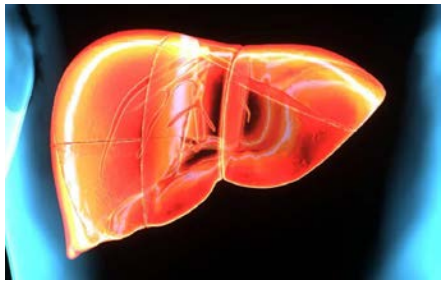


EMA stakeholder interaction on the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Session 2: Primary Sclerosing Cholangitis (PSC)

Potential trial design and suitable study populations

Michael Trauner

Div. of Gastroenterology & Hepatology

Dept. of Internal Medicine III, MedUni Wien

MEDICAL UNIVERSITY OF VIENNA

Division of
Gastroenterology and Hepatology
Department of Internal Medicine III

Financial Disclosures

- **Advisor**
  - Albireo, Falk, Genfit, Gilead, Intercept, MSD, Novartis, Phenex, Regulus
- **Grants / research support**
  - Albireo, Cymabay, Falk Pharma, Gilead, Intercept, MSD, Takeda
- **Speakers bureau**
  - Falk Foundation, Gilead, MSD, Roche
- **Travel grants**
  - Falk Foundation, Gilead, Roche
- **Property rights**
  - The Medical University of Graz has filed patents on medical use of *nor*UDCA and I am listed as co-inventor

Challenges in Clinical Trial Design for PSC

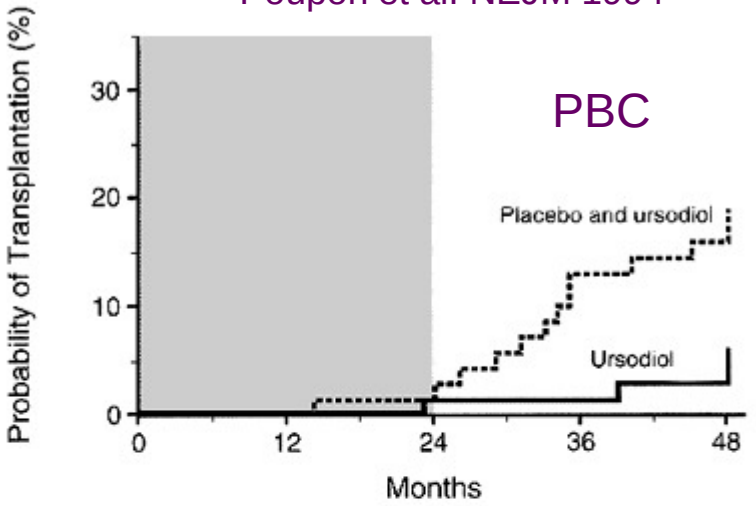
- Choosing the right endpoint … (Cyriel Ponsioen)
- Rare disease - number of patients for studies limited
- Disease heterogeneity - different prognostic & clinical implications
- Long, variable & undulating disease course
  - Limits study design (e.g., no lead-in phase followed by (re-)randomisation)
  - Slow progression (annual event rate 3-4%) - long study duration
- Variable confounding therapies (e.g. UDCA, IBD therapies, ABx)
  - UDCA (even if ineffective?) will impact on ALP-based recruitment
  - Exclusion of active IBD (to avoid IBD therapy bias / safety issues) may obscure potential efficacy signal (and does not reflect unmet clinical need)
- Multiple competing endpoints (‘liver’ vs ‘bile duct’ vs ‘colon’)

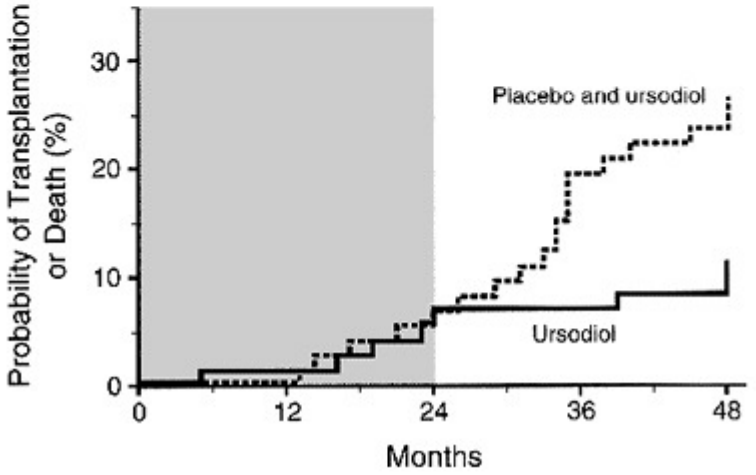
Clinical Trial Design for

- Phase 2
  - Safety, proof of concept (exploratory efficacy endpoints
  - Dose finding for phase 3; UDCA weaning for clear(er) s
  - Endpoints may depend on drug mechanism (cholestasi
  - Overlap with AIH, small duct may be allowed (cave: mil
- Phase 3
  - Intermediate endpoints for marketing authorisation mus
  - Combined use of histology evaluation and ALP change represent an acceptable intermediate endpoint (co-prim
  - Clinical outcomes: composite endpoint, totality of data?
  - 2 years for the interim endpoints, up to 5 years for the demonstration of long-term clinical outcomes
  - Open label or placebo extension?

Poupon et al. NEJM 1994

PBC





EMA Reflection Paper (draft)

Suitable Study Populations for PSC Trials

- Rare disease – practically all comers
  - Large duct PSC with/without IBD
  - Some phase II also allow small duct PSC, overlap with AIH
  - Exclude Child-Pugh B(>9)/C, need for (repeated) endoscopic Rx of DS, …
- ALP entry criterium (also for future studies?)
  - Impact of UDCA on study recruitment
- Stratification for UDCA use; IgG4?
  - Feasibility of further sub-stratification?
  - UDCA naive patients – shorter disease duration (~less advanced disease)?
- ‘Enrichement’ for risk of fibrosis progression and reaching clinical endpoints sufficiently considered?
  - Counterintuitive to early treatment of fibro-obliterative disease?

Clinical Heterogeneity of PSC – Currently Excluded Patient Subgroups (Phase III Studies)

