A Phase 3 Study to Evaluate the Efficacy and Safety of Docetaxel and Prednisone (DP) With or Without Lenalidomide in Patients With Castrate-resistant Prostate Cancer (CRPC): The MAINSAIL Trial

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VIENNA 2012 ESMO congress

www.esmo2012.org

Disclosure Slide

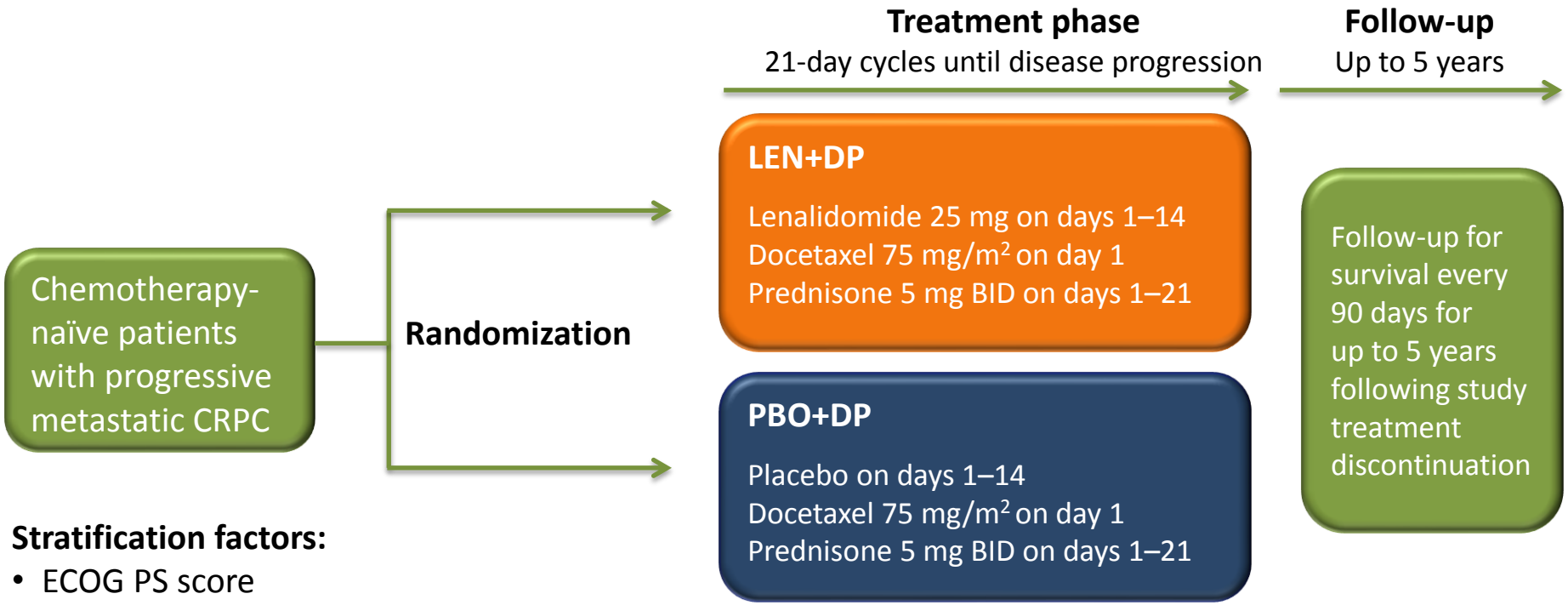
- Celgene Corporation – Research Funding and Advisory Board Member
- Sanofi-Aventis – Research Funding and Advisory Board Member

Introduction

- Lenalidomide is both antiangiogenic and a potent immunomodulator[1]
- Lenalidomide demonstrated activity and tolerability as a single agent and in combination with DP in phase 1/2 trials in CRPC[2–4]
- This phase 3, multicenter, randomized, double-blind, placebo (PBO)-controlled study evaluated the efficacy and safety of lenalidomide versus PBO in combination with DP as first-line treatment for metastatic CRPC

1. Dredge K, et al. Br J Cancer. 2002;10:1166-72.
2. Tohnya TM, et al. J Clin Oncol. 2006;24:13038.
3.Garcia JA, et al. J Clin Oncol. 2008;26:5143.
4. Petrylak DP, et al. J Clin Oncol. 2009;27:5156.

