Australian Government
Medical Services Advisory Committee

STAKEHOLDER MEETING OUTCOME STATEMENT

CAR-T CELL THERAPY FOR THE TREATMENT OF RELAPSED/REFRACTORY DLBCL, PMBCL & FML

Tuesday, 12 November, 2019

Introduction

Attendees

Meeting attendees included members of the Medical Services Advisory Committee (MSAC); clinicians with experience in treating lymphoma and CAR-T cell therapy; representatives of the applicants; representatives from consumer organisations; representatives from State/Territory health departments; and representatives from the Commonwealth Department of Health.

The Chair clarified that the Stakeholder meeting was not an MSAC decision making forum, but would inform the issues considered by MSAC following its August 2019 consideration of application 1519.1 (tisagenlecleucel (Kymriah®)) and application 1587 (axicabtagene ciloleucel (Yescarta®)) to be considered in November 2019.

The Chair reminded participants that this was a confidential discussion and an Outcome Statement would be published on the MSAC website.

Purpose

The key objectives of the meeting were to allow MSAC to seek input from stakeholders on:

- The criteria for eligibility for CAR-T cell therapy in diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma (PMBCL) and transformed follicular lymphoma (TFL).

- The response and assessment criteria to establish durability of response in clinical practice.

Other issues discussed included: Australian patient registries, equity of access across Australia, and treatment centre accreditation and readiness.

Conflicts of interest

The Chair noted the conflicts of interest declared.

1. Background

Kymriah and Yescarta are CAR-T cell therapies. Each dose is a customised treatment created using an individual patient's own genetically modified T-cells (a type of white blood cell). The single dose is delivered intravenously.

CAR-T cell therapy treatment involves six stages:

1. Collect of cells from the patient (apheresis).
2. Cell modification and re-programming at a specialised manufacturing centre.
3. The patient may undergo bridging therapy whilst the CAR-T cells are being manufactured
4. The patient receives cytotoxic preconditioning therapy
5. The patient receives the infusion of the modified cells.
6. The patient is monitored.

The process from apheresis to infusion can take a number of weeks. Patients need to stay within proximity of their treatment centre for 4 weeks after infusion for monitoring and for treatment of any side effects.

Currently, treatment can only take place in tertiary public hospitals with appropriate expertise and facilities.

At its August 2019 meeting, MSAC considered an application for the public funding of Kymriah for the treatment of r/r DLBCL (application 1519.1) and recommended the Department convene a discussion with relevant stakeholders including treating clinicians, consumers, and representatives of the applicants, Commonwealth and State/Territory governments to consider the criteria for eligibility for CAR-T therapy.

MSAC considered more work was needed to identify the patients most likely to benefit from CAR-T cell therapy. In particular, the MSAC noted:

- The population treated in the JULIET trial was narrower than the proposed subsidy population.
- Effectiveness, safety and cost-effectiveness in the broader population may not be the same as in JULIET trial.
- It is critically important that treatment is used only in patients likely to be fit enough to tolerate it.

The meeting noted that a second CAR-T cell therapy, Yescarta for r/r CD19-positive lymphoma was due to be considered at the upcoming November 2019 MSAC meeting.

2. Summary of discussion and outcomes

Eligibility criteria

There was consensus that patient eligibility criteria will require ongoing monitoring and potentially, revision, as treatment sites mature and gain experience in treating patients with CAR-T cell therapy.

1. Indication

In addition to r/r DLBCL, there was consensus that PMBCL should be in scope for treatment with CAR-T cell therapy. Patients with this condition were included in the ZUMA-1 clinical trial of Yescarta, patient numbers were noted as small, and current treatment options limited.

TFL was also considered in scope for treatment once the large cell component had met the DLBCL CAR-T cell therapy treatment criteria (i.e. patients must have failed or be refractory to two lines of systemic therapy after the disease had transformed).

The majority of attendees considered patients with secondary CNS disease should not be excluded from CAR-T treatment, unless this CNS disease was uncontrolled at the time of infusion. There is some evidence that their outcomes are comparable with patients without CNS disease. There was a consensus that patients with *primary* CNS lymphoma should not be offered CAR-T cell therapy due to an absence of clinical data in this entity.

These were the only lymphoma indications considered appropriate for treatment with CAR-T cell therapy at this time.

2. *Line of therapy*

There was consensus that CAR-T cell therapy should be indicated for use in the relapsed or refractory setting, following two lines of systemic therapy.

Depth of response to prior therapies was not considered to be an important criterion but it was agreed that patients with rampant progression may be more difficult to manage through the manufacturing period and be less likely to respond to CAR-T cell therapy.

It was considered appropriate for a note to be included in the eligibility criteria, to mitigate against treating patients unlikely to respond to treatment based on the tempo of disease and availability of effective bridging therapies. The final decision to proceed with treatment based on disease stability, should rest with the treatment team.

3. *Age*

The majority of attendees were of the opinion that there should not be an upper age limit for treatment, however some considered an upper age limit of 75 years reasonable.

