CCE
CANCER CENTER ESSLINGEN
Kompetenz in der Krebsbehandlung

Update Systemtherapie des fortgeschrittenen HCC

Henning Wege

Cancer Center Esslingen, Klinikum Esslingen
Universitätsklinikum Hamburg-Eppendorf

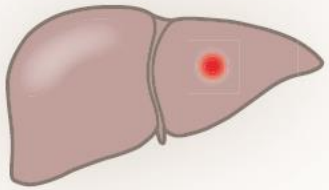
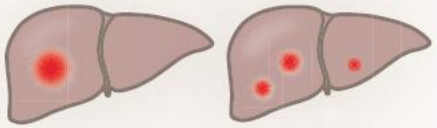
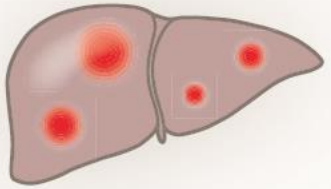
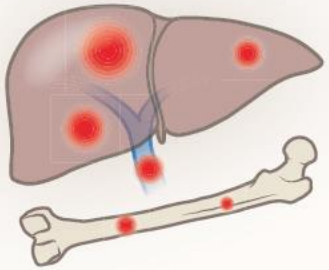
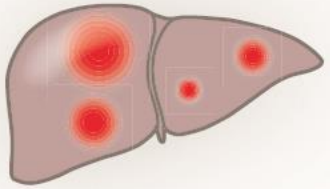
Hubertus Wald Tumorzentrum
Universitäres Cancer Center Hamburg
Ein Kompetenznetzwerk des UKE

DGHO
DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

Offenlegung potentieller Interessenkonflikte

Anstellungsverhältnis oder Führungsposition:	Klinikum Esslingen
Beratungstätigkeit:	Roche, MSD, Eisai, Ipsen, Lilly, BMS, AstraZeneca, Falk
Aktienbesitz:	Keine
Honorare:	Keine
Finanzierung wissenschaftlicher Untersuchungen:	Roche
Gutachtertätigkeit:	Keine
Andere finanzielle Beziehungen:	Keine

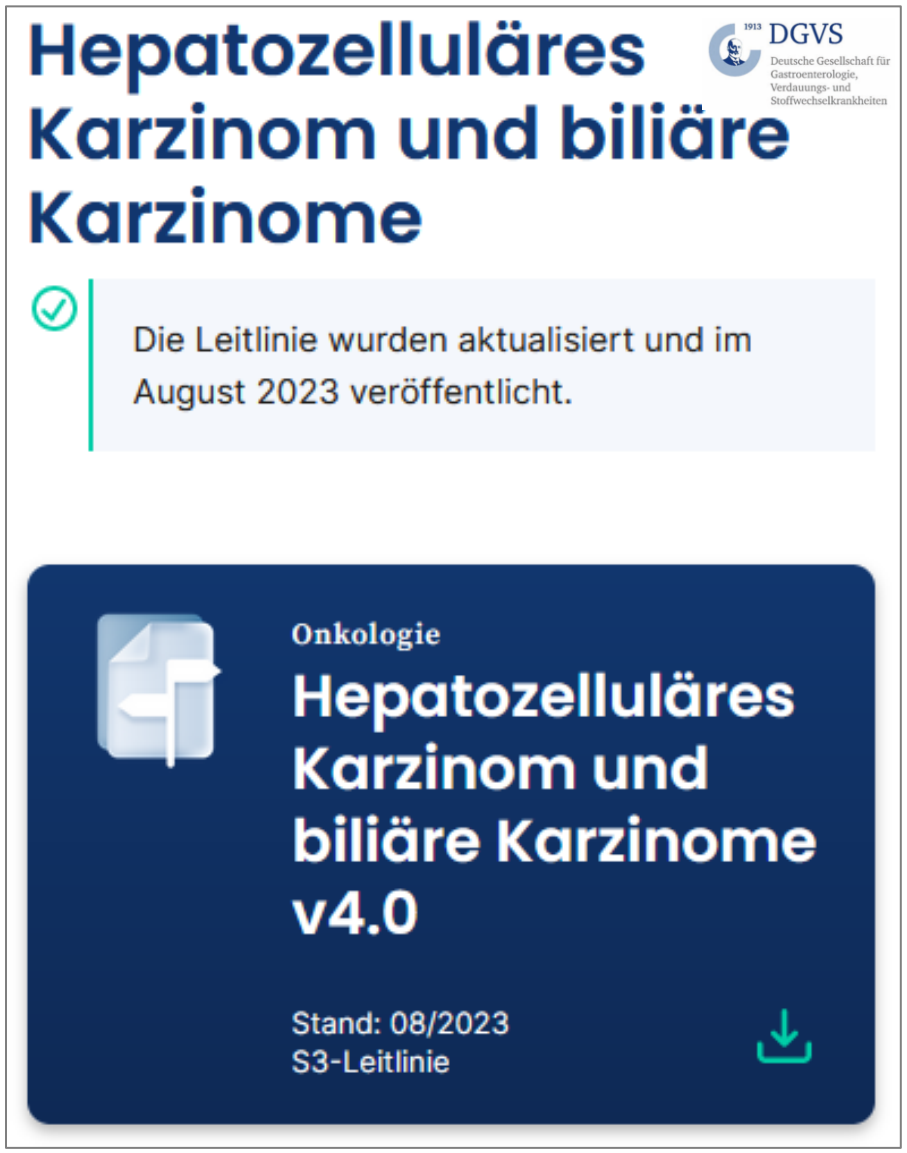
Therapie des HCC

Very early stage (0)	Early stage (A)	Intermediate stage (B)	Advanced stage (C)	Terminal stage (D)
Preserved liver function	Preserved liver function	Preserved liver function	Preserved liver function	End-stage liver function
ECOG-PS 0	ECOG-PS 0	ECOG-PS 0	ECOG-PS 1–2	ECOG-PS >2
				
Solitary nodule ≤2 cm	Solitary nodule >2 cm; 2 to 3 nodules, all ≤3 cm	Multinodular (>3 nodules, or ≥2 nodules if any >3 cm)	Macrovascular invasion or extrahepatic spread	Nontransplantable HCC

Resektion, Ablation | **TACE** | **Systemtherapie, BSC**

Villanueva et al., N Engl J Med 2019

Aktuelle S3-Leitlinie



Atezolizumab und Bevacizumab (A+B)

Durvalumab und 1x Tremelimumab (STRIDE)

Progress

Kontraindikationen IO-Therapie

Lenvatinib ⟷ **Sorafenib**

Progress

IMbrave150 (A+B)

- Erstlinie mOS 19,2 (17,0-23,7)

HIMALAYA (STRIDE)

- Erstlinie mOS 16,4 (14,2-16,9)

