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Clinical Trial Results

A Phase II Study with Lead-In Safety Cohort of 5-Fluorouracil, Oxaliplatin, and Lapatinib in Combination with Radiation Therapy as Neoadjuvant Treatment for Patients with Localized HER2-Positive Esophagogastric Adenocarcinomas

Gregg Shepard,[a,b] Edward R. Arrowsmith,[a,b] Patrick Murphy,[a,b] John H. Barton, Jr.,[a,b] James D. Peyton,[a,b] Mark Mainwaring,[a,b] Laura Blakely,[a,b] Noel A. Maun,[a,c] Johanna C. Bendell[a,b]

[a]Sarah Cannon Research Institute, Nashville, Tennessee, USA; [b]Tennessee Oncology, PLLC, Nashville, Tennessee, USA; [c]Florida Cancer Specialists, Venice, Florida, USA

Trial Information

- **Clinical Trials.gov Identifier**: NCT01769508
- **Sponsor(s)**: Sarah Cannon Research Institute
- **Principal Investigator**: Johanna C. Bendell
- **IRB Approved**: Yes

Lessons Learned

- Neoadjuvant 5-fluorouracil, oxaliplatin, and lapatinib in combination with radiation therapy is safe for neoadjuvant treatment for patients with localized human epidermal growth receptor 2-positive esophagogastric adenocarcinoma.
- Evaluation of this drug combination in a larger patient pool would allow for more accurate analysis of its efficacy.

Abstract

Background. The optimal design of neoadjuvant chemoradiation for the treatment of localized esophagogastric cancers is the subject of much debate. In this nonrandomized trial, we evaluated neoadjuvant 5-fluorouracil (5-FU), oxaliplatin, and lapatinib in combination with radiation therapy as neoadjuvant treatment for patients with localized human epidermal growth receptor 2 (HER2)-positive esophagogastric adenocarcinomas.

Methods. Patients received neoadjuvant 5-FU (225 mg/m^2 continuous intravenous infusion, days 1–42), oxaliplatin (85 mg/m^2 intravenously [IV], days 1, 15, and 29), and lapatinib (six patients, 1,000 mg p.o., days 1–42; six patients, 750 mg p.o., days 1–42) plus radiation (1.8 Gy/day Monday through Friday for 50.4 Gy total). Following restaging, eligible patients underwent definitive resection, and pathologic response to neoadjuvant therapy was assessed. Planned enrollment was 42 patients. The primary endpoint was the pathologic complete response (pCR) rate.

Results. Twelve patients (median age 64 years; 67% male) received a median of 5.6 weeks of treatment (range: 1.1–8.4). The pCR rate was 8%; four of the 12 patients underwent tumor resection and one patient had a pCR, with pathologic partial response in the remaining three. The most common lapatinib-related adverse events included (all grades) nausea (67%) and diarrhea (58%), although these were all grade 1 or 2. Enrollment was halted due to low accrual.

Conclusion. The treatment regimen was determined to be safe. The study was terminated early due to low accrual. ***The Oncologist*** 2017;22:1152–e98

Discussion

Based on the potential efficacy of lapatinib in HER2 gastric tumors, this multi-institutional phase II trial was designed to assess lapatinib, 5-FU, and oxaliplatin in combination with radiation therapy for the neoadjuvant treatment of localized esophagogastric cancers in patients with no prior therapy for the disease. It was hypothesized that the pCR primary endpoint would be increased from 30%–50% in a study population of 30 patients. Twelve patients (median age 64 years; 67% male, 58% moderately differentiated, 83% esophageal, 100% HER2-positive) received a median of 5.6 weeks of treatment (range: 1.1–8.4). Four patients underwent tumor resection, and one of the four patients (25%) had a pCR. However, the number of patients evaluated here was too low to make an accurate comparison with other studies. Response Evaluation Criteria in Solid Tumors response assessment was performed for three patients,

Correspondence: Johanna C. Bendell, M.D., Sarah Cannon Research Institute, Tennessee Oncology, PLLC, 250 25th Avenue North, Suite 200, Nashville, Tennessee 37203, USA. Telephone: 615-329-7274; e-mail: jbendell@tnonc.com Received October 21, 2016; accepted for publication April 23, 2017; published Online First on August 1, 2017. http://dx.doi.org/10.1634/theoncologist.2017-0186

Table 1. Summary of clinical activity

Clinical activity	Number of patients (%)
Patients enrolled, *n*	12
Patients evaluable for primary efficacy, *n*	4
Lapatinib dose level	1,000 mg: 6 (50%) 750 mg: 6 (50%)
Evaluation method (primary)	Pathologic response
Response assessment—pCR	1 (8%)
Underwent surgery	4
pCR	1 (25%)
Median PFS (95% CI)	3.253 months (1.183, 6.768)
Median TTP (95% CI)	6.768 months (6.604, 6.965)
Median OS (95% CI)	Not reached

Abbreviations: CI, confidence interval; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; TTP, time to progression.

of whom two (67%) had at least a partial response. The most common lapatinib-related adverse events included nausea (67%) and diarrhea (58%). Enrollment was halted due to low accrual. Only 12 patients were accrued from February 2013 to December 2014, due partly to the low number of patients with HER2-positive gastroesophageal junction tumors. Evaluation of this drug combination in a larger patient pool would allow for more accurate analysis of its efficacy.

