BRIEF REPORT

Evaluation of Major Pathologic Response and Pathologic Complete Response as Surrogate End Points for Survival in Randomized Controlled Trials of Neoadjuvant Immune Checkpoint Blockade in Resectable in NSCLC

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ABSTRACT

Introduction: Controversy remains as to whether pathologic complete response (pCR) and major pathologic response (MPR) represent surrogate end points for event-free survival (EFS) and overall survival (OS) in neoadjuvant trials for resectable NSCLC.

Methods: A search of PubMed and archives of international conference abstracts was performed from June 2017 through October 31, 2023. Studies incorporating a neoadjuvant arm with immune checkpoint blockade alone or in combination with chemotherapy were included. Those not providing information regarding pCR, MPR, EFS, or OS were excluded. For trial-level surrogacy, log ORs for pCR and MPR and log hazard ratios for EFS and OS were analyzed using a linear regression model weighted by sample size. The regression coefficient and R^2 with 95% confidence interval were calculated by the bootstrapping approach.

Results: Seven randomized clinical trials were identified for a total of 2385 patients. At the patient level, the R^2 of pCR

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and MPR with 2-year EFS were 0.82 (0.66–0.94) and 0.81 (0.63–0.93), respectively. The OR of 2-year EFS rates by response status was 0.12 (0.07–0.19) and 0.11 (0.05–0.22), respectively. For the 2-year OS, the R^2 of pCR and MPR were 0.55 (0.09–0.98) and 0.52 (0.10–0.96), respectively. At the trial level, the R^2 for the association of OR for response and HR for EFS was 0.58 (0.00–0.97) and 0.61 (0.00–0.97), respectively.

Conclusions: Our analyses reveal a robust correlation between pCR and MPR with 2-year EFS but not OS. Trial-level surrogacy was moderate but imprecise. More mature follow-up and data to assess the impact of study crossover are needed.

Keywords: Neoadjuvant; Immunotherapy; Chemoimmunotherapy; Surrogate end points; NSCLC; Pathologic response

Introduction

Advances in cancer immunotherapy have increased overall survival (OS) in patients with advanced NSCLC in randomized control trials (RCTs).[1–4] Neoadjuvant immune checkpoint inhibitors (ICIs) in the treatment of NSCLC may improve the long-term survival of patients with early-stage disease.[5–7] As outcomes with early-stage lung cancer improve, event-free survival (EFS) and OS have associated challenges in neoadjuvant trials owing to the need for long-term follow-up and the potential effect of future treatments.[8,9] Surrogate end points are needed to move advanced disease therapies to earlier stage disease while preserving the integrity of the clinical data.

Surrogate end points are biomarkers intended to substitute for clinical end points and accurately predict clinical benefit.[10] In a recent analysis of pathologic response in the CheckMate816 study, percent residual viable tumor (% RVT) was reported to be associated with EFS and manifested the overall treatment effect on the clinical outcome when assessed quantitatively from 0% to 100%RVT.[11] Whereas most neoadjuvant RCTs have not reported % RVT, many have reported pathologic complete response (pCR) (0% RVT in the primary tumor and lymph nodes) and major pathologic response (MPR) ($\leq$10% RVT in the primary tumor ± lymph nodes).[12–14]

Recent meta-analyses have reported higher pCR rates with the incorporation of neoadjuvant ICI in NSCLC,[15,16] and a correlation of pCR with OS.[17] The surrogacy of pCR has been reported in neoadjuvant chemotherapy trials for breast cancer[18] and urothelial cancer[19]; however, this has yet to be exhibited in a meta-analysis for NSCLC or with ICIs. We conducted a systematic review and meta-analysis of RCTs evaluating neoadjuvant ICIs for resectable NSCLC. Our primary objective was to evaluate the utility of pCR and MPR as surrogate markers for clinical outcomes after neoadjuvant immune checkpoint blockade in patients with operable and resectable NSCLC.

Materials and Methods

Literature Search

We performed a systematic review of literature after the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines[20] on PubMed from June 2017 to October 2023, using the terms "neoadjuvant," "non–small cell lung cancer," and "immunotherapy" to find studies published in English until the time of the search. The literature review was performed independently by two authors (JH and RBC). Those retrieved were then filtered and data was extracted as described in Supplementary Methods.

