HCC
Onkopedia Leitlinie

Prof. Sebastian Stintzing | 26. April 2024 | DGHO Berlin

Klinik für Hämatologie, Onkologie und Tumorimmunologie (CCM)

Charité – Universitätsmedizin Berlin

Offenlegung Interessenskonflikte

Stintzing Sebastian

1. **Anstellungsverhältnis oder Führungsposition**
   Charité – Universitaetsmedizin Berlin

2. **Beratungs- bzw. Gutachtertätigkeit**
   AMGEN, AstraZeneca, Bayer, BMS, CV6, Daiichi-Sanyko, ESAI, Lilly, Merck KGaA, MSD, Pierre-Fabre, Roche, Sanofi, Servier, Taiho, Takeda

3. **Besitz von Geschäftsanteilen, Aktien oder Fonds**
   keine

4. **Patent, Urheberrecht, Verkaufslizenz**
   keine

5. **Honorare**
   AMGEN, AstraZeneca, Bayer, BMS, Daiichi-Sanyko, ESAI, Leo-Pharma, Lilly, Merck KGaA, MSD, Pierre-Fabre, Roche, Sanofi, Servier, Taiho, Takeda

6. **Finanzierung wissenschaftlicher Untersuchungen**
   Merck KGaA, Pierre-Fabre, Servier, Roche

7. **Andere finanzielle Beziehungen**
   keine

8. **Immaterielle Interessenkonflikte**
   keine

Inhalt

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Onkopedia Leitlinie HCC
Grundlagen

Grundlagen

Epidemiologie

- ca. 6.000 Neuerkrankungen pro Jahr/Dtschl.

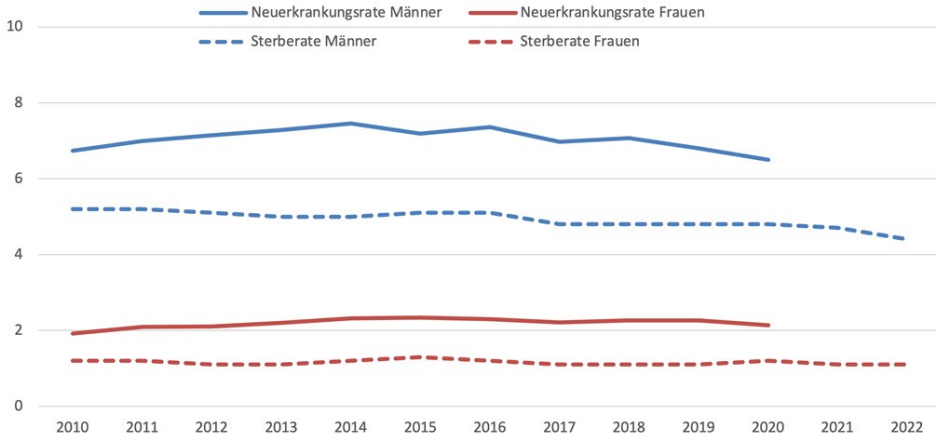
  →Inzidenz: 1: 3

- ca. 4.300 Sterbefälle pro Jahr

- Erkrankungsalter (median)

  → 75 Jahre; 71 Jahre

- Medianes Überleben:
  <60 Jahre: 13 Monate
  60-74 Jahre: 12 Monate
  >75 Jahre: 8 Monate



Weltweit:
- Ca. 910.000 Neuerkrankungen pro Jahr
- Ansteigende Inzidenz

Grundlagen

Epidemiologie

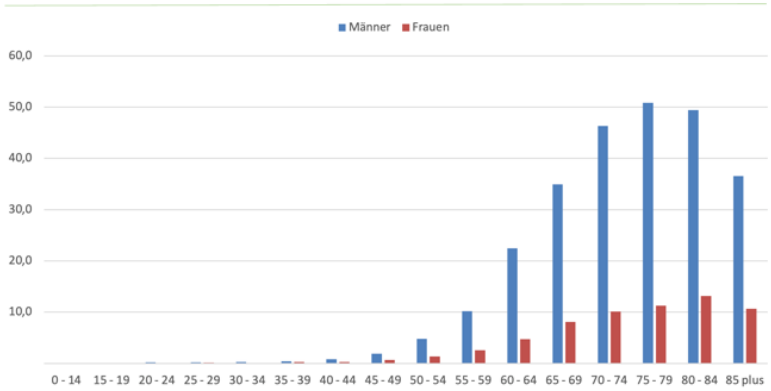


Abbildung 2: Inzidenzraten des HCC nach Alter in Jahren und Geschlecht (Deutschland 2018-2020, je 100.000 Personen)

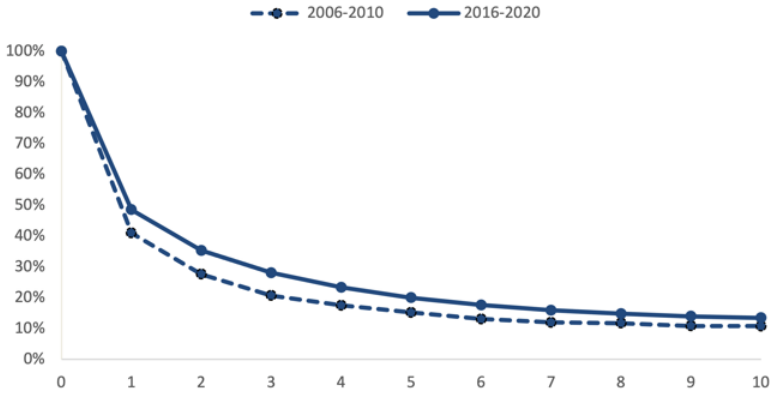


Abbildung 3: Relative Überlebensraten in Deutschland bis 10 Jahre nach Erstdiagnose eines HCC, nach Zeitperiode (Periodenanalyse, ausgewählte Register)

2

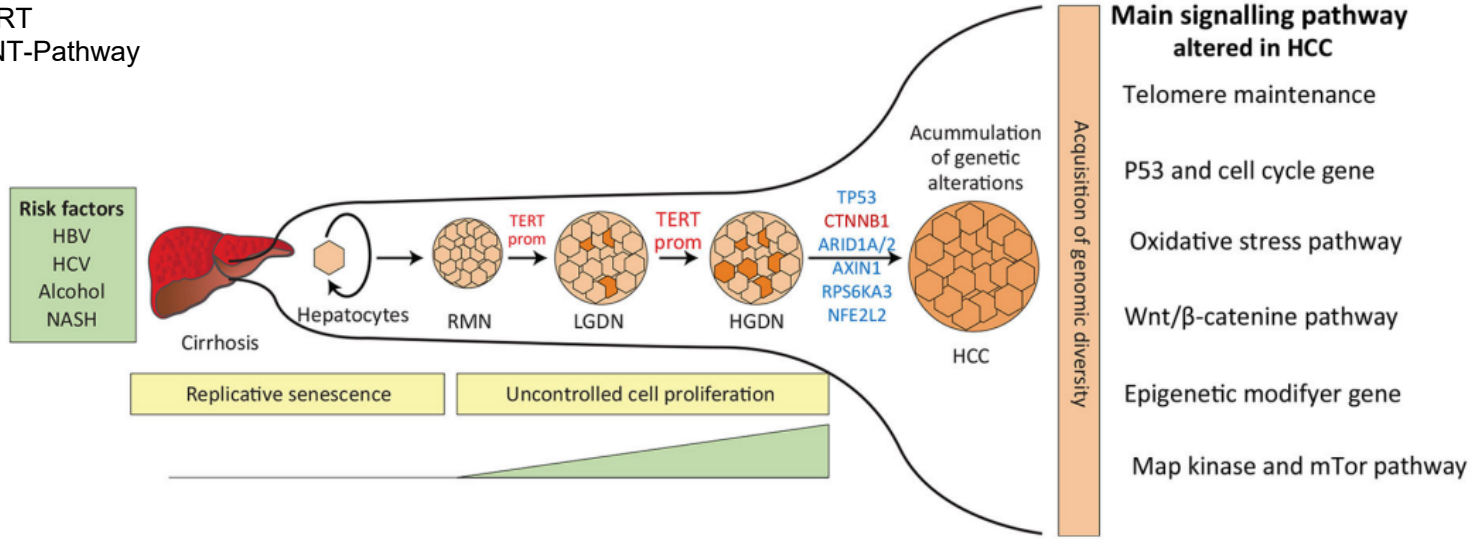
Onkopedia Leitlinie HCC
Prävention

Prävention

Karzinogenese

<u>Zentral ist:</u>

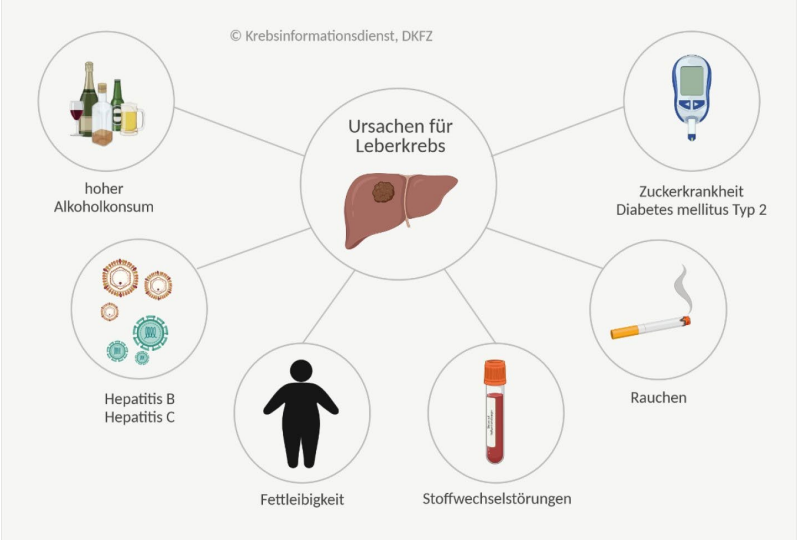
- TP53
- TERT
- WNT-Pathway



Gerbes A. et al Gut. 2018 February ; 67(2): 380–388. d

Prävention

Risikofaktoren



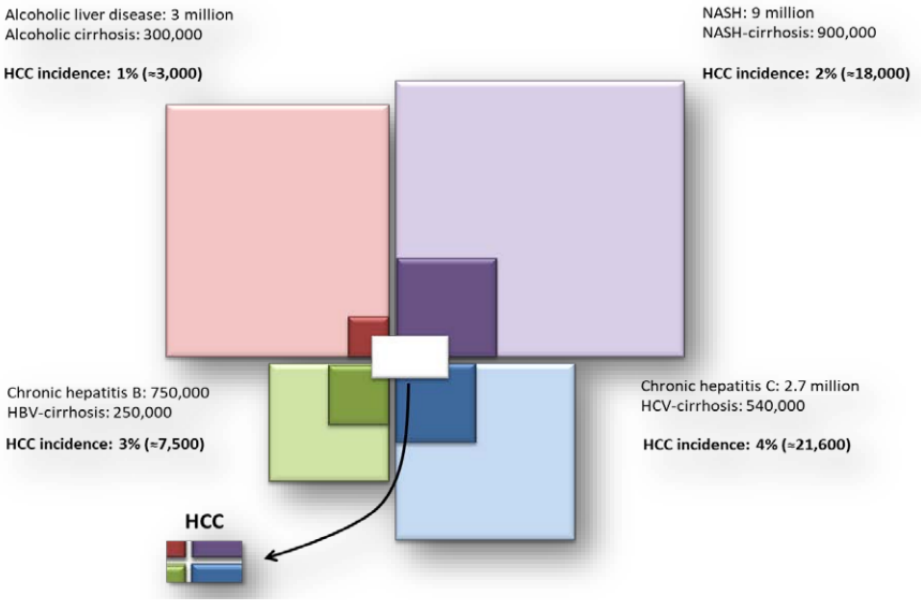
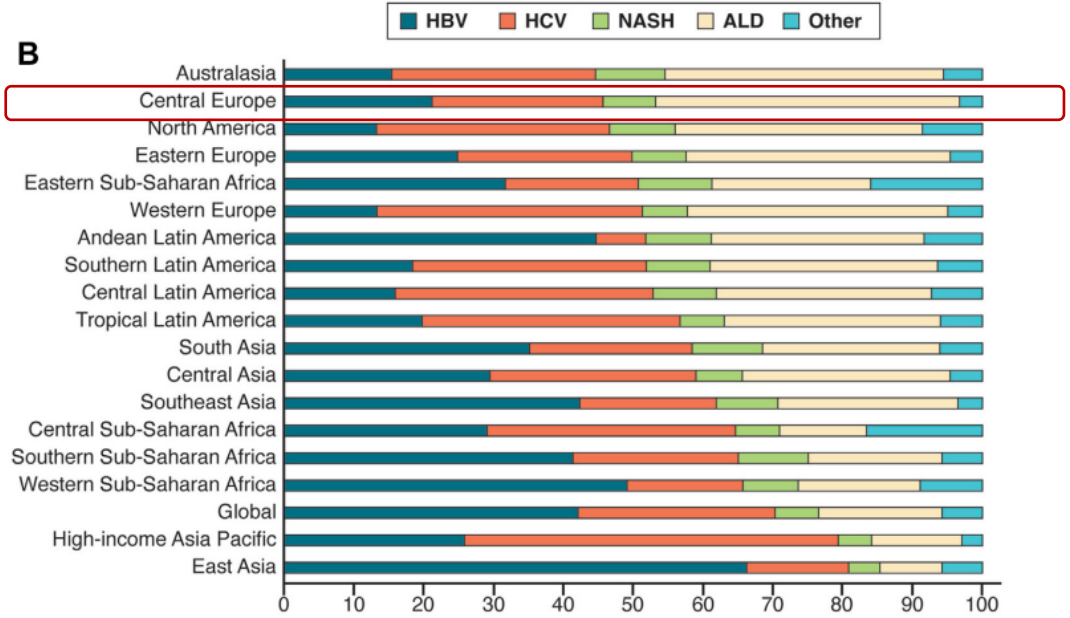


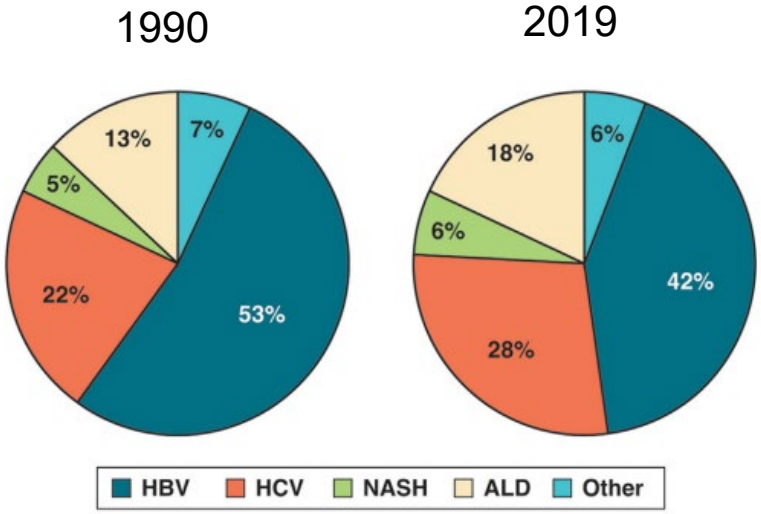
Figure 1. Relative contributions for HCC incidence from the most frequent causes of liver disease. HCC = hepatocellular carcinoma; NASH = non-alcoholic steato-hepatitis; HBV = hepatitis B virus; HCV = hepatitis C virus.

Torres et al Cancers 2020, 12, 1422;

Prävention

Globale Unterschiede





Torres et al Cancers 2020, 12, 1422;

Prävention

Risikofaktoren

- Genetische Prädispositionen

  →Alkoholbedingte Leberzirrhose:

  Erhöhtes Risiko: TM6SF2-Variante rs58542926, Phospholipase-PNPLA3-Variante rs738409

  Protektiv: TERT: rs2242652(A)

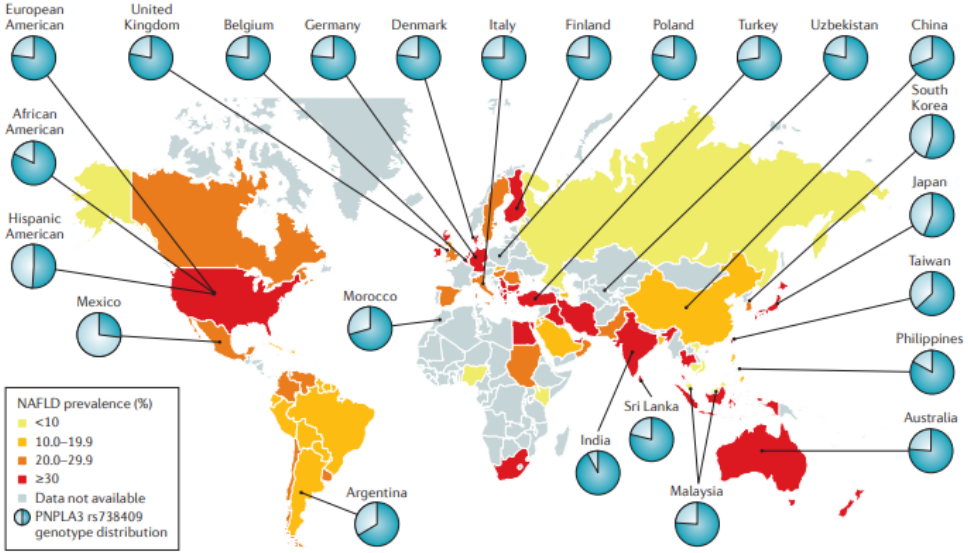


Figure 1 | **Worldwide estimated prevalence of NAFLD and distribution of *PNPLA3* genotypes.** *PNPLA3* is presented as minor allele frequency (light blue section of the pie chart).

