

# Analysis of the Role of Plasma 25-Hydroxyvitamin D Levels in Survival Outcomes in Patients from the Phase III MPACT Trial of Metastatic Pancreatic Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

## ABSTRACT

**Background.** We examined overall survival (OS) outcomes based on plasma 25-hydroxyvitamin D [25(OH)D] levels in this post hoc analysis of the phase III MPACT trial of metastatic pancreatic cancer.

**Materials and Methods.** Patients were subdivided based on 25(OH)D level: sufficient ( $\geq 30$  ng/mL), relatively insufficient ( $20 < 30$  ng/mL), or insufficient ( $< 20$  ng/mL).

**Results.** Of 861 patients randomized in MPACT, 422 were included in this analysis. In the all-patients group, the median OS among those with insufficient, relatively insufficient, and

sufficient 25(OH)D levels was 7.9, 9.4, and 7.8 months, respectively. No statistically significant OS difference was observed with relatively insufficient ( $p = .227$ ) or sufficient ( $p = .740$ ) versus insufficient 25(OH)D levels or with sufficient vs relatively insufficient ( $p = .301$ ) 25(OH)D levels.

**Conclusion.** No association was observed between plasma 25(OH)D levels and survival. Further investigations are needed to understand any role of vitamin D in pancreatic cancer. *Clinical trial identification number.* NCT00844649. *The Oncologist* 2021;26:e704–e709

## INTRODUCTION

The use of biomarkers has allowed for the identification of patients who may experience improved efficacy with certain treatments; however, few such biomarkers exist for pancreatic cancer. On the basis of the PRODIGE 4/ACCORD 11 and MPACT trials, folinic acid, fluorouracil, irinotecan, oxaliplatin (FOLFIRINOX) and *nab*-paclitaxel plus gemcitabine are preferred category 1 regimens per National Comprehensive Cancer Network guidelines for the treatment of patients with metastatic pancreatic cancer [1]. For patients with metastatic disease and *BRCA1/2* or *PALB2* mutations, FOLFIRINOX (category 1) as well as modified FOLFIRINOX and cisplatin plus gemcitabine (category 2A) are options [1]. Data from the POLO trial support the National Comprehensive Cancer Network recommendation for maintenance olaparib in patients with germline *BRCA1/2* mutations; however, germline *BRCA1/2* mutations are fairly rare among patients with pancreatic cancer [1, 2]. Pembrolizumab may be used as a second-line therapy for metastatic pancreatic cancer but only for patients with high microsatellite instability or mismatch repair-deficient tumors [1, 3]. Clearly, a need exists to identify a biomarker with broader applicability in pancreatic cancer management.

Studies have suggested a possible survival benefit for patients with pancreatic cancer and sufficient vitamin D levels. A study of patients with pancreatic cancer from five prospective U.S. cohorts revealed a significantly longer survival among patients with sufficient levels of plasma 25-hydroxyvitamin D [25(OH)D] versus those with insufficient levels [4]. A meta-analysis demonstrated a significant association between high plasma 25(OH)D levels and reduction in pancreatic cancer mortality [5]. In this analysis, we examined potential correlations between plasma 25(OH)D levels and overall survival (OS) outcomes in patients from the MPACT trial to test the hypothesis that plasma 25(OH)D sufficiency may be a marker of survival advantage in patients with metastatic pancreatic cancer.

