A Randomized Phase 2 Trial of Nivolumab Versus Nivolumab-Ipilimumab Combination in EGFR-Mutant NSCLC

Gillianne G. Y. Lai, MBBS, a Jia Chi Yeo, PhD, b Amit Jain, MBBS, PhD, a Siqin Zhou, MSc, c Mengyuan Pang, MSc, b Jacob J. S. Alvarez, BSc, b Ngak Leng Sim, BCS, b Aaron C. Tan, MBBS, FRACP, PhD, a Lisha Suteja, BSc, d Tze Wei Lim, BSc, c Yu Amanda Guo, PhD, b Meixin Shen, PhD, a Stephanie P. L. Saw, MBBS, a Neha Rohatgi, BSc, b Joe P. S. Yeong, MBBS, PhD, e Angela Takano, MBBS, f Kiat Hon Lim, MBBS, f Apoorva Gogna, MBBS, g Chow Wei Too, MBBS, g Kun Da Zhuang, MBBS, g Wan Ling Tan, MBBS, a Ravindran Kanesvaran, MBBS, a Quan Sing Ng, MBBS, a Mei Kim Ang, MBBS, a Tanujja Rajasekaran, MBBS, a Lanying Wang, MBBS, a Chee Keong Toh, MBBS, a Wan Teck Lim, MBBS, a Wai Leong Tan, PhD, b, h Sze Huey Tan, PhD, c Anders M. J. Skanderup, PhD, b Eng Huat Tan, MBBS, a
Daniel S. W. Tan, BSc, MBBS, MRCP, PhD, i, *

aDivision of Medical Oncology, National Cancer Centre Singapore, Singapore
bGenome Institute of Singapore, Singapore
cDivision of Clinical Trials and Epidemiological Sciences, National Cancer Centre Singapore, Singapore
dCancer Therapeutics Research Laboratory, National Cancer Centre Singapore, Singapore
eInstitute of Molecular and Cell Biology, Singapore
fDivision of Pathology, Singapore General Hospital, Singapore
gDepartment of Vascular and Interventional Radiology, Singapore General Hospital, Singapore
hCancer Science Institute of Singapore, National University of Singapore, Singapore

Received 22 July 2022; revised 25 August 2022; accepted 16 September 2022
Available online - 21 September 2022

ABSTRACT

Introduction: Although immune checkpoint inhibitors (ICIs) have dramatically improved outcomes for nononcogene-addicted NSCLC, monotherapy with programmed cell death protein-1 (PD1) inhibition has been associated with low efficacy in the EGFR-mutant setting. Given the potential for synergism with combination checkpoint blockade, we designed a trial to test the activity...
of combination nivolumab (N)-ipilimumab (NI) in EGFR-mutant NSCLC.

Methods: This is a randomized phase 2 study (NCT03091491) of N versus NI combination in EGFR tyrosine kinase inhibitor (TKI)–resistant NSCLC, with crossover permitted on disease progression. The primary end point was the objective response rate, and the secondary end points included progression-free survival, overall survival, and safety of ICI after EGFR TKI.

Results: Recruitment ceased owing to futility after 31 of 184 planned patients were treated. A total of 15 patients received N and 16 received NI combination. There were 16 patients (51.6%) who had programmed death-ligand (PDL1) 1 greater than or equal to 1%, and 15 (45.2%) harbored EGFR T790M. Five patients derived clinical benefits from ICI with one objective response (objective response rate 3.2%), and median progression-free survival was 1.22 months (95% confidence interval: 1.15–1.35) for the overall cohort. None of the four patients who crossed over achieved salvage response by NI. PDL1 and tumor mutational burden (TMB) were not able to predict ICI response. Rates of all grade immune-related adverse events were similar (80% versus 75%), with only two grade 3 events.

Conclusions: Immune checkpoint inhibition is ineffective in EGFR TKI–resistant NSCLC. Whereas a small subgroup of EGFR-mutant NSCLC may be immunogenic and responsive to ICI, better biomarkers are needed to select appropriate patients.

