אוגוסט 2022

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

הנדון : **Kymriah, dispersion for infusion [162-91-35711]**

חברת נוברטיס ישראל בע"מ מבקשת להודיע על רישום התוויה חדשה Follicular lymphoma (FL) עבור התכשיר בנדון. נוסח ההתוויה המאושרת הינו כדלקמן:

Kymriah is indicated for the treatment of: Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy

בנוסף מותווה התכשיר בישראל להתוויות הבאות:

Kymriah is indicated for the treatment of:

Paediatric and young adult patients up to and including 25 years of age with CD19+ B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.

Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.
Limitation of Use: KYMRIAH is not indicated for treatment of patients with primary or secondary central nervous system lymphoma

חומר פעיל:

Tisagenlecleucel (1.2×10^6 to 6×10^8 CAR- positive viable T cells)

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להלן פירוט השינויים העיקריים (טקסט באדום עם קו תחתי מציין טקסט שהוסף לעלון ואילו טקסט שהושמט מסומן באדום עם קו חוצה. החמרה במידע בטיחותי מודגשת בצהוב)

בעלון לרופא:

4.1 Therapeutic indications

Kymriah is indicated for the treatment of:

- Paediatric and young adult patients up to and including 25 years of age with CD19+ B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.
- Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.
  Limitation of Use: Kymriah is not indicated for treatment of patients with primary or secondary central nervous system lymphoma.
- Adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.

4.2 Posology and method of administration

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Posology

Dosage in paediatric and young adult CD19+ B-cell ALL patients

- For patients 50 kg and below: 0.2 to 5 x 10^6 CAR-positive viable T cells/kg body weight.
- For patients above 50 kg: 0.1 to 2.5 x 10^8 CAR-positive viable T cells (non-weight based).

Dosage in adult DLBCL and FL patients

- 0.6 to 6.0 x 10^8 CAR-positive viable T cells (non-weight based).

Pre-treatment conditioning (lymphodepleting chemotherapy)

~~Lymphodepleting chemotherapy is recommended to be administered before Kymriah infusion unless the white blood cell (WBC) count within one week prior to infusion is ≥1,000 cells/µL.~~

The availability of Kymriah must be confirmed prior to starting the lymphodepleting regimen. For B-cell ALL and DLBCL indications, Kymriah is recommended to be infused 2 to 14 days after completion of the lymphodepleting chemotherapy. For FL, Kymriah is recommended to be infused 2 to 6 days after completion of the lymphodepleting chemotherapy.

Lymphodepleting chemotherapy may be omitted if a patient is experiencing significant cytopenia, e.g., white blood cell (WBC) count ≤1,000 cells/µL within one week prior to infusion. ~~The availability of Kymriah must be confirmed prior to starting the lymphodepleting regimen.~~

If there is a delay of more than 4 weeks between completing lymphodepleting chemotherapy and the infusion and the WBC count is >1,000 cells/µL, then the patient should be re-treated with lymphodepleting chemotherapy prior to receiving Kymriah.

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DLBCL and FL

The recommended lymphodepleting chemotherapy regimen is:

- Fludarabine (25 mg/m^2 intravenous daily for 3 days) and cyclophosphamide (250 mg/m^2 intravenous daily for 3 days starting with the first dose of fludarabine).

If the patient experienced a previous Grade 4 haemorrhagic cystitis with cyclophosphamide, or demonstrated a chemorefractory state to a cyclophosphamide-containing regimen administered shortly before lymphodepleting chemotherapy, then the following should be used:

- Bendamustine (90 mg/m^2 intravenous daily for 2 days).

~~Lymphodepleting chemotherapy may be omitted if a patient's white blood cell (WBC) count is ≤1,000 cells/µL within 1 week prior to Kymriah infusion.~~

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Special populations

Paediatric population

CD19+ B-cell ALL: No formal studies have been performed in paediatric patients below 3 years of age.

DLBCL and FL: The safety and efficacy of Kymriah in children and adolescents below 18 years of age have not yet been established. No data are available.

Elderly

CD19+ B-cell ALL: The safety and efficacy of Kymriah in this population have not been established.

