J-C Health Care Ltd.
Kibbutz Shefayim 6099000,
ISRAEL
Tel +972-9-959-1111
Fax +972-9-958-3636

01-2026

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

הנדון: דארזלקס 120 מ"ג/מ"ל תת עורי 1,800 מ"ג
Darzalex 120mg/ml S.C 1800mg

חברת J-C Health Care Ltd מבקשת להודיעכם כי העלון לרופא של התכשיר שבנדון התעדכן ב 01-2026.

פרטי העדכון העיקריים מופיעים בהמשך (טקסט שנוסף מסומן באדום, טקסט שהושמט מסומן בטקסט ~~בחול עם קו חוצה~~, טקסט המהווה החמרה מודגש ברקע צהוב),אך קיימים עדכונים נוספים.

ההתוויות המאושרות לתכשיר בישראל:

DARZALEX is indicated:
Multiple Myeloma
• 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.
•for the treatment of adult patients with multiple myeloma in combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor.
•in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant
•in combination with bortezomib, lenalidomide, and dexamethasone, followed by maintenance treatment in combination with lenalidomide, for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.

Light chain (AL) amyloidosis
• in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic AL amyloidosis.

מרכיב פעיל: Daratumumab

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://israeldrugs.health.gov.il/#!/byDrug.

כמו כן, מצורפים לפרסום זה וניתן לקבל העתק מודפס שלהם באמצעות פנייה לבעל הרישום: J-C Health Care Ltd, קיבוץ שפיים, 6099000, טל': 09-9591111.

בברכה,

יעל לפידות מללי
רוקחת ממונה
J-C Health Care Ltd

J-C Health Care Ltd.
Kibbutz Shefayim 6099000,
ISRAEL
Tel +972-9-959-1111
Fax +972-9-958-3636

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העדכון בעלון לרופא הינו

4.1 Therapeutic indications

DARZALEX is indicated:

Multiple myeloma

~~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.
- for the treatment of adult patients with multiple myeloma in combination with pomalidomide and dexamethasone in patients who have received at least one prior line of therapy including lenalidomide and a proteasome inhibitor ~~(see section 5.1)~~.
- ~~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.~~
- in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
- in combination with bortezomib, lenalidomide, and dexamethasone, followed by maintenance treatment in combination with lenalidomide, for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.

Light chain (AL) amyloidosis

- i~~I~~n combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic AL amyloidosis.

4.2 Posology and method of administration

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Dosing schedule in combination with bortezomib, lenalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed patients eligible for autologous stem cell transplant (ASCT)

The recommended dose is 1800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in table 4.

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Kibbutz Shefayim 6099000,
ISRAEL
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Fax +972-9-958-3636

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

Treatment phase	Weeks	Schedule
Induction in combination with bortezomib, lenalidomide and dexamethasone	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 in combination with bortezomib, lenalidomide and dexamethasone	Weeks 17 to 24[b]	every two weeks (total of 4 doses)
Maintenance in combination with lenalidomide	Week 25 onwards until disease progression[c]	every four weeks

[a] First dose of the every-2-week dosing schedule is given at week 9.
[b] Week 17 corresponds to re-initiation of treatment following recovery from ASCT.
[c] DARZALEX can be discontinued for patients who have achieved MRD negativity that is sustained for 12 months and have been treated on maintenance for at least 24 months.

Dexamethasone should be administered at 40 mg on days 1-4 and days 9-12 of each 28-day cycle during induction and consolidation (cycles 1-6).

For dose and schedule of medicinal products administered with DARZALEX solution for subcutaneous injection, see section 5.1 and the corresponding prescribing information (PI).

Dosing schedule in combination with bortezomib, lenalidomide and dexamethasone (3-week cycle regimens) for treatment of newly diagnosed patients who are ineligible for ASCT

The recommended dose is 1800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in table 5.

Table 5: DARZALEX dosing schedule in combination with bortezomib, lenalidomide and dexamethasone ([VRd]; 3-week cycle dosing regimen)

Weeks	Schedule
Weeks 1 to 6	weekly (total of 6 doses)
Weeks 7 to 24[a]	every three weeks (total of 6 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 7.
[b] First dose of the every-4-week dosing schedule is given at week 25.

