Systemic treatment of HCC (and the age of immune checkpoint inhibitors….)

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Potential conflicts of Interest

E. De Toni has served as a paid consultant for AstraZeneca, Bayer, BMS, EISAI, Eli Lilly & Co, Pfizer, IPSE, and Roche.

He has received reimbursement of meeting attendance fees and travel expenses from Arqule, BMS, Bayer, and Celsion

and lecture honoraria from BMS and Falk.

He has received third-party funding for scientific research from Arqule, AstraZeneca, BMS, Bayer, Eli Lilly, and Roche.

Agenda

- Introduction: HCC epidemiology and therapeutic stratification
- Evolution of systemic treatment of HCC: TKI and VEGFi
- One comment about SIRT
- Checkpoint inhibitors in the treatment of advanced HCC
- Perspectives: Use them early?

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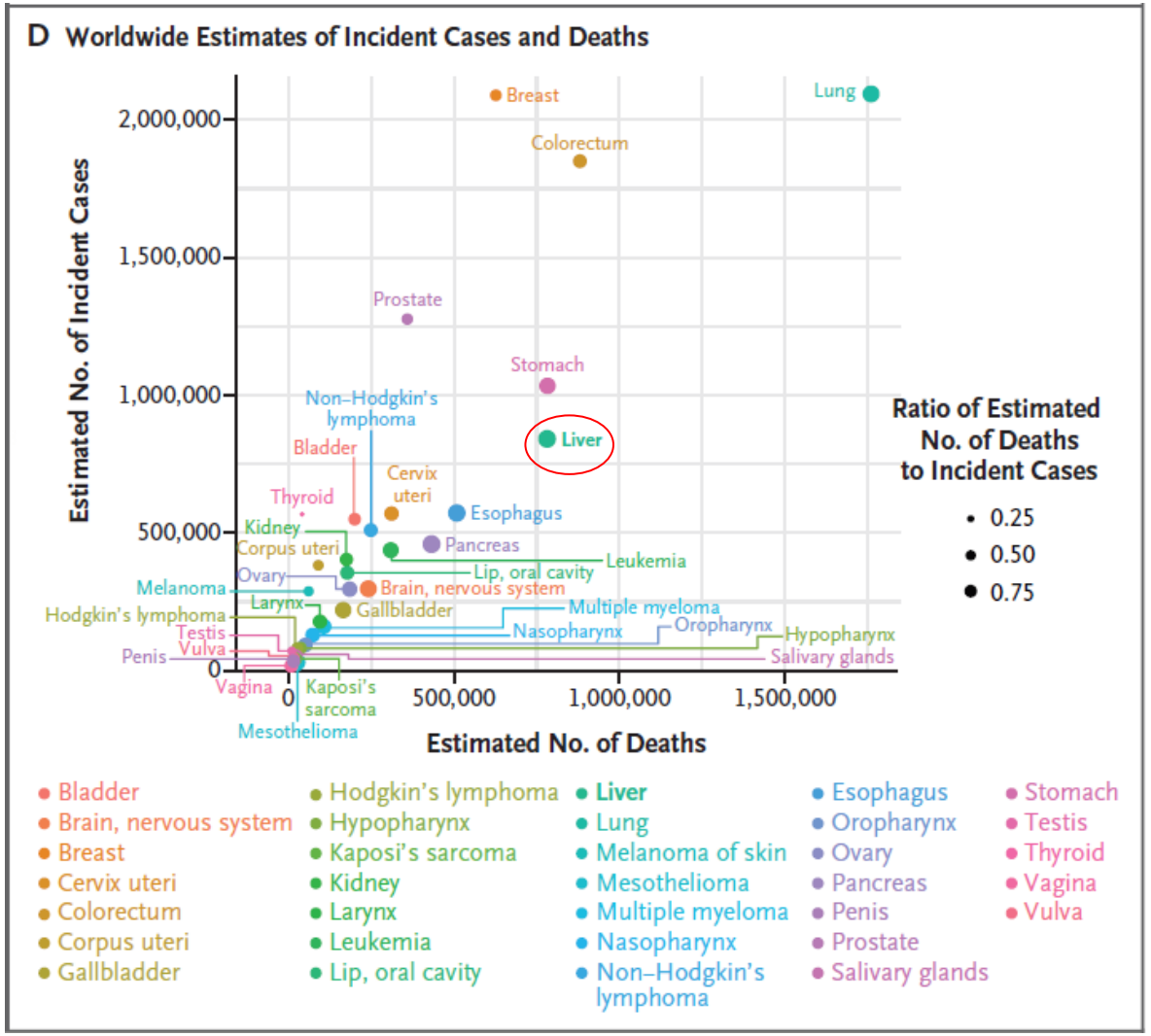
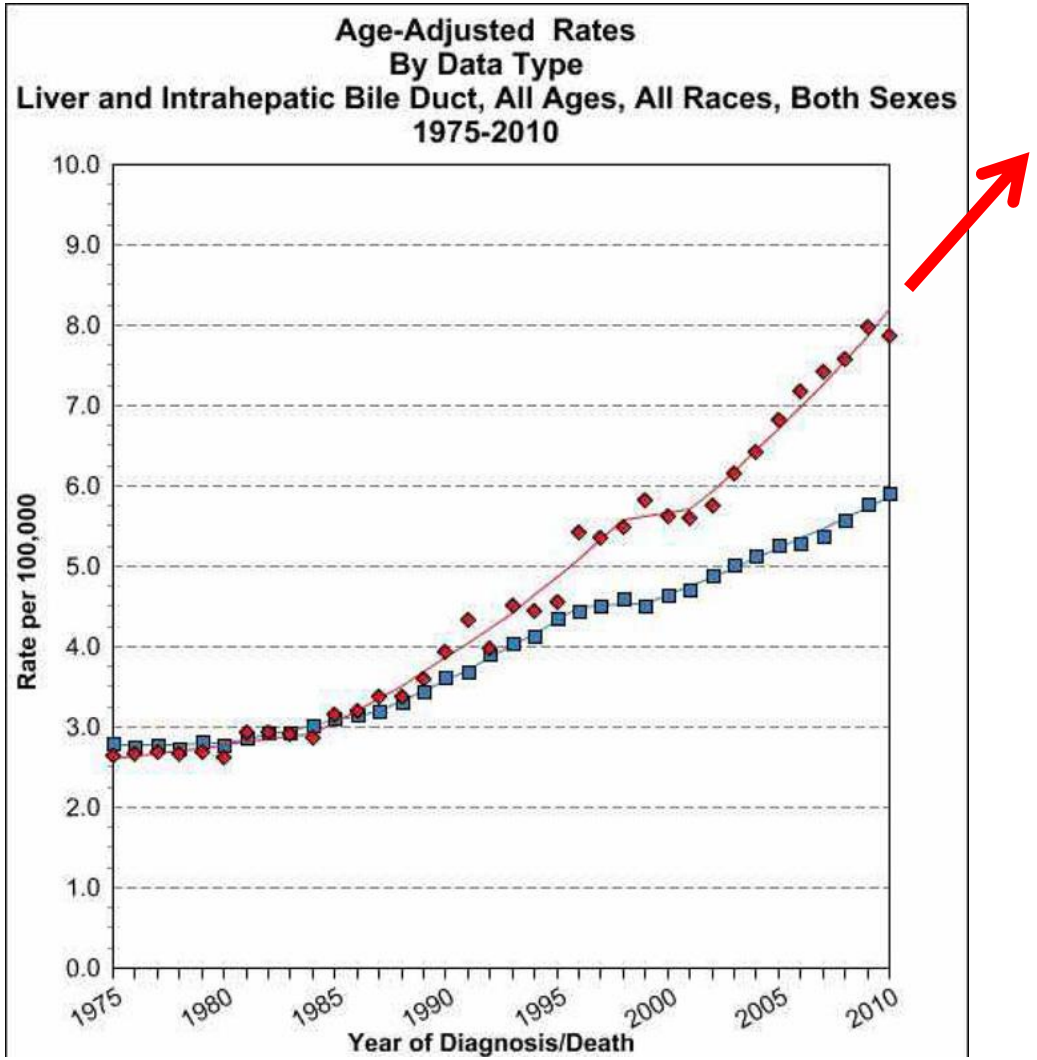
Introduction: Epidemiology of HCC



6th most common tumor (incidence)

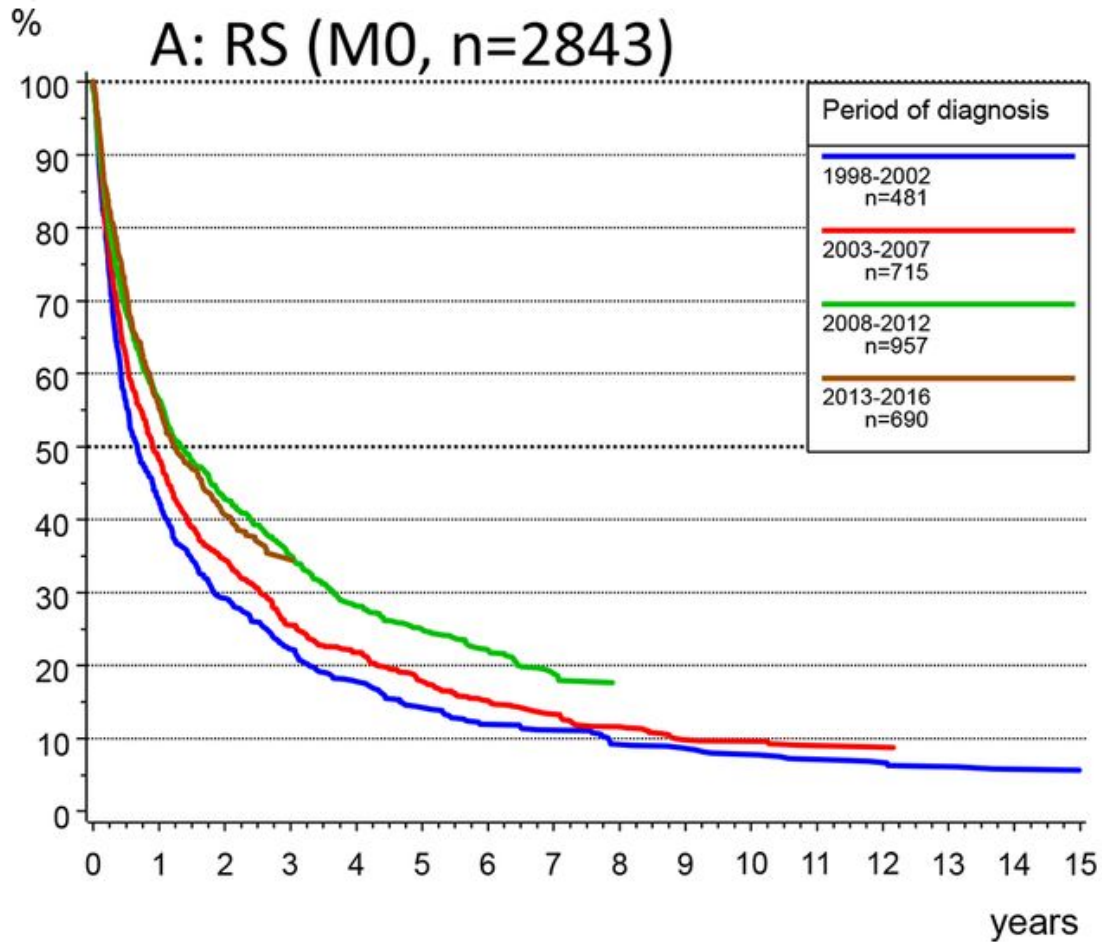
4th most common cause of cancer-related death

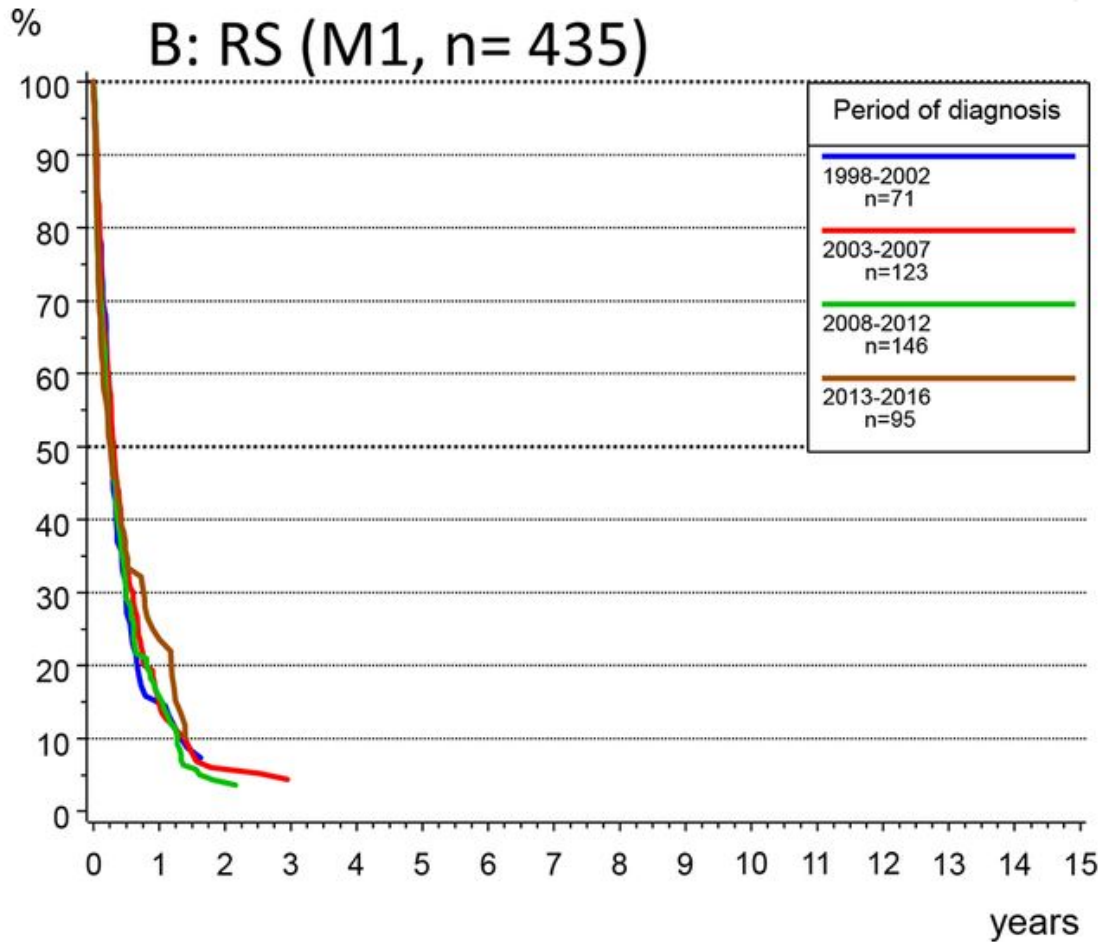
Villanueva N England J Med 2019: 380



El-Serag HB, *Gastrotenterology* 2012; 142, Myers RP, *Can J. Gastroenerol Hepatol* 2014

HCC: Survival according to M-Status



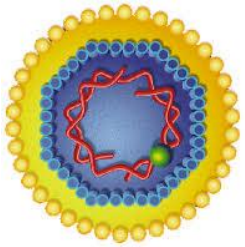


Median Overall survival: doubling from 6 (1998–2002) to 12 Months (2013–2016)

De Toni EN, et al. Gut 2019;0:1–9. doi:10.1136/gutjnl-2018-318193

Incidence and risk factors of HCC

90% of HCC in the context of a liver cirrhosis/chronic liver disease AND the first cause of death in patients with liver cirrhosis



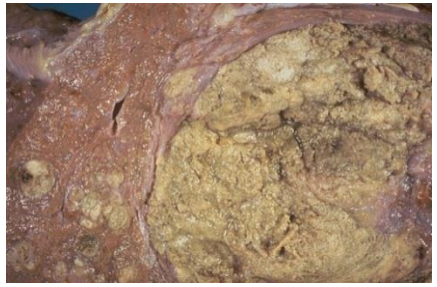
HCV 60-70%

HBV 10-15%

20%

alcohol

Liver cirrhosis



HCC

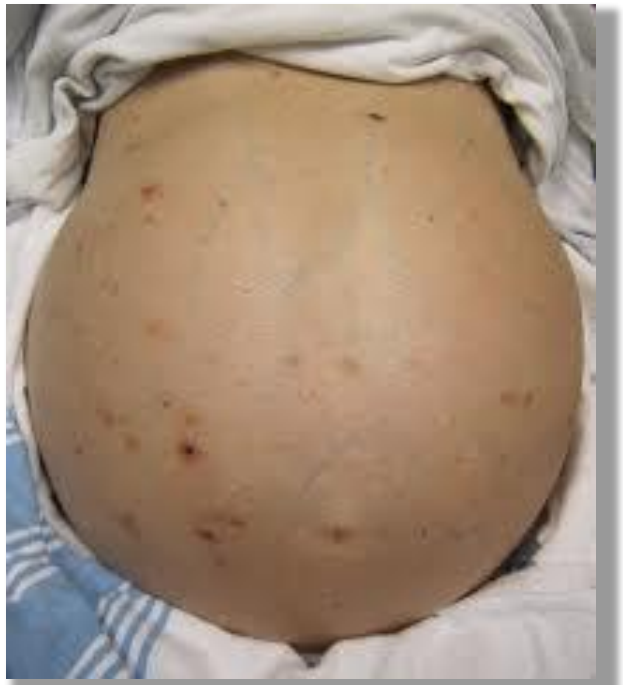
NASH **10%**

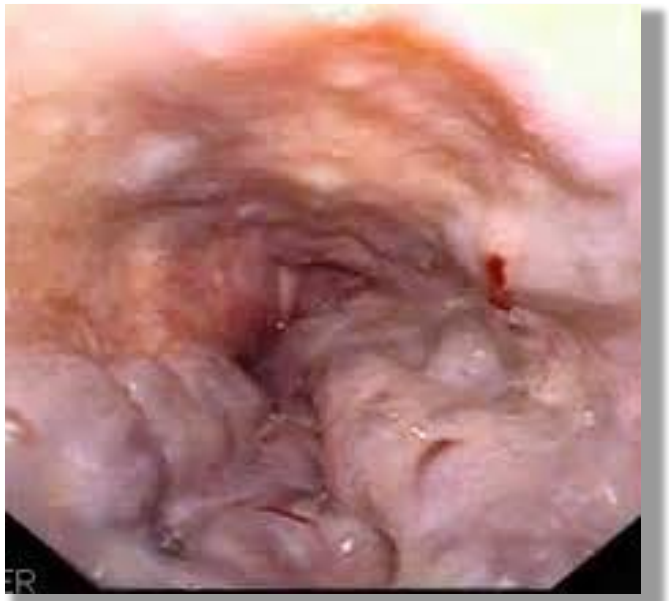
RELEVANCE

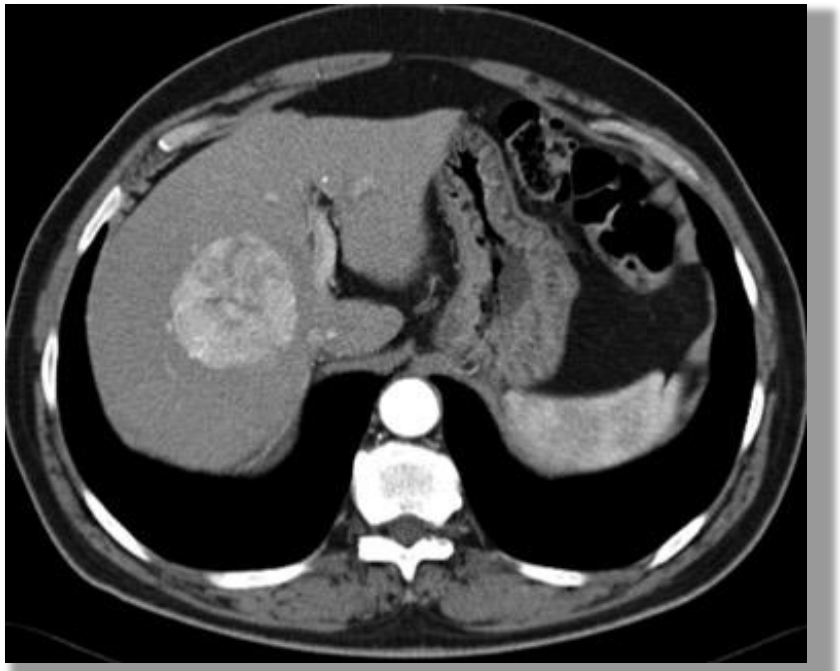
- Surveillance!
- Difficult to treat

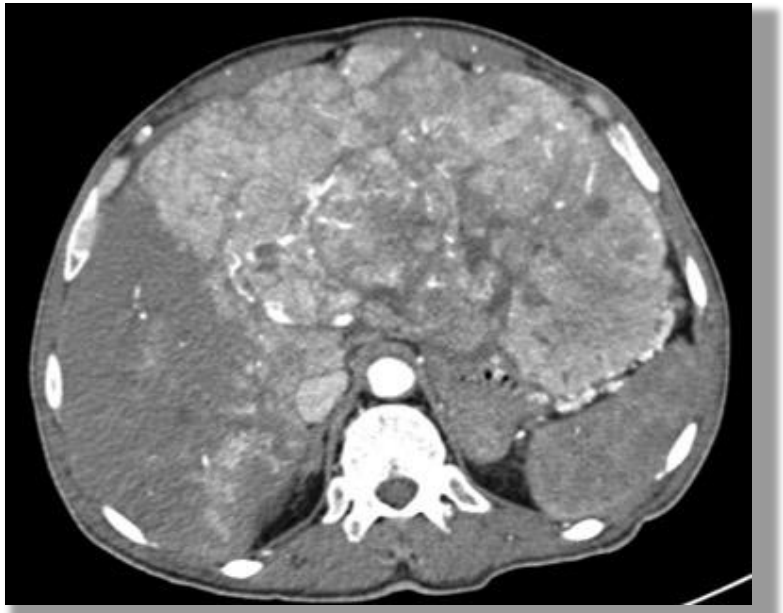
Llovet et al., *Nat Rev Dis Primers,* 2016 Apr 14;2:16018

