MPe Myeloma Patients Europe

REPORT

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Patient-based evidence requirements in the regulatory and reimbursement assessment of CAR-T cell therapies in Europe

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1. INTRODUCTION

Chimeric antigen receptor-T cell (CAR-T cell) therapy is a type of immunotherapy that harnesses the immune system by genetically modifying a patient's T-cells, a type of white blood cell, to find and destroy malignant blood cancer cells. CAR-T cell therapy has the potential to bring several major benefits to patients, the first of which is high response rates. A recent meta-analysis found the overall efficacy of CAR-T cell therapies included responses in about 89% of relapsed refractory multiple myeloma (RRMM) patients.[1] Another innovative benefit of the therapy is the long-lasting response: the genetically modified T-cells continue to live and multiply inside the patient's body even after the treatment is completed. However, it should be noted that CAR-T cell therapy is relatively new and not all patients will respond to it.

The therapy is also complicated to develop and administer. A patient undergoes leukapheresis, where T-cells are separated from the patient's blood and are then genetically modified and expanded in centralised manufacturing centres. The patient might receive chemotherapy before the CAR-T cells are infused. They may also need to remain in (or nearby) specialised care centres with access to intensive care units and various specialists, and monitored for two weeks or longer,[2] as CAR-T cell therapies are also associated with a unique toxicity profile - namely cytokine release syndrome (CRS) and neurotoxicity – which are side effects not often seen in the current standard of care treatments for myeloma.

The single arm design of many CAR-T cell therapy trials supporting the initial marketing authorisation, combined with affordability concerns and the specialised nature of treatment delivery, mean stakeholders really must articulate the patient benefits of these treatments to decision-makers. There are therefore increased interest and efforts to incorporate the patient voice via the submission of patient-based evidence in drug regulatory and reimbursement assessments. Patient-based evidence represents evidence or knowledge that originates directly from patients about their experiences of health, quality of life, health care, health services and health research. Conceptually, it could include not only experiences, but also perceptions, needs, or attitudes about their care and health.[3] Patient-based evidence should reflect data that is scientifically and robustly collected with a view to form part of the total evidence package submitted to and assessed by regulatory and reimbursement agencies. For the purposes of this report, patient-based evidence includes clinical outcome assessments (COAs), including patient reported outcomes (PROs), patient preference studies, and qualitative and quantitative studies.

The aim of the performed literature review (see appendix 2) and stakeholder interviews (see appendix 3) was two-fold: to investigate stakeholder perspectives on patient-based evidence in CAR-T cell therapies, and to share some lessons learned from the five CAR-T cell therapies' regulatory and reimbursement approvals in diffuse large B-cell lymphoma (Yescarta and Kymriah), acute lymphoblastic leukaemia (Kymriah), mantle cell lymphoma (Tecartus) and MM (Abecma and Carvykti) on patient-based evidence requirements in decision-making. All products have been granted orphan designation and have significantly improved survival in their respective disease areas.

The present discussion paper details findings and provides recommendations for different stakeholders (European regulators, health technology assessment [HTA] bodies, industry and patient organisations) involved in the development or assessment of CAR-T cell therapies and other innovative therapies in blood cancer on their responsibilities and requirements for gathering patient-based evidence. Ultimately, Myeloma Patients Europe (MPE) aims to drive forward thinking on patient-based evidence in CAR-T cell therapy development and assessments, and thereby ensure all stakeholders are adequately prepared for future regulatory and reimbursement assessments.

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2. KEY TAKE-AWAYS ON PATIENT-BASED EVIDENCE REQUIREMENTS

Here, we have summarised with key takeaways from our literature review and discussions with stakeholders on the current use of patient-based evidence in the European regulatory and reimbursement assessments of CAR-T cell therapies.

1. The best developed type of patient-based evidence is in the field of quality of life with PROs.

Probably the best developed type of patient-based evidence, conceptually and methodologically, is in the field of quality of life with PROs. PROs are "any report of the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response by a clinician or anyone else."[4] PROs are one of four types of clinical outcome assessments (COAs). The US Food Drug Administration (FDA) defines a COA as "a measure that describes or reflects how a patient feels, functions, or survives." The other three types of COAs are: clinician-reported outcome (ClinRO), observer-reported outcome (ObsRO) and performance outcome (PerfO).[5]

The most standard way of collecting PROs in the clinical development process is using patient report outcome measures (PROMs), which are validated self-report questionnaires. PROMs gather the impact a treatment or treatments have on patients according to four key domains: health-related quality of life (HRQoL), including functional status; symptom and symptom burden; experience with care; and health behaviours.[6] There are a wide variety of questionnaires designed for measuring PROs, which can be broadly classified into three categories: generic, disease-specific and symptom-specific measures. Generic measures are typically designed in a large population of patients with a variety of health conditions. Commonly used generic measures include Medical Outcomes Trust Short-Form-36 (SF-36), Euro-QoL EQ-5D-5L and Patient-Reported Outcomes Measurement Information System (PROMIS). Cancer-specific measures, which are commonly used in research and clinical practice, include Functional Assessment of Cancer Therapy-General (FACT-G) and EORTC-Quality of Life Questionnaire (EORTC-QLQ-C30). Examples of symptom- or intervention-specific measures include the EORTC QLQ-CIPN20 (on cancer induced peripheral neuropathy), the PRO CTCAE (on symptomatic toxicities) and the FACT-BMT (on bone marrow transplantation).

