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Quality-adjusted survival of nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone among treatment-naive patients with advanced melanoma: a quality-adjusted time without symptoms or toxicity (Q-TWiST) analysis

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Abstract

Purpose To compare the quality-adjusted survival of nivolumab plus ipilimumab combination and nivolumab alone versus ipilimumab alone among treatment-naive patients with advanced melanoma based on a minimum 36-month follow-up from the CheckMate 067 trial.

Methods Overall survival was partitioned into time without symptoms of progression or toxicity (TWiST), time with treatment-related grade ≥ 3 adverse events after randomization but before progression (TOX), and time from progression until end of follow-up or death (REL). Mean quality-adjusted TWiST (Q-TWiST) was calculated by multiplying the mean time spent in each health state by a utility of 1.0 for TWiST and 0.5 for TOX and REL. Sensitivity analyses included varying utilities of TOX and REL; Q-TWiST gains at different follow-up times were calculated using EQ-5D-3L utilities from the trial. Relative Q-TWiST gain of ≥ 10% was considered clinically important.

Results Compared with ipilimumab-treated patients, those who received nivolumab + ipilimumab combination had significantly longer TWiST and TOX but shorter REL; nivolumab-treated patients had significantly longer TWiST, shorter REL, and shorter but statistically nonsignificant TOX. Mean Q-TWiST was highest for nivolumab + ipilimumab (23.5 months; 95% CI 21.9–25.2), followed by nivolumab (21.8 months; 95% CI 20.2–23.4) and ipilimumab (15.3 months; 95% CI 13.9–16.6). Relative Q-TWiST gains were favorable and clinically important for nivolumab + ipilimumab combination (+ 36.81%) and nivolumab alone (+ 29.18%) versus ipilimumab alone. Relative gains increased with follow-up from 3 to 40 months for all comparisons. These gains remained consistent in magnitude and direction in the different sensitivity analyses.

Conclusions Nivolumab + ipilimumab combination and nivolumab alone resulted in a statistically significant and clinically important improvement in quality-adjusted survival compared with ipilimumab alone.

Keywords Q-TWiST · Advanced melanoma · Nivolumab · Ipilimumab · Quality-adjusted survival

Abbreviations

M stage	Metastases stage
PD-1	Programmed death 1
PD-L1	Programmed death ligand 1
Q-TWiST	Quality-adjusted time without symptoms or toxicity
RECIST	Response evaluation criteria in solid tumors

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REL	Time from progression until end of follow-up or death
TWiST	Time without disease progression or symptoms of toxicity
TOX	Time with grade ≥ 3 treatment-related adverse events after randomization but before progression
U	Utilities
ULN	Upper limit of normal

Introduction

Melanoma is the fifth most common cancer type in the United States, accounting for 5.2% of all new cases and 10,130 deaths annually [1]. Before 2011, the 5-year survival rate for patients with stage IV (distant metastatic or advanced) melanoma was < 10% [2].

Several immune checkpoint inhibitors are now indicated for the treatment of patients with advanced melanoma. Ipilimumab, an anti-cytotoxic T-lymphocyte antigen 4 antibody that upregulates antitumor immunity, was the first immunotherapy agent to show an overall survival benefit in phase 3 trials in this population [3, 4]. Nivolumab and pembrolizumab are fully human immunoglobulin G4 monoclonal antibodies that negatively regulate the programmed death 1 (PD-1) cell surface receptor. They inhibit the suppressive function of PD-1 upon binding, activating T cells and cell-mediated immune responses that can recognize and eliminate cancer cells [5, 6]. Nivolumab alone has been shown to be associated with prolonged survival benefit while not impairing quality of life [7] compared with dacarbazine among treatment-naive patients with advanced melanoma in a phase 3 clinical trial (NCT01721772) [8]. Ipilimumab and nivolumab are approved as monotherapies and in combination in patients with advanced melanoma, and pembrolizumab is approved as monotherapy.

The phase 3 CheckMate 067 (NCT01844505) trial, designed to compare nivolumab + ipilimumab combination or nivolumab alone with ipilimumab alone, demonstrated 3-year overall survival rates of 58%, 52%, and 34% with nivolumab + ipilimumab, nivolumab, and ipilimumab, respectively [9]. Median overall survival was not reached for nivolumab + ipilimumab, was 37.6 months for nivolumab, and was 19.9 months for ipilimumab [9]. Median progression-free survival was 11.5 months in the nivolumab + ipilimumab group, 6.9 months in the nivolumab group, and 2.9 months in the ipilimumab group. The incidence of grade 3/4 adverse events was highest in patients who received nivolumab + ipilimumab (59%), followed by ipilimumab (28%) and nivolumab (21%) [9]. An analysis of the quality-of-life data from the CheckMate 067 trial reported that both nivolumab + ipilimumab and nivolumab maintained health-related quality of life with no clinically meaningful deterioration over time, as compared with ipilimumab alone, despite the difference in grade 3/4 adverse events [10].

Understanding the relative clinical risk–benefit of oncology therapies, especially from a patient perspective, can be critical to treatment selection. Such patient-driven assessments are increasingly receiving attention from regulatory agencies [11–14] and professional societies, such as the European Society for Medical Oncology [15] and the American Society of Clinical Oncology [16]. These groups have proposed various methods to score the clinical benefits of oncology therapies based on overall survival, progression-free survival, and toxicities, among other factors. The quality-adjusted time without symptoms or toxicity (Q-TWiST) methodology has been used since the mid-1980s, and estimates "net health benefits" of cancer therapies by assessing the quality (i.e., preferences, quality of life) and quantity of time spent with toxicities, in relapse/progression, or before relapse/progression and without toxicities [17–20]. Q-TWiST has also been used to assess treatment benefits and risks in melanoma [21], immunotherapy [22–28], or both [21, 29].

