A randomized, open-label, phase 2 study of nivolumab plus ipilimumab or nivolumab monotherapy in patients with advanced or metastatic solid tumors of high tumor mutational burden

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Supplementary information

Online supplemental table S1. Distribution of tTMB-H and bTMB-H in the primary analysis population in CheckMate 848

	tTMB-H (n=135)†		bTMB-H (n=125)†	
	NIVO + IPI (n=88)	**NIVO (n=47)**	**NIVO + IPI (n=80)**	**NIVO (n=45)**
tTMB — no, (%)				
≥10 to <16 mut/Mb	48 (54.5)	25 (53.2)	–	–
≥16 mut/Mb	40 (45.5)	22 (46.8)	–	–
bTMB — no. (%)				
≥10 to <16 mut/Mb	–	–	42 (52.5)	22 (48.9)
≥16 mut/Mb	–	–	38 (47.5)	23 (51.1)
bTMB — no. (%)				
<10 mut/Mb	26 (29.5)	14 (29.8)	–	–
≥10 to <16 mut/Mb	17 (19.3)	10 (21.3)	–	–
≥16 mut/Mb	36 (40.9)	19 (40.4)	–	–
NR	9 (10.2)	4 (8.5)	–	–
tTMB — no. (%)				
<10 mut/Mb	–	–	31 (38.8)	18 (40.0)
≥10 to <16 mut/Mb	–	–	18 (22.5)	9 (20.0)

≥16 mut/Mb	–	–	21 (26.3)	11 (24.4)
NR	–	–	10 (12.5)	7 (15.6)

†201 patients were in the primary analysis population; 82 patients had both tTMB-H and bTMB-H.

bTMB, blood tumor mutational burden; bTMB-H, high bTMB; IPI, ipilimumab; mut/Mb, mutations per megabase; NIVO, nivolumab; NR, not reported; tTMB, tissue tumor mutational burden; tTMB-H, high tTMB.

Online supplemental table S2. Patients by tumor type in the randomized population in CheckMate 848

Disease diagnosis at study entry — n (%)	NIVO + IPI (n=136)	NIVO (n=76)	Total (N=212)
Breast cancer	10 (7.4)	5 (6.6)	15 (7.1)
Cervical cancer	11 (8.1)	5 (6.6)	16 (7.5)
Colorectal cancer	16 (11.8)	7 (9.2)	23 (10.8)
Esophageal cancer†	3 (2.2)	2 (2.6)	5 (2.4)
Gastric cancer	6 (4.4)	3 (3.9)	9 (4.2)
Gastroesophageal junction cancer	2 (1.5)	1 (1.3)	3 (1.4)
Head and neck cancer	5 (3.7)	1 (1.3)	6 (2.8)
Hepatocellular carcinoma	1 (0.7)	1 (1.3)	2 (0.9)
Merkel cell carcinoma	1 (0.7)	0	1 (0.5)
Ovarian cancer	7 (5.1)	4 (5.3)	11 (5.2)
Pancreatic cancer	4 (2.9)	2 (2.6)	6 (2.8)
Prostate cancer	3 (2.2)	3 (3.9)	6 (2.8)

Small cell lung carcinoma	8 (5.9)	8 (10.5)	16 (7.5)
Thyroid cancer	1 (0.7)	1 (1.3)	2 (0.9)
Urothelial cancer	4 (2.9)	4 (5.3)	8 (3.8)
Uterine cancer	9 (6.6)	6 (7.9)	15 (7.1)
Other cancers (see online supplemental table S4)	45 (33.1)	23 (30.3)	68 (32.1)

†Includes squamous cell carcinoma and adenocarcinoma.

IPI, ipilimumab; NIVO, nivolumab.

Online supplemental table S3. Other tumor types in the randomized population in CheckMate 848

Other tumors (n≥2)	n
Biliary cancers	9
Carcinoma unknown primary	8
Neuroendocrine cancer	7
Anal cancer	6
Squamous cell carcinoma	4
Glioblastoma	4
Adrenal	3
Basal cell carcinoma	3
Thymus	3
Vulvar	3
Penile	2
Sarcoma	2
Small bowel	2

