Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

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eMethods

Patients

- Patients were required to have adequate hematologic function (white blood cell count ≥2000/μL; neutrophil count ≥1500/μL; platelet count >60/L; hemoglobin ≥8.5 g/dL; prothrombin time international normalized ratio ≤2.3 or prothrombin time ≤6 seconds above control); adequate hepatic function (albumin ≥2.8 g/dL; total bilirubin ≤3 mg/dL; and aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤5 times the upper limit of the normal range); and adequate renal function (creatinine clearance >40 mL/min).
- Hepatitis B virus (HBV)–positive patients had detectable HBV surface antigen or HBV DNA and were required to be receiving antiviral therapy and have a viral load less than 100 IU/mL at screening. Hepatitis C virus (HCV)–positive patients had detectable HCV RNA or antibody and did not require antiviral therapy. Active coinfection with HBV and HCV was defined as detectable HBV surface antigen or HBV DNA, and detectable HCV RNA.

Outcomes

- Definition of key end points
  - Objective response rate: the proportion of all patients with a complete or partial response
  - Disease control rate: the proportion of patients whose best overall response was complete response, partial response, or stable disease
  - Duration of response: time from the first documented complete response or partial response to tumor progression or death from any cause
  - Overall survival: time from randomization to death from any cause
- Patient-reported health status was assessed using the 3-level version of the European Quality of Life-5 Dimensions questionnaire (EQ-5D-3L), which was completed in the local language prior to clinical activities at baseline and at designated visits during follow-up. Changes in EQ-5D visual analogue scale (VAS) and utility index (UI) scores were evaluated using descriptive analyses; UI was calculated using both US and UK value sets. Patients in arm A were compared with the combined group of arms B and C using a pre-specified mixed-model repeated-measures analysis that incorporated the baseline score as a covariate, presence of vascular invasion and/or extrahepatic spread as stratification factors, and time as a repeated measure. The minimally important difference used was 7 points for VAS and 0.08 (UK) and 0.06 (US) for UI.[1]

Statistical analysis

The sample size for each arm was decided based on safety and efficacy considerations. Sufficient follow-up for 40 patients per arm would allow a stable estimate of objective response rate (ORR), adequate safety follow-up, and information on duration of response. For ORR in the range of 20% to 40%, the maximum width of the 2-sided 95% confidence interval (CI) is 31.8%. eTable 1 summarizes the exact 95% CIs and 90% lower bound for a sample size of 40 patients per arm when observed ORRs are 20% to 40%.

Treatment summary

The percentage of nivolumab doses delayed (relative to the total number of doses received per arm) in arms A, B, and C were 11%, 10%, and 7%, respectively; the percentage of ipilimumab doses delayed in arms A, B, and C were 20%, 14%, and 14%, respectively. In most cases, the reason for a dose delay was an adverse event or not reported by the investigator. The median (range) number of nivolumab doses administered during the combination period were 4 (1-4), 4 (1-4), and 9 (1-77) in arms A, B, and C, respectively. The median (range) number of ipilimumab doses administered during the combination period were 4 (1-4), 4 (1-4), and 3 (1-26), respectively. During the nivolumab monotherapy period in arms A and B, the median (range) number of nivolumab doses were 24 (1-71) and 28 (3-62), respectively.

eTable 1. Observed Objective Response Rate with Exact 95% CI and 90% Lower Bound

Observed ORR	Exact 95% CI	90% Lower Bound
20%	9.1%-35.7%	12.0%
25%	12.7%-41.2%	16.2%
30%	16.6%-46.5%	20.5%
35%	20.6%-51.7%	24.9%
40%	24.9%-56.7%	29.4%

Abbreviations: CI, confidence interval; ORR, objective response rate.

