J-C Health Care Ltd.
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08-2025

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 08-2025.

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:

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.
- 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.

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
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העדכון בעלון לרופא הינו

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3. PHARMACEUTICAL FORM

Solution for injection.
The solution is clear to opalescent, colourless to yellow, with a pH of 5.6 and osmolality of 343 to 395 mOsm/kg.

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4.8 Undesirable effects

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Tabulated list of adverse reactions
Table 6 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). 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).

The safety data also reflects exposure to intravenous daratumumab (16 mg/kg) in 2324 patients with multiple myeloma including 1910 patients who received intravenous daratumumab in combination with background regimens and 414 patients who received intravenous daratumumab as monotherapy. Post-marketing adverse reactions are also included.

Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000) and very rare (< 1/10000).

Table 6: Adverse reactions in multiple myeloma and AL amyloidosis patients treated with intravenous daratumumab or subcutaneous daratumumab

System organ class	Adverse reaction	Frequency	Incidence (%)	
			Any grade	Grade 3-4
Infections and infestations	Upper respiratory tract infection[a]	Very common	~~45~~46	3
	COVID-19[a,g]		~~26~~23	~~7~~6
	Pneumonia[a]		19	11
	Bronchitis[a]		14	1
	Urinary tract infection	Common	~~8~~7	1
	Sepsis[a]		4	4

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	Cytomegalovirus infection[a]	Uncommon	< 1	< 1#
	Hepatitis B Virus reactivation[a]		< 1	< 1
Blood and lymphatic system disorders	Neutropenia[a]	Very common	~~43~~42	~~37~~36
	Thrombocytopenia[a]		~~32~~30	~~19~~18
	Anaemia[a]		~~27~~26	11
	Lymphopenia[a]		~~13~~12	10
	Leukopenia[a]		11	6
Immune system disorders	Hypogammaglobulinemia[a]	Common	3	< 1#
	Anaphylactic reaction[b]	Rare	-	-
Metabolism and nutrition disorders	Hypokalaemia[a]	Very common	~~11~~10	3
	Decreased appetite		10	<1
	Hyperglycaemia	Common	~~7~~6	3
	Hypocalcaemia		6	1
	Dehydration		2	1#
Psychiatric disorders	Insomnia	Very common	17	1#
Nervous system disorders	Peripheral neuropathy	Very common	~~33~~31	4
	Headache		~~10~~11	< 1#
	Dizziness	Common	9	< 1#
	Paraesthesia		9	< 1
	Syncope		3	2#
Cardiac disorders	Atrial fibrillation	Common	4	1
Vascular disorders	Hypertension[a]	Common	9	4
Respiratory, thoracic and mediastinal disorders	Cough[a]	Very common	22	< 1#
	Dyspnoea[a]		18	2
	Pulmonary oedema[a]	Common	1	< 1
Gastrointestinal disorders	Diarrhoea	Very common	33	5
	Constipation		~~29~~28	1
	Nausea		22	1#
	Abdominal pain[a]		~~13~~14	1
	Vomiting		13	1#
	Pancreatitis[a]	Common	1	<1
Skin and subcutaneous tissue disorders	Rash	Very common	12	1#
	Pruritus	Common	6	<1#
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[a,h]	Very common	35	3
	Arthralgia		14	1
	Muscle spasms		12	<1#
General disorders and administration site conditions	Fatigue	Very common	24	4
	Oedema peripheral[a]		24	1
	Pyrexia		22	1
	Asthenia		19	2
	Injection site reactions[d,e]		10	0
	Chills	Common	8	<1#
	~~Injection site reactions[d,e]~~		~~8~~	~~0~~
Injury, poisoning and procedural complications	Infusion-related reactions[c]			
	Daratumumab intravenous[f]	Very common	39	5
	Daratumumab subcutaneous[e]	Common	~~7~~9	1

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[#] No grade 4
[a] Indicates a grouping of terms.
[b] Based on post-marketing adverse reactions.
[c] Infusion-related reactions includes terms determined by investigators as related to infusion/injection of daratumumab.
[d] Injection site reactions includes terms determined by investigators as related to injection of daratumumab.
[e] Frequency based on daratumumab subcutaneous studies only (N=~~1380~~1573).
[f] Frequency based on daratumumab intravenous studies only (N=2324).
[g] Incidence is based on a subset of patients who received at least one dose of study treatment on or after 01 February 2020 (the start of the COVID-19 pandemic) from studies MMY3003, MMY3006, MMY3008 and MMY3013, and all daratumumab treated patients from studies MMY3014, ~~and~~ MMY3019, and SMM3001 (N=~~984~~1177).
[h] Musculoskeletal pain includes back pain, flank pain, groin pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, and pain in extremity.