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Keywords: Lung cancer; Epidermal growth factor receptor; Immunotherapy; Biomarkers

Introduction

Immune checkpoint inhibitors (ICIs) that abrogate the interaction of programmed cell death protein (PD-1) and programmed death-ligand 1 (PD-L1) have dramatically improved survival outcomes in patients with advanced NSCLC. Concomitant CTLA4 blockade has also been found to improve antitumor immunity through augmentation of effector T-cell activation and reducing regulatory T-cell dysfunction, and has been found to be a promising strategy to improve treatment outcomes in the metastatic setting with a tolerable safety profile. Notably, not all patients benefit from checkpoint blockade, and though several biomarkers that may predict response to ICI have emerged such as PD-L1 expression levels, tumor mutational burden (TMB), and T-cell-inflamed gene expression profile (GEP), the accuracy of these biomarkers are still unknown for many patient subsets.

The key to the treatment paradigm in the management of NSCLC is the presence of oncogenic drivers such as the EGFR and ALK, among others, in which there is a good response to tyrosine kinase inhibitors (TKIs). Nevertheless, acquired resistance to targeted therapies invariably develops, and strategies to overcome these mechanisms continue to be sought. Whereas several trials evaluating immunotherapy in NSCLC allowed patients with EGFR and ALK mutations, only a minority of these patients were included across the studies, with generally low efficacy of ICI monotherapy regardless of PD-L1 status. Other studies specifically investigating the activity of PD-1 blockade in oncogene-addicted NSCLC have also reported poor efficacy. Further attempts at inducing long-term disease control of these patients have included combinatorial approaches with ICI and targeted therapy, which, not only exhibited no synergistic or additive activity, but conversely have been found to result in increased grade 3 or higher toxicities. An increase in serious immune-related adverse events (irAEs) has also been reported in patients treated sequentially with ICI followed by targeted therapy, and thus, the clinical implications of this approach must be carefully considered.

We sought to compare the efficacy and safety of nivolumab (N) monotherapy against the N-ipilimumab (NI) combination in patients with advanced EGFR-mutant NSCLC who have progressed on EGFR TKI.

Materials and Methods

Patients

This is an open-label randomized phase 2 study done at the National Cancer Centre Singapore. Eligible patients were aged 21 years and older, with either histologically or cytologically documented advanced (stage IIIIB or IV according to the seventh edition of TNM classification by the American Joint Committee on Cancer) or recurrent NSCLC with a sensitizing EGFR mutation. Patients were required to have progressed on one line of standard EGFR TKI and not more than one line of chemotherapy. Patients with asymptomatic central nervous system (CNS) metastases were allowed, provided they had had no ongoing requirement for corticosteroids as therapy for CNS disease, no stereotactic radiation with 7 days or whole brain radiation within 14 days before randomization, and no evidence of interim progression between the completion of brain-directed therapy and screening radiographic study.

Key exclusion criteria included previous treatment with other anti–PD-1, anti–PD-L1, or anti–CTLA-4
therapies, active or previously documented autoimmune disease, or history of interstitial lung disease or pneumonitis (Appendix 1: NCT03091491 Protocol).

**Study Design and Treatment**

Eligible patients were randomized (1:1) to receive intravenous N 3 mg/kg administered every 2 weeks (N), or N 3 mg/kg every 2 weeks, and ipilimumab 1 mg/kg every 6 weeks (NI). Randomization was stratified by PD-L1 status (<1% versus ≥1%) and the presence of brain metastasis. Patients and investigators were not blinded to treatment.

Treatment in both arms was continued until radiographic progression, unacceptable toxicity, investigator decision, or patient withdrawal of consent. Patients randomized to the N arm were allowed to crossover to the NI combination arm at the time of progression. Patients were permitted to continue treatment beyond the initial progressive disease (as defined by the Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) as long as they continued to derive clinical benefit as per investigator assessment, tolerated study drug(s), and did not have progressive disease by immune-related RECIST.

**End Points and Assessments**

The primary end point for this trial was the objective response rate (ORR) or the proportion of patients who experienced complete or partial response (PR) on the basis of the RECIST criteria. Secondary end points included the following: (1) progression-free survival (PFS), or the time from randomization to the date of first documented disease progression or death owing to any cause (surviving patients who were free of progressive disease were censored at the date of last documented tumor scan); (2) overall survival (OS) or the time from randomization to the date of death owing to any cause (surviving patients were censored at the date of the last follow-up); (3) duration of response; (4) toxicity profiles of N with and without ipilimumab; and (5) the salvage capability of the addition of ipilimumab to patients who progress on N alone to achieve clinical benefit.

