CBP: manejo de los pacientes no respondedores a AUDC

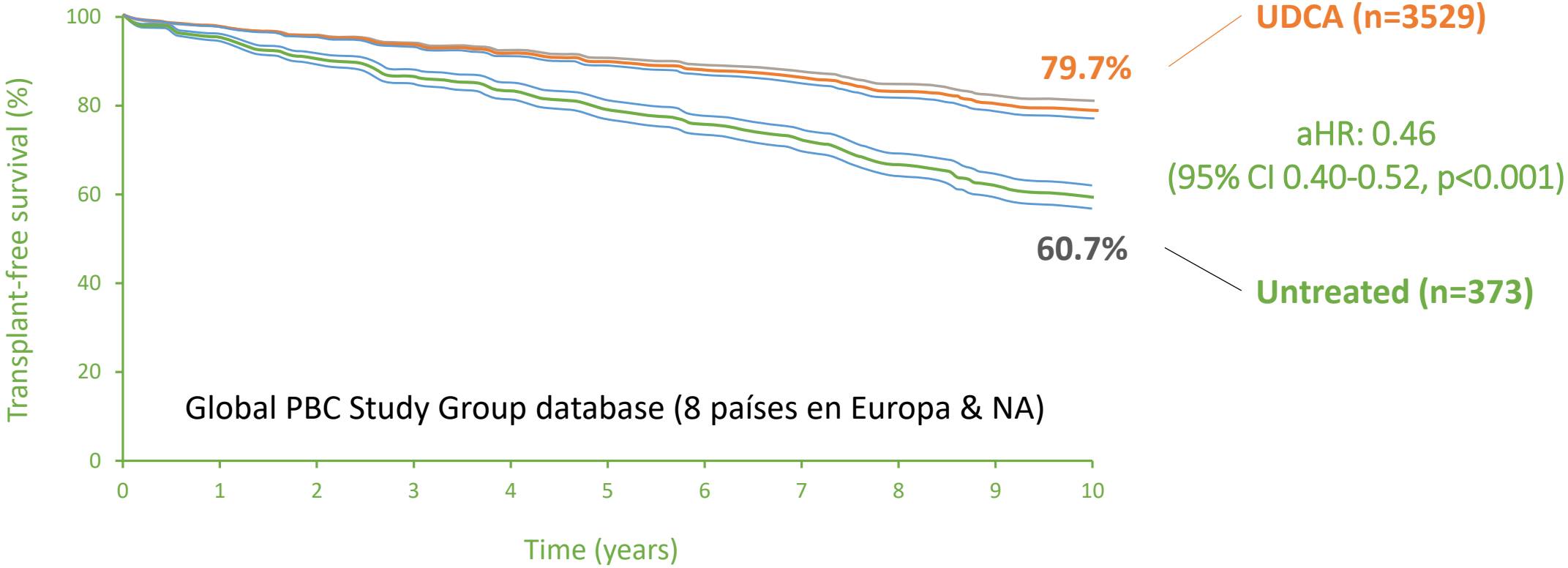
M.Berenguer

Caso

- Mujer 62 años
- HTA
- Fatiga pero st Prurito durante varios meses
- ALT 44 U/L, AST 43 U/L, FA 650 U/L, BT 0,8 mg/dl, GGT 320 U/L, Alb 4 g/dl, INR 1, plaq 162000/mm3
- AMA 1/640, IgM 330, Fibroscan 10, 7 kpas

AUDC 15 mg/kg/día

El tratamiento con UDCA mejora la supervivencia sin trasplante (análisis IPTW)



Independientemente de la respuesta bioquímica, fibrosis, edad y sexo

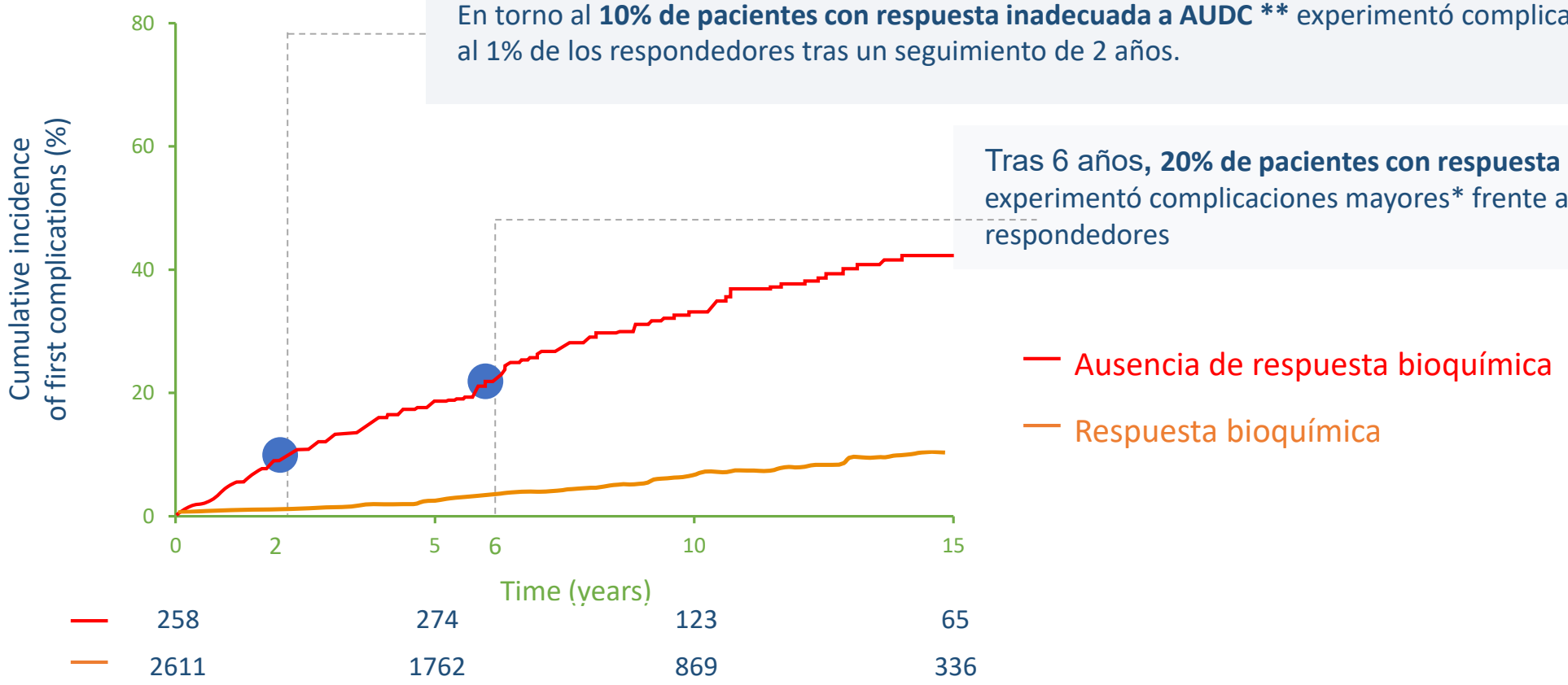
Survival figures were constructed using an IPTW-adjusted Cox proportional hazard model
aHR=adjusted hazard ratio;
CI=confidence interval; IPTW=inverse probability treatment weighting;
PBC=primary biliary cholangitis; UDCA=ursodeoxycholic acid

Harms MH, et al. J Hepatol 2019;71:357-65

Las complicaciones hepáticas y la progresión de la enfermedad ocurren más rápidamente en pacientes con respuesta inadecuada a AUDC

En torno al **10% de pacientes con respuesta inadecuada a AUDC **** experimentó complicaciones mayores* frente al 1% de los respondedores tras un seguimiento de 2 años.

Tras 6 años, **20% de pacientes con respuesta inadecuada a AUDC **** experimentó complicaciones mayores* frente al 2-3% de los respondedores



*Major hepatic complications include ascites, variceal bleeding and hepatic encephalopathy
**Age-dependent thresholds of the GLOBE score
UDCA=ursodeoxycholic acid

Harms MH, et al. Am J Gastroenterol. 2018;113:254-64.

¿ Cómo definir la respuesta ?

Criterios bioquímicos de respuesta al año con AUDC

Table 5. Assessing response to UDCA therapy in PBC.

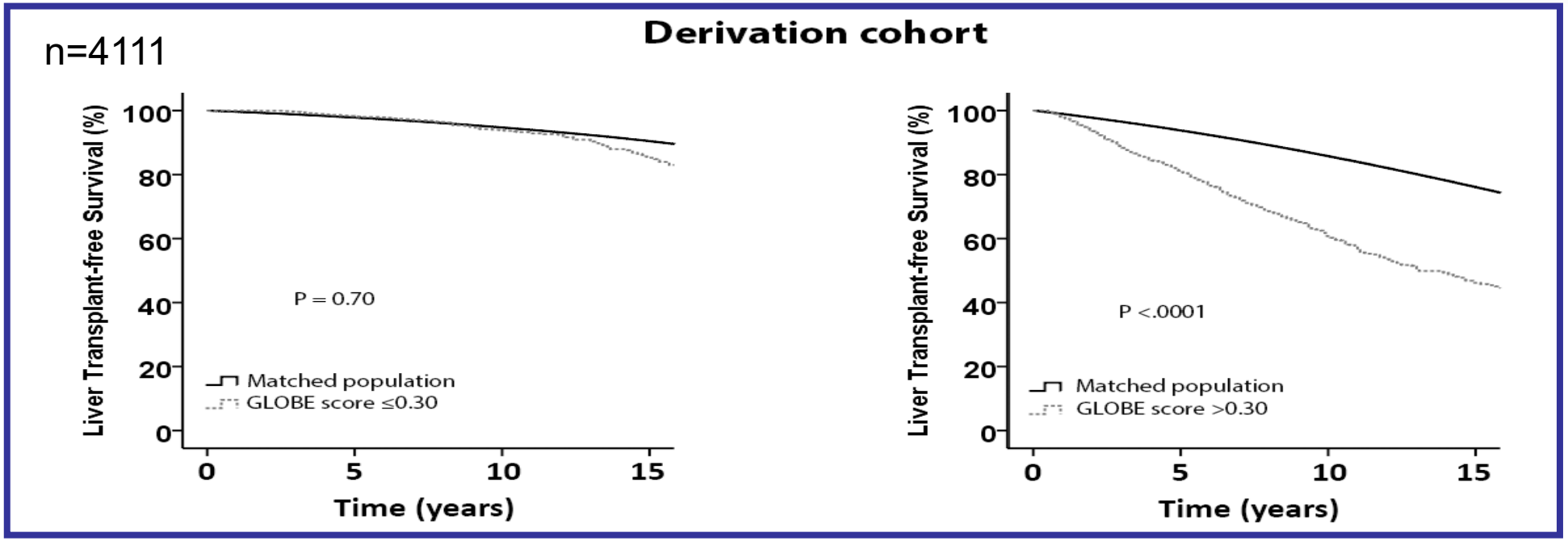
Qualitative binary definitions	**Time (months)**	**Treatment failure**
Rochester [101]	6	ALP ⩾2× ULN or Mayo score ⩾4.5
Barcelona [62]	12	Decrease in ALP ⩽40% and ALP ⩾1× ULN
Paris-I [63]	12	ALP ⩾3× ULN or AST⩾ 2× ULN or bilirubin >1 mg/dl
Rotterdam [102]	12	Bilirubin ⩾1× ULN and/or albumin <1× ULN
Toronto [98]	24	ALP >1.67× ULN
Paris-II [104]	12	ALP ⩾1.5× ULN or AST ⩾1.5× ULN or bilirubin >1 mg/dl
Ehime [103]	6	Decrease in GGT ⩽70% and GGT ⩾1× ULN
Continuous scoring systems	**Time (months)**	**Scoring parameters**
UK-PBC [107]	12	Bilirubin, ALP and AST (or ALT) at 12 mo. Albumin and platelet count at baseline
GLOBE [106]	12	Bilirubin, ALP, albumin, and platelet count at 12 mo. Age at baseline