eTable 2. Baseline Characteristics

	Arm A n = 50	Arm B n = 49	Arm C n = 49	All Patients N = 148
Median age (IQR), years	61 (54.0-67.0)	65 (56.0-67.0)	58 (47.0-65.0)	60 (52.5-66.5)
Male, No. (%)	43 (86)	37 (76)	40 (82)	120 (81)
Race, No. (%)				
White	12 (24)	20 (41)	15 (31)	47 (32)
Asian	37 (74)	27 (55)	30 (61)	94 (64)
Black	1 (2)	1 (2)	3 (6)	5 (3)
Other	0	1 (2)	1 (2)	2 (1)
BCLC stage, No. (%)[a]				
0	1 (2)	0	0	1 (1)
A	2 (4)	0	0	2 (1)
B	4 (8)	4 (8)	3 (6)	11 (7)
C	43 (86)	45 (92)	46 (94)	134 (91)
Child-Pugh class A, No. (%)	50 (100)	47 (96)	47 (96)	144 (97)
Vascular invasion, No. (%)	18 (36)	13 (27)	19 (39)	50 (34)
Extrahepatic spread, No. (%)	40 (80)	40 (82)	42 (86)	122 (82)
AFP ≥400 µg/L, No. (%)	25 (50)	18 (37)	22 (45)	65 (44)
Etiology,[b] No. (%)				
Uninfected	13 (26)	11 (22)	9 (18)	33 (22)
HBV	28 (56)	21 (43)	26 (53)	75 (51)
HCV	7 (14)	14 (29)	12 (24)	33 (22)
Prior systemic regimens, No. (%)				
0	0	1 (2)	1 (2)	2 (1)
1	35 (70)	36 (73)	37 (76)	108 (73)
2	11 (22)	5 (10)	9 (18)	25 (17)
≥3	4 (8)	7 (14)	2 (4)	13 (9)
Prior therapy, No. (%)				
Surgical resection	36 (72)	36 (73)	28 (57)	100 (68)
Radiotherapy	14 (28)	18 (37)	17 (35)	49 (33)
Local HCC treatment	29 (58)	33 (67)	29 (59)	91 (61)
Sorafenib[c]	50 (100)	48 (98)	48 (98)	146 (99)
Median duration of sorafenib therapy (IQR), months	4.8 (3.0-11.0)	3.8 (2.6-9.5)	4.2 (2.4-7.4)	4.3 (2.6-9.8)
Reason for sorafenib discontinuation, No. (%)				
Disease progression	44 (88)	41 (85)	38 (79)	123 (84)
Toxicity	5 (10)	6 (13)	10 (21)	21 (14)
Other	1 (2)	2 (4)	1 (2)	4 (3)

Arm A: nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks; arm B: nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks; arm C: nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks.
Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CRF, case report form; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.
[a] One patient classified as BCLC stage 0 in the CRF was found to have multiple liver nodules and metastatic disease upon

further review of the tumor data and so qualifies as BCLC stage C, and another patient classified as BCLC stage A in the CRF was found to have more than 1 liver nodule larger than 3 cm upon further review of the data and so qualifies as BCLC stage B.
[b] Seven patients overall were reported as having both HBV and HCV as risk factors for HCC; these patients did not have active coinfection with HBV and HCV.
[c] Data not available for 2 patients.

eTable 3. Efficacy by Baseline Hepatocellular Carcinoma (HCC) Etiology and PD-L1 Status

	Arm A n = 50	Arm B n = 49	Arm C n = 49
HCC etiology[a]			
Objective response rate,[b] No./total No. (%)			
Uninfected	4/13 (31)	1/11 (9)	0/9 (0)
HBV	9/28 (32)	6/21 (29)	8/26 (31)
HCV	2/7 (29)	6/14 (43)	5/12 (42)
Median OS (95% CI), months			
Uninfected	22.2 (8.5-NE)	11.8 (2.1-16.5)	7.4 (0.9-14.5)
HBV	22.8 (7.2-NE)	12.1 (3.9-24.2)	9.6 (6.0-NE)
HCV	14.9 (0.7-NE)	16.1 (6.5-NE)	33.0 (3.1-NE)
PD-L1 status[c]			
Objective response rate,[b] No./total No. (%)			
PD-L1 <1%	12/39 (31)	12/38 (32)	11/40 (28)
PD-L1 ≥1%	3/10 (30)	3/10 (30)	4/8 (50)
Median OS (95% CI), months			
PD-L1 <1%	22.2 (9.4-NE)	12.5 (8.0-16.5)	10.4 (6.8-33.0)
PD-L1 ≥1%	18.8 (2.5-NE)	10.2 (2.0-NE)	NE (0.6-NE)

Arm A: nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks; arm B: nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks; arm C: nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks.
Abbreviations: BICR, blinded independent central review; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NE, not evaluable; OS, overall survival; PD-L1, programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors.
[a] Seven patients overall were reported as having both HBV and HCV as risk factors for HCC; these patients did not have active coinfection with HBV and HCV.
[b] Reported by BICR using RECIST, version 1.1. Objective response rate defined as complete response + partial response.
[c] Overall PD-L1 was not quantifiable in 3 patients (PD-L1 tumor sample not available, PD-L1 not evaluable or indeterminate).

eTable 4. Overall Survival Rates

Overall survival rate, % (95% CI)	Arm A n = 50	Arm B n = 49	Arm C n = 49
12 month	61 (46-73)	56 (41-69)	51 (36-64)
18 month	52 (37-65)	30 (18-44)	47 (32-60)
24 month	48 (34-61)	30 (18-44)	42 (28-56)
30 month	44 (30-57)	28 (16-41)	40 (26-54)

eTable 5. Objective Response Rate, Best Overall Response, and Disease Control Rate for All Patients

	All patients N = 148
Objective response rate by BICR using RECIST v1.1,[a] No. (%; 95% CI)	46 (31; 24-39)
Best overall response, No. (%)	
Complete response	7 (5)
Partial response	39 (26)
Stable disease[b]	23 (16)
Progressive disease	65 (44)
Unable to determine[c]	11 (7)
Disease control rate,[d] No. (%)	72 (49)

