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Clinical Trial Results

Phase I Study of Lenvatinib and Capecitabine with External Radiation Therapy in Locally Advanced Rectal Adenocarcinoma

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Abstract

Background: Neoadjuvant chemoradiation with fluoropyrimidine followed by surgery and adjuvant chemotherapy has been the standard treatment of locally advanced stages II and III rectal cancer for many years. There is a high risk for disease recurrence; therefore, optimizing chemoradiation strategies remains an unmet need. Based on a few studies, there is evidence of the synergistic effect of VEGF/PDGFR blockade with radiation.

Methods: In this phase I, dose-escalation and dose-expansion study, we studied 3 different dose levels of lenvatinib in combination with capecitabine-based chemoradiation for locally advanced rectal cancer.

Results: A total of 20 patients were enrolled, and 19 were eligible for assessment of efficacy. The combination was well tolerated, with an MTD of 24 mg lenvatinib. The downstaging rate for the cohort and the pCR was 84.2% and 37.8%, respectively. Blood-based protein biomarkers TSP-2, VEGF-R3, and VEGF correlated with NAR score and were also differentially expressed between response categories. The NAR, or neoadjuvant rectal score, encompasses *cT* clinical tumor stage, *pT* pathological tumor stage, and *pN* pathological nodal stage and provides a continuous variable for evaluating clinical trial outcomes.

Conclusion: The combination of lenvatinib with capecitabine and radiation in locally advanced rectal cancer was found to be safe and tolerable, and potential blood-based biomarkers were identified.

Clinical Trial Registration: NCT02935309

Key words: lenvatanib, radiation, rectal cancer.

Lessons Learned

- In this phase I study, the combination of lenvatinib with capecitabine and radiation were considered safe for the treatment of patients with locally advanced rectal cancer.
- In the cohort of 20 enrolled patients, 19 were evaluable; the downstaging rate was 84.2% and the pCR was 37.8%.
- Some potential blood-based biomarkers were identified.

Discussion

Various strategies have been studied to define the ideal treatment for locally advanced rectal cancer. Pre–operative chemoradiation is known to result in better pCR rates than pre–operative radiation alone (13.7% vs 5.3%; odds ratio 2.84; 95% CI, 1.75-4.59; $P < .0001$) and has been

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Table 1. Patient characteristics at baseline and pathological outcomes (n = 19)

Age, years	
Mean (standard deviation)	54.8 (10.7)
Median (min, max)	51 (42, 72)
Sex, *n* (%)	
Male	13 (68.4)
Female	6 (31.6)
Race/ethnicity, *n* (%)	
Hispanic or Latino	2 (10.5)
White	17 (89.4)
Other/unknown	1 (5.3)
ECOG, *n* (%)	
0	18 (94.7)
1	1 (5.3)
Clinical stage at diagnosis, *n* (%)	
T2N1	2 (10.5)
T3N0	3 (15.8)
T3N1	12 (63.2)
T3N2	2 (10.5)
Interval between completion of chemoXRT and surgery	
Median (standard deviation), days	59 (21.7)
Type of surgery, *n* (%)	
LAR	14 (73.7)
APR	5 (26.3)
Pathological response, *n* (%)	
pCR	7 (36.8)
pPR	9 (47.4)
pNR	3 (15.8)
NAR (Neoadjuvant rectal) score	
Mean (min, max)	10.37 (0.94, 30.1)
Median ± standard deviation	8.43 ± 10.32

Abbreviations: LAR, low anterior resection; APR, abdominoperineal resection; pCR, pathological complete response; pPR, pathological partial response; pNR, pathological non response.

the standard for several years as a treatment for locally advanced rectal cancer.[1] Our study was able to achieve a pCR rate of 37.8%. However, we had no patients enrolled with T4 disease, which is known to be a characteristic of "high-risk" disease (Table 1).

