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Aflibercept (VEGF Trap) in Inoperable Stage III or Stage IV Melanoma of Cutaneous or Uveal Origin

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Abstract

Purpose: Aflibercept is a soluble decoy VEGF receptor and angiogenesis inhibitor with potent preclinical antitumor activity in melanoma. We conducted a multicenter phase II study in patients with inoperable stage III or IV melanoma and no prior chemotherapy.

Experimental Design: A two-stage design was adopted to evaluate 4-month progression-free survival rate (PFSR) and response rate. Aflibercept was given at 4 mg/kg intravenously every 2 weeks. Response was assessed every 8 weeks. First-stage accrual of 21 patients was specified and with an adequate 4-month PFSR accrual continued to a total of 41.

Results: Forty-one patients of ages 23 to 84 (median = 57) were enrolled. Thirty-nine had American Joint Committee on Cancer stage IV (5 M1a, 7 M1b, and 27 M1c) and 2 had inoperable stage IIIC (N3). Eastern Cooperative Oncology Group (ECOG) performance status was 0 (27 patients) or 1 (14 patients). Ten patients had primary uveal melanoma, 28 cutaneous, and 3 had unknown primaries. A median of 7 cycles were initiated (range: 1–56). Grade 3 and 4 toxicities included hypertension in 9 patients (22%) and proteinuria in 6 (15%). Among 40 patients evaluable for efficacy (those who initiated aflibercept), 3 (7.5%) had a confirmed partial response and 20 had progression-free survival of 4 months or above. The predicted 1-year survival rate derived from the Korn meta-analysis model is 36% ($N = 39$), whereas we observed a corresponding 56.4% survival rate at 1 year (95% CI, 43–74, $P < 0.005$). Median overall survival in this trial is 16.3 months (95% CI, 9.2 to not reached). We observed a significant association between severity of hypertension following aflibercept and survival improvement.

Conclusions: Aflibercept showed promising activity in patients with metastatic melanoma of cutaneous or uveal origin. Further evaluation of aflibercept as a single agent and in combination is warranted. *Clin Cancer Res; 17(20); 6574–81. ©2011 AACR.*

Introduction

The VEGF family of molecules play critical roles in tumor angiogenesis, lymphangiogenesis, and vasculogenesis as well as modulating host innate and adaptive immunity (1–2). In cancer, VEGF is not produced by endothelial cells but by tumor cells or stroma, consistent with a paracrine mode of action (3–5). Expression of VEGF, VEGF receptor 1, (VEGFR1) and VEGFR2 has been shown to be significantly higher in melanomas than in nevi ($P < 0.0001$), and differential expression has also been shown in metastatic melanoma compared with primary histospots (6). Serum VEGF-A and VEGF-C levels have been shown to be higher in patients with high tumor burden than in patients with low tumor burden (7–9). The role of excess VEGF on tumor angiogenesis is well documented and recently high-circulating serum levels of VEGF were associated with poor prognosis in patients with metastatic melanoma (10). VEGF has been shown to block maturation of dendritic cells and inhibit effective priming of T-cell responses (11, 12). These data support an important role for VEGF in the progression of cancer and evasion of antitumor immunity.

Aflibercept (VEGF Trap) is a fusion protein combining the Fc portion of human IgG_1 with the principal extracellular ligand–binding domains of human VEGFR1 and VEGFR2. It acts as a high-affinity soluble decoy VEGF receptor and potent angiogenesis inhibitor. Preclinical studies showed potent antitumor and antiangiogenic activity in a variety of tumors including melanoma. (13) A phase I study in subjects with treatment-refractory solid tumors or non–Hodgkin lymphoma evaluated 5 dose

