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HER2 Expression and Associated Real World Overall Survival (rwOS) in Patients With Select Solid Tumors

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Objective

- To describe rwOS by HER2 expression level for patients with locally advanced or metastatic endometrial cancer (EC), head and neck squamous cell cancer (HNSCC), non-small cell lung cancer (NSCLC), or ovarian cancer (OC) receiving first-line (1L) treatment

Conclusions

- HER2 expression was observed across EC, HNSCC, NSCLC, and OC tumor types
- rwOS differences were observed based on HER2 RNA expression
- Using RNA thresholds from GC and adjusting for confounding factors, HER2 positivity was associated with significantly worse rwOS compared with HER2-zero tumors in patients with OC, consistent with HER2 as a poor prognostic marker in OC[1]
- These data support additional studies using HER2 immunohistochemistry (IHC) and in situ hybridization (ISH) testing to further investigate the role of the HER2 pathway in solid tumors

Background

- HER2 is a known negative prognostic marker in gastric cancer (GC) and breast cancer (BC)[2,3]
- As a result of the approval of HER2-targeted therapies for GC and BC,[4] the presence of HER2-positive tumors is now recognized as a positive predictor of response to anti-HER2 cancer therapies[5,6]
- Studies suggest a role for HER2 in the prognosis and treatment of other cancers, such as HNSCC, EC, OC, and NSCLC,[1,7-9] but real-world efficacy outcomes based on HER2 expression are lacking for non-GC and non-BC

References

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Conflicts of interest

Katherine Moxley: nothing to disclose; Emilie Scherrer: former employment with Seagen Inc.; Sneha Nishtala: employment with Tempus AI; Sam Whitman: employment with Pfizer; Yan Liu: employment with Tempus AI; Naomi RM Schwartz: former employment with Seagen Inc.; Chithra Sangli: employment with Tempus AI; Charu Aggarwal: research funding from AstraZeneca, Genentech, Incyte, Macrogenics, Medimmune, MSD, and Lilly; and consulting or advisory fees from Genentech, Lilly, Celgene Merck, AstraZeneca, Blueprint Genetics, Shionogi, Daiichi-Sankyo/AstraZeneca, Regeneron/Sanofi, Eisai, BeiGene, Turning Point Therapeutics, Pfizer, Janssen, and Boehringer Ingelheim.

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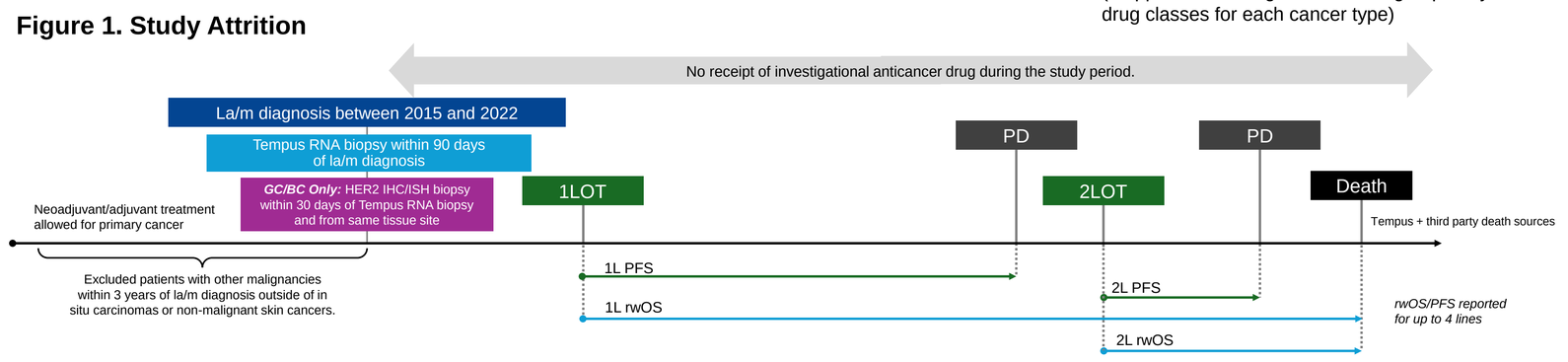
Methods

