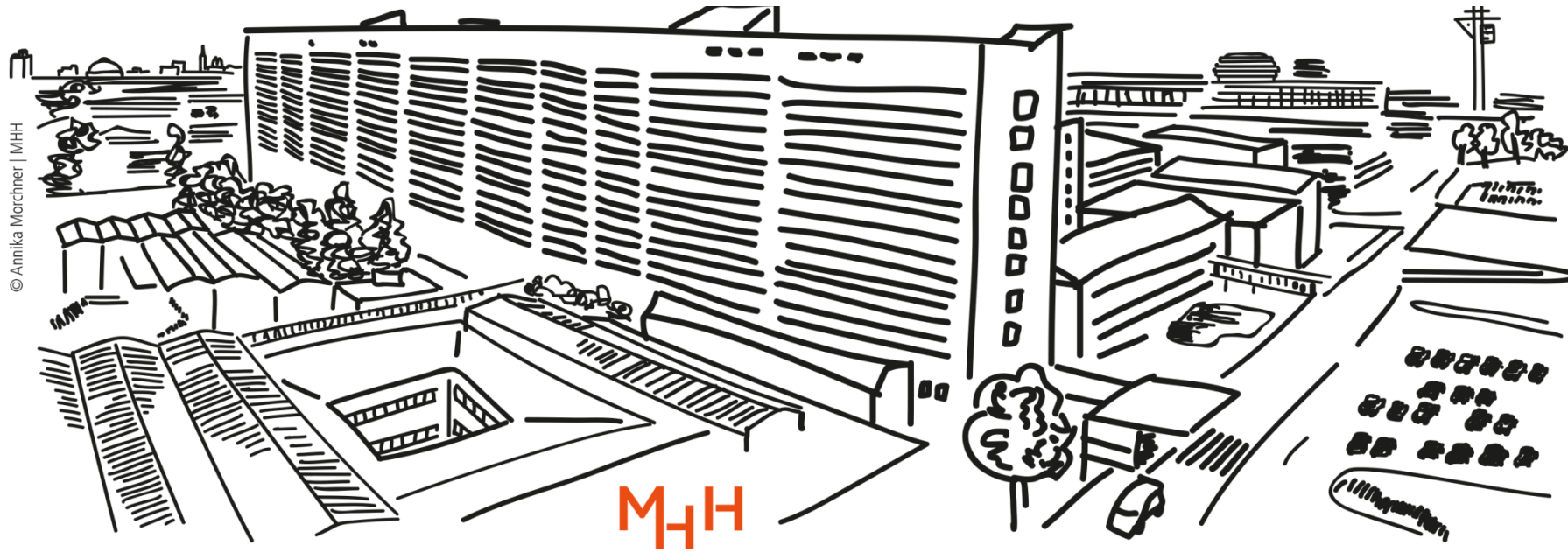


# The future of autoimmune liver diseases



MHH

**MICHAEL MANN**

**Hannover Medical School, Germany**

**PHC 2020, Paris, 13 January 2020**

# ACKNOWLEDGEMENTS

**Richard Taubert**

**Bastian Engel**

**Mirjam Wiestler**

**Heike Bantel**

**Elmar Jaeckel**

# CONFLICTS OF INTEREST

**Falk Pharma, Freiburg, Germany**

**Gilead Sciences, Foster City, USA**

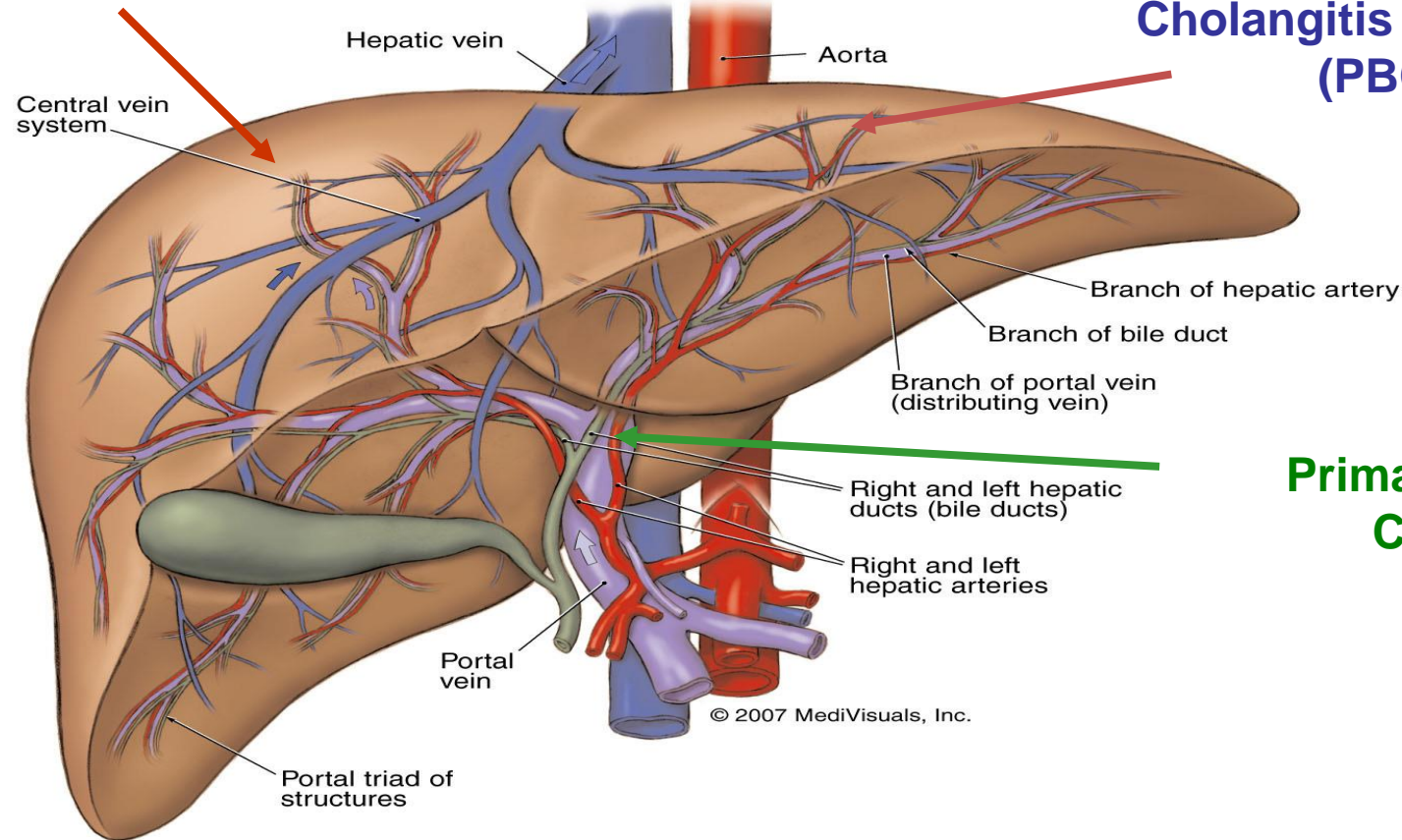
**Intercept**

**Novartis, Basel , Switzerland**

**Roche, Basel, Switzerland**

# Autoimmune Liver Diseases

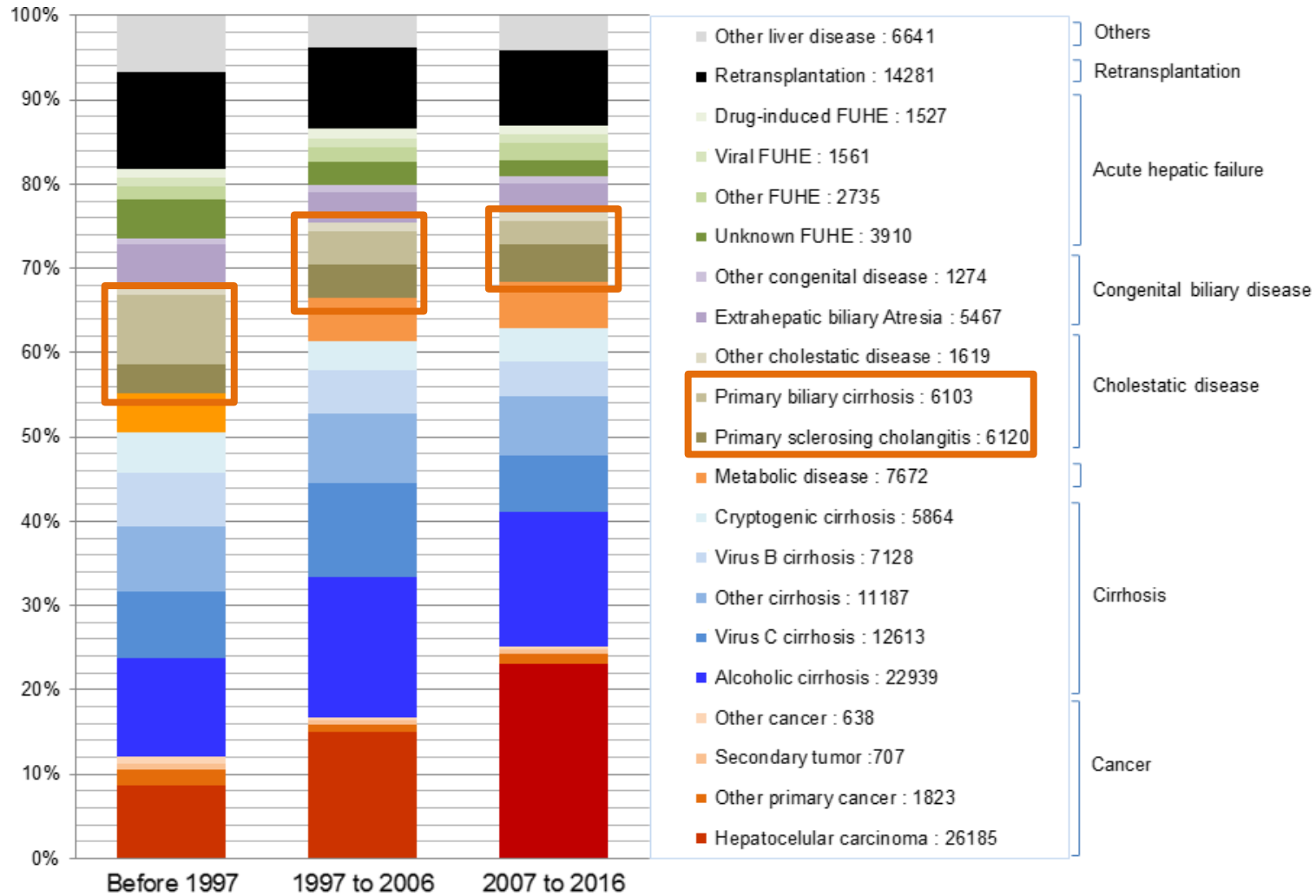
## Autoimmune hepatitis (AIH)



## Primary Biliary Cholangitis (Cirrhosis) (PBC)

## Primary Sclerosing Cholangitis (PSC)

# 2018 Annual Report of the European Liver Transplant Registry (ELTR)

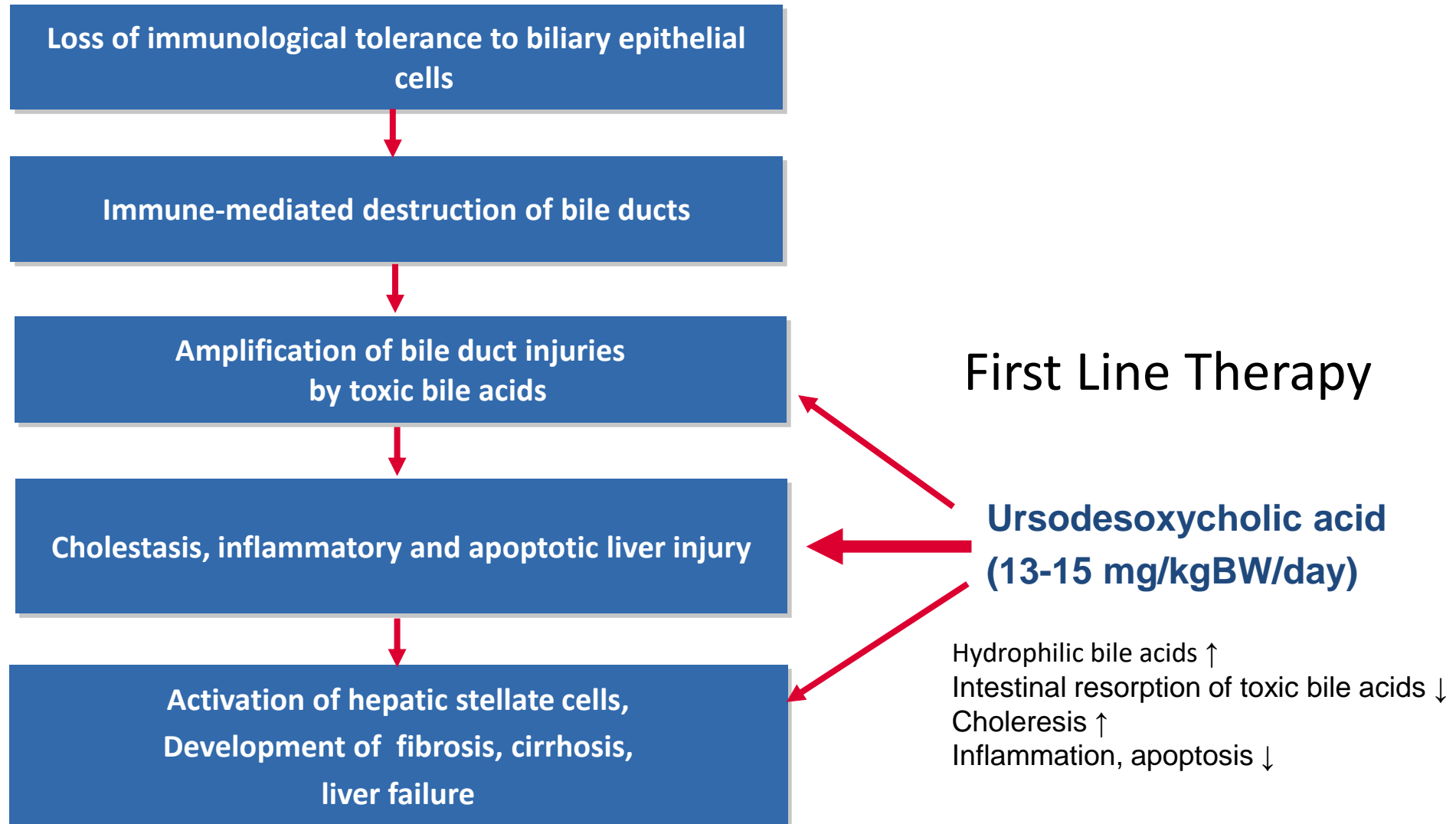


Adam et al. Transplant International 2018; 31: 1293–1317

# Primary Biliary Cholangitis

# Pathomechanisms of PBC

Modified according to U. Beuers



# Defining Inadequate Response to UDCA Treatment

Score [References]	Time (months)	Treatment Failure
Barcelona [Pares A, Gastroenterol 2006]	12	Decrease in ALP $\leq$ 40% and ALP $\geq$ 1 x ULN
Rotterdam [Kuiper EM, Gastroenterol 2009]	12	bilirubin $\geq$ 1 x ULN and/or albumin $<$ 1 x ULN
Paris-I [Corpechot C, Hepatology 2008]	12	ALP $\geq$ 3 x ULN or AST $\geq$ 2 x ULN, or bilirubin $>$ 1 mg/dL
Paris-II [Corpechot C, J Hepatol 2011]	12 (for early histological stages)	ALP $\geq$ 1,5 x ULN or AST $\geq$ 1,5 x ULN, or bilirubin $>$ 1 mg/dL
Toronto [Kumagi T, Am J Gastroenterol 2010]	24	ALP $>$ 1,67 x ULN
UK-PBC-Risk Score [Carbone M, Hepatology 2016]	12	Albumin and platelet count at baseline Bilirubin, ALP, AST or ALT at 12 mo
GLOBE-Score [Lammers WJ, Gastroenterol 2015]	12	Age at baseline Bilirubin, ALP, albumin, platelet count at 12 mo

