Impact of Prior Bevacizumab Treatment on VEGF-A and PlGF Levels and Outcome Following Second-Line Afibercept Treatment: Biomarker Post Hoc Analysis of the VELOUR Trial

Eric Van Cutsem¹, Caroline Paccard², Marielle Chiron³, and Josep Tabernero⁴

ABSTRACT

Purpose: Afibercept is a targeted anti-VEGF therapy used to treat patients with metastatic colorectal cancer (mCRC) following progression on oxaliplatin-based regimens. This post hoc study evaluated the effect of prior bevacizumab treatment and growth factor levels on patient outcomes associated with afibercept in the VELOUR phase III trial.

Experimental Design: Baseline biomarker plasma concentrations were measured using a bead-based multiplex assay. Patients were grouped according to prior bevacizumab treatment, second-line treatment, and serum biomarker concentrations, and analyzed for overall survival (OS) and progression-free survival (PFS).

Results: Plasma samples were available for 553 patients (placebo n = 265; afibercept n = 288), of which 169 had received prior bevacizumab. Nine biomarkers implicated in angiogenesis or bevacizumab resistance correlated with prior bevacizumab therapy.

Introduction

Colorectal cancer is the second most frequently diagnosed cancer and the second leading cause of cancer-related deaths worldwide (1). While patients diagnosed with localized colorectal cancer have a 5-year survival rate of approximately 90%, those diagnosed with distant metastases have a 5-year survival rate of just 13.8% reported in the United States (2, 3). Overall survival (OS) for patients with metastatic colorectal cancer (mCRC) has markedly decreased on oxaliplatin-based regimens. This post hoc study evaluated the effect of prior bevacizumab treatment and growth factor levels on patient outcomes associated with afibercept in the VELOUR phase III trial.

Experimental Design: Baseline biomarker plasma concentrations were measured using a bead-based multiplex assay. Patients were grouped according to prior bevacizumab treatment, second-line treatment, and serum biomarker concentrations, and analyzed for overall survival (OS) and progression-free survival (PFS).

Results: Plasma samples were available for 553 patients (placebo n = 265; afibercept n = 288), of which 169 had received prior bevacizumab. Nine biomarkers implicated in angiogenesis or bevacizumab resistance correlated with prior bevacizumab therapy.

Conclusion: High VEGF-A and PlGF serum levels may underlie development of resistance to bevacizumab in patients with mCRC. Afibercept retains its activity regardless of baseline VEGF-A and PlGF levels and may be an effective second-line treatment for patients with bevacizumab-induced resistance.
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Translational Relevance

There is a current unmet need in the field of metastatic colorectal cancer to identify which patients will benefit from the different treatment regimens available. This post hoc study analyzed biomarker data retrieved from patients on the phase III VELOUR trial. Patients had improved survival outcomes associated with aflibercept compared with placebo, regardless of prior bevacizumab treatment, which suggests that challenging patients with an alternative VEGF inhibitor is a viable treatment option. Furthermore, VEGF-A and placental growth factor (PiGF) were identified as potential biomarkers of bevacizumab resistance. However, patients responded to aflibercept regardless of baseline VEGF-A and PiGF levels. This supports the hypothesis that aflibercept is beneficial for patients who have received prior bevacizumab because of its broader anti-VEGF inhibition.

Advances in molecular biology and the understanding of colorectal carcinogenesis have provided opportunities to identify biomarkers that contribute to improved diagnostic, prognostic, and predictive treatment response information, which may have the potential to improve patient outcomes (22–25). Although several biomarkers have been identified to help guide treatment decisions for colorectal cancer (8, 13, 26), clinically relevant biomarkers are still scarce, with the majority of therapeutic considerations made regardless of individual characteristics (27). RAS and BRAF mutation status, primary tumor location, and microsatellite instability (MSI) have been validated as biomarkers and are used clinically to recommend treatment strategies for patients with mCRC (8, 13, 28). For example, patients with MSI are candidates for immune checkpoint inhibitors and patients with left-sided, KRAS and NRAS wild-type tumors derive greater benefit with anti-EGFR therapy (8, 13). Currently, no biomarkers have been validated to determine which patients with mCRC would benefit the most from anti-VEGF therapies. Post hoc data from the VELOUR study suggest that aflibercept may prolong survival in patients with BRAF mutations (29). Recent studies of patients treated with antiangiogenic therapies suggest that angiogenic plasma markers may have some prognostic or predictive value (30, 31).

