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Original Research

Nivolumab plus ipilimumab versus chemotherapy as first-line treatment in advanced non–small-cell lung cancer with high tumour mutational burden: patient-reported outcomes results from the randomised, open-label, phase III CheckMate 227 trial

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KEYWORDS
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Quality of life;
Surveys and questionnaires

Abstract
Background: In the phase III CheckMate 227 study, first-line nivolumab + ipilimumab significantly prolonged progression-free survival (co-primary end-point) versus chemotherapy in patients with advanced non–small-cell lung cancer (NSCLC) and high tumour mutational burden (TMB; ≥10 mutations/megabase).

Aim: To evaluate patient-reported outcomes (PROs) in this population.

Methods: Disease-related symptoms and general health status were assessed using the validated PRO questionnaires Lung Cancer Symptom Scale (LCSS) and EQ-5D, respectively. LCSS average symptom burden index (ASBI) and three-item global index (3-IGI) and EQ-5D visual analogue scale (VAS) and utility index (UI) scores and changes from baseline were analysed descriptively. Longitudinal changes were assessed by mixed-effect model repeated measures (MMRMs) and time to first deterioration/improvement analyses.

Results: In the high TMB population, PRO questionnaire completion rates were >90% at baseline and >80% for most on-treatment assessments. During treatment, mean changes from baseline with nivolumab + ipilimumab showed early, clinically meaningful improvements in LCSS ASBI/3-IGI and EQ-5D VAS/UI; with chemotherapy, symptoms and health-related quality of life remained stable (LCSS ASBI/3-IGI, EQ-5D UI) or improved following induction (EQ-5D VAS). MMRM-assessed changes in symptom burden were improved with nivolumab + ipilimumab versus chemotherapy. Symptom deterioration by week 12 was lower with nivolumab + ipilimumab versus chemotherapy (22.3% versus 35.0%; absolute risk reduction: 12.7% [95% confidence interval 2.4–22.5]), irrespective of discontinuation. Time to first deterioration was delayed with nivolumab + ipilimumab versus chemotherapy across LCSS and EQ-5D summary measures.

Conclusion: First-line nivolumab + ipilimumab demonstrated early, sustained improvements in PROs versus chemotherapy in patients with advanced NSCLC and high TMB.

Clinical trial registration: NCT02477826.

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1. Introduction

Advanced non–small-cell lung cancer (NSCLC) is associated with substantial symptom burden, which negatively affects patients’ health-related quality of life (HRQoL) [1,2]. Together with clinical efficacy evaluations, patient-reported outcome (PRO) data allow a broader view of treatment benefit by providing information collected directly from patients themselves, including symptoms and health status [3–5]. Nivolumab, an anti-programmed death 1 antibody, and ipilimumab, an anti-cytotoxic T-lymphocyte antigen 4 antibody, are immune checkpoint inhibitors with complementary mechanisms of action and are approved for co-administration in the treatment of several tumours [6]. Nivolumab monotherapy demonstrated an overall survival (OS) benefit that translated into improved PROs versus standard of care in phase III studies in previously treated, advanced squamous [7,8] and non-squamous [9,10] NSCLC.

Recent results from Part 1 of the CheckMate 227 study (NCT02477826) showed a significant progression-free survival benefit (co-primary study end-point) with first-line nivolumab plus ipilimumab versus chemotherapy in patients with advanced NSCLC and a high tumour mutational burden (TMB; ≥10 mutations/megabase); no new safety signals were observed with the combination [11]. Descriptive analyses of OS show positive trends for OS with nivolumab plus ipilimumab versus chemotherapy both in patients with high TMB and low (<10 mutations/megabase) TMB [12]. The second co-primary end-point of OS with nivolumab plus
ipilimumab versus chemotherapy in programmed death ligand 1 (PD-L1)–selected patients is ongoing. In CheckMate 227, disease-related symptoms and general health status were assessed as prespecified exploratory end-points using validated PRO measures [13–16].

Given the observed relationship between improved clinical outcomes and improved PROs with nivolumab monotherapy in previously treated NSCLC, we set out to evaluate whether the PFS benefit and manageable safety profile of first-line nivolumab plus ipilimumab versus chemotherapy in patients with high TMB, corresponding to the completed co-primary end-point population, would similarly translate into a meaningful benefit in PROs [8,10,11].