PROs can support both regulatory and HTA submissions, although use of this data in decision-making varies. With regards to the reimbursement process, PROs are added the clinical evidence data package and contribute to the clinical value dossier. In countries where a cost-effectiveness analysis is conducted as part of a health technology assessment, PROs can be used used to estimate utilities and quality-adjusted life years (QALYS)*, which are needed to run such analysis.

The use of PROs is especially relevant to the development and assessment of CAR-T cell therapies given their benefit balanced by a unique toxicity profile, and the logistics required to administer treatment and supportive care.

Other types of patient-based evidence include patient preference studies (using specific methodologies, like multi-criteria decision-making analysis and discrete choice experiments to understand how patients make choices on different treatment attributes), real world evidence, quantitative research (online patient surveys, large-scale structured interviews and symptom diaries), qualitative research (targeted structured interviews, focus groups and panel discussion) and testimonials.

The type of patient-based evidence produced by the patient community typically includes testimonials; online patient surveys investigating the care pathway, patient experience, health-related quality of life (HRQoL) and/or patient preferences (as above); structured interviews; and focus groups and patient panel discussions. This type of data is gathered to inform patient organisation strategy, contribute to the EMA and European HTA patient involvement processes, and underpin advocacy to policymakers, health care professionals and industry.

2. Results from PROs gathered in early single arm CAR-T cell therapy clinical trials have been considered exploratory and therefore could not adequately support further significant benefit.

Most CAR-T cell therapy clinical trials list PROs as exploratory or secondary endpoints, which leads to substantial weaknesses in the quality of the analysed outcomes from the patients who have completed PROs in these studies.[7] See Table 1 for more details.

In the absence of comparative data, PRO results are often not described in national and European public assessments reports. Insofar as the CARTITUDE-1 study was non-comparative, and the

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* *Health utilities are measures of value that an individual or society gives a particular health state. It is a number between 0, representing death, and one, i.e., perfect health. Health utilities are quality of life scores. QALY is a measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One quality-adjusted life year (QALY) is equal to one year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a health utility. It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance (https://www.nice.org.uk/glossary?letter=q).*

change in HRQoL was exploratory, the French National Authority for Health - HAS (the French HTA body) considered in its early access programme assessment that no formal conclusion could therefore be drawn for the assessment of quality of life. This lack of conclusive quality of life data did not negatively impact HAS's decision to grant early access to Carvykti.[8]

Continued collection of reliable PROs following CAR-T cell therapy is a major challenge.[7]

- Patients may already have HRQoL deficits resulting from the disease itself and prior treatments. Some patients were unable to distinguish impairment attributed to their condition from previous treatment or from CAR-T treatment.[9] This is why it is important to include baseline PROs in PRO assessment schedules.
- Missing data may be a particular issue in the acute phase when patients develop severe CRS or neurotoxicity potentially compromising their ability to complete PRO questionnaires. For example, considering most acute toxicities occur in the first two to four weeks after CAR-T cell therapy infusion, by not performing PRO assessments during that time after liso-cel infusion, investigators were unable to capture useful information on the immediate impact of liso-cel on HRQoL.[10]
- There is also the risk of missing data in the long term if no decision is taken a priori on who will collect and follow the long-term PROs once patients transition back from the specialised CAR-T cell therapy referral centres to their regular treatment centre/haematologist.[11]
- One additional challenge to address is with regards to patients that progress and subsequently receive another anti-cancer therapy. Without a rigorous analysis plan, inclusion of these patients in the analysis confounds PRO results. Again, of the 96 patients that received another anti-cancer therapy following liso-cel infusion, 42 answered the EORTC QLQ-C30 questionnaire after initiating the anti-cancer therapy, making it impossible to distinguish between the effects of anti-cancer therapies and those of liso-cel.[10]
- The long-term PROs from patients on CAR-T cell therapy only represents the patient-reported experience from some patient subgroups. Patients that fill in PRO questionnaires are typically patients with less disease and toxicity burden, but also those that are alive in the medium and longer term.[7]
- Understanding the longer-term observed effects on those patients' HRQoL and symptoms give a better indication of how some patients are feeling after recovering from toxicities and potentially achieving a therapeutic response.[10] It is also critical for optimal survivorship care.[12] Without rigorously incorporating PRO assessment beyond the clinical trial timeframe, we miss some patients' perspective of toxicity and efficacy as PROs are a better indicator of treatment toxicity and tolerability compared to clinician-reported outcomes.[11, 12]

3. Regulators and the European Federation of Pharmaceutical Industries and Associations (EFPIA) consider that guidance on how robust patient-based evidence can be generated is not clear enough.[13]

While the FDA has issued "Patient-Focused Drug Development (PFDD)" (guidance that ensures patients' experiences and perspectives are incorporated in drug development14), interviewed representatives of the EMA conceded that the EMA does not have clear guidelines on how PROs should be gathered.