Here, a comprehensive Q-TWiST analysis was conducted to assess the quality-adjusted survival benefits for nivolumab (alone or in combination with ipilimumab) versus ipilimumab alone while considering grade 3/4 adverse events and disease progression, to inform treatment selection and create a baseline for additional analyses.

Methods

Patient population and treatments

This was a post hoc analysis using data from the phase 3 CheckMate 067 clinical trial with ≥ 36 months of follow-up. Further information on the trial treatments, dosing, and patient inclusion/exclusion criteria is available in Online Appendix 1. As documented in the original report, the study was conducted in accordance with the provisions of the Declaration of Helsinki and with Good Clinical Practice guidelines as defined by the International Conference on Harmonisation, and all the patients (or their legal representatives) provided written informed consent before enrollment [30].

Q-TWiST health states

Overall survival was partitioned into three mutually exclusive health states: time without disease progression or symptoms of toxicity (TWiST); time with grade ≥ 3 treatment-related adverse events after randomization but before progression (TOX); and time from progression until end of follow-up or death (REL). Q-TWiST was calculated by

multiplying the mean time spent in each state by its respective utility (assumed patient preference for each state). At the time of database lock, all patients had a minimum follow-up of 36 months. The analysis was conducted until the last available observation. The maximum available follow-up in the available data cut was 40 months. Five key assumptions were considered in the base case:

- Fixed utility values were adopted ($U_{TWiST} = 1$, $U_{TOX} = 0.5$, $U_{REL} = 0.5$). These utilities are most traditionally used for the base-case scenario [17, 31].
- Regardless of the type, severity, or extent of adverse event-related symptoms, U_{TOX} was set at 0.5.
- Each adverse event had a start and end (the first day of resolution or disease progression) date. TOX duration was calculated as the number of days spent with grade 3/4 adverse events before disease progression, if observed, or end of the analysis.
- A day with multiple adverse events was counted only once.
- All days with adverse events before progression were grouped together to calculate total time in TOX, irrespective of whether adverse events occurred consecutively or not.

Statistical analysis

Partitioned survival analyses using the Kaplan–Meier product limit method were conducted to calculate the restricted mean duration of each health state as follows: (1) TOX, area under the toxicity curve; (2) TWiST, difference in area under the progression-free survival and toxicity curves; and (3) REL, difference in area under the overall survival and progression-free survival curves. The analyses did not adjust for subsequent treatments received or the potential toxicities of those treatments. Mean Q-TWiST values were calculated by taking the sum of the product of the time spent in each state by its respective utilities (U), according to the following equation:

$$\text{Q-TWiST} = U_{TOX} \times \text{TOX} + U_{TWiST} \times \text{TWiST} + U_{REL} \times \text{REL}.$$

To assess the precision of the mean restricted survival time in each state and Q-TWiST, 95% confidence intervals were computed via 1000 bootstrap (with replacement) samples of the trial patients.

The treatment benefit for each arm was defined as absolute gain (months) and relative gain (percentage) in Q-TWiST versus the comparator. The latter was calculated as the difference in Q-TWiST divided by the overall survival time of the comparator. Relative gains $\geq 10\%$ and $\geq 15\%$ were defined as clinically important and clearly clinically important, respectively [19]. The Q-TWiST gain function was calculated and plotted graphically to assess how Q-TWiST changed as a function of follow-up time.

Subgroup analyses

Stratified analyses were used to assess Q-TWiST for key prespecified subgroups, including age (< 65 vs. ≥65 years), sex, baseline Eastern Cooperative Oncology Group performance status (0 vs. 1), metastasis stage (M1c vs. M0/M1a/M1b), lactate dehydrogenase level (≤ upper limit of normal [ULN] vs. > ULN), tumor programmed death ligand 1 (PD-L1) status (positive vs. negative/indeterminate), and tumor *BRAF* status (mutation vs. wild-type)]. Subgroup analyses are presented within a forest plot showing the mean (95% confidence intervals) differences in Q-TWiST between treatments.

Analyses assessing the impact of utilities

Separate analyses were conducted to determine the effect of different utility weights on the Q-TWiST. First, in a threshold analysis, Q-TWiST was calculated over the full range of U_{TOX} and U_{REL}—that is, from 0.00 (time not counted toward total Q-TWiST) to a maximum of 1.00 (time fully counted toward total Q-TWiST). These results are presented graphically with diagonal bands of different color shading to reflect the magnitude of absolute Q-TWiST gain between arms. Second, utilities directly elicited from CheckMate 067 patients (via the EQ-5D-3L instrument) were used instead of traditional base-case utility values. The United States tariff was used to calculate the EQ-5D utilities [32]. Each completed measurement was assigned to 1 of 3 health states based on timing of assessment. Measurements obtained during ongoing grade 3/4 adverse events were attributed to TOX. Those obtained on or after the progression date or at discontinuation due to progression were attributed to REL. All other assessments were attributed to TWiST. For each arm, the mean utility for each state was calculated as the average of all assessments in that state.

