Gilead Sciences Israel Ltd.
4 HaHarash Street, Hod Hasharon
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דצמבר 2022

עדכון עלון לרופא ולצרכן לתכשיר:

Tecartus®

Cells dispersion for infusion

(brexucabtagene autoleucel)

ההתוויה הרשומה לתכשיר בישראל:

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

Limitation of use: Tecartus is not indicated for the treatment of patients with active central nervous system lymphoma.

Tecartus is indicated for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).

רופאים ורוקחים נכבדים,

חברת גיליאד סיאנסז ישראל בע"מ מבקשת להודיעכם על עדכון עלונים לתכשיר בנדון.

השינויים מסומנים בעלון המצורף כאשר הטקסט המודגש באדום הוסף לעלון ואילו הטקסט המחוק ~~בקו חוצה~~ נגרע ממנו. הסימונים בצהוב הינם החמרות במידע הבטיחותי.

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העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות
https://israeldrugs.health.gov.il/#!/byDrug/drugs/index.html.

כמו כן ,ניתן לקבלם מודפסים על ידי פנייה לבעל הרישום:

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התכשיר זמין בכל קופות החולים.

בברכה,

מאיה מלל

רוקחת ממונה, גיליאד סיאנסז ישראל בע"מ

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העדכונים המהותיים בעלון לרופא:

2.1 General description

Tecartus (brexucabtagene autoleucel~~autologous anti-CD19-transduced CD3+ cells~~) is a genetically modified autologous cell-based ~~gene therapy medicinal~~ product containing ~~autologous~~ T cells ~~genetically modified~~transduced *ex vivo* using a retroviral vector ~~encoding~~ expressing an anti-CD19 chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment (scFv) linked to CD28 co-stimulatory domain and CD3-zeta signalling domain.

2.2 Qualitative and quantitative composition

Mantle cell lymphoma

Each ~~patient~~ patient-specific ~~single~~ infusion bag of Tecartus contains brexucabtagene autoleucel at a batch-dependent concentration of autologous T cells genetically modified to express an ~~dispersion of~~ anti-CD19 chimeric antigen receptor (CAR-positive viable T cells). The medicinal product is packaged in one infusion bag overall containing a cell dispersion for infusion of ~~in approximately 68 mL for~~ a target dose of 2 ×~~x~~ 10^6 anti-CD19 CAR-positive viable T cells/kg body weight (range: 1 ×~~x~~ 10^6 – 2 ×~~x~~ 10^6 cells/kg), with a maximum of 2 ×~~x~~ 10^8 anti-CD19 CAR-positive viable T cells suspended in a Cryostor CS10 solution.

Each infusion bag contains approximately 68 mL of dispersion for infusion.

Acute lymphoblastic leukaemia

Each patient-specific infusion bag of Tecartus contains brexucabtagene autoleucel at a batch-dependent concentration of autologous T cells genetically modified to express an anti CD19 chimeric antigen receptor (CAR-positive viable T cells). The medicinal product is packaged in one infusion bag overall containing a cell dispersion for infusion of a target dose of 1×10^6 anti CD19 CAR positive viable T cells/kg body weight, with a maximum of 1×10^8 anti CD19 CAR positive viable T cells suspended in a Cryostor CS10 solution.

Each infusion bag contains approximately 68 mL of dispersion for infusion.

4.1 Therapeutic indications

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

Limitation of use: Tecartus is not indicated for the treatment of patients with active central nervous system lymphoma.

Tecartus is indicated for the treatment of adult patients with relapsed or refractory B-cell precursor acute lymphoblastic leukaemia (ALL).

- Posology

Tecartus is intended for autologous use only (see section 4.4).

Mantle cell lymphoma

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Treatment consists of a ~~A~~ single dose for infusion containing a dispersion for infusion of CAR-positive viable T cells in one container. The target dose is ~~of Tecartus contains~~ 2 × 10^6 CAR-positive viable T cells per kg of body weight (range: 1 ×~~x~~ 10^6–2 ×~~x~~ 10^6 cells/kg), or maximum of 2 × 10^8 CAR-positive viable T cells for patients 100 kg and above ~~in approximately 68 mL dispersion in an infusion bag~~.

Tecartus is recommended to be infused 3 to 14 days after completion of the lymphodepleting chemotherapy for MCL patients. The availability of the treatment must be confirmed prior to starting the lymphodepleting regimen.

Pre-treatment (lymphodepleting chemotherapy) for MCL patients

- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m² and fludarabine 30 mg/m² ~~should~~ must be administered prior to infusing Tecartus. The recommended days are~~intravenously~~ on the 5th, 4th, and 3rd day before infusion of Tecartus.

Acute lymphoblastic leukaemia

Treatment consists of a single dose for infusion containing a dispersion for infusion of CAR-positive viable T cells in one container. The target dose is 1 × 10^6 CAR-positive viable T cells per kg of body weight, with a maximum of 1 × 10^8 CAR-positive viable T cells for patients 100 kg and above.

Tecartus is recommended to be infused 2 to 14 days after completion of the lymphodepleting chemotherapy for ALL patients. The availability of the treatment must be confirmed prior to starting the lymphodepleting regimen.

Pre-treatment (lymphodepleting chemotherapy) for ALL patients

A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 900 mg/m^2 over 60 minutes must be administered prior to infusing Tecartus. This is recommended on the 2nd day before infusion of Tecartus. Fludarabine 25 mg/m^2 over 30 minutes must be administered prior to infusing Tecartus. The recommended days are on the 4th, 3rd, and 2nd day before infusion of Tecartus.

