Tisagenlecleucel (Kymriah®) for the treatment of relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy

General information

Drug description [1]	Indication [2]
Tisagenlecleucel (Kymriah®) is an autologous anti-CD19 chimeric antigen receptor (CAR)-T cell therapy.	Tisagenlecleucel (Kymriah®) is indicated for the treatment of adult patients with relapsed or refractory FL after two or more lines of systemic therapy.

Current treatment [3]

- Currently, NICE recommends the following treatment for patients with relapsed or refractory FL:
  - Obinutuzumab with bendamustine followed by obinutuzumab maintenance is recommended, within its marketing authorisation, as an option for treating FL that did not respond or progressed up to 6 months after treatment with rituximab or a rituximab-containing regimen.
  - Lenalidomide with rituximab is recommended, within its marketing authorisation, as an option for previously treated FL (grade 1 to 3A) in adults.
  - Rituximab monotherapy, within its marketing authorisation, is recommended as an option for the treatment of people with relapsed or refractory stage III or IV follicular non-Hodgkin's lymphoma, when all alternative treatment options have been exhausted (that is, if there is resistance to or intolerance of chemotherapy).

Regulatory status

EMA [2]

Approval status for this indication: On 24 March 2022, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Kymriah®.

The CHMP adopted a new indication as follows:

- Kymriah® is indicated for the treatment of adult patients with relapsed or refractory FL after two or more lines of systemic therapy.

Other indications: Kymriah® is indicated for the treatment of:

- Paediatric and young adult patients up to and including 25 years of age with 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.

✓ **Orphan status**
✓ **Medicine under additional monitoring**

FDA

Approval status for this indication: On 27 October 2021, the FDA had accepted a supplemental biologics license application and granted priority review to tisagenlecleucel for the treatment of adult patients with relapsed or refractory FL who have received two prior lines of therapy [4].

UPDATE: On 27 May 2022, the FDA granted accelerated approval to tisagenlecleucel (Kymriah®) for adult patients with relapsed or refractory FL after two or more lines of systemic therapy [5].

Other indications: Kymriah® is indicated:

- Patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse.
- Adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma and DLBCL arising from FL.

Costs

The costs for Kymriah® (Tisagenlecleucel) are approx. € 320,000 [6].

Posology [7]

- **Cytokine release syndrome (CRS),** including fatal or life-threatening reactions, occurred in patients receiving Kymriah®. Do not administer Kymriah® to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids.
- **Neurological toxicities,** which may be severe or life-threatening, can occur following treatment with Kymriah®, including concurrently with CRS. Monitor for neurological events after treatment with Kymriah®. Provide supportive care as needed.
- **Hypersensitivity reactions**: Monitor for hypersensitivity reactions during infusion.
- **Serious infections**: Monitor patients for signs and symptoms of infection; treat appropriately.
- **Prolonged cytopenias**: Patients may exhibit ≥ Grade 3 cytopenias for several weeks following Kymriah® infusion. Prolonged neutropenia has been associated with increased risk of infection.

- **Hypogammaglobulinemia**: Monitor and provide replacement therapy until resolution. Assess immunoglobulin levels in newborns of mothers treated with Kymriah®.
- **Secondary Malignancies**: In the event that a secondary malignancy occurs after treatment with Kymriah®, contact the manufacturer.
- **Effects on ability to drive and use machines**: Advise patients to refrain from driving and engaging in hazardous occupations or activities, such as operating heavy or potentially dangerous machinery, for at least 8 weeks after receiving Kymriah®.
- Kymriah® is available only through a restricted program under Risk Evaluation and Mitigation Strategy (REMS) called the **KYMRIAH REMS.**

Study characteristics [1, 8, 9]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
ELARA NCT03568461	98 (97[1])	95.9% of patients received the protocol-specified dose range of between 0.6 × 10^8 and 6.0 × 10^8 CAR+ viable T cells[2]	-	Complete response rate (CRR)	**ongoing**[3], open-label, single-arm, multinational trial phase 2	-	Novartis Pharmaceuticals Corporation	[1]

Efficacy
primary, prespecified interim analysis data

The PE of this study was met at the interim analysis with a median follow-up of 9.9 months (n = 52):
CRR: 65.4% (99.5% CI, 45.1–82.4), p<0.0001

Efficacy analysis set (n=94)
CRR: 69.1% (95% CI, 58.8–78.3)
ORR: 86.2% (95% CI, 77.5–92.4)
PR: 17.0%

Per-protocol-set[4] (n=85)
CRR: 72.9% (95% CI, 62.2–82.0)
ORR: 87.1% (95% CI, 78.0–93.4)
PR: 14.1%

Median DOR, PFS, OS and time to next anti-lymphoma treatment: not reached.
Estimated DOR rate at 9 months among patients who achieved CR: 86.5% (95% CI, 74.7–93.1)

Safety (n=97)
primary, prespecified interim analysis data

Any grade AES: 99%
AEs ≥ grade 3: 78.4%
SAEs (within 8 weeks post-infusion): 27.8%
SAEs (within 8 weeks post-infusion) suspected to be study drug related: 23.7%
AEs grade ≥3 suspected to be study drug related: 40.2%
Treatment-related AEs of any grade: 78.4%
Treatment-related AEs ≥grade 3: 46%.
CRS: 49%
Any-grade neurological events: 37.1%
Deaths: 5 deaths were due to progressive disease; 2 additional deaths were due to CRS and to general disorders and administration site conditions. None of the deaths was treatment-related.

