CONFIDENTIAL

Clinical Study Report to the Investigators

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E2208

Randomized Phase II Study of Paclitaxel With or Without the Anti-IGF-IR Mab Cixutumumab (IMC-A12) as Second Line Treatment for Patients with Metastatic Esophageal or GE Junction Cancer

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1 Summary

E2208 was a phase II study to evaluate the progression-free survival (PFS) of patients with metastatic esophageal or GE junction cancer treated with paclitaxel alone, Arm A or paclitaxel plus cixutumumab (IMC-A12), Arm B. This study was activated on September 21, 2010 and closed to accrual on October 15, 2012 with 94 patients. Data updated through July 15, 2014 were analyzed. Per protocol, the efficacy analyses include 87 eligible patients and the safety (toxicity) analysis includes all patients who started treatment (N=84).

The overall median progression-free survival (PFS) for all eligible patients was 2.6 (90% CL [2.0-3.5]) months. Median PFS for Arms A and B were 2.6 (90% CL [1.8-4.1]) and 2.3 (90% CL [2.0-3.6]) months, respectively. The one-sided stratified log rank test indicates no significant PFS differences between two treatment comparisons A vs. B (stratified by strata at randomization, gastroesophagealjunction vs.esophagus, squamous cell carcinoma vs.adenocarcinoma, with P value of 0.85).

The median overall survival for all eligible patients was 6.4 (90% CL, 5.0-7.9) months. Median OS for Arms A and B were 6.5 (90% CL, 4.6-9.5) and 6.4 (90% CL, 4.9-8.0) months, respectively. The one-sided stratified log rank tests indicate no significant OS differences between two comparisons (A vs. B), with P value of 0.50.

Overall, one patient experienced a complete response (CR) in Arm B and no patient experienced CR in Arm A. The objective response rates (CR+PR) for Arm A and B were 12% [90% CI: 5%, 23%], and 14% [90% CI: 6%, 25%], respectively.

The Grade 3+ toxicity proportions for Arms A and B were 53% [90% CI: 38%, 66%], and 52% [90% CI: 39%, 65%], respectively.

In conclusion, the addition of cixutumumab to paclitaxel in second-line therapy of metastatic esophageal/GE junction cancer was well tolerated but did not improve clinical outcomes.

2 Introduction

The incidence of esophageal cancer is rising in the United States and the prognosis remains poor. In the treatment of advanced disease, tumors arising in the esophagus, GE junction, and stomach are often treated in a similar manner. As initial therapy, two or three drug combinations have often been utilized. Cisplatin plus 5-FU has been considered a standard first line therapy. Limited data exist regarding choice of treatment in the 2nd-line metastatic disease setting. Paclitaxel has been tested in patients with advanced esophageal cancer. Paclitaxel has been tested in patients with advanced esophageal cancer. In refractory patients, data with paclitaxel are more limited. Given the limited benefit of second-line chemotherapy in metastatic esophagus cancer, the preclinical rationale for inhibiting IGF1-R in this disease, and evidence of preclinical synergy with the combination of cixutumumab and paclitaxel, we proposed the current randomized phase 2 trial of paclitaxel alone versus paclitaxel plus cixutumumab.

3 Objectives

The objectives of the trial were to:

- evaluate the progression-free survival of paclitaxel plus Cixutumumab versus paclitaxel alone as second-line therapy in patients with metastatic esophagus or GE junction cancer.
- evaluate the overall survival of paclitaxel plus Cixutumumab versus paclitaxel alone in this patient population.
- evaluate the response rate of paclitaxel plus Cixutumumab versus paclitaxel alone in this patient population.
- evaluate the toxicity of Cixutumumab plus paclitaxel versus paclitaxel alone in this patient population.

4 Eligibility

To be eligible for this study, the following were required:

- > =18 years of age

- life expectancy ≥ 12 weeks
- not pregnant or breast-feeding
- metastatic disease of the esophagus or gastroesophageal junction
- have received and progressed on one and only one line of prior systemic therapy
- no prior taxane or anti-IGFR therapy
- normal organ and marrow function
- ECOG performance status 0-2
- fasting serum glucose<160 mg/dL (8.8 mmol/L) or ≤ ULN, and hemoglobin A1C ≤7% (0.07 SI units) within 14 days of registration
- no allergic reactions attributed to compounds of similar chemical or biologic composition to cixutumumab (IMC-A12)
- no poorly controlled diabetes mellitus
- no recent major surgery, hormonal therapy (other than replacement) or chemotherapy, within 4 weeks prior to entering the study
- registration no fewer than 28 days from last chemotherapy

5 Treatment

Doses were based on actual body weight.

Arm A:

Paclitaxel was administered intravenously over one hour at a dose of 80 mg/m² on days 1,8,15 of every 28 day cycle.

Arm B: Cixutumumab (IMC-A12) was administered intravenously over one hour at a dose of 10 mg/kg days 1, and 15 of every 28 day cycle.

Paclitaxel was administered intravenously over one hour at a dose of 80 mg/m² on days 1,8,15 of every 28 day cycle.

NOTE: Cixutumumab (IMC-A12) was administered prior to chemotherapy. All patients were treated until progression or until they were unable to tolerate further therapy.

6 Statistical Methods

6.1 Design Summary

The primary endpoint was progression-free survival (PFS). Ninety patients were to be equally randomized between Arm A (paclitaxel alone) or Arm B (paclitaxel plus cixutumumab (IMC-A12)) using a permuted blocks within strata algorithm with stratification factors: gastroesophageal junction versus esophagus and squamous cell carcinoma versus adenocarcinoma. The primary objective was to compare the regimens via a 0.10 level one-sided log rank test after 15 months of accrual and 12 months of follow-up time (27 months total study time after the start of accrual). Assuming the control (Arm A) median PFS of 2 months this study had over 90% power to detect an alternative median PFS of 3.5 months in the experimental arm (Arm B).

The study was also monitored for potential futility stopping using an early look at PFS after 26 patients per arm had been treated for 2 cycles (2 month disease evaluation). After the first 26 patients on each arm had submitted disease evaluation case report forms after 2 cycles, PFS was to be evaluated using a binomial comparison of the proportion of PFS events at 2 months. If the observed proportion of PFS events in the experimental arm (Arm B) was higher than the observed proportion of PFS events in the control arm (Arm A) consideration would given to closing the study for futility. If the control median PFS was 3 months and the experimental median PFS was as low as 2 months, there was 79.2% probability of observing a higher proportion of PFS events in the experimental arm at 2

months. If the experimental median PFS was as low as 1.5 months, there was 94.1% probability of observing a higher proportion of PFS events in the experimental arm. At an accrual rate of 6 patients per month with two months of follow-up this monitoring analysis was projected to occur at roughly 11 months following the start of accrual.

With 45 expected patients on each randomized arm the study had sufficient precision to provide 90% confidence intervals on toxicity no wider than 26.1%. Additionally, there was greater than 60% probability of observing one or more rare (true probability 2%) toxicities on either treatment arm and greater than 75% probability of observing one or more rare (true probability 3%) toxicities on either treatment arm. Formal comparison of toxicity rates between the arms was not a goal of this trial as the sample size provided sufficient power to detect only relatively large differences in adverse events.