Comorbidity and HCC

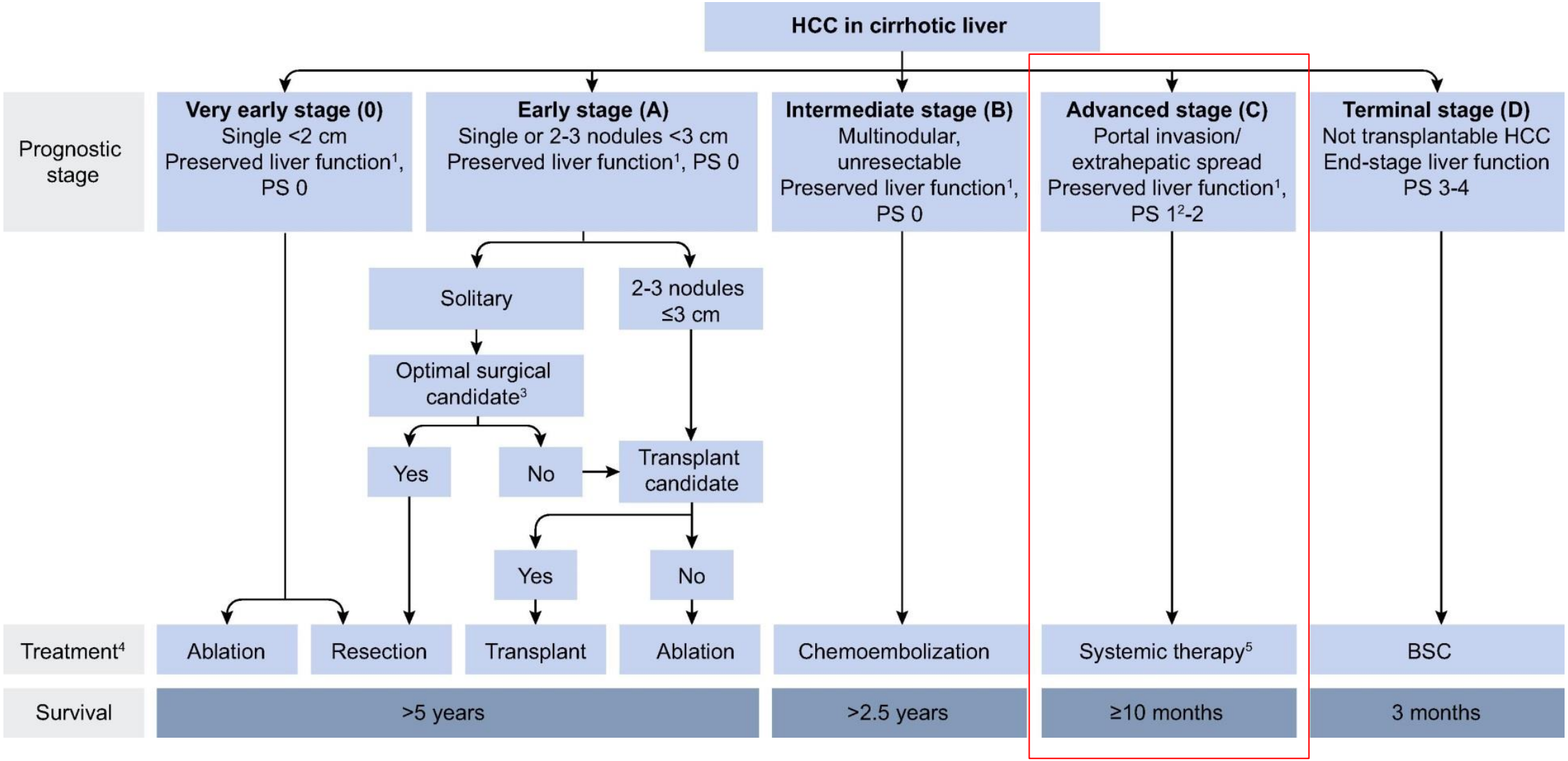








THE BCLC (Barcelona Clinic for Liver Cancer) ALGORYTHM FOR THE TREATMENT OF HCC – AN EVIDENCE-BASED SYSTEM



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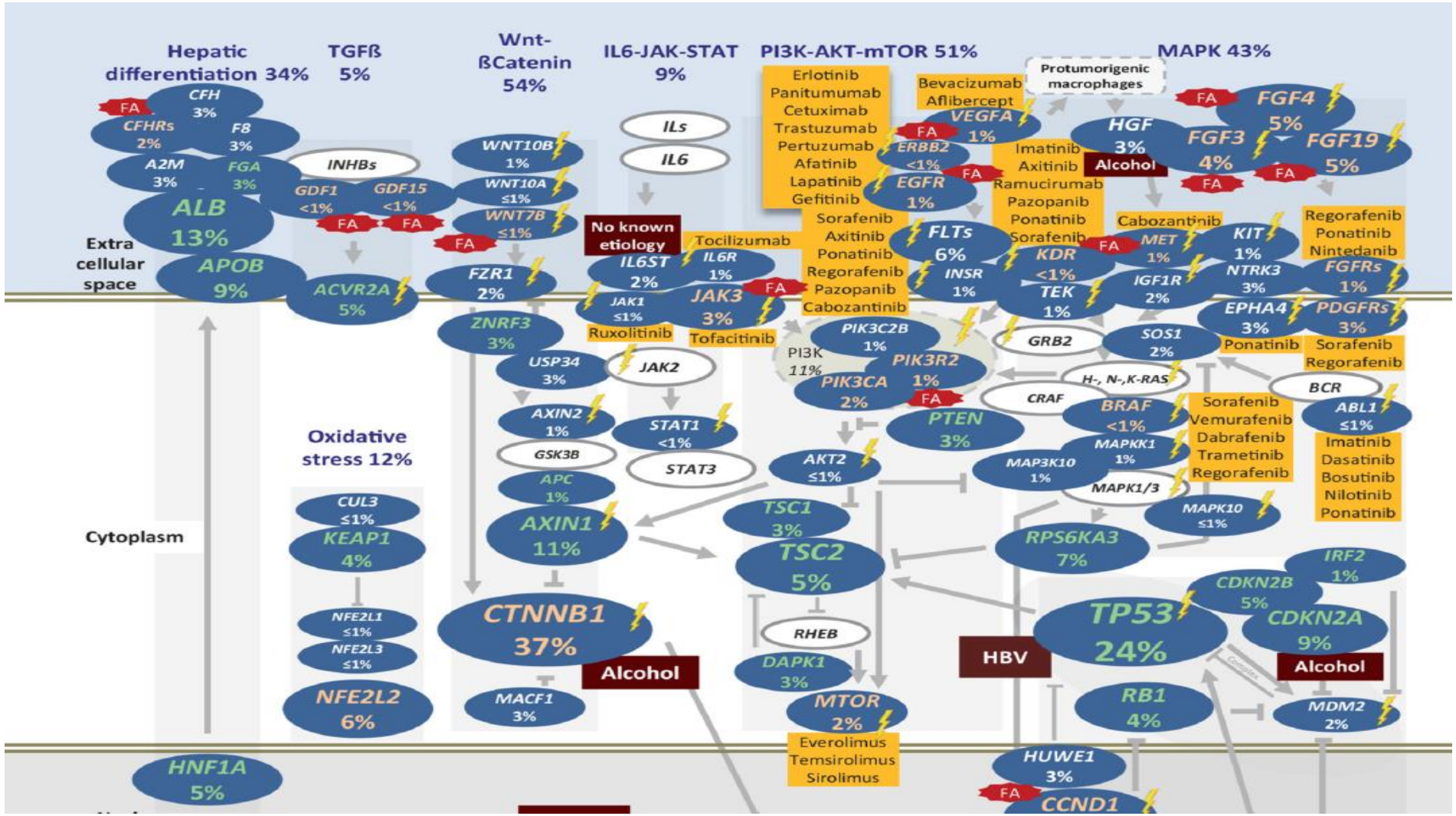
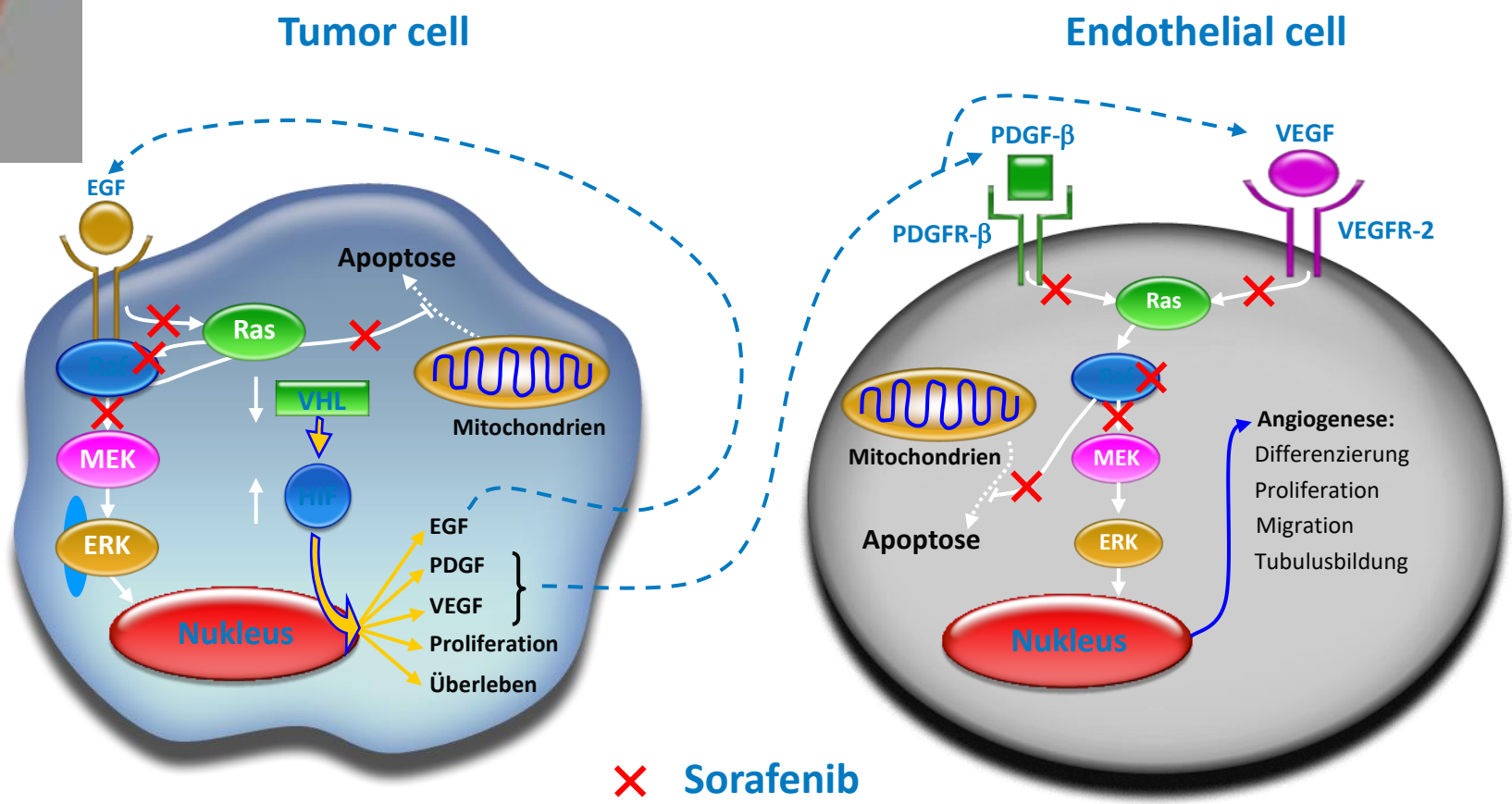
BIOLOGY AND POTENTIAL THERAPEUTIC TARGETS OF HCC

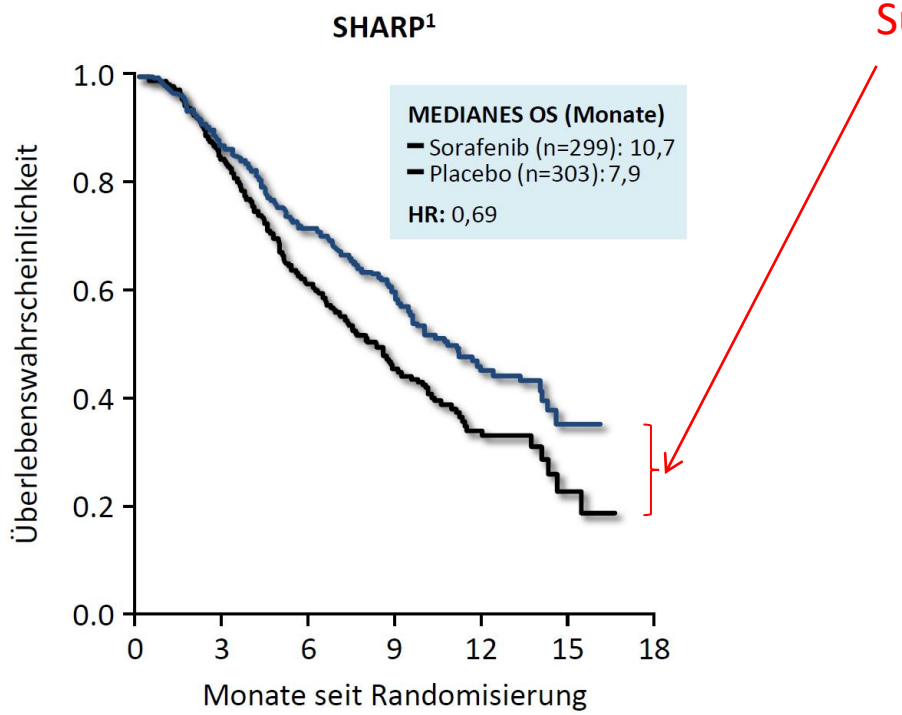


Sorafenib: Mechanisms of action



Adapted from Wilhelm et al, *Cancer Res* 2004;64

Sorafenib



Survival advantage: 3 Months

Llovet et al., *N Engl. J Med*. 2008;359:378

Sorafenib: Adverse events

Drug-related AEs

% of *n*	Child-Pugh A (*n*=1968)
Diarrhea	28.3
HFSR	31.8
Fatigue	15.8
Rash/desquamation	12.1
Anorexia	10.6
Hypertension	10.9
Alopecia	8.7
Nausea	5.4
Pain, abdomen NOS	3.2

64%
Dosis reduction

44%
Discontinuation

Pressiani T *Ann Oncol*. 2013;24 ; Marrero J et al. ASCO 2013 Abstract 4126

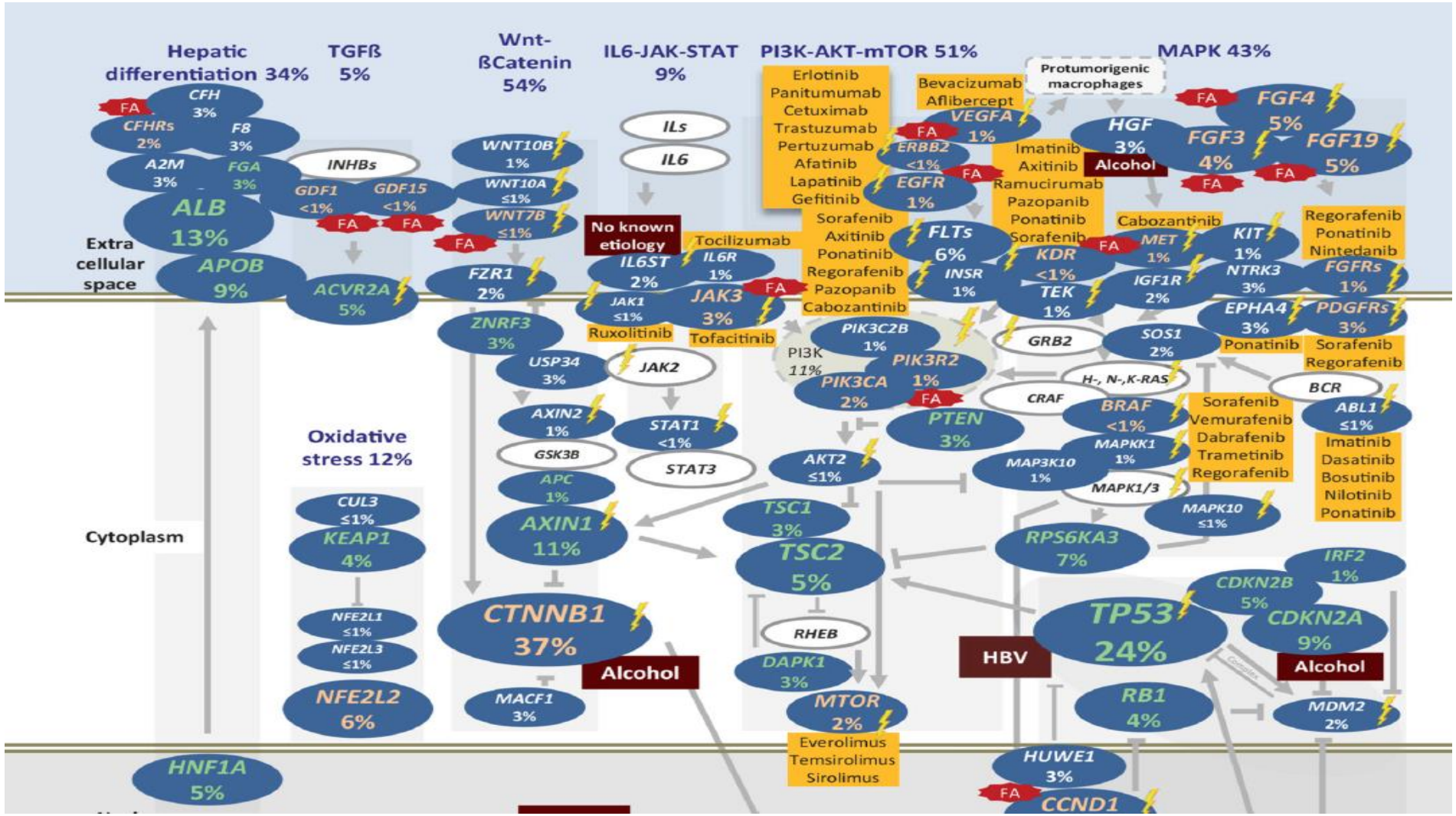
Sorafenib in the practice

- Child-Pugh A (Child-Pugh 7-8?)
- Initial Dosis 400 mg 1-0-1

  400 mg x 1 in Child-Pugh 7-8.
- Prescribe Loperamid – Frequent BP-Controls and application of Urea cream

- Staging: 8-10 W
- Discontinue
  - intolerance
  - **radiological progression**
- **Not upon AFP** increase

BIOLOGY AND POTENTIAL THERAPEUTIC TARGETS OF HCC



Not a triumphal march: 2007-2017: 1 approved substance!

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	

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… but if you persist…

2016-2018: 7 agents!