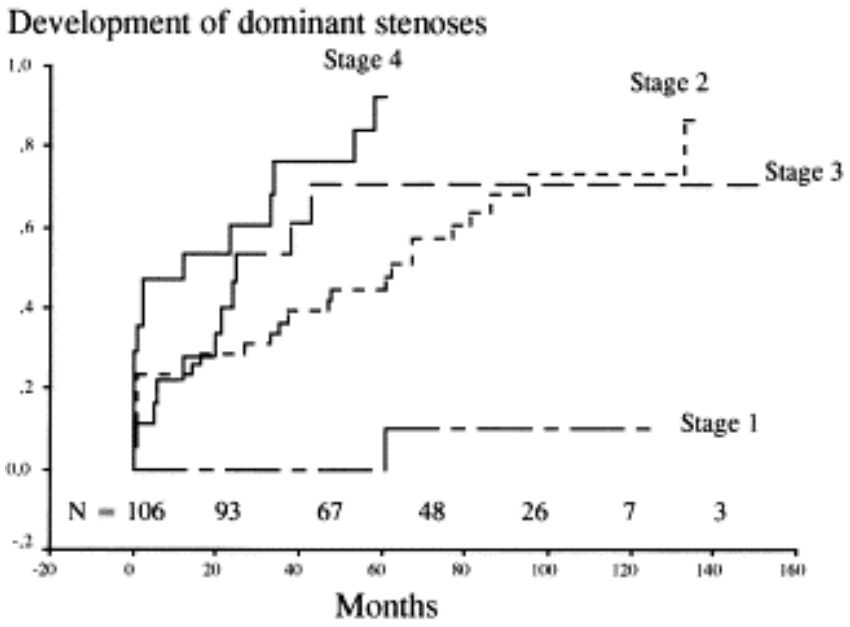
Too ‘benign‘ / early disease

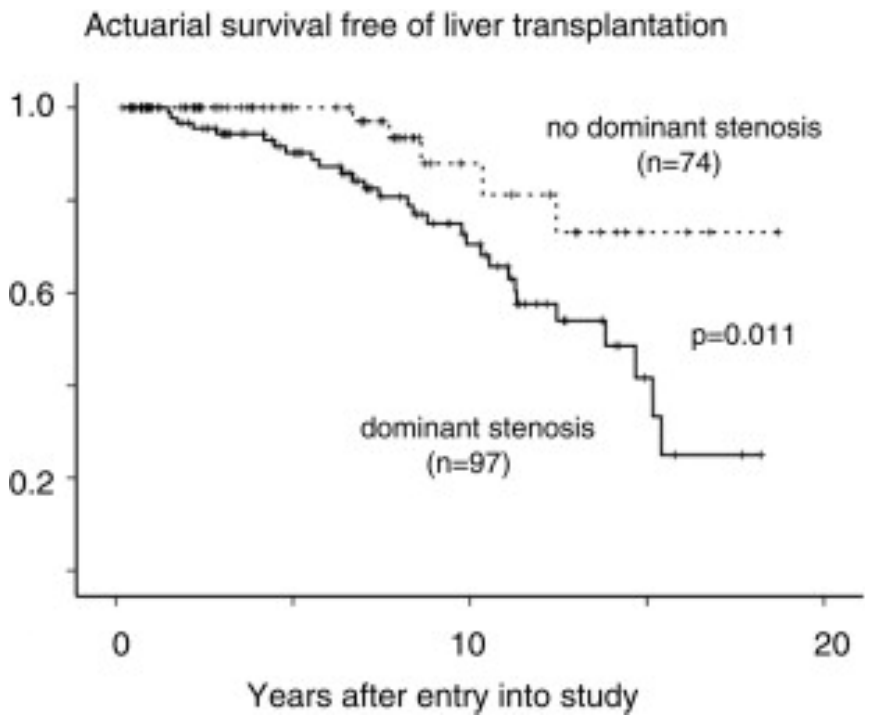
- Small duct PSC
- Overlap with AIH
- Early PSC changes on MR imaging with normal ALP (‘Norway experience‘)

Too ‘severe‘ / late disease

- Dominant strictures requiring endoscopic treatment
- Recurrent cholangitis
- Decompensated cirrhosis
- (Active IBD)

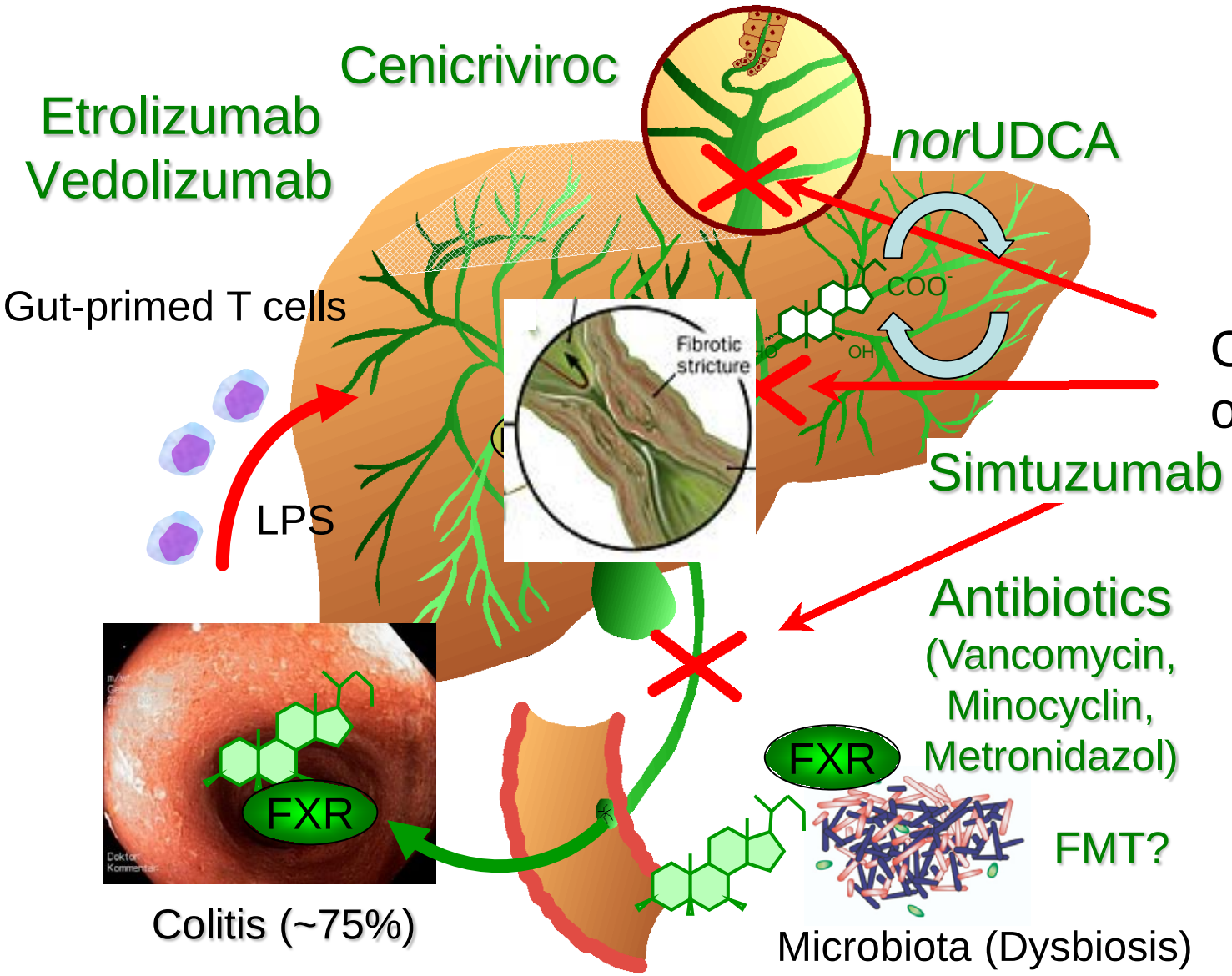
Advanced Fibrosis – Dominant Bile Duct Stenosis Dilemma in PSC?

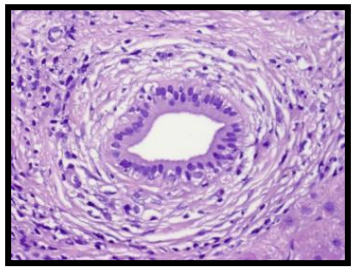




Stiehl et. al., *J Hepatol* 2002; 36: 151
Rudolph et al., *J Hepatol* 2009;51:149
Gotthardt et al., *GI Endosc* 2010; 71: 527

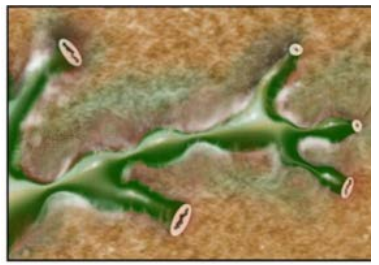
Novel Therapeutic Strategies in PSC
Currently Tested in Clinical Trials – Which Level of Action?





