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Durvalumab with or without tremelimumab in patients with persistent or recurrent endometrial cancer or endometrial carcinosarcoma: A randomized open-label phase 2 study

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Abstract

Introduction.—Our understanding of the biologic heterogeneity of endometrial cancer has improved, but which patients benefit from single-agent versus combination immune checkpoint blockade remains unclear.

Methods.—We conducted a single-center, randomized, open-label, phase 2 study of durvalumab 1500 mg (Arm 1) versus durvalumab 1500 mg plus tremelimumab 75 mg every 4 weeks (Arm 2) in patients with endometrial carcinoma. The primary endpoints were overall response rate (ORR) and progression-free survival (PFS) at 24 weeks. Patients were stratified by mismatch repair (MMR) status and carcinosarcoma histology. Using a Simon two-stage minimax design, we determined 40 patients per arm would provide 90% power and Type 1 error of 10%.

Results.—Eighty-two patients were enrolled; 77 were evaluable for toxicity (Arm 1: 38, Arm 2: 39) and 75 evaluable for efficacy (Arm 1: 37, Arm 2: 38). Patient were stratified by MMR status (Arm 1: 5, Arm 2: 4 were MMR-deficient). The ORR in Arm 1 was 10.8% (one-sided 90% CI: 4.8–100%); the ORR in Arm 2 was 5.3% (one-sided 90% CI: 1.4–100%). Since the primary endpoint of ORR was not met, 24-week PFS was not compared to historical controls per protocol specification. No new safety signals were identified.

Conclusions.—In these patients with predominantly MMR-proficient endometrial cancer, there was limited response with single-agent and combined immune checkpoint blockade. The pre-specified efficacy thresholds were not met for further evaluation. A deeper understanding of potential mechanisms of resistance to immunotherapy in MMR-proficient endometrial cancer is needed for the development of novel therapeutic approaches.

Keywords

Durvalumab; Tremelimumab; Endometrial cancer; Endometrial carcinosarcoma; Phase 2

1. Introduction

The incidence and disease-related mortality attributed to endometrial cancer are sharply rising. On a global scale, there were 417,000 new cases and 97,000 endometrial cancer–

associated deaths in 2020 [1]. In the US, there has been an annual 1.8% increase in endometrial cancer mortality over the past several years, and the mortality rate will soon surpass that of ovarian cancer [2,3]. Growing rates of obesity and sedentary lifestyle have had a much larger effect on the incidence of endometrial cancer (70% of cases) compared with ovarian cancer (4% of cases) [4]. Platinum-taxane combination chemotherapy for advanced/recurrent endometrial cancer is associated with finite efficacy, responses to second-line cytotoxic agents are modest, and tumors often become therapy resistant [5,6]. The recent approval of lenvatinib plus pembrolizumab has given patients further treatment options but at considerable cost and toxicity, making it unsuitable for all patients [7].

The characterization of endometrial cancer into 4 distinct (molecular and prognostic) subtypes has provided insight into how to rationally target this disease. These subtypes include: (1) *POLE* "ultramutated"; (2) microsatellite instability hypermutated (MSI-H) or mismatch repair deficient (dMMR); (3) copy number low (CNL); and (4) copy number high (CNH) [8]. Since the advent of this classification system, immune checkpoint blockade has proven to be an effective strategy for *POLE*-"ultramutated" and MSI-H/dMMR (MLH1, MSH2, MSH6, PMS2) endometrial cancers [9,10]. However, the majority of relapsed endometrial cancers are microsatellite stable (MSS) or MMR-proficient (pMMR), CNL, or CNH, with limited responses (<13%) to single-agent programmed cell death protein 1/programmed death-ligand 1 (PD-1/ PD-L1) therapies [11-15]. Combination PD-1/PD-L1 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade has shown improved outcomes in various malignancies, including melanoma, renal cell carcinoma, hepatocellular carcinoma, and non-small lung carcinoma [16-19].

Durvalumab is a selective, high-affinity, human IgG1 monoclonal antibody (mAb) that binds to PD-L1 and CD80. Tremelimumab is an IgG2 kappa isotype mAb directed against CTLA-4. Dual inhibition of CTLA-4 plus PD-L1 can enhance T-cell activation and cellular immune responses [20]. Given the non-overlapping mechanisms of action of CTLA-4 and PD-L1 inhibitors and the potential for synergistic activity, we investigated durvalumab with and without tremelimumab in advanced or recurrent endometrial cancer, regardless of MMR status, in this randomized phase 2 study.