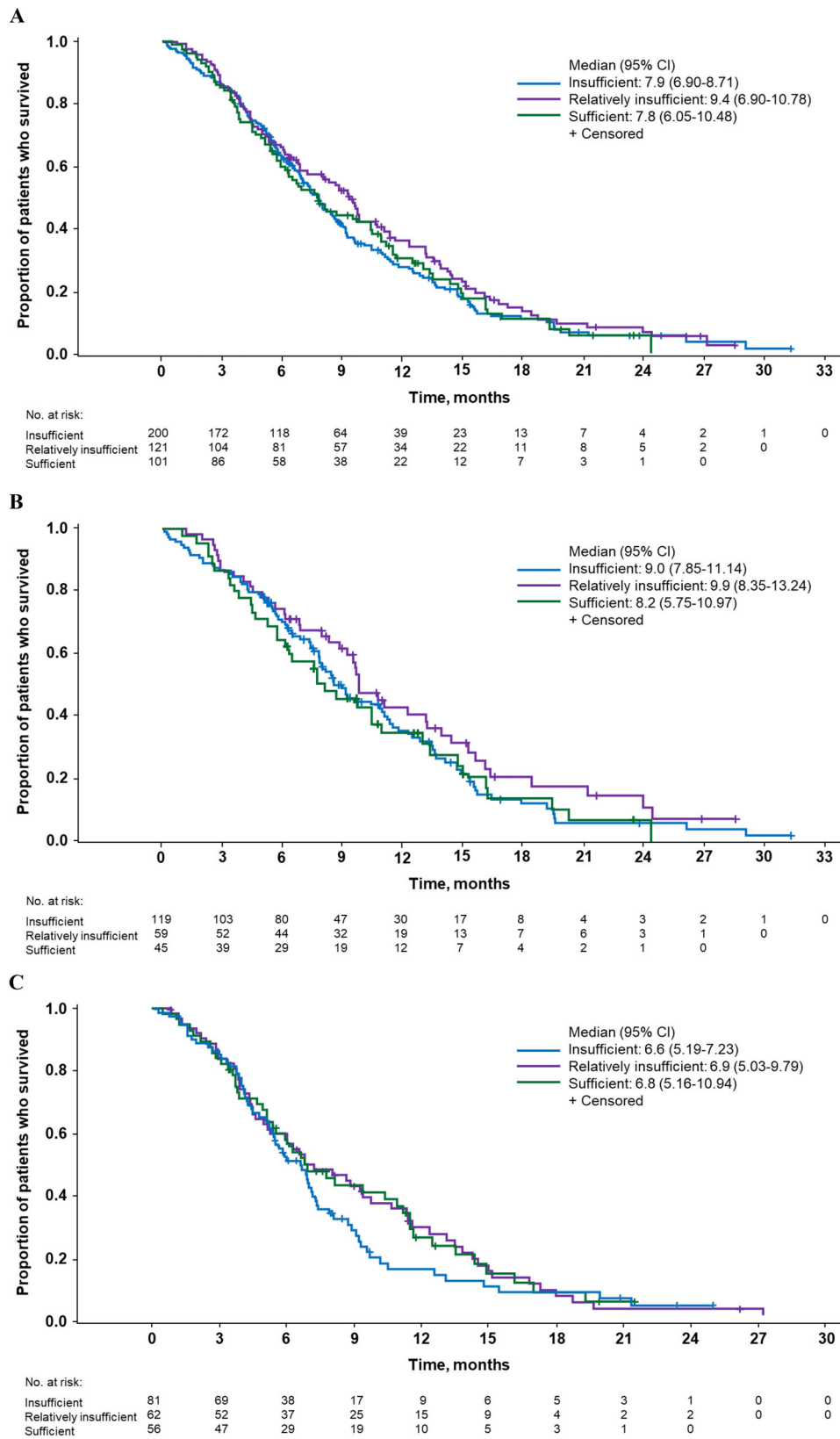
## MATERIALS AND METHODS

### Study Oversight

The MPACT trial was conducted in accordance with the International Council on Harmonisation E6 requirements for Good

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**Figure 1.** Kaplan-Meier curves for overall survival in **(A)** all patients, **(B)** patients treated with *nab*-paclitaxel plus gemcitabine, and **(C)** patients treated with gemcitabine alone (intent-to-treat population). Abbreviation: CI, confidence interval.