Mantle cell lymphoma and acute lymphoblastic leukaemia

Pre-medication

- To minimise potential acute infusion reactions, it is recommended that patients be pre-medicated with paracetamol 500 to 1,000 mg given orally and diphenhydramine 12.5 to 25 mg intravenous or oral (or equivalent) approximately 1 hour prior to infusion.
- Prophylactic use of systemic corticosteroids is not recommended (see section 4.5).

Monitoring prior to infusion

- In some patient groups at risk, a delay of the Tecartus infusion may be indicated (see section 4.4- Reasons to delay treatment).

Monitoring after infusion

Patients ~~should~~ must be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs/symptoms of CRS and/or neurologic events.

After the first 10 days following the infusion, the patient ~~should~~ is to be monitored at the physician's discretion.

Patients ~~should~~ must be instructed to remain within proximity (within 2 hours of travel) of a qualified treatment centre for at least 4 weeks following infusion.

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◦ Method of administration

Tecartus is for intravenous use only.

Tecartus must not be irradiated. Do NOT use a leukodepleting filter.

Before administration, it must be confirmed that the patient's identity matches the unique patient information on the Tecartus infusion bag and cassette.

~~*Precautions to be taken before handling or administering the medicinal product*~~
~~This medicinal product contains genetically modified human blood cells. Healthcare professionals handling Tecartus should take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases (see section 6.6).~~

~~*Preparation for infusion*~~
~~Verify that the patient's identity (ID) matches the patient identifiers on the Tecartus metal cassette.~~
~~The Tecartus infusion bag must not be removed from the metal cassette if the information on the patient-specific label does not match the intended patient.~~
~~Once the patient ID is confirmed, remove the infusion bag from the metal cassette.~~
~~Check that the patient information on the metal cassette label matches that on the bag label.~~
~~Inspect the infusion bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines for handling of waste of human-derived material (or immediately contact Kite).~~
~~Place the infusion bag inside a second bag.~~
~~Thaw Tecartus at approximately 37 °C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Tecartus should not be washed, spun down, and/or re-suspended in new media prior to infusion. Thawing should take approximately 3 to 5 minutes.~~
~~Once thawed, Tecartus is stable at room temperature (20 °C – 25 °C) for up to 3 hours. However, Tecartus infusion should begin within 30 minutes of thaw completion.~~

Administration
~~For autologous single use only.~~
~~Tocilizumab and emergency equipment should be available prior to infusion and during the monitoring period.~~
A leukodepleting filter must not be used.
~~Central venous access is recommended for the administration.~~
~~Verify the patient ID again to match the patient identifiers on the Tecartus bag.~~
~~Prime the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) prior to infusion.~~
~~Infuse the entire content of the Tecartus bag within 30 minutes by either gravity or a peristaltic pump.~~
~~Gently agitate the bag during infusion to prevent cell clumping.~~
~~After the entire content of the bag is infused, rinse the tubing at the same infusion rate with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) to ensure all the treatment is delivered.~~
Tocilizumab and emergency equipment must be available prior to infusion and during the monitoring period.
For autologous use only, verify the patient ID to match the patient identifiers on the Tecartus bag.
Once tubing has been primed, infuse the entire content of the Tecartus bag within 30 minutes by either gravity or a peristaltic pump.

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For detailed instructions on ~~the handling~~preparation, administration, accidental exposure ~~to~~ and disposal of ~~the medicinal product~~Tecartus, see section 6.6.

Active central nervous system (CNS) lymphoma

There is no experience of use of this medicinal product in patients with active CNS lymphoma defined as ~~detectable cerebrospinal fluid malignant cells or~~ brain metastases confirmed by imaging. In ALL, asymptomatic patients with a maximum of CNS-2 disease (defined as white blood cells <5/µL in cerebral spinal fluid with presence of lymphoblasts) without clinically evident neurological changes were treated with Tecartus, however, data is limited in this population. Therefore, the benefit/risk of Tecartus has not been established these populations~~in this population~~. Tecartus is not indicated for the treatment of patients with active central nervous system lymphoma.

Neurologic adverse reactions

Severe neurologic adverse reactions ~~(encephalopathy, confusional state or delirium, decreased level of consciousness, seizures, aphasia), which could be life-threatening, were very commonly~~ , also known as immune effector cell-associated neurotoxicity syndrome (ICANS), have been observed in patients treated with Tecartus which could be life-threatening or fatal. The~~with a~~ median time to onset ~~of 8~~was 7 days (range: 1 to 262 days) following Tecartus infusion (see section 4.8).

Patients who experience Grade 2 or higher neurologic ~~toxicities should~~ toxicity/ICANS must be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive-care supportive therapy for severe or life-threatening neurologic toxicity/ICANS~~toxicities~~. Non-sedating, anti-seizure medicines ~~should~~ are be considered as clinically indicated for Grade 2 or higher adverse reactions. Treatment algorithms have been developed to ameliorate the neurologic adverse reactions experienced by patients on Tecartus. These include the use of tocilizumab (if concurrent CRS) and/or corticosteroids for moderate, severe, or life-threatening neurologic adverse reactions as summarised in Table 2.

4.8 Undesirable effects

Summary of the safety profile

Mantle cell lymphoma

The safety data described in this section reflect exposure to Tecartus in ZUMA-2, a Phase 2 study in which a total of 82 patients with relapsed/refractory MCL received a single dose of CAR-positive viable T cells (2×10^6 or 0.5×10^6 anti-CD19 CAR T cells/kg) based on a recommended dose which was weight-based.