2. Methods

2.1. Study design

The design of Part 1 of the CheckMate 227 study has been reported previously (Supplementary Fig. S1) [11]. Briefly, patients with stage IV or recurrent NSCLC not previously treated with chemotherapy were enrolled. Those with a PD-L1 expression level of ≥1% were randomly assigned (1:1:1) to receive nivolumab (3 mg/kg intravenously every 2 weeks) plus ipilimumab (1 mg/kg intravenously every 6 weeks), nivolumab monotherapy, or chemotherapy, and those with a PD-L1 expression level of <1% were randomly assigned (1:1:1) to receive nivolumab plus ipilimumab, nivolumab plus chemotherapy, or chemotherapy. Intravenous platinum-doublet chemotherapy based on tumour histologic type was given every 3 weeks for up to four cycles. Full details on the different chemotherapies given, dosing regimens, and administration for each study arm are included in the supplementary material (Supplementary Fig. S1).

This study is being conducted in accordance with the International Conference on Harmonisation—Good Clinical Practice guidelines and the Declaration of Helsinki. An institutional review board or independent ethics committee at each centre approved the trial protocol. All patients gave written informed consent. The Bristol-Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html.

2.2. PRO assessments

The PRO assessment schedule is summarised in Figure 1. PRO assessments at study visits were administered before treatment. PROs were assessed using two validated measures, the Lung Cancer Symptom Scale (LCSS) [13–15] to examine the impact of treatment on lung cancer–specific symptoms and the EQ-5D [16] to examine the impact of treatment on general health status. The LCSS includes questions addressing six disease-associated symptoms (anorexia, fatigue, cough, dyspnoea, haemoptysis and pain) and three global items (symptom distress, interference with activity level and HRQoL) [13–15]. For each item, the degree of impairment was scored on a visual analogue scale (VAS; range 0–100). The LCSS average symptom burden index (ASBI) was calculated as the mean of the six symptom scores (range 0–100), with higher scores indicating greater symptom burden. The minimally important difference (MID), i.e. the smallest change considered clinically meaningful, was defined as 10 points for the individual items of the LCSS and LCSS ASBI [17]. We constructed a LCSS three-item global index (3-IGI) as the sum of the scores for the three global items (range 0–300), with higher scores representing better HRQoL; this exploratory end-point has been previously described [8,10,18]. An MID of 30 points (10% of the maximum possible score; based on the sum of the 10-point MIDs for the three global items) was selected for the LCSS 3-IGI as a reasonable estimate to guide interpretation in the absence of a formally established MID. The EQ-5D comprises a VAS of general health status ranging from 0 (worst imaginable) to 100 (best imaginable) and a descriptive system based on five dimensions of health status: mobility, self-care, usual activities, pain/discomfort and anxiety/depression [16]. Each question in the descriptive system has three levels of response (no problems, some problems, or extreme problems). The EQ-5D descriptive index responses were mapped into a single dimension health utility index (UI) ranging from death (0) to full health (1), with health states worse than death being possible (<0), by using utility weights for the UK population [19]. A MID was defined as 7 points and 0.08 points for the EQ-5D VAS and UI, respectively [19].

The PROs evaluated as prespecified exploratory end-points included deterioration rate by week 12 in the LCSS ASBI; mean scores and mean changes from baseline in the LCSS ASBI and 3-IGI, their individual components and the EQ-5D VAS and UI; longitudinal mixed-effect model repeated measures (MMRMs) analysis of scores on the LCSS ASBI and 3-IGI, their individual components and the EQ-5D VAS and UI and time to first deterioration/improvement in symptoms in the LCSS ASBI and 3-IGI, all individual components of the LCSS and the EQ-5D VAS and UI.

2.3. Statistical analysis

The statistical analysis for the prespecified exploratory PRO end-points was descriptive and did not include sample size calculation or hypothesis testing.

PRO questionnaire completion rates (on treatment) corresponded to the proportion of questionnaires received out of the expected number (i.e. the number of
patients still on treatment or in follow-up at each time point). Changes from baseline in PRO scores and mean PRO scores at each time point were evaluated using descriptive statistics in the PRO analysis population, defined as patients with PRO data at baseline and at least one postbaseline assessment.