Study Design



Stratification factors:

- ECOG PS score
- Geographic region
- Type of disease progression (rising PSA versus tumor progression)

Endpoints:

- Primary: overall survival (OS)
- Secondary: progression-free survival (PFS); objective response rate; safety

DP, docetaxel + placebo; LEN, lenalidomide; PBO, placebo; BID, twice daily; ECOG, Eastern Cooperative Oncology Group; PS, performance status; PSA, prostate-specific antigen.

Methods

- Eligibility
  - Chemotherapy-naive patients with progressive metastatic CRPC
    - Non-taxane based adjuvant/neoadjuvant treatment completed > 3 years prior randomization
  - Effective castration defined as serum testosterone levels < 50 ng/dL
  - ECOG PS score ≤ 2
  - Patients without prior orchiectomy continued treatment with LHRH agonists
    - Concurrent anti-androgen therapy not allowed, unless washout period compromised patient health and safety
  - Hemoglobin > 9 g/dL, absolute neutrophil count > 1.5 x 10^9 cells/L, platelet count > 100 x 10^9 cells/L, creatinine clearance > 50 mL/min, total bilirubin < 1.0 x ULN, serum AST and ALT < 1.5 x ULN, ALP < 2.5 x ULN
- Statistical analysis
  - OS and PFS were analyzed by Kaplan–Meier method and log-rank test

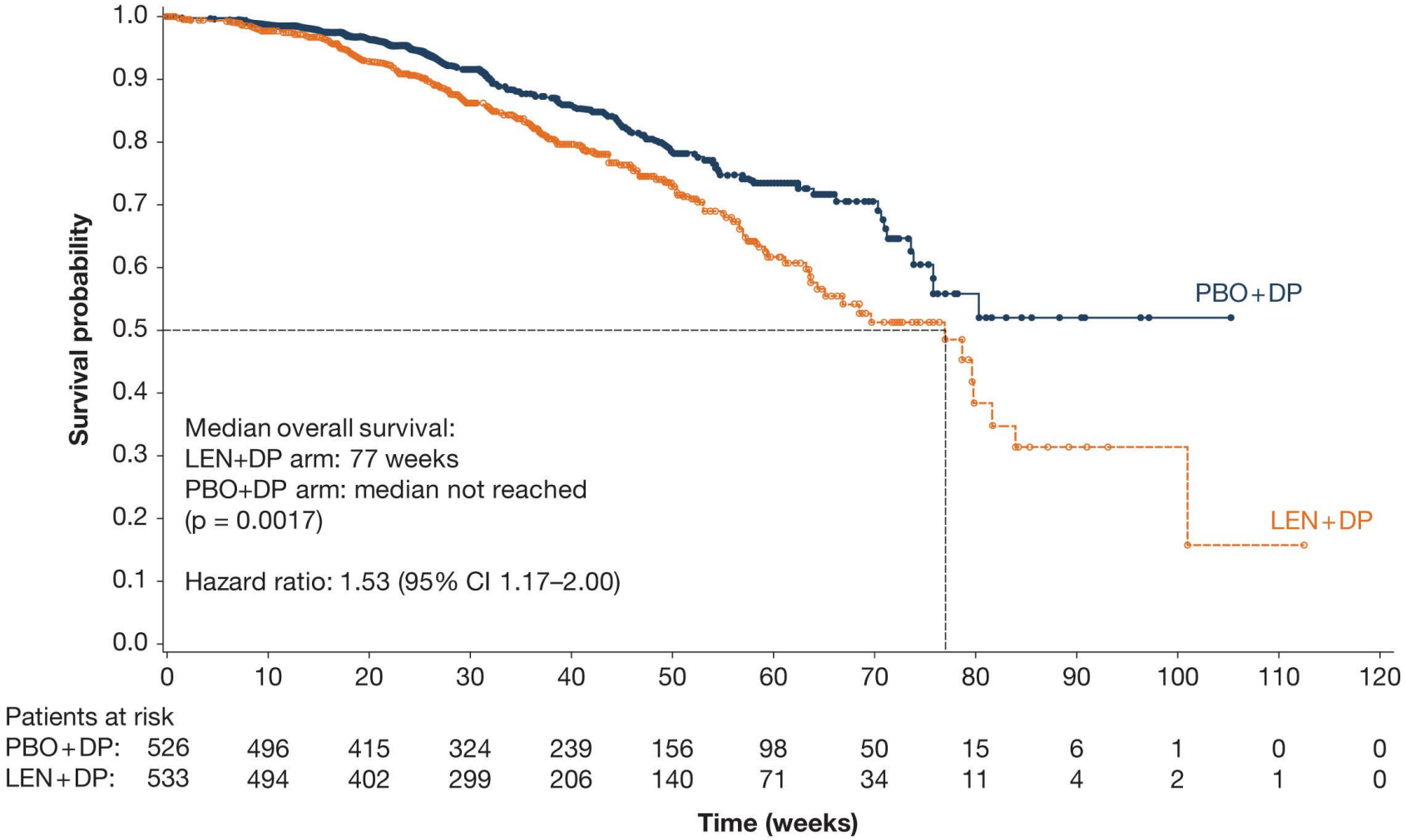
ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate amino transaminase; LHRH, luteinizing hormone-releasing hormone; ULN, upper limit of normal.

