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Phase II Trial of Trastuzumab in Women with Advanced or Recurrent, HER2-Positive Endometrial Carcinoma: a Gynecologic Oncology Group Study

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Abstract

Purpose—This study evaluated efficacy of single-agent trastuzumab against advanced or recurrent HER2-positive endometrial carcinoma (EC), and explored predictors for *HER2* amplification.

Patients and Methods—Eligible patients had measurable stage III, IV, or recurrent EC. There was no limit on prior therapy although total prior doxorubicin dose was limited to 320 mg/m². Tumors were required to have HER2 overexpression (2+ or 3+ immunohistochemical staining) or *HER2* amplification (FISH *HER2*/CEP 17 ratio >2.0). Trastuzumab was administered intravenously at a

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CONFLICT OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

dose of 4 mg/kg in week one, then 2 mg/kg weekly until disease progression. The primary endpoint was tumor response.

Results—Of the 286 tumors centrally screened by LabCorp, 33 (11.5%) were HER2-amplified. Three of eight clear (38%) cell carcinomas and 7 of 25 serous carcinomas (28%) screened exhibited *HER2* amplification compared with 7% (2/29) of endometrioid adenocarcinomas. *HER2* overexpression was correlated with *HER2* amplification ($r=0.459$; $p<0.0001$). Thirty four women were enrolled; one was excluded (refused treatment); 18 had tumors with known *HER2* amplification. No major tumor responses were observed. Twelve women experienced stable disease, 18 had increasing disease and three were indeterminate for tumor response. Neither *HER2* overexpression nor *HER2* amplification appeared to be associated with progression-free survival or overall survival.

Conclusion—Trastuzumab as a single agent did not demonstrate activity against endometrial carcinomas with *HER2* overexpression or *HER2* amplification, although full planned accrual of women with *HER2* amplified tumors was not achieved due to slow recruitment. Serous and clear cell endometrial carcinomas appear to be more likely to demonstrate *HER2* amplification.

INTRODUCTION

The anti-HER2 monoclonal antibody, trastuzumab, has improved the prognosis of women with HER2 positive breast cancer, both when used as part of adjuvant therapy and in the setting of metastatic disease [1]. In breast cancers both protein overexpression as shown by strong immunostaining and gene amplification appear to predict for benefit from trastuzumab, although gene amplification is often considered the better predictor.

Endometrial carcinomas are known to sometimes overexpress and/or amplify *HER2*. Aggressive tumors of high grade or serous histology appear more likely to be HER2 positive [2–3]. The Gynecologic Oncology Group (GOG) analyzed tumors of women with advanced or recurrent endometrial carcinoma treated on a front-line chemotherapy trial (GOG protocol #177), and found that 12% of tumors demonstrated *HER2* gene amplification and 20% demonstrated strong (3+) immunohistochemical (IHC) staining for HER2. Twenty one percent of grade 3 non-serous tumors and 21% of serous tumors were FISH positive [4].

The GOG undertook a phase II trial of single agent trastuzumab to evaluate its activity against advanced or recurrent HER2-positive endometrial carcinoma. Secondary exploratory objectives were to obtain more information on frequency and level of HER2 overexpression and the level of *HER2* amplification in endometrial carcinomas, the correlation of results using these two different assays in this population, and the relationship of *HER2* gene amplification to characteristics of the primary tumor such as grade and histologic subtype.

METHODS

Eligibility

Eligible patients had histologically documented stage III, stage IV, or recurrent HER2-positive endometrial carcinoma with measurable disease. “HER-2 positive” was initially defined using immunohistochemical (IHC) testing, but when there were no responses in 23 women with IHC positive tumors, the trial was amended to require *HER-2* amplification. An unlimited number of prior chemotherapy regimens was permitted but the total prior doxorubicin dose was limited to 320 mg/m². Exclusion criteria included GOG Performance Status (PS) >2, creatinine >2.0 mg/dL, bilirubin >1.5 mg/dL, serum glutamic oxaloacetic transaminase > 3x upper limits of institutional normal, left ventricular ejection fraction (LVEF) < 45%, requirement for supplemental oxygen, or unstable cardiac disease, including myocardial infarction within 6 months. Tumors of women treated on study (not those merely screened) had histology confirmed by central review of the GOG Pathology Committee. Written informed consent was

required prior to centralized HER2 testing from all participants, in accordance with national and local guidelines.

