Published in final edited form as:

Int J Radiat Oncol Biol Phys. 2017 April 01; 97(5): 995–1001. doi:10.1016/j.ijrobp.2016.12.018.

A Phase I/II Trial of a Combination of Paclitaxel and Trastuzumab with Daily Irradiation or Paclitaxel Alone with Daily Irradiation Following Transurethral Surgery for Non-Cystectomy Candidates with Muscle-Invasive Bladder Cancer (Trial ****)

M. Dror Michaelson, MD¹, Chen Hu, PhD^{2,10}, Huong T. Pham, MD³, Douglas M. Dahl, MD¹, Chin Lee-Wu, MD¹, Gregory P. Swanson, MD⁴, Jacqueline Vuky, MD⁵, R. Jeffrey Lee, MD⁶, Luis Souhami, MD⁷, Brian Chang, MD⁸, Asha George, MS², Howard Sandler, MD⁹, and William Shipley, MD¹

¹Massachusetts General Hospital Cancer Center, Boston, MA

²NRG Oncology Statistics and Data Management Center, Philadelphia, PA

³Virginia Mason CCOP, Seattle, WA

⁴University of Texas at San Antonio, San Antonio, TX

⁵Virginia Mason CCOP, Seattle, WA (during trial) - Oregon Health & Science University, Portland, OR (current)

⁶Intermountain Medical Center, Murray, UT

⁷McGill University, Montréal, QC

⁸Parkview Cancer Center - Parkview Hospital, Fort Wayne, IN

⁹Cedars-Sinai Medical Center, Los Angeles, CA

¹⁰Sydney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD

Summary

Standard treatment for muscle invasive urothelial cancer of the bladder is radical cystectomy. Bladder preservation with combination of radiation and chemotherapy is a well-established alternative to surgery. In this study we treated patients who were not surgical candidates with chemoradiation, to a high completion rate. Our findings suggest that in such patients radiation may

Corresponding Author: M. Dror Michaelson, MD, PhD, Massachusetts General Hospital Cancer Center, 55 Fruit Street, Yawkey 7E, Boston, MA 02114, T: 617-726-1594, F: 617-726-3440, dmichaelson1@partners.org.

Conflicts of interest: Dr. Souhami reports travel expenses from Varian Medical Systems, outside the submitted work. Dr. Sandler reports grants from ACR-RTOG, during the conduct of the study; consulting and advisory fees from Sanofi, Medivation, Clovis Oncology, Janssen, Ferring, NANT Health, and Blue Earth Diagnostics, speaking fees from Varian, outside the submitted work.

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be combined with weekly paclitaxel, and in her2/neu positive tumors with the further addition of trastuzumab, with moderate toxicity.

Purpose—Bladder preservation therapy is an effective treatment for muscle invasive urothelial carcinoma (UC). In this study we treated non-cystectomy candidates with daily radiation and weekly paclitaxel for seven weeks. Patients whose tumors exhibited her2/neu overexpression were additionally treated with weekly trastuzumab.

Methods and Materials—Sixty-eight evaluable patients were treated with radiation therapy and either paclitaxel + trastuzumab (Group 1) or paclitaxel alone (Group 2). Groups were assigned on the basis of her2/neu immunohistochemistry. Patients received 1.8 Gy fractions to a total dose of 64.8 Gy. The primary endpoint of the study was treatment-related toxicity, and secondary endpoints included complete response (CR) rate, protocol completion rate, and survival.

Results—A total of 20 evaluable patients were treated in Group 1, and 46 patients in Group 2. Acute treatment-related adverse events (AEs) were observed in 7 of 20 patients in Group 1 (35%) and 14 of 46 patients in Group 2 (30.4%). Protocol therapy was completed by 60% (Group 1) and 74% (Group 2) of patients. Most incompletions were due to toxicity and the majority of AEs were gastrointestinal, including one Grade 5 AE (Group 1). Two other deaths (both in Group 2) were unrelated to protocol therapy. No unexpected cardiac, hematologic or other toxicities were observed. The CR rate at 1 year was 72% for Group 1 and 68% for Group 2.

