Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med 2021;384:1191-203. DOI: 10.1056/NEJMoa2032125

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Contents

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Additional Key Inclusion and Exclusion Criteria

1. Inclusion criteria
    - Complete resection must have been performed within 4 to 16 weeks prior to randomization
    - Patients must have been disease free as documented by a complete physical examination and imaging studies within 4 weeks prior to randomization
    - Tumor tissue from the resected site of disease must have been provided for biomarker analyses, including tumor cell programmed death ligand 1 (PD-L1) status
2. Exclusion criteria
    - Patients with cervical esophageal carcinoma and those who did not receive concurrent chemoradiotherapy prior to surgery or who only received chemotherapy or only radiation prior to surgery, and those with stage IV resectable disease
    - Patients with previous malignancies unless a complete remission was achieved at least 5 years prior to trial entry and no additional therapy was required or anticipated (exceptions included, but were not limited to, non-melanoma skin cancers, in situ bladder cancer, in situ colon cancers, in situ cervical cancers/dysplasia, or in situ breast carcinoma)
    - Patients with active, known, or suspected autoimmune disease, except for those with diabetes mellitus or hypothyroidism requiring only hormone replacement or skin disorders (vitiligo, psoriasis, or alopecia) that did not require systemic treatment, or conditions that were not expected to recur in the absence of an external trigger

- Patients who required systemic treatment with either corticosteroids (>10 mg/daily) or other immunosuppressive medications within 14 days of trial drug administration, except for inhaled or topical steroids, or adrenal replacement steroids equivalent to more than 10 mg of prednisone
- Patients with symptomatic interstitial lung disease, human immunodeficiency virus or acquired immunodeficiency syndrome, and toxicities associated with prior anticancer therapy, as well as those who had received anti–programmed death (PD)-1, anti–PD-L1, anti–PD-L2, anti-CD137, or anti–CTLA-4 antibody therapies

Treatment Allocation, Blinding, and Randomization

The treatment allocation list was generated by the sponsor. The web registration system was implemented by a third party and ensured that the treatment assignment sequence was concealed to the investigator, patient, and sponsor. The study was double blinded; the sponsor, patients, investigators, and site staff were blinded to treatment allocation. Randomization was performed using interactive (voice/web) response technology with a block size of 3 and was stratified according to tumor cell PD-L1 expression (≥1% vs. <1% or indeterminate or nonevaluable), pathologic lymph node status (≥ypN1 vs. ypN0), and histology (squamous vs. adenocarcinoma).

Censoring Summary for Disease-free Survival

For patients who remained alive and without recurrence, disease-free survival was censored on the date of last evaluable disease assessment. Patients who started subsequent therapy (radiotherapy, surgery, or systemic anticancer therapy) or developed a second primary cancer without recurrence were censored on the last tumor assessment date prior to the start of subsequent therapy or diagnosis of a second primary cancer. At the clinical data cutoff, 398

(50%) randomized patients were censored for disease-free survival. Most of these patients (n = 379, 48%) were censored on their last tumor assessment date prior to the start of subsequent therapy or development of a second primary cancer. Of these 379 patients, 310 (39%) were in follow-up, 50 (6%) were receiving treatment, nine (1%) were off study (two lost to follow-up, six withdrawn consent, one other reason), and 10 (1%) developed a second primary cancer. The remaining 19 (2%) disease-free survival-censored patients were censored on the date of randomization for lack of an on-study tumor assessment.

Assessment of Distant Metastasis–free Survival and Health-related Quality of Life

Distant metastasis–free survival was defined as the time between the date of randomization and the date of first distant recurrence or date of death (whatever the cause), whichever occurred first. For patients who remained alive and distant recurrence free, distant metastasis–free survival data were censored on the date of last disease assessment. The hazard ratio for distant metastasis–free survival with its corresponding two-sided 95% confidence interval (CI) was estimated via a Cox model with treatment group as the only covariate in the model stratified by the three randomization stratification factors. Distant metastasis–free survival for each treatment group was estimated and plotted using the Kaplan–Meier product-limit method. Median distant metastasis–free survival time was computed using the Kaplan–Meier estimate, and a 95% CI for the median was computed based on a log-log transformation of the survivor function. The CIs for the median distant metastasis–free survival were not adjusted for multiplicity. Distant metastasis–free survival was an exploratory endpoint in the study and was not powered for statistical comparison.