Trial Information	
Disease	Esophageal cancer
Stage of Disease/Treatment	Neoadjuvant
Prior therapy	None
Type of Study - 1	Phase II
Type of Study - 2	Single arm
Primary Endpoint	Pathologic complete response
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Time to progression
Secondary Endpoint	Overall survival
Secondary Endpoint	Toxicity
Investigator's Analysis	Active, but patient numbers too low for accurate comparison

Drug Information for Phase II Control Arm	
Drug 1	
Generic/Working name	Lapatinib
Trade name	Tykerb/Tyverb
Company name	GlaxoSmithKline (GSK)
Drug type	Small molecule
Drug class	HER-2/neu
Dose	750 mg and 1,000 mg (2 dose levels in safety lead in) milligrams (mg) per square meter (m^2)
Route	oral (p.o.)
Schedule of administration	Continuous p.o. dosing during radiation therapy
Drug 2	
Generic/Working name	5-fluorouracil
Trade name	Adrucil

Company name	Teva
Drug type	Antineoplastic/cytotoxic
Drug class	Antimetabolite
Dose	225 mg/m^2 milligrams (mg) per square meter (m^2)
Route	Continuous intravenous infusion
Schedule of administration	Days 1–42 during radiation therapy
Drug 3	
Generic/Working name	Oxaliplatin
Trade name	Eloxatin
Company name	Sanofi
Drug type	Antineoplastic/cytotoxic
Drug class	Platinum compound
Dose	85 mg/m^2 milligrams (mg) per square meter (m^2)
Route	IV

Patient Characteristics for Phase II Control Arm	
Number of patients, male	8
Number of patients, female	4
Stage	Not collected
Age	Median (range): 64 (42–74)
Number of prior systemic therapies	Median (range): 0
Performance Status: ECOG	0 — 8 1 — 4 2 — 3 — unknown —
Cancer Types or Histologic Subtypes	Esophageal adenocarcinoma: 10 Gastroesophageal junction adenocarcinoma: 2 (17%)

Primary Assessment Method for Phase II Control Arm	
Total Patient Population	
Number of patients screened	12
Number of patients enrolled	12
Number of patients evaluable for toxicity	12
Number of patients evaluated for efficacy	12
Evaluation method	Pathologic response—primary assessment
Response assessment OTHER	$n = 1$ (8%)
(Median) duration assessments PFS	3.253 months, confidence interval (CI): 95%
(Median) duration assessments TTP	6.768 months, CI: 95%
RECIST 1.1, Secondary Assessment	
Number of patients evaluated for efficacy	3
Evaluation method	RECIST 1.1
Response assessment PR	$n = 2$ (67%)
Response assessment SD	$n = 1$ (33%)

Adverse Events, Phase II Control Arm

	All Cycles						
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All Grades**
Anemia	84%	8%	8%	0%	0%	0%	16%
Platelet count decreased	84%	8%	8%	0%	0%	0%	16%
Leukocytes (total WBC)	92%	8%	0%	0%	0%	0%	8%
Nausea	33%	25%	42%	0%	0%	0%	67%
Diarrhea	42%	25%	33%	0%	0%	0%	58%
Vomiting	58%	25%	17%	0%	0%	0%	42%
Gastrointestinal-mucosal inflammation	67%	8%	17%	8%	0%	0%	33%
Mucositis/stomatitis (functional/symptomatic)	83%	17%	0%	0%	0%	0%	17%
Anorexia	83%	17%	0%	0%	0%	0%	17%
Potassium, serum-low (hypokalemia)	80%	0%	0%	20%	0%	0%	20%
Constipation	92%	8%	0%	0%	0%	0%	8%
Dehydration	92%	0%	8%	0%	0%	0%	8%
Taste alteration (dysgeusia)	92%	0%	8%	0%	0%	0%	8%
Dysphagia (difficulty swallowing)	92%	8%	0%	0%	0%	0%	8%
Musculoskeletal/soft tissue—fall	92%	0%	8%	0%	0%	0%	8%
Glucose, serum-high (hyperglycemia)	92%	0%	0%	8%	0%	0%	8%
Allergic reaction/hypersensitivity (including drug fever)	92%	0%	0%	8%	0%	0%	8%
Magnesium, serum-low (hypomagnesemia)	92%	8%	0%	0%	0%	0%	8%
Insomnia	92%	8%	0%	0%	0%	0%	8%
Musculoskeletal/soft tissue—myalgia	92%	8%	0%	0%	0%	0%	8%
Neuropathy: sensory	92%	8%	0%	0%	0%	0%	8%
Edema: limb	92%	0%	8%	0%	0%	0%	8%
Thrombosis/embolism (vascular access-related)	92%	0%	8%	0%	0%	0%	8%
Pruritus/itching	92%	8%	0%	0%	0%	0%	8%
Dermatology/skin—rash, generalized	92%	0%	0%	8%	0%	0%	8%
Dermatology/skin—maculo-papular rash	92%	0%	0%	8%	0%	0%	8%
Cardiac arrhythmia—sinus tachycardia	92%	8%	0%	0%	0%	0%	8%
Constitutional symptoms—temperature intolerance	92%	8%	0%	0%	0%	0%	8%
Weight loss	92%	0%	8%	0%	0%	0%	8%