2. Methods

2.1. Study design

This was a single-institution, randomized, open-label, phase 2 study of durvalumab monotherapy or durvalumab plus tremelimumab in patients with metastatic, recurrent, or persistent endometrial carcinoma or endometrial carcinosarcoma. Patients were administered either 1500 mg durvalumab via intravenous (IV) infusion every 4 weeks (Arm 1) OR 1500 mg durvalumab and 75 mg tremelimumab via IV infusion every 4 weeks for up to 4 cycles, and then 1500 mg durvalumab every 4 weeks thereafter (Arm 2). The primary endpoints were overall response rate (ORR) and progression-free survival (PFS) at 24 weeks in each treatment arm. Tumor response was evaluated via Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, with response confirmation [21]. Secondary endpoints included clinical benefit rate (CBR), defined as the rate of complete response (CR), partial response (PR), and stable disease (SD) rate in each arm at 24 weeks; duration of response (DOR);

ORR evaluated by Immune-related RECIST (irRECIST) criteria in patients treated beyond progression, and safety per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Eligible patients had confirmed recurrent or persistent endometrial cancer of the following histologic subtypes: endometrioid, serous, undifferentiated, dedifferentiated, mixed epithelial, mucinous, squamous, transitional cell, adenocarcinoma not otherwise specified, or endometrial carcinosarcoma. All patients were 18 years of age or older; had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; had adequate organ function; and had at least one prior platinum-based chemotherapeutic regimen but no more than three additional cytotoxic regimens. Patients who had received prior anti–PD-1/PD-L1 or anti–CTLA-4 therapy or had inflammatory bowel disease, primary immunodeficiency, allogenic organ transplant, or interstitial lung disease were excluded.

Treatment cycles were 28 days, and treatment was continued until unacceptable toxicity, intolerance, withdrawal, or progression of disease (whichever occurred first). Radiologic assessments occurred every 8 weeks (+/− 7 days) for the first 48 weeks and then every 12 weeks (+/− 7 days) until progression. For patients who remained progression free 2 years after completion of protocol-directed treatment, radiologic assessments occurred every 6 months (+/− 1 month).

MMR status was determined by immunohistochemistry (IHC) staining for MMR proteins (MLH1, MSH2, MSH6, PMS2). M1 (prior to 2019) or ES05 antibodies were used for MLH1, G219–1129 antibody for MSH2, EP49 antibody for MSH6, and A16.4 antibody for PMS2 per our institutional standard guidelines. Microsatellite status was determined by MSI sensor testing of tumor, by known mutations found in MMR genes, or by MSK-IMPACT (Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets)-targeted sequencing [22,23]. Molecular subtype was assigned by our hybrid, hierarchical institutional algorithm, which includes principles from The Cancer Genome Atlas (TCGA) and The Proactive Molecular Risk Classifier of Endometrial Cancer (ProMisE) algorithms [8,24,25]. Briefly, we combined next-generation sequencing parameters, including *POLE* and *TP53* mutation status, MSI score, tumor mutational burden, and fraction of genome altered, with MMR and p53 IHC results. Our institutional database contains molecular subtype for tumors meeting a minimum of 20% tumor purity on MSK-IMPACT for proper classification [26].

The study protocol was approved by the Memorial Sloan Kettering Cancer Center (MSK) institutional review board (IRB) and was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines [27,28]. All patients provided written informed consent prior to study enrollment. The study was registered at ClinicalTrials.gov (NCT03015129). Patients consented to genomic analysis of their tissue samples through a separate MSK IRB-approved protocol (ClinicalTrials.gov, NCT01775072).

2.2. Statistical design and analysis

This single-institution, randomized, phase 2 study was not powered to show superiority of either arm, and the two treatment arms were analyzed separately.

Randomization was completed by random permuted blocks; within each treatment arm, patients were enrolled into two strata, and enrollment of stratum 1 was limited to 10 patients. Stratum 1 included patients with endometrial carcinosarcoma or dMMR/MSI endometrial carcinoma, and stratum 2 included patients with all other pMMR histologies (See Fig. 1).

