Risk of Further Progression or Death Among Durable Progression-Free Survivors With Melanoma or Non–Small-Cell Lung Cancer in PD-1 Blockade Trials: Implications for Imaging Surveillance

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ABSTRACT

PURPOSE Durable progression-free survivors (dPFSors) over 2 years have been reported among patients with melanoma or non–small-cell lung cancer (NSCLC) who received PD-(L)1 therapy. However, risk of progression still exists and the optimal imaging surveillance interval is unknown.

METHODS Individual patient data for progression-free survival (PFS) were extracted from PD-1 blockade clinical trials with a follow-up of at least 5 years. Patients with a PFS of at least 2 years were considered as dPFSors. Conditional risks of progression/death (P/D) every 3, 4, 6, and 12 months in each subsequent year were calculated. We prespecified three different levels of risk between scans (10%, 15%, or 20%) to allow clinicians and patients to decide on the scanning interval on the basis of considerations of imaging frequency and risk tolerance. An interval is considered acceptable if the upper bound of the 95% CI of the risk at each scan is lower than a prespecified level.

RESULTS Of 1,495 and 3,752 patients with melanoma and NSCLC, 474 (31.7%) and 586 (15.6%) were dPFSors, respectively. Among them, the PFS probability for an additional 3 years was 76.4% and 48.1%, respectively. Not more than 8% of patients had P/D in any quarter in the 3 years. With a risk threshold of 10%, melanoma dPFSors can be scanned every 6 months during the third year and then every 12 months in years 4 and 5. The interval for NSCLC would be every 3 months in the third year and every 4 months in years 4 and 5. The higher risk tolerance of 15% and 20% would allow for less frequent scans.

CONCLUSION On the basis of their own risk tolerance level, our findings allow clinicians and dPFSors make data-driven decisions regarding the imaging surveillance schedule beyond every 3 months.

ACCOMPANYING CONTENT

Appendix

Data Supplement

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INTRODUCTION

The advent of immune checkpoint inhibitors (ICIs), particularly anti-PD(L)1 therapy, has dramatically changed the treatment paradigms for patients with malignancies.[1,2] One of the hallmarks of ICI is the durable disease control across many tumor types, including but not limited to melanoma and non–small-cell lung cancer (NSCLC). Many prospective clinical trials with long-term follow-up reported relatively flat tails of progression-free survival (PFS) and overall survival (OS) curves beyond 2 years.[3-8]

However, some of those patients are still at risk of further progression. In CheckMate 066, patients with melanoma who received nivolumab had the PFS probability of 35% and 28% at 2 and 5 years, respectively.[6] In KEYNOTE 024, the rate was 22.8% versus 12.8%, respectively, among patients with NSCLC who received pembrolizumab monotherapy.[5] Therefore, albeit the risk is considerably lower compared with treatment initiation, it is not negligible among those durable progression-free survivors (dPFSors).

Currently, there is no guideline recommendation regarding the optimal imaging surveillance schedule for those patients. It would also be challenging to conduct a clinical trial with appropriate end points (eg, OS) and sufficient sample size to answer this question in a foreseeable future. A small randomized trial compared standard computed tomography

CONTEXT

Key Objective

Patients with non–small-cell lung cancer or melanoma with durable progression-free survival (≥2 years) after anti–PD1-based treatment are increasingly seen, but data of high quality are lacking in addressing the imaging surveillance intervals. We pooled clinical trials to report further progression or death risk among those patients. Three levels of risk were prespecified for interval progression between scans (10%, 15%, or 20%) to allow a personalized interval on the basis of considerations of imaging frequency and risk tolerance.

Knowledge Generated

Not more than 8.0% of patients had progression or death in any quarter, strongly supporting an imaging surveillance interval longer than 3 months in durable progression-free survivors. Per Scan risk under different intervals (every 3, 4, 6, and 12 months) was described.

Relevance

Our study allows a personalized decision on the imaging surveillance schedule ranging from every 3 to 12 months on the basis of one's own risk tolerance level.

(CT) scan versus less frequent CT scan plus web-based monitoring among European patients with NSCLC. However, the study was conducted before the ICI era and included both resectable and unresectable patients, limiting its modern application.[9]

By quantifying conditional risk of progression or death in different imaging schedules among dPFSors in melanoma or NSCLC ICI trials,[10,11] this study aims to assist clinicians and patients in making data-driven personalized decisions on imaging scanning frequency.

METHODS

Study Selection

On August 28, 2022, a literature search was conducted in PubMed. The following search terms were used: NSCLC, melanoma, checkpoint inhibitor, pembrolizumab, ipilimumab, nivolumab, avelumab, camrelizumab, durvalumab, sintilimab, cemiplimab, programmed death ligand, PD-L1, and PD-1. Additional studies were added according to the investigators' knowledge if published before October 15, 2022. Studies published before February 28, 2023, were further updated at the time of manuscript revision.

English literature that met the following criteria was included: (1) prospective clinical trials, (2) including patients with NSCLC or melanoma who were not treated with curative intent, (3) follow-up of at least 5 years from the date the last patient was enrolled, and (4) PFS curve with the number of risk tables was published. We further limited the search to studies published in or after 2014. This represents the year when pembrolizumab and nivolumab were first approved by US Food and Drug Administration.[12,13] Only trials with a follow-up of 5 years or long were included in this project, so it is unlikely that any trials of interest would have been published before 2014. The 5-year limit was set to ensure that the follow-up is sufficient to characterize the long-term outcomes in those patients. If more than one publication of the same clinical trial is found, the one with the longest follow-up beyond 5 years would have been included. Studies were excluded if (1) PFS curves of NSCLC or melanoma were not individually reported and (2) the sample size was <10 beyond 2 years.

