Asia Conversations in Oncology 2022

The Asia Conversations in Oncology onsite/virtual summit was held on 27 August 2022 in Kaohsiung, Taiwan. The event featured experts on NSCLC from across Asia, who discussed the latest evidence on treatments for *EGFR*m NSCLC, particularly those suited to Asian patients.

OVERVIEW OF THE TARGETED TREATMENT LANDSCAPE OF NSCLC IN ASIA

Prof. Tony Mok

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Tyrosine kinase inhibitors (TKIs) for *EGFR* mutation-positive (*EGFR*m) tumors have revolutionized therapy for NSCLC and there are currently three generations of such TKIs available. Osimertinib is a third-generation (3G) TKI, which has been shown to improve progression-free survival (PFS) by 5.7 months compared with platinum-pemetrexed treatment (hazard ratio [HR], 0.30; 95% confidence interval [CI], 0.23–0.41; p<0.001) in the second-line setting.[1] In the FLAURA study, first-line osimertinib improved PFS by 8.7 months compared with investigator's choice of a first-generation (1G) TKI (HR, 0.46; 95% CI, 0.37–0.57; p<0.001).[2]

Three generations of TKI are also available as treatment for *ALK*-positive NSCLC. Lorlatinib, a 3G ALK TKI, is particularly effective in reducing central nervous system (CNS) progression: 12-month cumulative incidence rates of CNS progression were 7% with lorlatinib versus 72% with crizotinib in patients with advanced *ALK*-positive NSCLC with baseline brain metastases (HR, 0.07; 95% CI, 0.02–0.24).[3]

Tumors with uncommon mutations comprise around 15% of all NSCLC tumors, making them an important treatment target.[4] Targeted treatments for patients with these tumors are already available, including agents against *ROS1, KRAS* G12C and *BRAF* V600E mutations.

ASIAN PERSPECTIVE: BROADEN THE HORIZON OF STRATEGIC LUNG CANCER TREATMENT

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Neoadjuvant and adjuvant chemotherapy offer a marginal overall survival (OS) benefit in patients with early-stage NSCLC.[5,6] In contrast, immunotherapy and targeted therapy have had more impactful survival results in this group of patients. Nivolumab plus neoadjuvant chemotherapy improved event-free survival in patients with resectable NSCLC by 10.8 months versus chemotherapy alone (HR, 0.63; 97.38% CI, 0.43–0.91; p=0.005),[7] and atezolizumab after adjuvant chemotherapy improved disease-free survival (DFS) compared with best supportive care after chemotherapy (not reached versus 35.3 months; HR, 0.66; 95% CI, 0.50–0.88; p=0.0039) in patients with early-stage resected NSCLC.[8] Adjuvant osimertinib greatly improved DFS versus placebo (HR, 0.17; 99.06% CI, 0.11–0.26; p<0.001) in stage IB to IIIA *EGFRm* NSCLC.[9]

Guidelines for the treatment of advanced NSCLC indicate that patients with no actionable driver mutations can be treated with an immune checkpoint inhibitor (ICI), with or without chemotherapy, depending on the degree of programmed death-ligand 1 (PD-L1) expression in their tumor.[10] When treating patients with an activating *EGFR* mutation, 1G and second-generation (2G) EGFR TKIs are known to generate less heterogeneous resistance than 3G TKIs: around 60% of tumors treated with 1G or 2G agents upfront acquire a T790M mutation, which is treatable with second-line osimertinib.[11,12]

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Interestingly, first-line osimertinib offered limited OS benefit in Asian patients with untreated, advanced *EGFR*m NSCLC compared with 1G TKIs in the FLAURA trial (HR, 1.00; 95% CI, 0.75–1.32), suggesting a more significant role for osimertinib in second-line therapy.[13]

EMERGING BIOMARKERS AS THE CORNERSTONE OF PERSONALIZED TREATMENTS IN NSCLC

Prof. Chia-Chi Lin

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PD-L1 expression is an important biomarker for selecting patients for ICI therapy: Guidelines recommend that patients with >50% of tumor cells expressing PD-L1 should receive ICI monotherapy, and tumors with 1–49% PD-L1 expression should be treated with a combination of ICI plus chemotherapy or ICI monotherapy.[10]