ALP, alkaline phosphatase; ULN, upper limit of normal; AST, aspartate aminotransferase; GGT, gamma-glutamyltranspeptidase.

1. Parés A, et al. Gastroenterology. 2006;130(3):715-720. 2. Corpechot C, et al. Hepatology. 2008;48(3):871-877. 3. Kuiper EMM, et al. Gastroenterology. 2009;136(4):1281-1287. 4. Kumagi T, et al. Am J Gastroenterol. 2010;105(10):2186-2194. 5. Angulo P, et al. Liver. 1999;19(2):115-121. 6. Momah N, et al. Liver Int. 2012;32(5):790-795. 7. Corpechot C, et al. J Hepatol. 2011;55(6):1361-1367. 8. Zhang LN, et al. Hepatology. 2013;58(1):264-272.

Puntuaciones de riesgo continuas – Puntuación GLOBE PBC: Identificación de “riesgo”

- Herramienta que permite identificar pacientes de alto riesgo de mortalidad/ necesidad TH en los siguientes 3, 5 y 10 años
- Utiliza variables fácilmente disponibles y objetivas
  - Edad
  - bilirrubina
  - Albúmina
  - Fosfatasa alcalina
  - Recuento de plaquetas

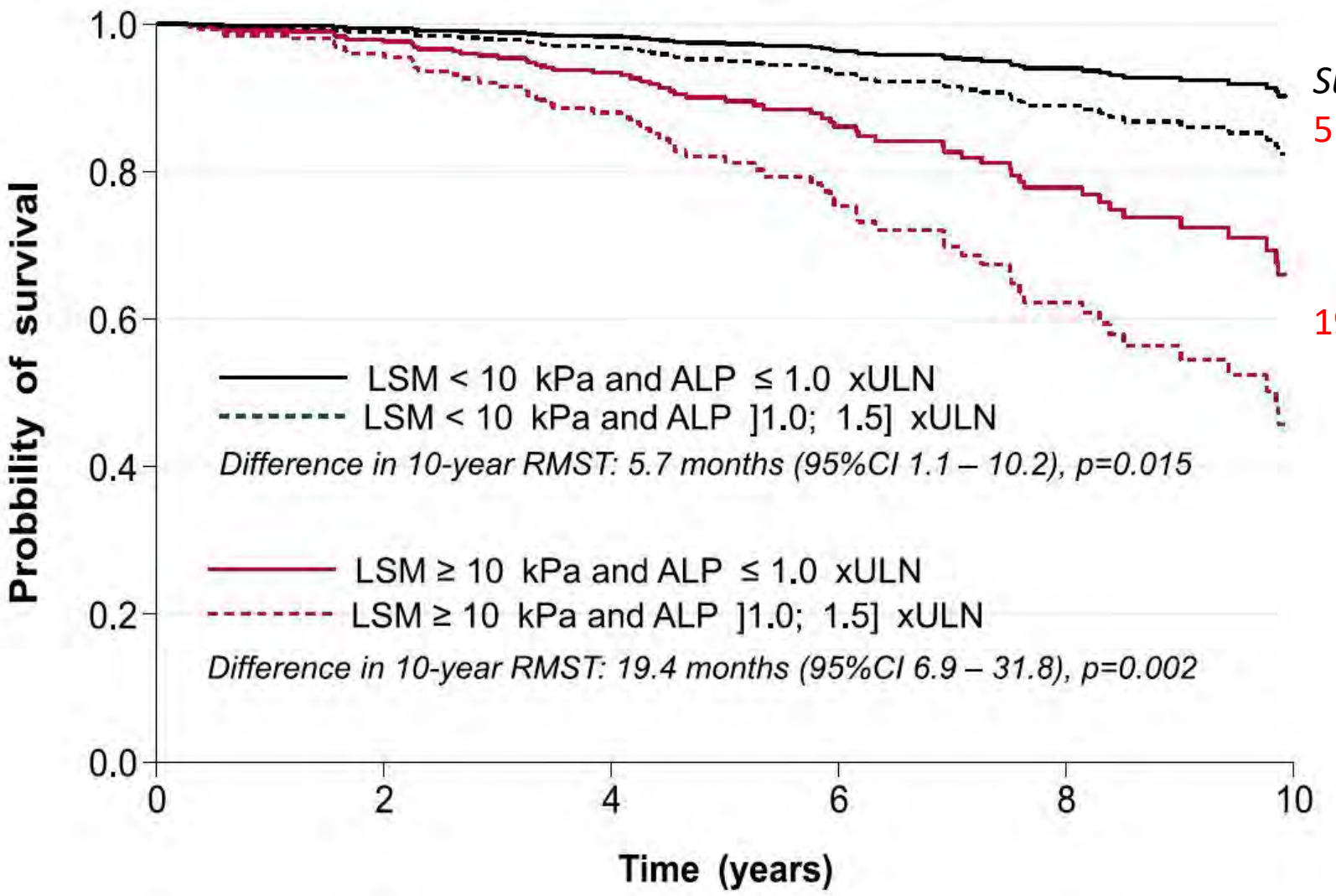


www.globALPbc.com/globe/
Lammers WJ, et al. Gastroenterology. 2015;149:1804-12

Lammers et al., Gastroenterology 2015;149:1804

LT=liver transplant; UDCA-ursodeoxycholic acid

Pronóstico en función de grado de respuesta bioquímica y la rigidez hepática



Survival gain
5.66 months

LSM < 10kpa

19.36 months

LSM ≥ 10kpa

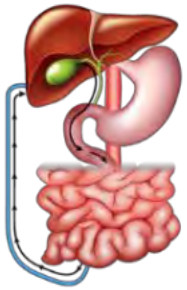
Corpechot C et al. ADEQUATE BIOCHEMICAL RESPONSE TO URSODEOXYCHOLIC ACID IN PATIENTS WITH PBC: IS NORMALIZATION OF SERUM LIVER TESTS IMPORTANT?*Hepatology*. 2022;76(Suppl. 1): P4722.

Caso

- Tras 6 meses de tratamiento con AUDC: FA: 480 U/L, BT 0,9 mg/dl
- Tras 12 meses de tratamiento con AUDC: FA 366 U/L y BT 0,8 mg/dl
- NO Respuesta por varios criterios
- GLOBE score 1,29 con una supervivencia esperada a 3 años del 88% vs 98% en población de misma edad/sexo.

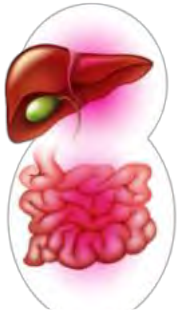
Agonismo FXR: un nuevo modo de acción en CBP*

FXR ACTIVATION



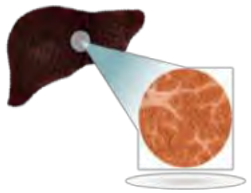
BILE ACID HOMEOSTASIS[1]

⬇ Synthesis, ⬆Secretion,
⬇ Absorption/reuptake



⬇ INFLAMMATION[2–4]

⬇Inflammation in the liver
⬇ Inflammation in the intestine



⬇ FIBROSIS[5]

Inhibits liver fibrosis progression and promotes fibrosis resolution
Inhibits hepatic stellate cell activity

1. Modica S, et al. Nucl Recept Signal. 2010;8:e005
2. Wang YD, et al. Hepatology. 2008;48:1632-43
3. Vavassori P, et al. J Immunol. 2009;183:6251-61
4. Gadaleta RM, et al. Gut. 2011;60:463-72
5. Verbeke L, et al. Sci Rep. 2016;6:33453

*Proposed roles based on in vivo and in vitro studies in multiple animal and cell models using different FXR agonists. In vivo/in vitro studies do not necessarily correlate with clinical response, and not all FXR agonists may produce the same effects.
BA=bile acid; FXR=farnesoid X receptor; OCA=obeticholic acid; RXR=retinoid X receptor.

Se debe considerar la terapia de segunda línea en pacientes que mantienen FA> 1.5 x LN y/o bilirrubina anormal a pesar de 12 meses de terapia con AUDC (25-50%)*

Checklist pre terapia de segunda línea

Respuesta a AUDC
Dosis, adherencia
ALP < 1.5 x ULN
Bilirrubina < ULN

Grado de afectación hepática
Pruebas no invasivas
Overlap con HAI?
Biopsia hepática?