The FACT-E (Functional Assessment of Cancer Therapy–Esophageal) questionnaire was used to assess the effects of underlying disease and its treatment on health-related quality of life.

This tool includes the 27-item FACT-General (FACT-G) and an additional 17 items (esophageal cancer subscale) specific to esophageal cancer that assess concerns related to swallowing, vocalization, breathing, and other symptoms. Thresholds for clinically meaningful change were 9.5 points for the FACT-E total score, with a sensitivity clinically meaningful change of 13.1 points.[1,2]

The European Quality of Life–5 Dimensions (EQ-5D) descriptive system assessed the overall health status of patients through the EQ-5D-3L Visual Analogue Scale and Utility Index. Changes from baseline of 7 and 0.08 points for the Visual Analogue Scale and Utility Index, respectively, were considered clinically meaningful.[3] Longitudinal mixed model analysis was used to compare the least squares mean score differences between treatment groups, with a separate analysis being performed for each patient-reported outcome.

The impact of missing data on the patient-reported outcomes analysis was analyzed within each treatment group by review of missing data patterns, reported reasons for missing data, and impact of the patient-reported outcome score prior to drop-out; the review of the observed data concluded that the amount of missing data was limited and was similar in each treatment group. Therefore, for the purposes for conducting the on-treatment MMRM models, a missing at random assumption was reasonable. Completion rates for patient-reported outcome measures were high for both treatment groups. A review of the missing data did not indicate any clear patterns; therefore, no imputation for missing data was performed. A mixed model repeated measures was used for the analysis of change from baseline; to aid interpretation, the number of patients with data at each visit is presented in Figure S3. Additionally, in Figure S4, missing data at each visit are presented to allow for the transparent review of the GP5 results.

Analysis Populations

- All enrolled patients: All patients who signed an informed consent form and were registered into the interactive web response system
- All randomized patients (efficacy population): All patients who were randomly assigned to any treatment group in the trial. This was the primary dataset for analyses of trial conduct, trial population, and efficacy
- All treated patients (safety population): All randomly assigned patients who received at least one dose of nivolumab or placebo during the trial. This was the primary dataset for analyses of exposure and safety
- Patient-reported outcomes population: Randomly assigned patients who had an assessment at screening/baseline and at least one follow-up assessment

Table S1. Prior Chemotherapy and Radiotherapy Treatment.

Prior Chemoradiotherapy Treatment	Nivolumab (N = 532)	Placebo (N = 262)
Patients who received prior concurrent CRT — no. (%)*	528 (99)	261 (>99)
Chemotherapy — no. (%)†		
Neoadjuvant	527 (99)	260 (99)
Carboplatin/paclitaxel	386 (73)	177 (68)
Cisplatin/fluorouracil	77 (14)	35 (13)
Fluorouracil/oxaliplatin	14 (3)	9 (3)
Other	50 (9)	39 (15)
Radiotherapy in prior concurrent CRT — no. (%)‡	528 (99)	261 (>99)
Median radiotherapy dosage — Gray (range)‡	45.0 (1.80−7560)	45.0 (4.14−5040)
Radiotherapy dosage, Gray — no. (%)‡§		
<41.4	66 (12)	26 (10)
<40	7 (1)	3 (1)
40–<41.4	59 (11)	23 (9)
41.4–50.4	339 (64)	165 (63)
>50.4	93 (18)	59 (23)
Not reported	30 (6)	11 (4)

CRT denotes chemoradiotherapy.

* Includes only regimens related to the latest concurrent CRT followed by complete resection.