6.2 Statistical Methods

Progression-free survival (PFS) is defined as the time from randomization to progression or death without evidence of progression. For cases without documentation of progression, follow-up was censored at the date of last disease assessment without progression, unless death occurred within a short period of time (4 months) following the date last known progression-free, in which case the death was counted as an event, or in the case of death within 4 months of randomization in the absence of disease evaluation before that time. Overall survival (OS) is defined as the time from randomization until death (event), or censored at last date known alive. OS and PFS were estimated using the Kaplan-Meier method[1], with 90% confidence intervals calculated using Greenwood's formula, and compared by the log rank test[2]. Cox regression models[3] of OS and PFS were utilized to provide hazard ratio estimates and associated inferences with use of the Wald test.

Objective response rates and 90% confidence intervals (CIs) were reported. Toxicities were assessed using the NCI Common Toxicity Criteria (CTC) Version 3.0. Categorical patient characteristics were compared using Fisher's exact tests. Continuous patient characteristics were compared using Wilcoxon rank sum tests.

Unless otherwise specified, all P-values reported are for two-sided significance tests and P-values under 0.05 are considered significant.

7 Results

7.1 Administrative Information

This study was activated on September 21, 2010 and closed to accrual on October 15, 2012 with 94 patients. Data updated through July 15, 2014 were analyzed.

Table 1 shows accrual status by ECOG-ACRIN institution. Table 2 provides case status. There were 7 ineligible cases (detailed in Table 3). There were 10 cases who never started assigned therapy (detailed in Table 4). Figure 2 summarizes case status. Per protocol, the efficacy analyses include 87 eligible patients and the safety (toxicity) analysis includes all patients who started treatment (N=84). Table 5a and 5b summarizes concordance rates between stratification factors at randomization and corresponding information on on-study forms among eligible patients.

7.2 Monitoring History

Per protocol, this study was monitored for potential futility stopping using an early look at PFS after 26 patients per arm had been treated for 2 cycles (2 month disease evaluation). On June 11, 2012, after the first 26 Intent-to-Treat patients on each arm had submitted disease evaluation case report forms after 2 cycles, PFS was evaluated in terms of the proportion of PFS events at 2 months. The 2-month PFS rate in the experimental arm (Arm B) was 0.624 and the 2-month PFS rate in the control arm (Arm A) was 0.508. In addition, at that time, twenty-three grade 3 adverse events had been reported: 12 on Arm A and 11 on Arm B. Five grade 4 adverse events had been reported: 2 on Arm A and 3 on Arm B. One grade 5 treatment related adverse event (case 22032) was reported on Arm B. In addition, seven patients (Arm A: cases 22028,22030; Arm B: 22018,22022,22027,22052,22067) experienced lethal toxicities reported via AdEERs, mostly related to underlying cancer, not treatment related and they were reflected in the PFS analysis. A study team and toxicity monitor conference call was held on June 12, 2012 to review the adverse events

on this protocol. It was decided to continue the study as planned with continued close monitoring for adverse events and to collect more information on baseline laboratory values.

7.3 Patient Characteristics

Table 6 presents patient demographics and baseline patient characteristics at entry for all 87 eligible patients. The median age was 62 years (range 40-89), and the majority of patients were male (78.2%), non-Hispanic white (94.3%), primarily gastroesophageal junction (54%) and ECOG PS 1 (56.3%). Race, age, gender, primary site, histology, ECOG PS and disease status were not statistically different between the treatment arms.

7.4 Treatment

Table 7 provides the total number and the breakdown of the number of treatment cycles received by treatment arm. The median number of treatment cycles was 2 for both arms. Table 8 provides the breakdown of the reasons for treatment termination, the distribution of which did not vary significantly between the two arms (P =0.34, Fisher's exact test).

7.5 Objective Response to Treatment

Overall, as shown in Table 9a, one patient experienced a complete response (CR) in Arm B and no patient experienced CR in Arm A. Twenty-nine (33%) patients experienced stable disease (SD), and 31 (36%) patients experienced progressive disease (PD) as their best response evaluation. The objective response rates (CR+PR) for Arm A and B are 12% [90% CI: 5%, 23%], and 14% [90% CI: 6%, 25%], respectively. In addition, 16 patients were "unevaluable" for response (detailed reasons for unevaluability are listed in Table 9b).

7.6 Toxicity

Tables 10-11 tabulate the frequency and percentage, respectively, of grades 1/2, 3, 4, and 5, treatment-related toxicities. Results are presented by treatment arm for all 84 treated patients.

The Grade 3+ toxicity percentages for Arms A and B were 53% [90% CI: 38%, 66%], and 52% [90% CI: 39%, 65%], respectively.

There were 11 patients experiencing lethal toxicities reported via AdEERs, mostly related to underlying cancer, not treatment (detailed in Table 12). Only 2 (cases 22085, 22032) Grade 5 toxicities were listed in Table 10 because nine were considered not treatment related. One exception is case 22028 who reported death possibly due to treatment via AdEERs but identified as Death NOS on the case report form.

7.7 Progression-Free and Overall Survival

7.7.1 Progression-free Survival

Among 87 eligible cases, there were 3 cases who did not contribute to the PFS analysis (2 cases in Arm A and 1 case in Arm B did not have disease status information and were therefore excluded from the analysis). Among the 84 cases in the PFS analysis there were a total of 79 events. Figure 3 shows the overall Kaplan-Meier PFS curve. Figure 4 demonstrates PFS Kaplan-Meier curves by treatment arm. The overall median progression-free survival (PFS) for all eligible patients was 2.6 (90% CL [2.0-3.5]) months. Median PFS for Arms A and B were 2.6 (90% CL [1.8-4.1]) and 2.3 (90% CL [2.0-3.6]) months, respectively. The one-sided stratified log rank test indicates no significant PFS differences between two treatment arms A vs. B, with P value of 0.85.

Results for the Cox Regression models for PFS for all eligible patients are summarized in Table 14a. The model parameters presented are given in the form of hazard ratios along with 95% Confidence Limits (CL) and p-values. The hazard ratio for B vs. A is 1.3 (with A better) (95% CL, 0.8-2.0) (two-sided P=0.27, univariate Cox-Regression), not statistically significant. The results are consistent with the log-rank tests.

In the Cox Regression analysis, no influence of patients' age (over 62 vs. under 62), gender, race, histology (squamous cell carcinoma vs. adenocarcinoma/adenosquamous carcinoma) and primary site (other vs. GE junction) on PFS were observed in the univariate analysis (two-sided P>0.05, Cox-Regression). PS (1, 2 vs. 0) was found to

influence the prognosis of patients, with hazard ratio PS 1, 2 vs. 0 of 1.59 [95% CI: 1.01-2.50] (two-sided P=0.04, univariable Cox-Regression). The significant factor in univariate analyses was included in the multivariable Cox proportional-hazards model (model 2 in Table 14a). Potentially important demographic and disease characteristic variables, such as age and primary site were also included the multivariable analysis (model 3 in Table 14a). As shown in Model 1-3, treatment effect was not statistically significant, even after adjusting for PS and other potential important factors.

7.7.2 Overall Survival

As of this report, 70 total patients have died out of 87 eligible cases. Figure 5 shows the Kaplan-Meier overall survival curve. Figure 6 demonstrates OS Kaplan-Meier curves by treatment arm. The median overall survival for all eligible patients was 6.4 (90% CL, 5.0-7.9) months. Median OS for Arms A and B were 6.5 (90% CL, 4.6-9.5) and 6.4 (90% CL, 4.9-8.0) months, respectively. The one-sided stratified log rank tests indicate no significant OS differences between two arms (A vs. B), with P value of 0.50.

