UCDAVIS SCHOOL OF MEDICINE

CHOLESTATIC LIVER DISEASE

Northern California Society for Clinical Gastroenterology (NCSCG)
3rd Annual Post-AASLD Symposium
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Outline

PBC

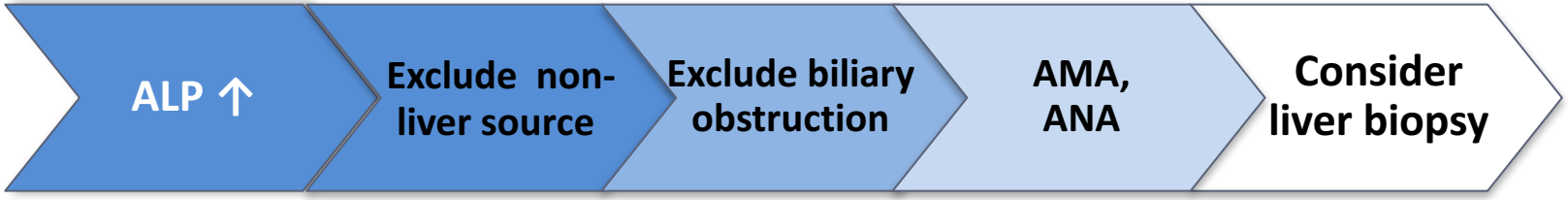
- Diagnosis
- Risk Stratification
- Second Line Treatments
  - OCA
  - Fenofibrate

PSC

- Natural History
- Prognosis
- Treatment

PBC

PBC Diagnostic process



Diagnostic criteria: must have 2 of 3[2]

- ❑ ALP >1.5 times ULN for >24 weeks
- ❑ Serum AMA >1:40 (or PBC specific ANA, i.e. GP210 or SP100)
- ❑ Liver biopsy showing nonsuppurative cholangitis and bile duct injury

Abbreviations: ALP, alkaline phosphatase; AMA, antimitochondrial antibodies; ANA, antinuclear antibodies; PBC, primary biliary cholangitis; ULN, upper limit of normal.

1. Lindor KD, et al. *Hepatology*. 2009;50:291-308. 2. Selmi C, et al. *Lancet*. 2011;377:1600-1609.

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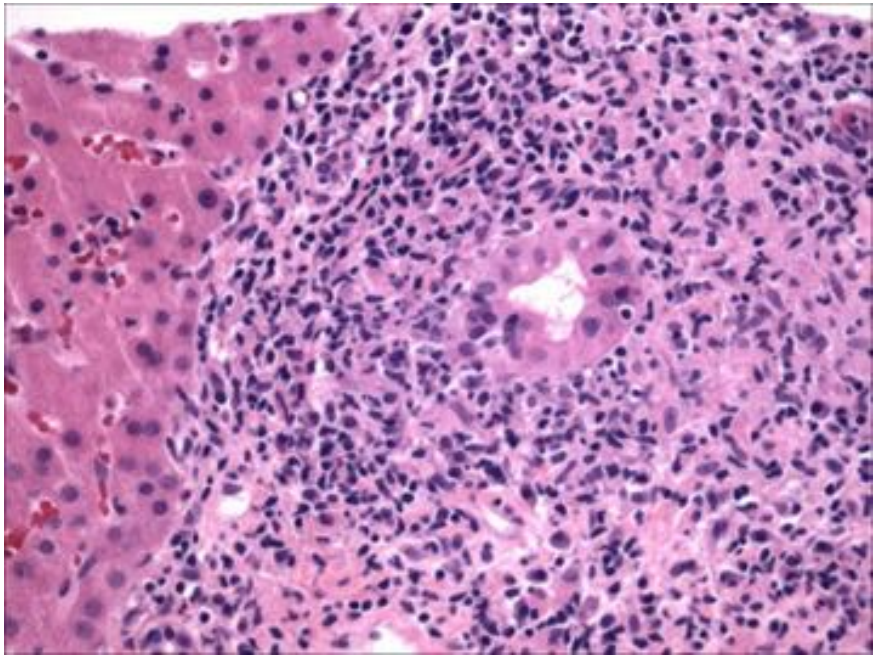
PBC Diagnosis on Biopsy

- Florid duct lesion
  - Inflammation
  - injury to bile duct epithelial cells
  - Disruption of the bile duct basement membrane
- Other features
  - Granulomas
  - Ductopenia
  - Ductular proliferation

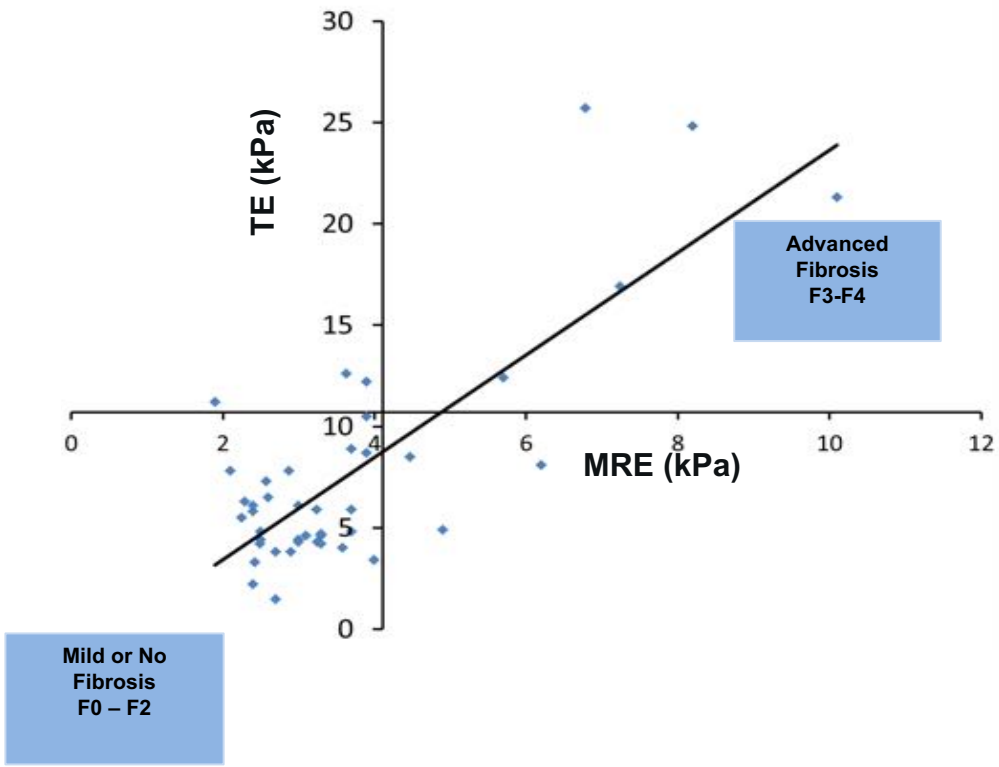


PBC Variant Syndromes

- AMA-negative PBC
  - 50% will have ANA[a]
  - PBC-specific ANA: anti-gp210, anti-sp100[b]
  - Same clinical presentation; may have reduced survival[c,d]
- Overlap syndrome with AIH[b]
  - Diagnosis requires 2 of 3
    - 1) ALT > 5 X ULN; 2) IgG > 2 X ULN *or* ASMA; 3) moderate to severe periportal or periseptal inflammation
- Premature ductopenic variant
  - Rapid onset of ductopenia, severe icteric cholestasis, rapid progression towards cirrhosis [b]

a. Bowlus CL, et al *Autoimm Rev.* 2014;13:441-444; b. Poupon R. *J Hepatol*. 2010;52:745-758; c. Fan X, et al. *Sci Rep*. 2017;7:6560; d. Juliusson G, et al. *Scand J Gastroenterol*. 2016;51:745-752.

Non-Invasive Staging in PBC



- Staging (F0-F2 versus F3-F4) was concordant in 86% at baseline (n = 43) and 93% at 1 year (n = 41).
- Liver stiffness by MRE and TE were strongly correlated at baseline (r = 0.70, P < 0.0001) and 1 year (r= 0.92, P < 0.0001).
- Changes in LS from Month 0 to Month 12 (median [range]) were 0.25 kPa [-8.2 – 16.1] for TE and -0.29 kPa [-2.7 – 1.7] for MRE.

Johnson CR, et al. *Hepatology*. 2017;66:204A.

Primary Biliary Cholangitis – Complete UDCA Response

55 year old woman found to have an elevated serum cholesterol on screening. No improvement after changes in diet. A statin is prescribed and liver enzymes are checked.

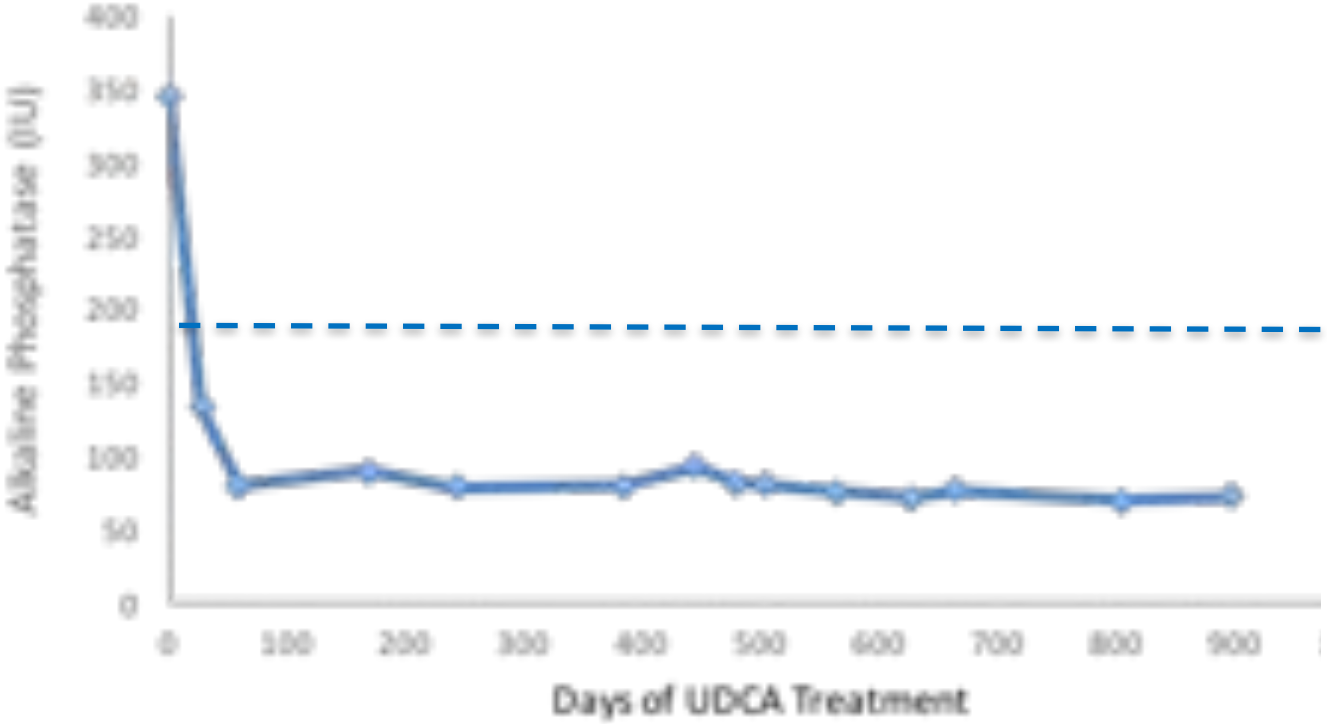
Alkaline phosphatase	346	IU
ALT	60	IU
Total bilirubin	0.8	mg/dL

Abdominal ultrasound is unremarkable

AMA is positive

UDCA started at 15 mg/kg/d

Complete Biochemical Response to UDCA



Primary Biliary Cholangitis – Incomplete UDCA Response

41 year old woman complaining of generalized pruritus, arthralgias, and abdominal pain. History of thyroid disease.

