Adverse Prognostic Impact of Intratumor Heterogeneous *HER2* Gene Amplification in Patients With Esophageal Adenocarcinoma

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ABSTRACT

Purpose

There is increasing recognition of the existence of intratumoral heterogeneity of the human epidermal growth factor receptor (*HER2*), which affects interpretation of *HER2* positivity in clinical practice and may have implications for patient prognosis and treatment. We determined the frequency and prognostic impact of heterogeneous *HER2* gene amplification and polysomy 17 in patients with esophageal adenocarcinoma (EAC).

Patients and Methods

HER2 amplification (by fluorescence in situ hybridization) was examined in surgical EAC specimens ($n = 675$). *HER2* heterogeneity was defined according to consensus guidelines as gene amplification (*HER2/CEP17* ratio ≥ 2.0) in more than 5% but less than 50% of cancer cells. No patient received neoadjuvant or *HER2*-targeted therapy. Cox models were used to assess disease-specific survival (DSS) and overall survival (OS).

Results

Overall, 117 EACs (17%) demonstrated *HER2* amplification, of which 20 (17%) showed *HER2* heterogeneity. All *HER2*-heterogeneous tumors were amplified. Among *HER2*-amplified tumors, heterogeneous tumors had significantly higher frequency of poor histologic grade and polysomy 17. In multivariable models that included number of metastatic lymph nodes, grade, tumor stage, and polysomy 17, only *HER2* heterogeneity and node number were prognostic among *HER2*-amplified tumors, with heterogeneity showing worse DSS (hazard ratio, 2.04; 95% CI, 1.09 to 3.79; $P = .025$) and OS ($P = .026$). Among *HER2*-nonamplified EACs, polysomy 17 was independently associated with worse DSS ($P = .012$) and OS ($P = .023$).

Conclusion

Among *HER2*-amplified EACs, 17% show *HER2* heterogeneity, which independently predicts for worse cancer-specific death. Among *HER2*-nonamplified EACs, polysomy 17 is independently associated with worse survival. These novel findings demonstrate aggressive subgroups in *HER2*-amplified and -nonamplified EACs that have important implications for *HER2* analysis and determination of benefit from *HER2*-targeted therapy.

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INTRODUCTION

Adenocarcinomas of the esophagus, gastroesophageal junction (GEJ), or gastric cardia (collectively referred to as esophageal adenocarcinomas [EACs]) have increased substantially in incidence over the past few decades and remain highly fatal.¹⁻⁴ Testing for human epidermal growth factor receptor 2 (*HER2*) status in patients with esophagogastric cancer is becoming routine, given recent data indicating that trastuzumab therapy can improve overall survival (OS) in patients with *HER2*-positive advanced GEJ or gastric adenocarcinoma.⁵ As we and others have shown, the frequency of *HER2* positivity in

esophagogastric cancers is 7% to 40%, which is similar to that of breast cancers where *HER2*-targeted therapy is routinely used.⁵⁻¹²

HER2 status is typically determined by identifying gene amplification by fluorescence in situ hybridization (FISH) or protein overexpression by immunohistochemistry (IHC). Recent data indicate that a subset of primary breast tumors displays intratumoral *HER2* heterogeneity¹³⁻¹⁵ whose frequency may be higher in gastric cancer.^{16,17} The reportedly higher rate of *HER2* heterogeneity in gastric cancer has led to a change in the interpretive criteria for *HER2* staining in esophagogastric cancer biopsies that differs from breast cancers.^{5,16,17}

However, studies to further characterize intratumoral *HER2* heterogeneity in esophagogastric cancers are needed and may have important clinical implications. Specifically, heterogeneity may contribute to inaccurate assessment of *HER2* status and, thereby, affect treatment decisions, including the selection of patients for *HER2*-targeted therapy.

