


Ziv-aflibercept (Zaltrap) for the Treatment of Metastatic Colorectal Cancer

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Abstract

Objective: Review pharmacology, pharmacokinetics, efficacy, and safety of ziv-aflibercept in combination with FOLFIRI for treatment of metastatic colorectal cancer (mCRC) resistant to or progressed following oxaliplatin-containing regimens. **Data Sources:** Articles indexed in PubMed (1948-August 2013), TOXLINE (2001-August 2013), and Google Scholar as well as meeting abstracts were identified using the search terms *ziv-aflibercept* and *colorectal cancer*. **Study Selection and Data Extraction:** Available English-language articles **Data Synthesis:** Ziv-aflibercept, a selective vascular endothelial growth factor antagonist, was evaluated as monotherapy for treatment of mCRC in a phase 2 study and added to FOLFIRI in a phase 3 trial. Patient response to ziv-aflibercept as monotherapy did not reach statistical significance. Results suggest that response to ziv-aflibercept treatment is not influenced by prior bevacizumab therapy. A phase 3 trial compared the safety and efficacy of ziv-aflibercept plus FOLFIRI with placebo plus FOLFIRI in patients with mCRC who experienced disease progression on an oxaliplatin-containing regimen. Patients in the ziv-aflibercept arm had a median overall survival of 13.5 months, versus 12.06 months for those receiving placebo (hazard ratio [HR] = 0.817, 95% CI = 0.713 to 0.937). Progression-free survival for patients receiving ziv-aflibercept was higher compared with placebo (HR = 0.758; 95% CI = 0.661 to 0.869). The most common adverse effects observed were anemia, diarrhea, and neutropenia. **Conclusions:** Ziv-aflibercept is a safe and effective option in combination with FOLFIRI for the treatment of mCRC in patients who progress on oxaliplatin-containing therapy. Superiority over other antiangiogenic treatment has not been established.

Keywords

ziv-aflibercept, vascular endothelial growth factor, FOLFIRI, metastatic colorectal cancer

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the United States.^{1,2} The lifetime risk of developing this type of cancer in American men and women is 1 in 20.² Of those who are diagnosed, 50% to 60% will develop metastatic CRC (mCRC).^{3–5} In metastatic disease, surgical resection and chemotherapy play vital roles in treatment. Therapy varies based on considerations of the goal of therapy, type and timing of prior therapy, and the toxicity profiles between agents. Guidelines recommend a choice of the following 5 chemotherapy regimens for initial therapy: FOLFIRI, FOLFOX, CapeOx, infusional fluorouracil/leucovorin or capecitabine, or FOLFOXIRI with or without biological agents (ie, bevacizumab, cetuximab, panitumumab; see Table 1).⁵ Following first progression of disease after initial therapy, these regimens are still utilized, but previous chemotherapy received by the patient is considered when choosing new regimens. For example, another regimen recommended

for initial therapy may be considered after disease progression in regimen-naïve patients. As indicated, ziv-aflibercept is reserved as an option for therapy following first progression. Resistance to treatment, including biological agents, is an issue that deters from desired therapeutic outcomes. New agents used in treating cancers play a role in providing alternative mechanisms of action and new targets of therapy. Such advancements further increase the effectiveness of cancer treatment.

In August 2012, the Food and Drug Administration (FDA) approved ziv-aflibercept, a selective vascular endothelial growth factor (VEGF) antagonist, for use in

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Table 1. Chemotherapy Regimens Used for Metastatic Colorectal Cancer.⁵

Regimen Abbreviation	Components
FOLFIRI	<ul style="list-style-type: none"> • Irinotecan 180 mg/m² IV over 30-90 minutes, day 1 • Leucovorin 400 mg/m² IV infusion to match duration of irinotecan, day 1 • Fluorouracil 400 mg/m² IV bolus day 1, then 1200 mg/m²/d continuous infusion, days 2 and 3 • Repeat every 2 weeks
FOLFOX 6	<ul style="list-style-type: none"> • Oxaliplatin 85 mg/m² IV over 2 hours, day 1 • Leucovorin 400 mg/m² IV over 2 hours, day 1 • Fluorouracil 400 mg/m² IV bolus day 1, then 1200 mg/m²/d continuous infusion, days 2 and 3 • Repeat every 2 weeks
CapeOx	<ul style="list-style-type: none"> • Oxaliplatin 130 mg/m² IV over 2 hours, day 1 • Capecitabine 850-1000 mg/m² twice daily po for 14 days • Repeat every 3 weeks
FOLFOXIRI ⁶	<ul style="list-style-type: none"> • Irinotecan 165 mg/m² IV over 30 minutes, day 1 • Oxaliplatin 85 mg/m² IV over 2 hours, day 1 • Leucovorin 200 mg/m² IV over 2 hours, day 1 • Fluorouracil 1600 mg/m² for 2 days, continuous infusion on day 1 • Repeat every 2 weeks