Extraction of Individual Patient Data

To pool PFS outcomes from different trials, individual patient data were extracted according to Guyot's and Liu's methods.[14-17] This method has been used in the literature across different medical specialties, when raw trial data were not available.[14,17-20] Briefly, Engauge Digitizer v12.1[21] was used to extract coordinates from Kaplan-Meier curves. The individual patient data reconstruction was then performed using R package IPDfromKM.[14] To assess the accuracy of reconstructed Kaplan-Meier curves, plots were first visually inspected for morphology. Then, reconstructed survival probability and numbers at risk were compared with reported numbers. Finally, four statistics were provided to aid assessment between read-in and reconstruction: root mean square error, mean absolute error, max absolute error, and *P* value of the Kolmogorov-Smirnov test. In general, a root mean square error of ≤0.05, a mean absolute error of ≤0.02, and a max absolute error of ≤0.05 indicate the good quality of reconstruction. The Kolmogorov-Smirnov *P* value < .05 is considered poorly extracted data.[14] In addition, we provided key statistics from reconstructed curves and original literature report for comparison: median survival with 95% CI, 3-year PFS probability, and 5-year PFS probability.

Statistical Analyses

Because 24 months is a typical landmark duration of PD-1 blockade in most of the clinical trials, patients with a PFS of ≥24 months were considered as dPFSors in this study.[5,22-24] The PFS probability was defined as the probability of progression- or death-free for a certain time period, estimated using the Kaplan-Meier method. Conditional survival or risk measures the additional survival or risk of a patient with cancer who has already survived a certain time period.[10,11] Individual PFS data were aggregated to construct pooled conditional PFS curves. Hazard rate refers to the rate of an event that will happen in the next moment among a population that has been event-free for a period of time. Conditional risk of progression or death was defined as the probability of events during a specific time period among patients who have been event-free for a certain amount of time. Conditional risk of progression or death was estimated on the basis of a piece-wise exponential survival model. The CIs were obtained using bootstrap methods. The risk was described every 3, 4, 6, and 12 months among dPFSors at each year. It was assumed that within each year from the beginning of the third year, the risk of progression or death was constant. To ensure that this is the correct assumption, pooled hazard rate plots were observed for hazard change against time. Scenarios of two different assumptions (constant hazard within 12 months and 3 months) were also examined.

We prespecified three different levels of risk between scans (10%, 15%, or 20%) to allow clinicians and patients to decide on the appropriate scanning interval for a patient on the basis of considerations of testing frequency and risk tolerance. A scanning interval is considered as acceptable if the 95% CI upper bound of the risk at each scan is lower than a prespecified risk level. All statistical analyses were performed using R (PBC, Boston, MA) or SAS software (SAS Institute, Cary, NC). α was designated at .05. All hypothesis tests were two-sided.

RESULTS

Study Selection and Data Extraction

The electronic search returned 830 publications. After screening, five publications were included from the electronic search. KEYNOTE-006 was excluded because the follow-up for PFS was <5 years.[7] An additional four publications were added according to the investigator's knowledge (flowchart in Fig 1). Among the four, three were published after data search (CheckMate 227, KEYNOTE 189 and 407) and one was not identified in the electronic search (Pooled CheckMate 017 + 057). During the time of revision, we further included KEYNOTE 042 that was published after initial literature search. In total, 10 publications (11 trials) were included in the final analyses, of which three were melanoma studies (CheckMate 066 and 067, KEYNOTE 001) and seven were NSCLC (CheckMate 017 + 057, 227 and KEYNOTE 024, 042, 010, 189, 407).[3-8,25-28]

The characteristics of included trials are summarized in Table 1. All studies enrolled patients who were not treated with curative intent. All studies reported PFS curves using RECIST v1.1, except KEYNOTE 001,[3] which used immune-related response criteria. All studies performed imaging scans every 12 weeks after 24 months, except KEYNOTEs 024 and 010,[4,5] which scanned every 9 weeks.

A total of 14 arms of the 10 publications were extracted to reconstruct individual patient data. The Data Supplement (Figs S1-S14, online only) provides graphical inspection of reconstructed and read-in curves, which show similar shapes and number of events to their original publications, across all studies. The reconstructed PFS curves yielded similar key summary statistics (median PFS with 95% CI, 3- and 5-year PFS probabilities) compared with the original reports (Appendix Table A1, online only). The errors between reconstructed and read-in curves were also extremely low. Kolmogorov-Smirnov tests showed no poorly reconstructed PFS curves (Appendix Table A1). The Data Supplement (Figs S15 and S16) shows the individual reconstructed PFS curves for melanoma and NSCLC, respectively.

Pooled Analysis of dPFSors

A total of 1,495 patients with melanoma and 3,752 patients with NSCLC were pooled, of whom 474 (31.7%) and 586 (15.6%) were dPFSors, respectively. Among them, the PFS probability for an additional 3 years was 76.4% (95% CI, 72.3 to 80.7) and 48.1% (95% CI, 43.9 to 52.8), respectively (Figs 2A and 2B).

Landmark Conditional Risk for Imaging Surveillance Guidance

Pooled hazard rate plots (Data Supplement, Figs S17 and S18) and different piecewise assumptions (Data Supplement, Figs S19 and S20) supported our assumption of constant hazard rate within each year (Data Supplement, Text). Sensitivity analysis showed a similar hazard rate trend in dPFSors with melanoma (Data Supplement, Text and Fig S21). The heterogeneity in dPFSors with NSCLC was not clinically meaningful (Data Supplement, Text).