Síntomas
Calidad de vida
Astenia
Prurito

Afectación extrahepática
Osteoporosis
TSH
Sjogren
Esclerodermia

→ Impacto del perfil del paciente en la decisión terapéutica

Nota: En un estudio* con hepatogastroenterólogos, el 24% creyó que la CBP estaba controlada a pesar de no mostrar respuesta bioquímica (*Pariente A, et al. Eur J Gastroenterol Hepatol. 2020 Nov 30.*)

Datos del estudio y registro POISE

OBJETIVO PRIMARIO COMPUESTO DEL ESTUDIO A LOS 12 MESES

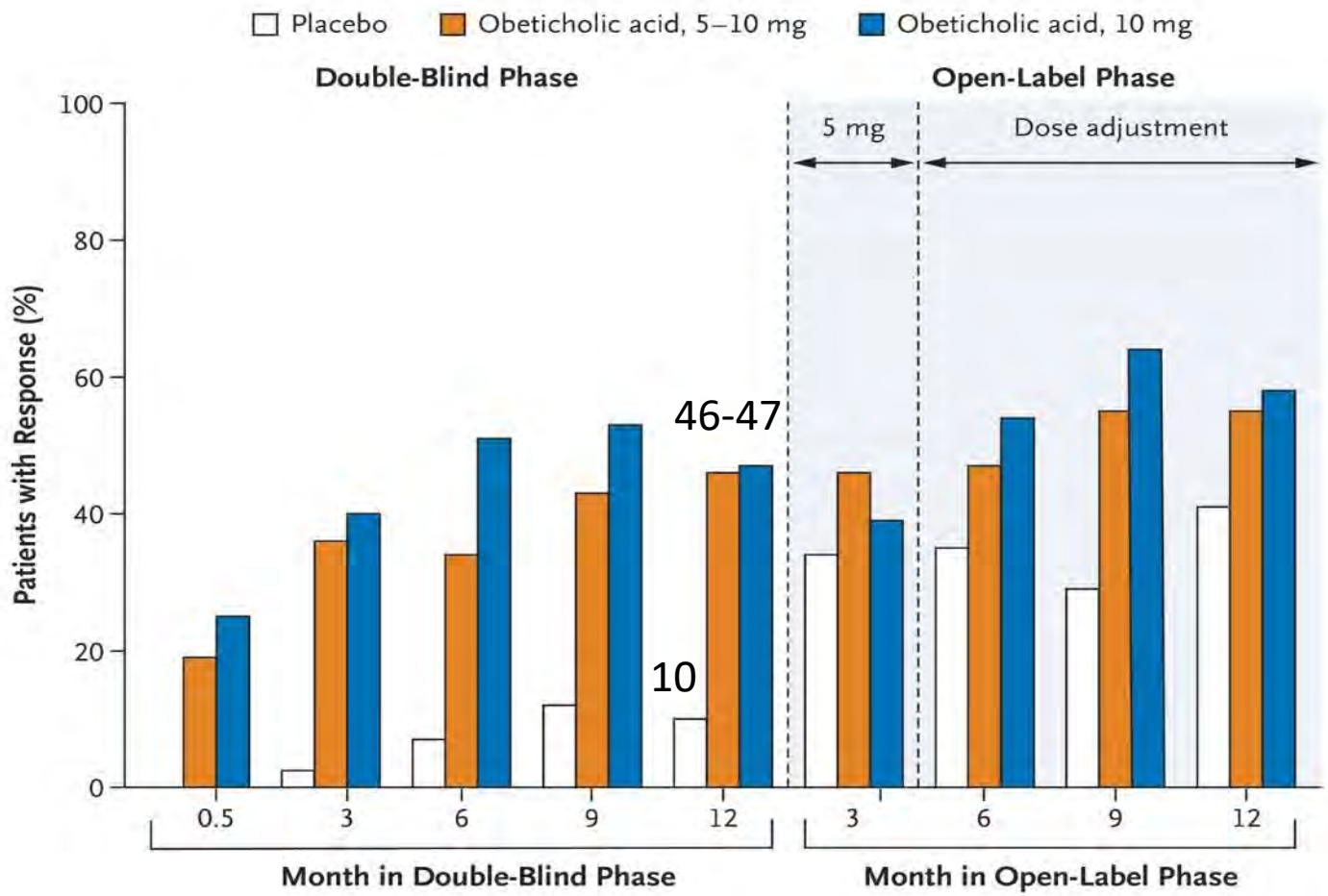
FA < 1.67x LSN

Y

bilirrubina normal

Y

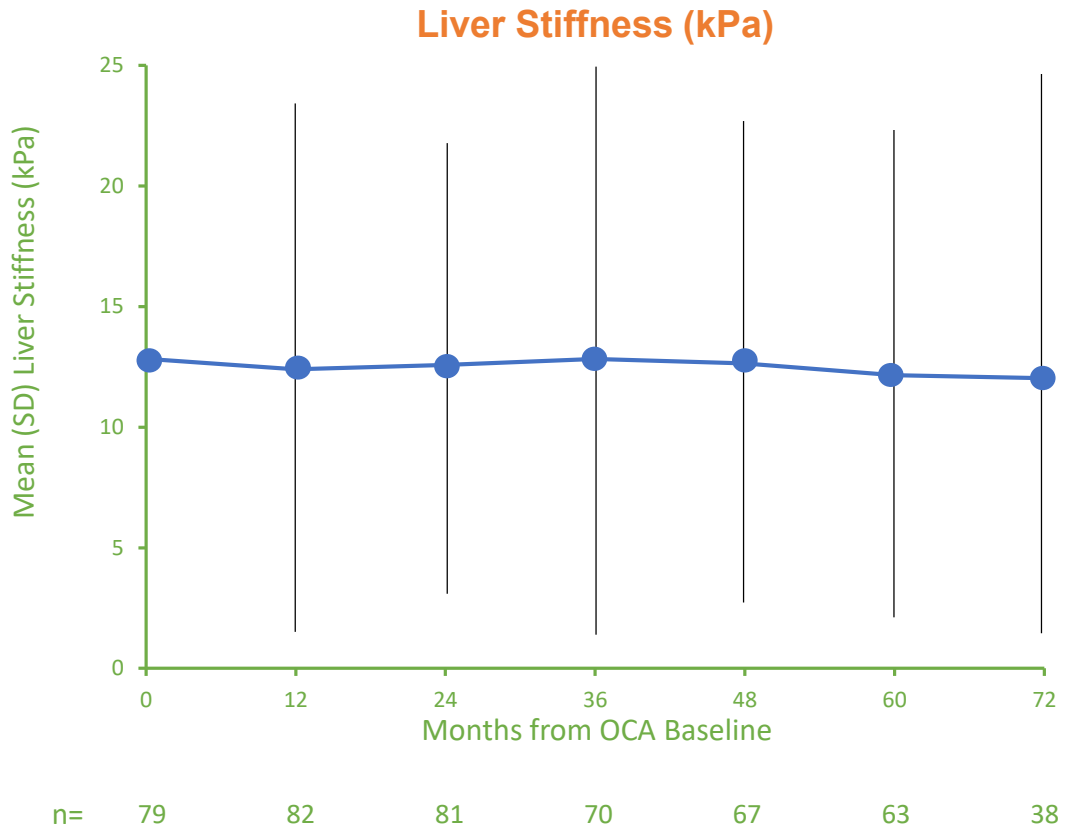
descenso de FA ≥ 15% desde niveles basales



No. of Patients									
Placebo	73	73	73	73	73	64	60	59	59
Obeticholic acid, 5–10 mg	70	70	70	70	70	63	62	62	60
Obeticholic acid, 10 mg	73	73	73	73	73	64	59	61	59

Nevens F et al A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis N Engl J Med. 2016;375:631-643.

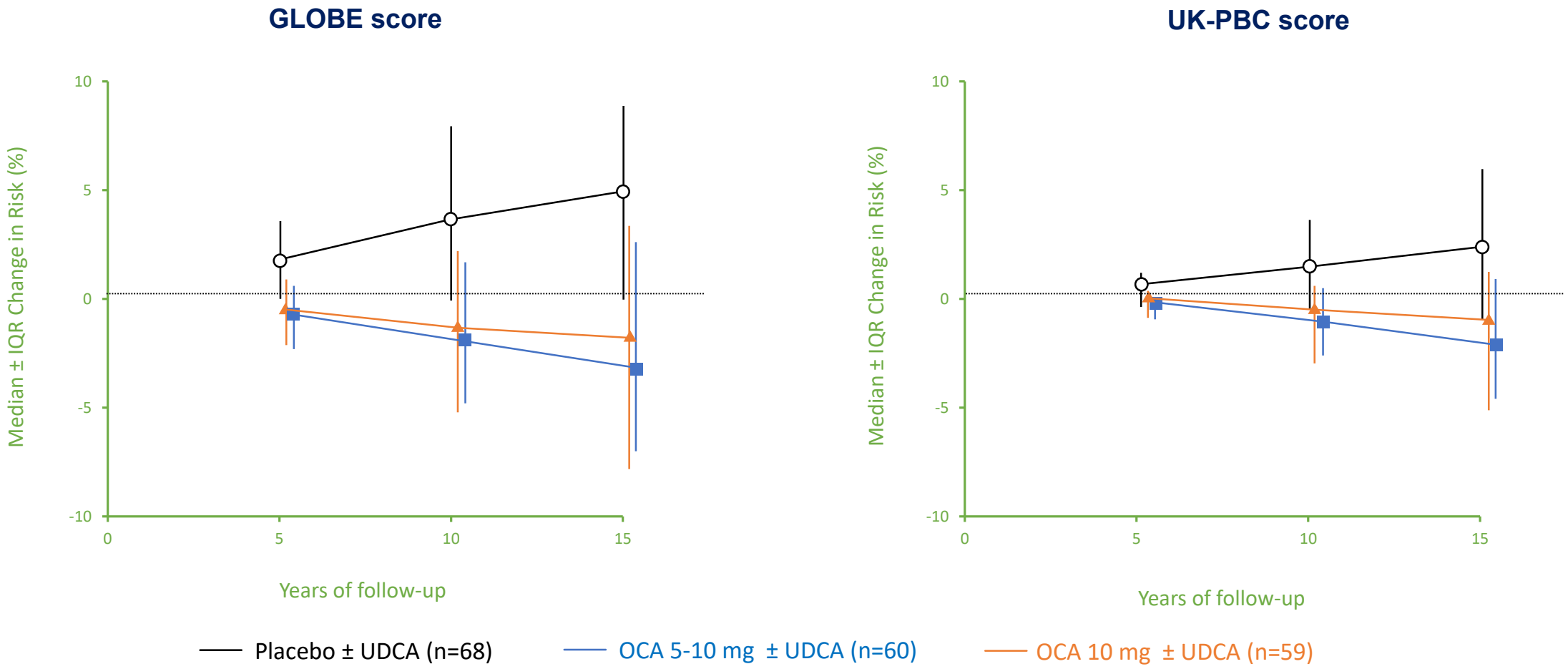
OCA estabiliza los resultados del Fibroscan® tras 6 años de tratamiento



Nevens F, et al. AASLD. 2019:LO6 (oral presentation)