combination with a FOLFIRI regimen for mCRC that is resistant or has progressed following an oxaliplatin-containing regimen.^{7,8} To minimize the potential for medication errors and facilitate reporting of adverse effects, the FDA requested that a prefix (ie, ziv) be added to the aflibercept product approved for mCRC to distinguish it from the FDA-approved formulation of aflibercept (Eylea) indicated for the treatment of neovascular age-related macular degeneration, administered by intravitreal injection only (W. Balcerski, Medical Information Services, Sanofi-Aventis, Bridgewater, NJ, written communication to Scott Perkins, August 30, 2013).⁹ The objectives of this article are to highlight the literature that led to FDA approval of ziv-aflibercept for treatment of mCRC and provide insight into its place in therapy.

Data Sources

English-language articles indexed in PubMed (1948-August 2013), TOXLINE (2001-August 2013), and Google Scholar as well as abstracts from the American Society of Clinical Oncology Annual Meeting and European Society of Medical Oncology were identified using the search terms *ziv-aflibercept* and *colorectal cancer*. Additional references were identified from the reference lists of the articles identified. Guidelines from the National Comprehensive Cancer Network were reviewed as well as the Zaltrap package insert from Regeneron Pharmaceuticals, Inc.

Pharmacology

Angiogenesis, the formation and differentiation of the vasculature, plays a key role in the growth of many solid tumors

and has been a target of drug development for agents to treat mCRC, among other solid tumors.¹⁰⁻¹⁴ The VEGF family of growth factors includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor. This family of growth factors is considered an important regulator of angiogenesis in solid tumors. VEGF growth factors activate the cell surface tyrosine kinase receptors, VEGFR-1, VEGFR-2, and VEGFR-3, and VEGF-A.^{10,11,13,15} Activation of these receptors is considered to be the strongest inducer and regulator of the angiogenic process.

Ziv-aflibercept, a recombinant fusion protein consisting of the Fc segment of immunoglobulin G1 fused with the second extracellular domain of VEGFR-1 and the third extracellular domain of VEGFR-2, acts as a decoy receptor and binds to human VEGF-A, VEGF-B, and placental growth factor and has high affinity for these growth factors.^{8,10,15,16} Ziv-aflibercept leads to inhibition of binding and subsequent activation by the ligand receptor, resulting in a decrease in abnormal angiogenesis and permeability of the tumor vasculature.^{8,10,14}

Pharmacokinetics

Ziv-aflibercept exhibits linear pharmacokinetics at doses of 2 to 9 mg/kg, with an elimination half-life of approximately 6 days following intravenous administration of 4 mg/kg every 2 weeks.⁸ Steady-state concentrations are achieved by the second dose of ziv-aflibercept, and age, race, or gender differences do not appear to have a clinically important effect on the exposure of free drug. No clinically relevant effects have been observed in patients with mild or moderate hepatic impairment or in patients with mild, moderate, or severe renal impairment, based on measurements of total

bilirubin, aspartate amino transferase, and alanine amino transferase and creatinine clearance, respectively. There is a lack of information regarding the distribution or metabolism characteristics of ziv-aflibercept.

Clinical Trials

Ziv-aflibercept has been evaluated in multiple phase 1 studies for patients with solid tumors. It has been studied in patients as monotherapy for patients with mCRC in 1 phase 2 study and in addition to standard of care, FOLFIRI, in a phase 3 trial.

Phase 2

A phase 2 study was conducted that compared the safety and efficacy of ziv-aflibercept in patients with mCRC. A total of 51 patients who had previously been treated with bevacizumab received ziv-aflibercept 4 mg/kg administered intravenously over 1 to 2 hours every 2 weeks and were compared with 24 patients who received the same ziv-aflibercept regimen but who had not received prior bevacizumab therapy.¹⁷ Previous medications included irinotecan (73%) or both irinotecan and oxaliplatin (61%). Patients could also have received prior treatment with an epidermal growth factor receptor inhibitor (47%), fluoropyrimidine (75%), or oxaliplatin (84%). The end points of this study were response rate and stable disease using 16-week progression-free survival (PFS). No response to therapy was observed in patients in the bevacizumab-naïve group based on Response Evaluation Criteria in Solid Tumors; however, 5 patients experienced PFS for at least 16 weeks. The median PFS for this group was 2 months. One patient in the prior bevacizumab group had a partial response that was sustained for 20 weeks, and 6 patients experienced PFS for 16 weeks; the median PFS was 2.4 months. Patient response to ziv-aflibercept as monotherapy was not found to be beneficial in this study. These data also suggest that response to ziv-aflibercept treatment is not significantly influenced by prior bevacizumab therapy.