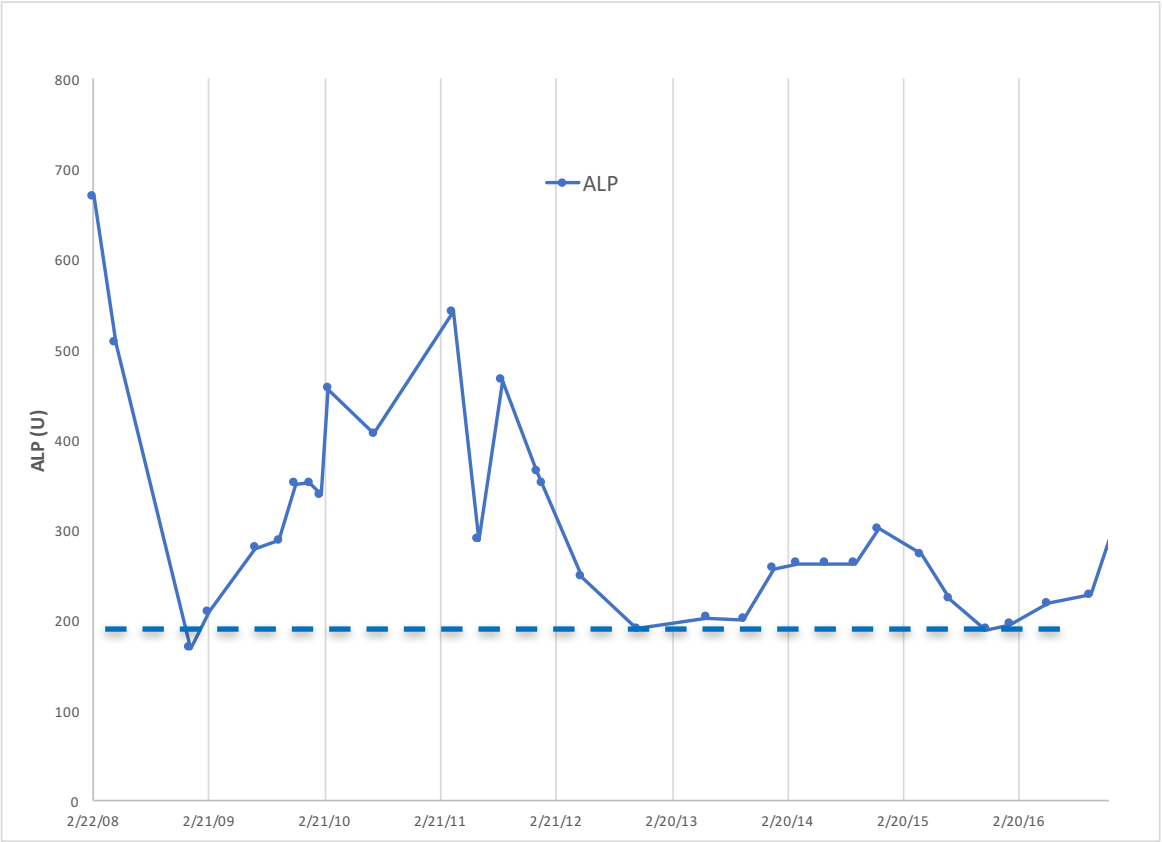
Alkaline phosphatase	670 IU
ALT	77 IU
Total bilirubin	1.2 mg/dL

Abdominal ultrasound is unremarkable

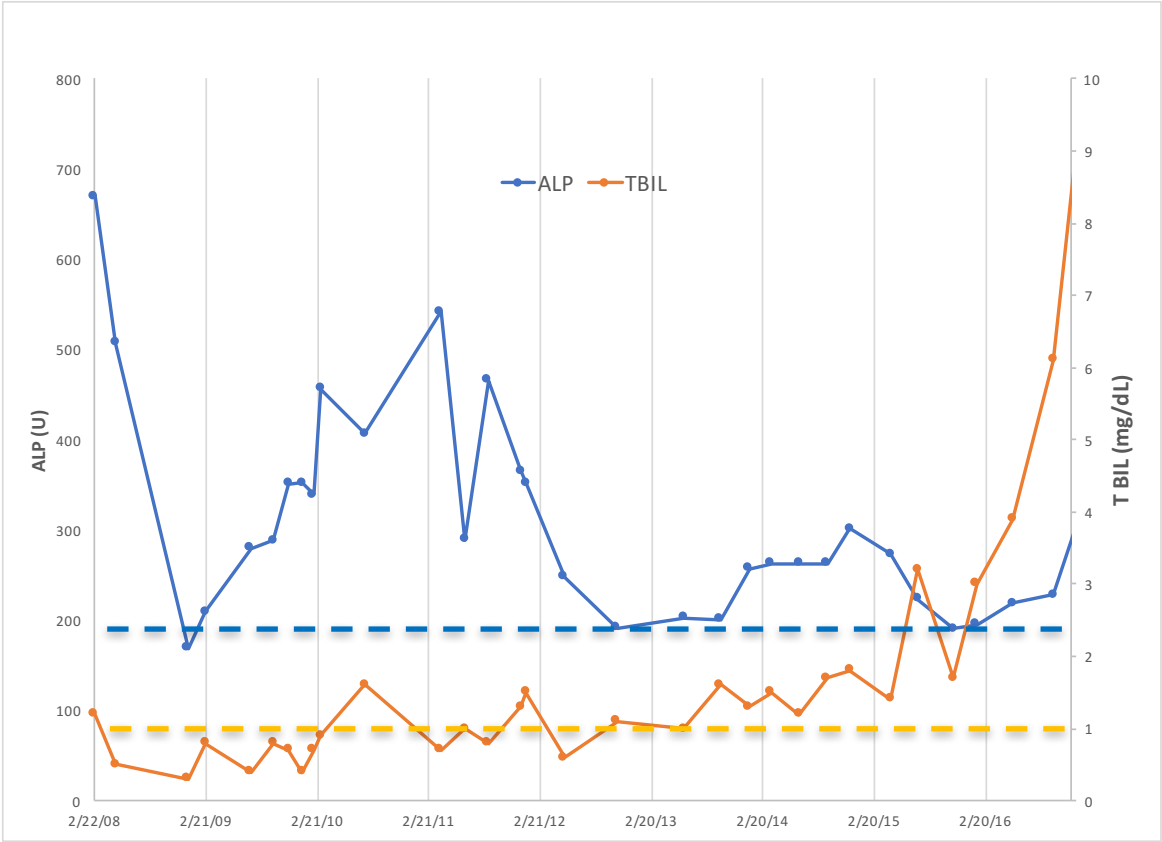
AMA is positive 1:320

UDCA started at 15 mg/kg/d

Incomplete Response to UDCA

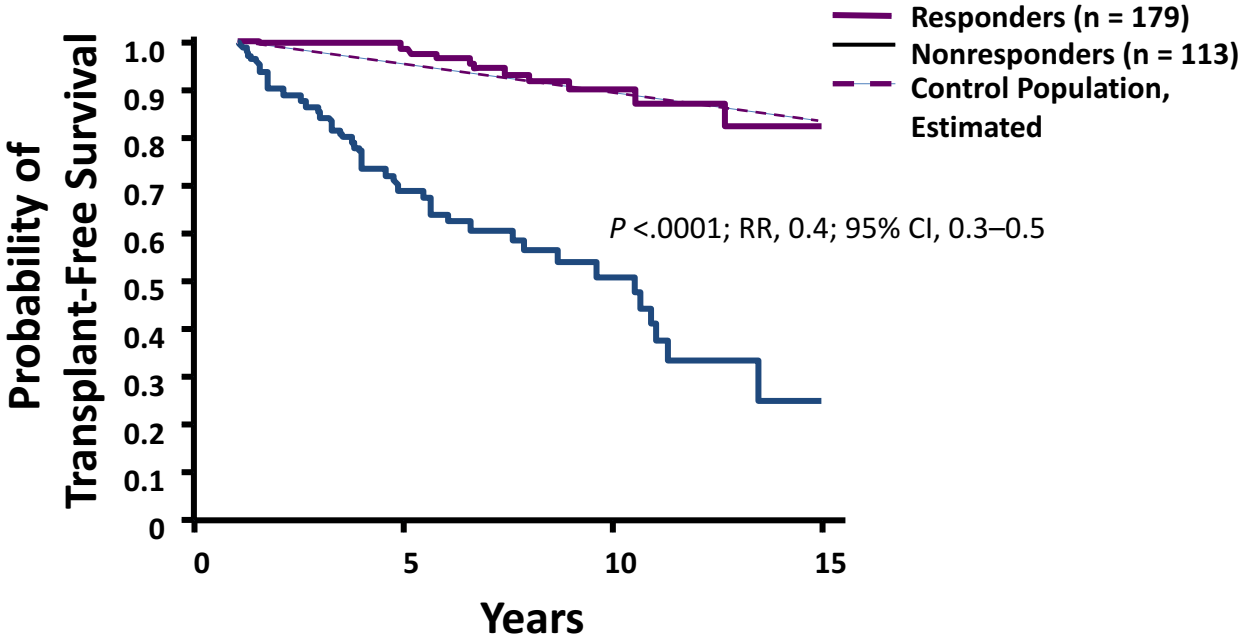


Incomplete Response to UDCA

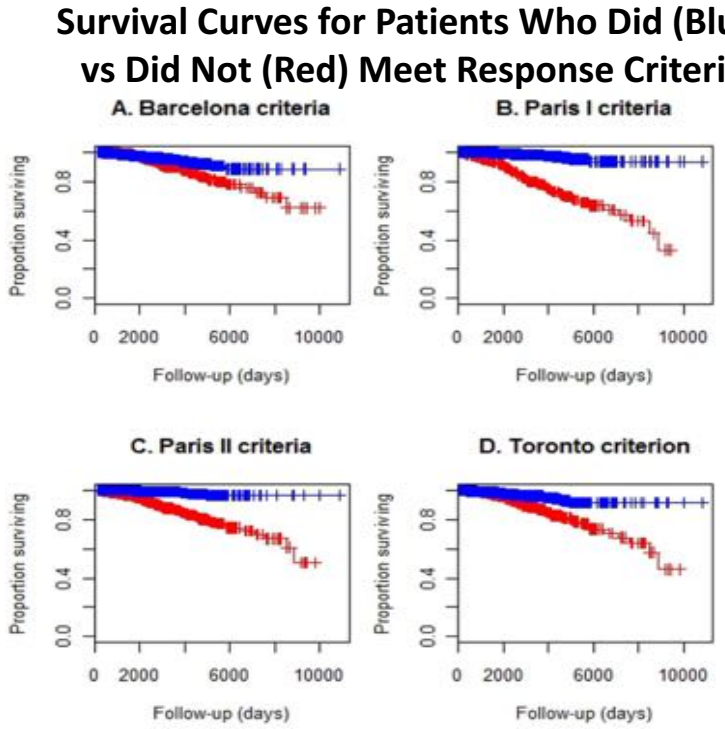


Biochemical Response to UDCA at 1 Year Predicts Survival

Ursodeoxycholic acid 13-15 mg/kg/d



Defining Response to UDCA



Barcelona

- Decrease in ALP level >40% of baseline level or a normal level

Paris I (all criteria met)

- ALP level ≤3 X ULN
- AST level ≤2 X ULN
- Normal bilirubin level

Paris II (all criteria met)

- ALP level ≤1.5 X ULN
- AST level ≤1.5 X ULN
- Normal bilirubin level

Toronto

- ALP level <1.67 X ULN*

*2-stage increase applied as per Kumagi T, et al. *Am J Gastroenterol*. 2010;105:2186-2194. Abbreviations: ALP, alkaline phosphatase; AST, aspartate aminotransferase; ULN, upper limiit of normal; UDCA, ursodeoxycholic acid. Carbone M et al. *Gastroenterology* 2013;144:560-569.

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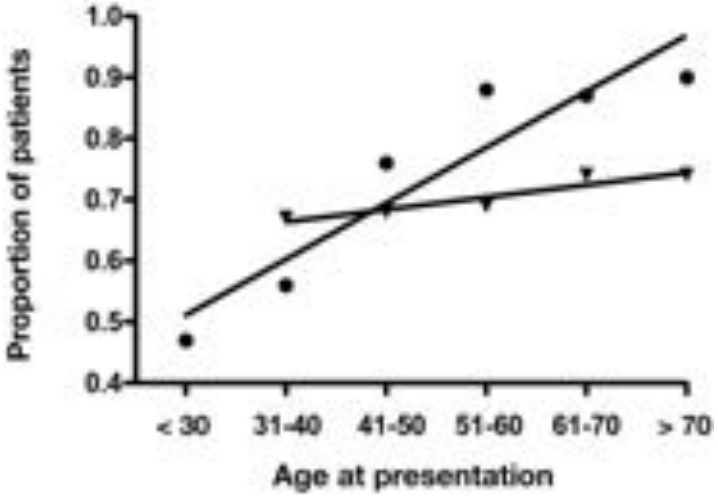
UDCA Response Is Associated with Age at Diagnosis and Sex

Percentage of PBC patients who did not meet Paris I criteria for response to UDCA after ≥2 years treatment



Female n =	19	112	266	366	176	49
Male n =	0	3	25	36	34	7

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal. Carbone M, et al. *Gastroenterology.* 2013;144:560-569.

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GLOBE Score Online Calculation

The GLOBE score for patients with Primary Biliary Cholangitis (PBC)

The GLOBE score is an internationally relevant and validated risk assessment tool, able to accurately stratify PBC patients to high and low risk.