Terminology used in this manuscript

Period A: First part of the study during which time eligibility required HER2 overexpression defined as 2+ or 3+ staining by IHC. Patients from Period A with IHC-positive tumors who were treated on study comprised **Sample A** and were evaluated using statistical **Design A**.

Period B: Second part of study during which time patient eligibility required *HER2* gene amplification by FISH defined as a *HER2*/CEP 17 ratio >2.0. Patients from Sample A with both IHC-positive and FISH-positive tumors as well as new patients from Period B with FISH-positive tumors who were treated on study comprised **Sample B** and were analyzed using statistical **Design B**.

HER2 Testing

IHC testing was required during Period A but was not performed during Period B. FISH testing was allowed during Period A and was required during Period B. During Period A, patients who had previously participated on GOG treatment protocol GOG#177 could be eligible based on testing performed as a part of that trial, as previously published [4]. For all other patients, IHC and FISH testing during Period A and FISH testing during Period B were performed centrally by LabCorp. In either case, the DAKO Herceptest® IHC assay and the Vysis Inc PathVision® DNA Probe Kit (Vysis/Abbot Inc., Des Plaines, IL) were used. With the DAKO Herceptest® assay 2+ staining was defined as a weak to moderate complete membrane staining in more than 10% of the tumor cells; 3+ staining was defined as a strong complete membrane staining in more than 10% of the tumor cells. Positive on the FISH assay was defined as a *HER2* to chromosome 17 ratio of greater than 2.0

Treatment

Trastuzumab was supplied by the Division of Cancer Treatment and Diagnosis (DCTD) or the National Cancer Institute (NCI), and was administered weekly, with a first dose of 4 mg/kg intravenously over 90 minutes and subsequent doses of 2 mg/kg over 30 minutes, and continued until progression or unacceptable adverse effects. One cycle was defined as four weeks of therapy.

Evaluations

Left ventricular ejection fraction was assessed every 12 weeks. Most patients did not remain on study long enough to have a repeat measurement. Toxicities were evaluated using CTC version 2.0. Response evaluation was performed every eight weeks through week 24 and then every 12 weeks. Complete response (CR) was defined as the disappearance of all gross evidence of disease for at least four weeks. Partial response (PR) was a 50% or greater reduction in the product of perpendicular diameters obtained from measurement of each lesion for at least four weeks. Progressive disease (PD) was a 50% or greater increase in the product of perpendicular diameters of any lesion or the appearance of any new lesion within eight weeks of study entry. Stable disease (SD) was disease meeting none of the above criteria. Overall survival (OS) was defined as the observed length of time from entry onto study until death or, for living patients, the date of last contact. Progression-free survival (PFS) was defined as date from entry on study to the date of disease progression, death (whichever occurred first), or the date of last contact.

Statistical Design

Design A utilized a 2-stage design as outlined by Chen and Ng [5]. A regimen yielding a response rate of 10% or less was considered not to be clinically interesting (null hypothesis)

and a regimen capable of producing a response rate of at least 25% (alternative hypothesis) would clearly mandate further study. The design specifications can be found with [5] in Table II where $(\alpha, \beta) = (0.10, 0.10)$.

