Alliance Study N1048 – A Phase II/III Trial of Neoadjuvant FOLFOX with Selective Use of Combined Modality Chemoradiation versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision

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1.0 OBJECTIVES

Primary

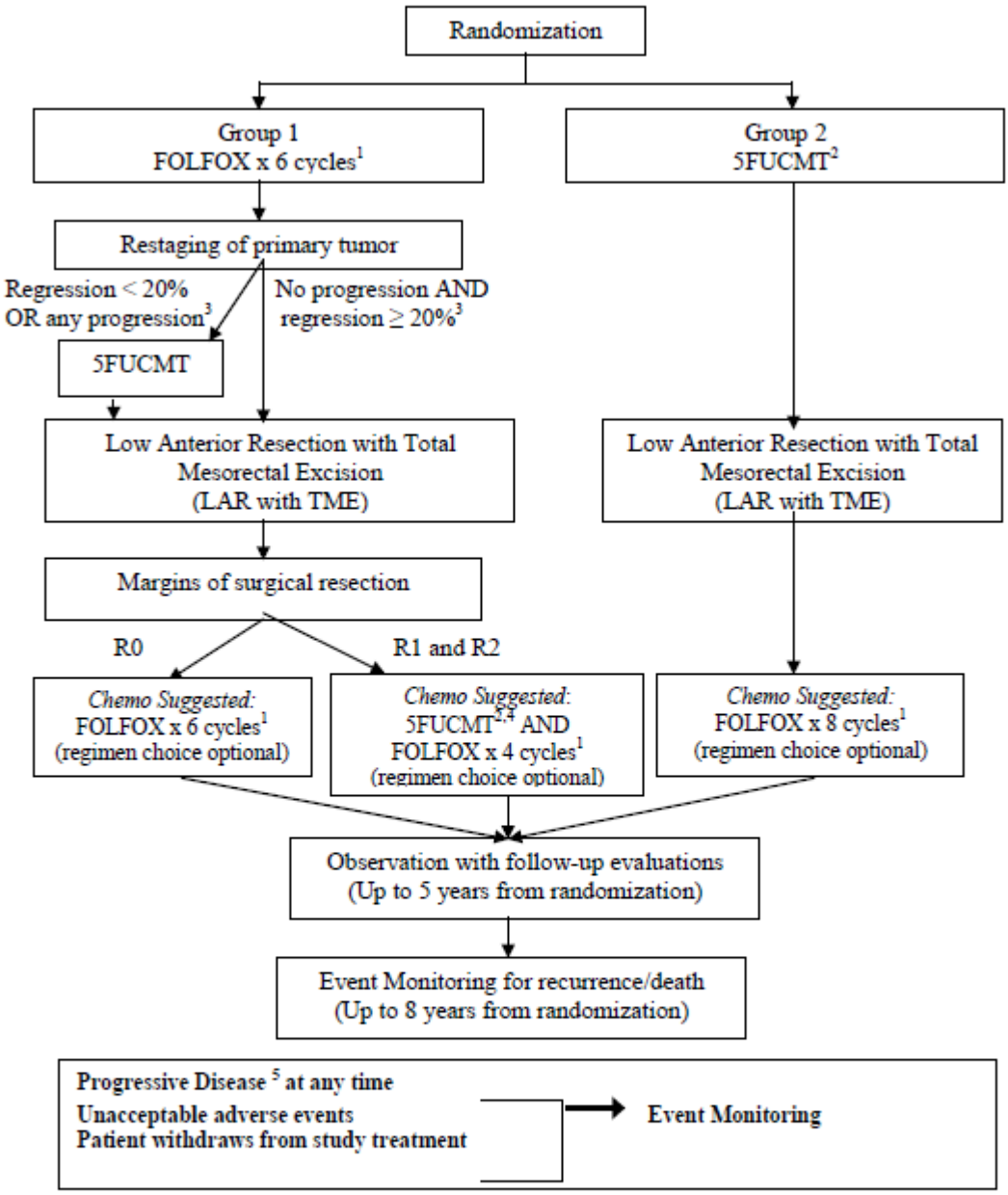
1. Phase II component: To assure that the selective use of 5FUCMT group (Group 1) maintains the current high rate of pelvic R0 resection and is consistent with non-inferiority for time to local recurrence (TLR).
2. Phase III component: To compare standard 5FUCMT (Group 2) to neoadjuvant FOLFOX followed by selective use of 5FUCMT (Group 1) with respect to the co-primary endpoints of the Time to Local Recurrence (TLR) and Disease Free Survival (DFS)

Secondary

1. To determine if the selective treatment group (Group 1) is non-inferior to the standard group (Group 2) with respect to the proportion of patients who achieve a pathologic complete response (pCR) at the time of surgical resection.
2. To determine if the intervention group (Group 1) is non-inferior to the standard group (Group 2) with respect to overall survival.
3. To evaluate and compare the adverse event profile and surgery complications between two groups.
4. To estimate the proportion of patients in the selective group who receive: 1) pre-operative 5FUCMT; 2) post-operative 5FUCMT; 3) either pre- or post-operative 5FUCMT.

2.0 CURRENT SCHEMA

Schema



[1]Cycle length = 14 days; [2] 5FUCMT duration = 5.5 weeks; 5FUCMT = 5-fluorouracil OR capecitabine + radiation theapy.; [3] This is a clinical estimation as to whether there has been at least a 20% decrease in the tumor in response to neoadjuvant FOLFOX treatment made on the basis of both tumor imaging and clinical tumor response based on proctoscopy (see Section 11); [4] No patient will receive 5FUCMT more than once; [5] If there is progressive disease at the restaging of primary tumor after 6 cycles of FOLFOX, Group 1 patients proceed to 5FUCMT instead instead of event monitoring.