MMRM analysis was performed in the PRO analysis population for longitudinal evaluation of PROs using data from common on-treatment assessments (every 6 weeks, corresponding to synchronised assessments between the 2-week nivolumab plus ipilimumab and 3-week chemotherapy cycles), with baseline PRO score and study stratification factors (PD-L1 expression level and histology) as covariates and change from baseline in score as the dependent variable. Data to week 42, where both treatment arms had ≥10 patients, were included in the model.

Disease-related symptom deterioration or improvement was defined as an individual change in score meeting or exceeding the MID for worsening or improvement, respectively. For each treatment arm, the disease-related symptom deterioration rate by 12 weeks and its corresponding 95% confidence interval (CI) were calculated using the Clopper–Pearson method and included all assessments on and off treatment within 12 weeks of baseline, with the all randomised, high TMB population in the denominator. Data to week 42, where both treatment arms had ≥10 patients, were included in the model.

Disease-related symptom deterioration or improvement was defined as an individual change in score meeting or exceeding the MID for worsening or improvement, respectively. For each treatment arm, the disease-related symptom deterioration rate by 12 weeks and its corresponding 95% confidence interval (CI) were calculated using the Clopper–Pearson method and included all assessments on and off treatment within 12 weeks of baseline, with the all randomised, high TMB population in the denominator. Time to first deterioration/improvement was defined as the time from randomisation until the first deterioration/improvement in PRO score meeting or exceeding the MID for each measure. Further details are described in the supplementary material. A stratified Cox proportional hazards model was used to estimate hazard ratios (HRs) and their 95% CIs; time to deterioration/improvement was estimated using unstratified Kaplan-Meier methodology.

Analyses were conducted using SAS software (version 9.4; SAS Institute, Cary, NC) and were based on a database lock of 15 March 2018. LCSS and EQ-5D data analysis and interpretation was limited to common assessment time points with ≥10 patients in each treatment group.

3. Results

3.1. Patients

Overall, 583 patients were randomised to nivolumab plus ipilimumab and 583 to chemotherapy (Supplementary Fig. S1). The minimum patient follow-up was 13.0 months. Of randomised patients, 139 patients assigned to nivolumab plus ipilimumab (135 of whom were treated) and 160 patients assigned to chemotherapy (159 of whom were treated) had high TMB (≥10 mutations/megabase). Among patients with high TMB assigned to nivolumab plus ipilimumab or chemotherapy, 83% (116/139) and 88% (141/160) of patients, respectively, had baseline and at least one postbaseline PRO assessment available for LCSS; these numbers were 83% (115/139) and 89% (142/160) of patients, respectively, for EQ-5D. Baseline characteristics for these PRO-evaluable patients were generally balanced between treatment groups and comparable with the overall population (Supplementary Table S1).

3.2. Descriptive analyses of on-treatment PROs

LCSS and EQ-5D completion rates among patients with high TMB were approximately 90% at baseline and generally remained high, >80% or approaching 80% for
most on-treatment assessments where ≥10 patients were eligible to respond (Supplementary Table S2). Completion rates were similar in the all randomised population (Supplementary Table S2).

In patients with high TMB, mean change from baseline in LCSS ASBI and LCSS 3-IGI scores at common assessment time points (every 6 weeks) on treatment are shown in Figure 2A and 2B. With nivolumab plus ipilimumab, improvements were seen from week 6 and reached clinically meaningful change by week 12. However, in the chemotherapy group, LCSS ASBI and LCSS 3-IGI scores showed little change from baseline over time. Across individual symptoms, a trend for improvement over time with nivolumab plus ipilimumab on treatment was observed for fatigue and dyspnoea (Figure 2C and 2D), as well as other symptoms, with one exception (Supplementary Fig. S2). For haemoptysis, the symptom score on average was very low compared with other symptoms, and the mean score was <10 at baseline; therefore, an improvement of >10 was not possible (Supplementary Fig. S2). The LCSS 3-IGI index items of global HRQoL and interference with