Conclusions—In patients with muscle-invasive UC who are not candidates for cystectomy, daily radiation combined with paclitaxel is an effective treatment strategy with high completion rate and moderate toxicity. In patients with her2/neu+ positive tumors, a group generally considered to have worse outcomes, the addition of trastuzumab appears to result in comparable efficacy and toxicity. Further biomarker-driven trials should be undertaken in advancing treatment of this challenging disease.

Introduction

Selective bladder preservation therapy is an attractive and effective alternative to radical cystectomy for the treatment of muscle invasive urothelial cancer (UC) of the bladder. Numerous prospective trials have established the efficacy and safety of this approach, along with a high success rate for preservation of the bladder.^{1–12} Though there have been no randomized studies comparing selective bladder preservation to cystectomy, retrospective analyses suggest that the outcomes with regard to cancer treatment are comparable.^{13–15}

A substantial percentage of patients with bladder cancer have important comorbidities, which often compromise their suitability for radical cystectomy. Similarly, such comorbidities may pose an absolute or relative barrier to typical bladder preservation approaches, which often include platinum-based chemotherapy, hyperfractionated radiation, and implementation of cystectomy for patients who fail to achieve a complete response to radiation therapy. We therefore set out to study bladder preservation in non-cystectomy candidates, using a modified non-platinum chemotherapy regimen and once daily radiation, and also recognizing that in this population, salvage cystectomy would not be possible.

Additionally, we have studied the addition of trastuzumab to the radiosensitizing chemotherapy regimen. Prior studies suggested that there is a high rate of her2/neu positive-tumors among patients with UC, and further that such tumors may have inferior outcomes with traditional therapy.^{16–22} In this study, we analyzed tumors for her2/neu expression, and added trastuzumab to paclitaxel chemotherapy in her2/neu positive cases.

Our overall goal was to establish the safety and efficacy of non-selective bladder preservation therapy, utilizing transurethral resection followed by once daily radiation combined with paclitaxel +/- trastuzumab therapy, in patients with muscle invasive UC who were not candidates for cystectomy.

Materials and Methods

Study Design and Participants

In this phase I/II study, patients were non-randomly assigned to treatment Group 1 or Group 2 based on immunohistochemical (IHC) expression of her2/neu. Patients with IHC 2+ or 3+ expression of her2/neu were treated with RT+paclitaxel+trastuzumab (Group 1), and patients with IHC negative or 1+ expression of her2/neu were treated with RT+paclitaxel (Group 2). Eligible patients had pathologically confirmed primary bladder UC with histologic evidence of muscularis propria invasion (T2 or higher), and no radiographic or clinical evidence of metastatic disease. Patients must have been judged to be medically inappropriate for radical cystectomy by the treating urologist. They were required to undergo a thorough TURB (transurethral bladder resection) along with bimanual examination, and had sufficient tumor tissue available for her2/neu analysis. CT scans of the abdomen/pelvis, and CT or X-ray of the chest, were required within 8 weeks of registration. Patients were required to have adequate bone marrow and liver function. Serum creatinine had to be ≤ 3.0 mg/dl, and cardiac ejection fraction $\geq 40\%$ by echocardiogram or nuclear (MUGA) scan. All patients signed informed consent, and the clinical trial was approved by central and institutional review boards. The study is registered with ClinicalTrials.gov, number NCT****.

Treatment Programs

All patients were treated with daily radiation therapy and weekly paclitaxel. Radiation therapy was administered in 1.8 Gy fractions once daily, 5 days/week, for a total of 36 fractions, as follows: 1.8 Gy small pelvic fields x 22 fractions, then reduction to whole bladder for 1.8 Gy x 8 fractions, and finally a reduction to the bulky tumor area with margin (partial sparing of the bladder if possible) for an additional 6 fractions at 1.8 Gy. Total dose was 64.8 Gy. The initial “small pelvic field” should encompass the entire bladder, prostate, and pelvic lymph nodes below the common iliac bifurcation. Field margins in the superior-inferior dimensions should extend from mid-sacro-iliac region to just below the obturator foramen. The anterior-posterior opposed fields should extend 1.5–2.0 cm laterally beyond the medial aspect of the pelvic bones to encompass the iliac lymph nodes. Customized blocks should be used on the inferior lateral edges of these fields to reduce exposure of the femoral heads and provide 2.5 cm margin around the bladder. On the lateral fields, additional blocking can be used to reduce the margin around bladder and lymph nodes to 1.5 cm if there is significant small bowel in the pelvis. We kept the field design similar to prior

