8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

DARZALEX can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models *(see Data)*. There are no available data on the use of DARZALEX in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

The combination of DARZALEX and lenalidomide, pomalidomide, or thalidomide is contraindicated in pregnant women, because lenalidomide, pomalidomide, and thalidomide may cause birth defects and death of the unborn child. Lenalidomide, pomalidomide, and thalidomide are only available through a REMS program. Refer to the lenalidomide, pomalidomide, or thalidomide prescribing information on use during pregnancy.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to DARZALEX *in utero* until a hematology evaluation is completed.

Data

Animal Data

Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

8.2 Lactation

Risk Summary

There is no data on the presence of daratumumab in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and

infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX is administered with lenalidomide, pomalidomide, or thalidomide, advise women not to breastfeed during treatment with DARZALEX. Refer to lenalidomide, pomalidomide, or thalidomide prescribing information for additional information.

8.3 Females and Males of Reproductive Potential

DARZALEX can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

With the combination of DARZALEX with lenalidomide, pomalidomide, or thalidomide, refer to the lenalidomide, pomalidomide, or thalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX and for 3 months after the last dose. Additionally, refer to the lenalidomide, pomalidomide, or thalidomide labeling for additional recommendations for contraception.

8.4 Pediatric Use

Safety and effectiveness of DARZALEX in pediatric patients have not been established.

8.5 Geriatric Use

Of the 2,459 patients who received DARZALEX at the recommended dose, 38% were 65 to 74 years of age, and 15% were 75 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. The incidence of serious adverse reactions was higher in older than in younger patients *[see Adverse Reactions (6.1)]*. Among patients with relapsed and refractory multiple myeloma (n=1,213), the serious adverse reactions that occurred more frequently in patients 65 years and older were pneumonia and sepsis. Within the DKd group in CANDOR, fatal adverse reactions occurred in 14% of patients 65 years and older compared to 6% of patients less than 65 years. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=710), the serious adverse reaction that occurred more frequently in patients 75 years and older was pneumonia.

11 DESCRIPTION

Daratumumab is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody that binds to CD38 antigen. It is produced in Chinese Hamster Ovary (CHO) cells using recombinant DNA technology. The molecular weight of daratumumab is approximately 148 kDa.

DARZALEX® (daratumumab) injection is supplied as a colorless to pale yellow preservative-free solution for intravenous use in a single-dose vial. The pH is 5.5.

Each DARZALEX 20 mL single-dose vial contains (NDC 57894-502-20) 400 mg daratumumab, glacial acetic acid (3.7 mg), mannitol (510 mg), polysorbate 20 (8 mg), sodium acetate trihydrate (59.3 mg), sodium chloride (70.1 mg), and Water for Injection, USP.

Each DARZALEX 5 mL single-dose vial contains (NDC 57894-502-05) 100 mg daratumumab, glacial acetic acid (0.9 mg), mannitol (127.5 mg), polysorbate 20 (2 mg), sodium acetate trihydrate (14.8 mg), sodium chloride (17.5 mg), and Water for Injection, USP.

Each DARZALEX 20 mL single-dose vial contains (NDC 57894-505-20) 400 mg daratumumab, L-histidine (7 mg), L-histidine hydrochloride monohydrate (32.6 mg), L-methionine (20 mg), polysorbate 20 (8 mg), sorbitol (1093 mg), and Water for Injection, USP.

Each DARZALEX 5 mL single-dose vial contains (NDC 57894-505-05) 100 mg daratumumab, L-histidine (1.8 mg), L-histidine hydrochloride monohydrate (8.2 mg), L-methionine (5 mg), polysorbate 20 (2 mg), sorbitol (273.3 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CD38 is a transmembrane glycoprotein (48 kDa) expressed on the surface of hematopoietic cells, including multiple myeloma and other cell types and tissues and has multiple functions, such as receptor mediated adhesion, signaling, and modulation of cyclase and hydrolase activity. Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to CD38 and inhibits the growth of CD38 expressing tumor cells by inducing apoptosis directly through Fc mediated cross linking as well as by immune-mediated tumor cell lysis through complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP). A subset of myeloid derived suppressor cells (CD38+MDSCs), regulatory T cells (CD38+T_{regs}) and B cells (CD38+B_{regs}) are decreased by daratumumab.

12.2 Pharmacodynamics

NK cells express CD38 and are susceptible to daratumumab mediated cell lysis. Decreases in absolute counts and percentages of total NK cells (CD16+CD56+) and activated (CD16+$CD56^{dim}$) NK cells in peripheral whole blood and bone marrow were observed with DARZALEX treatment.

Exposure-Response Relationship

The exposure-response relationship and time course of pharmacodynamics of DARZALEX have not been fully characterized.

Cardiac Electrophysiology

DARZALEX as a large protein has a low likelihood of direct ion channel interactions. There is no evidence from non-clinical or clinical data to suggest that DARZALEX has the potential to delay ventricular repolarization.

12.3 Pharmacokinetics

Daratumumab area under the concentration-time curve (AUC) increases more than proportionally over a dosage range from 1 to 24 mg/kg (0.06 to 1.5 times the approved recommended dosage) as monotherapy or 1 to 16 mg/kg (0.06 to 1 time the approved recommended dosage) as combination therapy.

Following administration of the approved recommended dosage of DARZALEX as monotherapy or in combination therapy, the mean serum maximal concentration (C_{max}) was approximately 2.7 to 3-fold higher at the end of weekly dosing compared to the first dose. The mean ± standard deviation (SD) trough serum concentration (C_{min}) at the end of weekly dosing was 573 ± 332 µg/mL when DARZALEX was administered as monotherapy and 502 ± 196 to 607 ± 231 µg/mL when DARZALEX was administered as combination therapy. Split dosing of the first dose resulted in a different PK profile in the first day compared to single dosing; however, similar C_{max} and C_{min} concentrations were both predicted and observed following the administration of the second split dose on Week 1 Day 2.

When DARZALEX was administered as monotherapy, daratumumab steady state was achieved approximately 5 months into the every 4-week dosing period (by the 21st infusion). At steady state, daratumumab mean ± SD accumulation ratio for C_{max} was 1.6 ± 0.5.

Distribution

Daratumumab volume of distribution was 4.7 ± 1.3 L as monotherapy and 4.4 ± 1.5 L as combination therapy following administration of the approved dosage.

Elimination

Daratumumab clearance decreased with increasing dose and with multiple dosing. The mean ± SD linear clearance was estimated to be 171.4 ± 95.3 mL/day and the mean ± SD estimated terminal half-life associated with linear clearance was 18 ± 9 days following administration of the approved recommended dosage of DARZALEX as monotherapy. Terminal half-life was similar when DARZALEX was administered as combination therapy.

Specific Populations

No clinically significant differences in the pharmacokinetics of daratumumab as monotherapy or as combination therapy were observed based on sex, age (31 to 93 years), mild [total bilirubin 1 to 1.5 times upper limit of normal (ULN) or aspartate aminotransaminase (AST)>ULN] and moderate (total bilirubin 1.5 to 3 times ULN and any AST) hepatic impairment, or renal impairment [Creatinine clearance (CLcr) 15-89 mL/min]. The effect of severe (total bilirubin >3 times ULN and any AST) hepatic impairment on daratumumab pharmacokinetics is unknown.