Only limited and conflicting data exist for the prognostic impact of *HER2* heterogeneity in breast cancer,^{14,15} and data are nonexistent in esophagogastric cancer. Existing studies on intratumoral *HER2* heterogeneity in esophagogastric cancer are limited by modest sample sizes, nonuniform definitions of heterogeneity, reliance on *HER2* protein expression rather than gene amplification, and the use of tissue microarrays (TMAs) rather than whole tissue sections.^{7,16-18} Assessing *HER2* heterogeneity in formalin-fixed, paraffin-embedded human tissues by using FISH may have advantages over IHC.^{19,20} In this regard, the American Society of Clinical Oncology and College of American Pathologists (CAP) have developed a specific definition of *HER2* heterogeneity at the genetic, but not protein, level.¹³ Routinely ordered *HER2* FISH assays also include information on chromosome 17 copy number. Extra copies of chromosome 17 (ie, polysomy 17) reflect aneuploidy and chromosomal instability that may confer prognostic information, but polysomy 17 has not been studied in EAC.

We analyzed the frequency and prognostic impact of heterogeneous *HER2* amplification and chromosome 17 copy number in a large cohort of surgically resected EACs. In contrast to prior studies that analyzed biopsies or TMAs, we examined surgical resection specimens, which can enable more optimal assessment for heterogeneity. Because of the potential effects of chemoradiotherapy on tumor viability and *HER2* expression,^{21,22} we studied patients with EAC before routine use of neoadjuvant therapy.²³ We excluded squamous cell carcinoma and subcardial gastric cancers because their epidemiology and biology are distinct from EAC.²⁴⁻²⁶

PATIENTS AND METHODS

Development of Study Cohort

The parent cohort (N = 787) derives from the Mayo Esophageal Cancer Outcomes Database, as previously described,²⁷ which consists of patients with

newly diagnosed adenocarcinoma of the esophagus, GEJ, or gastric cardia who underwent surgical resection with cancer-free margins (from 1980 to 1997). Subcardial gastric cancers and tumors with only nonadenocarcinoma histology were excluded, as were the nine patients who received neoadjuvant chemotherapy and/or radiotherapy. Among samples where invasive carcinoma was available (n = 713), *HER2* gene amplification was evaluable in 675 patients (95%), who form the current study population. Adjuvant chemotherapy plus concurrent radiotherapy, chemotherapy alone, or radiotherapy alone was delivered in 48 (7.1%), 15 (2.2%), and 23 patients (3.4%), respectively; adjuvant therapy status was unknown in 41 patients (6.1%).

HER2 Testing Methods and Interpretive Criteria

***HER2* by FISH.** *HER2* tests approved by the US Food and Drug Administration (FDA) were used for FISH. *HER2* amplification was assessed in formalin-fixed, paraffin-embedded 5- μ m sections using the PathVysion *HER-2* DNA Probe Kit (*HER2* and centromere 17 [*CEP17*] probes; Abbott Molecular, Des Plaines, IL), as described.²⁸ For each case, a parallel hematoxylin and eosin–stained slide was examined for regions of invasive carcinoma by a pathologist (W.R.S.). The complete section was scanned by certified cytogenetic technologists to detect any subpopulation of amplified cells. A total of 60 representative nuclei from the invasive tumor were scored, with an overall evaluation performed by an experienced cytogeneticist (R.B.J.).^{13,28} A specimen with an *HER2/CEP17* ratio ≥ 2.0 in invasive cells was classified as *HER2* amplified, consistent with the definition used in the Trastuzumab for Gastric Cancer (ToGA) trial, in accordance with criteria developed for classification of *HER2* and *CEP17* abnormalities as previously described.^{19,29}

Polysomy 17. Chromosome 17 gain or loss was determined using *CEP17* signal patterns based on methodology and cutoffs that we previously validated using two large independent breast cancer sets.²⁹ Accordingly, polysomy 17 (gain) was defined as $\geq$ three *CEP17* signals in more than 30% of nuclei; monosomy 17 (loss) was defined as $\leq$ one *CEP17* signal in more than 60% of nuclei; and all other cases were considered normal.²⁹ Both cutoffs clearly distinguish chromosome 17 polysomic and monosomic cancers from cancers without chromosome 17 centromere anomalies.²⁹ All categorization thresholds were selected to reduce the rate of false-positive findings for gene amplification, gene deletion, and chromosome loss or gain. These criteria have worked well to correct for truncation and nuclear overlap, as well as the increase in four *CEP17* signals as a result of the G2 and mitosis phases of the cell cycle for nearly all solid tumors.²⁹ Quality control of the *HER2* FISH test is routinely assessed according to standard CAP and American College of Medical Genetics guidelines.³⁰⁻³²