Period A of the study closed after the first stage for inactivity. The trial was modified to focus on patients with FISH-positive tumors. This subsequent analysis was termed Design B, and analyzed together those patients who were treated in Sample A with tumors that were FISH-positive as well as new patients from Period B with FISH-positive tumors. In order to allow for the inclusion of results from patients in Sample A with FISH-positive tumors, design B utilized a Bayesian paradigm which readily adapts to repeated updating of posterior distributions based on available evidence. A method related to Heitjan [6] with “Bayesian persuasion probabilities” was used. For applications to this study, the prior distribution for the probability of response was uniform from 0 to 1. The distribution of the number of responses was assumed to be binomial. The targeted sample size for stage 1 of Design B was 25 women. Period B of the study would close early after completion of the first stage of accrual if the posterior probability of the null hypothesis was greater than 10% and the posterior probability of the alternative hypothesis was less than 10%. Otherwise, the study would proceed to the second stage with a targeted cumulative sample size of 42 patients. The regimen would be declared interesting if the posterior probability of the null hypothesis being true was less than 10%, and the posterior probability of the alternative hypothesis being true was greater than 10%. The marginal operating characteristics of the design yielded a 9.5% probability of a type I error with 87.5% power of detecting active agents when the targeted sample sizes were met. See online description for additional details. Secondary endpoints of interest were the duration of PFS and OS. Exploratory endpoints included the degree of FISH amplification and cell type of tumor. The correlation between HER2 overexpression and *HER2* amplification was examined in the cohort centrally tested by LabCorp during Period A of this study where both FISH and IHC results were available. During Period B screening, there was also an attempt to collect pathologic information on tumors screened, including histologic subtype, tumor grade, and type of tumor tissue used for FISH testing to examine the relationship between these covariates and *HER2* amplification. This information was reported by the screening institution, and (unlike pathology data for patients treated on study) was not confirmed by central pathology review. Given the large number of exploratory analyses, the level of significance for statistical tests could not be meaningfully assessed. Instead, interesting results were marked as “notable.”

RESULTS

The trial opened in 2000 to women with IHC-positive tumors (Period A), was suspended in November of 2002 after completing the first stage of accrual (Sample A: 23 women from Period A with IHC-positive tumors who were treated on study and analyzed using Design A), and reopened in 2004 (Period B) after a protocol amendment limited eligibility to women with FISH-positive tumors and the development of an on-line tool for reporting screening results. It was permanently closed in May, 2007 because of poor accrual (Sample B: eight women with FISH-positive tumors from Sample A and the 10 of 11 new women with FISH-positive tumors from Period B who were treated on study and analyzed using Design B).

Screening

A summary of the HER2 testing and results is provided in Table 1 and Figure 1A. A total of 286 tumors were centrally screened for overexpression of the HER2 protein and/or amplification of the *HER2* gene. Of the 132 tumors tested by Lab Corp by IHC during Period A, 77 were IHC-negative, 36 were IHC-positive (22 with 2+ staining, 14 with 3+ staining) and 19 were not evaluable for HER2 overexpression (Table 1). By design, the 154 tumors screened during Period B were evaluated only for amplification (FISH) and not for overexpression

(IHC). FISH data were available for 122/132 (92%) and 145/154 (94%) of the women screened by LabCorp during Periods A and B, respectively; 234 were FISH-negative (107 from Period A, 127 from Period B) and 33 (12%) were FISH-positive (15 from Period A, 18 from Period B) (Table 1, Figure 1A). Of the cases with FISH-positive tumors, 24 displayed low level *HER2* amplification (FISH *HER2*/CEP17 ratio >2 to 4) and nine exhibited high level *HER2* amplification (FISH *HER2*/CEP17 ratio >4) (Figure 1 A).

Predictors of *HER2* Amplification

Analyses were performed to examine the correlation between *HER2* immunohistochemical staining and *HER2* amplification in the 107 women from Period A who were tested centrally by LabCorp with both IHC and FISH data (Figure 1B). A notable correlation was observed between immunohistochemical staining for *HER2* protein (0, 1+, 2+, 3+) and FISH *HER2*/CEP17 ratio (Spearman's correlation coefficient = 0.354; 95% unadjusted C.I. 0.17 – 0.51) or *HER2* amplification categorized as negative or positive (Kendall's tau-b correlation coefficient = 0.459).