The most significant and frequently occurring adverse reactions were ~~cytokine release syndrome~~CRS (91%), infections (~~56~~55%) and encephalopathy (51%).

Serious adverse reactions occurred in ~~57~~56% of patients. The most common serious adverse reactions included encephalopathy (26%), infections (28%) and cytokine release syndrome (15%).

Grade 3 or higher adverse reactions were reported in ~~65~~67% of patients. The most common Grade 3 or higher non-haematological adverse reactions included infections (~~32~~34%) and encephalopathy (24%). The

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most common Grade 3 or higher haematological adverse reactions included neutropenia (99%), leukopenia (98%), lymphopenia (96%), thrombocytopenia (65%) and anaemia (56%).

Acute lymphoblastic leukaemia
The safety data described in this section reflect exposure to Tecartus in ZUMA-3, a Phase 1/2 study in which a total of 100 patients with relapsed/refractory B-cell precursor ALL received a single dose of CAR-positive viable T cells (0.5×10^6, 1×10^6, or 2×10^6 anti-CD19 CAR T cells/kg) based on a recommended dose which was weight based.

The most significant and frequently occurring adverse reactions were CRS (91%), encephalopathy (57%), and infections (41%).

Serious adverse reactions occurred in 70% of patients. The most common serious adverse reactions included CRS (25%), infections (22%) and encephalopathy (21%).

Grade 3 or higher adverse reactions were reported in 76% of patients. The most common Grade 3 or higher non-haematological adverse reactions included infections (27%), CRS (25%) and encephalopathy (22%).

Tabulated list of adverse reactions

Adverse reactions described in this section were identified in a total of 182 patients exposed to Tecartus in two multi-centre pivotal clinical studies, ZUMA-2 (n=82) and ZUMA-3 (n=100). 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). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3 Adverse drug reactions identified with Tecartus

System Organ Class (SOC)	Frequency	Adverse reactions
Infections and infestations		
	Very common	Unspecified pathogen infections ~~Viral infections~~ Bacterial infections Fungal infections Viral Infections
Blood and lymphatic system disorders		
	Very common	Leukopenia[a] Neutropenia[a] Lymphopenia[a] ~~Leukopenia[a]~~ ~~Anaemia[a]~~ Thrombocytopenia[a] Anaemia[a] Febrile neutropenia ~~Coagulopathy~~
	Common	Coagulopathy
Immune system disorders		
	Very common	Cytokine Release Syndrome[b] Hypogammaglobulinaemia
	Common	Hypersensitivity Haemophagocytic lymphohistiocytosis
Metabolism and nutrition disorders		
	Very common	Hypophosphataemia[a]

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System Organ Class (SOC)	Frequency	Adverse reactions
		Decreased appetite Hypomagnesaemia Hyperglycaemia[a]
	Common	~~Dehydration~~ Hypoalbuminemia[a] Dehydration
Psychiatric disorders		
	Very common	Delirium Anxiety Insomnia ~~Delirium~~ ~~Anxiety~~
Nervous system disorders		
	Very common	Encephalopathy Tremor Headache Aphasia Dizziness Neuropathy
	Common	Seizure Ataxia ~~Seizure~~ Increased intracranial pressure
Cardiac disorders		
	Very common	Tachycardias Bradycardias
	Common	Non-ventricular arrhythmias
Vascular disorders		
	Very common	Hypotension Hypertension Haemorrhage ~~Thrombosis~~
	Common	Thrombosis ~~Haemorrhage~~
Respiratory, thoracic and mediastinal disorders		
	Very common	Cough Dyspnoea Pleural effusion ~~Dyspnoea~~ Hypoxia
	Common	Respiratory failure Pulmonary oedema
Gastrointestinal disorders		
	Very common	Nausea Diarrhoea Constipation ~~Nausea~~ ~~Diarrhoea~~ ~~Oral pain~~ Abdominal pain Vomiting ~~Dysphagia~~Oral pain
	Common	Dry mouth Dysphagia
Skin and subcutaneous tissue disorders		
	Very common	Rash Skin disorder

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System Organ Class (SOC)	Frequency	Adverse reactions
Musculoskeletal and connective tissue disorders		
	Very common	~~Motor dysfunction~~ Musculoskeletal pain Motor dysfunction
Renal and urinary disorders		
	Very common	Renal insufficiency ~~Urine output decreased~~
	Common	Urine output decreased
General disorders and administration site conditions		
	Very common	Oedema Fatigue ~~Oedema~~ Pyrexia Pain Chills
Eye Disorders		
	Common	Visual impairment
Investigations		
	Very common	Alanine aminotransferase increased[a] Blood uric acid increased[a] Aspartate aminotransferase increased[a] Hypocalcaemia[a] ~~Hypokalaemia[a]~~ Hyponatraemia[a] ~~Hypocalcaemia[a]~~ ~~Blood uric acid increased[a]~~ Direct bilirubin increased[a] Hypokalaemia[a]
	Common	Bilirubin increased[a]

Only cytopenias that resulted in (i) new or worsening clinical sequelae or (ii) that required therapy or (iii) adjustment in current therapy are included in Table 3.
[a] Frequency based on Grade 3 or higher laboratory parameter.
[b] See section Description of selected adverse reactions.
ZUMA-2 data cutoff: 24 July 2021; ZUMA-3 data cutoff: 23 July 2021

Description of selected adverse reactions from ZUMA-2 and ZUMA-3 (n=182)

Cytokine release syndrome
CRS occurred in 91% of patients. ~~Fifteen~~ Twenty percent (~~15~~20%) of patients experienced Grade 3 or higher (severe or life-threatening) CRS. The median time to onset was 3 days (range: 1 to 13 days) and the median duration was ~~10~~ 9 days (range: 1 to ~~50~~ 63 days). ~~All~~Ninety-seven percent (97%) of patients ~~(100%)~~ recovered from CRS.