The objective of this post hoc analysis was to investigate the effect of plasma growth factor levels on patient outcomes in patients with mCRC treated with aflibercept versus placebo in the VELOUR trial, according to prior bevacizumab treatment.

Materials and Methods

VELOUR study

Details of the VELOUR trial, including patient eligibility, trial design, randomization, dose administration, and statistical analyses have been published previously (21). Briefly, VELOUR was a phase III, randomized, placebo-controlled study investigating the efficacy of aflibercept plus FOLFIRI in patients with mCRC who had disease progression while receiving, or after completing, an oxaliplatin-based regimen. Patients were randomized to receive either aflibercept 4 mg/kg (n = 612) or placebo (n = 614) intravenously (i.v.), over 1 hour on day 1 every 2 weeks, followed immediately by the FOLFIRI regimen (irinotecan 180 mg/m² i.v. over 90 minutes, with leucovorin 400 mg/m² i.v. over 2 hours, followed by 5-fluorouracil (FU) 400 mg/m² bolus and FU 2,400 mg/m² continuous infusion over 46 hours), until disease progression or unacceptable toxicity. Randomization was stratified according to prior therapy with bevacizumab (yes or no) and Eastern Cooperative Oncology Group performance status (ECOG PS: 0, 1, or 2; ref. 21).

This study was conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from each subject or each subject’s guardian. The human investigations were performed after approval by an institutional review board and in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services.

Biomarker measurement

Blood samples (4 mL) were collected in citrate phosphate dextrose tubes and were centrifuged at 4°C at 2,000 g for 20 minutes. Plasma was transferred into two polypropylene screw cap tubes and frozen immediately at −80°C, within 1 hour after the puncture. All specimens were stored frozen until shipped to central laboratory for analysis. Plasma concentrations of 98 angiogenic factors and inflammatory cytokines were measured centrally prior to treatment using Luminex Technology (98 plasma proteins) and ELISA for VEGF, FGF-acidic, and PiGF. The Myriad Multiplex Assay Rules Based Medicine approach used for the 98 analyses is based on the capture–sandwich format using capture antibodies attached to fluorescently encoded microspheres. After capture of antigen from a biological sample, the antigen was then detected using specific detection antibodies coupled to a fluorescent probe.

Biomarkers with >70% of values below the lower limit of quantification were excluded from the analysis. This allowed to keep a majority of biomarkers in the analysis, removing only those with very high percentage of values below the lower limit of quantification. The intention-to-treat (ITT) population included all patients who gave informed consent and were randomized to a treatment arm, while the biomarker population included all treated patients from the ITT population who had a plasma sample drawn and successfully analyzed at baseline (32).

Statistical analysis

Correlation analysis between biomarkers and clinical variables was performed using Pearson correlation for association between numeric variables and using ANOVA for association between numeric and categorical variables. P values were adjusted using Benjamini–Hochberg procedure to control FDR with a cutoff equal to 0.05. Patients were stratified into four groups according to prior bevacizumab treatment status (yes vs. no) and second-line treatment (aflibercept vs. placebo). Mean levels of growth factors at baseline, median OS, and median PFS were calculated for each of these groups. Median VEGFA and PiGF levels for all patients were 144 pg/mL and 8 pg/mL, respectively. Median OS and PFS were calculated for patients with VEGFA and PiGF levels above the median. HR values for PFS and OS were calculated using a stratified Cox procedure, with ECOG PS and prior bevacizumab as stratification factors. The Breslow method was used to approximate likelihood in presence of ties in the failure time. Analyses were performed using SAS version 9.2 and R version 3.2.3.

Efficacy analysis

On the basis of the previous VELOUR article, OS was defined as the time interval from randomization to death from any cause. PFS was
defined as the interval from randomization to the first observation of disease progression (according to an independent review committee review) or death from any cause (21).