Body Weight

The central volume of distribution and clearance of daratumumab increased with increasing body weight.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with daratumumab. No animal studies have been performed to evaluate the potential effects of daratumumab on reproduction or development, or to determine potential effects on fertility in males or females.

14 CLINICAL STUDIES

14.1 Newly Diagnosed Multiple Myeloma

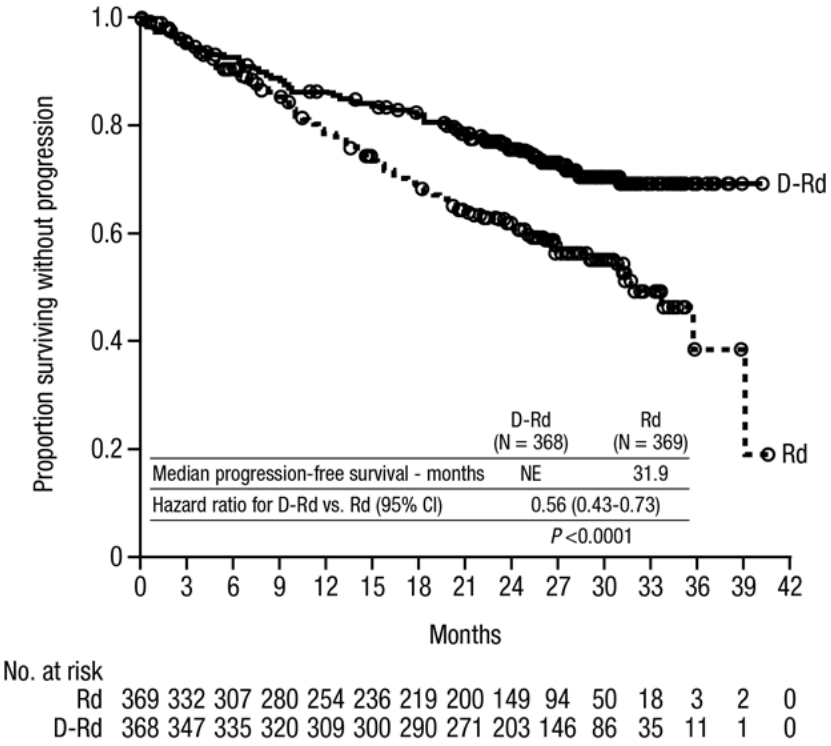
Combination Treatment with Lenalidomide and Dexamethasone in Patients Ineligible for Autologous Stem Cell Transplant

MAIA (NCT02252172), an open-label, randomized, active-controlled trial, compared treatment with DARZALEX 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with newly diagnosed multiple myeloma ineligible for autologous stem cell transplant. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5). On DARZALEX infusion days, the dexamethasone dose was given as a pre-infusion medication. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 737 patients were randomized: 368 to the DRd arm and 369 to the Rd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 73 (range: 45-90) years, with 44% of the patients ≥75 years of age. Fifty-two percent (52%) of patients were male, 92% White, 4% Black or African American, and 1% Asian. Three percent (3%) of patients reported an ethnicity of Hispanic or Latino. Thirty-four percent (34%) had an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 50% had an ECOG performance score of 1 and 17% had an ECOG performance score of ≥2. Twenty-seven percent had International Staging System (ISS) Stage I, 43% had ISS Stage II and 29% had ISS Stage III disease. Efficacy was evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

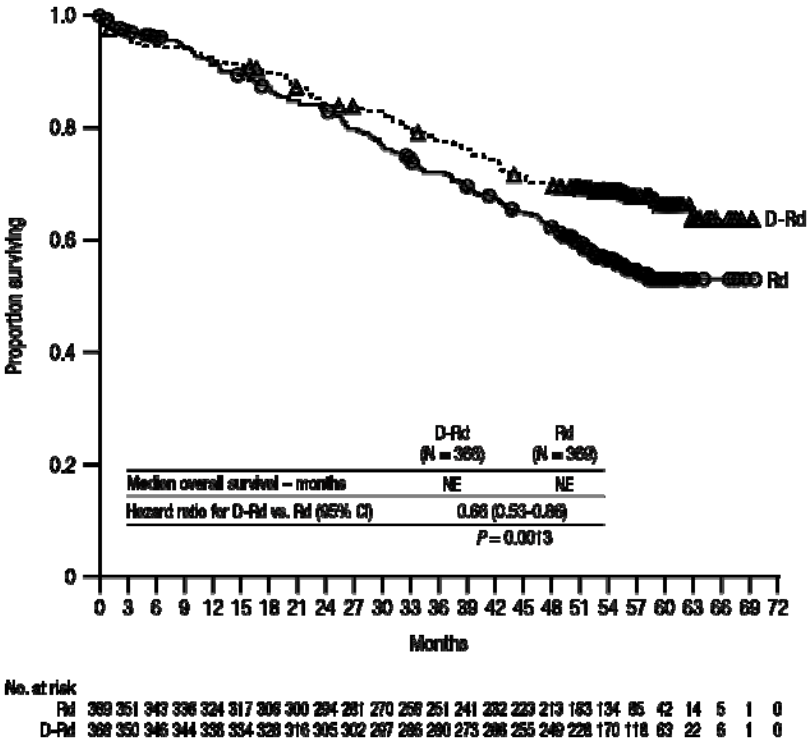
MAIA demonstrated an improvement in Progression Free Survival (PFS) in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 31.9 months in the Rd arm (hazard ratio [HR]=0.56; 95% CI: 0.43, 0.73; p<0.0001), representing 44% reduction in the risk of disease progression or death in patients treated with DRd.

Figure 1: Kaplan-Meier Curve of PFS in MAIA



After a median follow-up of 56 months, MAIA demonstrated an improvement in overall survival (OS) in the DRd arm as compared to the Rd arm (HR=0.68; 95% CI: 0.53, 0.86; p=0.0013), representing a 32% reduction in the risk of death in patients treated in the DRd arm. Median OS was not reached for either arm.

Figure 2: Kaplan-Meier Curve of OS in MAIA



Additional efficacy results from MAIA are presented in Table 23.

Table 23: Additional Efficacy Results From MAIA[a]

	DRd (N=368)	**Rd (N=369)**
Overall response (sCR+CR+VGPR+PR) n(%)[a]	342 (92.9%)	300 (81.3%)
p-value[b]	<0.0001	
Stringent complete response (sCR)	112 (30.4%)	46 (12.5%)
Complete response (CR)	63 (17.1%)	46 (12.5%)
Very good partial response (VGPR)	117 (31.8%)	104 (28.2%)
Partial response (PR)	50 (13.6%)	104 (28.2%)
CR or better (sCR + CR)	175 (47.6%)	92 (24.9%)
p-value[b]	<0.0001	
VGPR or better (sCR + CR + VGPR)	292 (79.3%)	196 (53.1%)
p-value[b]	<0.0001	
MRD negativity rate[a, c] n(%)	89 (24.2%)	27 (7.3%)
95% CI (%)	(19.9%, 28.9%)	(4.9%, 10.5%)
p-value[d]	<0.0001	
MRD negativity rate in patients with CR or better[c]		
Number of patients with CR or better	**N=175**	**N=92**
MRD negativity rate n(%)	89 (50.9%)	27 (29.3%)
95% CI (%)	(43.2%, 58.5%)	(20.3%, 39.8%)

DRd=daratumumab-lenalidomide-dexamethasone; Rd=lenalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval

[a] Based on intent-to-treat population

[b] p-value from Cochran Mantel-Haenszel Chi-Squared test.