ELF, Enhanced liver fibrosis; OCA, Obeticholic acid, SD, Standard deviation

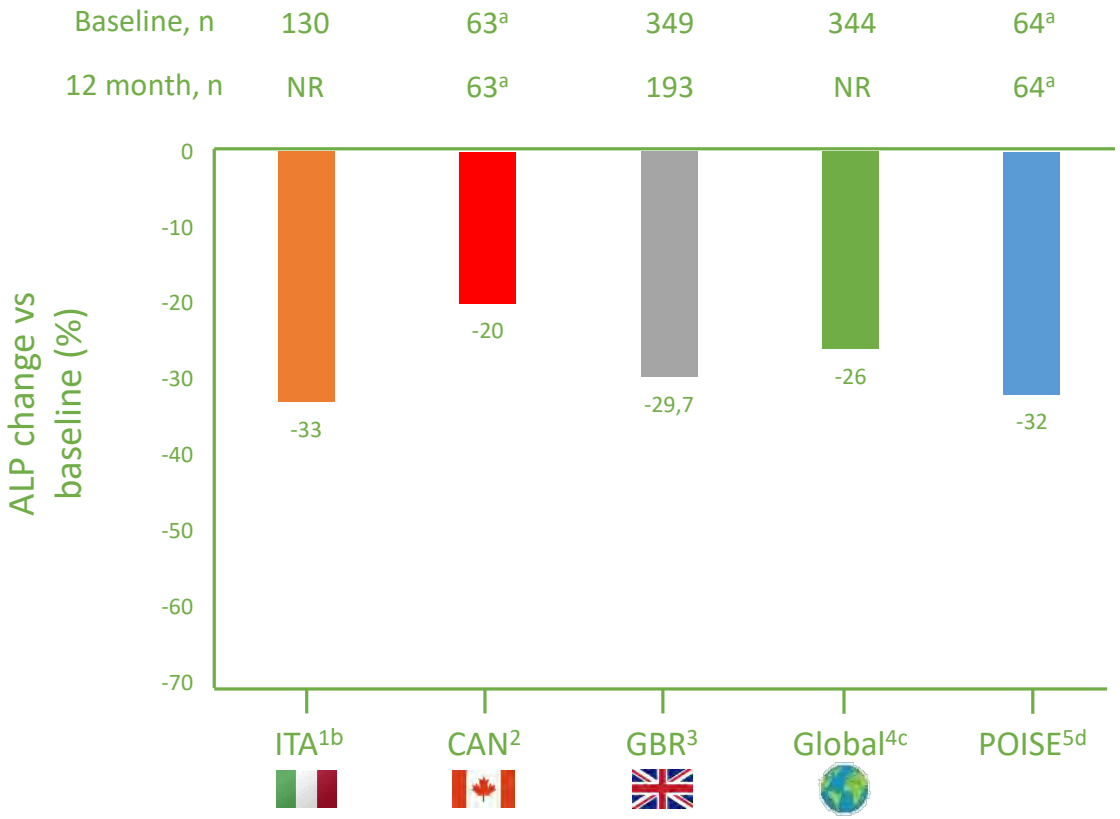
OCA mejora las predicciones (supervivencia libre de TH) hechas con los modelos GLOBE y UK-PBC

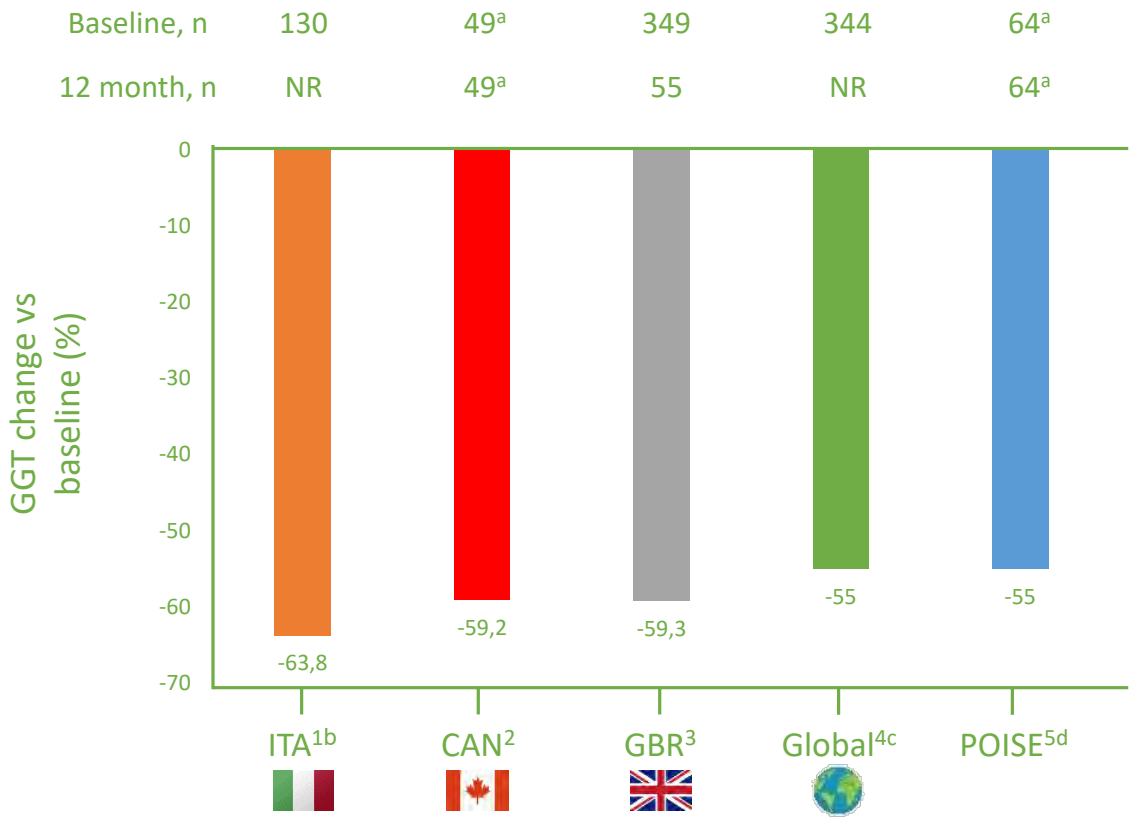


Carbone M, et al. Hepatol Comm. 2018;2:683-92

IQR=interquartile range; OCA=obetichold acid;
PBC=primary biliary cholangitis; UDCA=ursodeoxycholic acid

Los resultados son parecidos en series de vida real





The graphical representation of the data is for illustrative purposes only. Cross trial comparisons can not be made due the differences in patient populations, characteristics, numbers and clinical environment

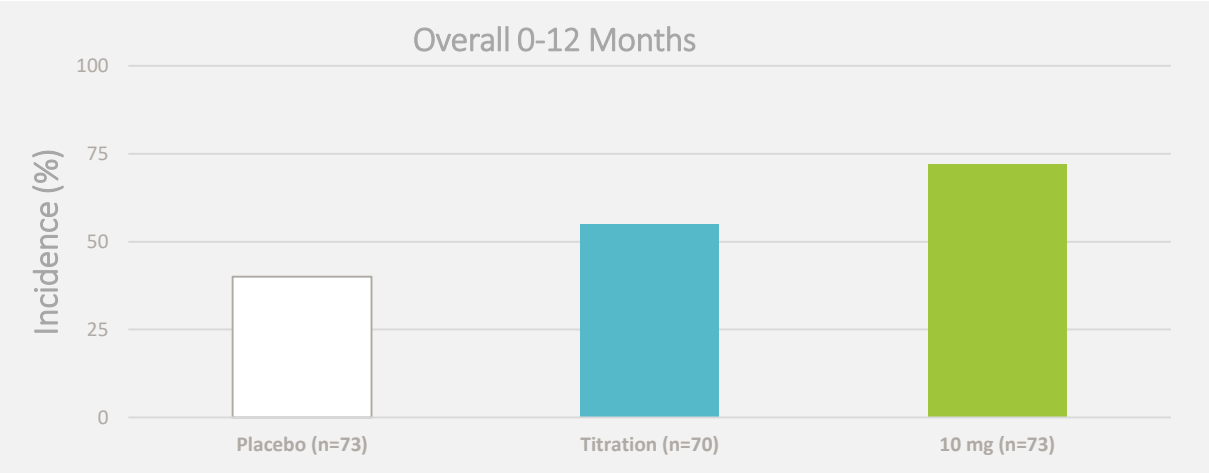
[a]Patients with ALP/GGT data at 12 months only. [b]In non-cirrhotic patients only.
[c]Data at 20 months shown. [d]5–10 mg dose titration data shown.
AIH=autoimmune hepatitis; ALP=alkaline phosphatase;
GGT=gamma-glutamyl transferase; NR=not reported.

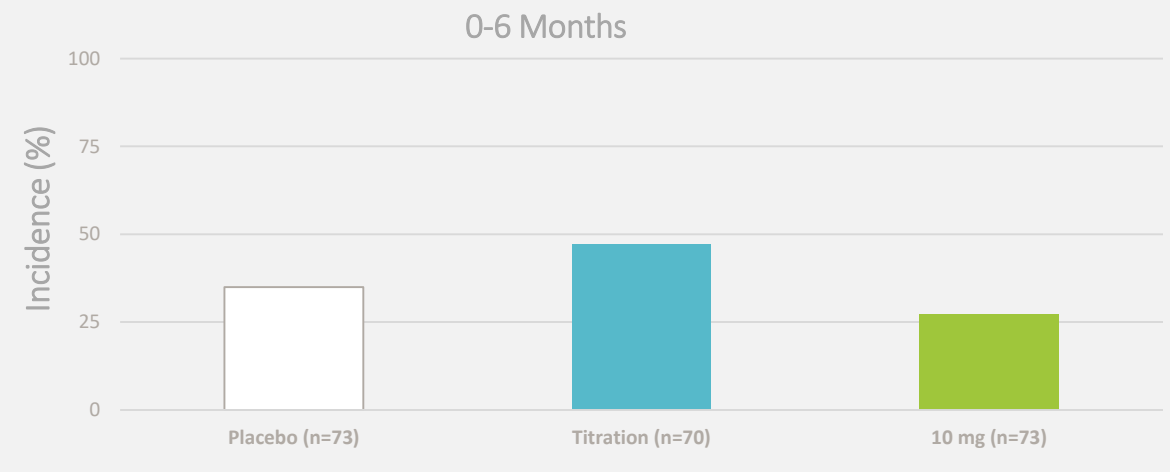
1. D'Amato D, et al. JHEP Rep. 2021;3(2):100248;
2. Roberts SB, et al. Hepatol Commun. 2020;4:1332-45; 3. Abbas N et al. EASL 2021: 770 (poster);
4. Gulamhusein A, et al. EASL-ILC. 2020: 1267 (poster); 5. Nevens F, et al. N Engl J Med. 2016;375:631-43

