Characterization of 648 non-small cell lung cancer (NSCLC) cases with 28 unique *HER2* exon 20 insertions

Sai-Hong Ignatius Ou[1], Russell Madison[2], Jacqueline Robichaux[3], Jeffrey S. Ross[2,4], Vincent A. Miller[1], Siraj M. Ali[1], Alexa B. Schrock[1], John Heymach[3]

[1]Chao Family Comprehensive Cancer Center, University of California Irvine, Orange, CA, [2]Foundation Medicine, Inc., Cambridge, MA, [3]MD Anderson Cancer Center, Houston, TX, [4]Upstate Medical University, Upstate University Hospital, Syracuse, NY

ABSTRACT

Background: *EGFR* and *HER2* (*ERBB2*) exon 20 insertion (ex20ins) mutations represent a subset of driver alterations in NSCLC, which historically have largely not responded to available targeted therapies. Recently, inhibitors specifically targeting ex20ins have shown efficacy in the clinic. Previous studies have described the landscape of *EGFR* ex20ins in NSCLC (PMID: 29981927), but similar descriptions of *HER2* ex20ins are lacking.

Methods: Hybrid capture-based comprehensive genomic profiling (CGP) was performed on 39,644 tissue and 4,062 blood-based circulating tumor DNA (ctDNA) samples from 43,706 unique patients with advanced NSCLC. Tumor mutational burden (TMB) was determined on 0.8-1.1 Mbp of sequenced DNA for tissue samples and reported as mutations/Mb.

Results: *HER2* ex20ins were detected in 1.5% (648/43,706) of NSCLC cases (614 tissue and 34 ctDNA). *HER2* ex20ins represented 35% (648/1,845) of *HER2*-altered NSCLCs overall, while 46% (843/1,845) of cases had *HER2* amplification (≥5 copies), 17% (320/1,845) had a non-ex20ins *HER2* short variant (SV; most commonly S310F in 84 cases and V659E in 29 cases), and 1.8% (34/1,845) had *HER2* amplification + SV. There were 28 unique ex20ins including most commonly A775_G776insYVMA (69%, 450/648), G776>VC (12%, 76/648) and P780_Y781insGSP (8.6%, 56/648). Cases with *HER2* ex20ins were significantly enriched for adenocarcinoma histology (89% vs 66%), female gender (64% vs 51%) and low TMB (95% vs 65% TMB <10 mut/Mb) compared to *HER2* wild-type cases (all p <0.0001). *HER2* amplification (7 median copies, range 5-39) co-occurred in 16% (103/648) of *HER2* ex20ins cases. Co-occurrence of other known NSCLC drivers in *HER2* ex20ins cases was rare (0.8%, 5/648). In contrast, non-*HER2*ex20ins cases with *HER2* amplification or other *HER2* SVs each had co-occurring known driver alterations in ~30% of cases. There was no significant difference in histology, gender, age, *HER2* co-amplification or TMB in cases with YVMA vs non-YVMA ex20ins.

Conclusion: *HER2* ex20ins are found in 1.5% of NSCLCs and are generally mutually exclusive of other known drivers. Detection of these alterations may be critical to identify matched targeted therapy options for this subset of patients.

MATERIALS AND METHODS

- 39,644 FFPE tissue samples and 4,062 peripheral blood samples from 43,706 unique patients with NSCLC were submitted by clinicians as part of routine clinical care (8/2012-12/2018).
- Genomic profiling was performed in a CLIA-certified, NY State-accredited, CAP-accredited laboratory (Foundation Medicine, Inc, Cambridge MA).
- Results were analyzed for substitutions, short insertions/deletions and rearrangements, and copy number changes.
- Tumor mutational burden (TMB) was determined on 0.83- 1.1 Mbp of sequenced DNA for tissue samples.

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Contact: aschrock@foundationmedicine.com

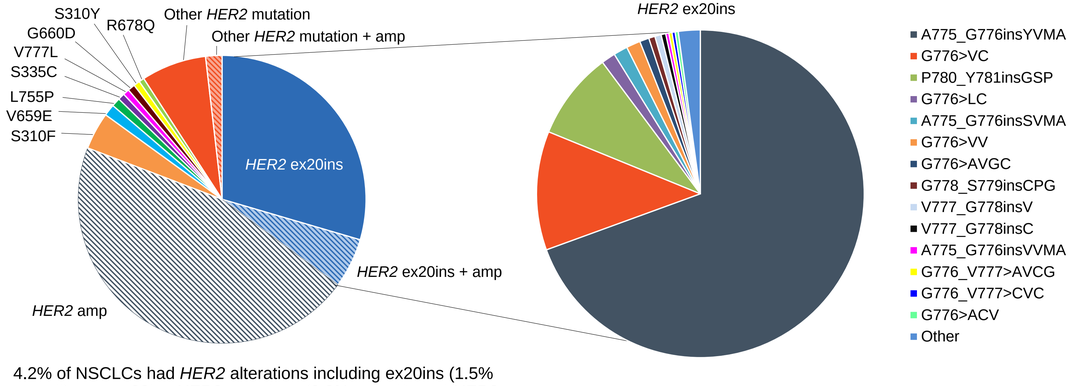
RESULTS

Table 1. Clinical and genomic characteristics of tumor samples from patients with NSCLC harboring *HER2* ex20ins versus non-ex20ins *HER2* point mutations and indels versus *HER2* wild-type cases.