Note: Based on ~~3704~~ 3897 multiple myeloma and AL amyloidosis patients treated with daratumumab intravenous or daratumumab subcutaneous.

Description of selected adverse reactions

Infusion-related reactions (IRRs)

In clinical studies (monotherapy and combination treatments; N=~~1380~~1573) with DARZALEX subcutaneous formulation, the incidence of any grade IRRs was ~~6.4~~7.5% with the first injection of DARZALEX (1800 mg, week 1), 0.~~3~~5% with the week 2 injection, and 1.~~2~~3% with subsequent injections. Grades 3 and 4 IRRs were seen in 0.~~7~~8% and 0.1% of patients, respectively.

Signs and symptoms of IRR may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritus, chills, vomiting, nausea, blurred vision and hypotension. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension tachycardia and ocular adverse reactions (including choroidal effusion, acute myopia and acute angle closure glaucoma) (see section 4.4).

Injection site reactions (ISRs)

In clinical studies (N=~~1380~~1573) with DARZALEX subcutaneous formulation, the incidence of any grade injection site reaction was ~~7.8~~10.2%. There were no grade 3 or 4 ISRs. The most common (≥ 1%) ISR at the site of injection was erythema and rash.

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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).

Elderly patients

Of the ~~4238~~ 4553 patients who received daratumumab (n=~~1422~~ 1615 subcutaneous; n=~~2816~~ 2938 intravenous) at the recommended dose, 38% were 65 to less than 75 years of age, and 15% were 75 years of age or older. No overall differences in effectiveness were observed based on age. The incidence of serious adverse reactions was higher in older than in younger patients. Among patients with relapsed and refractory multiple myeloma (n=1976), the most common serious adverse reactions that occurred more frequently in elderly (≥65 years of age) were pneumonia and sepsis. Among patients with newly diagnosed multiple myeloma who were ineligible for autologous stem cell transplant (n=777), the most common serious adverse reaction that occurred more frequently in

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elderly (≥75 years of age) was pneumonia. Among patients with newly diagnosed multiple myeloma who were eligible for autologous stem cell transplant (n=351), the most common serious adverse reaction that occurred more frequently in elderly (≥ 65 years of age) was pneumonia. Among patients with newly diagnosed multiple myeloma for whom transplant was not planned as initial therapy or who were ineligible for autologous stem cell transplant (n=197), the most common serious adverse reaction that occurred more frequently in elderly (≥ 65 years of age) was pneumonia. Among patients with newly diagnosed AL amyloidosis (n=193), the most common serious adverse reaction that occurred more frequently in elderly (≥65 years of age) was pneumonia.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, ~~CD38 (Clusters of Differentiation 38) inhibitors,~~ ATC code: L01FC01.
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Combination treatment with bortezomib, cyclophosphamide and dexamethasone in patients with AL amyloidosis
Study AMY3001, an open-label, randomised, active-controlled phase III study, compared treatment with DARZALEX subcutaneous formulation (1800 mg) in combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd) to treatment with bortezomib, cyclophosphamide and dexamethasone (VCd) alone in patients with newly diagnosed systemic AL amyloidosis. Randomisation was stratified by AL amyloidosis Cardiac Staging System, countries that typically offer autologous stem cell transplant (ASCT) for patients with AL amyloidosis, and renal function.

All patients enrolled in study AMY3001 had newly diagnosed AL amyloidosis with at least one affected organ, measurable hematologic disease, cardiac stage I-IIIA (based on European Modification of Mayo 2004 cardiac stage), and NYHA class I-IIIA. Patients with NYHA class IIIB and IV were excluded.