Online supplemental table S4. ORR by treatment arm, tTMB-H, or bTMB-H subgroup analysis in the primary analysis population in CheckMate 848

	tTMB-H (n=135)†		bTMB-H (n=125)†	
	NIVO + IPI (n=88)	**NIVO (n=47)**	**NIVO + IPI (n=80)**	**NIVO (n=45)**
ORR by subgroup — no./No. (%)				
95% CI				
tTMB/bTMB cutoff‡				
≥10 mut/Mb	34/88 (38.6)	14/47 (29.8)	18/80 (22.5)	7/45 (15.6)
	28.4 to 49.6	17.3 to 44.9	13.9 to 33.2	6.5 to 29.5
≥13 mut/Mb	29/61 (47.5)	13/30 (43.3)	14/54 (25.9)	6/29 (20.7)
	34.6 to 60.7	25.5 to 62.6	15.0 to 39.7	8.0 to 39.7
≥16 mut/Mb	20/40 (50.0)	11/22 (50.0)	13/38 (34.2)	5/23 (21.7)
	33.8 to 66.2	28.2 to 71.8	19.6 to 51.4	7.5 to 43.7
≥20 mut/Mb	19/36 (52.8)	9/16 (56.3)	10/27 (37.0)	5/15 (33.3)
	35.5 to 69.6	29.9 to 80.2	19.4 to 57.6	11.8 to 61.6
10-16 mut/Mb	14/48 (29.2)	3/25 (12.0)	5/42 (11.9)	2/22 (9.1)
	17.0 to 44.1	2.5 to 31.2	4.0 to 25.6	1.1 to 29.2
bTMB/tTMB status				
bTMB-H and tTMB-H	22/53 (41.5)	9/29 (31.0)	13/39 (33.3)	6/20 (30.0)
	28.1 to 55.9	15.3 to 50.8	19.1 to 50.2	11.9 to 54.3

	tTMB-H (n=135)†		bTMB-H (n=125)†	
	NIVO + IPI (n=88)	**NIVO (n=47)**	**NIVO + IPI (n=80)**	**NIVO (n=45)**
bTMB-L and tTMB-H	10/26 (38.5) 20.2 to 59.4	5/15 (33.3) 11.8 to 61.6	-	-
bTMB-H and tTMB-L	-	-	3/31 (9.7) 2.0 to 25.8	0/18 (0.0) 0.0 to 18.5
bTMB NR/NE and tTMB-H	2/9 (22.2) 2.8 to 60.0	0/3 (0.0) 0.0 to 70.8	-	-
tTMB NR/NE and bTMB-H	-	-	2/10 (20.0) 2.5 to 55.6	1/7 (14.3) 0.4 to 57.9
bTMB cutoff in tTMB patients				
bTMB ≥16 mut/Mb	17/36 (47.2) 30.4 to 64.5	8/19 (42.1) 20.3 to 66.5	-	-
bTMB 10-16 mut/Mb	5/17 (29.4) 10.3 to 56.0	1/10 (10.0) 0.3 to 44.5	-	-
tTMB cutoff in bTMB patients				
tTMB ≥16 mut/Mb	-	-	10/21 (47.6) 25.7 to 70.2	5/11(45.5) 16.7 to 76.6
tTMB 10-16 mut/Mb	-	-	3/18 (16.7) 3.6 to 41.4	1/9 (11.1) 0.3 to 48.2
PD-L1 expression				

