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Phase II Feasibility and Biomarker Study of Neoadjuvant Trastuzumab and Pertuzumab With Chemoradiotherapy for Resectable Human Epidermal Growth Factor Receptor 2–Positive Esophageal Adenocarcinoma: TRAP Study

Charlotte I. Stroes¹; Sandor Schokker, MD¹; Aafke Creemers, MD¹; Remco J. Molenaar, MD, PhD¹; Maarten C.C.M. Hulshof, MD, PhD¹; Stephanie O. van der Woude, MD¹; Roel J. Bennink, MD, PhD¹; Ron A.A. Mathôt, PharmD, PhD¹; Kausilia K. Krishnadath, MD, PhD¹; Cornelis J.A. Punt, MD, PhD¹; Rob H.A. Verhoeven, PhD²; Martijn G.H. van Oijen, PhD¹; Geert-Jan Creemers, MD, PhD³; Gard A.P. Nieuwenhuijzen, MD, PhD³; Maurice J.C. van der Sangen, MD, PhD³; Laurens V. Beerepoot, MD, PhD⁴; Joos Heisterkamp, MD, PhD⁴; Maartje Los, MD, PhD⁵; Marije Slingerland, MD, PhD⁵; Annemieke Cats, MD, PhD⁷; Geke A.P. Hospers, MD, PhD⁸; Maarten F. Bijlsma, PhD^{1,9}; Mark I. van Berge Henegouwen, MD, PhD¹; Sybren L. Meijer, MD, PhD¹; and Hanneke W.M. van Laarhoven, MD, PhD¹

PURPOSE Approximately 15% to 43% of esophageal adenocarcinomas (EACs) are human epidermal growth factor receptor 2 (HER2) positive. Because dual-agent HER2 blockade demonstrated a survival benefit in breast cancer, we conducted a phase II feasibility study of trastuzumab and pertuzumab added to neoadjuvant chemoradiotherapy (nCRT) in patients with EAC.

PATIENTS AND METHODS Patients with resectable HER2-positive EAC received standard nCRT with carboplatin and paclitaxel and 41.4 Gy of radiotherapy, with 4 mg/kg of trastuzumab on day 1, 2 mg/kg per week during weeks 2 to 6, and 6 mg/kg per week during weeks 7, 10, and 13 and 840 mg of pertuzumab every 3 weeks. The primary end point was feasibility, defined as $\geq 80\%$ completion of treatment with both trastuzumab and pertuzumab. An exploratory comparison of survival with a propensity score–matched cohort receiving standard nCRT was performed, as were exploratory pharmacokinetic and biomarker analyses.

RESULTS Of the 40 enrolled patients (78% men; median age, 63 years), 33 (83%) completed treatment with trastuzumab and pertuzumab. No unexpected safety events were observed. R0 resection was achieved in all patients undergoing surgery, with pathologic complete response in 13 patients (34%). Three-year progression-free and overall survival (OS) were 57% and 71%, respectively (median follow-up, 32.1 months). Compared with the propensity score–matched cohort, a significantly longer OS was observed with HER2 blockade (hazard ratio, 0.58; 95% CI, 0.34 to 0.97). Results of pharmacokinetic analysis and activity on [¹⁸F]fluorodeoxyglucose positron emission tomography scans did not correlate with survival or pathologic response. Patients with HER2 3+ overexpression or growth factor receptor–bound protein 7 (Grb7)–positive tumors at baseline demonstrated significantly better survival ($P = .007$) or treatment response ($P = .016$), respectively.

CONCLUSION Addition of trastuzumab and pertuzumab to nCRT in patients with HER2-positive EAC is feasible and demonstrates potentially promising activity compared with historical controls. HER2 3+ overexpression and Grb7 positivity are potentially predictive for survival and treatment response, respectively.

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INTRODUCTION

In resectable esophageal cancer (EC), a significant median gain in survival of 25 months can be achieved with neoadjuvant chemoradiotherapy (nCRT) administered according to the CROSS regimen compared with surgery alone.^{1,2} Nevertheless, survival remains poor; EC accounts for 508,600 deaths per year worldwide.³

In esophageal adenocarcinoma (EAC), 15% to 43% of tumors demonstrate human epidermal growth factor receptor 2 (HER2; ErbB-2) positivity,⁴⁻⁹ and inconsistent conclusions regarding the relationship between HER2 overexpression and clinical outcome have been published.^{8,10-12} In the phase III ToGA trial,¹³ the HER2-targeting monoclonal antibody trastuzumab significantly improved survival in patients with

ASSOCIATED CONTENT

Data Supplement Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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HER2-positive advanced gastric cancer. After positive results in a phase I/II study, the randomized RTOG 1010 trial (ClinicalTrials.gov identifier: NCT01196390) is currently investigating the addition of trastuzumab to carboplatin and paclitaxel and 50.4 Gy of radiotherapy in EAC.⁷ In patients with early breast cancer, the combination of trastuzumab and pertuzumab, a monoclonal antibody inhibiting ligand-dependent HER2 heterodimerization, has demonstrated higher pathologic complete response (pCR) compared with chemotherapy and trastuzumab alone.¹⁴ Preclinical studies^{15,16} in gastric cancer have demonstrated a synergistic effect on tumor inhibition with dual-agent HER2 blockade. In advanced HER2-positive gastric or gastroesophageal junction cancer, the JACOB study showed that the addition of pertuzumab to trastuzumab and chemotherapy resulted in a nonsignificant median survival benefit of 3.3 months, along with a manageable increase in grade ≥ 3 toxicity.¹⁷ Given the potential of dual-agent HER2 targeting, we hypothesized that addition of trastuzumab and pertuzumab to nCRT in resectable HER2-positive EAC could potentially improve survival. Because no data are available on the safety of this combination before major surgery, we first conducted a feasibility study.

