

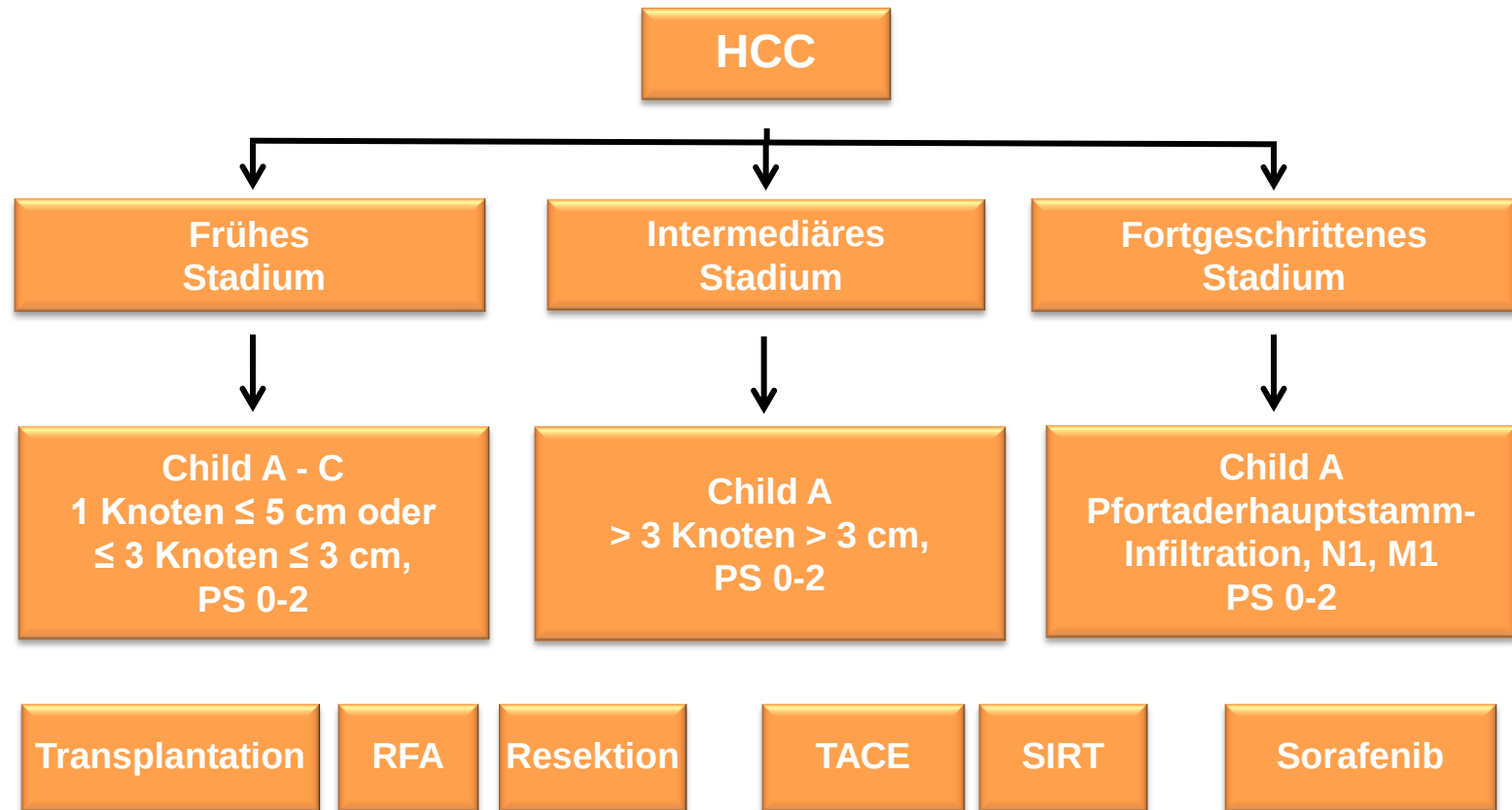
Tumoren der Leber: Update der Therapieoptionen



Arndt Vogel

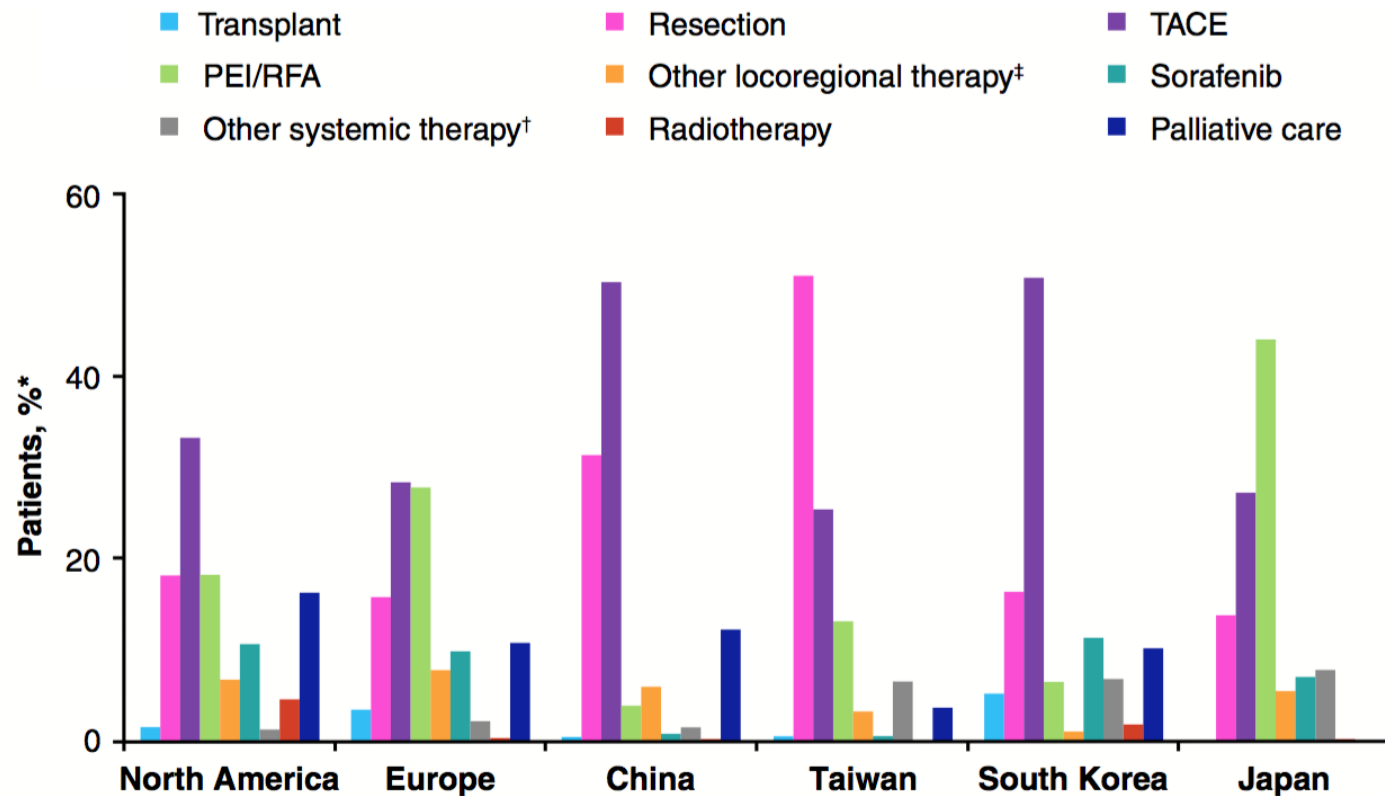
Medizinische Hochschule
Hannover

Therapie des HCC



Wie wird welt-weit behandelt?

BRIDGE Study: 18301 Patienten in 14 Ländern



Viel TACE, wenig Systemische Therapie!

Systemische Therapie des HCC

10 Jahre

2 Jahre

1 Substanz

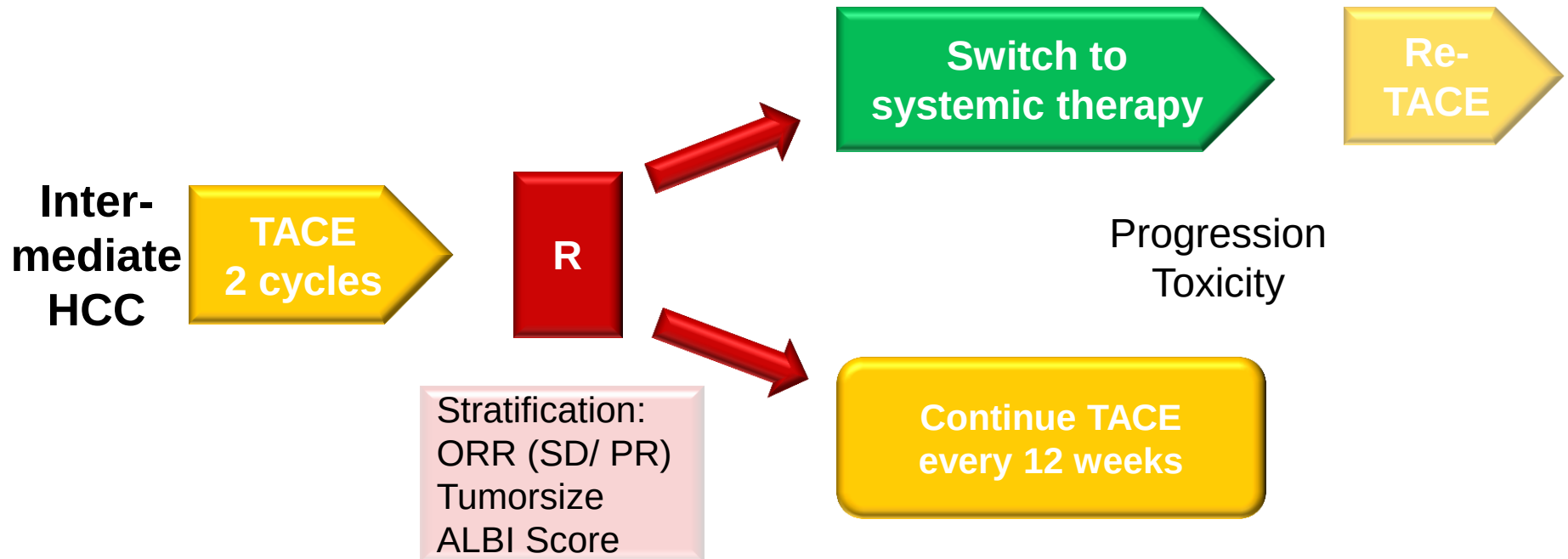
5 Substanzen!

2007 - 2017

2016 - 2018

TACEnd Phase-II Study

TACE followed by systemic therapy compared to continuous TACE in intermediate stage hepatocellular carcinoma (HCC)



Primary Endpoint: OS

2nd EP: PFS, TTP, ORR, QoL

Fall – Herr S., 73 Jahre

09/2015 ED pulm.+ lymph. metastasiertes HCC

Keine Zirrhose, exzellenter AZ

09/ 15



Start Sorafenib

09/ 15 - 08/ 16



Progress unter Sorafenib

Regorafenib beim HCC, 2. Linie

RESORCE trial design

Clinicaltrials.gov NCT01774344

- HCC patients with documented radiological progression during sorafenib treatment
- Stratified by:
 - Geographic region (Asia vs ROW)
 - Macrovascular invasion
 - Extrahepatic disease
 - ECOG PS (0 vs 1)
 - AFP (<400 ng/mL vs ≥400 ng/mL)

R
2:1

Regorafenib
160 mg po once daily
3 weeks on / 1 week off
(4-week cycle)
(n=379)

N= 573

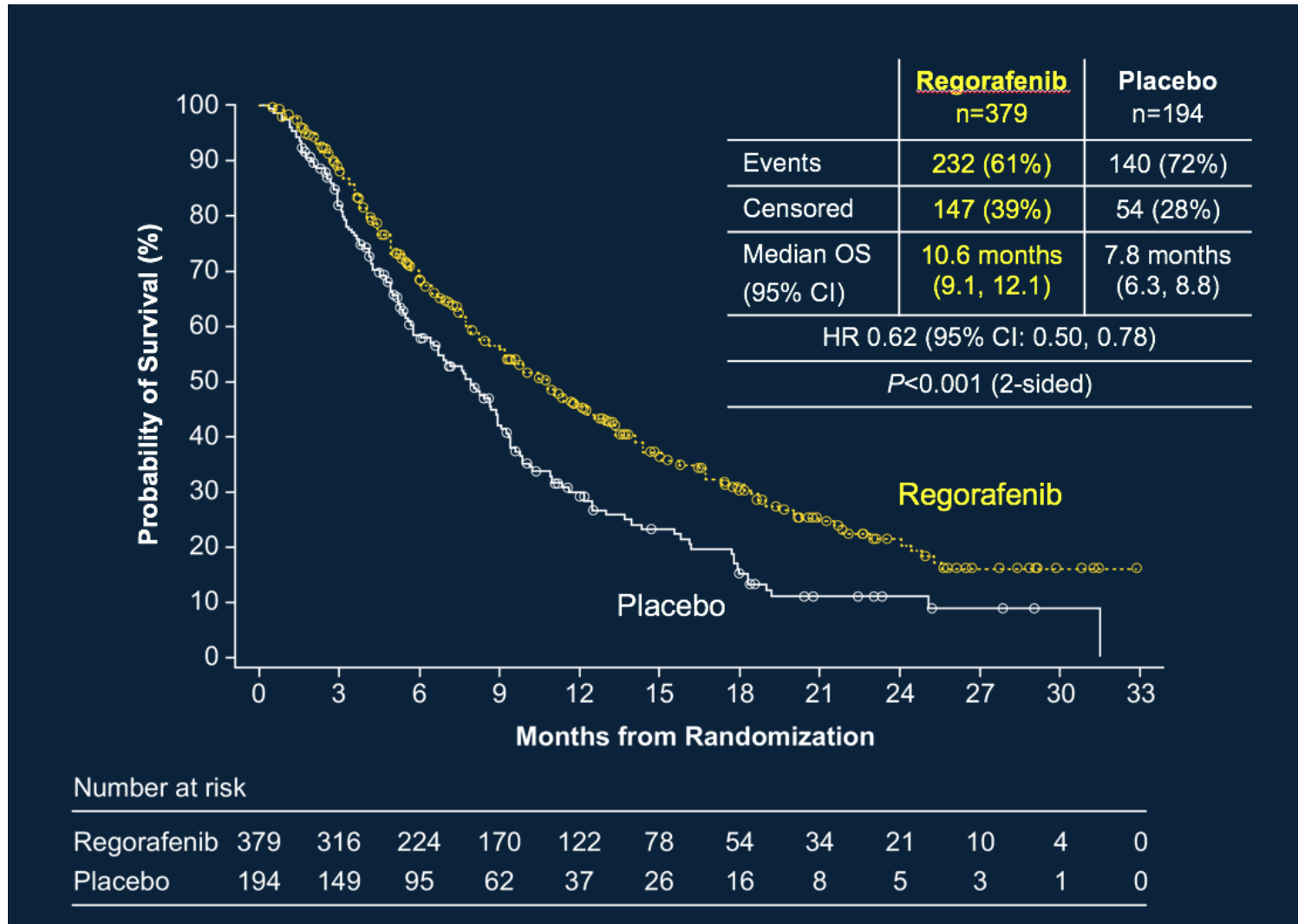
Placebo
(n=194)

- 152 centers in 21 countries in North and South America, Europe, Australia, Asia
- All patients received best supportive care
- Treat until progression, unacceptable toxicity, or withdrawal

ROW, rest of the world; ECOG PS, Eastern Cooperative Oncology Group performance status; AFP, alpha-fetoprotein

Bruix J, et al. Presented at World Congress on Gastrointestinal Cancer 2016

Regorafenib beim HCC, mOS

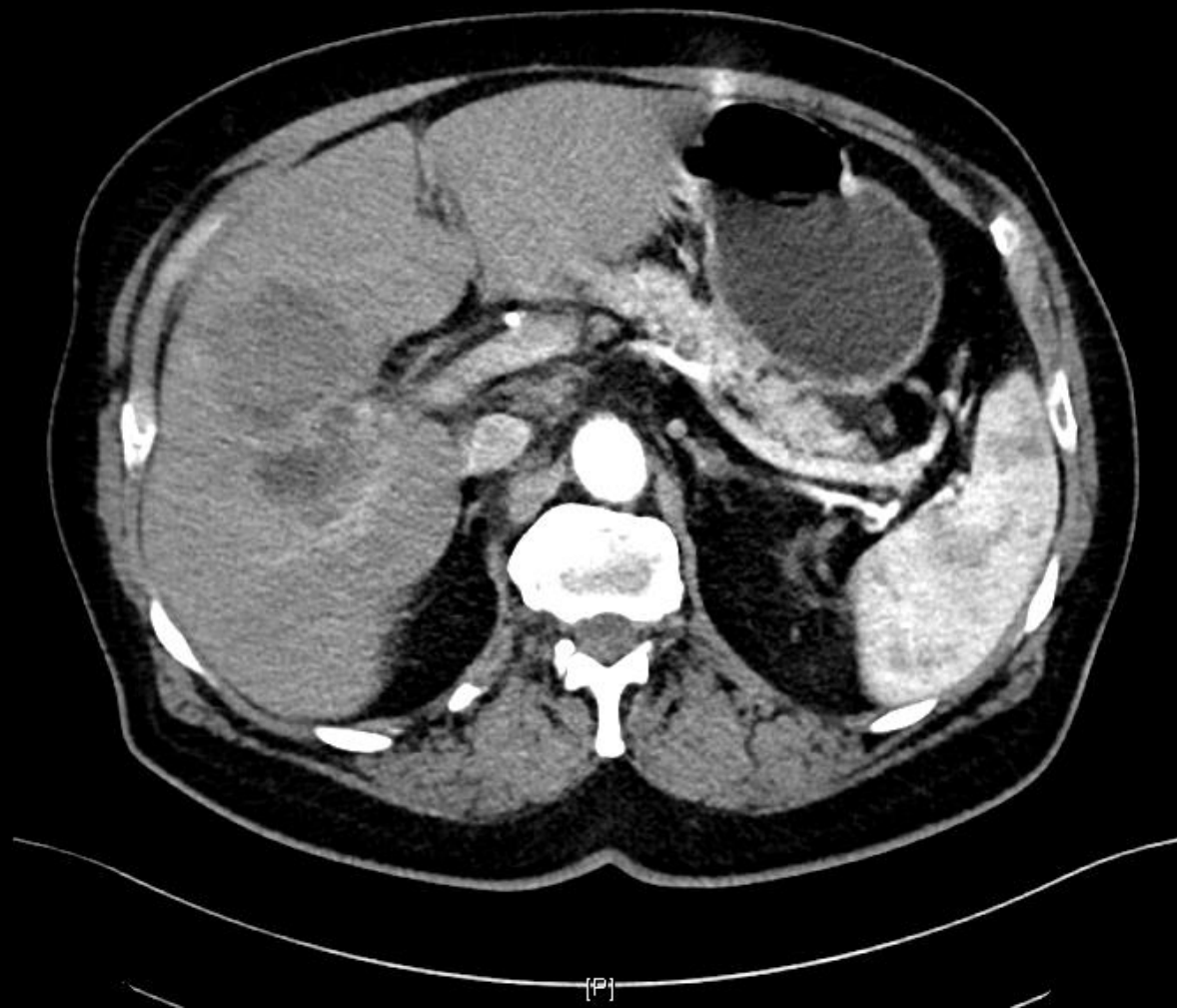


08/ 16



Start Regorafenib

11/ 16



Response unter Regorafenib

08/ 16 – 01/ 17



Progress unter Regorafenib

Immuntherapie beim HCC

CHECKMATE-040

All Patients (N = 262)

Sorafenib
Naive
N = 80

Sorafenib
Experienced
N = 182

Dose
Escalation

Nivolumab
0.1 – 10 mg/kg
n = 11

Dose
Expansion

Nivolumab
3 mg/kg
n = 69

Dose
Escalation

Nivolumab
0.1 – 10 mg/kg
n = 37

Dose
Expansion

Nivolumab
3 mg/kg
n = 145

HCV Infected

HBV Infected

Uninfected

Study Endpoints

Primary

- Safety and tolerability (ESC)
- ORR (EXP)^a

Secondary

- ORR (ESC)^a
- Disease control rate
- Time to response
- Duration of response
- Overall survival

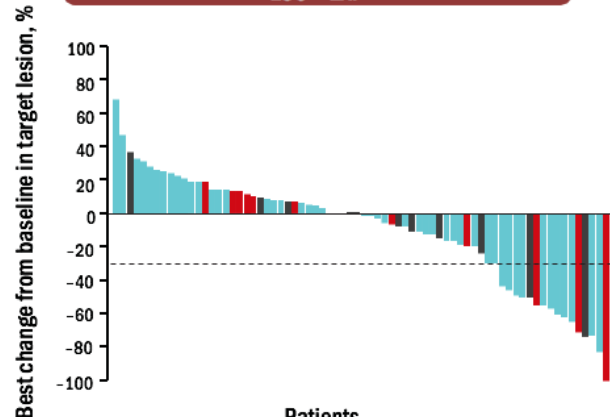
Other

- Biomarker assessments

Immuntherapie & down-staging/ neoadjuvante Therapie?

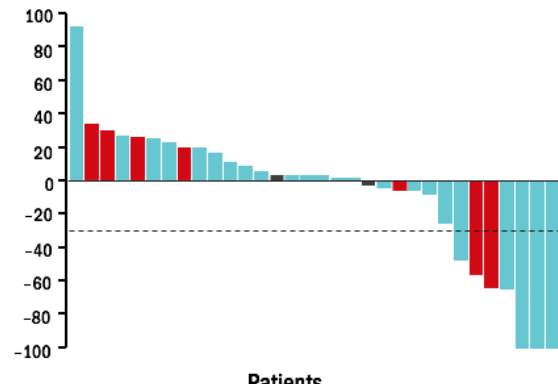
Sorafenib Naive

ESC + EXP



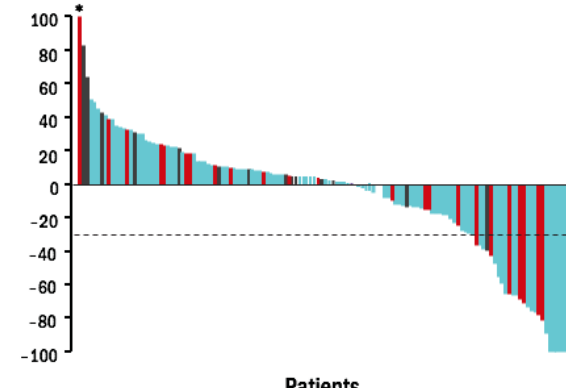
Sorafenib Experienced

ESC

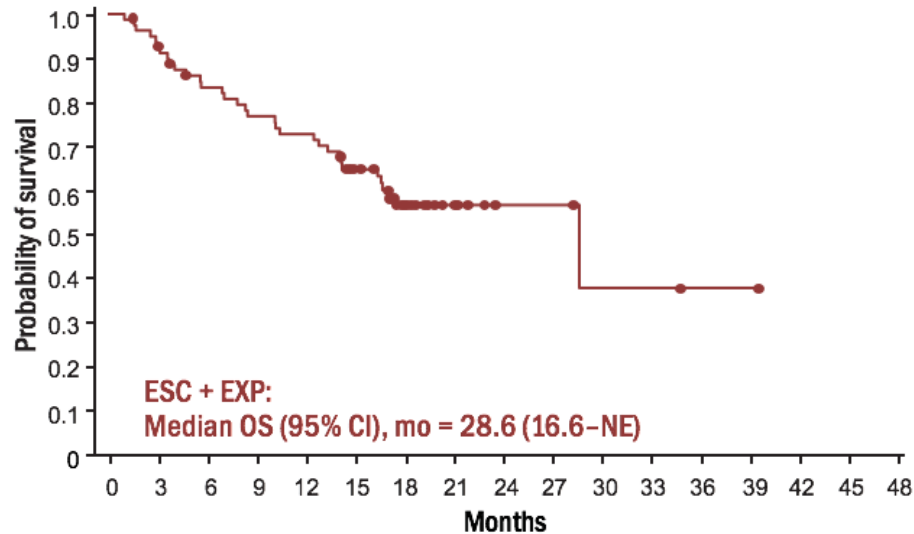


Sorafenib Experienced

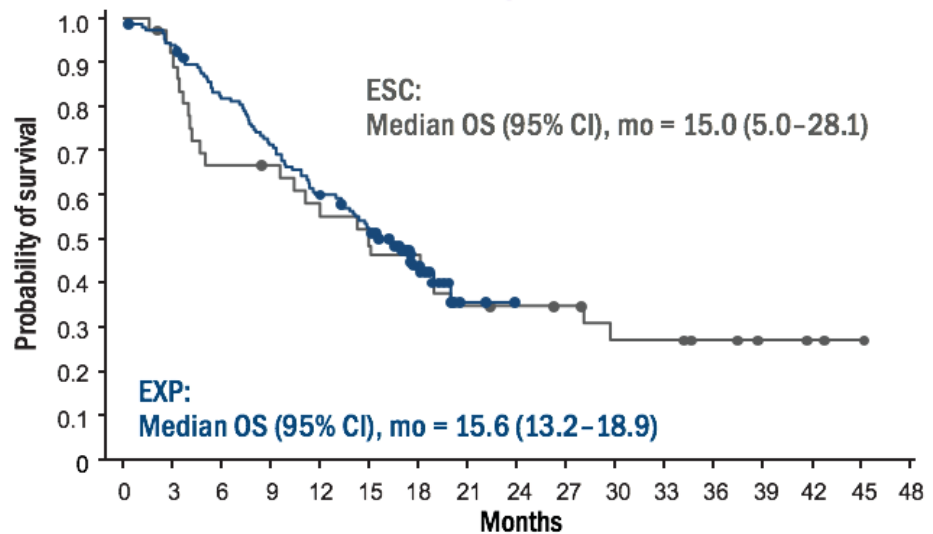
EXP



Sorafenib Naive



Sorafenib Experienced



Immuntherapie des HCC

AIO

IMMULAB

RFA, d1 of cycle 3



Frühes HCC

Pembrolizumab q3w 200 mg

IMMUTACE

TACE, d1 of cycle 1 and 3



Intermediäres HCC

Nivolumab q2w 3 mg/kg

IMMUNIB

Fortgeschrittenes
HCC

Lenvatinib 12/ 16 mg

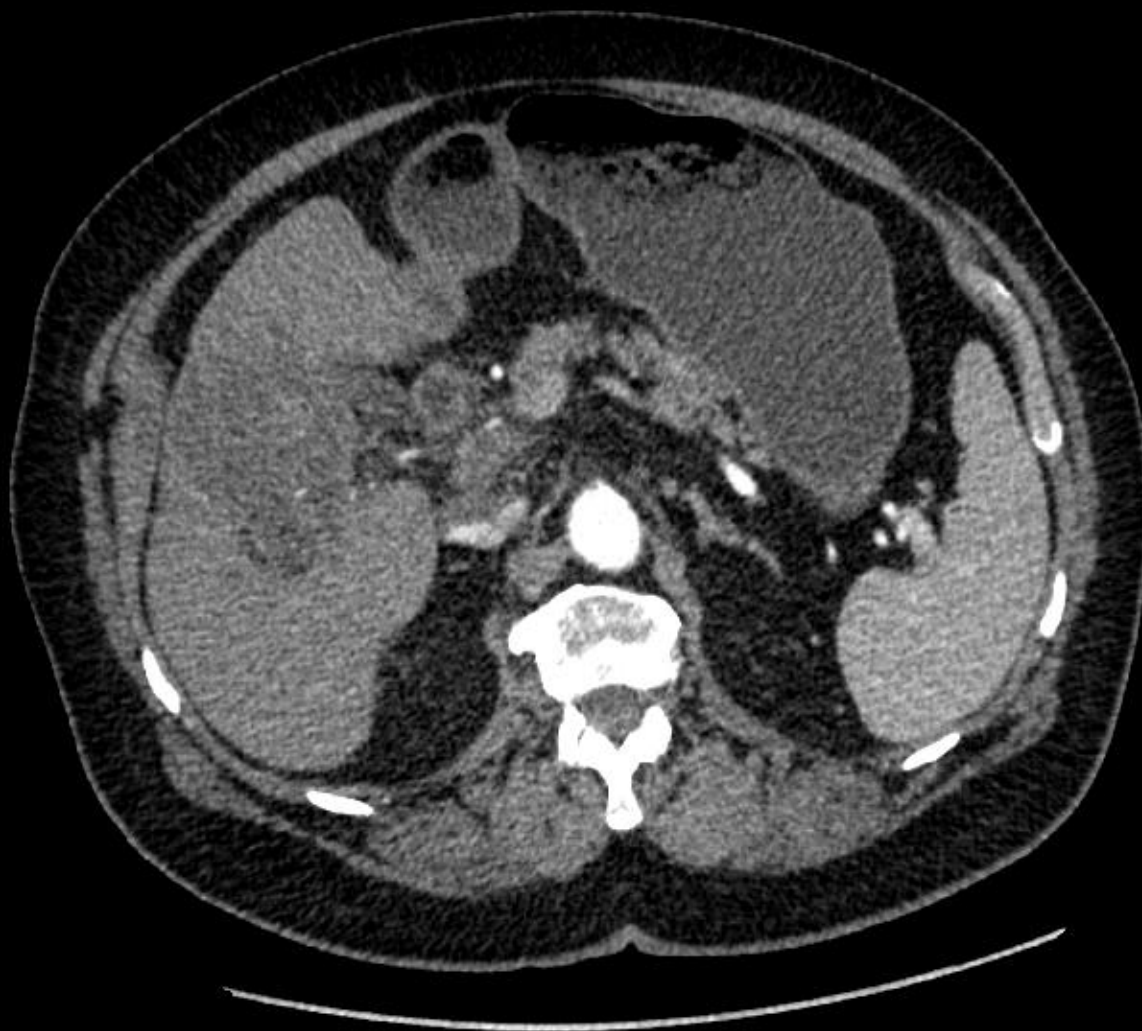
Nivolumab q2w 3 mg/kg

01/ 17



Start Nivolumab

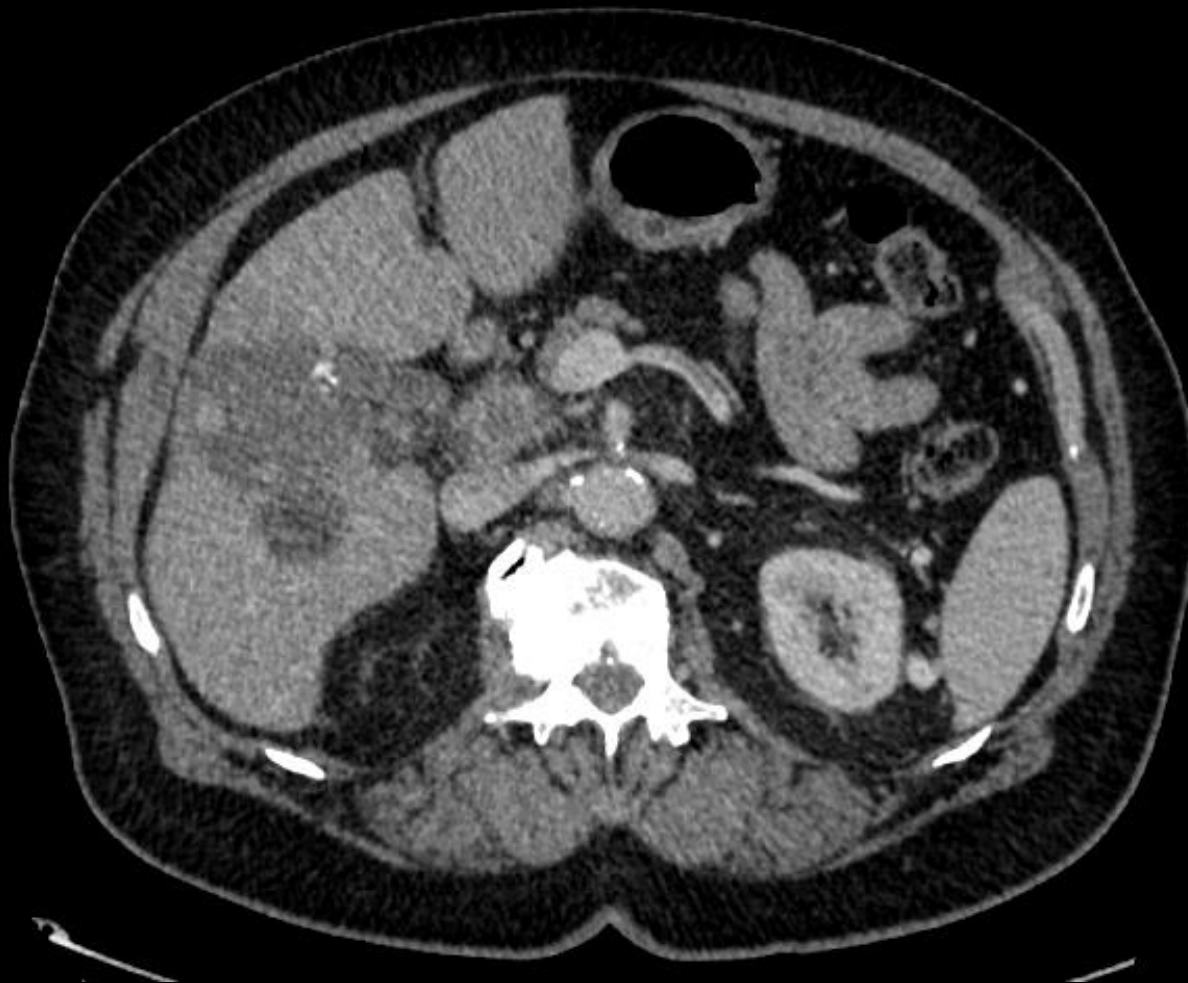
03/ 17



[P]

Response unter Nivolumab

01/ 17 – 09/ 17



Progress unter Nivolumab

Lenvatinib beim HCC, 1. Linie

Study Schema

Global, randomized, open-label, phase 3 noninferiority study

Patients with unresectable HCC (N = 954)

- No prior systemic therapy for unresectable HCC
- ≥ 1 Measurable target lesion per mRECIST
- BCLC stage B or C
- Child-Pugh A
- ECOG PS ≤ 1
- Adequate organ function
- Patients with $\geq 50\%$ liver occupation, clear bile duct invasion, or portal vein invasion at the main portal vein were excluded

Stratification

- Region: (Asia-Pacific or Western)
- MVI and/or EHS: (yes or no)
- ECOG PS: (0 or 1)
- Body weight: (< 60 kg or ≥ 60 kg)

Randomization 1:1

Lenvatinib (n = 478)

8 mg (BW < 60 kg) or
12 mg (BW ≥ 60 kg)
once daily

Sorafenib (n = 476)

400 mg twice daily

Primary endpoint:

- OS

Secondary endpoints:

- PFS
- TTP
- ORR
- Quality of life
- PK lenvatinib exposure parameters

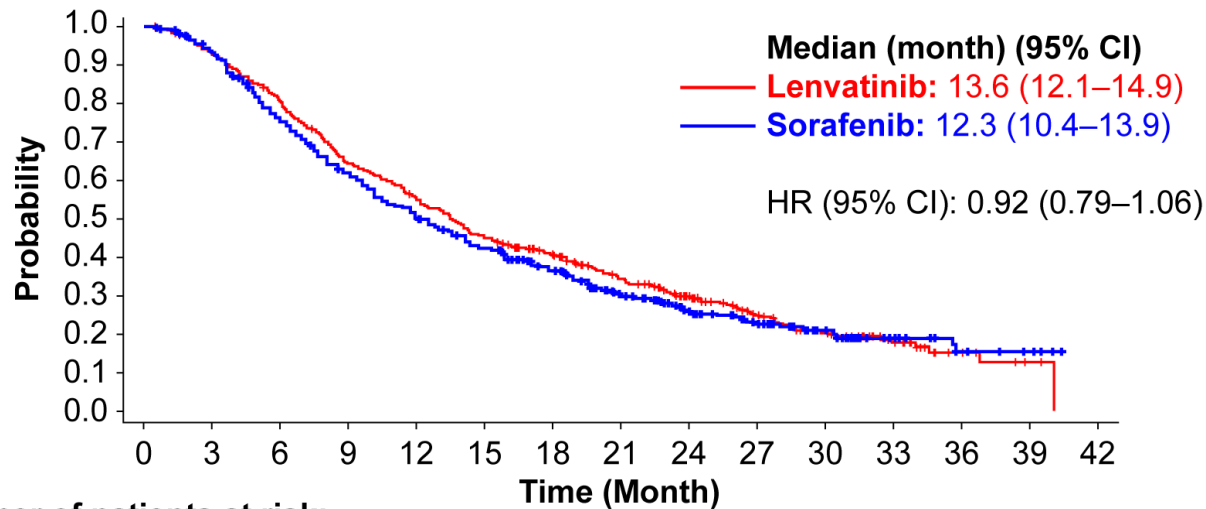
Tumor assessments were performed according to mRECIST by the investigator

BCLC, Barcelona Clinic Liver Cancer; BW, body weight; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EHS, extrahepatic spread; MVI, macroscopic portal vein invasion; mRECIST, modified Response Evaluation Criteria In Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to progression.

PRESENTED AT: **ASCO ANNUAL MEETING '17** | **#ASCO17**

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REFLECT Studie: Gesamtüberleben und Ansprechen

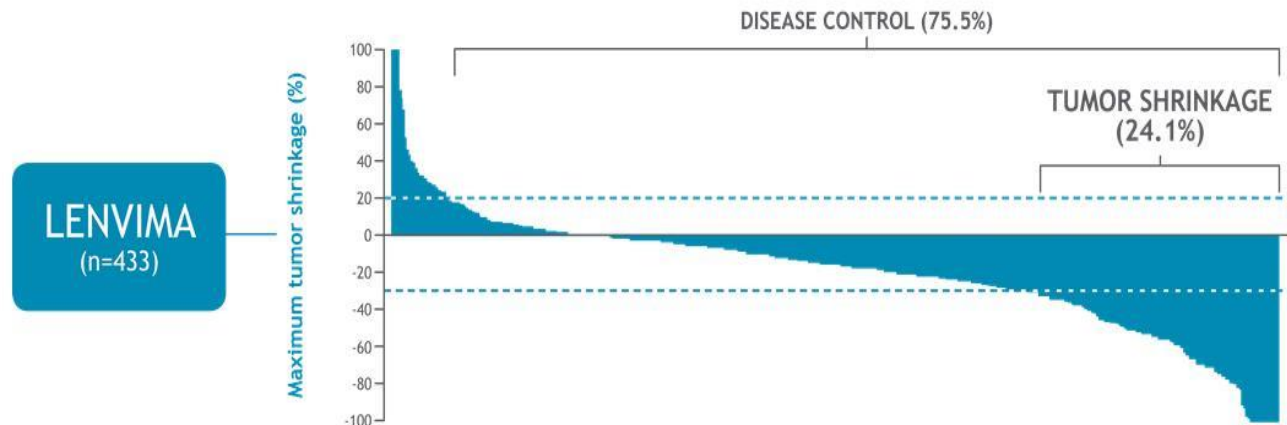


Non-inferiority margin
assumption: **1.08**
Upper HR limit, 95% CI

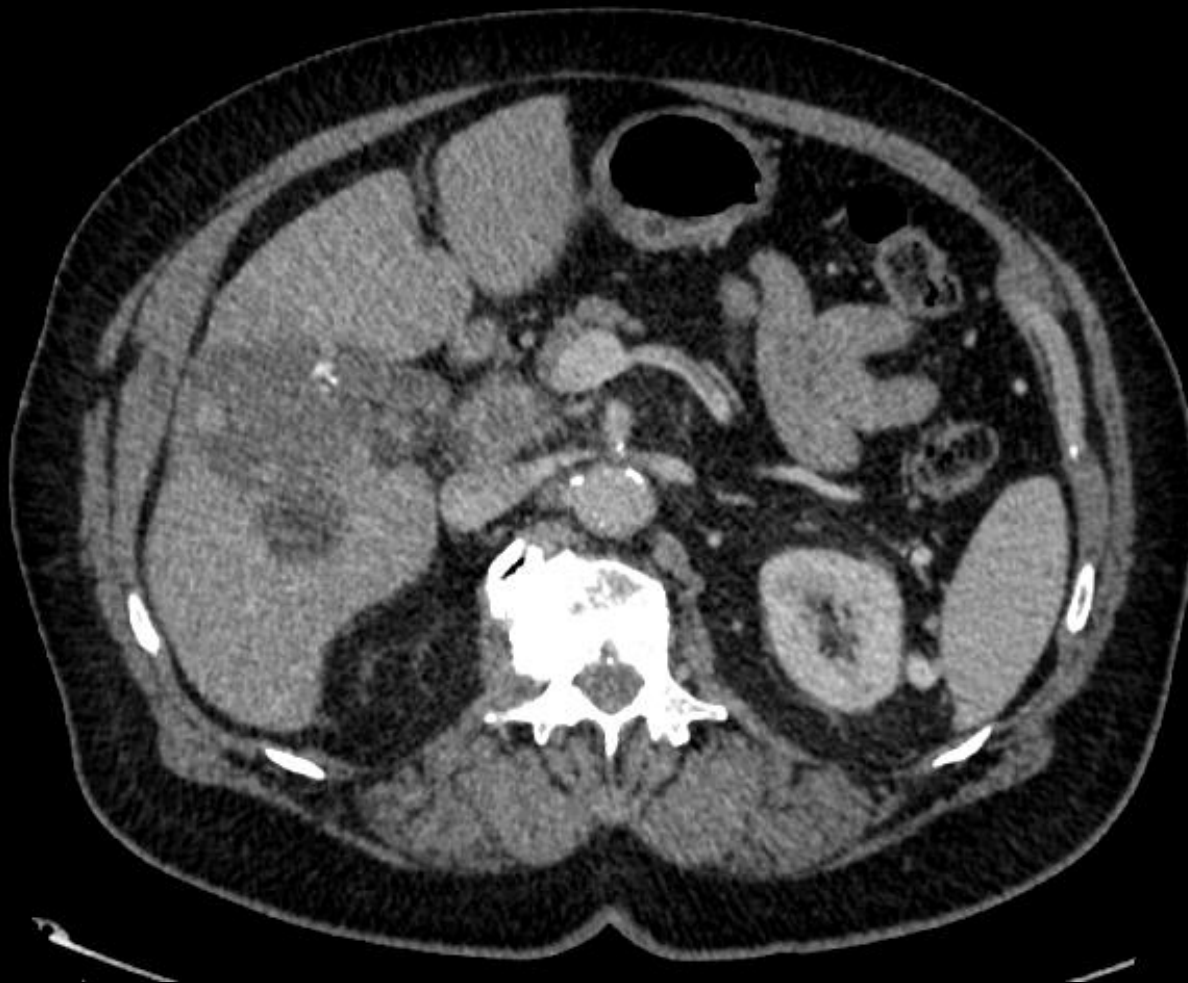
Actual result:
1.06
Upper HR limit, 95% CI

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

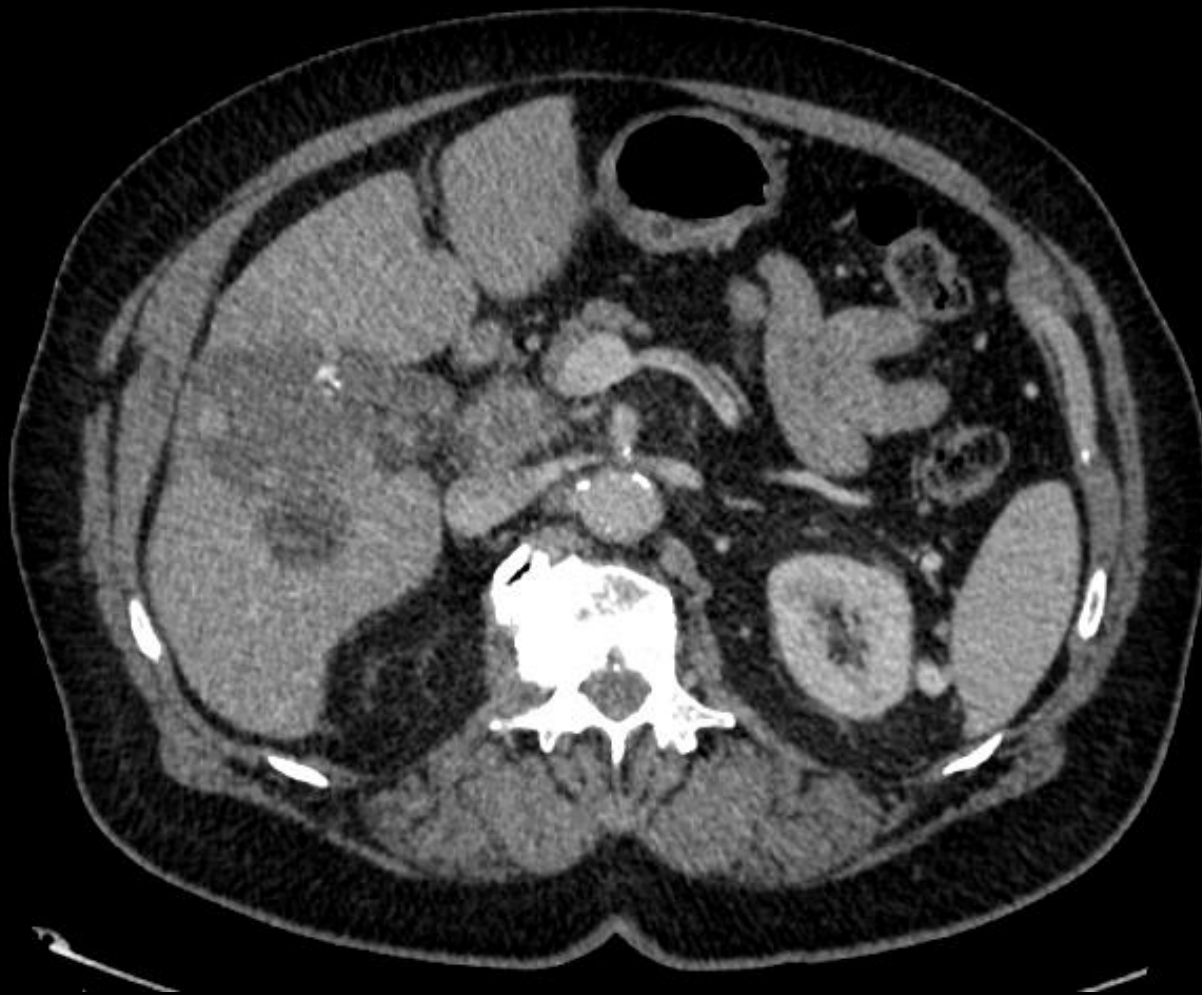


09/ 17



Start Lenvatinib

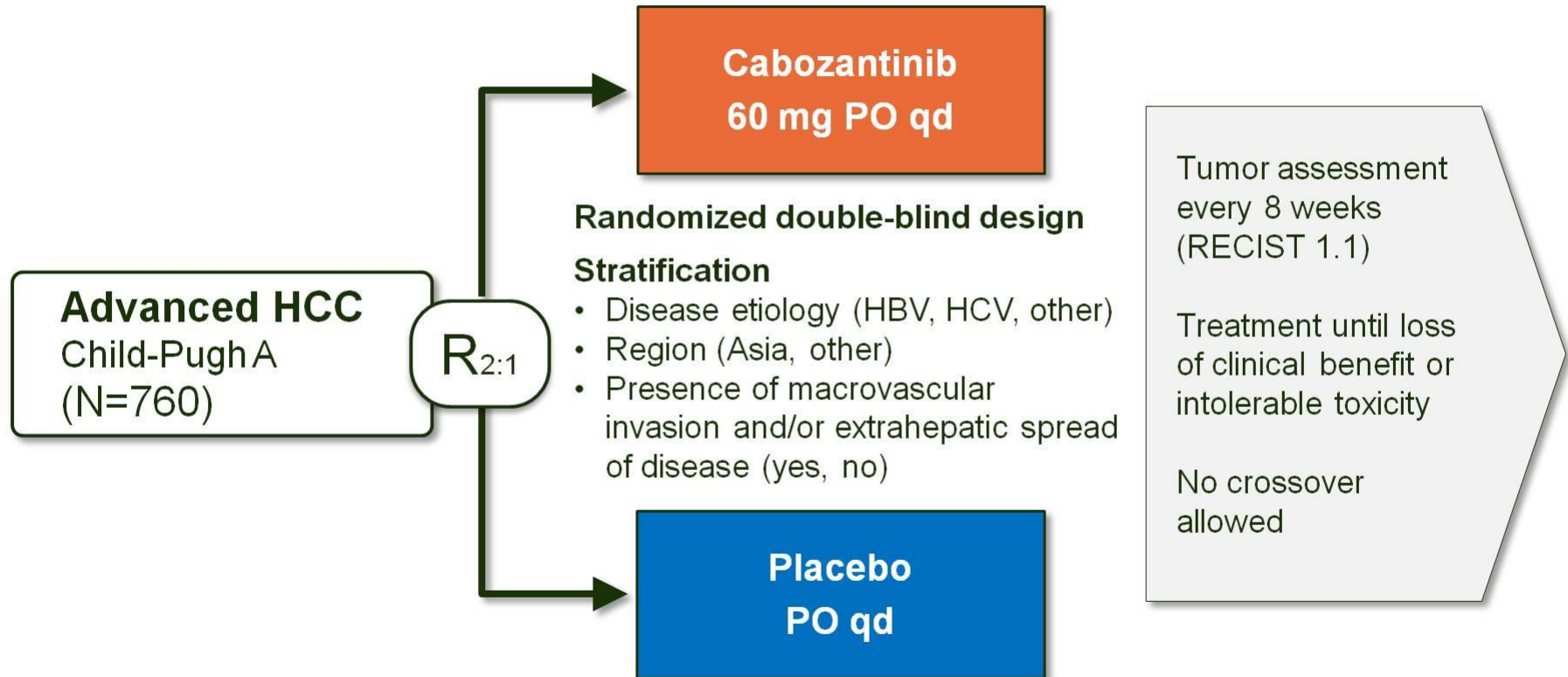
01/ 18



SD unter Lenvatinib

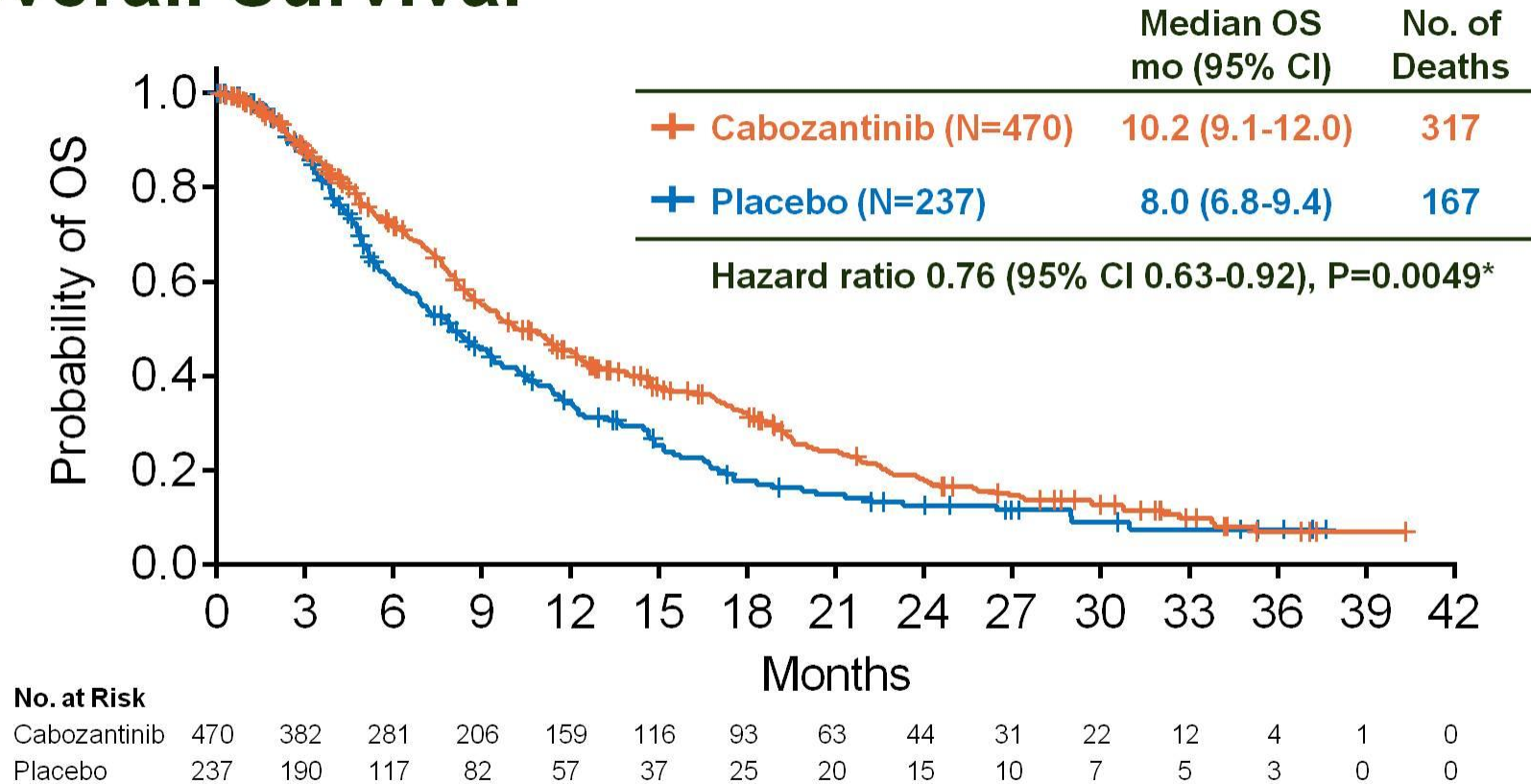
Carbozantinib beim HCC, 2. und 3. Linie

CELESTIAL Study Design



Carbozantinib beim HCC, 2. Linie

Overall Survival



*Critical p-value ≤ 0.021 for second interim analysis

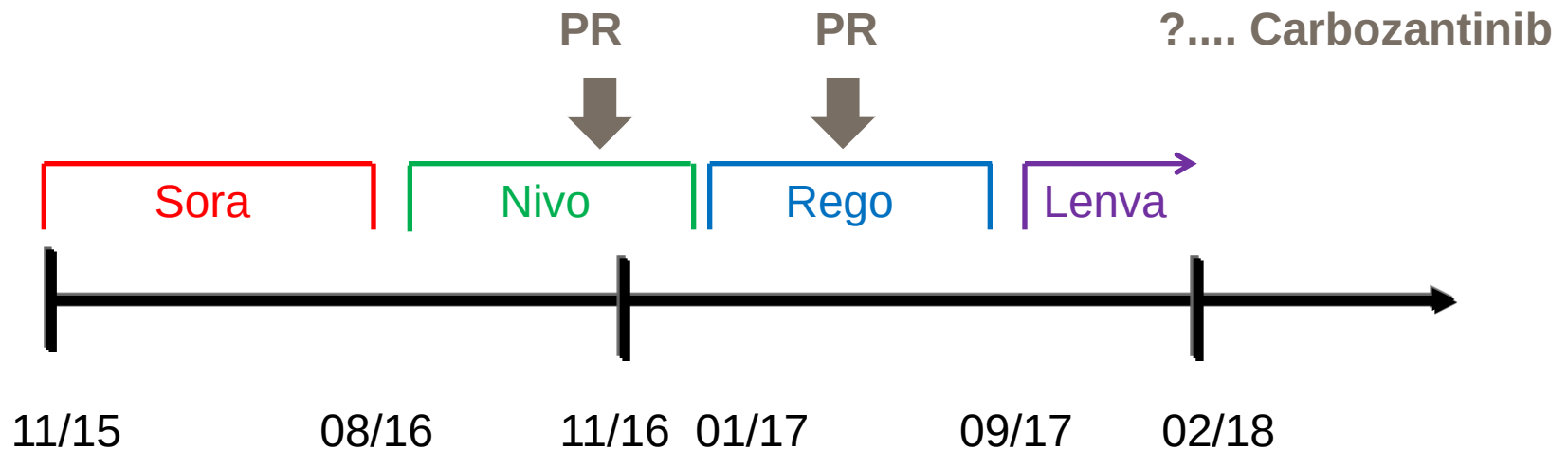
PRESENTED AT: **2018 Gastrointestinal Cancers Symposium** | #GI18