† Adjuvant carboplatin/paclitaxel was given to one patient in the nivolumab group, and adjuvant fluorouracil/leucovorin/oxaliplatin was given to one patient in the placebo group (protocol violations).

‡ Includes the sum of radiotherapies received from the start of concurrent CRT until complete resection. Radiotherapy exposure occurred prior to the conduct of the trial and was not under the control of the study investigators; dose received was as reported in the case report form and following database lock, investigators amended the total dose of radiotherapy for seven patients in the <40 Gray group to 41.4–50.4 Gray.

§ Percentages are out of 528 nivolumab patients and 261 placebo patients who received prior concurrent CRT followed by complete resection.

Table S2. Demographics and Baseline Clinical Characteristics by Time from Complete Resection to Randomization.

	Time from Complete Resection to Randomization <10 weeks		Time from Complete Resection to Randomization ≥10 weeks	
	Nivolumab (n = 182)	**Placebo (n = 74)**	**Nivolumab (n = 350)**	**Placebo (n = 188)**
Median age (range) — yr	62.0 (36–82)	60.5 (26–86)	62.0 (26–82)	62.0 (30–84)
Male — no. (%)	155 (85)	64 (86)	294 (84)	158 (84)
Race* — no. (%)				
White	128 (70)	53 (72)	304 (87)	163 (87)
Asian	50 (27)	18 (24)	33 (9)	16 (9)
ECOG PS — no. (%)				
0	113 (62)	49 (66)	195 (56)	107 (57)
1	69 (38)	25 (34)	155 (44)	81 (43)
Disease stage at initial diagnosis — no. (%)				
II	60 (33)	27 (36)	119 (34)	72 (38)
III	122 (67)	47 (64)	229 (65)	116 (62)
Tumor location — no. (%)				
EC	124 (68)	47 (64)	196 (56)	108 (57)
GEJC	58 (32)	27 (36)	154 (44)	80 (43)
Histology — no. (%)				
Squamous cell carcinoma	77 (42)	24 (32)	78 (22)	51 (27)

Adenocarcinoma	105 (58)	50 (68)	271 (77)	137 (73)
Pathologic lymph node status ≥ ypN1 — no. (%)	99 (54)	43 (58)	206 (59)	109 (58)
Tumor cell PD-L1 expression† — no. (%)				
≥1%	36 (20)	14 (19)	53 (15)	26 (14)
<1%	117 (64)	51 (69)	257 (73)	145 (77)
Indeterminate/nonevaluable	29 (16)	9 (12)	40 (11)	17 (9)

EC denotes esophageal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJC, gastroesophageal junction cancer; PD-L1, programmed death ligand 1.

* Other races not shown.

† Tumor cell PD-L1 expression determined from surgical specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako).

Table S3. Subsequent Therapies.

Therapy	Nivolumab (N = 532)	Placebo (N = 262)
	no. of patients (%)	
Patients with any subsequent therapies	157 (30)	111 (42)
Radiotherapy	43 (8)	41 (16)
Surgery	28 (5)	20 (8)
Systemic therapy	125 (23)	89 (34)
Immunotherapy	4 (<1)	19 (7)
Targeted therapy	13 (2)	11 (4)
Other systemic anticancer therapy/chemotherapy	123 (23)	85 (32)

Table S4. Exposure.

Variable	Nivolumab* (N = 532)	Placebo* (N = 260)
Median duration of treatment (range) — mo	10.1 (<0.1–14.2)	9.0 (<0.1–15.0)
Relative dose intensity — no. (%)		
≥90%	459 (86)	NA
70% – <90%	67 (13)	NA
50% – <70%	4 (<1)	NA
<50%	2 (<1)	NA
≥1 dose delay — no. (%)	226 (42)	113 (43)
Doses delayed per patient — no. (%)		
0	306 (58)	147 (57)
1	148 (28)	68 (26)
2	51 (10)	30 (12)
3	17 (3)	9 (3)
≥4	10 (2)	6 (2)

NA denotes not applicable.