Recruited patients were required to have baseline imaging with computed tomography or magnetic resonance imaging and tissue biopsy, followed by 6-weekly evaluation imaging, and thereafter every 12 weeks until disease progression. EGFR mutations were determined using Sanger sequencing at the time of initial diagnosis. PD-L1 testing was done at the point of randomization after exposure to EGFR TKI in the first-line setting. Adverse events and laboratory abnormalities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. An on-treatment tissue biopsy was required after 6 doses of treatment, and for patients progressing on N monotherapy before crossover to NI. Pretreatment and posttreatment biopsies were subject to whole-exome sequencing and total RNA sequencing, as previously described.27

**Trial Oversight**

The study protocol was conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization. The study was approved by the institutional review board at each participating center and was conducted in compliance with the protocol. All patients provided written informed consent before enrolment. This trial was, in part, sponsored by Bristol Myers Squibb.

**Statistical Analysis**

Given the published trial results of CheckMate-057 and CheckMate-012, we aimed to investigate whether the difference in ORR between patients treated with N combination and N monotherapy was 20%, assuming 10% ORR in the N monotherapy group and 30% ORR in the NI combination group. With a two-sided significance level of 5% and power of 90%, 184 patients (92 per treatment arm) were needed to compare the ORR of 10% versus 30% between the two treatments, on the basis of the chi-square test with Yates’ continuity correction.

Efficacy was analyzed on an intention-to-treat basis. The ORR for the two treatment arms was compared using the chi-square test. Logistic regression, adjusting for the stratification factors, was performed to assess the robustness of the result. Patients with nonassessable tumor response were treated as nonresponders for the ORR primary analysis. Survival distribution for the secondary end points of the duration of response, PFS, and OS was estimated using the Kaplan-Meier method. The median duration of follow-up was estimated using the reverse Kaplan-Meier method. Safety analyses included all patients who received at least one dose of study treatment (as-treated population). All analyses were performed using the Statistical Analysis Software version 9.4 and R software version 3.6.3.

**Results**

**Patients**

A total of 31 patients were enrolled in the trial between April 2017 and December 2018. Three additional patients were screened but did not meet inclusion criteria (Fig. 1). There were 15 patients who were randomized to the N monotherapy arm, and 16 patients to the NI combination arm. Baseline clinical characteristics
revealed that 19.3% of the entire cohort were smokers and ex-smokers, and nearly half (45.2%) were PD-L1–negative (Table 1). In addition, 45.2% harbored an EGFR T790M mutation, nearly all (13 of 14) of whom previously received third-generation EGFR TKI. Of the overall cohort, 61.3% previously received third-generation EGFR TKI before enrolment in the trial. Approximately half (16 of 31) had brain metastases at baseline, 11 of whom (68.8%) had previously received brain-directed radiation therapy with stereotactic radiosurgery or whole-brain radiation therapy. At the time of data cutoff, the median duration of follow-up was 24.3 months (interquartile range: 15.45–24.33) and all patients had discontinued study treatment. The trial was terminated early in June 2019 owing to clinical futility.

**Efficacy of Immune Checkpoint Inhibition**

Among the 30 patients with assessable disease, only one had an objective response to immunotherapy (ORR 3.2%) (Fig. 2A). This patient was randomized to the combination NI arm. There were no differences in PFS between the two arms, with a median PFS of 1.22 months (95% confidence interval: 1.15–1.35) (Fig. 2B) and a median OS of 5.65 months (95% confidence interval: 3.81–10.59) for the overall cohort. There were four patients who crossed over from the N monotherapy arm to the NI combination arm (patient numbers 4, 5, 9, and 20), but no salvage response was observed.

A total of five patients were found to have derived clinical benefits from immunotherapy, defined either by ongoing PR or stable disease at 6 months, or the best response of PR (Fig. 2C). All five patients were non-smokers and harbored an EGFR exon 19 deletion, with only one harboring a concomitant EGFR T790M mutation (Supplementary Table 1). In these patients, there was no evidence to suggest an association between PD-L1 status and response to immune checkpoint inhibition, with only one patient having a PD-L1 expression greater than 50%. The median time to treatment failure on first-line EGFR TKI for these patients was 18 months (range: 9–76).

