LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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HER2-Targeted Therapies in Non–Small Cell Lung Cancer

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H&O What types of human epidermal growth factor receptor 2 (HER2) alterations occur in non–small cell lung cancer (NSCLC)?

JM We see several types of targetable HER2 alterations in NSCLC: *HER2* mutations, *HER2* amplification, and HER2 overexpression. *HER2* mutations occur in 1% to 4% of patients with NSCLC, the most common of which is an insertion mutation in exon 20. *HER2* amplification occurs in 2% to 5% of patients, and HER2 overexpression occurs in 2% to 30% of patients.

H&O What methods are used to detect HER2 alterations?

JM Mutations and amplification in *HER2* can be confirmed with targeted sequencing or polymerase chain reaction, but the preferred methodology is broad next-generation sequencing (NGS) because it captures many different alterations. HER2 overexpression can be detected with immunohistochemistry (IHC).

H&O When should testing take place?

JM The usual recommendation is to conduct broad NGS when a patient has a new diagnosis of stage IV NSCLC, to detect HER2 alterations and other targetable alterations. If a patient did not receive broad NGS at the time of diagnosis, it should be carried out at the time of progression on initial therapy.

H&O How does the finding of a HER2 alteration affect prognosis and treatment in NSCLC?

JM We are fortunate to have a treatment approved by the US Food and Drug (FDA), trastuzumab deruxtecan (T-DXd; Enhertu, Daiichi-Sankyo/AstraZeneca), for pretreated patients with unresectable or metastatic NSCLC who have *HER2* mutations. This antibody-drug conjugate (ADC), which targets HER2, is the preferred agent in the second-line setting. Identifying patients with *HER2* mutations provides additional treatment options for them beyond the usual standard of care with chemotherapy, immunotherapy, or a combination of both. As a result, the finding of a HER2 alteration can improve the prognosis. The prognosis varies among patients who have *HER2* amplification or HER2 overexpression. We do not have any approved therapies for *HER2* amplification, although options are being investigated. The FDA has approved the use of T-DXd as second-line or later therapy in patients with solid tumors who have HER2 overexpression and an IHC score of 3+ or higher. T-DXd is not approved for use in the first-line setting, although first-line use is being investigated.

H&O Could you discuss the study that served as the basis for the approval of T-DXd in NSCLC?

JM In the phase 2 DESTINY-Lung01 study, 91 patients with metastatic *HER2*-mutant NSCLC that was refractory to standard treatment received T-DXd. At a median

follow-up of 13.1 months, the objective response rate was 55%, the median duration of response was 9.3 months, median progression-free survival was 8.2 months, and median overall survival was 17.8 months. Responses occurred across different *HER2* mutation subtypes.[1] Toxicities included neutropenia, mucositis, and interstitial lung disease.

H&O Which HER2-targeting tyrosine kinase inhibitors (TKIs) are being investigated for use in patients with NSCLC who have HER2 alterations?

JM Several TKIs are being investigated for use in patients with NSCLC who have HER2 alterations. For example, the phase 1 Beamion LUNG-1 trial is investigating the use of the HER2-targeting TKI zongertinib in patients who have advanced or metastatic solid tumors with HER2 aberrations (NCT04886804). In early results from 24 evaluable patients with lung cancer, which were presented at 2023 European Society for Medical Oncology Congress, 11 patients had a partial response and 12 patients had stable disease.[2] We look forward to seeing more data on this agent.

> We would like to be able to use HER2-targeted therapies in the first-line setting, and ongoing studies are looking at this use.

H&O What types of combination therapies with ADCs are being tested?

JM Multiple trials are being conducted. At least one trial is combining an ADC with a programmed death 1 inhibitor (NCT04042701). Other trials are combining ADCs with chemotherapeutic agents. Finally, ongoing trials are looking at combinations of an ADC plus a novel compound, such as an EZH 1/2 inhibitor (NCT06244485).

One phase 1/2 study is looking at the HER2-directed TLR8 therapeutic SBT6050 in combination with T-DXd; in combination with tucatinib (Tukysa, Seagen) and trastuzumab; and in combination with tucatinib, trastuzumab, and capecitabine in patients who have pretreated, unresectable, advanced or metastatic *HER2*-expressing or *HER2*-amplified cancer (NCT05091528).

H&O What other important studies with HER2-targeting agents are ongoing?

JM The phase 3 Beamion LUNG-2 study is looking at zongertinib as first-line treatment in advanced NSCLC with *HER2* mutations (NCT06151574). In addition, the phase 2 eNRGy study is examining the use of zenocutuzumab, a HER2/3-targeting bispecific agent, in patients with solid tumors harboring an *NRG1* fusion (NCT02912949).

H&O What do you see as the future of HER2-targeted therapies in NSCLC?

JM We would like to be able to use HER2-targeted therapies in the first-line setting, and ongoing studies are looking at this use. We also would like to be able to use HER2-targeted therapies in patients who have untreated brain metastasis, so researchers are investigating whether certain patients with brain metastasis can receive first-line treatment with HER2-targeted therapy rather than upfront localized radiation (NCT06250777).

I think that ADCs and TKIs have the potential to complement each other, but we need to prove that this is the case and determine the ideal way to sequence these agents. In the future, I expect to see an increasing number of agents in the treatment landscape that target HER2.

Disclosures

Dr Malhotra has served on the advisory boards of Astra Zeneca, Janssen, AbbVie, Jazz Pharmaceuticals, Sanofi, Bristol Myers Squibb, Catalyst Pharmaceuticals, Takeda, and Daiichi Sankyo; is a Data Safety and Monitoring Committee member for BioAtla; and has received research funding from Bristol Myers Squibb, Biohaven, BeyondSpring, Celldex, and Daiichi Sankyo.

References

1. Li BT, Smit EF, Goto Y; DESTINY-Lung01 Trial Investigators. Trastuzumab deruxtecan in *HER2*-mutant non-small-cell lung cancer. *N Engl J Med*. 2022;386(3):241-251.

2. Opdam F, Heymach J, Ruiter G, et al. Beamion Lung 1, an ongoing phase Ia/Ib trial of the HER2 TKI, BI 1810631 in patients (pts) with advanced solid tumors with HER2 aberrations [ESMO abstract 1375P]. *Ann Oncol*. 2023;34(2)(suppl):789-S790.