

דצמבר 2025

**Breyanzi / בריאנזי**  
**(lisocabtagene maraleucel)**  
**תרחיף לעירוי תוך ורידי / Dispersion for IV infusion**

רופא/ה, רוקח/ת יקר/ה,

חברת בריסטול-מאירס סקוויב (ישראל) שמחה לעדכן על רישום שתי התוויות נוספות לתכשיר Breyanzi ועדכונים בעלוניים לרופא ולצרכן בהתאם וכן על עדכונים נוספים.

התוויות התכשיר כפי שאושרו ע"י משרד הבריאות (ההתוויות החדשות מסומנות בצבע **אדום**):

Breyanzi is indicated for the treatment of adult patients with large B-cell lymphoma (LBCL), including diffuse large B-cell lymphoma (DLBCL) not otherwise specified (including DLBCL arising from indolent lymphoma), high grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma grade 3B who have:

- refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or
- refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age.

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), after two or more lines of systemic therapy.

**Breyanzi is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.**

**Breyanzi is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.**

המרכיב הפעיל:

lisocabtagene maraleucel (1.1-70 x 10<sup>6</sup> CAR-positive viable T cells/ml / 1.1-70 x 10<sup>6</sup> CAR-positive viable T cells/ml)

להלן העדכונים בעלון לרופא ובעלון לצרכן (ללא פירוט שיניים לא מהותיים ו/או עריכתיים).

תוספת טקסט מסומנת **בין תחתון אדום**, מחיקת טקסט **בין אמצעי אדום**, **החמרה מודגשת בצהוב**, שינוי מיקום **בצבע ירוק**.

העלון לרופא והעלון לצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפסים על ידי פנייה לבעל הרישום בריסטול-מאירס סקוויב (ישראל) בע"מ.

בברכה,  
יפעת זלינגר בן דוד

למידע מלא על התרופה יש לעיין בעלון לרופא ובעלון לצרכן כפי שנשלחו למשרד הבריאות.

#### **4.1 Therapeutic indications**

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

Breyanzi is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

#### **4.4 Special warnings and precautions for use**

[...]

Cytokine release syndrome

[...]

For patients who received Breyanzi for FL, the median time to onset was 6 days (range: 1 to 17 days). For patients who received Breyanzi for MCL, the median time to onset was 4 days (range: 1 to 10 days).

[...]

Monitoring and management of CRS

[...]

Patients and caregivers should be informed about the potential late onset of CRS and instructed to seek immediate medical attention if patients experience any signs or symptoms of CRS. Patients should be counselled to seek immediate medical attention should signs or symptoms of CRS occur at any time, and treated promptly

[...]

Neurologic adverse reactions

[...]

, for patients who received Breyanzi for FL, the median time to onset of the first event was 8 days (range: 4 to 16 days), and for patients who received Breyanzi for MCL, the median time to onset of the first event was 8 days (range: 1 to 25 days)

[...]

Monitoring and management of neurologic toxicities

Patients and caregivers should be informed about the potential late onset of neurologic toxicities and instructed to seek immediate medical attention if patients experience any signs or symptoms of neurologic toxicities. Patients should be counselled to seek immediate medical attention should signs and symptoms of neurologic toxicity occur at any time, and treated promptly.

[...]

#### **4.8 Undesirable effects**

[...]

FL

The adverse reactions described in this section were characterised in 130 patients infused with Breyanzi from study TRANSCEND-FL (FOL-001).

The most common adverse reactions of any grade were neutropenia (68%), CRS (58%), anaemia (40%), headache (29%), thrombocytopenia (29%) and constipation (21%).

The most common serious adverse reactions were CRS (9%), aphasia (4%), febrile neutropenia (3%), pyrexia (2%) and tremor (2%).

The most common Grade 3 or higher adverse reactions included neutropenia (61%), leukopenia (12%), lymphopenia (12%), thrombocytopenia (12%) and anaemia (10%).

## MCL

The adverse reactions described in this section were characterised in 88 patients infused with Breyanzi from study TRANSCEND-MCL Cohort [017001].

The most common adverse reactions of any grade were CRS (61%), neutropenia (59%), anaemia (44%), fatigue (35%), thrombocytopenia (30%), and headache (23%).

The most common serious adverse reactions were CRS (24%), confusional state (6%), pyrexia (3%), mental status changes (2%), encephalopathy (2%), upper respiratory tract infection (2%), and pleural effusion (2%).

The most common Grade 3 or higher adverse reactions included neutropenia (56%), anaemia (38%), thrombocytopenia (25%), hypophosphataemia (9%), and leukopenia (7%).

## Tabulated list of adverse reactions

The frequencies of adverse reactions are based on pooled data from 67 studies (TRANSCEND [017001], including LBCL and MCL Cohorts, TRANSCEND WORLD [JCAR017-BCM-001, eCohort 1, 2, 3 and 7], PLATFORM [JCAR017-BCM-002], OUTREACH [017007], TRANSFORM [BCM-003], and PILOT [017006]) and TRANSCEND-FL (JCAR017-FOL-001), in 561 779 adult patients and from post-marketing reports within the dose range of 44–120 x 10<sup>6</sup> CAR-positive viable T-cells with R/R LBCL, defined as DLBCL, HGBCL, PMBCL and FL3B, who received a dose of lisocabtagene maraleucel. The adverse reaction frequencies from clinical studies are based on all-cause adverse event frequencies, where a proportion of the events for an adverse reaction may have other causes.

[...]

**Table 3: Adverse drug reactions identified with Breyanzi**

System Organ Class (SOC)	Frequency	Adverse reaction
Blood and lymphatic system disorders	Very common	Neutropenia Anaemia Thrombocytopenia Leukopenia Lymphopenia
	Common	Febrile neutropenia Hypofibrinogenaemia <sup>w</sup>
	Uncommon	Pancytopenia
Immune system disorders	Very common	Cytokine release syndrome
	Common	Hypogammaglobulinaemia <sup>x</sup>
	Uncommon	Haemophagocytic lymphohistiocytosis

[...]

<sup>c</sup> Headache includes headache, migraine, ~~ophthalmic migraine~~migraine with aura, sinus headache

[...]

<sup>h</sup> Peripheral neuropathy includes ~~carpal tunnel syndrome~~, demyelinating polyneuropathy, hyperaesthesia, hypoaesthesia, hyporeflexia, ~~loss of proprioception~~, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, sensory loss, ~~carpal tunnel syndrome~~

[...]