Clinical Practice and with the ethical principles of the Declaration of Helsinki. The independent ethics committee at each

participating institution approved the study. Written informed consent was provided by all patients before study initiation.

**Table 1.** Patient demographics and baseline clinical characteristics for all patients and by treatment arm (intent-to-treat population)

Characteristic	All patients						nab-Paclitaxel + gemcitabine			Gemcitabine		
	25(OH)D level						Relatively insufficient (20 to <30 ng/mL)			Relatively insufficient (20 to <30 ng/mL)		
	Insufficient (<20 ng/mL), (n = 200)	Relatively insufficient (20 to <30 ng/mL), (n = 121)	Sufficient (≥30 ng/mL), (n = 101)	Total (n = 422)	Insufficient (<20 ng/mL) (n = 119)	Relatively insufficient (20 to <30 ng/mL) (n = 59)	Sufficient (≥30 ng/mL) (n = 45)	Total (n = 223)	Insufficient (<20 ng/mL) (n = 81)	Relatively insufficient (20 to <30 ng/mL) (n = 62)	Sufficient (≥30 ng/mL) (n = 56)	Total (n = 199)
25(OH)D, median (range), ng/mL	13 (6–19)	24 (20–29)	35 (30–74)	21 (6–74)	12 (6–19)	25 (20–29)	35 (30–51)	19 (6–51)	14 (6–19)	24 (20–29)	35 (30–74)	23 (6–74)
Age				63 (27–86)								
Median (range), yr	61 (32–82)	64 (27–82)	66 (37–86)	242 (57)	59 (34–81)	63 (27–82)	63 (37–83)	61 (27–83)	63 (32–82)	66 (42–80)	66 (42–86)	64 (32–86)
<65 yr, n (%)	131 (66)	62 (51)	49 (49)	180 (43)	82 (69)	34 (58)	24 (53)	140 (63)	49 (61)	28 (45)	25 (45)	102 (51)
≥65 yr, n (%)	69 (35)	59 (49)	52 (52)		37 (31)	25 (42)	21 (47)	83 (37)	32 (40)	34 (55)	31 (55)	97 (49)
Sex, n (%)												
Female	85 (43)	46 (38)	51 (51)	182 (43)	54 (45)	25 (42)	26 (58)	105 (47)	31 (38)	21 (34)	25 (45)	77 (39)
Male	115 (58)	75 (62)	50 (50)	240 (57)	65 (55)	34 (58)	19 (42)	118 (53)	50 (62)	41 (66)	31 (55)	122 (61)
BMI category, n (%)												
<25.0 kg/m <sup>2</sup>	103 (52)	55 (46)	52 (52)	210 (50)	67 (56)	26 (44)	22 (49)	115 (52)	36 (44)	29 (47)	30 (54)	95 (48)
25.0–29.9 kg/m <sup>2</sup>	60 (30)	51 (42)	29 (29)	140 (33)	28 (24)	24 (41)	14 (31)	66 (30)	32 (40)	27 (44)	15 (27)	74 (37)
≥30.0 kg/m <sup>2</sup>	37 (19)	15 (12)	20 (20)	72 (17)	24 (20)	9 (15)	9 (20)	42 (19)	13 (16)	6 (10)	11 (20)	30 (15)
Geographic region, n (%)												
Australia	27 (14)	20 (17)	14 (14)	61 (15)	17 (14)	10 (17)	5 (11)	32 (14)	10 (12)	10 (16)	9 (16)	29 (15)
Eastern Europe	54 (27)	15 (12)	6 (6)	75 (18)	33 (28)	4 (7)	3 (7)	40 (18)	21 (26)	11 (18)	3 (5)	35 (18)
Western Europe	30 (15)	10 (8)	3 (3)	43 (10)	19 (16)	4 (7)	1 (2)	24 (11)	11 (14)	6 (10)	2 (4)	19 (10)
North America	89 (45)	76 (63)	78 (78)	243 (58)	50 (42)	41 (70)	36 (80)	127 (57)	39 (48)	35 (57)	42 (75)	116 (58)
KPS, n (%)												
90–100	118 (59)	78 (65)	60 (59)	256 (61)	68 (57)	38 (64)	26 (58)	132 (59)	50 (62)	40 (65)	34 (61)	124 (62)
70–80	82 (41)	43 (36)	40 (40)	165 (39)	51 (43)	21 (36)	18 (40)	90 (40)	31 (38)	22 (36)	22 (39)	75 (38)
<70	0	0	1 (1)	1 (<1)	0	0	1 (2)	1 (<1)	0	0	0	0
Primary pancreatic cancer location, n (%)												
Head	102 (51)	52 (43)	40 (40)	194 (46)	61 (51)	23 (39)	20 (44)	104 (47)	41 (51)	29 (47)	20 (36)	90 (45)
Other	98 (49)	69 (57)	61 (60)	228 (54)	58 (49)	36 (61)	25 (56)	119 (53)	40 (49)	33 (53)	36 (64)	109 (55)
Site of metastatic disease, n (%)												
Hepatic/liver	169 (85)	101 (84)	86 (85)	356 (84)	102 (86)	51 (86)	36 (80)	189 (85)	67 (83)	50 (81)	50 (89)	167 (84)
Lung/thoracic	82 (41)	52 (43)	38 (38)	172 (41)	43 (36)	22 (37)	20 (44)	85 (38)	39 (48)	30 (48)	18 (32)	87 (44)
Abdomen/peritoneum	175 (88)	104 (86)	93 (92)	372 (88)	100 (84)	48 (81)	42 (93)	190 (85)	75 (93)	56 (90)	51 (91)	182 (92)