Small Duct PSC

Obliterative fibrosis of bile ducts



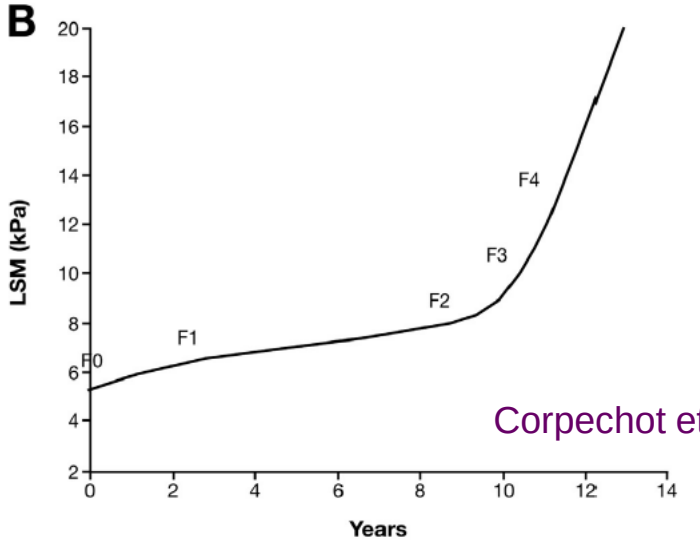
Large Duct PSC

www.mayoclinic.org

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

Further Patient Selection / Risk PSC

- NASH as role model?
  - Caveat: NASH = epidemic (restricting treatment
- Fibrosis stage – progression, reversal
  - NIT (e.g. ELF), VCTE, histology

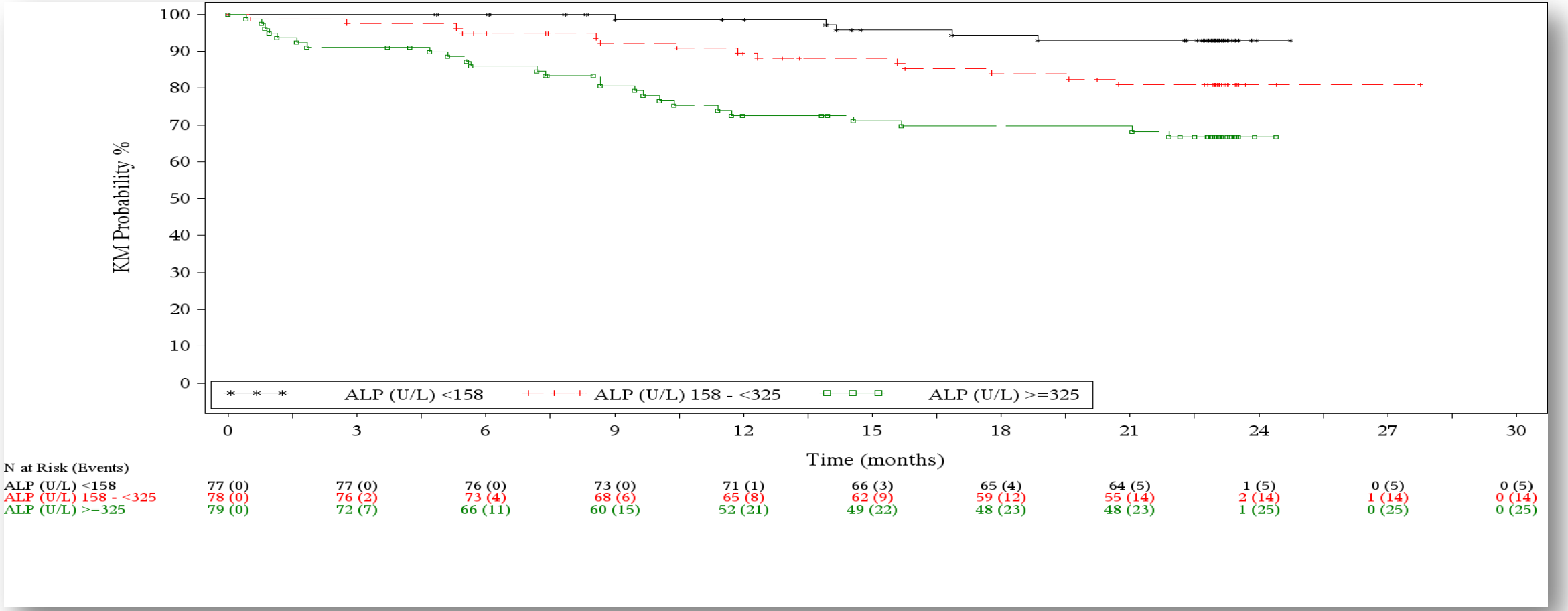


Corpechot et al., *Gastro* 2014

- Compensated cirrhosis – F4 reversal, clinical decomp., (HVPG?)
  - Composite endpoint including the manifestation (histological dg.) of cirrhosis, MELD score above 14, decompensation events (such as encephalopathy, variceal bleeding, ascites, SBP), as well as liver transplantation and death
  - Bile duct related endpoints: cholangitis, need for interventions (subjective!)
  - Malignancy: CCC, HCC, CRC
- ALP baseline levels (naïve vs. UDCA)
- Symptom severity

EMA Reflection Paper (draft)

Survival Free of PSC-Related Events According to Tertiles of Serum ALP at Baseline



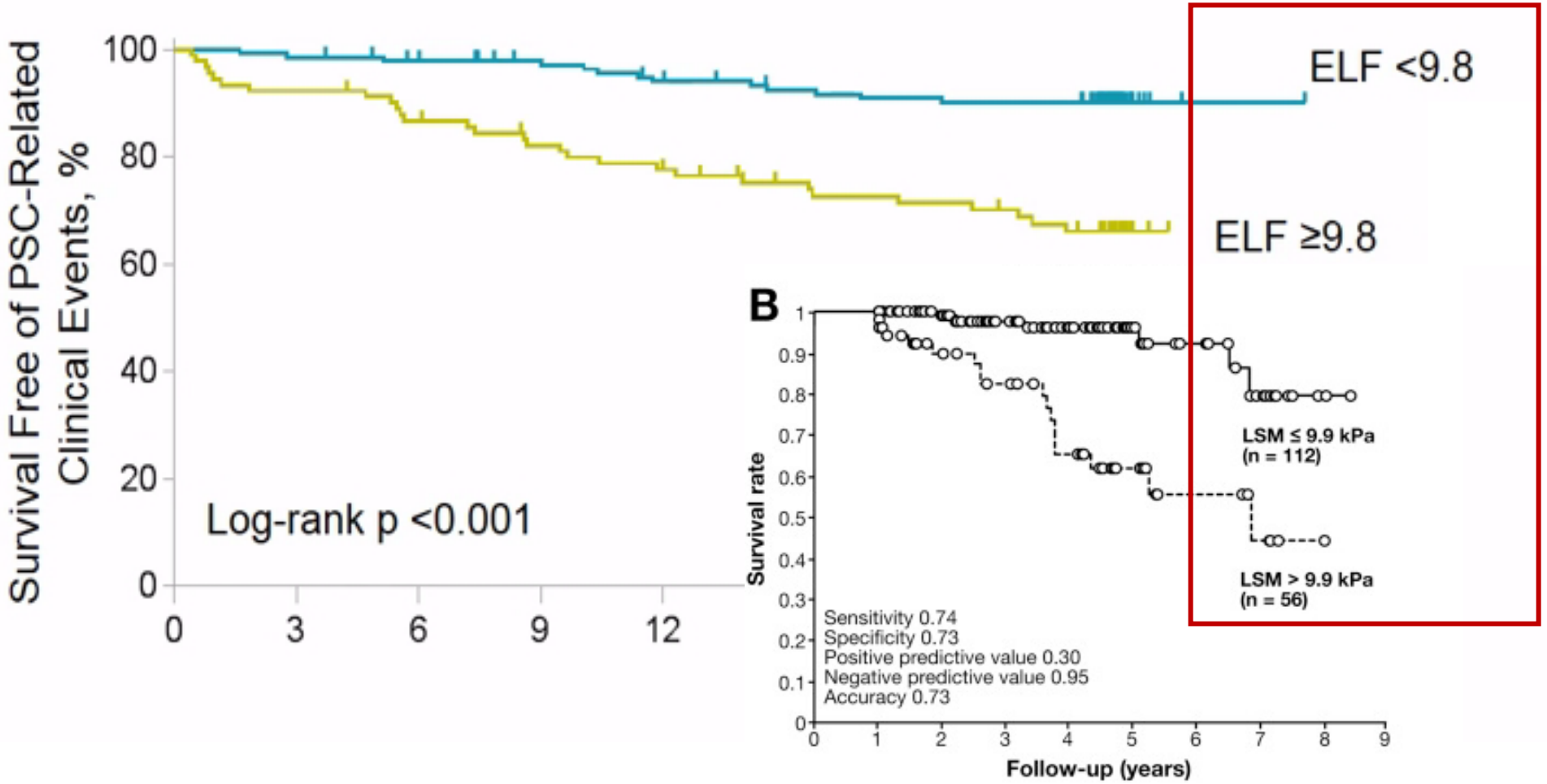
N at Risk (Events)