- A retrospective analysis was performed using the Tempus database, a library of clinical and molecular data with ≥7 million de-identified research records
- Data were analyzed from adults diagnosed with advanced or metastatic GC, BC, EC, HNSCC, NSCLC, or OC in the US between 2015 and 2021 (**Figure 1**)
- Patients had to have received 1L treatment and had next-generation sequencing (NGS) testing within 90 days of advanced or metastatic diagnosis
- Patients with GC and BC who underwent HER2 IHC/ISH testing were categorized as:
  - HER2 zero: IHC 0
  - HER2 low: IHC 1+ or IHC 2+/ISH-negative
  - HER2 positive: IHC 2+/ISH+ or IHC 3+
- To identify thresholds separating HER2 subgroups in EC, HNSCC, NSCLC, and OC, a logistic regression model was fit to NGS and IHC status data in BC and GC using bootstrapped samples
- RNA thresholds as a surrogate for IHC were applied to these solid tumors to determine HER2 expression categories
- Detailed methods have been presented previously,[10] and only GC-based models are presented here
- GC RNA thresholds were applied to HER2 categories using the following criteria:
  - RNA-zero: *ERBB2* Log_2(TPM+1)<7.042
  - RNA-low: 7.042≤*ERBB2* Log_2(TPM+1)<8.093
  - RNA-positive: *ERBB2* Log_2(TPM+1)≥8.093
- The outcome of interest was rwOS, which was analyzed with the risk set adjustment method to account for patients whose observation began upon sequencing, instead of at treatment initiation (ie, immortal time between treatment initiation and sequencing)
  - The index date was defined as the date 1L treatment was initiated in the locally advanced or metastatic setting
  - The duration of follow-up was calculated from the index date to death, or the earliest of the last known follow-up date or 3 years post index
- Univariate and multivariable Cox proportional hazards models for rwOS were fit for each cancer type (EC, HNSCC, NSCLC, and OC) using RNA thresholds
  - The multivariable models were adjusted for relevant clinical traits, including age, race, geographical region, stage at diagnosis, metastatic site, and treatment (mapped to NCCN guidelines and grouped by relevant drug classes for each cancer type)

Figure 1. Study Attrition



1L, first line; 1LOT, first line of treatment; 2L, second line; 2LOT, second line of treatment; BC, breast cancer; GC, gastric cancer; IHC, immunohistochemistry; ISH, in situ hybridization; la/m, locally advanced/metastatic; rwOS, real-world overall survival; PD, progressive disease; PFS, progression-free survival.
Subgroups with sample size <20 patients were removed from OS estimates. For inclusion in the multivariate model, each level must have had ≥10 patients. For univariate and multivariate CoxPH models, variables with more than 40% missingness were removed. Significance was set at P≤0.05.

Results

- 3431 patients were included in the survival analyses (199 EC, 415 HNSCC, 2289 NSCLC, 528 OC)

EC Cohort

- In the univariate model based on RNA thresholds from GC, the HER2-positive group had significantly shorter OS than the HER2-zero group (**Figure 2**)
  - After adjusting for confounding factors in the multivariate CoxPH model, the difference between HER2-positive and HER2-zero subgroups was no longer statistically significant
- No significant differences between HER2 subgroups were observed in the models using RNA thresholds from BC (**data not shown**)

HNSCC Cohort

- No statistical significance was seen between HER2 categories with either the univariate or multivariate CoxPH models based on RNA thresholds from GC (**Figure 3**)
- No significant differences between HER2 subgroups were observed in the models using RNA thresholds from BC (**data not shown**)

NSCLC Cohort

- The HER2-low subgroup had significantly longer OS than the HER2-zero subgroup in the univariate CoxPH model based on HER2 RNA thresholds from GC (**Figure 4**)
  - In the multivariate model, the difference between categories was no longer significant
- There was no significant difference between the HER2-positive vs HER2-zero subgroup in the univariate or multivariate models based on HER2 RNA thresholds from GC (**Figure 4**)
- No significant differences between HER2 subgroups were observed in the models using RNA thresholds from BC (**data not shown**)

OC Cohort

- In the multivariate model derived from GC HER2 RNA thresholds, the HER2-positive subgroup had significantly worse OS than the HER2-zero subgroup (**Figure 5**)
- In the BC model, directionality was the same as in the GC model, but no significance was seen between HER2 subgroups (**data not shown**)

