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Clinical and Molecular Characteristics Associated With Survival Among Patients Treated With Checkpoint Inhibitors for Advanced Non–Small Cell Lung Carcinoma
A Systematic Review and Meta-analysis

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IMPORTANCE Checkpoint inhibitors have replaced docetaxel as the new standard second-line therapy in advanced non–small cell lung carcinoma (NSCLC), but little is known about the potential predictive value of clinical and molecular characteristics.

OBJECTIVE To estimate the relative efficacy of checkpoint inhibitor vs docetaxel overall and in subgroups defined by clinicopathological characteristics.

DATA SOURCES This systematic review and meta-analysis searched MEDLINE, Embase, PubMed, and the Cochrane Central Register of Controlled Trials for randomized clinical trials published in the English language between January 1, 1996, and January 30, 2017.

STUDY SELECTION Randomized clinical trials that compared a checkpoint inhibitor (nivolumab, pembrolizumab, or atezolizumab) with docetaxel. For each trial included in this study, the trial name, year of publication or conference presentation, patients' clinicopathological characteristics, type of chemotherapy, and type of checkpoint inhibitor were extracted. Data collection for this study took place from February 1 to March 31, 2017.

DATA EXTRACTION AND SYNTHESIS Two reviewers performed study selection, data abstraction, and risk of bias assessment. Hazard ratios (HR) and 95% CIs for the overall population and subgroups were extracted. Pooled treatment estimates were calculated using the inverse-variance-weighted method.

RESULTS In total, 5 trials involving 3025 patients with advanced NSCLC were included in this meta-analysis. These patients were randomized to receive a checkpoint inhibitor (nivolumab, 427 [14.1%]; pembrolizumab, 691 [22.8%]; or atezolizumab, 569 [18.8%]) or docetaxel (1338 [44.2%]). Checkpoint inhibitors were associated with prolonged overall survival, compared with docetaxel (HR, 0.69; 95% CI, 0.63-0.75; $P < .001$). They prolonged overall survival in the *EGFR* wild-type subgroup (HR, 0.67; 95% CI, 0.60-0.75; $P < .001$), but not in the *EGFR* mutant subgroup (HR, 1.11; 95% CI, 0.80-1.53; $P = .54$; interaction, $P = .005$), and they prolonged overall survival in the *KRAS* mutant subgroup (HR, 0.65; 95% CI, 0.44-0.97; $P = .03$) but not in the *KRAS* wild-type subgroup (HR, 0.86; 95% CI, 0.67-1.11; $P = .24$; interaction, $P = .24$). The relative treatment benefits were similar according to smoking status (never smokers [HR, 0.79] vs ever smokers [HR, 0.69]; interaction, $P = .40$), performance status (0 [HR, 0.69] vs 1 [HR, 0.68]; interaction, $P = .85$), age (<65 years [HR, 0.71] vs ≥65 years [HR, 0.69]; interaction, $P = .74$), histology (squamous [HR, 0.67] vs nonsquamous [HR, 0.70]; interaction, $P = .71$), or sex (male [HR, 0.69] vs female [HR, 0.70]; interaction, $P = .82$).

CONCLUSION AND RELEVANCE Checkpoint inhibitors, compared with docetaxel, are associated with significantly prolong overall survival in second-line therapy in NSCLC. The finding of no overall survival benefit for patients with *EGFR* mutant tumors suggests that checkpoint inhibitors should be considered only after other effective therapies have been exhausted. The findings of this meta-analysis could also assist in the design and interpretation of future trials and in economic analyses.

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Supplemental content

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Advanced non-small cell lung carcinoma (NSCLC) is an incurable disease that is associated with a poor prognosis. Globally, it is the leading cause of cancer-related death.[1] Docetaxel has been the standard of care for advanced NSCLC following disease progression with platinum doublet chemotherapy.[2,3] However, docetaxel is associated with only modest efficacy but substantial toxicity. With the recent advancement in immune checkpoint inhibitor therapies[4-8] that target the PD-L1 (programmed cell death 1 ligand 1) and PD-1 (programmed cell death 1) pathways, these agents have recently replaced docetaxel as the new standard second or later line of treatment.