* All randomized patients who received at least one dose of trial treatment (safety population).

Table S5. Treatment-related Adverse Events with Potential Immunologic Etiology.

Select Treatment-related Adverse Events†‡	Nivolumab* (N = 532)		Placebo* (N = 260)	
	Any Grade	Grade 3–4	Any Grade	Grade 3–4
	no. of patients (%)			
Endocrine	93 (17)	5 (<1)	6 (2)	0
Gastrointestinal	91 (17)	4 (<1)	40 (15)	3 (1)
Hepatic	49 (9)	6 (1)	18 (7)	4 (2)
Pulmonary	23 (4)	6 (1)	4 (2)	1 (<1)
Renal	7 (1)	1 (<1)	2 (<1)	0
Skin	130 (24)	7 (1)	28 (11)	1 (<1)

* All randomized patients who received at least one dose of trial treatment (safety population).

† Select treatment-related adverse events are those with potential immunologic etiology that require frequent monitoring/intervention.

‡ Events reported between first dose and 30 days after last dose of trial drug.

Figure S1. CONSORT Diagram for Patient Disposition.

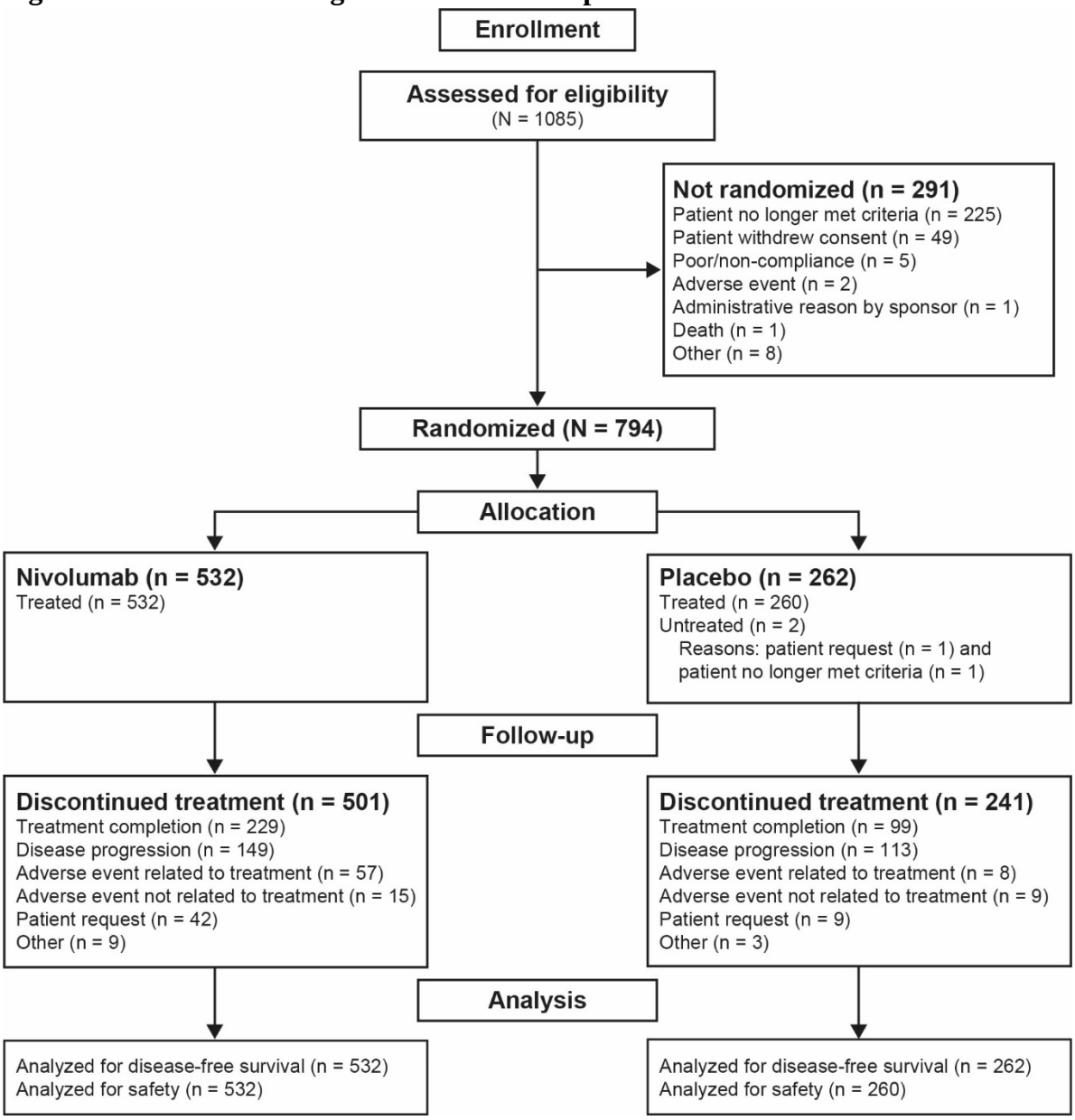
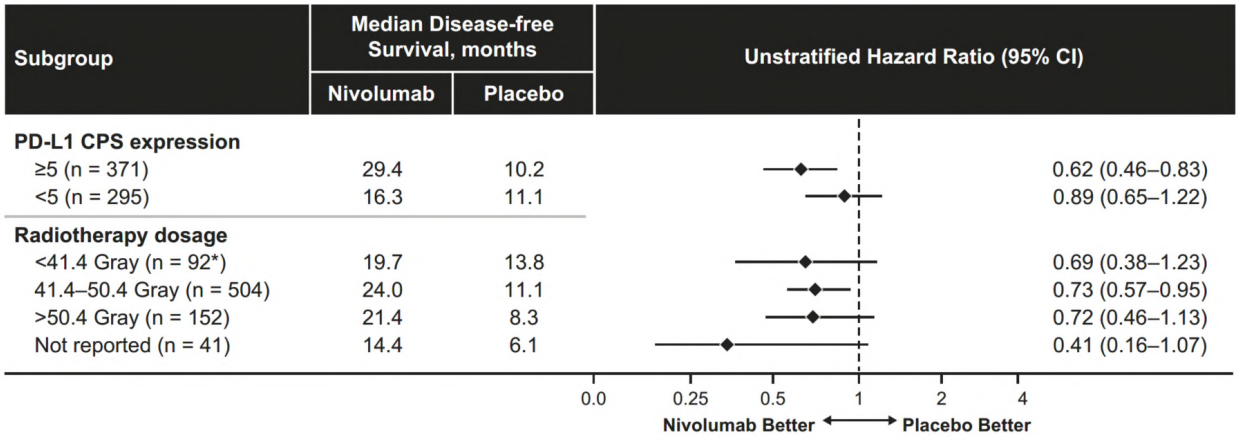