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Translational Relevance

Melanoma is known to be a highly vascular tumor where VEGF is linked to pathogenesis and where elevated VEGF levels in patients with melanoma are associated with a poor prognosis, cancer progression, and evasion of antitumor immunity. This phase II study has shown significant clinical activity of aflibercept as a single agent with 50% of patients to be progression free at 4 months. These data support further testing of aflibercept in combination with other agents active in cutaneous melanoma such as interleukin 2, ipilimumab, vemurafenib, and chemotherapy. In addition, among a subset of 10 patients with uveal melanoma, 50% were progression free at 4 months, supporting further testing of aflibercept as monotherapy or in combination with chemotherapy in uveal melanoma. On the basis of the results of this study, an immunotherapeutic strategy combining aflibercept and high-dose interleukin 2 is currently being tested in a randomized phase II trial (NCI 8628).

levels (intravenously; ref. 14). In this study, 2- to 4-mg/kg dose levels given biweekly have shown steady-state concentrations of bound aflibercept at or near saturation, and free aflibercept in excess of bound aflibercept throughout the biweekly dosing intervals has been documented. Decreased tumor vascular permeability and perfusion by dynamic contrast enhanced-MRI within 24 hours of the first dose has also been observed at these dose levels (14). At the 24-hour time point, formation of VEGF–aflibercept complex is maximal, and free aflibercept accumulates, consistent with evidence of biological activity in this dose range (14). Therefore, 4 mg/kg intravenously every 2 weeks has been determined to be the recommended phase II dose schedule.

We hypothesized that aflibercept would induce antitumor and antiangiogenic activity as well as immunomodulation that would improve the progression-free survival rate and/or tumor response rate in patients with inoperable stage III/IV melanoma. Therefore, we conducted this multicenter phase II study of the single-agent aflibercept.

Patients and Methods

Patients

Patients 18 years or older were eligible if they had histologically confirmed inoperable American Joint Committee on Cancer stage III and IV melanoma and had measurable disease [Response Evaluation Criteria in Solid Tumors (RECIST)], no previous chemotherapy, and no history of brain metastases. Patients were required to have Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less (Karnofsky $\geq$ 60%) and adequate hematologic, hepatic, and renal function. Patients were considered ineligible for specific cardiovascular, cerebrovascular, bleeding, or thrombosis risk. All patients provided a written informed consent.

Study design and treatment

This is a safety and efficacy phase II single arm study. Patients received aflibercept 4 mg/kg intravenously over at least 1 hour on day 1 of each 14-day cycle. Aflibercept was provided by Sanofi-Aventis and the National Cancer Institute (NCI), NIH.

Toxicity and response assessments

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 were used for adverse event grading and reporting.

Response assessment (by the individual investigators) was carried out every 8 weeks (4 cycles) using RECIST version 1.0. In the absence of limiting toxicities, patients without evidence for disease progression were offered additional cycles of therapy.

Dose modifications

Doses could be reduced to levels −1 (3 mg/kg) and −2 (2 mg/kg) for drug-related toxicity. Specific guidelines were provided for the management of hypertension and proteinuria.

Statistical methods

A 2-stage design was adopted to detect a promising 4-month progression-free survival rate (PFSR) or a promising tumor response rate (response rate = complete response + partial response). Progression-free survival was calculated as the duration of time from start of treatment to time of progression or death. In the first stage, accrual continued until 21 patients, with a final accrual goal of 41.

The targeted 4-months PFSR was based on 3 recently reported (at the time of study design) phase III randomized clinical trials (15–17). Therefore, we took a median of 2.3 months progression-free survival as a conservative external standard. If this regimen improved median progression-free survival from 2.3 to 4 months, corresponding to an improvement in the 4-month PFSR from 30% to 50% using a constant hazard model, we concluded that it would warrant further study. Therefore, we chose a design that simultaneously discriminates between tumor response rates of 15% versus 3% and a 4-month PFSR of 50% versus 30%. In particular, we decided that if no responses, and no more than 7 patients with 4-month progression-free survival (no more than 33%), were observed among the initial 21 patients, the study should be terminated. If at least 4 responses (10%), or at least 17 instances of 4-month progression-free survival (at least 41%), were observed among the 41 evaluable patients, we decided that this agent would be worthy of further evaluation in this disease. This design yields at least 87% power to detect a true response rate of at least 15%. It yields at least 85% power to detect a true 4-month PFSR of at least 50%. It yields at least 0.90 probability of a negative result if the true response rate is no more than 3% and the true 4-month PFSR is no more than 30%, with approximately 0.38 probability, at least, of early negative stopping.