**Results**

**Study population**

Of the 1,226 patients in the VELOUR ITT population, 553 had eligible biomarker data at baseline. Of these, 288 and 265 received aflibercept and placebo, respectively (Fig. 1). Baseline characteristics were comparable with those of the ITT population (Supplementary Table S1). Similarly, efficacy outcomes were aligned between the biomarker and ITT populations, with aflibercept prolonging both OS and PFS compared with placebo in the biomarker population (Table 1).

**Effect of prior bevacizumab on OS and PFS in the biomarker population**

Of the 553 patients analyzed, 169 were previously treated with bevacizumab (aflibercept: n = 90; placebo: n = 79). In the group of patients with no prior bevacizumab, patients who received aflibercept plus FOLFIRI had a median OS of 12.9 months and those who received placebo plus FOLFIRI had a median OS of 11.4 months [HR (95% confidence interval (CI)); 0.80 (0.63–1.01); P = 0.06]. In the group of patients who had received prior bevacizumab, those treated with aflibercept plus FOLFIRI had a median OS of 12.1 months, while those treated with placebo plus FOLFIRI had a median OS of 10.6 months [HR (95% CI), 0.84 (0.59–1.19); P = 0.33].

Similar trends were seen for PFS (Table 1). In the no prior bevacizumab group, patients receiving aflibercept plus FOLFIRI had a median PFS of 6.8 months and patients receiving placebo plus FOLFIRI had a median PFS of 4.9 months, with a HR of 0.79 (0.63–1.00; P = 0.053). In the group of patients who had received prior bevacizumab, patients treated with aflibercept plus FOLFIRI had a median PFS of 7.2 months, while those treated with placebo plus FOLFIRI had a median PFS of 3.9 months, with a HR of 0.71 (0.49–1.04; P = 0.078).

**Serum biomarker levels**

Of the 98 angiogenic factors analyzed in the biomarker population, nine biomarkers (VEGF-A, PlGF, endoglin, T-cadherin, VEGRF-3, serum amyloid P-component, vitamin D–binding protein, neuropilin-1, and C-reactive protein) implicated in angiogenesis or bevacizumab resistance correlated with prior bevacizumab therapy (P < 0.01; Fig. 2; Supplementary Table S2). This association was most significant for VEGF-A (P = 1e-58) and PlGF (P = 2.8e-13) levels, which were elevated at baseline in patients that had received prior bevacizumab treatment. Mean VEGF-A was 156.9 pg/mL in patients who had not previously received bevacizumab and 758.2 pg/mL in those who had. Mean PlGF was 11.7 pg/mL in patients who had not previously received bevacizumab and 22.0 pg/mL in those who had. Several biomarkers were elevated post-aflibercept treatment, including VEGF-A and PlGF (Supplementary Fig. S1; Supplementary Table S3).

**Influence of serum VEGF-A and PlGF on efficacy outcomes**

As the factors most significantly associated with prior bevacizumab, patients were grouped on the basis of their baseline serum levels being above or below the median level for VEGF-A (144 pg/mL) and PlGF (8 pg/mL). Among patients treated with placebo, those with baseline VEGF-A plasma levels above the median (>144 pg/mL) had worse OS (9.6 vs. 12.9 months) and PFS (4.0 vs. 5.5 months) compared with
patients who had baseline VEGF-A below the median (Fig. 3A). Similarly, among patients treated with placebo, those with high baseline PlGF (>8 pg/mL) had worse OS (9.7 vs. 11.7 months) and PFS (4.0 vs. 5.3 months) compared with patients who had low baseline PlGF (Fig. 4). However, among the patients treated with aflibercept, OS was similar for patients with high or low baseline VEGF-A (12.5 vs. 12.8 months) or PlGF levels (12.2 vs. 12.8 months). Similarly, PFS was similar for patients who received aflibercept with high or low baseline VEGF-A (12.8 vs. 13.0 months) or PlGF levels (12.2 vs. 12.5 months).
VEGF-A (6.9 vs. 6.8 months) or PlGF levels (6.6 vs. 6.9 months). Patients with high baseline VEGF-A had improved OS [HR (95% CI), 0.673 (0.508–0.892); P = 0.00566] and PFS [HR (95% CI), 0.660 (0.493–0.885); P = 0.00521] associated with a fiblercept versus placebo. Similarly, patients with high PlGF had improved OS [HR (95% CI), 0.586 (0.405–0.849); P = 0.00429] and PFS OS [HR (95% CI), 0.535 (0.366–0.783); P = 0.0011]; Patients with low baseline VEGF-A had similar OS [HR (95% CI), 0.974 (0.735–1.291); P = 0.854] and PFS [HR (95% CI), 0.898 (0.681–1.185); P = 0.448] for a fiblercept and placebo. Likewise, patients with low PlGF had similar OS [HR (95% CI), 0.947 (0.746–1.202); P = 0.653] and PFS [HR (95% CI), 0.586 (0.682–1.101); P = 0.24] for a fiblercept and placebo.

