SUPPLEMENTARY APPENDIX

This appendix has been provided by the authors to give readers additional information about their work. Supplement to: Melero I, Yau T, Kang Y-K, et al. Nivolumab plus ipilimumab combination therapy in patients with advanced hepatocellular carcinoma: 5-year results from CheckMate 040

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Additional Methods

Definitions of terms

- Disease control rate: proportion of all treated patients with a best overall response of complete response (CR), partial response (PR) or stable disease (SD) (including non-CR/non-PD per blinded independent central review)
- Overall survival (OS): time from first dose to death from any cause
- Progression-free survival: time from first dose to the first radiographic progression or death due to any cause
- Time to progression: time from first dose to the first radiographic progression
- Time to response (TTR): time from first dose to the first confirmed CR or PR. TTR is derived for responders only

Biomarker methods

- For the analysis of biomarkers, peripheral blood samples were collected prior to initiation of therapy and at selected timepoints during treatment. Tumor specimens were obtained at baseline to characterize immune cell populations and expression of programmed death ligand 1 (PD-L1)
- Serologic testing was completed centrally, while alpha-fetoprotein (AFP) was measured in blood samples locally using a standard laboratory test. 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

- PD-L1 expression was determined using Dako 28-8 pharmDx IHC assay (Santa Clara, CA, USA). Tumor cell PD-L1 expression was defined as the percentage of viable tumor cells with partial or complete membrane staining for PD-L1 in a minimum of 100 viable tumor cells
- Cluster of differentiation 8 (CD8) immunohistochemistry (clone C8/144B) was performed by Mosaic Laboratories (Lake Forest, CA, USA) on pre-treatment fresh or archival tumor samples; CD8 levels were scored as the percentage of CD8-positive cells out of all nucleated cells. The median cutoff of 5.7% was based on CD8 data across the three treatment arms. *P* values were calculated by log-rank test.
- Statistical methods for comparison of baseline characteristics that impact OS: Due to the descriptive nature of these analyses, no association tests were conducted

Additional Results

Table S1. Subsequent cancer therapy

Patients,[a] *n* (%)	Arm A NIVO1 + IPI3 Q3W (*n* = 50)	Arm B NIVO3 + IPI1 Q3W (*n* = 49)	Arm C NIVO3 Q2W + IPI1 Q6W (*n* = 49)
Any subsequent therapy	20 (40)	22 (45)	25 (51)
Subsequent radiotherapy	5 (10)	8 (16)	9 (18)
Subsequent surgery	0	3 (6)	7 (14)
Subsequent systemic therapy	15 (30)	15 (31)	16 (33)
Atezolizumab	1 (2)	1 (2)	0
Bevacizumab	2 (4)	2 (4)	2 (4)
BLU 554	1 (2)	2 (4)	0
BLU 554 1101	0	1 (2)	0
BMS 986183	0	1 (2)	0
Cabozantinib/placebo	0	0	1 (2)
Cabozantinib	2 (4)	0	0
Capecitabine	3 (6)	3 (6)	5 (10)
Cisplatin	1 (2)	1 (2)	3 (6)
Cyclophosphamide	0	1 (2)	0
Doxorubicin	1 (2)	1 (2)	6 (12)
Enzalutamide/placebo	1 (2)	0	0
Epirubicin	0	1 (2)	1 (2)
Etoposide	0	3 (6)	1 (2)
Fluorouracil	4 (8)	3 (6)	3 (6)

Gemcitabine	1 (2)	0	1 (2)
H3B-6527 clinical trial	0	0	1 (2)
Ipilimumab	0	1 (2)	0
Lenvatinib	3 (6)	3 (6)	1 (2)
Leucovorin	0	0	1 (2)
NIS 793 & PDR001	1 (2)	0	0
NIS 793	0	0	1 (2)
Nivolumab	3 (6)	0	0
Oxaliplatin	5 (10)	4 (8)	4 (8)
Paclitaxel	1 (2)	0	1 (2)
PDR001	0	0	1 (2)
Pembrolizumab	0	1 (2)	0
Ramucirumab	0	0	1 (2)
Regorafenib	3 (6)	5 (10)	1 (2)
Sorafenib	2 (4)	0	2 (4)
Tegfur/Uracil	0	0	1 (2)
Thalidomide	0	1 (2)	1 (2)
Subsequent non-systemic treatment for HCC (local only)	4 (8)	10 (20)	4 (8)

[a]Patients may have received more than one type of subsequent therapy.