Results for the Cox Regression models for OS for all eligible patients are summarized in Table 14b. The model parameters presented are given in the form of hazard ratios along with 95% Confidence Limits (CL) and p-values. The hazard ratio for B vs. A is 1.1(with A better) (95% CL, 0.7-1.7) (two-sided P=0.83, univariate Cox-Regression), not statistically significant. The results are consistent with the log-rank tests.

In the Cox Regression analysis, no influence of patients' age (over 62 vs. under 62), gender, race, histology (squamous cell carcinoma vs. adenocarcinoma/adenosquamous carcinoma) and primary site (other vs. GE junction) on PFS were observed in the univariate analysis (two-sided P>0.05, Cox-Regression). PS (1, 2 vs. 0) was found to influence the prognosis of patients, with hazard ratio PS 1, 2 vs. 0 of 1.09 [95% CI: 1.04-1.14] (two-sided P=0.0001, univariate Cox-Regression). The significant factor in univariate analyses was included in the multivariable analysis of the Cox proportional-hazards model (model 2 in Table 14b). Potentially important demographic and disease characteristic variables, such as age and primary site were also included the multivariable analysis (model 3 in Table 14b). As shown in Model 1-3, treatment effect was not statistically significant, even after adjusting for PS and other potential important factors.

7.7.3 Intent-to-Treat Analysis

PFS and OS were also evaluated using all 94 patients, including those ineligible patients and patients who refused treatment.

The median overall PFS for all patients was 2.6 (95% CL [2.0-3.4]) months. Median PFS for Arms A and B were 2.6 (90% CL, 1.8-3.5) and 2.3 (90% CL, 2.0-3.5) months, respectively. The one-sided stratified log rank test indicates no significant PFS differences between two treatments A vs. B, with P value of 0.86.

The median overall survival for all patients was 6.7 (90% CL, 5.0-7.9) months. Median OS for Arms A and B were 6.7 (90% CL, 4.9-9.5) and 7.2 (90% CL, 4.9-8.1) months, respectively. The one-sided stratified log rank test indicates no significant OS differences between two treatments A vs. B, with P value of 0.56.

In the Cox Regression models for PFS, the hazard ratio B vs. A is 1.3 (95% CI, 0.8-2.0) (P=0.28, univariate Cox-Regression). In the Cox Regression models for OS, the hazard ratio B vs. A is 1.0 (95% CI, 0.6-1.6) (P=0.94, univariate Cox-Regression).

These analyses indicate that the overall conclusions of the OS and PFS comparisons are not affected by exclusion or inclusion of those ineligible patients and patients who refused treatment.

7.8 Second Malignancies

Two patients (both on Arm B) developed second primary cancers and details are shown in Table 15.

8 Conclusion

In summary, the overall median progression-free survival (PFS) for all eligible patients was 2.6 (90% CL [2.0-3.5]) months. Median PFS for Arms A and B were 2.6 (90% CL [1.8-4.1]) and 2.3 (90% CL [2.0-3.6]) months, respectively. The one-sided stratified log rank test indicates no significant PFS differences between the two treatment arms, with P value of 0.85.

The median overall survival for all eligible patients was 6.4 (90% CL, 5.0-7.9) months. Median OS for Arms A and B were 6.5 (90% CL, 4.6-9.5) and 6.4 (90% CL, 4.9-8.0) months, respectively. The one-sided stratified log rank tests indicate no significant OS differences between the two arms, with P value of 0.50.

Overall, one patient experienced a complete response (CR) in Arm B and no patient experienced CR in Arm A. The objective response rates (CR+PR) for Arm A and B were 12% [90% CI: 5%, 23%], and 14% [90% CI: 6%, 25%], respectively.

The Grade 3+ percentages toxicity for Arms A and B were 53% [90% CI: 38%, 66%], and 52% [90% CI: 39%, 65%], respectively.

In conclusion, the addition of cixutumumab to paclitaxel in second-line therapy of metastatic esophageal/GE junction cancer was well tolerated but did not improve clinical outcomes.

9 References

[1] Kaplan, E.L. and Meier P. Nonparametric estimation from incomplete observations. Journal of the American Statistical Association 1958; 53:457-481.

[2] Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep. 1966 Mar; 50 (3):163–170.

[3] Cox, D.R. Regression models and life tables. Journal of the Royal Statistical Society 1972; B34:187-220.

10 Tables

Table 1: Accrual by ECOG-ACRIN Institution

Institution Name	Step 1
Albert Einstein College of Medicine	4
CWRU - MetroHealth Medical Center	1
Cedar Rapids CCOP	1
Central Illinois CCOP	3
Christiana Care CCOP	3
Duluth CCOP	1
Fox Chase Cancer Center	16
Geisinger CCOP	4
Ill ORA CCOP	3
Indiana University Hospital/MBSCC	3
Iowa CCOP	4
Johns Hopkins University	2
Kalamazoo CCOP	1
LewisCa&ResPvln@StJoseph's/Candler	1
Mayo Clinic	5
Metro-Minnesota CCOP	4
Michigan Ca Res Consortium CCOP	3
Missouri Valley CA Consortium CCOP	2
Northern Indiana CRC CCOP	1
Northwestern University	6
Sioux Community CA Consortium CCOP	1
St. Vincent Hosp Reg Ca Ctr CCOP	2
Stanford University	6
Toledo CCOP	1
Univ of Pittsburgh Cancer Institute	6
Wichita CCOP	1
Wisconsin, University of	9
Total	94

Table 2: Case Status by Arm

	A	B	Total
Cases Entered	47	47	94
Ineligible	4	3	7
Never Started Assigned Therapy	7	3	10
Total Treated	40	44	84
Included In Efficacy Analysis	43	44	87
Included In Safety Analysis	40	44	84

Table 3: Ineligible Cases (n=7)*

Case	Arm	Reason
22008	A	Appears to have had 2 prior regimens
22033, 22044	A	Last chemotherapy end date within 28 days of registration
22080	A	Had not progressed at entry-disease stable after chemo
22007	B	Registered in belief that meds stopped 9/2010, but pt continued capecitabine to 2/14/11, when protocol treatment to begin.
22049	B	Treatment start 27 days after last chemo, not >/=28
22063	B	Renal cell cancer

** Included in analysis of toxicity, if treated*

Table 4: Cases Never Starting Assigned Therapy (n=10)

Case	Arm	Reason
22005, 22024,22054, 22072	A	Withdrawal
22006	A	Death before starting treatment
22080	A	Ineligible
22058	A	Had MI before starting treatment
22079	B	Withdrawal
22007, 22063	B	Ineligible

Table 5a: Concordance Rates between Stratification Factor at Randomization and Corresponding Information on on-study Forms among Eligible Patients (Histology)

		Histology at Randomization	
	Total (n=87)	Adenocarcinoma (n=73)	Squamous Cell Carcinoma (n=14)
Histology on-study		[n (%)]	[n (%)]
Adenocarcinoma	71	71 (97.3)	0 (0)
Adenosquamous Carcinoma	2	2(2.7)	0 (0)
Squamous Cell Carcinoma	14	0 (0)	14 (100.0)