**25 - 50% UDCA treatment failure (depending on which definition was used)**

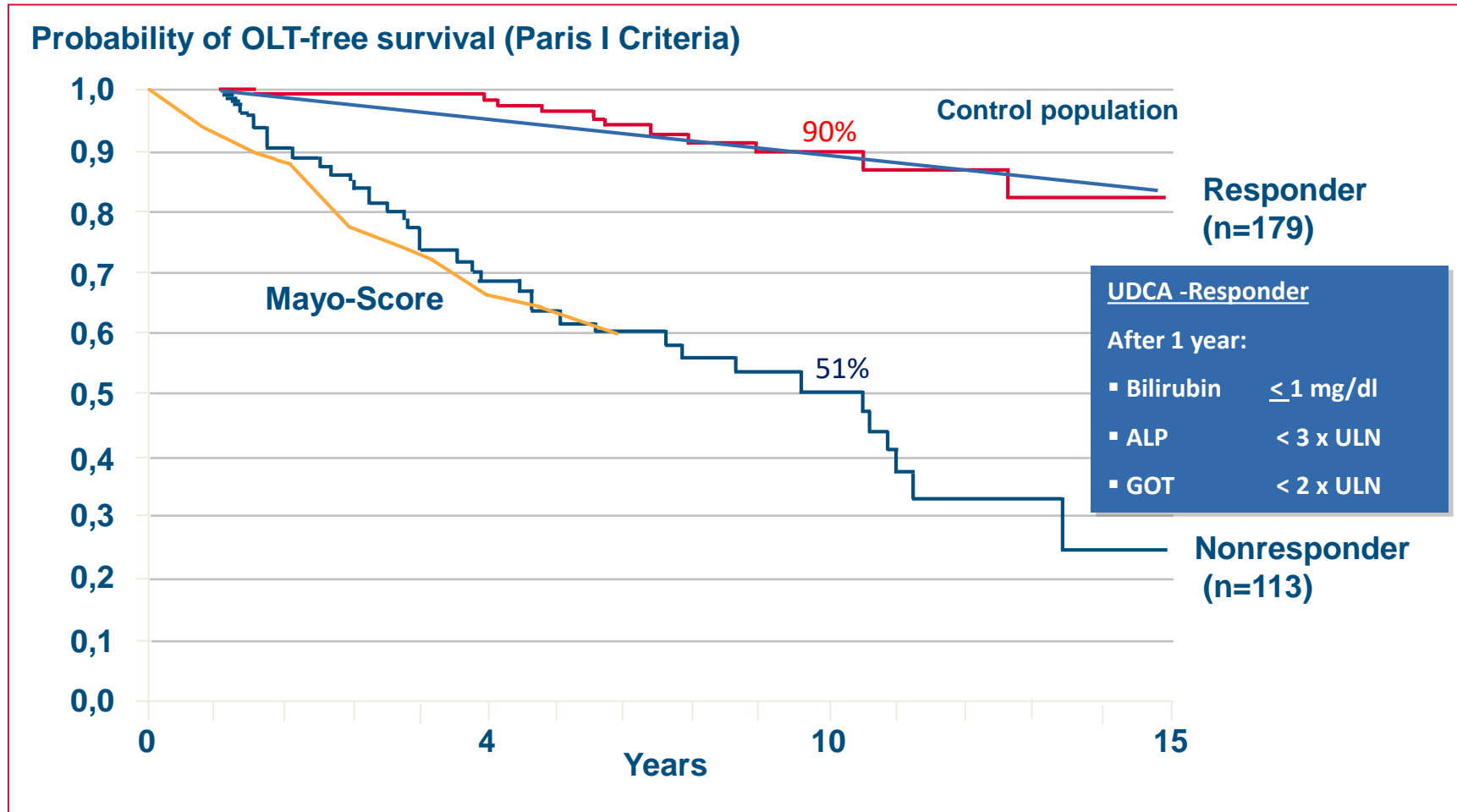


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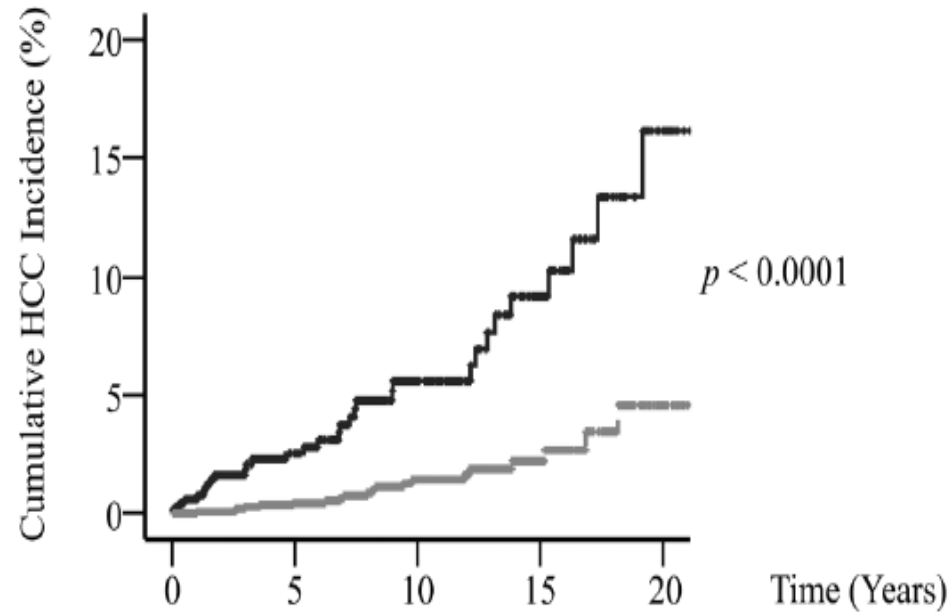
# Long-Term Survival of PBC Patients with Biochemical Response to UDCA



Corpechot et al. *Hepatology* 2008;48:871

# UDCA Treatment Failure – Increased Risk for HCC Development

Paris-I



—	Non-responders	691	373	191	92	18	Patients at Risk
- - -	Responders	1734	1149	602	224	38	Patients at Risk

Trivedi PJ et al., Gut 2016; 65:321-329

# POISE (Phase 3) Trial: Obeticholic Acid (OCA) vs. Placebo in PBC Patients with Inadequate Response to UDCA

Primary endpoint at 12 months:

OCA 5-10 mg: 46%

OCA 10 mg: 47%

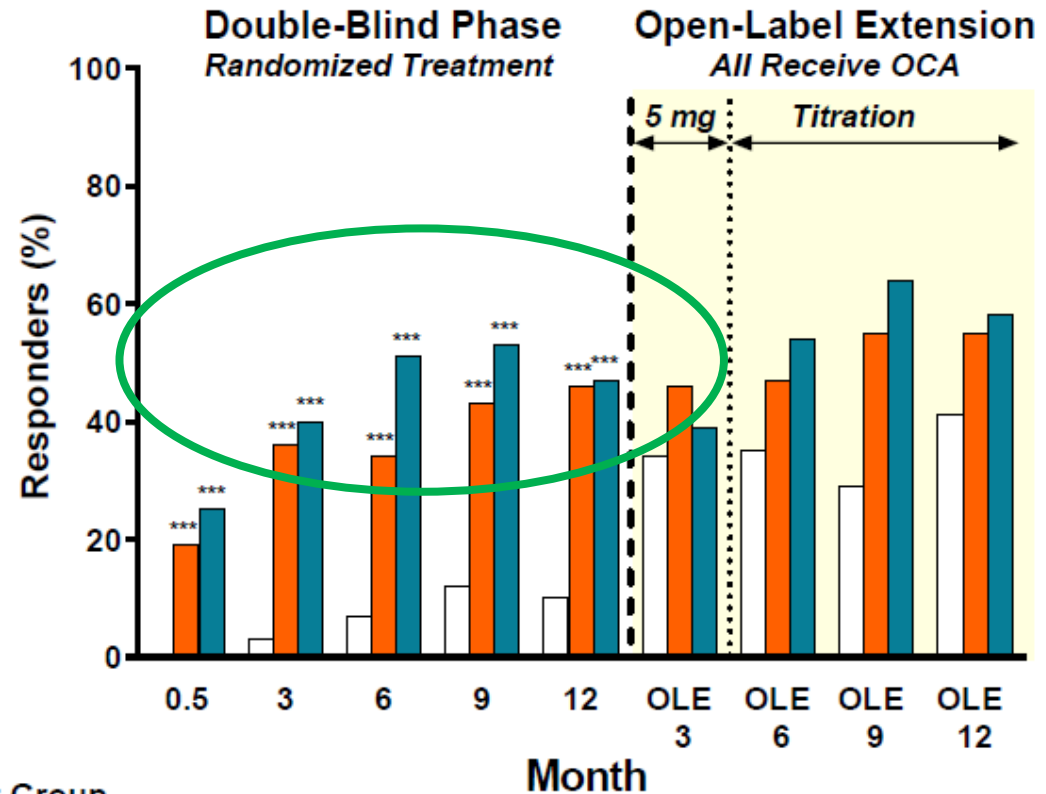
Placebo: 10%

Side effects:

Dose-dependent increase of pruritus

(leading to OCA discontinuation in 1-10%)

LDL-increase (long-term cardiovascular risk?)



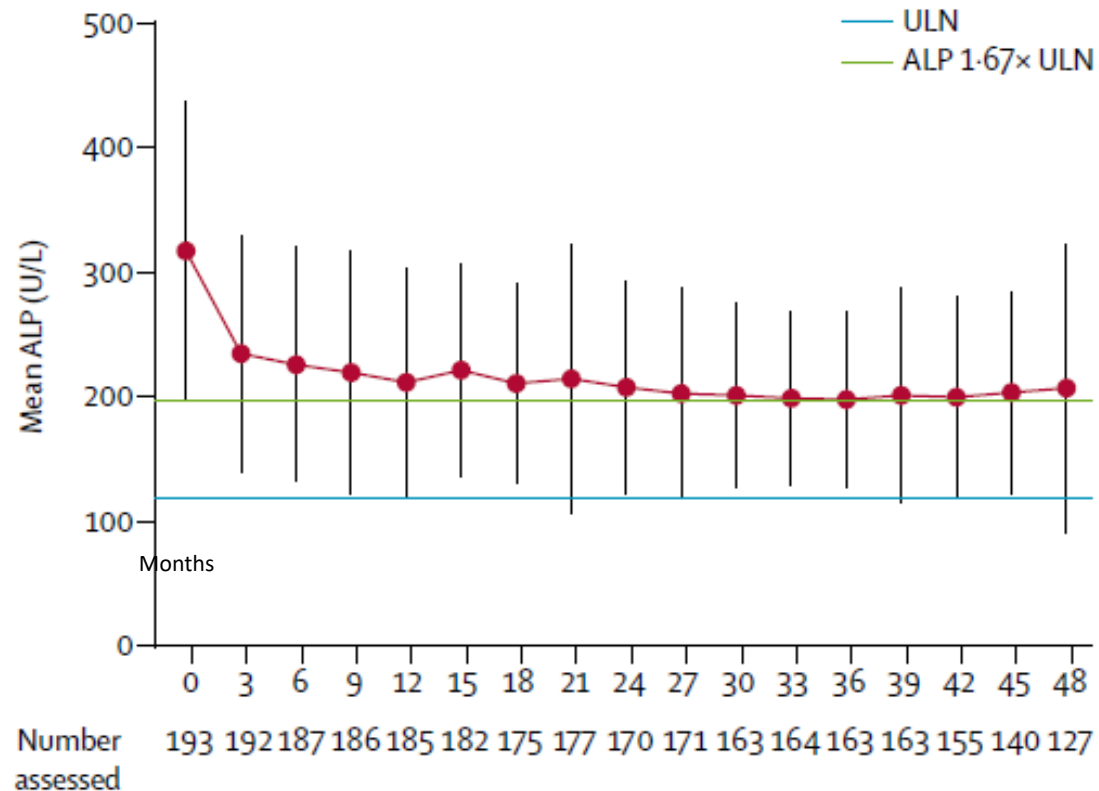
**DB Treatment Group**

□ Placebo ± UDCA, n	73	73	73	73	73	64	60	59	59
■ OCA 5-10 mg ± UDCA, n	70	70	70	70	70	63	62	62	60
■ OCA 10 mg ± UDCA, n	73	73	73	73	73	64	59	61	59

Nevens F, New Engl J Med 2016

# OCA Therapy for PBC – Long term results

## OCA Add-on UDCA (POISE-Study, OLE) (3 years results)



### Response rates

(AP < 1.67xULN, AP decrease  $\geq$  15%, normal bilirubin)

Month 24: 53%

Month 48: 51%

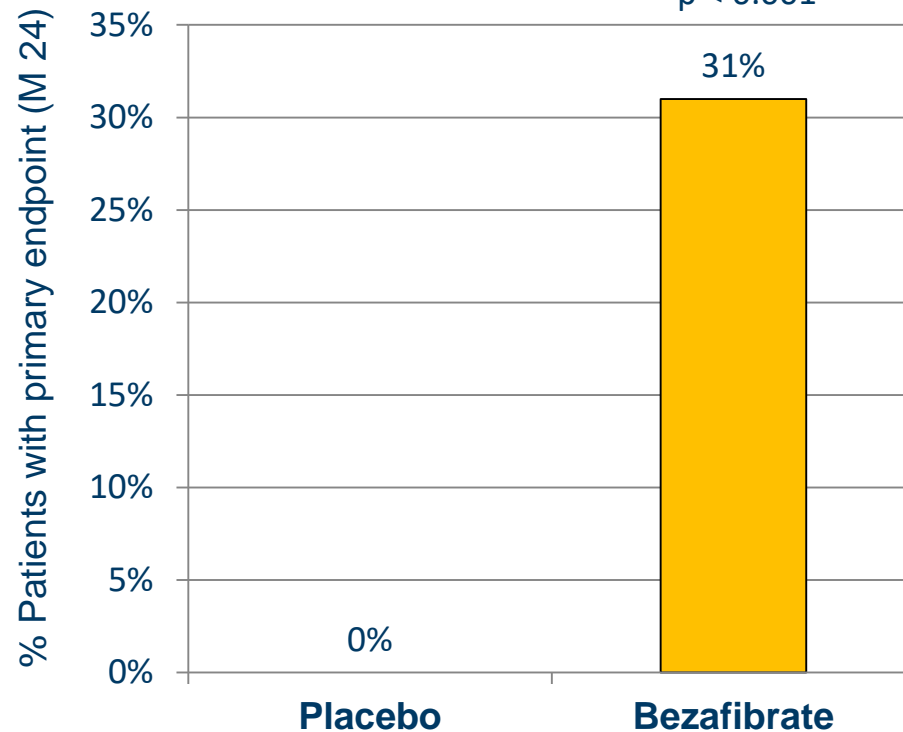
Trauner M et al., Lancet Gastroenterol Hepatol 2019

# BEZURSO (Phase 3) Trial: Bezafibrate vs. Placebo in PBC Patients with Inadequate Response to UDCA

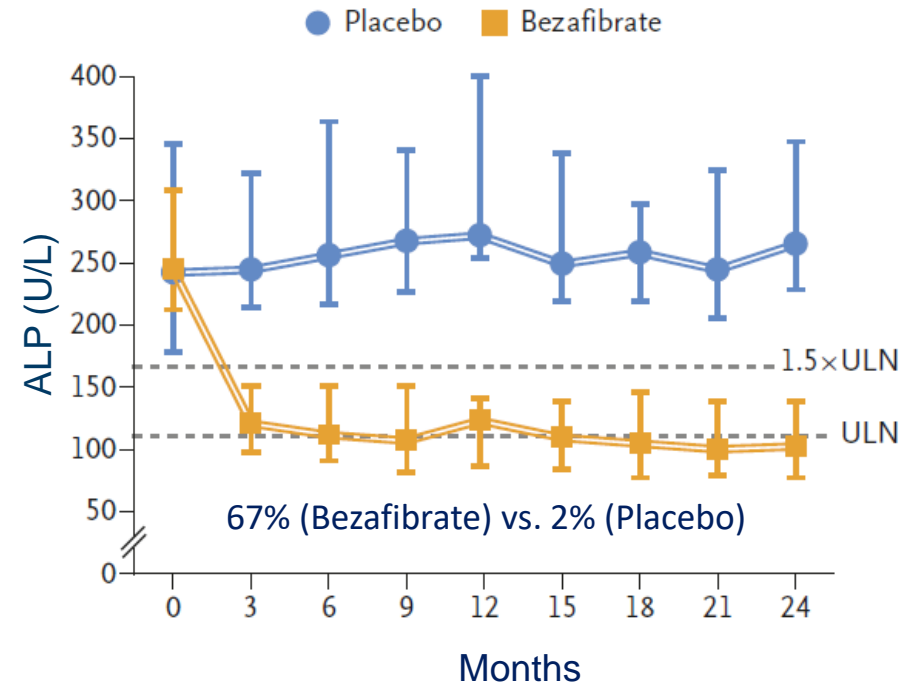
## Primary endpoint: Complete biochemical response at month 24

(Normalization of Bilirubin, AP, AST, ALT, Albumin, Prothrombin-Index)

$p < 0.001$

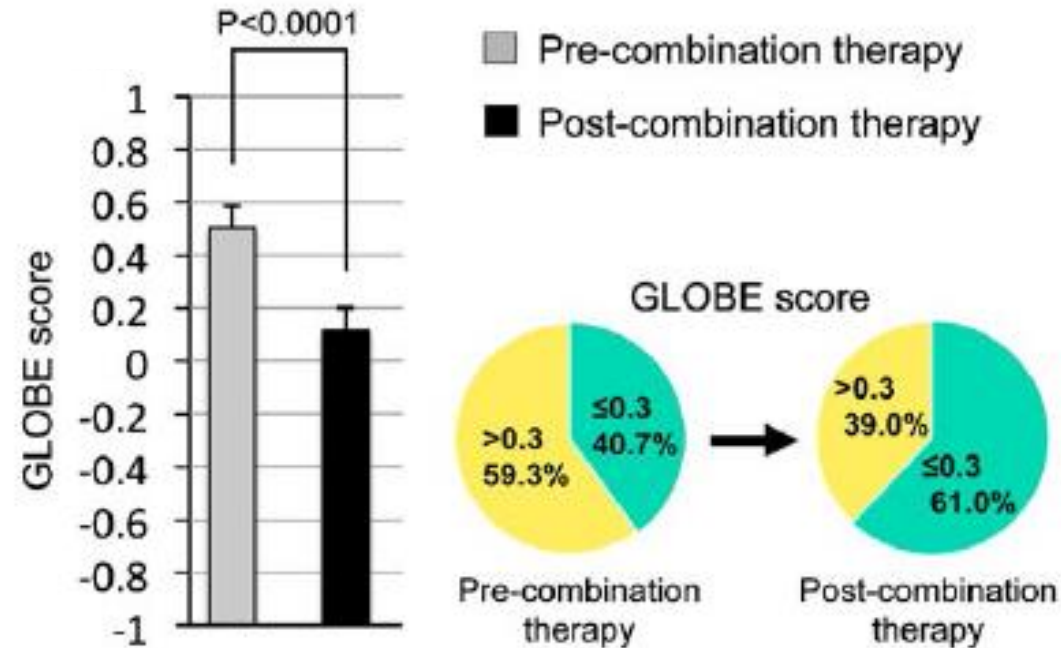


## Secondary endpoint: Normalization of AP at month 24



Carpechot C et al. N Engl J Med 2018;378(23):2171-81.

