J-C Health Care Ltd.

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יולי 2020

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

ברצוננו להביא לידיעתכם את העדכונים בעלון לרופא ובעלון לצרכן של התכשיר:
העדכון כולל תוספת התוויה ושינוי במשטר המינון, כמפורט מטה.

Darzalex

המאושר להתוויות הבאות:

השינויים המהותיים בעלון לרופא מופיעים בסעיפים הבאים:

4.1 Therapeutic indications

DARZALEX is indicated:

- in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

- in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration

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Dosing schedule in combination with bortezomib (3 , thalidomide and dexamethasone (4-week cycle regimenregimens) for treatment of newly diagnosed patients eligible for autologous stem cell transplant (ASCT)):
The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in Table 3.

Table 3: DARZALEX dosing schedule in combination with bortezomib (3, thalidomide and dexamethasone ([VTd]; 4-week cycle dosing regimen)

Treatment phase	Weeks	Schedule
Induction	Weeks 1 to 8	weekly (total of 8 doses)
	Weeks 9 to 16[a]	every two weeks (total of 4 doses)
Stop for high dose chemotherapy and ASCT		
Consolidation	Weeks 1 to 8[b]	every two weeks (total of 4 doses)

[a] First dose of the every-2-week dosing schedule is given at Week 9
[b] First dose of the every-2-week dosing schedule is given at Week 1 upon re-initiation of treatment following ASCT

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For dose and schedule of medicinal products administered with DARZALEX, see section 5.1 and the corresponding Summary of Product Characteristics.

Dosing schedule in combination with bortezomib (3-week cycle regimen):
The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in Table 4.

Table 4: DARZALEX dosing schedule in combination with bortezomib (3-week cycle dosing regimen)

Weeks	**Schedule**
Weeks 1 to 9	weekly (total of 9 doses)
Weeks 10 to 24[a]	every three weeks (total of 5 doses)
Week 25 onwards until disease progression[b]	every four weeks

[a] First dose of the every-3-week dosing schedule is given at Week 10

[b] First dose of the every-4-week dosing schedule is given at Week 25

For dose and schedule of medicinal products administered with DARZALEX, see section 5.1 and the corresponding Summary of Product Characteristics.

Infusion rates
Following dilution the DARZALEX infusion should be intravenously administered at the initial infusion rate presented in Table 45 below. Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.
To facilitate administration, the first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days i.e. 8 mg/kg on Day 1 and Day 2 respectively, see Table 5 below.

Table 45: Infusion rates for DARZALEX (16 mg/kg) administration

	Dilution volume	**Initial rate (first hour)**	**Rate ~~Increments~~ [a]Increment[a]**	**Maximum rate**
Week 1 Infusion				
Option 1 (Single dose infusion)				
Week 1 ~~Infusion~~Day 1 (16 mg/kg)	1,000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Option 2 (Split dose infusion)				
Week 1 Day 1 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 1 Day 2 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 2 (16 mg/kg)infusion[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent (Week 3 onwards, 16 mg/kg) ~~infusions~~[c] infusions[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.

[b] -A dilution volume of 500 mL for the 16 mg/kg dose should be used only if there were no IRRs the previous week. Otherwise, use a dilution volume of 1,000 mL.

[c] -A modified initial rate (100 mL/hour) for subsequent infusions (i.e. Week 3 onwards) should only be used only if there were no IRRs during the previous infusion. Otherwise, continue to use instructions indicated in the table for the Week 2 infusion rate.

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4.8 Undesirable effects

Summary of the safety profile
The most frequent adverse reactions (≥ 20%) were infusion reactions, fatigue, nausea, diarrhoea, constipation, -pyrexia, dyspnoea, cough, ~~back pain,~~ neutropenia, thrombocytopenia~~-~~,

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anaemia, oedema peripheral, asthenia, peripheral sensory neuropathy and upper respiratory tract infection. Serious adverse reactions were pneumonia, bronchitis, upper respiratory tract infection, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea and atrial fibrillation.

Tabulated list of adverse reactions

Table 56 summarises the adverse drug reactions that occurred in patients receiving DARZALEX.

The data reflects exposure to DARZALEX (16 mg/kg) in 15302066 patients with multiple myeloma including 13741910 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy. Post-marketing adverse reactions are also included.

In Study MMY3006, the number of CD34+ cell yield was numerically lower in the D-VTd arm compared with the VTd arm (Median: D-VTd: 6.3 x 10^6/kg; VTd 8.9 x 10^6/kg) and among those who completed mobilisation, more patients in the D-VTd group received plerixafor compared to those in the VTd arm (D-VTd: 21.7%; VTd: 7.9%). The rates of engraftment and haematopoietic reconstitution was similar among the transplanted subjects in the D-VTd and VTd arms (D-VTd: 99.8%; VTd: 99.6%; as measured by the recovery of neutrophils > 0.5 x 10^9/L, leukocytes > 1.0 x 10^9/L, and platelets > 50 x 10^9/L without transfusion).

Frequencies are defined as very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness.

Table 56: Adverse reactions in multiple myeloma patients treated with DARZALEX 16 mg/kg

System Organ Class	Adverse reaction	Frequency	Incidence (%)	
			Any Grade	Grade 3-4
Infections and infestations	Pneumonia[a]	Very Common	1816	1210
	Bronchitis[a]		1617	2
	Upper respiratory tract infection[a]		4641	3
	Urinary tract infection	Common	98	21
	Influenza		5	1*
	Hepatitis B Virus reactivation[b]	Uncommon	-	-
Blood and lymphatic system disorders	Neutropenia[a]	Very Common	4845	4139
	Thrombocytopenia[a]		3531	2219
	Anaemia[a]		3227	1512
	Lymphopenia[a]		1214	1011
	Leukopenia[a]		1412	86
Immune system disorders	Anaphylactic reaction[b]	Rare	-	-
Metabolism and nutrition disorders	Decreased appetite	Very Common	1412	1*
	Hyperglycemia	Common	97	43
	Hypocalcemia		76	21
	Dehydration		3	1*
Nervous system disorders	Peripheral sensory neuropathy	Very Common	2332	23
	~~Headache~~		13	~~< 1*~~
	Paraesthesia	~~Common~~	711	<1
	Headache		12	<1*

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Cardiac disorders	Atrial fibrillation	Common	4	~~2~~1
Vascular disorders	Hypertension[a]	Very Common	~~11~~10	5
Respiratory, thoracic and mediastinal disorders	Cough[a]	Very Common	~~28~~25	<~~-~~1*
	Dyspnoea[a]		~~22~~21	3
	Pulmonary oedema[a]	Common	1	<1
Gastrointestinal disorders	Diarrhoea	Very Common	~~37~~32	4
	Constipation		~~27~~33	1
	Nausea		~~24~~26	~~1~~2*
	Vomiting		16	1*
	Pancreatitis[a]	Common	1	1
Musculoskeletal and connective tissue disorders	Back pain	Very Common	~~21~~19	2
	Muscle spasms		~~17~~14	<~~-~~1*
General disorders and administration site conditions	Fatigue	Very Common	~~31~~26	~~5~~4
	Oedema peripheral[a]		~~25~~26	1
	Pyrexia		~~21~~23	~~1*~~2
	Asthenia		~~17~~21	2
	Chills	Common	9	<~~-~~1*
Injury, poisoning and procedural complications	Infusion-related reaction[c]	Very Common	~~42~~40	~~5~~4

* No Grade 4

[a] Indicates grouping of terms

[b] Post-marketing adverse reaction

[c] Infusion-related reaction includes terms determined by investigators to be related to infusion, see below

Infusion-related reactions

In clinical trials (monotherapy and combination treatments; N=~~1530~~2066) the incidence of any grade infusion-related reactions was ~~40~~37% with the first (16 mg/kg, Week 1) infusion of DARZALEX, 2% with the Week 2 infusion, and cumulatively ~~4~~6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction with the Week 2 or subsequent infusions.

The median time to onset of a reaction was 1.5 hours (range: 0 to 72.8 hours). The incidence of infusion modifications due to reactions was ~~37~~36%. Median durations of 16 mg/kg~~-~~ infusions for the 1st Week, 2nd Week and subsequent infusions were approximately 7, 4 and 3 hours respectively.