Identifying clinical or molecular factors that predict benefit of checkpoint inhibitors in advanced NSCLC remains crucial for the selection of appropriate patients for this class of therapy. The PD-L1 expression on tumor cells is regarded as the best available biomarker to predict the efficacy of checkpoint inhibitors in NSCLC and other tumors.[9] Although there is a linear relationship between the size of the benefit of checkpoint inhibitors and the level of tumor PD-L1 expression in NSCLC,[4,5,7,8,10] tumor responses have still been observed in those with low or undetectable PD-L1 expression. Furthermore, among the 4 PD-1 and PD-L1 inhibitors in clinical development or approved for routine use in NSCLC, unique assays have been used as "companion diagnostics" for determining tumor PD-L1 expression.[11] The thresholds used to determine PD-L1 positivity for the different PD-1 and PD-L1 inhibitors have been defined differently. The limited predictive value of this test, together with the lack of harmonization between assays, represents a major limitation to the routine clinical use of PD-L1 assay. However, efforts are under way to address these issues. Specifically, the Blueprint PD-L1 immunohistochemistry assay comparison project[11] has reported similar analytic performances for 3 (22C3, 28-8, and SP263) of the 4 assays examined, suggesting that these assays could be used interchangeably.

In this meta-analysis, we examined the potential predictive value of routinely collected data on patient, disease, and molecular characteristics to guide the selection of patients with advanced NSCLC for checkpoint inhibitors in second and later lines of therapy. Because individual randomized clinical trials were not designed nor adequately powered to demonstrate a treatment difference between subgroups of patients on the basis of their clinical or tumor characteristics, a meta-analysis of trials comparing an immune checkpoint inhibitor with chemotherapy, with overall survival (OS) as the main end point, will help address this clinically important need.

Key Points

Question What is the relative efficacy, overall and in subgroups, of checkpoint inhibitor vs docetaxel for second-line advanced non–small cell lung carcinoma defined by clinicopathological characteristics?

Findings In this systematic review and meta-analysis of 5 randomized clinical trials involving 3025 patients with advanced non–small cell lung carcinoma, checkpoint inhibitors improved overall survival over docetaxel and had a significantly greater benefit for *EGFR* wild-type over *EGFR* mutant tumors.

Meaning In second-line checkpoint inhibitor therapy for advanced non–small cell lung carcinoma, *EGFR* mutational status could assist in patient selection, design, and interpretation of future trials and economic analyses.

Methods

Study Eligibility and Identification

Eligible randomized controlled trials that compared checkpoint inhibitors with docetaxel in the second-line setting were identified from MEDLINE, Embase, PubMed, and the Cochrane Central Register of Controlled Trials. We included articles published in the English language between January 1, 1996, and January 30, 2017, using the following terms: advanced or metastatic lung neoplasm, cancer, or carcinoma; checkpoint inhibitor; PD-1; PD-L1; ipilimumab; nivolumab; pembrolizumab; atezolizumab; and randomized controlled clinical trial. To identify unpublished studies, we searched abstracts from conference proceedings of the American Society of Clinical Oncology, the European Society for Medical Oncology, and the World Conference on Lung Cancer.

Data Extraction

For each included trial, we extracted the trial name, year of publication or conference presentation, patients' clinicopathological characteristics, type of chemotherapy, and type of checkpoint inhibitor. We also retrieved the hazard ratio (HR) and 95% CI for OS of the intention-to-treat population and the following predefined subgroups: epidermal growth factor receptor (*EGFR*) status (mutation vs wild type), Kirsten RAS (*KRAS*) status (mutation vs wild type), smoking status (never smokers vs ever [current or former] smokers), age (<65 years vs ≥65 years), sex (female vs male), performance status (PS; 0 vs 1), tumor histology (squamous vs nonsquamous), and central nervous system metastasis (present vs absent). Two of our authors (C. K. L. and J. M.) extracted data independently, and we resolved the discrepancies by consensus.