ALP (U/L) <158	77 (0)	77 (0)	76 (0)	73 (0)	71 (1)	66 (3)	65 (4)	64 (5)	1 (5)	0 (5)	0 (5)
ALP (U/L) 158 - <325	78 (0)	76 (2)	73 (4)	68 (6)	65 (8)	62 (9)	59 (12)	55 (14)	2 (14)	1 (14)	0 (14)
ALP (U/L) >=325	79 (0)	72 (7)	66 (11)	60 (15)	52 (21)	49 (22)	48 (23)	48 (23)	1 (25)	0 (25)	0 (25)

Slide courtesy Cynthia Levy

Levy C et al. ILC 2017 # FRI-386

Survival Free of PSC-Related Events According to ELF and LSM at Baseline



Bowlus C et al. ILC 2017

Corpechot et al., *Gastro* 2014; 146: 970-9

		PLACEBO (N=40)	NU 500mg (N=39)	NU 1000mg (N=41)	NU 1500mg (N=39)
ALP at baseline (U/L)	Mean (SD)	456 (234.4)	495 (282.4)	369 (200.6)	464 (241.6)

Fickert et al., *J Hepatol* 2017

Spontaneous enrichement?

	Placebo n = 25	OCA 1.5-3 mg n = 25	OCA 5-10 mg n = 26
Current UDCA use, n (%)	12 (48)	12 (48)	12 (46)
ALP, U/L	562.8 (300.2)	422.5 (123.1)	428.5 (178.2)

Kowdley et al., AASLD 2017

	SIM 125 mg n=77	SIM 75 mg n=79	Placebo n=78
UDCA therapy, n (%)	50 (65)	42 (53)	52 (67)
ALP, U/L	271 (151, 474)	273 (134, 392)	237 (119, 336)
Ishak F3–F6, n (%)	44 (57)	40 (51)	35 (45)

Muir et al., *Hepatology* 2018

	GS-9674 100 mg n=22	GS-9674 30 mg n=20	Placebo n=10
UDCA therapy	10 (46)	9 (45)	5 (50)
ALP, U/L	350 (312, 387)	344 (271, 460)	380 (265, 547)
ELF	9.26 (8.73, 9.66)	9.77 (9.26, 10.31)	9.09 (8.87, 9.60)
Liver stiffness, kPa	7.3 (6.2, 10.6)	10.1 (6.9, 12.5)	9.8 (7.9, 10.1)

Trauner et al., AASLD 2018

	Placebo (n=20)	NGM282 1.0 mg (n=21)	NGM282 3.0 mg (n=21)
ALP, U/L	356 (138)	383 (181)	354 (194)
ELF score	10.1 (1.4)	10.4 (1.2)	9.7 (1.2)

Hirschfield et al., *J Hepatol* 2018

Lessons from Simtuzumab Trial - The Natural History of PSC?

2yr Outcome	Total (N=234)
Worsening of fibrosis (Ishak)	**37%**
No change	34%
≥ 1 stage improvement	29%
≥ 2 stage improvement	9%
PSC related clinical events	**20%**
- ascending cholangitis	13%
- ascites	3%
- cholangio carcinoma	1%
New onset of UC	0.4%

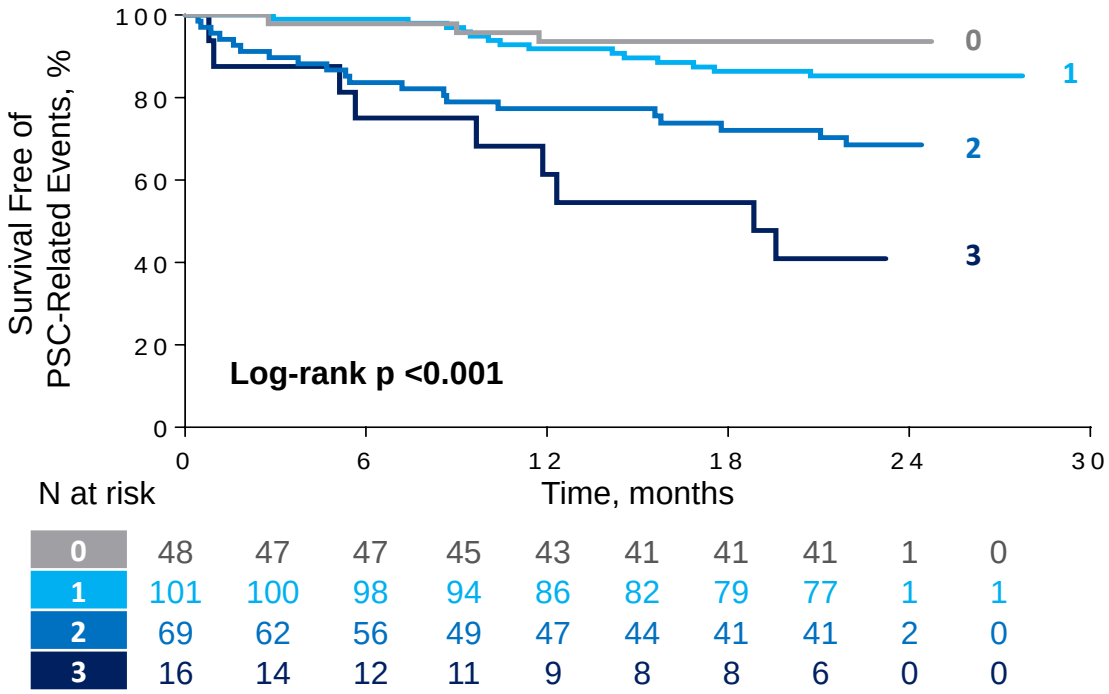
Risk factors for events:

- Advanced fibrosis
- High ALP
- High ELF

Muir et al., *Hepatology* 2018 ePub

Prognostic Utility of the MRCP-RS

PSC-Related Events



MRCP-RS	PSC-Related Events (n=47)	HR (95% CI)
0	**6%** (3/48)	Ref
1	**14%** (14/101)	2.28 (0.65, 7.92)
2	**30%** (21/69)	6.05 (1.80, 20.30)
3	**56%** (9/16)	12.46 (3.37, 46.10)

- c-statistic of MRCP-RS for PSC-related clinical events, 0.71 (95% CI 0.63, 0.79)
- MRCP-RS associated with clinical events (HR 2.09; 95% CI 1.44, 3.04) after adjustment for serum ALP (HR 1.001; 95% CI 1.000, 1.002; p=0.006) and ELF (HR 1.14; 95% CI 0.90, 1.45; p=0.28)

Slide courtesy Cynthia Levy

Muir AJ, et al. AASLD 2017 (Presidential Plenary Presentation #140).