This trend was seen in those who had, and had not, received prior bevacizumab (Fig. 5; Supplementary Fig. S2). In the group of patients with no prior bevacizumab and baseline VEGF-A levels > median (144 pg/mL), a fiblercept was associated with a longer median OS [13.0 vs. 9.4 months; HR (95% CI), 0.56 (0.38–0.82); P = 0.003] and PFS [6.6 vs 4.0 months; HR (95% CI), 0.65 (0.44–0.97); P = 0.032] versus placebo. Patients with baseline VEGF-A > median (144 pg/mL) who had received prior bevacizumab had numerical improvements in OS and PFS associated with a fiblercept versus placebo [OS: 11.9 vs. 9.8 months; HR (95% CI), 0.83 (0.55–1.24); P = 0.36 and PFS: 7.3 vs. 3.9 months; HR (95% CI), 0.67 (0.43–1.04); P = 0.073].

Similarly, patients with baseline PlGF plasma levels above the median (>8 pg/mL) had higher OS and PFS with a fiblercept versus placebo, regardless of prior bevacizumab treatment (Fig. 5; Supplementary Fig. S2). In the group of patients with no prior bevacizumab and high PlGF levels, a fiblercept was associated with significantly improved OS [14.4 vs. 8.65 months; HR (95% CI), 0.42 (0.25–0.72); P = 0.001] and PFS [5.7 vs. 4.2 months; HR (95% CI), 0.53 (0.31–0.89); P = 0.014]. In the group of patients with high PlGF levels who had received prior bevacizumab, a fiblercept was associated with a significant improvement in PFS [7.3 vs. 3.9 months; HR (95% CI), 0.55 (0.31–0.95); P = 0.031]; however, the OS benefit did not reach significance [OS: 11.5 vs. 10.2 months; HR (95% CI), 0.80 (0.48–1.32); P = 0.38].

**Discussion**

In the ITT population of the phase III VELOUR trial, a fiblercept in combination with FOLFIRI was associated with a statistically significant survival benefit over FOLFIRI combined with placebo in patients with mCRC previously treated with oxaliplatin. Although samples could only be analyzed from 553 (45%) patients randomized in VELOUR, baseline characteristics and efficacy outcomes for the biomarker population were consistent with the VELOUR ITT population, suggesting that the biomarker population is representative of the entire VELOUR population (21). Correlation between key biomarkers implicated in angiogenesis and prior bevacizumab treatment suggests that prior treatment with first-line bevacizumab induced cytokine changes. Of the biomarkers investigated, VEGF-A and PlGF were the most significantly elevated biomarkers at baseline, suggesting that these plasma growth factors correlate with the acquisition of resistance to bevacizumab in patients with mCRC (32). The results presented here support earlier articles reporting that bevacizumab treatment in mCRC, as well as...
other cancers, was associated with elevated levels of VEGF-A and PlGF (33–39). In one study, plasma from 32 patients with mCRC had significantly higher VEGF-A and PlGF levels associated with bevacizumab treatment compared with plasma taken from patients before bevacizumab treatment and not receiving bevacizumab (33). Another study evaluated 45 patients with mCRC treated with bevacizumab and 15 who had not received bevacizumab and found that VEGF-A levels increased following bevacizumab treatment. It also identified that much of the VEGF-A was bound to bevacizumab, suggesting that this elevated VEGF-A was inactive. However, the unbound VEGF-A may still provide an escape mechanism and contribute to bevacizumab resistance (34). In a phase II study evaluating 43 patients with mCRC who received first-line bevacizumab plus FOLFIRI, several cytokines and growth factors associated with angiogenesis and myeloid recruitment, including PlGF, were increased compared with baseline. Importantly, these changes occurred before radiographic progression, which could suggest a prognostic role (39). In another study evaluating 25 patients with mCRC treated with FOLFIRI plus bevacizumab, PlGF levels increased. This was also seen in another phase II study evaluating 57 patients with mCRC treated with first-line FOLFOXIRI plus bevacizumab (40). However, in both of these studies, serum concentration of VEGF-A initially decreased after the onset of treatment, which contrasts with previous reports. This may emphasize the deeper role of PlGF, rather than VEGF-A, in bevacizumab resistance (40, 41).