Statistical Analysis

We used the fixed-effects inverse-variance-weighted method to pool results to estimate the size of the treatment benefit. Tests of interaction were used to assess the differences in treatment effect across these subgroups.

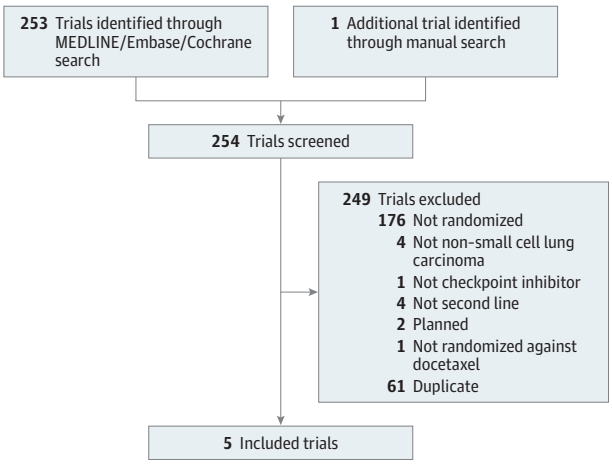
We performed a sensitivity analysis by excluding trials of PD-L1 inhibitors (atezolizumab), recognizing that it may have a different efficacy from PD-1 inhibitors (nivolumab and pembrolizumab). Publication bias was evaluated by examining the funnel plot of the effect size for each trial against the reciprocal of its SE.

We used the χ^2 Cochran Q test to detect any heterogeneity across the different trials and between subgroups. The nominal level of significance was set at 5%. All 95% CIs were 2-sided.

Results

The search strategy identified 5 eligible trials (**Figure 1**). The **Table** shows a summary of the patient, tumor, and treatment

Figure 1. Flow Diagram of Study Inclusion and Exclusion



characteristics for each trial.[4-8] Data from all included trials were obtained from published manuscripts.

Benefit of Immune Checkpoint Inhibitors for OS

In total, 3025 patients were randomized to receive a checkpoint inhibitor (nivolumab, 427 patients [14.1%]; pembrolizumab, 691 [22.8%]; or atezolizumab, 569 [18.8%]) or docetaxel (1338 [44.2%]). Treatment with a checkpoint inhibitor compared with chemotherapy was statistically significantly associated with a 31% reduction in the risk of death (HR, 0.69; 95% CI, 0.63-0.75; $P < .001$) in the intention-to-treat population. There was no significant heterogeneity in the overall treatment effect across the 5 trials ($\chi^2 = 3.11$; $P = .68$).

Subgroup Analyses by *EGFR* and *KRAS* Mutation Status

Treatment effect was evaluable for 2261 patients (74.7%), with data available on *EGFR* status from 4 trials.[4,6-8,12] A total of 764 patients (25.3%) for whom the *EGFR* status was not known were excluded from analysis. In the *EGFR* wild-type subgroup (1990 [88.0%]), the pooled HR was 0.67 (95% CI, 0.60-0.75; $P < .001$; heterogeneity, $P = .98$). In the *EGFR* mutant subgroup (271 [12.0%]), the pooled HR was 1.11 (95% CI, 0.80-1.53; $P = .54$; heterogeneity, $P = .88$). There was a statistically significant treatment-*EGFR* mutation interaction ($P = .005$) (**Figure 2**A).

Treatment effect was evaluable for 519 patients (17.2%), with data available on *KRAS* status from 3 trials.[4,7,8,12] In the *KRAS* wild-type subgroup (371 [71.5%]), the pooled HR was 0.86 (95% CI, 0.67-1.11; $P = .24$; heterogeneity, $P = .62$). In the *KRAS* mutant subgroup (148 [28.5%]), the pooled HR was 0.65 (95% CI, 0.44-0.97; $P = .03$; heterogeneity, $P = .62$). There was no significant treatment-*KRAS* mutation interaction ($P = .24$) (Figure 2B).

