PBC: Definition, natural history and current therapeutic interventions

Gideon Hirschfield

EMA stakeholder interaction
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TORONTO CENTRE FOR LIVER DISEASE

@AutoImmuneLiver
gideon.hirschfield@uhn.ca

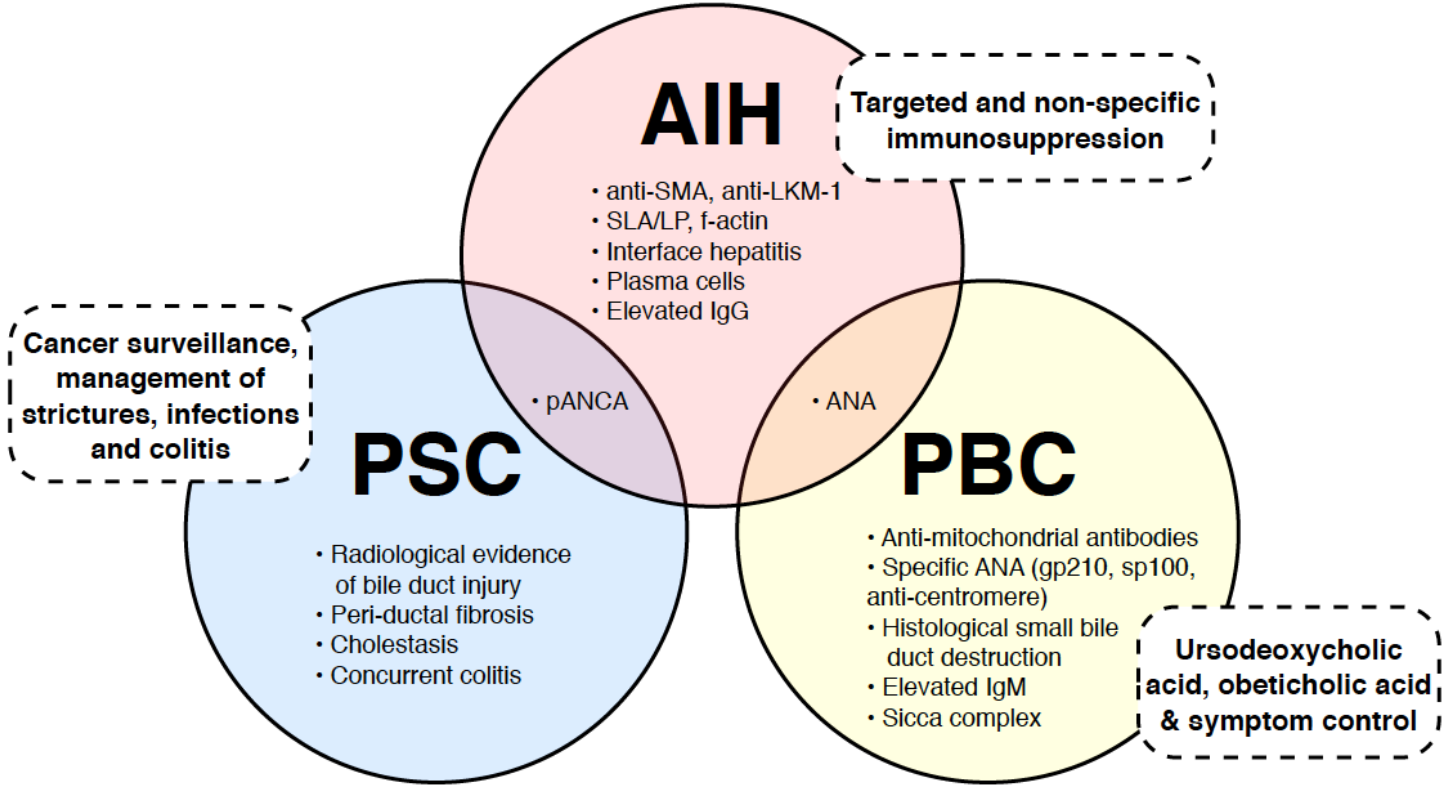
Medicine
UNIVERSITY OF TORONTO

Disclosure of Conflict of Interest

I have a relationship with a for-profit and/or a not-for-profit organization to disclose:

Nature of relationship(s)	Name of for-profit or not-for-profit organization(s)	Description of relationship(s)
Any direct financial payments including receipt of honoraria	Intercept, Cymabay, GSK, Novartis, CiVi, BiomX, Finch	Scientific consultancy in the development of new drugs for patients with PBC,PSC, NASH
Membership on advisory boards or speakers' bureaus	Intercept, Falk	I have presented my own slides at CME meetings with Industry sponsorship
Funded grants or clinical trials	Gilead	Educational grant to support operating costs of UK-PSC, a national observational study
Patents on a drug, product or device	N/A	N/A
All other investments or relationships that could be seen by a reasonable, well-informed participant as having the potential to influence the content of the educational activity	Intercept, Gilead, Novartis, GSK, Falk, NGM Bio, Cymabay	I have been the local study investigator of early stage industry sponsored clinical trials in patients with PBC and PSC.

The three autoimmune liver diseases

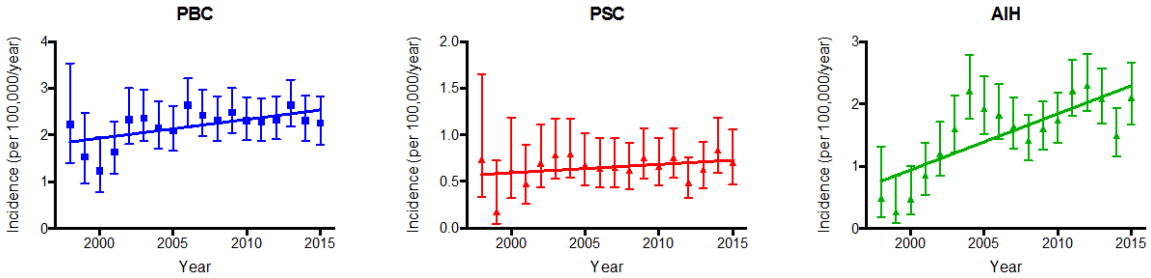


Webb and Hirschfield

How many new patients get AILD each year?

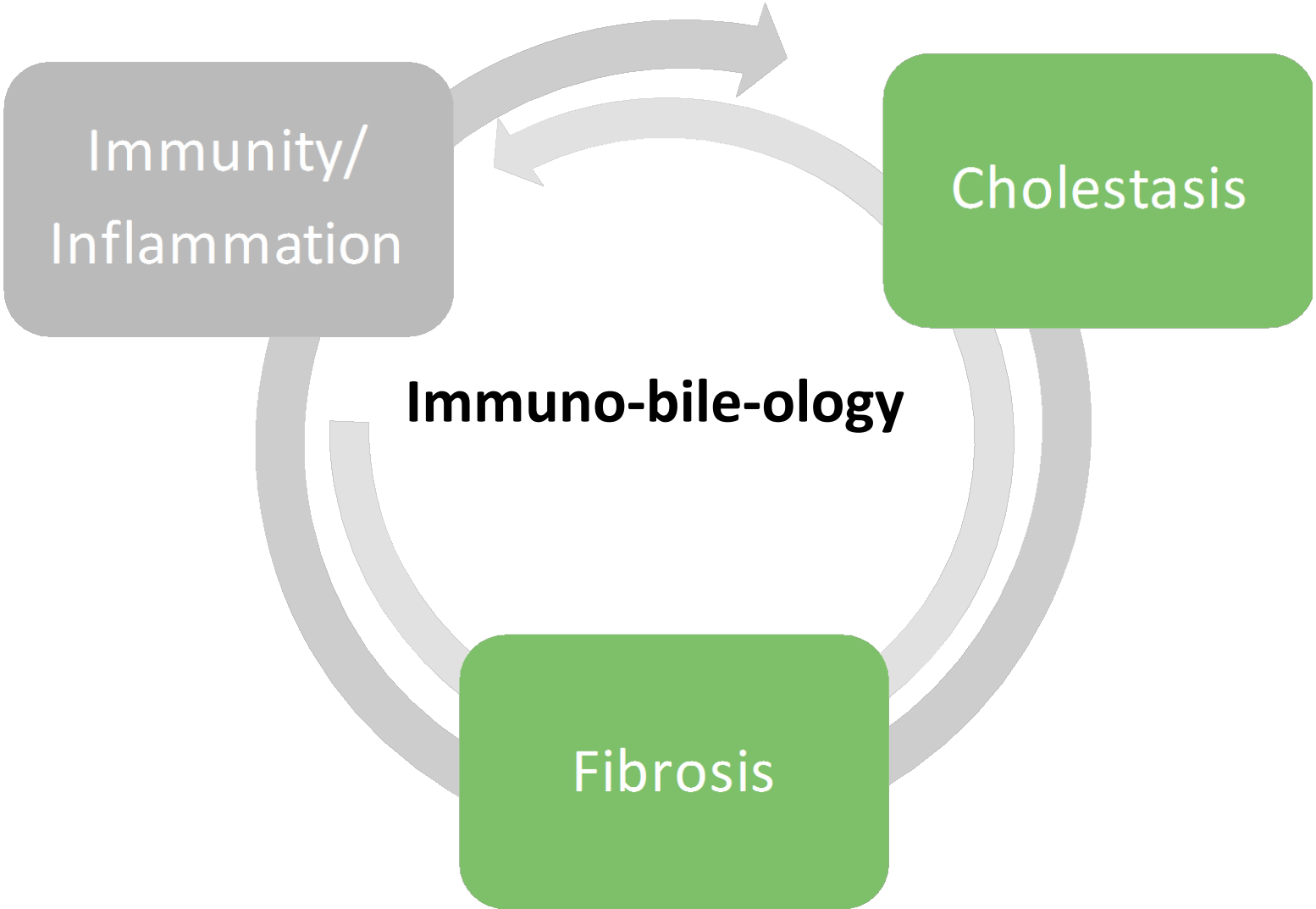
- **PBC –** 2.3 (2.2-2.4) *cf.* 0.3-5.8
- **PSC –** 0.7 (0.6-0.7) *cf.* 0-1.3
- **AIH** – 1.7 (1.6-1.8) *cf.* 1.68 (1.60 to 1.76) Denmark
  - cases/100,000/year from 1998-2015