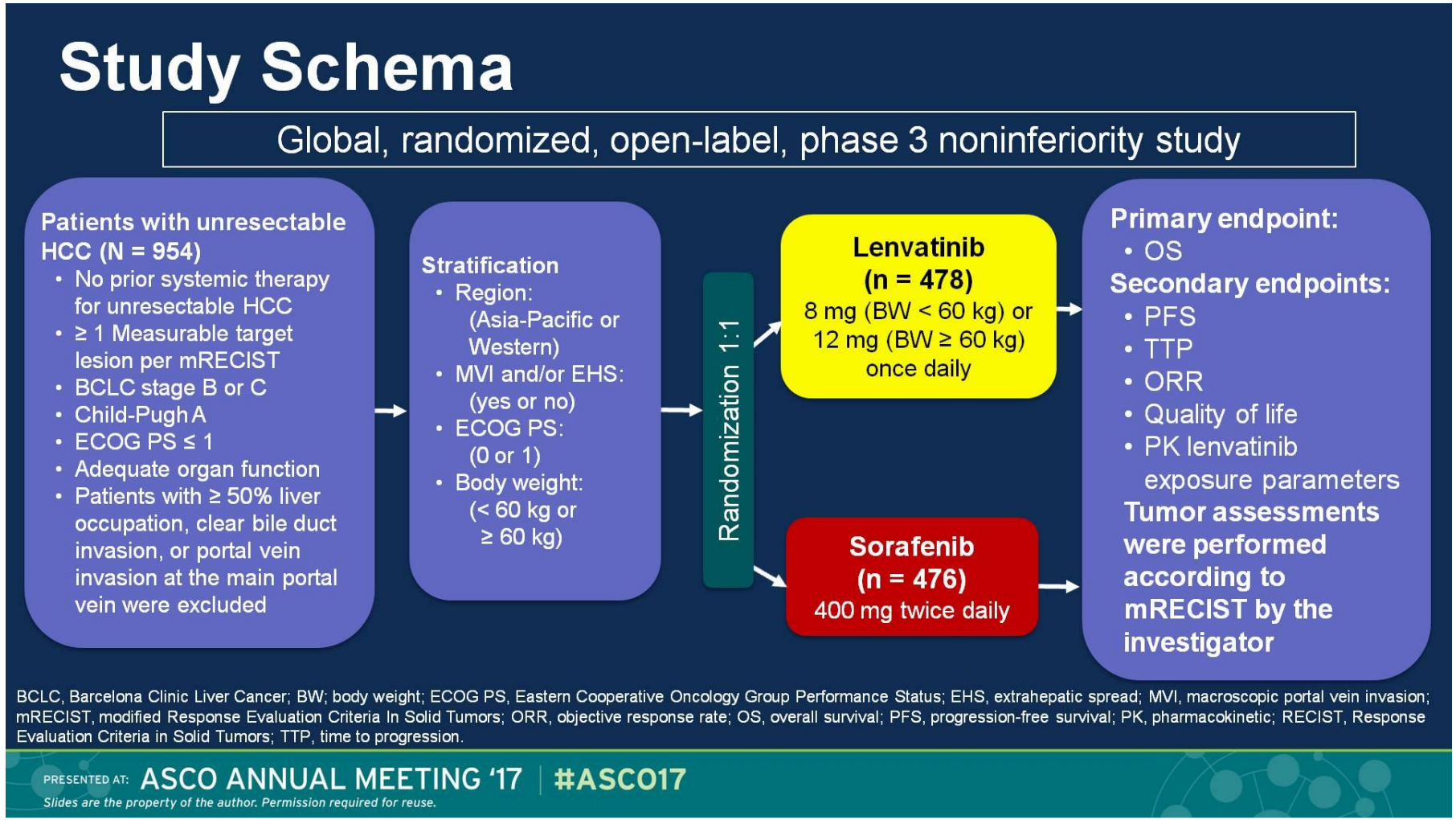
Systemic treatment of HCC

FIRST LINE

Sorafenib

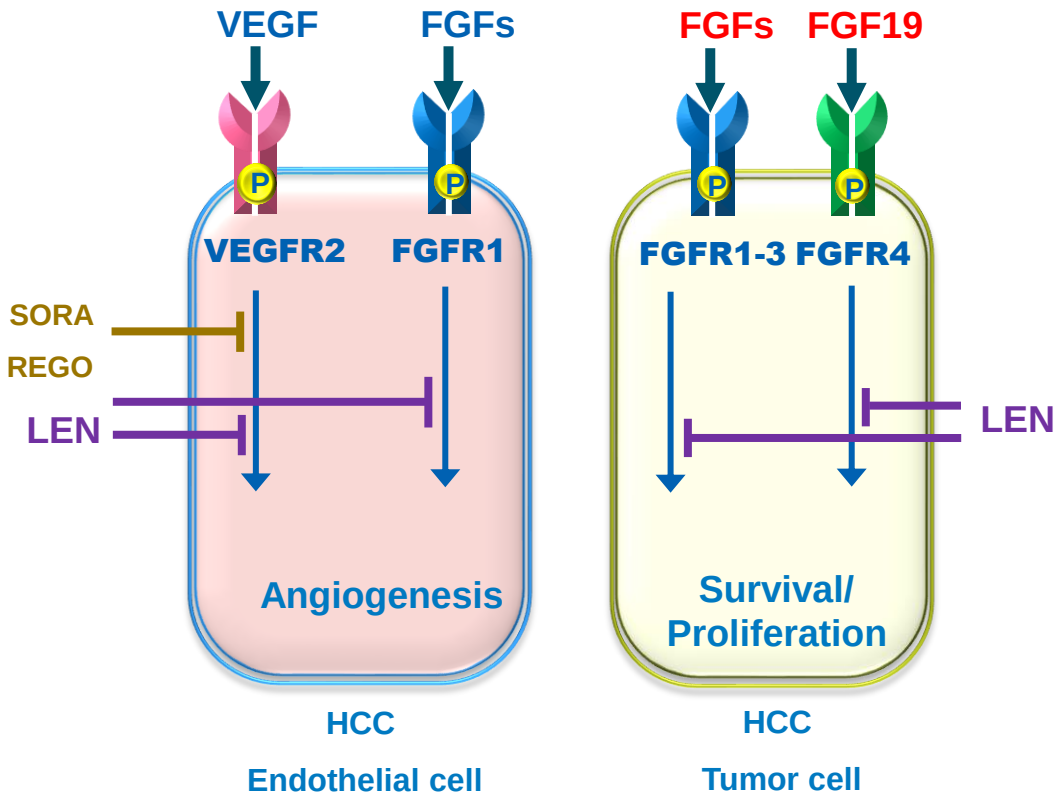
SECOND LINE

Lenvatinib beim HCC, 1. Linie



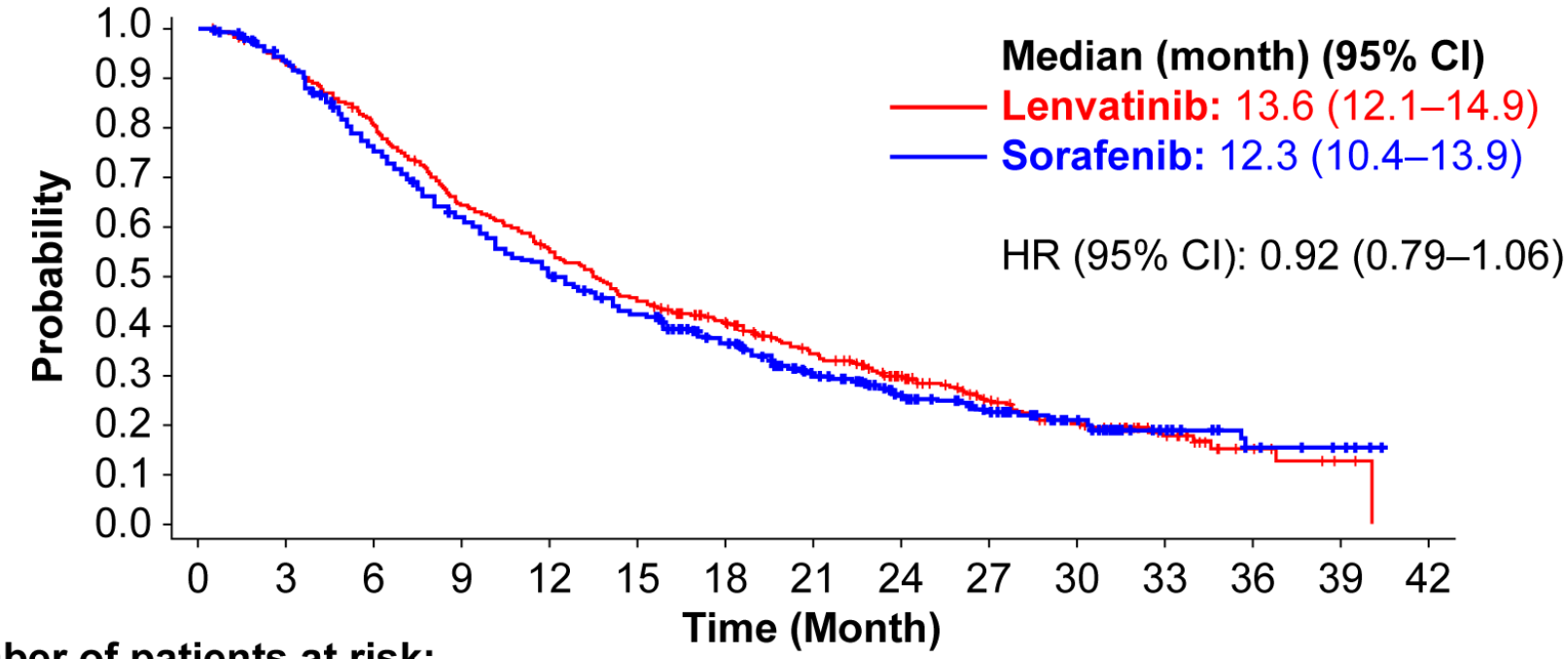
Dual Inhibition of VEGF- und FGF-Signaling

TKR	IC_{50} (nmol/L)	
	Sorafenib	Lenvatinib
VEGFR-1	21	4,7
VEGFR-2	21	3
VEGFR-3	16	2,3
FGFR1	340	61
FGFR2	150	27
FGFR3	340	52
FGFR4	3400	43
PDGFRα	1,6	29
PDGFRβ	27	160
c-KIT	140	85
RET	15	6,4



Tohyama O et al. J Thyroid Res. 2014;2014:638747.

REFLECT Study: primary endpoint reached



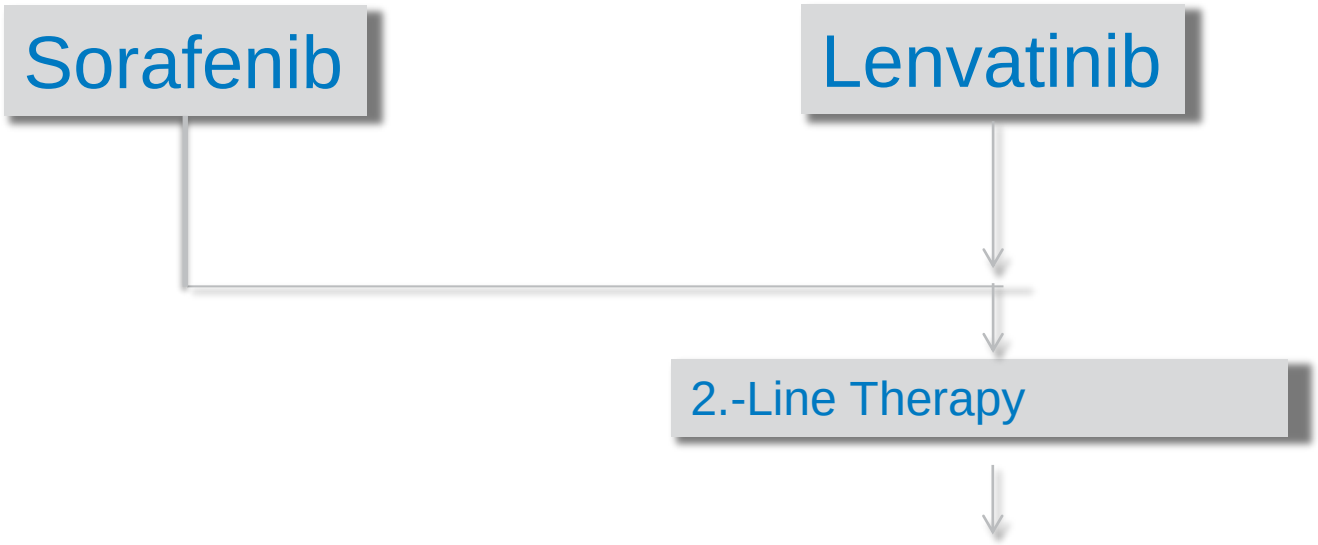
Number of patients at risk:

Lenvatinib	478	436	374	297	253	207	178	140	102	67	40	21	8	2	0
Sorafenib	476	440	348	282	230	192	156	116	83	57	33	16	8	4	0