The most common signs or symptoms associated with CRS among the patients who experienced CRS included pyrexia (~~99~~94%), hypotension (~~60~~64%), hypoxia (~~37~~32%), chills (~~33~~31%), tachycardia (27%), sinus tachycardia (23%), headache (~~24~~22%), fatigue (16%), and nausea (13%)~~, alanine aminotransferase increased (13%), aspartate aminotransferase increased (12%), diarrhoea (11%), and sinus tachycardia (11%).~~ . Serious adverse reactions that may be associated with CRS included hypotension (22%), pyrexia (15%), hypoxia (9%), ~~acute kidney injury, and~~ tachycardia (3%), dyspnoea (2%) and sinus tachycardia (2%). See section 4.4 for monitoring and management guidance.

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Neurologic events and adverse reactions
Neurologic adverse reactions occurred in ~~68~~69% of patients. Thirty-~~three~~ two percent (~~33~~32%) of patients experienced Grade 3 or higher (severe or life-threatening) adverse reactions. The median time to onset was ~~8~~ 7 days (range: 1 to 262 days). Neurologic events resolved for ~~47~~ 113 out of ~~56~~ 125 patients (90.4%) with a median duration of ~~13~~ 12 days (range: 1 to ~~567~~ 708 days). Three patients had ongoing neurologic events at the time of death, including one patient with the reported event of serious encephalopathy and another patient with the reported event of serious confusional state. The remaining unresolved neurologic events were Grade 2. ~~Eighty-five~~Ninety-three percent of all treated patients experienced the first CRS or neurological event within the first 7 days after Tecartus infusion.

The most common neurologic adverse reactions included tremor (32%), confusional state (27%), encephalopathy (~~51~~27%), ~~tremor (38%),~~ aphasia (~~20~~21%), and ~~delirium~~ agitation (~~18~~11%). Serious adverse reactions including encephalopathy (~~26~~15%), aphasia (6%) and confusional state~~seizure~~ (~~2~~5%) have been reported in patients administered ~~with~~ Tecartus. ICANS was reported as a serious adverse neurologic reaction at a low frequency (2%) in clinical trials. ICANS observed during clinical studies are represented under the adverse reaction encephalopathy. Serious cases of cerebral oedema which may become fatal have occurred in patients treated with Tecartus. See section 4.4 for monitoring and management guidance.

ICANS was reported in the context of neurologic toxicity in the post marketing setting.

Febrile neutropenia and infections
Febrile neutropenia was observed in ~~6~~12% of patients after Tecartus infusion. Infections occurred in ~~56~~87% of the 182 patients treated with Tecartus in ZUMA-2 and ZUMA-3. Grade 3 or higher (severe, life-threatening or fatal) infections occurred in ~~32~~30% of patients including unspecified pathogen, bacterial, fungal and viral infections in 23%, 8%, 2% ~~26%, 6%,~~ and 4% of patients respectively. See section 4.4 for monitoring and management guidance.

Prolonged cytopenias
Cytopenias are very common following prior lymphodepleting chemotherapy and Tecartus therapy.

Prolonged (present on or beyond Day 30 or with an onset at Day 30 or beyond) Grade 3 or higher cytopenias occurred in ~~55~~48% of patients and included neutropenia (34%), thrombocytopenia (~~38~~27%)~~, neutropenia (37%),~~ and anaemia (~~17~~15%). See section 4.4 for management guidance.

Hypogammaglobulinaemia
~~In ZUMA-2, h~~Hypogammaglobulinaemia occurred in ~~16~~12% of patients. Grade 3 or higher hypogammaglobulinemia occurred in 1% of patients. See section 4.4 for management guidance.

Immunogenicity

The immunogenicity of Tecartus has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. To date, no anti-CD19 CAR T-cell antibody immunogenicity has been observed in MCL patients. Based on an initial screening assay, 17 patients in ZUMA-2 at any time point tested positive for antibodies; however, a confirmatory orthogonal cell-based assay demonstrated that all 17 patients ~~were antibody negative at all time points tested.~~ in ZUMA-2 were antibody negative at all time points tested. Based on an initial screening assay, 16 patients in ZUMA-3 tested positive for antibodies at any timepoint. Among patients with evaluable samples for confirmatory testing, two patients were confirmed to be antibody-positive after treatment. One

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of the two patients had a confirmed positive antibody result at Month 6. The second patient had a confirmed positive antibody result at retreatment Day 28 and Month 3. There is no evidence that the kinetics of initial expansion, CAR T-cell function and persistence of Tecartus, or the safety or effectiveness of Tecartus, ~~was~~ were altered in these patients.

For the primary analysis, the~~An~~ analysis set was defined a priori which consisted of the first 60 patients treated with Tecartus who were evaluated for response 6 months after the Week 4 disease assessment after Tecartus infusion. In this analysis set of 60 patients the ORR was 93% with a CR rate of 67%. The ORR was significantly higher than the prespecified historical control rate of 25% at a 1-sided significance level of 0.025 ($p < 0.0001$).