	HER2 ex20ins (%)	Non-ex20ins *HER2* alteration¥ (%)	HER2 WT (%)	P value ex20ins vs non-ex20ins	P value ex20ins vs WT
# unique cases	648	1197	41861	-	-
Adenocarcinoma	578 (89)	836 (70)	27444 (66)	<0.0001	<0.0001
NSCLC NOS	57 (9)	183 (15)	6670 (16)	-	-
SCC	8 (1)	156 (13)	6237 (15)	-	-
AdSCC	5 (1)	9 (1)	324 (1)	-	-
Large cell	0	10 (1)	826 (2)	-	-
Sarcomatoid	0	3 (0.25)	360 (1)	-	-
Gender (M:F)	231 (36):417 (64)	667 (56):530 (44)	20609 (49):21252 (51)	<0.0001	<0.0001
Median Age, years	62	65	67	0.0002	<0.0001
Median TMB*, mut/Mb	3	9	7	<0.0001	<0.0001
TMB ≥20	5 (1)	237 (20)	4484 (12)	-	-
TMB 10-20	23 (2)	273 (18)	8683 (17)	-	-
TMB 5-10	140 (23)	293 (25)	9931 (27)	-	-
TMB <5	446 (75)	355(40)	14295 (50)	-	-
NCCN driver#	4 (1)	236 (20)	10403 (25)	<0.0001	<0.0001
KRAS mutation	1 (0.15)	127 (11)	11758 (28)	<0.0001	<0.0001

¥Non-ex20ins alterations included point mutations, indels, and HER2 gene amplification; #TMB only available for tissue samples; *NCCN rivers: *EGFR* activating mutation, *MET* amplification/ex14 mutation, BRAF V600E, *ALK/RET/ROS1* fusion

Figure 1. Distribution of *HER2* alterations in NSCLC.



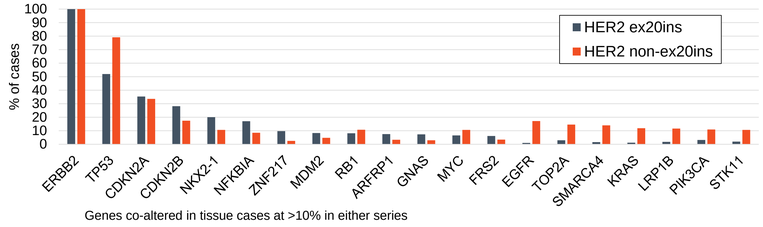
- 4.2% of NSCLCs had *HER2* alterations including ex20ins (1.5% overall), non-ex20ins *HER2* mutations (0.8% overall), and *HER2* amplification alone (1.9% overall)
- *HER2* ex20ins represented 35% of *HER2*-altered NSCLCs
- 16% of *HER2* ex20ins cases had co-*HER2* amplification (amp)
- 28 unique *HER2* ex20ins were identified, 14 of which were recurrent in our NSCLC dataset
- HER2 YVMA represented 69% of *HER2* ex20ins alterations

Table 2. Comparison of clinical and genomic characteristics of cases with *HER2* ex20 YVMA insertions vs non-YVMA ex20ins .

	HER2 YVMA ex20ins (%)	Non-YVMA *HER2* ex20ins (%)	P value
# unique cases	450	198	-
Adenocarcinoma	402 (89)	176 (89)	0.98
NSCLC NOS	42 (9)	15 (8)	-
SCC	2 (0.4)	6 (3)	-
AdSCC	4 (1)	1 (0.5)	-
Large cell	0	0	-
Sarcomatoid	0	0	-
Gender (M:F)	166 (37):284 (63)	65 (33):133 (67)	0.37
Median Age, years	63	61.5	0.15
Median TMB*, mut/Mb	2.6	2.6	0.13
TMB ≥20	3 (1)	2 (1)	-
TMB 10-20	16 (4)	5 (3)	-
TMB 5-10	84 (19)	52 (26)	-
TMB <5	321 (71)	124 (63)	-
Co-*HER2* amplification	76 (17)	27 (14)	0.35

TMB only available for tissue samples

Figure 2. Longtail of frequently co-altered genes in *HER2* ex20ins and *HER2* non-ex20ins NSCLC cases.



Genes co-altered in tissue cases at >10% in either series

CONCLUSIONS

- *HER2* ex20 insertions were detected in 1.5% advanced NSCLCs overall and represented 35% of *HER2*-altered NSCLCs
- Co-amplification of *HER2* was present in 16% of cases with *HER2* ex20ins, but other drivers were largely mutually exclusive
- 28 distinct *HER2* ex20ins were identified, including most commonly YVMAins (69%)
- Cases with *HER2* ex20ins were significantly enriched for adenocarcinoma histology, female gender, and low TMB compared to *HER2* wild-type cases (all p <0.0001).
- No significant differences were seen between cases with YVMA and non-YVMA *HER2*ex20ins
- Given the diverse spectrum of *HER2* ex20ins identified, comprehensive genomic profiling to identify these alterations may be critical to match patients with therapies targeting ex20ins for which multiple clinical trials are currently recruiting (NCT03318939, NCT02716116, NCT03805841)