Published Data with and Appropriate Integration of Immune Checkpoint Inhibitors into the Care of Patients with Progressive Metastatic HCC

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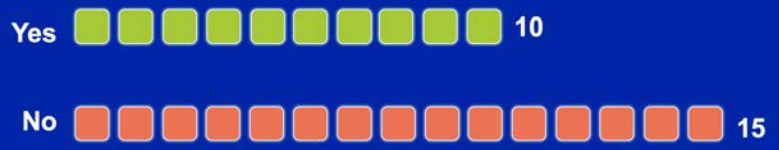
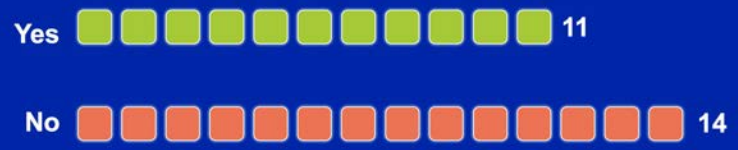
Do you believe that patients with unresectable HCC limited to the liver who in the past underwent liver-directed therapy such as TACE should now instead receive initial systemic treatment (eg, atezolizumab/bevacizumab)?

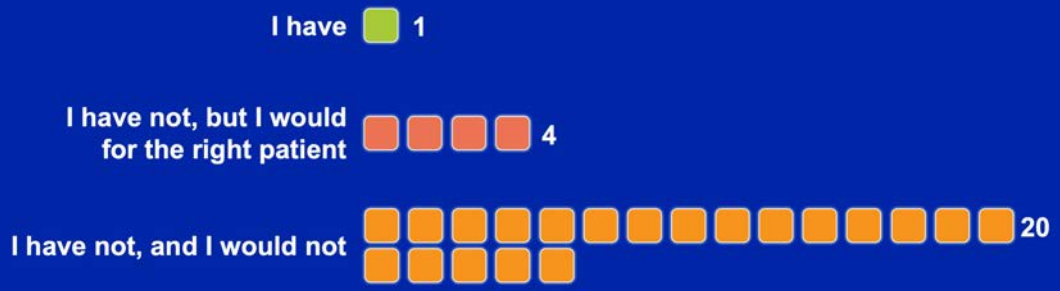


Do you generally test for microsatellite instability in your patients with HCC?



Approximately how many patients with MSI-high HCC have you encountered in your practice?

Outside of a protocol setting, have you or would you offer an anti-PD-1/anti-PD-L1 antibody to a patient with HCC who has undergone a liver transplant?



Immunotherapy issues in HCC

- Checkpoint inhibitors for hepatic-only disease
- Management of autoimmune toxicity
- Use in special populations
- Treatment discontinuation
- MSI-high disease

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Disclosures

Advisory Committee	Agenus Inc, Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb Company, Exelixis Inc, Genentech, Merck, Roche Laboratories Inc
Contracted Research	Astex Pharmaceuticals, AstraZeneca Pharmaceuticals LP, Merck

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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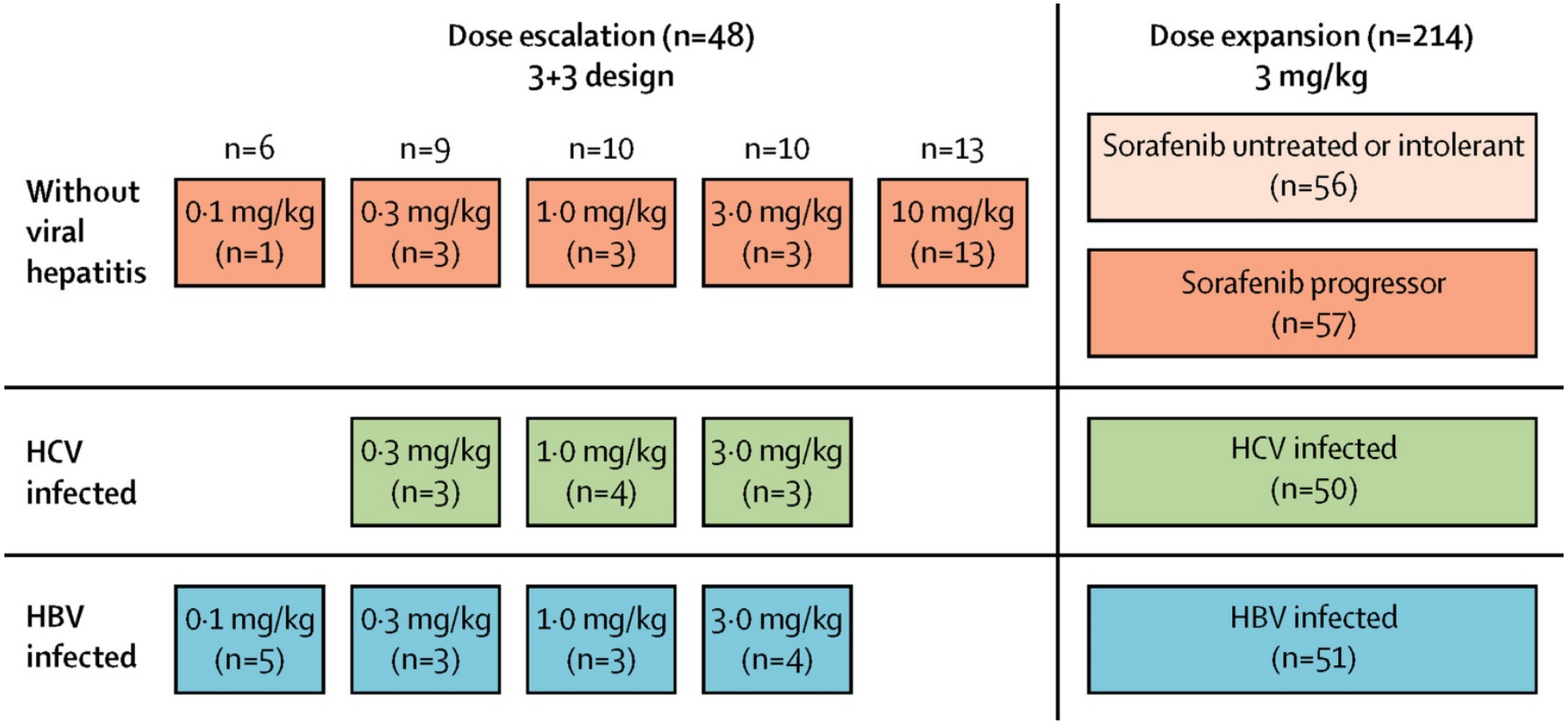


