

Data S1

Restricted cubic spline construction. Restricted cubic spline analyses were performed separately for each biomarker and endpoint using univariable Cox proportional hazards models. A centered natural cubic spline with three effective degrees of freedom, corresponding to four total knots, was used. The spline basis was generated using `patsy.dmatrix` with `cr(x, df=3, constraints='center')`. Cox models were fitted using `lifelines.CoxPHFitter`, and the figures were generated using `matplotlib`. For lymphocyte-albumin-neutrophil ratio (LANR), the knot locations were 2.18, 7.39, 13.36 and 64.23. For baseline vitamin D, the knot locations were 0.80, 11.33, 23.67 and 56.00 ng/ml. The lower and upper boundary knots corresponded to the observed minimum and maximum values, while the two internal knots were selected automatically at equally spaced quantiles of the distinct observed biomarker values. The reference values were set at the cohort medians: 10.49 for LANR and 11.0 ng/ml for vitamin D. The spline analyses were unadjusted; no additional clinical covariates were included, and LANR and vitamin D were evaluated in separate models.

Spline inferential verification. Overall associations were evaluated using joint Wald tests of all three spline coefficients. Non-linearity was assessed using likelihood-ratio tests

comparing the full three-degree-of-freedom spline model with the corresponding model containing the biomarker as a single linear term.

Fixed-horizon area under the curve implementation. Fixed-horizon discrimination was evaluated at 12 and 24 months. Area under the receiver operating characteristic curve values were calculated using `sklearn.metrics.roc_auc_score` in Python 3.12. Because higher LANR and vitamin D values were associated with lower hazards, their negative values were used as risk-oriented marker scores. For the combined biomarker analysis, endpoint-specific Cox proportional hazards models containing continuous LANR and vitamin D were fitted, and the resulting linear predictors were used as risk scores.

Clinically selected sensitivity model dimension. The clinically selected sensitivity models used the same covariate set for overall survival and progression-free survival (PFS) and contained nine regression coefficients. All 141 patients were included, with 88 deaths and 124 PFS events. These counts refer to the full-cohort clinically selected sensitivity analyses. By contrast, the primary progression-free survival model was restricted to 138 patients treated with folinic acid, fluorouracil and oxaliplatin- or folinic acid, fluorouracil and irinotecan-based regimens and included 121 PFS events because the capecitabine treatment contrast was not estimable.

Table SI. Tests of overall association and non-linearity for LANR and baseline 25-hydroxyvitamin D in restricted cubic spline Cox models.

Biomarker	Endpoint	Overall association: Wald χ^2 (3 df)	Non-linearity: Likelihood-ratio χ^2 (2 df)
Vitamin D	OS	11.852; P=0.0079	1.312; P=0.519
Vitamin D	PFS	10.163; P=0.0172	0.409; P=0.815
LANR	OS	19.872; P=0.00018	3.975; P=0.137
LANR	PFS	11.307; P=0.0102	0.609; P=0.737

LANR, lymphocyte-albumin-neutrophil ratio; df, degrees of freedom; OS, overall survival; PFS, progression-free survival.

Table SII. Survival outcomes from the clinically selected sensitivity models.

A, Survival outcomes (n=141)	
Outcome	Value
Median follow-up, months (95% CI)	30.7 (27.8 to 36.9)
Deaths, n (%)	88 (62.4)
PFS events, n (%)	124 (87.9)
Median OS, months (95% CI)	23.5 (19.3 to 31.5)
Median PFS, months (95% CI)	12.4 (11.0 to 13.6)

Values are presented as n (%) or medians with 95% confidence intervals. The model included age group, Eastern Cooperative Oncology Group performance status, primary tumor location, metastatic burden (two or more vs. fewer than two involved sites), BRAF status, targeted therapy class, LANR and baseline 25-hydroxyvitamin D. Estimates for the adjustment covariates are not shown. CI, confidence interval; HR, hazard ratio; LANR, lymphocyte-albumin-neutrophil ratio; OS, overall survival; PFS, progression-free survival.

Table SIII. Univariable Cox regression results for variables not entered into the multivariable models.