Pharmacokinetic analyses in gastroesophageal cancer have suggested that exposure to low trastuzumab serum concentrations correlate with worse prognosis¹⁸ and that lower pertuzumab concentrations are reached in gastric¹⁹ compared with breast cancer.²⁰ Therefore, we additionally assessed the pharmacokinetics of trastuzumab and pertuzumab. Furthermore, because definite predictors for response are lacking in EAC, we performed exploratory biomarker analyses to identify relevant biomarkers for HER2-targeted therapy, including HER2/HER3 and growth factor-binding protein 7 (Grb7) expression^{8,21-27}, HER2 extracellular domain (sHER2) level, and activity on [¹⁸F] fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT).

PATIENTS AND METHODS

Study Design and Patient Eligibility Criteria

We performed a multicenter phase II study with trastuzumab and pertuzumab added to nCRT followed by esophagectomy in patients with HER2-positive EAC. Eligible patients had surgically resectable, histologically proven HER2-positive adenocarcinoma of the esophagus or gastroesophageal junction, without evidence of metastatic spread. Patients with celiac nodes and paraesophageal lymph nodes, including subcarinal and paratracheal lymph nodes, were considered eligible; those with other mediastinal nodes and nodes distal from the celiac trunk were considered ineligible. Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 and adequate hematologic, renal, and hepatic function were required. Patients who had received prior treatment with chemotherapy, radiotherapy, or HER2-targeted therapy or had severely

impaired lung function or clinically significant cardiovascular disease, including a left ventricular ejection fraction (LVEF) $< 55\%$ (Data Supplement) were excluded.

The trial was approved by the medical ethical review committee of the Amsterdam University Medical Center and conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided written, informed voluntary consent.

Treatment Plan

Patients received paclitaxel (50 mg/m²), carboplatin (area under the curve [AUC], 2), and radiotherapy (23 \times 1.8 Gy over 5 weeks).¹ Trastuzumab was administered at a loading dose of 4 mg/kg on day 1, 2 mg/kg once per week during weeks 2 to 6, and 6 mg/kg once every 3 weeks during weeks 7 to 13. Pertuzumab was administered at a dose of 840 mg once every 3 weeks (Data Supplement). Surgery was performed in week 14, with a transthoracic or transhiatal approach and a two-field lymph node dissection.

Dose Modifications

Dose reductions were not allowed for trastuzumab; pertuzumab dose was reduced if grade 3 to 4 diarrhea or rash occurred, without dose re-escalation thereafter. Dose delays for trastuzumab and pertuzumab were permitted for treatment-related adverse events (AEs).

Study End Points and Statistical Analyses

The primary objective was to assess the feasibility of neoadjuvant treatment, in terms of completion of trastuzumab and pertuzumab, using a one-sample test for a binomial proportion with normal approximation and a one-sided *P* value of $< .05$. Treatment would be regarded feasible if $\geq 80\%$ of patients completed treatment; a rate of $\leq 62\%$ would be considered unfeasible. On the basis of a single-stage Fleming design, 40 patients were required to achieve an α of 0.05 and a power of 0.80.

Secondary end points were safety, response, and survival. Exploratory end points were pharmacokinetics in relation to safety, response, and survival and biomarker analyses in relation to response and survival. All tests were two sided, with *P* values $< .05$ considered statistically significant. SPSS Statistics for Windows (version 25.0; IBM, Armonk, NY) was used for statistical analyses.

Safety. The safety population included all patients who received at least one dose of trastuzumab and pertuzumab. AEs were graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events (version 4.03) and the Radiation Oncology Group criteria; postoperative complications were graded according to Clavien-Dindo. Left ventricular systolic dysfunction (LVSD) was defined as $\geq 10\%$ absolute decrease from baseline to an absolute value of $< 50\%$ with (symptomatic) or without (asymptomatic) cardiac failure symptoms.^{28,29}

Response and survival. Pathologic response was assessed according to the criteria of Mandard et al.³⁰ Patients were clinically assessed through physical examination, laboratory tests, and multigated acquisition and CT scans before treatment. During treatment, weekly screening was performed using laboratory tests and physical examination.

Survival analyses included all patients who received at least one dose of trastuzumab and pertuzumab. Progression-free (PFS) and overall survival (OS) were estimated using Kaplan-Meier analyses, measured from treatment initiation to documented disease progression or death, respectively.