Generic name: Oxaliplatin Brand name(s): Eloxatin® Abbreviation: OXAL Availability: Commercial	Generic name: Leucovorin Brand name(s): Abbreviation: CF Availability: Commercial	Generic name: Capecitabine Brand name(s): Xeloda® Abbreviation: CAPCIT Availability: Commercial	Generic name: Fluorouracil Brand name(s): Adrucil® Abbreviation: 5-FU Availability: Commercial

3. ELIGIBILITY CRITERIA

Registration – Inclusion Criteria

- Age ≥ 18 years at diagnosis.

- Diagnosis of rectal adenocarcinoma.
- Radiologically measurable or clinically evaluable disease as defined in section 11.0 of the protocol.
- ECOG Performance Status (PS): 0, 1 or 2.
- For this patient, the standard treatment recommendation in the absence of a clinical trial would be combined modality neoadjuvant chemoradiation followed by curative intent surgical resection.
- Candidate for sphincter-sparing surgical resection prior to initiation of neoadjuvant therapy according to the primary surgeon.
- Clinical Stage: T2N1, T3N0, T3N1.
    - N2 disease is to be estimated as four or more lymph nodes that are ≥10 mm.
    - Clinical staging should be estimated based on the combination of the following assessments: physical exam by the primary surgeon, CT or PET/CT scan of the chest/abdomen/pelvis and either a pelvic MRI or an ultrasound (ERUS). If a pelvic MRI is performed, it is acceptable to perform CT of the chest/abdomen, omitting CT imaging of the pelvis.
- The following laboratory values obtained ≤ 28 days prior to registration.
    - Absolute neutrophil count (ANC) ≥ 1500/mm3
    - Platelet count ≥ 100,000/mm3
    - Hemoglobin > 8.0 g/dL
    - Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
    - SGOT (AST) ≤ 3 x ULN
    - SGPT (ALT) ≤ 3 x ULN
    - Creatinine ≤1.5 x ULN
- Negative pregnancy test done ≤ 7 days prior to registration, for women of childbearing potential only.
- Patient of child-bearing potential is willing to employ adequate contraception.
- Provide informed written consent.
- Willing to return to enrolling medical site for all study assessments.

Registration - Exclusion Criteria

- Clinical T4 tumors.
- Primary surgeon indicates need for abdominoperineal (APR) at baseline.
- Evidence that the tumor is adherent to or invading the mesorectal fascia on imaging studies such that the surgeon would not be able to perform an R0 resection (one with negative margins). Please reference the end of Section 7.4.2 for details.
- Tumor is causing symptomatic bowel obstruction (patients who have had a temporary diverting ostomy are eligible).
- Chemotherapy within 5 years prior to registration. (Hormonal therapy is allowable if the disease free interval is ≥ 5 years.)
- Any prior pelvic radiation.
- Other invasive malignancy ≤ 5 years prior to registration. Exceptions are colonic polyps, non-melanoma skin cancer or carcinoma-in-situ of the cervix.
- Any of the following because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.
    - Pregnant women
    - Nursing women
    - Men or women of childbearing potential who are unwilling to employ adequate contraception
- Co-morbid illnesses or other concurrent disease which, in the judgment of the clinician obtaining informed consent, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.

4.0 TREATMENT SCHEDULE

Group 1 Pre-Operative Treatment Schedule (FOLFOX)

FOLFOX (5-fluorouracil + leucovorin + oxaliplatin)

Agent	Dose	Route	Day	Retreatment
Oxaliplatin	85 mg/m^2	IV over 2 hours	Day 1	Repeat every 14 days for a total of 6 cycles
Leucovorin	400 mg/m^2 bolus	IV over 2 hours	Day 1	Repeat every 14 days for a total of 6 cycles
5FU	400 mg/m^2 bolus over 5-15 minutes then 2400 mg/m^2 continual over 46-48h total dose	IV	Day 1 Days 1 to 2	Repeat every 14 days for a total of 6 cycles

Group 2 Pre-Operative Treatment Schedule (5FUCMT)

5FUCMT (5-fluorouracil OR capecitabine + radiation therapy)

Agent	Dose	Route	Day
5FU	225 mg/m^2 per day	Continuous IV infusion administered concurrently with RT	Continuous IV infusion 7 days per week during RT
Capecitabine[1,2,3]	825 mg/m^2 bid	Orally administered concurrently with RT	5 days per week on days of planned RT
Radiation Therapy (RT)	See Section 7.4		5 days per week

Radiation Therapy

Field	Dose (Gy)	Number of Fractions	Fraction Size	Rx Length	Rx Days
Initial	45	25	1.8 Gy	5 weeks	Monday through Friday
Boost	5.4	3		3 days	
Total	50.4	28			

5.0 STUDY DESIGN

5.1 Study Phase/Type of Design/Stratification Factors

Randomized Phase II/III study with stratification factor of ECOG Performance Status: (0 or 1) vs. 2. The trial has 2 treatment groups: Group 1 and Group 2.