Additionally, European regulatory and HTA agencies do not provide any specific methodology on what and how patient organisations should collect and analyse their own patient-based evidence. While European regulators and HTA bodies favour robust, objective and measurable patient-based

evidence over individual patient anecdotes and surveys etc, they consider it is up to patient organisations to determine how they collect data and provide feedback to agencies. EMA guidance to patient organisations on how they -generate evidence should develop organically as EMA acquires more and more experience with product evaluations. It is an iterative process with patient organisations playing an influencing role within that process.

The EMA and European HTA bodies do not suggest any methodologies on how patient organisations can generate data, but acknowledge that data published in peer reviewed journals is considered robust. Early data submission in the assessment process from a large pool of patients, presented in a structured way, is the most helpful to the EMA and HTA bodies. Interviewed European HTA and regulatory representatives confirmed they prefer quantitative over qualitative patient-based evidence.

4. While the EMA and the European HTA agencies mandate survival data collection, they mostly recommend the provision of PROs to contextualise unmet needs and the treatment pathway.

The European Public Assessment Reports (EPAR) of Kymriah[15] and Yescarta[16] showed the absence of submitted PROs did not impact EMA's decision-making. The EMA has since placed increasing importance on PROs as complementary to other clinical data regarding novel oncology therapies,[17] especially as PROs are crucial for assessing tolerability and comparative effectiveness.[11]

The EMA and European HTA agencies acknowledge they need to hear from organisations other than manufacturers on what the data means and why certain improvements in survival are important. However, it is not clear how PROs are considered in decision-making. As a result, in September 2022, the EMA organised a multi-stakeholder patient experience data workshop to initiate a discussion about how PRO, patient preferences and patient-based evidence should be gathered by different stakeholders and considered in decision-making.

PROs are factored in the EMA's benefit-risk analysis, but they hold less weight than key endpoints such as overall survival, progression-free survival and safety. Similarly, although the Italian Medicines Agency considers positive PROs as an equal criterion to disease-free intervals in the evaluation of a product's therapeutic added value, improvements in overall survival, progression-free survival and safety remain the key decision-making criteria.[18, 19]

Table 1: Patient-reported outcomes data collection in CAR-T cell therapy trials

CAR-T cell therapy	Study objectives and PRO tools	PRO collection schedule and compliance rates	Results/assessments
Kymriah (tisagenlecleucel)[20, 21, 22] **Indication:** Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. [09/2018] **Study:** JULIET, single-arm, open-label, international, multicentre phase II.	Secondary endpoints • Functional Assessment of Cancer Therapy-Lymphoma (FACT-lym) • Short Form-36 (SF-36)	• Baseline: 108/115 (94%) • Month 3: 47/62 (76%) • Month 6: 35/43 (81%) • Month 12: 31/36 (86%) • Month 18: 22/34 (65%)	PROs results • 115/167 treated patients • 60/115 achieved complete or partial response • 108/115 completed QoL assessments (of which 57 achieved complete or partial response) • Overall, patients' HRQoL deteriorated from baseline, with only minimal improvement throughout the study
Kymriah (tisagenlecleucel) [20, 21, 22] **Indication**: 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. [09/2018] **Study**: ELIANA, single-arm, open-label, international, multicentre, phase II.	Prespecified secondary endpoints • PedsQL • EQ-5D-VAS (EQ-5D-Y for patients aged 8–12 years), and EQ-5D-3L for patients aged 13 years or older)	Baseline • 50/58 (86%) for PedsQL • 48/58 (83%) for EQ-5D VAS At day 28 • 37/48 responders (77%) for PedsQL & EQ-5D-VAS • 6/10 non-responders (60%° of non-responders for PedsQL • 7/10 non-responders (70%) for EQ-5D VAS PROs also collected at months 3, 6, 9 and 12 after treatment.	PROs results • 92 enrolled patients, 75 treated patients, 58 patients aged 8-23 included in the analysis of QoL (48 responders and 10 non-responders) • Small clinically meaningful improvement in HRQoL: • Improvement observed for all QoL measures after 3 months of infusion: among the 48 responders, the mean (SD) change from baseline in the PedsQL total score was 13.5 (13.5) at month 3, 16.9 (17.6) at month 6 and 27.2 (21.7) at month 12, and the mean (SD) change from baseline in the EQ-5D VAS score was 16.5 (17.5) at month 3, 15.9 (20.1) at month 6 and 24.7 (18.6) at month 12

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CAR-T cell therapy	Study objectives and PRO tools	PRO collection schedule and compliance rates	Results/assessments
Kymriah (tisagenlecleucel) [23] Adult patients with follicular lymphoma (FL) after 2 or more lines of therapy that are refractory, or have relapsed during or within 6 months after completion of anti-CD20 antibody maintenance, or relapsed after autologous haematopoietic stem cell transplantation. (HSCT) [05/2022]	• FACT-Lym • SF-36v2 • EQ-5D-3L	• Baseline • Month 3 • Month 6 • Month 9 • Month 12 • Month 18 • Month 24	FACT Lym and SF-36 scores showed improvement in QoL over time in the majority of patients post-infusion. FACT Lym - minimal clinically-important differences (MIDs) • From 5.5 to 11 for the FACT-Lym TOI • From 6.5 to 11.2 for the FACT-Lym total score • From 3 to 7 for FACT-G • From 2.9-5.4 for FACT-Lym-S SF-36 - MIDs • 3 for physical component score (PCS) • 3 for mental component score (MCS) EQ-5D-3L • At month 12, scores were similar to baseline with no evidence of deterioration EQ-VAS (visual analog scale) mean scores indicated an overall improvement in HRQoL • Baseline: 69.4 (mean score) • Month 6: 72.9 • Month 12: 75.3