Immuno-oncology-specific sensitivity analyses

Four additional sensitivity analyses were conducted. First, results were recalculated after excluding all grade 3/4 adverse events from TOX that had an impact on < 5% of patients. Second, grade 2 adverse events treated with steroids and grade 2 endocrine adverse events lasting ≤ 4 weeks were added to TOX. Third, post-progression adverse events were included in TOX (as opposed to being counted as part of REL, as is usually done in traditional Q-TWiST), as adverse events related to immuno-oncology therapies may persist after treatment discontinuation [33]. For this scenario, the REL stage was partitioned into REL with adverse

event ($U_{REL} = 0.25$) and without adverse event ($U_{REL} = 0.5$). The utility for REL with adverse event was set at 0.25 by multiplying TOX and REL utilities (0.50×0.50). Fourth, progression was redefined whereby patients were considered progressed only if they discontinued treatment after a diagnosis of disease progression as per response evaluation criteria in solid tumors (RECIST) version 1.1 [34]. This analysis was conducted because many CheckMate 067 trial patients continued treatment after disease progression due to the potential for pseudo-progression. SAS version 9.4 (SAS Institute Inc, Cary, NC) was used for all analyses.

Results

Baseline characteristics

A total of 945 patients were randomized (nivolumab + ipilimumab, 314; nivolumab, 316; ipilimumab, 315). No differences in baseline characteristics were observed across treatment groups (Online Appendix 1, Table A1).

Duration of time in each health state

Table 1 reports base-case mean restricted durations of time spent in TOX, TWiST, and REL at 40 months' follow-up. Partitioned survival curves are presented in Online Appendix 1 (Fig. A1). TWiST time was longest in nivolumab + ipilimumab combination, followed by nivolumab and ipilimumab. Mean Q-TWiST was 23.5 months for nivolumab + ipilimumab (95% CI 21.9–25.2 months), 21.8 months for nivolumab (95% CI 20.2–23.4 months), and 15.3 months for ipilimumab (95% CI 13.9–16.6 months). In the base-case scenario, both nivolumab + ipilimumab combination and nivolumab alone treated patients experienced statistically significant Q-TWiST gains in mean (95% CI) quality-adjusted overall survival of 8.2 months (6.1–10.2 months) and 6.5 months (4.4–8.7 months) versus ipilimumab, respectively. A nonsignificant improvement of 1.7 months (95% CI −0.6 to 4.2 months) was observed for nivolumab + ipilimumab versus nivolumab, although CheckMate 067 was not powered to detect this difference. These gains translated into relative Q-TWiST improvements of 36.81% (95% CI 26.16%–47.77%), 29.18% (95% CI 18.98%–41.39%), and 6.35% (95% CI −2.01% to 15.97%) at 40 months for nivolumab + ipilimumab (vs. ipilimumab), nivolumab (vs. ipilimumab), and nivolumab + ipilimumab (vs. nivolumab), respectively. Relative Q-TWiST gains consistently increased with longer follow-up for all three comparisons (Fig. 1).

Table 1 Restricted mean durations of health states at 40 months

Health state	Nivolumab + Ipilimumab ($n = 314$)	Nivolumab ($n = 316$)	Ipilimumab ($n = 315$)	Nivolumab + ipilimumab versus ipilimumab	Nivolumab versus ipilimumab	Nivolumab + ipilimumab versus nivolumab
Mean PFS, month (95% CI)	19.8 (17.9, 21.7)	17.2 (15.3, 19.2)	8.5 (7.1, 9.9)	11.3 (8.9, 13.7)	8.7 (6.3, 11.1)	2.6 (−0.3, 5.4)
Mean OS, month (95% CI)	28.0 (26.3, 29.6)	26.8 (25.1, 28.4)	22.3 (20.6, 23.9)	5.7 (3.2, 7.9)	4.5 (2.2, 6.9)	1.2 (−1.2, 3.6)
Mean TOX, month (95% CI)	0.8 (0.5, 1.0)	0.5 (0.2, 0.7)	0.2 (0.1, 0.3)	0.5 (0.3, 0.8)	0.2 (0, 0.5)	0.3 (0, 0.7)
Mean TWiST, month (95% CI)	19.0 (17.2, 20.9)	16.7 (14.9, 18.8)	8.3 (6.9, 9.6)	10.7 (8.4, 13.2)	8.4 (6.1, 10.8)	2.3 (−0.6, 5.1)
Mean REL, month (95% CI)	8.2 (6.6, 9.6)	9.6 (8.0, 11.1)	13.8 (12.3, 15.4)	−5.6 (−7.8, −3.6)	−4.2 (−6.5, −2.0)	−1.4 (−3.6, 0.7)
Mean Q-TWiST, month (95% CI)	23.5 (21.9, 25.2)	21.8 (20.2, 23.4)	15.3 (13.9, 16.6)	8.2 (6.1, 10.2)	6.5 (4.4, 8.7)	1.7 (−0.6, 4.2)
Mean relative Q-TWiST gain, % (95% CI)	–	–	–	36.81 (26.16, 47.77)	29.18 (18.98, 41.39)	6.35 (−2.01, 15.97)
Threshold analysis for Q-TWiST gain, range in month	–	–	–	5.1–11.3	4.3–8.7	0.9–2.6
Threshold analysis for relative Q-TWiST gain, range in %	–	–	–	23.1–50.6	19.2–38.9	3.3–9.7

CI confidence interval, *OS* overall survival, *PFS* progression-free survival, *Q-TWiST* quality-adjusted TWiST, *REL* time after progression, *TOX* toxicity, *TWiST* time without disease progression or symptoms of toxicity