Statistical Analysis

Linear regression models weighed by sample size were used to evaluate correlation and surrogacy between biomarkers and clinical end points. From each study, we extracted the following: (1) antitumor activities, expressed as proportions of patients achieving pCR or MPR; (2) treatment effects, expressed as ORs for pCR and MPR; and (3) HRs for EFS and OS. For each study, the weight was the inverse of the variance of the log of the HR (i.e., inverse variance method). Proportions were considered on the natural scale in the models, whereas ORs and HRs were considered on the log scale in the models. The regression models were built and estimated using the SGplot procedure in Statistical Analysis System software (SAS Institute, Cary, NC). Maximum likelihood was used to fit regression models. The coefficient of determination (R^2) and the linear regression slope (β) were used to estimate the proportion of variation in clinical end points explained by pathologic response and the magnitude of change in clinical end points as a function of the magnitude of change in pathologic response, respectively. R^2 values greater than or equal to 0.7 represent strong correlations, values between 0.69 and 0.5 represent moderate correlations, and values less than 0.5 represent weak correlations.[21] The 95% confidence intervals (CIs) of R^2 and the regression coefficient β were obtained by the bootstrap method with 5000 replications.

Table 1. Trial Characteristics

RCT	Arm	Sample Size	% pCR	pCR OR	% MPR	MPR OR	% 1-year EFS	% 2-year EFS	EFS HR	% 1-year OS	% 2-year OS	OS HR
NADIM_II[1]	EXP	57	36.80	7.88	52.60	6.94	90.00	67.20	0.47	98.00	85.00	0.43
	CTR	29	6.90	.	13.80	.	60.00	40.90	.	85.00	63.60	.
CM816[2]	EXP	179	24.00	13.83	36.90	5.95	76.10	63.80	0.65	90.30	82.70	0.57
	CTR	179	2.20	.	8.90	.	63.40	45.30	.	90.10	80.60	.
NEOTORCH[3]	EXP	202	24.80	32.89	48.50	10.25	84.40	64.70	0.40	94.40	81.20	0.62
	CTR	202	1.00	.	8.40	.	57.00	38.70	.	89.60	74.30	.
KN671[4]	EXP	397	18.10	5.32	30.20	3.51	73.20	62.40	0.58	87.90	80.90	0.73
	CTR	400	4.00	.	11.00	.	59.90	40.60	.	87.90	77.60	.
AEGEAN[5]	EXP	366	17.20	4.65	33.10	3.52	73.40	63.30	0.68	.	.	.
	CTR	374	4.30	.	12.30	.	64.50	52.40	.	.	.	.
CM77T[30]	EXP	229	25.30	6.64	35.40	4.01	73.00	65.00	0.58	.	.	.
	CTR	232	4.70	.	12.10	.	59.00	45.00	.	.	.	.
TD FOREKNOW[31]	EXP	43	32.60	4.95	65.10	10.13	93.00	76.90	0.52	.	.	.
	CTR	45	8.90	.	15.60	.	76.90	67.60	.	.	.	.

CM816, CheckMate816; KN671, Keynote671; CM77T, CheckMate-77T; CTR, control; EXP, experimental; pCR, pathologic complete response; MPR, major pathologic response; EFS, event-free survival; HR, hazard ratio; OS, overall survival.

Characteristics of included studies and patients were described using median as a measure of central tendency and range as a measure of dispersion in the case of quantitative variables, and absolute and percentage frequencies in the case of categorical variables.

Statistical analysis was generated using SAS software, version 9.4 of the SAS System for Linux. R statistical software, version 4.2.1 (R Core Team 2022, Vienna, Austria) was used for statistical graphics. Statistical graphs were made using the ggplot2 package in R.[22]