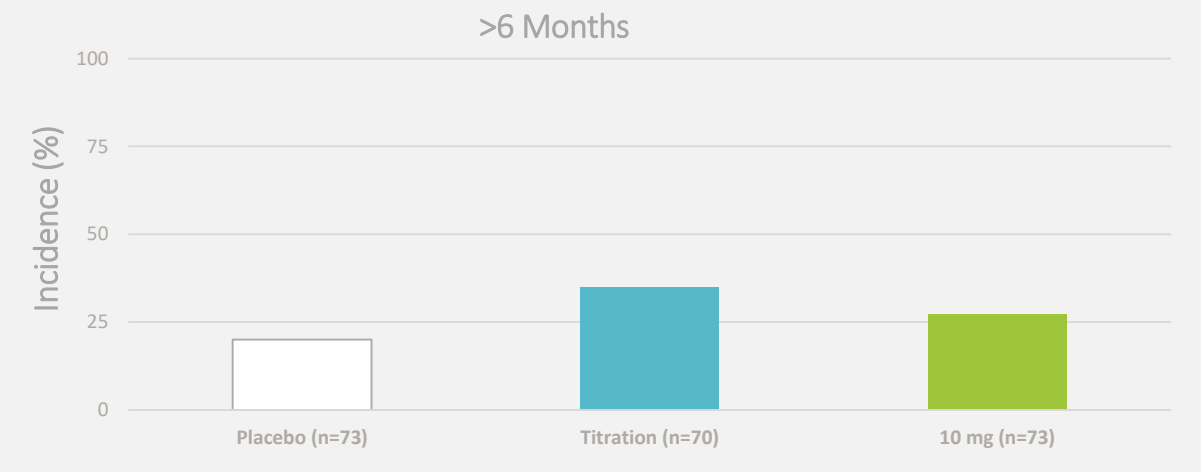
Estudio POISE: Incidencia de prurito con OCA dosis dependiente

Table 2. Incidence of Adverse Events of 10% or More in any Treatment Group.*

Event	Double-Blind Phase			Open-Label Extension
	Placebo (N=73)	Obeticholic Acid, 5–10 mg (N=70)	Obeticholic Acid, 10 mg (N=73)	Total Obeticholic Acid (N=193)
	number of patients (percent)			
Pruritus	28 (38)	39 (56)	50 (68)	138 (72)







Nevens F, et al. A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis. N Engl J Med. 2016 Aug 18;375(7):631-43

¿Cómo iniciar OCA?

UDCA 15 mg/kg

OCA 5 mg/día

5 mg tres veces por semana; si historia de prurito

Evaluación Inicial

Aumentar la dosis a 5 mg/día tras 4 semanas

Manejo de los síntomas

Los síntomas, en particular el prurito y la fatiga, son una parte importante de la CBP y deben evaluarse cuidadosamente

- **Existen intervenciones efectivas para el prurito que se deben ofertar activamente al paciente**

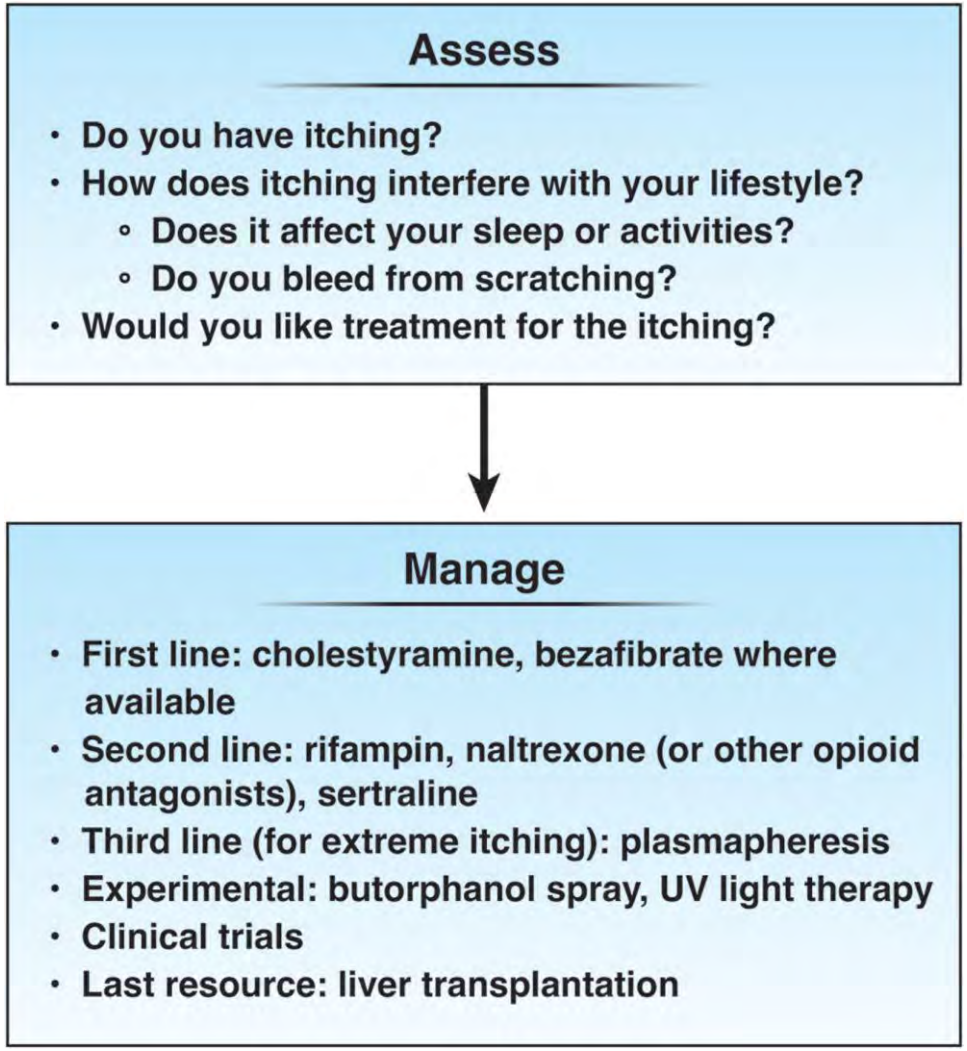
Recomendaciones

La fatiga y el prurito deben evaluarse en la primera consulta del paciente y en consultas posteriores.

Tanto la autoevaluación del paciente como la consulta por parte del médico son adecuadas.

Prurito: se debe ofrecer tratamiento (Cremas emolientes, resina de intercambio aniónico, rifampicina, sertralina, fibratos…)

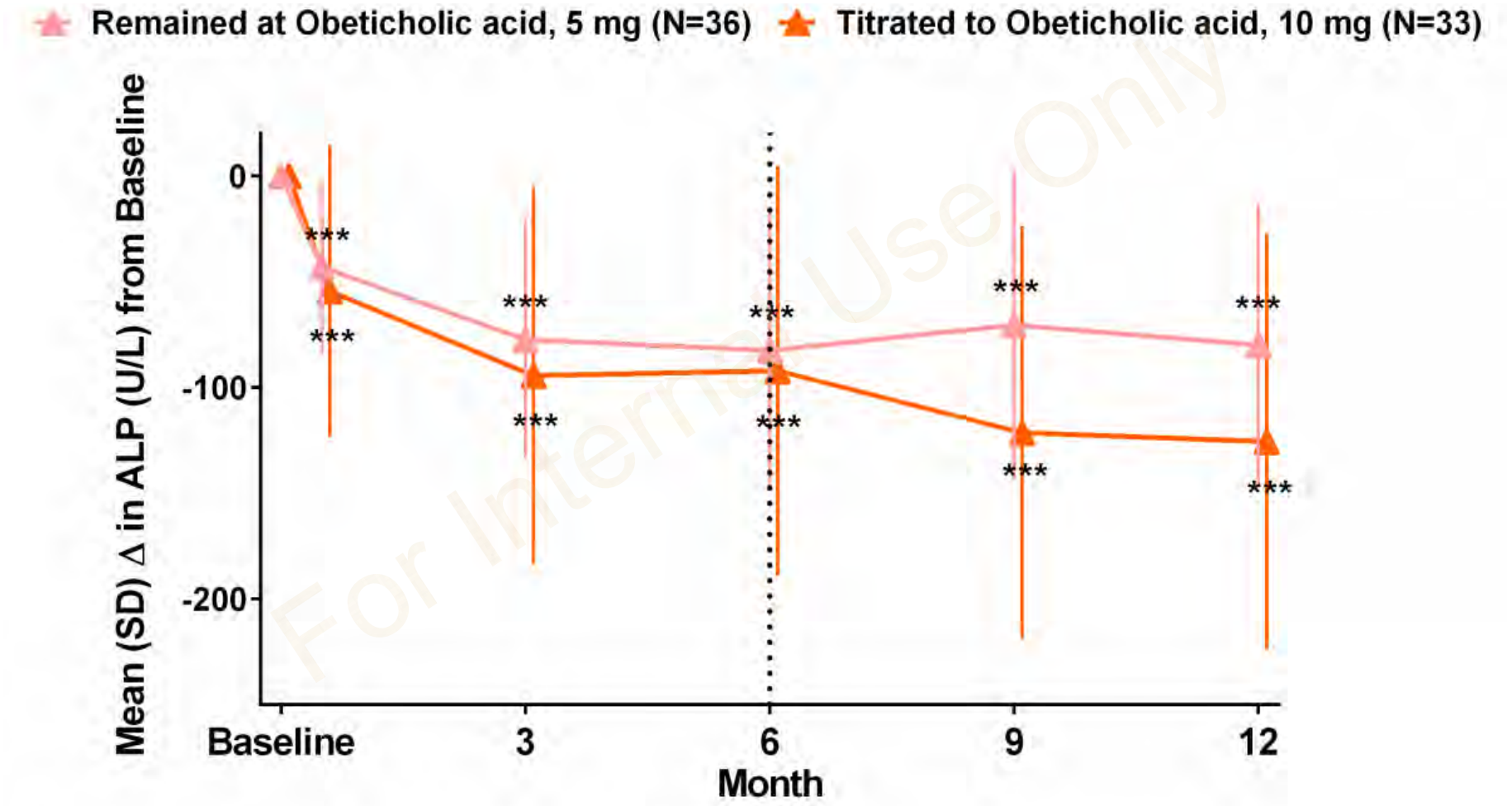
Fatiga: se debe ofrecer tratamiento (Ejercicio, Mindfulness, descartar depresión, hipotiroidismo, anemia, problemas sueño por prurito…)



Clinical Gastroenterology and Hepatology DOI: (10.1016/j.cgh.2023.02.005)

¿Necesita aumentar a 10 mg/día en el mes 3-6?