Subgroup Analyses by Patient and Disease Factors

None of the patient factors predicted OS benefit with checkpoint inhibitors compared with docetaxel. Treatment effect was evaluable for 1963 patients (64.9%), and data were available on self-reported smoking status from 4 trials.[4,5,7,8,12] In the ever (current or former) smoker subgroup (1633 [83.2%]), the pooled HR was 0.69 (95% CI, 0.62-0.78; $P < .001$; heterogeneity, $P = .66$). In the never smoker subgroup (330 [16.8%]), the pooled HR was 0.79 (95% CI, 0.60-1.05; $P = .07$; heterogeneity, $P = .36$). There was no significant treatment-smoking interaction ($P = .40$) (eFigure 1A in the Supplement). Age (<65 years HR, 0.71 vs ≥65 years HR, 0.69; interaction, $P = .85$) (eFigure 1B in the Supplement), PS (0 HR, 0.69 vs 1 HR, 0.68; interaction, $P = .74$) (eFigure 1A in the Supplement), and sex (female HR, 0.70 vs male HR, 0.69; interaction, $P = .82$) (eFigure 2 in the Supplement) did not predict OS benefit from checkpoint inhibitors.

None of the disease factors examined predicted OS benefit from checkpoint inhibitors over docetaxel. The NSCLC tumors were classified histologically as squamous or nonsquamous, with treatment effect evaluable for 2921 patients (96.6%) from all included trials. In the squamous subgroup (813 [27.8%]), the pooled HR was 0.67 (95% CI, 0.57-0.80; $P < .001$; heterogeneity, $P = .73$). In the nonsquamous subgroup (2108 [72.2%]), the pooled HR was 0.70 (95% CI, 0.62-0.78; $P < .001$; heterogeneity, $P = .78$). There was no significant treatment-histology interaction ($P = .71$) (eFigure 2C in the Supplement). The treatment effect was evaluable for 1687 patients (55.8%), with data on central nervous system (CNS) metastasis reported in 3 trials.[4,5,7] There was no difference in benefit from checkpoint inhibitors among those with no CNS metastasis (1534 [90.9%]; HR, 0.71; 95% CI, 0.63-0.80; $P < .001$; heterogeneity, $P = .43$) and those with CNS metastasis (153 [10.0%]; HR, 0.76; 95% CI, 0.52-1.12; $P = .39$; heterogeneity, $P = .09$; treatment-CNS metastasis interaction, $P = .71$) (eFigure 2D in the Supplement). The eTable in the Supplement provides key inclusion and exclusion criteria of each trial for patients with CNS metastasis.

Sensitivity Analysis

When the trials of PD-L1 inhibitors[7,8] were excluded, the overall treatment effect was similar (eFigure 3A in the Supplement). Subgroup analyses according to *KRAS* status, smoking status, and CNS metastasis were not possible because of an insufficient number of PD-1 trials that report these results. We observed a consistent result for the *EGFR* wild-type vs mutant subgroups (HR, 1.05 vs 0.66; interaction, $P = .04$) (eFigure 3B in the Supplement) and for other subgroups (eFigure 3C and eFigure 4 in the Supplement).

Publication Bias

A funnel plot of the effect size for each trial against the precision showed no asymmetry (data not shown).