Table 1: Patient-reported outcomes data collection in CAR-T cell therapy trials

CAR-T cell therapy	Study objectives and PRO tools	PRO collection schedule and compliance rates	Results/assessments
Yescarta (axicabtagene ciloleucel)[24, 25, 26,] **Indication:** In adults, relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL) after 2or more lines of systemic therapy. [06/2018] **Study:** ZUMA-1, single arm, multicentre phase I/II.	Secondary/exploratory endpoint • EQ-5D scores in cohort 3 of ZUMA-1 No assessment of quality of life was planned in cohorts 1 and 2 of phase II of the ZUMA-1 study.	• Baseline • Month 6	• No data/evidence was reported in the EPAR assessment report • The French HTA agency pointed out that only preliminary data from cohort 3 is available • Not all patients in this very small patient population were assessed on QoL, but cohort 3 featured different patient characteristics from ZUMA-1's cohorts 1 and 2 (disease and advanced stage), making any change over time difficult to interpret
Yescarta (axicabtagene ciloleucel or axi-cel)[26, 27, 28] **Indication:** In adults: relapsed or refractory follicular lymphoma (FL) after 3or more lines of systemic therapy. [07/2022] **Studies:** • ZUMA-5, single arm multicentre phase II • SCHOLAR-5, international, multicentre, retrospective external control cohort (supportive study)	SCHOLAR-5 - Exploratory objective • Description of patients' QoL based on available PROs ZUMA-5: no planned QoL analysis.	N/A	The French HTA agency considers that the impact of axicabtagene ciloleucel or axi-cel on QoL could be not demonstrated.

Table 1: Patient-reported outcomes data collection in CAR-T cell therapy trials

CAR-T cell therapy	Study objectives and PRO tools	PRO collection schedule and compliance rates	Results/assessments
Yescarta (axicabtagene ciloleucel)[29, 30, 31] **Indication:** Adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphom-a (HGBL) that relapse within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy. [12/2022] **Study:** ZUMA-7, phase III randomised, open-label, multicentre.	Secondary study objective • Changes in EQ-5D 5L and VAS scores	Number of patients included in the QoL analysis • Axi-cel 165 (92%) • Standard of care: 131 (73%) • Overall: 296 (82%) EORTC QLQ-C30 & EQ-5D-5L VAS • Baseline • Day 100 • Day 150	Reported EQ-5D-5L VAS data • Comparable baseline mean EQ-5D-5L VAS scores: axi-cel (72.4 [95% CI: 69.5, 75.2]) and SoC (74.4 [95% CI: 70.9, 77.9]) • Statistically significant and clinically meaningful difference in the mean change of scores from baseline to Study Day 100 in favour of axi-cel: 13.7 [95% CI: 8.5, 18.8]; adjusted p < 0.0001 • Statistically significant and clinically meaningful difference in the mean change of scores from baseline to Study Day 150 in favour of axi-cel: 11.3 [95% CI: 5.4, 17.1]; adjusted p = 0.0004) Reported EORTC data • Comparable baseline mean EORTC QLQ-C30 global health status scores: axi-cel (68.6 [95% CI: 65.6, 71.7]) and SoC (70.1 [95% CI: 66.1, 74.1]) • Statistically significant and clinically meaningful difference in the mean change of scores from baseline to Study Day 100 in favour of axi-cel: (18.1 [95% CI: 12.3, 23.9]) adjusted p < 0.0001

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CAR-T cell therapy	Study objectives and PRO tools	PRO collection schedule and compliance rates	Results/assessments
			Despite those results, the Canadian Agency for Drugs and Technologies in Health (CADTH) considered that the findings were uncertain due to the large amount of missing data which was imbalanced between the groups. It is thus unclear, based on this data, if axi-cel affords better HRQoL compared to SOC in patients with relapsed or refractory DLBCL. The French HTA agency considered PRO data as exploratory. It nonetheless approved axi-cel for early access.
Tecartus (brexucabtagene autoleucel)[32, 33] **Indication:** Relapsed or refractory mantle cell lymphoma in adults after 2or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor [01/2021]. **Study:** ZUMA-2, phase II single-arm, open-label, international, multicentre.	Secondary endpoint • Changes in EQ-5D & visual analog scale (VAS) scores	• Baseline • Month 6	Reported VAS median score • At screening: 85.0 (range: 45 to 100) • Week 4: 78.0 (range: 38 to 100) • Month 3: 83.0 (range: 40 to 100) • Month: 90.0 (range: 20 to 100) Proportion of patients with a decrease of ≥ 10 points in VAS scores relative to screening • Week 4: 50% • Month 3: 29% • Month 6: 12%