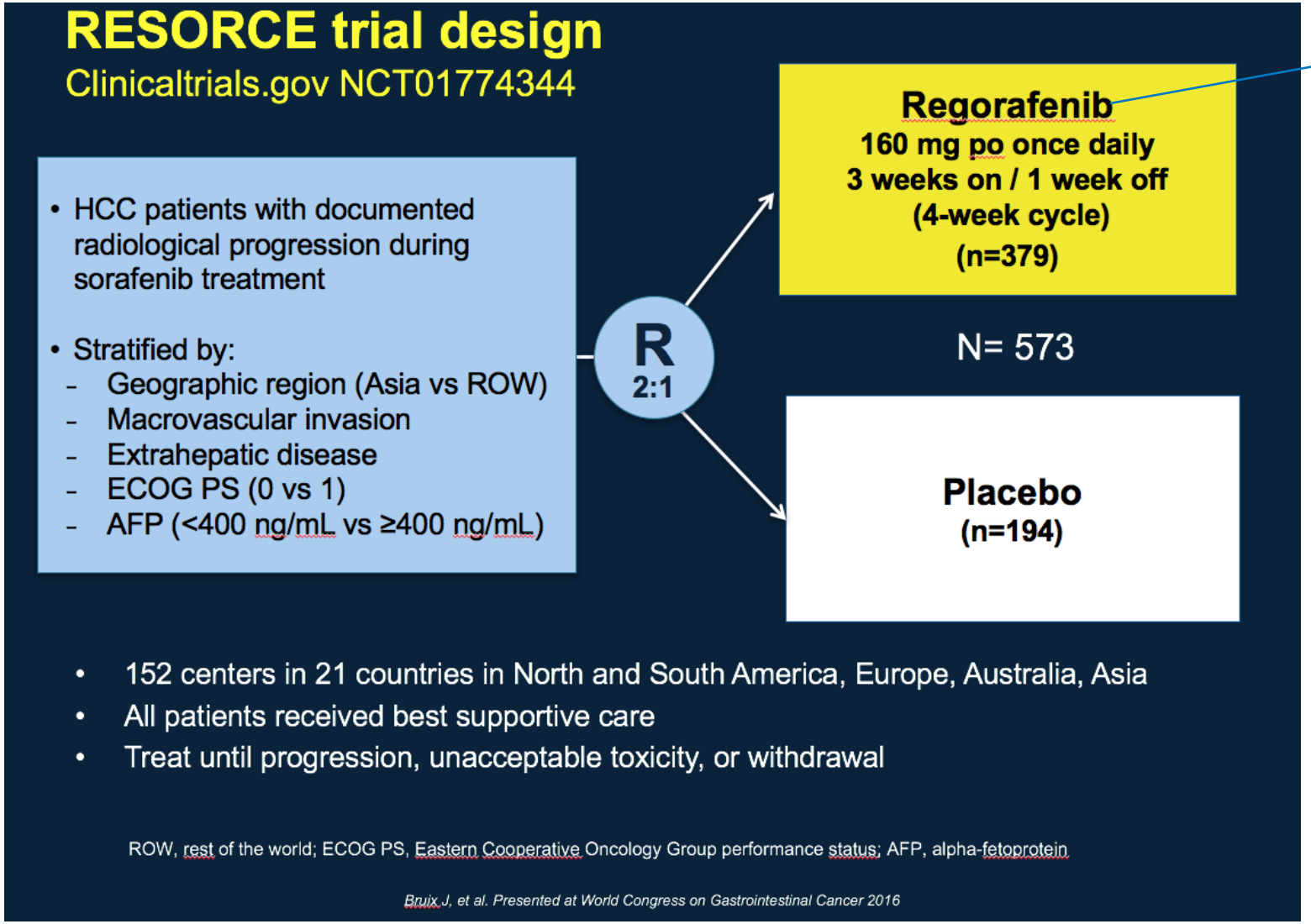
Systemic treatment of HCC

FIRST LINE

SECOND LINE



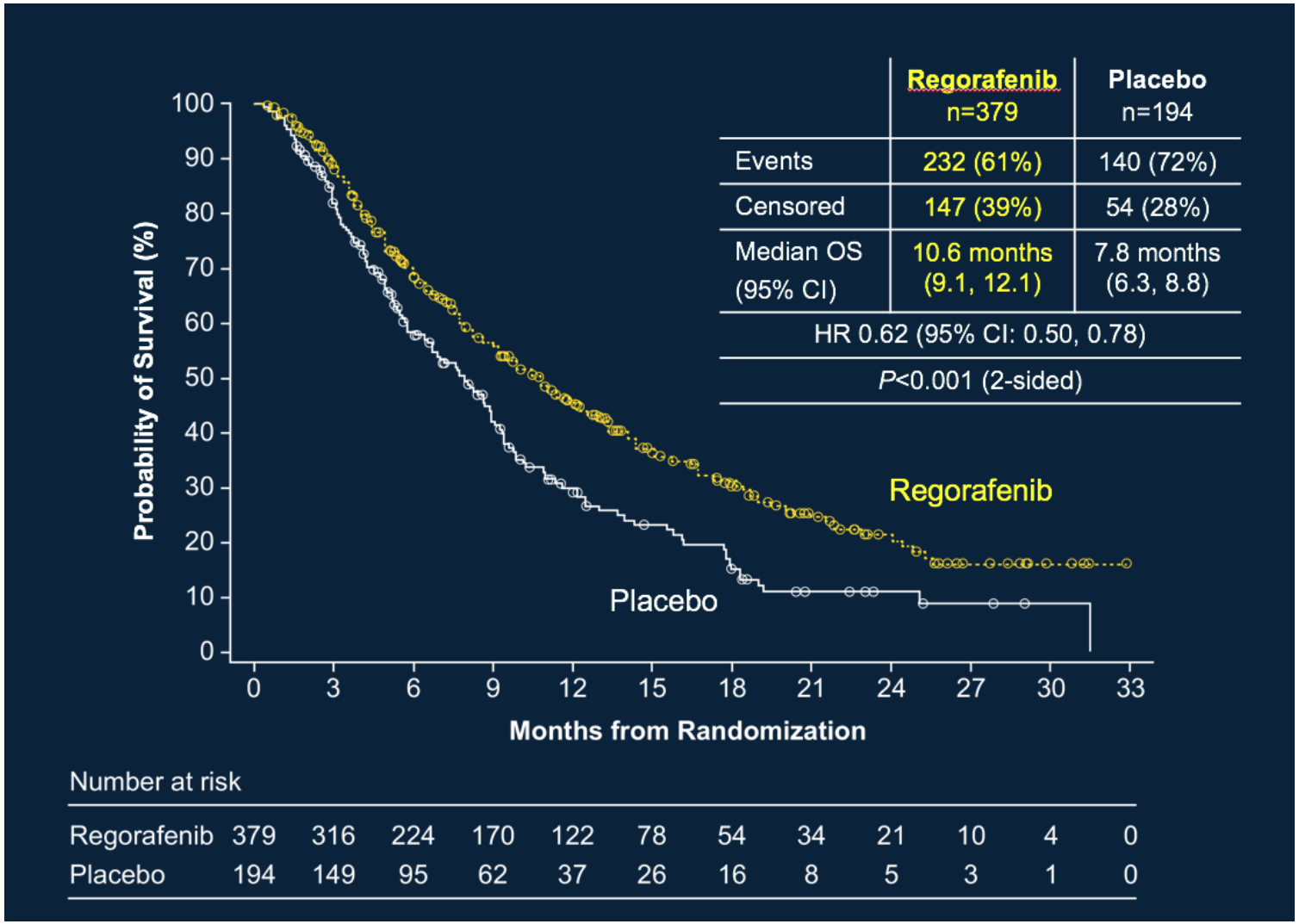
Regorafenib: second line



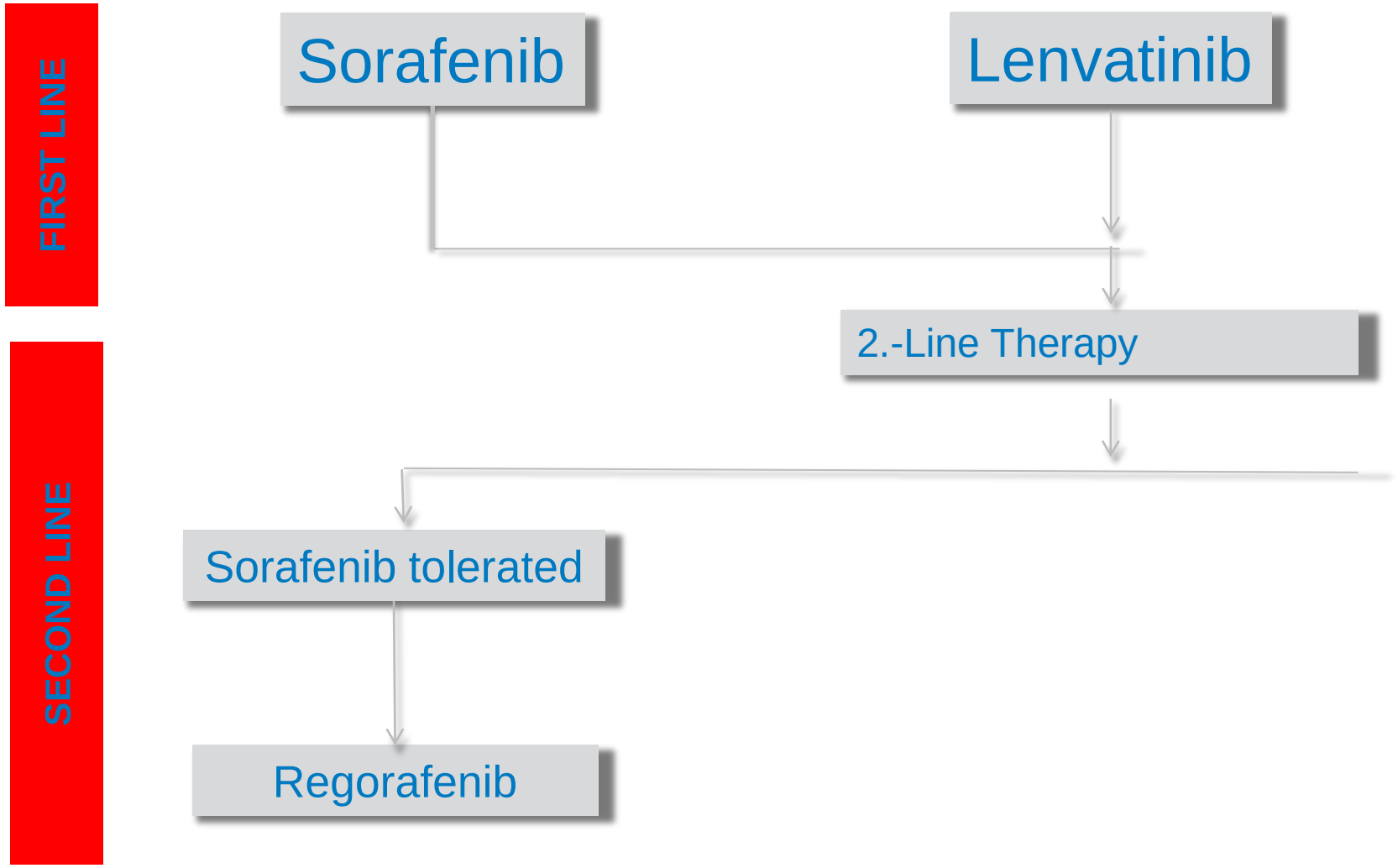
More powerful form of Sorafenib

Bruix J, et al. WCGI 2016

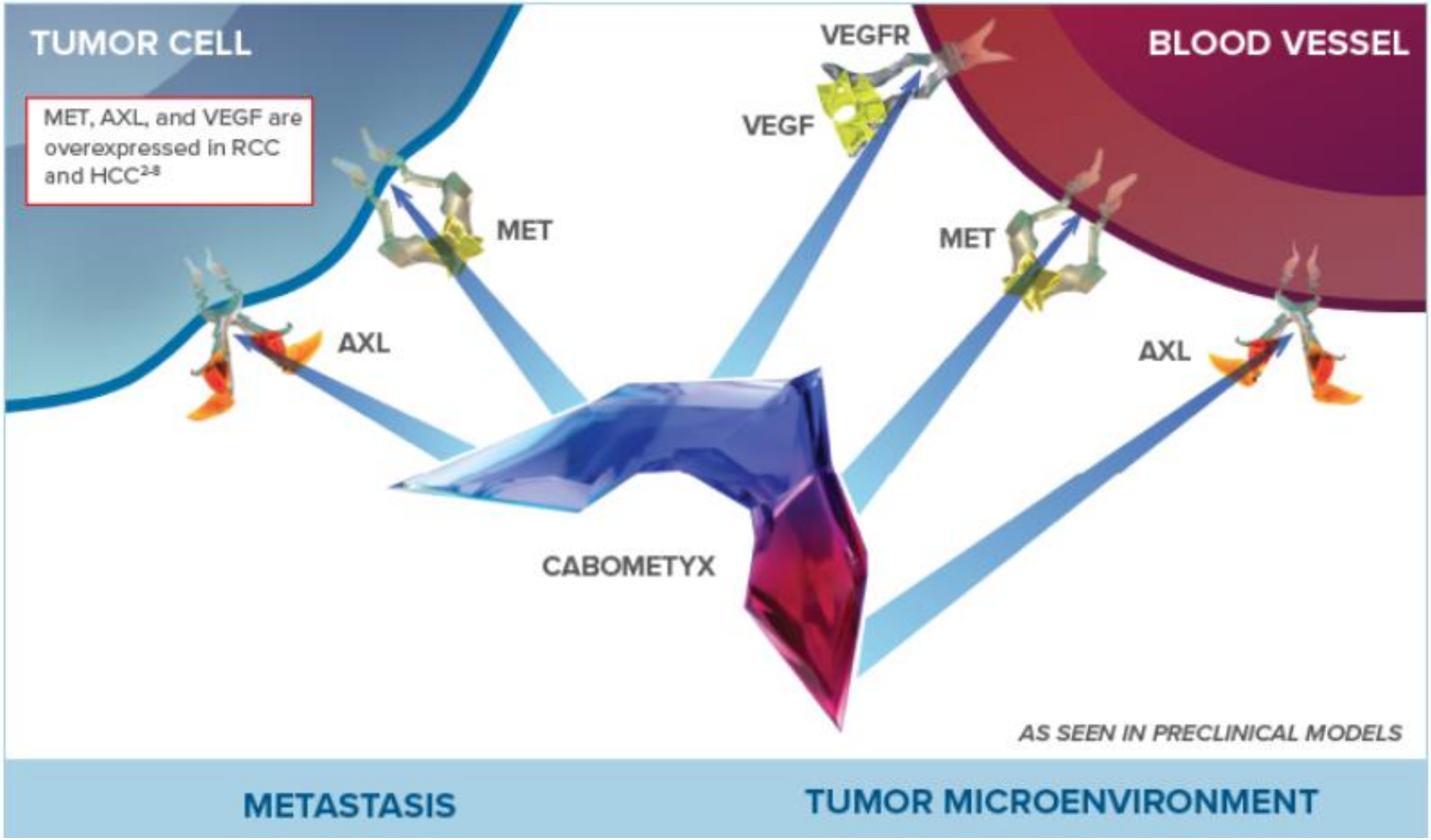
Regorafenib beim HCC, mOS



Systemic treatment of HCC

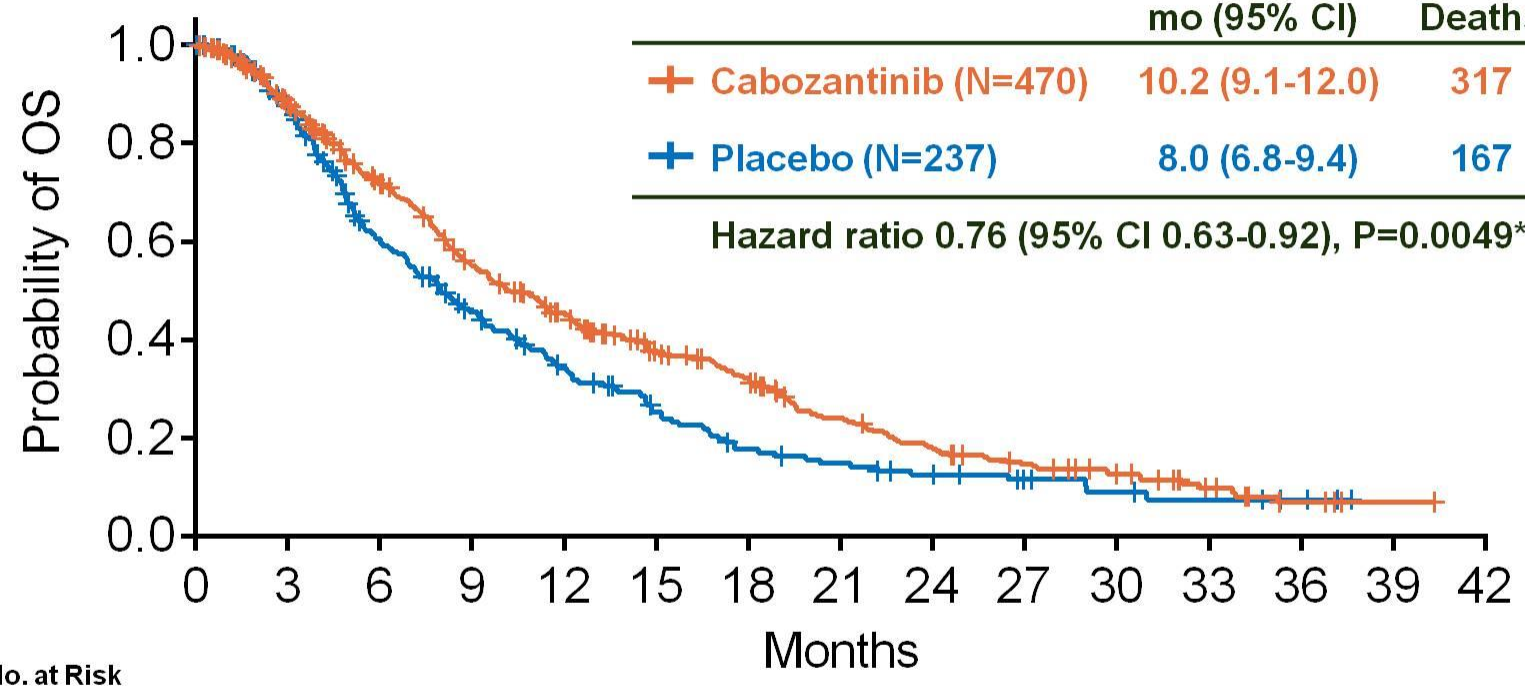


Carbozantinib, second line



Carbozantinib beim HCC, 2. Linie

Overall Survival

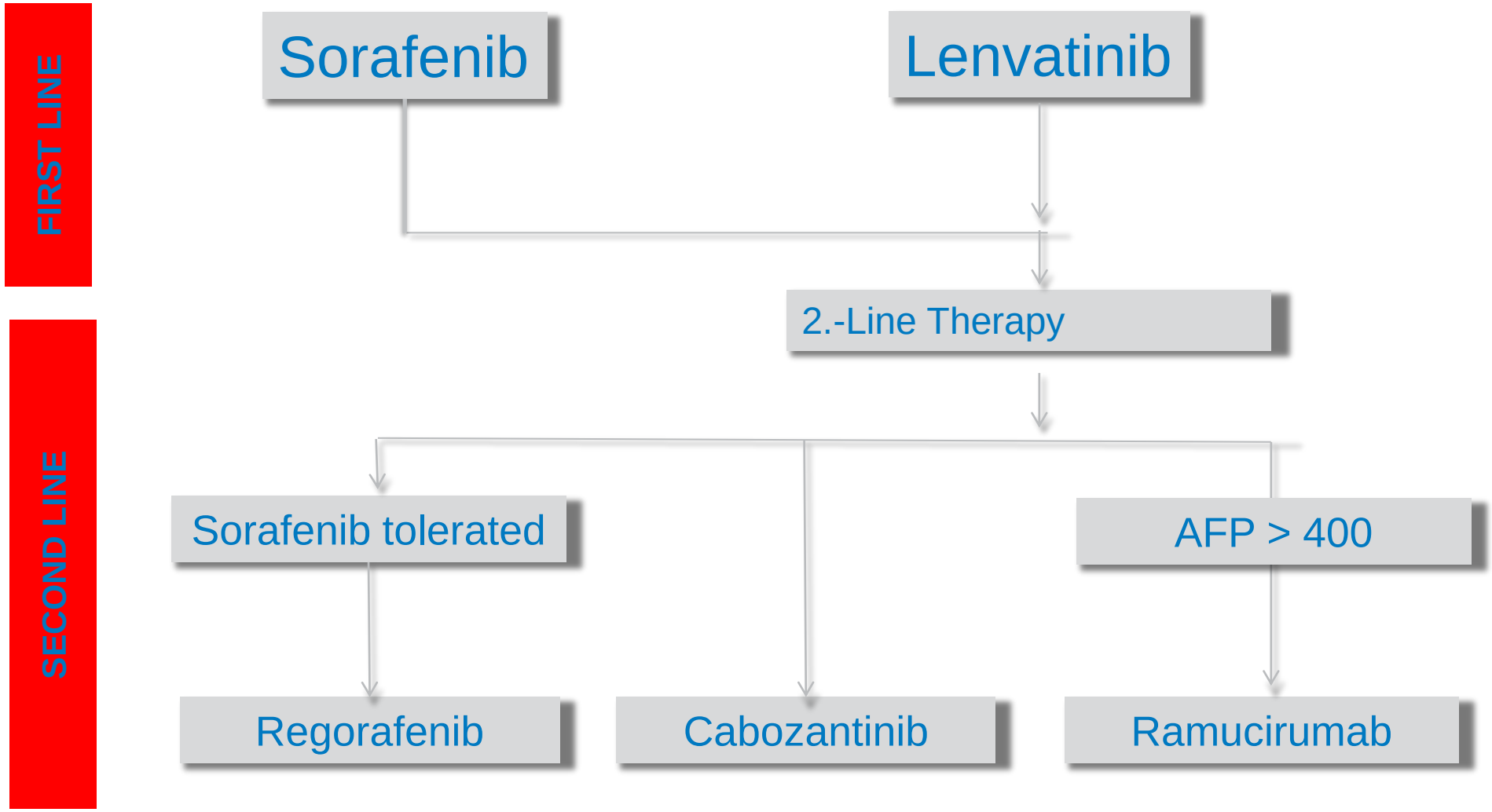


No. at Risk

Cabozantinib	470	382	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

*Critical p-value ≤ 0.021 for second interim analysis

Systemic treatment of HCC



Evolution of systemic treatment of HCC

Sorafenib[2] → 10.7 mOS

Sorafenib-Regorafenib (sequence)[8] → 26 mOS

* Not intention to treat

De Toni EN, Gut. 2019 Oct 14

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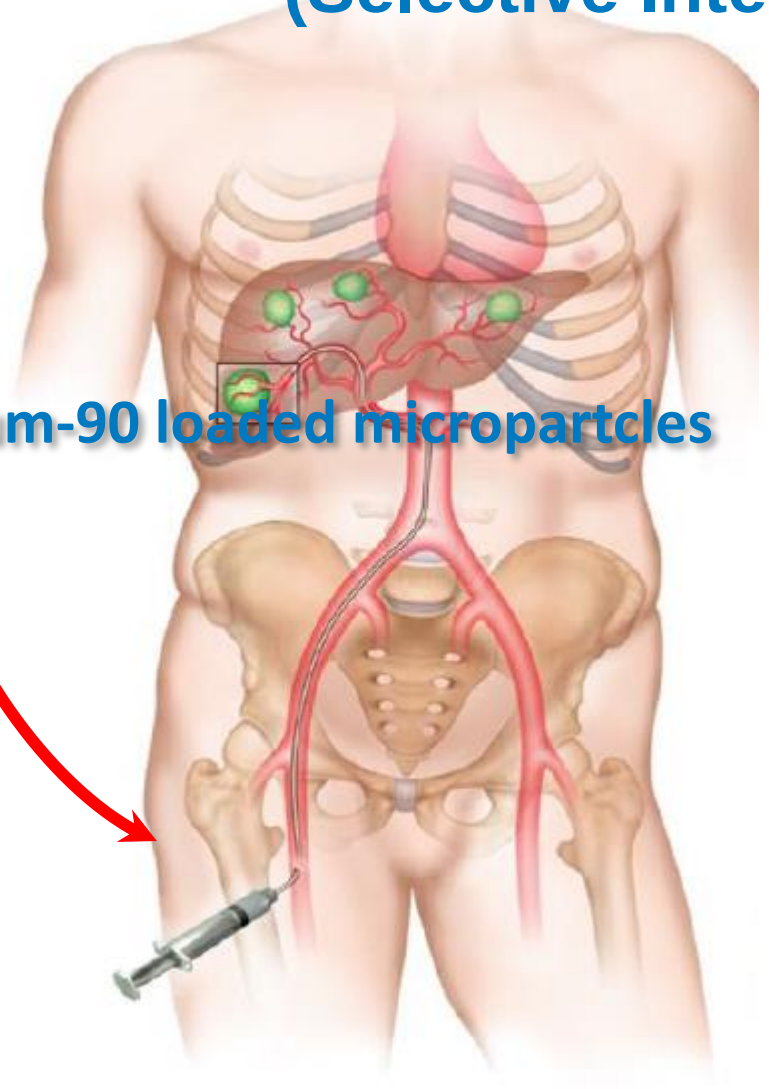
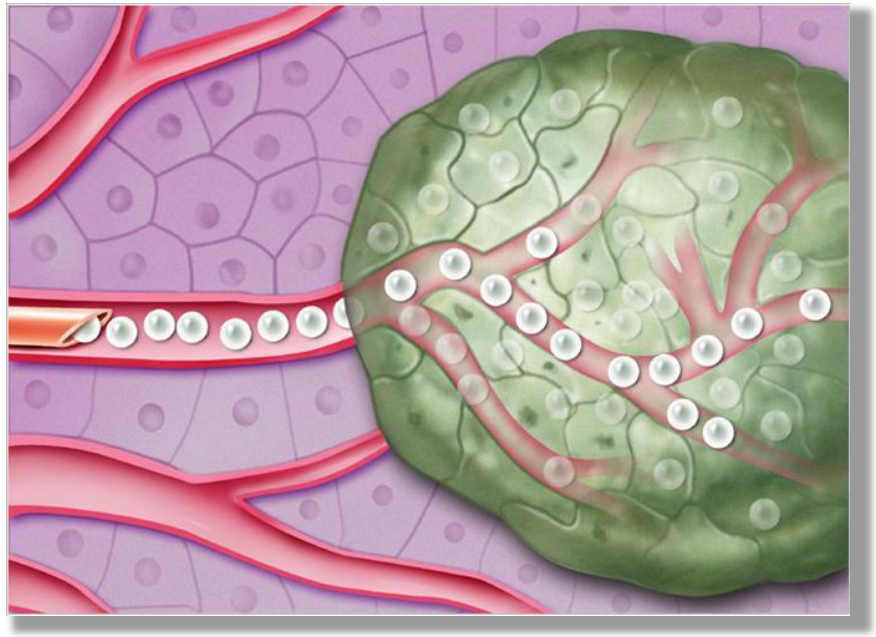
SIRT
(Selective Internal Radio-Therapy)



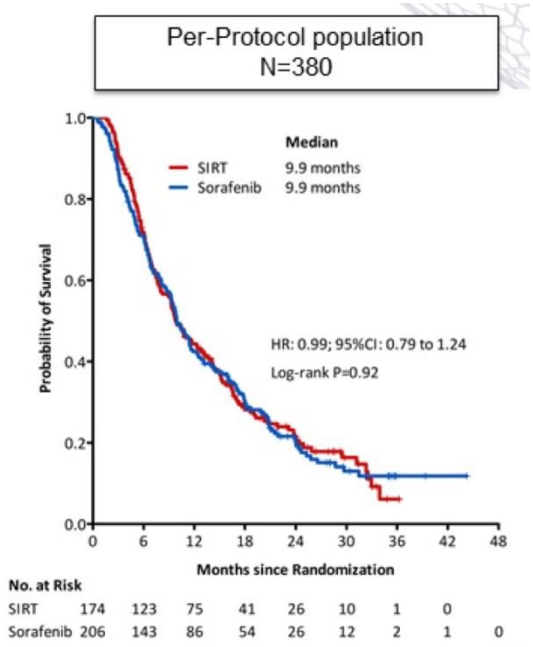
Yttrium-90 loaded micropartcles



SIRT IN PATIENTS WITH ADVANCED HCC

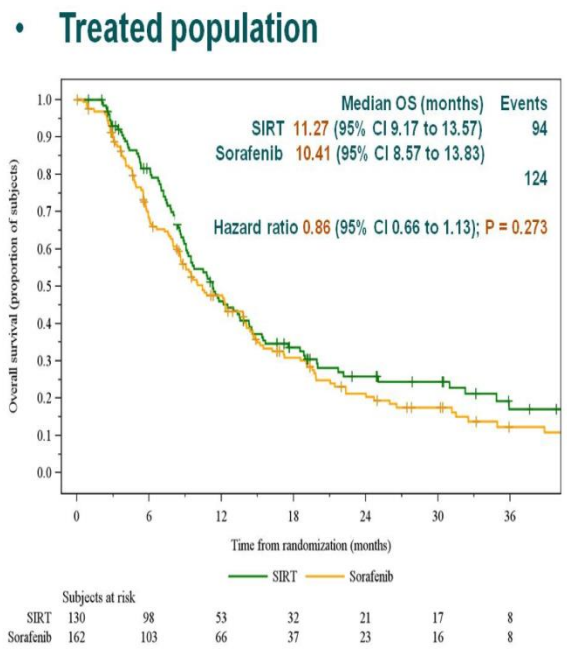
THREE NEGATIVE STUDIES

SARAH



Vilgrain et al., EASL 2017

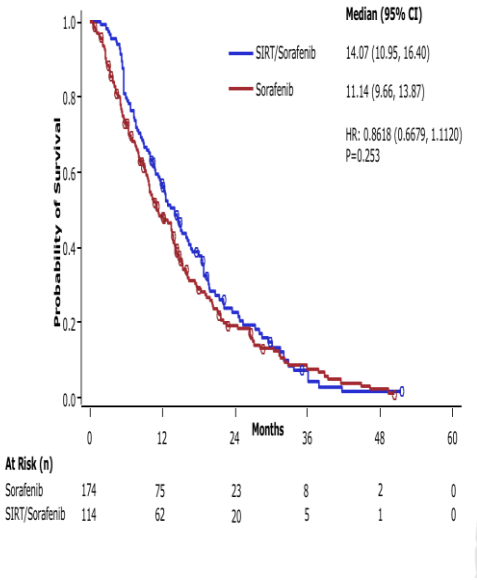
SIRveNIB



Chow et al., ASCO 2017

SORAMIC

per protocol population



Ricke et al., EASL 2018

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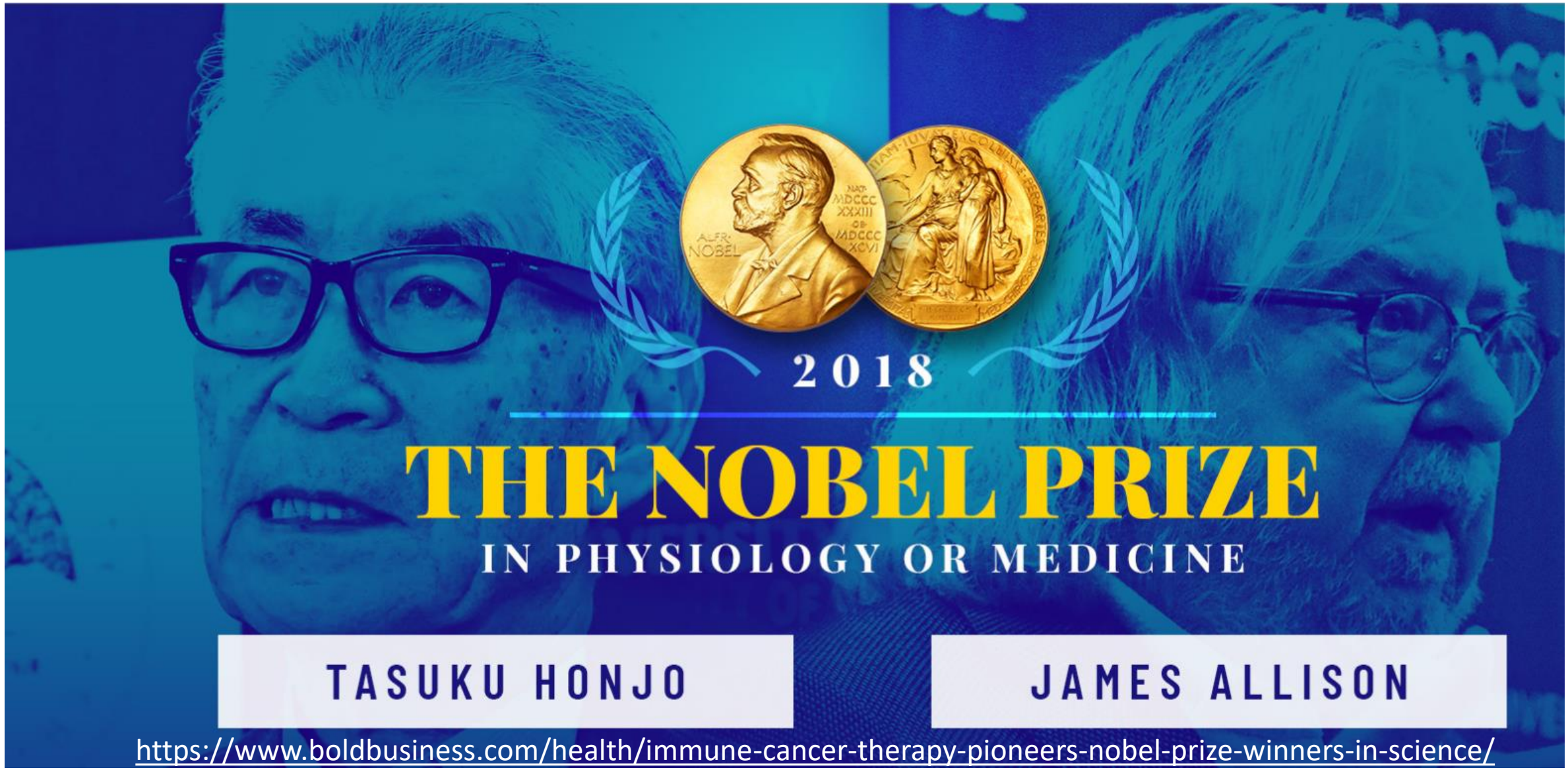
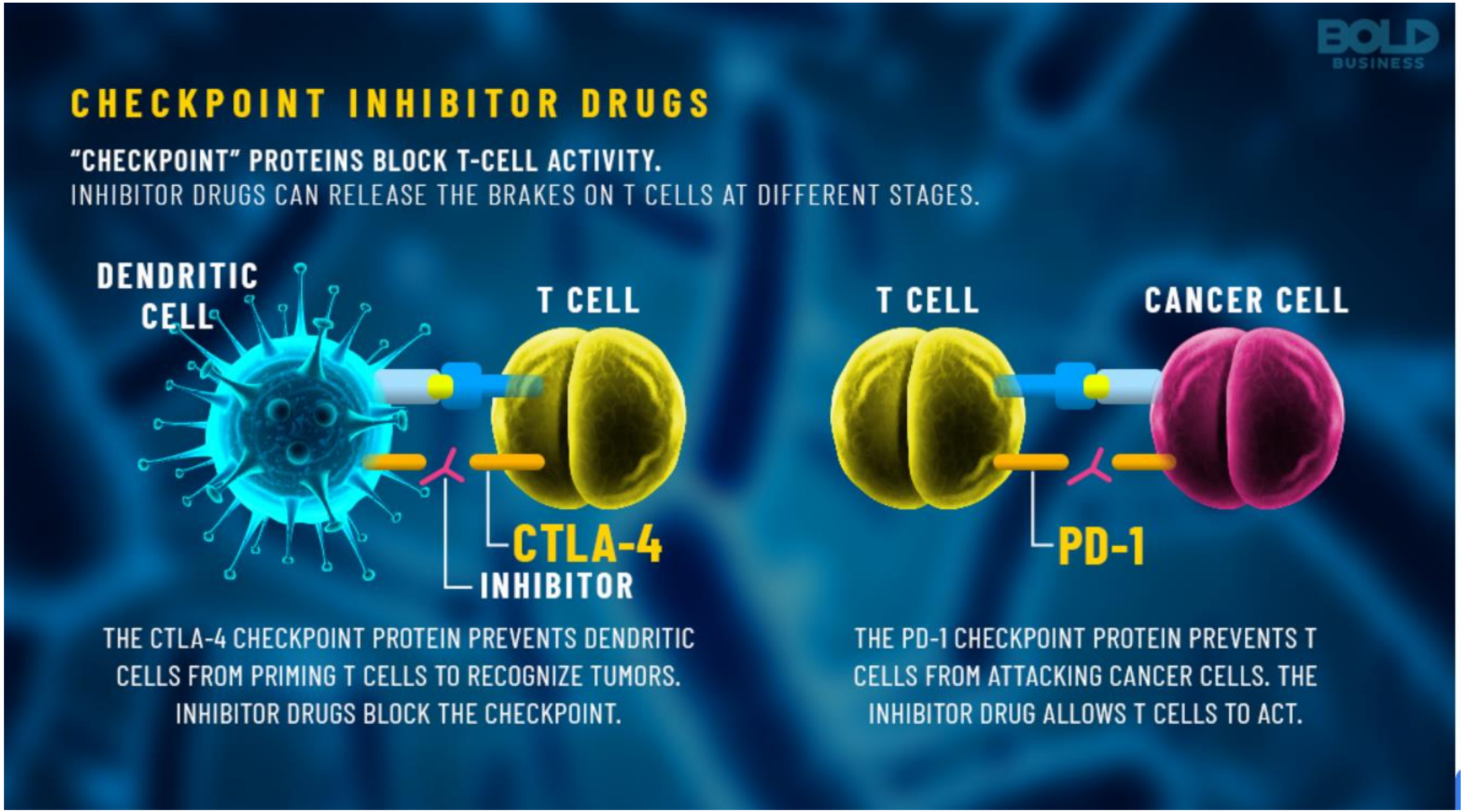
- ASCO update
- Perspectives: Use them early?