***HER2* heterogeneity by FISH.** Following CAP breast cancer guidelines,¹³ a sample was considered to have heterogeneous *HER2* amplification if there were more than 5% but less than 50% infiltrating tumor cells with an *HER2/CEP17* ratio greater than 2.2 (results were the same for a 2.0 cut point). An

Table 1. Heterogeneous *HER2* Gene Amplification in Relation to Clinicopathologic Characteristics in Patients With Resected Esophageal Adenocarcinoma

Table 3. Heterogeneous HER2 Gene Amplification in Relation to Clinicopathologic Characteristics in Patients With Resected Esophageal Adenocarcinoma									
Characteristic	Total (N = 675)		HER2 Amplified (n = 117)						P
			HER2 Nonamplified (n = 558)		HER2 Heterogeneous (n = 20)		HER2 Nonheterogeneous (n = 97)		
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Median age, years	64.8		65.2		64.4		63.8		.402
Tumor grade									
Low-moderate	399	60	306	55	12	63	81	85	< .001
High	270	40	249	45	7	27	14	15	
Signet ring cells									
No	606	90	492	88	19	95	95	98	.0044
Yes	69	10	66	12	1	5	2	2	
Tumor stage									
T1-2	217	32	169	30	7	35	41	42	.0685
T3-4	454	68	385	70	13	65	56	58	
Median No. of metastatic nodes	2.0		2.0		1.5		1.0		.0076

Table 2. Heterogeneous *HER2* Gene Amplification in Relation to Polysomy 17 in Primary Esophageal Adenocarcinomas

Polysomy 17	<i>HER2</i> Nonamplified (n = 558)		<i>HER2</i> Amplified				<i>P</i>
	No. of Tumors	%	<i>HER2</i> Heterogeneous (n = 20)		<i>HER2</i> Nonheterogeneous (n = 97)		
			No. of Tumors	%	No. of Tumors	%	
Absent (n = 182)	141	25	2	10	39	40	.0023
Present (n = 493)	417	75	18	90	58	60	

HER2/CEP17 ratio was determined separately for the amplified and nonamplified subpopulation of each heterogeneous tumor. The primary *HER2/CEP17* ratio for each heterogeneous case was determined by calculating a mean ratio across the amplified and nonamplified subpopulations weighted by the percentage that each subpopulation comprised the entire tumor. *HER2*-heterogeneous tumors were further characterized by the distribution of the amplified subpopulation—that is, clustered (amplified cells adjacent to each other, tending to be arranged in groups) versus diffuse (amplified cells scattered among the nonamplified cells and relatively evenly distributed throughout the tumor).

Statistical Analysis

The Wilcoxon rank sum and χ^2 tests were used to compare variables between groups. For survival analysis, outcome variables were OS and

disease-specific survival (DSS). OS was defined as the time from surgery to death from any cause and was censored at the date of last contact for surviving patients. DSS was defined as the time from surgery to death related to index cancer and was censored at the date of death as a result of postoperative complications or other nonmalignant causes. Death beyond 5 years was censored. The Kaplan-Meier method and Cox proportional hazards models were used to assess the association between predictor variables and time-to-event outcomes. Hazard ratios (HRs) were reported. All *P* values are two-sided. *P* < .05 was considered statistically significant. Analyses were conducted in SAS version 9.1 (SAS Institute, Cary, NC). Study data were collected and managed in part using REDCap electronic data capture tools hosted at Mayo Clinic. The study was approved by the Mayo Clinic Institutional Review Board.

Fig 1. Among patients with esophageal adenocarcinoma who underwent surgical resection with curative intent, the prognostic impact of (A and B) *HER2* gene amplification in the overall cohort (N = 675) and (C and D) heterogeneous *HER2* gene amplification in the subgroup of patients with *HER2*-amplified tumors (n = 117) is shown. Hazard ratios (HRs) were adjusted for tumor stage, grade, number of malignant nodes, and polysomy 17. Prognosis end points were disease-specific survival and overall survival.

