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# Plasma Arginine Levels as Predictive Biomarkers of Response to Immune Checkpoint Inhibitors in Metastatic Colorectal Cancer: Insights from the CCTG CO.26 Trial

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## Abstract

Nutritional deprivation serves as a strategy for cancer cells to avoid detection by the immune system. Arginine (ARG), an amino acid with important roles in immune regulation, influences T-cell function and the body's defense against tumors. Low levels of ARG within the tumor surroundings can hinder T-cell effectiveness, while increasing ARG availability might boost anti-cancer immune responses.In this exploratory follow-up analysis of the randomized phase II CO.26 study, researchers assessed whether blood levels of ARG could help forecast treatment outcomes with immune checkpoint inhibitors (ICI) in individuals with microsatellite-stable metastatic colorectal cancer (mCRC) that no longer responds to standard therapies.The CO.26 study randomized patients with treatment-refractory metastatic colorectal cancer to receive either the combination of durvalumab and tremelimumab (D+T) or best supportive care (BSC). Baseline plasma arginine (ARG) concentrations were quantified from pre-treatment blood samples using high-performance liquid chromatography with tandem mass spectrometry. Patients were divided into two groups—ARG-high (≥10,700 ng/mL) and ARG-low (<10,700 ng/mL)—based on the median ARG level. Survival outcomes were evaluated using the Kaplan-Meier approach, with differences between groups assessed by the log-rank test. Additionally, Cox proportional hazards models were applied to determine the prognostic and predictive value of ARG for overall survival.Of the 180 patients enrolled in CO.26, 161 had available pre-treatment plasma samples for arginine (ARG) assessment, including 114 receiving durvalumab plus tremelimumab (D+T) and 47 receiving best supportive care (BSC). The patients analyzed were representative of the overall trial population, with no meaningful differences in baseline characteristics between ARG-high and ARG-low groups. In the BSC cohort, median overall survival (OS) was slightly shorter in ARG-high patients (3.09 months) compared to ARG-low patients (4.27 months; HR 0.89, 95% CI 0.49–1.65; p=0.72). Among patients treated with D+T, ARG-high individuals had a longer median OS of 7.62 months versus 5.27 months for ARG-low patients (HR 0.68, 95% CI 0.48–1.0; p=0.048). Importantly, D+T conferred a significant survival benefit in the ARG-high subgroup relative to BSC (7.62 vs 3.09 months; HR 0.61, 95% CI 0.37–0.99; p=0.047; adjusted interaction p=0.042), whereas no such benefit was observed in ARG-low patients (5.27 vs 4.27 months; HR 0.87, 95% CI 0.52–1.46; p=0.61).Elevated baseline plasma arginine (ARG) was associated with longer overall survival in metastatic colorectal cancer patients receiving D+T. These findings warrant further studies to confirm ARG as a predictive biomarker. Additionally, interventions aimed at modulating the ARG pathway could potentially enhance the efficacy of immune checkpoint inhibitors.

**Keywords:** Biomarker, Colorectal cancer, Immune checkpoint inhibitors , Plasma arginine

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## Introduction

Immune checkpoint inhibitors (ICIs) have dramatically changed how solid tumors are treated, enabling lasting responses and better survival rates for many patients with advanced cancer. Medications that target PD-1, PD-L1, and CTLA-4 have become essential in managing several

types of solid tumors, including melanoma, lung cancer, kidney cancer, and liver cancer [1-6].

In the context of colorectal cancer, the KEYNOTE-177 study showed that pembrolizumab (a PD-1 blocker) offers prolonged tumor control and reduced side effects compared to standard chemotherapy for individuals with dMMR or MSI-H tumors.[7] However, this group accounts for just around 5% of colorectal cases [7-10]. In contrast, ICIs have shown much weaker effects in patients with pMMR or MSS colorectal cancer. The phase II CO.26 trial from the Canadian Cancer Trials Group compared tremelimumab combined with durvalumab against best supportive care in patients with advanced, treatment-resistant colorectal cancer (mainly MSS), revealing a meaningful improvement in overall survival with the dual ICI approach, albeit limited in scale (median OS of 6.6 months versus 4.1 months; HR 0.72) [11].

