

## Phase II Study of Irinotecan Plus Panitumumab as Second-Line Therapy for Patients with Advanced Esophageal Adenocarcinoma

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### TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT00836277
- **Sponsor(s):** Amgen
- **Principal Investigator:** Harry Yoon
- **IRB Approved:** Yes

### LESSON LEARNED

- Panitumumab plus irinotecan is not active for the treatment of esophageal adenocarcinoma.

### ABSTRACT

**Background.** Esophageal adenocarcinoma (EAC) is a lethal cancer with increasing incidence. Panitumumab (Pa) is a fully humanized IgG2 monoclonal antibody against human EGFR. Cetuximab (Cx) combined with irinotecan (Ir) is active for second-line treatment of colorectal cancer. This phase II study was designed to evaluate Pa plus Ir as second-line therapy for advanced EAC.

**Methods.** The primary endpoint was response rate (RR). Patients with one prior treatment were given Pa 9 mg/m<sup>2</sup> on day 1 and Ir 125 mg/m<sup>2</sup> on days 1 and 8 of each 21-day cycle. Inclusion criteria were confirmed EAC, measurable disease, no prior Ir or Pa, performance status <2, and normal organ function.

**Results.** Twenty-four patients were enrolled; 18 were eligible and evaluable. These patients were all white, with a median age of 62.5 years (range, 33–79 years), and included 15 men and 3 women. The median number of cycles was 3.5. The most common grade 1–2 adverse events were fatigue, diarrhea, anemia, leukopenia, and hypoalbuminemia. Grade 3–4 adverse events included hematologic, gastrointestinal, electrolyte, rash, fatigue, and weight loss. The median follow-up was 7.2 months (range, 2.3–14 months). There were no complete remissions. The partial response rate was 6% (1/18; 95% confidence interval [CI], 0.01–0.26). The clinical benefit (partial response [PR] plus stable disease [SD]) rate was 50%. The median overall survival was 7.2 months (95% CI, 4.1–8.9) with an 11.1% 1-year survival rate. The median progression-free survival was 2.9 months (95% CI, 1.6–5.3).

**Conclusion.** Irinotecan and panitumumab as second-line treatment for advanced EAC are not active. *The Oncologist* 2018;23:1004–e102

### DISCUSSION

To our knowledge, this is the first study to evaluate panitumumab in combination with irinotecan as second-line treatment for advanced esophageal adenocarcinoma.

The primary objective of this study was to evaluate the effect of panitumumab and irinotecan on the response rate of patients with EAC. A Simon two-stage design [11] was used with a power of 80% and a type I error of 0.05. The optimal two-stage design [12] to test the null hypothesis that  $p \leq .100$  versus the alternative that  $p \geq .250$  had an expected sample size of 24.66 and a probability of early termination of 0.734. If the drug was actually not effective, there was a 0.048 probability of concluding that it was (the target for this value was 0.050). If the drug was actually effective, there was a 0.200 probability of concluding that it was not (the target for this value was 0.200). After testing the drug on 18 patients in the first stage, the trial would be terminated if 2 or fewer had a partial or complete response. If the trial proceeded to the second stage, a total of 43 patients would be enrolled. If the total number responding were less than or equal to 7, the drug would be rejected.

Based on our findings, use of panitumumab in combination with irinotecan is not indicated for advanced EAC. No

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unexpected adverse events occurred, and toxicity of this two-drug combination was compatible with the safety profile of each drug. However, only one patient had a partial response, whereas 2 of 18 patients with responses were required to declare the trial of interest. Therefore, the trial was terminated because of not meeting the criteria for stage 2, and this combination is not recommended.

#### Adverse events

Adverse event	Grade 1–2, <i>n</i>	Grade $\geq$ 3, <i>n</i>
Anorexia	3	0
Nausea	8	1
Vomiting	1	2
Abdominal pain	2	1
Constipation	1	0
Diarrhea	6	8
Neutropenia	5	2
Thrombocytopenia	3	1
Anemia	12	1
Hepatic toxicity	5	0
Neurological toxicity	4	0
Allergic reaction	1	0
Fatigue	8	2
Cutaneous toxicity	8	1
Dyspnea	2	0
Asthenia	3	0
Electrolyte imbalance	8	2