To compare the observed survival with that of patients receiving conventional nCRT according to CROSS, we performed propensity score matching with data from the Netherlands Cancer Registry (NCR). Using a logistic regression model, we matched on sex, performance status, number of comorbidities, age, hospital volume, tumor stage, and tumor length. Because determination of HER2 status is not standard clinical practice for patients without metastases, it could not be included as a matching variable. Matching was performed at a one-to-four ratio with a maximum allowable absolute difference in propensity score of 0.1, optimized to match patients with the fewest number of matches first. Survival was analyzed using a Cox proportional hazards model, after confirmation of the proportional hazards assumption.

Pharmacokinetic and biomarker analyses. For pharmacokinetic assessments, predose serum samples were obtained on days 1, 8, 15, 22, 29, 43, 64, and 85 to measure trough concentrations (C_{\min}), and postdose serum samples were obtained on days 1, 22, 43, 64, and 85 to measure peak concentrations (C_{\max}). Trastuzumab and pertuzumab were isolated from serum and analyzed using liquid chromatography with mass spectrometry. In serum samples collected on days 1, 22, 43, 64, and 85, sHER2 was measured using a fully automated, two-site sandwich immunoassay (ADVIA Centaur XP, Siemens, Munich, Germany;³¹ Data Supplement).

Tissue tumor samples for biomarker analyses obtained at baseline and post-treatment were stained for HER2/HER3 and Grb7 using anti-HER2/neu, HER3, and anti-Grb7 rabbit monoclonal antibodies. Slides were scored for HER2 using the Hoffman scoring system, with HER2 positivity defined as immunohistochemistry (IHC) 3+ or IHC2+ with amplification of HER2, as assessed with silver in situ hybridization.^{32,33} Membranous HER3 expression was scored using the HER2 IHC scoring guidelines,³² and IHC2+ and IHC3+ scores were defined as positive. For Grb7, the percentage of positive membranous stained cells and the maximal intensity of staining were assessed. Tumors were Grb7 positive when scoring at least IHC2+ in 10% of tumor cells (Data Supplement). Survival for HER2 IHC3+ and IHC2+ with amplification was assessed using a Gehan-Breslow-Wilcoxon survival curve.³⁴

Associations between the difference in FDG uptake on pre- and post-treatment PET/CT scans and pathologic response and survival were analyzed. Scans were performed according to the standard clinical protocols at each institution and reviewed using an Hermes workstation (Hermes Medical Solutions, Stockholm, Sweden). Volumes of interest were drawn over the primary tumor, from which maximum standardized uptake values (SUV_{\max}) were calculated. The associations of secondary outcomes with the degree of pathologic response and survival were assessed using nonparametric tests. Additional methods are described in the Data Supplement.

RESULTS

Patient Characteristics

Forty patients were enrolled between April 2014 and September 2016 and were observed through February 2019. A majority of included patients were men ($n = 33$; 83%) and had an ECOG performance score of 0 ($n = 33$; 83%). Median age was 63 years (interquartile range [IQR], 57-69). Most tumors were cT3 (65%) and cN1 (58%; Table 1).

Adherence to Treatment

Thirty-three of 40 patients completed treatment with trastuzumab and pertuzumab without dose modifications (completion rate, 83%). One or more doses of trastuzumab and/or pertuzumab were omitted in seven patients because of LVEF decrease ($n = 3$), trial discontinuation at the patient's request ($n = 3$), or death ($n = 1$). Three (8%) of 40 patients missed one dose of chemotherapy because of LVEF decrease ($n = 2$) or hospitalization ($n = 1$).

Safety

Overall toxicity. The most common AEs of any grade were fatigue (76%), diarrhea (73%), and nausea (70%; Table 2). One patient (3%) died as a result of pulmonary fibrosis during the trial. Of the grade ≥ 3 AEs ($n = 19$; 48%), diarrhea (20%) and dysphagia (18%) were most common.

Eleven patients (28%) had one or more serious AE (SAE), requiring (prolongation of) hospitalization; vomiting ($n = 4$), nausea ($n = 3$), and GI hemorrhage ($n = 2$) were the most prevalent causes (Data Supplement). All but one patient recovered from the SAEs; aggravation of preexisting pulmonary fibrosis led to a fatal outcome.

Cardiotoxicity. Thirty-seven patients were included in the cardiac safety analysis. Because of early non-cardiac-related discontinuation ($n = 2$) or death ($n = 1$), post-treatment measurements were not performed in three patients. The mean (\pm standard deviation [SD]) pre-treatment LVEF was 64% ($\pm 7.8\%$); it was 59% ($\pm 8.4\%$) post-treatment. Five patients (14%) developed LVSD, of whom one patient had symptomatic LVSD and one patient missed a dose of trastuzumab and pertuzumab because of

TABLE 1. Baseline Demographic and Clinical Characteristics (N = 40)

Characteristic	No.	%
Age, years		
Median	63	
Range	44-78	
Sex		
Male	33	83
Female	7	17
HER2 status		
2+	11	27
3+	29	73
ECOG PS		
0	33	83
1	7	17
Tumor length, cm		
Mean	6.3	
SD	2.7	
Clinical tumor stage		
cT2	11	28
cT3	26	65
cT4	1	3
cTx	2	5
Clinical nodal stage		
cN0	8	20
cN1	27	68
cN2	5	13
LVEF		
Median	64	
Range	52-87	

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; HER2, human epidermal growth factor receptor 2; LVEF, left ventricular ejection fraction; SD, standard deviation.