Abbreviations: BICR, blinded independent central review; RECIST, Response Evaluation Criteria in Solid Tumors.
[a] Defined as complete response + partial response.
[b] Stable disease does not include 2 patients in arm A and 1 patient in arm B who were reported as non-complete response/non-progressive disease.
[c] Eleven patients overall did not have a scan; therefore, best overall response could not be determined
[d] Defined as complete response + partial response + stable disease + non-complete response/non-progressive disease.

eTable 6. Treatment-Related and Immune-Mediated Adverse Events

	Arm A n = 49		Arm B n = 49		Arm C n = 48	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**	**Any grade**	**Grade 3-4**
Any treatment-related adverse event,[a] No. (%)	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 (13)	2 (4)
Hypothyroidism	10 (20)	0	4 (8)	0	4 (8)	0
Fatigue	9 (18)	1 (2)	6 (12)	0	5 (10)	0
ALT increase	8 (16)	4 (8)	7 (14)	3 (6)	4 (8)	0
Lipase increased	7 (14)	6 (12)	6 (12)	3 (6)	8 (17)	4 (8)
Adrenal insufficiency	7 (14)	1 (2)	3 (6)	0	2 (4)	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
Nausea	5 (10)	0	4 (8)	0	1 (2)	0
Pyrexia	2 (4)	0	4 (8)	0	5 (10)	0
Immune-mediated adverse events requiring immune modulating medication,[b] No. (%)						
Rash	17 (35)	3 (6)	14 (29)	2 (4)	8 (17)	0
Hepatitis	10 (20)	10 (20)	6 (12)	5 (10)	3 (6)	3 (6)
Hypothyroidism	10 (20)	0	5 (10)	0	6 (13)	0
Adrenal insufficiency	9 (18)	2 (4)	3 (6)	0	3 (6)	0
Diarrhea/colitis	5 (10)	3 (6)	1 (2)	1 (2)	1 (2)	1 (2)
Pneumonitis	5 (10)	3 (6)	0	0	0	0
Hyperthyroidism	5 (10)	0	4 (8)	0	3 (6)	0
Hypophysitis	2 (4)	0	1 (2)	1 (2)	1 (2)	1 (2)

	Arm A n = 49		Arm B n = 49		Arm C n = 48	
	Any grade	**Grade 3-4**	**Any grade**	**Grade 3-4**	**Any grade**	**Grade 3-4**
Thyroiditis	1 (2)	0	3 (6)	0	2 (4)	0
Nephritis/renal dysfunction	0	0	1 (2)	0	1 (2)	1 (2)
Hypersensitivity	0	0	1 (2)	1 (2)	1 (2)	0
Diabetes mellitus	0	0	0	0	0	0
Immune-mediated AEs leading to discontinuation,[b] No. (%)						
Hepatitis	3 (6)	2 (4)	2 (4)	2 (4)	0	0
Pneumonitis	3 (6)	2 (4)	0	0	0	0
Diarrhea/colitis	2 (4)	2 (4)	0	0	0	0
Rash	0	0	1 (2)	1 (2)	0	0
Nephritis/renal dysfunction	0	0	0	0	1 (2)	1 (2)
Hypothyroidism	0	0	0	0	1 (2)	0
Adrenal insufficiency	0	0	0	0	0	0
Hyperthyroidism	0	0	0	0	0	0
Hypophysitis	0	0	0	0	0	0
Hypersensitivity	0	0	0	0	0	0
Thyroiditis	0	0	0	0	0	0
Diabetes mellitus	0	0	0	0	0	0

Arm A: nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks; arm B: nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks; arm C: nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks. MedDRA v21.1.
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MedDRA, *Medical Dictionary for Regulatory Activities*.
[a] Listed are treatment-related adverse events that occurred in at least 10% of patients in any arm, in decreasing order of frequency according to any-grade events in arm A. Includes events reported between first dose and 30 days after last dose of study therapy.
[b] Immune-mediated adverse events are specific events considered as potential immune-mediated events by investigator, regardless of causality, and, with the exception of endocrine events, are treated with immune-modulating medication. Includes events reported within 100 days of last dose. Listed in decreasing order of frequency according to any-grade events in arm A.