Phase 3

Van Cutsem et al¹⁶ conducted VELOUR (aflibercept versus placebo in combination with irinotecan and fluorouracil in the treatment of patients with mCRC after failure of an oxaliplatin-based regimen). The study was a pivotal phase 3 multinational, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of ziv-aflibercept and FOLFIRI ($n = 612$) with placebo and FOLFIRI ($n = 614$). This study was conducted with patients who had mCRC and experienced disease progression and had already completed a treatment regimen that included oxaliplatin.¹⁶ Patients were eligible for inclusion if they were older than

18 years, with an Eastern Cooperative Oncology Group performance status of 0 to 2 and experienced relapse within 6 months of receiving adjuvant treatment with an oxaliplatin-based therapy. Those with prior malignancies or metastasis to the brain were excluded. Patients with prior irinotecan treatment were excluded, but those with prior bevacizumab were included, and their data were stratified. Ziv-aflibercept 4 mg/kg was administered as an intravenous infusion over 1 hour on day 1 every 2 weeks followed by FOLFIRI (irinotecan 180 mg/m² IV over 90 minutes, with leucovorin 400 mg/m² IV over 2 hours, followed by a fluorouracil 400 mg/m² bolus and 2400 mg/m² continuous infusion over 46 hours). Dose adjustments for each component of these regimens as well as delays in cycles of up to 2 weeks were permitted if toxicity arose. Patients were treated until disease progression or unacceptable toxicity. Clinical examination and laboratory assessments of each patient occurred at each cycle. Disease assessment was performed every 6 weeks until disease progression was noted. The primary end point was overall survival (OS), defined as the interval from randomization to death from any cause. Patients who discontinued treatment before disease progression were followed every 6 weeks for PFS. If disease progression was observed, these patients were followed every 8 weeks for survival, until death or end of study.

Patients in the ziv-aflibercept arm had a median OS of 13.5 months versus 12.06 months for those in the placebo group (hazard ratio [HR] = 0.817; 95% CI = 0.713 to 0.937). Two-year survival rates were significantly higher in the ziv-aflibercept arm, at 28% (95% CI = 23.7% to 32.4%), compared with the rate in the placebo arm of 18.7% (95% CI = 14.9% to 22.5%). PFS for patients receiving ziv-aflibercept was higher compared with that for placebo (HR = 0.758; 95% CI = 0.661 to 0.869). Median PFS was significantly higher in the ziv-aflibercept arm, at 6.9 months, compared with the placebo arm, which had a PFS of 4.7 months. PFS was increased in the ziv-aflibercept arm compared with the placebo arm regardless of patients' prior bevacizumab use (HR = 0.797, 95% CI = 0.678 to 0.936; and HR = 0.661, 95% CI = 0.512 to 0.852, respectively). It should be noted that this does not imply equivalent efficacy between the 2 agents themselves. The response rate in the ziv-aflibercept arm was 19.8%, and it was 11.1% in the placebo arm ($P < .001$).

A subgroup analysis of 138 North American patients in the VELOUR study was performed and included 63 patients who received ziv-aflibercept and FOLFIRI and 75 patients who received placebo and FOLFIRI.¹⁸ Median OS and PFS favored the ziv-aflibercept arm, but results were not statistically significant. The median OS was 17.94 months in the ziv-aflibercept arm and 12.88 months in the placebo arm (HR = 0.691; 95% CI = 0.442-1.079). PFS in the ziv-aflibercept and placebo arms were 6.01 and 4.17 months (HR = 0.536; 99.99% CI = 0.222-1.296), respectively.

The incidence of adverse effects associated with treatment in this study was high in both groups, with 99.2% and 97.9% reported in patients in the ziv-aflibercept and placebo arms, respectively.¹⁶ A greater number of grade 3 or 4 adverse events were reported in the ziv-aflibercept arm when compared with the placebo arm (83.5% vs 62.5%, respectively). Increased incidence of grade 3 and 4 events was observed with ziv-aflibercept compared with placebo for arterial thromboembolic events (1.8% vs 0.5%, respectively), hemorrhage (2.9% vs 1.7%, respectively), hypertension (19.1% vs 1.5%, respectively), proteinuria (7.9% vs 1.2%, respectively), and venous thromboembolism (7.9% vs 6.3%, respectively). Adverse events commonly associated with chemotherapeutic agents were also reported at higher incidences in the ziv-aflibercept arm compared with the placebo arm, including diarrhea, stomatitis, infections, neutropenia, and thrombocytopenia.