The discovery of PD-L1 and CTLA-4

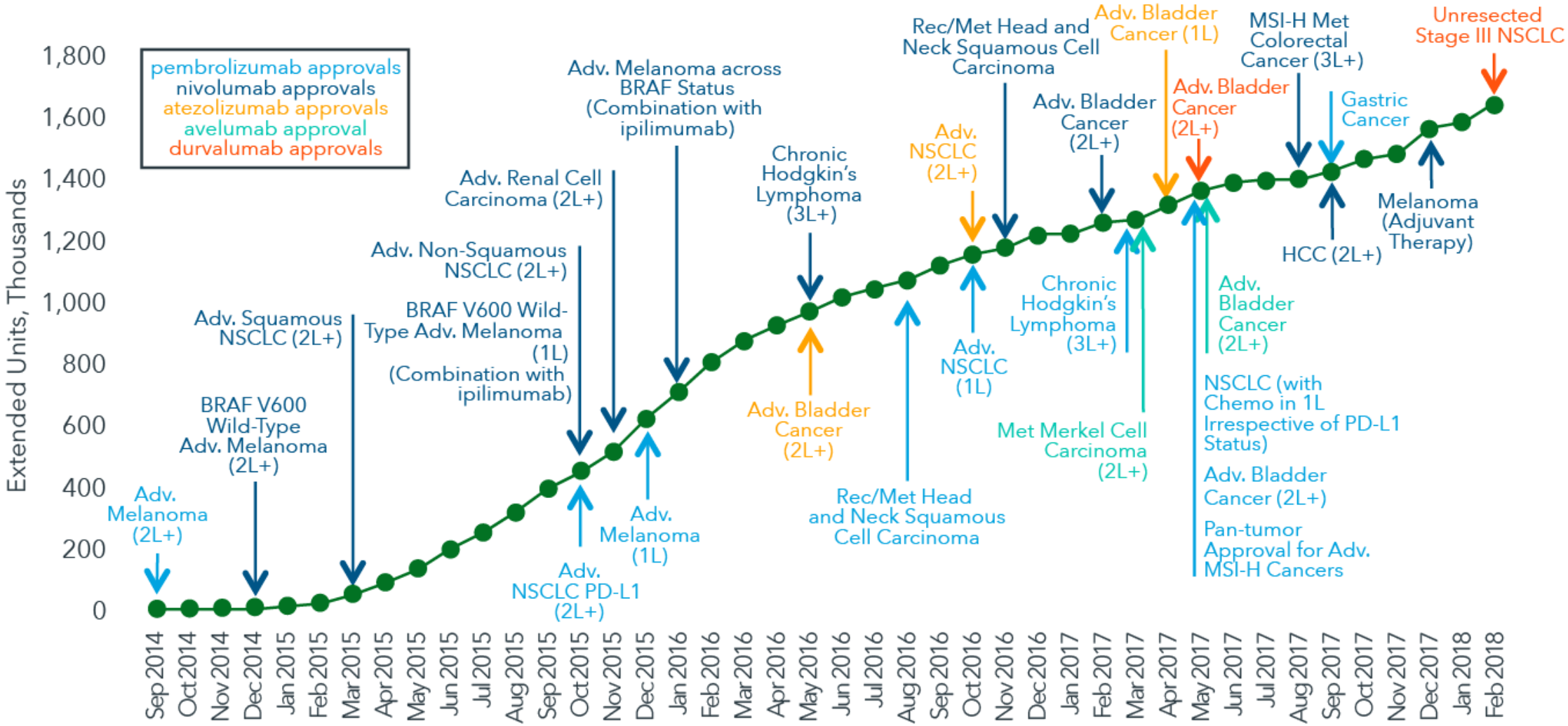


https://www.boldbusiness.com/health/immune-cancer-therapy-pioneers-nobel-prize-winners-in-science/

Background: CPI, pathophysiology



Immuno-Oncology PD-1 and PD-L1 Inhibitor Uptake in the United States



Source: U.S. FDA, IQVIA, National Sales Perspectives, Feb 2018; IQVIA Institute, Apr 2018

Notes: Met = metastatic; rec/met = recurrent/metastatic; 1L+ = 1st line; 2L+ = 2nd line; HCC = hepatocellular carcinoma.

Report: Global Oncology Trends 2018: Innovation, Expansion and Disruption. IQVIA Institute for Human Data Science, May 2018

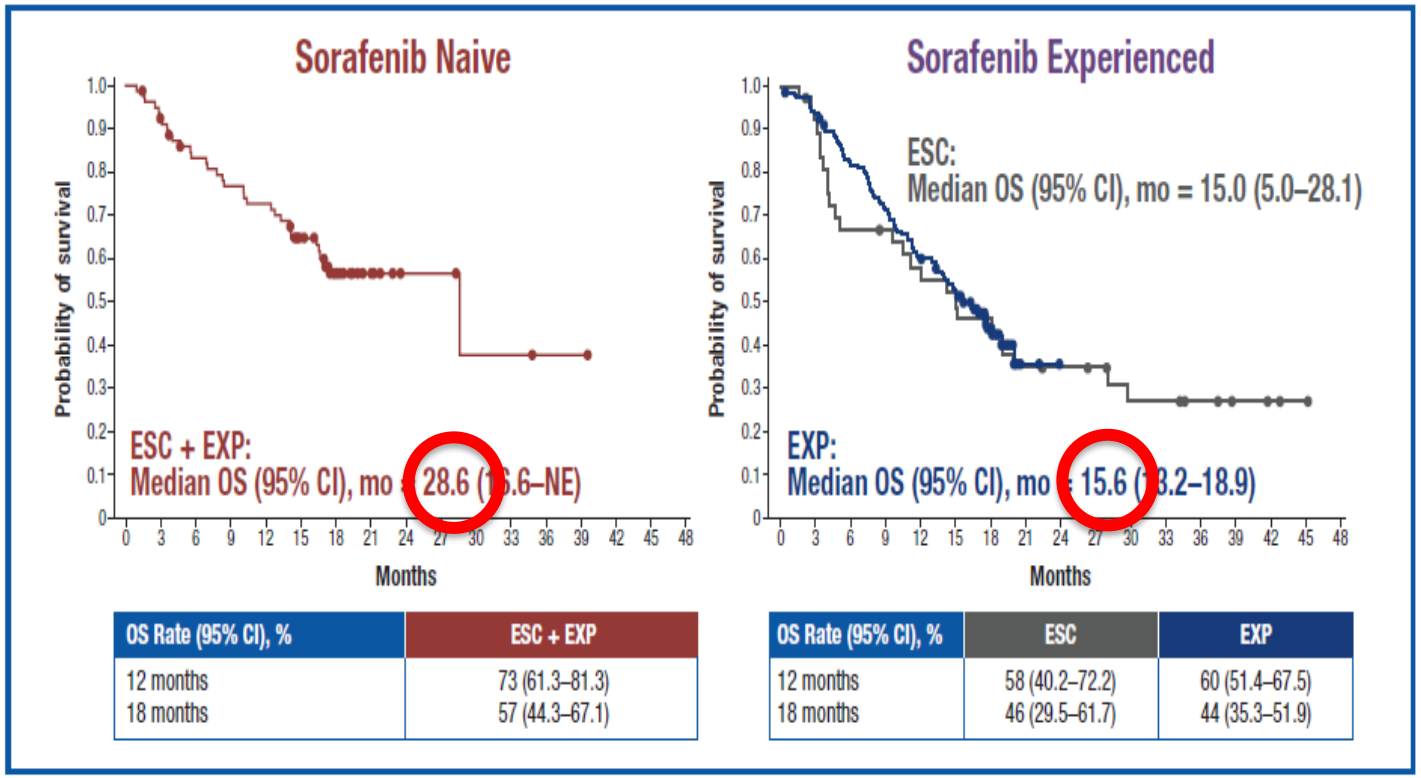
Nivolumab in Sorafenib-Naive and -Experienced Patients With Advanced Hepatocellular Carcinoma: CheckMate 040 Study

Todd S. Crocenzi,[1] Anthony B. El-Khoueiry,[2] Thomas Yau,[3] Ignacio Melero,[4,5] Bruno Sangro,[6] Masatoshi Kudo,[7] Chiun Hsu,[8] Jörg Trojan,[9] Tae-You Kim,[10] Su-Pin Choo,[11] Tim Meyer,[12] Yoon-Koo Kang,[13] Winnie Yeo,[14] Akhil Chopra,[15] Adyb Baakili,[16] Christine dela Cruz,[16] Lixin Lang,[16] Jaclyn Neely,[16] Theodore H. Welling, III[17]

[1]Providence Cancer Center, Portland, OR, USA; [2]USC Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [3]University of Hong Kong, Hong Kong, China; [4]Clínica Universidad de Navarra and CIBERONC, Pamplona, Spain; [5]Center for Applied Medical Research (CIMA), Pamplona, Spain; [6]Clínica Universidad de Navarra and CIBEREHD, Pamplona, Spain; [7]Kindai University Faculty of Medicine, Osaka, Japan; [8]National Taiwan University Hospital, Taipei, Taiwan; [9]Goethe University Hospital and Cancer Center, Frankfurt, Germany; [10]Seoul National University Hospital, Seoul, Korea; [11]National Cancer Center, Singapore; [12]Royal Free Hospital, London, UK; [13]Asan Medical Center, University of Ulsan, Seoul, Korea; [14]Chinese University of Hong Kong, Hong Kong, China; [15]Johns Hopkins Singapore International Medical Centre, Singapore; [16]Bristol-Myers Squibb, Princeton, NJ, USA; [17]University of Michigan School of Medicine, Ann Arbor, MI, USA

- Long-term survival was observed across sorafenib-naive and -experienced cohorts (**Figure 4**)

Figure 4. Overall Survival With Nivolumab



OS Rate (95% CI), %	ESC + EXP
12 months	73 (61.3–81.3)
18 months	57 (44.3–67.1)

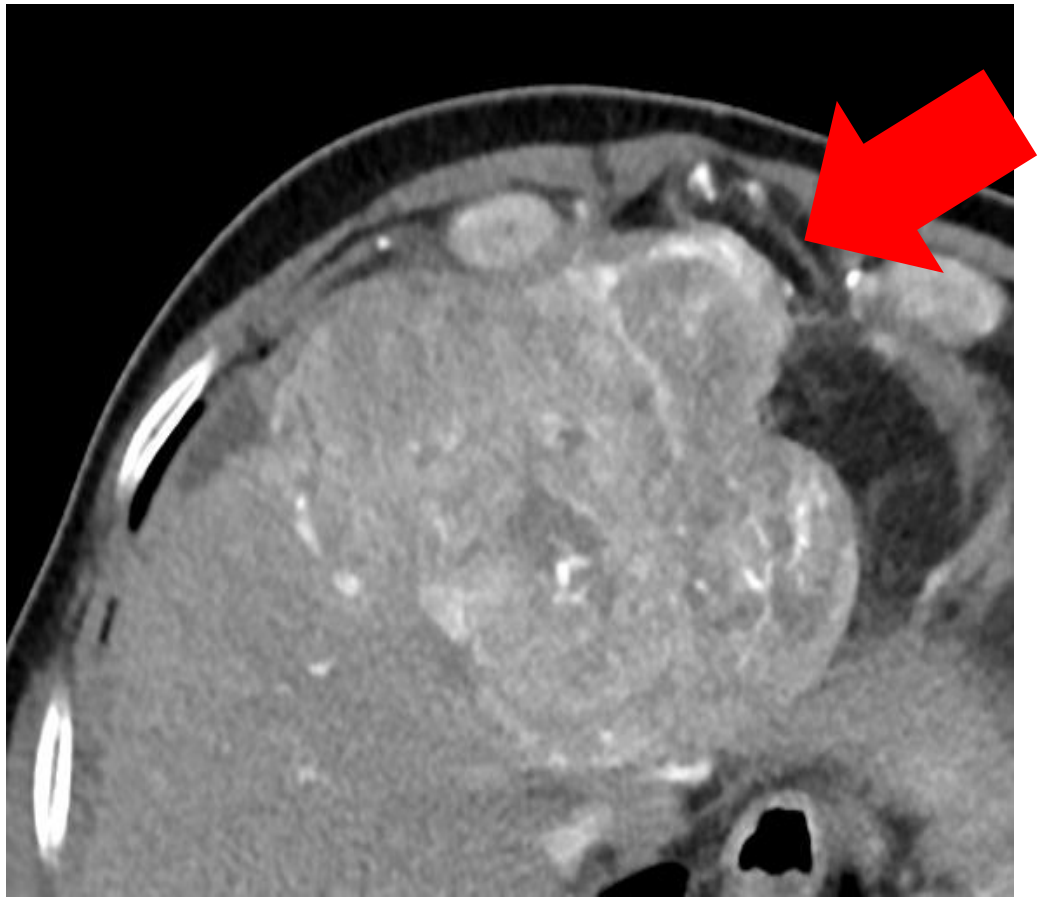
OS Rate (95% CI), %	ESC	EXP
12 months	58 (40.2–72.2)	60 (51.4–67.5)
18 months	46 (29.5–61.7)	44 (35.3–51.9)

Kaplan-Meier method; closed circles denote censored patients.

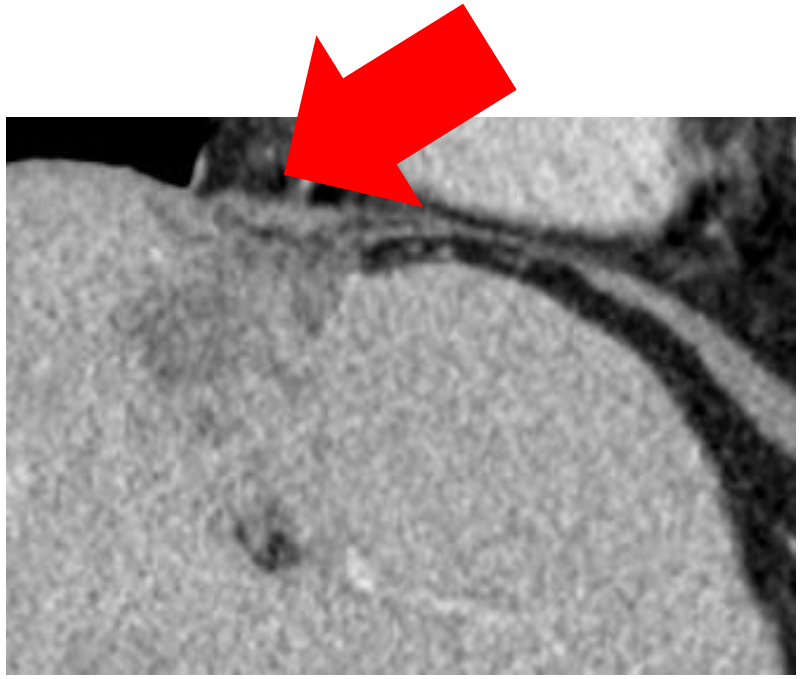
ORR: 14.3%

Presented By Crocenzi @2017 ASCO

Baseline



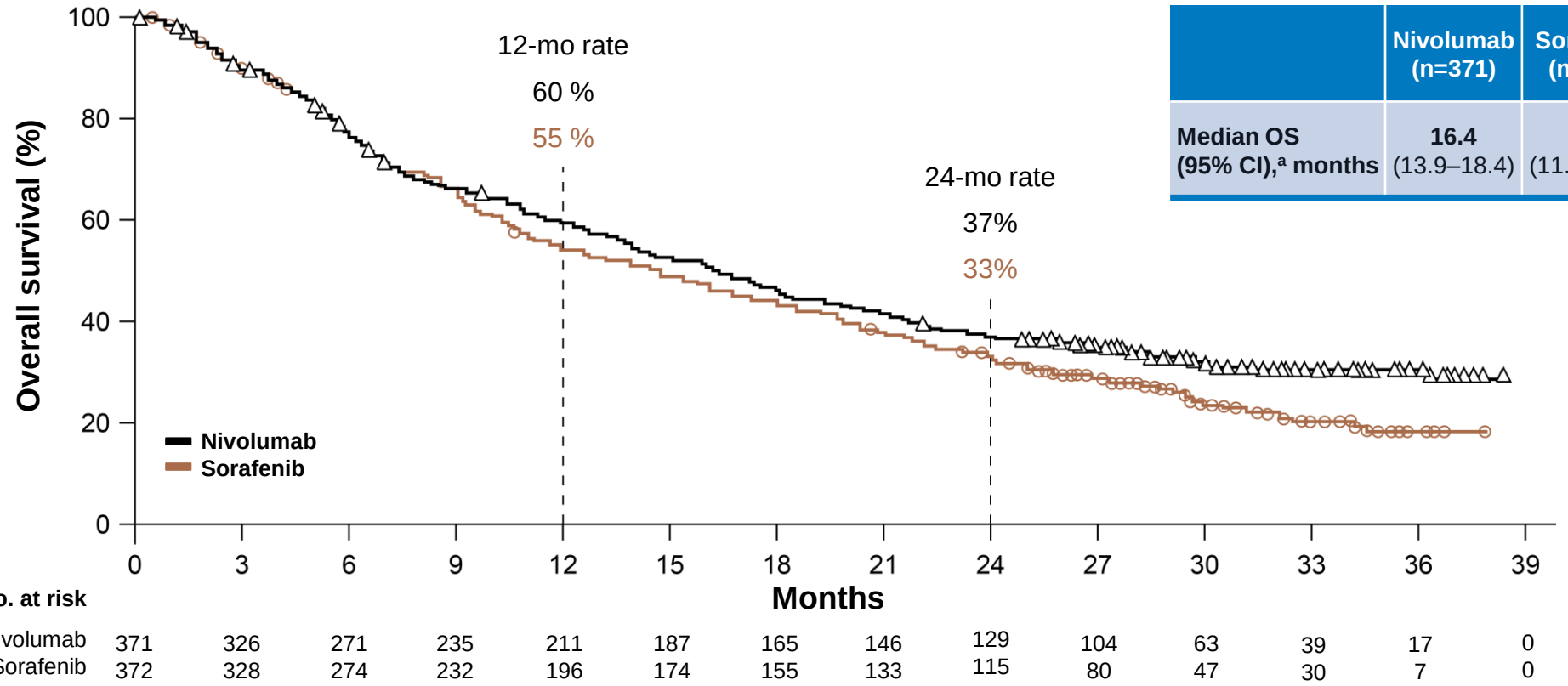
3 Months after Nivo initiation



Case example: BCLC C Patient with extrahepatic mets (including brain metastasis). Nivo off Label: complete remission of tumor manifestations. (EDT, University of Munich)

CheckMate 459 – Results

Overall Survival



	Nivolumab (n=371)	Sorafenib (n=372)	HR (95% CI)[b]	p value[c]
Median OS (95% CI),[a] months	**16.4** (13.9–18.4)	**14.7** (11.9–17.2)	**0.85** (0.72–1.02)	**0.0752**

ORR: 14%

The predefined threshold of statistical significance for OS with Nivolumab was not met, although Nivolumab demonstrated clinical benefit

[a]Based on Kaplan-Meier estimates; [b]Stratified Cox proportional hazards model. HR is Nivolumab over Sorafenib; [c]p value from log-rank test; final OS boundary: 0.0419 for a 2-sided nominal p value. HR, hazard ratio.

Mod. Yau T et al. ESMO 2019, Proffered Paper Session 1 – Gastrointestinal tumours, non-colorectal, Abstract No. LBA38_PR

CheckMate 459 – Results

Subsequent Therapy

Still: Nivo was approved in USA as second-line treatment of HCC

	Nivolumab (n=371)	Sorafenib (n=372)
Any subsequent therapy,[a] n (%)	181 (49)	196 (53)
Systemic therapy, n (%)	140 (38)	170 (46)
Tyrosine kinase inhibitor	132 (36)	86 (23)
Chemotherapy	15 (4)	25 (7)
Investigational agent[b]	10 (3)	40 (11)
I-O	7 (2)	76 (20)
Other	2 (1)	4 (1)
Local therapy, n (%)	63 (17)	61 (16)
Radiotherapy, n (%)	52 (14)	38 (10)
Surgery, n (%)	10 (3)	14 (4)

- 140 patients (38%) in the Nivolumab arm and 170 patients (46%) in the Sorafenib arm received subsequent systemic therapy
  - 20% of patients in the Sorafenib arm received subsequent I-O therapy

[a]Patient may have received more than 1 type of subsequent therapy; [b]Includes indeterminate therapies received in subsequent clinical trials, including I-O.
I-O, immuno-oncology.