With pooled individual patient data with time to PFS outcomes, we calculated the landmark conditional risk of progression or death at each year from 2 to 5 years. Conditional risk at intervals of 3, 4, 6, and 12 months was provided for imaging surveillance guidance for melanoma and NSCLC, respectively (Fig 3). Of note, the quarterly risk of progression or death was extremely low—no patients had a risk above 8% in any quarter. The highest quarterly risk was dPFSors with NSCLC during the third year—7.2% (95% CI, 6.7 to 7.7). The yearly risk was 13.3% (95% CI, 12.1 to 14.4), 7.7% (95% CI, 6.3 to 9.0), and 5.0% (95% CI, 3.5 to 6.5) for melanoma at 2 years, 3 years, and 4 years, respectively. The yearly risk was 25.8% (95% CI, 24.2 to 27.5), 20.8% (95% CI,

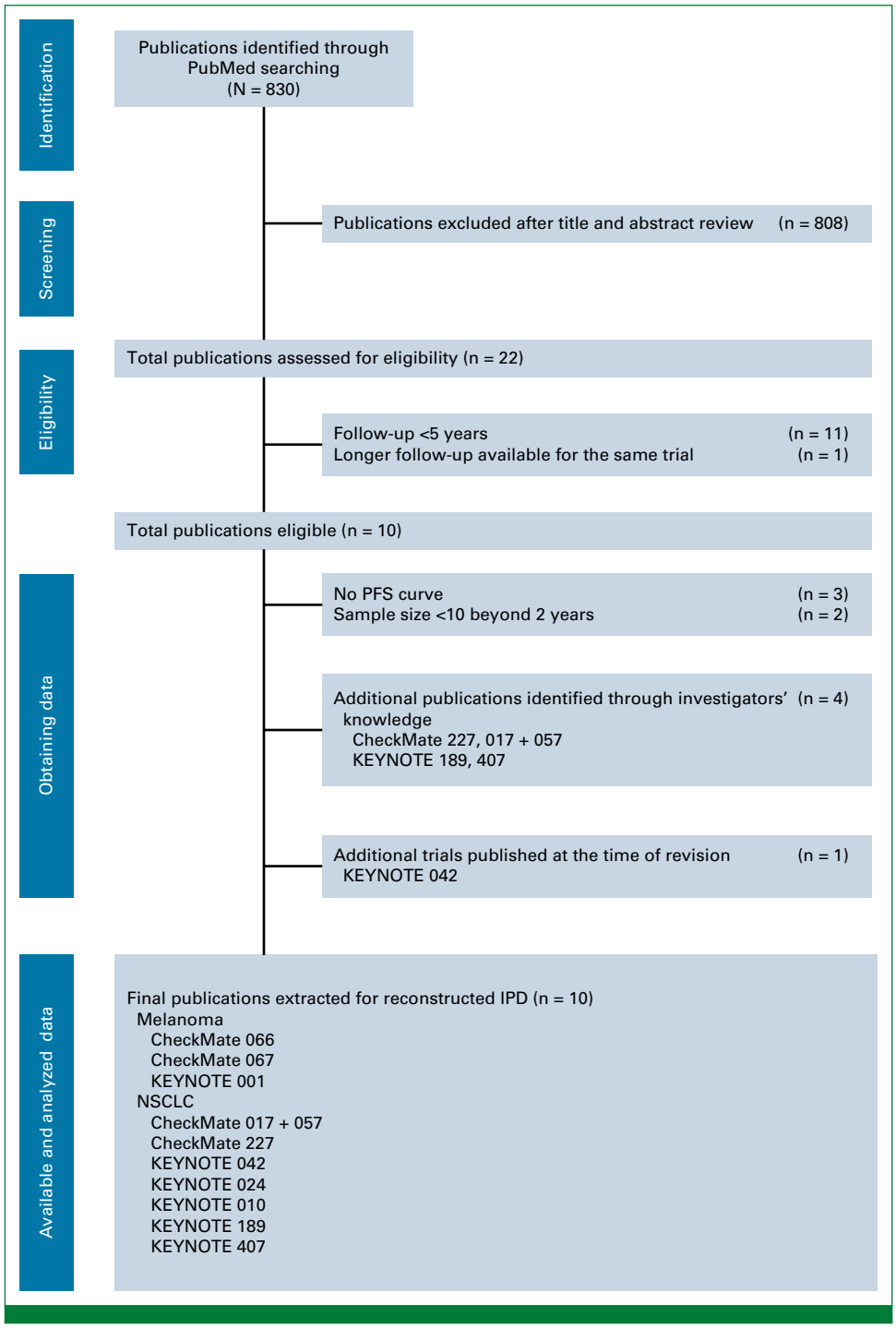

FIG 1. Flowchart of study search. IPD, individual patient data; NSCLC, non–small-cell lung cancer; PFS, progression-free survival.

18.2 to 23.4), and 17.7% (95% CI, 13.4 to 21.9) for NSCLC, respectively.

Proposed Imaging Surveillance Schedule on the Basis of Individualized Risk Tolerance

Assuming that the risk of progression of <10% per scan is the acceptable level, dPFSors with melanoma can be scanned every 6 months in the third year and then every 12 months in the fourth and fifth years; dPFSors with NSCLC can be scanned every 3 months in the third year and then every 4 months in the fourth and fifth years (Figs 4A and 5A).

Under <15% per scan level, dPFSors with melanoma can be scanned every 12 months in the following 3 years and dPFSors with NSCLC can be scanned every 6 months (Figs 4B and 5B).

