

Vitamin D Status and Survival of Metastatic Colorectal Cancer Patients: Results From CALGB/SWOG 80405 (Alliance)

Abstract 507

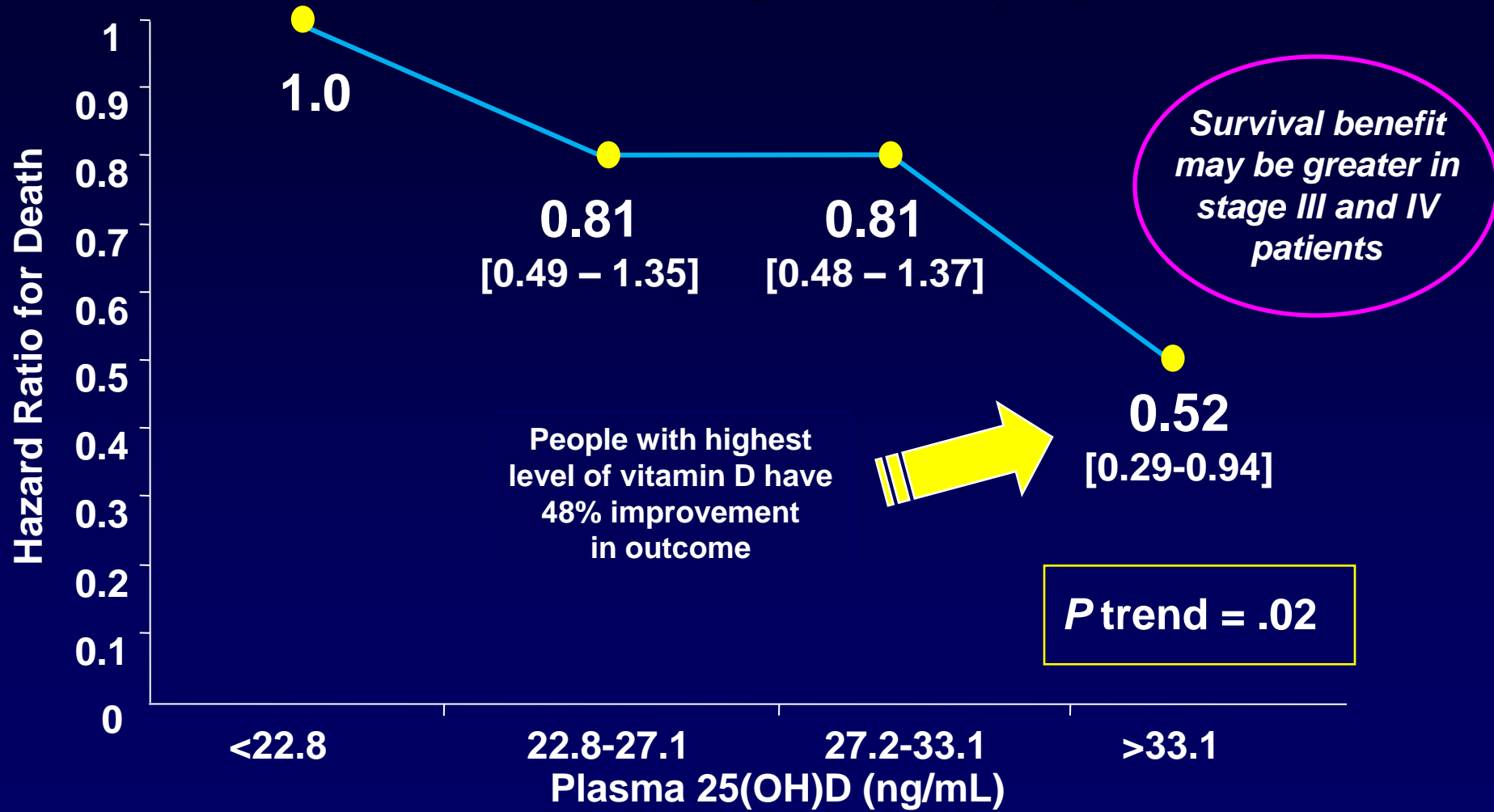
**Ng K, Venook AP, Sato K, Hollis BW, Niedzwiecki D, Ye C,
Chang I-W, O'Neil BH, Innocenti F, Lenz H-J, Blanke CD, Mayer RJ,
Fuchs CS, Meyerhardt JA**

Background: Vitamin D and Colorectal Cancer

- Vitamin D inhibits cell proliferation and angiogenesis, induces cell differentiation and apoptosis, and has anti-inflammatory effects
- Vitamin D receptor (VDR) and 1- α -hydroxylase are expressed in colorectal cancer (CRC) cells
 - Anti-proliferative effects greatest in cell lines with high VDR¹
- Treatment of *APC^{min}* mice with vitamin D decreases tumor burden,² whereas adenoma numbers and size are increased in VDR-null *APC^{min}* mice³
- Low plasma 25(OH)D levels associated with risk of CRC

1. Evans SR, et al. *Clin Cancer Res.* 1998;4(11):2869-2876. 2. Huerta S, et al. *Cancer Res.* 2002;62(3):741-746. 3. Zheng W, et al. *Int J Cancer.* 2011;130(1):10-19. 4. Ma Y, et al. *J Clin Oncol.* 2011;29(28):3775-3782.