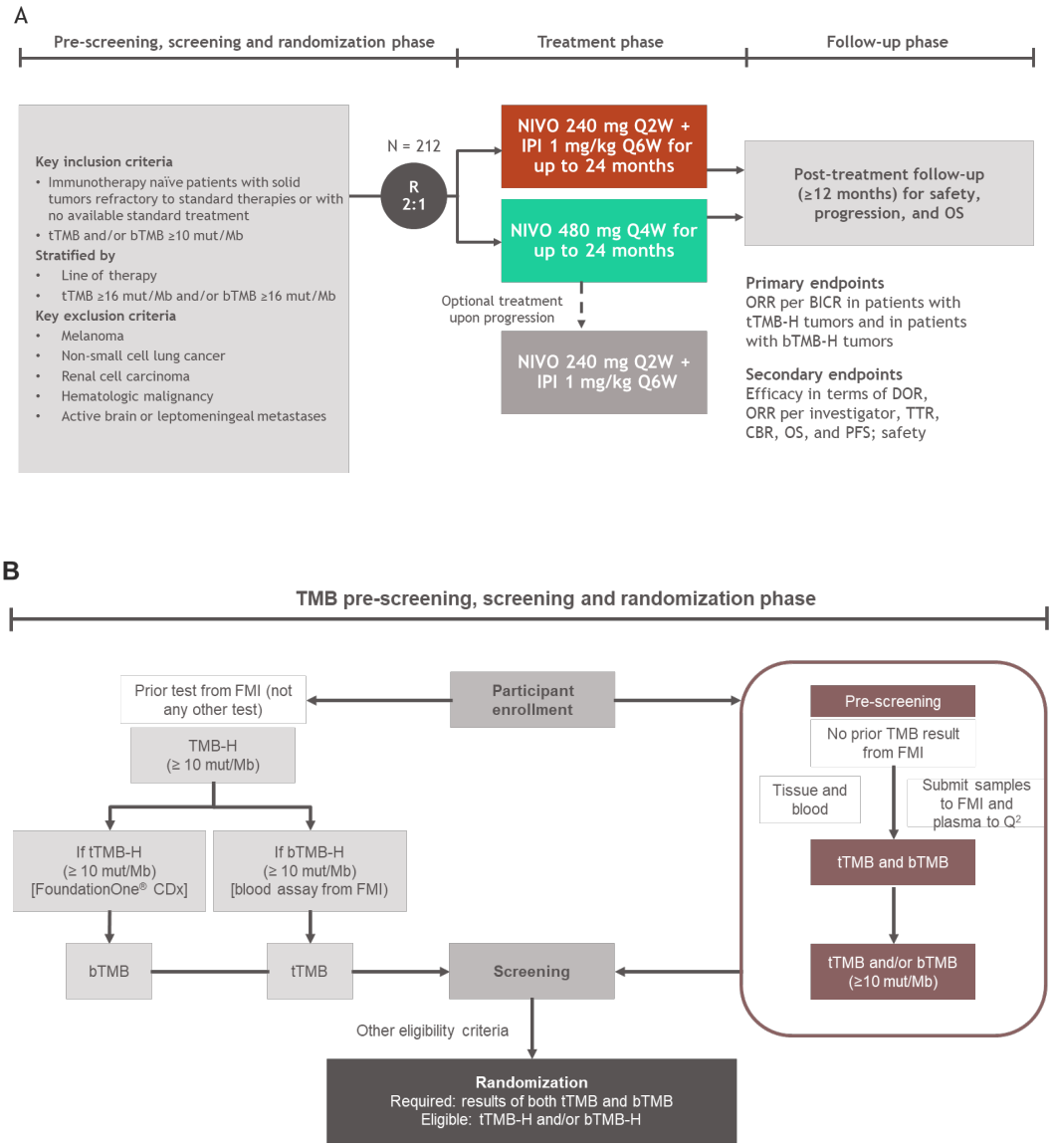
	tTMB-H (n=135)†		bTMB-H (n=125)†	
	NIVO + IPI (n=88)	**NIVO (n=47)**	**NIVO + IPI (n=80)**	**NIVO (n=45)**
PD-L1 ≥1%	6/11 (54.5) 23.4 to 83.3	3/8 (37.5) 8.5 to 75.5	4/13 (30.8) 9.1 to 61.4	1/5 (20.0) 0.5 to 71.6
PD-L1 <1%	15/43 (34.9) 21.0 to 50.9	4/19 (21.1) 6.1 to 45.6	9/38 (23.7) 11.4 to 40.2	3/25 (12.0) 2.5 to 31.2
MSI status				
MSI-H	8/13 (61.5) 31.6 to 86.1	4/10 (40.0) 12.2 to 73.8	1/5 (20.0) 0.5 to 71.6	3/7 (42.9) 9.9 to 81.6
Non–MSI-H	23/70 (32.9) 22.1 to 45.1	10/36 (27.8) 14.2 to 45.2	15/68 (22.1) 12.9 to 33.8	3/31 (9.7) 2.0 to 25.8
NR	3/5 (60.0) 14.7 to 94.7	0/1 (0.0) 0.0 to 97.5	2/7 (28.6) 3.7 to 71.0	1/7 (14.3) 0.4 to 57.9

†201 patients were in the primary analysis population; 82 patients had both tTMB-H and bTMB-H.

‡tTMB cutoff in the tTMB cohort and bTMB cutoff in the bTMB cohort.

