uct Universitäres Centrum für Tumorerkrankungen Frankfurt
University Cancer Center

UNIVERSITÄTS KLINIKUM FRANKFURT

ASCO 2020
Hepatobiliäre Tumoren – was gibt es Neues?

Jörg Trojan, Universitätsklinikum Frankfurt

2020ASCO ANNUAL MEETING #ASCO20

MEDIZINISCHE KLINIK 1
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Interessenskonflikte

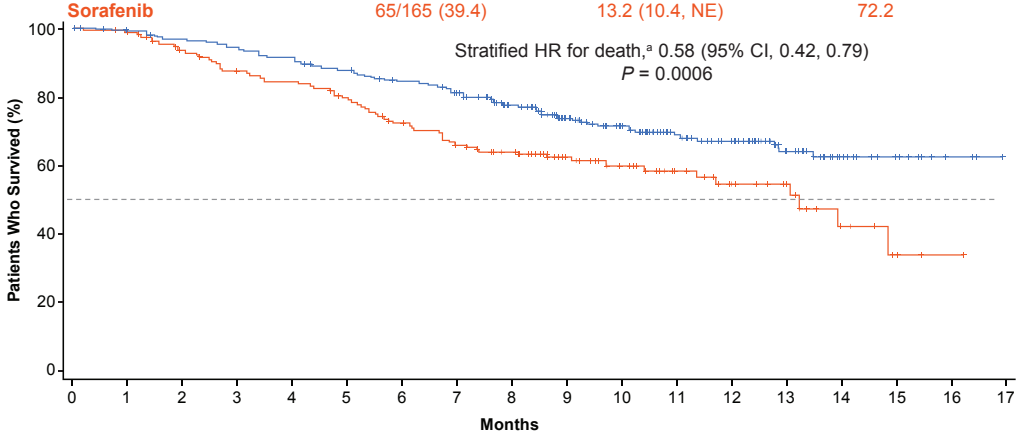
- Beratungshonorare: Amgen, Bayer Healthcare, Bristol Myers-Squibb, Eisai, Ipsen, Merck Serono, Merck Sharp & Dome, Lilly Imclone, Onkowissen TV, PCI Biotech, Roche und Servier
- Referentenhonorare: Amgen, Bioprojet, Bristol Myers-Squibb, Eisai, Ipsen, Merck Serono, Merck Sharp & Dome, Lilly Imclone, Roche, Servier und streammedup!
- Forschungsförderung: Roche und Ipsen

Erstlinientherapie des fortgeschrittenen HCC – Atezolizumab+Bevacizumab vs. Sorafenib

IMbrave150: OS und PFS (ITT-Population)

A

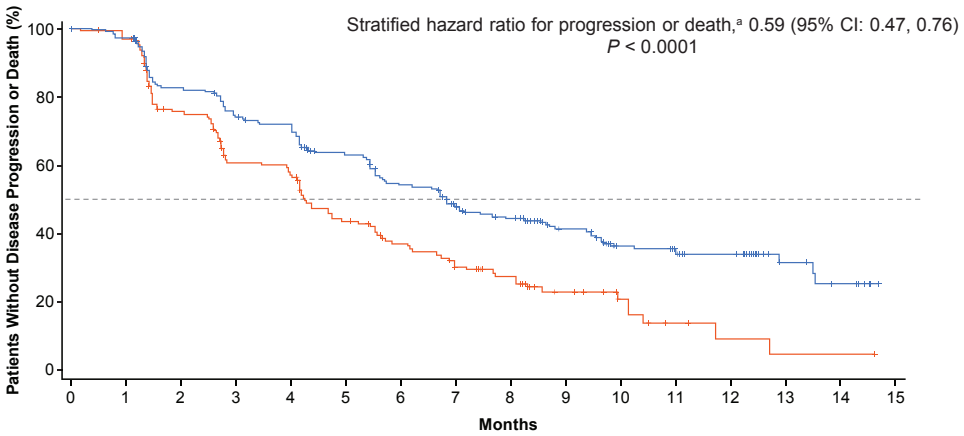
	No. of Events/ No. of Patients (%)	Median OS, months, (95% CI)	OS at 6 Months (%)
Atezolizumab + bevacizumab	96/336 (28.6)	NE	84.8
Sorafenib	65/165 (39.4)	13.2 (10.4, NE)	72.2



No. at risk																	
Atezo + Bev	336	329	320	312	302	288	275	255	222	165	118	87	64	40	20	11	3	NE
Sorafenib	165	157	143	132	127	118	105	94	86	60	45	33	24	16	7	3	1	NE

B

	No. of Events/ No. of Patients (%)	Median PFS, months (95% CI)	PFS at 6 Months (%)
Atezolizumab + bevacizumab	197/336 (58.6)	6.8 (5.7, 8.3)	54.5
Sorafenib	109/165 (66.1)	4.3 (4.0, 5.6)	37.2



No. at risk																	
Atezo + Bev	336	322	270	243	232	201	169	137	120	74	50	46	34	11	7	NE	
Sorafenib	165	148	109	84	80	57	44	34	27	15	9	4	2	1	1	NE	

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Complete responses (CR) in patients receiving atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in IMbrave150: A phase III clinical trial for unresectable hepatocellular carcinoma (HCC)
Richard S. Finn, et al. J Clin Oncol 38: 2020 (suppl; abstr 4596)

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Erstlinientherapie des fortgeschrittenen HCC – Atezolizumab+Bevacizumab – komplettes Tumoransprechen 6%

mediane Zeitdauer bis zum ersten Ansprechen 2,8 Mon (1,2 – 9,7) / bis CR 5,7 Monate (1,2 – 11,3)

Table 1. Secondary efficacy and exploratory TTR outcomes in IMbrave150 (ITT population)

	IRF RECIST 1.1[a]		IRF HCC mRECIST[b]	
	Atezo + Bev (n = 326)	**Sorafenib (n = 159)**	**Atezo + Bev (n = 325)**	**Sorafenib (n = 158)**
Confirmed ORR, n (%)[c] [95% CI]	89 (27) [23, 33]	19 (12) [7, 18]	108 (33) [28, 39]	21 (13) [8, 20]
CR, n (%)	18 (6)	0	33 (10)	3 (2)
PR, n (%)	71 (22)	19 (12)	75 (23)	18 (11)
Stratified *P* value[d]	< 0.0001		< 0.0001	
SD, n (%)	151 (46)	69 (43)	127 (39)	66 (42)
DCR[e], n (%)	240 (74)	88 (55)	235 (72)	87 (55)
PD, n (%)	64 (20)	39 (25)	66 (20)	40 (25)
Not evaluable, n (%)	8 (2)	14 (9)	10 (3)	14 (9)
Missing, n (%)	14 (4)	18 (11)	14 (4)	17 (11)
Ongoing response at data cutoff, n (%)	77 (87)	13 (68)	84 (78)	13 (62)
TTR in all responders, n	89	19	108	21
Median (range), months	2.8 (1.2-11.3)	3.3 (1.2-7.2)	2.7 (1.1-11.3)	2.6 (1.2-5.6)

Table 3. Duration from first response (CR/PR) to progression/death in patients with best objective response of CR per IRF-assessed RECIST 1.1 and HCC mRECIST

	Atezolizumab + Bevacizumab Treatment	
	IRF RECIST 1.1 (n = 18)	**IRF HCC mRECIST 1.1 (n = 33)**
Patients without progression/death at cutoff, n (%)	17 (94)	31 (94)
Time to progression (months)		
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	1.3+ to 13.0+	1.3+ to 13.0+
6-month analysis		
Patients remaining at risk	10	21
Event-free rate (95% CI), %	94 (83, 100)	97 (91, 100)

Data cut off: 29. August 2019; median Follow-up 8,6 Mon.