Prospective Cohort Study of 304 CRC Patients Suggests Association Between Prediagnosis 25(OH)D and Survival



Adjusted for age, gender, stage, grade, site, year of diagnosis, season of blood draw, BMI, and post-diagnosis physical activity

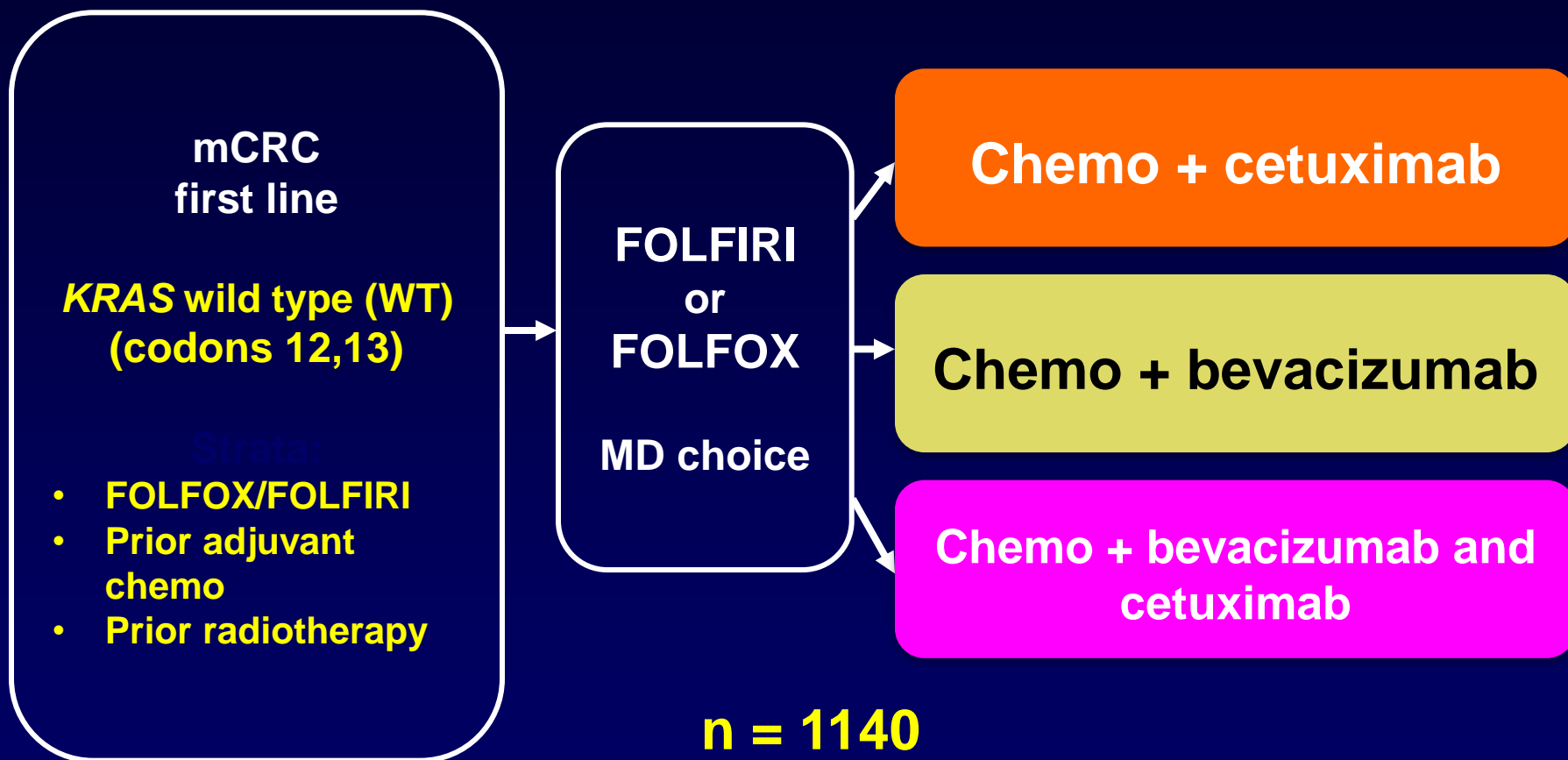
Ng, K et al. *J Clin Oncol.* 2008;26(18):2984-3991.

Ng K, et al. *J Clin Oncol.* 2015;33(suppl 3): Abstract 507.