Tumor mutational burden (TMB) is an emerging biomarker for ICI response; patients with high TMB treated with ICIs have improved OS and PFS versus patients with low TMB.[14,15] However, TMB is currently limited in its utility in clinical practice due to a lack of trials investigating it as an isolated biomarker, differing/arbitrary TMB cut-off values across trials, heterogeneity in the use of tissue or plasma for testing and the specific assay used for testing.[15]

Additional emerging biomarkers include non-driver mutations (predictive of poor response),[16] tumor-infiltrating lymphocytes (predictive of good response),[17] T-cell receptor repertoire (as an indicator of tumor-specific T-cell clonal expansion)[18] and the composition of the gut microbiota.[19]

PANEL DISCUSSION 1

Moderator - Prof. Keunchil Park

Samsung Medical Center
Sungkyunkwan University School of Medicine, Seoul, Korea

The panelists discussed issues primarily related to the practicalities of molecular testing for guiding treatment decisions in patients with NSCLC. Prof. Mok noted that multiplex polymerase chain reaction (PCR) and next-generation sequencing (NGS) have different strengths. Multiplex PCR is cheaper, faster and usually sufficient for guiding first-line treatment; however, NGS is more comprehensive, which can help guide subsequent lines of therapy. Prof. Mok and the other panelists agreed that turnaround time would be an issue only if the patient were progressing rapidly and needed to start treatment quickly.

With regard to obtaining samples for testing, the panelists agreed that tissue biopsies were usually preferable, but if the patient were in poor physical condition or the tissue had been stored for a prolonged period, then they would consider a less-invasive liquid biopsy instead.

DEEP-DIVE INTO TARGETING THERAPIES FOR L858R, UNCOMMON OR COMPOUND MUTATIONS IN EGFR-MUTATED NSCLC

Dr. Akito Hata

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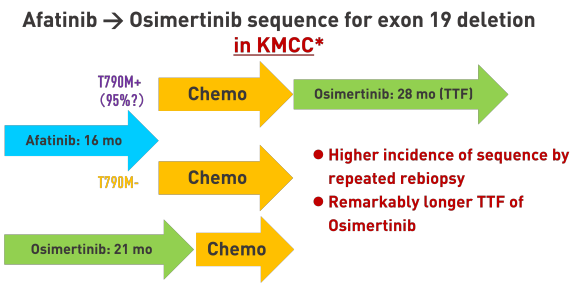
Given that the FLAURA trial showed that Asian patients with *EGFR*m advanced NSCLC had no improvement in OS with first-line osimertinib compared with a 1G TKI,[13] there may be a role for sequential treatment with a 1G TKI as first-line treatment, followed by osimertinib in the second line. In the LUX-Lung 7 trial, treatment with afatinib or

gefitinib followed by a 3G EGFR TKI resulted in OS of 'not reached' and 46.0 months, respectively (HR, 0.51; 95% CI, 0.17–1.52), but the subgroup analysis had a limited sample size.[20] Real-world data from Taiwan showed that NSCLC patients with a T790M mutation who received osimertinib following afatinib therapy had a median OS of 61.8 months.[21] However, second-line osimertinib is an option only for the ~60% of patients whose tumors acquire a T790M mutation with first-line 1G TKI therapy.[11] A retrospective review of NSCLC patients with *EGFR* mutations at the Kobe Minimally Invasive Cancer Center (KMCC) showed that multiple repeated rebiopsies increased the T790M detection rate; the overall T790M-positive rate increased from 36% to 80%, resulting in more patients subsequently being treated with osimertinib.[22] Time to treatment failure (TTF) was similar in patients whose tumors were identified as T790M-positive on first or on subsequent rebiopsy (22.6 versus 20.9 months, respectively), indicating that osimertinib was effective regardless of whether T790M positivity was detected on the first or on subsequent rebiopsies.[22]

Figure 1. Sequential treatment strategy for 19del *EGFR*m tumors at KMCC (unpublished data)



Please note that this figure reflects the personal opinion of Dr Hata, based on his experience at a single center (KMCC)

19del, exon 19 deletion; *EGFR*m, *EGFR* mutation-positive; KMCC, Kobe Minimally Invasive Cancer Center; mo, months; TTF, time to treatment failure