5.2 Primary Endpoint

Phase II component: The primary goal of the phase II component of this trail is to 1) assure that the selective use RT group achieves acceptable pelvic R0 resection rate (RRR) compared to the treat all group and 2) assure that the selective use RT group does not result in inferior time to local recurrence (TLR). The testing for non-inferiority for the TLR endpoint in the phase II portion will be conducted as an interim analysis integrated into the phase III component at the time of the last pelvic R0 resection rate analysis. Therefore, the power and sample size considerations are only presented for RRR. It is expected that the pelvic R0 resection rate will be approximately 90% on each group. A sample size of 366 patients will provide 82% power to detect that the RRR in the treat all group is higher than the RRR in selective use group by at least 0.06 (absolute percentage difference) assuming the RRR in selective use group is 87%, based on one-sided test at

significance level of 0.20. After the surgery data are available on all 366 patients, the final phase II analysis regarding RRR will be conducted. If the p-value is less than or equal to 0.114, then we will terminate the study and not proceed to phase III component, and conclude that the treat all group is preferred.

Phase III component: The primary goal of the phase III component of this trial is to compare combined modality neoadjuvant chemoradiation to the selective use of chemoradiation with respect to the co-primary endpoints of the Disease Free Survival (DFS) and time to local recurrence (TLR). Co-primary endpoints are chosen due to the particularly devastating nature of local recurrence in rectal cancer. The two co-primary endpoints will be considered jointly based on a sequential decision strategy in the final determination of which approach (selected use versus treat all) is preferred. The selective use group will be favored if either the selective use group results in superior DFS compared to the treat-all group (regardless of the TLR results), or if the selective use group is at least non-inferior to the treat all group on both DFS and TLR. The final sequential hypothesis testing procedure for the phase III component will proceed as follows. First, DFS will be compared between the two groups for non-inferiority of the selective RT use group. If non-inferiority is supported, then the selective use group will be tested for superiority regarding to DFS based on a one-sided test. If non-inferiority is not demonstrated, the treat all group will be declared to be the preferred group. I superiority of the selective use group on the DFS endpoint is determined, further formal testing will stop for the primary aims and we will conclude that the selective use group is preferred. If however non-inferiority but not formal superiority of the selective use group is found based on decision rules for the DFS endpoint, then the co-primary endpoint of TLR will be tested for non-inferiority. If non-inferiority in TLR is supported, the selective use group will be declared to be the preferred group. Otherwise, the treat all group will be declared to be the preferred group. Assuming an accrual rate of 200 patients per year with 3 years of minimum follow-up, 1000 total patients provides 85% power to detect non-inferiority of the DFS and TLR jointly at the overall alpha level of 0.05, if the true DFS in the selective use group is slightly superior (approximately 2% absolute percentage superior at 3 years) to the treat all approach (equivalent to HR=0.91), and the true local recurrence-free in the selective use group is the same as in the treat all group (equivalent to HR=1). These joint power and overall type I error rate calculations are based on simulation studies with 10,000 replicates, assuming an exponential survival function and a constant accrual rate, including 3 interim analyses for DFS and phase II decision making for TLR. The final analysis will be conducted when there are at least 406 and 75 events observed for DFS and TLR, respectively. If the HR comparing DFS in the selective use group to the treat all group is greater than 1.115 (in favor of the treat all group), then the treat all group is declared to be preferred, otherwise proceed to the following steps: If the HR comparing DFS in selective use group to treat all group is less than 0.8367, then selective use group is declared to be preferred, otherwise proceed to the following step: If the HR comparing TLR in selective use group to treat all group is less than or equal to 1.44, then the selective use group is declared to be preferred, otherwise the treat all group is declared to be preferred.

5.3 Target Accrual

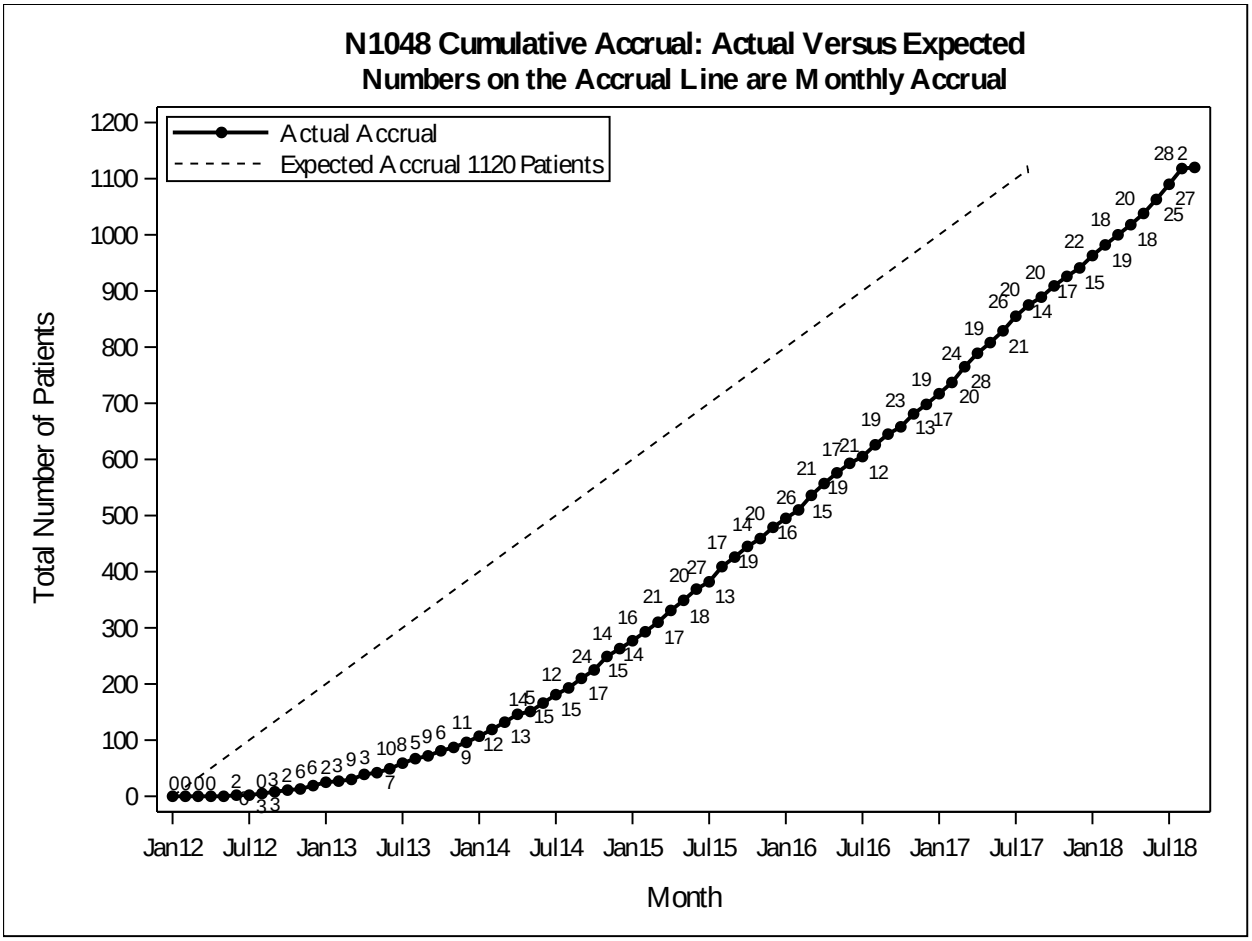
The target accrual for this study is 1120 patients using a 1:1 randomization. The target accrual rate is 17 patients per month.