(continued)

**Table 1. (continued)**

Characteristic	All patients											
	25(OH)D level				nab-Paclitaxel + gemcitabine				Gemcitabine			
	Insufficient (<20 ng/mL), (n = 200)	Sufficient (≥30 ng/mL), (n = 101)	Total (n = 422)	Relatively insufficient (20 to <30 ng/mL), (n = 121)	Insufficient (<20 ng/mL), (n = 119)	Relatively insufficient (20 to <30 ng/mL), (n = 59)	Sufficient (≥30 ng/mL), (n = 45)	Total (n = 223)	Insufficient (<20 ng/mL), (n = 81)	Relatively insufficient (20 to <30 ng/mL), (n = 62)	Sufficient (≥30 ng/mL), (n = 56)	Total (n = 199)
Disease stage at diagnosis, n												
I–III	30 (15)	17 (14)	57 (14)	10 (17)	23 (19)	10 (17)	4 (9)	37 (17)	7 (9)	7 (11)	6 (11)	20 (10)
IV	156 (78)	101 (84)	340 (81)	48 (81)	91 (77)	48 (81)	37 (82)	176 (79)	65 (80)	53 (86)	46 (82)	164 (82)
Unknown	14 (7)	3 (3)	25 (6)	1 (2)	5 (4)	1 (2)	4 (9)	10 (5)	9 (11)	2 (3)	4 (7)	15 (8)
No. of metastatic sites, n (%)												
1	14 (7)	8 (7)	24 (6)	4 (7)	10 (8)	4 (7)	2 (4)	16 (7)	4 (5)	4 (7)	0	8 (4)
2	91 (46)	53 (44)	200 (47)	27 (46)	59 (50)	27 (46)	20 (44)	106 (48)	32 (40)	26 (42)	36 (64)	94 (47)
3	68 (34)	44 (36)	141 (33)	21 (36)	35 (30)	21 (36)	15 (33)	71 (32)	33 (41)	23 (37)	14 (25)	70 (35)
>3	27 (14)	16 (13)	57 (14)	7 (12)	15 (13)	7 (12)	8 (18)	30 (14)	12 (15)	9 (15)	6 (11)	27 (14)
CA19-9 level, n (%)												
Normal	34 (17)	17 (14)	61 (15)	8 (14)	22 (19)	8 (14)	5 (11)	35 (16)	12 (15)	9 (15)	5 (9)	26 (13)
ULN to <59 × ULN	60 (30)	32 (26)	119 (28)	15 (25)	34 (29)	15 (25)	15 (33)	64 (29)	26 (32)	17 (27)	12 (21)	55 (28)
≥ 59 × ULN	90 (45)	56 (46)	201 (48)	26 (44)	50 (42)	26 (44)	22 (49)	98 (44)	40 (49)	30 (48)	33 (59)	103 (52)
CA19-9												
n	184	105	381	49	106	49	42	197	78	56	50	184
Median (range), U/mL	1,842 (0.3–1,161,996)	2,216 (3.3–973,209)	2,392 (0.3–2,564,235)	2,176 (4.4–671,110)	1,755 (2.9–1,161,996)	2,176 (4.4–671,110)	3,746 (4.2–2,564,235)	1,924 (2.9–2,564,235)	2,599 (0.3–1,138,680)	2,564 (3.3–973,209)	5,408 (2.6–597,568)	3,508 (0.3–1,138,680)
Previous therapy, n (%)												
