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Highlights 2023: Hepatologie

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UniversitätsSpital Zürich

Gastro Highlights 2023, Wien – 9. Dezember 2023

Potentielle Interessenskonflikte

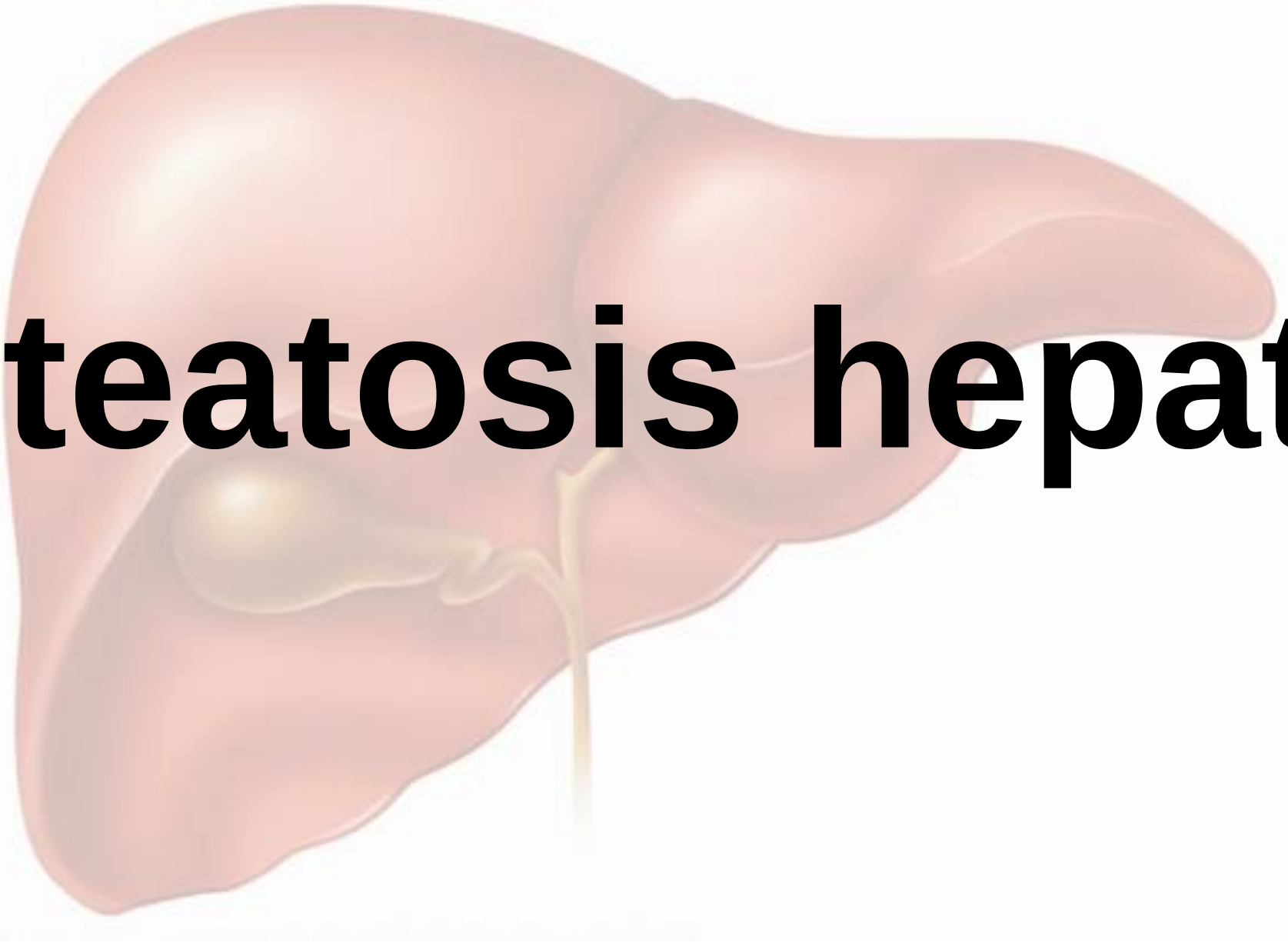
Subjektive Auswahl an Publikationen aus 2023

- Consultant / Advisor: Abbvie, Advanz, Alentis, AlphaSigma, AstraZenca, Avior, Bayer, CymaBay, Eisai, Escient, Falk, FMC, Gilead, GSK, Guidepoint, Intercept, Mirum, Medscape, MSD, Myr, Roche, Viofor

- Speaker: Abbvie, Advanz, AOP Orphan, Bayer, BMS, CMS, CymaBay, Falk, Gilead, GSK, Intercept, Newbridge, Novartis, Lilly, Mirum, MSD, Roche, Zambon

- Clinical Studies: Bayer, BMS, CymaBay, Eli Lilly, Falk, Genkyotex, Gilead, GSK, Intercept, Lilly, Mirum, MSD, NGM, Novartis, Pliant

- Unrestricted grants: Gilead, Intercept



Steatosis hepatis

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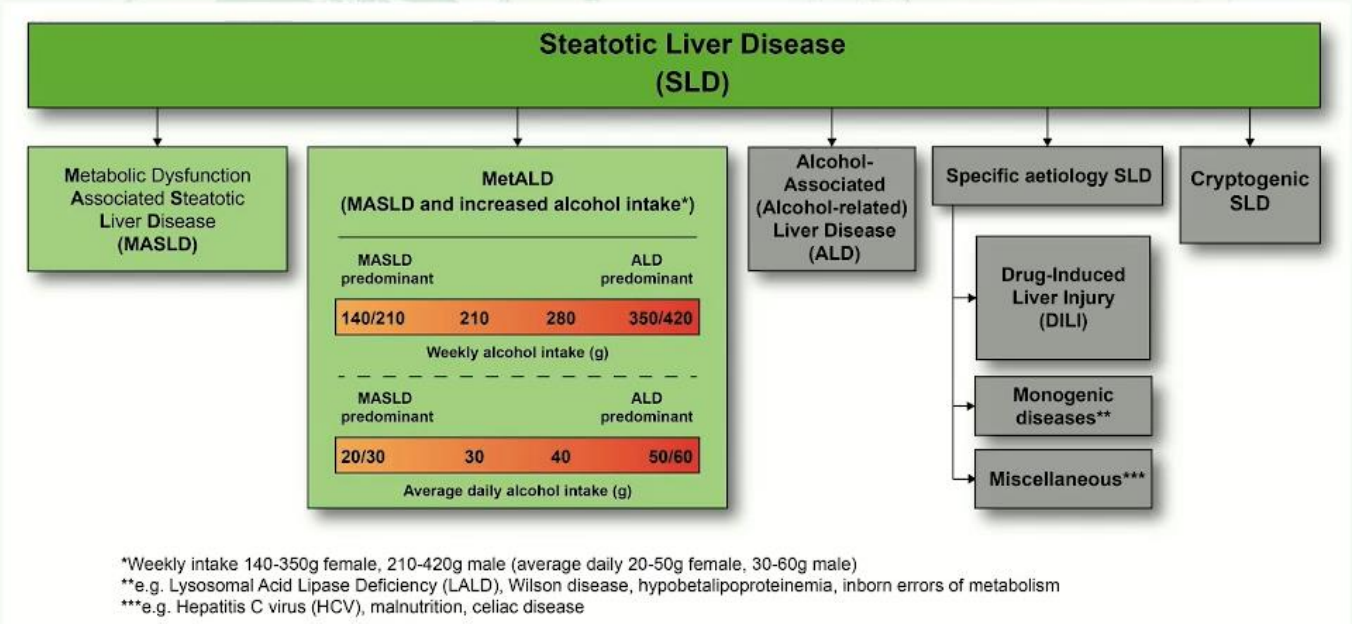
Keine NASH / NAFLD / MAFLD mehr!
Neue Nomenklatur: Steatotische Lebererkrankungen (SLD)

Consensus nomenclature



*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease

EASL CONGRESS
Vienna, Austria
21–24 June
2023

easlcongress.eu

#EASLCongress

ALEH

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

EASL
The Home of Hepatology

Rinella ME et al., J Hep 2023; 24: S0168

Neue Klassfikation steatotischer Lebererkrankungen

MASLD – Metabolic Dysfunction Associated Steatotic Liver Disease:

Metabolic

Dysfunction

Associated

Steatotic

Liver

Disease

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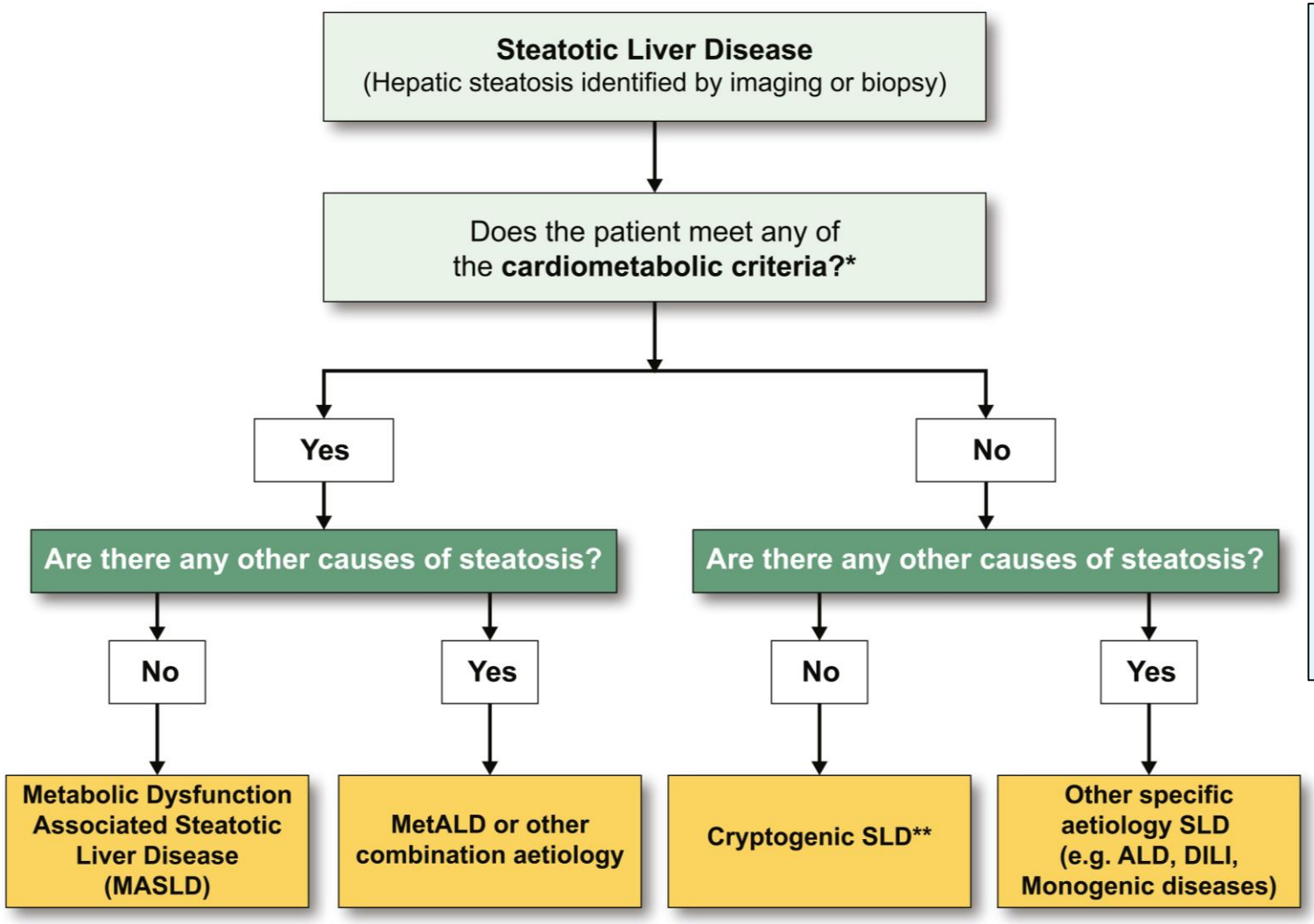
Rinella ME et al., J Hep 2023; 24: S0168

MASLD – diagnostische Kriterien



Cardiometabolic Criteria for Adults (at least 1 out of 5):

- ❑ **BMI ≥ 25 kg/m²** (23 Asia) or **waist circumference 94 cm** (m) 80 cm (f) or ethnicity adjusted
- ❑ **Fasting serum glucose ≥ 5.6 mmol/L** or 2h post-load glucose level ≥ 7.8 mmol/L or **HbA1c ≥ 5.7%** or type 2 DM or treatment for **type 2 DM**
- ❑ **Blood pressure ≥ 130/85** mmHg or specific antihypertensive drug **treatment**
- ❑ **Plasma triglycerides ≥ 1.70 mmol/l** or lipid lowering **treatment**
- ❑ **Plasma HDL cholesterol ≤ 1.0 mmol/l** (m) and ≤ 1.3 mmol/L (f) or lipid lowering **treatment**

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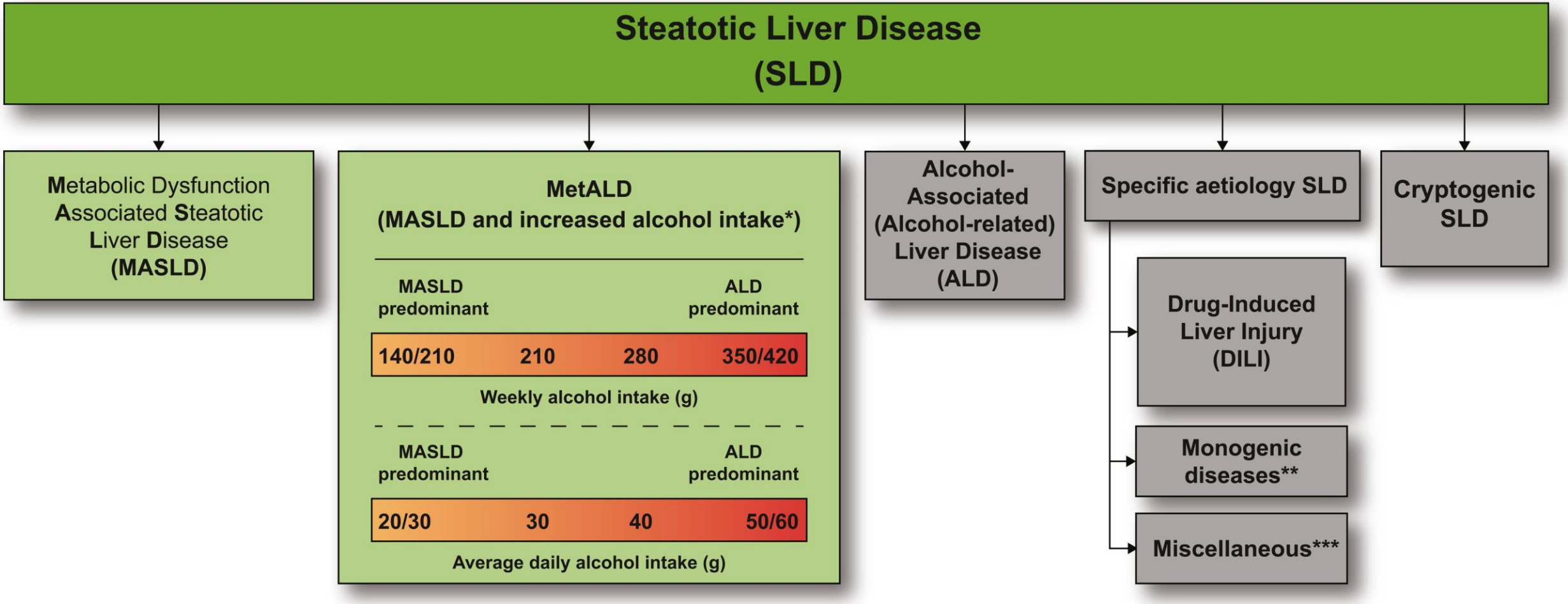
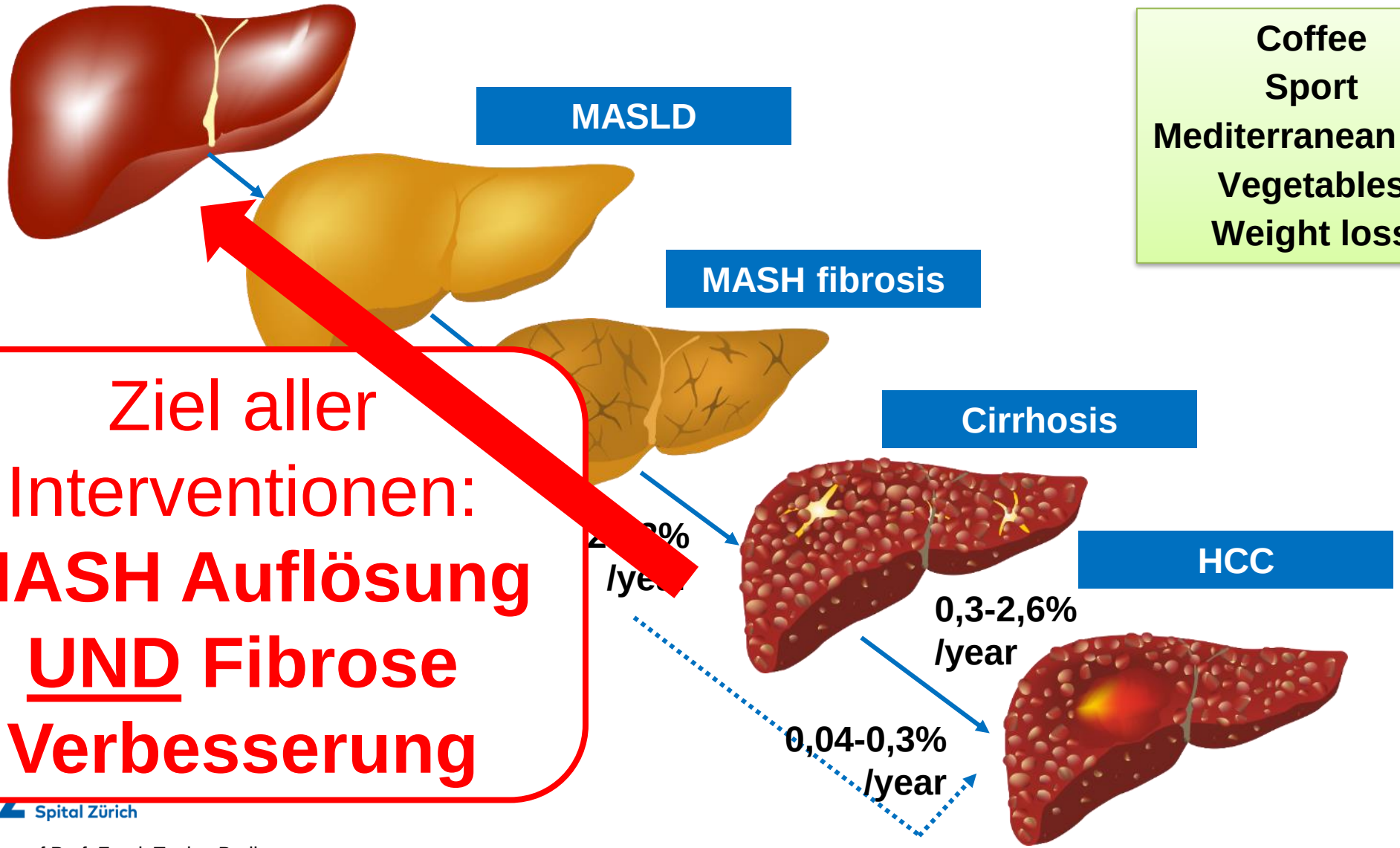
Rinella ME et al., J Hep 2023; 24: S0168



*Weekly intake 140-350g female, 210-420g male (average daily 20-50g female, 30-60g male)
**e.g. Lysosomal Acid Lipase Deficiency (LALD), Wilson disease, hypobetalipoproteinemia, inborn errors of metabolism
***e.g. Hepatitis C virus (HCV), malnutrition, celiac disease

Rinella ME et al., J Hep 2023; 24: S0168

Natürlicher Verlauf der MASLD



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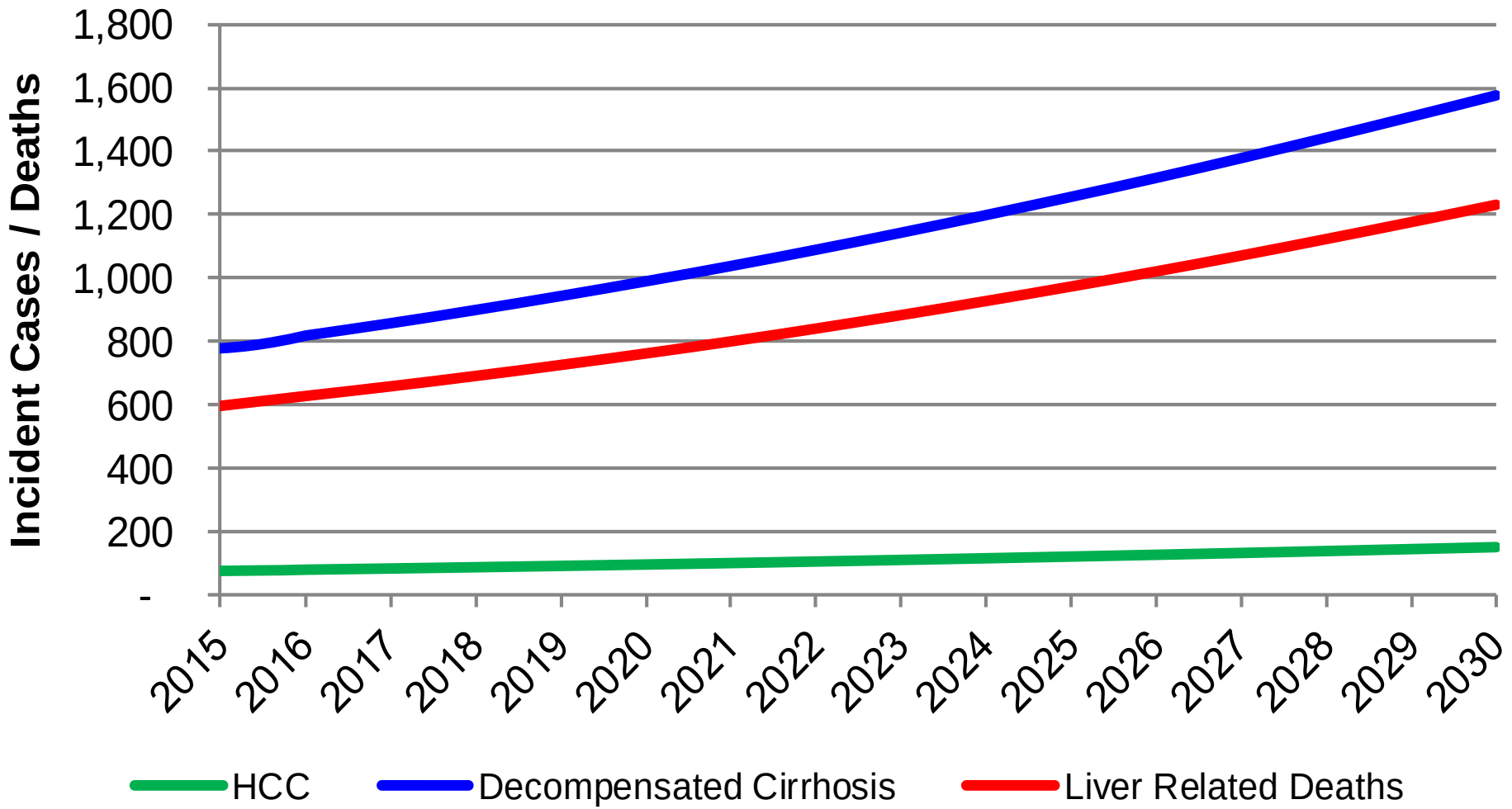
Courtesy of Prof. Frank Tacke, Berlin

