

# Protein Expression and Prognostic Value of HER3 and HER2 in a Real-World Cohort of Danish Patients With Metastatic Non–Small-Cell Lung Cancer

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## Background

- Human epidermal growth factor receptor 3 (HER3) and human epidermal growth factor receptor 2 (HER2) are promising therapeutic targets in non–small-cell lung cancer (NSCLC), with multiple therapeutic agents currently under clinical investigation<sup>1,2</sup>
- Although HER3 overexpression has been associated with poor prognosis in NSCLC,<sup>3,4</sup> there are limited data available on the protein expression of HER3 in NSCLC
- Available data on HER2 expression and its prognostic value are inconsistent due to the heterogeneity in underlying patient populations, testing methods, and scoring methods<sup>2,5</sup>
- This was a single-center, retrospective cohort study evaluating the protein expression, as measured by immunohistochemistry (IHC), of HER3 and HER2, and the association with real-world overall survival (OS) in patients with metastatic NSCLC receiving usual care in the clinical setting in Denmark

## Methods

### Study design and participants

- This retrospective cohort study included adult patients with a confirmed diagnosis of metastatic (stage IV) NSCLC without known *ALK* or *ROS1* mutations between January 1, 2011, and December 31, 2020, who received usual clinical care at Aarhus University Hospital in Denmark
- Patients must have had available formalin-fixed paraffin embedded (FFPE) tumor tissue samples that were collected at advanced stage and before initiation of any systemic anticancer therapy
- The study cohort was divided into 3 groups
  - EGFR*-mutated (*EGFRm*) nonsquamous
  - EGFR*-wildtype (*EGFRwt*) nonsquamous
  - EGFR*-wildtype squamous
- The study follow-up period ended on December 31, 2022

### Immunohistochemistry

- HER3 protein expression in FFPE tumor tissue samples was determined by IHC using SP438 monoclonal antibody (Roche Diagnostics, Basel, Switzerland); H-score was used to quantify protein expression
- HER2 protein expression was determined by HercepTest (Agilent Technologies, Santa Clara, CA, USA) and quantified using IHC staining scores (0, 1+, 2+, and 3+)
- PD-L1 expression was assessed locally, the majority of which was performed using IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA); tumor proportion score (TPS) was used to quantify PD-L1 expression

### Statistical analysis

- Differences in HER3 and HER2 protein expression between study groups were tested for statistical significance using the ANOVA or Kruskal–Wallis test for continuous variables and Chi-square or Fisher’s exact test for small sample size for categorical variables
- Analysis of real-world OS was performed using the Kaplan-Meier method, and a multivariate Cox proportional hazard regression was used to explore the association between HER3 protein expression and real-world OS, with adjustment for age at diagnosis, Eastern Cooperative Oncology Group performance status (ECOG PS), number of metastatic sites, PD-L1 expression, and first-line treatment

## Results

### Participants

- A total of 209 patients were included (**Table 1**); there were some imbalances in certain baseline characteristics between the study groups, including sex, smoking status, ECOG PS, and sites of metastasis
- In the *EGFRm* nonsquamous group, 15 (34.1%) patients had exon 19 deletions and 14 (31.8%) had L858R mutations
- In the *EGFRwt* nonsquamous group, 29 (50%) of 58 evaluated patients had *KRAS* mutations; no other targetable genomic mutations were reported across the study groups
- The median (range) duration of follow-up from the time of metastatic NSCLC diagnosis was 14.3 (0.86–131.9), 10.4 (0–84.5), and 6.7 (1.2–91.3) months in the *EGFRm* nonsquamous, *EGFRwt* nonsquamous, and *EGFRwt* squamous groups, respectively
- Treatment patterns
  - EGFRm* nonsquamous: in the first-line setting, 80.0% of patients received first-line EGFR TKIs and 20.0% received platinum chemotherapy; in the second-line setting, 73.7% received EGFR TKIs
  - EGFRwt* nonsquamous: 50.0% of patients received first-line platinum chemotherapy and 39.1% received immunotherapy; the remaining patients received immunotherapy plus platinum chemotherapy (7.8%), non-platinum chemotherapy (1.6%), or other targeted therapy (1.6%)
  - EGFRwt* squamous: 78.4% of patients received first-line platinum chemotherapy and 21.6% received immunotherapy as first-line treatment