Based on data from prior immune checkpoint studies in gynecologic malignancies at the time of study inception, we determined an ORR of 10% was not promising and an ORR of ≥25% was considered promising for further study. Using a Simon two-stage minimax design, we determined that 40 patients per treatment arm would provide 90% power and Type 1 error of 10%. Interim analysis was planned after the accrual of 27 patients per arm, whereby 3 or more responders out of 27 would be enough to continue to the second stage. Arm 1 or Arm 2 would be worthy of further investigation if ≥7 patients achieved a CR or PR in each individual arm at final analysis. If the ORR criteria were met, then the PFS rate at 24 weeks would be tested against historical controls from Gynecologic Oncology Group (GOG) studies in similar patient populations [29-31]. The primary and secondary efficacy objectives as CBR were reported with a one-sided 90% CI, which was estimated using exact binomial proportion. The Kaplan-Meier method was used to estimate the median PFS, overall survival (OS), and DOR, as well as their corresponding rates at 24 weeks.

3. Results

3.1. Patient characteristics

Eighty-two patients consented for study enrollment. Three patients failed screening and 2 were randomized but developed rapid progression of disease prior to starting treatment, leaving 77 evaluable patients for toxicity assessment (Arm 1: 38, Arm 2: 39). Two patients received treatment on cycle 1, day 1, but died prior to first radiologic assessment, leaving 75 evaluable patients for efficacy assessment (Arm 1: 37, Arm 2: 38). Demographic and tumor characteristics are outlined in Table 1.

3.2. Efficacy

At the time of data cut-off (December 10, 2021), there were 4 responders among 37 efficacy-evaluable patients in Arm 1 (ORR, 10.8%; one-sided 90% CI: 4.8–100%); 2 patients achieved a CR and 2 achieved a PR as best response (Table 2). Of the 2 patients who achieved a PR, progression of disease was noted at 16 and 24 weeks, respectively, and both had pMMR tumors. The patients who achieved a CR had dMMR tumors, had not progressed at time of data cut-off, and were censored at 73 and 183 weeks. In Arm 2, there were 2 responders among 38 efficacy-evaluable patients (ORR, 5.3%; one-sided 90% CI: 1.4–100%); both patients achieved a CR, had dMMR tumors, and were censored at 60 weeks and 224 weeks. The median DOR was 24 weeks (one-sided 90% CI: 16-Inf) for Arm 1 and had not been reached for Arm 2. Since the primary endpoint of ORR was not met, PFS at 24 weeks was not compared to historical controls per protocol specifications. Additionally,

2 patients had unconfirmed PR (one in each arm) during the first stage of enrollment. In Arm 1, a patient with PR had SD on confirmation. In Arm 2, one patient achieved an initial PR but was removed from the study due to the development of grade 3 immune-mediated adrenal insufficiency and experienced progression at a subsequent time point. The median PFS for Arm 1 was 7.4 weeks (one-sided 90% CI: 7 weeks-Inf), and the median PFS for Arm 2 was 7.9 weeks (one-sided 90% CI: 7 weeks-Inf). The CBR at 24 weeks was 13.5% (one-sided 90% CI: 6.7–100%) in Arm 1 and 10.5% (one-sided 90% CI: 4.7–100%) in Arm 2. ORR for carcinosarcoma patients was 0% in both arms and all patients were MSS or pMMR. Seventeen (43.6%) of 39 patients in Arm 1 completed 4 cycles of durvalumab plus tremelimumab combination therapy.

Among 14 patients (Arm 1: 6, Arm 2: 8) treated beyond progression and evaluated by irRECIST criteria, there were no differences in best overall response between irRECIST and RECIST assessments. Of the patients treated beyond progression, one patient (Arm 1) who had achieved SD as best response received clinical benefit and continued treatment approximately 1 year after radiographic progression.

3.3. Safety

The most frequent (≥25%) adverse events (AEs) of any cause are outlined in Table 3. In Arm 1, the most common grade 3 or higher treatment-related AEs (TRAEs) were anemia (n = 3, 8%), hyperglycemia (n = 2, 5%), elevated lipase (n = 2, 5%), diarrhea, elevated alanine transaminase, hyponatremia, and lymphocyte decrease (each n = 1, 3%). In Arm 2, the most common grade 3 or higher TRAEs were colitis (n = 4,10%), hyperglycemia, elevated lipase, and lymphocyte decrease (each n = 2, 5%). There were more immune-mediated TRAEs in the combination arm (Arm 2), including colitis/diarrhea (n = 4), myositis (n = 1), myocarditis (n = 1), pneumonitis (n = 1), and adrenal insufficiency (n = 1).