Mod. Yau T et al. ESMO 2019, Proffered Paper Session 1 – Gastrointestinal tumours, non-colorectal, Abstract No. LBA38_PR

NEXT STEPS…

Sorafenib
Regorafenib
Lenvatinib
Cabozantinib
Ramucirumab

PLD-1 Inhibitors
CTLA-4 Inhibitors

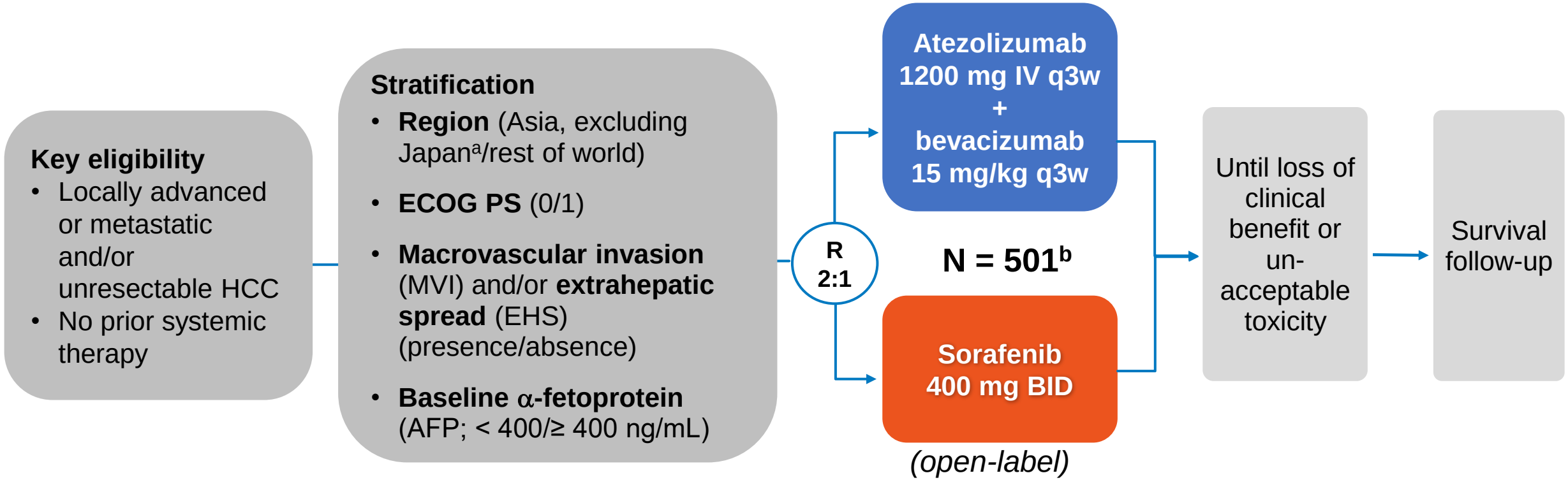
Atezolizumab▼ + bevacizumab vs sorafenib in patients with unresectable hepatocellular carcinoma: Phase 3 results from IMbrave150

Ann-Lii Cheng,[1] Shukui Qin,[2] Masafumi Ikeda,[3] Peter R. Galle,[4] Michel Ducreux,[5] Andrew X. Zhu,[6] Tae-You Kim,[7] Masatoshi Kudo,[8] Valeriy Breder,[9] Philippe Merle,[10] Ahmed Kaseb,[11] Daneng Li,[12] Wendy Verret,[13] Derek-Zhen Xu,[14] Sairy Hernandez,[13] Juan Liu,[14] Chen Huang,[14] Sohail Mulla,[15] Ho Yeong Lim,[16] Richard S. Finn[17]

[1]National Taiwan University Cancer Center and National Taiwan University Hospital, Taipei, Taiwan; [2]People's Liberation Army Cancer Center, Jinling Hospital, Nanjing, People's Republic of China; [3]National Cancer Center Hospital East, Kashiwa, Japan; [4]University Medical Center Mainz, Mainz, Germany; [5]Gustave Roussy Cancer Center, Villejuif, France; [6]Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, MA, USA; [7]Seoul National University College of Medicine, Seoul, Korea; [8]Kindai University Faculty of Medicine, Osaka, Japan; [9]N.N. Blokhin Russian Cancer Research Center, Moscow, Russia; [10]Hospital La Croix-Rousse, Lyon, France;
[11]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [12]City of Hope Comprehensive Cancer Center and Beckman Research Institute, Duarte, CA, USA; [13]Genentech, Inc., South San Francisco, CA, USA; [14]Roche Product Development, Shanghai, People's Republic of China; [15]Hoffmann-La Roche Limited, Mississauga, ON, Canada; [16]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [17]Jonsson Comprehensive Cancer Center, Geffen School of Medicine at UCLA, Los Angeles, CA, USA

▼ Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Dies ermöglicht eine schnelle Identifizierung neuer Erkenntnisse über die Sicherheit. Angehörige von Gesundheitsberufen sind aufgefordert, jeden Verdachtsfall einer Nebenwirkung zu melden. Bitte melden Sie Nebenwirkungen an die Roche Pharma AG (grenzach.drug_safety@roche.com oder Fax +49 7624/143183) oder an das Paul-Ehrlich-Institut (https://humanweb.pei.de oder Fax: +49 6103/77-1234).

IMbrave150 study design



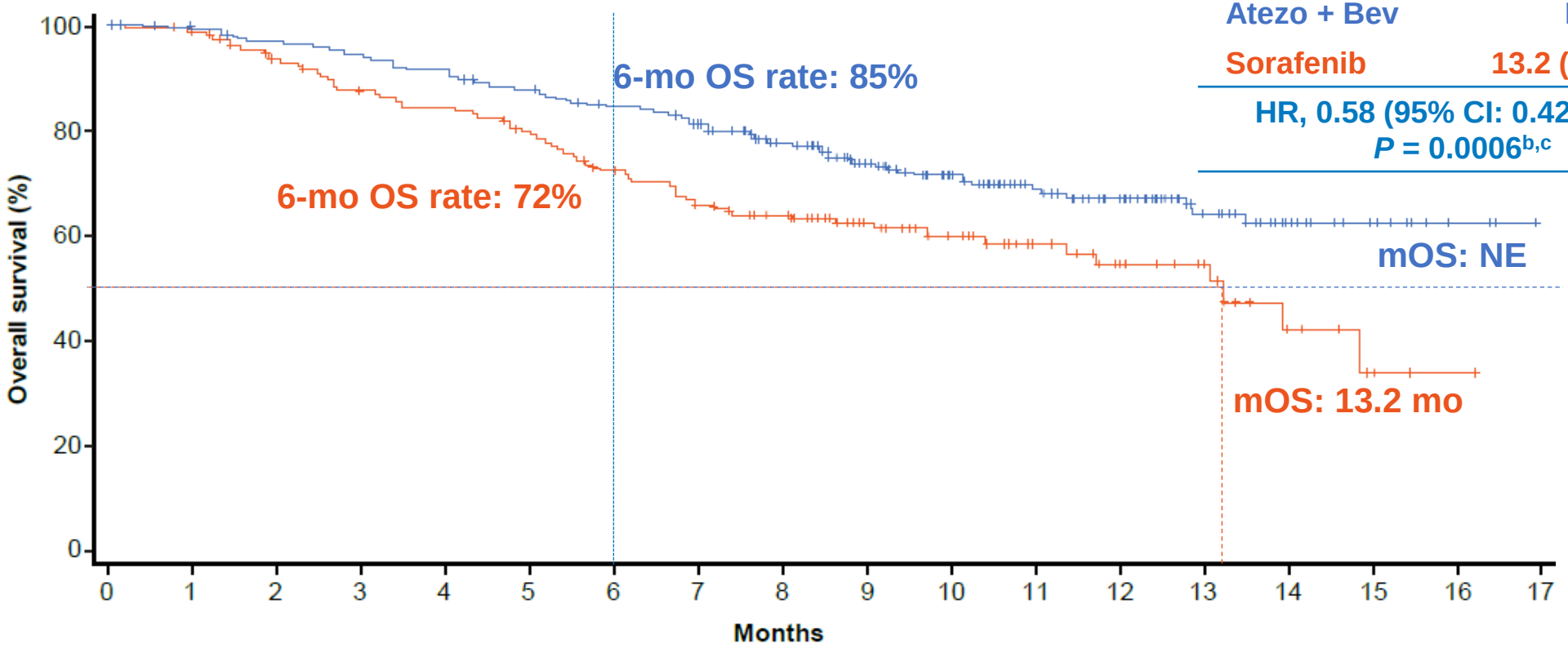
Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

Key secondary endpoints (in testing strategy)
- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST

[a] Japan is included in rest of world.
[b] An additional 57 Chinese patients in the China extension cohort were not included in the global population/analysis.

OS: co-primary endpoint

Median OS (95% CI), mo[a]	
Atezo + Bev	NE
Sorafenib	13.2 (10.4, NE)
HR, 0.58 (95% CI: 0.42, 0.79)[b] *P* = 0.0006[b,c]	



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

NE, not estimable. [a] 96 patients (29%) in the Atezo + Bev arm vs 65 (39%) in the sorafenib arm had an event. [b] HR and *P* value were from Cox model and log-rank test and were stratified by geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] The 2-sided *P* value boundary based on 161 events is 0.0033. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

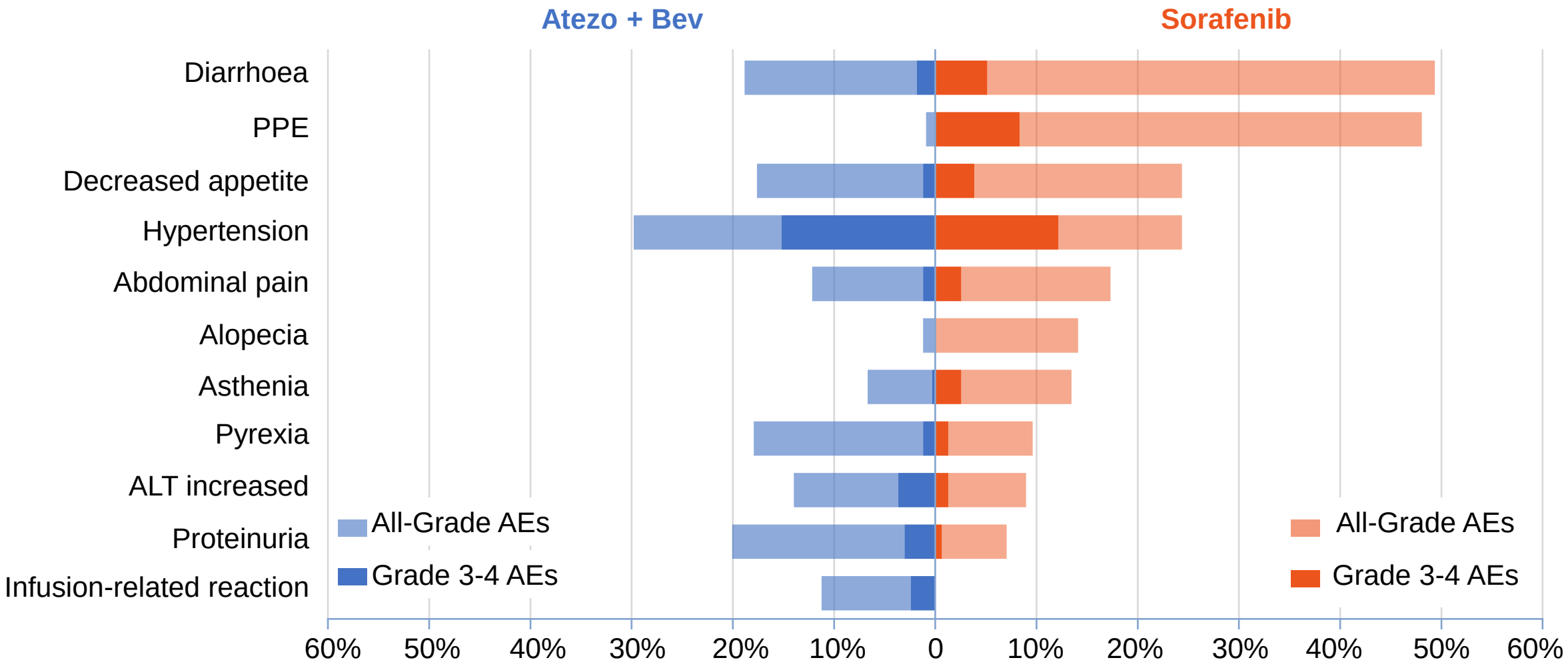
Response rate and duration of response

	IRF RECIST 1.1		IRF HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)[a]	Sorafenib (n = 158)
Confirmed ORR, n **(%)** (95% CI)	89 **(27)** (23, 33)	19 **(12)** (7, 18)	108 **(33)** (28, 39)	21 **(13)** (8, 20)
CR	18 (6)	0	33 (10)	3 (2)
PR	71 (22)	19 (12)	75 (23)	18 (11)
Stratified *P* value[b]	**< 0.0001**		**< 0.0001**	
SD, n (%)	151 (46)	69 (43)	127 (39)	66 (42)
PD, n (%)	64 (20)	39 (25)	66 (20)	40 (25)
DCR, n (%)	240 (74)	88 (55)	235 (72)	87 (55)
Ongoing response, n (%)[c]	77 (87)	13 (68)	84 (78)	13 (62)
Median DOR, months (95% CI)	NE	6.3 (4.7, NE)	NE	6.3 (4.9, NE)
Event-free rate at 6 months, n (%)	88	59	82	63

[a] IRF HCC mRECIST–evaluable population was based on patients who presented with measurable disease at baseline per HCC mRECIST criteria.
[b] Stratification factors included geographic region (Asia vs rest of world, including Japan), AFP level (< 400 vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (yes vs no) per IxRS. [c] Denominator is patients with confirmed CR/PR. Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Safety[a]

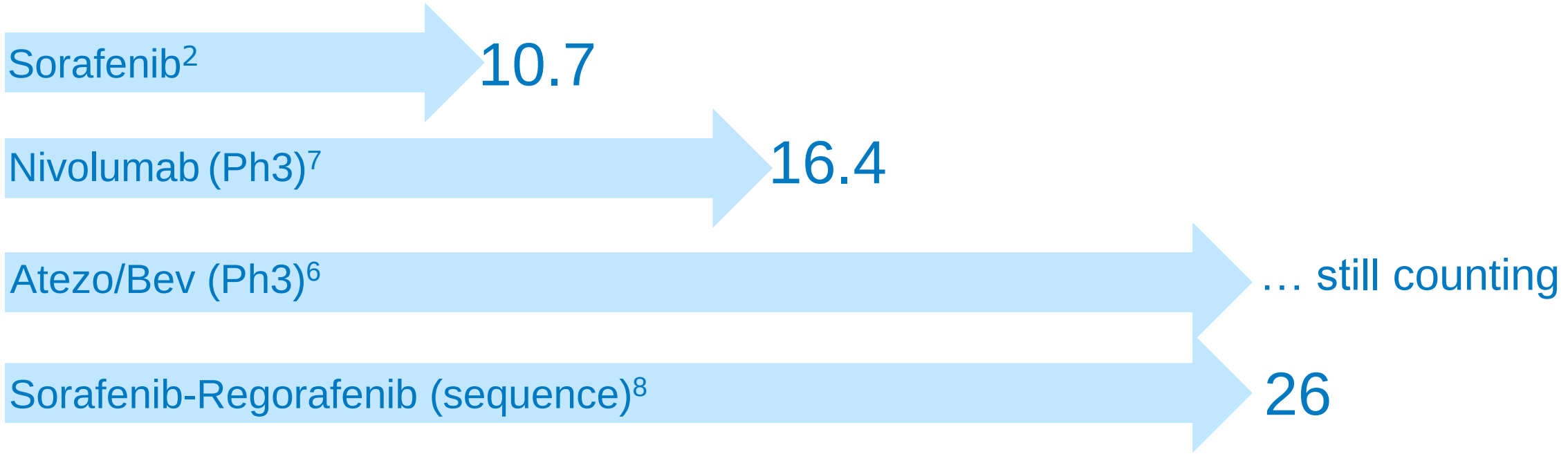
≥ 10% frequency of AEs in either arm and > 5% difference between arms



PPE, palmar-plantar erythrodysaesthesia.

[a] Safety-evaluable population.

Evolution of systemic treatment of HCC

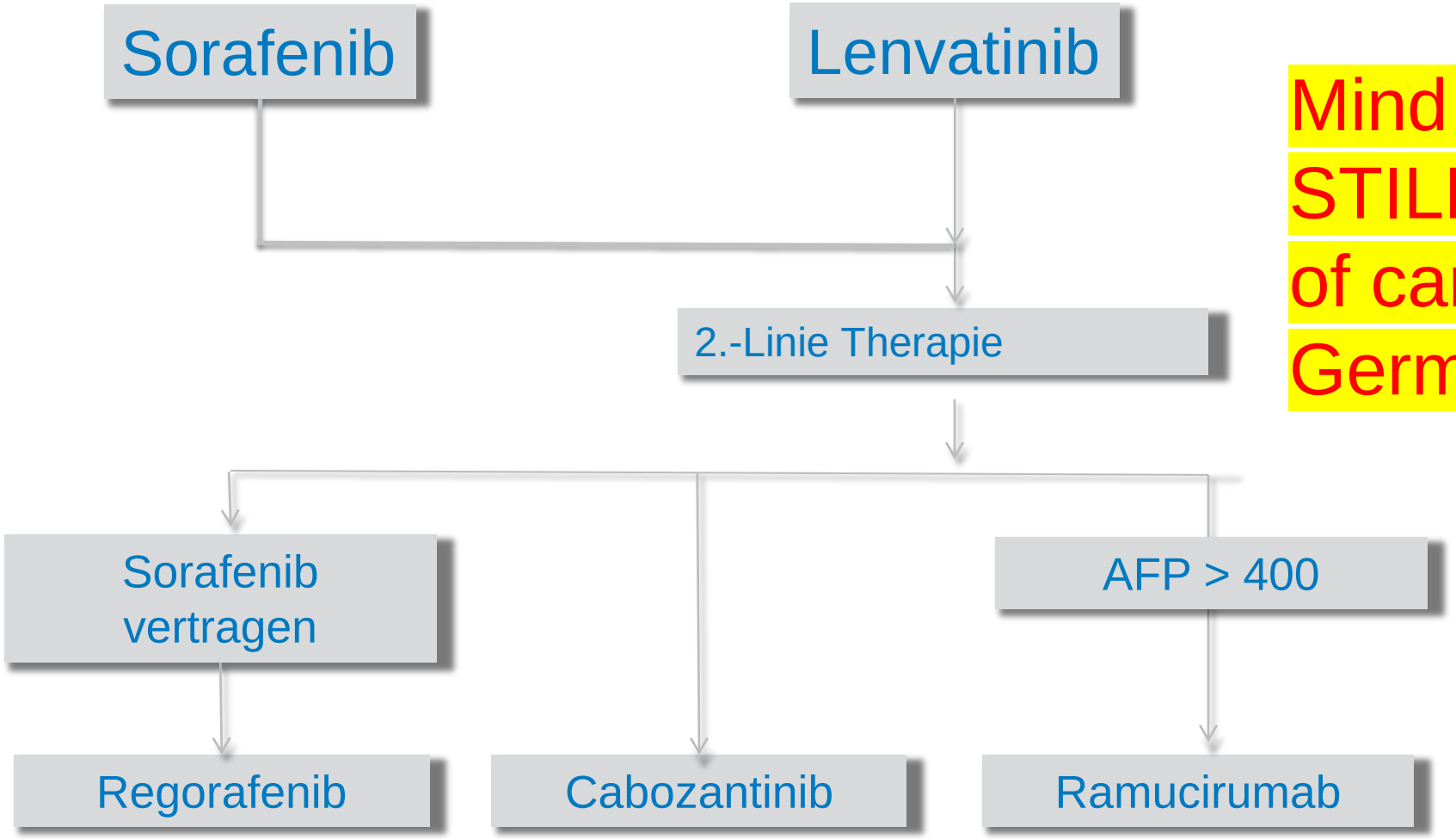


De Toni EN, Gut. 2019 Oct 14

Systemic treatment of HCC

FIRST LINE

SECOND LINE +



Mind this is STILL standard of care in Germany

THE FUTURE - HCC systemic therapy – Patient suitable for immunotherapy

FIRST LINE

SECOND LINE +

Atezo/Bev

2nd line therapy

Sorafenib

Lenvatinib

3rd line therapy

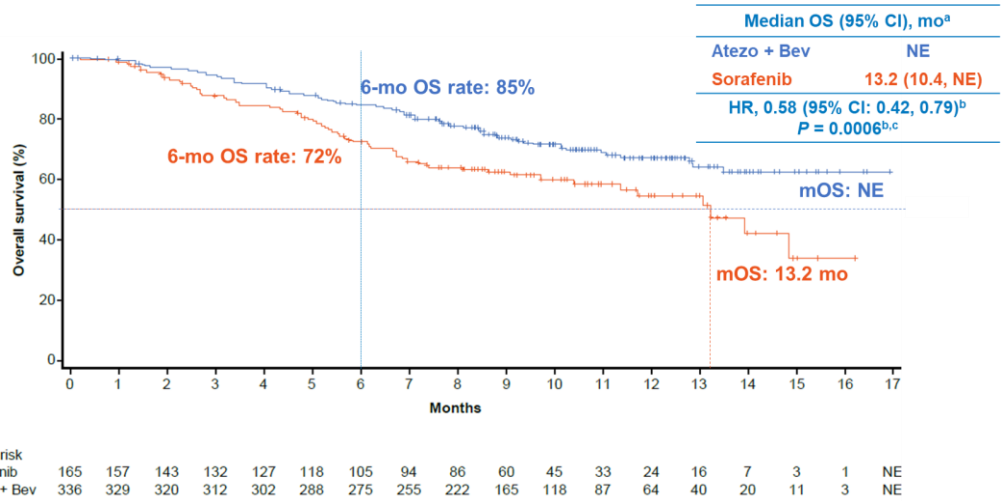
Tolerance of Sorafenib

AFP > 400

Regorafenib

Cabozantinib

Ramucirumab



Coming soon: ~ Q3 2020 in Germany?

Agenda

- Introduction: HCC epidemiology and therapeutic stratification
- Evolution of systemic treatment of HCC: TKI and VEGFi
- One word about SIRT
- Checkpoint inhibitors in the treatment of advanced HCC
- The latest novelties (update ASCO 2020)
- Perspectives: Use them early?

