J-C Health Care Ltd.

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11-2021

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

ברצוננו להביא לידיעתכם את העדכונים בעלון לרופא של התכשיר:

Darzalex 120mg/ml S.C 1800mg

המאושר להתוויות הבאות:

- 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.

השינויים המהותיים בעלון לרופא מופיעים בסעיפים הבאים:

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number ~~tradename~~ of the administered product should be clearly recorded.
~~It is recommended to record the batch number as well~~

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4.8 Undesirable effects

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Table 5: Adverse reactions in multiple myeloma 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	38%	2%
	Bronchitis[a]	Very Common	14%	2%
	Pneumonia[a]	Very Common	14%	9%
	Urinary tract infection	Common	7%	1%
	Influenza	Common	4%	1%[#]

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	Sepsis[a]	Common	4%	3%
	Cytomegalovirus infection[a]	Common	1%	<1%[#]
	Hepatitis B Virus reactivation[a]	Uncommon	<1%	<1%
Blood and lymphatic system disorders	Neutropenia[a]	Very Common	40%	33%
	Thrombocytopenia[a]	Very Common	30%	18%
	Anaemia[a]	Very Common	27%	12%
	Lymphopenia[a]	Very Common	13%	11%
	Leukopenia[a]	Very Common	11%	6%
Immune system disorders	Hypogammaglobulinemia[a]	Common	2	<1[#]
	Anaphylactic reaction[b]	Rare	-	-
Metabolism and nutrition disorders	Decreased appetite	Very Common	10%	1%
	Hyperglycaemia	Common	6%	3%
	Hypocalcaemia	Common	5%	1%
	Dehydration	Common	2%	1%[#]
Psychiatric disorders	Insomnia	Very Common	14%	1%[#]
Nervous system disorders	Peripheral sensory neuropathy	Very Common	26%	3%
	Headache	Very Common	11%	<1%[#]
	Dizziness	Common	9%	<1%[#]
	Paraesthesia	Common	9%	<1%
	Syncope	Common	3	2[#]
Cardiac disorders	Atrial fibrillation	Common	3%	1%
Vascular disorders	Hypertension[a]	Very Common	10%	5%
Respiratory, thoracic and mediastinal disorders	Cough[a]	Very Common	22%	<1%[#]
	Dyspnoea[a]	Very Common	18%	2%
	Pulmonary oedema[a]	Common	1%	<1%
Gastrointestinal disorders	Diarrhoea	Very Common	29%	3%
	Constipation	Very Common	28%	1%
	Nausea	Very Common	23%	1%[#]
	Vomiting	Very Common	14%	1%[#]
	Pancreatitis[a]	Common	1%	<1%
Skin and subcutaneous tissue disorders	Rash	Common	9%	<1%[#]
	Pruritus	Common	5%	<1%[#]
Musculoskeletal and connective tissue disorders	Back pain	Very Common	17%	2%
	Muscle spasms	Very Common	12%	<1%[#]
	Arthralgia	Very Common	10%	1%[#]
	Musculoskeletal chest pain	Common	6%	<1%[#]
General disorders and administration site conditions	Fatigue	Very Common	23%	3%
	Oedema peripheral[a]	Very Common	22%	1%
	Pyrexia	Very Common	22%	1%
	Asthenia	Very Common	18%	2%
	Chills	Common	9%	<1%[#]
	Injection site erythema[e]	Common	4%	0
	Injection site reactions[d,e]	Common	8%	0
Injury, poisoning and procedural complications	Infusion-related reactions[c]			
	Daratumumab intravenous[f]	Very Common	39%	5%
	Daratumumab subcutaneous[e]	Very Common	11%	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=490).
[f] Frequency based on daratumumab intravenous studies only (N=2324).
Note: Based on 2814 multiple myeloma patients treated with daratumumab intravenous or daratumumab subcutaneous.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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Table 6: Key results from Study MMY3012

	Subcutaneous Daratumumab (N=263)	**Intravenous Daratumumab (N=259)**
Primary Endpoint		
Overall response (sCR+CR+VGPR+PR), n (%)[a]	108 (41.1%)	96 (37.1%)
95% CI (%)	(35.1%, 47.3%)	(31.2%, 43.3%)
Ratio of response rates (95% CI)[b]		1.11 (0.89, 1.37)
CR or better, n (%)	5 (1.9%)	7 (2.7%)
Very good partial response (VGPR)	45 (17.1%)	37 (14.3%)
Partial response (PR)	58 (22.1%)	52 (20.1%)
Secondary Endpoint		
Rate of Infusion-related Reaction, n (%)[c]	33 (12.7%)	89 (34.5%)
Progression-free Survival, months		
Median (95% CI)	5.59 (4.67, 7.56)	6.08 (4.67, 8.31)
Hazard ratio (95% CI)		0.99 (0.78, 1.26)

[a] Based on intent-to-treat population.
[b] p-value <0.0001 from Farrington-Manning test for non-inferiority hypothesis.
[c] Based on safety population. P-value<0.0001 from Cochran-Mantel-Haenszel Chi-Squared test.

