USC Norris Comprehensive Cancer Center
Keck Medicine of USC

Hepatocellular and Biliary Cancers: Recent Advances

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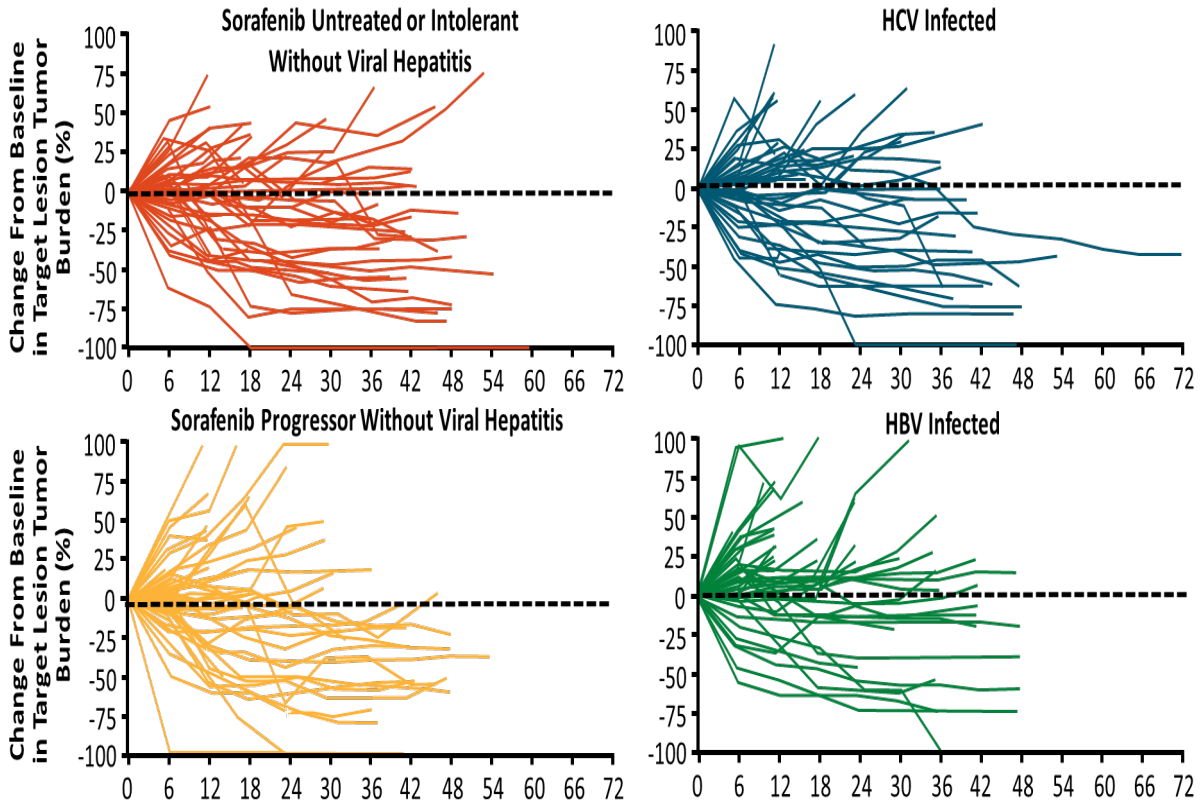
Single Agent Immune checkpoint Inhibitors in HCC

Checkmate 040: Nivolumab



Keynote 224: Pembrolizumab

Anti-tumor Activity

Response†	Total N=104 n (%)	95% CI‡
ORR (CR+PR)	17 (16.3)	9.8 - 24.9
Disease control (CR+PR+SD)	64 (61.5)	51.5 - 70.9
Best overall response		
CR	1 (1.0)	0.0 - 5.2
PR	16 (15.4)	9.1- 23.8
SD	47 (45.2)	35.4 - 55.3
PD	34 (32.7)	23.8 - 42.6
No Assessment§	6 (5.8)	2.1-12.1

†Confirmed best response by independent central review per RECIST v1.1. ‡Based on binomial exact confidence interval method. §Subjects who had a baseline assessment by investigator review or central radiology but no post-baseline assessment on the data cutoff date including discontinuing or death before the first post-baseline scan. Data cutoff date: Aug 24, 2017.

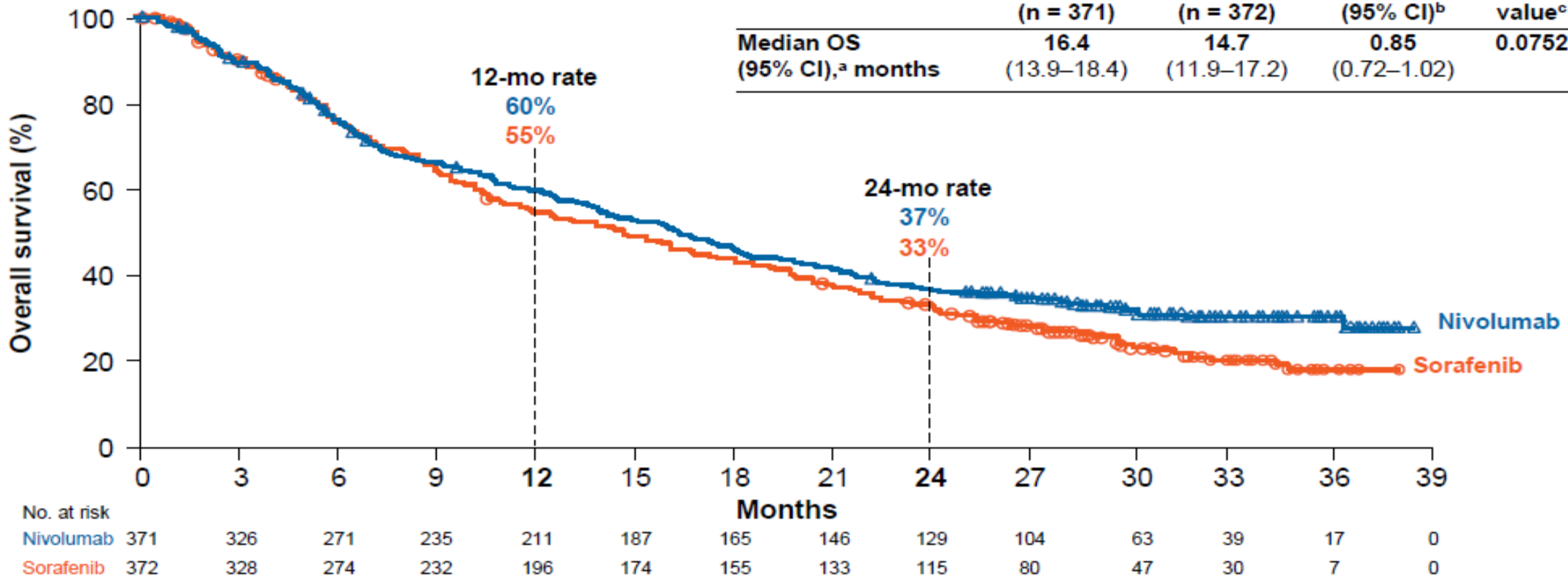
El-Khoueiry A et al. Lancet. 2017;389:2492
Yau T, et al. ESMO 2019. Abstr LBA38
Zhu AX, et al. Lancet Oncol. 2018 Jul;19(7):940-952
Finn R et al, ESMO GI 2019

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 T et al, Lancet Oncol. 2022

IMBRAVE150 STUDY DESIGN

Key eligibility

- Locally advanced or metastatic and/or unresectable HCC
- No prior systemic therapy
- ECOG PS 0-1
- Child-Pugh class A liver function

Stratification

- **Region** (Asia excluding Japan[a]/Rest of world)
- **ECOG** (0/1)
- **Macrovascular invasion** and/or **extrahepatic spread** (Presence/Absence)
- **Baseline AFP** (<400/≥400 ng/mL)

R 2:1

Atezolizumab 1200 mg IV q3w + Bevacizumab 15 mg/kg q3w

N = 501

Sorafenib 400 mg bid

(open-label)

Until loss of clinical benefit or un-acceptable toxicity[b]

Survival follow-up

Co-primary endpoints

- OS
- IRF-assessed PFS per RECIST 1.1

Secondary endpoints included:

- IRF-assessed ORR, DOR per RECIST 1.1 and HCC mRECIST[b]
- PROs: TTD[c] of QOL, physical and role functioning (EORTC QLQ-C30)
- Safety and tolerability assessed based on the nature, frequency and severity of AEs per NCI CTCAE version 4.0

[a] Japan is included in rest of world. [b] Tumor assessment by computed tomography or magnetic resonance imaging was done at baseline and every 6 weeks until 54 weeks, then every 9 weeks thereafter.
[c] Time from randomization to first decrease from baseline of ≥ 10 points maintained for 2 consecutive assessments or 1 assessment followed by death from any cause within 3 weeks.
AFP, α-fetoprotein; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality-of-life questionnaire for cancer; IRF, independent review facility; mRECIST, modified RECIST; NCI, National Cancer Institute; PRO, patient-reported outcomes; QOL, quality of life; TTD, time to deterioration.

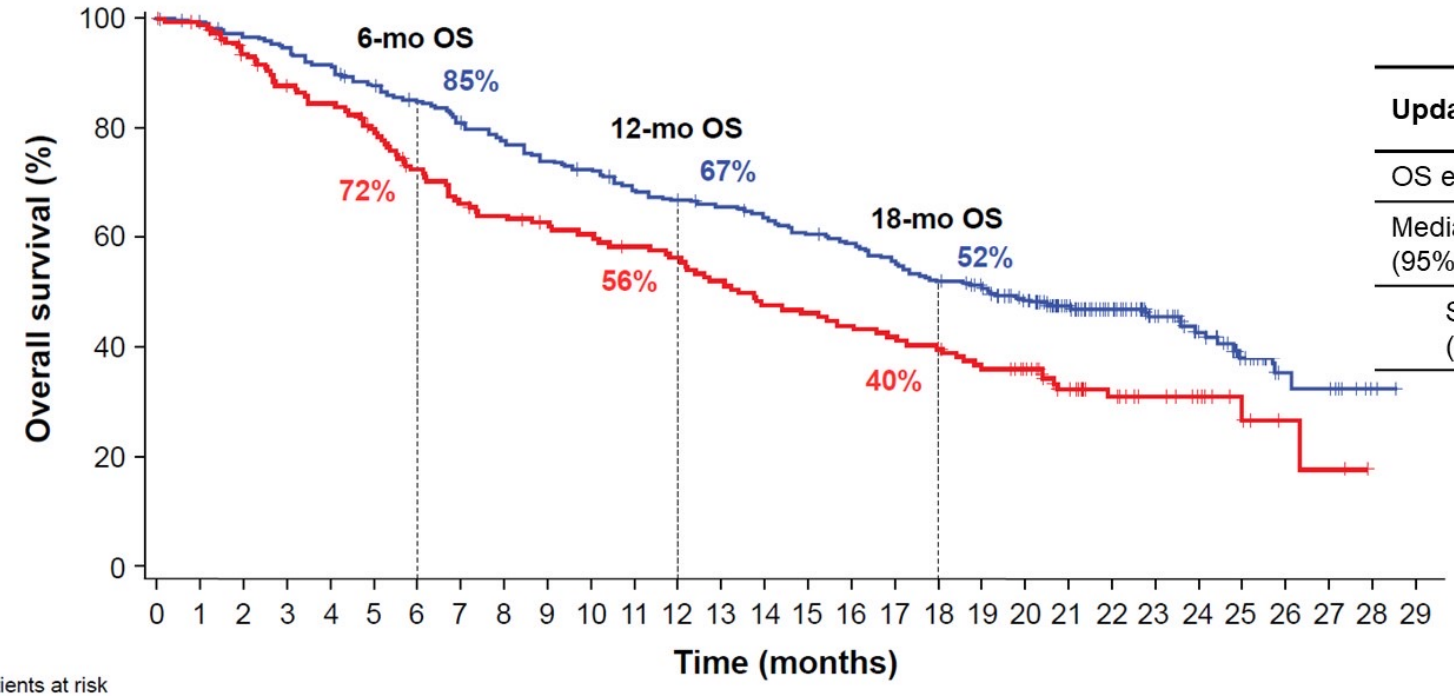
IMBRAVE 150 BASELINE CHARACTERISTICS

Characteristic	Atezolizumab + bevacizumab (n = 336)	Sorafenib (n = 165)
Median age (IQR), years	64 (56, 71)	66 (59, 71)
Male, n (%)	277 (82)	137 (83)
Geographic region, n (%)		
Asia excluding Japan	133 (40)	68 (41)
Rest of the world[a]	203 (60)	97 (59)
ECOG performance status score, n (%)		
0	209 (62)	103 (62)
1	127 (38)	62 (38)
Child-Pugh score		
A5	239 (72)	121 (73)
A6	94 (28)	44 (27)
Barcelona Clinic Liver Cancer stage		
A	8 (2)	6 (4)
B	52 (15)	26 (16)
C	276 (82)	133 (81)

Characteristic	Atezolizumab + bevacizumab (n = 336)	Sorafenib (n = 165)
AFP at baseline ≥ 400 ng/mL	126 (38)	61 (37)
Macrovascular invasion and/or extrahepatic spread present, n (%)	258 (77)	120 (73)
Macrovascular invasion present, n (%)	129 (38)	71 (43)
Extrahepatic spread present, n (%)	212 (63)	93 (56)
Varices at baseline	88 (26)	43 (26)
Varices treated at baseline	36 (11)	23 (14)
Cause of hepatocellular carcinoma, n (%)		
Hepatitis B	164 (49)	76 (46)
Hepatitis C	72 (21)	36 (22)
Nonviral[a]	100 (30)	53 (32)
Prior local therapy for hepatocellular carcinoma, n (%)	161 (48)	85 (52)

Finn et al. New Engl J Med. 2020

Updated OS



Updated OS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
OS events, n (%)	180 (54)	100 (61)
Median OS, mo (95% CI)	**19.2** (17.0, 23.7)	**13.4** (11.4, 16.9)
Stratified HR (95% CI)[a]	**0.66** (0.52, 0.85) *P* = 0.0009[b]	

No. of patients at risk

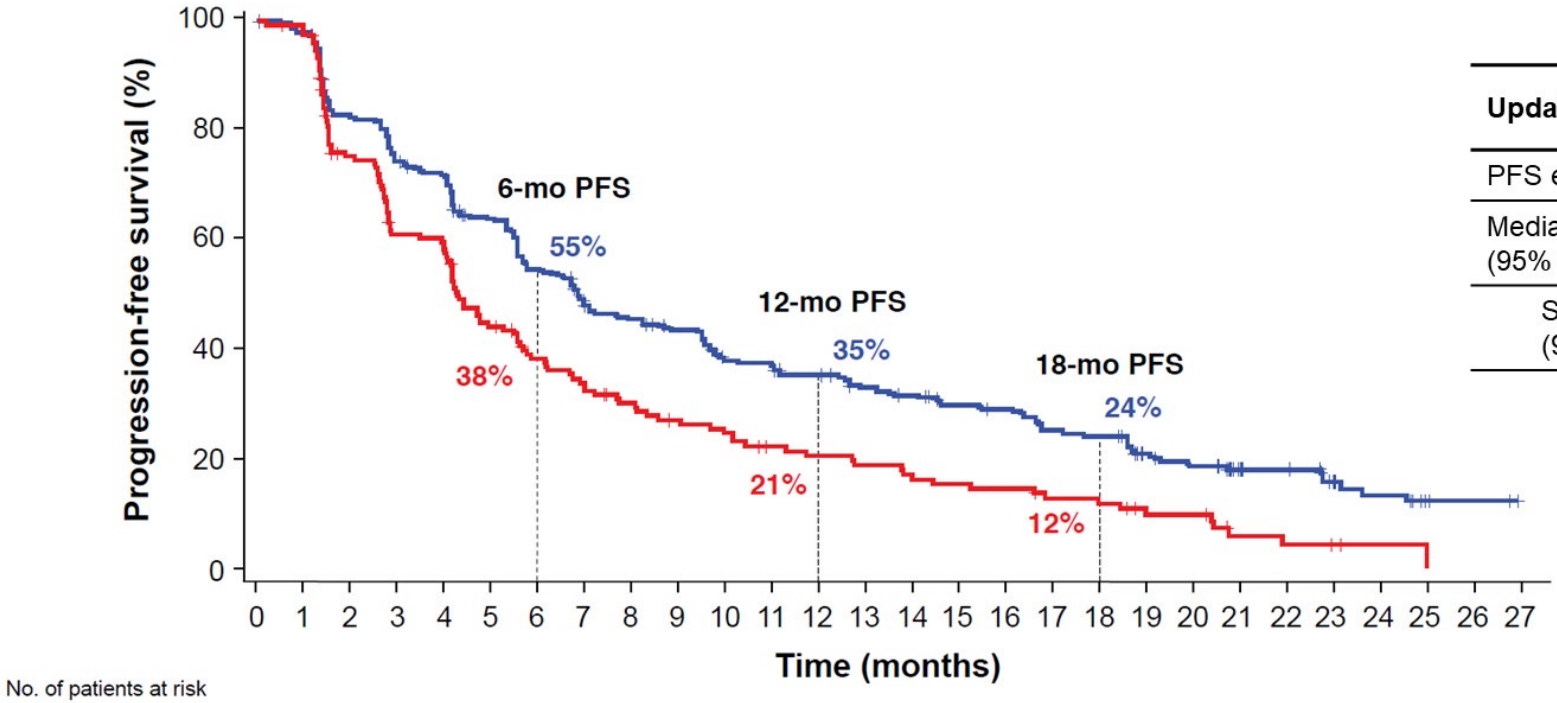
Atezo + Bev	336	329	320	312	302	288	276	263	252	240	233	221	214	209	202	192	186	175	164	156	134	105	80	57	42	24	12	11	2	NE
Sorafenib	165	158	144	133	128	119	106	96	92	88	85	81	78	72	66	64	61	58	55	49	44	32	24	18	12	7	3	2	NE	NE

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo.

[a] Stratification factors included in the Cox model are geographic region (Asia excluding Japan vs Rest of World), AFP level (< 400 ng/mL vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (Yes vs No) per interactive voice/web response system (IxRS).[b] *P* value for descriptive purposes only.

Finn et al. New Engl J Med. 2020

Updated PFS by IRF RECIST 1.1



No. of patients at risk

Atezo + Bev	336	323	271	245	234	204	174	149	141	132	113	111	102	93	88	80	77	67	64	47	41	27	25	17	12	4	3	NE
Sorafenib	165	150	110	88	84	63	52	44	39	34	31	26	24	22	19	18	17	14	13	9	9	4	3	2	1	1	NE	NE

Updated PFS	Atezo + Bev (n = 336)	Sorafenib (n = 165)
PFS events, n (%)	257 (76)	130 (79)
Median PFS, mo (95% CI)	**6.9** (5.7, 8.6)	**4.3** (4.0, 5.6)
Stratified HR (95% CI)[a]	**0.65** (0.53, 0.81) *P* = 0.0001[b]	

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo.

[a] Stratification factors included in the Cox model are geographic region (Asia excluding Japan vs Rest of World), AFP level (< 400 ng/mL vs ≥ 400 ng/mL) at baseline and MVI and/or EHS (Yes vs No) per interactive voice/web response system (IxRS).[b] *P* value for descriptive purposes only.

Finn et al. New Engl J Med. 2020

Updated response and duration of response

	Updated analysis[a]			
	RECIST 1.1		HCC mRECIST	
	Atezo + Bev (n = 326)	Sorafenib (n = 159)	Atezo + Bev (n = 325)	Sorafenib (n = 158)
Confirmed ORR (95% CI), %	**30 (25, 35)**	**11 (7, 17)**	**35 (30, 41)**	**14 (9, 20)**
CR, n (%)	25 (8)	1 (< 1)	39 (12)	4 (3)
PR, n (%)	72 (22)	17 (11)	76 (23)	18 (11)
SD, n (%)	144 (44)	69 (43)	121 (37)	65 (41)
DCR, n (%)	241 (74)	87 (55)	236 (73)	87 (55)
PD, n (%)	63 (19)	40 (25)	65 (20)	40 (25)
Ongoing response, n (%)	54 (56)	5 (28)	58 (50)	6 (27)
Median DOR (95% CI), mo[b]	**18.1 (14.6, NE)**	**14.9 (4.9, 17.0)**	**16.3 (13.1, 21.4)**	**12.6 (6.1, 17.7)**

Clinical cutoff: August 31, 2020; median follow-up: 15.6 mo. DCR, disease control rate.
[a] Only patients with measurable disease at baseline were included in the analysis of ORR.
[b] Only confirmed responders were included in the analysis of ORR and DOR.

Finn et al. New Engl J Med. 2020

HIMALAYA: Tremelimumab and Durvalumab combination rationale

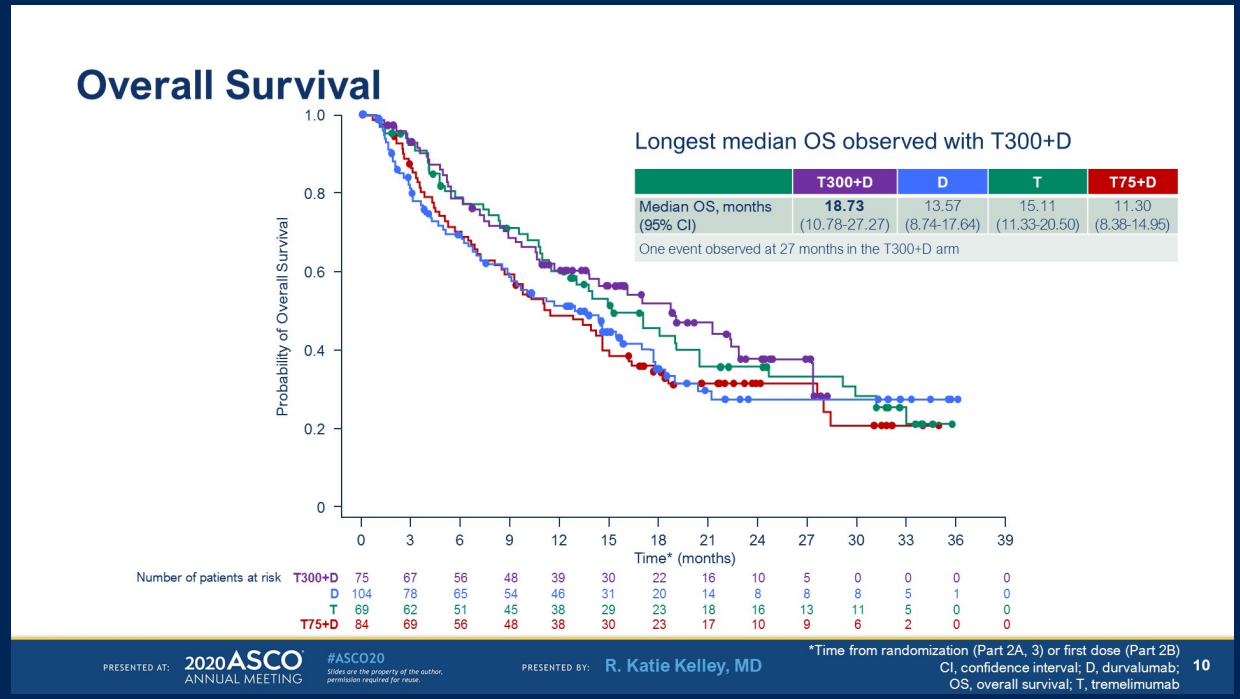
Targeting PD-1/ PD-L1

- Affects differentiated CD8+ T cells in tumor microenvironment
- Does not increase clonal diversity
- Does not move T cells into tumors
- Single agent activity in HCC
  - ORR 15 to 20%

Targeting CTLA-4

- Blocks suppressive T cell signaling in lymph nodes
- Modulates CD4 effector compartment
  - Expands ICOS+Th1 like effector subsets
- Single agent tremelimumab activity
  - ORR 17.6%

STUDY 22



T300+D ORR 24%

J Immunother Cancer. 2018; 6
Wei SC et al, Cell 2017
Rotte A, J Exp Clin Cancer Res 2019

Sangro B et al. J Hepatol. 2013
El-Khoueiry A et al, Lancet 2017
Zhu AX, et al. Lancet Oncol. 2018
Kelley RK et al, J Clin Oncol 2021

HIMALAYA study design

HIMALAYA was an open-label, multicenter, global, Phase 3 trial

Study population
- Patients aged ≥18 years with uHCC
- BCLC stage B (not eligible for locoregional therapy) and stage C
- No prior systemic therapy
- ECOG PS 0–1
- Child-Pugh A
- No main portal vein thrombosis
- EGD was not required

R
N=1324

STRIDE (n=393):
Tremelimumab 300 mg × 1 dose + durvalumab 1500 mg Q4W*

Durvalumab (n=389):
Durvalumab monotherapy 1500 mg Q4W*

Sorafenib (n=389):
Sorafenib 400 mg BID*

T75+D (n=153): *arm closed* †
Tremelimumab 75 mg Q4W × 4 doses + durvalumab Q4W*

Stratification factors
- Macrovascular invasion: yes vs no
- Etiology of liver disease: HBV vs HCV vs others
- Performance status: ECOG 0 vs 1

*Treatment continued until disease progression. Patients with progressive disease who, in the investigator's opinion, continued to benefit from treatment and met the criteria for treatment in the setting of progressive disease could continue treatment. †The T75+D arm was closed following a preplanned analysis of a Phase 2 study. Patients randomized to this arm (n=153) could continue treatment following arm closure. Results from this arm are not reported in this presentation.

BID, twice a day; EGD, esophagogastroduodenoscopy; Q4W, every 4 weeks; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

Baseline characteristics

Characteristic	STRIDE (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
Male sex, n (%)	327 (83.2)	323 (83.0)	337 (86.6)
Median age (range), years	65.0 (22–86)	64.0 (20–86)	64.0 (18–88)
Region, n (%) Asia (excluding Japan) Rest of world (including Japan)	 156 (39.7) 237 (60.3)	 167 (42.9) 222 (57.1)	 156 (40.1) 233 (59.9)
Viral etiology,*,† n (%) HBV HCV Nonviral	 122 (31.0) 110 (28.0) 161 (41.0)	 119 (30.6) 107 (27.5) 163 (41.9)	 119 (30.6) 104 (26.7) 166 (42.7)
ECOG PS, n (%) 0 1	 244 (62.1) 148 (37.7)	 237 (60.9) 150 (38.6)	 241 (62.0) 147 (37.8)
MVI,† n (%)	103 (26.2)	94 (24.2)	100 (25.7)
EHS,† n (%)	209 (53.2)	212 (54.5)	203 (52.2)
PD-L1 positive, n (%)	148 (37.7)	154 (39.6)	148 (38.0)
AFP ≥400 ng/ml,† n (%)	145 (36.9)	137 (35.2)	124 (31.9)

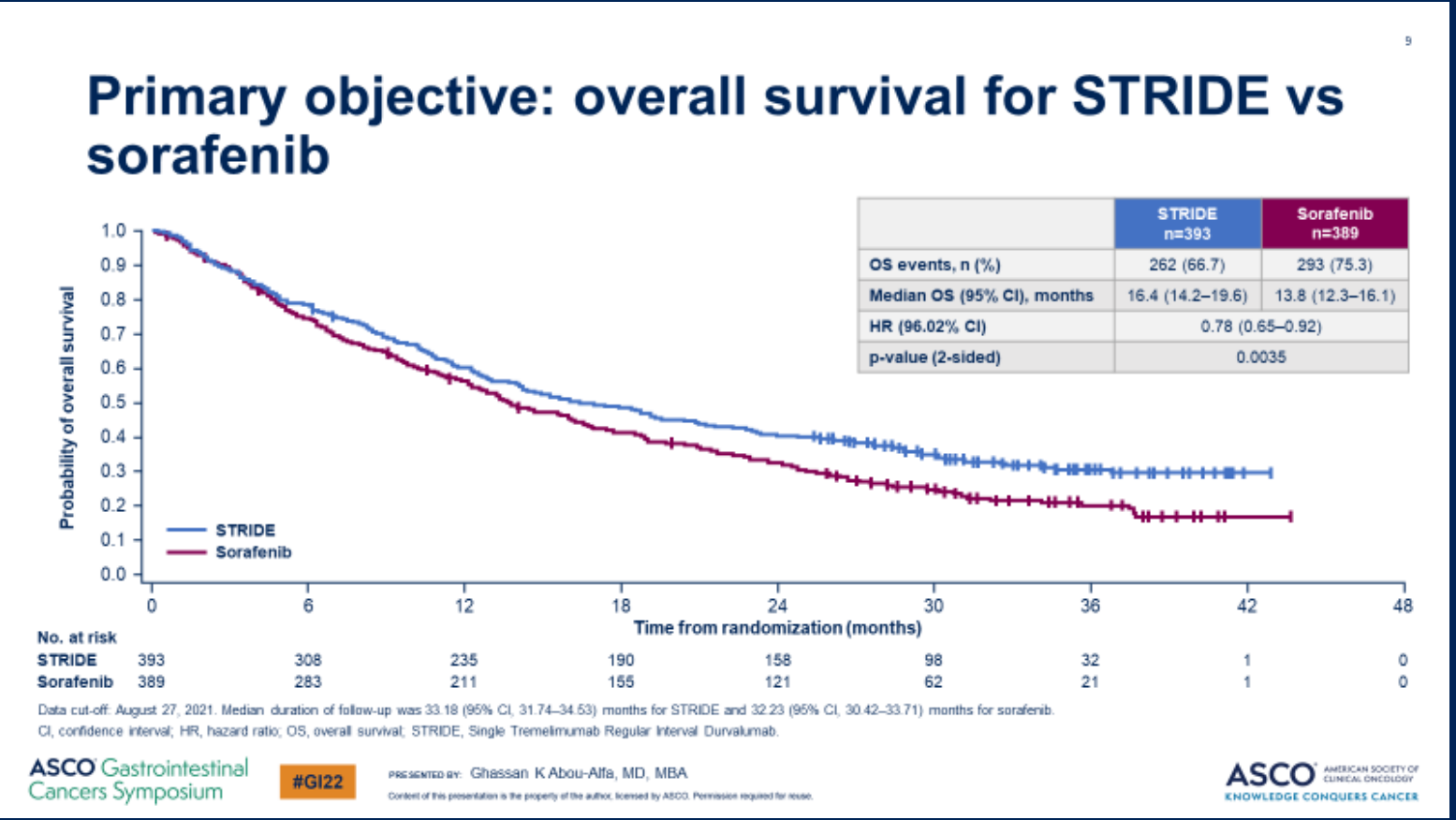
Biomarker evaluable samples were collected for all but 20 patients across all treatment arms.

*HBV: patients who tested positive for HBsAg or anti-HBc with detectable HBV DNA; HCV: patients who tested positive for HCV or had history of HCV infection; Nonviral: no active viral hepatitis identified. †Determined at screening.

AFP, alfa-fetoprotein; ECOG, Eastern Cooperative Oncology Group; EHS, extrahepatic spread; HBc, hepatitis B core; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; MVI, macrovascular invasion; PD-L1, programmed cell death ligand-1; PS, performance status; STRIDE, Single Tremelimumab Regular Interval Durvalumab.

Results Summary

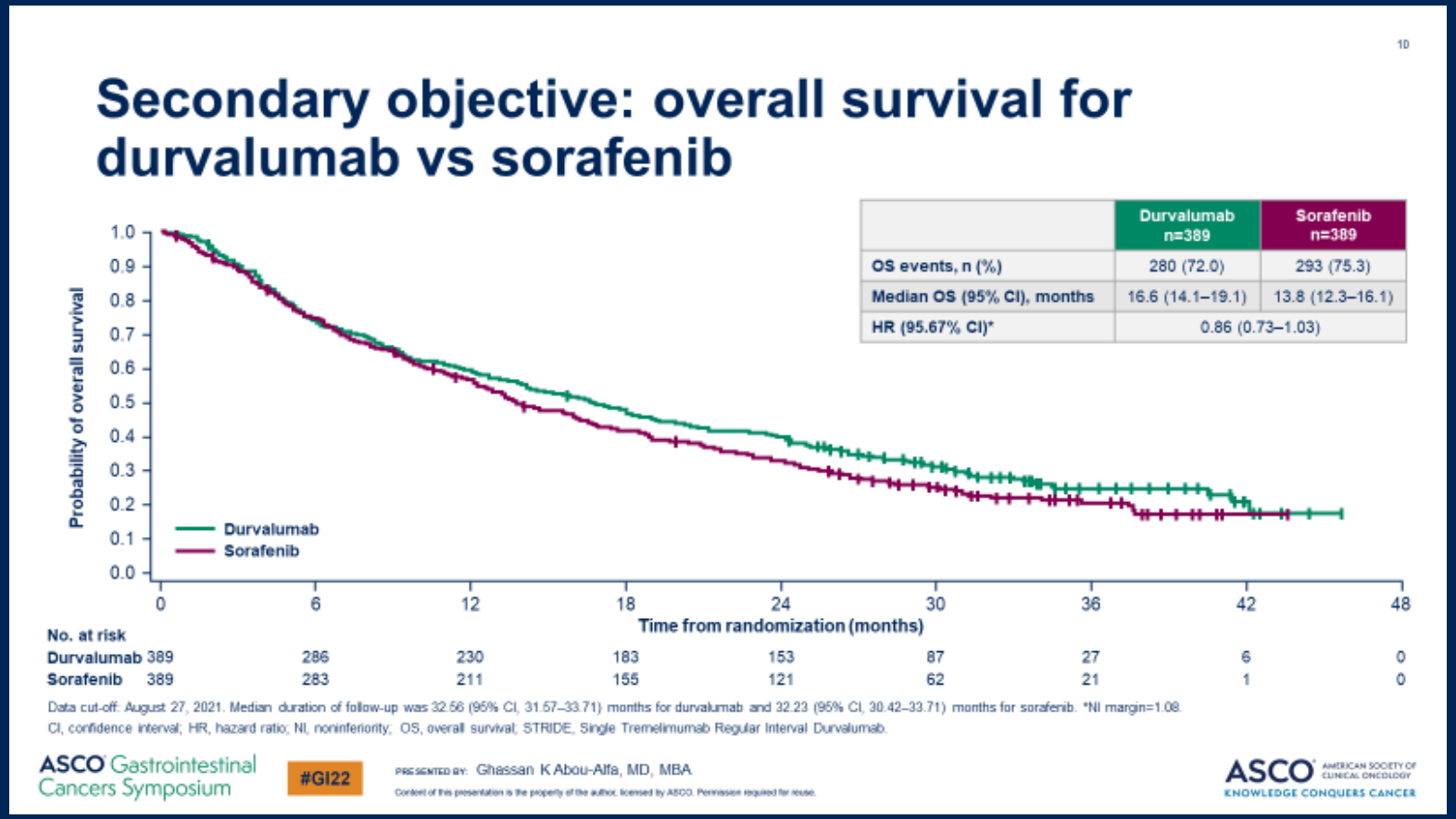
Primary Endpoint: OS
STRIDE superior to Sorafenib



- No difference in PFS
- ORR 20.1%
  - CR 3.1%
- Median DoR 22.34 mo
  - 65.8% remaining in response at 12 months
- 30.7% OS at 36 months

Results Summary

Secondary Endpoint: OS
Durvalumab non-inferior to Sorafenib



- No difference in PFS
- ORR 17%
  - CR 1.5%
- Median DoR 16.82 mo
  - 57.8% remaining in response at 12 months
- 24.7% OS at 36 months

Tumor response

	STRIDE (n=393)	Durvalumab (n=389)	Sorafenib (n=389)
ORR,* %	20.1	17.0	5.1
CR, n (%)	12 (3.1)	6 (1.5)	0
PR, n (%)	67 (17.0)	60 (15.4)	20 (5.1)
SD,† n (%)	157 (39.9)	147 (37.8)	216 (55.5)
PD, n (%)	157 (39.9)	176 (45.2)	153 (39.3)
DCR, %	60.1	54.8	60.7
Median DoR,‡ months 25th percentile 75th percentile	22.34 8.54 NR	16.82 7.43 NR	18.43 6.51 25.99
Median TTR (95% CI), months	2.17 (1.84–3.98)	2.09 (1.87–3.98)	3.78 (1.89–8.44)
Remaining in response,‡ % 6 months 12 moths	 82.3 65.8	 81.8 57.8	 78.9 63.2

*By investigator assessment according to RECIST v1.1. Responses are confirmed. †Defined as neither sufficient decrease in sum of diameters to qualify for PR nor sufficient increase to qualify for PD. ‡Calculated using Kaplan-Meier technique.

CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; STRIDE, Single Tremelimumab Regular Interval Durvalumab; TTR, time to response.

Immune-mediated adverse events

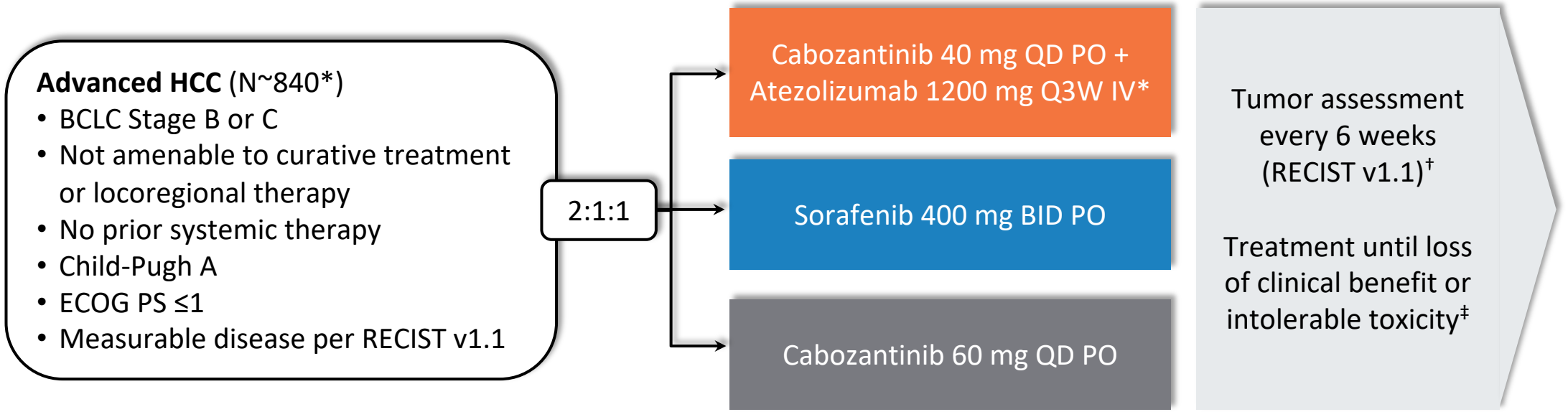
Event, n (%)	STRIDE (n=388)				Durvalumab (n=388)			
	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation	All grades	Grade 3 or 4	Received high-dose steroids	Leading to discontinuation
Patients with immune-mediated event	139 (35.8)	49 (12.6)	78 (20.1)	22 (5.7)	64 (16.5)	25 (6.4)	37 (9.5)	10 (2.6)
Pneumonitis	5 (1.3)	0	4 (1.0)	1 (0.3)	3 (0.8)	1 (0.3)	3 (0.8)	2 (0.5)
Hepatic events	29 (7.5)	16 (4.1)	29 (7.5)	9 (2.3)	26 (6.7)	17 (4.4)	25 (6.4)	5 (1.3)
Diarrhea/colitis	23 (5.9)	14 (3.6)	20 (5.2)	5 (1.3)	3 (0.8)	1 (0.3)	2 (0.5)	1 (0.3)
Adrenal insufficiency	6 (1.5)	1 (0.3)	1 (0.3)	0	6 (1.5)	3 (0.8)	3 (0.8)	0
Hyperthyroid events	18 (4.6)	1 (0.3)	2 (0.5)	0	4 (1.0)	0	0	0
Hypophysitis	4 (1.0)	0	1 (0.3)	0	1 (0.3)	0	0	0
Hypothyroid events	42 (10.8)	0	1 (0.3)	0	19 (4.9)	0	0	0
Thyroiditis	6 (1.5)	0	1 (0.3)	0	2 (0.5)	0	0	0
Renal events	4 (1.0)	2 (0.5)	3 (0.8)	2 (0.5)	0	0	0	0
Dermatitis/rash	19 (4.9)	7 (1.8)	12 (3.1)	2 (0.5)	3 (0.8)	1 (0.3)	3 (0.8)	1 (0.3)
Pancreatic events	9 (2.3)	7 (1.8)	7 (1.8)	0	2 (0.5)	1 (0.3)	2 (0.5)	0

Includes adverse events with onset or increase in severity on or after the date of the first dose through 90 days following the date of the last dose or the date of initiation of the first subsequent therapy. Patients may have had >1 event. Events include those that occurred in ≥1% of patients in either treatment arm.

STRIDE, Single Tremelimumab Regular Interval Durvalumab.

Abou Alfa G et al, ASCO Gastrointestinal Cancers Symposium 2022

COSMIC-312 Study Design

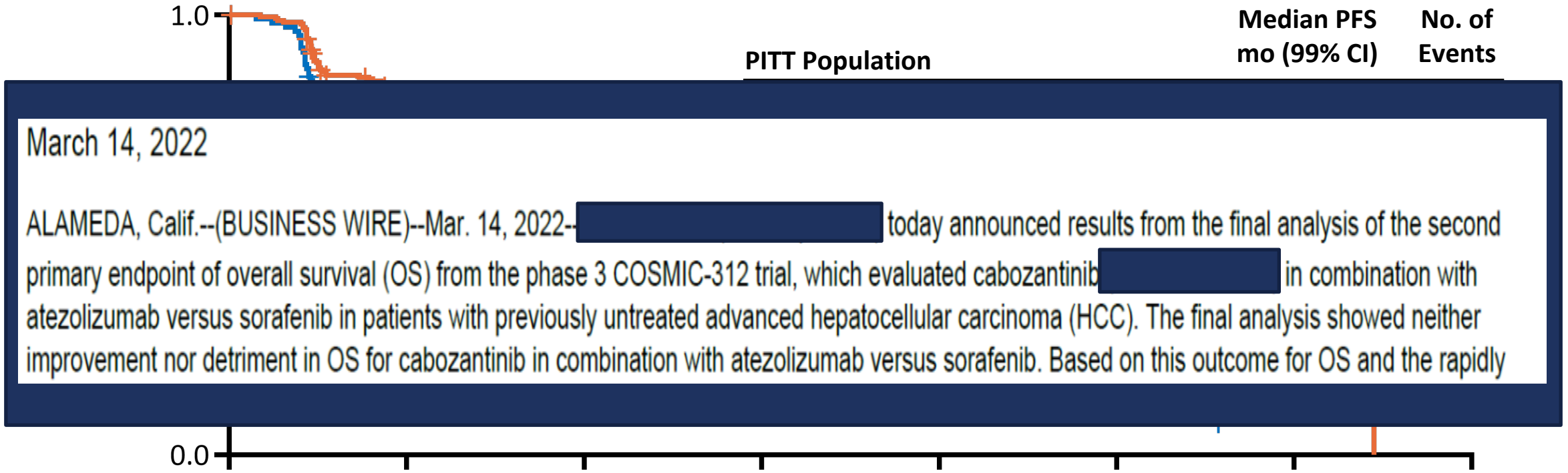


Stratification
- Disease etiology (HBV, HCV [without HBV], non-viral)
- Region (Asia, other)
- Presence of extrahepatic disease and/or macrovascular invasion (yes, no)

*Doses for the combination were determined from the phase 1b COSMIC-021 trial (NCT03170960)
†Every 6 weeks for the first 48 weeks, then every 12 weeks thereafter
‡Patients may be treated beyond progression if there is a clinical benefit in the opinion of the investigator

Kelley RK, ESMO ASIA 2021

Primary Endpoint of PFS: Final Analysis Cabozantinib + Atezolizumab vs Sorafenib



March 14, 2022

ALAMEDA, Calif.--(BUSINESS WIRE)--Mar. 14, 2022-- [redacted] today announced results from the final analysis of the second primary endpoint of overall survival (OS) from the phase 3 COSMIC-312 trial, which evaluated cabozantinib [redacted] in combination with atezolizumab versus sorafenib in patients with previously untreated advanced hepatocellular carcinoma (HCC). The final analysis showed neither improvement nor detriment in OS for cabozantinib in combination with atezolizumab versus sorafenib. Based on this outcome for OS and the rapidly

Median follow-up (range): 15.8 (12.8-27.0) months
PFS per RECIST v1.1 by BIRC

*Critical p-value 0.01

Kelley RK, ESMO ASIA 2021

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

- Multicenter, double-blind, phase III trial

Aug 3, 2022

"…the Phase 3 LEAP-002 trial …did not meet its dual primary endpoints of overall survival (OS) and progression-free survival (PFS) as a first-line treatment for patients with unresectable hepatocellular carcinoma (uHCC).

*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.

First Line Reported Positive Trials

	IMBRAVE 150		HIMALAYA	
	Atezo/Bev	Sorafenib	STRIDE	Sorafenib
mOS (mo)	19.2 HR 0.66 (0.52,0.85)	13.4	16.4 HR 0.78 (0.65-0.92)	13.8
mPFS (mo)	6.9 HR 0.65(0.53,0.81)	4.3	3.78 HR 0.9 (0.77-1.05)	4.07
ORR (RECIST 1.1)	30%	11%	20.1%	5.1%
CR	8%		3.1%	
PD	39.9%		19%	
Median DoR (months)	18.1	14.9	22.3	18.4
DCR	74%	55%	60.1%	60.7%
IMAEs requiring steroids	12.2%		20.1%	
All grade bleeding events	25%	17.3%	1.8%	4.8%
Grade 3/4 bleeding events	6.4%	5.8%	0.5%	1.6%

Bleeding events less common in HIMALAYA but trial did exclude patients with main PVT who are at highest risk for bleeding

Cheng Al et al., *Hepatol,* 2021.
Finn R et al., *N Engl J Med,* 2020

Is there a role for single agent PD-1/PD-L1 in first line HCC

HIMALAYA: Durvalumab non-inferior to Sorafenib

- ORR 17%
- Median OS 16.6 mo

Checkmate 459: Nivolumab not superior to Sorafenib

- ORR 16%
- Median OS 16.4 mo

CheckMate 040 cohort 5: A phase I/II study of nivolumab in patients with advanced hepatocellular carcinoma and Child-Pugh B cirrhosis

First line treatment option for select patients:
- Poor candidates for combination therapy
- VEGF contraindications

Consider Child Pugh B patients

Yau T et al, Lancet Oncol. 2022; Kudo M et al, J Hepatol 2021

Patient with advanced HCC
Candidate for first line systemic therapy

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

IO contraindications

CP B option

Sorafenib or Lenvatinib

Atezolizumab Bevacizumab

Bevacizumab contraindications
High Bleeding Risk
No EGD

STRIDE

Not candidate for combination therapy
OR
VEGF contraindications

CP B option

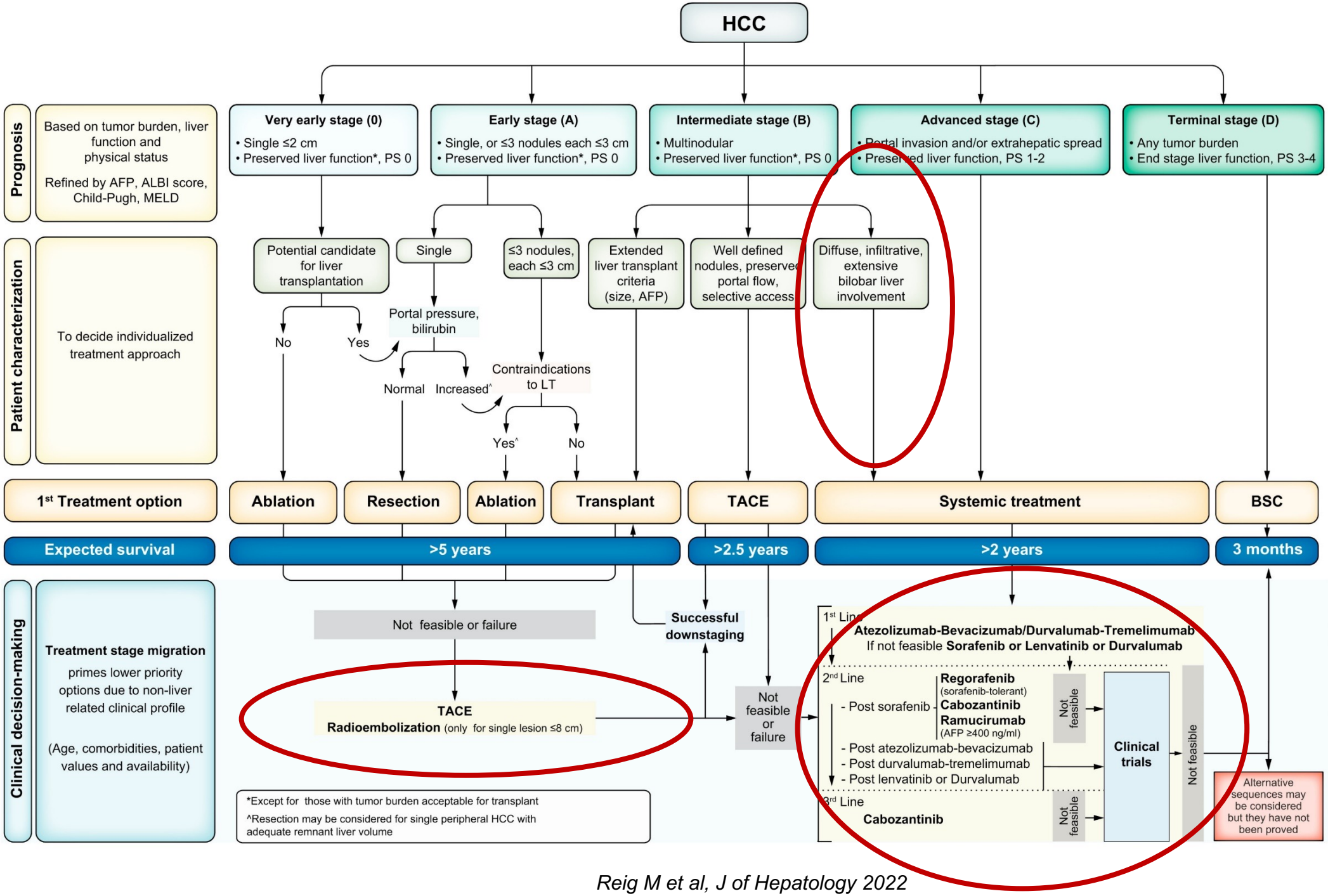
Durvalumab/ Single agent PD-1

Overview of second line and beyond 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/ Ipilimumab	Phase I/II	Sorafenib (Other lines allowed)	ORR: 32% Median OS: 22.8 mo	Accelerated Approval
Pembrolizumab vs. Placebo	Phase 3	Sorafenib	Keynote 240: 13.9 vs 10.6 mo HR 0.78 (0.61-1.00) Keynote 394: 14.6 vs 13 mo HR 079 (0.63-0.99)	Accelerated Approval

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



Reig M et al, J of Hepatology 2022

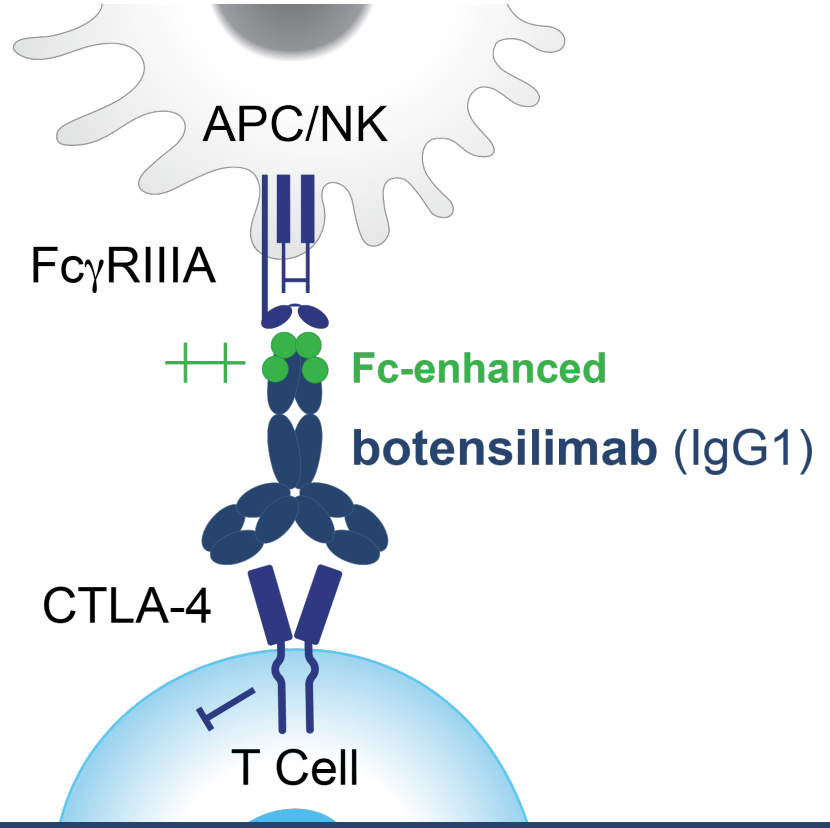
USC Norris Comprehensive Cancer Center
Keck Medicine of USC

Novel and Emerging Therapies in HCC

Novel Immunotherapy Agents

botensilimab

Fc-enhanced CTLA-4 Inhibitor



Active in cold and IO refractory tumors[1] :

Design:

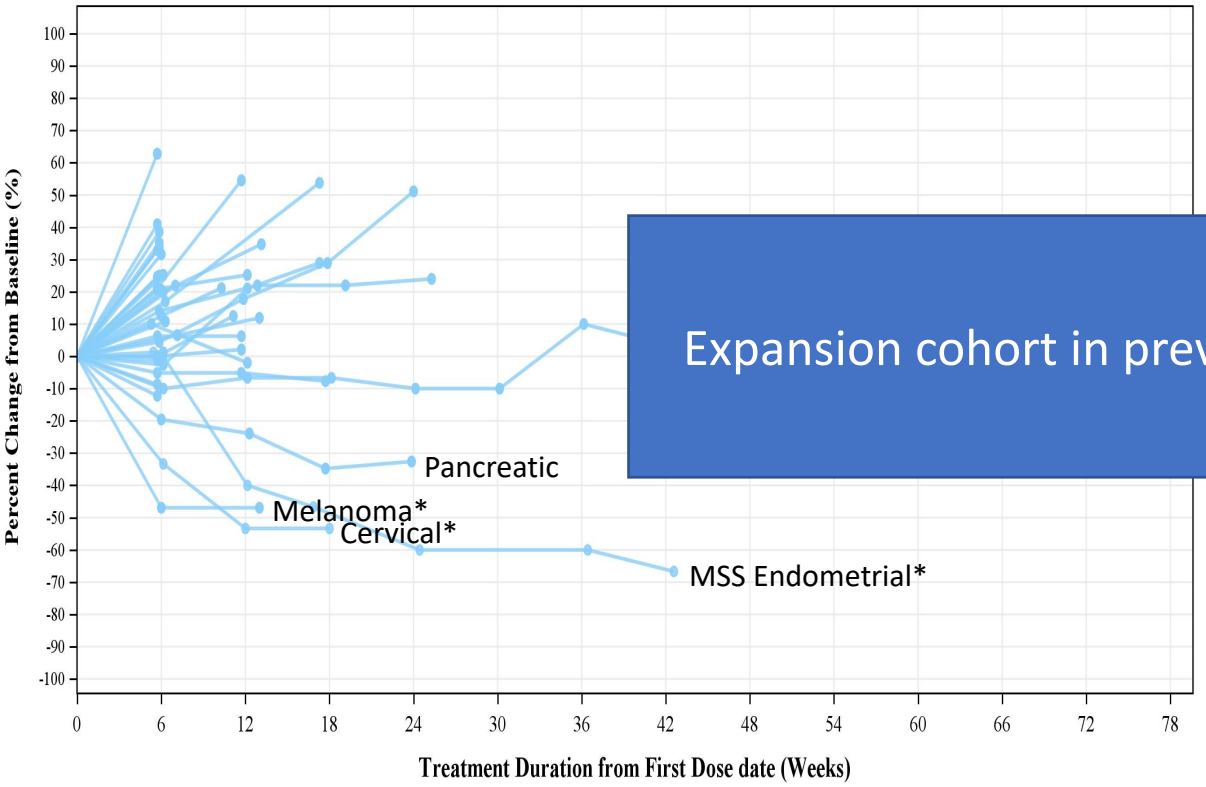
- Improved binding to activating FcγRs on APCs and NK cells
- Reduced complement binding

Function (relative to first-gen CTLA-4)[2,3]:

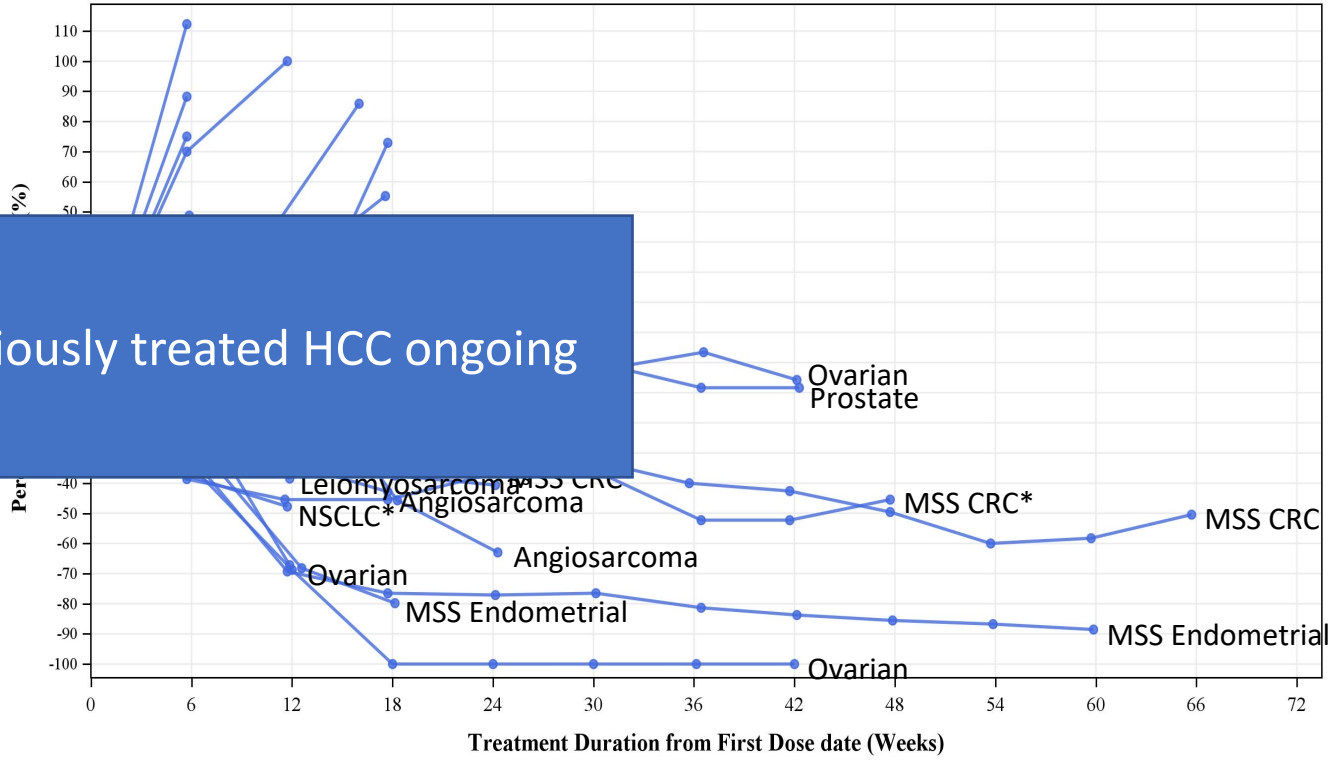
- ↑ Frequency of activated DCs
- ↑ T cell priming, expansion, memory
- ↑ Treg depletion
- ↓ Complement mediated toxicity

1. El-Khoueiry AB. SITC 2021 Annual Meeting. Poster #479. 2. Waight et al. *Cancer Cell*. 2018;33(6): 1033-1047. 3. Data on File. Agenus Inc. June 2022.

AGEN1181: broad and durable activity as monotherapy and in combination with anti PD-1 antibody



Expansion cohort in previously treated HCC ongoing



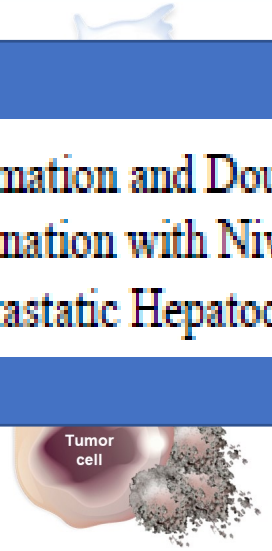
EL-Khoueiry A et al, SITC 2021

DUAL PD-1 and LAG-3 inhibition in Melanoma

RELATIVITY-047

Rationale for RELA + NIVO

- LAG-3 and PD-1 are distin
  checkpoints, often co-exp
  tumor-infiltrating lympho
  contribute to tumor-medi
  exhaustion[1,2]
- In preclinical models, LAG
  blockade demonstrated sy
  antitumor activity[1]
- RELA + NIVO demonstrate
  clinically meaningful anti
  including durable objectiv
  and was well tolerated in
  melanoma that was relapsed/refractory
  to anti-PD-1 therapy[3,4]



APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor.
1. Woo S-R, et al. *Cancer Res* 2012;72:917-927; 2. Anderson AC, et al. *Immunity* 2016;44:989-1004; 3. Ascierto PA, et al. Oral presentation at ASCO Annual Meeting; June 2-6, 2017; Chicago, IL. Abstract 9520; 4. Ascierto PA, et al. Oral presentation at ESMO Congress; September 8-12, 2017; Madrid, Spain. Abstract LBA18.

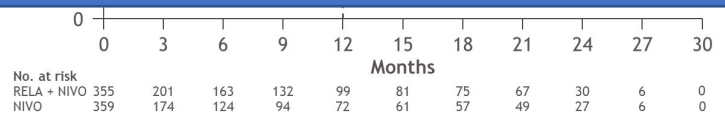
3

A Phase 1/2, Safety Confirmation and Double-blind, Placebo-controlled, Randomized Study of Relatlimab in Combination with Nivolumab and Bevacizumab in Treatment-naive Advanced/Metastatic Hepatocellular Carcinoma (RELATIVITY-106)

RELATIVITY-047

RELATIVITY 047 demonstrated superior PFS benefit by BICR for RELA + NIVO FDC vs NIVO

NIVO (n = 359)
4.63
(3.38-5.62)
.92)

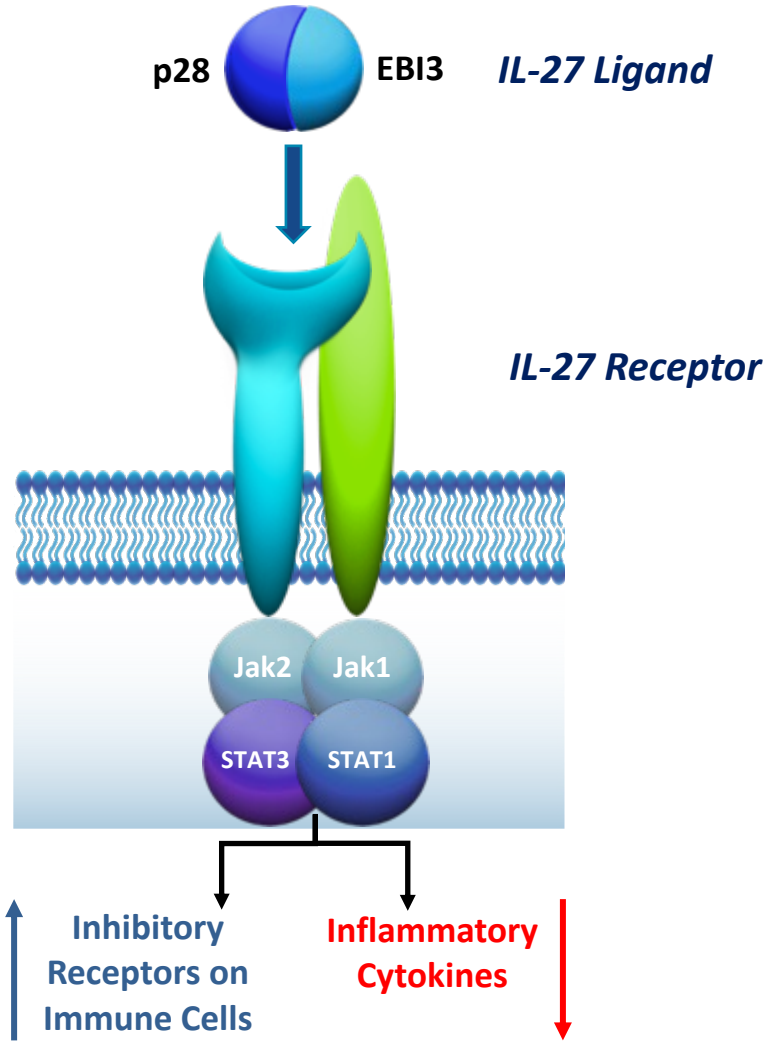


CI, confidence interval; HR, hazard ratio.
All randomized patients. Statistical model for HR and *P* value: stratified Cox proportional hazard model and stratified log-rank test. Stratified by LAG-3 (≥ 1% vs < 1%), *BRAF* (mutation positive vs mutation wild-type), AJCC M stage (M0/M1any[0] vs M1any[1]). PD-L1 was removed from stratification because it led to subgroups with < 10 patients.

12

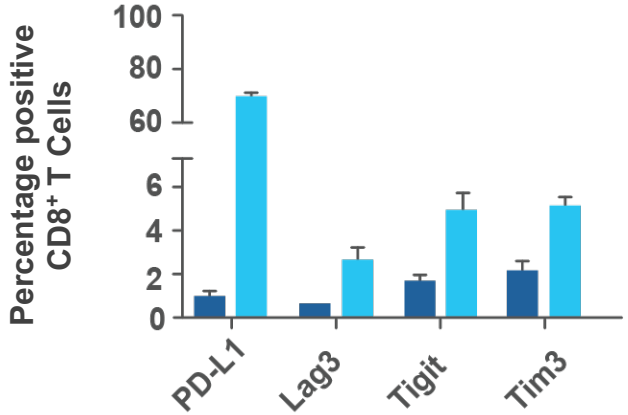
Lipson E et al, ASCO Annual Meeting 2021

IL-27 Upregulates Checkpoint Receptors, Downregulates Proinflammatory Cytokines

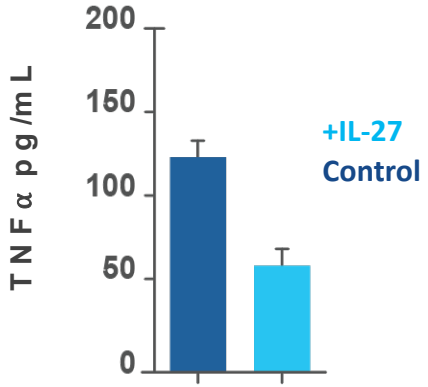


IL-27

Upregulates Checkpoint Receptors



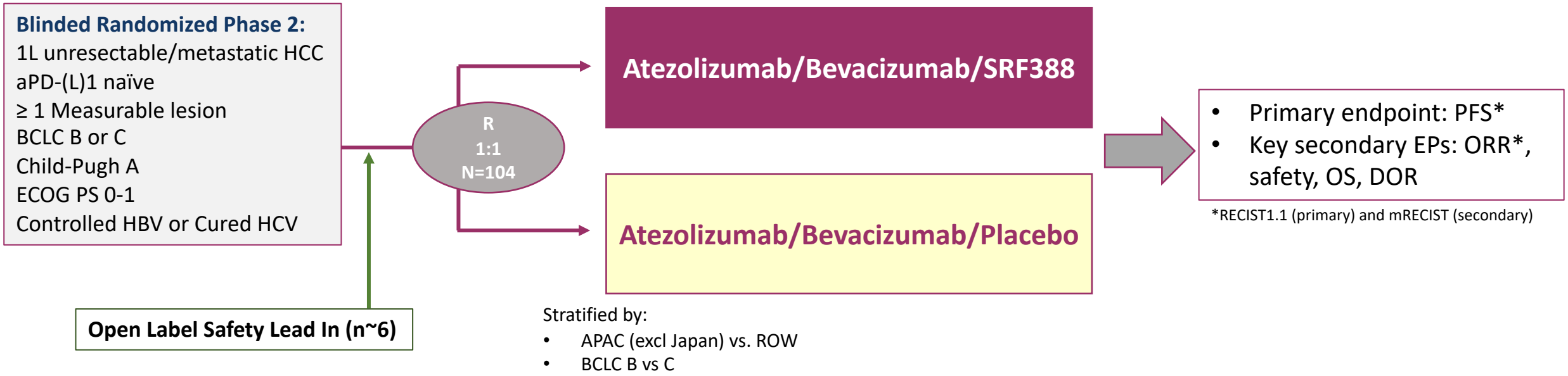
Downregulates Pro-Inflammatory Cytokines



Chihara et al, Nature 558, 2018
DeLong et al, Immunohorizons 3, 2019

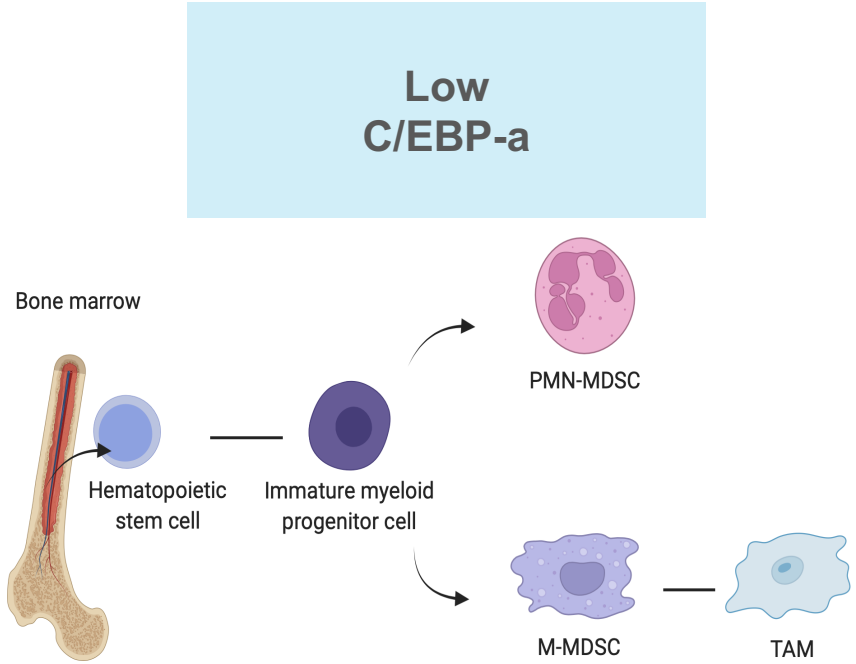
Robust Randomized Testing of IL-27 Blockade with Atezolizumab/Bevacizumab in IO naïve 1L HCC

SRF388-201



Targeting MDSCs and TAMs through CEBPA

- CCAAT/enhancer binding protein alpha (C/EBPa) is a transcription factor involved in differentiation of myeloid cells as well as in proliferation, metabolism, and immunity
- Deregulation of C/EBPa has been reported in several solid tumors, including liver, breast, and lung
- Upregulation of C/EBPa inhibits tumor growth in rodent liver cancer models

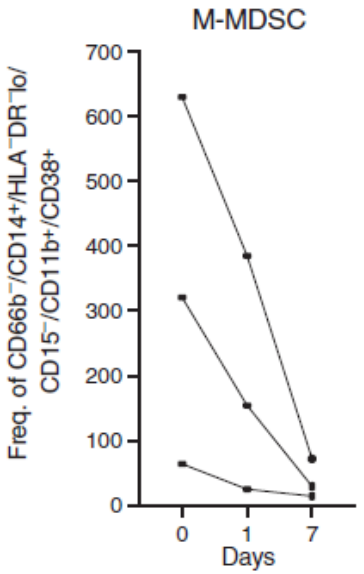


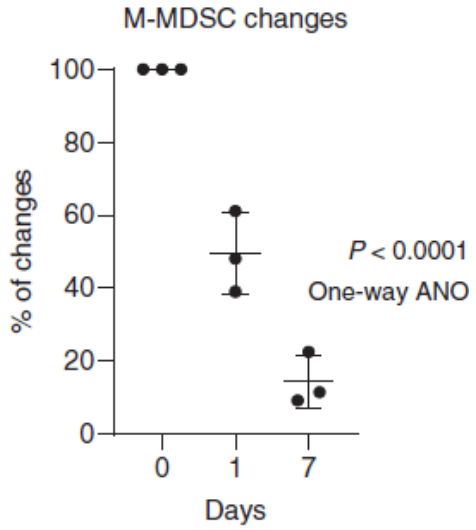
Infiltration of tumor microenvironment and promotion of immune suppression

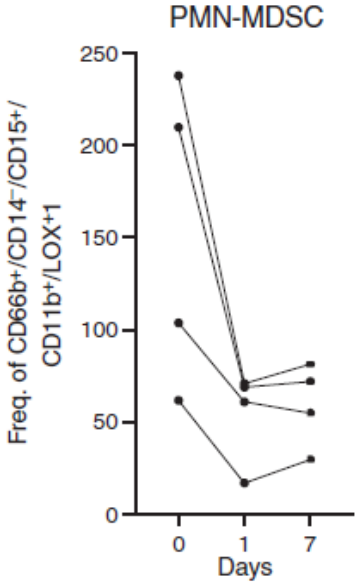
Image courtesy of Prof Nagy Habib
Mina Therapeutics

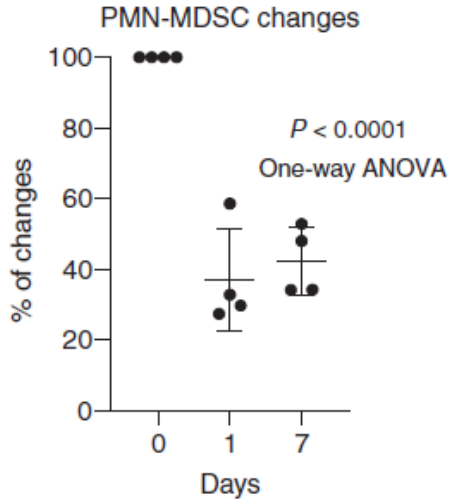
Avellino R et al. Blood 2017
Lourenco AR et al. Oncogene 2017
Yamanaka R et al, PNAS 1997
Hashimoto A, CCR Clin Cancer Res 2021

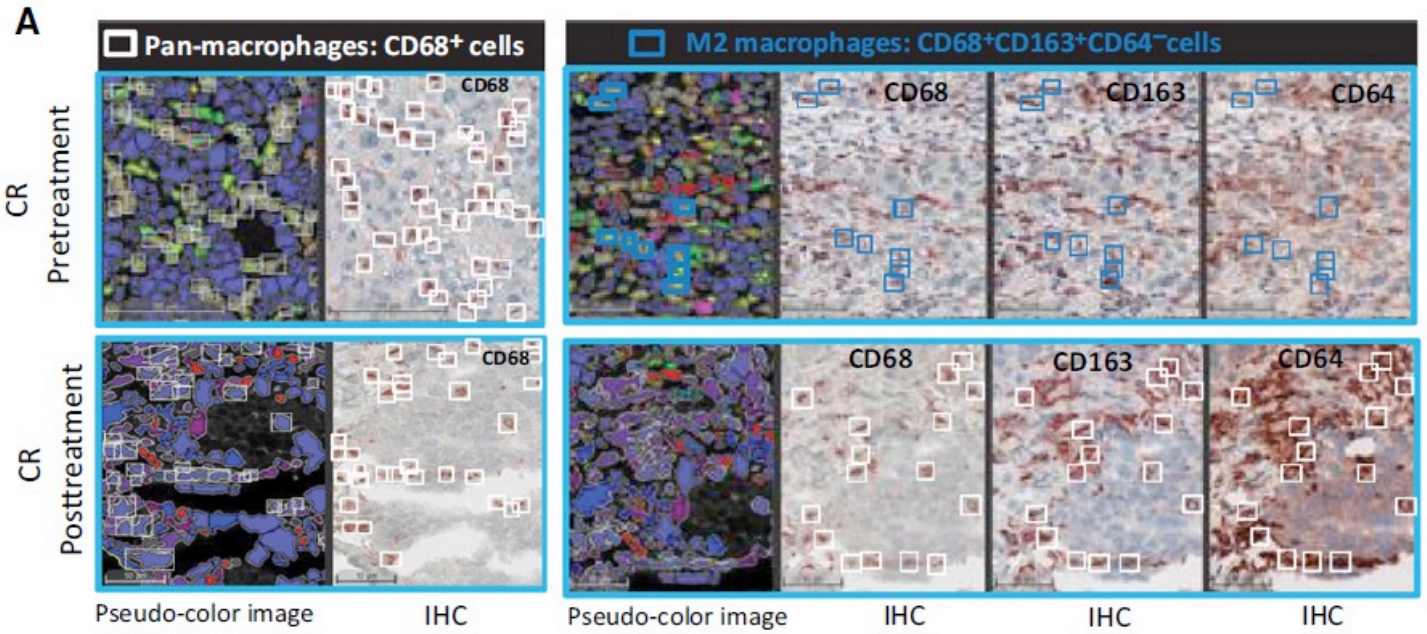
MTL-CEBPA effect on MDSCs and macrophages











Hashimoto A, CCR Clin Cancer Res 2021

OUTREACH-2: Multi-center, Open-label, Randomized Ph 2 Study of MTL-CEBPA and Sorafenib vs. Sorafenib in Advanced Pre-treated HCC

MiNA Therapeutics

Eligibility

- Progression or recurrence to atezolizumab or bevacizumab
- TKI-naïve
- BCLC B or C

2:1
n=150

MTL-CEBPA QW 130 mg/m^2 + Sorafenib BID 400 mg

Sorafenib BID 400 mg`

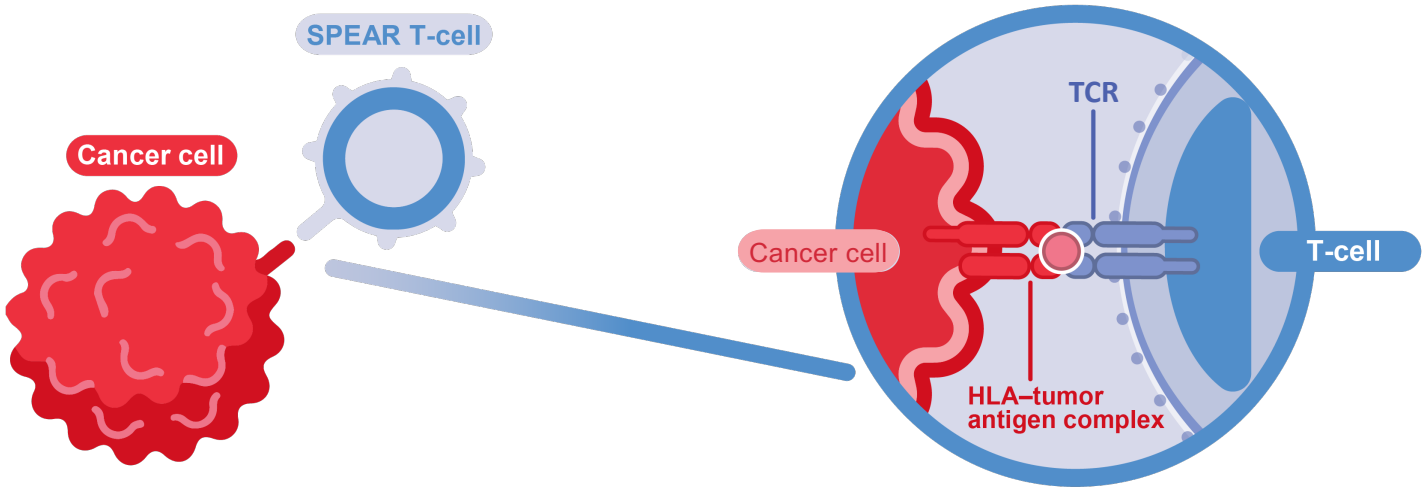
Primary endpoint:
PFS

Secondary endpoints:
ORR, DoR, TTP OS, QoL, PD

Control med PFS	Experimental median PFS	HR	N of events	Appr. number of patients	FPI	Recruitment / FU
4m	7m	0.57	112	150	Q4 2021	18 months / 21-23 months

- Drug Safety Monitoring Board; Independent radiology review (BICR)
- Global study: US, Europe and Asia (60 sites overall planned)

SPEAR T-cells

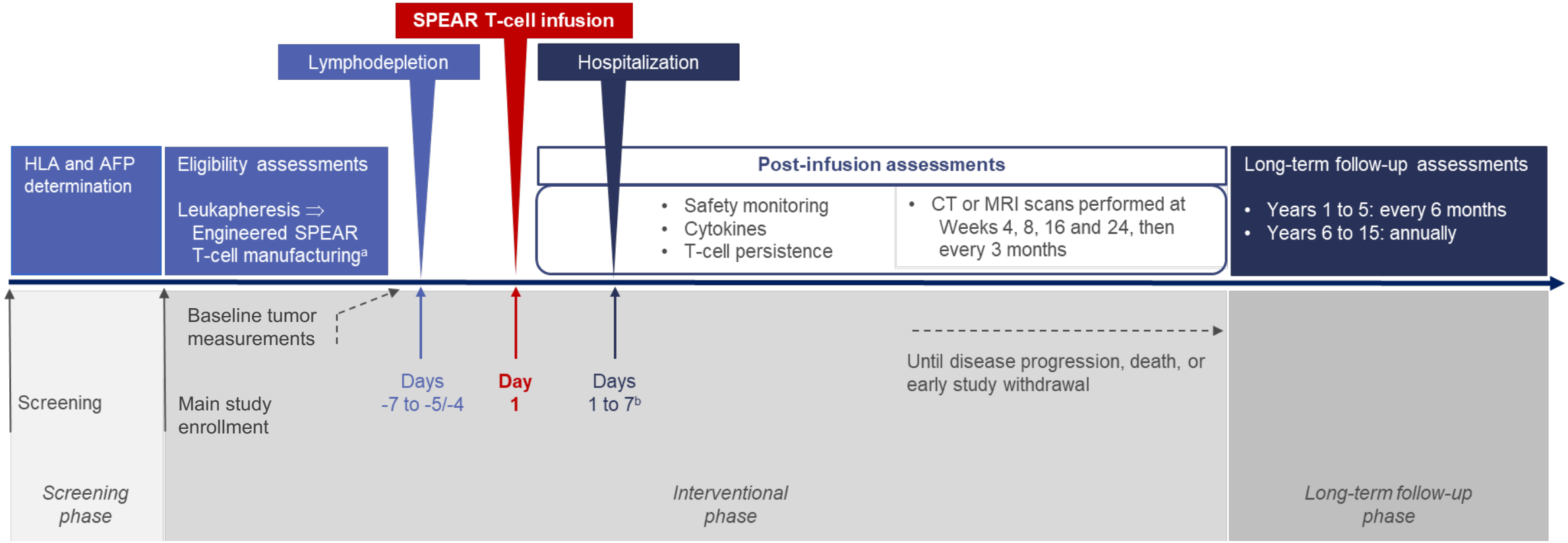


TCR-BASED RECOGNITION

- T-cells scan HLA-peptides with TCRs
- Access to broader spectrum of intra- and extracellular proteins
- TCR is T-cell's natural receptor construct
- Ability to target solid tumors

HLA, human leukocyte antigen; SPEAR, specific peptide enhanced affinity receptor; TCR, T-cell receptor

Phase 1, first-in-human trial (NCT03132792) of ADP-A2AFP SPEAR T-cells in patients with advanced hepatocellular carcinoma (HCC)[1]

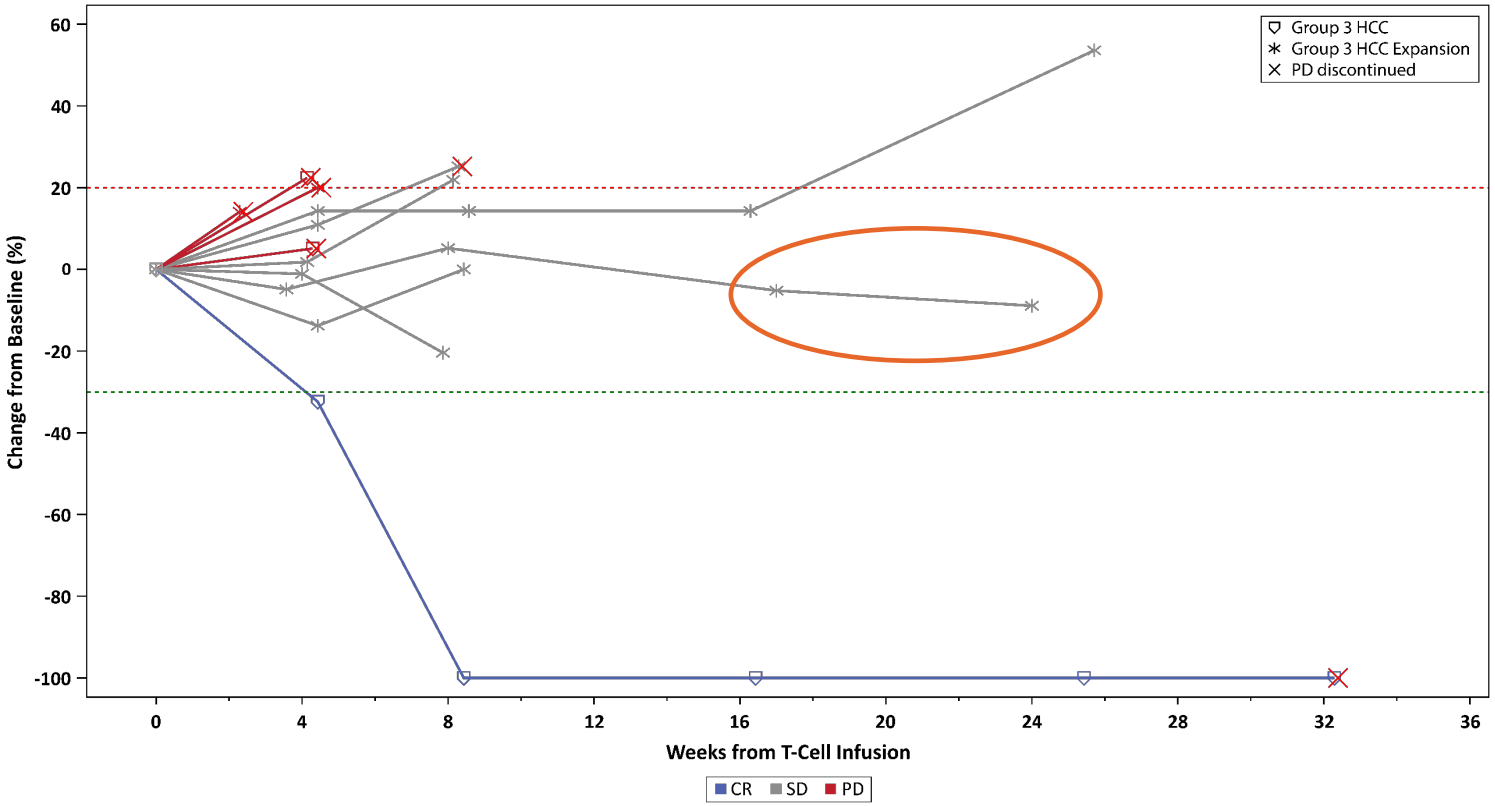


[a]T-cell selection; lentiviral gene transfer of affinity-enhanced TCR; T-cell expansion
[b]14 days in the United Kingdom

AFP, alpha fetoprotein; HCC, hepatocellular carcinoma; HLA, human leukocyte antigen; SPEAR, specific peptide enhanced affinity receptor; TCR, T-cell receptor

Sangro B et al, ILCA 2021

Best overall response: RECIST v1.1



Best overall response	Group 3 and expansion (N=13), n (%)
Complete response	1 (8)
Stable disease (total)	6 (46)
Stable disease (<16 weeks' duration)	4 (31)
Stable disease (≥16 weeks' duration)	2 (15)
Progressive disease	4 (31)
Not evaluated	2 (15)*

- Disease control rate: 7/11 (64%)*

*Two patients did not have first scans at the time of the data cut-off

CR, complete response; HCC, hepatocellular carcinoma; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

Data cut-off April 5, 2021

Sangro B et al, ILCA 2021

USC Norris Comprehensive Cancer Center
Keck Medicine of USC

Biliary Cancers

TOPAZ Study Design

Key eligibility
- Locally advanced or metastatic BTC (ICC, ECC, GBC)
- Previously untreated if unresectable or metastatic at initial diagnosis
- Recurrent disease >6 months after curative surgery or adjuvant therapy
- ECOG PS 0 or 1

Stratification factors
- Disease status
  - (initially unresectable versus recurrent)
- Primary tumor location
  - (ICC versus ECC versus GBC)

R (1:1) (N=685)

Durvalumab 1500 mg Q3W + GemCis (up to 8 cycles) → **Durvalumab 1500 mg Q4W until PD**

Placebo Q3W + GemCis (up to 8 cycles) → **Placebo Q4W until PD**

Primary objective
- Overall survival

Secondary objectives
- Progression-free survival
- Objective response rate
- Duration of response
- Efficacy by PD-L1 status
- Safety

GemCis treatment: gemcitabine 1000 mg/m2 and cisplatin 25 mg/m2 on Days 1 and 8 Q3W administered for up to 8 cycles.

BTC, biliary tract cancer; ECC, extrahepatic cholangiocarcinoma; ECOG, Eastern Cooperative Oncology Group; GBC, gallbladder cancer; GemCis, gemcitabine and cisplatin; ICC; intrahepatic cholangiocarcinoma; PD, progressive disease; PD-L1, programmed cell death ligand-1; PS, performance status; QnW, every n weeks; R, randomization.

Oh DY et al, NEJM 2022

TOPAZ Demographics

	Durvalumab + GemCis (n=341)	Placebo + GemCis (n=344)
Median age (range), years	64 (20–84)	64 (31–85)
Sex, female, n (%)	172 (50.4)	168 (48.8)
Race, n (%)		
Asian	185 (54.3)	201 (58.4)
White	131 (38.4)	124 (36.0)
Black or African American	8 (2.3)	6 (1.7)
American Indian or Alaska Native	0	1 (0.3)
Other	17 (5.0)	12 (3.5)
Region, n (%)		
Asia	178 (52.2)	196 (57.0)
Rest of the world	163 (47.8)	148 (43.0)
ECOG PS 0 at screening, n (%)	173 (50.7)	163 (47.4)
Primary tumor location at diagnosis, n (%)		
Intrahepatic cholangiocarcinoma	190 (55.7)	193 (56.1)
Extrahepatic cholangiocarcinoma	66 (19.4)	65 (18.9)
Gallbladder cancer	85 (24.9)	86 (25.0)
Disease status at randomization, n (%)		
Initially unresectable	274 (80.4)	279 (81.1)
Recurrent	67 (19.6)	64 (18.6)
Disease classification at diagnosis,* n (%)		
Metastatic	303 (88.9)	286 (83.1)
Locally advanced	38 (11.1)	57 (16.6)
PD-L1 expression,* n (%)		
TAP ≥1%	197 (57.8)	205 (59.6)
TAP <1%	103 (30.2)	103 (29.9)

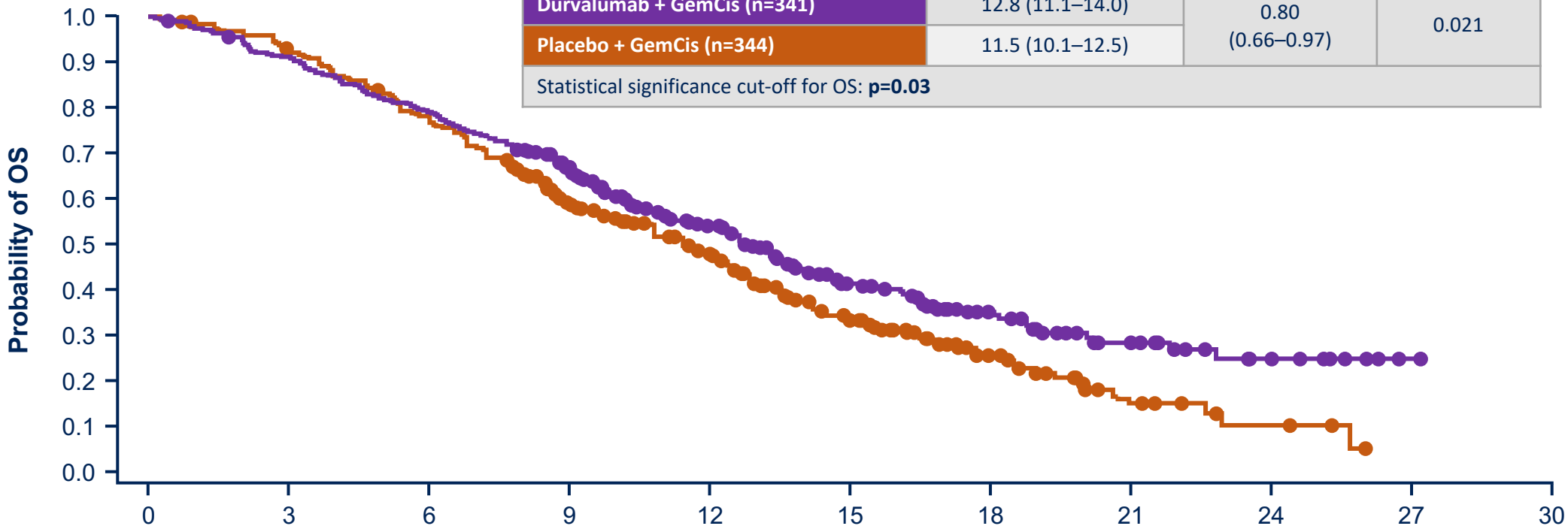
*Data missing for remaining patients. Unless otherwise indicated, measurements were taken at baseline.

ECOG, Eastern Cooperative Oncology Group; GemCis, gemcitabine and cisplatin; PD-L1, programmed cell death ligand-1; PS, performance status; TAP, tumor area positivity.

Oh DY et al, NEJM 2022

TOPAZ Primary endpoint: OS

	Median OS (95% CI), months	Hazard ratio (95% CI)	p-value
Durvalumab + GemCis (n=341)	12.8 (11.1–14.0)	0.80 (0.66–0.97)	0.021
Placebo + GemCis (n=344)	11.5 (10.1–12.5)		
Statistical significance cut-off for OS: **p=0.03**			



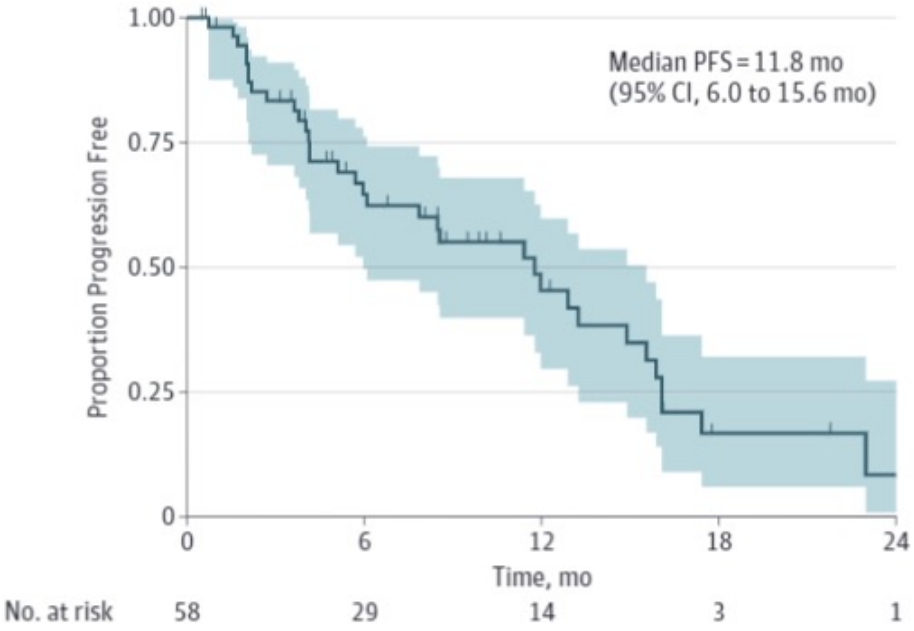
Number of subjects at risk										
Durvalumab + GemCis	341	309	268	208	135	79	49	24	9	1
Placebo + GemCis	344	317	261	183	125	65	29	10	4	0

Median duration of follow-up (95% CI) was 16.8 (14.8–17.7) months with durvalumab + GemCis and 15.9 (14.9–16.9) months with placebo + GemCis.
CI, confidence interval; GemCis, gemcitabine and cisplatin; HR, hazard ratio; mo, month; OS, overall survival.

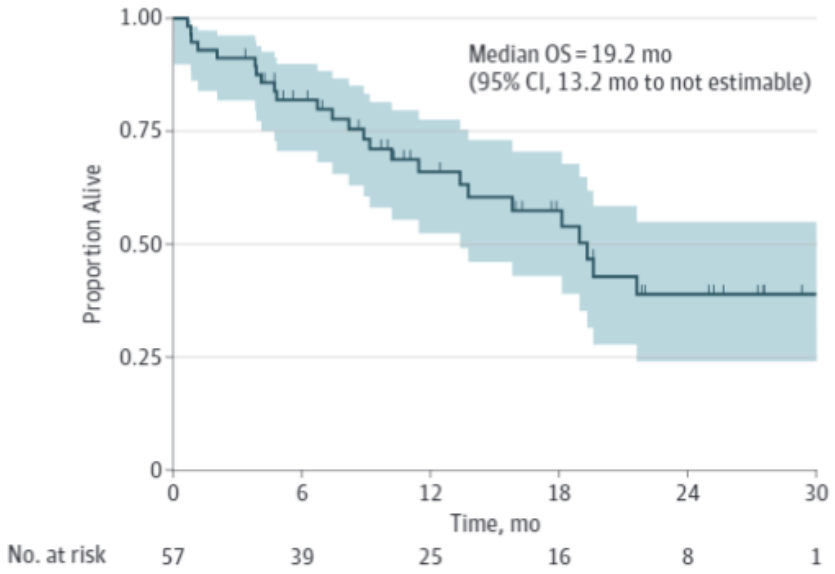
Oh DY et al, NEJM 2022

Gemcitabine, Cisplatin, and Nab-Paclitaxel for Advanced BTC (Phase 2 Clinical Trial)

Survival Among All Patients in the Intention-to-Treat Population for Whom Data Were Available



Median PFS



Median OS

- **Patients received gemcitabine (1000 mg/m²), cisplatin (25 mg/m²), and nab-paclitaxel (125 mg/m²), on days 1 and 8 of 21-day cycles (n = 60)**
- **Due to hematologic AEs among the first 32 patients enrolled, starting doses were reduced to 800, 25, and 100 mg/m², respectively, for the remaining 28 patients**

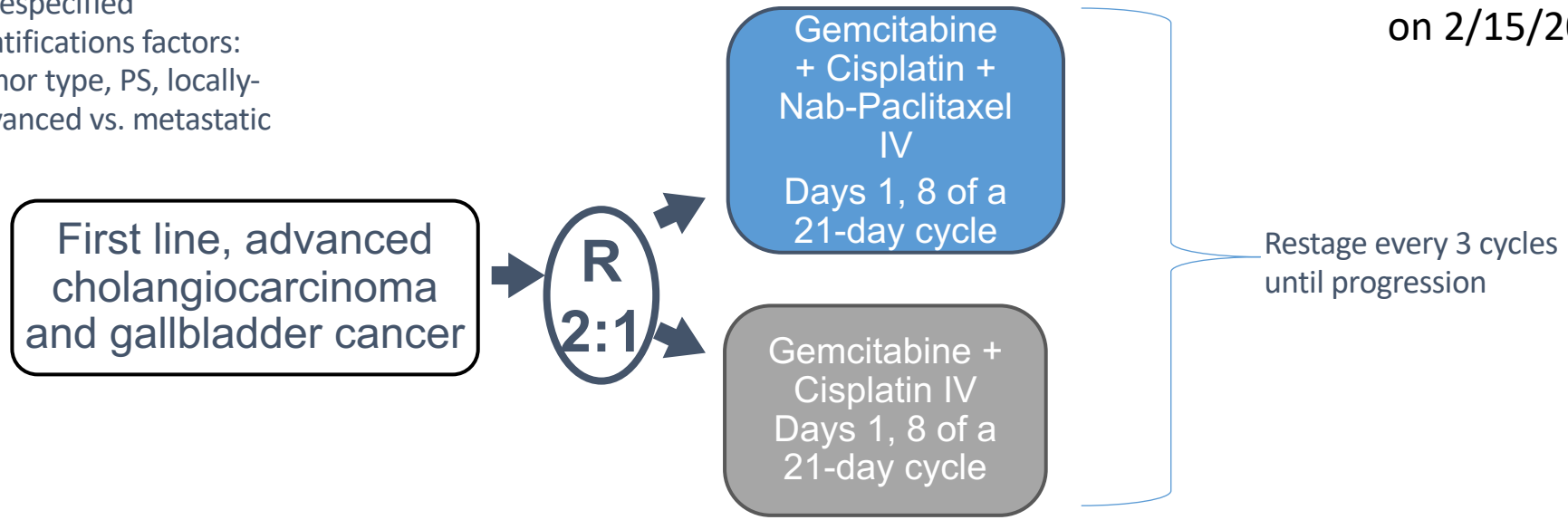
Shroff RS, et al. JAMA Oncol. 2019;5:824-830.

S1815: Study Design

N = 268 → NOW 441

CLOSED TO ACCRUAL on 2/15/2021!!

*Prespecified stratifications factors: tumor type, PS, locally-advanced vs. metastatic

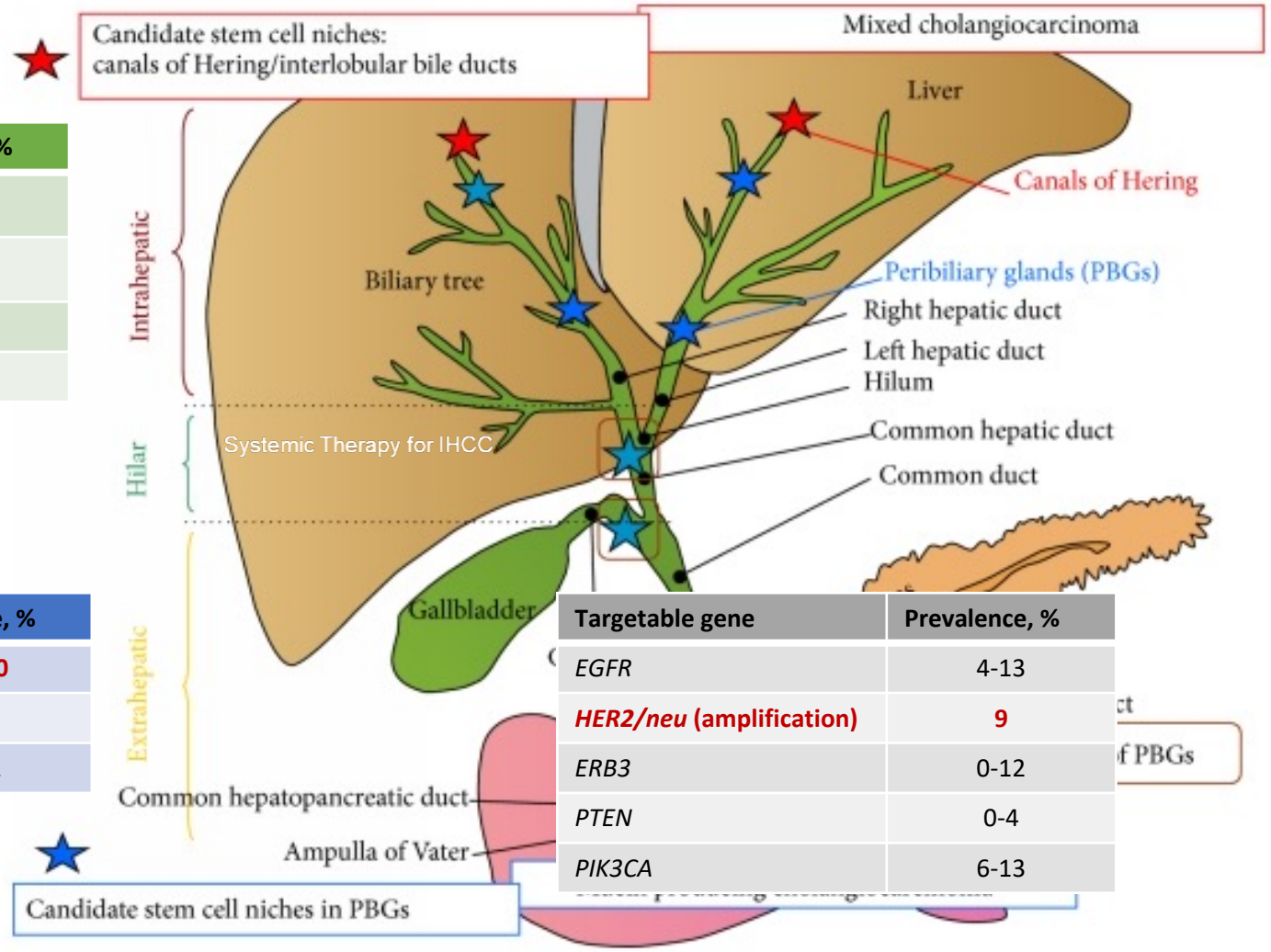


Primary EP: OS; Target HR 0.7
Secondary: ORR, PFS, DCR, safety, CA 19-9 changes

Archival blood and tissue specimens to be banked

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**

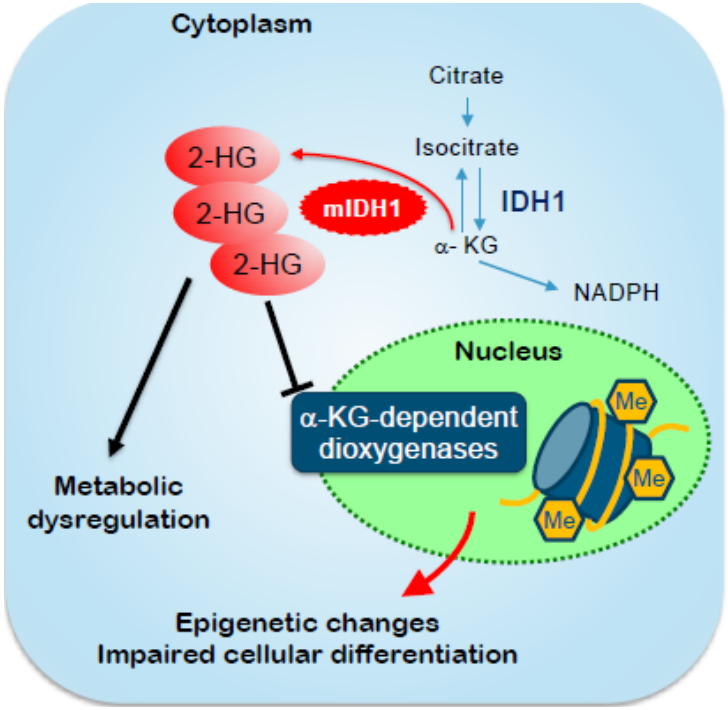


Targetable gene	Prevalence, %
***Her2/neu* (mutation)**	**11-20**
PRKACA and *PRKACB*	9
ARID1A	5-12

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

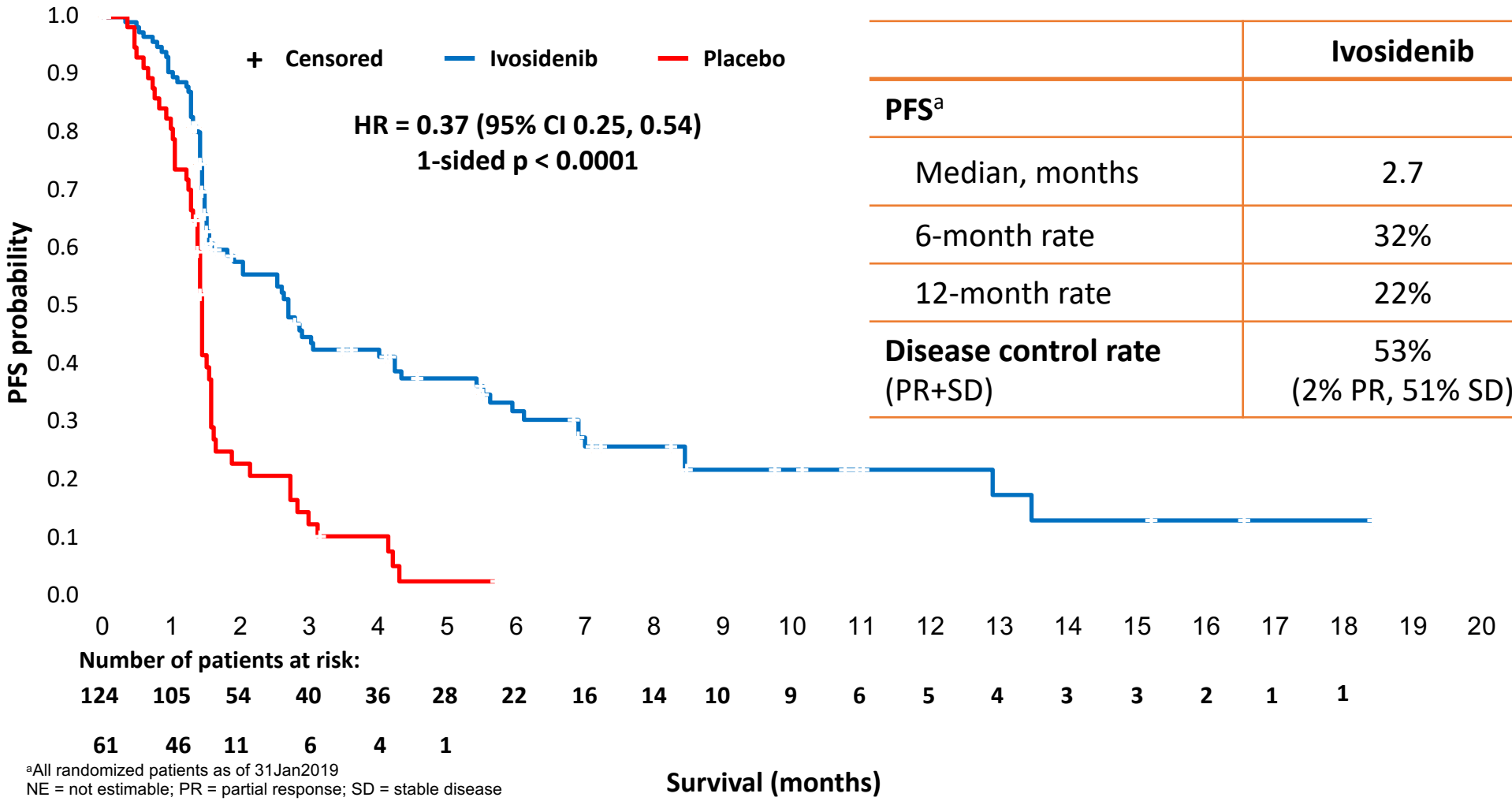
Ivosidenib 500 mg QD orally in continuous 28-day (±2 days) cycles (n=124)

Placebo (n=61)

Crossover permitted at radiographic disease progression

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

Primary endpoint of PFS by IRC was met

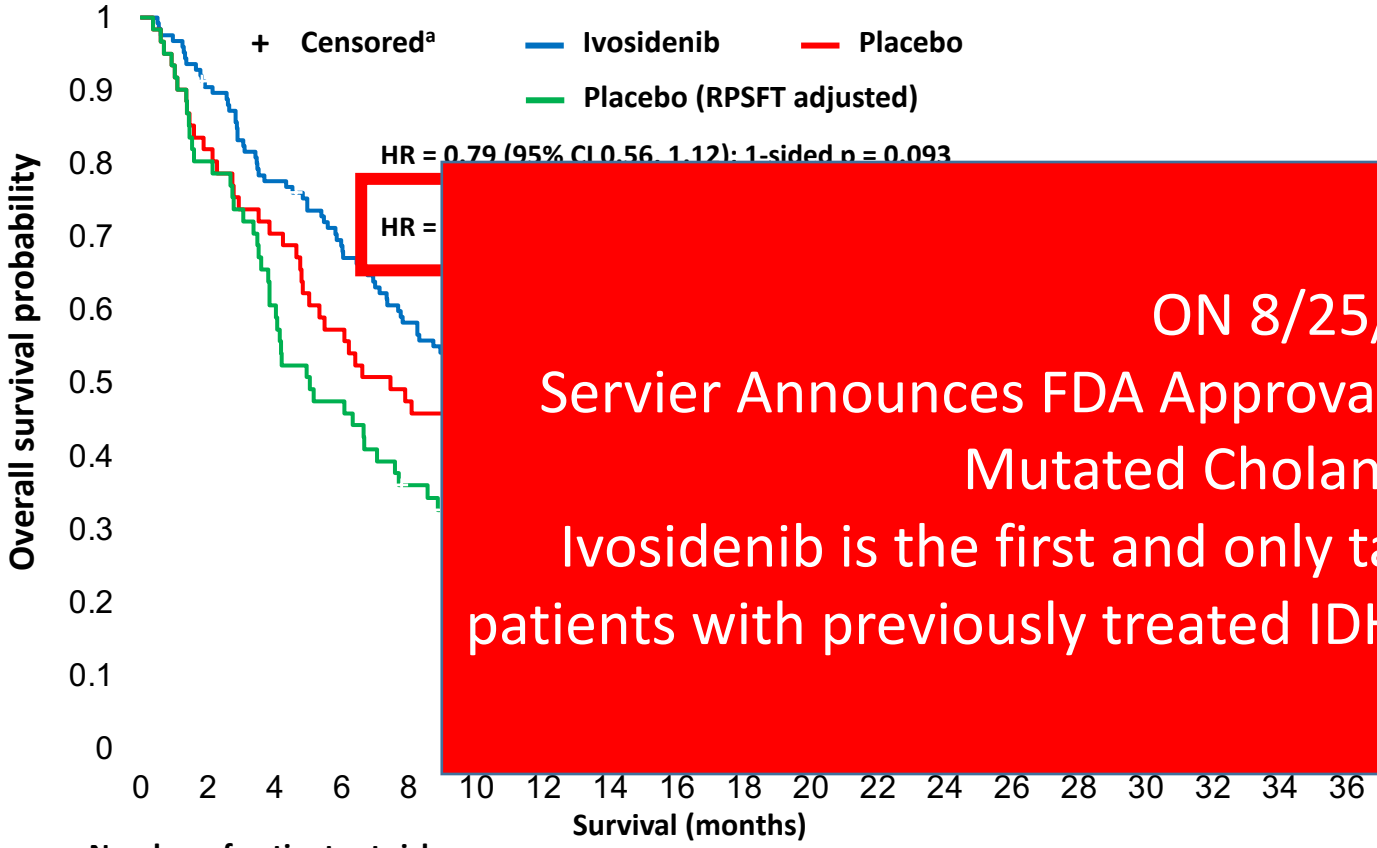


	Ivosidenib	Placebo
PFS[a]		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

[a]All randomized patients as of 31Jan2019
NE = not estimable; PR = partial response; SD = stable disease
Abou-Alfa GK et al. Lancet Oncol. 2020;21:796-807.

Zhu A, et al. GI ASCO 2021

Overall survival (final analysis)



	Ivosidenib n = 126	Placebo n = 61
		50 (82.0%)
		7.5
		57%
		36%

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- The median OS for placebo after adjustment for crossover was **5.1 months**

ON 8/25/2021:
Servier Announces FDA Approval of ivosidenib tablets in IDH1-Mutated Cholangiocarcinoma
Ivosidenib is the first and only targeted therapy approved for patients with previously treated IDH1-mutated cholangiocarcinoma.

[a]Patients without documentation of death at the data cutoff date were censored at the date the patient was last known to be alive or the data cutoff date, whichever was earlier
[b]All randomized patients as of 31May2020

1. Watkins C et al. *Pharm Stat*. 2013;12:348-57. **2.** Robins JM, Tsiatis AA. *Commun Stat Theory Methods*.1991;20:2609-31.

Zhu A, et al. GI ASCO 2021

FGFR Inhibitors in *FGFR2* Fusion/Rearrangements in CCA

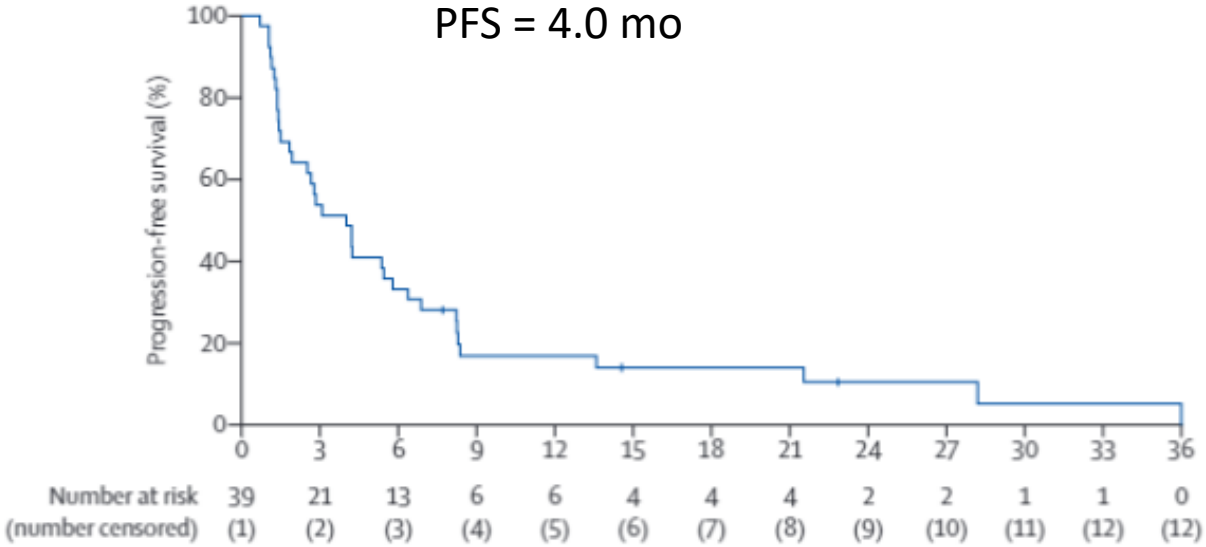
	Infigratinib[a]	Pemigatinib*,[b]	Derazantinib[c]	Futibatinib[d]	Erdafitinib[e]
N	108	127	29	67	7
Patient demographics	**Prior lines of treatment** 1: 46% 2: 30% 3+: 24%	**Prior lines of treatment** 1: 61% 2: 27% 3+: 12%	**Prior lines of treatment** 1: 52% 2: 35% 3+: 13%	**Prior lines of treatment** 1: 45% 2: 28% 3+: 27%	**Prior lines of treatment** 1: 36% 2: 36% 3+: 27%
ORR (confirmed), %	30.6	35.5	20.7	37.0	57.1
mPFS, mo	7.3	6.9	5.7	7.2	5.6 (includes 4 nonfusion patients)
mOS, mo	12.2	21.1	NR	NR	NR

FGFR, fibroblast growth factor receptor; NR, not reached; mPFS, median progression free survival; mOS, median overall survivial.
Data presented for FGFR2 fusion patients only, unless otherwise noted.
*Pemigatinib received accelerated FDA approval (along with companion diagnostic) in April 2020.
a. Javle M, et al. J Clin Oncol. 2021;39(3_suppl):265; b. Abou-Alfa GK, et al. Lancet Oncol. 2020;21(5):671-684; c. Saleh M, et al. Cancer Res. 2017;77(13 suppl):CT111; d. Mazzaferro V, et al. Br J Cancer. 2019;120:165-171; e. Goyal L, et al. J Clin Oncol. 2020;38(15_suppl):108.

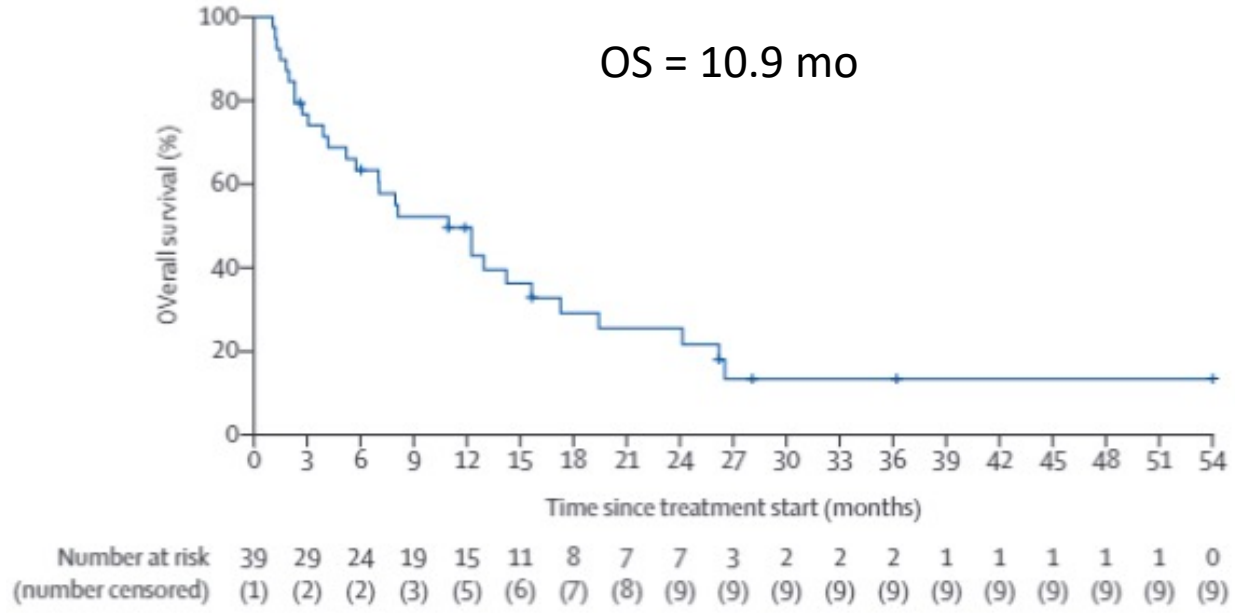
Pertuzumab and Trastuzumab for HER2-Positive, Metastatic BTC *(MyPathway)*

- **Multicenter, Open-Label, Phase 2a, Multiple Basket Study (n = 39)**

PFS = 4.0 mo



OS = 10.9 mo

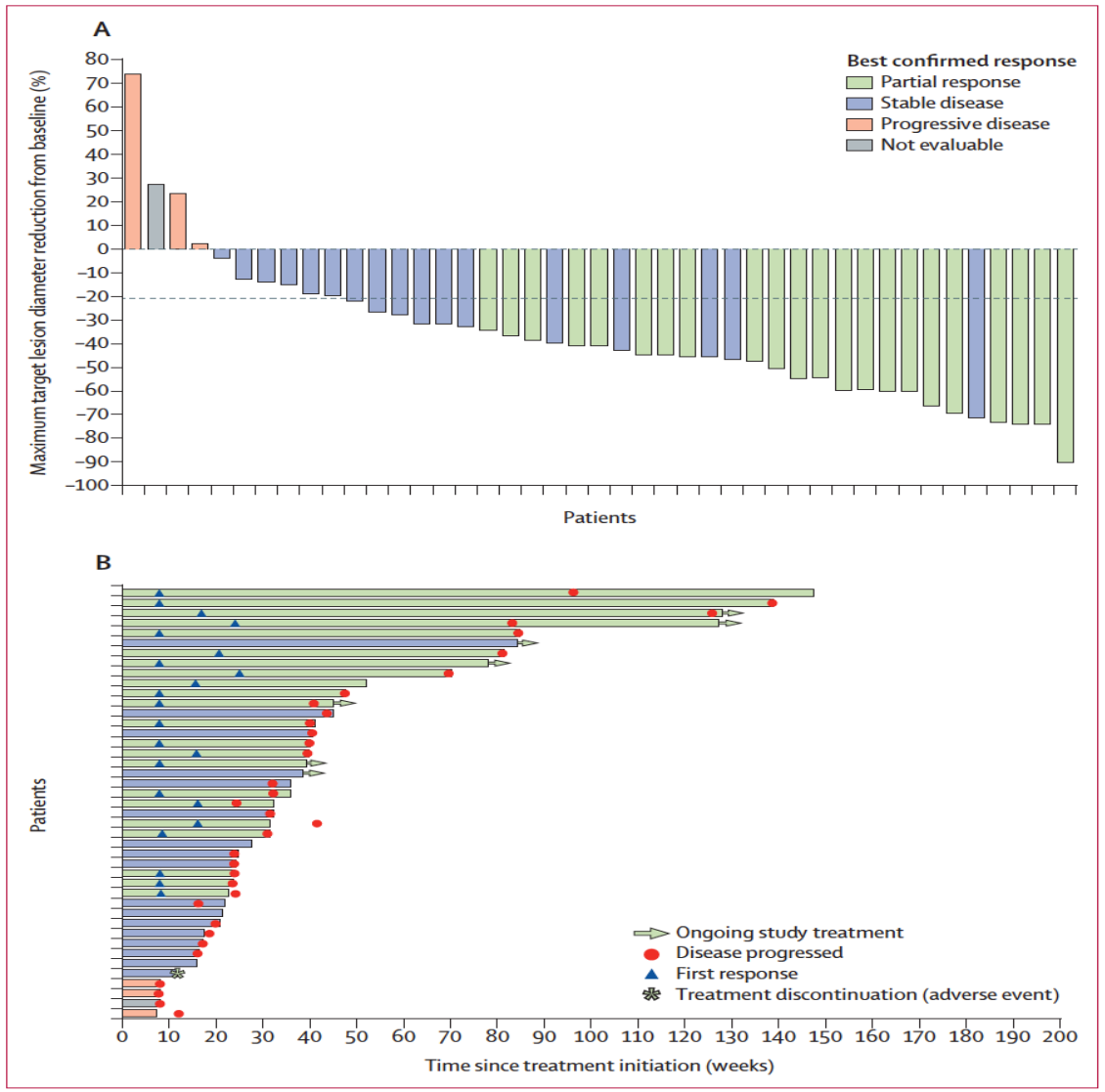


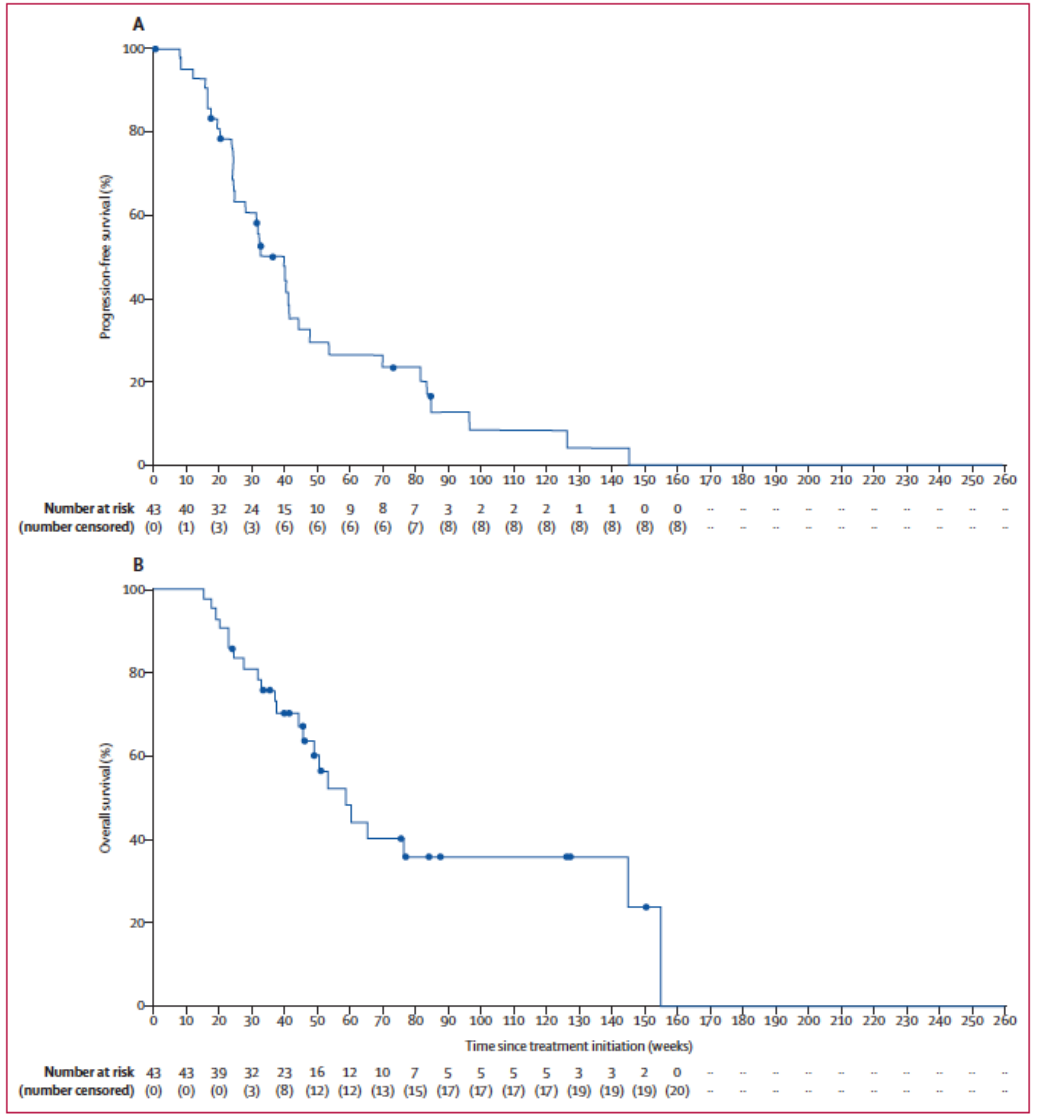
- ORR in this population was achieved in 9 of 39 (23%; 95% CI: 11, 39)
- Disease control rate was achieved in 20 patients (51%; 95% CI: 35, 68)
- Although median PFS was modest, 6 patients had prolonged PFS > 1 year
- Grade 3–4 trAEs were reported in 46% of patients, most commonly increased alanine aminotransferase and increased aspartate aminotransferase (each 13%)

- Javle M, et al. Lancet Oncol. 2021;22:1290-1300.

Subbiah et al. Lancet Oncol 2020

ROAR: Dabrafenib/Trametinib for BRAF V600E





Biliary Cancers Summary and Conclusions

- First line therapy evolving
  - TOPAZ: gemcitabine, cisplatin and durvalumab
  - Triplet chemotherapy? Awaiting results of SWOG 1815

- Heterogeneous disease with molecular subsets and actionable mutations
  - Biliary cancers should be offered tumor profiling early
  - Targeted therapies moving into first line (ongoing trials with FGFR2 agents and IDH1 in first line)
  - Therapies to target FGFR2, IDH1, Her2 and RAF are now available!