Study Objective

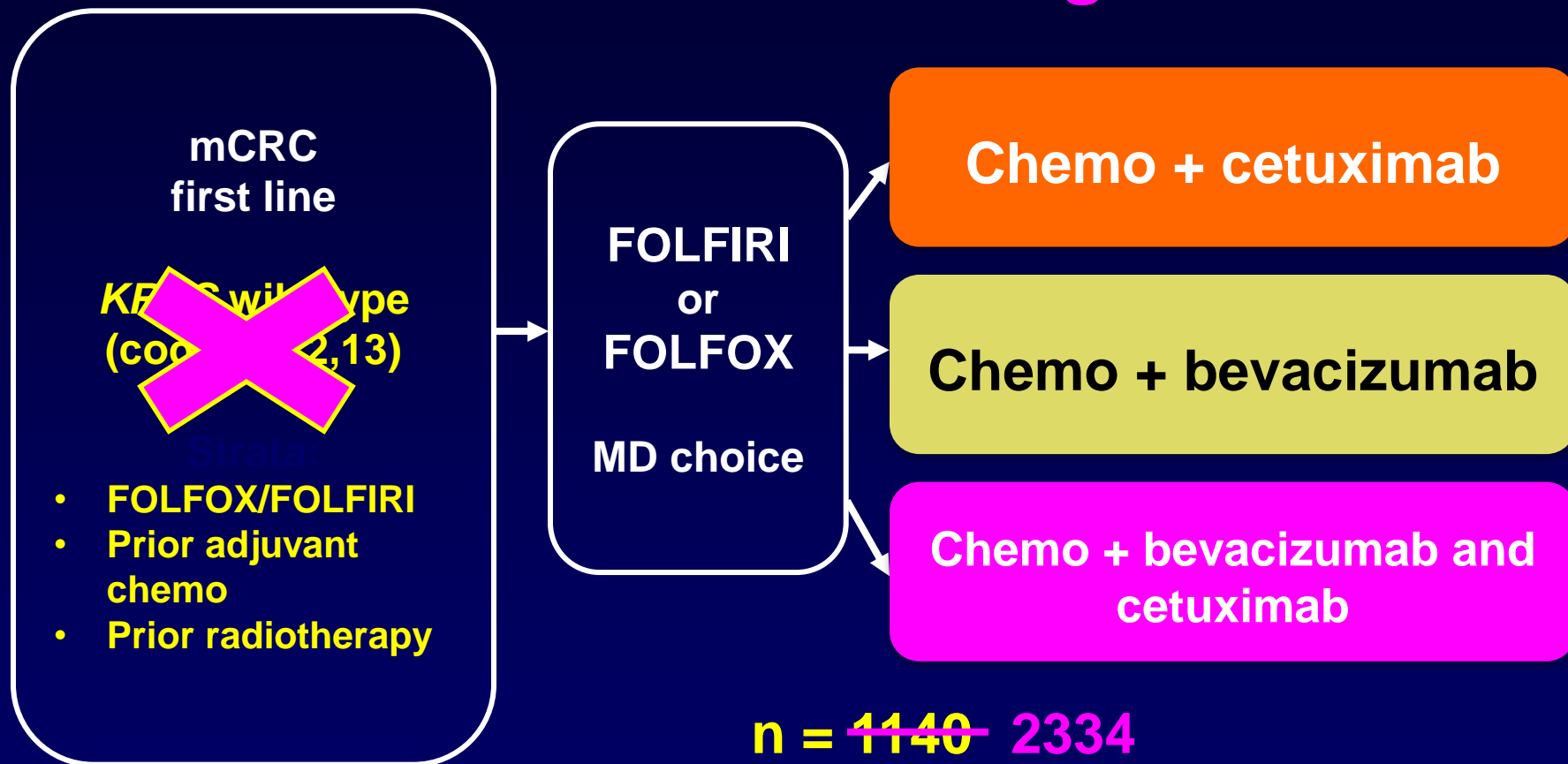
Are higher vitamin D levels associated with improved survival in patients with metastatic CRC?

