Adjuvant therapy with nivolumab versus placebo in patients with resected stage IIB/C melanoma (CheckMate 76K)

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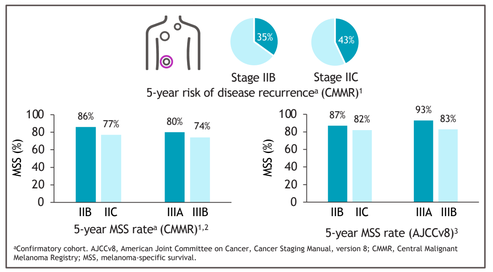
Background

- Approximately one-third of patients with stage IIB and half with stage IIC disease experience recurrence within 5 years (**Figure 1**)[1]
  - Prognosis of patients with stage IIB and IIC disease is similar to those with stage IIIA and IIIB melanoma, respectively,[1-3] highlighting the need for effective and tolerable adjuvant therapies in this population
- Checkpoint inhibitors have transformed the adjuvant treatment of resected stage III or IV melanoma[4-8]
- In KEYNOTE-716, adjuvant pembrolizumab vs placebo (PBO) in resected stage IIB or IIC melanoma improved recurrence-free survival (RFS): hazard ratio (HR), 0.65 (95% CI, 0.46-0.92)[9]

Objective

- The purpose of this report was to present the primary results of CheckMate 76K evaluating nivolumab (NIVO) vs PBO as adjuvant treatment in patients with resected stage IIB or IIC melanoma

Figure 1. Recurrence risk of stage IIB and IIC disease

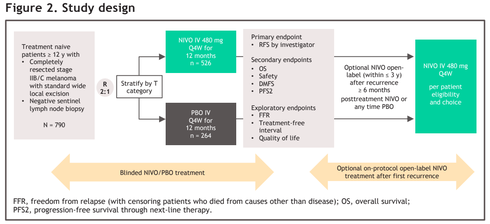


[a]Confirmatory cohort. AJCCv8, American Joint Committee on Cancer, Cancer Staging Manual, version 8; CMMR, Central Malignant Melanoma Registry; MSS, melanoma-specific survival.

Methods

- In CheckMate 76K (NCT04099251), treatment-naive patients ≥ 12 years with completely resected stage IIB or IIC melanoma were randomized 2:1 to receive NIVO or PBO as shown in **Figure 2**
- The primary endpoint was investigator-assessed RFS (time between randomization and first recurrence)
  - Recurrence events included the following: local, regional, or distant recurrence; new primary melanoma and melanoma in situ; death (due to any cause)
  - Imaging assessments occurred every 26 weeks during years 1-3 and every 52 weeks in years 4 and 5
- Key secondary endpoints were distant metastasis-free survival (DMFS; time between randomization and first distant recurrence or death) and safety
- Recurrence was investigator-assessed with imaging assessments approximately every 6 months in the first 3 years and annually in years 4 and 5
  - Tumor assessments were performed per contrast-enhanced computed tomography (CT) of the chest, abdomen, pelvis, and all other known and suspected sites of disease, unless known contraindications for CT intravenous contrast
- The design of CheckMate 76K includes an optional on-protocol NIVO open-label portion following recurrence on either NIVO (at ≥ 6 months from treatment) or PBO (at any time after recurrence)
  - The results presented here are from the initial blinded phase portion of the study
- The interim RFS analysis was planned when approximately 123 RFS events occurred (80% information fraction); a final analysis is planned at approximately 154 events
- The clinical cutoff for the interim analysis was June 28, 2022
  - 135 RFS events (88% information fraction); 76.8% power and 0.678 critical HR
- OS is event driven and follow-up is ongoing

Figure 2. Study design



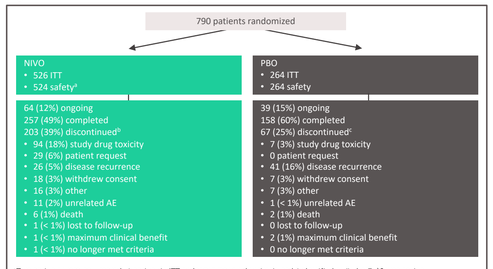
FFR, freedom from relapse (with censoring patients who died from causes other than disease); OS, overall survival; PFS2, progression-free survival through next-line therapy.