6.0 CURRENT ACCRUAL

Study Activation Date	01/13/2012
Target Accrual (n)	1120*
Current Accrual (n)	1120
Expected Accrual Rate	16.67/month
Accrual Rate – Since activation	14.0 / month
Accrual Rate – Past 12 months	20.3 / month
Accrual Rate – Past 6 months	22.0 / month
Projected closure date for a trial open for more than	09/24/2018*

one year (based on accrual rate from past 12 months)	

*Amendment 9 will increase the target accrual to 1180. The projected closure date will be early December 2018.



7.0 CURRENT STUDY STATUS

The trial opened 1/13/2012 and has accrued 1120 of a targeted 1120 patients (per amendment 8), with an accrual rate of 22/month for the last 6 months. The trial has met the accrual target (n = 366) for phase II portion. For R0 resection endpoint of phase II portion, three interim analyses were conducted in Oct 2014, April 2015, and Oct 2015, and the final analysis was conducted in April 2016. None of the analyses results crossed the stopping boundary and all supported continuing the study accrual. For time to local recurrence (TLR) endpoint of the phase II portion, the interim analysis was conducted in March 2018. The result does not cross stopping boundary. Hence the study continued to Phase III portion.

8.0 PATIENT CHARACTERISTICS

All patients are included in the tables below.

Table 8a. Demographics

	Group 1 (N=560)	Group 2 (N=560)	Total (N=1120)
Age			
N	560	560	1120
Mean (SD)	57.4 (11.03)	56.9 (11.14)	57.2 (11.08)
Median	57.0	57.0	57.0
Q1, Q3	50.0, 65.0	49.0, 65.0	50.0, 65.0
Range	19.0, 91.0	25.0, 84.0	19.0, 91.0
Race			
White	473 (84.5%)	482 (86.1%)	955 (85.3%)
Black or African American	29 (5.2%)	18 (3.2%)	47 (4.2%)
Native Hawaiian or Other Pacific Islander	2 (0.4%)	0 (0.0%)	2 (0.2%)
Asian	30 (5.4%)	21 (3.8%)	51 (4.6%)
American Indian or Alaska Native	4 (0.7%)	8 (1.4%)	12 (1.1%)
Not reported: patient refused or not available	14 (2.5%)	15 (2.7%)	29 (2.6%)
Unknown: Patient unsure	8 (1.4%)	16 (2.9%)	24 (2.1%)
Gender			
Female	207 (37.0%)	184 (32.9%)	391 (34.9%)
Male	353 (63.0%)	376 (67.1%)	729 (65.1%)

Table 8b. Stratification Factors

	Group 1 (N=560)	Group 2 (N=560)	Total (N=1120)
ECOG Performance Status			
0 or 1	558 (99.6%)	558 (99.6%)	1116 (99.6%)
2	2 (0.4%)	2 (0.4%)	4 (0.4%)

9.0 ADVERSE EVENTS

9.1 Adverse Event Summary

This study uses CTCAE version 4.
1018 patients are evaluable for adverse event (AE) analyses (Group 1: 531, Group 2: 487). Commonly occurring grade 3+ AE include Lymphocyte count decreased (1%: Group 1, 9%: Group 2), Neutrophil count decreased (21%: Group 1, 3%: Group 2), and Diarrhea (5%:Group 1, 11%: Group 2).

Overall, 65 (12%) and 26 (5%) of Group 1 and 2 patients, respectively, experienced at least one grade 4+ adverse event via case report form. For Group 1 patients, the commonly occurring grade 4+ AE includes Neutrophil count decrease (6%), Sepsis (1%), Thromboembolic event (1%), Acute kidney injury (1%), and Respiratory failure (1%). For Group 2 patients, the commonly occurring grade 4+ AE include White blood cell decreased (1%), Sepsis (1%), Neutrophil count decreased (1%), Lymphocyte count decreased (1%), Hyponatremia (1%), and Respiratory failure (1%).