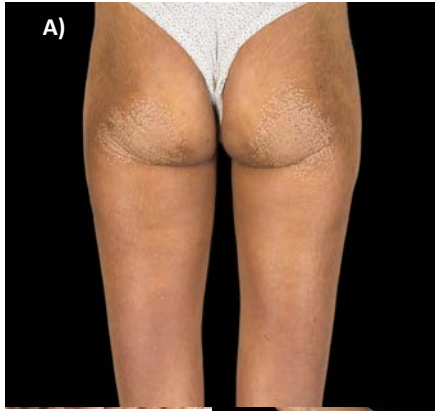
- *cf.* **Multiple Sclerosis –** 5.5 (5.1-5.9) and **T2DM –** 396 (394-398)

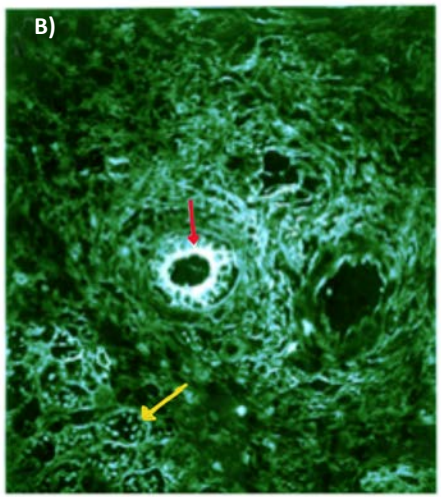


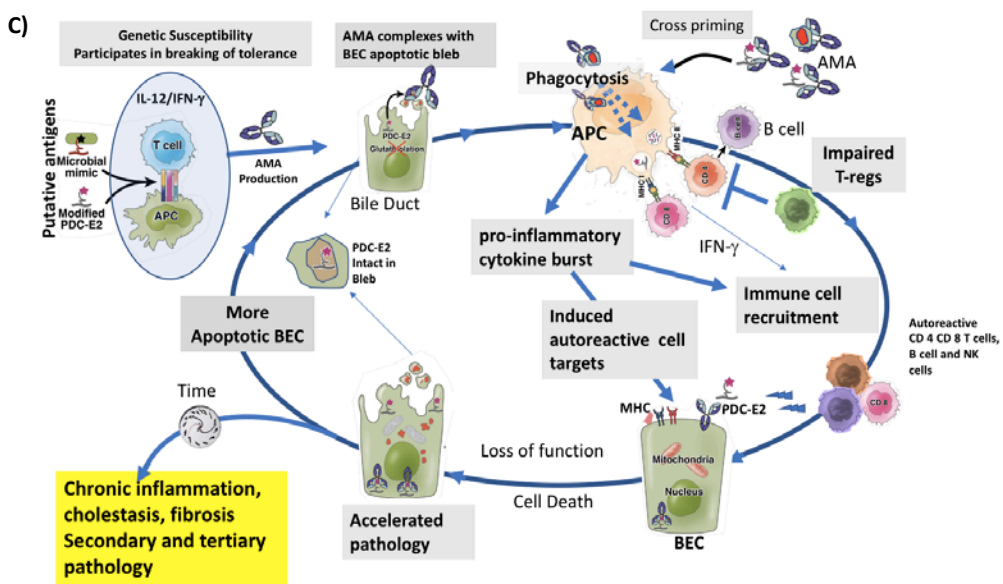
Boonstra, K., et al/.(2012). *JHep*, 56(5), 1181–1188; Alonso, A., et al., (2007) *J. Neurology*, 254(12), 1736–1741; Sharma, M., et al., (2017) BMJ Open, 6(1), e010210.

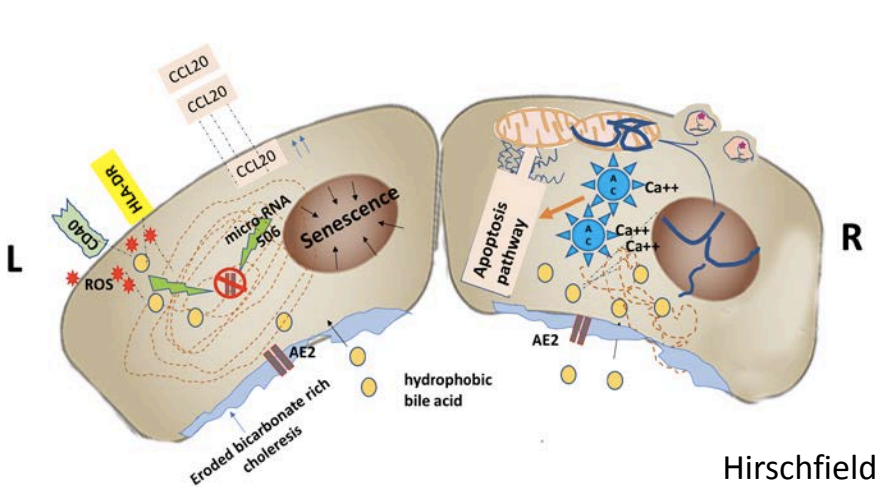
Webb et al. In Preparation


Immunity/
Inflammation
Cholestasis
Immuno-bile-ology
Fibrosis









Hirschfield and Gershwin 2018

How do you diagnose PBC?

PBC is diagnosed when:

i) There is no extrahepatic biliary obstruction;

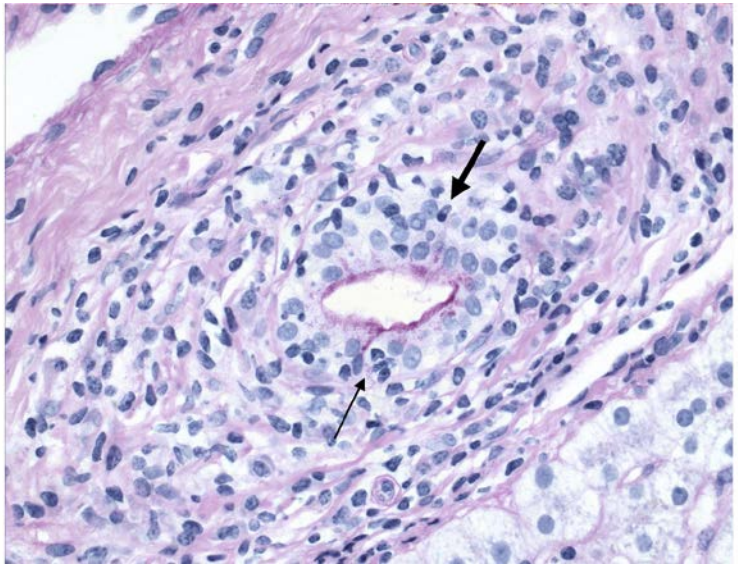
ii) The clinical context doesn't suggest systemic or infiltrative disease and

iii) The patient has at least two of the following:

a) persistent rise in ALP e.g. x 1.5 normal;

b) presence of anti-mitochondrial antibodies (AMA) at a titre of 1:40 or higher (or diagnostic anti-nuclear antibody reactivity by immunofluorescence);

c) A liver biopsy consistent with PBC.

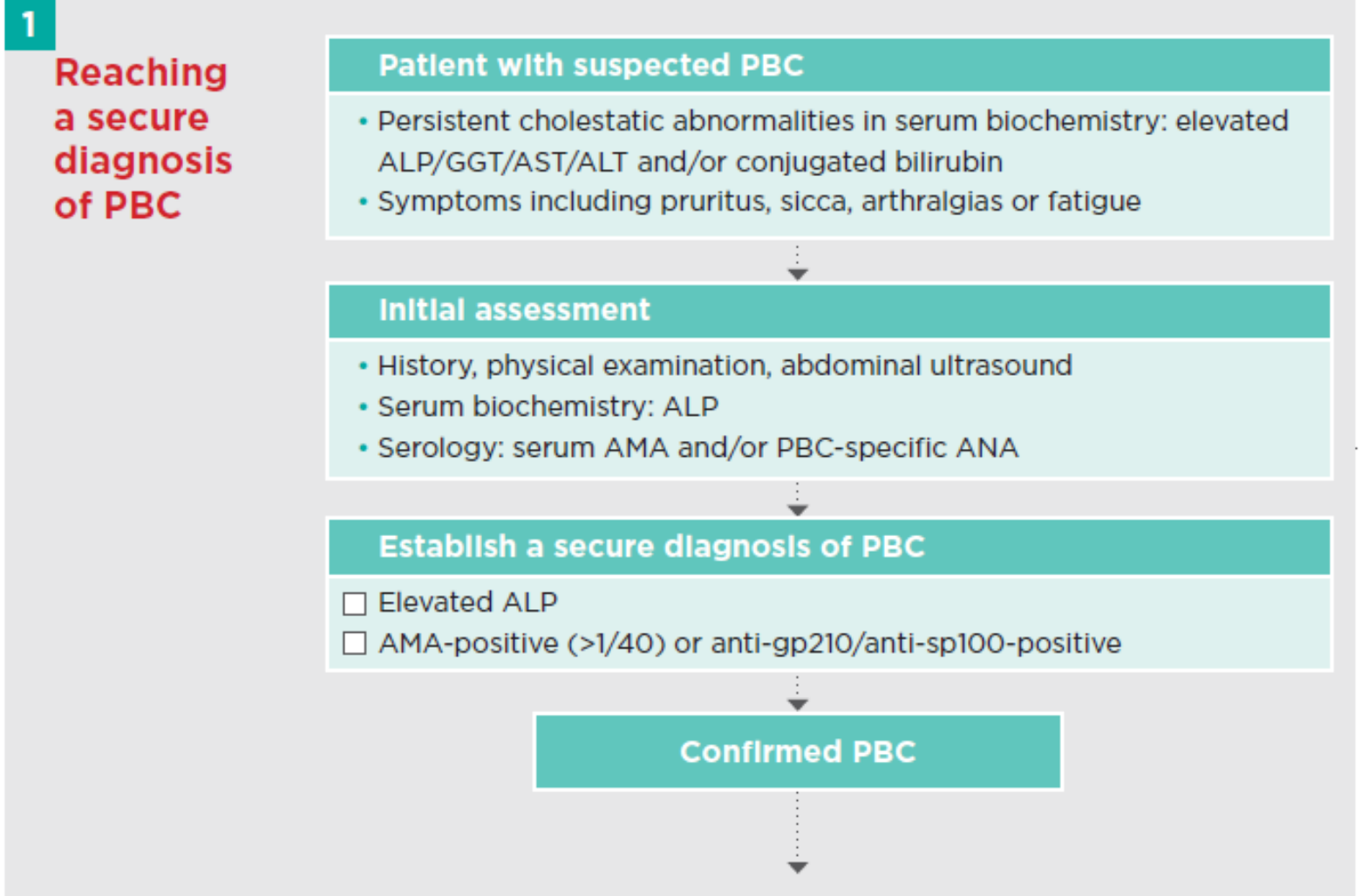


Take home message

1 in 1000 women over the age of 40 live with PBC and for most diagnosis can confidently be made based on cholestatic blood tests and the presence of anti-mitochondrial antibodies