Age, years *at initiation of UDCA therapy*	63		
Total bilirubin level, µmol/L or mg/dl *after one year of UDCA therapy*	0.7	Upper limit of normal:	1.2
Alkaline phosphatase level, U/L *after one year of UDCA therapy*	143	Upper limit of normal:	115
Albumin, g/L *after one year of UDCA therapy*	37	Lower limit of normal:	34
Platelets, x 10^9/L *after one year of UDCA therapy*	210		

Interpretation of the GLOBE score:

GLOBE score: 0.57

Threshold: 1.01

Is the transplant-free survival diminished when comparing with an age- and sex-matched population?

NO

Liver transplant-free survival

	GLOBE score	mean survival of age- and sex-matched patients in age group 58-66 years
3-year	93.9%	98.2%
5-year	89.4%	96.1%
10-year	73.9%	89.0%
15-year	56.2%	78.4%

GlobalPBC.com. Accessed 12/8/2017 at: http://www.globalpbc.com/globe

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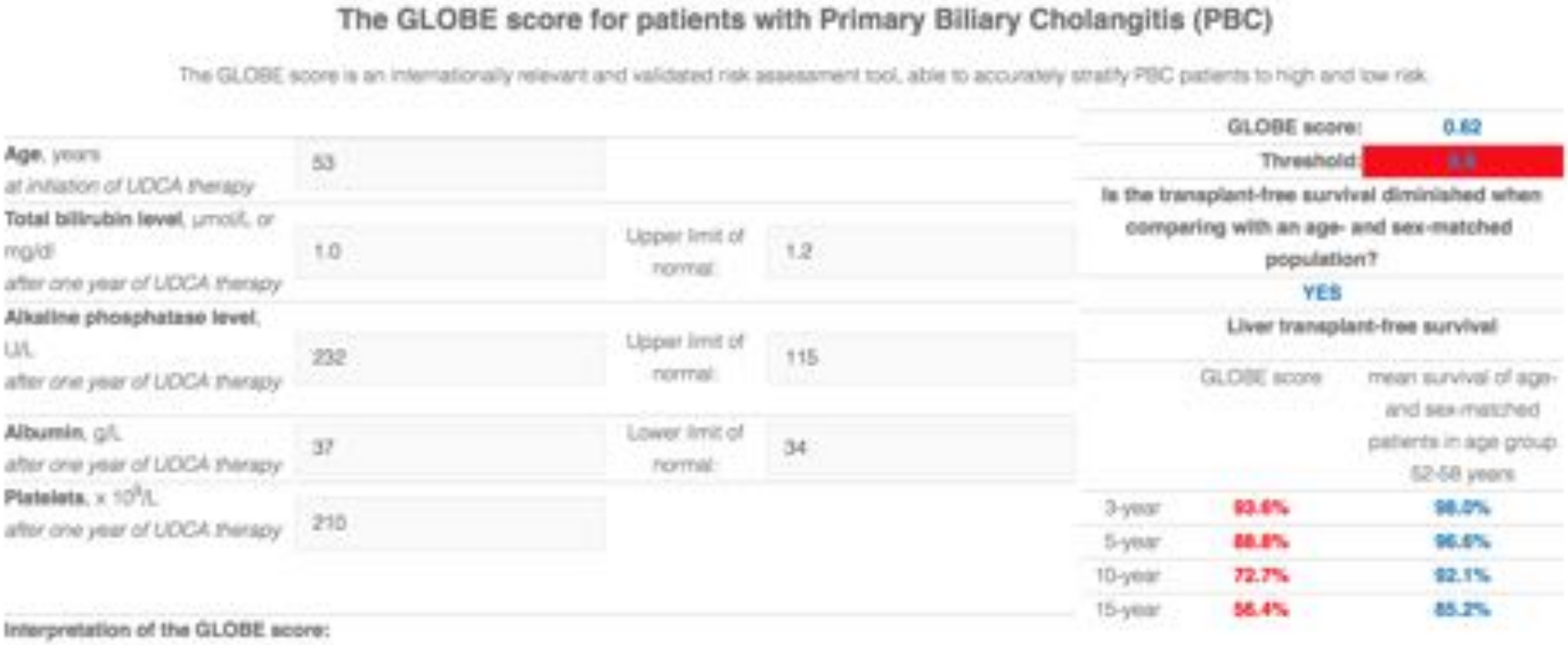
GLOBE Score Online Calculation



The GLOBE score for patients with Primary Biliary Cholangitis (PBC)

The GLOBE score is an internationally relevant and validated risk assessment tool, able to accurately stratify PBC patients to high and low risk.

Age, years *at initiation of UDCA therapy*	53		
Total bilirubin level, umol/L or mg/dl *after one year of UDCA therapy*	1.0	Upper limit of normal	1.2
Alkaline phosphatase level, U/L *after one year of UDCA therapy*	232	Upper limit of normal	115
Albumin, g/L *after one year of UDCA therapy*	37	Lower limit of normal	34
Platelets, x 10^9/L *after one year of UDCA therapy*	210		

Interpretation of the GLOBE score:

GLOBE score: 0.62

Threshold: 0.5

Is the transplant-free survival diminished when comparing with an age- and sex-matched population?

YES

Liver transplant-free survival

	GLOBE score	mean survival of age- and sex-matched patients in age group 52-58 years
3-year	93.6%	98.0%
5-year	88.8%	96.6%
10-year	72.7%	92.1%
15-year	56.4%	85.2%

GlobalPBC.com. Accessed 12/8/2017 at: http://www.globalpbc.com/globe

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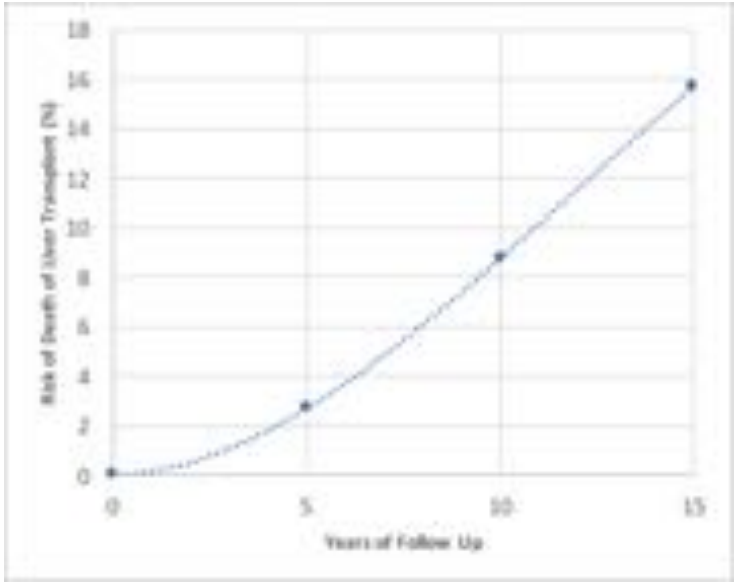
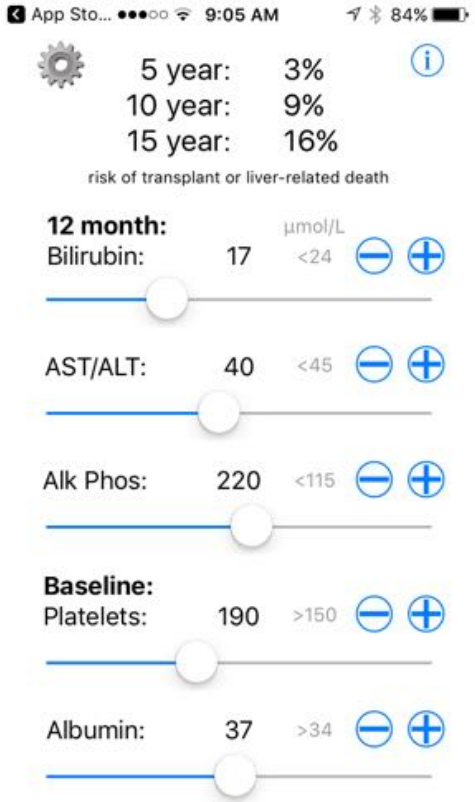
UK-PBC Risk App



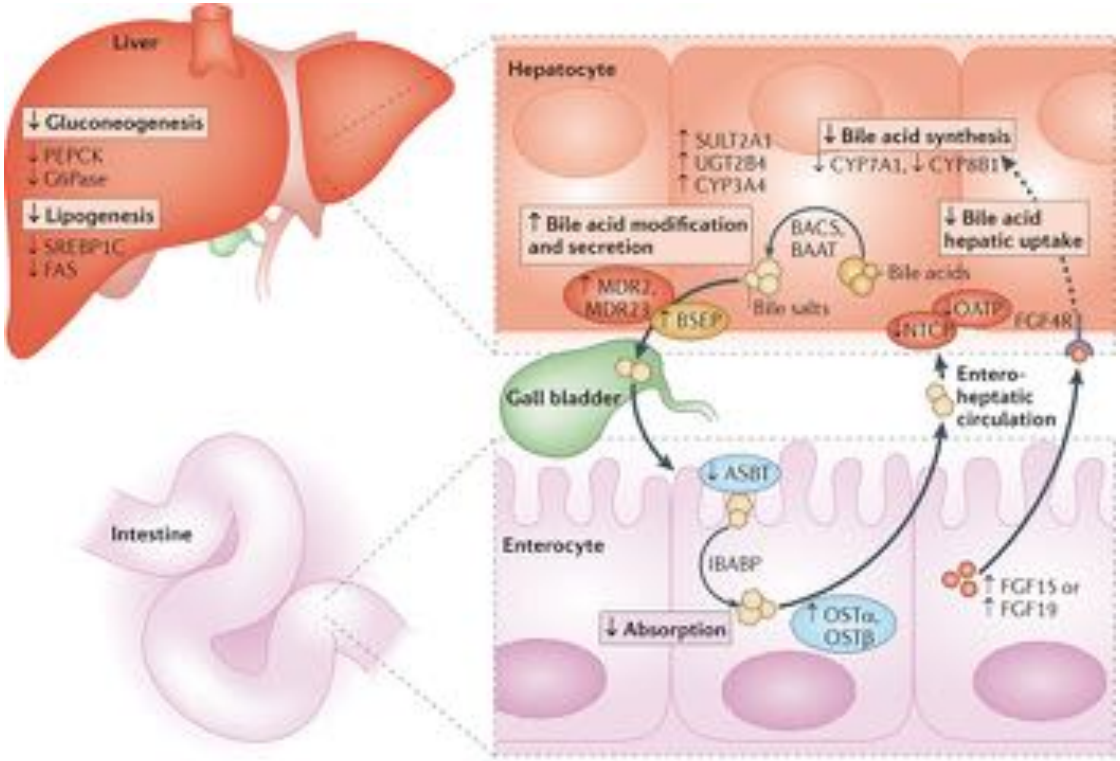


A Brief History of Treatment Trials in PBC

DRUG	COMMENT
	FDA APPROVED THERAPIES
URSODEOXYCHOLIC ACID (URSODIOL)	Decreases liver transplantation; delays progression of liver fibrosis and development of portal hypertension
OBETICHOLIC ACID (OCALIVA)	Decreases alkaline phosphatase in patients with inadequate response or intolerant to UDCA. High rate of itching and increases in cholesterol
	PREVIOUSLY STUDIED THERAPIES
FIBRATES	Some efficacy in small controlled trials. Recent promising results in Phase 2 study. Some safety issues.
COLCHICINE	Efficacy not proven in double-blind trials
METHOTREXATE	Efficacy not proven in double-blind trials
PREDNISONE	Limited, if any, efficacy; worsens osteoporosis
BUDESONIDE	Improves liver histology and results of biochemical tests of liver function when used with UDCA.
CYCLOSPORINE, AZATHIOPRINE, MYCOPHENOLATE	Limited efficacy; many side effects
RITUXIMAB	No efficacy; serious adverse effects

Farnesoid X Receptor (FXR)

- Nuclear Hormone Receptor
- Bile Acid Sensor
  - Natural ligand is chenodeoxycholic acid (CDCA)
- Expressed in ***liver, intestine***, kidney and adrenal glands
- Regulator of genes involved in
  - Bile acid synthesis
  - Glucose, lipid, and cholesterol metabolism
  - Inflammation
  - Tissue Regeneration

