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THE STATE UNIVERSITY
OF NEW JERSEY

Primary Biliary Cholangitis

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PBC is a Chronic, Progressive Autoimmune? Disease

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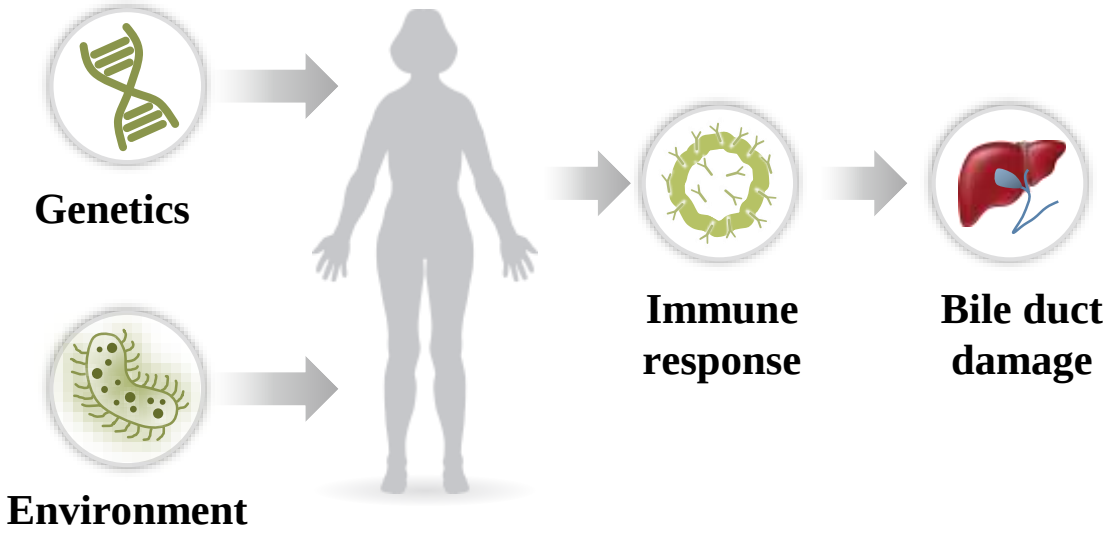
- Factors possibly associated with onset and perpetuation of bile-duct injury in PBC



PBC is characterized by destruction of the interlobular and septal bile ducts that may lead to cirrhosis

Poupon R. *J Hepatol*. 2010;52(5):745-758; Selmi C, et al. *Lancet*. 2011;377(9777):1600-1609; Carey EJ, et al. *Lancet*. 2015;386(10003):1565-1575.

If Left Inadequately Treated, PBC May Result in Liver Failure, Transplant, Death[1-3]

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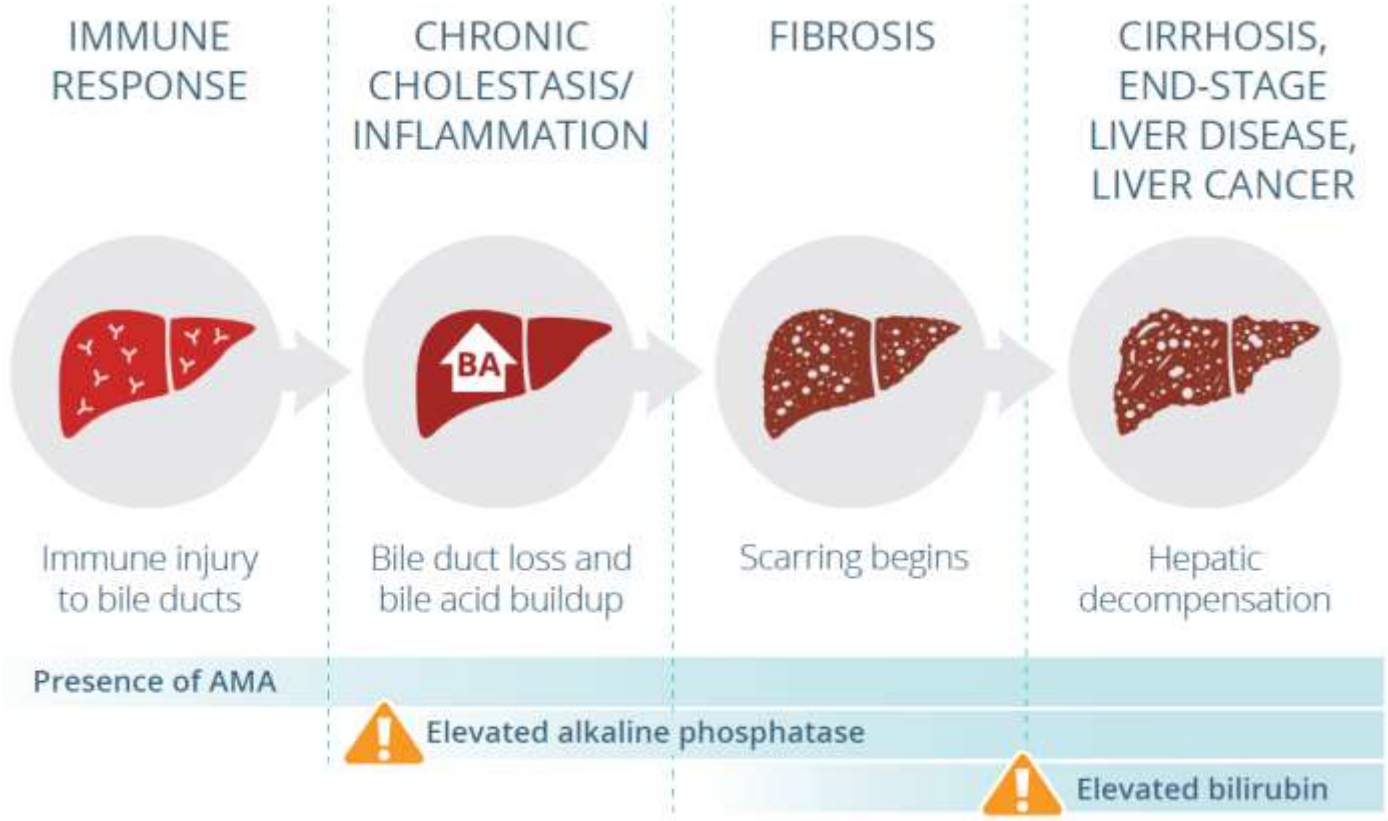
Persistent, toxic exposure to bile acid buildup ultimately leads to end-stage disease[1,2,4,5,*]



*Progression from cholestasis to cirrhosis, and from cirrhosis to liver-related mortality, can vary by patient.
AMA, antimitochondrial antibody.

1. Poupon R. *J Hepatol.* 2010;52(5):745-758. 2. Dyson JK, et al. *Nat Rev Gastroenterol Hepatol.* 2015;12(3):147-158. 3. Lammers WJ, et al. *Gastroenterology*. 2014;147(6):1338-1349. 4. Selmi C, et al. *Lancet.* 2011;377(9777):1600-1609. 5. Lindor KD, et al. *Hepatology*. 2009;50(1):291-308.

Impact on Survival of Liver Stiffness Measurement in PBC

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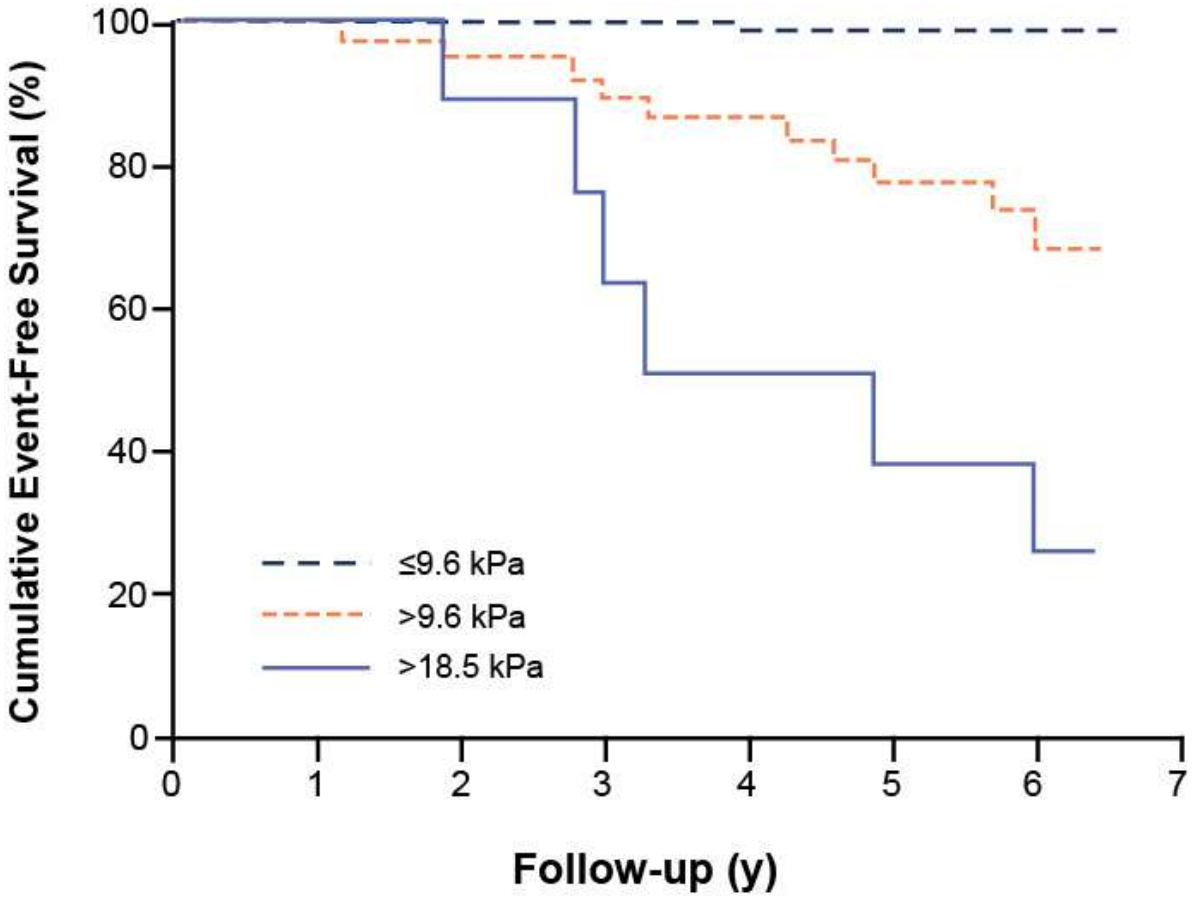
150 PATIENTS



Corpechot C et al. Utility of Noninvasive Markers of Fibrosis in Cholestatic Liver Diseases. *Clin Liver Dis*. 2016;20:143-158.

