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ORIGINAL RESEARCH

The value of disease-free survival (DFS) and osimertinib in adjuvant non-small-cell lung cancer (NSCLC): an international Delphi consensus report

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Background: Rates of disease recurrence and death following surgery remain high in early-stage non-small-cell lung cancer (NSCLC), despite adjuvant treatment and curative intent. Recently, osimertinib showed overwhelming evidence for disease-free survival (DFS), as demonstrated by an overall reduction in the risk of disease recurrence or death in the adjuvant setting of 80% versus control in the ADAURA study (stage IB-IIIA; hazard ratio 0.20; 99.12% confidence interval 0.14-0.30; $P < 0.001$). However, due to the early unblinding of ADAURA and lack of mature overall survival data, there is a need to qualitatively confirm consensus on the clinical and patient relevance of DFS.

Materials and methods: We conducted a modified Delphi panel study consisting of two rounds of surveys, followed by a consensus meeting. An international panel of experts in the field of NSCLC and epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) ($n = 13$) was asked to rate agreement and comment on a list of pre-defined statements covering key consensus gaps. Statements were eliminated or updated between surveys, depending on the level of agreement. A final list of agreed-upon statements was drafted in the consensus meeting.

Results: Consensus was reached on 32 qualitative statements, with topics including unmet needs in early-stage NSCLC, the value of DFS, and the value of osimertinib. Crucially, DFS was agreed to be a clinically and patient-relevant endpoint in adjuvant NSCLC. The relevance of DFS was found to relate to the ability of an adjuvant therapy, such as osimertinib, to keep patients in the clinically valuable curative intent setting, while preventing the burden associated with distant and locoregional recurrence, and progressive disease.

Conclusions: Addressing the need for measures that reflect clinical benefit is essential to continue improving outcomes for NSCLC patients. To that end, this work provides a qualitative framework for clinicians to consider the clinical and patient relevance of DFS in adjuvant NSCLC and the benefit demonstrated in ADAURA thus far.

Key words: NSCLC, DFS, early stage, adjuvant treatment, EGFRm, ADAURA

INTRODUCTION

Lung cancer is among the most common forms of cancer and is responsible for over 1.7 million deaths/year worldwide.[1] Non-small-cell lung cancers (NSCLCs) account for ~85% of all lung cancers, and patient outcomes for NSCLC are highly dependent on the stage of disease.[2] Most patients with NSCLC present with advanced disease and for these patients, treatment is no longer curative.[3] However, ~30% of patients with NSCLC present with resectable disease at diagnosis,[4] for which the current standard of care is surgery with curative intent.[3]

Despite early-stage curative intent, treatment failure and patient mortality remain high, which is largely driven by distant recurrence.[5] Therefore, depending on the disease stage and findings during surgery, adjuvant treatment may be required.[3] Standard of care for these patients is currently an adjuvant two-drug, cisplatin-based regimen, which results in a 4%-5% absolute survival improvement at 5 years for

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patients with early-stage disease.[6] Nevertheless, rates of disease recurrence following adjuvant chemotherapy remain high (30%-60% depending on disease stage), resulting in significant disease burden.[7,8] As such, there is a high unmet need for early-stage NSCLC patients, particularly around the prevention of distant and central nervous system (CNS) recurrence. While the brain is a common site of distant metastasis after resection,[9] adjuvant chemotherapy does not readily pass the blood—brain barrier and has been shown to have no effect on the risk of developing this type of metastasis.[10] Importantly, patients with brain metastases show significantly worse prognosis as compared to those with local disease or metastases outside of the brain.[11] Patients with brain metastases also display significantly faster deterioration in health-related quality of life (QoL) compared to those without,[12] and show significantly lower QoL compared to patients with adrenal, liver, or lung metastases.[13] Thus, there is a need for more effective adjuvant therapies to improve the clinical outcomes of patients with stage I-III NSCLC.

