Supplementary Online Content

Ng K, Nimeiri HS, McCleary NJ, et al. Effect of high-dose vs standard-dose vitamin D_3 supplementation on progression-free survival among patients with advanced or metastatic colorectal cancer: the SUNSHINE randomized clinical trial. *JAMA*. doi:10.1001/jama.2019.2402

eTable 1. Summary of chemotherapy and vitamin D3 treatment administration for patients with advanced or metastatic colorectal cancer who were enrolled on a randomized phase 2 trial of high-dose vs. standard-dose vitamin D3 and who received at least one dose of chemotherapy or vitamin D3

eTable 2. Multivariable hazard ratios (HR) of progression or death comparing high-dose to standard-dose vitamin D3 in subgroups of patients defined by prespecified clinical and pathologic characteristics

eFigure. Hybrid parallel line plot of change in plasma 25-hydroxyvitamin D [25(OH)D] levels (ng/mL) from baseline to either first or second restaging among patients randomized to high dose (H, orange) vs. standard-dose (S, blue) vitamin D3 who have both a baseline and at least one on-treatment plasma 25(OH)D assessment (n=109)

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Summary of chemotherapy and vitamin D3 treatment administration for patients with advanced or metastatic colorectal cancer who were enrolled on a randomized phase 2 trial of high-dose vs. standard-dose vitamin D3 and who received at least one dose of chemotherapy or vitamin D3 (n=135).

VARIABLE **Median (range)**	**HIGH-DOSE VITAMIN D3 (n=68)**	**STANDARD-DOSE VITAMIN D3 (n=67)**
No. cycles of chemotherapy treatment[a]	14.0 (1-57)	15.0 (0-56)
No. cycles with bevacizumab	12.5 (1-56)	13.0 (0-56)
No. cycles with oxaliplatin	11.0 (1-35)	10.0 (0-26)
Adherence with vitamin D3[b], %	98 (0-100)	98 (0-100)

[a] Each cycle of treatment is 14 days.

[b] Adherence was calculated as the % of expected vitamin D3 capsules taken.

eTable 2. Multivariable hazard ratios (HR) of progression or death comparing high-dose vs. standard-dose vitamin D3 in subgroups of patients defined by prespecified clinical and pathologic characteristics.

VARIABLE	NO. PATIENTS	MULTIVARIABLE HR (ONE-SIDED 95% CI)[a] COMPARING HIGH-DOSE VS. STANDARD-DOSE VITAMIN D3	*P* interaction[b]
Age (years)[c]			0.10
<55	70	0.82 (0-1.29)	
≥55	69	0.48 (0-0.80)	
Gender			0.42
Male	79	0.67 (0-1.03)	
Female	60	0.61 (0-1.03)	
Race/Ethnicity			0.40
White	107	0.66 (0-0.96)	
All others	32	0.58 (0-1.08)	
Body-mass index, kg/m2			0.04
<25	44	0.70 (0-1.16)	
25 to <30	58	0.35 (0-0.63)	
≥30	37	1.19 (0-2.27)	
Baseline ECOG performance status[d]			0.25
0	69	0.55 (0-0.92)	
1	70	0.73 (0-1.13)	
Primary tumor location[e]			0.29
Right and transverse colon	47	0.88 (0-1.52)	
Left colon	52	0.58 (0-1.07)	
Rectum	40	0.53 (0-1.03)	
Primary tumor resected			0.14
Yes	47	0.87 (0-1.53)	
No	92	0.54 (0-0.83)	
Received prior adjuvant chemotherapy			0.18
Yes	11	0.34 (0-1.07)	
No	128	0.68 (0-0.96)	
Number of metastatic sites[c]			0.02
<2	59	1.13 (0-1.91)	
≥2	80	0.47 (0-0.72)	

VARIABLE	NO. PATIENTS	MULTIVARIABLE HR (ONE-SIDED 95% CI) COMPARING HIGH-DOSE VS. STANDARD-DOSE VITAMIN D3	*P* interaction[a]
Baseline CEA, ng/mL[c]			0.29
<50.7	68	0.72 (0-1.75)	
≥50.7	69	0.58 (0-0.93)	
Baseline 25(OH)D, ng/mL			0.40
≤20	77	0.73 (0-1.18)	
>20	47	0.82 (0-1.47)	
***KRAS* mutation status**			0.04
Wild type	75	0.48 (0-0.77)	
Mutated	54	1.00 (0-1.70)	
***BRAF* mutation status, No. (%)**			0.23
Wild type	77	1.18 (0-1.86)	
Mutated	14	0.67 (0-2.15)	

Abbreviations: ECOG = Eastern Cooperative Oncology Group; CEA = carcinoembryonic antigen; 25(OH)D = 25-hydroxyvitamin D

[a] Multivariable models were adjusted for the following *a priori* covariates: age (continuous), gender (male vs. female), race/ethnicity (white vs. all others), body-mass index (<25 vs. 25 to <30 vs. ≥30 kg/m^2), ECOG performance status (0 vs. 1), and number of metastatic sites (continuous).

[b] One-sided *P* value calculated using the likelihood ratio test.

[c] Cut-point determined by the median value.

[d] An ECOG performance status of 0 indicates a patient with normal activity, who is fully active and able to carry on all pre-disease performance without restriction. An ECOG performance status of 1 indicates a patient with symptoms who is restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).

[e] Right colon defined as cecum, ascending colon, and hepatic flexure. Left colon defined as splenic flexure, descending colon, sigmoid colon, and rectum.

eFigure. Hybrid parallel line plot of change in plasma 25-hydroxyvitamin D [25(OH)D] levels (ng/mL) from baseline to either first or second restaging among patients randomized to high-dose (H, orange) vs. standard-dose (S, blue) vitamin D3 who have both a baseline and at least one on-treatment plasma 25(OH)D assessment (n=109). Cancer status as determined by objective tumor response at the time of the follow-up plasma 25(OH)D measurement is represented by different colored lines: green = partial response (PR), purple = stable disease (SD), and pink = progressive disease (PD). Each box plot displays the minimum, interquartile range (encompassed by the box), mean (horizontal dotted line within box), median (horizontal solid line within box), and maximum 25(OH)D value. Suspected outliers (i.e., outside 1.5 times the interquartile range above the upper quartile or below the lower quartile) are not included in the box plot.