PBC Phenotype

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Age	Usually >45 years
Gender	Female > Male (9:1)
Serology	AMA in ~95%; disease-specific ANA in ~30%-50%; ASMA may be present
Immunoglobulin	IgM typically elevated
MRCP	Normal
Liver Histology	Lymphocytic infiltrate; inflammatory duct lesion; granuloma may be present
Coexisting IBD	Not typical

Abbreviations: AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth-muscle antibody; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiography; PBC, primary biliary cholangitis.

Trivedi PJ, et al. *Aliment Pharmacol Ther*. 2012;36:517-533.

Concomitant Autoimmune Disease in Women with PBC

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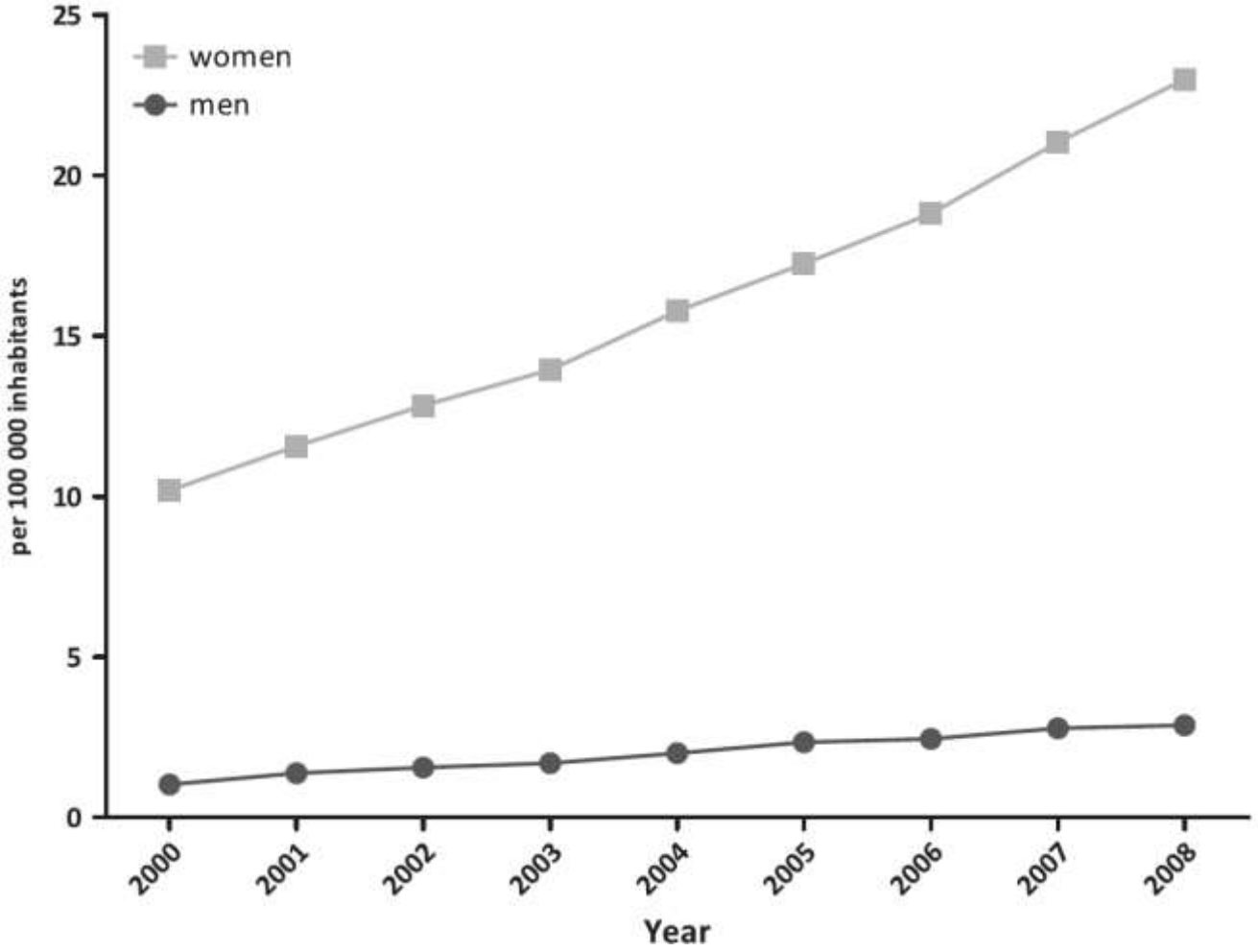
	Frequency (%)
Sjögren's syndrome	7-34
Raynaud's syndrome	9-13
Hashimoto's thyroiditis	11-13
Rheumatoid arthritis	3-8
Psoriasis	6
Scleroderma or CREST*	1-2
Inflammatory bowel disease	1
Any autoimmune disease	33-55

*CREST (calcinosis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia)

Carey EJ, Ali AH, Lindor KD. Primary Biliary Cirrhosis. *The Lancet.* 2015 Oct.; 386(10003):1565-1575.

PBC Prevalence



Boonstra K, Kunst A, Stadhouders P, et al. Rising incidence and prevalence of primary biliary cirrhosis: a large population-base study. *Liver International*. 2014;34:e35.

Diagnostic Considerations

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Spectrum of Autoimmune Liver Injuries[1]

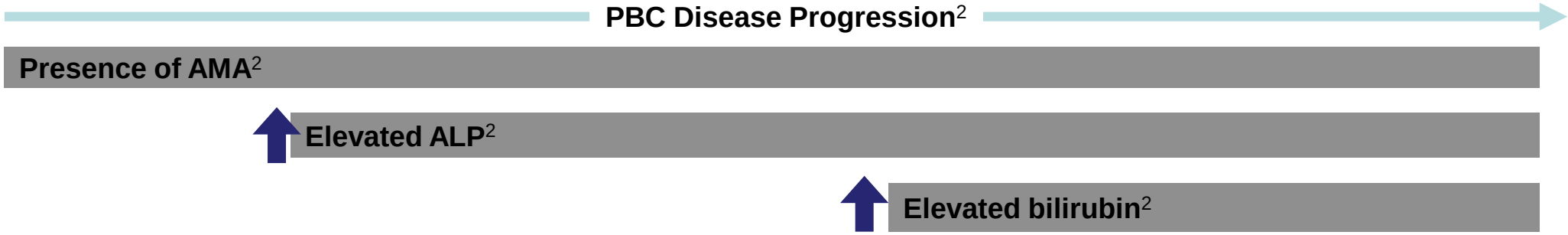
- Autoimmune hepatitis[1]
- Primary biliary cholangitis[1]
- Primary sclerosing cholangitis[1]
- IgG4-related disease[2]

Differential for Cholestatic Liver Biochemistry[3]

- Drug-induced liver injury
- Inherited cholestasis
- Idiopathic ductopenia
- Malignant infiltration
- Nonalcoholic fatty liver disease
- Obstructive biliary lesion
- Primary biliary cholangitis
- Primary sclerosing cholangitis
- Sarcoidosis

1. Trivedi PJ, et al. *Aliment Pharmacol Ther*. 2012;36:517-533; 2. Joshi D, et al. *Aliment Pharmacol Ther*. 2014;40:1251-1261; 3. Hirschfield GM, et al. *Best Pract Res Clin Gastroenterol*. 2011;25:701-712.