Bortezomib (SC; 1.3 mg/m^2 body surface area), cyclophosphamide (oral or IV; 300 mg/m^2 body surface area; max dose 500 mg), and dexamethasone (oral or IV; 40 mg or a reduced dose of 20 mg for patients >70 years or body mass index [BMI] < 18.5 or those who have hypervolemia, poorly controlled diabetes mellitus or prior intolerance to steroid therapy) were administered weekly on days 1, 8, 15, and 22 of repeated 28-day [4-week] cycles. On the days of DARZALEX dosing, 20 mg of the dexamethasone dose was given as a pre-injection medicinal product and the remainder given the day after DARZALEX administration. Bortezomib, cyclophosphamide and dexamethasone were given for six 28-day [4-week] cycles in both treatment arms, while DARZALEX treatment was continued until disease progression, start of subsequent therapy, or a maximum of 24 cycles (~2 years) from the first dose of study treatment. Dose adjustments for bortezomib, cyclophosphamide and dexamethasone were applied according to manufacturer's prescribing information.

A total of 388 patients were randomised: 195 to the D-VCd arm and 193 to the VCd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The majority (79%) of patients had lambda free light chain disease. The median patient age was 64 years (range: 34 to 87); 47% were ≥ 65 years; 58% were male; 76% Caucasian, 17% Asian, and 3% African American; 23% had AL amyloidosis Clinical Cardiac stage I, 40% had stage II, 35% had stage IIIA, and 2% had stage IIIB. All patients had one or more affected organs and the median number of organs involved was 2 (range: 1-6) and 66% of patients had 2 or more organs involved. Vital organ involvement was: 71% cardiac, 59% renal and 8% hepatic. Patients with grade 2 sensory or grade 1 painful peripheral neuropathy were excluded. The primary efficacy endpoint was hematologic complete response (HemCR) rate as determined by the Independent Review Committee assessment based on

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International Concensus Criteria. Study AMY3001 demonstrated an improvement in HemCR in the D-VCd arm as compared to the VCd arm. Efficacy results are summarised in table 10.

Table 10: Efficacy results from study AMY3001[a]

	D-VCd (n=195)	**VCd (n=193)**	**P value**
Hematologic complete response (HemCR), n (%)	104 (53.3%)	35 (18.1%)	<0.0001[b]
Very good partial response (VGPR), n (%)	49 (25.1%)	60 (31.1%)	
Partial response (PR), n (%)	26 (13.3%)	53 (27.5%)	
Hematologic VGPR or better (HemCR + VGPR), n (%)	153 (78.5%)	95 (49.2%)	<0.0001[b]
Major organ deterioration progression-free survival (MOD-PFS), Hazard ratio with 95% CI[c]	0.58 (0.36, 0.93)		0.0211[d]

D-VCd=daratumumab-bortezomib-cyclophosphamide-dexamethasone; VCd=bortezomib-cyclophosphamide-dexamethasone

[a] All results from the planned analysis after a median follow-up of 11.4 months ~~B~~based on intent-to-treat population

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

[c] MOD-PFS defined as hematologic progression, major organ (cardiac or renal) deterioration or death

[d] Nominal p-value from inverse probability censoring weighted log-rank test

With a median follow-up of 11.4 months, ~~I~~in responders, the median time to HemCR was 60 days (range: 8 to 299 days) in the D-VCd group and 85 days (range: 14 to 340 days) in the VCd group. The median time to VGPR or better was 17 days (range: 5 to 336 days) in the D-VCd group and 25 days (range: 8 to 171 days) in the VCd group. The median duration of HemCR had not been reached in either arm.

After a median follow-up of 61.4 months, the overall HemCR rates were 59.5% (95% CI: 52.2, 66.4) in the D-VCd group and 19.2% (95% CI: 13.9, 25.4) in the VCd group (odds ratio [D-VCd versus VCd] 6.03 with 95% CI: 3.80, 9.58).

Results of a MOD-PFS analysis after a median follow-up of 61.4 months showed an improvement in MOD-PFS for patients in the D-VCd group compared with the VCd group. The hazard ratio (HR) for MOD-PFS was 0.44 (95% CI: 0.31, 0.63) and the p-value was <0.0001. The median MOD-PFS was not reached in the D-VCd arm and was 30.2 months in the VCd arm. The Kaplan-Meier estimated 60-month MOD-PFS rate was 60% (95% CI: 52, 67) in the D-VCd arm and was 33% (95% CI: 23, 44) in the VCd arm.