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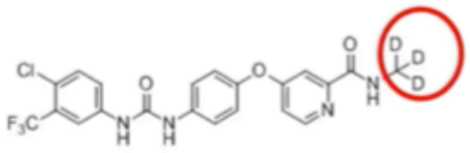
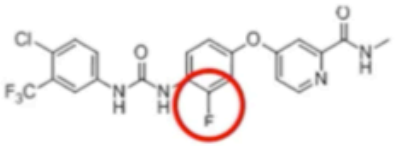
Erstlinientherapie des fortgeschrittenen HCC – Donafenib vs. Sorafenib (chinesische Phase 3)

Donafenib: a new agent with enhanced stability

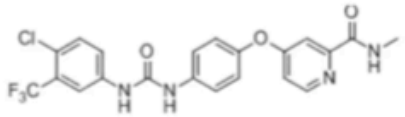
- A patented novel multikinase inhibitor that inhibits tumor-cell proliferation and tumor angiogenesis
- A deuterated derivative of sorafenib
- A phase Ib study showed donafenib 0.2 g bid was well tolerated and might be an appropriate first-line therapeutic option for HCC[1]



Donafenib



Regorafenib



Sorafenib

D: Deuterium „schwerer Wasserstoff“

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Donafenib versus sorafenib as first-line therapy in advanced hepatocellular carcinoma: An open-label, randomized, multicenter phase II/III trial. Feng Biet al. J Clin Oncol 38: 2020 (suppl; abstr 4506)

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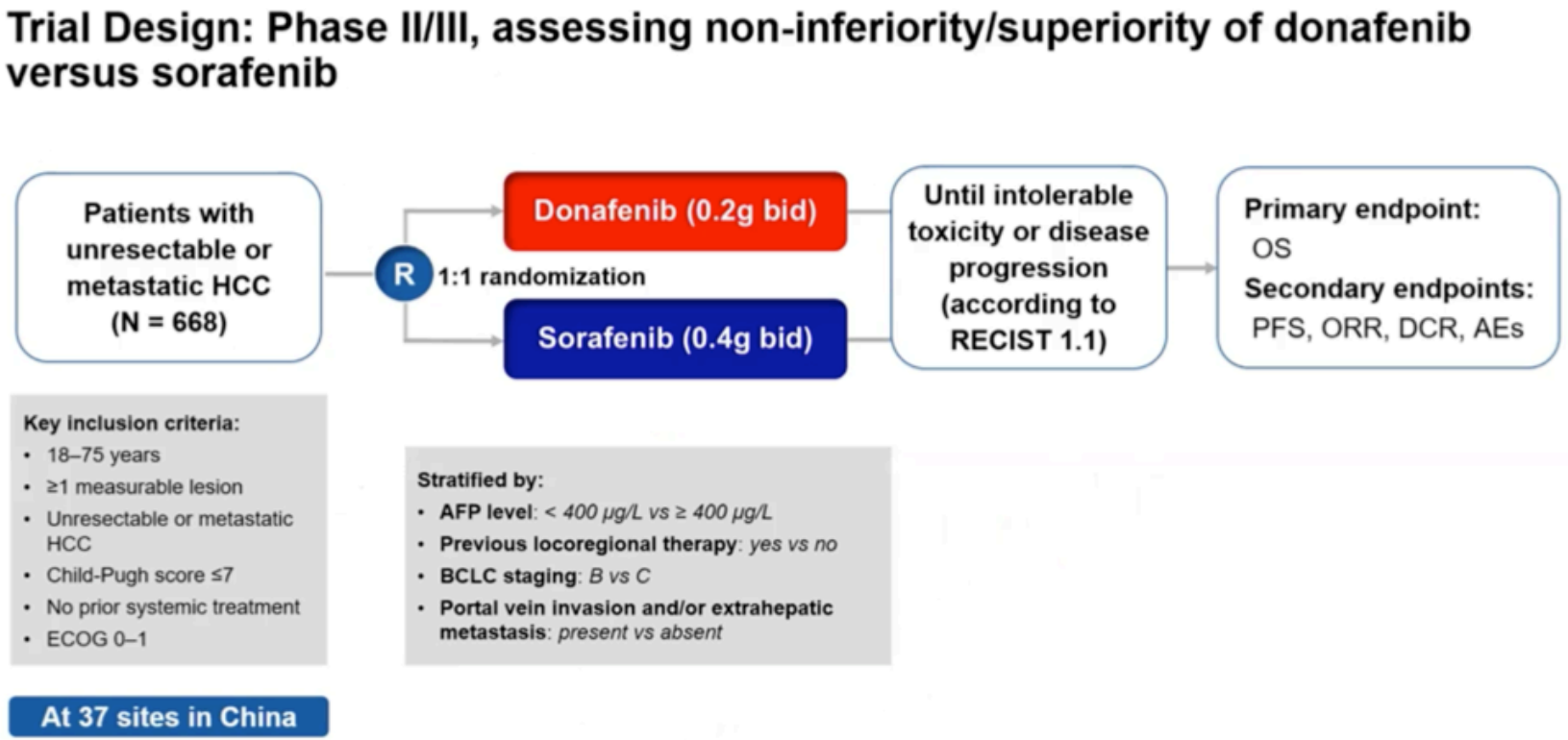

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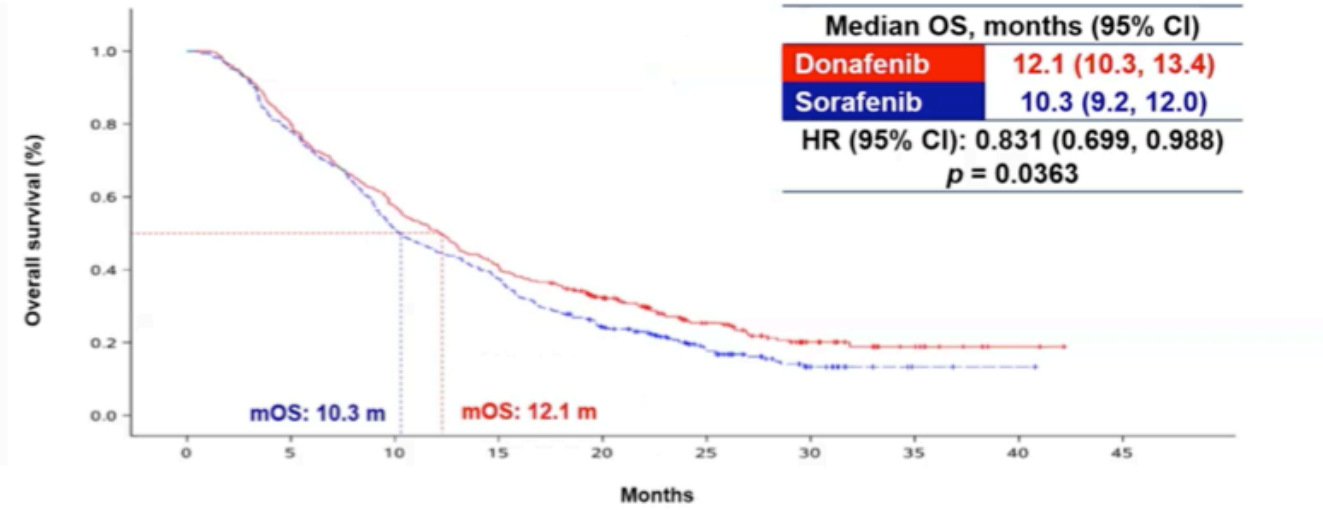
Erstlinientherapie des fortgeschrittenen HCC – Donafenib vs. Sorafenib (chinesische Phase 3)

Donafenib was associated with a significantly longer overall survival than sorafenib (FAS); superiority was demonstrated



Donafenib	328	262	188	134	95	54	25	10	2	0
Sorafenib	331	258	170	124	75	39	15	2	1	0