Severe~~-~~ infusion-related reactions included bronchospasm, dyspnoea, laryngeal oedema, pulmonary oedema, hypoxia, and hypertension. Other adverse infusion-related reactions included nasal congestion, cough, chills, throat irritation, vomiting and nausea (see section 4.4~~) .~~).

When DARZALEX dosing was interrupted in the setting of ASCT (Study MMY3006) for a median of 3.75 (range: 2.4; 6.9) months, upon re-initiation of DARZALEX the incidence of IRRs was 11% at first infusion following ASCT. Infusion rate/dilution volume used upon re-initiation was that used for the last DARZALEX infusion prior to interruption due to ASCT. IRRs occurring at re-initiation of DARZALEX following ASCT were consistent in terms of symptoms and severity (Grade 3/4: <1%) with those reported in previous studies at Week 2 or subsequent infusions.

In Study MMY1001, patients receiving daratumumab combination treatment (n=97) were administered the first 16 mg/kg daratumumab dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2 respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction

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was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 h for Week 1-Day 1, 4.2 h for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Infections
In patients receiving DARZALEX combination therapy, Grade 3 or 4 infections were reported as follows:
-Relapsed/refractory patient studies: DVd: 21%, Vd: 19%; DRd: 27%, Rd: 23%; DPd: 28%.%
Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%.%; D-VTd: 22%, VTd: 20%.
-Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies.
In the active controlled studies, discontinuations from treatment due to infections (1-4%) and fatal infections were generally infrequent and balanced between the DARZALEX containing regimens and active control arms. Fatal infections were primarily due to pneumonia and sepsis.
Key: D=daratumumab; Vd=bortezomib-dexamethasone; Rd=lenalidomide-dexamethasone; Pd=pomalidomide-dexamethasone; VMP=bortezomib-melphalan-prednisone; VTd=bortezomib-thalidomide-dexamethasone.

Haemolysis
There is a theoretical risk of haemolysis. Continuous monitoring for this safety signal will be performed in clinical studies and post-marketing safety data.

Other special populations
In the Phase III study MMY3007, which compared treatment with D-VMP to treatment with VMP in patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, safety analysis of the subgroup of patients with an ECOG performance score of 2 (D-VMP: n=89, VMP: n=84), was consistent with the overall population (see section 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC24

Mechanism of action
Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to the CD38 protein expressed at a high level on the surface of multiple myeloma tumour cells, as well as other cell types and tissues at various levels. CD38 protein has multiple functions such as receptor mediated adhesion, signalling and enzymatic activity.

Daratumumab has been shown to potently inhibit the *in vivo* growth of CD38-expressing tumour cells. Based on *in vitro* studies, daratumumab may utilise multiple effector functions, resulting in immune mediated tumour cell death. These studies suggest that daratumumab can

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induce tumour cell lysis through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis in malignancies expressing CD38. 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 mediated cell lysis. T cells (CD3+, CD4+, and CD8+) are also known to express CD38 depending on the stage of development and the level of activation. Significant increases in CD4+ and CD8+ T cell absolute counts, and percentages of lymphocytes, were observed with daratumumab treatment in peripheral whole blood and bone marrow. In addition, T-cell receptor DNA sequencing verified that T-cell clonality was increased with daratumumab treatment, indicating immune modulatory effects that may contribute to clinical response.

Daratumumab induced apoptosis *in vitro* after Fc mediated cross-linking. In addition, daratumumab modulated CD38 enzymatic activity, inhibiting the cyclase enzyme activity and stimulating the hydrolase activity. The significance of these *in vitro* effects in a clinical setting, and the implications on tumour growth, are not well-understood.

Pharmacodynamic effects

Natural killer (NK) cell and T-cell count

NK cells are known to express high levels of 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 daratumumab treatment. However, baseline levels of NK cells did not show an association with clinical response.

Immunogenicity

~~Patients treated with daratumumab monotherapy (n=199) and combination therapy (n=750) were evaluated for anti-therapeutic antibody responses to daratumumab at multiple time points during treatment and up to 8 weeks following the end of treatment. Following the start of daratumumab treatment, none of the monotherapy patients and 2 of the 750 combination therapy patients tested positive for anti-daratumumab antibodies; 1 of the combination therapy patients developed transient neutralising antibodies against daratumumab.~~

~~However, the employed assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab. Therefore, the incidence of antibody development might not have been reliably determined.~~

In patients treated with intravenous daratumumab in clinical trials, less than 1% of patients developed treatment-emergent anti-daratumumab antibodies.

Clinical efficacy and safety

Newly diagnosed multiple myeloma

Combination treatment with lenalidomide and dexamethasone in patients ineligible for autologous stem cell transplant:

Study MMY3008, an open-label, ~~randomized~~randomised, active-controlled Phase III study, 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. 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. 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.

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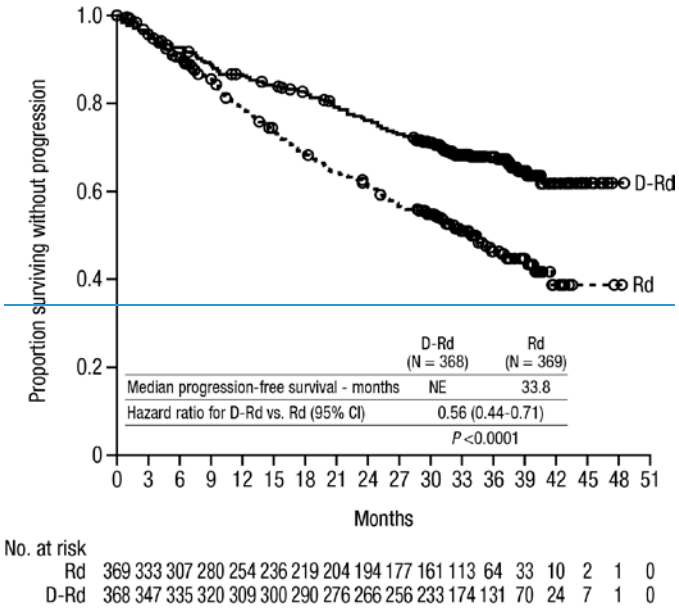
A total of 737 patients were ~~randomized~~randomised: 368 to the DRd arm and 369 to the Rd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 73 (range: 45-90) years, with 44% of the patients ≥75 years of age. The majority were white (92%), male (52%), 34% had an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 49.5% 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.

Study MMY3008 showed 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. Results of an updated PFS analysis approximately 9 months after the original clinical cutoff, continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was not reached in the DRd arm and was 33.8 months in the Rd arm (HR=0.56; 95% CI: 0.44, 0.71; p<0.0001).