Fig. 2. Changes from baseline at common assessment time points on treatment in LCSS ASBI (A), LCSS 3-IGI (B) and LCSS ASBI selected individual symptoms: fatigue (C) and dyspnoea (D) in patients with high TMB (≥10 mutations/megabase). Analysis includes patients with complete data at baseline and at the given assessment time points. Circles indicate point estimates and bars indicate 95% CIs. Common assessment time points across treatment arms are represented in the figure and denoted on the x-axes; only time points that had PRO data available for ≥10 patients in either treatment arm are plotted on the graph. The mean (95% CI) baseline scores for nivolumab plus ipilimumab and chemotherapy, respectively, were as follows LCSS ASBI, 27.7 (24.6–30.8) and 24.8 (22.2–27.5); LCSS 3-IGI, 195.8 (183.0–208.6) and 197.6 (185.4–209.8); fatigue, 35.8 (31.2–40.4) and 36.0 (31.5–40.5); dyspnoea, 28.8 (23.9–33.8) and 24.8 (20.4–29.1). 3-IGI, 3-Item Global Index; ASBI, Average Symptom Burden Index; CI, confidence interval; LCSS, Lung Cancer Symptom Scale; MID, minimally important difference; PRO, patient-reported outcome; TMB, tumour mutational burden.
activity showed improvements with nivolumab plus ipilimumab from week 6, which reached clinically meaningful change by week 12 and were sustained on treatment; symptom distress also showed improvement at week 6 that approached or exceeded the MID at most subsequent common postbaseline assessments (Supplementary Fig. S2). In the chemotherapy group, individual component scores generally remained stable over time.

Mean change from baseline in EQ-5D VAS and EQ-5D UI scores at common assessment time points on treatment are shown in Figure 3A and 3B. With nivolumab plus ipilimumab, changes from baseline in EQ-5D VAS and EQ-5D UI showed rapid (by week 6) and clinically meaningful (by week 12) improvement, which was sustained on treatment. For chemotherapy, the EQ-5D VAS scores were similar to baseline through week 12, followed by sustained improvement from week 18 onwards; the EQ-5D UI scores remained similar to baseline or appeared to worsen (weeks 30 and 36).

Mean EQ-5D VAS and EQ-5D UI scores were similar to published data on patients with lung cancer [19] at baseline and increased over time on treatment in both arms (Figure 3C and D). Patients treated with nivolumab plus ipilimumab, but not with chemotherapy, reached the general population norm (i.e. values for the average person in the general population, 82.8 and 0.86, respectively) [20] in EQ-5D VAS and EQ-5D UI at week 60, and the scores remained at or close to this level at most subsequent time points.

3.3. Longitudinal MMRM analysis

In the MMRM analysis, differences between treatments in change from baseline (Figure 4; Supplementary Table S3) and mean score (Supplementary Table S3) in LCSS

![Figure 3. Changes from baseline (A and B) and mean scores (C and D) at common assessment time points on treatment for EQ-5D VAS and EQ-5D UI, respectively, in patients with high TMB (≥10 mutations/megabase). Analysis includes patients with complete data at baseline and at the given assessment time points. Circles indicate point estimates, and bars indicate 95% CIs. Common assessment time points across treatment arms are represented in the figure and denoted on the x-axes; only time points that had PRO data available for ≥10 patients in either treatment arm are plotted on the graph. CI, confidence interval; MID, minimally important difference; PRO, patient-reported outcome; TMB, tumour mutational burden; UI, utility index; VAS, visual analogue scale.](image-url)
ASBI showed lower symptom burden with nivolumab plus ipilimumab versus chemotherapy overall and across individual symptoms, except for haemoptysis, with treatment differences exceeding or approaching the MID. Differences in mean changes from baseline in LCSS 3-IGI favoured nivolumab plus ipilimumab versus chemotherapy, with the difference being higher than the MID for the overall score (mean change 27.5 versus −5.1; difference 32.6) and higher than or approaching the MID for individual items (Supplementary Table S3). Similarly, differences in EQ-5D VAS and EQ-5D UI mean scores and changes from baseline favoured nivolumab plus ipilimumab versus chemotherapy, although the magnitude of difference was small for EQ-5D VAS; for EQ-5D U1, differences were clinically meaningful (difference in least squares mean change of 0.091; Supplementary Table S3).