TABLE 1. Summary of Included Studies

Disease Site	Trial	Arm	No. of Patients	Median Age, Years	Male, No. (%)	Nonsquamous NSCLC, No. (%)	PD-L1	Line of Treatment	No. of Durable Progression-Free Survivors, No. (%)	Radiographic Response Evaluation	Imaging Scan Schedule After 24 Months
Melanoma	CHECKMATE 066	Nivolumab monotherapy	210	64.5	121 (58)	—	—	First	59 (28.1)	RECIST v1.1	Every 12 weeks
	CHECKMATE 067	Nivolumab + ipilimumab	314	Mean: 59	202 (63.9)	—	—	First	109 (34.7)	RECIST v1.1	Every 12 weeks
		Nivolumab monotherapy	316	Mean: 59	212 (64)	—	—	First	97 (30.7)	RECIST v1.1	Every 12 weeks
	KEYNOTE 001	Pembrolizumab monotherapy	655	61	161 (57.7)	—	—	First: 23% Second and beyond: 67%	209 (31.9)	Immune-related response criteria	Every 12 weeks
NSCLC	CHECKMATE 017 + 057	Nivolumab monotherapy	427	61	262 (61.4)	295 (69.1)	≥1%: 53.2% <1%: 46.8%	Second and beyond	43 (10.1)	RECIST v1.1	Every 12 weeks
	CHECKMATE 227	Nivolumab	396	64	272 (68.7)	279 (70.5)	≥1% only	First	42 (10.6)	RECIST v1.1	Every 12 weeks
		Nivolumab + chemotherapy	177	Not reported	Not reported	Not reported	<1% only	First	11 (6.2)	RECIST v1.1	Every 12 weeks
		Nivolumab + ipilimumab	583	64	393 (67.4)	419 (71.9)	≥1%: 32.1% <1%: 67.9%	First	90 (15.4)	RECIST v1.1	Every 12 weeks
	KEYNOTE 024	Pembrolizumab monotherapy	154	64.5	92 (59.7)	125 (81.2)	≥50% only	First	38 (24.7)	RECIST v1.1	Every 9 weeks
	KEYNOTE 010	Pembrolizumab monotherapy	690	63	425 (61.6)	486 (70.4)	≥1% only	Second and beyond	109 (15.8)	RECIST v1.1	Every 9 weeks
	KEYNOTE 042	Pembrolizumab monotherapy	637	63	450 (71)	394 (62)	≥1% only	First	106 (16.6)	RECIST v1.1	Every 12 weeks
	KEYNOTE 189	Pembrolizumab + chemotherapy	410	65	254 (62.0)	410 (100)	≥1%: 63.4% <1%: 31.0%	First	91 (22.2)	RECIST v1.1	Every 12 weeks
	KEYNOTE 407	Pembrolizumab + chemotherapy	278	65	220 (79.1)	0	≥1%: 63.3% <1%: 34.2%	First	56 (20.1)	RECIST v1.1	Every 12 weeks

Abbreviation: NSCLC, non–small-cell lung cancer.