The updated 24-month follow-up analyses of efficacy were conducted using the modified intent to treat (mITT) analysis set, which consisted of 68 patients treated with Tecartus. In the 24-month follow up analysis, the ORR and CR rates in the 68 patients in the mITT analysis set were 91% and 68% respectively

Results in the FAS from both the primary analysis and 24-month follow-up analysis ~~ITT set~~ are shown in Table 5.

Table 5 Summary of efficacy results for ZUMA-2

Category	**All leukapheresed [a](~~ITT~~FAS) (N = 74)**	
	Primary Analysis	**24-month Follow-Up**
Objective response rate (ORR), n (%) [95% CI]	**62 (84%)** [73.4, 91.3]	**62 (84%)** [73.4, 91.3]
CR n (%) [95% CI]	44 (59%) [47.4, 70.7]	46 (62%) [50.1, 73.2]
PR n (%) [95% CI]	18 (24%) [15.1, 35.7]	16 (22%)[12.9, 32.7]
Duration of response (DOR)[b]		
Median in months [95% CI]	NR [10.4, NE]	28.2 (13.5, 47.1)
Range [c] in months	0.0+, 35.0+	0.0+, 53.0+
Ongoing responses, CR+PR, CR, n (%) [d]	32 (43%), 30 (41%)	25 (34%), 25 (34%)
Progression free survival		
Median, months [95% CI]	16.2 [9.9, NE]	24.0 (10.1, 48.2)
Overall survival		
Median, months [95% CI]	NR [24.6, NE]	47.4 (24.6, NE)
6 month OS (%) [95% CI]	83.6 [72.9, 90.3]	83.6 [72.9, 90.3]
12 month OS (%) [95% CI]	76.6 [65.1, 84.8]	76.7 [65.3, 84.8]
24 month OS (%) [95% CI]	66.5 [52.8, 77.1]	63.0 [50.9, 70.3]
30 month OS (%) [95% CI]	Not applicable	56.2 (44.1, 66.7)
36 month OS (%) [95% CI]	Not applicable	53.9 (41.5, 64.8)
54 month OS (%) [95% CI]	Not applicable	38.7 (24.8, 52.4)
Median Follow-up in months (min, max)	16.8 [7.2, 37.6]	36.6 (27.3, 57.0)

CI, confidence interval; CR, complete remission; FAS, full analysis set;~~ITT, intent to treat;~~ NE, not estimable; NR, not reached; OS, overall survival; PR, partial remission.

a Of the 74 patients that were enrolled (*i.e.* leukapheresed), 69 patients received lymphodepleting chemotherapy, and 68 patients received Tecartus.

b Among all responders. DOR is measured from the date of first objective response to the date of progression or death.

c A + sign indicates a censored value.

d At the data cutoff date. Percentages are calculated using the total number of patients in the analysis set as the denominator.

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Relapsed or refractory B-cell precursor ALL: ZUMA-3

A Phase 2, open-label, multicenter trial evaluated the efficacy and safety of Tecartus in adult patients with relapsed or refractory B-precursor ALL. Relapsed or refractory was defined as one of the following: primary refractory; first relapse following a remission lasting ≤ 12 months; relapsed or refractory after second-line or higher therapy; relapsed or refractory after allogeneic stem cell transplant (allo-SCT) (provided the transplant occurred ≥ 100 days prior to enrollment and that no immunosuppressive medications were taken ≤ 4 weeks prior to enrollment). The study excluded patients with active or serious infections, active graft-vs-host disease, and any history of CNS disorders. Patients with CNS-2 disease without clinically evident neurologic changes were eligible. In ZUMA-3 Phase 2, a total of 71 patients were enrolled (i.e. leukapheresed) and 55 patients were treated with Tecartus. Six patients did not receive Tecartus due to manufacturing failure. Eight other patients were not treated, primarily due to AEs following leukapheresis. Two patients who underwent leukapheresis and received lymphodepleting chemotherapy were not treated with Tecartus; one patient experienced bacteremia and neutropenic fever and the other patient did not meet eligibility criteria after lymphodepleting chemotherapy. The FAS included all patients who underwent leukapheresis and the modified intent to treat (mITT) analysis set includes all patients leukapheresed and treated with Tecartus in Phase 2. A summary of patient baseline characteristics is provided in Table 6.

Table 6 Summary of baseline characteristics for ZUMA-3 Phase 2

Category	**All leukapheresed (FAS) (N=71)**	**All treated (mITT) (N=55)**
Age (years)		
Median (min, max)	44 (19 to 84)	40 (19 to 84)
Male gender	58%	60%
White ethnicity	72%	67%
Primary refractory disease	30%	33%
Relapsed/refractory disease after ≥ 2 lines of therapy	76%	78%
Relapse with first remission ≤ 12 months	28%	29%
Number of Lines of Prior Therapy		
Median (min, max)	2 (1 to 8)	2 (1 to 8)
≥ 3	48%	47%
Prior Therapies		
Allo-SCT	39%	42%
Blinatumomab	46%	45%
Inotuzumab	23%	22%
Philadelphia chromosome (Ph^+)	27%	27%
Allo-SCT, allogenic stem cell transplant; Max, maximum; Min, minimum		

Following lymphodepleting chemotherapy, Tecartus was administered to patients as a single intravenous infusion at a target dose of 1×10^6 anti-CD19 CAR T cells/kg (maximum permitted dose: 1×10^8 cells). The lymphodepleting regimen consisted of cyclophosphamide 900 mg/m^2 intravenously over 60 mins on the 2nd day before Tecartus infusion and fludarabine 25 mg/m^2 intravenously over 30 mins on the 4th, 3rd, and 2nd day before Tecartus infusion. Of the 55 patients who recived Tecartus, 51 patients received bridging therapy between leukapheresis and lymphodepleting chemotherapy to control disease burden.