Clinical Utility

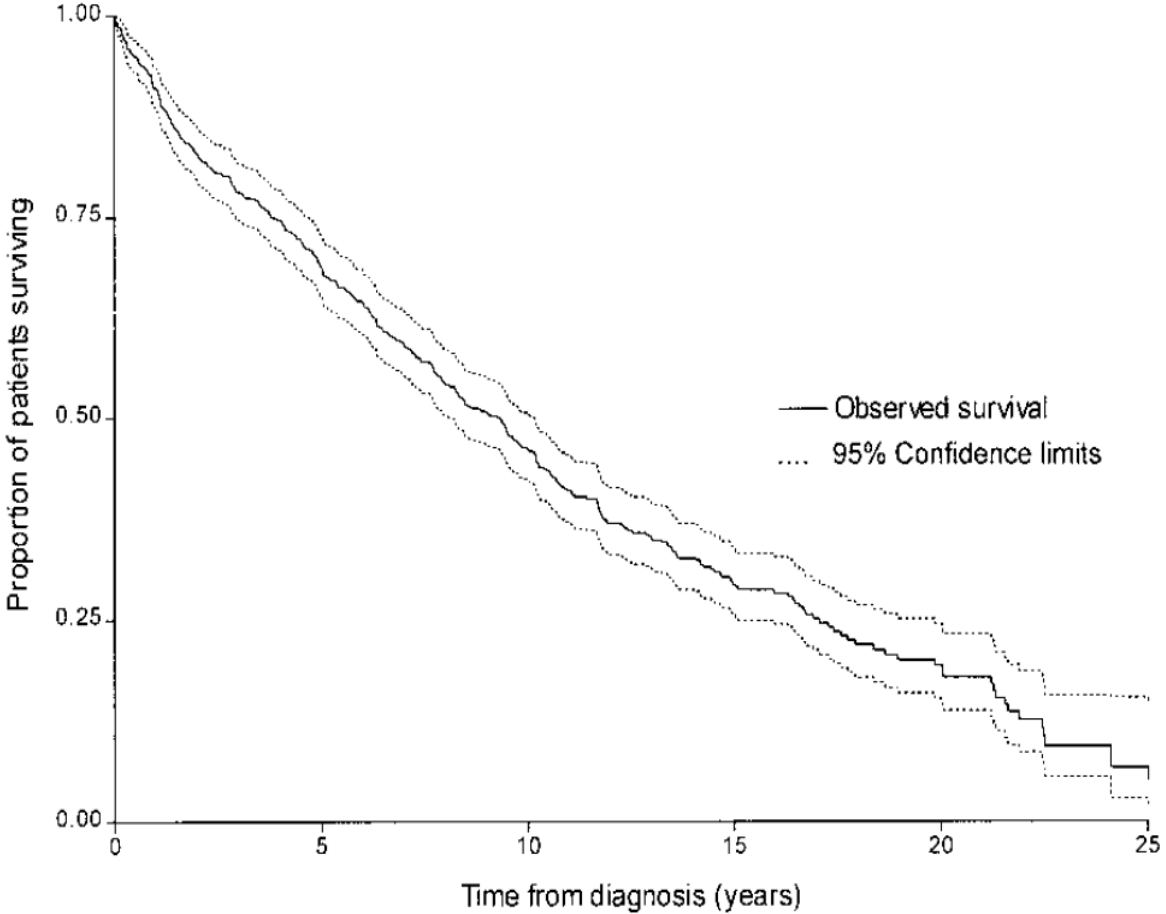
s can non-invasive liver fibrosis evaluation by elastrography



AASLD 2018- International consensus Care Pathway for the diagnosis and management of Primary Biliary Cholangitis

Gideon M Hirschfield, Marco Carbone, Helena Cortez-Pinto, Guilherme Macedo, Victor de Lédinghen, Olivier Chazouilleres, Femi Adekunle

Newcastle study: Prince et al. 2002



Median Survival

9.3 years

n = 770; 1987-1994

Mean age= 61 years

Median FU=7.4 years

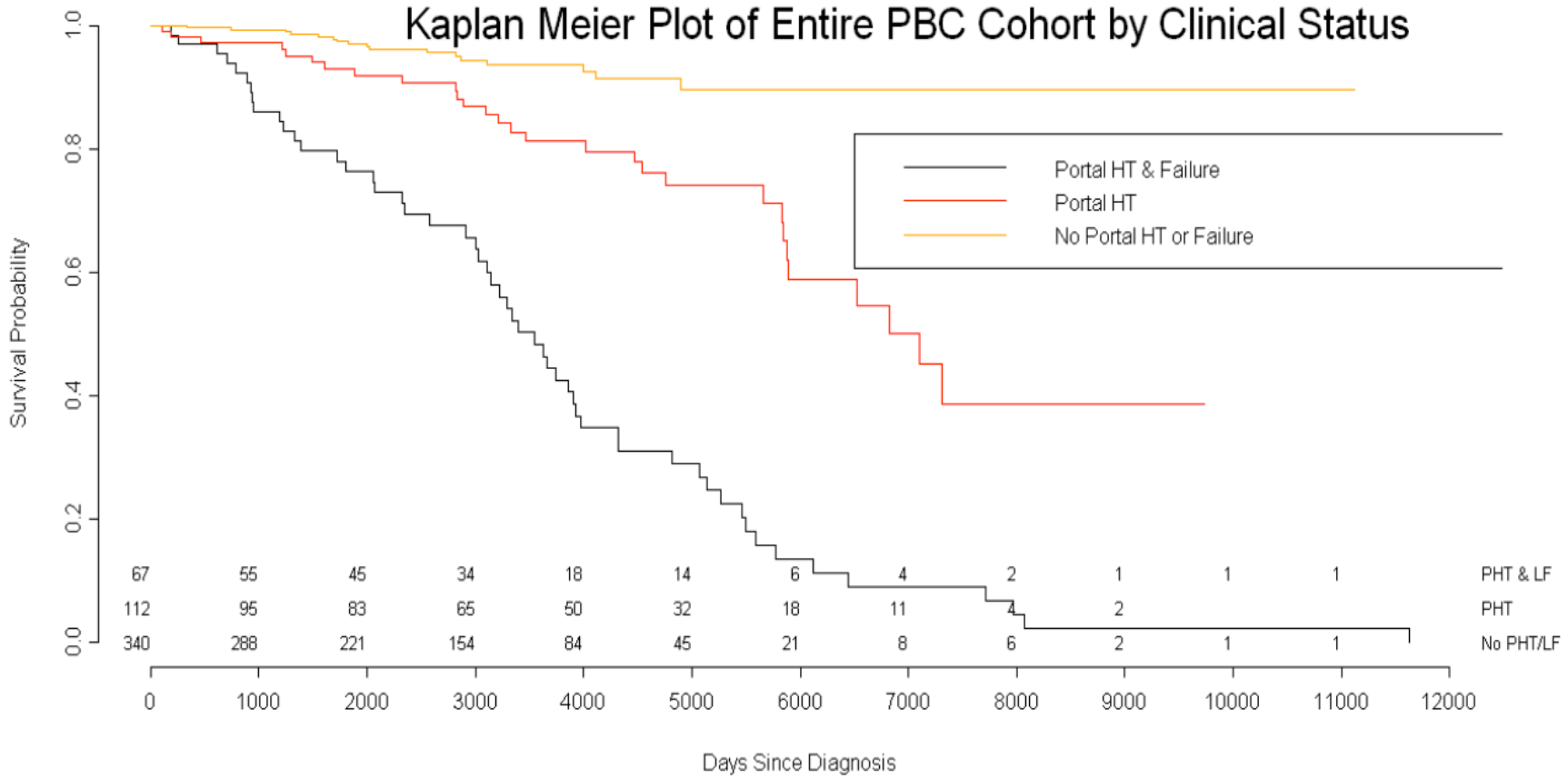
Deaths = 417 (54%)