CI, confidence interval; FAS, full analysis set; HR, hazard ratio; OS, overall survival

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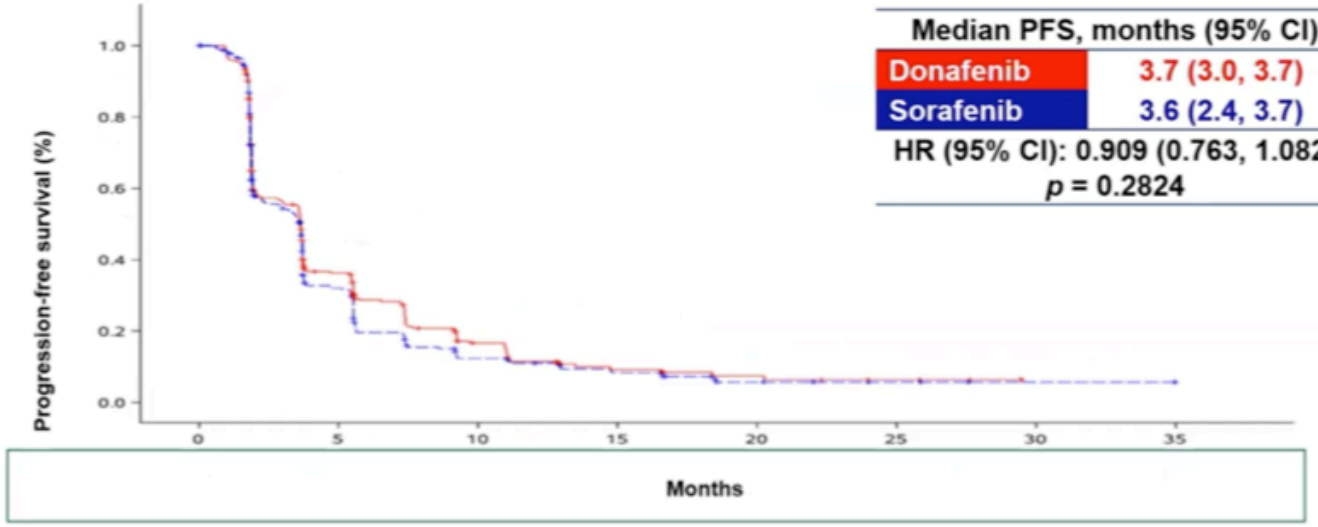
Erstlinientherapie des fortgeschrittenen HCC – Donafenib vs. Sorafenib (chinesische Phase 3)

Progression-free survival for patients treated with donafenib and sorafenib were comparable (FAS; IRC)



Median PFS, months (95% CI)	
Donafenib	3.7 (3.0, 3.7)
Sorafenib	3.6 (2.4, 3.7)

HR (95% CI): 0.909 (0.763, 1.082)
p = 0.2824

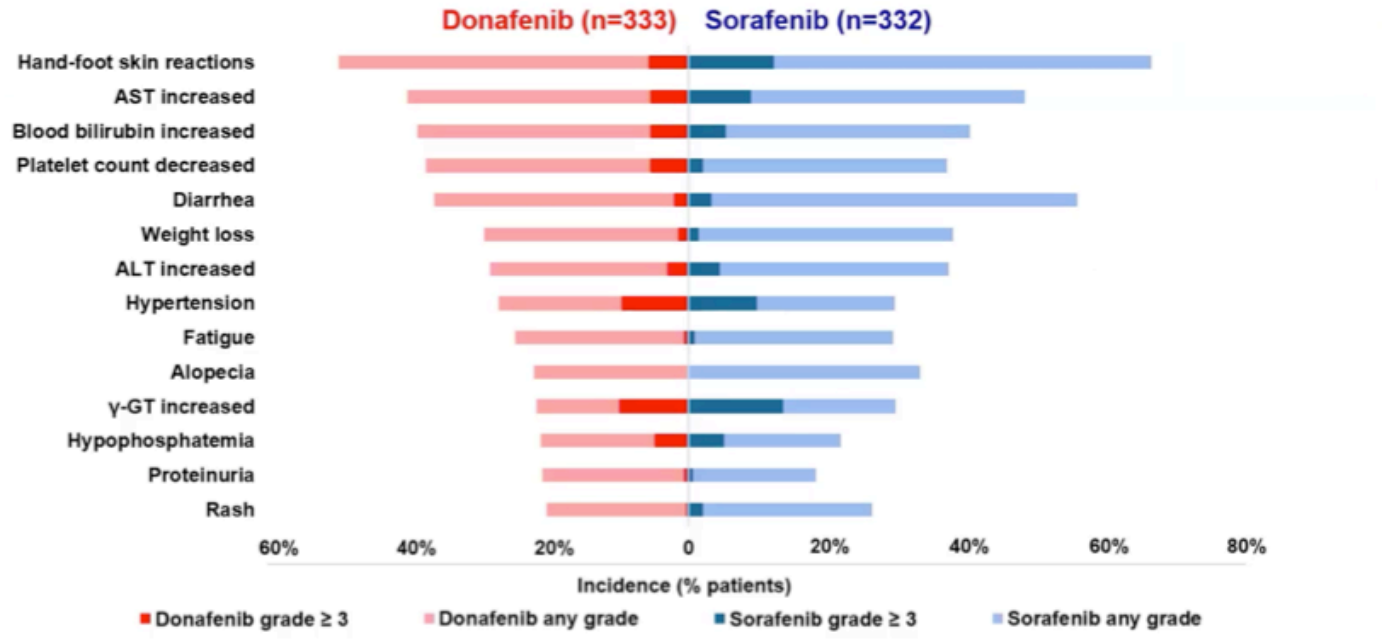
Donafenib	328	84	29	12	7	4	0	0
Sorafenib	331	85	27	16	6	3	1	0

CI, confidence interval; FAS, full analysis set; HR, hazard ratio; IRC, independent review committee; PFS, progression free survival

Donafenib versus sorafenib as first-line therapy in advanced hepatocellular carcinoma: An open-label, randomized, multicenter phase II/III trial. Feng Biet al. J Clin Oncol 38: 2020 (suppl; abstr 4506)

Erstlinientherapie des fortgeschrittenen HCC – Donafenib vs. Sorafenib (chinesische Phase 3)

Trend towards a lower incidence of AEs overall and AEs ≥ Grade 3 in patients treated with donafenib than with sorafenib



AEs shown occurred in >20% of patients in donafenib arm (most frequent); AE: adverse event; ALT: alanine aminotransferase; AST, aspartate aminotransferase; γ-GT: γ-glutamyl transpeptidase

Donafenib versus sorafenib as first-line therapy in advanced hepatocellular carcinoma: An open-label, randomized, multicenter phase II/III trial. Feng Biet al. J Clin Oncol 38: 2020 (suppl; abstr 4506)

Optimierung der Immuntherapie bei fortgeschrittenem HCC – Pembrolizumab+Lenvatinib (Phase 1b, extension)

Data cut off: 31. Oktober 2019 (37% der Patienten weiterhin unter Therapie)

Lenvatinib 12 or 8 mg daily orally (based on body weight) + **pembrolizumab** 200 mg IV on Day 1 (21-day cycle)

DLT Evaluation (Part 1)
- n = 6
- Patients ineligible for other therapies
- Tolerability evaluated by DLTs during cycle 1

Expansion (Part 2)
- n = 98
- No prior systemic therapy for uHCC

Key Eligibility Criteria
- uHCC
- BCLC Stage B (not applicable for TACE) or C
- Child–Pugh class A
- ECOG performance status 0–1
- At least 1 measurable target lesion according to mRECIST