El-Khoueiry A et al, Lancet, online April 2017

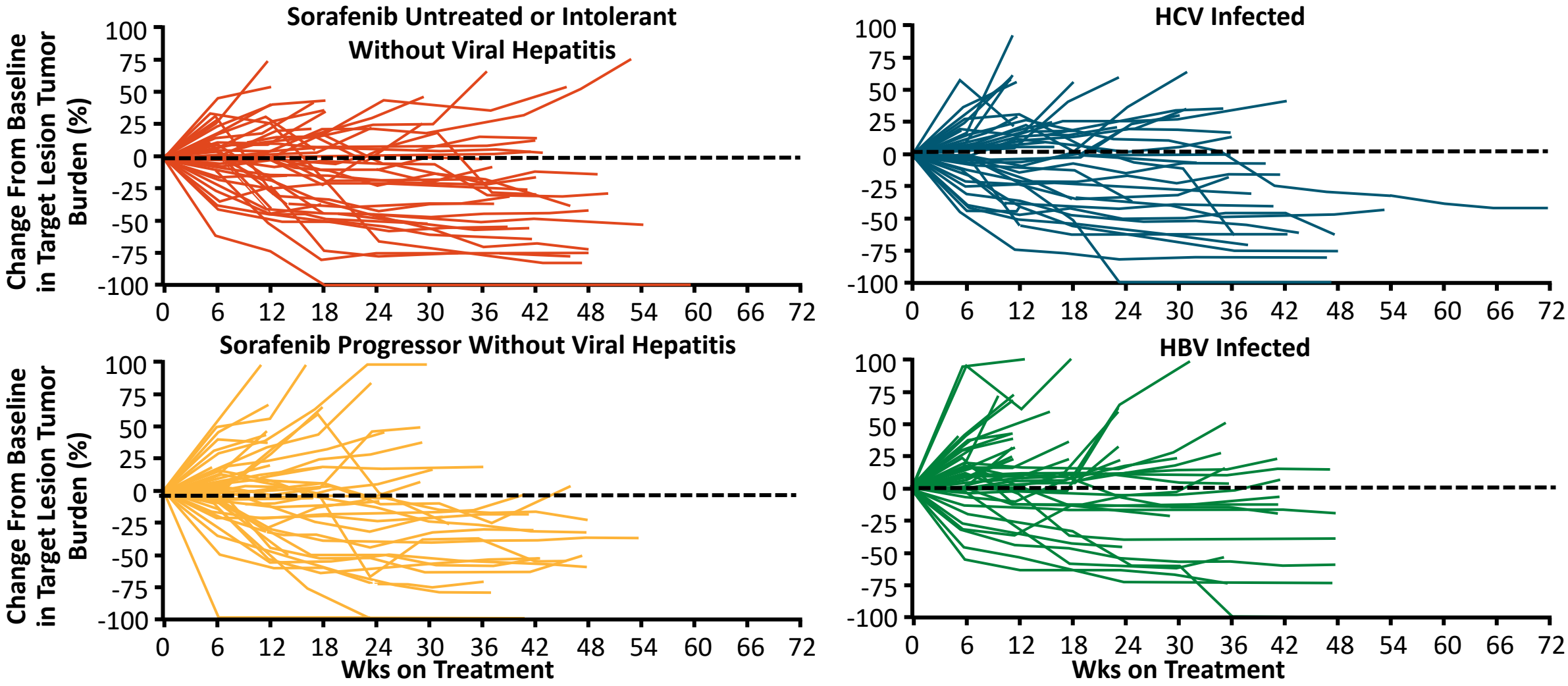
Dose expansion: treatment related adverse events

	Uninfected (n = 112)		HCV (n = 51)		HBV (n = 51)		Total (N = 214)	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Patients with any TRAE, n (%)	72 (64)	21 (19)	37 (73)	15 (29)	30 (59)	3 (6)	139 (65)	39 (18)
Symptomatic TRAEs reported in > 4% of all patients								
Fatigue	31 (28)	2 (2)	7 (14)	0	7 (14)	0	45 (21)	2 (1)
Pruritus	11 (10)	0	11 (22)	0	11 (22)	0	33 (15)	0
Rash	12 (11)	1 (1)	8 (16)	0	6 (12)	0	26 (12)	1 (0.5)
Diarrhea	16 (14)	2 (2)	3 (6)	0	1 (2)	1 (2)	20 (9)	3 (1)
Nausea	8 (7)	0	6 (12)	0	0	0	14 (7)	0
Decreased appetite	5 (5)	0	2 (4)	0	3 (6)	0	10 (5)	0
Dry mouth	5 (4)	0	1 (2)	0	2 (4)	0	8 (4)	0
Laboratory-value TRAEs reported in > 4% of all patients								
ALT increased	6 (5)	2 (2)	7 (14)	4 (8)	2 (4)	0	15 (7)	6 (3)
AST increased	7 (6)	3 (3)	6 (12)	6 (12)	0	0	13 (6)	9 (4)
Platelet count decreased	4 (4)	1 (1)	3 (6)	2 (4)	5 (10)	1 (2)	8 (4)	3 (1)
Anemia	2 (2)	0	3 (6)	1 (2)	3 (6)	0	8 (4)	1 (0.5)