[c] Based on threshold of 10^{-5} using a next-generation sequencing assay (clonoSEQ).

[d] p-value from Fisher's exact test

In responders, the median time to response was 1.05 months (range: 0.2 to 12.1 months) in the DRd group and 1.05 months (range: 0.3 to 15.3 months) in the Rd group. The median duration of response had not been reached in the DRd group and was 34.7 months (95% CI: 30.8, not estimable) in the Rd group.

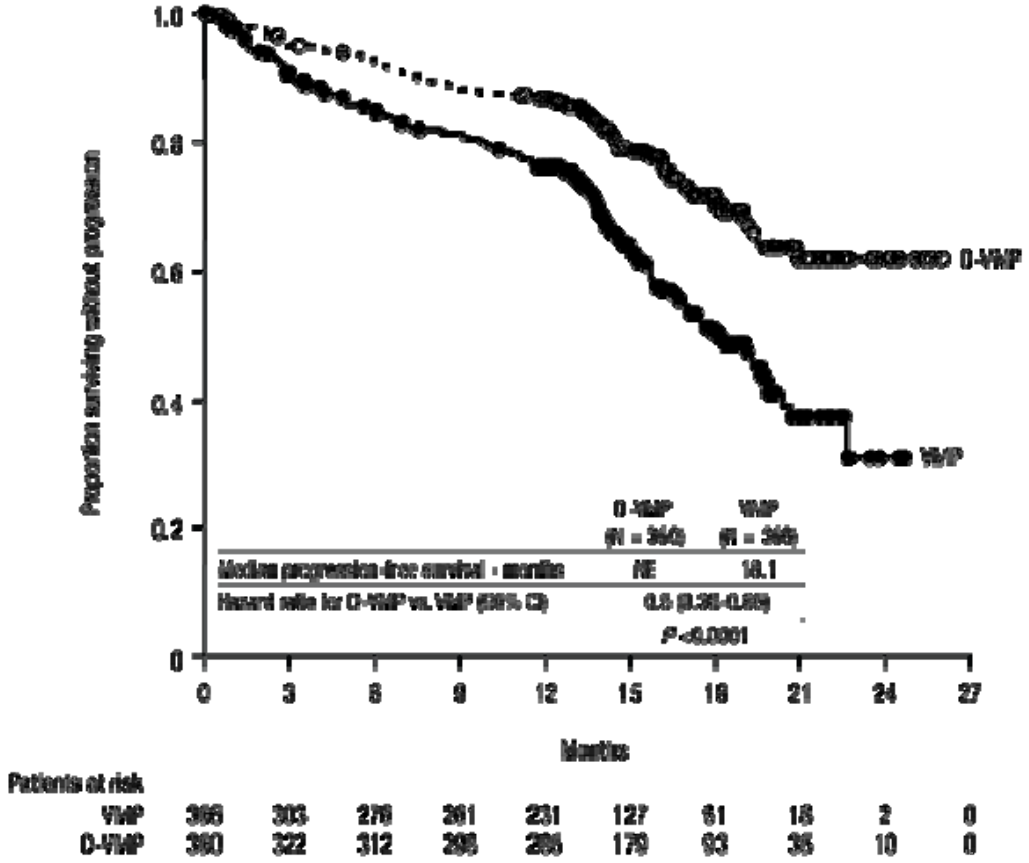
Combination Treatment with Bortezomib, Melphalan and Prednisone (VMP) in Patients Ineligible for Autologous Stem Cell Transplant

ALCYONE (NCT02195479), an open-label, randomized, active-controlled trial, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib, melphalan and prednisone (D-VMP), to treatment with VMP in patients with newly diagnosed multiple myeloma ineligible for autologous stem cell transplant. Bortezomib was administered by subcutaneous (SC) injection at a dose of 1.3 mg/m^2 body surface area twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle (Cycle 1; 8 doses), followed by once weekly administrations at Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4 doses per cycle). Melphalan at 9 mg/m^2, and prednisone at 60 mg/m^2 were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). DARZALEX was continued until disease progression or unacceptable toxicity.

A total of 706 patients were randomized: 350 to the D-VMP arm and 356 to the VMP arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 71 (range: 40-93) years, with 30% of the patients ≥75 years of age. The majority were white (85%), female (54%), 25% had an ECOG performance score of 0, 50% had an ECOG performance score of 1 and 25% had an ECOG performance score of 2. Nineteen percent of patients had ISS Stage I, 42% had ISS Stage II and 38% had ISS Stage III disease. Efficacy was evaluated by PFS based on IMWG criteria and overall survival (OS).

ALCYONE demonstrated an improvement in PFS in the D-VMP arm as compared to the VMP arm (HR=0.50; 95% CI: 0.38, 0.65; p<0.0001), representing a 50% reduction in the risk of disease progression or death in patients treated with D-VMP. After a median follow-up of 40 months, the median PFS was 36.4 months (95% CI: 32.1, 45.9) in the D-VMP arm and 19.3 months (95% CI: 18.0, 20.4) in the VMP arm.

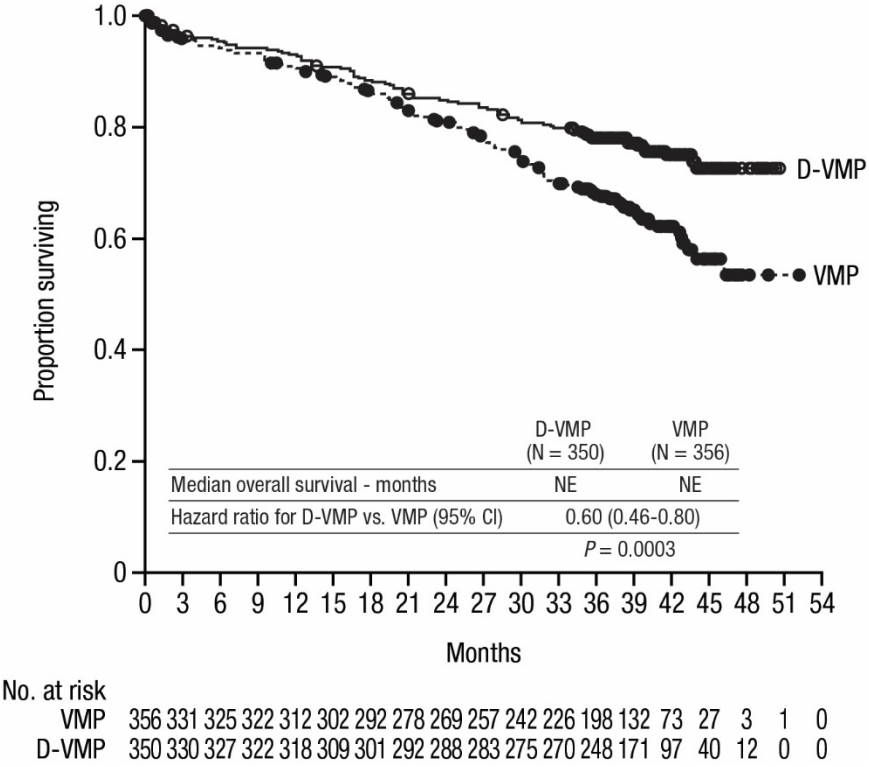
Figure 3: Kaplan-Meier Curve of PFS in ALCYONE[a]



[a] PFS median follow-up of 16.5 months

After a median follow-up of 40 months, ALCYONE demonstrated an improvement in overall survival (OS) in the D-VMP arm as compared to the VMP arm (HR=0.60; 95% CI: 0.46, 0.80; p=0.0003), representing a 40% reduction in the risk of death in patients treated in the D-VMP arm. Median OS was not reached for either arm.

