

HER3 Expression in Archived Tissue Samples From Patients With NSCLC Across Various Genomic Subtypes and Characteristics



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PURPOSE

The objective of this noninterventional study (NCT05769764) was to characterize HER3 expression and its possible associations with clinical or tumor characteristics

CONCLUSIONS

- In this study, membrane HER3 was expressed in 98.5% of NSCLC tumor samples, and expression was observed in all genomic subtypes that were evaluated
- Additionally, membrane HER3 expression was present in patients regardless of prior treatment with systemic anticancer therapy
- This study confirms results of previous studies indicating that targeting this cell surface protein may be broadly applicable to patients with diverse subtypes of NSCLC

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ABBREVIATIONS

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; GRN, Guardian Research Network; HER3, human epidermal growth factor receptor 3; IHC, immunohistochemistry; KRAS G12C, kirsten rat sarcoma viral oncogene homolog glycine-to-cysteine mutation; MET, MET proto-oncogene, receptor tyrosine kinase; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; TKI, tyrosine kinase inhibitor.

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FUNDING

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INTRODUCTION

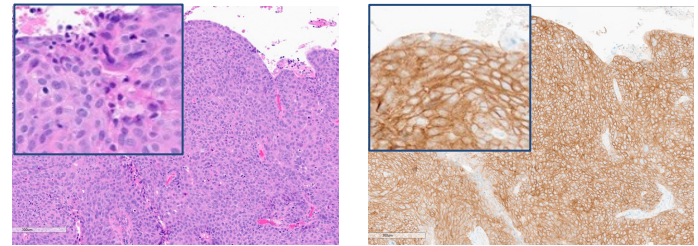
- Previous studies reporting data on protein expression of human epidermal growth factor receptor 3 (HER3) in NSCLC indicate that HER3 is a promising target for the development of new therapies
 - Upon heterodimerization with other HER family members, HER3 can activate signaling pathways associated with oncogenesis, proliferation, migration, and metastasis^{1,3}
 - Membrane HER3 expression has been shown to increase in tumor samples from patients with epidermal growth factor receptor (EGFR)-mutated NSCLC that has acquired resistance to first-line EGFR TKIs⁴
 - HER3 expression has been observed in 83% of primary NSCLC tumors⁴
 - HER3 expression has been linked to poor prognosis in malignant solid tumors^{2,5}
- The objective of this noninterventional study (NCT05769764) was to characterize HER3 expression and its possible associations with clinical or tumor characteristics

METHODS

- HER3 expression was evaluated in archival tissue samples (Guardian Research Network) from patients with advanced or metastatic NSCLC
- HER3 expression was assessed centrally by immunohistochemistry (IHC) on formalin-fixed, paraffin-embedded tissue using an HER3 (SP438) antibody (Investigational Use Only; Ventana Medical Systems, Inc.) (Figure 1)
 - Samples were scored for % tumor cell membrane staining intensity^a
 - Membrane H-scores were calculated^a (Table 1)
 - All specimens were scored by an experienced surgical pathologists at Roche Tissue Diagnostics
- Data on genomic alterations and programmed cell death ligand 1 (PD-L1) expression were evaluated based on physician and/or laboratory reports
 - Presence or absence was assessed for common EGFR-activating mutations (exon 19 deletion and/or L858R), EGFR exon 20 insertions, ALK rearrangements, KRAS G12C mutations, and MET exon 14 skipping mutations

^aSamples were also evaluated for % tumor cell cytoplasm staining intensity and cytoplasm H scores; these data will be shared at a later date.

Figure 1: Staining example^a



Case ID: 072-0038-0084

Membrane 0	Membrane 1+	Membrane 2+	Membrane 3+	Membrane H score
5	5	50	40	225

^aH&E and HER3 IHC image showing tumor-cell staining at various intensity.
H&E, hematoxylin and eosin staining; HER3, human epidermal growth factor receptor 3; IHC, immunohistochemistry

Table 1: Membrane HER3 expression scoring criteria

Score	Staining pattern
0	No staining is observed, or membrane staining is observed in <10% of the tumor cells.
1+	A faint/barely perceptible membrane staining is detected in ≥10% of tumor cells. The cells exhibit incomplete membrane staining.
2+	A weak to moderate complete membrane staining is observed in ≥10% of tumor cells.
3+	A strong complete membrane staining is observed in ≥10% of tumor cells.