DLBCL and FL: No dose adjustment is required in patients over 65 years of age.

4.4 Special warnings and precautions for use

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Cytokine release syndrome

Cytokine release syndrome, including fatal or life-threatening events, has been frequently observed after Kymriah infusion (see section 4.8). In almost all cases, development of cytokine release syndrome occurred between 1 to 10 days (median onset 3 days) after Kymriah infusion in paediatric and young adult B-cell ALL patients, ~~and~~ between 1 and 9 days (median onset 3 days) after Kymriah infusion in adult DLBCL patients and between 1 to 14 days (median onset 4 days) after Kymriah infusion in adult FL patients. The median time to resolution of cytokine release syndrome was 8 days in B-cell ALL patients, ~~and~~ 7 days in DLBCL patients and 4 days in FL patients.

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Neurological adverse reactions

Neurological events, in particular encephalopathy, confusional state or delirium, occur frequently with Kymriah and can be severe or life-threatening (see section 4.8). Other manifestations included depressed level of consciousness, seizures, aphasia and speech disorder. The majority of neurological events occurred within 8 weeks following Kymriah infusion and were transient. The median time to onset of the first neurological events occurring at any time following Kymriah infusion was 8 days in B-cell ALL, ~~and~~ 6 days in DLBCL, and 9 days in FL. The median time to resolution was 7 days for B-cell ALL, ~~and~~ 13 days for DLBCL, and 2 days for FL. Neurological events can be concurrent with cytokine release syndrome, following resolution of cytokine release syndrome or in the absence of cytokine release syndrome.

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Prolonged cytopenias

Patients may continue to exhibit cytopenias for several weeks following lymphodepleting chemotherapy and Kymriah infusion and should be managed according to standard guidelines. The majority of patients who had cytopenias at day 28 following Kymriah treatment resolved to Grade 2 or below within three months after treatment for paediatric ALL and DLBCL patients, and within six months for FL patients. Prolonged neutropenia has been associated with increased risk of infection. Myeloid growth factors, particularly granulocyte macrophage-colony stimulating factor (GM-CSF), have the potential to worsen cytokine release syndrome symptoms and are not recommended during the first 3 weeks after Kymriah infusion or until cytokine release syndrome has resolved.

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4.8 Undesirable effects

Summary of the safety profile

Safety assessment was based on a total of ~~194~~291 patients (with paediatric and young adult B-cell ALL, ~~and~~ DLBCL and FL) who received Kymriah in three ~~two~~ multicentre pivotal clinical studies.
...

FL
The adverse reactions described in this section were characterised in 97 patients infused with Kymriah in one global multicentre international study, i.e. the ongoing pivotal clinical study CCTL019E2202.

The most common non-haematological adverse reactions (>25%) were cytokine release syndrome (50%), infections (50%) and headache (26%).

The most common haematological laboratory abnormalities were decreased haemoglobin (94%), decreased lymphocytes (92%), decreased white blood cells (91%), decreased neutrophils (89%) and decreased platelets (89%).

Grade 3 and 4 adverse reactions were reported in 75% of patients. The most common Grade 3 and 4 non-haematological adverse reactions were infections (16%).

The most common (>25%) Grade 3 and 4 haematological laboratory abnormalities were lymphocyte count decreased (87%), white blood cell count decreased (74%), neutrophil count decreased (71%), platelet count decreased (26%) and haemoglobin decreased (25%).

Grade 3 and 4 adverse reactions were more often observed within the initial 8 weeks post-infusion (70%) compared to after 8 weeks post-infusion (40%).

Tabulated list of adverse drug reactions
The adverse reactions described in this section were identified in 79, ~~and~~ 115 and 97 patients in the ongoing multicentre pivotal clinical studies (CCTL019B2202, ~~and~~ CCTL019C2201 and CCTL019E2202). Adverse drug reactions from these clinical studies (Table 2) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first, using the following convention: 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); not known (cannot be estimated from the available data). Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 2 Adverse drug reactions observed in clinical studies