CALGB/SWOG 80405: Final Design



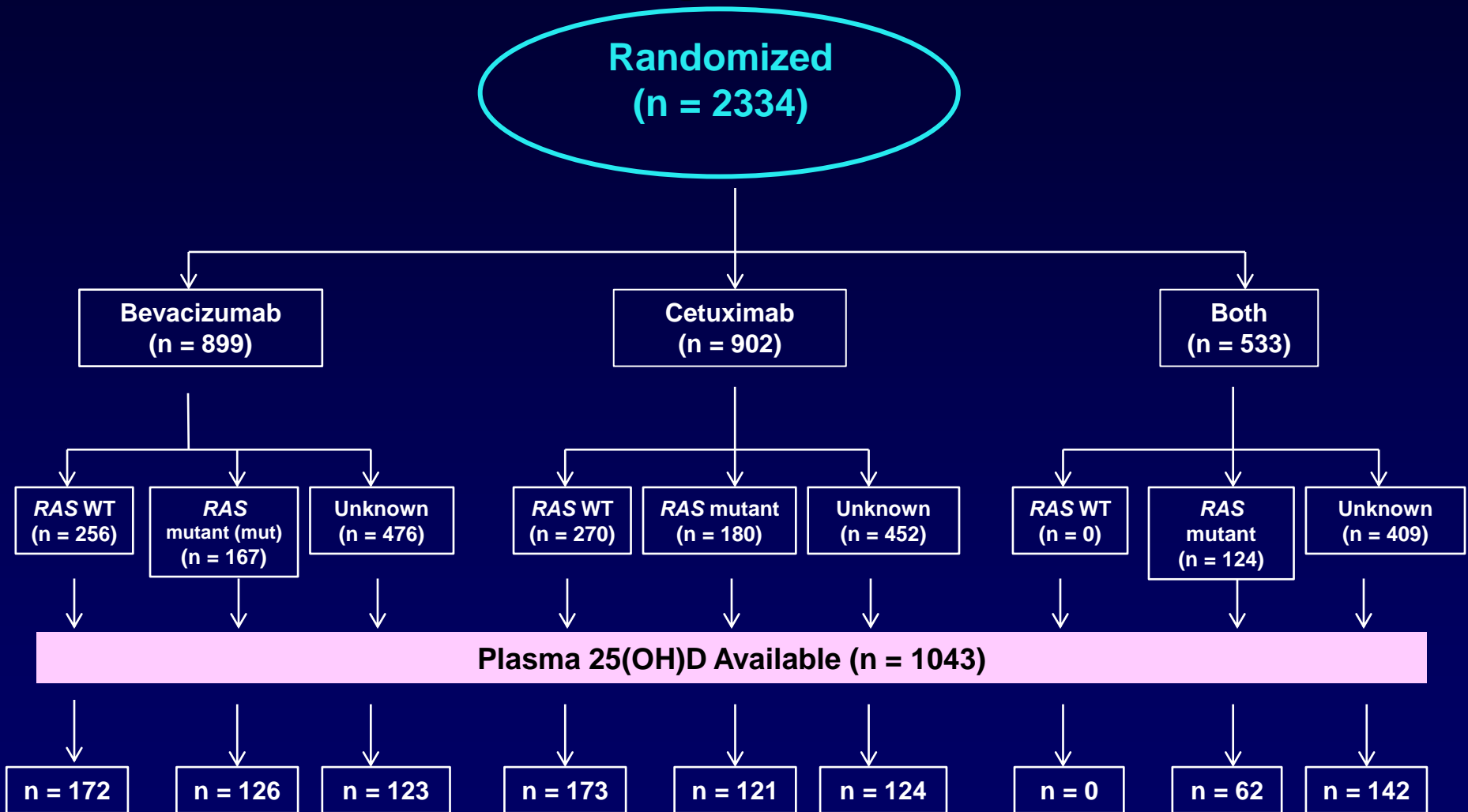
Primary endpoint: Overall Survival

CALGB/SWOG 80405: ~~Final~~ Design *Original*



Primary endpoint: Overall Survival

Study Cohort



Statistical Methods

- Preplanned, prospective, observational cohort study
- Primary endpoint: Overall survival
 - Kaplan-Meier method
 - Log rank test
- Plasma 25(OH)D measured by radioimmunoassay prior to treatment
- Validated diet and lifestyle questionnaires prior to treatment
- Multivariable analyses using Cox proportional hazards models
- All *P* values two-sided and considered significant at the .05 level

Vitamin D Cohort vs Final Trial Cohort

	Vitamin D (n = 1043)	Final Trial (n = 1137)
Median age, years	60	59
Male, %	58	61
ECOG PS 0 / 1, %	61 / 39	58 / 42
Primary tumor in place, %	25	28
Palliative intent, %	82	84
FOLFOX / FOLFIRI, %	77 / 23	73 / 27

All *P* values >.05

Baseline Characteristics (1)