Table 1. Baseline participant and disease characteristics

| Characteristic                             | <i>EGFRm</i> nonsquamous<br>n = 44 | <i>EGFRwt</i> nonsquamous<br>n = 100 | <i>EGFRwt</i> squamous<br>n = 65 | Total<br>N = 209 |
|--------------------------------------------|------------------------------------|--------------------------------------|----------------------------------|------------------|
| Age at mNSCLC diagnosis, median (range), y | 70.0 (50–88)                       | 68.5 (41–87)                         | 72.3 (51–92)                     | 70.0 (41–92)     |
| Sex                                        |                                    |                                      |                                  |                  |
| Female                                     | 30 (68.2)                          | 46 (46.0)                            | 29 (44.6)                        | 105 (50.2)       |
| Male                                       | 14 (31.8)                          | 54 (54.0)                            | 36 (55.4)                        | 104 (49.8)       |
| Smoking status                             |                                    |                                      |                                  |                  |
| Patients with data, n                      | 44                                 | 97                                   | 64                               | 205              |
| Active/former                              | 28 (63.6)                          | 93 (95.9)                            | 63 (98.4)                        | 184 (89.8)       |
| Never                                      | 16 (36.4)                          | 4 (4.1)                              | 1 (1.6)                          | 21 (10.2)        |
| ECOG PS                                    |                                    |                                      |                                  |                  |
| Patients with data, n                      | 39                                 | 96                                   | 63                               | 198              |
| 0                                          | 12 (30.8)                          | 18 (18.8)                            | 5 (7.9)                          | 35 (17.7)        |
| 1                                          | 13 (33.3)                          | 47 (49.0)                            | 23 (36.5)                        | 83 (41.9)        |
| ≥2                                         | 14 (35.9)                          | 31 (32.3)                            | 35 (55.6)                        | 80 (40.4)        |
| Metastatic site <sup>a</sup>               |                                    |                                      |                                  |                  |
| Bone                                       | 26 (59.1)                          | 29 (29.0)                            | 20 (30.8)                        | 75 (35.9)        |
| Brain                                      | 8 (18.2)                           | 29 (29.0)                            | 9 (13.8)                         | 46 (22.0)        |
| Liver                                      | 10 (22.7)                          | 13 (13.0)                            | 13 (20.0)                        | 36 (17.2)        |
| Adrenal glands                             | 11 (25.0)                          | 16 (16.0)                            | 4 (6.2)                          | 31 (14.8)        |
| Lymph nodes                                | 9 (20.5)                           | 14 (14.0)                            | 7 (10.8)                         | 30 (14.4)        |
| Lung                                       | 4 (9.1)                            | 14 (14.0)                            | 11 (16.9)                        | 29 (13.9)        |
| Number of metastatic sites                 |                                    |                                      |                                  |                  |
| 1                                          | 22 (50.0)                          | 60 (60.0)                            | 38 (58.5)                        | 120 (57.4)       |
| 2                                          | 11 (25.0)                          | 15 (15.0)                            | 9 (13.8)                         | 35 (16.7)        |
| ≥3                                         | 7 (15.9)                           | 8 (8.0)                              | 3 (4.6)                          | 18 (8.6)         |
| Not reported/missing                       | 4 (9.1)                            | 17 (17.0)                            | 15 (23.1)                        | 36 (17.2)        |
| Year of mNSCLC diagnosis                   |                                    |                                      |                                  |                  |
| 2011–2015                                  | 21 (47.7)                          | 0                                    | 0                                | 21 (10.0)        |
| 2016–2020                                  | 23 (52.3)                          | 100 (100.0)                          | 65 (100.0)                       | 188 (90.0)       |
| Specimen type                              |                                    |                                      |                                  |                  |
| Metastatic lesion                          | 23 (52.3)                          | 63 (63.0)                            | 32 (49.2)                        | 118 (56.5)       |
| Primary                                    | 21 (47.7)                          | 35 (35.0)                            | 32 (49.2)                        | 88 (42.1)        |
| Thoracic lymph node                        | 0                                  | 2 (2.0)                              | 1 (1.5)                          | 3 (1.4)          |
| PD-L1 TPS                                  |                                    |                                      |                                  |                  |
| Patients with data, n                      | 26                                 | 94                                   | 49                               | 169              |
| <1%                                        | 12 (46.2)                          | 37 (39.4)                            | 15 (30.6)                        | 64 (37.9)        |
| 1%–49%                                     | 9 (34.6)                           | 18 (19.1)                            | 15 (30.6)                        | 42 (24.9)        |
| ≥50%                                       | 5 (19.2)                           | 39 (41.5)                            | 19 (38.8)                        | 63 (37.3)        |

mNSCLC, metastatic NSCLC.  
Data are n (%) unless otherwise specified. Percentages are out of total n unless otherwise indicated with “patients with data, n.”  
\*2 patients (1.0%) with *EGFRwt* squamous NSCLC had an “other” metastatic site.