Infections and infestations[1)]	
Very common:	Infections - pathogen unspecified, viral infections, bacterial infections
Common:	Fungal infections
Blood and lymphatic system disorders	
Very common:	Anaemia, haemorrhage[2)], febrile neutropenia, neutropenia, thrombocytopenia
Common:	Haemophagocytic lymphohistiocytosis, leukopenia, pancytopenia, coagulopathy, lymphopenia
Uncommon:	B-cell aplasia
Immune system disorders	
Very common:	Cytokine release syndrome, hypogammaglobulinaemia[3)]
Common:	Infusion-related reaction, graft-versus-host disease[4)]
Metabolism and nutrition disorders	
Very common:	Decreased appetite, hypokalaemia, hypophosphataemia, hypomagnesaemia
Common:	Hypoalbuminaemia[5)], hyperglycaemia, hyponatraemia, hyperuricaemia, hypercalcaemia, tumour lysis syndrome, hyperkalaemia, hyperphosphataemia, hypernatraemia, hypermagnesaemia, hyperferritinaemia[6)], hypocalcaemia

Psychiatric disorders	
Common:	Anxiety, delirium[7)], sleep disorder[8)]
Nervous system disorders	
Very common:	Headache[9)], encephalopathy[10)]
Common:	Dizziness[11)], peripheral neuropathy[12)], tremor[13)], motor dysfunction[14)], seizure[15)], speech disorders[16)], neuralgia[17)], immune effector cell-associated neurotoxicity syndrome**
Uncommon:	Ischaemic cerebral infarction, ataxia[18)]
Eye disorders	
Common:	Visual impairment[19)]
Cardiac disorders	
Very common:	Tachycardia[20)]
Common:	Cardiac failure[21)], cardiac arrest, atrial fibrillation
Uncommon:	Ventricular extrasystoles
Vascular disorders	
Very common:	Hypotension[22)]
Common:	Thrombosis[23)], capillary leak syndrome, hypertension
Uncommon:	Flushing
Respiratory, thoracic and mediastinal disorders	
Very common:	Cough[24)], dyspnoea[25)], hypoxia
Common:	Oropharyngeal pain[26)], pulmonary oedema[27)], nasal congestion, pleural effusion, tachypnoea, acute respiratory distress syndrome
Uncommon:	Lung infiltration
Gastrointestinal disorders	
Very common:	Diarrhoea, nausea, vomiting, constipation, abdominal pain[28)]
Common:	Stomatitis, abdominal distension, dry mouth, ascites
Hepatobiliary disorders	
Very common:	Hepatic enzyme increased[29)]
Common:	Hyperbilirubinaemia
Skin and subcutaneous tissue disorders	
Very common:	Rash[30)]
Common:	Pruritus, erythema, hyperhidrosis, night sweats
Musculoskeletal and connective tissue disorders	
Very common:	Arthralgia, musculoskeletal pain[31)]
Common:	Myalgia
Renal and urinary disorders	
Very common:	Acute kidney injury[32)]
General disorders and administration site conditions	
Very common:	Pyrexia, fatigue[33)], oedema[34)], pain[35)]
Common:	Influenza-like illness, asthenia, multiple organ dysfunction syndrome, chills
Investigations	
Very common:	Lymphocyte count decreased*, white blood cell count decreased*, haemoglobin decreased*, neutrophil count decreased*, platelet count decreased*
Common:	Blood bilirubin increased, weight decreased, blood fibrinogen decreased, international normalised ratio increased, fibrin D dimer increased, activated partial thromboplastin time prolonged, prothrombin time prolonged
1) Infections and infestations presented reflect high-level group terms.	

[2] Haemorrhage includes anal haemorrhage, blood blister, blood urine present, catheter site haemorrhage, cerebral haemorrhage, conjunctival haemorrhage, contusion, cystitis haemorrhagic, duodenal ulcer haemorrhage, disseminated intravascular coagulation, epistaxis, eye contusion, gastrointestinal haemorrhage, gingival bleeding, haematochezia, haemarthrosis, haematemesis, haematoma, haematuria, haemoptysis, heavy menstrual bleeding, large intestinal haemorrhage, melaena, mouth haemorrhage, mucosal haemorrhage, oral blood blister, peritoneal haematoma, petechiae, pharyngeal haemorrhage, post-procedural haemorrhage, pulmonary haemorrhage, purpura, retinal haemorrhage, subdural haematoma, traumatic haematoma, tumour haemorrhage, upper gastrointestinal haemorrhage and vaginal haemorrhage.