After a median follow-up of 29.3 months, the median OS was 28.2 months (95% CI: 22.8, NE) in the DARZALEX subcutaneous formulation arm and was 25.6 months (95% CI: 22.1, NE) in the intravenous daratumumab arm.

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

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Table 10: 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.~~

With a median follow-up of 18.8 months, the primary analysis of PFS ~~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. Results of an updated PFS analysis with a median follow-up of 44.5 months, censoring patients who were randomised to daratumumab maintenance in the second randomisation, showed HR=0.43; 95% CI: 0.33, 0.55; p<0.0001. Median PFS was not reached in the D-VTd arm and was 37.8 months in the VTd arm.

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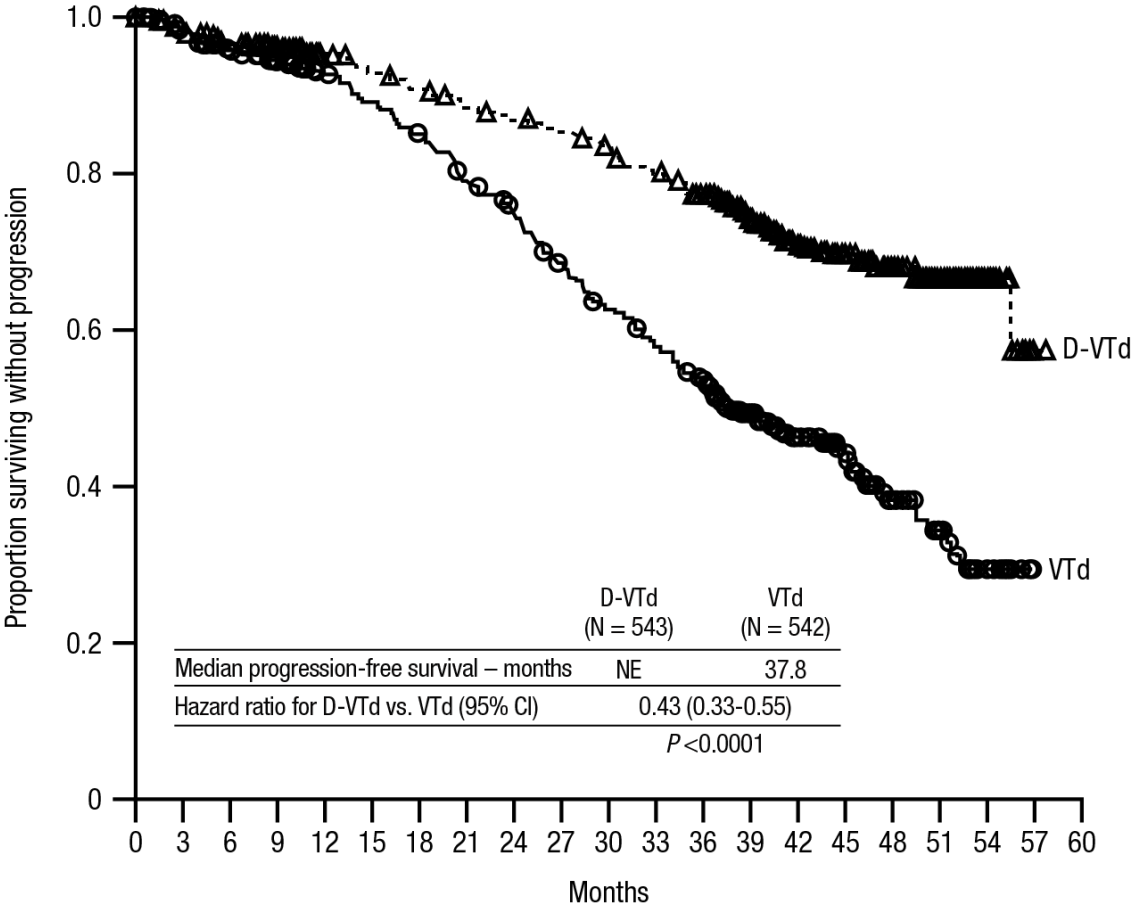
Figure 4: Kaplan-Meier Curve of PFS in Study MMY3006



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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).

העלון לרופא נשלח לפרסום במלואו למאגר התרופות שבאתר משרד הבריאות. כמו כן, ניתן לקבלו מודפס בפניה אלינו לטלפון 09-9591111 .

בברכה,
צפריר כהן
רוקח ממונה