### References

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### Acknowledgments

This study was sponsored by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD). The authors would like to thank Fansen Kong (MSD) for programming support. Medical writing assistance was provided by Tina Nie, PhD, of ICON plc (Blue Bell, PA, USA). This assistance was funded by MSD.

### Biomarker expression and association with real-world OS

- HER3 protein expression differed by histology and *EGFR* mutation status (**Figure 1** and **Table 2**)
- HER2 protein expression was generally low (**Table 3**)
- There was no observed association between HER3 H-scores and HER2 IHC staining status (**Figure 2**)
- HER3 H-score and HER2 IHC staining score were not significantly associated with real-world OS in any group (**Table 4**)

Table 2. Protein expression of HER3 in patients with metastatic NSCLC

| HER3 protein expression – H-score | <i>EGFRm</i> nonsquamous<br>n = 44 | <i>EGFRwt</i> nonsquamous<br>n = 100 | <i>EGFRwt</i> squamous<br>n = 65 |
|-----------------------------------|------------------------------------|--------------------------------------|----------------------------------|
| Patients with data, n             | 43                                 | 100                                  | 65                               |
| Median (range)                    | 56.0 (0–195)                       | 97.5 (0–295)                         | 9.0 (0–138)                      |
| H-score                           |                                    |                                      |                                  |
| 0                                 | 3 (7.0)                            | 6 (6.0)                              | 12 (18.5)                        |
| 1–149                             | 32 (74.4)                          | 67 (67.0)                            | 53 (81.5)                        |
| ≥150                              | 8 (18.6)                           | 27 (27.0)                            | 0 (0.0)                          |

Data are n (%) unless otherwise specified.

