TPS8608

Twin Randomized Studies of Daratumumab (DARA) Plus Standard of Care (Lenalidomide/ Dexamethasone or Bortezomib/Dexamethasone [DRd or DVd]) Versus Rd or Vd Alone in Relapsed or Refractory Multiple Myeloma (MM): 54767414MMY3003 (Pollux) and 54767414MMY3004 (Castor)

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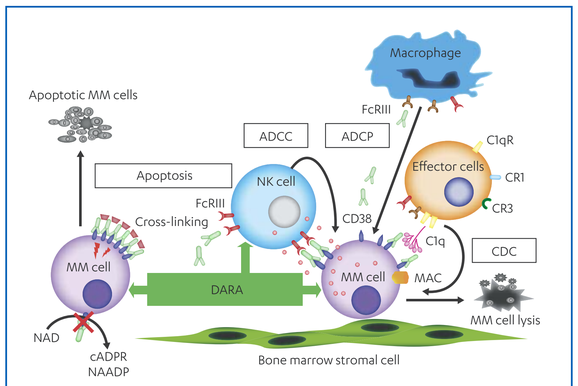
INTRODUCTION

- Although immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) prolong progression-free survival (PFS) and overall survival (OS) in patients with multiple myeloma (MM), the majority of patients will relapse[1]
  - Patients who relapse following IMiD and PI treatment or who are refractory to these agents have very poor prognoses,[2] and therapies that target novel pathways are needed
- CD38 is highly and ubiquitously expressed on the surface of myeloma cells,[3,4] but is expressed at low levels on normal myeloid, lymphoid, and non-hematopoietic cells,[5] making it a promising target for MM therapy
- Daratumumab (DARA) is a human anti-CD38 immunoglobulin G1 (IgG1) monoclonal antibody that binds CD38 with high affinity, inducing tumor cell death through multiple pathways that include complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, apoptosis, and direct enzymatic inhibition[6,7] (**Figure 1**)



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DARA, daratumumab; MM, multiple myeloma; ADCC, antibody-dependent cell-mediated toxicity; ADCP, antibody-dependent cell-mediated phagocytosis; NK, natural killer; CDC, complement-dependent cytotoxicity; MAC, membrane attack complex; NAD, nicotinamide adenine dinucleotide; cADPR, cyclic ADP-ribose; NAADP, nicotinic acid adenine dinucleotide phosphate.

Figure 1. DARA mechanism of action.

- An open-label, phase 1/2 study of DARA in combination with lenalidomide and dexamethasone demonstrated promising safety and efficacy in patients with relapsed or relapsed and refractory MM, with 15 of 20 patients achieving partial response (PR) or better[8]
- Two global, phase 3, randomized trials, Castor (54767414MMY3004; NCT02136134) and Pollux (54767414MMY3003; NCT02076009) are in progress to evaluate DARA in combination with bortezomib (Velcade®) plus dexamethasone (DVd) or lenalidomide (Revlimid®) plus dexamethasone (DRd), respectively, in patients with relapsed or refractory MM

OBJECTIVES

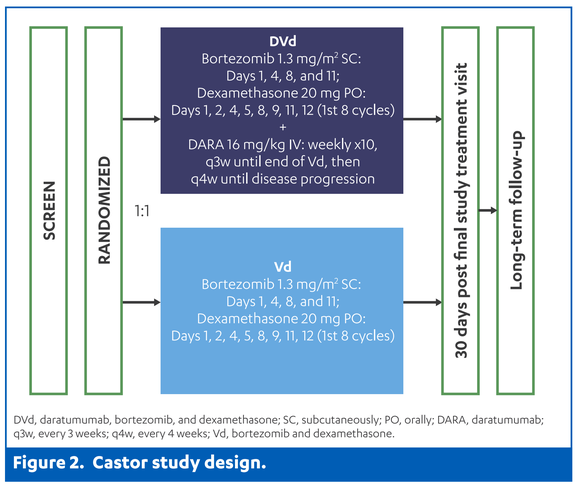
- Primary objectives
  - To compare PFS of patients with relapsed or refractory MM treated with DARA plus standard-of-care (DVd [Castor] or DRd [Pollux]) versus patients treated with standard-of-care alone (bortezomib plus dexamethasone [Vd; Castor] or lenalidomide plus dexamethasone [Rd; Pollux])
- Secondary objectives
  - To compare clinical outcomes of the 2 treatment groups in each study, including time to disease progression, overall response rate, OS, duration of response, and time to response
  - To evaluate the proportion of patients with very good partial response or better
  - To assess safety and tolerability of DARA when combined with standard-of-care treatments
  - To assess minimal residual disease (MRD) in patients with complete response (CR) or stringent CR (sCR)
- Exploratory objectives
  - To explore biomarkers predictive of response to DARA (both studies) and potential mechanisms of disease resistance (Castor)