#### TRIAL INFORMATION

Disease	Esophageal cancer
Stage of Disease/Treatment	Metastatic/advanced. This study accrued patients between 2007 and 2010
Prior Therapy	One prior regimen
Type of Study - 1	Phase II
Type of Study - 2	Single-arm
Primary Endpoint	Overall response rate
Secondary Endpoint	Overall survival
Investigator's Analysis	Level of activity did not meet planned endpoint

#### DRUG INFORMATION

<b>Drug 1</b>	
Generic/Working Name	Panitumumab
Company Name	Amgen Pharmaceuticals
Drug type	Antibody
Drug Class	
Dose	9 milligrams (mg) per kilogram (kg)
Route	IV
Schedule of Administration	Patients received panitumumab 9 mg/kg on day 1 and irinotecan 100 mg/m <sup>2</sup> on days 1 and 8 of each 21-day cycle for a maximum of six cycles. For patients without progression after six cycles, panitumumab alone was continued at the same dose and schedule until disease progression. Panitumumab was administered intravenously by an infusion pump through a peripheral line or indwelling catheter over 1 hour $\pm$ 15 minutes.
<b>Drug 2</b>	
Generic/Working Name	Irinotecan
Company Name	Pfizer
Drug Type	cytotoxic chemotherapy
Drug Class	
Dose	100 milligrams (mg) per squared meter (m <sup>2</sup> ); irinotecan 100 mg/m <sup>2</sup> on days 1 and 8 of each 21-day cycle to a maximum of 6 cycles
Route	IV
Schedule of Administration	irinotecan 100 mg/m <sup>2</sup> on days 1 and 8 of each 21-day cycle to a maximum of 6 cycles

PATIENT CHARACTERISTICS	
Number of Patients, Male	15
Number of Patients, Female	3
Age	Median (range): 62.5 (33–79)
Number of Prior Systemic Therapies	Six patients received prior radiation, 13 received prior surgery, and 13 patients received prior chemotherapy.
Performance Status: ECOG	0 — 14 1 — 4 2 — 0 3 — 0 Unknown — 0

PRIMARY ASSESSMENT METHOD	
Title	Total Patient Population
Number of Patients Screened	24
Number of Patients Enrolled	18
Number of Patients Evaluable for Toxicity	18
Number of Patients Evaluated for Efficacy	18
Evaluation Method	RECIST 1.1
Response Assessment PR	<i>n</i> = 1 (6%)
Response Assessment SD	<i>n</i> = 8 (44%)
Response Assessment PD	<i>n</i> = 9 (50%)
(Median) Duration Assessments PFS	2.9 months
(Median) Duration Assessments OS	7.2 months

ADVERSE EVENTS		
Adverse event	Grade 1–2, <i>n</i>	Grade ≥3, <i>n</i>
Anorexia	3	0
Nausea	8	1
Vomiting	1	2
Abdominal pain	2	1
Constipation	1	0
Diarrhea	6	8
Neutropenia	5	2
Thrombocytopenia	3	1
Anemia	12	1
Hepatic toxicity	5	0
Neurological toxicity	4	0
Allergic reaction	1	0
Fatigue	8	2
Cutaneous toxicity	8	1
Dyspnea	2	0
Asthenia	3	0
Electrolyte imbalance	8	2

ASSESSMENT, ANALYSIS, AND DISCUSSION	
Completion	Study completed
Investigator's Assessment	Level of activity did not meet planned endpoint

Esophageal cancer is the eighth most common cancer worldwide and sixth most common cause of cancer-related death. Despite the increased incidence of esophageal adenocarcinoma (EAC) in the U.S., effective treatment is still lacking, and median survival of patients presenting with advanced disease is less than 1 year [4]. The standard treatment combination of infusional 5-fluorouracil and cisplatin was developed in an era when squamous histology was predominant. It achieves a response rate and median survival of approximately 40% and 6 months, respectively. Modern two- and three-drug regimens used for adenocarcinoma may include oxaliplatin, fluoropyrimidines, taxanes, and anthracyclines [13–17]. Patients with overexpression of the HER2 receptor on their tumors also benefit from the addition of trastuzumab to chemotherapy [18]. Median survival may reach 10–12 months.