In a study of *KRAS*-mutated rectal cancer, the combination of capecitabine and sorafenib with radiation yielded a pCR rate of 60%.[2] The downstaging rate on this study was 81.6%, comparable to the 84.2% seen in our study. The study with sorafenib did report 15% grade 3 adverse events with diarrhea and 12.5% grade 3 adverse events with hand-foot-syndrome.[2] Our study did not have excess of 10% of grade 3 adverse events, and this was mostly related to hypertension more commonly seen with lenvatinib than sorafenib. Patients with high NAR scores (>16) are associated with poor overall survival, those with low scores (<8) are associated with superior overall survival, and those in the middle have intermediate survival.[3] In our study, the median NAR was 8.43 and mean was 10.37, and these scores are in the intermediate range. Overall, this was a well-tolerated regimen with few adverse events and no dose-limiting toxicities. There were no treatment interruptions due to treatment. No excess post–operative complications were reported due to the study treatment except for 1 patient who had wound dehiscence that was not attributed to the study treatment. Most adverse events were low grade and in line with some side effects expected of lenvatinib. In our study, baseline levels of 3 biomarkers, TSP-2, VEGF-R3, and VEGF, correlated with NAR score, and these levels were significantly different across different response group categories (Figure 1). While previous studies with the combination of bevacizumab did not lead to success in unselected patient population, our blood-based biomarkers may be extremely beneficial to enable discernment as to which patients will benefit the most from the addition of anti-angiogenic or a mixed protein kinase inhibitor that targets other receptors in the tumor stroma to chemoradiation.

Author disclosures and references available online.

Trial Information	
Disease	Colorectal cancer
Stage of disease/treatment	Neo-adjuvant
Prior therapy	None
Type of study	Phase I, 3 + 3
Primary endpoint	Maximum tolerated dose
Investigator's Analysis	Active but results overtaken by other developments

Additional Details of Endpoints or Study Design

Blood Biomarker Analyses

EDTA plasma was isolated from each patient by venipuncture at baseline (within 42 days preceding Day 1) and after completion of chemoradiation prior to surgery. The plasma levels of 25 biomarkers, including Ang-2, GP130, HGF, ICAM-1, IL-6, IL-6R, OPN, PDGF-AA, PDGF-BB, PlGF, SDF-1, TGF-b1, TGF-b2, TIMP-1, TSP-2, VCAM-1, VEGF, VEGF-C, VEGF-D, VEGF-R1, VEGF-R2, and VEGF-R3 were measured with the CircaScan multiplex platform (Quanterix, Billerica, Massachusetts), whereas BMP-9[17], CD73[18], and TGFb-R3[19] were tested as described previously.

Statistical Plan and Analyses

A standard "3+3" design was used to determine the MTD. In this study design, 3 patients were planned to be treated with a pre–determined dose of lenvatinib. The dose escalation was planned to stop with more than one DLT occurrence at any dose. Three additional patients were planned to be added if one out of 3 patients had DLT at any dose. With no DLT occurrence, three new patients were planned to be recruited to the study for the next dose of lenvatinib. The MTD of lenvatinib was defined as the highest dose level at which no more than 1 out of 6 subjects experienced DLT. At the MTD of lenvatinib, an additional expansion cohort of 10 patients was planned to be enrolled in the study to further assess the safety and efficacy of this agent in combination with capecitabine and radiation.

The pathological response rate was used to assess efficacy. The response was categorized as complete response (CR), partial response (PR), and no response (NR). To test biomarker changes in response to treatment, log transformed ratios (Lratios) were calculated using the formula: $\log_2$ (post–treatment level/baseline level). Fold changes were calculated post–treatment defined as post–treatment/baseline. Waterfall plots are shown to graphically illustrate changes. The Kruskal–Wallis test was used to test the association of the different biomarkers with treatment response and bees warm plots were used to depict this graphically. Spearman's correlation coefficient was used to test the association of the biomarkers with NAR score and scatterplots were used to depict these graphically. NAR score was calculated as $[5\,pN - 3(cT - pT) + 12]^2/9.61$. A two-sided P-value of <.05 was considered statistically significant.

Drug Information	
Generic/working name	**Lenvatinib**
Drug type	Small molecule
Drug class	Angiogenesis—VEGF
Route	Oral (po)
Schedule of administration	In this 3+3 dose-escalation study, patients received lenvatinib with capecitabine (850 mg/m^2/BID daily) and radiation on days 1–5 each week (Monday–Friday) for a total of 5½–6 weeks (28 fractions with a total intended dose of 5040 cGy). The doses of lenvatinib tested were 14 mg daily for cohort 1, 20 mg for cohort 2, and 24 mg for cohort 3.
Generic/working name	**Capecitabine**
Drug type	Chemotherapy
Route	Oral (po)

Dose Escalation Table			
Dose level	**Dose of drug: lenvatinib (mg)**	**Dose of drug: capecitabine (mg/m^2)**	**Number enrolled (cGy)**
1	14	850	5040
2	20	850	5040
3	24	850	5040

Patient Characteristics	
Number of patients, male	13
Number of patients, female	6
Age	Median (range): 51 (42-72) years
Performance status: ECOG	0-18, 1-1, 2-0, 3-0, Unknown-0
Detailed patient characteristics are shown in Table 1.	

