ספטמבר 2019

Empliciti (elotuzumab) 300 mg & 400mg
Powder for concentrate for solution for infusion

רופא/ה ,רוקח/ת יקר/ה,

ברצוננו להודיעך על עדכון בעלון לרופא של התכשיר **אמפליסיטי** (elotuzumab) בישראל.

התוויות התכשיר כפי שאושרו ע"י משה"ב:

Empliciti is indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy.

Empliciti is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor, and have demonstrated disease progression on the last therapy.

בפירוט שלהלן כלולים העדכונים המהותיים בלבד (טקסט שנוסף מסומן בצבע אדום ובקו תחתון,טקסט שהוסר מסומן בצבע אדום ~~ובקו אמצעי~~).

למידע מלא על התרופה יש לעיין בעלון לרופא כפי שאושר על ידי משרד הבריאות.

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס על ידי פנייה לבעל הרישום בריסטול-מאיירס סקוויב (ישראל) בע"מ.

בכבוד רב,
שירן קלאורה,
רוקחת ממונה

עדכונים מהותיים בעלון לרופא:

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Empliciti is indicated in combination with lenalidomide and dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy (see sections 4.2 and 5.1).

Empliciti is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy (see sections 4.2 and 5.1).

4.2 Posology and method of administration

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Posology for administration with pomalidomide and dexamethasone

The length of each treatment cycle is 28 days, see Table 2 for the dosing schedule.
Treatment should continue until disease progression or unacceptable toxicity.

The recommended dose of Empliciti is 10 mg/kg administered intravenously every week on days 1, 8, 15, and 22 of each treatment cycle for the first two cycles and then 20 mg/kg administered on day 1 of each treatment cycle thereafter.

The recommended dose of pomalidomide is 4 mg orally once daily on days 1-21 of repeated 28-day cycles, and at least 2 hours after Empliciti infusion when administered on the same day.

The administration of dexamethasone is as follows:

- On days that Empliciti is administered, patients ≤ 75 years old give dexamethasone 28 mg orally between 3 and 24 hours before Empliciti plus 8 mg intravenously between 45 and 90 minutes before Empliciti and for patients > 75 years old give dexamethasone 8 mg orally between 3 and 24 hours before Empliciti plus 8 mg intravenously between 45 and 90 minutes before Empliciti.
- On days that Empliciti is not administered but a dose of dexamethasone is scheduled (Days 8, 15 and 22 of cycle 3 and all subsequent cycles), give 40 mg orally to patients ≤ 75 years old and 20 mg orally to patients > 75 years old.

Table 2: Recommended dosing schedule of Empliciti in combination with pomalidomide and dexamethasone

Cycle	28-Day Cycles 1 and 2				28-Day Cycles 3+			
Day of Cycle	1	8	15	22	1	8	15	22
Premedication	✓	✓	✓	✓	✓			
Empliciti (mg/kg) intravenously	10	10	10	10	20			
Pomalidomide (4 mg) orally	Days 1-21				Days 1-21			
Dexamethasone (mg) intravenously	8	8	8	8	8			
Dexamethasone (mg) orally ≤ 75 years old	28	28	28	28	28	40	40	40
Dexamethasone (mg) orally > 75 years old	8	8	8	8	8	20	20	20
Day of Cycle	1	8	15	22	1	8	15	22

For additional information concerning pomalidomide and dexamethasone, see the corresponding prescribing information leaflets.

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Method of administration

Empliciti is for intravenous use only.

Infusion rate for Empliciti 10 mg/kg
The administration of the reconstituted and diluted solution must be initiated at an infusion rate of 0.5 mL/min. If the infusion is well tolerated the infusion rate may be increased in a stepwise fashion as described in Table ~~2~~3. The maximum infusion rate should not exceed 5 mL/min.