HCC, hepatocellular carcinoma; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks.

Table S2. Efficacy by baseline characteristics in all randomized patients

Baseline characteristics	ORR,[a,b] *n/n* (%) [95% CI]			Median OS (95% CI), months		
	Arm A NIVO1 + IPI3 Q3W (*n* = 50)	**Arm B NIVO3 + IPI1 Q3W (*n* = 49)**	**Arm C NIVO3 Q2W + IPI1 Q6W (*n* = 49)**	**Arm A NIVO1 + IPI3 Q3W (*n* = 50)**	**Arm B NIVO3 + IPI1 Q3W (*n* = 49)**	**Arm C NIVO3 Q2W + IPI1 Q6W (*n* = 49)**
HCC etiology[c]						
Uninfected	4/13 (31) [9–61]	1/11 (9) [0.2–41]	0/9 (0) [0–34]	21.9 (8.5–61.8)	11.8 (2.1–16.5)	7.4 (0.9–14.5)
HCV	2/7 (29) [4–71]	6/14 (43) [18–71]	5/12 (42) [15–72]	14.9 (0.7–NE)	16.1 (6.5–NE)	30.9 (3.1–62.8)
HBV	9/28 (32) [16–52]	6/21 (29) [11–52]	8/26 (31) [14–52]	22.8 (7.2–46.1)	12.1 (3.9–24.2)	9.6 (6.0–26.4)
Tumor cell PD-L1 expression[d,e]						
≥ 1%	3/10 (30) [7–65]	3/10 (30) [7–65]	4/8 (50) [16–84]	18.8 (2.5–59.3)	10.2 (2.0–33.0)	31.2 (0.6–NE)
< 1%	12/39 (31) [17–48]	12/38 (32) [18–49]	11/40 (28) [15–44]	21.9 (9.4–46.1)	12.5 (8.0–16.5)	10.4 (6.8–27.8)
AFP levels						
AFP ≥ 400 µg/L	7/25 (28) [12–49]	6/18 (33) [13–59]	5/22 (23) [8–45]	10.8 (7.2–22.8)	12.3 (3.6–16.7)	9.1 (3.1–31.2)
AFP < 400 µg/L	9/25 (36) [18–58]	9/31 (29) [14–48]	10/27 (37) [19–58]	46.1 (16.4–61.8)	13.0 (7.6–16.5)	14.5 (7.4–35.9)

AFP, alpha-fetoprotein; BICR, blinded independent central review; CI, confidence interval; CR, complete response; CRF, case report form; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NE, not evaluable; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks.

[a]Per BICR assessment.

[b]Objective response was defined as the proportion of patients with a best overall response of CR + PR.

[c]Seven patients (arm A: *n* = 2; arm B: *n* = 3; arm C: *n* = 2) had both HBV and HCV etiology in their CRF.

[d]Tumor cell PD-L1 expression levels were determined from archival or fresh biopsies.

[e]PD-L1 was not quantifiable in three patients (one in each arm; PD-L1 tumor samples not evaluable or indeterminate).