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

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

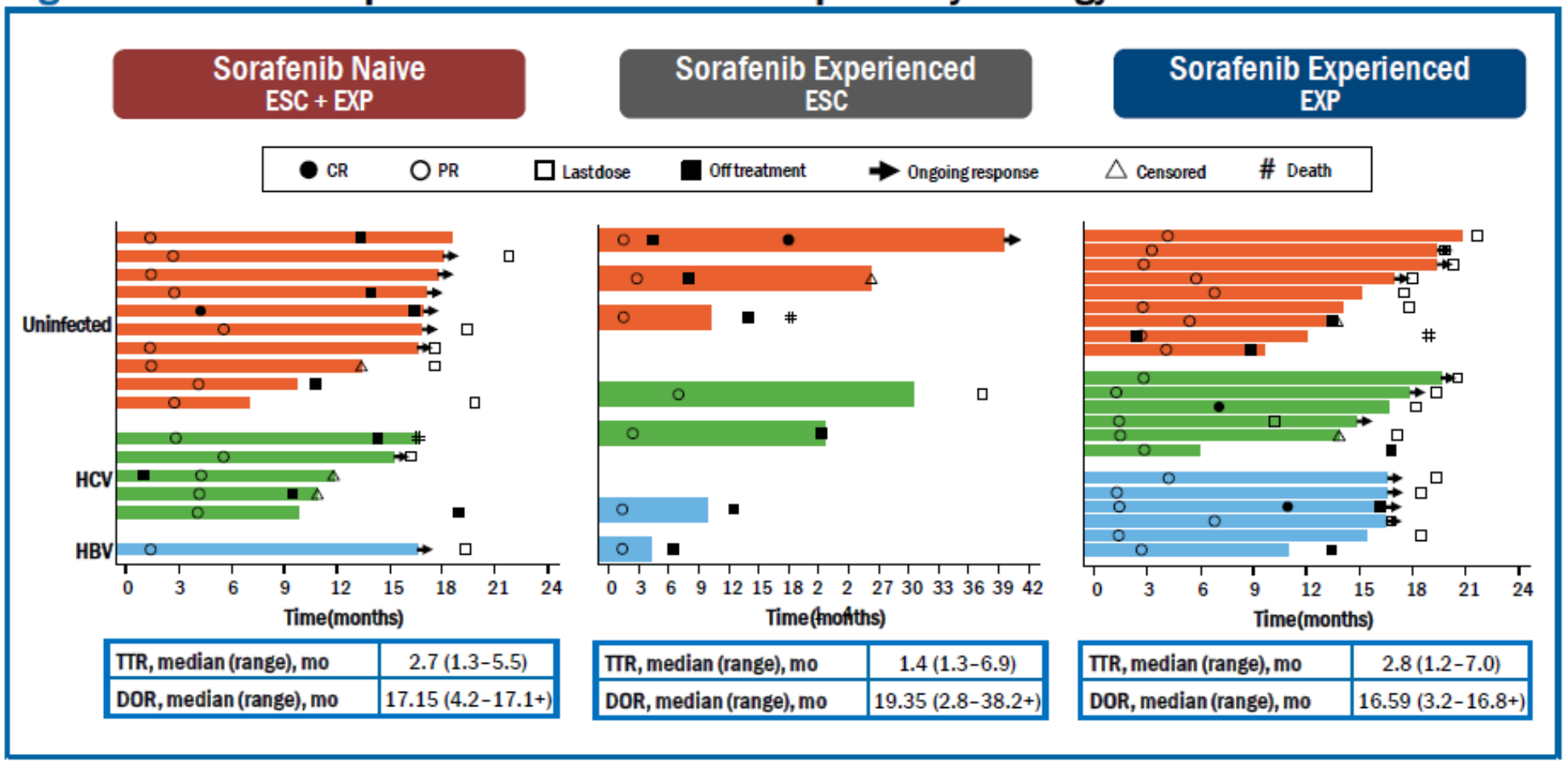
ORR (RECIST 1.1): in expansion cohorts, 20%; in post-sorafenib patients, 14.3%