Figure 4: Kaplan-Meier Curve of OS in ALCYONE



Additional efficacy results from ALCYONE are presented in Table 24.

Table 24: Additional Efficacy Results From ALCYONE

	D-VMP (N=350)	**VMP (N=356)**
Overall response (sCR+CR+VGPR+PR) n(%)[a]	318 (90.9%)	263 (73.9%)
p-value[b]	<0.0001	
Stringent complete response (sCR)	63 (18.0%)	25 (7.0%)
Complete response (CR)	86 (24.6%)	62 (17.4%)
Very good partial response (VGPR)	100 (28.6%)	90 (25.3%)
Partial response (PR)	69 (19.7%)	86 (24.2%)
MRD negativity rate[a, c] n(%)	78 (22.3%)	22 (6.2%)
95% CI (%)	(18.0, 27.0)	(3.9, 9.2)
p-value[d]	<0.0001	
MRD negativity rate in patients with CR or better[c]		
Number of patients with CR or better	**N=149**	**N=87**
MRD negativity rate n(%)	74 (49.7%)	22 (25.3%)
95% CI (%)	(41.4, 58.0)	(16.6, 35.7)

D-VMP = daratumumab-bortezomib-melphalan-prednisone; VMP = bortezomib-melphalan-prednisone; MRD = minimal residual disease; CI = confidence interval

[a] Based on intent-to-treat population

[b] p-value from Cochran Mantel-Haenszel Chi-Squared test.

[c] Based on threshold of 10^{-5} using a next-generation sequencing assay (clonoSEQ).

[d] p-value from Fisher's exact test.

In responders, the median time to response was 0.79 months (range: 0.4 to 15.5 months) in the D-VMP group and 0.82 months (range: 0.7 to 12.6 months) in the VMP group. The median

duration of response had not been reached in the D-VMP group and was 21.3 months (range: 0.5+, 23.7+) in the VMP group.

Combination Treatment with Bortezomib, Thalidomide and Dexamethasone in Patients Eligible for Autologous Stem Cell Transplant (ASCT)

CASSIOPEIA (NCT02541383), an open-label, randomized, active-controlled trial compared induction and consolidation treatment with DARZALEX 16 mg/kg in combination with bortezomib, thalidomide and dexamethasone (DVTd) to treatment with bortezomib, thalidomide and dexamethasone (VTd) in patients with newly diagnosed multiple myeloma eligible for ASCT. The consolidation phase of treatment began a minimum of 30 days post-ASCT, when the patient had recovered sufficiently, and engraftment was complete. The trial was limited to patients 65 years of age and younger. Bortezomib was administered by subcutaneous (SC) injection or intravenous (IV) injection at a dose of 1.3 mg/m^2 body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 28-day (4-week) induction treatment cycles (Cycles 1-4) and two consolidation cycles (Cycles 5 and 6) following ASCT after Cycle 4. Thalidomide was administered orally at 100 mg daily during the six bortezomib cycles. Dexamethasone (oral or intravenous) was administered at 40 mg on Days 1, 2, 8, 9, 15, 16, 22 and 23 of Cycles 1 and 2, and at 40 mg on Days 1-2 and 20 mg on subsequent dosing days (Days 8, 9, 15, 16) of Cycles 3-4. Dexamethasone 20 mg was administered on Days 1, 2, 8, 9, 15, 16 in Cycles 5 and 6. On the days of DARZALEX infusion, the dexamethasone dose was administered intravenously as a pre-infusion medication.

A total of 1,085 patients were randomized: 543 to the DVTd arm and 542 to the VTd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 58 years (range: 22 to 65 years). The majority were male (59%), 48% had an ECOG performance score of 0, 42% had an ECOG performance score of 1 and 10% had an ECOG performance score of 2. Forty percent had ISS Stage I, 45% had ISS Stage II and 15% had ISS Stage III disease.

Efficacy was evaluated by stringent Complete Response (sCR) rate at Day 100 post-transplant, Complete Response Rate (CR) at Day 100 post-transplant, and Progression-Free Survival (PFS).

Table 25: Efficacy Results From CASSIOPEIA at Day 100 Post-Transplant

	DVTd (N=543)	**VTd (N=542)**
Overall response (sCR+CR+VGPR+PR) n(%)[a]	503 (92.6%)	487 (89.9%)
Stringent complete response (sCR)	157 (28.9%)	110 (20.3%)
p-value[b]	0.0010	
Complete response (CR)	54 (9.9%)	31 (5.7%)
Very good partial response (VGPR)	242 (44.6%)	282 (52.0%)
Partial response (PR)	50 (9.2%)	64 (11.8%)

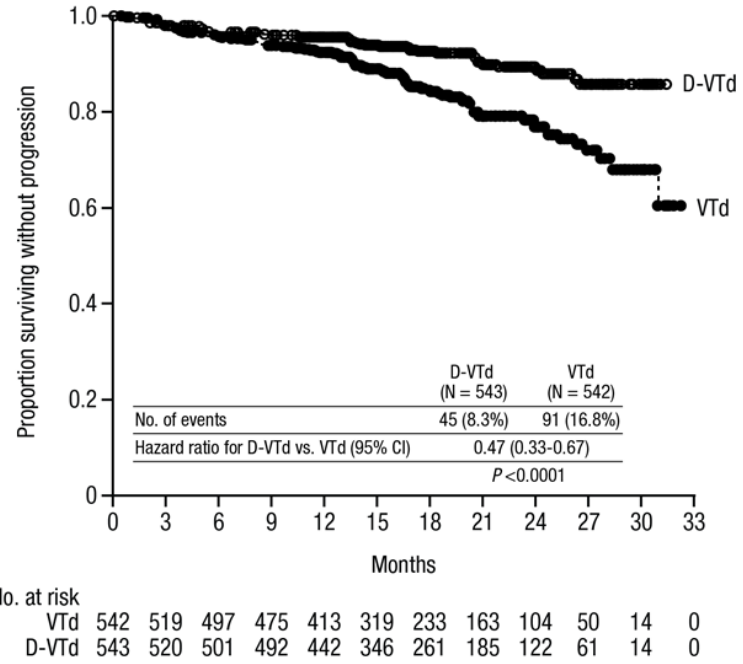
D-VTd = daratumumab-bortezomib-thalidomide-dexamethasone; VTd = bortezomib-thalidomide-dexamethasone

[a] Based on intent-to-treat population

[b] p-value from Cochran Mantel-Haenszel Chi-Squared test.