As of the freeze date, 19 pts that reported 20 grade 4 AEs and 1 grade 5 via AdEERs that had not been reported via CRF's. The grade 5 AE was a Thromboembolic event (1 patient). Commonly occurring grade 4 AEs were Sepsis (2 patients), Hyponatremia (2 patients), and Postoperative hemorrhage (2 patients).
As of the freeze date, 13 pts that reported 23 grade 4 AEs and 1 grade 5 via AdEERs that had not been reported via CRF's. The grade 5 AE was a Respiratory failure (1 patient). Commonly occurring grade 4 AEs were Sepsis (4 patients), Respiratory failure (2 patients), and Hyponatremia (3 patients).

Regarding safety stopping rules:

On study death:
There has been 7 on study death in Group 1 and 4 on study deaths in Group 2 reported on CRF and AdEERs. Overall, 11 (1.1%) out of 1018 patients having any AE data have died: the 80% exact binomial confidence interval of (0.69% to 1.63%). **The on study death stopping rule is not crossed.**

Grade 4+ AEs:
The overall rate (CRF and AdEERs data) of grade 4+ adverse events among patients who **completed all protocol specified therapy** (i.e., preoperative treatment, surgery and postoperative chemotherapy) is 35/350 (10.0%) for Group 1 and 12/316 (3.8%) for Group 2. At the reporting time, the rate of Grade 4+ adverse events in group 1 (experimental group) is 2.63 times greater than that in group 2 (control group). More details see blow.

The G4+ stopping rule is crossed. The study team reviewed full AE data and reported this event to Alliance DSMB and CTEP on September 25, 2018. The consensus of the ALLIANCE DSMB is to continue accrual to Protocol N1048 and at the same time have the Study Team submit the amendment to Section 16.5 as detailed in Dr. Schrag's letter to the DSMB on 9-25-18, which would temporarily suspend accrual if Grade 4 adverse events in either arm exceeds 15%. We appreciate the details in Deb's letter which strongly support continuing the study and anticipate completion of accrual in the next few months. The communications between study team and DSMB were included in Appendix H.

	Group 1	**Group 2**
N	350	316
N (%) of pts experienced at least one grade 4 AE	35 (10.0%)	12 (3.8%)
Most common grade 4 AEs	Neutrophil count decreased (20 [5.7%]) Thromboembolic event (3 [0.9%]) Sepsis (2 [0.6%]) Lymphocyte count decreased (2 [0.6%]) Febrile neutropenia (2 [0.6%])	Neutrophil count decreased (4 [1.3%]) White blood cell decreased (4 [1.3%]) Sepsis (2 [0.6%]) Lymphocyte count decreased (2 [0.6%]) Respiratory failure (2 [0.6%])

Since this is a subset of patients who received treatment, to provide a full picture, we also include the AE summaries per group for patients who ended protocol treatment earlier below:

The overall rate (CRF and AdEERs data) of grade 4+ adverse events among patients who ended protocol therapy prior to completing all treatment is 24/78 (26.7%) for Group 1 and 15/83 (18.1%) for Group 2. At the reporting time, the rate of Grade 4+ adverse events in group 1 experimental group) is 1.48 times greater than that in group 2 (control group).

	Group 1	**Group 2**
N	90	83
N (%) of pts experienced at least one grade 4 AE	19 (21.1%)	13 (15.7%)
Most common grade 4 AEs	Neutrophil count decreased (6 [6.7%]) Sepsis (4 [4.4%]) Respiratory failure (2 [2.2%]) Acute kidney injury (2 [2.2%]) Rectal perforation (1 [1.1%])	Sepsis (2 [2.4%]) Respiratory failure (2 [2.4%]) Aspiration (2 [2.4%]) Lymphocyte count decreased (2 [2.4%]) Hyponatremia (2 [2.4%])
N of on study death	7	4
Grade 5 Aes	Sepsis (1 [1.1%]) Sudden death NOS (2 [2.2%]) Rectal perforation (1 [1.1%]) Thromboembolic event (1 [1.1%]) Stroke (1 [1.1%]) Death NOS (1 [1.1%])	Sepsis (1 [1.2%]) Respiratory failure (1 [1.2%]) Death NOS (1 [1.2%]) Acute kidney injury (1 [1.2%])

Conclusions: The adverse event stopping rule has not been met.

The adverse event stopping rule has not been met.

Summary of Grade 3+ Adverse Events
Max Grade per Patient Per Event
Regardless of Attribution
Number of Evaluable Patients
Arm 1=531 Arm 2=487

Patients with a maximum:	**Arm**	**n**	**(%)**
Total			
Grade 3 Event	1	203	*(37.0%)*
	2	164	*(32.0%)*
Grade 4 Event	1	64	*(11.7%)*
	2	29	*(5.7%)*
Grade 5 Event	1	7	*(1.3%)*
	2	4	*(0.8%)*
Hematologic Adverse Events			
Grade 3 Event	1	94	*(17.1%)*
	2	54	*(10.5%)*
Grade 4 Event	1	35	*(6.4%)*

Summary of Grade 3+ Adverse Events
Max Grade per Patient Per Event
Regardless of Attribution
Number of Evaluable Patients
Arm 1=531 Arm 2=487

Patients with a maximum:	Arm	n	(%)
	2	10	*(2.0%)*
Grade 5 Event	1	0	*(0.0%)*
	2	0	*(0.0%)*
Non-Hematologic Adverse Events			
Grade 3 Event	1	170	*(31.0%)*
	2	143	*(27.9%)*
Grade 4 Event	1	32	*(5.8%)*
	2	21	*(4.1%)*
Grade 5 Event	1	7	*(1.3%)*
	2	4	*(0.8%)*
Note: Summaries are based on available patient data			

Listing of Grade 3+ Adverse Events
Max Grade per Patient Per Event
Regardless of Attribution
Number of Evaluable Patients
Arm 1=531 Arm 2=487

		Grade of Adverse Event					
	Arm	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
Hematologic Adverse Events							
Blood/Bone Marrow							
Anemia	1	7	*(1%)*	1	*(0%)*	0	*(0%)*
	2	10	*(2%)*	0	*(0%)*	0	*(0%)*
Blood and lymph sys disorders - Oth Spec	1	1	*(0%)*	1	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
CD4 lymphocytes decreased	1	1	*(0%)*	0	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Hemoglobin increased	1	1	*(0%)*	0	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Leukocytosis	1	1	*(0%)*	0	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Lymphocyte count decreased	1	6	*(1%)*	2	*(0%)*	0	*(0%)*
	2	41	*(8%)*	4	*(1%)*	0	*(0%)*

Listing of Grade 3+ Adverse Events
Max Grade per Patient Per Event
Regardless of Attribution
Number of Evaluable Patients
Arm 1=531 Arm 2=487

		Grade of Adverse Event					
	Arm	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
Lymphocyte count increased	1	0	*(0%)*	0	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Neutrophil count decreased	1	82	*(15%)*	31	*(6%)*	0	*(0%)*
	2	10	*(2%)*	5	*(1%)*	0	*(0%)*
Platelet count decreased	1	5	*(1%)*	0	*(0%)*	0	*(0%)*
	2	1	*(0%)*	1	*(0%)*	0	*(0%)*
White blood cell decreased	1	13	*(2%)*	1	*(0%)*	0	*(0%)*
	2	7	*(1%)*	5	*(1%)*	0	*(0%)*
Non-Hematologic Adverse Events							
Blood and lymphatic sys disord							
Febrile neutropenia	1	10	*(2%)*	2	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Thrombotic thrombocytopenic purpura	1	1	*(0%)*	1	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Cardiac disorders							
Acute coronary syndrome	1	0	*(0%)*	0	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Atrial fibrillation	1	2	*(0%)*	0	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Atrial flutter	1	1	*(0%)*	0	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Cardiac arrest	1	0	*(0%)*	1	*(0%)*	0	*(0%)*
	2	0	*(0%)*	1	*(0%)*	0	*(0%)*
Cardiac disorders - Other, specify	1	1	*(0%)*	1	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Chest pain - cardiac	1	1	*(0%)*	0	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Heart failure	1	1	*(0%)*	0	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Mitral valve disease	1	0	*(0%)*	0	*(0%)*	0	*(0%)*
	2	0	*(0%)*	1	*(0%)*	0	*(0%)*

Listing of Grade 3+ Adverse Events
Max Grade per Patient Per Event
Regardless of Attribution
Number of Evaluable Patients
Arm 1=531 Arm 2=487

		Grade of Adverse Event					
	Arm	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
Mobitz (type) II atrioventricular block	1	0	(0%)	1	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Myocardial infarction	1	2	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Pericardial effusion	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Sinus tachycardia	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Ventricular fibrillation	1	0	(0%)	1	(0%)	0	(0%)
	2	0	(0%)	1	(0%)	0	(0%)
Ventricular tachycardia	1	1	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Gastrointestinal disorders							
Abdominal distension	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Abdominal pain	1	1	(0%)	0	(0%)	0	(0%)
	2	5	(1%)	0	(0%)	0	(0%)
Anal hemorrhage	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Anal pain	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Colitis	1	1	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Colonic obstruction	1	2	(0%)	2	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Colonic perforation	1	0	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	1	(0%)	0	(0%)
Constipation	1	5	(1%)	1	(0%)	0	(0%)
	2	2	(0%)	0	(0%)	0	(0%)
Diarrhea	1	24	(5%)	0	(0%)	0	(0%)
	2	43	(9%)	1	(0%)	0	(0%)
Dysphagia	1	0	(0%)	0	(0%)	0	(0%)

Listing of Grade 3+ Adverse Events
Max Grade per Patient Per Event
Regardless of Attribution
Number of Evaluable Patients
Arm 1=531 Arm 2=487

		Grade of Adverse Event					
	Arm	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Enterocolitis	1	0	*(0%)*	0	*(0%)*	0	*(0%)*
	2	2	*(0%)*	1	*(0%)*	0	*(0%)*
Esophageal obstruction	1	0	*(0%)*	0	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Gastric hemorrhage	1	0	*(0%)*	0	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Gastrointestinal disorders - Oth spec	1	2	*(0%)*	1	*(0%)*	0	*(0%)*
	2	5	*(1%)*	0	*(0%)*	0	*(0%)*
Ileal fistula	1	0	*(0%)*	0	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Ileal obstruction	1	1	*(0%)*	1	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Ileus	1	3	*(1%)*	0	*(0%)*	0	*(0%)*
	2	5	*(1%)*	0	*(0%)*	0	*(0%)*
Lower gastrointestinal hemorrhage	1	2	*(0%)*	0	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Mucositis oral	1	12	*(2%)*	0	*(0%)*	0	*(0%)*
	2	6	*(1%)*	0	*(0%)*	0	*(0%)*
Nausea	1	11	*(2%)*	0	*(0%)*	0	*(0%)*
	2	13	*(3%)*	0	*(0%)*	0	*(0%)*
Pancreatitis	1	0	*(0%)*	0	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Proctitis	1	0	*(0%)*	0	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Rectal hemorrhage	1	2	*(0%)*	0	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Rectal obstruction	1	2	*(0%)*	0	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Rectal pain	1	1	*(0%)*	0	*(0%)*	0	*(0%)*
	2	2	*(0%)*	0	*(0%)*	0	*(0%)*
Rectal perforation	1	1	*(0%)*	1	*(0%)*	1	*(0%)*