Figure 1: Kaplan-Meier Curve of PFS in Study MMY3008



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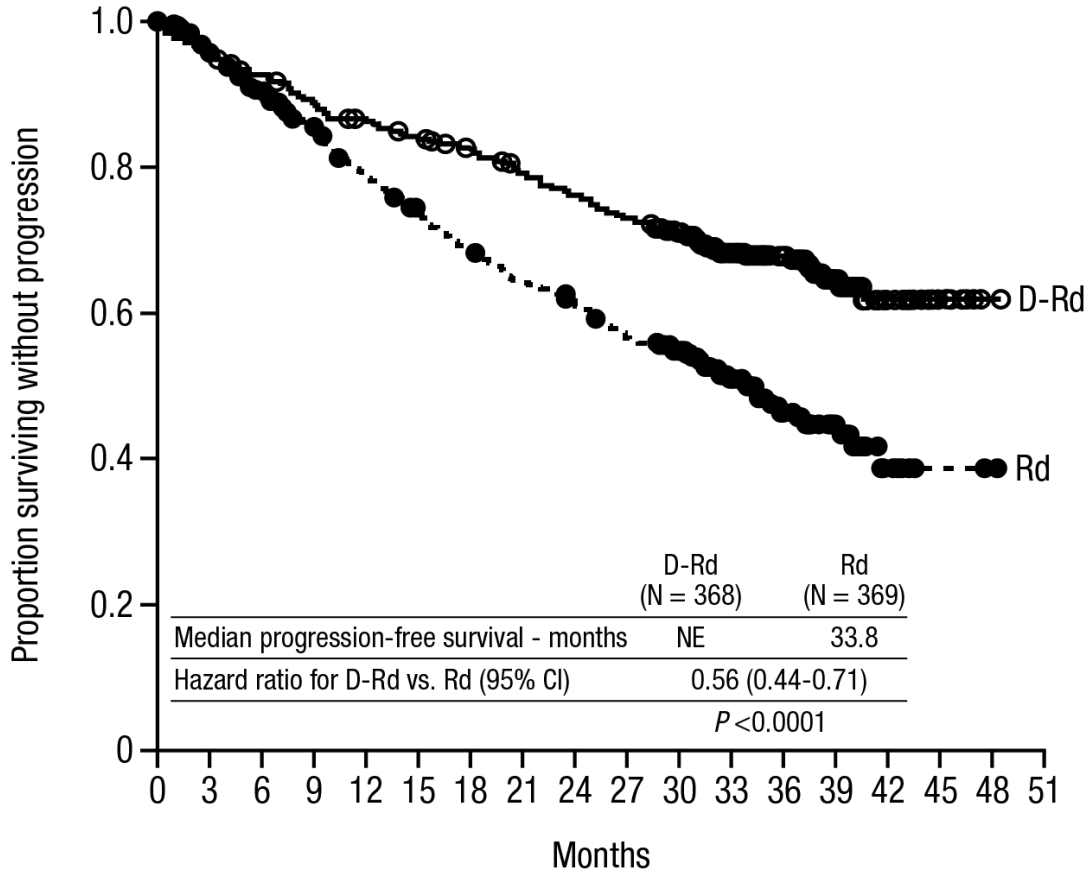

No. at risk

Rd	369	333	307	280	254	236	219	204	194	177	161	113	64	33	10	2	1	0
D-Rd	368	347	335	320	309	300	290	276	266	256	233	174	131	70	24	7	1	0

Additional efficacy results from Study -MMY3008 are presented in Table ~~6~~7 below.

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Table 67: Additional efficacy results from Study MMY3008[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%)
Odds ratio with 95% CI[d]	4.04 (2.55, 6.39)	
p-value[e]	<0.0001	

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}
[d] Mantel-Haenszel estimate of the odds ratio for un-stratified tables is used. An odds ratio >1 indicates an advantage for DRd.
[e] 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:
Study MMY3007, an open-label, randomised, active-controlled Phase III study, 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. 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 treatment was continued until disease progression or unacceptable toxicity.
A total of 706 patients were randomised: 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. Patients had IgG/IgA/Light chain myeloma in 64%/22%/10% of instances, 19% had ISS Stage I, 42% had ISS Stage II, 38% had ISS Stage III disease and 84% had standard risk cytogenetics. Efficacy was evaluated by PFS based on IMWG criteria and overall survival (OS).

TheWith a median follow-up of 16.5 months, the primary analysis of PFS in Study MMY3007 showed an improvement in the D-VMP arm as compared to the VMP arm; the median PFS had

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not been reached in the D-VMP arm and was 18.1- months in the VMP arm (HR=0.5; 95% CI: 0.38, 0.65; p<0.0001~~), representing 50% reduction in the risk of disease progression or death in patients treated with D-VMP.~~). Results of an updated PFS analysis ~~approximately 4~~ after a median follow-up of 40 months ~~after the original clinical cutoff,~~ continued to show an improvement in PFS for patients in the D-VMP arm compared with the VMP arm. Median PFS was ~~not reached~~36.4 months in the D-VMP arm and ~~was~~ 19.3 months in the VMP arm (HR=0.~~46; 42;~~ 95% CI: 0.~~36~~34, 0.~~60; p<0.0001).~~51; p<0.0001), representing a 58% reduction in the risk of disease progression or death in patients treated with D-VMP.

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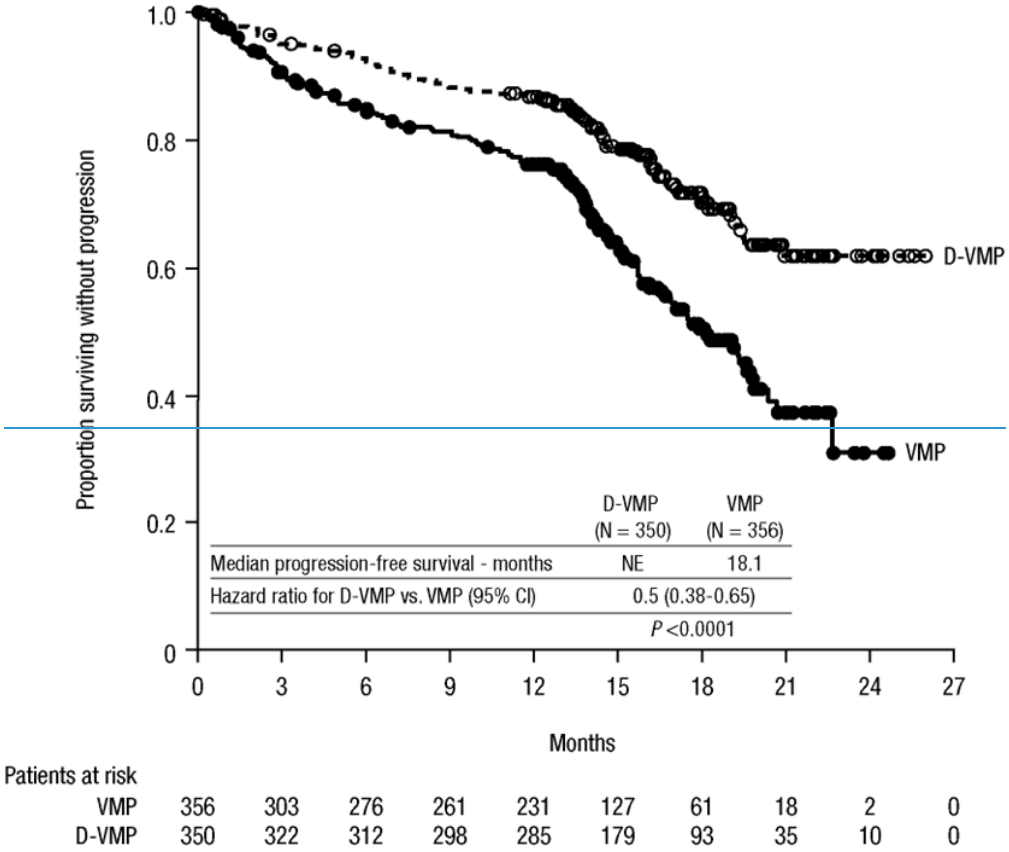
Figure 2: Kaplan-Meier Curve of ~~Primary Analysis of~~ PFS in Study MMY3007