ASCO 2020 ausgewählte Abstracts

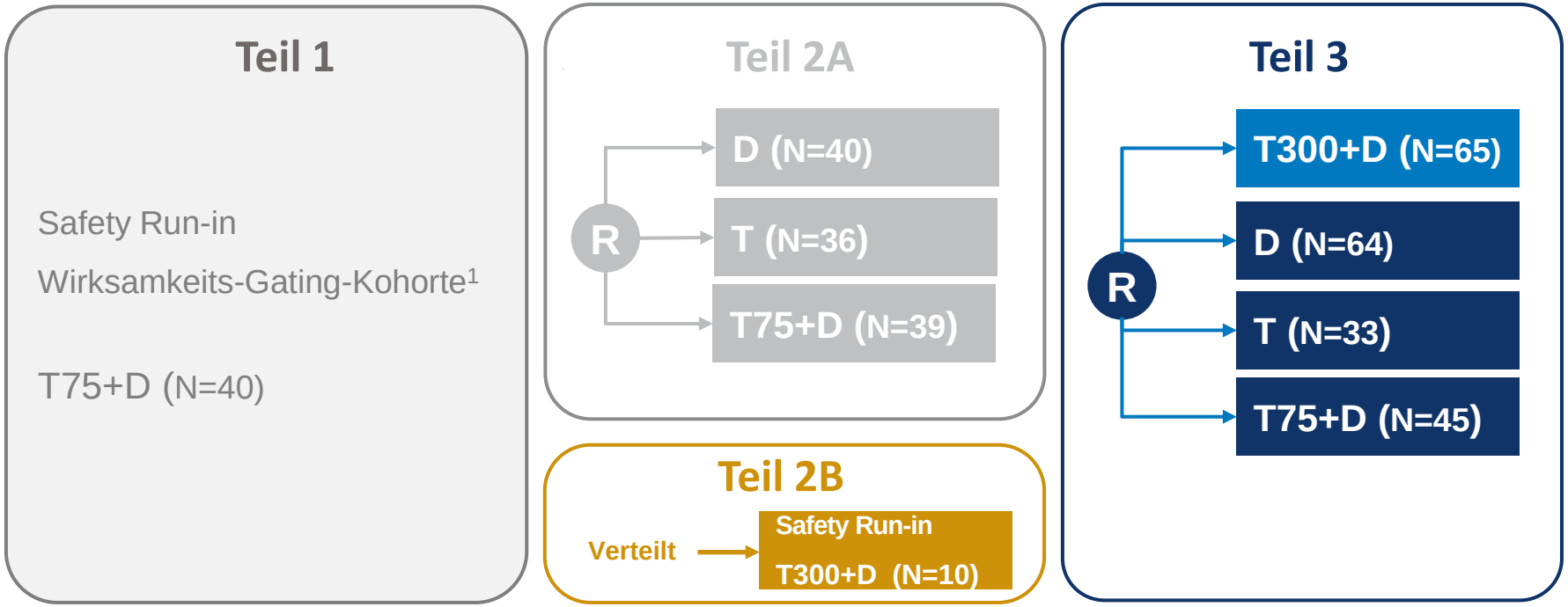
1) Efficacy, tolerability, and biologic activity of a novel regimen of tremelimumab in combination with durvalumab for patients with advanced HCC

2) A phase Ib study of lenvatinib plus pembrolizumab in unresectable HCC

3) Final results of a randomised, open label, perioperative Phase II study evaluating nivolumab alone or nivolumab + ipilimumab in patients with resectable HCC

Treme ± Durva bei aHCC

Studiendesign



Wichtigste Meilensteine

FSI Teil 2A	Februar 2017
FSI Teil 2B	Oktober 2017

Wichtigste Meilensteine

FSI Teil 3	Februar 2018
LSI Teil 3	April 2019

Therapien

T300+D	Tremelimumab 300 mg × 1 Dosis + Durvalumab 1500 mg Q4W
D	Durvalumab 1500 mg Q4W
T	Tremelimumab Monotherapie 750 mg Q4W × 7 Dosen, danach Q12W
T75+D	Tremelimumab 75 mg × 4 Dosen + Durvalumab 1500 mg Q4W

Ziele und Assessments

Primärer Endpunkt: Sicherheit

Wichtigste sekundäre Endpunkte

- Gesamtüberleben
- Objektive Ansprechrate
- Ansprechdauer

Andere sekundäre Endpunkte

- Progressionsfreies Überleben
- Krankheitskontrollrate
- Zeit bis zum Ansprechen

Wichtigste Assessments

- Triphasische Bildgebung Q8W
- Zirkulierende Immunzellen
- PD-L1 Status (Ventana SP263)

1. Kelley RK et al., JCO, 2017.35:4073-4073

Treme ± Durva bei aHCC

Patientendemographie

Zum Zeitpunkt des Data Cut-off (28.2.2020), wurden 332 Patienten in Teil 2 und 3 für Sicherheit und Wirksamkeit evaluiert

	T300+D (N=75)	D (N=104)	T (N=69)	T75+D (N=84)
Patienten mit Therapie, N	74	101	69	82
Medianes Alter, Jahre	66,0	64,5	62,0	61,5
Männlich, N (%)	65 (86,7)	92 (88,5)	57 (82,6)	70 (83,3)
Ethnizität, N (%)				
Weiß	27 (36,0)	35 (33,7)	26 (37,7)	30 (35,7)
Schwarz	4 (5,3)	10 (9,6)	2 (2,9)	5 (6,0)
Asiatisch	44 (58,7)	55 (52,9)	39 (56,5)	47 (56,0)
Andere	0	4 (3,8)	2 (2,9)	2 (2,4)
Region, N (%)				
Asien (außer Japan)	31 (41,3)	47 (45,2)	29 (42,0)	38 (45,2)
Restliche Welt (einschließlich Japan)	44 (58,7)	57 (54,8)	40 (58,0)	46 (54,8)
Vorherige Sorafenib-Therapie, N (%)				
Progression	43 (57,3)	52 (50,0)	30 (43,5)	47 (56,0)
Nicht toleriert	12 (16,0)	15 (14,4)	14 (20,3)	10 (11,9)
Abgelehnt	20 (26,7)	37 (35,6)	25 (36,2)	27 (32,1)

Treme ± Durva bei aHCC

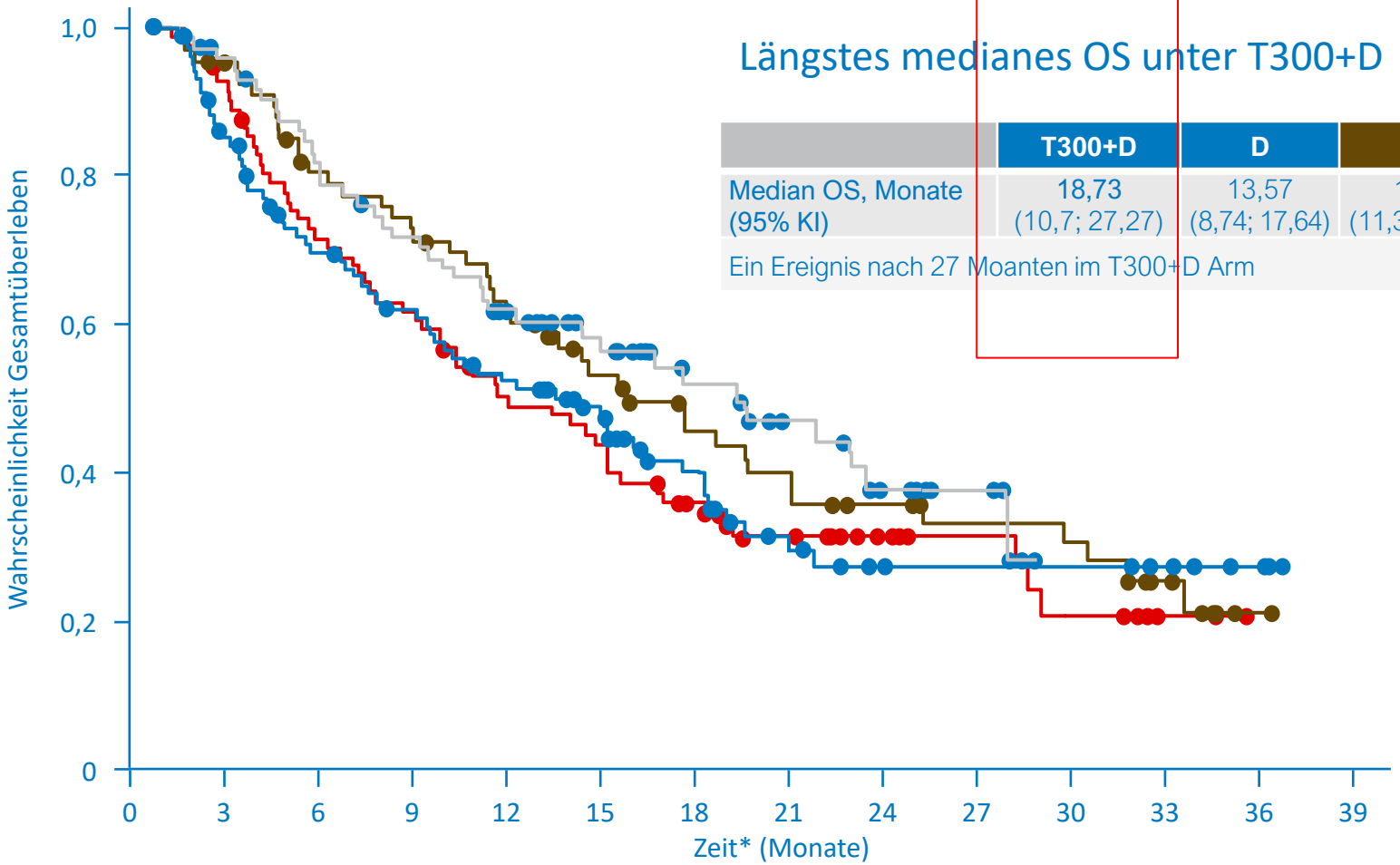
AEs

N (%)	T300+D (N=74)	D (N=101)	T (N=69)	T75+D (N=82)
AEs, alle Grade	73 (98,6)	95 (94,1)	67 (97,1)	80 (97,6)
TRAEs, alle Grade	61 (82,4)	61 (60,4)	58 (84,1)	57 (69,5)
AEs Grad 3 oder 4	43 (58,1)	56 (55,4)	46 (66,7)	50 (61,0)
TRAEs Grad 3 oder 4	26 (35,1)	20 (19,8)	30 (43,5)	20 (24,4)
Alle AEs, die zum Tode führten	4 (5,4)	4 (4,0)	2 (2,9)	2 (2,4)
TRAE, die zum Tode führten[a]	**1 (1,4)**	**3 (3,0)**	**0**	**1 (1,2)**
Alle SAEs (inkl. zum Tode führende Ereignisse)	31 (41,9)	43 (42,6)	36 (52,2)	36 (43,9)
TRSAEs (inkl. zum Tode führende Ereignisse)	**12 (16,2)**	**11 (10,9)**	**17 (24,6)**	**12 (14,6)**
Alle AEs, die zum Abbruch der Studientherapie führten	9 (12,2)	12 (11,9)	13 (18,8)	11 (13,4)
TRAEs, die zum Abbruch der Studientherapie führten	**8 (10,8)**	**8 (7,9)**	**9 (13,0)**	**5 (6,1)**
TRAEs, die zum Kortikosteroid-Einsatz führten	**18 (24,3)**	**10 (9,9)**	**18 (26,1)**	**20 (24,4)**
TRAEs Grad 3 oder 4, die zum Kortikosteroid-Einsatz führten	8 (10,8)	7 (6,9)	14 (20,3)	8 (9,8)

[a]T300+D Arm (Pneumonie), D Arm (Pneumonie, Leberversagen, Leberfunktion beeinträchtigt), T75+D Arm (Leberversagen)

Treme ± Durva bei aHCC

OS



Längstes medianes OS unter T300+D

	T300+D	D	T	T75+D
Median OS, Monate (95% KI)	18,73 (10,7; 27,27)	13,57 (8,74; 17,64)	15,11 (11,33; 20,50)	11,30 (8,38; 14,95)

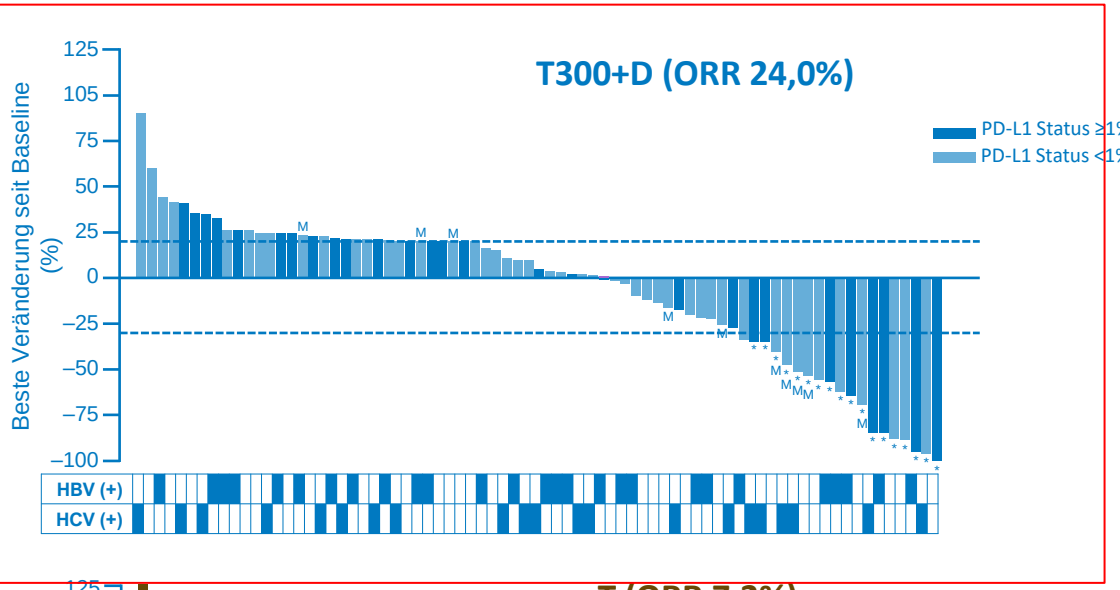
Ein Ereignis nach 27 Moanten im T300+D Arm

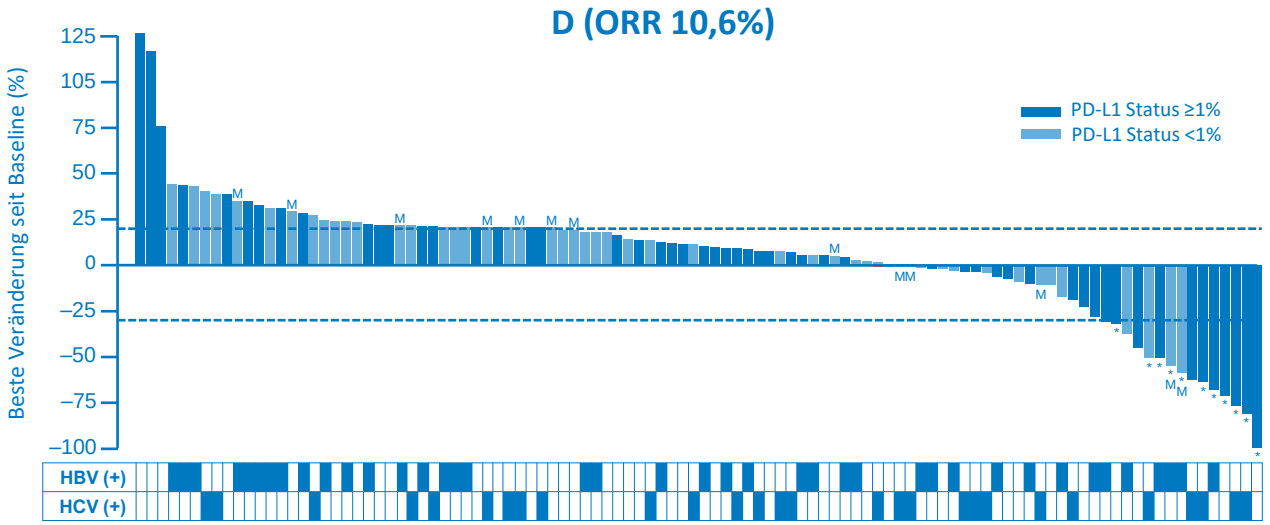
Anzahl Patienten														
	T300+D	75	67	56	48	39	30	22	16	10	5	0	0	0	0
	D	104	78	65	54	46	31	20	14	8	8	8	5	1	0
	T	69	62	51	45	38	29	23	18	16	13	11	5	0	0
	T75+D	84	69	56	48	38	30	23	17	10	9	6	2	0	0

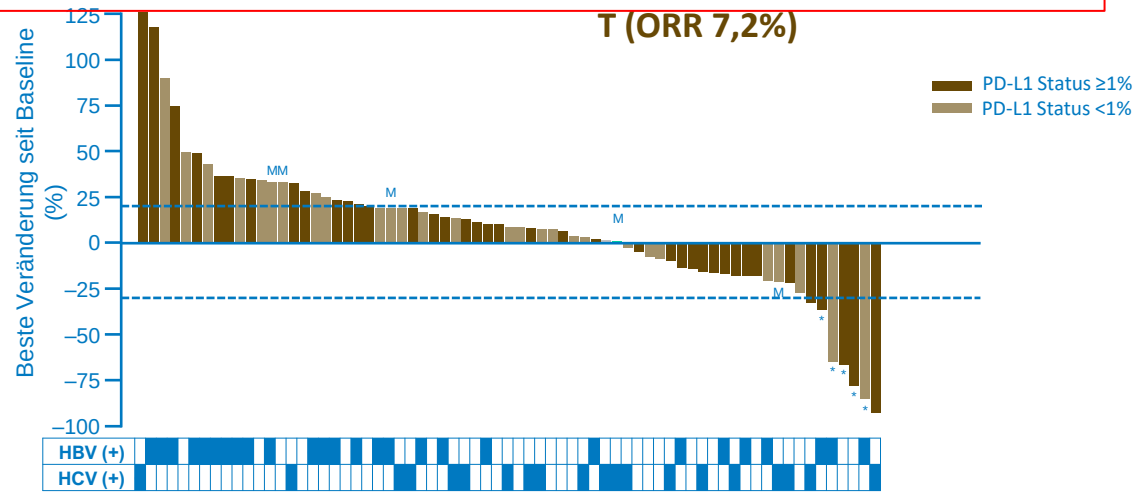
*Zeit seit Randomisierung (Teil 2A, 3) oder erster Dosis (Teil 2B)

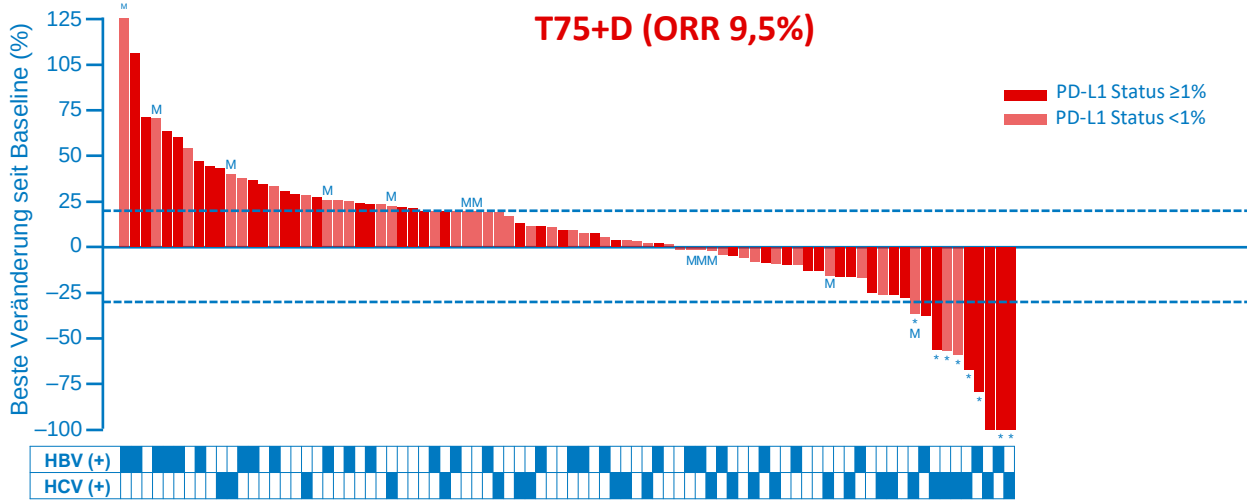
Treme ± Durva bei aHCC

Ansprechen (unabhängig von PD-L1- oder viralem Status)









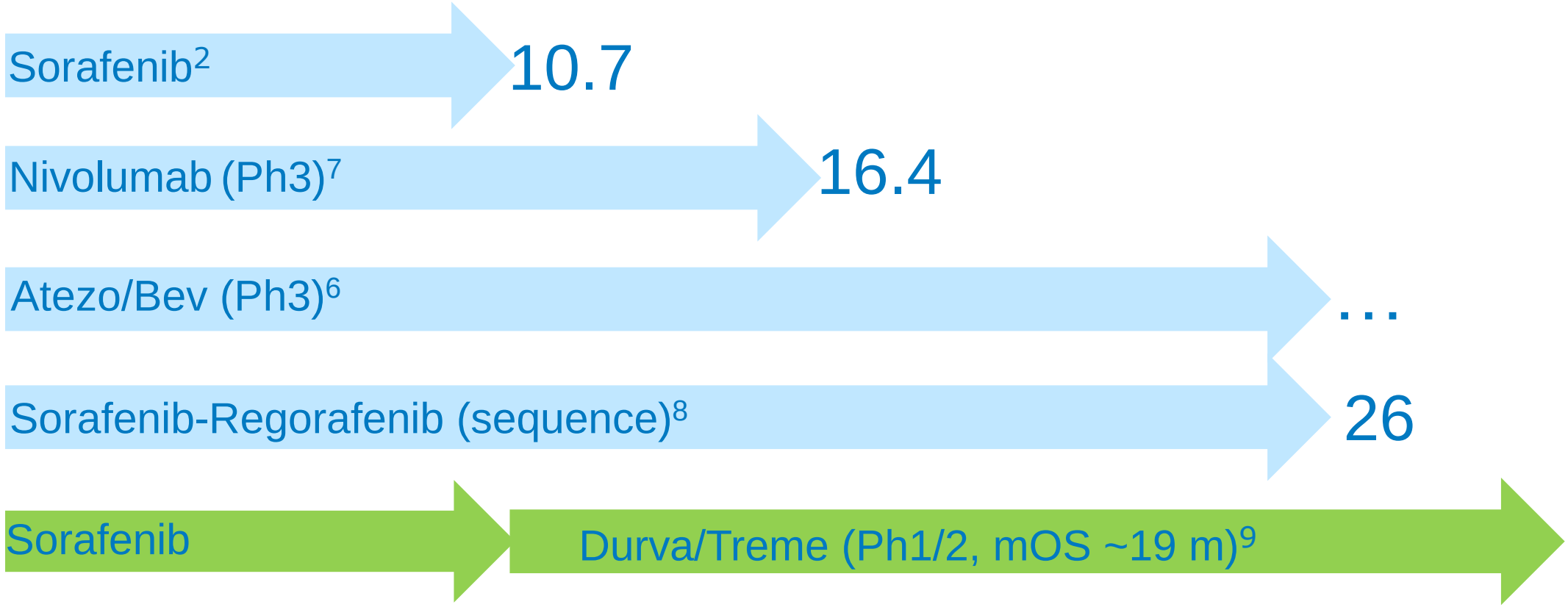
*Responder; M, PD-L1 Status fehlend

PD-L1 Status kalkuliert als Gesamtzahl von PDL1-positiven Tumorzellen und tumorassoziierten Immunzellen pro Tumorbereich

ZUSAMMENFASSUNG

- Durva+Treme: vielversprechende Überlebensdaten (mOS in second-line setting: ca. 19 mo)
- Gute Tolerabilität
- „One-shot“ hochdosiertes Tremelimumab (ähnlich wie Nivo+ hochdosiertes Ipi in der Checkmate 040 Studie)
- → Ergebnisse der entsprechende Ph III Studie (Himalaya): coming soon

Evolution of systemic treatment of HCC



De Toni EN, Gut. 2019 Oct 14

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Lenva + Pembro bei uHCC

Studiendesign

Phase 1b Studie zu Lenvatinib + Pembrolizumab beim unresektablen HCC

Lenvatinib 12 oder 8 mg/Tag po (je nach Körpergewicht)
+ **Pembrolizumab** 200 mg iv an Tag 1 (21-Tage Zyklus)

Teil 1:

Evaluation der Dosis limitierenden Toxizität (DLT)
N=6
Patienten ohne Option für andere Therapien
Tolerabilität evaluiert mittels DLTs in Zyklus 1

Teil 2:
Expansion

N = 98 vorherige Therapie der uHCC

Keine

Haupteinschlusskriterien
- uHCC
- BCLC-Stadium B (nicht geeignet für TACE) oder C
- Child-Pugh Klasse A
- ECOG PS 0-1
- ≥1 messbarer Referenzherd (mRECIST)

Tolerabilität evaluiert bei Patienten ohne Option für andere angemessene Therapien (inkl. Sorafenib) nach 3 +3 Design