[3] Hypogammaglobulinaemia includes immunoglobulins decreased, blood immunoglobulin A decreased, blood immunoglobulin G decreased, blood immunoglobulin M decreased, immunodeficiency, immunodeficiency common variable and hypogammaglobulinaemia.

[4] Graft-versus-host Disease (GvHD) includes GvHD, GvHD in gastrointestinal tract, GvHD in skin

[5] Hypoalbuminaemia includes blood albumin decreased, hypoalbuminaemia

[6] Hyperferritinaemia includes hyperferritinaemia, serum ferritin increased

[7] Delirium includes agitation, delirium, hallucination, hallucination visual, irritability and restlessness.

[8] Sleep disorder includes sleep disorder, insomnia and nightmare.

[9] Headache includes headache and migraine.

[10] Encephalopathy includes depressed level of consciousness, mental status changes, automatism, cognitive disorder, confusional state, disturbance in attention, encephalopathy, somnolence, lethargy, memory impairment, metabolic encephalopathy and thinking abnormal.

[11] Dizziness includes dizziness, presyncope and syncope.

[12] Peripheral neuropathy includes dysaesthesia, paraesthesia, peripheral sensory neuropathy, neuropathy peripheral, hyperaesthesia and hypoaesthesia.

[13] Tremor includes dyskinesia and tremor.

[14] Motor dysfunction includes muscle spasms, muscle twitching, myoclonus and myopathy.

[15] Seizure includes seizure, generalised tonic-clonic seizures and status epilepticus.

[16] Speech disorders includes speech disorders, dysarthria and aphasia.

[17] Neuralgia includes neuralgia and sciatica.

[18] Ataxia includes ataxia and dysmetria.

[19] Visual impairment includes vision blurred and visual impairment.

[20] Tachycardia includes sinus tachycardia, supraventricular tachycardia, tachycardia

[21] Cardiac failure includes cardiac failure, left ventricular dysfunction, cardiac failure congestive and right ventricular dysfunction.

[22] Hypotension includes hypotension and orthostatic hypotension.

[23] Thrombosis includes deep vein thrombosis, embolism, pulmonary embolism, thrombosis, vena cava thrombosis and venous thrombosis.

[24] Cough includes cough, productive cough and upper-airway cough syndrome.

[25] Dyspnoea includes acute respiratory failure, dyspnoea, dyspnoea exertional, respiratory distress and respiratory failure.

[26] Oropharyngeal pain includes oral pain and oropharyngeal pain.

[27] Pulmonary oedema includes acute pulmonary oedema and pulmonary oedema.

[28] Abdominal pain includes abdominal pain, abdominal pain upper and abdominal discomfort.

[29] Hepatic enzyme increased includes alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, hepatic enzyme increased, transaminases increased.

[30] Rash includes dermatitis, dermatitis acneiform, dermatitis contact, rash, rash maculo-papular, rash papular and rash pruritic.

[31] Musculoskeletal pain includes back pain, bone pain, flank pain, musculoskeletal chest pain, musculoskeletal pain, neck pain, non-cardiac chest pain.

[32] Acute kidney injury includes acute kidney injury, anuria, azotaemia, blood creatinine abnormal, blood creatinine increased, renal failure, renal tubular dysfunction and renal tubular necrosis.

33)	Fatigue includes fatigue and malaise.
34)	Oedema includes fluid retention, fluid overload, oedema peripheral, generalised oedema, localised oedema, face oedema and peripheral swelling.
35)	Pain includes pain and pain in extremity.
*	Frequency is based on laboratory values. Patients are counted only for the worst grade observed post baseline.
**	Abbreviated as ICANS. Symptoms or signs can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizures, and cerebral oedema.

Description of selected adverse drug reactions

Cytokine release syndrome

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In the ongoing clinical study in FL (N=97), cytokine release syndrome was reported in 50% of patients. No Grade 3 or 4 events were reported.