Abbreviations: NC/NA, no change from baseline/no adverse event.

Assessment, Analysis, and Discussion

Completion	Study terminated before completion
Terminated Reason	Did not fully accrue
Investigator's Assessment	Active, but patient numbers too low for accurate comparison

Neoadjuvant chemoradiation therapy for patients with localized esophagogastric cancers has been the subject of much discussion and controversy, with conflicting results compared with surgery alone seen in previous randomized clinical trials [1–3]. Pathologic complete response (pCR) rates after neoadjuvant chemoradiation therapy are in the 25% range [1–3].

Approximately 22% of patients with gastric or gastroesophageal junction (GEJ) adenocarcinomas have tumors that are human epidermal growth factor receptor 2 (HER2)-positive [4]. The ToGA trial found that patients with HER2-positive gastric/GEJ adenocarcinomas had a significant improvement in overall survival (11.1 months to 13.8 months) when trastuzumab was added to the chemotherapy. Response rate and progression-free survival were improved (47% vs. 35% and 6.7 months vs. 5.5 months, respectively) [5].

Lapatinib is a tyrosine kinase inhibitor of EGFR and HER2. It is U.S. Food and Drug Administration approved in combination with capecitabine for first-line treatment of HER2-positive advanced or metastatic breast cancer. In vivo, lapatinib has shown antitumor activity in gastric cancer cell lines when combined with 5-fluorouracil (5-FU), cisplatin, oxaliplatin, or

paclitaxel [6, 7]. A recent phase III trial to assess potential benefit of lapatinib in combination with chemotherapy for the first-line treatment of HER2-positive metastatic gastric cancer showed that while overall survival was not improved with the addition of lapatinib, the response rate was significantly higher in the lapatinib arm [8]. Similarly, results of the TyTAN trial of paclitaxel with or without lapatinib as treatment for Asian patients with HER2-positive gastric cancer did not show improvement in overall survival [9].

Based on the potential efficacy of lapatinib in HER2 gastric tumors, we designed a multi-institutional phase II trial of lapatinib, 5-FU, and oxaliplatin in combination with radiation therapy for the neoadjuvant treatment of localized esophagogastric cancers in patients with no prior therapy for the disease. It was hypothesized that the pCR primary endpoint would be increased from 30%–50% in a study population of 30 patients. Twelve patients (median age 64 years; 67% male, 58% moderately differentiated, 83% esophageal, 100% HER2-positive) received a median of 5.6 weeks of treatment (range: 1.1–8.4). Four patients underwent tumor resection and one of the four patients (25%) had a pCR, which was similar to the pCR rates of previously reported studies [1–3]. However, the number of patients evaluated in the present study was too low to make an accurate comparison with other studies. Response Evaluation Criteria in Solid Tumors response assessment was performed for three patients, of which two (67%) had at least a partial response. The most common lapatinib-related adverse events included nausea (67%) and diarrhea (58%).

Enrollment was halted due to low accrual. Only 12 patients were accrued from February 2013 to December 2014, due partly to the low number of patients with HER2-positive gastroesophageal junction tumors. Evaluation of this drug combination in a larger patient pool would allow for more accurate analysis of its efficacy.

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Disclosures

The authors indicated no financial relationships.