PBC Diagnosis Is Predominantly Based on Elevated ALP and the Presence of Anti-mitochondrial Antibodies[1]



AASLD Guidelines:

PBC diagnosis can be established when 2 of these 3 criteria are met[1,3]

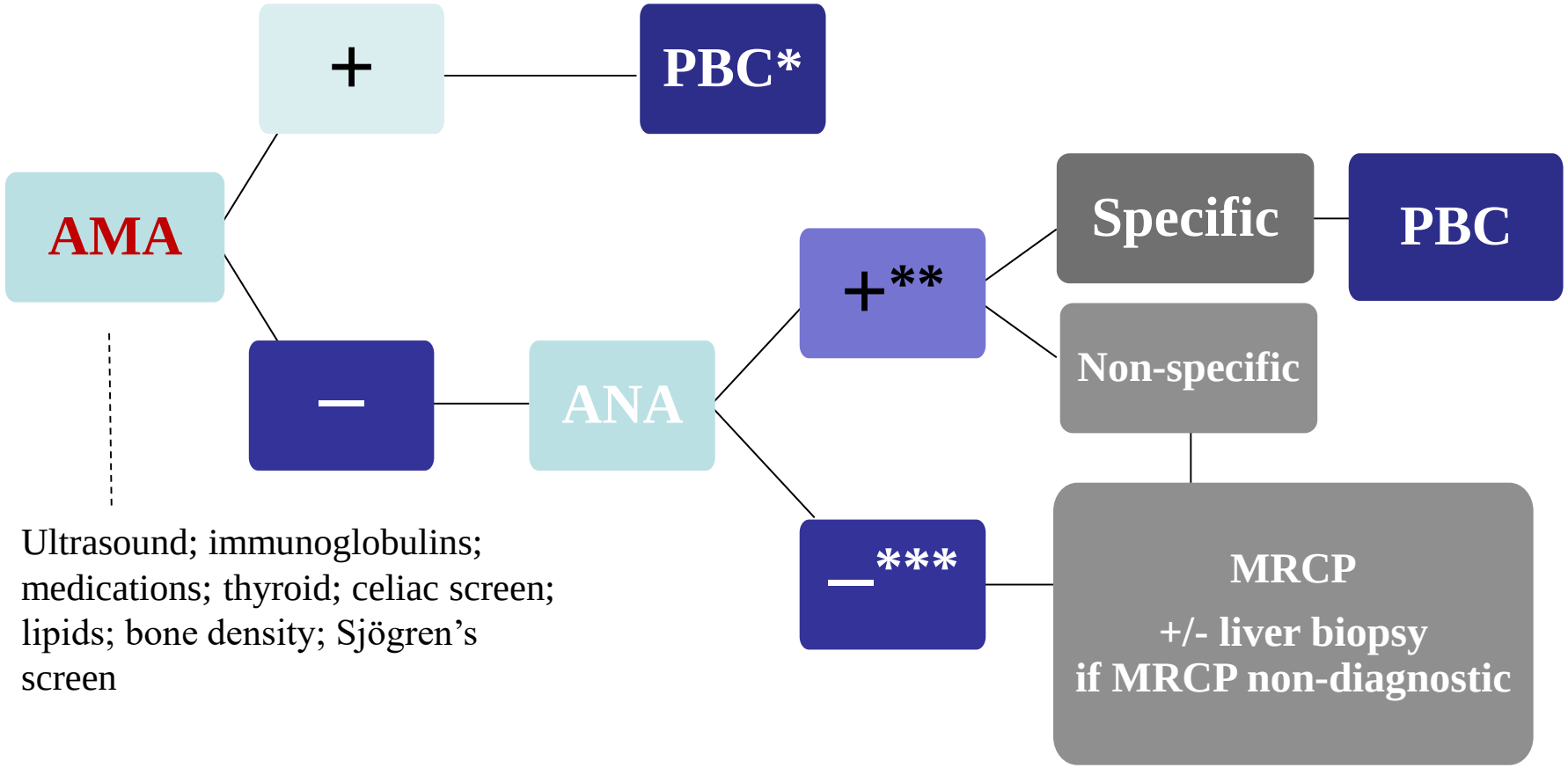
1. Biochemical evidence of cholestasis based on **elevated ALP level**
2. Presence of **AMA** or other PBC-specific autoantibodies, including sp100 or gp210, if AMA is negative
3. Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts if biopsy is performed

Liver biopsy can be used to further substantiate the diagnosis but is no longer considered necessary in most patients[1]

AASLD, American Association for the Study of Liver Diseases; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibodies; PBC, primary biliary cholangitis.

1. Lindor KD et al. *Hepatology*. 2019;69(1):394-419; 2. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172; 3. Kaplan MM, Gershwin ME, et al. *N Engl J Med*. 2005;353(12):1261-1273.

Evaluation of Patients with Cholestatic Profile



*0.5%–1% of healthy individuals are AMA+; **>85% patients with AMA–PBC are ANA+;
***Differential is among PSC, antibody- negative PBC, and alternate ductopenic disorders.
Abbreviations: AMA, antimitochondrial antibody; ANA, antinuclear antibody; MRCP, magnetic resonance cholangiography; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.
Hirschfield GM, et al. *Best Pract Res Clin Gastroenterol.* 2011;25:701-712.

Interpretation of AMA, ANA, and Immunoglobulin Testing in PBC

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- AMA
  - Positive in >90% of patients with PBC, depending on assay[1]
  - In the correct context, AMA reactivity, with an elevated ALP and no significant elevation in AST, is associated with a >95% PPV of histologic PBC[2]
- ANA
  - 2 ANA immunofluorescent patterns are specific to PBC: multiple nuclear dots and perinuclear/rim-like membranous[3]
  - Automated ANA assays will likely not detect these reactivities
  - Laboratories should perform immunofluorescence if ELISA-based assays for gp210 and sp100 are not available
- Immunoglobulins
  - Elevated IgM is a sensitive but not specific characteristic of PBC[1]
  - Elevated IgG is primarily observed in AIH[1]

Abbreviations: PPV, positive predictive value; AIH, autoimmune hepatitis; IgM, immunoglobin M; IgG, immunoglobin G

1. Trivedi PJ, et al. *Aliment Pharmacol Ther*. 2012;36:517-533; 2. Zein CO, et al. *Clin Gastroenterol Hepatol*. 2003;1:89-95; 3. Zeman MV, Hirschfield GM. *Can J Gastroenterol*. 2010;24:225–231.

Extra-Hepatic Disease Management

Clinical Features Vary Greatly Between Patients…[1-3]

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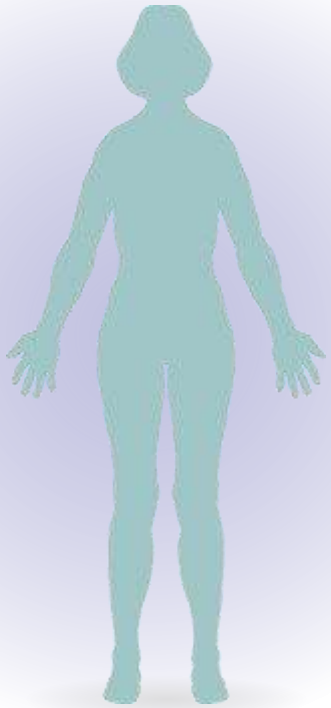
…but there are disease-associated symptoms, clinical manifestations, and co-existing autoimmune diseases that are recognized[1-3]



- **Fatigue**[1,2]
- **Pruritus**[1,2]

→ Most common symptoms of PBC[2]

- **Xanthoma and xanthelasma**[2,3]
- **Hyperlipidemia**[1,2]
- **Osteoporosis**[1,2]
- **Co-existing autoimmune diseases**[1,2]

The absence of symptoms at diagnosis may not predict prognosis
(as many as ~60% of patients may be asymptomatic at diagnosis)[4]*

PBC, primary biliary cholangitis.

*Based on an examination of the natural history of a 770-patient cohort in Northeast England (incident cases, 1987-1994).[4]

1. Selmi C, et al. *Lancet*. 2011;377(9777):1600-1609. 2. Carey EJ, et al. *Lancet*. 2015;386(10003):1565-1575. 3. Lindor KD, et al. *Hepatology*. 2018. doi:10.1002/hep.30145. 4. Prince MI, et al. *Gut.* 2004;53(6):865-870.

Fatigue Is the Most Common Symptom in PBC[1,2]

- Present in up to 85% of patients with PBC[3]
    - >40% report moderate to severe[1]
- Mechanism not well understood[1,2]
- Unrelated to disease activity or stage
    - Tends to wax and wane throughout the course of illness[2]
- Typically characterized as daytime somnolence
    - Can impair QoL[1]

Despite sparse correlation between fatigue and severity of liver disease, fatigue can be associated with decreased overall survival[1]

QoL, quality of life.

1. Selmi C, et al. *Lancet*. 2011;377(9777):1600-1609. 2. Carey EJ, et al. *Lancet*. 2015;386(10003):1565-1575. 3. Huet PM, et al. *Am J Gastroenterol*. 2000;95(3):760-767.

Assessing and Managing Fatigue

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- Though fatigue caused by PBC may not be reversible, associated causes of fatigue should be actively excluded—or identified and managed[1,2]

Rule Out:
Associated causes of fatigue (disease or medication): • Anemia[2] • Depression[2] • Sleep disorder[2] • Hypothyroidism[1-3] • Medications that can cause or contribute to fatigue (eg, excessive antihypertensive medication)[1]

Consider Fatigue Management Strategies:
Fatigue may be improved by: • Maintaining regular physical activity[4,5] • Modafinil (100-200 mg)[6,7] • Methotrexate for patients with severe fatigue[8]

1. European Association for the Study of the Liver. *J Hepatol*. 2009;51(2):237-267; 2. Lindor KD, et al. *Hepatology*. 2009;50(1):291-308; 3. Elta GH, et al. *Dig Dis Sci*. 1983;28(11):971-975; 4. Cook NF, et al. *Br J Nurs*. 1997;6(14):811-815; 5. Graydon JE, et al. *Cancer Nurs*. 1995;18(1):23-28; 6. Jones DEJ, et al. *Aliment Pharmacol Ther*. 2007;25(4):471-476; 7. Ian Gan S, et al. *Dig Dis Sci*. 2009;54(10):2242-2246; 8. Babatin MA, et al. *Aliment Pharmacol Ther*. 2006;24(5):813-820.

Pruritus Is Very Common Among PBC Patients

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- Prevalence reported as high as 69%[1]
- Unknown etiology[1,2]
  - Bile salts, endogenous opioids, histamine, serotonin, progesterone/ estrogen, and autotaxin/lysophosphatidic acid are suspected pruritogens[2]
- Diurnal variation – most intense itch in the late evening[2]
- Localization reported at limbs – soles of feet, palms of hands[2]
- Exacerbated by pregnancy or contact with wool/heat[3]

1. Imam MH, et al. *J Gastroenterol Hepatol.* 2012;27(7):1150-1158; 2. Beuers U, et al. *Hepatology.* 2014;60(1):399-407; 3. Lindor KD, et al. *Hepatology.* 2009;50(1):291-308.