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Cytokine release syndrome was graded per the Lee criteria in the FL study as follows: Grade 1: mild general symptoms requiring symptomatic treatment; Grade 2: symptoms requiring moderate intervention such as low-flow oxygen supplementation or low-dose vasopressor; Grade 3: symptoms requiring aggressive intervention, such as high-flow oxygen supplementation and high-dose vasopressor; Grade 4: life-threatening symptoms requiring intubation; Grade 5: death.

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Infections and febrile neutropenia

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In FL patients severe infections (Grade 3 or 4), occurred in 16% of patients. The overall incidence (all grades) was 50% (unspecified 36%, viral 17%, bacterial 6%, and fungal 2%) (see section 4.4). 19% of the patients experienced an infection of any type within 8 weeks.

Severe febrile neutropenia (Grade 3 or 4) was observed in 34% of paediatric and young adult B-cell ALL patients, ~~and~~ 17% of DLBCL patients and 12% of FL patients. See section 4.4 for the management of febrile neutropenia before and after Kymriah infusion.

Prolonged cytopenias

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In adult patients with FL, 99% had Grade 3 and 4 cytopenias at any time post Kymriah infusion. Grade 3 and 4 cytopenias not resolved by day 28 after Kymriah infusion based on laboratory findings included a decreased count of lymphocytes (23%), thrombocytes (17%), neutrophils (16%), white blood cells (13%) and decreased haemoglobin (3%).

Neurological adverse reactions

... In FL patients, these occurred in 9% of patients (1% Grade 3 or 4) within 8 weeks after Kymriah infusion. Among the neurotoxic events in FL patients, immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 4% of patients (1% Grade 3 or 4), all within 8 weeks of Kymriah infusion.

Immunogenicity

In clinical studies, humoral immunogenicity of tisagenlecleucel was measured by determination of anti-murine CAR19 antibodies (anti-mCAR19) in serum pre- and post-administration. The majority of patients tested positive for pre-dose anti-mCAR19 antibodies in paediatric and young adult ALL (B2202, 91.1%), ~~and~~ adult DLBCL (C2201, 93.9%) and adult FL (E2202, 66.0%) patients.

Treatment-induced anti-mCAR19 antibodies were found in 40.5% of paediatric and young adult ALL, ~~and~~ 8.7% of adult DLBCL and 28.7% of adult FL patients. Pre-existing and treatment-induced antibodies were not associated with an impact on clinical response nor did they have an impact on the expansion and persistence of tisagenlecleucel. There is no evidence that the presence of pre-existing and treatment-induced anti-mCAR19 antibodies impacts the safety or effectiveness of Kymriah.

T-cell immunogenicity responses were not observed in paediatric and young adult B-cell ALL, ~~and~~ adult r/r DLBCL and adult FL patients.

5.1 Pharmacodynamic properties

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Follicular lymphoma (FL)
The safety and efficacy of Kymriah treatment in adult patients with relapsed or refractory (r/r) follicular lymphoma (FL) were evaluated in an open label, multicentre, single-arm, phase II study (E2202, N=97).

The pivotal study E2202 (ELARA) included patients who were refractory to or relapsed within 6 months after completion of a second or later line of systemic therapy (including an anti-CD20 antibody and an alkylating agent), relapsed during or within 6 months after completion of anti-CD20 antibody maintenance therapy following at least two lines of therapy, or relapsed after autologous haematopoietic stem cell transplant (HSCT). The study excluded patients with active or serious infections, transformed lymphoma or other aggressive lymphomas, including patients with FL Grade 3b, those who had received prior allogeneic HSCT, or who had disease with active CNS involvement.

Of 98 patients who were enrolled and underwent leukapheresis, 97 patients received infusion with Kymriah. One patient achieved a complete response prior to infusion which was attributed to their prior last line of therapy and was subsequently discontinued from the study due to physician decision prior to infusion. All patients had leukapheresis products collected and cryopreserved prior to or during study entry. Kymriah was delivered for all enrolled patients. The median duration of study follow-up defined as the time from Kymriah infusion to date of completion or discontinuation from follow-up prior to the data cut-off date was 18.6 months (range: 1.8-29.9). The median time from Kymriah infusion to the data cut-off date was 20.8 months (range: 14.4-29.9). The study is still ongoing.