RESULTS

- Samples from 228 patients were obtained; 203 were evaluable (1 sample from each patient)
 - The median age was 67 years
 - 119 (58.6%) were male
 - 148 (72.9%) were White
 - 172 (84.7%) had a history of smoking
 - 42 (20.7%) had not previously received systemic anticancer therapy (Table 2)
 - The largest percentages of patients received immunotherapy plus chemotherapy (43.3%), or chemotherapy alone (16.7%) as prior systemic anticancer therapy (Table 2)
 - Nearly 60% of specimens were from lung tumor samples; 17.2% were from brain metastases (Figure 2)
 - The most common histological type was adenocarcinoma (64%); Table 3)

Table 2. Treatment history and membrane HER3 expression

	Patients	Any intensity of membrane HER3 expression	HER membrane IHC 3+ score	HER3 membrane IHC H-score
All patients	N	n (%)	n (%)	Mean (SD)
	203	200 (98.5)	143 (70.4)	129.55 (67.70)
Treatment history^a	n	n (%)	n (%)	Mean (SD)
Treatment naïve	42	41 (97.6)	32 (76.2)	140.69 (69.85)
EGFR TKI only	10	10 (100.0)	8 (80.0)	117.80 (64.54)
IO only	12	12 (100.0)	6 (50.0)	129.08 (80.49)
Chemo only	34	32 (94.1)	22 (64.7)	117.59 (67.77)
EGFR TKI + chemo only	6	6 (100.0)	1 (16.7)	135.83 (63.59)
IO + chemo only	88	88 (100.0)	66 (75.0)	130.84 (68.07)
EGFR TKI + IO only	1	1(100.0)	0 (0.0)	100.00
EGFR TKI + chemo + IO	5	5 (100.0)	5 (100.0)	155.00 (33.73)
Unknown	5	5 (100.0)	3 (60.0)	92.20 (60.72)

chemo, chemotherapy; HER3, human epidermal growth factor receptor 3; IHC, immunohistochemistry; IO, immuno-oncology agent; TKI, tyrosine kinase inhibitor.

^aIdentified using treatment flags provided by GRN. After manual review of regimens, 3 patients were reclassified from being flagged as having chemotherapy treatment to being flagged as not having chemotherapy treatment, due to insufficient information.

Figure 2: Specimen sites

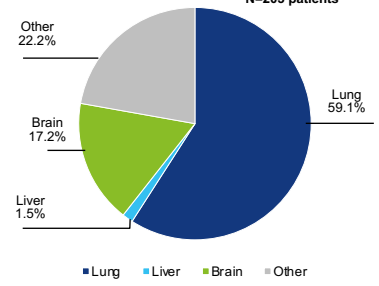


Table 3: Tumor histology

Tumor Histology	Patients (N=203)
Adenocarcinoma	130 (64.0)
Large cell	17 (8.4)
Squamous	46 (22.7)
Other	10 (4.9)

- Membrane HER3 expression was observed in 200 of the 203 patient samples (98.5%), and the mean membrane H-score was 129.55 (range, 0-250) (Table 2)
 - Membrane HER3 expression was observed regardless of treatment history
 - Across evaluated samples, patients displayed a large range of membrane HER3 staining intensities (Figure 3)
 - All 19 samples (28.7% of 66 samples tested for EGFR mutation status) with EGFR-activating mutations exhibited membrane HER3 expression (mean H-score was 122.26) (Table 4)
 - Other mutations reported included EGFR exon 20 insertions (n=4), ALK rearrangements (n=4), and KRAS G12C mutations (n=13); no MET exon 14 skipping mutations were reported in the 203 patients
 - Membrane HER3 expression was observed in 20 of these 21 samples
 - Among patients with available PD-L1 status, membrane HER3 expression was similar across the range of PD-L1 expression levels (Table 5)

Table 4. Membrane HER3 expression by select mutations status

Mutation status	Patients		Any intensity of membrane HER3 expression	Membrane HER3 IHC 3+ score	Membrane HER3 IHC H-score
	Tested, n	Positive, n	n (%)	n (%)	Mean (SD)
EGFR activating ^a	66	19	19 (100.0)	12 (63.2)	122.26 (57.06)
EGFR exon 20 insertion ^a	55	4	4 (100.0)	2 (50.0)	137.25 (22.91)
ALK rearrangement	77	4	3 (75.0)	1 (25.0)	128.75 (114.19)
KRAS G12C	36	13	13 (100.0)	10 (76.9)	155.00 (53.31)

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HER3, human epidermal growth factor receptor 3; IHC, immunohistochemistry; KRAS G12C, kirsten rat sarcoma viral oncogene homolog glycine-to-cysteine mutation.

^aTwo patients, who had both an EGFR-activating mutation and an EGFR exon 20 insertion, are included in both mutation subgroup calculations.

Table 5. Membrane HER3 expression by PD-L1 status

PD-L1 status	Patients		Any intensity of membrane HER3 expression	Membrane HER3 IHC 3+ score	Membrane HER3 IHC H-score
	n (%)	n (%)	n (%)	n (%)	Mean (SD)
≥50%	40	39 (97.5)	22 (55.0)	108.63 (66.04)	
1%-49%	50	49 (98.0)	40 (80.0)	130.62 (63.82)	
<1% or negative	33	33 (100.0)	24 (72.7)	160.15 (59.41)	
PD-L1 unknown/no result	80	79 (98.8)	57 (71.3)	126.73 (70.64)	

PD-L1, programmed cell death ligand 1.

Figure 3: Membrane HER3 expression by patient