Baseline Characteristic	N = 100
Median age, years (range)	66.5 (47, 86)
Sex, n (%)	
Male	81 (81)
Female	19 (19)
ECOG performance status, n (%)	
0	62 (62)
1	38 (38)
BCLC stage, n (%)	
B	29 (29)
C	71 (71)
Serum AFP level[a], n (%)	
< 400 ng/mL	67 (67)
≥ 400 ng/mL	30 (30)
Child-Pugh Score, n (%)	
5	71 (71)
6	27 (27)
7	2 (2)[b]
MPVI, extrahepatic spread or both, n (%)	62 (62)

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A phase Ib study of lenvatinib (LEN) plus pembrolizumab (PEMBRO) in unresectable hepatocellular carcinoma (uHCC). Andrew X. Zhu, et al. J Clin Oncol 38: 2020 (suppl; abstr 4519)

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Optimierung der Immuntherapie bei fortgeschrittenem HCC – Pembrolizumab+Lenvatinib (Phase 1b, extension)

Safety

- Median duration of exposure
  - Overall treatment duration[a]: 7.9 months
    - Range: 0.2 to 31.1
  - Lenvatinib: 7.6 months
    - Range: 0.2 to 31.1
  - Pembrolizumab: 7.4 months
    - Range: 0.03 to 23.5
- 95% Of patients had ≥ 1 TRAE
- 67% Of patients had grade ≥ 3 TRAEs
  - Grade 3: 63%
  - Grade 4: 1%
  - Grade 5: 3%

Most Common TRAEs
(≥ 25% of Patients With Any-Grade TRAE)

Preferred term, n (%)	N = 100			
	Any Grade	Grade 1	Grade 2	Grade 3
Hypertension	36 (36)	1 (1)	18 (18)	17 (17)
Diarrhea	35 (35)	19 (19)	11 (11)	5 (5)
Fatigue	30 (30)	12 (12)	14 (14)	4 (4)
Decreased appetite	28 (28)	12 (12)	16 (16)	0
Hypothyroidism	25 (25)	11 (11)	14 (14)	0

- Grade 5 TRAEs
  - Acute respiratory failure/acute respiratory distress syndrome (n = 1)
  - Abnormal hepatic function (n = 1)
  - Intestinal perforation (n = 1)
- Grade 4 TRAE
  - Leukopenia/neutropenia (n = 1)

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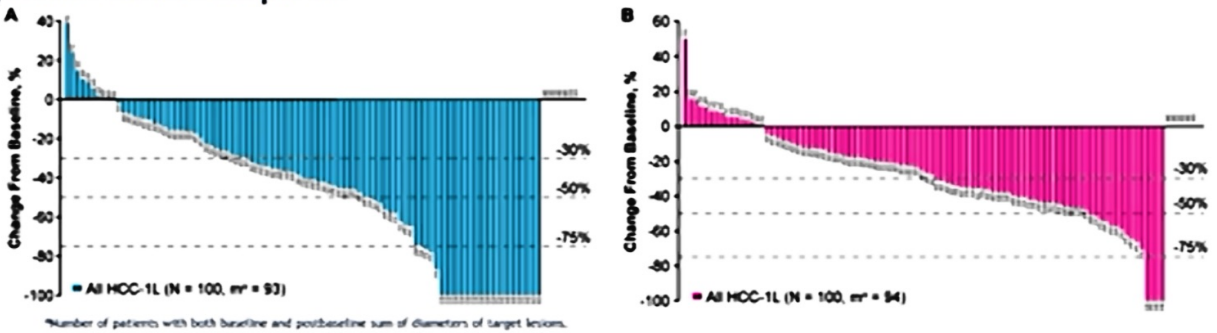
Optimierung der Immuntherapie bei fortgeschrittenem HCC – Pembrolizumab+Lenvatinib (Phase 1b, extension)

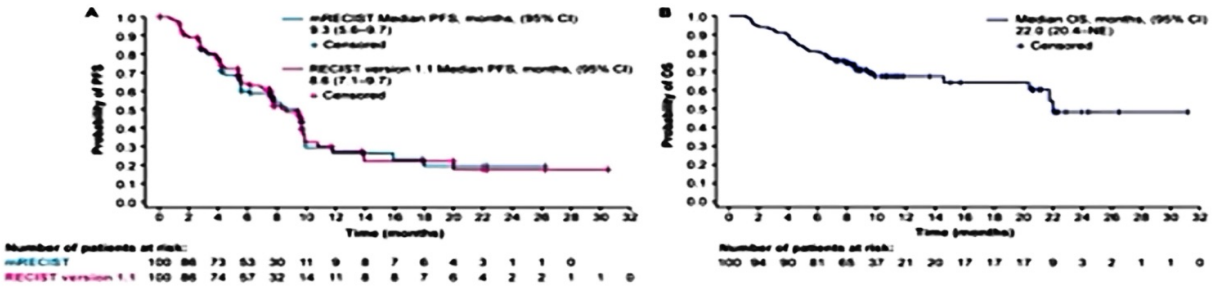
ORR: 36% (CR 1%, PR 35% per RECIST 1.1), OS: 22,0 Mon.

Percentage Change From Baseline in Sums of Diameters of Target Lesions (A) by mRECIST per IIR and (B) by RECIST Version 1.1 per IIR



*Number of patients with both baseline and postbaseline sum of diameters of target lesions.

Kaplan–Meier Estimates of (A) PFS, by mRECIST and RECIST Version 1.1 per IIR; and (B) OS (Efficacy Analysis Set)



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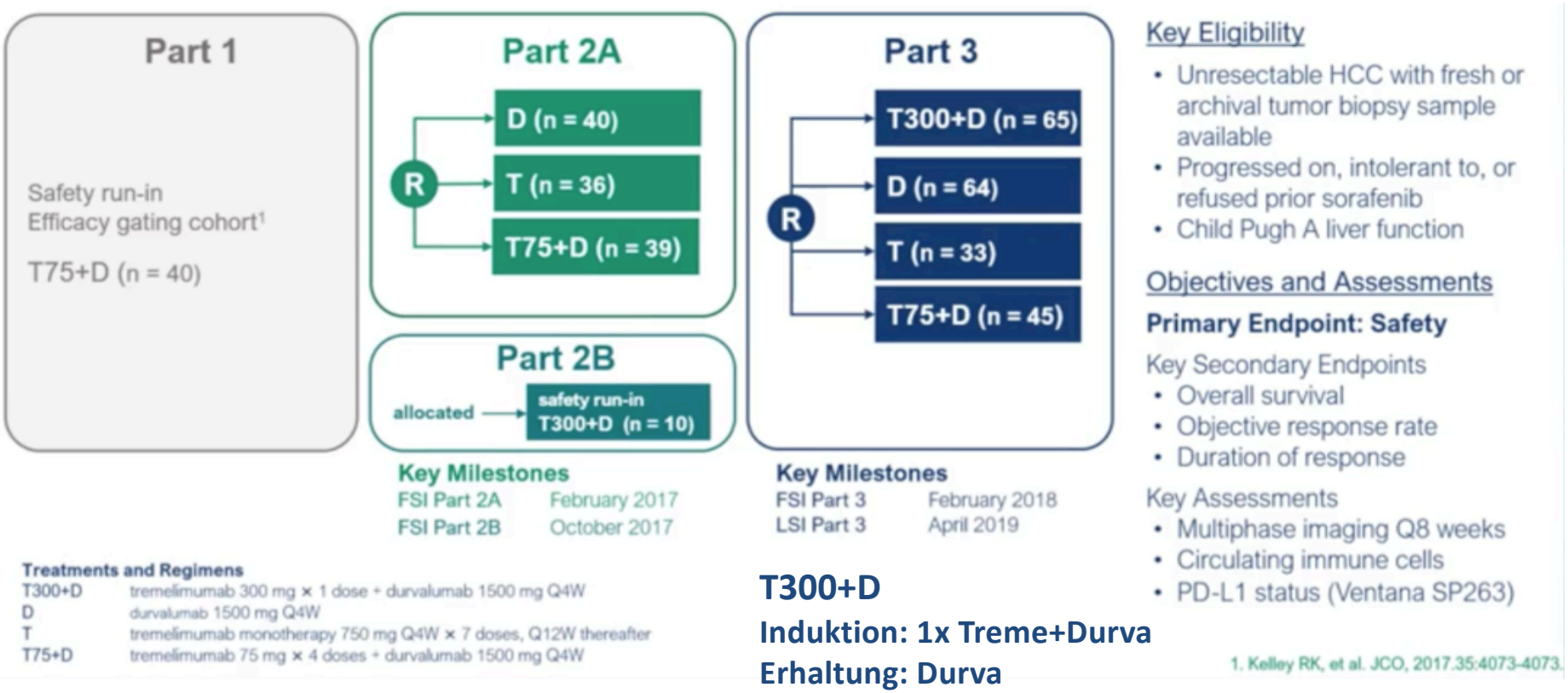
Optimierung der Immuntherapie bei fortgeschrittenem HCC – Tremelimumab+Durvalumab (Phase 1/2, extension)