LVEF decrease. However, cardiotoxicity did not result in delay of surgery in any of these patients.

Postoperative complications. Two patients did not undergo surgery (5%); one patient died before surgery as a result of pulmonary fibrosis, and one patient developed interval metastases. No patient died within 30 and 90 days after surgery, and no unforeseen complications were reported. A majority of postoperative complications were pulmonary (24%) or cardiac complications (16%; [Table 3](#)). Four patients (11%) experienced anastomotic leakage.

Response and Survival

R0 resection was achieved in all 38 patients undergoing surgery (100%), of whom 13 (34%) had a pCR (Mandard 1). Mandard 2, 3, 4, and 5 responses were observed in 10 (26%), 10 (26%), three (8%), and two patients (5%), respectively (Data Supplement).

TABLE 2. AEs in Enrolled Patients (N = 40)

AE	Grade 1-2		Grade 3	
	No.	%	No.	%
Fatigue	29	73	1	3
Nausea	24	60	4	10
Diarrhea	21	53	8	20
Pain	18	45	0	0
Vomiting	16	40	2	5
Rash	14	35	0	0
Constipation	13	33	1	3
Infection	11	28	0	0
Odynophagia	10	25	1	3
Flu-like/malaise	10	25	0	0
Dysphagia	9	23	7	18
Anorexia	9	23	2	5
Alopecia	9	23	0	0
Epistaxis	9	23	0	0
Dysgeusia	7	18	0	0
Fever	7	18	0	0
Hoarseness	6	15	0	0
Infusion-related reaction	5	13	0	0
Peripheral sensory neuropathy	5	13	0	0
Dry skin	5	13	0	0
Dyspepsia	5	13	1	3
Dehydration	4	10	1	3
Cardiac symptoms*	4	10	2	5
Chills	4	10	0	0
Oral mucositis	4	10	0	0
Headache	4	10	0	0
Sore throat	4	10	0	0
Cough	4	10	0	0
Dyspnea	4	10	0	0
Esophagitis	3	8	2	5
Hypophosphatemia	2	5	1	3
Hematemesis	0	0	1	3
Pulmonary fibrosis	0	0	1†	3

Abbreviation: AE, adverse event.

*Cardiac symptoms were atrial fibrillation and hypertension.

†Indicates a grade five event.

Median follow-up was 32.1 months (IQR, 28.3-39.4). Median PFS and OS were not achieved during follow-up. One- and 3-year PFS rates were 82.5% and 56.8%, respectively. One- and 3-year OS rates were 90.0% and 71.3%, respectively ([Fig 1](#)).

Results were compared with the propensity score-matched cohort from the NCR receiving nCRT (Data Supplement). The assumption of proportional hazards was met ($P = .671$).

TABLE 3. Postoperative Complications in Patients Undergoing Surgery (n = 38)

Complication*	No.	%
Pulmonary†	9	24
Cardiac‡	6	16
Anastomotic leakage	4	11
Neurologic§	4	11
Wound infection	4	11
Aspiration	3	8
Constipation	2	5
Gastric tube	2	5
Hoarseness	2	5
Mediastinitis	2	5
Abdominal fluid collection	1	3
Cachexia-related symptom	1	3
Gastric tube retention	1	3
Depression	1	3
Diarrhea	1	3
Hypernatremia	1	3
Hypertriglyceridemia	1	3
Hypokalemia	1	3
Pyelonephritis	1	3
Pylorus stenosis	1	3
Rash	1	3
Stomach distension	1	3
Uncontrolled hyperglycemia	1	3

*Postoperative complications were graded according to the Clavien Dindo Criteria.

†Pulmonary complications were pneumonia, pneumothorax, atelectasis, and pleural effusion.

‡Cardiac complications were atrial fibrillation and hypertension.

§Neurological complications were vocal cord/nervus recurrence paresis, Horner syndrome, and myoclonus.

Patients receiving nCRT, trastuzumab, and pertuzumab were at significantly lower hazards of death compared with patients receiving nCRT only (hazard ratio, 0.58; 95% CI, 0.34 to 0.97; Fig 1).

Pharmacokinetic Analysis

Pharmacokinetic data were evaluable for 37 patients. The mean (\pm SD) observed C_{\min} and C_{\max} for trastuzumab were 38.4 (\pm 10.8) and 128.9 $\mu\text{g/mL}$ (\pm 23.2), respectively (Fig 2A); for pertuzumab, they were 89.5 (\pm 24.8) and 292.3 $\mu\text{g/mL}$ (\pm 52.5), respectively (Fig 2B). All patients had a pertuzumab C_{\min} $>$ 20 $\mu\text{g/mL}$. The AUC concentration of trastuzumab and pertuzumab did not correlate with cardiac toxicity ($P = .652$ and $P = .728$, respectively). Between patients with and without pCR or disease progression, C_{\min} concentrations of trastuzumab and pertuzumab were not significantly different (all $P > .05$).

