**National Institute for Health and Care Excellence**

**Single Technology Appraisal (STA)**

# Tisagenlecleucel-T for treating relapsed or refractory diffuse large B-cell lymphoma [ID1166]

**Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)**

**Please note:** Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

## Comment 1: the draft remit

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| Appropriateness | - | - | - |
| Wording | Janssen | Yes, the wording of the remit does reflect the issues. | Comment noted. No action required. |
| | Novartis Pharmaceuticals UK Limited | Novartis anticipates that the marketing authorisation for tisagenlecleucel as a treatment for relapsed or refractory (r/r) diffuse large B cell lymphoma (DLBCL) will be as follows:<br>"Adult patients with relapsed or refractory diffuse large B cell lymphoma who are ineligible for autologous stem cell transplant"<br>Novartis therefore requests that the wording in the draft remit be updated to reflect this wording. | Comment noted. No action required. NICE will appraise the treatment within its marketing authorisation |
| | Roche Products Ltd | None | Comment noted. No action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| Timing Issues | Novartis Pharmaceuticals UK Limited | There is a considerable unmet need for new treatment options that can provide sustained remissions, improve health-related quality of life and provide the hope of a cure for adult patients with r/r DLBCL who are ineligible for autologous stem cell transplant (SCT).<br>This appraisal is therefore highly relevant to the NHS and should be treated accordingly as a matter of urgency by NICE. | Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ta10269. No action required. |
| | Roche Products Ltd | None | Comment noted. No action required. |
| Additional comments on the draft remit | Novartis Pharmaceuticals UK Limited | No additional comments | Comment noted. No action required. |
| | Roche Products Ltd | None | Comment noted. No action required. |