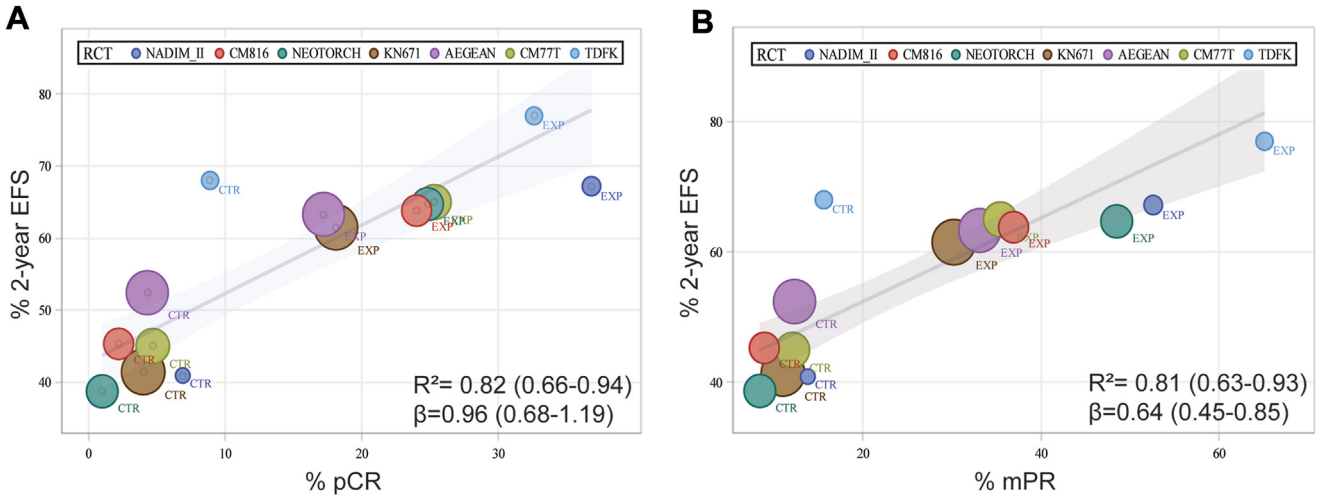
Results

As illustrated in Supplementary Figure 1, 354 records were identified, yielding 39 clinical trials of neoadjuvant ICI in NSCLC. Of these, 36 trials reported pCR, MPR, and EFS. Of these, 7 trials were RCTs of chemotherapy plus ICI versus chemotherapy alone.[23–29] A total of 2940 patients participating in the seven RCTs were included (Table 1 and Supplementary Table 1).

Among the included trials, pCR was achieved in a median of 24.8% (IQR 18.1, 32.6) of patients receiving chemotherapy plus ICI and a median of 4.3% (IQR 2.2, 6.9) of patients receiving chemotherapy alone. The respective values for MPR were 36.9% (IQR 19.5, 33.1) for chemotherapy plus ICI and 12.1% (IQR 8.9, 13.8) for chemotherapy alone. The median 2-year EFS among included trials was 64.7% (IQR 63.3, 67.2) in patients receiving chemotherapy plus ICI and 45.0% (IQR 40.9, 52.4) in patients receiving chemotherapy alone.

For the seven included RCTs, there was a strong correlation between 2-year EFS and rate of pCR with an R^2 of 0.82 (95% CI: 0.66–0.94) and β of 0.96 (95% CI: 0.68–1.19) (Fig. 1*A*). The correlation between 2-year EFS and MPR was similarly strong with an R^2 of 0.81 (95% CI: 0.63-0.93) and β of 0.64 (95% CI: 0.45–0.85) (Fig. 1*B*). We confirmed these findings with a subgroup analysis of treatment groups in each trial assessing the association between EFS and pathologic response (Fig. 1*C* and *D*). The OR of 2-year EFS was 0.12 (95% CI 0.07–0.19) and 0.11 (95% CI 0.05–0.22) for patients achieving pCR and MPR, respectively. These data indicate that at the patient level, pCR and MPR account for increases in 2-year EFS, regardless of the treatment that results in such a pathologic response.

Evaluating the association between 2-year OS and pathologic response, the correlation between 2-year OS and pCR was moderate but imprecise with an R^2 of 0.55 (95% CI: 0.09–0.98) and β of 0.26 (95% CI: 0.09–0.98) (Fig. 2*A*). For MPR, the correlation with 2-year OS was moderate but imprecise with an R^2 of 0.52 (95% CI: 0.10–0.96) and β of 0.18 (95% CI: 0.05–0.30) (Fig. 2*B*). The lower slopes indicate that changes in OS are less accounted for by pathologic response alone.



C

Study or Subgroup	pCR Yes Events	Total	pCR No Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
CM77T_CH	3	11	126	221	12.6%	0.28 [0.07, 1.09]
CM77T_CH_IO	7	58	74	171	32.2%	0.18 [0.08, 0.42]
KEY671_CH	2	16	238	384	10.3%	0.09 [0.02, 0.39]
KEY671_CH_IO	4	72	143	325	21.6%	0.07 [0.03, 0.21]
NADIM_CH	0	2	17	27	2.3%	0.12 [0.01, 2.75]
NADIM_CH_IO	0	21	18	36	2.8%	0.02 [0.00, 0.41]
NEOTORCH_CH	0	2	126	200	2.5%	0.12 [0.01, 2.49]
NEOTORCH_CH_IO	3	50	70	152	15.7%	0.07 [0.02, 0.25]
Total (95% CI)		**232**		**1516**	**100.0%**	**0.12 [0.07, 0.19]**
Total events	19		812			