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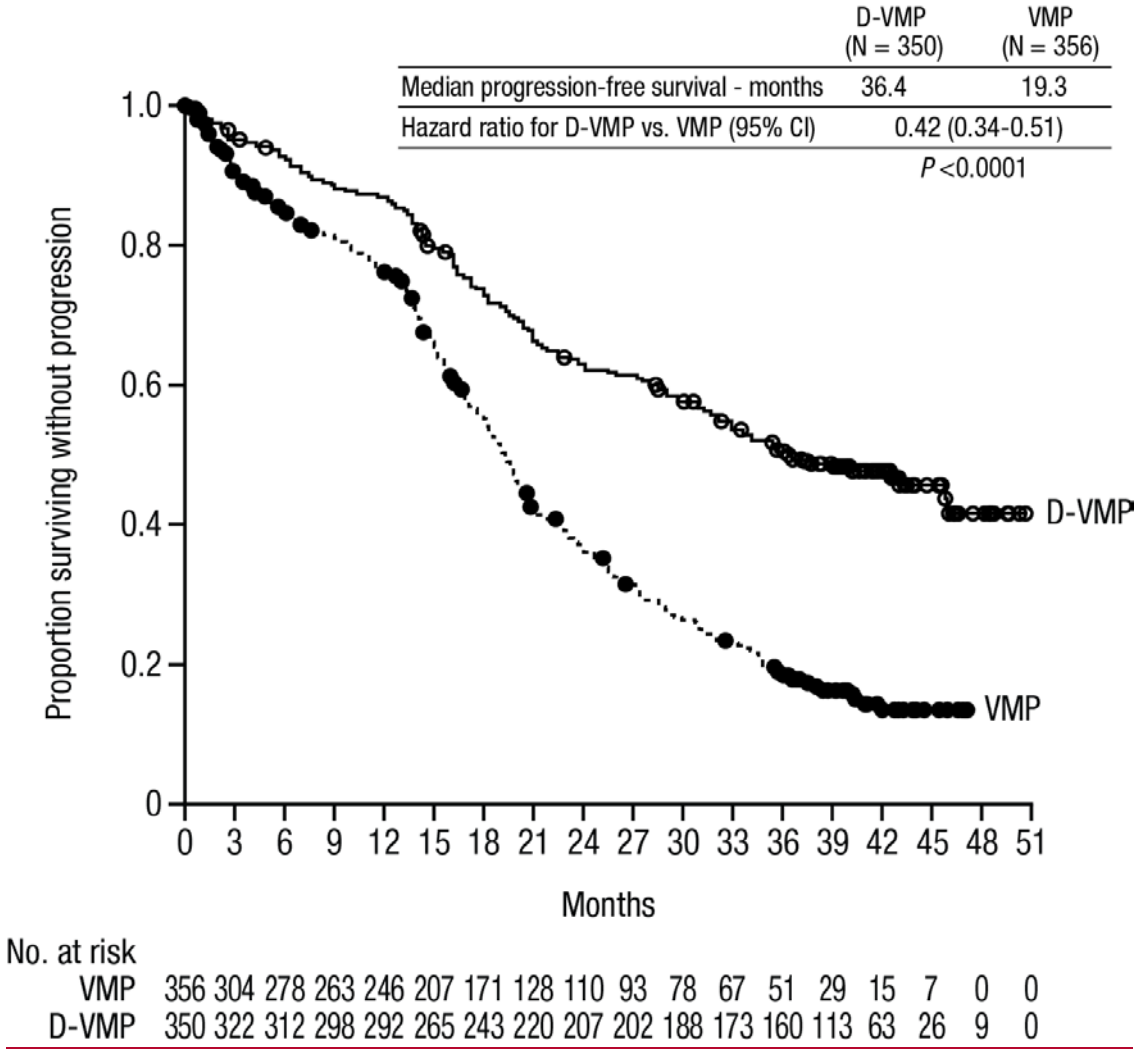

After a median follow-up of 40 months, D-VMP has shown an overall survival (OS) advantage over the VMP arm (HR=0.60; 95% CI: 0.46, 0.80; p=0.0003), representing a 40% reduction in the risk of death in patients treated in the D-VMP arm. Median OS was not reached for either arm.

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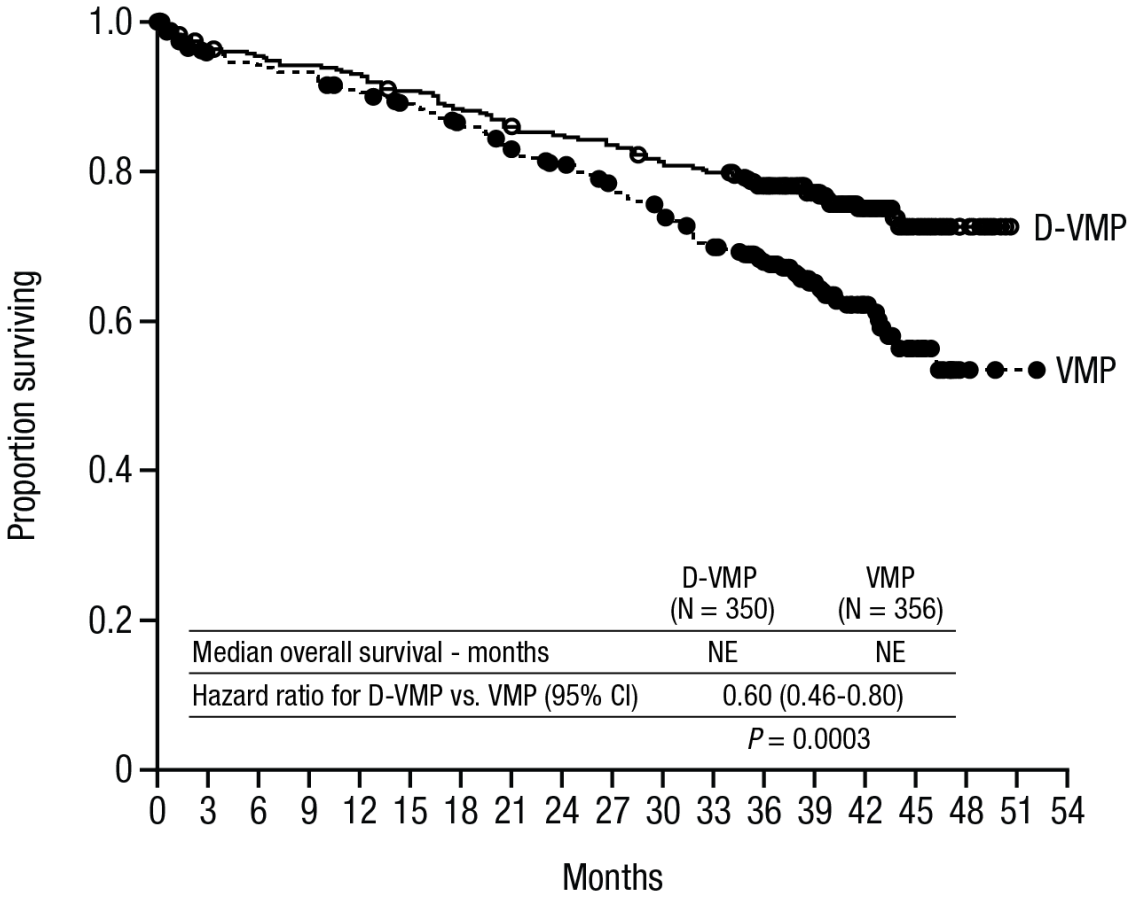
Figure 3: Kaplan-Meier Curve of OS in Study MMY3007



No. at risk

VMP	356	331	325	322	312	302	292	278	269	257	242	226	198	132	73	27	3	1	0
D-VMP	350	330	327	322	318	309	301	292	288	283	275	270	248	171	97	40	12	0	0

Additional efficacy results from Study MMY3007 are presented in Table ~~7~~8 below.

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Table ~~7~~8: Additional efficacy results from Study MMY3007[a]

	D-VMP (n=350)	VMP (n=356)
Overall response (sCR+CR+VGPR+PR) [n(%)]	318 (90.9)	263 (73.9)
p-value[b]	<0.0001	
Stringent complete response (sCR) [n(%)]	63 (18.0)	25 (7.0)
Complete response (CR) [n(%)]	86 (24.6)	62 (17.4)
Very good partial response (VGPR) [n(%)]	100 (28.6)	90 (25.3)
Partial response (PR) [n(%)]	69 (19.7)	86 (24.2)
MRD negativity rate (95% CI) [c] (%)	22.3 (18.0, 27.0)	6.2 (3.9, 9.2)
Odds ratio with 95% CI[d]	4.36 (2.64, 7.21)	
p-value[e]	<0.0001	

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}
[d] A Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. An odds ratio >1 indicates an advantage for D-VMP.
[e] 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: 18.4, not estimable) in the VMP group.