<sup>p</sup> Arrhythmia includes arrhythmia, atrial fibrillation, atrioventricular block complete, atrioventricular block second degree, ~~extrasystoles~~, supraventricular tachycardia, ~~extrasystoles~~, ventricular extrasystoles, ventricular tachycardia

[...]

<sup>q</sup> Thrombosis includes deep vein thrombosis, embolism, ~~embolism venous~~, pulmonary embolism, thrombosis, vena cava thrombosis, venous thrombosis, venous thrombosis limb

<sup>v</sup> Hypogammaglobulinemia includes blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, hypogammaglobulinaemia, immunoglobulins decreased.

<sup>w</sup> Hypofibrinogenaemia includes blood fibrinogen decreased, hypofibrinogenaemia

## Description of selected adverse reactions

### *Cytokine release syndrome*

For patients who received one prior line of therapy for LBCL, CRS occurred in 45% of patients, 1% of whom experienced Grade 3 CRS (~~no fatal events~~). The median time to onset was 4 days (range: 1 to 63 days, with the upper limit due to CRS onset, without fever, reported in one patient) and the median duration of CRS was 4 days (range: 1 to 16 days).

[...]

For patients who received two or more prior lines of therapy for LBCL, CRS occurred in 38% of patients, 2% of whom experienced Grade 3 or 4 (severe or life-threatening) CRS. ~~There were no fatal events.~~ Among patients who died after receiving Breyanzi, 4 had ongoing CRS events at the time of death. The median time to onset was 4 days (range: 1 to 14 days) and the median duration was 5 days (range: 1 to 17 days).

[...]

For patients who received Breyanzi for FL, CRS occurred in 58% of patients, 0.8% of whom experienced Grade 3 CRS. The median time to onset was 6 days (range: 1 to 17 days) and the median duration of CRS was 3 days (range: 1 to 10 days).

The most common manifestations of CRS included pyrexia (57%), hypotension (14%), chills (4%) hypoxia (2%) and tachycardia (0.8%).

In the FL clinical study, 33 of 130 (25%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of Breyanzi. Eighteen (14%) patients received tocilizumab only, 15 (12%) received tocilizumab and a corticosteroid and no patients received corticosteroids only. See section 4.4 for monitoring and management guidance.

For patients who received Breyanzi for MCL, CRS occurred in 61% of patients, 1% of whom experienced Grade 3 or 4 CRS. The median time to onset was 4 days (range: 1 to 10 days) and the median duration of CRS was 4 days (range: 1 to 14 days).

The most common manifestations of CRS included pyrexia (60%), hypotension (22%), hypoxia (11%) tachycardia (10%), chills (8%), headache (8%), nausea (3%), and dyspnoea (2%).

In the TRANSCEND-MCL Cohort, 24 of 88 (27%) patients received tocilizumab and/or a corticosteroid for CRS after infusion of Breyanzi. 15 (17%) patients received tocilizumab only, 8 (9%) received tocilizumab and a corticosteroid and 1 (1%) patient received corticosteroids only.

See section 4.4 for monitoring and management guidance.

[...]

### *Neurologic adverse reactions*

For patients who received one prior line of therapy for LBCL, CAR T-cell-associated neurologic toxicities, assessed by the investigator, occurred in 18% of patients receiving Breyanzi, including Grade 3 in 5% of patients (~~no fatal events~~). The median time to onset of the first event was 8 days (range: 1 to 63 days); 84% of all neurologic toxicities occurred within ~~2~~the first 8 weeks following Breyanzi infusion. The median duration of neurologic toxicities was 6 days (range: 1 to 89 days).

The most common neurologic toxicities included encephalopathy (10%), tremor (8%), aphasia (5%), dizziness (2%), and headache (1%).

For patients who received two or more prior lines of therapy for LBCL, CAR T-cell-associated neurologic toxicities assessed by the investigator occurred in 26% of patients receiving Breyanzi, including Grade 3 or 4 in 10% of patients (~~no~~

~~fatal events~~). The median time to onset of the first event was 9 days (range: 1 to 66 days); ~~83~~99% of all neurologic toxicities occurred within 2 ~~the first 8~~ weeks following Breyanzi infusion. The median duration of neurologic toxicities was 10 days (range: 1 to 84 days).

[...]

For patients who received Breyanzi for FL, CAR T-cell-associated neurologic toxicities, assessed by the investigator, occurred in 16% of patients receiving Breyanzi, including Grade 3 in 3% of patients. The median time to onset of the first event was 8 days (range: 4 to 16 days); 95% of all neurologic toxicities occurred within 2 weeks following Breyanzi infusion. The median duration of neurologic toxicities was 3 days (range: 1 to 17 days).

The most common neurologic toxicities included tremor (8%), aphasia (8%), encephalopathy (5%), delirium (4%) and headache (2%). See section 4.4 for monitoring and management guidance of neurologic toxicities.

For patients who received Breyanzi for MCL, CAR T-cell-associated neurologic toxicities, assessed by the investigator, occurred in 31% of patients receiving Breyanzi, including Grade 3 or 4 in 9% of patients. The median time to onset of the first event was 8 days (range: 1 to 25 days); 100% of all neurologic toxicities occurred within the first 8 weeks following Breyanzi infusion. The median duration of neurologic toxicities was 5 days (range: 1 to 45 days).

The most common neurologic toxicities included encephalopathy (26%), tremor (7%), delirium (6%), aphasia (6%), headache (5%), and dizziness (3%). Seizures (1%) have occurred in patients treated with Breyanzi.

See section 4.4 for monitoring and management guidance of neurologic toxicities.

[...]

#### *Febrile neutropenia and infections*

Febrile neutropenia has been observed in 7% ~~and 9%~~ of patients ~~after receiving who received~~ Breyanzi ~~who received for~~ LBCL ~~after one prior line of therapy and two or more prior lines of therapy, respectively, in 5% of patients who received Breyanzi for FL and in 6% of patients after receiving Breyanzi for MCL.~~

~~for LBCL and 9% of patients after receiving Breyanzi who received two or more prior lines of therapy.~~

[...]

For patients who received Breyanzi for FL, infections (all grades) occurred in 20% of patients. Grade 3 occurred in 5% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 4% of patients, bacterial infections occurred in 2% of patients, viral and fungal infections occurred in 1% and none of patients, respectively.