Prince et al. Gastro 2002

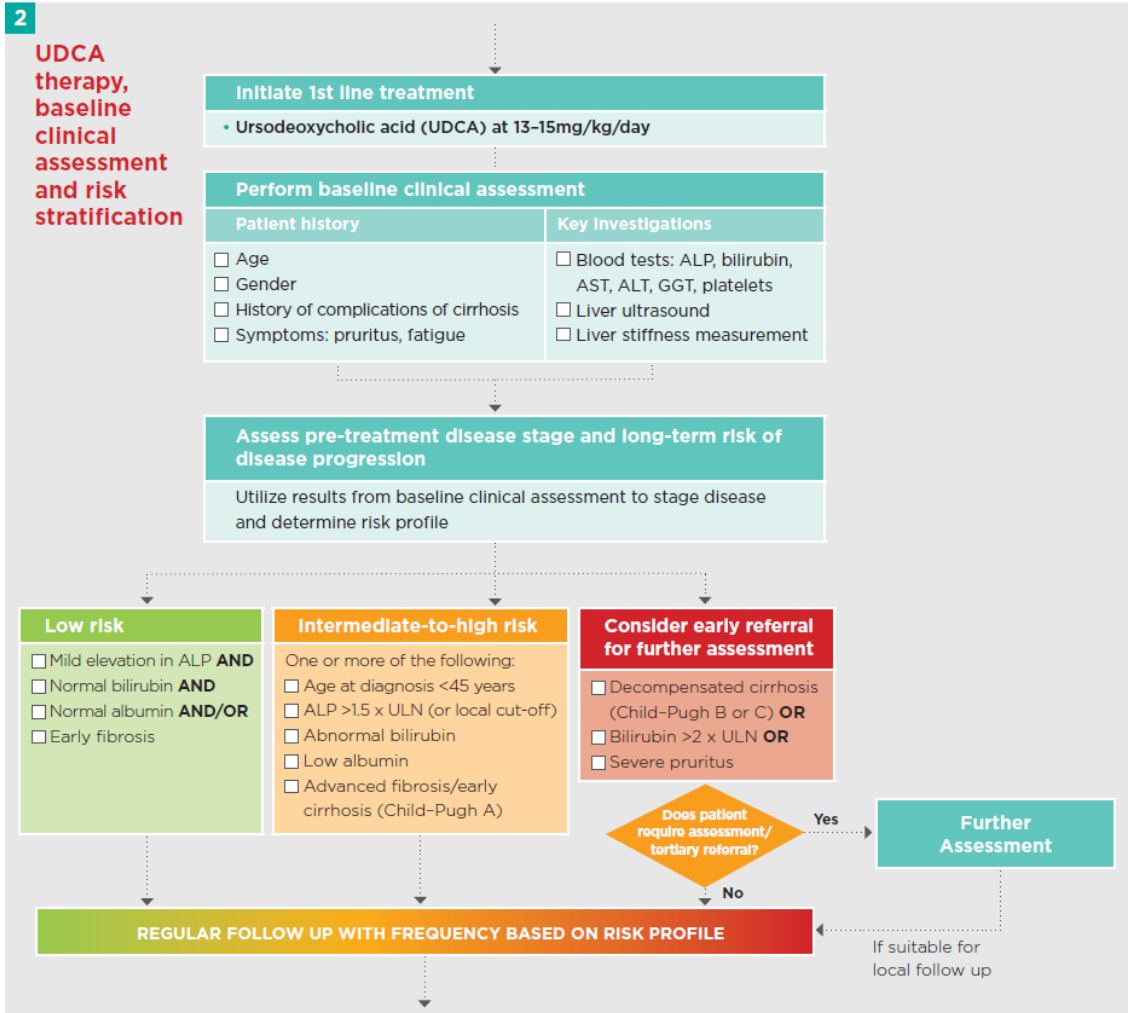
‘Natural History’

- The average survival of untreated PBC patients is approximately 9 – 10 years from presentation, with ~25 % developing liver failure during this time
  - Gastroenterology. 2002;123:1044–1051
- In the absence of effective therapy, the median time to develop extensive liver fibrosis is ~2 years, with a probability of remaining in early stage disease of 29% over 4 years
  - Gastroenterology. 1980;78:236–246; Hepatology. 1996;23:52–56; Hepatology. 2000;32:1196–1199.
- Early studies from the Mayo Clinic indicate that the rates of progression to cirrhosis after a follow-up period of 6 years were ~49% in a group of patients receiving pencillamine or placebo (n = 51), which was significantly greater than the rate observed in patients receiving UDCA (13% of n = 16) ($p = 0.009$)
  - Hepatology. 1999;29:644–647
- Moreover, the Corpechot study from 2000, indicate a 5-fold lower annual progression rate from early stage liver disease to extensive fibrosis / cirrhosis in patients taking UDCA (7% vs. 34% under placebo, $p < 0.002$), with a 4-year probability of remaining in early stage disease of 76% (vs. 29% in the placebo-treated arm).
  - Hepatology. 2000;32:1196–1199

PBC Disease Course



Kumagi and Hirschfield, TCLD, 2011



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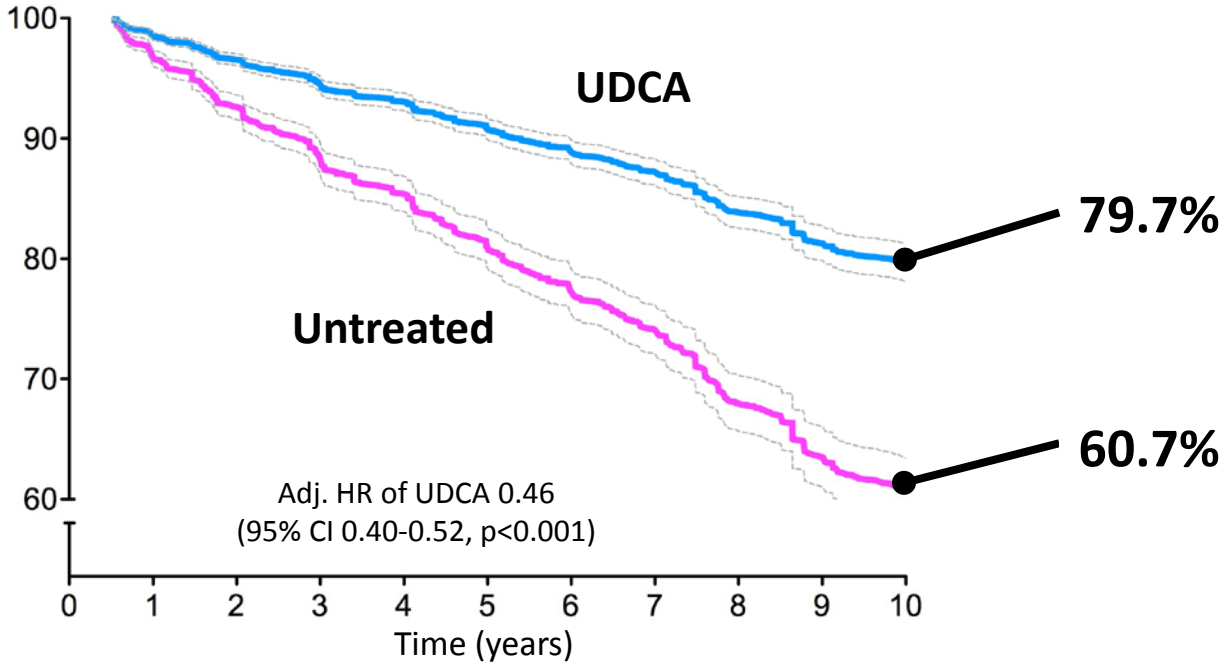
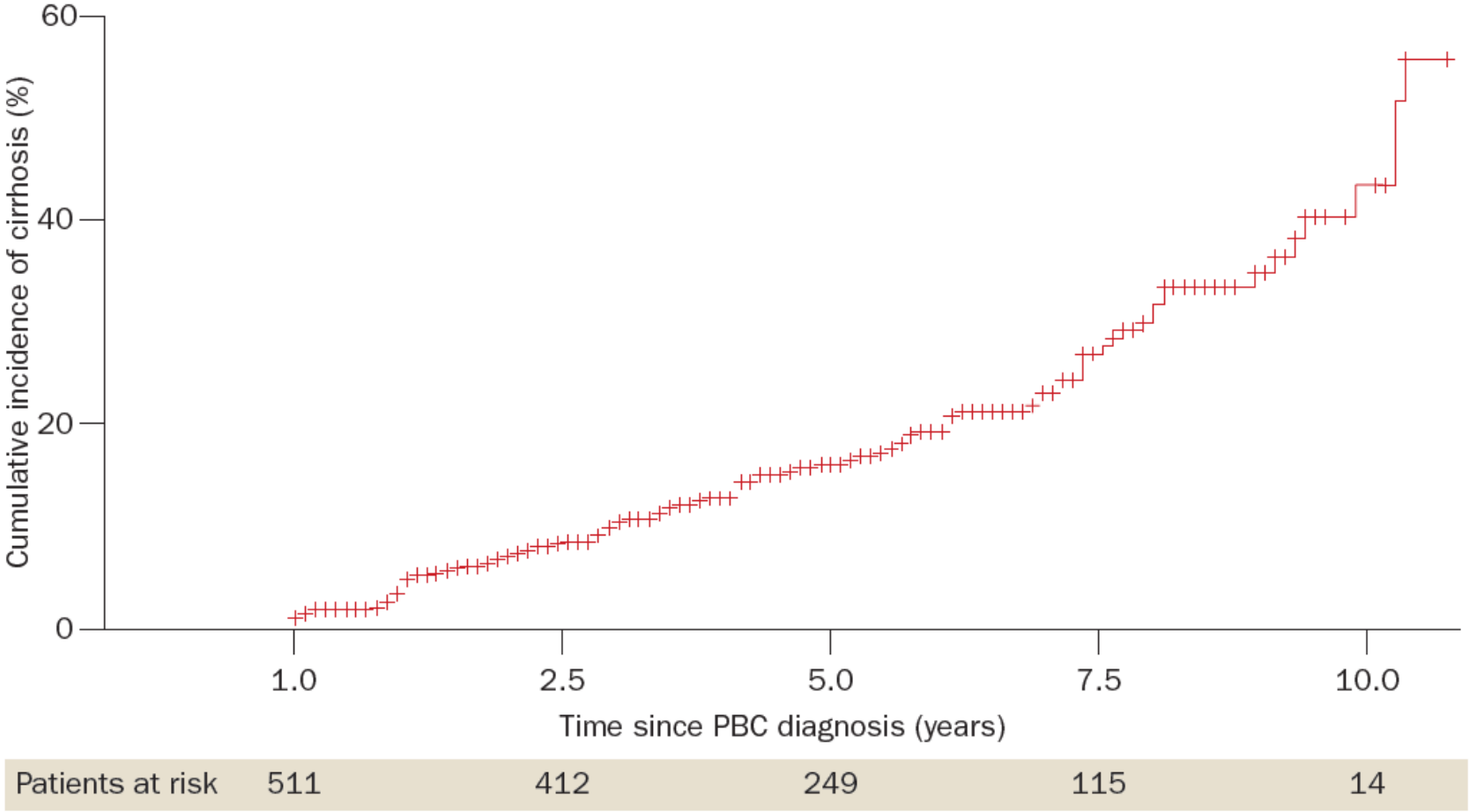
UDCA therapy is Associated with Prolonged Transplant-free Survival