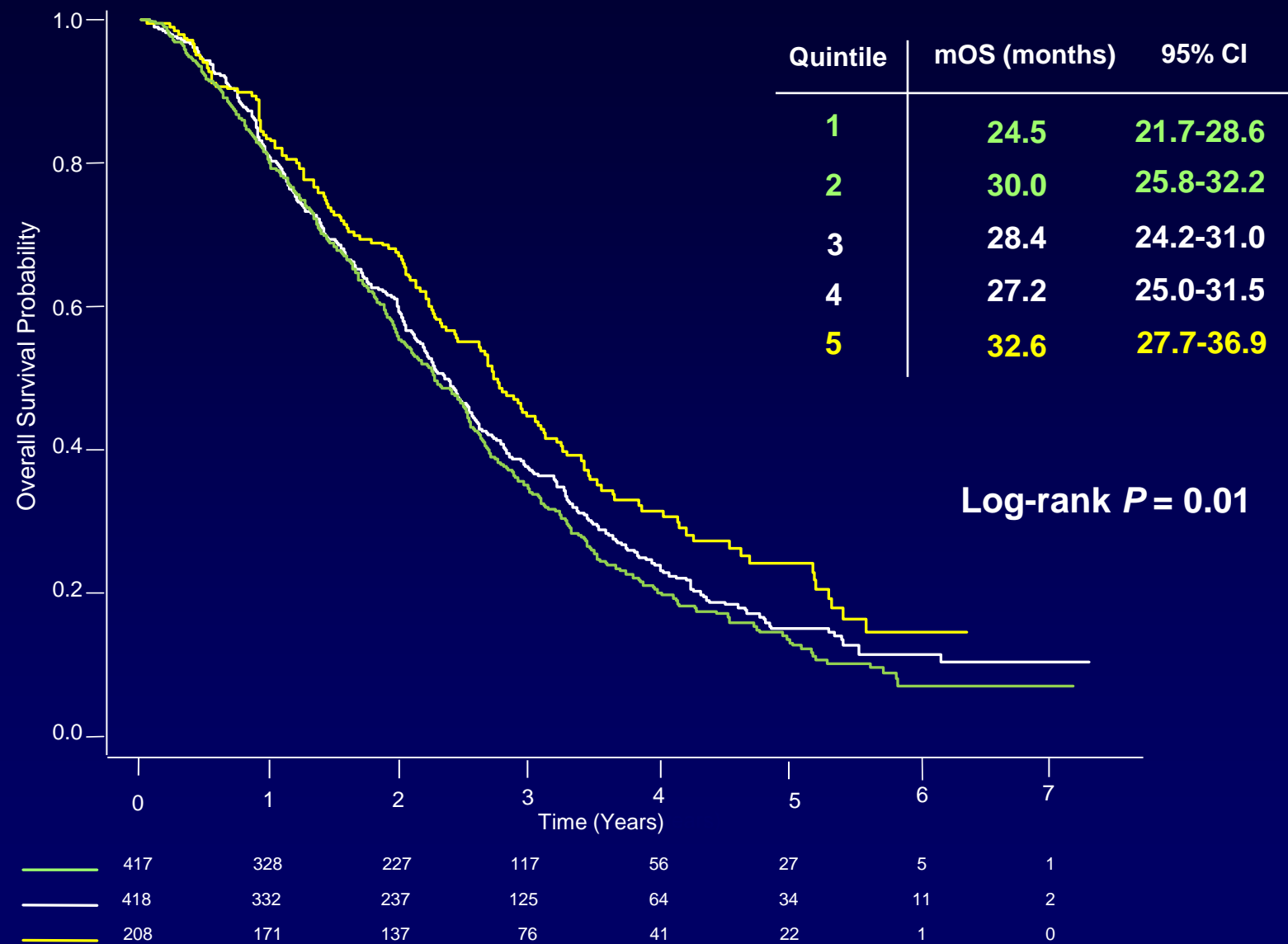
Median 25(OH)D = 17.2 ng/mL

	Q1 (n = 208)	Q2 (n = 209)	Q3 (n = 208)	Q4 (n = 210)	Q5 (n = 208)	P
Median 25(OH)D, ng/mL (range)	8.0 (2.2-10.8)	13.6 (10.9-15.4)	17.2 (15.4-19.2)	21.4 (19.3-24.0)	27.5 (24.1-72.7)	--
Median age, years	59	60	60	61	61	.07
Male, %	48	64	58	64	55	.004
Black, %	25	12	6	7	2	<.0001
ECOG 0 / 1, %	49 / 50	64 / 36	58 / 42	63 / 37	70 / 30	.002
RAS WT / mut / unknown, %	33 / 30 / 37	31 / 30 / 39	26 / 39 / 35	38 / 29 / 33	37 / 21 / 42	.02

Baseline Characteristics (2)

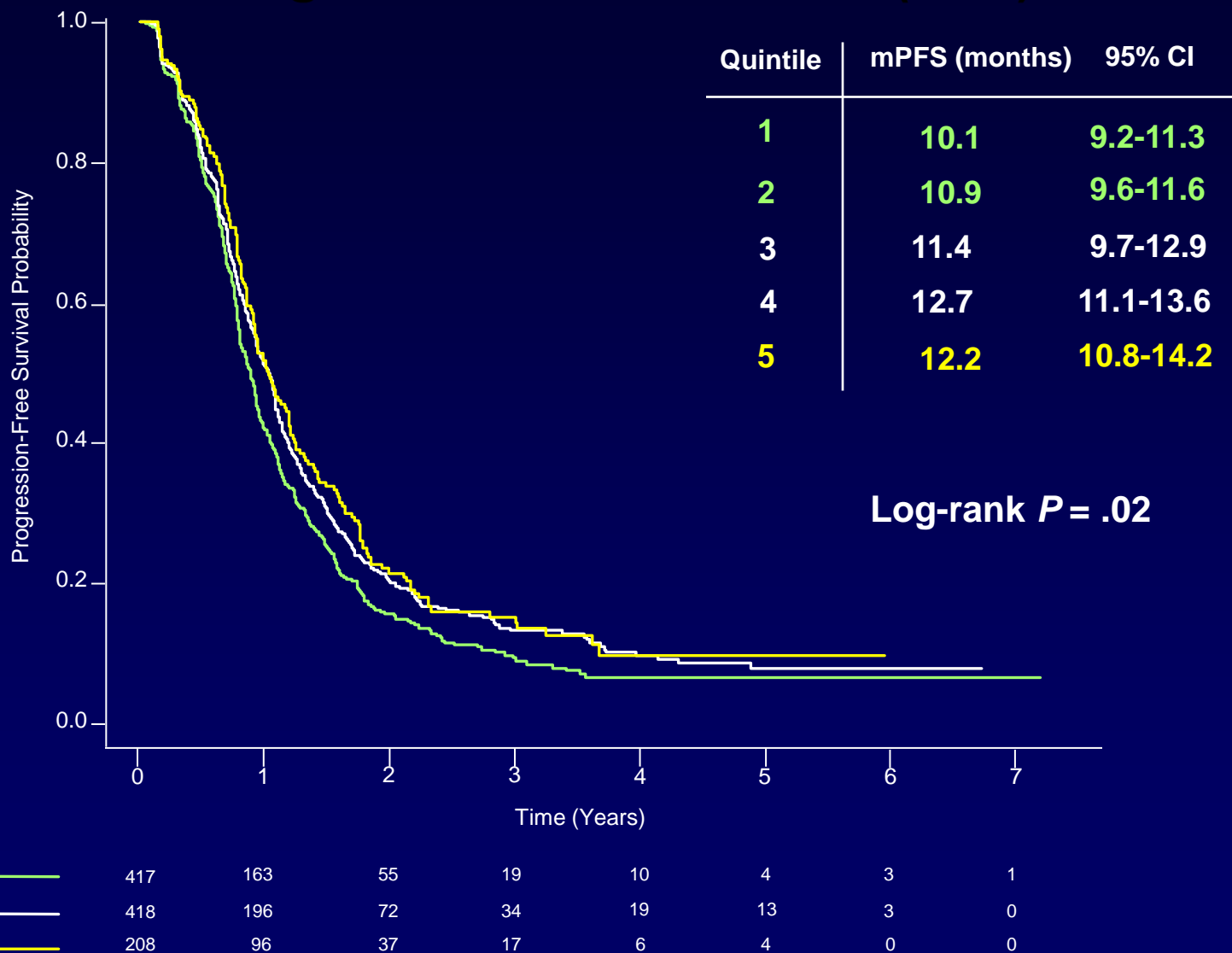
- No significant difference in chemotherapy backbone, history of prior adjuvant therapy, or assigned biologic between quintiles of 25(OH)D
- Significantly lower 25(OH)D seen in:
 - Patients living in the north and northeast ($P < .0001$)
 - Patients with blood drawn in winter and spring ($P = .03$)
 - Obese patients ($P = .0006$)
 - Less physically-active patients ($P = .004$)
 - Patients not reporting vitamin D supplement use ($P < .0001$)