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have shown promising results in improving disease-free survival (DFS) in EGFR-mutated (EGFRm) stage I-III NSCLC patients.[14] Approximately 10%-15% of NSCLC patients in the United States and Europe and 30%-40% of patients in Asia have sensitizing mutations which activate the tyrosine kinase domain in EGFRs.[15] Recent studies have indicated a role for next-generation EGFR-TKIs, such as osimertinib, in the treatment of CNS metastases.[16] Osimertinib is a third-generation EGFR-TKI approved in many countries around the world for first-line EGFRm advanced NSCLC and EGFR T790M mutation-positive advanced NSCLC,[17,18] and is now recommended as the preferred EGFR-TKI in guidelines, in part due to its proven CNS efficacy. In the recent ADAURA trial, adjuvant osimertinib reduced the risk of disease recurrence or death by 80% for stage IB-IIIA patients [hazard ratio (HR) 0.20; 99.12% confidence interval (CI) 0.14-0.30; $P < 0.001$] compared to a placebo.[19] Furthermore, adjuvant osimertinib achieved an 82% reduction in the risk of CNS recurrence compared to the control arm (HR 0.18; 95% CI 0.10-0.33; $P < 0.0001$; stage IB-IIIA).[19] Driven by its overwhelming efficacy, an independent data monitoring committee recommended for the ADAURA trial to be unblinded on a study level 2 years early in April 2020, with patients still continuing the trial.[20] However, due to the early unblinding of ADAURA and the lack of mature overall survival (OS) data, consensus on the clinical and patient relevance of DFS (the primary and secondary endpoint in ADAURA) in adjuvant NSCLC remains unclear. At the same time, no other EGFR-TKI has been able to demonstrate long-term DFS and OS benefits, as is exemplified by the outcomes of the erlotinib RADIANT trial.[21] Despite these data limitations, consensus on measures that reflect clinical benefit is essential to improving outcomes for NSCLC patients.

Considering the limitations in quantitative data, this study utilized the Delphi technique to qualitatively confirm clinical consensus on the ADAURA outcomes and the broader value of DFS in adjuvant NSCLC. The Delphi technique indeed comprises a well-established methodology allowing assessment of expert clinical consensus by means of a set of controlled surveys and discussions.[22-24] Importantly, the Delphi methods allows for making qualitative predictions of possible future circumstances.[24] As such, this study also sought to understand the expected impact of osimertinib on long-term patient outcomes, durability, and potential translation of effect to OS benefit. Together, this work provides, for the first time, a qualitative framework for clinicians to consider the clinical and patient relevance of DFS in adjuvant NSCLC and the benefit demonstrated in ADAURA thus far.

MATERIALS AND METHODS

Delphi methodology and statement development

To develop consensus statements on the value of DFS and osimertinib, this study utilized a modified Delphi method. As opposed to traditional Delphi methodology, which is anonymous throughout and involves rounds of surveys and feedback until consensus is reached, this study includes a consensus meeting in addition to two rounds of surveys to allow panel discussions on consensus statements.[25] Throughout the process, expert feedback served as a basis for modification of the statements which were subsequently put forward for a vote until consensus was reached.[26]

In the first round, a combination of open and closed survey questions was used to gauge experts' opinions on a set of key issues covering the clinical, humanistic, and economic burden of NSCLC, unmet needs in the current treatment paradigm, the value of DFS, and the perception of osimertinib (Table 1). Responses from the first round were collected, evaluated, and reported back in the second round as consolidated feedback. Based on this feedback, statements were modified, where applicable, or restructured and reintroduced in the second-round survey. Here, each panellist received a personalized survey consisting of closed questions, consolidated group feedback, and the original scores from the first round. Statements were accompanied with aggregated scores as well as the panellists' own score, to provide panellists with an understanding of group opinion. In addition, this round included extra statements that had been derived based on the initial feedback in the first round.

Following the two surveys, a virtual consensus meeting was conducted where panellists were encouraged to critique the supporting evidence for each statement and to provide their own perspectives on the clinical question. To facilitate consensus, one expert was randomly appointed to moderate the discussion on modification of statements. An overview of statements that had been modified to reach consensus was presented throughout the session, after which panellists were asked to vote on each statement anonymously.