Erwartete Komplikationen der MASLD in der Schweiz



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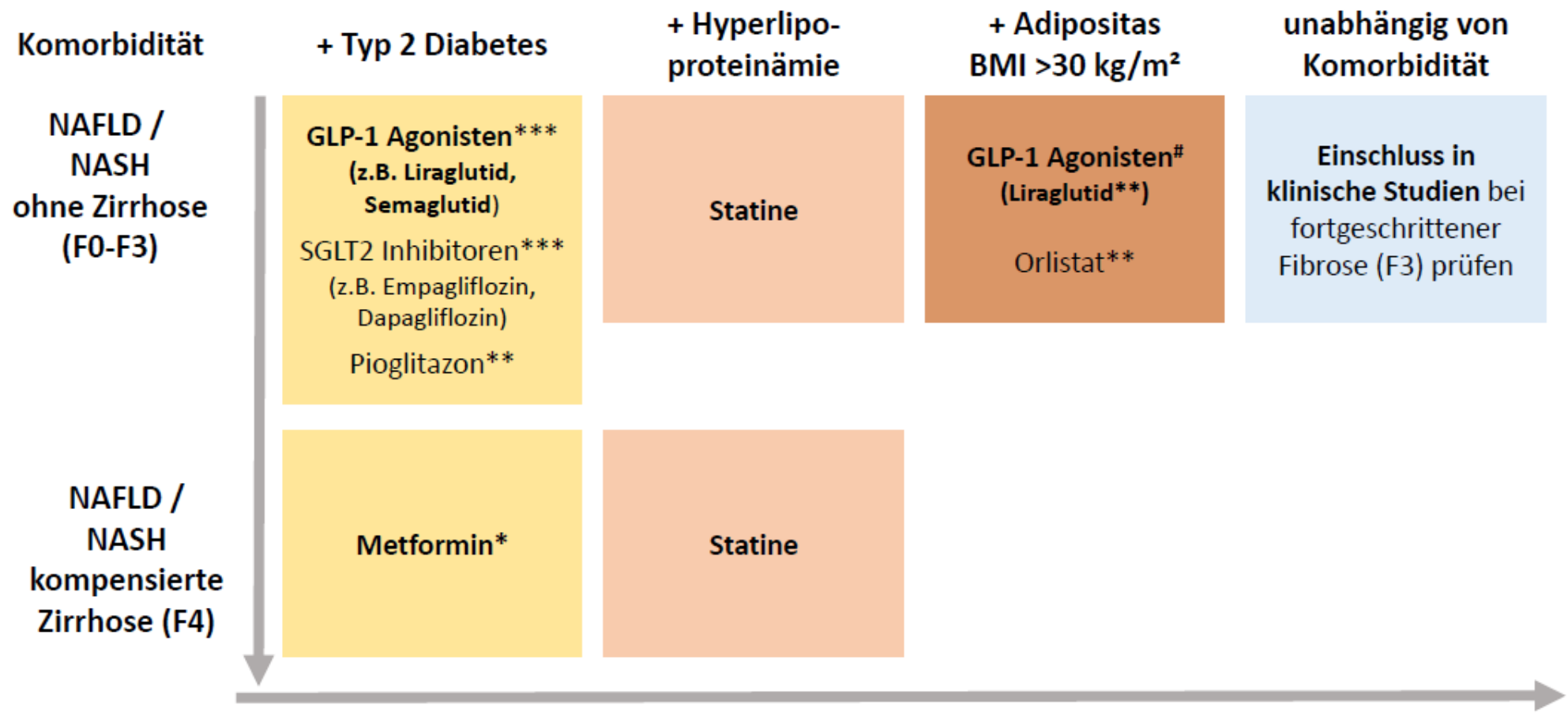
Goossens N et al., Swiss Med Wkly 2019

Medikamentöse Behandlung der MASLD – S2k-Leitlinie



*sofern GFR > 30ml/min; **derzeit nicht erstattungsfähig in der gesetzlichen Krankenversicherung;
***Zulassung in Kombination mit Metformin; #bislang liegt hier nur eine Zulassung für Liraglutid vor

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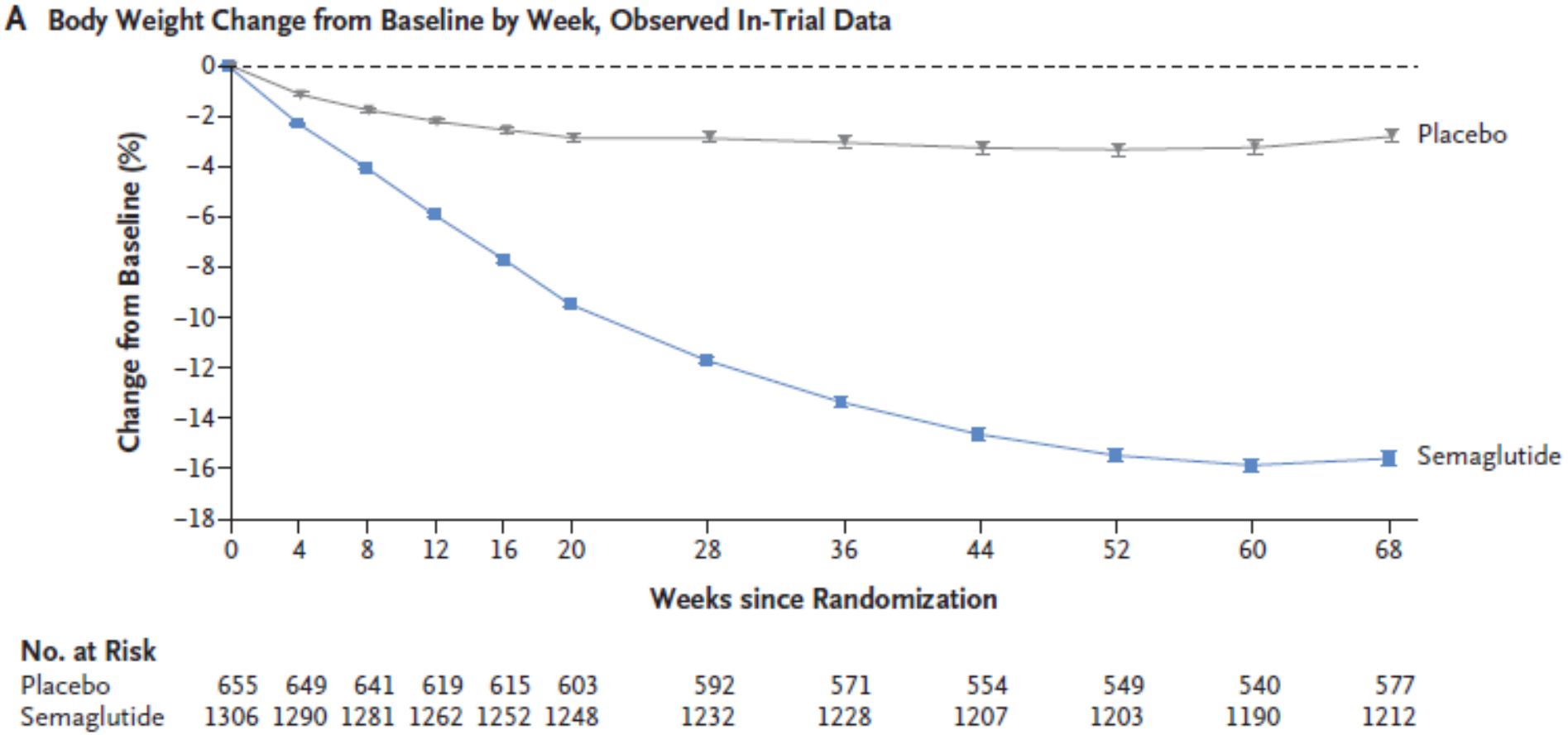
Update S2k-Leitlinie Nicht-alkoholische Fettlebererkrankung DGVS, Stand: 2023

Semaglutid induziert starken Gewichtsverlust bei Adipositas
(N = 1961; mittlerer BMI: 37.8 kg/m^2)



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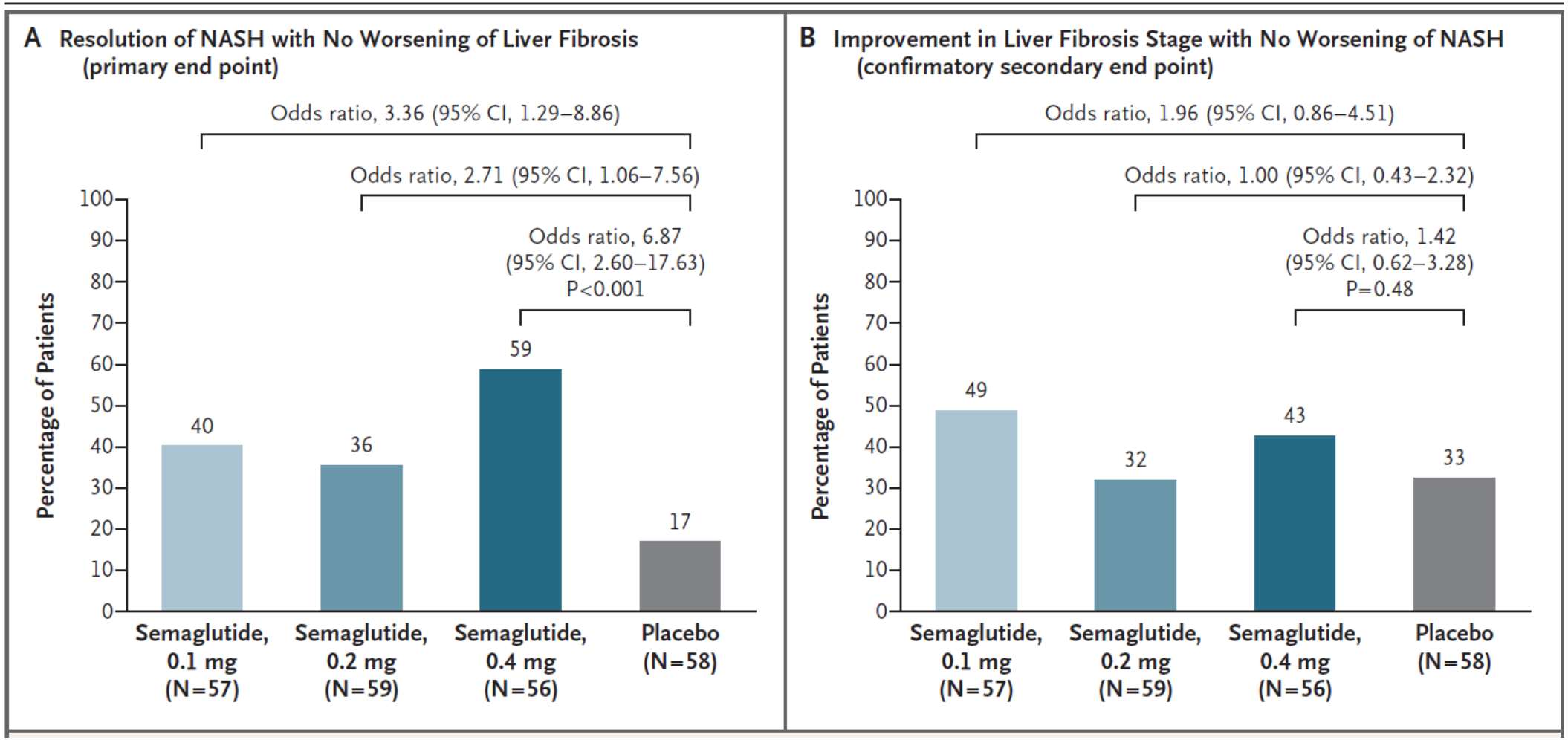
Wilding JP et al., New Engl J Med 2021; 384:989

Semaglutid in nicht-zirrhotischer MASLD



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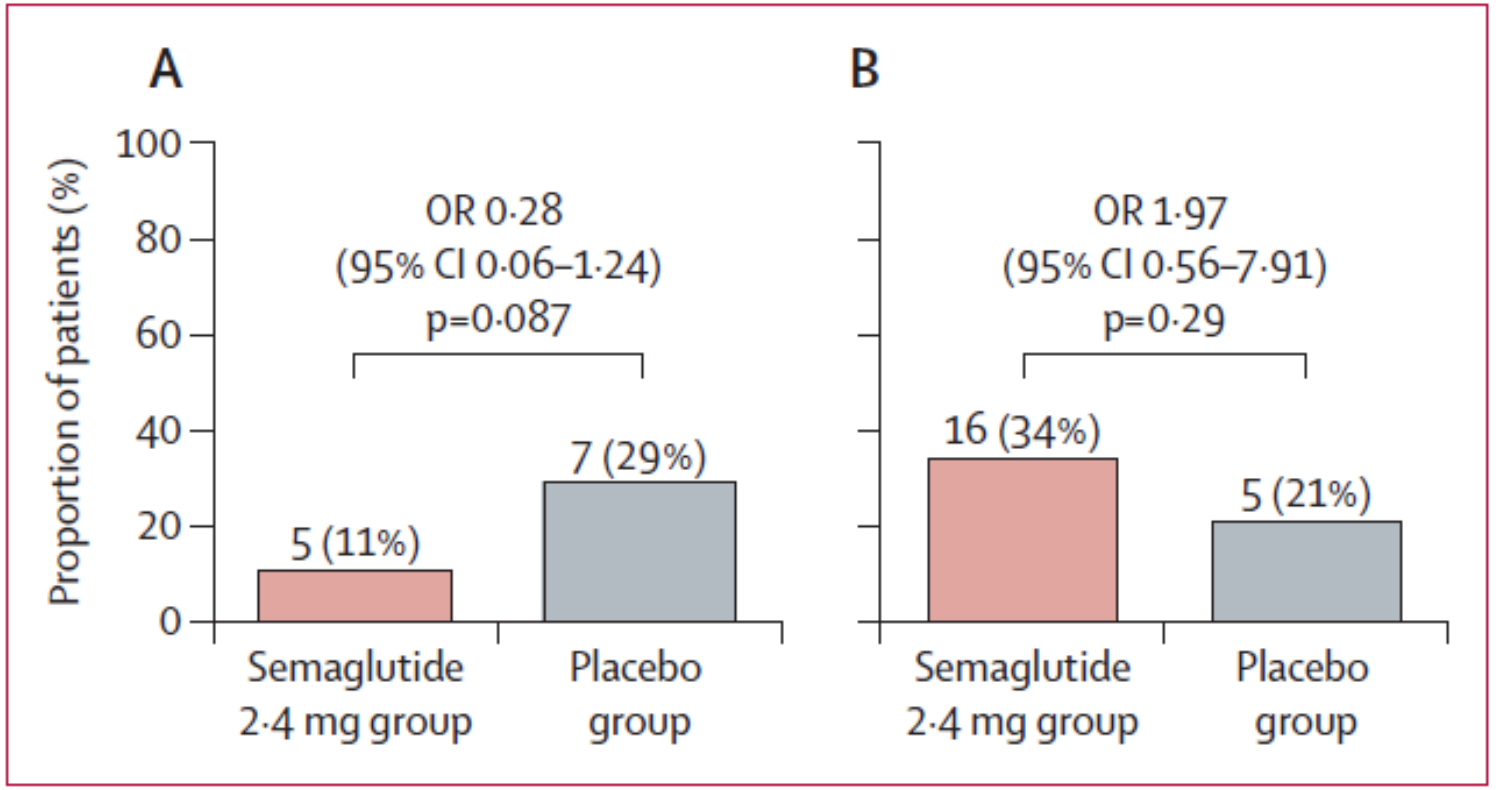
Newsome PN et al., NEJM 2021;384:1113

Semaglutid bei MASLD Zirrhose ?

- N=71; BMI > 27 mg/kg2; Start 0.25 mg; Steigerung bis 2.4 mg/Wo -

Fibrosis improvement
without worsening of NASH

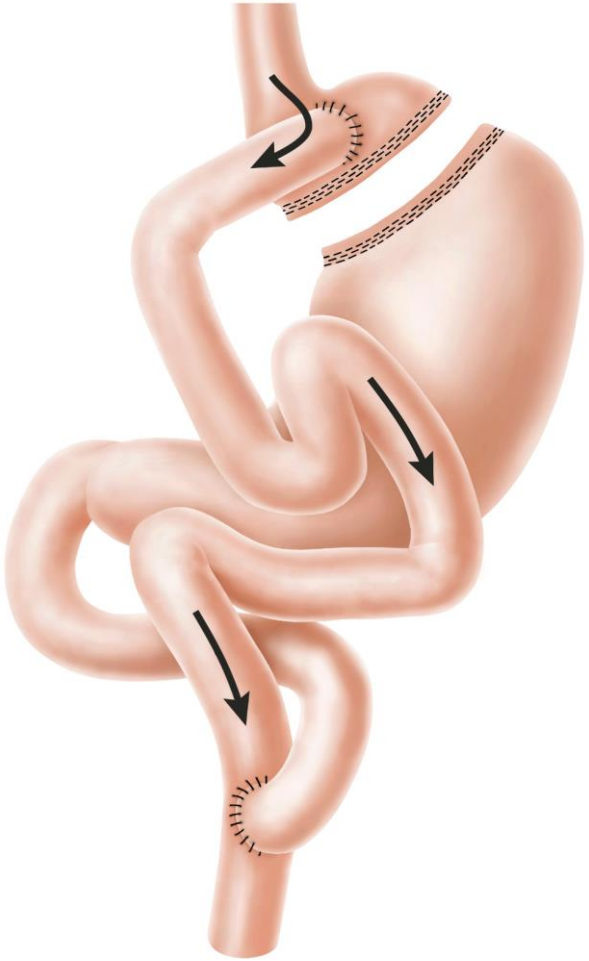
NASH resolution
without worsening of fibrosis



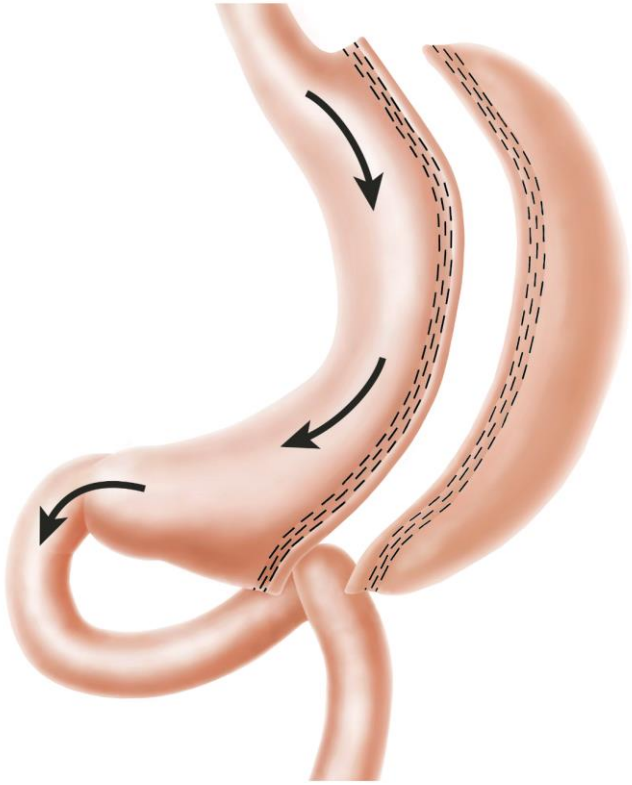
Gewichtsreduktion: 8.7 kg; Verbesserung kardio-metabolischer Parameter
Keine Sicherheitsbedenken

Loomba R et al., Lancet Gastro Hepatol 2023;8:511

Bariatrische Chirurgie bei MASLD

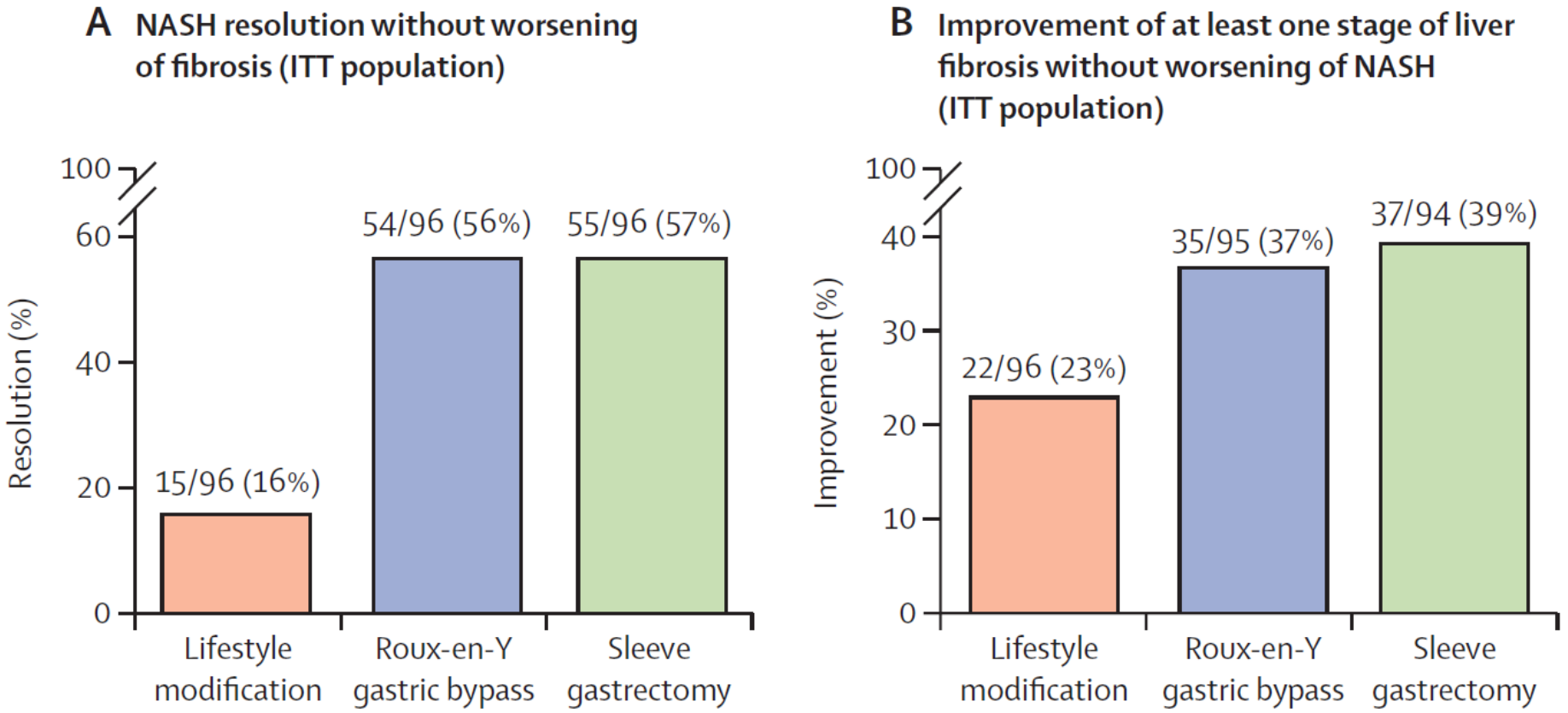


Roux-en-Y Gastric Bypass



Sleeve Gastrectomy

Bariatrische Chirurgie versus Lifestyle-Intervention
- Open-label, randomisierte Studie (N=288); BMI: 42 kg/m2 -



Lifestyle inkl. Liraglutid und Pioglitazon

SAE in 6% nach bariatrischer Chirurgie!