Table 5b: Concordance Rates between Stratification Factor at Randomization and Corresponding Information on on-study Forms among Eligible Patients (Tumor Location)

		Tumor Location at Randomization	
Tumor Location on-study	Total (n=87)	Esophagus (n=45) [n (%)]	Gastroesophageal Junction (n=42) [n (%)]
Esophagus	40	36 (80.0)	4* (5.5)
Gastroesophageal junction	47	9[+] (20.0)	38(94.5)

***Case 22005: lower thoracic esophagus on-study; case 22017: upper thoracic esophagus on-study; cases 22039, 22054: esophagus NOS on-study**
[+]Cases 22003, 22011, 22015, 22021, 22031, 22050, 22064, 22092 and 22093

Table 6: Baseline Clinical Characteristics of Eligible Patients (n=87)

	Total (n=87)	Treatment A (n=43)	Treatment B (n=44)	P-value*
Age				
N	87	43	44	0.80[W]
Mean	62.0	61.8	62.1	
Standard Deviation	10.6	11.8	9.4	
Median	62	63	62	
Min	40	40	40	
Max	89	89	82	
Sex [n (%)]				
Male	68 (78.2)	35 (81.4)	33 (75.0)	0.61[F]
Female	19 (21.8)	8 (18.6)	11 (25.0)	
Race [n (%)]				
Hispanic	1 (1.1)	0 (0)	1 (2.3)	0.22[E]
Non-Hispanic White	82 (94.3)	40 (93.0)	42 (95.5)	
Non-Hispanic Black	3 (3.4)	3 (7.0)	0 (0)	
Other	1 (1.1)	0 (0)	1 (2.3)	
Histology [n (%)]				
Adenocarcinoma	71 (81.6)	37 (86.0)	34 (77.3)	0.35[E]
Adenosquamous carcinoma	2 (2.3)	0 (0)	2 (4.5)	
Squamous cell carcinoma	14 (16.1)	6 (14.0)	8 (18.2)	
Primary Site [n (%)]				
Upper thoracic esophagus	1 (1.1)	0 (0)	1 (2.3)	0.88[E]
Mid-thoracic esophagus	10 (11.5)	6 (14.0)	4 (9.1)	
Lower thoracic esophagus (excludes GE junction)	16 (18.4)	7 (16.3)	9 (20.5)	
Gastro-esophageal junction	47 (54.0)	24 (55.8)	23 (52.3)	
Esophagus, nos	13 (14.9)	6 (14.0)	7 (15.9)	
P S on study [n (%)]				
0	34 (39.1)	15 (34.9)	19 (43.2)	0.81[E]
1	49 (56.3)	26 (60.5)	23 (52.3)	
2	4 (4.6)	2 (4.7)	2 (4.5)	

[E] Exact Test for RxC Tables
[F] Fisher's Exact Test
[W] Wilcoxon Rank Sum Test

Table 7: Total Number of Cycles

	Total (n=84)	Treatment A (n=40)	Treatment B (n=44)
N	84	40	44
Standard deviation	3.9	4.7	3.0
Median	2.0	2.0	2.0
Min	1.0	1.0	1.0
Max	26.0	26.0	12.0
Mean	4.0	4.2	3.9
Total Cycles [n (%)]			
1	15 (17.9)	10 (25.0)	5 (11.4)
2	31 (36.9)	12 (30.0)	19 (43.2)
3	5 (6.0)	3 (7.5)	2 (4.5)
4	8 (9.5)	3 (7.5)	5 (11.4)
5	5 (6.0)	2 (5.0)	3 (6.8)
6	5 (6.0)	3 (7.5)	2 (4.5)
7	3 (3.6)	1 (2.5)	2 (4.5)
8	4 (4.8)	1 (2.5)	3 (6.8)
10	1 (1.2)	1 (2.5)	0 (0)
11	2 (2.4)	2 (5.0)	0 (0)
12	4 (4.8)	1 (2.5)	3 (6.8)
26	1 (1.2)	1 (2.5)	0 (0)

Table 8: Reason Off Treatment by Arm

	Total (n=84)	Treatment A (n=40)	Treatment B (n=44)
Reason [n (%)]			
Disease progression, relapse during active treatment	52 (61.9)	21 (52.5)	31 (70.5)
Adverse events/side effects/complications	14 (16.7)	9 (22.5)	5 (11.4)
Death on study	5 (6.0)	3 (7.5)	2 (4.5)
Patient withdrawal / refusal after beginning protocol therapy	8 (9.5)	5 (12.5)	3 (6.8)
Alternative therapy	1 (1.2)	1 (2.5)	0 (0)
Patient off treatment for other complications	2 (2.4)	0 (0)	2 (4.5)
Other	2 (2.4)	1 (2.5)	1 (2.3)

Table 9a: Best Overall Response Among Eligible Patients (n=87)

		Treatment	
	Total (n=87)	A (n=43)	B (n=44)
Best Overall Response [n (%)]			
Complete response	1 (1.1)	0 (0)	1 (2.3)
Partial response	10 (11.5)	5 (11.6)	5 (11.4)
No change/stable	29 (33.3)	14 (32.6)	15 (34.1)
Progression	31 (35.6)	13 (30.2)	18 (40.9)
Insufficient evaluation to determine	16 (18.3)	11 (25.6)	5 (11.4)

Table 9b: Reasons Unevaluable for Response among Eligible Patients (n=12)

Case	Treatment	Reason
22005, 22024	A	Withdrawal
22006, 22058, 22054,22072	A	Did not receive treatment
22048,22085	A	Unknown
22001,22028,22029	A	No follow up measure or re-assessment
22068, 22086, 22022	B	No follow up measure or re-assessment
22070	B	Early death
22079	B	Never started treatment

Table 10. Toxicity by Arm (Frequency)

	Treatment Arm							
	A (n=40)				B (n=44)			
	Grade				Grade			
	1,2	3	4	5	1,2	3	4	5
Toxicity Type	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)
Hearing impaired	-	-	-	-	2	-	-	-
Tinnitus	-	-	-	-	1	-	-	-
Anemia	28	4	-	-	27	3	1	-
Leukocytosis	-	1	-	-	-	1	-	-
Atrial fibrillation	-	-	-	-	-	1	-	-
Left ventricular systolic dysfunction	-	-	-	-	-	1	-	-
Chills	2	-	-	-	1	-	-	-
Death NOS	-	-	-	1	-	-	-	-
Edema limbs	4	-	-	-	1	-	-	-
Fatigue	26	3	-	-	27	1	-	-
Fever	2	-	-	-	-	-	-	-
Infusion related reaction	-	1	-	-	-	-	-	-
Infusion site extravasation	1	-	-	-	-	-	-	-
Malaise	1	-	-	-	-	-	-	-
Non-cardiac chest pain	-	-	-	-	1	-	-	-
Pain	1	-	-	-	1	-	-	-
Alopecia	13	-	-	-	12	-	-	-
Dry skin	1	-	-	-	1	-	-	-
Nail discoloration	1	-	-	-	-	-	-	-
Nail loss	1	-	-	-	-	-	-	-
Nail ridging	1	-	-	-	-	-	-	-
Pain of skin	1	-	-	-	-	-	-	-
Palmar-plantar erythrodysesthesia	1	-	-	-	1	-	-	-
Pruritus	3	-	-	-	5	-	-	-
Rash acneiform	1	-	-	-	5	-	-	-
Rash maculo-papular	2	1	-	-	8	-	-	-
Skin hyperpigmentation	1	-	-	-	-	-	-	-
Skin hypopigmentation	1	-	-	-	-	-	-	-
Skin ulceration	-	-	-	-	1	-	-	-
Urticaria	1	-	-	-	1	-	-	-
Abdominal pain	1	1	-	-	1	-	-	-
Constipation	4	-	-	-	2	-	-	-
Diarrhea	8	-	-	-	10	-	-	-
Dry mouth	-	-	-	-	1	-	-	-
Dyspepsia	-	-	-	-	1	-	-	-
Dysphagia	2	-	-	-	-	-	-	-
Gastric perforation	-	-	1	-	-	-	-	-
Mucositis oral	2	-	-	-	3	2	-	-
Nausea	8	1	-	-	13	1	-	-
Oral pain	1	-	-	-	-	-	-	-
Upper gastrointestinal hemorrhage	-	-	1	-	-	-	-	-
Vomiting	6	-	-	-	8	2	-	-
Allergic reaction	1	-	-	-	2	-	-	-
Mucosal infection	-	-	-	-	1	-	-	-