A subgroup analysis was performed on patients at least 70 years old, or those 65-69 years old with ECOG performance score of 2, or aged less than 65 years of age with significant comorbidity or ECOG performance score of 2 (D-VMP: n=273, VMP: n=270). The efficacy results in this subgroup were consistent with the overall population. In this subgroup, median PFS was not reached in the D-VMP group and was 17.9 months in the VMP group (HR=0.56; 95% CI: 0.42, 0.75); p<0.0001). The overall response rate was 90% in the D-VMP group and 74% in theVMP group (VGPR rate:29% in D-VMP group and 26% in VMP group; CR: 22% in D-VMP group and 18% in VMP group; sCR rate: 20% in D-VMP group and 7% in VMP group). The safety results of this subgroup were consistent with the overall population. Furthermore, safety analysis of the subgroup of patients with an ECOG performance score of 2 (D-VMP: n=89, VMP: n=84), was also consistent with the overall population.

Combination treatment with bortezomib, thalidomide and dexamethasone (VTd) in patients eligible for autologous stem cell transplant (ASCT):
Study MMY3006 is a 2 Part, open-label, randomised, active-controlled Phase III study. Part 1 compared induction and consolidation treatment with DARZALEX 16 mg/kg in combination with bortezomib, thalidomide and dexamethasone (D-VTd) 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. In Part 2, subjects with at least a partial response (PR) by Day 100 post-transplant were re-randomised in a 1:1 ratio to daratumumab maintenance or observation only. Only results from Part 1 are described henceforth.

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 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

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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. Dose adjustments for bortezomib, thalidomide and dexamethasone were applied according to manufacturer's prescribing information.

A total of 1085 patients were randomised: 543 to the D-VTd 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 (range: 22 to 65) years. All patients were ≤ 65 years: 43% were in the age group ≥ 60-65 years, 41% were in the age group ≥ 50-60 years and 16% below age of 50 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 International Staging System (ISS) Stage I, 45% had ISS Stage II and 15% had ISS Stage III disease.

Efficacy was evaluated by the stringent Complete Response (sCR) rate at Day 100 post-transplant and Progression free survival (PFS).

Table 9: Efficacy results from Study MMY3006[a]

	D-VTd (n=543)	**VTd (n=542)**	**P value[b]**
Response assessment Day 100 post-transplant			
Stringent Complete Response (sCR)	157 (28.9%)	110 (20.3%)	0.0010
CR or better (sCR+CR)	211 (38.9%)	141 (26.0%)	<0.0001
Very Good Partial Response or better (sCR+CR+VGPR)	453 (83.4%)	423 (78.0%)	
MRD negativity[c, d] n(%)	346 (63.7%)	236 (43.5%)	<0.0001
95% CI (%)	(59.5%, 67.8%)	(39.3%, 47.8%)	
Odds ratio with 95% CI[e]	2.27 (1.78, 2.90)		
MRD negativity in combination with CR or better[c] n(%)	183 (33.7%)	108 (19.9%)	<0.0001
95% CI (%)	(29.7%, 37.9%)	(16.6%, 23.5%)	
Odds ratio with 95% CI[e]	2.06 (1.56, 2.72)		

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

[d] Regardless of response per IMWG

[e] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used.

Results of a PFS analysis by censoring patients who were randomised to daratumumab maintenance in the second randomisation, at the date of the second randomisation showed HR=0.50; 95% CI: 0.34, 0.75; p=0.0005.

Relapsed/Refractory multiple myeloma
Monotherapy:
The clinical efficacy and safety of DARZALEX monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who had demonstrated disease progression on the last therapy, was demonstrated in two open-label studies.

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In Study MMY2002, 106 patients with relapsed and refractory multiple myeloma received 16 mg/kg DARZALEX until disease progression. The median patient age was 63.5 years (range, 31 to 84 years), 11% of patients were ≥75 years of age, 49% were male and 79% were Caucasian. 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 (IMiD), 77% were refractory to alkylating agents, 63% were refractory to pomalidomide and 48% of patients were refractory to carfilzomib.

Efficacy results of the pre-planned interim analysis based on Independent Review Committee (IRC) assessment are presented in Table 810 below.

Table 810: IRC assessed efficacy results for study MMY2002

Efficacy endpoint	**DARZALEX 16 mg/kg N=106**
Overall response rate[1] (ORR: sCR+CR+VGPR+PR) [n (%)] 95% CI (%)	31 (29.2) (20.8, 38.9)
Stringent complete response (sCR) [n (%)]	3 (2.8)
Complete response (CR) [n]	0
Very good partial response (VGPR) [n (%)]	10 (9.4)
Partial response (PR) [n (%)]	18 (17.0)
Clinical Benefit Rate (ORR+MR) [n (%)]	36 (34.0)
Median Duration of Response [months (95% CI)]	7.4 (5.5, NE)
Median Time to Response [months (range)]	1 (0.9; 5.6)

[1] Primary efficacy endpoint (International Myeloma Working Group criteria)
CI=confidence interval; NE=not estimable; MR=minimal response

Overall response rate (ORR) in MMY2002 was similar regardless of type of prior anti-myeloma therapy.
At a survival update with a median duration of follow-up of 14.7 months, median Overall Survival (OS) was 17.5 months (95% CI:13.7, not estimable).

In Study GEN501, 42 patients with relapsed and refractory multiple myeloma received 16 mg/kg DARZALEX until disease progression. The median patient age was 64 years (range, 44 to 76 years), 64% were male and 76% were Caucasian. 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% were refractory to both a PI and IMiD, 60% were refractory to alkylating agents, 36% were refractory to pomalidomide and 17% were refractory to carfilzomib.

Pre-planned interim analysis showed that treatment with daratumumab at 16 mg/kg led to a 36% ORR with 5% CR and 5% VGPR. The median time to response was 1 (range: 0.5 to 3.2) month. The median duration of response was not reached (95% CI: 5.6 months, not estimable).

At a survival update with a median duration of follow-up of 15.2 months, median OS was not reached (95% CI: 19.9 months, not estimable), with 74% of subjects still alive.

Combination treatment with lenalidomide:

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Study MMY3003, an open-label, randomised, active-controlled Phase III 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 relapsed or refractory 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 dexamethasone at 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. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 569 patients were randomised; 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) and 11% were ≥75 years. The majority of patients (86%) received a prior PI, 55% of patients had received a prior IMiD, including 18% of patients who had received prior lenalidomide; and 44% of patients had received both a prior PI and IMiD. 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. Patients refractory to lenalidomide were excluded from the study.

~~Study~~With a median follow-up of 13.5 months, the primary analysis of PFS in study MMY3003 demonstrated an improvement in ~~PFS in~~ the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (HR=0.37; 95% CI: 0.27, 0.52; p<0.0001). Results of an updated PFS analysis after a median follow-up of 55 months continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was 45.0 months in the DRd arm and 17.5 months in the Rd arm (HR=0.44; 95% CI: 0.35, 0.54; p<0.0001), representing ~~63~~a 56% reduction in the risk of disease progression or death in patients treated with DRd (see Figure ~~3~~4).

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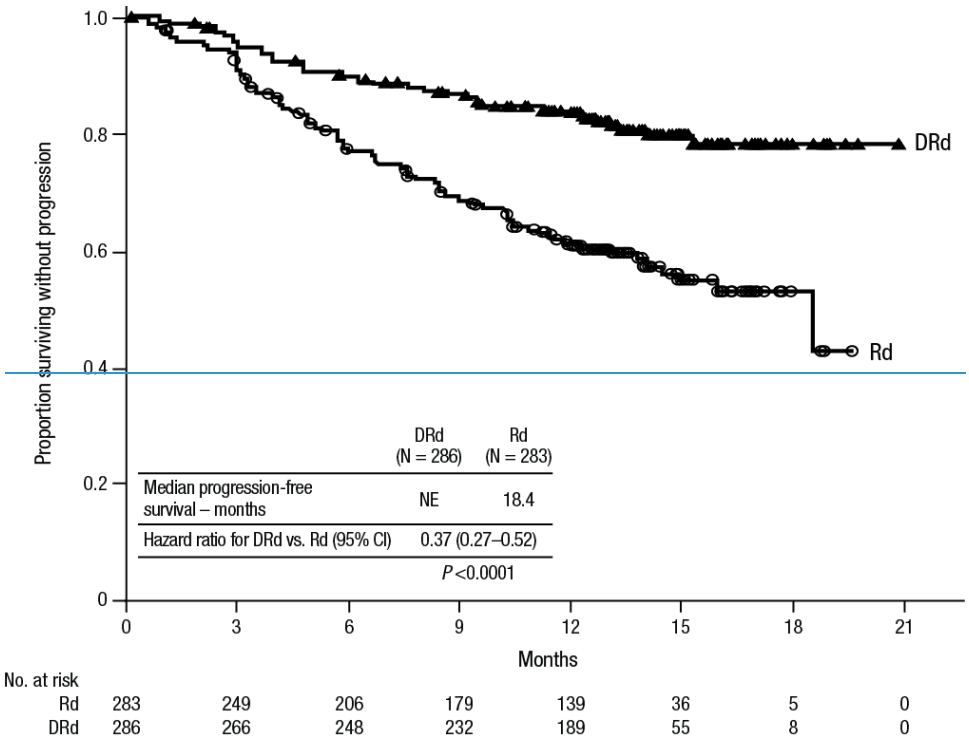
Figure 34: Kaplan-Meier Curve of PFS in Study MMY3003