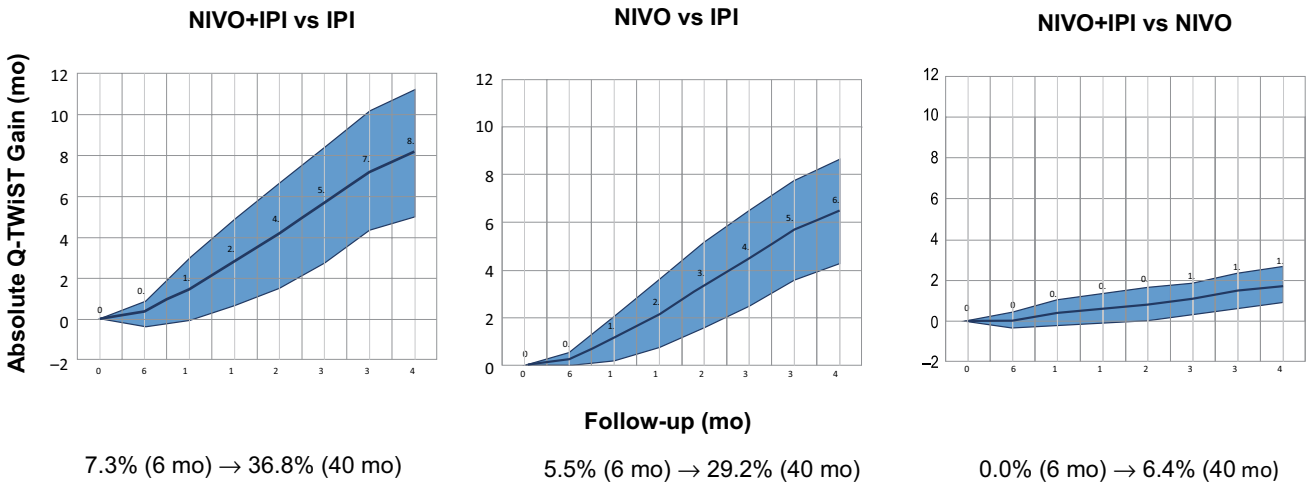

Fig. 1 Q-TWiST gain function over follow-up by comparison. The solid line represents the incremental mean differences in Q-TWiST over time with utilities of 1.00 for TWiST and 0.50 for TOX and REL. The shaded area depicts the range of differences in Q-TWiST, as the utility values for REL and TOX vary between 0.00 and 1.00. *IPI* ipilimumab, *mo* month, *NIVO* nivolumab, *Q-TWiST* quality-adjusted TWiST, *REL* time after progression, *TOX* toxicity, *TWiST* time without disease progression or symptoms of toxicity

Subgroup analysis

The results across all prespecified subgroups were statistically significant in favor of nivolumab + ipilimumab combination (Fig. 2a) and nivolumab alone (Fig. 2b) compared with ipilimumab. The results of subgroup analyses comparing nivolumab + ipilimumab and nivolumab are included in Online Appendix 1 (Table A2).

Analyses assessing the impact of utilities

In threshold analyses, the absolute gain in Q-TWiST at 40 months ranged from 5.1 to 11.3 months for nivolumab + ipilimumab (vs. ipilimumab), 4.3 to 8.7 months for nivolumab (vs. ipilimumab), and 0.9 to 2.6 months for nivolumab + ipilimumab (vs. nivolumab) as U_{TOX} and U_{REL} increased from 0.0 to 1.0 (Table 1). The gains were statistically significant for all values of U_{TOX} and U_{REL} for nivolumab + ipilimumab and nivolumab versus ipilimumab (Fig. 3). The corresponding relative Q-TWiST gains were clearly clinically important for nivolumab + ipilimumab and nivolumab versus ipilimumab irrespective of the values of U_{TOX} and U_{REL} (data not shown). Applying EQ-5D-3L utilities elicited from trial assessments (Online Appendix 1, Table A3) resulted in relative gains of 21.55%, 17.51%, and 3.74% for nivolumab + ipilimumab (vs. ipilimumab), nivolumab (vs. ipilimumab), and nivolumab + ipilimumab (vs. nivolumab), respectively (Table 2).

Immuno-oncology-specific sensitivity analyses

Results remained consistent with the base-case scenario in all five sensitivity analyses (Table 2). Absolute and relative Q-TWiST gains were highest in the fifth scenario (relative gains of 43.09%, 32.32%, and 8.96% for nivolumab + ipilimumab vs. ipilimumab, nivolumab vs. ipilimumab, and nivolumab + ipilimumab vs. nivolumab, respectively). In this scenario, progression was delayed (relative to RECIST) for 100 patients with nivolumab + ipilimumab, 59 with nivolumab, and 52 with ipilimumab.

Discussion

Q-TWiST allows for a comprehensive comparison of clinical benefit of therapies by combining the quality (with and without toxicities) and quantity of time spent before and after progression into a single metric [35]. It is conceptually similar to other clinical benefit summary measures, such as the American Society of Clinical Oncology Value Framework's net heath benefit [16]. These methods, developed in part to facilitate shared treatment decision making by patients and physicians, help consider trade-offs between clinical benefits and toxicity of various treatments [36]. Over time, these methods have become relevant to regulatory agencies who seek to incorporate the patient's perspective [11–14].