Ramucirumab
Bei AFP >400 ng/ml

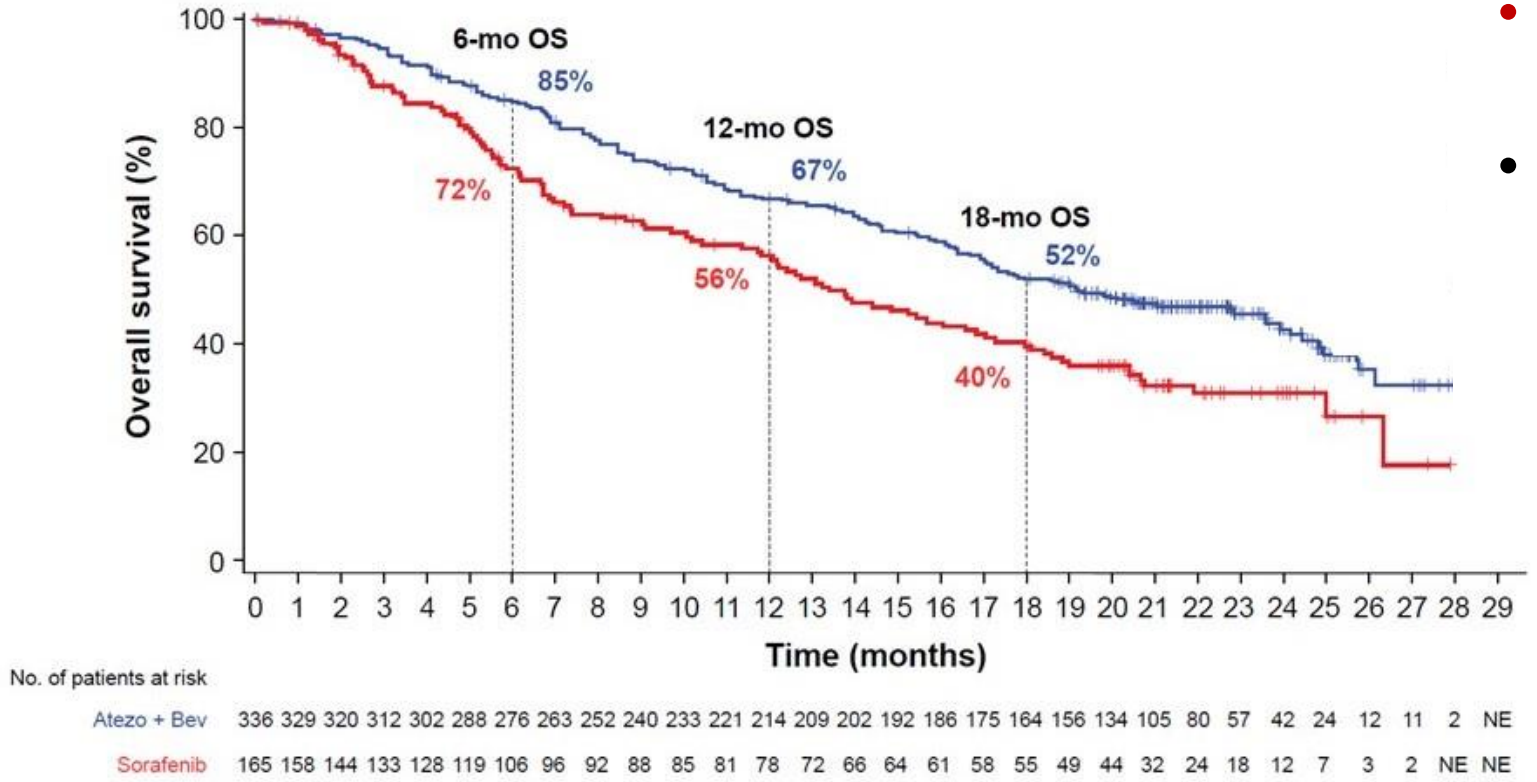
Regorafenib
Bei Toleranz Sorafenib

Cabozantinib
Auch als Drittlinie

Leitlinienprogramm Onkologie, Leitlinie (Langversion), Version 4.0 - August 2023

IMbrave 150 – Endpunkte

Atezolizumab 1200 mg + Bevacizumab 15 mg/kg alle 3 Wochen



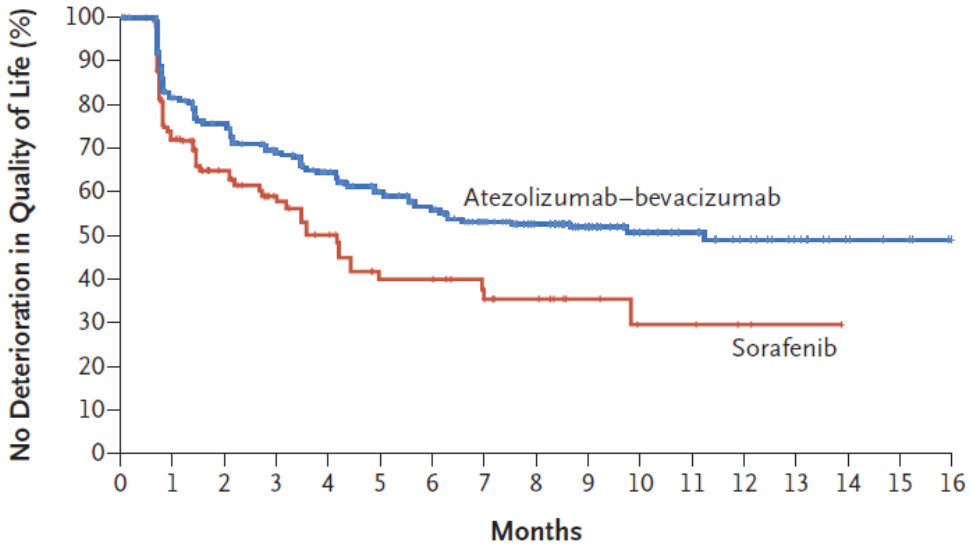
Update ASCO-GI 2021

- mOS 19,2 vs. 13,4 Monate (HR 0,66, p<0,001)
- mPFS 6,9 vs. 4,3 Monate (HR 0,65, p<0,001)
- ORR (CR+PR) 30 vs. 11% RECIST

Finn et al., New Engl J Med 2020; Finn et al. @ ASCO-GI 2021

IMbrave 150 – Lebensqualität

IMbrave 150 – Lebensqualität



No. at Risk

Atezolizumab–bevacizumab	336	239	208	181	157	134	121	99	78	58	40	32	20	14	7	5	NE
Sorafenib	165	93	60	39	31	22	22	14	12	7	4	4	2	1	NE	NE	NE

	Quality of Life — Median Time to Deterioration (95% CI)
	mo
Atezolizumab–Bevacizumab	11.2 (6.0–NE)
Sorafenib	3.6 (3.0–7.0)

Hazard ratio, 0.63 (95% CI, 0.46–0.85)

Patient Reported Outcome

- Erhalt einer stabilen QoL 11,2 vs. 3,6 Monate (HR 0,63)

Cheng et al. @ ESMO Asia 2019

AB-Real – Real life


European Journal of Cancer 175 (2022) 204–213

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

ELSEVIER

Original Research

Reproducible safety and efficacy of atezolizumab plus bevacizumab for HCC in clinical practice: Results of the AB-real study

Prospektive Datenbank

- 14 Zentren, 01/19-01/22
- N=296 Erstlinie, Child-Pugh A, ECOG 0/1
- Zirrhose 75%, HBV 40,6%
- 68,9% BCLC C, PVT 35%, Metastasen 51,7%