KEY ELIGIBILITY CRITERIA

- Age ≥18 years
- Measurable documented MM, defined by presence of monoclonal plasma cells in the bone marrow ≥10% at some point during disease or a biopsy, confirming plasmacytoma
- At least 1 prior line of treatment and at least 1 PR or better with a prior treatment
- Disease progression following the last line of treatment
- ECOG performance status score of ≤2
- Absolute neutrophil count >1.0 × 10^9/L, hemoglobulin level >7.5 g/dL, and platelet count >75 × 10^9/L for patients for whom <50% of bone marrow nucleated cells are plasma cells (otherwise, platelet count >50 × 10^9/L)
- Creatinine clearance >20 mL/min/1.73 m^2 (Castor) or ≥30 mL/min/1.73 m^2 (Pollux)
- Adequate cardiopulmonary function
- Not intolerant of or refractory to bortezomib (Castor) or lenalidomide (Pollux)
- No previous anti-CD38 therapies, including DARA

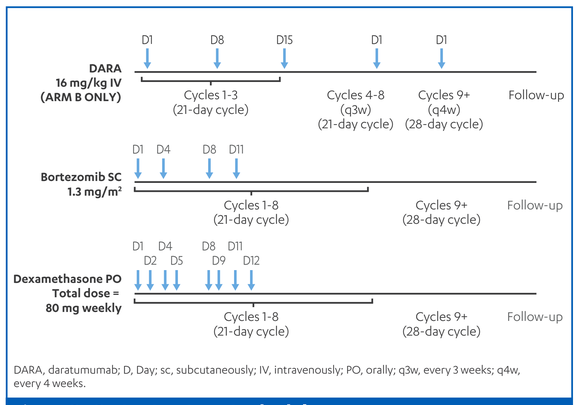
STUDY DESIGN: CASTOR

- Phase 3, randomized, open-label, active-controlled, multicenter study (**Figure 2**)
- Patients will be randomized 1:1 to receive DVd or Vd, and stratified by International Staging System (ISS), number of prior lines of therapy, and previous treatment with bortezomib
- A total of approximately 480 patients are expected to be enrolled
- As shown in **Figure 3**, patients will receive
  - Vd: bortezomib (1.3 mg/m^2, subcutaneously) plus dexamethasone (20 mg, orally) or
  - DVd: bortezomib and dexamethasone as above plus DARA (16 mg/kg, intravenously; IV)
- Patients will participate in the study until withdrawal of consent, lost to follow-up, death, or end of study



DVd, daratumumab, bortezomib, and dexamethasone; SC, subcutaneously; PO, orally; DARA, daratumumab; q3w, every 3 weeks; q4w, every 4 weeks; Vd, bortezomib and dexamethasone.

Figure 2. Castor study design.