Figure 1. HER3 protein expression in patients with metastatic NSCLC

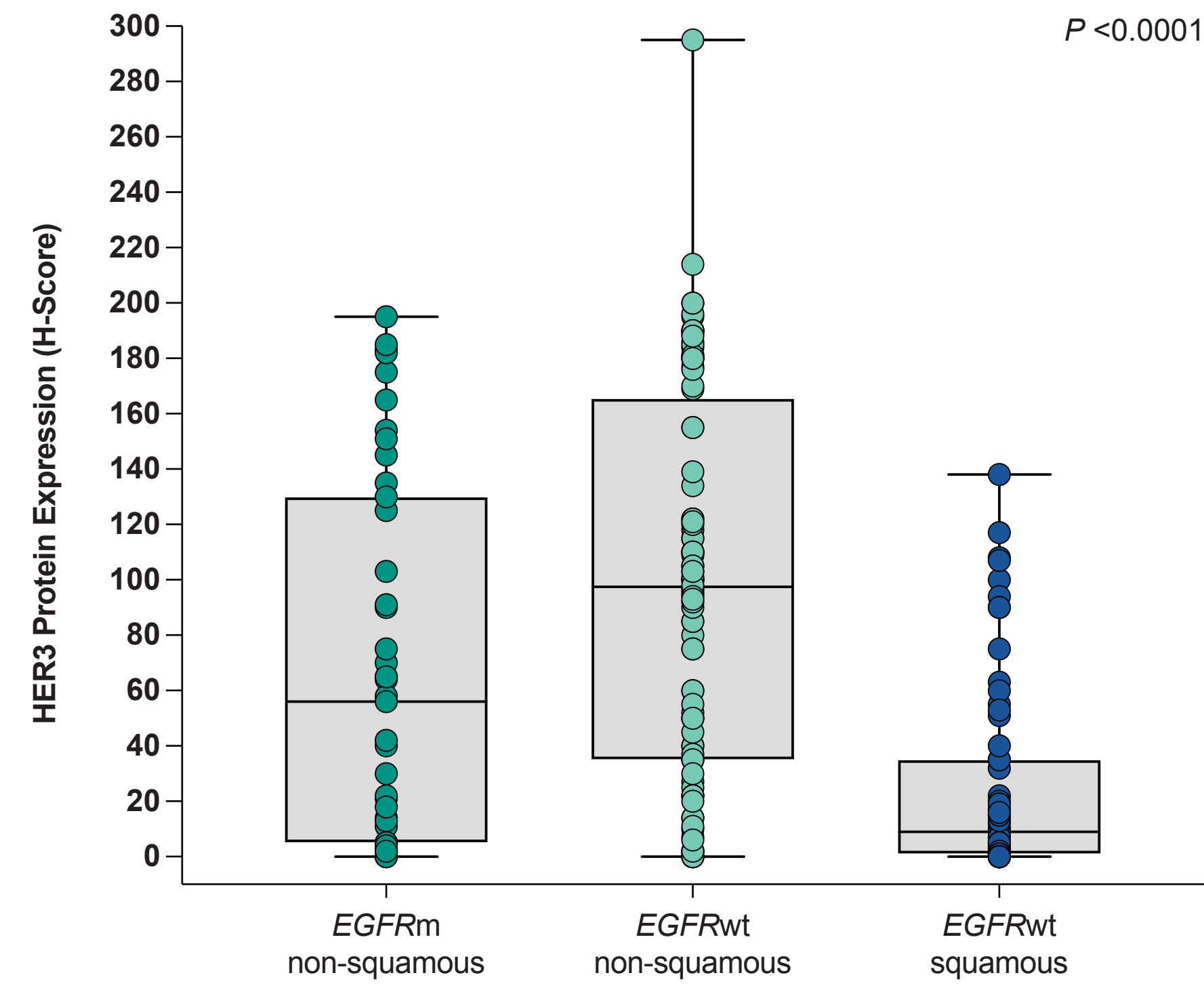


Table 3. Protein expression of HER2 in patients with metastatic NSCLC

| HER2 IHC staining score | <i>EGFRm</i> nonsquamous<br>n = 44 | <i>EGFRwt</i> nonsquamous<br>n = 100 | <i>EGFRwt</i> squamous<br>n = 65 |
|-------------------------|------------------------------------|--------------------------------------|----------------------------------|
| Patients with data, n   | 42                                 | 100                                  | 65                               |
| 0                       | 30 (71.4)                          | 70 (70.0)                            | 52 (80.0)                        |
| 1+                      | 10 (23.8)                          | 10 (10.0)                            | 10 (15.4)                        |
| 2+                      | 2 (4.8)                            | 19 (19.0)                            | 3 (4.6)                          |
| 3+                      | 0                                  | 1 (1.0)                              | 0                                |

Data are n (%) unless otherwise specified.

### Disclosures

Ke (Kirsten) Zu is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, who may own stock and/or hold stock options in Merck & Co., Inc., Rahway, NJ, USA.