Table S3. Baseline characteristics comparison: OS at < 1 year versus ≥ 3 years

Characteristic		Arm A NIVO1 + IPI3 Q3W		Arm B NIVO3 + IPI1 Q3W		Arm C NIVO3 Q2W + IPI1 Q6W	
		OS < 1 year (*n* = 20)[a]	OS ≥ 3 years (*n* = 18)[a]	OS < 1 year (*n* = 23)[a]	OS ≥ 3 years (*n* = 12)[a]	OS < 1 year (*n* = 24)[a]	OS ≥ 3 years (*n* = 14)[a]
Median age (range), years		57.5 (38.0–73.0)	62.5 (43.0–80.0)	63.0 (41.0–80.0)	65.0 (45.0–74.0)	54.5 (32.0–74.0)	60.0 (37.0–75.0)
Sex	Female	3 (15)	2 (11)	4 (17)	6 (50)	6 (25)	1 (7)
	Male	17 (85)	16 (89)	19 (83)	6 (50)	18 (75)	13 (93)
Race[b]	Asian	15 (75)	13 (72)	14 (61)	6 (50)	16 (70)	9 (64)
	Black/Other	0	0	0	0	2 (9)	1 (7)
	White	5 (25)	5 (28)	9 (39)	6 (50)	5 (22)	4 (29)
BCLC stage	A	0	2 (11)	0	0	0	0
	B	2 (10)	1 (6)	2 (9)	1 (8)	1 (4)	1 (7)
	C	18 (90)	15 (83)	21 (91)	11 (92)	23 (96)	13 (93)
Child-Pugh score	5	16 (80)	14 (78)	17 (74)	10 (83)	13 (54)	10 (71)
	6	4 (20)	4 (22)	5 (22)	1 (8)	9 (38)	4 (29)
	> 6	0	0	1 (4)	1 (8)	2 (8)	0
AFP	< 400 µg/L	6 (30)	14 (78)	15 (65)	7 (58)	12 (50)	8 (57)
	≥ 400 µg/L	14 (70)	4 (22)	8 (35)	5 (42)	12 (50)	6 (43)
Tumor cell PD-L1	< 1%	17 (85)	14 (78)	17 (74)	10 (83)	20 (83)	11 (79)
	≥ 1%	3 (15)	3 (17)	5 (22)	2 (17)	3 (13)	3 (21)
	Not evaluable	0	1 (6)	1 (4)	0	1 (4)	0
Vascular invasion	No	14 (70)	11 (61)	16 (70)	10 (83)	12 (50)	9 (64)
	Yes	6 (30)	7 (39)	7 (30)	2 (17)	12 (50)	5 (36)
Extrahepatic spread	No	2 (10)	5 (28)	3 (13)	3 (25)	2 (8)	4 (29)
	Yes	18 (90)	13 (72)	20 (87)	9 (75)	22 (92)	10 (71)
HCC etiology	HCV positive	3 (15)	2 (11)	5 (22)	6 (50)	2 (8)	4 (29)
	HBV positive	14 (70)	9 (50)	10 (43)	5 (42)	15 (63)	7 (50)
	HCV–HBV positive	0	2 (11)	1 (4)	0	0	2 (14)
	Uninfected	3 (15)	5 (28)	7 (30)	1 (8)	7 (29)	1 (7)

Data are *n* (%) unless otherwise noted.

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; OS, overall survival; PD-L1, programmed death ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks.

[a]Percentages are calculated based on number of patients with the OS outcome, not the overall population.

[b]One patient with unknown race was not included in NIVO3 Q2W + IPI1 Q6W OS < 1 year.

Table S4. Subsequent therapies in long-term survivors (overall survival ≥3 years)

Patients,[a] *n* (%)	Arm A NIVO1 + IPI3 Q3W (*n* = 18)	Arm B NIVO3 + IPI1 Q3W (*n* = 12)	Arm C NIVO3 Q2W + IPI1 Q6W (*n* = 14)
Any subsequent therapy	9 (50)	6 (50)	8 (57)
Subsequent systemic therapy	6 (33)	6 (50)	4 (29)
Monotherapy[b]	6 (33)	8 (67)	5 (36)
Immunotherapy	1 (6)	0	0
Combination therapy[c]	3 (17)	4 (33)	1 (7)
Immunotherapy-based regimen	2 (11)	1 (8)	0

IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks.

[a]Patients may have received more than one type of subsequent therapy, therefore percentages may not add up.

[b]Monotherapy includes capecitabine, regorafenib, nivolumab, lenvatinib, cabozantinib, thalidomide, etoposide, doxorubicin and ramucirumab.