3.4. Molecular analysis

This study included all-comers but stratified patients by MMR status. MMR IHC was not available for 4 patients (Arm 1: 2, Arm 2: 2). Three of these 4 patients had confirmed MSS tumors. Five patients in Arm 1 had dMMR tumors by IHC, and of these, 2 achieved a CR and 1 had SD as best response. Four patients in Arm 2 had dMMR tumors by IHC, and of these, 2 patients achieved a CR and 2 had SD as best response.

4. Discussion

We aimed to explore the efficacy of durvalumab and durvalumab plus tremelimumab in this all-comer, but predominantly pMMR/MSS, endometrial cancer population. Both monotherapy durvalumab (Arm 1) and in combination with tremelimumab (Arm 2) demonstrated modest efficacy of 10.8% and 5.3%, respectively, and neither treatment arm met the pre-specified efficacy endpoints worthy of further evaluation. Although this trial was not designed to compare the two treatment arms, we observed similar low response rates in both arms. Not surprisingly, responses in both Arm 1 and Arm 2 appeared to be driven by the patients with dMMR tumors. There were no new safety signals identified; however, as

expected, there were more frequent treatment-related, immune-mediated adverse events in the combination arm.

The continued molecular characterization of endometrial cancer is critical to direct treatment for advanced and recurrent disease. Despite our improved understanding of the biologic heterogeneity of endometrial cancer, the incidence and disease-associated mortality of endometrial cancer is rising, and until very recently, there were limited therapeutic options beyond carboplatin and paclitaxel chemotherapy [3,8,32,33]. Immune checkpoint inhibitor monotherapy in pMMR/MSS endometrial cancer has shown modest activity, with response rates of 3–13% and median PFS of 1.4–1.9 months [12,14,15,34]. Our study, which included a predominately pMMR/MSS population, is consistent with these previously reported trials. With regard to pMMR endometrial cancer, potentially a small subset may benefit from checkpoint inhibitor therapy, and identifying markers for response in this subset is a priority.

In contrast, deep and durable responses to immune checkpoint inhibitors have been demonstrated in patients with dMMR/MSI-H tumors with pembrolizumab, with an ORR of 48%, a median PFS of 13.1 months, and with 88% of patients having a response duration of longer than 1 year [35]. Similarly, findings from the GARNET trial demonstrated an ORR of 45.5%, a median duration of response that had not been reached, and probabilities of response at 12 and 24 months of 93.3% and 83.7%, respectively [9]. Even with dMMR disease, however, there are still critical unanswered questions regarding duration of therapy in complete responders and mechanisms of intrinsic and acquired resistance.

For the majority patients with pMMR endometrial cancer and for those with dMMR/MSI-H disease who do not benefit from immune checkpoint inhibition, combination treatment strategies should be considered. The recent addition of lenvatinib (a multi-kinase inhibitor of VEGFR, FGFR, PGFRα, RET, and KIT) to pembrolizumab has been practice changing for the treatment of pMMR/MSS endometrial cancer, with an improved median PFS (6.6 months vs 3.8 months, HR: 0.6), median OS (17.4 months vs 12 months, HR: 0.68) and ORR (30% vs 15%) compared to standard chemotherapy [7]. This further bolsters the rationale for investigating targeted combination immune checkpoint therapies.

Further characterization of endometrial cancer is essential to identify which patients are most likely to benefit from specific treatments, and a separate molecular and immune analyses with these patients is planned. In conclusion, data from our randomized trial suggest that durvalumab and durvalumab plus tremelimumab have meager efficacy in patients with predominantly pMMR endometrial cancers and that other combination immune checkpoint strategies should be investigated. There are planned molecular and immune analyses to better understand mechanisms of resistance to these available therapies, and investigation of therapeutic approaches to improve checkpoint inhibitor therapy is urgently needed.

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HIGHLIGHTS

- Durvalumab has limited efficacy in all-comers but predominately mismatch repair-proficient (pMMR) endometrial cancer.
- Combination durvalumab and tremelimumab similarly has limited efficacy in this predominately pMMR population.
- Further molecular integration is needed to identify patients who may benefit from combination targeted/immunotherapies.

