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See next page for additional authors

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Authors

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Paclitaxel With or Without Cixutumumab as Second-Line Treatment of Metastatic Esophageal or Gastroesophageal Junction Cancer: A Randomized Phase II ECOG-ACRIN Trial

Shannon Stockton[*,1,] , **Paul Catalano**[2], **Steven J. Cohen**[‡,3], **Barbara A. Burtness**[4], **Edith P. Mitchell**[5], **Efrat Dotan**[6,] , **Sam J. Lubner**[7], **Pankaj Kumar**[8], **Mary F. Mulcahy**[9], **George A. Fisher Jr.**[10], **Theodore L. Crandall**[11], **Al Benson**[9]

[1]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA
[2]Dana-Farber Cancer Institute, ECOG-ACRIN Biostatistics Center, Boston, MA, USA
[3]Jefferson Health System/Abington Memorial Hospital, Abington, PA, USA
[4]Yale University, New Haven, CT, USA
[5]Thomas Jefferson University, Philadelphia, PA, USA
[6]Fox Chase Cancer Center, Philadelphia, PA, USA
[7]University of Wisconsin, Madison, WI, USA
[8]Illinois CancerCare, Peoria, IL, USA
[9]Northwestern University, Evanston, IL, USA
[10]Stanford Cancer Center, Stanford University, Palo Alto, CA, USA
[11]University of Pittsburgh, Pittsburgh, PA, USA

*Corresponding author: Shannon Stockton, MD, Division of Hematology and Oncology, Department of Medicine, Vanderbilt University Medical Center, 2220 Pierce Ave, Nashville, TN 37232, USA. Email: shannon.somer@gmail.com
‡Principal Investigator: Steven J. Cohen, MD

Abstract

Background: Patients with advanced esophageal cancer carry poor prognoses; limited data exist to guide second-line therapy in the metastatic setting. Paclitaxel has been used yet is associated with limited efficacy. There is preclinical evidence of synergy between paclitaxel and cixutumumab, a monoclonal antibody targeting insulin-like growth factor-1 receptor. We conducted a randomized phase II trial of paclitaxel (arm A) versus paclitaxel plus cixutumumab (arm B) in the second-line for patients with metastatic esophageal or gastroesophageal junction (GEJ) cancers.

Methods: The primary endpoint was progression-free survival (PFS); 87 patients (43 in arm A, 44 in arm B) were treated.

Results: Median PFS was 2.6 months in arm A [90% CL 1.8-3.5] and 2.3 months in arm B [90% 2.0-3.5], P = .86. Stable disease was observed in 29 (33%) patients. Objective response rates for Arms A and B were 12% [90% CI, 5-23%] and 14% [90% CI, 6-25%]. Median overall survival was 6.7 months [90% CL 4.9-9.5] in arm A and 7.2 months [90% CL 4.9-8.1] in arm B, P = 56.

Conclusion: The addition of cixutumumab to paclitaxel in second-line therapy of metastatic esophageal/GEJ cancer was well tolerated but did not improve clinical outcomes relative to standard of care (ClinicalTrials.gov Identifier: NCT01142388).

Key words: esophageal; gastroesophageal junction; insulin-like growth factor-1 receptor; xixutumumab.

Lessons Learned

- The addition of insulin-like growth factor-1 receptor monoclonal antibody cixutumumab to paclitaxel was well-tolerated as second-line therapy in patients with metastatic esophageal or gastroesophageal junction (GEJ) carcinomas.
- The primary endpoint was not met, as this combination of agents did not significantly improve progression-free survival.
- Since the time of study completion, changes in the treatment landscape of esophageal and gastroesophageal junction cancer have highlighted the need for histology and biomarker-directed therapy.
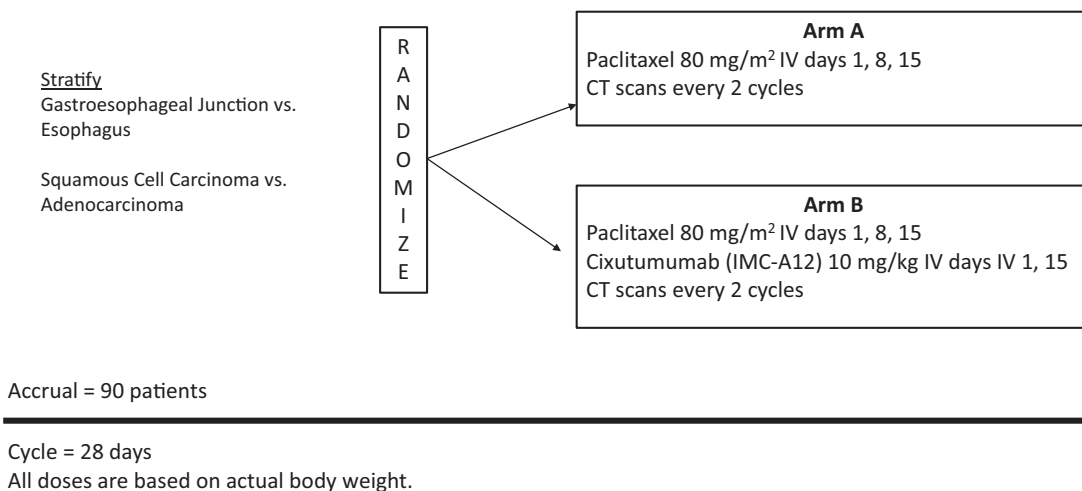
Figure 1. Study schema.

Discussion

This randomized, multicenter, phase II trial evaluated paclitaxel (arm A) versus paclitaxel plus cixutumumab (arm B) as second-line therapy in patients with metastatic esophageal or gastroesophageal junction (GEJ) cancers (Fig. 1). The study was conducted from September 2010 to October 2012 and analyzed in 2014. Each regimen was well tolerated, with >Grade 3 toxicities observed in 53% [90% CI, 38-66%] of arm A patients and 52% [90% CI, 39-65%] of arm B patients. There was no improvement in clinical outcomes. The primary endpoint of improved progression-free survival (PFS) was not met. Meaningful differences were not detected in secondary endpoints, including overall survival (OS) and overall response rate (ORR).

Taxanes have served as a cornerstone therapy for patients with platin-refractory metastatic esophageal and GEJ malignancies; however, treatment resistance is inevitable. As such, enhancing therapeutic potential of a single agent taxane is an appealing area of exploration. The insulin-like growth factor-1 receptor (IGF-1R) was of interest as such a therapeutic target, based on preclinical evidence for its role in treatment resistance in esophageal and GEJ tumors. In addition to the negative trial we report here, other studies of IGF-1R inhibition in gastrointestinal malignancies have also been negative. While IGF-1R inhibition is not currently advancing in studies in esophagogastric cancer, a number of other targets have now been validated in the clinic. Specifically, anti-angiogenic therapies directed against the VEGF receptor family have demonstrated meaningful clinical anti-tumor activity. Ramucirumab and paclitaxel gained FDA approval November 5, 2014 for the second-line treatment of unselected metastatic GEJ adenocarcinoma. Data from this trial were analyzed just prior to this regulatory licensure, based on data updates through July 15, 2014. It has also become clear that histology profoundly impacts treatment response in esophageal cancers. In squamous cell subtypes, immunotherapy has emerged as a second-line option, which was not standard of care at the time of enrollment on this trial. In adenocarcinomas, the development of biomarker-directed agents has created additional options for patients with tumors that overexpress certain protein markers (eg, Her2, FGFR2). Going forward, expanding the treatment landscape for refractory metastatic esophageal cancer will require special attention to histology and improved patient selection approaches.

Author disclosures and references available online.

TRIAL INFORMATION

Disease	Esophageal or GEJ cancer
Stage of disease/treatment	Stage IV
Prior therapy	One line of prior systemic therapy
Type of study	Phase II randomized
Primary endpoint	Median PFS
Secondary endpoints	Toxicity, median OS, ORR
Investigator's analysis	Level of activity did not meet planned end point
Additional details of endpoints or study design	Patients were randomized 1:1 to arm A (paclitaxel) or arm B (paclitaxel plus cixutumumab).

DRUG INFORMATION

	ARM A	ARM B
Generic/working name	Paclitaxel	Paclitaxel plus cixutumumab
Company name drug type	Taxol	Taxol, IMC-A12
Drug class	Taxane	Taxane, monoclonal antibody against IGF-1R
Dose	80 mg/m²	80 mg/m², 10 mg/kg
Route	IV	IV, IV
Schedule of administration	Days 1, 8, 15 of every 28 day cycle	Days 1, 8, 15 of every 28 day cycle; days 1, 15 of every 28 day cycle

PATIENT CHARACTERISTICS: OVERALL STUDY POPULATION

Number of patients, male	68
Number of patients, female	19
Stage	IV (87)
Age: median (range)	62 (40-89) years
Number of prior systemic therapies: median (range)	1
Performance status: ECOG	0: 34 1: 49 2: 4 3: 0 4: 0
Cancer types or histologic subtypes	Adenocarcinoma, 71; adenosquamous carcinoma, 2; squamous cell carcinoma, 14

PRIMARY ASSESSMENT METHOD: MEDIAN PROGRESSION-FREE SURVIVAL, ARM A

Number of patients enrolled	94
Number of patients evaluable for toxicity	87 (43 in Arm A, 44 in Arm B)
Number of patients evaluated for efficacy	84
Evaluation method	RECIST 1.1
Response assessment, CR	0 (0%)
Response assessment, PR	5 (11.6%)
Response assessment, SD	14 (32.6%)
Response assessment, PD	13 (30.2)
Median duration assessments, PFS	2.6 months (95% CI, 1.8-3.5)
Median duration assessments, OS	6.7 months (95% CI, 4.9-9.5)
Median duration of treatment	2.0 cycles

PRIMARY ASSESSMENT METHOD: MEDIAN PROGRESSION-FREE SURVIVAL, ARM B

Number of patients evaluable for toxicity	87 (43 in Arm A, 44 in Arm B)
Evaluation method	RECIST 1.1
Response assessment, CR	1 (2.3%)
Response assessment, PR	5 (11.4%)
Response assessment, SD	15 (34.1%)
Response assessment, PD	18 (40.9)
Median duration assessments, PFS	2.3 months (95% CI, 2.0-3.5)
Median duration assessments, OS	7.2 months (95% CI, 4.9-8.1)
Median duration of treatment	2.0 cycles

ASSESSMENT, ANALYSIS, AND DISCUSSION	
Completion	Study completed
Investigator's assessment	Level of activity did not meet planned end point

Our trial began enrollment on September 21, 2010 and closed to accrual on October 15, 2012. The data presented here represents updates through July 15, 2014. At the time when this study was conducted, IGF1-R was being investigated as a potential therapeutic target in various gastrointestinal malignancies. This randomized phase II trial assessed paclitaxel (arm A) and paclitaxel plus IGF1-R inhibitor cixutumumab (arm B) in the second-line setting for patients with esophageal or GEJ cancer. A total of 94 patients enrolled, with 7 patients deemed ineligible after enrollment. All 87 eligible patients were included in efficacy analyses, and the 84 patients who started treatment were included in safety analyses. Of the total study population, 40 patients had tumors of the esophagus, and 47 had GEJ tumors. By histology, there were 71 patients with adenocarcinoma, 2 with adenosquamous carcinoma, and 14 with squamous cell carcinoma. The majority of patients were male (78.2%) non-Hispanic White (94.3%) and possessed an ECOG PS of 1 (56.3%). The GEJ was the most common primary site represented (54%). Patients completed a median of 2.0 cycles of therapy in each arm. Toxicity rates were similar between arms (Table 1). Grade ≥3 toxicity rates were 53% in arm A [90% CI, 38-66%] and 52% [90% CI 39,-65%] in arm B; these were predominantly hematologic toxicities. Notably, 2 patients experienced grade 5 toxicities classified as treatment-related adverse events: one in arm A defined as death not otherwise specified, and one in arm B defined as death due to respiratory failure. Per intention-to-treat analysis, median mPFS for arm s A and B was 2.6 (90% CI, 1.8-3.5) and 2.3 (90% CI, 2.0-3.5) months, respectively ($P = 0.86$), and thus the primary endpoint was not met (Fig. 2). The median (mOS) for arms A and B were 6.7 (90% CI, 4.9-9.5) and 7.2 (90% CI, 4.9-8.1) months, respectively ($P = .56$). There were five partial responses in arm A, and five partial response and one complete response in arm B. Overall response rates were 11.6% in arm A and 13.7% in arm B. Despite the study treatment being relatively well-tolerated, we did not find meaningful clinical benefit from adding cixutumumab to paclitaxel in this patient population.

When this trial was designed, preclinical data suggested that IGF-1R may serve as a therapeutic target in esophageal cancer, with in vitro tumor models demonstrating overexpression of IGF-1R.[1,2] In numerous tumor types, including gastric cancer, IGF-1R overexpression has been associated with poor prognosis and chemoresistance.[3–5] Monoclonal antibodies against IGF-1R have since been studied in multiple gastrointestinal malignancies without evidence of clinical activity. In a phase II trial of cixutumumab with or without cetuximab in patients with cetuximab or panitumumab-refractory metastatic colorectal cancer, neither monotherapy nor combination therapy improved overall response rate meaningfully for patients.[6] Istiratumab, a monoclonal antibody targeting both IGF-1R Her3, was evaluated with and without gemcitabine and nab-paclitaxel in patients with metastatic pancreatic adenocarcinoma in the randomized phase II CARRIE trial. This study also failed to find a clinical benefit, with no meaningful difference in PFS between the trial arms.[7] Studies investigating the resistance mechanisms to IGF-1R inhibition have suggested downstream receptor tyrosine kinase (RTK) activation as a compensatory response. It has been proposed that antibody targeting of IGF-1R can bias the receptor to association with arrestin-1 and, thus, actually promote ERK1/2 signaling.[8] In theory, giving combination therapy to target downstream RTKs could augment the poor response rates seen to IGF-1R inhibitor monotherapy. However, in clinical trials of multikinase inhibitors targeting IGF-1R and downstream RTKs, it does not appear that there were meaningful improvement in objective response over other RTKs that do not target IGF-1R.[9,10]

In the time, since this study was completed, the treatment landscape for esophageal and GEJ cancers has evolved. Histology has emerged as a key consideration in formulating a treatment plan, as management of esophageal adenocarcinoma is now distinct from squamous cell carcinoma. Our study predominantly consisted of patients with adenocarcinoma as is observed mostly in Western patient populations. The preclinical data, however, suggest greater expression of IGF-1R in esophageal squamous cell carcinoma, suggesting that perhaps this might have been a more ideal patient population to test the agent.[11] While taxanes remain an acceptable second-line treatment option for patients with refractory metastatic esophageal cancer, immunotherapy, and biomarker-selected agents are now available as well.[12] In patients with adenocarcinoma, Her2, and FGFR2b are potentially actionable targets. For instance, based on the phase 2 trial DESTINY-Gastric02, patients with Her2-overexpressing GEJ cancers can now receive trastuzumab deruxtecan in the second-line setting.[13] Anti-VEGF targeting combination therapy has also emerged as standard of care therapy for GEJ adenocarcinoma based on the RAINBOW trial, a phase III randomized controlled trial of ramucirumab plus paclitaxel versus paclitaxel monotherapy.[14] In patients with squamous cell esophageal cancers, immunotherapy is now widely used in the second-line setting, with nivolumab approved regardless of irrespective of tumor PD-L1 status and pembrolizumab approved in patients with tumor PD-L1 expression levels of CPS of ≥10.[15,16] Despite these advances, the prognosis of patients with metastatic esophageal and GEJ cancer remains poor; there remains a need to continue to look for novel targets and tolerable therapeutics for these targets.