**** bladder studies but used daily fractionation (rather than BID) and shrinking field technique to make it easier on this patient population to be able comply to the treatment regimen. The dose of 39.6 Gy to the pelvic lymph nodes and shrinking fields technique was also designed to keep small bowel dose down. 3D-CT based treatment planning was employed in this study. Intensity modulated radiation therapy (IMRT) was not permitted. Paclitaxel was administered as a one-hour infusion once per week, generally corresponding with the first day of radiation therapy in each week (days 1, 8, 15, 22, 29, 36, 43), at a dosage of 50 mg/m². Dose reduction was permitted to 50% of the starting dose.

In Group 1, those with her2/neu overexpression by IHC, patients additionally were treated once weekly with trastuzumab, generally corresponding with the first day of radiation therapy in each week. On day 1, a loading dose of 4 mg/kg was administered intravenously, and subsequent weekly doses were 2 mg/kg. No dose reductions were permitted. In the event of unacceptable toxicity, including grade 3 or 4 cardiac or infusional toxicity, trastuzumab was to be discontinued.

History and physical, vital signs, and routine laboratory studies were obtained weekly during the active treatment program.

Patients continued treatment until completion of all seven weeks of chemotherapy and 36 fractions of radiation, or until:

- Progression of disease
- Unacceptable toxicity
- Delay in treatment of > 3 weeks
- Inability of patient to comply with study regulations
- Withdrawal of informed consent

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Serious adverse events were reported via the AdEERS (Adverse Event Expedited Reporting System) application accessed via the CTEP web site.

Following completion of treatment, evaluation was performed with cystoscopy and urine cytology. Repeat imaging of the chest, abdomen and pelvis were done to exclude development of metastatic or recurrent disease, and repeat MUGA to assess cardiac function. Additional cystoscopies were recommended every three months for the first year after completion of treatment.

Tissue Analysis

At least one paraffin-embedded tissue block of the tumor for each patient was submitted to the **** Biospecimen Resource at the University of California San Francisco, for the purposes of her2/neu analysis. Slides created from the block were evaluated for her2 expression by immunohistochemistry using HercepTest. The interpretation of the slides was done using image analysis on the ACIS system. Results of her2 testing were available 1–2

business days after receipt of the block from institutions, and results were immediately provided to the submitting institution for patient grouping.

Outcomes

The study primary endpoint, acute treatment related toxicity, was defined as acute treatment-related toxicity that did not resolve to Grade 1 within 7 days or a reasonable timeframe as determined by the study chairs and treating physicians. These included:

- Grade 4 neutropenia or grade 4 febrile neutropenia
- Grade 3 diarrhea, nausea, or vomiting
- Grade 3 thrombocytopenia or grade 3 for all of the following non-hematologic toxicities: renal, pulmonary, hepatic, or neurologic toxicity; rectal or genitourinary bleeding; left ventricular failure (or grade 2 for all other cardiac toxicity)
- Inability to complete the chemoradiation due to treatment-related toxicity

Secondary endpoints included complete response rate of the primary tumor, disease free and overall survival, and ability of patients who are non-cystectomy candidates to complete this treatment program.