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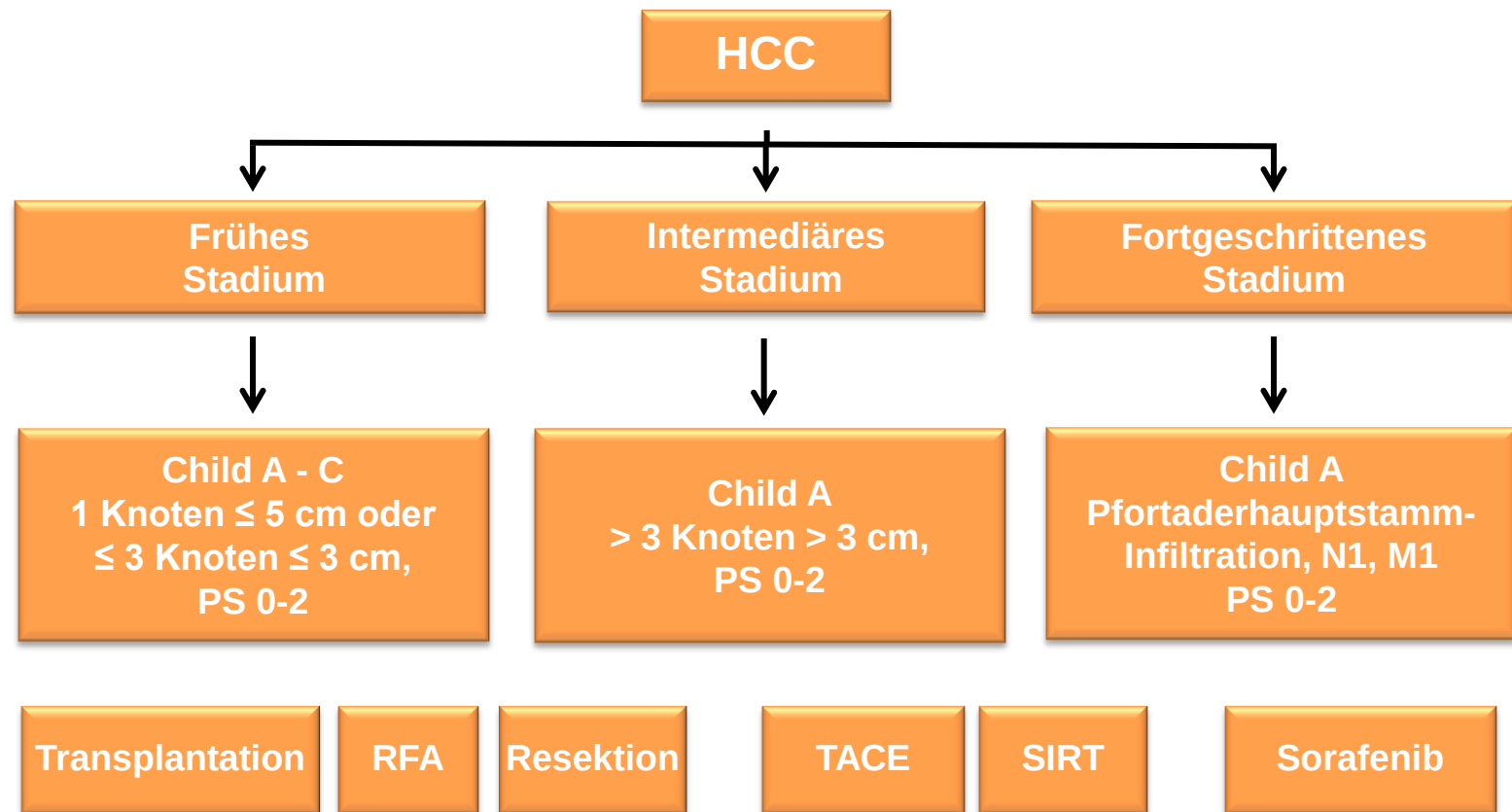
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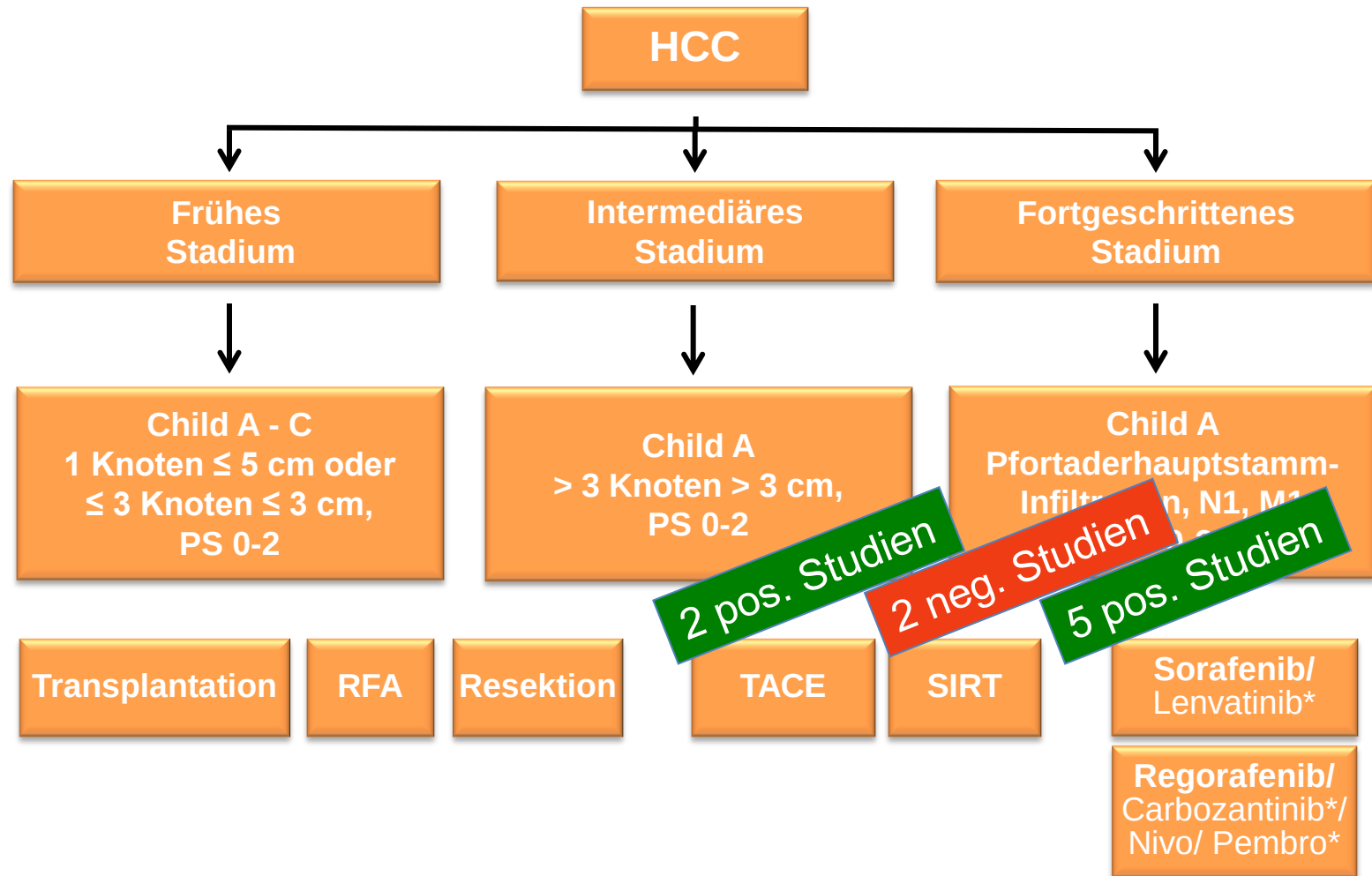
Keine Zirrhose, exzellenter AZ



Take Home HCC.....



Take Home HCC.....



HCC Phase-III Studien: 2011 - 2017

SPACE	20,4		
BRISK	26,4	vs.	26,4
ORIENTAL	31,1	vs.	32,2

TACE
≈ 26 Monate

SHARP	7,9	vs	10,7
SUN	7,9	vs.	10,3
BRISK-FL	9,5	vs.	9,9
SEARCH	8,5	vs.	9,5
LIGHT	9,1	vs.	9,8
Nintendanib	11,9	vs.	11,5
Dovitinib	8,6	vs.	9,2
Axitinib	12,7	vs.	9,7
Sarah	9,9	vs.	9,9
Sirvenib	11,3	vs.	10,4
REFLECT	13,6	vs	12,3

1st line
Sorafenib/
Lenvatinib
≈ 12 Monate

EVOLVE-1	7,6	vs.	7,3
BRISK-SL	8,2	vs.	9,4
REACH	7,5	vs.	9,2
METIV	8,4	vs.	9,1
RESORCE	10,6	vs	7,8
CELESTIAL	10,2	vs	8,2

2nd line
Regorafenib/
Carbozantinib
≈ 8 Monate