CASSIOPEIA demonstrated an improvement in PFS in the DVTd arm as compared to the VTd arm; with a median follow up of 18.8 months, the median PFS had not been reached in either arm. Treatment with DVTd resulted in a reduction in the risk of progression or death by 53% compared to VTd alone (HR=0.47; 95% CI: 0.33, 0.67; p<0.0001).

Figure 5: Kaplan-Meier Curve of PFS in CASSIOPEIA[a]



[a] based on interim analysis and the boundary for PFS was crossed.

14.2 Relapsed/Refractory Multiple Myeloma

Combination Treatment with Lenalidomide and Dexamethasone

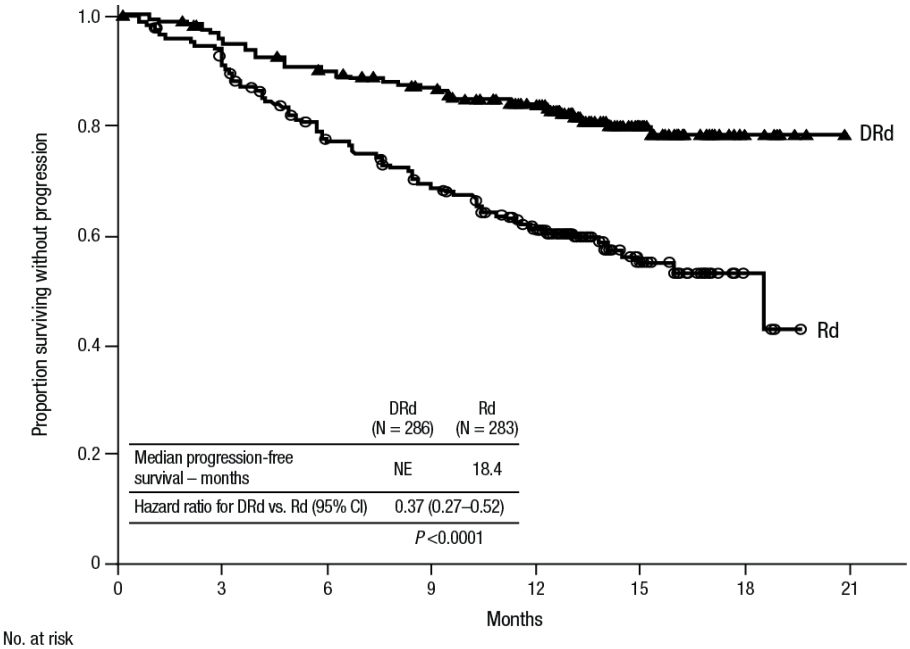
POLLUX (NCT02076009), an open-label, randomized, active-controlled trial, compared treatment with DARZALEX 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with multiple myeloma who had received at least one prior therapy. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or BMI <18.5). On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication. Dose adjustments for lenalidomide and dexamethasone were applied according to manufacturer's prescribing information. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 569 patients were randomized; 286 to the DRd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the

control arm. The median patient age was 65 years (range 34 to 89 years), 11% were ≥75 years, 59% were male; 69% White, 18% Asian, and 3% African American. Patients had received a median of 1 prior line of therapy. Sixty-three percent (63%) of patients had received prior autologous stem cell transplantation (ASCT). The majority of patients (86%) received a prior PI, 55% of patients had received a prior immunomodulatory agent, including 18% of patients who had received prior lenalidomide; and 44% of patients had received both a prior PI and immunomodulatory agent. At baseline, 27% of patients were refractory to the last line of treatment. Eighteen percent (18%) of patients were refractory to a PI only, and 21% were refractory to bortezomib. Efficacy was evaluated by PFS based on IMWG criteria.

POLLUX demonstrated an improvement in PFS in the DRd arm as compared to the Rd arm (HR=0.37; 95% CI: 0.27, 0.52; p<0.0001), representing a 63% reduction in the risk of disease progression or death in patients treated with DRd. After a median follow-up of 55 months, the median PFS was 45.0 months (95% CI: 34.1, 53.9) in the DRd arm and was 17.5 months (95% CI: 13.9, 20.8) in the Rd arm.

Figure 6: Kaplan-Meier Curve of PFS in POLLUX[a]



[a] PFS median follow-up of 13.5 months

Additional efficacy results from POLLUX are presented in Table 26.

Table 26: Additional Efficacy Results From POLLUX[a]

	DRd (N=286)	Rd (N=283)
Overall response (sCR+CR+VGPR+PR)	261 (91.3%)	211 (74.6%)
p-value[b]	<0.0001	
Stringent complete response (sCR)	51 (17.8%)	20 (7.1%)
Complete response (CR)	70 (24.5%)	33 (11.7%)
Very good partial response (VGPR)	92 (32.2%)	69 (24.4%)
Partial response (PR)	48 (16.8%)	89 (31.4%)

DRd = daratumumab- lenalidomide-dexamethasone; Rd = lenalidomide-dexamethasone

[a] Based on Intent-to-treat population

[b] p-value from Cochran Mantel-Haenszel Chi-Squared test.

In responders, the median time to response was 1 month (range: 0.9 to 13 months) in the DRd group and 1.1 months (range: 0.9 to 10 months) in the Rd group. The median duration of response had not been reached in the DRd group (range: 1+ to 19.8+ months) and was 17.4 months (range: 1.4 to 18.5+ months) in the Rd group.

With a median follow-up of 13.5 months, 75 deaths were observed; 30 in the DRd group and 45 in the Rd group.

Combination Treatment with Bortezomib and Dexamethasone

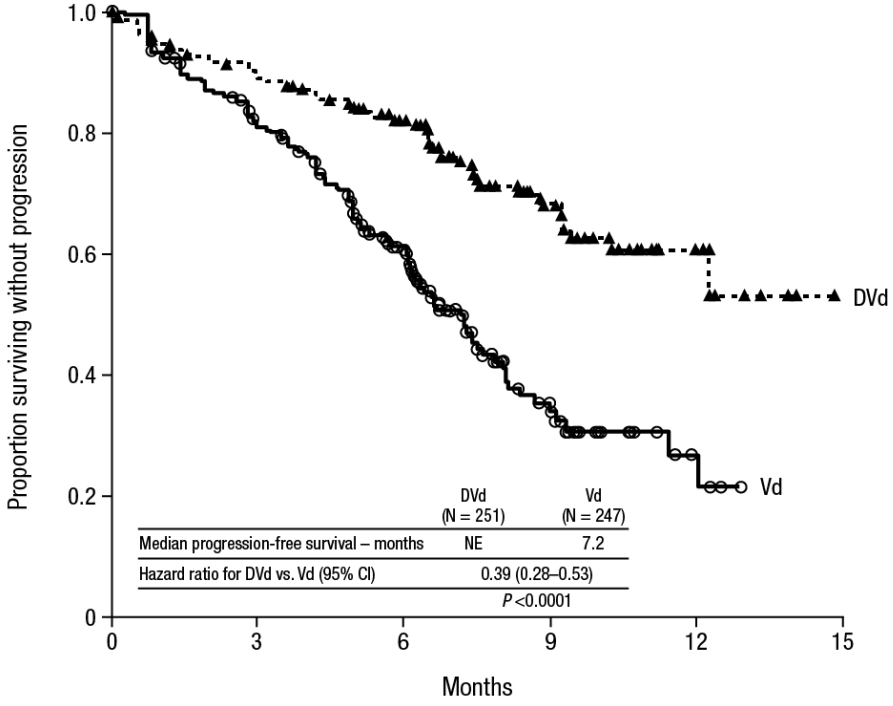
CASTOR (NCT02136134), an open-label, randomized, active-controlled Phase 3 trial, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd) in patients with multiple myeloma who had received at least one prior therapy. Bortezomib was administered by SC injection or IV injection at a dose of 1.3 mg/m^2 body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 21 day (3-week) treatment cycles, for a total of 8 cycles. Dexamethasone was administered orally at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each of the 8 bortezomib cycles (80 mg/week for two out of three weeks of the bortezomib cycle) or a reduced dose of 20 mg/week for patients >75 years, BMI <18.5, poorly controlled diabetes mellitus or prior intolerance to steroid therapy. On the days of DARZALEX infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medication. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication. Bortezomib and dexamethasone were given for 8 three-week cycles in both treatment arms; whereas DARZALEX was given until disease progression. However, dexamethasone 20 mg was continued as a DARZALEX pre-infusion medication in the DVd arm. Dose adjustments for bortezomib and dexamethasone were applied according to manufacturer's prescribing information.