The results of this biomarker post hoc analysis suggest that patients who received placebo and had either high VEGF-A (>144 pg/mL) or PlGF (>8 pg/mL) levels at baseline were associated with worse OS and PFS compared with patients with lower levels at baseline. Conversely, patients treated with afiblercept plus FOLFIRI had prolonged OS and PFS compared with placebo, regardless of VEGF-A and PlGF levels at baseline. The benefit of afiblercept versus placebo was particularly marked in patients with high VEGF-A or PlGF levels at baseline and no prior bevacizumab. This suggests that bevacizumab treatment may lead to increased VEGF-A and PlGF levels, which may contribute to bevacizumab resistance. Importantly, VEGF-A and PlGF levels seem not to be predictive of response to afiblercept, possibly as a result of the latter’s affinity for multiple ligands (18, 19).

The fact that high baseline VEGF-A and PlGF levels in patients treated with placebo are associated with poor outcomes is supported by previous reports (42–44). High VEGF-A serum levels (>5.1 pg/mL) at baseline were associated with worse OS and PFS in patients with mCRC who received either mFOLFOX6 or FOLFIRI with first-line bevacizumab (44). In contrast, a study of 813 patients with mCRC who received bevacizumab did not identify a link between poor response to bevacizumab and high VEGF-A expression in the tumor by IHC, and this may be an important factor that differentiates this study from the studies reporting VEGF-A serum levels, including the one presented here (45). To our knowledge, the association of high plasma PlGF levels at baseline with poor prognosis has not been previously reported in mCRC. However, PlGF expression within the tumor has been shown to increase with the stage of colorectal cancer, higher values being associated with worse OS (46). It has also been recently suggested that serum PlGF levels could improve the sensitivity of colorectal cancer.

Figure 4. Efficacy of afiblercept according to PlGF levels. OS (A) and PFS (B) for patients with baseline PlGF above or below the median (8 pg/mL). * adjusted for stratification factors (ECOG, prior bevacizumab).
Future studies are needed to confirm the importance of VEGF-A and PlGF serum levels at various stages of the disease and the place of aflibercept in this setting. Other reports suggest that changes in angiogenic factors during treatment may also be prognostic for response to antiangiogenic therapies. In 23 patients with mCRC who received first-line bevacizumab, early rises in VEGF-A were associated with worse response to therapy (41). In another study, which evaluated the mRNA of several potential biomarkers in circulating tumor cells from patients with mCRC receiving FOLFOX or FOLFIRI plus bevacizumab, improvements in OS and PFS were associated with patients who experienced a decrease of ≥30% in VEGF-A levels or eNOS levels from baseline after 8 weeks (43). Patients with mCRC who received regorafenib also had improved OS and PFS if their VEGF-A levels decreased between baseline and day 21 posttreatment initiation (42). As discussed earlier, aflibercept is associated with an increase in VEGF-A and PlGF, as well as other factors. However, high levels at baseline do not influence response to aflibercept. It may be valuable to evaluate how changes in VEGF-A and PlGF levels following aflibercept affect survival outcomes.

In this study, patients who received aflibercept had similar OS and PFS regardless of baseline VEGF-A or PlGF levels. Aflibercept uniquely targets both VEGF-A and PlGF with a higher affinity than other antiangiogenic therapies, and VEGF-A and PlGF bind aflibercept with higher affinity than their native receptors (48). These findings suggest that tumors progressing under blockade of a single antiangiogenic therapy, such as bevacizumab, most likely use numerous non-VEGF-A mechanisms to sustain their growth. Switching to a different therapy, such as aflibercept, to target these alternative mechanisms may be beneficial.