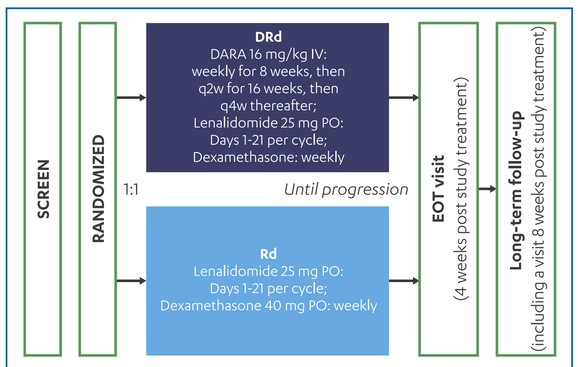


DARA, daratumumab; D, Day; sc, subcutaneously; IV, intravenously; PO, orally; q3w, every 3 weeks; q4w, every 4 weeks.

Figure 3. Castor treatment schedule.

STUDY DESIGN: POLLUX

- Phase 3, randomized, open-label, active-controlled, parallel-group, multicenter study (**Figure 4**)
- Patients will be randomized 1:1 to receive DRd or Rd, and stratified by ISS, number of prior lines of therapy, and previous treatment with lenalidomide
- A total of approximately 560 patients are expected to be enrolled
- As shown in **Figure 5**, patients will receive
  - Rd: lenalidomide (25 mg, orally) on Days 1 through 21; dexamethasone (40 mg) weekly, or
  - DRd: lenalidomide and dexamethasone, as above, plus DARA (16 mg/kg, IV) weekly for 8 weeks, every other week for 16 weeks, and monthly thereafter
- Patients will participate in the study until withdrawal of consent, lost to follow-up, death, or end of study; follow-up will continue until death



DRd, daratumumab, lenalidomide, and dexamethasone; DARA, daratumumab; q2w, every 2 weeks; q4w, every 4 weeks; Rd, lenalidomide and dexamethasone; EOT, end-of-treatment.

Figure 4. Pollux study design.

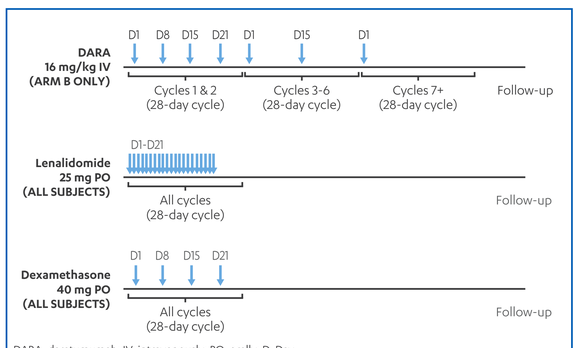


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Figure 5. Pollux treatment schedule.

VISIT SCHEDULE

- Treatment
  - Serum and urine tests will be performed:
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    - Every 28 days for the first 18 months, and every other month thereafter (Pollux)
  - Responses and disease progression will be assessed by IMWG response criteria in 2 consecutive assessments
  - Patients with CR or sCR will have a bone marrow biopsy and/or aspirate at CR/sCR and at Day 1 of Cycles 9 and 15 (Castor) or at 3 and 6 months after CR (Pollux), in patients maintaining CR, to evaluate MRD
  - The end of treatment visit will occur within 4 weeks after the final dose of study treatment is administered
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STUDY ENDPOINTS AND EVALUATIONS

Efficacy and Safety

- In both studies, the primary efficacy endpoint is PFS
- Two interim analyses will be performed; the first will evaluate safety and the second will evaluate safety and efficacy, with stopping boundaries defined for superiority and futility

Exploratory

- Sensitivity analyses will be performed based upon molecular markers
- Correlation of baseline expression of biomarkers, or changes in their expression with treatment, will be correlated with response or time-to-event data to identify responsive or resistant subgroups

CONCLUSIONS

- **Castor and Pollux are randomized, open-label, active-controlled, multicenter trials that evaluate the efficacy and safety of combining DARA with the standard-of-care regimens bortezomib plus dexamethasone or lenalidomide plus dexamethasone in patients with relapsed or refractory MM**
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REFERENCES

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ACKNOWLEDGMENTS

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These studies (ClinicalTrials.gov Identifiers: NCT02076009 and NCT02136134) are sponsored by Janssen Research & Development, LLC. Editorial and medical writing support, provided by Erica S. Chevalier-Larsen, PhD, of MedErgy, was funded by Janssen Global Services.