A total of 498 patients were randomized; 251 to the DVd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 64 years (range 30 to 88 years); 12% were ≥75 years, 57% were male; 87% White, 5% Asian and 4% African American. Patients had received a median of 2 prior lines of therapy and 61% of patients had received prior autologous stem cell transplantation (ASCT). Sixty-nine percent (69%) of patients had received a prior PI (66%

received bortezomib) and 76% of patients received an immunomodulatory agent (42% received lenalidomide). At baseline, 32% of patients were refractory to the last line of treatment and the proportions of patients refractory to any specific prior therapy were in general well balanced between the treatment groups. Thirty-three percent (33%) of patients were refractory to an immunomodulatory agent only, with 24% patients in the DVd arm and 33% of patients in the Vd arm respectively refractory to lenalidomide. Efficacy was evaluated by PFS based on IMWG criteria.

CASTOR demonstrated an improvement in PFS in the DVd arm as compared to the Vd arm (HR=0.39; 95% CI: 0.28, 0.53; p<0.0001), representing a 61% reduction in the risk of disease progression or death for patients treated with DVd versus Vd. After a median follow-up of 50 months, the median PFS was 16.7 months (95% CI: 13.1, 19.4) in the DVd arm and was 7.1 months (95% CI: 6.2, 7.7) in the Vd arm.

Figure 7: Kaplan-Meier Curve of PFS in CASTOR[a]



No. at risk

Vd	247	182	106	25	5	0
DVd	251	215	146	56	11	0

[a] PFS median follow-up of 7.4 months

Additional efficacy results from CASTOR are presented in Table 27.

Table 27: Additional Efficacy Results From CASTOR[a]

	DVd (N=251)	Vd (N=247)
Overall response (sCR+CR+VGPR+PR)	199 (79.3%)	148 (59.9%)
P-value[b]	<0.0001	
Stringent complete response (sCR)	11 (4.4%)	5 (2.0%)
Complete response (CR)	35 (13.9%)	16 (6.5%)
Very good partial response (VGPR)	96 (38.2%)	47 (19.0%)
Partial response (PR)	57 (22.7%)	80 (32.4%)

DVd = daratumumab- bortezomib-dexamethasone; Vd = bortezomib-dexamethasone

[a] Based on Intent-to-treat population

[b] p-value from Cochran Mantel-Haenszel Chi-Squared test.

In responders, the median time to response was 0.8 months (range: 0.7 to 4 months) in the DVd group and 1.5 months (range: 0.7 to 5 months) in the Vd group. The median duration of response had not been reached in the DVd group (range: 1.4+ to 14.1+ months) and was 7.9 months (1.4+ to 12+ months) in the Vd group.

With a median follow-up of 7.4 months, 65 deaths were observed; 29 in the DVd group and 36 in the Vd group were observed.

Combination Treatment with Twice-Weekly (20/56 mg/m^2) Carfilzomib and Dexamethasone

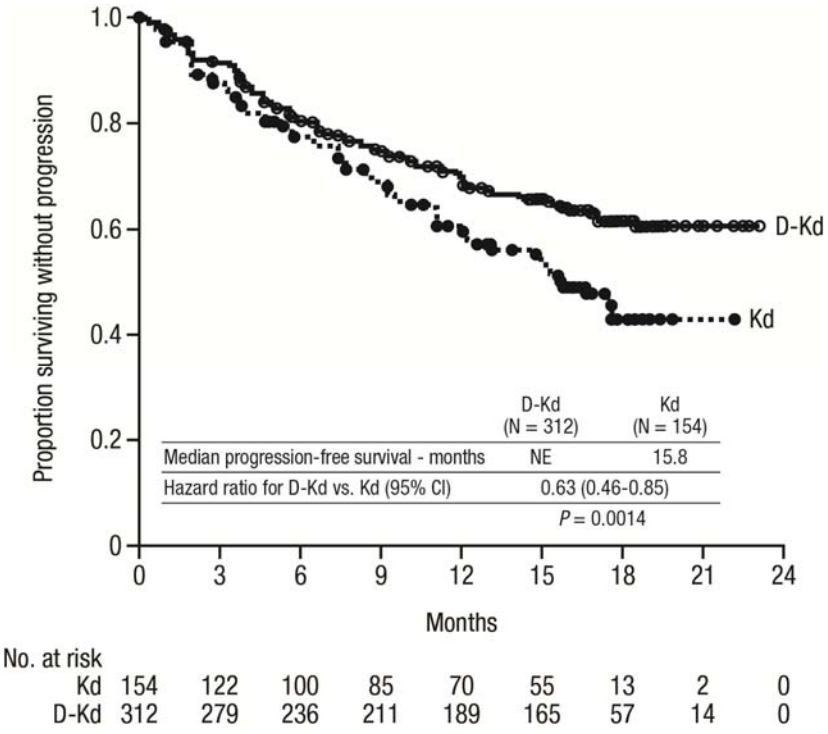
CANDOR (NCT03158688) was a randomized, open-label, multicenter trial which evaluated the combination of DARZALEX with twice-weekly carfilzomib and dexamethasone (DKd) versus twice-weekly carfilzomib and dexamethasone (Kd) in patients with relapsed or refractory multiple myeloma who had received at least 1 to 3 prior lines of therapy. Patients who had the following were excluded from the trial: known moderate or severe persistent asthma within the past 2 years, known chronic obstructive pulmonary disease (COPD) with a FEV1 <50% of predicted normal, and active congestive heart failure. Randomization was stratified by the ISS (stage 1 or 2 vs stage 3) at screening, prior proteasome inhibitor exposure (yes vs no), number of prior lines of therapy (1 vs ≥2), or prior cluster differentiation antigen 38 (CD38) antibody therapy (yes vs no).