Whipple procedure	18 (9)	12 (10)	33 (8)	6 (10)	14 (12)	6 (10)	2 (4)	22 (10)	4 (5)	6 (10)	1 (2)	11 (6)
Biliary stent	33 (17)	26 (22)	76 (18)	14 (24)	18 (15)	14 (24)	11 (24)	43 (19)	15 (19)	12 (19)	6 (11)	33 (17)
Serum albumin												
n	199	121	421	59	118	59	45	222	81	62	56	199
Median (range), g/dL	4.2 (2.7–5.3)	4.2 (3.1–5.0)	4.3 (3.3–5.1)	4.2 (2.7–5.0)	4.2 (2.7–5.0)	4.2 (3.1–5.0)	4.2 (3.6–5.1)	4.2 (2.7–5.1)	4.2 (3.2–5.3)	4.1 (3.1–4.8)	4.3 (3.3–4.9)	4.2 (3.1–5.3)

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; BMI, body mass index; CA19-9, carbohydrate antigen 19-9; KPS, Karnofsky performance status; ULN, upper limit of normal.

## Patients and Treatments

Patients included in this post hoc exploratory analysis were enrolled in the international, multicenter, open-label, randomized, phase III MPACT trial (NCT00844649); eligibility criteria have been published previously [6]. Patients were randomly assigned 1:1 to receive *nab*-paclitaxel 125 mg/m<sup>2</sup> plus gemcitabine 1,000 mg/m<sup>2</sup> on days 1, 8, 15, 29, 36, and 43 of an 8-week cycle or gemcitabine 1,000 mg/m<sup>2</sup> alone (weekly for 7 of 8 weeks) for cycle 1; in subsequent cycles, all patients were treated on days 1, 8, and 15 every 4 weeks. Treatment continued until disease progression or unacceptable adverse events.

## Statistical Analysis

Median OS was estimated using the Kaplan-Meier method, and the associated hazard ratios (HRs) and two-sided 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model. The *p* values were based on a log-rank test. Patients were subdivided into three groups based on plasma 25(OH)D levels: sufficient ( $\geq 30$  ng/mL), relatively insufficient ( $20 < 30$  ng/mL), or insufficient ( $< 20$  ng/mL) [7]. Plasma 25(OH)D levels were determined at various time points (pretreatment and post-treatment) throughout the trial. Levels of 25(OH)D<sub>2</sub> and 25(OH)D<sub>3</sub> were quantified by liquid chromatography–tandem mass spectrometry using multiple reaction monitoring and reported individually and as a sum with a clinical reference range attached to the sum.