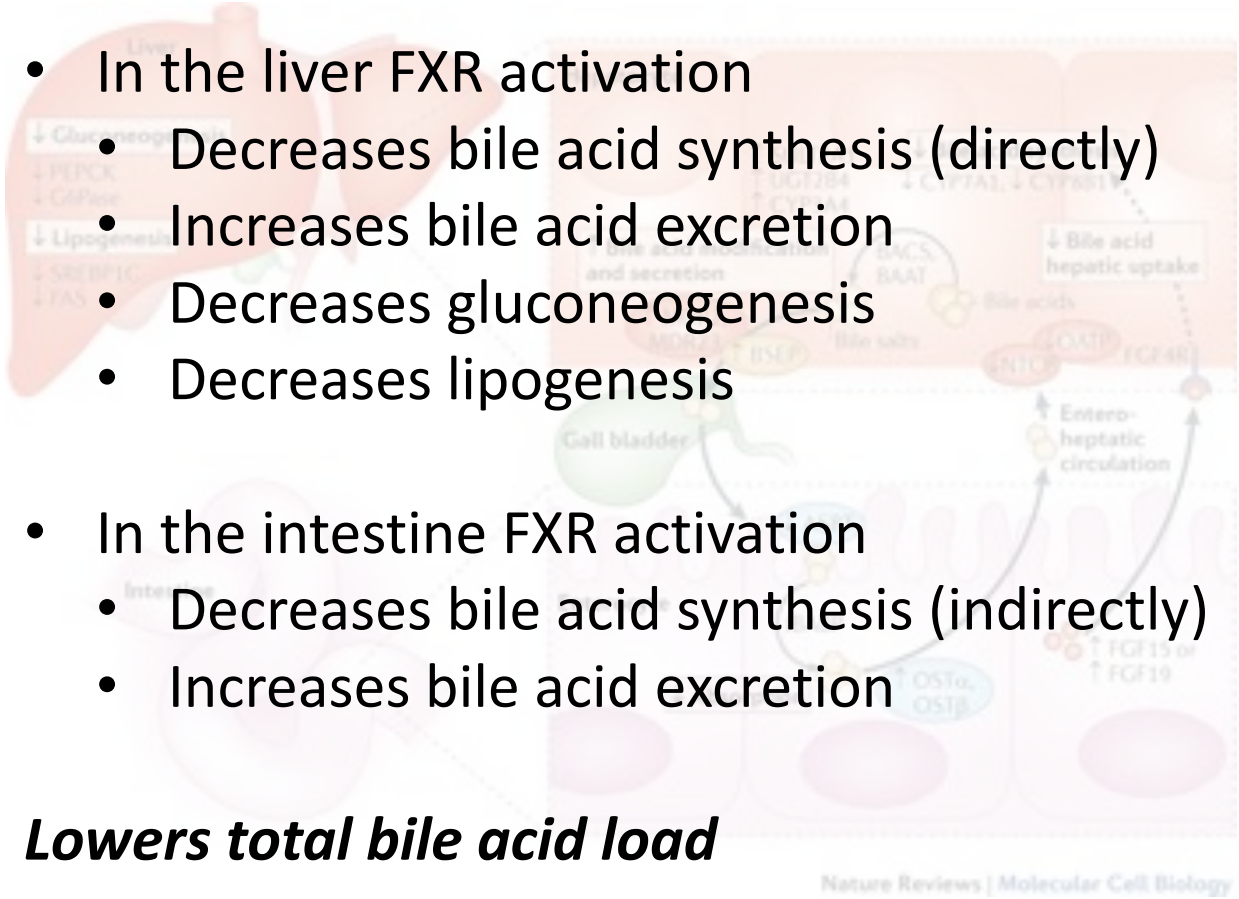


Calkin AC & Tontonoz P. Nature Reviews Molecular Cell Biology. 2012;13:213-224.

- In the liver FXR activation
  - Decreases bile acid synthesis (directly)
  - Increases bile acid excretion
  - Decreases gluconeogenesis
  - Decreases lipogenesis

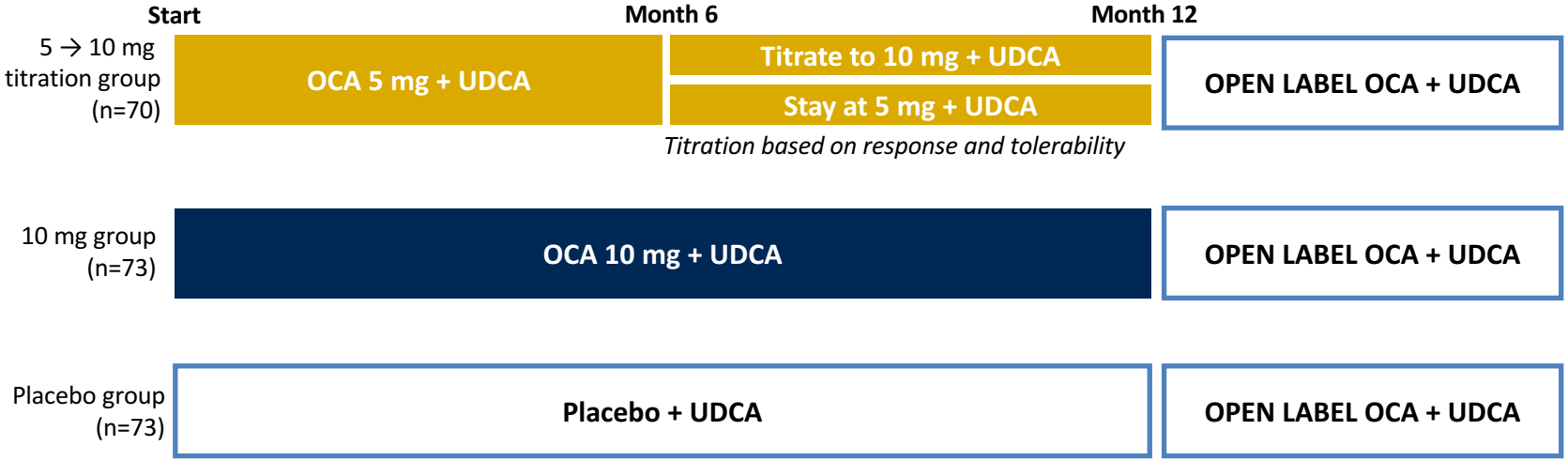
- In the intestine FXR activation
  - Decreases bile acid synthesis (indirectly)
  - Increases bile acid excretion

Lowers total bile acid load



POISE Trial Design (obeticholic acid)

Randomized, double-blind, placebo-controlled, parallel-group, 12-month study of 216 patients with PBC and an inadequate response or intolerant to UDCA



Nevens F et al. N Engl J Med 2016;375:631-643

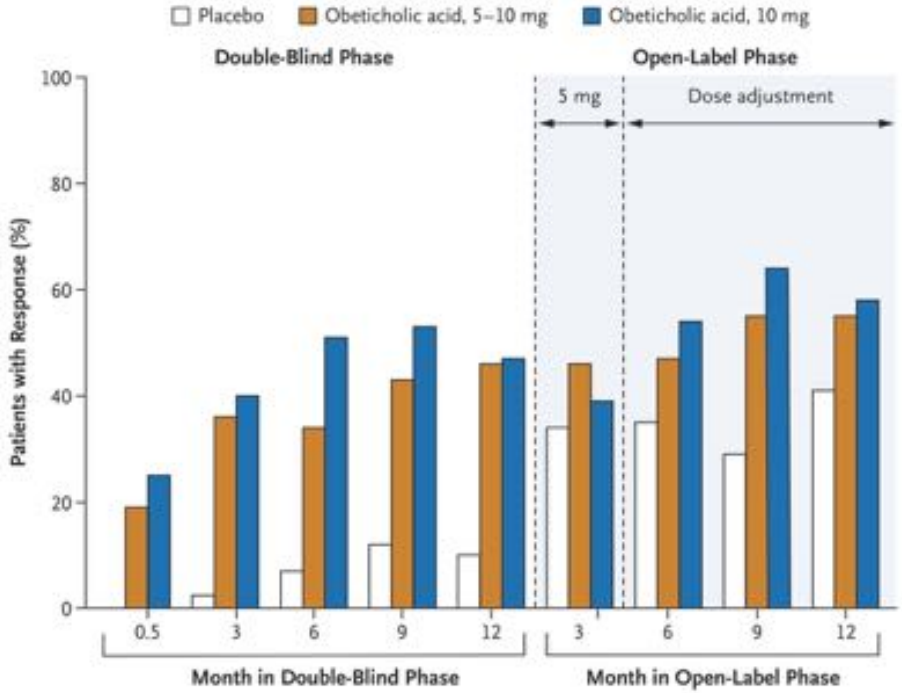
POISE Baseline Characteristics

	Placebo (n=73)	OCA Titration (n=70)	10 mg OCA (n=73)
Age, years	56±10	56±11	56±10
Female, n (%)	68 (93)	65 (93)	63 (86)
Caucasian, n (%)	66 (90)	67 (96)	70 (96)
ALP, U/L	327±115	326±116	316±104
Bilirubin, µmol/L	12±7	10±6	11±7
UDCA use, n (%)	68 (93)	65 (93)	67 (92)
Daily UDCA dose, mg/kg	15±4	17±5	16±5

Data are mean ± SD where applicable.

Nevens F et al. N Engl J Med 2016;375:631-643

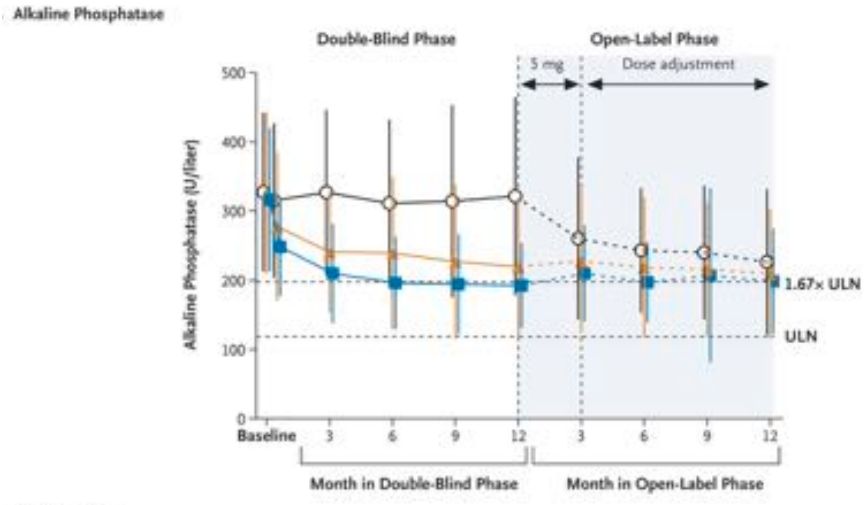
POISE Primary Endpoint

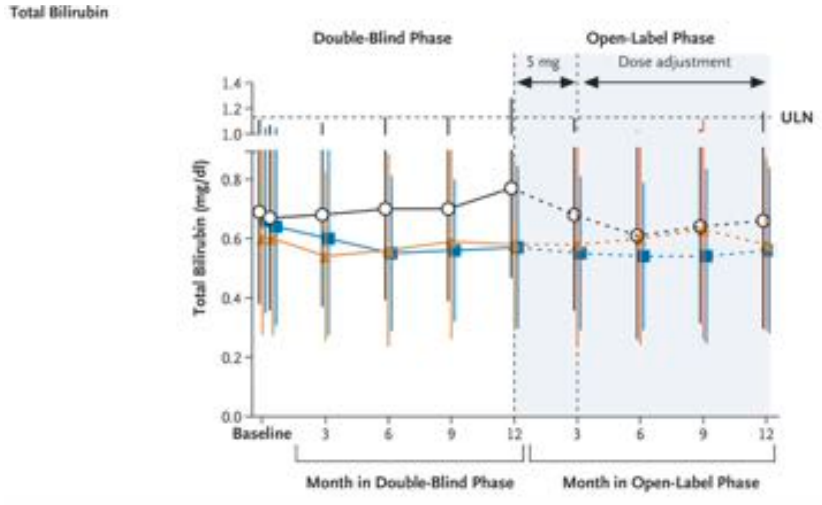


- Composite Endpoint
  - ALP < 1.67 X ULN
  - >15% Reduction in ALP
  - Normal total bilirubin
- Primary Endpoint at Month 12
  - 5–10-mg group (46%)
  - 10-mg group (47%)
  - Placebo group (10%)
  - P<0.001 for both comparisons

