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Evaluating for Pseudoprogression in Colorectal and Pancreatic Tumors Treated with Immunotherapy

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Abstract

Pseudoprogression has been observed in patients with various tumor types treated with immunotherapy. However, the frequency of pseudoprogression is unknown in gastrointestinal malignancies. Metastatic colorectal cancer (mCRC) and advanced pancreatic ductal adenocarcinoma (PDAC) patients who progressed on treatment with immunotherapy beyond RECIST v1.1 criteria were analyzed. Degree of progression, tumor markers, time-to-progression, OS, ECOG PS, and costs were analyzed for patients treated beyond progression (TBP) and not treated beyond progression (NTBP). Fifty-nine of 159 (37%) patients with mCRC or PDAC were TBP (31 mCRC, 28 PDAC). Fifty-four of 59 (92%) patients were microsatellite stable. Zero of these 59 patients with initial treatment-beyond-progression demonstrated subsequent radiographic tumor shrinkage at a median 42 days from first scan documenting progression. A pseudoprogression rate of >6% could be excluded with 95% confidence. Compared to baseline, median growth on the first and second scan that showed progression was 29.8% and 43%, respectively. In those NTBP, median growth at first restaging was 31.2%. The trend in change in tumor size positively correlated with the trend in tumor markers in all patients TBP. Fifteen

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patients (25%) experienced Grade 3/4 AEs by continuing treatment-beyond-progression, whereas 19 (32%) experienced deterioration in ECOG PS. Pseudoprogression was not seen in microsatellite stable patients with mCRC or PDAC treated with immunotherapy. Changes in tumor markers correlated with changes in tumor volume. This data may help inform future treatment decisions and/or trial design in patients with mCRC or advanced PDAC treated with immunotherapy.

Keywords

Pseudoprogression; immunotherapy; colorectal cancer; pancreatic cancer; tumor response evaluation

BACKGROUND

In the United States, colorectal cancer (CRC) is the third most prevalent cancer, with approximately 135,000 new diagnoses projected in 2017.¹ Overall, it is the second leading cause of cancer death, with over 50,000 Americans expected to succumb to this disease in 2017.¹ Approximately 25% of patients with CRC present with metastases, and 50% of patients presenting with locoregional disease eventually develop metastatic disease.² For patients with surgically unresectable/metastatic colorectal cancer (mCRC), the expected 5-year relative survival is less than 15%.³ Despite significant advances in treatment of mCRC with currently available cytotoxic regimens, response rates for those that progress after first-line treatment are only 4–17%.^{4,5}

Immune-checkpoint inhibitors have recently received regulatory approval in multiple cancers, including microsatellite instability-high (MSI-H) mCRC, melanoma, renal, bladder, lung, gastric, gastroesophageal junction, hepatocellular carcinoma, and head and neck cancers, based on durable clinical responses demonstrated in a subset of patients.^{6–14} However, response rates to these agents were low in unselected patients with CRC.^{6,7,15} The more recent demonstration of responses in MSI-H mCRC to checkpoint inhibitors was a turning point^{16,17}, and led to approval by the FDA for the use of checkpoint inhibitors in the second line setting in this subset of patients. This has also led to several clinical trials and increased efforts to obtain responses in patients with pancreatic ductal adenocarcinoma (PDAC) and microsatellite stable (MSS) CRC, and to identify other predictive biomarkers.¹⁶

Immunotherapeutic agents produce antitumor effects by inducing cancer-specific immune responses or by modifying native immune processes. Resulting clinical response patterns extend beyond those of cytotoxic agents, and in a variety of different tumor types, tumor shrinkage has been identified after an initial increase in tumor burden or the appearance of new lesions.^{10,18–21} The phenomenon of “pseudoprogression” in patients treated with immunotherapies may be due to transient immune cell infiltration into the tumor while the immune system prepares for a response.²² This has prompted the occasional use of immune-related response criteria (irRC) in the radiographic assessment of tumors being treated with immune therapy, instead of the standard RECISTv.1.1²³. Unlike RECIST, which defines progressive disease (PD) as an increase in tumor volume beyond a certain threshold or upon the appearance of new lesions, irRC allows for confirmation of PD on two successive scans