Table ~~2~~ 3: Infusion rate for Empliciti 10 mg/kg

Cycle 1, Dose 1		Cycle 1, Dose 2		Cycle 1, Dose 3 and 4 and all subsequent Cycles
Time interval	**Rate**	**Time interval**	**Rate**	**Rate**
0 - 30 min	0.5 mL/min	0 - 30 min	3 mL/min	5 mL/min*
30 - 60 min	1 mL/min	≥ 30 min	4 mL/min*	
≥ 60 min	2 mL/min*	-	-	

* Continue this rate until infusion is completed~~, approximately 1 hour based on patient weight~~.

Infusion rate for Empliciti 20 mg/kg
The administration of reconstituted and diluted solution must be initiated at an infusion rate of 3 mL/min. If the infusion is well tolerated, the infusion rate maybe increased in a stepwise fashion as described in Table 4. The maximum infusion rate should not exceed 5 mL/min.
Patients who have escalated to 5 mL/min at 10 mg/kg dose must decrease the rate to 3 mL/min at the first infusion at 20 mg/kg.

Table 4: Infusion rate for Empliciti 20 mg/kg

Dose 1		Dose 2 and all subsequent doses
Time interval	**Rate**	**Rate**
0-30 min	3 mL/min	5 mL/min*
≥ 30 min	4 mL/min*	

* Continue this rate until infusion is completed.

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4.6 Fertility, pregnancy and lactation

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Pregnancy
There is no human experience with elotuzumab during pregnancy. Elotuzumab will be given in combination with lenalidomide, which is contraindicated during pregnancy. No animal data are present regarding the effect on reproductive toxicity because of the lack of an adequate animal model. Empliciti should not be used during pregnancy unless the clinical condition of the woman requires treatment with elotuzumab.

The prescribing information leaflets ~~Summary of Product Characteristics~~ for all medicinal products used in combination with Empliciti must be consulted before starting therapy. When Empliciti is used with lenalidomide or pomalidomide there is a risk of foetal harm, including severe life-threatening human birth defects associated with these agents and the need to follow requirements regarding pregnancy avoidance, including testing and contraception. Lenalidomide ~~is~~and pomalidomide are present in the blood and sperm of patients receiving the medicine. Refer to the prescribing information leaflets~~Summary of Product Characteristics~~ for requirements regarding contraception due to presence and transmission in sperm and for additional detail. Patients receiving Empliciti in combination with lenalidomide or pomalidomide should adhere to the pregnancy prevention programme of lenalidomide or pomalidomide respectively.

Breast-feeding
Elotuzumab is not expected to be excreted into human milk. Elotuzumab will be given in combination with lenalidomide or pomalidomide and breast-feeding should be stopped because of the use of lenalidomide or pomalidomide.
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4.8 Undesirable effects

Summary of safety profile
The safety data of elotuzumab have been assessed from a total of ~~554~~682 patients with multiple myeloma treated with elotuzumab in combination with lenalidomide and dexamethasone (451 patients~~) or~~), bortezomib and dexamethasone (103 patients) or pomalidomide and dexamethasone (128 patients) pooled across ~~6~~8 clinical trials. The majority of adverse reactions were mild to moderate (Grade 1 or 2).

The most serious adverse reaction that may occur during elotuzumab treatment is pneumonia.

The most common adverse reactions (occurring in > 10% of patients) with elotuzumab treatment were infusion related reactions, diarrhoea, herpes zoster, nasopharyngitis, cough, pneumonia, upper respiratory tract infection, lymphopenia and weight decreased.

Tabulated list of adverse reactions
Adverse reactions reported in ~~554~~682 patients with multiple myeloma who were treated with elotuzumab in ~~6~~8 clinical trials are presented in Table ~~3~~5.

These reactions are presented by system organ class and by frequency. 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); very rare (< 1/10,000); and not known (cannot be estimated from available data).

