Real world outcome analysis of advanced gastric and gastroesophageal adenocarcinoma patients with HER2-low expression treated with 1L therapy

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INTRODUCTION

HER2-low tumors, defined as a score of 1+ on immunohistochemical (IHC) analysis or as an IHC score of 2+ and negative results on in situ hybridization (ISH), are not well characterized among gastric or gastroesophageal junction (GEJ) adenocarcinomas. More importantly, this patient population is currently treated as HER2-negative (HER2-low or IHC score of 0) without anti-HER2 directed therapy. Here, we describe a real-world outcome analysis of this distinct genomically defined patient population.

METHODS

De-identified, multimodal real-world data (RWD) of 403 advanced gastric, esophageal, and GEJ adenocarcinomas from the Tempus database were analyzed. Inclusion criteria were a diagnosis of advanced gastric, esophageal, or GEJ adenocarcinoma between January 2017 and May 2021 and treatment with first-line therapy.

The overall cohort was stratified by HER2 IHC status: negative (HER2-), low (HER2-low), positive (HER2+), and unknown/missing status. IHC/ISH percentages were used to threshold ERBB2 RNA expression to derive RNA-based HER2-groups.

Median overall survival (mOS) was estimated using Kaplan-Meier methods.

SIGNIFICANCE

- Our real-world, biomarker outcome analyses suggest that advanced gastric and GEJ patients with HER2-low expression identified by IHC and RNA expression trend toward a poor prognosis and short survival.
- Across the time interval from 0 to 24 months, HER2-low group has significantly lower overall survival outcomes compared to the HER2+ group (Cox PH p-value = 0.03, HR = 0.66).
- Our data suggest that there is a heterogeneity of PD-L1 enrichment within the HER2-low group; most HER2-low tumors do not express PD-L1.
- Future prospective studies are necessary to validate and evaluate the efficacy of targeting patients with HER2-low expression with anti-HER2 therapies alone or in combination with immunotherapy.