DARZALEX was administered intravenously at a dose of 8 mg/kg in Cycle 1 on Days 1 and 2. Thereafter, DARZALEX was administered intravenously at a dose of 16 mg/kg on Days 8, 15 and 22 of Cycle 1; Days 1, 8 and 15 and 22 of Cycle 2; Days 1 and 15 of Cycles 3 to 6; and Day 1 of each 28-day cycle until disease progression. Carfilzomib was administered intravenously at a dose of 20 mg/m^2 in Cycle 1 on Days 1 and 2; at a dose of 56 mg/m^2 in Cycle 1 on Days 8, 9, 15, and 16; and at a dose 56 mg/m^2 on Days 1, 2, 8, 9, 15, and 16 of each 28-day cycle thereafter. Dexamethasone 20 mg was administered orally or intravenously on Days 1, 2, 8, 9, 15 and 16 and then 40 mg orally or intravenously on Day 22 of each 28-day cycle. For patients >75 years on a reduced dexamethasone dose of 20 mg, the entire 20 mg dose was given as a DARZALEX pre-infusion medication on days when DARZALEX was administered. Dosing of dexamethasone was otherwise split across days when carfilzomib was administered in both study arms. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 466 patients were randomized; 312 to the DKd arm and 154 to the Kd arm. The baseline demographic and disease characteristics were similar between arms. The median age was 64 years (range 29 to 84 years), 9% were ≥75 years, 58% were male; 79% White, 14% Asian, and 2% Black. Patients had received a median of 2 prior lines of therapy and 58% of patients had received prior autologous stem cell transplantation (ASCT). The majority of patients (92%) received a prior PI and of those 34% were refractory to PI including regimen. Fourty-two percent (42%) of patients had received prior lenalidomide and of those, 33% were refractory to a lenalidomide containing regimen.

Efficacy was evaluated by IRC evaluation of PFS based on the IMWG response criteria. Efficacy results are provided in Figure 8. CANDOR demonstrated an improvement in PFS in the DKd arm as compared to the Kd arm; the median PFS had not been reached in the DKd arm and was 15.8 months in the Kd arm (hazard ratio [HR]=0.63; 95% CI: 0.46, 0.85; p=0.0014), representing 37% reduction in the risk of disease progression or death for patients treated with DKd versus Kd.

Figure 8: Kaplan-Meier Curve of PFS in CANDOR



Additional efficacy results from CANDOR are presented in Table 28.

Table 28: Additional Efficacy Results From CANDOR (Intent-to-Treat Population)

	DKd (N=312)	Kd (N=154)
Overall response (sCR+CR+VGPR+PR) n(%)	263 (84%)	115 (75%)
95% CI (%)	(80, 88)	(67, 81)
p-value[a] (1-sided)	0.0040	
Complete response (CR)	89 (28%)	16 (10%)
Very good partial response (VGPR)	127 (41%)	59 (38%)
Partial response (PR)	47 (15%)	40 (26%)
MRD [-] CR rate at 12 months n(%)[b]	39 (12%)	2 (1.3%)
95% CI (%)	(9, 17)	(0.2, 4.6)
p-value[a] (1-sided)	<0.0001	
MRD [-] CR[b]	43 (14%)	5 (3.2%)

DKd = daratumumab-carfilzomib-dexamethasone; Kd =carfilzomib-dexamethasone; MRD [-] CR=minimal residual disease; CI=confidence interval

[a] p-value from the stratified Cochran Mantel-Haenszel Chi-Squared test

[b] MRD[-]CR (at a 10^{-5} level) is defined as achievement of CR per IMWG-URC and MRD[-] status as assessed by the next-generation sequencing assay (ClonoSEQ)

The median time to response was 1 month (range: 1 to 14 months) in the DKd group and 1 month (range: 1 to 10 months) in the Kd group. The median duration of response had not been reached in the DKd group and was 16.6 months (95% CI: 13.9, not estimable) in the Kd group.

Combination Treatment with Once-Weekly (20/70 mg/m^2) Carfilzomib and Dexamethasone

EQUULEUS (NCT01998971) was an open-label, multi-cohort trial which evaluated the combination of DARZALEX with one-weekly carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma who had received at least 1 to 3 prior lines of therapy. Patients who had the following were excluded from the trial: known moderate or severe persistent asthma within the past 2 years, known chronic obstructive pulmonary disease (COPD) with a FEV1 <50% of predicted normal, or active congestive heart failure (defined as New York Heart Association Class III-IV).

Ten patients were administered DARZALEX at a dose of 16 mg/kg intravenously on Cycle 1, Day 1 and the remaining patients were administered DARZALEX at a dose of 8 mg/kg intravenously on Cycle 1, Days 1 and 2. Thereafter, DARZALEX was administered intravenously at a dose of 16 mg/kg on Days 8, 15 and 22 of Cycle 1; Days 1, 8, 15 and 22 of Cycle 2; Days 1 and 15 of Cycles 3 to 6; and then Day 1 for the remaining cycles of each 28 day cycle. Carfilzomib was administered intravenously once weekly at a dose of 20 mg/m^2 on Cycle 1 Day 1 and escalated to dose of 70 mg/m^2 on Cycle 1 Days 8 and 15, and Days 1, 8, and 15 of each subsequent 28-day cycle. In Cycles 1 and 2, dexamethasone 20 mg was administered orally or intravenously on Days 1, 2, 8, 9, 15, 16, 22 and 23; in cycles 3 to 6, dexamethasone 20 mg was administered orally or intravenously on Days 1, 2, 15 and 16 and at a dose of 40 mg on Day 8 and 22; and in cycles 7 and thereafter, dexamethasone 20 mg was administered orally or intravenously on Days 1 and 2 and at a dose of 40 mg on Days 8, 15, and 22. For patients >75 years of age, dexamethasone 20 mg was administered orally or intravenously weekly after the first week. Treatment continued until disease progression or unacceptable toxicity.

The EQUULEUS trial enrolled 85 patients. The median patient age was 66 years (range: 38 to 85 years) with 9% of patients ≥75 years of age; 54% were male; 80% were White, 3.5% were Black and 3.5% were Asian. Patients in the study had received a median of 2 prior lines of therapy. Seventy-three percent (73%) of patients had received prior ASCT. All patients received prior bortezomib, and 95% of patients received prior lenalidomide. Fifty-nine percent (59%) of patients were refractory to lenalidomide and 29% of patients were refractory to both a PI an IMiD.

Efficacy results were based on overall response rate using IMWG criteria. Efficacy results are provided in Table 29. The median time to response was 0.95 months (range: 0.9, 14.3). The median duration of response was 28 months (95% CI: 20.5, not estimable).

Table 29: Efficacy results for EQUULEUS

	N=85
Overall response rate (ORR) 95% CI (%)	69 (81%) (71, 89)
Stringent complete response (sCR)	18 (21%)
Complete response (CR)	12 (14%)
Very good partial response (VGPR)	28 (33%)
Partial response (PR)	11 (13%)

ORR = sCR+CR+VGPR+PR
CI = confidence interval

Combination Treatment with Pomalidomide and Dexamethasone

EQUULEUS (NCT01998971) was an open-label trial in which 103 patients with multiple myeloma who had received a prior PI and an immunomodulatory agent, received 16 mg/kg DARZALEX in combination with pomalidomide and low-dose dexamethasone until disease progression. Pomalidomide (4 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (reduced dose of 20 mg/week for patients >75 years or BMI <18.5). On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication.