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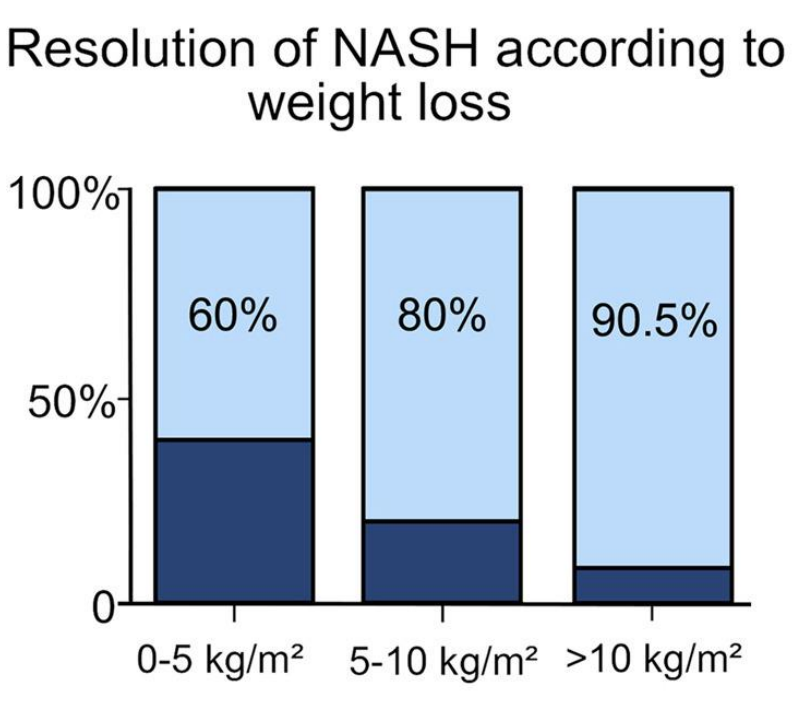
Verrastro O et al., Lancet 2023; 401: 1786

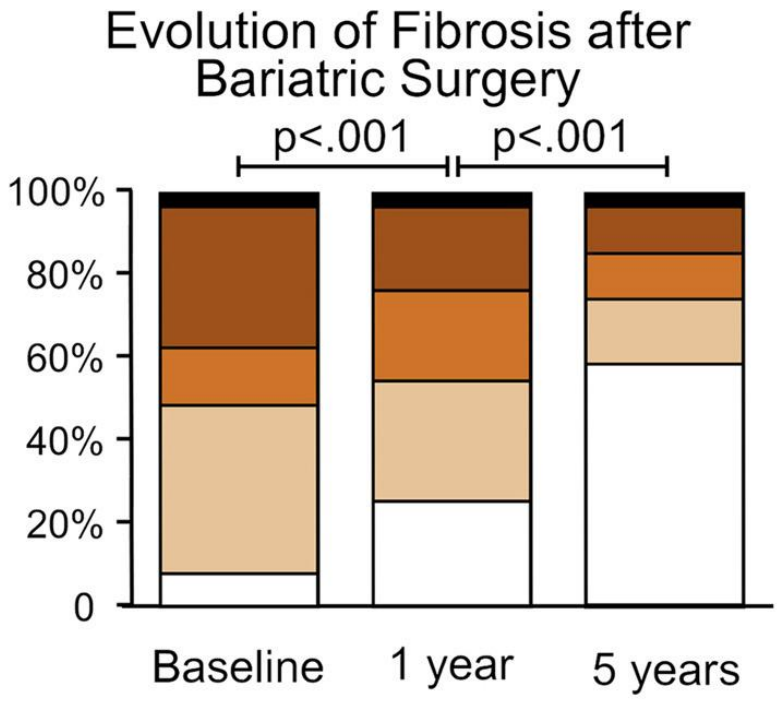
Bariatrische Chirurgie verbessert nicht MASLD-Zirrhose

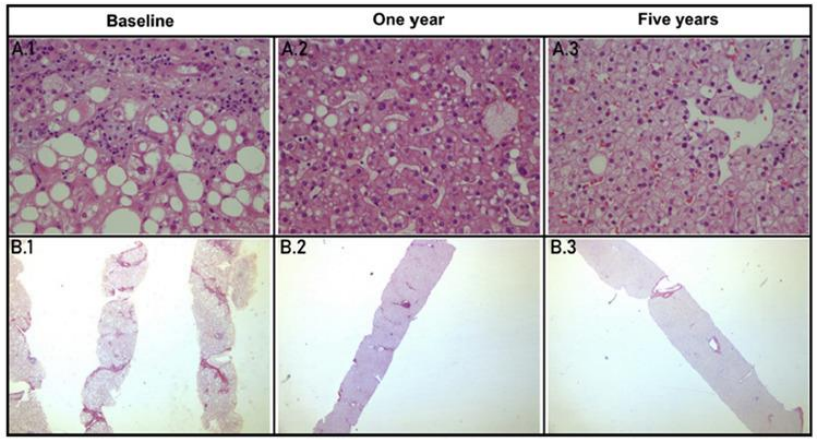
N=196: advanced MASH

- **Age: 51 ± 9; 62% female; Mean weight: 130 ± 24 kg; Diabetes: 89%**

→ bariatric surgery: Roux-en-Y / Sleeve = 4 : 1







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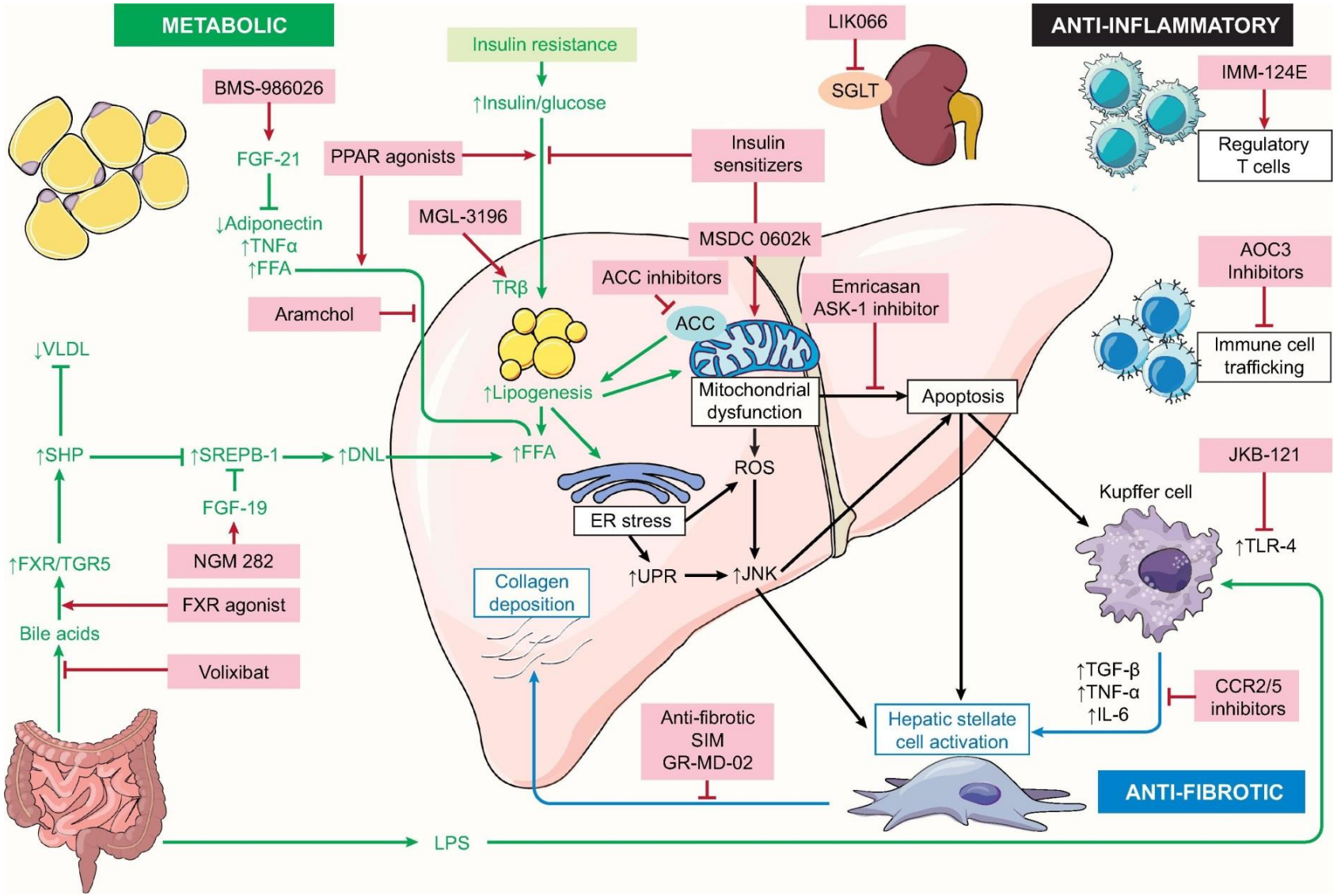
Pais R et al., Hepatology 2022; 76: 456;

Aktuell untersuchte pharmakologische Interventionen in MASLD



Konerman MA et al., J Hep 2018; 68:362.

Resmetriom – selektiver Thyroid Receptor beta-Agonist

nature medicine

Article

https://doi.org/10.1038/s41591-023-02603-1

Resmetirom for nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled phase 3 trial

Received: 6 March 2023

Accepted: 20 September 2023

Published online: 16 October 2023

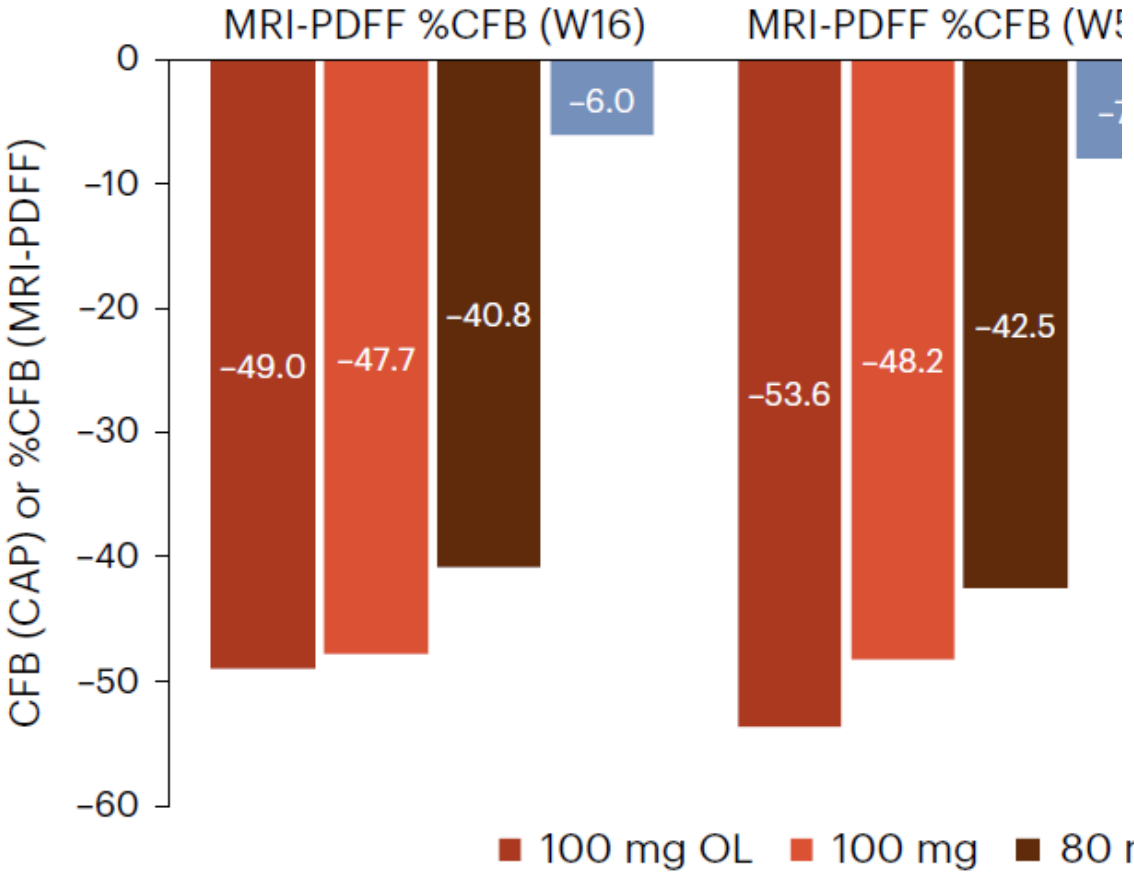
Stephen A. Harrison[1], Rebecca Taub[2], Guy W. Neff[3], K. Jean Lucas[4], Dominic Labriola[2], Sam E. Moussa[5], Naim Alkhouri[6] & Mustafa R. Bashir[7]

Nonalcoholic steatohepatitis (NASH) is a progressive liver disease with

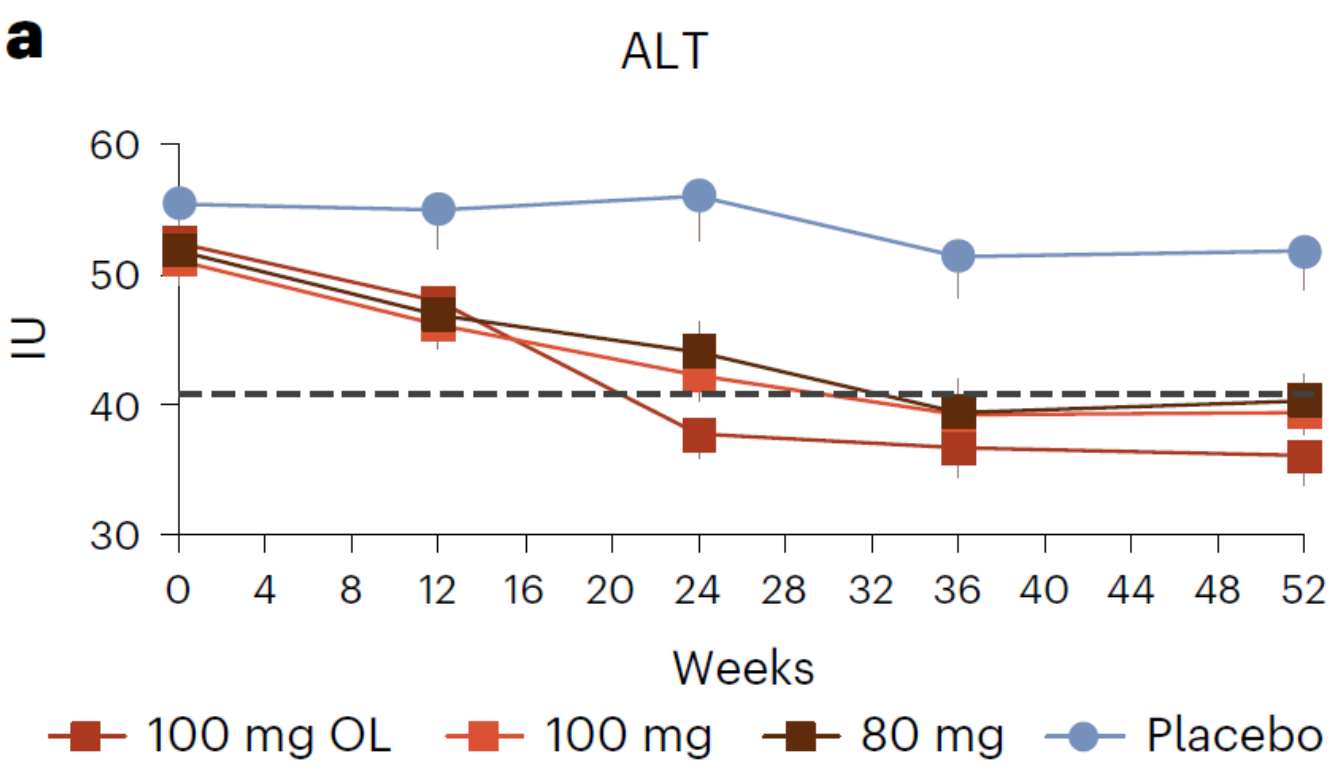
Thyroid Rezeptor beta-Agonist Resmetriom in MASLD

- Phase III-Studie (N=972), BMI: 36 kg/m^2; 66% Typ 2 DM -

Reduktion der Leberfettgehaltes



Reduktion der Inflammation

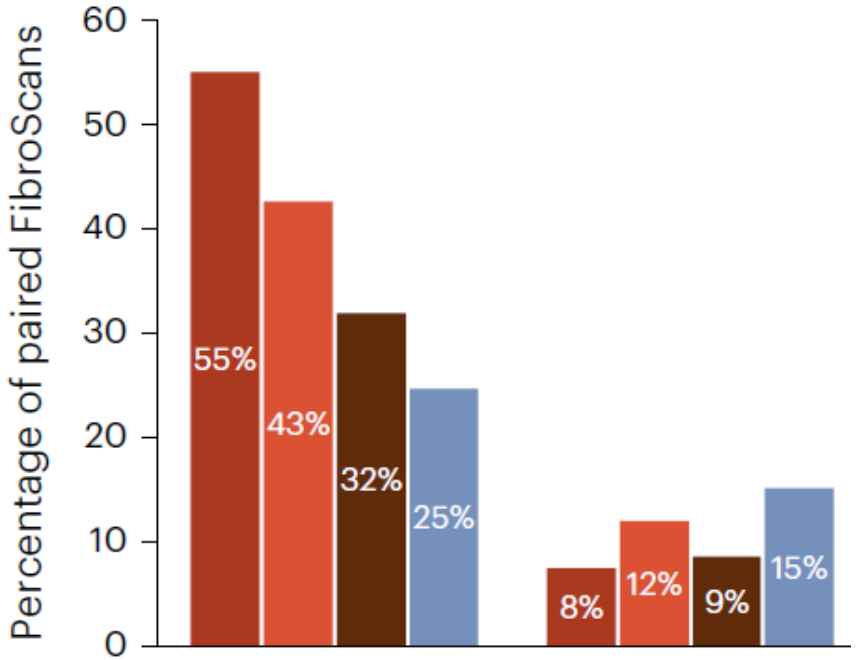


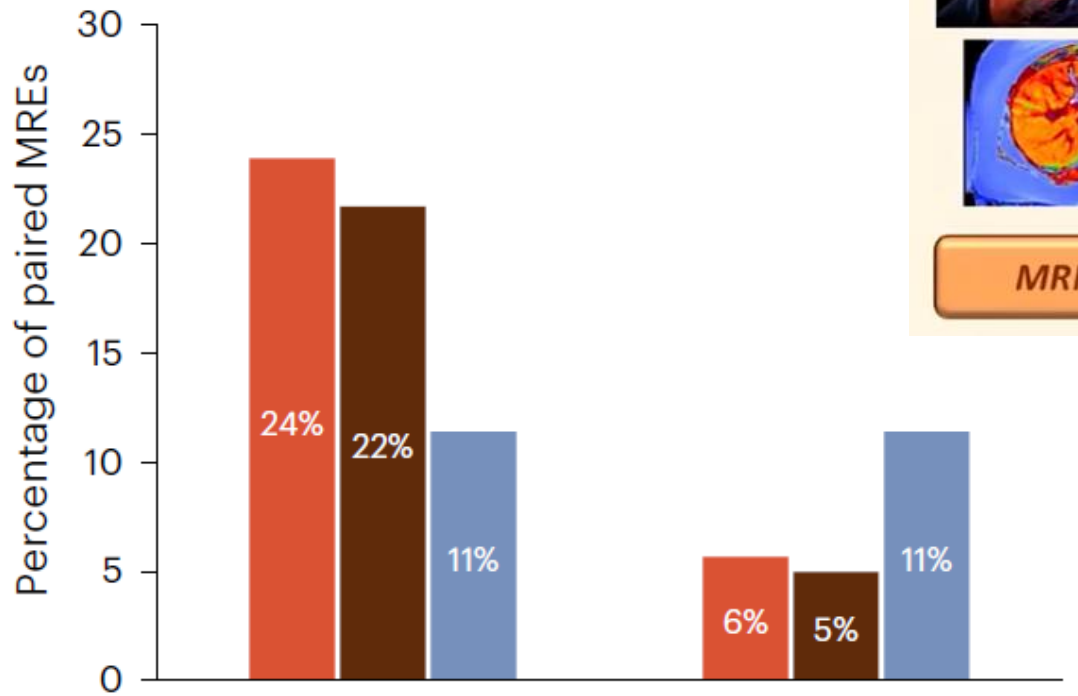
Harrison SA et al., Nat Med 2023; Epub

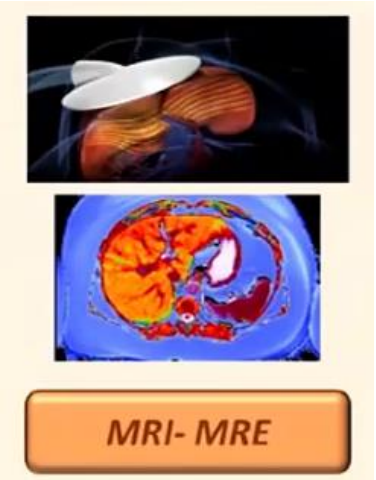
Thyroid Rezeptor beta-Agonist Resmetriom in MASLD

- Phase III-Studie (N=972), BMI: 36 kg/m^2; 66% Typ 2 DM -

Reduktion der Fibrose



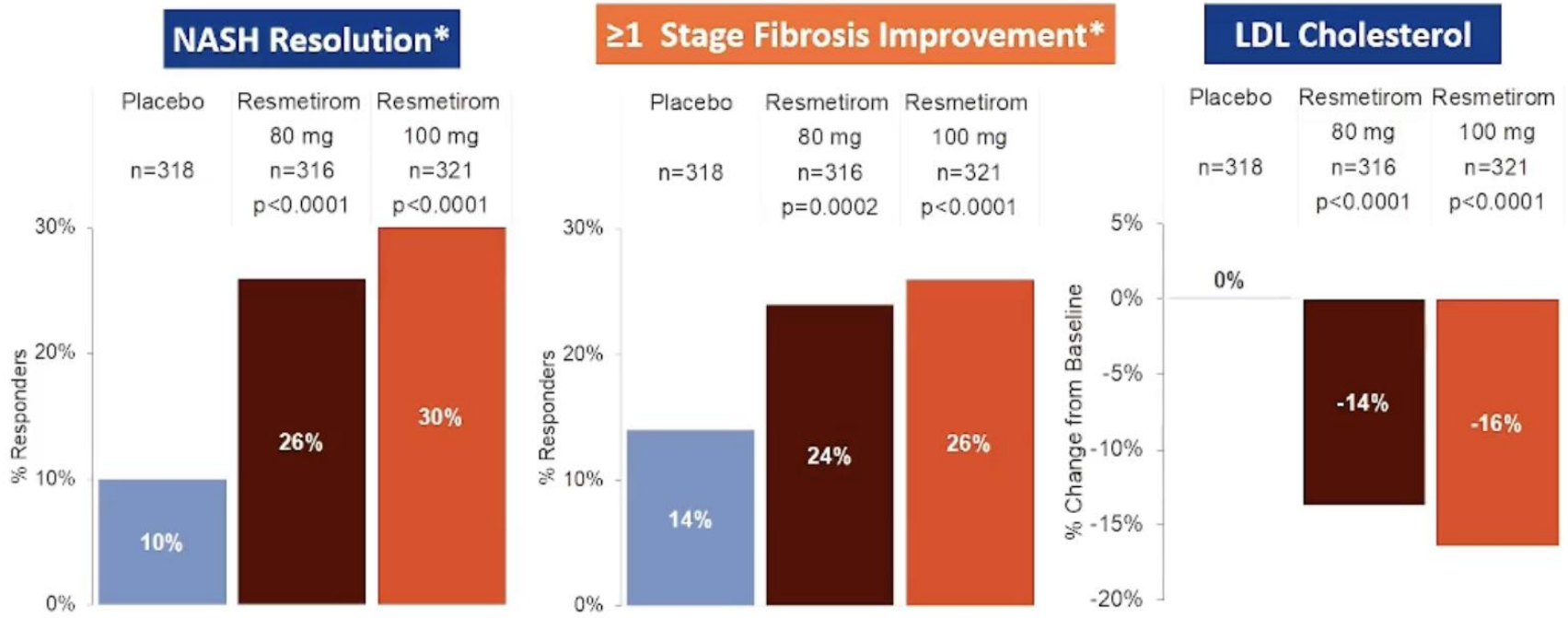




100 mg OL (*n* = 40) 100 mg DB (*n* = 75) 80 mg DB (*n* = 47) Placebo (*n* = 73)

Harrison SA et al., Nat Med 2023; Epub

Thyroid Rezeptor beta-Agonist Resmetriom in MASLD
- Phase III-Studie (N=972), BMI: 36 kg/m^2; 66% Typ 2 DM -



Both primary liver biopsy endpoints and the key secondary endpoint of LDL cholesterol lowering were met

Insgesamt gute Verträglichkeit, v.a. GI Nebenwirkungen (Übelkeit, Diarrhoe)
Etwas mehr Abbrüche (7.7%) bei 100 mg vs. 80 mg (2.8%) und Placebo (3.7%)

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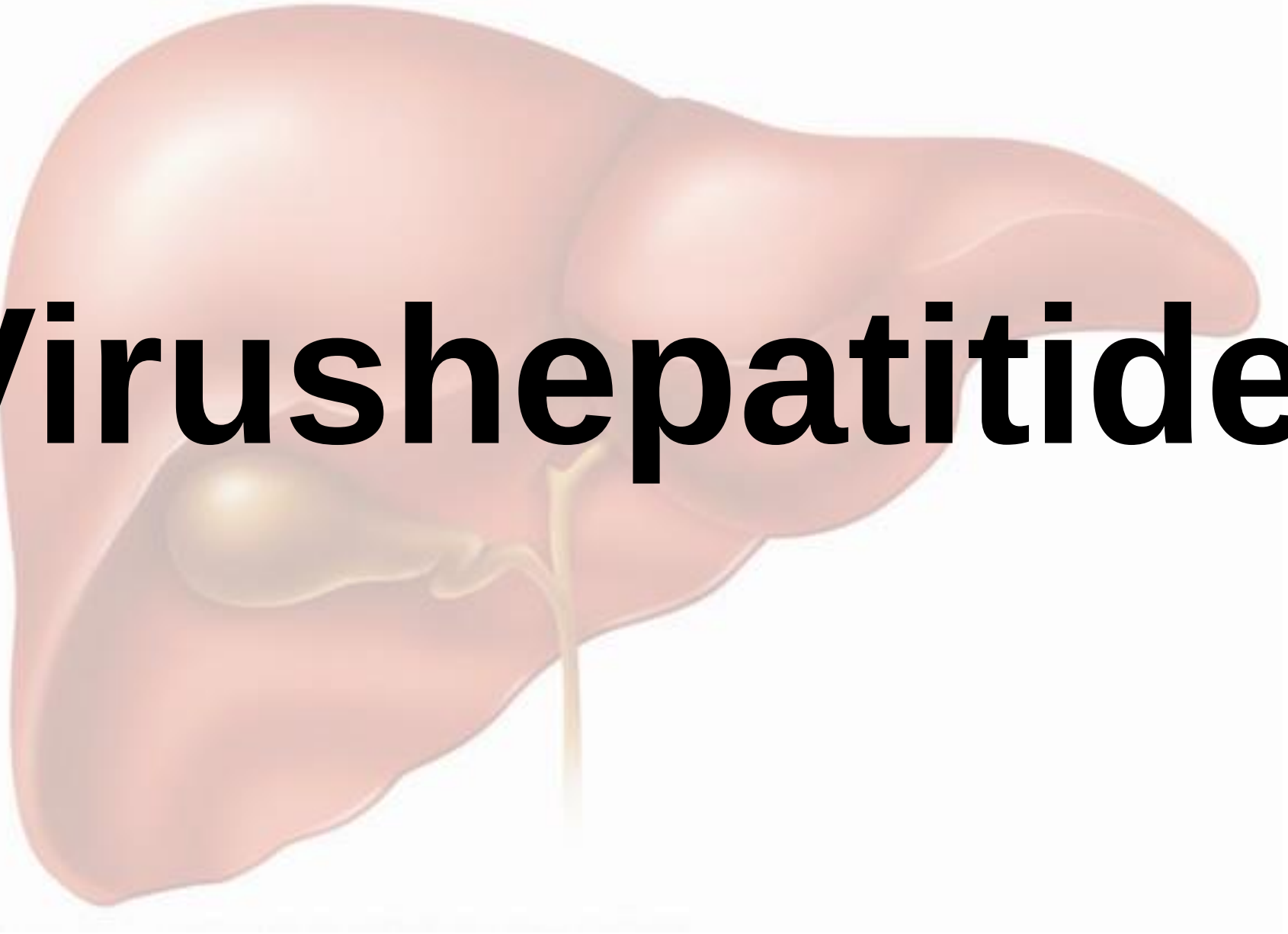
Harrison SA et al., Nat Med 2023; Epub; Harrison S et al., EASL 2023 Late Braker; Pressemitteilung Madrigal