There are some limitations of this study that must be considered. Biomarkers were collected in only 45% of patients randomized in VELOUR. Although clinical outcomes in the biomarker population were consistent with the VELOUR ITT population, results may not

Figure 5. OS in patients with high VEGF-A or PlGF levels according to prior bevacizumab treatment. Patients with VEGF-A above the median (>144 pg/mL) who had no prior bevacizumab (A) and prior bevacizumab (B). Patients with PlGF above the median (>8 pg/mL) who had no prior bevacizumab (C) and prior bevacizumab (D). * adjusted for stratification factors (ECOG, bevacizumab). Bev, bevacizumab
be extrapolated to the whole VELOUR population. Furthermore, the size of the biomarker population reduced the statistical power of the analysis, possibly explaining the lack of significant differences seen between subgroups. Further populations or studies designed for biomarker analysis are warranted. The analysis focused on VEGF-A and PIGF as these had the strongest association with prior bevacizumab therapy. However, nine other factors were also associated with bevacizumab and should be explored further. The biomarker analysis was also limited to assessing 98 angiogenic factors. It may be that other proangiogenic factors or tumor microenvironment proteins may have contributed to bevacizumab resistance. It was recently reported that tumor-infiltrating neutrophils may confer resistance to bevacizumab (49). Therefore, it may be valuable to expand the type of biomarkers measured. It should also be acknowledged that the patient population used for this analysis received treatment between 2007 and 2011, and therefore the treatment landscape and categorization of colorectal cancer has changed. Consequently, it would be beneficial to validate the findings in a more recent trial population or using patients treated in routine clinical practice. This would also facilitate a more direct comparison between the effect of VEGF-A and PI GF levels and response to different antiangiogenic therapies. The biomarkers under evaluation in this study were only analyzed once pretreatment and during cycles 3, 5, and 30 days following end of treatment. It may be valuable for future studies to evaluate which patients experience changes in VEGF-A and PI GF. Furthermore, it may be beneficial to collect more timepoints so that the changes during pretreatment are also considered.

In summary, this study identifies VEGF-A and PI GF as potential negative prognostic markers in patients with mCRC. As afilibercept targets VEGF-A and PI GF with greater affinity than other antiangiogenic therapies, it may provide benefit to patients who have high VEGF-A or PI GF serum levels. Measurement of VEGF-A and PI GF serum levels is not standard practice; further studies are needed to clarify the importance of these biomarkers in guiding management of patients with colorectal cancer.

Disclosure of Potential Conflicts of Interest
E. Van Cutsem is a paid consultant for Array, AstraZeneca, Bayer, Biocartis, Bristol-Myers Squibb, Celgene, Daisichi, Håkonyne, GlassoSmithKline, Pierre-Fabre, Incyte, Ipsen, Lilly, MSD, Merck KGaA, Novartis, Roche, Servier, Sirtex, and Taiho. C. Paccard is an employee of Sanofi. M. Chiron is an employee of Sanofi. J. Tabernero is a paid consultant for Array Biopharma, AstraZeneca, Bayer, BerGen, Biothering Ingelheim, Chugai, Genentech, Inc., Genmab A/S, Halomyne, Imugene Limited, Inflection Biosciences Limited, Ipsen, Kura Oncology, Lilly, MSD, Menarini, Merck Serono, Merrimack, Merus, Molecular Partners, Novartis, Peptonyx, Pfizer, Pharmacyclics, Pierre Fabre, ProtoolDesign SL, Rafad Pharmaceuticals, E. Hoffmann-La Roche Ltd, Sanofi, SeaGen, Seattle Genetics, Servier, Symphogen, Taiho, VCN Biosciences, Biocartis, Foundation Medicine, HalioDX SA5, and Roche Diagnostics.

Authors’ Contributions
Conception and design: E. Van Cutsem, M. Chiron, J. Tabernero Development of methodology: E. Van Cutsem, M. Chiron, J. Tabernero Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): E. Van Cutsem, M. Chiron, J. Tabernero Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): E. Van Cutsem, C. Paccard, M. Chiron, J. Tabernero Writing, review, and/or revision of the manuscript: E. Van Cutsem, C. Paccard, M. Chiron, J. Tabernero Study supervision: M. Chiron, J. Tabernero

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References
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