New Developments in Cancer Research
Hepatocellular and biliary cancers

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A new reality for patients with advanced HCC

First line	Second line	Third line
Sorafenib	Regorefanib	
Lenvatinib	Nivolumab	Nivolumab
	Cabozantinib	Cabozantinib
Ongoing phase 3 of Nivolumab versus Sorafenib	Ramucirumab	
	Pembrolizumab	

Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

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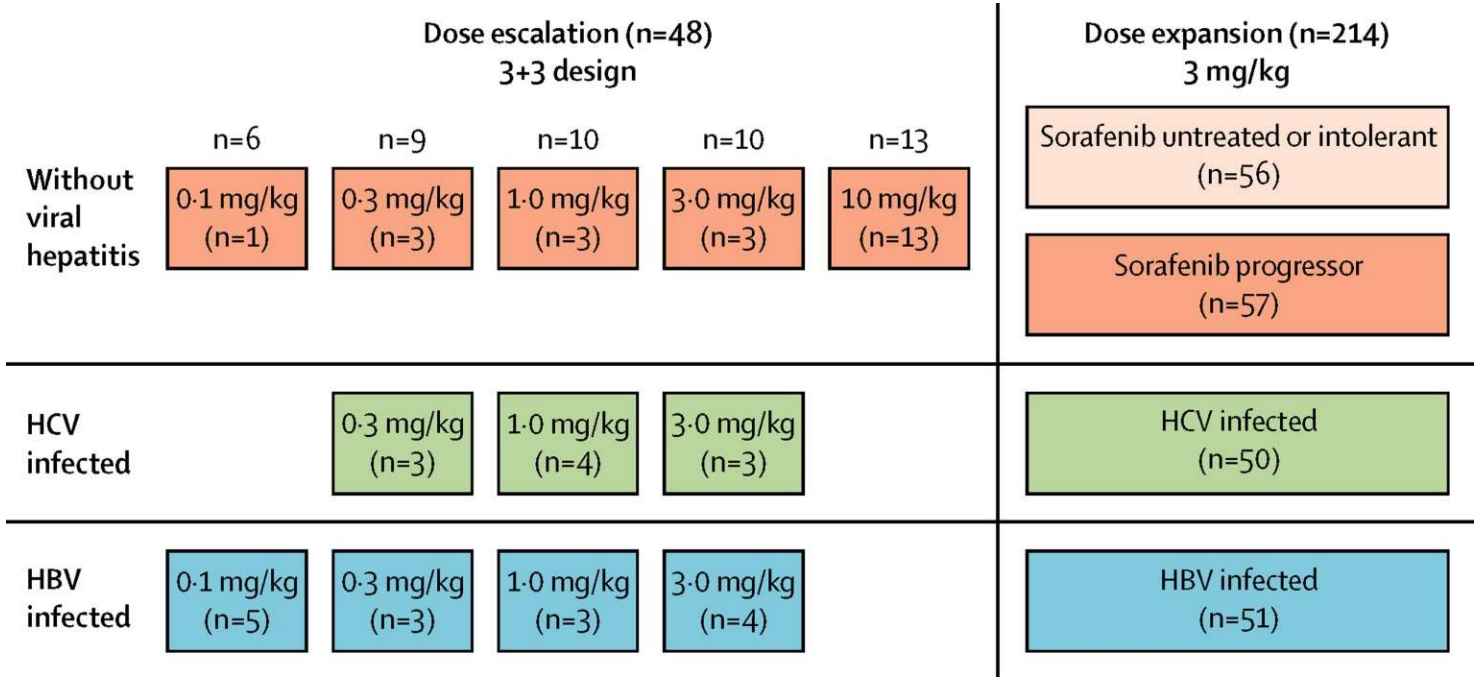


El-Khoueiry A et al, Lancet, online April 2017

Checkmate 040: Nivolumab efficacy

	Uninfected untreated/ intolerant (n=56)	Uninfected progressor (n=57)	HCV infected (n=50)	HBV infected (n=51)	All patients (n=214)
Objective response*	13 (23%; 13 to 36)	12 (21%; 11 to 34)	10 (20%; 10 to 34)	7 (14%; 6 to 26)	42 (20%; 15 to 26)
Complete response	0	2 (4%)	0	1 (2%)	3 (1%)
Partial response	13 (23%)	10 (18%)	10 (20%)	6 (12%)	39 (18%)
Stable disease	29 (52%)	23 (40%)	23 (46%)	21 (41%)	96 (45%)
Progressive disease	13 (23%)	18 (32%)	14 (28%)	23 (45%)	68 (32%)
Not evaluable	1 (2%)	4 (7%)	3 (6%)	0	8 (4%)
Duration of response*					
KM median	8·4 (8·3 to NE)	NR	9·9 (4·5 to 9·9)	NR	9·9 (8·3 to NE)
Ongoing, n/N (%)	8/13 (62%)	7/12 (58%)	8/10 (80%)	5/7 (71%)	28/42 (67%)
Disease control*	42 (75%; 62 to 86)	35 (61%; 48 to 74)	33 (66%; 51 to 79)	28 (55%; 40 to 69)	138 (64%; 58 to 71)
Disease control with stable disease for ≥6 months	22 (39%; 27 to 53)	22 (39%; 26 to 52)	17 (34; 21 to 49)	18 (35%; 22 to 50)	79 (37%; 30 to 44)
Overall survival					
6 months	89% (77 to 95)	75% (62 to 85)	85% (72 to 93)	84% (71 to 92)	83% (78 to 88)
9 months	82% (68 to 90)	63% (49 to 74)	81% (66 to 90)	70% (55 to 81)	74% (67 to 79)
KM median	NR	13·2 (8·6 to NE)	NR	NR	NR
Progression-free survival*					
KM median	5·4 (3·9 to 8·5)	4·0 (2·6 to 6·7)	4·0 (2·6 to 5·7)	4·0 (1·3 to 4·1)	4·0 (2·9 to 5·4)

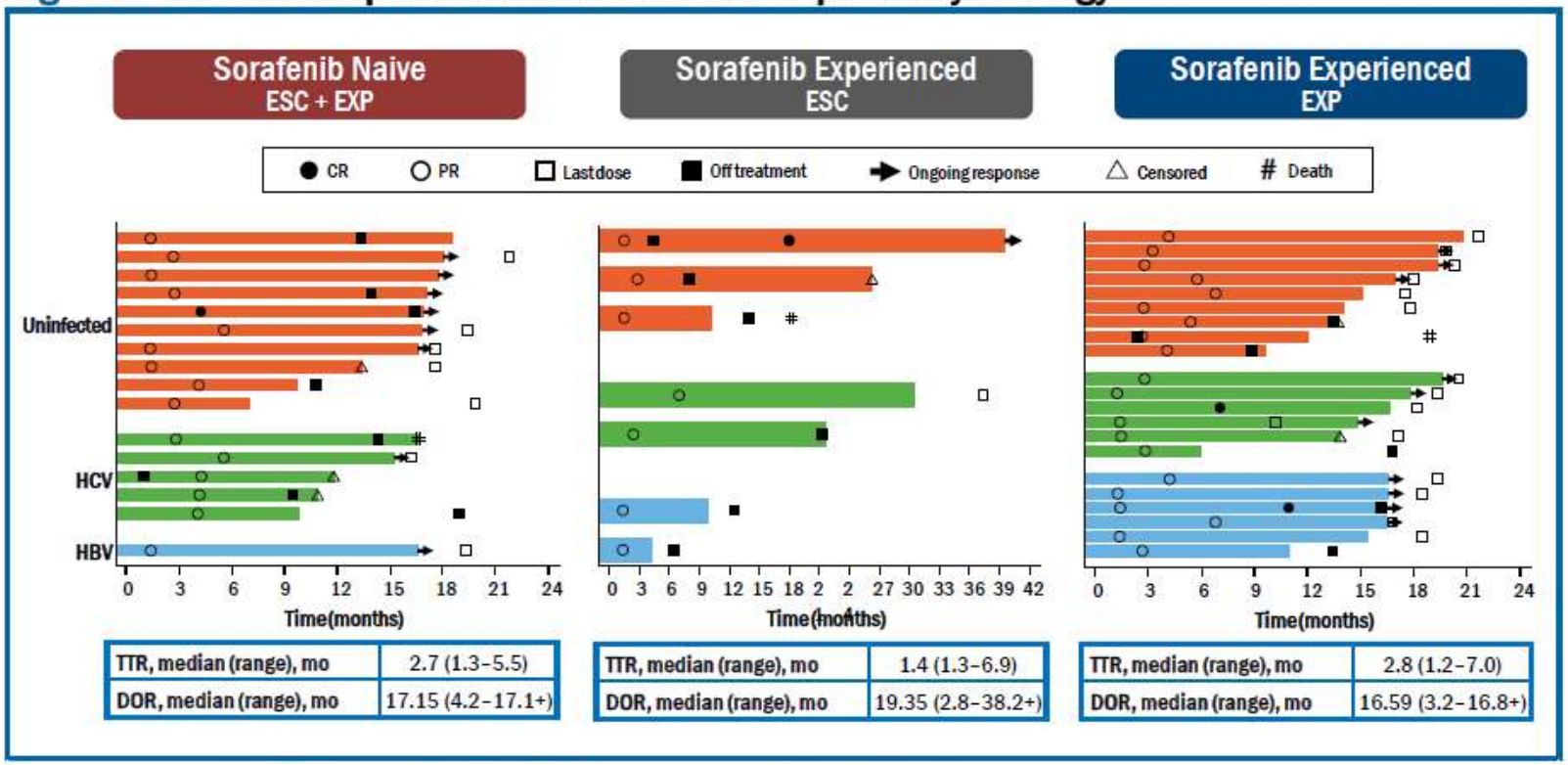
Unless otherwise indicated, data are n (%; 95% CI); n (%); months (95% CI); or % (95% CI). HCV=hepatitis C virus. HBV=hepatitis B virus. KM=Kaplan-Meier estimate. NR=not reached. NE=not estimable. RECIST=Response Evaluation Criteria In Solid Tumors. *Determined by investigator assessment using RECIST version 1.1.