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POSTER PRESENTED AT THE ANNUAL MEETING OF THE AMERICAN SOCIETY FOR CLINICAL ONCOLOGY (ASCO); MAY 29-JUNE 2, 2015; CHICAGO, ILLINOIS.

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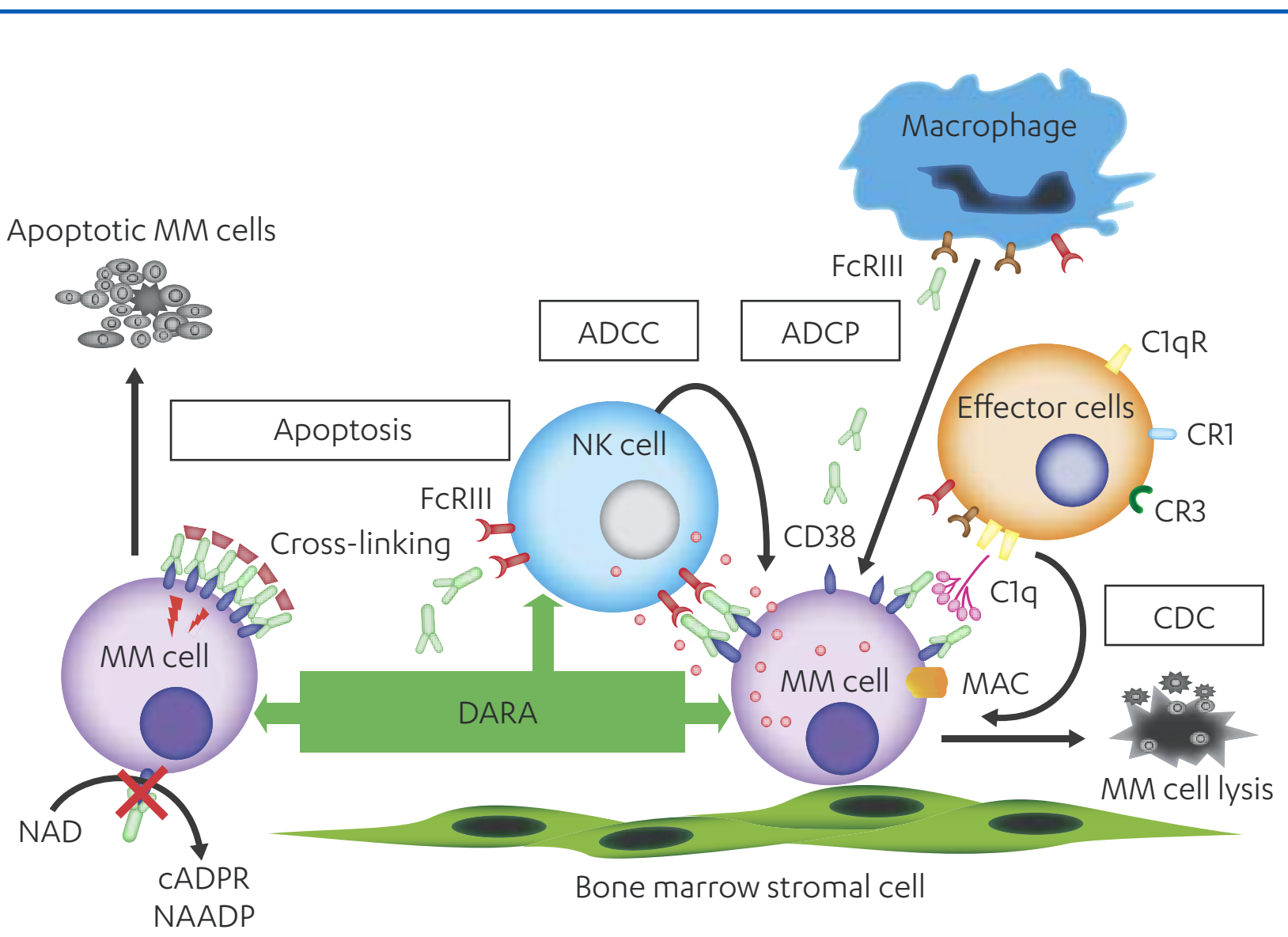