Listing of Grade 3+ Adverse Events
Max Grade per Patient Per Event
Regardless of Attribution
Number of Evaluable Patients
Arm 1=531 Arm 2=487

		Grade of Adverse Event					
	Arm	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Rectal stenosis	1	1	*(0%)*	0	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Small intestinal obstruction	1	2	*(0%)*	1	*(0%)*	0	*(0%)*
	2	8	*(2%)*	0	*(0%)*	0	*(0%)*
Vomiting	1	9	*(2%)*	0	*(0%)*	0	*(0%)*
	2	8	*(2%)*	0	*(0%)*	0	*(0%)*
Gen disord and admin site cond							
Chills	1	1	*(0%)*	0	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Death NOS	1	0	*(0%)*	0	*(0%)*	1	*(0%)*
	2	0	*(0%)*	0	*(0%)*	1	*(0%)*
Fatigue	1	14	*(3%)*	0	*(0%)*	0	*(0%)*
	2	13	*(3%)*	0	*(0%)*	0	*(0%)*
Fever	1	1	*(0%)*	0	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Pain	1	26	*(5%)*	0	*(0%)*	0	*(0%)*
	2	12	*(2%)*	0	*(0%)*	0	*(0%)*
Sudden death NOS	1	0	*(0%)*	0	*(0%)*	2	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Hepatobiliary disorders							
Cholecystitis	1	2	*(0%)*	0	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Hepatobiliary disorders - Other, specify	1	0	*(0%)*	0	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Immune system disorders							
Allergic reaction	1	1	*(0%)*	1	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Anaphylaxis	1	3	*(1%)*	0	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Immune system disorders - Other, specify	1	1	*(0%)*	0	*(0%)*	0	*(0%)*

Listing of Grade 3+ Adverse Events
Max Grade per Patient Per Event
Regardless of Attribution
Number of Evaluable Patients
Arm 1=531 Arm 2=487

		Grade of Adverse Event					
	Arm	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
	2	0	(0%)	0	(0%)	0	(0%)
Infections and infestations							
Abdominal infection	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Appendicitis	1	2	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Bladder infection	1	1	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Bone infection	1	0	(0%)	0	(0%)	0	(0%)
	2	2	(0%)	0	(0%)	0	(0%)
Catheter related infection	1	2	(0%)	0	(0%)	0	(0%)
	2	2	(0%)	0	(0%)	0	(0%)
Device related infection	1	1	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Endocarditis infective	1	1	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Infections and infestations - Oth spec	1	3	(1%)	0	(0%)	0	(0%)
	2	8	(2%)	0	(0%)	0	(0%)
Kidney infection	1	1	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Lung infection	1	3	(1%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Meningitis	1	1	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Peritoneal infection	1	0	(0%)	0	(0%)	0	(0%)
	2	2	(0%)	0	(0%)	0	(0%)
Sepsis	1	0	(0%)	5	(1%)	1	(0%)
	2	0	(0%)	4	(1%)	1	(0%)
Skin infection	1	3	(1%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Stoma site infection	1	1	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)

Listing of Grade 3+ Adverse Events
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Arm 1=531 Arm 2=487

		Grade of Adverse Event					
	Arm	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
Tooth infection	1	1	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Urinary tract infection	1	2	(0%)	0	(0%)	0	(0%)
	2	2	(0%)	0	(0%)	0	(0%)
Wound infection	1	0	(0%)	0	(0%)	0	(0%)
	2	3	(1%)	0	(0%)	0	(0%)
Inj, pois and procedur complic							
Ankle fracture	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Dermatitis radiation	1	0	(0%)	0	(0%)	0	(0%)
	2	2	(0%)	0	(0%)	0	(0%)
Fall	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Gastrointestinal anastomotic leak	1	1	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Inj, pois and proced complic - Oth spec	1	1	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Postoperative hemorrhage	1	0	(0%)	1	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Prolapse of intestinal stoma	1	1	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Rectal anastomotic leak	1	0	(0%)	0	(0%)	0	(0%)
	2	3	(1%)	0	(0%)	0	(0%)
Vascular access complication	1	5	(1%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Wound dehiscence	1	2	(0%)	1	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Investigations							
Alanine aminotransferase increased	1	8	(2%)	1	(0%)	0	(0%)
	2	2	(0%)	0	(0%)	0	(0%)

Listing of Grade 3+ Adverse Events
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Arm 1=531 Arm 2=487