[c]Combination therapies include bevacizumab + nivolumab, capecitabine + oxaliplatin, atezolizumab + bevacizumab, fluorouracil + oxaliplatin, bevacizumab + capecitabine + oxaliplatin, and cisplatin + doxorubicin + etoposide + fluorouracil.

Table S5. Dose intensity and exposure in all treated patients

	Arm A NIVO1 + IPI3 Q3W (*n* = 49)	Arm B NIVO3 + IPI1 Q3W (*n* = 49)	Arm C NIVO3 Q2W + IPI1 Q6W (*n* = 48)
Whole treatment period			
Duration of treatment, median (range), months	5.1 (0 to 66+)	2.3 (0 to 63+)	4.0 (0 to 67+)
Number of long term survivors			
Nivolumab + ipilimumab combination period			
Number of nivolumab doses received	4.0 (1–4)	4.0 (1–4)	9.0 (1–146)
Duration of nivolumab treatment, months	2.1 (0–5)	2.1 (0–4)	4.0 (0–67)
Cumulative nivolumab dose, mg/kg	4.0 (1–10)	11.7 (3–13)	27.9 (3–438)
Relative dose intensity of nivolumab ≥ 90%, *n* (%)	33 (67)	42 (86)	35 (73)
Number of ipilimumab doses received	4.0 (1–4)	4.0 (1–4)	3.0 (1–49)
Duration of ipilimumab treatment, months	2.1 (0–5)	2.0 (0–3)	3.2 (0–67)
Cumulative ipilimumab dose, mg/kg	12.0 (3–13)	3.9 (1–4)	3.1 (1–49)
Relative dose intensity of ipilimumab ≥ 90%, *n* (%)	33 (67)	42 (86)	40 (83)
Patients completing 4 doses of ipilimumab, *n* (%)	33 (67)	25 (51)	NA
Nivolumab monotherapy period			
Patients entering monotherapy phase, *n* (%)	31 (63)	22 (45)	NA
Number of nivolumab doses received	24.0 (1–138)	27.5 (3–130)	NA
Duration of nivolumab treatment, months	10.8 (0–63)	12.6 (1–60)	NA
Cumulative nivolumab dose, mg	5760.0 (240–33120)	6600.0 (720–31200)	NA

Data are median (range) unless otherwise noted.

IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NA, not applicable; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks.

Table S6. Summary of all deaths during the study

Patients,[a] *n* (%)	Arm A NIVO1 + IPI3 Q3W (*n* = 49)	Arm B NIVO3 + IPI1 Q3W (*n* = 49)	Arm C NIVO3 Q2W + IPI1 Q6W (*n* = 48)
Deaths	33 (67)	38 (78)	39 (81)
Primary reason for death[b]			
Disease progression	29 (59)	32 (65)	35 (73)
Treatment-related adverse events	1 (2)	0	0
Other[c]/unknown	3 (6)	6 (12)	4 (8)

IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks.

[a]Deaths were reported regardless of timeframe.

[b]Percentages may not add up due to rounding.

[c]Other causes of death include one case each of acute respiratory failure in arm A; sepsis and fungal infection in arm B; and possible biloma infection, hemoperitoneum, and respiratory failure in arm C.