**Comment 2: the draft scope**

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| Background information | Novartis Pharmaceuticals UK Limited | Novartis believes that the description of the treatments available for patients with r/r DLBCL who are ineligible for autologous SCT is incomplete with respect to recommendations from relevant treatment guidelines, and does not adequately capture the unmet need associated with this indication. | Comments noted. This section of the scope aims to provide a brief overview of the |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| | | Novartis therefore requests that additional information is added to the background information, for example (in red text):<br>"… further chemotherapy or immunotherapy may be used alone. Treatment guidelines from the European Society of Medical Oncologists (ESMO) recommend that patients who are not eligible for transplant should also be considered for entry into clinical trials with novel drugs, with enrolment in clinical trials preferable to currently available therapies for patients who have experienced more than two relapses. NICE technology appraisal 306 recommends pixantrone monotherapy…."<br><br>Novartis would also recommend including the latest survival estimates and clinical outcomes for patients with refractory DLBCL as reported from the SCHOLAR-1 study:<br>"For patients with refractory DLBCL receiving the next line of therapy, an objective response rate of 26% (complete response, 7%) and median overall survival of 6.3 months has been reported from the SCHOLAR-1 study.[1] Outcomes from this study were consistently poor across patient subgroups and study cohorts. SCHOLAR-1 is the largest patient-level pooled retrospective analysis that characterises response rates and survival for a population of patients with refractory DLBCL."<br>**References**<br><br>1. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130:1800-1808. | background for the appraisal; additional details may be considered by the committee, if appropriate, at the time of the appraisal. No action required. |
| | Roche Products Ltd | None | Comment noted. No action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| | Servier Laboratories Limited | Typo – sentence on Pixantrone should read "NICE TA 306 …….are in the 3rd/4th Line of treatment" | Comment noted. Typo amended. |
| The technology/ intervention | Novartis Pharmaceuticals UK Limited | Novartis requests that the description of the technology be amended to note that CAR-T therapy modifies the patient's T-cells (rather than "blood cells").<br>Further text may also be added to the description of the technology to provide more details about the mechanism of action of tisagenlecleucel and to align this with the draft scope for ID1167:<br>"… target a protein called CD19. When tisagenlecleucel-T binds to CD-19 expressing cells, the T-cell is activated to destroy the target cancer cell." | Comments noted. The text has been amended to "Tisagenlecleucel-T also known as CTL019 (Kymriah, Novartis) is a chimeric antigen receptor (CAR) T cell therapy that changes the patient's T-cells to target a protein called CD19. When tisagenlecleucel-T binds to CD-19 expressing cells, the T-cell is activated to destroy the target cancer cell. |
| | Roche Products Ltd | None | Comment noted. No action required. |
| | Servier Laboratories Limited | No comments | Comment noted. No action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| Population | Janssen | Yes, the population seems appropriately defined | Comment noted. No action required. |
| | Novartis Pharmaceuticals UK Limited | As for the draft remit, Novartis requests that the wording for 'Population' be updated to be consistent with the anticipated wording for the licensed indication.<br>"Adult patients with relapsed or refractory diffuse large B cell lymphoma who are ineligible for autologous stem cell transplant" | Comment noted. The population has been amended to "Adults with relapsed or refractory diffuse large B-cell lymphoma".<br>NICE will appraise the treatment within its marketing authorisation |
| | Roche Products Ltd | None | Comment noted. No action required. |
| | Servier Laboratories Limited | The population is appropriately defined, however, definitions of relapsed and refractory disease should be included. Additionally the positioning after ASCT / not suitable for ASCT should be more clearly defined as we consider that this is not clear. | Comments noted. This section provides a brief overview of the population for the appraisal; additional details may be considered by the committee, if appropriate, at the time of the appraisal. No action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| Comparators | Janssen | Yes, these seem to represent standard treatments currently used in the NHS. | Comment noted. No action required. |