Variable	OS univariable	OS multivariable	PFS univariable	PFS multivariable
Male vs. female	0.84 (0.55 to 1.29); P=0.436	Not entered	1.00 (0.70 to 1.44); P=0.985	Not entered
Left-sided colon vs. right-sided colon	0.81 (0.52 to 1.26); P=0.344	Not entered	0.81 (0.56 to 1.17); P=0.251	Not entered
Rectum vs. right-sided colon	0.92 (0.57 to 1.50); P=0.743	Not entered	1.09 (0.73 to 1.63); P=0.666	Not entered
Peritoneal metastasis, present vs. absent	1.33 (0.83 to 2.12); P=0.231	Not entered	0.92 (0.61 to 1.39); P=0.692	Not entered
Lung metastasis, present vs. absent	0.73 (0.43 to 1.23); P=0.239	Not entered	0.72 (0.47 to 1.12); P=0.143	Not entered
Bone metastasis, present vs. absent	1.42 (0.69 to 2.92); P=0.339	Not entered	1.26 (0.61 to 2.59); P=0.529	Not entered
Ovarian metastasis, present vs. absent	1.86 (0.66 to 5.27); P=0.243	Not entered	1.41 (0.55 to 3.60); P=0.473	Not entered
Anti-VEGF vs. anti-EGFR-based treatment	1.75 (0.87 to 3.50); P=0.114	Not entered	1.12 (0.67 to 1.87); P=0.673	Not entered
Capecitabine-based vs. FOLFOX-based chemotherapy	Not estimable	Not entered	Not estimable	Not entered
KRAS alteration, present vs. absent	1.12 (0.69 to 1.81); P=0.637	Not entered	1.03 (0.69 to 1.52); P=0.890	Not entered
NRAS alteration, present vs. absent	1.24 (0.55 to 2.82); P=0.604	Not entered	1.16 (0.55 to 2.47); P=0.699	Not entered
HER2 positivity, present vs. absent	1.16 (0.39 to 3.46); P=0.790	Not entered	1.14 (0.44 to 2.94); P=0.790	Not entered
MSI-H vs. MSS	1.29 (0.40 to 4.12); P=0.671	Not entered	1.07 (0.39 to 2.92); P=0.899	Not entered
CEA, log-transformed	1.05 (0.95 to 1.17); P=0.339	Not entered	1.03 (0.94 to 1.13); P=0.514	Not entered
Platelet count, per 100,000/ μ l increase	1.05 (0.87 to 1.26); P=0.620	Not entered	1.00 (0.86 to 1.18); P=0.952	Not entered

Variables that did not enter either endpoint-specific multivariable model are displayed; variables entering at least one multivariable model are shown in Table II. Univariable Cox regression was performed for all baseline variables. LANR was modeled per 5-unit increase and baseline 25-hydroxyvitamin D per 10 ng/ml increase. Albumin, neutrophil count and lymphocyte count were not entered separately because they are components of LANR. The primary multivariable model for PFS was restricted to the 138 patients treated with FOLFOX- or FOLFIRI-based regimens, because the capecitabine contrast could not be estimated. ACCI, age-adjusted Charlson Comorbidity Index; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HR, hazard ratio; LANR, lymphocyte-albumin-neutrophil ratio; MSI-H, microsatellite instability-high; MSS, microsatellite stable; OS, overall survival; PFS, progression-free survival; NRAS, neuroblastoma RAS viral oncogene homolog.

Table SIV. Biomarker outcomes from the clinically selected multivariable Cox models (n=141).

Variable	OS HR (95% CI)	P-value	PFS HR (95% CI)	P-value
LANR, per 5-unit increase	0.80 (0.68 to 0.96)	0.013	0.83 (0.73 to 0.94)	0.004
Baseline 25-hydroxyvitamin D, per 10 ng/ml increase	0.79 (0.60 to 1.05)	0.108	0.82 (0.66 to 1.02)	0.077

The model includes age group, Eastern Cooperative Oncology Group performance status, primary tumor location, metastatic burden (two or more vs. fewer than two involved sites), BRAF status, targeted therapy class, LANR and baseline 25-hydroxyvitamin D. Estimates for the adjustment covariates are not shown. OS, overall survival; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; LANR, lymphocyte-albumin-neutrophil ratio.

Table SV. Sensitivity analysis with baseline 25-hydroxyvitamin D as a binary variable: Overall survival.