Table ~~3~~5: Adverse reactions in patients with multiple myeloma treated with Empliciti

System Organ Class	Adverse reactions	Frequency overall	Grade 3/4 frequency
Infections and infestations	Herpes zoster[a]	Common ~~Very common~~	Uncommon ~~Common~~
	Nasopharyngitis	Very common	None reported
	Pneumonia[b]	Very common	Common ~~Very common~~
	Upper respiratory tract infection	Very common	Common
Blood and lymphatic system disorders	Lymphopenia[c]	Very common	Common ~~Very common~~
	Leukopenia	Common	Common
Immune system disorders	Anaphylactic reaction	Uncommon	Uncommon
	Hypersensitivity	Common	Uncommon
Psychiatric disorders	Mood altered	Common	None reported
Nervous system disorders	Headache	Very common	Uncommon
	Hypoaesthesia	Common	Uncommon
Vascular disorders	Deep vein thrombosis	Common	Common
Respiratory, thoracic and mediastinal disorders	Cough[d]	Very common	Uncommon
	Oropharyngeal pain	Common	None reported
Gastrointestinal disorders	Diarrhoea	Very common	Common
Skin and subcutaneous tissue disorders	Night sweats	Common	None reported
General disorders and administration site conditions	Chest pain	Common	Common
	Fatigue	Very common	Common
	Pyrexia	Very common	Common
Investigations	Weight decreased	Very common	Uncommon
Injury, poisoning and procedural complications	Infusion related reaction	Common	Uncommon ~~Common~~

[a] The term herpes zoster is a grouping of the following terms: herpes zoster, oral herpes, and herpes virus infection.

[b] The term pneumonia is a grouping of the following terms: pneumonia, atypical pneumonia, bronchopneumonia, lobar pneumonia, bacterial pneumonia, fungal pneumonia, pneumonia influenza, and pneumococcal pneumonia.

[c] The term lymphopenia includes the following terms: lymphopenia and lymphocyte count decreased.

[d] The term cough includes the following terms: cough, productive cough, and upper airway cough syndrome.

Exposure-adjusted rates for adverse reactions (all Grades and Grade 3/4) in ~~Study 1~~CA204004, a clinical trial in patients with multiple myeloma comparing Empliciti combined with lenalidomide and dexamethasone treatment (N = 318) to lenalidomide and dexamethasone treatment (N = 317), is shown in Table ~~4~~6.

Table ~~4:~~ ~~6:~~ CA204004 Exposure-adjusted rates for adverse reactions for Empliciti-treated patients versus lenalidomide and dexamethasone-treated patients [includes multiple occurrences ~~of~~ all treated patients]

	Empliciti + Lenalidomide and Dexamethasone N = 318				Lenalidomide and Dexamethasone N = 317			
	All grades		Grade 3/4		All grades		Grade 3/4	
Adverse reaction	**Event count**	**Rate (incidence rate/100 patient years)**	**Event count**	**Rate (incidence rate/100 patient years)**	**Event count**	**Rate (incidence rate/100 patient years)**	**Event count**	**Rate (incidence rate/100 patient years)**
Diarrhoea	303	59.2	19	3.7	206	49.3	13	3.1
Pyrexia	220	43.0	8	1.6	116	27.7	10	2.4
Fatigue	205	40.0	33	6.4	145	34.7	26	6.2
Cough[a]	170	33.2	1	0.2	85	20.3	-	-
Nasopharyngitis	151	29.5	-	-	116	27.7	-	-
Upper respiratory tract infection	129	25.2	2	0.4	95	22.7	4	1.0
Lymphopenia[b]	90	17.6	65	12.7	57	13.6	31	7.4
Headache	88	17.2	1	0.2	40	9.6	1	0.2
Pneumonia[c]	80	15.6	54	10.5	54	12.9	34	8.1
Leukopenia	70	13.7	19	3.7	65	15.5	21	5.0
Herpes zoster[d]	51	10.0	5	1.0	24	5.7	3	0.7
Oropharyngeal pain	45	8.8	-	-	17	4.1	-	-
Weight decreased	44	8.6	4	0.8	20	4.8	-	-
Night sweats	31	6.1	-	-	12	2.9	-	-
Chest pain	29	5.7	2	0.4	12	2.9	1	0.2
Deep vein thrombosis	26	5.1	18	3.5	12	2.9	7	1.7
Hypoaesthesia	25	4.9	1	0.2	12	2.9	-	-
Mood altered	23	4.5	-	-	8	1.9	-	-
Hypersensitivity	10	2.0	-	-	4	1.0	1	0.2