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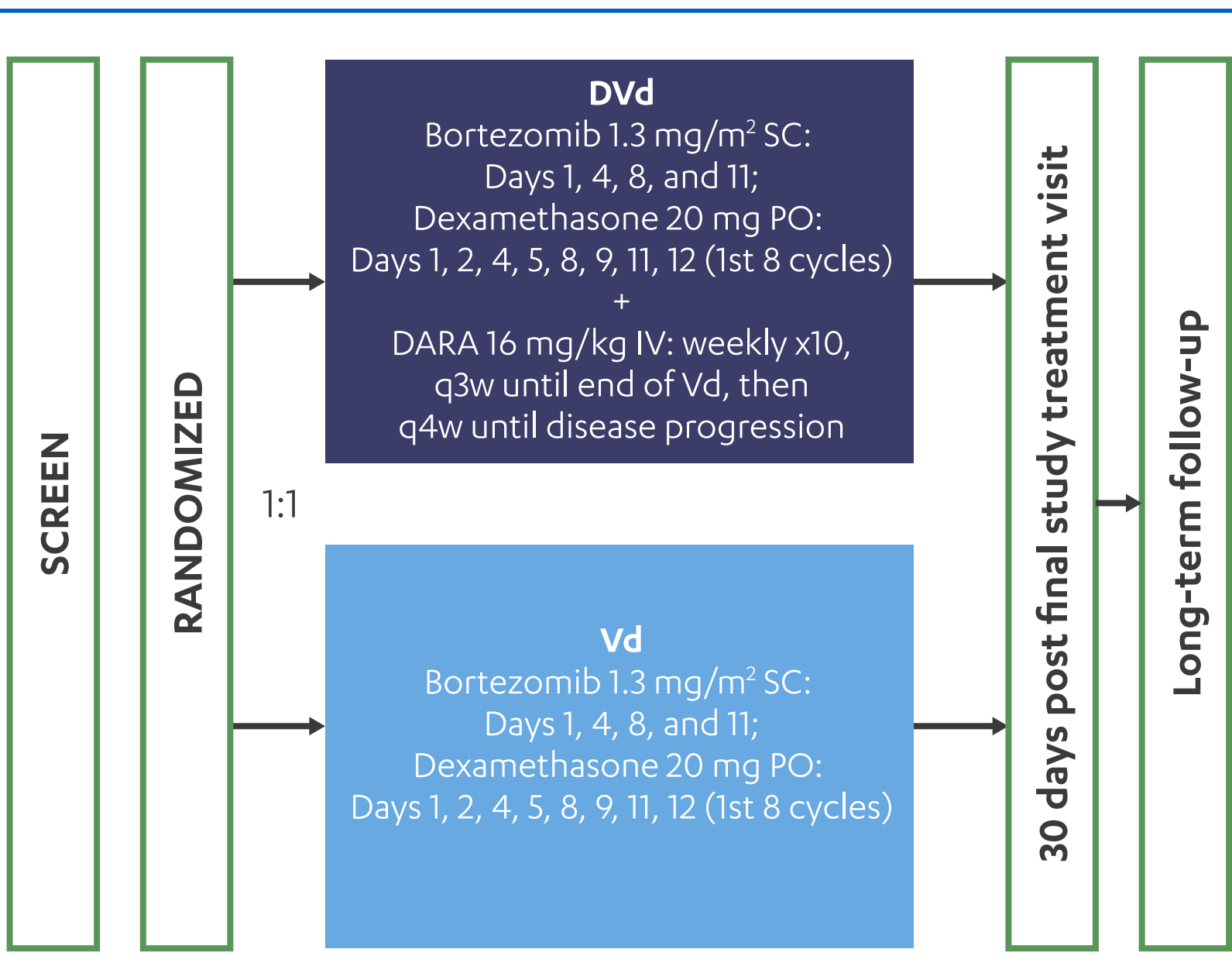