![Figure 1. CONSORT diagram. N, nivolumab; NI, nivolumab-ipilimumab.](image-url)
In terms of intracranial activity, nine of the 16 patients (56.3%) with baseline brain metastases had intracranial progression. For the overall cohort, a total of 13 patients (41.9%) developed symptomatic brain metastases in the study, three of whom had isolated intracranial progression.

**Safety**

Data regarding irAEs are provided in Figure 3 and Supplementary Table 2. The rates of all grade irAE were similar in both arms (80% versus 75%). Dermatologic toxicity was the most frequently encountered irAE, followed by endocrine and gastrointestinal toxicities (Fig. 3 and Supplementary Table 2). One case of grade 1 pneumonitis was observed in a patient in the N monotherapy arm. Two grade 3 or worse adverse events were observed in the overall cohort, despite the previous use of EGFR TKI immediately before trial entry for most of the cohort (22 of 31). Both grade 3 toxicities were observed in the same patient (type 1 diabetes mellitus and myositis) from the NI combination arm. Among the four patients who crossed over from N to NI, there was generally no change in the severity of irAE except for one patient who experienced a grade 1 to 2 change in rash on crossover (Supplementary Fig. 1).

### Effect of Tumor Microenvironment on Response to Immunotherapy

To investigate tumor characteristics that may predict the response to immunotherapy, we identified eight patients with target lesions that either revealed shrinkage or had a stable tumor size of 6 months or more and underwent tumor biopsy. We then performed detailed molecular analysis on these cases with adequate tumor tissue at baseline biopsy (n = 7) (Supplementary Fig. 2).

To correlate treatment response with tumor inflammation status, a k-means clustering method of classification was applied to all baseline tumor transcriptome profiles (RNA data analysis) (Supplementary Methods).
Figure 2. Clinical outcomes for EGFR TKI-resistant patients on N with or without ipilimumab. (A) Waterfall plot for patients with evaluable radiographic images. (B) PFS of patients on N and NI. (C) Spider plot of individual tumor responses. CI, confidence interval; N, nivolumab; NI, nivolumab-ipilimumab; PD, progressive disease; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
This revealed that EGFR-mutated tumors were generally immune-cold before immune checkpoint inhibition (n = 21 of 24) (Fig. 5). However, this baseline inflammation state of the tumor was not predictive of the eventual patient response to ICI therapy (P = 1; Fisher’s exact test) (Fig. 5). Similarly, using immune-cell gene expression signatures from Danaher et al.,33 we did not observe a correlation between inferred tumor immune-cell populations and treatment response (Supplementary Fig. 3A).

To study the dynamics of treatment responses to immunotherapy, eight paired baseline, and on-treatment tumor samples were obtained from patients in the study. Four of these paired samples were obtained from biopsies of tumor lesions with either shrinkage or stability in size for 6 months or more (“biopsy-site responders”). Using a previously defined transcriptomic score for high immune infiltration (GEP<sup>hi</sup> definition of −0.318<sup>18</sup>), two of the four samples obtained from these biopsy-site responders were found to become GEP<sup>hi</sup> while on treatment, whereas the third was already GEP<sup>hi</sup> before treatment (Supplementary Fig. 3B). In contrast, none of the tumor samples obtained from patients without a response to immunotherapy were classified as GEP<sup>hi</sup> either before or during their course of treatment (Supplementary Fig. 3B), suggesting that an immune-active tumor microenvironment, or the ability to engage an antitumor immune response, plays an essential role in patients with EGFR-mutant NSCLC during immunotherapy.

The inability of traditional biomarkers to predict treatment response in our study prompted the search for novel biological mechanisms that could potentially account for the response to immune checkpoint inhibition in EGFR-mutant NSCLC. To this end, exploratory differential gene expression analysis was conducted, and RNA-sequencing data of baseline tumor samples from biopsy-site responders (n = 7) was compared against that of nonresponders (n = 17).

Enrichment of several extracellular matrix (ECM)-related genes such as CILP, EFEMP1, and DPT, and the up-regulation of the epithelial-to-mesenchymal promoting transcription factor PRRX1<sup>34</sup> was observed in tumor tissue obtained from biopsy-site responders.
Concurrent with gene set enrichment analysis, we also observed the enrichment of matrisomal-related terms in the responders to immunotherapy at baseline (Supplementary Fig. 4D), suggesting that the permissive effect of the ECM on the tumor microenvironment may be beneficial toward positive immunotherapy response within EGFR-mutant NSCLC.