T300+D

Induktion: 1x Treme+Durva

Erhaltung: Durva

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Efficacy, tolerability, and biologic activity of a novel regimen of tremelimumab (T) in combination with durvalumab (D) for patients (pts) with advanced hepatocellular carcinoma (aHCC).

Robin Kate Kelley, et al. J Clin Oncol 38: 2020 (suppl; abstr 4508)

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Optimierung der Immuntherapie bei fortgeschrittenem HCC – Tremelimumab+Durvalumab (Phase 1/2, extension)

Treatment-related Adverse Events (≥5% by Category)

n (%)	T300+D (n = 74)		D (n = 101)		T (n = 69)		T75+D (n = 82)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Patients with any TRAE	61 (82.4)	27 (36.5)	61 (60.4)	21 (20.8)	58 (84.1)	30 (43.5)	57 (69.5)	20 (24.4)
Endocrine								
Hyperthyroidism	6 (8.1)	0	2 (2.0)	0	0	0	4 (4.9)	1 (1.2)
Hypothyroidism	6 (8.1)	0	10 (9.9)	0	2 (2.9)	0	7 (8.5)	0
Skin and subcutaneous tissue disorders								
Pruritus	24 (32.4)	0	11 (10.9)	0	19 (27.5)	1 (1.4)	13 (15.9)	0
Rash	24 (32.4)	2 (2.7)	7 (6.9)	0	15 (21.7)	2 (2.9)	11 (13.4)	0
Rash maculo-papular	2 (2.7)	1 (1.4)	2 (2.0)	0	7 (10.1)	0	5 (6.1)	0
Urticaria	2 (2.7)	0	0	0	2 (2.9)	0	1 (1.2)	0
Musculoskeletal and connective tissue disorders								
Arthralgia	0	0	2 (2.0)	0	3 (4.3)	0	2 (2.4)	0
Myalgia	2 (2.7)	0	1 (1.0)	0	1 (1.4)	1 (1.4)	1 (1.2)	0
Myositis	0	0	1 (1.0)	1 (1.0)	0	0	0	0
General disorders and administration site conditions								
Fatigue	8 (10.8)	0	9 (8.9)	1 (1.0)	11 (15.9)	0	8 (9.8)	0
Investigations								
Amylase increased	11 (14.9)	5 (6.8)	2 (2.0)	1 (1.0)	3 (4.3)	0	6 (7.3)	1 (1.2)
Lipase increased	9 (12.2)	5 (6.8)	1 (1.0)	0	9 (13.0)	4 (5.8)	4 (4.9)	4 (4.9)

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Optimierung der Immuntherapie bei fortgeschrittenem HCC – Tremelimumab+Durvalumab (Phase 1/2, extension)

Treatment-related Adverse Events (≥5% by Category), cont.

n (%)	T300+D (n = 74)		D (n = 101)		T (n = 69)		T75+D (n = 82)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Patients with any TRAE	61 (82.4)	27 (36.5)	61 (60.4)	21 (20.8)	58 (84.1)	30 (43.5)	57 (69.5)	20 (24.4)
Gastrointestinal disorders								
Abdominal pain	2 (2.7)	0	0	0	5 (7.2)	0	4 (4.9)	0
Ascites	1 (1.4)	0	0	0	1 (1.4)	0	0	0
Immune-mediated pancreatitis	0	0	0	0	0	0	2 (2.4)	1 (1.2)
Colitis	3 (4.1)	2 (2.7)	0	0	1 (1.4)	1 (1.4)	1 (1.2)	1 (1.2)
Diarrhea	7 (9.5)	1 (1.4)	9 (8.9)	1 (1.0)	14 (20.3)	6 (8.7)	10 (12.2)	1 (1.2)
Hepatobiliary disorders								
Hepatic failure	0	0	1 (1.0)	1 (1.0)	0	0	1 (1.2)	1 (1.2)
Hepatitis	0	0	1 (1.0)	1 (1.0)	1 (1.4)	1 (1.4)	2 (2.4)	1 (1.2)
Portal vein thrombosis	1 (1.4)	1 (1.4)	0	0	0	0	0	0
Investigations (Hepatic)								
ALT increased	11 (14.9)	3 (4.1)	5 (5.0)	0	7 (10.1)	3 (4.3)	8 (9.8)	2 (2.4)
AST increased	12 (16.2)	9 (12.2)	8 (7.9)	3 (3.0)	10 (14.5)	6 (8.7)	12 (14.6)	7 (8.5)
Blood alkaline phosphatase increased	6 (8.1)	3 (4.1)	7 (6.9)	1 (1.0)	1 (1.4)	0	1 (1.2)	0
Blood bilirubin increased	4 (5.4)	1 (1.4)	3 (3.0)	0	2 (2.9)	0	4 (4.9)	0
GGT increased	2 (2.7)	2 (2.7)	2 (2.0)	0	2 (2.9)	1 (1.4)	1 (1.2)	0

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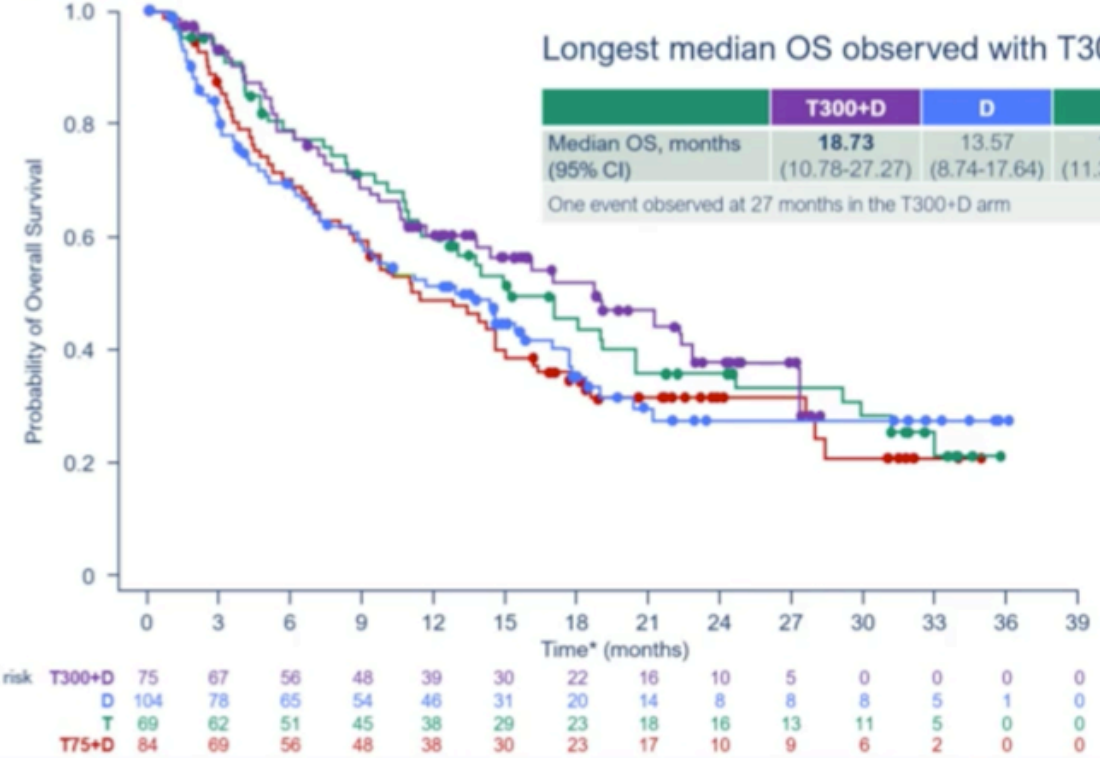
Robin Kate Kelley, et al. J Clin Oncol 38: 2020 (suppl; abstr 4508)