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

Time to response and duration of response

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



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

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

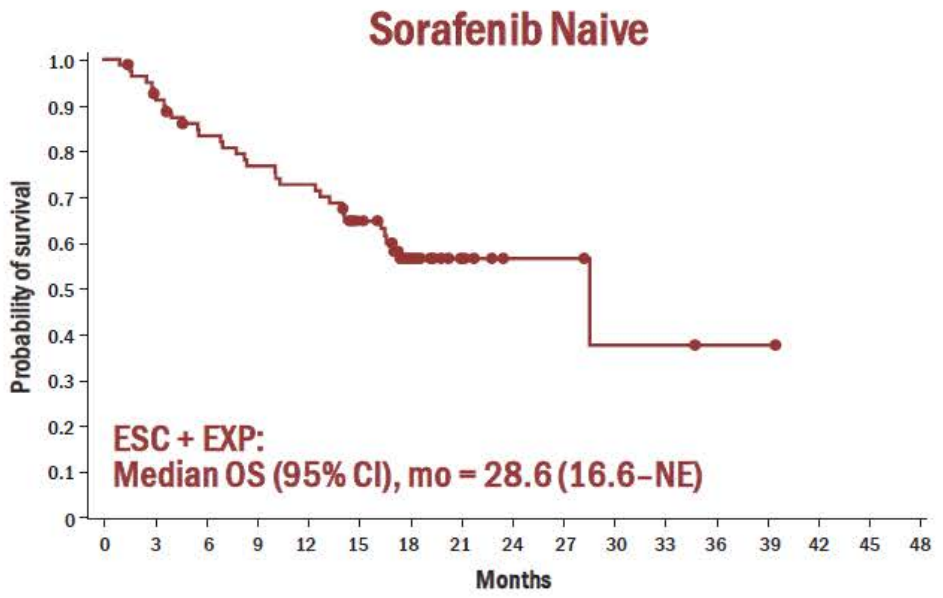
Sorafenib Experienced EXP	
TTR, median (range), mo	2.8 (1.2–7.0)
DOR, median (range), mo	16.59 (3.2–16.8+)

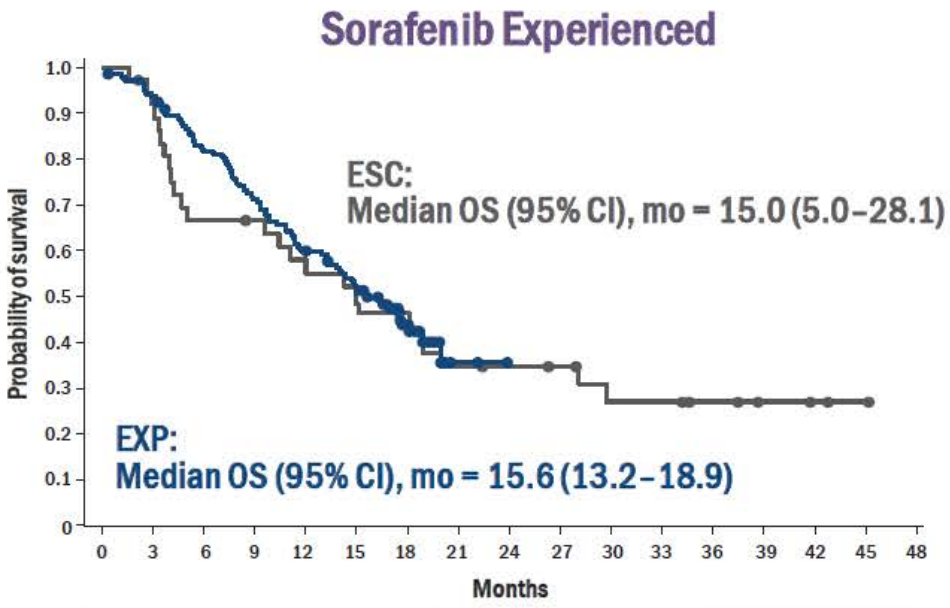
Tumor response assessed by BICR using RECIST v1.1. TTR, time to response; DOR, duration of response.

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

Survival based on sorafenib exposure

Figure 4. Overall Survival





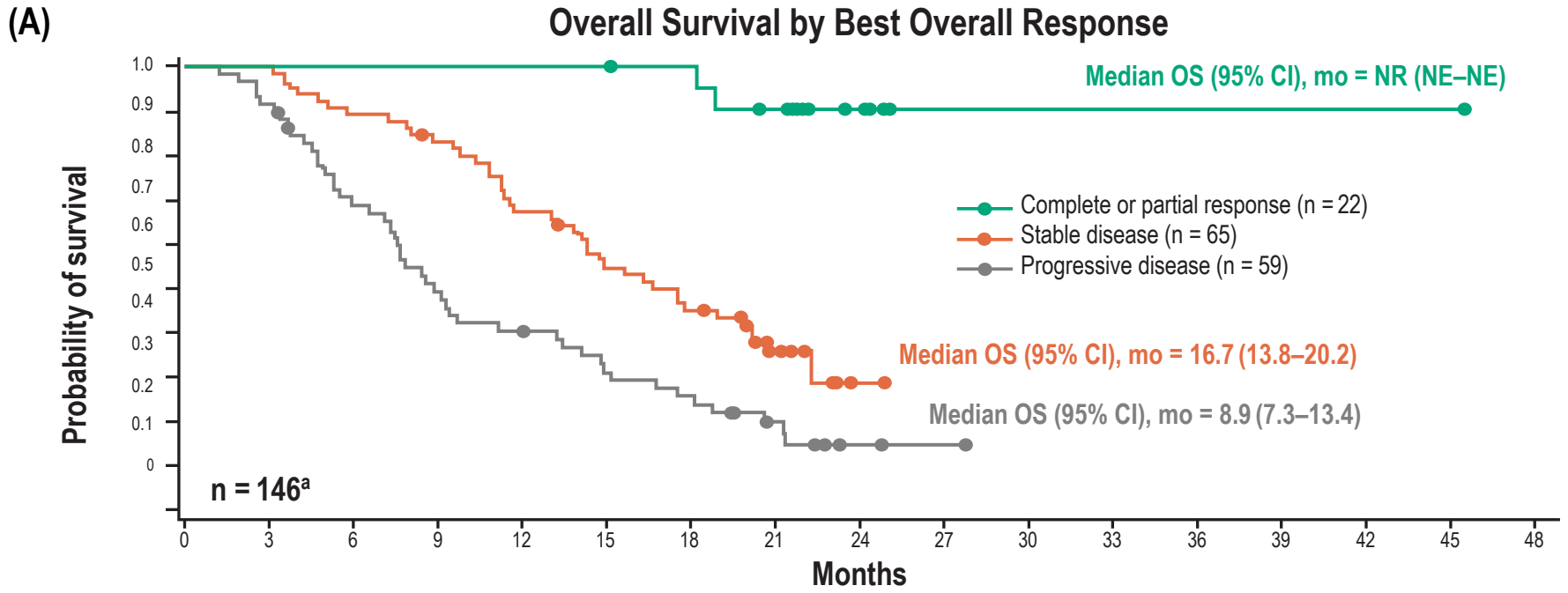
OS Rate (95% CI), %	ESC + EXP
12 months	73 (61.3–81.3)
18 months	57 (44.3–67.1)