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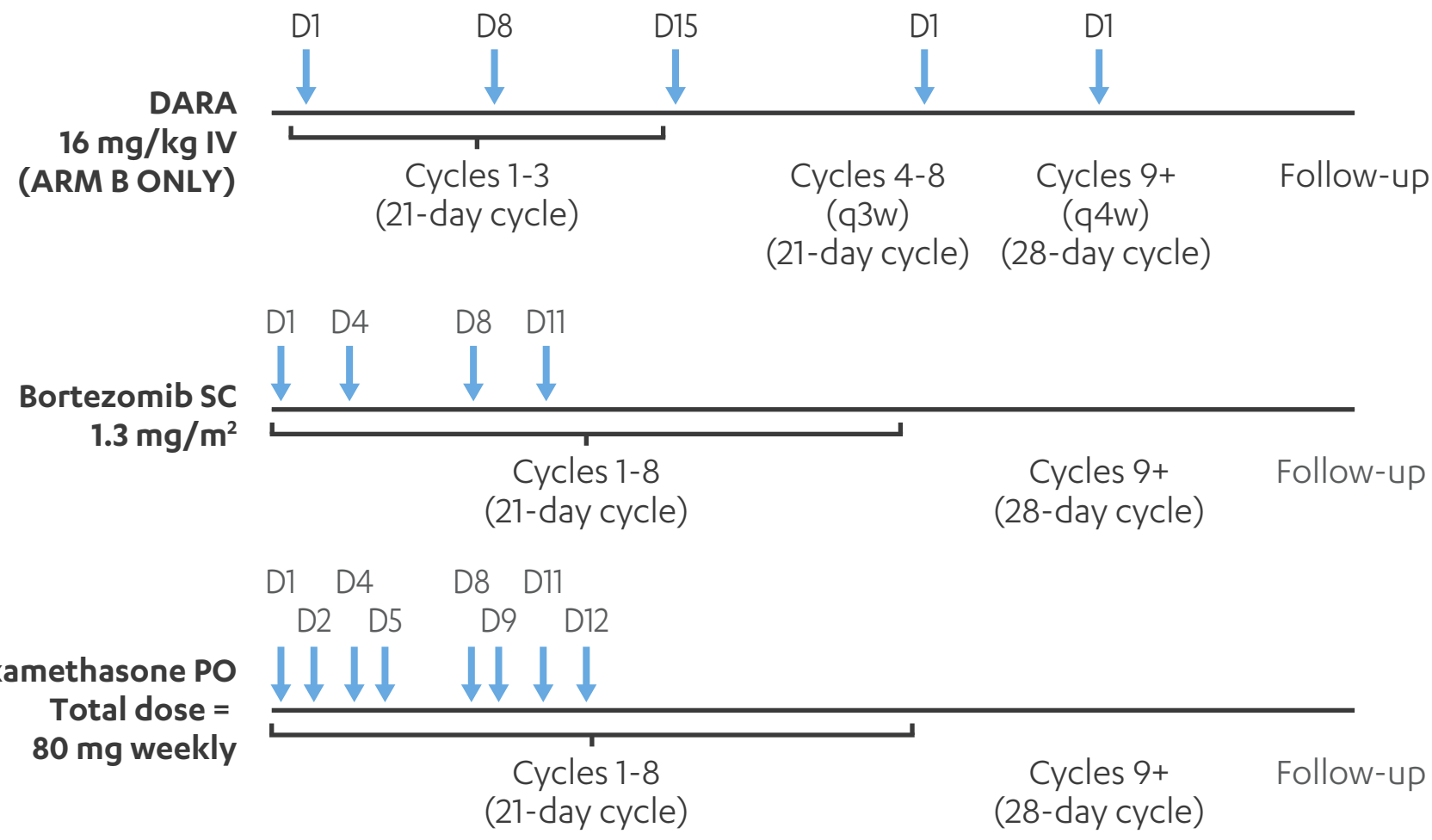