Baseline Characteristics

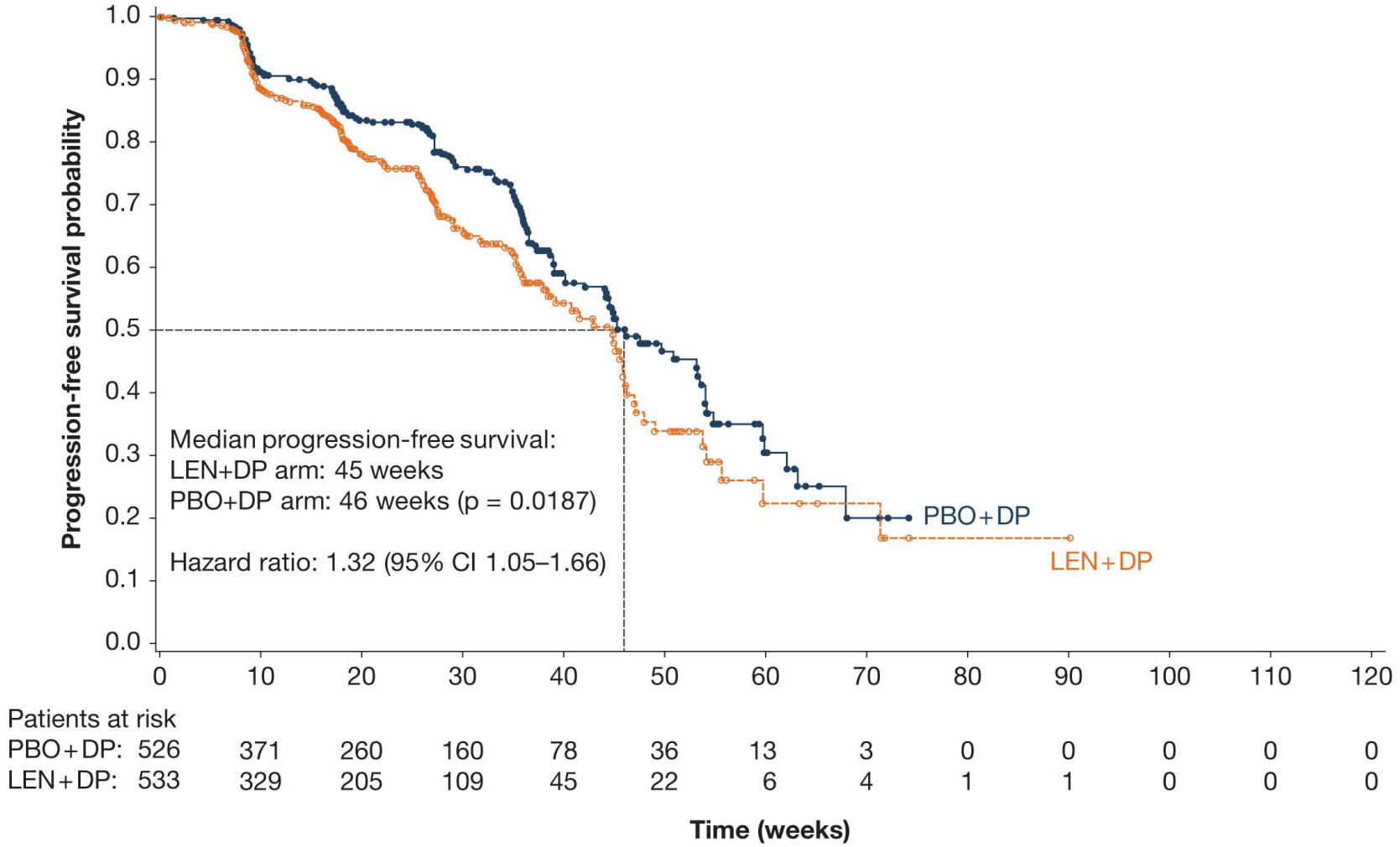
	LEN+DP (N = 533)	PBO+DP (N = 526)
Median age, years (range)	69.6 (43–89)	68.6 (47–90)
Region, n (%)		
USA or Canada	140 (26.3)	136 (25.9)
EU or Australia	330 (61.9)	329 (62.5)
Rest of world (ROW)	63 (11.8)	61 (11.6)
ECOG PS score, n (%)		
0	252 (47.3)	257 (48.9)
≥ 1	280 (52.5)	269 (51.1)
Not specified	1 (0.2)	-
Type of disease progression		
Rising PSA only	159 (29.8)	146 (27.8)
Radiographic progression	374 (70.2)	380 (72.2)
Metastatic sites		
Bone	169 (31.7)	157 (29.8)
Soft tissues	104 (19.5)	94 (17.9)
Both bone and soft tissues	259 (48.6)	273 (51.9)
None	1 (0.2)	2 (0.4)
Median PSA, ng/mL (range)	105.0 (0.10–10,759)	84.9 (0.01–6,807)