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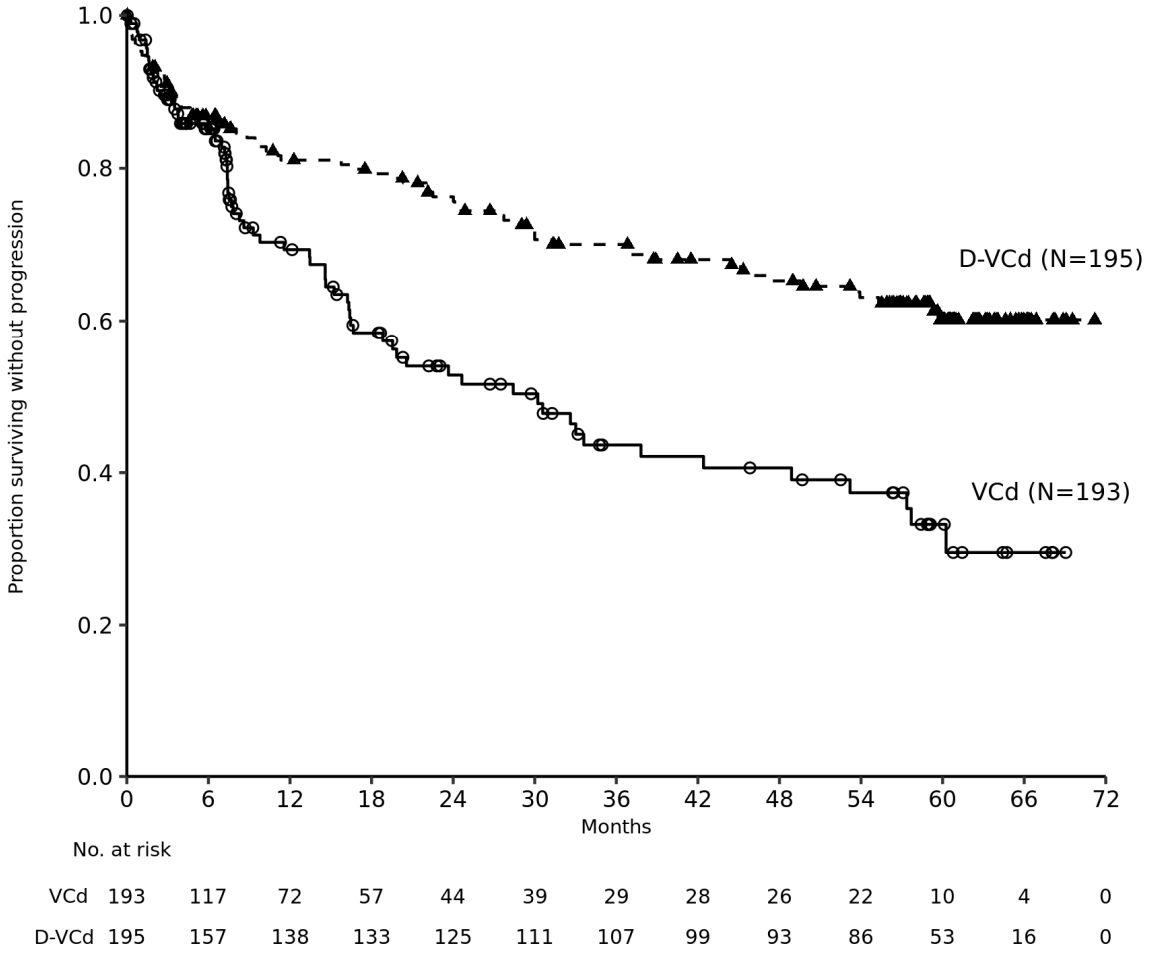
Figure 2: Kaplan-Meier curve of MOD-PFS in study AMY3001



~~The median follow-up for the study is 11.4 months. The median major organ deterioration progression-free survival (MOD-PFS) was not reached for patients in either arm.~~

~~Overall survival (OS) data were not mature.~~ After a median follow-up of 61.4 months, a total of 112 deaths were observed [n=46 (23.6%) D-VCd *vs*. n=66 (34.2%) VCd group]. The median OS was not reached for either arm; however, the HR for OS was 0.62 (95% CI: 0.42, 0.90) and the p-value was 0.0121. ~~A total of 56 deaths were observed [n=27 (13.8%) D-VCd vs. n=29 (15%) VCd group].~~ The 60-month OS rate was 76% (95% CI: 69, 82) in the D-VCd arm and was 65% (95% CI: 57, 71) in the VCd arm.

