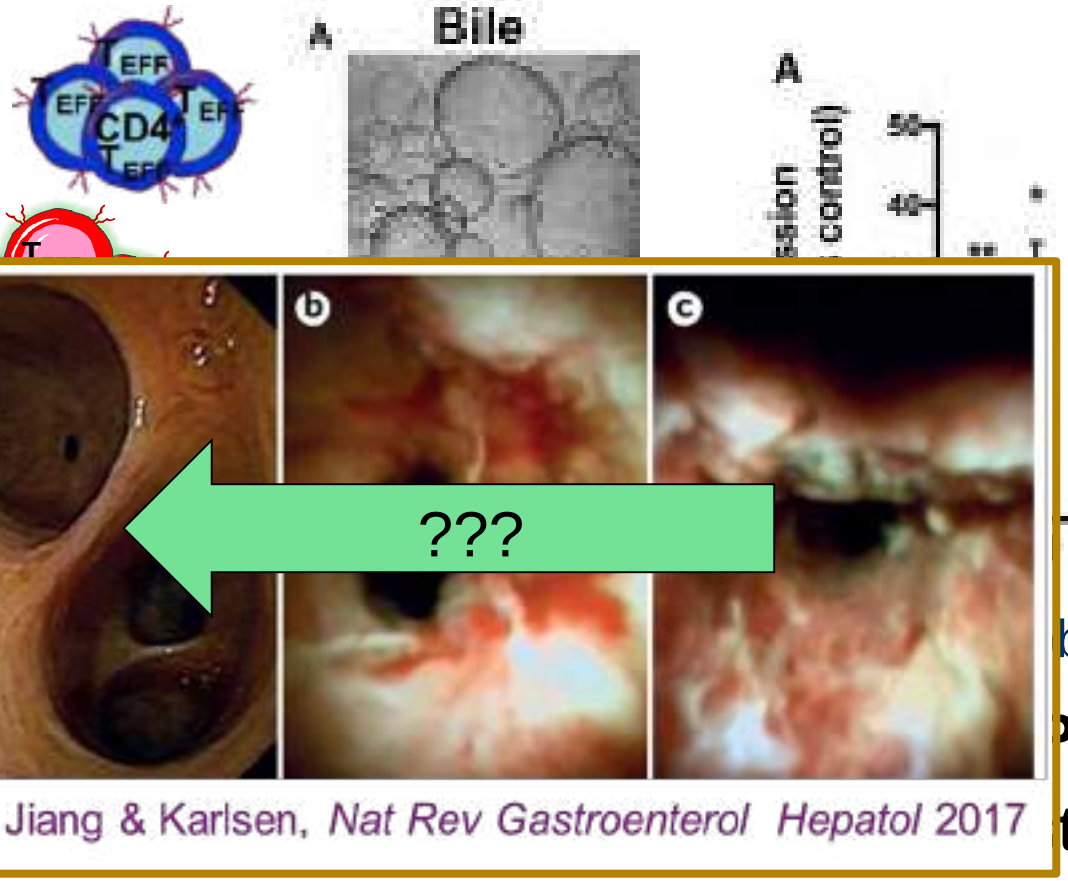
Emerging Treatment Options for PSC - Overview
Candidates for Recent & Ongoing Clinical Trials



Modified after: Slide courtesy Chris Bowlus 2024

Biliary Organoids - Personalized Medicine in PSC?

- **Biopsy-, iPSC-, bile-derived organoids** [1]
  - Recapitulate inflammatory IL17 response [2]



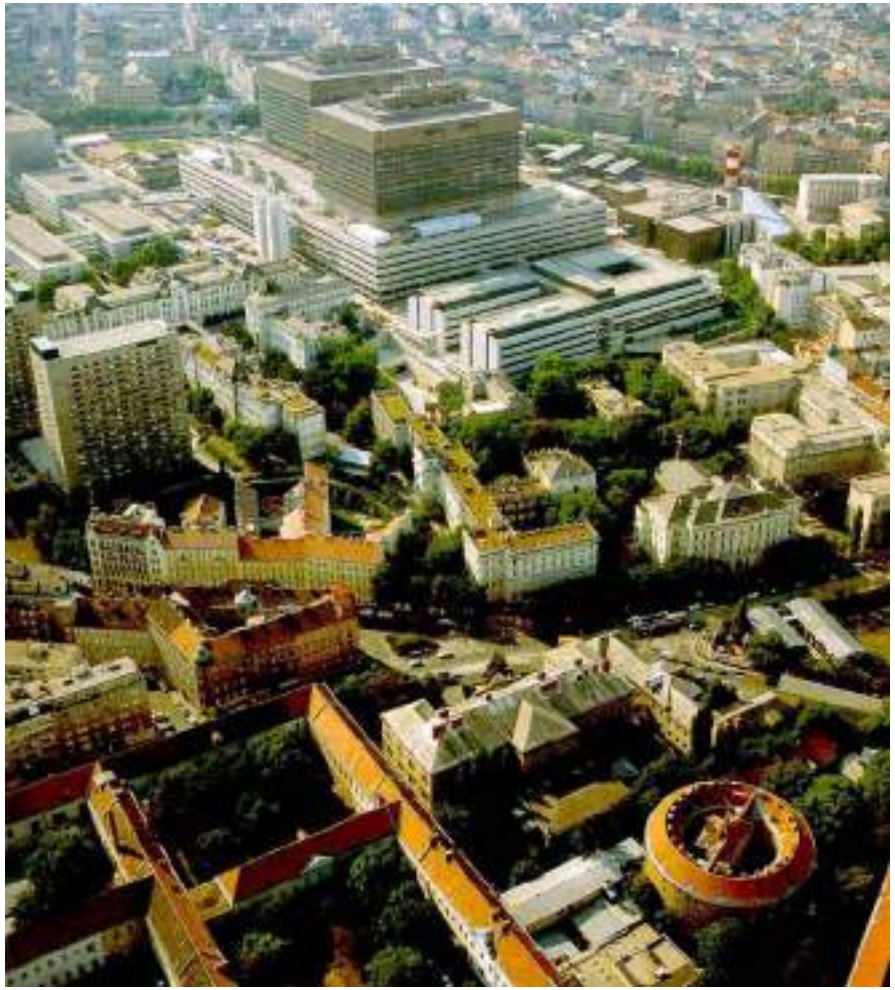
- blasts, … , microbiota /metabolites?
- PSC-IBD)?
- ting [3]
- **Regenerative medicine** [4]

1: Brevini & Sampaziotis, *J Hepatol* 2020
2: Soroka et al., *Hepatology* 2019; Garcia Moreno et al., *Hepatol Commun* 2024
3: Assis et al., EASL DILC 2020 AS055
4: Sampaziotis et al., *Nature Medicine* 2017 & *Science* 2021

Primary sclerosing cholangitis: current and future medical approaches

Key points – take home messages

- Multiple causes of SC, PSC remains a heterogenous condition
- Non-invasive tests (NITs) help to assess prognosis in PSC
  - Fibrosis NITs (Fibroscan, ELF), MR scores (Anali), Amsterdam-Oxford
  - Individual risk for malignancy hard to predict → surveillance
- Several conceptually appealing therapeutic targets & strategies



Thank you for your attention!

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