Figure 2. HER3 protein expression by HER2 protein expression

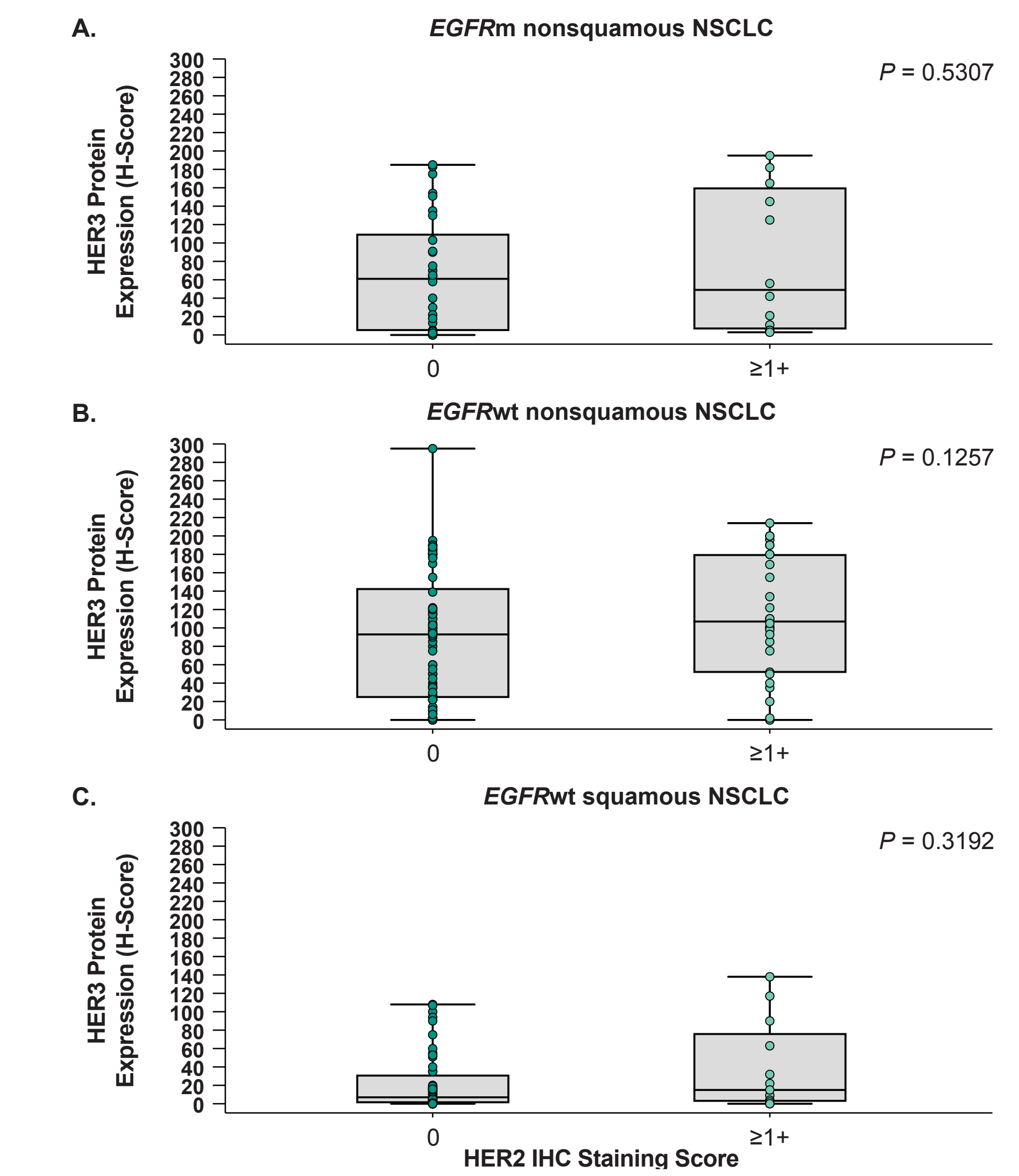


Table 4. Association between HER3 and HER2 protein expression and real-world OS in patients with metastatic NSCLC

|                                               | <i>EGFRm</i> nonsquamous<br>n = 44 | <i>EGFRwt</i> nonsquamous<br>n = 100 | <i>EGFRwt</i> squamous<br>n = 65 |
|-----------------------------------------------|------------------------------------|--------------------------------------|----------------------------------|
| <b>HER3</b>                                   |                                    |                                      |                                  |
| Univariate survival analysis                  |                                    |                                      |                                  |
| Crude HR for H-score (continuous)             | 1.06                               | 1.01                                 | 1.02                             |
| 95% CI                                        | 0.98–1.14                          | 0.94–1.08                            | 0.94–1.10                        |
| Multivariate survival analysis                |                                    |                                      |                                  |
| HR for H-score (continuous)                   | 1.07                               | 0.98                                 | 1.01                             |
| 95% CI                                        | 0.98–1.17                          | 0.92–1.04                            | 0.92–1.10                        |
| <b>HER2</b>                                   |                                    |                                      |                                  |
| Univariate survival analysis                  |                                    |                                      |                                  |
| Crude HR for IHC staining score 1+/2+/3+ vs 0 | 1.33                               | 0.89                                 | 1.14                             |
| 95% CI                                        | 0.65–2.70                          | 0.55–1.43                            | 0.61–2.16                        |

## Conclusions

- HER3 protein expression in metastatic NSCLC varied by histology and *EGFR* mutation status and was not associated with real-world OS
- HER2 IHC positivity was low in metastatic NSCLC and no association with real-world OS was observed
- These findings provide valuable insight to inform the clinical developmental strategies for novel therapeutic agents targeting these biomarkers

### Contact information

Contact Dr. Ke (Kirsten) Zu at kirsten.ke.zu@merck.com for questions or comments

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