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Concordance of HER2 Overexpression by IHC and ERBB2 Gene Amplification by NGS in Lung Cancer

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Objective

- Evaluate the concordance between HER2 overexpression (HER2-OE) by IHC test and ERBB2 amplification (ERBB2-amp) by NGS test among lung cancer patient samples evaluated simultaneously by IHC and NGS tests based on Neogenomics database.

Conclusions

- Considering NGS-based testing is the current standard practice, if patient samples were only tested for ERBB2-amp by NGS test and not tested for HER2-OE by IHC test, nearly 1 in 3 samples from the IHC 3+ and 2 out of 3 samples from the IHC 2+ group will be missed from appropriately classifying as samples meeting HER2-OE criteria.
- Patient samples with no or lower levels of HER2 expression may be misclassified as HER2-OE if only tested for ERBB2 gene amplification by NGS test.
- Findings highlight the importance of incorporating HER2 IHC testing into routine diagnostic workup for lung cancer patients to accurately identify patients eligible for HER2-directed therapy such as Trastuzumab deruxtecan (T-DXd).

Plain language summary

Why did we perform this research?

- HER2-targeted treatments like Trastuzumab deruxtecan are approved for advanced cancers with high HER2 protein expression levels, but there are no clear testing guidelines for HER2 overexpression in lung cancer.
- Most lung cancer patients get NGS testing done, for identifying HER2 alterations such as mutation and amplification, which may miss HER2 overexpression that can only be found with HER2 IHC testing.
- We wanted to find out how often HER2-OE and ERBB2-amp occur in lung cancer, to avoid missing patients who could benefit from HER2-targeted therapy.

How did we perform this research?

We reviewed tissues samples from patients with lung cancer who had both HER2 IHC and NGS ERBB2 testing. This allowed us to see how often HER2 protein overexpression matched with ERBB2 gene amplification.

What were the findings of this research?

Real-world data shows that NGS testing alone can miss nearly 1 in 3 IHC3+ and 2 in 3 IHC2+ lung cancer cases.

What are the implications of this research?

This study reinforces the need for multimodal diagnostic approach – combining both IHC and NGS testing as needed to optimize patient identification and avoid undertreatment of patients who could benefit from targeted therapies.

Poster

Poster presented at IASCLC by Samrat Yeramaneni. Corresponding author email address: *sandhya.mehta@daiichisankyo.com*

Introduction

- HER2-positivity indicates the overexpression of HER2 protein on the surface of cancer cells (HER2-OE) and is associated with poor prognosis in a wide range of solid tumor cancer types.[1]
- In April 2024, based on the results from the DESTINY-PanTumor02 (DP-02), DESTINY-Lung01, and DESTINY-CRC02 studies, T-DXd was granted accelerated approval in the US and other countries for adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors that have progressed after prior treatment and have no alternative therapies[2-4]
- In the absence of lung-specific criteria, by applying gastric or breast-specific scoring criteria, previous clinical trial and real-world studies have reported the HER2-OE score of IHC2+ in the range of 1-19% and IHC3+ in 1-5% of tissue samples from patients with lung cancer.[5-8]
- For patients with advanced non-small cell lung cancer (NSCLC), testing patients with broad-based next generation sequencing (NGS) is standard practice, but it primarily detects ERBB2-mutation or ERBB2-amp and not HER2-OE.
- While there is a known strong correlation between HER2-OE and ERBB2-amp in other malignancies such as breast cancer, little is known of the correlation in lung cancers.
- Assessing only ERBB2-amp by NGS without evaluating HER2-OE by IHC may limit the optimal identification of patients with HER2-OE advanced NSCLC who are more likely to benefit from targeted therapies such as T-DXd, potentially resulting in suboptimal treatment decisions.

Methods

- **Study Design**: A retrospective observational study analyzing tissue samples from individual lung cancer patients who received the NeoTYPE® Lung Tumor (NTP)[9] profiling at Neogenomics Laboratories between May 2023-June 2024.
- The lung cancer patients were identified using a proxy algorithm[a]
- The NTP analyzes 49 biomarkers (simultaneously) through a combination of NGS, FISH, IHC and other molecular methods using the same tissue sample.[9]
- For the **HER2 IHC assay** (clone 4B5), the ASCO/CAP scoring criteria for breast cancer was utilized. HER-OE criteria was met if samples were IHC2+/IHC3+.
- For the **NGS ERBB2 assay**, copy number variants (CNVs) are detected on the DNA level with a sensitivity of 88% and specificity of 82%. ERBB2 test was considered positive (amplification detected) if the copy number variant gain was $\geq$ 2.8.
- **Statistical Analysis**: Proportion of samples with overlapping HER2 IHC and ERBB2 NGS test results by:
  - HER2-OE (IHC 2+/ IHC 3+)
  - No HER2-OE (IHC 1+/ IHC 0)
  - ERRB2-amp detected (CNV $\geq$ 2.8 copy numbers)
  - ERBB2-amp not detected
- Association between HER2 IHC and NGS ERBB2-amp was examined using Chi-square and concordance using spearman rank's correlation test.