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

- Key eligibility criteria
  - ≥18 y
  - Pathologically confirmed HCC
  - Progression on or intolerance to sorafenib treatment
  - Child Pugh class A
  - ECOG PS 0-1
  - BCLC Stage C or B disease
  - Predicted life expectancy >3 mo

→ **Pembrolizumab** 200 mg Q3W for 2y or until PD, intolerable toxicity, withdrawal of consent or investigator decision → **Survival follow-up**

- Response assessed Q9W
- Primary endpoint: ORR (RECIST v1.1, central review)
- Secondary endpoint: DOR, DCR, PFS, OS, and safety and tolerability

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

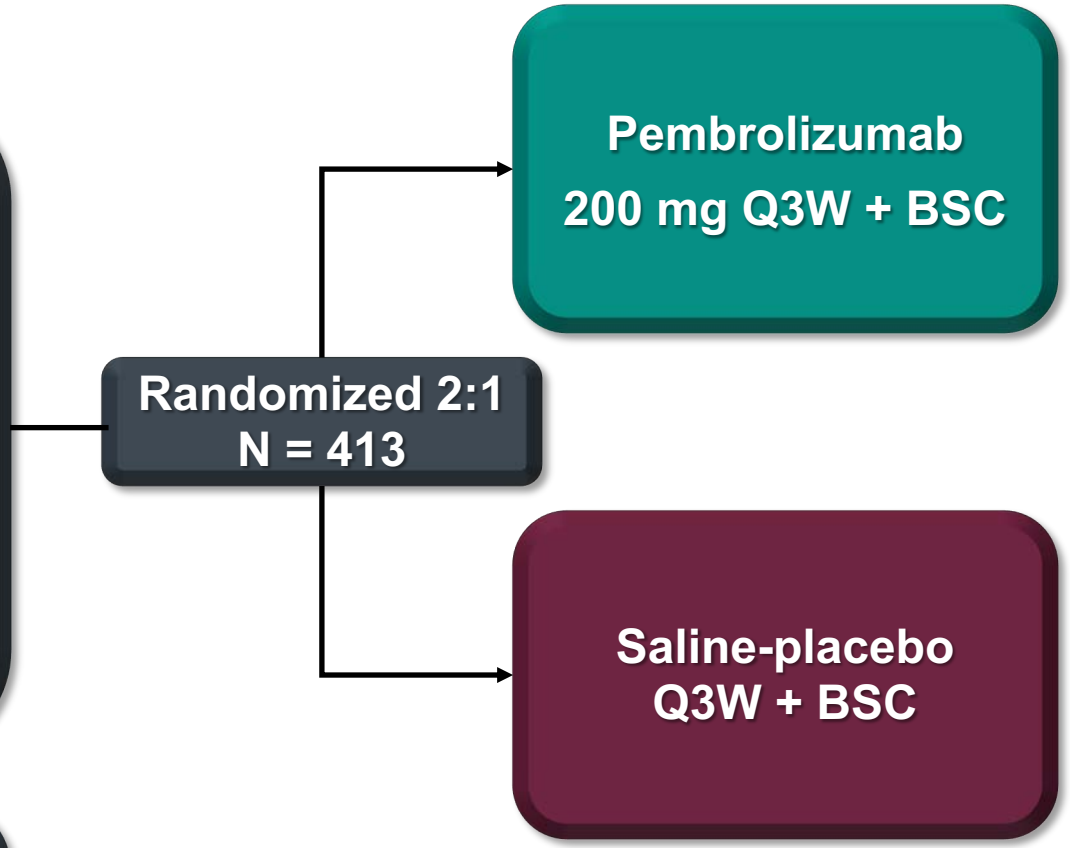
†Confirmed best response by independent central review per RECIST v1.1. ‡Based on binomial exact confidence interval method. §Subjects who had a baseline assessment by investigator review or central radiology but no post-baseline assessment on the data cutoff date including discontinuing or death before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

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

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)