Table S7. Summary of immune-mediated adverse events in all treated patients

n (%)[a]	Arm A NIVO1 + IPI3 Q3W (*n* = 49)		Arm B NIVO3 + IPI1 Q3W (*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
IMAEs requiring immune-modulating medications						
Rash	17 (35)	3 (6)	15 (31)	2 (4)	11 (23)	0
Hypothyroidism/thyroiditis	12 (24)	0	7 (14)	0	8 (17)	0
Hypothyroidism	11 (22)	0	5 (10)	0	6 (13)	0
Hepatitis	10 (20)	10 (20)	7 (14)	6 (12)	4 (8)	3 (6)
Adrenal insufficiency	5 (10)	2 (4)	1 (2)	0	3 (6)	0
Pneumonitis	5 (10)	3 (6)	0	0	0	0
Diarrhea/colitis	5 (10)	3 (6)	1 (2)	1 (2)	2 (4)	1 (2)
Hyperthyroidism	4 (8)	0	4 (8)	0	3 (6)	0
Hypophysitis	2 (4)	0	1 (2)	1 (2)	1 (2)	1 (2)
Thyroiditis	1 (2)	0	3 (6)	0	2 (4)	0
Nephritis and renal dysfunction	1 (2)	1 (2)	1 (2)	0	1 (2)	1 (2)
Hypersensitivity	0	0	1 (2)	1 (2)	1 (2)	0
IMAEs leading to discontinuation						
Rash	0	0	1 (2)	1 (2)	0	0
Hepatitis	3 (6)	2 (4)	2 (4)	2 (4)	0	0
Adrenal insufficiency	0	0	0	0	1 (2)	0
Pneumonitis	3 (6)	2 (4)	0	0	0	0
Diarrhea/colitis	2 (4)	2 (4)	0	0	0	0
Nephritis and renal dysfunction	0	0	0	0	1 (2)	1 (2)

IMAE, immune-mediated adverse events; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks.

[a]IMAEs are those adverse events assessed as potentially immune-mediated by the investigator, occurring within 100 days after the last dose of study treatment regardless of causality, and, with the exception of endocrine events, treated with immune-modulating medication.

Table S8. Time to onset and resolution of immune-mediated adverse events in all treated patients

IMAEs[a–c]	Arm A NIVO1 + IPI3 Q3W (*n* = 49)				Arm B NIVO3 + IPI1 Q3W (*n* = 49)				Arm C NIVO3 Q2W + IPI1 Q6W (*n* = 48)			
	Any grade/ grade 3/4 *n* (%)/ *n* (%)	TTO, weeks[d] Median (range)	TTR,[d–h] weeks Median (range)	Patients with resolution[g,h] *n* (%)	Any grade/ grade 3/4 *n* (%)/ *n* (%)	TTO, weeks[d] Median (range)	TTR,[d–h] weeks Median (range)	Patients with resolution[g,h] *n* (%)	Any grade/ grade 3/4 *n* (%)/ *n* (%)	TTO, weeks[d] Median (range)	TTR,[d–h] weeks Median (range)	Patients with resolution[g,h] *n* (%)
Rash	17 (35)/ 3 (6)	2.1 (0.9–13.4)	8.9 (1.6–97.1+)	14 (82)	15 (31)/ 2 (4)	5.9 (1.1–108.3)	10.2 (2.1+ to 81.7)	12 (80)	11 (23)/0	69.1 (0.4–194.3)	39.1 (0.9–237.9+)	7 (64)
Hypothyroidism	11 (22)/0	18.0 (5.9–73.1)	NR (3.0–237.3+)	3 (27)	5 (10)/0	10.9 (7.0–19.0)	NR (6.1+ to 256.1+)	0	6 (13)/0	33.6 (8.0–101.6)	NR (1.7–227.9+)	2 (33)
Hepatitis	10 (20)/ 10 (20)	5.6 (3.1–17.9)	6.6 (0.4–58.7)	9 (90)	7 (14)/ 6 (12)	7.1 (1.1–12.3)	7.9 (1.6–16.0)	5 (71)	4 (8)/3 (6)	7.2 (3.6–148.1)	19.0 (6.1–88.6+)	3 (75)
Adrenal insufficiency	5 (10)/ 2 (4)	12.9 (9.0–34.9)	NR (1.1–268.1+)	1 (20)	1 (2)/0	31.1 (31.1–31.1)	NR (238.0+ to 238.0+)	0	3 (6)/0	58.2 (5.1–233.9)	NR (5.4–171.9+)	2 (50)
Pneumonitis	5 (10)/ 3 (6)	36.0 (5.4–76.0)	13.0 (2.4–156.4+)	3 (60)	0	NA	NA	NA	0	NA	NA	NA
Diarrhea/colitis	5 (10)/ 3 (6)	8.4 (4.9–84.1)	4.3 (2.3–6.7)	5 (100)	1 (2)/ 1 (2)	10.1 (10.1–10.1)	3.9 (3.9–3.9)	1 (100)	2 (4)/1 (2)	109.4 (24.6–194.1)	1.7 (1.6–1.9)	2 (100)
Hyperthyroidism	4 (8)/0	6.1 (5.9–12.3)	7.1 (5.0–98.7+)	4 (80)	4 (8)/0	6.6 (5.9–7.0)	9.1 (4.6–35.0+)	3 (75)	3 (6)/0	6.0 (4.0–10.1)	NR (6.3+ to 192.6+)	0
Hypophysitis	2 (4)/0	15.9 (13.1–18.7)	NR (4.6–97.9+)	1 (50)	1 (2)/ 1 (2)	31.1 (31.1–31.1)	0.6 (0.6–0.6)	1 (100)	1 (2)/ 1 (2)	120.1 (120.1–120.1)	NR (155.6+ to 155.6+)	0
Thyroiditis	1 (2)/0	12.3 (12.3–12.3)	8.3 (8.3–8.3)	1 (100)	3 (6)/0	13.0 (6.0–36.1)	12.1 (12.1–256.1+)	2 (67)	2 (4)/0	5.6 (4.1–7.1)	11.1 (10.1–12.1)	2 (100)