Estudio POISE: impacto del aumento de dosis



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

Estudio Copec: Mejoría de la Supervivencia Libre de Trasplante (TX hepático y exitus)

Tratados

POISE

- Ensayo clínico
- 59 centros, 39 países
- N=209

Controles externos 1 & 2

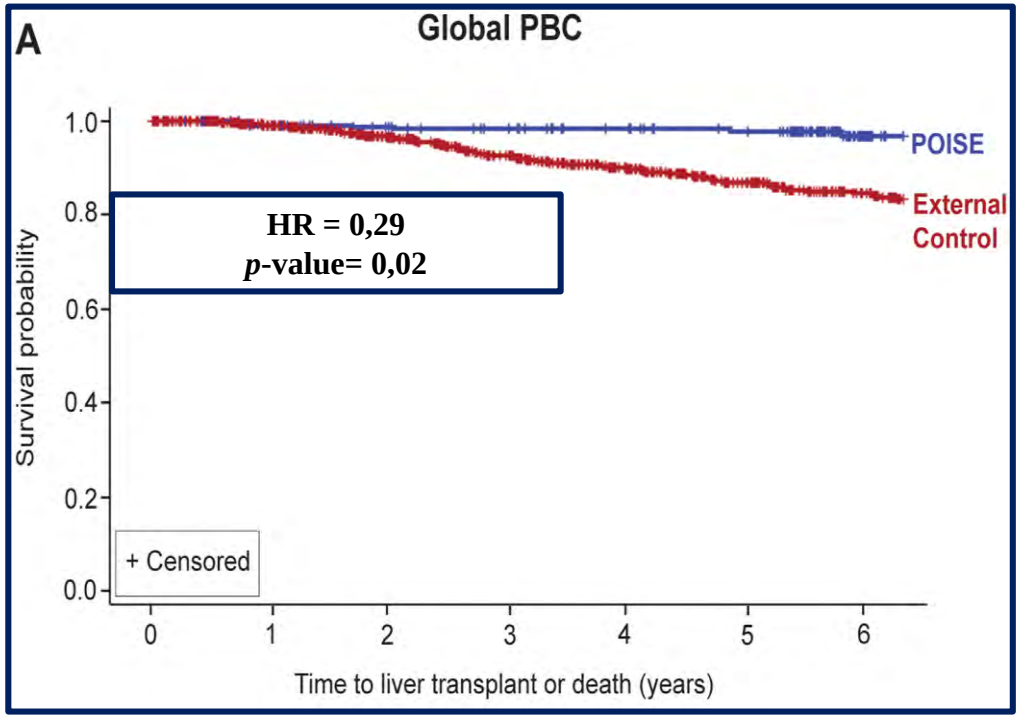
- Registro Internacional CBP
- 17 centros Europa & NA
- > 5000 CBP naïve-OCA

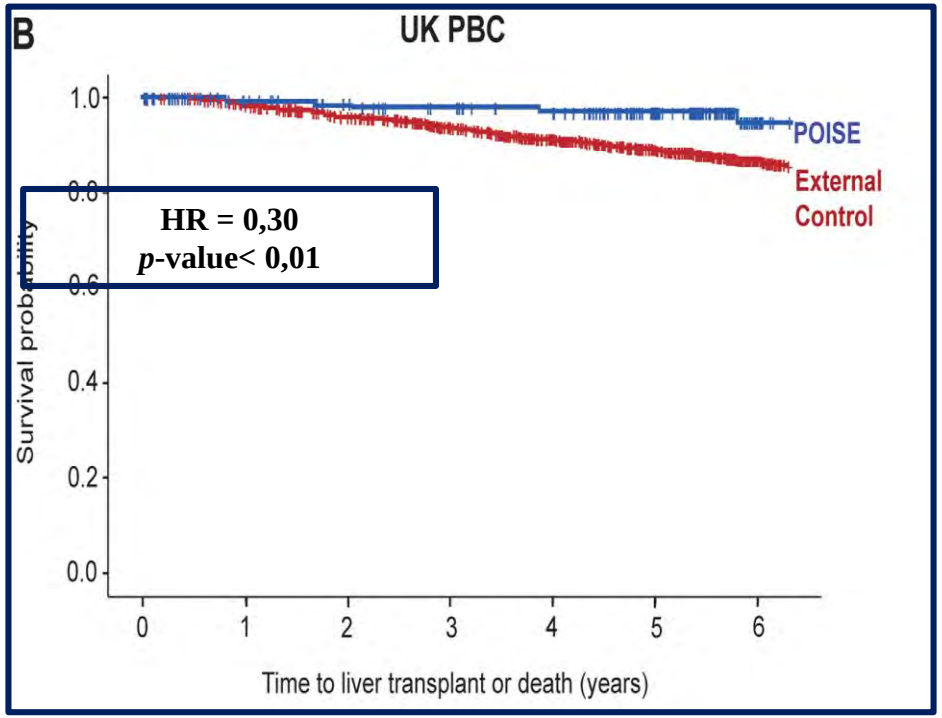
Control externo 2

- Registro UK CBP
- 161 Centros en UK
- > 6900 CBP naïve-OCA

Los pacientes de control externo cumplen los criterios de inclusión/exclusión de POISE

Weighted Kaplan-Meier Plots

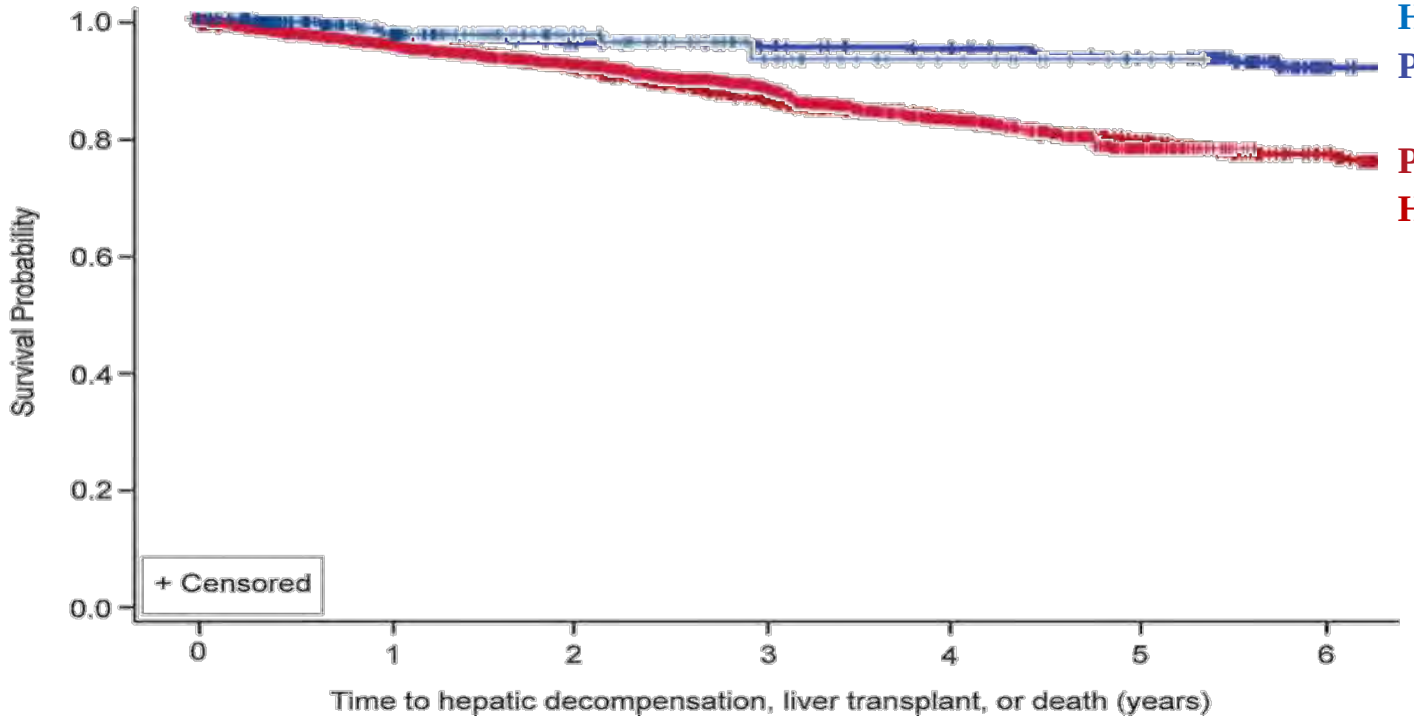




Total Number of Events	POISE (n=5)	Global PBC (n=135)	UK PBC (n=281)
Liver transplantation	2	51	119
Death	3	84	162

Murillo Perez CF, et al. Greater Transplant-Free Survival in Patients Receiving Obeticholic Acid for Primary Biliary Cholangitis in a Clinical Trial Setting Compared to Real-World External Controls. Gastroenterology. 2022 Dec;163(6):1630-1642.e3.