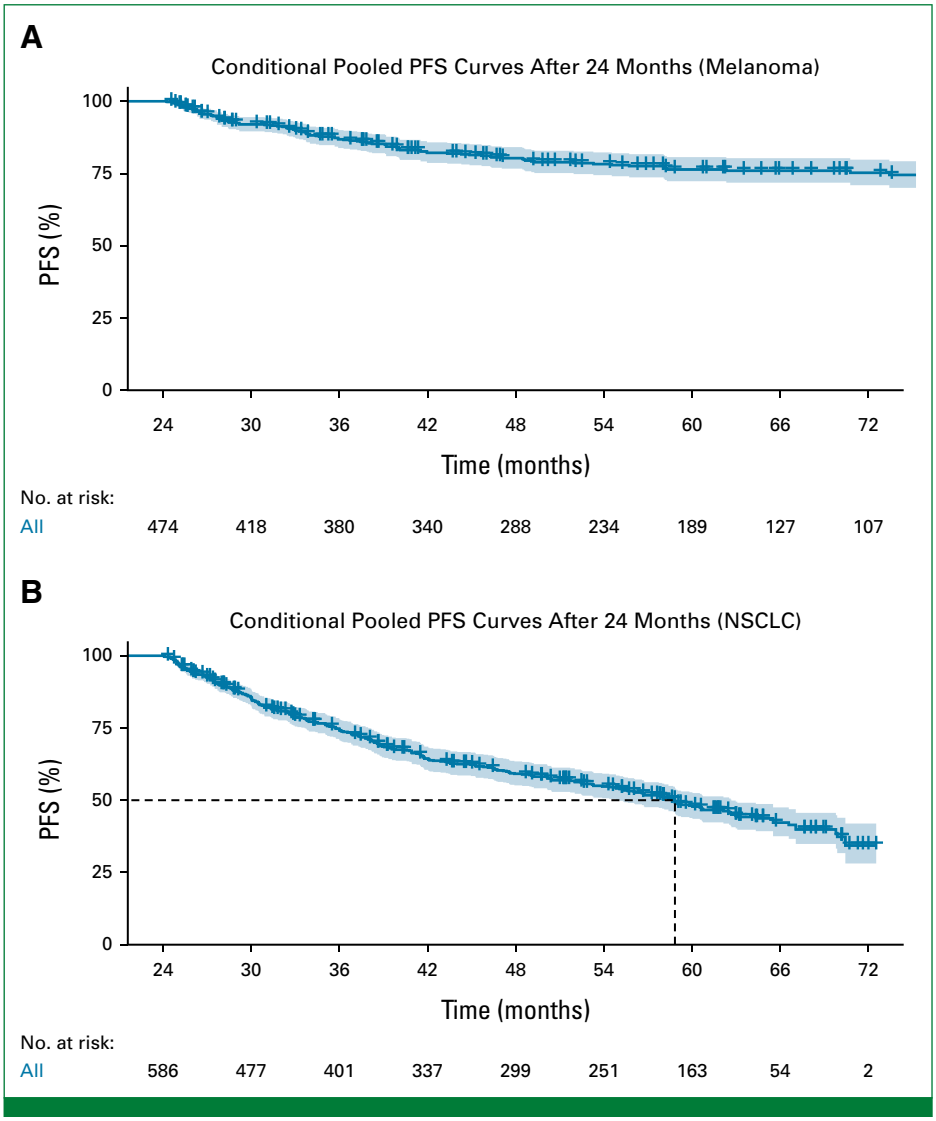

FIG 2. Conditional pooled PFS curves of durable progression-free survivors with (A) melanoma and (B) NSCLC. The PFS probability was estimated using the Kaplan-Meier method. NSCLC, non–small-cell lung cancer; PFS, progression-free survival.

Under <20% per scan level, dPFSors with melanoma can be scanned every 12 months in the following 3 years and dPFSors with NSCLC can be scanned every 6 months (Figs 4C and 5C).

DISCUSSION

Leveraging a large sample size, our study described the further risk of progression or death among patients with melanoma or NSCLC who have achieved durable PFS by anti–PD-1-based treatment for more than 2 years. Of note, not more than 8.0% of patients had progression/death in any quarter, arguing for longer imaging surveillance intervals for patients with melanoma or NSCLC. However, the additional 3-year PFS probability is 76.4% and 48.1% for dPFSors with melanoma and NSCLC, respectively, showing that a significant portion of patients may still progress in the following 3 years. Interestingly, PD-L1 status (positive or negative) did not appear to be associated with PFS outcomes in NSCLC dPFSors (Data Supplement, Fig S22).

A common clinical dilemma is how far can we extend imaging surveillance intervals without delaying the detection of recurrence in this group of patients. In this study, we proposed three risk levels per scan—10%, 15%, and 20%—and the corresponding imaging surveillance schedules. Patients and clinicians can jointly make data-driven individualized decisions on the basis of their own risk tolerance. For example, should a 20% interval risk of progression be considered acceptable by the clinician and patient (meaning an 80% chance of no progression between scans), then dPFSors with melanoma can be scanned every 12 months