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Table 1. Demographics and baseline patient characteristics

Variable	No. of patients ($N = 41$)
Age, y	57 (23–84)
Sex	
Male	26
Female	15
Ethnicity—Caucasian	41
Performance status (ECOG)	
0	27
1	14
Primary cutaneous	28
Primary ocular	10
Unknown primary	3
Prior drug therapy	12
IFN (adjuvant)	9
IFN, anti-CTLA4	1
Melphalan (isolated limb perfusion)	1
CRO11-VCMMAE[a]	1
Classification	
M1a	5
M1b	7
M1c	27
IIIC (N3)	2

[a]CRO11-VCMMAE (CDX-011) is a monoclonal antibody–drug conjugate that targets glycoprotein NMB.

Results

Patient characteristics

Forty-one patients were enrolled between June 2007 and April 2009. Table 1 summarizes the demographics of the study population and baseline patient characteristics.

Treatment details

Patients received a median of 7 cycles (range: 1–56) of aflibercept. All patients have since discontinued aflibercept. Among the 41 patients, the reason for discontinuation was disease progression in 30 (73%), adverse event in 6 (15%), patient/investigator decision in 4 (10%), and co-morbid conditions (poorly controlled diabetes mellitus and poor compliance) in 1 (2%; Table 2).

Adverse events leading to treatment discontinuation included recurrent grade 3 proteinuria in 2 patients (after 252 and 651 days on aflibercept), 1 with grade 3 hypertension/renal failure/proteinuria and grade 4 confusion/memory impairment after 49 days, 1 with grade 3 chest pain and grade 3 proteinuria after 29 days, and grade 4 cerebrovascular ischemia and grade 3 left ventricular diastolic dysfunction after 35 days in 1, and 1 patient with history of external beam radiation therapy to the head and neck area who developed osteonecrosis of the mandibular bone after 160 days.

Table 2. Treatment details

Number of cycles completed	
Median	7
Range	1–56
No. of patients on therapy (%)	0
No. of patients off therapy (%)	41 (100)
Reason for discontinuation (n = 41)	
Disease progression (%)	30 (73)
Adverse event (%)	6 (15)
Patient/investigator decision (%)	4 (10)
Comorbid conditions (%)	1 (2)

Three patients refused to continue treatment but did not otherwise meet protocol criteria for discontinuation. These include one who experienced grade 3 fatigue (42 days on therapy) and one patient with no significant noted toxicities (151 days). The third patient experienced a grade 2 allergic reaction during the second drug infusion. One patient with uveal melanoma and biopsy-proven liver and omental metastases has had surgical resection as well as liver radiofrequency ablation followed by disease progression. At baseline, he was considered to have measurable disease by computed tomographic scan and was enrolled on the study. However, upon further evaluation following 8 weeks (4 cycles) of treatment, it was not clear whether his liver lesions are viable tumor or treated lesions secondary to the prior radiofrequency (RFA) ablation. Therefore, because of this clinical uncertainty about the liver lesions, it was decided to consider the subject not evaluable for efficacy analysis and treatment was discontinued.

Efficacy

One patient who refused additional aflibercept after 2 doses (the second dose was terminated because of a grade 2 allergic reaction) was started on temozolomide. This patient went on to have progression on temozolomide and was considered to have disease progression in our analysis. Another patient, also discussed in the preceding paragraph, had prior RFA ablation of liver metastases that may confound response assessment and was excluded from efficacy analysis. This patient was progression free by positron emission tomography-computed tomography for 875+ days but was excluded from response rate and survival calculations as a result of the prior RFA.

Response rate

Response rate is based on 40 patients (excluding the patient with RFA ablation). There were 3 (7.5%, 95% CI, 2–20) with a confirmed partial response (see Table 3).