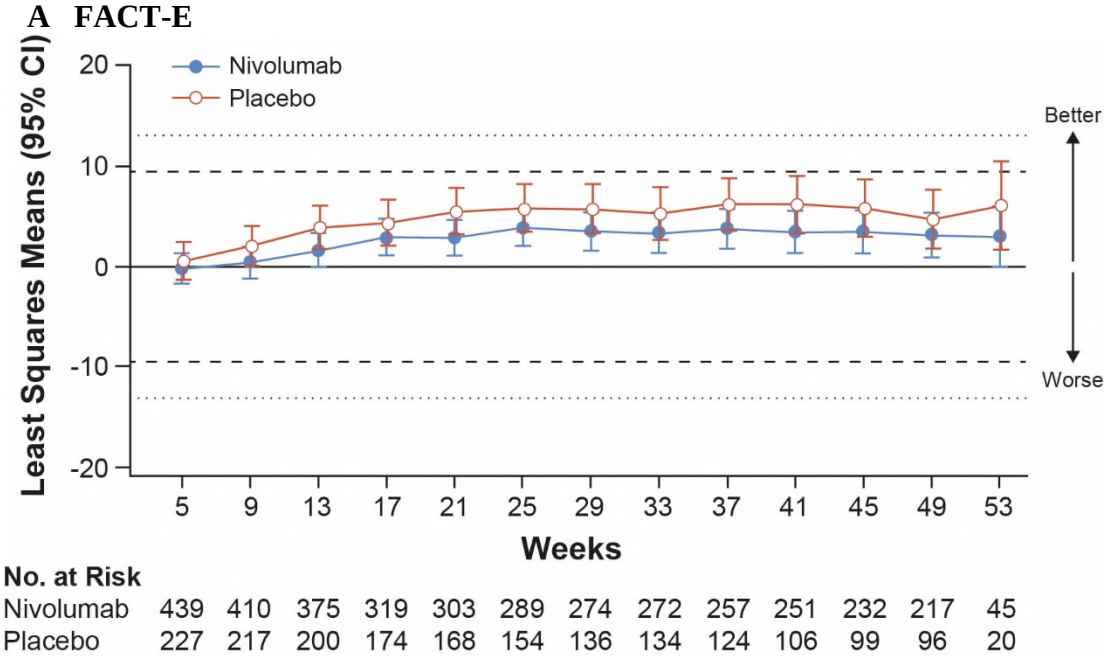
Figure S2. Post Hoc Assessment of Disease-free Survival by Subgroups.



CI denotes confidence interval; CPS, combined positive score; PD-L1, programmed death ligand 1.

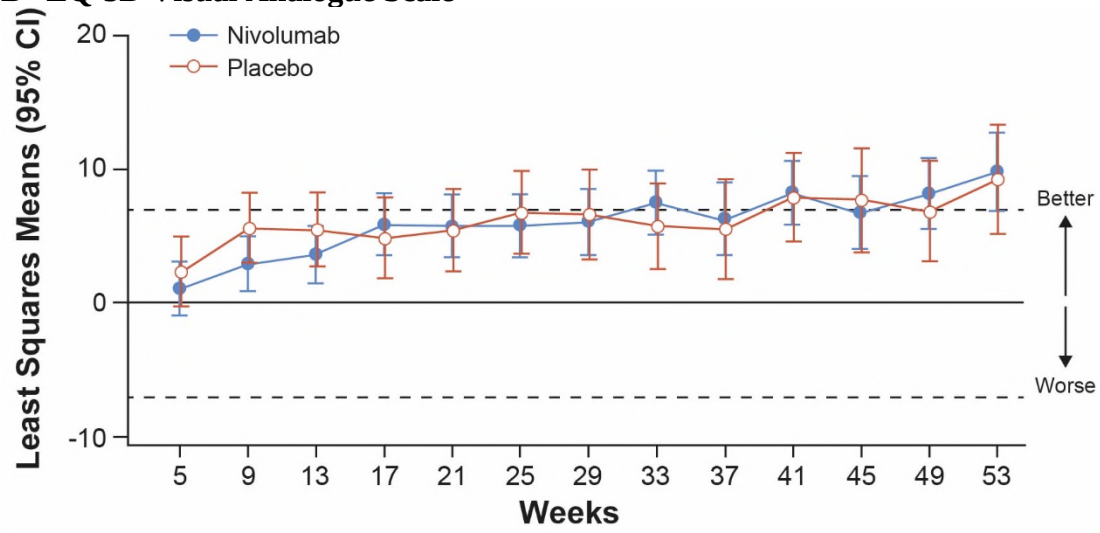
* 10 patients (seven in the nivolumab group and three in the placebo group) received total exposure less than 40 Gray (following database lock, investigators amended the total dose of radiotherapy for seven of these patients to 41.4–50.4 Gray).

Figure S3. Least Squares Means (95% CI) Changes from Baseline for Nivolumab and Placebo in the Patient-reported Outcomes Population.