***Table 4*: Nivolumab efficacy in the dose-expansion phase**

El-Khoueiry A et al, Lancet, online April 2017

Time to response and duration of response

Figure 2. Time to Response and Duration of Response by Etiology



TTR, median (range), mo	2.7 (1.3–5.5)
DOR, median (range), mo	17.15 (4.2–17.1+)

TTR, median (range), mo	1.4 (1.3–6.9)
DOR, median (range), mo	19.35 (2.8–38.2+)

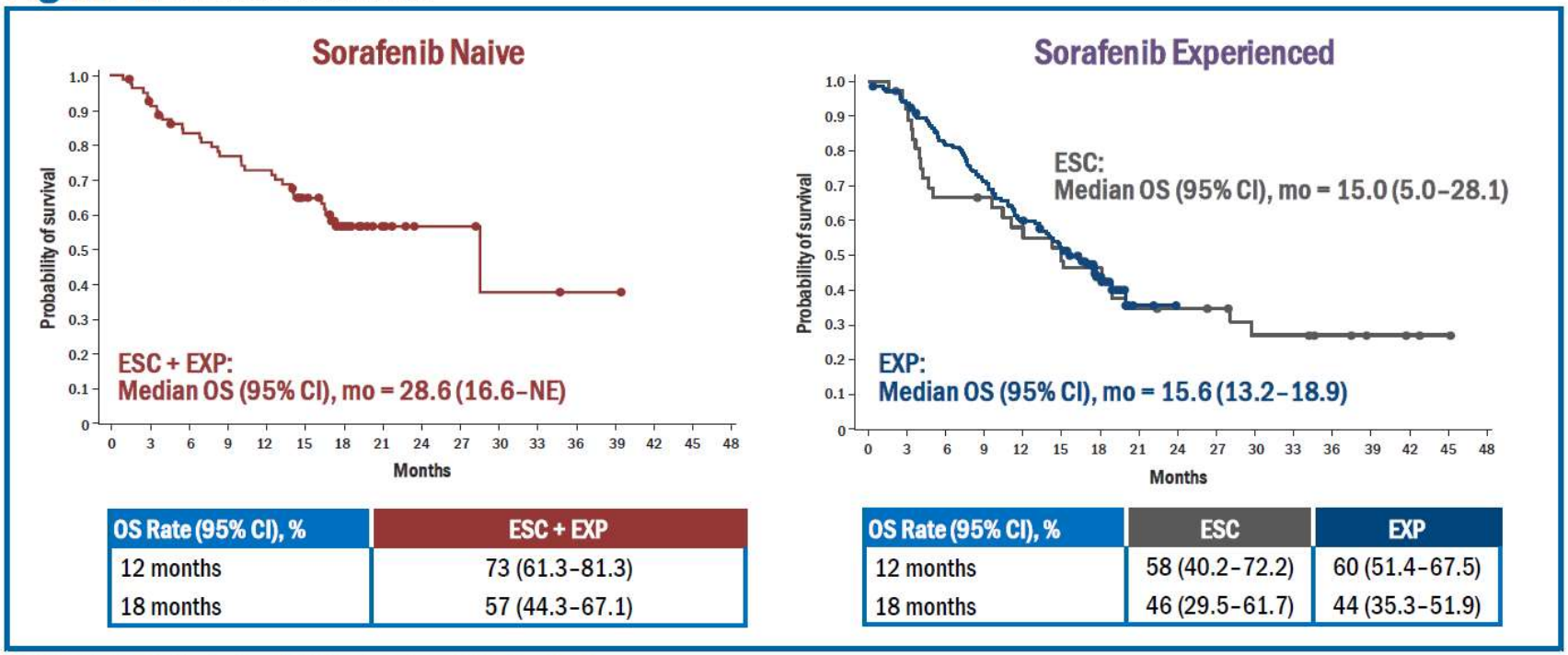
TTR, median (range), mo	2.8 (1.2–7.0)
DOR, median (range), mo	16.59 (3.2–16.8+)

Tumor response assessed by BICR using RECIST v1.1. TTR, time to response; DOR, duration of response.

Crocenzi T et al, J Clin Oncol 35, 2017 (suppl; abstr 4013)

Survival based on sorafenib exposure

Figure 4. Overall Survival



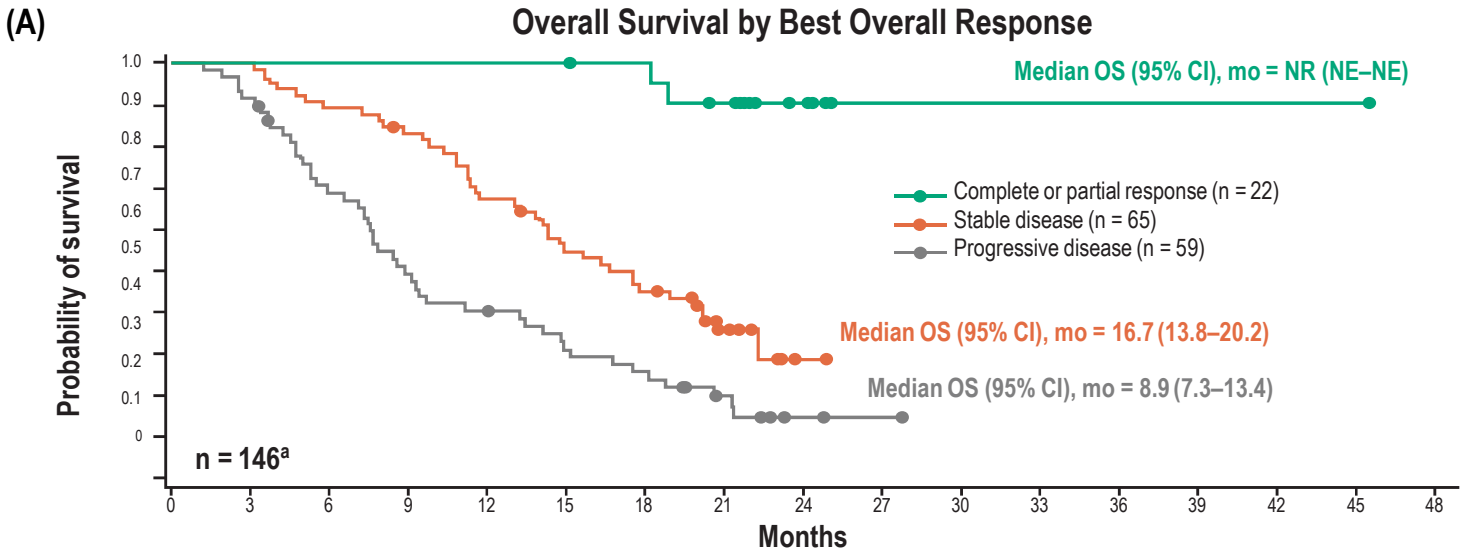
OS Rate (95% CI), %	ESC + EXP
12 months	73 (61.3–81.3)
18 months	57 (44.3–67.1)

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.

Crocenzi T et al, J Clin Oncol 35, 2017 (suppl; abstr 4013)

Checkmate 040: Overall survival analyzed by best overall response or change in target lesion size



OS rate (95% CI), %	Complete/partial response n = 22	Stable disease n = 65	Progressive disease n = 59
12 month	100 (100–100)	67 (55–77)	41 (28–53)
18 month	100 (100–100)	45 (33–57)	26 (15–38)

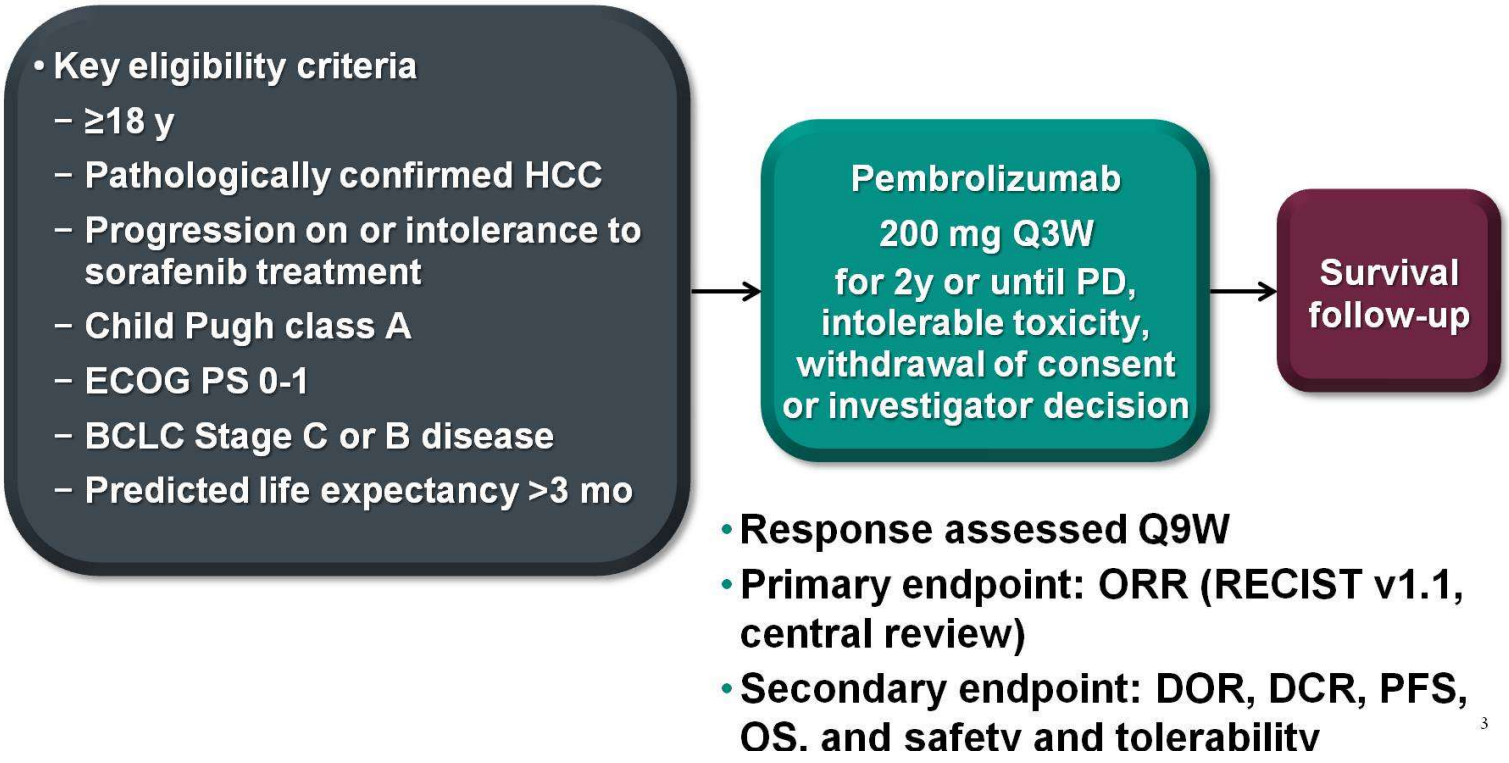
[a]Best overall response was unable to be determined in 8 patients

- Median OS was 15.1 months (95% CI, 13.2–18.8) in the overall analysis population (N = 154)

El-Khoueiry A et al, GI Cancers Symposium, 2018

Keynote 224: Pembrolizumab in advanced HCC

Study Design



Zhu AX, et al. Lancet Oncol. 2018 Jul;19(7):940-952.

Keynote 224: Pembrolizumab in advanced HCC

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.

Zhu AX, et al. Lancet Oncol. 2018 Jul;19(7):940-952.