Four-month PFSR

A total of 20 patients had a progression-free survival of 4 months or longer (50%, 95% CI, 0.34–0.66; see Table 3).

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Table 3. Efficacy summary: patients with 4-month progression-free survival ($N = 40$)[a]

Primary	*n*	Classification (*n*)	PFS, d
First 21 patients			
Uveal	5	M1c (5)	382, 280, 185, 174, 151+
Cutaneous	5	M1b (2)	937, 764+
		M1c (3)	207, 186, 177
Unknown	1	M1a (1)	148
Next 20 patients			
Cutaneous	9	N3 (2)	168, 173
		M1a (3; 2 PR)	338, 452, 819
		M1b (1)	225
		M1c (3; 1 PR)	231, 447, 610+

NOTE: Summary: 3 PRs, with 20 patients PFS > 4 months.
Abbreviation: PFS, progression-free survival; PR, partial response.
[a]Excluding 1 patient (PFS: 875+ days) considered not evaluable for efficacy.

Analysis of efficacy data

At the end of stage I enrollment ($N = 21$), there were no objective responses by RECIST. However, there were 11 patients with progression-free survival of 4 months or longer. On the basis of these 4-month progression-free survival data, the study moved into stage II enrollment (see Table 3).

At the end of stage II ($N = 41$), there were 3 objective responders (<target of 4) and 20 instances of 4-month progression-free survival (>target of 17), excluding the patient unevaluable for efficacy. Therefore, the study is considered to have met its efficacy criteria and this agent is considered worthy of further testing in this disease based on the original design.

For the 40 patients evaluable for survival endpoints, median follow-up was 25.4 months among those alive (1 patient declined follow-up at 5.0 months, with the remainder followed for 15–36 months). Median overall survival is 16.3 months (95% CI, 9.2 to not reached). Median progression-free survival is 3.7 months (95% CI, 2.8–6.8). Fig. 1 shows the Kaplan–Meier plots of the probability of progression-free survival and overall survival.

Supplementary Table S1 provides a summary of efficacy parameters for uveal ($N = 9$) and cutaneous-unknown ($N = 31$) primary melanoma, presented separately. While all 3 responders had cutaneous melanoma, the table suggests comparable efficacy among uveal and non-uveal melanomas in terms of 4-month PFSR (56% vs. 48%), median progression-free survival (5.7 vs. 3.7 month), and median overall survival (19.0 vs. 16.3 month).

Safety

Table 4 summarizes adverse events by severity that were considered possibly, probably, or definitely related to aflibercept. As expected, the most common adverse events were hypertension occurring in 28 patients (68%) and proteinuria in 13 patients (32%). Among grade 3 and 4 toxicities, 9 patients (22%) had hypertension, 6 had proteinuria (15%), 1 had renal failure (2%), 1 had gastrointestinal bleed (2%), 2 had hyponatremia (5%), 1 had cerebrovascular ischemia (2%), 1 had reversible extraocular muscle paresis (2%), and 1 had osteonecrosis (2%) of the mandibular bone in a patient with a history external beam radiation therapy to the head and neck area.

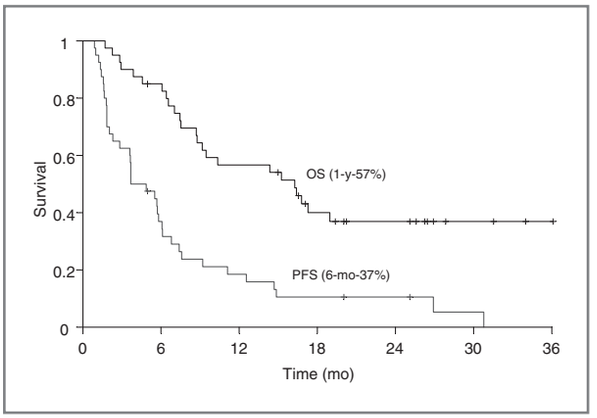

Figure 1. Kaplan–Meier plots of the probability of overall survival and progression-free survival.