Results

Patient population

- A total of 790 patients were randomized (**Figure 3**)
  - 39% of patients treated with NIVO and 25% of PBO-treated patients discontinued treatment, most commonly due to study drug toxicity for NIVO at 18% of patients and due to disease recurrence for PBO at 16% of patients
- At a minimum overall study follow-up of 7.8 months, patients had a median follow-up of 15.8 months in the NIVO arm and 15.9 months in the PBO arm
- Median number of doses received was 12 in the NIVO arm and 13 in the PBO arm, with a mean (range) duration of treatment of 8.8 (0-12.1) and 9.9 (0-12.7) months, respectively
- Patient demographic and disease characteristics were well balanced, with 60% of the population being male and 40% at stage IIC disease (**Table 1**)
  - One-half of the patients had nodular melanoma subtype across arms

Figure 3. Patient treatment disposition



[a]Two patients were not treated: 1 patient in ITT no longer met study criteria and 1 classified as "other". [b]Seven patient discontinuations were related to COVID: patient request (n = 1), death (n = 1), study drug toxicity (n = 2), unrelated AE (n = 3). [c]Two patient discontinuations were related to COVID: withdrew consent (n = 1) and death (n = 1). AE, adverse event; COVID, coronavirus disease; ITT, intention-to-treat.

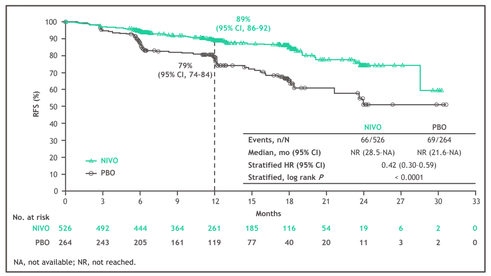
Table 1. Patient baseline characteristics

	NIVO (n = 526)	PBO (n = 264)
Mean age, years (SD)	59.9 (13.9)	59.3 (13.6)
Male, n (%)	322 (61%)	161 (61%)
ECOG PS 0, n (%)	495 (94%)	245 (93%)
Stage, n (%)		
IIB	316 (60%)	163 (62%)[a]
IIC	210 (40%)	101 (38%)
T category, n (%)		
T3b	204 (39%)	104 (39%)
T4a	112 (21%)	58 (22%)
T4b	210 (40%)	102 (39%)
Melanoma subtype, n (%)		
Nodular	266 (51%)	133 (50%)
Superficial spreading	151 (29%)	82 (31%)
Acral lentiginous	28 (5%)	15 (6%)
Other/Not reported	81 (15%)[b]	34 (13%)[c]
Region, n (%)		
Western Europe	303 (58%)	160 (61%)
US and Canada	97 (18%)	46 (17%)
Australia	68 (13%)	30 (11%)
Eastern Europe	58 (11%)	28 (11%)

[a]One of these patients was incorrectly categorized as stage IIB instead of IIC. [b]Categorized as: desmoplastic melanoma (n = 21, 4%), lentigo maligna (n = 13, 2%), "other" (n = 44, 8%), and not reported (n = 3, 1%). [c]Categorized as: desmoplastic melanoma (n = 8, 3%), lentigo maligna (n = 3, 1%), "other" (n = 22, 8%), and not reported (n = 1, < 1%).

- NIVO significantly reduced the risk of recurrence vs PBO, with a stratified HR of 0.42 (95% CI, 0.30-0.59) and 12-month RFS rates of 89% vs 79% (**Figure 4**)
  - Overall, 13% of patients treated with NIVO and 26% of PBO-treated patients experienced an RFS event (**Table 2**)
    - RFS benefit was driven by reductions in the incidence of both distant recurrences (5% for NIVO vs 12% for PBO) and regional recurrences (2% for NIVO vs 8% for PBO)
    - New melanoma lesions occurred in 2% vs 3% of patients, respectively, and likely did not have an impact on the observed RFS benefit
- The RFS forest plot shows that the RFS benefit with NIVO was consistent across prespecified patient subgroups, which is illustrated by the clustering of HRs around the overall ITT unstratified HR of 0.43 (**Table 3**)
  - Of particular interest, RFS benefit was consistent across T categories with an expected slightly overall worse prognosis for patients with T4b disease (**Figure 5**)

Figure 4. Primary endpoint: RFS



NA, not available; NR, not reached.

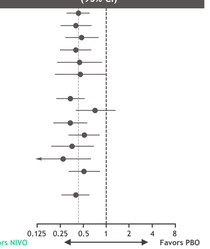
Table 2. Patterns of first RFS events

	NIVO (n = 526)	PBO (n = 264)
RFS events, n (%)	**66 (13%)**	**69 (26%)**
Recurrence[a]	**45 (9%)**	**58 (22%)**
Distant recurrence	26 (5%)	31 (12%)
Regional node recurrence	11 (2%)	20 (8%)
Local recurrence	8 (2%)	7 (3%)
In-transit metastases	0	0
New melanoma lesions	**11 (2%)**	**8 (3%)**
New primary invasive melanoma	4 (1%)	3 (1%)
Melanoma in situ	7 (1%)	5 (2%)
Deaths prior to recurrence	**10 (2%)**	**3 (1%)**

[a]For patients who had multiple recurrences that were identified on the same day, the most serious type is tabulated according to the displayed prespecified hierarchy.