Table 1: Patient-reported outcomes data collection in CAR-T cell therapy trials

CAR-T cell therapy	Study objectives and PRO tools	PRO collection schedule and compliance rates	Results/assessments
			Reported EQ-5D data • At screening: patients reporting no health problems across all 5 domains ranged from 66% to 95% (mobility, 85%; self-care, 95%; and usual activity, 82%) • Month 3: increases in HRQoL of ≥ 16 percentage points • Month 6: proportion of subjects reporting more severe problems for mobility, self-care and usual activities relative to screening improved significantly While very welcome on a principle level, both the EMA and the French HTA agency consider that interpretation of EQ-5D and VAS data is hampered by a lack of control and an open label design. Despite a lack of relevant QoL data, the French HTA agency approved it for reimbursement due to very relevant efficacy data.
Tecartus (brexucabtagene autoleucel) [34] **Indication:** Adult patients with relapsed or refractory (r/r) B-cell acute lymphoblastic leukaemia. (B-ALL) adult patients with relapsed or refractory (r/r) B-cell acute lymphoblastic leukaemia. (B-ALL) [12/2022] **Study:** ZUMA-3, Phase 1/2 multicentre study.	Secondary endpoint • Change in EQ-5D scores	N/A	Not available in January 2023.

Table 1: Patient-reported outcomes data collection in CAR-T cell therapy trials

CAR-T cell therapy	Study objectives and PRO tools	PRO collection schedule and compliance rates	Results/assessments
Abecma (idecabtagene vicleucel or ide-cel) [35] [36, 37, 38] **Indication:** Relapsed or refractory multiple myeloma in adults, who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy. **Study:** MM-001 - KarMMa study, open label single arm, international, multicentre phase 1/2 study.	Secondary endpoints HRQoL changes in EORTC QLQ-C30, EORTC QLQ-MY20 and EQ-5D	PRO collection schedule • Screening • Baseline • Day 1 Months 1 to 6, then every 3 months up to 24 months or until study completion. Completion rates nearly identical across HRQoL questionnaires • Baseline (98%) • Months 1 to 6: to 70% to 90% • Months 9 & 12: (60%-70%) Results reported until month 15 since few subjects (>10) had responded to the questionnaires after month 15.	According to the EMA, the argument that ide-cel offers a major contribution to patient care over other approved therapies and further support significant benefit of ide-cel in MM is currently not considered supported by the available HRQoL data from the pivotal study MM-001. Only five domains from the EORTC QLQ-C30 (Fatigue, Pain, Physical Functioning, Cognitive Functioning and Global Health/QoL) and two subscales of the EORTC QLQ-MY20 (Disease Symptoms and Side Effects) were analysed. • EORTC QLQ-C30 Fatigue and Pain subscale scores: clinically meaningful decreases (improvement) in mean scores from baseline to month 9 • EORTC QLQC30 Physical Functioning subscale score and the Global Health/QoL domain: clinically meaningful increase (improvement) in mean score from baseline were seen • EORTC QLQ-MY20 Side Effects subscale score: gradual increase (deterioration) in mean scores observed from baseline to month 9, though statistically not significant nor clinically meaningful • EORTC QLQ-MY20 Disease Symptoms subscale score: small clinically meaningful decreases (improvements) observed from baseline to months 4 through 15 post-treatment • EORTC QLQ-C30 Cognitive Functioning subscale scores: stability from baseline to month 9 and beyond with baseline mean scores close to that of the general population. The applicant has compared the baseline scores on the EORTC QLQ-C30 and EORTC QLQMY20 domains only with the scores for the general population (Nolte, 20192). Since no data for comparison of HRQoL in RRMM patient treated with standard of care is provided, contextualisation of the HRQoL data based on this single arm study is limited

Table 1: Patient-reported outcomes data collection in CAR-T cell therapy trials

CAR-T cell therapy	Study objectives and PRO tools	PRO collection schedule and compliance rates	Results/assessments
Carvykti (ciltacabtagene autoleucel or cilta-cel)[39] **Indication:** Relapsed or refractory multiple myeloma in adults, who have received at least 3 prior therapies, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 antibody, and have demonstrated disease progression on the last therapy. **Study:** MMY2002-CARTITUDE-1: open-label, single arm, phase 1b/2.	Secondary endpoints • Changes in HRQoL after treatment • Sustained benefit of subject's perceived HRQoL • PROMs used: • EQ-5D-5L • EORTC QLQ-C30 • EORTC QLQ-MY20 • Patient Global Impression of Change (PGIC) • The Patient Global Impression of Severity (PGIS)	Compliance for the EORTC QLQ-C30 • Baseline: 92.6% • Day 100: 83.1% • Declined in the post-treatment follow-up phase (for the most part due to COVID-19 pandemic restrictions)	Patients achieving meaningful change in EORTC QLQ-C30 Day 28 • Physical functional scale: 13/56 (23.2%) • Global health status scale: 28/56 (50.0%) • Pain symptom scale: 28/56 (50.0%) • Fatigue symptom scale: 21/56 (37.5%) Day 56 • Physical functional scale: 31/56 (56.4%) • Global health status scale: 35/56 (63.6ù) • Pain symptom scale: 22/56 (40.0%) • Fatigue symptom scale: 29/56 (52.7%) Day 78 • Physical functional scale: 28/56 (56.0%) • Global health status scale: 33/56 (66.0%) • Pain symptom scale: 23/56 (46.0%) • Fatigue symptom scale: 32/56 (64.0%) Day 100 • Physical functional scale: 30/56 (57.0%) • Global health status scale: 29/56 (53.7%) • Pain symptom scale: 39/56 (72.2%) • Fatigue symptom scale: 28/56 (53.8%)

