Clinical outcomes and characterization of *HER2* alterations in Non-Small Cell Lung Cancer

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Background

Subsets of NSCLC carry alterations in the human epidermal growth factor receptor 2 (*HER2*) gene such as mutations (mt), amplification (amp), and protein overexpression. These alterations reflect distinct patient (pt) populations and disease biology, translating to variable outcomes with immunotherapy +/- chemotherapy. *HER2*-directed therapies have shown significant efficacy for *HER2* mt and to a lesser extent *HER2* overexpression NSCLC. We describe the genomic landscape of *HER2*-altered NSCLC in a large cohort of tumors from the Caris database and explore patient outcomes.

Methods

Next-generation sequencing of DNA (592-gene or WES) and RNA (WTS) was performed on NSCLC samples (n = 52,690, Caris Life Sciences, Phoenix, AZ). IHC was performed on FFPE sections (HER2 staining intensity of 2+, > 5%). HER2 amp was defined as copy number > 6. Tumor microenvironment studies were calculated by QuantiSeq. Significance was calculated using chi-square, Fisher's exact, or Mann-Whitney U test, with p-values adjusted for multiple comparisons (q < 0.05). Overall survival (OS) was estimated from insurance claims data using Cox proportional hazards model to calculate hazard ratio (HR) and log-rank tests to calculate P values.

Table 1: Patient demographics ** p<0.05 compared to HER2 MT

		HER2 MT	*HER2* Amplified	*HER2* IHC (2+ 5%)
Sex	Male	270 (40.3%)	241 (60.3%)**	121 (44.5%)
	Female	400 (59.7%)	159 (39.8%)**	151 (55.5%)
Age	Median Age	68	69	67
Smoking status	Current Smoker	21 (3.1%)	25 (6.3%)	10 (3.7%)
	Light Smoker (<15 packs_yr)	81 (12.1%)	64 (16.0%)	27 (9.9%)
	Lifelong Non-smoker	37 (5.5%)	3 (0.8%)**	4 (1.5%)
	Unknown smoking status	531 (79.3%)	308 (77.0%)	231 (84.9%)
Primary	Primary	439 (65.5%)	224 (56.0%)	131 (48.2%
Metastatic	Brain metastasis	18 (2.7%)	22 (5.5%)**	25 (9.2%)**
	Other metastasis	213 (31.8%)	154 (38.5%)	116 (42.6%)

Results

Figure 1A: Significantly different mutations for *HER2* MT vs *HER2* amplified (p<0.01)

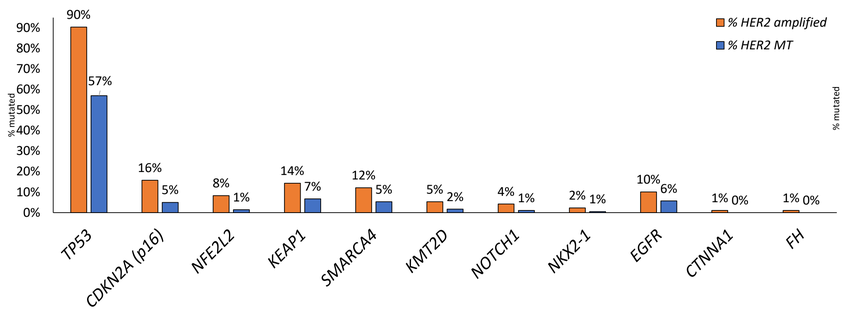

Figure 1B: Significantly different mutations for *HER2* MT vs *HER2* 2+5% by IHC (p<0.01)