	IMbrave 150 Atezo + Bev vs. Sorafenib	AB-real Atezo + Bev
mOS	**19,2** vs. 13,4 Monate HR 0,66 (0,52-0,85)	**15,7** Monate (95%CI 14,5-NE)
mPFS	**6,9** vs. 4,3 Monate HR 0,65 (0,53-0,81)	**6,9** Monate (95% CI 6,1-8,3)
ORR (CR+PR)	**30%** vs. 11%	**30,8%** (N=273)

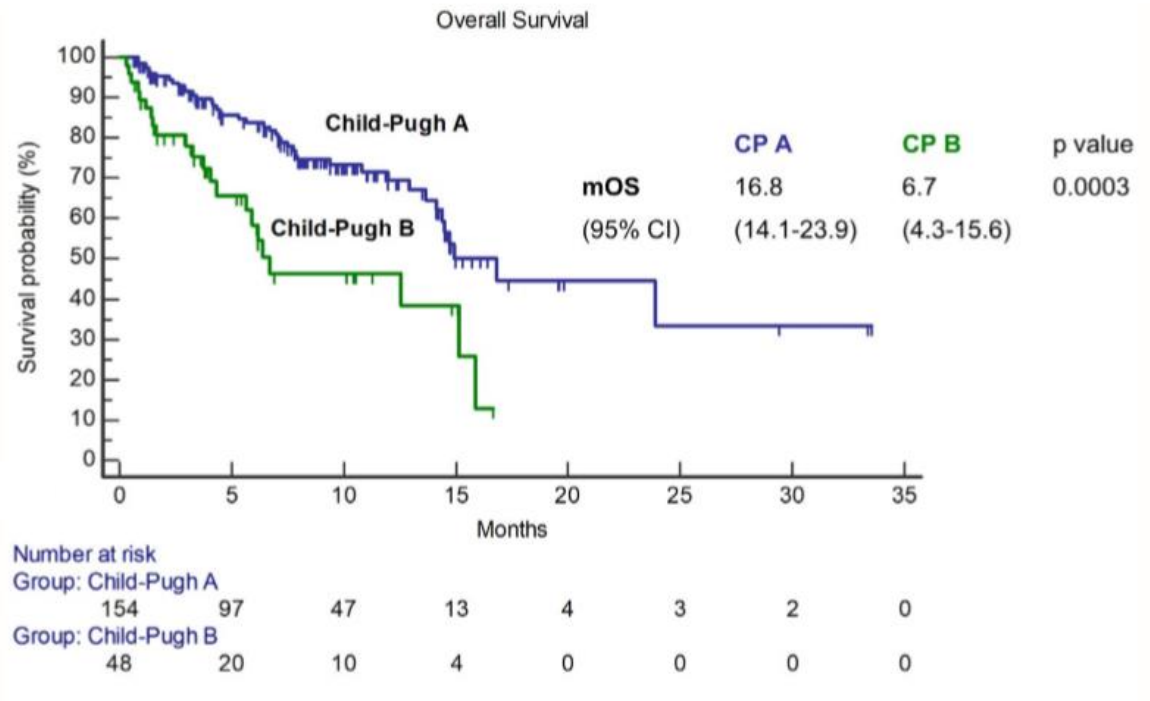
Fulgenzi et al., Euro J Cancer 2022

Atezo/Bev – Real life

Received: 27 January 2022 | Revised: 25 February 2022 | Accepted: 10 March 2022
DOI: 10.1002/hep.32468

ORIGINAL ARTICLE

Preliminary evidence of safety and tolerability of atezolizumab plus bevacizumab in patients with hepatocellular carcinoma and Child-Pugh A and B cirrhosis: A real-world study



Retrospektive Analyse

- 216 Patienten, 11 Zentren
- mOS Child-Pugh A 16,8 (14,1-23,9) Monate
- G3 trAEs 26%, G4 trAE 2%

Atezolizumab plus Bevacizumab	Overall Population (*n* = 174[a])	CP-A (*n* = 140)	CP-B (*n* = 34)
ORR[b], %	25%	26%	21%
DCR[c], %	73%	74%	68%
CR	1%	1%	0
PR	24%	25%	21%
SD	48%	48%	47%
Progressive disease	27%	26%	32%