In KMCC, repeated rebiopsies identify the T790M mutation in >90% of exon 19 deletion (19del)-mutated, afatinib-refractory tumors (unpublished data), increasing the number of patients eligible for osimertinib and resulting in a median TTF of 28 months **(Figure 1)**.[22]

KNOWLEDGE GAPS AND MANAGEMENT OF ACQUIRED RESISTANCE TO EGFR TKIS

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Future EGFR-dependent approaches to managing acquired resistance include fourth-generation (4G) TKIs and EGFR TKIs plus monoclonal antibodies (mAbs). Some 4G TKIs, such as BBT-176[23] and BLU-945,[24] have demonstrated promising phase I efficacy against *EGFR* compound mutations. Necitumumab is an EGFR-directed mAb that is being studied in combination with osimertinib in patients whose disease has progressed on 1G to 3G TKIs.[25] Early data show some partial responses but short median PFS rates in T790M-negative and -positive disease (1.5 and 3.9 months, respectively).[25]

EGFR-independent approaches include MET inhibitors, ICI, antibody-drug conjugates and bispecific antibodies. *MET* amplification is reported in about 15% of osimertinib-resistant tumors, making it one of the major resistance mechanisms against osimertinib.[12] Phase I and II trials of MET inhibitors have offered promising initial data, with objective response rates of 48–68% in TKI-refractory tumors with a high *MET* gene copy number(≥5) or high tissue MET expression (2+ in ≥50% of tumor cells).[26,27]

ICIs have limited efficacy in *EGFR*m tumors when used as monotherapy. However, in the ORIENT-31 phase III trial, the ICI sintilimab used in combination with chemotherapy and an anti-angiogenic agent increased PFS by 2.6 months compared with chemotherapy (6.9 versus 4.3 months; HR, 0.46; 95% CI, 0.34–0.64; p<0.0001).[28] Antibody-drug conjugates have also shown promise in early-phase trials, with an overall response rate (ORR) of 58% for telisotuzumab (anti-cMET)-vedotin plus osimertinib[29] and an ORR of 39% for patritumab (anti-HER3)-deruxtecan.[30] Amivantamab, a bispecific antibody against EGFR and MET, has also demonstrated efficacy against a range of *EGFR* mutations: In patients with *EGFR* 19del or L858R NSCLC who had been previously treated with chemotherapy and osimertinib, amivantamab plus lazertinib produced an ORR of 36%.[31]

EGFR-MUTATED NSCLC CONCERTO:
HOW TO TAILOR TKIS FOR DIFFERENT PATIENT POPULATIONS IN ASIA?

CASE SHARING ON 3G EGFR TKIS

Dr. Sheng-Kai Liang

National Taiwan University Cancer Center, Taipei, Taiwan

Dr. Liang emphasized that the treatment goal for patients with NSCLC is to extend survival. He queried whether the therapeutic benefits in Asian patients are comparable with global study results, considering that elderly patients could be excluded from clinical trials because they cannot tolerate chemotherapy due to more comorbidities and poor performance status compared with younger patients. Dr Liang presented two clinical cases to highlight the optimal treatment strategy in elderly Asian patients with *EGFR*m NSCLC.

The first case was an 80-year-old male who was diagnosed with stage IVB NSCLC with multiple liver metastases and a 19del *EGFR* mutation. The patient was treated with first-line osimertinib and remained progression-free for 17 months. He then developed reduced left ventricular ejection fraction (31.9%), was considered unfit to receive second-line chemotherapy, and died 2 months later. The second case was an 81-year-old male with stage IVA NSCLC with lung metastases and 19del and G719C *EGFR* mutations. Upon progression after first-line afatinib, a T790M mutation was identified, and he was treated with second-line osimertinib, followed by localized radiotherapy after 9 months. He is still alive more than 6 years later.

Real-world data from Taiwan also support the impressive efficacy of second-line osimertinib in Asian patients with advanced *EGFR*m NSCLC and acquired T790M mutation, with a median OS of 61.3 months.[32] As such, first-line afatinib followed by osimertinib may be an important option for elderly, Asian patients with *EGFR*m NSCLC.