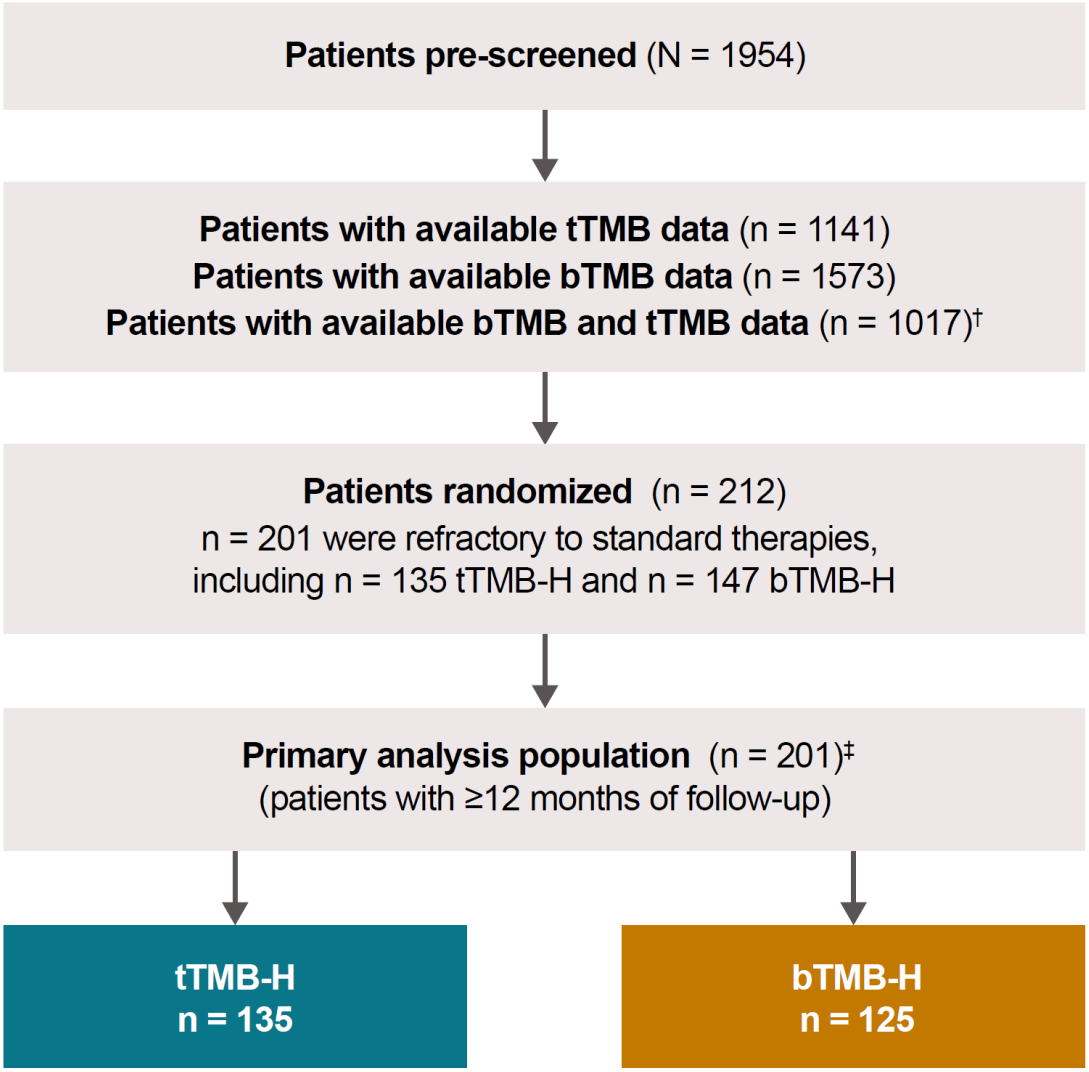
bTMB, blood tumor mutational burden; bTMB-H, high bTMB; bTMB-L, low bTMB; CI, confidence interval; IPI, ipilimumab; MSI, microsatellite instability; MSI-H, high MSI; mut/Mb, mutations per megabase; NIVO, nivolumab; NE, not evaluable; NR, not reported; ORR, objective response rate; PD-L1, programmed death ligand 1; tTMB, tissue tumor mutational burden; tTMB-H, high tTMB; tTMB-L, low tTMB.

Online supplemental figure S1. (A) CheckMate 848 study design and (B) TMB pre-screening, screening, and randomization phase



BICR, blinded independent central review; bTMB-H, high blood tumor mutational burden; CBR, clinical benefit rate; DOR, duration of response; FMI, Foundation Medicine, Inc.; IPI, ipilimumab; mut/Mb, mutations per megabase; NIVO, nivolumab; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2/4/6W, every 2/4/6 weeks; R, randomized; tTMB-H, high tissue tumor mutational burden; TTR, time to response.