This analysis suggests that patients receiving nivolumab + ipilimumab combination or nivolumab alone would likely experience statistically significant gains in quality-adjusted survival of 8.2 and 6.5 months, respectively, versus those who received ipilimumab alone. Although CheckMate 067 was not designed to detect a difference between nivolumab + ipilimumab combination versus nivolumab monotherapy, patients receiving the

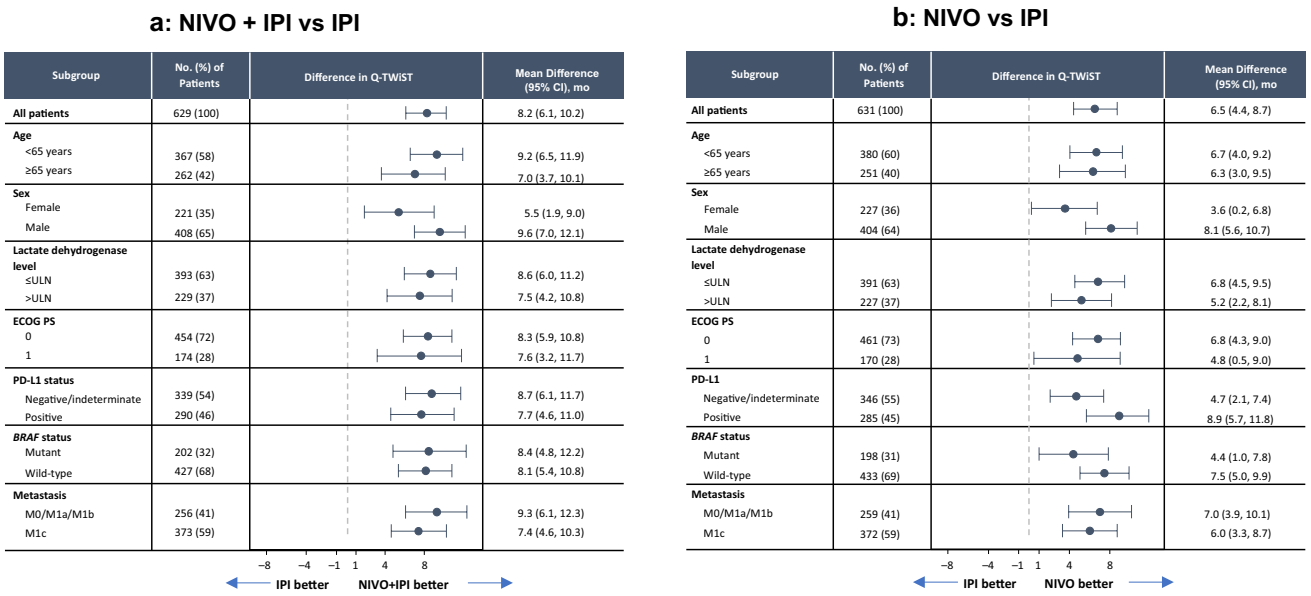

Fig. 2 Q-TWiST subgroup analysis for nivolumab + ipilimumab versus ipilimumab (**a**) and nivolumab versus ipilimumab (**b**). Mean differences in Q-TWiST between groups are presented in months. *BRAF BRAF* mutation test, *CI* confidence interval, *ECOG PS*, Eastern Cooperative Oncology Group performance status, *IPI* ipilimumab, *LDH* lactate dehydrogenase, *M0* no detectable evidence of distant metastases, *M1a* metastases to skin, subcutaneous, or distant lymph nodes, normal serum LDH level, *M1b* lung metastases, normal LDH level, *M1c* metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH level, *mo* month, *NIVO* nivolumab, *PD-L1* programmed death ligand 1, *Q-TWiST* quality-adjusted time without disease progression or symptoms of toxicity; *ULN* upper limit of normal

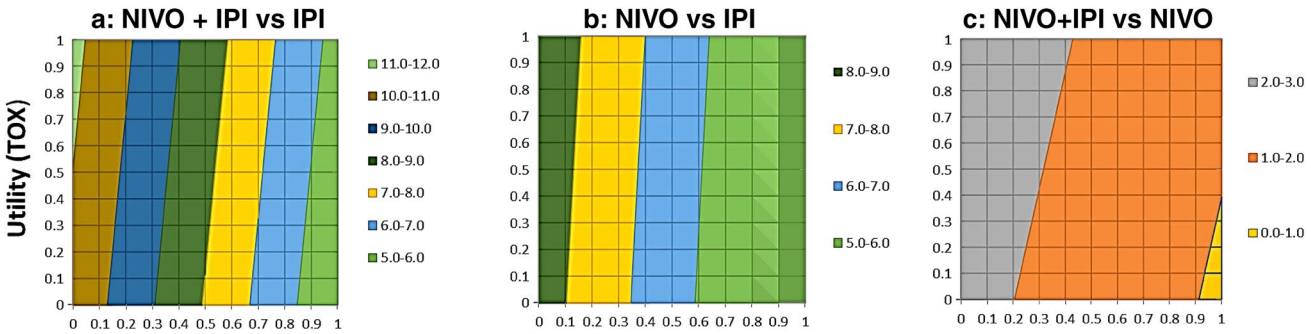

Fig. 3 Absolute Q-TWiST threshold utility analysis. Each panel is associated with one of the three comparisons. The y-axis on each panel represents the utility for toxicity (U_{TOX}) time and the x-axis represents the utility for time after disease progression (U_{REL}). Both vary from 0.0 to 1.0, while the utility of TWiST (U_{TWiST}) is fixed at 1.0. The diagonal bands of different colors represent increasing absolute Q-TWiST gains (from the lower right corner to the upper left corner of the panel). To understand absolute Q-TWiST gain associated with a given combination of U_{TOX} and U_{REL}, one must select the corresponding values of U_{TOX} and U_{REL} on the y-axis and x-axis, respectively. The intersection of these two values inside the plot indicates to which band of absolute Q-TWiST gain the results from this combination belong. For instance, in the comparison between nivolumab + ipilimumab versus ipilimumab, the base case uses $U_{TOX} = 0.5$ and $U_{REL} = 0.5$, which intersect in the band of absolute Q-TWiST gain ranging from 8.0 to 9.0 in the first panel, consistent with the base-case estimate of 8.2 months. All Q-TWiST gains in panels **a** and **b** are statistically significant. None of the Q-TWiST gains in panel **c** are statistically significant. *IPI* ipilimumab, *NIVO* nivolumab, *Q-TWiST* quality-adjusted time without disease progression or symptoms of toxicity, *REL* time after progression, *TOX* toxicity