Higher Vitamin D Levels Associated With Better Survival



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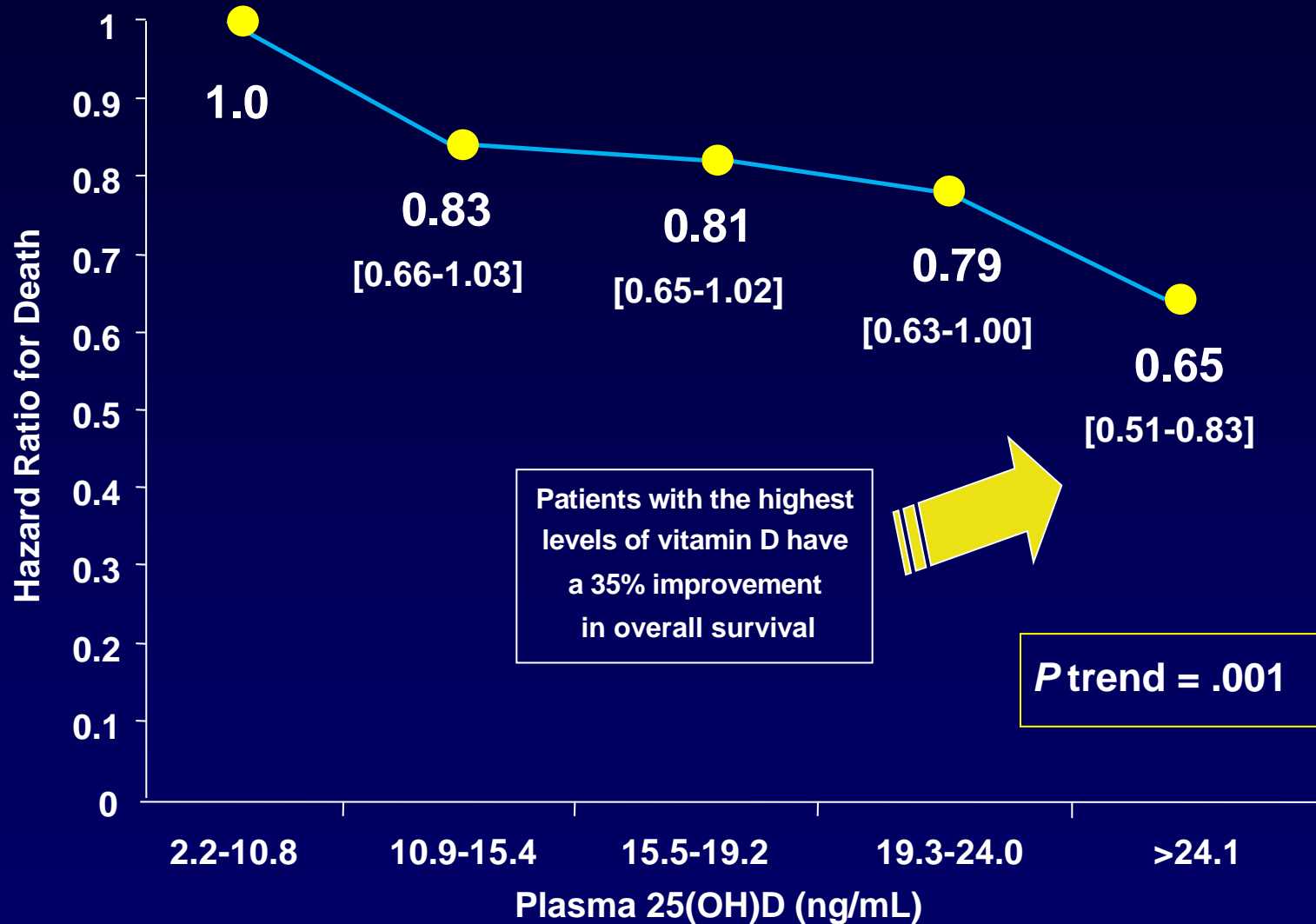
Higher Vitamin D Levels Also Associated with Better Progression-Free Survival (PFS)



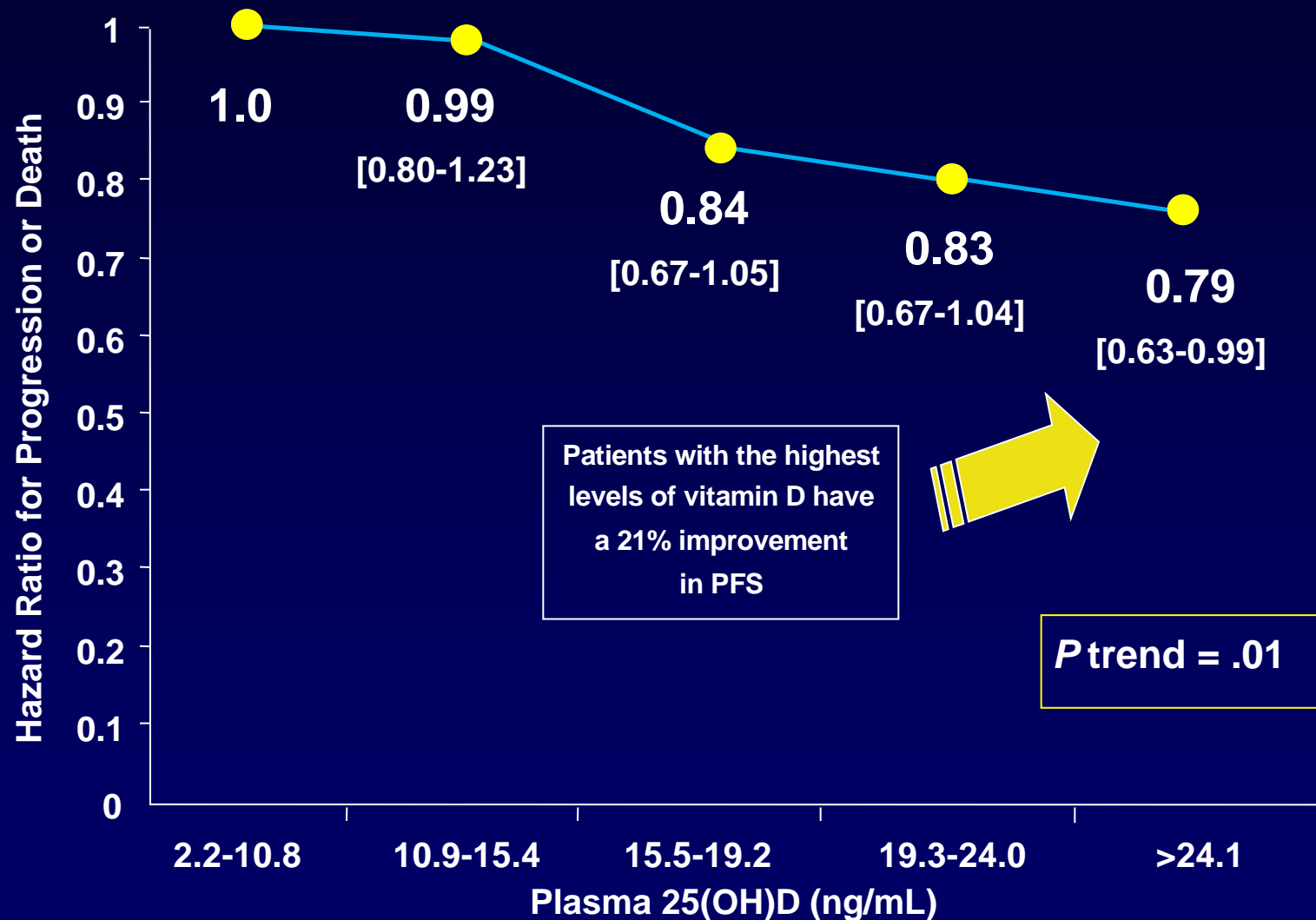
Multivariate Analysis

- Final model adjusted for:
 - Age
 - Sex
 - Race
 - ECOG performance status
 - Chemotherapy backbone
 - Previous adjuvant therapy
 - Assigned biologic
 - *RAS* mutation status
 - Season of blood draw
 - Geographic region of residence
 - Body-mass index
 - Physical activity

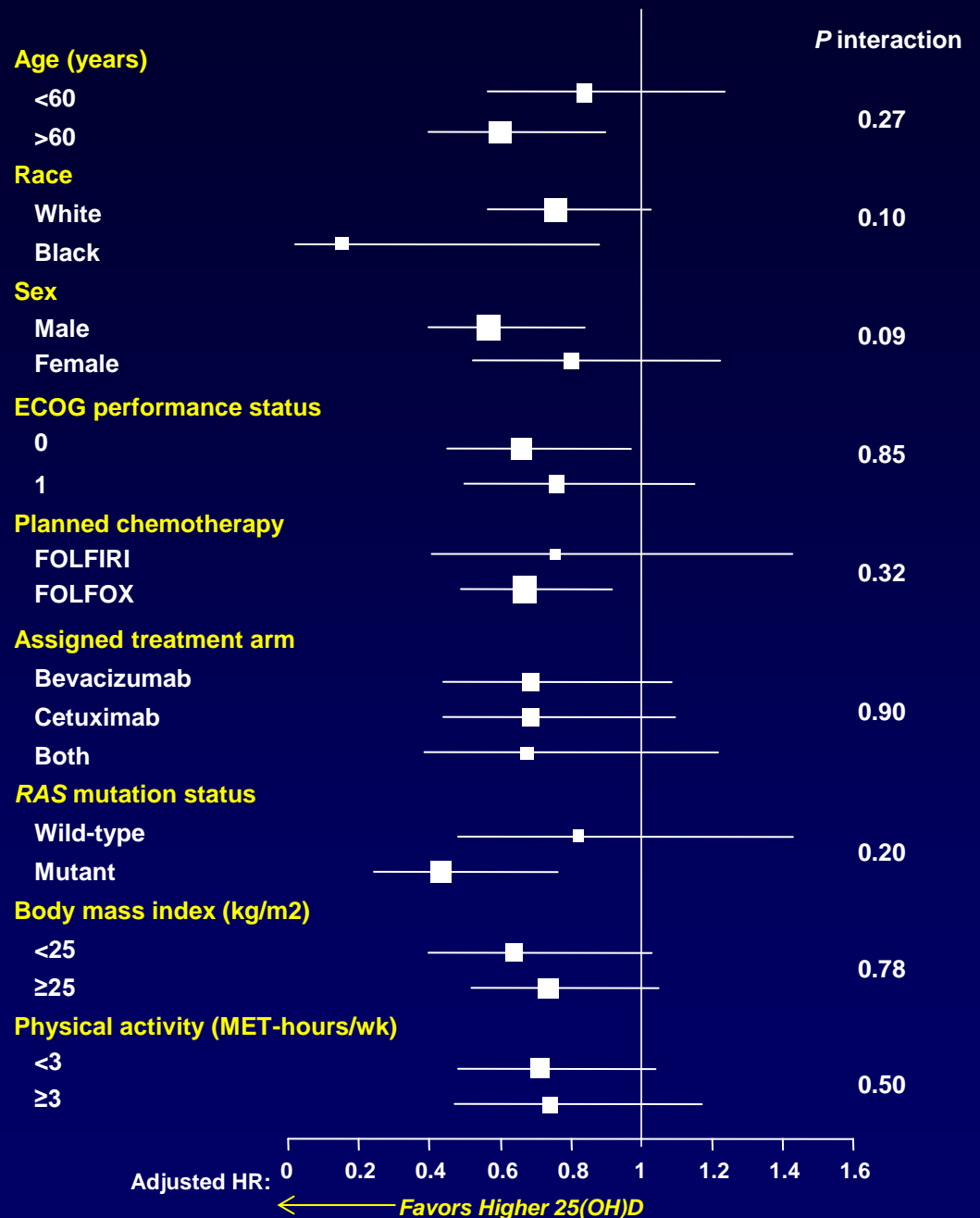
Multivariate Hazard Ratios: Overall Survival