IMAEs[a–c]	Arm A NIVO1 + IPI3 Q3W (*n* = 49)				Arm B NIVO3 + IPI1 Q3W (*n* = 49)				Arm C NIVO3 Q2W + IPI1 Q6W (*n* = 48)			
	Any grade/ grade 3/4 *n* (%)/ *n* (%)	TTO, weeks[d] Median (range)	TTR,[d–h] weeks Median (range)	Patients with resolution[g,h] *n* (%)	Any grade/ grade 3/4 *n* (%)/ *n* (%)	TTO, weeks[d] Median (range)	TTR,[d–h] weeks Median (range)	Patients with resolution[g,h] *n* (%)	Any grade/ grade 3/4 *n* (%)/ *n* (%)	TTO, weeks[d] Median (range)	TTR,[d–h] weeks Median (range)	Patients with resolution[g,h] *n* (%)
Nephritis and renal dysfunction	1 (2)/ 1 (2)	254.3 (254.3–254.3)	1.0 (1.0–1.0)	1 (100)	1 (2)/0	15.0 (15.0–15.0)	6.0 (6.0–6.0)	1 (100)	1 (2)/ 1 (2)	34.3 (34.3–34.3)	1.3 (1.3–1.3)	1 (100)
Hypersensitivity	0	NA	NA	NA	1 (2)/ 1 (2)	6.0 (6.0–6.0)	0.3 (0.3–0.3)	1 (100)	1 (2)/0	4.0 (4.0–4.0)	0.1 (0.1–0.1)	1 (100)

IMAE, immune-mediated adverse event; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NA, not applicable; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; NR, not reached; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; TTO, time to onset; TTR, time to resolution.

[a]Patients who received at least one dose of study treatment.

[b]Includes events reported between first dose and 100 days after last dose of study therapy.

[c]IMAEs include events, regardless of causality, occurring within 100 days of the last dose for which patients received immune-modulating medication for treatment, with the exception of endocrine events.

[d]Patients who experienced any-grade events.

[d]Symbol + indicates a censored value.

[e]Based on Kaplan-Meier estimates.

[f]Patients who experienced an IMAE without worsening from baseline were excluded from the time to resolution analysis.

[g]Events without a stop date or with a stop date of death, and grade 5 events are considered unresolved.