For fifty-two percent (80/154) of the women screened during Period B, both FISH data and screening information including histologic cell type, tumor grade or the type of tumor tissue that was used for FISH testing were available. *HER2* amplification was observed in 38% (3/8) of clear cell carcinomas and 28% (7/25) of serous adenocarcinomas compared with 7% (2/29) of endometrioid adenocarcinomas. Both of the endometrioid adenocarcinomas and all three of the mixed epithelial adenocarcinomas that exhibited *HER2* amplification were poorly differentiated (G3) tumors. The rate of positivity among poorly differentiated endometrioid tumors was 11% (2/18), and the rate of positivity among mixed epithelial cancers was 3/11 (27%).

Enrollment and Treatment

A total of 34 patients were registered, including 23 women in Sample A and 18 women in Sample B (eight patients with FISH-positive tumors treated in Sample A and 10/11 new patients enrolled from Period B with FISH-positive tumors and treated on study). Twenty-nine of those enrolled were screened by LabCorp for *HER2* overexpression and/or *HER2* amplification (Table 1, Figure 1A). The additional five women were enrolled based on testing performed as part of GOG protocol #177 (Table 1). One patient registered from Period B was considered inevaluable, as she never received treatment with trastuzumab. Characteristics of the 33 patients who received at least one dose of trastuzumab are shown in Table 2. The median number of cycles administered was two.

Toxicity

Adverse events occurring on study with attribution listed as at least possible are shown in Table 3. Two deaths on treatment were considered possibly related to trastuzumab. One patient developed severe chills and hypotension during treatment; her fingers were noted to be "cold and dusky". Symptoms resolved and the infusion was completed. She suffered acute cardiac arrest one week later. Left ventricular hypertrophy with a normal stress test had been documented about nine months earlier. No autopsy was performed. A second patient with known hypertension and diabetes suffered a myocardial infarction during her first course of therapy. One patient with no known lung metastases developed grade 4 dyspnea that was considered to be possible pulmonary fibrosis; biopsy was not performed.

Efficacy

No major objective tumor responses were observed. The 90% frequentist, one-sided confidence interval for the probability of response for patients in Sample A of the study was 0% to 9.5%.

Although Sample B did not reach its targeted size of 25 patients, the posterior Bayes estimate [7] for the probability of response (minimizing the squared error loss function) can be made, and is 5%. The 90% highest posterior density Bayesian credible set [8] for the probability of responding in Sample B (assuming a uniform prior) was 0% to 11%. The posterior probability that the null hypothesis (response rate less than 10%) is true was found to be 86.5%, and the posterior probability that the alternative hypothesis is true is 0.4%. The posterior probability that neither hypothesis holds (i.e. the true response rate is between 10% and 25%) is 13.1%.

The median PFS for patients in Sample A of the study with IHC-positive tumors was 1.84 months and the median OS was 7.85 months (Figure 2). The median PFS and OS for patients in Sample B with FISH-positive tumors were 1.81 months and 6.80 months, respectively. The logrank tests on the entire set of patients for the impact of *HER2* amplification on PFS or OS were not significant. Twelve women had SD, 18 had PD and three were indeterminate for tumor response. There was no evidence to suggest that *HER2* overexpression or *HER2* amplification was associated with tumor response, PFS (Figures 2A, 2C), or OS (Figures 2B, 2D), respectively. Of the tumors that progressed, two progressed in the brain.