Panel selection, recruitment, and briefing

The robustness of the Delphi technique relies upon receiving and collating diverse opinions from experts with

Table 1. Key issues used for consensus statement development[a]

Key issue	Description
Treatment paradigm and burden	Understand the current treatment paradigm, unmet needs, and the clinical and humanistic burden of NSCLC in the adjuvant setting
Patient and clinical relevance of DFS	Gain insights into clinical and patient relevance of DFS as an endpoint for adjuvant treatment in the NSCLC setting and understand other endpoints that are most relevant for these patients
Magnitude of DFS benefit	Seek insights into the expert panel's perception of the magnitude of DFS benefit demonstrated in ADAURA and the relevance to clinical practice
Durability of DFS benefit	Understand the panel's opinion on the likelihood of continuation of the magnitude of DFS benefit demonstrated by osimertinib for up to 5 years and beyond as RCT data collection is ongoing
Relevance and impact of CNS metastases reduction	Understand how evidence for osimertinib on the significant reduction in risk of CNS metastases as observed in both ADAURA and metastatic NSCLC versus other EGFR-TKIs could indicate a continued magnitude of DFS benefit and an extension in OS versus placebo for patients treated with adjuvant osimertinib
Impact of OS evidence	Understand whether OS evidence from metastatic NSCLC treatment settings impacts interpretation of early data from adjuvant treatment and could indicate the likelihood of an OS benefit for patients treated with adjuvant osimertinib

CNS, central nervous system; DFS, disease-free survival; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; NSCLC, non-small-cell lung cancer; OS, overall survival; RCT, randomized, controlled trial.

[a]The table displays key issues in the context of adjuvant NSCLC and early-stage NSCLC, which formed the basis of consensus statement development.

relevant understanding of the clinical problem.[25,26] As such, this study recruited a panel of international clinical experts in the fields of NSCLC and EGFR-TKIs ($n = 13$), while applying the following selection criteria: specialist in NSCLC; based in specialist cancer centre; has between 10 and 30 years of experience in practice since completing residence/fellowship; spends over 60% of time diagnosing, treating, and managing patients with NSCLC directly; regularly treats and manages patients across all stages on NSCLC (stage I-IV); active advisor/member of a national or international society for lung cancer with participation in guideline creation for NSCLC in the last 5 years (consulted on clinical guidelines, etc.); has recent (within the last 5 years) publications on the treatment of patients with stage I-III NSCLC in international peer-reviewed journals. To support data-driven discussion, experts were sent a briefing document ahead of receiving the first-round survey, which contained an overview of osimertinib's product features and available ADAURA clinical data, as well as the Delphi study objectives.

Defining consensus

Closed statements were ranked on the Likert scale (1-9) where 1 represented 'strongly disagree with the statement' and 9 'strongly agree with the statement'. In this study, consensus was defined as ≥80% of experts ranking their agreement 7 or higher. In this case, the statements were directly taken to the consensus meeting to confirm. Conversely, when statements were scored 3 or lower by ≥80% of experts, this indicated consensus had been reached that experts disagreed with the statement. These statements were discarded and not included in the final consensus meeting. Statements that received neither full agreement nor disagreement were adapted based on panellist feedback and reassessed in the second survey. For statements whereby 80% of agreement/disagreement has not been reached by the end of this process, it was considered that consensus could not be reached, and this statement was then discarded.

Defining DFS

In order to standardize definitions between the ADAURA study and this work, DFS was defined in line with Wu et al.[19] as the time from treatment to disease recurrence (determined by computed tomography or magnetic resonance imaging, pathological disease on biopsy, or both) or death from any cause.

Limiting bias

Although the Delphi approach is particularly well suited for investigation of novel areas of inquiry, there is a possibility for unintentional bias that could negatively affect the collected data and lead to inaccurate conclusions. The Delphi technique is designed so that the surveys are conducted in complete anonymity which is only lost for the consensus meeting. Therefore, measures were taken to minimize bias during the consensus meeting and a final anonymous vote was conducted to avoid dominant members swaying the panel. Furthermore, the sponsor of this study (AstraZeneca Ltd.) was not present during the consensus meeting and was not involved in the preparation of the manuscript. An independent third party, Charles River Associates (CRA), designed the study, co-moderated the consensus meeting, and provided support for manuscript development.