There was consensus that other indicators of fitness for treatment such as performance status, comorbidity and frailty scores were appropriate measures of a patient's suitability for treatment with CAR-T cell therapy.

4. *Performance status*

Requirement of an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 for treatment was considered appropriate.

A statement about the patient's anticipated ability to survive the manufacturing duration and bridging therapy should be included in the criteria.

5. *Organ function*

Attendees considered the inclusion of eligibility criteria relating to organ function was appropriate. Cardiac, pulmonary and renal function were considered to be most indicative of patient fitness for consideration of lymphodepleting chemotherapy and CAR-T cell therapy.

6. *Comorbidities*

Attendees considered most patients with controlled comorbidities at time of infusion should be considered for treatment.

Patients with uncontrolled infection at the time of infusion should not receive treatment.

Response criteria and assessment

Attendees agreed the response and assessment criteria should be objective, reliable, simple and independently verifiable based on the Lugano 2014[1] criteria, in comparison with a PET performed after the last cycle of salvage, and/or bridging therapy.

FDG PET-CT scan, with or without IV contrast, was considered the best modality for establishing patient response. A score of 1-2 using the 5-point Deauville scale would represent a complete metabolic response at the end-of-treatment assessment[2]. Partial metabolic response, stable and progressive disease should also be recorded.

There was consensus that a requirement for a FDG PET-CT scan at 12 months was appropriate for collecting national data on the durability of response to CAR-T cell therapy in clinical practice, as based on currently available evidence, most CAR T-cell failures will have occurred prior to this time point. The consumer group representatives considered patients would not object to this, and recommended the consent process include the reason for this scan.

The attendees noted that a patient would be considered to have experienced treatment failure with CAR-T cell therapy for the purpose of the 12 month reporting measure, if they had experienced lymphoma relapse requiring any systemic therapy (excluding localised radiation treatment to a single site of disease that was persistent post CAR-T cell therapy) earlier than 12 months after infusion. In this case, a FDG PET-CT scan at 12 months would not be required.

Overall, patient response at 12 months among those who have not received post-CAR-T systemic therapy could be reported using three (3) questions:

1. What was the patient's best response?
2. Has patient had subsequent progression?
3. What does the FDG PET-CT currently show in comparison to previous scan results?

The appropriate method of assessment of patients with extra-medullary disease occurring in e.g. the bowel or CNS was discussed. It was agreed that such patients represent a small pool of the total population and therefore additional organ appropriate (e.g. endoscopy, MRI) response assessment was clinically appropriate, however was not required for the purpose of collecting national data at the 12 month assessment point[3].

Records and registries

The Australian Bone Marrow Transplant Recipient Registry (ABMTRR) will be used to capture information on Australian patients treated with Kymriah for acute lymphoblastic leukemia (ALL).

The ABMTRR representatives confirmed it has the capability to capture data for the DLBCL population.

[1] Cheson JCO 2014 and, Barrington JCO 2014.
[2] The Clinical Trial Protocol for the Juliet study stipulated a score of 1 or 2 with or without a residual mass on a 5-PS must be achieved for a complete metabolic response (Juliet Trial Protocol CCTL019C2201, Version 5, page 144, source ct1019c2201p01-legacy-clinical-strudy-report, p 4342.)
[3] Lugano criteria and Imaging consensus: Barrington JCO 2014, Cheson JCO 2014

Attendees considered that in addition to the data-set recommended by MSAC for capture by the ABMTRR for ALL, any future data-set for DLBCL should ideally also capture: the date of first referral, postcode of patient and referring physician, date of apheresis and infusion for treated patients; and the number of patients referred but not accepted, for treatment with CAR-T cell therapy, including the reason.

Representatives from the ABMTRR confirmed that the registry was now congruent with the Center for International Blood and Marrow Transplant Research (CIBMTR) and is working towards becoming congruent with other registries, such as the Research Electronic Data Capture (REDCap) used by the Peter MacCallum Cancer Centre,and the Australian Lymphoma and related Diseases Registry (based at Monash University).

Implementation issues

Monitoring for and ensuring equity of access to therapy for patients in non-treating states and in rural/remote areas was identified as important, including the need to support patient and carer travel and accommodation costs. This includes any costs incurred for the purpose of post-treatment assessment.

Treatment site accreditation was identified as a potential hurdle to rolling out CAR-T cell therapy centres, if publicly funded for DLBCL. In addition to accreditation, sites are required to undergo separate qualification processes by both companies before delivering CAR-T cell therapy.

Currently, the Peter MacCallum Cancer Centre, Victoria, and Royal Price Alfred Hospital in NSW are the only centres fully qualified (by the company) to deliver Kymriah for adults. Royal Prince Alfred Hospital is expected to start treating patients in early 2020.

Multiple other sites across the country were identified as potential sites for delivering CAR-T cell therapy once qualification processes are complete.

FACT or JACIE accreditation were considered the gold standard for sites providing these therapies, however it was not considered that a site which had not undergone this accreditation process should be excluded from providing CAR-T cell therapy while working towards FACT and/or JACIE accreditation within a reasonable time period. The FACT or JACIE accreditation process can take up to 2 years to complete.