Hypertension and survival

We have observed a significant association between hypertension following aflibercept administration and improved survival. Patients experiencing higher grades of hypertension (CTCAE v.3) had a superior progression-free survival: patients with grade 0, 1, 2, and 3 hypertension had median progression-free survival of 1.8, 2.1, 4.9, and 11.8 months, respectively [log-rank (3 degrees of freedom); $P < 0.01$]. Similarly, superior overall survival was observed in patients with higher grade hypertension, where those patients with grade 0, 1, 2, and 3 hypertension had a median overall survival of 6.6, 21.1, and 16.8 months, and no median was reached for patients with grade 3 hypertension ($P < 0.001$; see Fig. 2). As suggested by Supplementary Table S2, while higher hypertension grades tended to occur in slightly later cycles, they tended to occur early, and the increase was a far smaller signal than the increase in the total number of cycles where a specific grade of hypertension occurred. This suggests that the observed correlation is not likely a mere manifestation of time spent on trial and is worth validating in future larger trials.

Discussion

Inhibiting tumor angiogenesis is an important goal of therapy for melanoma supported by a significant role for angiogenesis in tumor pathogenesis, progression, and immune evasion. VEGF family plays a critical role in tumor angiogenesis, and VEGF levels have been significantly

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Table 4. Summary of adverse events by severity (possible, probable, and definite; $N = 41$ patients)

	All grades No. of participants (%)	Grade 3/4 Grade 3, *N* (%)	Grade 4, *N* (%)
Hematologic			
Anemia	5 (12)	0 (0)	0 (0)
Lymphopenia	7 (17)	0 (0)	0 (0)
Thrombocytopenia	1 (2)	1 (2)	0 (0)
Cardiovascular			
Hypertension	28 (68)	9 (22)	0 (0)
Hypotension	1 (2)	1 (2)	0 (0)
LV diastolic dysfunction	1 (2)	1 (2)	0 (0)
Gastrointestinal/hepatic			
Abdominal pain	5 (12)	0 (0)	0 (0)
Nausea	9 (22)	0 (0)	0 (0)
Increased AST/ALT	10 (24)	0 (0)	0 (0)
Hemorrhage			
Gastrointestinal bleed	2 (5)	1 (2)	0 (0)
Epistaxis	9 (22)	0 (0)	0 (0)
Neurologic			
Cerebrovascular ischemia	1 (2)	0 (0)	1 (2)
Headache	17 (41)	1 (2)	0 (0)
Other			
Cough	6 (15)	0 (0)	0 (0)
Extraocular muscle paresis	1 (2)	1 (2)	0 (0)
Fatigue	17 (41)	1 (2)	0 (0)
Hyperkalemia	5 (12)	0 (0)	0 (0)
Hyponatremia	11 (27)	2 (5)	0 (0)
Limb edema	7 (17)	0 (0)	0 (0)
Osteonecrosis of mandibular bone (h/o XRT to head and neck)	1 (2)	1 (2)	0 (0)
Rash	7 (17)	0 (0)	0 (0)
Pain			
Back	3 (7)	1 (2)	0 (0)
Chest	3 (7)	1 (2)	0 (0)
Joint	6 (15)	0 (0)	0 (0)
Oral, pharynx	8 (20)	0 (0)	0 (0)
Renal			
Increased creatinine	7 (17)	1 (2)	0 (0)
Proteinuria	13 (32)	6 (15)	0 (0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; h/o, heterotopic ossification; LV, left ventricular; XRT, x-ray therapy.

correlated with a high microvascular density of melanoma (18). Melanoma is known to be a highly vascular tumor where VEGF is linked to pathogenesis and where elevated VEGF levels in patients with melanoma are associated with a poor prognosis (19, 20). Therefore, on the basis of clinical and pathologic findings, as well as preclinical research suggesting the therapeutic value of antiangiogenic approaches, studies targeting this progression pathway have been undertaken with a variety of agents that differ in potency, selectivity, and mechanism of action.