Virushepatitiden



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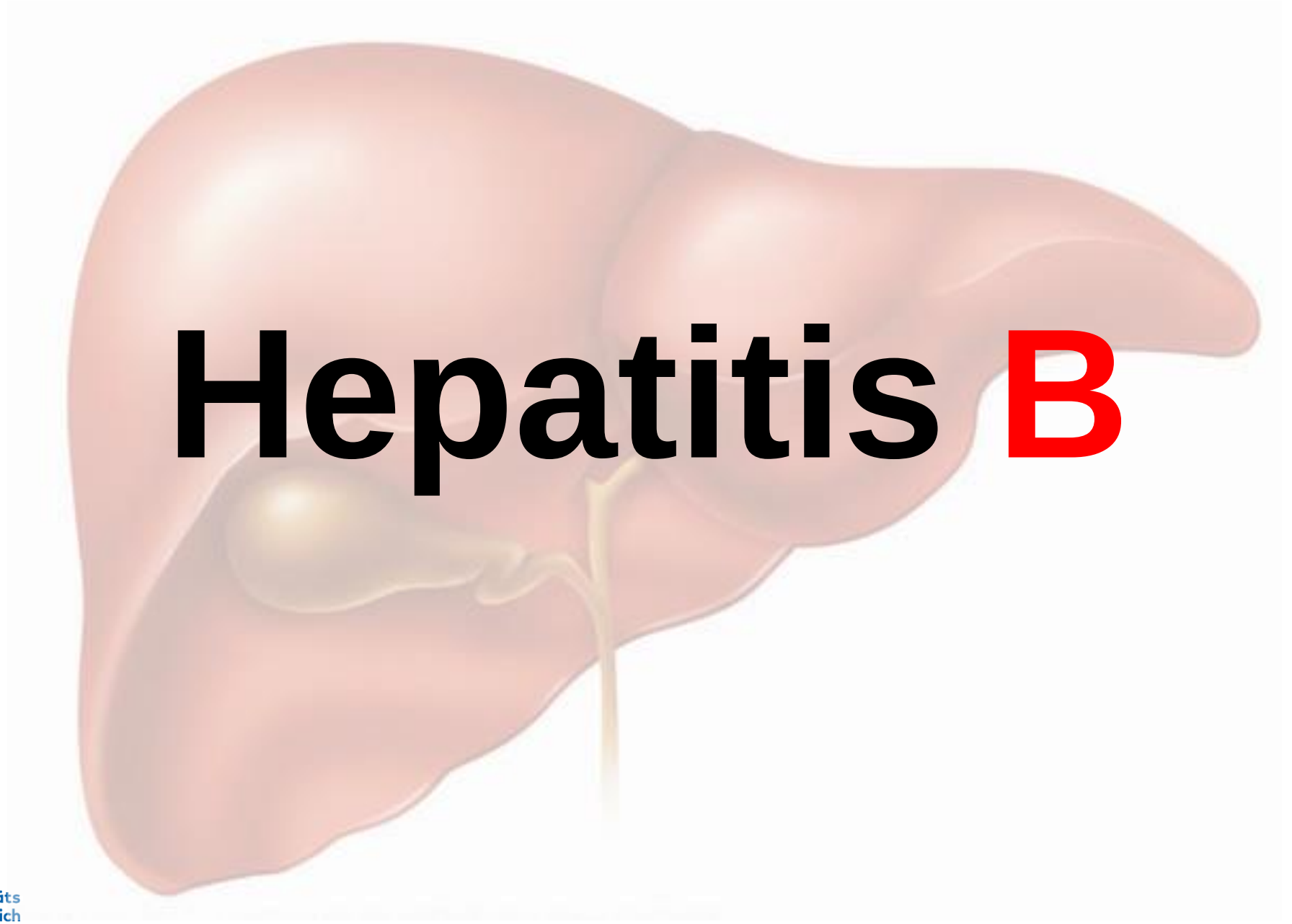

Hepatitis B

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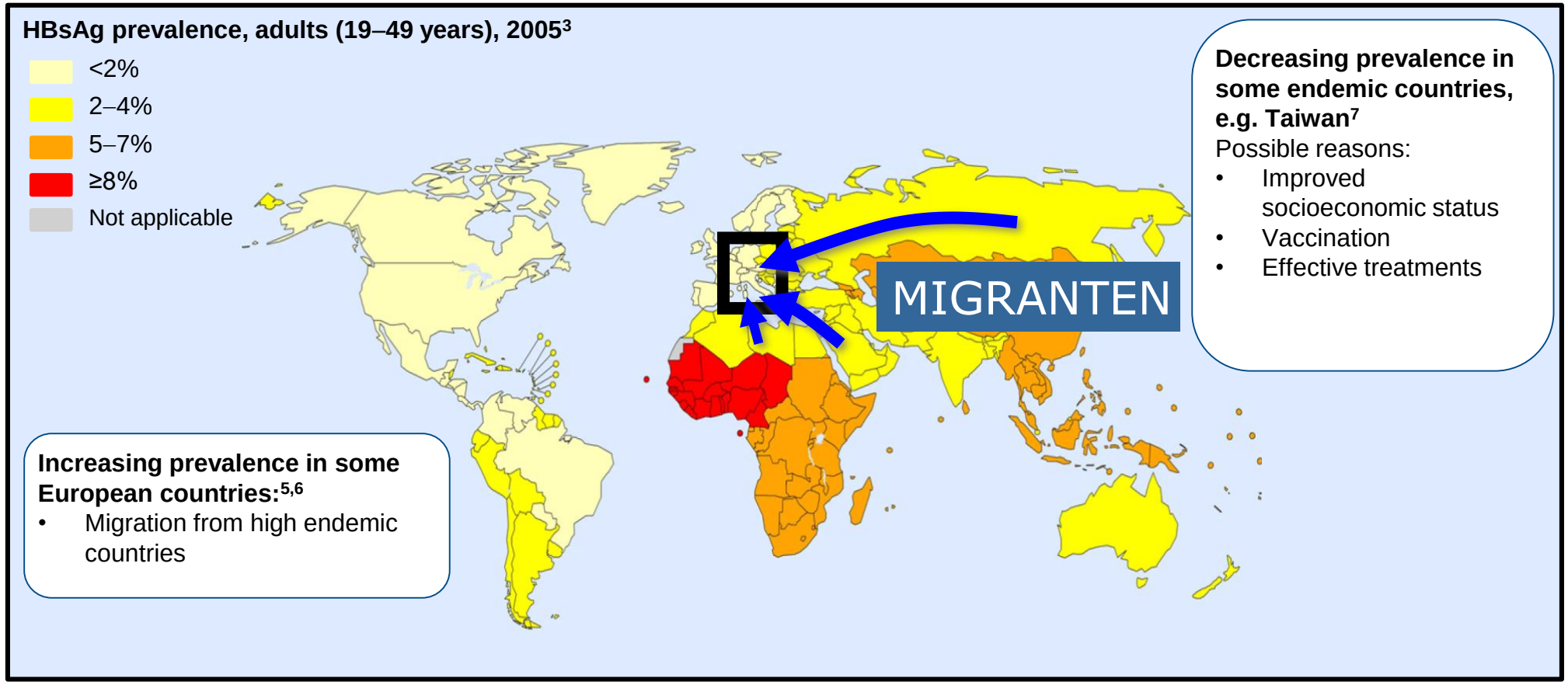
Hepatitis B Virusinfektion – Prävalenz
- Weltweit ca. 300 Millionen Träger -



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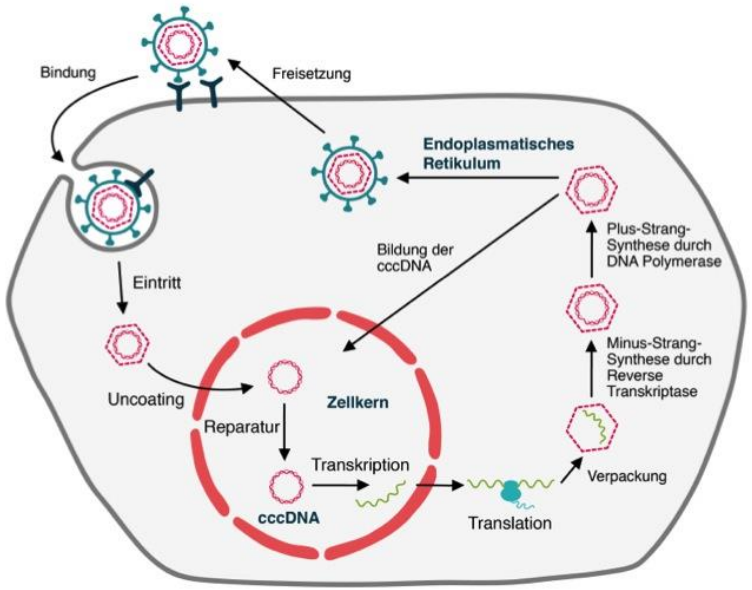
1. EASL CPG HBV. J Hepatol 2017;67:370; 2. Schweitzer A, et al. Lancet 2015;386:1546; 3. Ott JJ, et al. Vaccine 2012;30:2212; 4. GBD 2013. Lancet 2015;385:117–71; 5. Coppola N, et al. Euro Surveill 2015;20:30009; 6. Hampel A, et al. BGG 2016;59:578; 7. Chen C-L, et al. J Hepatol 2015;63:354.

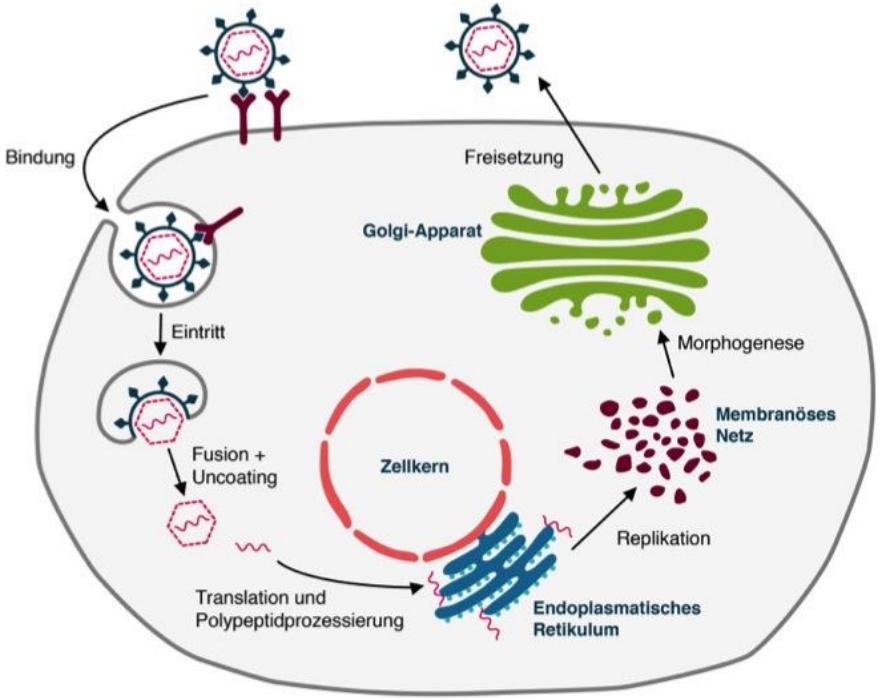
Viruskontrolle versus Viruselimination
- HBV versus HCV -

Hepatitis B Virus[1]



Hepatitis B ist kontrollierbar, aber nicht heilbar, weil immer eine Virusabschrift im Zellkern abliegt

Hepatitis C Virus[2]



Hepatitis C ist heilbar, weil der Zellkern nicht berührt wird

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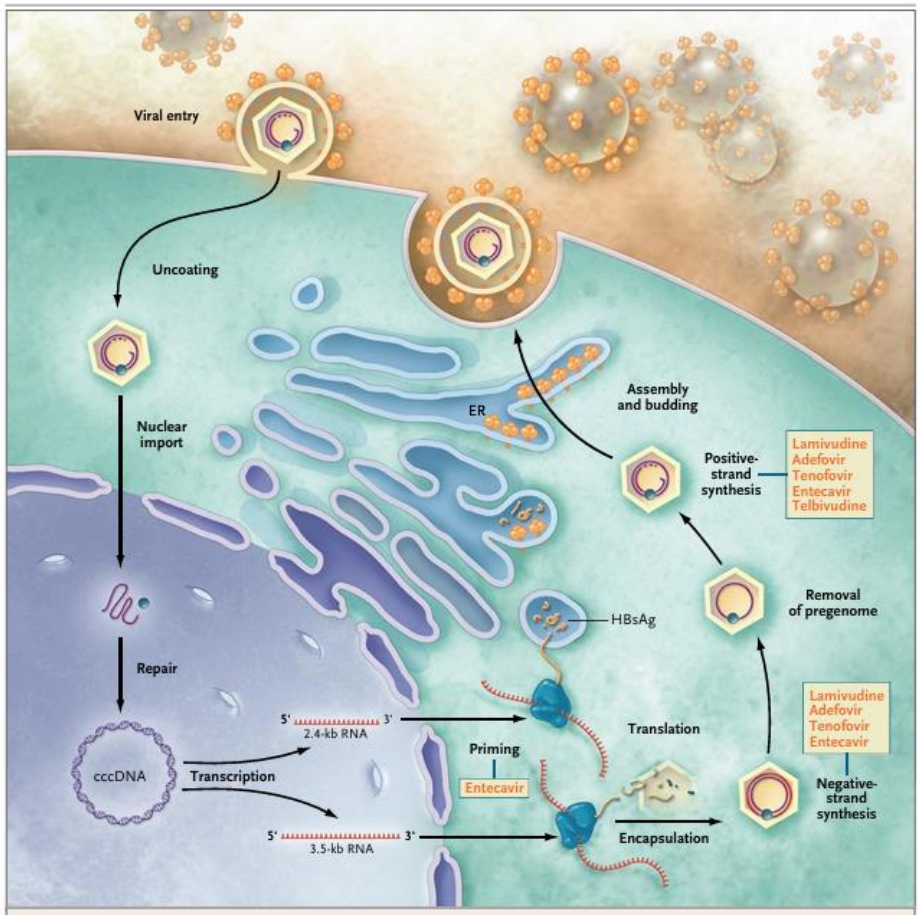
1 Modifiziert nach Fung SK, Lok AS. Nat Clin Pract Gastroenterol Hepatol. 2004 Dec;1(2):90-7. 2 Modifiziert nach Manns MP, Cornberg M. Lancet Infect Dis. 2013 May;13(5):378-9.

Viruskontrolle mittels Nukleos(t)id-Analoga
- Hohe Resistenzbarriere -

- **Entecavir**

- **Tenofovir disoproxil fumarat**

- **Tenofovir alafenamid**



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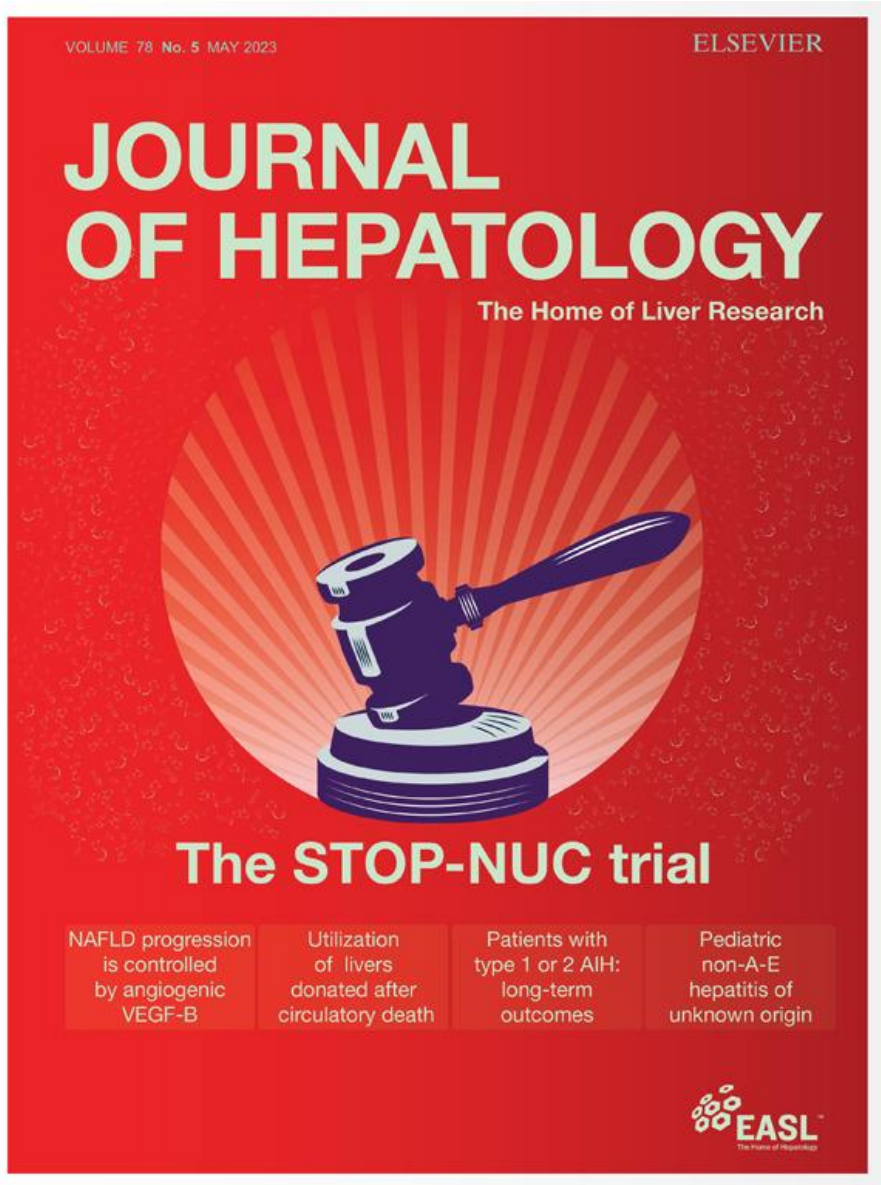
Dienstag et al., NEJM 2008

STOPP-NUC
- Kann die Therapie mit NUCs beendet werden? -



25 Zentren in Deutschland

Screening von 11/2014 bis 01/2018
Einschluss von 166 Patienten

Extensive Inclusion/Exclusion Criteria

- HBeAg negative chronic hepatitis B (HBsAg positive)
- Continuous NUC therapy with adefovir dipivoxil (ADV), lamivudine (LMV), telbivudine (LdT), entecavir (ETV) or tenofovir disoproxil fumarate (TDF) for at least 4 years prior to screening.
- Documented **undetectable** HBV DNA level during treatment for at least 4 years prior to screening.
- **Undetectable** HBV DNA level at screening
- Normal serum ALT levels

- liver cirrhosis
- History of decompensated liver disease
- Advanced fibrosis – F3 and/or TE ≥ 10 kPa
- Evidence of hepatocellular carcinoma (HCC)
- HIV, HDV or HCV co-infection
- Immunosuppression
- HBV associated extra hepatic
- Significant alcohol consumption (> 30 g/day for women and > 50 g/day for men)
- Suspected lack of compliance

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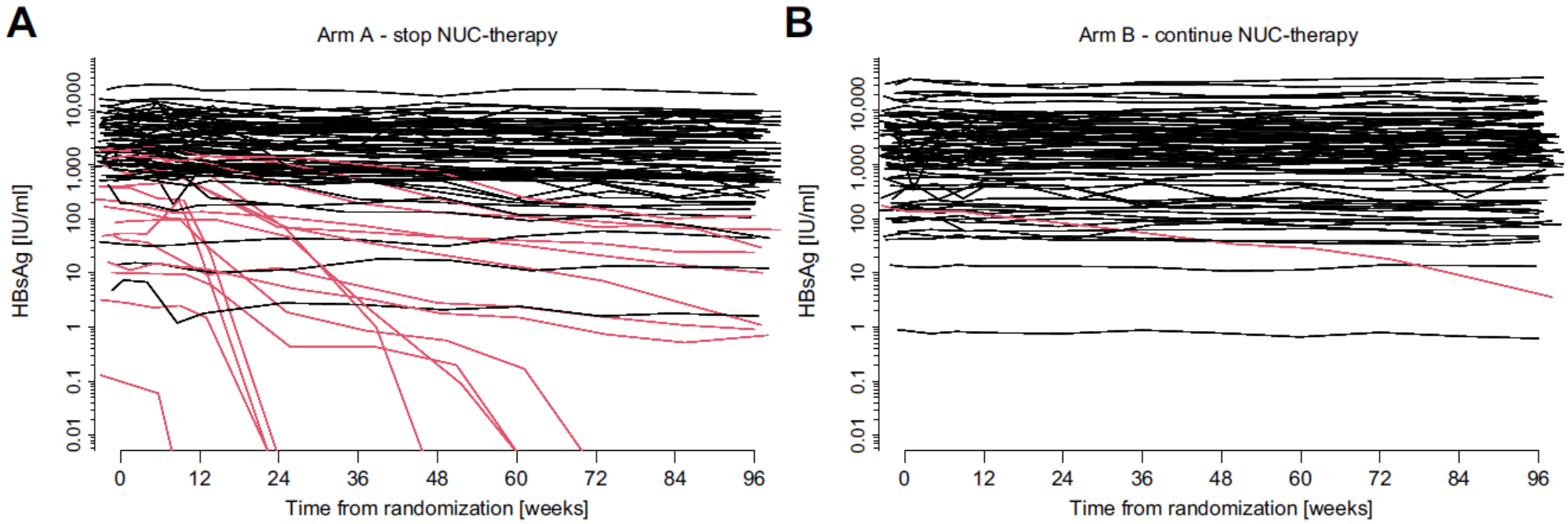
Van Bömmel F et al., J Hep 2023;

STOPP-NUC
- Kann die Therapie mit NUCs beendet werden? -



10% HBsAg-Verlust in 4 Jahren (bei HBsAg > 1000 IU/mL praktisch nicht!)
36% Flares, 14% Re-Therapie

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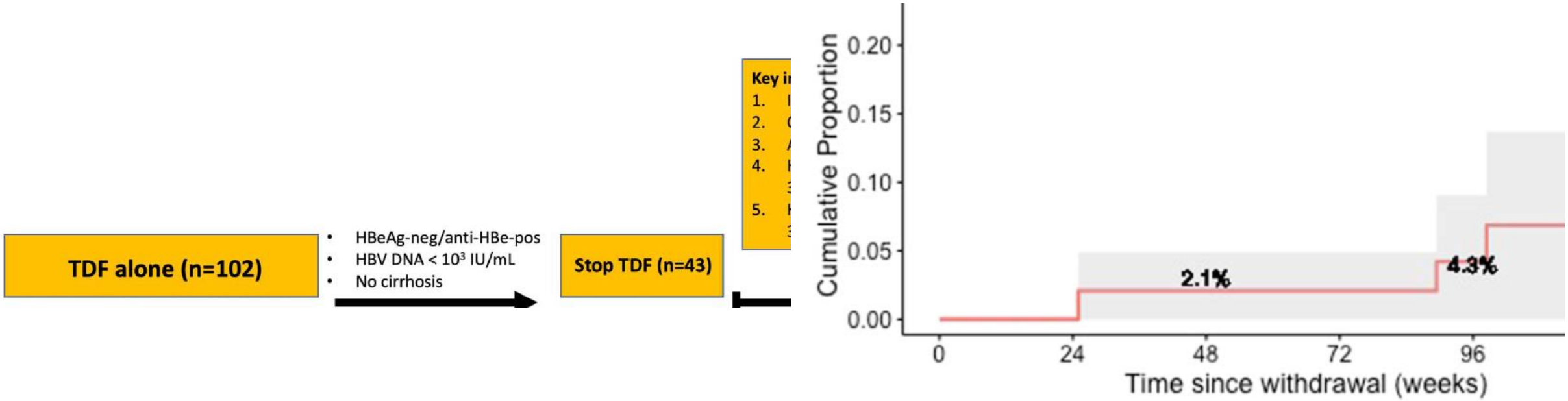
Van Bömmel F et al., J Hep 2023; 78:926

STOPP-NUC
- Kann die Therapie mit NUCs beendet werden? -

Withdrawal of Long-Term Nucleotide Analog Therapy in Chronic Hepatitis B: Outcomes From the Withdrawal Phase of the HBRN Immune Active Treatment Trial

Jordan J. Feld, MD, MPH[1,2], Abdus S. Wahed, PhD[3,4], Michael Fried, MD[5], Marc G. Ghany, MD[6], Adrian M. Di Bisceglie, MD[7], Robert P. Perrillo, MD[8], Mandana Khalili, MD[9], Xue Yang, PhD[3], Steven H. Belle, PhD[3,4], Harry L.A. Janssen, MD, PhD[1,2], Norah Terrault, MD[10] and Anna S. Lok, MD[11] for the Hepatitis B Research Network (HBRN)



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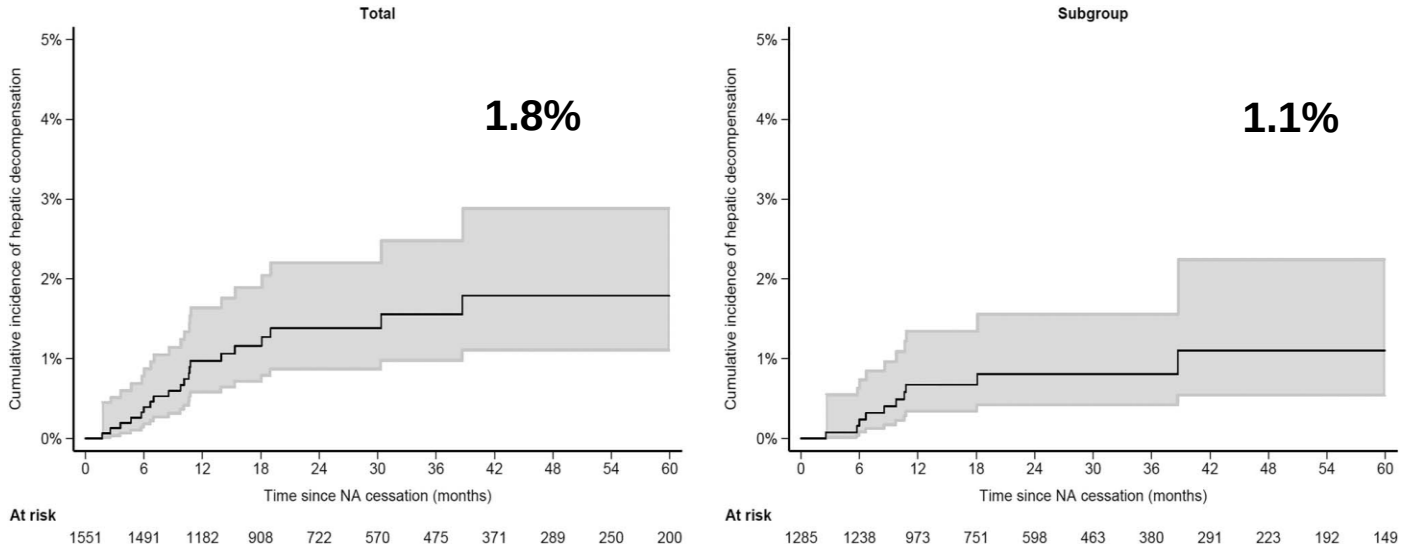
Feld JJ, et al; Am J Gastro 2023;7:1226.