[a] The term cough includes the following terms: cough, productive cough, and upper airway cough syndrome.

[b] The term lymphopenia includes the following terms: lymphopenia and lymphocyte count decreased.

[c] The term pneumonia is a grouping of the following terms: pneumonia, atypical pneumonia, bronchopneumonia, lobar pneumonia, bacterial pneumonia, fungal pneumonia, pneumonia influenza, and pneumococcal pneumonia.

[d] The term herpes zoster is a grouping of the following terms: herpes zoster, oral herpes, and herpes virus infection.

Exposure-adjusted rates for adverse reactions (all Grades and Grade 3/4) in CA204125, a clinical trial in patients with multiple myeloma comparing Empliciti combined with pomalidomide and dexamethasone treatment (N = 60) to pomalidomide and dexamethasone treatment (N = 55), is shown in Table 7.

Table 7: CA204125 Exposure-adjusted rates for adverse reactions for Empliciti-treated patients versus pomalidomide and dexamethasone-treated patients [includes multiple occurrences in all treated patients]

	Empliciti + Pomalidomide and Dexamethasone N = 60				Pomalidomide and Dexamethasone N = 55			
	All grades		Grade 3/4		All grades		Grade 3/4	
Adverse reaction	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)
Cough[a]	12	25.2	1	2.1	9	26.2	-	-
Nasopharyngitis	12	25.2	-	-	10	29.1	-	-
Upper respiratory tract infection	9	18.9	-	-	10	29.1	1	2.9
Leukopenia	13	27.3	9	18.9	3	8.7	2	5.8
Lymphopenia[b]	10	21.0	6	12.6	1	2.9	1	2.9
Pneumonia[c]	6	12.6	4	8.4	9	26.2	8	23.3
Herpes zoster[d]	5	10.5	-	-	3	8.7	-	-
Infusion related reaction	2	4.2	1	2.1	1	2.9	-	-
Chest pain	2	4.2	-	-	1	2.9	-	-
Night sweats	1	2.1	-	-	-	0.0	-	-
Hypoaesthesia	1	2.1	-	-	1	2.9	-	-
Mood altered	1	2.1	-	-	1	2.9	-	-

[a] The term cough includes the following terms: cough, productive cough, and upper airway cough syndrome.
[b] The term lymphopenia includes the following terms: lymphopenia and lymphocyte count decreased.
[c] The term pneumonia is a grouping of the following terms: pneumonia, atypical pneumonia, bronchopneumonia, lobar pneumonia, bacterial pneumonia, fungal pneumonia, pneumonia influenza, and pneumococcal pneumonia.
[d] The term herpes zoster is a grouping of the following terms: herpes zoster, oral herpes, herpes virus infection and ophthalmic herpes zoster.

Description of selected adverse reactions

Infusion reactions

In ~~a~~the clinical ~~trial~~trials of patients with multiple myeloma ~~(Study 1),~~ infusion reactions were reported in approximately 10% of premedicated patients treated with Empliciti combined with lenalidomide and dexamethasone (N = 318) and 3% of premedicated patients treated with Empliciti combined with pomalidomide and dexamethasone (N=60) (see section 4.4). The rate of mild to moderate infusion reactions was > 50% in patients who were not premedicated. All reports of infusion reaction were ≤ Grade 3. Grade 3 infusion reactions occurred in 1% of patients. ~~The~~In study CA204004, the most common symptoms of an infusion reaction included fever, chills, and hypertension. Five percent (5%) of patients required interruption of the administration of Empliciti for a median of 25 minutes due to infusion reaction, and 1% of patients discontinued due to infusion reactions. Of the patients who experienced an infusion reaction, 70% (23/33) had the reaction during the first dose. In study CA204125, all of the reported infusion reactions occurred during the first treatment cycle and were ≤ Grade 2.