Irinotecan is another agent studied in the management of advanced EAC, either given alone or in combination as part of a platinum doublet. Following on the success of this drug for the treatment of advanced colorectal cancer, several studies for esophageal cancer were undertaken by the groups at Memorial Sloan Kettering and MD Anderson [19]. The combination of irinotecan with cisplatin has been tested in 21 treatment-naive patients with advanced esophageal cancer. The objective response rate with this regimen was 53% and did not vary with histology. The toxicity profile was acceptable. A trial using 125 mg/m<sup>2</sup> irinotecan alone for 4 weeks followed by a 2-week rest had a 14% response rate in a heavily pretreated population.

Colon cancer studies showed that adding anti-epidermal growth factor receptor (anti-EGFR) inhibitors to irinotecan improved progression-free survival (PFS; 4.1 months in combined group vs. 1.5 months in irinotecan group;  $p < .001$ ) of irinotecan-resistant metastatic colorectal cancer. Patients in the combined group also had a higher response rate (RR; 22.9% vs. 10.8%;  $p = .007$ ). *KRAS* mutations have been associated with resistance to anti-EGFR therapy in patients with metastatic colon cancer. *KRAS* was not a known panitumumab resistance factor at the time this study was carried out, although data later emerged to show that panitumumab should not be administered in patients with *KRAS*-mutated colorectal cancer. Notably, *KRAS* mutations are extremely rare in esophageal cancer (2%).

Given these data, we studied the combination of irinotecan and panitumumab as second-line treatment for advanced EAC. Panitumumab is a fully humanized monoclonal antibody against EGFR approved by the U.S. Food and Drug Administration and the European Medicines Agency for the treatment of colorectal cancer. The dosing regimen was adapted from schedules of irinotecan used in esophageal cancer (EC) and panitumumab used in colorectal cancer.

The results demonstrated poor activity of our regimen, resulting in cessation of the study at the completion of stage 1. Toxicities were as expected.

This is one of several studies that show no benefit from the addition of anti-EGFR monoclonal antibodies to chemotherapy for EAC. In the setting of local disease, RTOG 0436, which was definitive chemoradiotherapy (CRT) without surgery, was a negative trial for the efficacy of cetuximab combined with CRT. The REAL-3 trial evaluated epirubicin, oxaliplatin, and capecitabine (EOC) chemotherapy with or without panitumumab in metastatic and/or recurrent gastroesophageal (GE) junction cancer [14]. Median overall survival (OS) was 11.3 months with

EOC compared with 8.8 months with EOC + panitumumab (hazard ratio [HR], 1.37; 95% confidence interval [CI], 1.07–1.76;  $p = .013$ ). Median PFS was 7.4 and 6.0 months, respectively (HR 1.22; 95% CI, 0.98–1.52;  $p = .068$ ). The EXPAND trial evaluated cetuximab plus capecitabine/cisplatin for the treatment of advanced, nonresectable GE junction cancer [20]. Cetuximab did not prolong OS (9.4 vs. 10.7 months), PFS (4.4 vs. 5.6 months), or RR (29 vs. 30%). In the phase II CALGB 80403/ECOG 1206 trial, the efficacy of cetuximab was tested with various combinations of cytotoxic chemotherapy [21]. The most efficacious combinations were epirubicin/cisplatin/infusional 5-FU/cetuximab and cetuximab/FOLFOX with overall response rates of 58% and 54%, respectively. Several phase II trials investigated the activity of the EGFR tyrosine kinase inhibitors, erlotinib and gefitinib, in advanced EAC refractory to cytotoxic chemotherapy. In each study, the response rate reached 10%, and median survival was 2–3 months.

To our knowledge, this is the first study to evaluate panitumumab in combination with irinotecan as second-line treatment for advanced esophageal adenocarcinoma. Based on our findings, the use of panitumumab in combination with irinotecan is not indicated for advanced EAC. No unexpected adverse events occurred, and toxicity of this two-drug combination was compatible with the safety profile of each drug. However, only one patient had a partial response. Therefore, the trial was terminated because it did not meet the criteria for stage 2, and this combination is not recommended.