3.4. Time to first disease-related deterioration/ improvement

A numerically higher proportion of patients treated with chemotherapy versus nivolumab plus ipilimumab had disease-related symptom deterioration either on or off treatment by week 12 (Figure 5A). Absolute risk reduction was 12.7% (95% CI = 2.4–22.5). Time to first deterioration by LCSS ASBI (Figures 5B and 6) and by LCSS 3-IGI (Figure 6; Supplementary Fig. S3A) was delayed with nivolumab plus ipilimumab, with HRs (95% CIs) for nivolumab plus ipilimumab over chemotherapy of 0.40 (0.26–0.63) and 0.56 (0.38–0.82), respectively. Similar delays in deterioration by EQ-5D VAS and U1 were observed (Figure 6; Supplementary Figs. S3B and S3C). Nivolumab plus ipilimumab delayed the time to deterioration versus chemotherapy across individual LCSS ASBI symptoms, except for haemoptysis; delays were also observed for LCSS 3-IGI individual items; however, the 95% CI for symptom distress included no difference (HR = 1) (Figure 6).

Estimates from the time to first improvement analyses showed similar patterns in favour of nivolumab plus ipilimumab (Figure 7 and Supplementary Fig. S4), although the 95% CIs included no difference (HR = 1) for LCSS ASBI individual symptoms of anorexia, haemoptysis and pain, LCSS 3-IGI (overall and individual items) and EQ-5D VAS.

4. Discussion

In patients with advanced NSCLC and high TMB, first-line nivolumab plus ipilimumab provided early and sustained improvements in PROs versus chemotherapy. The two PRO instruments used in this study provided distinct information on the patient experience. Given the high symptom burden in advanced NSCLC [21], the assessment of impact on patients’ symptoms provided by the LCSS ASBI and 3-IGI are particularly relevant. As a general health status measure, the EQ-5D provides the ability to evaluate health status of patients in this study relative to other, non-NSCLC populations and indicates how changes in health status would be reflected in health technology assessments. Descriptive and longitudinal analyses of LCSS ASBI and 3-IGI scores on treatment favoured nivolumab plus ipilimumab over chemotherapy. Although study instruments and the study assessments schedule were designed to assess lung cancer symptoms and health status rather than side-effects of treatment, improvements with nivolumab plus ipilimumab in individual lung cancer symptoms within the LCSS ASBI, such as fatigue and
dyspnoea, are notable given their potential association with immune-related adverse events observed with immunotherapy regimens. For haemoptysis, which had a very low symptom score on average compared with other symptoms, differences in change from baseline analyses numerically favoured chemotherapy but were small in magnitude, and the 95% CI of the estimates included no change. Findings for patients’ overall health status measured by EQ-5D UI were similar to those for LCSS ASBI and 3-IGI. With the EQ-5D VAS, improvements were observed in both treatment groups; however, the improvement seen with chemotherapy
from week 18 in those patients who continued to complete assessments may be attributed to completion of the doublet chemotherapy induction, with its accompanying well-known toxicities.

Incorporating information from all available on-treatment and off-treatment assessments, a lower proportion of patients treated with nivolumab plus ipilimumab had symptom deterioration by week 12. Analyses including common on-treatment and follow-up PRO data also demonstrated that nivolumab plus ipilimumab delayed time to first deterioration and shortened time to improvement across multiple PRO measures.

Our findings are consistent with previous reports showing an improved impact on symptom burden and HRQoL for immunotherapy versus chemotherapy across first-line [22] and previously treated [8,10,23,24] NSCLC. Immunotherapies have also shown a similar trend in other tumour types [25,26]. It should be noted that it is difficult to compare PRO results across studies given differences in disease setting and study design. This caution acknowledged, the results from two studies in previously treated NSCLC comparing nivolumab with docetaxel using the LCSS and EQ-5D showed improvement in symptom burden and health status [8,10]; however, our results for first-line nivolumab plus ipilimumab in patients with high TMB suggest a faster and more clinically meaningful improvement. Recent studies have evaluated PROs in patients treated with immunotherapy plus chemotherapy versus chemotherapy alone in first-line NSCLC [27,28]; however, these studies used other PRO measures and assessed different end-points, making comparisons with our study difficult. PRO assessment using the LCSS and EQ-5D is incorporated in the other ongoing cohorts of CheckMate 227 Part 1, as well as CheckMate 227 Part 2, which is evaluating first-line nivolumab plus chemotherapy versus chemotherapy; this will provide additional information on the impact of nivolumab-based combinations on PROs in patients with advanced NSCLC.