Infections

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In a clinical trial of patients with multiple myeloma (CA204125), infections were reported in 65% of patients in the Empliciti combined with pomalidomide and dexamethasone arm (N = 60) and 65.5% in the pomalidomide and dexamethasone arm (N = 55). Grade 3-4 infections were noted in 13.3% and 21.8% of Empliciti combined with pomalidomide and dexamethasone and pomalidomide and dexamethasone treated patients, respectively. Fatal infections (i.e. Grade 5 infections) were reported in 5% of Empliciti combined with pomalidomide and dexamethasone and 3.6% of pomalidomide and dexamethasone treated patients.

Second Primary Malignancies

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There were no SPM events reported in patients treated in the Empliciti combined with pomalidomide and dexamethasone study arm (N = 60) and 1 (1.8%) in patients treated in the pomalidomide and dexamethasone arm (N = 55) in study CA204125.

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Immunogenicity

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Of the 53 patients in CA204125 treated with Empliciti and evaluable for the presence of anti-product antibodies, 19 patients (36%) tested positive , of whom 1 patient tested persistent positive, for treatment-emergent anti-product antibodies by an ECL assay. In these 19 patients, anti-product antibodies occurred within the first 2 months of the initiation of Empliciti treatment. Anti-product antibodies resolved by 2 to 3 months in 18 (95%) of these 19 patients. Neutralizing antibodies were detected in 2 of 53 patients.

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. ~~Healthcare professionals are asked to report any suspected adverse reactions.~~

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

~~(http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il).~~

https://sideeffects.health.gov.il/

4.9 Overdose

One patient was reported to be overdosed with 23.3 mg/kg of elotuzumab in combination with lenalidomide and dexamethasone. The patient had no symptoms, did not require any treatment for the overdose, and was able to continue on elotuzumab therapy.

~~In clinical studies, approximately 78 patients were evaluated with elotuzumab at 20 mg/kg without apparent toxic effects.~~

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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Clinical efficacy and safety

~~Two randomised, open-label studies were conducted to evaluate the efficacy and safety of Empliciti (elotuzumab) in adult patients with multiple myeloma who have received one or more prior therapies. Study 1 provided the pivotal data for the indication for~~ *Empliciti in combination with lenalidomide and dexamethasone*~~.~~ *(CA204004)*

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Empliciti in combination with pomalidomide and dexamethasone (CA204125)
CA204125 is a randomised, open-label study conducted to evaluate the efficacy and safety of Empliciti in combination with pomalidomide and dexamethasone (E-Pd) in patients with refractory or relapsed and refractory multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and had disease progression on or within 60 days of their last therapy. Patients were refractory if they had progressed on or within 60 days of treatment with lenalidomide and a PI and on or within 60 days of their last treatment, or relapsed and refractory if they had achieved at least a partial response to previous treatment with lenalidomide and a PI but progressed within 6 months and had developed progressive disease on or within 60 days after completing their last treatment. Patients with Grade 2 or higher peripheral neuropathy were excluded from the clinical studies with E-Pd.

A total of 117 patients were randomised in a 1:1 ratio to receive treatment: 60 to elotuzumab in combination with pomalidomide and dexamethasone (E-Pd) and 57 to pomalidomide and dexamethasone (Pd). Treatment was administered in 4-week cycles (28-day cycle) until disease progression or unacceptable toxicity. Elotuzumab 10 mg/kg was administered intravenously each week for the first 2 cycles and 20 mg/kg every 4 weeks thereafter.