HEROES (Pacientes de vida real *vs.* Pacientes vida real) replica los resultados de CoPEC



HEROES/Komodo: OCA Treated
POISE Open-label Extension[1]

POISE Global PBC External Control[1]
HEROES/Komodo: Non-OCA Treated

Study	HR	95% CI	*p-value*
POISE Global PBC External Control	0.42	0.21, 0.85	0.02
HEROES	0.37	0.14, 0.75	<0.001

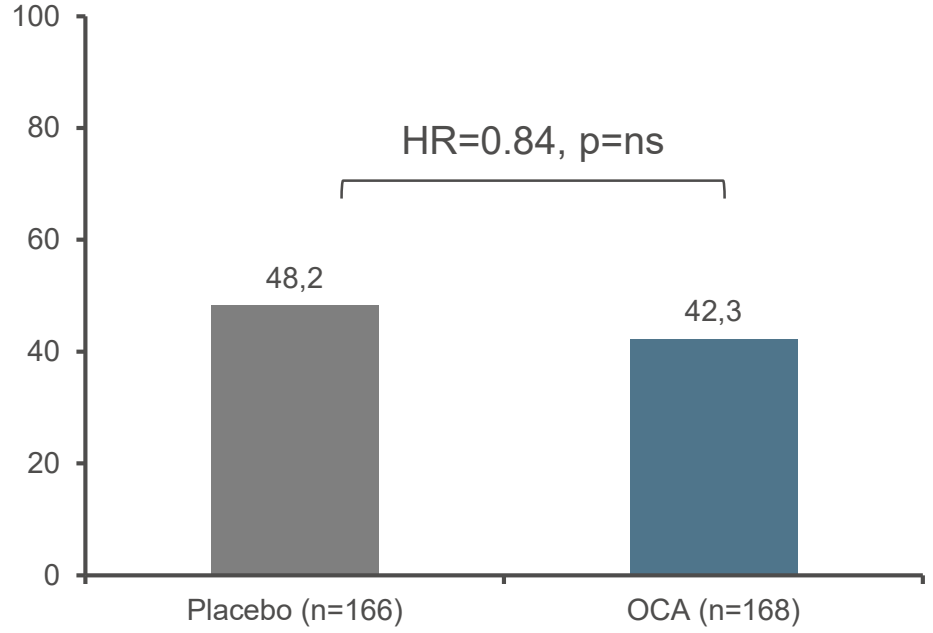
1. Murillo Perez. *Gastroenterology*. 2022;S0016-5085(22)0160-165. doi:10.1053/j.gastro.2022.08.054.

Brookhart A et al. RESULTS OF THE HEROES STUDY: TREATMENT EFFICACY OF OBETICHOLIC ACID ON HEPATIC REAL-WORLD OUTCOMES IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS. Hepatology 2022. 2022;76(Suppl. 1): P 223.

Incluso en la era de la terapia de segunda línea, el tratamiento temprano sigue siendo importante

COBALT trial of OCA in advanced PBC[1]

- Terminated early due to slow patient recruitment
- Available data was not able to identify a treatment effect from OCA



This has led to a "Dear Healthcare Professional" from the EMA

- OCA no longer recommended for patients with a history of, or concomitant decompensated cirrhosis

Ocaliva®▼ (obeticholic acid): New contraindication for the treatment of primary biliary cholangitis (PBC) in patients with decompensated liver cirrhosis or a history of prior hepatic decompensation

Dear Healthcare Professional,

Intercept, in agreement with the European Medicines Agency (EMA) and the <National Competent Authority>, would like to inform you of the following:

Summary

Taking into consideration the inability to establish the safety and efficacy of obeticholic acid through clinical trials in patients with PBC with decompensated liver cirrhosis, or with a prior history of hepatic decompensation, as well as new safety information from post-marketing reports, the use of obeticholic acid is now contraindicated in patients with PBC with decompensated cirrhosis (including Child-Pugh Class B or C) or a prior decompensation event.

- **Treatment should be discontinued in patients with PBC with decompensated cirrhosis currently receiving obeticholic acid.**
- **Patients should be routinely monitored for progression of PBC and treatment with obeticholic acid should be permanently discontinued in patients with laboratory or clinical evidence of hepatic decompensation including progression to Child-Pugh class B or C.**
- **Treatment with obeticholic acid should not be started if the patient has decompensated cirrhosis or a history of a decompensation event prior to treatment initiation.**
- **The SmPC and the patient leaflet are being updated to reflect this new contraindication and additional warnings based on newly available safety data.**

1. Intercept Press Release June 3, 2022. https://ir.interceptpharma.com/news-releases/news-release-details/intercept-announces-new-clinical-trial-and-real-world-outcomes (accessed June 2022)

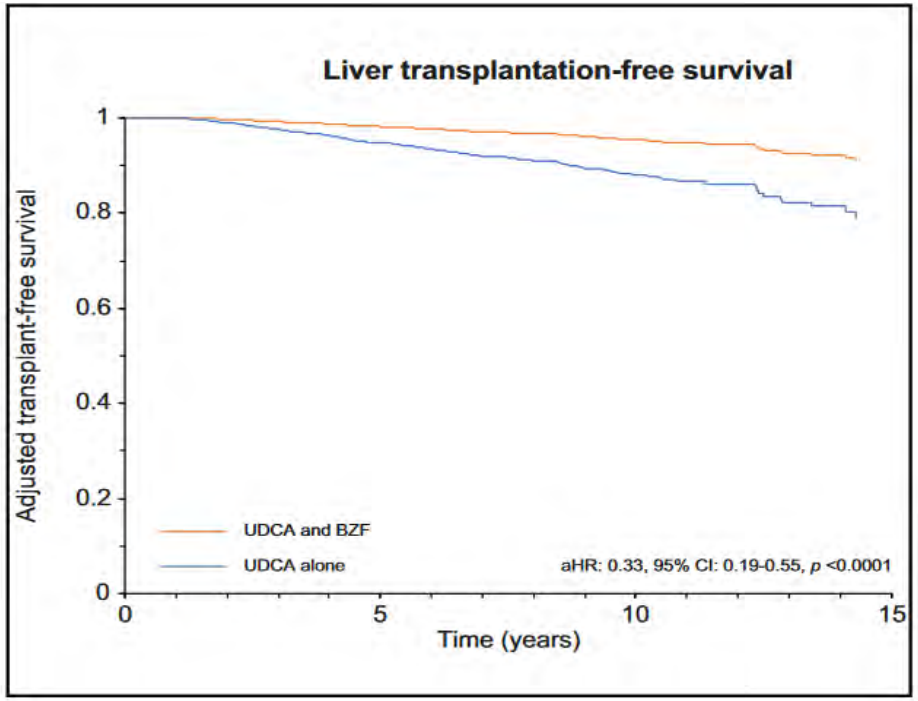
Tratamiento de 2ª linea off label: Fibratos

AUDC + BZ se asoció con mejoría de la supervivencia libre de TH, mejoría de la supervivencia global y la asociada con mortalidad hepatica.

Bezurso Trial

- Ensayo clínico doble ciego, aleatorizado (n=100)
- No R a AUDC (Paris II)
- BZF+AUDC vs AUDC (2 años)
- Normalización FA: 66% vs 2%
- RC (normal FA, transas, BT, alb, PT): 30% vs 0%
- Mejoría prurito y LS

Corpechot, NEJM 2018



BZF ha demostrado mejorar síntomas, marcadores bioquímicos y eventos a largo plazo

Estudio retrospective de cohort Nacional Japonesa (n = 3,908) .

Journal of Hepatology 2021 vol. 75 j 565–571

Caso

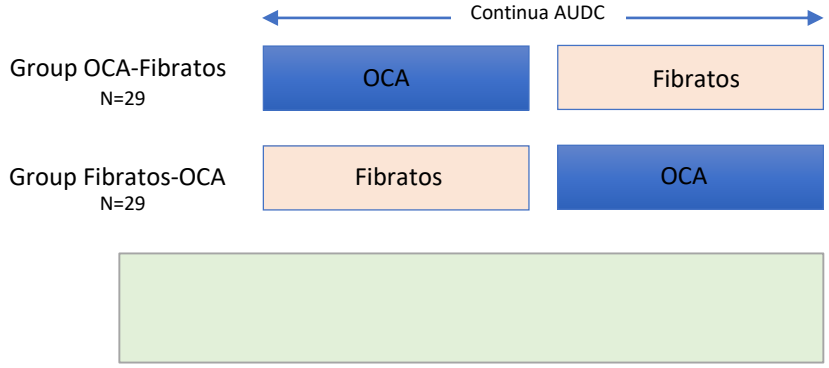
- OCA: 5 mg al día
- **PLAN:**
- Aumentar a 10 mg al día en caso de no RC a los 3 meses
- Si tras 6 meses ausencia de RC: combinación con bezafibrato

Consideraciones:

- Haber iniciado tratamiento de 2ª línea a los 6 en vez de 12 meses.
- Considerar RC (normalización enzimas) en pacientes, st aquellos con enfermedad hepática avanzada
- Confirmar antes de iniciar OCA: no prurito o controlado, no signos HPTp en ECO/Fibroscan, no descompensación o Hª descompensación previa

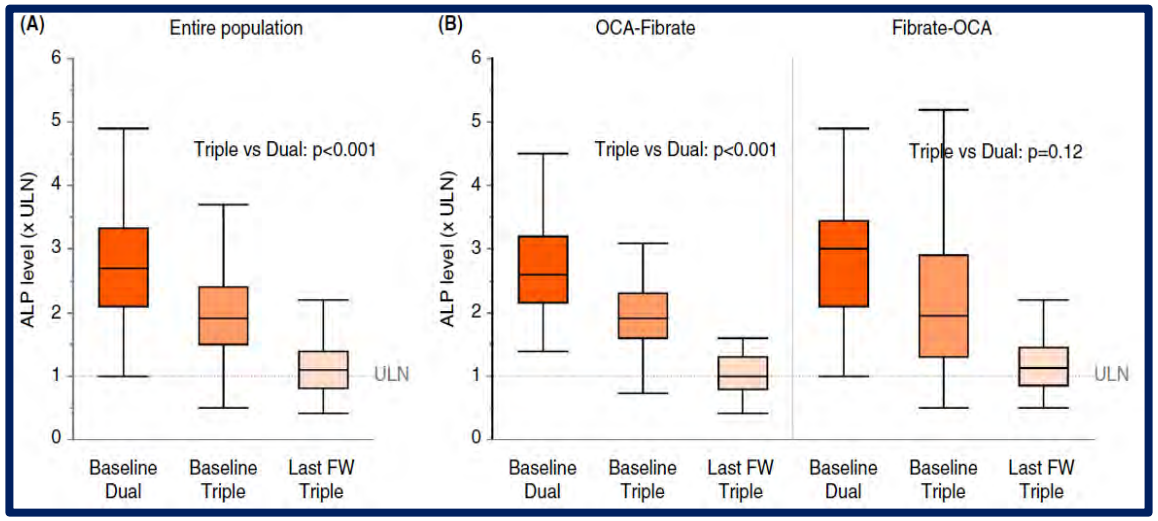
Ausencia de respuesta a 2ª línea (≥3ms)- añadir 3ª línea