Younossi Z et al Nat Rev Gastroenterology & Hepatology15, pages11–20 (2018)

Prävention

Risikofaktoren

- Leberzirrhose: jährliches Risiko ein HCC zu entwickeln: 2,5%

  →Zirrhose + Hepatitis C : 3-8%

  →Zirrhose + Hepatitis B: 2%

  →Zirrhose bei MASLD/MASH: 0,004-7.6%

- HCC ohne vorherige Zirrhose:

  →Hepatitis B / Hepatitis C: 0,12-1,3%

	Risk factor			
	Hepatitis C virus	Hepatitis B virus*	Alcohol	Other
Europe	60–70%	10–15%	20%	10%
North America	50–60%	20%	20%	10%
Asia and Africa†	20%	70%	10%	<10%‡

*Estimates from HbsAg carriers. Occult hepatitis B virus infection might involve additional patients. †Except Japan, for which hepatitis C virus 70%, hepatitis B virus 10–20%, alcohol 10%, other <10%. ‡Aflatoxin is main co-factor enhancing oncogenetic risk of patients with hepatitis B virus infection. Modified from reference 6.

Llovet LANCET • Vol 362 • December 6, 2003

Prävention

Vorbeugung und Früherkennung

- Schutzimpfung gegen Hepatitis B
- Behandlung der Ursachen einer chronischen Lebererkrankung, insbesondere Alkoholkarenz, Gewichtskorrektur bei Adipositas (Ramai, Aliment Pharmacol Ther 2021)
- Behandlung von Hyperlipidämien mit Statinen, insbesondere bei Vorliegen einer Phospholipase-PNPLA3-Variante rs738409 (Singh, Gastroenterology 2013; Simon, AIM 2019; Vell, JAMA-NO 2023)
- Metformin-Therapie bei nicht-insulinpflichtigem Diabetes mellitus (Chen, Gut 2013; Singal, NRCO 2023)
- Niedrig dosierte ASS zusätzlich zu Metformin (Simon, NEJM 2020; Singal, NRCO 2023)
- Antivirale Behandlung bei chronischer HBV-/HCV-Infektion mit und ohne HCC, bei Hepatitis C vorzugsweise mit Tenofovir (Ogawa, JAMA-IM 2023)

Prävention –nicht gesichert: retrospektive Daten

Vorbeugung und Früherkennung

- Zufuhr von ≥ 3 Tassen koffeinhaltigen Kaffees pro Tag: relative Risikoreduktion 41-50% (Kennedy, BMJ Open 2017; Bhurwal, J Gastrointestin Liver Dis 2020)
- Bei entkoffeiniertem Kaffee nicht belegt (Bhurwal)
- Für grünen Tee ebenfalls nicht belegt (Filippini T, Cochrane 2020)

Früherkennung

Vorbeugung und Früherkennung

- Screeninguntersuchung

  → Patienten mit Leberzirrhose:

    → Alle 6 Monate: Sonographie Abdomen plus AFP: Verbessert Überleben und Operabilität

    → AFP Bestimmung: AFP Werte ≥ 20 ng/mL: Sensitivität 49-71% Spezifität 49-86% für ein HCC <5cm

    → AFP Bestimmung verbessert vermutlich Überleben (retrospektive koreanische Daten)

  → Patienten ohne Leberzirrhose

    → Hämochromatose: Screening ab Fibrosegrad 3 (METAVIR F3)

    → Heaptitis B: analog ***PAGE B Score***:
    <10 Punkte: neg. Vorhersage von 99%
    ein HCC in den nächsten 5 Jahren

Altersgruppe (Punkte)		Geschlecht (Punkte)		Thrombozytenwert (Punkte)	
16-29	0	weiblich	0	>200/nl	0
30-39	2	männlich	6	100-199/nl	6
40-49	4			<100/nl	9
50-59	6				
60-69	8				
>70	10				

PAGE B Score Berechung: J Hepatol. 2016

3

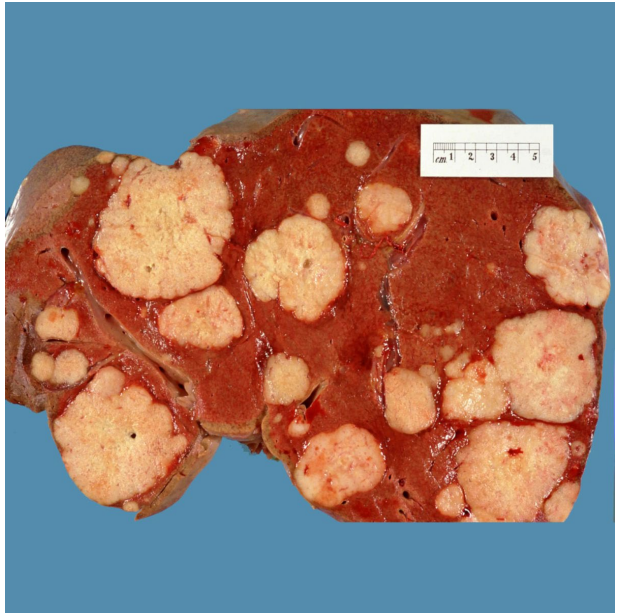
Klinisches Bild

Klinisches Bild

Keine Symptome im kurativen Frühstadium!

Spätstadium

- Druckschmerz im Oberbauch
- Tastbare Schwellung unter dem rechten Rippenbogen
- Appetitlosigkeit, Übelkeit oder erhöhte Körpertemperatur ungeklärter Ursache
- Schwäche, Leistungsminderung
- Ungewollte Gewichtsabnahme
- Zunehmender Ikterus und Juckreiz
- Zunahme des Bauchumfangs durch Aszites (bereits fortgeschrittene Zirrhose)



Quelle: doccheck flexikon

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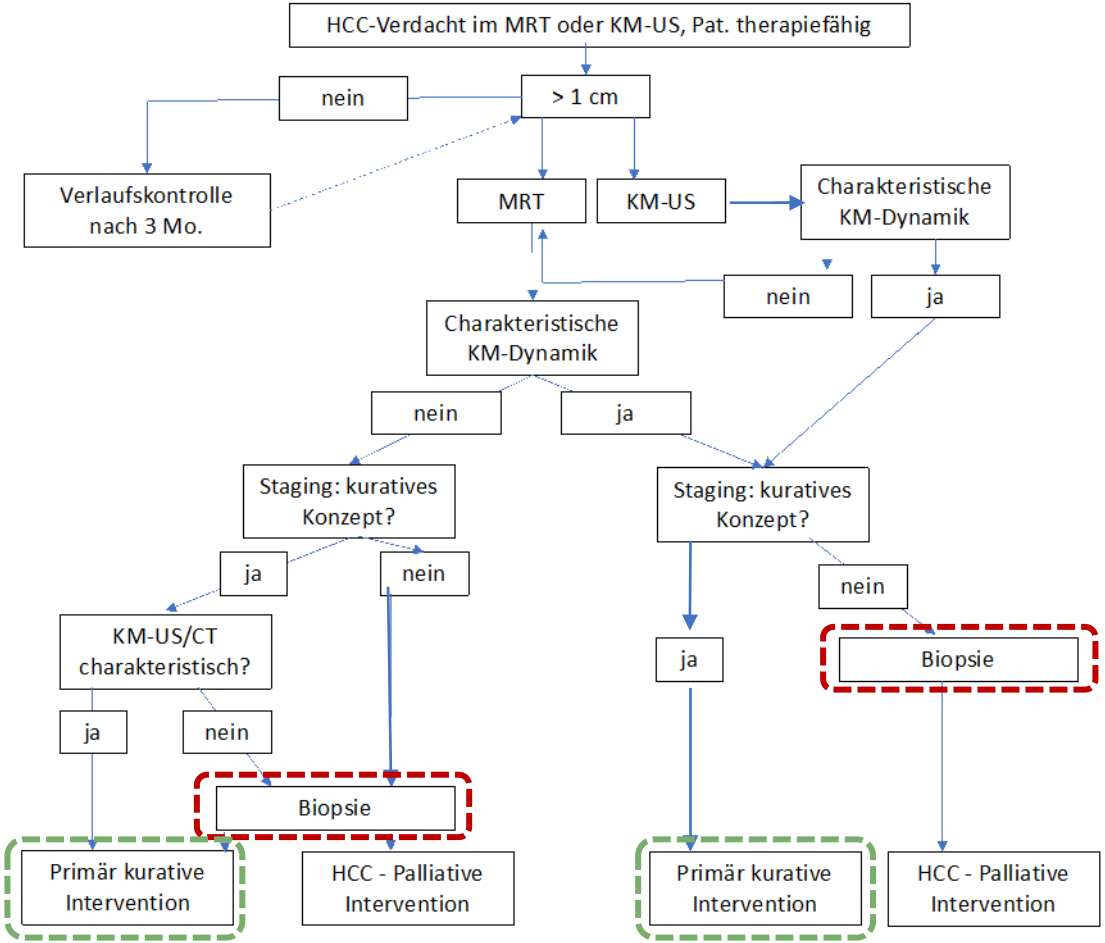
Diagnostik

Diagnostik


HCC-Verdacht im MRT oder KM-US, Pat. therapiefähig
nein
> 1 cm
Verlaufskontrolle nach 3 Mo.
MRT
KM-US
Charakteristische KM-Dynamik
nein
ja
Charakteristische KM-Dynamik
nein
ja
Staging: kuratives Konzept?
Staging: kuratives Konzept?
ja
nein
nein
KM-US/CT charakteristisch?
ja
Biopsie
ja
nein
Biopsie
Primär kurative Intervention
HCC - Palliative Intervention
Primär kurative Intervention
HCC - Palliative Intervention

Diagnostik

HCC-Kriterien in der bildgebenden Diagnostik

MRT Kriterien: LI-RADS (Liver Imaging Reporting and Data System)

- Tumorgröße
- Kontrastmitteldynamik (arterielle Phase und Auswaschphase)
- Kapselenhancement
- Wachstumsdynamik (≥ 50% Zunahme in ≤ 6 Monaten, ≥ 100% Zunahme in > 6 Monaten, neue Raumforderung ≥ 10 mm)

→ CAVE: 9% falsch negative Beurteilungen!

Unbehandelte Observation ohne histologischen Nachweis bei Patienten mit hohem HCC-Risiko

- Bei fehlender Beurteilbarkeit aufgrund fehlender oder schlechter Bildgebung → LR-NC
- Bei definitivem Nachweis von Tumorinfiltration in die Vene (TIV) → LR-TIV
- Wenn definitiv gutartig → LR-1
- Wenn wahrscheinlich gutartig → LR-2
- Wenn wahrscheinlich oder definitiv maligne aber nicht HCC-spezifisch (z. B. Schießscheibenzeichen) → LR-M

Andernfalls wenden Sie die CT/MRT-Diagnosetabelle unten an

- Bei mittlerer Wahrscheinlichkeit für Malignität → LR-3
- Wenn wahrscheinlich HCC → LR-4
- Wenn definitiv HCC → LR-5

CT/MRT Diagnosetabelle

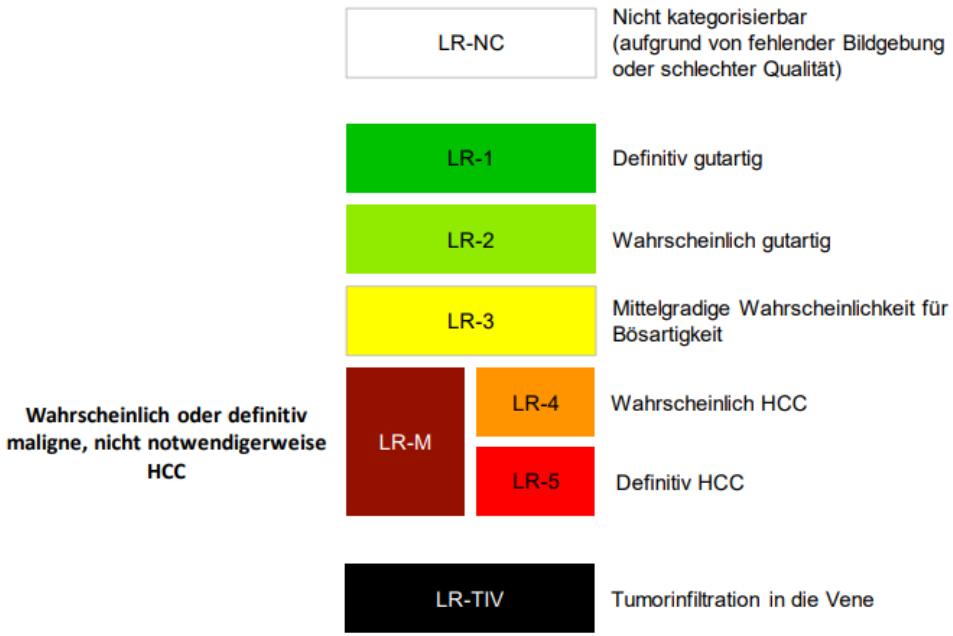
Hyperenhancement in der arterielle Phase (APHE)		Kein APHE		APHE (kein Rim-Zeichen)		
Größe der Observation (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Beachte Hauptmerkmale: • Anreichernde "Kapsel" • "Washout" (nicht peripher) • Schwellenwachstum	Keines	LR-3	LR-3	LR-3	LR-3	LR-4
	Eines	LR-3	LR-4	LR-4	LR-4 / LR-5	LR-5
	≥ zwei	LR-4	LR-4	LR-4	LR-5	LR-5

LR-4 / LR-5: Observationen in dieser Kategorie werden nach zusätzlichem Hauptmerkmal kategorisiert:
- LR-4 - bei anreichernder Kapsel
- LR-5 – bei nicht-peripherem Washout oder Schwellenwachstum

https://www.acr.org/-/media/ACR/Files/RADS/LI-RADS/Translations/LI-RADS-2018-CT-MRI-Core-German.pdf?la=en

Diagnostik

HCC-Kriterien in der bildgebenden Diagnostik

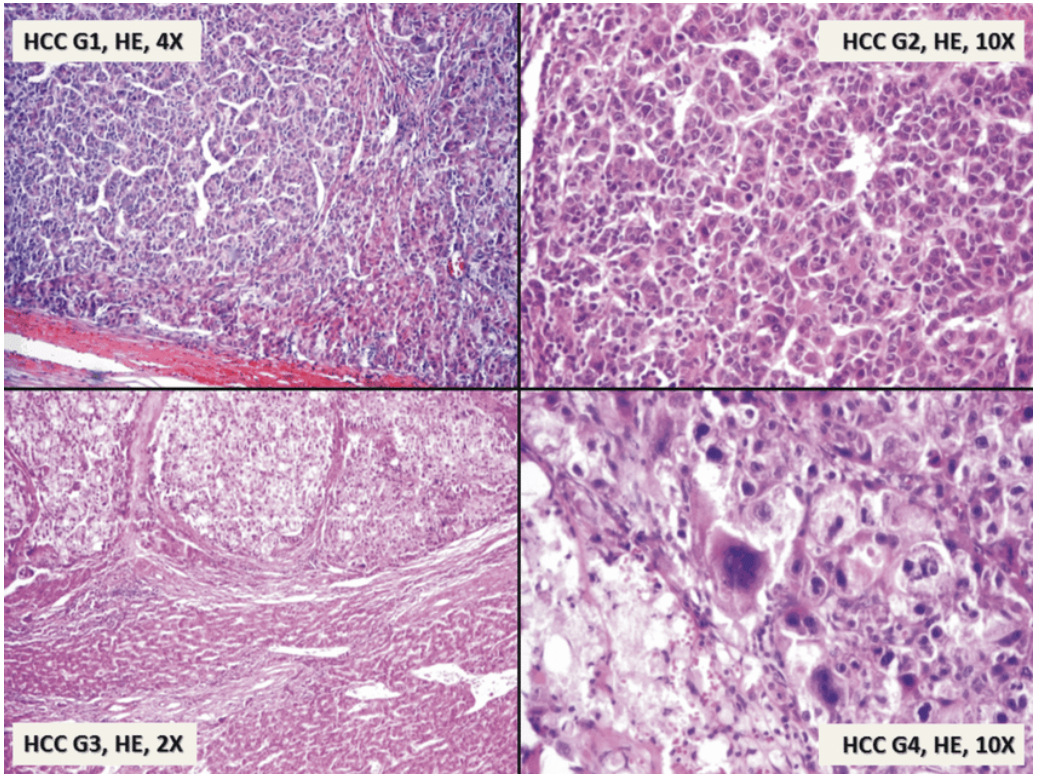


https://www.acr.org/-/media/ACR/Files/RADS/LI-RADS/Translations/LI-RADS-2018-CT-MRI-Core-German.pdf?la=en

Diagnostik

Histologie

- Typisierung nach aktueller WHO Klassifikation
- Sonderformen:
  - →fibrolamelläres HCC
  - →mischdifferenzierte Tumoren
- Im Zweifelsfall
  - →Glypican, HSP70 und Glutaminsythetase: wenn ≥ 2 Marker positiv: Spezifität für HCC 100% (Di Tommaso 2009/ Tremosini2012)



Romanian Journal of Morphology and Embryology 53(3 Suppl):719-24

Diagnostik

Staging

Barcelona Stadien des HCC

Stage	Definition
Very early stage (0)	• Single ≤2 cm • Preserved liver function,[a] PS 0
Early stage (A)	• Single, or ≤3 nodules each ≤3 cm • Preserved liver function,[a] PS 0
Intermediate stage (B)	• Multinodular • Preserved liver function,[a] PS 0
Advanced stage (C)	• Portal invasion and/or extrahepatic spread • Preserved liver function, PS 1-2
Terminal stage (D)	• Any tumor burden • End stage liver function, PS 3-4

PS = Pugh-Score

Reig, J Hepatol 2022

CHILD-Pugh Score

Chemical and Biochemical Parameters	Scores (Points) for Increasing Abnormality		
	1	2	3
Encephalopathy (grade)[1]	None	1–2	3–4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time[2] Seconds over control INR	 <4 <1.7	 4–6 1.7–2.3	 >6 >2.3
Bilirubin (mg/dL) • For primary biliary cirrhosis	<2 <4	2–3 4–10	>3 >10

Class A = 5–6 points; Class B = 7–9 points; Class C = 10–15 points.