Camrelizumab (SHR-1210) in HCC

- 84% of patients had hepatitis B
- All had failed ≥ 1 prior line of systemic therapy

	All (N=217)	q2w group (N=109)	q3w group (N=108)
Confirmed ORR, n (%) 95% CI	30 (13.8%) 9.5–19.1	12 (11.0%) 5.8–18.4	18 (16.7%) 10.2–25.1
Best overall response, n (%)			
Complete response	0	0	0
Partial response	30 (13.8)	12 (11.0)	18 (16.7)
Stable disease	67 (30.9)	40 (36.7)	27 (25.0)
Progressive disease	98 (45.2)	44 (40.4)	54 (50.0)
Not evaluable	22 (10.1)	13 (11.9)	9 (8.3)
6-month OS rate, % (95% CI)	74.7 (68.3–79.9)	76.1 (67.0–83.1)	73.1 (63.7–80.5)

* Tumor response was assessed based on the RECIST version 1.1 guideline by blinded independent central review (BICR).

	All (N=217)	q2w group (N=109)	q3w group (N=108)
Median TTP (95% CI), months	2.6 (2.0–3.3)	3.2 (1.9–3.4)	2.1 (2.0–3.4)

	All (N=217)	q2w group (N=109)	q3w group (N=108)
Median PFS (95% CI), months	2.1 (2.0–3.2)	2.3 (1.9–3.2)	2.0 (2.0–3.2)

Qin S et al, ESMO 2018

Summary of anti PD-1 agents in HCC post sorafenib

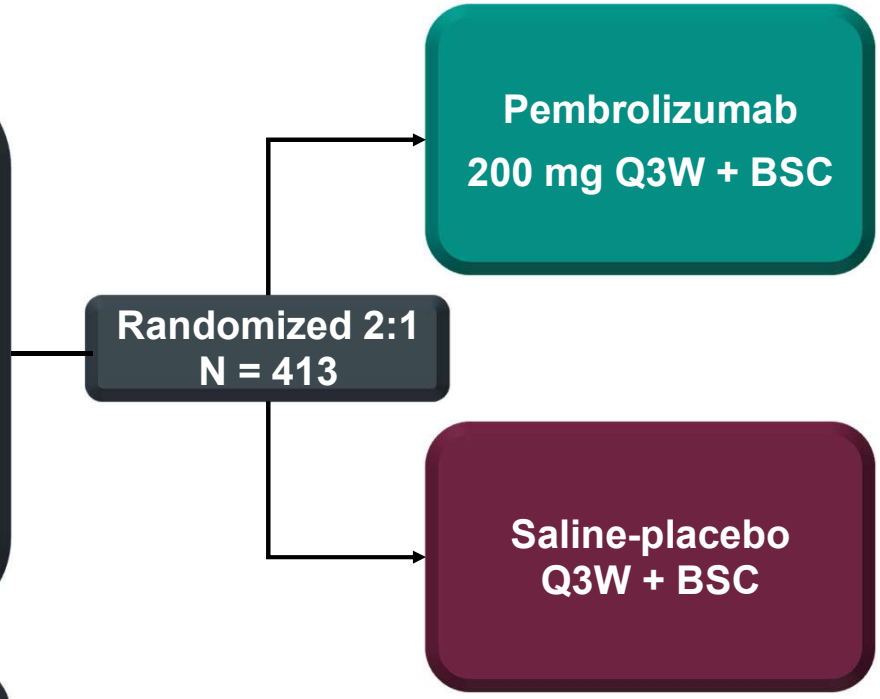
	Subjects received prior sorafenib & other drugs *		Subjects received sorafenib only before enrollment #	
	Camrelizumab	Nivolumab [1,2]	Camrelizumab	Pembrolizumab [3,4]
n	157	154	117	104
ECOG PS of 1, %	80.3	35	80.3	39
AFP≥400 ng/mL, %	52.9	37	50.4	NA (>200 ng/mL: 41%)
Extrahepatic spread, %	82.8	71	78.6	64
HBV infection, %	86.0	31	82.9	21
BCLC-C stage, %	94.9	NA	94.0	76
Lines of prior systemic therapies ≥2, %	24.2	19	0	0
ORR, % (95% CI)	15.9 (10.6–22.6)	14.3 (9.2–20.8) [1]	17.9 (11.5–26.1)	17 (11–26) [3]; 16.3 (9.8–24.9) [4]
6-moths OS, % (95% CI)	75.8 (68.3–81.8)	NA	76.9 (68.2–83.5)	77.9 [4]
Treatment-Related AEs of all grades, %	91.1	77 [2]	92.3	73 [3]
Grade ≥3 treatment-Related AEs, %	21.0	18 [2]	23.9	26 [3]
Treatment-Related Serious AEs, %	9.6	NA	7.7	15 [3]

Qin S et al, ESMO 2018

KEYNOTE-240 Study Design

Key Eligibility Criteria
- Pathologically/radiographically confirmed HCC
- Progression on/intolerance to sorafenib
- Child Pugh class A
- BCLC stage B/C
- ECOG PS 0-1
- Measurable disease per RECIST v1.1
- Main portal vein invasion was excluded

Stratification Factors
- Geographic region (Asia w/o Japan vs non-Asia w/Japan)
- Macrovascular invasion (Y vs N)
- AFP level (≥200 vs <200 ng/mL)



- **Enrollment May 31, 2016 – November 23, 2017**

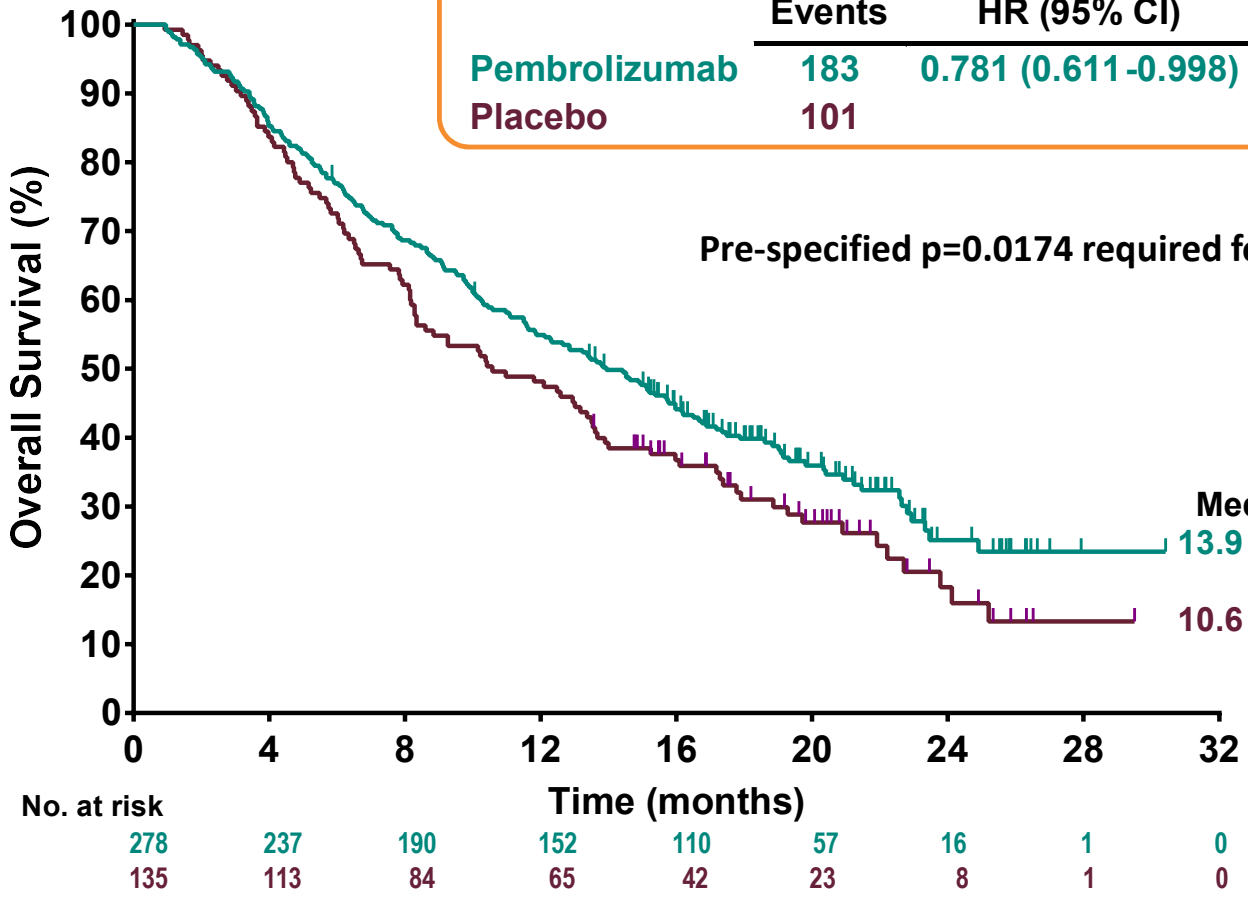
Statistical Considerations

- Overall Type I error (α)=0.025 controlled across testing of PFS, OS and ORR[1]
  - Initial α allocation
    - PFS α=0.002; OS α=0.023
    - ORR α=0.0 (tested only if OS or PFS criteria met)
  - α re-allocated per multiplicity strategy specified in the protocol
- OS testing by group sequential design
  - α controlled over 2 interim and final efficacy analyses (O'Brien-Fleming spending function[2])
  - Primary analysis of PFS and ORR at 1st interim cut-off
- Efficacy boundaries
  - p=0.0174 for OS (final analysis cutoff, Jan 2, 2019, based on 284 observed events)
  - p=0.0020 for PFS (at 1st interim cutoff, Mar 26, 2018)
- Study power
  - 92% for OS with 273 deaths at α=2.3%, HR=0.65
  - 94% for PFS with 331 PFS events at α=0.2%, HR=0.60

1. Maurer W, Bretz F. *Stat Biopharm Res* 2013; 5(4): 311-20. 2. Lan KKG, Demets DL. *Biometrika* 1983; 70(3): 659-63.

Overall Survival

	Events	HR (95% CI)	*P*
Pembrolizumab	183	0.781 (0.611-0.998)	0.0238
Placebo	101		



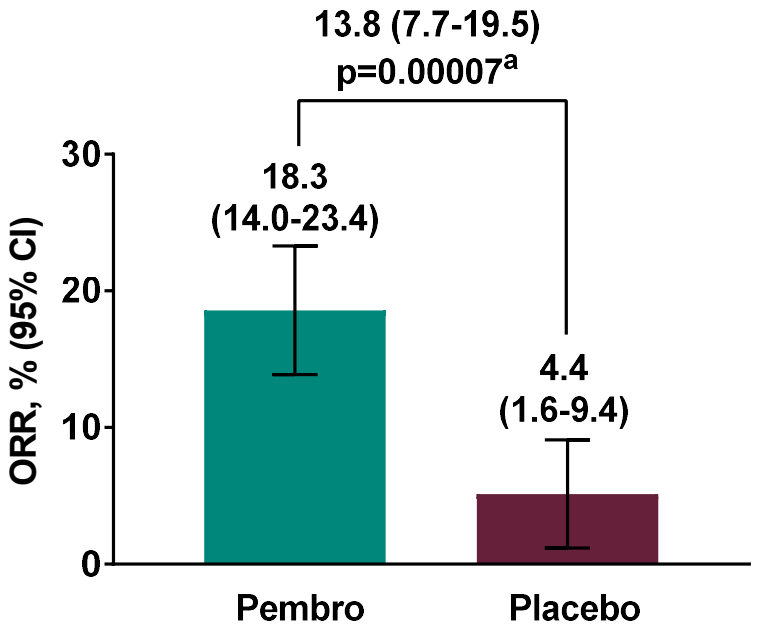
Pre-specified p=0.0174 required for statistical significance

Median (95% CI)
13.9 mo (11.6-16.0)
10.6 mo (8.3-13.5)

Data Cutoff: Jan 2, 2019.