DISCUSSION

This trial was closed early due to poor accrual. Possible issues include investigator fatigue from low levels of *HER2*-positivity on screening. Of note, the percentage of patients with grade 3 endometrioid tumors whose tumors were FISH positive for *HER2* was only 11% in this series, and no grade 1–2 endometrioid tumors were FISH positive. In contrast, GOG #177 reported that 21% of grade 3 “non-endometrioid” tumors were *HER2* amplified [4]. This disparity is likely due to chance or the fact that in the analysis of GOG #177, mixed tumors which have a high rate of *HER2*-positivity in this series, were included with “non-serous” tumors. The rate of *HER2*-positivity for serous tumors was 21% in GOG #177 and 28% in the current series. Treatment was generally well tolerated. Two deaths on study were considered possibly related to therapy. One was possibly related to an infusion reaction, which occasionally occurs with trastuzumab. The second patient had multiple cardiovascular risk factors, and although the event occurred during therapy, the relationship is uncertain. The overall cardiac safety profile of trastuzumab is well known, and does not include a marked excess of cardiovascular events other than decreased ejection fraction which is primarily seen in patients treated with prior anthracyclines. Although most of our patients did not stay on study long enough to get a second ejection fraction, no clinically obvious heart failure was observed.

Our trial found no evidence of activity of trastuzumab against *HER2*-positive endometrial cancer. There have been case reports in the literature suggesting responses of endometrial cancer to single agent trastuzumab or trastuzumab with chemotherapy [9–11]. Is it possible that, despite our negative results, trastuzumab could benefit some women with *HER2*-positive endometrial carcinoma? Possibly results would be better in chemotherapy-naïve disease. Early trials of single agent trastuzumab in women with pretreated breast cancer demonstrated response rates of only 12%–15% [12,13]. It has also been suggested that serous tumors might be particularly sensitive to trastuzumab, as they are biologically different from other endometrial cancers and have a relatively high frequency of *HER2* amplification [14]. Of the 11 serous cancers treated on our trial, eight were FISH-positive, 1 was FISH-negative, and FISH data was missing for two cases.

Mechanisms of resistance to trastuzumab in *HER2* amplified cancers of either breast or another origin remain largely speculative. A dramatic example of the importance of activation of a second pathway in the response to a biologic agent has recently been reported in colon cancer, where only patients whose tumors do not express K-RAS appear to benefit from the anti-EGFR monoclonal antibody, cetuximab [15]. Potential mechanisms of resistance to trastuzumab

include signaling from other members of the HER family, cross talk from the insulin-like growth factor-I receptor to HER2, Met activation, and increased signaling through the PI3-kinase pathway by a variety of mechanisms, including *PTEN* or *PIK3CA* gene mutation [16–21]. A broad study of gene expression in *HER2*-amplified endometrial cancers might identify strategies for overcoming trastuzumab resistance, such as combining trastuzumab with mTOR inhibitors or cMET inhibitors.

In the treatment of *HER2*-positive breast cancer, combination therapy with chemotherapy plus trastuzumab is generally more effective than single agent trastuzumab. Directly moving to a randomized trial testing chemotherapy versus the combination of trastuzumab plus chemotherapy is the approach taken in gastric cancer, which is one of the few tumor types which appears to demonstrate *HER2*-positivity (both gene amplification and gene expression) at rates similar to those seen in breast cancer [22]. A large multinational trial (ToGA) randomized 594 patients with advanced gastric cancer to chemotherapy with a cisplatin/fluoropyrimidine-based regimen versus the same chemotherapy plus trastuzumab [23,24]. Median overall survival was improved from 11.1 months with chemotherapy alone to 13.5 months with chemotherapy plus trastuzumab (HR 0.74, $p=0.0048$). A similar large scale first-line approach may be needed to demonstrate a benefit of trastuzumab in the treatment of *HER2*-positive endometrial cancer. Such a trial could target patients with serous tumors, clear cell tumors, tumors of mixed histology, and possibly carcinosarcomas, which have also been reported to amplify/overexpress *HER2* in about 20–25% of cases [25].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1A