# Improvement of GLOBE Score by the Combination of UDCA with Bezafibrate in PBC



Honda A et al. Hepatology 2019

# Addition of Bezafibrate to OCA +/- UDCA

Add on Bezafibrate (400 mg/d) after 5 y OCA (5/10 mg/d) +/- UDCA in 11 POISE study patients  
Bezafibrate termination in 2/11 patients due to myalgia

- After 6 month triple treatment, ALP further decreased in 100% of patients ( $p < 0.001$ ) and bilirubin decreased in 67% of patients ( $p=0.184$ )
- ALP was normal in 4/9 patients and bilirubin was normal in 8/9 patients, reaching the primary endpoint in 44% of the patients

**Table 1. Biochemical parameters (Median [IQR])**

	<b>start OCA (n = 11)</b>	<b>6 m OCA (n = 11)</b>	<b>4 – 5 y OCA (n = 11)</b>	<b>6 m OCA + bezafibrate (n = 9)</b>
ALP (U/L)	315.0 [275.0 - 408.4]	233.2 [194.4 - 259.4]	190.2 [157.4 - 252.0]	94.0 [90.0 - 143.5]
BILI (µMOL/L)	7.7 [6.8 - 20.9]	8.6 [5.8 - 18.0]	7.7 [6.8 - 14.7]	6.8 [5.0 - 10.5]
AST (U/L)	37.2 [27.9 - 67.9]	35.9 [23.8 - 69.0]	29.3 [26.3 - 47.8]	37.0 [27.5 - 48.5]
ALT (U/L)	45.6 [27.2 - 67.8]	29.3 [17.4 - 46.0]	21.9 [15.5 - 32.0]	27.0 [19.5 - 37.0]
GGT (U/L)	274.7 [97.3 - 397.7]	71.0 [52.1 - 189.9]	37.2 [27.6 - 87.8]	32.0 [26.5 - 103.0]



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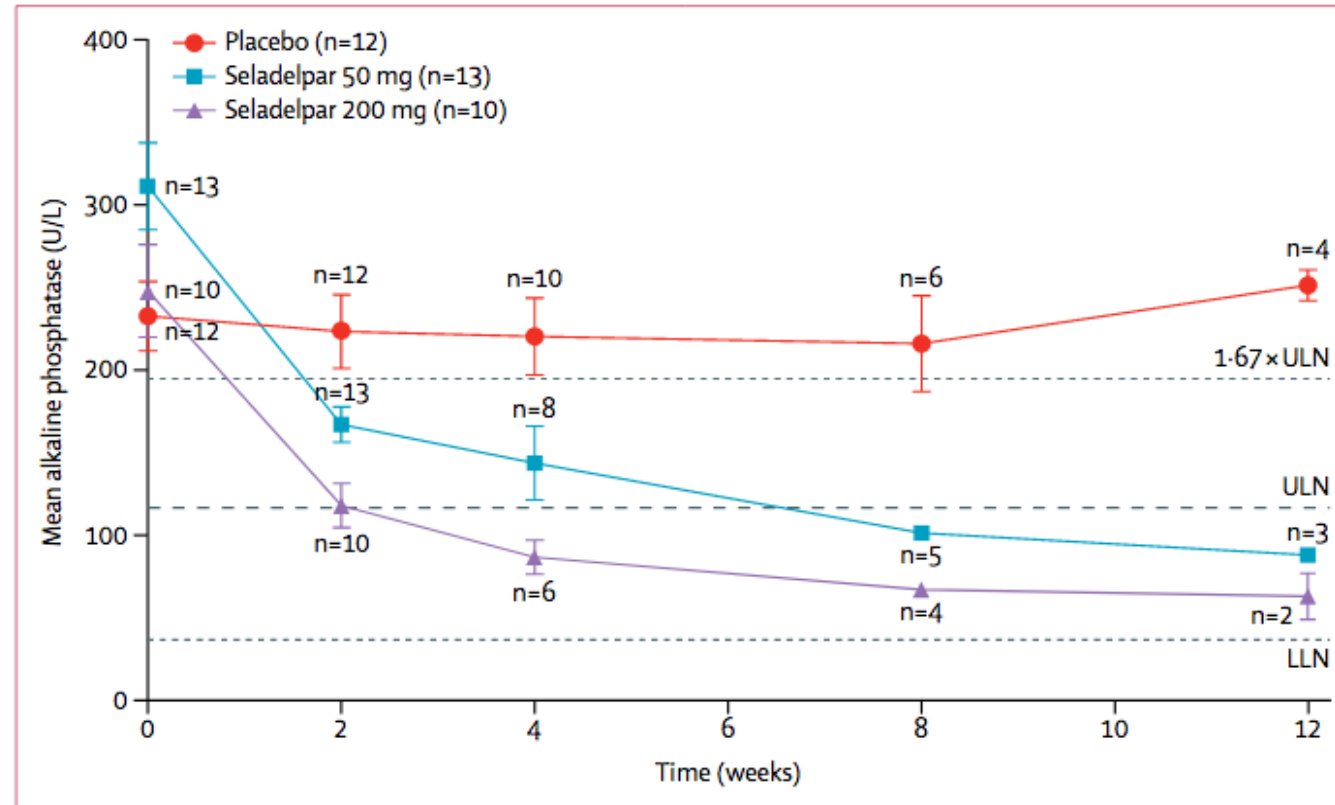
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# Clinical Trials in PBC

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- Seladelpar (PPAR- $\delta$  Agonist; CYMABAY)
- Elafibranor (PPAR- $\alpha/\delta$  Agonist; GENFIT)
- Cilofexor (Non-steroidal / Non bile acid FXR-Agonists; GILEAD, NOVARTIS)
- FGF-19 Agonist (NGM282; NGMBio)

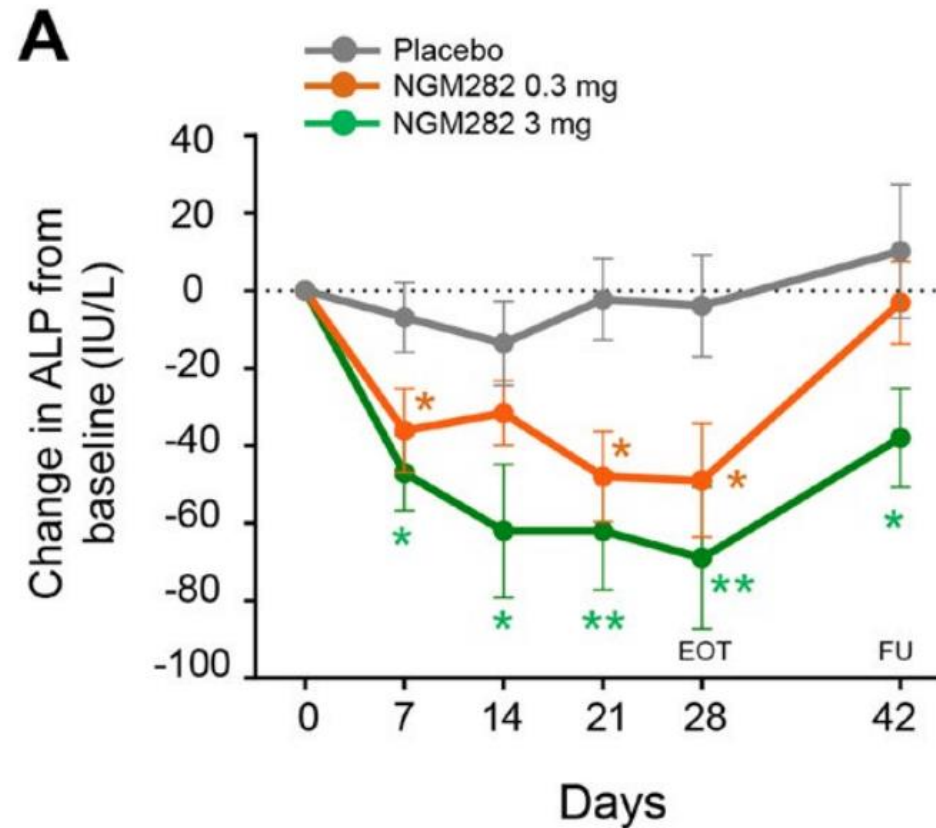
# Seladelpar (PPAR- $\delta$ Agonist; CYMABAY)



**Figure 3: Mean changes in alkaline phosphatase over 12 weeks for each treatment group**  
ULN=upper limit of normal. LLN=lower limit of normal. Bars are SE.

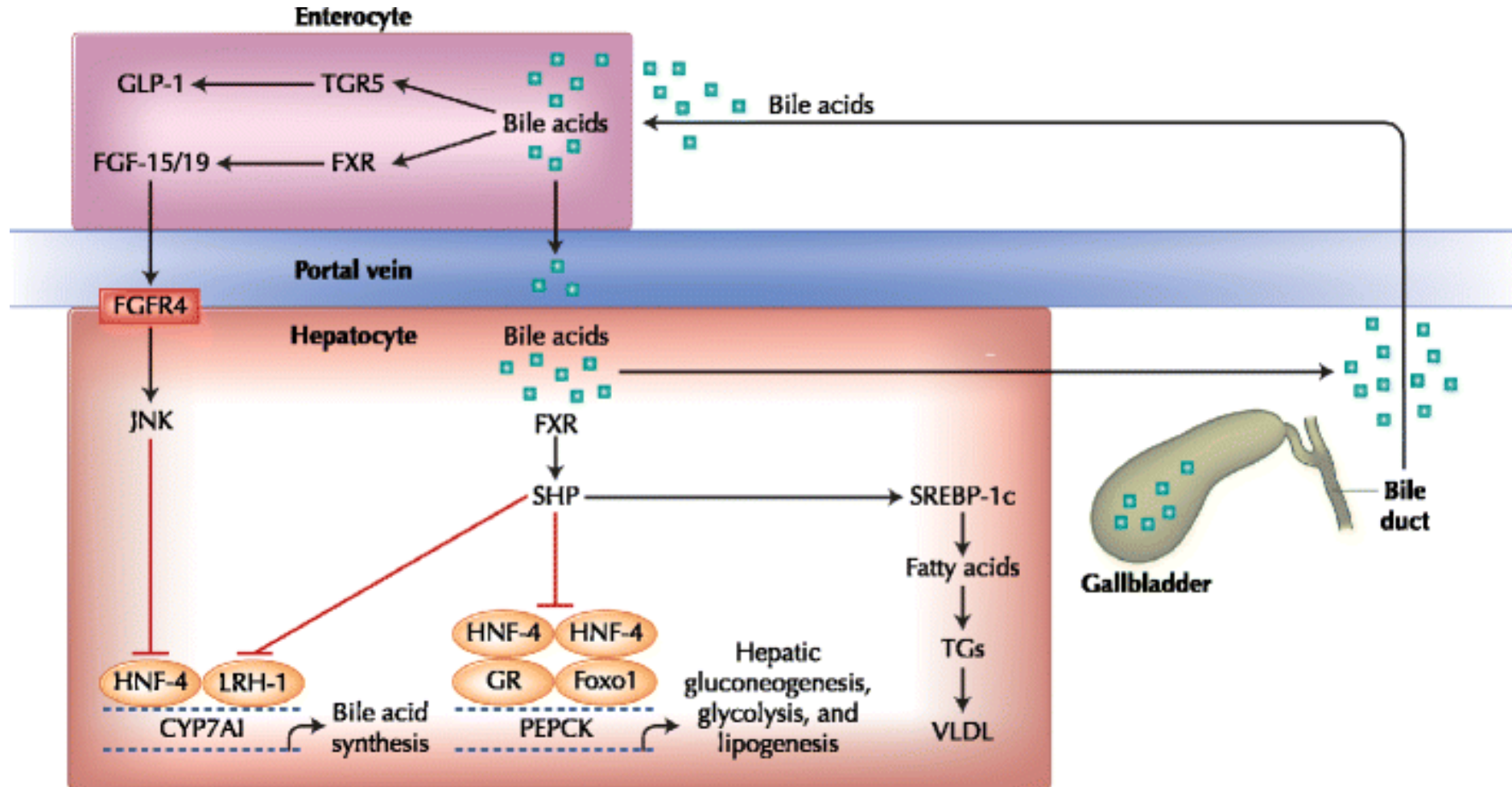
Jones, D., Boudes, P. F., Swain, M. G., Bowlus, C. L., Galambos, M. R., Bacon, B. R., ... Hirschfield, G. M. (2017). *Seladelpar (MBX-8025), a selective PPAR- $\delta$  agonist, in patients with primary biliary cholangitis with an inadequate response to ursodeoxycholic acid: a double-blind, randomised, placebo-controlled, phase 2, proof-of-concept study. The Lancet Gastroenterology & Hepatology, 2(10), 716–726. doi:10.1016/s2468-1253(17)30246-7*

# FGF-19 Agonist (NGM282; NGMBio)



Mayo MJ, Wigg AJ, Leggett BA, et al. NGM 282 for Treatment of Patients With Primary Biliary Cholangitis: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. *Hepatol Commun*. 2018. doi:10.1002/hep4.1209

# Role of FGF15/19 as Therapeutic Target



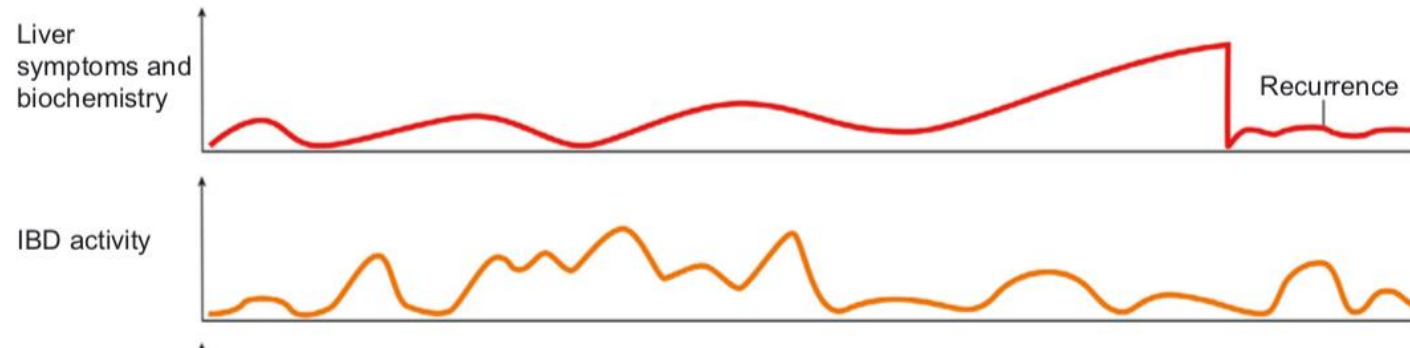
Staels, B., Handelsman, Y. & Fonseca, V. Curr Diab Rep (2010) 10: 70

# Current therapeutic trials for PBC

Mesenchymal stem cell transplantation for refractory primary biliary cholangitis	RCT, assessment of change of ALP after mesenchymal stem cell transplantation vs. placebo	?
Study to evaluate safety, tolerability and efficacy of saroglitazar Mg in patients with primary biliary cholangitis (EPICS)	Phase 2 placebo controlled study measuring change in ALP levels after 16 weeks of treatment	PPAR $\alpha$ / $\gamma$ -agonism
Clinical Trial on the effect of the sublimated mare milk supplement on primary biliary cholangitis	Changes of liver chemistry, histology, asthenia and hepatic encephalopathy in PBC patients after 4 months of treatment	?
ENHANCE: Seladelpar in Subjects with primary biliary cholangitis (PBC) and an inadequate response to or an intolerance to ursodeoxycholic acid (UDCA)	Phase 3 study to determine safety and efficacy of Seladelpar against placebo; composite endpoint of change in ALP and total bilirubin within 12 months	PPAR $\delta$ -agonism
Mindfulness - based intervention in the treatment of fatigue in patients with primary biliary cholangitis	Change in fatigue severity over 16 weeks of mindfulness - based intervention	Behavioral intervention
A study to assess the safety, tolerability, pharmacokinetics and efficacy of EDP-305 in subjects with primary biliary cholangitis	Phase 2 to measure proportion of subjects with at least 20% reduction in ALP within 12 weeks of treatment	small molecule FXR agonist
Safety, Tolerability of OP-724 in patients with primary biliary cholangitis (Phase I)	Phase 1 study looking primarily for occurrence of adverse events	CBP/beta-catenin antagonist (potentially antifibrotic)
Combination antiretroviral therapy (cART) for PBC	ALP change > 10 % within 12 months of tenofovir/raltegravir/emtricitabine treatment (Phase 2)	
Curative effect observation of UDCA combined probiotics therapy in PBC of poor response to UDCA (CEBOFUCPTIP)	Change of fecal flora after 6 month and biochemical response	
Phase 4 study of obeticholic acid evaluating clinical outcomes in patients with primary biliary cholangitis (COBALT)	Study long term outcomes of OCA treatment (death, LTX, hospitalization)	FXR-agonist
Study of OCA evaluating pharmacokinetics and safety in patients with PBC and hepatic impairment	Safety study Phase 4 in patients with PBC and hepatic malfunction	FXR-agonist
Study to evaluate the safety and efficacy of oral CR845 (Difelikefalin) in patients with primary biliary cholangitis and moderate-to-severe pruritus	Phase 2 trial to evaluate change in itching measured by worst itching intensity numeric rating scale (WI-NRS) within 16 weeks of treatment	$\kappa$ -opioid receptor agonist
Dose Response Study of GSK2330672 for the Treatment of Pruritus in Patients With Primary Biliary Cholangitis	Phase 2 study to evaluate the change in itching measured by WI-NRS within 16 weeks of treatment	ASBT(apical sodium-dependent bile acid transporter) inhibitor