Figure S1. Trial profile

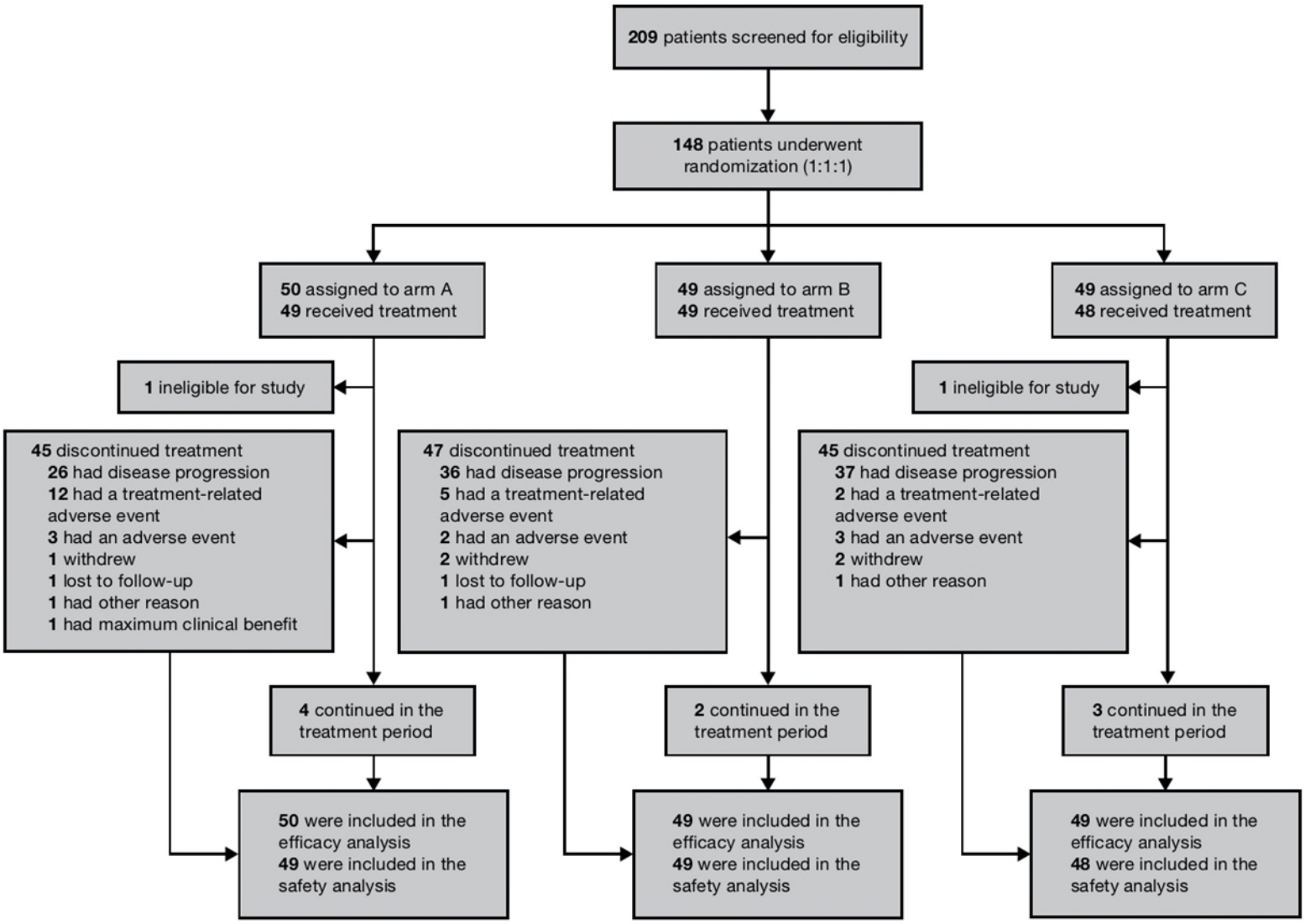

Figure S2. Best reduction in target lesions

Horizontal reference line indicates the 30% reduction consistent with a response per RECIST v1.1. Asterisks denote responders (best overall response of CR or PR).

[a]Best reduction is the maximum reduction in the sum of diameters of target lesions.