Class A: Good operative risk
Class B: Moderate operative risk
Class C: Poor operative risk

Pugh, Br J Surg 1973

5

Therapie

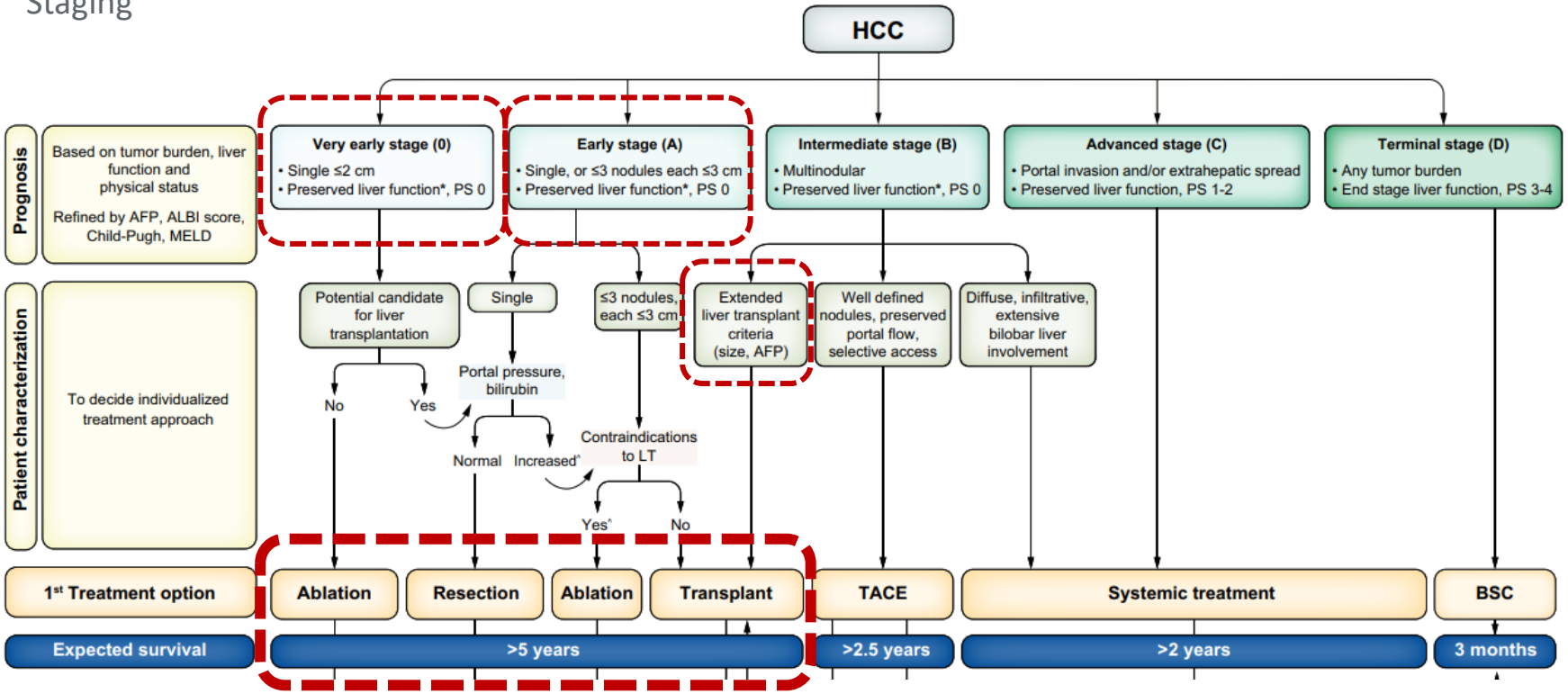
Therapie des HCC

Vorstellung im Tumorboard assoziiert zu einem Lebertransplantationszentrum!

https://www.ccc-muenchen.de/arzte/tumorboards/f7a057e895624192

Therapiealgorithmus

Staging



REIG et al Journal of Hepatology 2022 vol. 76 j 681–693

Therapie HCC

Ablation: Herde bis 3cm Durchmesser

Table 2. Cure proportions and years of life lost (YLLs) resulting from flexible parametric cure model.

Variables	Proportion cured (95% C.I.)	*p*	Median age (IQR)	Median YLL (IQR)	*p*
Age					
<60 years	19.0% (15.7, 22.7)	Ref.	52 (47, 56)	23.7 (21.1, 27.7)	Ref.
60–70 years	17.4% (13.9, 21.3)	0.470	65 (62, 68)	15.4 (13.1, 17.2)	0.001
71–80 years	17.2% (12.6, 22.5)	0.510	74 (72, 77)	9.4 (7.8, 10.6)	0.001
>80 years	23.4% (10.6, 39.3)	0.555	83 (81, 85)	4.4 (3.5, 4.9)	0.001
Gender					
Male	16.9% (14.2, 19.8)	Ref.	61 (53, 69)	17.4 (12.1, 22.7)	Ref.
Female	23.0% (18.2, 28.1)	0.014	65 (56, 73)	16.6 (11.3, 22.7)	0.144
Year of diagnosis					
2004–2008	14.7% (10.2, 20.2)	Ref.	62 (53, 69)	18.7 (13.6, 25.3)	Ref.
2009–2013	17.5% (14.3, 21.1)	0.346	61 (52, 69)	18.0 (12.5, 23.9)	0.206
2014–2018	20.5% (16.8, 24.4)	0.056	62 (54, 70)	16.1 (11.4, 21.7)	0.001
Hepatitis B					
Negative	20.1% (16.8, 23.6)	Ref.	67 (59, 73)	14.7 (10.2, 19.9)	Ref.
Positive	16.1% (13.0, 19.5)	0.043	57 (50, 65)	20.0 (15.0, 25.1)	0.001
Hepatitis C					
Negative	19.3% (16.4, 22.3)	Ref.	61 (52, 69)	17.2 (12.3, 23.5)	Ref.
Positive	14.4% (10.6, 18.8)	0.033	64 (57, 74)	16.6 (10.2, 22.4)	0.001
Alcohol					
Negative	18.6% (15.9, 21.6)	Ref.	61 (53, 70)	17.6 (12.0, 23.4)	Ref.
Positive	15.8% (10.9, 21.6)	0.323	65 (58, 69)	15.5 (12.1, 20.4)	0.002
ALBI grade					
1	23.8% (19.8, 28.0)	Ref.	60 (51, 69)	16.5 (11.7, 22.6)	Ref.
2	14.8% (12.0, 18.0)	0.001	63 (56, 71)	17.0 (12.2, 22.9)	0.573
3	12.0% (6.8, 18.9)	0.003	61 (53, 69)	20.0 (13.5, 25.4)	0.002
Ablation technique					
RFA	18.5% (15.8, 21.5)	Ref.	61 (53, 69)	17.6 (12.2, 23.4)	Ref.
MWA	16.7% (11.7, 22.3)	0.498	67 (59, 71)	15.7 (11.5, 20.2)	0.001
Largest tumour size					
<2 cm	26.9% (21.7, 32.3)	Ref.	62 (53, 70)	15.1 (10.6, 20.9)	Ref.
2–3 cm	19.2% (15.8, 23.0)	0.007	61 (54, 70)	17.4 (12.0, 22.5)	0.006
3.1–5 cm	12.7% (9.5, 16.4)	0.001	63 (55, 70)	17.5 (12.5, 23.8)	0.001
>5 cm	4.6% (1.9, 9.4)	0.001	56 (48, 67)	23.7 (16.2, 31.2)	0.001
Tumour number					
Single	20.8% (17.8, 24.0)	Ref.	62 (53, 70)	16.7 (11.8, 22.4)	Ref.
2 or 3 nodules	11.5% (8.1, 15.5)	0.001	62 (55, 70)	18.3 (12.2, 24.2)	0.037
4+ nodules	2.5% (0.7, 6.3)	0.001	63 (57, 69)	19.5 (14.6, 24.6)	0.012
Very-early stage					
Within	30.9% (24.9, 37.1)	Ref.	61 (53, 70)	14.5 (9.9, 20.4)	Ref.
Beyond	15.4% (12.8, 18.2)	0.001	62 (54, 70)	17.7 (12.3, 23.7)	0.001
Milan criteria					
Within	20.7% (17.7, 23.8)	Ref.	62 (54, 70)	16.5 (11.5, 22.2)	Ref.
Beyond	5.2% (3.0, 8.1)	0.001	60 (52, 68)	20.8 (14.5, 26.9)	0.001

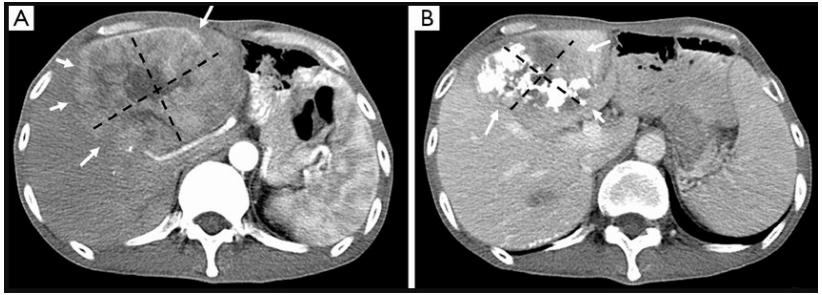
Variables affecting cure proportion entered into the multivariable flexible parametric model. Variables affecting YLLs were used through the generalised linear model to produce approximated YLLs values. Very-early stage and Milan criteria were not entered in the models because their components (size and number) were already retained.

Cucchetti British Journal of Cancer (2023) 128:1665 – 1671

Therapie HCC

TACE

- Prinzipiell palliative Therapieoption
- Bridging zur LTX
- kann mehrfach sequentiell durchgeführt werden
- Alternativ zur TACE kann bei Pat. mit erhaltener Leberfunktion im intermediären HCC-Stadium eine transarterielle Radioembolisation mit 90-Yttrium-Mikrosphären (TARE oder SIRT) → Nur Metaanalysen!



Cucchetti British Journal of Cancer (2023) 128:1665 – 1671

Therapie HCC

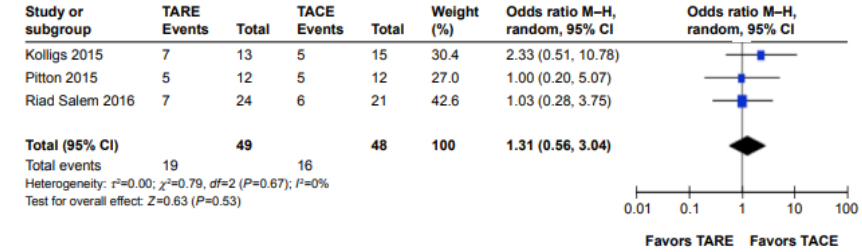
SIRT / TARE vs. TACE

Table 1 Patient characteristics in the three randomized clinical trials

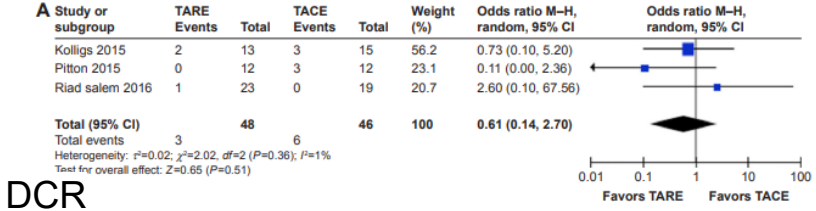
Trial		SIRTACE[6]		Mainz[7]		PREMIERE[8]	
Group		**TARE n=13**	**TACE n=15**	**TARE n=12**	**TACE n=12**	**TARE n=24**	**TACE n=21**
Age, years		65.8	66.7	71.8	70.5	62	64
Males, %		84.6	86.7	83.4	75	71	76
ECOG, n (%)	0 1	10 (76.9) 3 (23.1)	12 (80.0) 3 (20.0)	12 (100) 0 (0)	12 (100) 0 (0)	24 (100) 0 (0)	21 (100) 0 (0)
Child–Pugh class, n (%)	A B	12 (92.3) 1 (7.7)	13 (86.6) 2 (13.4)	10 (83.3) 2 (16.7)	9 (75) 3 (25)	18 (75) 6 (25)	17 (81) 4 (19)
BCLC stage, n (%)	A B C	5 (38.4) 5 (38.4) 3 (23.0)	4 (26.6) 8 (53.3) 3 (20.0)	13 (86.6) 2 (13.4) 0 (0)	10 (83.3) 2 (16.7) 0 (0)	18 (75) 6 (25) 0 (0)	17 (81) 4 (19) 0 (0)
Bilobar disease		ND	ND	8 (67)	7 (58)	7 (29)	7 (33)
Tumor size, mm		ND	ND	61.3 (36.4)[a]	60.8 (37.6)[a]	32 (27–37)	30 (23–36)
Tumor volume, mL		137.7 (237.6)[a]	235.6 (349.4)[a]	ND	ND	ND	ND
Total bilirubin (mg/dL)		1.00 (0.60)[a]	1.08 (0.45)[a]	1.17 (0.38–2.10)	1.26 (0.59–2.04)	1.3 (1.2–1.7)	0.9 (0.8–1.5)
Albumin (g/L)		36.3 (3.9)[a]	42.0 (8.0)[a]	34.1 (28–43)	31.9 (24–39)	31 (27–33)	32 (29–34)
AFP (ng/mL)		636.0 (2,171.8)[a]	2,624.7 (9,525.3)[a]	14.0 (6.2–32,346)	7.8 (2.7–1,847)	<200: 88% >200: 10%	<200: 90% >200: 12%

Notes: [a]Mean (SD). Values are expressed as median (IQR) unless otherwise indicated. Data from Salem R et al; Pitton MB; Kolligs FT.[6–8]
Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; ND, not determined; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