>4 weeks apart and allows for the addition of new lesion measurements to the total tumor volume.^{24–26} Indeed, treatment beyond RECIST progression has resulted in subsequent tumor reduction in upwards of 15% of melanoma patients¹⁹ and 13% of renal cell carcinoma patients¹⁸ treated with immune-checkpoint therapies, whereas in non-small cell lung cancer and head and neck squamous cell carcinoma, the rate appears to be closer to 2–3%.^{10,20,21}

The frequency of pseudoprogression is unknown in gastrointestinal malignancies treated with immunotherapy, and whether treatment beyond progression is beneficial in this patient population remains unclear. This information would greatly improve clinical decision-making, when the choice must be made to continue therapy under the premise of pseudoprogression, or change therapy out of fear of true progression. The use of standard therapies may pose additional challenges, as treatment termination decisions are not determined by specific trial protocols. Economic considerations further add to the challenge as the high costs of these novel therapies impose substantial financial burden to payers, patients, and their families.²⁷ Thus, the purpose of this analysis was to evaluate the potential benefit of treatment with a variety of immunotherapy regimens beyond RECIST-defined first progression in CRC and PDAC, to determine characteristics of patients and tumors that may correlate with true progression, and to assess the cost implications of this treatment.

PATIENTS AND METHODS

Patient selection and treatment

All metastatic CRC and PDAC patients who received immunotherapy in the Gastrointestinal Medical Oncology and Phase I Departments at U.T. MD Anderson Cancer Center from October 1, 2012 through May 23, 2017 were evaluated. Immunotherapy administered included programmed death-ligand-1 (PD-L1) or programmed cell death protein-1 (PD-1) inhibitors, CTLA-4 antibodies, combination PD-1 inhibitors and CTLA-4 antibodies, personalized vaccines, pegylated recombinant human interleukin-10 (IL-10), and tumor antigen-specific T-effector cell activators. In those patients treated on trial, the trial protocols were evaluated and per protocol, treatment beyond investigator-assessed RECISTv1.1-defined first progression²³ was permitted in all trials if patients tolerated therapy and exhibited investigator-assessed clinical benefit. Identical practices were followed in the 6 patients treated with a PD-1 inhibitor as a standard of care regimen in mCRC.

For the purpose of this analysis, patients were considered to have been treated beyond first progression (TBP) if they received their last treatment 4 weeks after the date of initial progression.

Outcomes

Efficacy assessments occurred from baseline to first RECIST-defined progression, at second progression, and from first progression to death or therapy discontinuation. Disease assessments were performed by contrast-enhanced computed tomography and all images were re-reviewed, with measurements retaken using RECISTv1.1 by an independent radiologist for the purposes of this study.

Assessments of performance status were made at baseline, time of first progression, and at time of second progression using the Eastern Cooperative Oncology Group Performance Status (ECOG PS) scoring system.²⁸ Safety assessments were from baseline to first progression and after first progression until the end of treatment, using the NCI-CTCAEv4.0.

When comparing treatment costs between the two practice patterns explored in this study, TBP and not treated beyond progression (NTBP), we focused on the difference in costs in the duration between the date of the first and second progression, as clinical management outside this time period would be similar between these two groups. For the NTBP group, there was no cost information available at the time of second progression because patients no longer received treatment after the first sign of progression; thus, we assumed a 6-week duration as the comparable time window to contrast the costs between the two groups.

To obtain information on treatment costs for study participants, we first extracted charges data for services incurred in the above duration from the institutional billing record. We then converted charges to costs using nationally representative cost measures.^{29–31} A challenge we faced in obtaining cost information for immunotherapies was that costs were often covered by trials, and thus, were not captured in the billing records. Furthermore, some agents were experimental drugs that had not yet been approved by the FDA. Therefore, we determined the costs of immunotherapies in two steps. First, for those that were approved by the FDA and had an established billing code, we quantified their costs by applying the 6% mark-up to their corresponding average sales price. Next, for those without an established billing code, we identified FDA-approved immunotherapy agents with similar mechanisms of action as proxies and approximated their costs using Medicare payments associated with these proxy therapies. For the TBP arm, we estimated costs for continuing immunotherapy between the first and second progression, as after the second progression, immunotherapy was discontinued. For the NTBP, we included all costs incurred at MD Anderson within 6 weeks of the first progression, which would be the cost of standard of care/best supportive care once patients progressed. We stopped tracking costs after the date of second progression for the TBP group, or 6 weeks after the date of first progression for the NTBP group, as by that time both groups would be treated as patients with progressive disease, and costs were expected to be similar. We reported costs both in terms of mean costs per patient and the distribution by service categories.³²