## RESULTS

### Demographics

Of the 861 patients randomized in the MPACT trial, 422 had adequate-to-measure plasma 25(OH)D levels (supplemental online Fig. 1). Demographic and baseline clinical characteristics between the two treatment groups were generally balanced (Table 1).

### Survival Outcomes

In the all-patients group, the median OS was 7.9, 9.4, and 7.8 months in patients with insufficient, relatively insufficient, and sufficient 25(OH)D levels, respectively (Fig. 1A). Compared with patients with insufficient plasma 25(OH)D levels, no statistically significant differences in OS were observed in patients with relatively insufficient (HR, 0.85; 95% CI, 0.66–1.10; *p* = .227) or sufficient (HR, 0.99; 95% CI, 0.76–1.29; *p* = .740) levels. No significant OS difference was observed among patients with sufficient versus relatively insufficient 25(OH)D levels (HR, 1.17; 95% CI, 0.87–1.57; *p* = .301).

In the *nab*-paclitaxel plus gemcitabine group, median OS in patients with insufficient, relatively insufficient, and sufficient plasma 25(OH)D levels was 9.0, 9.9, and 8.2 months, respectively; no statistically significant difference was noted by comparing any cohorts (Fig. 1B).

In the gemcitabine group, median OS in patients with insufficient, relatively insufficient, and sufficient plasma 25(OH)D levels was 6.6, 6.9, and 6.8 months, respectively; no statistically significant difference was noted by comparing any cohorts (Fig. 1C).

## DISCUSSION

In this analysis of the MPACT trial, we found no statistically significant differences in median OS based on degree of plasma 25(OH)D sufficiency. The MPACT trial was not designed to compare survival outcomes based on levels of plasma 25(OH)D. As such, plasma 25(OH)D levels were quantified at varying time points throughout the trial, and measurable samples were available for only 49% of the randomized patients from the MPACT trial. The relatively low number of patients with measurable plasma 25(OH)D levels was a limitation. However, despite a low availability of measurable plasma 25(OH)D levels, the availability was generally balanced between treatment arms. In addition, subgroup analyses by ethnicity were not conducted because the vast majority (87%) of patients in the MPACT trial were White. [6].

Although cross-study comparisons are problematic and the underlying reasons for divergent outcomes with prior studies of different design are indiscernible,  $< 50\%$  of patients [41%–47% across plasma 25(OH)D cohorts] in the aforementioned five-cohort U.S. study had metastatic disease [4], far lower than the  $> 99\%$  of patients in our study. Additionally, although the meta-analysis by Zhang et al. showed a significant reduction in pancreatic cancer mortality for patients with high versus low plasma 25(OH)D levels, a subgroup analysis of patients with locally advanced or metastatic disease demonstrated a trend in favor of high plasma 25(OH)D levels, but did not reach statistical significance [5]. Thus, it is possible that stage of disease could be a contributing factor to associations between plasma 25(OH)D levels and survival.

## CONCLUSION

Overall, our results call into question the role, if any, of plasma 25(OH)D as a biomarker in pancreatic cancer. However, prospective investigation of vitamin D in pancreatic cancer may be warranted. Recent data suggest that vitamin D or its analogs may act as therapeutic tools in pancreatic cancer treatment. The vitamin D receptor (VDR) has been reported to be involved in modulating immune responses, and VDR agonists are currently under investigation in combination with immune checkpoint inhibitors. It has been hypothesized that VDR agonists may facilitate delivery of chemotherapeutic agents to pancreatic tumors, enhance immune checkpoint inhibition and reduce immune-related adverse events [8, 9]. Additionally, a phase II clinical trial is currently investigating paricalcitol, a vitamin D<sub>2</sub> analog, combined with pembrolizumab for maintenance therapy in patients with metastatic pancreatic cancer [10]. Results from these studies should facilitate a deeper understanding of the role of vitamin D in pancreatic cancer tumor biology.

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#### DISCLOSURES

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