Biomarker Analyses

Serum samples from 40 patients were available. Median baseline sHER2 was 11.9 $\mu\text{g/mL}$ (IQR, 10.7-14.6; Data Supplement). sHER2 baseline levels were not significantly different in patients with and without disease progression ($P = .890$), nor were they different in patients with pCR or residual disease ($P = .158$).

Patients with HER2 IHC3+ tumors at baseline (n = 29) demonstrated a significantly better OS compared with HER2 IHC2+ patients with gene amplification (n = 11; $P = .016$; Fig 3A). HER3 expression and Grb7 expression were positive in 58% (n = 23) and 55% (n = 22) of patients, respectively (Figs 3B and 3C; Data Supplement). Treatment response was significantly better for patients with Grb7-positive tumors at baseline ($P = .001$; Fig 3D). No correlation between pretreatment HER2 expression and Mandard score was observed, nor did pre- or post-treatment HER3 expression demonstrate a correlation with treatment response or survival.

Baseline PET/CT scans were available from 38 patients. Scans from two patients could not be analyzed because of logistic reasons. Six patients did not have post-treatment scans because of death (n = 1) or discretion of the local investigator (n = 5). Post-treatment scans were performed at a median time of 8.1 weeks (IQR, 7.0-8.3) after completing nCRT, with five scans prematurely performed within 6 weeks after nCRT completion. Median SUV_{\max} at baseline was 12.1 (IQR, 8.7-15.9); it was 4.5 (IQR, 3.5-5.5) after treatment. No significant difference in ΔSUV_{\max} was identified in patients with ν without disease progression ($P = .417$), nor in patients with high ν low Mandard scores ($P = .349$). After exclusion of prematurely performed scans, still no relationship between ΔSUV_{\max} and Mandard score or progression was observed (all $P > .05$). Baseline SUV_{\max} did not predict progression or death ($P = .846$).

DISCUSSION

This is the first study to our knowledge demonstrating the feasibility of the addition of both trastuzumab and pertuzumab to standard nCRT with carboplatin and paclitaxel in patients with resectable HER2-positive EAC, with 83% of patients receiving the complete treatment schedule.

Toxicity was similar to that with standard nCRT (CROSS), with the exception of increased incidences of rash and grade 3 diarrhea compared with the CROSS trial¹ (35% ν 0% and 20% ν 1%, respectively), most likely because of pertuzumab-induced inhibition of the epidermal growth factor receptor.^{29,35,36} AEs were manageable and did not result in treatment discontinuation of trastuzumab or pertuzumab or in delay of surgery. In the JACOB trial,¹⁷ cardiac toxicity was similar in patients with and without pertuzumab. Incidence of LVSD was higher in our study compared with the JACOB trial. It should, however, be noted that LVEF changes cannot directly be attributed to trastuzumab and

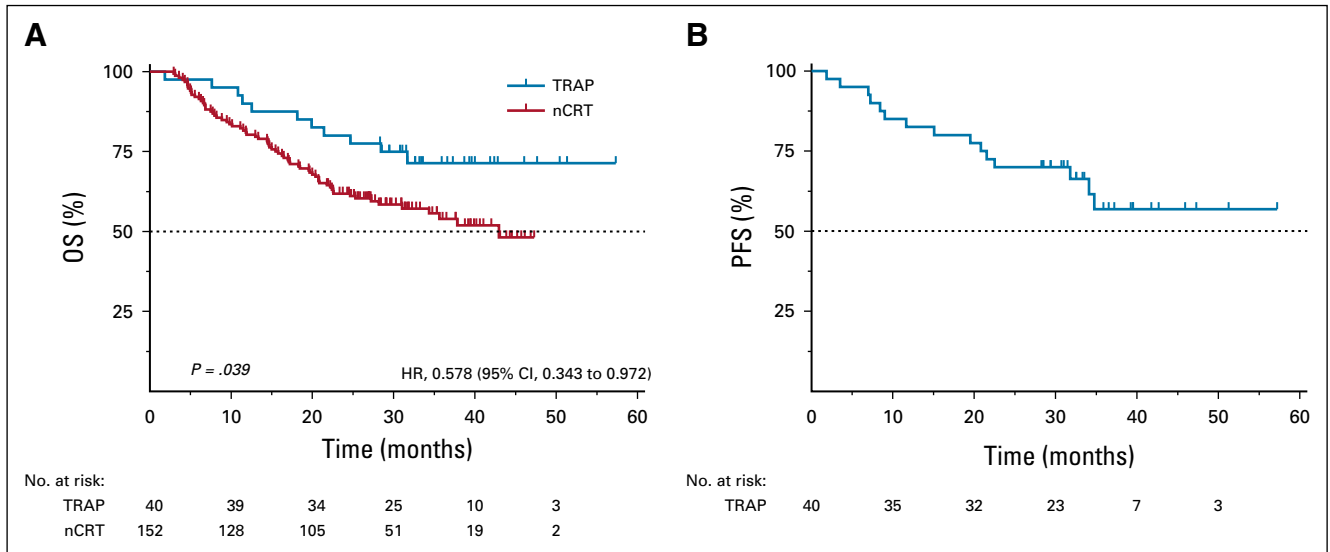


FIG 1. (A) Overall survival (OS) and (B) progression-free survival (PFS) in patients receiving neoadjuvant chemoradiotherapy (nCRT) alone or nCRT plus trastuzumab and pertuzumab (TRAP). HR, hazard ratio.

pertuzumab alone, because CRT may also influence cardiac function.^{37,38} Nevertheless, because no cardiac toxicity was observed in a phase I/II study⁷ investigating trastuzumab with chemotherapy and 50.4 Gy of radiotherapy, the extent to which radiotherapy influences cardiac toxicity remains unclear. Postoperative complication rates were lower in the TRAP study compared with the CROSS trial,¹ with anastomotic leakage reported in 10% versus 22% and pulmonary complications in 24% versus 46%, respectively.

Compared with the CROSS trial,¹ higher R0 resection and pCR rates were observed (100% v 92% and 34% v 23% for EAC, respectively). Direct comparison with a propensity score-matched cohort treated with the CROSS regimen

may also suggest that addition of trastuzumab and pertuzumab to nCRT is more effective than nCRT alone. Unfortunately, a major limitation is that HER2 status could not be retrieved for the propensity score-matched cohort. Nonetheless, in previous retrospective cohort studies of patients with EAC treated with nCRT,^{8,12} no significant association between baseline HER2 status and survival was observed, and therefore, the influence of HER2 status on prognosis is probably limited.

In contrast to the ToGA trial,¹³ we identified no correlation between the pharmacokinetics of trastuzumab and pathologic response or survival. Furthermore, compared with a phase IIIb study³⁹ in advanced gastric cancer, our patients achieved higher trastuzumab C_{min} values. However,

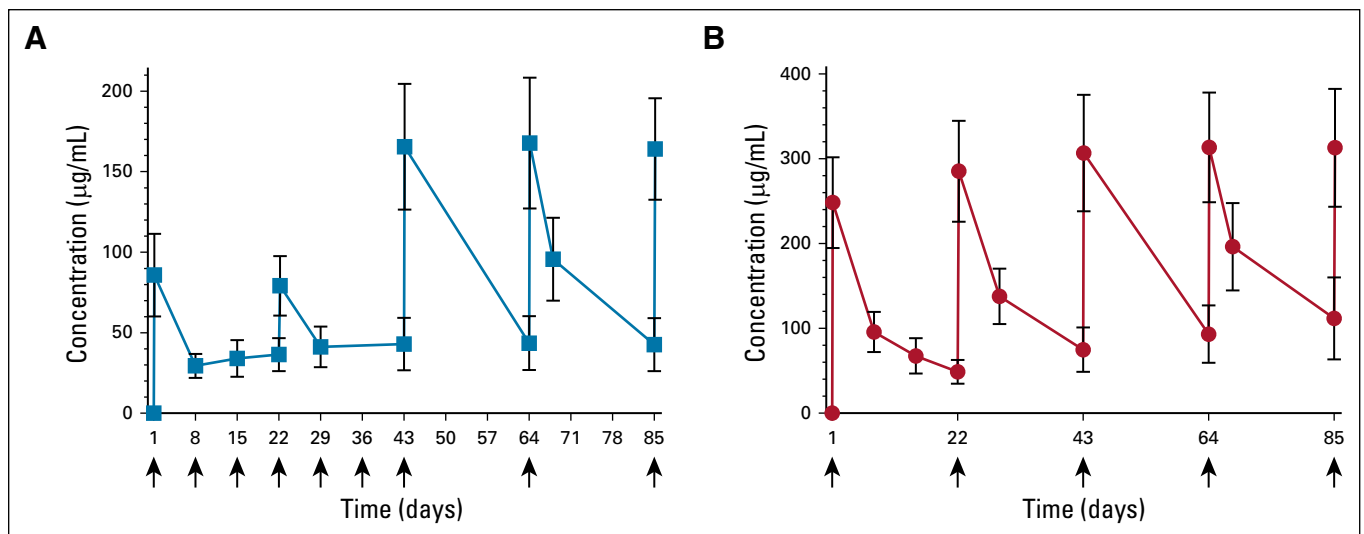


FIG 2. Mean trough and peak concentrations of (A) trastuzumab and (B) pertuzumab in serum. Horizontal bars indicate standard deviations.