The median patient age was 64 years (range: 35 to 86 years) with 8% of patients ≥75 years of age. Patients in the study had received a median of 4 prior lines of therapy. Seventy-four percent (74%) of patients had received prior ASCT. Ninety-eight percent (98%) of patients received prior bortezomib treatment, and 33% of patients received prior carfilzomib. All patients received prior lenalidomide treatment, with 98% of patients previously treated with the combination of bortezomib and lenalidomide. Eighty nine percent (89%) of patients were refractory to lenalidomide and 71% refractory to bortezomib; 64% of patients were refractory to bortezomib and lenalidomide.

Efficacy results were based on overall response rate as determined by Independent Review Committee using IMWG criteria (see Table 30).

Table 30: Efficacy Results for EQUULEUS

	N=103
Overall response rate (ORR) 95% CI (%)	61 (59.2%) (49.1, 68.8)
Stringent complete response (sCR)	8 (7.8%)
Complete response (CR)	6 (5.8%)
Very good partial response (VGPR)	29 (28.2%)
Partial response (PR)	18 (17.5%)

ORR = sCR+CR+VGPR+PR
CI = Confidence Interval

The median time to response was 1 month (range: 0.9 to 2.8 months). The median duration of response was 13.6 months (range: 0.9+ to 14.6+ months).

Monotherapy

SIRIUS (NCT01985126), was an open-label trial evaluating DARZALEX monotherapy in patients with relapsed or refractory multiple myeloma who had received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who were double-refractory to a proteasome inhibitor and an immunomodulatory agent. In 106 patients, DARZALEX 16 mg/kg was administered with pre- and post-infusion medication. Treatment continued until unacceptable toxicity or disease progression.

The median patient age was 63.5 years (range: 31 to 84 years), 49% were male and 79% were White. Patients had received a median of 5 prior lines of therapy. Eighty percent of patients had received prior autologous stem cell transplantation (ASCT). Prior therapies included bortezomib (99%), lenalidomide (99%), pomalidomide (63%) and carfilzomib (50%). At baseline, 97% of patients were refractory to the last line of treatment, 95% were refractory to both, a proteasome inhibitor (PI) and immunomodulatory agent, and 77% were refractory to alkylating agents.

Efficacy results were based on overall response rate as determined by the Independent Review Committee assessment using IMWG criteria (see Table 31).

Table 31: Efficacy Results for SIRIUS

	N=106
Overall response rate (ORR) 95% CI (%)	31 (29.2%) (20.8, 38.9)
Stringent complete response (sCR)	3 (2.8%)
Complete response (CR)	0
Very good partial response (VGPR)	10 (9.4%)
Partial response (PR)	18 (17.0%)

ORR = sCR+CR+VGPR+PR
CI = confidence interval

The median time to response was 1 month (range: 0.9 to 5.6 months). The median duration of response was 7.4 months (range: 1.2 to 13.1+ months).

Study GEN501 (NCT00574288) was an open-label dose escalation trial evaluating DARZALEX monotherapy in patients with relapsed or refractory multiple myeloma who had received at least 2 different cytoreductive therapies. In 42 patients, DARZALEX 16 mg/kg was administered with pre- and post-infusion medication. Treatment continued until unacceptable toxicity or disease progression.

The median patient age was 64 years (range: 44 to 76 years), 64% were male and 76% were White. Patients in the study had received a median of 4 prior lines of therapy. Seventy-four percent of patients had received prior ASCT. Prior therapies included bortezomib (100%), lenalidomide (95%), pomalidomide (36%) and carfilzomib (19%). At baseline, 76% of patients were refractory to the last line of treatment, 64% of patients were refractory to both, a PI and an immunomodulatory agent, and 60% of patients were refractory to alkylating agents.

Overall response rate was 36% (95% CI: 21.6, 52.0%) with 1 CR and 3 VGPR. The median time to response was 1 month (range: 0.5 to 3.2 months). The median duration of response was not estimable (range: 2.2 to 13.1+ months).

15 REFERENCES

1. Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, Transfusion, 55:1545-1554 (accessible at http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

DARZALEX® (daratumumab) injection is a colorless to pale yellow, preservative-free solution for intravenous infusion.

NDC 57894-502-05 and NDC 57894-505-05 each contain one 100 mg/5 mL single-dose vial

NDC 57894-502-20 and NDC 57894-505-20 each contain one 400 mg/20 mL single-dose vial

Storage and Stability

Store in a refrigerator at 2°C to 8°C (36°F to 46°F).

Do not freeze or shake. Protect from light. This product contains no preservative.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Infusion-Related Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion-related reactions: itchy, runny or blocked nose; fever, chills, nausea, vomiting, throat irritation, cough, headache, dizziness or lightheadedness, tachycardia, chest

- Your healthcare provider will give you medicines before each dose of DARZALEX and after each dose of DARZALEX to help reduce the risk of infusion-related reactions.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of DARZALEX?

DARZALEX may cause serious reactions, including:

- **Infusion-related reactions.** Infusion-related reactions are common with DARZALEX. Serious allergic reactions and reactions due to release of certain substances by your body (systemic) that can lead to death, can happen with DARZALEX**.** Your healthcare provider may temporarily stop your infusion or completely stop treatment with DARZALEX if you have infusion-related reactions. Get medical help right away if you get any of the following symptoms:
  - shortness of breath or trouble breathing
  - dizziness or lightheadedness (hypotension)
  - cough
  - wheezing
  - heart beating faster than usual
  - low oxygen in the blood (hypoxia)
  - throat tightness or irritation
  - runny or stuffy nose
  - headache
  - itching
  - high blood pressure
  - nausea
  - vomiting
  - chills
  - fever
  - chest discomfort
  - blurred vision
- **Changes in blood tests.** DARZALEX can affect the results of blood tests to match your blood type. These changes can last for up to 6 months after your final dose of DARZALEX. Your healthcare provider will do blood tests to match your blood type before you start treatment with DARZALEX. **Tell all of your healthcare providers that you are being treated with DARZALEX before receiving blood transfusions.**
- **Decreases in blood cell counts.** DARZALEX can decrease white blood cell counts which help fight infections and blood cells called platelets which help to clot blood. Your healthcare provider will check your blood cell counts during treatment with DARZALEX. Tell your healthcare provider if you develop fever or have signs of bruising or bleeding.

The most common side effects of DARZALEX include:

- tiredness
- nausea
- diarrhea
- shortness of breath
- feeling weak
- fever
- cough
- cold-like symptoms (upper respiratory infection)
- nerve damage causing tingling, numbness or pain
- swollen hands ankles or feet
- constipation

These are not all the possible side effects of DARZALEX.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of DARZALEX

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about DARZALEX that is written for health professionals.

What are the ingredients in DARZALEX?

Active ingredient: daratumumab

Inactive ingredients: may include glacial acetic acid, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, mannitol, polysorbate 20, sodium acetate trihydrate, sodium chloride, sorbitol, and water for injection.

Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044 U.S. License Number 1864

For more information, call 1-800-526-7736 or go to www.DARZALEX.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 3/2022