Interestingly, in our analysis, improvements with nivolumab plus ipilimumab were observed relatively early, within the first 12 weeks of treatment, corresponding to the previously reported median time to objective response in this treatment group (2.7 months) [11]. We therefore speculate that improvement in disease-specific and generic PROs may serve as an early indicator for treatment response. Further analyses are needed to explore the correlation of PRO changes with tumour response and OS.

Potential reporting biases owing to the open-label study design may be a limitation of our analysis; however, two recent studies found no evidence to support the hypothesis that patients in open-label studies randomised to the experimental arm report better outcomes [29,30]. Exclusion of data on patients who discontinued therapy from the on-treatment descriptive and MMRM results may understate the difference in HRQoL between the two treatment groups because patients who progress and discontinue treatment more quickly in the chemotherapy arm are frequently those with inferior HRQoL [9]. Although treatment-related adverse events were measured and reported in the primary manuscript [11], symptomatic side-effects of treatment may be underreported by physicians [31,32]. Patients’ assessments of the incidence and bother-someness of these side-effects were not captured in this study; instruments and methods designed to focus on these effects and how they may differ by method of action (e.g. immunotherapies) are the subject of ongoing research.

In conclusion, patients treated with nivolumab plus ipilimumab experienced more rapid, durable and
clinically meaningful improvements in PROs than those treated with chemotherapy. These results, together with the demonstrated efficacy and manageable safety profile previously reported for nivolumab plus ipilimumab in this study [11], provide further evidence of the benefits of first-line nivolumab plus ipilimumab in patients with advanced NSCLC and high TMB.

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Conflict of interest statement

M.R. reports receiving lecture and consultant fees from AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Lilly, Merck, MSD, Novartis, Pfizer and Roche. M.S. reports receiving personal and institutional fees from Bristol-Myers Squibb during the conduct of the study, and personal and institutional fees for clinical trial activities in the field of immunotherapy from AstraZeneca, Bristol-Myers Squibb, Merck, Merck-Serono, Pfizer, Regeneron and Roche, outside the submitted work. K.H.L. reports receiving personal fees from Bristol-Myers Squibb and MSD, outside the submitted work. K.L.-K. reports receiving investigator fees from Roche and personal fees from Bristol-Myers Squibb during the conduct of the study, grants and personal fees from AstraZeneca, MSD and Roche and personal fees from Celgene, outside the submitted work. M.N. reports receiving research funding from Astellas, consultant fees as honoraria from Daiichi Sankyo Healthcare and Merck Serono and speaker and consultant fees as honoraria and research funding from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly, MSD, Novartis, Ono Pharmaceutical, Pfizer and Taiho Pharmaceutical, all outside the submitted work. K.L.-K. reports receiving investigator fees and fees for the hospital from Bristol-Myers Squibb during the conduct of the study; personal and lecture fees from Amgen; lecture fees from Bayer, Merck and TEVA; travel, accommodation and congress fees from Roche and investigator fees from AbbVie, Bayer, Lilly, MSD, Regeneron, Roche and Servier, outside the submitted work. R.S. reports receiving advisory board fees from Novartis, honoraria from Pfizer and advisory board fees and honoraria from AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Lundbeck, Merck, Roche/Genentech and Takeda, all outside the submitted work. S.A. reports receiving consultancy fees and travel grants from Bristol-Myers Squibb during the conduct of the study. J.R., K.F. and F.A.F. have nothing to disclose. R.C. reports receiving advisory board fees from Bristol-Myers Squibb outside the submitted work. E.R. reports receiving grants from Bristol-Myers Squibb outside the submitted work. J.R.P. reports employment by and stock ownership in Bristol-Myers Squibb. Y.Y., F.E.N. and P.B. report employment by Bristol-Myers Squibb. M.D., F.T. and R.L. are employees of Adelphi Values, a consulting firm receiving payment from Bristol-Myers Squibb for statistical data analysis. J.B. reports an advisory committee/consulting agreement with Bristol-Myers Squibb and receiving grants from Bristol-Myers Squibb during the conduct of the study and grants from MedImmune/AstraZeneca, an advisory committee/consulting agreement, grants and personal fees from Merck and advisory board fees from Genentech, outside the submitted work.

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Appendix A. Supplementary data

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