eTable 7. Treatment-Related Adverse Events by Baseline Disease Etiology

	Uninfected		HBV Infected		HCV Infected	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4	Any Grade	Grade 3–4
Arm A, No.	12	12	28	28	7	7
Any TRAE,[a] No. (%)	11 (92)	9 (75)	28 (100)	12 (43)	5 (71)	4 (57)
Pruritus	4 (33)	2 (17)	17 (61)	0	1 (14)	0
Diarrhea	4 (33)	2 (17)	7 (25)	0	1 (14)	0
AST increase	4 (33)	3 (25)	4 (14)	3 (11)	1 (14)	1 (14)
ALT increase	3 (25)	2 (17)	3 (11)	1 (4)	1 (14)	1 (14)
Nausea	3 (25)	0	2 (7)	0	0	0
Fatigue	2 (17)	0	3 (11)	0	4 (57)	1 (14)
Rash	2 (17)	1 (8)	10 (36)	1 (4)	1 (14)	0
Hypothyroidism	2 (17)	0	5 (18)	0	2 (29)	0
Lipase increased	2 (17)	2 (17)	4 (14)	3 (11)	1 (14)	1 (14)
Arthralgia	2 (17)	0	1 (4)	0	0	0
Adrenal insufficiency	1 (8)	1 (8)	6 (21)	0	0	0
Arm B	11	11	21	21	14	14
Any TRAE,[a] No. (%)	7 (64)	2 (18)	14 (67)	5 (24)	11 (79)	7 (50)
Pruritus	4 (36)	0	8 (38)	0	3 (21)	0
Diarrhea	2 (18)	0	1 (5)	0	3 (21)	1 (7)
Fatigue	2 (18)	0	1 (5)	0	3 (21)	0
Rash	2 (18)	1 (9)	5 (24)	0	4 (29)	1 (7)
Decreased appetite	2 (18)	0	1 (5)	0	1 (7)	0
AST increase	1 (9)	0	5 (24)	2 (10)	3 (21)	2 (14)
ALT increase	0	0	3 (14)	1 (5)	4 (29)	2 (14)
Arm C	9	9	26	26	11	11
Any TRAE,[a] No. (%)	8 (89)	3 (33)	19 (69)	5 (19)	10 (91)	5 (45)
Pruritus	2 (22)	0	9 (35)	0	2 (18)	0
Blood bilirubin increased	2 (22)	0	0	0	0	0
Diarrhea	1 (11)	0	5 (19)	0	1 (9)	0

	Uninfected		HBV Infected		HCV Infected	
	Any Grade	**Grade 3–4**	**Any Grade**	**Grade 3–4**	**Any Grade**	**Grade 3–4**
AST increase	1 (11)	0	4 (15)	1 (4)	1 (9)	1 (9)
Lipase increased	1 (11)	1 (11)	5 (19)	1 (4)	1 (9)	1 (9)
Fatigue	0	0	3 (12)	0	2 (18)	0
Rash	0	0	4 (15)	0	4 (36)	0
Hypothyroidism	0	0	2 (8)	0	2 (18)	0
Pyrexia	0	0	2 (8)	0	2 (18)	0

Arm A: nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks; arm B: nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks; arm C: nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks. MedDRA version 21.1.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MedDRA, *Medical Dictionary for Regulatory Activities*; TRAE, treatment-related adverse event.
[a] Listed are treatment-related adverse events that occurred in at least 15% of patients in the treatment arm, in decreasing order of frequency according to any-grade events in arm A. Includes events reported between first dose and 30 days after last dose of study therapy. Seven patients overall were reported as having both HBV and HCV as risk factors for HCC; these patients did not have active coinfection with HBV and HCV.

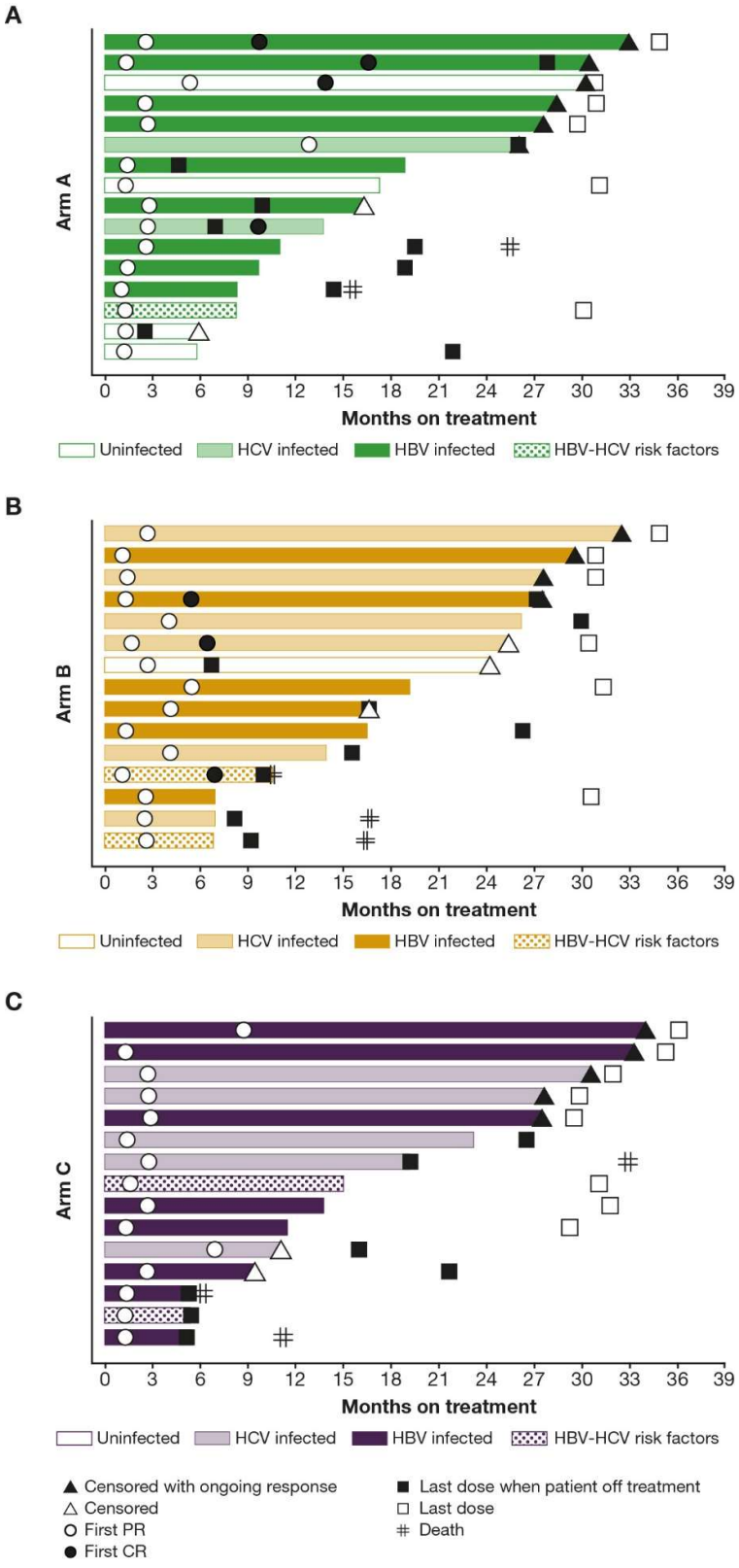
eTable 8. Summary of Patients With an Any-Grade Immune-Mediated Adverse Event Rechallenged With Nivolumab or Ipilimumab