Statistical Considerations

The sample size for each group was calculated separately and independently. Using Fleming's one-sample multiple test procedure²³ with a 10% type-1 error (1-sided) and 90% power, 40 analyzable cases for each group are required to reject a null hypothesis that the true toxicity rate to the respective therapy was greater than 25% (i.e., <75% toxicity-free rate) and favor an alternative hypothesis that the true rate was no more than 10% (i.e., 90% toxicity-free rate). Guarding against a 10% rate of ineligible or inevaluable cases, the targeted accrual for each group was 44 patients. All eligible patients receiving any protocol treatment were included in the analysis. Binomial exact test was used for hypothesis testing of the primary endpoint (protocol-specified acute treatment-related toxicity). Clopper-Pearson method was used to compute the 95% confidence interval of complete response rate.

Results

Study Enrollment and Patient Characteristics

This study was opened to accrual on September 26, 2005, by the **** and National Clinical Trials Network (NCTN) of National Cancer Institute (NCI). After endorsement by **** and ****, the trial was also opened through the Cancer Trials Support Unit (CTSU) and was therefore available to all United States cooperative groups, United States independent research sites, and the NCIC CTG in Canada. The study was temporarily closed to accrual in June 2009, to amend for the addition of risk for bowel perforation, and reopened to accrual in August 2009. The study was temporarily closed to accrual in October 2011 for planned safety interim analysis and reopened in January 2012. The study permanently closed to accrual in February 2013 with a total of 76 patients entered, of whom 70 had sufficient tissue

for her2/neu. Three patients, two from Group 1 and one from Group 2, were excluded due to not meeting eligibility criteria (chemotherapy treatment initiation beyond the 8-week window after transurethral bladder resection (TURB), echocardiogram not done prior to enrollment, T4b disease), and one from group 2 was excluded due to not receiving protocol treatment. A total of 66 evaluable patients were ultimately included in this analysis. There were 20 patients with her2/neu overexpression who received radiation therapy + paclitaxel + trastuzumab (Group 1), and 46 patients without her2/neu overexpression who received radiation therapy and paclitaxel (Group 2).

The pretreatment characteristics are listed in Table 1. The median ages of the Group 1 and 2 patients were 80 and 73, respectively. Most of the patients were male and Caucasian. More than 90% of patients had a performance status of 0 or 1 in both groups. The TNM clinical stage in both groups was predominantly T2, and more than 80% of patients were stage N0. All patients were stage M0.

Treatment Related Toxicities

Regarding the primary toxicity endpoint of this study, acute protocol-specified treatment related adverse events (AEs), 7 of 20 patients in Group 1 (35.0%, 95% CI: 15.4–59.2%) and 14 of 46 patients in Group 2 (30.4%, 95% CI: 17.7–45.8%) met these criteria (Table 2). Among the first 40 patients in Group 2, 11 patients had protocol-specified AEs. Table 3 lists the details. For Group 1, one grade 5 AE (colonic perforation) was deemed possibly related to protocol treatment; the remaining AEs were grade 3 (except one grade 2), and 4 of the 7 patients had grade 3 gastrointestinal toxicities. In Group 2, one patient experienced grade 4 pneumonia and pneumonitis that was possibly related to treatment, and one patient experienced grade 4 personality change that was related to treatment; the rest of the AEs were all grade 3, and 9 of the 14 patients had grade 3 gastrointestinal toxicities. In addition, there was two grade 5 AEs in Group 2 that was unrelated to protocol treatment. Of note, the incidence of cardiac toxicity in Group 1 was low, with one grade 3 and one grade 2 cardiac AEs. Table 4 reports the summary of worst AEs (per patient) that were definitely, probably or possibly related to treatment. Because 7 of 20 patients in Group 1 and 11 of the first 40 patients in Group 2 had protocol-specific AEs, the null hypothesis that the true toxicity rate to the respective therapy was greater than 25% cannot be rejected for either group.

Tumor Response

The complete response (CR) rates for Group 1 and Group 2 at 12 weeks, defined as no gross tumor at cystoscopy or negative biopsies or both by week 12 after completion of protocol treatment, were 61.5% (8 responses of 13 evaluable cases, 95% CI: 31.6%–86.1%) and 62.5% (20 responses of 32 evaluable cases, 95% CI: 43.7–78.9%), respectively (Table 5). There were 7 patients in Group 1 and 14 patients in Group 2 deemed unevaluable for response because cystoscopy and tumor biopsy were not done at 12 weeks. When analyzed at 1 year, the CR rate was 72.2% (13 responses of 18 evaluable cases, 95% CI: 46.5–90.3%) for Group 1 and 67.6% (25 responses of 37 evaluable cases, 95% CI: 50.2–82.0%) for Group 2. Among the 11 unevaluable cases at 1 year, 10 died without a response evaluation, and 1 had the initial response evaluation beyond 1 year.