RESULTS

The study population of 675 patients is from the Mayo Esophageal Cancer Outcomes Database.²⁷ Table 1 lists key baseline clinicopathologic variables. All patients had resected adenocarcinomas. Most patients were male (88%) and had locally advanced tumor stage (67% T3-4, 73% node positive). Among 454 patients with T3-4 tumors, 426 had T3 tumors, and 28 had T4a tumors; there were no T4b tumors. By anatomic site, 234 tumors were located in the esophagus, 405 were located at the GEJ, and 36 were limited to the gastric cardia. No patients received neoadjuvant therapy, and 548 patients (81%) did not receive postoperative adjuvant therapy. No patients received *HER2*-targeted therapy. Median follow-up for vital status for surviving patients was 12.6 years. All-cause and disease-specific deaths within 5 years of surgery were experienced by 492 patients (72.9%) and 458 patients (67.9%), respectively.

HER2 Heterogeneity by FISH

HER2 amplification was detected in 117 (17%) of 675 tumors. Within the *HER2*-amplified group ($n = 117$), 20 tumors (17%) showed heterogeneous *HER2* amplification (Appendix Fig A1, online only). No tumors in the *HER2*-nonamplified group ($n = 558$) showed heterogeneous *HER2* amplification. Among heterogeneous tumors, the intratumoral distribution of *HER2*-amplified clones was clustered in 70% of tumors (14 of 20 tumors) and diffuse in 30% (six of 20 tumors).

The frequency of high-grade histology was highest in *HER2*-nonamplified EACs, followed by tumors with heterogeneous and nonheterogeneous *HER2* amplification (45% ν 27% ν 15%, respectively; $P < .001$; Table 1). Likewise, *HER2*-heterogeneous tumors were intermediate between *HER2*-amplified nonheterogeneous tumors and nonamplified tumors in the frequency of deep invasion (T3-4) and the median number of metastatic regional lymph nodes (Table 1).

Polysomy 17

Overall, polysomy 17 was detected in 73% of EACs (493 of 675 EACs). The frequency of polysomy 17 was highest in *HER2*-heterogeneous tumors (90%) compared with *HER2*-amplified tumors without heterogeneity (60%) or *HER2*-nonamplified tumors (75%; $P = .0023$), as shown in Table 2. Monosomy 17 was detected in four tumors in the entire population.

Prognostic Impact of *HER2* and Chromosome 17 Abnormalities

In the overall cohort, *HER2* amplification status was not significantly prognostic in univariate or multivariable analyses (Figs 1A and 1B). The presence of polysomy 17 was significantly associated with worse DSS ($P = .019$) and OS ($P = .026$) in univariate analysis, but not after adjustment for tumor stage, grade, and the number of metastatic lymph nodes ($P = .062$ for DSS and $P = .087$ for OS).

Because all *HER2*-heterogeneous tumors were *HER2* amplified, we determined the prognostic impact of heterogeneity stratified by amplification status. Among *HER2*-amplified tumors ($n = 117$), univariate analysis showed that the presence of heterogeneous *HER2* amplification was not significantly associated with DSS ($P = .086$) or OS ($P = .103$); higher tumor stage and the number of metastatic regional lymph nodes were significant prognostic variables (Table 3). In multivariable analysis, only *HER2* heterogeneity and the number of malignant nodes were independently prognostic after adjustment for covariates including polysomy 17. *HER2* heterogeneity was independently associated with two-fold worsened DSS (HR, 2.04; 95% CI, 1.09 to 3.79; $P = .025$) and OS (HR, 2.02; 95% CI, 1.09 to 3.74; $P = .026$; Table 3, Figs 1C and 1D). Polysomy 17 was not prognostic in the *HER2*-amplified subgroup (Table 3, Figs 2A and 2B).