Optimierung der Immuntherapie bei fortgeschrittenem HCC – Tremelimumab+Durvalumab (Phase 1/2, extension)

Overall Survival



Longest median OS observed with T300+D

	T300+D	D	T	T75+D
Median OS, months (95% CI)	**18.73** (10.78-27.27)	13.57 (8.74-17.64)	15.11 (11.33-20.50)	11.30 (8.38-14.95)

One event observed at 27 months in the T300+D arm

	T300+D (n = 75)
Objective Response Rate[a] (95% CI), %	24.0 (14.9-35.3)
CR, n (%)	1 (1.3)
PR, n (%)	17 (22.7)
SD, n (%)	16 (21.3)
Disease Control Rate, n (%)	34 (45.3)
Median Duration of Response,[b] months	**NR**
Median Time to Response, months	1.86
PFS, months, median (95% CI)	2.17 (1.91-5.42)

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Optimierung der Immuntherapie bei fortgeschrittenem HCC – Y^{90}-Radioembolisation + Nivolumab

Überwiegend chinesische Patienten mit BCLC C (weit fortgeschritten!) bei HBV

Patient Characteristics (n=36)	No. (%)
Median Age (range)	64 (23.3-78.7)
ECOG 0	26 (72.2)
Male	29 (80.6)
Ethnicity Chinese Indian Other Asian	25 (69.4) 2 (5.6) 9 (25.0)
BCLC stage A B C	 2 (5.6)^ 11 (30.6) 23 (63.9)
Extrahepatic metastases	9 (25.0)
Macro-vascular invasion	14 (38.9)
Child-Pugh score A5 A6	 27 (75.0) 9 (25.0)

Patient Characteristics (n=36)c	No. (%)
Aetiology Hepatitis B Hepatitis C Hep B and C co-infection Non-viral	 23 (63.9) 3 (8.3) 1 (2.8) 9 (25.0)
Median number of liver nodules (range)	5 (1->20)
Median size of largest liver lesion (range) mm	80 (14.0-177.0)
Liver involvement by tumour > 50% No Yes	 26 (72.2) 10 (27.8)
Median ALBI score (range)	-2.4 (-3.0-1.6)
AFP score >400	18 (50.0)
Prior systemic therapy	5 (13.9)
Prior TACE/RFA	13 (36.1)

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A phase II open-label, single-center, nonrandomized trial of Y90-radioembolization in combination with nivolumab in Asian patients with advanced hepatocellular carcinoma: CA 209-678

David Tai, et al. J Clin Oncol 38: 2020 (suppl; abstr 4590)

Optimierung der Immuntherapie bei fortgeschrittenem HCC – Y^{90}-Radioembolisation + Nivolumab

Deutliche Steigerung der Regressionsraten radioembolisierter Targetläsionen (78%)

Table 2: Summary of Y-90 RE received

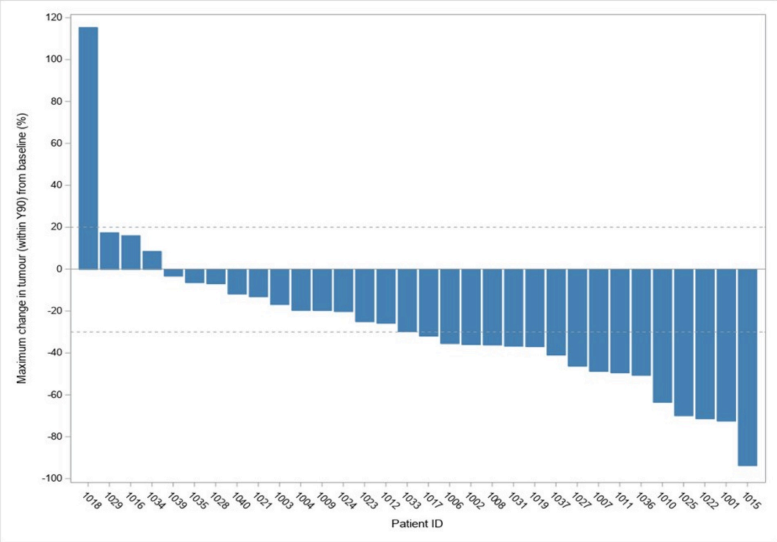

Figure 1: Maximum tumour regression within Y90-RE field

Table 3: Response rates

- With a median follow up of 16.4 months, ORR was 30.5% (95% CI 16.4 - 48.1). DCR was 61.1% (95% CI 43.5-76.9). (Table 3)
- Median PFS and OS were 4.6 months (95% CI 2.3 - 8.4) and 15.1 months (95% CI 7.8 - NE) respectively.
- Six- and 12-month PFS rates were 44.3% (95% CI 27.3 – 60.0%) and 26.1% (95% CI 11.2 - 43.8%) respectively.
- Eight out of 11 responders had not progressed at study cut-off.
- 78% of target lesions within Y90-RE field regressed (Figure 1)

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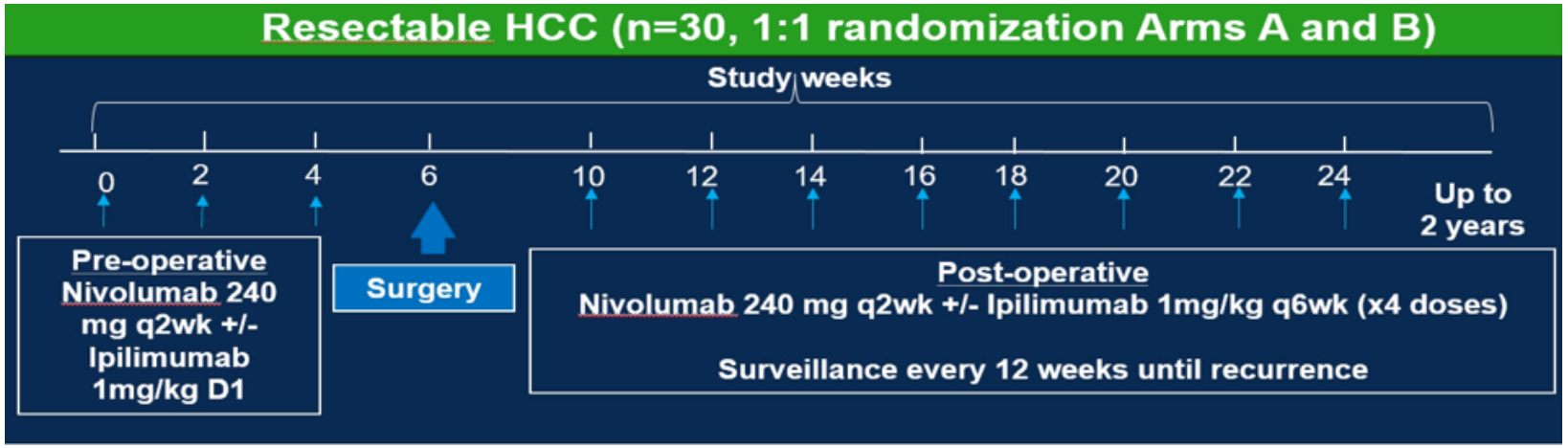
Perioperative Immuntherapie bei resektablem HCC – Nivolumab±Ipilimumab