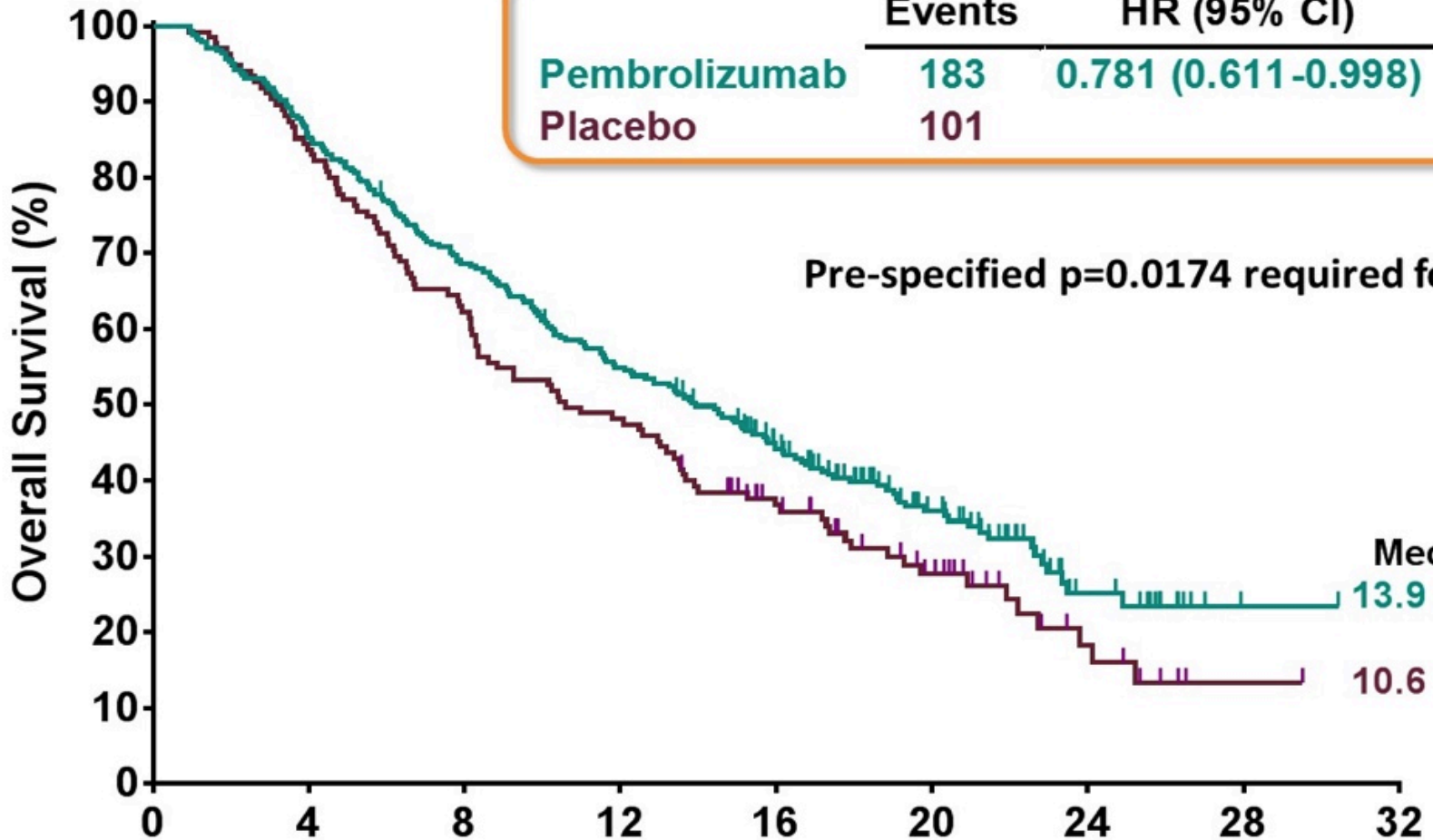


- **Enrollment May 31, 2016 – November 23, 2017**

Finn R et al, ESMO GI 2019

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)

No. at risk								
278	237	190	152	110	57	16	1	0
135	113	84	65	42	23	8	1	0

Data Cutoff: Jan 2, 2019.