In *HER2*-nonamplified tumors ($n = 558$), polysomy 17 was prognostic for worse survival in univariate and multivariable analysis (Table 3, Figs 2C and 2D). Specifically, polysomy 17 was independently associated with worsened DSS (HR, 1.36; 95% CI, 1.07 to 1.74;

Table 3. Survival Impact of *HER2* Heterogeneity and Polysomy 17 in Univariate and Multivariable Analyses Stratified by *HER2* Amplification Status in Patients With Resected Esophageal Adenocarcinoma

Variable	Univariate Analysis						Multivariable Analysis*						
	DSS			OS			DSS			OS			
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	
HER2-amplified subgroup (n = 117)													
HER2 heterogeneity: yes v no	1.62	0.93 to 2.82	.086	1.58	0.91 to 2.74	.103	2.04	1.09 to 3.79	.025	2.02	1.09 to 3.74	.026	
Tumor grade: high v low-moderate	1.65	0.97 to 2.81	.064	1.60	0.94 to 2.72	.080	1.09	0.61 to 1.94	.765	1.07	0.61 to 1.90	.810	
Tumor stage: T3-4 v T1-2	1.77	1.10 to 2.84	.019	1.74	1.09 to 2.78	.021	1.34	0.81 to 2.20	.256	1.33	0.81 to 2.17	.260	
No. of metastatic nodes: each additional node	1.15	1.09 to 1.21	< .001	1.14	1.08 to 1.20	< .001	1.14	1.07 to 1.20	< .001	1.13	1.07 to 1.20	< .001	
Polysomy 17: yes v no	0.99	0.61 to 1.58	.963	0.97	0.61 to 1.54	.903	0.67	0.40 to 1.12	.127	0.66	0.40 to 1.10	.115	
HER2-nonamplified subgroup (n = 558)													
HER2 heterogeneity: yes v no	NA			NA			NA			NA			
Tumor grade: high v low-moderate	1.47	1.20 to 1.80	< .001	1.46	1.20 to 1.77	< .001	1.31	1.06 to 1.61	.011	1.31	1.08 to 1.60	.007	
Tumor stage: T3-4 v T1-2	2.79	2.16 to 3.60	< .001	2.60	2.05 to 3.31	< .001	2.00	1.53 to 2.62	< .001	1.89	1.46 to 2.44	< .001	
No. of metastatic nodes: each additional node	1.11	1.09 to 1.12	< .001	1.10	1.08 to 1.12	< .001	1.09	1.07 to 1.11	< .001	1.08	1.06 to 1.10	< .001	
Polysomy 17: yes v no	1.36	1.06 to 1.73	.014	1.31	1.04 to 1.65	.023	1.36	1.07 to 1.74	.012	1.31	1.04 to 1.65	.023	

Abbreviations: DSS, disease-specific survival; HR, hazard ratio; NA, not applicable because the *HER2*-nonamplified subgroup had no *HER2*-heterogeneous tumors; OS, overall survival.

*HRs and P values were adjusted for all variables shown.

Fig 2. Among patients with esophageal adenocarcinoma who underwent surgical resection with curative intent, the prognostic impact of polysomy 17 is shown in the subgroup of patients with (A and B) *HER2*-amplified tumors (n = 117) and (C and D) *HER2*-nonamplified tumors (n = 558). Hazard ratios (HRs) were adjusted for tumor stage, grade, and number of malignant nodes. Prognosis end points were disease-specific survival and overall survival.

P = .012) and OS (HR, 1.31; 95% CI, 1.04 to 1.65; *P* = .023) after adjustment for covariates.

DISCUSSION

In the current study, we analyzed *HER2* heterogeneity in patients with EAC who underwent surgical resection with curative intent. Using FDA-approved assays, we detected heterogeneous *HER2* amplification in 17% of *HER2*-amplified tumors and in none of the nonamplified tumors. Importantly, we used the American Society of Clinical Oncology/CAP consensus definition of *HER2* genetic heterogeneity that was developed in human breast cancers.¹³ In two breast cancer studies where this definition was used,^{14,15} the rate of *HER2* heterogeneity among *HER2*-amplified tumors was 11% to 17%, which is similar to our finding in EAC. Sparse data exist for *HER2* genetic heterogeneity within primary esophagogastric cancers. In a study in 325 primary gastric adenocarcinomas, *HER2* heterogeneity, defined as the presence of discordant amplification among three tissue cores, was analyzed in TMAs, and 23% were heterogeneous among 35 adenocarcinomas that showed amplification in one or more cores.³³