Table 10. Toxicity by Arm (Frequency)

	Treatment Arm							
	A (n=40)				B (n=44)			
	Grade				Grade			
	1,2	3	4	5	1,2	3	4	5
Toxicity Type	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)
Sepsis	-	-	1	-	-	-	-	-
Skin infection	1	-	-	-	-	-	-	-
Alanine aminotransferase increased	5	-	-	-	4	-	-	-
Alkaline phosphatase increased	5	-	-	-	10	-	-	-
Aspartate aminotransferase increased	5	-	-	-	8	-	-	-
Blood bilirubin increased	-	-	-	-	1	-	-	-
Creatinine increased	-	-	-	-	4	-	-	-
Hemoglobin increased	-	-	-	-	1	-	-	-
Lymphocyte count decreased	13	7	1	-	12	7	1	-
Neutrophil count decreased	8	3	-	-	10	5	3	-
Platelet count decreased	6	-	-	-	10	1	-	-
Weight loss	8	-	-	-	8	1	-	-
White blood cell decreased	11	2	-	-	15	5	1	-
Investigations - Other, specify	2	-	-	-	2	-	-	-
Anorexia	7	-	-	-	12	-	-	-
Dehydration	1	-	-	-	1	1	-	-
Glucose intolerance	3	-	-	-	4	1	-	-
Hypercalcemia	1	-	-	-	1	-	-	-
Hyperglycemia	9	2	-	-	15	5	-	-
Hyperkalemia	2	-	-	-	1	-	-	-
Hypermagnesemia	1	-	-	-	-	-	-	-
Hypertriglyceridemia	1	-	-	-	1	-	-	-
Hypoalbuminemia	3	-	-	-	4	-	-	-
Hypocalcemia	-	-	-	-	5	-	-	-
Hypokalemia	3	1	-	-	3	-	-	-
Hypomagnesemia	5	-	-	-	6	-	-	-
Hyponatremia	3	-	-	-	8	1	-	-
Hypophosphatemia	2	2	-	-	2	1	-	-
Arthralgia	1	-	-	-	3	-	-	-
Generalized muscle weakness	1	-	-	-	-	2	-	-
Muscle weakness left-sided	-	-	-	-	1	-	-	-
Muscle weakness lower limb	-	-	-	-	1	-	-	-
Myalgia	1	1	-	-	5	-	-	-
Neck pain	-	1	-	-	-	-	-	-
Pain in extremity	-	-	-	-	4	-	-	-
Dizziness	2	-	-	-	5	-	-	-
Dysgeusia	1	-	-	-	5	-	-	-
Headache	1	-	-	-	4	-	-	-
Movements involuntary	-	-	-	-	1	-	-	-
Paresthesia	3	-	-	-	-	-	-	-
Peripheral motor neuropathy	2	-	-	-	-	1	-	-
Peripheral sensory neuropathy	13	1	-	-	15	1	-	-
Syncope	-	1	-	-	-	-	-	-
Nervous system disorders - Other	-	-	-	-	1	-	-	-
Flashing lights	-	-	-	-	7	-	-	-

Table 10. Toxicity by Arm (Frequency)

	Treatment Arm							
	A (n=40)				B (n=44)			
	Grade				Grade			
	1,2	3	4	5	1,2	3	4	5
Toxicity Type	(n)	(n)	(n)	(n)	(n)	(n)	(n)	(n)
Floaters	-	-	-	-	3	-	-	-
Watering eyes	1	-	-	-	1	-	-	-
Depression	-	-	-	-	1	-	-	-
Insomnia	1	-	-	-	1	-	-	-
Allergic rhinitis	-	-	-	-	2	-	-	-
Cough	-	-	-	-	2	-	-	-
Dyspnea	2	-	-	-	-	1	-	-
Epistaxis	-	-	-	-	2	-	-	-
Hiccups	-	-	-	-	1	-	-	-
Nasal congestion	1	-	-	-	1	-	-	-
Pharyngeal mucositis	-	-	-	-	1	-	-	-
Pneumonitis	-	1	-	-	-	-	-	-
Respiratory failure	-	-	-	-	-	-	-	1
Urinary retention	-	-	-	-	1	-	-	-
Reproductive system and breast - Other	-	-	-	-	1	-	-	-
Hypertension	-	-	-	-	1	1	-	-
Hypotension	-	-	-	-	2	1	-	-
Vascular disorders - Other, specify	-	-	-	-	-	1	-	-
WORST DEGREE	**19**	**16**	**4**	**1**	**20**	**18**	**4**	**1**

Table 11. Toxicity by Arm (Percentage)

	Treatment Arm							
	A (n=40)				B (n=44)			
	Grade				Grade			
	1,2	3	4	5	1,2	3	4	5
Toxicity Type	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Hearing impaired	-	-	-	-	5	-	-	-
Tinnitus	-	-	-	-	2	-	-	-
Anemia	70	10	-	-	61	7	2	-
Leukocytosis	-	3	-	-	-	2	-	-
Atrial fibrillation	-	-	-	-	-	2	-	-
Left ventricular systolic dysfunction	-	-	-	-	-	2	-	-
Chills	5	-	-	-	2	-	-	-
Death NOS	-	-	-	3	-	-	-	-
Edema limbs	10	-	-	-	2	-	-	-
Fatigue	65	8	-	-	61	2	-	-
Fever	5	-	-	-	-	-	-	-
Infusion related reaction	-	3	-	-	-	-	-	-
Infusion site extravasation	3	-	-	-	-	-	-	-
Malaise	3	-	-	-	-	-	-	-
Non-cardiac chest pain	-	-	-	-	2	-	-	-
Pain	3	-	-	-	2	-	-	-
Alopecia	33	-	-	-	27	-	-	-
Dry skin	3	-	-	-	2	-	-	-
Nail discoloration	3	-	-	-	-	-	-	-
Nail loss	3	-	-	-	-	-	-	-
Nail ridging	3	-	-	-	-	-	-	-
Pain of skin	3	-	-	-	-	-	-	-
Palmar-plantar erythrodysesthesia	3	-	-	-	2	-	-	-
Pruritus	8	-	-	-	11	-	-	-
Rash acneiform	3	-	-	-	11	-	-	-
Rash maculo-papular	5	3	-	-	18	-	-	-
Skin hyperpigmentation	3	-	-	-	-	-	-	-
Skin hypopigmentation	3	-	-	-	-	-	-	-
Skin ulceration	-	-	-	-	2	-	-	-
Urticaria	3	-	-	-	2	-	-	-
Abdominal pain	3	3	-	-	2	-	-	-
Constipation	10	-	-	-	5	-	-	-
Diarrhea	20	-	-	-	23	-	-	-
Dry mouth	-	-	-	-	2	-	-	-
Dyspepsia	-	-	-	-	2	-	-	-
Dysphagia	5	-	-	-	-	-	-	-
Gastric perforation	-	-	3	-	-	-	-	-
Mucositis oral	5	-	-	-	7	5	-	-
Nausea	20	3	-	-	30	2	-	-
Oral pain	3	-	-	-	-	-	-	-
Upper gastrointestinal hemorrhage	-	-	3	-	-	-	-	-
Vomiting	15	-	-	-	18	5	-	-
Allergic reaction	3	-	-	-	5	-	-	-
Mucosal infection	-	-	-	-	2	-	-	-