Prognostic Models

Mayo Clinic Model	King's College Model	Multicenter Model	Revised Mayo Model	Amsterdam-Oxford Model	PREsTo
		Predictors of Survival			
Age	Age	Age	Age	Age	Age
Bilirubin	Hepatomegaly	Bilirubin	Bilirubin	Bilirubin	Bilirubin
Histologic stage	Histologic stage	Histologic stage	Albumin	Albumin	Albumin
Hgb	Splenomegaly	Splenomegaly	AST	AST	AST
IBD	Alkaline phosphatase		Variceal bleeding	Alkaline phosphatase	Alkaline phosphatase
				Platelets	Platelets
				PSC subtype	Duration of PSC
					Sodium
					Hemoglobin

Slide courtesy Cynthia Levy

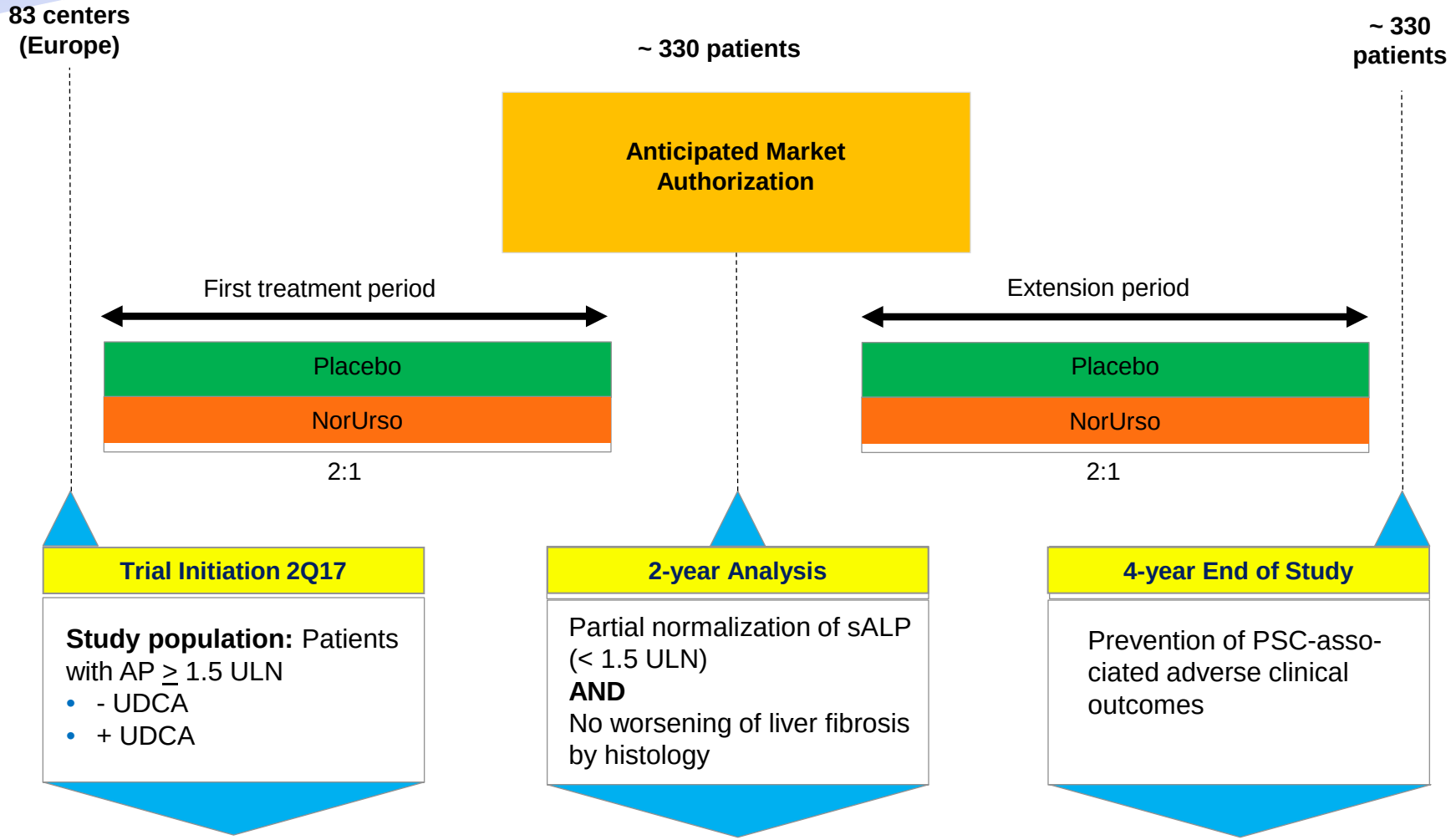
NorUrso: Clinical Studies in PSC

Phase III (NUC-5): Study Outline

Design:	**Randomized (2:1), double-blind, placebo-controlled, multicentre**
Sample size:	**N=330**
Dose groups:	**a) NU 1500mg OD** **b) Placebo** ***Stratification by concomitant treatment with UDCA***
Duration:	**2 yrs + 2 yrs extension**
Subjects:	**PSC, with AP ≥ 1.5 ULN without or on UDCA**
Primary endpoint:	**% patients with partial normalization of sALP (< 1.5 ULN) AND no worsening of staging (Nakanuma) by histology at 2 yrs**
Secondary endpoints:	**• % patients with no worsening of liver fibrosis by elastography at 2 yrs** **• % patients with partial normalization of AP** **• Course of ELF-test** **• At 4 yrs: % patients with adverse clinical outcome**
Safety:	**AE, laboratory parameters**

NorUrso: Clinical Studies in PSC

NUC-5: Flow Chart



Efficacy Endpoints (NUC-5)

- **Primary efficacy endpoint**
  - Partial normalization of ALP to < 1.5x ULN

    and **Co-primary endpoint**
  - No worsening of disease stage as determined by the overall Nakanuma stage at the week 96 visit compared to baseline
- **Secondary efficacy endpoints**
  - Changes in liver stiffness, fibrosis stage (Ludwig & Ishak) & morphometry, histological grading (Ishak)
  - Various lab based endpoints (including ELF, IL-8), MRI
  - Clinical events (incl. DS), Hannover score, pruritus, fatigue, QoL

Evaluation of a new histologic staging and grading system for primary biliary cirrhosis in comparison with classical systems