D'Allesio et al., Hepatology 2022

Atezo/Bev – Real life

cancers
MDPI

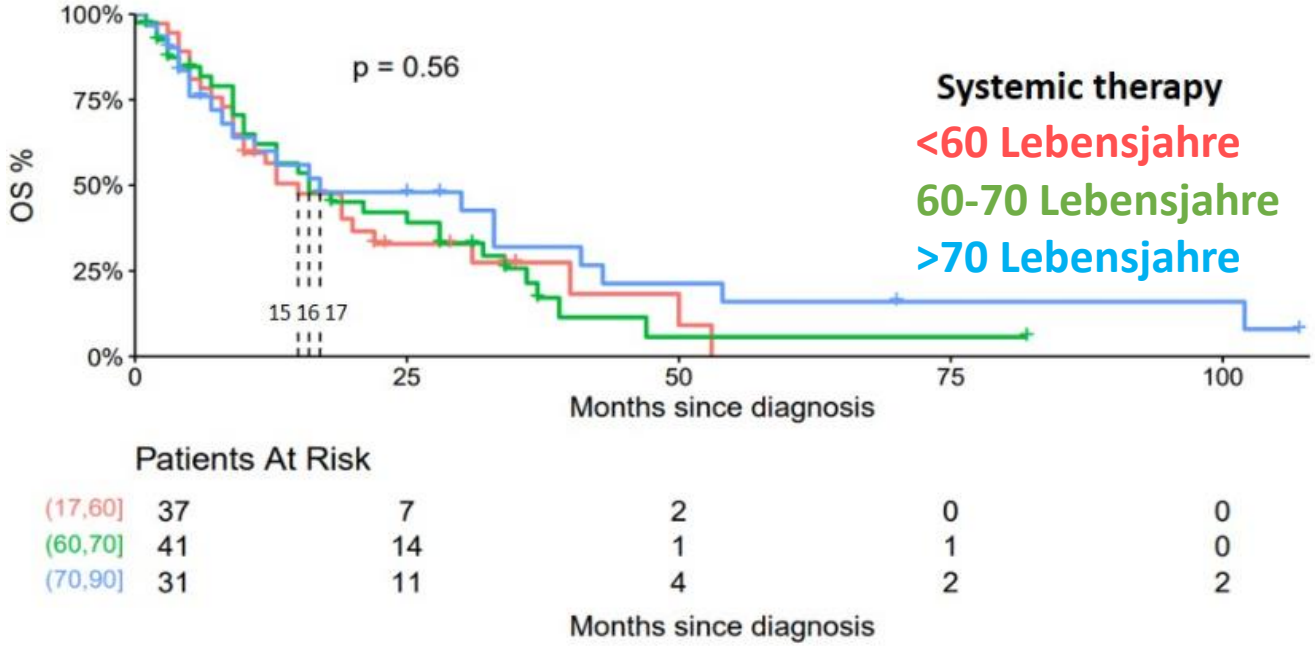
Article

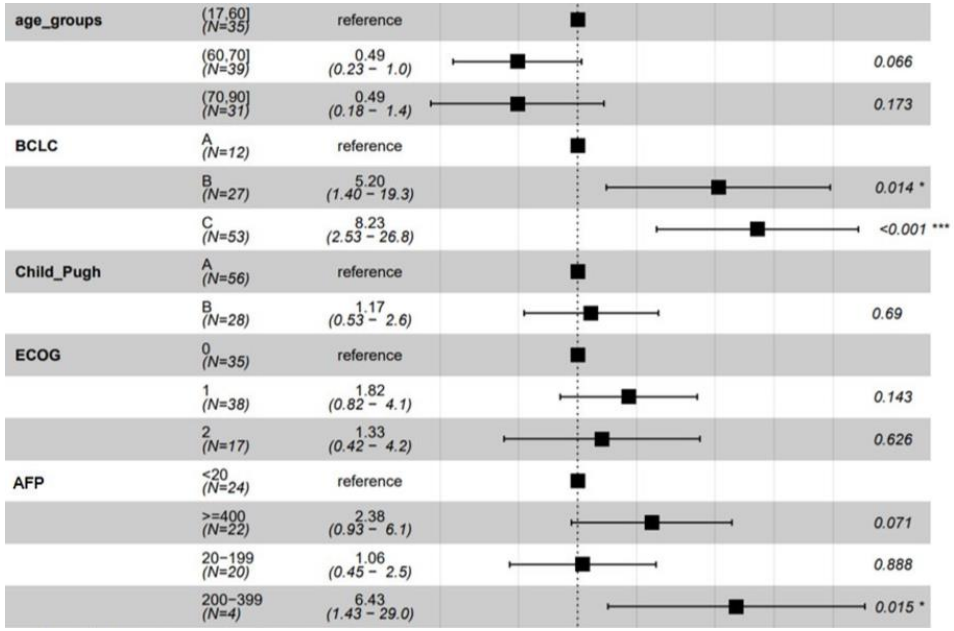
Equal Efficacy and Safety Profile in Elderly Patients with Hepatocellular Carcinoma Receiving Palliative Treatment

Thorben W. Fründt [1,*,†], Christian Casar [2,†], Johann von Felden [1], Ulrike Schöler [1], Maximilian Priebe [1], Jenny Kraczyk [2], Hannes Ahrend [3], Johannes Salamon [4], Gerhard Adam [4], Samuel Huber [1], Ansgar W. Lohse [1], Henning Wege [1,5] and Kornelius Schulze [1]

Retrospektive Analyse

- 656 Patienten UKE, 105 mit Systemtherapie
- 3 Altersgruppen
- AEs ohne Unterschied
- Multivariate Analyse BCLC, AFP (nicht Alter)





Fründt et al., Cancers 2022

HIMALAYA – Design

Study population

- Number of patients screened, N=1600
- Histologically confirmed advanced HCC
- No prior systemic therapy for HCC

Stratification

- Macrovascular invasion (yes vs. no)
- Aetiology of liver disease (HBV vs. HCV vs. other)
- ECOG PS (0 vs. 1)

Randomized
N = 1310

Arm 1 (N=385)
Durvalumab 1500 mg Q4W IV

Arm 2 (N=300)
Tremelimumab 75 mg IV x 4 doses
+ Durvalumab 1500 mg Q4W IV

Arm 3 (N=385)
Tremelimumab 300 mg IV x 1 dose
+ Durvalumab 1500 mg IV Q4W

Active Comparator
Arm 4 (N=385)
Sorafenib 400 mg BID, as per SOC

Primary Endpoint[3]

OS: Arm 1 vs Arm 4 and Arm 3 vs. Arm 4

Secondary Endpoints

Key Endpoint

- OS: Arm 3 and Arm 1 vs Arm 4

Other Endpoints

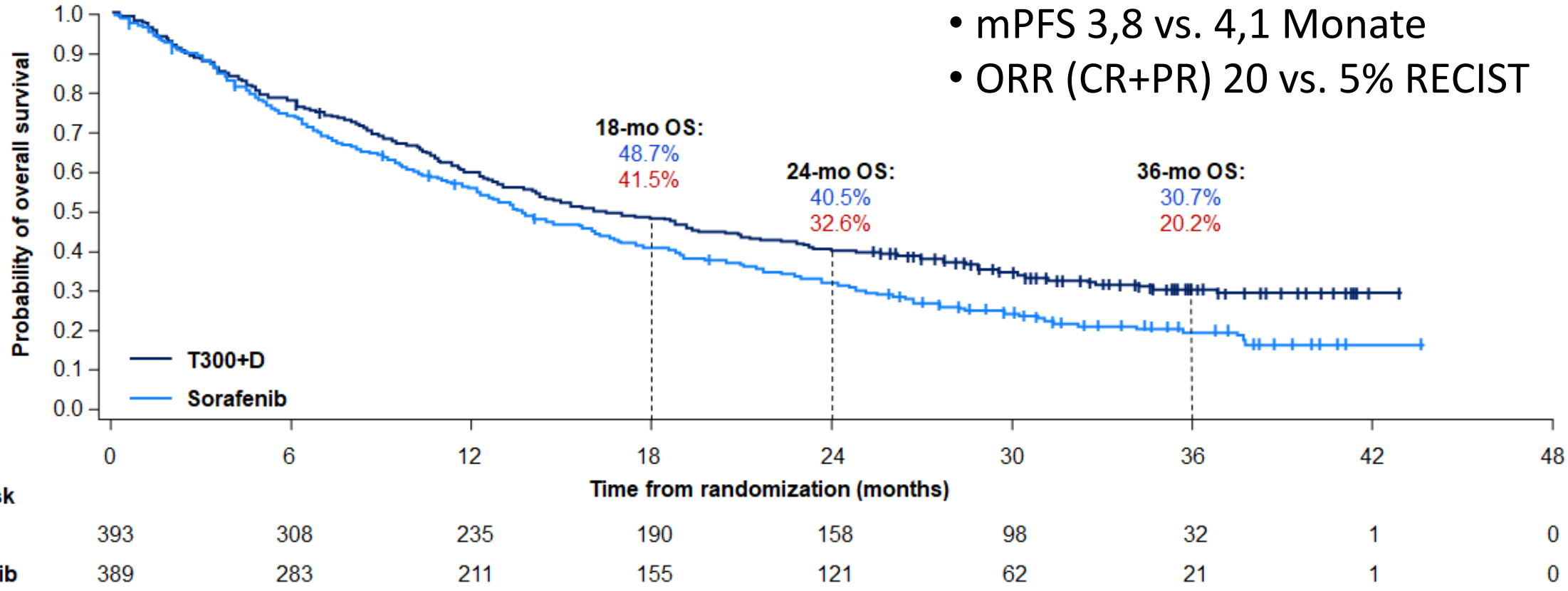
- PFS
- ORR
- DCR
- DoR
- HRQoL
- Efficacy by PD-L1 expression
- Time to Progression
- Safety and tolerability
- Disease related symptoms
- Pharmacokinetics
- Immunogenicity

Key Exploratory Endpoints

- Changes in alpha-fetoprotein level
- Efficacy of immunotherapy arms versus SOC
- Association of candidate biomarker with efficacy 75mg

HIMALAYA – Endpunkte

Tremelimumab 300 mg 1x + Durvalumab 1500 mg alle 4 Wochen



No.at risk									
T300+D	393	308	235	190	158	98	32	1	0
Sorafenib	389	283	211	155	121	62	21	1	0