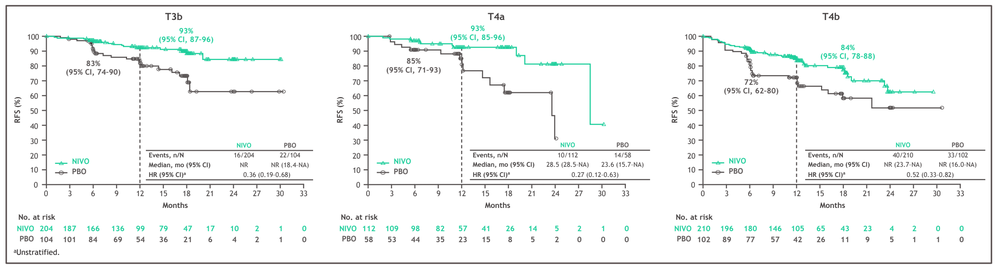
Table 3. RFS by subgroup with unstratified HR

Subgroup		NIVO n/N	NIVO 12-mo RFS rate, (95% CI)	PBO n/N	PBO 12-mo RFS rate, (95% CI)	Unstratified HR (95% CI)[a]
Overall[b]	Overall	66 (526)	89.0 (85.6-91.6)	69 (264)	79.4 (73.5-84.1)	0.43 (0.31-0.61)
Age category I	< 65 years	33 (305)	91.5 (87.4-94.4)	39 (155)	81.2 (73.5-86.9)	0.40 (0.25-0.64)
	≥ 65 years	33 (221)	85.4 (79.3-89.8)	30 (109)	76.8 (66.8-84.2)	0.48 (0.29-0.78)
Age category II	≥ 18- < 65	33 (305)	91.5 (87.4-94.4)	39 (155)	81.2 (73.5-86.9)	0.40 (0.25-0.64)
	≥ 64- < 75	16 (140)	89.2 (81.9-93.6)	18 (77)	79.7 (67.9-87.5)	0.45 (0.23-0.88)
	≥ 75- < 85	17 (77)	78.2 (65.6-86.6)	11 (30)	68.4 (46.1-83.0)	0.46 (0.21-0.99)
	≥ 85	0 (4)	NA	1 (2)	100.0 (100.0-100.0)	–
Sex	Male	39 (322)	89.9 (85.6-93.0)	51 (161)	76.5 (68.6-82.7)	0.33 (0.22-0.51)
	Female	27 (204)	87.6 (81.6-91.7)	18 (103)	83.9 (74.1-90.2)	0.71 (0.39-1.29)
Disease stage	IIB	26 (316)	92.6 (88.6-95.2)	36 (163)	84.1 (76.8-89.3)	0.34 (0.20-0.56)
	IIC	40 (210)	83.8 (77.5-88.4)	33 (101)	72.0 (61.6-80.0)	0.51 (0.32-0.81)
T category	T3b	16 (204)	92.6 (87.2-95.7)	22 (104)	83.4 (73.8-89.7)	0.36 (0.19-0.68)
	T4a	10 (112)	92.6 (85.1-96.4)	14 (58)	85.2 (70.7-92.8)	0.27 (0.12-0.63)
	T4b	40 (210)	83.8 (77.5-88.4)	33 (102)	72.3 (61.9-80.2)	0.52 (0.33-0.82)
Region	US and Canada	8 (97)	92.7 (84.2-96.7)	8 (46)	84.2 (67.8-92.7)	–
	Western Europe	41 (303)	89.0 (84.5-92.3)	46 (160)	78.0 (70.0-84.0)	0.40 (0.26-0.61)
	Eastern Europe	8 (58)	84.5 (71.3-92.0)	9 (28)	80.2 (58.6-91.3)	–
	Australia	9 (68)	87.9 (76.2-94.1)	6 (30)	78.8 (58.7-89.9)	–



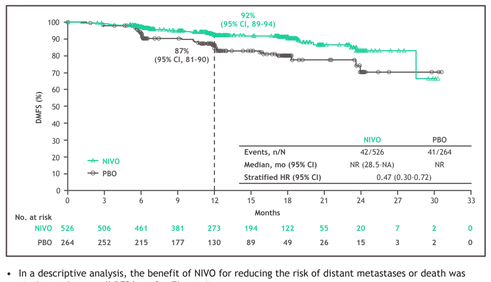
[a]Per statistical analysis plan, HR is not computed for subset categories with less than 10 events per treatment group. [b]Stratified RFS is 0.42 (0.30-0.59).

Figure 5. Subgroup analysis of RFS: T category



[a]Unstratified.