Table 1: Patient-reported outcomes data collection in CAR-T cell therapy trials

CAR-T cell therapy	Study objectives and PRO tools	PRO collection schedule and compliance rates	Results/assessments
			GHS and physical functional subscales • Decline in scores between day 1 and day 7 consistent with the onset of cilta-cel adverse events • Improvements around day 28 with steady increase through day 352 Pain symptom subscale • Overall reduction in pain severity starting at day 7 through day 352 Fatigue symptom subscale • Initial increase in fatigue at day 7 consistent with the onset of cilta-cel related adverse events • Overall reduction through day 352 Day 7 • Restless or agitated: 41/57 (71.9%) • Thinking about illness: 15/57 (26.3%) • Worrying about dying: 20/57 (35.1%) • Worrying about health in the future: 15/57 (26.3%) • Future perspective scale: 28/57 (49.1%) Day 28 • Restless or agitated: 50/55 (90.9%) • Thinking about illness: 21/55 (38.2%) • Worrying about dying: 19/55 (34.5%) • Worrying about health in the future: 23/55 (41.8%) • Future perspective scale: 33/55 (60.0%)

Table 1: Patient-reported outcomes data collection in CAR-T cell therapy trials

CAR-T cell therapy	Study objectives and PRO tools	PRO collection schedule and compliance rates	Results/assessments
			Day 56 • Restless or agitated: /55 (81.8%) • Thinking about illness: /55 (47.3%) • Worrying about dying: /55 (38.2%) • Worrying about health in the future: /55 (41.8%) • Future perspective scale: /55 (60.0%) Day 78 • Restless or agitated: 40/49 (81.6%) • Thinking about illness: 25/49 (51.0%) • Worrying about dying: 20/49 (40.8%) • Worrying about health in the future: 26/49 (53.1%) • Future perspective scale: 36/49 (73.5%) Day 100 • Restless or agitated: 43/53 (81.1%) • Thinking about illness: 27/53 (50.9%) • Worrying about dying: 22/53 (41.5%) • Worrying about health in the future: 17/53 (32.1%) • Future perspective scale: 35/53 (66.0%) • Improvement starting at Day 7 and continuing to show positive improvement through Day 380

Table 1: Patient-reported outcomes data collection in CAR-T cell therapy trials

CAR-T cell therapy	Study objectives and PRO tools	PRO collection schedule and compliance rates	Results/assessments
Breyanzi (lisocabtagene maraleucel or liso-cel) [10,40, 41] **Indication**: Relapsed or refractory DLBCL PMBCL and FL grade 3B (FL3B) in adults, after 2 or more lines of systemic therapy. **Studies:** • 017001 – TRANSCEND, single arm, open label, multicentre • BCM-001 (Cohorts 1 and 3)	Secondary endpoint HRQoL changes in EORTC QLQ-C30, EQ-5D-5L and FACT-LymS (only in BCM-001=	Of the 269 DLBCL treated subjects in study 017001 • 181 were evaluable for EORTC-QLQ C30 • 186 were evaluable for EQ-5D-5L PRO collection schedule • Baseline • Month 1 (day 29), 3, 6, 9, 12 and 18 after treatment Compliance rates in evaluable population for EQ-5D-5L • Month 9: (65.6%) • Month 18: (65.8%)	Study 017001 Mean scores at baseline • EQ-5D-5L: 0.8 • EQ-VAS: 68.3 EORTC QLQ-C30 analysis • Improvement in global health status starting from month 2 post-infusion • Improvement in fatigue starting from month 9 post-infusion. Other HRQoL domain scores remained stable up until month 18 Study BCM-001 • Comparable baseline scores The French HTA agency considered that PRO data was considered exploratory due to the open-label and uncontrolled nature of studies. It nonetheless approved liso-cel for early access.

5. Survival has taken precedence in decision-making over HRQoL in the last lines of therapy.

Although HRQoL have become increasingly important in differentiating treatment options, especially for conditions in which refractory disease is common and/or PFS is short,[9] European regulators' and HTA agencies' primary focus is on survival data. HRQoL has been, until now, secondary to efficacy regardless of the technology or disease area assessed. Although the purpose of regulatory assessments differs from that of reimbursement assessments (i.e., deciding whether there is a positive benefit-risk balance vs. making funding decisions), more importance in both processes should be given to patient-based data collection, including HRQoL.

The fact that CAR-T cell therapies have so far been indicated in patients that have exhausted all treatment options may have impacted on HRQoL and other PROs collection during clinical development of some CAR-T cell therapies.