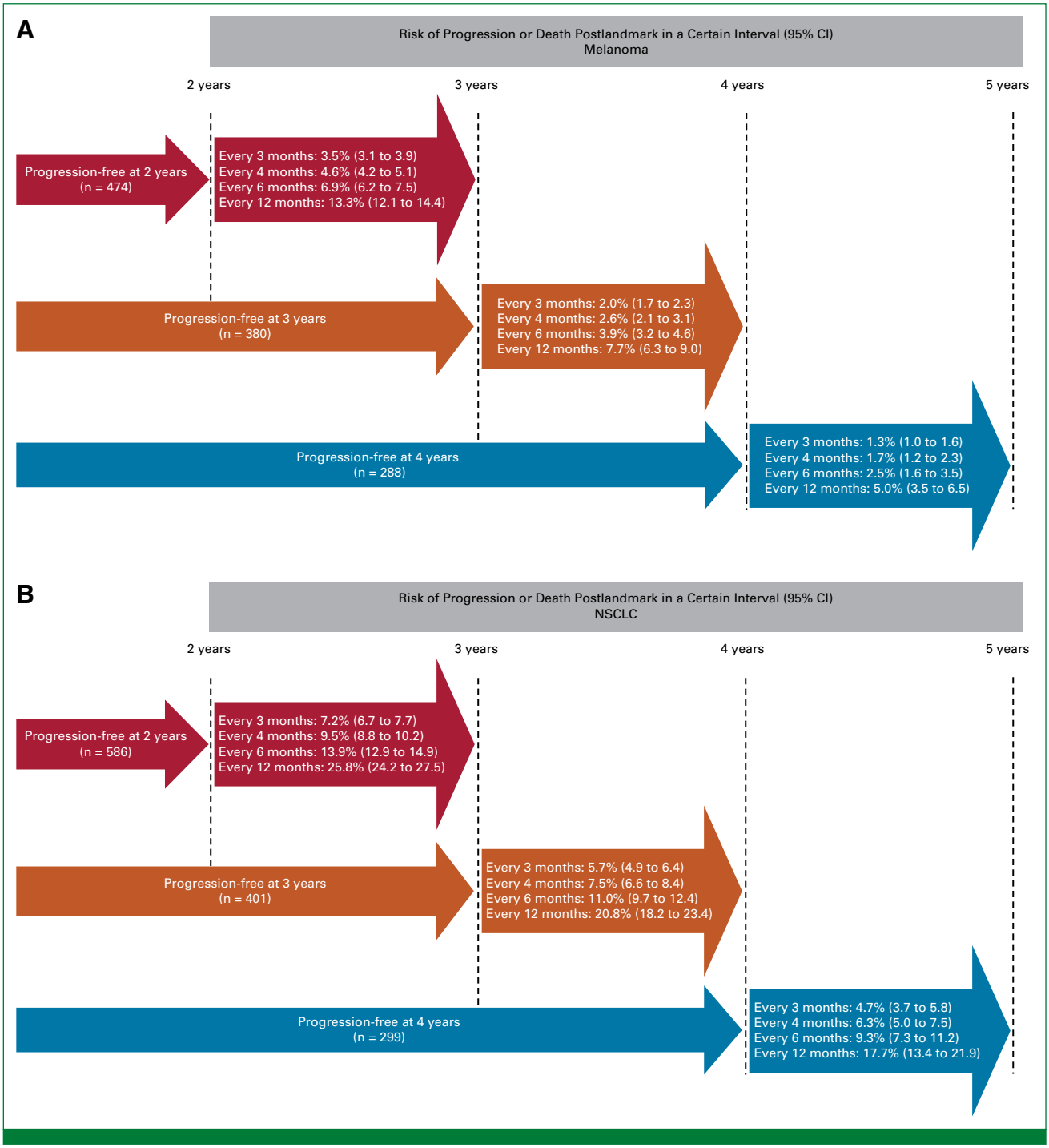

FIG 3. Conditional risk of progression or death postlandmark for durable progression-free survivors with (A) melanoma and (B) NSCLC. NSCLC, non–small-cell lung cancer.

beginning from 2 years; dPFSors with NSCLC can be scanned every 6 months (Figs 4 and 5). Admittedly, each individual's comfort level varies. The arbitrarily defined risk intervals of 10%, 15%, and 20% are three examples to serve as a quick reference in a busy clinic practice. Clinicians or patients with differing risk tolerance thresholds may refer to Figure 3 to design an individualized surveillance schedule.

It is difficult to define the optimal imaging surveillance schedule through clinical trials, because of the large sample size required for a noninferiority design and the rapidly evolving changes in treatment. Optimal imaging surveillance schedule is challenging to be answered by clinical trials, because of the large sample size required for noninferiority design and rapidly evolving oncologic treatment paradigms nowadays. A French randomized clinical trial compared

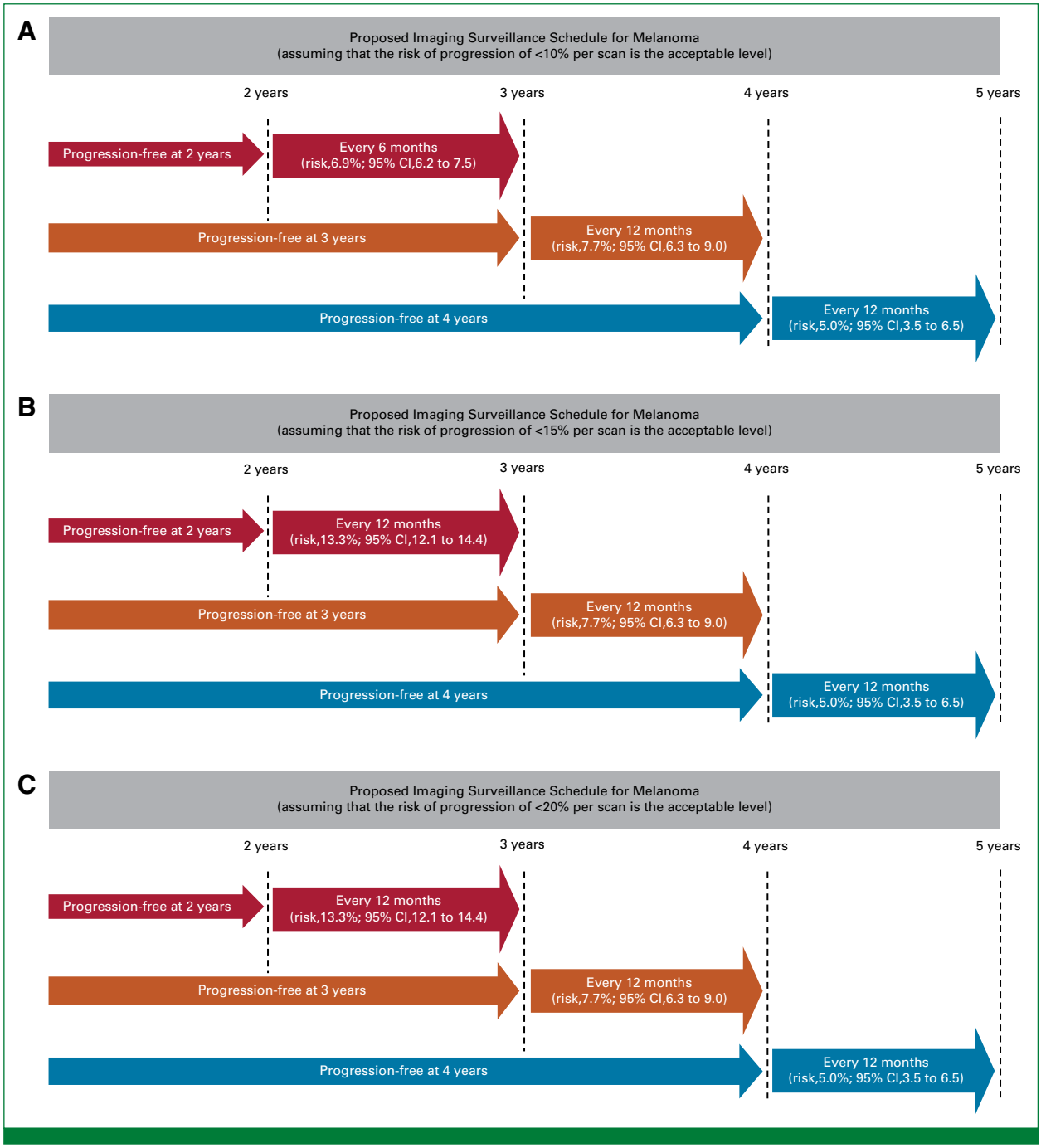

FIG 4. Proposed imaging surveillance schedule on the basis of three risk tolerance levels (A <10%; B <15%; C <20%) at each scan and the risk of progression or death with 95% CI for durable progression-free survivors with melanoma.