Table 11. Toxicity by Arm (Percentage)

	Treatment Arm							
	A (n=40)				B (n=44)			
	Grade				Grade			
	1,2	3	4	5	1,2	3	4	5
Toxicity Type	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Sepsis	-	-	3	-	-	-	-	-
Skin infection	3	-	-	-	-	-	-	-
Alanine aminotransferase increased	13	-	-	-	9	-	-	-
Alkaline phosphatase increased	13	-	-	-	23	-	-	-
Aspartate aminotransferase increased	13	-	-	-	18	-	-	-
Blood bilirubin increased	-	-	-	-	2	-	-	-
Creatinine increased	-	-	-	-	9	-	-	-
Hemoglobin increased	-	-	-	-	2	-	-	-
Lymphocyte count decreased	33	18	3	-	27	16	2	-
Neutrophil count decreased	20	8	-	-	23	11	7	-
Platelet count decreased	15	-	-	-	23	2	-	-
Weight loss	20	-	-	-	18	2	-	-
White blood cell decreased	28	5	-	-	34	11	2	-
Investigations - Other, specify	5	-	-	-	5	-	-	-
Anorexia	18	-	-	-	27	-	-	-
Dehydration	3	-	-	-	2	2	-	-
Glucose intolerance	8	-	-	-	9	2	-	-
Hypercalcemia	3	-	-	-	2	-	-	-
Hyperglycemia	23	5	-	-	34	11	-	-
Hyperkalemia	5	-	-	-	2	-	-	-
Hypermagnesemia	3	-	-	-	-	-	-	-
Hypertriglyceridemia	3	-	-	-	2	-	-	-
Hypoalbuminemia	8	-	-	-	9	-	-	-
Hypocalcemia	-	-	-	-	11	-	-	-
Hypokalemia	8	3	-	-	7	-	-	-
Hypomagnesemia	13	-	-	-	14	-	-	-
Hyponatremia	8	-	-	-	18	2	-	-
Hypophosphatemia	5	5	-	-	5	2	-	-
Arthralgia	3	-	-	-	7	-	-	-
Generalized muscle weakness	3	-	-	-	-	5	-	-
Muscle weakness left-sided	-	-	-	-	2	-	-	-
Muscle weakness lower limb	-	-	-	-	2	-	-	-
Myalgia	3	3	-	-	11	-	-	-
Neck pain	-	3	-	-	-	-	-	-
Pain in extremity	-	-	-	-	9	-	-	-
Dizziness	5	-	-	-	11	-	-	-
Dysgeusia	3	-	-	-	11	-	-	-
Headache	3	-	-	-	9	-	-	-
Movements involuntary	-	-	-	-	2	-	-	-
Paresthesia	8	-	-	-	-	-	-	-
Peripheral motor neuropathy	5	-	-	-	-	2	-	-
Peripheral sensory neuropathy	33	3	-	-	34	2	-	-
Syncope	-	3	-	-	-	-	-	-
Nervous system disorders - Other	-	-	-	-	2	-	-	-
Flashing lights	-	-	-	-	16	-	-	-

Table 11. Toxicity by Arm (Percentage)

	Treatment Arm							
	A (n=40)				B (n=44)			
	Grade				Grade			
	1,2	3	4	5	1,2	3	4	5
Toxicity Type	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Floaters	-	-	-	-	7	-	-	-
Watering eyes	3	-	-	-	2	-	-	-
Depression	-	-	-	-	2	-	-	-
Insomnia	3	-	-	-	2	-	-	-
Allergic rhinitis	-	-	-	-	5	-	-	-
Cough	-	-	-	-	5	-	-	-
Dyspnea	5	-	-	-	-	2	-	-
Epistaxis	-	-	-	-	5	-	-	-
Hiccups	-	-	-	-	2	-	-	-
Nasal congestion	3	-	-	-	2	-	-	-
Pharyngeal mucositis	-	-	-	-	2	-	-	-
Pneumonitis	-	3	-	-	-	-	-	-
Respiratory failure	-	-	-	-	-	-	-	2
Urinary retention	-	-	-	-	2	-	-	-
Reproductive system and breast - Other	-	-	-	-	2	-	-	-
Hypertension	-	-	-	-	2	2	-	-
Hypotension	-	-	-	-	5	2	-	-
Vascular disorders - Other, specify	-	-	-	-	-	2	-	-
WORST DEGREE	**48**	**40**	**10**	**3**	**45**	**41**	**9**	**2**

Table 12: Lethal Toxicities

Case	Arm	Description of Event
22028	A	Death NOS (possibly related to treatment; probably related to cancer)
22030	A	Ventricular fibrillation (unrelated to treatment, definitely related to cancer)
22085	A	Death NOS (possibly related to treatment; definitely related to cancer)
22018	B	Death NOS (progression, unrelated to treatment)
22022	B	Stroke (unlikely related to treatment; possibly related to cancer)
22027	B	Death NOS (unrelated to treatment; definitely related to cancer)
22032	B	Respiratory failure (possibly related to treatment; possibly related to cancer)
22052	B	Neoplasms-other (unrelated to treatment, definitely related to cancer)
22067	B	Neoplasms-other (unrelated to treatment, definitely related to cancer)
22070	B	Upper gastrointestinal hemorrhage (unrelated to treatment, probably related to cancer)
22088	B	Aspiration (unrelated to treatment, definitely related to cancer)

Table 13a: Univariate Analyses of Overall and Progression-Free Survival, Among Eligible Patients, Stratified by Strata at Randomization

	Overall Survival			Progression-Free Survival		
	Median (mos)	90% LCL	90% UCL	Median (mos)	90% LCL	90% UCL
All Eligible and Treated Patients	6.4	5.0	7.9	2.6	2.0	3.5
Treatment						
A	6.5	4.6	9.5	2.6	1.8	4.1
B	6.4	4.9	8.0	2.3	2.0	3.6

Table 13b: Univariate Analyses of Overall and Progression-Free Survival, Among Eligible Patients, Stratified by Strata at Randomization

	Overall Survival	Progression-Free Survival
	One-Sided Log-Rank P-Value	One-Sided Log-Rank P-Value
Arm A vs. Arm B	0.50	0.85