| | Novartis Pharmaceuticals UK Limited | Novartis considers salvage chemotherapy (with or without rituximab) to best represent current standard of care in England, as per NICE clinical guidelines for the management of r/r DLBCL (NG52) and treatment guidelines from the British Society of Haematology (BSH) and ESMO.[2-4] Salvage chemotherapy regimens should therefore be considered as the most relevant comparators for this appraisal. Evidence for the use of salvage chemotherapy in r/r DLBCL (including patients who relapse after autologous SCT) is available from randomised trials and the SCHOLAR-1 study.[1, 5, 6]<br>Although recommended by NICE as part of TA306, Novartis understands that pixantrone monotherapy (as a 3rd or 4th line therapy for patients previously treated with rituximab) is not routinely used in clinical practice and notes that ESMO guidelines consider enrolment in to clinical trials to be preferable to pixantrone monotherapy.[3, 7] Pixantrone monotherapy is therefore not considered to be a relevant comparator for this appraisal.<br>Finally, the NICE guide to the methods of technology appraisal states that when considering the appropriateness of comparators, the following three criteria are considered: established NHS practice in England; existing NICE guidance; and the licensing status of the comparator. Based on each of these criteria, Novartis does not consider axicabtagene ciloleucel to represent a relevant comparator for this appraisal:<br>• Axicabtagene ciloleucel has not yet received an EU marketing authorisation for this indication and has not yet been appraised by NICE. | Comments noted. Pixantrone monotherapy has been retained as there may be some patients who use it in clinical practice.<br>Axicabtagene ciloleucel has been retained but is subject to the outcome of the ongoing NICE appraisal |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| | | • Axicabtagene ciloleucel does not represent established clinical practice in the NHS in England as it is only available to patients as part of a clinical trial.<br>Therefore, as axicabtagene ciloleucel will not be routinely displaced by tisagenlecleucel it should not be considered a comparator.<br>Furthermore, the patient populations in the axicabtagene ciloleucel and tisagenlecleucel phase II trials differ:<br>• The axicabtagene ciloleucel population was broader, including patients with primary mediastinal B-cell lymphoma and those with primary refractory disease.<br>• Bridging chemotherapy was disallowed prior to infusion in the axicabtagene ciloleucel trial but allowed in the tisagenlecleucel trial to treat patients who had failed 2 or more lines of therapy and were not eligible for SCT.[8]<br>Novartis therefore requests that axicabtagene ciloleucel be removed as a comparator from the scope.<br>**References**<br>1. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130:1800-1808.<br>2. National Institute for Health and Care Excellence. Non-Hodgkin's lymphoma: diagnosis and management. Available at: https://www.nice.org.uk/guidance/NG52/chapter/Recommendations#management-of-diffuse-large-bcell-lymphoma. [Last accessed: 14 November 2017].<br>3. Tilly H, Gomes da Silva M, Vitolo U, et al. Diffuse large B-cell lymphoma (DLBCL): ESMO Clinical Practice Guidelines for | |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| | | diagnosis, treatment and follow-up. Ann Oncol 2015;26 Suppl 5:v116-25.<br>4. Chaganti S, Illidge T, Barrington S, et al. Guidelines for the management of diffuse large B-cell lymphoma. Br J Haematol 2016;174:43-56.<br>5. Van Den Neste E, Schmitz N, Mounier N, et al. Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. Bone marrow transplantation 2017;52:216-221.<br>6. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone marrow transplantation 2016;51:51-57.<br>7. National Institute for Health and Care Excellence. TA306: Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B‑cell lymphoma. Available at: https://www.nice.org.uk/guidance/ta306. [Last accessed: 16 November 2017].<br>8. Neelapu S.S, Locke F.L, Bartlet N.L, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. NEJM published ahead of print Dec 10th. DOI: 10.1056/NEJMoa1707447 | |
| | Roche Products Ltd | There is no preferred standard of care regimen in this setting, in particular for patients ineligible for transplant. Other chemotherapy regimens (e.g. bendamustine) than the salvage regimens mentioned may be used with rituximab. | Comments noted. The comparators section emphasises that the listed interventions are not the only possible options: “Established clinical management without tisagenlecleucel-T |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| | | | including but not limited to …". No action required. |
| | Servier Laboratories Limited | There are a significant number of treatment options used in the 3rd line setting, albeit without NICE recommendation. This comparator section needs to be expanded to reflect usage in the real world. | Comments noted. The comparators section emphasises that the listed interventions are not the only possible options: "Established clinical management without tisagenlecleucel-T including but not limited to …". No action required. |
| Outcomes | Janssen | Yes, these outcome measures capture the most important health related benefits and harms of the technology. | Comment noted. No action required. |
| | Novartis Pharmaceuticals UK Limited | Novartis agrees with the outcome measures proposed in the draft scope. In addition to response rates, Novartis considers duration of response to also represent a meaningful outcome for patients with r/r DLBCL. | Comment noted. 'Duration of response' would be covered by the outcome 'response rates' included in the scope. No action required. |
| | Roche Products Ltd | None | Comment noted. No action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| | Servier Laboratories Limited | No comment | Comment noted. No action required. |
| Economic analysis | Janssen | A lifetime horizon would seem appropriate. | Comment noted. No action required. |
| | Novartis Pharmaceuticals UK Limited | Novartis considers a lifetime time horizon to be most appropriate for the modelling of tisagenlecleucel, which has the potential to offer a 'cure' for some patients.<br>In accordance with the NICE reference case, a lower annual discount rate of 1.5% may also be explored by Novartis as part of the appraisal. | Comments noted. No action required. |