Finn R et al, ESMO GI 2019

Objective Response Rate at Final Analysis
(RECIST 1.1, BICR)



Response n (%)	Pembrolizumab N=278	Placebo N=135
Best Overall Response		
CR	6 (2.2)	0 (0)
PR	45 (16.2)	6 (4.4)
SD	122 (43.9)	66 (48.9)
SD ≥23 wks	37 (13.3)	20 (14.8)
Progressive Disease	90 (32.4)	57 (42.2)
Disease Control Rate (CR+PR+SD)	173 (62.2)	72 (53.3)

Duration of response, median (range)[b,c]:
- Pembrolizumab: 13.8 mo (1.5+ mo − 23.6+ mo)
- Placebo: not reached (2.8 mo−20.4+ mo)

Finn R et al, ESMO GI 2019

[a]Nominal one-sided P-value based on the Miettinen and Nurminen method stratified by randomization factors. [b]From product-limit (Kaplan-Meier) method for censored data. [c] "+" indicates no PD by the time of last disease assessment. Data cutoff: Jan 2, 2019.

Exploratory Sensitivity Analyses: Impact of Post-Treatment Anticancer Medications on OS

Analysis	Median OS (95% CI)		HR (95% CI)[a]	*P*-value[b]
	Pembrolizumab N=278	Placebo N=135		
Intention-to-treat	13.9 (11.6-16.0)	10.6 (8.3-13.5)	0.78 (0.61-1.00)	0.0238
Censored at start of subsequent therapy	16.0 (11.9-19.8)	11.0 (8.1-13.7)	0.68 (0.49-0.94)	0.0096
IPCW	13.9 (11.1-17.2)	9.3 (7.9-13.5)	0.67 (0.48-0.92)	0.0066[c]
2-stage model without recensoring	10.6 (9.5-11.6)	7.6 (6.2-9.3)	0.68 (0.53-0.86)	0.0011[d]

Finn R et al, ESMO GI 2019

Adjusted for treatment switches in both arms. IPCW, inverse probability of censoring weighting. [a]HR based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by geographic region, macrovascular invasion and AFP (ng/mL), and bootstrap 95% CI for both the 2-stage model and IPCW. [b]One-sided p-value based on the IPCW log-rank test; based on stratified log-rank test, adjusted for treatment switch for the 2-stage model. [c] p=0.0090 and [d] p=0.002, one-sided p-values based on bootstrap percentiles.

Trial: NCT02576509
CHECKMATE-459: Phase III trial of nivolumab vs sorafenib in first-line advanced HCC patients[1]

Key Eligibility Criteria

N=726

- Advanced HCC not eligible for or progressive after surgical and/or

CheckMate -459, a randomized Phase 3 study evaluating *Opdivo* (nivolumab) versus sorafenib as a first-line treatment in patients with unresectable hepatocellular carcinoma (HCC). The trial did not achieve statistical significance for its primary endpoint of overall survival (OS) per the pre-specified analysis (HR=0.85 [95% CI: 0.72-1.02]; p=0.0752).

Other Endpoints: ORR, PFS, biomarkers

HCC, hepatocellular carcinoma; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PK, pharmacokinetics; TTP, time to progression.

. **Mellman I et al. *Nature*. 2011;480(7378):480-489.**

My preliminary thoughts on the negative phase 3 trials

- Is it a statistics issue?
  - Co-primary endpoints (Keynote 240)
  - Ambitious HR
  - Adequate power
- Is it a problem of the “median” versus “tail of the curve”
- Is OS a challenge in the age of multiple therapeutic options and cross-over?
- Is the activity not sufficient
  - Need patient selection?
  - Combinations?

Moving forward with checkpoint inhibition in HCC

- Biomarkers for patient selection and enrichment strategies
  - Hypothesis: the main benefit is from the responders and long stable disease
- Smart combinations
  - Will the same combination work for all?
  - Is combination therapy needed for all up-front?

Checkmate 040: Best Overall Response by Tumor Cell PD-L1 Status

PD-L1 cutoff		Overall population (SOR-naïve and SOR-experienced) n = 195	SOR-experienced population n = 137
PD-L1 <1%	Total, n (%)	159 (81.5)	110 (80.2)
	Objective response rate, % (95% CI)	**15.7 (10.8–22.2)**	**12.7 (7.6–20.3)**
	Complete response, n (%)	6 (3.7)	4 (3.6)
	Partial response, n (%)	19 (11.9)	10 (9)
	Stable disease, n (%)	66 (41.5)	49 (44.5)
	Progressive disease, n (%)	59 (37.1)	42 (38.1)
PD-L1 ≥1%	Total, n (%)	36 (18.4)	27 (19.7)
	Objective response rate, % (95% CI)	**27.7 (15.7–44.1)**	**25.9 (12.9–44.9)**
	Complete response, n (%)	2 (5.5)	1 (3.7)
	Partial response, n (%)	8 (22.2)	6 (22.2)
	Stable disease, n (%)	9 (25)	8 (29.6)
	Progressive disease, n (%)	15 (41.6)	10 (37)

- Clinically meaningful responses were observed in all patients, including those with PD-L1 <1% (6 patients had a complete response)
  - In the overall population, numerically higher ORRs were observed in patients with PD-L1 ≥1% versus PD-L1 <1% with overlapping 95% CI
  - The SOR-experienced population had ORRs comparable to the overall population

Melero I et al, AACR 2019
El-Khoueiry et al, JSMO 2019

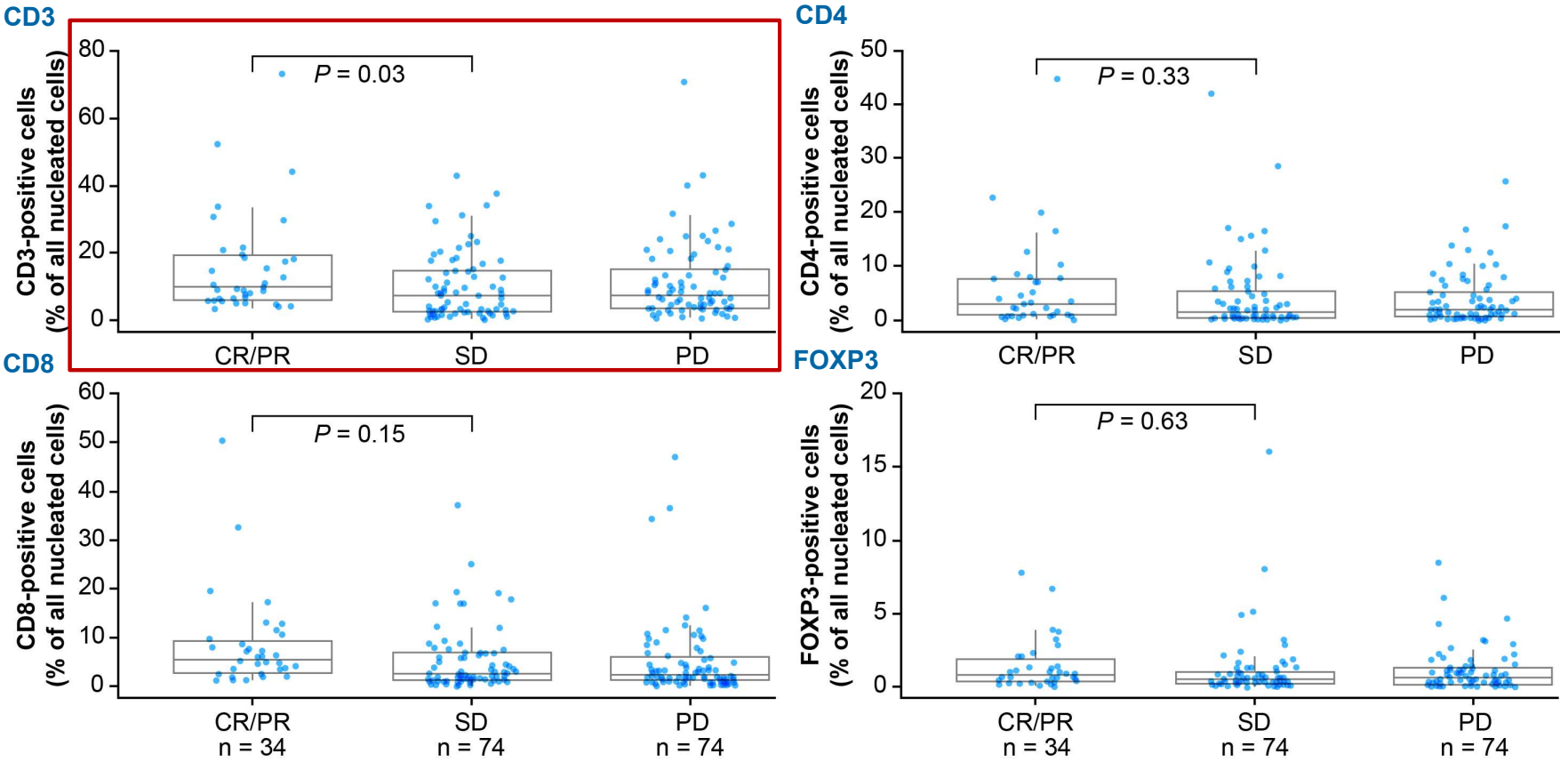
Keynote 224: Association of CPS score with outcome

N=52	CPS ≥1	CPS <1	TPS ≥1	TPS <1
ORR	32% (7/22)	20% (6/30)	43% (3/7)	22% (10/45)

	Objective response (confirmed best overall response)		Progression-free survival	
	Number of responders* (%)	p value†	Number of events* (%)	p value†
Combined positive score	13 (25%)	0·021	43 (83%)	0·026
Tumour proportion score	13 (25%)	0·088	43 (83%)	0·096

Zhu AX, et al. Lancet Oncol. 2018 Jul;19(7):940-952.

Best Overall Response by T-Cell Markers



- In the tumor microenvironment, CD3-positive cell frequency was higher versus the other T-cell markers assessed (data not shown)
- CD3-positive cell frequency was associated with response (CR/PR vs SD; *P* = 0.03)

Melero I et al, AACR 2019
El-Khoueiry et al, JSMO 2019

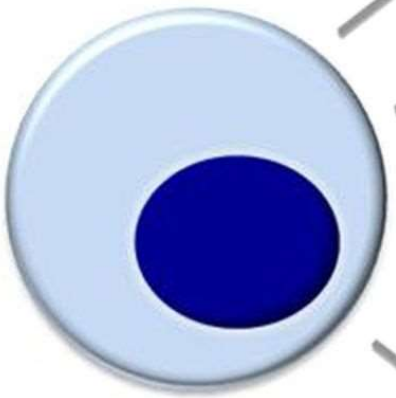
Gene Expression Signatures and Response

Gene signatures	ORR *P*-value[a]	OS *P*-value
BMS 4-Gene Inflammatory Signature	0.05	0.01
Cytolytic Activity Signature[1]	0.1	0.2
Gajewski 13-Gene Inflammatory Signature[2]	0.04	0.05
Merck 6-Gene Interferon Gamma Signature[3]	0.05	0.009
NanoString® Antigen Presenting Cells Signature[3]	0.6	0.08
NanoString® Interferon Gamma Biology Signature[3]	0.07	0.008
NanoString® T-cell Exhaustion Signature[3]	0.03	0.04
NanoString® T/NK Cell Signature[3]	0.3	0.04
Ribas 10-gene Interferon Gamma Signature[3]	0.07	0.02

- For the subset of patients in CheckMate 040 for whom RNA sequencing data were available (n = 37):
  - Several inflammatory signatures, such as the BMS 4-gene, Gajewski, Merck 6-gene interferon gamma, NanoString interferon gamma biology, and NanoString T-cell exhaustion signatures correlated significantly with improved response and OS

Melero I et al, AACR 2019
El-Khoueiry et al, JSMO 2019

How do we expand the benefit of immunotherapy to more patients with 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) →

Migrate into the tumour →

- Anti VEGF combinations (TKI, Bevacizumab)
- 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*

Combination of PD-1/PDL-1 and CTLA4 antibodies

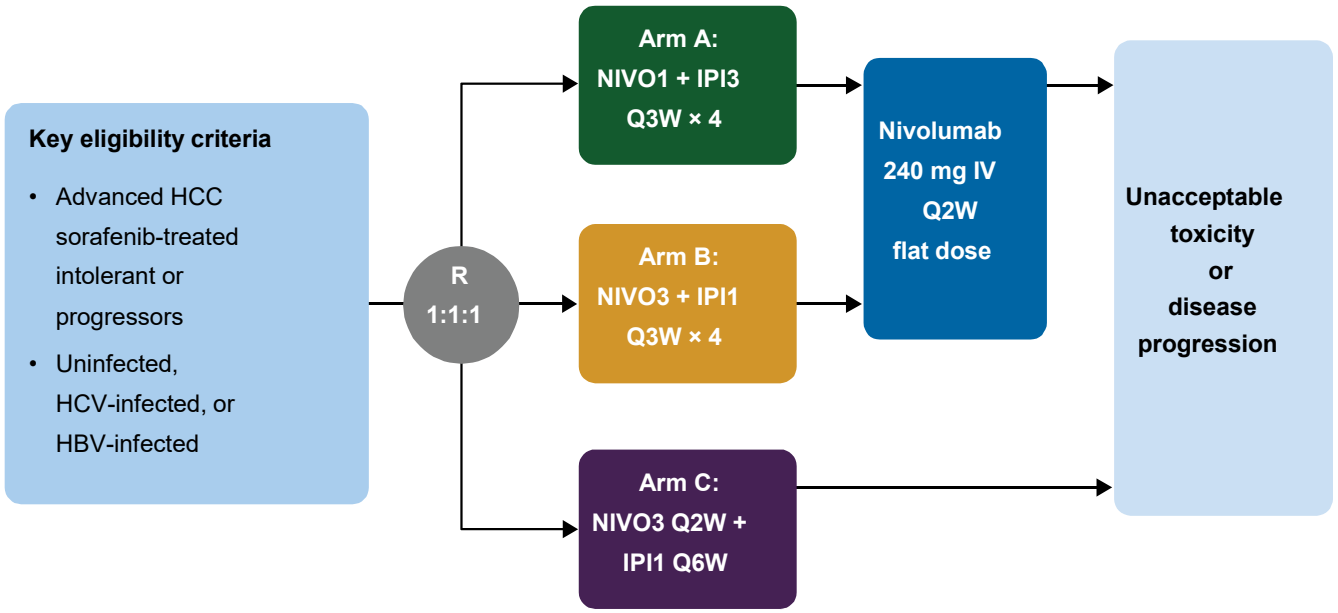
- **Phase I/II of durvalumab and tremelimumab**
  - 40 pts enrolled (11 HBV+, 9 HCV+, 20 uninfected)
  - 30% had no prior systemic therapy
  - 93% Child Pugh Class A
  - Most common (≥15%) treatment-related AEs: fatigue (20%), increased ALT (18%), pruritus (18%), and increased AST (15%).

Investigator-assessed response	HBV+ (N = 11)	HCV+ (N = 9)	Uninfected (N = 20)	All (N = 40)
Confirmed ORR (all PR), % (95% CI)	0 (0.0–28.5)	11.1 (0.3–48.2)	30.0 (11.9–54.3)	17.5 (7.3–32.8)
CR + PR (confirmed + unconfirmed), % (95% CI)	9.1 (0.2–41.3)	11.1 (0.3–48.2)	40.0 (19.1–63.9)	25.0 (12.7–41.2)
CR + PR + SD ≥16 weeks (DCR16), % (95% CI)	45.5 (16.7–76.6)	44.4 (13.7–78.8)	70.0 (45.7–88.1)	57.5 (40.9–73.0)

- **Phase I/II of nivolumab and ipilumumab ongoing (Checkmate 040)**

Kelley RK et al, J Clin Oncol 35, 2017 (suppl; abstr 4073)

Checkmate 040: Nivolumab+Ipilimumab



Study endpoints

Primary

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

Secondary

- DCR
- PFS
- OS
- TTP
- TTR

Other

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

EA1

Checkmate 040: Nivolumab+Ipilimumab

	Arm A NIVO1/IPI3 Q3W[a] n = 50	Arm B NIVO3/IPI1 Q3W[b] n = 49	Arm C NIVO3 Q2W/IPI1 Q6W n = 49
ORR by BICR using RECIST v1.1,[c] n (%)	16 (32)	15 (31)	15 (31)
BOR, n (%)			
CR	4 (8)	3 (6)	0
PR	12 (24)	12 (24)	15 (31)
SD[d]	9 (18)	5 (10)	9 (18)
PD	20 (40)	24 (49)	21 (43)
Unable to determine	3 (6)	4 (8)	4 (8)
DCR,[e] n (%)	27 (54)	21 (43)	24 (49)
Median TTR (range), months	2.0 (1.1–12.8)	2.6 (1.2–5.5)	2.7 (1.2–8.7)
Median DOR (range), months	17.5 (4.6 to 30.5+)	22.2 (4.2 to 29.9+)	16.6 (4.1+ to 32.0+)
ORR by investigator assessment using RECIST v1.1, n (%)	16 (32)	13 (27)	14 (29)

OS parameter	Arm A NIVO1/IPI3 Q3W[a] n = 50	Arm B NIVO3/IPI1 Q3W[b] n = 49	Arm C NIVO3 Q2W/IPI1 Q6W n = 49
12-mo OS rate, % (95% CI)	61 (46–73)	56 (41–69)	51 (36–64)
18-mo OS rate, % (95% CI)	52 (37.5–65)	30 (18–43.5)	47 (32–60)
24-mo OS rate, % (95% CI)	48 (34–61)	30 (18–43.5)	42 (28–56)
30-mo OS rate, % (95% CI)	44 (29.5–57)	28 (16–41)	40 (26.5–54)

Yau T et al, ASCO 2019

Slide 27

EA1 El-Khoueiry, Anthony, 8/18/2019

Checkmate 040: Nivolumab+Ipilimumab

	Arm A NIVO1/IPI3 Q3W[a] n = 49		Arm B NIVO3/IPI1 Q3W[b] n = 49		Arm C NIVO3 Q2W/IPI1 Q6W n = 48	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE, n (%)	46 (94)	26 (53)	35 (71)	14 (29)	38 (79)	15 (31)
Pruritus	22 (45)	2 (4)	16 (33)	0	14 (29)	0
Rash	14 (29)	2 (4)	11 (22)	2 (4)	8 (17)	0
Diarrhea	12 (24)	2 (4)	6 (12)	1 (2)	8 (17)	1 (2)
AST increase	10 (20)	8 (16)	10 (20)	4 (8)	6 (12.5)	2 (4)
Lipase increased	7 (14)	6 (12)	6 (12)	3 (6)	8 (17)	4 (8)
Fatigue	9 (18)	1 (2)	6 (12)	0	5 (10)	0
ALT increase	8 (16)	4 (8)	7 (14)	3 (6)	4 (8)	0
Hypothyroidism	10 (20)	0	4 (8)	0	4 (8)	0
Rash maculo-papular	7 (14)	2 (4)	4 (8)	0	3 (6)	0
Decreased appetite	6 (12)	0	4 (8)	0	3 (6)	0
Malaise	6 (12)	1 (2)	3 (6)	0	3 (6)	0
Adrenal insufficiency	7 (14)	1 (2)	3 (6)	0	2 (4)	0
Nausea	5 (10)	0	4 (8)	0	1 (2)	0
Pyrexia	2 (4)	0	4 (8)	0	5 (10)	0

Yau T et al, ASCO 2019

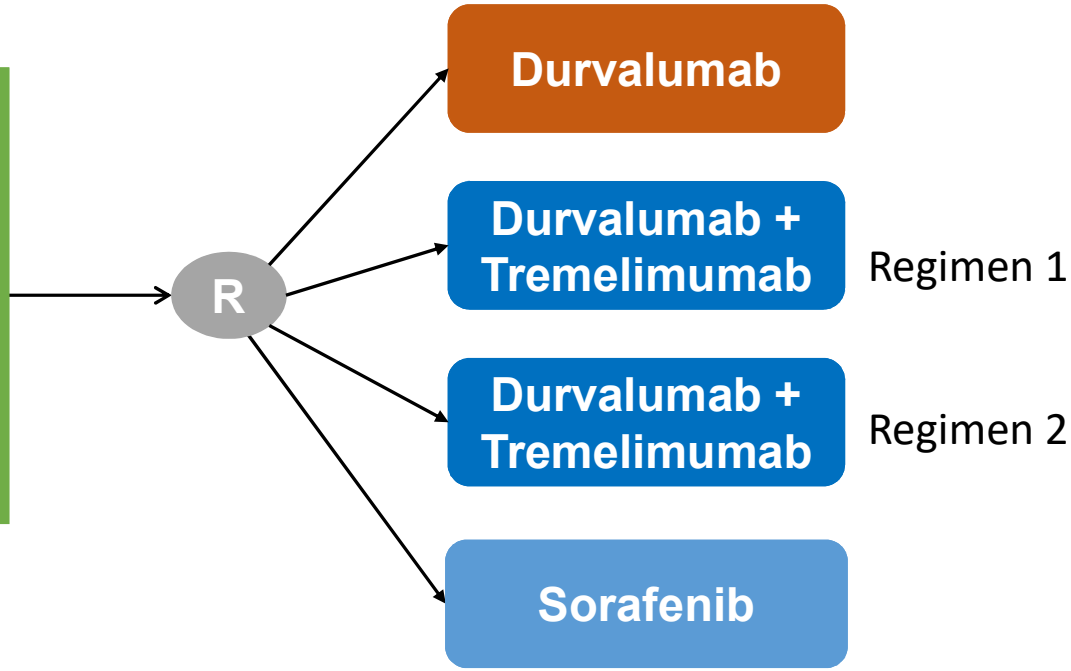
HIMALAYA: Durvalumab + Tremelimumab vs Sorafenib in the Frontline[1]

Phase 3

Key Eligibility Criteria

- Unresectable HCC not eligible for locoregional therapies
- BCLC B or C
- Child–Pugh A
- No prior systemic therapy

N ~ 1200



Endpoints

- Primary endpoints: OS
- Other endpoints: TTP, PFS, ORR, DCR, DoR, QoL

1. https://clinicaltrials.gov/ct2/show/NCT03298451. Accessed January 3, 2018.

Targeting OX-40 (P-8600) in solid tumors including HCC

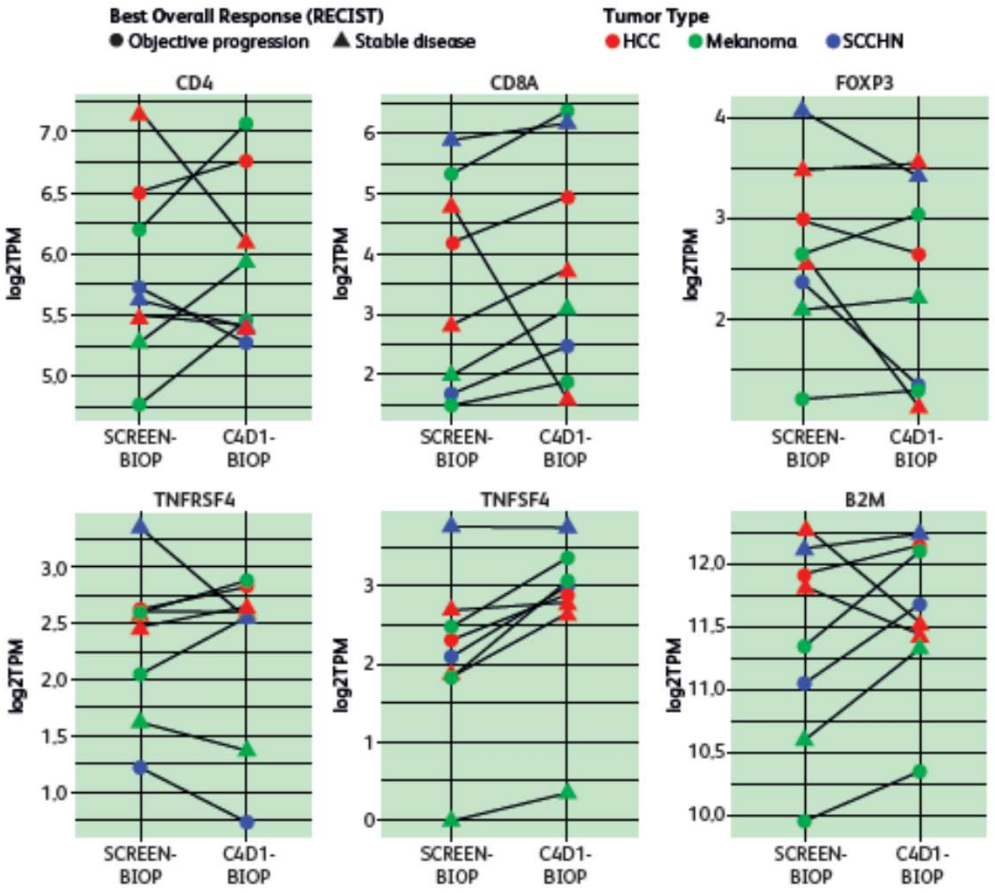


Figure 2: Gene Sets Enriched in Tumor Tissue in Response to Dosing with PF-8600

A.

Pathway	Gene ranks	NES	p val	p adj
ALLOGRAFT_REJECTION		2.21	1.6e-05	6.5e-04
INTERFERON_GAMMA_RESPONSE		1.74	3.1e-05	6.5e-04
INFLAMMATORY_RESPONSE		1.68	6.2e-05	6.5e-04
KRAS_SIGNALING_UP		1.68	6.2e-05	6.5e-04
MYC_TARGETS_V1		1.66	7.8e-05	6.7e-04
MYOGENESIS		1.63	1.1e-04	7.1e-04
HEME_METABOLISM		1.63	1.6e-04	9.0e-04
OXIDATIVE_PHOSPHORYLATION		1.62	1.9e-04	9.7e-04
XENOBIOTIC_METABOLISM		1.59	3.1e-04	1.5e-03
MTORC1_SIGNALING		1.58	4.0e-04	1.8e-03
PI3K_AKT_MTOR_SIGNALING		1.68	4.6e-04	1.8e-03
IL2_STAT5_SIGNALING		1.47	2.3e-03	7.5e-03
COMPLEMENT		1.42	5.7e-03	1.6e-02
REACTIVE_OXIGEN_SPECIES_PATHWAY		1.58	8.7e-03	2.3e-02
KRAS_SIGNALING_DN		1.34	1.8e-02	4.0e-02

0 10000 20000 30000

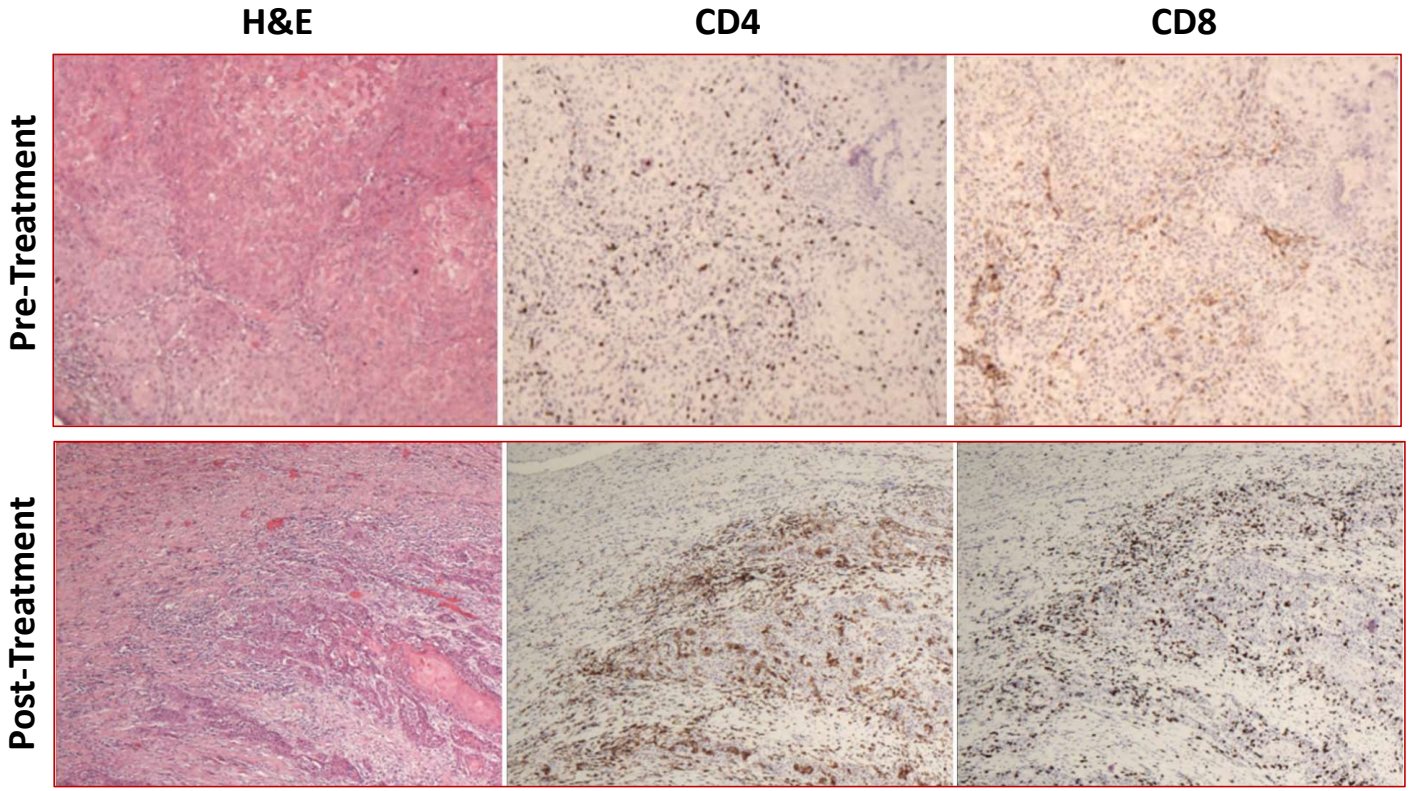
B.

Pathway	Gene ranks	NES	p val	p adj
MITOTIC_SPINDLE		−1.64	5.6e-05	6.5e-04
HYPOXIA		−1.50	8.1e-04	3.0e-03
EPITHELIAL_MESENCHYMAL_TRANSITION		−1.47	1.4e-03	4.9e-03
APICAL_JUNCTION		−1.38	5.9e-03	1.6e-02
TNFA_SIGNALING_VIA_NFKB		−1.38	6.0e-03	1.6e-02
UV_RESPONSE_DN		−1.39	1.1e-02	2.7e-02
HEDGEHOG_SIGNALING		−1.58	1.3e-02	3.1e-02