Reliable markers to identify which pMMR/MSS colorectal cancer patients might benefit from ICIs or to anticipate their response are still largely unavailable. New research suggests that studying cellular metabolism could reveal useful indicators of ICI success, particularly since tumors often use nutrient deprivation to dodge immune attack. Arginine (ARG), an amino acid critical for various cell processes including immune modulation, is key to T-cell performance and the immune system's fight against cancer [12-14]. One recent analysis of blood ARG levels in patients with late-stage cancers undergoing ICI therapy found that lower starting ARG concentrations correlated strongly with inferior results and reduced survival [15]. Through this follow-up exploratory review of the CO.26 trial data, we assessed whether pre-treatment plasma ARG concentrations could serve as an indicator of ICI effectiveness in individuals with progressive MSS colorectal cancer.

## Materials and Methods

*Study design and patients*

The details of the CO.26 trial—including its structure, inclusion criteria, and interventions—have been detailed in a prior publication.11 In short, individuals 18 years or older with progressive colorectal adenocarcinoma unresponsive to all approved systemic options were allocated 2:1 to receive either the combination of durvalumab (1500 mg IV every four weeks) and tremelimumab (75 mg IV every four weeks for the first four doses) along with best supportive care (D+T + BSC), or best supportive care by itself. Therapy persisted until confirmed disease advancement (via imaging or clinical signs), severe side effects, patient decision to stop, or passing away. The chief measure of success was overall survival (calculated from the date of randomization to death regardless of cause), with additional measures encompassing progression-free survival (from randomization to confirmed progression or death from any reason).

*Procedures*

Blood specimens were obtained before the initiation of trial treatment. Levels of arginine (ARG) in plasma were measured via high-performance liquid chromatography coupled with tandem mass spectrometry. Patients were divided into high-ARG (≥ 10,700 ng/mL) and low-ARG (< 10,700 ng/mL) categories based on the median plasma ARG concentration as the threshold.

*Statistical analysis*

Overall survival (OS) was calculated with the Kaplan-Meier approach and differences between groups were assessed via the log-rank test (analyses conducted in R version 3.6.3 with the survival package version 3.1.8 and survminer package version 0.4.7). Cox proportional hazards regression models were employed to evaluate both the prognostic and predictive effects of arginine (ARG) levels on OS. A multivariable model was also fitted to account for key baseline factors, including the presence of liver metastases and plasma tumor mutational burden (pTMB). Additional sensitivity analyses were carried out by dichotomizing patients into ARG-high and ARG-low groups using (1) the mean plasma ARG concentration and (2) an optimal cut-off determined through a minimum p-value method.

## Results and Discussion

The CO.26 trial enrolled 180 patients in total, randomizing 119 to the durvalumab plus tremelimumab arm (D+T) and 61 to best supportive care (BSC). Baseline plasma specimens were obtainable for 161 participants overall—representing 114 out of 119 (96%) in the D+T group and 47 out of 61 (77%) in the BSC group.

Baseline features showed no notable differences between the patients analyzed here and the overall trial cohort **(Table 1).** Demographic and clinical characteristics at baseline were comparable across the high-ARG and low-ARG categories **(Table 1).** Plasma ARG concentrations

displayed no correlation with the previous treatments patients had undergone **(Table 2).**

Consistent with the primary trial findings, the D+T regimen linked to better overall survival among the 161 patients with pretreatment plasma data (univariable HR 0.71, 95% CI 0.49–1.01, p=0.053; median OS 6.62 months versus 3.61 months).