		Grade of Adverse Event					
	Arm	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
Aspartate aminotransferase increased	1	1	(0%)	2	(0%)	0	(0%)
	2	2	(0%)	0	(0%)	0	(0%)
Creatinine increased	1	2	(0%)	1	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
INR increased	1	1	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Investigations - Other, specify	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Lipase increased	1	0	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	1	(0%)	0	(0%)
Weight loss	1	0	(0%)	0	(0%)	0	(0%)
	2	3	(1%)	0	(0%)	0	(0%)
Metabolism and nutrition dis							
Acidosis	1	0	(0%)	2	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Anorexia	1	6	(1%)	0	(0%)	0	(0%)
	2	5	(1%)	1	(0%)	0	(0%)
Dehydration	1	7	(1%)	1	(0%)	0	(0%)
	2	16	(3%)	0	(0%)	0	(0%)
Glucose intolerance	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Hyperglycemia	1	8	(2%)	1	(0%)	0	(0%)
	2	5	(1%)	0	(0%)	0	(0%)
Hyperkalemia	1	2	(0%)	1	(0%)	0	(0%)
	2	3	(1%)	1	(0%)	0	(0%)
Hypermagnesemia	1	1	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Hypertriglyceridemia	1	1	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Hyperuricemia	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Hypoalbuminemia	1	2	(0%)	0	(0%)	0	(0%)

Listing of Grade 3+ Adverse Events
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Arm 1=531 Arm 2=487

		Grade of Adverse Event					
	Arm	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
	2	4	(1%)	0	(0%)	0	(0%)
Hypocalcemia	1	3	(1%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Hypokalemia	1	9	(2%)	1	(0%)	0	(0%)
	2	6	(1%)	0	(0%)	0	(0%)
Hypomagnesemia	1	1	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Hyponatremia	1	7	(1%)	2	(0%)	0	(0%)
	2	4	(1%)	3	(1%)	0	(0%)
Hypophosphatemia	1	2	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Metabolism, nutrition disord - Oth spec	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Musculosk and connect tis dis							
Generalized muscle weakness	1	1	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Musculoskeletal, conn tissue - Oth spec	1	1	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Neck pain	1	1	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Pain in extremity	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Nervous system disorders							
Dizziness	1	2	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Encephalopathy	1	0	(0%)	1	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Headache	1	1	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Peripheral motor neuropathy	1	1	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)

Listing of Grade 3+ Adverse Events
Max Grade per Patient Per Event
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Arm 1=531 Arm 2=487

		Grade of Adverse Event					
	Arm	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
Peripheral sensory neuropathy	1	13	(2%)	0	(0%)	0	(0%)
	2	4	(1%)	0	(0%)	0	(0%)
Seizure	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Stroke	1	0	(0%)	0	(0%)	1	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Syncope	1	9	(2%)	0	(0%)	0	(0%)
	2	5	(1%)	0	(0%)	0	(0%)
Tremor	1	2	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Psychiatric disorders							
Anxiety	1	0	(0%)	0	(0%)	0	(0%)
	2	2	(0%)	0	(0%)	0	(0%)
Depression	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Renal and urinary disorders							
Acute kidney injury	1	4	(1%)	3	(1%)	0	(0%)
	2	6	(1%)	1	(0%)	1	(0%)
Renal and urinary disorders - Oth spec	1	1	(0%)	0	(0%)	0	(0%)
	2	0	(0%)	0	(0%)	0	(0%)
Renal calculi	1	0	(0%)	0	(0%)	0	(0%)
	2	2	(0%)	0	(0%)	0	(0%)
Urinary tract pain	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Reprod system and breast dis							
Dyspareunia	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Prostatic pain	1	0	(0%)	0	(0%)	0	(0%)
	2	1	(0%)	0	(0%)	0	(0%)
Respir, thorac and mediast dis							
Aspiration	1	0	(0%)	1	(0%)	0	(0%)
	2	1	(0%)	2	(0%)	0	(0%)

Listing of Grade 3+ Adverse Events
Max Grade per Patient Per Event
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Arm 1=531 Arm 2=487

		Grade of Adverse Event					
	Arm	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
Dyspnea	1	1	*(0%)*	1	*(0%)*	0	*(0%)*
	2	1	*(0%)*	1	*(0%)*	0	*(0%)*
Hypoxia	1	0	*(0%)*	0	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Laryngopharyngeal dysesthesia	1	1	*(0%)*	0	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Pleural effusion	1	0	*(0%)*	0	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Pneumothorax	1	1	*(0%)*	0	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*
Respiratory failure	1	0	*(0%)*	3	*(1%)*	0	*(0%)*
	2	0	*(0%)*	3	*(1%)*	0	*(0%)*
Skin and subcutaneous tiss dis							
Palmar-plantar erythrodysesthesia syndrm	1	1	*(0%)*	0	*(0%)*	0	*(0%)*
	2	5	*(1%)*	0	*(0%)*	0	*(0%)*
Skin and subcut tissue disord - Oth spec	1	2	*(0%)*	0	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Skin ulceration	1	0	*(0%)*	0	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Surgical and medical proceds							
Surgical and medical proced - Oth spec	1	3	*(1%)*	0	*(0%)*	0	*(0%)*
	2	1	*(0%)*	0	*(0%)*	0	*(0%)*
Vascular disorders							
Hypertension	1	20	*(4%)*	0	*(0%)*	0	*(0%)*
	2	12	*(2%)*	0	*(0%)*	0	*(0%)*
Hypotension	1	8	*(2%)*	1	*(0%)*	0	*(0%)*
	2	4	*(1%)*	0	*(0%)*	0	*(0%)*
Thromboembolic event	1	10	*(2%)*	5	*(1%)*	0	*(0%)*
	2	6	*(1%)*	1	*(0%)*	0	*(0%)*

Listing of Grade 3+ Adverse Events
Max Grade per Patient Per Event
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Arm 1=531 Arm 2=487

		Grade of Adverse Event					
	Arm	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
Vascular disorders - Other, specify	1	1	*(0%)*	0	*(0%)*	0	*(0%)*
	2	0	*(0%)*	0	*(0%)*	0	*(0%)*

10.0 IMBEDDED CORRELATIVES

Not applicable