Of the 97 patients infused with Kymriah, 94 patients had measurable disease at baseline per Independent Review Committee (IRC) and are included in the efficacy analysis set (EAS).

Key baseline information for the enrolled set and EAS is presented in Table 7. Approximately half of the patients (44/94; 47%) received bridging therapy for disease stabilisation between leukapheresis and administration of Kymriah and all patients received lymphodepleting chemotherapy. For all infused patients, Kymriah was administered as a single dose intravenous infusion in a qualified treatment centre in an inpatient or outpatient (18%) setting.

Table 7 Study E2202: Baseline information across the enrolled and the EAS patient populations

	Enrolled N=98 n (%)	EAS* N=94 n (%)
Age (years)		
Mean (standard deviation)	56.5 (10.34)	56.4 (10.54)
Median (minimum – maximum)	57.5 (29-73)	57.0 (29-73)
Age category (years) – n (%)		
<65 years	74 (75.5)	70 (74.5)
≥65 years	24 (24.5)	24 (25.5)
Sex – n (%)		
Male	65 (66.3)	64 (68.1)
Female	33 (33.7)	30 (31.9)
Stage III/IV disease at study entry – n (%)	84 (85.7)	81 (86.2)
High FLIPI score[1] – n (%)	59 (60.2)	57 (60.6)
Bulky disease at baseline[2] – n (%)	62 (63.3)	61 (64.9)
Number of prior lines of antineoplastic therapy – n (%)		
2	24 (24.5)	24 (25.5)
3	21 (21.4)	19 (20.2)
4	25 (25.5)	24 (25.5)
≥5	28 (28.6)	27 (28.7)
Median (minimum – maximum)	4.0 (2.0 -13.0)	4.0 (2.0 - 13.0)
Disease status – n (%)		
Refractory to last line of therapy	76 (77.6)	74 (78.7)
Relapse to last line of therapy	17 (17.3)	17 (18.1)
Double refractory[3] – n (%)	67 (68.4)	65 (69.1)
Progression of disease within 24 months (POD24)[4] – n (%)	61 (62.2)	61 (64.9)
Prior haematopoietic stem cell transplant (HSCT) – n (%)	36 (36.7)	35 (37.2)
Prior PI3K inhibitor – n (%)	21 (21.4)	19 (20.2)

* Infused patients who had measurable disease at baseline per Independent Review Committee (IRC) and are included in the efficacy analysis set.

[1] FLIPI includes 5 labelled prognostic factors; FLIPI = sum (where prognostic factor = 'Yes'); Low: 0-1 criteria met; intermediate: 2 criteria met; high: 3 or more met.

[2] Bulky disease defined per IRC as imaging showing any nodal or extra nodal tumour mass that is >7 cm in diameter or involvement of at least 3 nodal sites, each with a diameter >3 cm.

[3] Double refractory is defined as patients who failed to respond or relapsed within 6 months following therapy with anti-CD20 and alkylating agents, any regimen

[4] POD24: subjects with primary refractory or experiencing progression of disease within 24 months from initiation of a first-line anti-CD20 mAb containing treatment.

Efficacy was evaluated through the primary endpoint of complete response rate (CRR), recorded from infusion until progressive disease or start of new therapy. CRR was determined by IRC based on Lugano classification criteria (Cheson 2014). Secondary endpoints included overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), overall survival (OS). Median time from enrolment to infusion was 46 days (range: 23 to 127). The first disease assessment was scheduled to be performed at month 3 post-infusion.

Table 8 Study E2202: Efficacy results in adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of therapy

	Enrolled patients N=98	EAS patients* N=94
Complete response rate (CRR)[1], per IRC		
n (%)	67 (68.4)	65 (69.1)
95% CI	(58.9, 78.1)	(58.8, 78.3)
Overall response rate (ORR)[2], per IRC		
n (%)	84 (85.7)	81 (86.2)
Duration of response (DOR)[3], per IRC	**N=84**	**N=81**
Median (months) (95% CI)	NE (20.9, NE)	NE (15.6, NE)
% event-free probability at 9 months (95% CI)	75.9 (64.8, 83.9)	76.2 (64.9, 84.3)

CI=Confidence interval, NE=Not estimable

* Infused patients who had measurable disease at baseline per Independent Review Committee (IRC) and are included in the efficacy analysis set.