0 10000 20000 30000

Diab A, ….El-Khoueiry A, AACR 2018

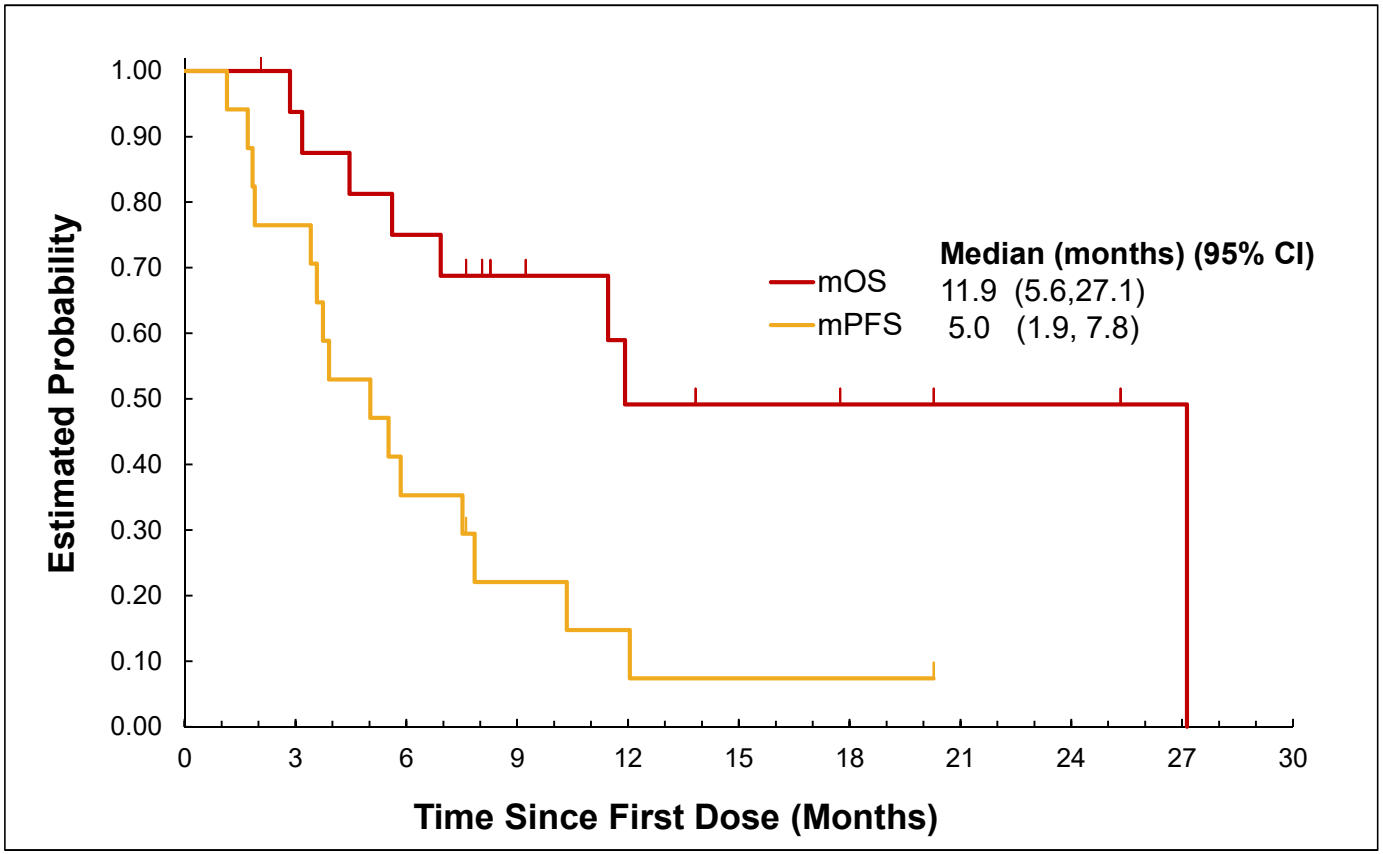
sEphB4-HSA promotes CD4 and CD8 infiltration in the tumor



- Pre and post treatment tissue samples from 12 patients were evaluated.
- On therapy, 6 patients showed marked increase in CD4, CD8, CD3 cell infiltration.

Thomas J et al, ASCO GI 2018

sEphB4-HSA single agent expansion in HCC



Thomas J et al, ASCO GI 2018

A phase Ib trial of Lenvatinib and Pembrolizumab in patients with HCC

Table 2. Summary of TEAEs (Safety Analysis set)

Parameter, n (%)	LEN + PEM		
	Part 1 (n = 6)	Part 2 (n = 24)	Overall (N = 30)
TEAEs	6 (100.0)	24 (100.0)	30 (100.0)
Treatment-related TEAEs	6 (100.0)	22 (91.7)	28 (93.3)
TEAEs ≥ grade 3	5 (83.3)	13 (54.2)	18 (60.0)
Serious AEs	2 (33.3)	6 (25.0)	8 (26.7)
Fatal AEs[a]	0	3 (12.5)	3 (10.0)
Dose modifications			
LEN or PEM dose interruptions due to TEAEs	5 (83.3)	13 (54.2)	18 (60.0)
LEN dose reductions due to TEAEs	5 (83.3)	13 (54.2)	18 (60.0)
Discontinuation of LEN or PEM due to TEAE(s)[b]	0	5 (20.8)	5 (16.7)

[a]Acute respiratory distress syndrome (n = 1); intestinal perforation (n = 1); bacterial peritonitis (n = 1)

Table 4. Summary of Tumor Response (Investigator Assessment by mRECIST; Efficacy Analysis set[a])

Parameter, n (%)	LEN + PEM		
	Part 1 (n = 6)	Part 2 (n = 20)	Overall (n = 26)
BOR, n (%)			
CR[b]	0	1 (5.0)	1 (3.8)
PR[c]	4 (66.7)	6 (30.0)	10 (38.5)
SD	2 (33.3)	13 (65.0)	15 (57.7)
PD	0	0	0
ORR (including unconfirmed responses), n (%)	4 (66.7)	7 (35.0)	11 (42.3)
95% CI	22.3, 95.7	15.4, 59.2	23.4, 63.1
ORR (excluding unconfirmed responses), n (%)	3 (50.0)	4 (20.0)	7 (26.9)
95% CI	11.8, 88.2	5.7, 43.7	11.6, 47.8

[a]Patients with post-evaluable tumor assessment; [b]0 CR confirmed; [c]7 PR confirmed.

Ikeda M et al, ASCO 2018

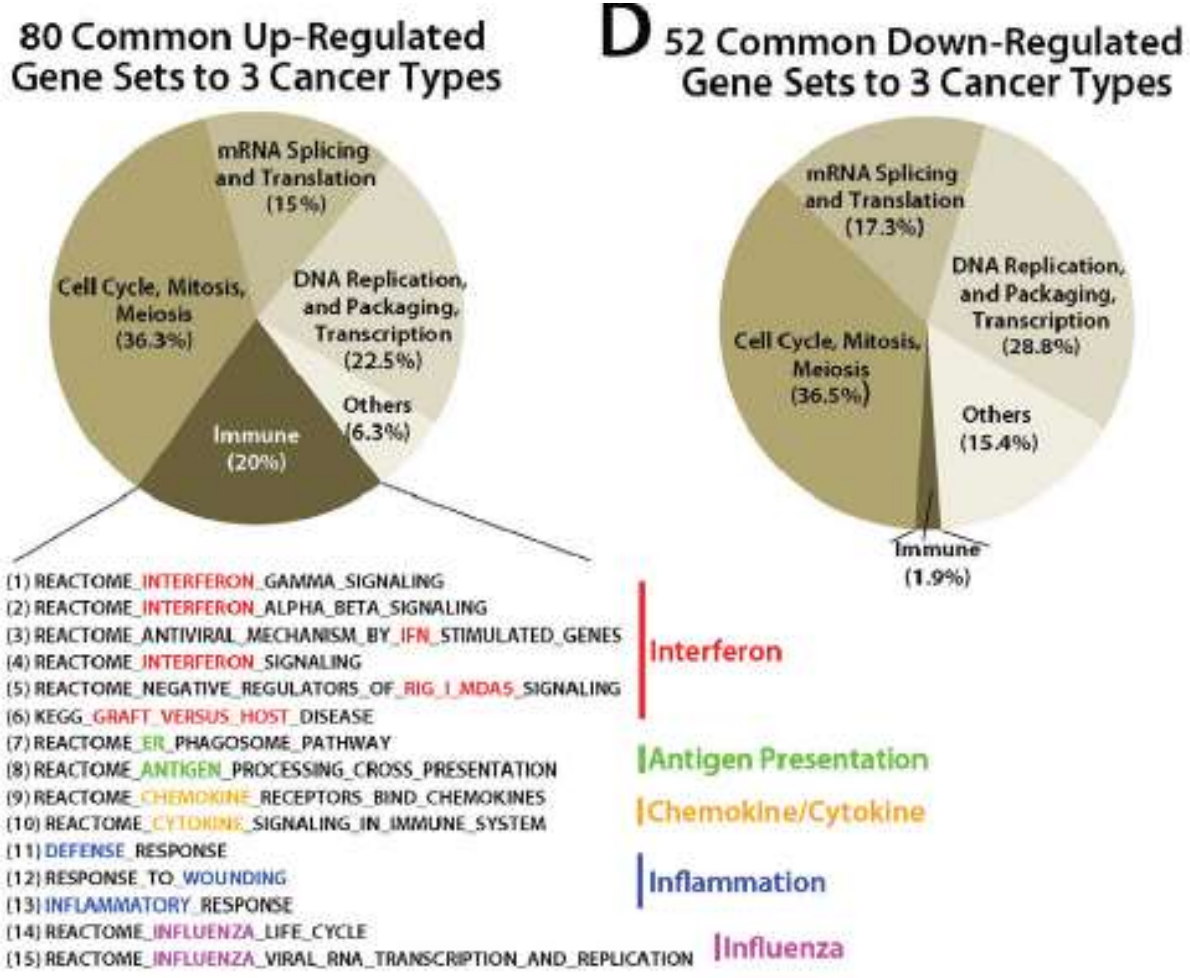
A phase Ib of Atezolizumab and Bevacizumab in advanced HCC

AEs, n (%)	N = 103
Any-grade AEs	95 (92)
Treatment related	84 (82)
Grade 3/4 AEs	41 (40)
Treatment related	28 (27)
Grade 5 AEs	5 (5)
Treatment related[a]	2 (2)
Serious AEs	36 (35)
Treatment related	19 (18)
Atezolizumab any-grade AESIs	56 (54)
Bevacizumab any-grade AESIs	48 (47)
AE leading to withdrawal from	
Atezolizumab	8 (8)
Bevacizumab	10 (10)
Both treatments	6 (6)

ORR	
Overall, n/n (%)[a]	**20/73 (27)**
CR	4/73 (5)
PR	16/73 (22)
SD	35/73 (48)
DCR (CR+PR+SD)	55/73 (75)
PD	14/73 (19)
By aetiology, n/n (%)	
HBV	9/36 (25)
HCV	9/23 (39)
Non-viral	2/14 (14)
By EHS/MVI, n/n (%)[b]	
EHS and/or MVI	16/64 (25)
MVI negative	11/32 (34)
EHS negative	8/22 (36)
Neither EHS nor MVI	4/8 (50)
Median DOR (range), mo	NR (1.6+ to 22.0+)
≥ 6 mo, n/n (%)	9/20 (45)
≥ 12 mo, n/n (%)	5/20 (25)

Pishvaian M et al, ESMO 2018

Upregulation of immunomodulatory pathways with 5Aza



Li H et al, Oncotargets 2014

Multiple Solid Tumor Project

A phase Ib study of guadecitabine and durvalumab in patients with hepatocellular carcinoma (HCC), biliary cancers, and pancreatic cancer.