Nevens F et al. N Engl J Med 2016;375:631-643

POISE Changes in ALP and Bilirubin





Nevens F et al. N Engl J Med 2016;375:631-643

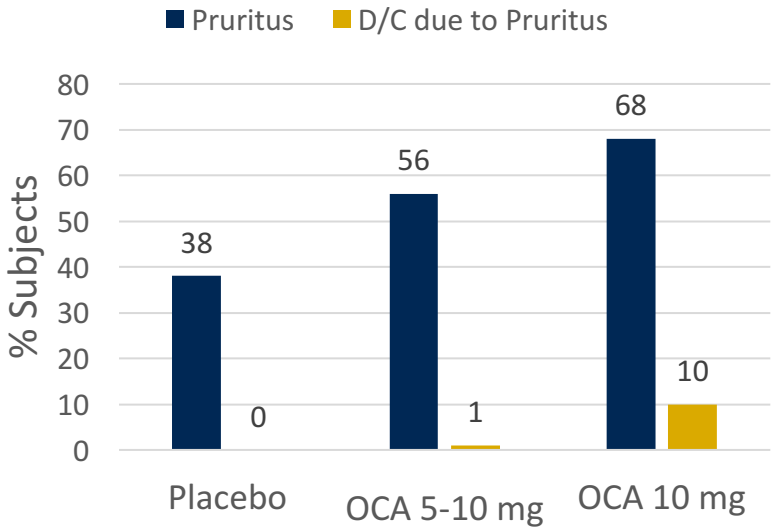
OCA Adverse Events and Caveats

Pruritus
- Common, dose related

Cholesterol Changes
- Decrease in Total Cholesterol

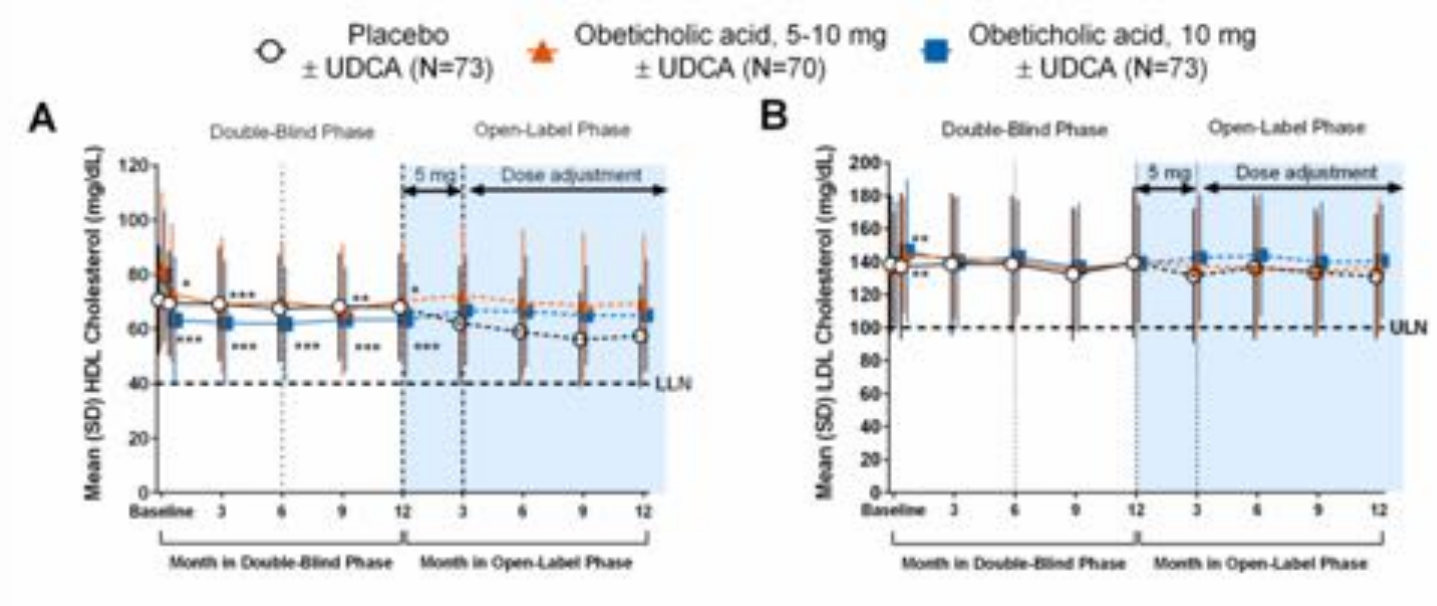
Potential risk of chronic increase in FGF19
- Increase risk of HCC in mouse models

Warning in decompensated cirrhosis



Nevens F et al. N Engl J Med 2016;375:631-643

POISE Changes in HDL and LDL Cholesterol



Nevens F et al. N Engl J Med 2016;375:631-643

FDA Post-Marketing Letter

"Ocaliva (obeticholic acid) is being incorrectly dosed in some patients with moderate to severe decreases in liver function, resulting in an increased risk of serious liver injury and death."

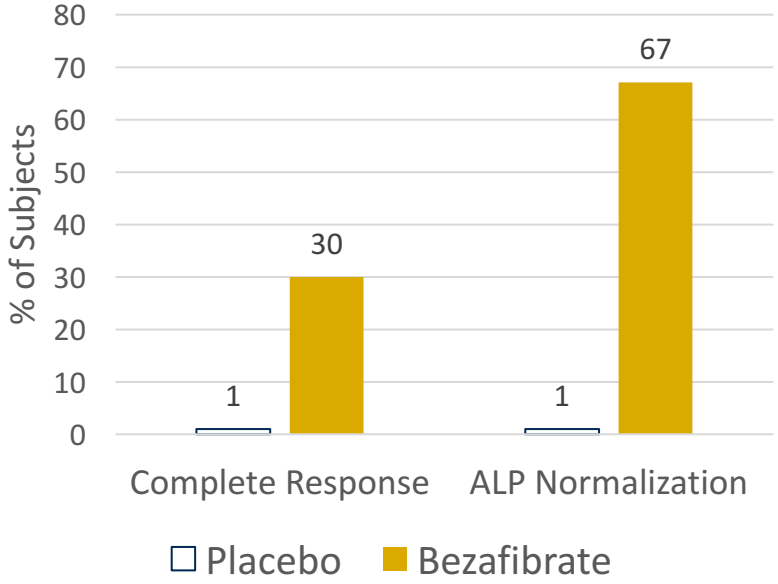
- 19 deaths, 8 with reported causes
    - 7 cases of Child B or C cirrhosis and receiving 5 mg ***daily***
- 8 additional cases of serious liver injury without death
    - 3 cases of Child B or C cirrhosis and receiving 5 mg ***daily***
    - 5 cases with Child A or no reported liver dysfunction
        - 2 resolved, 3 unreported

Bezafibrate for PBC

Randomized, double-blind, placebo-controlled, parallel-group, 24-month study of 100 patients with PBC and an inadequate response to UDCA (Paris 2 criteria)

Corpechot C et al. EASL 2017

Bezafibrate Endpoints and Outcomes



Primary Composite Endpoint at 24 months

- ALP ≤ ULN
- AST & ALT ≤ ULN
- Total Bilirubin ≤ ULN
- PT ≤ ULN
- Albumin ≥ ULN

Corpechot C et al. EASL 2017

Bezafibrate Adverse Events

Transaminases > 5 X ULN

- 1 with placebo
- 3 with bezafibrate, 2 discontinued

CPK > 5 X ULN

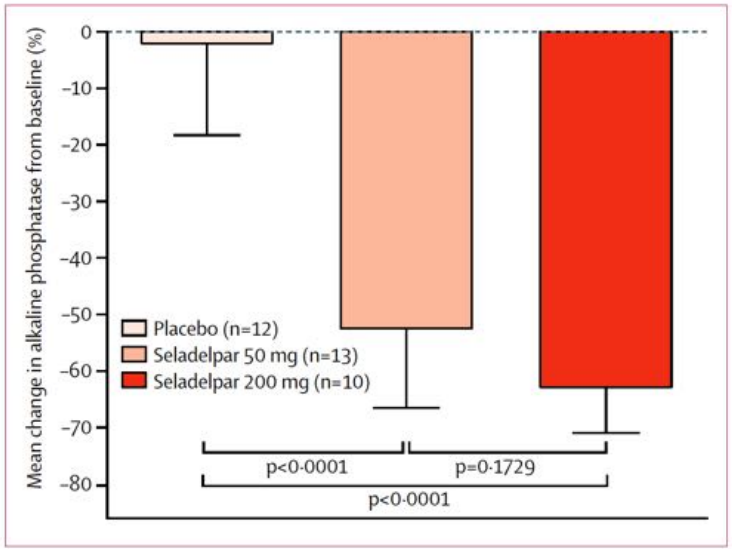
- 1 with bezafibrate, discontinued

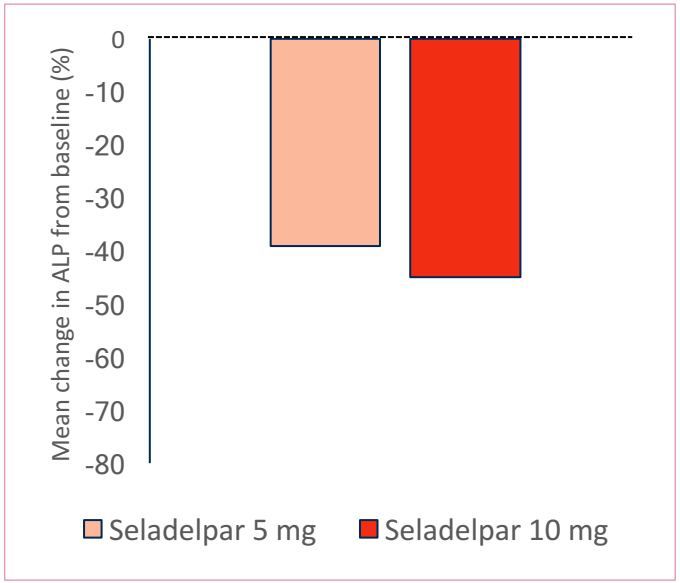
Serum creatinine

- +5% with bezafibrate
- – 3% with placebo at 24 months ($p < 0.01$)

Corpechot C et al. EASL 2017

Seladelpar (PPAR-delta agonist)





Jones D, *et al. Lancet Gastroenterol Hepatol* 2017;2:716-726.
Hirschfield G.M. *et al*. *Hepatology* 2017;66:

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PBC Drugs in Development

- FXR Agonist
  - LJN452 (Novartis)
  - GS9674 (Gilead)
- FGF19 Agonist
  - NGM282 (NGM Biopharmaceuticals)
- PPAR Agonists
  - Seladelpar (Cymabay)
  - Elafibranor (Genfit)
  - Saroglitazar (Zydus Discovery)
- NOX-4 Inhibitor (Anti-Fibrotic)
  - GKT137831 (Genkyotex)

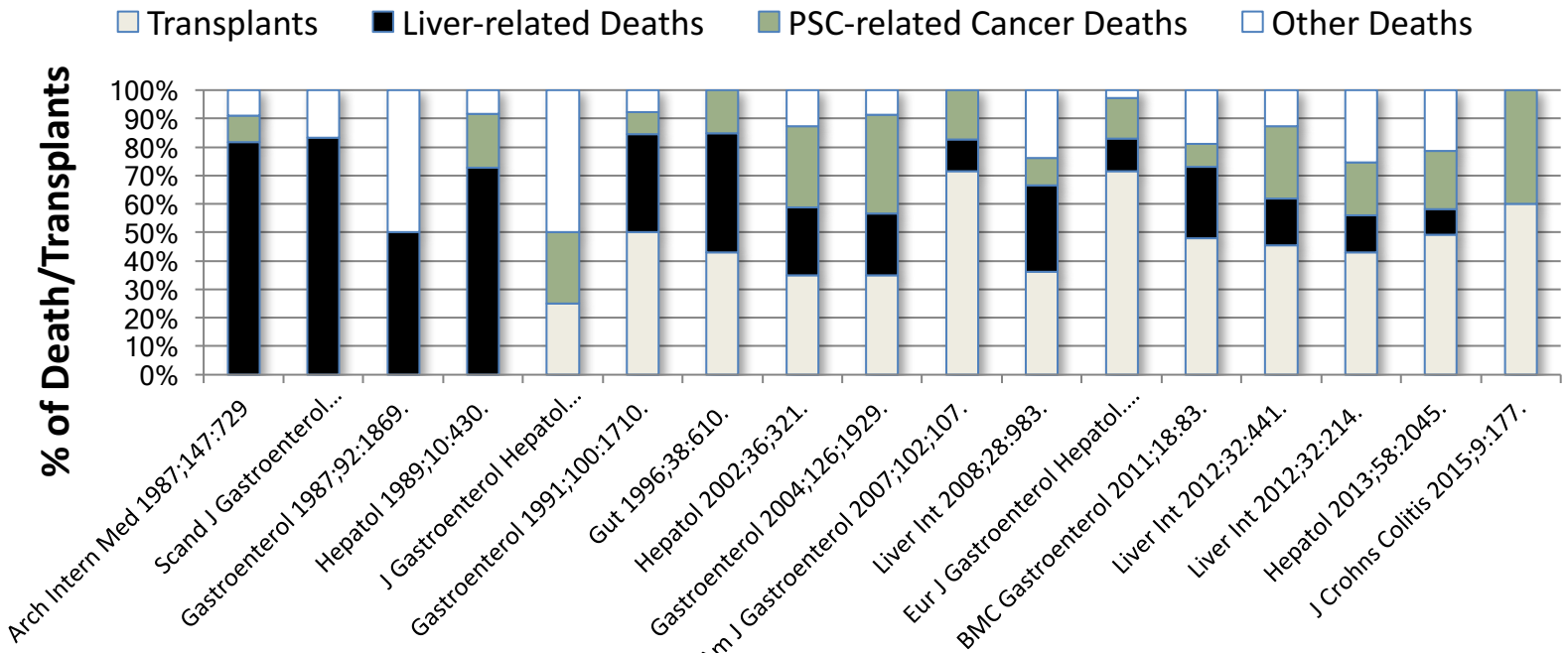
Clinicaltrials.gov accessed November 24, 2017.