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Conflict of Interest

Sam J. Lubner reported consulting for Elephas Bio and research support from AstraZeneca, Iincyte, and BMS. Al Benson reported consulting or advisory role for Bristol-Myers Squibb DMC, Novartis DMC, Pfizer, Therabionic, Mirati Therapeutics, GSK, Tempus, Boehringer-Ingelheim, Astrellas DMC, Mirati, and AM Immunotech and research funding from ITM, Elevar Therapeutics INC, Merk Sharp and Dohme LLC, ST Pharm CO Ltd, The Nathan Cummings Foundation, and Cardiff Oncology. The other authors indicated no financial relationships.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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FIGURES AND TABLES

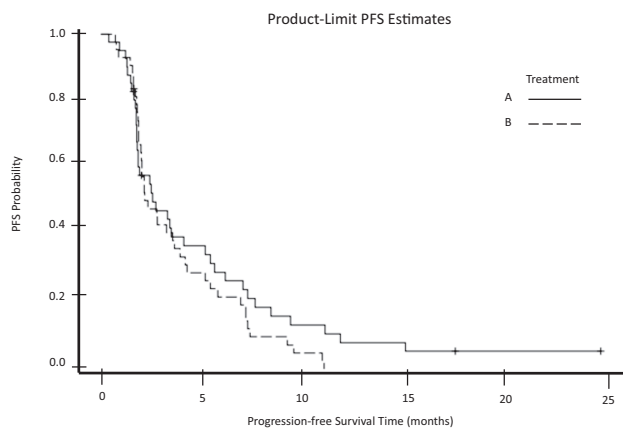**Figure 2.** Progression-free survival (PFS) by arm.

Table 1. Toxicity by arm (frequency)

Toxicity type	Treatment arm			
	A (*n* = 40)		B (*n* = 44)	
	Grade		Grade	
	1,2	≥3[a]	1,2	≥3[a]
Hematologic				
Anemia	28	4	27	4
White blood cell count decreased	11	2	15	6
Lymphocyte count decreased	13	8	12	8
Neutrophil count decreased[b]	8	3	10	8
Platelet count decreased	6	—	10	1
Constitutional				
Fatigue	26	3	27	1
Pruritis	3	—	5	—
Weight loss	8	—	8	1
Myalgia	1	1	5	—
Dizziness	2	—	5	—
Anorexia	7	—	12	—
Gastrointestinal				
Constipation	4	—	2	—
Diarrhea	8	—	10	—
Mucositis	2	—	3	2
Nausea	8	1	13	1
Vomiting	6	—	8	2
Alanine aminotransferase increased	5	—	4	—
Alkaline phosphatase increased	5	—	10	—
Aspartate aminotransferase increased	5	—	8	—
Dysgeusia	1	—	5	—
Electrolyte abnormality				
Hypocalcemia	—	—	5	—
Hypokalemia	3	1	3	—
Hypomagnesemia	5	—	6	—
Hyponatremia	3	—	8	1
Hypophosphatemia	2	2	2	1
Endocrine				
Glucose intolerance	3	—	4	1
Hyperglycemia	9	2	15	5
Dermatologic				
Acneiform rash	1	—	5	—
Maculopapular rash	2	1	8	—
Other				
Peripheral sensory neuropathy	13	1	15	1
Edema of limbs	4	—	—	—
Alopecia	13	—	12	—
Visual flashing lights	—	—	7	—

[a]One treatment-related Grade 5 event was observed in each arm - death not otherwise specified in arm A, and death due to respiratory failure in arm B.
[b]No neutropenic fever was observed.