Dexamethasone should be administered at 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle of cycles 1-8. For patients > 75 years or underweight (BMI < 18.5), dexamethasone may be administered at 20 mg on days 1, 4, 8, and 11.

For dose and schedule of medicinal products administered with DARZALEX solution for subcutaneous injection, see section 5.1 and the corresponding prescribing information (PI).

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4.8 Undesirable effects

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Tabulated list of adverse reactions

Table ~~6~~8 summarises the adverse reactions that occurred in patients receiving DARZALEX subcutaneous formulation or intravenous formulation of daratumumab.

The data reflects exposure to DARZALEX subcutaneous formulation (1800 mg) in 1187 patients with multiple myeloma (MM). The data includes 260 patients from a phase III active-controlled study (MMY3012) who received DARZALEX solution for subcutaneous injection as monotherapy, 149 patients from a phase III active-controlled study (MMY3013) who received DARZALEX subcutaneous formulation in combination with pomalidomide and dexamethasone (D-Pd), 351 patients from a phase III active-controlled study (MMY3014) who received DARZALEX subcutaneous formulation in combination with bortezomib, lenalidomide and dexamethasone (D-VRd), and 197 newly diagnosed multiple myeloma patients for whom transplant was not planned as initial therapy or who were ineligible for transplant from a phase III active-controlled study (MMY3019) who received DARZALEX subcutaneous formulation in combination with bortezomib, lenalidomide and dexamethasone (D-VRd). The data also reflects three open-label, clinical studies in which patients received DARZALEX solution for subcutaneous injection either as monotherapy (N=31, MMY1004 and MMY1008) and MMY2040 in which patients received DARZALEX solution for subcutaneous injection in combination with either bortezomib, melphalan and prednisone (D-VMP, n=67), lenalidomide and dexamethasone (D-Rd, n=65) or bortezomib, lenalidomide and dexamethasone (D-VRd, n=67). Additionally, data reflect exposure to 193 patients with newly diagnosed AL amyloidosis from a phase III active-controlled study (AMY3001) in which patients received DARZALEX subcutaneous formulation in combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd).

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In patients with multiple myeloma receiving DARZALEX subcutaneous formulation combination therapy, the following were reported:
Grade 3 or 4 infections: DPd: 28%, Pd: 23%, D-VRd (transplant eligible): 35%, VRd (transplant eligible): 27%; D-VRd (transplant ineligible):40%, VRd (transplant ineligible): 32%

Grade 5 (fatal) infections: DPd: 5%, Pd: 3%; D-VRd (transplant eligible): 2%, VRd (transplant eligible): 3%; D-VRd (transplant ineligible):8%, VRd (transplant ineligible): 6%
Key: D=daratumumab; Vd=bortezomib-dexamethasone; Rd=lenalidomide-dexamethasone; Pd=pomalidomide-dexamethasone; VMP=bortezomib-melphalan-prednisone; VTd=bortezomib-thalidomide-dexamethasone.
VRd=bortezomib-lenalidomide-dexamethasone.
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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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Immunogenicity

In multiple myeloma and AL amyloidosis patients treated with subcutaneous daratumumab in monotherapy and combination clinical studies, less than 1% of patients developed treatment-emergent anti-daratumumab antibodies and 7 patients tested positive for neutralising antibodies.

In multiple myeloma and AL amyloidosis patients, the incidence of treatment-emergent non-neutrali~~z~~sing anti-rHuPH20 antibodies was ~~7.3~~8.9% (~~55~~115/~~750~~1298)) in patients who received either monotherapy DARZALEX subcutaneous formulation or combination DARZALEX subcutaneous formulation and 1 patient tested positive for neutralising antibodies. The anti-rHuPH20 antibodies did not appear to impact daratumumab exposures. The clinical relevance of the development of

J-C Health Care Ltd.
Kibbutz Shefayim 6099000,
ISRAEL
Tel +972-9-959-1111
Fax +972-9-958-3636

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anti-daratumumab or anti-rHuPH20 antibodies after treatment with DARZALEX subcutaneous formulation is not known.