Tumorassessments mit Komplett- oder partieller Remission wurden ≥4 Wochen nach initialem Ansprechen bestätigt

Primäre Endpunkte:
- Sicherheit und Tolerabilität (Teil 1)
- ORR und DOR (mRECIST und RECIST v1.1 basierend auf IIR (Teil 2)

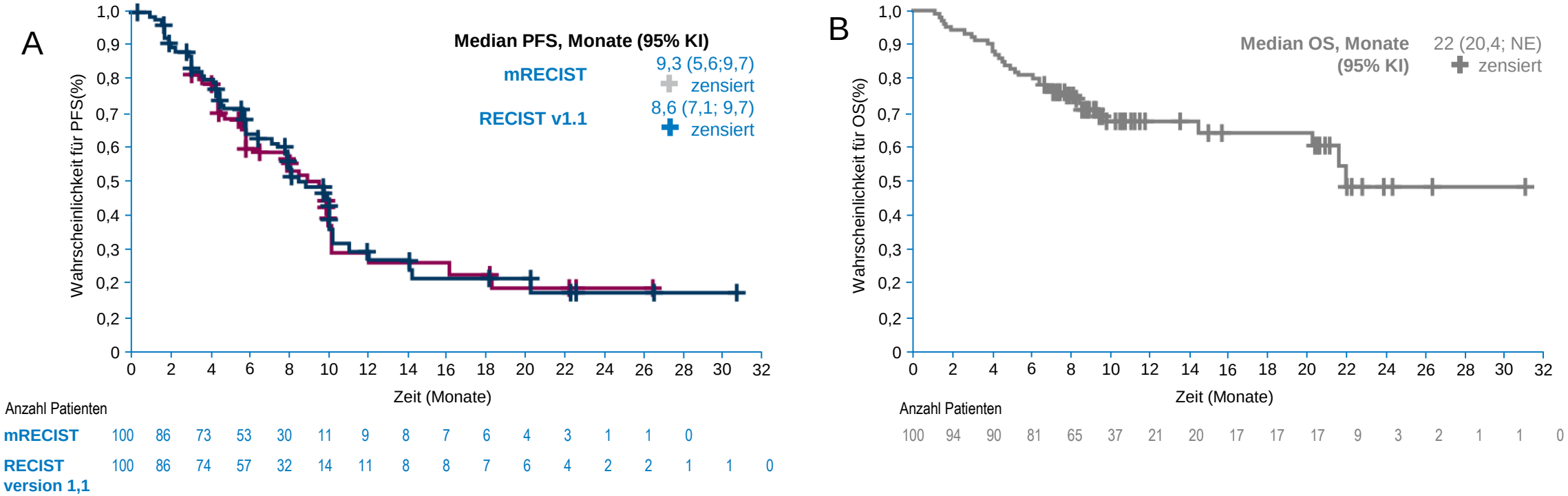
Ausgewählte sekundäre und explorative Endpunkte:
- PFS
- Zeit bis zur Progression
- OS
- Pharmakokinetik
- Anti-Pembrolizumab-Antikörper

Tumorassessments nach mRECIST (IR und IIR) und RECIST v1.1 (IIR)

Lenva + Pembro bei uHCC

Progressionsfreies Überleben und Gesamtüberleben

Kaplan-Meier-Schätzungen von (A) PFS nach mRECIST und RECIST v1.1 (IIR) und (B) OS (Wirksamkeitsanalyse-Set)



Zhu AX et al. | Abstract 4519 | ASCO 2020

Lenva + Pembro bei uHCC

Sicherheit und Nebenwirkungen

- Im Erstlinien-Setting lag die mittlere Levantinib+Pembrolizumab-Exposition bei 7,9 Monaten (0,2-31,1); 7,6 Monate für Lenvatinib (0,2-31,1) und 7,4 Monate für Pembrolizumab (0,03-23,5)
- Grad ≥3 TRAEs traten bei 67 Patienten auf (N=63 Grad 3 (63%), N=1 Grad 4 (1%) und N=3 Grad 5 (3%))
  - Die TRAEs Grad 5 waren ARF/ARDS (N=1), Leberfunktionsstörungen (N=1) und Darmperforation (N=1), alles bereits beschriebene potentielle TRAEs dieser Substanzklasse
  - Es gab 1 TRAE Grad 4: Leukopenie/Neutropenie

Häufigste TRAEs (bei ≥20% Patienten mit jeglichen TRAEs)

Adverse Events, N (%)	Lenvatinib + Pembrolizumab (N=100)			
	Alle Grade	Grad 1	Grad 2	Grad 3
Bluthochdruck	36 (36)	1 (1)	18 (18)	17 (17)
Diarrhö	35 (35)	19 (19)	11 (11)	5 (5)
Fatigue	30 (30)	12 (12)	14 (14)	4 (4)
Verminderter Appetit	28 (28)	12 (12)	16 (16)	0
Hypothyreose	25 (25)	11 (11)	14 (14)	0
Hand-Fuß-Syndrom	23 (23)	13 (13)	9 (9)	1 (1)
Vermindertes Gewicht	22 (22)	8 (8)	11 (11)	3 (3)
Dysphonie	21 (21)	19 (19)	1 (1)	1 (1)
AST-Anstieg	20 (20)	4 (4)	5 (5)	11 (11)
Proteinurie	20 (20)	9 (9)	7 (7)	4 (4)

Therapiebedingte AEs führten zu Lenvatinib Therapieabbruch bei 14 Patienten (14%), zu Pembrolizumab Therapieabbruch bei 10 Patienten (10%) und beiden Medikamenten bei 6 Patienten (6%)

ARF/ARDS: acute respiratory failure/acute respiratory distresss syndrome

Zhu AX et al. | Abstract 4519 | ASCO 2020

Mögliche Entwicklung der systemischen Therapie des HCC

FIRST LINE

SECOND LINE +

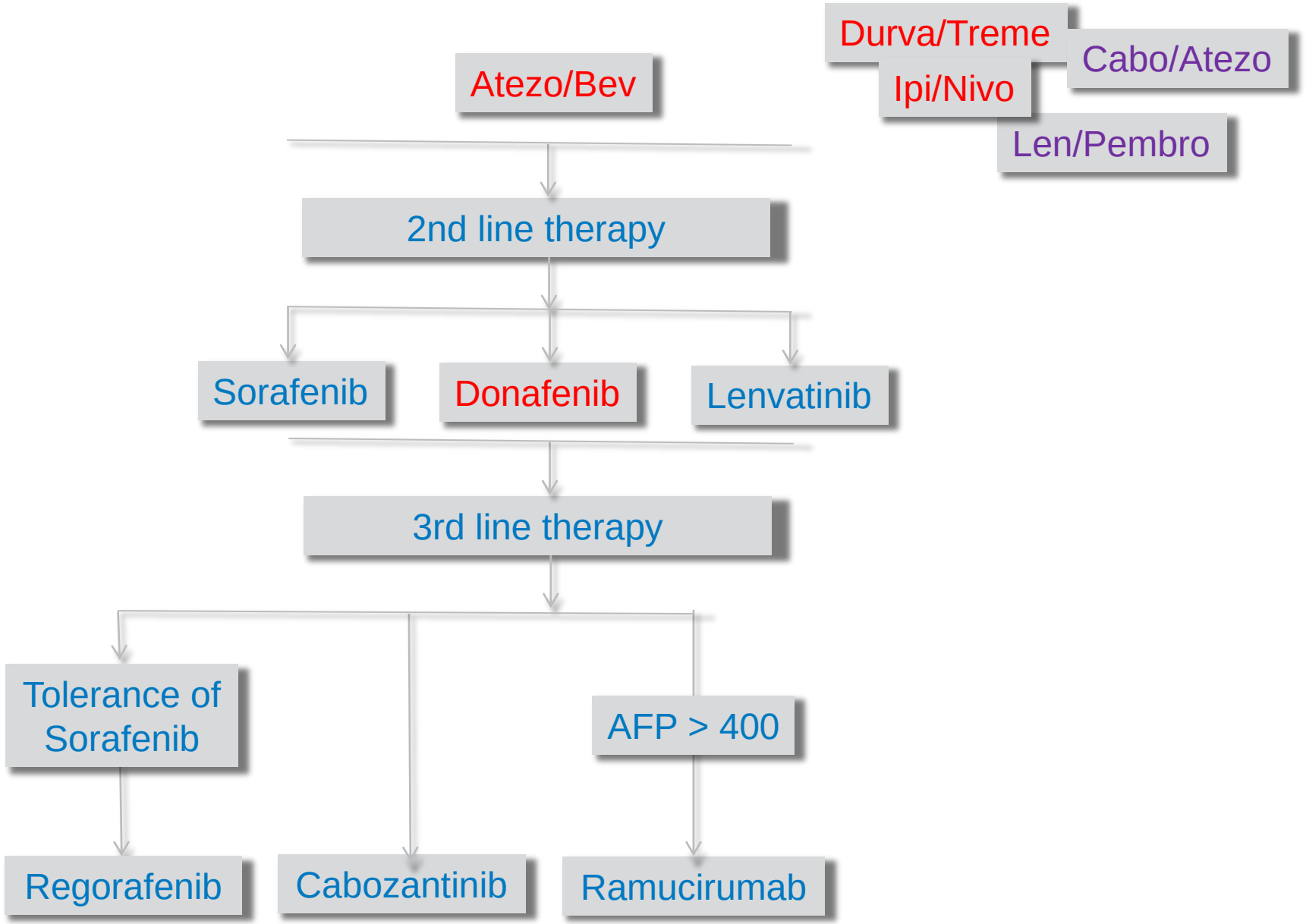


Abbildung: Najib Ben Khaled

Agenda

- Introduction: HCC epidemiology and therapeutic stratification
- Evolution of systemic treatment of HCC: TKI and VEGFi
- One word about SIRT
- Checkpoint inhibitors in the treatment of advanced HCC
- The latest novelties (update ASCO 2020)
- Perspectives: Use them early?

ASCO 2020 ausgewählte Abstracts

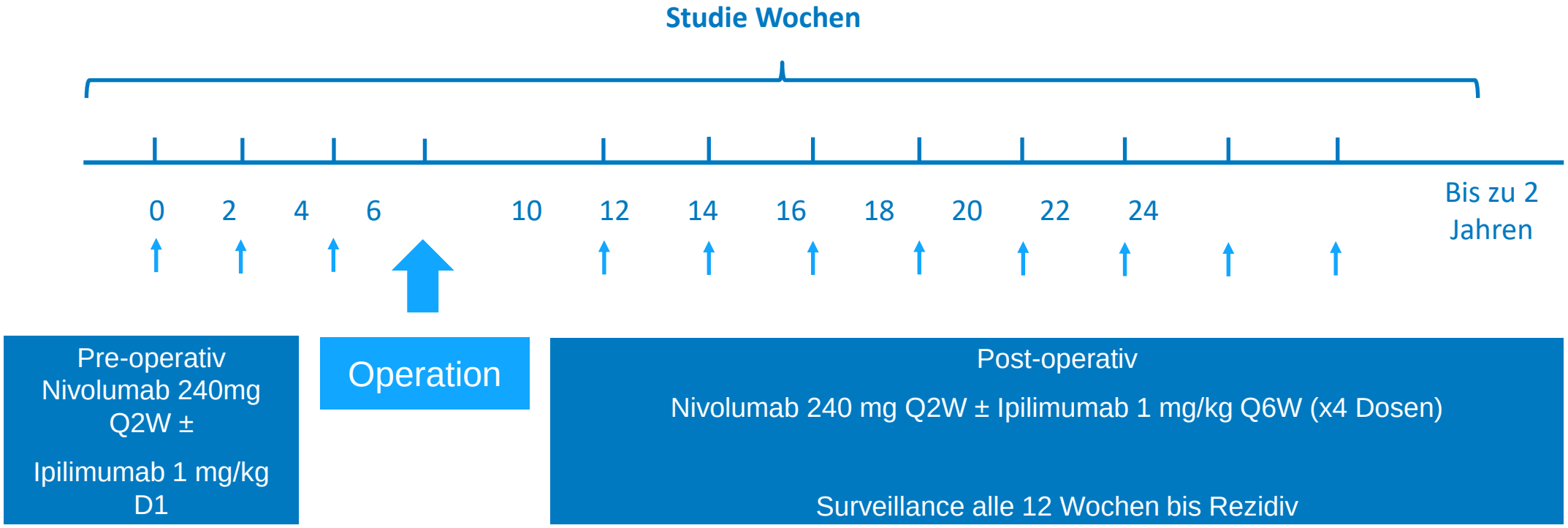
1) Efficacy, tolerability, and biologic activity of a novel regimen of tremelimumab in combination with durvalumab for patients with advanced HCC

2) A phase Ib study of lenvatinib plus pembrolizumab in unresectable HCC

3) Final results of a randomised, open label, perioperative Phase II study evaluating nivolumab alone or nivolumab + ipilimumab in patients with resectable HCC

Nivo ± Ipi bei resektablem HCC

Studiendesign



Primärer Endpunkt: Sicherheit

Nivo ± Ipi bei resektablem HCC

Ergebnisse und Zusammenfassung

Ergebnisse

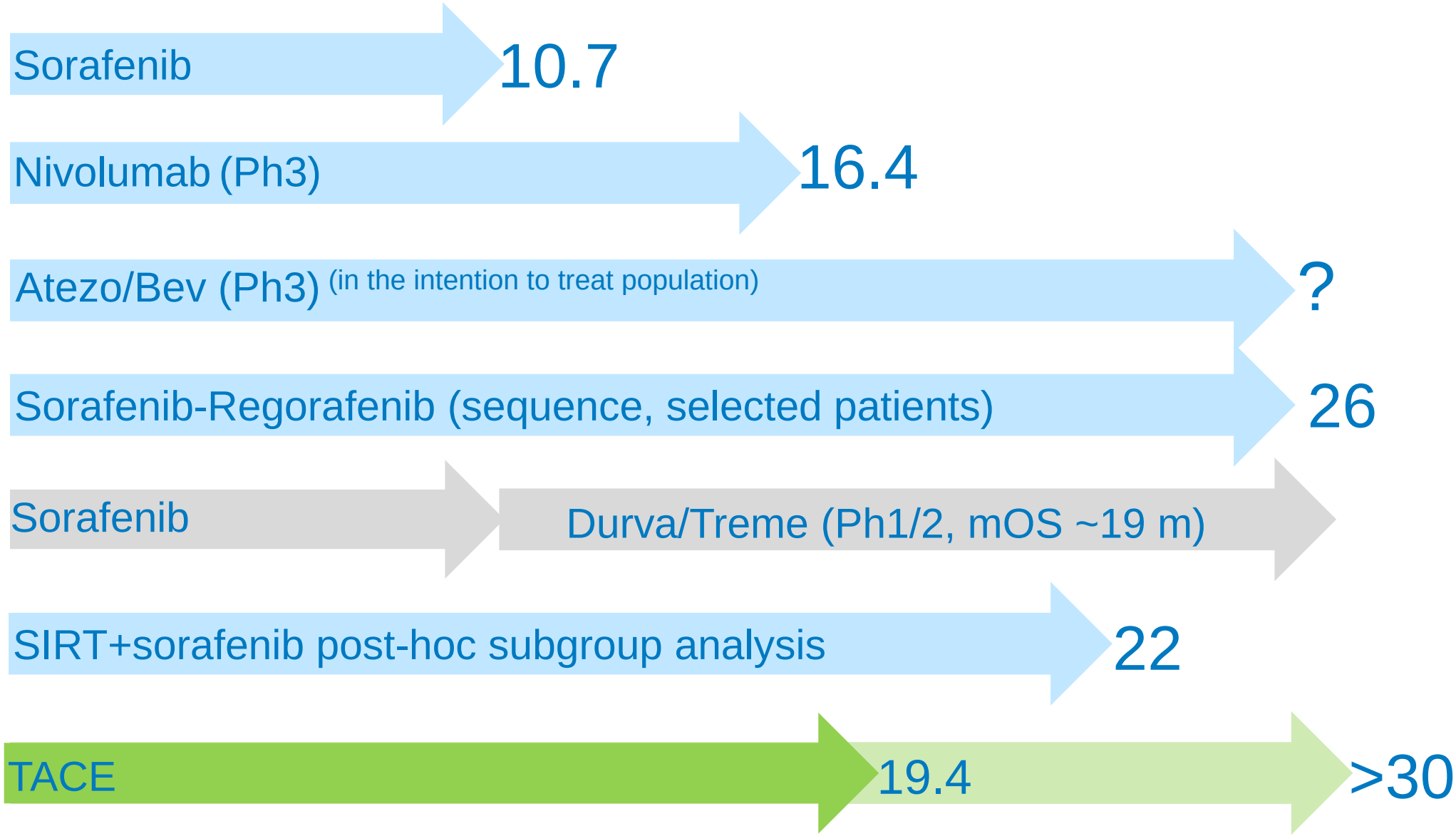
- 30 Patienten wurden eingeschlossen und 27 davon randomisiert (2 zogen ihr Einverständnis zurück, 1 war zum Zeitpunkt der Therapie nicht verfügbar); bei 21 Patienten wurde die Resektion wie geplant durchgeführt, bei 6 Patienten wurde die Operation ausgesetzt (1x wegen Frozen Abdomen nach vorheriger Operation, 2x wegen kleinem Residualherd und 3x wegen Progression; keine Operation wurde wegen Toxizitäten abgesetzt). Baseline Charakteristika: Alter 32-83 Jahre, 75% männlich, je 7x HCV, HBV und keine Hepatitis

	Arm A, N=13	Arm B, N=14	Gesamt, N=27
pCR, N (%)	2	3	5 (19%)
Major pCR*, N (%)	1	2	3 (11%)
Grad ≥3 AEs	4	2	6

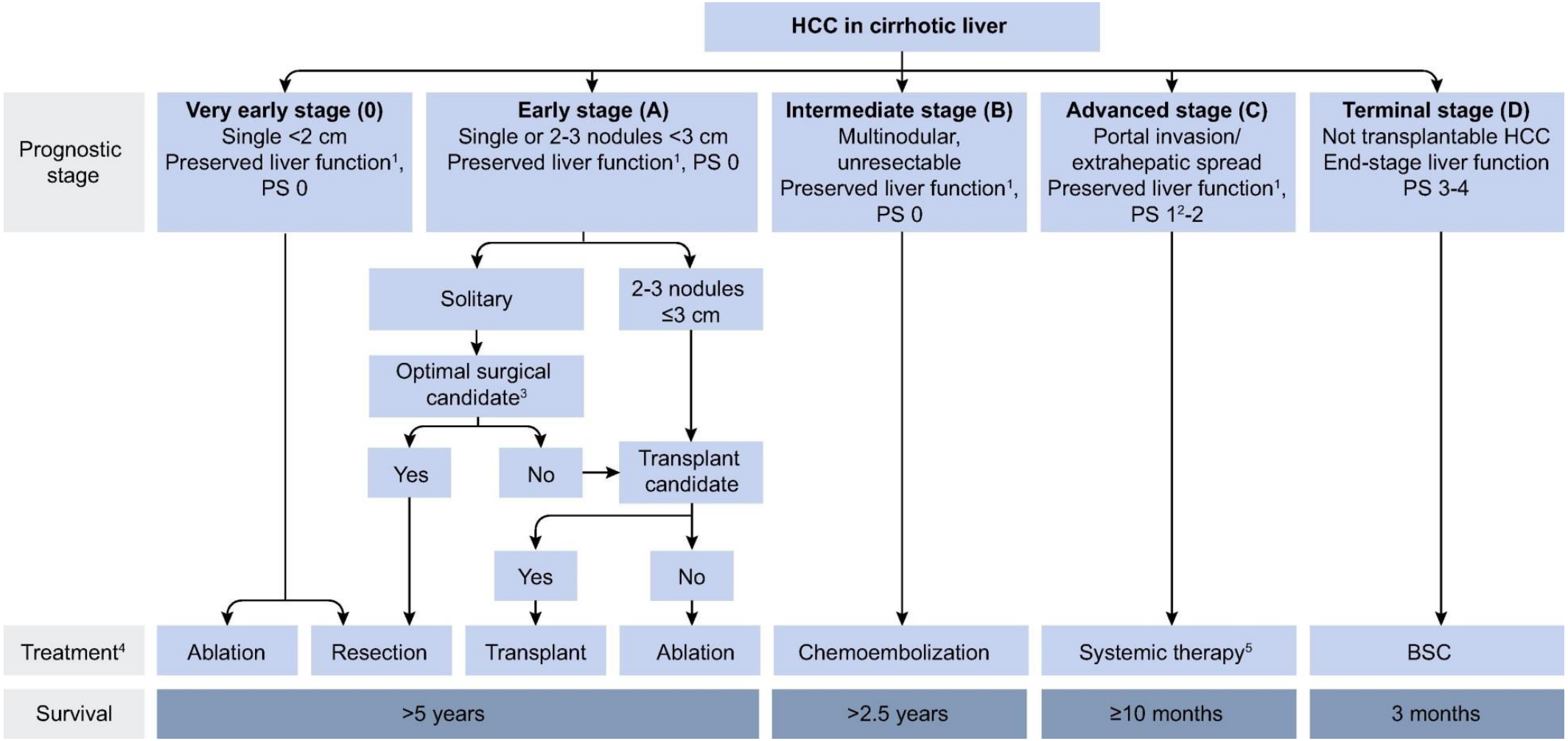
Zusammenfassung

- Die Phase-2-Studie erreichte ihren primären Endpunkt zur Sicherheit beim resektablem HCC nach präoperativer Immuntherapie: 40% pathologische Remissionsrate (24% pCR und 16% Major-Nekrose-Rate).
- Nach Validierung der Ergebnisse könnten diese vielversprechenden Resultate zu einem Paradigmenwechsel der perioperativen Therapie beim operablen HCC führen.

*Nekrose-Effekt von 50-99%)



De Toni EN, Gut. 2019 Oct 14



- Adjuvant therapies in early HCC (after resection/ablation)

a) Nivolumab vs placebo
b) Pembrolizumab vs placebo
c) Atezolizumab+pembrolizumab vs placebo
d) Durvalumab+ bevacizumab vs placebo

EMAND

Advanced HCC (first line)

a) Lenvatinib+ pembrolizumab vs lenvatinib
b) Durvalumab+tremelinumab vs sorafenib
c) Nivolumab + ipilinumab vs lenvatinib/sorafenib
d) Cabozantinib + atezolizumab vs sorafenib

Conclusion

- Survival of advanced HCC has increased in recent years due to the established schemas of TKI-based treatment sequence
- A major achievement is the advent of immune checkpoint inhibitors used in combination (CPI+CPI, CPI+VEGFi, CPI+TKI)
- Do not use SIRT (or SIRT+sorafenib in subgroups) outside of clinical studies with clinical endpoint
- Atezo/Bev is coming soon → until then. INCLUDE YOUR PATIENTS IN CLINICAL TRIALS
- Next step: use of CPI in combination with TACE, Adjuvant, perioperative → BEFORE YOU TACE SEARCH FOR A SUITABLE TRIAL OF TACE+CPI


THANK YOU