Dexamethasone was administered on day 1, 8, 15 and 22 of each cycle. On weeks with Empliciti infusion, dexamethasone was administered before Empliciti as a divided dose: subjects ≤ 75 years an oral dose of 28 mg and an intravenous dose of 8 mg, and in subjects > 75 years an oral dose of 8 mg and an intravenous dose of 8 mg. On weeks without an Empliciti infusion and in the control group, dexamethasone was administered in subjects ≤ 75 years as an oral dose of 40 mg and in subjects > 75 years as an oral dose of 20 mg dexamethasone. Assessment of tumour response was conducted every 4 weeks.

Demographics and baseline characteristics were balanced between treatment arms. The median age was 67 years (range 36 to 81); 62% of patients were older than 65 years; 57% of patients were male; whites comprised 77% of the study population, Asians 21%, and blacks 1%. The International Staging System (ISS) Stage was I in 50%, II in 38% and III in 12% of patients. The chromosomal abnormalities as determined by the FISH of del(17p), t(4;14) and t(14;16) were present in 5-%, 11% and 7% of patients, respectively. Eleven (9.4%) patients had high-risk myeloma. The median number of prior therapies was 3. Eighty-seven percent (87%) of the patients were refractory to lenalidomide, 80% refractory to a PI and 70% were refractory to both lenalidomide and a PI. Prior therapies included stem cell transplant (55%), bortezomib (100%), lenalidomide (99%), cyclophosphamide (66%), melphalan (63%), carfilzomib (21%), ixazomib (6%), and daratumumab (3%).

The median number of treatment cycles was 9 for the E-Pd arm and 5 for the Pd arm.
The primary endpoint was investigator assessed PFS by modified International Myeloma Working Group (IMWG) criteria. The median PFS per ITT was 10.25 months (95% CI: 5.59, NE) in the E-Pd arm and 4.67 months (95% CI: 2.83, 7.16) in the Pd arm. PFS and ORR were also assessed by the IRC.

PFS results per the investigator and IRC are summarised in Table 10 (minimum follow-up of 9.1 months). Kaplan-Meier curve for PFS per the investigator is provided in Figure 3.

Table 10: CA204125 Efficacy results

	Investigator Assessed		IRC Assessed[f]	
	E-Pd N = 60	Pd N = 57	E-Pd N = 60	Pd N = 57
PFS (ITT)				
Hazard Ratio [95% CI]	0.54 [0.34, 0.86]		0.51 [0.32, 0.82]	
Stratified log-rank test p-value[a]	0.0078		0.0043	
Median PFS in months [95% CI]	10.25 [5.59, NE]	4.67 [2.83, 7.16]	10.25 [6.54, NE]	4.70 [2.83,7.62]
Response				
Overall Response (ORR)[b] n (%) [95% CI]	32 (53.3) [40.0, 66.3]	15 (26.3) [15.5, 39.7]	35 (58.3) [44.9, 70.9]	14 (24.6) [14.1, 37.8]
p-value[c]	0.0029		0.0002	
Complete Response (CR + sCR)[d] n (%)	5 (8.3)[e]	1 (1.8)	0 (0.0)[e]	0 (0.0)
Very Good Partial Response (VGPR) n (%)	7 (11.7)	4 (7.0)	9 (15.0)	5 (8.8)
Partial Response (RR/PR) n (%)	20 (33.3)	10 (17.5)	26 (43.3)	9 (15.8)
Combined Responses (CR+sCR+VGPR) n (%)	12 (20.0)	5 (8.8)	9 (15.0)	5 (8.8)

[a] p-value based on the log-rank test stratified by stage of disease at study entry (International Staging System I-II vs III) and number of prior lines of therapy (2-3 vs ≥ 4) at randomization.

[b] modified International Myeloma Working Group (IMWG) criteria.