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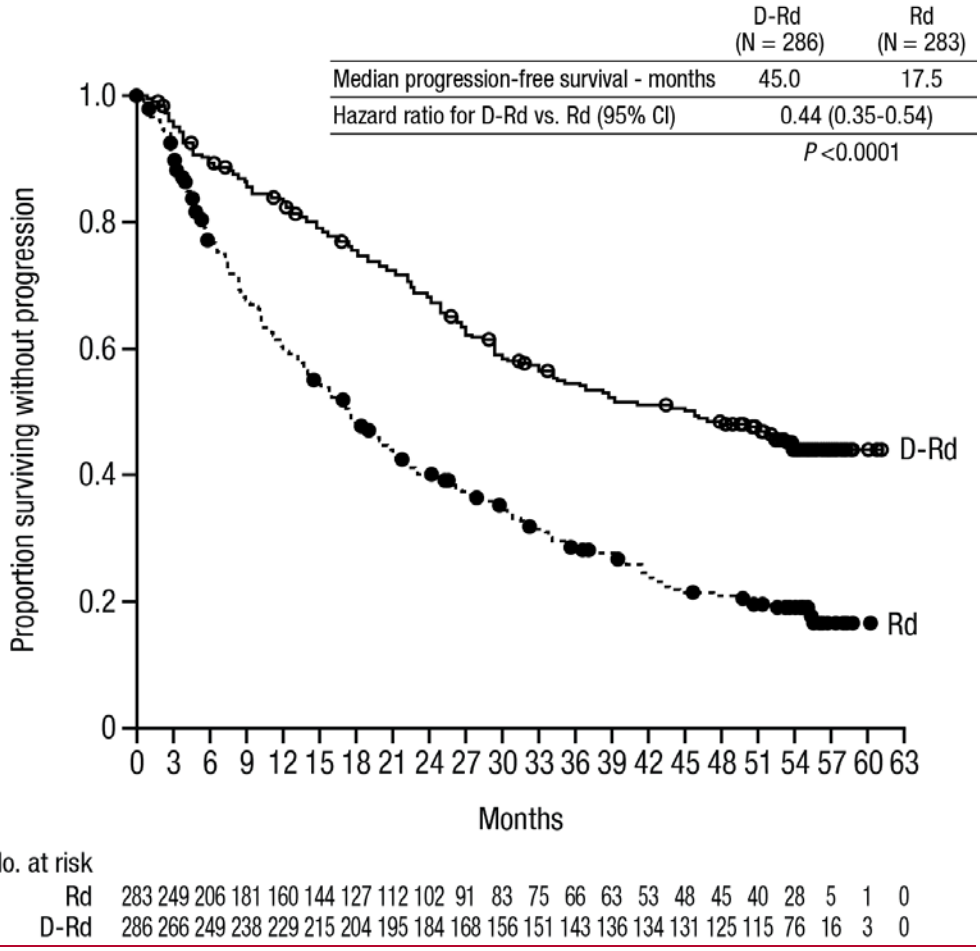

Additional efficacy results from Study MMY3003 are presented in Table ~~9~~11 below.

Table ~~9~~11: Additional efficacy results from Study MMY3003

Response evaluable patient number	**DRd (n=281)**	**Rd (n=276)**
Overall response (sCR+CR+VGPR+PR) n(%)	261 (92.9)	211 (76.4)
p-value[a]	<-0.0001	
Stringent complete response (sCR)	51 (18.1)	20 (7.2)
Complete response (CR)	70 (24.9)	33 (12.0)
Very good partial response (VGPR)	92 (32.7)	69 (25.0)
Partial response (PR)	48 (17.1)	89 (32.2)
Median Time to Response [months (95% CI)]	1.0 (1.0, 1.1)	1.3 (1.1, 1.9)
Median Duration of Response [months (95% CI)]	NE (NE, NE)	17.4 (17.4, NE)
MRD negative rate (95% CI)[b] (%)	~~29~~21.0 (~~23.8, 34.7~~16.4, 26.2)	~~7~~2.8 (~~4.9, 11~~1.2, 5.5)
Odds ratio with 95% CI[c]	9.31 (~~4.85 (2.93, 8.03~~31, 20.09)	
P-value[d]	<-0.~~000001~~0001	

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DRd=daratumumab-lenalidomide-dexamethasone; Rd=lenalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval; NE=not estimable.

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

[b] Based on Intent-to-treat population and threshold of 10^{-4}5

[c] ~~A Chi-Squared~~Mantel-Haenszel estimate of the common odds ratio is used. An odds ratio >-1 indicates an advantage for DRd.

[d] p-value is from a ~~likelihood-ratio Chi-Squared~~Fisher's exact test.

Median OS was not reached for either treatment group. With an overall median follow-up of 13.5 months, the hazard ratio for OS was 0.64 (95% CI: 0.40, 1.01; p=0.0534).

Combination treatment with bortezomib:
Study MMY3004, an open-label, randomised, active-controlled Phase- III 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 relapsed or refractory multiple myeloma who had received at least one prior therapy. Bortezomib was administered by SC injection or IV infusion 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. DARZALEX treatment was continued until disease progression or unacceptable toxicity.

A total of 498 patients were randomised; 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) and 12% were ≥-75 years. Sixty--nine percent (69%) of patients had received a prior PI (66% received bortezomib) and 76% of patients received an IMiD (42% received lenalidomide). At baseline, 32% of patients were refractory to the last line of treatment. Thirty-three percent (33%) of patients were refractory to an IMiD only, and 28% were refractory to lenalidomide. Patients refractory to bortezomib were excluded from the study.

~~Study~~With a median follow-up of 7.4 months, the primary analysis of PFS in study MMY3004 demonstrated an improvement ~~in PFS~~ in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.53]; p-value<0.0001). Results of an updated PFS analysis after a median follow-up of 50 months continued to show an improvement in PFS for patients in the DVd arm compared with the Vd arm. Median PFS was 16.7 months in the DVd arm and 7.1 months in the Vd arm (HR [95% CI]: 0.31 [0.24, 0.39]; p-value<0.0001), representing a ~~61~~69% reduction in the risk of disease progression or death ~~for~~in patients treated with DVd versus Vd- (see Figure 45).