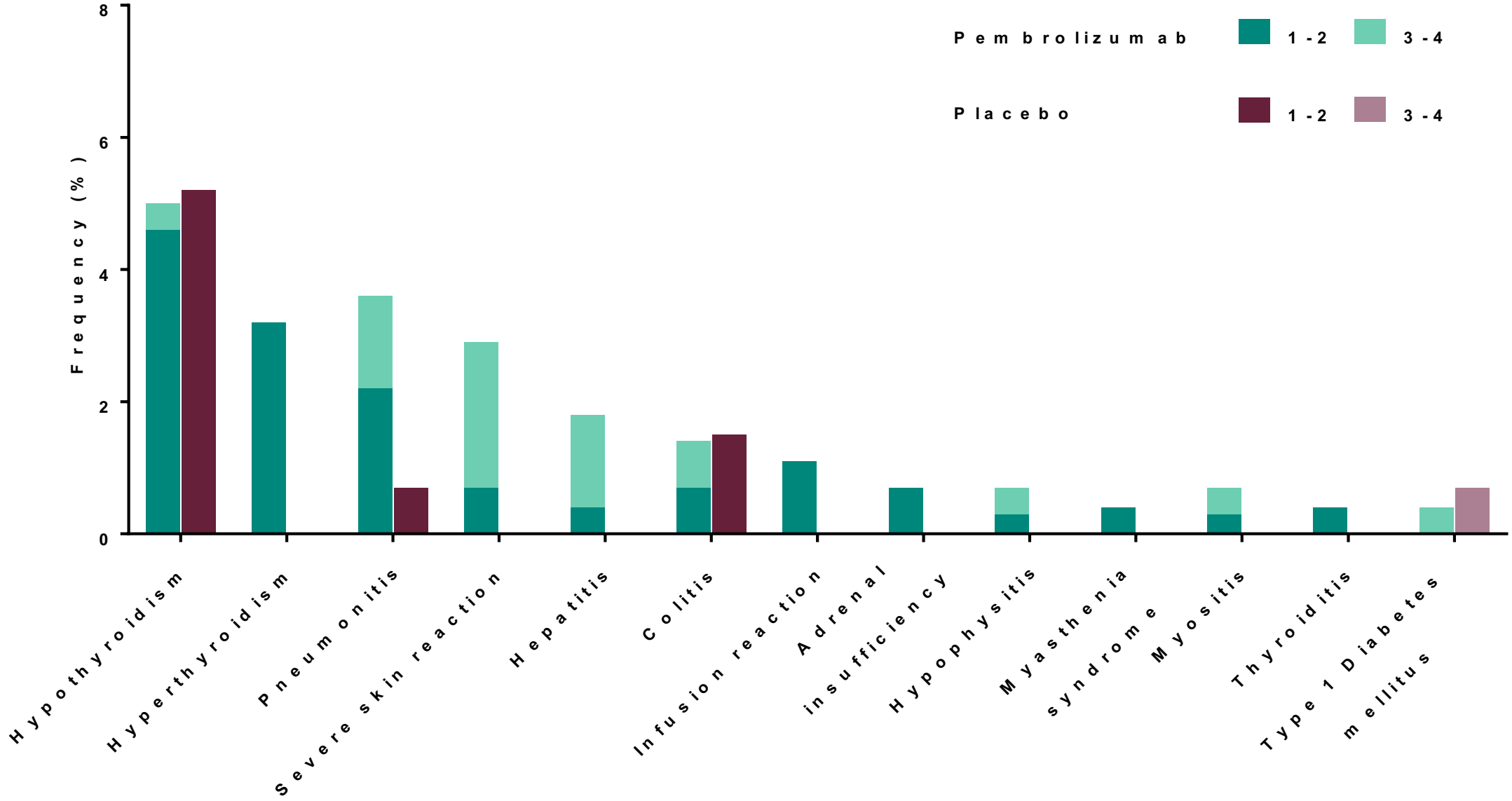
Finn R et al, ESMO GI 2019

Summary of Adverse Events

Adverse Events n (%)	Pembrolizumab N=279	Placebo N=134
≥1 All cause	269 (96.4)	121 (90.3)
Grade 3-5	147 (52.7)	62 (46.3)
Led to discontinuation	48 (17.2)	12 (9.0)
Led to treatment interruption	84 (30.1)	21 (15.7)
Led to death	7 (2.5)	4 (3.0)
Treatment-related[a]	170 (60.9)	65 (48.5)
Grade 3-4[b]	51 (18.3)	10 (7.5)
Led to discontinuation	18 (6.5)	1 (0.7)
Led to death	1 (0.4)[c]	0 (0)
Immune-mediated[d]	51 (18.3)	11 (8.2)
Grade 3-4[e]	20 (7.2)	1 (0.7)
Led to discontinuation	10 (3.6)	0 (0)
Immune-mediated hepatic-related[f]	10 (3.6)	0 (0)

[a]Attributed to treatment by the investigator. [b]One grade 5 event occurred in 1 patient (death) in the pembrolizumab group. [c]Death attributed to malignant neoplasm progression, possibly related to study treatment by investigator. [d]Any atttribution. [e]No grade 5 immune-mediated AEs reported. [f]Based on sponsor assessment; no HBV/HBC viral flares identified. Data cutoff: Jan 2, 2019.

Immune-Mediated Adverse Events and Infusion Reactions



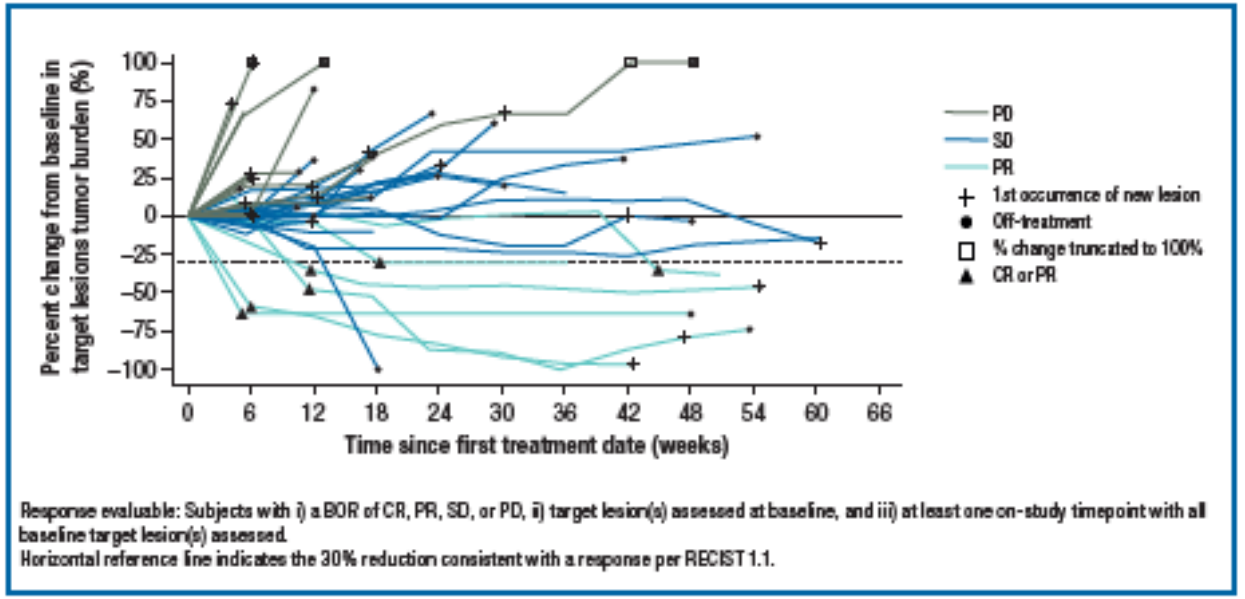
Event of any attribution in order of decreasing frequency for pembrolizumab. No grade 5 immune-mediated events reported. Data cutoff: Jan 2 , 2019