Category	Rechallenge	Arm A n = 49	Arm B n = 49	Arm C n = 48
Rash	Patients rechallenged, No./total No. (%)	16/17 (94)	11/14 (79)	8/8 (100)
	Positive, No. (%)	0	0	0
	Negative, No. (%)	9 (56)	8 (73)	5 (63)
Hepatitis	Patients rechallenged, No./total No. (%)	6/10 (60)	4/6 (67)	2/3 (67)
	Positive, No. (%)	0	0	0
	Negative, No. (%)	4 (67)	3 (75)	0
Hypothyroidism	Patients rechallenged, No./total No. (%)	7/10 (70)	5/5 (100)	5/6 (83)
	Positive, No. (%)	0	0	0
	Negative, No. (%)	1 (14)	0	2 (40)
Adrenal insufficiency	Patients rechallenged, No./total No. (%)	8/9 (89)	2/3 (67)	2/3 (67)
	Positive, No. (%)	0	0	0
	Negative, No. (%)	1 (13)	1 (50)	1 (50)
Hyperthyroidism	Patients rechallenged, No./total No. (%)	4/5 (80)	3/4 (75)	1/3 (33)
	Positive, No. (%)	0	0	0
	Negative, No. (%)	2 (50)	2 (67)	0
Diarrhea/colitis	Patients rechallenged, No./total No. (%)	3/5 (60)	1/1 (100)	1/1 (100)
	Positive, No. (%)	0	0	0
	Negative, No. (%)	3 (100)	1 (100)	1 (100)
Pneumonitis	Patients rechallenged, No./total No. (%)	2/5 (40)	0/0	0/0
	Positive, No. (%)	0	0	0
	Negative, No. (%)	1 (50)	0	0
Hypophysitis	Patients rechallenged, No./total No.	2/2 (100)	0/1	1/1 (100)

Category	Rechallenge	Arm A n = 49	Arm B n = 49	Arm C n = 48
	(%)			
	Positive, No. (%)	0	0	0
	Negative, No. (%)	0	0	0
Thyroiditis	Patients rechallenged, No./total No. (%)	1/1 (100)	3/3 (100)	1/2 (50)
	Positive, No. (%)	0	0	0
	Negative, No. (%)	1 (100)	2 (67)	1 (100)
Diabetes mellitus	Patients rechallenged, No./total No. (%)	0	0	0
	Positive, No. (%)	0	0	0
	Negative, No. (%)	0	0	0
Nephritis/renal dysfunction	Patients rechallenged, No./total No. (%)	0	1/1 (100)	0/1
	Positive, No. (%)	0	0	0
	Negative, No. (%)	0	1 (100)	0
Hypersensitivity	Patients rechallenged, No./total No. (%)	0	1/1 (100)	1/1 (100)
	Positive, No. (%)	0	0	0
	Negative, No. (%)	0	1 (100)	1 (100)