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Combination therapies in multiple myeloma

Combination treatment with bortezomib, lenalidomide and dexamethasone (VRd) in patients with newly diagnosed multiple myeloma eligible for autologous stem cell transplant (ASCT)
Study MMY3014 was an open-label, randomised, active-controlled phase III study that compared induction and consolidation treatment with DARZALEX subcutaneous formulation (1800 mg) in combination with bortezomib, lenalidomide and dexamethasone (D-VRd), followed by maintenance with DARZALEX in combination with lenalidomide, to treatment with bortezomib, lenalidomide and dexamethasone (VRd), followed by maintenance with lenalidomide, in patients 70 years of age and younger with newly diagnosed multiple myeloma eligible for ASCT until documented disease progression or unacceptable toxicity. An emergency short course of corticosteroid (equivalent of dexamethasone 40 mg/day for a maximum 4 days) was permitted before treatment. Patients received DARZALEX subcutaneous formulation (1800 mg) administered subcutaneously once weekly (days 1, 8, 15, and 22) for cycles 1-2 followed by once every two weeks (days 1 and 15) for cycles 3-6. For maintenance (cycles 7+), patients received DARZALEX subcutaneous formulation (1800 mg) once every four weeks. Patients who achieved MRD negativity that was sustained for 12 months and had been treated on maintenance for at least 24 months discontinued treatment with DARZALEX subcutaneous formulation (1800 mg). Bortezomib was administered by subcutaneous (SC) 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) cycles 1-6. Lenalidomide was administered orally at 25 mg daily on days 1 to 21 during cycles 1-6. For maintenance (cycles 7+), patients received 10 mg lenalidomide daily on days 1-28 (continuously) of each cycle until documented disease progression or unacceptable toxicity. Dexamethasone (oral or intravenous) was administered at 40 mg on days 1-4 and days 9-12 of cycles 1-6. On the days of DARZALEX subcutaneous formulation (1800 mg) injection, the dexamethasone dose was administered orally or intravenously as a pre-injection medicinal product. Dose adjustments for bortezomib, lenalidomide and dexamethasone were applied according to manufacturer's prescribing information.

A total of 709 patients were randomised: 355 to the D-VRd arm and 354 to the VRd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 60 (range: 31 to 70 years). The majority were male (59%), 64% had an ECOG performance score of 0, 31% had an ECOG performance score of 1 and 5% had an ECOG performance score of 2. Additionally, 51% had ISS stage I, 34% had ISS stage II, 15% had ISS stage III disease, 75% had a standard cytogenetic risk, 22% had a high cytogenetic risk (del17p, t[4;14], t[14;16]), and 3% had an indeterminate cytogenetic risk.

With a median follow-up of 47.5 months, the primary analysis of PFS in study MMY3014 demonstrated an improvement in PFS in the D-VRd arm as compared to the VRd arm (HR=0.42; 95% CI: 0.30, 0.59; p<0.0001). The median PFS was not reached in either arm.

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Kibbutz Shefayim 6099000,
ISRAEL
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Fax +972-9-958-3636

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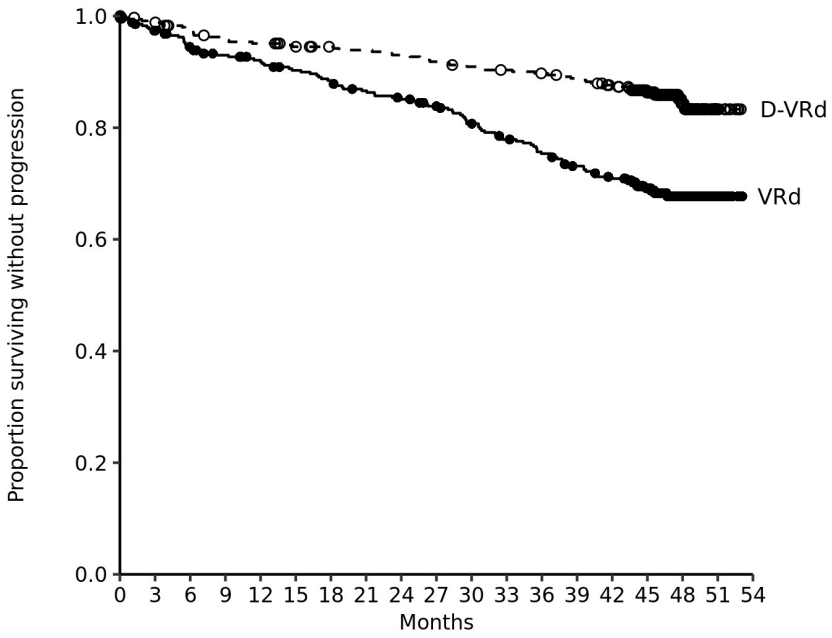
Figure 1: Kaplan-Meier curve of PFS in study MMY3014



No. at risk

VRd	354	335	321	311	304	297	291	283	278	270	258	247	238	228	219	175	67	13	0
D-VRd	355	345	335	329	327	322	318	316	313	309	305	302	299	295	286	226	90	11	0

Additional efficacy results from study MMY3014 are presented in table 10 below.