Finn R et al, ESMO GI 2019

Nivolumab in Child-Pugh B patients

n (%)	Child-Pugh B*						Child-Pugh A	
	Sorafenib-naïve n = 25		Sorafenib-treated n = 24		All subjects N = 49		Cohorts 1 & 2 N = 262	
	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
TOTAL	11 (44.0)	4 (16.0)	14 (58.3)	8 (33.3)	25 (51.0)	12 (24.5)	206 (78.6)	59 (22.5)
Skin and subcutaneous tissue disorders	8 (32.0)	2 (8.0)	3 (12.5)	0	11 (22.4)	2 (4.1)	103 (39.3)	6 (2.3)
Pruritus	5 (20.0)	0	1 (4.2)	0	6 (12.2)	0	56 (21.4)	1 (0.4)
General disorders	2 (8.0)	0	5 (20.8)	0	7 (14.3)	0	84 (32.1)	4 (1.5)
Asthenia	0	0	3 (12.5)	0	3 (6.1)	0	5 (1.9)	0
Blood and lymphatic system disorders	3 (12.0)	1 (4.0)	2 (8.3)	0	5 (10.2)	1 (2.0)	23 (8.8)	6 (2.3)
Gastrointestinal disorders	3 (12.0)	1 (4.0)	2 (8.3)	1 (4.2)	5 (10.2)	2 (4.1)	91 (34.7)	7 (2.7)
Metabolism and nutrition disorders	1 (4.0)	0	3 (12.5)	1 (4.2)	4 (8.2)	1 (2.0)	39 (14.9)	7 (2.7)
Nervous system disorders	2 (8.0)	0	1 (4.2)	0	3 (6.1)	0	22 (8.4)	0
Infections and infestations	1 (4.0)	0	1 (4.2)	0	2 (4.1)	0	5 (1.9)	0
Musculoskeletal & connective tissue disorders	1 (4.0)	0	1 (4.2)	0	2 (4.1)	0	30 (11.5)	1 (0.4)
Endocrine disorders	0	0	1 (4.2)	0	1 (2.0)	0	17 (6.5)	1 (0.4)
Eye disorders	0	0	1 (4.2)	0	1 (2.0)	0	5 (1.9)	0
Vascular disorders	1 (4.0)	0	0	0	1 (2.0)	0	7 (2.7)	0
Hepatic TRAEs								
Investigations	1 (4.0)	0	5 (20.8)	4 (16.7)	6 (12.2)	4 (8.2)	74 (28.2)	37 (14.1)
Aspartate aminotransferase increased	0	0	2 (8.3)	2 (8.3)	2 (4.1)	2 (4.1)	27 (10.3)	15 (5.7)
Alanine aminotransferase increased	0	0	1 (4.2)	0	1 (2.0)	0	26 (9.9)	10 (3.8)
Liver function test increased	0	0	1 (4.2)	0	1 (2.0)	0	1 (0.4)	1 (0.4)
Hepatobiliary disorders	0	0	3 (12.5)	3 (12.5)	3 (6.1)	3 (6.1)	7 (2.7)	1 (0.4)
Hypertransaminasemia	0	0	2 (8.3)	2 (8.3)	2 (4.1)	2 (4.1)	2 (0.8)	0
Hepatic function abnormal	0	0	1 (4.2)	1 (4.2)	1 (2.0)	1 (2.0)	NR	NR
Hyperbilirubinemia	0	0	1 (4.2)	0	1 (2.0)	0	3 (1.1)	0

	Child-Pugh B			Child-Pugh A
	Sorafenib-naïve n = 25	Sorafenib-treated n = 24	All subjects N = 49	Cohorts 1 & 2 N = 262
Objective response using RECIST v1.1, n (%)	3 (12.0)	3 (12.5)	6 (12.2)	53 (20.2)
BOR				
Complete response	0	0	0	8 (3.1)
Partial response	3 (12.0)	3 (12.5)	6 (12.2)	45 (17.2)
Stable disease	12 (48.0)	9 (37.5)	21 (42.9)	107 (40.8)
Progressive disease	7 (28.0)	8 (33.3)	15 (30.6)	88 (33.6)
Unable to determine	3 (12.0)	4 (16.7)	7 (14.3)	14 (5.3)
DCR, n (%)	15 (60.0)	12 (50.0)	27 (55.1)	160 (61.1)



Response evaluable: Subjects with i) a BOR of CR, PR, SD, or PD, ii) target lesion(s) assessed at baseline, and iii) at least one on-study timepoint with all baseline target lesion(s) assessed.
Horizontal reference line indicates the 30% reduction consistent with a response per RECIST 1.1.

Median DOR 9.9 months (1.4+-9.9)
Median OS 7.6 months

Kudo M et al, ASCO GI 2019

Summary and Conclusions

- Single agent anti PD-1 activity in second line and beyond HCC consistent across multiple phase I/II trials with durable responses
  - Nivolumab, Pembrolizumab, Camrelizumab
- Phase 3 KEYNOTE-240 of Pembrolizumab versus Placebo post sorafenib did not reach statistical significance
  - However, clinical benefit still noted
  - Attenuating circumstances: statistical design with co-primary endpoints and cross-over
- Potential factors that influence clinicians to use anti PD-1 agents post sorafenib or lenvatinib:
  - Poor tolerability of TKIs (however only RESORCE trial with regorafenib excluded patients who did not tolerate 400 mg or sorafenib for 20 days)
  - Available Child-Pugh B data with Nivolumab
  - Hope for a deep long lasting response (especially in patients who may not make it to third line therapy)