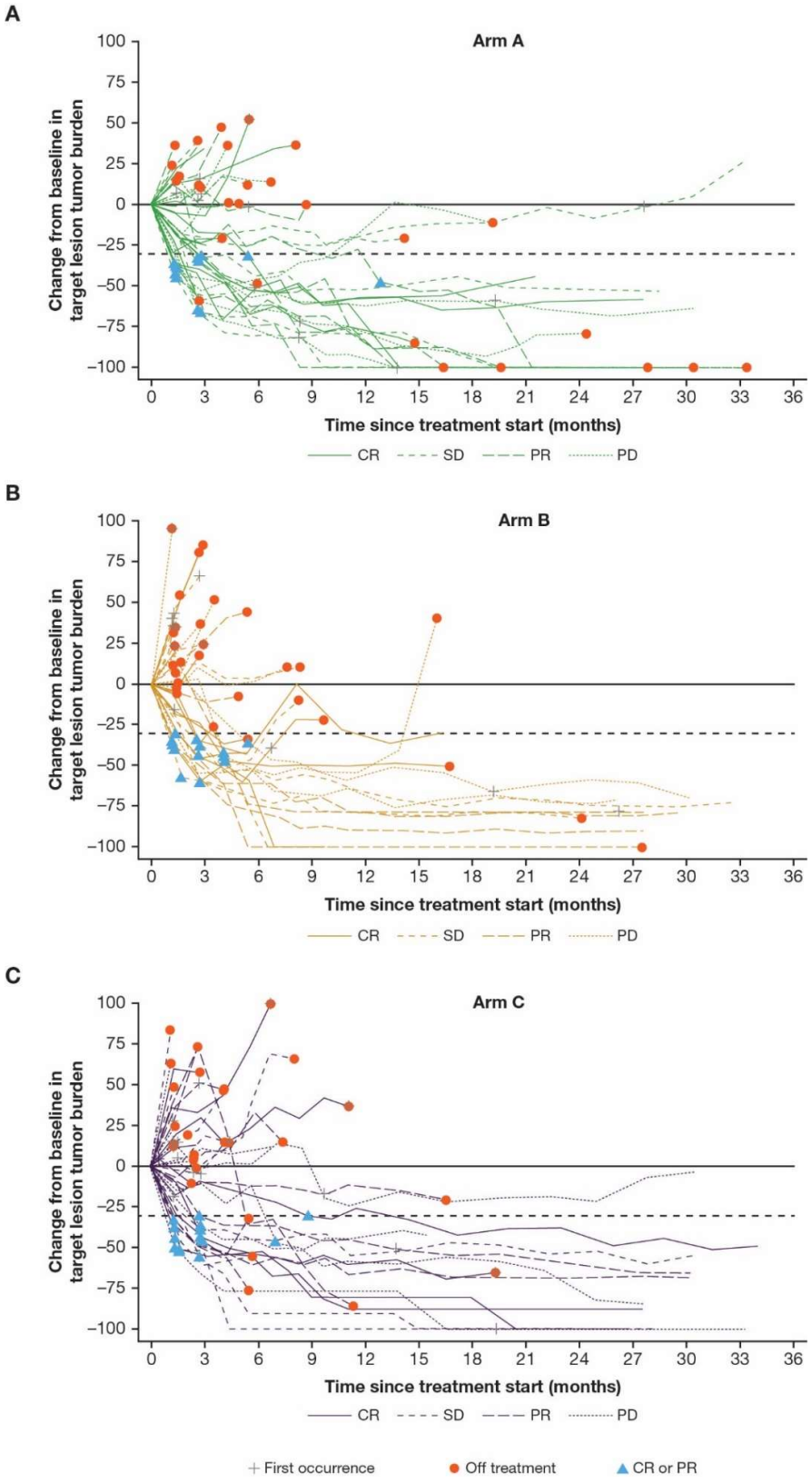
A rechallenge is considered to have occurred when the last nivolumab or ipilimumab infusion was administered after the onset of an immune-mediated adverse event. A rechallenge was considered as a positive rechallenge if the rechallenge occurred after adverse event resolution and the event recurred on or post rechallenge. A rechallenge was considered as a negative rechallenge if the rechallenge occurred after adverse event resolution and the event did not recur. Immune-mediated adverse events are specific events considered as potential immune-mediated events by investigator, regardless of causality, and, with the exception of endocrine events, treated with immune-modulating medication. Includes events reported within 100 days of last dose. Listed in decreasing order of frequency according to any-grade events in arm A.

eFigure 1. Time to Response and Duration of Response by Treatment Arm



Panel A shows the duration of response (months) for the patients who achieved a complete or partial response to arm A: nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks; panel B shows arm B: nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks; panel C shows arm C: nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks. Overall, 7 patients were reported as having both HBV and HCV as risk factors for HCC; these patients did not have active coinfection with HBV and HCV.
Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