For patients who received Breyanzi for MCL, infections (all grades) occurred in 35% of patients. Grade 3 or higher occurred in 15% of patients. Grade 3 or higher infections with an unspecified pathogen occurred in 6% of patients, bacterial infections occurred in 5% of patients, viral and fungal infections occurred in 5% and 1% of patients, respectively.

[...]

Opportunistic infections (all grades) have been observed in 0.8% of the 130 patients treated with Breyanzi who received Breyanzi for FL, with no Grade 3 or higher opportunistic infections observed. Opportunistic infections (all grades) have been observed in 1% of the 88 patients who received Breyanzi for MCL, all of which were Grade 3 or higher.

Two fatal infections were reported from the 177 patients treated with Breyanzi who received one prior line of therapy for LBCL. Four fatal infections were reported from the 384 patients treated with Breyanzi who received two or more prior lines of therapy for LBCL among pooled LBCL studies. Of these, 1 was reported as a fatal opportunistic infection. No fatal infections were reported in the 130 patients treated with Breyanzi for FL. Two fatal infections were reported in the 88 patients treated with Breyanzi for MCL.

[...]

#### *Prolonged cytopenias*

[...]

For patients who received Breyanzi for FL, Grade 3 or higher cytopenias present at Day 29 following Breyanzi administration, occurred in 22% of patients, and included thrombocytopenia (15%), neutropenia (15%) and anaemia (5%). See section 4.4 for monitoring and management guidance.

Of the 130 total patients treated in TRANSCEND -FL who had Day 29 laboratory findings of Grade 3-4 thrombocytopenia (n = 19) or Grade 3- 4 neutropenia (n = 20) or Grade 3-4 anaemia (n = 6), for whom follow-up laboratory cytopenia results were available, the median time (min, max) to resolution (cytopenia recovering to Grade 2 or less) was as follows in days: thrombocytopenia 36 days (16, 694); neutropenia 30 days (5, 110); and anaemia 36 days (8, 64).

For patients who received Breyanzi for MCL, Grade 3 or higher cytopenias present at Day 29 following Breyanzi administration, occurred in 40% of patients, and included thrombocytopenia (32%), neutropenia (24%) and anaemia (5%).

Of the 88 total patients treated in the TRANSCEND-MCL Cohort who had Day 29 laboratory findings of Grade 3-4 thrombocytopenia (n = 28) or Grade 3-4 neutropenia (n = 21) or Grade 3-4 anaemia (n = 4), for whom follow-up laboratory cytopenia results were available, the median time (min, max) to resolution (cytopenia recovering to Grade 2 or less) was as follows in days: thrombocytopenia 30 days (5, 302); neutropenia 30 days (8, 275); and anaemia 18 days (9, 32).

See section 4.4 for monitoring and management guidance.

#### *Hypogammaglobulinaemia*

For patients who received one prior line of therapy for LBCL, adverse events of hypogammaglobulinemia occurred in 7% of patients. For patients who received two or more prior line of therapy for LBCL, adverse events of hypogammaglobulinaemia occurred in 11% of patients. For patients who received Breyanzi for FL, adverse events of hypogammaglobulinaemia occurred in 2% of patients. For patients who received Breyanzi for MCL, adverse events of hypogammaglobulinaemia occurred in 7% of patients. See section 4.4 for monitoring and management guidance.

#### Immunogenicity

[...]

In patients who received Breyanzi for FL (TRANSCEND-FL), pre-existing anti-therapeutic antibodies (ATAs) were detected in 1.6% (2/124) of patients, and treatment-induced or treatment-boosted ATAs were detected in 26.8% (33/123) of patients. In patients who received Breyanzi for MCL (TRANSCEND-MCL Cohort), pre-existing ATAs were detected in 13% (11/88) of patients, and treatment-induced or treatment-boosted ATAs were detected in 20% (17/86) of patients. The relationships between ATA status and efficacy, safety or pharmacokinetics were not conclusive due to the limited number of patients with ATAs at the study level.

[...]

#### **5.1 Pharmacodynamic properties**

[...]

The results of the final subsequent primary analysis (shown in Table 5 and Figure 1), with a median on-study follow-up time of 33.8617.5 months (range 0.9 to 53.037 months), were consistent with both the interim and primary analysesanalysis.

**Table 5: TRANSFORM study: Response rate, event-free survival, progression-free survival and overall survival in patients with relapsed or refractory LBCL (ITT analysis set)**

Outcome <sup>a</sup>	Breyanzi arm (N = 92)	SOC arm (N = 92)
<b>Event-free survival, (months)</b>		
Number of events n, (%)	<u>4448 (47.852.2)</u>	<u>7173 (77.279.3)</u>
Median [95% CI] <sup>b</sup>	NR <u>29.5</u> (9.5, NR)	2.4 (2.2, 4.9)
Hazard ratio [95% CI] <sup>c</sup>	<u>0.356 0.375 [0.243, 0.5220.259, 0.542]</u>	

Outcome <sup>a</sup>	Breyanzi arm (N = 92)	SOC arm (N = 92)
<b>Complete response rate</b>		
n (%)	68 (73.9)	40 (43.5)
Two sided [95% CI]	[63.7, 82.5]	[33.2, 54.2]
One-sided p-value <sup>d,e</sup>	<0.0001	
<b>Progressionfree survival, (months)</b>		
Number of events n, (%)	<del>37</del> 41 (40.244.6)	<del>52</del> 54 (56.558.7)
Median [95% CI] <sup>b</sup>	NR (12.6, NR)	6.2 (4.3, 8.6)
Hazard ratio [95% CI] <sup>c</sup>	0.4000.422 [0.261, 0.6150.279, 0.639]	
One-sided p-value <sup>e,d</sup>	<0.0001	
<b>Overall survival (OS), (months)</b>		
Number of events n, (%)	<del>28</del> 34 (30.437.0)	<del>38</del> 42 (41.345.7)
Median [95% CI] <sup>b</sup>	NR ( <del>29.5</del> 42.8, NR)	<del>29.9</del> NR ( <del>17.9</del> 18.2, NR)
Hazard ratio [95% CI] <sup>c</sup>	<del>0.724</del> 0.757 [0.443, 1.1830.481, 1.191]	

NR = not reached; CI = confidence interval.

<sup>a</sup> Per the Lugano criteria [2014](#), as assessed by an IRC.

<sup>b</sup> Kaplan-Meier estimate.

<sup>c</sup> Based on a stratified Cox proportional hazards model.

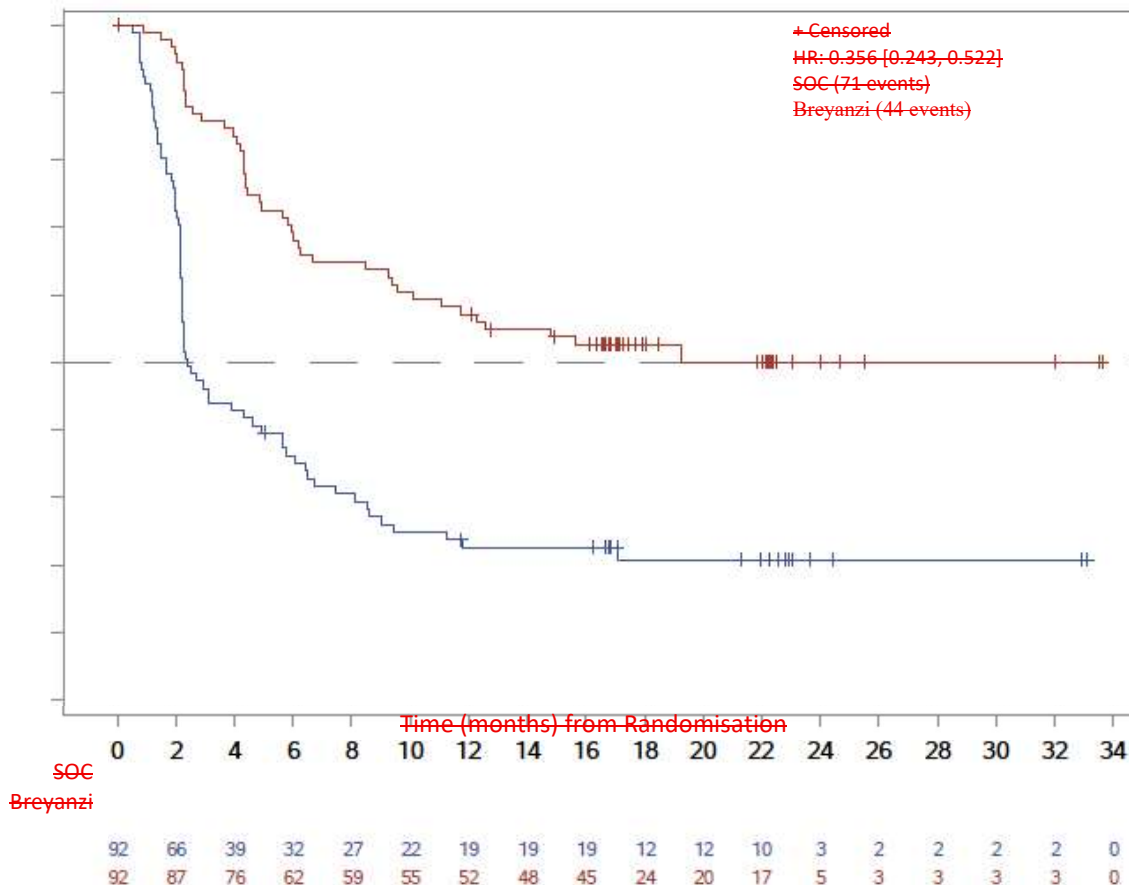
<sup>d</sup> Greenwood's formula

<sup>d</sup>-p-value was compared with 0.021 of the allocated alpha for the primary analysis.

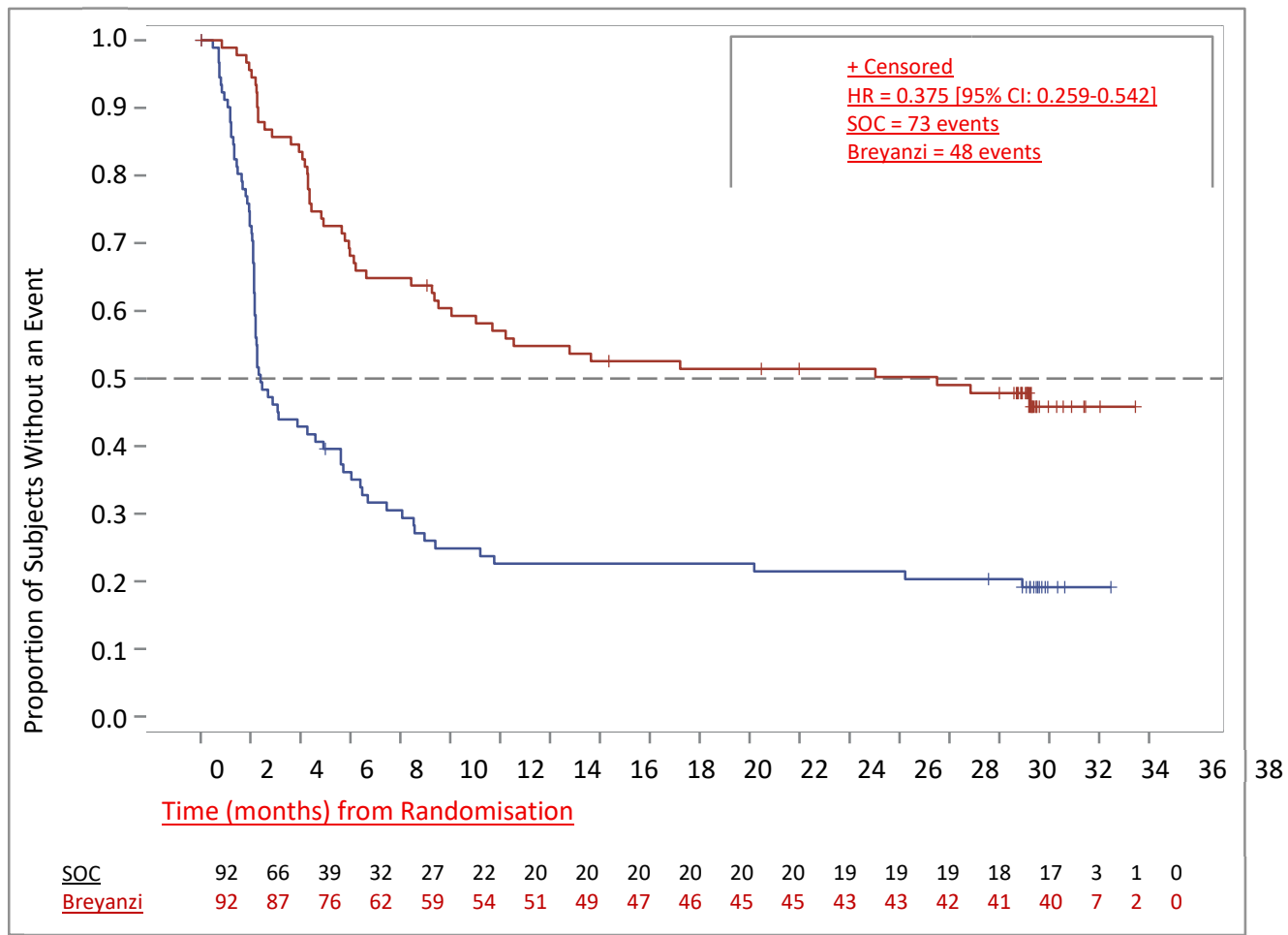
<sup>e</sup>-Cochran-Mantel-Haenszel test.