Guidelines Provide Recommendations for Pruritus Management[1,2]

Non-Pharmacologic Strategies (EASL Guidelines)[1]

- Use of emollients and oatmeal extract to improve dry and inflamed skin
- Use of cold water for baths or showers to provide some symptom relief of pruritus triggered or exacerbated by heat/warmth (at night)
- Psychologic intervention for addictive scratching/scratch dependence
- Searching for added allergens, especially in patients with associated hypereosinophilia or IgE-mediated allergy

Pharmacologic Strategies (AASLD, EASL, and ACG Guidelines)[1-3]

- Cholestyramine* is considered first-line pharmacologic treatment for pruritus in PBC[1-3]
  - 4 g per dose to a maximum of 16 g/day taken 1 hour before, or 4 hours after, taking UDCA and at least 4 hours before or after taking OCA[2-4]
- Guidelines include treatment recommendations for patients refractory to cholestyramine or 1L treatment with other bile acid sequestrants[1-3]

1L, first line; AASLD, American Association for the Study of Liver Diseases; IgE, immunoglobulin E.
*For patients taking bile acid binding resins and OCALIVA, take OCALIVA at least 4 hours before or 4 hours after (or at as great an interval as possible) taking a bile acid binding resin.
1. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172. 2. Lindor KD, et al. *Hepatology*. 2019;69(1):394-419. 3. Younossi ZM, et al. *Am J Gastroenterol*. 2019;114:48-63.
4. OCALIVA [package insert]. New York, NY: Intercept Pharmaceuticals, Inc; 2020.

The Absence of Symptoms at Diagnosis May Not Predict Prognosis

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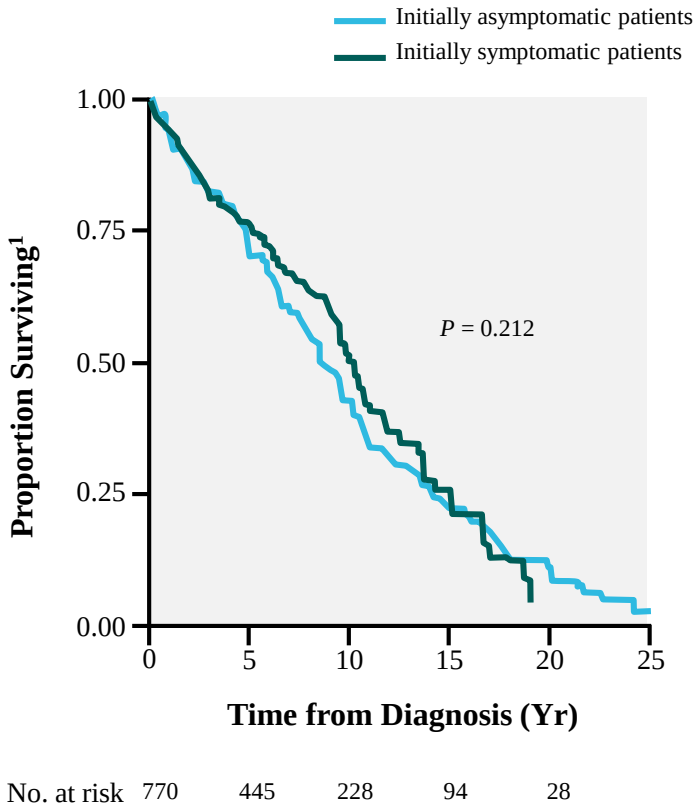
- Examination of the natural history of a 770-patient cohort in Northeast England (incident cases, 1987–1994)[1]
  - 61.8% asymptomatic at diagnosis
- Median survival time from diagnosis was not significantly different between patients who were symptomatic and asymptomatic at diagnosis[1]
- The relationship between symptom severity and disease progression can vary by patient[2]



1. Prince MI, et al. *Gut.* 2004;53:865-870; 2. Lindor KD, et al. *Hepatology*. 2009;50:291-308.

ALP and Bilirubin Are Important Markers of Disease Progression and Response to Treatment[1]

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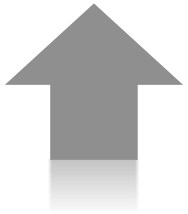

Elevated **ALP** is an early and ongoing indicator of PBC progression[1,2]

- Lowering ALP is associated with longer transplant-free survival

Bilirubin is an important predictor of survival in PBC[1]

- Elevations usually occur in later stages

ALP, alkaline phosphatase; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

1. Lammers WJ et al. *Gastroenterology*. 2014;147(6):1338-1349. 2. Lindor KD et al. *Hepatology*. 2019;69(1):394-419.

As ALP and Bilirubin Increase, So Does the Risk of Transplant or Death[1]

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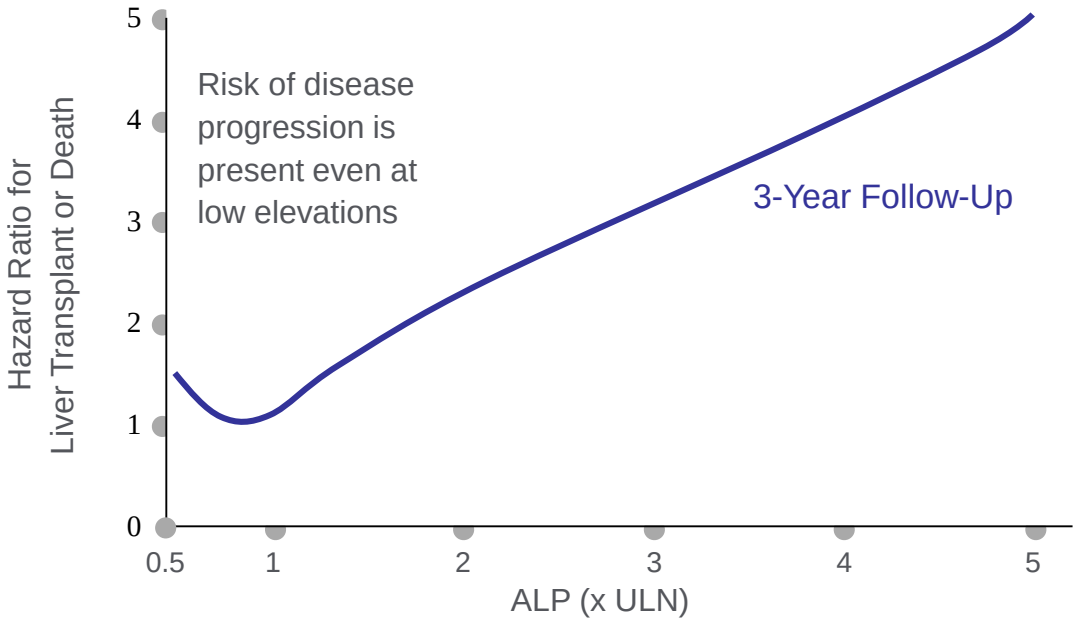
Even modest ALP elevations above normal increase risk[1]



- ALP >1x ULN is associated with **2x greater** risk for transplant or death vs normal levels[1*†]
- Bilirubin levels >1x ULN are associated with **5x greater risk** for transplant or death vs normal levels[1*†]
- 15-year transplant-free survival rate is 79% when bilirubin is normal and alkaline phosphatase is ≤2x ULN[1]

*Compared to patients who were ≤1x ULN at any timepoint during the study period.[1]
†Based on an analysis of nearly 5,000 patients with PBC (85% treated with UDCA).[1]

1. Lammers WJ, et al. *Gastroenterology*. 2014;147(6):1338-1349. 2. OCALIVA [package insert]. New York, NY: Intercept Pharmaceuticals, Inc; 2020.

Treatment Options

First Line: Ursodeoxycholic Acid/Ursodiol (UDCA)