ROW = all other participating countries, i.e. South Africa, Russia, Israel and Mexico.

Efficacy Results: Overall Survival



Efficacy Results: Progression-free Survival



Efficacy Results: Response Rates

n (%)	**LEN+DP** (N = 533)	**PBO+DP** (N = 526)	**p value**
Confirmed PSA response			
50% decline from baseline	313 (58.7)	305 (58.0)	
30% decline from baseline	358 (67.2)	353 (67.1)	
Best response			
Complete response	5 (0.9)	8 (1.5)	
Partial response	113 (21.2)	120 (22.8)	
Stable disease	287 (53.8)	314 (59.7)	
Progressive disease	47 (8.8)	31 (5.9)	
Not evaluable	81 (15.2)	53 (10.1)	
Objective response rate	118 (22.1)	128 (24.3)	0.3975

Treatment Exposure

	LEN+DP (n = 525)	**PBO+DP** (n = 521)
Median number of cycles (range)	6 (1–30)	8 (1–30)
Dose reductions, n (%)		
LEN/PBO	78 (14.9)	41 (7.9)
Docetaxel	109 (20.8)	81 (15.5)
Median relative dose intensity, % (range)		
LEN/PBO	93.4 (17–105)	96.9 (14–103)
Docetaxel	94.4 (50–105)	95.6 (49–109)
Median cumulative dose, (range)		
LEN/PBO, mg	1,825 (25–10,125)	2,450 (50–10,325)
Docetaxel, mg/m^2	442.3 (59–1,635)	550.7 (65–2,190)

- All dose reductions were due to adverse events, except for 2 dose reductions of docetaxel due to other reasons*

* Clinical decision in view of medical history of ongoing thrombocytopenia and investigator decision not specifically related to a particular adverse event