RESULTS

Delphi consensus statements

A cumulative total of 59 statements were tested across the first two surveys and consensus meeting (Supplementary Tables S1-S3 available at https://doi.org/10.1016/j.esmoop.2022.100572). Between surveys and the consensus meeting, statements were either adapted and brought forward to the second survey or discarded, based on the median agreement score for each statement (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2022.100572, see Materials and methods). Final consensus was reached on 32 key qualitative statements, covering a range of topics, including unmet needs in early-stage NSCLC, the value of DFS, and the value of osimertinib in adjuvant NSCLC (Table 2). Detailed results showing the median consensus scores for each statement, across the two surveys and consensus meeting, are shown in Supplementary Tables S1-S3, available at https://doi.org/10.1016/j.esmoop.2022.100572.

Table 2. Summary of consensus statements by key topic[a]

Key topic		Statement	Consensus reached
Unmet need and current treatment paradigm	1	In my experience, after surgery with or without adjuvant therapy, usual care for patients is 'watch and wait'	First round
	2	In my experience, patients remaining in the curative intent setting (i.e. remaining metastasis-free after surgery with curative intent) is clinically valuable and valuable from a patient perspective	First round
	3	Despite surgery with curative intent with or without adjuvant chemotherapy, most patients with resected NSCLC will have disease recurrence within 5 years with stage IIIA NSCLC	First round
	4	I believe that an effective adjuvant treatment that extends time living cancer-free versus 'watch and wait', if available, would be valued by patients	First round
	5	I would be likely to prescribe an effective adjuvant treatment, if it were available, for patients with stage II-IIIA	First round
	6	I would be likely to prescribe an additional effective treatment, if it were available, to patients with stage IB-IIIA NSCLC who have completed adjuvant chemotherapy	Second round
	7	Reducing risk of CNS metastases is clinically important	Second round
	8	Reducing risk of CNS metastases is important to patients	Second round
	9	I would be likely to prescribe an effective adjuvant treatment, if it were available, for patients with features of high risk of recurrence with stage IB NSCLC	Consensus meeting
Value of DFS as a clinical endpoint	10	DFS is clinically relevant in the adjuvant NSCLC setting	Consensus meeting
	11	DFS is patient relevant in the adjuvant NSCLC setting	Consensus meeting
	12	The greater the magnitude of improvement in DFS, the higher the likelihood to improve OS in adjuvant NSCLC	Consensus meeting
	13	A reduction in CNS metastases could improve OS and QoL in adjuvant NSCLC	Consensus meeting
Humanistic burden of NSCLC	14	NSCLC diagnosis substantially impacts patient's: QoL, daily activities, mood, and emotional well-being	First round
	15	NSCLC recurrence substantially impacts patient's: QoL, daily activities, mood, emotional well-being, and perception of disease burden versus initial diagnosis	First round
	16	Patients who are disease-free after complete resection have an improved health-related quality of life (HRQoL) compared to those living with advanced NSCLC	First round
Economic burden of NSCLC	17	Patients who are disease-free require fewer in-patient visits to the hospital compared with patients who have active disease	First round
Definition of cure	18	I would consider cure to be more likely if a patient with stage IB-IIIA NSCLC is cancer-free at 5 years	Consensus meeting
Osimertinib features	19	Based upon its mechanism of action as an irreversible EGFR-TKI, I believe there is a rationale for the use of osimertinib in the adjuvant treatment of EGFRm NSCLC	First round
	20	Based upon preclinical evidence demonstrating CNS activity and blood—brain barrier penetration of osimertinib, I believe there is a rationale for the use of osimertinib in the adjuvant treatment of EGFRm NSCLC	First round
	21	Based on the consistency of clinically meaningful outcomes with osimertinib treatment in other NSCLC settings, I believe there is a rationale for the use of osimertinib in the adjuvant treatment of EGFRm NSCLC	First round
Osimertinib value	22	Based upon the data from the ADAURA interim analysis, I believe osimertinib will demonstrate clinically meaningful improvement in DFS in clinical practice	First round
	23	I believe osimertinib has the potential to continue to demonstrate a high magnitude of DFS benefit up to the availability of mature ADAURA trial data. This belief is based upon the consistency in benefit with osimertinib versus placebo across subgroups in ADAURA	First round
	24	The availability of osimertinib for patients with stage IB-IIIA NSCLC, after complete resection, will significantly delay recurrence and may prevent progression to metastatic NSCLC	Consensus meeting
	25	Based upon the data from the ADAURA interim analysis, it is possible that a significant DFS benefit with osimertinib could be observed beyond 3 years in clinical practice. Additional evidence is needed to determine benefit beyond 5 years	Consensus meeting
Translation of osimertinib DFS results into OS	26	I believe that the reduction in risk of distant and CNS metastases observed in ADAURA (HR 0.18 versus placebo) is likely to be a contributing factor to the reduction in risk of death at the maturation of the ADAURA trial data	Second round
	27	Based upon the data from the ADAURA trial interim analysis, I believe that osimertinib would extend the lives of patients with stage IB-IIIA NSCLC, if it was available	Second round
	28	I believe osimertinib has the potential to demonstrate significant improvement in OS in the adjuvant setting based upon the magnitude of DFS benefit shown in the ADAURA interim analysis (HR 0.20 in overall population versus placebo)	First round
	29	Osimertinib has the potential to demonstrate improvement in OS in the adjuvant setting based upon the outcomes reported in the ADAURA trial	Consensus meeting
	30	The reduction in risk of CNS metastases observed in ADAURA (HR 0.18 versus placebo) has the potential to prolong OS for patients treated with osimertinib	Consensus meeting
	31	The reduction in risk of developing CNS metastases observed in ADAURA (HR 0.18 versus placebo) has the potential to differentiate osimertinib from first-generation EGFR-TKIs in the adjuvant setting	Consensus meeting
Retreatment	32	More evidence is required to understand the best treatment options for patients with first-line metastatic NSCLC after treatment with osimertinib in the adjuvant setting	Consensus meeting