[...]

Figure 1: Kaplan-Meier plot of event-free survival based on IRC Assessment (ITT analysis set)



**Figure 1: Kaplan-Meier plot of event-free survival based on IRC Assessment (ITT analysis set)**



[...]

**TRANSCEND-FL**

The efficacy and safety of Breyanzi was evaluated in a Phase 2, open-label, multicentre, single-arm study (TRANSCEND-FL) in adult patients with relapsed or refractory FL grades 1, 2 and 3A after two or more lines of systemic therapy. The study enrolled patients with ECOG performance status of  $\leq 1$ . The study excluded patients with a creatinine clearance of less than 30 mL/min, alanine aminotransferase  $> 5$  times the upper limit of normal or, left ventricular ejection fraction (LVEF)  $\leq 40\%$ . There was no prespecified threshold for blood counts; patients were eligible to enroll if they were assessed by the investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy.

Treatment consisted of lymphodepleting (LD) chemotherapy, fludarabine 30 mg/m<sup>2</sup>/day and cyclophosphamide 300 mg/m<sup>2</sup>/day for 3 days, followed by Breyanzi 2 to 7 days later. The median dose of Breyanzi was 100 x 10<sup>6</sup> CAR-positive viable T-cells (range: 93.4 - 109.2 x 10<sup>6</sup> CAR-positive viable T-cells).

Anticancer therapy for disease control (bridging therapy) was permitted between apheresis and lymphodepletion. Of the 107 patients treated with Breyanzi, 44 (41%) received anticancer therapy, for disease control at the discretion of the investigator.

Of 114 patients who underwent leukapheresis, 107 (93.8%) patients received Breyanzi, and 4 (3.5%) patients received non-conforming product. Three (2.7%) patients did not receive Breyanzi for the following reasons: 1 (0.9%) patient due to an adverse event, 1 (0.9%) patient did not meet study criteria and 1 (0.9%) patient due to other reasons.

The number of patients who were evaluable for efficacy was 103 (efficacy set). Four patients were not evaluable for efficacy, as those patients did not have baseline PET-positive disease, or confirmation of PET-positive disease after anticancer therapy for disease control by IRC.

The median time from leukapheresis to product availability was 29 days (range: 20 to 55 days), and the median time from leukapheresis to product infusion was 50 days (range: 31 to 313 days).

**Table 9: Baseline demographic and disease-related characteristics for TRANSCEND-FL**

<u>Characteristic</u>	<u>All leukapheresed (N = 114)</u>	<u>Breyanzi-treated (N = 107)</u>
<u>Median age, years (range)</u>	<u>62.0 (23, 80)</u>	<u>62.0 (23, 80)</u>
<u>≥ 65 to &lt;75 years, n (%)</u>	<u>36 (31.6)</u>	<u>32 (29.9)</u>
<u>≥ 75 years, n (%)</u>	<u>10 (8.8)</u>	<u>10 (9.3)</u>
<u>Male gender, n (%)</u>	<u>72 (63.2)</u>	<u>66 (61.7)</u>
<u>Prior HSCT, n (%)</u>		
<u>Autologous HSCT</u>	<u>34 (29.8)</u>	<u>33 (30.8)</u>
<u>High FLIPI score (3-5), n (%)</u>	<u>66 (57.9)</u>	<u>61 (57.0)</u>
<u>Stage III-IV disease at screening, n (%)</u>	<u>102 (89.4)</u>	<u>95 (88.7)</u>
<u>ECOG performance status (at screening)</u>		
<u>ECOG 0, n (%)</u>	<u>68 (59.6)</u>	<u>65 (60.7)</u>
<u>ECOG 1, n (%)</u>	<u>46 (40.4)</u>	<u>42 (39.3)</u>
<u>Double refractory, n (%)</u>	<u>74 (64.9)</u>	<u>69 (64.5)</u>
<u>Progression within 24 months of first line therapy with anti-CD20 and alkylator, n (%)</u>		
<u>Yes</u>	<u>63 (55.3)</u>	<u>58 (54.2)</u>
<u>No</u>	<u>50 (43.9)</u>	<u>48 (44.9)</u>
<u>Not estimable</u>	<u>1 (0.9)</u>	<u>1 (0.9)</u>
<u>Median number of prior systemic treatments (range)</u>	<u>3 (2,10)</u>	<u>3 (2, 10)</u>

Efficacy was based on overall response rate (ORR), defined as the percentage of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) after Breyanzi infusion as determined by an IRC (Table 10). The median on-study follow-up time was 30.0 months (range 0.3 to 39.6 months).

The median time to first response (CR or PR) and median time to first CR was 0.95 months (range: 0.6 to 3.3 months).