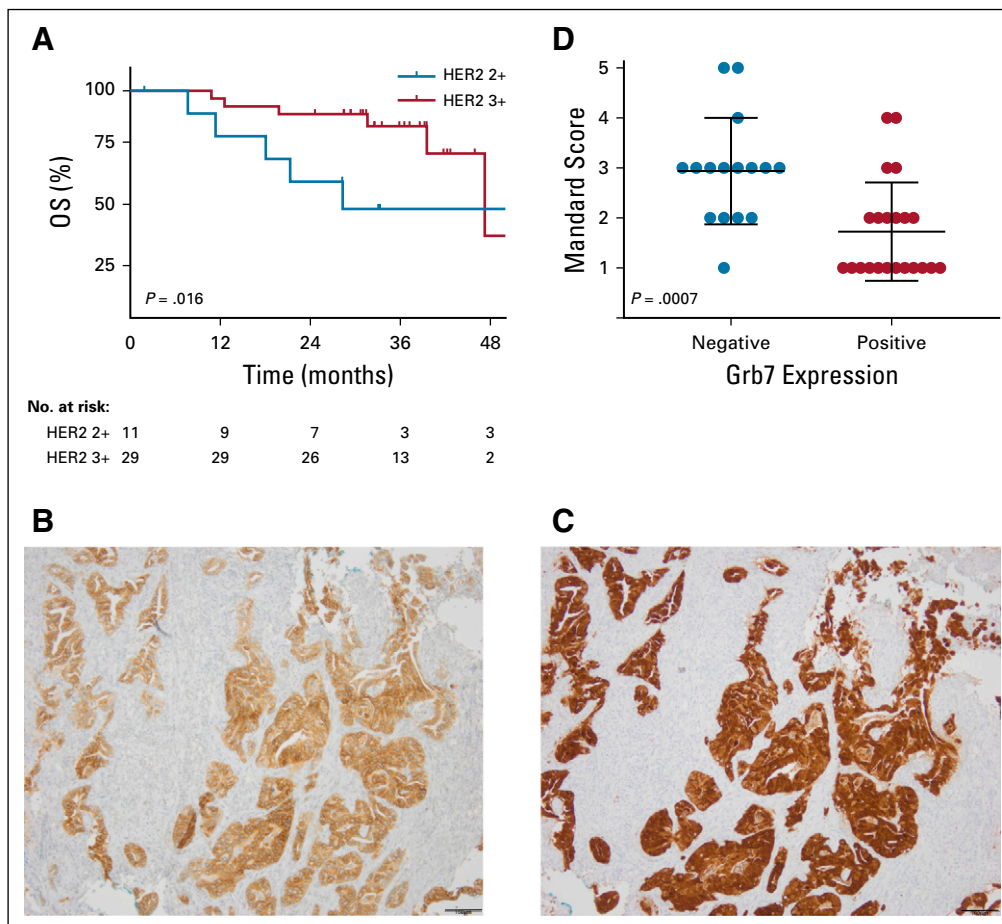


FIG 3. (A) Overall survival (OS) of patients with human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) 2+ and IHC3+ tumors. (B) HER2 and (C) growth factor-binding protein 7 (Grb7) expression at 10 \times magnification. (D) Treatment response by Mandard score in patients with Grb7-positive and -negative tumors.

as this trial also demonstrated,³⁹ we observed no association with increased efficacy. All patients reached the pertuzumab target concentration of $> 20 \mu\text{g/mL}$, and our results on pertuzumab trough values were comparable to those of previous studies in breast²⁰ and gastroesophageal cancers.¹⁹ Similar to previous studies on gastroesophageal cancer in the metastatic setting,^{17,19} we chose to double the pertuzumab dose compared with that used in breast cancer studies.⁴⁰ This suggests that higher doses are needed in upper GI compared with breast cancer to reach similar pharmacokinetic concentrations, although the mechanism underlying this difference remains unknown.¹⁹

Exploratory biomarker analysis were performed to identify subgroups that benefit most from HER2 targeting.⁴¹ Our data support previous reports^{21,22,24} showing that patients with high HER2 expression potentially benefit most from HER2-targeting agents. However, available studies on the relationship between HER2 status and survival of patients treated with nCRT^{8,12} have not investigated the difference in survival between HER2 IHC3+ and HER2 IHC2+ with amplification. Therefore, it is still an open question whether high HER2 expression is a true predictive, and potentially prognostic, biomarker in this population. We also identified Grb7 as a potential treatment response biomarker. This is in

line with previous observations of Grb7 as a therapeutic target in esophageal²⁷ and breast cancers,⁴² because it strongly binds HER2 and could play an essential role in HER2 signaling. Therefore, patients with Grb7-overexpressing tumors may be more sensitive to HER2-targeting treatment.^{26,27,42} Alternatively, this could be a result of coamplification of Grb7 with HER2, located on chromosome 17, which has been reported in breast cancer.^{42,43} Nevertheless, here we report Grb7 negativity in 45% of HER2-positive patients. Therefore, Grb7 holds potential value as a predictive biomarker, and further investigation is warranted. The previous finding of sHER2 as a prognostic and predictive marker^{22,44,45} could not be confirmed in this trial, as also has been reported by others.²⁴

PET/CT scans performed in our study were executed at a prolonged interval after nCRT (8 rather than 4-6 weeks), considering previous studies demonstrating the substantial influence of radiation-induced inflammation on pathologic response assessment by PET/CT.⁴⁶⁻⁴⁸ Nevertheless, we did not observe a correlation between decreased FDG uptake and pathologic response.^{49,50} Exclusion of prematurely performed scans did not influence outcome. Although FDG PET/CT scanning is valuable to determine the presence of metastases,⁴⁹ its value as a predictive tool for treatment response seems questionable.⁵¹

In conclusion, the addition of trastuzumab and pertuzumab to nCRT is safe and tolerable for patients with HER2-positive EAC, and preliminary efficacy results seem promising. Because data on an HER2-positive control group are lacking,

a randomized phase III study is warranted to demonstrate the superiority of the addition of trastuzumab and pertuzumab. High HER2 and Grb7 may serve as biomarkers to predict survival and treatment response, respectively.