CNS, central nervous system; DFS, disease-free survival; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; EGFRm, EGFR-mutated; HR, hazard ratio; NSCLC, non-small-cell lung cancer; OS, overall survival; QoL, quality of life.

[a]The table displays consensus statements as defined by the expert panel ($n = 13$). The stage at which consensus was reached is indicated next to each statement.

Value of DFS as a clinical endpoint

Panellists defined the clinical meaning of DFS as delaying recurrence, with the intention to prolong survival. In this context, the panel agreed to highlight that DFS is both 'clinically relevant' (statement 10) and 'patient relevant' in the adjuvant NSCLC setting (statement 11). Several experts

highlighted that DFS may be more relevant to patients at an early disease stage, as 'becoming and remaining cancer-free is more of a concern than survival at this stage of disease'. Another expert mentioned that while DFS is likely to improve QoL, the trade-off between QoL and safety and adverse events should always be considered.

Translation of DFS into OS

When consulted about the translation of a high-magnitude DFS benefit into OS, the panel agreed that as the HR for DFS improves, the likelihood of OS improvement increases. In this context, the DFS HR observed in ADAURA (HR 0.2 for patients with stage IB-IIIA disease)[19] would be considered 'of a high magnitude'. Considering the aforementioned caveats, the panel agreed to state (based on their qualitative assessment) that the greater the magnitude of improvement in DFS, the higher the likelihood to improve OS in adjuvant NSCLC (statement 12).

Impact of reducing CNS metastases

Given the impact of CNS metastases on QoL and survival in NSCLC,[11-13] the panel discussed the likelihood that a reduction in CNS recurrence would have an impact on OS in adjuvant NSCLC. Panellists agreed that reducing CNS metastases should have an impact on survival and highlighted its importance, although they caveated that evidence in the adjuvant NSCLC setting was too limited to warrant any certainty on a direct link between CNS recurrence and survival. As such, the panel agreed to state that a reduction in CNS metastases could improve OS and QoL in adjuvant NSCLC (statement 13).