Table 1 Scoring for the staging of PBC

Score	Criterion
A. Fibrosis	
0	No portal fibrosis or fibrosis limited to portal tracts
1	Portal fibrosis with periportal fibrosis or incomplete septal fibrosis
2	Bridging fibrosis with variable lobular disarray
3	Liver cirrhosis with regenerative nodules and extensive fibrosis
B. Bile duct loss	
0	No bile duct loss
1	Bile duct loss in less than one-third of portal tracts
2	Bile duct loss in one-third to two-thirds of portal tracts
3	Bile duct loss in more than two-thirds of portal tracts
C. Deposition of orcein-positive granules[a]	
0	No deposition of granules
1	Deposition of granules in a couple of zone 1 hepatocytes at less than one-third of portal tracts
2	Deposition of granules in a variable number of zone 1 hepatocytes at one-third to two-thirds of portal tracts
3	Deposition of granules in most zone 1 hepatocytes at more than two-thirds of portal tracts

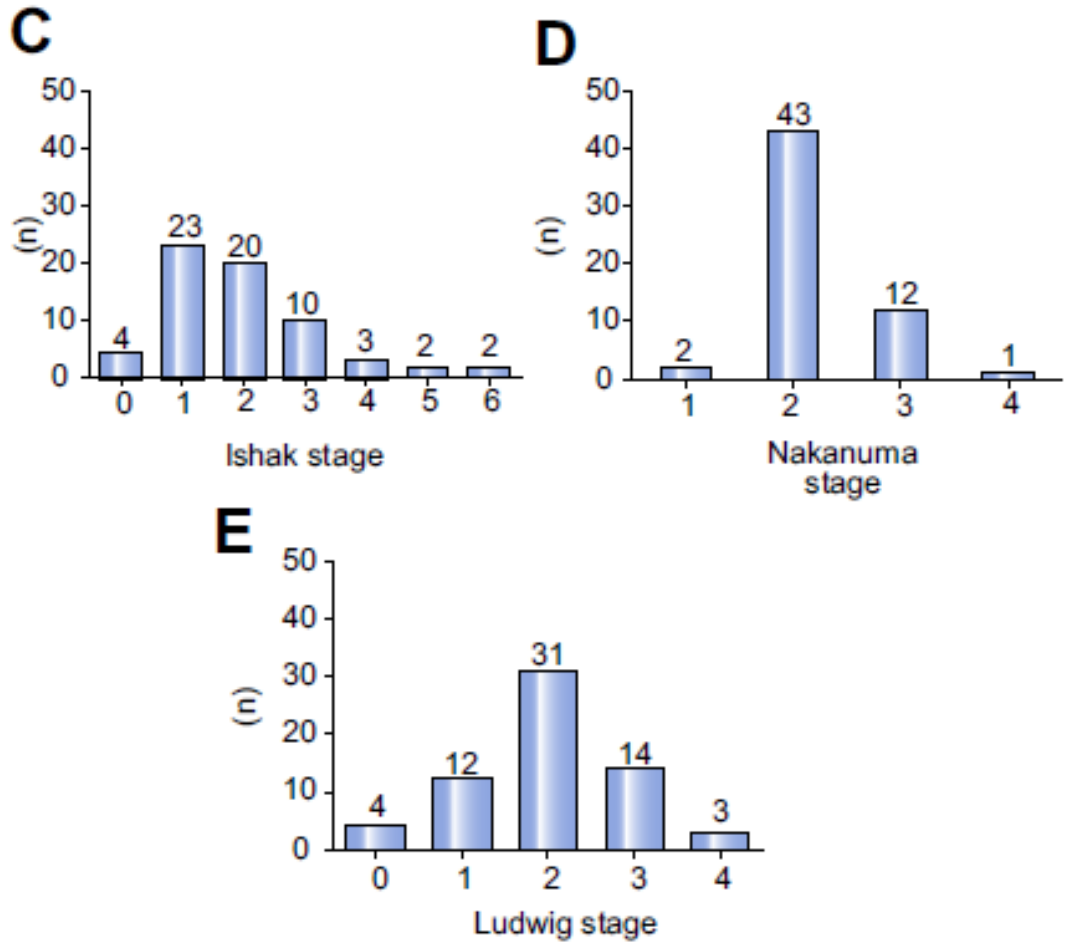
Human Pathology (2013) **44**, 1107–1117

Applicability and prognostic value of histologic scoring systems in primary sclerosing cholangitis

Elisabeth M.G. de Vries[1], Joanne Verheij[2], Stefan G. Hubscher[3], Mariska M.G. Leeflang[4], Kirsten Boonstra[1], Ulrich Beuers[1], Cyriel Y. Ponsioen[1,*]

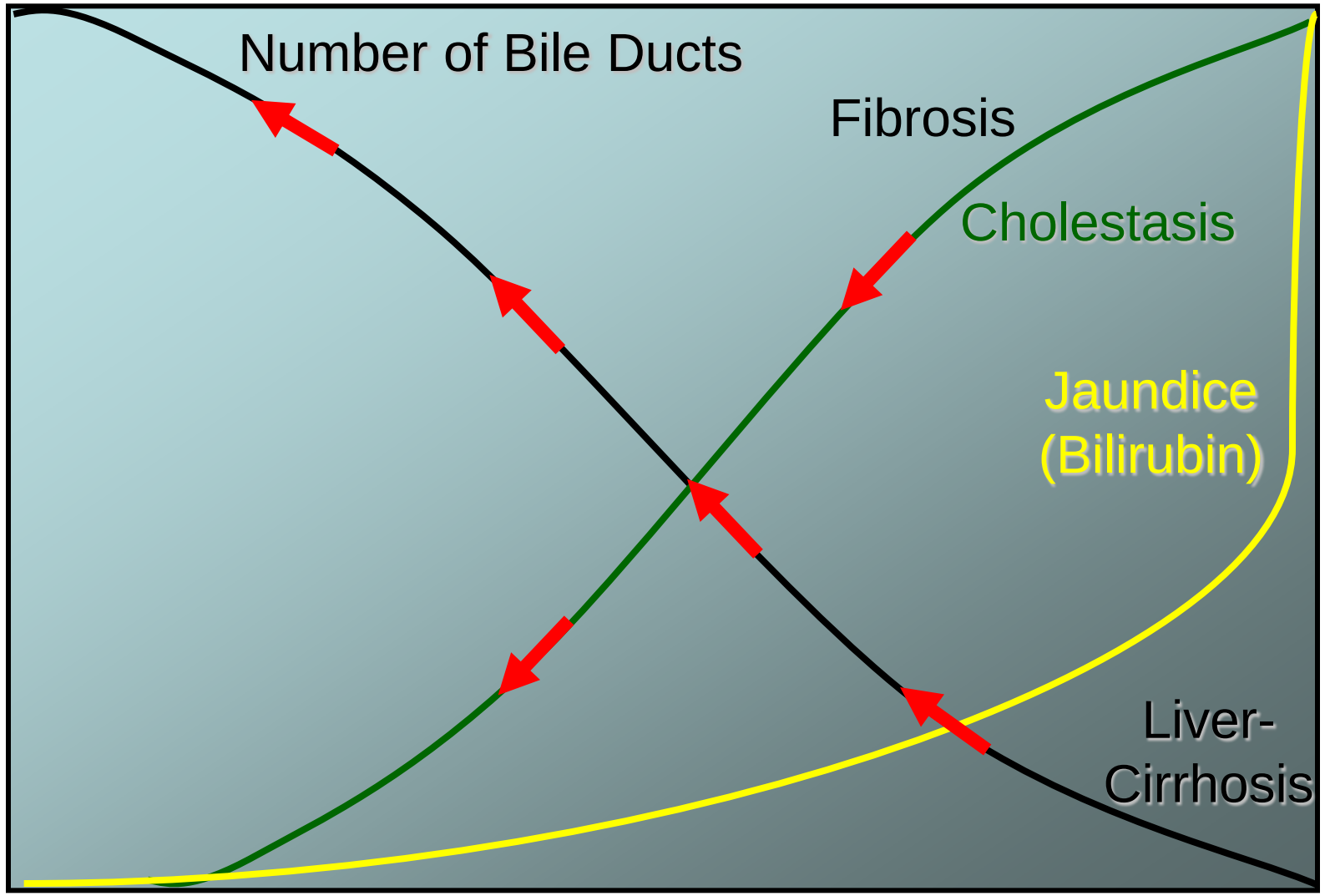
Table 1. Patient characteristics.