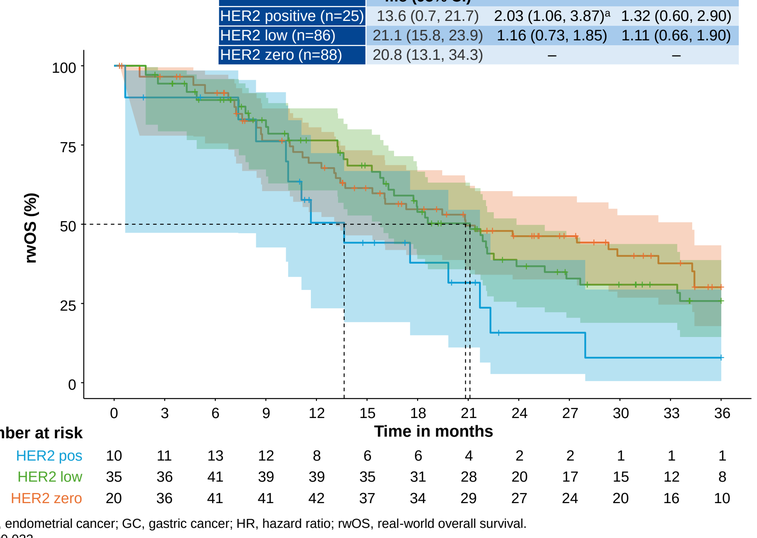
Table 1. Summary of Follow-Up by Cohort

Cohort	Patients in cohort, N	Patients in OS analysis, n (%)	Follow-up from 1L start, mo, median (Q1, Q3)	1L start to NGS, mo, median (Q1, Q3)	Deaths, n (%)
EC	295	199 (67.5)	16.27 (8.17, 27.60)	7.13 (1.12, 16.19)	87 (29.5)
HNSCC	630	415 (65.9)	16.14 (8.56, 27.08)	9.89 (3.43, 18.73)	233 (37.0)
NSCLC	2945	2289 (77.7)	14.76 (7.17, 26.99)	0.82 (-0.36, 16.44)	1082 (36.7)
OC	855	528 (61.8)	20.41 (9.32, 36.01)	7.96 (2.25, 24.41)	168 (19.6)

1L, first line; EC, endometrial cancer; HNSCC, head and neck squamous cell cancer; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; OC, ovarian cancer; OS, overall survival; Q, quartile.

Figure 2. EC: rwOS Based on HER2 RNA Thresholds From the GC Univariate and Multivariate Models

HER2 subgroup	Median rwOS, mo (95% CI)	Univariate (vs HER2 zero) HR (95% CI)	Multivariate (vs HER2 zero) HR (95% CI)
HER2 positive (n=25)	13.6 (0.7, 21.7)	2.03 (1.06, 3.87)[a]	1.32 (0.60, 2.90)
HER2 low (n=86)	21.1 (15.8, 23.9)	1.16 (0.73, 1.85)	1.11 (0.66, 1.90)
HER2 zero (n=88)	20.8 (13.1, 34.3)	–	–

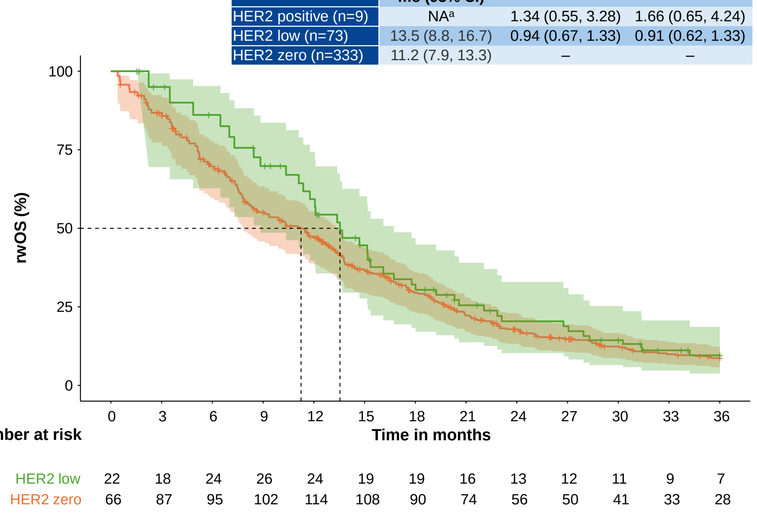


Number at risk													
HER2 pos	10	11	13	12	8	6	6	4	2	2	1	1	1
HER2 low	35	36	41	39	39	35	31	28	20	17	15	12	8
HER2 zero	20	36	41	41	42	37	34	29	27	24	20	16	10

EC, endometrial cancer; GC, gastric cancer; HR, hazard ratio; rwOS, real-world overall survival.
[a]*P*=0.032.

Figure 3. HNSCC: rwOS Based on HER2 RNA Thresholds From the GC Univariate and Multivariate Models

HER2 subgroup	Median rwOS, mo (95% CI)	Univariate (vs HER2 zero) HR (95% CI)	Multivariate (vs HER2 zero) HR (95% CI)
HER2 positive (n=9)	NA[a]	1.34 (0.55, 3.28)	1.66 (0.65, 4.24)
HER2 low (n=73)	13.5 (8.8, 16.7)	0.94 (0.67, 1.33)	0.91 (0.62, 1.33)
HER2 zero (n=333)	11.2 (7.9, 13.3)	–	–