Heterogeneity: Tau² = 0.00; Chi² = 5.40, df = 7 (P = 0.61); I² = 0%
Test for overall effect: Z = 8.73 (P < 0.00001)

D

Study or Subgroup	mPR Yes Events	Total	mPR No Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
CM77T_CH	10	28	118	204	17.7%	0.40 [0.18, 0.92]
CM77T_CH_IO	11	81	72	148	18.7%	0.17 [0.08, 0.34]
KEY671_CH	3	44	238	356	14.3%	0.04 [0.01, 0.12]
KEY671_CH_IO	5	120	156	277	16.7%	0.03 [0.01, 0.09]
NEOTORCH_CH	3	17	120	185	13.6%	0.12 [0.03, 0.42]
NEOTORCH_CH_IO	15	98	65	104	19.0%	0.11 [0.06, 0.21]
Total (95% CI)		**388**		**1274**	**100.0%**	**0.11 [0.05, 0.22]**
Total events	47		769			

Heterogeneity: Tau² = 0.65; Chi² = 21.20, df = 5 (P = 0.0007); I² = 76%
Test for overall effect: Z = 5.89 (P < 0.00001)

Figure 1. Association between pathologic response and 2-year event-free survival. (*A*) Association of rate of pCR and (*B*) MPR with 2-year EFS. Each circle represents an arm of an RTC. The size of each circle is proportional to the sample size/weight of each arm. Lines represent best fit as determined by linear regression with a coefficient of determination R^2 representing the strength of correlation and slope β representing the strength of the effect of (*A*) pCR and (*B*) MPR on 2-year EFS. (*C*) The forest plots summarize the relative effect (OR) of achieving a pCR or a (*D*) MPR on 2-year EFS in each of the RCTs analyzed individually and in aggregate. An OR greater than 1 indicates a deterioration in EFS with achieving a pathologic response; an OR less than 1 indicates an improvement in EFS with achieving a pathologic response. The 95% CIs crossing 1 indicate statistically not significant results. EFS, event-free survival; RCT, randomized clinical trial; CTR, control arm; EXP, experimental arm; pCR, pathologic complete response; MPR, major pathologic response.

Finally, we evaluated the associations between pathologic response and EFS at the trial level. The correlation between HR_{EFS} and OR_{pCR} was moderate but imprecise with an R^2 of 0.58 (95% CI: 0.00–0.97) and a β of 0.19 (95% CI: −0.15 to 0.62) (Fig. 3*A*). We observed a similarly moderate but imprecise correlation between HR_{EFS} and OR_{MPR} with an R^2 of 0.61 (95% CI: 0.00–0.97) and a β of 0.32 (95% CI: 0.04–0.51) (Fig. 3*B*). The lower slopes suggest that for a given trial, greater increases in pCR or MPR rates are needed for clinically significant