Discussion

This meta-analysis demonstrates that checkpoint inhibitors are statistically significantly associated with a 31% reduction in the risk of death compared with docetaxel in second and later lines of therapy for advanced NSCLC. Although there was an OS advantage for patients with *EGFR* wild-type tumors (pooled HR, 0.67; $P < .001$), there was no OS advantage seen for those with

Table. Characteristics of Patients in Included Trials

Trials	Treatment Comparison	Median OS, mo[a]	Patients, No. (%)								
			EGFR Mutation	*KRAS* Mutation	Squamous Carcinoma	Age, ≥65 y	PS 1	Male, Sex	Ever Smoker	CNS Metastasis	Only 1 Previous Line of Therapy
CheckMate 017,[5] 2015	Nivolumab vs docetaxel	9.2 vs 6.0			272 (100)	120 (44)	206 (76)	208 (76)	250 (92)	17 (6)	271 (100)
CheckMate 057,[4] 2015	Nivolumab vs docetaxel	12.2 vs 9.4	82 (14)	62 (11)	0	243 (42)	402 (69)	319 (55)	458 (79)	68 (12)	515 (88)
Keynote 010,[6] 2016	Pembrolizumab vs docetaxel	10.4 vs 12.7[b] vs 8.5[c]	86 (8)		222 (21)	429 (41)	678 (66)	209 (61)	833 (81)	152 (15)	713 (69)
OAK,[7] 2017	Atezolizumab vs docetaxel	13.8 vs 9.6	85 (10)	59 (7)	222 (26)	397 (47)	535 (63)	520 (61)	694 (82)	85 (10)	640 (75)
POPLAR,[8] 2016	Atezolizumab vs docetaxel	12.6 vs 9.7	18 (6)	27 (9)	97 (34)	113 (39)	193 (67)	169 (59)	231 (80)		189 (66)

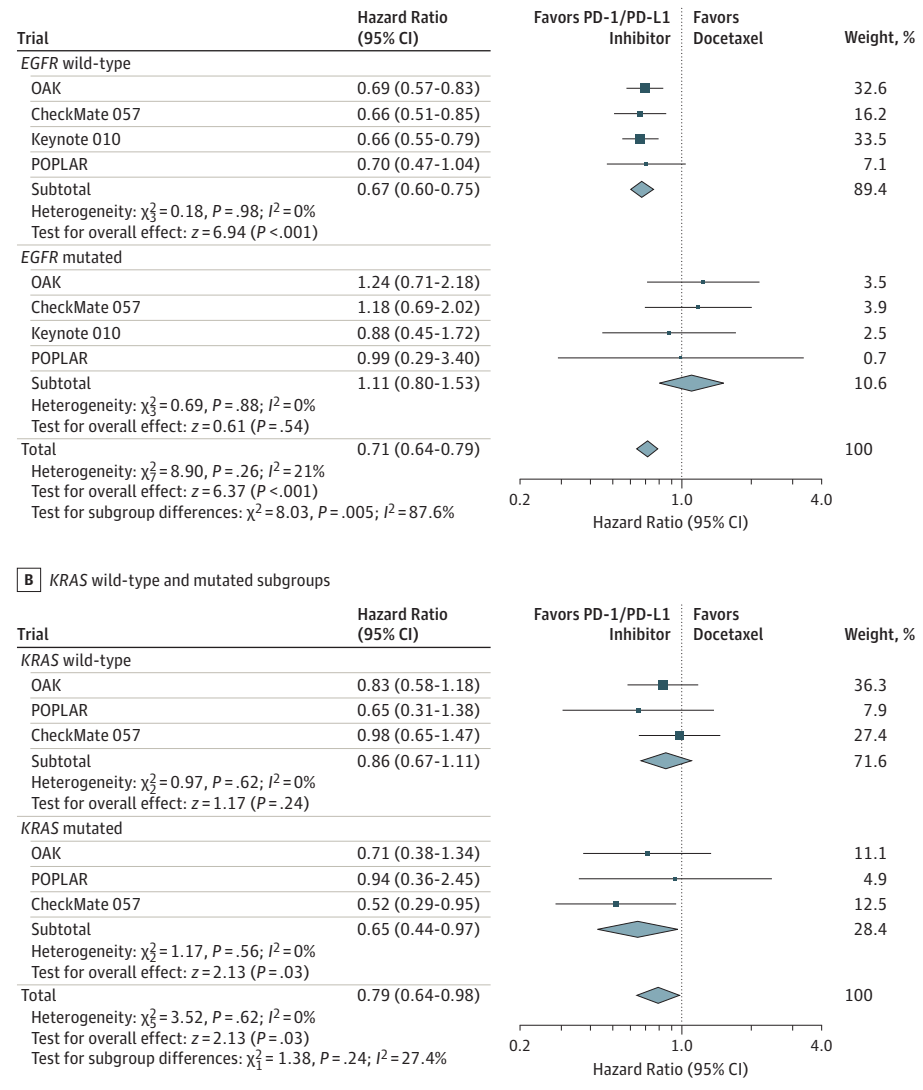
Abbreviations: CNS, central nervous system; *EGFR*, epidermal growth factor receptor; OS, overall survival; PS, performance status.