Dashed lines indicate a clinically meaningful change of 9.5 points, and dotted lines indicate a sensitivity score change of 13.1 points.[1,2] Error bars indicate 95% confidence intervals.

B EQ-5D Visual Analogue Scale

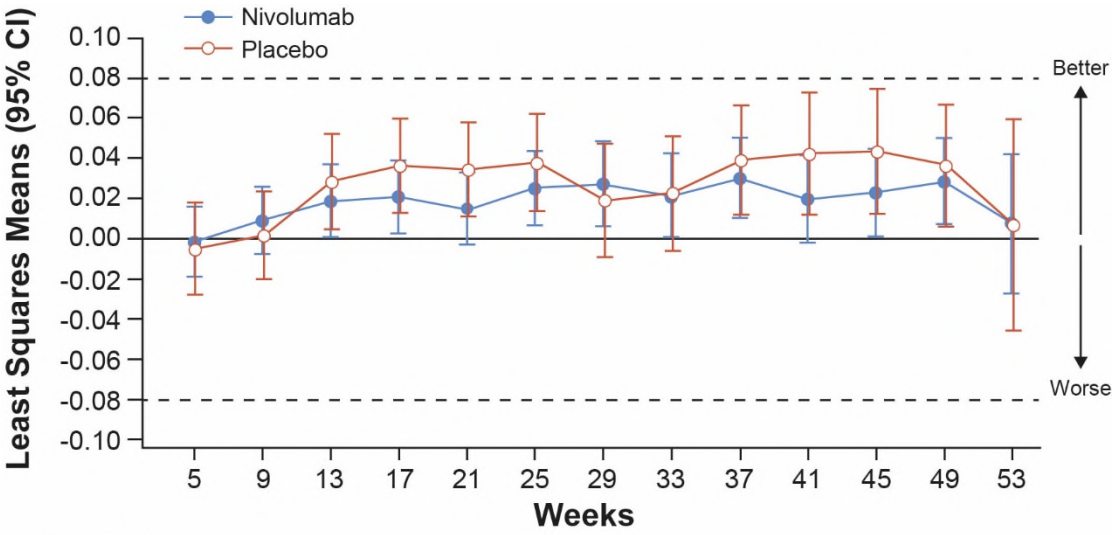


No. at Risk

Nivolumab	446	420	383	323	312	299	280	283	268	256	241	221	48
Placebo	220	219	202	172	169	155	136	131	124	108	100	96	21

Dashed lines indicate clinically meaningful change (7 points).[3] Error bars indicate 95% confidence intervals.