Hepatische Dekompensation nach Beendigung von NUCs

- Bili > 2 mg/dl, INR > 1.5, ascites, variceal bleeding, ascites



Incidence of Hepatic Decompensation After Nucleos(t)ide Analog Withdrawal: Results From a Large, International, Multiethnic Cohort of Patients With Chronic Hepatitis B (RETRACT-B Study)

Grishma Hirode, MSc[1,2], Bettina E. Hansen, PhD[3], Chien-Hung Chen, MD[4], Tung-Hung Su, MD, PhD[5], Grace Wong, MD[6], Wai-Kay Seto, MD[7], Stijn Van Hees, PhD[8], Margarita Papatheodoridi, MD, PhD[9], Sylvia M. Brakenhoff, MD[10], Sabela Lens, MD[11], Hannah S.J. Choi, PhD[1], Rong-Nan Chien, MD[12], Jordan J. Feld, MD, MPH[1,2], Xavier Forns, MD[11], Milan J. Sonneveld, MD, PhD[10], George V. Papatheodoridis, MD, PhD[9], Thomas Vanwolleghem, MD, PhD[8], Man-Fung Yuen, MD, PhD[7], Henry L.Y. Chan, MD[13], Jia-Horng Kao, MD, PhD[5], Yao-Chun Hsu, MD, PhD[14], Markus Cornberg, MD[15], Wen-Juei Jeng, MD[12] and Harry L.A. Janssen, MD, PhD[10], on behalf of the RETRACT-B study group

Research article JHEP|Reports

Serious adverse events after cessation of nucleos(t)ide analogues in individuals with chronic hepatitis B: A systematic review and meta-analysis

Authors
Cheng-Hao Tseng, Tzu-Haw Chen, Jia-Ling Wu, Teng-Yu Lee, John A. Borghi, Jaw-Town Lin, Mindie H. Nguyen, Yao-Chun Hsu

J Hep Reports 2023

- 65% Hepatitis Flares (Cave: „good flares“)
- 85% Re-Therapie, **35% verstorben**

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Hirode et al., Am J Gastro 2023; Epub

Akutes Leberversagen nach Beendigung von NUCs

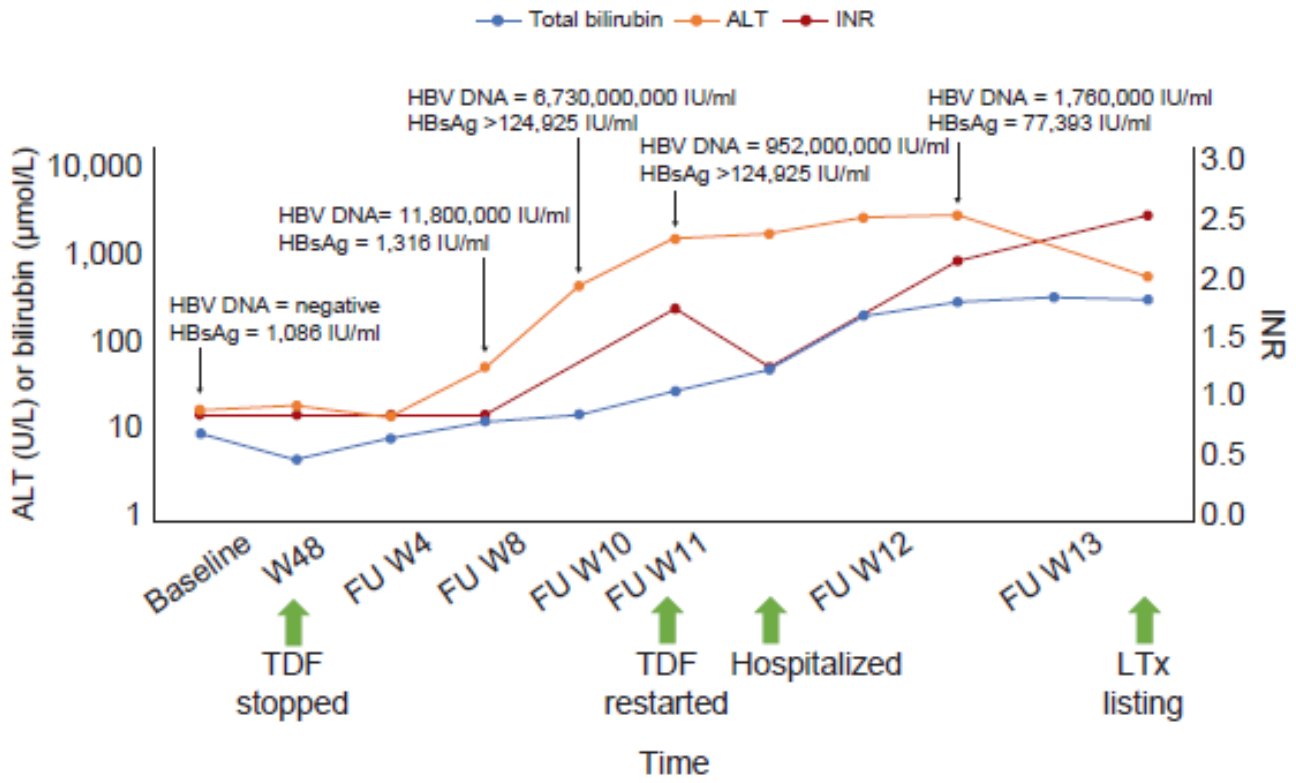
Case Report

JOURNAL OF HEPATOLOGY

A case of HBV-induced liver failure in the REEF-2 phase II trial: Implications for finite treatment strategies in HBV 'cure'

Kosh Agarwal[1,*], James Lok[1], Ivana Carey[1], Yatin Shivkar[2], Michael Biermer[2], Thomas Berg[3], Isabelle Lonjon-Domanec[2]

- Keine Zirrhose
- Keine HBV-DNA unter Tenofovir seit 2009
- HBsAg 652 IU/ml



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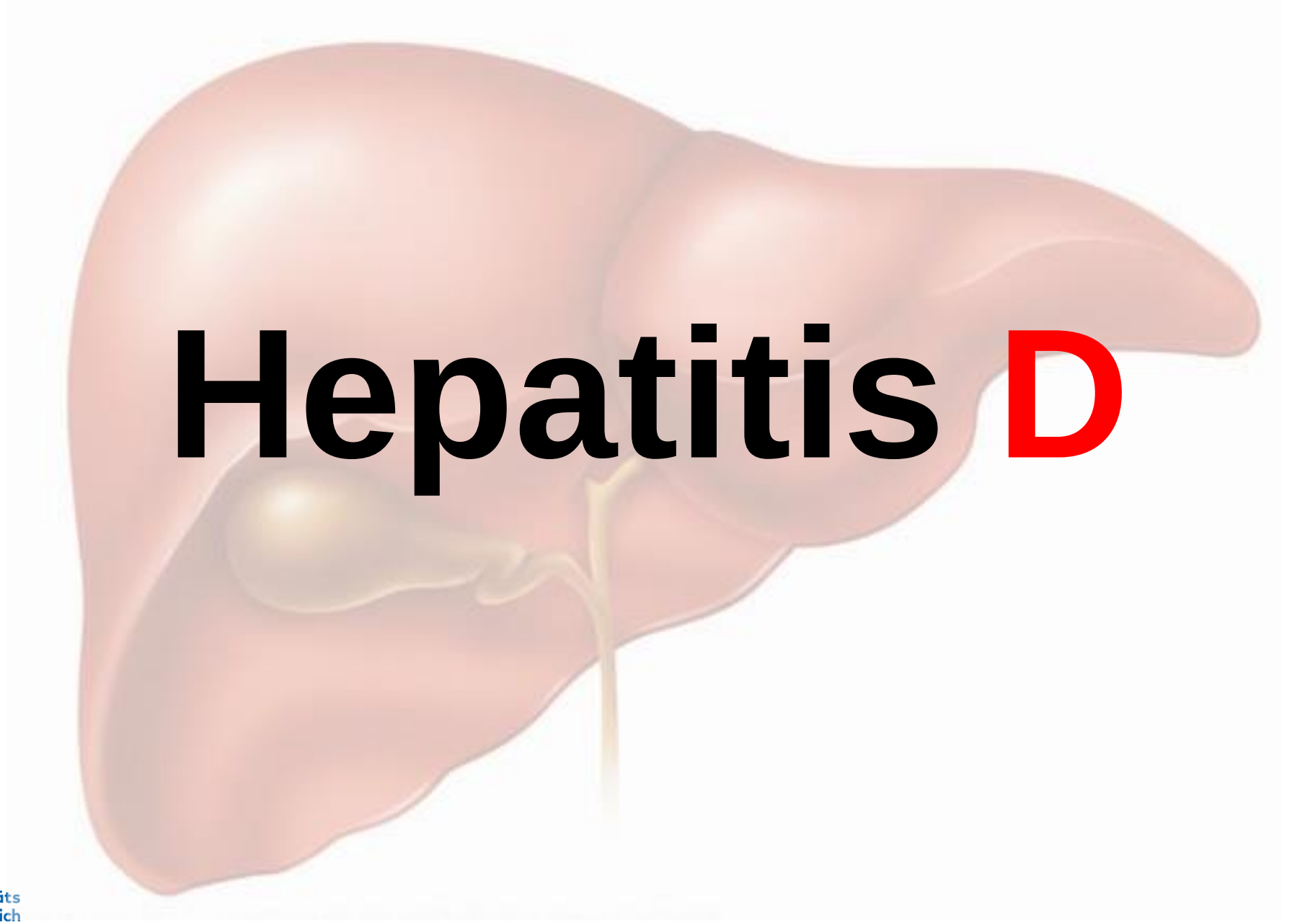
Agarwal et al., JHep 2023; Epub



Hepatitis D

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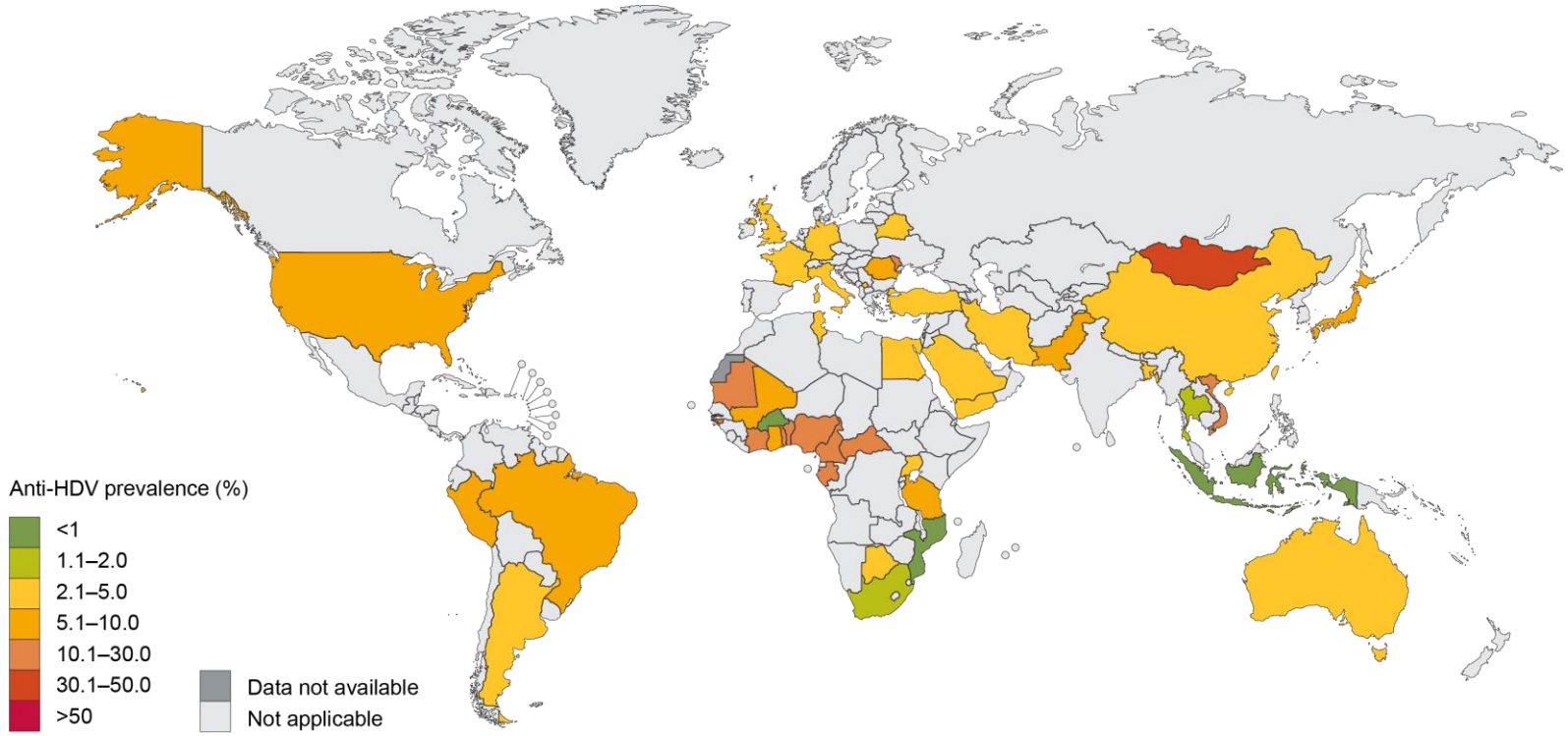
Hepatitis D Virusinfektion – Prävalenz
- Weltweit 12–60 Millionen Träger -



12–60 million people are estimated to have been exposed to HDV worldwide

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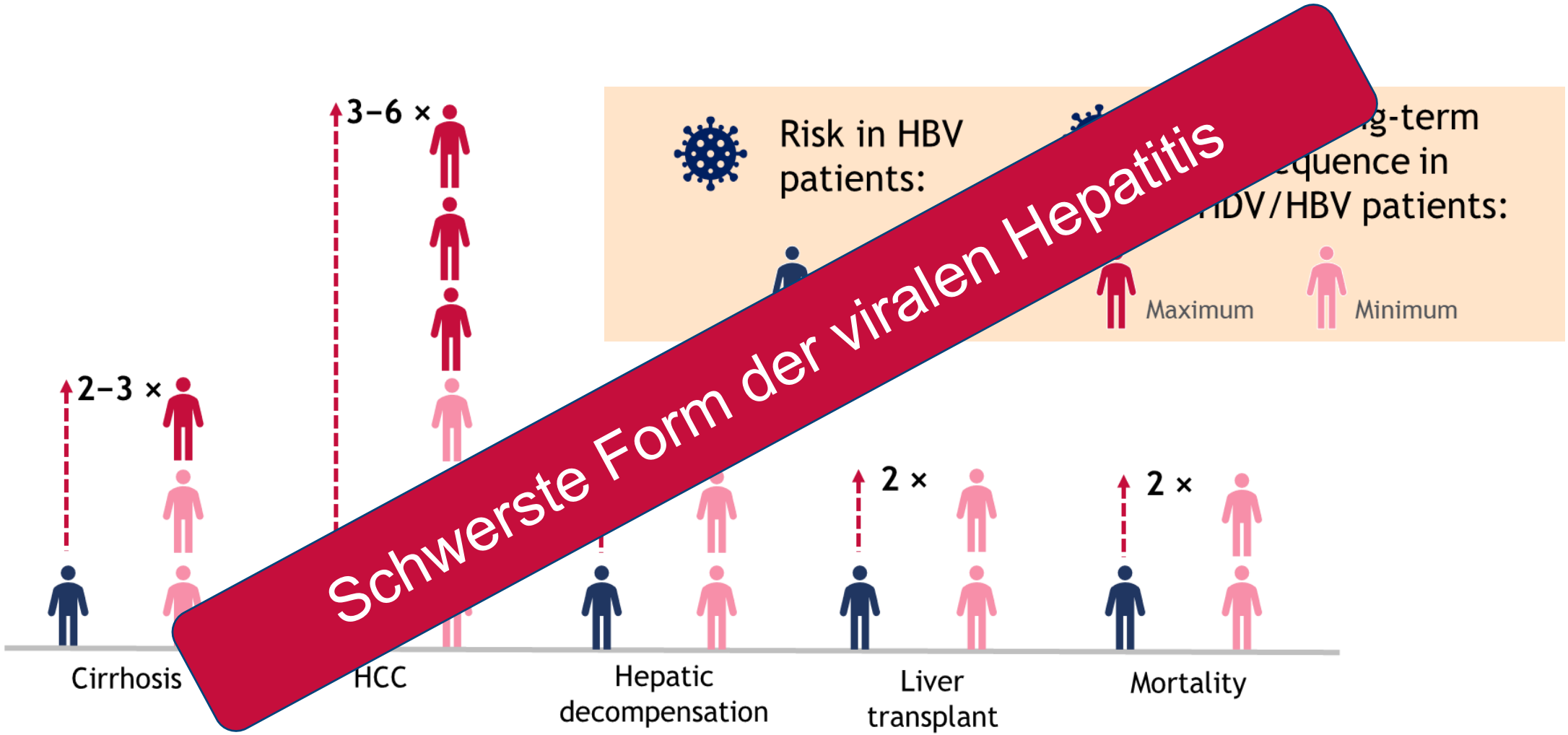
Figure adapted from Stockdale AJ, et al. J Hepatol 2020;73:523; Miao Z, et al. J Infect Dis 2020;221:1677.

Deutlich erhöhtes Risiko bei HBV-HDV-Coinfektion



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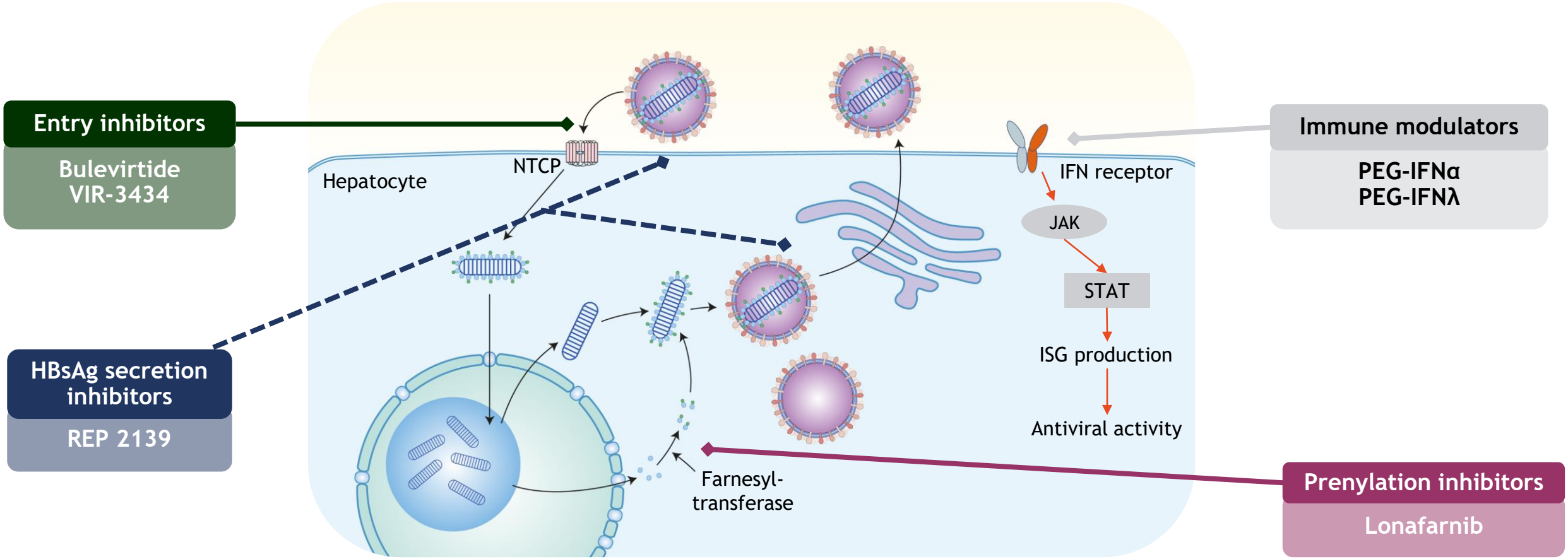
Da BL, et al. Gastroenterol Rep 2019;7:231; Chen VL, et al. Clin Gastroenterol Hepatol 2016;14:887.