**Table 10: TRANSCEND-FL study: Response rate, duration of response (IRC assessment)**

	<b>All leukapheresed (N = 114)</b>	<b>Efficacy set (N = 103)</b>
<b>Overall response rate<sup>a</sup>, n (%)</b> [95% CI] <sup>b</sup>	<u>106 (93.0)</u> <u>[86.6, 96.9]</u>	<u>100 (97.1)</u> <u>[91.7, 99.4]</u>
<b>Complete response, n (%)</b> [95% CI] <sup>b</sup>	<u>103 (90.4)</u> <u>[83.4, 95.1]</u>	<u>97 (94.2)</u> <u>[87.8, 97.8]</u>
<b>Partial response, n (%)</b> [95% CI] <sup>b</sup>	<u>3 (2.6)</u> <u>[0.5, 7.5]</u>	<u>3 (2.9)</u> <u>[0.6, 8.3]</u>
<b>Duration of response (DOR) (months)</b>		
Median [95% CI] <sup>c</sup>	<u>NR [30.85, N.R]</u>	<u>NR [30.85, NR]</u>
Range	<u>1.9, 35.0+</u>	<u>1.9, 35.0+</u>
<b>Rate of continued remission<sup>d</sup>, %</b> [95% CI]		
At 18 months	<u>76.1 (66.7, 83.2)</u>	<u>75.7 (66.0, 83.0)</u>

CI = confidence interval; CR = complete response; NR = not reached;

+ indicates a censored value

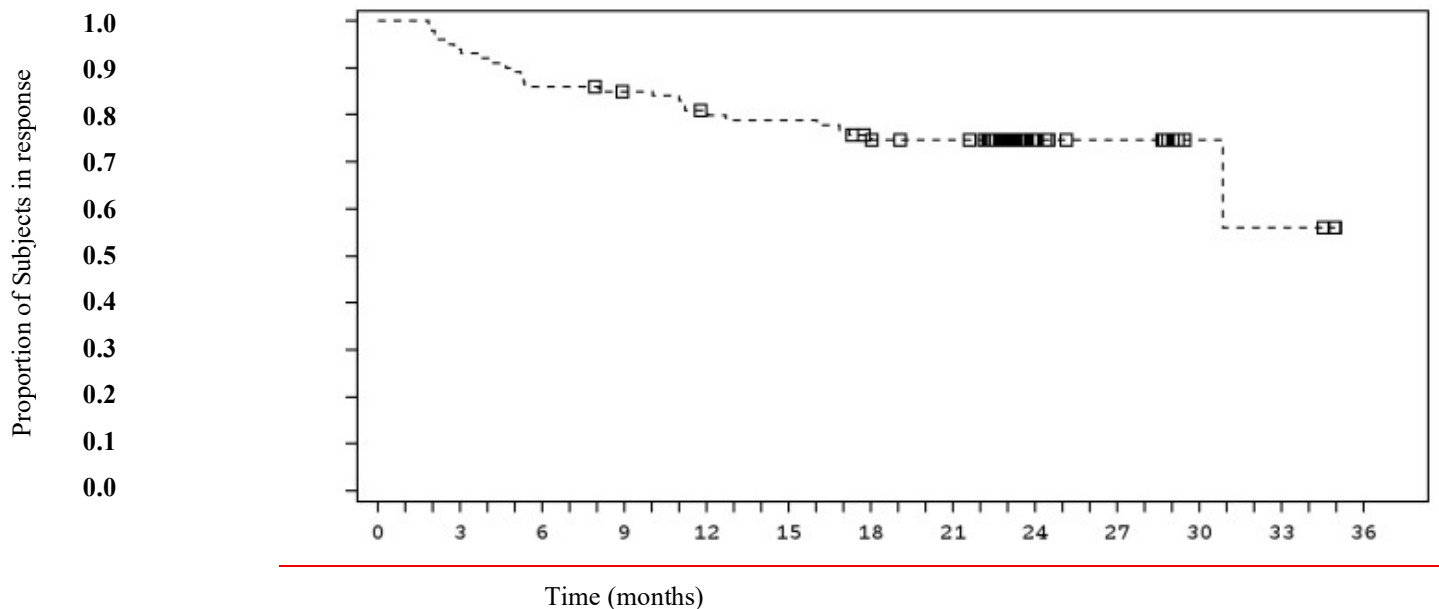
<sup>a</sup> Per the Lugano 2014 criteria, as assessed by an IRC

<sup>b</sup> Two-sided 95% confidence interval based on exact Clopper-Pearson method.

<sup>c</sup> Median, Q1, Q3 are estimated from KM product-limit estimates

<sup>d</sup> Based on KM estimates of duration of response

**Figure 3: Duration of response by IRC assessment, TRANSCEND-FL Efficacy set**



Number of subjects at risk (censored)

3L + 100 (0) 94 (0) 86 (0) 83 (2) 78 (1) 76 (0) 71 (2) 68 (2) 14 (54) 10 (4) 4 (6) 3 (0) 0 (3)

#### TRANSCEND-MCL Cohort

The efficacy and safety of Breyanzi were evaluated in an open-label, multicenter, single-arm trial (TRANSCEND-MCL Cohort) in adult patients with relapsed or refractory MCL who had received at least 2 prior lines of therapy including a Bruton's tyrosine kinase (BTK) inhibitor, an alkylating agent, and an anti-CD20 agent. The study included patients with ECOG performance status of  $\leq 2$ , prior autologous and/or allogeneic HSCT, and secondary CNS lymphoma involvement. The study excluded patients with a creatinine clearance  $\leq 30$  mL/min, alanine aminotransferase  $> 5$  times the upper limit

of normal or left ventricular ejection fraction (LVEF) < 40%. There was no prespecified threshold for blood counts; patients were eligible to enroll if they were assessed by the investigator to have adequate bone marrow function to receive lymphodepleting chemotherapy.

Treatment consisted of LD chemotherapy, fludarabine 30 mg/m<sup>2</sup>/day and cyclophosphamide 300 mg/m<sup>2</sup>/day for 3 days, followed by Breyanzi 2 to 7 days later.

Anticancer therapy for disease control (bridging therapy) was permitted between apheresis and lymphodepletion. Of the 88 patients treated with Breyanzi, 58 (65.9%) received anticancer therapy for disease control, at the discretion of the investigator.

Of 104 patients who underwent leukapheresis, 88 (84.6%) patients received Breyanzi; the median dose of Breyanzi was 99.5 × 10<sup>6</sup> CAR-positive viable T-cells (range: 46-103 × 10<sup>6</sup> CAR positive viable T-cells). Four (3.8%) patients received non-conforming product. Twelve (11.5%) patients did not receive Breyanzi for the following reasons: 8 (7.6%) patients due to death, 1 (0.9%) patient no longer met eligibility criteria, and 3 (2.8%) patients due to other reasons.

Of the 88 patients who received Breyanzi, 81 patients were evaluable for efficacy and received at least 2 prior lines of systemic therapy including a BTK inhibitor, and were included in the efficacy set: five patients were not evaluable for efficacy as these patients did not have baseline PET-positive disease or confirmation of PET-positive disease after anticancer therapy for disease control by IRC, 1 patient did not receive at least 2 prior lines of systemic therapy and a BTK inhibitor and 1 patient did not receive a prior BTK inhibitor.