# Primary Sclerosing Cholangitis

# PSC remains one of the greatest unmet needs in hepatology



## THE BLACK BOX OF HEPATOLOGY

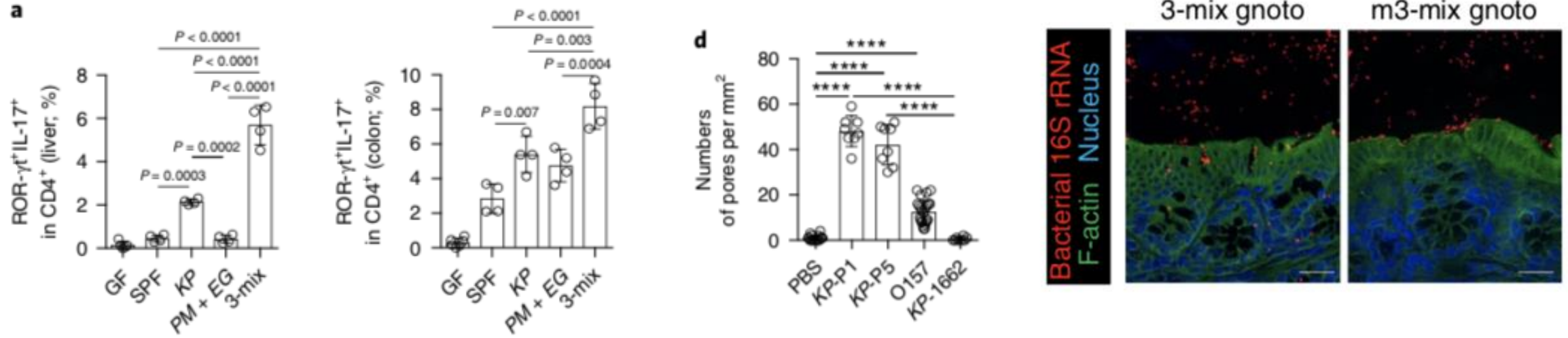
- ✓ un-defined aetiology and ill defined pathogenesis.
- ✓ Risk of malignancy
- ✓ Critical absence of medical therapies.
- ✓ Liver transplantation remains the only life-saving intervention for patients.

Karlsen TH et al. Journal of Hepatology 2017



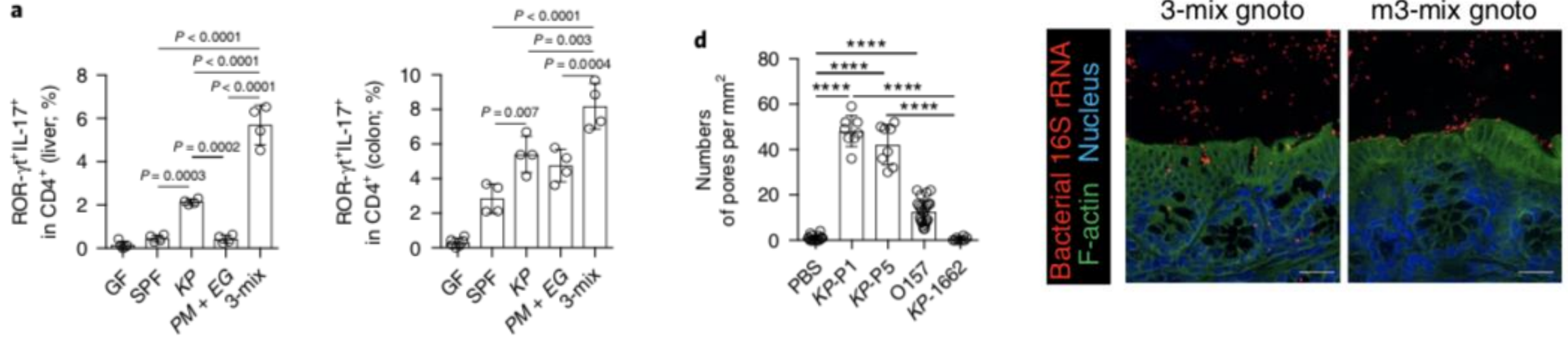
# What's new about **the pathophysiology of PSC ?**

# Gut pathobionts underlie intestinal barrier dysfunction and liver T helper 17 cell immune response in PSC



- ✓ This study highlights the role of pathobionts in intestinal barrier dysfunction and liver inflammation.
- ✓ *K.pneumoniae*, *P.mirabilis* and *E.gallinarum* were found to be prevalent in patients with PSC and responsible for bacterial translocation and subsequent hepatobiliary inflammation in the gnotobiotic mouse models.
- ✓ PSC-derived *K. pneumoniae* possess epithelial-damaging abilities that contribute to bacterial translocation.
- ✓ The 3-mix bacteria cooperatively promote the hepatobiliary disease progression through the TH17 response.

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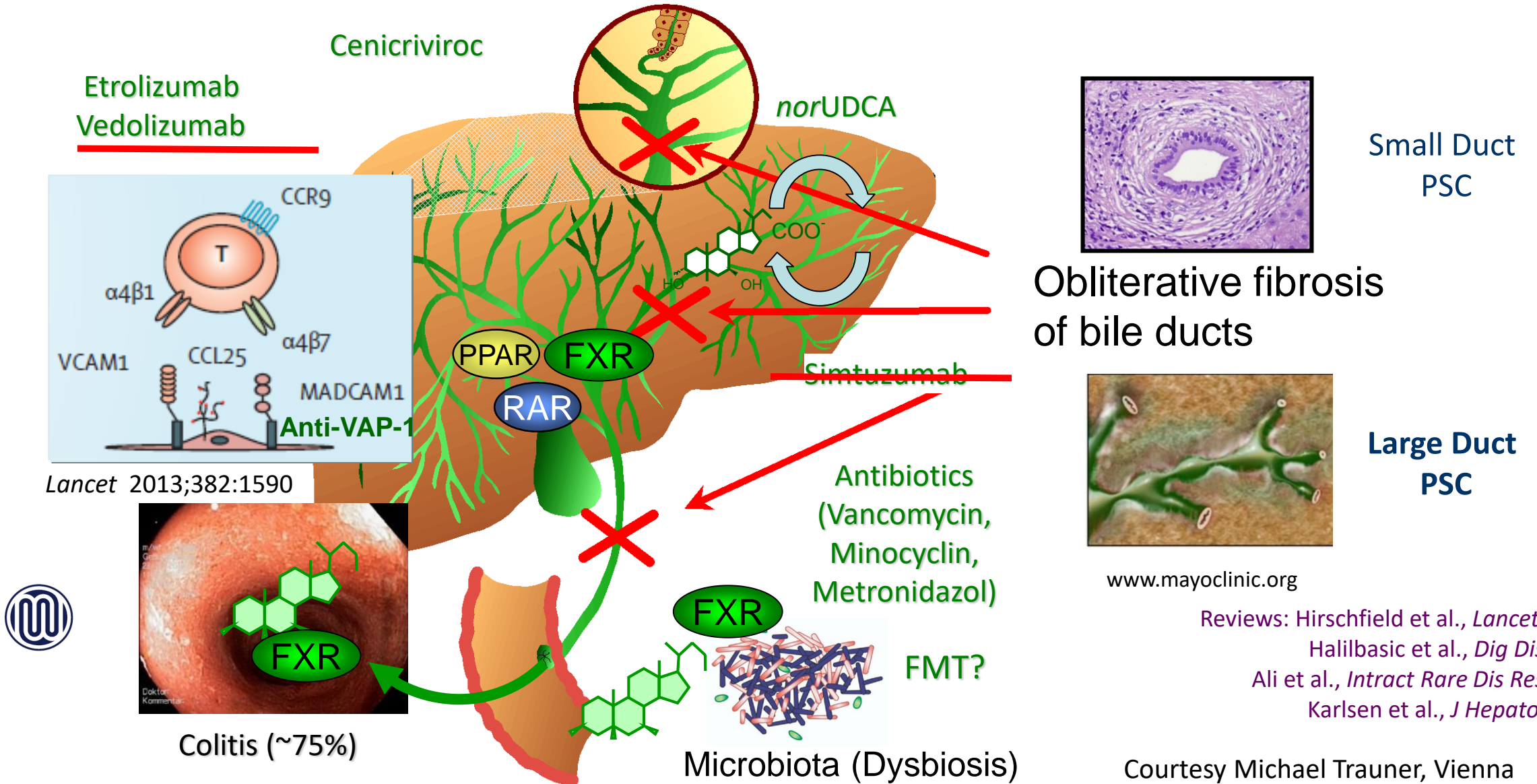


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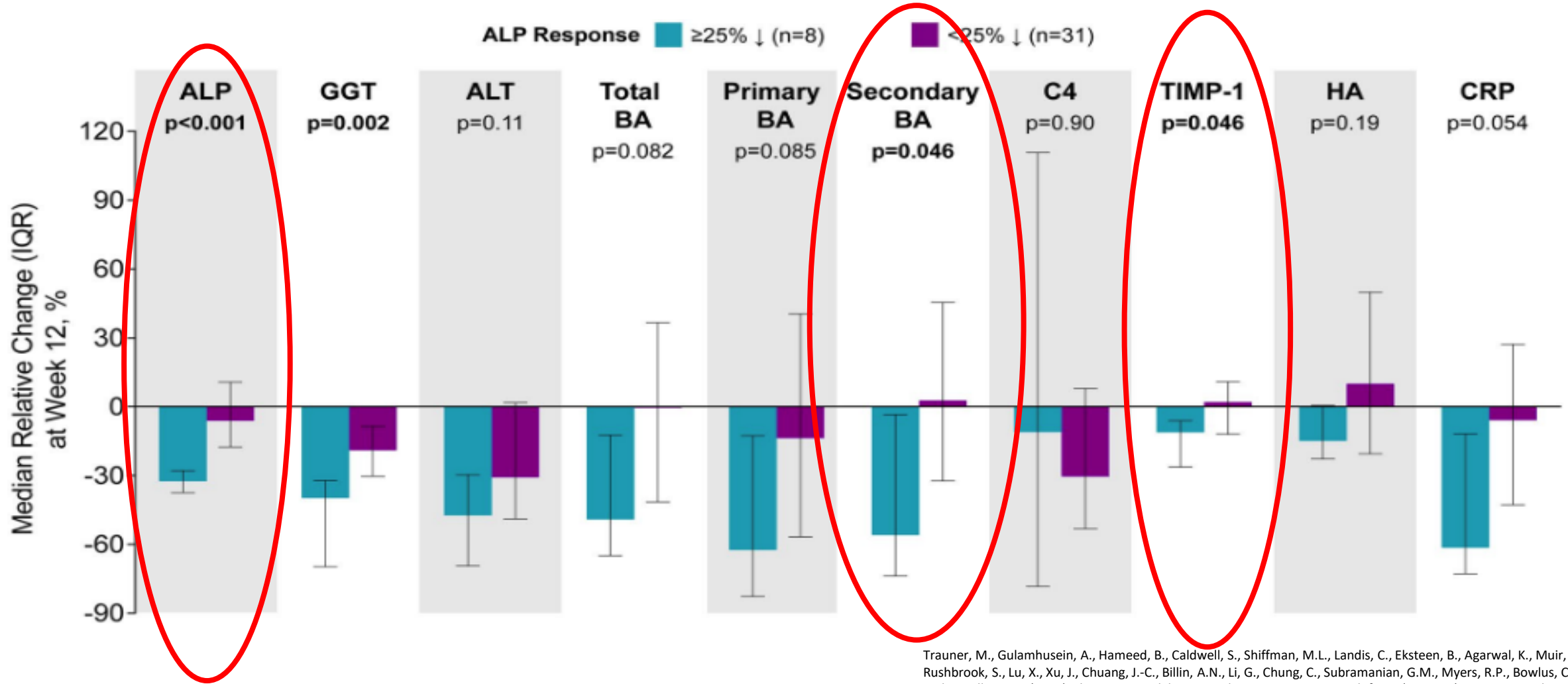
# What's new about **future therapies for PSC** ?

# Novel Therapeutic Strategies in PSC- Overview

## Candidates for Recent & Future Clinical Trials



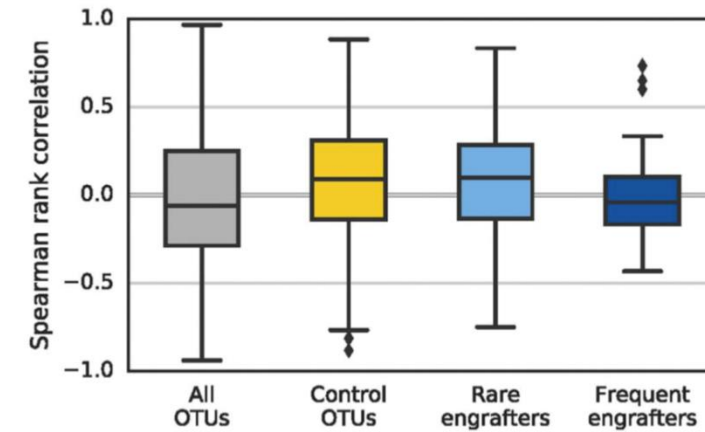
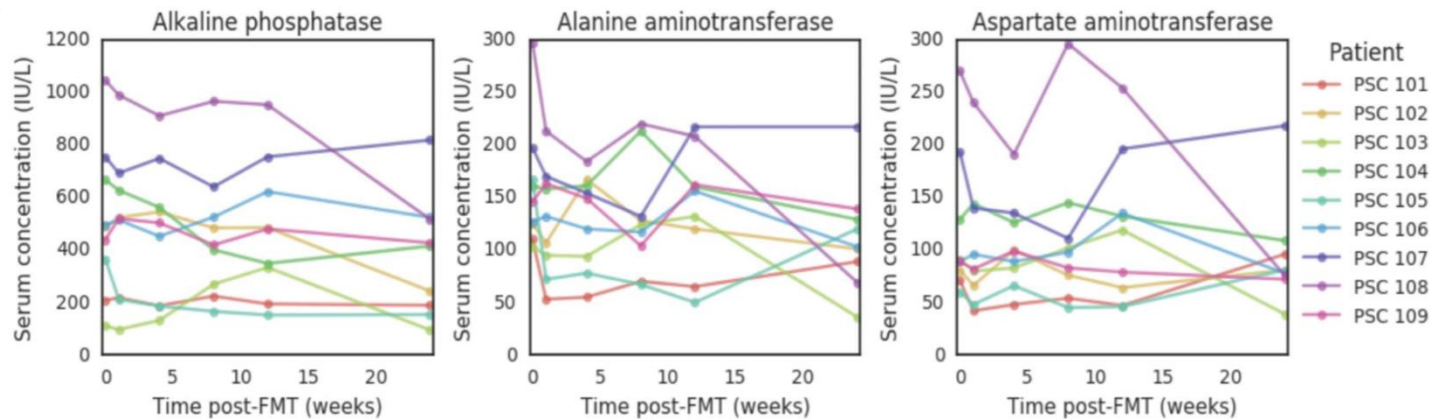
# Cilofexor for the treatment of PSC



Trauner, M., Gulamhusein, A., Hameed, B., Caldwell, S., Shiffman, M.L., Landis, C., Eksteen, B., Agarwal, K., Muir, A., Rushbrook, S., Lu, X., Xu, J., Chuang, J.-C., Billin, A.N., Li, G., Chung, C., Subramanian, G.M., Myers, R.P., Bowlus, C.L. and Kowdley, K.V. (2019), The Nonsteroidal Farnesoid X Receptor Agonist Cilofexor (GS-9674) Improves Markers of Cholestasis and Liver Injury in Patients With Primary Sclerosing Cholangitis. *Hepatology*, 70: 788-801. doi:10.1002/hep.30509

# Fecal Microbiota Transplantation in Patients with PSC

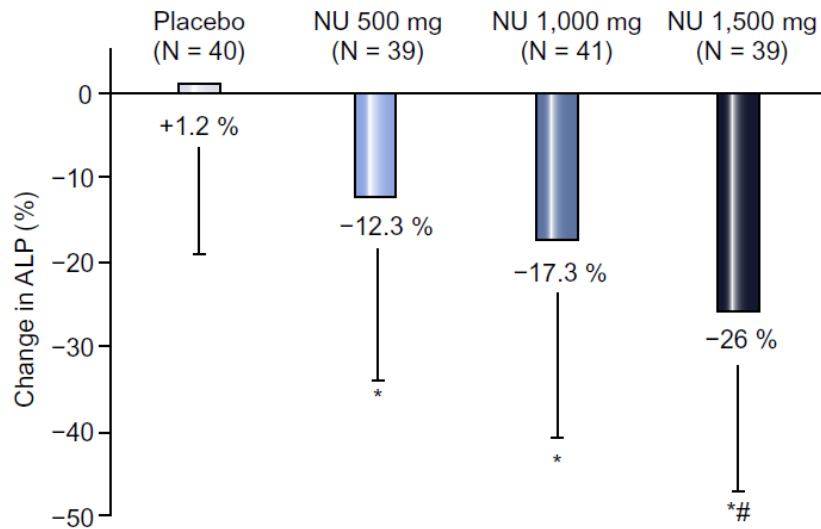
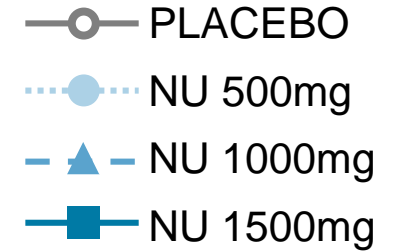
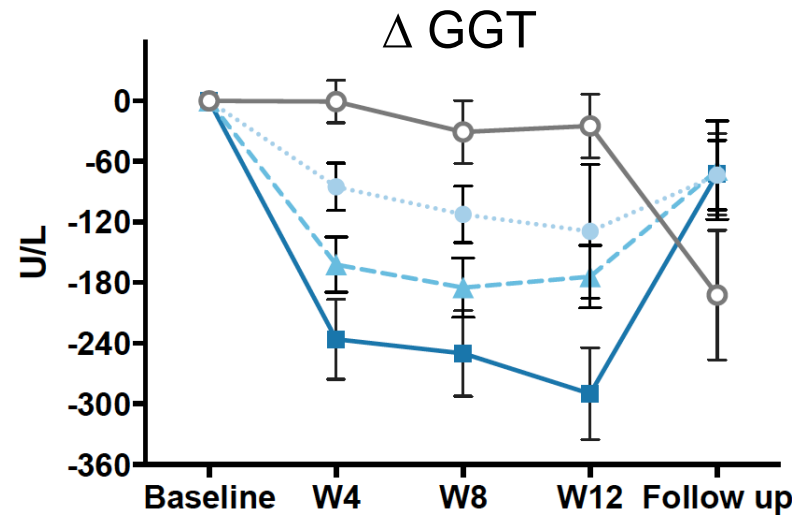
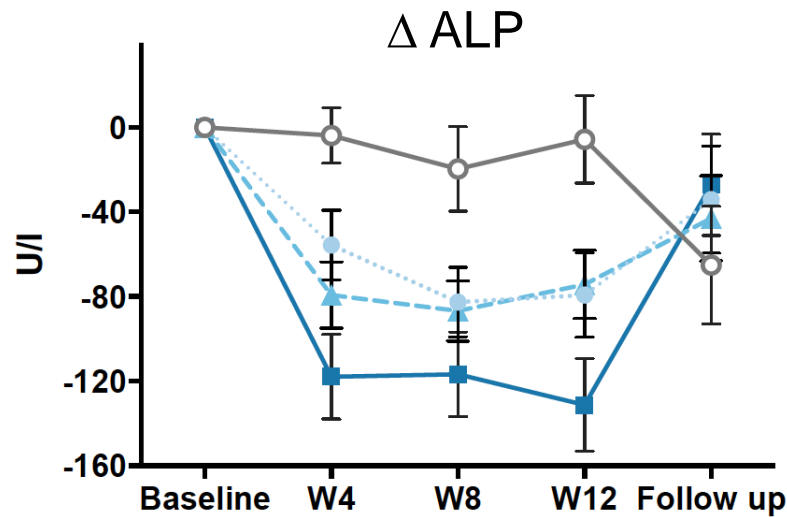
Study Design: An open-label pilot study of 10 patients with PSC with concurrent inflammatory bowel disease and alkaline phosphatase (ALP)  $> 1.5 \times$  the upper limit of normal. The patients underwent a single FMT by colonoscopy.



Correlation between change in ALP and change in OTU abundance post-FMT

- ✓ FMT is safe in patients with PSC - there were no related adverse events.
- ✓ Overall, 30% (3/10) experienced a  $> 50\%$  decrease in ALP levels
- ✓ Abundance of engrafter operational taxonomic units in patients post-FMT correlated with decreased ALP levels

# norUDCA Improves Cholestasis in PSC: Results of a European Multicenter Phase II RCT (NUC-3)

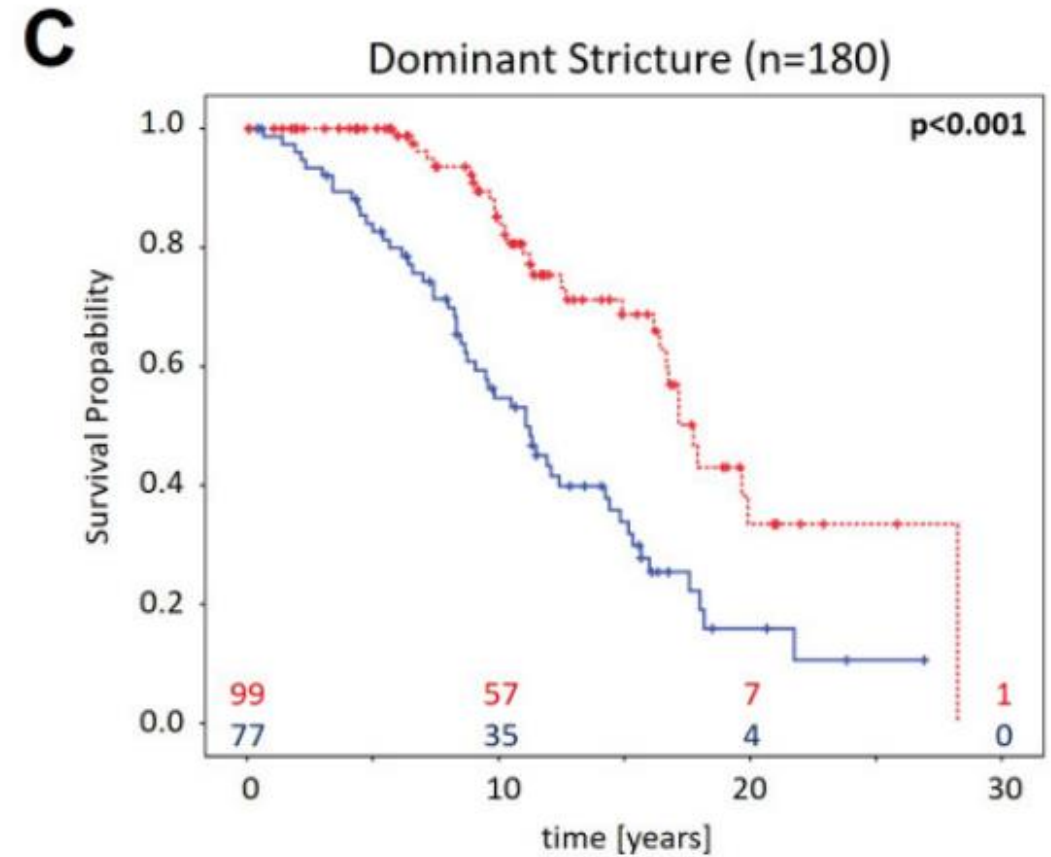
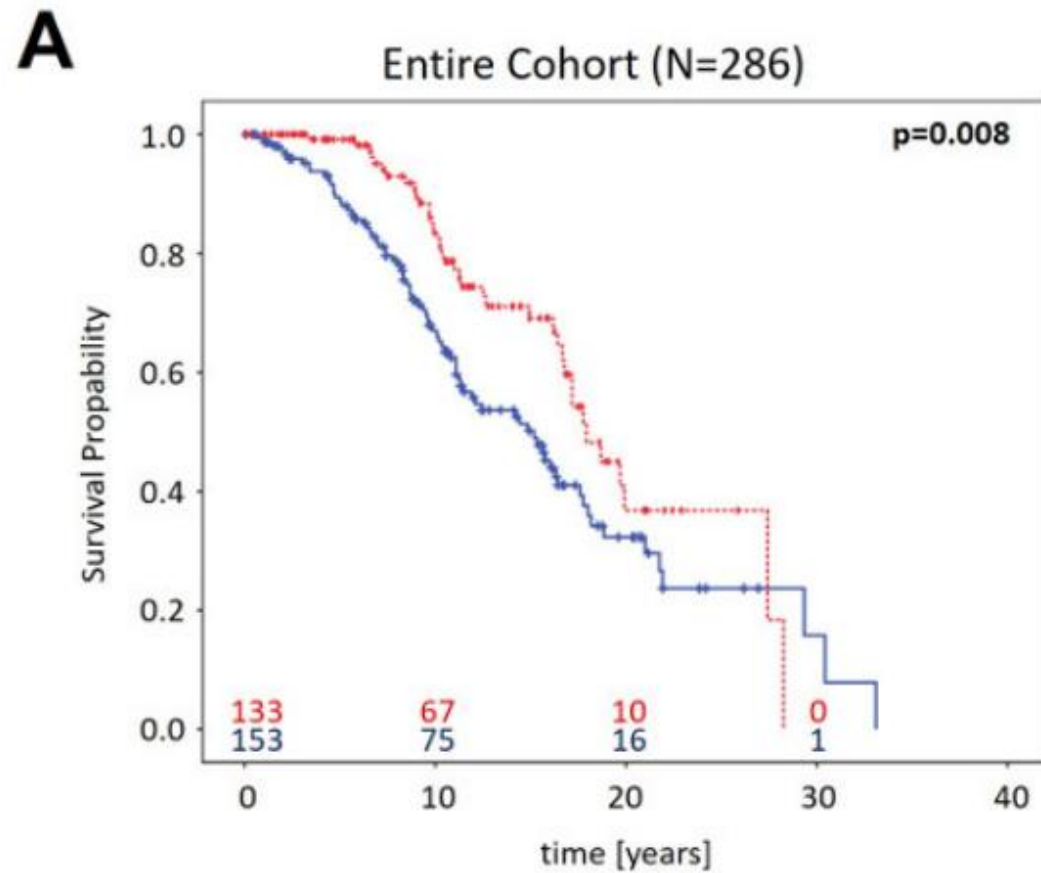


● **Phase III initiated (NUC-5)**

Fickert, ..., Manns, Trauner, *J Hepatol* 2017; 67: 549-558



# Scheduled ERCP with dilatation of dominant stenosis improves survival in PSC patients



red = scheduled ERCP; blue = ERCP o-demand

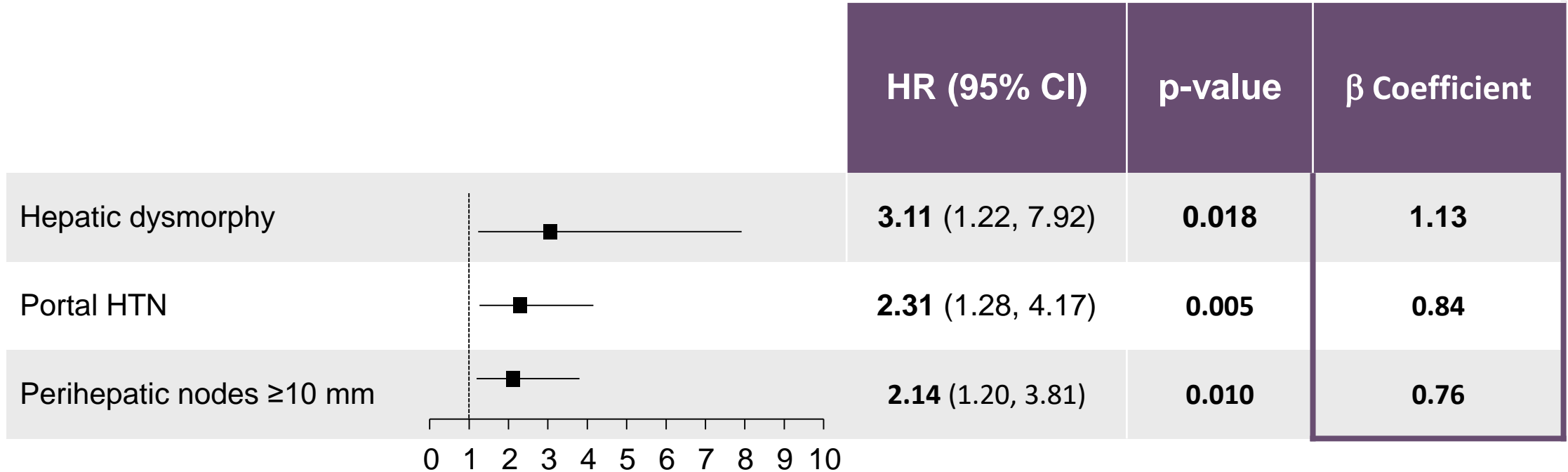
Rupp C, Hippchen T, Bruckner T, et al. Effect of scheduled endoscopic dilatation of dominant strictures on outcome in patients with primary sclerosing cholangitis. *Gut*. 2019. doi:10.1136/gutjnl-2018-316801

# What is the biggest challenge in PSC ?

## Therapy - Endpoints !

# Results: MRCP Predictors of PSC-Related Clinical Events

## Multivariate Analysis



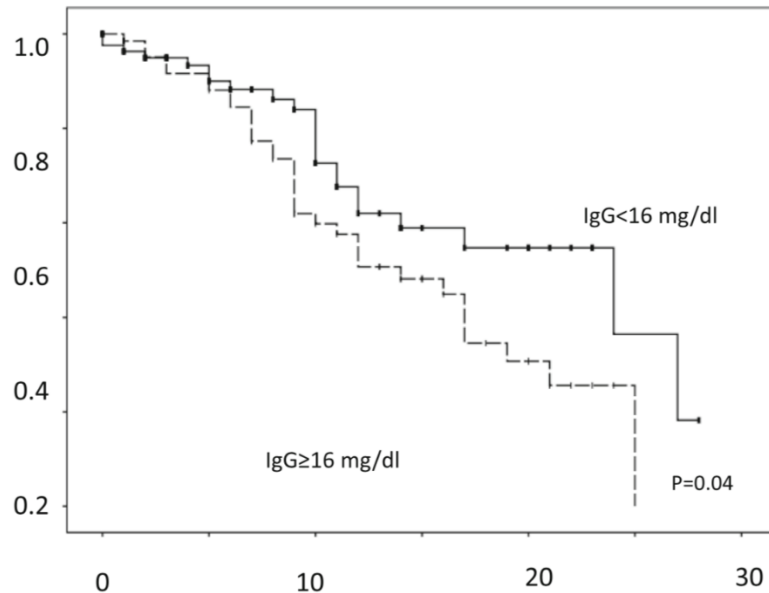
### MRCP Risk Score (MRCP-RS)

$$= 1 \times \text{Hepatic dysmorphism} + 1 \times \text{Portal HTN} + 1 \times \text{Perihepatic nodes}$$

Multivariate Cox regression with backward selection ( $p < 0.05$  for variable retention).

Muir, ...Manns, ..... et al, AASLD 2017

# Association between serum IgG levels and clinical course in PSC



Numbers at risk						
0	10	20	30	40	50	
82	78	73	68	63	58	IgG < 16 mg/dl
66	61	56	51	46	41	IgG ≥ 16 mg/dl

**Table 4** Uni- und multivariate analysis cox regression analyses

Risk factors	Univariate			Multivariate		
	$\beta$ -estimate	Exp (B) CL 95%	<i>p</i> -value	$\beta$ -estimate	Exp (B) CL 95%	<i>p</i> -value
Gender	0.8	0.5–1.4	0.5	1.3	0.5–3.8	0.6
Age of diagnose [years]	1.0	0.9–1.0	0.07	0.9	0.9–1.0	0.8
Presence of IBD	1.7	0.9–3.4	0.1	0.8	0.3–1.9	0.8
Presence of dominant stenosis	2.6	1.4–4.9	<b>0.003</b>	3.3	1.1–9.8	<b>0.04</b>
Mayo Risk score	1.7	1.3–2.2	<b>0.001</b>	1.5	1.0–2.1	<b>0.03</b>
Immunosuppression	0.5	0.1–2.1	0.4	0.0	0.0–0.0	1.0
Biochemical response	2.0	1.2–3.4	<b>0.01</b>	2.3	1.1–5.4	<b>0.04</b>
Elevated Serum IgG-levels	2.4	1.1–5.0	<b>0.02</b>	2.4	1.0–5.7	<b>0.04</b>

Table shows prospective factors for longer survival until death or liver transplantation. In univariate analysis Mayo Risk Score (MRS), presence of dominant stenosis, biochemical response to UDCA and elevated serum IgG levels were associated with reduced survival. In multivariate analysis, MRS, presence of dominant stenosis, biochemical response to UDCA and elevated serum IgG-levels were independently associated with reduced transplantation-free survival ( $p < 0.05$ ). Bold values indicates significant *P*-values ( $< 0.05$ )