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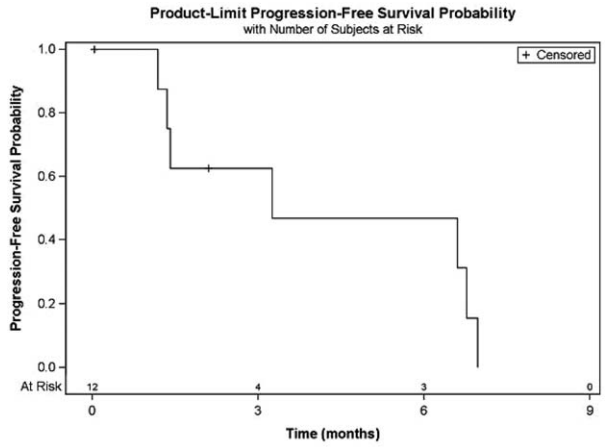
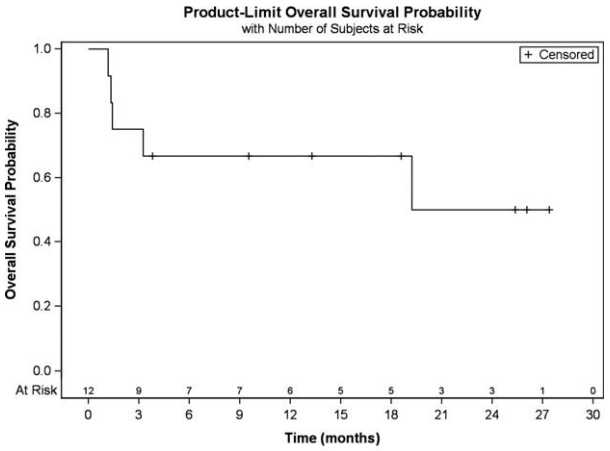
Figures and Tables



	All Patients
Sample Size	12
Median PFS (95% CI)	3.253 (1.183, 6.768)
Number Censored (pct.)	5 (41.67)
3-Month PFS Probability (95% CI)	0.6250 (0.2293, 0.8607)
6-Month PFS Probability (95% CI)	0.4688 (0.1199, 0.7629)

Figure 1. Progression-free survival ($n = 12$).

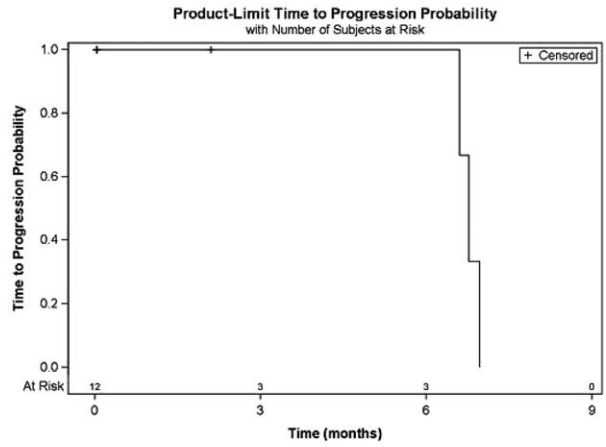
Abbreviations: CI, confidence interval; pct, percent; PFS, progression-free survival.



	All Patients
Sample Size	12
Median OS (95% CI)	NA
Number Censored (pct.)	7 (58.33)
6 Month OS Probability (95% CI)	0.6667 (0.3370, 0.8597)
12 Month OS Probability (95% CI)	0.6667 (0.3370, 0.8597)
18 Month OS Probability (95% CI)	0.6667 (0.3370, 0.8597)
24 Month OS Probability (95% CI)	0.5000 (0.1520, 0.7749)

Figure 3. Overall survival ($n = 12$).

Abbreviations: CI, confidence interval; NA, not applicable; OS, overall survival; pct, percent.



	All Patients
Sample Size	12
Median TTP (95% CI)	6.768 (6.604, 6.965)
Number Censored (pct.)	9 (75.00)

Figure 2. Time to progression ($n = 12$).

Abbreviations: CI, confidence interval; pct, percent; TTP, time to progression.

Table 2. Patient characteristics ($n = 12$)

Patient characteristics	Number of patients (%)
Patients enrolled	12
Median age, years (range)	64 (42–74)
Race	
Caucasian	12 (100%)
Sex	
Male	8 (67%)
Female	4 (33%)
Tumor type	
Esophageal	10 (83%)
GE junction	2 (17%)
HER2 FISH status	
HER2 positive	12 (100%)
HER2 IHC status	
2+	1 (8%)
3+	5 (42%)
Unknown	6 (50%)
Pathology	
Moderately differentiated	7 (58%)
Poorly differentiated	2 (17%)
Other	2 (17%)
Unknown	1 (8%)
Stage	
I	1 (8%)
II	4 (33%)
III	6 (50%)
IVa	1 (8%)

Abbreviations: FISH, fluorescent in situ hybridization; GE, gastroesophageal; HER2, human epidermal growth receptor 2; IHC, immunohistochemistry.