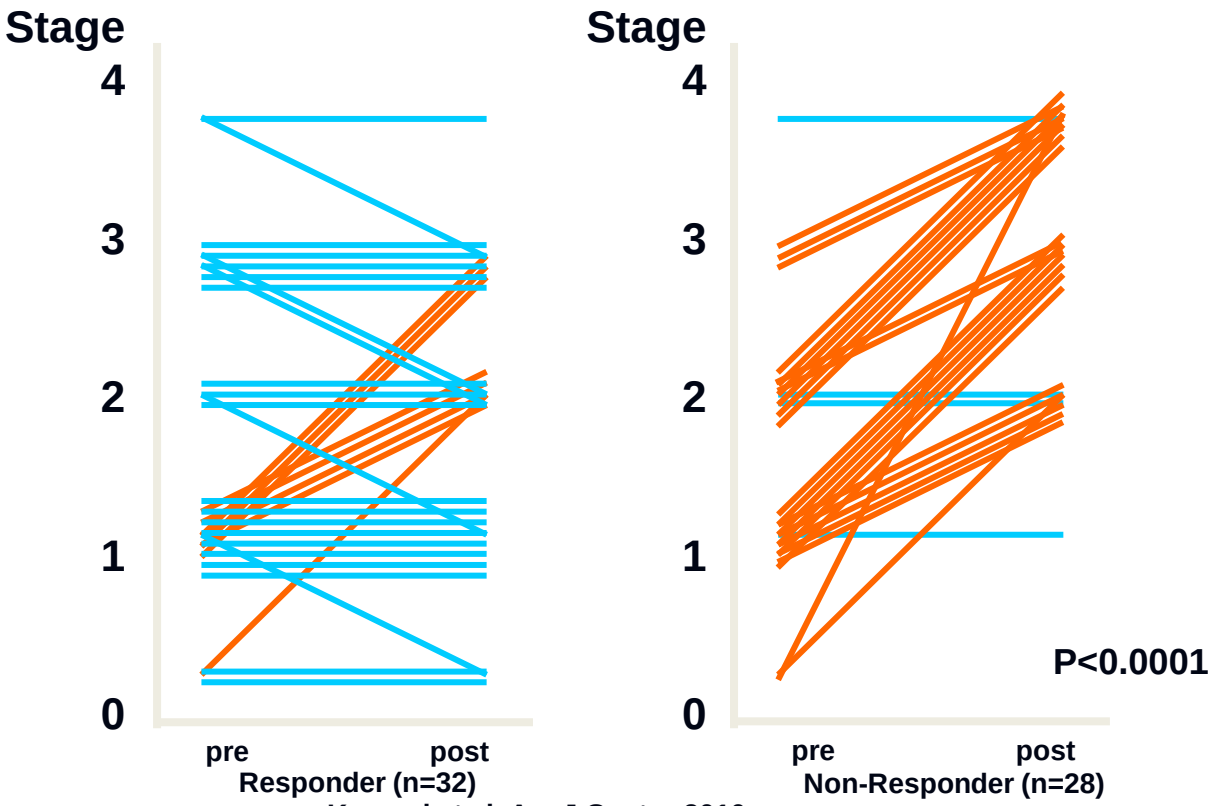
Harms et al. Global PBC Under Review

Development of liver cirrhosis as part of living with PBC



Trivedi and Hirschfield, Nature Reviews 2015

Treatment Response and Histological Progression

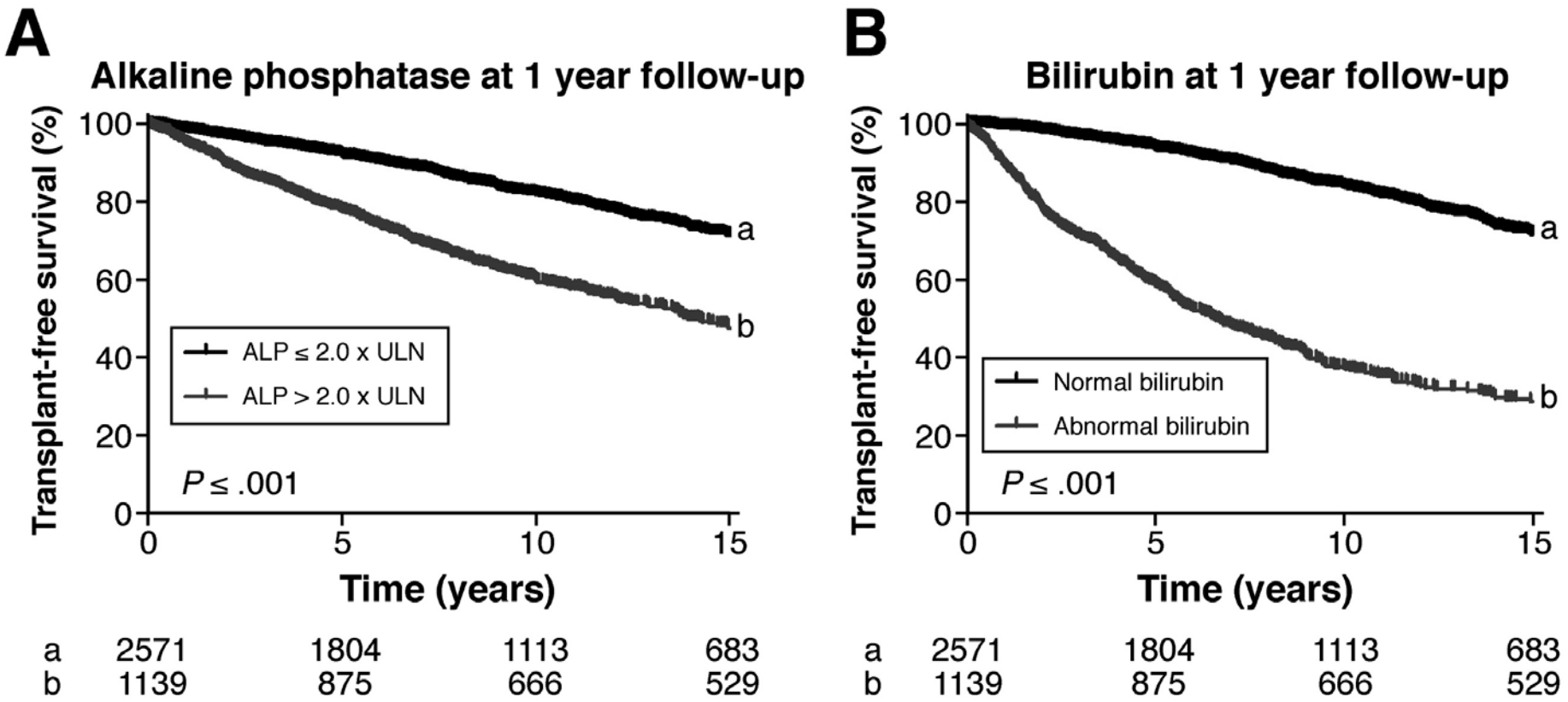


Kumagi et al. Am J Gastro 2010

Factors Influencing Outcome and Treatment Response

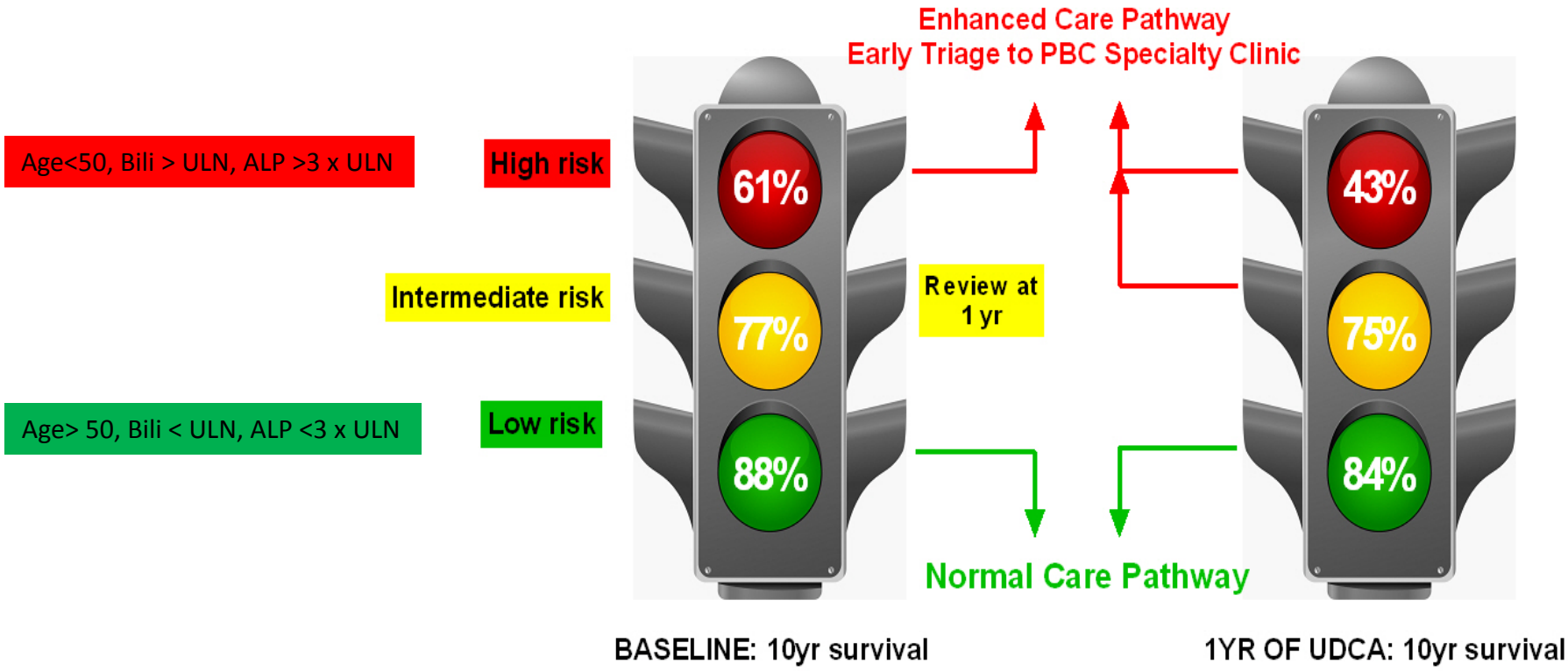
- Younger age
- Gender
- Antinuclear specific antibodies
- Biochemical markers of fibrosis
- Liver stiffness
- Cirrhosis/portal hypertension
- Ductopenia