[a] Median OS as reported for each treatment arm of the intention-to-treat population.

[b] Pembrolizumab 2 mg/kg arm.

[c] Pembrolizumab 10 mg/kg arm.

Figure 2. Forest Plot of Hazard Ratios Comparing Overall Survival in Patients Who Received PD-1 (Programmed Cell Death 1) or PD-L1 (Programmed Cell Death 1 Ligand 1) Immune Checkpoint Inhibitors vs Docetaxel



A, Epidermal growth factor receptor (*EGFR*) wild-type and mutated subgroups. B, Kirsten RAS (*KRAS*) wild-type and mutated subgroups. Hazard ratios for each trial are represented by the squares, and the horizontal line crossing the square represents the 95% CI. The diamonds represent the estimated overall effect, based on the meta-analysis fixed-effect method. All statistical tests were 2-sided.

EGFR mutant tumors, and there was a nonsignificant trend toward worsened OS compared with docetaxel (pooled HR, 1.11; $P = .54$; *EGFR* status-treatment interaction, $P = .005$).

In addition, there was a greater benefit in *KRAS* mutant subgroups, with a 35% reduction in the risk of death. Our findings confirm that *EGFR* mutation status can be used to predict checkpoint inhibitor benefits, with no OS advantage observed for *EGFR* mutant tumors and with a statistically significant interaction between *EGFR* status and treatment effect (*EGFR* mutant HR, 0.67 vs *EGFR* wild-type HR, 1.11; $P = .005$). In the absence of a statistically significant interaction between *KRAS* status and treatment effect (*KRAS* mutant HR, 0.86 vs *KRAS* wild-type HR, 0.65; $P = .24$), this meta-analysis does not provide sufficient evidence to recommend *KRAS* as a predictive biomarker for the selection of patients for checkpoint inhibitor therapy. This meta-analysis also confirms that age, sex, and PS 0 or 1 were not predictive of OS benefit with checkpoint inhibitors. However, this analysis does not allow an evaluation of the effect of these agents on patients with PS 2, who represent a large proportion of patients in routine clinical practice but were excluded from all recently conducted trials.

Our findings are consistent with those of previous studies[13,14] that have reported the benefit of checkpoint inhibitor monotherapy, if any, are modest in tumors harboring *EGFR* mutations. Despite the high expression of PD-L1 in *EGFR* mutant tumors,[15,16] we have previously hypothesized that the low mutational load[17,18] associated with these tumors, as compared with other types of NSCLC, might provide a biological explanation for our findings. Other recent insights that may help to further elucidate the mechanisms of resistance include the finding that *EGFR* mutant tumors are associated with a high frequency of inactive tumor-infiltrating lymphocytes even though lymphocytes are present in the tumor microenvironment.[19] The finding that high CD73 expression on NSCLC and other tumors is associated with low PD-L1 expression and low densities of $CD8^+$ tumor-infiltrating lymphocytes[20] may also provide an explanation given that *EGFR* activation is thought to induce CD73 expression. One hypothesis raised is that in the *EGFR* mutant tumors with overexpression of CD73, which is also associated with reduced expression of interferon gamma messenger RNA signature,[21] CD73 results in immunosuppression via decreased T-cell activation and effector function and hence reduced benefit from checkpoint inhibitor therapies.