The median time from leukapheresis to product delivery was 16 days (range: 11 to 42 days) and the median time from leukapheresis to Tecartus infusion was 29 days (range: 20 to 60 days). The median dose was

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1.0×10^6 anti-CD19 CAR T cells/kg. All patients received Tecartus infusion on day 0 and were hospitalized until day 7 at the minimum.

The primary endpoint was overall complete remission rate (OCR) (complete remission [CR] + complete remission with incomplete hematologic recovery [CRi]) in patients treated with Tecartus as determined by an independent review. In the 55 patients treated with Tecatrus (mITT), the OCR rate was 70.9% with a CR rate of 56.4% (Table 7), which was significantly greater than the prespecified control rate of 40%. Among the 39 patients who achieved a CR or CRi, the median time to response was 1.1 months (range: 0.85 to 2.99 months).

All treated patients had potential follow-up for ≥ 18 months with a median follow-up time of 20.5 months (95% CI: 0.3, 32.6 months) and a median follow-up time for OS of 24.0 months (95% CI: 23.3, 24.6).

Table 7 Summary of efficacy results for ZUMA3 Phase 2

	FAS N = 71	**mITT[a] N = 55**
OCR rate (CR + CRi) n (%) [95% CI]	39 (54.9) [43, 67]	39 (70.9) [57.0, 82.0]
CR rate, n (%) [95% CI]	31 (43.7) [32, 56]	31 (56.4) [42.0, 70.0]
Minimal Residual Disease (MRD) negative rate among OCR (CR or CRi) patients, n (%)	n = 39 38 (97%)	n = 39 38 (97%)
Duration of Remission, median in months [95% CI] [b] Median range in months	14.6 [9.4, NE][c] (0.03+, 24.08+)	14.6 [9.4, NE][c] (0.03+, 24.08+)

CI, confidence interval; CR, complete remission; NE, not estimable

a. Of the 71 patients that were enrolled (and leukapheresed), 57 patients received conditioning chemotherapy, and 55 patients received Tecartus.

b. Subjects were censored at their last evaluable disease assessment before initiation of a new anticancer therapy (excluding resumption of a tyrosine kinase inhibitor) or allo-SCT to exclude any contribution that the new therapy might have on DOR that could confound the contribution of KTE-X19. The results of the analyses that did not censor for subsequent allo-SCT or the initiation of new anti-cancer therapy were consistent with the analyses that did censor the events.

c. The duration of remission was defined only for subjects achieving an OCR, therefore the results of the analysis in the FAS and mITT were identical.

Figure 2 Kaplan Meier DOR in the mITT Analysis Set[a]

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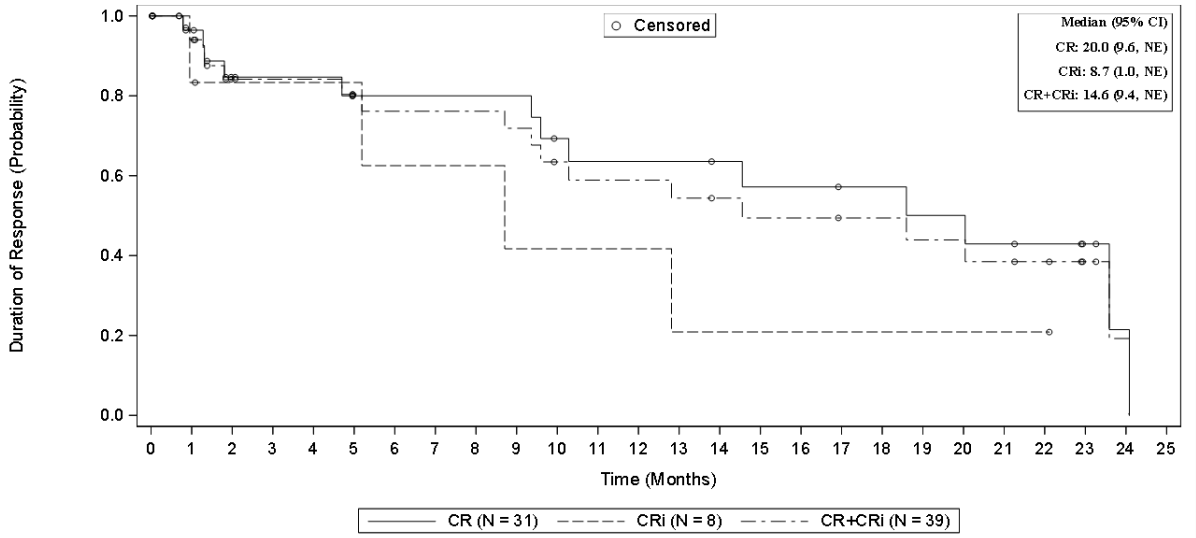

a. The DOR was defined only for subjects achieving an OCR, therefore the results of the analysis in the FAS and mITT were identical.

Acute lymphoblastic leukaemia

Following infusion of a target dose of 1 × 10^6 anti-CD19 CAR T cells/kg of Tecartus in ZUMA-3 (Phase 2), anti-CD19 CAR T cells exhibited an initial rapid expansion followed by a decline to near baseline levels by 3 months. Median time to peak levels of anti-CD19 CAR T cells was within the first 15 days after Tecartus infusion.

A summary of the Tecartus pharmacokinetics over time, based on central assessment by overall response, is provided in Table 9.