Aflibercept is a high-affinity soluble decoy VEGF receptor and potent angiogenesis inhibitor. This phase II single arm study has shown notable clinical activity of aflibercept as a single agent. It has met its primary endpoint with 50% of patients having a progression-free survival of 4 months or longer. By RECIST, aflibercept has shown a limited response rate, with only 3 patients achieving partial response (9%). The exploration of overall survival and progression-free survival has been suggested as a more appropriate approach to the development of new therapeutic agents for melanoma in phase II studies, beyond the traditional tumor response rate (21). On the basis of a meta-analysis of previously collected data from 42 cooperative group melanoma phase II trials, Korn and

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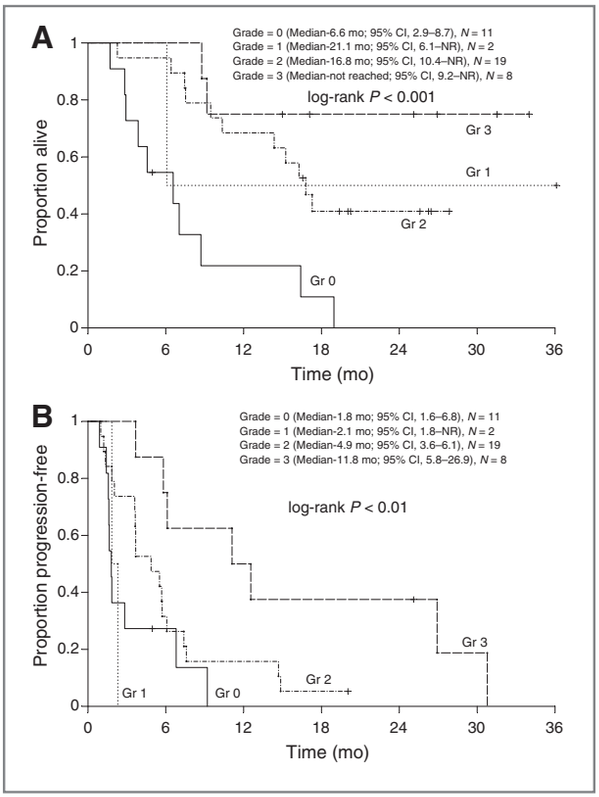

Figure 2. Overall survival (A) and progression-free survival (B) association was observed between hypertension grades after aflibercept. NR, not reached.

colleagues have suggested the use of 1-year overall survival and 6-month progression-free survival as benchmarks for future phase 2 studies (22). Four significant prognostic factors were advanced, including performance status, presence of visceral metastasis, gender, and the presence of brain metastasis (exclusion of patients with brain metastasis). The authors suggested defining the null hypothesis target for a particular phase II trial, based on the prognostic variables observed in the trial and provided a table that contains the relevant information for a trial using 1-year OS rate as the endpoint. These predicted values are based on a logistic regression analysis with effects included for the 4 significant prognostic factors. We used this model for our study, accommodating the mix of patients in terms of performance status, incidence of visceral disease, gender distribution, and the exclusion of brain metastasis. Excluding 1 patient who was ineligible for efficacy analysis, 40 patients have been analyzed among which 23 are alive at 1 year. We also excluded 1 patient who was formally censored prior to 1-year because of patient refusal. Of the remaining 39 patients, the predicted 1-year survival rate by the Korn model is 36.1%. For these 39 patients, the 1-year survival rate is 56.4% (95% CI, 0.43–0.74), which is distinct from the Korn estimate of 36.1% ($P < 0.005$). We also evaluated the potential influence of additional therapy post-aflibercept. One patient received ipilimumab prior to the 1-year mark. Excluding that patient resulted in a Korn 1-year survival estimate of 36.6%, with the observed 1-year survival rate in the remaining 38 patients of 55% ($P < 0.005$). Two patients received tremelimumab prior 1 year; excluding all such patients ($N = 36$), the Korn estimate was 35.5%, and the observed rate was 53% ($P < 0.01$). Supplementary Table S3 summarizes the Korn model analysis for calculating the predicted 1-year overall survival rate.