routine imaging surveillance versus web-based symptom monitoring with less frequent scans.[9] Among 133 patients enrolled, about 70% were stage IIIB-IV, who were randomly assigned to CT scan every 6 versus 12 months plus web-based monitoring. The study showed improved OS in the web-based group. However, it was limited in small patient number and in its execution in the pre-ICI era. It is also unclear without web-based symptom monitoring, which is largely lacking in many parts of the world, whether less frequent interval would still not compromise survival. IFCT-0302 is another randomized controlled trial, which questioned the role of chest CT scanning instead of asking surveillance intervals in patients with completely resected disease.[29] In this trial, patients underwent imaging every 6 months for 2 years and then annually in both arms. However, this cannot be extrapolated to patients with metastatic disease.

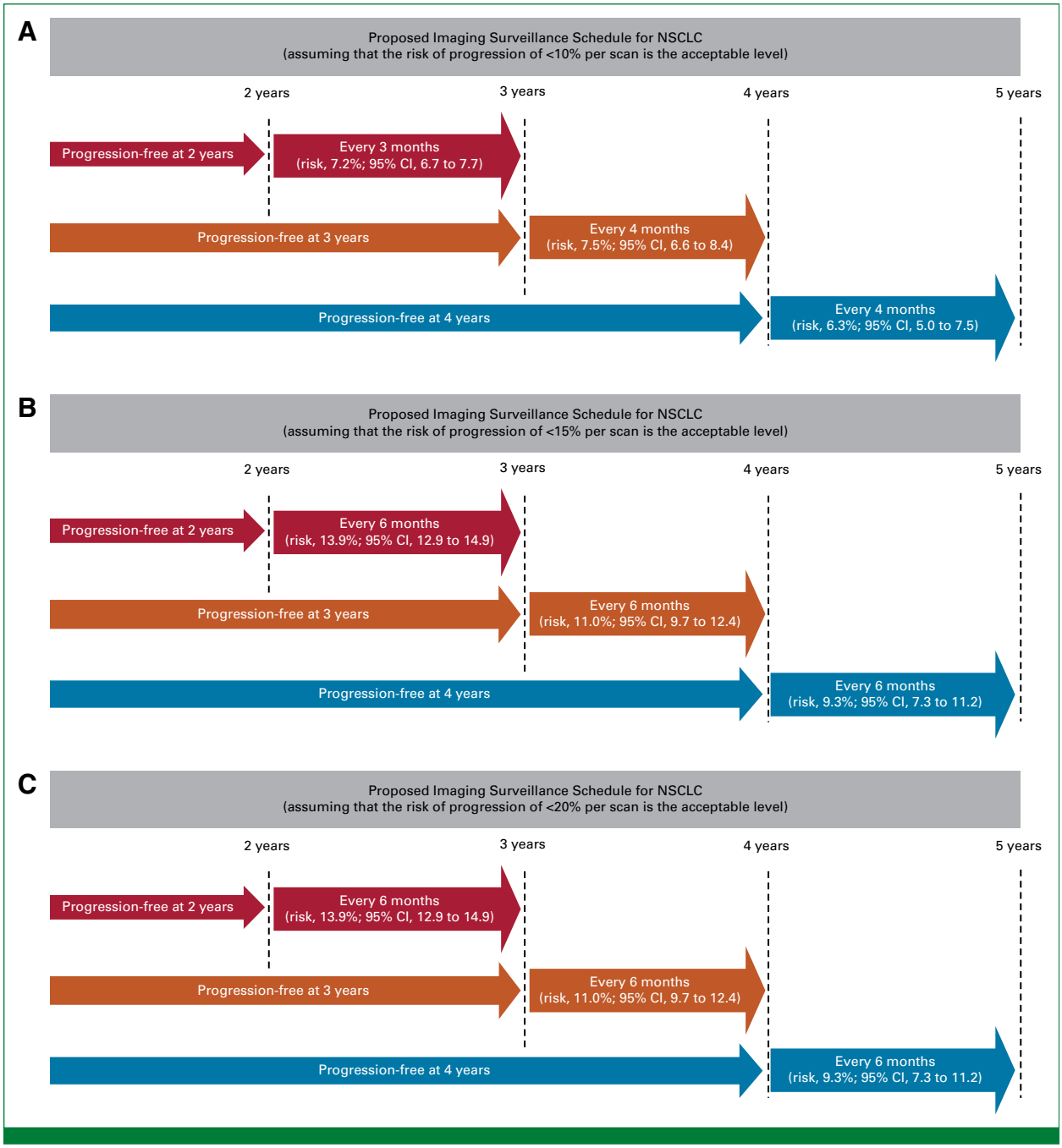

FIG 5. Proposed imaging surveillance schedule on the basis of three risk tolerance levels (A <10%; B <15%; C <20%) at each scan and the risk of progression or death with 95% CI for durable progression-free survivors with NSCLC. NSCLC, non–small-cell lung cancer.

To the best of our knowledge, there are no guideline recommendations or clinical trials of high quality regarding the imaging surveillance intervals in dPFSors with melanoma or NSCLC treated by anti–PD1-based treatment.[30,31] The follow-up recommendations for melanoma by the National Comprehensive Cancer Network (NCCN) are for recurrence detection in patients with resected disease and are largely based on retrospective studies, clinical practice, and expert consensus. The NSCLC panel of NCCN only addressed surveillance for patients with no clinical or radiographic evidence of disease after completing definitive therapy, which apparently does not apply to dPFSors.