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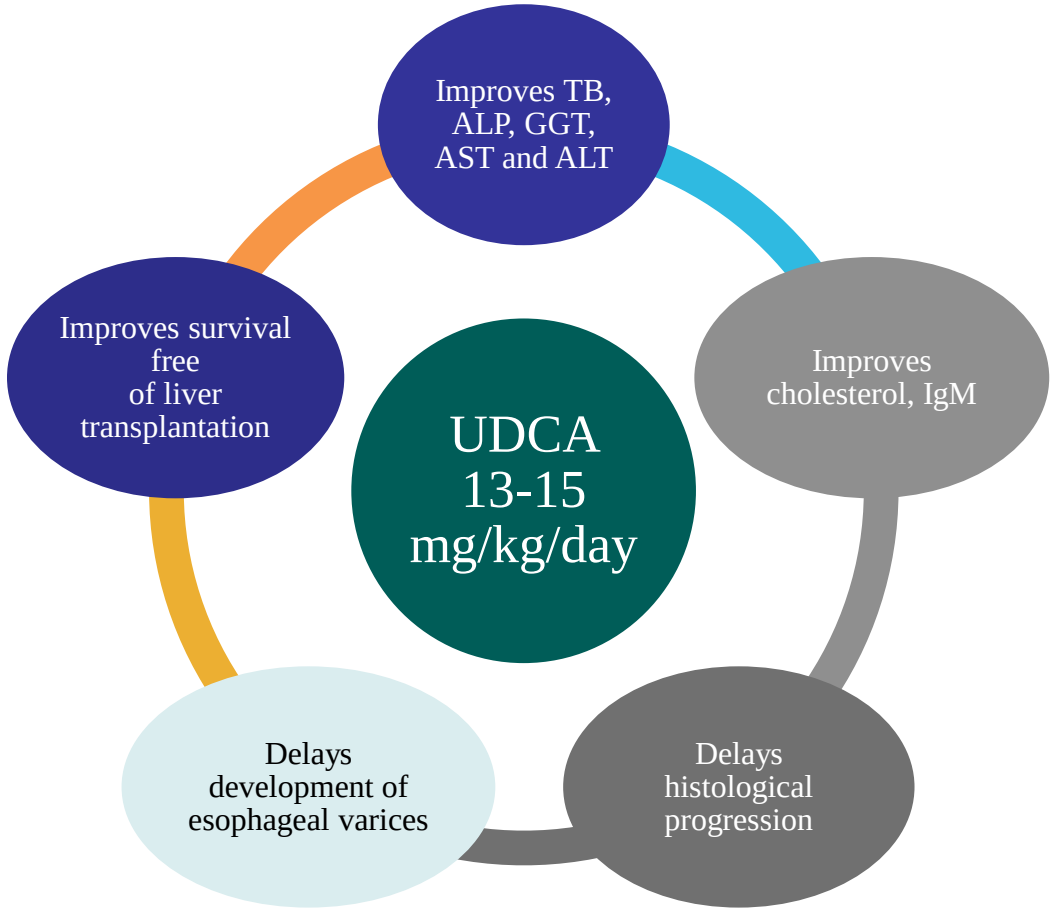
- Orally administered, naturally occurring, hydrophilic secondary bile acid
- Dose: 13-15 mg/kg/day
- Improvement in liver tests may be seen within a few weeks and 90% of the improvement usually occurs within 6-9 months
- After 1 year of treatment, the number of patients with biochemical response according to Paris Criteria was 66% and according to Barcelona Criteria was 62% (Kuiper et al)
  - Up to 40% treated with UDCA have a suboptimal response

Abbreviation: UDSA, ursodeoxycholic acid

Kuiper, et al. *Gastroenterology* 2009; 136(4): 1281-7.

Therapeutic Effects: UDCA

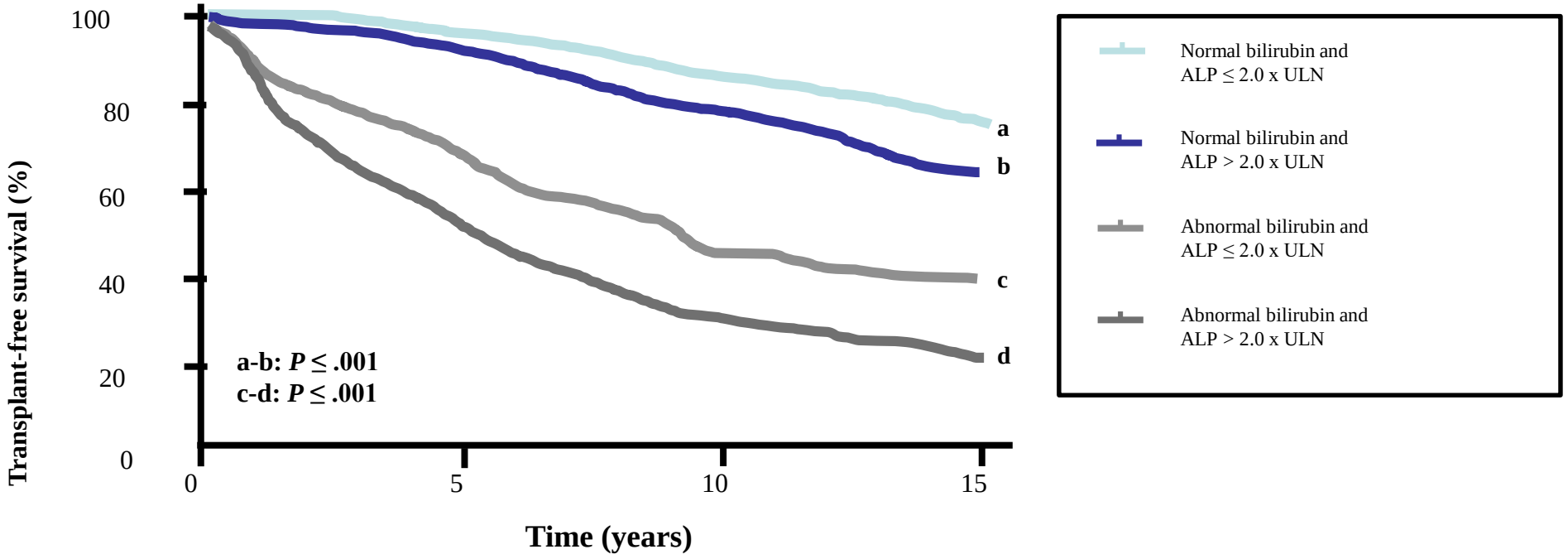


Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; IgM, immunoglobulin M; TB, total bilirubin; UDCA, ursodeoxycholic acid.

Levy C and Lindor KD. In: *Zakim and Boyer's Hepatology: A Textbook of Liver Disease.* Elsevier Inc;2011:738-753.

Graphic courtesy of Dr. Cynthia Levy.

UDCA: Transplant-free Survival Based on Bilirubin and Alkaline Phosphatase Levels at 1 Year Follow-up



a	2112	1482	887	504
b	681	489	337	228
c	271	193	153	137
d	400	345	302	283

Lammers, et al. *Gastroenterology*. 2014; 147:1338-1349.

GLOBE Score to Predict Outcomes of PBC Patients Receiving UDCA

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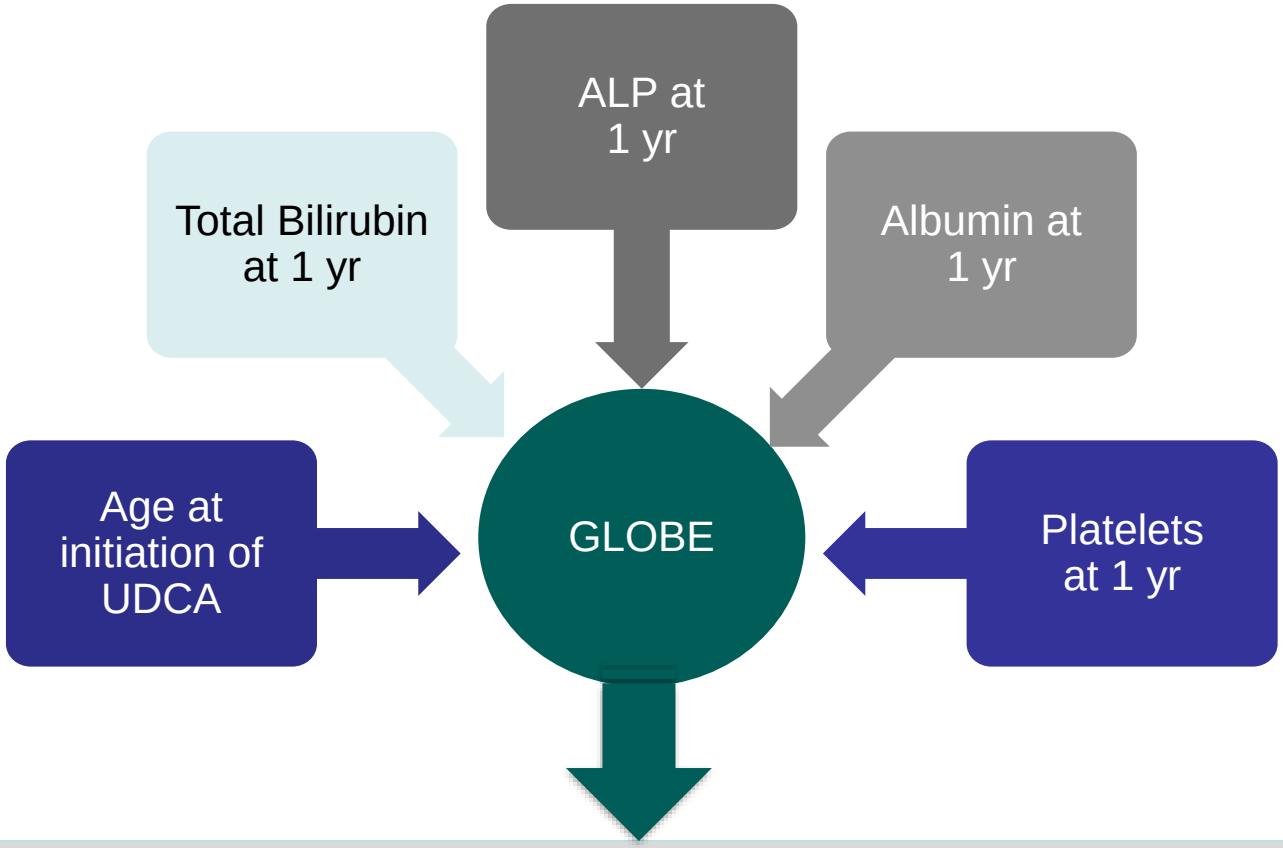
- International collaborative meta-analysis
- >4000 patients with PBC from 15 centers in 8 European and North American countries
  - On UDCA for at least 1 year
  - Median follow-up 7.8 years
- Risk score developed and validated to predict transplant-free survival