combination had a numerical improvement in Q-TWiST compared with nivolumab, which increased over time. This was driven in part by increases in TWiST and reduction in REL. Patients who received nivolumab + ipilimumab spent more time with grade 3/4 adverse events versus those on nivolumab or ipilimumab; however, because most adverse events resolve relatively quickly, this increase in time spent in the TOX state was small compared with the increase in TWiST and reduction in REL, as evidenced by the overall

Table 2 Difference in Q-TWiST and relative Q-TWiST gain – sensitivity analyses

Health state	Nivolumab + ipilimumab ($n=314$)	Nivolumab ($n=316$)	Ipilimumab ($n=315$)	Nivolumab + ipilimumab versus ipilimumab	Nivolumab versus ipilimumab	Nivolumab + ipilimumab versus nivolumab
EQ-5D-3L used as utilities						
Mean TOX, month (95% CI)	0.8 (0.5, 1.0)	0.5 (0.2, 0.7)	0.2 (0.1, 0.3)	0.5 (0.3, 0.8)	0.2 (0.0, 0.5)	0.3 (0.0, 0.7)
Mean TWiST, month (95% CI)	19.0 (17.2, 21.0)	16.7 (14.8, 18.7)	8.3 (6.9, 9.7)	10.7 (8.4, 13.1)	8.4 (6.1, 10.8)	2.3 (−0.3, 5.0)
Mean REL, month (95% CI)	8.2 (6.6, 9.7)	9.6 (8.1, 11.2)	13.8 (12.1, 15.3)	−5.6 (−7.8, −3.5)	−4.2 (−6.5, −2.0)	−1.4 (−3.7, 0.6)
Mean Q-TWiST, month (95% CI)	22.9 (21.6, 24.3)	22.3 (21.1, 24.0)	18.2 (16.5, 19.3)	4.8 (2.8, 6.6)	3.9 (2.0, 5.9)	1.0 (−1.0, 3.0)
Mean relative Q-TWiST gain, % (95% CI)	–	–	–	21.55 (11.78, 31.50)	17.51 (8.61, 28.37)	3.74 (−3.68, 11.43)
Exclude adverse events occurring in < 5% of patients						
Mean TOX, month (95% CI)	0.2 (0.1, 0.2)	0.1 (0.0, 0.2)	0.1 (0.0, 0.1)	0.1 (0.0, 0.2)	0.0 (−0.1, 0.1)	0.1 (0.0, 0.2)
Mean TWiST, month (95% CI)	19.6 (17.7, 21.6)	17.1 (15.2, 19.1)	8.4 (7.1, 9.9)	11.2 (8.8, 13.7)	8.6 (6.3, 11.0)	2.5 (−0.2, 5.3)
Mean REL, month (95% CI)	8.2 (6.6, 9.7)	9.6 (8.0, 11.1)	13.8 (12.1, 15.3)	−5.6 (−7.8, −3.5)	−4.2 (−6.5, −2.0)	−1.4 (−3.7, 0.6)
Mean Q-TWiST, month (95% CI)	23.8 (22.2, 25.4)	15.4 (13.9, 16.7)	15.4 (13.9, 16.7)	8.4 (6.3, 10.4)	6.6 (4.5, 8.7)	1.9 (−0.5, 4.1)
Mean relative Q-TWiST gain, % (95% CI)	–	–	–	37.70 (26.92, 49.55)	29.62 (19.38, 41.67)	7.10 (−1.82, 16.03)
Toxicities include grade 2 adverse events with steroids treatment, grade 2 adverse events in endocrine toxicity that lasted 4 weeks						
Mean TOX, month (95% CI)	3.3 (2.4, 4.2)	1.3 (0.8, 1.7)	0.7 (0.4, 1.0)	2.6 (1.7, 3.6)	0.6 (0.0, 1.1)	2.1 (1.1, 3)
Mean TWiST, month (95% CI)	16.5 (14.7, 18.4)	15.9 (14.2, 17.9)	7.8 (6.6, 9.2)	8.6 (6.6, 11)	8.1 (5.9, 10.4)	0.5 (−1.9, 3.3)
Mean REL, month (95% CI)	8.2 (6.6, 9.7)	9.6 (8.0, 11.1)	13.8 (12.1, 15.3)	−5.6 (−7.8, −3.5)	−4.2 (−6.5, −2.0)	−1.4 (−3.7, 0.6)
Mean Q-TWiST, month (95% CI)	22.2 (20.7, 23.7)	21.3 (19.8, 23)	15.1 (13.7, 16.4)	7.2 (5.2, 9.1)	6.3 (4.3, 8.4)	0.9 (−1.4, 3.1)
Mean relative Q-TWiST gain, % (95% CI)	–	–	–	32.32 (21.89, 43.23)	28.28 (18.43, 40.08)	3.36 (−4.78, 12.24)
Include post-progression adverse events into TOX						
Mean TOX pre-progression, month (95% CI)	0.8 (0.5, 1.0)	0.5 (0.2, 0.7)	0.2 (0.1, 0.3)	0.5 (0.3, 0.8)	0.2 (0.0, 0.5)	0.3 (0.0, 0.7)
Mean TOX post-progression, month (95% CI)	0.2 (0.1, 0.3)	0.1 (0.0, 0.1)	0.1 (0.0, 0.2)	0.1 (−0.1, 0.2)	0.0 (−0.1, 0.0)	0.1 (0.0, 0.3)
Mean TWiST, month (95% CI)	19.2 (17.4, 21.3)	16.9 (15.0, 18.9)	8.5 (7.1, 9.9)	10.8 (8.5, 13.1)	8.4 (6.1, 10.8)	2.4 (−0.2, 5.1)
Mean REL, month (95% CI)	7.9 (6.2, 9.2)	9.5 (7.8, 10.9)	13.6 (11.9, 15.0)	−5.6 (−7.9, −3.7)	−4.1 (−6.4, −1.9)	−1.5 (−3.9, 0.4)
Mean Q-TWiST, month (95% CI)	23.7 (22.0, 25.1)	21.8 (20.2, 23.4)	15.4 (13.9, 16.7)	8.2 (6.1, 10.2)	6.4 (4.3, 8.6)	1.8 (−0.5, 4.1)
Mean relative Q-TWiST gain, % (95% CI)	–	–	–	36.81 (25.92, 48.32)	28.73 (18.96, 41.09)	6.72 (−1.76, 15.84)
Progression defined as including discontinuation						
Mean TOX, month (95% CI)	0.4 (0.3, 0.5)	0.2 (0.1, 0.2)	0.1 (0.1, 0.2)	0.3 (0.2, 0.4)	0.0 (−0.1, 0.1)	0.3 (0.1, 0.4)
Mean TWiST, month (95% CI)	25.8 (23.3, 28.0)	22.2 (20.2, 24.3)	12.3 (10.4, 14.2)	13.4 (10.5, 16.4)	9.9 (7.2, 12.8)	3.5 (0.2, 6.6)
Mean REL, month (95% CI)	1.8 (−0.5, 4.0)	4.4 (2.5, 6.1)	9.8 (7.8, 11.7)	−8.0 (−10.9, −5.2)	−5.4 (−8.1, −2.8)	−2.6 (−5.5, 0.1)
Mean Q-TWiST, month (95% CI)	26.9 (25.0, 28.5)	24.5 (22.9, 26.1)	17.3 (15.8, 18.7)	9.6 (7.3, 11.6)	7.2 (5.1, 9.5)	2.4 (−0.2, 4.7)
Mean relative Q-TWiST gain, % (95% CI)	–	–	–	43.09 (31.29, 55.49)	32.32 (21.84, 44.47)	8.96 (−0.61, 18.25)