ASCO-GI 2022

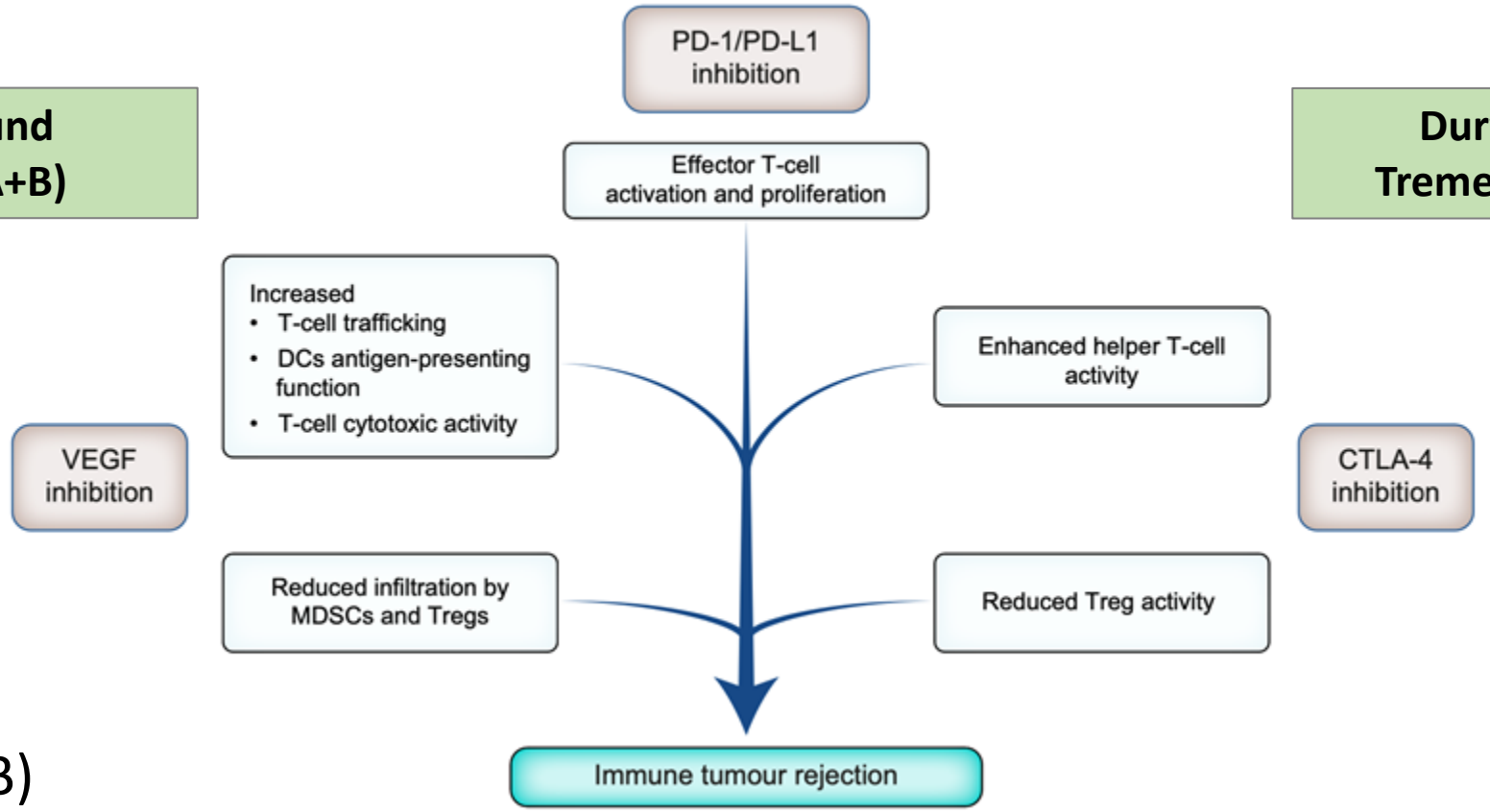
- mOS 16,4 vs. 13,8 Monate (HR 0,78, p<0,0035)
- mPFS 3,8 vs. 4,1 Monate
- ORR (CR+PR) 20 vs. 5% RECIST

Abou-Alfa et al. @ ASCO-GI 2022

IO-Therapie bei HCC

Atezolizumab und Bevacizumab (A+B)

Durvalumab und 1x Tremelimumab (STRIDE)



IMbrave150 (A+B)

- Erstlinie mOS 19,2 (17,0-23,7)

HIMALAYA (STRIDE)

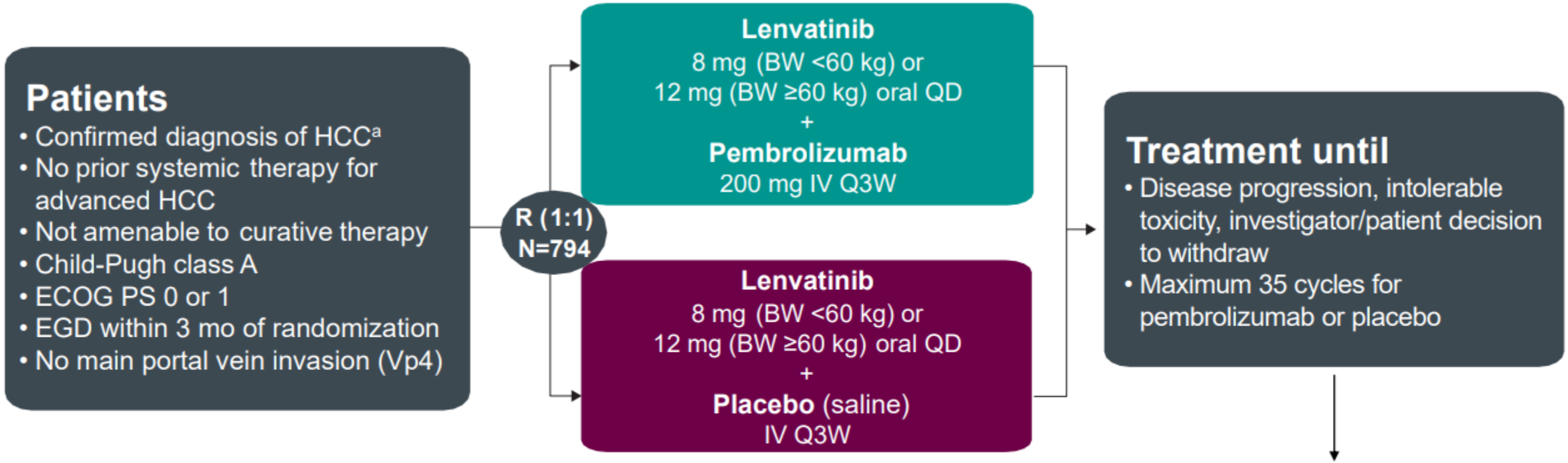
- Erstlinie mOS 16,4 (14,2-16,9)