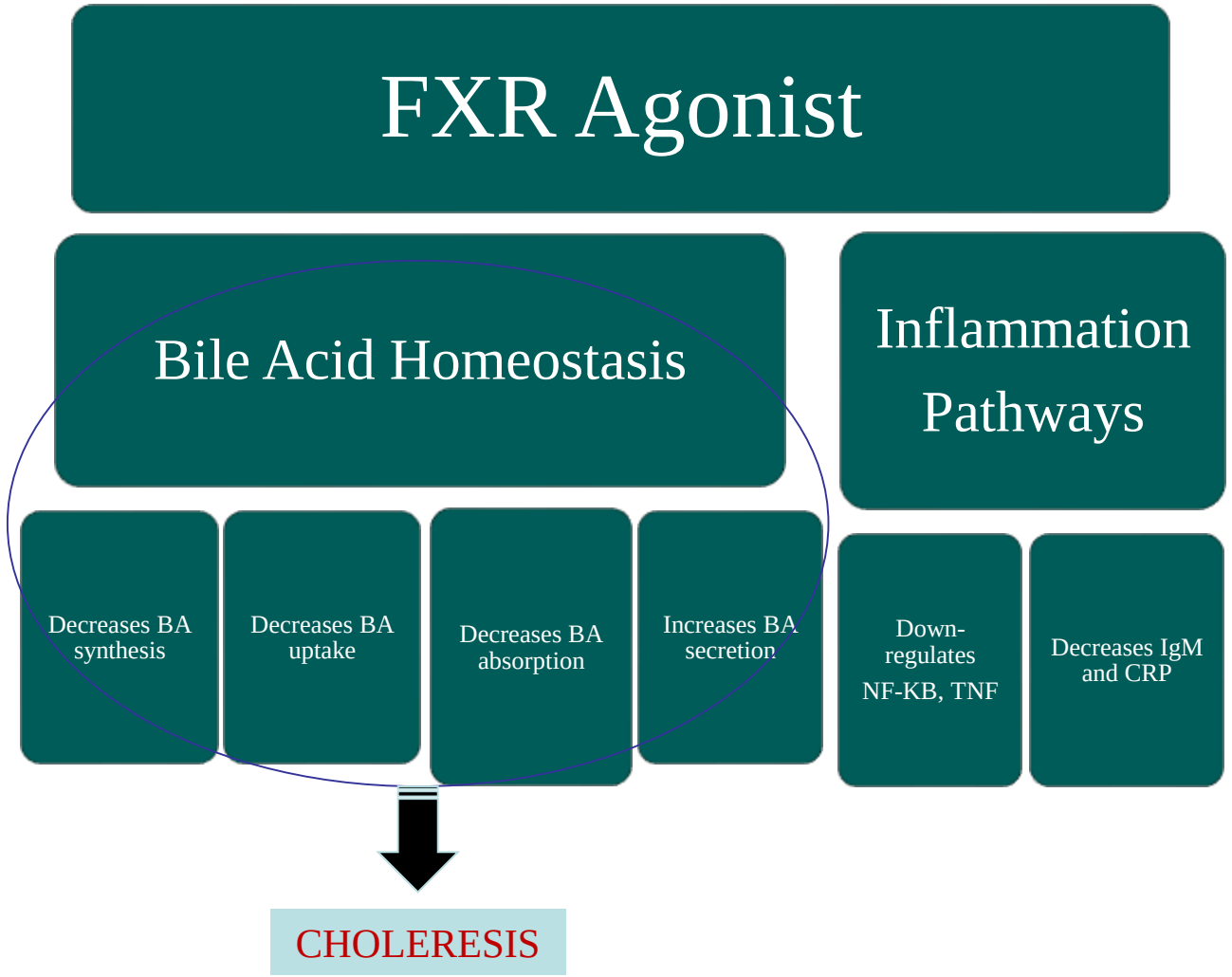
Lammers WJ, et al. *Gastroenterology.* 2015;149:1804-1812.

GLOBE Score: Online Calculation



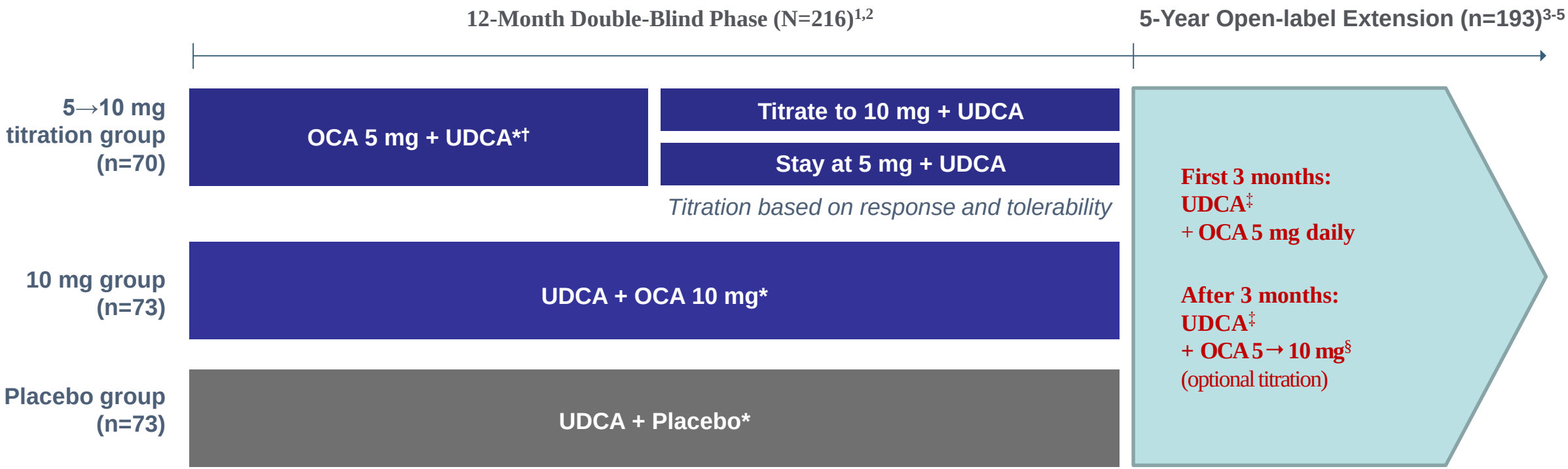
Predicts 3-, 5- and 10-year survival compared to age-matched population

Second Line: Obeticholic Acid (OCA)



Abbreviations: BA, bile acid; NF-KB, nuclear factor kappa beta; TNF, tumor necrosis factor; CRP, C-reactive protein

POISE Was a 1-year, Double-Blind, Placebo-Controlled, Randomized Phase 3



Primary composite endpoint: ✓ ALP <1.67x ULN ✓ ALP decrease of ≥15% ✓ Total bilirubin ≤ULN

Study limitations: In this open-label extension, no placebo or other comparators were included and therefore no clinical conclusions should be made.[3]

*16 patients (7%) who were intolerant did not receive concomitant UDCA: 6 patients (8%) in the OCALIVA 10 mg arm, 5 patients (7%) in the OCALIVA 5→10 mg titration arm, and 5 patients (7%) in the placebo arm.
†In the 5→10 mg titration group, 36 patients stayed at 5 mg and 33 were titrated to 10 mg after 6 months.
‡Among patients who entered the open-label extension, 13 (7%) were intolerant and did not receive concomitant UDCA during double-blind or open-label treatment with OCALIVA.
§Protocol initially allowed doses up to 25 mg, but was later amended to a maximum daily dose of OCALIVA 10 mg to ensure dosing per the approved label.

1. OCALIVA [package insert]. New York, NY: Intercept Pharmaceuticals, Inc; 2020. 2. Data on file: GL-PB-MED-00067. 3. Data on file: INT-PB-MED-00009. 4. Trauner M, et al. *Lancet Gastroenterol Hepatol*. 2019;4(6):445-453.

Primary Objective and Patient Population

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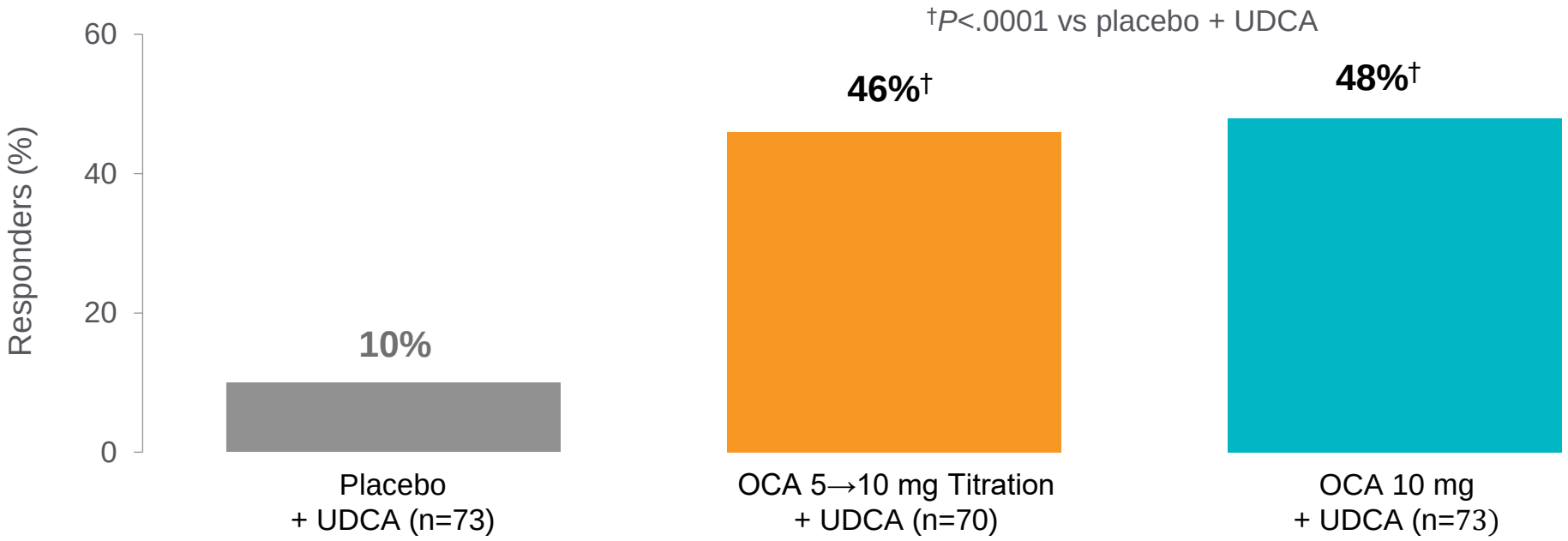
- To assess the proportion of patients achieving ALP <1.67 x ULN and a decrease of ≥15% and total bilirubin ≤ULN
- Inclusion
  - PBC diagnosis (EASL and AASLD guidelines)
  - ALP ≥1.67 x ULN and/or total bilirubin >ULN to <2 x ULN
  - Stable UDCA or unable to tolerate UDCA
- Exclusion
  - Concomitant liver diseases, decompensation, severe pruritus requiring treatment
- Randomization Strata
  - UDCA (yes/no)
  - Paris 1: ALP >3x ULN and/or AST >2x ULN and/or total bilirubin >ULN