Table 14a: Cox Regression Models for Progression-Free Survival, Among Eligible Patients (Stratified by Strata at Randomization)

	Hazard Ratio	95% LCL	95% HCL	Two-sided P-value
Model 1:				
Arm B vs. Arm A(Unadjusted)	1.3	0.8	2.0	0.27
Model 2:				
Arm B vs. Arm A	1.4	0.9	2.3	0.15
PS (1, 2 vs. 0)	1.8	1.1	2.9	0.02
Model 3:				
Arm B vs. Arm A	1.4	0.9	2.3	0.15
PS (0 vs. 1, 2)	1.8	1.1	2.9	0.01
Age 62+ vs. Age < 62	1.1	0.7	1.7	0.81
Primary site (other vs. GE junction)	1.5	0.7	3.5	0.33

Table 14b: Cox Regression Models for OS, Among Eligible Patients (Stratified by Strata at Randomization)

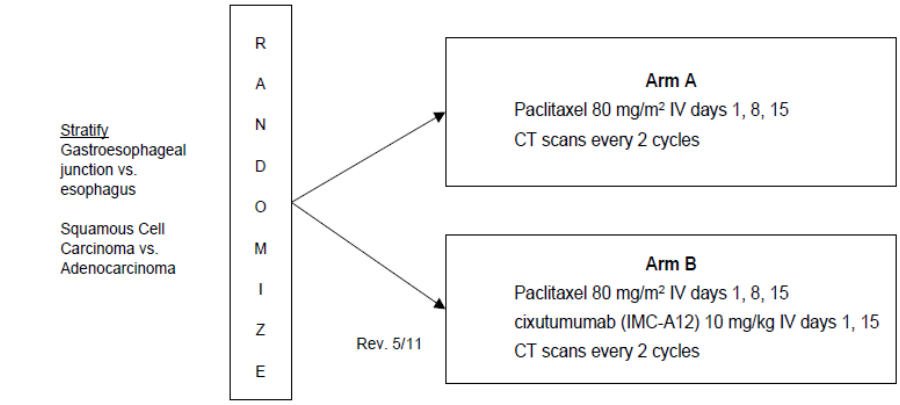
	Hazard Ratio	95% LCL	95% HCL	Two-sided P-value
Model 1:				
Arm B vs. Arm A(Unadjusted)	1.1	0.7	1.7	0.83
Model 2:				
Arm B vs. Arm A	1.1	0.7	1.8	0.74
PS (1, 2 vs. 0)	2.9	1.7	5.0	0.0001
Model 3:				
Arm B vs. Arm A	1.1	0.7	1.8	0.77
PS (0 vs. 1, 2)	2.9	1.7	5.0	0.0002
Age 62+ vs. Age < 62	0.9	0.5	1.4	0.56
Primary site (other vs. GE junction)	1.1	0.5	2.4	0.76

Table 15. Second Primary Cancers

Site	Arm B
Liver, Gall Bladder, Bile Duct	1
Renal Cell	1

11 Figures

Figure 1: Schema



Accrual = 90 patients

Cycle = 28 days

Rev. 5/11 All doses are based on actual body weight.