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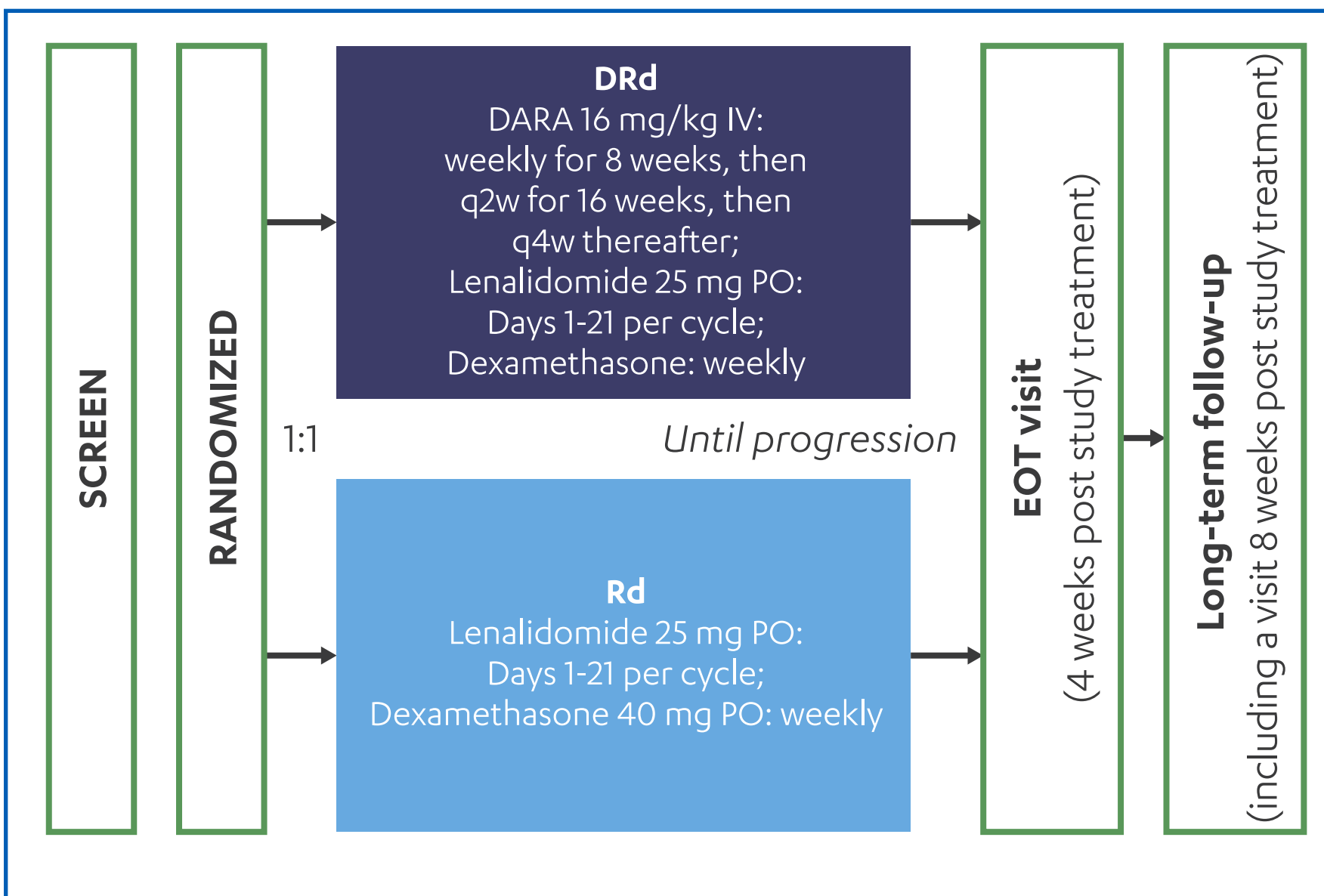