Multiple factors could potentially account for our finding that checkpoint inhibitors had a greater therapeutic benefit for *KRAS* mutant than for *KRAS* wild-type NSCLC. Unlike *EGFR* mutant tumors, tumor-infiltrating lymphocytes are frequently present in the microenvironment of *KRAS* mutant tumors and are almost always active.[19] Mutations in *STK11* or *LKB1* and *TP53* tumor suppressor genes commonly co-occur in *KRAS* mutant NSCLC.[22] Loss of *TP53* function is associated with an increase in expression of PD-L1[23] and an increase in mutation burden.[18,24] A recent study of 165 patients with *KRAS* mutant NSCLC who received PD-1 or PD-L1 therapy demonstrated that *TP53* comutations are associated with a high likelihood of response, but mutational inactivation of *STK11* or *LKB1* is associated with de novo resistance.[25] However, *KRAS* status was available for only 519 patients (17.2%), limiting the study power to exclude a treatment benefit in *KRAS* wild-type tumors and statistically test for a treatment-*KRAS* mutation interaction. Furthermore, *KRAS* mutant NSCLC is a heterogeneous disease, and better classification of these patients is still required.[26] Therefore, this hypothesis-generating finding should be confirmed in larger studies of checkpoint inhibitors in NSCLC.

Consistent with a previous report,[27] this study demonstrates comparable benefits with checkpoint inhibitor therapy for squamous and nonsquamous NSCLC (HR, 0.67 vs 0.70; interaction, $P = .71$). Patients with squamous tumors are often believed to receive less benefit from checkpoint inhibitors. However, these patients have worse OS, as demonstrated in the control (docetaxel) arm of CheckMate 017 trial (median OS, 6.0 months),[5] than those with nonsquamous tumors, as demonstrated in the control arm of CheckMate 057 trial (median OS, 9.4 months).[4] This meta-analysis shows checkpoint inhibitors offer similar benefits relative to docetaxel for both histological subtypes.

Our finding of a nonsignificant difference in treatment benefit for checkpoint inhibitors in current and former smokers vs never smokers (HR, 0.69 vs 0.79; interaction, $P = .40$) does not support previous uncontrolled studies[10,28,29] that have reported that smokers treated with checkpoint inhibitors have greater tumor shrinkage. Smoking has been hypothesized to induce greater tumor mutation burden[30] and thereby greater benefit from checkpoint inhibitors. Reasons for these conflicting findings include the uncontrolled design and small sample size of previous studies, the possibility that the tumor response rate does not translate to OS improvement, the unknown consequence of crossover at disease progression, and the possibility that a molecular smoking signature but not self-reported smoking status correlates with treatment efficacy.[17] In our study, we were unable to ascertain how smoking status was defined in the different trials. The duration and quantity of tobacco exposure used to distinguish among never smokers, former smokers, and current smokers may therefore have differed across trials. Nevertheless, our results do not support the use of self-reporting smoking status in patient selection for checkpoint inhibitor therapy.

With data available on more than half of the included patients, our study also demonstrates that the presence or absence of CNS metastases did not alter the OS benefit of checkpoint inhibitors (HR, 0.76 vs 0.71; treatment-CNS metastasis interaction, $P = .71$). Although these results are generalizable only to patients with good PS and who met the trial eligibility criteria, they are nevertheless encouraging. A previous phase 2 trial of patients with advanced cancer and untreated brain metastasis that reported a response rate of 33% in the NSCLC cohort[31] supports the result of our meta-analysis. As the PD-1 or PD-L1 inhibitors do not cross the blood-brain barrier, the ability of these agents to mobilize activated T cells into the CNS to control brain metastases represents a major therapeutic advance in the treatment of advanced NSCLC. With only a limited number of patients with known CNS metastasis in the included trials, future research is still required, including evalu-

ation of the differences in efficacy of PD-1 vs PD-L1 inhibitor for patients with CNS metastasis.