CI confidence interval, *EQ-5D* standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal, *Q-TWiST* quality-adjusted TWiST; *REL* time after progression, *TOX* toxicity, *TWiST* time without disease progression or symptoms of toxicity

large net Q-TWiST gain for nivolumab + ipilimumab versus nivolumab or ipilimumab.

The relative Q-TWiST gains observed for nivolumab + ipilimumab combination (36.81%) and nivolumab alone (29.18%) compared with ipilimumab alone may be viewed as clearly clinically important (≥ 15%) based on Revicki et al's criteria [19]. These gains are historically large relative to previously reported estimates for oncology treatments. Specifically, results of a recent benchmark review of 51 studies reporting on 81 Q-TWiST comparisons across 13 cancers showed mean relative Q-TWiST gains of 9.3% and 8.6% for studies using interferon and targeted therapy, respectively [17, 20]. Furthermore, the relative Q-TWiST gains reported herein for nivolumab + ipilimumab and nivolumab versus ipilimumab are larger than ~ 97.5% of the relative Q-TWiST gains reported in the benchmark review. A Q-TWiST analysis among previously untreated patients with advanced melanoma found that quality-adjusted overall survival gains increased from 0.50 to 3.28 months at 4 years for ipilimumab plus dacarbazine versus placebo plus dacarbazine [21]. The higher gains observed in CheckMate 067 as reported here may be attributed to treatment benefit with nivolumab + ipilimumab combination or nivolumab alone as the trial populations were similar. The present analysis also showed that these gains increased with longer follow-up (Fig. 1), suggesting that additional benefits may be observed as data continue to mature. The 6.35% increase in Q-TWiST with the nivolumab + ipilimumab versus nivolumab comparison was in line with historical benchmarks observed with targeted therapy. In addition, the difference between the two arms was clinically important (≥ 10%) in several key subgroups of patients, including *BRAF* mutant, PD-L1 negative, lactate dehydrogenase > ULN, and Eastern Cooperative Oncology Group performance status of 1.

Prespecified subgroup analyses provided reassurance that the results pertaining to nivolumab-containing arms versus ipilimumab are robust. In line with previous Q-TWiST analyses, the present analysis adopted key assumptions regarding how patients may value time spent in TOX, TWiST, and REL. However, threshold sensitivity analyses demonstrated that the quality-adjusted survival advantage of nivolumab (alone or combined with ipilimumab) versus ipilimumab remained statistically significant regardless of utility weights assigned to TOX and REL. This implies that, within the Q-TWiST framework, there is a reasonably good degree of certainty that nivolumab + ipilimumab combination or nivolumab alone may be preferred relative to ipilimumab alone. In addition, sensitivity analyses using EQ-5D-3L utilities from the CheckMate 067 trial patients also confirmed the superiority of nivolumab-containing treatments in terms of absolute and relative Q-TWiST gains. It should be noted that the timing of measurement of EQ-5D-3L in CheckMate 067 did not always match up exactly with the adverse event start or resolution or the start of disease progression. Therefore, utilities elicited from trial patients may not provide us with an accurate estimate for the three health states.