Pathologische Ansprechrate von 40% nach 3-maliger Gabe



- 27 Patienten wurden randomisiert (A: Nivo n=13; B: Nivo+Ipi n=14), Op bei 21 Patienten
- Komplettes pathologisches Ansprechen: 5/27 (24%; Arm A:2, Arm B: 3)
- „Major“ pathologisches Ansprechen (Nekrose 50-99%) : 3/27 (16%; Arm A:1, Arm B: 2)

Final results of a randomized, open label, perioperative phase II study evaluating nivolumab alone or nivolumab plus ipilimumab in patients with resectable HCC.
Ahmed Omar Kaseb, et al. J Clin Oncol 38: 2020 (suppl; abstr 4599)

Personalisierte Therapie bei Cholangiokarzinom – Futibatinib bei FGF-Rezeptor2 Fusionen

Futibatinib: irreversibler FGFR1-3 Inhibitor

- iCCA is molecularly heterogeneous disease with nearly 50% of tumors harboring an actionable alteration[5]
- Approximately ~15% of iCCA tumors contain *FGFR2* fusions;[6,7] therefore, this pathway is being investigated as a therapy option for patients with *FGFR* alterations[8,9]

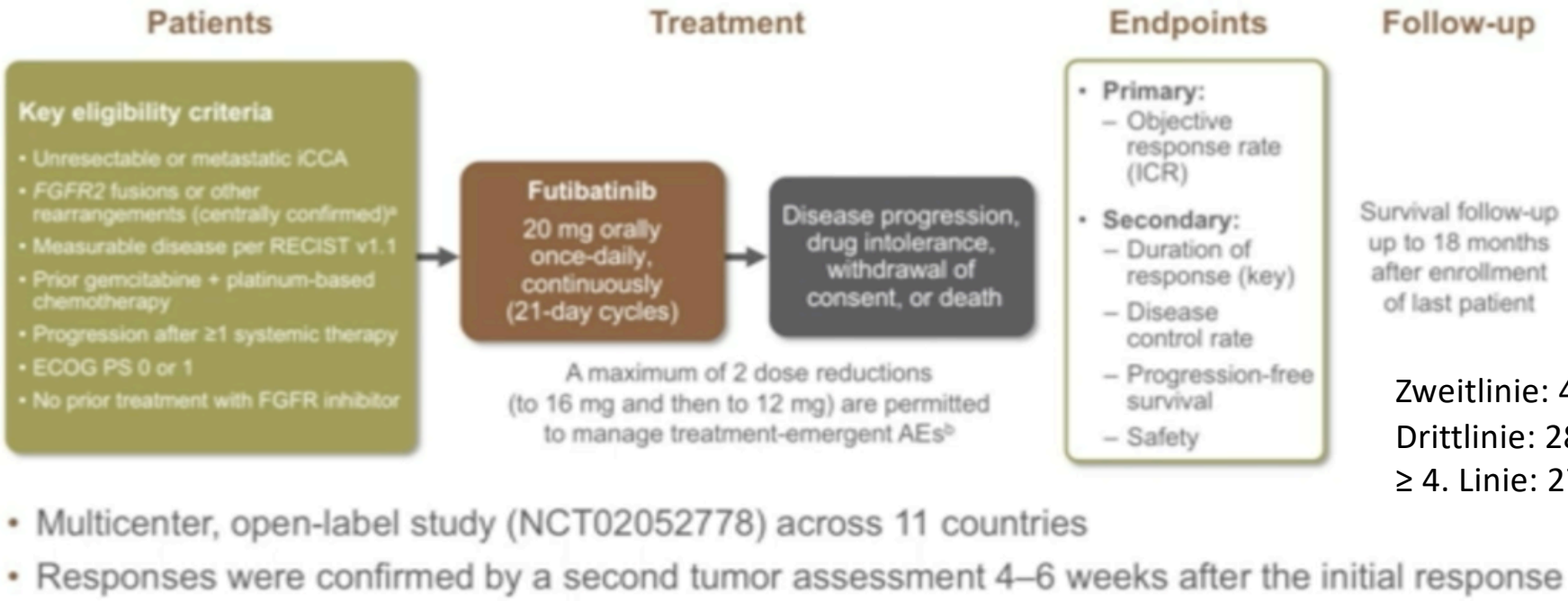
	Drug name	Inhibitory MoA	Clinical trial phase (number)	Tumor type	Approved indication
FGFR1–3	Debio 1347[10]	Selective	1/2 (NCT01948297)	Solid tumors	
	Derazantinib[11]	Multikinase	1/2 (NCT03230318)	iCCA	
	Pemigatinib[12]	Selective	3 (NCT02924376)	CCA	Second-line advanced/metastatic CCA with *FGFR2* alterations
FGFR1–4	Erdafitinib[13]	Selective	2 (NCT04083976)	Solid tumors	Second-line advanced/metastatic urothelial carcinoma with *FGFR2,3* alterations
	Futibatinib[14]	Selective, irreversible	1/2 (NCT02052778); 3 (NCT04093362)	Solid tumors, breast; iCCA	
	Infigratinib[15]	Selective	1/2 (NCT04228042); 2 (NCT04233567, NCT02150967); 3 (NCT03773302, NCT04233567)	Upper tract urothelial; CCA, solid tumors; CCA, urothelial carcinoma	

FGFR, fibroblast growth factor receptor; iCCA, intrahepatic cholangiocarcinoma; MoA, mechanism of action.

FOENIX-CCA2: A phase II, open-label, multicenter study of futibatinib in patients (pts) with intrahepatic cholangiocarcinoma (iCCA) harboring *FGFR2* gene fusions or other rearrangements.
Lipika Goyal, et al. J Clin Oncol 38: 2020 (suppl; abstr 108)

Personalisierte Therapie bei Cholangiokarzinom – Futibatinib bei FGF-Rezeptor2 Fusionen