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

In the Pivotal Phase 3 POISE Trial, Nearly 5x as Many Patients Taking OCA +

Patients Achieving the Primary Composite Endpoint at Month 12*



Patients taking OCA were **2.5x more likely** to achieve a reduction in ALP ≥15%

- 77% of patients taking OCA + UDCA vs 29% on UDCA alone (*P*<.001)

*16 patients (7%) who were intolerant did not receive concomitant UDCA.

OCALIVA [package insert]. New York, NY: Intercept Pharmaceuticals, Inc; 2020.

Alkaline Phosphatase in the Double-blind and Open-label Phases

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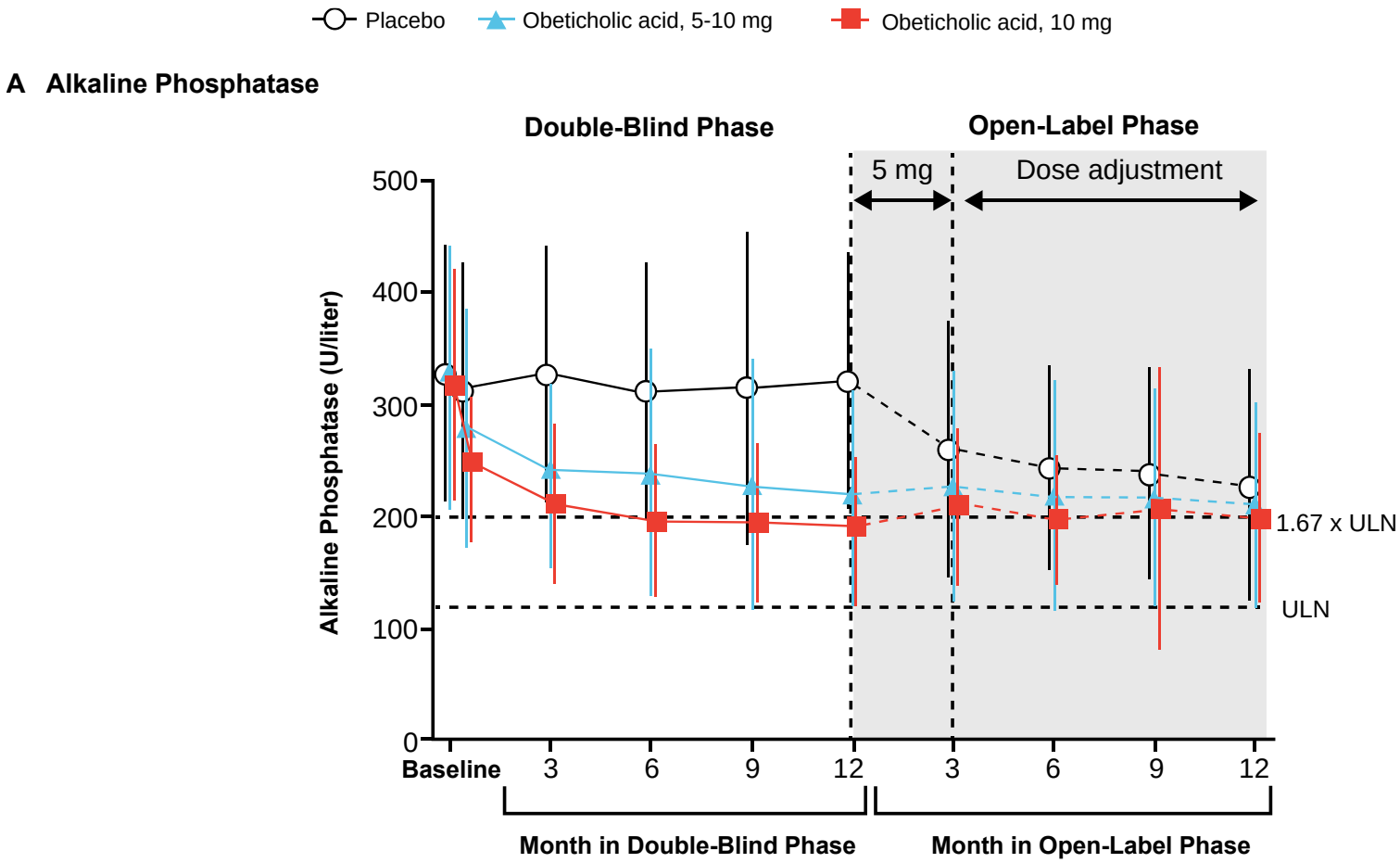

No. of Patients									
Placebo	73	69	71	69	70	64	60	59	59
Obeticholic acid, 5-10 mg	70	69	69	66	64	63	62	62	60
Obeticholic acid, 10 mg	73	66	64	64	62	64	59	61	59

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

Total Bilirubin During the Double-blind and Open-label Phases

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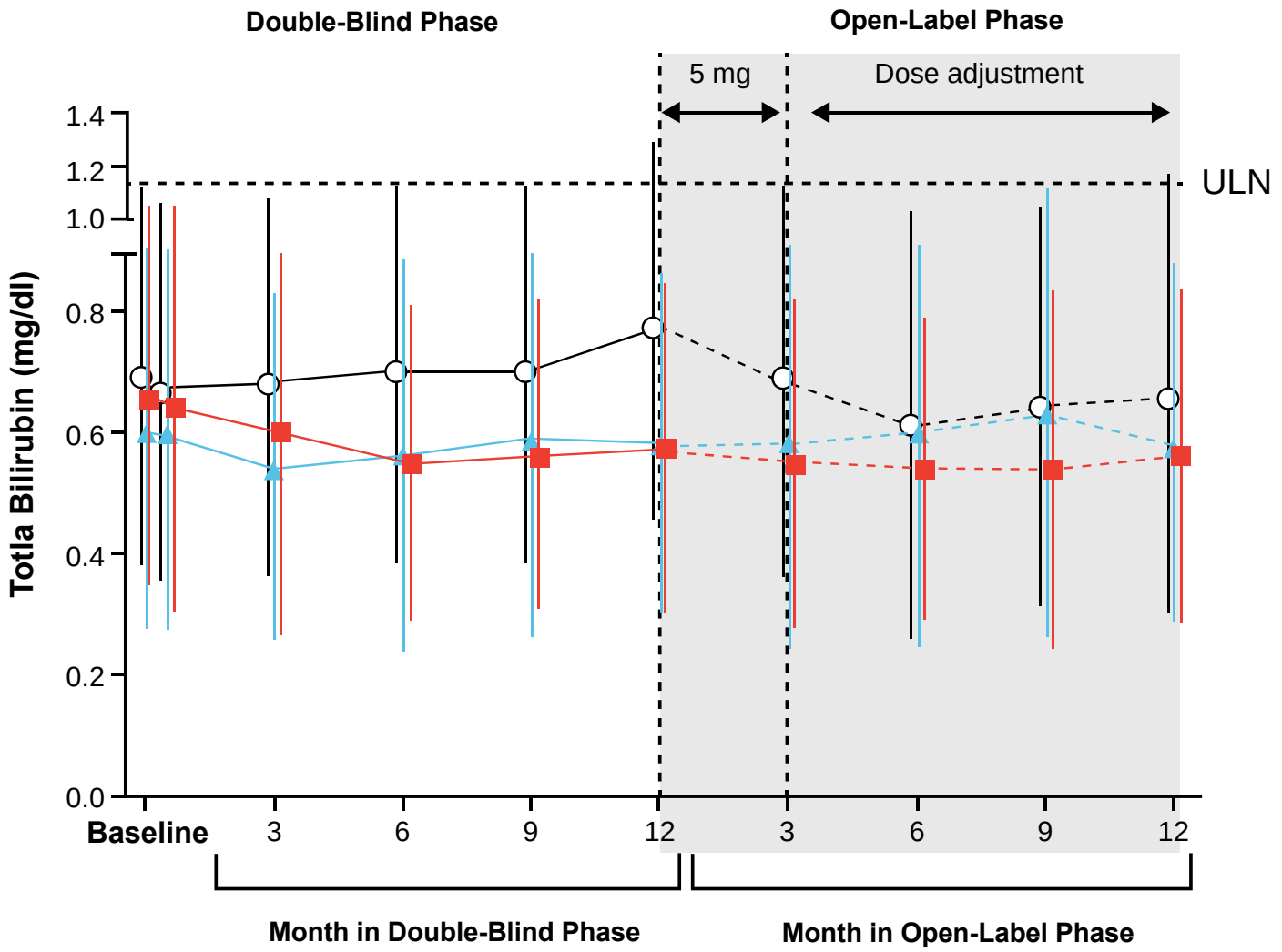
B Total Bilirubin

