Poster 99—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

Despite curative intent, treatment failure and patient mortality in early-stage NSCLC remains high, which is largely driven by distant recurrence.[1,2] Recently, 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.[3]

Osimertinib is an EGFR-TKI approved in the US, Japan, China, the EU and many countries around the world for 1st-line EGFRm advanced NSCLC and EGFR T790M mutation-positive advanced NSCLC. Osimertinib recently 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% vs control in the ADAURA study (Stage IB-IIIA; HR 0.20; 99.12% CI, 0.14 to 0.30; P<0.001).[4]

However, due to the early unblinding of ADAURA at the study level and the lack of mature overall survival (OS) data at the point of unblinding, consensus on the clinical and patient relevance of DFS (the primary and secondary endpoint in ADAURA) in adjuvant NSCLC remains unclear. Despite these data limitations, consensus on measures that reflect clinical benefit is essential to improving outcomes for NSCLC patients.

To overcome this knowledge gap, we employed the **Delphi technique** to qualitatively assess expert clinical consensus on:

- **The value of DFS as an endpoint**
- **The value of the DFS benefit shown in the ADAURA trial**
- **The perceived potential for osimertinib to demonstrate OS**

The Delphi technique is a **validated, academically rigorous and structured process involving multiple rounds of questionnaires** to reliably gather group opinion on a defined clinical question, which arises from existing data

The questionnaires are distributed anonymously to **a panel of experts with direct and relevant experience** of the topic so that meaningful and non-biased insights can be gathered

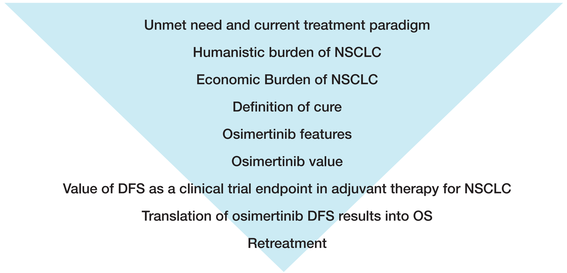
Controlled feedback between questionnaire iterations encourage panellists **to reassess their initial judgements** based on information provided by other panellists as they reach consensus

The process generates a **robust and academically sound consensus** which can bridge the gap in the existing clinical data

Methods

- An international panel of experts in the field of NSCLC and EGFR-TKIs (n=13, see Acknowledgments), was asked to rate agreement and comment on a list of pre-defined statements covering key consensus gaps **(Figure 1)**

Figure 1. Key consensus gaps covered in the Delphi study.



- In the first two rounds, 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 **(Figure 2)**
- 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**
- **Statements were then either updated or discarded based on the level of consensus reached (Figure 2)**

Figure 2. Modified Delhi approach used in this study.

1st round survey

Experts were asked a range of open and closed questions regarding NSCLC and osimertinib to gauge initial insights into consensus gaps based on their own expertise, as well as the existing ADAURA data

2nd round survey

Experts were asked a similar range of questions, reconsidering their initial viewpoint in the light of other experts' opinions, and considered new questions that had arisen from this

Consensus meeting

Conducted a consensus meeting where experts discussed their viewpoints with other experts to enable a standardised group stance on the clinical question

Results

- A cumulative total of 59 statements were tested across the first two surveys and consensus meeting
- **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 (Figure 3)**

Figure 3. Final consensus statements on the value of DFS in adjuvant NSCLC.

Unmet need and current treatment paradigm

- In my experience, after surgery with or without adjuvant therapy, usual care for patients is watch and wait
- 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
- 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
- I believe that an effective adjuvant treatment that extends time living cancer-free vs watch and wait, if available, would be valued by patients
- I would be likely to prescribe an effective adjuvant treatment, if it were available, for patients with stage II-IIIA
- 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
- Reducing risk of CNS metastases is clinically important
- Reducing risk of CNS metastases is important to patients
- 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

Humanistic burden of NSCLC

- NSCLC diagnosis substantially impacts patients': QoL, daily activities, mood, and emotional wellbeing
- NSCLC recurrence substantially impacts patients': QoL, daily activities, mood, emotional wellbeing, and perception of disease burden vs initial diagnosis
- Patients who are disease-free after complete resection have an improved health related quality of life (HRQOL) compared to those living with advanced NSCLC

Economic Burden of NSCLC

- Patients who are disease-free require fewer in-patient visits to the hospital compared with patients who have active disease

Definition of cure

- I would consider cure to be more likely if a patient with stage IB-IIIA NSCLC is cancer-free at 5 years

Osimertinib features

- 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
- 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
- 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

Osimertinib value

- Based upon the data from the ADAURA interim analysis, I believe osimertinib will demonstrate clinically meaningful improvement in DFS in clinical practice
- 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 vs placebo across subgroups in ADAURA
- 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
- 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

Value of DFS as a clinical trial endpoint in adjuvant therapy for NSCLC

- Disease-free survival (DFS) is clinically relevant in the adjuvant NSCLC setting
- Disease-free survival (DFS) is patient relevant in the adjuvant NSCLC setting
- The greater the magnitude of improvement in DFS, the higher the likelihood to improve overall survival (OS) in adjuvant NSCLC
- A reduction in CNS metastases could improve OS and QoL in adjuvant NSCLC

Translation of osimertinib DFS results into OS

- I believe that the reduction in risk of distant and CNS metastases observed in ADAURA (HR 0.18 vs placebo) is likely to be a contributing factor to the reduction in risk of death at the maturation of the ADAURA trial data
- 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
- 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 vs placebo)
- Osimertinib has the potential to demonstrate improvement in OS in the adjuvant setting based upon the outcomes reported in the ADAURA trial
- The reduction in risk of CNS metastases observed in ADAURA (HR 0.18 vs placebo) has the potential to prolong OS for patients treated with osimertinib
- The reduction in risk of developing CNS metastases observed in ADAURA (HR 0.18 vs placebo) has the potential to differentiate osimertinib from 1st generation EGFR-TKIs in the adjuvant setting

Retreatment

- More evidence is required to understand the best treatment options for patients with 1L metastatic NSCLC after treatment with osimertinib in the adjuvant setting

Conclusions

An international panel of experts reached consensus on DFS being a relevant endpoint in the adjuvant setting of NSCLC and ADAURA, both clinically and from a patient perspective. The relevance of DFS relates to the ability of an adjuvant therapy, such as osimertinib, to keep early-stage NSCLC patients in the clinically valuable curative intent setting, while preventing the burden associated with loco-regional and distant (CNS) recurrence, and progressive disease. At the same time, consensus 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.

Acknowledgements

The authors would like to acknowledge the consensus study panelists for their support: Raffaele Califano, Rosario García Campelo, Christian Grohe, Min Hee Hong, Geoffrey Liu, Shun Lu, Filippo de Marinis, Maurice Pérol, Ross A. Soo, Brandon M. Stiles, Marcello Tiseo, and Masahiro Tsuboi

The authors would like to thank Aisha Asra, Ross Alexander, and Oriol Viader Llargués for their valuable contributions to this work.

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This study was supported by AstraZeneca, Cambridge, UK

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