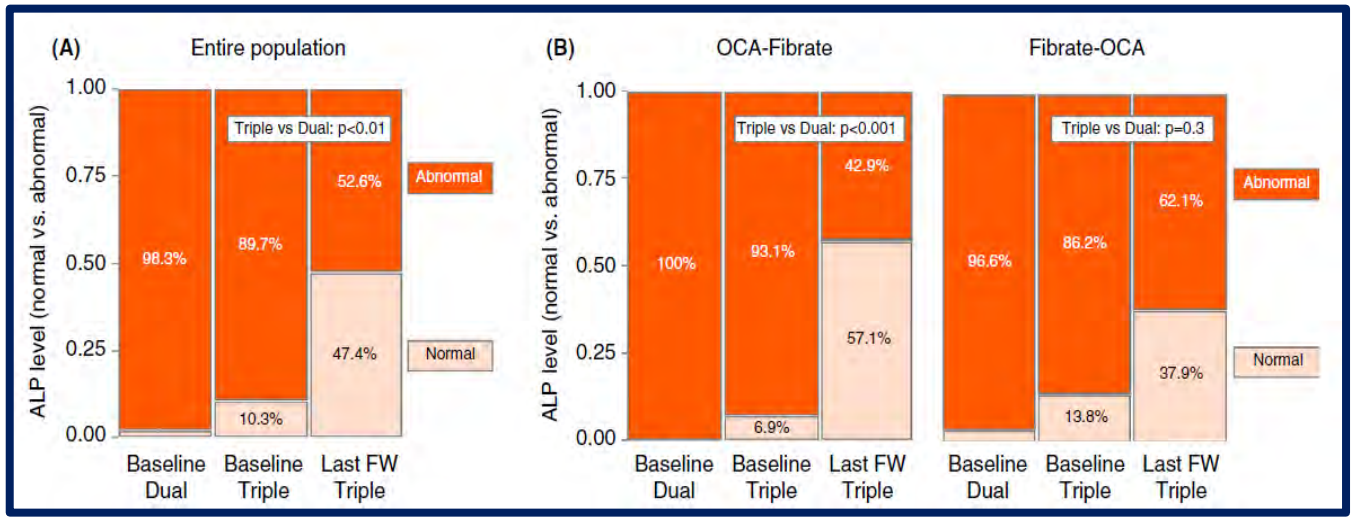
Estudio retrospective multicéntrico (01-12/2019)



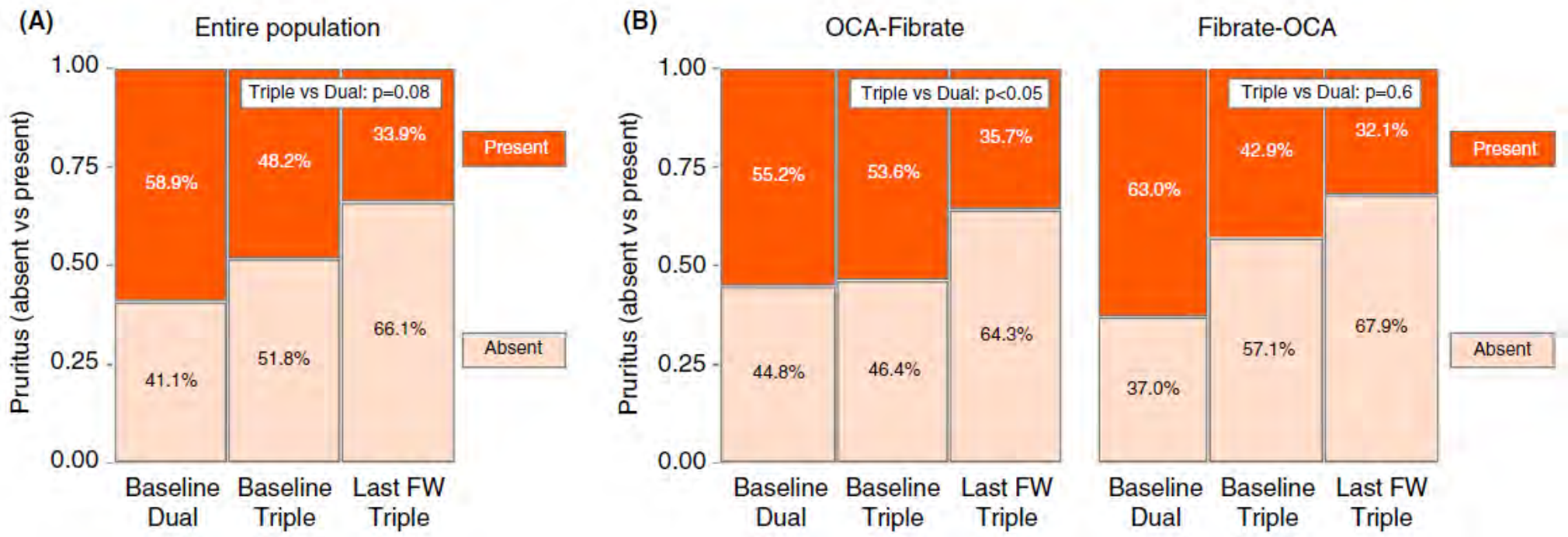
Años	OCA-Fibratos	Fibratos-OCA	P-value
Seguimiento global	9.6 (12.2)	8.2 (0.9)	0.35
Terapia doble	4.8 (5.1)	2.4 (3.1)	0.41
Terapia triple	0.9 (0.5)	0.8 (0.9)	0.31

	Grupo: OCA-Fibratos	Grupo: Fibratos-OCA
OCA	5 mg (rango: 1.7-10)	5 mg (rango: 0.7-10)
BZF	400 mg (rango: 200-400)	400 mg (rango: 200-400)
FNF	160 mg (range: 72.5-200)	180 mg (rango: 160-200)





Tasa de prurito



No pruritus: TT vs dual con OR 2.5 /año (95% CI 0.9-6.9, p=0.08) en la población global

OCA-Fibrate: OR 9.9 /año (95% CI 1.5-67.1; p<0.05)

Fibrate-OCA: OR 1.4 /año (95% CI 0.4-4.9,p=0.6)

Soret PA, et al. *Aliment Pharmacol Ther.* 2021;00:1-9.

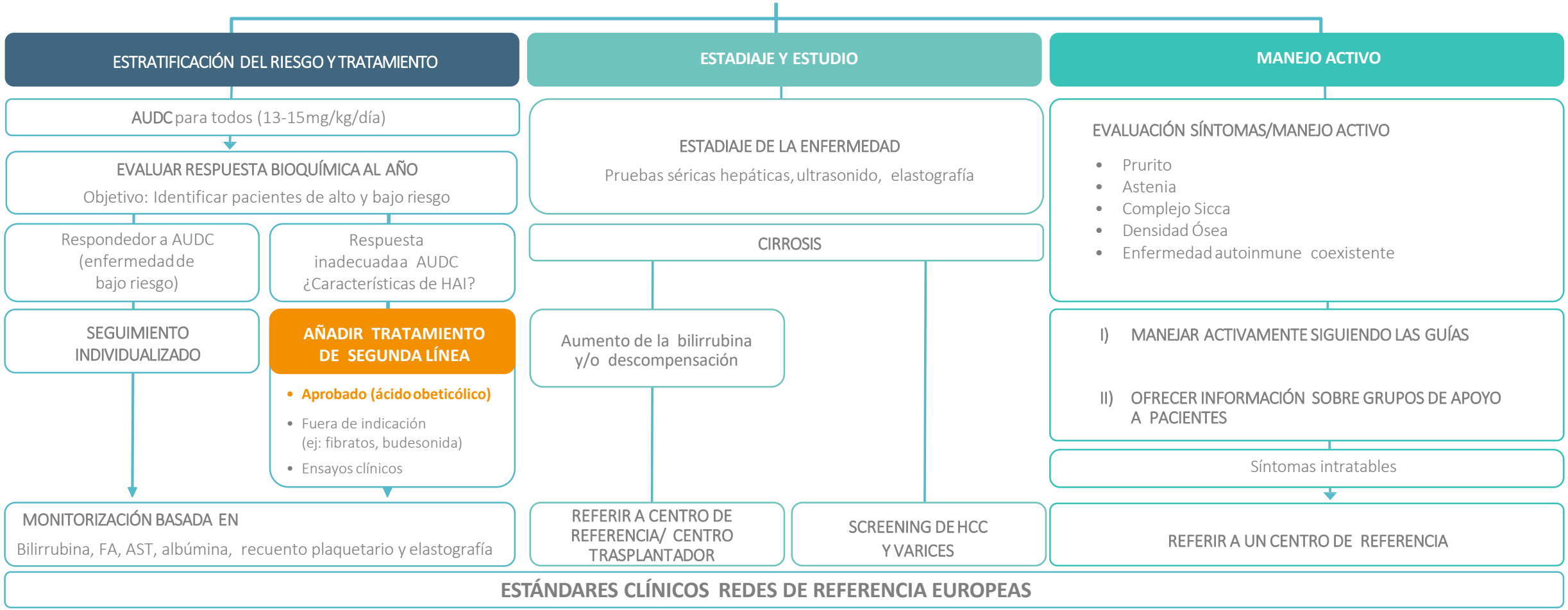
Expectativas futuras (Fase 3 Trials) en CBP/prurito

Drug, NCT	Mechanism of action	No. of patients in phase 2 trial, study duration	Summary of findings to date
Seladelpar NCT04620733	PPAR-delta agonist	N = 112, 1 year; Long-term extension in progress	69% met POISE with 10 mg/day at 1 year, 79% at 2 years 33% normalized ALP at 1 year Improvement in pruritus Improvement in sleep
Elafibranor NCT04526665	PPAR-alpha/delta agonist	N = 45, 12 weeks	79% met POISE with 120 mg/day 21% normalized ALP Improvement in pruritus
Saroglitazar NCT05133336	PPAR-alpha/gamma agonist	N = 37, 16 weeks	71% met POISE
Setanaxib NCT05014672	NOX 1/4 inhibitor	N = 111, 24 weeks	24% reduction in ALP among patients with liver stiffness >9.6 kPa treated with 400 mg twice a day; post hoc analyses with improvement in fatigue scores
Linerixibat NCT04950127	ASBT inhibitor	N = 147, 12 weeks; Long-term extension in progress	Improvement in itching; Improvement in sleep

ALP, alkaline phosphatase; ASBT, apical sodium-bile acid transporter (same as IBAT, ileal bile acid transporter); NCT, National Clinical Trial; NOX, NADPH oxidase;
PBC, primary biliary cholangitis; POISE, composite score for response to treatment indicating ALP <1.67 ULN, with reduction >15% from baseline and total bilirubin (TB) < ULN; PPAR, peroxisome proliferator-activated receptor.

COLANGITIS BILIAR PRIMARIA

Los objetivos del tratamiento de la CBP consisten en prevenir las complicaciones de enfermedad hepática avanzada y el manejo de los síntomas asociados



European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol (2017), http://dx.doi.org/10.1016/j.jhep.2017.03.022