Primary Assessment Method	
Title	**Maximum tolerated dose**
Number of patients screened	24
Number of patients enrolled	20
Number of patients evaluable for toxicity	20
Number of patients evaluated for efficacy	19
Evaluation method	Safety assessment was made using CTCAE v4.0. Efficacy assessment was based on pathological response evaluated by post–operative pathological staging and Neoadjuvant Rectal (NAR) score to compare the initial clinical and final pathological staging. The TNM AJCC 7th edition was used to determine the pathological staging.
Response assessment CR	*n* = 7 (37.8%)
Response assessment other	*n* = 9 (47.4%)

Outcome Notes

Safety assessment was made using CTCAE v4.0. Assessment of efficacy was determined based on pathological response evaluated by post–operative pathological staging as well as Neoadjuvant Rectal (NAR) score to compare the initial clinical and final pathological staging. The TNM AJCC 7th edition was used to determine the pathological staging.

Seven (37.8%) patients achieved pathological complete response and additional nine patients (47.4%) had pathological downstaging. The total downstaging for the overall cohort was 84.2%. Three patients (15.8%) had no treatment response to lenvatinib and capecitabine-based neoadjuvant chemoradiation. The mean and median neoadjuvant rectal (NAR) score was 10.37 and 8.43, respectively. The median interval between completion of chemoradiation and surgery was 59 days.

Toxicities

No dose-limiting toxicities were noted. There were 5 patients treated on dose level 1 of 14 mg of lenvatinib, 3 patients on dose level 2 of 20 mg lenvatinib, and 12 patients on dose level 3 of 24 mg of lenvatinib. The most common any grade adverse events due to any cause were fatigue (*n* = 15), hypertension (*n* = 13), nausea (*n* = 13), radiation dermatitis (*n* = 10), diarrhea (*n* = 9) and urinary tract infection pain (*n* = 9). The only grade 3 adverse events due to any cause were hypertension (*n* = 3), decreased lymphocyte count (*n* = 3), increase in ALT (*n* = 1) and rectal pain (*n* = 1). The most common any grade adverse events attributed to study treatment were fatigue (*n* = 15), nausea (*n* = 13), hypertension (*n* = 12) and radiation dermatitis (*n* = 10). The only grade 3 adverse events attributed to the study drug were hypertension and a decrease in lymphocyte count (each *n* = 3). No treatment-related mortality occurred. The most common adverse events in cohort 3 (expansion cohort) were fatigue (*n* = 9), nausea (*n* = 8), diarrhea (*n* = 5) and hypertension (*n* = 5). The dose level 3 of 24 mg lenvatinib was established as the MTD.

Surgical Outcomes and Pathological Response

All patients enrolled in the study completed preplanned chemoradiation with concurrent capecitabine and lenvatinib and underwent surgical resection of primary rectal cancer. The median interval between completion of chemoradiation and surgery was 59 days. Fourteen patients (73.7%) underwent low anterior resection (LAR). Among patients who underwent abdominal perineal resection (APR), 1 patient died due to infectious complications from a perineal wound dehiscence. The event occurred more than 30 days but less than 90 days after surgery. Post–operative specimens were reviewed for pathological tumor regression. Seven (37.8%) patients achieved pathological complete response and additional 9 patients (47.4%) had pathological downstaging. The total downstaging for the overall cohort was 84.2%. Three patients (15.8%) had no treatment response to lenvatinib and capecitabine-based neoadjuvant chemoradiation. The mean and median neoadjuvant rectal (NAR) score were 10.37 and 8.43, respectively.

Biomarker Analyses

Specimens for biomarker analyses were available from 18 patients. Of all the biomarkers evaluated, the highest median fold change from baseline to post-treatment was seen with PDGF-BB and PDGF-AA, with median values of 2.83 and 2.55, respectively. Expression levels of all biomarkers at baseline and post-treatment can be provided upon request. Baseline biomarker levels were also correlated with NAR score. The most significant markers were TSP-2, VEGF-R3, and VEGF with correlation coefficients being −0.672 (*P* = .0023), −0.529 (*P* = .00241) and −0.502 (*P* = .0337), respectively. The baseline expression of these same three markers, TSP-2, VEGF-R3, and VEGF, significantly differed across the response categories: pCR, pPR, and pNR with the highest values noted in pCR cases (*P* = .0031, .0078, and .0165, respectively) (Figure 1). The biomarkers that showed significant changes from baseline to post-treatment were TIMP-1 (*P* = .0024), BMP-9 (*P* = .0049), PlGF (*P* = .0068), VEGF-R3 (*P* = .0068), ICAM-1 (*P* = .0342), and TGF-b1 (*P* = .0425) (Table 2).