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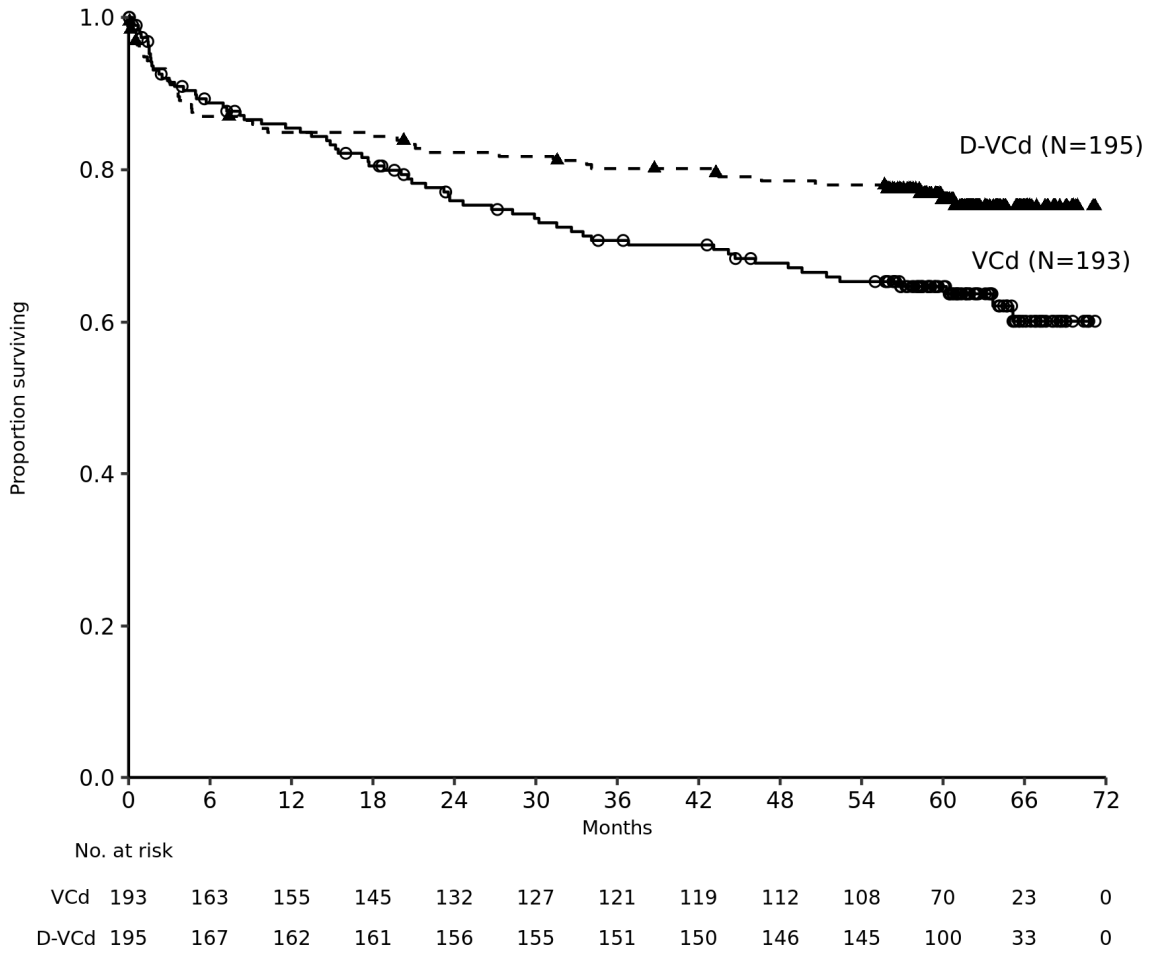
Figure 3: Kaplan-Meier curve of OS in study AMY3001



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