Protocol Treatment Completion

All patients underwent protocol treatment reviews. Fifteen of 20 patients (75%) in Group 1 and 38 of 46 patients (82.6%) in Group 2 received radiotherapy per protocol or with acceptable variation. Nineteen patients (95.0%) in Group 1 and 43 patients (93.5%) in Group 2 received chemotherapy per protocol. As one of the pre-specified secondary endpoints, Table 6 shows the treatment completion information for the 2 groups. Twelve patients (60.0%) in Group 1 and 34 patients (73.9%) in Group 2 completed treatment per protocol. The percentage of treatment incompleteness per protocol due to toxicity (whether radiotherapy alone, chemotherapy alone, or both) was numerically higher in Group 1 (40.0%) than Group 2 (19.5%).

Discussion

We have studied combination radiation and chemotherapy for non-cystectomy candidates with invasive urothelial bladder cancer. This study specifically addressed a patient population that is particularly challenging, namely those who are medically unfit for either radical cystectomy or platinum-based radiosensitizing chemotherapy. In contrast to a series of prior protocols of selective bladder sparing therapy conducted by the *****, which relied on salvage cystectomy for patients who did not respond fully to an induction course of chemoradiation,^{1-5,7,12,24} this study treated patients with radiation and chemotherapy without interval cystoscopy. Response evaluation at the end of treatment found that a majority of patients in both groups successfully completed therapy, and a majority of evaluable patients manifested a complete response to treatment. Therefore, this treatment approach is a reasonable strategy in this patient population.

Overall, the rate of adverse events was similar to that seen in prior protocols of bladder sparing therapy. As expected for a relatively unfit population, there was a slightly higher rate of serious adverse events (AEs). One death that may have been treatment-related was caused by colonic perforation, which occurred 10 days after treatment completion. The most common grade 3 and grade 4 AEs in both groups were gastrointestinal, particularly diarrhea. In trial XXXX, treatment with radiation therapy in combination with cisplatin and paclitaxel led to a 26% rate of grade 3–4 gastrointestinal AEs.^{7,12} Similarly, in trial YYYY, 35% of patients receiving cisplatin and paclitaxel had grade 3–4 AEs, the majority of which were gastrointestinal in nature.⁷ A lower rate of GI toxicity was observed in the cisplatin/fluorouracil (5-FU) group in trial YYYY, suggesting that paclitaxel may be the primary chemotherapeutic driver of GI toxicity in combination therapy. Our findings are consistent with these prior experiences, and incorporating image guidance and/or intensity modulated radiation therapy (IMRT) in future trials may help improve the gastrointestinal toxicity. IMRT was not allowed on this study since this protocol was written in 2005 and there was little written or known about the use of IMRT for bladder cancer at that time. This also allowed for comparison of toxicity with prior **** bladder studies.

The rate of cardiac adverse events was low in both groups in our study. In the trastuzumab group, there was one patient with grade 3 and one patient with grade 2 cardiac AEs. Hematologic toxicity was manageable as well, with one grade 4 AE in the RT+paclitaxel

group and one grade 4 AE in the RT+paclitaxel+trastuzumab group. Given the nature of the patient population, the low rates of both cardiac and hematologic toxicity were reassuring.

While platinum-based radiosensitizing chemotherapy has been a standard approach to bladder sparing therapy for many years, a large and favorable experience with mitomycin/5-FU has validated an appealing alternative.²⁵ In the BC2001 study, 306 patients were randomized to treatment with radiation with or without concurrent mitomycin/5-FU. Regional control was superior among patients treated with combination therapy compared with radiation therapy alone, and AEs were similar in the two groups. Approximately 35% of patients experienced grade 3 or higher AEs in the RT+mitomycin/5-FU group, a lower rate than we have observed in a more compromised patient population. The results of the BC2001 study further support a non-surgical and non-platinum based approach to the treatment of muscle-invasive bladder cancer.