Safety Results: Adverse Events

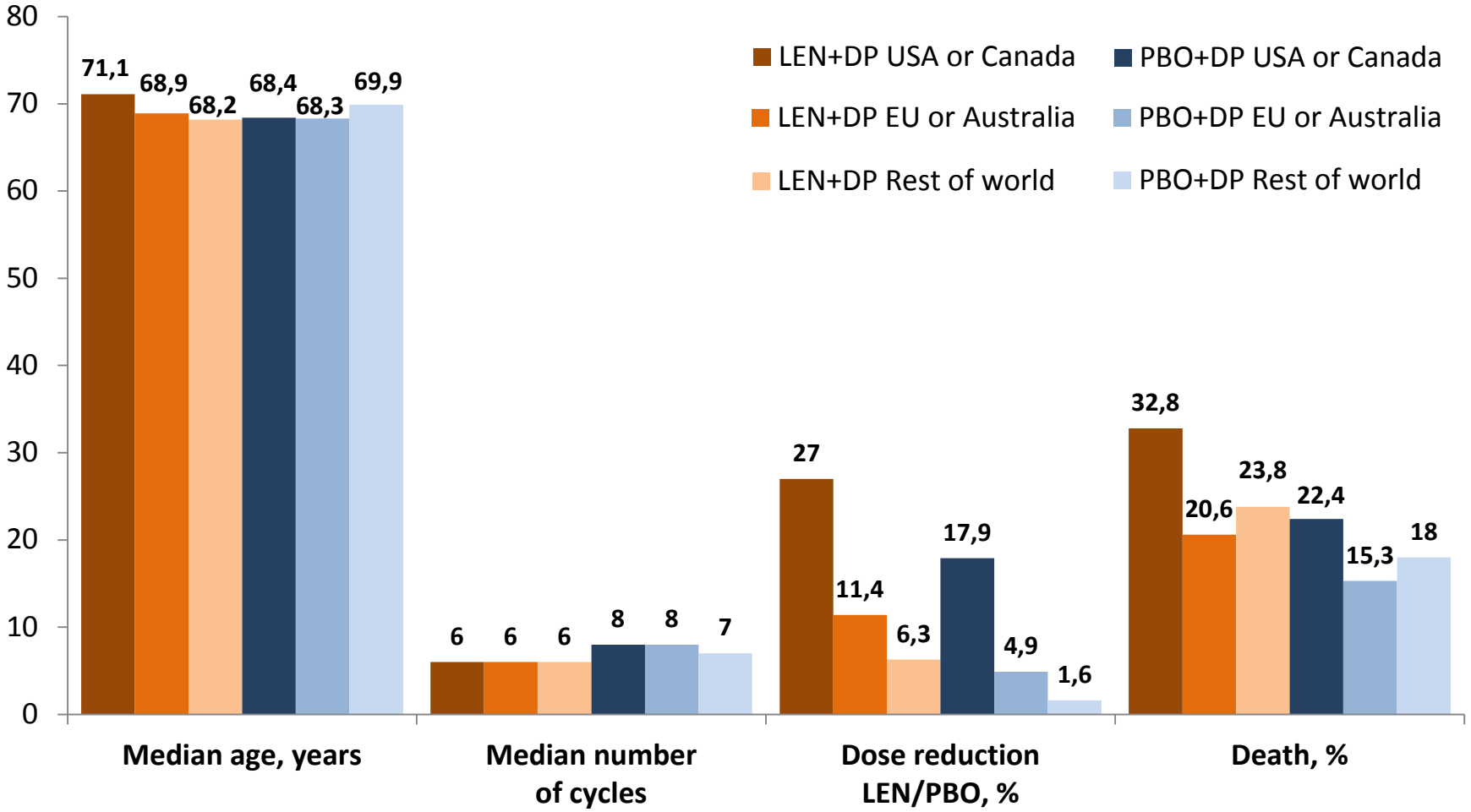
Main grade ≥ 3 TEAEs, n (%)	**LEN+DP** (n = 525)	**PBO+DP** (n = 521)	**p value**
Hematologic			
Neutropenia	114 (21.7)	85 (16.3)	0.027511
Febrile neutropenia	62 (11.8)	24 (4.6)	0.000024
Anemia	33 (6.3)	27 (5.2)	0.506653
Leukopenia	24 (4.6)	18 (3.5)	0.431494
Nonhematologic			
Fatigue	43 (8.2)	32 (6.1)	0.230824
Diarrhea	37 (7.0)	12 (2.3)	0.000346
Asthenia	29 (5.5)	17 (3.3)	0.096313
Pulmonary embolism	34 (6.5)	8 (1.5)	0.000050
Dyspnea	22 (4.2)	9 (1.7)	0.027146
Pneumonia	24 (4.6)	6 (1.2)	0.001228

TEAEs, treatment-emergent adverse events.

Deaths

n (%)	**LEN+DP** (n = 525)	**PBO+DP** (n = 521)	**p value**
Deaths during treatment or ≤ 28 days from last LEN/PBO dose	18 (3.4)	13 (2.5)	0.467
Death from malignant disease	5 (1.0)	2 (0.4)	
Death due to toxicity	2 (0.4)	1 (0.2)	
Death due to other cause	11 (2.1)	10 (1.9)	
Deaths > 28 days from last LEN/PBO dose	109 (20.8)	78 (15.0)	0.016
Death from malignant disease	94 (17.9)	72 (13.8)	

Regional Differences



Conclusions

- The addition of lenalidomide to DP in patients with CRPC did not improve overall survival
  - May be attributed to shorter treatment duration, lower dose intensity of docetaxel, and earlier treatment discontinuation
  - The three-drug regimen was associated with greater toxicity than a two-drug regimen in this patient population
- Pharmacokinetic interactions could not be ruled out
- Further analysis of the data is underway to help elucidate the observed results in the lenalidomide arm

The authors would like to thank all study sites and the patients who participated in this study