6. Patient preferences have had limited scope in last lines of therapy but will grow in importance as CAR-T cell therapies are indicated in earlier treatment lines and when second-generation CAR-T cell therapies are available.

Patient preference studies have not been used in heavily pre-treated settings, the assumption being that patients always prefer survival and will accept the risks of treatment. Arguably more studies are required to show how patients make decisions and what they value in terms of benefits and risks. For example, the side-effect profile of some CAR-T cell therapies and other treatments might be such that they would prefer palliative care, participation in a different clinical trial, or rescue treatment.

When CAR-T cell therapies are offered earlier in the treatment pathway, they will be compared to more therapeutic options. There will therefore be more scope to hear what patients think of the benefits, risks and trade-offs of CAR-T cell therapies vs. standards of care.

7. Current PRO questionnaires may not be adequate to capture the HRQoL impact of CAR-T cell therapies.

Because there are no specific validated PRO questionnaires for CAR-T cell therapy, previously validated questionnaires, such as the EORTC QLQ-C30, FACT-General10 and EQ-5D, have been used in clinical trials to assess general health status. The literature review shows that patient-reported experiences with CAR-T cell therapy are limited and have not been well characterised. It is possible that a CAR T-therapy-specific questionnaire would be needed to assess the impact of treatment-related toxicities such as CRS and neurotoxicity side effects. Given the uniqueness of its toxicity profile, the specific side-effects and their impact on HRQoL are unlikely to be covered in just one questionnaire.[9]

Patient organisations believe that the current PRO questionnaires mentioned above are not adapted to capture patient HRQoL with CAR-T cell therapies. These questionnaires were developed when the mainstay of the treatments was continuous chemotherapy, while CAR-T cell therapy is a single infusion. Current PRO questionnaires are not adequate to capture novel side effects and patient experience, such as CRS, neurotoxicity, recovery and psychological patient status post CAR-T cell therapy (especially after failure of the production process or the absence of remission post-treatment). Side-effects make it very challenging for patients to answer any questionnaires for several weeks post-infusion. Data related to extreme situations are not adequately captured with current PRO questionnaires: the voices of those who died after receiving CAR-T cell therapies are not factored in,[20, 37, 42] while the experiences of super-

responders are not recorded accordingly. The literature review also highlighted that there is variation in the time-points in which PROs are documented across studies, making it very difficult for regulatory and HTA decision-making.

Patient organisations currently face a decision – should they push for agreement on a standardised way of measuring HRQoL in CAR-T using existing PRO questionnaires? If so, what does this approach look like? Should they push for a CAR-T specific PRO tool to be validated and used? Regardless of the chosen strategy, consistency in measurement (and the timepoints of measurements) is important.

8. Most manufacturers of first-generation CAR-T cell therapies did not make it compulsory for investigators to have their patients fill PRO questionnaires.

PRO data collection was at best partial in most CAR-T cell development programmes. For example, in the JULIET study investigating Kymriah, the HRQoL was assessed using the FACT-Lym and SF-36 questionnaires. For both questionnaires, the return rates were below 70% during the course of the study. The German Federal Joint Committee (G-BA) therefore considered them to be unusable.[43] Additionally, only nine Kymriah clinical non-responders completed the FACT-Lym S questionnaire at month three, while none of the clinical non-responders completed the questionnaire during subsequent visits at months six, 12 and 18).[44] Even in the case of the more recently approved Breyanzi, the manufacturer chose a PRO analysis based on response to treatment, which was limited by the small number of non-responders completed assessments at later time points. Only five treatment non-responders included in the EORTC QLQ-C30–evaluable population remained on the study at 12 months and only one treatment non-responder remained at 18 months.[10] This explains in part the lack of submitted PROs in European regulatory and HTA submissions.

The fact that more and more HTA bodies mandate manufacturers to request investigators to implement PRO data collection will improve data availability and quality. For example, the French National Authority for Health now requires manufacturers to commit to collecting PROs once they are granted an early access programme.

9. CAR-T cell therapy is a two-person journey and there is a potential for caregiver-reported outcomes questionnaires.

Like bone marrow and stem cell transplant, receiving CAR-T cell therapy requires a caregiver to accompany and assist patients throughout their treatment. There is a role for caregivers to report outcomes when severe toxicity impedes patients from completing PRO questionnaires. Caregivers have a more objective opinion than the patient themselves. Alternatively, haematology nurses must be involved when patients are not able to communicate effectively. Caregivers also play a vital role in the well-being of patients treated with CAR-T cell therapies and their HRQoL should also be taken into consideration when evaluating treatment outcomes.

10. Despite PRO questionnaires not always being fit-for-purpose for patients treated with CAR-T cell therapies, there is a need for PROs to be measured in a more standardised fashion by academic and industry researchers throughout the product lifecycle.

PRO data collection should begin as early as possible in clinical trials and continue post-marketing authorisation and beyond reimbursement decisions. Patient input should be involved in the selection of questionnaires and the frequency of administration.