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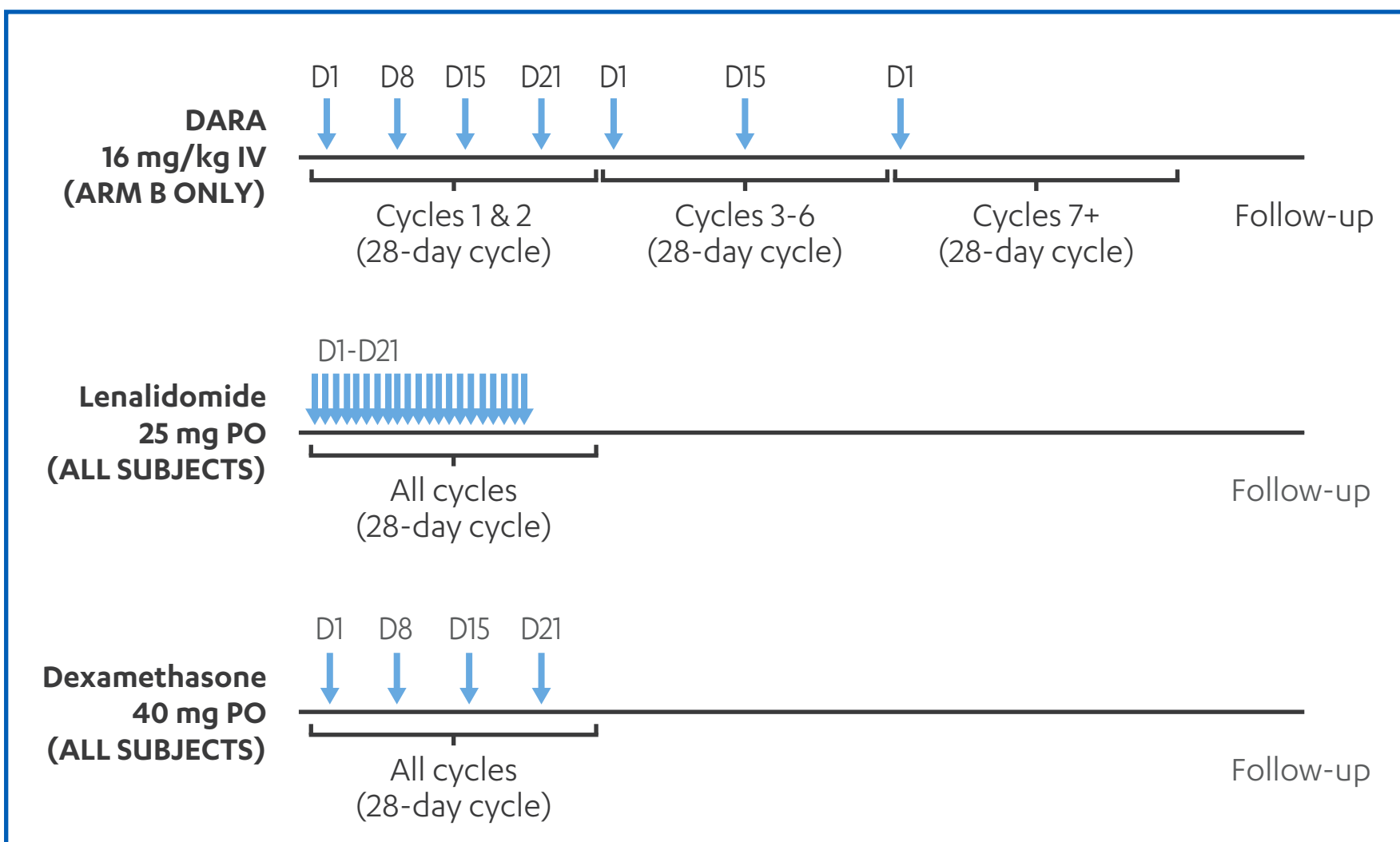

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castor JNJ-54767414MMY3004

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