Despite the negative findings of our study, some other completed studies of agents directed at other targets for advanced EAC showed promise but with mixed results. Monoclonal antibodies against c-met/hepatocyte growth factor (HGF) complex (rilotumumab) and VEGF-A (bevacizumab) were evaluated in randomized trials in combination with cytotoxic chemotherapy. The AVAGAST trial did not reach the efficacy endpoint, whereas RILOMET-1 unexpectedly revealed a worse outcome in the experimental arm [22, 23]. Other approaches to angiogenesis inhibition were also studied. In particular, the REGARD and RAINBOW-2 trials showed activity of ramucirumab, an antibody against VEGFR2 Kinase insert domain receptor (KDR), in advanced disease [24, 25]. Perhaps the most promising development is in the area of immune checkpoint inhibition. Immunotherapy is active in many cancers, and the recently published KEYNOTE-028 trial demonstrates this in esophageal cancer as well [26]. In this multi-cohort, phase Ib trial, 23 previously treated patients with programmed cell death ligand 1-positive tumors (78% squamous cell carcinoma (SCC)) were given single-agent pembrolizumab. The overall response rate was 30% with a median duration of response of 15 months. In aggregate, this cohort of trials, despite several negative studies, suggests that real progress is being made in the treatment of advanced esophageal cancer. This is a basis for hope that advancements will continue.

#### DISCLOSURES

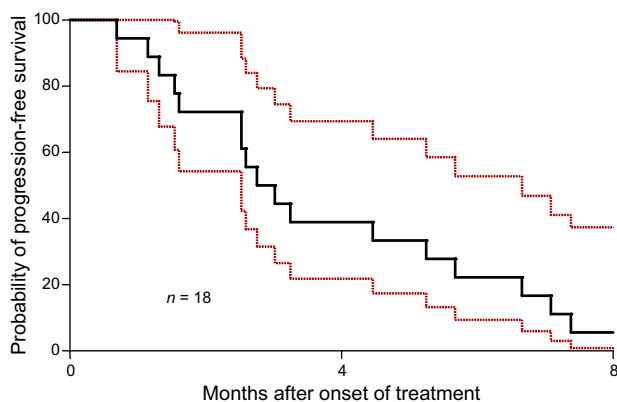
**Harry Yoon:** Astellas, LSK BioPharma, Merck, Eli Lilly & Co., Genentech (RF); **Michael K. Gibson:** Amgen (C/A), Bristol-Myers Squibb (H), NCCN (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

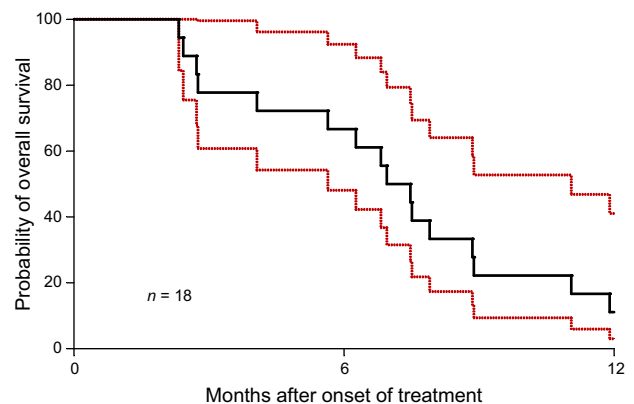
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## FIGURES AND TABLES



**Figure 1.** Kaplan-Meier estimation of progression-free survival (95% CI).



**Figure 2.** Kaplan-Meier estimation of overall survival (95% CI).

**Table 1.** Baseline patient characteristics

Characteristic	n (%)
Age, years, median (range)	62.5 (33–79)
Sex	
Male	15 (83)
Female	3 (17)
Race, white	18 (100)
Tumor location	
Esophagus	10 (56)
EGJ	8 (44)
PS, 0–1	18 (100)
Extent of disease	
Locally advanced	6 (33)
Metastatic	12 (67)

Abbreviations: EGJ, gastroesophageal junction; PS, performance score.

**Table 2.** Multivariate analysis of progression-free survival

Factor	HR	95% CI of HR	p value
Age ( $\geq$ 62.5 yrs vs. $<$ 62.5 yrs)	3.04	0.88–10.51	.079
Gender (female vs. male)	1.74	0.42–7.19	.445
Location (lower vs. NOS)	3.51	0.98–12.58	.054

Abbreviations: CI, confidence interval; HR, hazard ratio; NOS, not otherwise specified.

**Table 3.** Multivariate analysis of overall survival

Factor	HR	95% CI of HR	p value
Age ( $\geq$ 62.5 yrs vs. $<$ 62.5 yrs)	1.36	0.44–4.17	.594
Gender (female vs. male)	0.83	0.19–3.67	.81
Location (lower vs. NOS)	1.59	0.52–4.9	.418

Abbreviations: CI, confidence interval; HR, hazard ratio; NOS, not otherwise specified.

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