Therapeutische Ziele im HDV Replikationszyklus



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Gilman C, et al. World J Gastroenterol 2019;25:4580; Bazinet M, et al. Lancet Gastroenterol Hepatol 2017;2:877; Park A, Iwasaki A. Cell Host Microbe 2020;27:870

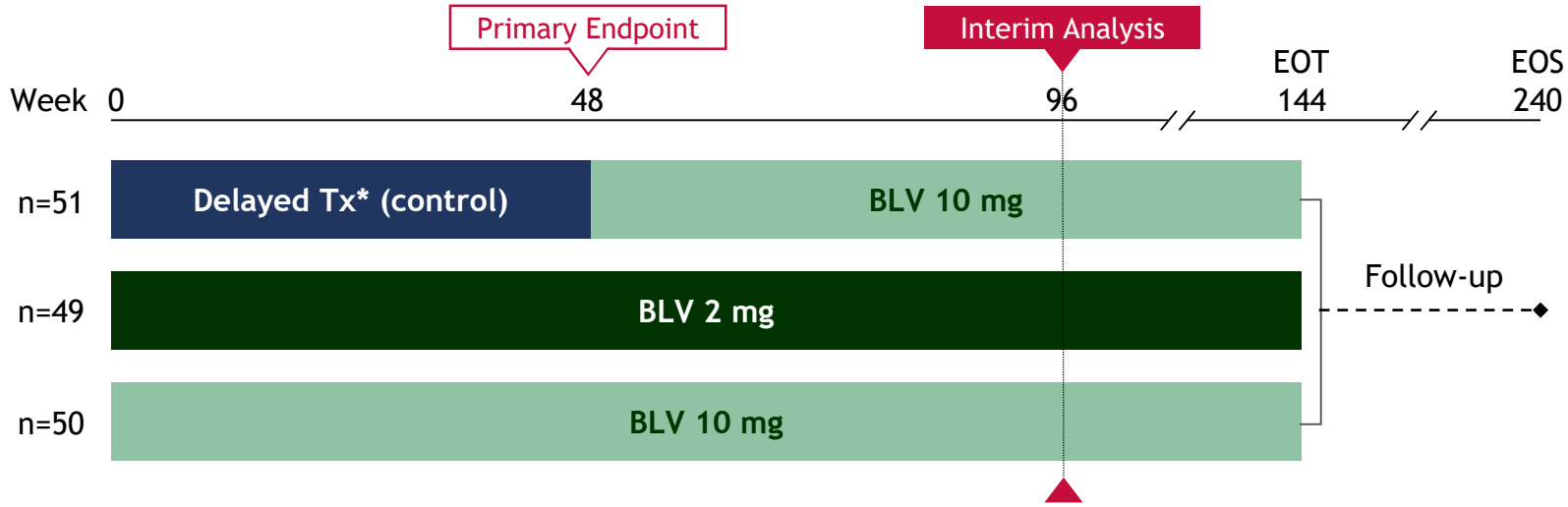
Bulevirtid Monotherapie – Phase III-Studie

Primary endpoint: HDV RNA undetectable or decrease by ≥2 log10 IU/mL from baseline and ALT normalization

Key inclusion criteria:

- Adults with chronic hepatitis delta
- With or without compensated cirrhosis
- ALT >1× to <10× ULN, and positive serum HDV RNA

MYR301:
N=150
Randomized
1:1:1



Multicenter, open-label, randomized, Phase 3 study

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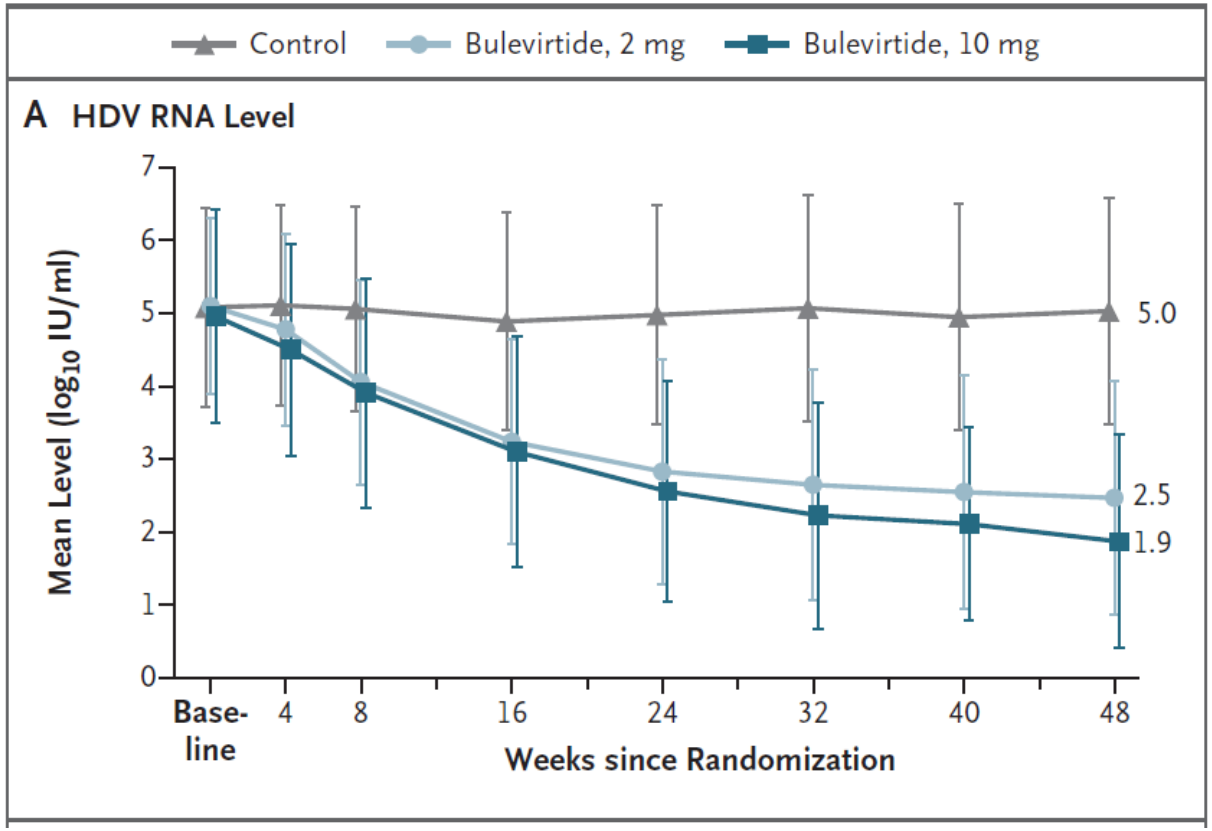
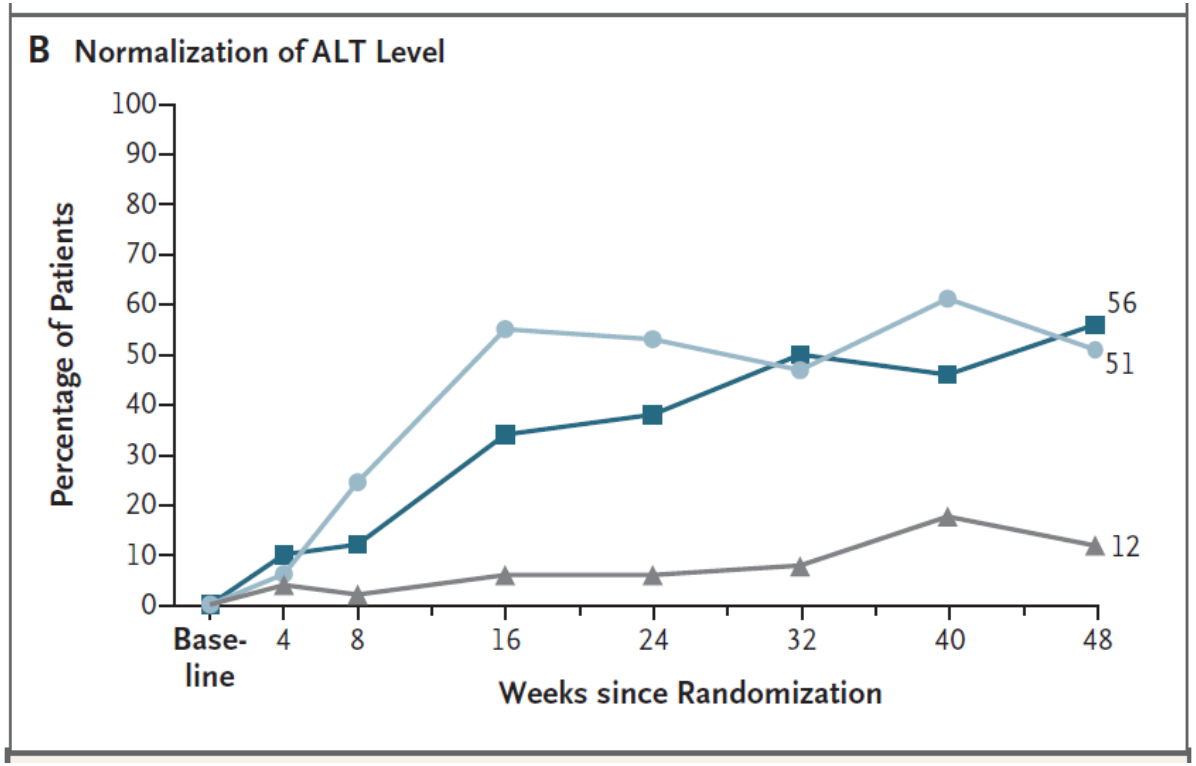
Wedemeyer H et al., NEJM 2023; 389: 22; Wedemeyer H, et al. EASL 2023. Oral #OS-068

Bulevirtid Monotherapie – Ansprechen nach 48 Wochen





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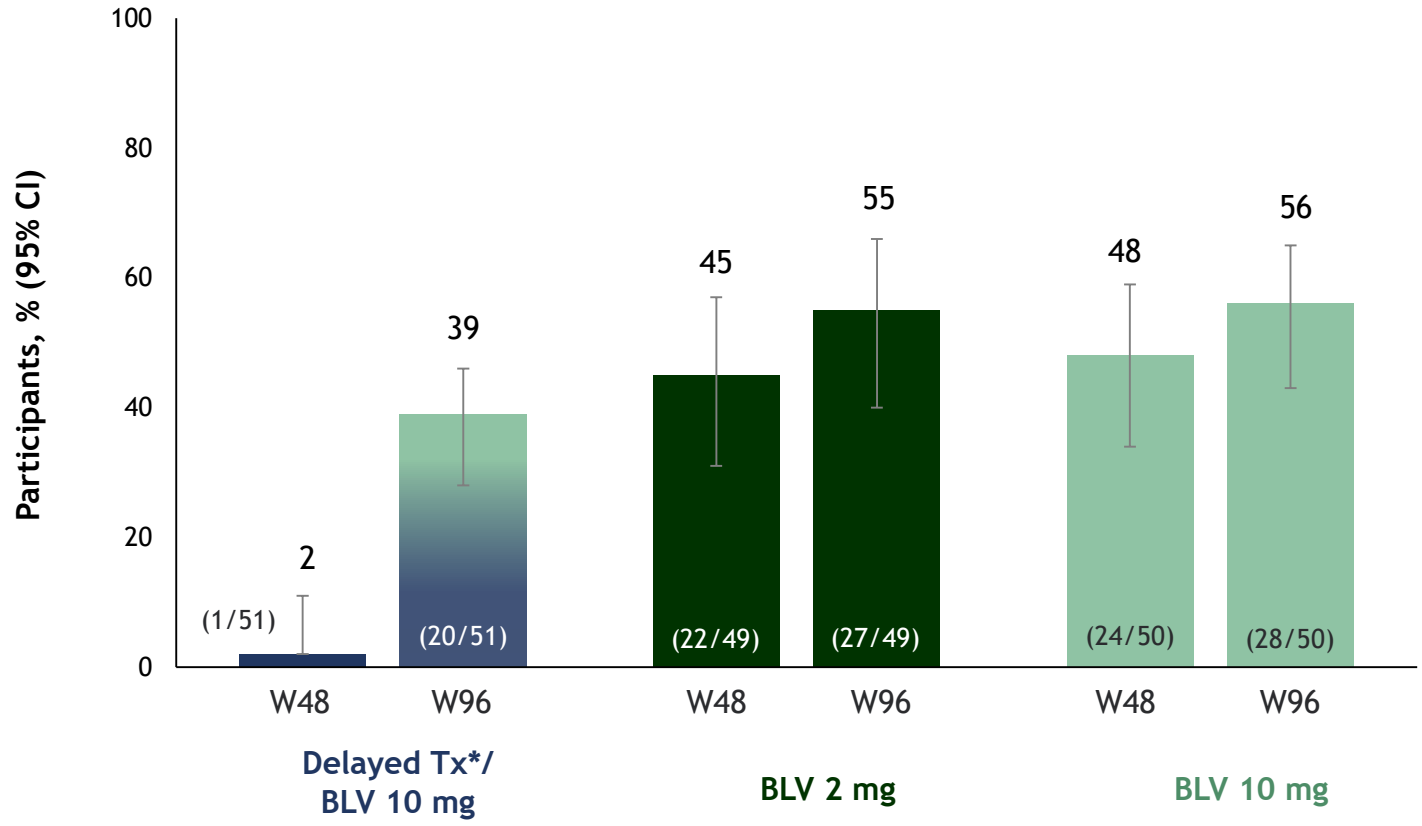
Wedemeyer H et al., NEJM 2023; 389: 22; Wedemeyer H, et al. EASL 2023. Oral #OS-068

Bulevirtid Monotherapie – Ansprechen nach 96 Wochen

Primary endpoint: HDV RNA undetectable or decrease by ≥2 log10 IU/mL from baseline and ALT normalization



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Wedemeyer H et al., NEJM 2023; 389: 22; Wedemeyer H, et al. EASL 2023. Oral #OS-068

Bulevirtid Monotherapie – Sicherheitsprofil

n (%)	Delayed Tx*/BLV 10 mg n=51		BLV 2 mg n=49		BLV 10 mg n=50	
	Week 48	Week 48-96**	Week 48	Week 96	Week 48	Week 96
Any AE	39 (77)	42 (84)	41 (84)	47 (96)	44 (88)	48 (96)
Any AE related to BLV	0	22 (44)	24 (49)	25 (51)	36 (72)	36 (72)
Any SAE	1 (2)	2 (4)	2 (4)	2 (4)	1 (2)	4 (8)
Any SAE related to BLV	0	0	0	0	0	0
AE leading to withdrawal of BLV	0	0	0	0	0	0
Grade 3-4 AE	4 (8)	3 (6)	5 (10)	9 (18)	4 (8)	8 (16)
Death	0	1 (2)†	0	0	0	0
AEs of interest‡						
Headache	0	7 (14)	9 (18)	9 (18)	10 (20)	12 (24)
Dizziness	0	1 (2)	2 (4)	2 (4)	3 (6)	4 (8)
Nausea	2 (4)	1 (2)	3 (6)	3 (6)	4 (8)	6 (12)
Pruritis	0	0	6 (12)	6 (12)	8 (16)	9 (18)
Fatigue	1 (2)	2 (4)	5 (10)	7 (14)	7 (14)	9 (18)
ISR¶	0	3 (6)	9 (18)	10 (20)	15 (30)	15 (30)

BLV was well-tolerated, with no BLV-related SAEs and no AEs leading to BLV discontinuation

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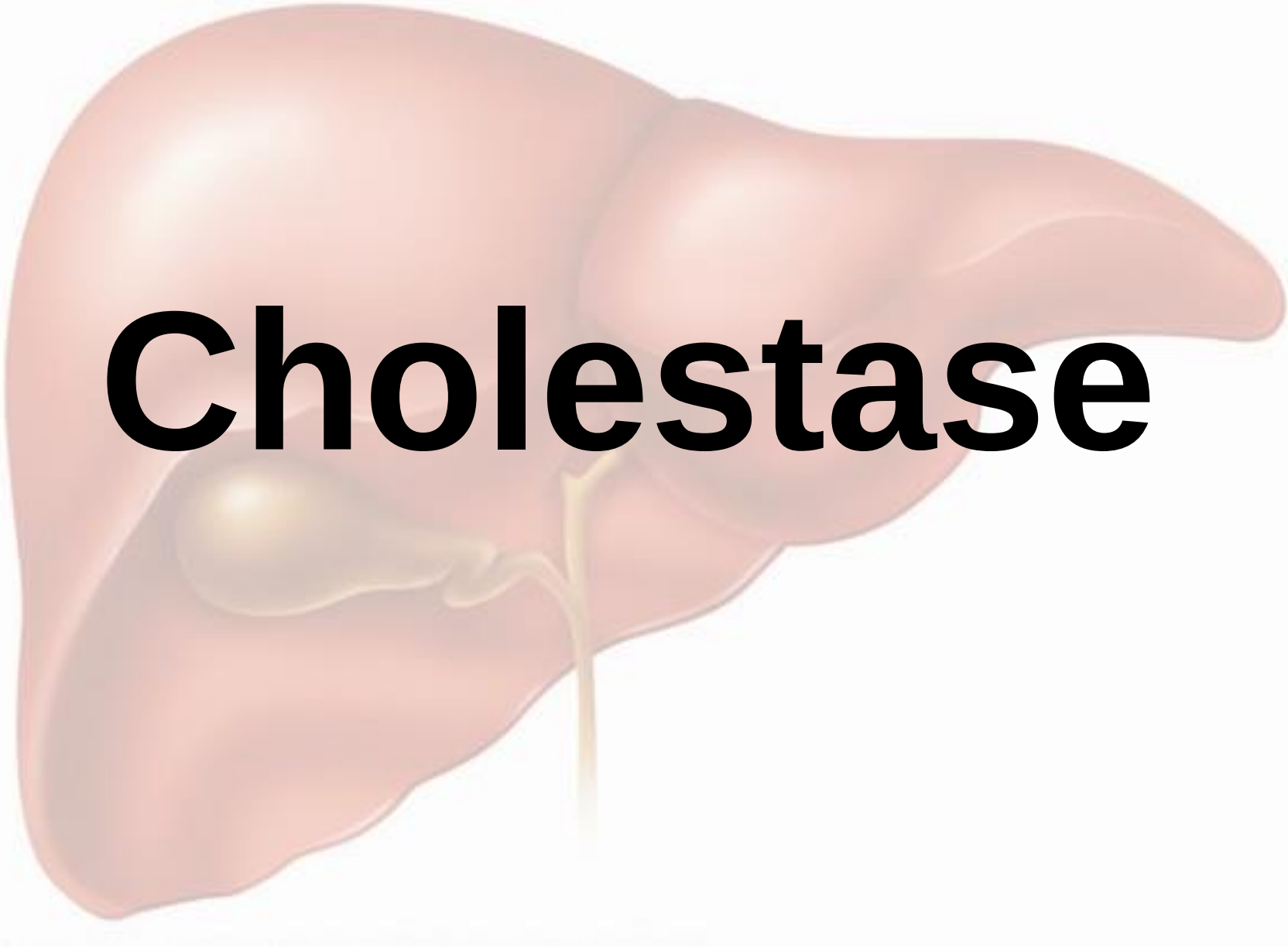
Wedemeyer H et al., NEJM 2023; 389: 22; Wedemeyer H, et al. EASL 2023. Oral #OS-068

Cholestase



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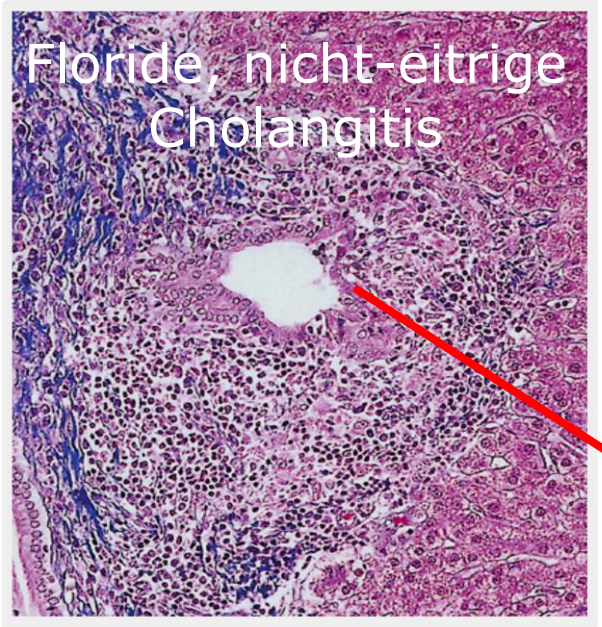
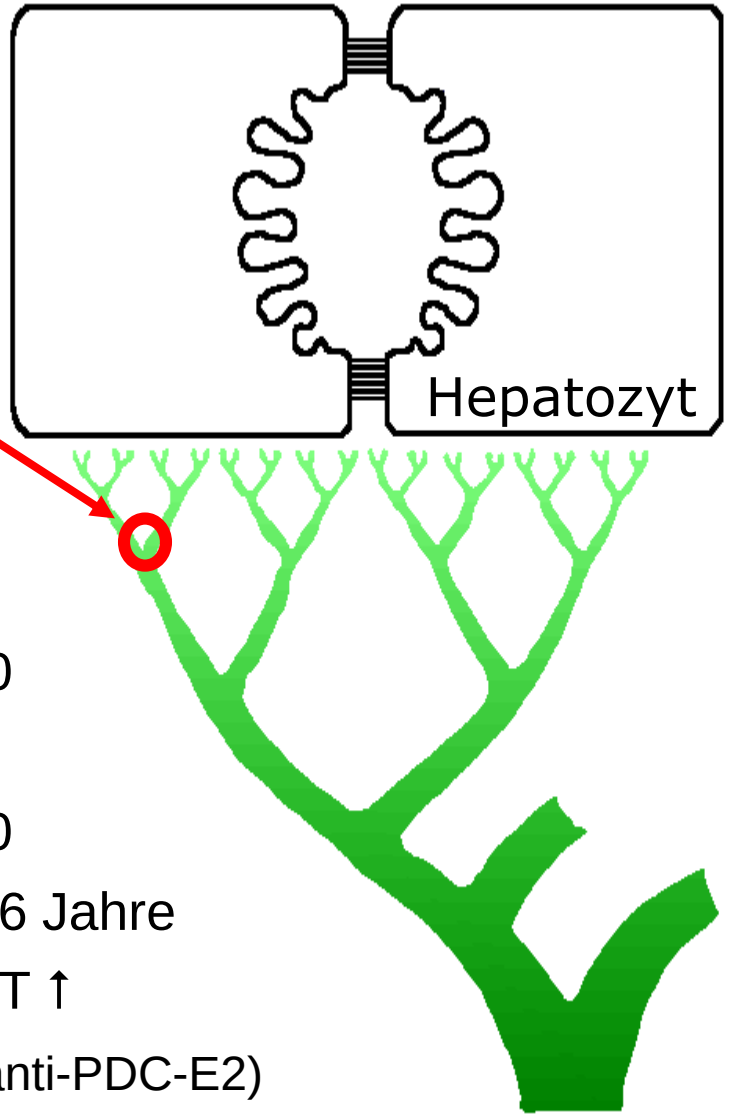
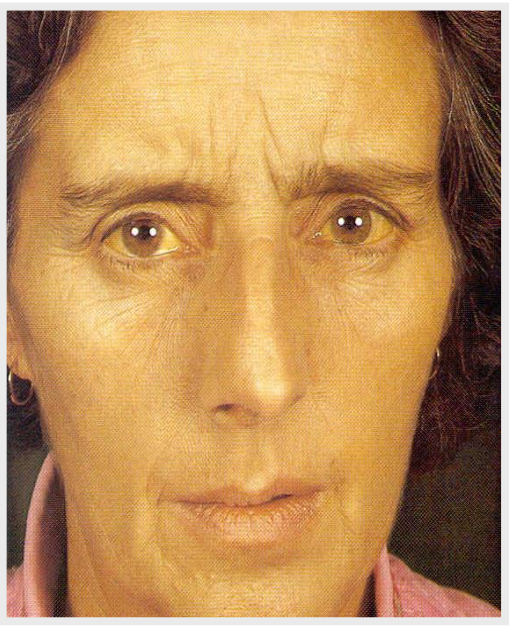
Primär Biliäre Cholangitis
- Klinische Aspekte -







Sherlock and Summerfield 1979

Prävalenz (pro 100.000)	25 – 40
Geschlecht (w : m)	9 : 1
Manifestationsalter	40 – 60
Überleben (ohne Therapie)	7,5 – 16 Jahre
Cholestase	AP/ γGT ↑
Auto-Antikörper	AMA (anti-PDC-E2)
	ANA (sp100, gp210)

Symptome
- Fatigue
- Pruritus
- Sicca-Syndrom
- Gelenkbeschwerden
- …

Personalisiertes Therapiekonzept der PBC

UDCA 13–15 mg/kg/Tag

nach 6 –12 Monaten

Biochemisches Ansprechen

Ja

Niedrigrisiko-Pfad

AP normalisiert
Bilirubin normalisiert
Keine Fibrose /
Risikofaktoren

UDCA lebenslang
Jährliche Kontrolle*

Risikostratifizierung!