CR, complete response; HBV, hepatitis B virus; HCV, hepatitis C virus; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

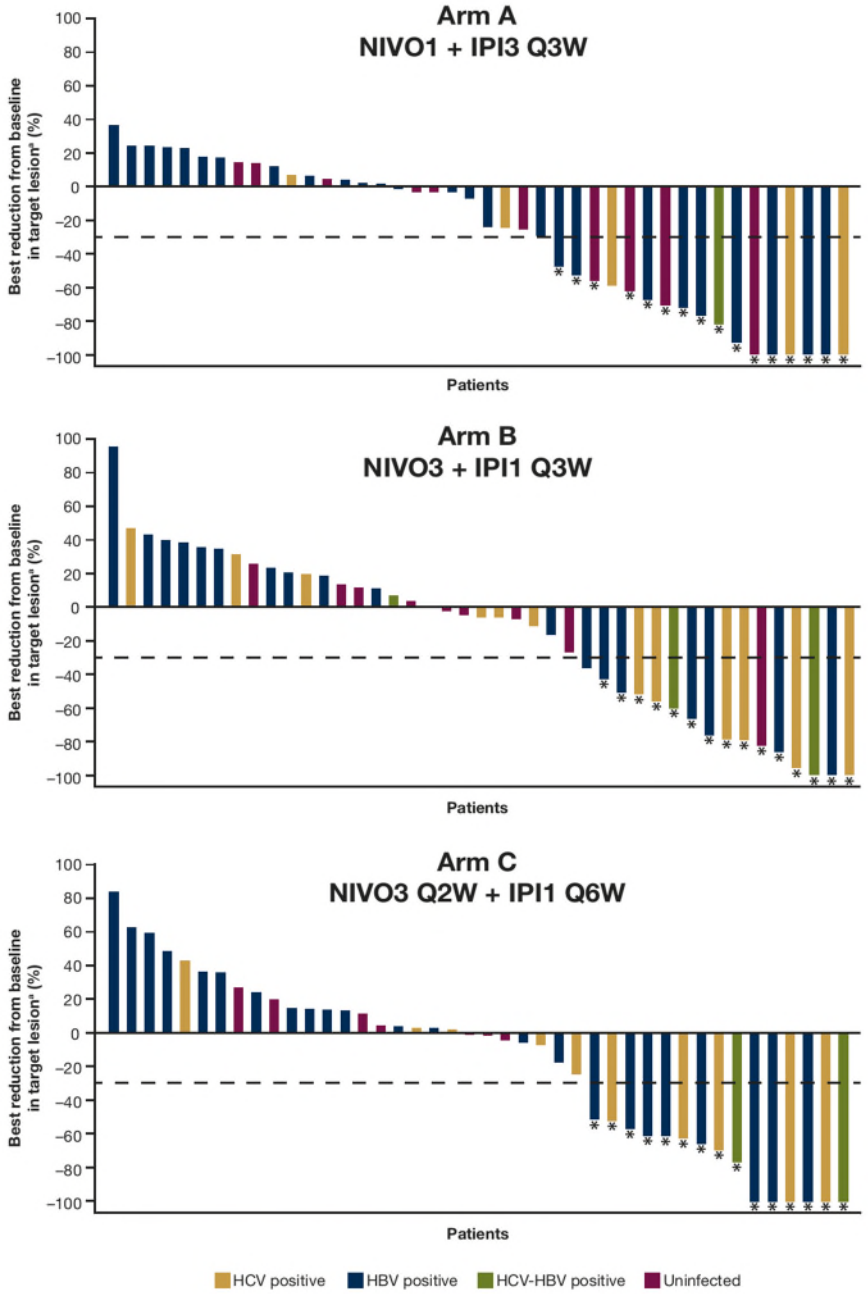

Figure S3. Change in tumor burden over time

[a]Per BICR.

Horizontal reference line indicates the 30% reduction consistent with a response per RECIST v1.1. "+" denotes the first occurrence of new lesion; "●" off treatment; "▼" CR or PR.

BICR, blinded independent central review; CR, complete response; HBV, hepatitis B virus; HCV, hepatitis C virus; IPI1, ipilimumab 1 mg/kg; IPI3, ipilimumab 3 mg/kg; NIVO1, nivolumab 1 mg/kg; NIVO3, nivolumab 3 mg/kg; PR, partial response; Q2W, every 2 weeks; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.