Rimassa et al., J Hepatol 2023

Erstlinientherapie HCC

Substanzen	Studie	Oral	Endpunkte	Fazit
Atezolizumab + Cabozantinib vs. Sorafenib	**COSMIC-312**	ESMO 2021	mOS 15,4 vs. 15,5 Monate (HR 0,90, p=0,438) mPFS 6,8 vs. 4,2 Monate (HR 0,63, p=0,0012)	**Keine Verbesserung OS Verbesserung PFS**
Durvalumab + Tremelimumab vs. Sorafenib	**HIMALAYA**	ASCO-GI 2022	mOS 16,4 vs. 13,8 Monate (HR 0,78, p=0,0035)	**Leitlinienempfehlung**
Pembrolizumab + Lenvatinib vs. Lenvatinib	**LEAP-002**	ESMO 2022	mOS 21,2 vs. 19,0 Monate (HR 0,84, p=0,00227) mPFS 8,2 vs. 8,0 Monate (HR 0,87, p=0,0466)	**Endpunkte nicht erreicht**
Camrelizumab + Rivoceranib vs. Sorafenib	**NCT03764293**	ESMO 2022	mOS 22,1 vs. 15,5 Monate (HR 0,62, p<0,0001) mPFS 5,6 vs. 3,7 Monate (HR 0,52, p<0,0001)	**Endpunkte erreicht 82,7% Asiaten, 76,5% HBV**

LEAP-002 – Design



Stratification Factors
- Geographic region (Asia vs Japan and rest of world)
- Macroscopic portal vein invasion/extrahepatic spread (yes vs no)
- AFP level (≤400 vs >400 ng/mL)
- ECOG PS (0 vs 1)

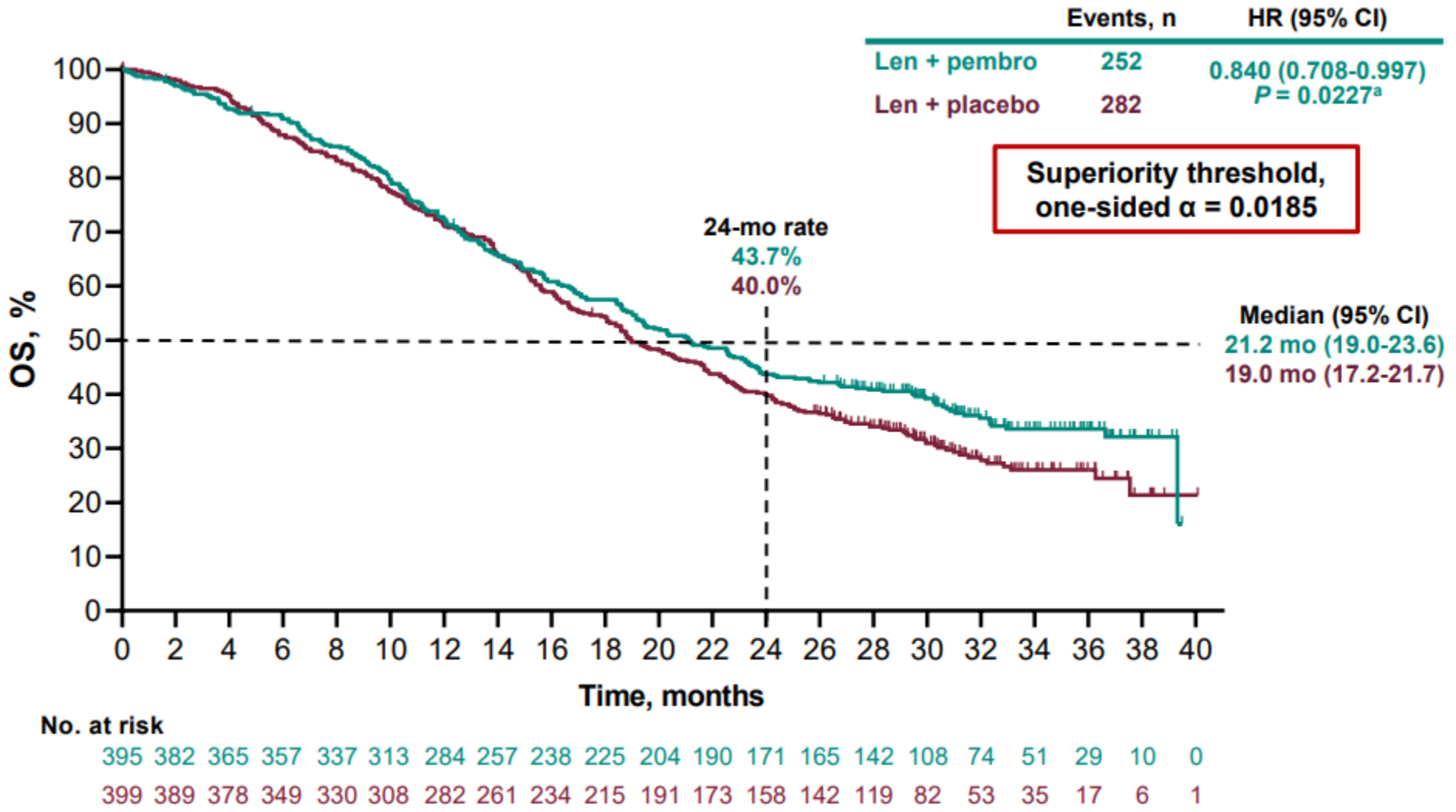
Dual primary endpoints:
- OS
- PFS[b] per RECIST v1.1 by BICR

Secondary endpoints included:
- ORR and DOR per RECIST v1.1 and mRECIST by BICR
- Safety/tolerability