Variable	Univariable HR (95% CI)	P-value	Multivariable HR (95% CI)	P-value
LANR, per 5-unit increase	0.76 (0.65 to 0.89)	P<0.001	0.81 (0.68 to 0.96)	P=0.016
Baseline 25-hydroxyvitamin D, <20 vs. ≥20 ng/ml	1.68 (0.98 to 2.87)	P=0.057	1.15 (0.66 to 2.00)	P=0.621
Metformin use, present vs. absent	0.43 (0.26 to 0.69)	P<0.001	0.38 (0.23 to 0.63)	P<0.001
Age, ≥65 vs. <65 years	0.90 (0.58 to 1.41)	P=0.648	Not entered	
Male vs. female	0.85 (0.55 to 1.29)	P=0.436	Not entered	
ECOG PS, 2-3 vs. 0-1	2.82 (1.77 to 4.49)	P<0.001	1.73 (1.01 to 2.96)	P=0.046
ACCI, <8 vs. ≥8	0.77 (0.45 to 1.29)	P=0.317	Not entered	
Left-sided colon vs. right-sided colon	0.81 (0.52 to 1.26)	P=0.344	Not entered	
Rectum vs. right-sided colon	0.92 (0.57 to 1.50)	P=0.743	Not entered	
Peritoneal metastasis, present vs. absent	1.33 (0.83 to 2.12)	P=0.231	Not entered	
Liver metastasis, present vs. absent	1.59 (0.94 to 2.67)	P=0.084	1.47 (0.86 to 2.52)	P=0.160
Lung metastasis, present vs. absent	0.73 (0.43 to 1.23)	P=0.239	Not entered	
Bone metastasis, present vs. absent	1.42 (0.69 to 2.92)	P=0.339	Not entered	
Ovarian metastasis, present vs. absent	1.86 (0.66 to 5.27)	P=0.243	Not entered	
Distant lymph node metastasis, present vs. absent	2.04 (1.18 to 3.57)	P=0.012	2.33 (1.28 to 4.17)	P=0.005
Anti-VEGF vs. anti-EGFR-based treatment	1.75 (0.88 to 3.50)	P=0.114	Not entered	
FOLFIRI vs. FOLFOX-based chemotherapy	1.13 (0.71 to 1.80)	P=0.611	Not entered	
Capecitabine-based vs. FOLFOX-based chemotherapy	Not estimable		Not entered	
KRAS alteration, present vs. absent	1.12 (0.70 to 1.81)	P=0.637	Not entered	
NRAS alteration, present vs. absent	1.24 (0.55 to 2.82)	P=0.604	Not entered	
BRAF alteration, present vs. absent	2.08 (1.00 to 4.37)	P=0.052	3.96 (1.79 to 8.74)	P<0.001
HER2 positivity, present vs. absent	1.16 (0.39 to 3.46)	P=0.790	Not entered	
HER2 status, not assessed vs. absent	1.63 (1.03 to 2.60)	P=0.038	1.41 (0.88 to 2.27)	P=0.152
MSI-H vs. microsatellite stable	1.29 (0.40 to 4.12)	P=0.671	Not entered	
BMI, per 1 kg/m ² increase	0.94 (0.90 to 0.99)	P=0.018	0.94 (0.90 to 0.99)	P=0.023
CEA, log-transformed	1.05 (0.95 to 1.17)	P=0.339	Not entered	
CA19-9, log-transformed	1.12 (1.01 to 1.26)	P=0.038	1.11 (0.98 to 1.26)	P=0.105
Hemoglobin, per 1 g/dl increase	0.87 (0.77 to 0.98)	P=0.025	0.93 (0.81 to 1.06)	P=0.270
Platelet count, per 100,000/μl increase	1.05 (0.87 to 1.26)	P=0.620	Not entered	

In this sensitivity analysis, baseline 25-hydroxyvitamin D was analyzed as a binary variable defined as less than 20 versus 20 ng/ml or higher, rather than as a continuous variable. Univariable Cox regression was performed for all listed baseline variables. Variables with P<0.10 in univariable analysis were entered into the multivariable model. LANR was modeled per 5-unit increase. Albumin, neutrophil count and lymphocyte count were not entered separately because they are components of LANR. The capecitabine contrast could not be estimated. ACCI, age-adjusted Charlson Comorbidity Index; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HR, hazard ratio; LANR, lymphocyte-albumin-neutrophil ratio; MSI-H, microsatellite instability-high; NRAS, neuroblastoma RAS viral oncogene homolog.

Table SVI. Sensitivity analysis with baseline 25-hydroxyvitamin D as a binary variable: Progression-free survival.