One major limitation is that the reconstructed algorithm does not enable retrieval of patient-level covariates. However, this method has been used in the literature across different medical specialties, when raw trial data were not available.[14,17-20] In addition, our reconstructed data were broadly concordant with the original reports. All reconstructed data underwent careful scrutiny of data quality,

including visual shape inspection, the errors between reconstructed and read-in curves, Kolmogorov-Smirnov tests, and key summary statistics of median survival with 95% CI and 3- and 5-year PFS probabilities. We are also limited in lack of granularity of participant characteristics, including radiographic response, and ICI treatment duration. Because of limited follow-up, we are unable to describe further risk beyond 5 years. We were also unable to include some of the major phase III ICI trials because of short follow-up time at the time of data search. It is unclear how many progressions were detected by imaging or clinical symptoms and signs, but patients enrolled in those trials were frequently scanned at every 9-12 weeks in the study period of our interest, so it is highly probable that those events were detected by imaging. In clinical practice, RECIST v1.1 does not necessarily dictate clinical management, but represents an objective and standardized common language to assess disease status. Clinical judgment of progression as an alternative is difficult to be harmonized and significantly differs among treating physicians, which would be even more challenging for surveillance recommendations.

In conclusion, our findings support extending the imaging surveillance interval beyond every 3 months among dPFSors with melanoma or NSCLC. The proposed individual tolerance-based approach empowers clinicians and dPFSors with data-driven risk estimates for personalized decisions regarding the imaging surveillance schedule. PD-L1 status did not appear to be associated with further PFS among dPFSors. Further studies are needed for more granular analysis on risk stratification. Longer follow-ups are needed to define risk beyond 5 years.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Risk of Further Progression or Death Among Durable Progression-Free Survivors With Melanoma or Non–Small-Cell Lung Cancer in PD-1 Blockade Trials: Implications for Imaging Surveillance

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APPENDIX

TABLE A1. Quality Control of Extracted Individual Patient Data

Trial	Median PFS (95% CI)		Three-Year PFS Probability, %		Five-Year PFS Probability, %		Error Between Estimated and Read-in Survival Probabilities			Kolmogorov-Smirnov *P*
	Extracted IPD	Reported	Extracted IPD	Reported	Extracted IPD	Reported	Root Mean Square Error	Mean Absolute Error	Max Absolute Error	
CheckMate 066 nivolumab	5.2 (3.9 to 12.7)	5.1 (3.5 to 12.2)	32.5	32.0	28.0	28.0	0.002	0.001	0.003	1.00
CheckMate 067 nivolumab	6.9 (4.5 to 11.4)	6.9 (5.1 to 10.2)	31.7	Not reported	29.1	29.0	0.002	0.001	0.002	.89
CheckMate 067 nivolumab + ipilimumab	11.7 (9.5 to 21.1)	11.5 (8.7 to 19.3)	38.9	Not reported	36.3	36.0	0.001	0.001	0.003	1.00
KEYNOTE 001 pembrolizumab, total population	8.8 (6.5 to 12.9)	8.3 (5.8 to 11.1)	29.0	Not reported	21.4	21.0	0.001	0.001	0.002	1.00
KEYNOTE 042 pembrolizumab	5.7 (4.3 to 6.2)	5.6 (4.3 to 6.2)	13.2	12.9	7.3	6.9	0.001	0.001	0.002	1.00
KEYNOTE 024 pembrolizumab	7.8 (6.3 to 12.4)	7.7 (6.1 to 10.2)	24.0	22.8	12.7	12.8	0.002	0.002	0.004	1.00
KEYNOTE 010 pembrolizumab	4.1 (3.2 to 4.2)	4.0 (3.1 to 4.1)	13.8	13.8	9.3	9.4	0.001	0.000	0.002	1.00
CheckMate 017 + 057 nivolumab	2.6 (2.2 to 3.5)	2.5 (2.2 to 3.5)	10.1	10.2	7.9	8.0	0.001	0.001	0.003	.84
CheckMate 227 nivolumab + chemotherapy, PD-L1 <1%	5.7 (4.7 to 6.9)	5.6 (4.6 to 6.9)	7.7	8.0	6.7	7.0	0.003	0.002	0.004	.18
CheckMate 227 nivolumab + ipilimumab, PD-L1 <1%	5.2 (4.2 to 6.7)	5.1 (3.5 to 6.4)	13.7	13.0	9.1	10.0	0.002	0.002	0.004	.94
CheckMate 227 nivolumab, PD-L1 ≥1%	4.3 (3.2 to 5.8)	4.2 (3.0 to 5.3)	11.5	12.0	9.3	9.0	0.001	0.001	0.002	.98
CheckMate 227 nivolumab + ipilimumab, PD-L1 ≥1%	5.0 (4.0 to 6.6)	5.1 (4.1 to 6.3)	18.6	19.0	12.0	12.0	0.001	0.001	0.002	.99
KEYNOTE 407 pembrolizumab + chemotherapy	8.1 (6.4 to 8.6)	8.0 (6.3 to 8.5)	16.1	16.1	12.2	10.8	0.001	0.001	0.002	1.00
KEYNOTE 189 pembrolizumab + chemotherapy	9.1 (8.2 to 10.8)	9.0 (8.1 to 10.4)	12.9	13.1	7.4	7.5	0.001	0.001	0.002	1.00

Abbreviations: IPD, individual patient data; PFS, progression-free survival.