We found that the presence of heterogeneous *HER2* amplification independently predicted worse DSS and OS, compared with amplified tumors with nonheterogeneous *HER2* amplification. A

study in human breast cancers found a similar association of *HER2* heterogeneity with worse prognosis compared with nonheterogeneous *HER2*-amplified cancers,¹⁵ although another study found no clear association.¹⁴ Although the biologic factors underlying the poor prognosis of tumors with *HER2* heterogeneity await further study, molecular heterogeneity may promote tumor survival, and aggressive clones may also promote paracrine-mediated interactions with less aggressive neighbors.³⁴⁻³⁶ In addition, molecular heterogeneity, representing diverse subpopulations that can arise through accumulated genetic changes, may improve adaptation to selective pressures in the environment.^{37,38} We found that *HER2* heterogeneity was associated with a higher frequency of polysomy 17, as was shown in breast cancer.³⁹ Among the larger group of nonamplified EACs, the presence of polysomy 17 was independently associated with poorer survival. Polysomy 17 has been associated with worse prognosis in other tumor types, which may be related to its association with chromosomal instability and aneuploidy.⁴⁰⁻⁴³ Extra copies of *CEP17* may coincide with alterations on chromosome 17, which contains multiple genes with established roles in malignancy (eg, *BRCA1*, *TP53*, *RAD51C*, *WNT*).⁴⁴

An important but yet unresolved issue is whether *HER2*-heterogeneous EACs respond differently to *HER2*-targeted therapy compared with nonheterogeneous amplified tumors. By definition,

tumors with heterogeneous *HER2* amplification demonstrate a lower level of *HER2* amplification overall. In an exploratory analysis of the ToGA trial, a lack of trastuzumab benefit was seen in tumors that showed *HER2* amplification and faint to absent protein expression,⁵ which, in turn, may have been associated with a lower level of amplification.⁴⁵ These data suggest the possibility that tumors with *HER2* heterogeneity or low-level amplification may have decreased responsiveness to trastuzumab. In support of this hypothesis, recent data in patients with established breast cancers with low-level amplification showed reduced responsiveness to neoadjuvant trastuzumab-based therapy.⁴⁶ In the adjuvant setting, however, no dose effect for trastuzumab benefit by *HER2* amplification level was found in a large breast cancer trial.²⁹ These data underscore the need for prospective studies to address this issue. Our finding for the prognostic impact of *HER2* heterogeneity suggests that trials assessing *HER2*-targeted therapies should report and consider stratifying by *HER2*-heterogeneous status.

Strengths of our study include the size of our study population, representing, to our knowledge, the largest examination of *HER2* in EAC to date. We used FDA-approved assays and a consensus definition of *HER2* heterogeneity. We analyzed 60 nuclei for *HER2* gene amplification, which exceeds the number (ie, 20 nuclei) typically used to assess amplification in the community and may enable more accurate determination of genetic abnormalities, particularly heterogeneity.⁴⁷ Although our design was retrospective, ascertainment and collection of study variables (eg, pathologic stage, vital status) did not differ by *HER2* status. Our study cohort is generalizable to other patients with resected EAC in Western countries by numerous parameters, including age, sex, and stage.^{2,48} We recognize that a relatively modest number of tumors were found to have *HER2* heterogeneity, underscoring the importance of validating these data in an independent cohort. Given the well-described advantages of FISH over IHC in analyzing *HER2* abnormalities,¹⁹ we limited our analysis of *HER2* heterogeneity using gene amplification data. However, studies are ongoing in our laboratory to determine the correlation between *HER2* genetic heterogeneity and *HER2* protein expression. We used published criteria¹³ for the analysis of *HER2* heterogeneity, which, although dichotomous, avoid selection of data-driven optimal cut points and multiple comparisons. Although our criteria for defining heterogeneity were based on a guideline, analysis of intratumor het-

erogeneity by examination of continuous measures may be of interest in future studies.

In conclusion, 17% of *HER2*-amplified EACs show *HER2* heterogeneity, which was found to independently predict for worse cancer-specific mortality. Polysomy 17 was most common in tumors with *HER2* heterogeneity, and among *HER2*-nonamplified tumors, polysomy 17 was independently associated with worse survival. These novel findings demonstrate aggressive subgroups in *HER2*-amplified and -nonamplified EACs and indicate the importance of routinely determining the presence of *HER2* genetic heterogeneity. The detection of *HER2* heterogeneity has implications for the evaluation of benefit from *HER2*-targeted therapy, and studies to address this issue are eagerly awaited.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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