Table 9 Summary of brexucabtagene autoleucel pharmacokinetics in ZUMA-3 Phase 2

Number of anti-CD19 CAR T cell	Patients with overall complete remission (CR/CRi) (N=39)	Patients with non-complete remission[a] (N=16)	P-Value
Peak (cells/µL) Median [min; max], n	38.35 [1.31, 1 533.4], 36[b]	0.49 [0.00, 183.50], 14[b]	0.0001[c]
$AUC_{0–28}$ (cells/µL·day) Median [min; max], n	424.03 [14.12 to 19 390.42], 36[b]	4.12 [0.00, 642.25], 14[b]	0.0001[c]

a. Three of 39 subjects who achieved CR or CRi and 2 of 16 subjects who were non-CR/CRi had no anti-CD19 CAR T-cell data at any postinfusion visit.
b. Noncomplete remission includes all non-CR/CRi subjects whose response is classified incomplete remission response with partial hematologic recovery, blast-free hypoplastic or aplastic bone marrow (N = 4), partial response (N = 0), no response (N = 9), or not evaluable (N = 3).
c. P-value is calculated by Wilcoxon test

Median peak anti-CD19 CAR T-cell values were 34.8 cells/µL in ALL patients ≥65 years of age (n=8) and 17.4 cells/µL in ALL patients <65 years of age (n=47). Median anti-CD19 CAR T-cell AUC values were 425.0 cells/µL·day in ALL patients ≥65 years of age and 137.7 cells/µL·day in ALL patients <65 years of age.

In MCL and ALL patients, gender~~Gender~~ had no significant impact on $AUC_{Day\ 0–28}$ and C_{max} of Tecartus.

Studies of Tecartus in patients with hepatic and renal impairment were not conducted.

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6.6 Special precautions for disposal and other handling

Irradiation could lead to inactivation of the product.

Precautions to be taken ~~for the transport and disposal~~before handling or administrating the ~~of the~~ medicinal product

Tecartus ~~should~~ must be transported within the facility in closed, break-proof, leak-proof containers.

This medicinal product~~Tecartus~~ contains ~~genetically modified~~ human blood cells. Healthcare professionals~~Local guidelines on~~ handling Tecartus must take appropriate precautions (wearing gloves and eye protection) to avoid potential transmission of infectious diseases.

Preparation prior to administration

Verify that the patient's identity (ID) matches the patient identifiers on the Tecartus metal cassette.
The Tecartus infusion bag must not be removed from the metal cassette if the information on the patientspecific label does not match the intended patient.
Once the patient ID is confirmed, remove the infusion bag from the metal cassette.
Check that the patient information on the metal cassette label matches that on the bag label.
Inspect the infusion bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines for handling of waste of human-derived material (and immediately contact Kite).

Thawing

Place the infusion bag inside a second bag.
Thaw Tecartus at approximately 37 °C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. Tecartus must not be washed, spun down, and/or re-suspended in new media prior to infusion. Thawing should take approximately 3 to 5 minutes.
Once thawed, Tecartus is stable at room temperature (20 °C – 25 °C) for up to 3 hours. However, Tecartus infusion must begin within 30 minutes of thaw completion.

Administration

For autologous single use only.
Tocilizumab and emergency equipment must be available prior to infusion and during the monitoring period.
Central venous access is recommended for the administration of Tecartus.
Verify the patient ID again to match the patient identifiers on the Tecartus bag.
Prime the tubing with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) prior to infusion.
Infuse the entire content of the Tecartus bag within 30 minutes by either gravity or a peristaltic pump.
Gently agitate the bag during infusion to prevent cell clumping.
After the entire content of the bag is infused, rinse the tubing at the same infusion rate with sodium chloride 9 mg/mL (0.9%) solution for injection (0.154 mmol sodium per mL) to ensure all the treatment is delivered.

Precautions to be taken for the disposal of the medicinal product

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Unused medicinal product and all ~~of waste of human-derived material should be followed for unused medicinal products or waste material. All~~ material that has been in contact with Tecartus (solid and liquid waste) ~~should~~ must be handled and disposed of as potentially infectious waste in accordance with local guidelines on the handling of waste of human-derived material.

Accidental exposure
In case of accidental~~Accidental~~ exposure to Tecartus ~~must be avoided. L~~local guidelines on handling of human-derived material ~~should~~ must be followed. ~~in case of accidental exposure, which may include washing of the contaminated skin and removal of contaminated clothes.~~ Work surfaces and materials which have potentially been in contact with Tecartus must be decontaminated with appropriate disinfectant.

העדכונים המהותיים בעלון לצרכן:

2. לפני השימוש בתרופה

...

טקארטוס ~~™~~®
10^8 ~~×~~× 2 – 0.4 תאים מורחפים לעירוי

חומרים פעילים:
החומר הפעיל הוא ברקסוקבטגן אוטולצל brexucabtagene autoleucel ($0.4 – 2 \times 10^8$ תאים מורחפים לעירוי). כל שקית עירוי יעודית לחולה, כוללת תאי T חיוביים מורחפים לאחר התאמה גנטית מסוג CAR (chimeric antigen receptor) נוגדי CD19 בנפח המוערך של כ-68 מ״ל למנת יעד של 10^6 anti-CD19 CAR-positive viable T cells/kg ~~×~~× 2 עבור חולים עם לימפומה של תאי המעטפת ומנת יעד של 1×10^6 anti-CD19 CAR-positive viable T cells/kg עבור חולים עם לוקמיה לימפובלסטית חריפה של תאי B.

. למה מיועדת התרופה?