Table 10: Efficacy results from study MMY3014[a]

	D-VRd (n=355)	VRd (n=354)	Odds ratio (95% CI)[d]
Overall response (sCR+CR+VGPR+PR) n(%)[a]	343 (96.6%)	332 (93.8%)	
Stringent complete response (sCR)	246 (69.3%)	158 (44.6%)	
Complete response (CR)	66 (18.6%)	90 (25.4%)	
Very good partial response (VGPR)	26 (7.3%)	68 (19.2%)	
Partial response (PR)	5 (1.4%)	16 (4.5%)	
CR or better (sCR+CR)	312 (87.9%)	248 (70.1%)	3.13 (2.11, 4.65)
95% CI (%)	(84.0%, 91.1%)	(65.0%, 74.8%)	
P-value[b]			< 0.0001
Overall MRD negativity rate[a,c]	267 (75.2%)	168 (47.5%)	3.40 (2.47, 4.69)
95% CI (%)	(70.4%, 79.6%)	(42.2%, 52.8%)	
P-value[b]			< 0.0001

D-VRd=daratumumab-bortezomib-lenalidomide-dexamethasone; VRd=bortezomib-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] Patients achieved both MRD negativity (threshold of 10^{-5}) and CR or better

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

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Kibbutz Shefayim 6099000,
ISRAEL
Tel +972-9-959-1111
Fax +972-9-958-3636

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Combination treatment with bortezomib, lenalidomide and dexamethasone (VRd) in patients with newly diagnosed multiple myeloma for whom ASCT is not planned as initial therapy or who are ineligible for ASCT

Study MMY3019 was an open-label, randomised, active-controlled phase III study that compared treatment with DARZALEX subcutaneous formulation (1800 mg) in combination with bortezomib, lenalidomide and dexamethasone (D-VRd) to treatment with bortezomib, lenalidomide and dexamethasone (VRd) in patients with newly diagnosed multiple myeloma for whom ASCT was not planned as initial therapy or who were not eligible for ASCT. An emergency short course of corticosteroid (equivalent of dexamethasone 40 mg/day for a maximum 4 days) was permitted before treatment. Patients received DARZALEX subcutaneous formulation (1800 mg) administered subcutaneously once weekly (days 1, 8, and 15) for cycles 1 to 2 followed by once every three weeks for cycles 3 to 8, and once every four weeks in cycle 9 and beyond until documented disease progression or unacceptable toxicity. Bortezomib was administered by subcutaneous injection at a dose of 1.3 mg/m^2 body surface area twice weekly (days 1, 4, 8, and 11) of repeated 21-day (3-week) cycles 1-8. Lenalidomide was administered orally at 25 mg daily on days 1 to 14 during cycles 1-8 and on days 1-21 during cycle 9 and beyond. Dexamethasone was administered orally at 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day (3-week) cycles 1-8 and days 1, 8, 15, and 22 of each 28-day (4-week) during cycle 9 and beyond. On the days of DARZALEX subcutaneous formulation (1800 mg) injection, the dexamethasone dose was administered orally or intravenously as a pre-injection medication. Dose adjustments for bortezomib, lenalidomide and dexamethasone were applied according to manufacturer's prescribing information.

A total of 395 patients were randomised: 197 to the D-VRd arm and 198 to the VRd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 70 (range: 31 to 80 years). Fifty percent were male, 39% had an ECOG performance score of 0, 51% had an ECOG performance score of 1 and 9% had an ECOG performance score of 2. Eighteen percent were less than 70 years of age and transplant ineligible and 27% were less than 70 years of age and were transplant deferred. Additionally, 34% had ISS stage I, 38% had ISS stage II, 28% had ISS stage III disease, 75% had a standard cytogenetic risk, 13% had a high cytogenetic risk (del17p, t[4;14], t[14;16]), and 11% had an indeterminate cytogenetic risk.

With a median follow-up of 22.3 months, the primary analysis of MRD in study MMY3019 demonstrated an improvement in overall MRD negativity rate (by NGS at or below 10^{-5}) for patients reaching CR or better in the D-VRd arm as compared to the VRd arm. Overall MRD negativity rates were 53.3% (95% CI: 46.1, 60.4) in the D-VRd arm and 35.4% (95% CI: 28.7, 42.4) in the VRd arm (odds ratio [D-VRd versus VRd] 2.07 with 95% CI: 1.38, 3.10; p=0.0004).

At the time of primary MRD analysis, an improvement in overall CR or better rate was observed in the D-VRd arm as compared to the VRd arm. Overall CR or better rates were 76.6% (95% CI: 70.1, 82.4) in the D-VRd arm and 59.1% (95% CI: 51.9, 66.0) in the VRd arm (odds ratio [D-VRd versus VRd] 2.31; 95% CI: 1.48, 3.60; p=0.0002).

With a median follow-up of 39 months, an interim analysis of PFS in Study MMY3019 demonstrated an improvement in PFS in the D-VRd arm as compared to the VRd arm (HR=0.61; 95% CI: 0.42, 0.90; p=0.0104). The median PFS had not been reached in either arm. With more mature PFS data at the final PFS analysis, treatment effect for PFS was improved with a hazard ratio of 0.57 (95% CI: 0.41, 0.79). The median PFS had not been reached in the D-VRd arm and was 52.6 months in the VRd arm.

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Kibbutz Shefayim 6099000,
ISRAEL
Tel +972-9-959-1111
Fax +972-9-958-3636

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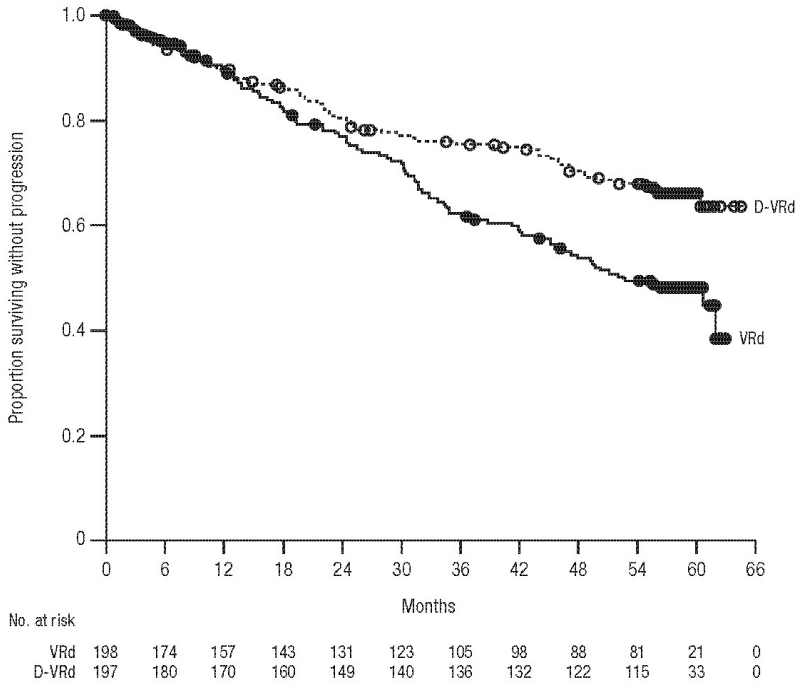
Figure 2: Kaplan-Meier curve of PFS at final analysis in study MMY3019



At the time of interim PFS analysis, an improvement in 1-year sustained MRD negativity rate (by NGS at or below 10^{-5}) for patients reaching CR or better was observed in the D-VRd arm as compared to the VRd arm. Sustained MRD negativity rates were 42.6% (95% CI: 35.6, 49.9) in the D-VRd arm and 25.3% (95% CI: 19.4, 31.9) in the VRd arm (odds ratio [D-VRd versus VRd] 2.18 with 95% CI: 1.42, 3.34; p=0.0003).

Additional efficacy results from Study MMY3019 are presented in table 11 below.