1-Jahres-Überleben



DFS



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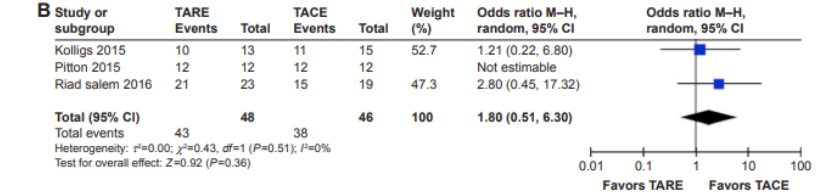
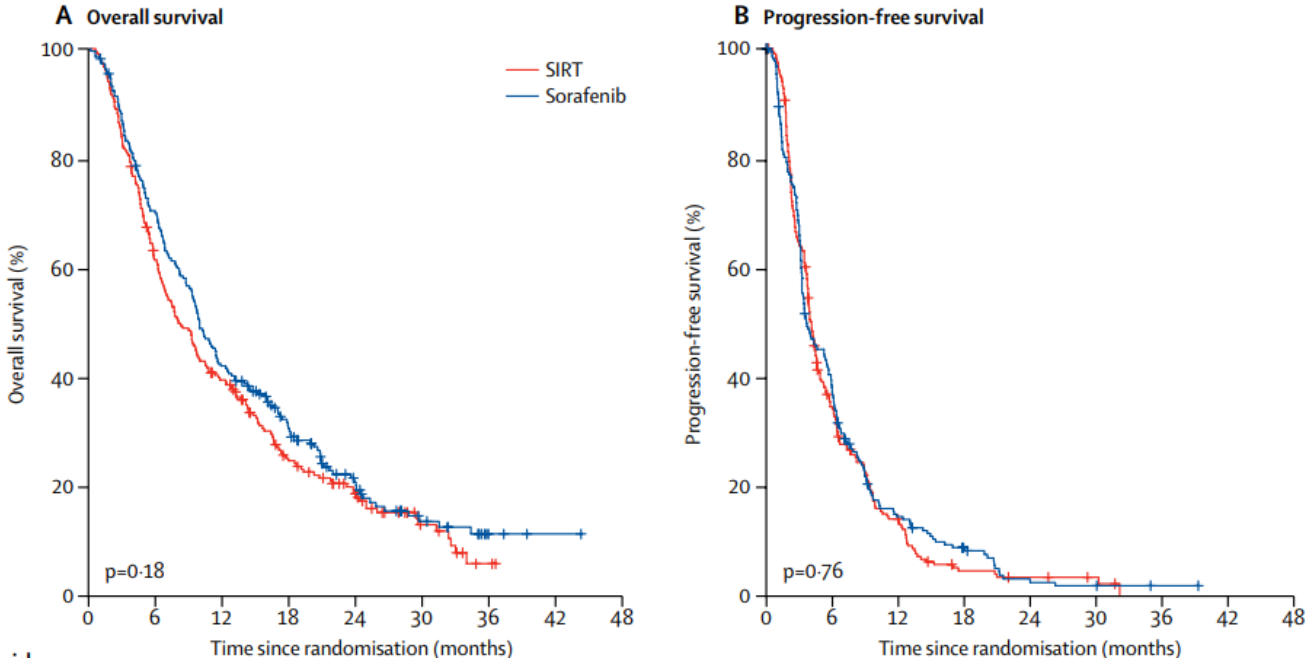


Cucchetti British Journal of Cancer (2023) 128:1665 – 1671

Therapie HCC

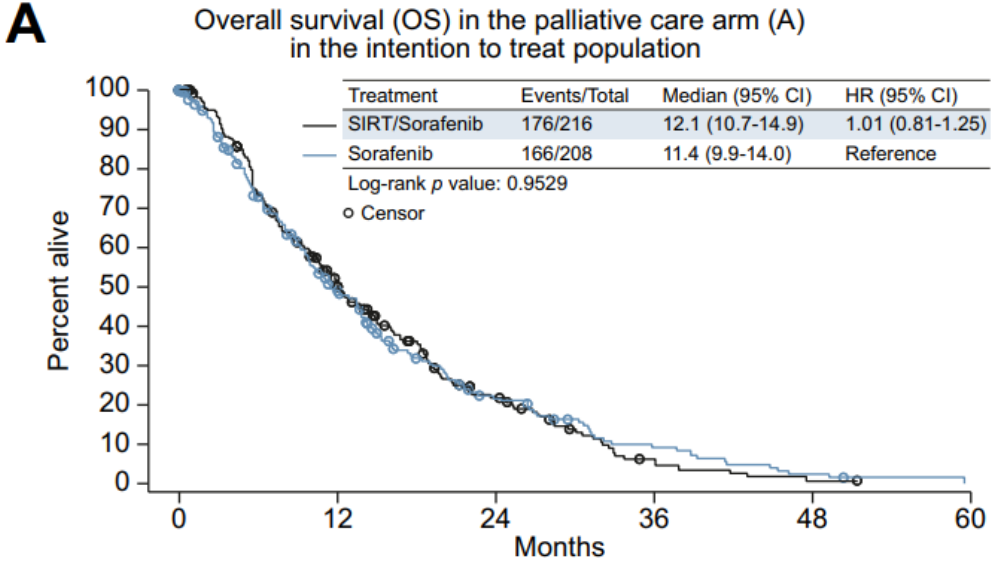
SIRT in der palliativen Situation Phase-3 SARAH Studie



Vilgrain et al Lancet Oncol 2017; 18: 1624–36

Therapie HCC

SIRT in der palliativen Situation Phase-3 SORAMIC Studie

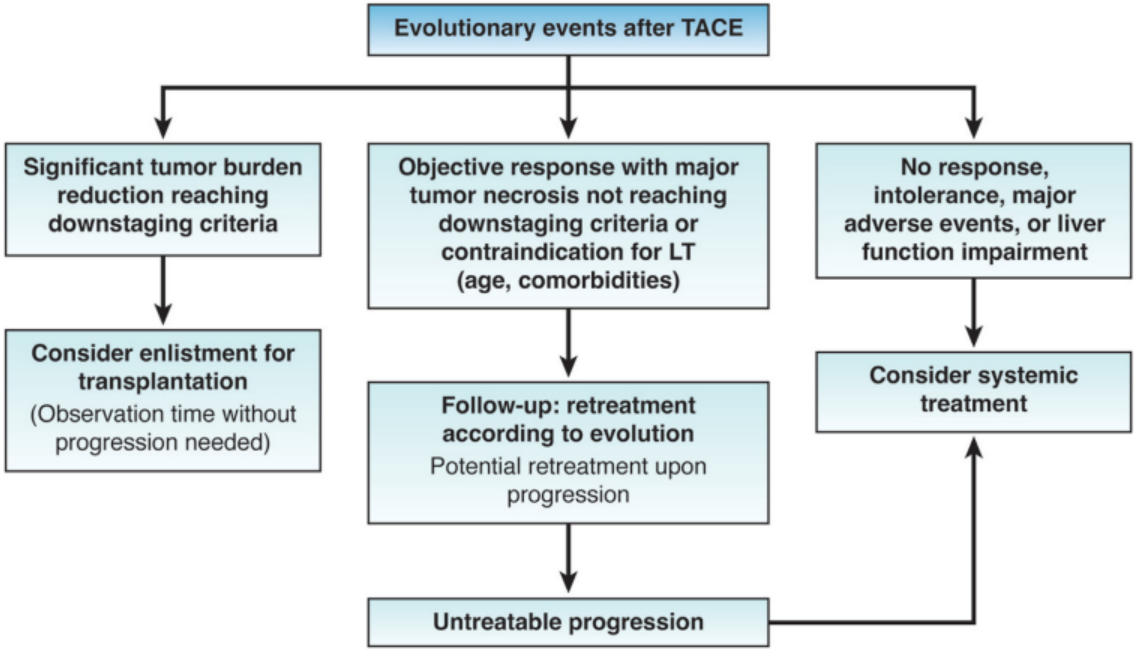


Patients-at-risk						
SIRT /Sorafenib	216	99	33	7	1	0
Sorafenib	208	86	30	11	3	0

Vilgrain et al Lancet Oncol 2017; 18: 1624–36

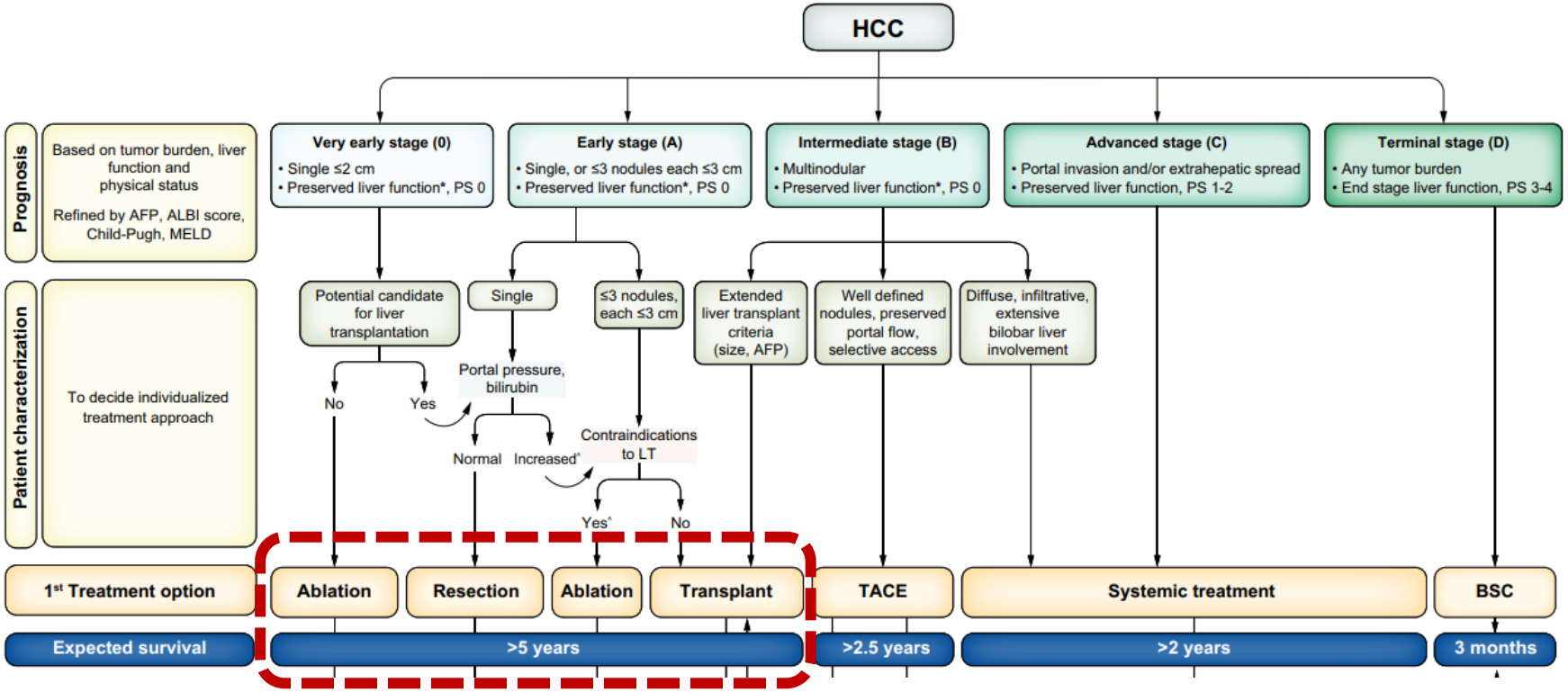
Was tun nach TACE?

Lokales HCC



Singal et al Clinical Gastroenterology and Hepatology 2023;21:2135–2149

Therapiealgorithmus



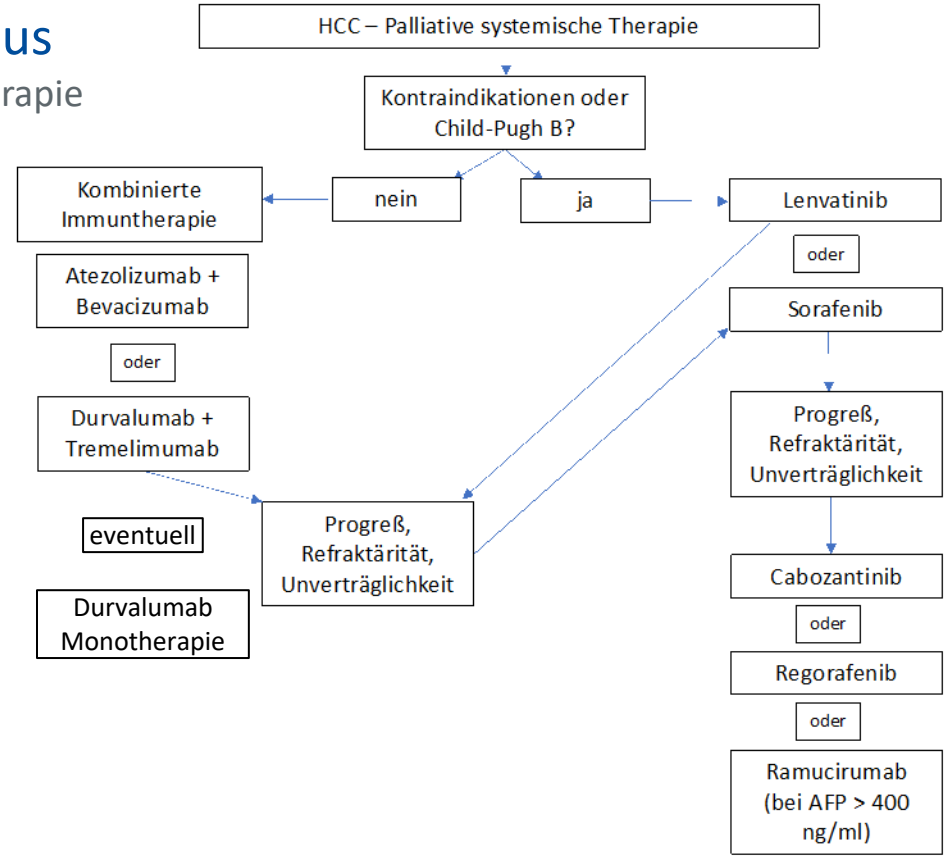
REIG et al Journal of Hepatology 2022 vol. 76 j 681–693

5a

Erstlinienlinientherapie

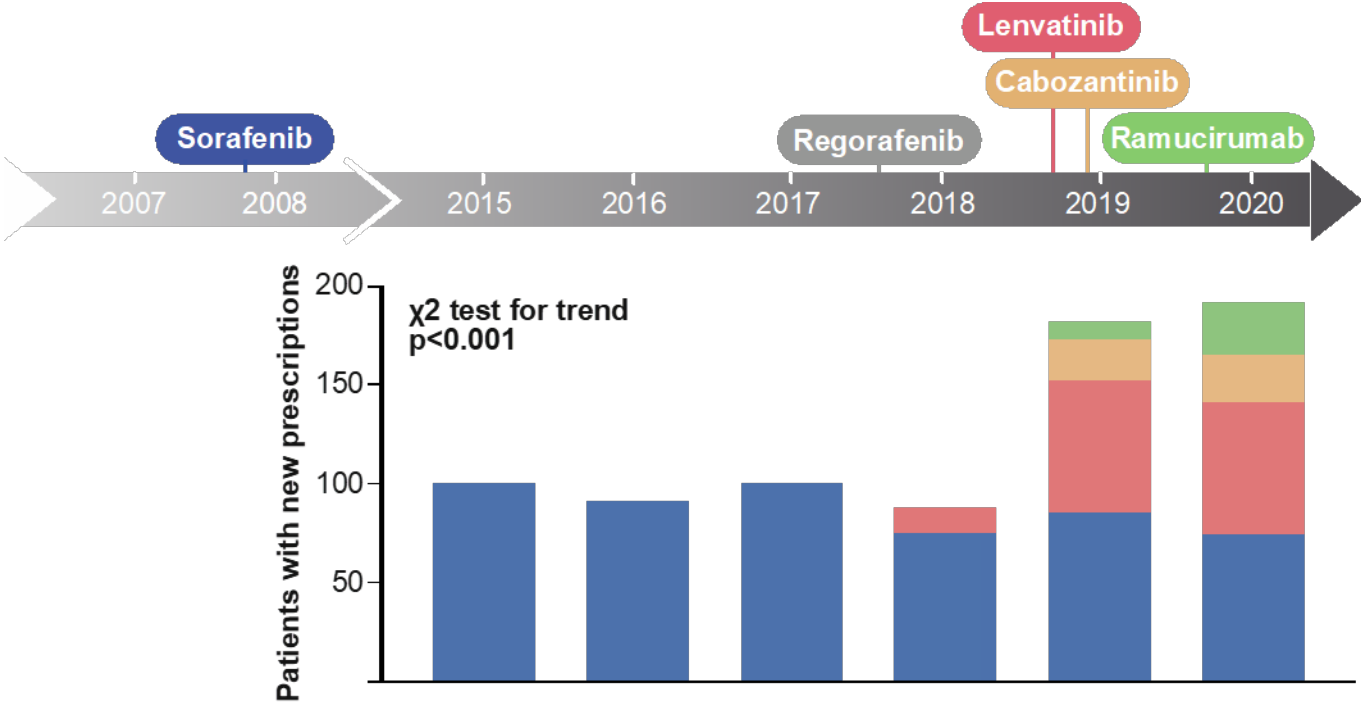
Therapiealgorithmus

Palliative systemische Therapie



Therapiealgorithmus

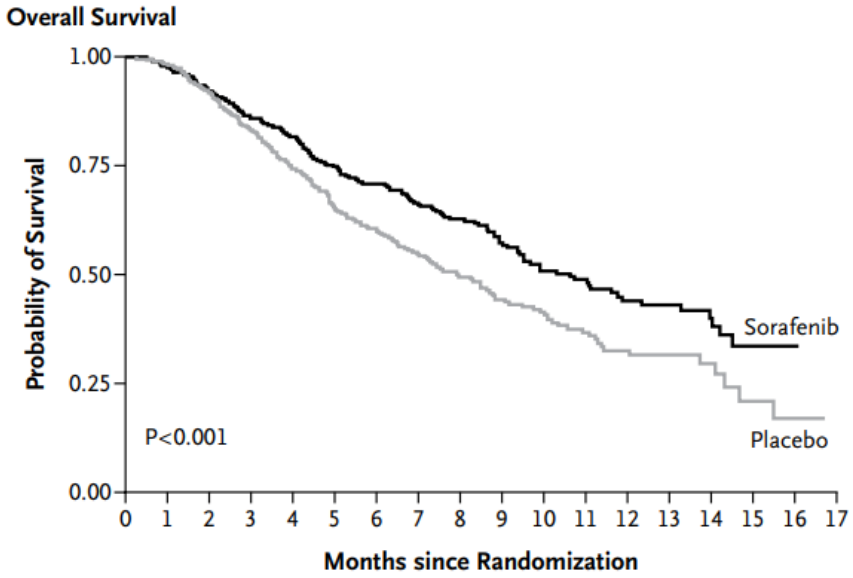
Palliative systemische Therapie



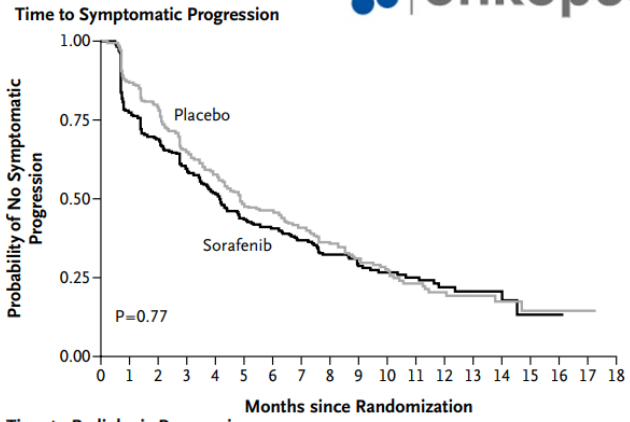
Ben Khaled et al., GASL 2023

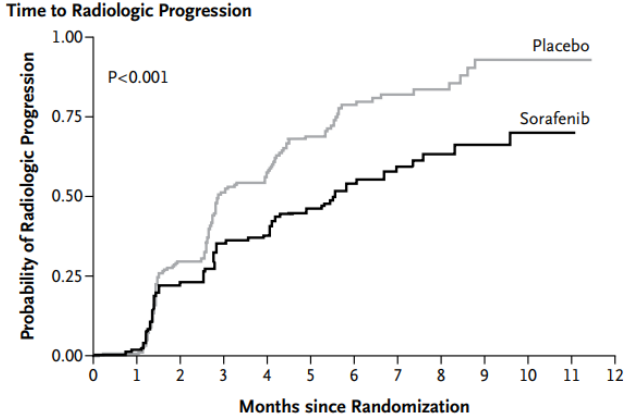
Palliative systemische Therapie - Erstlinie

Sorafenib SHARP Studie



medianes OS: 10,7mo vs. 7.9mo





Llovet et al N Engl J Med 2008;359:378-90.

Palliative systemische Therapie - Erstlinie

Andere TKI´s: Studien 2007-2017

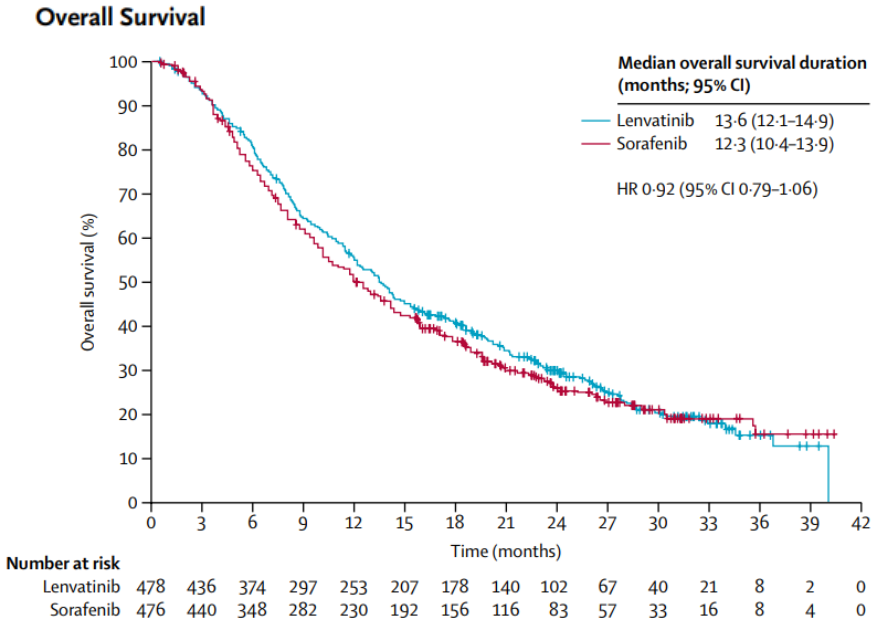
Table 1. Phase III trials in advanced hepatocellular carcinoma conducted in the last decade.

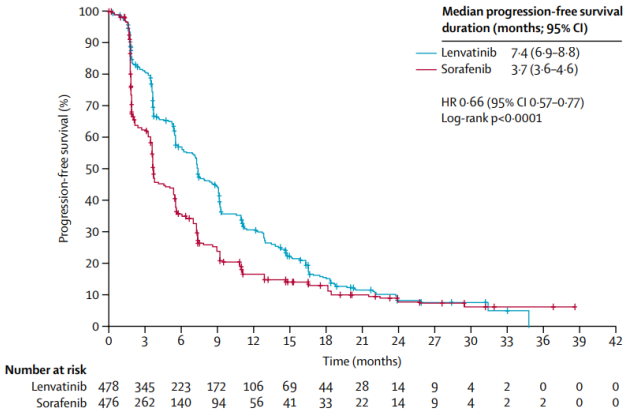
	Trial	Arms	N	ORR	TTP		PFS		OS	
					Median	HR	Median	HR	Median	HR
First-line	SHARP[7]	Sorafenib	299	2.3	5.5	***0.58 (0.45–0.74)***		NR	10.7	***0.69 (0.55–0.87)***
		Placebo	303	0.7	2.8				7.9	
	Asian-Pacific[8]	Sorafenib	150	3.3	2.8	***0.57 (0.42–0.79)***		NR	6.5	***0.68 (0.50–0.93)***
		Placebo	76	1.3	1.4				4.2	
	SUN1170[9]	Sunitinib	530	6.6	4.1	1.13 (0.98–1.31)	3.6	1.13 (0.99–1.30)	7.9	1.30 (1.13–1.50)
		Sorafenib	544	6.1	3.8		3		10.2	
	BRISK-FL*[10]	Brivanib	577	12.0	4.2	1.01 (0.88–1.16)		NR	9.5	1.07 (0.94–1.23)
		Sorafenib	578	8.8	4.1				9.9	
	LIGHT[11]	Linifanib	514	10.1	5.4	***0.76 (0.64–0.90)***	4.2	***0.81 (0.70–0.95)***	9.1	1.05 (0.90–1.22)
		Sorafenib	521	6.1	4		2.9		9.8	
	SEARCH[12]	Sorafenib + erlotinib	362	6.6	3.2	1.14 (0.94–1.37)	NR	1.11 (0.94–1.31)	9.5	0.93 (0.78–1.11)
		Sorafenib	476	9.2	3.7		3.7		12.3	
	SARAH[14]	Y90	237	15.2		NR	4.1	1.03 (0.85–1.25)	8	1.15 (0.94–1.41)
		Sorafenib	222	10.4			3.7		9.9	
	SIRveNIB[15]	Y90	182	16.5	6.1	0.88 (0.7–1.1)	5.8	0.89 (0.70–1.10)	8.8	1.10 (0.90–1.40)
		Sorafenib	178	1.7	5.4		5.1		10	
	EACH[16]	Folfox4	184	8.2		NR	2.93	***0.62 (0.49–0.79)***	6.4	0.80 (0.63–1.02)
		Doxorubicin	187	2.7			1.77		4.97	
	CALGB80802[17]	Sorafenib + doxorubicin	173	NR		NR	3.6	0.90 (0.72–1.20)	9.3	1.06 (0.80–1.40)
		Sorafenib	173	NR			3.2		10.5	
	SILIUS*[18]	Sorafenib + HAIC	103	36.3	5.3	***0.65 (0.48–0.87)***	4.8	0.75 (0.57–1.00)	11.8	1.01 (0.74–1.37)
		Sorafenib	103	17.5	3.5		3.5		11.5	

Journal of Hepatol. 2019 vol. 70: 1262-1277

Palliative systemische Therapie - Erstlinie

Levantinib – REFLECT Studie



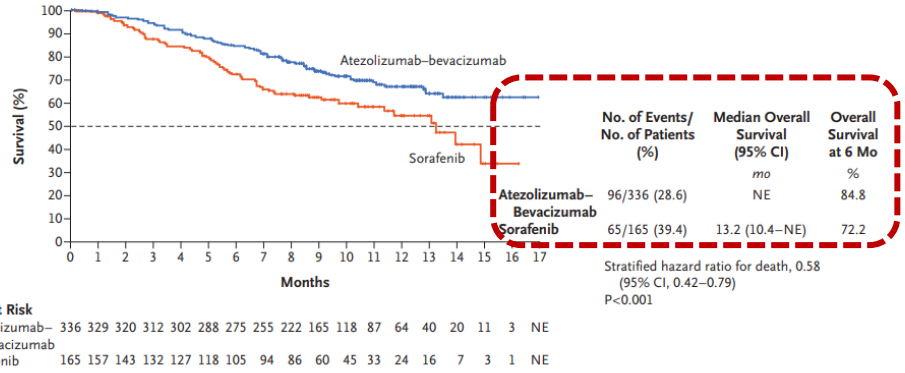


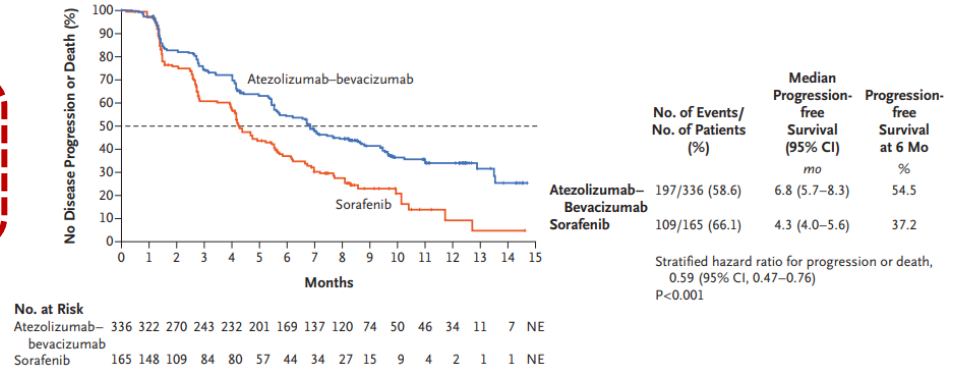
	Lenvatinib (n=478)	Sorafenib (n=476)	Effect size (95% CI)	p value
Investigator review according to mRECIST				
Overall survival (months)	13·6 (12·1–14·9)	12·3 (10·4–13·9)	HR 0·92 (0·79–1·06)	..
Progression-free survival (months)	7·4 (6·9–8·8)	3·7 (3·6–4·6)	HR 0·66 (0·57–0·77)	<0·0001
Time to progression (months)	8·9 (7·4–9·2)	3·7 (3·6–5·4)	HR 0·63 (0·53–0·73)	<0·0001
Objective response (%, 95% CI)	115 (24·1%, 20·2–27·9)	44 (9·2%, 6·6–11·8)	OR 3·13 (2·15–4·56)	<0·0001
Complete response	6 (1%)	2 (<1%)	..	..
Partial response	109 (23%)	42 (9%)	..	..
Stable disease	246 (51%)	244 (51%)	..	..
Durable stable disease lasting ≥23 weeks	167 (35%)	139 (29%)	..	..
Progressive disease	71 (15%)	147 (31%)	..	..
Unknown or not evaluable	46 (10%)	41 (9%)	..	..
Disease control rate (%, 95% CI)	361 (75·5%, 71·7–79·4)	288 (60·5%, 56·1–64·9)	..	..

Kudo et al Lancet 2018; 391: 1163–73

Palliative systemische Therapie - Erstlinie

Atezolizumab + Bevacizumab - IMbrave150

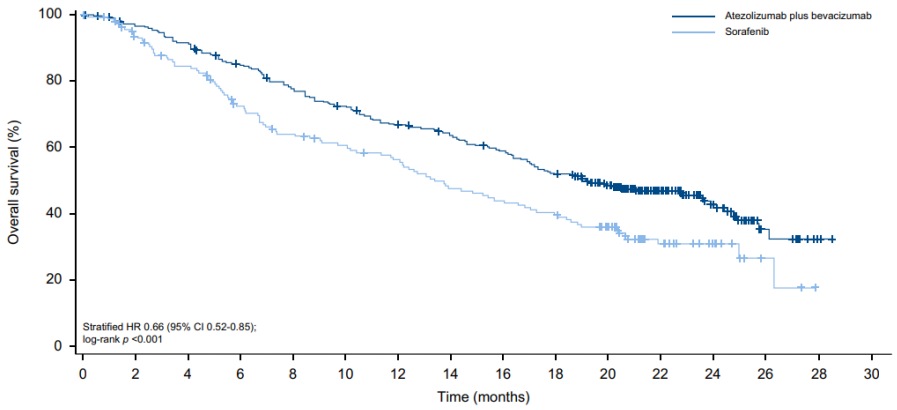




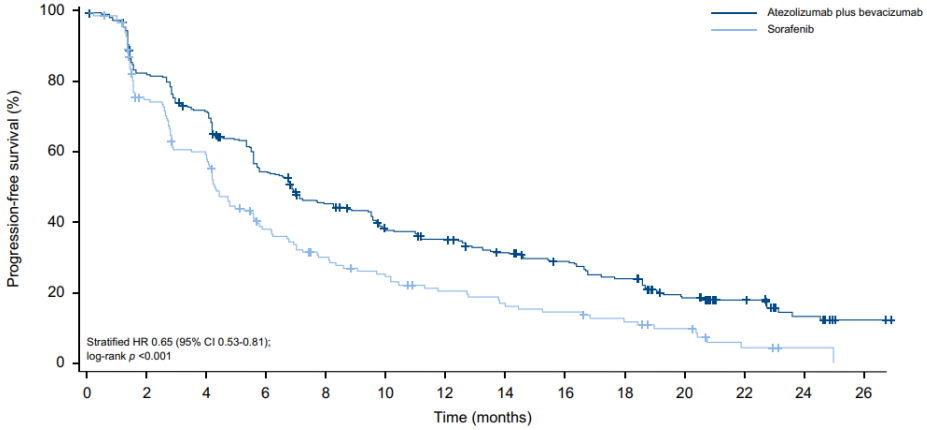
Finn et al N Engl J Med 2020;382:1894-905.

Palliative systemische Therapie - Erstlinie

Atezolizumab + Bevacizumab - IMbrave150



medianes OS: 19,2mo vs. 13,4mo

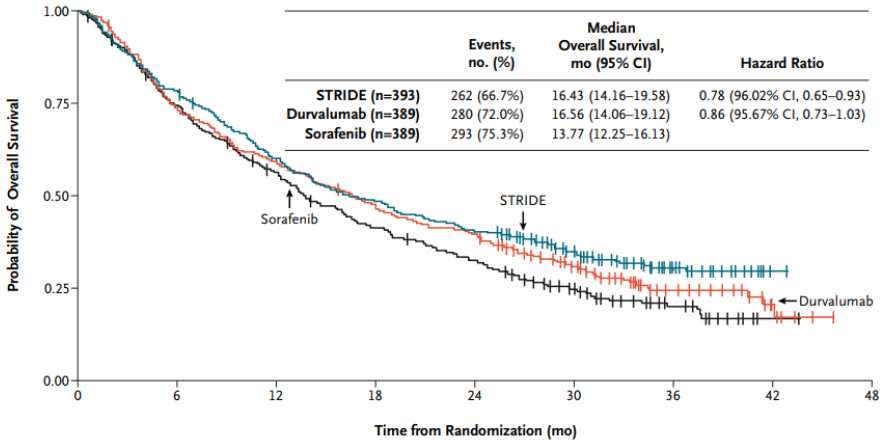


medianes PFS: 6,9mo vs. 4,3mo

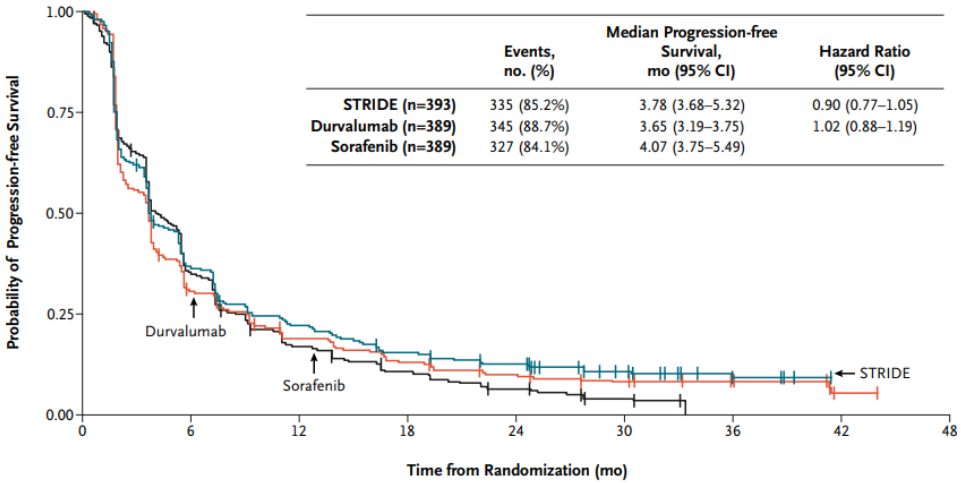
Cheng et al J Hepatol 2022 Apr;76(4):862-873.

Palliative systemische Therapie - Erstlinie

Durvalumab + Tremelimumab – HIMALAYA Studie



	Events, no. (%)	Median Overall Survival, mo (95% CI)	Hazard Ratio
STRIDE (n=393)	262 (66.7%)	16.43 (14.16–19.58)	0.78 (96.02% CI, 0.65–0.93)
Durvalumab (n=389)	280 (72.0%)	16.56 (14.06–19.12)	0.86 (95.67% CI, 0.73–1.03)
Sorafenib (n=389)	293 (75.3%)	13.77 (12.25–16.13)	

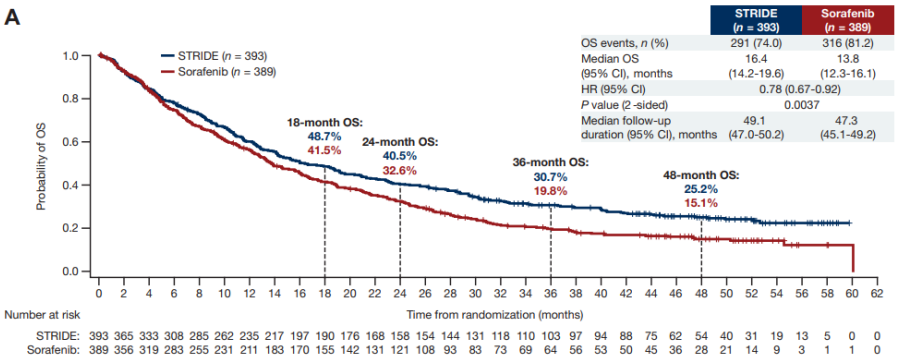


	Events, no. (%)	Median Progression-free Survival, mo (95% CI)	Hazard Ratio (95% CI)
STRIDE (n=393)	335 (85.2%)	3.78 (3.68–5.32)	0.90 (0.77–1.05)
Durvalumab (n=389)	345 (88.7%)	3.65 (3.19–3.75)	1.02 (0.88–1.19)
Sorafenib (n=389)	327 (84.1%)	4.07 (3.75–5.49)	

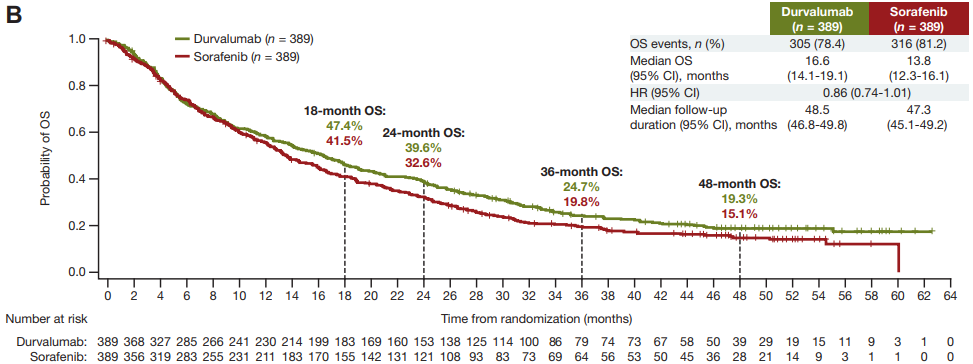
Abou-Alfa et al NEJM Evid 2022; 1 (8)

Palliative systemische Therapie - Erstlinie

Durvalumab + Tremelimumab – HIMALAYA Studie



	STRIDE (n = 393)	Sorafenib (n = 389)
OS events, n (%)	291 (74.0)	316 (81.2)
Median OS (95% CI), months	16.4 (14.2-19.6)	13.8 (12.3-16.1)
HR (95% CI)	0.78 (0.67-0.92)	
P value (2-sided)	0.0037	
Median follow-up duration (95% CI), months	49.1 (47.0-50.2)	47.3 (45.1-49.2)



	Durvalumab (n = 389)	Sorafenib (n = 389)
OS events, n (%)	305 (78.4)	316 (81.2)
Median OS (95% CI), months	16.6 (14.1-19.1)	13.8 (12.3-16.1)
HR (95% CI)	0.86 (0.74-1.01)	
Median follow-up duration (95% CI), months	48.5 (46.8-49.8)	47.3 (45.1-49.2)

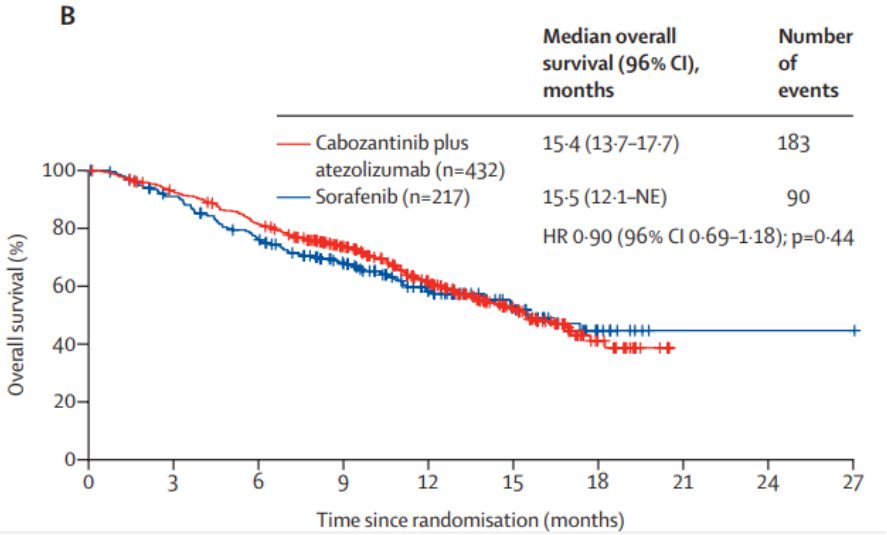
medianes OS: 16,4mo vs. 13.8mo

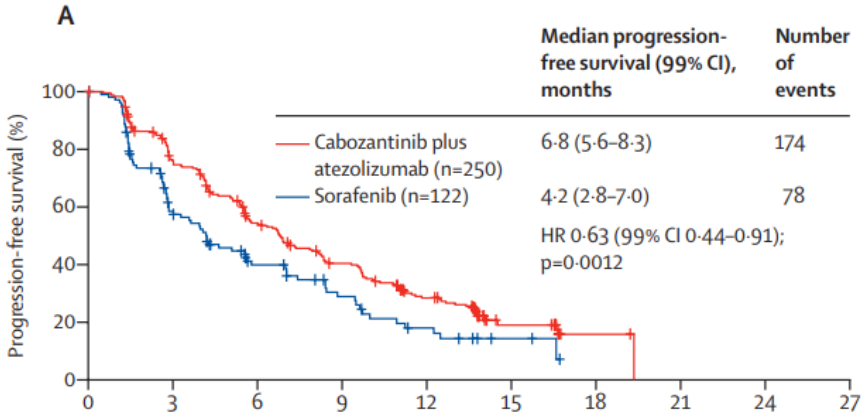
medianes PFS: 16,6mo vs. 13,8mo

Sandro B et al Ann Oncol. 2024

Palliative systemische Therapie - Erstlinie

Cabozantinib + Atezolizumab – COSMIC-312 Studie



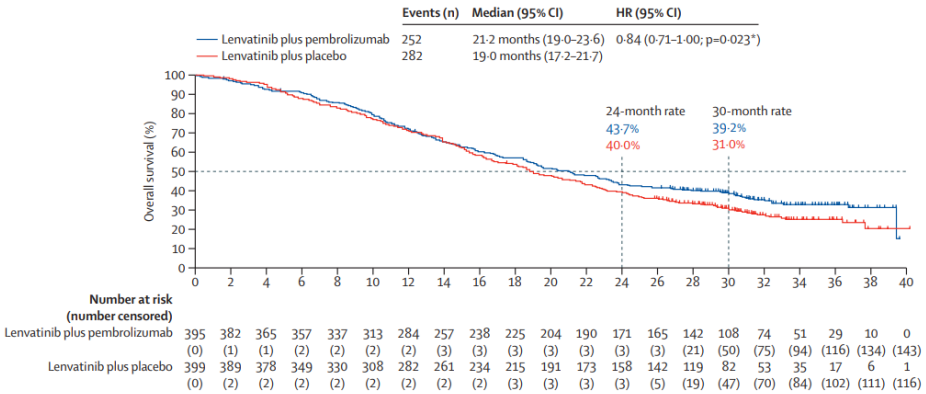


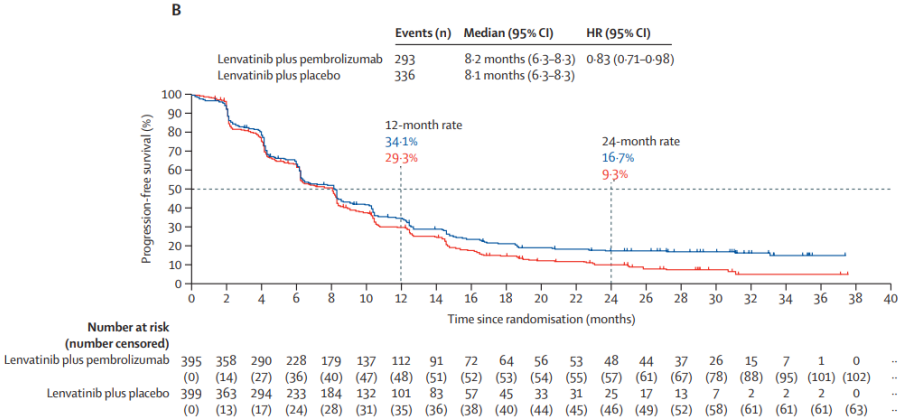
➔ Negative Studie!

Rimassa et al Lancet Oncol. 2022 Aug;23(8):995-1008

Palliative systemische Therapie - Erstlinie

Levantinib + Pembrolizumab– LEAP-002 Studie





➔ Negative Studie!

Llovet et al Lancet Oncol 2023; 24: 1399–410

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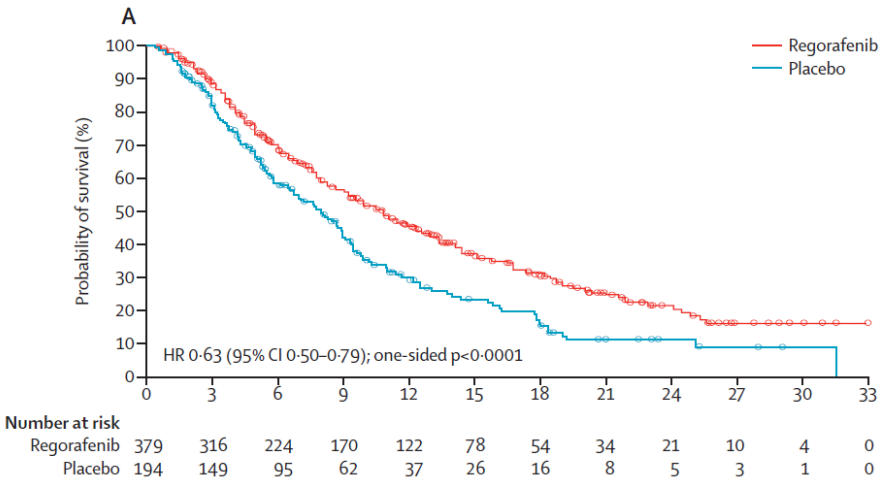
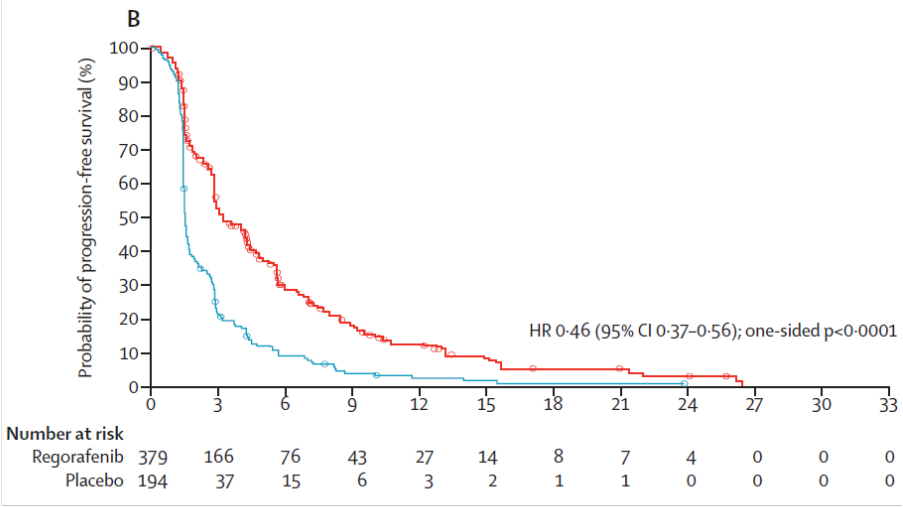
Zweitlinientherapie

Palliative systemische Therapie – Zweitlinie

Regorafenib

➔ Zugelassen nach Sorafenib





medianes OS: 10,6mo vs. 7,8mo

medianes PFS: 3.1mo vs. 1.5mo

Bruix J et al. Lancet 2017 Jan 7;389(10064):56-66.

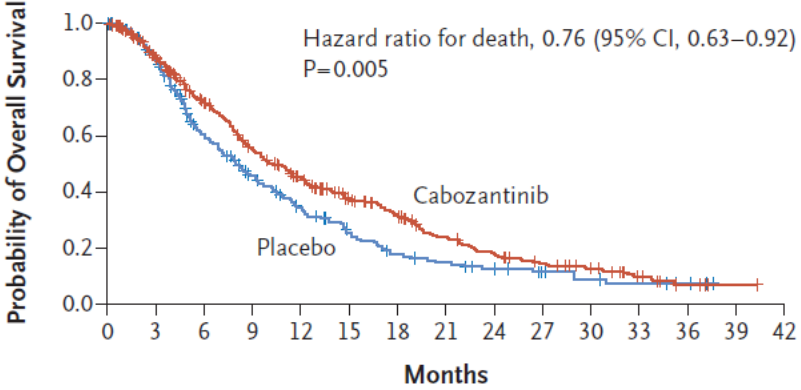
Palliative systemische Therapie – Zweitlinie

Cabozantinib

➔ Zugelassen nach Sorafenib

A Overall Survival

	No. of Patients	Median Overall Survival *mo (95% CI)*	No. of Events
Cabozantinib	470	10.2 (9.1–12.0)	317
Placebo	237	8.0 (6.8–9.4)	167

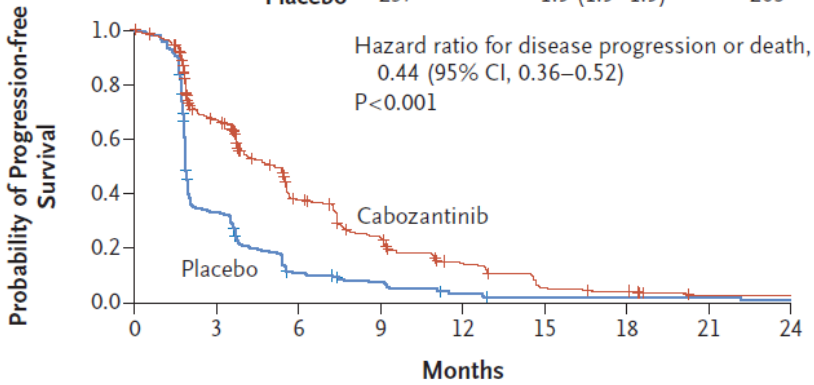


No. at Risk

Cabozantinib	470	328	281	206	159	116	93	63	44	31	22	12	4	1	0
Placebo	237	190	117	82	57	37	25	20	15	10	7	5	3	0	0

B Progression-free Survival

	No. of Patients	Median Progression-free Survival *mo (95% CI)*	No. of Events
Cabozantinib	470	5.2 (4.0–5.5)	349
Placebo	237	1.9 (1.9–1.9)	205



No. at Risk

Cabozantinib	470	266	131	80	39	15	10	3	3
Placebo	237	70	21	13	5	2	2	2	1

Abou-Alfa et al N Engl J Med 2018;379:54-63.