N	64
Male [n (%)]	40 (63)
Age follow-up (years) [mean (SD)]	49 (±15)
Age at diagnosis PSC (years) [mean (SD)]	38 (±14)
Large duct PSC [n (%)]	54 (84)
Inflammatory bowel disease [n (%)]	43 (67)
Ulcerative colitis [n (%)]	32 (50)
Crohn's disease [n (%)]	8 (12)
Unspecified [n (%)]	3 (5)
Portal tracts [median (IQR)]	13 (9-19)
Biopsy length (mm) [median (IQR)]	14 (11-19)
Disease duration at time of biopsy (months) [median (range)]	0 (0-20)
Follow-up time (months) [median (IQR)]	112 (70-172)
AST xULN [median (IQR)]*	1.40 (1.04-2.64)
ALT xULN [median (IQR)]*	2.04 (1.40-4.43)
ALP xULN [median (IQR)]*	1.65 (1.24-3.39)
γGT xULN [median (IQR)]*	5.80 (3.02-11.10)
Total bilirubin xULN [median (IQR)]*	0.82 (0.52-1.21)
MRS*	-0.28 (-0.77-0.78)



de Vries et al., *J Hepatol* 2015 (& *Hepatology* 2017)

Holy Grail of Disease Regression?



Duration (Years – Decades)

Future Perspectives for Clinical Trial Design in PSC

- Combination therapy
  - Again NASH as role model?
- More emphasis on PRO
  - SF 36
  - Fatigue Scores; autonomic dysfunction
  - New PSC PRO [1]
    - High correlations with relevant domains of other scores: PBC-40, SF-36
  - Could be part of combined endpoints
  - Role model systemic sclerosis (e.g. CRISS) [2]
- Focus on (functional) imaging
  - Non-invasive
  - Heterogenity with the liver

1: Younossi et al., *Hepatology* 2018; 68:155-165
2: Khanna et al., *Arthritis Rheumatol* 2016; 68: 299-311

Nerve growth factor antibody cuts OA pain with low AEs

CONFERENCE COVERAGE

CRISS hailed as transforming systemic sclerosis drug development

Publish date: July 10, 2018

By Mitchel L. Zoler; Rheumatology News

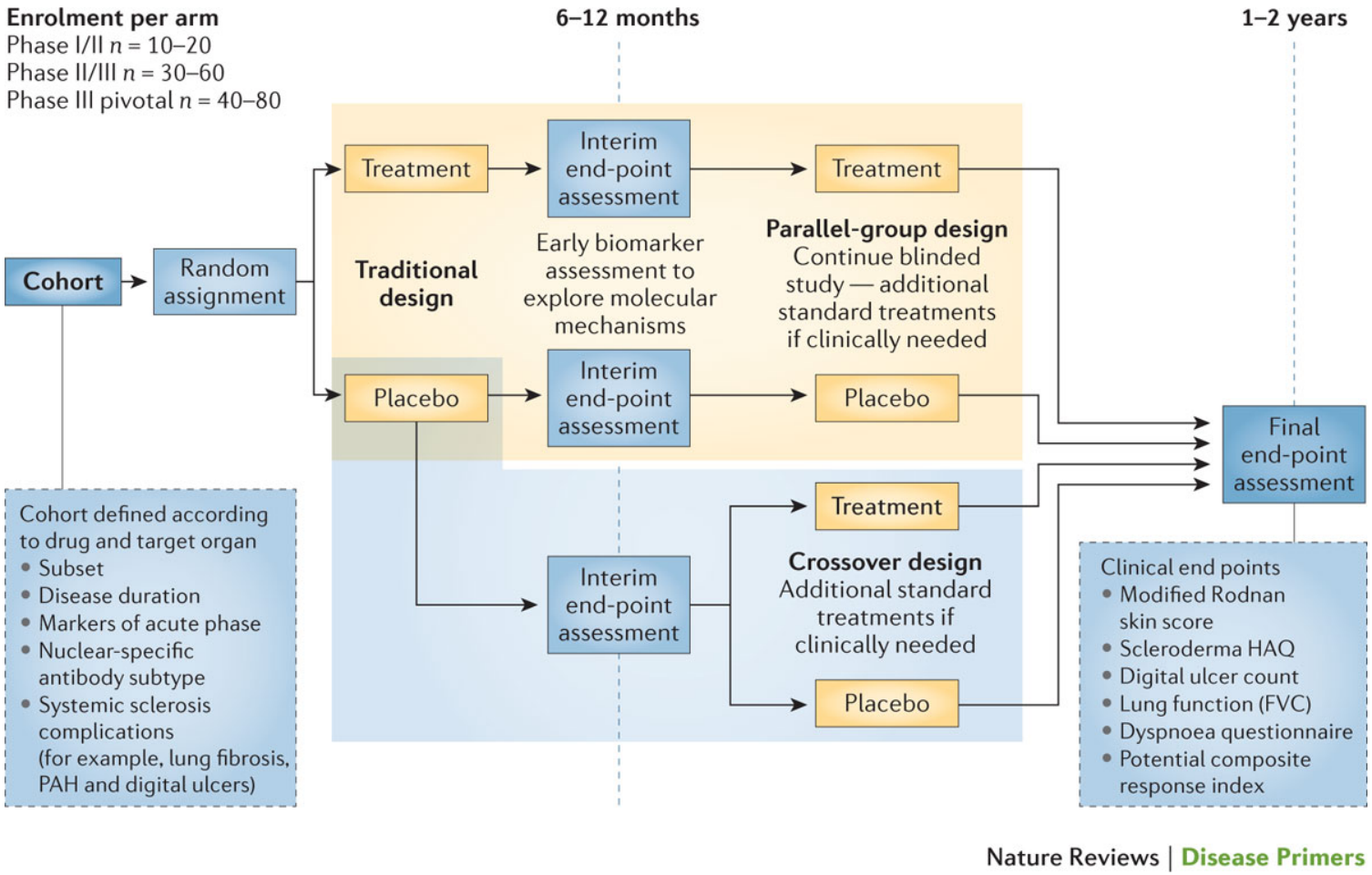
REPORTING FROM THE EULAR 2018 CONGRESS

Table 2. Predictive characteristics of the final CRISS model consisting of the 5 core items with the highest face validity*

Overall area under the curve	0.9861
Overall sensitivity (95% CI)	0.9821 (0.9816–0.9827)
Overall specificity (95% CI)	0.9310 (0.9300–0.9321)
Unadjusted beta coefficient (by core item)	
MRSS	−0.81
FVC % predicted	0.21
HAQ DI	−0.40
Patient global assessment	−0.44
Physician global assessment	−3.41
Standard error (by core item)	
MRSS	0.21
FVC % predicted	0.08
HAQ DI	0.24
Patient global assessment	0.26
Physician global assessment	1.75