PBC Symptom Management

- Dry eyes /mouth
  - Artificial tears and saliva are often helpful
  - Pilocarpine can be used for refractory symptoms
- Fatigue
  - Seek and treat associated and alternate causes of fatigue, particularly anemia, hypothyroidism, celiac disease, and sleep disturbance
- Pruritus
  - Conservative measures
  - Stepwise medical approach

PSC

CHANGING CAUSES OF DEATH IN PSC



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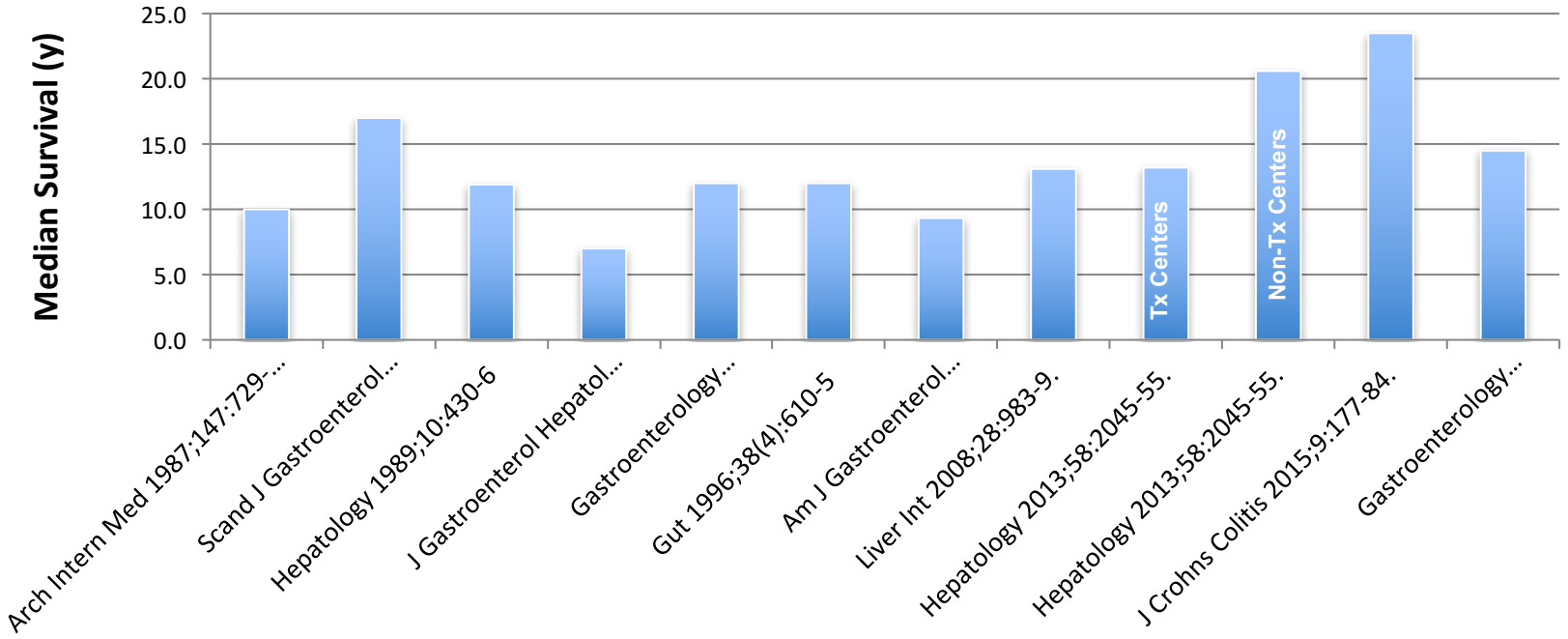
TRANSPLANT-FREE SURVIVAL IN PSC



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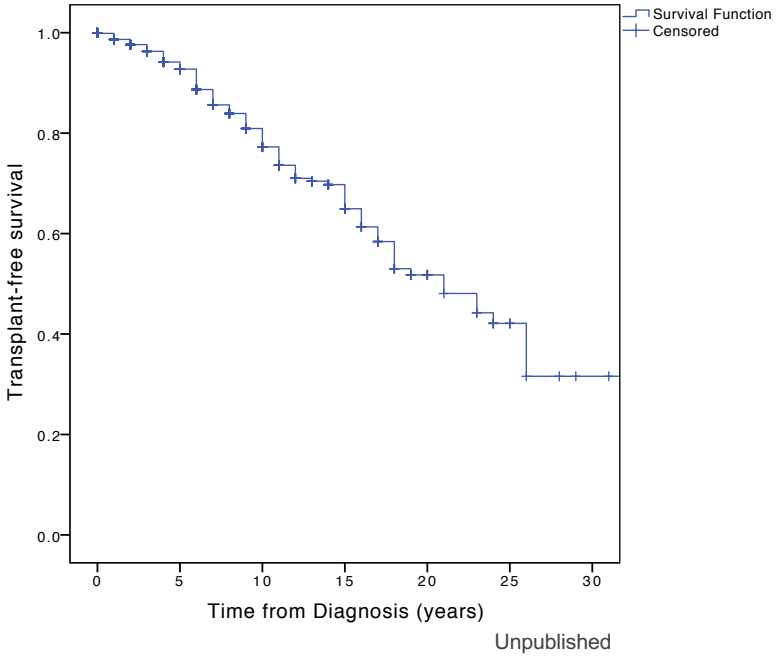
Transplant-Free Survival in PSC Partners Registry

811 self-identified PSC Patients
- 65.1% confirmed diagnosis
- Mean age 41.7 ± 15.5 years
- Mean age at diagnosis 32.4 ± 14.5 years
- 67.1% with IBD

Median transplant-free survival 21 years
- 95% CI 17.2 – 24.8 years



Unpublished

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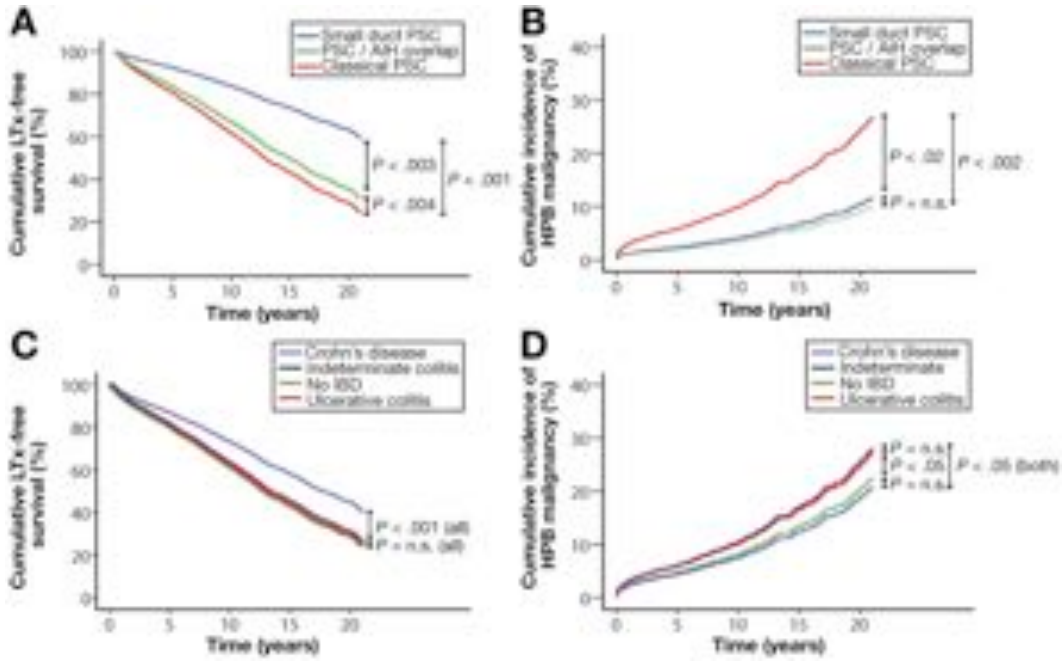
Factors Associated with Better Outcomes

Demographic

- Female Sex
- Young Age of Diagnosis
- White Race

Clinical

- Crohn's Disease
- Small duct PSC
- Normal alkaline phosphatase



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

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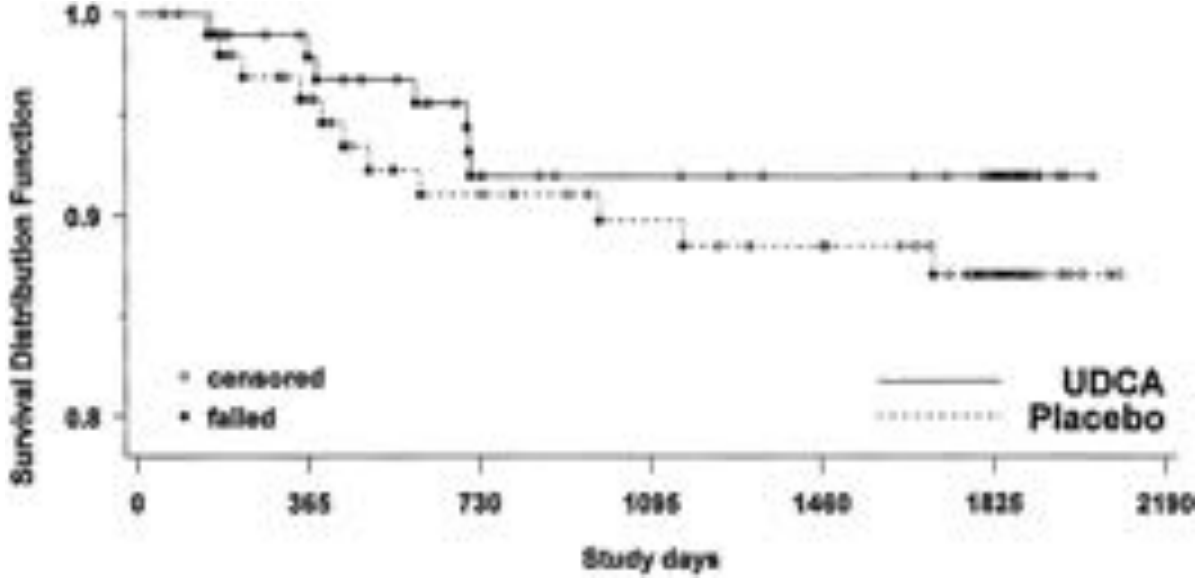
UDCA for PSC (17-23 mg/kg)



Olsson R et al. Gastro 2005.

