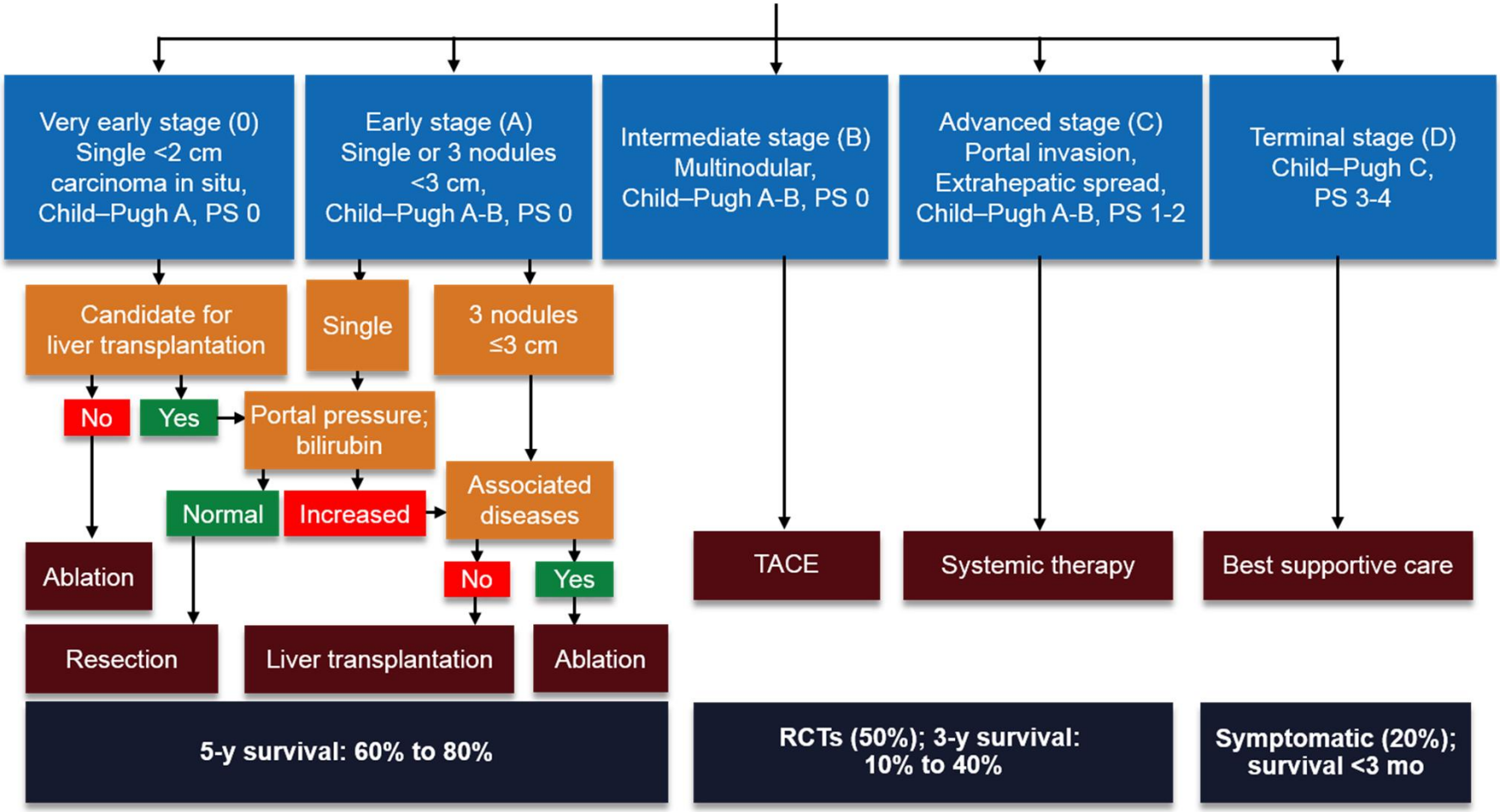
USC Norris Comprehensive Cancer Center
Part of the Keck School of Medicine of USC

Hepatocellular and Biliary Cancers

Anthony El-Khoueiry, MD
Associate Professor of Medicine
Phase I Program Director
Director of Clinical Investigations Support Office
USC Norris Comprehensive Cancer Center

HCC: Barcelona Clinic Liver Cancer Staging

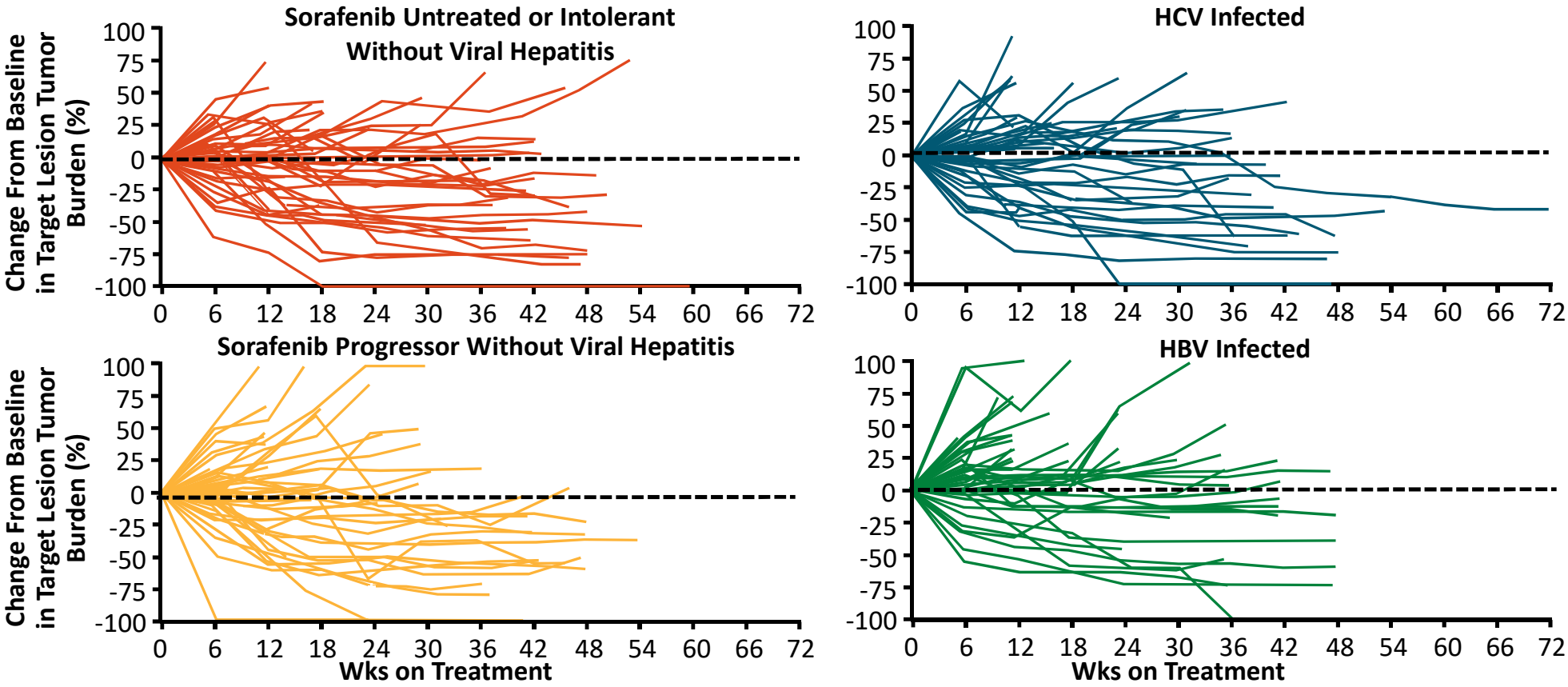


1. Bruix J et al. *Gastroenterology*. 2016;150:835-853. 2. Llovet JM et al. *N Engl J Med*. 2008;359:378-390.

The Evolving First Line Treatment Landscape for Advanced HCC

CheckMate 040: Phase I/II of single agent Nivolumab in HCC

ORR (RECIST 1.1): in expansion cohorts, 20%; in post-sorafenib patients, 14.3%



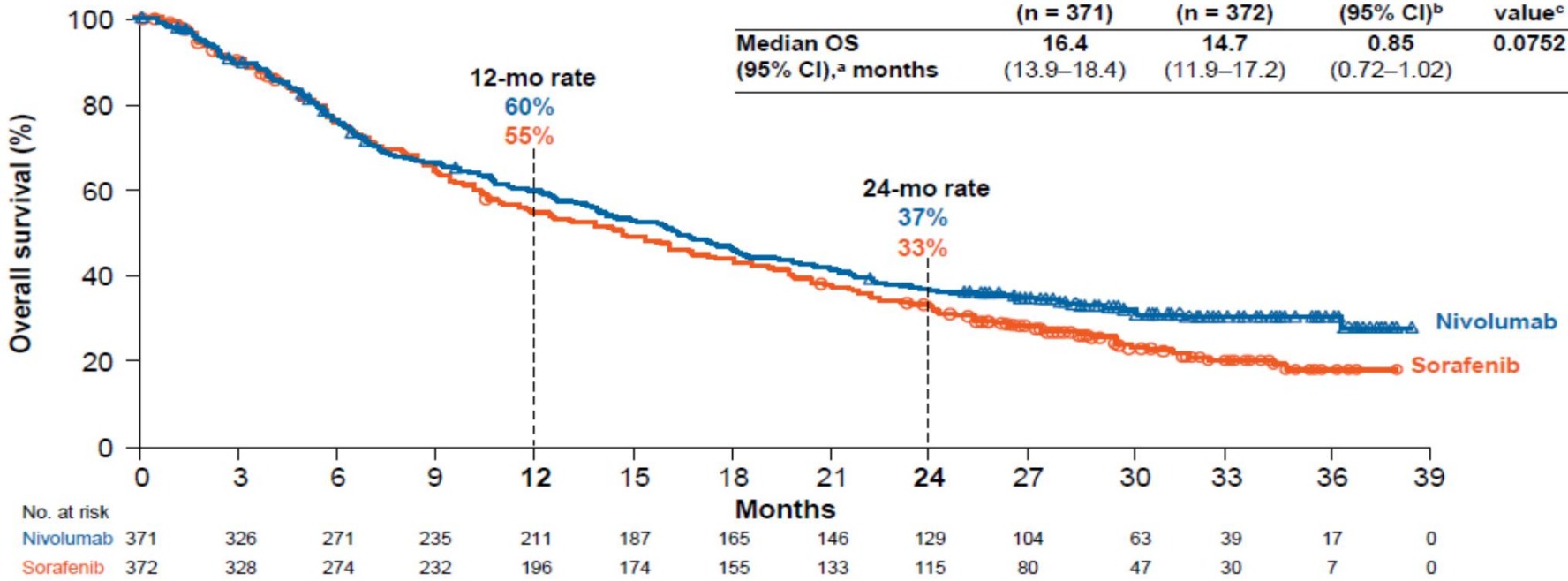
El-Khoueiry. Lancet. 2017;389:2492.

Checkmate 459: First line Nivolumab vs. Sorafenib

CheckMate 459

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

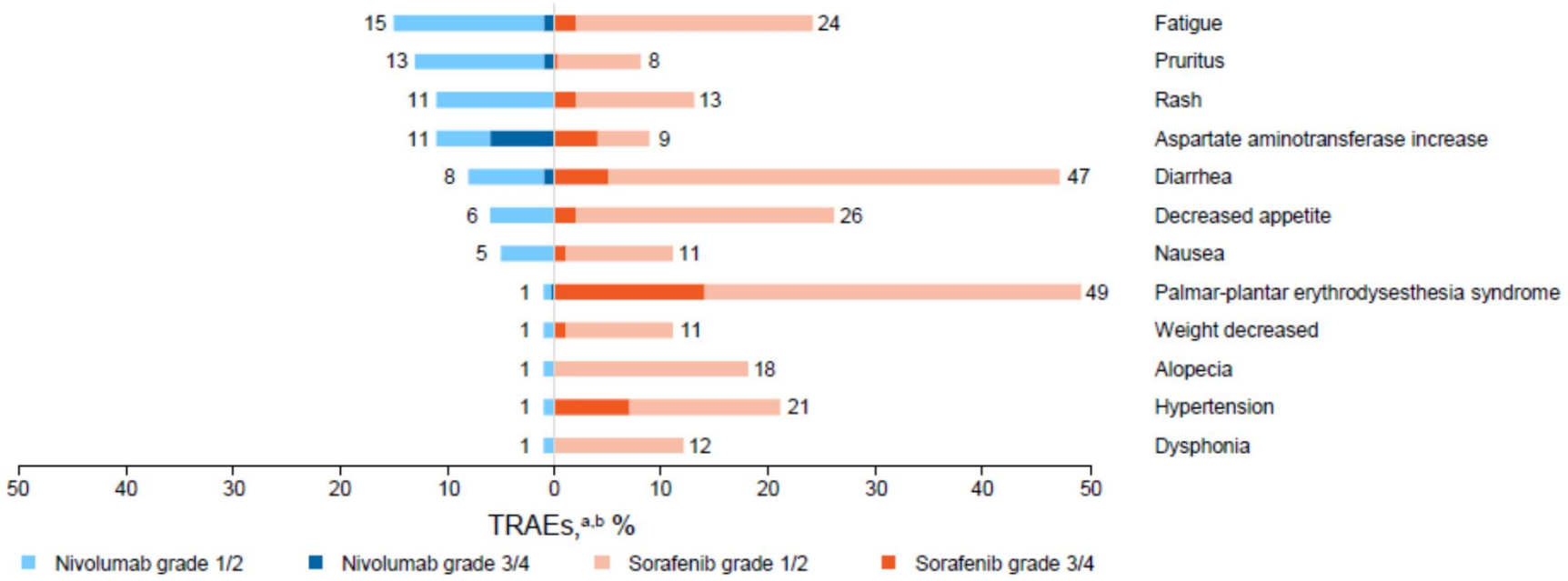


- The predefined threshold of statistical significance for OS with nivolumab was not met, although nivolumab demonstrated clinical benefit

[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.

Yau. ESMO 2019. Abstr LBA38_PR. NCT02576509.

Summary of Treatment-Related Adverse Events

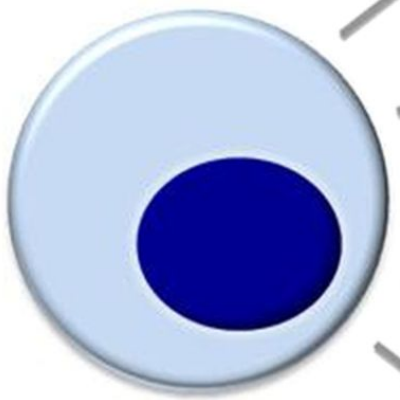


- Nivolumab demonstrated an improved safety profile compared with sorafenib, with fewer grade 3/4 TRAEs and TRAEs leading to discontinuation versus sorafenib
  - Grade 3/4 TRAEs were reported in 81 patients (22%) in the nivolumab arm and 179 patients (49%) in the sorafenib arm

[a]Events occurring in > 10% of patients in either treatment arm. Includes events reported between first dose and 30 days after last dose of study therapy; data labels represent rates of any-grade events; [b]One grade 5 event was reported in the nivolumab arm (cerebrovascular event), and 1 was reported in the sorafenib arm (hepatic failure).
TRAE, treatment-related adverse event.

Yau. ESMO 2019. Abstr LBA38_PR. NCT02576509.

How do we expand the benefit of anti PD-1 or PD-L-1 agents in patients with advanced hepatocellular carcinoma? .



Tumour-specific → - Enhance tumor associated antigen exposure (SBRT, locoregional tx,Intra-tumoral tx)

Intrinsic activity (CTLA4, PD1 blockade) →
- Beyond PD-1: OX40, LAG-3
- IO/IO combinations

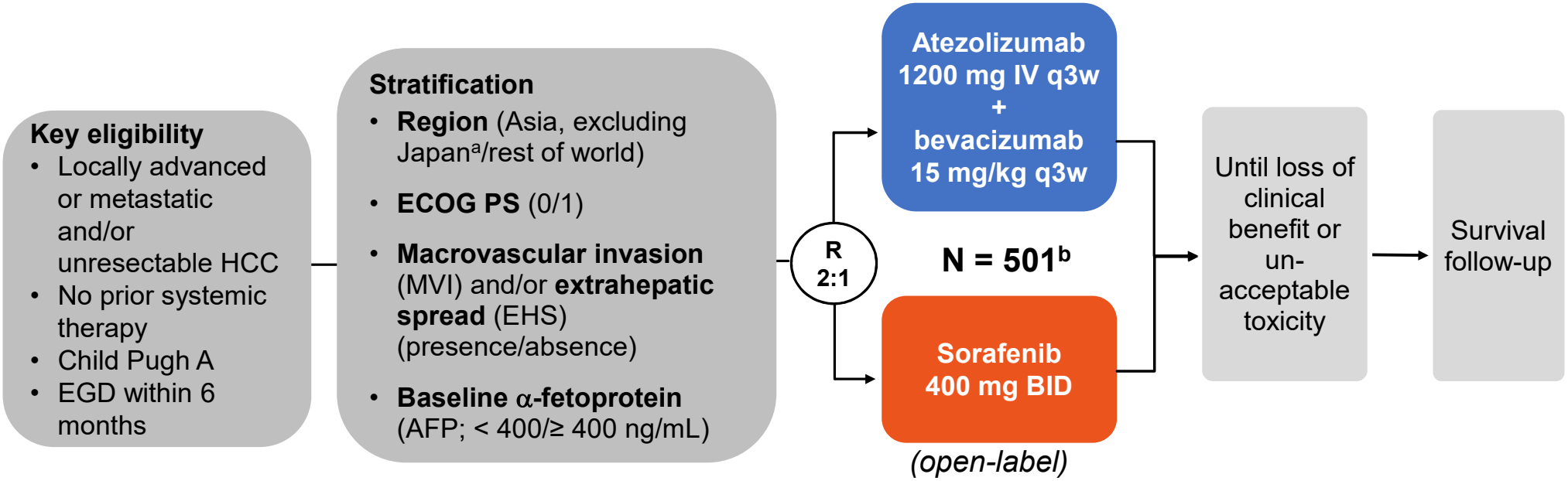
Extrinsic activity (immunosuppressive microenvironment) →
- Anti VEGF combinations (TKI, Bevacizumab)

Migrate into the tumour →
- Other ongoing preclinical and early clinical research

1. *Chen Y et al. Hepatology. 2015;61(5):1591-1602.*
2. *Greten et al. Rev Recent Clin Trial. 2008*
3. *Hedge PS, Semin Cancer Biol 2017*
4. *Tim F Greten et al. Gut 2015;64:842-848*

Checkpoint inhibitor + anti VEGF therapy

IMbrave150 study design



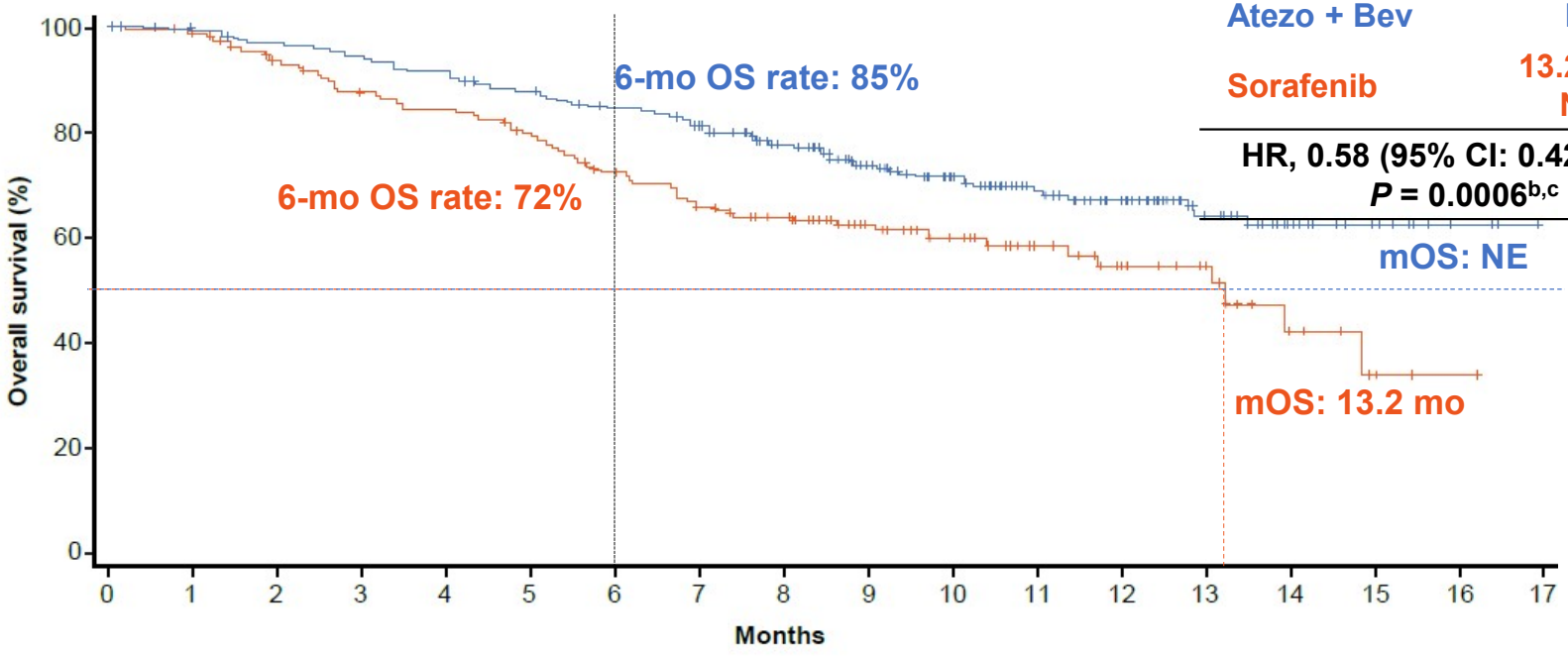
Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

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

Finn R et al, N Engl J Med 2020

IMbrave150 study: OS

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.

Finn R et al, N Engl J Med 2020

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.

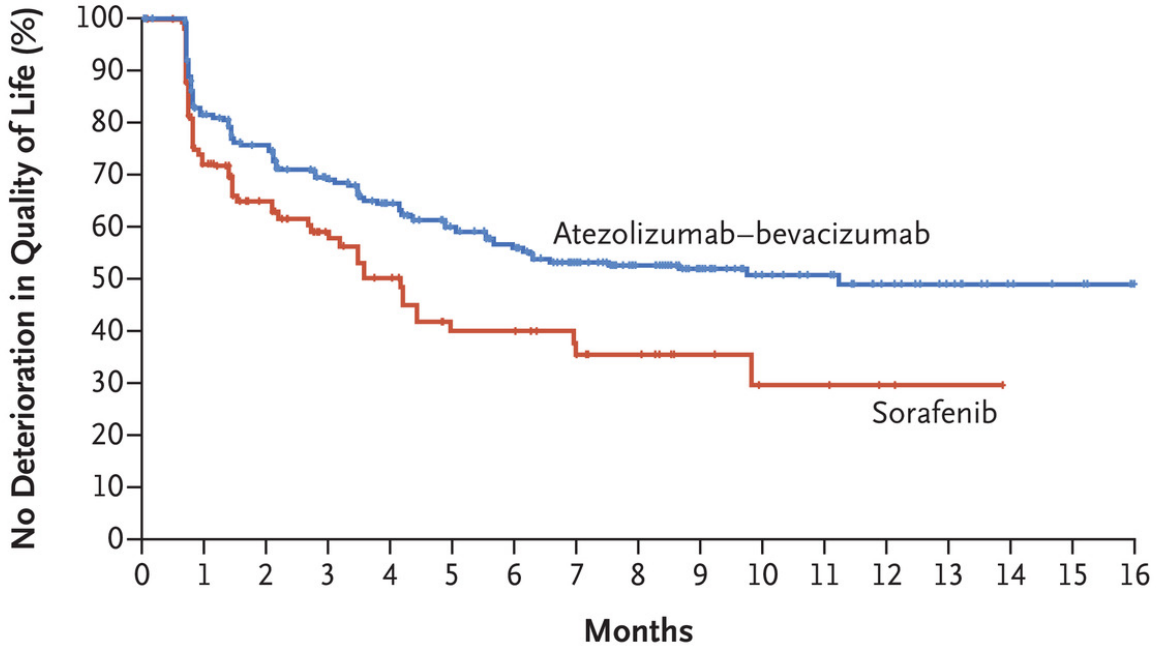
Finn R et al, N Engl J Med 2020

IMbrave150: Safety summary

Characteristic	Atezo + Bev (n = 329)	Sorafenib (n = 156)
Treatment duration, median, mo	**Atezo = 7.4; Bev = 6.9**	**2.8**
All-Grade AEs, any cause, n (%)	323 (98)	154 (99)
Treatment-related all-Grade AEs	276 (84)	147 (94)
Grade 3-4 AE , n (%)[b]	186 (57)	86 (55)
Treatment-related Grade 3-4 AE[b]	117 (36)	71 (46)
Serious adverse event, n (%)	125 (38)	48 (31)
Treatment-related SAE	56 (17)	24 (15)
Grade 5 AE, n (%)	15 (5)	9 (6)
Treatment-related Grade 5 AE	6 (2)	1 (< 1)
AE leading to withdrawal from any component, n (%)	51 (16)	16 (10)
AE leading to withdrawal from both components	23 (7)	16 (10)
AE leading to dose interruption of any study treatment, n (%)	163 (50)	64 (41)
AE leading to dose modification of sorafenib, n (%)[c]	0	58 (37)

[a] Safety-evaluable population. [b] Highest grade experienced.
[c] No dose modification allowed for Atezo + Bev arm.

Quality of Life with Atezo/Bev versus Sorafenib



	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)

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

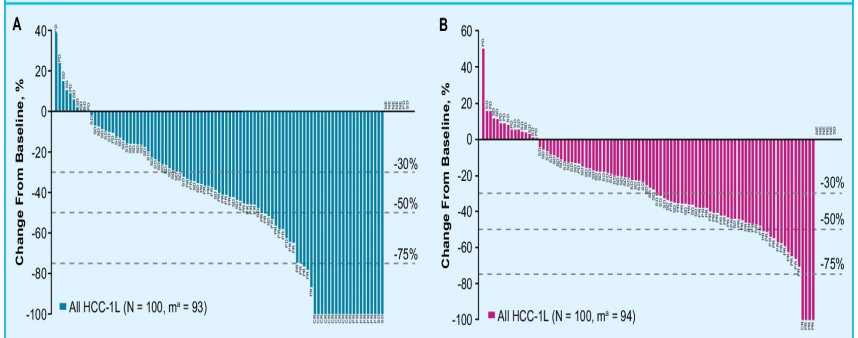
Finn R et al, N Engl J Med 2020

Phase Ib of Pembrolizumab and Lenvatinib

Table 3. Summary of Efficacy Outcomes

Parameter	Lenvatinib + Pembrolizumab (N = 100)		
	mRECIST per IIR	RECIST Version 1.1 per IIR	mRECIST per IR
ORR (confirmed responses), n (%) (95% CI)[a]	46 (46) (36.0–56.3)	36 (36) (26.6–46.2)	41 (41) (31.3–51.3)
Best overall response, n (%)			
Complete response	11 (11)	1 (1)	5 (5)
Partial response	35 (35)	35 (35)	36 (36)
Stable disease[b]	42 (42)	52 (52)	45 (45)
Progressive disease	7 (7)	7 (7)	7 (7)
Unknown/not evaluable	5 (5)	5 (5)	7 (7)
Median DOR[c] for confirmed responders, months (95% CI)[d]	8.6 (6.9–NE)	12.6 (6.9–NE)	12.6 (6.2–18.7)
Median TTR for confirmed responders, months (range)	1.9 (1.2–5.5)	2.8 (1.2–7.7)	2.7 (1.2–11.8)
Disease control rate, n (%) (95% CI)[a]	88 (88) (80.0–93.6)	88 (88) (80.0–93.6)	86 (86) (77.6–92.1)

Figure 2. 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

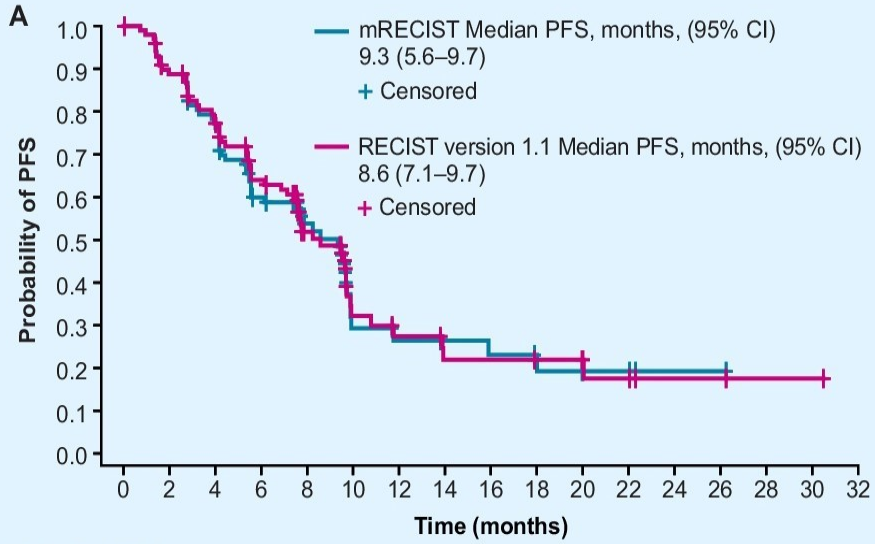


[a]Number of patients with both baseline and postbaseline values for the sum of diameters of target lesions.
1L, first-line; HCC, hepatocellular carcinoma; IIR, independent imaging review; (m)RECIST, (modified) Response Evaluation Criteria In Solid Tumors.

Zhu A et al, ASCO 2020
Finn R et al, J Clin Oncol 2020

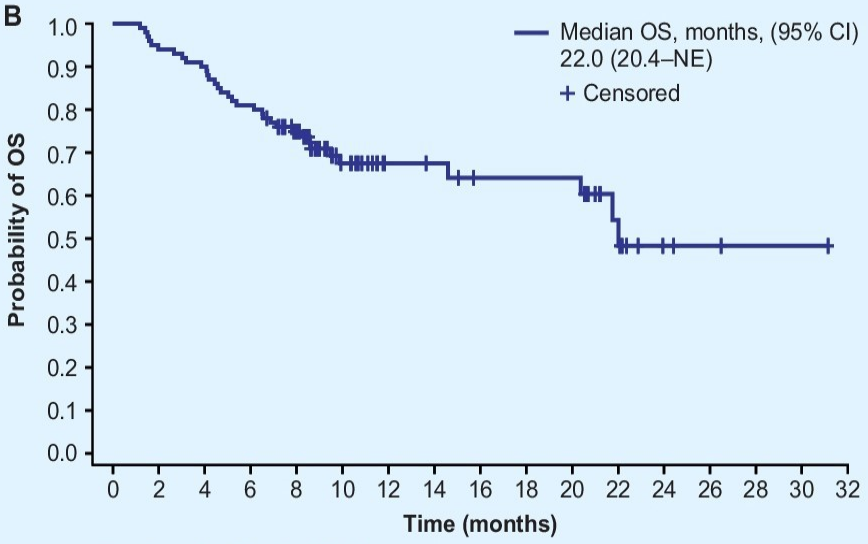
Phase Ib of Pembrolizumab and Lenvatinib

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



Number of patients at risk:

mRECIST	100	86	73	53	30	11	9	8	7	6	4	3	1	1	0	
RECIST version 1.1	100	86	74	57	32	14	11	8	8	7	6	4	2	2	1	1	0



Number of patients at risk:

100	94	90	81	65	37	21	20	17	17	17	9	3	2	1	1	0

CI, confidence interval; IIR, independent imaging review; (m)RECIST, (modified) Response Evaluation Criteria In Solid Tumors; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Zhu A et al, ASCO 2020
Finn R et al, J Clin Oncol 2020

Phase Ib of Pembrolizumab and Lenvatinib

Grade ≥3 TRAEs in 67% of patients
Treatment related SAEs in 36% of patients
3 treatment related deaths (3%)

Treatment interruptions of Lenvatinib 62%
Treatment discontinuations of Lenvatinib 14%

Treatment interruptions of Pembrolizumab 43%
Treatment discontinuations of Pembrolizumab 10%

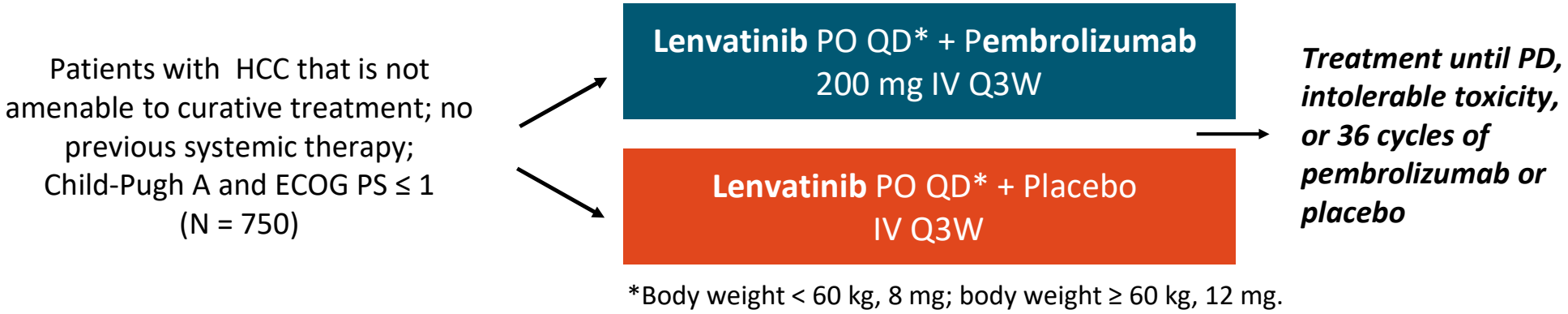
Table 2. Most Common Treatment-Related AEs (≥ 20% of Patients With Any-Grade Treatment-Related AEs)

Preferred Term, n (%)	Lenvatinib + Pembrolizumab (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
Palmar-plantar erythrodysesthesia syndrome	23 (23)	13 (13)	9 (9)	1 (1)
Weight decreased	22 (22)	8 (8)	11 (11)	3 (3)
Dysphonia	21 (21)	19 (19)	1 (1)	1 (1)
Aspartate aminotransferase increased	20 (20)	4 (4)	5 (5)	11 (11)
Proteinuria	20 (20)	9 (9)	7 (7)	4 (4)

Finn R et al, J Clin Oncol 2020

LEAP-002: First-Line Lenvatinib Plus Pembrolizumab Versus Lenvatinib Plus Placebo in Advanced HCC

- Multicenter, double-blind, phase III trial



*Body weight < 60 kg, 8 mg; body weight ≥ 60 kg, 12 mg.

- Primary endpoints: PFS, OS
- Secondary endpoints: ORR, DoR, DCR, TTP, safety

Llovet. ASCO 2019. Abstr TPS4152. NCT03713593.

Phase Ib of Pembrolizumab and Regorefanib

n (%)	Regorafenib 120 mg + pembrolizumab (n=31*)
Best overall response	
Complete response	0
Partial response	8 (26)
Stable disease	20 (65)
Progressive disease	2 (6)
Not evaluable	0
Not assessed	0
Overall response rate	8 (26)
Disease control rate	28 (90)

*One patient assessed at Week 2 is not shown because the 6-week time point for assessment was not reached.
RECIST, Response Evaluation Criteria in Solid Tumors.

Table 3. Most common grade 3 or 4 treatment-emergent adverse events (≥10% of patients)

TEAEs, n (%)	Regorafenib 120 mg + pembrolizumab (n=35)					
	Regardless of relation to study drug		Regorafenib related		Pembrolizumab related	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
AST increased	7 (20)	0	5 (14)	0	4 (11)	0
Lipase increased	5 (14)	1 (3)	1 (3)	1 (3)	2 (6)	1 (3)
Hypertension	5 (14)	0	4 (11)	0	0	0
ALT increased	4 (11)	2 (6)	4 (11)	1 (3)	4 (11)	1 (3)
Bilirubin increased	4 (11)	0	3 (9)	0	3 (9)	0

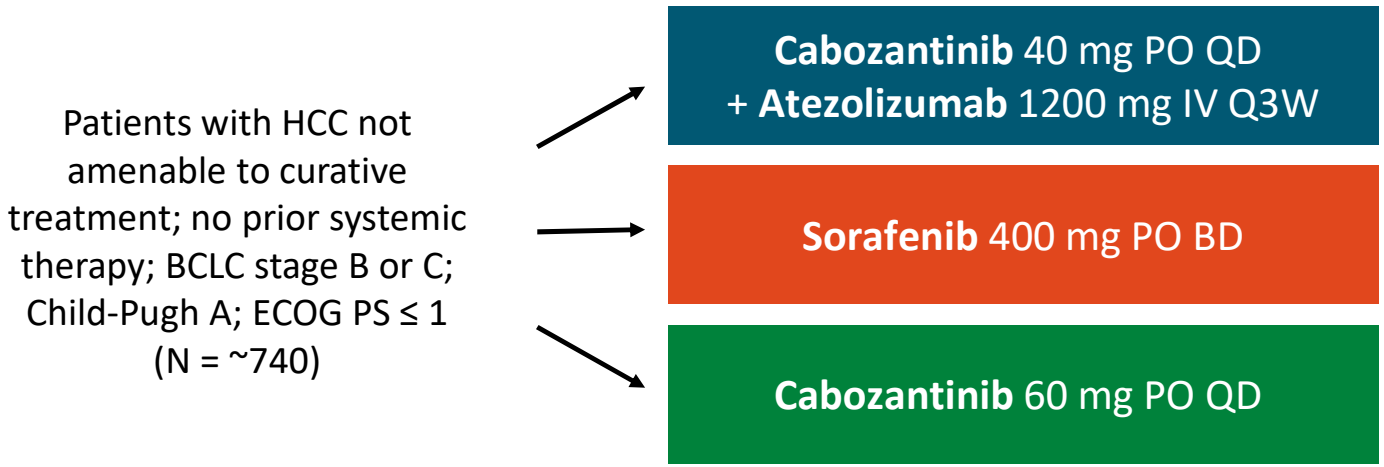
Events listed are those that occurred (grade 3 or 4) in ≥10% of patients regardless of relation to study drug(s).
MedDRA v22.1; NCI-CTCAE v4.03 grade.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Regorefanib treatment modification in 71% of patients
Pembrolizumab treatment interruption in 54% of patients
Ongoing cohort of Pembrolizumab with Regorefanib at 80 mg

El-Khoueiry A et al, Gastrointestinal Cancers Symposium 2020

COSMIC-312: Cabozantinib ± Atezolizumab vs Sorafenib in Advanced HCC

- Multicenter, randomized, open-label phase III trial

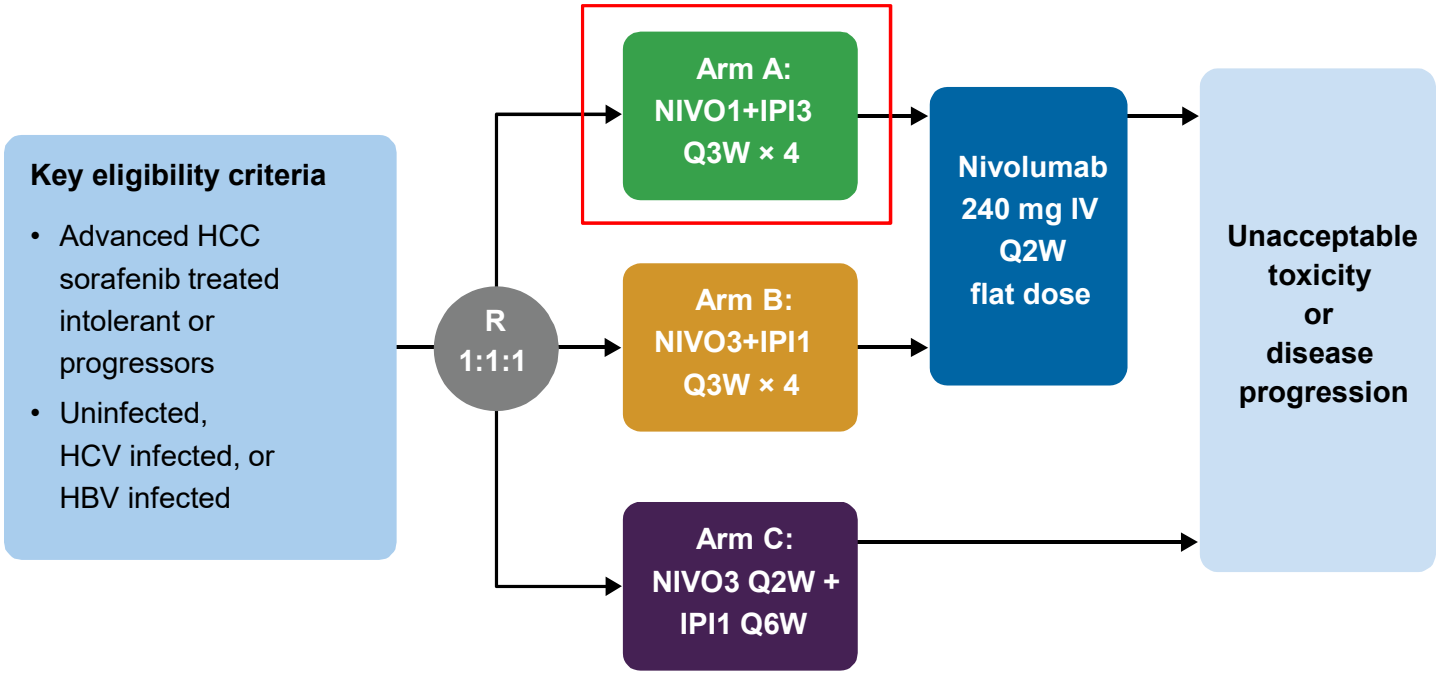


- Primary endpoints: PFS (cabozantinib + atezolizumab vs sorafenib), OS
- Secondary endpoints: PFS (cabozantinib vs sorafenib), ORR, TTP, DoR, safety

Kelley. ASCO 2019. Abstr TPS4157. NCT03755791.

IO/IO combinations

CheckMate 040 Nivolumab Plus Ipilimumab



Study endpoints

Primary

- Safety and tolerability using NCI CTCAE v4.0
- ORR and DOR based on investigator assessment[b]

Secondary

- DCR
- TTP
- PFS
- TTR
- OS

Other

- BOR and ORR based on BICR-assessed tumor response[b]

[a]ClinicalTrials.gov, NCT01658878; [b]Using RECIST v1.1.
Minimum follow-up at time of data cutoff: 28 months.
BICR, blinded independent central review; BOR, best overall response; DOR, duration of response; HBV, hepatitis B virus; HCV, hepatitis C virus; IPI1, ipilimumab 1 mg/kg; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NIVO3, nivolumab 3 mg/kg; PFS, progression-free survival; Q6W, every 6 weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to progression; TTR, time to response.

Response, Disease Control, and Durability

	Arm A NIVO1+IPI3 Q3W[a] n = 50
ORR by BICR using RECIST v1.1,[b] n (%)	16 (32)
BOR, n (%)	
CR	4 (8)
PR	12 (24)
SD	9 (18)
PD	20 (40)
Unable to determine	3 (6)
DCR,[c] n (%)	27 (54)
Median TTR (range),[d] months	2.0 (1.1–12.8)
Median DOR (range),[d] months	17.5 (4.6 to 30.5+)

- Four patients had a CR, and the DCR (CR + PR + SD + non-CR/non-PD) was > 50%

[a]Four doses, followed by NIVO 240 mg IV Q2W flat dose; [b]Defined as CR + PR; [c]Defined as CR + PR + SD + non-CR/non-PD; [d]Patients with CR or PR.
BICR, blinded independent central review; BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; IPI3, ipilimumab 3 mg/kg; NIVO1, nivolumab 1 mg/kg; PD, progressive disease; PR, partial response; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TTR, time to response.
Yau T, et al. Presented at the American Society of Clinical Oncology Annual Meeting 2019; May 31–June 4, 2019; Chicago, IL. Poster 4012.

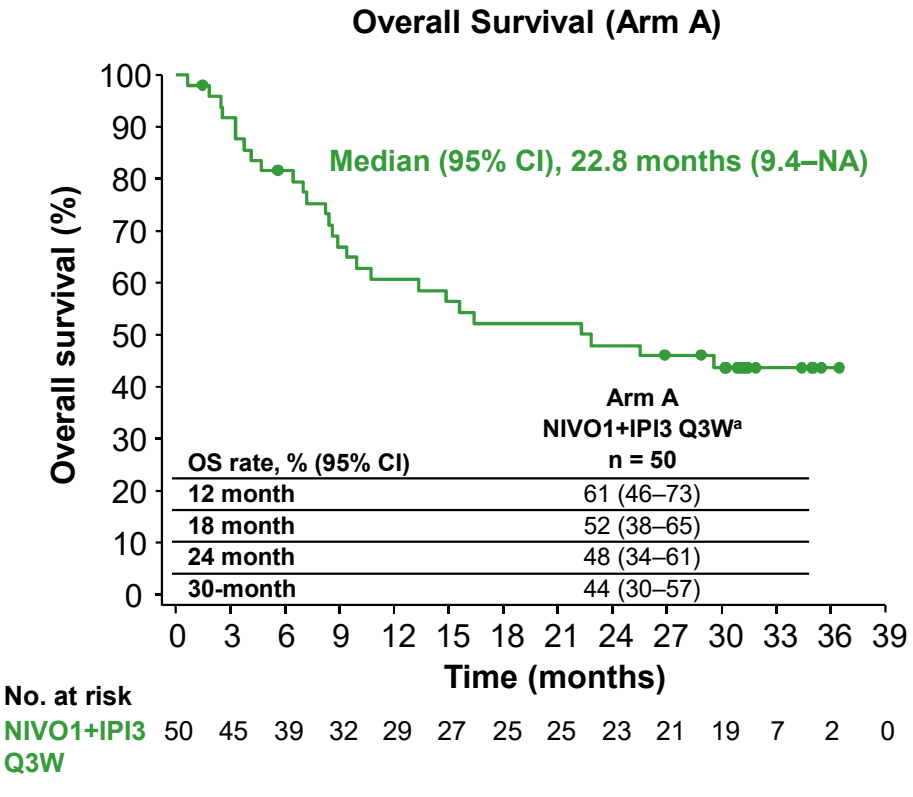
Summary of TRAEs by Category

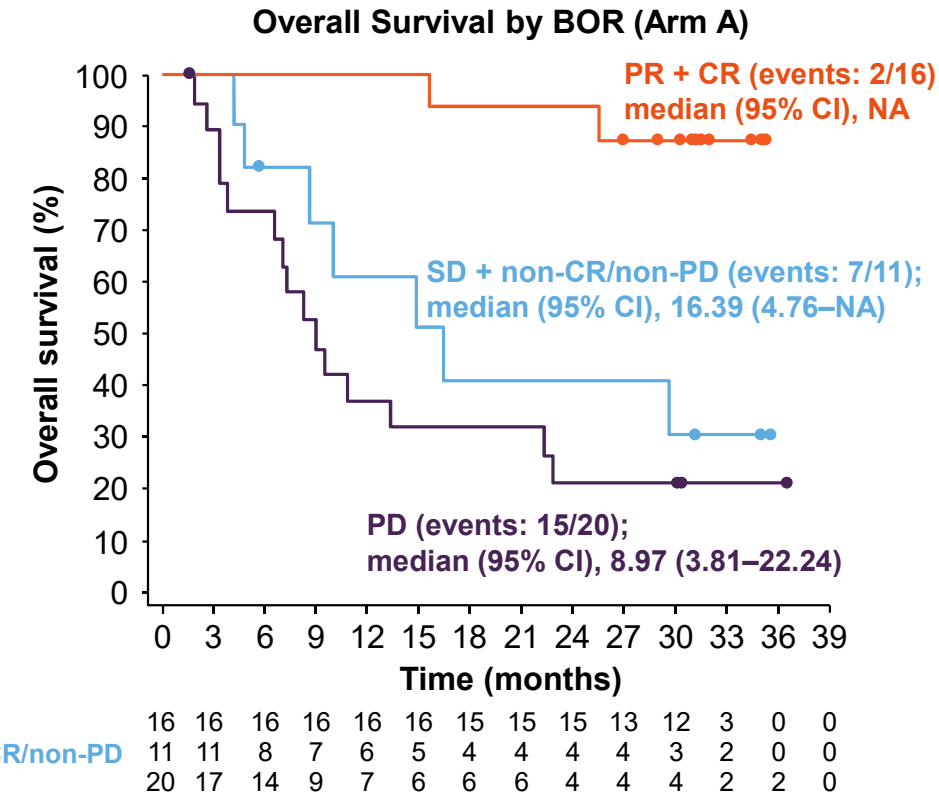
	Arm A NIVO1+IPI3 Q3W[a] n = 49	
	Any grade	Grade 3–4
Any TRAE, n (%)	**46 (94)**	**26 (53)**
Skin and subcutaneous tissue	30 (61)	4 (8)
Investigations (including liver laboratory abnormalities)	24 (49)	16 (33)
General and administration site	19 (39)	2 (4)
Gastrointestinal	18 (37)	3 (6)
Endocrine	16 (33)	1 (2)
Metabolism and nutrition	14 (29)	7 (14)
Respiratory, thoracic, and mediastinal	7 (14)	1 (2)
Nervous system	7 (14)	0
Musculoskeletal and connective tissue	6 (12)	0
Hepatobiliary	3 (6)	3 (6)

- No new safety signals were observed, and most TRAEs were manageable and reversible
- Serious TRAEs were reported in 11 patients (22%)
  - Two serious hepatic TRAEs were reported: 1 drug-induced liver injury (grade 3–4) and 1 elevated AST (grade 3–4)

[a]Four doses, followed by NIVO 240 mg IV Q2W flat dose.
Listed in the table are any-grade TRAEs that occurred in ≥ 10% of patients in any arm and grade 3–4 TRAEs that occurred in ≥ 5% of patients in any arm. Includes events reported between first dose and 30 days after last dose of study therapy.
AST, aspartate aminotransferase; TRAE, treatment-related adverse event.
El-Khouiery AB, et al. Presented at the International Liver Cancer Association Meeting 2019; September 20–22, 2019; Chicago, IL. Oral O-13.

Overall Survival





- Median OS was 22.8 months, with an OS rate of 44% through 30 months

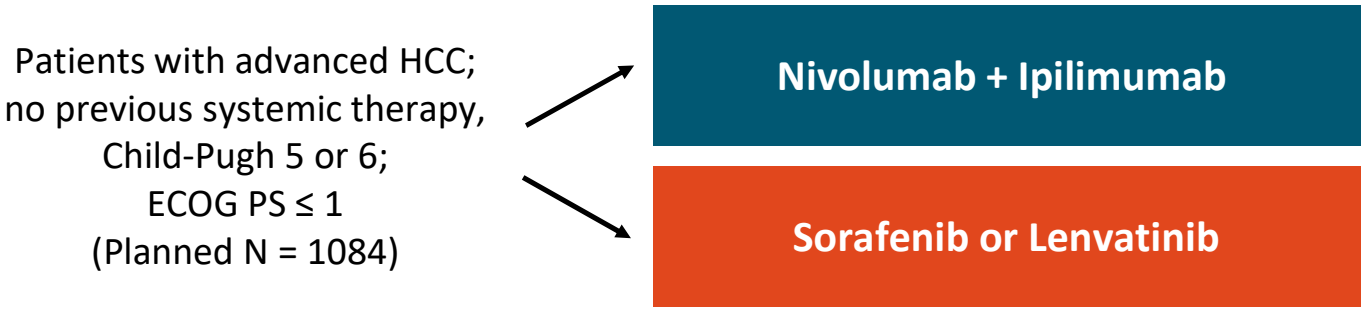
- Median OS for patients with PR + CR (2/16 events) was not achieved at the time of database lock

[a]Four doses, followed by NIVO 240 mg IV Q2W flat dose.
NA, not achieved.

El-Khoueiry A et al, HCC-TAG 2020

CheckMate 9DW: Nivolumab + Ipilimumab vs Sorafenib or Lenvatinib as First-Line Treatment for Advanced HCC

- Multicenter, randomized, open-label, phase III trial

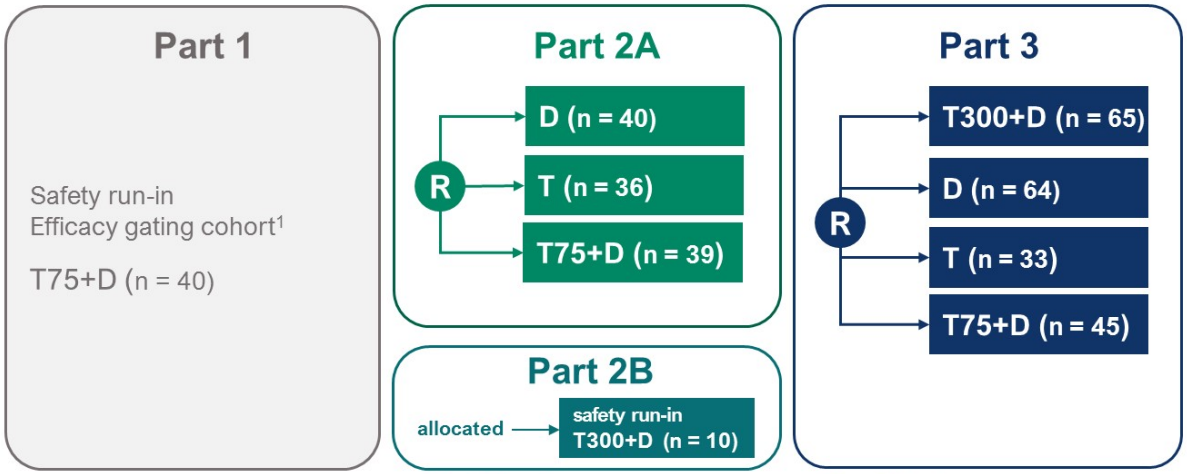


- Primary endpoints: OS
- Secondary endpoints: ORR, DOR, TTSD

NCT04039607.

Novel Regimen of Tremelimumab with Durvalumab

Study 22 Design



Key Milestones

FSI Part 2A	February 2017
FSI Part 2B	October 2017

Key Milestones

FSI Part 3	February 2018
LSI Part 3	April 2019

Treatments and Regimens

T300+D	tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W
D	durvalumab 1500 mg Q4W
T	tremelimumab monotherapy 750 mg Q4W × 7 doses, Q12W thereafter
T75+D	tremelimumab 75 mg × 4 doses + durvalumab 1500 mg Q4W

Key Eligibility

- Unresectable HCC with fresh or archival tumor biopsy sample available
- Progressed on, intolerant to, or refused prior sorafenib
- Child Pugh A liver function

Objectives and Assessments

Primary Endpoint: Safety

Key Secondary Endpoints

- Overall survival
- Objective response rate
- Duration of response

Key Assessments

- Multiphase imaging Q8 weeks
- Circulating immune cells
- PD-L1 status (Ventana SP263)

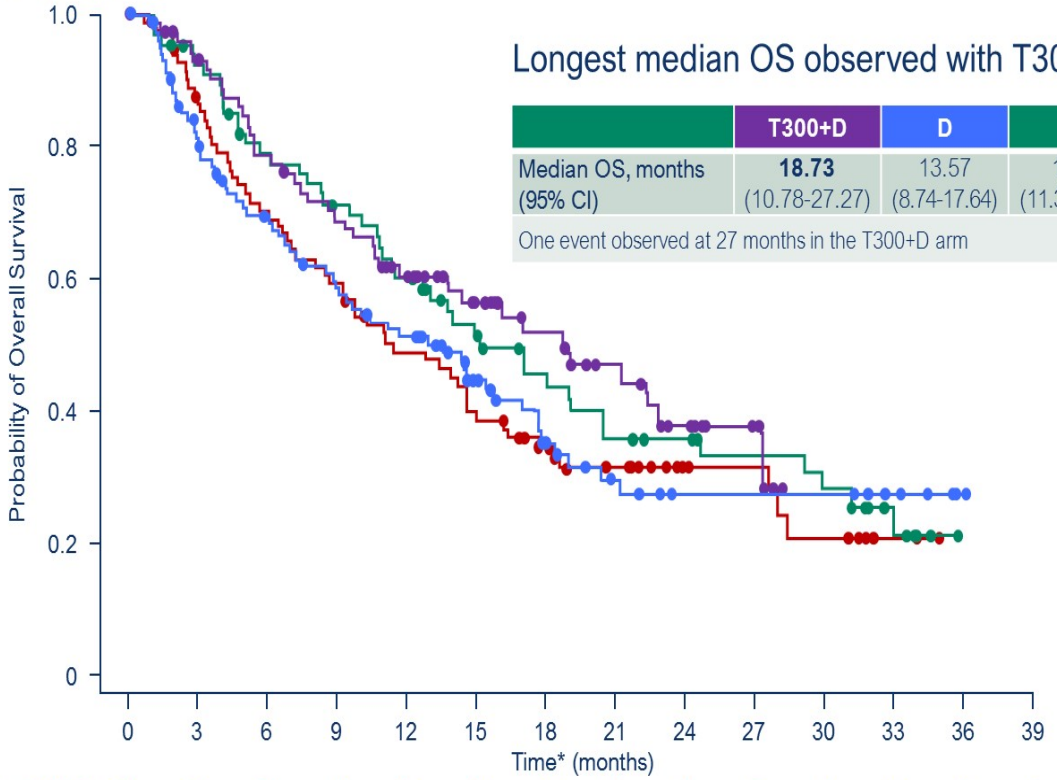
1. Kelley RK, et al. JCO, 2017.35:4073-4073.

Summary of Adverse Events

n (%)	T300+D (n = 74)	D (n = 101)	T (n = 69)	T75+D (n = 82)
Any-grade AE	73 (98.6)	95 (94.1)	67 (97.1)	80 (97.6)
Any-grade TRAE	61 (82.4)	61 (60.4)	58 (84.1)	57 (69.5)
AE grade 3 or 4	43 (58.1)	56 (55.4)	46 (66.7)	50 (61.0)
TRAE grade 3 or 4	26 (35.1)	18 (17.8)	30 (43.5)	19 (23.2)
Any SAE (including events with outcome of death)	31 (41.9)	43 (42.6)	36 (52.2)	36 (43.9)
TRSAE (including events with outcome of death)	**12 (16.2)**	**11 (10.9)**	**17 (24.6)**	**12 (14.6)**
Any AE with outcome of death	4 (5.4)	4 (4.0)	2 (2.9)	2 (2.4)
TRAE with outcome of death[a]	**1 (1.4)**	**3 (3.0)**	**0**	**1 (1.2)**
Any AE leading to discontinuation of study treatment	9 (12.2)	12 (11.9)	13 (18.8)	11 (13.4)
TRAE leading to discontinuation of study treatment	**8 (10.8)**	**8 (7.9)**	**9 (13.0)**	**5 (6.1)**
TRAEs requiring systemic steroids	**18 (24.3)**	**10 (9.9)**	**18 (26.1)**	**20 (24.4)**
TRAEs Grade 3 or 4 requiring systemic steroids	8 (10.8)	7 (6.9)	14 (20.3)	8 (9.8)

[a]T300+D arm (pneumonia), D arm (pneumonia, hepatic failure, abnormal hepatic function), T75+D arm (hepatic failure)
AE, adverse event; TR, treatment-related; SAE, severe adverse event

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

Number of patients at risk														
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

*Time from randomization (Part 2A, 3) or first dose (Part 2B)
CI, confidence interval; D, durvalumab; OS, overall survival; T, tremelimumab

Secondary Efficacy Endpoints

	T300+D (n = 75)	D (n = 104)	T (n = 69)	T75+D (n = 84)
Objective Response Rate[a] (95% CI), %	**24.0** (14.9-35.3)	**10.6** (5.4-18.1)	**7.2** (2.4-16.1)	**9.5** (4.2-17.9)
CR, n (%)	1 (1.3)	0	0	2 (2.4)
PR, n (%)	17 (22.7)	11 (10.6)	5 (7.2)	6 (7.1)
SD, n (%)	16 (21.3)	28 (26.9)	29 (42.0)	23 (27.4)
Disease Control Rate, n (%)	34 (45.3)	39 (37.5)	34 (49.3)	31 (36.9)
Median Duration of Response,[b] months	**NR**	**11.17**	**23.95**	**13.21**
Median Time to Response, months	1.86	3.65	1.81	2.86
PFS, months, median (95% CI)	2.17 (1.91-5.42)	2.07 (1.84-2.83)	2.69 (1.87-5.29)	1.87 (1.77-2.43)

[a]By blinded independent central review using RECIST v1.1

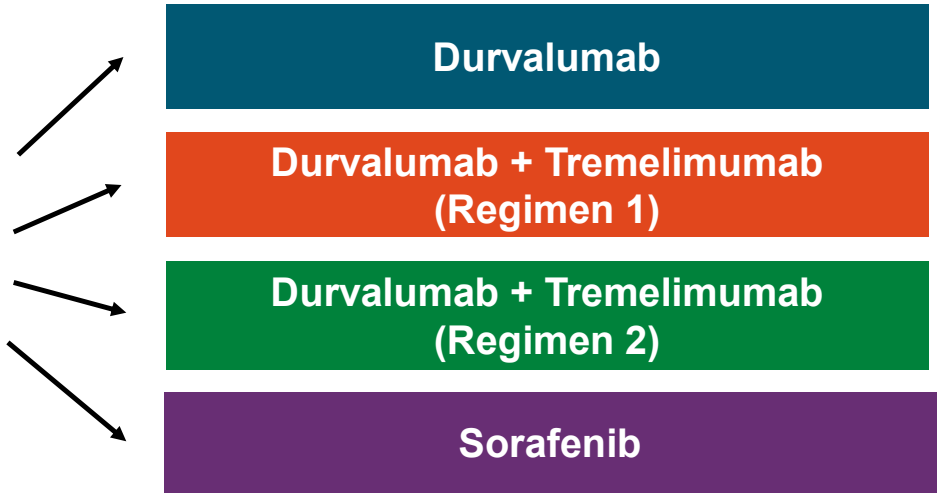
[b]Time from the first documentation of a confirmed CR/PR until the date of progression, death, or the last evaluable RECIST assessment

CI, confidence interval; CR, complete response; D, durvalumab; NR, not reached; PFS, progression-free survival; PR, partial response; SD, stable disease; T, tremelimumab

HIMALAYA: Durvalumab + Tremelimumab vs Sorafenib As First-Line Treatment For HCC

- Multicenter, randomized, open-label phase III trial

Patients with unresectable HCC and no prior systemic therapy; BCLC stage B or C disease ineligible for LRT; Child-Pugh A; ECOG PS ≤ 1 (N = 1200)



- Primary endpoint: OS
- Secondary endpoints: TTP, PFS, ORR, DCR, DoR, QOL, safety

Abou-Alfa. ASCO 2018. Abstr TPS4144. NCT03298451.

The evolving role of checkpoint inhibitors in advanced HCC

- Atezolizumab+Bevacizumab: standard of care BUT multiple emerging combinations
  - Higher response rates and improved survival
    - Synergistic efficacy versus additive effect?
    - IO+VEGF: high disease-control rates
    - IO+IO: deep long-lasting responses with “long tail”
  - Toxicity considerations
    - TKI versus bevacizumab
    - IO/IO combinations: IMAES

The evolving role of checkpoint inhibitors in advanced HCC

- Would some patients still benefit from a sequential approach?
  - Single agent checkpoint inhibitors for patients with:
    - Child Pugh B cirrhosis
    - Poor performance status
    - Contraindications to anti-VEGF therapy?
  - Can biomarkers drive improved patient selection and stratification?

Second Line and Beyond

Overview of second line and beyond single agent options

AGENT	Study phase	Prior therapy	Primary Endpoint	Comments
Regorefanib vs. Placebo	Phase 3	Sorafenib	Median OS: 10.6 vs 7.8 mo HR 0.62 (95% CI: 0.50, 0.78)	Eligibility: tolerated sorafenib at 400 mg daily or higher for 20 of last 28 days
Cabozantinib vs. Placebo	Phase 3	Sorafenib (Up to 2 prior lines)	Median OS: 10.2 vs. 8 mo HR 0.76 (95% CI: 0.76-0.92)	30% of patients had 2 prior lines of therapy No requirement for sorafenib tolerability
Ramucirumab vs. Placebo AFP≥ 400	Phase 3	Sorafenib	Median OS: 8.5 vs. 7.3 mo HR 0.710 (0.531-0.949)	
Nivolumab	Phase I/II	Sorafenib (Other lines allowed)	ORR: 14% Median OS: 15 mo	Accelerated Approval First line phase 3 did not reach OS endpoint
Pembrolizumab vs. Placebo	Phase 3	Sorafenib	13.9 vs 10.6 0.78 (0.61-1.00)	Accelerated Approval Second line phase 3 did not reach OS endpoint

Bruix J et al, Lancet 2017
Abou-Alfa G et al. N Engl J Med. 2018
Zhu A et al, Lancet Oncol 2019
El-Khoueiry A, Lancet. 2017
Finn R et al, ESMO GI 2019

The upcoming reality for patients with advanced HCC

Pathway 1

Nivolumab+Ipilimumab

Atezolizumab+Bevacizumab

Regorefanib

Ramucirumab

There is a clear need for data on Sequencing agents post atezo/Bev

Pathwa

Sorafenib

Regorefanib

Atezolizumab+Bevacizumab

Ramucirumab

Lenvatinib

Cabozantinib

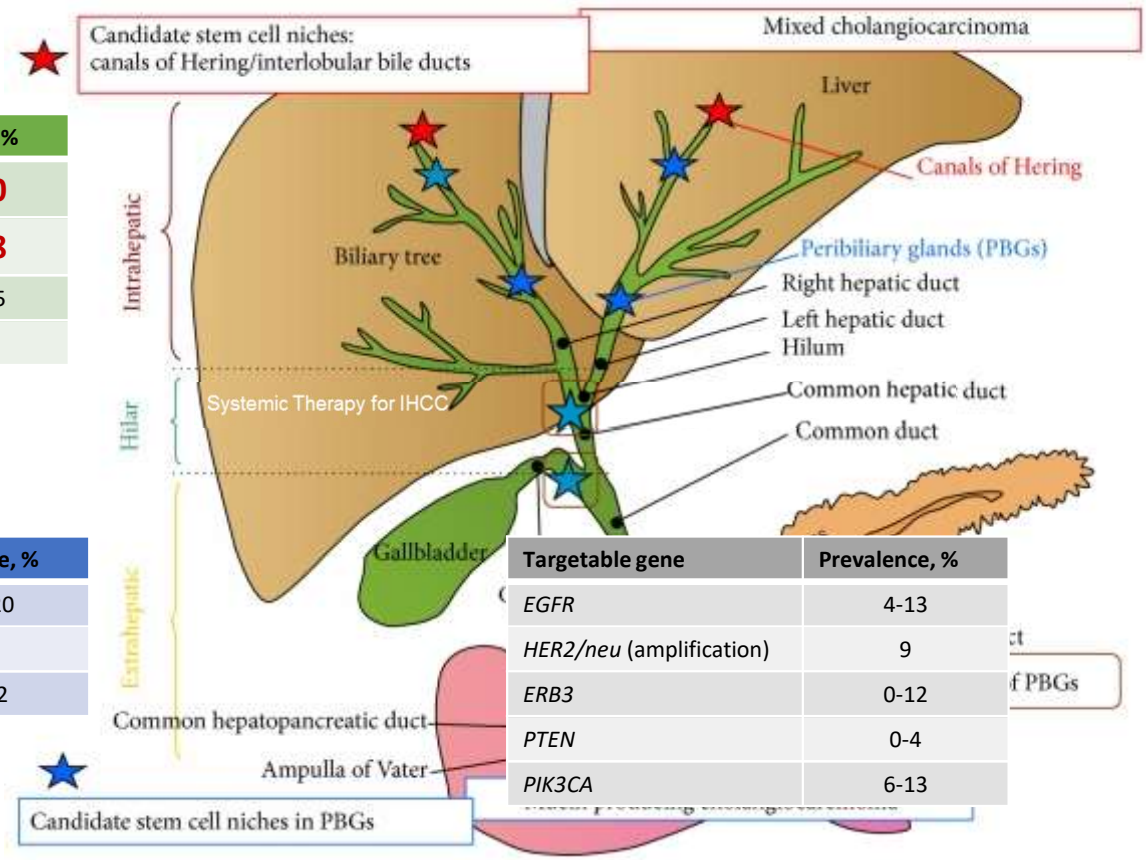
General Forward Looking Thoughts

- Multiple systemic therapy options available now
- Critical to transition patients from liver directed therapy to systemic therapy “at the right time”
  - Absence of CR after two TACEs
  - Worsening liver function
- Some BCLC B patients may be candidates for systemic therapy upfront
- Combination of systemic therapy with checkpoint inhibitors and liver directed therapy being evaluated
- Multiple adjuvant and neoadjuvant studies in progress
- Accrual to clinical trials and data generation remain critical

The evolving treatment landscape of Cholangiocarcinoma

Targetable gene	Prevalence, %
***FGFR2* (fusions)**	**10-20**
IDH1/2	**22-28**
BAP1	15 to 25
BRAF V600 (mutation)[1,2]	5-7

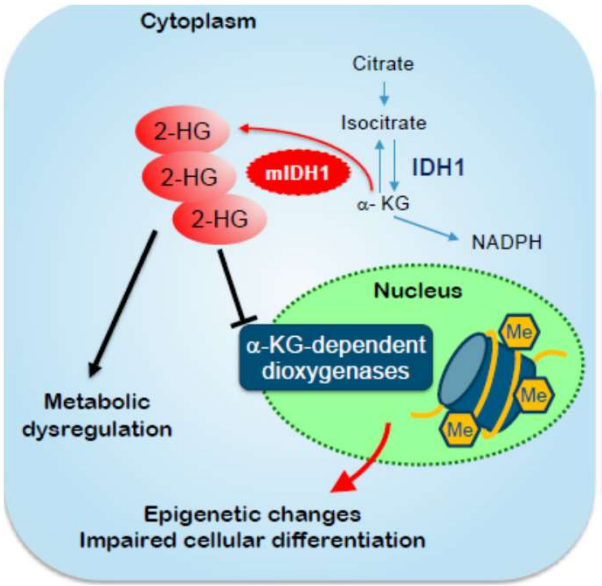
Targetable gene	Prevalence, %
Her2/neu (mutation)	11-20
PRKACA and *PRKACB*	9
ARID1A	5-12



Targetable gene	Prevalence, %
EGFR	4-13
HER2/neu (amplification)	9
ERB3	0-12
PTEN	0-4
PIK3CA	6-13

Cardinale et al, Adv Hepatol 2014
Jain A, Javle M J Gastrointest Oncol. 2016;7(5):797-803

Targeting IDH1: ClarIDHy phase3 trial



Key eligibility criteria

- ≥18 years of age
- Histologically confirmed diagnosis of cholangiocarcinoma
- Centrally confirmed mIDH1* status by NGS
- ECOG PS score 0 or 1
- 1-2 prior therapies (at least 1 gemcitabine- or 5-FU-containing regimen)
- Measurable lesion as defined by RECIST v1.1
- Adequate hematologic, hepatic, and renal function

NCT02989857

Pre-screening for IDH1 mutation

2:1 double-blind randomization (n=185)

Stratified by number of prior therapies

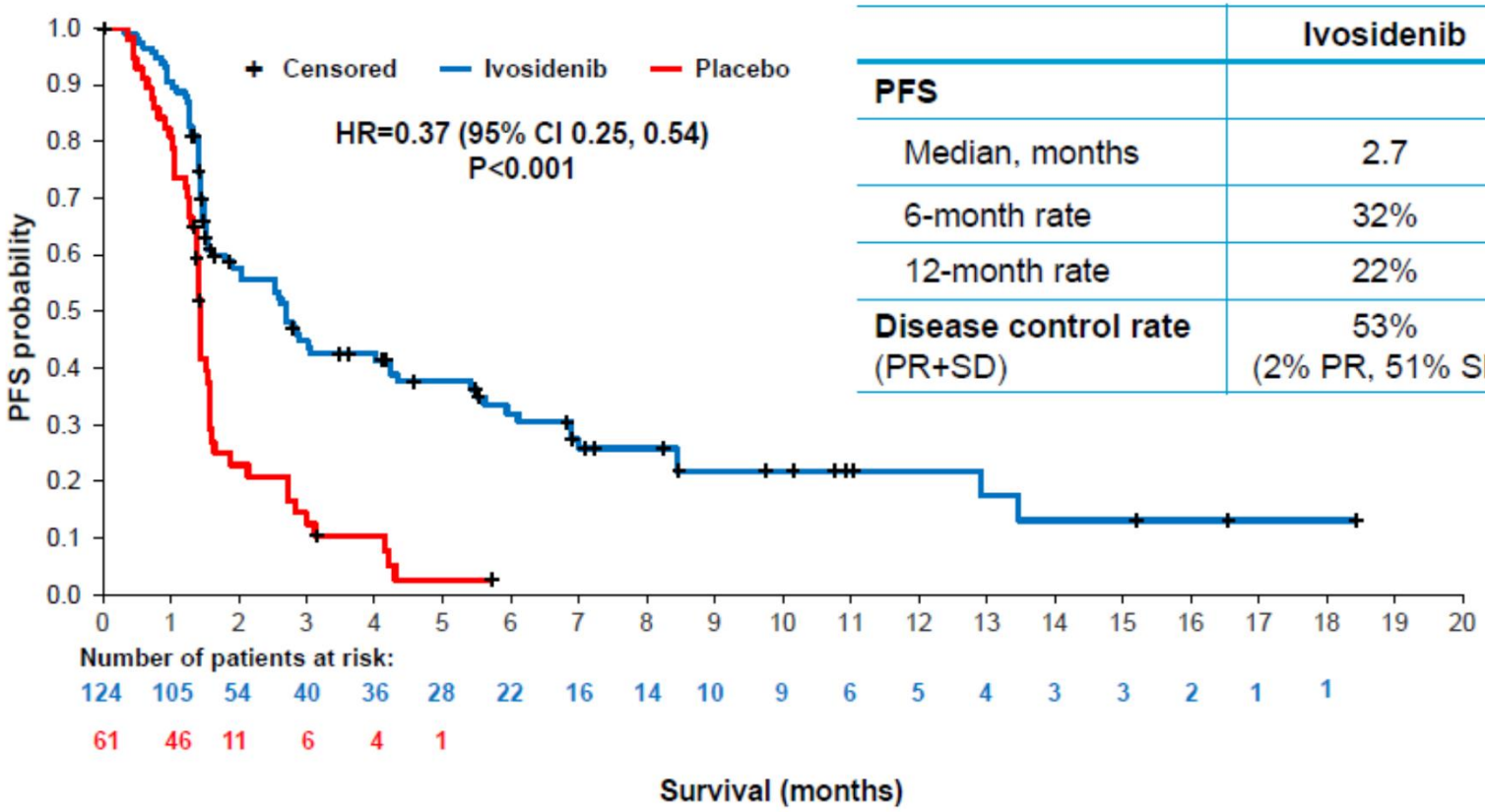
Ivosidenib 500 mg QD orally in continuous 28-day (±2 days) cycles (n=124)

Placebo (n=61)

Crossover permitted at radiographic disease progression

An independent data monitoring committee monitored the safety data throughout the study

ClarIDHy: PFS



	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

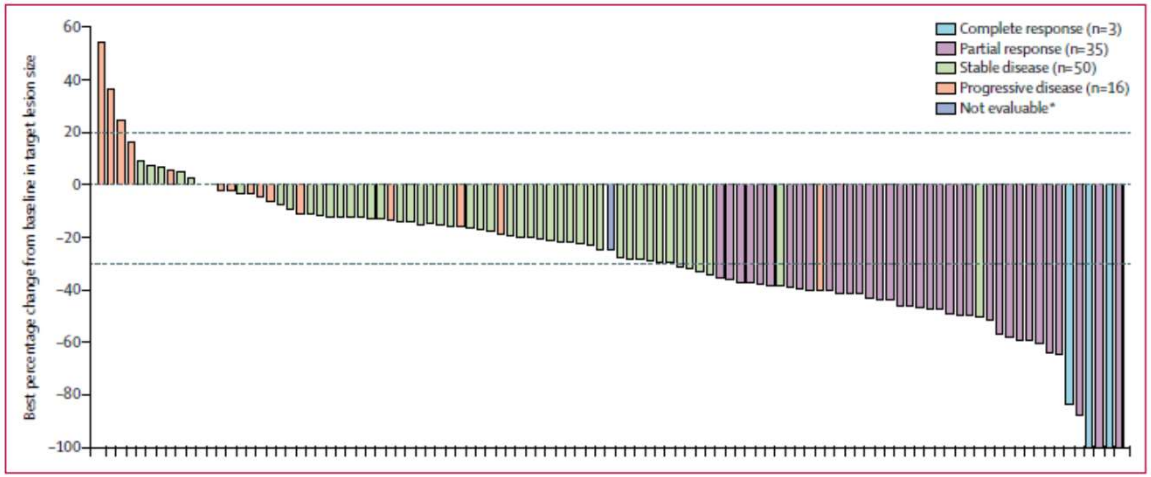
Lancet Oncol. 2020 Jun;21(6):796-807

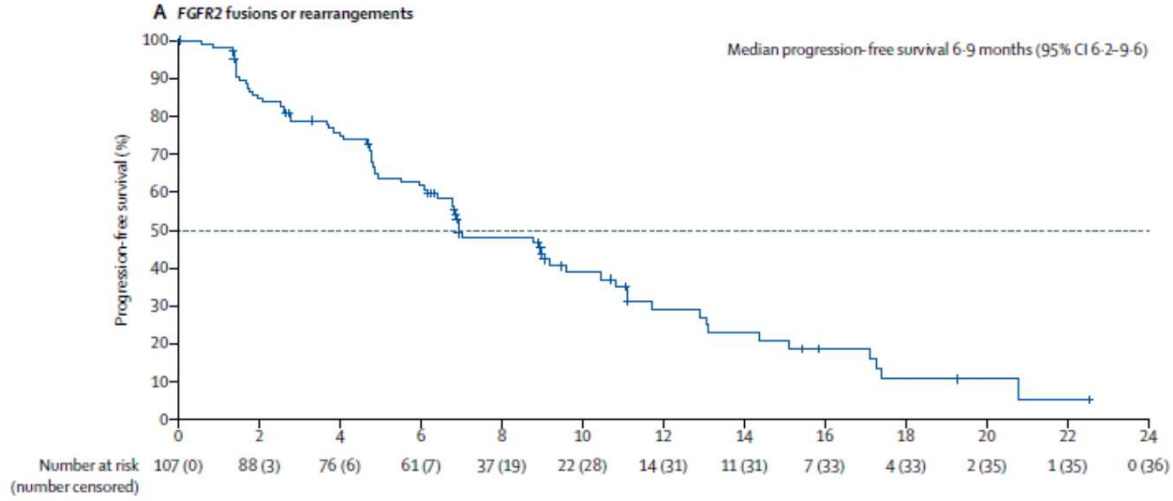
Agios Announces Final Overall Survival Data from Phase 3 ClarIDHy Study of TIBSOVO® (ivosidenib tablets) in Previously Treated IDH1-Mutant Cholangiocarcinoma Patients

– Supplemental New Drug Application Planned for Submission in Q1 2021 –

CAMBRIDGE, Mass., September 21, 2020 – Agios Pharmaceuticals, Inc. (NASDAQ:AGIO), a leader in the field of cellular metabolism to treat cancer and rare genetic diseases, today announced the results of the final overall survival (OS) analysis from its global Phase 3 ClarIDHy trial of TIBSOVO® (ivosidenib tablets) in previously treated cholangiocarcinoma patients with an isocitrate dehydrogenase 1 (IDH1) mutation. A consistent trend in improved OS was observed in patients treated with TIBSOVO® compared to those randomized to placebo, but was not statistically significant. The OS endpoint can be affected by crossover, so these results should be taken in the context of the large proportion (70%) of patients in the placebo arm who crossed over to receive TIBSOVO® following radiographic disease progression; additional analyses performed to take crossover into account further support that TIBSOVO® may improve OS. The safety profile observed in the study was consistent with previously published data. OS was a secondary endpoint in the ClarIDHy study; as previously announced, the study met its primary endpoint of progression-free survival (HR 0.37, p-value < 0.0001).

Pemigatinib: Targeting FGFR2 fusions in biliary cancers





Abou Alfa G et al, Lancet Oncol 2020

Targeting FGFR2: Infigratinib in advanced cholangiocarcinoma

Efficacy outcome in all fusion patients	n=71
Overall response rate (ORR; confirmed & unconfirmed), % (95% CI)	31.0 (20.5–43.1)
Complete response, n (%)	0
Partial response – confirmed, n (%)	18 (25.4)
Stable disease, n (%)	41 (57.7)
Progressive disease, n (%)	8 (11.3)
Unknown, n (%)	4 (5.6)
Efficacy outcome in patients with potential for confirmation*	
cORR, % (95% CI)	26.9 (16.8–39.1)
cORR in patients receiving prior lines of treatment, % ≤1 (n=28) ≥2 (n=39)	 39.3 17.9
Disease control rate (DCR), % (95% CI)	83.6 (72.5–91.5)
Median duration of response, months (95% CI)	5.4 (3.7–7.4)
Median PFS, months (95% CI)	6.8 (5.3–7.6)
Median OS, months (95% CI)	12.5 (9.9–16.6)

*Patients completed (or discontinued prior to) 6 cycles. Investigator-assessed.

Javle, M et al, ESMO 2018

Summary and Conclusions

- Biliary Cancers do represent a heterogeneous group of molecularly distinct subsets
  - Emerging role of targeted therapies
- Single agent PD-1 or PD-L1 targeting antibodies have shown modest activity overall with high variability related to disease heterogeneity and lack of uniform patient selection
- Immune checkpoint based on combinations are being actively evaluated