These data suggest that ziv-aflibercept plus FOLFIRI is a safe and effective treatment option for patients with mCRC previously treated with oxaliplatin. Further comparison with standard treatment for mCRC would prove useful in determining its comparative efficacy with other chemotherapeutic options in advanced mCRC.

Dosing and Administration

Ziv-aflibercept is administered as an intravenous infusion at the recommended dose of 4 mg/kg over 1 hour on day 1 every 2 weeks immediately followed by the FOLFIRI regimen, which includes irinotecan 180 mg/m² administered intravenously over 90 minutes on day 1, leucovorin 400 mg/m² administered intravenously at the same infusion duration as irinotecan on day 1, and fluorouracil 400 mg/m² administered as intravenous bolus, followed by 1200 mg/m²/d for 2 days administered by continuous infusion for a total of 2400 mg/m² administered over 46 to 48 hours.^{5,8,16} Although there are no clinical trial data specifically evaluating the effects of hepatic or renal impairment on the pharmacokinetic profile of ziv-aflibercept, patients with mild and moderate hepatic impairment and mild, moderate, and severe renal impairment observed in clinical trials had similar exposure to the medication compared with those with normal end-organ function.⁸ Similarly, no dosage modification is warranted in the geriatric population.

Dosage discontinuation is warranted for selected adverse events, including severe hemorrhage, gastrointestinal perforation, compromised wound healing (treatment should be temporarily discontinued at least 4 weeks prior to elective surgical procedures), development of fistulae, hypertensive crisis or encephalopathy, arterial thromboembolic events, nephritic syndrome or thrombotic microangiopathy, and reversible posterior leukoencephalopathy syndrome. Temporary treatment discontinuation is warranted for recurrent or severe hypertension or proteinuria of at least 2 g per

24 hours. Treatment may be resumed at a reduced dose of 2 mg/kg when blood pressure is controlled or when proteinuria is less than 2 g per 24 hours. In cases of recurrent proteinuria, a permanent dose reduction of 2 mg/kg should be used when proteinuria is less than 2 g per 24 hours.

Ziv-aflibercept is commercially available in single-use vials of 100-mg/4-mL or 200-mg/8-mL solutions.⁸ The commercially available product should be diluted with 0.9% sodium chloride or 5% dextrose in water for a final concentration of 0.6 to 8 mg/mL. The prepared solution should be administered over 1 hour with a 0.2- μ m polyethersulfone filter, not in combination with other medications.

Adverse Effects

Adverse events, which occurred in greater than 40% of patients taking ziv-aflibercept plus FOLFIRI included leukopenia, diarrhea, neutropenia, proteinuria, asthenic conditions, stomatitis, thrombocytopenia, and hypertension.⁸ Table 2 lists the adverse drug events observed in clinical trials. Treatment-emergent adverse effects that led to the discontinuation of therapy most often in the ziv-aflibercept arm and placebo arm were asthenic conditions, infections, diarrhea, and hypertension (see Table 3).¹⁶ Asthenic conditions, which were considered grades 3 or 4, occurred in 16.8% of patients in the ziv-aflibercept group and 10.6% of patients in the placebo arm. High rates of grade 3 or 4 infections were also seen in the ziv-aflibercept arm, with 12.3% of patients experiencing adverse effects compared with 6.9% in the placebo arm. Grade 3 or 4 diarrhea was reported in 19% of patients treated with ziv-aflibercept, and grade 3 or 4 dehydration was reported in 4%. This incidence was increased in patients older than 65 years. Of those who specifically experienced grade 3 or 4 hypertension, 54% experienced it during the first 2 cycles of treatment.⁸ Median initial occurrence of hypertension was 3.5 days in a phase 1 study.¹⁹ Fistulae have been reported with the use of ziv-aflibercept, including anal, enterovesicular, colovaginal, and rectal fistulae.^{8,16,17} Severe or fatal gastrointestinal perforation has also been reported, with grade 3 and 4 perforations being reported at less than 2%.⁸ Commonly experienced adverse effects associated with ziv-aflibercept are similar to those of other antiangiogenic agents and do not set it apart from these other therapies. Ziv-aflibercept is pregnancy category C; there are no adequately controlled trials in pregnant women, but use of ziv-aflibercept in rabbits showed teratogenic and embryotoxic effects. The use of ziv-aflibercept has not been studied in pediatrics.