Adverse Events

Tables 3 and 4.

Assessment, Analysis, and Discussion	
Completion	Study completed
Investigator's assessment	Active but results overtaken by other developments

The current standard for the treatment of locally advanced stage II/III rectal cancer is pre–operative chemoradiation with fluoropyrimidine. When compared to post–operative radiation, pre–operative radiation has some advantages: decreasing tumor volume, radiating surgery naïve tissue to potentially increase the radiation sensitivity, reducing the risk of exposing post–surgical bowel tissue and anastomosis from radiation, and increasing the likelihood of R0 resection. Various strategies have been studied to define the ideal treatment for locally advanced rectal cancer. Pre–operative chemoradiation is known to result in better pCR rates than pre–operative radiation alone (13.7% vs 5.3%; odds ratio 2.84; 95% CI, 1.75-4.59; $P < .0001$) and has been the standard for several years as a treatment for locally advanced rectal cancer.[1] Several studies have been conducted to improve radiation sensitivity. The most common strategy studied has been to add oxaliplatin. Some studies have shown significant improvement in pCR rates[4,5] with one study showing improvement in disease-free survival.[4] However, the body of evidence indicates an overall higher risk for toxicities with the addition of oxaliplatin without clear overall survival benefit.[5-9] In a study comparing pre–operative chemoradiation with 5FU or capecitabine with or without the addition of oxaliplatin, the pCR rates were 17.8% and 19.5%, respectively. However, the addition of oxaliplatin resulted in a significantly greater percentage of grades 3–5 diarrhea (16.5% vs 6.9%; $P < .001$).[8] The three-year locoregional recurrence rate was similar with 5FU or capecitabine and with or without oxaliplatin.[10] Similarly, the preliminary data from the ARISTOTLE trial assessing the benefit of the addition of irinotecan to capecitabine-based chemoradiation, did not reveal a statistically improved pCR rate, and showed less compliance to radiation and capecitabine along with more adverse events.[11] Various studies have been conducted testing the efficacy of adding EGFR inhibitors such as cetuximab or panitumumab and anti-angiogenesis drugs such as bevacizumab to chemoradiation. However, these studies have not demonstrated significant improvement in pCR rates or have caused too much toxicity.[12-14] Bevacizumab has been studied in some phase I–II trials in combination with chemoradiation. On an average, the pCR rate is 19%, but some studies have shown delay or failure to receive adjuvant therapy.[15] The addition of EGFR inhibitors to chemoradiation has also not resulted in significant improvement in pCR rates and KRAS status has not been shown to be a predictor of response.[12,13] The pCR rates with chemoradiation have not exceeded 20% in most studies.

Our study was able to achieve a pCR rate of 37.8%. However, we had no T4 cases in the study, which is known to be a characteristic of "high-risk" disease. In a study of patients with *KRAS*-mutated rectal cancer, the combination of capecitabine and sorafenib with radiation yielded a pCR rate of 60%.[2] Sorafenib is a protein kinase inhibitor with activity against VEGF, PDGFR and RAS, similar to lenvatinib. The downstaging rate on this study was 81.6% very comparable to 84.2% seen in our study. We did not collect information on KRAS mutation status in our study and therefore, it might be possible that the combination has better efficacy in patients with tumors bearing KRAS mutations. The study with sorafenib did report 15% grade 3 adverse events with diarrhea and 12.5% grade 3 adverse events with hand-foot-syndrome. Our study did not have an excess of 10% of grade 3 adverse events and this was mostly related to hypertension more commonly seen with lenvatinib than sorafenib. Our group has also previously evaluated the combination of 5FU and sorafenib with radiation. We showed that the pCR rate was 33% and downstaging occurred in 85.7%.[16] These results were demonstrated in patients unselected based on KRAS mutation status.