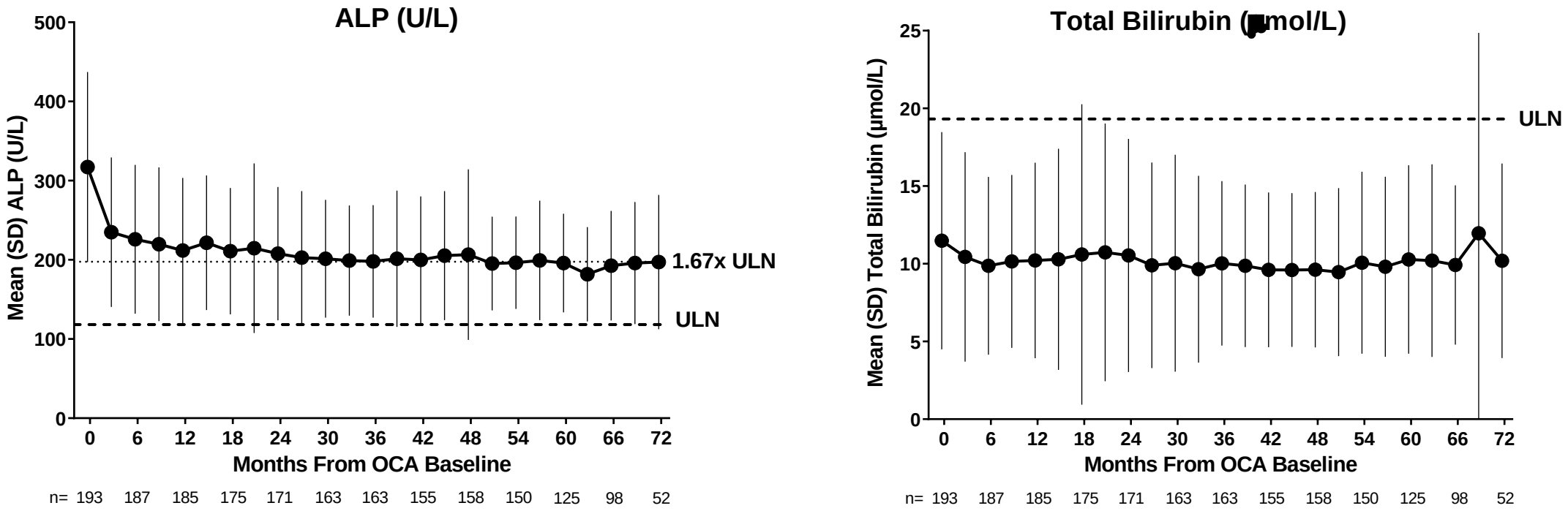


Nevens F, et al. *N Engl J Med.* 2016;375:631-643.

Sustained Reductions in ALP and Bilirubin With OCA Treatment (5 Years)

POISE was a pivotal phase-3 12-month randomised controlled trial of OCA in patients with PBC followed by a five year open label extension (LTSE). The primary endpoint was achievement of ALP <1.67 xULN, ALP reduction ≥15% from baseline, and total bilirubin ≤ULN, achieved by 46% of patients in the 5–10-mg group vs. 10% in the placebo group (P<0.001)[1]

Results from the POISE LTSE[2]



ALP = alkaline phosphatase; LTSE = long-term safety extension; OCA = obeticholic acid; SD = standard deviation; ULN = upper limit of normal.

1. Nevens F et al. *N Engl J Med*. 2016;375(7):631–643. 2. Nevens F et al. *Presented at AASLD*. 2019. Boston, MA (Oral LO6).

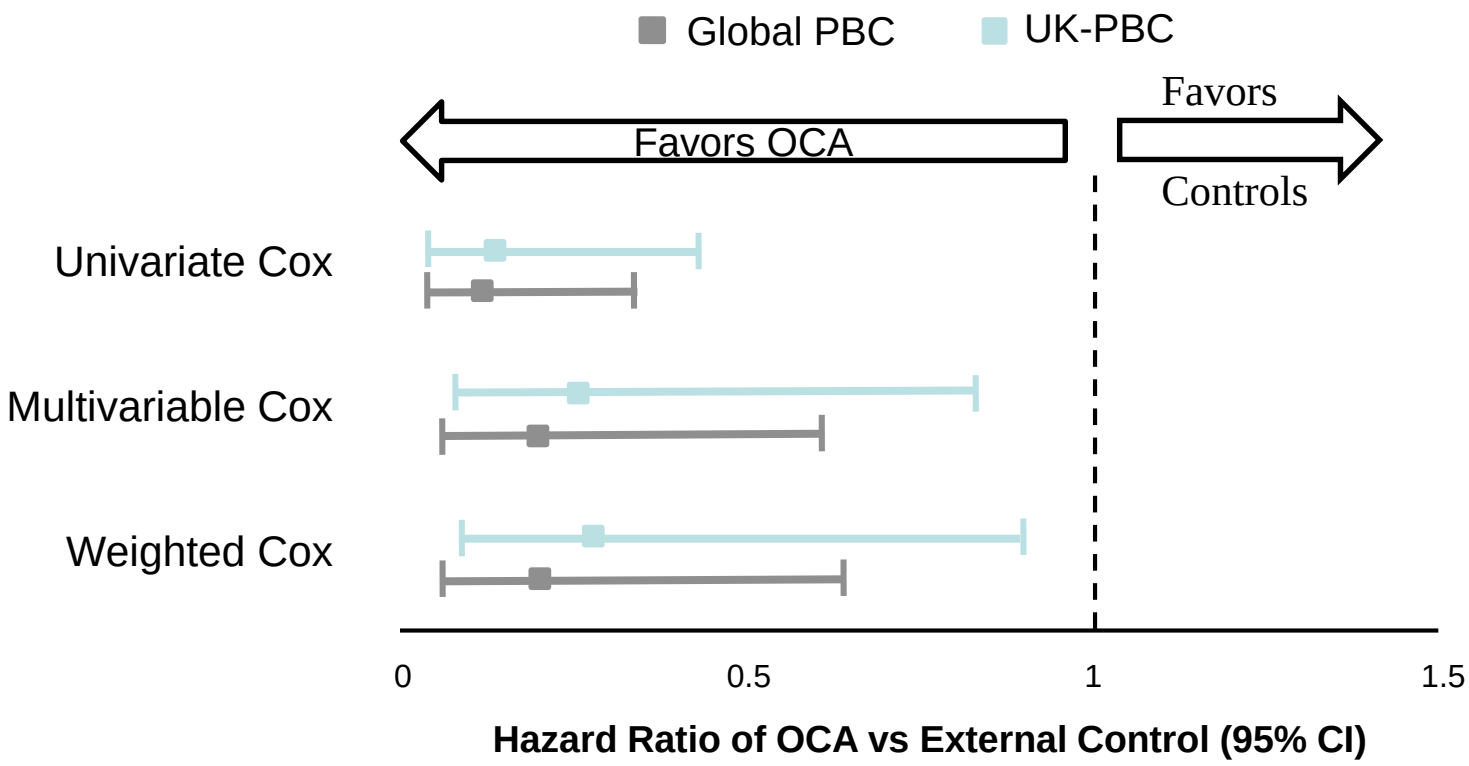
May 2021 Update to OCA Licenced Dosing

RUTGERS

Without cirrhosis	5mg once daily → 10 mg once daily Titration at 3 months
Compensated cirrhosis without CSPH	5mg once daily → 10 mg once daily Titration at 3 months
Compensated cirrhosis with CSPH	**Contraindicated**
Decompensated cirrhosis	**Contraindicated**

Titration is dependent of patients not achieving adequate biochemical response and not experiencing tolerability issues at the lower dose
CSPH = clinically significant portal hypertension; OCA = obeticholic acid
Ocaliva [Full Prescribing Information]. New York, NY: *Intercept Pharmaceuticals*, Inc.; 2021

OCA Associated With Lower Risk for Liver Transplant or Death



	HR (95%CI)	P value
Univariate Cox	0.14 (0.04-0.42)	<0.001
	0.12 (0.04-0.34)	<0.001
Multivariable Cox	0.24 (0.08-0.76)	0.015
	0.20 (0.06-0.61)	0.005
Weighted Cox	0.28 (0.09-0.91)	0.034
	0.20 (0.06-0.64)	0.007

Long-term Management of Patients with PBC

RUTGERS

- Liver tests every 3-6 months ➔ *consider OCA if non response to UDCA*
- Thyroid status (TSH) annually
- DEXA at diagnosis and every 2-4 years
- Monitor for associated autoimmune conditions
- In the presence of severe cholestasis ➔assess levels of vitamins A and D. May need to administer Vit K prior to procedures.
- Upper endoscopy every 1-3 years if cirrhotic or Mayo risk score >4.1
- Ultrasound ± AFP every 6 months in patients with known or suspected cirrhosis

Abbreviations: TSH, thyroid stimulating hormone; DEXA, dual energy X-ray absorptiometry; AFP, alpha fetoprotein

Lindor K, et al. *Hepatology* 2009;50:291-308; EASL clinical guidelines. *J Hepatology* 2009; Japanese guidelines – Hepatology Research 2014.

Summary

RUTGERS

- PBC is most common in middle-aged women.
- Taking a good history is essential.
- Diagnosis can typically be made based on persistent cholestatic liver profile and AMA positivity after other common liver diseases have been excluded.
- Manage patient with UDCA and/or OCA based on response.