Online supplemental figure S2. Patient disposition in CheckMate 848

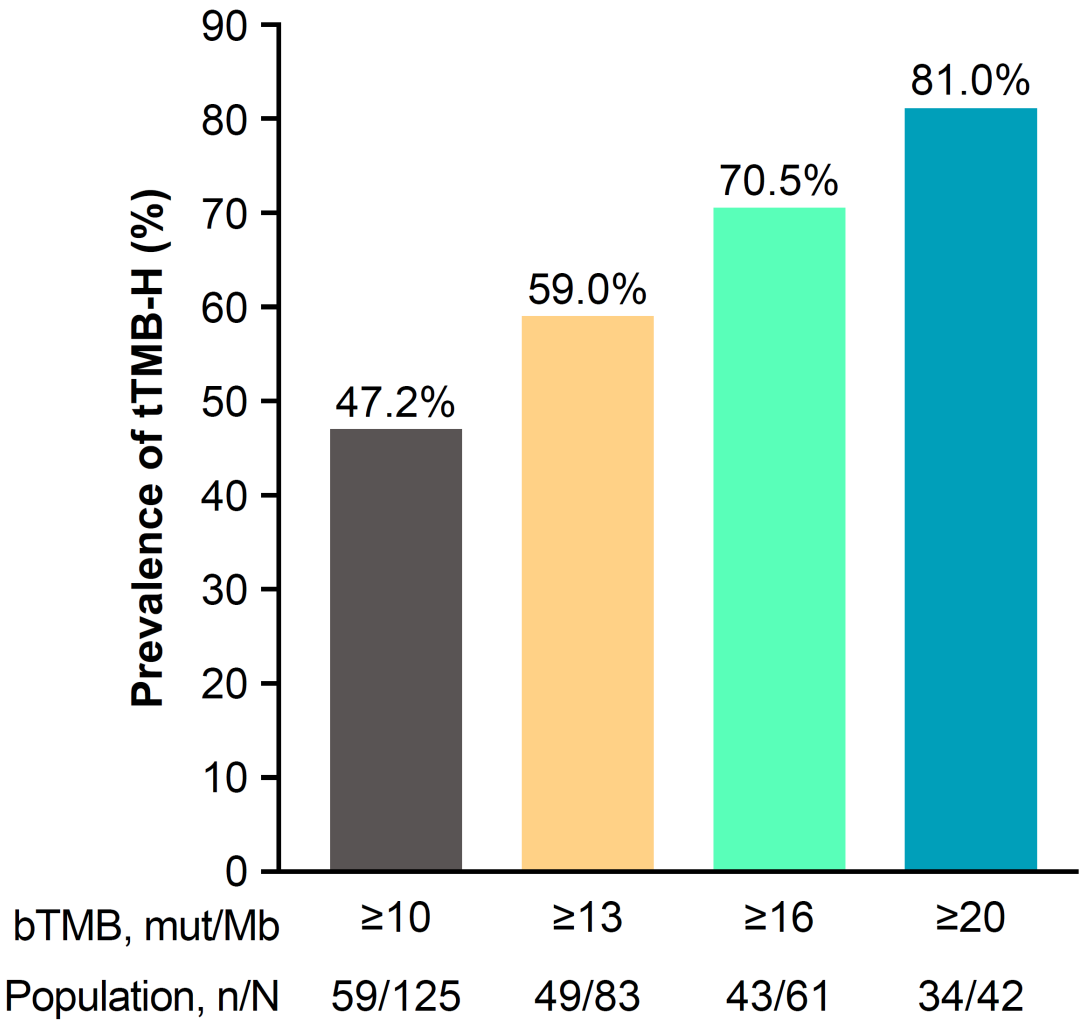


†Overall percentage agreement between tTMB and bTMB assays was 84%.[3]

‡Primary analysis population is the salvage bTMB-H population randomized before December 20, 2019 (23 patients with bTMB-H randomized after December 2019 were excluded) and salvage patients with tTMB-H with ≥12 months of follow-up.

bTMB, blood tumor mutational burden; bTMB-H, high bTMB; tTMB, tissue tumor mutational burden; tTMB-H, high tTMB.

Online supplemental figure S3. Prevalence of tTMB-H by bTMB cutoff in CheckMate 848†



†Salvage population randomized prior to December 20, 2019; rates across both the nivolumab + ipilimumab and nivolumab monotherapy arms.

bTMB, blood tissue mutational burden; mut/Mb, mutations per megabase; tTMB-H, high tissue tumor mutational burden.