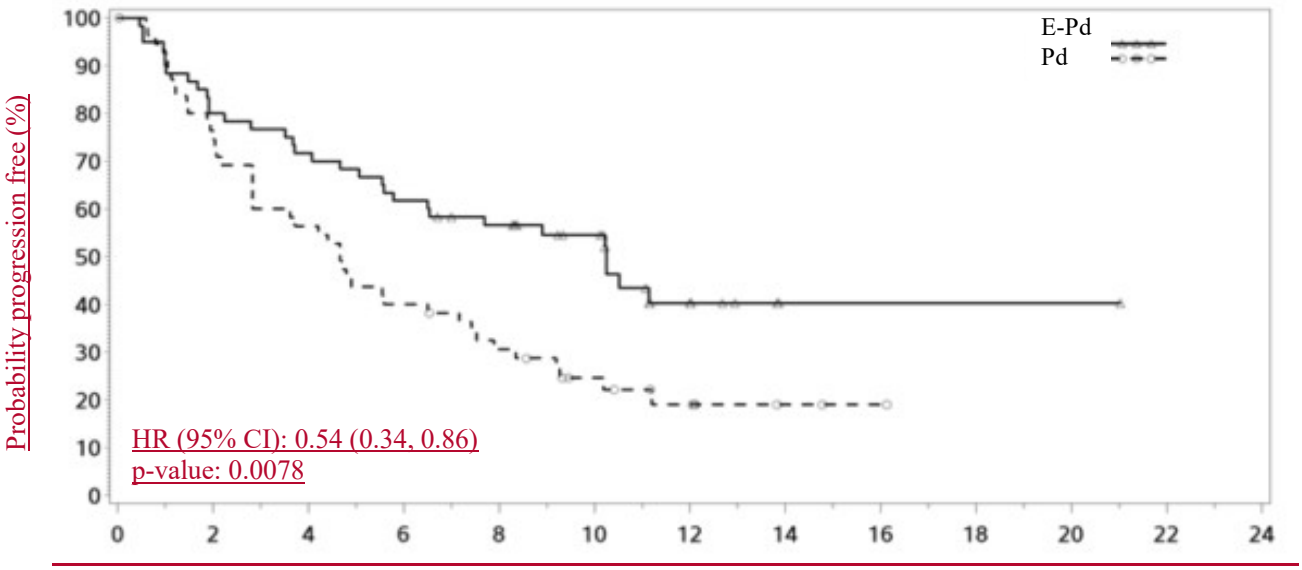
[c] p-value based on the Cochran-Mantel-Haenszel chi-square test stratified by stage of disease at study entry (International Staging System I-II vs III) and number of prior lines of therapy (2-3 vs ≥ 4) at randomization.

[d] Complete response (CR) + stringent complete response (sCR).

[e] Complete response rates in Empliciti group may be underestimated due to interference of elotuzumab monoclonal antibody with immunofixation assay and serum protein electrophoresis assay.

[f] IRC assessment was performed post-hoc.

Figure 3: CA204125 Progression free survival per investigator



Number of subjects at risk

E-Pd	60	48	43	37	32	25	7	1	1	1	1
Pd	57	42	31	22	16	10	6	2	1		

PFS ITT assessment per investigator was evaluated in several subgroups including age (< 65 versus ≥ 65), race, ISS stage, prior therapies, transplant, risk category, ECOG status, creatinine clearance, and cytogenic abnormalities. Regardless of the subgroup evaluated, PFS was generally consistent with that observed in the ITT population for the treatment groups. However, results should be taken with caution as assessment of consistency of effect within the different subgroups was hampered by the very limited number of patients included in the different subgroups.

Overall survival (OS) was a key secondary study endpoint. The OS data from the exploratory analysis were not mature at the data cut-off (29 November 2018) with a minimum follow up of 18.3 months. A total of 40 (67%) patients were alive in the E-Pd arm and 29 (51%) in the Pd arm. Median OS was not reached for E-Pd treatment group. The hazard ratio and 95% CI were 0.54 (0.30, 0.96).