Post-treatment follow-up to assess
- Safety
- Disease status
- Survival status

Finn et al. @ ESMO 2022

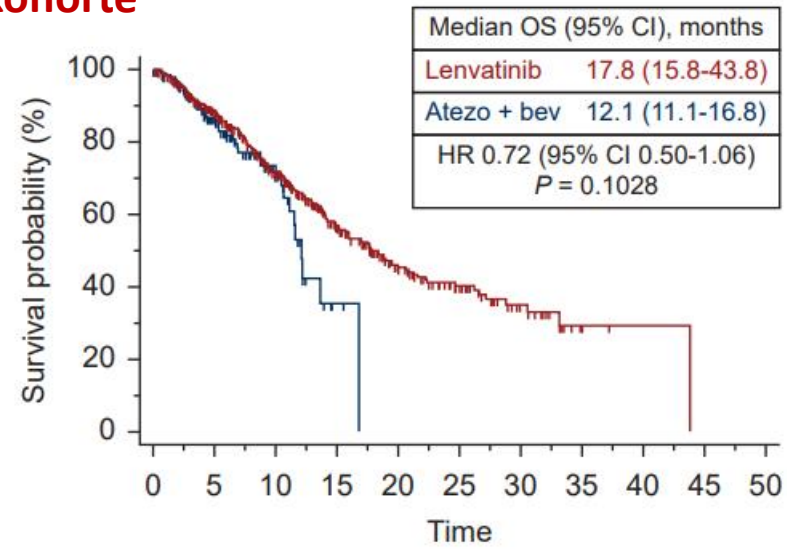
LEAP-002 – OS



Finn et al. @ ESMO 2022

Lenvatinib vs. Atezo/Bev

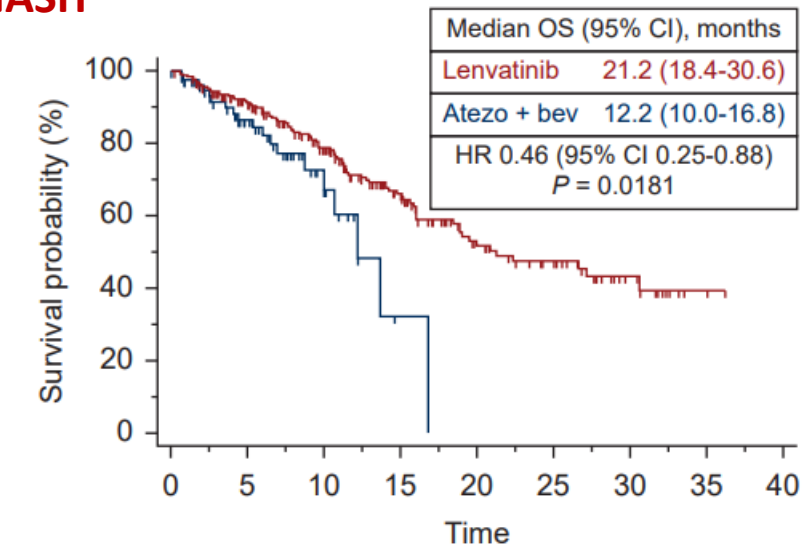
Gesamte Kohorte



Number at risk

Group: atezo + bev	190	95	26	2	0	0	0	0	0	0
Group: lenvatinib	569	429	273	149	74	42	18	3	1	0

NAFLD/NASH



Number at risk

Group: atezo + bev	82	43	11	1	0	0	0	0	0
Group: lenvatinib	254	203	135	80	41	29	12	2	0

- Retrospektive Auswertung (Propensity Score Match) an 36 Zentren
- Nicht-virales HCC, Erstlinientherapie mit Atezo/Bev oder TKI

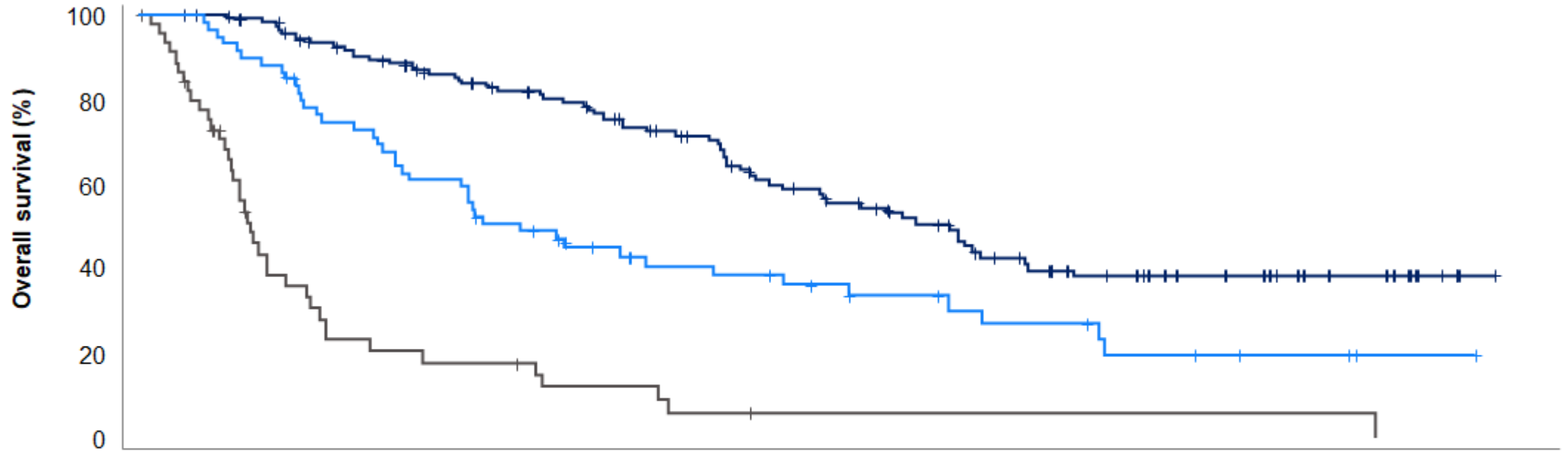
Rimini et al., ESMO Open 2022

Fazit HCC

Aktueller Stand der Systemtherapie beim fortgeschrittenen HCC (10/2023)

- **Atezolizumab + Bevacizumab (IMbrave 150)** ist die empfohlene Erstlinientherapie für alle Patienten mit fortgeschrittenem HCC
- **Tremelimumab + Durvalumab (HIMALAYA)** stellt eine mögliche Alternative bei Kontraindikationen für Bevacizumab dar
- **Lenvatinib** steht als TKI bei Kontraindikationen für eine immunonkologische Therapie zur Verfügung

IMbrave 150 – Beyond PD



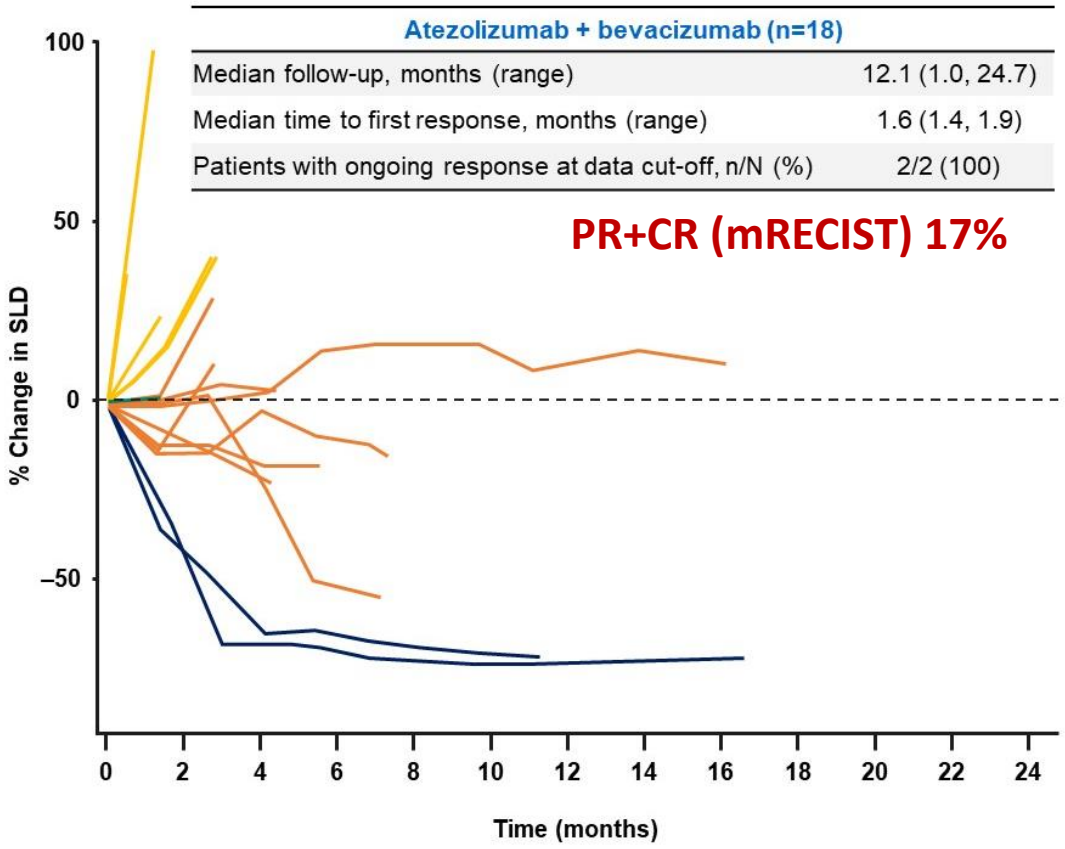
No. at risk																									
Atezo ± Bev	130	129	124	114	108	98	92	88	83	76	69	57	54	48	41	31	27	23	19	17	16	11	10	4	1	NE
Other therapies	60	60	54	45	42	35	31	27	22	19	18	17	14	11	11	9	8	7	5	4	3	3	1	1	NE	NE
No treatment	46	35	19	13	9	8	7	6	4	4	2	1	1	1	1	1	1	1	1	1	1	1	NE	NE	NE	NE