eFigure 2. Spider Plots of Change in Tumor Burden From Baseline by Treatment Arm

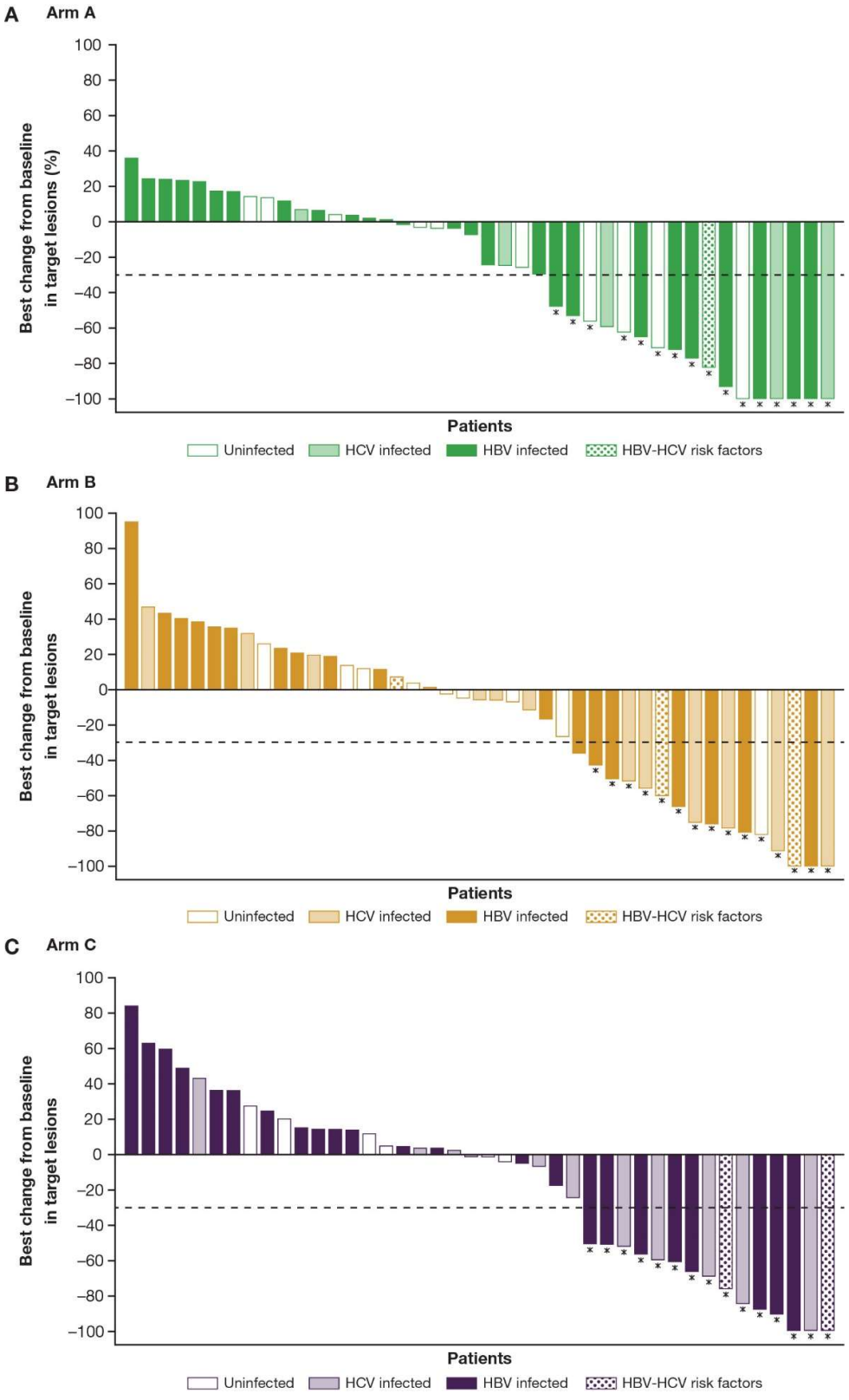


Panel A shows arm A: nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks; Panel B shows arm B: nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks; Panel C shows arm C: nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks. Response evaluable patients with a best overall response of complete response, partial response, stable disease,[a] or progressive disease; target lesion(s) assessed at baseline; and at least one on-study timepoint with all baseline target lesion(s) assessed. Horizontal reference line indicates 30% reduction consistent with a response according to RECIST, version 1.1.

Abbreviations: BICR, blinded independent central review; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

[a] Stable disease was reported as non-complete response/non-progressive disease in two patients in arm A and one patient in arm B. These were patients who only had non-target lesions at baseline and did not meet the definition of stable disease by BICR.

eFigure 3. Waterfall Plots of Percentage Change in Tumor Burden From Baseline by Treatment Arm