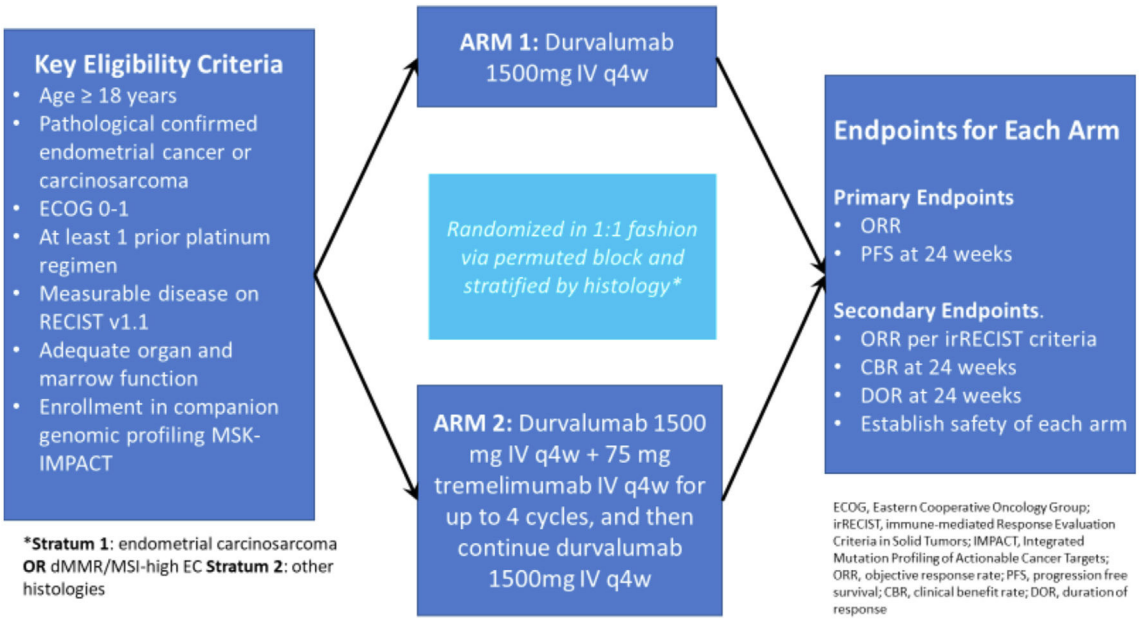

Fig. 1. Patients and study schema.

ECOG, Eastern Cooperative Oncology Group; RECIST, Response Evaluation Criteria in Solid Tumors; MSK-IMPACT, Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets; ORR, overall response rate; PFS, progression-free survival; irRECIST, immune-related RECIST; CBR, clinical benefit rate; DOR, duration of response.

Table 1

Patient and baseline characteristics.

Characteristic	Durvalumab (*n* = 38)	Durvalumab + Tremelimumab (*n* = 39)
Median Age, years (range)	64 (45-78)	67 (52-84)
ECOG Status		
0	26 (68.4%)	24 (61.5%)
1	12 (31.6%)	15 (38.5%)
Race, n (%)		
White	27 (71.1%)	27 (69.2%)
African-American	4 (10.5%)	5 (12.8%)
Asian	4 (10.5%)	2 (5.1%)
Unknown/Other	3 (7.9%)	5 (12.8%)
Stage at Diagnosis, n (%)		
Stage I	9 (23.7%)	10 (25.6%)
Stage II	4 (10.5%)	1 (2.6%)
Stage III	11 (28.9%)	16 (41.0%)
Stage IV	14 (36.8%)	12 (30.8%)
Histology, n (%)		
Endometrioid, Grade 1/2	7 (18.4%)	8 (20.5%)
dMMR	*3 (7.9%)*	*2 (5.1%)*
pMMR	*4 (10.5%)*	*6 (15.4%)*
Endometrioid, Grade 3	0	8 (20.5%)
dMMR	*0*	*0*
pMMR	*0*	*7 (17.9%)*
unknown	*0*	*1 (2.6%)*
Serous	11 (28.9%)	6 (15.4%)
dMMR	*0*	*1 (2.6%)*
pMMR	*10 (26.3%)*	*5 (12.8%)*
unknown	*1 (2.6%)**	*0*
Clear Cell	5 (13.2%)	1 (2.6%)
dMMR	*0*	*0*
pMMR	*5 (13.2%)*	*1 (2.6%)*
Carcinosarcoma	6 (15.8%)	10 (25.6%)
dMMR	*0*	*0*
pMMR	*5 (13.2%)*	*9 (23.0%)*
unknown	*1 (2.6%)**	*1 (2.6%)*
Mixed/Dedifferentiated Histology	9 (23.7%)	6 (15.4%)
dMMR	*2 (5.3%)*	*4 (10.3%)*
pMMR	*7 (18.4)*	*1 (2.6%)*
unknown	*0*	*1 (2.6%)**
All Histology Total		