Discussion

To the best of our knowledge, our study is the first published trial of combination PD-1/CTLA4 inhibition in patients with EGFR-mutant NSCLC. At the time of study initiation, Hellmann et al.9 reported an ORR of 50% (four of eight) for EGFR-mutant NSCLC in CheckMate-012, providing a rationale for combination checkpoint inhibition in this context. In this phase 2 randomized clinical trial, we established the futility of immune checkpoint inhibition in the EGFR-mutant subgroup, which led to the decision for early termination of the study. Data from our cohort also revealed the inability of CTLA4 blockade to salvage failure of PD-1 inhibition and adds to the existing evidence that immune checkpoint inhibition has poor efficacy in EGFR TKI–resistant NSCLC.

Genomic and transcriptomic profiling of the EGFR TKI–resistant tumor samples from our cohort revealed an immune-cold phenotype, which is in keeping with
previous reports of an uninflamed tumor microenvironment with immunologic tolerance and weak immunogenicity in the EGFR-mutant NSCLC context.\textsuperscript{35} This has been postulated to account for a poor response to immunotherapy, and the identification of predictive biomarkers of immunotherapy response in the context of EGFR-mutant NSCLC remains a challenge. Whereas PD-L1 expression thresholds are now often used in clinical practice to select patients with the highest likelihood of clinical response to immunotherapy, its role in this molecular subtype remains controversial, with conflicting reports regarding the correlation between EGFR mutation and PD-L1 expression.\textsuperscript{36–39} The limitation of PD-L1 as a biomarker in EGFR TKI-resistant NSCLC was also revealed in our study, and possibly reflects the impact that an immune suppressive TME comprising mainly of T-regulatory cells, myeloid-derived suppressor cells, and tumor-associated macrophages have on ICI resistance.

Figure 5. Tumor immune phenotype of EGFR-mutant NSCLC before receiving ICI. Tumors were classified into “immune-hot” or “immune-cold” status on the basis of gene expression levels of the GEP genes with CTLA4, ENTPD1, and CD38 expression included (see Supplementary Methods). Genes that are up-regulated are expressed as positive Z-scores (red), whereas down-regulated genes are distinguished by negative Z-scores (blue). Ex19del, exon 19 deletion; GEP, gene expression profile; ICI, immune checkpoint inhibitor; Nivo + Ipi, nivolumab + ipilimumab; Nivo, nivolumab.

Given the data from our previous work\textsuperscript{27} in which we observed an association between an inflamed tumor microenvironment and TKI-resistant states, a further attempt was made to investigate baseline tumor immune phenotype and its impact on clinical response to ICI, but no association was found (Supplementary Fig. 5A and B). Transcriptomic analysis of the pre-ICI tumor samples in our cohort also determined that previously described biomarkers for immunotherapy response, such as TMB,\textsuperscript{17} GEP score,\textsuperscript{18} CXCL9/13 expression,\textsuperscript{29,30} and CD39/CD73\textsuperscript{31} or IDO pathway up-regulation,\textsuperscript{32} were unable to predict for response in the EGFR TKI-resistant setting. Similarly, we did not observe an overlap in genes associated with response in our study and a previously published cohort of anti-PD-1/ PD-L1–treated EGFR wild-type NSCLC. Overall, these results led us to hypothesize that an immune-favorable ECM environment may potentially predict positive immunotherapy response in the context of EGFR-mutated, TKI-resistant
tumors, and thus, plans to validate select ECM or TME-related genes are underway. Interestingly, a T-cell inflammation profile switch from a GEPlo to GEPhi phenotype was observed in two (of four) of the biopsy site responders, suggesting that EGFR-mutant NSCLC may still retain the ability to mount an antitumor response, and that other yet-to-be uncovered immune mechanisms are at play to influence T-cell responses and ICI efficacy.

The issue of CNS control in the context of EGFR-mutant NSCLC is also an important point of consideration in the approach of patients who have progressed on targeted therapy. EGFR-mutated tumors have a known predilection for brain metastasis, with a baseline incidence of 20% to 30%, and a 5% to 20% risk of CNS progression while on EGFR TKI. In our study, more than 40% of our overall cohort developed intracranial failure on ICI, highlighting the inadequacy of this approach in attaining intracranial control in oncogene-addicted cancers when CNS-penetrant TKIs are discontinued. Whereas combination EGFR TKI and T-cell–based therapy was previously investigated on the hypothesis of enhanced antitumor immunity through down-regulation of PD-L1, the challenge of overcoming additive toxicities remains, with potentially fatal consequences such as interstitial lung disease. To this end, novel therapeutic approaches, which aim to more specifically increase the immunogenicity of EGFR TKI–resistant tumor cells or inhibit immunosuppressive signaling in the TME, deserve further evaluation in this area of clinical unmet need.