Table 11: Efficacy results from the final PFS analysis of study MMY3019[a]

	D-VRd (n=197)	VRd (n=198)
Overall MRD negativity rate[b]	120 (60.9%)	78 (39.4%)
Odds ratio (95% CI)[c]	2.37 (1.58, 3.55)	
Sustained MRD negativity rate[d]	96 (48.7%)	52 (26.3%)
Odds ratio (95% CI)[c]	2.63 (1.73, 4.00)	
Overall CR or better (sCR+CR)	160 (81.2%)	122 (61.6%)
Odds ratio (95% CI)[c]	2.73 (1.71, 4.34)	
Overall response (sCR+CR+VGPR+PR) n (%)[a]	191 (97.0%)	184 (92.9%)
Stringent complete response (sCR)	128 (65.0%)	88 (44.4%)
Complete response (CR)	32 (16.2%)	34 (17.2%)
Very good partial response (VGPR)	23 (11.7%)	50 (25.3%)
Partial response (PR)	8 (4.1%)	12 (6.1%)

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Kibbutz Shefayim 6099000,
ISRAEL
Tel +972-9-959-1111
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D-VRd=daratumumab-bortezomib-lenalidomide-dexamethasone; VRd=bortezomib-lenalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval

[a] Based on intent-to-treat population, median follow-up of 59 months

[b] Patients achieved both MRD negativity (threshold of at or below 10^{-5}) and CR or better

[c] Mantel-Haenszel estimate of the common ratio for stratified tables is used. The stratification factors are: ISS staging (I, II, III), age/transplant eligibility (< 70 years ineligible, or age< 70 years and refusal to transplant, or age ≥ 70 years) as randomised. An odds ratio > 1 indicates an advantage for D-VRd.

[d] Sustained MRD negativity is defined as MRD negative and confirmed by at least 1 year apart without MRD positive in between.

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5.2 Pharmacokinetic properties

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In patients with newly diagnosed multiple myeloma eligible for ASCT, daratumumab exposure in a combination study with bortezomib, lenalidomide and dexamethasone (MMY3014) was similar to that in monotherapy, with the maximum C_{trough} (cycle 3 day 1 pre-dose) mean ± SD of 526±209 µg/mL following the recommended 1800 mg administration of DARZALEX solution for subcutaneous injection weekly for 8 weeks, biweekly for 16 weeks, monthly thereafter).

In patients with newly diagnosed multiple myeloma for whom ASCT was not planned as initial therapy or who were ineligible for ASCT, daratumumab exposure in a combination study with bortezomib, lenalidomide and dexamethasone (MMY3019) was similar to that in monotherapy and other combination therapies following similar dosing schedule, with the maximum C_{trough} (cycle 3 day 1 pre-dose) mean ± SD of 407 ± 183 µg/mL following the recommended 1800 mg administration of DARZALEX solution for subcutaneous injection (weekly for 6 weeks, triweekly for 18 weeks, monthly thereafter).

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Metabolism and elimination

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A population PK analysis was conducted using data from DARZALEX solution for subcutaneous injection monotherapy and combination therapy multiple myeloma studies, and the predicted PK exposures are summarised in table ~~17~~21. Daratumumab exposures were similar between patients treated with DARZALEX solution for subcutaneous injection monotherapy and combination therapies.

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The predicted PK expsosures for 526 patients with transplant eligible multiple myeloma who received DARZALEX solution for subcutaneous injection in combination with VRd are summarised in table 22.

Table 22: Daratumumab exposure following administration of DARZALEX subcutaneous formulation (1800 mg) in combination with VRd in patients with transplant eligible multiple myeloma

PK parameters	Cycles	subcutaneous daratumumab Median (5^{th}; 95^{th} percentile)
C_{trough} (µg/mL)	Cycle 1, 1^{st} weekly dose	113 (66; 171)
	Cycle 2, last weekly dose (cycle 3 day 1 C_{trough})	651 (413; 915)
C_{max} (µg/mL)	Cycle 1, 1^{st} weekly dose	117 (67; 179)
	Cycle 2, last weekly dose	678 (431; 958)
$AUC_{0\text{-}7\ days}$ (µg/mL•day)	Cycle 1, 1^{st} weekly dose	643 (322; 1027)

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