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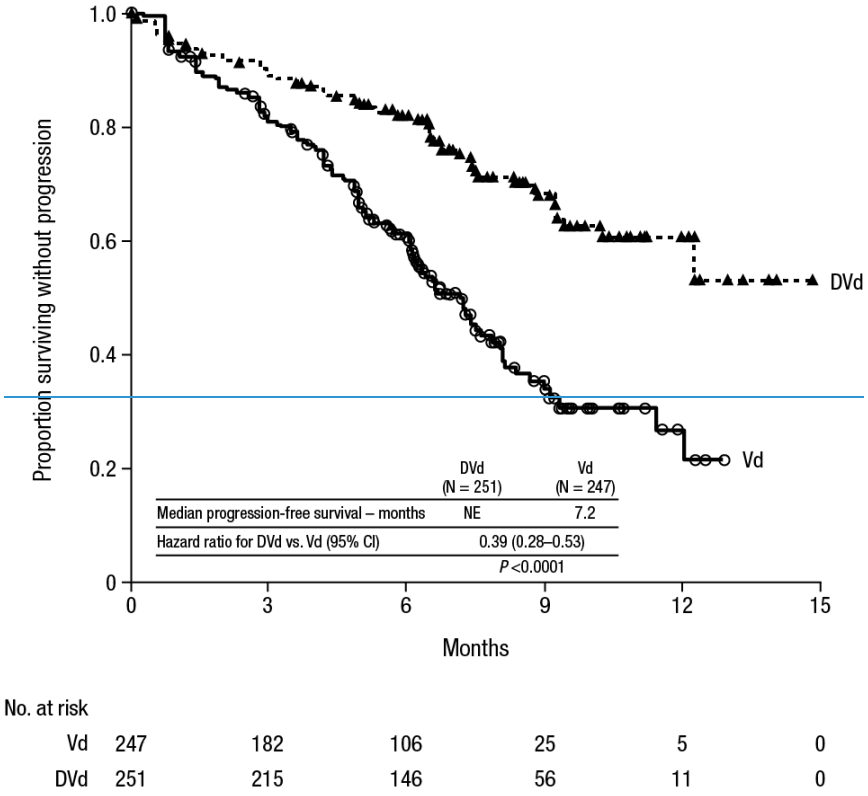
Figure 45: Kaplan-Meier Curve of PFS in Study MMY3004



No. at risk

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

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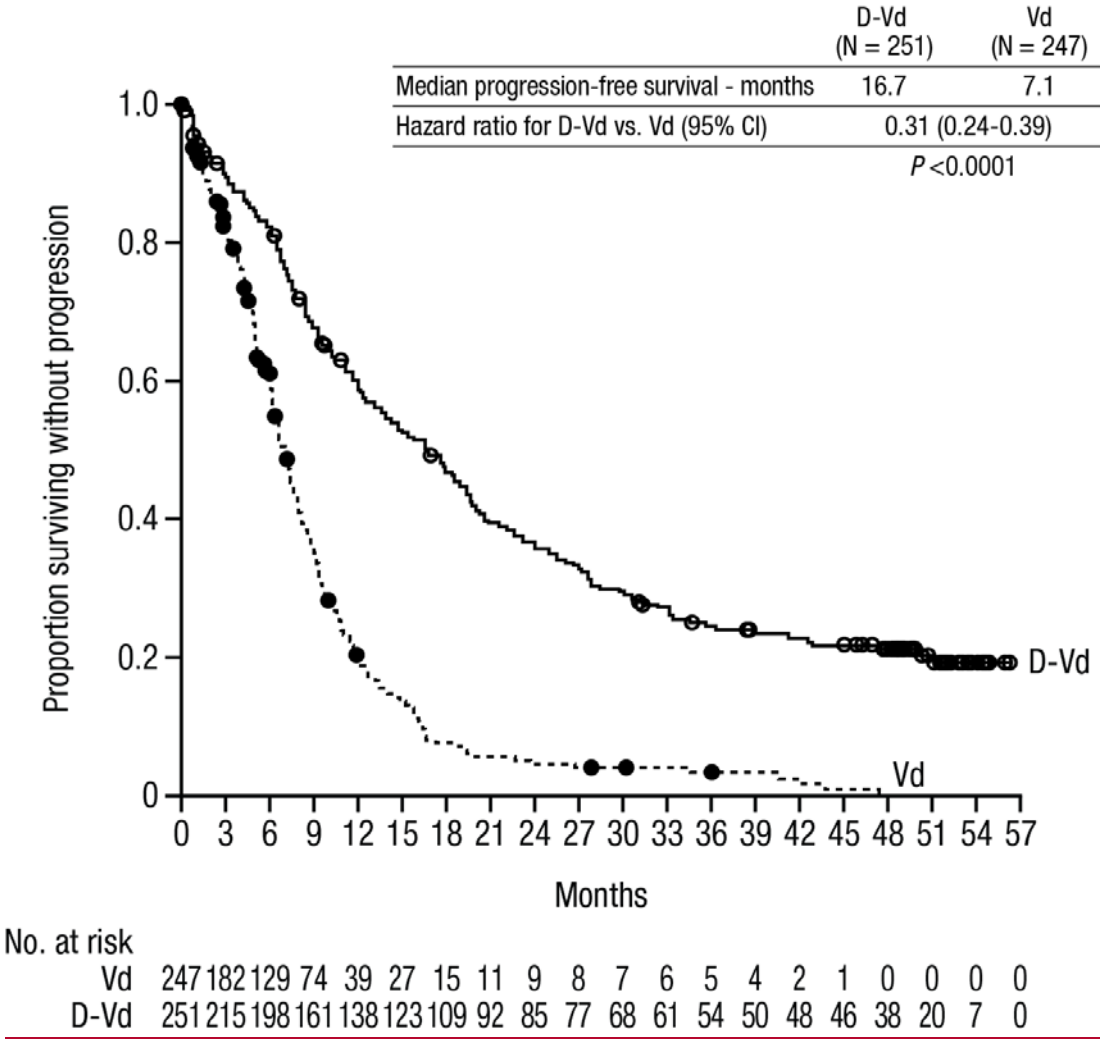

Additional efficacy results from Study MMY3004 are presented in Table ~~10~~12 below.

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Table ~~10~~12: Additional efficacy results from Study MMY3004

Response evaluable patient number	DVd (n=240)	Vd (n=234)
Overall response (sCR+CR+VGPR+PR) n(%)	199 (82.9)	148 (63.2)
P-value[a]	<-0.0001	
Stringent complete response (sCR)	11 (4.6)	5 (2.1)
Complete response (CR)	35 (14.6)	16 (6.8)
Very good partial response (VGPR)	96 (40.0)	47 (20.1)
Partial response (PR)	57 (23.8)	80 (34.2)
Median Time to Response [months (range)]	0.9 (0.8, 1.4)	1.6 (1.5, 2.1)
Median Duration of Response [months (95% CI)]	NE (11.5, NE)	7.9 (6.7, 11.3)
MRD negative rate (95% CI)[b]	~~13.~~8.8% (5~~% (9~~.6%, ~~18.4~~13.0%)	~~2.8% (~~1.~~1%, ~~2% (0.3%, 3.5~~.8%)
Odds ratio with 95% CI[c]	~~5.37~~9.04 (2.~~33, 12.37~~53, 32.21)	
P-value[d]	0.~~000006~~0001	

DVd=daratumumab- bortezomib-dexamethasone; Vd=bortezomib-dexamethasone; MRD=minimal residual disease; CI=confidence interval; NE=not estimable.

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

[b] Based on Intent-to-treat population and threshold of 10^{-4}~~5~~

[c] ~~A Chi-Squared~~Mantel-Haenszel estimate of the common odds ratio is used. An odds ratio >-1 indicates an advantage for DVd.

[d] p-value is from ~~a likelihood-ratio chi-squared~~Fisher's exact test.

Median OS was not reached for either treatment group.With an overall median follow-up of 7.4 months (95% CI: 0.0, 14.9), the hazard ratio for OS was 0.77 (95% CI: 0.47, 1.26; p=0.2975).

Cardiac electrophysiology

Daratumumab as a large protein has a low likelihood of direct ion channel interactions. The effect of daratumumab on the QTc interval was evaluated in an open-label study for 83 patients (Study GEN501) with relapsed and refractory multiple myeloma following daratumumab infusions (4 to 24- mg/kg). Linear mixed PK-PD analyses indicated no large increase in mean QTcF interval (i.e~~.~~., greater than 20- ms) at daratumumab C_{max}.

Paediatric population

Darzalex is indicated for use in adults above the age of 18 (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of daratumumab following intravenous administration of daratumumab monotherapy were evaluated in patients with relapsed and refractory multiple myeloma at dose levels from 0.1 mg/kg to 24 mg/kg.