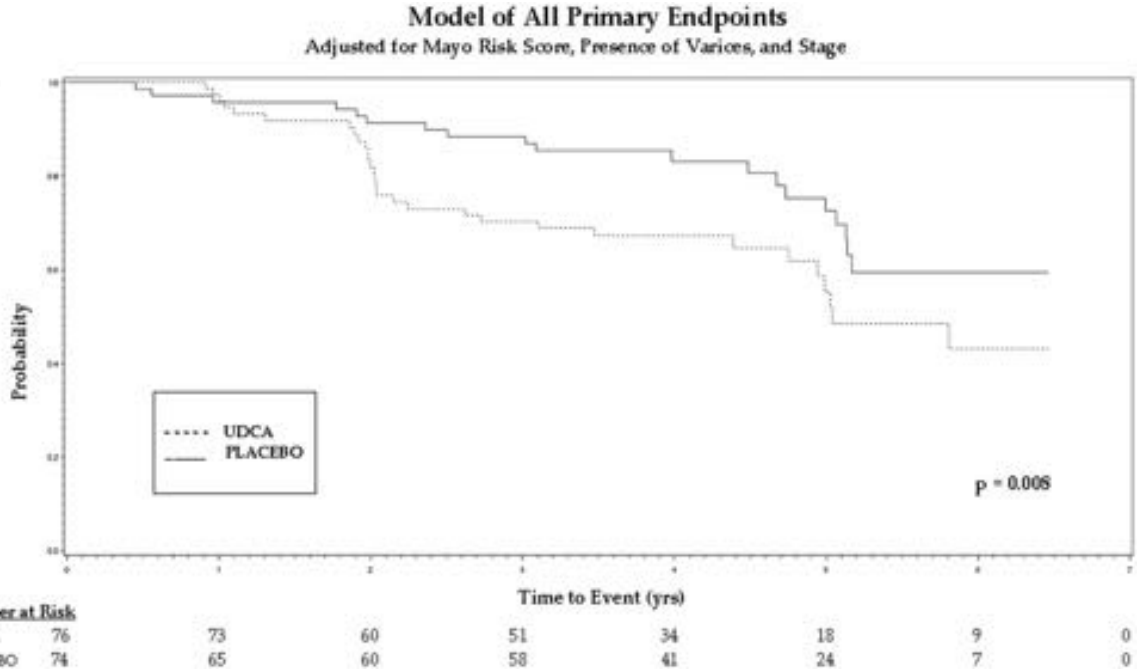
HIGH DOSE UDCA PSC TRIAL

Randomized controlled trial of high-dose UDCA (28-30 mg/kg/d)

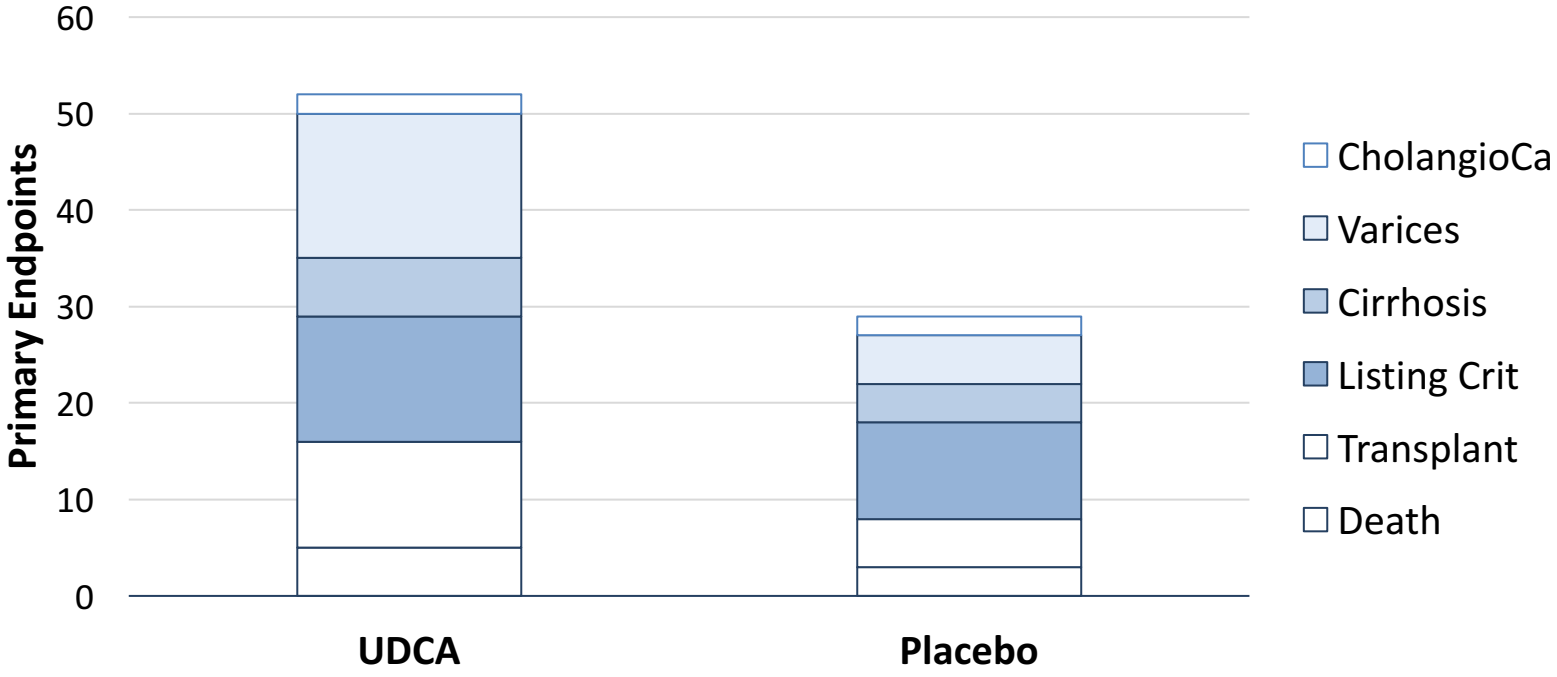
15 of 74 (20%) allocated to placebo reached a primary endpoint (death, transplant, minimal listing criteria)

150 patients enrolled out of 455 screened

Few events in first 2 years



HIGH DOSE UDCA



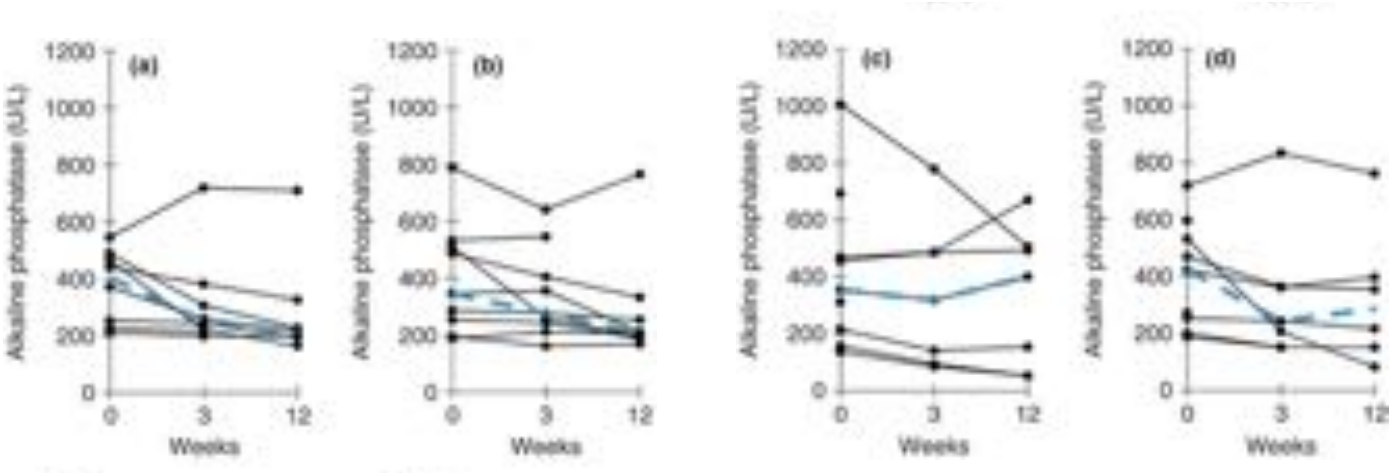
Lindor KD, et al. Hepatology 2009.

UCDAVIS

Vancomycin versus Metronidazole in Adults with PSC

Vancomycin

Metronidazole



125 mg QID

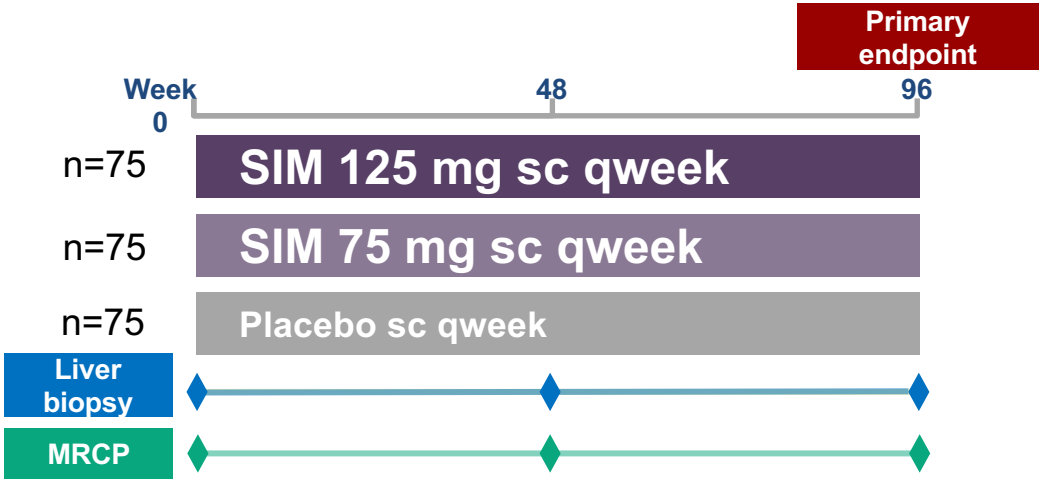
250 mg QID

250 mg TID

500 mg TID

P < 0.05 at each dose

Simtuzimab in PSC



- Key inclusion criteria
  - Compensated PSC, confirmed on biopsy and MRCP
  - Inactive IBD (partial Mayo score ≤2; no corticosteroids or anti-TNF-α therapy)
- 1:1:1 randomization stratified by baseline serum IgG4 (> or ≤140 mg/dL)

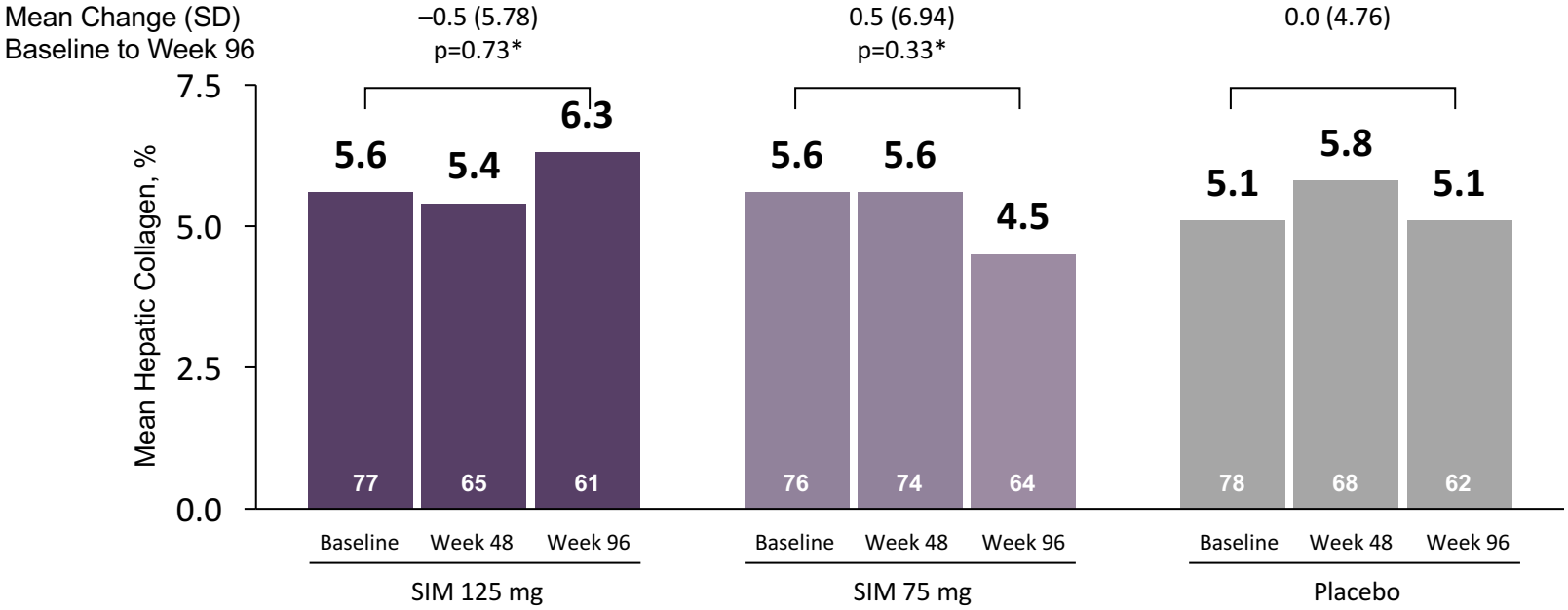
IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiopancreatography; TNF-α, tumor necrosis factor-α).

Muir A. et al. J Hepatol. 2017;66:S73.

UCDAVIS

Results: No Effect of SIM on Hepatic Collagen Content

SIM had no effect on hepatic collagen content



p-values vs placebo are from a mixed effect model for repeated measures at Week 96.

Muir A. et al. J Hepatol. 2017;66:S73.