**Table 1.** Patient baseline characteristics stratified by plasma arginine (ARG) levels.

| Characteristic | All (N=161) | ARG-low (< 10 700 ng/mL) (N=80) | ARG-high (≥ 10 700 ng/mL) (N=81) | P value |
|---|---|---|---|---|
| Age (years) | | | | 0.37 |
| Median (range) | 65 (36–87) | 68 (39–87) | 64 (42–85) | |
| Sex | | | | 1.00 |
| Male | 110 (68.32) | 55 (68.75) | 55 (67.90) | |
| Female | 51 (31.68) | 25 (31.25) | 26 (32.10) | |
| Race | | | | 0.37 |
| White | 135 (83.85) | 70 (87.50) | 65 (80.25) | |
| Asian | 18 (11.18) | 6 (7.50) | 12 (14.81) | |
| Other | 8 (4.97) | 4 (5.00) | 4 (4.94) | |
| ECOG | | | | 0.22 |
| 0 | 46 (28.57) | 19 (23.75) | 27 (33.33) | |
| 1 | 115 (71.43) | 61 (76.25) | 54 (66.67) | |
| Disease site | | | | 0.69 |
| Left colon/rectum | 114 (70.81) | 54 (67.50) | 60 (74.07) | |
| Right colon/transverse | 45 (27.95) | 25 (31.25) | 20 (24.69) | |
| Unknown | 2 (1.24) | 1 (1.25) | 1 (1.23) | |
| Number of prior cancer therapies | | | | 0.98 |
| Median (range) | 5 (3–8) | 5 (3–8) | 5 (3–7) | |
| Treatment arm | | | | 0.30 |
| D+T | 114 (70.81) | 60 (75.00) | 54 (66.67) | |
| BSC | 47 (29.19) | 20 (25.00) | 27 (33.33) | |
| Liver metastasis | | | | 0.60 |
| Yes | 115 (71.43) | 59 (73.75) | 56 (69.14) | |
| No | 46 (28.57) | 21 (26.25) | 25 (30.86) | |
| Plasma TMB (n=158 samples with plasma) | | | | 0.85 |
| <28 | 122 (77.22) | 61 (76.25) | 61 (78.21) | |
| ≥28 | 36 (22.78) | 19 (23.75) | 17 (21.79) | |

ARG: arginine BSC: best supportive care D+T: durvalumab combined with tremelimumab ECOG: Eastern Cooperative Oncology Group TMB: tumor mutational burden

*Assessment of overall survival as a prognostic factor related to initial plasma arginine (ARG) concentrations*

In the subgroup of patients allocated to best supportive care (BSC) without active treatment, those with elevated ARG levels had a median overall survival (OS) of 3.09 months, compared to 4.27 months for individuals with lower ARG levels (univariable HR 0.89, 95% CI 0.49–1.65, p=0.72).

Among those receiving D+T treatment, median OS was longer in the high-ARG category at 7.62 months, versus 5.27 months in the low-ARG category (univariable HR 0.68, 95% CI 0.46–1.0, p=0.048).

*Assessment of overall survival as a predictive factor based on initial plasma arginine (ARG) concentrations*

Patients with high ARG levels who were treated with D+T showed substantially prolonged median OS relative to those on BSC alone (7.62 months versus 3.09 months; HR 0.61, 95% CI 0.37–0.99, p=0.047; adjusted interaction p-value=0.042; refer to **Figure 1** and **Table 2**).

Conversely, in patients with low ARG levels, there was no notable difference in median OS between the D+T and BSC groups (5.27 months versus 4.27 months; HR 0.87, 95% CI 0.52–1.46, p=0.61; refer to **Figure 1** and **Table 2**).

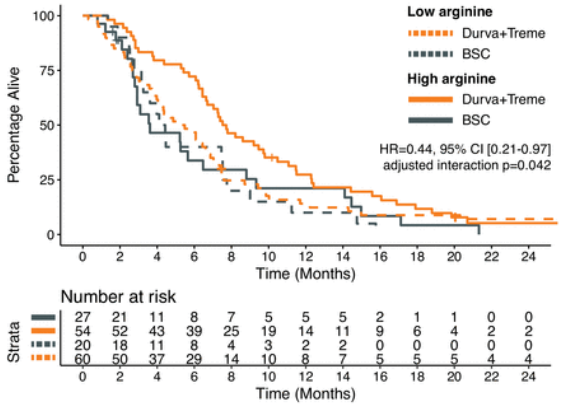


**Figure 1.** Overall survival curves for patients receiving durvalumab combined with tremelimumab (D+T) compared to best supportive care (BSC), grouped according to pretreatment plasma arginine (ARG) concentrations. OS: overall survival.