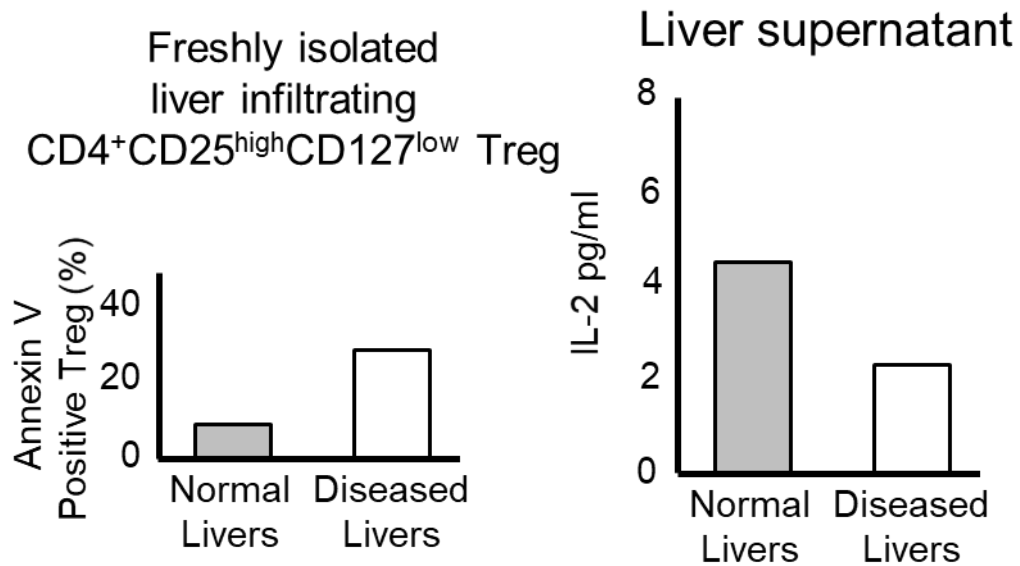
- ✓ Elevated serum IgG levels at first diagnosis count as an independent risk factor for reduced transplant free-survival in patients with PSC
- ✓ Serum igG levels might be taken into account for planning individual, risk-adapted screening and surveillance strategies
- ✓ Further validation is needed

Hippchen T et al. BMC Gastroenterology 2019

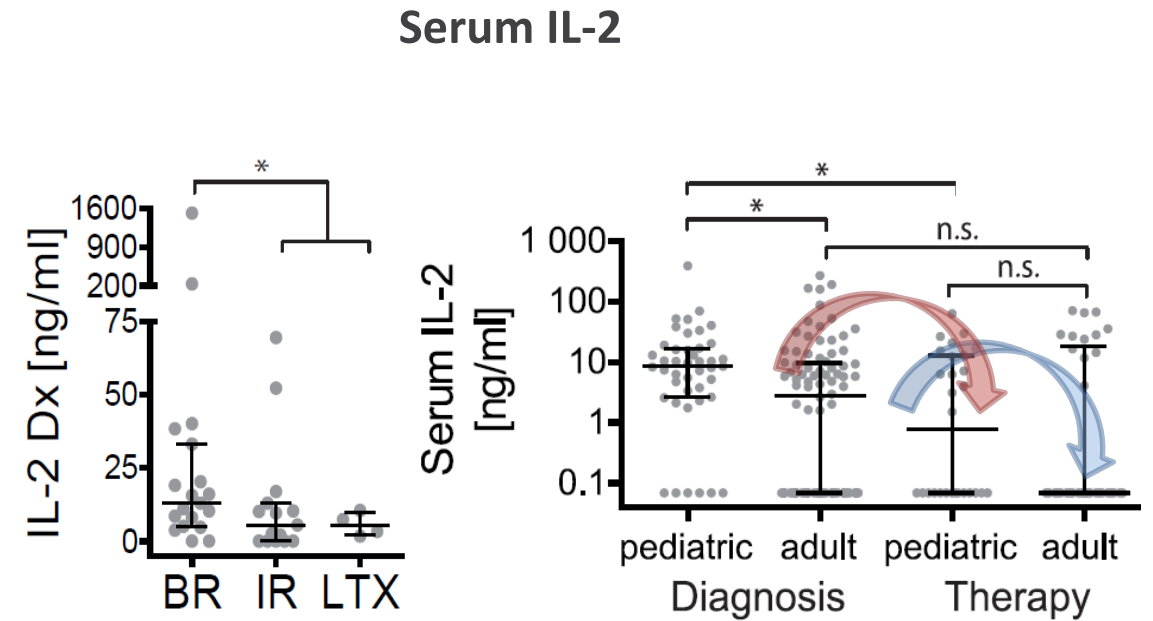
# Autoimmune hepatitis

# What's new about **the pathophysiology of AIH** **with relevance to treatment ?**

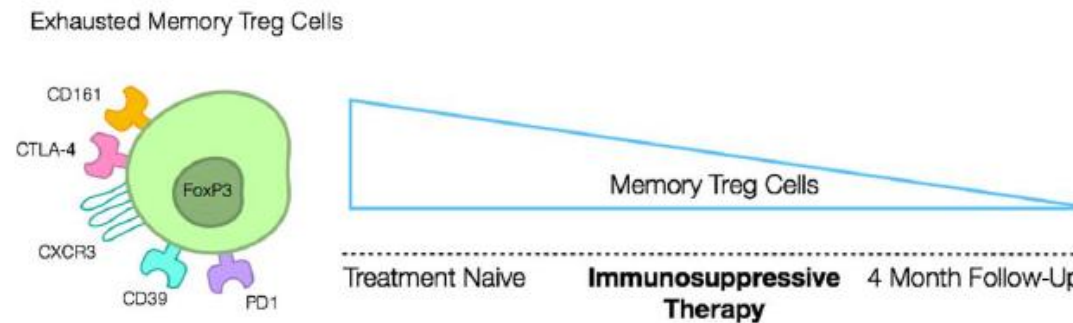
# Regulatory T cells (Treg): Numbers and function



Chen et al. Hepatology. 2016 Jul;64(1):138-50



Diestelhorst et al. PLoS One. 2017;12(7):e0181107  
Diestelhorst et al. Sci Rep. 2018 Jan 11;8(1):419.

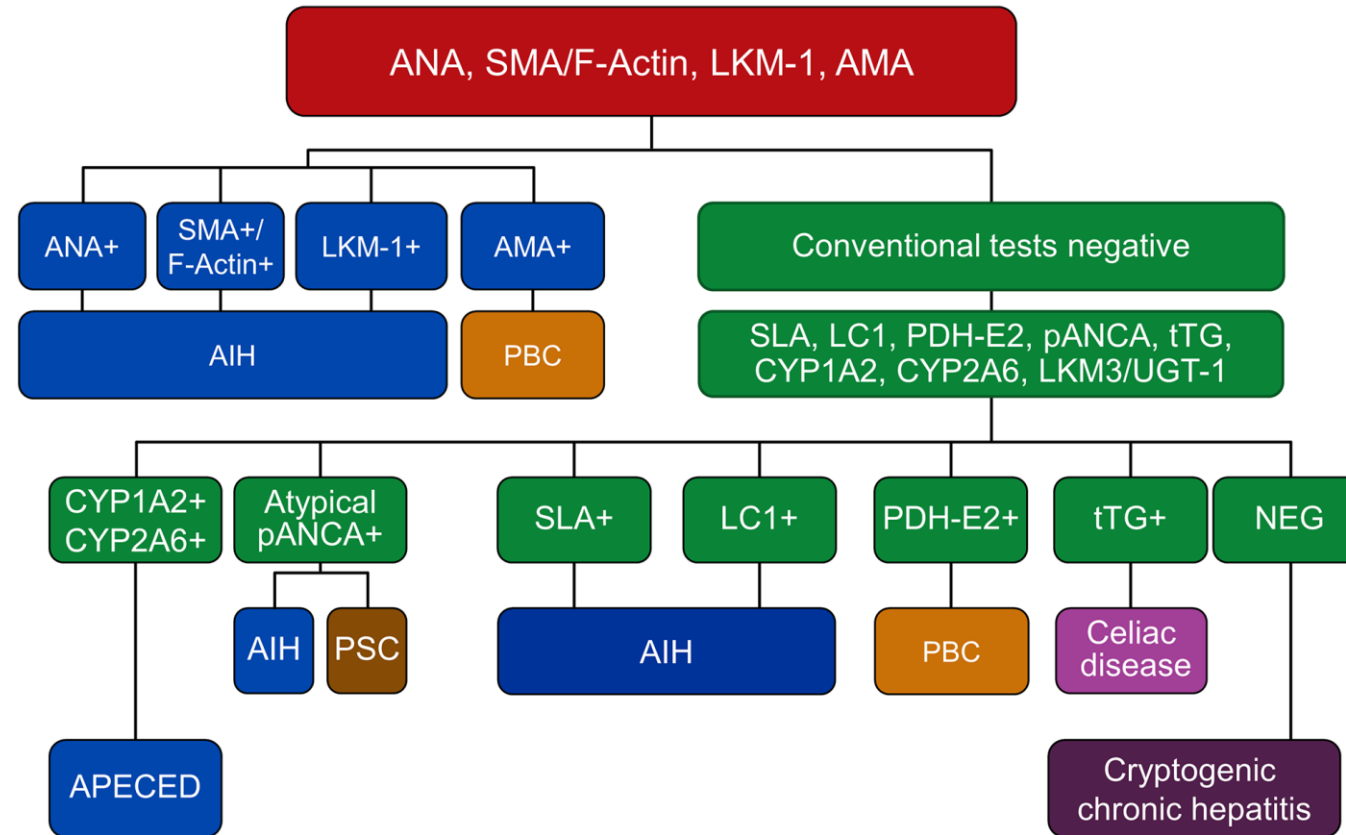


modified from: Jeffery et al. HEPATOLOGY COMMUNICATIONS, Vol. 2, No. 4, 2018

# What's new about **diagnosing AIH** ?



# Diagnostic Autoantibody Algorithm for the Diagnosis of Autoimmune Liver Disease

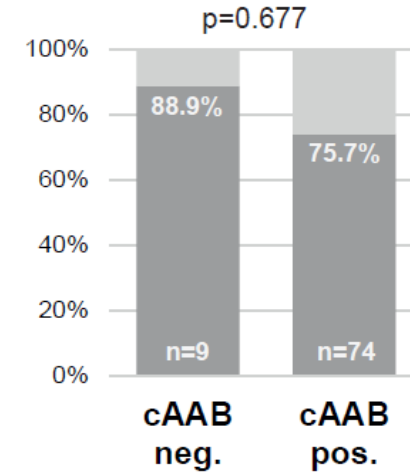
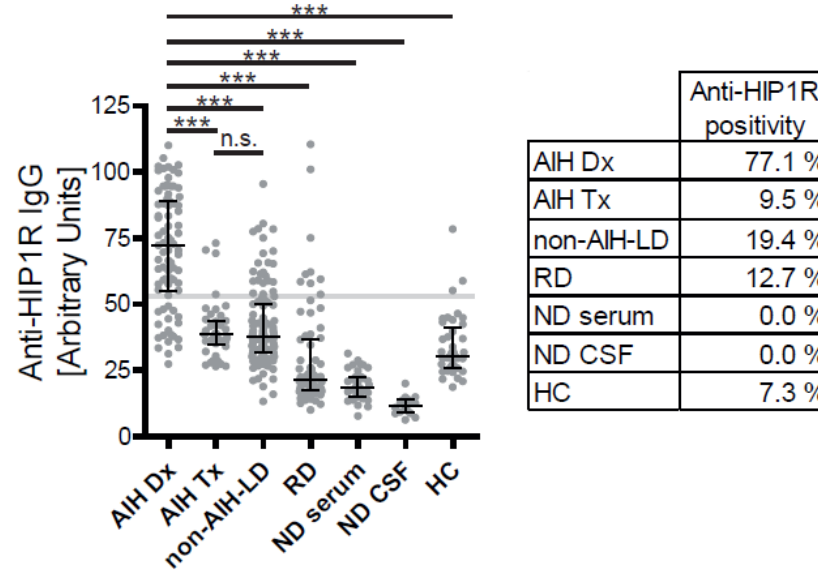


Mack....., Manns,....et al AASLD AIH CPG, in press 2020

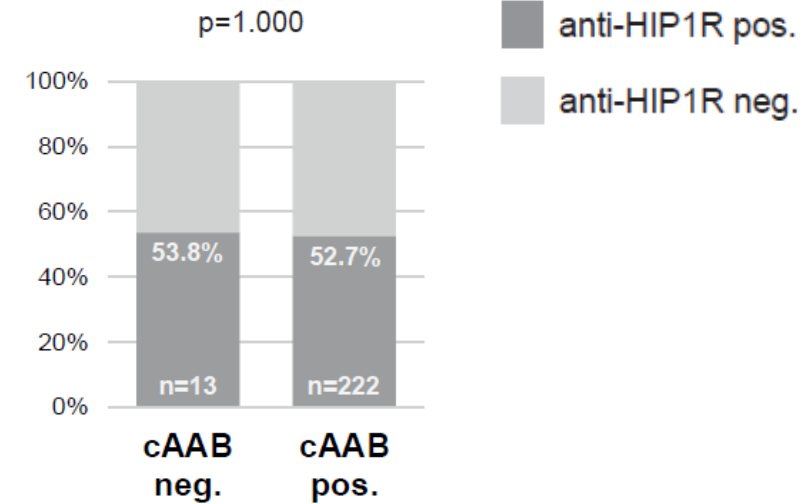
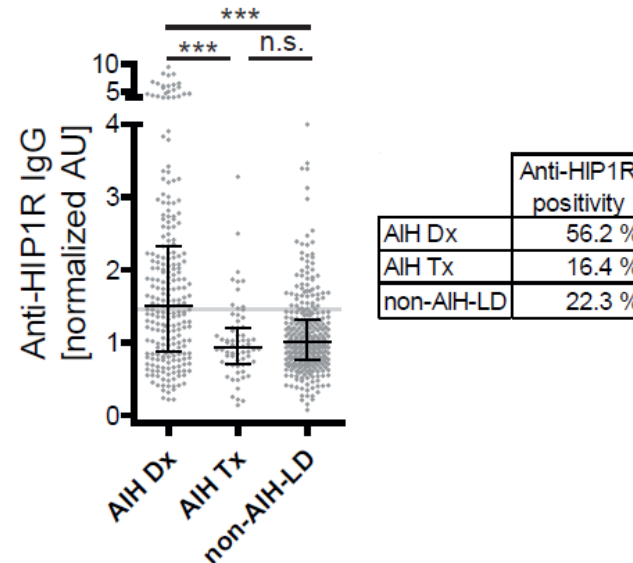
# Anti-HIP1R\* for the diagnosis AIH



Hannover  
Training  
Cohort  
(n=207)



European  
Validation  
Cohort  
(n=558)



AIH Dx = untreated AIH  
AIH Tx = AIH under treatment  
non-AIH-LD = non-AIH-liver disease  
RD = rheumatological disease  
ND = neurological disease  
HC = healthy control  
cAAB= conventional autoantibodies

Equal sensitivity in  
autoantibody negative AIH

Taubert, Engel, ... Manns, Jaeckel submitted

\*Huntingtin interacting protein 1 related protein - ubiquitin protein

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13.01.2020

M<sub>H</sub>H

Medizinische Hochschule  
Hannover

# Anti-HIP1R for the diagnosis AIH

		Sample number	Sensitivity	p vs HIP1R	Specificity	p vs HIP1R	Accuracy	CI
Retrospective training cohort (Hannover)	anti-HIP1R	207	0.771		0.806		0.792	0.729-0.844
	ANA	207	0.819	0.572	0.677	0.033	0.734	0.668-0.792
	SMA	207	0.427	<0.001	0.637	0.002	0.553	0.483-0.622
	anti-LKM	205	0.037	<0.001	1.000	not applicable	0.620	0.549-0.686
European multicenter validation cohort	anti-HIP1R	558	0.528		0.802		0.686	0.646-0.724
	ANA	558	0.711	<0.001	0.591	<0.001	0.642	0.600-0.681
	SMA	558	0.672	0.002	0.728	0.020	0.704	0.664-0.742
	anti-LKM	395	0.027	<0.001	0.994	<.0001	0.448	0.399-0.499

Anti-HIP1R more specific than ANA and SMA

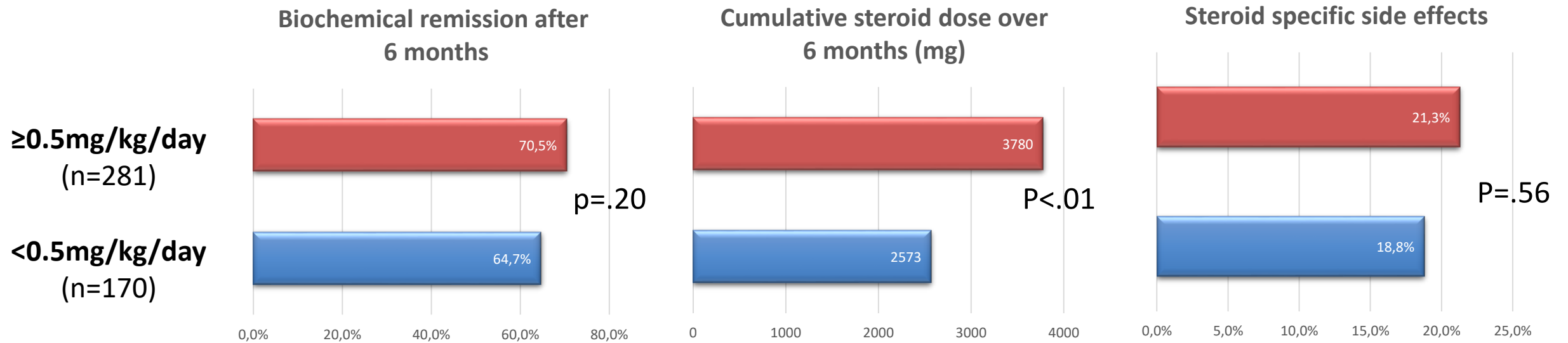
Taubert, Engel, ... Manns, Jaeckel submitted

# What's new about **therapies for AIH?**

## **Induction therapy**

# Differences of high ( $\geq 0.5\text{mg/kg}$ ) and low ( $< 0.5\text{mg/kg}$ ) dose predniso(lo)ne regimen during first line therapy

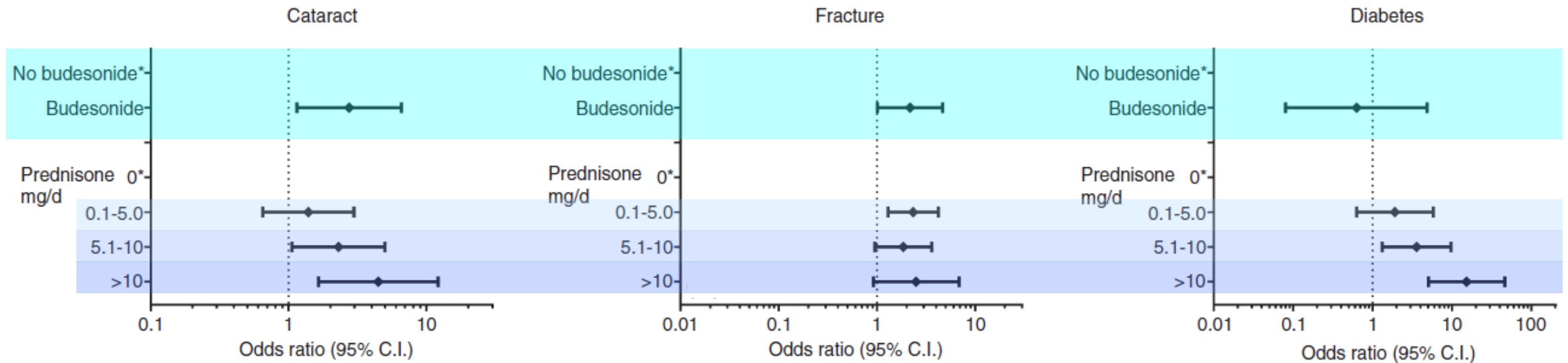
451 AIH patients from 9 centers in 5 European countries treated between 1978 and 2017



Pape et al. Clin Gastroenterol Hepatol. 2019 Jan 5.