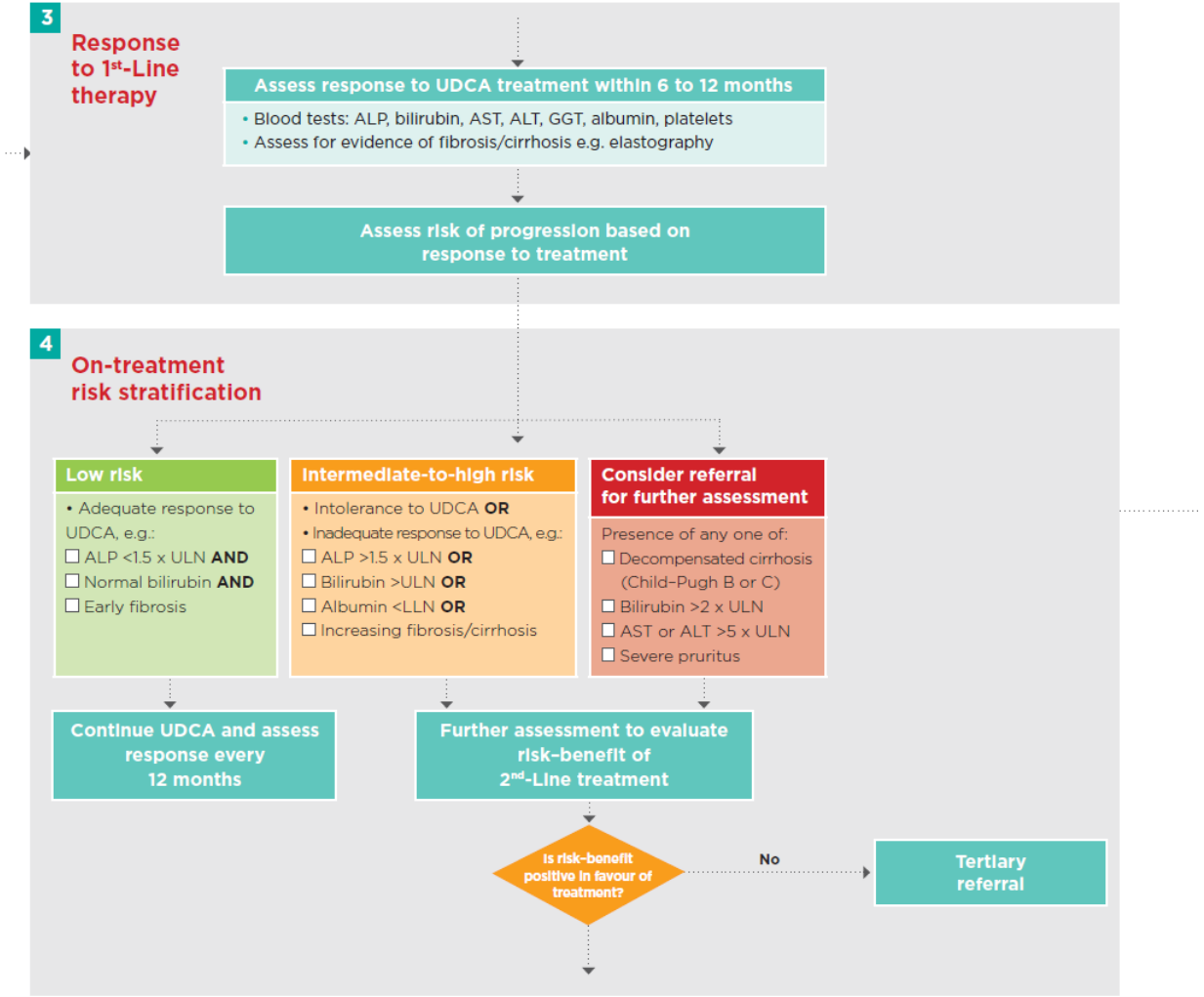
Stratification of risk



Lammers WJ, van Buuren HR, Hirschfield GM, et al. *Gastroenterol.* 2014;147:1338-1349;

The one-stop PBC Traffic Light Evaluation





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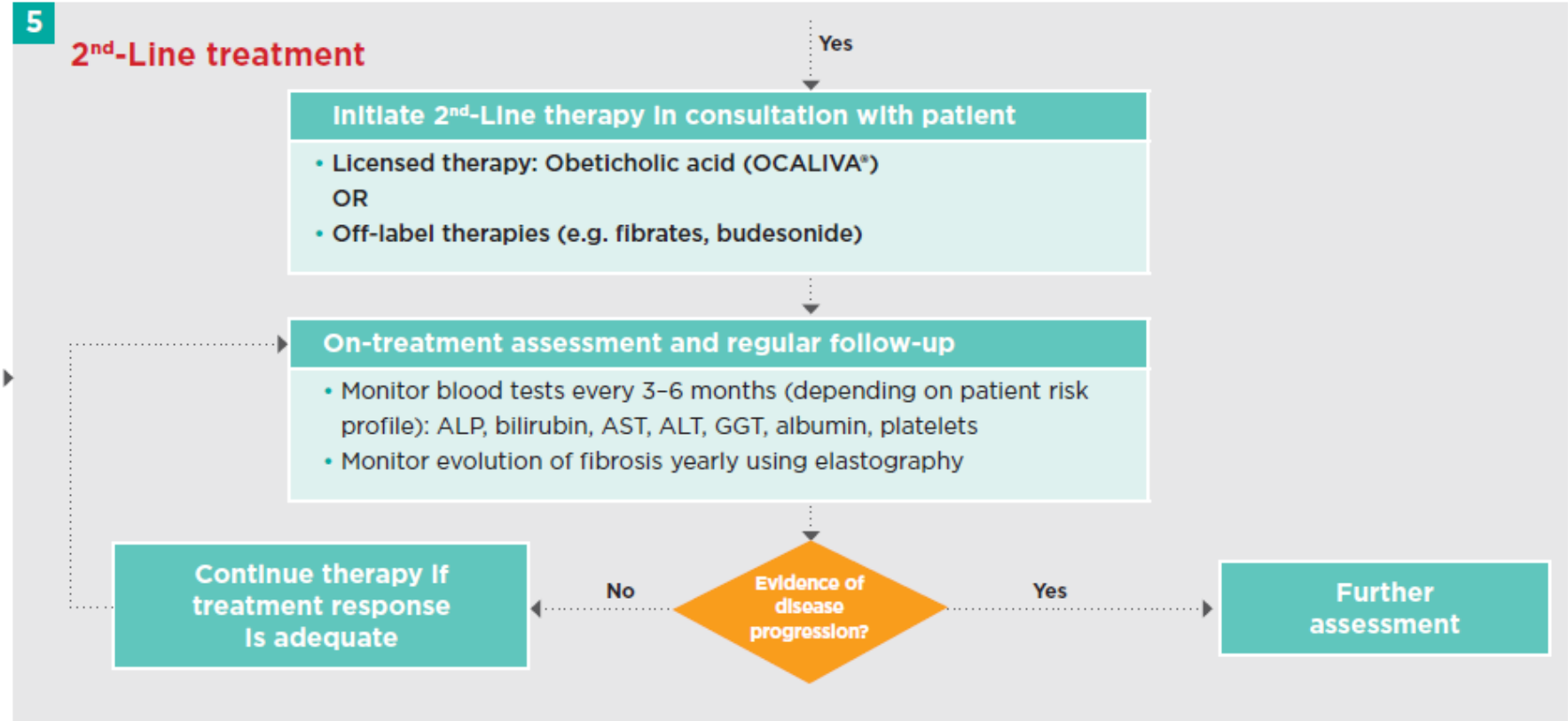