Our results have several important clinical and research implications. They might be useful for the selection of patients for checkpoint inhibitor therapy and would enhance drug development and the design and interpretation of future clinical trials. For patients with *EGFR* mutant NSCLC, our findings suggest immunotherapy should be considered only after exhaustion of other effective therapeutic options, such as *EGFR* tyrosine kinase inhibitors and chemotherapy. With differences in OS benefits for various subgroups, this meta-analysis will be important for economic analyses where the costs required to achieve these benefits will vary.

Strengths and Limitations

This meta-analysis has several strengths. We performed a comprehensive review using the most up-to-date trial data. We also overcame the problem of inadequate power of individual trials, allowing us to examine clinically important subgroup comparisons. The major limitation of this study is that *EGFR* and *KRAS* mutations were not determined universally by centralized testing, with *EGFR* not assessed in 764 patients (25.3%) and *KRAS* status not assessed in 2506 patients (82.8%), and where the different types of mutations were also unknown. In addition, the results were generalizable only to patient groups eligible for these trials. Importantly, we were unable to examine the effect of these agents in patients with poor PS, who represent a large proportion in routine clinical practice. Despite these limitations, to our knowledge this meta-analysis remains the largest study so far that incorporates results from 5 trials with more than 3000 patients.

Conclusions

Checkpoint inhibitors, compared with docetaxel, significantly prolonged OS in second and later lines of treatment for advanced NSCLC. Our findings of no OS benefit for *EGFR* mutant tumors suggest that checkpoint inhibitors should be considered only for this group after exhaustion of other effective therapies. In the absence of a statistically significant interaction between *KRAS* status and treatment effect, we cannot recommend *KRAS* as a predictive biomarker and larger studies are warranted to further investigate its predictive value. The findings of this meta-analysis could also assist in the design and interpretation of future trials and in economic analyses.

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Lee, Herbst, Gralla, Mok, Yang.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Lee, Herbst, Gralla, Mok.
Critical revision of the manuscript for important intellectual content: Lee, Man, Lord, Cooper, Links, Gebski, Gralla, Mok, Yang.
Statistical analysis: Lee, Gebski, Gralla.
Administrative, technical, or material support: Lee, Yang.
Study supervision: Lee, Gebski, Mok, Yang.

Conflict of Interest Disclosures: Dr Lee reported serving on the scientific advisory board of and receiving honorarium from AstraZeneca. Dr Cooper reported serving on the scientific advisory board of and receiving honorarium from Bristol Myers Squibb, MSD, and AstraZeneca. Dr Hersbt reported being a consultant for AstraZeneca, Genentech, Eli Lilly, Merck, and Pfizer and receiving research funding from Genentech and Merck. Dr Mok reported serving on the scientific advisory board of and receiving honorarium and research funding from AstraZeneca, Roche/Genentech, Eli Lilly, Bristol-Myers Squibb, Boehringer Ingelheim, Novartis, Pfizer, Merck Serono, Clovis Oncology, Vertex, SFJ, ACEA BioSciences, MSD, geneDecode, Oncogenex, Celgene, Ignyta, Taiho Pharmaceutical Co Ltd, and Eisai Co Ltd. Dr Yang reported serving as a consultant for Bristol-Myers Squibb and on the scientific advisory board of Astellas Pharma EMEA, Bayer Plc, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene Ltd, Clovis Oncology, Eli Lilly and Company, Merck Serono, Merrimack Pharmaceuticals, MSD, Novartis, Ono Pharmaceutical Co Ltd, Pfizer Inc, Roche/Genentech, and Yuhan Pharmaceuticals. No other disclosures were reported.

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