This level of single-agent activity is notable in metastatic melanoma. In addition, the toxicity profile we have observed is acceptable with toxicities that are manageable. Further testing of aflibercept as a single agent is therefore warranted in both metastatic melanoma randomized phase II and III trials. However, given the recent promising findings with BRAF kinase inhibitors and anti-CTLA4 blocking antibodies, the future assessment of aflibercept may be best envisioned in combinations and in second and subsequent line therapy.

Ten patients with uveal melanoma were enrolled on this study. Among these, 1 nonevaluable patient had a progression-free survival of 875+ days. In addition, 5 evaluable patients had progression-free survival of 382, 280, 185, 174, and 151+ days. Therefore, aflibercept may be active in patients with ocular melanoma with 50% of patients in our cohort having progression-free survival of more than 4 months. These data support further testing of aflibercept in this population both as a single agent and in combinations that may include chemotherapy or immunotherapy.

VEGF has been shown to block maturation of dendritic cells and inhibit effective priming of T-cell responses (11, 12). The importance of VEGF in cancer progression and evasion of antitumor immunity has been less emphasized than in angiogenesis. Pretreatment VEGF-C levels have been shown to be higher in patients refractory to biochemotherapy [cisplatin (CDDP), recombinant interleukin (IL)-2, IFN-α] than in responding patients (7). In addition, recent studies have identified baseline serum VEGF as a marker of immune resistance that predicts nonresponse to high-dose IL-2 (23). These data, taken together, support an immunotherapeutic strategy combining VEGF inhibitors (aflibercept) and other immunotherapeutic agents active in melanoma such as high-dose IL-2 (NCI 8628; a randomized phase II study), IFN-α, or CTLA4 blockade.

VEGF inhibition, in combination with chemotherapy, has previously been tested in melanoma. A phase II study of carboplatin/paclitaxel plus bevacizumab showed promising activity in 53 patients treated (24). The trial, known as the BEAM trial, tested carboplatin/paclitaxel/bevacizumab ($N = 143$) randomized versus carboplatin/paclitaxel ($N = 71$; ref. 25). The combination showed nonsignificant improvements in all endpoints (response rate: 25.5% vs. 16.4%, $P = 0.16$; progression-free survival: 5.6 vs. 4.2 months, $P = 0.14$; overall survival: 12.3 vs. 9.2 months, $P = 0.06$). Subgroup analysis showed significant overall survival improvement in the subgroup with the worst prognosis (M1c). A single arm phase II study has recently reported first-line temozolomide combined with bevacizumab in metastatic melanoma and has also shown

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promising clinical activity with a progression-free survival of 4.2 months (26). These data support the investigation of aflibercept combined with chemotherapy in metastatic melanoma, given the single-agent activity of aflibercept observed in our study.

It was not surprising to observe hypertension associated with aflibercept, as hypertension has been reported with several prior angiogenesis inhibitors including axitinib (27), bevacizumab (28), sorafenib (29), sunitinib (30), pazopanib (31), and cediranib (32). The underlying mechanism of the hypertension with each of these may derive from the observation that angiogenic agents lead to decreased blood pressure (33). Several factors have been implicated, including production of the vasodilator nitric oxide and decreasing vascular resistance, through the generation of new blood vessels (34–37). The significant association between the development of hypertension and response to therapy has been reported with other angiogenesis inhibitors (38–40), although it has not been seen in all studies (41). In our study, we see significant association with progression-free survival and overall survival where the induction of hypertension by aflibercept appears to be a surrogate marker of clinical benefit. As suggested by Supplementary Table S2, the observed correlation is not likely a mere manifestation of time spent on study and is worth validating in future larger trials.

Conclusion

Aflibercept has shown promising clinical activity in patients with advanced inoperable melanoma of cutaneous or uveal origin. Further testing of aflibercept as monotherapy and in combinations should be pursued in these populations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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