In summary, despite the small cohort size, our study was able to exhibit the futility of ICI in the EGFR TKI–resistant NSCLC setting. No new safety concerns were identified despite the sequential use of EGFR TKI followed by ICI in most patients. Though a small subgroup of patients with EGFR-mutant lung cancer having a GEPlo phenotype may potentially benefit from ICI, the real-time clinical application remains challenging, and with the lack of better biomarkers to select appropriate patients, PD-1/CTLA-4 inhibition alone is inadequate to confer clinical benefit in the treatment of EGFR TKI–resistant NSCLC.

CRediT Authorship Contribution Statement

Gillian G. Y. Lai: Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Roles/Writing - original draft, Writing – review and editing.

Jia Chi Yeo: Data curation, Formal analysis, Investigation, Methodology, Visualization, Roles/Writing - original draft, Writing – review and editing.

Amit Jain: Investigation, Writing – review and editing.

Siqin Zhou: Formal analysis, Methodology, Validation, Visualization, Writing – review and editing.

Mengyuan Pang: Formal analysis, Validation, Writing – review and editing.

Jacob J. S. Alvarez: Formal analysis, Writing – review and editing.

Ngak Leng Sim: Formal analysis, Validation, Writing – review and editing.

Aaron C. Tan: Investigation, Writing – review and editing.

Lisda Suteja: Data curation, Formal analysis, Investigation, Roles/writing – review and editing.

Tze Wei Lim: Data curation, Project administration, Writing – review and editing.

Yu Amanda Guo: Data curation, Formal analysis, Validation, Writing – review and editing.

Meixin Shen: Project administration, Writing – review and editing.

Stephanie P. L. Saw: Investigation, Writing – review and editing.

Neha Rohatgi: Formal analysis, Validation, Writing – review and editing.

Joe P. S. Yeong: Validation, Writing – review and editing.

Angela Takano: Investigation, Writing – review and editing.

Kiat Hon Lim: Investigation, Writing – review and editing.

Apoorva Gogna: Investigation, Writing – review and editing.

Chow Wei Too: Investigation, Writing – review and editing.

Kun Da Zhuang: Investigation, Writing – review and editing.

Wan Ling Tan: Investigation, Writing – review and editing.

Ravindran Kanesvaran: Investigation, Writing – review and editing.

Quan Sing Ng: Investigation, Writing – review and editing.

Mei Kim Ang: Investigation, Writing – review and editing.

Tanuza Rajasekaran: Investigation, Writing – review and editing.

Lanying Wang: Data curation, Project administration, Writing – review and editing.

Chee Keong Toh: Investigation, Writing – review and editing.

Wan-Teck Lim: Investigation, Writing – review and editing.

Wai Leong Tam: Investigation, Writing – review and editing.
Sze Huey Tan: Data curation, Formal analysis, Methodology, Validation, Visualization, Writing – review and editing.

Anders M. J. Skanderup: Formal analysis, Funding acquisition, Visualization, Writing – review and editing.

Eng-Huat Tan: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – review and editing.

Daniel S. W. Tan: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Writing – review and editing.

Acknowledgments
This work was funded by the National Medical Research Council (NMRC; Singapore) through the Open-Fund Large Collaborative Grant “Next-Generation Clinical Trials and Integrative Research for Fighting Lung Cancer” (NMRC/OFILCG/002-2018 and the Clinical Trial Grant-Industry Collaborative Grant “Immuno-Oncology Biomarker Discovery in EGFR-mutant NSCLC” (NMRC/CTGICT/0002/2017). This was also in part supported by the NMRC Open-Fund Individual Research Grant programme (OPIRG18may-0075) and Bristol Myers Squibb. The authors thank the Lung Cancer Consortium Singapore (LCCS) for assistance with data collection.

Supplementary Data
Note: To access the supplementary material accompanying this article, visit the online version of the JTO Clinical and Research Reports at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2022.100416.

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