The median time from leukapheresis to product availability was 24.5 days (range: 17 to 80 days). In addition, the median time from leukapheresis to product infusion was 39 days (range: 28 to 489 days).

**Table 11: Baseline demographic and disease-related characteristics for the TRANSCEND-MCL Cohort**

<u>Characteristic</u>	<u>All leukapheresed (N = 104)</u>	<u>Breyanzi-treated (N = 88)</u>
<u>Median age, years (range)</u>	<u>68.0 (36, 86)</u>	<u>68.5 (36, 86)</u>
<u>≥ 65, n (%)</u>	<u>71 (68.3)</u>	<u>64 (72.7)</u>
<u>≥ 75 years, n (%)</u>	<u>22 (21.2)</u>	<u>18 (20.5)</u>
<u>Sex, n (%)</u>		
<u>Male</u>	<u>81 (77.9)</u>	<u>67 (76.1)</u>
<u>Female</u>	<u>23 (22.1)</u>	<u>21 (23.9)</u>
<u>Prior HSCT, n (%)</u>		
<u>Autologous HSCT</u>	<u>33 (31.7)</u>	<u>26 (29.5)</u>
<u>Allogeneic HSCT</u>	<u>8 (7.7)</u>	<u>6 (6.8)</u>
<u>ECOG performance status (at screening)</u>		
<u>ECOG 0, n (%)</u>	<u>56 (53.8)</u>	<u>48 (54.5)</u>
<u>ECOG 1, n (%)</u>	<u>47 (45.2)</u>	<u>40 (45.5)</u>
<u>ECOG 2, n (%)</u>	<u>1 (1.0)</u>	<u>0</u>
<u>High risk features, n (%)</u>		
<u>Ki67 proliferation fraction ≥ 30%</u>	<u>82 (78.8)</u>	<u>66 (75.0)</u>
<u>TP53 mutation</u>	<u>25 (24.0)</u>	<u>20 (22.7)</u>
<u>Blastoid morphology</u>	<u>30 (28.8)</u>	<u>27 (30.7)</u>
<u>Complex Karyotype</u>	<u>30 (28.8)</u>	<u>26 (29.5)</u>
<u>Secondary CNS lymphoma at time of Breyanzi infusion, n (%)</u>	<u>7 (6.7)</u>	<u>7 (8.0)</u>

<b>Characteristic</b>	<b>All leukapheresed (N = 104)</b>	<b>Breyanzi-treated (N = 88)</b>
<b>Median number of prior systemic treatments (range)</b>	<b>3 (1, 11)</b>	<b>3 (1, 11)</b>
<b>Refractory or relapsed to last prior therapy, n (%)</b>		
<b>Refractory<sup>a</sup></b>	<b>70 (67.3)</b>	<b>58 (65.9)</b>
<b>Relapsed<sup>b</sup></b>	<b>34 (32.7)</b>	<b>30 (34.1)</b>

<sup>a</sup> The status was refractory if a patient achieved less than a complete response (CR) to last prior therapy.

<sup>b</sup> The status was relapsed if a patient achieved CR to last prior therapy.

Efficacy was based on overall response rate (ORR), defined as the percentage of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) after Breyanzi infusion as determined by an IRC (Table 12). The median on-study follow-up time was 19.5 months (range 0.4 to 72 months).

Among the 81 patients included in the efficacy set, the median time to first response (CR or PR) was 0.95 month (range: 0.7 to 3.0 months) and the median time to first CR was 0.95 month (range: 0.7 to 4.9 months). Response durations were longer in patients who achieved a BOR of CR, as compared to patients with a BOR of PR.

**Table 12: TRANSCEND-MCL Cohort: Response rate, duration of response (IRC assessment)**

	<b>All Leukapheresed (N = 104)</b>	<b>Efficacy set (N = 81)</b>
<b>Overall response rate<sup>a</sup>, n (%)</b> [95% CI]	<b>73 (70.2)</b> [60.4, 78.8]	<b>67 (82.7)</b> [72.7, 90.2]
<b>Complete response, n (%)</b> [95% CI] <sup>b</sup>	<b>64 (61.5)</b> [51.5, 70.9]	<b>58 (71.6)</b> [60.5, 81.1]
<b>Partial response, n (%)</b> [95% CI] <sup>b</sup>	<b>9 (8.7)</b> [4.0, 15.8]	<b>9 (11.1)</b> [5.2, 20.0]
<b>Number of responders</b>		
<b>Duration of response (DOR) (months)</b>		
Median [95% CI] <sup>c</sup>	15.2 [7.0, 24.0]	11.5 [6.2, 24.0]
Range	0.0+, 24.0	0.0+, 24.0
<b>Rate of continued remission<sup>d</sup>, %</b> [95% CI]		
At 24 months	44.8 (32.9; 55.9)	41.2 (29.2, 52.9)
<b>Median follow-up for DOR (months)</b>		
Median [95% CI]	23.0 [22.8, 23.1]	22.9 [22.8, 23.0]
Range	0.0+, 24.0	0.0+, 24.0

CI = confidence interval; CR = complete response; NR = not reached;