Results

- Of the 2,960 samples included, 28.2% (n=836) met the HER2-OE (IHC 2+/3+) criteria and 22.2% (n=657) tested positive for ERBB2-amp **(Table 1)**
- Concordance between IHC and NGS testing was observed in 69.4% (2055/2960) of samples.
- Specifically, 10% (294/2960) of samples were identified as HER-OE and ERBB2-amp, while 59.5% (1761/2960) were classified as neither meeting HER2-OE nor ERBB2-amp criteria (**Figure 1**).

Table 1. Frequency of Samples by HER2 IHC and NGS ERBB2 Test Results

	ERBB2-amp Positive	ERBB2-amp Negative	Total N=2,960
Meets HER2-OE criteria, n (%)	294 (35.2)	542 (64.8)	836 (28.2)
IHC 2+	265 (33.4)	529 (66.6)	794 (26.8)
IHC 3+	29 (69.0)	13 (31.0)	42 (1.4)
Does not meet HER2-OE criteria, n (%)	363 (17.1)	1,761 (82.9)	2,124 (71.8)
IHC 0	240 (15.7)	1,291 (84.3)	1,531 (51.7)
IHC 1+	123 (20.7)	470 (79.3)	593 (20.0)

Figure 1: Concordance between HER2-OE by IHC and ERBB2-amp by NGS tested simultaneously in 2960 samples from lung cancer patients between May 2023-Jun 2024

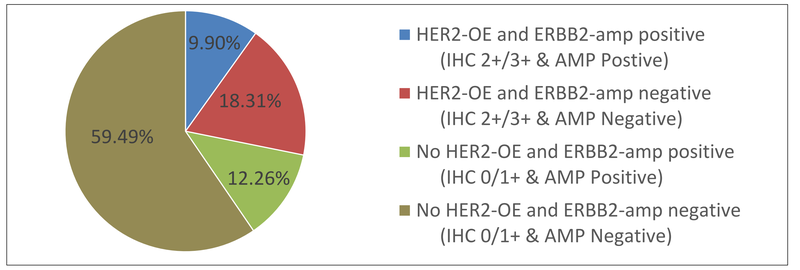
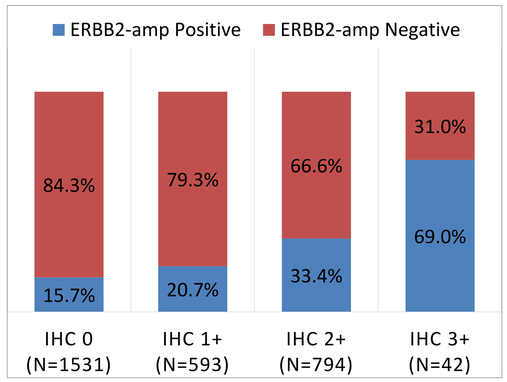


Figure 2: Frequency of ERBB2-amp by NGS test in relation to HER2-OE by IHC test

- A statistically significant association was observed between HER2 IHC scores and ERBB2-amp status, demonstrating an increasing trend in positive ERBB2-amp rates from IHC 0 to IHC 3+ (correlation coefficient 0.19, p-value<0.001)
- However, 66.6% of IHC 2+ (529/794) and 31.0% of IHC 3+ (13/42) samples were not found to be ERBB2-amplified by NGS test **(Figure 2)**.



Study Limitations

- The proportion of HER2-OE samples are likely underestimated due to:
  - Use of breast scoring algorithm for HER IHC scoring which is unstandardized in lung cancer, although gastric scoring algorithm is the standard for tumor agnostic.
  - Use of proxy measures to define lung cancer cohort and unable to examine frequency of HER2 status by lung cancer type due to missing baseline characteristics such as tumor grade, histology, stage of cancer patients, and timing of the test
- Sample selection bias limiting the generalizability of the findings due to:
  - Restricting the sample to those patients with NTP® profile panel with available IHC and ERBB2 NGS test results only.
  - Unable to distinguish between patients from real-world practice setting, enrolled or under consideration for a clinical trial.
- Further research is warranted using a large sample with robust patient clinical data and standardized HER2 IHC scoring algorithm and assay to confirm the study findings.

Footnotes

a Lung cancer cases were identified based on the ICD10 code (C34, C78.0, DO2.2, D14.3, D38.1 or body site (bronch, carina, hilar, lobe, lung, pleura, pulmonary, thoracentesis, trachea, EBUS, LLL, RLL, RUL, 10L, 10R, 11L, 11R, 12R, 14L, 14R, 4L, 4R, or test/panel used (ALK lung test and panel contains "Lung) or reason for referrals/keywords (neoplasm of bronchus, neoplasm of lung, non-small cell cancer, non-small cell lung carcinoma)

Abbreviations

- **HER2:** Human epidermal growth factor receptor 2
- **IHC:** Immunohistochemistry
- **NGS:** Next Generation Sequencing
- **T-DXd:** Trastuzumab deruxtecan
- **ASCO:** American Society of Clinical Oncology
- **CAP**: College of American Pathologist

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Disclosures

Samrat Yeramaneni, Sandhya Mehta, Kevin Wang, Michele Sue-Ann Woo, Amruta Ashtekar, and Amy Hanlon Newell are employees of Daiichi Sankyo Inc. Anne Shah, Sabra Zaraa, Liam C. Lee are employees of AstraZeneca. Jennifer A. Marks is on advisory board for Mersus, Johnson and Johnson, Astra Zeneca, Gilead, and Regeneron and acts as consultant on HEOR for Daiichi Sankyo.

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