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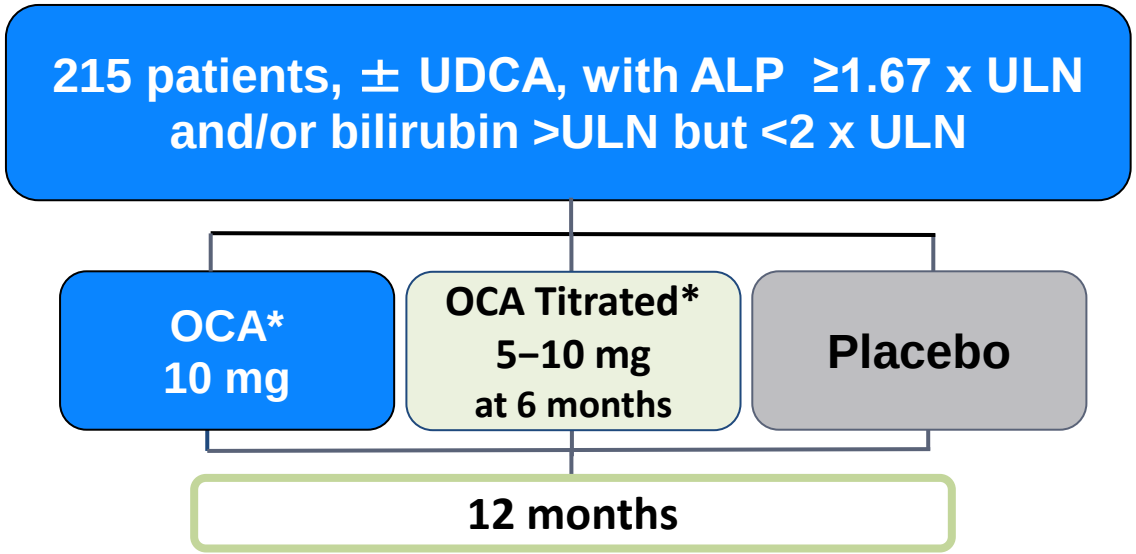
Obeticholic Acid: Phase III POISE Trial



Primary endpoint: Achieving response of ALP <1.67 x ULN with normal bilirubin and ≥15% ALP reduction

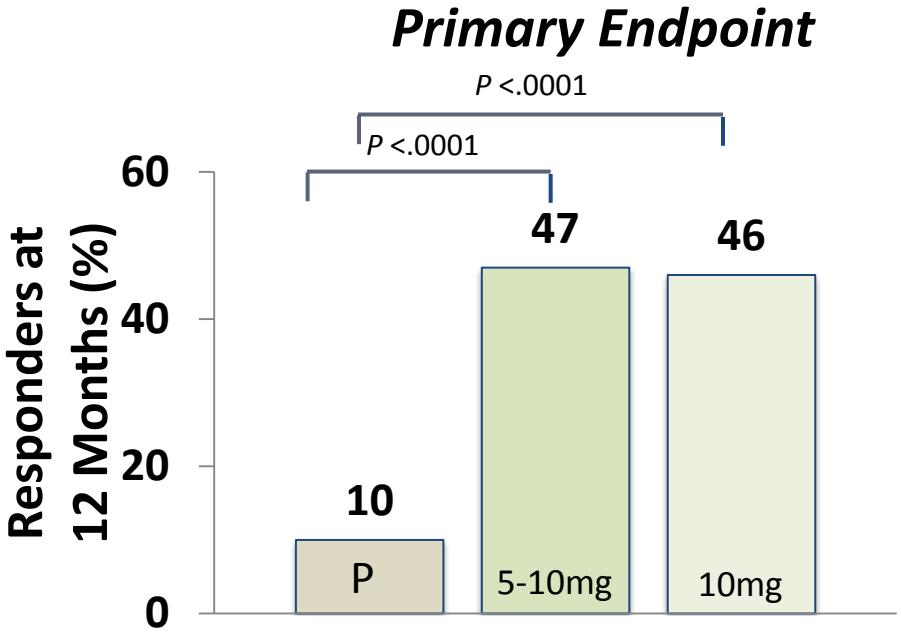
*Prestudy UDCA continued.
Abbreviations: ALP, alkaline phosphatase; OCA, obeticholic acid; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
Nevens F, et al.

Variables	Placebo ±UDCA (n=73)	OCA 5-10 mg ±UDCA (n=70)	OCA 10 mg ±UDCA (n=73)
Age, y	56 ± 10	56 ± 11	56 ± 11
Sex, Female, n (%)	68 (93)	65 (93)	63 (86)
Race/Ethnicity, n (%)			
White	66 (90)	67 (96)	70 (96)
Non-White	7 (10)	3 (4)	3 (4)
ALP, U/L	327 ± 115	326 ± 116	316 ± 104
Total Bilirubin, mg/dL	0.7 ± 0.4	0.6 ± 0.3	0.7 ± 0.4
Mayo Risk Score	4.3 ± 1.1	4.3 ± 1.2	4.3 ± 1.2
UDCA use, n (%)	68 (93)	65 (93)	67 (92)
Daily UDCA dose, mg/kg	15 ± 4	17 ± 5	16 ± 5
Age at PBC diagnosis, y	47.3 ± 9.3	47.6 ± 11.7	47.1 ± 10.6
Duration PBC, y	8.3 ± 5.4	8.3 ± 5.8	9.2 ± 6.9
Pruritus at Baseline[a], n (%)	47 (64)	37 (53)	44 (60)

Data are mean ± SD where applicable.

POISE Data Intercept

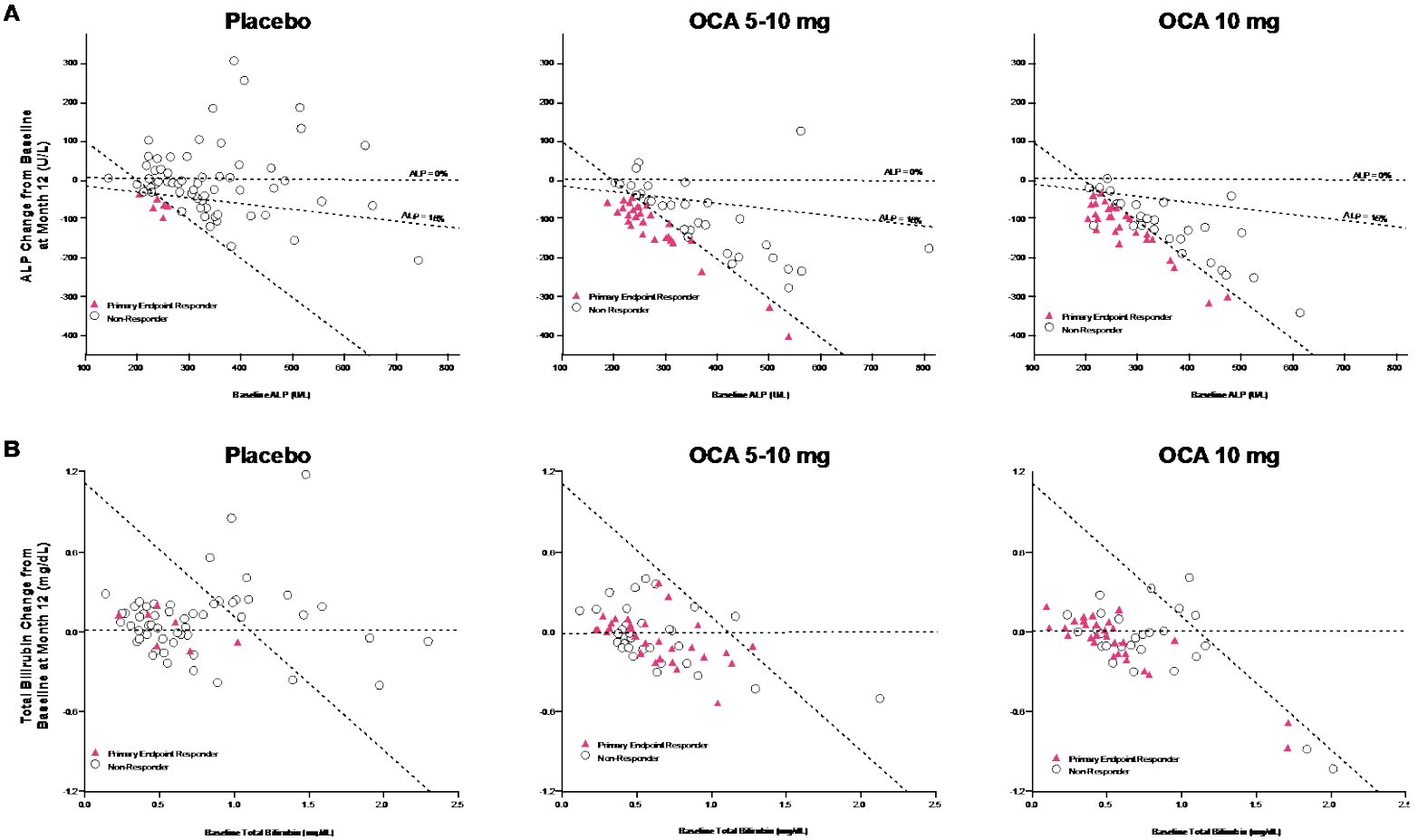
OCA: Phase III POISE Trial



Response: ALP <1.67 x ULN <u>with</u> normal bilirubin <u>and</u> ≥15% ALP reduction (primary endpoint)