+ indicates a censored value

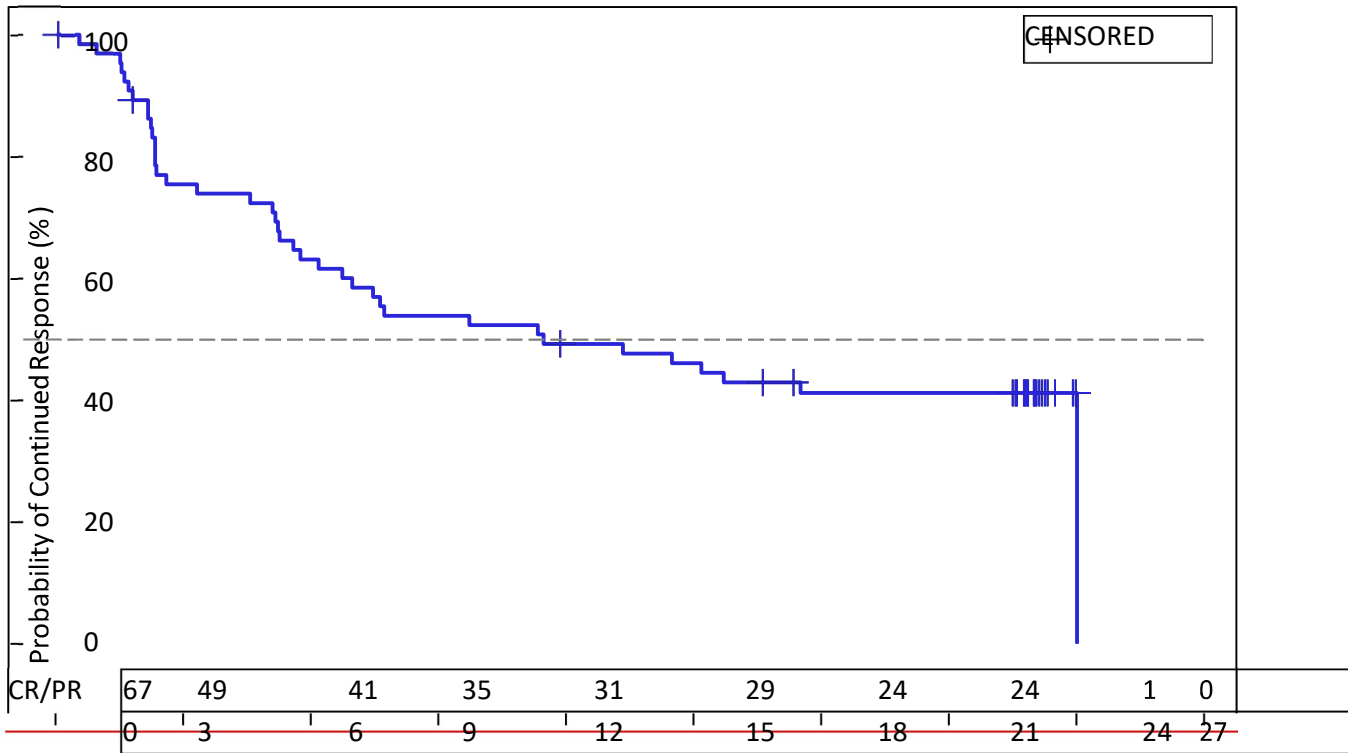
<sup>a</sup> Per the Lugano 2014 criteria, as assessed by an IRC

<sup>b</sup> Two-sided 95% confidence interval based on exact Clopper-Pearson method.

<sup>c</sup> Median, Q1, Q3 are estimated from KM product-limit estimates

<sup>d</sup> Based on KM estimates of duration of response

**Figure 4 Duration of response by IRC assessment, TRANSCEND-MCL Cohort efficacy set**



### Duration of Response (Months)

Response Group: CR/PR

CR = complete response; PR = partial response.  
 PD/Death after initiation of anti-cancer treatment were considered as events

## 5.2 Pharmacokinetic properties

### FL

In TRANSCEND-FL, in patients who received two or more prior lines of therapy for FL, the median time of maximal expansion in peripheral blood occurred 10 days after the first infusion. Breyanzi was present in peripheral blood for up to 3 years.

Among patients who received Breyanzi for FL (TRANSCEND-FL), the median  $C_{max}$  in responders (N = 100) and non-responders (N = 2) were 31,336 and 15,568 copies/ $\mu$ g, respectively. The median  $AUC_{0-28d}$  in responders (N = 96) and non-responders (N = 2) were 245,730 and 161,935 day\*copies/ $\mu$ g, respectively.

### MCL

In the TRANSCEND-MCL Cohort, in patients who received two or more prior lines of therapy for MCL, the median time of maximal expansion in peripheral blood occurred 10 days after the first infusion. Breyanzi was present in peripheral blood for up to 2 years.

Among patients who received Breyanzi for MCL (TRANSCEND-MCL Cohort), the median  $C_{max}$  in responders (N = 67) and non-responders (N = 8) were 31,631 and 12,444 copies/ $\mu\text{g}$ , respectively. The median  $AUC_{0-28d}$  in responders (N = 67) and non-responders (N = 8) were 309,578 and 142,462 day\*copies/ $\mu\text{g}$ , respectively.

## עדכונים בעלון לצרכן

### 1. למה מיועדת התרופה?

- בריאנזי מיועדת לטיפול במבוגרים עם לימפומה של תאי B גדולים (Large B-Cell Lymphoma (LBCL)), כולל לימפומה ממושטת של תאי B גדולים (Diffuse Large B-Cell Lymphoma (DLBCL)), ללא סיווג אחר (כולל לימפומה ממושטת של תאי B גדולים המתפתחת מלימפומה אינדולנטית), לימפומה של תאי B בדרגה גבוהה (High Grade B-Cell Lymphoma (HGBCL)), לימפומה מיצרית ראשונית של תאי B גדולים (Primary Mediastinal B-Cell Lymphoma (PMBCL)) ולימפומה זקיקית בדרגה 3B (Follicular Lymphoma Grade 3B (FL3B)) שיש להם:
  - מחלה עמידה בפני כימו-אימונותרפיה קו ראשון או הישנות בתוך 12 חודשים מכימו-אימונותרפיה קו ראשון; או
  - מחלה עמידה בפני כימו-אימונותרפיה קו ראשון או הישנות אחרי כימו-אימונותרפיה קו ראשון ושאינם מתאימים להשתלת מח עצם עקב מחלות נלוות או גיל.
- בריאנזי מיועדת לטיפול במבוגרים עם לימפומה ממושטת של תאי B גדולים (DLBCL), לימפומה מיצרית ראשונית של תאי B גדולים (PMBCL) ולימפומה זקיקית בדרגה 3B (FL3B), נשנית או עמידה, אחרי שניים או יותר קווי טיפול סיסטמיים לאחר שקיבלו שני קווי טיפול סיסטמיים או יותר.
- בריאנזי מיועדת לטיפול במבוגרים עם לימפומה זקיקית (Follicular Lymphoma) נשנית או עמידה, לאחר שקיבלו שני קווי טיפול סיסטמיים או יותר.
- בריאנזי מיועדת לטיפול במבוגרים עם לימפומה של תאי המעטפת (Mantle Cell Lymphoma) נשנית או עמידה, לאחר שקיבלו שני קווי טיפול סיסטמיים או יותר, כולל טיפול עם מעכב טירוזין קינאז של ברטון (BTK) (Bruton's tyrosine kinase).