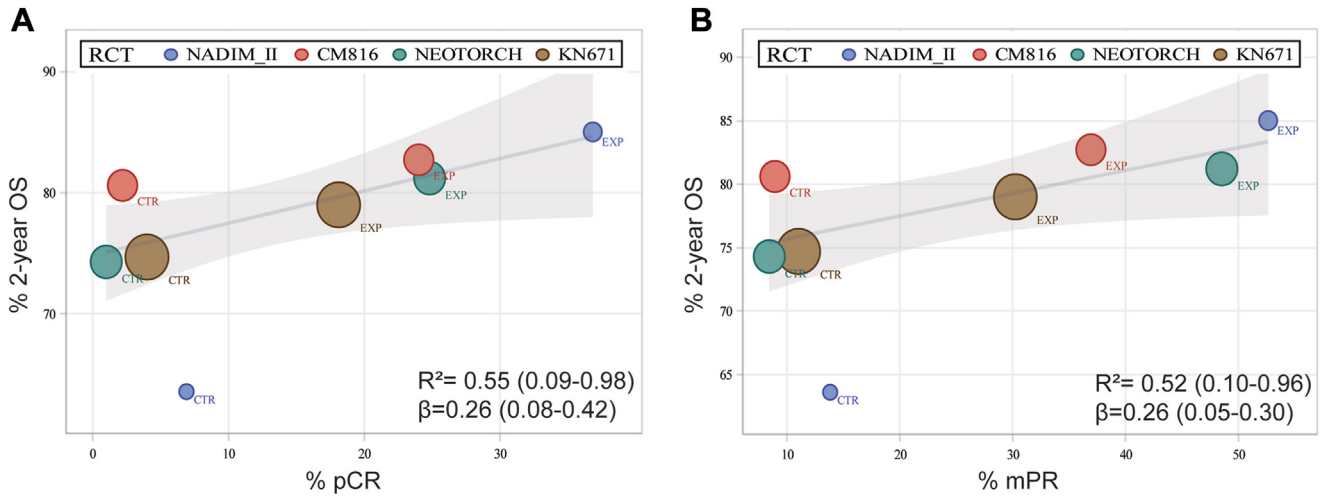


Figure 2. Association between pathologic response and 2-year OS. (*A*) Association of rate of pCR and (*B*) MPR with 2-year OS. Each circle represents an arm of an RTC. The size of each circle is proportional to the sample size/weight of each arm. Lines represent best fit as determined by linear regression with the coefficient of determination R^2 representing the strength of correlation and slope β representing the strength of the effect of pCR (*A*) and MPR (*B*) on 2-year OS. OS, overall survival; RCT, randomized clinical trial; CTR, control arm; EXP, experimental arm; pCR, pathologic complete response; MPR, major pathologic response.

reductions in the HR for EFS. Interestingly, we also observed poor surrogacy of EFS for OS in these trials (Supplementary Fig. 2).

Discussion

In this meta-analysis, we assessed pCR and MPR as surrogate end points for EFS and OS in early-stage resectable NSCLC. If validated, these end points could be used as primary end points in future clinical trials and expedite the development and implementation of novel therapies. Neoadjuvant ICIs for early-stage resectable NSCLC have exhibited marked increases in the rates of pCR and MPR at surgical resection with approximately 20% of patients achieving a pCR.[15,26,32–35] This incidence, coupled with the short time frame for evaluation compared with the long-term follow-up needed for EFS and OS, supports the development of pathologic end points as surrogates for effective and meaningful clinical trial execution.

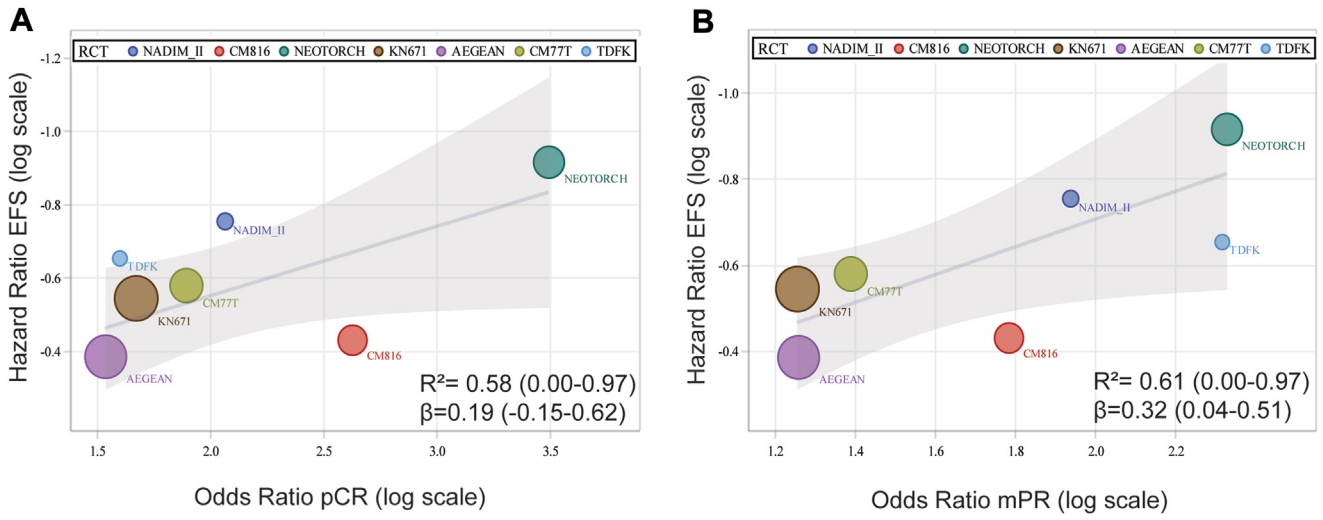


Figure 3. Trial level surrogacy of pathologic response for event-free survival. The linear regressions illustrate the association between the relative effect of pathologic response (OR for [*A*] pCR and [*B*] MPR) and EFS (hazard ratio). Each circle represents the data from an individual RCT with the size of the circle proportional to the sample size/weight of each trial. Lines represent best fit as determined by linear regression with the coefficient of determination R^2 representing the strength of correlation and slope β representing the strength of the effect. EFS, event-free survival; RCT, randomized clinical trial; pCR, pathologic complete response; MPR, major pathologic response.

In contrast to other studies including single-arm and retrospective studies, our analysis included only randomized phase 3 clinical trials comparing chemotherapy over a combination of chemotherapy plus ICI to reduce potential confounding bias.[26,32–35] At the patient level, our analysis revealed a robust correlation of both pCR and MPR with 1- and 2-year EFS. However, this correlation was not replicated in terms of OS at the same intervals, and notably, EFS and OS did not correlate at the trial level. Several hypotheses could explain this discrepancy. First, data from all of the included trials are immature, and with time, we may observe a stronger correlation. Alternatively, a treatment crossover effect (e.g., adjuvant treatment, treatment of recurrent or metastatic disease) might have influenced the results for OS, thereby weakening the correlation with other end points.

An in-depth evaluation of the data revealed that trial-level surrogacy of pathologic response remains imprecise for EFS and OS; this could be attributed to several potential factors. The differences in HRs may not be substantial enough to identify an appreciable difference. Second, the number of events may be still limited by data immaturity and many censored events, with more events needed to definitively understand the association. Heterogeneity exists across trials in terms of clinicopathologic features and design (Supplementary Table 1 and Supplementary Fig. 3). Whereas efforts are ongoing to harmonize these differences in tumor- and host-factors and standardize investigator-related variability, this heterogeneity may have played a role in impacting our results.[36] There is the intrinsic limitation of the pooled analysis, a well-known factor in meta-analyses, referred to as measurement error in the X variable.[37–39] Finally, different histologic scoring systems were used for the assessment of pathologic response in the included trials.[16,40,41] The systems used have been found to be reproducible,[41–43] and most studies are thought to have met recently described histologic sampling minimums.[44] It is possible that pathologic response end points beyond pCR and MPR may be of value in predicting outcomes in this setting. Efforts to standardize pathologic assessments within and across tumor types are underway, which would facilitate meta-analyses to test the utility of other pathologic end points.

Future studies include updated analyses of the data with upcoming results from pending large phase 3 trials (IMpower030).[39,45,46] Data sharing, including % RVT on a per-patient basis beyond pCR and MPR, would facilitate individual patient data meta-analyses—a crucial step in pushing the boundaries of our understanding.[47] Standardized and granular data reporting will greatly strengthen key post hoc analyses, thereby aiding the ongoing efforts to optimize cancer treatment strategies and establish scientific associations with the guidance of the regulatory authorities. As we forge ahead in our quest for efficient research and trial design, we should not overlook other potential end points, the development of which will require broad access to patient-level data.

In conclusion, we preliminarily conclude that although pCR and MPR are undoubtedly exciting potential end points of clinical benefit, they are not yet adequate surrogates for OS in clinical trials; this may change as neoadjuvant and perioperative immune checkpoint blockade studies mature. Currently, these end points should be considered as co-primary end points in clinical trials assessing the benefit of neoadjuvant and perioperative immunotherapy. Given the strong association with EFS at the patient level, these end points provide valuable data to inform clinical treatment decisions.

CRediT Authorship Contribution Statement

Drs. Hines and Cameron take responsibility for the integrity of the data and the accuracy of the data analysis.

Conceptualization: Hines, Cameron, Garassino, Torri.

Data curation, Formal analysis, Validation: Hines, Cameron, Porcu, Garassino, Torri.

Role/Writing – original draft: Hines, Cameron, Cascone, Esposito, Garassino, Torri.

Critical revision of the manuscript: Hines, Cameron, Cascone, Esposito, Taube, Garassino, Torri.

Writing – review & editing: Hines, Cameron, Cascone, Taube, Kim, Porcu, Nuccio, Viscardi, Ferrara, Veronesi, Forde, Vokes, Bestvina, Garassino, Torri.

Methodology: Porcu, Monteforte, Torri

Funding: Hines.

Supervision: Garassino, Cascone, Torri.

Role of the Funder/Sponsor

The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclosure

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2024.03.010.

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