A Phase 1b Study of Durvalumab (MEDI4736) Alone or in Combination With Pomalidomide With or Without Low-Dose Dexamethasone in Patients With Relapsed and Refractory Multiple Myeloma

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INTRODUCTION

Despite the availability of newer therapeutic options, outcomes for patients (pts) with multiple myeloma (MM) that is relapsed and/or refractory to current treatments (Tx) are poor.1

- Tx that activate the pt’s immune response may potentially address this unmet need.2
- Pomalidomide (POM), a distinct immunomodulatory agent with tumoricidal and immunoregulatory effects,3 plus low-dose dexamethasone (LoDEX), is approved in the United States and European Union (EU) for the Tx of pts with relapsed/refractory MM (RRMM) who have had ≥ 2 prior Tx, including lenalidomide (LEN) and a proteasome inhibitor (bortezomib in the EU)4,5

- MM cells express programmed cell death ligand 1 (PD-L1), an immune checkpoint receptor ligand.6,7 Durvalumab (MEDI4736) is a selective, high-affinity human IgG1 monoclonal antibody (mAb) that blocks PD-L1 binding to programmed cell death protein 1 (PD-1; IC50 0.1 nM) and CD80 (B7.1; IC50 0.04 nM; Figure 1).8

METHODS

Study Design

- MEDI4736-MM-001 (NCT02616640) is a multicenter, international, open-label, phase 1b study
- Consists of a dose-finding phase and a parallel dose-expansion phase
- Dose-Finding Phase
- Eligible pts (up to n = 54) will be randomized into 1 of 3 dose-finding arms (Figure 2)
  - Arm A: durvalumab monotherapy
  - Arm B: durvalumab + POM
  - Arm C: durvalumab + POM + LoDEX
  - A rolling-6 design will be used.9
- Dose-Expansion Phase
- Pending data from the dose-finding phase of the study, an expansion phase can enroll up to n = 84 additional pts
- Pts randomized to durvalumab monotherapy (arm A) or durvalumab in combination with pomalidomide (arm B) who have progressive disease (PD) or lack of efficacy (stable disease [SD] for ≥ 4 cycles) can receive additional treatment with POM + LoDEX (arm A) or LoDEX (arm B) at the discretion of the investigator.
- Pts can remain on study treatment until PD, unacceptable toxicity, or withdrawal of consent
- End-of-treatment visit
- Assessment within 7 days of decision to discontinue study treatment
- Safety follow-up period
- Assessment 28 days after end-of-treatment visit
- Assessment 90 days after last dose of durvalumab

Key Inclusion Criteria
- Pts ≥ 18 years of age with documented MM
- Measurable disease by serum protein analysis (≥ 0.5 g/dL) or urine protein electrophoresis (≥ 200 mg/24 hours)
- Two or more prior regimens including LEN and a proteasome inhibitor (≥ 2 consecutive cycles of each)
- Bone marrow transplant with or without induction therapy is considered one regimen
- Response of ≥ SD for ≥ 1 cycle to at least 1 prior anti-myeloma therapy

Key Exclusion Criteria
- Prior treatment with immunotherapy (eg, other anti-CTLA-4, anti-PD-1, or anti-PD-L1 mAbs)
- Prior treatment with POM without a response ≥ SD
- Prior organ or oligoclonal stem cell transplant
- Laboratory values:
  - Creatinine clearance < 45 mL/min
  - Platelet count < 75,000/mL
  - Absolute neutrophil count < 1000/µL
  - Corrected serum calcium > 13.5 mg/dL
  - Hemoglobin < 8 g/dL
  - Serum bilirubin > 1.5 x upper limit of normal (ULN) > 3.0 mg/dL for patients with documented Gilbert syndrome
- Serum aspartate aminotransferase or alanine aminotransferase ≥ 2.5 x ULN
- Peripheral neuropathy grade ≥ 2

Dosing (28-Day Cycle)

- Durvalumab will be administered intravenously on day 1 (Figure 3)
- POM will be administered orally at 4 mg on days 1, 8, 15, and 22
- LoDEX will be administered orally at 40 mg (20 mg on days > 75 years of age) on days 1, 8, 15, and 22

OBJECTIVES

Primary Objective
- To determine the optimal dose and regimen of durvalumab as a monootherapy or in combination with POM ± LoDEX in pts with RRMM

Secondary Objectives
- To evaluate safety, preliminary efficacy (overall response rate, time to response, duration of response), and pharmacokinetics

Exploratory Objectives
- To conduct assessments, including evaluation of biomarkers and minimal residual disease

COMMENTS

This study will help determine whether combining durvalumab with LoDEX can enhance anti-myeloma effects by preventing PD-1/PD-L1–mediated immune quiescence in patients with RRMM

Pt enrollment to the MEDI4736-MM-001 study is ongoing

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ACKNOWLEDGEMENTS

The authors acknowledge the contributions of the investigators, sites, and patients involved in this study. Celgene Corporation provided financial support for this study. The authors received editorial assistance from William Ho, PhD, and Peter J. Simon, PhD and printing support from MedTech Media, sponsored by Celgene Corporation.

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DISCLOSURES

D.S. reports honoraria, consulting/advisory, speakers bureau, travel accommodations and expenses for Celgene, Takeda, Amgen, BMS, Novartis, Merck, Janssen, and stock ownership in COTA. N.V.d.D. reports consulting or advisory role and research funding from Celgene, Janssen, Amgen, P.S. reports honoraria from Celgene, Janssen, Amgen, Karyopharm, and consulting or advisory role and research funding from Celgene, Janssen, Amgen, C.H. reports consulting or advisory role from InCyte for his institution and Sanofi for himself; research funding from Takeda, Celgene, ARNO, Karyopharm for his institution, and patrons, royalties, or other intellectual property from OSU Innovation Foundation for his institution; N.B. reports honoraria and consulting or advisory role from Celgene, Takeda, Johnson & Johnson, Amgen, research funding from Celgene, and expert testimony for Celgene and Johnson & Johnson; R.N. reports research support and PI consultancy from Celgene, Takeda, Amgen, Janssen, BMS, speakers bureau/scientific advisory board for Celgene, Millennium, Onyx/Amgen, Janssen, BMS, S.A.S., and J.W. reports employment with Celgene; L.S., T.P., and M.Z. report employment with and stock ownership in Celgene; J.S.M. reports consulting or advisory committee for Janssen, BMS, MSD, Millennium, Celgene, Novartis, Onyx.

Presented at the ASCO 2016 Annual Meeting, June 3-7, Chicago, Illinois