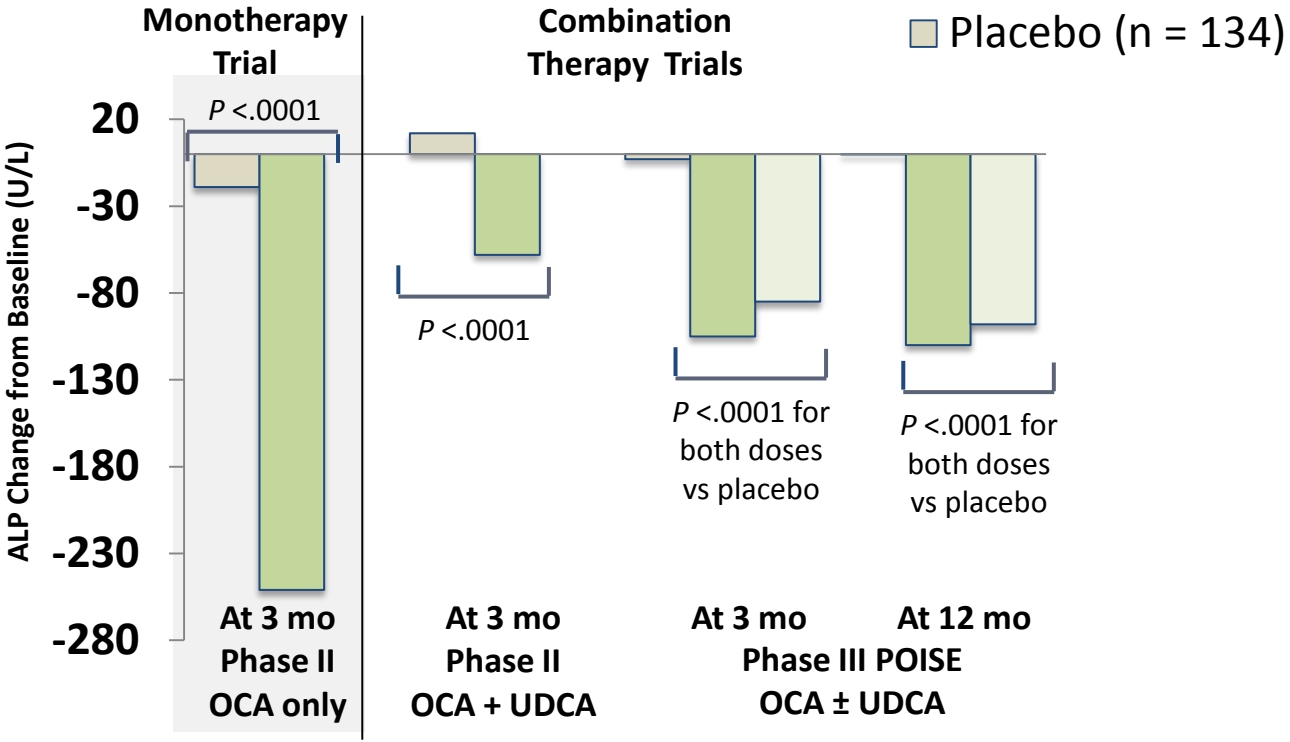
*Prestudy ursodeoxycholic acid continued.
Abbreviations: ALP, alkaline phosphatase; OCA, obeticholic acid; ULN, upper limit of normal.
Nevens F, et al.

Effect is Greater than Just the Dichotomous Primary End Point



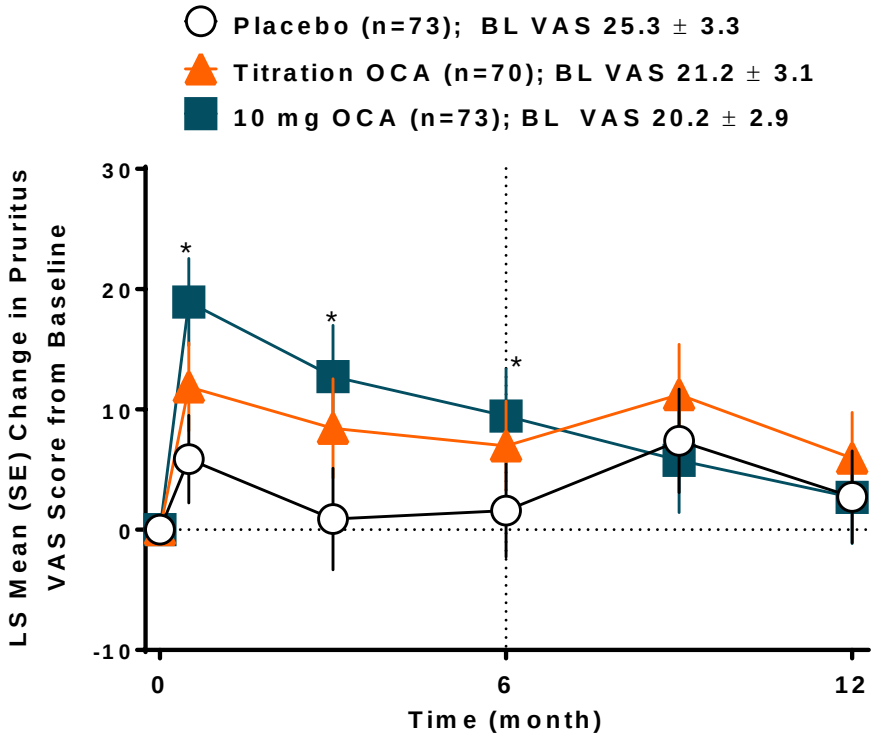
Nevens, et al. *N Engl J Med.* 2016.

OCA International Trials: Changes in Serum Alkaline Phosphatase



Abbreviations: ALP, alkaline phosphatase; OCA, obeticholic acid; UDCA, ursodeoxycholic acid.
Kowdley K, et al. Paper presented at: DDW 2015; May 16-19, 2015; Washington, DC. Abstract 657.

At End of Study Pruritus Experience Was Similar for All Subjects Using a Visual Analog Score



*p<0.05 vs placebo; VAS scores range from 0 (no pruritus) to 100 (severe pruritus)
p values obtained using Cochran-Mantel-Haenszel stratified by randomization strata factor

Nevens, et al. *N Engl J Med.* 2016.

A Placebo-Controlled Trial of Bezafibrate in Primary Biliary Cholangitis

C. Corpechot, O. Chazouillères, A. Rousseau, A. Le Gruyer, F. Habersetzer, P. Mathurin, O. Goria, P. Potier, A. Minello, C. Silvain, A. Abergel, M. Debette-Gratien, D. Larrey, O. Roux, J.-P. Bronowicki, J. Boursier, V. de Ledinghen, A. Heurgue-Berlot, E. Nguyen-Khac, F. Zoulim, I. Ollivier-Hourmand, J.-P. Zarski, G. Nkontchou, S. Lemoinne, L. Humbert, D. Rainteau, G. Lefèvre, L. de Chaisemartin, S. Chollet-Martin, F. Gaouar, F.-H. Admane, T. Simon, and R. Poupon

ABSTRACT

BACKGROUND

Patients with primary biliary cholangitis who have an inadequate response to therapy with ursodeoxycholic acid are at high risk for disease progression. Fibrates, which are agonists of peroxisome proliferator–activated receptors, in combination with ursodeoxycholic acid, have shown potential benefit in patients with this condition.

METHODS

In this 24-month, double-blind, placebo-controlled, phase 3 trial, we randomly assigned 100 patients who had had an inadequate response to ursodeoxycholic acid according to the Paris 2 criteria to receive bezafibrate at a daily dose of 400 mg (50 patients), or placebo (50 patients), in addition to continued treatment with ursodeoxycholic acid. The primary outcome was a complete biochemical response, which was defined as normal levels of total bilirubin, alkaline phosphatase, aminotransferases, and albumin, as well as a normal prothrombin index (a derived measure of prothrombin time), at 24 months.

RESULTS

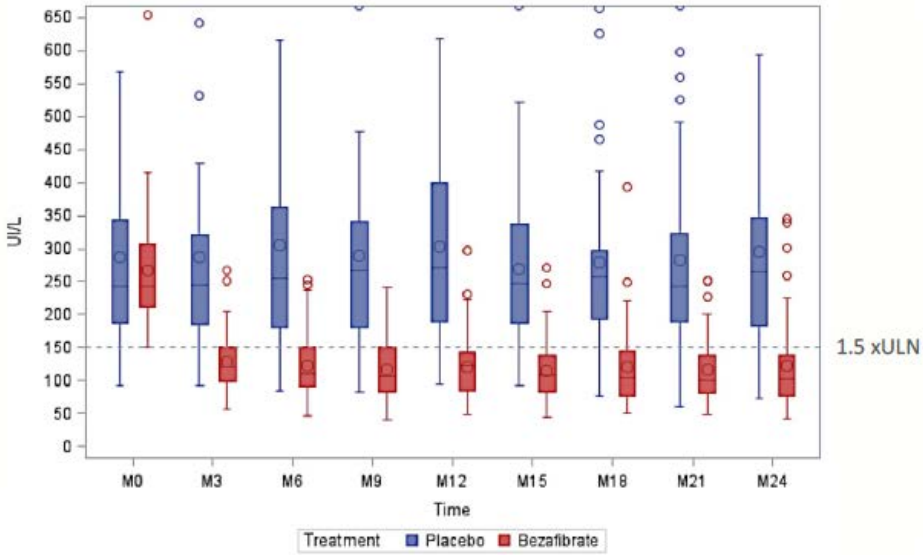
The primary outcome occurred in 31% of the patients assigned to bezafibrate and in 0% assigned to placebo (difference, 31 percentage points; 95% confidence interval, 10 to 50; P<0.001). Normal levels of alkaline phosphatase were observed in 67% of the patients in the bezafibrate group and in 2% in the placebo group. Results regarding changes in pruritus, fatigue, and noninvasive measures of liver fibrosis, including liver stiffness and Enhanced Liver Fibrosis score, were consistent with the results of the primary outcome. Two patients in each group had complications from end-stage liver disease. The creatinine level increased 5% from baseline in the bezafibrate group and decreased 3% in the placebo group. Myalgia occurred in 20% of the patients in the bezafibrate group and in 10% in the placebo group.

CONCLUSIONS

Among patients with primary biliary cholangitis who had had an inadequate response to ursodeoxycholic acid alone, treatment with bezafibrate in addition to ursodeoxycholic acid resulted in a rate of complete biochemical response that was significantly higher than the rate with placebo and ursodeoxycholic acid therapy. (Funded by Programme Hospitalier de Recherche Clinique and Arrow Génériques; BEZURSO ClinicalTrials.gov number, NCT01654731.)

Course of alkaline phosphatase level

Secondary endpoint



A 2-YEAR MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF BEZAFIBRATE FOR THE TREATMENT OF PRIMARY BILIARY CHOLANGITIS IN PATIENTS WITH INADEQUATE BIOCHEMICAL RESPONSE TO URSODEOXYCHOLIC ACID THERAPY (BEZURSO, NCT01654731)

Beyond the liver

- Sicca complex
- Bone ache
- Pruritus
- Concurrent autoimmune diseases
- Fatigue
- Reduced bone density
- Abdominal pain

PBC has the complexity of need that encompasses both quantity and quality of life