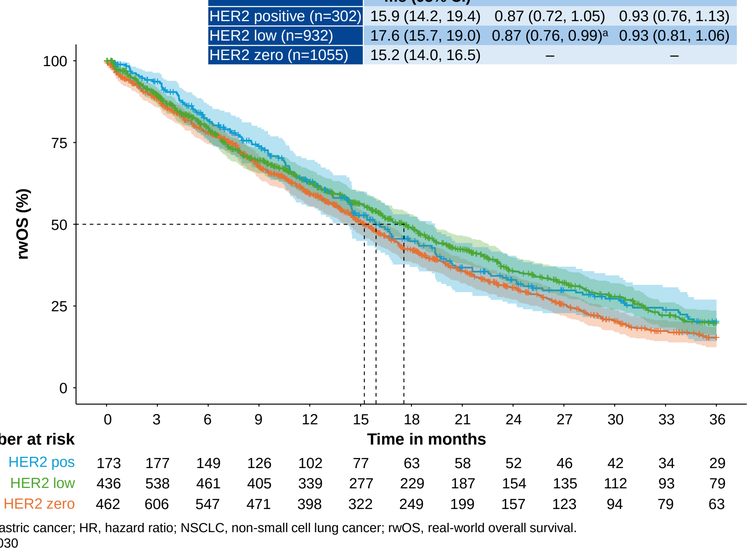


Number at risk													
HER2 low	22	18	24	26	24	19	19	16	13	12	11	9	7
HER2 zero	66	87	95	102	114	108	90	74	56	50	41	33	28

GC, gastric cancer; HNSCC, head and neck squamous cell cancer; HR, hazard ratio; NA, not available; rwOS, real-world overall survival.
[a]n=9 patients in subgroup.

Figure 4. NSCLC: rwOS Based on HER2 RNA Thresholds From the GC Univariate and Multivariate Models

HER2 subgroup	Median rwOS, mo (95% CI)	Univariate (vs HER2 zero) HR (95% CI)	Multivariate (vs HER2 zero) HR (95% CI)
HER2 positive (n=302)	15.9 (14.2, 19.4)	0.87 (0.72, 1.05)	0.93 (0.76, 1.13)
HER2 low (n=932)	17.6 (15.7, 19.0)	0.87 (0.76, 0.99)[a]	0.93 (0.81, 1.06)
HER2 zero (n=1055)	15.2 (14.0, 16.5)	–	–

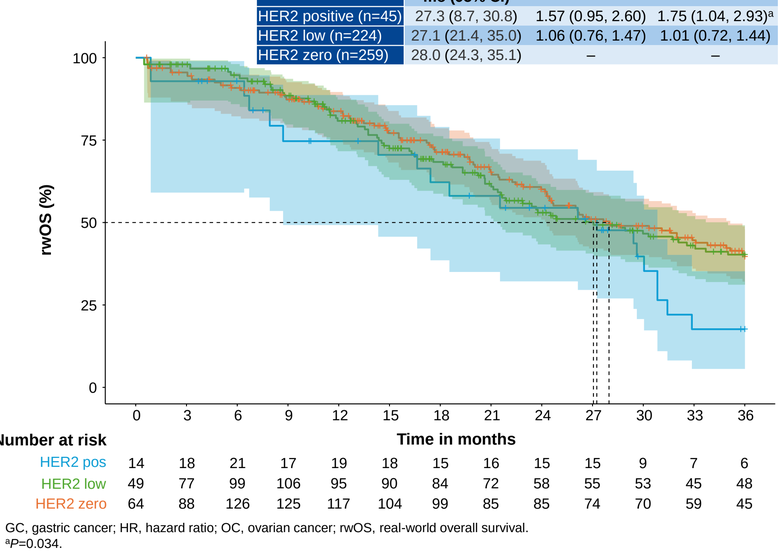


Number at risk													
HER2 pos	173	177	149	126	102	77	63	58	52	46	42	34	29
HER2 low	436	538	461	405	339	277	229	187	154	135	112	93	79
HER2 zero	462	606	547	471	398	322	249	199	157	123	94	79	63

GC, gastric cancer; HR, hazard ratio; NSCLC, non-small cell lung cancer; rwOS, real-world overall survival.
[a]*P*=0.030

Figure 5. OC: rwOS Based on HER2 RNA Thresholds From the GC Univariate and Multivariate Models

HER2 subgroup	Median rwOS, mo (95% CI)	Univariate (vs HER2 zero) HR (95% CI)	Multivariate (vs HER2 zero) HR (95% CI)
HER2 positive (n=45)	27.3 (8.7, 30.8)	1.57 (0.95, 2.60)	1.75 (1.04, 2.93)[a]
HER2 low (n=224)	27.1 (21.4, 35.0)	1.06 (0.76, 1.47)	1.01 (0.72, 1.44)
HER2 zero (n=259)	28.0 (24.3, 35.1)	–	–



Number at risk													
HER2 pos	14	18	21	17	19	18	15	16	15	15	9	7	6
HER2 low	49	77	99	106	95	90	84	72	58	55	53	45	48
HER2 zero	64	88	126	125	117	104	99	85	85	74	70	59	45

GC, gastric cancer; HR, hazard ratio; OC, ovarian cancer; rwOS, real-world overall survival.
[a]*P*=0.034.