The NAR score has been validated in many datasets, but prospective validation of its association with overall survival is lacking. There can be potentially 3 different NAR categories depending on the value. Patients with high NAR scores (>16) are associated with poor overall survival, those with low scores (<8) are associated with superior overall survival and those in the middle have intermediate survival.[3] In our study, the median NAR was 8.43 and the mean was 10.37, and these scores are in the intermediate range. It would be useful to validate the association of NAR score with survival in a larger study of this combination.

Overall, this was a well-tolerated regimen with few adverse events and no dose-limiting toxicities. There were no treatment interruptions due to treatment. No excess post–operative complications were reported due to the study treatment except for 1 patient who had wound dehiscence but was not attributed to the study treatment. Most adverse events were low grade and in line with some side effects expected of lenvatinib.

To this date, there are no reliable predictive biomarkers for TKIs. In our study, the baseline level of 3 biomarkers TSP-2, VEGF-R3, and VEGF correlated with NAR score and these levels were significantly different across different response group categories. TSP-2 encodes of thrombospondin-2 which has anti-angiogenesis properties.[17] Patients with lower levels of TSP-2 at baseline did not show significant pathological response, possibly due to TSP-2 induced hypoxia. Hypoxia overall can lead to radioresistance. However, hypoxia can lead to the secretion of angiogenic factors such as VEGF and when combined with anti-angiogenesis agents can increase sensitivity to radiation.[18] Thus, we postulate that tumors in a hypoxic environment have activation of angiogenic signaling that may increase the sensitivity to radiation combined with antiangiogenic agents. While previous studies with the combination of bevacizumab did not lead to success in unselected patient population, our blood-based biomarkers may be beneficial to enable discernment as to which patients will benefit the most from the addition of anti-angiogenic or a mixed protein kinase inhibitor that targets other receptors in the tumor stroma to chemoradiation.

There are some limitations to this study. This is a single-arm, single-institution study. Therefore, the results of the trial will need to be confirmed in a larger randomized trial. In the NRG-GI002 study, the TNT approach was tested with independent arms of combination chemoradiation with pembrolizumab or veliparib. The experimental arms with combination pembrolizumab or veliparib did not significantly improve pCR or NAR score; however, the combination of pembrolizumab or veliparib was considered safe when administered with chemoradiation for locally advanced rectal cancer.[19,20] In the era of total neoadjuvant treatment (TNT), this approach may seem outdated. However, we believe that this approach can be integrated as a treatment arm for the chemoradiation portion to help ensure more superior pCR rates and increase the chances for non–operative management. There is also increasing use of circulating tumor DNA (ctDNA) in stages II and III

colorectal cancers. There are currently prospective trials ongoing to assess the utilization of ctDNA for escalation/de-escalation of systemic therapy in locally advanced colorectal cancer.[21] This study is the first of its kind that has reported safety, efficacy, and correlative biomarker analyses of the novel combination of lenvatinib with capecitabine and radiation in locally advanced rectal cancer. We believe that the integration of ctDNA with the blood-based biomarkers will add significant value in designing a large trial with the combination of lenvatinib and capecitabine with radiation and identify the patients that will most likely benefit from the combination.

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Conflict of Interest

Rutika Mehta: Eli Lilly (C/A), BMS, Astellas (SAB), Daiichi Sankyo, Natera (H); **Andrew Nixon:** Eli Lilly, GSK, Promega Corporation, Leap Therapeutics, AdjuVolt Therapeutics (C/A), Genentech, HTG Molecular Diagnostics, MedImmune/AstraZeneca, Medpacto, Promega Corporation, Seattle Genetics (RF), Core Correlatives Sciences Committee (NCTN-CCSC, Chair); **Richard Kim:** QED, Lilly, BMS, Bayer (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Figures and Tables

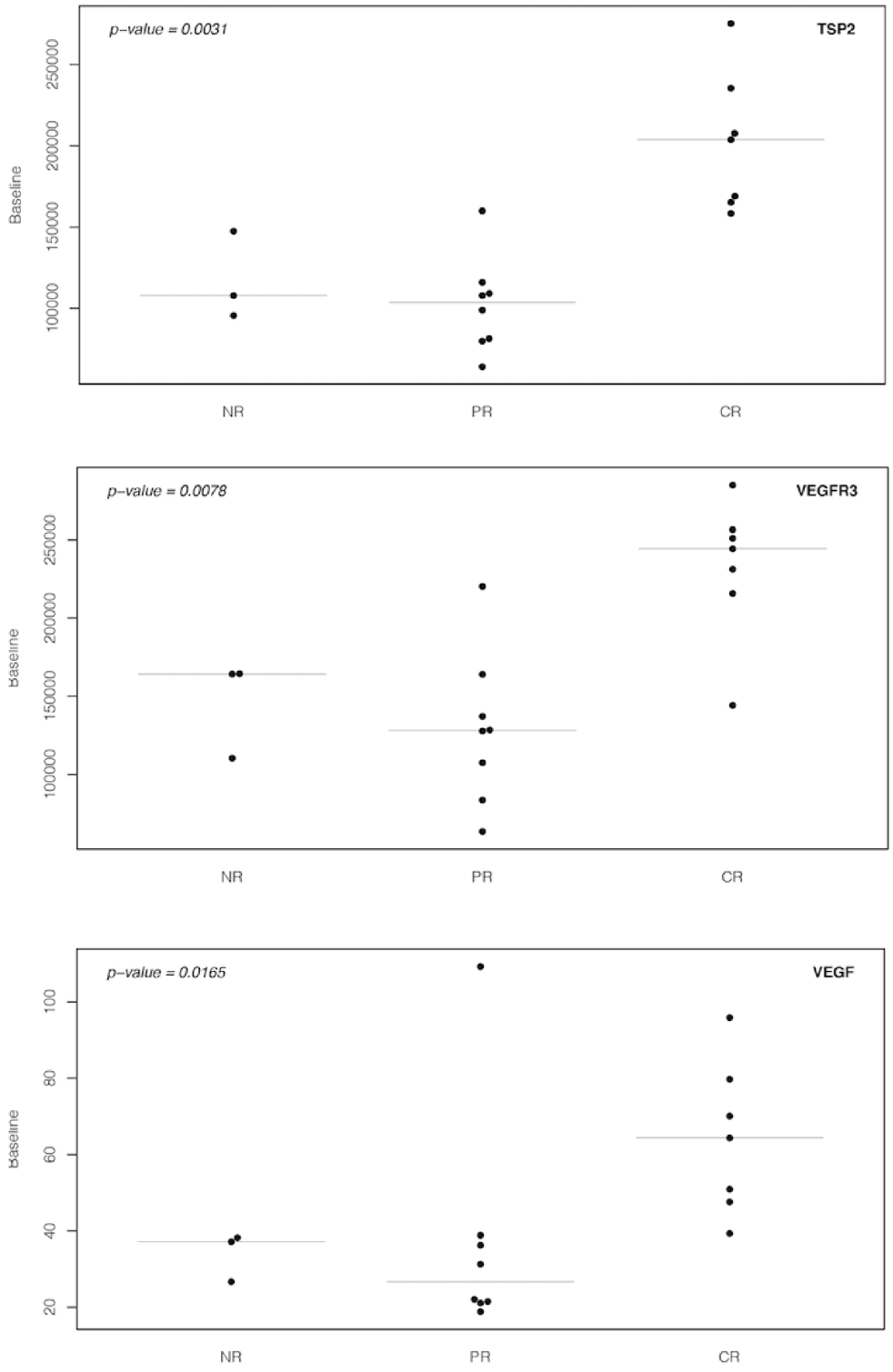

Figure 1. Baseline levels of three markers significantly differ across outcome groups.

Table 2. Biomarker levels at baseline and post-treatment. Fold change (post-chemo/baseline) was calculated for each patient and averaged.

Biomarker	Unit	Baseline (*n* = 18)	Post-chemo (*n* = 12)	Fold change: median (range)
Ang2	pg/mL	396.65 (170.06-959.7)	375.9 (184.69-827.5)	1.01 (0.48-1.89)
BMP9	pg/mL	87.64 (37.39-382.25)	163.49 (41.34-318.91)	1.58 (0.89-5.53)
CD73	pg/mL	0.25 (0.01-23.29)	0.39 (0.02-9.91)	1.12 (0.03-143.52)
GP130	ng/mL	279.05 (187.10-432.95)	315.30 (208.00-468.15)	1.1 (0.5-2)
HGF	pg/mL	139.48 (47.19-292.9)	160.83 (34.26-357.6)	1.1 (0.28-2.05)
ICAM1	ng/mL	449.65 (284.10-889.05)	436.50 (310.55-649.90)	1.07 (0.89-1.3)
IL6	pg/mL	2.63 (0.49-6.47)	1.98 (0.4-6.9)	1.31 (0.13-3.37)
IL6R	ng/mL	35.13 (23.08-48.36)	39.88 (23.06-56.01)	1.03 (0.93-1.51)
OPN	ng/mL	87.35 (43.96-235.39)	93.41 (67.89-205.43)	1.08 (0.65-1.75)
PDGFAA	pg/mL	126.06 (7.84-1714.88)	291.19 (69.55-3182.5)	2.55 (0.36-22.16)
PDGFBB	pg/mL	515.92 (54.34-10325)	1893.75 (191.43-10015)	2.83 (0.23-13.07)
PlGF	pg/mL	11.8 (4.72-24.7)	16.03 (9.43-32.54)	1.5 (0.9-2.41)
SDF1	ng/mL	1.62 (0.58-3.17)	1.79 (0.25-4.38)	1.16 (0.31-3.07)
TGFb1	ng/mL	17.17 (9.72-107.88)	26.41 (11.93-114.68)	1.37 (0.33-6.22)
TGFb2	pg/mL	55.71 (36.04-93.22)	79.32 (32.75-194.47)	1.28 (0.35-3.18)
TGFbR3	ng/mL	125.93 (79.32-171.63)	120.68 (84.08-194.68)	1.18 (0.63-1.45)
TIMP1	ng/mL	61.58 (40.56-112.85)	83.79 (56.82-139.55)	1.33 (0.93-2.22)
TSP2	ng/mL	131.70 (64.05-275.30)	189.15 (115.88-242.48)	1.13 (0.72-2.15)
VCAM1	ug/mL	1.97 (1.49-3.40)	2.37 (1.50-3.02)	0.92 (0.84-1.68)
VEGF	pg/mL	38.55 (18.84-109.3)	46.59 (23.11-77.54)	1.31 (0.24-1.88)
VEGFC	pg/mL	574.06 (321.22-2488.03)	773.27 (378.33-2669.72)	1.25 (0.39-3.58)
VEGFD	ng/mL	1.12 (0.81-2.79)	1.27 (1.05-2.96)	1.15 (0.75-2.67)
VEGFR1	pg/mL	63.14 (13.55-98.42)	67.4 (29.2-146.96)	1.15 (0.45-1.83)
VEGFR2	ng/mL	4.84 (1.13-7.28)	4.82 (3.08-7.30)	0.97 (0.7-1.25)
VEGFR3	ng/mL	164.04 (63.40-285.03)	245.03 (150.23-342.40)	1.18 (0.94-1.97)

Table 3. Adverse events reported due to any cause with lenvatinib combined with capecitabine based chemoradiation in locally advanced rectal cancer ($N = 20$)

Adverse events	Cohort 1 dose level (14 mg) ($N = 5$)			Cohort 2 dose level (20 mg) ($N = 3$)			Cohort 3 dose level (24 mg) ($N = 12$)			Total	Total grade 3
	NCI-CTC grade			NCI-CTC grade			NCI-CTC grade				
	1	2	3	1	2	3	1	2	3		
Blood and lymphatic system disorders											
White blood cell count decreased							2			2	0
Lymphocyte count decrease	1	1	2					2	1	7	3
Neutrophil count decrease		1								1	0
Platelet count decreased							2			2	0
Gastrointestinal disorders											
Anorexia	2			1			3			6	0
Buttock pain	1									1	0
Alanine aminotransferase increased									1	1	1
Aspartate aminotransferase increased								1		1	0
Constipation	2			1			1	1		5	0
Diarrhea	1			3			5			9	0
Dry mouth							1			1	0
Dyspepsia		1								1	0
Fecal Incontinence		1								1	0
Flatulence				1			1	1		3	0
Hemorrhoids				1						1	0
Hiccups	1									1	0
Nausea	2			3			7	1		13	0
Oral dysesthesia							1			1	0
Oral pain							1			1	0
Rectal Pain	2	1	1					2		4	1
Proctitis	2	2			2			2		8	0
Vomiting							2			2	0
GI disorders—others		1		3			2			6	0
GU/GYN disorders											
Creatinine elevation	1									1	0
Erectile dysfunction								2		2	0
Hematuria	1									1	0
Proteinuria		1								1	0
Urinary frequency	1									1	0
Urinary incontinence		1								1	0
Urinary urgency							2			2	0
Urinary tract infection		1								1	0
Other renal and urinary disorders								1		1	0
Urinary tract pain	2			1			6			9	0
Breast pain	1									1	0