**Table 2.** Analysis of the predictive value of baseline arginine (ARG) concentrations (split at the median) for overall survival.

| Plasma ARG Level | D+T (N=114) | | BSC (N=47) | | Treatment Effect | Adjusted Interaction Between Biomarker and Treatment* |
|---|---|---|---|---|---|---|
| | N | Median OS (IQR) (months) | N | Median OS (IQR) (months) | HR (95% CI) (log-rank p-value) | HR (95% CI) (p-value) |
| High (≥10 700 ng/mL) | 54 | 7.62 (5.49–12.09) | 27 | 3.09 (2.25–7.64) | 0.61 (0.37 to 0.99) p=0.047 | 0.44 (0.21 to 0.97) |
| Low (<10 700 ng/mL) | 60 | 5.27 (2.76–7.54) | 20 | 4.27 (3.06–7.58) | 0.87 (0.52 to 1.46) p=0.61 | p=0.042 |

ARG: arginine, BSC: best supportive care, D+T: durvalumab in combination with tremelimumab, OS: overall survival

In a multivariable model that controlled for plasma tumor mutational burden (pTMB) and liver metastases, patients with high baseline arginine levels (ARG-high) still demonstrated a statistically significant improvement in overall survival when treated with D+T (HR 0.65, 95% CI 0.44–0.95, p=0.026; refer to **Table 3).**

**Table 3.** Multivariable evaluation of overall survival among patients receiving durvalumab plus tremelimumab (D+T).

| Covariate | Category | Hazard Ratio (95% CI) | P Value |
|---|---|---|---|
| Arginine Level | Low | Reference | |
| | High | 0.65 (0.44 to 0.95) | 0.026 |
| Liver Metastases | Present | Reference | |
| | Absent | 0.44 (0.29 to 0.69) | 0.00026 |
| Plasma Tumor Mutational Burden (TMB) | Low (<28) | Reference | |
| | High (≥28) | 0.98 (0.61 to 1.58) | 0.94 |

**D+T**: durvalumab plus tremelimumab, **OS**: overall survival, **TMB**: tumor mutational burden

*Sensitivity analyses*

Using the mean baseline plasma ARG and a minimum p-value approach to define ARG-high versus ARG-low, high plasma ARG consistently remained a significant prognostic and predictive factor for OS in patients receiving D+T. A positive correlation was observed

between plasma ARG levels and OS in the D+T-treated cohort (r = 0.34, p = 0.00023), whereas no significant correlation was seen in patients receiving BSC (r = −0.058, p = 0.7) **(Figure 2).**

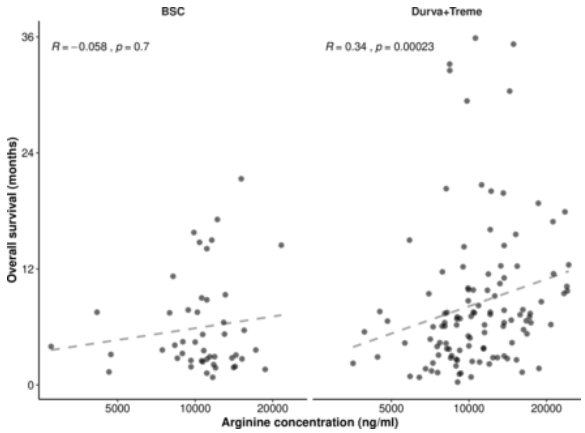


**Figure 2.** Scatter plot of plasma arginine levels versus overall survival (OS) in patients receiving best supportive care (BSC; left panel) or durvalumab plus tremelimumab (D+T; right panel).

Best supportive care (BSC); durvalumab plus tremelimumab (D+T); overall survival (OS).

This exploratory analysis of the CO.26 trial suggests that baseline plasma arginine (ARG) may serve as a predictive biomarker in advanced colorectal cancer. Patients with higher ARG levels who received D+T exhibited significantly improved overall survival (OS), whereas those with low ARG showed no meaningful benefit from immune checkpoint inhibition. To our knowledge, this represents the first study to investigate plasma ARG as a predictor of ICI response in colorectal cancer.