# Adverse events related to low dose corticosteroids in autoimmune hepatitis

476 AIH patients with a total of 6634 patient years from Dutch AIH Study Group Registry since 2008



Van den Brand et al. Aliment Pharmacol Ther. 2019 Oct 15. doi: 10.1111/apt.15528

# What's new about **therapies for AIH** ?

## **Salvage therapy**

# First Meta-Analyses for AIH 2017-2019

Study	Study cohort	Patients	Drugs	Treatment response	Adverse events (AE)	Conclusion	
Yu et al. 2019	Meta-Analysis of 7 studies	MMF as first line therapy	583	MMF+prednisone Standard of care (SOC)	ALT/AST normalization: 55-89% vs 33-87% (p < 0.05) IgG normalization: 62-89% (p < 0.01) non-response 6-33% (p < 0.01) AST/ALT/IgG normalization: 33-87% non-response 15-67% (p < 0.01)		MMF+Pred superior to SOC
De Lemos-Bonotto et al. 2018	Meta-Analysis of 15 studies	Second line therapy agents	283	MMF+prednisone Tacrolimus+prednisone	improvement of aminotransferases 79% histological remission 89% improvement of aminotransferases 94%	liver transplantation 11% mortality 7%	Tac+Pred best for improvement of aminotranferases
Santiago et al. 2019	Meta-Analysis of 12 studies						switch to MMF was effective (better for intolerance than for non response)
Zizzo et al. 2017	Meta-Analysis of 15 studies	Second line therapy agents in children	76	MMF Ciclosporin Tacrolimus	normalization of ALT/AST at 6 months: 36% normalization of ALT/AST at 6 months: 83% normalization of ALT/AST at 6 months: 50%	pooled estimates for AE: 45% pooled estimates for AE: 78% pooled estimates for AE: 42%	CsA most effective but most AEs

**None of the second line therapies for AIH treatment failure are approved yet !**

Yu et al. Eur J Gastroenterol Hepatol. 2019 Jul;31(7):873-877.

De Lemos-Bonotto et al. Eur J Gastroenterol Hepatol. 2018 Feb;30(2):212-216.


Santiago et al. Aliment Pharmacol Ther. 2019 Apr;49(7):830-839.

Zizzo et al. J Pediatr Gastroenterol Nutr. 2017 Jul;65(1):6-15.



# Management of Treatment Failures after Standard of Care: SOC

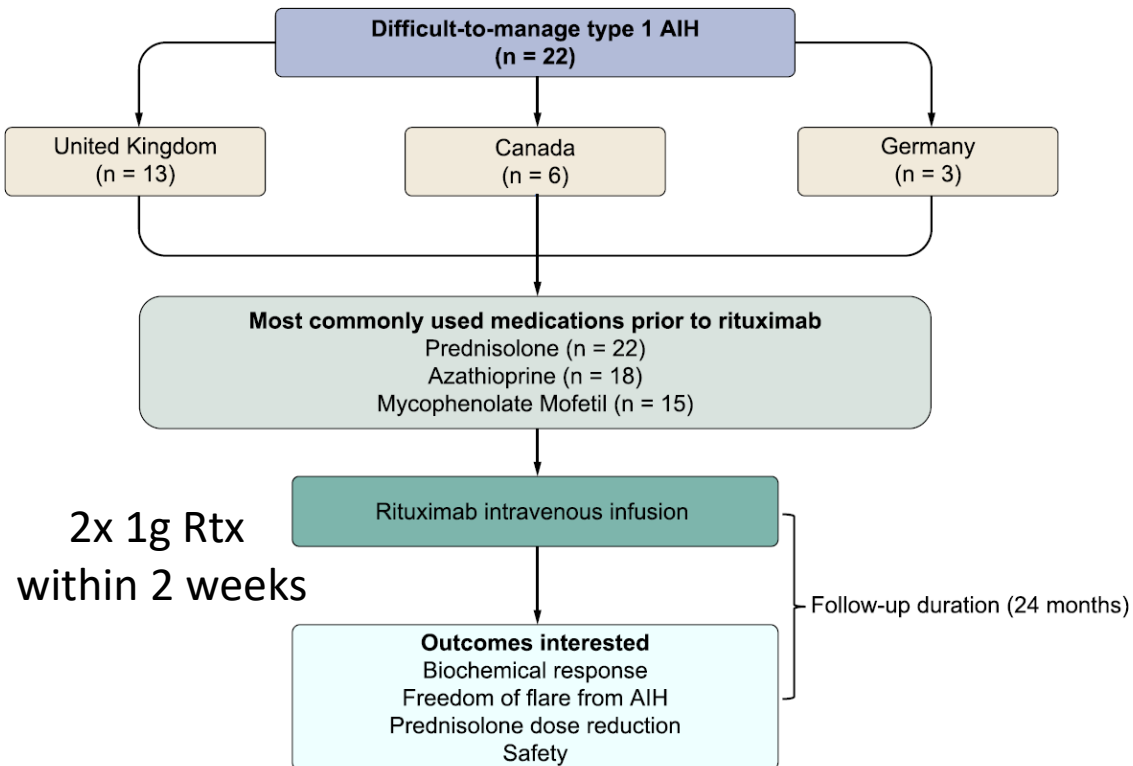
## – Biologics

- Anti TNF
- Anti CD 20 (Rituximab) 
- Anti B cell and anti BAFF-R (VAY736)

# Rituximab for difficult to manage AIH

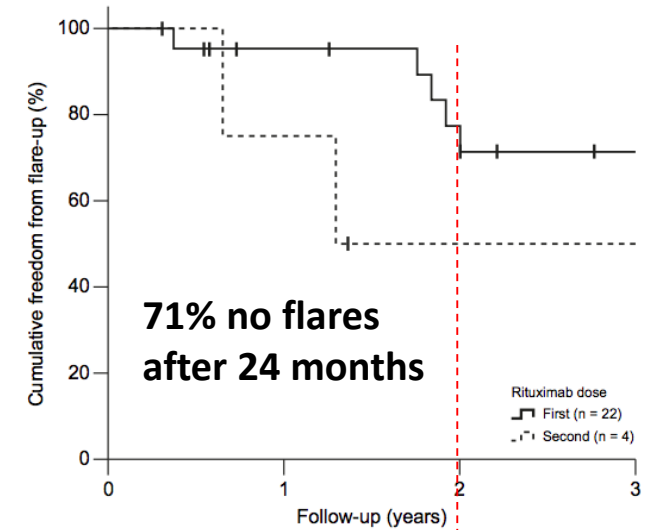
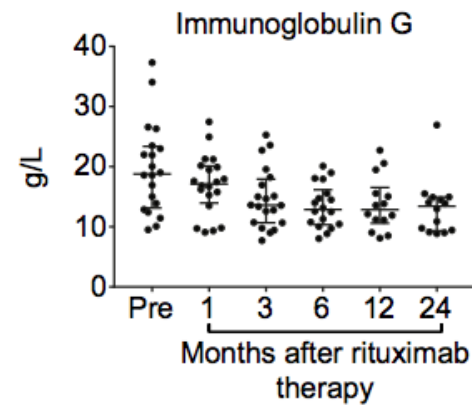
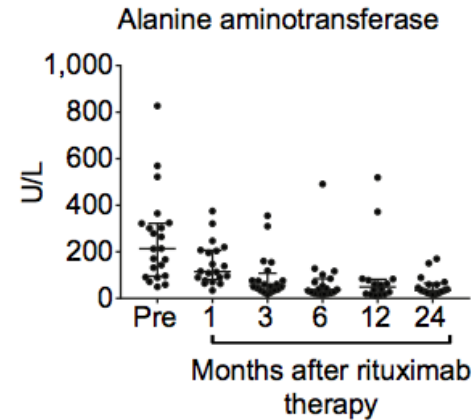
## retrospective IAIH group study

incl. 3x Cirrhosis (2x CP A; 1x CP C)

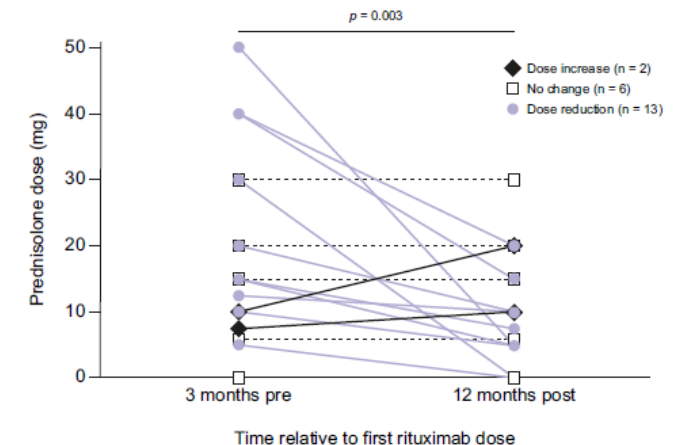


**➔ No serious adverse event**

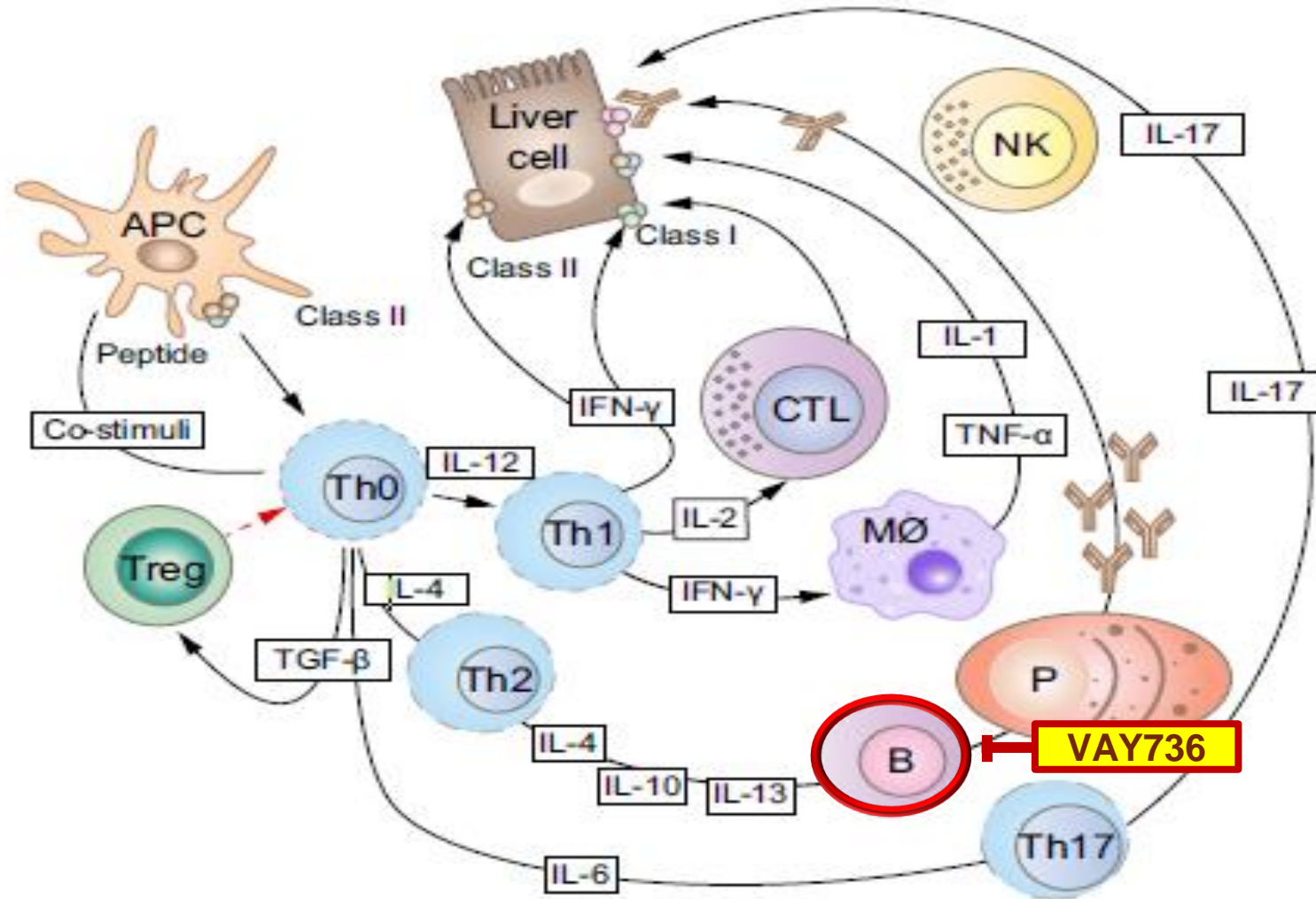
Modified from Than NN, .... Taubert R ... Manns MP, ... et al.  
JHEP Reports, Volume 1, Issue 6, 437 – 445, 2019



## 62% Steroid dose reduction



# Molecular Pathogenesis of autoimmune hepatitis



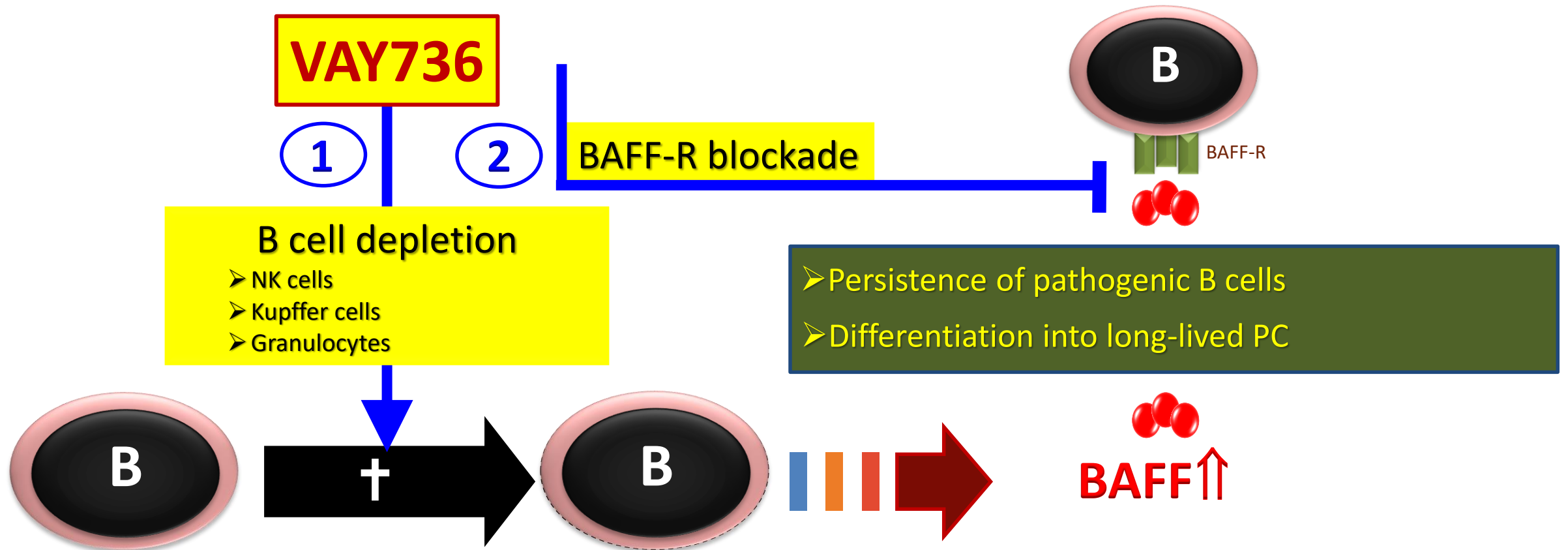
Manns et al., Journal of Hepatology, 2015

© 2017 AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES WWW.AASLD.ORG

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# VAY736: Anti-BAFF-R antibody with dual action