Variable	Univariable HR (95% CI)	P-value	Multivariable HR (95% CI)	P-value
LANR, per 5-unit increase	0.81 (0.73 to 0.91)	P<0.001	0.83 (0.72 to 0.94)	P=0.006
Baseline 25-hydroxyvitamin D, <20 vs. ≥20 ng/ml	1.74 (1.12 to 2.72)	P=0.014	1.18 (0.74 to 1.88)	P=0.483
Metformin use, present vs. absent	0.94 (0.66 to 1.35)	P=0.747	Not entered	
Age, ≥65 vs. <65 years	0.72 (0.49 to 1.04)	P=0.078	0.77 (0.46 to 1.28)	P=0.316
Male vs. female	1.00 (0.70 to 1.44)	P=0.985	Not entered	
ECOG PS, 2-3 vs. 0-1	1.43 (0.92 to 2.20)	P=0.110	Not entered	
ACCI, <8 vs. ≥8	0.62 (0.40 to 0.96)	P=0.033	0.94 (0.51 to 1.74)	P=0.846
Left-sided colon vs. right-sided colon	0.81 (0.56 to 1.17)	P=0.251	Not entered	
Rectum vs. right-sided colon	1.09 (0.73 to 1.63)	P=0.666	Not entered	
Peritoneal metastasis, present vs. absent	0.92 (0.61 to 1.39)	P=0.692	Not entered	
Liver metastasis, present vs. absent	1.63 (1.07 to 2.47)	P=0.022	1.48 (0.94 to 2.33)	P=0.092
Lung metastasis, present vs. absent	0.72 (0.47 to 1.12)	P=0.143	Not entered	
Bone metastasis, present vs. absent	1.26 (0.61 to 2.59)	P=0.529	Not entered	
Ovarian metastasis, present vs. absent	1.41 (0.55 to 3.60)	P=0.473	Not entered	
Distant lymph node metastasis, present vs. absent	2.03 (0.90 to 4.24)	P=0.176	Not entered	
Anti-VEGF vs. anti-EGFR-based treatment	1.12 (0.67 to 1.87)	P=0.673	Not entered	
FOLFIRI vs. FOLFOX-based chemotherapy	1.47 (0.99 to 2.19)	P=0.059	1.64 (1.07 to 2.53)	P=0.025
Capecitabine-based vs. FOLFOX-based chemotherapy	Not estimable		Not entered	
KRAS alteration, present vs. absent	1.03 (0.69 to 1.52)	P=0.890	Not entered	
NRAS alteration, present vs. absent	1.16 (0.55 to 2.47)	P=0.699	Not entered	
BRAF alteration, present vs. absent	1.35 (0.65 to 2.78)	P=0.421	Not entered	
HER2 positivity, present vs. absent	1.14 (0.44 to 2.94)	P=0.790	Not entered	
HER2 status not assessed vs. absent	1.19 (0.81 to 1.74)	P=0.380	Not entered	
MSI-H vs. microsatellite stable	1.07 (0.39 to 2.92)	P=0.899	Not entered	
BMI, per 1 kg/m ² increase	0.97 (0.93 to 1.01)	P=0.110	Not entered	
CEA, log-transformed	1.03 (0.94 to 1.13)	P=0.514	Not entered	
CA19-9, log-transformed	1.06 (0.96 to 1.16)	P=0.248	Not entered	
Hemoglobin, per 1 g/dl increase	0.93 (0.84 to 1.03)	P=0.169	Not entered	
Platelet count, per 100,000/μl increase	1.00 (0.86 to 1.18)	P=0.952	Not entered	

In this sensitivity analysis, baseline 25-hydroxyvitamin D was analyzed as a binary variable defined as less than 20 versus 20 ng/ml or higher, rather than as a continuous variable. Univariable Cox regression was performed for all listed baseline variables. Variables with P<0.10 in univariable analysis were entered into the multivariable model. LANR was modeled per 5-unit increase. Albumin, neutrophil count and lymphocyte count were not entered separately because they are components of LANR. The capecitabine contrast could not be estimated. ACCI, age-adjusted Charlson Comorbidity Index; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFIRI, folinic acid, fluorouracil and irinotecan; FOLFOX, folinic acid, fluorouracil and oxaliplatin; HR, hazard ratio; LANR, lymphocyte-albumin-neutrophil ratio; MSI-H, microsatellite instability-high; NRAS, neuroblastoma RAS viral oncogene homolog.

Table SVII. Fixed-horizon areas under the receiver operating characteristic curve at 12 and 24 months.

Endpoint	Time point	Cases/controls	Excluded censored patients	LANR AUC (95% CI)	Baseline 25(OH)D AUC (95% CI)	Combined model AUC (95% CI)
OS	12 months	34 / 107	0	0.761 (0.657 to 0.849)	0.575 (0.452 to 0.668)	0.716 (0.579 to 0.804)
OS	24 months	74 / 53	14	0.635 (0.530 to 0.744)	0.659 (0.558 to 0.751)	0.688 (0.590 to 0.776)
PFS	12 months	68 / 73	0	0.605 (0.523 to 0.692)	0.659 (0.561 to 0.758)	0.636 (0.549 to 0.729)
PFS	24 months	110 / 25	6	0.620 (0.476 to 0.736)	0.606 (0.489 to 0.726)	0.636 (0.522 to 0.765)

AUCs were calculated using cumulative case/dynamic control definitions among patients with an evaluable outcome status at each time point. Patients censored without an event before the specified horizon were excluded, and inverse probability of censoring weighting was not used. Higher-risk orientation was obtained using the negative values of LANR and vitamin D. The combined biomarker score was the linear predictor from an endpoint-specific Cox model containing both continuous biomarkers. 95% CIs were estimated using 1,000 percentile bootstrap resamples. 25(OH)D, 25-hydroxyvitamin D; AUC, area under the receiver operating characteristic curve; CI, confidence interval; LANR, lymphocyte-albumin-neutrophil ratio; OS, overall survival; PFS, progression-free survival.