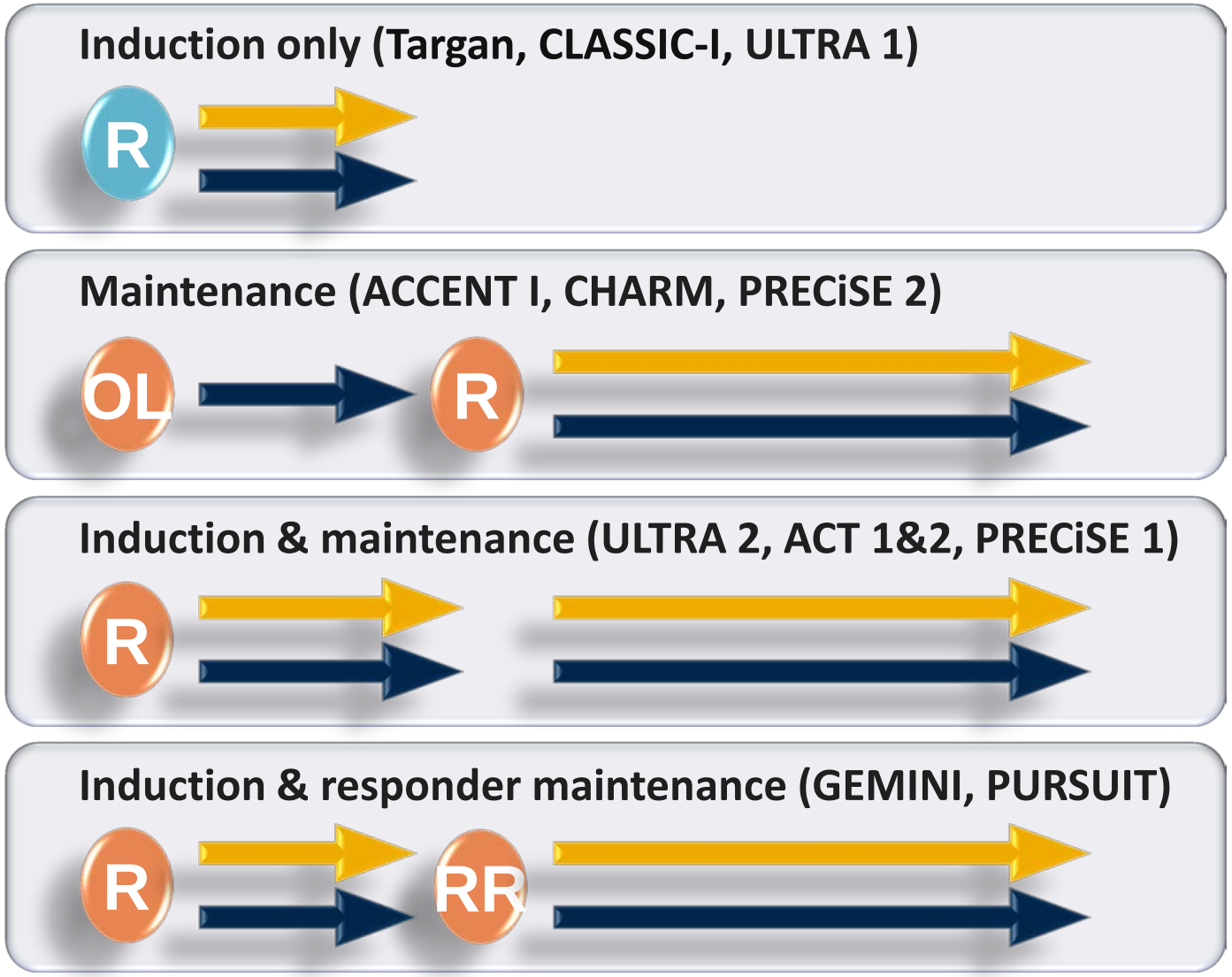
* CRISS = composite response index in diffuse cutaneous systemic sclerosis; 95% CI = 95% confidence interval; MRSS = modified Rodnan skin thickness score; FVC = forced vital capacity; HAQ DI = Health Assessment Questionnaire disability index.

Figure 6 Future of clinical trial design in systemic sclerosis

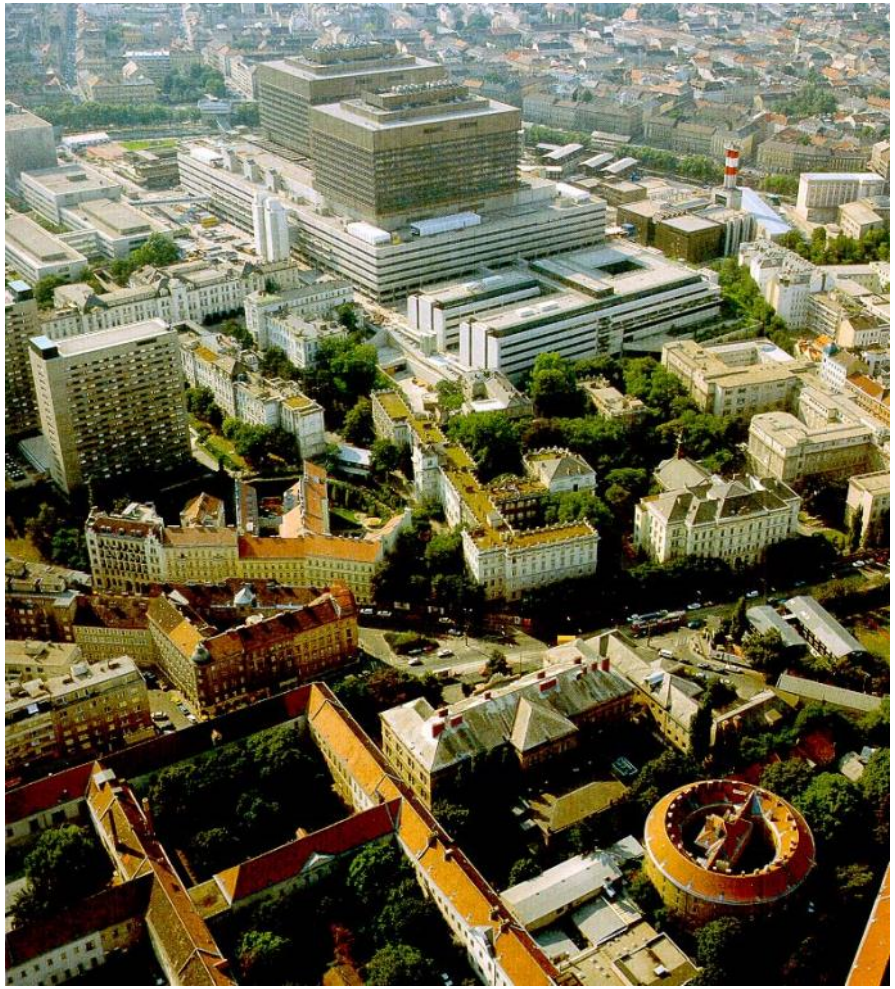


Varga, J. *et al.* (2015) Systemic sclerosis
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2015.2

Trial Designs in IBD



Slide courtesy Walter Reinisch, Vienna



Thank you for your attention!

michael.trauner@meduniwien.ac.at

MEDICAL UNIVERSITY OF VIENNA

Division of
Gastroenterology and Hepatology
Department of Internal Medicine III