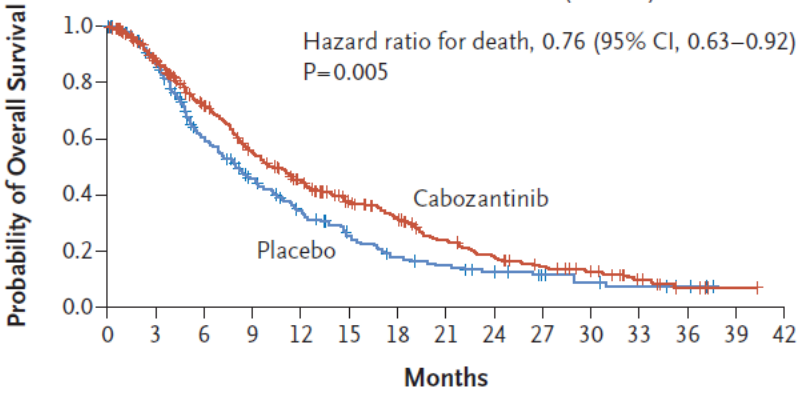
Palliative systemische Therapie – Zweitlinie

Ramucirumab

➔ Zugelassen nach Sorafenib

A Overall Survival

	No. of Patients	Median Overall Survival *mo (95% CI)*	No. of Events
Cabozantinib	470	10.2 (9.1–12.0)	317
Placebo	237	8.0 (6.8–9.4)	167

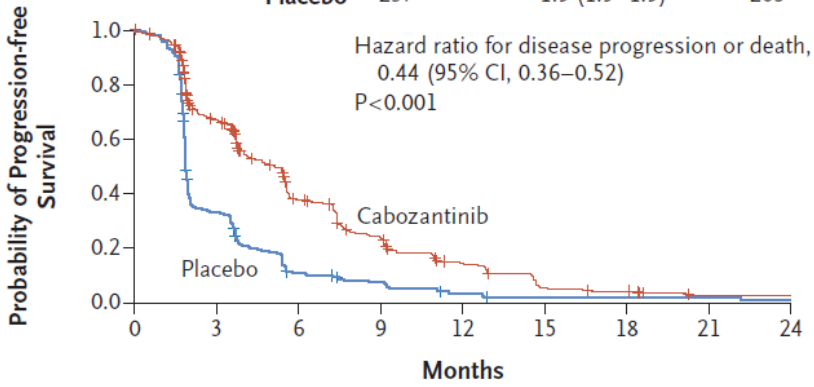


No. at Risk

Cabozantinib	470	328	281	206	159	116	93	63	44	31	22	12	4	1	0
Placebo	237	190	117	82	57	37	25	20	15	10	7	5	3	0	0

B Progression-free Survival

	No. of Patients	Median Progression-free Survival *mo (95% CI)*	No. of Events
Cabozantinib	470	5.2 (4.0–5.5)	349
Placebo	237	1.9 (1.9–1.9)	205



No. at Risk

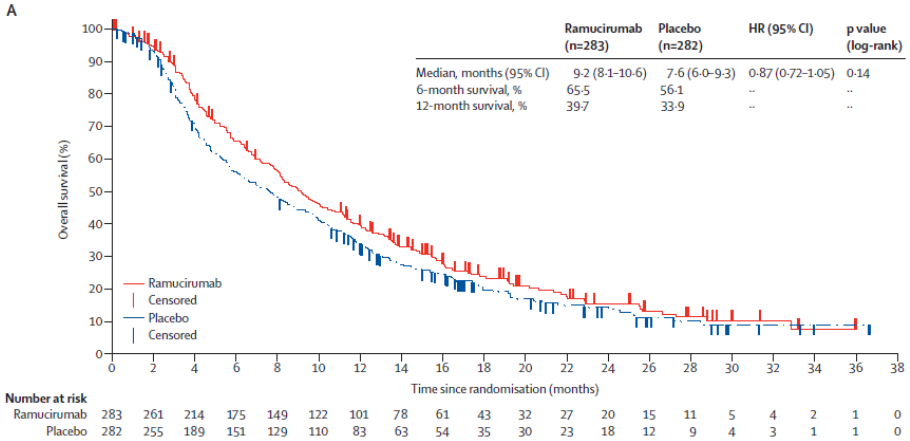
Cabozantinib	470	266	131	80	39	15	10	3	3
Placebo	237	70	21	13	5	2	2	2	1

Abou-Alfa et al N Engl J Med 2018;379:54-63.

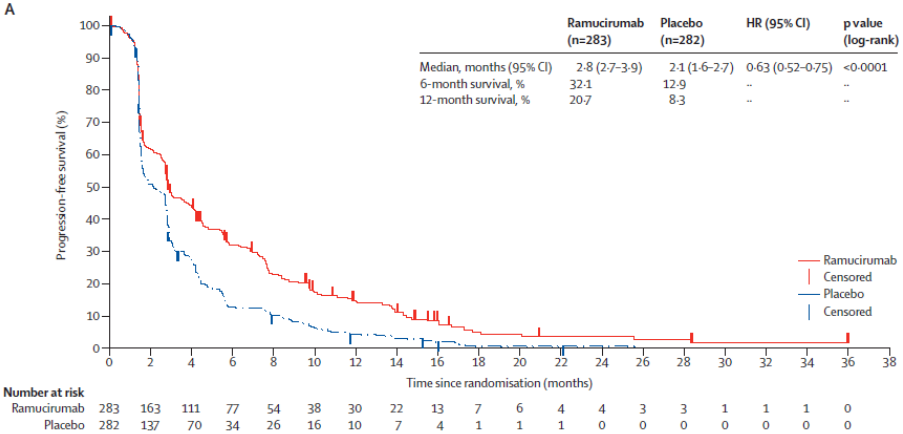
Palliative systemische Therapie – Zweitlinie

Ramucirumab REACH

➔ Zugelassen nach Sorafenib



	Ramucirumab (n=283)	Placebo (n=282)	HR (95% CI)	p value (log-rank)
Median, months (95% CI)	9·2 (8·1–10·6)	7·6 (6·0–9·3)	0·87 (0·72–1·05)	0·14
6-month survival, %	65·5	56·1	..	..
12-month survival, %	39·7	33·9	..	..

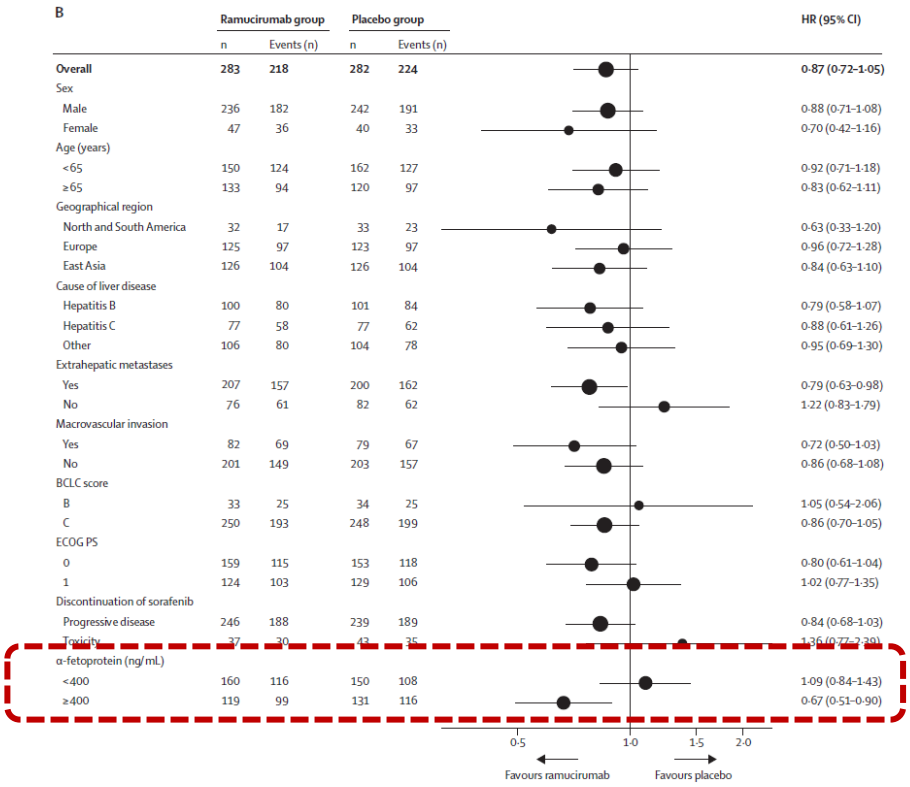


	Ramucirumab (n=283)	Placebo (n=282)	HR (95% CI)	p value (log-rank)
Median, months (95% CI)	2·8 (2·7–3·9)	2·1 (1·6–2·7)	0·63 (0·52–0·75)	<0·0001
6-month survival, %	32·1	12·9	..	..
12-month survival, %	20·7	8·3	..	..

Zhou et al Lancet Oncol 2015

Palliative systemische Therapie – Zweitlinie

Ramucirumab REACH



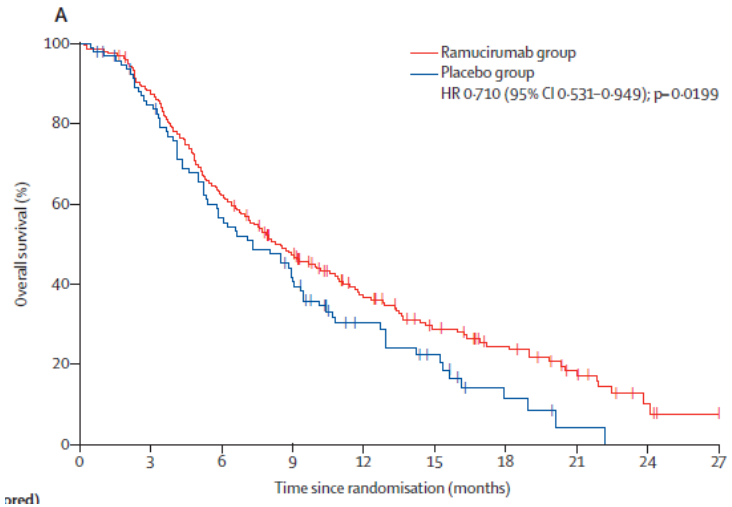
B	Ramucirumab group n	Ramucirumab group Events (n)	Placebo group n	Placebo group Events (n)	HR (95% CI)
Overall	**283**	**218**	**282**	**224**	**0·87 (0·72–1·05)**
Sex					
Male	236	182	242	191	0·88 (0·71–1·08)
Female	47	36	40	33	0·70 (0·42–1·16)
Age (years)					
<65	150	124	162	127	0·92 (0·71–1·18)
≥65	133	94	120	97	0·83 (0·62–1·11)
Geographical region					
North and South America	32	17	33	23	0·63 (0·33–1·20)
Europe	125	97	123	97	0·96 (0·72–1·28)
East Asia	126	104	126	104	0·84 (0·63–1·10)
Cause of liver disease					
Hepatitis B	100	80	101	84	0·79 (0·58–1·07)
Hepatitis C	77	58	77	62	0·88 (0·61–1·26)
Other	106	80	104	78	0·95 (0·69–1·30)
Extrahepatic metastases					
Yes	207	157	200	162	0·79 (0·63–0·98)
No	76	61	82	62	1·22 (0·83–1·79)
Macrovascular invasion					
Yes	82	69	79	67	0·72 (0·50–1·03)
No	201	149	203	157	0·86 (0·68–1·08)
BCLC score					
B	33	25	34	25	1·05 (0·54–2·06)
C	250	193	248	199	0·86 (0·70–1·05)
ECOG PS					
0	159	115	153	118	0·80 (0·61–1·04)
1	124	103	129	106	1·02 (0·77–1·35)
Discontinuation of sorafenib					
Progressive disease	246	188	239	189	0·84 (0·68–1·03)
Toxicity	37	30	43	35	1·36 (0·77–2·39)
α-fetoprotein (ng/mL)					
<400	160	116	150	108	1·09 (0·84–1·43)
≥400	119	99	131	116	0·67 (0·51–0·90)

Zhou et al Lancet Oncol 2015

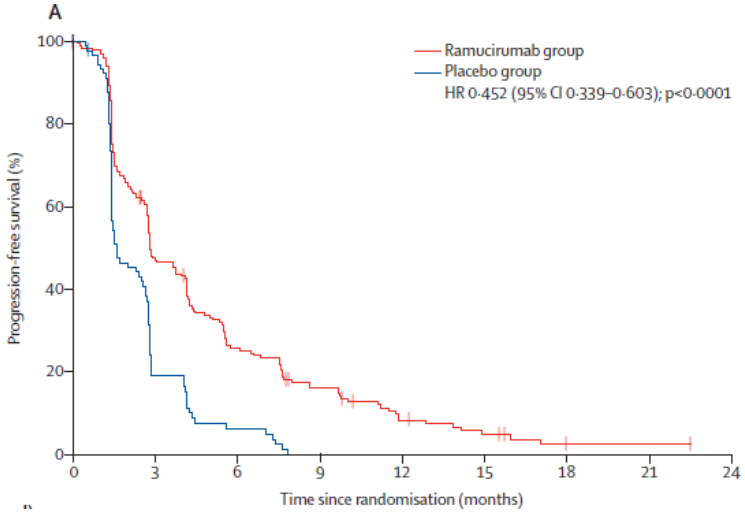
Palliative systemische Therapie – Zweitlinie

Ramucirumab REACH-2: AFP ≤400ng/mL

➔ Zugelassen nach Sorafenib



medianes OS: 8.5mo vs. 7.3mo

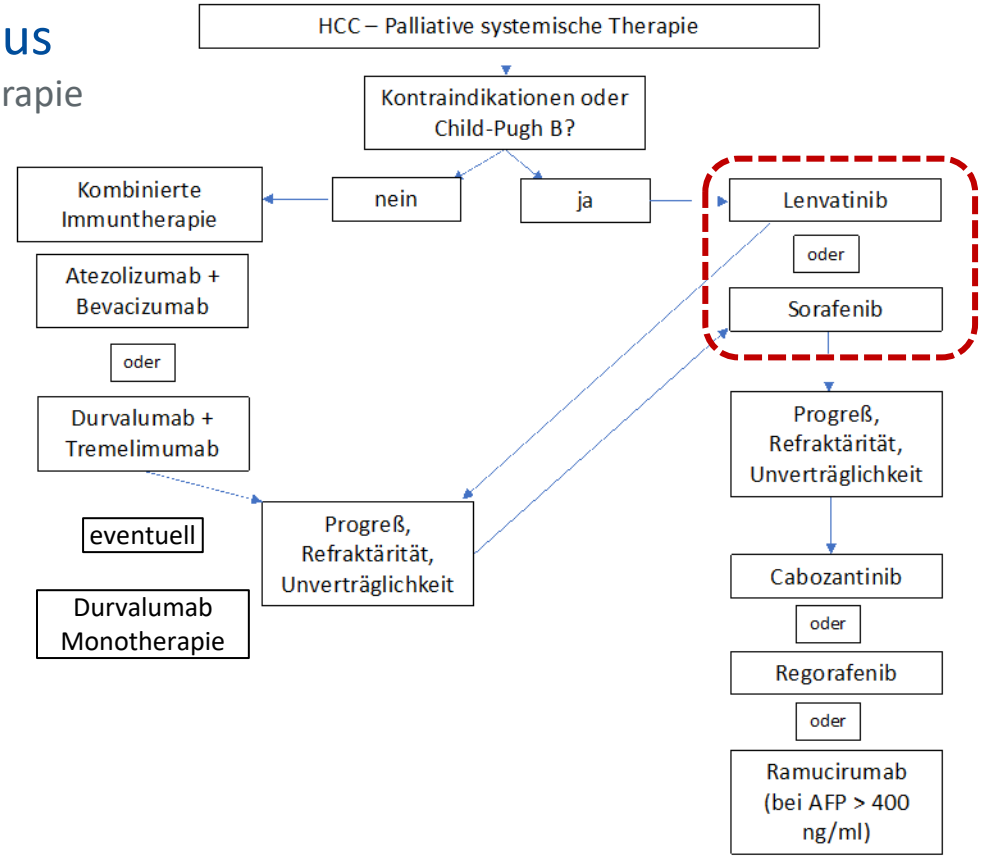


medianes PFS: 2.8mo vs. 1.6mo

Zhou et al Lancet Oncol 2019

Therapiealgorithmus

Palliative systemische Therapie



Therapiealgorithmus

Levantinib oder Sorafenib?