To understand the impact of adverse events on the Q-TWiST values, three additional sensitivity analyses were conducted: (1) excluding adverse events occurring with a low frequency (impacting < 5% of the intent-to-treat population); (2) including grade 2 adverse events treated with steroids and endocrine grade 2 adverse events that persisted longer than 4 weeks; and (3) including adverse events that occurred or lasted after progression, because adverse events with immuno-oncology therapies may persist after treatment discontinuation [33]. Although all analyses showed that the proportion of patients with treatment-related grade 3/4 adverse events was highest with nivolumab + ipilimumab and lowest with nivolumab, time spent with grade 3/4 adverse events was highest for nivolumab + ipilimumab and lowest for ipilimumab. A similar trend was observed for grade 2 adverse events captured during the second scenario. As most adverse events are resolved within 3–4 weeks [9], inclusion of grade 2 endocrine adverse events that lasted ≤ 4 weeks or adverse events that lasted after progression did not affect the Q-TWiST gains observed in the study. In the third scenario, the utility estimate for the REL with adverse event health state (0.25) was conservative because these toxicities had a short duration (0.1–0.2 months) and were well managed using immune-modulating treatments. In all scenarios, the absolute and relative quality-adjusted survival gains were consistent with base-case results.

A fourth sensitivity analysis was conducted to acknowledge that the traditional definition of progression (based on RECIST criteria) may be inadequate when assessing the treatment effect of cancer immunotherapies [34]. Evidence suggests that RECIST may neglect the importance of the "flare effect," i.e., the initial increase in tumor size that occurs due to the ability of immunotherapy to create inflammation of the cancer tissue. Thus, with immunotherapy, imaging studies may reveal worsening of existing or new lesions during initial therapy evaluation, but these may not reflect progression indicating a worsened prognosis [37]. Consequently, a sensitivity analysis was conducted in which progression followed by treatment discontinuation was considered true progression. Similar trends in quality-adjusted survival gains were observed as seen in the base-case scenario. Future Q-TWiST studies in immuno-oncology may consider incorporating health state definitions based on immune RECIST criteria to accurately capture disease progression [38].

The limitations with this analysis were largely inherent to Q-TWiST methodology. First, multiple adverse events

on the same day were counted as one adverse event, as in most Q-TWiST analyses. Second, consistent with previous Q-TWiST analyses, irrespective of the severity or duration of the adverse events, all toxicities were assigned the same utility weight and combined into one contiguous time period at the start of therapy. Third, quality-adjusted survival gains were potentially underestimated because the analysis ignored treatment switches observed more frequently in patients on ipilimumab versus those on nivolumab-containing treatments [9]. Finally, as this Q-TWiST comparison was a post hoc analysis conducted using the CheckMate 067 trial data, statistical significances and confidence intervals should be interpreted with caution. Future studies should try to replicate these results using prospectively generated hypotheses and power/sample size calculations.

Conclusions

Patients receiving nivolumab with or without ipilimumab experienced statistically significant and clinically important improvements in quality-adjusted survival compared with those receiving ipilimumab alone. Although CheckMate 067 was not designed to detect a difference between nivolumab + ipilimumab combination and nivolumab monotherapy, patients receiving the combination therapy had a numerical improvement in quality-adjusted survival versus nivolumab that increased over time. These findings were consistent across threshold, sensitivity, and subgroup analyses. The results support the clinical benefit of nivolumab alone and in combination with ipilimumab over ipilimumab monotherapy in patients with advanced melanoma and provide information for shared decision making among clinicians and patients who seek to balance the clinical risks and benefits of therapies.

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Compliance with ethical standards

Conflict of interest David F. McDermott served as a consultant or advisor for Bristol-Myers Squibb, Pfizer, Merck, Novartis, Eisai, Exelixis, Array BioPharma, and Genentech; and his institution received research funding from Prometheus Laboratories and Bristol-Myers Squibb. Ruchit Shah, Linlin Luo, and Marc Botteman are employed by Pharmerit International. Marc Botteman also reports stock ownership in Pharmerit International. Pharmerit International has received research funding from Bristol-Myers Squibb to conduct this research. Pharmerit International is a global health economics and outcomes research consulting firm that receives research funding and fees related to consulting and other advisory roles from numerous private organizations from the pharmaceutical, biotech, device, and medical industry. Komal Gupte-Singh and Sumati Rao are employed by Bristol-Myers Squibb and own stock in Bristol-Myers Squibb. Javier Sabater was a Bristol-Myers Squibb employee at the time this work was conducted and owns stock in Bristol-Myers Squibb. Meredith M. Regan served as a consultant or advisor for Merck and Ipsen; received funding for travel, accommodations and expenses from Bristol-Myers Squibb; and her institution received research funding from Veridex, OncoGenex, Pfizer, Ipsen, Novartis, Merck, Ferring, Celgene, AstraZeneca, Pierre Fabre, Bayer, and Bristol-Myers Squibb. Michael Atkins served as a consultant or advisor for Genentech, Pfizer, Novartis, GlaxoSmithKline, C-Cam, X4 Pharma, Amgen, Lilly, Alkermes, Infinity Pharmaceuticals, Genoptix, Bristol-Myers Squibb, Nektar, and Merck.

Ethical approval All procedures performed in the CheckMate 067 study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the CheckMate 067 study.

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