Place in Therapy

The safety and efficacy of ziv-aflibercept has been demonstrated in clinical trials. Given the established role of

Table 2. Adverse Events Associated With Ziv-aflibercept ($\geq 10\%$).⁸

Primary System Organ Class, Preferred term	Ziv-aflibercept/FOLFIRI (n = 611)		Placebo/FOLFIRI (n = 605)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Leukopenia	78%	16%	72%	12%
Neutropenia	67%	37%	57%	30%
Thrombocytopenia	48%	3%	35%	2%
Decreased appetite	32%	3%	24%	2%
Headache	22%	2%	9%	0.3%
Hypertension	41%	19%	11%	1.5%
Epistaxis	28%	0.2%	7%	0%
Dysphonia	25%	0.5%	3%	0%
Dyspnea	12%	0.8%	9%	0.8%
Diarrhea	69%	19%	57%	8%
Stomatitis	50%	13%	33%	5%
Abdominal pain	27%	4%	24%	2%
Abdominal pain (upper)	11%	1%	8%	1%
Palmar-plantar erythrodysesthesia syndrome	11%	3%	4%	0.5%
Proteinuria	62%	8%	41%	1%
Serum creatinine increase	23%	0	19%	0.5%

Table 3. Patients Discontinuing Therapy Because of Adverse Effects.¹⁵

Treatment-Emergent Adverse Effect	Ziv-aflibercept + FOLFIRI (n = 611)	Placebo + FOLFIRI (n = 605)
Asthenic conditions	3.8%	1.3%
Infections	3.4%	1.7%
Diarrhea	2.3%	0.7%
Hypertension	2.3%	0%

bevacizumab, another anti-VEGF agent, in the treatment of mCRC, a discussion on the potential role for ziv-aflibercept is warranted.^{5,20} Ziv-aflibercept may have a higher binding affinity for VEGF-A than bevacizumab, providing a theoretical advantage. However, in a separate study, OS with continued bevacizumab in addition to chemotherapy after first progression was shown to be greater than with chemotherapy alone by 1.4 months, similar to what was found in the VELOUR study with aflibercept.^{11,16,17,21} Kubicka et al²² published a subgroup analysis of this trial and concluded that continued therapy with bevacizumab beyond first progression in patients with mCRC who were previously treated with chemotherapy in addition to bevacizumab may be an option for patients regardless of Kirsten rat sarcoma virus oncogene (KRAS) mutation status, a mutation present in approximately 40% of patients with mCRC. It should be noted that the designs of these trials do not allow an appropriate direct comparison between ziv-aflibercept and bevacizumab. Currently, no study directly compares these 2 medications, and comparisons between studies are not fully reliable. Although, the VELOUR trial established significant improvement in OS and PFS for patients in the ziv-aflibercept group without regard to prior treatment with bevacizumab, this should not be taken to indicate superiority of ziv-aflibercept over bevacizumab. The most common grade 3 or 4 adverse

effects associated with ziv-aflibercept include hematological abnormalities, proteinuria, gastrointestinal effects, and hypertension, whereas grade 3 or 4 adverse effects with bevacizumab include hypertension, bleeding, vomiting, and neuropathy.^{10,20,23} Although they are similar, it appears that the incidence of these high-grade events may be higher with ziv-aflibercept.^{16,20,23} Lack of available information currently prevents a clear understanding of which of these 2 antiangiogenic medications is superior, so cost comparison may play a vital role in medication selection. A month's supply of ziv-aflibercept for an 80-kg patient at \$10 240 is more than double the cost of bevacizumab.^{24,25} From a medication cost perspective, bevacizumab is favorable. This may be more pronounced if the cost of severe adverse drug reactions is considered. Because ziv-aflibercept's effectiveness in bevacizumab-experienced patients has been shown, it may prove useful in patients where bevacizumab therapy has already been stopped, especially if continued bevacizumab is not desirable. A new tyrosine kinase inhibitor, regorafenib, has been approved as a single agent for refractory mCRC and has antiangiogenic effects. Like bevacizumab and ziv-aflibercept, the OS for this agent was significant—1.4 months greater than that for placebo.²⁶ Although similar in price to ziv-aflibercept, it is important to note that regorafenib was studied in patients who had previously received all standard

therapies.^{24,26} In conclusion, limited availability of treatment options for patients experiencing disease progression with oxaliplatin-containing chemotherapeutic regimens and clinical efficacy warrants consideration of ziv-aflibercept in combination with FOLFIRI, but it may prove more appropriate to use this agent in bevacizumab-experienced patients than in those who are bevacizumab-naïve.

Declaration of Conflicting Interests

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