Osimertinib value

The panel agreed that the benefit of osimertinib would change the treatment paradigm for patients with stage IB-IIIA NSCLC and that the benefit demonstrated in ADAURA would translate into clinical practice (statements 22 and 23). The panel also agreed that osimertinib has already demonstrated evidence to support delaying recurrence in the adjuvant setting and may prevent progression to metastatic disease (statement 24). Importantly, considering the evidence demonstrated in ADAURA, the panel believes that osimertinib will extend the lives of patients with stage IB-IIIA NSCLC (statement 27) and has the potential to prolong OS for these patients (statements 28 and 29). Here, the reduction in CNS recurrences demonstrated in ADAURA was recognized by the panel as clinically important and important to patients, as discussed above (statements 26 and 30). Finally, a benefit is expected to be observed beyond 3 years and up until 5 years in clinical practice, in line with the post-unblinding ADAURA follow-up period,[19] although longer-term evidence is required to determine a benefit beyond 5 years (statement 25).

DISCUSSION

Addressing the need for outcome measures that reflect clinical benefit is essential to further improve patient outcomes. Toward this objective, our consensus study serves as a key framework for clinicians to consider the clinical and patient relevance of DFS in adjuvant NSCLC and the benefit demonstrated in ADAURA thus far.

Recently, several meta-analyses revealed that DFS is a valid surrogate for OS in various cancers, including lung cancer.[27-30] Crucially, Mauguen et al. reported a strong association between DFS and OS in patients with NSCLC who received adjuvant chemotherapy, suggesting that DFS is a valid surrogate endpoint for OS in this context.[27] Similarly, the expert panel states that the magnitude of improvement in DFS relates to the likelihood to improve OS in adjuvant NSCLC. Indeed, novel targeted therapies, such as osimertinib, have significantly improved outcomes for patients with both early-stage and advanced NSCLC, resulting in improved PFS/DFS, OS, and QoL.[19,31,32] Preventing symptoms associated with progressive disease, while mitigating the psychological burden and uncertainty that come with disease progression, is highly valuable to patients as many cancer survivors experience emotional and psychological issues at the end of treatment. Importantly, fear of cancer recurrence is cited as one of the most distressing concerns for cancer patients.[33-35] Experts in this study similarly view NSCLC recurrence as having a substantial impact on patients' QoL and their perception of the disease burden. Remaining in the curative intent setting is thus clinically valuable and valuable from a patient perspective. As such, an effective adjuvant treatment that extends living cancer-free, as opposed to the current 'watch and wait' practice, would be valued by patients. The value of DFS therefore lies in the ability of adjuvant therapy to keep patients in the curative intent setting, while preventing symptoms associated with progressive advanced disease.

For EGFRm NSCLC, CNS progression results in particularly poor prognosis, as is recognized in this study. Brain metastases can be detrimental to a patient's QoL and result in a significant disease burden.[11-13] Despite the use of adjuvant EGFR-TKIs in a number of trials, many patients still developed recurrent CNS disease.[21,36] This leads to the question whether any disease- or progression-free period in EGFRm NSCLC is valuable without protection against CNS recurrence. In this context, adjuvant osimertinib showed an 82% reduction in the risk of CNS disease (HR 0.18; 95% CI 0.10-0.33; $P < 0.0001$; stage IB-IIIA).[19] Experts in this study see reducing the risk of CNS metastases as both clinically important and important to patients. As such, the value of DFS and adjuvant treatment in NSCLC is closely linked to the ability of any such treatment to prevent CNS recurrence and its detrimental impact on QoL.

Conclusions

The relevance of DFS as an endpoint relates to the ability of an adjuvant therapy to keep patients in the clinically valuable curative intent setting, while preventing the burden associated with locoregional and distant (CNS) recurrence and progressive disease. At the same time, our qualitative assessment shows that the likelihood to improve OS in

adjuvant NSCLC relates to the magnitude of DFS benefit (HR), with a higher magnitude increasing the likelihood of OS improvement. Taken together, our study shows that DFS is a relevant endpoint in adjuvant NSCLC, both clinically and from a patient perspective.