RESULTS

Table 1. Cohort Demographics and Characteristics

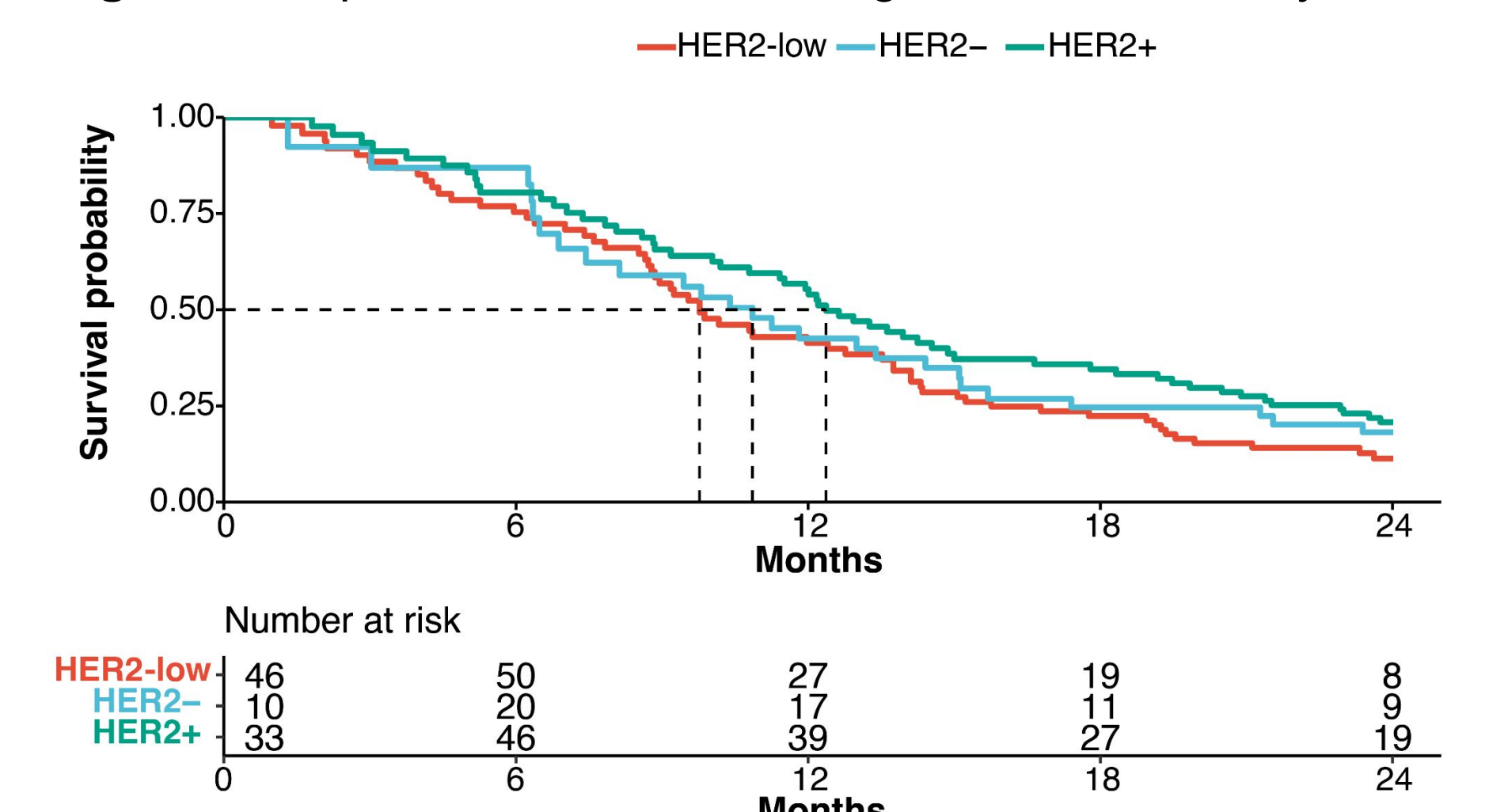| Characteristic	Overall (n=403)	HER2- (n=46)	HER2-low (n=108)	HER2+ (n=102)
Gender				
Female	117 (29.0%)	15 (32.6%)	32 (29.6%)	24 (23.5%)
Male	286 (71.0%)	31 (67.4%)	76 (70.4%)	78 (76.5%)
Self-Reported Race				
White	197 (48.9%)	22 (47.8%)	55 (50.9%)	52 (51.0%)
Black or African American	23 (5.7%)	1 (2.2%)	11 (10.2%)	7 (6.9%)
American Indian or Alaska Native	1 (0.2%)	-	-	-
Asian	10 (2.5%)	1 (2.2%)	3 (2.8%)	2 (2.0%)
Other	13 (3.2%)	2 (4.3%)	3 (2.8%)	4 (3.9%)
Ethnicity				
Hispanic/Latino	23 (5.7%)	4 (8.7%)	2 (1.9%)	4 (3.9%)
Non-Hispanic/Latino	116 (28.8%)	12 (26.1%)	36 (33.3%)	27 (26.5%)
Median Age at Diagnosis [Min, Max]	62.0 [20.0, 87.0]	62.5 [36.0, 81.0]	62.0 [34.0, 84.0]	63.5 [22.0, 85.0]
Histology				
adenocarcinoma + intestinal type	354 (87.8%)	43 (93.5%)	88 (81.5%)	98 (96.1%)
carcinoma, diffuse type	17 (4.2%)	1 (2.2%)	8 (7.4%)	2 (2.0%)
other	32 (7.9%)	2 (4.3%)	12 (11.1%)	2 (2.0%)
1L Therapy				
trastuzumab + chemotherapy	89 (22.1%)	1 (2.2%)	3 (2.8%)	85 (83.3%)
chemotherapy alone	271 (67.2%)	37 (80.4%)	94 (87.0%)	10 (9.8%)
chemotherapy + IO	34 (8.4%)	8 (17.4%)	10 (9.3%)	-
other	9 (2.2%)	-	1 (0.9%)	7 (6.9%)
PDL1 TPS				
intermediate (1-10%)	45 (11.2%)	6 (13.0%)	13 (12.0%)	6 (5.9%)
negative (<1%)	144 (35.7%)	12 (26.1%)	40 (37.0%)	40 (39.2%)
positive (>10%)	9 (2.2%)	1 (2.2%)	3 (2.8%)	2 (2.0%)

Characteristics with missing data are excluded from the table.