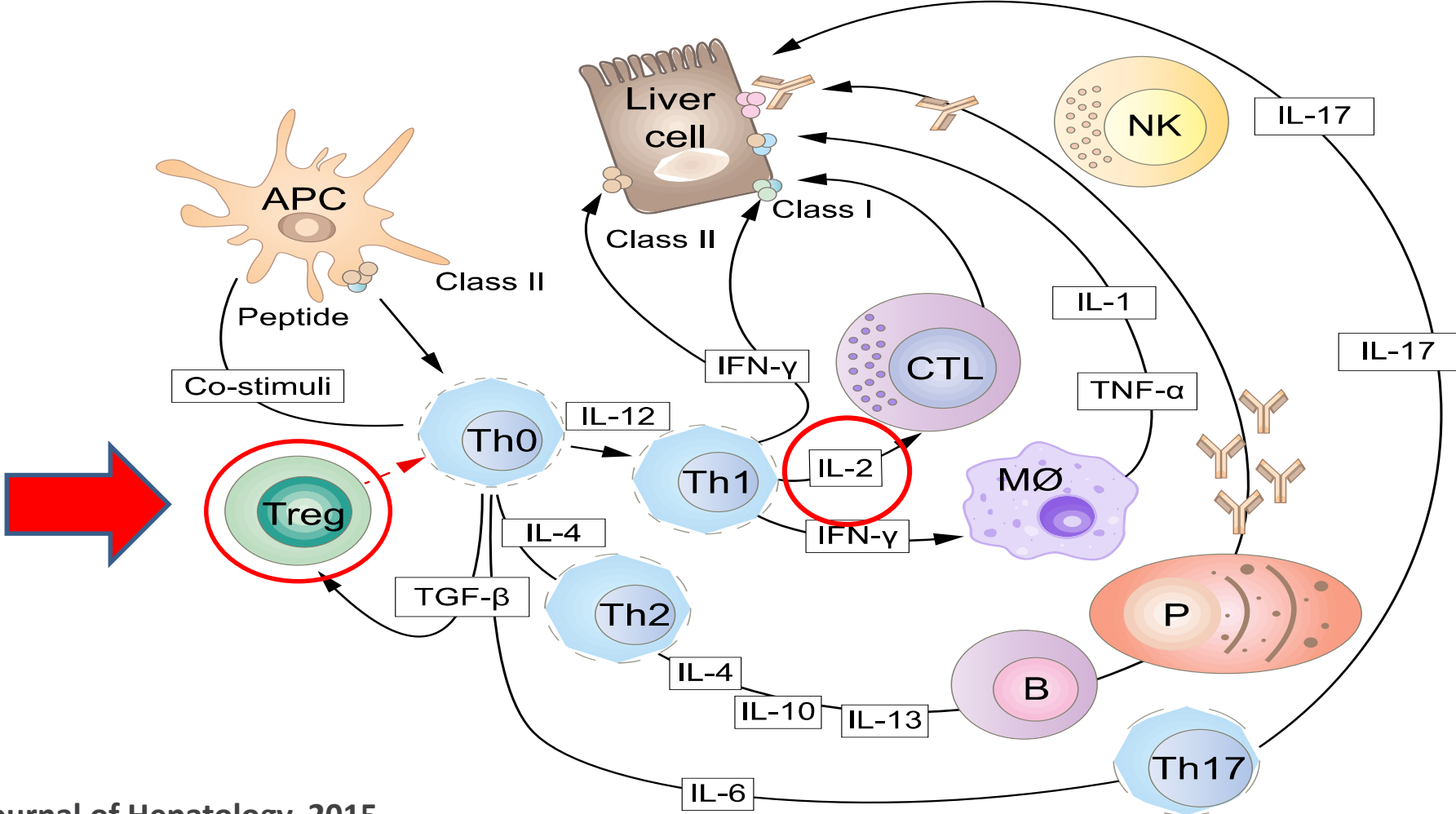
1) ADCC mediated B cell depletion; 2) Functional BAFF-R blockade



Rapid and profound B cell depletion | Prevention of BAFF-induced hardening of autoimmunity

[www.clinicaltrials.gov](http://www.clinicaltrials.gov): NCT03217422

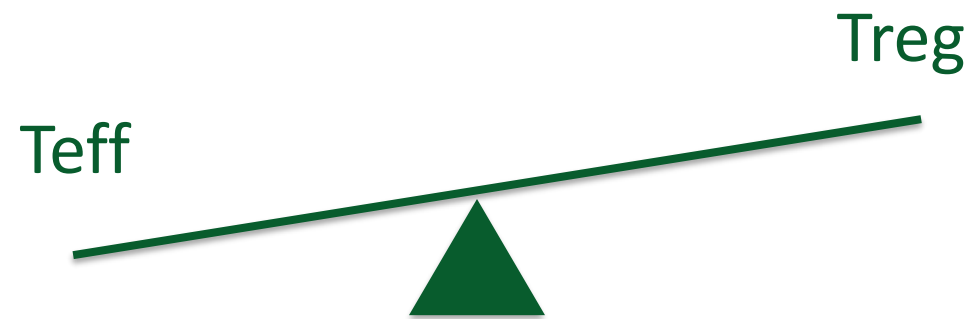
# Molecular pathogenesis of autoimmune hepatitis



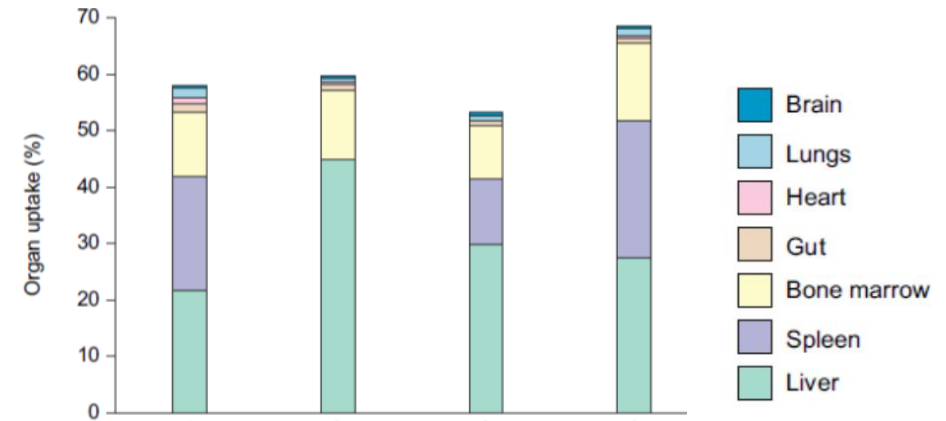
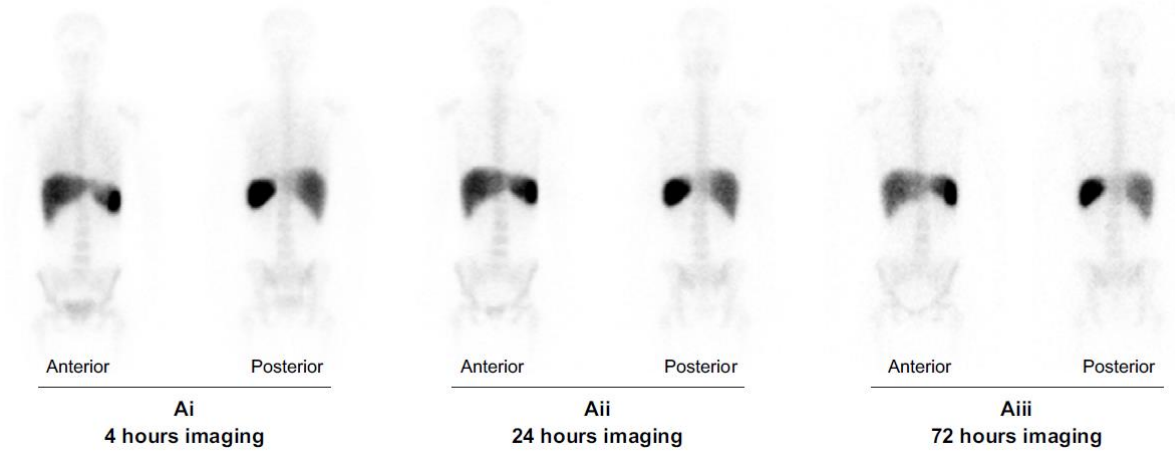
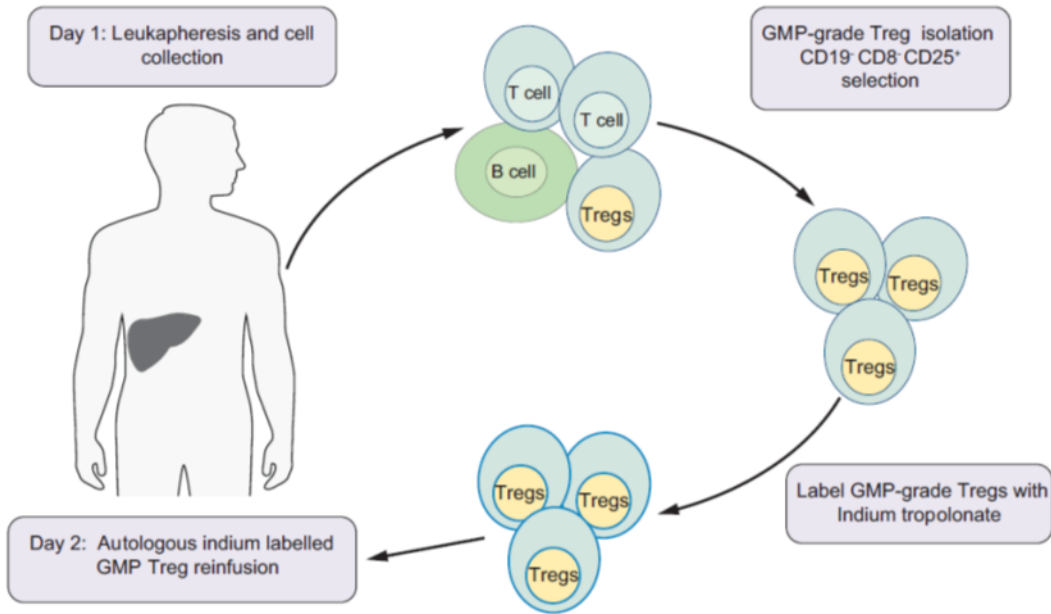
Manns et al., Journal of Hepatology, 2015

# AIH: Future Therapies

- Can we increase therapeutic response by strengthening immunoregulation ?
- Adoptive transfer of Tregs ?
- Low dose IL-2 ?



# Clinical Treg infusion in AIH patients – a pilot trial

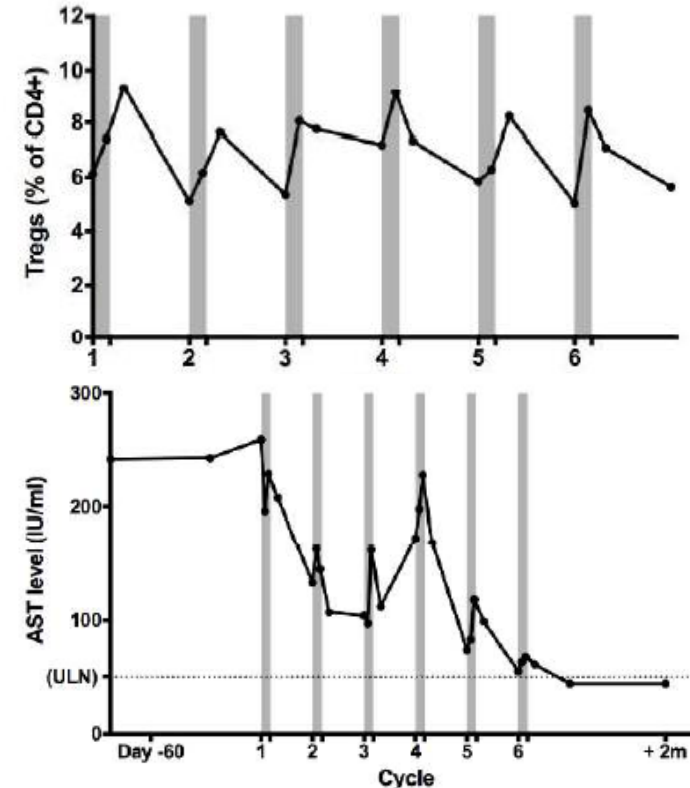
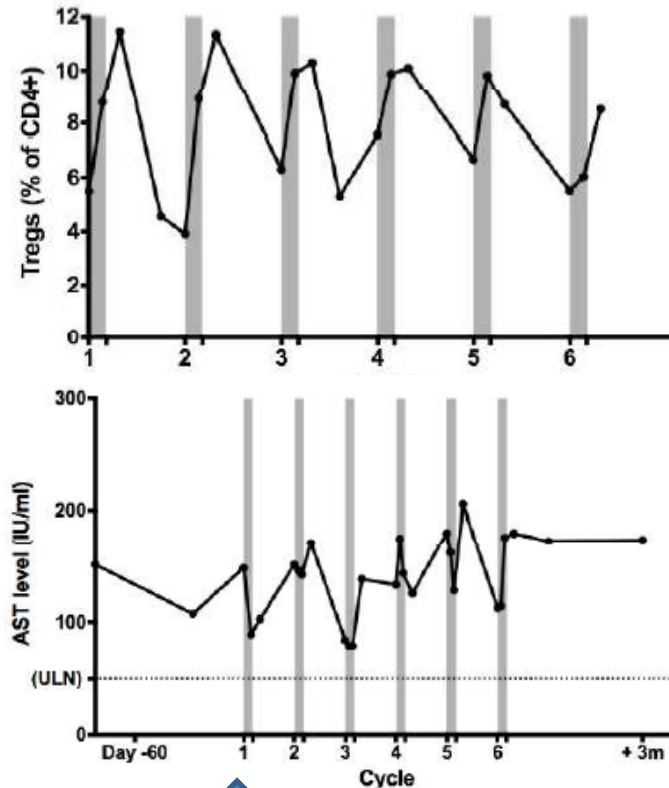


- Inclusion 5 pts; Treg infusion in 4 pats. (labelling failure)
- Isolated Treg were functional
- 22-44% of Treg homed and were retained in the liver
- No off target accumulation beside spleen and bone marrow
- No infusion reaction or serious adverse event

# Low dose IL-2 in refractory AIH

female 20 yrs. with cirrhosis  
(pediatric AIH-1)

female 56 yrs. with bridging fibrosis  
(adult AIH-3)



IL-2 ↑ (1 Mio. Units s.c. 5x/month over 6 months)

Modified from Lim et al., Hepatology. 2018 Oct;68(4):1649-1652



# What's new about **initiatives for AIH as orphan disease ?**



# European Reference Network

for rare or low prev complex diseases

 **Network**  
Hepatological Disease  
(ERN RARE-LIVER)

Lead:  
Prof. Lohse  
Hamburg/Germany

## Full Members

 BE	University Hospitals Saint-Luc University Hospital Leuven University Hospital Ghent
 DK	Copenhagen University Hospital Rigshospitalet
 FR	Assistance Publique-Hôpitaux de Paris, Hôpital Bicêtre Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Antoine Assistance Publique-Hôpitaux de Paris, Hôpital Beaujon
 DE	Medizinische Hochschule Hannover Universitätsklinikum des Saarlandes Universitätsklinikum Tübingen Uniklinik RWTH Aachen Universitätsklinikum Hamburg-Eppendorf
 IT	S. Gerardo Hospital - Monza Hospital San Paolo - Milan AO Padua
 NL	Academic Medical Center Amsterdam University Medical Center Groningen Radboud University Medical Center Nijmegen
 PL	University Hospital, Banacha, Warsaw

 PT	Centro Hospitalar e Universitário de Coimbra, EPE
 ES	Hospital Clinic i Provincial de Barcelona Hospital Universitario La Paz
 SE	Karolinska University Hospital Sahlgrenska University Hospital
 UK	The Newcastle upon Tyne Hospitals NHS Foundation Trust Royal Free London NHS Foundation Trust University Hospitals Birmingham NHS Foundation Trust Birmingham Children's Hospital NHS Foundation Trust

Brexit ???

The network aims to improve the standards of care and clinical knowledge in rare liver diseases across Europe.

**+ ERN registry (prospective registry)**  
**+ CPMS (EU Clinical patient management systems)**



# International AIH Group Initiatives

www.iaihg.org

**Retrospective Registry** in addition to prospective ERN Rare Liver registry



Creating „critical mass“ for research in orphan diseases

Contact: Ynto de Boer ([y.deboer1@amsterdamumc.nl](mailto:y.deboer1@amsterdamumc.nl)) and  
Rodrigo Liberal ([rodrigo.liberal@kcl.ac.uk](mailto:rodrigo.liberal@kcl.ac.uk))

# Take Home Messages: The Future of Autoimmune Liver Diseases

- New biomarkers are needed to predict non-response to UDCA in PBC
- Obeticholic acid (OCA) and bezafibrate are used for non-response to UDCA in PBC, the combination of both and novel drugs like Selective peroxisome proliferator-activated receptor (PPAR) and fibroblast growth factor 19 (FGF19) agonists are under development.
- There is no existing treatment that alters the natural course of PSC apart from transplantation
- Several medical therapies for PSC are under clinical development like Nor-UDCA, Fecal Microbiota Transplantation (FMT) and others.
- However, generally accepted treatment endpoints as well as biomarkers for the risk-stratification are still needed for the development of novel PSC therapies
- Therapies for non-responders to standard-of-care are an unmet need for AIH patients
- Promising AIH therapies under development are targeting B cells, cytokines like TNF, IL 2 and Tregs

**Michael Manns**

**PHC 2020, Paris, 13 Januar 2020**

THANK YOU FOR YOUR ATTENTION