[1] The primary endpoint was CRR per IRC based on Lugano response criteria (Cheson 2014) and defined as the proportion of patients with a best overall response (BOR) of complete response (CR). The non-infused patient was treated as a non-responder.

[2] ORR was defined as the proportion of patients with a BOR of CR or partial response (PR). The non-infused patient was treated as a non-responder.

[3] DOR was defined as time from achievement of CR or PR to relapse or death due to FL, whichever occurs first.

All responders achieved their first response (CR or PR) at the first disease assessment performed post-infusion, at 3 months. Of the 65 patients who eventually achieved a CR, 15 patients (16%) initially had a PR. The majority of patients converted from PR to CR within 6 months post-infusion. No patient who received Kymriah infusion went to transplant while in response (CR or PR).

The probability for a patient to remain in response (DOR) ≥9 months was 76% (95% CI: 64.9, 84.3), while the probability for a patient who achieved a CR to remain in response ≥9 months was 87% (95% CI: 75.6, 93.3).

Subgroup analyses demonstrated a generally consistent CRR across all subgroups, including the following high-risk prognostic subgroups: high FLIPI score (CRR of 63%), prior HSCT (CRR of 66%), POD24 (CRR of 59%), and double refractoriness (CRR of 66%).

Special populations

There are not enough data to determine whether there are any differences in efficacy or safety between different age subgroups, although the clinical benefit and safety experience in elderly patients with DLBCL and FL above the age of 65 years (23% and 24.7% of the study population for DLBCL and FL, respectively) were comparable to the overall population.

5.2 Pharmacokinetic properties

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Cellular kinetics in FL patients

A summary of cellular kinetic parameters of tisagenlecleucel in FL patients by BOR is provided in Table 11 below.

The geometric mean $AUC_{0\text{-}28d}$ value of responders was 2.9 fold higher compared to non-responders, while the geometric mean C_{max} value was 2.1 fold higher in responders compared to non-responders.

Table 11 Cellular kinetic parameters of tisagenlecleucel in r/r FL patients

Parameter	Summary statistics	Responding patients (CR and PR) N=81	Non-responding patients (SD/PD) N=12
C_{max} (copies/micrograms)	Geometric mean (CV%), n	6280 (331), 67	3000 (1190), 8
T_{max} (day)	Median [min;max], n	9.92 [2.62; 28.0], 67	13.0 [7.73; 16.0], 8
AUC_{0-28d} (copies/micrograms*day)	Geometric mean (CV%), n	57500 (261), 66	20100 (18100), 7
$T_{½}$ (day)	Geometric mean (CV%), n	43.8 (287), 43	24.4 (180), 6
T_{last} (day)	Median [min;max], n	191 [19.9; 558], 73	107 [18.7; 366], 10

Distribution

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In adult FL patients (Study E2202), tisagenlecleucel has been detected for up to 18 months in peripheral blood and up to month 3 in bone marrow for complete responder patients. The blood to bone marrow partitioning in bone marrow was nearly 54% of that present in blood at month 3 in both responder and non-responder patients.

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Special populations

Elderly

The scatter plots of cellular kinetic parameters versus age (22 to 76 years in DLBCL patients and 29 to 73 years in FL patients) revealed no relevant relationship between cellular kinetic parameters (AUC_{0-28d} and C_{max}) with age.

Gender

Gender has not been identified as a significant characteristic influencing tisagenlecleucel expansion in B-cell ALL, ~~and~~ DLBCL and FL patients. In Study B2202, there were 43% female and 57% male patients, ~~and~~ in Study C2201 38% female and 62% male patients and in Study E2202 34% female and 66% male patients who received Kymriah. Further, in Study E2202, the geometric means of the exposure parameters (C_{max} and AUC_{0-28d}) were shown to be 111% and 106% higher, respectively, in female patients compared to male patients. Although the interpretation of expansion in relation to gender is difficult due to overlapping ranges and high inter-subject variability.