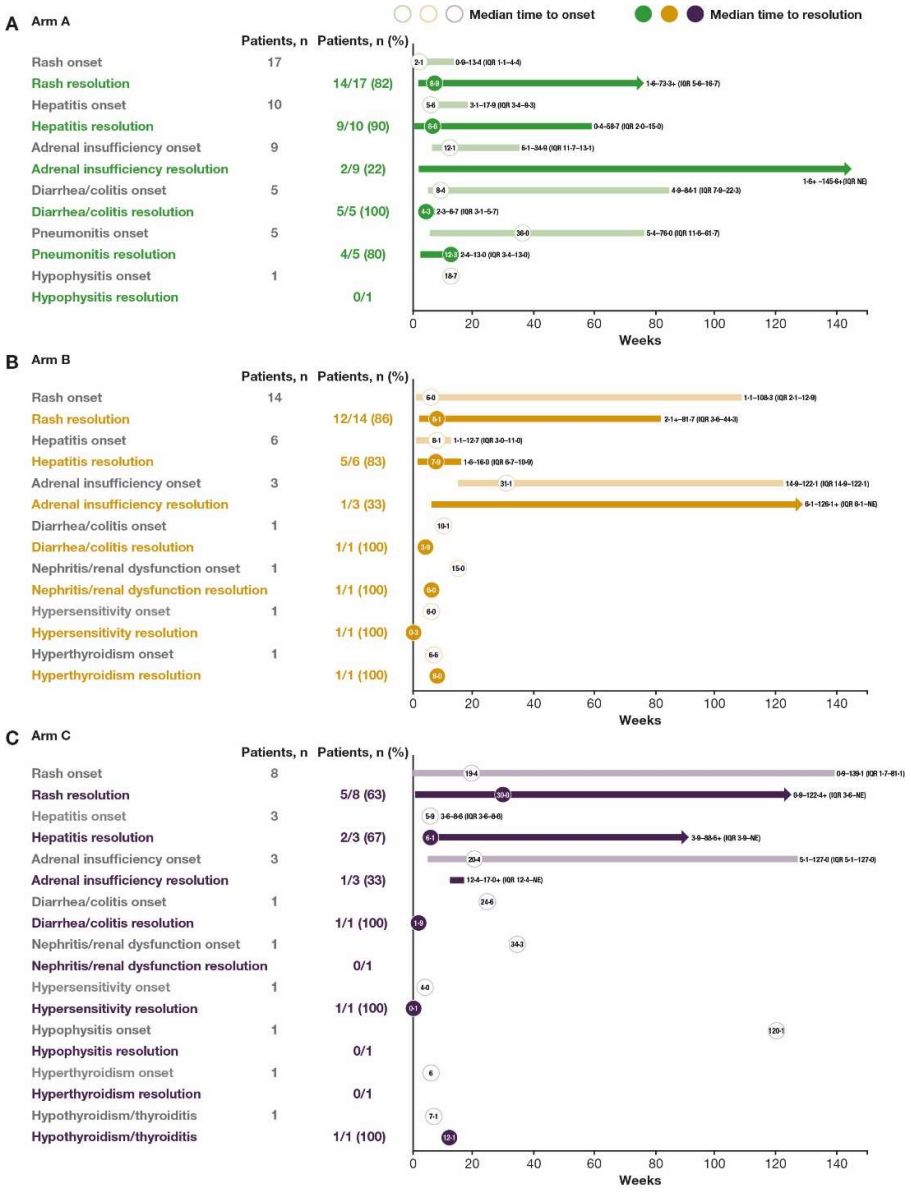
Panel A shows arm A: nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks; panel B shows arm B: nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks; panel C shows arm C: nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks. Response evaluable patients with a best overall response of complete response, partial response, stable disease,[a] or progressive disease; target lesion(s) assessed at baseline; and at least 1 on-study timepoint with all baseline target lesion(s) assessed. Negative/positive values represent maximum tumor reduction or minimum tumor increase, respectively. Best change from baseline is based on evaluable target lesion measurements up to progression or start of subsequent therapy. Horizontal reference line indicates 30% reduction consistent with a response per RECIST v1.1. Overall, 7 patients were reported as having both HBV and HCV as risk factors for HCC; these patients did not have active coinfection with HBV and HCV.

Abbreviations: BICR, blinded independent central review; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV; hepatitis C virus; RECIST; Response Evaluation Criteria in Solid Tumors.

* BICR-confirmed responders.

[a] Stable disease was reported as non-complete response/non-progressive disease in 2 patients in arm A and 1 patient in arm B. These were patients who only had non-target lesions at baseline and did not meet the definition of stable disease by BICR.

eFigure 4. Time to Onset (Median, Range [IQR]) and Time to Resolution (Median, Range [IQR]) of Immune-Mediated Adverse Events by Treatment Arm



Panel A shows arm A: nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks; Panel B shows arm B: nivolumab 3 mg/kg + ipilimumab 1 mg/kg every 3 weeks (4 doses) followed by nivolumab 240 mg intravenously every 2 weeks; Panel C shows arm C: nivolumab 3 mg/kg every 2 weeks + ipilimumab 1 mg/kg every 6 weeks. Immune-mediated adverse events are specific events considered as potential immune-mediated events by investigator, regardless of causality, treated with immune-modulating medication. Time to onset measured from treatment initiation and time to resolution measured from onset of immune-mediated adverse event. Includes events that occurred in >1 patient, reported within 100 days of last dose.
Abbreviations: IQR, interquartile range; NE, not estimable.

Reference

1. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes*. 2007;5:70.