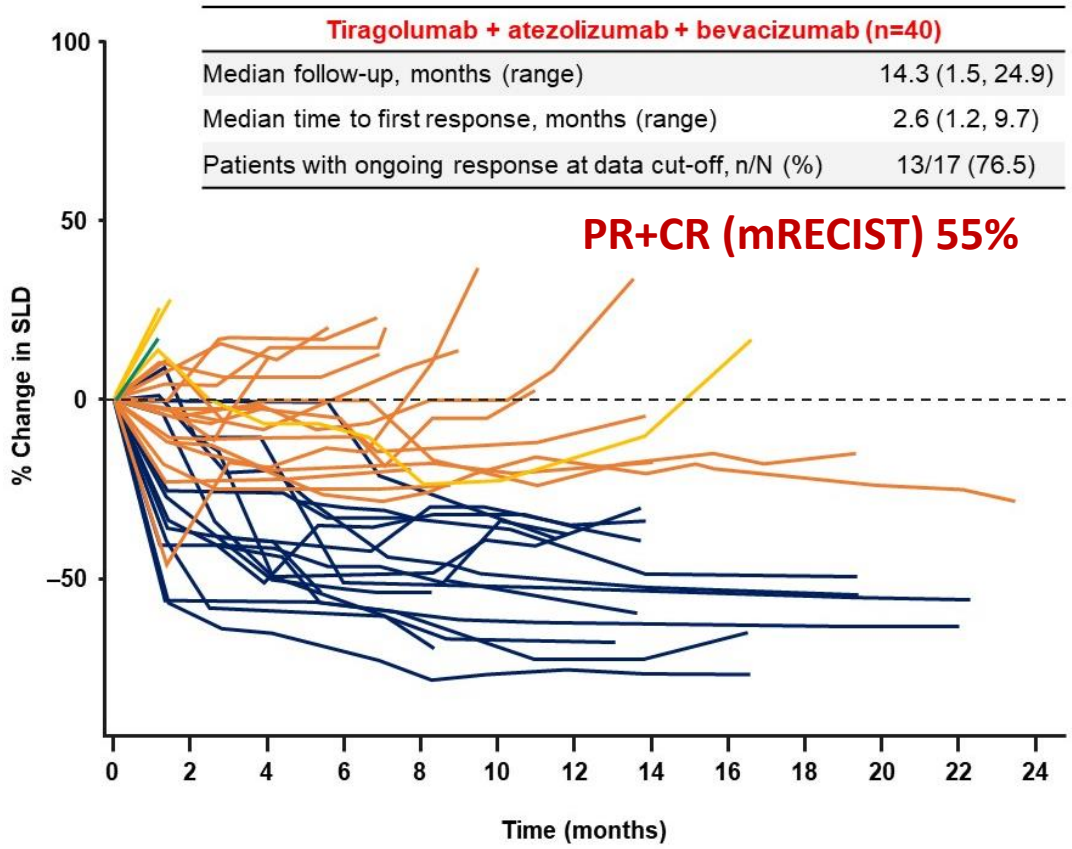
Atezolizumab beyod PD

- IMbrave 150 mOS nach PD 14,5 vs. 6,8 Monate, mOS ab Studienbeginn 24 Monate
- Phase 3 randomisiert Atezo/TKI vs. TKI IMbrave 251 mit deutschen Zentren

Toh et al. @ ASCO-GI 2022

Erstlinientherapie HCC





MORPHEUS-Liver

- Phase 1b/2 mit 18 vs. 40 Patienten, Erweiterung IO-Therapie durch Hemmung TIGIT
- Phase 3 IMbrave 152/SKYSCRAPER-14 mit deutschen Zentren

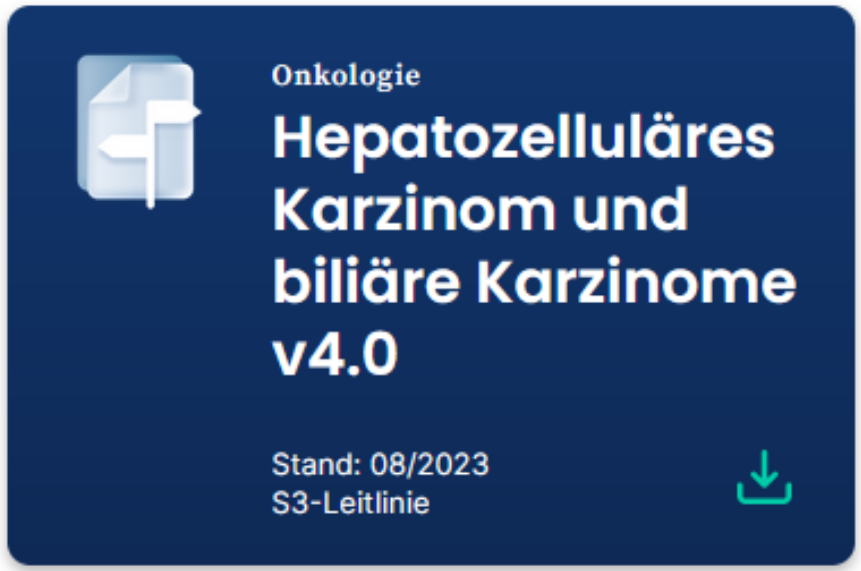
Finn @ ASCO 2023

Aktuelle S3-Leitlinie

Hepatozelluläres Karzinom und biliäre Karzinome

DGVS Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten

Die Leitlinie wurden aktualisiert und im August 2023 veröffentlicht.



Atezolizumab und Bevacizumab (A+B)

Durvalumab und 1x Tremelimumab (STRIDE)

Progress

Kontraindikationen IO-Therapie

Lenvatinib ⟷ **Sorafenib**

Progress

IMbrave150 (A+B)

- Erstlinie mOS 19,2 (17,0-23,7)

HIMALAYA (STRIDE)

- Erstlinie mOS 16,4 (14,2-16,9)

LEAP-002 (Lenvatinib)

- Erstlinie mOS 19,0 (17.2-21,7)

Ramucirumab
Bei AFP >400 ng/ml

Regorafenib
Bei Toleranz Sorafenib

Cabozantinib
Auch als Drittlinie

Leitlinienprogramm Onkologie, Leitlinie (Langversion), Version 4.0 - August 2023