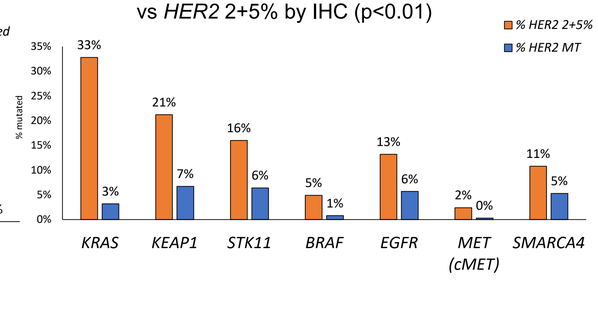

Figure 3: Tumor immune microenvironment for *HER2* mt vs *HER2* 2+5% ** p<0.001

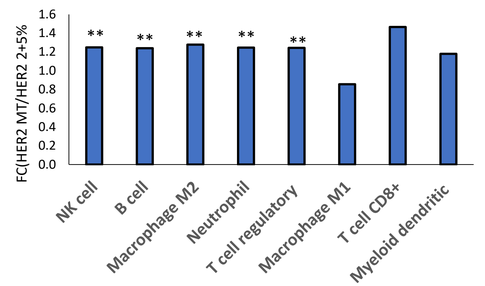

Figure 2A: Overall survival (OS) for *HER2* MT vs NSCLC Driverless tumors.

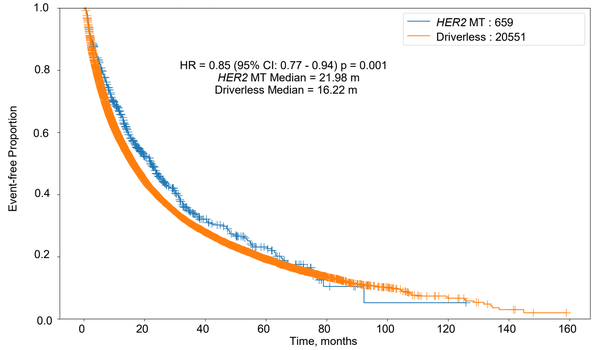

Figure 2B: Overall survival (OS) for *HER2* MT vs *HER2* amplified tumors.

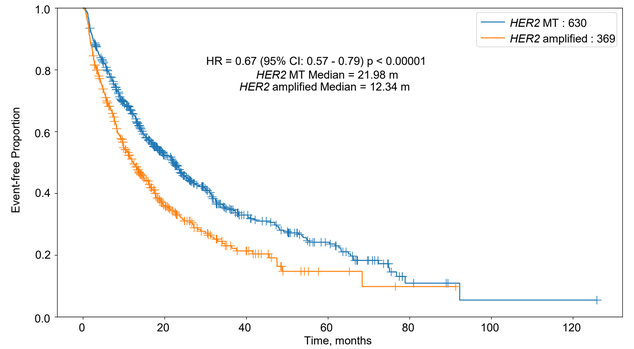

Table 2: NSCLC cohorts compared to HER2 mt cohort (22.0 months)

NSCLC cohort	Survival (months)	HR, 95% CI	P-value
HER2 amp	12.3	0.67 (0.57-0.79)	<0.001
HER2 2+	14.1	0.92 (0.77-1.09)	0.33
Driverless	16.2	0.85 (0.77-0.94)	<0.01
ROS1 fusion	35.3	1.3 (1.0-1.7)	0.02
ALK fusion	47.4	1.9 (1.6-2.3)	<0.001
EGFR mt	30.7	1.3 (1.2-1.5)	<0.001

Study Highlights

- Treatment (tx) received prior to tumor sample collection is not reported in 64.2% HER2 mt, 68.8% HER2 2+, 56.5% HER2 amp (may reflect tx naive pts).
- Among female pts, HER2 mt was more common than amp or overexpressed 3+ (59.7% vs. 39.8% vs 36.2% p < 0.01).
- When compared to ROS1+, ALK+ and EGFR mt, HER2 mt had shorter OS (Table).
- HER2 mt tumors had greater infiltration of NK cells, B cells, M2 macrophages, neutrophils and Tregs (FC 1.2-1.3) vs. HER2 IHC 2+.

Conclusions

- This study highlights the significant differences in OS and co-alterations for HER2 mt vs other HER2 altered and NSCLC driverless tumors.
- This data confirms the unmet need to further explore the differences in OS and co-alterations for *HER2* mt vs other *HER2* altered and NSCLC driverless tumors to optimize therapy and improve overall survival.

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