In the 1- to 24 mg/kg cohorts, peak serum concentrations (C_{max}) after the first dose increased in approximate proportion to dose and volume of distribution was consistent with initial distribution into the plasma compartment. Following the last weekly infusion, C_{max} increased in a greater than dose-proportional manner, consistent with target mediated drug disposition. Increases in AUC were more than dose-proportional and clearance (CL) decreased with increasing dose. These observations suggest CD38 may become saturated at higher doses, after which the impact of target binding clearance is minimised and the clearance of daratumumab

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approximates the linear clearance of endogenous IgG1. Clearance also decreased with multiple doses, which may be related to tumour burden decreases.

Terminal half-life increases with increasing dose and with repeated dosing. The mean (standard deviation [SD]) estimated terminal half-life of daratumumab following the first 16 mg/kg dose was 9 (4.3) days. The estimated terminal half-life of daratumumab following the last 16 mg/kg dose increased, but there are insufficient data for a reliable estimation. Based on population PK analysis, the mean (SD) half-life associated with non-specific linear elimination was approximately 18 (9) days; this is the terminal half-life that can be expected upon complete saturation of target mediated clearance and repeat dosing of daratumumab.

At the end of weekly dosing for the recommended monotherapy schedule and dose of 16 mg/kg, the mean (SD) serum C_{max} value was 915 (410.3) micrograms/mL, approximately 2.9-fold higher than following the first infusion. The mean (SD) predose (trough) serum concentration at the end of weekly dosing was 573 (331.5) micrograms/mL.

Four population PK analyses were performed to describe the PK characteristics of daratumumab and to evaluate the influence of covariates on the disposition of daratumumab in patients with multiple myeloma; Analysis 1 (n=223) in patients receiving DARZALEX monotherapy while Analysis 2 (n=694)), Analysis 3 (n=352) and Analysis 4 (n=355) were conducted in patients with multiple myeloma that received daratumumab combination therapies. Analysis 2 included 694 patients (n=326 for lenalidomide-dexamethasone; n=246 for bortezomib-dexamethasone; n=99 for pomalidomide-dexamethasone; n=11 for bortezomib-melphalan-prednisone; and n=12 for bortezomib-thalidomide-dexamethasone), Analysis 3 included 352 patients (bortezomib-melphalan-prednisone) and Analysis 4 included 355 patients (lenalidomide-dexamethasone).

Based on the population PK analysis of daratumumab monotherapy (Analysis 1), daratumumab steady state is achieved approximately 5 months into the every 4-week dosing period (by the 21st infusion), and the mean (SD) ratio of C_{max} at steady-state to C_{max} after the first dose was 1.6 (0.5). The mean (SD) central volume of distribution is 56.98 (18.07) mL/kg.

Three additional population PK analyses (Analysis 2, Analysis 3 and Analysis 4) were conducted in patients with multiple myeloma that received daratumumab combination therapies. Daratumumab concentration--time profiles were similar following the monotherapy and combination therapies. The mean estimated terminal half-life associated with linear clearance in combination therapy was approximately 15--23 days.

Based on the four population PK analyses (Analyses 1-4) body weight was identified as a statistically significant covariate for daratumumab clearance. Therefore, body weight based dosing is an appropriate dosing strategy for the multiple myeloma patients.

Simulation of daratumumab pharmacokinetics was conducted for all recommended dosing schedules in 1,309 patients with multiple myeloma. The simulation results confirmed that the split and single dosing for the first dose provide similar PK, with the exception of the PK profile in the first day of the treatment.

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השינויים המהותיים בעלון לצרכן מופיעים בסעיפים הבאים:

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המינון ההתחלתי המקובל של דארזלקס הוא 16 מ"ג לכל ק"ג משקל גוף. דארזלקס יכולה להינתן לך כטיפול יחיד או יחד עם תרופות נוספות לטיפול במיאלומה נפוצה.

דארזלקס ניתנת כטיפול יחיד באופן הבא:

- פעם בשבוע במשך 8 השבועות הראשונים
- לאחר מכן, פעם בשבועיים, למשך 16 שבועות
- לאחר מכן, פעם ב- 4 שבועות, ~~כל~~ כל עוד שמצבך לא מחמיר.

כאשר דארלזקס ניתנת בשילוב תרופות נוספות, ייתכן והרופא ישנה את הזמנים שבין המנות וכן את מספר הטיפולים שתקבל.

בשבוע הראשון הרופא יכול לתת לך את מנת הדרלקס מחולקת על פני 2 ימים עוקבים.

אין לעבור ~~את~~ על המנה המומלצת

כיצד ניתנת התרופה

דארזלקס ניתנת על ידי רופא או אחות בטפטוף לוריד (עירוי תוך-ורידי), לאורך מספר שעות.

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2. תופעות לוואי

כמו בכל תרופה, השימוש בדארזלקס עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. יתכן ולא תסבול מאף אחת מהן.

תגובות הנובעות מהעירוי

פנה לרופא או לאחות באופן מידי, במידה ובמהלך העירוי או ב-3 ימים שלאחריו אתה חווה אחת מהתופעות הבאות המיוחסות לעירוי. יתכן ותזדקק לתרופות נוספות או להאטה או הפסקה של העירוי.

תופעות לוואי אלו הן שכיחות מאד – **(**very common**)** תופעות שמופיעות ביותר ממשתמש אחד מעשרה

- צמרמורת
- כאב גרון, שיעול
- בחילה
- הקאה
- גרד באף, נזלת או גודש באף
- קוצר נשימה או בעיות נשימה אחרות

תופעות לוואי שכיחות ~~נוספות~~ אחרות (common) (תופעות שמופיעות ב 1-10 משתמשים מתוך 100

- אי נוחות בחזה
- סחרחורת (הקשורה ללחץ דם נמוך)

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- גרד
- צפצוף נשימתי

תופעות לוואי נדירות (rare) תופעות שמופיעות ב 1-10 משתמשים מתוך 10,000

תגובה אלרגית חמורה אשר עלולה להתבטא בהתנפחות הפנים, השפתיים, הפה, הלשון או הגרון, בקשיי בליעה או נשימה או בפריחה מגרדת (חרלת)

במידה ואתה חווה אחת מהתופעות מעלה הנובעות מהעירוי, פנה לרופא או לאחות באופן מידי

תופעות לוואי אחרות

תופעות לוואי שכיחות מאד – (very common) תופעות שמופיעות ביותר ממשתמש אחד מעשרה

- חום
- תחושת עייפות מוגברת
- שלשול
- עצירות
- ירידה בתאבון
- כאב ראש
- נזק עצבי העלול לגרום לתחושה של דקירות קלות, נמלול או כאב
- לחץ דם גבוה
- התכווציות שרירים
- נפיחות בידיים, בקרסוליים או רגליים
- חולשה
- כאב גב
- צמרמורות
- דלקת ריאות
- ברונכיטיס
- דלקת בדרכי הנשימה – באף, בסינוסים או ~~דלקת~~ בגרון
- ספירה נמוכה של תאי דם אדומים הנושאים חמצן בדם (אנמיה)
- ספירה נמוכה של תאי דם לבנים המסייעים להילחם בזיהומים (נויטרופניה, לימפופניה, לויקופניה)
- ספירת נמוכה של טסיות דם, תאי דם המסייעים בקרישת הדם (טרומבוציטופניה)
- תחושה לא רגילה בעור (כמו עקצוץ או תחושת מחטים וסיכות בעור)

תופעות לוואי שכיחות – (common) תופעות שמופיעות ב-1-10 משתמשים מתוך 100

- הפרעות בקצב הלב (פרפור פרוזדורים)
- צבירת נוזלים בריאות אשר גורמת לקוצר נשימה
- שפעת
- זיהום בדרכי השתן
- התייבשות
- רמה גבוהה של סוכר בדם

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- רמה נמוכה של סידן בדם
- ~~תחושה לא רגילה בעור (כמו עקצוץ או תחושת מחטים וסיכות בעור)~~

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העלון לרופא והעלון לצרכן נשלחו לפרסום במלואם למאגר התרופות שבאתר משרד הבריאות. כמו כן, ניתן לקבלם מודפסים בפניה אלינו לטלפון 09-9591111 .

בברכה,
צפריר כהן
רוקח ממונה