C EQ-5D Utility Index Score

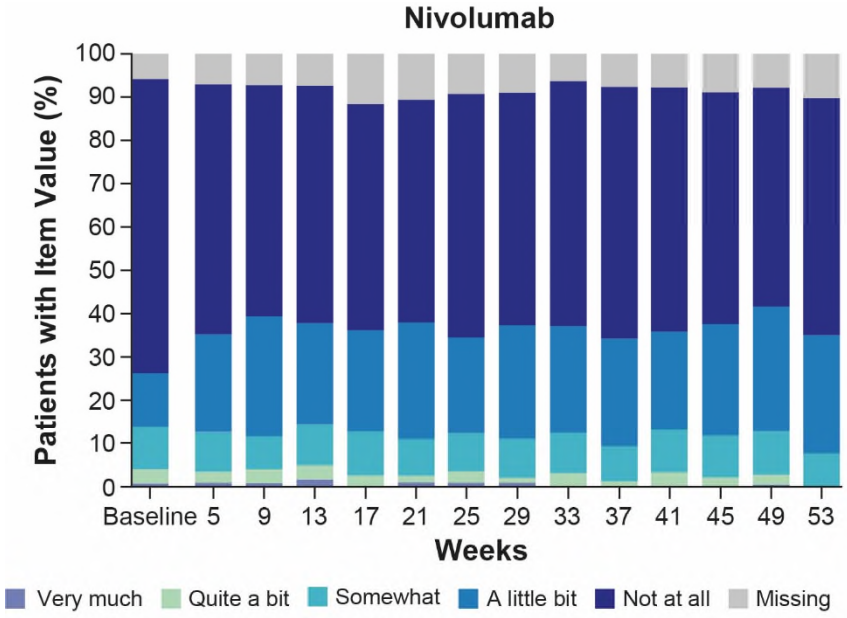


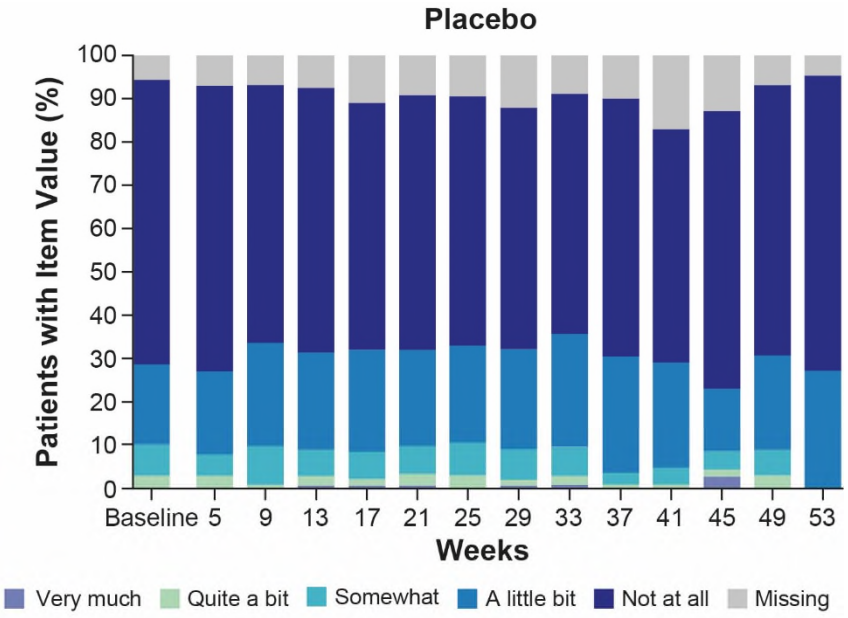
No. at Risk

Nivolumab	445	419	386	322	310	300	279	282	265	256	241	221	48
Placebo	217	214	198	170	167	154	137	129	123	109	97	95	20

Dashed lines indicate clinically meaningful change (0.08 points).[3] Error bars indicate 95% confidence intervals.

Figure S4. FACT-E GP5 ("I am bothered by side effects of treatment") Item Values.





No. of Patients with Assessments

Very much	4	4	4	7	0	4	3	3	1	1	0	0	1	0
Quite a bit	17	13	15	14	10	5	9	4	9	3	10	6	6	0
Somewhat	50	44	34	40	37	30	29	28	28	23	27	25	24	4
A little bit	62	111	127	96	86	95	73	82	75	73	64	68	70	14
Not at all	341	280	242	226	191	180	185	167	171	168	157	140	122	28
Missing	27	32	31	29	41	36	29	27	18	21	21	22	18	5

No. of Patients with Assessments

Very much	0	0	1	1	1	1	0	1	1	0	0	3	0	0
Quite a bit	7	7	1	5	3	5	5	2	3	1	1	2	3	0
Somewhat	18	12	21	13	12	12	13	11	10	4	5	5	6	0
A little bit	47	48	57	49	46	42	39	37	39	38	32	17	23	6
Not at all	164	163	141	132	110	110	99	88	82	84	70	75	65	15
Missing	14	17	16	16	21	17	16	19	13	14	22	15	7	1

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2. Ringash J, O'Sullivan B, Bezjak A, Redelmeier DA. Interpreting clinically significant changes in patient-reported outcomes. Cancer 2007;110:196-202.
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