Phase 2-Studie nach GemCis-Versagen



Zweitlinie: 45%
Drittlinie: 28%
≥ 4. Linie: 27%

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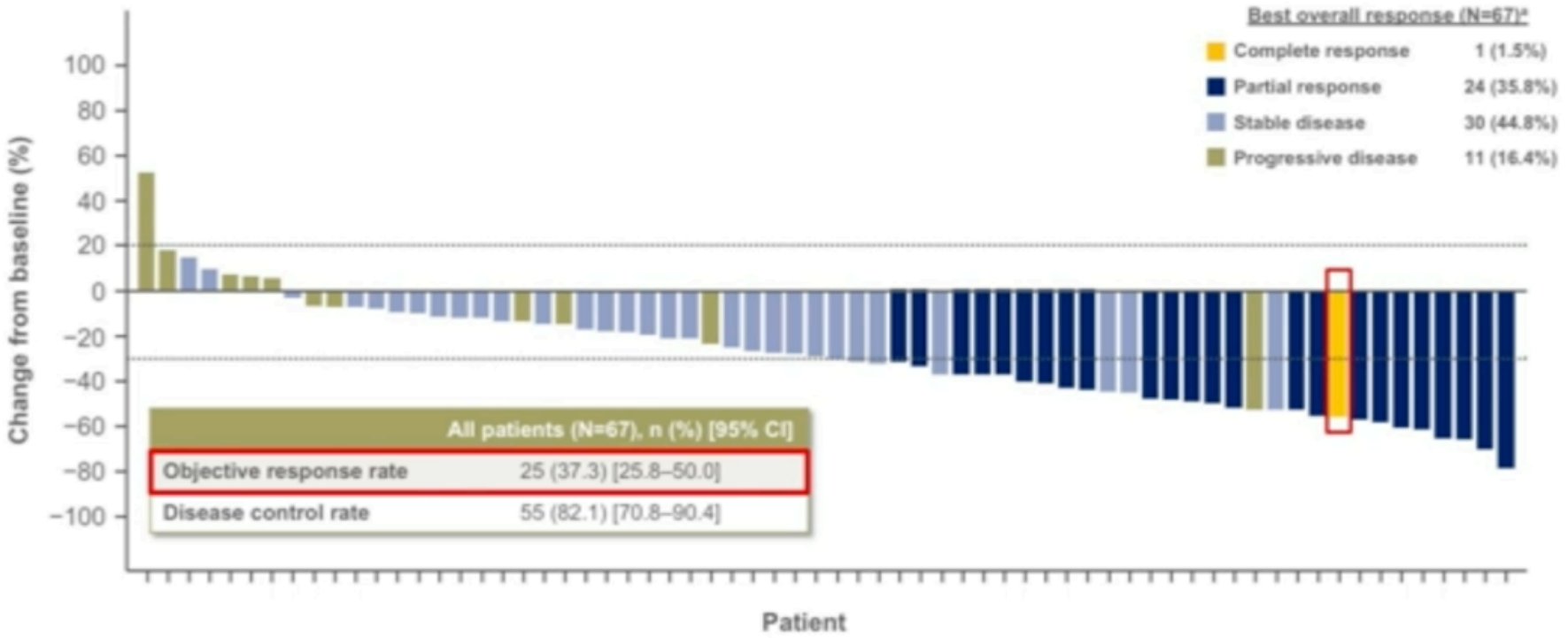
Personalisierte Therapie bei Cholangiokarzinom – Futibatinib bei FGF-Rezeptor2 Fusionen

Phase 2-Studie nach GemCis-Versagen: PR 37%



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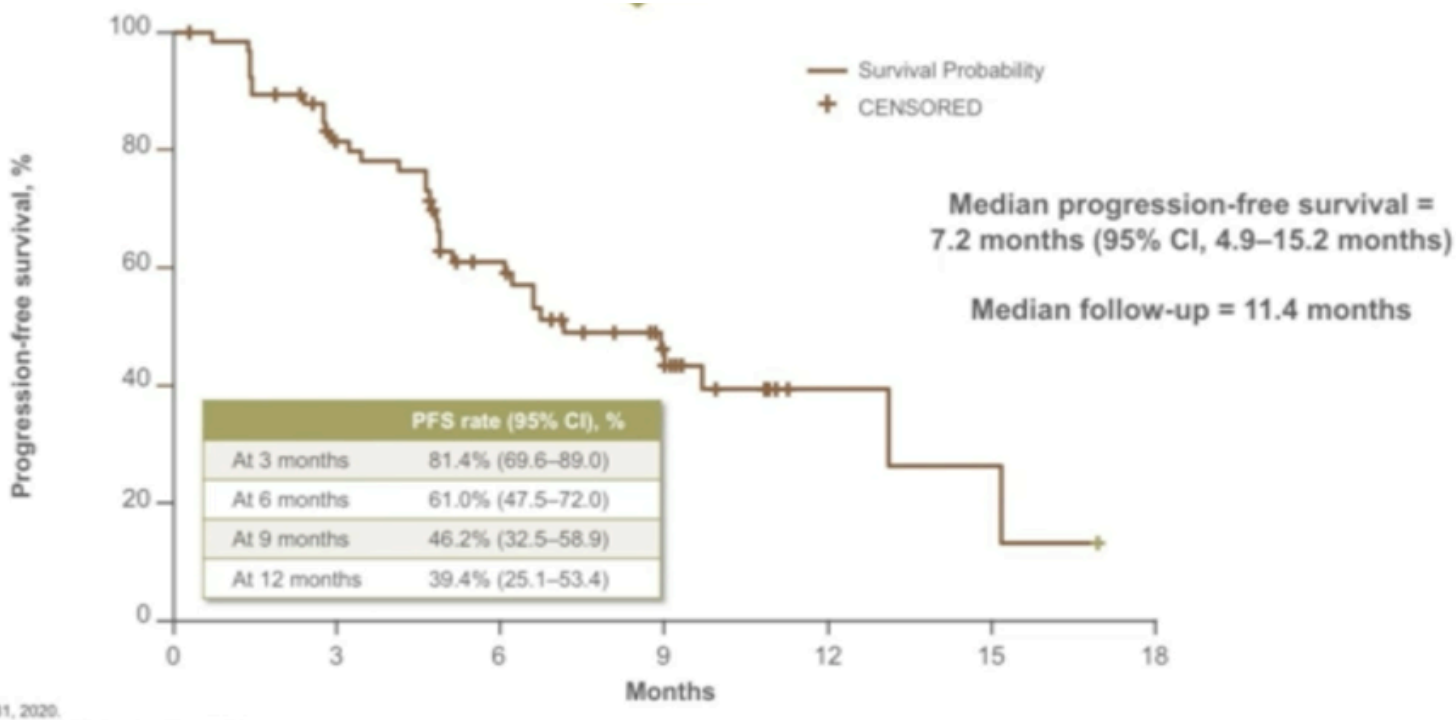
Personalisierte Therapie bei Cholangiokarzinom – Futibatinib bei FGF-Rezeptor2 Fusionen

Phase 2-Studie nach GemCis-Versagen: PFS 7,2 Mon.



Data cutoff March 31, 2020.
CI, confidence interval; PFS, progression-free survival.
*PFS is calculated from the date of the first dose of the study drug to the date of first objective evidence of disease progression or date of death due to any cause, whichever occurs first.

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Personalisierte Therapie bei Cholangiokarzinom – Futibatinib bei FGF-Rezeptor2 Fusionen

Phase 2-Studie nach GemCis-Versagen: gute Verträglichkeit

	All patients[a] (N=67), n (%)			
MedDRA (v18.1) preferred term	Grade 1	Grade 2	Grade 3	Total
Patients with at least one AE	6 (9.0)	23 (34.3)	38 (56.7)	67 (100)
Hyperphosphatemia	4 (6.0)	32 (47.8)	18 (26.9)	54 (80.6)
Diarrhea	18 (26.9)	7 (10.4)	0	25 (37.3)
Dry mouth	19 (28.4)	3 (4.5)	0	22 (32.8)
Alopecia	15 (22.4)	5 (7.5)	0	20 (29.9)
Dry skin	13 (19.4)	5 (7.5)	0	18 (26.9)
Fatigue	10 (14.9)	2 (3.0)	4 (6.0)	16 (23.9)
Aspartate aminotransferase increased	6 (9.0)	1 (1.5)	6 (9.0)	13 (19.4)
Dry eye	10 (14.9)	2 (3.0)	1 (1.5)	13 (19.4)
Dysgeusia	9 (13.4)	4 (6.0)	0	13 (19.4)
Alanine aminotransferase increased	3 (4.5)	5 (7.5)	4 (6.0)	12 (17.9)
Constipation	8 (11.9)	4 (6.0)	0	12 (17.9)
Palmar-plantar erythrodysesthesia syndrome	4 (6.0)	7 (10.4)	1 (1.5)	12 (17.9)
Nail disorder	8 (11.9)	3 (4.5)	0	11 (16.4)
Stomatitis	6 (9.0)	3 (4.5)	2 (3.0)	11 (16.4)

Data cutoff March 31, 2020.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities.
[a]The highest grade event was used for patients with ≥2 AEs in the same system organ class (or with the same preferred term) with different CTCAE grades.

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