Characteristic	**Durvalumab (*n* = 38)**	**Durvalumab + Tremelimumab (*n* = 39)**
dMMR	***5 (13.2%)***	**4 (10.3%)**
pMMR	***31 (81.6%)***	***32 (82.0%)***
unknown	***2 (5.3%)*** *	***3 (7.7%)*** *
Prior Cytotoxic Therapy, n (%)		
1 Line	13 (34.2%)	9 (23.1%)
2 Lines	16 (42.1%)	16 (41.0%)
3 Lines	9 (23.7%)	14 (35.9%)
Prior Radiation, n (%)		
Yes	20 (52.6%)	26 (66.7%)
No	18 (47.4%)	13 (33.3%)

ECOG, Eastern Cooperative Oncology Group; dMMR, mismatch repair deficient; pMMR, mismatch repair proficient.

*Microsatellite Stable confirmed with unknown MMR status.

Table 2

Efficacy outcomes.

Objective	Durvalumab	Durvalumab + Tremelimumab
Primary Objectives (90% CI)	*n* = 37	n = 38
ORR	10.8% (4.8–100%)	13.5% (6.7–100%)
PFS at 24 weeks	5.3% (1.4–100%)	13.2% (6.5–100%)
Secondary Objectives (90% CI)	n = 37	n = 38
Median PFS	7.4 weeks (7–Inf)	7.9 weeks (7–Inf)
CBR	13.5% (6.7–100%)	10.5% (4.7–100%)
DOR	24 weeks (16-Inf)	Not Reached
irRECIST Objective (90% CI) *	*n* = 6	*n* = 8
ORR	33.3% (9.3–100%)	0%

ORR, overall response rate; PFS, progression-free survival; CBR, clinical benefit rate; DOR, duration of response.

* reported for patients who were treated beyond disease progression.

Table 3

Adverse events of any cause with an incidence of ≥25%.

Adverse event	Arm 1 n = 38		Arm 2 n = 39	
	Any grade n (%)	Grade ≥ 3 n (%)	Any grade n (%)	Grade ≥ 3 n (%)
Hyperglycemia	36 (95)	4 (11)	36 (92)	7 (18)
Anemia	31 (82)	11 (29)	34 (87)	11 (28)
Hypoalbuminemia	26 (68)	1 (3)	34 (87)	1 (3)
Hypomagnesemia	23 (61)	0	30 (77)	0
Lymphocyte Count Decrease	20 (53)	10 (26)	26 (67)	15 (38)
WBC Decrease	19 (50)	0	17 (44)	5 (13)
AST Increase	16 (42)	1 (3)	20 (51)	2 (5)
Fatigue	16 (42)	0	22 (56)	2 (5)
Alkaline Phosphatase Increase	14 (37)	1 (3)	18 (46)	3 (8)
Abdominal Pain	12 (32)	0	19 (49)	3 (8)
Hyponatremia	11 (29)	5 (13)	15 (38)	9 (23)
Nausea	11 (29)	0	23 (59)	2 (5)
ALT Increase	10 (26)	1 (3)	14 (36)	1 (3)
INR Increase	10 (26)	1 (3)	12 (31)	1 (3)
Platelet Count Decrease	10 (26)	1 (3)	21 (54)	1 (3)
Arthralgias	9 (24)	0	4 (10)	0
Amylase Increase	8 (21)	0	12 (31)	0
Hypocalcemia	8 (21)	1 (3)	15 (38)	3 (8)
Pruritis	8 (21)	0	10 (26)	0
Constipation	7 (18)	0	12 (31)	1 (3)
Creatinine Increase	7 (18)	0	19 (49)	2 (5)
Dyspnea	7 (18)	1 (3)	7 (18)	0
Pain	7 (18)	0	11 (28)	2 (5)
Prolonged APTT	7 (18)	1 (3)	14 (36)	0
Diarrhea	6 (16)	1 (3)	13 (33)	4 (10)
Hyperkalemia	6 (16)	1 (3)	11 (28)	2 (5)
Hypokalemia	4 (11)	1 (3)	13 (33)	5 (13)
Weight loss	0	0	10 (26)	0

WBC, white blood count; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; APTT, activated partial thromboplastin time.