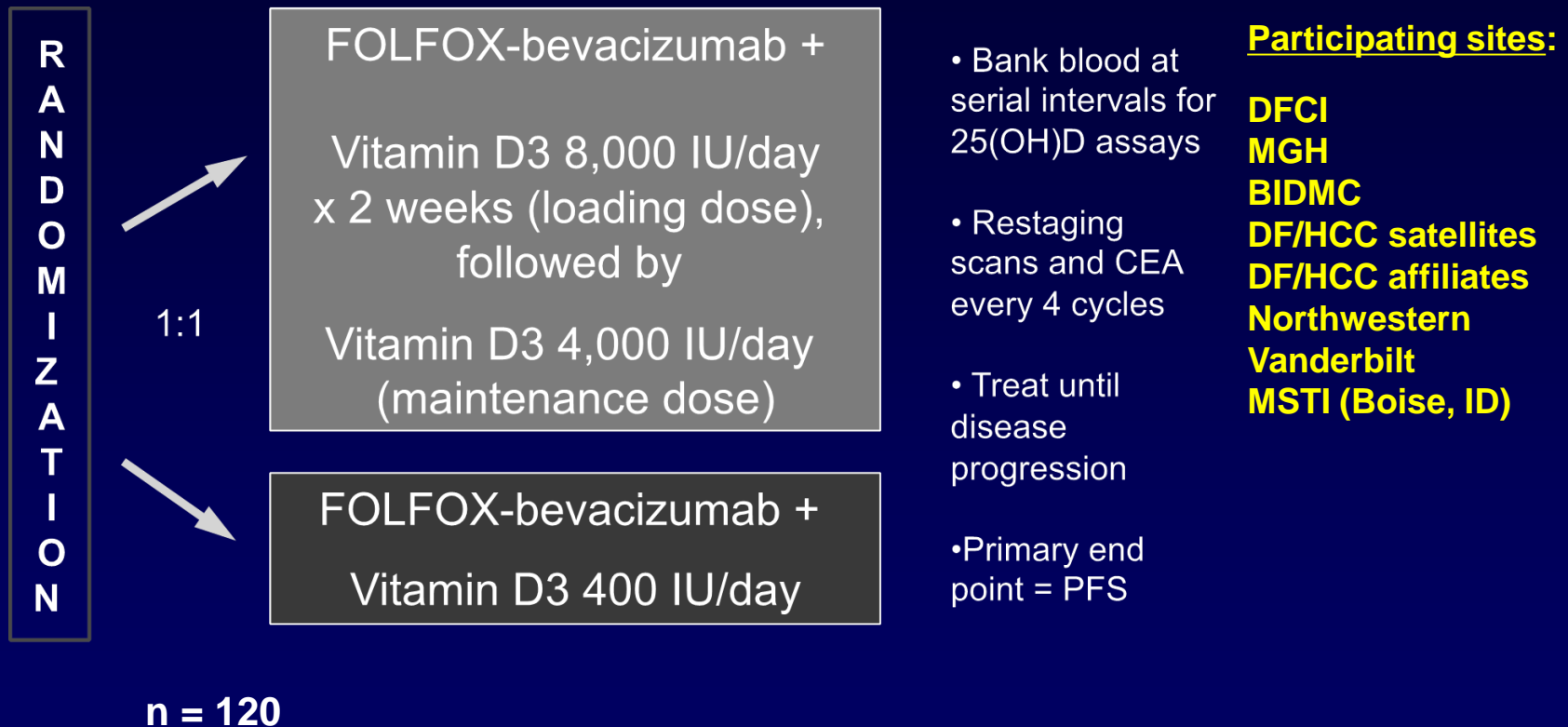
Multivariate Hazard Ratios: PFS



Subgroup Analyses of Overall Survival, Comparing Extreme Quintiles of 25(OH)D



Randomized Double-Blind Phase II Trial of Vitamin D in Metastatic CRC



Conclusions

- **Metastatic CRC patients are frequently vitamin D deficient**
- **Higher vitamin D levels are associated with significantly improved overall survival and PFS**
- **This association persists across all patient subgroups and after adjusting for multiple prognostic factors**
- **A phase II randomized trial to evaluate the impact of vitamin D supplementation as an adjunct to chemotherapy is currently ongoing**