טקארטוס מיועדת לטיפול במבוגרים עם מחלה חוזרת או עמידה הסובלים מלימפומה של תאי המעטפת (MCL), לאחר שני קוי טיפול מערכתיים או יותר כולל טיפול במעכב של ברוטון טירוזין קינאז (BTK) אלא אם אינם מתאימים לטיפול במעכב BTK.

הגבלות שימוש: טקארטוס אינה מיועדת לטיפול בחולים עם לימפומה פעילה של מערכת העצבים המרכזית.

טקארטוס מיועדת לטיפול במבוגרים עם לוקמיה לימפובלסטית חריפה של תאי B קודמניים (ALL) אשר מחלתם נשנתה או עמידה.

קבוצה תרפויטית: תרופות אנטיאופלסטיות אחרות.

לימפומה של תאי המעטפת ~~הינה~~ ולוקמיה לימפובלסטית חריפה של תאי B ~~טרטן~~ הינן מחלות סרטן של חלק מהמערכת החיסונית (הגנת הגוף). ~~הטרטן~~ המחלות משפיעות על תאי דם לבנים הנקראים לימפוציטים מסוג B. גם בלימפומה של תאי המעטפת והן בלוקמיה לימפובלסטית חריפה של תאי B, תאים לימפוציטים מסוג B גדלים באופן לא מבוקר ומצטברים ברקמת הלימפה, במח העצם או בדם.

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תופעות לוואי שכיחות מאוד (עלולות להשפיע על יותר מ-1 מכל 10 אנשים)

- מספר נמוך באופן חריג של תאי דם לבנים ~~באופן חריג~~, מה שעלול להגדיל את הסיכוי לזיהום.
- מספר נמוך של תאי דם העוזרים לקרישת הדם (*טרומבוציטופניה*)~~, שינוי ביכולת הדם להיקרש~~:
  סימפטומים יכולים לכלול דימום ~~מוגזם~~ מוגבר או ממושך או נטייה לחבורות~~חבלות~~.
- לחץ דם גבוה.
- ירידה במספר תאי הדם האדומים (תאים הנושאים חמצן): ~~סימפטומים~~ תסמינים יכולים לכלול עייפות קיצונית וירידה ברמת האנרגיה.
- עייפות קיצונית.
- קצב לב מהיר או איטי.
- ירידה בכמות החמצן המגיעה לרקמות הגוף: ~~סימפטומים~~ תסמינים יכולים לכלול שינויים בצבע העור, בלבול, נשימה מהירה.
- קוצר נשימה, שיעול.
- דימום מוגבר.
- בחילה, עצירות, שלשול, כאב בטני, הקאות~~, קושי בבליעה~~.
- כאבי שרירים, כאבי פרקים, כאבי עצמות, כאבים בגפיים.
- חוסר אנרגיה או כוח, חולשת שרירים, קושי בתנועה, התכווצות שרירים.
- כאב ראש.
- בעיות בכליות הגורמות לגופך לעצור נוזלים, להצטברות נוזלים ברקמות (בצקת) מה שעלול לגרום לעלייה במשקל ולקושי בנשימה~~, ירידה במתן שתן~~.
- רמות גבוהות של חומצת שתן וסוכר *(גלוקוז)* הנצפות בבדיקת דם.
- רמות נמוכות של נתרן, מגנזיום, פוספט, אשלגן או סידן הנצפות בבדיקות דם.
- ירידה בתאבון, כאבים בפה.
- קושי בשינה, חרדה.
- נפיחות בגפיים, נוזל מסביב לריאות (*תפליט קרום הריאה*).
- פריחה בעור או בעיות בעור.
- רמות נמוכות של אימונוגלובולינים הנצפות בבדיקת דם, מה שעלול להוביל לזיהומים.
- עליה ברמת אנזימי הכבד הנצפית בבדיקות דם.
- ~~קרישי דם: סימפטומים יכולים לכלול כאב בחזה או בגב עליון, קושי בנשימה, שיעול דמי או כאבי התכווצויות, התנפחות של רגל אחת, עור כהה יותר וחם סביב אזור כואב.~~
- כאב עצבי.

תופעות לוואי שכיחות (עלולות להשפיע על עד 1 מכל 10 אנשים)

- רמות נמוכות של אלבומין בבדיקות דם.
- רמות גבוהות של בילירובין הנצפות בבדיקות הדם.
- ~~דימום מוגזם.~~
- קצב לב לא סדיר (*ארית‌מיה*).
- איבוד שליטה על תנועות הגוף.
- יובש בפה, התייבשות, קושי בבליעה.
- ירידה במתן תפוקת השתן (כתוצאה מבעיות בכליות אשר תוארו לעיל).
- קוצר נשימה (*אי ספיקה נשימתית*).

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- קושי בנשימה הגורם לחוסר יכולת לומר משפטים שלמים, להשתעל בעקבות נוזלים בריאות.
- עליה בלחץ התוך גולגולתי.
- קרישי דם: תסמינים יכולים לכלול כאב בחזה או בגב עליון, קושי בנשימה, שיעול דמי או כאב המלווה בהתכווצויות, התנפחות של רגל אחת, עור כהה יותר וחם סביב אזור כואב.
- שינוי ביכולת הדם להתקרש (*קואגולופתיה*): תסמינים יכולים לכלול דימום מוגבר או מתמשך או נטייה לחבורות.
- שינוי בראייה דבר המקשה לראות דברים (*פגיעה בראייה*).
- אלרגיה: תסמינים כגון פריחה, אורטקריה, גירוד, התנפחות ואנפילקסיס.