AFFILIATIONS

¹Amsterdam University Medical Center, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, the Netherlands

²Netherlands Comprehensive Cancer Organization, Utrecht, the Netherlands

³Catharina Hospital, Eindhoven, the Netherlands

⁴Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands

⁵Sint Antonius Hospital, Nieuwegein, the Netherlands

⁶Leiden University Medical Center, Leiden, the Netherlands

⁷Netherlands Cancer Institute, Amsterdam, the Netherlands

⁸University Medical Center Groningen, Groningen, the Netherlands

⁹Oncode Institute, Amsterdam, the Netherlands

CORRESPONDING AUTHOR

Hanneke W.M. van Laarhoven, MD, PhD Meibergdreef 9 1105 AZ Amsterdam, the Netherlands; e-mail: h.vanlaarhoven@amsterdamumc.nl.

EQUAL CONTRIBUTION

C.I.S., S.S., A. Creemers, and R.J.M. contributed equally to this work.

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CLINICAL TRIAL INFORMATION

[NCT02120911](https://clinicaltrials.gov/ct2/show/study/NCT02120911)

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AUTHOR CONTRIBUTIONS

Conception and design: Maarten C.C.M. Hulshof, Ron A.A. Mathôt, Cornelis J.A. Punt, Maurice J.C. van der Sangen, Mark I. van Berge Henegouwen, Hanneke W.M. van Laarhoven

Administrative support: Ron A.A. Mathôt, Hanneke W.M. van Laarhoven
Provision of study material or patients: Kausilia K. Krishnadath, Rob H.A. Verhoeven, Laurens V. Beerepoot, Maartje Los, Hanneke W.M. van Laarhoven

Collection and assembly of data: Charlotte I. Stroes, Sandor Schokker, Aafke Creemers, Stephanie O. van der Woude, Roel J. Bennink, Kausilia K. Krishnadath, Rob H.A. Verhoeven, Geert-Jan Creemers, Grard A.P. Nieuwenhuijzen, Laurens V. Beerepoot, Joos Heisterkamp, Maartje Los, Annemieke Cats, Geke A.P. Hospers, Mark I. van Berge Henegouwen, Hanneke W.M. van Laarhoven

Data analysis and interpretation: Charlotte I. Stroes, Sandor Schokker, Aafke Creemers, Remco J. Molenaar, Roel J. Bennink, Ron A.A. Mathôt, Cornelis J.A. Punt, Rob H.A. Verhoeven, Martijn G.H. van Oijen, Geert-Jan Creemers, Maurice J.C. van der Sangen, Laurens V. Beerepoot, Joos Heisterkamp, Marije Slingerland, Annemieke Cats, Geke A.P. Hospers, Maarten F. Bijlsma, Mark I. van Berge Henegouwen, Sybren L. Meijer, Hanneke W.M. van Laarhoven

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Phase II Feasibility and Biomarker Study of Neoadjuvant Trastuzumab and Pertuzumab With Chemoradiotherapy for Resectable Human Epidermal Growth Factor Receptor 2-Positive Esophageal Adenocarcinoma: TRAP Study**

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Sandor Schokker

Travel, Accommodations, Expenses: Roche

Ron A.A. Mathôt

Consulting or Advisory Role: Merck Sharp & Dohme, Bayer, CSL Behring, Zeria Pharmaceutical

Research Funding: Bayer, CSL Behring, Shire

Cornelis J.A. Punt

Consulting or Advisory Role: Bayer (Inst)

Travel, Accommodations, Expenses: Nordic Pharma

Rob H.A. Verhoeven

Research Funding: Bristol-Myers Squibb (Inst)

Martijn G.H. van Oijen

Research Funding: Roche (Inst), Nordic Group (Inst), Servier (Inst), Amgen (Inst), Merck (Inst)

Grard A.P. Nieuwenhuijzen

Consulting or Advisory Role: Medtronic (Inst)

Research Funding: Medtronic (Inst)

Laurens V. Beerepoot

Consulting or Advisory Role: Servier

Geke A.P. Hospers

Consulting or Advisory Role: Roche (Inst), Merck Sharp & Dohme (Inst), Amgen (Inst), Bristol-Myers Squibb (Inst), Novartis (Inst)

Research Funding: Bristol-Myers Squibb (Inst)

Maarten F. Bijlsma

Consulting or Advisory Role: Servier

Research Funding: Celgene

Travel, Accommodations, Expenses: Servier

Mark I. van Berge Henegouwen

Consulting or Advisory Role: Medtronic (Inst), Johnson & Johnson (Inst), Mylan (Inst)

Research Funding: Olympus (Inst), Stryker (Inst)

Travel, Accommodations, Expenses: Johnson & Johnson

Hanneke W.M. van Laarhoven

Honoraria: Lilly/ImClone

Consulting or Advisory Role: Lilly/ImClone, Nordic Group, Bristol-Myers Squibb, Servier

Research Funding: Bristol-Myers Squibb (Inst), Bayer Schering Pharma (Inst), Celgene (Inst), Janssen-Cilag (Inst), Lilly (Inst), Nordic Group (Inst), Philips Healthcare (Inst), Roche (Inst), Merck Sharp & Dohme (Inst), Servier (Inst)

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