| | Roche Products Ltd | None | Comment noted. No action required. |
| | Servier Laboratories Limited | No comment | Comment noted. No action required. |
| Equality and Diversity | Novartis Pharmaceuticals UK Limited | Novartis has not identified any issues related to equality that should be covered in the remit or scope of this appraisal. | Comment noted. No action required. |
| | Roche Products Ltd | None | Comment noted. No action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| | Servier Laboratories Limited | No comment | Comment noted. No action required. |
| Innovation | Janssen | Yes, we consider the technology to be innovative.<br><br>No, we do not believe that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation. | Comments noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required. |
| | Novartis Pharmaceuticals UK Limited | Tisagenlecleucel represents a paradigm shift in the management of r/r DLBCL for adult patients who are ineligible for autologous SCT.<br>Established clinical management for these patients currently consists of salvage chemotherapy (with or without rituximab) and patients who are ineligible for autologous SCT have a limited life expectancy (<12 months) with current treatment options.[1, 5, 6]<br>Tisagenlecleucel is a CAR-T therapy which works via harnessing the body's own immune system to destroy cancer cells, which is in contrast to the indiscriminate cytotoxic effects of chemotherapy. Tisagenlecleucel may offer a potential 'cure' for some patients, returning them to a level of quality of life and life expectancy similar to the general population.<br>Evidence of the efficacy of tisagenlecleucel as a treatment for adult patients with r/r DLBCL who are ineligible for autologous SCT (in terms of response rates and overall survival) will be available from a single-arm, phase II trial (JULIET).[9]<br>**References** | Comments noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have an opportunity to provide evidence on the innovative nature of its product in its submission. No action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| | | 1. Crump M, Neelapu SS, Farooq U, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130:1800-1808.<br>5. Van Den Neste E, Schmitz N, Mounier N, et al. Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. Bone marrow transplantation 2017;52:216-221.<br>6. Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone marrow transplantation 2016;51:51-57.<br>9. Schuster SJ, Bishop MR, Tam CS, et al. 577 Primary Analysis of Juliet: A Global, Pivotal, Phase 2 Trial of CTL019 in Adult Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Presented at the 59th Annual Meeting of the American Society of Hematology, 2017. | |
| | Roche Products Ltd | None | Comment noted. No action required. |
| | Servier Laboratories Limited | Yes, the introduction of CAR-T therapy is a new innovative therapy area. Servier therefore consider this to be a potential step-change in management of DLBCL for appropriate populations | Comments noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required. |
| Other considerations | Novartis Pharmaceuticals UK Limited | No comment | Comment noted. No action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| | Roche Products Ltd | None | Comment noted. No action required. |
| Questions for consultation | Novartis Pharmaceuticals UK Limited | Comments have been provided above with regards to the population, comparators and outcomes specified in the draft scope, as well as issues related to equality, and the innovativeness of tisagenlecleucel.<br><br>In addition:<br>Novartis does not consider there to be any clinically-relevant subgroups of patients for whom tisagenlecleucel will be more clinically- or cost-effective when compared to the overall population covered by the indication.<br>Novartis would like to highlight the fact that the population of patients eligible for tisagenlecleucel is already specific and for a discrete subset of DLBCL patients with particularly poor prognosis and limited treatment options.<br>Novartis expects that tisagenlecleucel will be positioned within the existing NICE pathway according to the anticipated licensed indication, i.e. as a treatment for r/r DLBCL for adult patients who are ineligible for autologous SCT.<br>Novartis accepts that the Single Technology Appraisal process is suitable for this appraisal.<br><br>Finally:<br>CAR-T therapy represents an entirely novel type of treatment, the delivery of which will require sites to have specific capabilities and facilities (e.g. for performing leukapheresis and also handling, storing, and disposing of human cells that have been genetically modified with a lentivirus). Novartis is therefore [redacted], and hopes to work with NICE and NHS | Comment noted. Please see specific sections for response to comments on population, comparators, outcomes, equality and innovation. No action required.<br><br>Comments noted. No action required. |

| Section | Consultee/ Commentator | Comments [sic] | Action |
|---|---|---|---|
| | | England going forwards in order to support the introduction of CAR-T therapy into the NHS. | |
| | Roche Products Ltd | None | Comment noted. No action required. |
| Additional comments on the draft scope | Novartis Pharmaceuticals UK Limited | No additional comments | Comment noted. No action required. |
| | Roche Products Ltd | None | Comment noted. No action required. |

**The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope**