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Clinical Trial Results

Modulation of Premetastatic Niche by the Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitor Pazopanib in Localized High-Risk Prostate Cancer Followed by Radical Prostatectomy: A Phase II Randomized Trial

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT01832259
- **Sponsor(s):** Novartis
- **Principal Investigators:** Benjamin L. Maughan, Sumanta K. Pal, David Gill
- **IRB Approved:** Yes

Lessons Learned

- Pazopanib was not effective in altering the premetastatic niche in the neoadjuvant setting.
- Pazopanib was safe and well tolerated without any new safety signals.

Abstract

Background. Vascular endothelial growth factor receptor 1 (VEGFR1) expressing myeloid-derived suppressor cells (VEGFR1+ MDSCs) potentially foster metastases by establishing a premetastatic niche. In a preclinical study, VEGFR1 + clustering in lymph nodes (LNs) independently predicted time to biochemical recurrence (TTBR) in localized prostate cancer [1]. The hypothesis was that neoadjuvant pazopanib therapy will decrease VEGFR1+ clusters in pelvic lymph nodes and improve outcomes.

Methods. This is a phase II trial (NCT01832259) of neoadjuvant pazopanib 800 mg versus placebo daily for 4 weeks in high-risk localized prostate cancer. The primary endpoint was a decrease in VEGFR1+ MDSC clustering assessed by immunohistochemistry (IHC) analysis. Secondary endpoints were safety, feasibility, and TTBR.

Results. Thirty patients were randomized to pazopanib versus placebo, with 15 patients randomized to each arm. Demographic and disease characteristics were similar in both arms. There was no difference in the VEGFR1+ clustering between the treatment arms (p = .345). Neoadjuvant therapy with pazopanib was well tolerated, and surgical complications were similar in both arms.

Conclusion. Neoadjuvant pazopanib therapy did not alter the premetastatic niche; however, treatment targeting vascular endothelial growth factor (VEGF) in the preoperative period was safe and feasible, which may open up the avenue to investigate novel combinatorial regimens, including a VEGF inhibitor in combination with immune checkpoint inhibitor in this setting. ***The Oncologist*** 2018;23:1413–e151

Discussion

Many patients with high-risk localized prostate cancer will have disease relapse after definitive therapy. One longstanding theory for progression to metastatic disease is termed the "seed and soil" theory. It postulates that tumor cells are "seeds" that preferentially metastasize to certain tissues or "fertile soils" based on the immune-suppressed

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microenvironment and underlying stroma, chemokines, and growth factors [2]. Recent evidence has shown that tumor cells may even be able to "fertilize" their premetastatic soil through releasing VEGF and stimulating VEGFR1+ cells in these eventual metastatic sites [3].

Tumor-led activation of VEGFR1 causes tissues to increase metalloproteinase-9 to facilitate tumor invasion and also stimulates fibronectin as a tumor chemokine [4]. Extrapolating these findings to prostate cancer, one retrospective study used a multivariate analysis to show that levels of VEGFR1+ MDSCs expressed in benign LNs independently predicts TTBR [5]. In a subsequent retrospective cohort of 46 patients who had undergone definitive therapy, Pal et al. validated these results, showing that greater levels of VEGFR-1 cell expression in benign LNs correlated with shorter TTBR [1]. In a secondary objective, the investigators sought to modify VEGFR1 expression by giving patients 4 weeks of axitinib, a VEGF tyrosine kinase inhibitor, for 4 weeks prior to definitive treatment. Unfortunately, the neoadjuvant trial with axitinib couldn't be completed because of slow accrual [1].

In this placebo-controlled, randomized phase II trial, we enrolled 30 patients with National Comprehensive Cancer Network-defined high-risk, localized prostate cancer and randomly assigned them to receive pazopanib 800 mg daily versus placebo for 4 weeks followed by radical prostatectomy. The primary endpoint was level of VEGRF1 expression in benign LNs obtained during radical prostatectomy by IHC. Statistical analysis was performed with Student's *t* test, using a one-sided alpha of 0.05 as a cutoff for predetermined significance. There was no significant difference in the primary outcome between pazopanib and placebo treatment. Neoadjuvant pazopanib therapy was well tolerated, with grade 3 liver enzyme elevations more frequent in patients receiving pazopanib (p = .042); hypertension (p = .05) and hoarseness (p = .006) were also more frequent. There were no grade 4–5 toxicities. The Clavian-Dindo complication rates were similar between the two groups: one grade 1 (rectal pain) and one grade 2 (incision site infection) event in the pazopanib group and three grade 1 (nausea/pain, postoperative hematoma and postoperative fever) and no grade 2 events in the placebo group.

Table 1. Vascular endothelial growth factor receptor 1 clustering

Pazopanib		Placebo	
Patient[a]	Number of positive cell clusters/HPF	Patient	Number of positive cell clusters/HPF
2	0.192148	1	Not evaluable
3	0.174367	4	0.330547
5	0.349642	8	0.309873
7	0.250327	11	0.455570
9	0.279976	12	Not evaluable
10	0.360911	14	0.345029
13	0.370427	16	0.314199
15	0.574301	18	0.234391
17	Not evaluable	20	0.162769
19	0.292445	21	0.273056
22	0.212668	23	0.231076
24	Not evaluable	27	0.130922
25	0.225461	29	0.187807
26	0.111981	30	0.159846
28	0.109085	31	0.135198

[a]Pazopanib group, mean (SD): 0.269518 (0.120773334); placebo group: mean (SD): 0.251560 (0.093458902); p = .345.
Abbreviations: HPF, high-power field; SD, standard deviation.

Although pazopanib did not decrease VEGFR1+ cell clusters in pelvic nodes and modulate the premetastatic niche in this study, the treatment was safe and feasible. A longer follow-up is required to determine if pazopanib had any effects on TTBR.

Trial Information	
Disease	Prostate cancer
Stage of Disease/Treatment	Neoadjuvant
Prior Therapy	None
Type of Study - 1	Phase II
Type of Study - 2	Randomized
Primary Endpoint	Correlative endpoint
Secondary Endpoint	Toxicity
Additional Details of Endpoints or Study Design	
In multivariate analysis, VEGFR1+ clustering in pelvic lymph nodes was an independent predictor of time to biochemical recurrence, with an optimal cutoff of 1.65 clusters per high-power field (hpf). The primary hypothesis for this study is that treatment with pazopanib (compared with control) will result in a decrease in premetastatic niche formation, as characterized by VEGFR1+ cell clusters, in pelvic lymph nodes. The primary efficacy endpoint will be the mean number of VEGFR1+ clusters in pelvic lymph nodes. The mean number of VEGFR1+ clusters per high-power field in the study described above was 3.13, with an SD = 1.43 and a range of 0–6.25. With 15 subjects per arm (30 subjects in all), there will be 80% power to detect a difference of 1.33 in the mean number of VEGFR+1 clusters/hpf between the reference and experimental arms using a Students *t* test at the one-sided alpha = 0.05 significance level. Assuming the number of clusters/hpf follows a Gaussian distribution, this difference corresponds to a substantial improvement from 15% of subjects with <1.65 clusters/hpf in the standard therapy arm to 46% of subjects with <1.65 clusters/hpf in the experimental therapy arm.	
Investigator's Analysis	Inactive because results did not meet primary endpoint

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Drug Information for Experimental Arm	
Generic/Working Name	Pazopanib
Trade Name	Votrient
Company Name	Novartis
Drug Type	Small molecule
Drug Class	VEGFR
Dose	800 mg per flat dose
Route	p.o.
Schedule of Administration	Daily for 4 weeks

Drug Information for Placebo Arm	
Generic/Working Name	Placebo
Route	p.o.
Schedule of Administration	Daily for 4 weeks

Patient Characteristics for Experimental Arm	
Number of Patients, Male	15
Cancer Types or Histologic Subtypes	Prostate adenocarcinoma, 15

Patient Characteristics for Placebo Arm	
Number of patients, Male	15
Cancer Types or Histologic Subtypes	Prostate adenocarcinoma, 15

Primary Assessment Method	
Title	VEGF clustering
Number of Patients Enrolled	15
Number of Patients Evaluable for Toxicity	15
Number of Patients Evaluated for Efficacy	13
Evaluation Method	Tumor marker
Response Assessment OTHER	*n* = 15
Outcome Notes	Outcome assessed by VEGFR1+ positive cell clusters/hpf. See Table 1.

Adverse Events

	Pazopanib (*n* = 15)				Placebo (*n* = 15)				*p* value	
Adverse event[a]	**All grades**	**Incidence**	**Grade 3–5**	**Incidence**	**All grades**	**Incidence**	**Grade 3–5**	**Incidence**	**All grades**	**Grade 3–5 only**
Fatigue	8	53.30%	0	0.00%	5	33.30%	0	0.00%	.462	>0.9
HTN	8	53.30%	1	6.70%	2	13.30%	0	0.00%	.050	>0.9
Hoarseness	7	46.70%	0	0.00%	0	0.00%	0	0.00%	.006	>0.9
Diarrhea	6	40.00%	0	0.00%	5	33.30%	0	0.00%	>0.9	>0.9
Transaminase or bilirubin elevation	5	33.30%	3	20.00%	0	0.00%	0	0.00%	.042	.224
Nausea	5	33.30%	0	0.00%	4	26.70%	0	0.00%	>0.9	>0.9
Rash	3	20.00%	0	0.00%	1	6.70%	0	0.00%	.598	>0.9
Anorexia	2	13.30%	0	0.00%	0	0.00%	0	0.00%	.483	>0.9
Dysgeusia	2	13.30%	0	0.00%	2	13.30%	0	0.00%	>0.9	>0.9

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Abdominal pain	1	6.70%	0	0.00%	2	13.30%	0	0.00%	>0.9	>0.9
Dry mouth	1	6.70%	0	0.00%	1	6.70%	0	0.00%	>0.9	>0.9
Dry skin	1	6.70%	0	0.00%	0	0.00%	0	0.00%	>0.9	>0.9
Dyspepsia	1	6.70%	0	0.00%	0	0.00%	0	0.00%	>0.9	>0.9
Eye disorder (NOS)	1	6.70%	0	0.00%	0	0.00%	0	0.00%	>0.9	>0.9
GERD	1	6.70%	0	0.00%	1	6.70%	0	0.00%	>0.9	>0.9
Headache	1	6.70%	0	0.00%	1	6.70%	0	0.00%	>0.9	>0.9
Hot flashes	1	6.70%	0	0.00%	0	0.00%	0	0.00%	>0.9	>0.9
Generalized pain	1	6.70%	0	0.00%	0	0.00%	0	0.00%	>0.9	>0.9
Thrombocytopenia	1	6.70%	0	0.00%	1	6.70%	0	0.00%	>0.9	>0.9
Stomach pain	1	6.70%	0	0.00%	0	0.00%	0	0.00%	>0.9	>0.9
Bloating	0	0.00%	0	0.00%	1	6.70%	0	0.00%	>0.9	>0.9
Flatulence	0	0.00%	0	0.00%	1	6.70%	0	0.00%	>0.9	>0.9
Oral pain	0	0.00%	0	0.00%	1	6.70%	0	0.00%	>0.9	>0.9
Peripheral sensory neuropathy	0	0.00%	0	0.00%	1	6.70%	0	0.00%	>0.9	>0.9

[a]Adverse events occurring in over 5% of patients.
Abbreviations: GERD, gastroesophageal reflux disease; HTN, hypertension; NOS, not otherwise specified.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Inactive because results did not meet primary endpoint

Localized prostate cancer represents a spectrum of disease. Although men with very low or low-risk prostate cancer may not need definitive therapy with surgery or radiation therapy, approximately 30% of men with high-risk prostate cancer eventually experience relapse and progression to metastatic disease after definitive therapy [6]. Trials with neoadjuvant and adjuvant therapy have previously been attempted with chemotherapy [7–9] or androgen deprivation therapy (ADT) [10, 11] to increase the proportion of patients cured of disease. The most robust study to date with chemotherapy was recently published [7]. This phase III study randomized 376 patients after prostatectomy to either docetaxel with ADT therapy or ADT therapy alone. Patients were eligible if they had intermediate- or high-risk disease as defined as T2 with Gleason score of 4 + 3 and a prostate-specific antigen (PSA) level of ≥ 10; or T2 with a Gleason score of 8–10 regardless of PSA; or T3 disease regardless of PSA. There was no difference in the primary endpoint of biochemical disease-free survival between the two arms (p = .631). To date, there are no effective perioperative therapies for these patients. This is a population of significant unmet need.

The mechanism of prostate cancer metastasis is currently not entirely understood; however, evidence suggests a significant role for vascular endothelial growth factor (VEGF) and its associated receptor (VEGFR) in prostate cancer progression [12]. Primary tumor-derived circulating VEGF mediates recruitment of VEGFR1-positive myeloderived immune suppressor cells (MDSCs) in noncancerous tissue (premetastatic niche), which eventually creates an immunosuppressive microenvironment (fertile soil) for the cancer cells (seeds) when they venture into these niches [13, 14]. Figure 1 shows formalin-fixed paraffin-embedded section of the benign pelvic lymph node showing VEGFR1-positive cell clusters (immunohistochemistry, ×10 and ×40 resolution). Prior studies have suggested that targeting the VEGF axis may be a promising strategy in advanced prostate cancer. For instance, a phase II single-arm study in 20 patients with metastatic castration-resistant prostate cancer who previously progressed on docetaxel was conducted [15]. All patients were treated with docetaxel 60 mg/m^2 in combination with bevacizumab 10 mg/m^2 every 3 weeks. The primary endpoint was PSA response. Major PSA responses, defined as a ≥ 50% PSA reduction that was confirmed with a repeat PSA test 2 weeks later, were observed in 11 patients (55%). Minor PSA responses, defined as a PSA decline of 25%–49% confirmed with a repeat PSA in 2 weeks, were observed in two patients (10%). Two patients (10%) had stable disease as defined by no change in the PSA. In total, 15 patients (75%) experienced clinical benefit from treatment with bevacizumab.

We hypothesized that pazopanib, being a VEGF inhibitor, would decrease the VEGFR1-positive MDSCs in the pelvic lymph nodes, the most frequent sites of prostate cancer metastasis, abrogate these premetastatic niches, and subsequently improve outcomes. This was based on a retrospective study showing that greater levels of VEGFR1 cell expression in benign pelvic nodes correlated with shorter time to biochemical recurrence in these men. However, we did not see a pharmacodynamic response supporting our hypothesis. It is possible that specifically pazopanib is ineffective whereas other more potent VEGF tyrosine kinase inhibitors (TKIs) may still be effective. Alternatively, it is possible that the duration of pazopanib therapy in our trial was insufficient. Another potential issue is the relatively low incidence

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of VEGF clusters observed in our study (0.27 clusters per high-power field [hpf]) compared with previous studies using VEGF-directed therapy (3 clusters/hpf). This may be related to population differences between the studies and not from the therapies used. Finally, it is worthwhile noting that monotherapy with VEGF inhibitor therapy may be insufficient but a combinatorial regimen of a VEGF TKI and an immune checkpoint inhibitor may be efficacious. In fact, recent clinical trials in metastatic renal cell carcinoma show that VEGF targeted therapy in combination with immune checkpoint inhibitors demonstrates an improved clinical benefit and much higher response rate [16] than those observed with monotherapy with VEGF inhibitors [17, 18]. The hypothesis of clinical efficacy with VEGF targeted therapy (cabozantinib) in combination with checkpoint inhibitor (atezolizumab) in metastatic castration-resistant prostate cancer is currently being tested in a phase I clinical trial (NCT03170960). If this clinical trial shows clinical activity in this setting, it may provide the rationale for testing similar combinations in the neoadjuvant prostate cancer setting in the near future.

This study is particularly important in demonstrating the safety of VEGF inhibition in the perioperative setting. We did not observe any increase in surgery-related morbidity or mortality, especially any effect on the surgery-associated bleeding or wound healing. The Clavien-Dindo surgical complications were minimal and tolerable with no grade 3–5 events. Systemic adverse events were well tolerated, easily manageable, and similar to those observed in other clinical trials of pazopanib including hypertension, fatigue, and asymptomatic elevation of transaminases. There were no grade 4 or 5 adverse events observed. New treatment strategies are urgently needed in this high-risk population. Our study confirms the safety of neoadjuvant therapy with VEGF inhibitors, which may open the avenue for development of trials employing a combination regimen of a VEGF inhibitor plus an immune checkpoint inhibitor.

Disclosures

Sumanta K. Pal: Pfizer, Genentech, Novartis, Exelexis, Aveo, Eisai, Roche, Ipsen, Bristol-Myers Squib, Astellas Pharma (C/A), Genentech (H); **Roberto Nussenzveig:** Tempus Labs, Inc. (C/A); **Neeraj Agarwal:** Pfizer, Novartis, Merck, Genentech, Eisai, Exelexis, Clovis Oncology, EMD Serono, Inc., Bristol-Myers Squibb, AstraZeneca, Astellas Pharma, Eli Lilly and Co., Bayer (C/A), Active Biotech, Astra Zeneca, Bavarian Nordic, BMS, Calithera, Celldex, Eisai, Exelixis, Genetech, GSK (glaxosmithkline), Immunomedics, Janssen, Medivation, Merck, New link Genetics, Novartis, Pfizer, Prometheus, Rexahn, Sanofi, Takeda, Tracon (RF [institutional funding]). 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

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Figure

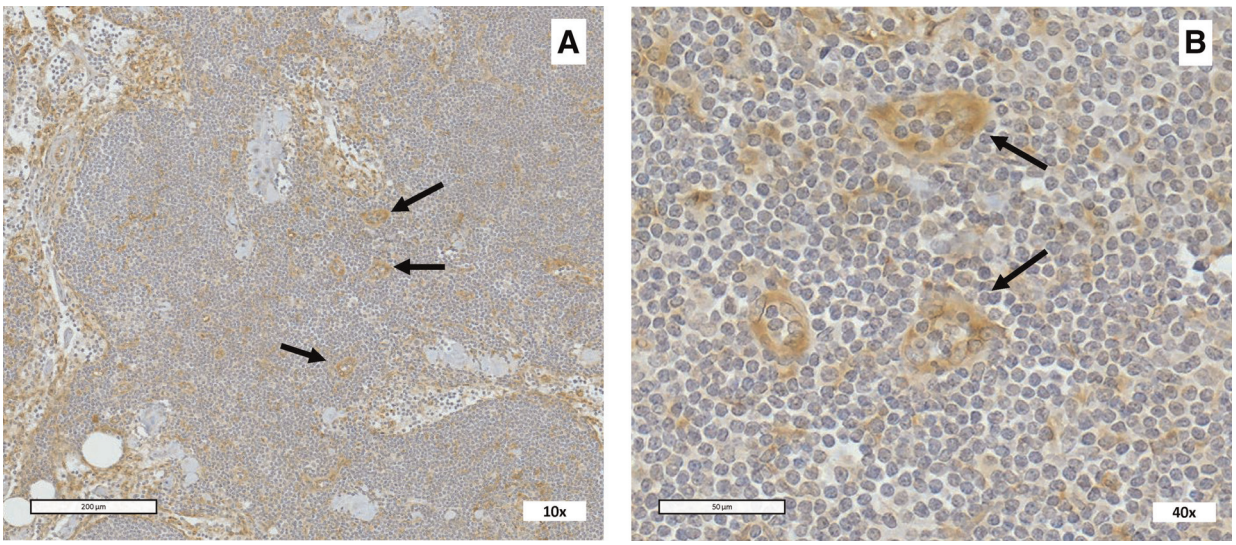

Figure 1. Formalin-fixed paraffin-embedded section of the benign pelvic lymph node showing vascular endothelial growth factor receptor 1-positive cell clusters (immunohistochemistry, ×10 and ×40 resolution).

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