**Figure 1.** Kaplan-Meier OS according to HER2 status by IHC

Number at risk					
HER2-low	31	56	32	25	16
HER2–	15	24	18	9	8
HER2+	39	46	44	34	19
	0	6	12	18	24
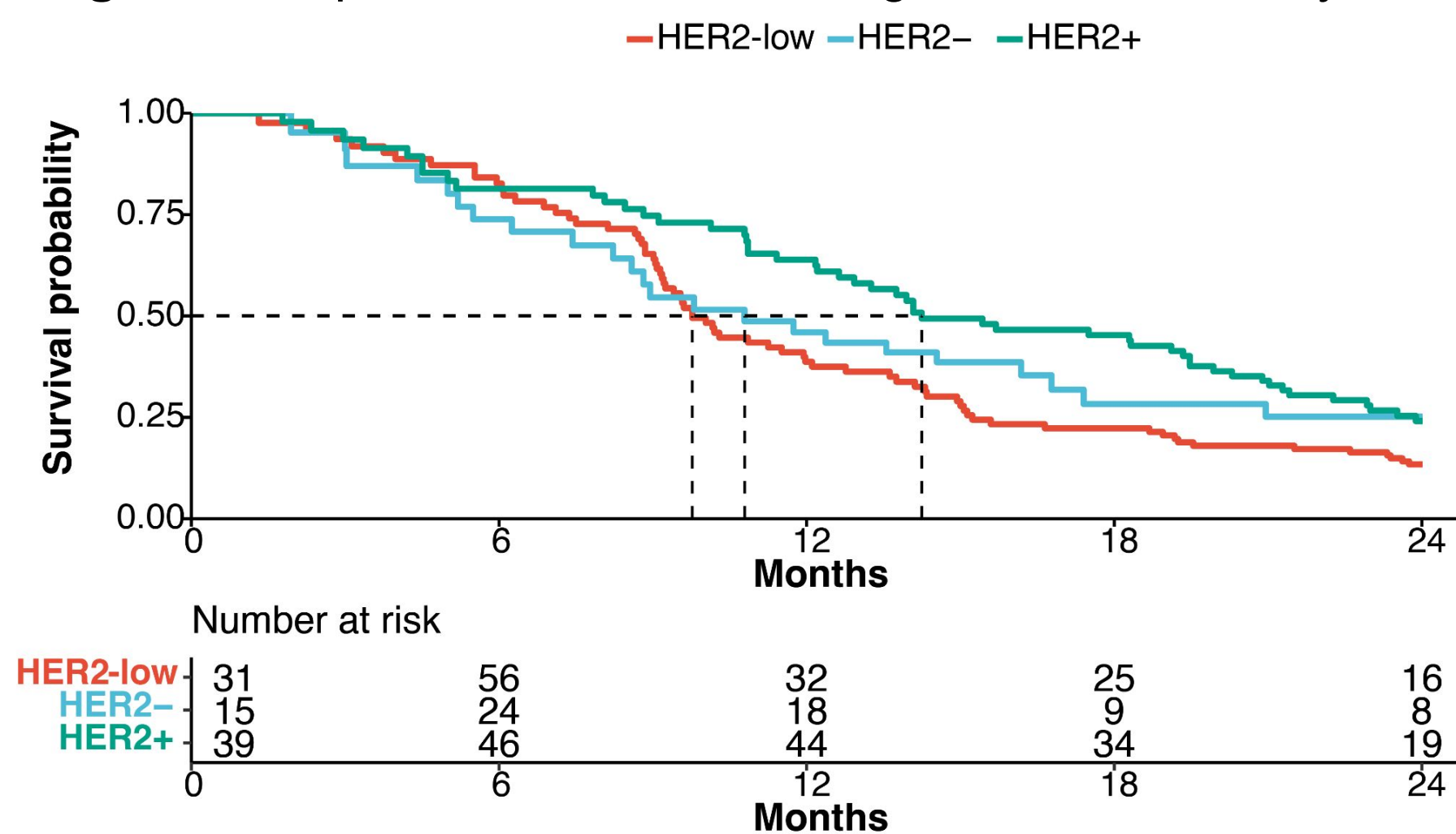
Median OS (mOS, months) was 9.8 (9.1, 12.8) for HER2-low, 10.8 (8.2, 17.4) for HER2(-), and 14.2 (12.2,19.9) for HER2(+).