Figure 2: CONSORT Diagram

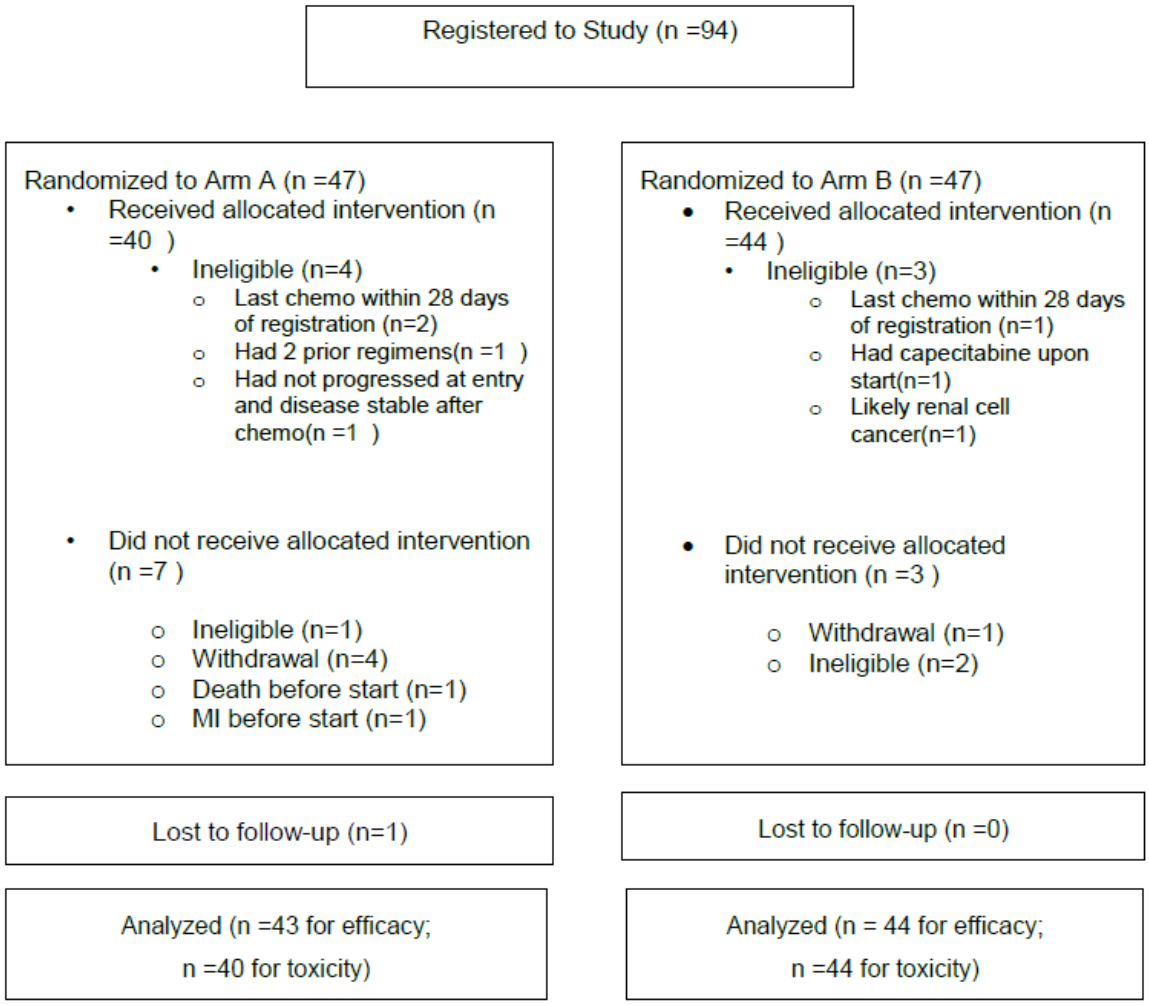


Figure 3: Progression-Free Survival

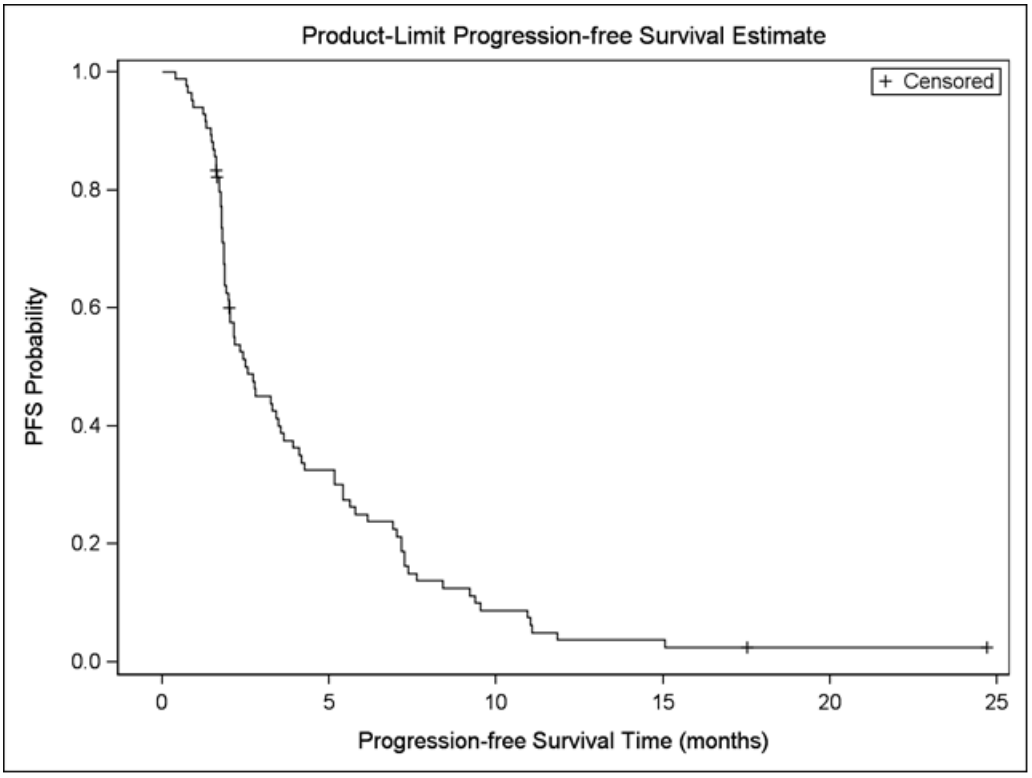


Figure 4: Progression-Free Survival by Arm

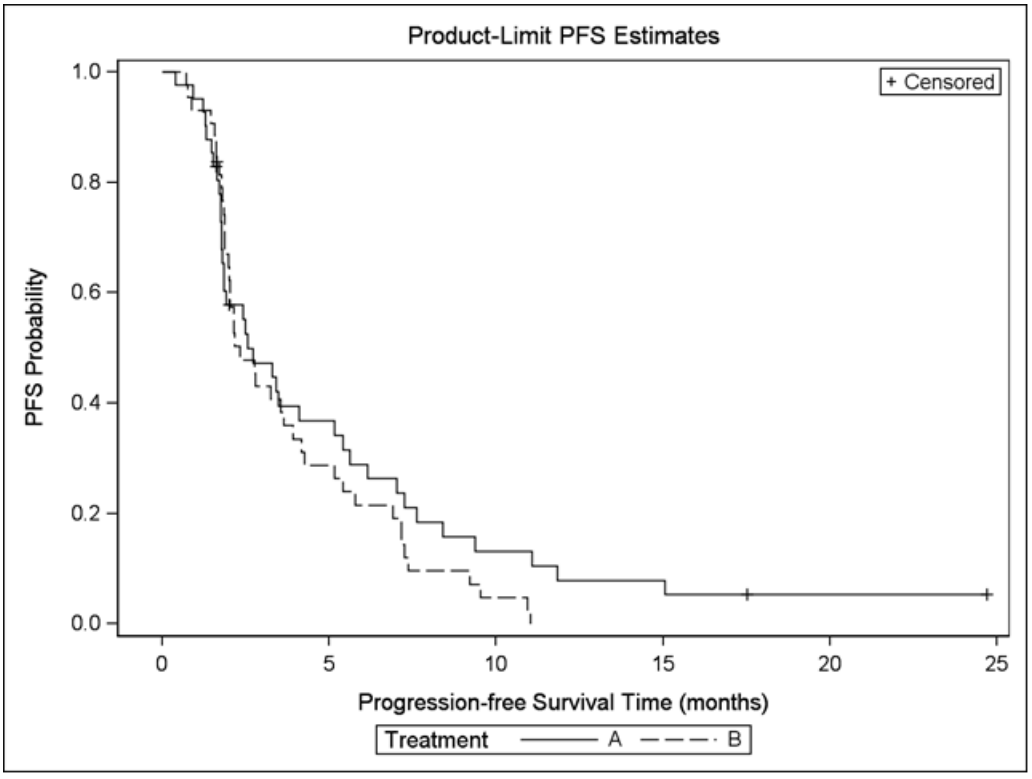


Figure 5: Overall Survival

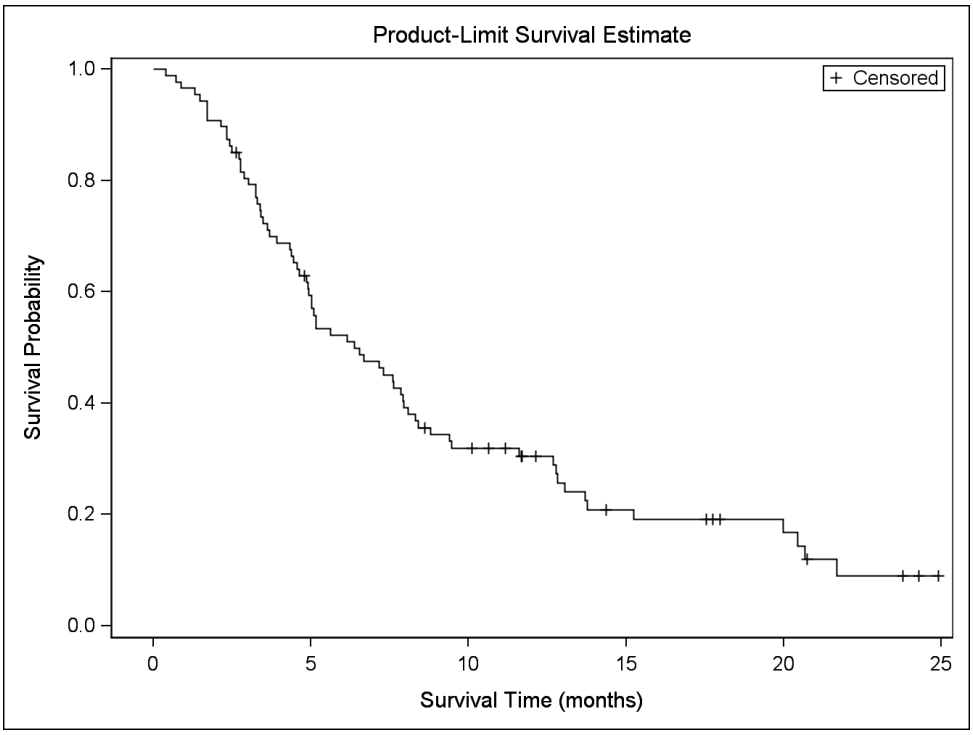


Figure 6: Overall Survival by Arm