Nein (20-40%)

Hochrisiko-Pfad

AP > 1.5 ULN
Bilirubin > 1.0 ULN
Alter < 50. LJ
Höhergradige Fibrose / Zirrhose

Engmaschigere Kontrollen (3-6 Monate)
Leberbiopsie / Elastographie
Zweit-/Drittlinientherapie

Obetichol-säure (OCA)

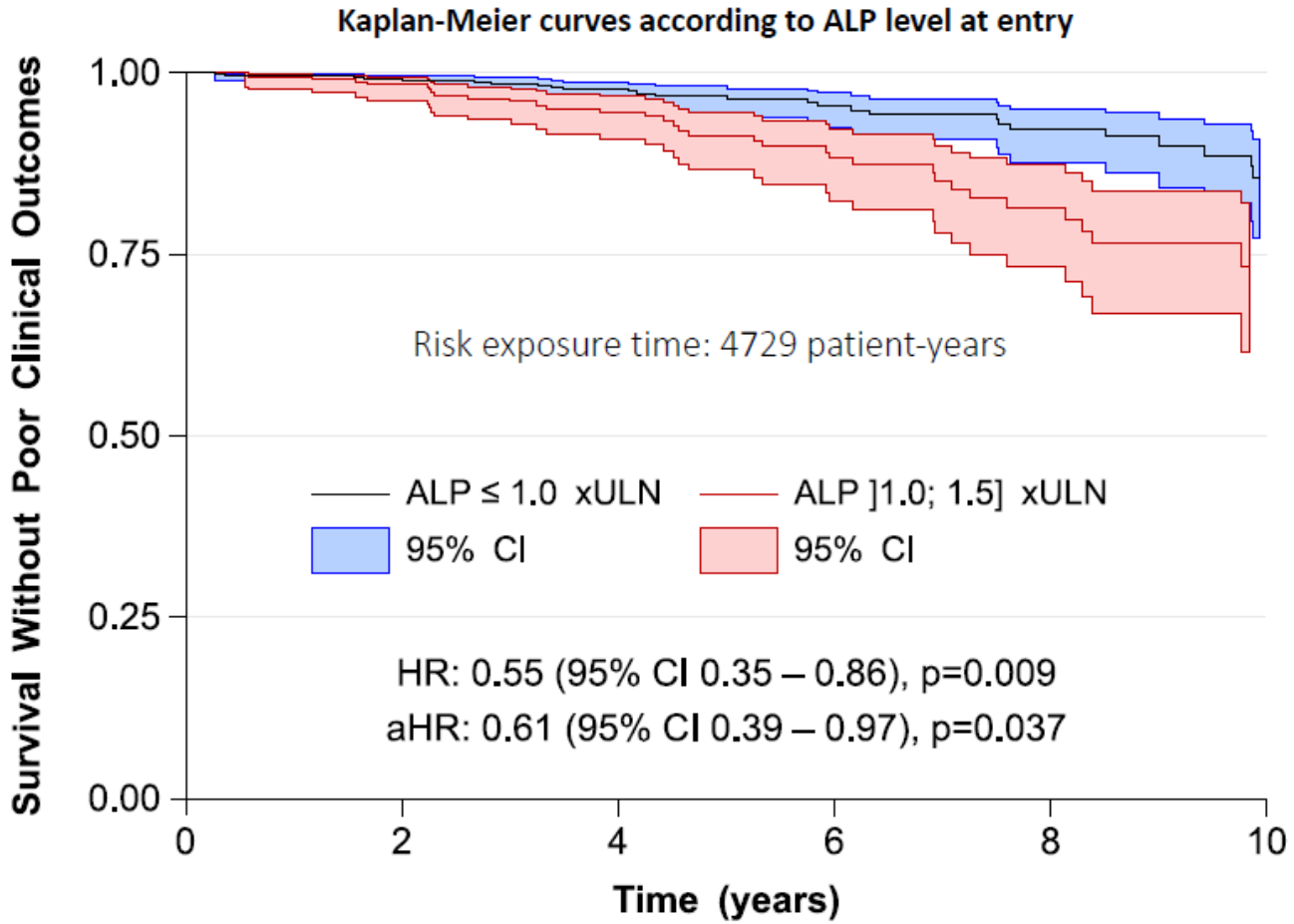
Bezafibrat Fenofibrat

Klinische Studien

* bei Gastroenterologen / Hepatologen

Überlebensvorteil bei Normalisierung der Leberwerte?

N=1047
mit gutem Ansprechen auf UDCA (Paris II: AP < 1.5, GOT < 1.5, Bilirubin normal)



85.3%

73.0%

Number at risk

ALP ≤ 1.0 xULN	687	536	312	190	116	54
ALP]1.0; 1.5] xULN	360	276	176	103	56	22

Kein Vorteil für Transaminasen oder yGT < 1.0 ULN

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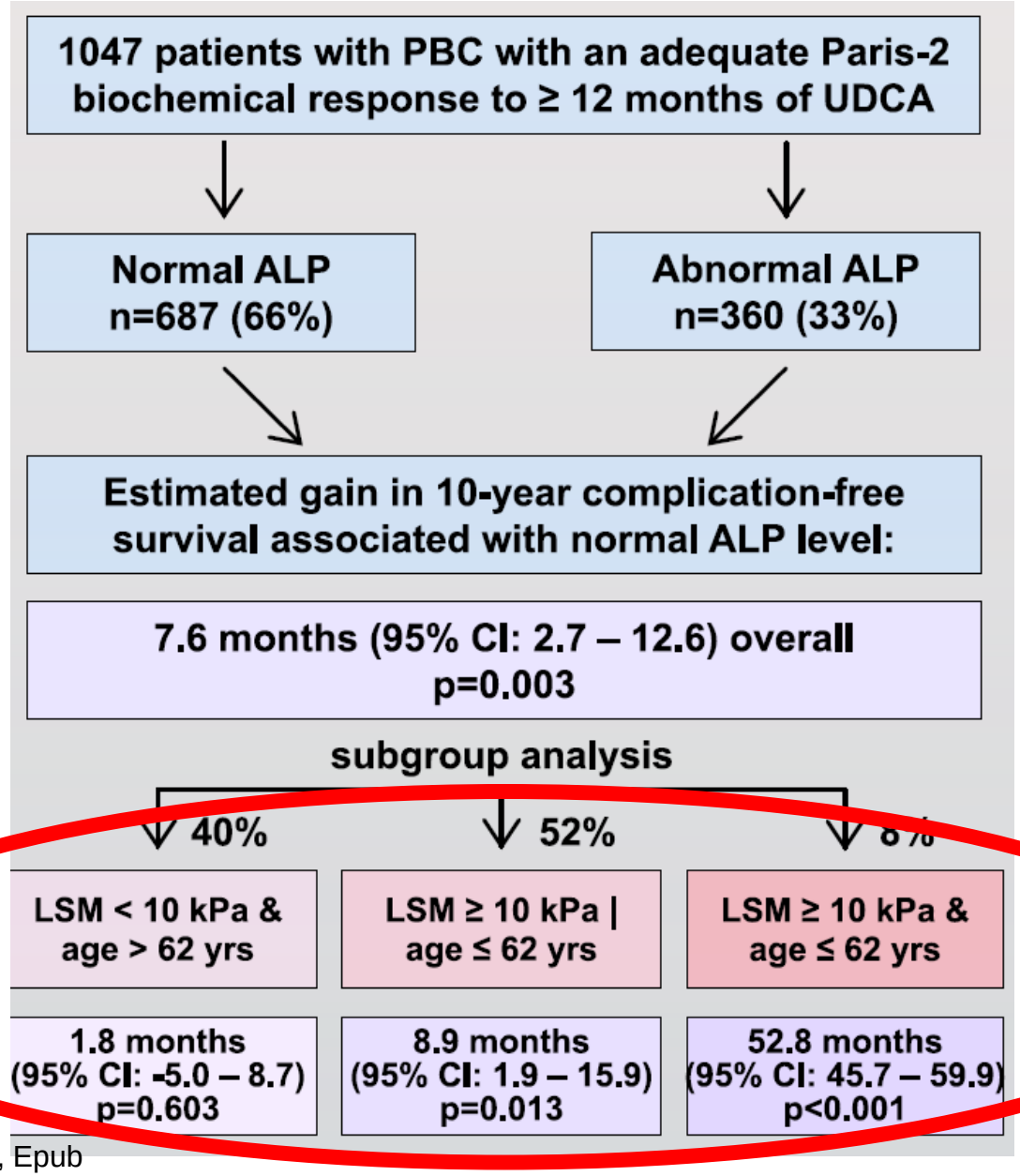
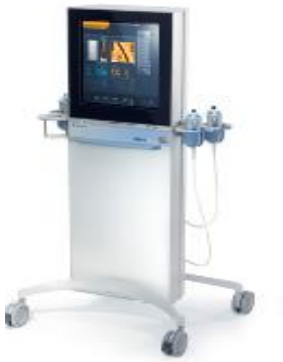
Corpechot C et al., Hepatology 2023, Epub

Überlebensvorteil bei Normalisierung der Alkalischen Phosphatase





TE > 10 kPa
und/oder
Alter < 62 Jahre

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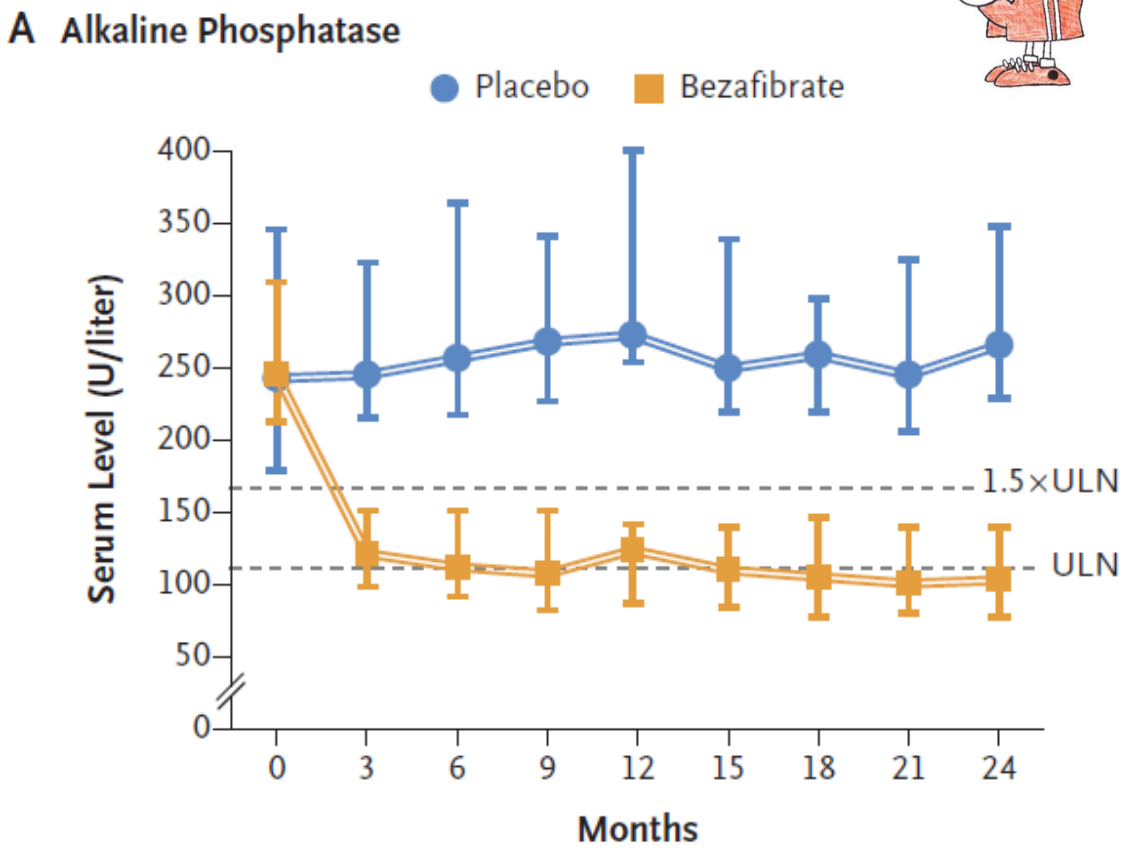
Corpechot C et al., Hepatology 2023, Epub

Obeticholsäure versus Bezafibrat bei PBC
- Ergebnisse der Phase III-Studien -

OCA

Nevens F et al. NEJM 2016; 375:7;

BEZA

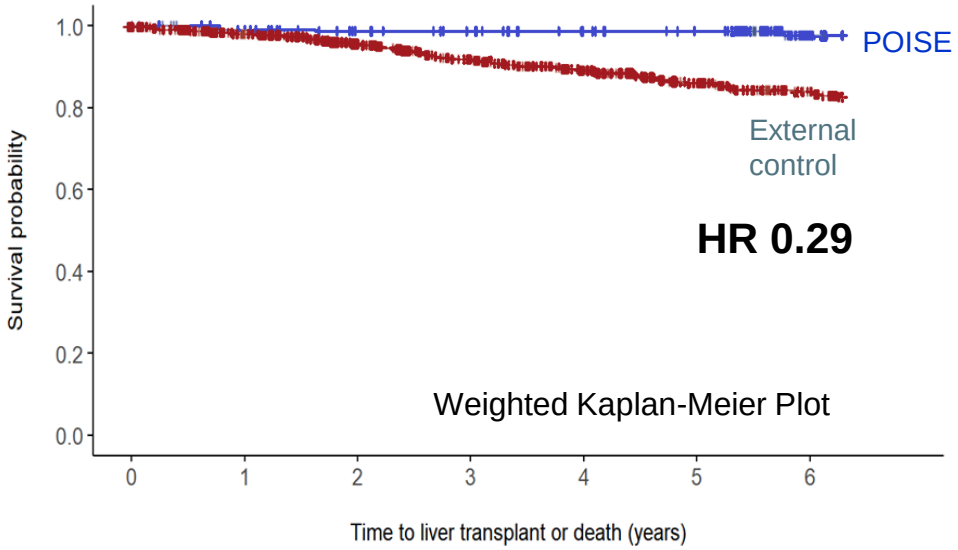


Corpechot C et al., NEJM 2018; 378: 2171;

Obeticholsäure versus Bezafibrat bei PBC
- Verbessertes Gesamtüberleben in Registeranalysen -

OCA

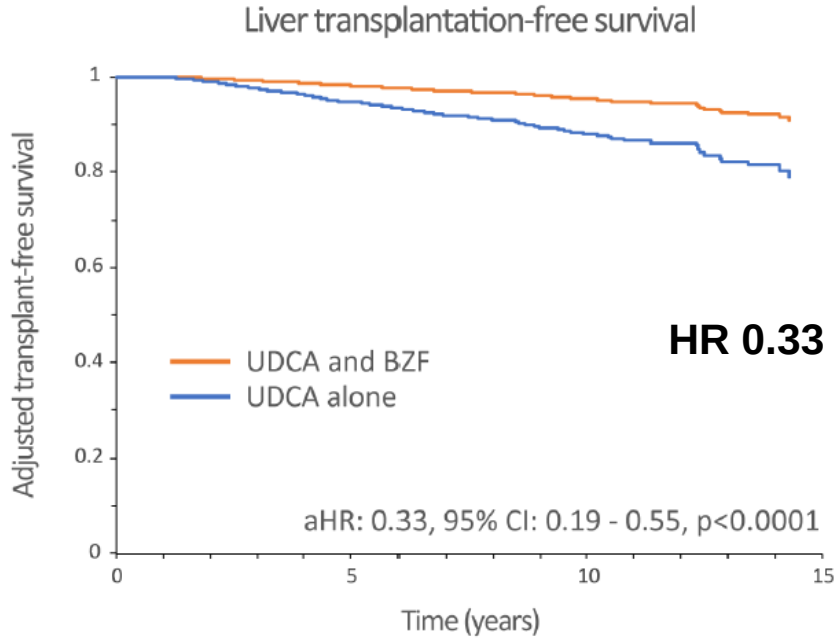
GLOBAL PBC



HR 0.29

Weighted Kaplan-Meier Plot

BEZA



HR 0.33

Sicherheitsprofil:

Pruritus; Dekompensation bei Zirrhose; LDL **Hepatotoxizität, Myopathie, Nephrotoxizität**

Murillo-Perez CF et al., Gastroenterology 2022; 163: 1630

Tanaka A et al., J Hep 2021; 75: 565

PPAR-Agonisten – Wirkmechanismus

Decrease Bile Acids

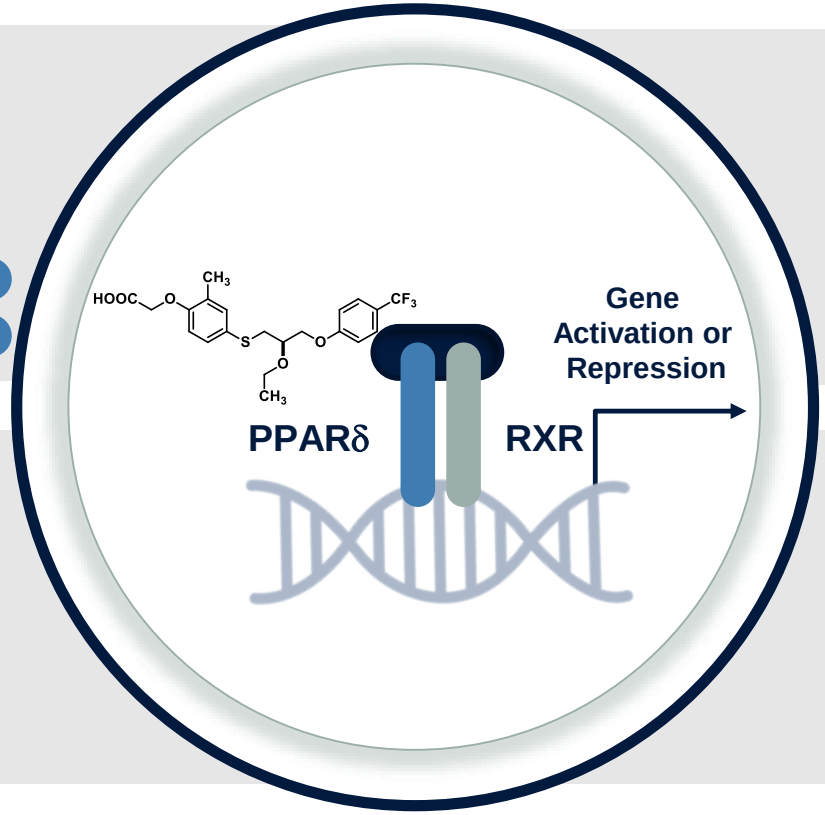
- ↓ Cholesterol synthesis
- ↓ Bile acid synthesis (C4)
- ↑ Transport

Hepatocyte
Cholangiocyte

Anti-Inflammatory

- ↓ NFκB-dependent gene activation
- ↓ Inflammatory cytokines
- ↓ hs-C-Reactive Protein

Kupffer Cell
Macrophage



Anti-Fibrotic

- ↓ Profibrotic genes
- ↓ Stellate cell activation
- ↓ Collagen synthesis/deposition

Stellate Cell

Increase Lipid Metabolism

- ↓ Cholesterol/LDL-C
- ↑ Fatty acid oxidation

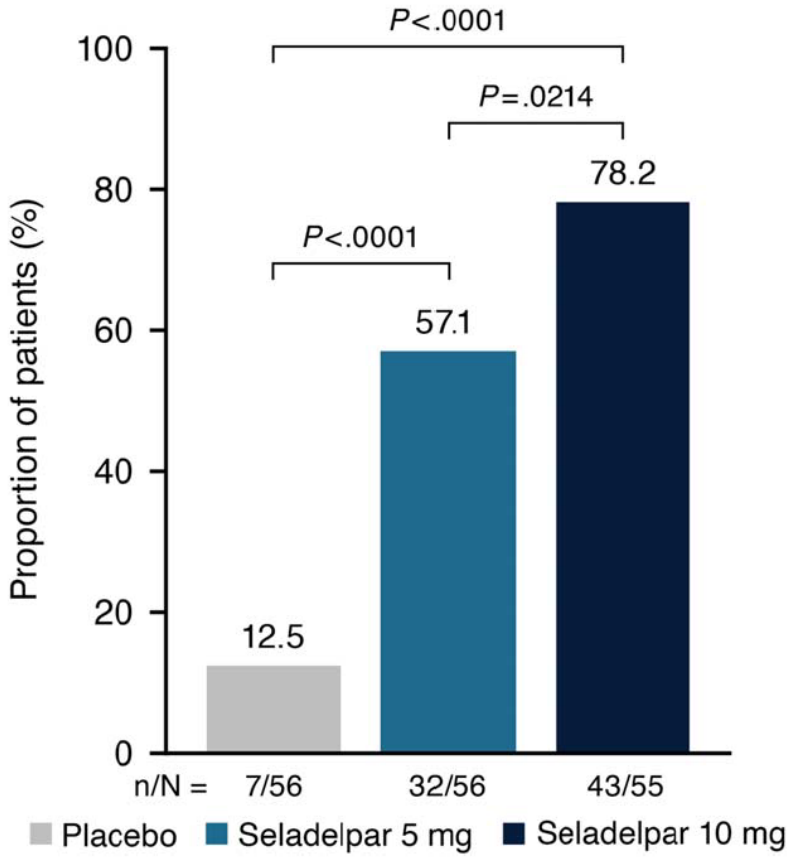
Hepatocyte
Myocyte
Adipocyte
Enterocyte

Regulates Genes That Control Pathways in Liver Health and Disease

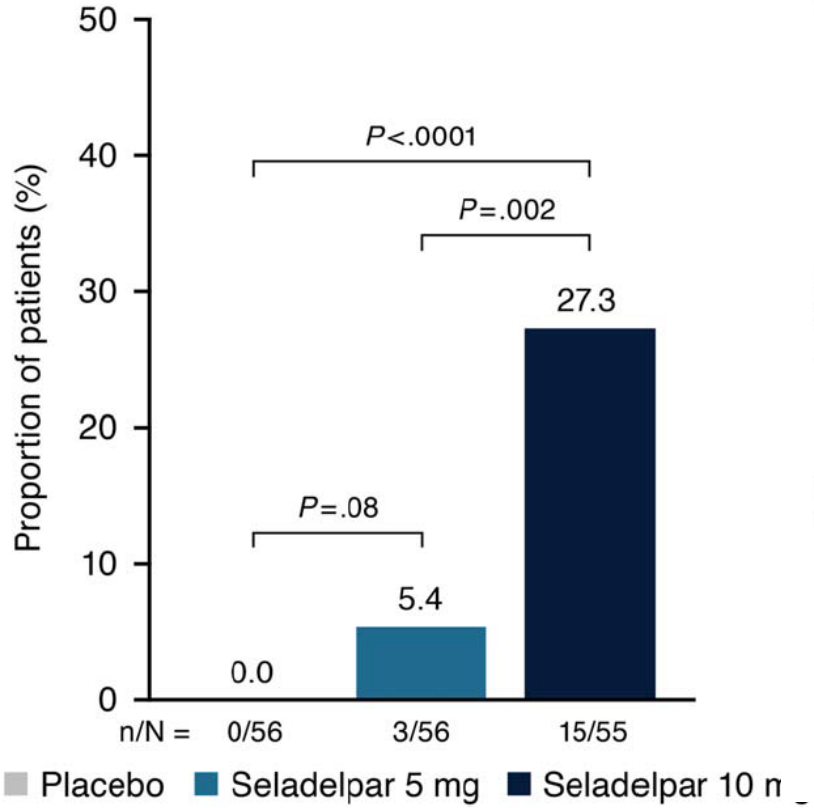
Kindly provided by CymaBay Therapeutics

Neue PPAR-Agonisten: Seladelpar bei PBC
- Phase III-Studie (N=265; Placebo vs. 5 mg vs. 10 mg) -

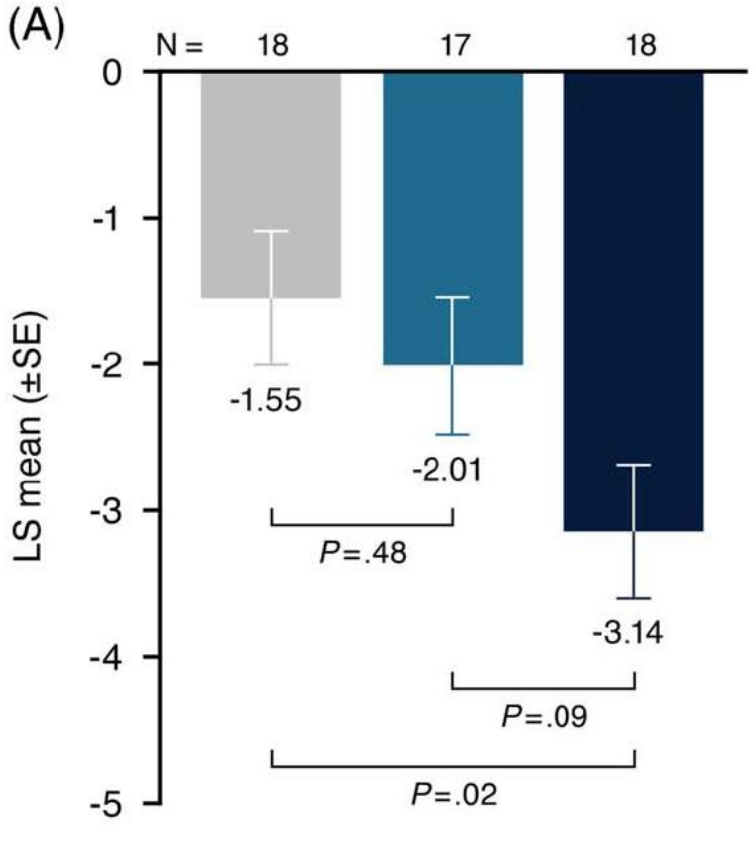
Composite Endpoint:
AP < 1.67, AP-Abfall > 15%, Bilirubin < 1.0