Statistical analyses

Descriptive statistics for continuous variables are presented as medians and ranges; categorical variables are presented as frequencies and percentages. Data are presented at baseline, at first progression, and after first progression. Associations between tumor markers and tumor size were assessed using Spearman's rank correlation coefficient. Overall survival (OS) was estimated as the time of therapy initiation to death, and 3 months post initial progression (landmark) to death using the Kaplan-Meier method; median and corresponding two-sided 95% CI were reported using Brookmeyer and Crowley methodology. Analyses were performed using S+ Version 8.2 for Windows (TIBCO Software Inc.).

RESULTS

A total of 159 patients with metastatic CRC or PDAC who were enrolled on a clinical trial with immunotherapy, or planned to begin treatment with immunotherapy as a standard of care option, were evaluated for this study. Of these, 16 patients with partial response (PR) to treatment and 8 patients with stable disease (SD) were excluded from this analysis. Nineteen of 24 of these patients with PR or SD were MSI-H. An additional 8 patients were excluded for never starting therapy, and 13 patients were excluded for awaiting restaging scans at the time of this analysis. Eight patients died from complications of progressive disease prior to restaging imaging (Figure 1). Of the 108 remaining patients with progression on first restaging scan, 59 and 49 patients were TBP and NTBP, respectively.

Demographics and baseline characteristics for patients TBP and NTBP are summarized in Table 1. Disease characteristics were generally similar; however patients treated with PD-1 inhibitors were more likely to be TBP, whereas those receiving IL-10 inhibitors were not. In the TBP group, 31 patients had advanced CRC and 28 had advanced PDAC compared to 25 and 24 in the NTBP group, respectively.

Disease characteristics from baseline to first progression

A summary of disease characteristics and efficacy results from baseline to first progression is presented in Table 2. Prior to first progression, patients TBP had a longer median time-to-progression (TTP) (51[95% CI, 38–64] days) than those NTBP (43[95% CI, 40–46] days). Tumor burden changes relative to baseline (%) at the time of first progression ranged from 3.2–133.0% (median, 29.8%) in patients TBP and from 2.4–262% (median, 31.2%) in those NTBP.

Upon first progression, a greater number of patients with new lesions were TBP (24%) vs those NTBP (14%), while fewer patients with growth in target lesions alone were TBP (76%) vs those NTBP (84%). The location of new lesions varied, but most commonly included the lymph nodes in patients TBP and the liver in patients NTBP. In addition to radiographic progression, at the time of first progression a greater number of patients NTBP (34[69%]) experienced a deterioration of their ECOG PS vs. those TBP (8[14%]), Table 2. Ultimately, 49/49 patients NTBP discontinued therapy due to disease progression (Figure 2).

Disease characteristics at time of second progression

Change in tumor volume after first progression in patients TBP is shown in Figure 2. Following initial progression, 58/59 patients TBP experienced subsequent tumor growth in target lesions at a median of 42 days (range, 28–95) from their first scan that demonstrated radiographic progression. The one remaining patient had a slight decrease in target lesion size, however did have new liver, adrenal, spleen and osseous metastatic disease. Of the 59 patients with progression, 42 (71%) had greater than or equal to a 20% increase in tumor volume by the time of first progression. A pseudoprogression rate of >6% could be excluded with 95% confidence (0, 6%). Compared to baseline, the median growth on the first scan that showed progression was 29.9% (range, 3.2–133%), while the median growth on the second restaging scan was 55% (range, 9.3–194%), Table 2.

In those patients TBP, the trend in change in tumor size positively correlated with the change in CEA levels at the time of second progression (Spearman rank correlation (r)=0.28, P =0.13). In all patients, the median percentage change in the CEA level was 32% and 112% at the time of the first scan that showed progression and the second restaging scan, respectively. In those patients with PDAC, CA 19-9 levels also positively correlated with change in tumor size at the time of second progression (r =0.46, P =0.04). In these patients, the median percentage change in the CA 19-9 level was 23% and 97% at the time of the first scan that showed progression and the second restaging scan, respectively.

In those patients NTBP, the median percentage change in CEA was 107% at first restaging. In patients with PDAC NTBP, the median percentage change in CA 19-9 was 237% at first restaging.

Eighty percent of patients TBP experienced continued growth of their known tumors at the time of their second restaging, while 2% developed new lesions alone, and 19% had increase in their known tumor volume in addition to development of new lesions. Most common sites of new metastases included lymph nodes, lung and peritoneum, Table 2. In a subset analysis of only MSI-H patients (n =5), we also did not observe any evidence of pseudoprogression (Supplemental Figure 1).

Patients TBP experienced continued deterioration in their ECOG PS. Thirty-three percent of patients experienced a decline in their performance status compared to that at the time of their initial radiographic progression, Table 2. Fifteen patients (25%) suffered a grade 3/4 adverse event (AE) as a result of continuation on treatment after first progression, Table 3.

Long-term Clinical outcomes

Median duration of therapy was 3.7 months (range, 1.3–13.5, TBP) and 1.8 months (range, 0.06–16.6, NTBP). Median follow-up time was 17.2 months (range, 2.1–44.2, TBP), and 24.8 months (1.8–40.3, NTBP). Of patients NTBP, 13 of 49 (27%) went on to receive subsequent systemic therapy, median 1 (range 1–3), whereas 22 of 59 (37%) of patients TBP went on to receive a median of 1 (range, 1–3) subsequent systemic therapies.

By Kaplan-Meier analysis, there was seemingly an OS benefit to treatment-beyond-progression (median OS 10.2 vs. 4.8 months, HR =0.5(0.3, 0.8), P =0.0061). However, in a landmark analysis of evaluable patients beginning at 12 weeks from first progression, there was only a modest non-significant benefit to treatment beyond progression (median OS: 10.6 vs. 7.6 months, HR =0.6 (0.4, 1.1), P =0.099) (Figure 3).

Cost analysis

Mean cost per patient in the TBP group was \$60,335 in the duration between first and second progression. Of those, \$52,352 (87%) were costs of immunotherapy drugs and the remaining 13%, or \$7,983, were other costs associated with clinical management of patients with metastatic CRC or PDAC (Figure 4). After progression, the patients NTBP were treated with the following regimens: best supportive care in 86% of patients, 5-Fluorouracil (5-FU) plus oxaliplatin in 6%, gemcitabine plus paclitaxel in 2%, 5-FU plus oxaliplatin plus irinotecan in 2%, 5-FU plus irinotecan in 2%, and 5-FU, irinotecan plus cetuximab in 2% of

patients. In this NTBP cohort, the mean cost per patient was \$7,637 within 6 weeks of the first date of progression. This value included the cost of standard of care regimens used after progression and routine follow up care. Costs associated with the practice pattern of continuing immunotherapy beyond progress were captured by the difference in mean cost per patient between the two groups: \$52,698 ($=\$60,335 - \$7,637$).

The breakdown of non-immunotherapy costs by service categories for each group is shown in Supplemental Table 1. Overall, the distribution was similar between the two groups. Pathology and laboratory procedures accounted for approximately 60% of the costs for both groups, followed by medicine and administered drugs.

DISCUSSION

Pseudoprogression and immune-related patterns of mixed response are proving to be increasingly challenging in the clinical setting. Growing numbers of patients with a variety of solid tumors are being exposed to immunotherapy, and tumor shrinkage has been identified after an initial increase in tumor burden or the appearance of new lesions in several studies.^{10,18–21} Yet, with the limited use of immune-modulating agents in gastrointestinal malignancies to date, the question of how best to treat these patients in the presence of tumor growth or new tumor lesions remains extremely relevant.

In this retrospective analysis, all patients who continued treatment beyond first progression based on investigator-assessed clinical response exhibited continued tumor growth. This is in contrast to the upwards of 13% and 15% rates of pseudoprogression documented in renal cell carcinoma and melanoma, respectively.^{18,19} The etiology of these differences is yet to be determined, as the use of immunotherapy in gastrointestinal malignancies is still in its infancy. One possible explanation is that the degree of mutational load and tumor neoepitopes in gastrointestinal malignancies is not as profound as that seen in melanoma and renal cell carcinoma. Still, in colorectal tumors that harbor microsatellite instability, the impaired mismatch repair system predisposes these tumors to higher mutational loads and tumor neoepitopes, making them more immunogenic, as exemplified in previous clinical trials.^{17,33} Thus, if our analysis included more MSI-H patients it is possible that we may have seen increased rates of pseudoprogression. However, in a subset analysis of only MSI-H patients (n=5), we did not observe any pseudoprogression (Supplemental Figure 2).

The understanding that tumor growth by RECIST did not necessarily translate to biologic disease progression in patients treated with immunotherapy led to the development of immune-related response criteria to better surveil these patients.^{25,34} Still, these criteria have a number of limitations and do not convey all pertinent patterns of clinical activity.²⁵ To address these shortcomings, composite endpoints, biomarkers such as circulating tumor DNA, time to symptomatic progression, and quality of life have all been considered as potential measures to gauge efficacy and/or serve as clinical trial endpoints for studies evaluating immunotherapy.^{35–37} It is important to note that the whole clinical picture—and not just response criteria—should be taken into account when deciding which patients to treat beyond first progression. Although physicians in this study were not directly asked how they chose which patients to treat beyond first progression, based on retrospective

assessment of the patient characteristics, those with better ECOG PS, fewer AEs, longer TTP, indolent biology, lower rate of change of tumor markers and appearance of new lesions (predominantly lymph nodes) were chosen to continue treatment. Indeed, immunotherapy-related sarcoidosis-like syndrome or lymphadenopathy represents a well-known challenge to treating physicians, and often represents pseudoprogression.^{38,39} Thus, differences observed in length of treatment and tumor growth stress the value of an individualized approach to decisions regarding treatment with immunotherapy beyond progression.

Another important aspect of this work was the evaluation of AEs and costs for patients TBP. In this study, patients NTBP had an increased frequency of treatment-related AEs from initial treatment to first progression compared to those TBP, suggesting that toxicity may have guided the decision to stop or continue treatment. As may be expected, incidence of treatment-related AEs was higher after progression in patients TBP, suggesting that most AEs occurred later, or continued to compound, in the course of the ultimately ineffective treatment. Fifteen patients (25%) suffered a grade 3/4 AE as a result of continuation on treatment after first progression. Further, our cost analysis showed that the continuation of immunotherapy under the premise of pseudoprogression had substantial economic impact, incurring over \$52,000/patient in the short duration between the first and second progression.

Our analysis had several limitations. This work included a small number of patients treated beyond RECIST-defined progression with a variety of immune-modulating therapies. Further, there was a lack of direct assessment of physician rationale for treating patients beyond progression. It is possible that patients chosen to be TBP based on clinical improvement and treatment tolerance survived longer than those who passed soon after initiating treatment, and hence, were not TBP. To address this inherent bias, we conducted a landmark analysis of patients beginning 12 weeks from first progression and found a smaller difference in OS between patients TBP and NTBP. Still, this OS analysis has inherent biases, as those patients TBP had a superior ECOG PS, allowing them to continue on therapy. Thus, the small OS benefit seen in this group is unlikely to be due to continued treatment beyond progression, and more likely to be due to pre-treatment characteristics. Finally, although our initial cohort of patients included 28 patients with microsatellite instability, 19 of these patients had sustained PR or SD at the time of this analysis, which limited our ability to comment on pseudoprogression rates in the MSI-H population. Further analysis must be done in the MSI-H population to clarify the rate of pseudoprogression in this subset of patients that is more likely to be treated with immunotherapy as a standard of care. To date, one case of pseudoprogression in a patient with MSI-H mCRC has been documented in the literature.⁴⁰

Improved reporting of immune related responses in ongoing clinical trials is necessary to determine whether pseudoprogression occurs in gastrointestinal malignancies, if it is a marker for clinical benefit, and to further understand the complexities of tumor interactions with the immune system. Future prospective trials should be designed to reduce bias and may include a second randomization of patients at progression. Further research must be done in the MSI-H population, however, based on the results of this initial analysis, clinical

trials designed to observe the efficacy of immunotherapy in mCRC and PDAC should not mandate treatment beyond progression, particularly in the MSS population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flow diagram of all patients

Figure 2.

A. Change in tumor burden in patients TBP. *Although target lesions decreased in size, there was new liver and osseous metastatic disease. **B.** Change in tumor burden in patients NTBP.

Figure 3.
Overall survival of patients TBP versus NTBP by Kaplan-Meier analysis.

Figure 4.
Estimated costs of hospital care and immunotherapy drugs for patients TBP and NTBP.

Table 1

Demographic and Baseline Patient Characteristics at Study Entry

Characteristic	Patients Treated Beyond Progression (<i>n</i> = 59)	Patients Not Treated Beyond Progression (<i>n</i> = 49)
Median Age (range), y	61 (32–78)	60 (21–77)
Sex, <i>n</i> (%)		
Female	30 (51)	21 (43)
Male	29 (49)	28 (57)
Race, <i>n</i> (%)		
Caucasian	46 (78)	37 (76)
Hispanic	8 (14)	5 (10)
African American	4 (7)	4 (8)
Asian/Pacific Islander	1 (2)	3 (6)
Histology, <i>n</i> (%)		
Colorectal Adenocarcinoma	31 (53)	25 (51)
Pancreatic Adenocarcinoma	28 (47)	24 (49)
Microsatellite Status, <i>n</i> (%)		
MSS	54 (92)	45 (92)
MSI High	5 (8)	4 (8)
ECOG, <i>n</i> (%)		
0	20 (34)	13 (27)
1	39 (66)	36 (73)
Number of Mutations identified^{a,b}		
Median (range)	2 (0–7)	2 (0–17)
Number of Prior Lines of Systemic Therapy		
Median (range)	3 (1–10)	3 (1–9)
Type of Immunotherapy, <i>n</i> (%)		
PD-1/PD-L1 inhibitor	27 (46)	13 (27)
Personalized Vaccine	13 (22)	9 (18)
CTLA-4 inhibitor	5 (8)	4 (8)
PD-1 + CTLA-4 inhibitor	5 (8)	4 (8)
Pegylated Recombinant Human IL-10	4 (7)	13 (27)
Other	5 (8)	6 (12)

MSS= microsatellite stable; MSI H = high microsatellite instability; ECOG = Eastern Cooperative Oncology Group; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1

^aFor those patients that had gene sequencing (*n* =32)

^bIdentified by Next Generation Sequencing Panel of at least 50 genes

Table 2

Characteristics at Time of First and Second Progression

Characteristic	First Progression		Second Progression
	Patients Treated Beyond Progression (<i>n</i> = 59)	Patients Not Treated Beyond Progression (<i>n</i> = 49)	Patients Treated Beyond Progression (<i>n</i> = 59)
ECOG, <i>n</i> (%)			
0	15 (25)	4 (8)	11 (19)
1	41 (69)	18 (37)	32 (54)
2	3 (5)	13 (27)	11 (17)
3	0	14 (29)	5 (8)
Change in ECOG^a, <i>n</i> (%)			
Deterioration	8 (14)	34 (69)	19 (32)
Improvement	0	0	0
Target lesion status at first progression, <i>n</i> (%)			
Increase in target lesions	45 (76)	41 (84)	47 (80)
Appearance of new lesions	0	1 (2)	1 (2)
Increase in target lesions and appearance of new lesions	14 (24)	7 (14)	11 (19)
Site of new lesions, <i>n</i> (%)			
Lymph node	6 (10)	2 (4)	6 (10)
Liver	3 (5)	6 (12)	2 (3)
Peritoneum	4 (7)	1 (2)	3 (5)
Lung	1 (2)	2 (4)	5 (8)
Bone	1 (2)	0	1 (2)
Spleen	0	1 (2)	1 (2)
Adrenal	0	1 (2)	2 (3)
Median progression^b, % (95% CI)	29.8 (3.2–133)	31.5 (2.4–262)	44 (9.3–194)
Median TTP^c, d (95% CI)	51 (28–288)	43 (28–69)	42 (28–95)
Median duration of therapy, mo (95% CI)	3.0 (1.3–15.1)	1.8 (1.0–5.0)	3.0 (1.3–15.1)
Median follow up time, mo (95% CI)	17.2 (2.1–44.2)	24.8 (1.8–40.3)	17.2 (2.1–44.2)

ECOG = Eastern Cooperative Oncology Group; TTP = Time to progression; OS = Overall survival.

^aAt time of first progression, ECOG was compared to performance status at baseline. At time of second progression, ECOG was compared to performance status at time of first progression.^bMedian progression at time of first and second progression was defined as % of progression above baseline.^cMedian time to progression was defined as time to first progression from baseline imaging, and time from first progression to second progression, respectively.

Table 3

Therapy-related Complications

Complication	From Randomization to First Progression			After First Progression		
	Patients Treated Beyond Progression (n = 59)	Patients Not Treated Beyond Progression (n = 49)	Patients Treated Beyond Progression (n = 59)	Patients Treated Beyond Progression (n = 49)	Patients Treated Beyond Progression (n = 59)	Patients Treated Beyond Progression (n = 49)
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Fatigue	16 (27)	2 (3)	15 (31)	1 (2)	14 (24)	2 (3)
Anemia	7 (12)	3 (5)	5 (10)	2 (4)	3 (5)	2 (3)
Rash	7 (12)	1 (2)	6 (12)	2 (4)	4 (7)	2 (3)
Diarrhea	7 (12)	0	1 (2)	1 (2)	2 (3)	2 (3)
Nausea/Vomiting	3 (5)	1 (2)	6 (12)	0	4 (7)	0
Anorexia	3 (5)	0	6 (12)	0	5 (8)	0
Transaminitis	3 (5)	0	7 (14)	1 (2)	4 (7)	1 (2)
Burning at injection site	3 (5)	0	3 (6)	0	0	0
Elevated amylase/lipase	3 (5)	1 (2)	0	0	0	0
Fever	2 (3)	0	4 (8)	0	5 (8)	0
Hyperbilirubinemia	2 (3)	0	4 (8)	0	2 (3)	0
Myalgias	2 (3)	0	3 (6)	0	3 (5)	0
Neutropenia	2 (3)	0	1 (2)	1 (2)	2 (3)	1 (2)
Abdominal pain	2 (3)	0	1 (2)	0	1 (2)	0
Hypothyroidism	2 (3)	0	1 (2)	0	0	0
Dry mouth	2 (3)	0	1 (2)	0	1 (2)	0
Neuropathy	2 (3)	0	0	0	3 (5)	0

Complication	From Randomization to First Progression				After First Progression			
	Patients Treated Beyond Progression (n = 59)		Patients Not Treated Beyond Progression (n = 49)		Patients Treated Beyond Progression (n = 59)		Patients Treated Beyond Progression (n = 59)	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Thrombocytopenia	1 (2)	0	9 (18)	3 (6)	7 (12)	4 (7)		
Constipation	1 (2)	0	2 (4)	0	1 (2)	0		
Proteinuria	1 (2)	0	2 (4)	0	2 (3)	0		
Hyperglycemia	1 (2)	0	1 (2)	0	1 (2)	0		
Mucositis	1 (2)	0	1 (2)	0	0	0		
Arthralgias	1 (2)	0	1 (2)	0	1 (2)	0		
Dyspnea	1 (2)	0	0	0	1 (2)	0		
Pruritis	0	1 (2)	1 (2)	0	1 (2)	0		
Obstructive jaundice	0	0	2 (4)	1 (2)	1 (2)	1 (2)		