[1] One patient discontinued before receiving infusion due to investigator discretion based on CR to antineoplastic bridging therapy before tisagenlecleucel infusion.
[2] 4 patients received a lower dose of between 0.1 × 10^8 and 0.46 × 10^8 CAR-T cells. In addition, 2 patients received out-of-specification (product that does not meet the release criteria approved by the FDA) CAR-T cells, one due to low cell viability and the other to high cell count; both patients were infused with doses within the protocol-specified dose range of 0.8 × 108 to 6.0 × 108 CAR+ cells, respectively.
[3] The ELARA trial is currently ongoing; the estimated study completion date is 11/2022.
[4] The per-protocol-set consisted of a subset of patients in the efficacy analysis set with none of the following protocol deviations: diagnosis of disease other than FL at baseline, missing or incomplete documentation of disease at baseline and receiving less than the recommended dose of 0.6 × 10^8 CAR+ viable T cells.

Estimated PFS rate at 12 months among patients who achieved CR: 85.5% (95% CI, 74.0–92.2)
PFS rate for the overall population at 12 months: 67% (95% CI, 56–76)

Patient-reported QoL [10]:

- QoL instruments were completed by 81% of patients at baseline.
- FACT-Lym and SF-36 assessments were completed by 74% and 71% of patients at 3 months and by 65% and 64% of patients at 6 months, respectively.
- The FACT-Lym subscales showed improvement in the emotional, functional, and physical domains. No deterioration in the social/family domain by month 6 was reported, although minimal clinically important differences of 2 were not reached.
- Similarly, numeric improvement was observed in mean change scores from baseline through month 3 for the SF-36 mental health component scores and through month 6 for the physical health component scores, including general health, vitality, physical functioning, role-emotional, and role-physical.
- **Overall, 40%-49% of patients demonstrated clinically meaningful improvements in QoL based on FACT-Lym and SF-36 at month 3; 68%-83% of patients' QoL did not deteriorate.** Similar trends were observed at month 6.
- Mean change scores for FACT-Lym improved from baseline to month 3 and to month 6.

Risk of bias - study level (case series) [11]

1.	2.	3.	4.	5.	6.	7.	8.	9.
Was the hypothesis/ aim/ objective of the study clearly stated?	Were the cases collected in more than one centre?	Were patients recruited consecutively?	Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Did participants enter the study at similar point in the disease?	Was the intervention clearly described?	Were additional interventions (co-interventions) clearly described?	Were relevant outcome measures established a priori?	Were outcome assessors blinded to the intervention that patients received?
yes	yes	yes	yes	partial	yes	yes	unclear	no
10.	11.	12.	13.	14.	15.	16.	17.	18.
Were the relevant outcomes measured using appropriate objective/ subjective methods?	Were the relevant outcomes measured before and after intervention?	Were the statistical tests used to assess the relevant outcomes appropriate?	Was the length of follow-up reported?	Was the loss to follow-up reported?	Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Were adverse events reported?	Were the conclusions of the study supported by results?	Were both competing interest and source of support for the study reported?
yes	unclear	yes	yes	no	yes	yes	unclear[5]	yes
Overall risk of bias: moderate								

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Abbreviations: AE=adverse event, AJ=adjustment, ALL=acute lymphoblastic leukaemia, C=comparator, CAR=chimeric antigen receptor, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CRR=complete response rate, CRS=cytokine release syndrome, DLBCL= diffuse large B-cell lymphoma, DOR=duration of response, EMA=European Medicines Agency, ESMO-MCBS= European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FACT-LYM=Functional Assessment of Cancer Therapy-Lymphoma, FDA=Food and Drug Administration, FL=follicular lymphoma, FM=final magnitude of clinical benefit grade, HR=hazard ratio, I=intervention, Int.=intention, MG=median gain, n=number of patients, NICE=National Institute for Health and Care Excellence, ORR=overall response rate, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, PR=partial response, QoL=quality of life, SAE=serious adverse event, SF-36=Short Form-36 Health Survey v2, ST=standard treatment

[5] The ELARA trial is ongoing; currently, only primary, prespecified interim analysis data is available.

References:

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