Figure 2. Kaplan-Meier OS according to HER2 status by RNA

Number at risk					
HER2-low	46	50	27	19	8
HER2–	10	20	17	11	9
HER2+	33	46	39	27	19
	0	6	12	18	24

For RNA expression analysis, the mOS was 9.8 (8.8, 13.8) months for HER2-low, 10.9 (6.9, 15.7) months for HER2(-), and 12.4 (10.2, 16.6) months for HER2(+).

Figure 3. PD-L1 Distribution within HER2-Low Cohort
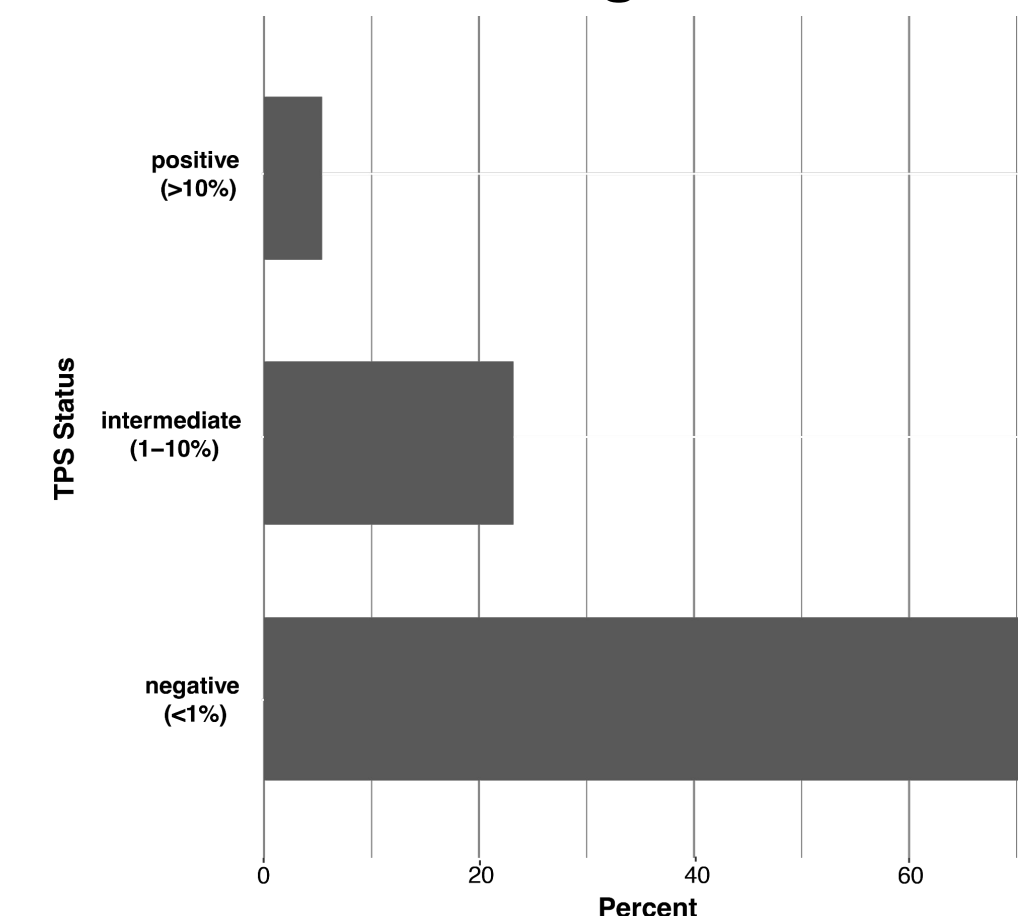
PD-L1 TPS status was available in only 51.9% (56/108) of the HER2-low group. TPS distribution was: 71.4% (40/56) for TPS <1, 23.2% (13/56) for TPS >=1-<10, and 5.4% (3/56) for TPS >= 10.

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