UCDAVIS

PSC-Related Clinical Events

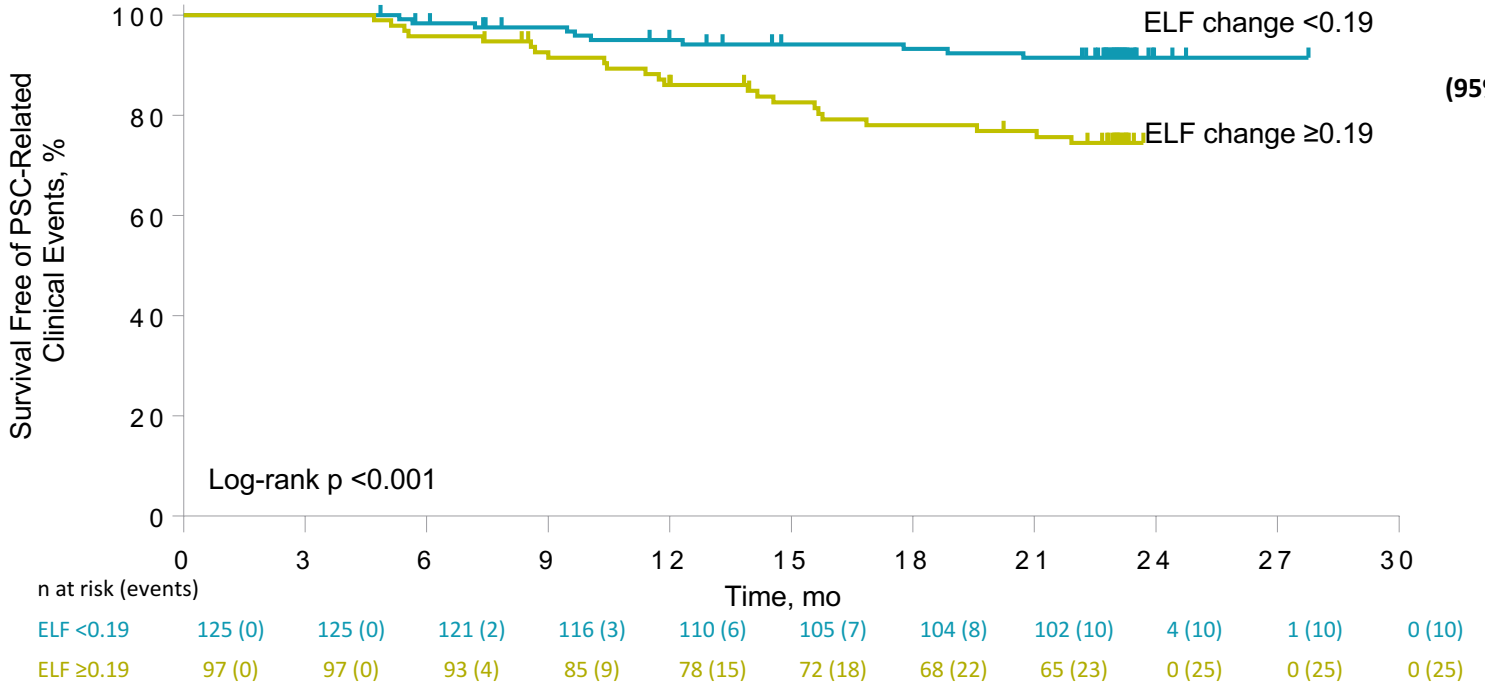
44 patients (19%) had clinical events over a median follow-up of 23.0 months (IQR 23.0, 23.2)

Patients With Events, n (%)*	Total: N=234
Total	44 (19)
Ascending cholangitis	26 (11)
Jaundice	8 (3)
Cholangiocarcinoma	3 (1)
Ascites	2 (<1)
Hepatic encephalopathy	2 (<1)
Variceal hemorrhage	2 (<1)
Sepsis	1 (<1)

* Only first events are listed in patients with multiple events.

Bowlus C.L et al. J Hepatology. 2017;66:S359.

Survival Free of PSC-Related Clinical Events
Change From Baseline ELF at Week 12



* HR adjusted for baseline ELF.

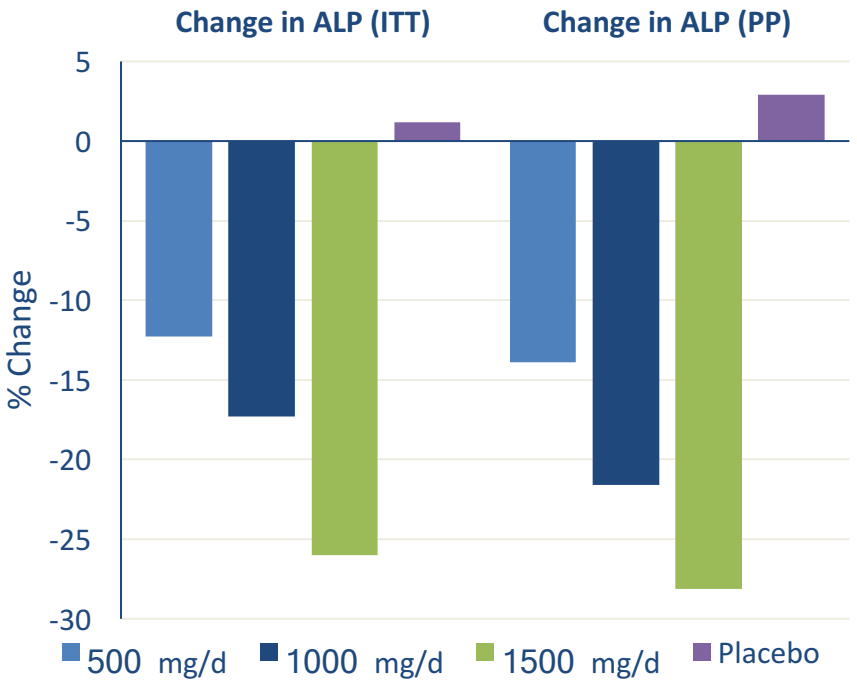
Bowlus C.L et al. J Hepatology. 2017;66:S359.

UCDAVIS

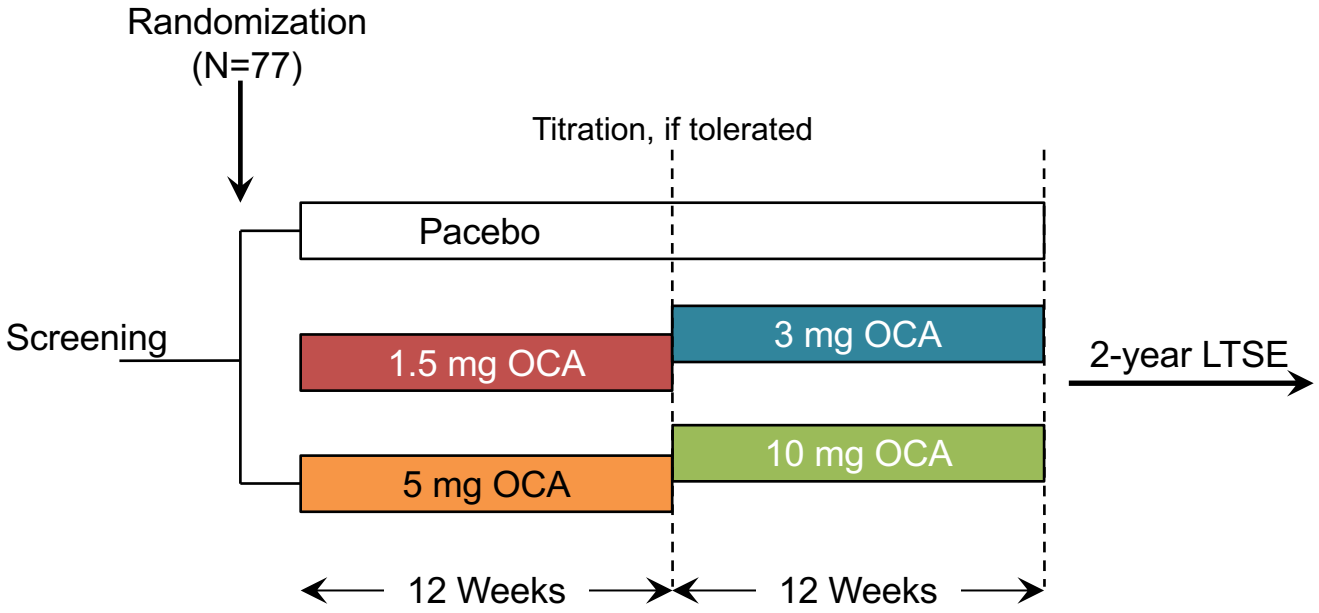
NOR-URSO: PHASE II DOSE FINDING STUDY

Double-blind, placebo-controlled trial of PSC patients with elevated ALP > 1.5 X ULN

- No UDCA for 8 weeks
- 12 weeks treatment
- 222 pts. screened
  - 159 randomized
  - 126 PP analysis



AESOP (obeticholic acid)

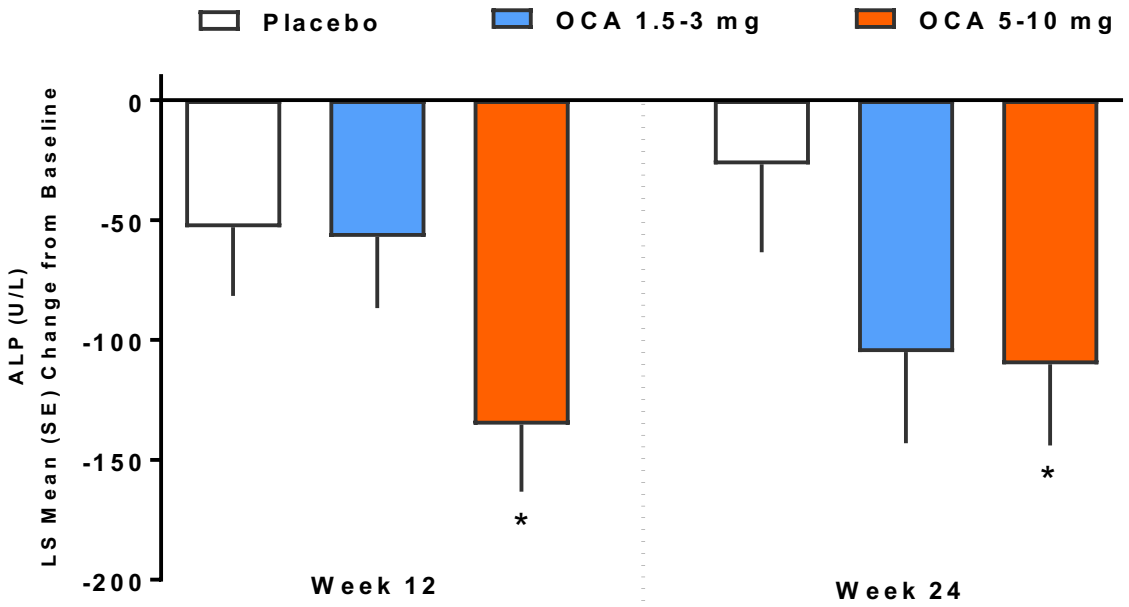


Kowdley K. *et al*. *Hepatology* 2017;66:

Intercept Press Release July 31, 2017

AESOP (obeticholic acid)

- ALP > 2 X ULN at baseline
- Approximately half receiving UDCA at baseline



PSC Drugs in Development

- FXR Agonist
  - OCA (Intercept)
  - GS9674 (Gilead)
- FGF19 Agonist
  - NGM282 (NGM Biopharmaceuticals)
- CCR5 Antagonist
  - Cenicriviroc (Allergan)

Clinicaltrials.gov accessed November 24, 2017.

Take Home Messages - PBC

- Few PBC patients require a liver biopsy for diagnosis
- Start all PBC patients on UDCA 13-15 mg/kg/d
    - Twice daily dosing regardless of preparation
- Assess biochemical response
    - Consider additional therapies in incomplete responders
        - ALP < 200 IU/L and normal bilirubin likely to do well
        - OCA 5 mg daily if pruritus is not an issue
        - Consider fenofibrate (off-label) but monitor CPK, renal function and liver tests
        - Refer for clinical trials
- Address associated symptoms and diseases

Take Home Messages - PSC

- PSC outcomes are variable but better than estimated in past
- Consider trial of UDCA 13-15 mg/kg/d if ALP is elevated
    - Discontinue if no response
    - Consider referral for clinical trial if ALP is elevated
- Surveillance for malignancies
    - Colon cancer (only if IBD present)
    - Cholangiocarcinoma and gallbladder cancer

Patient Resources

www.pscpartners.org

www.pbcers.org