CASE SHARING ON 2G EGFR TKIS

Dr. Chiao-En Wu

Chang Gung Memorial Hospital, Taoyuan City, Taiwan

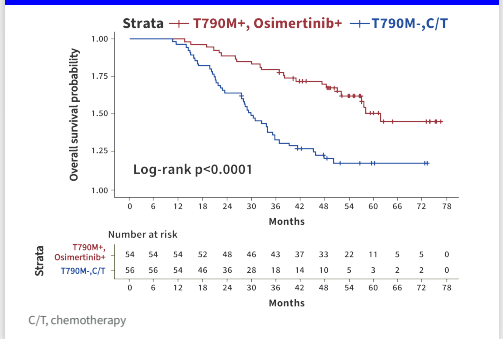
Table. CREATE study: Outcomes by T790M mutation status in real-world patients[21]

T790M mutation status	Second-line treatment	Median OS, months
Positive	**Osimertinib**	**61.8**
Positive	Chemotherapy	34.6
Negative	Chemotherapy	30.1

Dr. Wu highlighted that there are several considerations for sequential afatinib and osimertinib treatment versus first-line osimertinib. First, 40% of patients do not have the T790M mutation after afatinib treatment and will not be eligible for second-line osimertinib.[11] These patients will have to opt for chemotherapy or best supportive care, with no third-line option. Second, efficacy varies among the TKIs, depending on the underlying *EGFR* mutation, e.g. tumors with a 19del mutation have a higher chance of acquiring a T790M resistance mutation when treated with a 1G or 2G TKI.[34]

Results of The Chang Gung Memorial Hospital Real-world Afatinib Treatment Experience (CREATE) study that assessed OS when using first-line afatinib in different settings showed that osimertinib as subsequent treatment is a feasible and effective therapeutic strategy in Asian patients (**Table, Figure 2**).[21]

Figure 2. CREATE study: OS for patients undergoing second-line treatment after first-line afatinib[21]



C/T, chemotherapy

Dr. Wu asked the audience at the start and end of his presentation whether they would prefer to use hypothetical treatment A (analogous to first-line osimertinib), which conferred an OS of 3 years, or treatment

B, which conferred an OS of 5 years in 50% of patients and an OS of 2 to 3 years in the other 50% (analogous to first-line afatinib followed by osimertinib). The majority of the audience (85% at the start and 88% at the end of the presentation) chose treatment B.

PANEL DISCUSSION 2

Moderator - Prof. James Chih-Hsin Yang
National Taiwan University Cancer Center, Taipei, Taiwan

Prof. Yang asked which generation of TKI should be used as first-line treatment for patients with compound *EGFR* mutations. Prof. Park replied that afatinib would be his first choice, because of its broad spectrum of activity against uncommon and compound mutations. For rare mutations without documented TKI efficacy, Dr. Liang noted that in vitro studies could be an early source of evidence to guide decision-making. Prof. Yang noted that a database of real-world patient treatment outcomes for a variety of *EGFR*m tumors treated with afatinib has been created, and Prof. Park concurred that it is currently the biggest database for uncommon *EGFR* mutations and is a good reference source.[33]

Prof. Park discussed how TKIs tend to be more efficacious in NSCLC with 19del than with L858R mutations and that 19del is associated with a higher frequency of T790M mutations as an acquired resistance mechanism.[34] This means that patients with 19del mutations have a higher likelihood of being eligible for second-line osimertinib.

Prof. Park asked how Prof. Yang manages patients with brain metastases and a 19del mutation. Prof. Yang said that he is part of an ongoing trial investigating whether patients with brain metastases who receive upfront radiotherapy in addition to osimertinib have better outcomes than those who receive only osimertinib, and the outcome of this study will likely affect his practice.

SUMMARY

In Asian patients, first-line osimertinib does not confer an OS benefit compared with a 1G TKI.[13] However, real-world data have shown that sequential treatment with first-line afatinib followed by second-line osimertinib is a highly effective strategy for Asian patients whose tumors acquire a T790M resistance mutation.[21] The rate of T790M as a resistance mechanism to afatinib is ~50–60%,[11] but may be increased to ~80% with repeated rebiopsies, thus increasing the number of patients eligible for second-line osimertinib.[22]

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