PI: Anthony El-Khoueiry, M.D., USC Norris Comprehensive Cancer Center

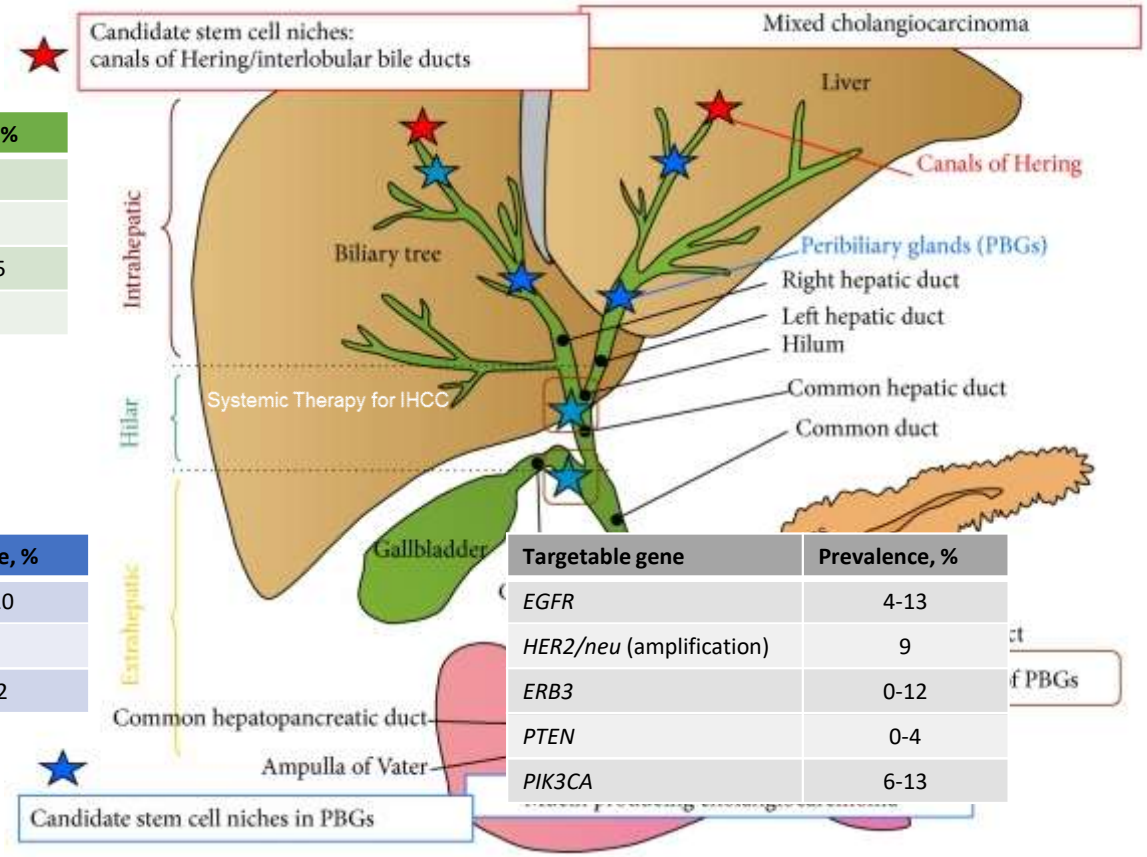
Co-I: Nilofer Azad., Sidney Kimmel Comprehensive Cancer Center

Gallbladder Cancer and Cholangiocarcinoma

Is this one disease?

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

Clinical activity of infigratinib in advanced cholangiocarcinoma

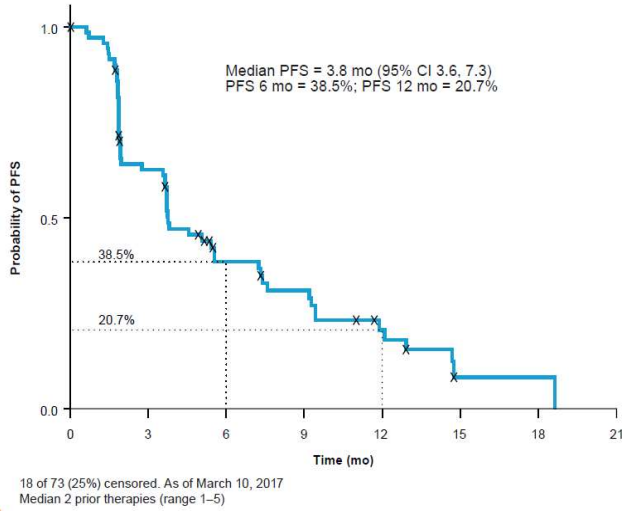
Efficacy outcome in all fusion patients	n=71
Overall response rate (ORR; confirmed & unconfirmed), % (95% CI)	31.0 (20.5–43.1)
Complete response, n (%)	0
Partial response – confirmed, n (%)	18 (25.4)
Stable disease, n (%)	41 (57.7)
Progressive disease, n (%)	8 (11.3)
Unknown, n (%)	4 (5.6)
Efficacy outcome 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.

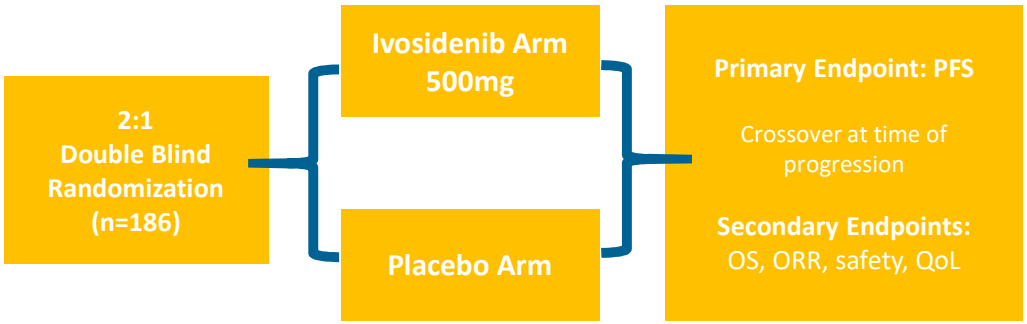
Javle, M et al, ESMO 2018

Targeting IDH1: Phase 1 study of AG-120: cholangiocarcinoma cohort

Response	<500 mg QD (n=6)	500 mg QD (n=62)	>500 mg QD (n=5)	Overall (n=73)
Best response, n (%)				
PR	1 (17)	3 (5)		4 (5)
SD	3 (50)	36 (58)	2 (40)	41 (56)
PD	1 (17)	21 (34)	2 (40)	24 (33)
Not assessed[a]	1 (17)	2 (3)	1 (20)	4 (5)

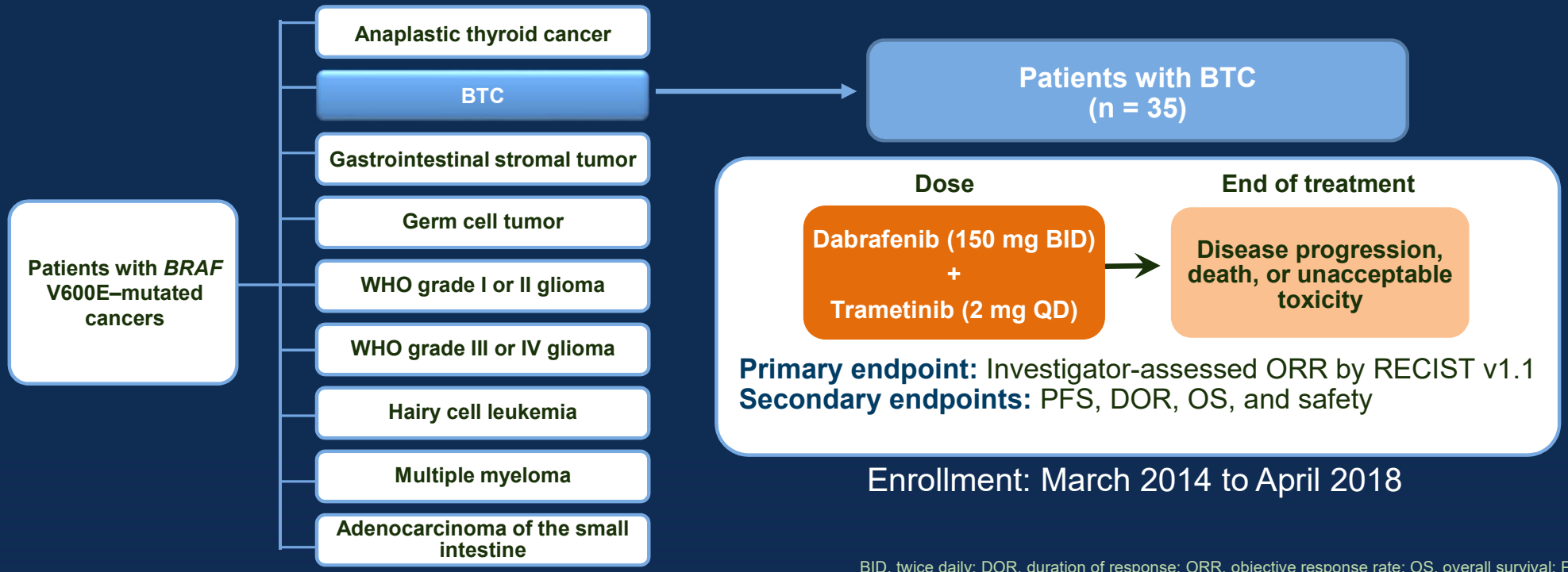


Global Phase 3 Previously Treated Advanced IDH1m Cholangiocarcinoma (no more than 2 prior therapies)



Lowery MA et al, ASCO 2017

ROAR: A Phase 2, Open-Label, Multicenter Study (NCT02034110)



Enrollment: March 2014 to April 2018

BID, twice daily; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization.

Best Overall Response

Response	Investigator-Assessed Response ITT/Evaluable Population (n = 33)	Response by Independent Review ITT/Evaluable Population (n = 33)
Best overall response, n (%)		
CR	0	0
PR	14 (42)	12 (36)
SD	15 (45)	13 (39)
PD	4 (12)	4 (12)
Not evaluable[a]	0	2 (6)
Missing	0	2 (6)
ORR (CR + PR), n (%)	14 (42)	12 (36)
95% CI	25.5-60.8	20.4-54.9

Median PFS was 9.2 months by investigator assessment (95% CI, 5.4-10.1 months)

Median OS was 11.7 months (95% CI, 7.5-17.7 months)

- The median duration of follow-up was 8 months (range, 2-34 months)

CR, complete response; ITT< intent to treat; overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a] Patients were not evaluable if they had only nontarget lesions and the response did not qualify for CR or PD.

Summary and Conclusions

- Multiple new drugs are approved in HCC but the majority are tyrosine kinase inhibitors with median OS of 10 to 13 months in first line and 10 to 11 months in second line
- Checkpoint inhibitors activity established but phase 3 trials have not met primary endpoints
  - Need for biomarkers
  - Smart combinations
- Biliary cancer is a group of molecular subsets
  - Emerging targets