5.2 Pharmacokinetic properties

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Distribution

The geometric mean volume of distribution of elotuzumab at ~~10 mg/kg (~~the recommended dosing regimen in combination with lenalidomide~~ and /~~dexamethasone~~)~~ or pomalidomide/dexamethasone at steady state is ~~6.02~~5.7 L (CV:~~ 22.1%).~~ 23%) and 5.6 L (CV: 21%) respectively.

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Elimination

The geometric mean total clearance of elotuzumab at 10 mg/kg (in combination with lenalidomide and dexamethasone) at steady state is 0.194 L/day (CV: 62.9%). Upon discontinuation of elotuzumab in combination with lenalidomide and dexamethasone or in combination with pomalidomide and dexamethasone, concentrations of elotuzumab will decrease to approximately 3% (approximately 97% washout as estimated by 5 half-lives) of the population predicted steady-state maximal serum concentration by 3 months.

Special populations
Based on a population PK analysis using data from ~~375~~440 patients, the clearance of elotuzumab increased with increasing body weight supporting a weight-based dose. ~~The population~~Population PK analysis suggested that the following factors had no clinically important effect on the clearance of elotuzumab: age ~~(37 to 88 years),~~ gender, race, baseline LDH, albumin, renal impairment, ~~and~~ mild hepatic impairment, and coadministration with lenalidomide/dexamethasone or pomalidomide/dexamethasone.
Target-mediated clearance of elotuzumab increased with higher serum M-protein concentrations.
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6. PHARMACEUTICAL PARTICULARS

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6.6 Special precautions for disposal and other handling

Calculating the dose

Calculate the dose (mg) and determine the number of vials needed for the dose (10 mg/kg ~~dose~~or 20 mg/kg) based on patient weight. More than one vial of Empliciti may be needed to give the total dose for the patient.

- The total elotuzumab dose in mg ~~=~~equals the patient's weight in kg ~~× 10.~~ multiplied by the elotuzumab dose (10 or 20 mg/kg, see section 4.2).

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~~Once the reconstitution is completed, withdraw~~Preparation of the solution for infusion
The reconstituted solution should be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or 5% glucose injection to obtain a final infusion concentration range between 1 mg/mL and 6 mg/mL. The volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 5% glucose injection should be adjusted so as to not exceed 5 mL/kg of patient weight at any given dose of Empliciti.

Calculate the volume (mL) of diluent (either sodium chloride 9 mg/mL (0.9%) solution for injection or 5% glucose injection) needed to make up the solution for infusion for the patient.

- Withdraw the necessary volume for the calculated dose from each vial, up to a maximum of 16 mL from 400 mg vial and 12 mL from 300 mg vial. ~~Dilute the reconstituted solution with 230 mL of either sodium chloride 9 mg/mL (0.9%) solution for injection or 5% glucose injection, into an infusion bag made of polyvinyl chloride or polyolefin. The volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 5% glucose injection should be adjusted so as not to exceed 5 mL/kg of patient weight at any given dose of Empliciti~~Each vial contains a slight overfill to ensure sufficient extractable volume.

Transfer the withdrawn volumes of all vials needed according to the calculated dose for this patient into one single infusion bag made of polyvinyl chloride or polyolefin containing the calculated volume of diluent. Gently mix the infusion by manual rotation. Do not shake.

Empliciti is for single use only. Discard any unused portion left in the vial.

Administration
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Empliciti should be initiated at an infusion rate of 0.5 mL/min for 10 mg/kg dose and 3 mL/min for 20 mg/kg dose. If well tolerated, the infusion rate may be increased stepwise as described in Tables ~~2~~ 3 and 4 (see section 4.2 Method of administration). The maximum infusion rate should not exceed 5 mL/min.

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