Lenvatinib a better option if:

- PS ECOG 0-1
- < 50% liver occupation.
- no bile duct/main portal vein invasion.
- HBV chronic infection
- AFP > 200 ng/mL
- Child Pug A
- < 45 y/o
- lower costs
- (downstaging)

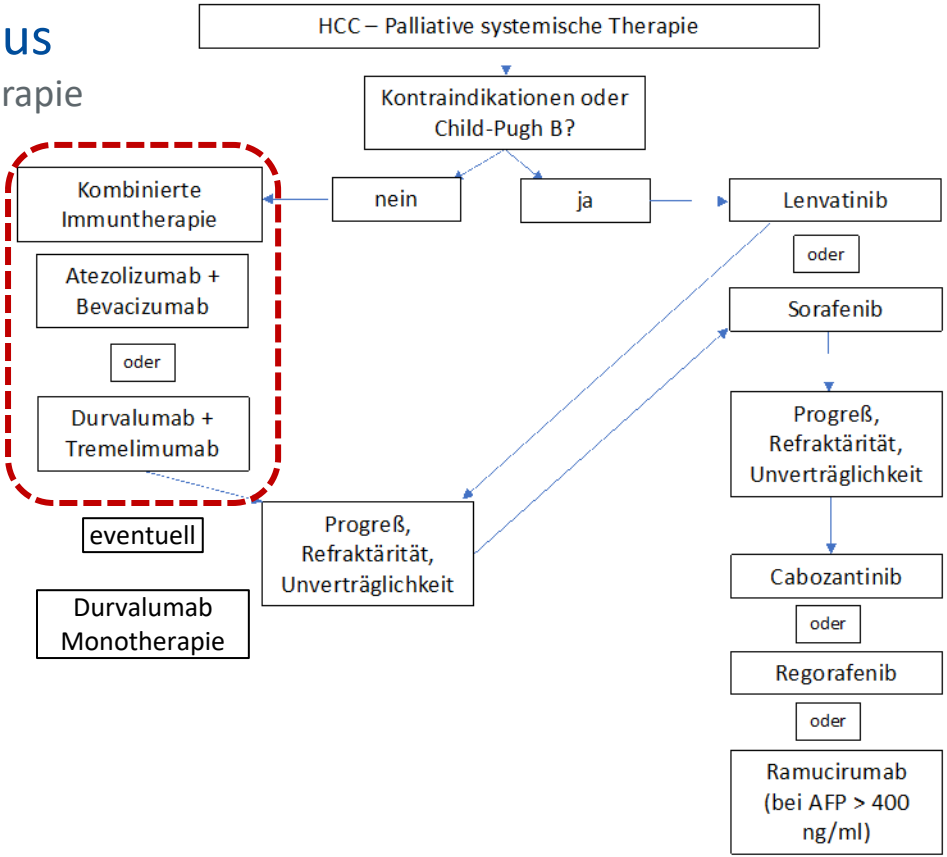
Sorafenib a better option if:

- PS ECOG
- > 50% liver occupation.
- bile duct/main portal vein invasion
- HCV chronic infection.
- AFP < 200 ng/mL
- Child Pug B(7)
- ≥ 75 y/o
- higher costs
- transplant recipients, HIV infection, CKD

Dipasquale et al J Hepatovcell Carcinoma 2021; 8: 241–251.

Therapiealgorithmus

Palliative systemische Therapie



Therapiealgorithmus

HIMALAYA (STRIDE) oder IMBrave150?

Durvalumab + Tremelimumab

- Autoimmunerkrankung?

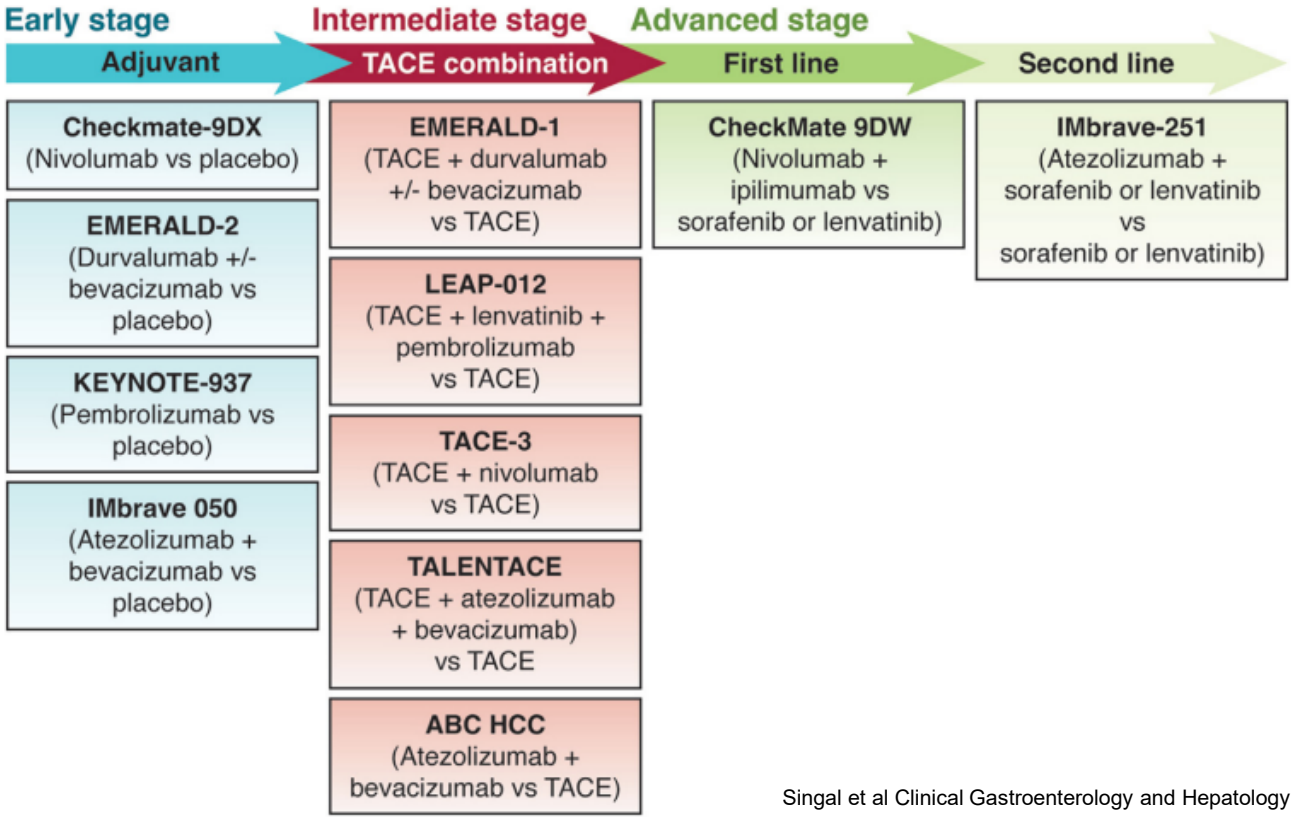
Atetzolizumab + Bevacizumab

- Anwendung von BEV in Pat. mit Ösophagusvarizen!
- Gastroskopie erforderlich vor Einleitung Therapie

6

Wie geht’s weiter?

Studienkonzepte 2023



Singal et al Clinical Gastroenterology and Hepatology 2023;21:2135–2149

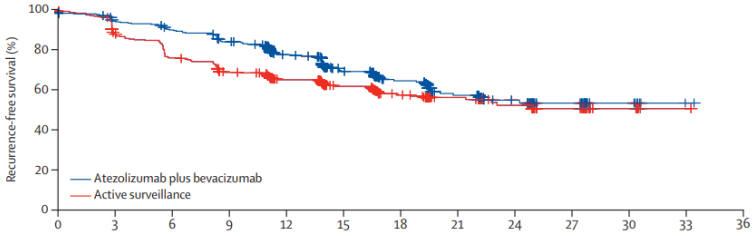
Adjuvante Therapie

Atezolizumab plus Bevacizumab – IMBrave-050 Studie

➔ *Keine Zulassung*

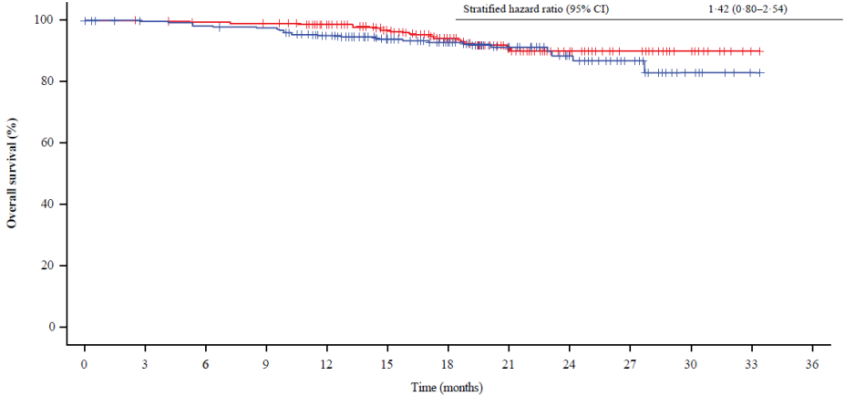
A

	Atezolizumab plus bevacizumab (n=334)	Active surveillance (n=334)	
Patients with events, n (%)	110 (33%)	133 (40%)	
Median RFS, months (95% CI)	NE (22·1–NE)	NE (21·4–NE)	
12-month IRF-RFS event-free rate, % (95% CI)	78% (73–82)	65% (60–71)	
Stratified hazard ratio (adjusted 95% CI)			0·72 (0·53–0·98)
p value (log rank)			0·012



Number at risk (number censored)													
Atezolizumab plus bevacizumab	334 (0)	305 (10)	290 (12)	268 (15)	211 (53)	139 (105)	97 (139)	63 (164)	37 (188)	22 (202)	9 (215)	1 (223)	NE (N
Active surveillance	334 (0)	283 (12)	245 (12)	214 (20)	179 (44)	131 (84)	93 (114)	57 (148)	36 (166)	20 (181)	6 (195)	1 (200)	NE (N

	Atezolizumab plus bevacizumab (n=334)	Active surveillance (n=334)
Median overall survival, months (95% CI)	NE (NE)	NE (NE)
Stratified hazard ratio (95% CI)	1·42 (0·80–2·54)	



No. at risk (No. censored)													
Atezolizumab plus bevacizumab	334 (0)	327 (6)	322 (6)	319 (7)	278 (40)	204 (111)	151 (162)	96 (215)	56 (253)	30 (278)	10 (297)	1 (306)	NE (NE)
Active surveillance	334 (0)	327 (6)	323 (9)	321 (10)	288 (42)	221 (104)	160 (160)	102 (213)	60 (254)	31 (283)	13 (301)	1 (313)	NE (NE)

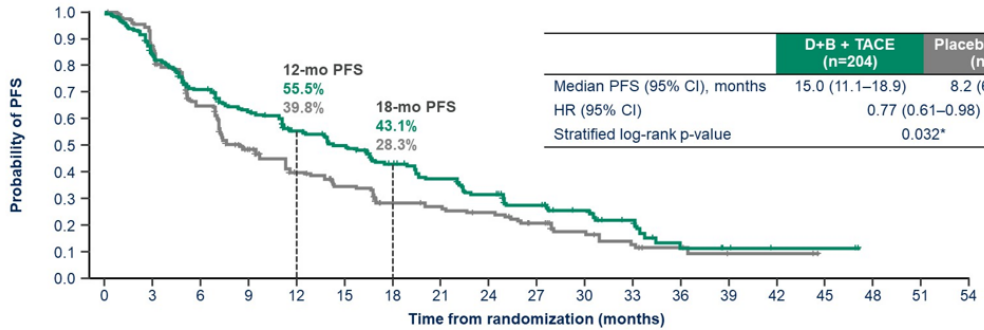
Quin S et al Lancet 2023; 402: 1835–47

Verbesserung der TACE

TACE + Durvalumab +/- Bevacizumab

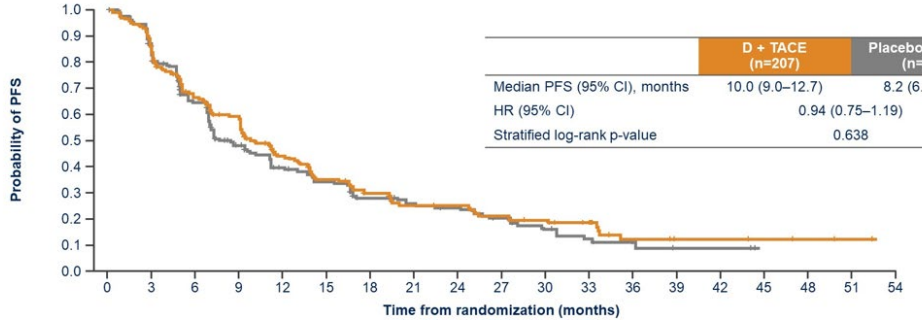
➔ *Keine Zulassung*

Median PFS was improved by 6.8 months with D+B + TACE versus placebos + TACE



	D+B + TACE (n=204)	Placebos + TACE (n=205)
Median PFS (95% CI), months	15.0 (11.1–18.9)	8.2 (6.9–11.1)
HR (95% CI)	0.77 (0.61–0.98)	
Stratified log-rank p-value	0.032*	

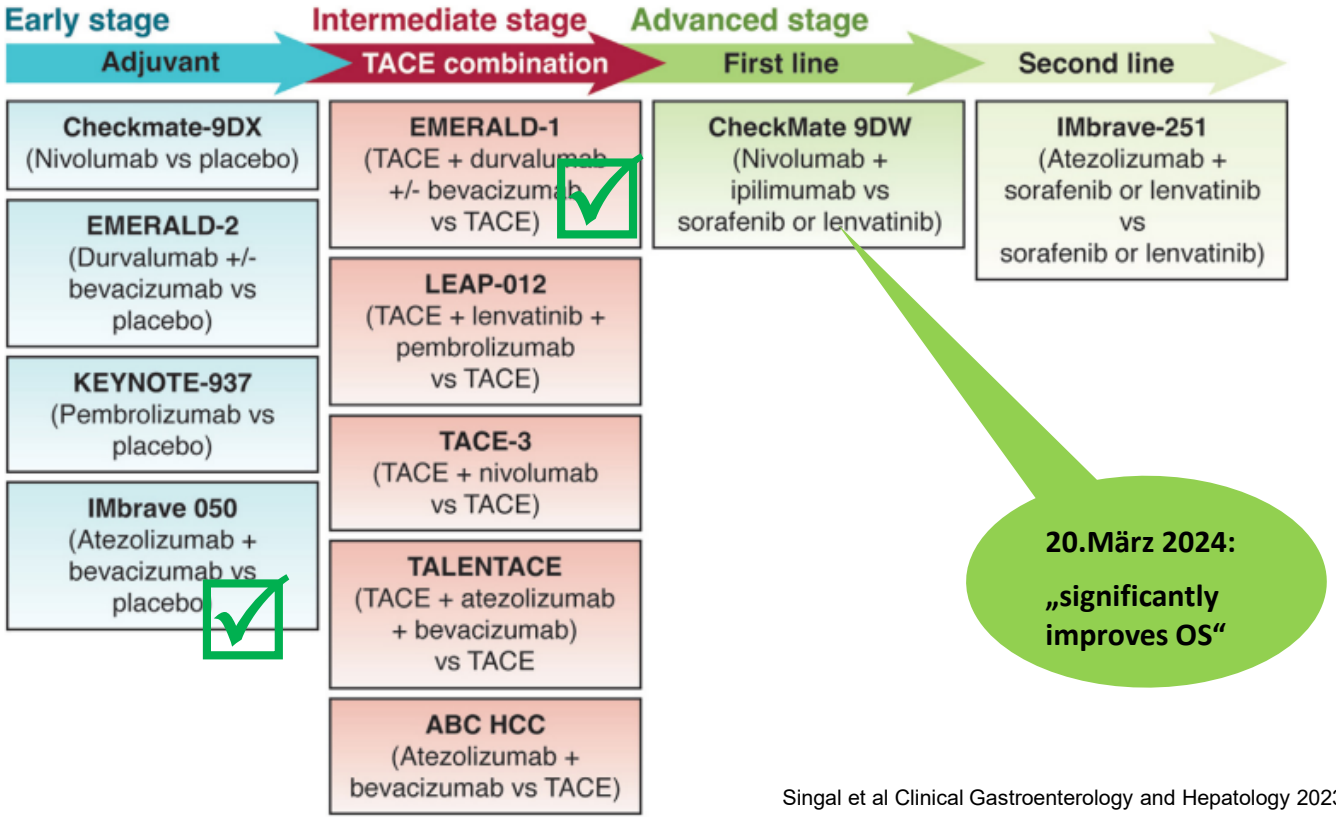
PFS was not significantly improved with D + TACE versus placebos + TACE



	D + TACE (n=207)	Placebos + TACE (n=205)
Median PFS (95% CI), months	10.0 (9.0–12.7)	8.2 (6.9–11.1)
HR (95% CI)	0.94 (0.75–1.19)	
Stratified log-rank p-value	0.638	

Lencioni R et al ASCO GI 2024

Studienkonzepte 2023



Singal et al Clinical Gastroenterology and Hepatology 2023;21:2135–2149

Vielen Dank für Ihre Aufmerksamkeit!

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