Prior translational studies had suggested that the rate of her2/neu 2+ positivity by IHC might be as high as 50% in urothelial cancer, though the fluorescence in situ hybridization (FISH) positivity rate was considerably lower.^{16,18,20,21,26-32} Among the eligible patients of Trial ****, we found a lower rate of IHC 2+, and consequently less than one third of enrolled patients were treated in Group 1 with trastuzumab. One limitation of our study is the limited number of patients in Group 1, which challenges any definitive conclusions regarding the treatment regimen of RT+paclitaxel+trastuzumab. While the Group 1 CR rate of 62% compares favorably with historical controls, no clear efficacy conclusions may be drawn. Our experience suggests a reasonable safety profile to this regimen. Based on experience in other malignancies, future studies of her2/neu-based treatment in urothelial cancer should probably focus on FISH-positive cancers, rather than on IHC 2+ cancers.

It is notable that the accrual to this cooperative group study took place over seven years, which highlights the difficulty of conducting trials in this niche population of medically compromised bladder cancer patients. While comprehensive evaluation of such a population remains an unmet need, we believe that both paclitaxel and mitomycin/5-FU based combination treatments with radiation are feasible approaches that may be utilized in this patient population, and are likely superior to radiation therapy alone. At the same time, a substantial percentage patients treated in this fashion are destined to relapse, generally with distant metastases, and ongoing research should focus on more effective and tolerable systemic therapy options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This project was supported by RTOG grant U10 CA21661, and CCOP grant U10 CA37422 from the National Cancer Institute (NCI). This manuscript's contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

We are grateful for the valuable contributions of ****, MD who served as the **** Co-Chair during the trial.

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Table 1

Pretreatment Characteristics

	RT + Paclitaxel + Trastuzumab (Group 1) (n=20)	RT + Paclitaxel (Group2) (n=46)
Age (years)		
Median	79.5	73
Min - Max	51 – 86	55 – 90
Q1 - Q3	72.5 – 81.5	65 – 80
Gender		
Male	18 (90.0%)	36 (78.3%)
Female	2 (10.0%)	10 (21.7%)
Race		
Asian	0 (0.0%)	1 (2.2%)
White	20 (100.0%)	45 (97.8%)
Ethnicity		
Not Hispanic or Latino	20 (100.0%)	44 (95.7%)
Unknown	0 (0.0%)	2 (4.3%)
Zubrod Performance Status		
0	7 (35.0%)	26 (56.5%)
1	12 (60.0%)	16 (34.8%)
2	1 (5.0%)	4 (8.7%)
T Stage		
T1	1 (5.0%)	2 (4.3%)
T2	15 (75.0%)	39 (84.8%)
T3	3 (15.0%)	3 (6.5%)
T4	1 (5.0%)	2 (4.3%)
N Stage		
N0	18 (90.0%)	38 (82.6%)
N1	0 (0.0%)	4 (8.7%)
NX	2 (10.0%)	4 (8.7%)
M Stage		
M0	20 (100.0%)	46 (100.0%)
Q1 = first quartile; Q3 = third quartile.		

Table 2

Incidence of Protocol-Specified Acute Treatment-Related Toxicity

	Number of Patients with acute toxicities	p-value*
RT + Paclitaxel + Trastuzumab (n=20)	7 (35.0%) (15.4%, 59.2%)**	0.90
RT + Paclitaxel (n=46)	14 (30.4%) (17.7%, 45.8%)**	0.85
RT + Paclitaxel (first 40)	11 (27.5%) (14.6%, 43.9%)**	0.72