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DISCLOSURE

MP reports being an advisor to Takeda, Pfizer, Roche, Novartis, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Merck Sharp & Dohme, Eli Lilly, Amgen, Sanofi, Gritstone, GlaxoSmithKline; speaker fees from Takeda, Pfizer, Roche, Chugai, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Merck Sharp & Dohme, Illumina; institutional research grants from Takeda, AstraZeneca, Roche, Boehringer Ingelheim. BMS reports being a consultant to Pfizer, AstraZeneca, Galvanize Therapeutics, Flame Therapeutics; advisory boards for AstraZeneca, Pfizer, Genentech, Bristol Myers Squibb; research support to Bristol Myers Squibb; board of Lung Cancer Research Foundation; employment at Xalud Therapeutics, PPD, Pfizer. CG reports receiving honoraria, speaker's bureau and advisory board fees from AstraZeneca, Boehringer-Ingelheim, and MSD; received travel and accommodation fees from Boehringer-Ingelheim. RC reports honoraria and consultancy fees from AstraZeneca, Boeringher Ingelheim, Lilly Oncology, Roche, Pfizer, MSD, Bristol Myers Squibb, Janssen, Takeda, Bayer, Sanofi, and Novartis; grants paid to institution for conduct of clinical trials or contracted research by Roche, AstraZeneca, Pfizer, Clovis, Lilly Oncology, MSD, BMS, Abbvie, Takeda, Janssen, and Novartis. FdM reports advisor fees from AstraZeneca, Roche, BMS, Novartis, MSD, XCovery, Takeda, Eli Lilly. RAS reports participation in advisory boards for Amgen, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Lily, Merck, Novartis, Pfizer, Roche, Taiho, Takeda, Yuhan; research grant from AstraZeneca, Boehringer Ingelheim. MT reports honoraria and lecture fees from Johnson & Johnson Japan, AstraZeneca KK, Eli Lilly Japan, Chugai Pharmaceutical CO., LTD, Taiho Pharma, Medtronic Japan, Ono Pharmaceutical CO.,LTD, MSD, Bristol-Myers Squibb KK, Teijin Pharma; consulting or advisory roles for AstraZeneca KK, Chugai Pharmaceutical CO Ltd, MSD, Novartis; receiving facilities research grant and commissioned research for Boehringer-Ingelheim Japan, MSD, AstraZeneca KK, Ono Pharmaceutical CO Ltd, MSD, Bristol-Myers Squibb KK, Eli Lilly Japan. SL reports receiving research support from AstraZeneca, Hutchison, BMS, Heng Rui Beigene and Roche, Hansoh; receiving speaker fees from AstraZeneca, Roche, Hansoh, Hengrui Therapeutics; advisor/consultant for Astra Zeneca, Pfizer, Hutchison MediPharma, ZaiLab, GenomiCare, Yuhan Corporation, Menarini, InventisBio Co. Ltd., and Roche. GL reports honoraria and advisory board membership/chair from AstraZeneca, Novartis, Hoffman La Roche, Pfizer, Abbvie, Merck, Bristol Myers Squibb, and Takeda; industry research funding from Takeda, AstraZeneca, and Boehringer Ingelheim; educational sessions for AstraZeneca, Takeda, EMD-Serono, Pfizer. RGC reports participating in advisory boards for MSD, Bristol-Myers, Roche, Boehringer Ingelheim, Pfizer, Novartis, AstraZeneca, Lilly, Takeda; consulting for MSD, Bristol-Myers, Roche, Boehringer Ingelheim, Pfizer, Novartis, AstraZeneca, Lilly, Takeda; receiving speaker honoraria from MSD, Bristol-Myers, Roche, Boehringer Ingelheim, Pfizer, Novartis, AstraZeneca, Lilly, Takeda. MT reports speaker and consultancy fees from AstraZeneca, Pfizer, Eli-Lilly, BMS, Novartis, Roche, MSD, Boehringer Ingelheim, Otsuka, Takeda, Pierre Fabre, Amgen, Merck; received institutional research grants from AstraZeneca, Boehringer Ingelheim. All other authors have declared no conflicts of interest

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