Race/ethnicity

There is limited evidence that race/ethnicity impact the expansion of Kymriah in paediatric and young adult ALL, ~~and~~ DLBCL and FL patients. In Study B2202 there were 73.4% Caucasian, 12.7% Asian and 13.9% other ethnic patients. In Study C2201 there were 85% Caucasian, 9% Asian, 4% Black or African American patients, and 3 patients (3%) of unknown race. In Study E2202, there were 75% Caucasian, 13% Asian, 1% Black or African American patients, and 10% of unknown race.

Body weight

In ALL, ~~and~~ DLBCL and FL patients, across the weight ranges (ALL; 14.4 to 137 kg; DLBCL: 38.4 to 186.7 kg, FL: 44.3 to 127.7 kg), the scatter plots of qPCR cellular kinetic parameters versus weight revealed no apparent relationship between cellular kinetic parameters with weight.

Prior transplantation

Prior transplantation did not impact the expansion/persistence of Kymriah in paediatric and young adult B-cell ALL patients, ~~or~~ adult DLBCL or adult FL patients~~patients~~.

בעלון לצרכן

1. למה מיועדת התרופה?

קימריה מיועדת לטיפול ב:

1. ילדים ובמבוגרים צעירים, עד גיל 25 שנים (כולל) עם לוקמיה לימפובלסטית חריפה (acute lymphoblastic leukaemia) של תאי B, המבטאים CD19 (+CD19), עמידה, נשנית לאחר השתלה או נשנית פעם שניה ויותר.
2. מבוגרים עם לימפומה מפושטת של תאי B גדולים (diffuse large B-cell lymphoma), עמידה או נשנית ולאחר לפחות שני קווי טיפול סיסטמי.

הגבלה: קימריה לא מיועדת למטופלים עם לימפומה ראשונית או שניונית של מערכת העצבים המרכזית.

3. מבוגרים עם לימפומה פוליקולרית עמידה או נשנית ולאחר לפחות שני קווי טיפול סיסטמי.

2. לפני השימוש בתרופה

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ילדים ומתבגרים

- לוקמיה לימפובלסטית חריפה של תאי B: לא קיימים נתונים מבוססים ממחקרים קליניים על ילדים מתחת לגיל 3.
- לימפומה מפושטת של תאי B גדולים ולימפומה פוליקולרית: אין להשתמש בקימריה בילדים ובמתבגרים מתחת לגיל 18 לטיפול ב-DLBCL (diffuse large B-cell lymphoma), או ב-FL (Follicular lymphoma) מאחר והתכשיר לא נבדק בקבוצת גיל זו.

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4. תופעות לוואי

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תופעות לוואי שכיחות מאוד (תופעות שמופיעות ביותר ממשתמש אחד מעשרה)

- חום גבוה וצמרמורות. אלו עשויים להיות תסמינים של מצב רציני המכונה תסמונת שחרור ציטוקינים שעלול להיות מסכן חיים או קטלני. תסמינים אחרים של תסמונת שחרור ציטוקינים הם קשיי נשימה, בחילה, הקאה, שלשול, חוסר תיאבון, עייפות, כאבי שרירים, כאבי מפרקים, נפיחות, לחץ דם נמוך, דפיקות לב מואצות, כאב ראש, אי ספיקת לב, ריאות וכליות ופגיעה בכבד. תסמינים אלה מתרחשים כמעט תמיד במהלך 14 הימים הראשונים שלאחר העירוי.
- בעיות כגון שינוי חשיבה או ירידה בהכרה, אובדן קשר עם המציאות, בלבול, סערת נפש, פרכוסים, קשיים בדיבור ובהבנת דיבור, קושי בהליכה. אלה יכולים להיות תסמינים של מצב הנקרא תסמונת נוירוטוקסית של תאים אפקטוריים חיסוניים immune (effector cell-associated neurotoxicity syndrome, ICANS).
- תחושת חום, חום, צמרמורות או רעידות, כאב גרון או כיבים בפה עשויים להיות סימנים של זיהום. זיהומים מסוימים עשויים להיות מסכני חיים או קטלניים.