* One-sided exact binomial exact test

** 95% Clopper-Pearson exact confidence interval

Table 3

Acute protocol-specified treatment related adverse events*

Category Term	RT + Paclitaxel + Trastuzumab (n=20) Grade					RT + Paclitaxel (n=46) Grade				
	1	2	3	4	5	1	2	3	4	5
BLOOD/BONE MARROW	0	0	0	0	0	0	0	1	0	0
Neutrophil count	0	0	0	0	0	0	0	1	0	0
CARDIAC GENERAL	0	1	1	0	0	0	0	0	0	0
Hypotension NOS	0	1	0	0	0	0	0	0	0	0
Myocardial ischemia	0	0	1	0	0	0	0	0	0	0
GASTROINTESTINAL	0	0	4	0	1	0	0	9	0	0
Colonic perforation	0	0	0	0	1	0	0	0	0	0
Dehydration	0	0	1	0	0	0	0	0	0	0
Diarrhea NOS	0	0	4	0	0	0	0	8	0	0
Fecal incontinence	0	0	1	0	0	0	0	0	0	0
Proctitis NOS	0	0	1	0	0	0	0	0	0	0
Enteritis	0	0	0	0	0	0	0	1	0	0
HEMORRHAGE/BLEEDING	0	0	2	0	0	0	0	0	0	0
Hematoma	0	0	1	0	0	0	0	0	0	0
Rectal hemorrhage	0	0	1	0	0	0	0	0	0	0
INFECTION	0	0	1	0	0	0	0	1	1	0
Urinary tract infection NOS	0	0	1	0	0	0	0	0	0	0
Kidney infection NOS	0	0	0	0	0	0	0	1	0	0
Pneumonia NOS	0	0	0	0	0	0	0	0	1	0
NEUROLOGY	0	0	0	0	0	0	0	1	1	0
Dizziness	0	0	0	0	0	0	0	1	0	0
Personality change	0	0	0	0	0	0	0	0	1	0
PULMONARY/UPPER RESPIRATORY	0	0	1	0	0	0	0	0	1	0
Dyspnea	0	0	1	0	0	0	0	0	0	0
Pneumonitis NOS	0	0	0	0	0	0	0	0	1	0
RENAL/GENITOURINARY	0	0	2	0	0	0	0	1	0	0

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Category	Term	RT + Paclitaxel + Trastuzumab (n=20) Grade					RT + Paclitaxel (n=46) Grade				
		1	2	3	4	5	1	2	3	4	5
	Cystitis NOS	0	0	1	0	0	0	0	0	0	0
	Pollakiuria	0	0	2	0	0	0	0	1	0	0

*The line of each category represents the worst grade reported per patient across all terms within the category.

Table 4

Overall Worst Treatment Related Adverse Events per Patient

Adverse Event	Grade	Group 1(n=20)	Group 2 (n=46)
Worst non-hematologic	1	4 (20.0%)	10 (21.7%)
	2	4 (20.0%)	9 (19.6%)
	3	8 (40.0%)	7 (15.2%)
	4	0 (0%)	1 (2.2%)
	5	1 (5.0%)	0 (0%)
Worst overall	1	0 (0.0%)	5 (10.9%)
	2	4 (20.0%)	14 (30.4%)
	3		23 (50.0%)
	4	1 (5.0%)	4 (8.7%)
	5	1 (5.0%)	0 (0.0%)

Table 5

Complete Response to Treatment at 12 Weeks

	Group 1 (n=13[*])	Group 2 (n=33[*])
Complete Response	8 (61.5%) (31.6%, 86.1%) ^{**}	20 (62.5%) (43.7%, 78.9%) ^{**}
No Response	5 (38.5%)	12 (37.5%)

^{*} cases with 'Not available' or 'Missing' status are not counted towards the complete response

^{**} 95% Clopper-Pearson exact confidence interval.

Table 6

Treatment Completion

Reason Treatment Terminated	Group 1 (n=20)	Group 2 (n=46)
Completed per protocol	12 (60.0%)	34 (73.9%)
Death	0 (0.0%)	2 (4.3%)
Patient withdrawal or refusal after beginning protocol therapy	0 (0.0%)	1 (2.2%)
Toxicity	8 (40.0%)	9 (19.5%)