AP-Normalisierung



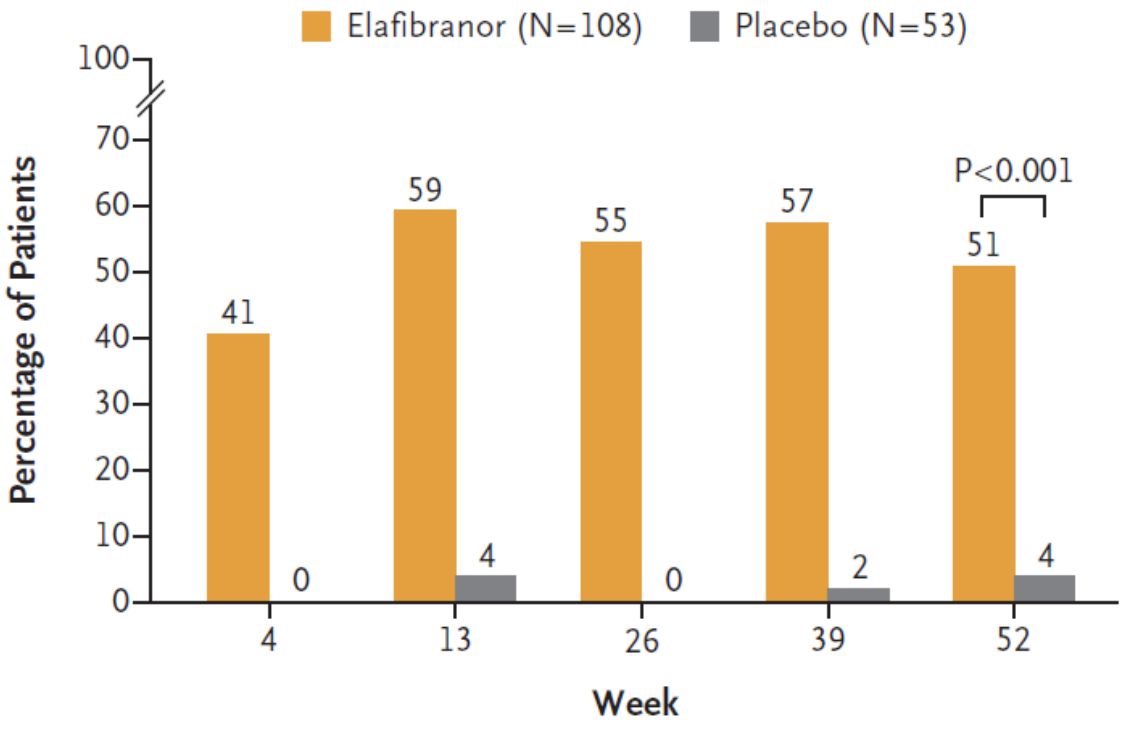
Pruritus-Verbesserung



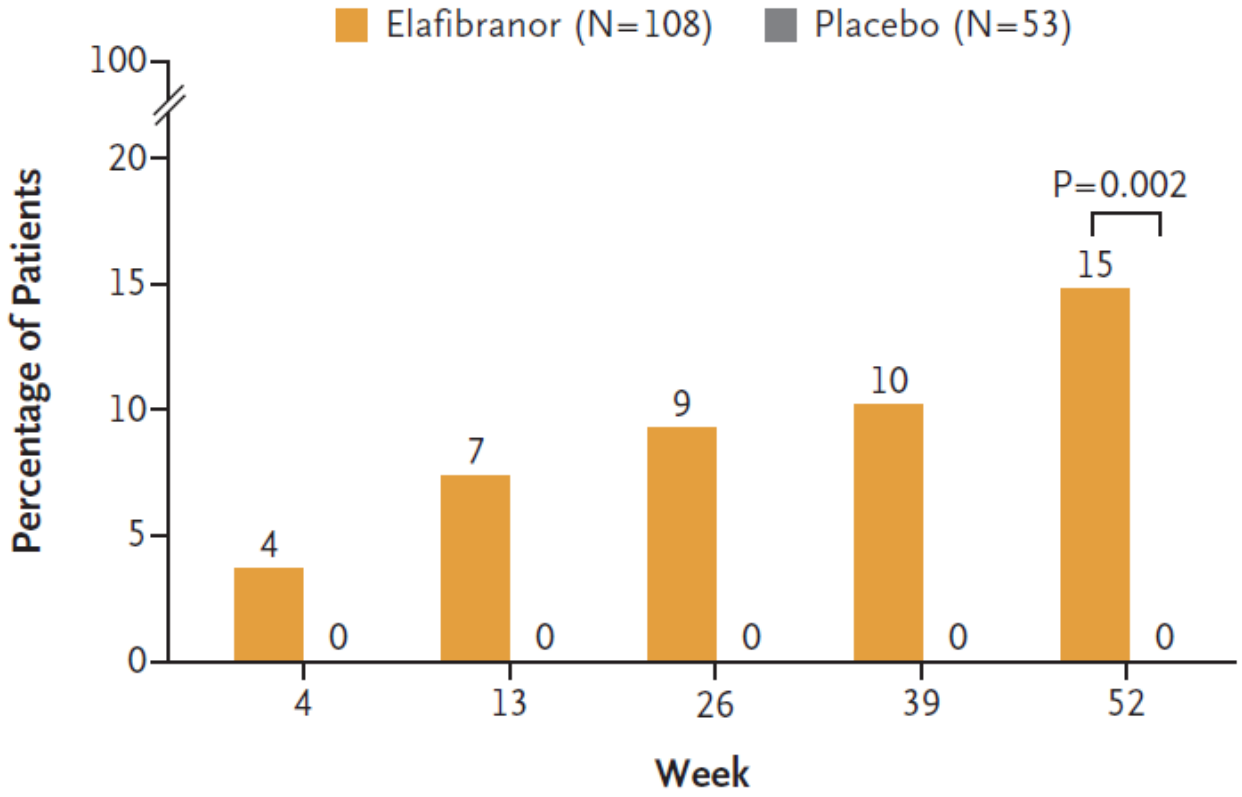
Hirschfield GM et al., Hepatology 2023; 78:397

Neue PPAR-Agonisten: Elafibranor bei PBC
- Phase III-Studie (N=161; Placebo vs. 80 mg) -

Composite Endpoint:
AP < 1.67, AP-Abfall > 15%, Bilirubin < 1.0



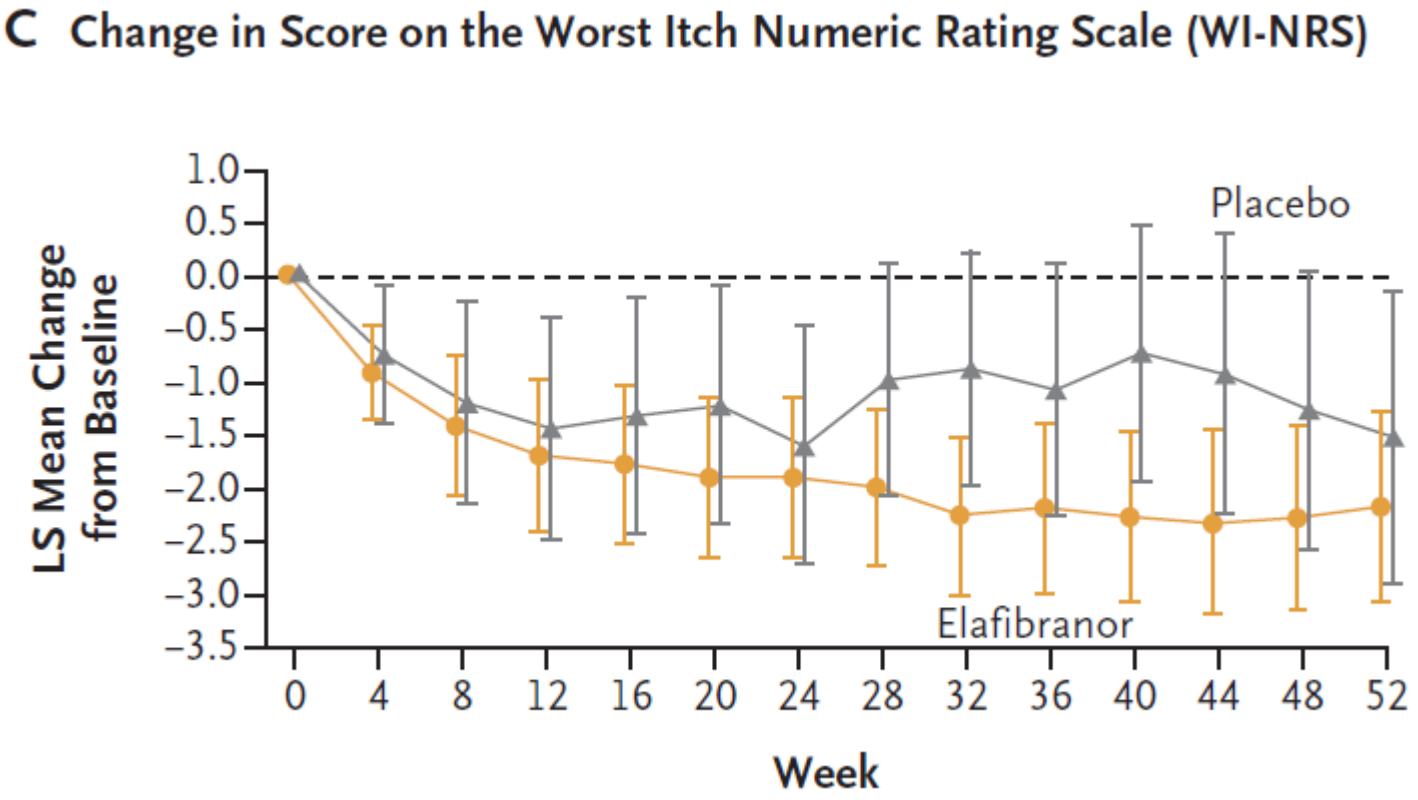
AP-Normalisierung



Kowdley K et al., NEJM 2023; Epub

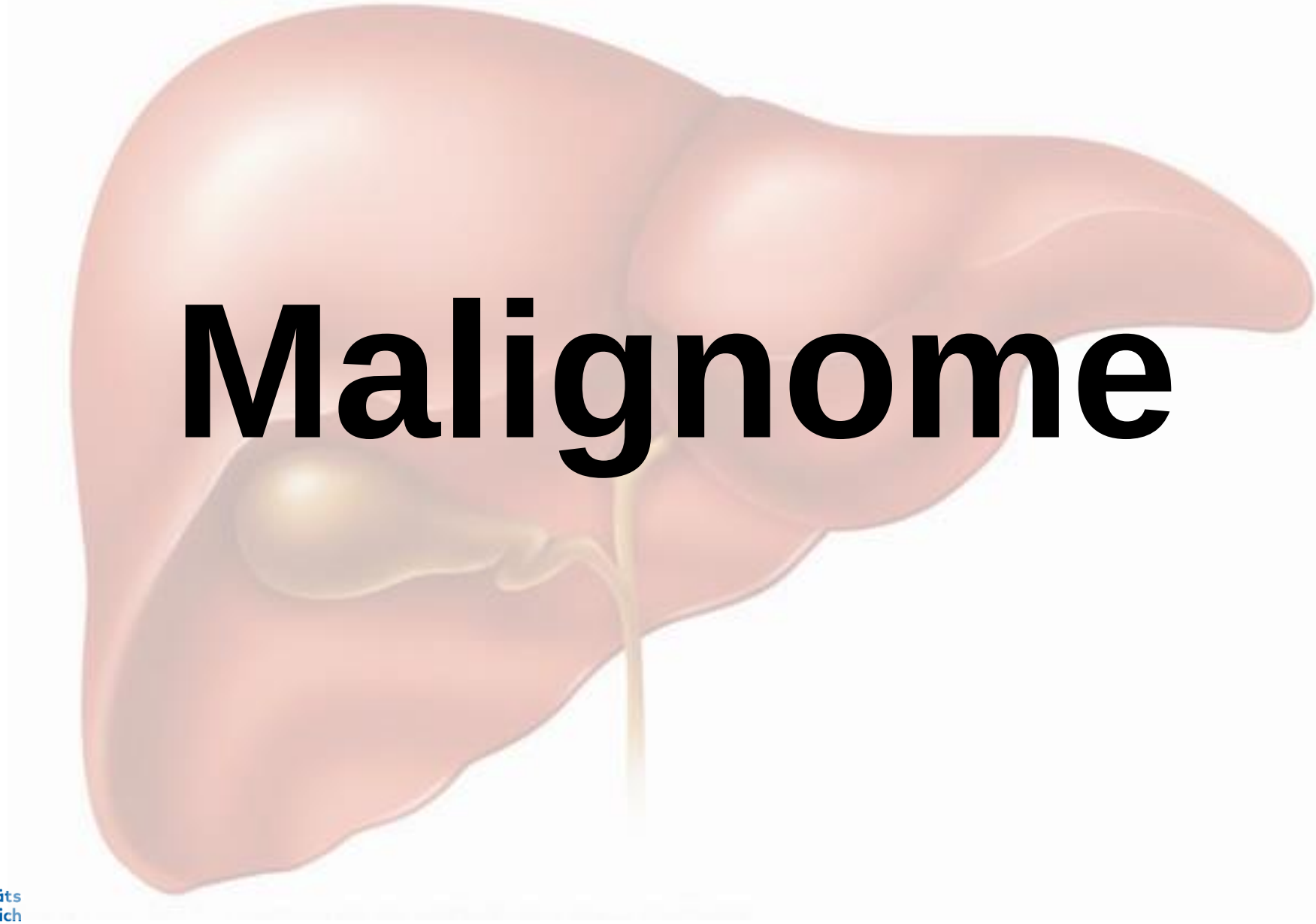
Neue PPAR-Agonisten: Seladelpar bei PBC
- Phase III-Studie (N=161; Placebo vs. 80 mg) -

Pruritusverbesserung



Sig. Verbesserung
- 5D-Itch und
- PBC-40

Kowdley K et al., NEJM 2023; Epub



Malignome

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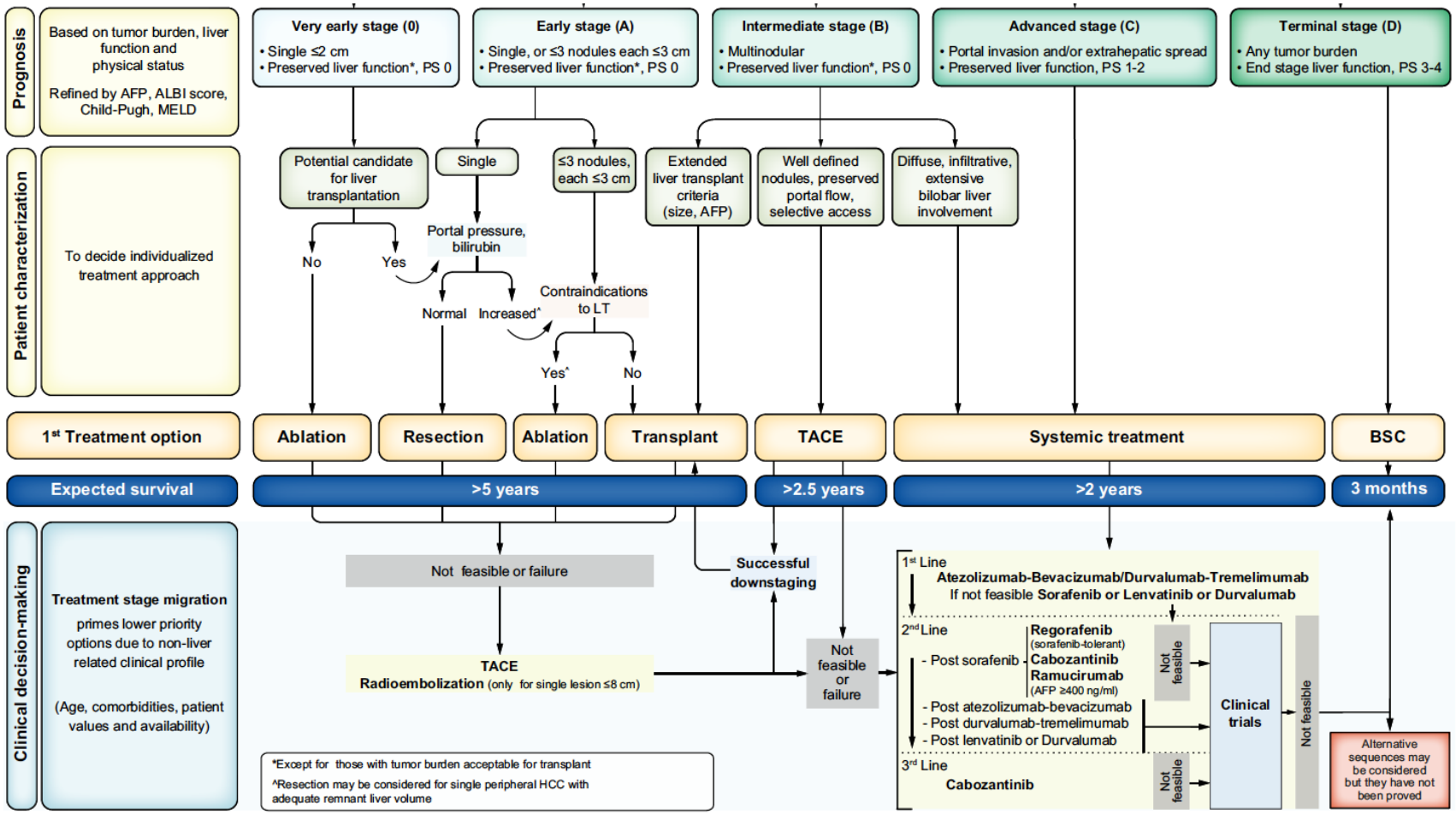
Barcelona Clinic Liver Cancer Algorithmus



Evidence based

Clinical desicion

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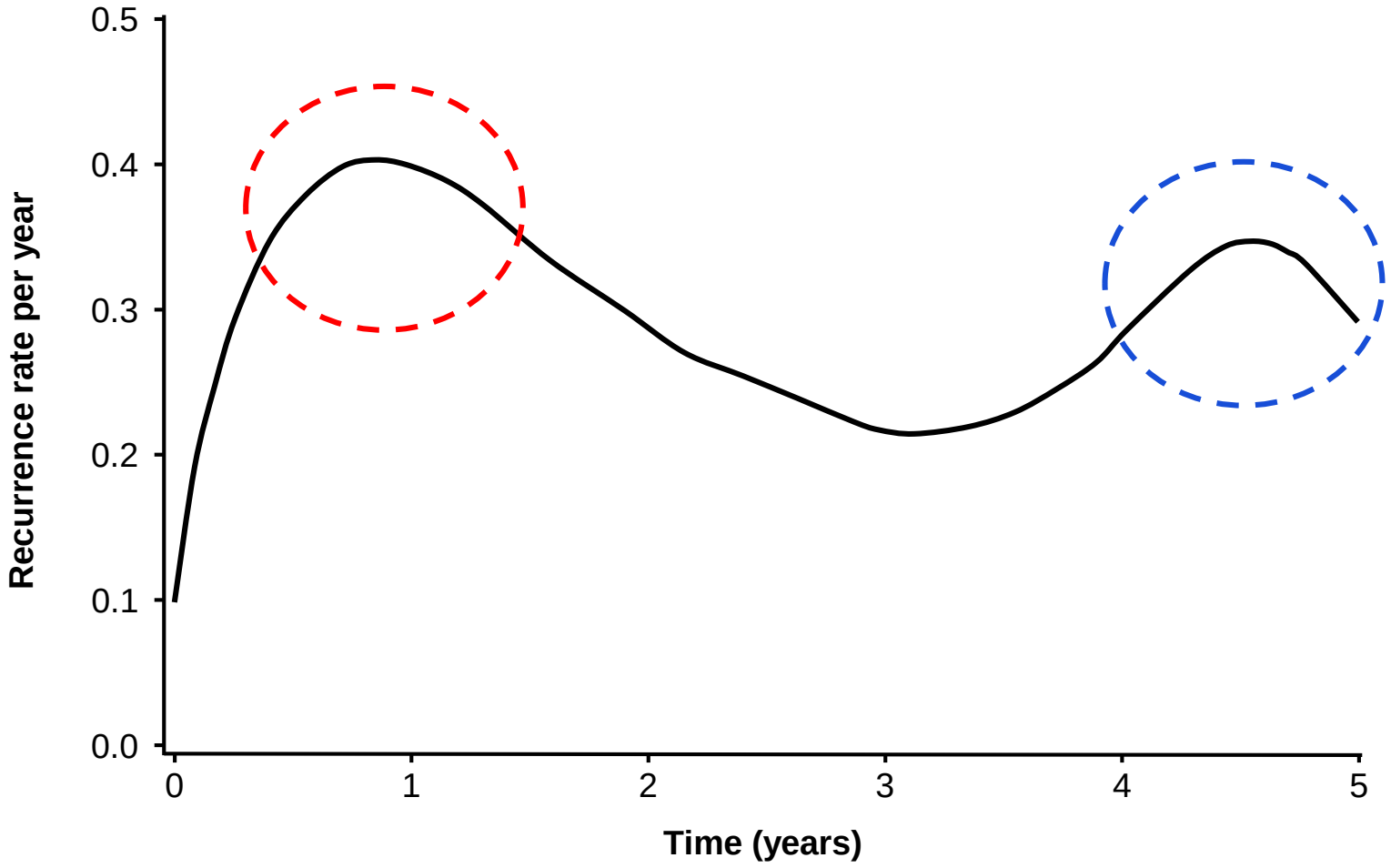
Reig et al. J Hepatol. 2022;76:681–693

Bimodale Rekurrenz nach HCC-Resektion



- Recurrence rate after resection peaks at around **1 year**, then gradually decreases over the next 2 years.[1] Current consensus is that these recurrences are from **micro-metastases**
- A second lower postoperative recurrence peak occurs at **4-5 years**[1]
- The second peak is currently understood to be due to **de novo tumors** associated with underlying liver disease[2]

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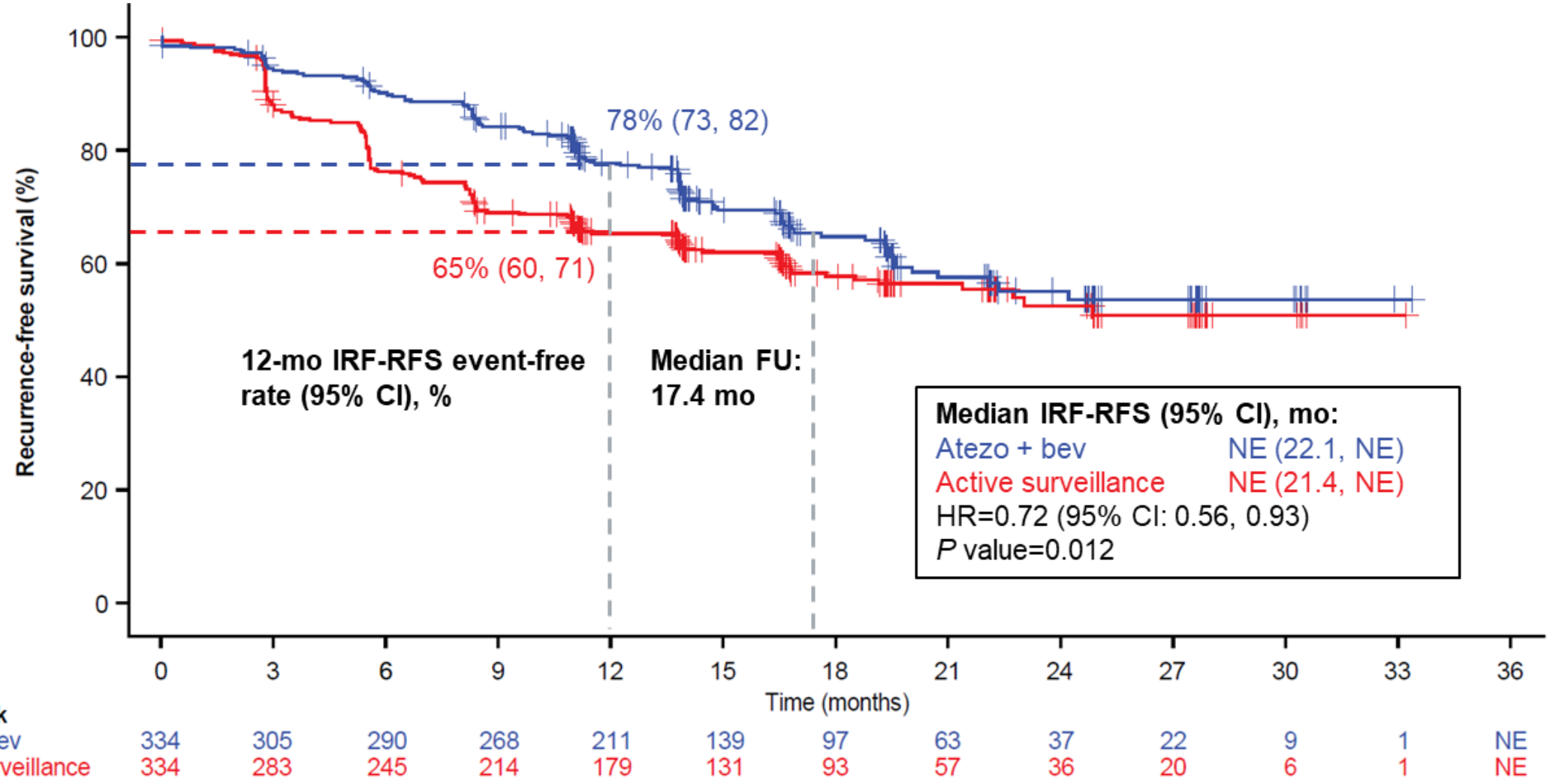
1. Imamura et al. J Hepatol 2003. 2. Yao et al. Ann Surg Oncol 2022

Imbrave050: Atezolizumab+Bevacizumab verbessert Rezidivfreiheit

- Phase III Studie (N=688; Resektion /Ablation; high-risk; 1 Jahr Therapie) -



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Qin S et al. Lancet 2023: Epub

Vielen Dank!

Backup Slides