Table 3. Continued

Adverse events	Cohort 1 dose level (14 mg) (*N* = 5)			Cohort 2 dose level (20 mg) (*N* = 3)			Cohort 3 dose level (24 mg) (*N* = 12)			Total	Total grade 3
	NCI-CTC grade			NCI-CTC grade			NCI-CTC grade				
	1	2	3	1	2	3	1	2	3		
Skin/cutaneous											
Dermatitis radiation	2	1		2	1		3	1		10	0
Limb edema				1						1	0
Palmar-plantar erythrodysesthesia syndrome		1								1	0
Pruritis	3			1			4			8	0
Papulopustular rash	1									1	0
Rash-maculo-papular							1			1	0
Thorax/cardiovascular											
Chest pain		1					1			2	0
Dyspnea	1	1					1			3	0
Hypertension	1		3		3		3	3		13	3
Hypotension		1								1	0
Palpitations							1			1	0
Sinus bradycardia								1		1	0
Electrolyte abnormalities											
Hyperglycemia	1						1			2	0
Hypokalemia		1								1	0
Others											
Anxiety	2						1			3	0
Arthralgia	1									1	0
Back pain				1						1	0
Blurred vision				1						1	0
Chills				2						2	0
Depression	1						1			2	0
Dizziness							1			1	0
Fatigue	3	1		2			9			15	0
Fever				1						1	0
Non-cardiac chest pain				1			1			2	0
Headache				1			3	1		5	0
Hoarseness							3			3	0
Infections	1						1			2	0
Insomnia	2			2			1			5	0
Myalgia	2									2	0
Pain				1			2			3	0
Pain in extremity							1			1	0
Photophobia							1			1	0
Somnolence	1									1	0
Weight loss				1						1	0
Other general disorders, non-specified				1						1	0

Table 4. Adverse events related to treatment with lenvatinib combined with capecitabine based chemoradiation in locally advanced rectal cancer ($N = 20$)

Adverse events	Cohort 1 dose level ($N = 5$)			Cohort 2 dose level ($N = 3$)			Cohort 3 dose level ($N = 12$)			Total	Total grade 3
	NCI-CTC grade			NCI-CTC grade			NCI-CTC grade				
	1	2	3	1	2	3	1	2	3		
Blood and lymphatic system disorder											
Neutrophil count decreased		1								1	0
Lymphocyte count decreased	1	1	2					2	1	7	3
Platelet count decreased							2			2	0
White blood cell count decreased							2			2	0
Gastrointestinal disorders											
Anorexia	2			1			3			6	0
Buttock pain	1									1	0
Constipation	1						1			2	0
Diarrhea	1			3			5			9	0
Fecal incontinence		1								1	0
Nausea	2			3			7	1		13	0
Oral pain							1			1	0
Proctitis	2	2			2			1		7	0
Rectal pain	1	1								2	0
Vomiting							2			2	0
Oral dysesthesia							1			1	0
Other gastrointestinal disorders		1		2			2			5	0
General disorders and administration site conditions											
Dry mouth							1			1	0
Fatigue	3	1		2			9			15	0
Injury, poisoning and procedural complications											
Aspartate aminotransferase increased								1		1	0
Skin and subcutaneous tissue disorders											
Palmar plantar erythrodysesthesia syndrome		1								1	0
Papulopustular rash	1									1	0
Dermatitis radiation	2	1		2	1		3	1		10	0
Pruritis	3			1			1			5	0
Rash maculo-papular							1			1	0
Cardiovascular disorders											
Sinus bradycardia								1		1	0
Hypertension	1		3		3		2	3		12	3
Infections and cutaneous											
Urinary tract infection		1								1	0
Other infections and infestations	1									1	0

Table 4. Continued

Adverse events	Cohort 1 dose level ($N = 5$)			Cohort 2 dose level ($N = 3$)			Cohort 3 dose level ($N = 12$)			Total	Total grade 3
	NCI-CTC grade			NCI-CTC grade			NCI-CTC grade				
	1	2	3	1	2	3	1	2	3		
Miscellaneous											
Arthralgia	1									1	0
Creatinine increased	1									1	0
Headache							2	1		3	
Myalgia	1									1	0
Urinary frequency	1									1	0
Urinary incontinence		1								1	0
Urinary urgency							1			1	0
Urinary tract pain	1						1			2	0
Erectile dysfunction								1		1	0
Hiccups	1									1	0
Hoarseness							3			3	0
Other renal and urinary disorders								1		1	0