Currently, dMMR/MSI-H status is the only biomarker routinely used to guide ICI therapy in colorectal cancer, yet its predictive performance is limited. In KEYNOTE-177, pembrolizumab elicited an objective response in 44% of MSI-H tumors [8], while 29% of patients experienced progressive disease as their best response, indicating that primary resistance occurs even among previously untreated tumors. Additionally, dMMR/MSI-H tumors represent only ~5% of advanced colorectal cancers. In contrast, CO.26 demonstrated that a subset of MSS patients may derive clinical benefit from ICIs. Secondary analyses highlighted liver metastases as a negative prognostic factor in ICI-treated patients [16], consistent with findings from the phase III LEAP-017 trial, which evaluated pembrolizumab plus lenvatinib versus standard therapy in previously treated MSS colorectal cancer [17]. These data underscore the pressing need for additional biomarkers to refine patient selection.

Other candidate predictors, such as tumor mutational burden (TMB) and PD-L1 expression, have shown promise in other malignancies. KEYNOTE-158 demonstrated higher response rates to pembrolizumab in solid tumors with tissue TMB ≥10 muts/Mb, supporting FDA approval for tissue-agnostic use [18, 19]. Colorectal cancer patients were not included in this study. In CO.26, plasma TMB ≥28 muts/Mb was associated with the greatest OS benefit from D+T (HR 0.34, p=0.004), though correlations between TMB and ICI outcomes in colorectal cancer have been inconsistent, and the threshold for high TMB varies [11, 20-23]. PD-L1 expression, while useful in other cancers, is limited by assay variability and lacks validation as a predictive biomarker in colorectal cancer.

Tissue-based markers such as TMB and PD-L1 are further constrained by spatial and temporal heterogeneity. Archival specimens may not reflect the tumor immune environment at treatment initiation, and repeat biopsies can be invasive, risky, and delay therapy. Plasma-based biomarkers, including cellular metabolomics, provide a minimally invasive, real-time assessment of tumor biology and potential ICI responsiveness.

ARG metabolism is increasingly recognized as a key modulator of immune function. In vitro studies show that ARG depletion inhibits T-cell proliferation and activation [24]. Within tumors, arginase-expressing myeloid cells reduce ARG availability, impairing T-cell function through mechanisms including CD3ζ downregulation and reduced IFN-γ production [12, 14, 25, 26]. ARG supplementation enhances T-cell antitumor activity [13]. Our findings suggest that circulating ARG may serve as a noninvasive biomarker of ICI responsiveness, warranting prospective validation.

Beyond its predictive value, ARG represents a potential therapeutic target. Oral arginase inhibitors are being investigated alone or in combination with ICIs (NCT02903914; NCT03910530), while peptide vaccines targeting arginase-1 and T-cell engineering strategies to restore ARG metabolism in CAR-T cells are under exploration [27, 28].

This study has several limitations. As a retrospective, post hoc analysis, there is an inherent risk of type I error.

Plasma ARG was used as a surrogate for intratumoral ARG levels, which could not be directly measured. Baseline plasma samples were unavailable for all patients, particularly in the BSC group. While OS appeared lower in ARG-high patients receiving BSC, sample size limitations preclude definitive conclusions. Immunoscore data, another emerging biomarker, were not available; future studies could evaluate correlations with plasma ARG and ICI benefit.

Despite these limitations, this analysis provides the first evidence supporting plasma ARG as a predictive biomarker for ICI outcomes in metastatic colorectal cancer. While no single biomarker is likely to perfectly predict response, plasma ARG is inexpensive, easily measured, and could complement existing clinical and molecular markers. These results support prospective validation and highlight ARG-targeted strategies as potential adjuncts to immunotherapy in colorectal cancer.

## Conclusion

Elevated baseline plasma arginine (ARG) levels demonstrated predictive significance in patients with metastatic colorectal cancer (mCRC) receiving durvalumab plus tremelimumab. Prospective clinical trials are required to confirm the role of ARG as a reliable biomarker for selecting colorectal cancer patients who are most likely to derive benefit from immune checkpoint inhibitors (ICIs). Furthermore, exploration of novel therapeutic strategies aimed at modulating the ARG pathway warrants serious consideration.

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**Conflict of Interest:** None

**Financial Support:** None

**Ethics Statement:** The CO.26 study was approved by the institutional review board of each participating center and was conducted according to the principles of the Declaration of Helsinki. All patients provided voluntary informed consent to participate. This correlative analysis was approved by the University Health Network Research Ethics Board (CAPCR 16-5948).

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