Figure 6. Secondary endpoint: DMFS



- In a descriptive analysis, the benefit of NIVO for reducing the risk of distant metastases or death was similar to the overall RFS benefit (**Figure 6**)
  - HR was 0.47 (95% CI, 0.30-0.72) with 12-month DMFS rates of 92% for NIVO and 87% for PBO
- The safety profile of NIVO was similar to the known anti-PD-1 monotherapy profile observed across many trials
- Grade 3-4 treatment-related adverse events (TRAEs) were 10% in the NIVO group and 2% in the placebo group and any grade TRAE leading to discontinuation was 15% vs 3% (**Table 4**)
  - There was 1 treatment-related death (0.2% of patients) with NIVO due to heart failure and acute kidney injury that was not related to myocarditis
- As expected, the most common TRAE was fatigue, which occurred at a similar incidence in the NIVO and PBO arms (**Figure 7**)
  - The most frequent grade 3-4 TRAEs in the NIVO arm were diarrhea, rash, and increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and blood creatine phosphokinase, all at 1% each
- The only grade 3-4 immune-mediated AE in more than 1% of patients treated with NIVO was hepatitis at 3% (**Table 5**)

Table 4. Safety summary

	NIVO (n = 524)		PBO (n = 264)	
AE, n (%)	**Any grade**	**Grade 3-4**	**Any grade**	**Grade 3-4**
Any AE	502 (96%)	115 (22%)[a]	229 (87%)	32 (12%)[a]
TRAE	433 (83%)	54 (10%)	142 (54%)	6 (2%)
Immune-mediated AE	213 (41%)	41 (8%)	45 (17%)	3 (1%)
Any AE leading to discontinuation	91 (17%)	37 (7%)	9 (3%)	2 (1%)
TRAE leading to discontinuation	77 (15%)	29 (6%)	7 (3%)	2 (1%)

[a]In addition, there was 1 grade 5 event in each treatment group, considered unrelated to study treatment, myocardial ischemia for NIVO and "sudden death" for PBO.

Figure 7. TRAEs in ≥ 5% patients in the NIVO group

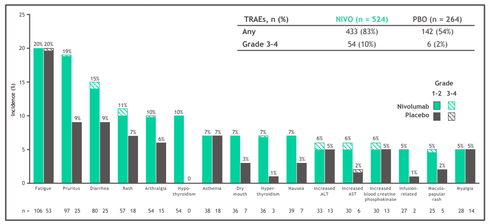


Table 5. Immune-mediated AEs by category[a]

	NIVO (n = 524)		PBO (n = 264)	
AE, n (%)	**Any grade**	**Grade 3-4**	**Any grade**	**Grade 3-4**
Non-endocrine immune-mediated AEs where immune-modulating medication was initiated				
Rash	45 (9%)	4 (1%)	4 (2%)	0
Diarrhea/colitis	24 (5%)	6 (1%)	2 (1%)	1 (< 1%)
Hepatitis	22 (4%)	14 (3%)	1 (< 1%)	0
Hypersensitivity	7 (1%)	0	0	0
Pneumonitis	4 (1%)	1 (< 1%)	2 (1%)	0
Nephritis and renal dysfunction	3 (1%)	2 (< 1%)	1 (< 1%)	0
Endocrine immune-mediated AEs regardless of immune-modulating medication initiation				
Hypothyroidism	60 (11%)	0	0	0
Adrenal insufficiency	12 (2%)	3 (1%)	3 (1%)	0
Hyperthyroidism	40 (8%)	1 (< 1%)	4 (2%)	0
Hypophysitis	9 (2%)	5 (1%)	2 (1%)	0
Thyroiditis	6 (1%)	0	0	0
Diabetes (Type I)	3 (1%)	3 (1%)	0	0

[a]Immune-mediated AEs, reported between the first dose and 100 days after the last dose of study therapy, included both non-endocrine events requiring immune-modulating medication and endocrine events, regardless of treatment and not requiring specific laboratory criteria.

Conclusions

- NIVO significantly reduced the risk of recurrence by 58% compared with PBO in patients with resected stage IIB or IIC melanoma
  - HR, 0.42 (95% CI, 0.30-0.59; stratified $P < 0.0001$)
  - Higher 12-month RFS rates of 89% vs 79%
- Benefit of NIVO vs PBO was observed across prespecified subgroups, including T category and disease stage
- Clinically meaningful improvement in DMFS was observed with NIVO vs PBO at this initial assessment (HR, 0.47; 95% CI, 0.30-0.72)
- Safety profile of NIVO was consistent with previous reports and manageable using well-established treatment algorithms
- These results support NIVO as an effective adjuvant treatment option in resected stage IIB or IIC melanoma

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