HER2 Amplification	Screened By LabCorp			Enrolled Based on Testing By			
				GOG#177	LabCorp		
	Period A	Period B	Total	Period A		Period B	Total
No (Ratio ≤ 2.0)	107	127	234	3	8	0	11
Moderate							
Ratio 2.1 to 2.5	5	2	7	0	1	1	19 *
Ratio 2.6 to 3.0	5	3	8	0	4	1	
Ratio 3.1 to 4.0	2	7	9	0	1	5 *	
Extensive (Ratio >4.0)	3	6	9	0	2	4	
Not Evaluable	10	9	19	2	2	0	4
Total	132	154	286	23		11 *	34 *

* One was never treated

23 in Sample A

18* in Sample B

Figure 1B

	HER2 Immunostaining				
<i>HER2</i> Amplification	0	1+	2+	3+	
No (Ratio $\leq$ 2)	32	40	18	4	94
Moderate (Ratio >2 to 4)	0	1	3	6	10
Extensive (Ratio >4)	0	0	0	3	3
	32	41	21	13	107

Figure 1.

- Summary of HER2 testing results on patients screened (left side of figure) and patients enrolled (right side of figure)
- Cases Screened by LabCorp during Period A with Evaluable IHC and FISH Data

A.

B.

Figure 2.

Progression-free survival (panels A and C) and overall survival (panels B and D) and for patients treated on study and categorized by *HER2* overexpression as 2+ or 3+ IHC (panels A and B) or *HER2* amplification as low or high FISH (panels C and D).

Table 1
Summary of screening, enrollment and treatment activities by type of HER2 testing and results

	Screened by Lab Corp					Enrolled Based on Testing By					Treated					
	Period A		Period B			GOG#177		LabCorp								
	HER2 Amplification		HER2 Amplification			HER2 Amplification		HER2 Amplification								
	-	+	na	-	+	na	-	+	na							
HER2 IHC Score																
IHC-negative	0	32	0	2	-	-	-	0	0	0	0	0				
	1+	40	1	2	-	-	-	0	0	0	0	0				
IHC-positive	2+	18	3	1	-	-	-	2	0	0	7	1	11			
	3+	4	9	1	-	-	-	1	0	2	1	7	1	12		
	Unk	13	2	4	127	18	9	173	0	0	0	0	11 ^f	0	11	10
Total		107	15	10	127	18	9	286	3	0	2	8	19	2	34	33

na = not available
^f One of these women was never treated and was not evaluable for response.

Table 2

Patient Characteristics

Characteristic	Number of Cases
Age	
50–59	8
60–69	11
70–79	12
80–89	2
Performance Status	
0	18
1	13
2	2
Race	
White	24
Black	7
Asian	2
Cell Type	
Adenocarcinoma, unspecified	1
Clear cell carcinoma	3
Endometrioid adenocarcinoma	13
Mixed epithelial	5
Serous adenocarcinoma	11
Pathology Grade	
1	4
2	3
3	26
Prior Radiotherapy	
No	16
Yes	17
Prior Chemotherapy	
0 Regimens	8
1 Regimen	16
2 Regimens	6
3+ Regimens	3
Disease	
Advanced	7
Recurrent	26

Table 3

Adverse Events (N=33)

Adverse Event	Grade			
	1	2	3	4
Leukopenia	2	0	0	0
Thrombocytopenia	4	0	0	0
Neutropenia	2	0	0	0
Anemia	13	3	2	0
Other hematologic	0	0	2	0
Allergy	1	1	0	0
Cardiovascular	4	2	0	2*
Constitutional	14	6	0	0
Dermatologic	2	0	0	0
Gastrointestinal	5	1	3	0
Genitourinary/Renal	4	2	0	0
Hepatic	4	0	0	0
Infection	1	0	0	0
Lymphatics	1	0	0	0
Metabolic	5	1	1	0
Neuropathy	3	0	0	0
Other neurologic	3	1	0	0
Pain	5	4	1	0
Pulmonary	1	1	2	1

* Two deaths: 1 infarction, 1 cardiopulmonary arrest. Both are possibly attributed to drug.