A PHASE 1B TRIAL OF ZIV-AFLIBERCEPT PLUS PEMBROLIZUMAB IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background Angiogenic factors play a role in regulating immune suppression in the tumor microenvironment and driving resistance to immune checkpoint inhibitor therapy.¹ Ziv-aflibercept is a soluble decoy receptor that "traps" endogenous vascular endothelial growth factor (VEGF) with 100-fold increased binding affinity compared to Bevacizumab.² The combination of ziv-aflibercept with either cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or programmed cell death protein 1 (PD-1) blockade has shown promising antitumor efficacy in mouse models.³⁻⁴ We hypothesized that a novel combination of ziv-aflibercept and anti-PD-1 would be tolerable and lead to clinical benefits in tumors that traditionally do not respond to checkpoint blockade.

Methods This is a multicenter phase 1B dose escalation study (NCT02298959) of the combination of ziv-aflibercept (at 2–4 mg/kg) plus pembrolizumab (at 2 mg/kg) administered intravenously every 2 weeks with expansion cohorts in PD-1/PD-L1 naïve melanoma, renal cell carcinoma (RCC), microsatellite stable colorectal cancer (MSS CRC), and ovarian cancer (figure 1). The primary objective was to determine the maximum tolerated dose (MTD) and recommended dose of the combination. Secondary endpoints included overall response rate (ORR) and overall survival (OS). Exploratory objectives included correlation of clinical efficacy and immune population densities in the tissue and periphery.

Results Overall, 33 patients were enrolled during dose escalation (n=3) and dose expansion (n=30). No dose-limiting toxicities (DLTs) were reported in the initial dose level. Ziv-aflibercept 4 mg/kg plus pembrolizumab 2 mg/kg every 2 weeks was established as the MTD. Grade ≥3 treatment-related adverse events occurred in 19/33 patients (58%), the most common being hypertension (36%) and proteinuria (18%). ORR in the dose expansion cohort was 16.7% (5/30; 95% CI, 7–32%). Complete responses occurred in melanoma (n=2), partial responses occurred in RCC (n=1), mesothelioma (n=1), and melanoma (n=1). Efficacy outcomes by tumor type are shown in table 1 and figure 2. Median OS was as follows: melanoma, not reached; RCC, 15.7 months (90% CI, 2.5–15.7); CRC, 3.3 months (90% CI, 0.6–3.4), ovarian, 12.5 months (90% CI, 3.8–13.6), other solid tumors, not reached (figure 3). Activated tumor infiltrating CD8 T cells at baseline (CD8+PD1+), high CD40L expression (figure 4), and increased memory CD8 T cells in the periphery (figure 5) correlated with clinical response to the combination therapy.

Abstract 374 Figure 1 Study Schema of dose escalation and dose expansion. (A) Cohort 1 included the following tumors: clear cell sarcoma, triple negative breast cancer (TNBC), and mesothelioma. (B) Other solid tumors in Cohort 2 were: epithelioid mesothelioma (2) and TNBC (1).

Abstract 374 Table 1 Efficacy outcomes by dose level and tumor type

Best response	Overall (n = 33)	Dose level 1 (n = 3)	Dose level 2 (n = 30)	CRC (n = 6)	Solid Tumor* (n = 6)	Ovarian (n = 8)	RCC (n = 7)	Melanoma (n = 6)
Complete Response (CR)	2 (6%)	0	2 (7%)	0	0	0	0	2 (33%) ^b
Partial Response (PR)	3 (9%)	0	3 (10%)	0	1 (16.7%)	0	1 (14%)	1 (17%)
Stable Disease (SD)	8 (24%)	1 (33%)	7 (23%)	0	2 (33%)	2 (25%)	4 (57%)	0
Progressive Disease (PD)	15 (45%)	2 (67%)	13 (43%)	3 (50%)	3 (50%)	6 (75%)	2 (29%)	1 (17%)
Unknown	5 (15%)	0	5 (17%)	3 (50%)	0	0	0	2 (33%)

B. Solid tumors included clear melanoma (1), breast cancer (2), mesothelioma (3).

Abstract 374 Figure 2 Waterfall plot of best RECIST response. Waterfall plot of maximum change from baseline in sum of target lesions for 28 patients with tumor measurements over time. Plot is color-coded by tumor type. Triangles indicate patients who developed new lesions, yellow circles indicate the 3 patients who received DL1.

Abstract 374 Figure 3 Progression and overall survival by tumor type. Kaplan-Meier curves for (A) progression-free survival and (B) overall survival based on tumor type.

Abstract 374 Figure 4 Luminex assay analysis of clinical response. Luminex analysis of baseline biomarkers. Patients were analyzed by clinical response (complete response [CR] and partial response [PR]) and durable clinical benefit (DCB) which includes patients with CR, PR, and stable disease (SD). (A) Baseline levels of IL-6 were lower in responders vs. non-responders (median 2.605 vs. 9.847 pg/mL, $p = 0.009$). Baseline CD40L was increased in responders (median 2,840 vs. 2,267 pg/mL, $p = 0.06$). (B) Baseline levels of GroB (median 1,272 vs. 592 pg/mL, $p = 0.006$), CXCL5 (median 547.5 vs. 296.2 pg/mL, $p = 0.02$), and CD40L (median 2,807 vs. 1,595 pg/mL, $p = 0.001$) were higher in patients with DCB vs. no DCB. P-values for baseline comparisons were obtained through Wilcoxon rank-sum test. The solid black line indicates median. Violins show range and kernel density estimate distributions of each group. (*) $p < 0.05$, (**) $p < 0.01$.

Abstract 374 Figure 5 Flow cytometry analysis. Flow cytometry analysis comparing T cell populations and monocytes between patients with clinical response (CR or PR, $n = 5$) and non-responders ($n = 18$) and patients with disease control (CR, PR, or SD, $n = 12$) and no disease control ($n = 11$). (A) CD4+ populations were increased in responders vs. non-responders at all time points. (B) CD8+ populations were decreased in responders vs. non-responders at all time points. (C) Treg CD4+/CD25+/FoxP3+ was decreased at baseline in responders. (D) Treg CD4+/CD25+/FoxP3+ were decreased at baseline and 1-month in patients with disease control vs. no disease control. (E) TCM CD8+/CD45RO+/CCR7+ was increased at all time points in responders vs. non-responders. (F) TEMRA CD8+/CD45RO-/CCR7- was decreased in responders at baseline. (G) Non-classical TIE2 was increased at baseline in non-responders. (H) Classical monocytes were increased at all time points in non-responders.

Conclusions The combination of ziv-aflibercept and pembrolizumab demonstrated an acceptable safety profile with antitumor activity in solid tumors. The combination is currently being studied in sarcoma and anti-PD-1 resistant melanoma.

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Trial Registration NCT02298959

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Ethics Approval This trial (NCT02298959) was approved by all participating IRBs.

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