The question asked in a Phase I trial is not whether it works, but at what dose does it work. PROs inform whether efficacy and safety endpoints are met. The collection of PROs in clinical trials is crucial for assessing the tolerability and comparative effectiveness of CAR-T cell therapies.[12] Any Phase II trials could have PROs as a co-primary endpoint along with overall survival and progression-free survival, rather than as a secondary endpoint. At the very least, PROs should be collected in trials intended to support European regulatory and reimbursement decisions. The lack of consistency regarding the use of PRO questionnaires, the time-points at which patients fill those questionnaires and the statistical design to handle missing data is a major challenge for interpreting PROs.[45]

11. Real-world data (RWD) is important to help understand the impact of CAR-T cell therapy outside of clinical trials and to support European regulatory and reimbursement approvals.

The French DESCAR-T registry was set up to collect RWD before the EBMT set up its own CAR-T registry.[7] DESCART collects not only effectiveness and safety data, but also PROs. It feeds into the EBMT CAR-T registry, which does not make the collection of PROs mandatory. As a result, the European blood cancer community does not have any data to show whether the new generation of CAR-T cell therapies is doing better than the first generation.

EMA and national reimbursement / HTA bodies are increasingly requiring the collection of RWD to support schemes such as conditional approval and outcomes-based reimbursement schemes. Whilst this approach is important, consistency and guidance on the collection of RWD is crucial to ensure it is done uniformly and minimises the administrative burden for healthcare systems.

Patient-based evidence should be captured both in drug development and in the real-world setting to inform European regulatory and reimbursement approvals. Likewise, collecting RWD is key as patient experience in clinical practice may differ from the clinical trial setting. This is due in part to the fact that leading centres of excellence are the ones where CAR-T cell therapies are administered during clinical trials. Centres of excellence are better equipped and have more available qualified staff than regular transplant and cellular therapy hospitals. Also, patient populations often differ in both settings due to frequent stringent exclusion criteria in a clinical trial setting.

12. Patient organisations' access to manufacturers' dossiers is even more important in the assessment of technologies, such as CAR-T cell therapies, as it is challenging to identify and survey in due time the very few patients that received such innovative treatments.

The capacity of patient organisations to access manufacturers' dossiers - or at least the part that deals with PROs - is critical for them to efficiently contextualise data. This is especially important as it is difficult to obtain feedback from such a small number of treated patients. For example, there was only one UK patient that had experienced Yescarta at the time of NICE's assessment for reimbursement, which made it difficult for patient organisations to collect patient insights.

13. Even in countries such as France and the UK where patient involvement processes have been more institutionalised, patient organisations felt that patient-generated evidence did not influence the decision-making on CAR-T cell therapies.

The EMA, UK and French HTA bodies do not always provide any feedback on the impact of patient-generated evidence on decision-making. It has been, therefore, difficult for patient organisations to see how their contribution influenced decision-making. There have been very few cases where patient-generated evidence made the EMA reconsider its decision. Regulatory assessment of CAR-T cell therapies is not one of them. In countries where patient involvement is less structured, it has been even more challenging. In Italy, for example, although there isn't any formal patient involvement, patient organisations can theoretically take part to the hearing of AIFA's Technical Scientific Committee.[46]

3. RECOMMENDATIONS ON PATIENT-BASED EVIDENCE REQUIREMENTS

Based on our key takeaways, here are recommendations to help stakeholders better prepare for integrating patient-based evidence in future European regulatory and reimbursement assessments of CAR-T cell therapies.

1. Clear and detailed guidance should be provided to ensure the patient-based evidence generated by the industry is adequately robust to be included in the decision-making process, in decision documents (for ex. EPAR) and, where appropriate, in the product information.[13]

The adequate collection and analysis of PROs and RWD are critical to properly support drug development and access.

2. Patient organisations are encouraged to secure resources, where possible, to organise their own data collection and be developers of scientifically validated methodologies.

To support patient involvement in regulatory and HTA decisions in CAR-T cell therapies and other drug assessments, ongoing data collection is key to meaningfully contribute to drug evaluations. Running ad hoc surveys on treatments under evaluation, but also a yearly survey on the patient treatment pathway, means patient organisations would be equipped when consulted during drug appraisal.

Patient organisations can also be a driving force for generating criteria on how they should collect and analyse data. They should collaborate with scientific societies such as EHA, EBMT and ESMO to define those criteria in haemato-oncology. Furthermore, patient organisations should secure resources from other stakeholders for training in evidence generation at the right timepoints. Patient organisations

could use the power of digital solutions to collect data and generate evidence in patient populations that do not experience digital divide (i.e., younger patient populations).

3. Clear guidance and feedback to patient organisations from European regulatory and HTA bodies on what constitutes robust and useful data to support their decision-making are needed.

Patient organisations should call for European regulatory and HTA agencies to provide guidance on the type of data they can collect, and the methodology they should use, to be considered as strong evidence. Until there is guidance clearly specifying what patient-based evidence/QoL should be collected, it will not be considered as a major endpoint of the benefit-risk balance.

4. Multi-stakeholder collaborative efforts to support patient organisations in generating patient-based evidence should be fostered.

Patient organisations are encouraged to team up with haematologists to inform the patient contribution questionnaire. The example of the French lymphoma patient organisation ELLyE is of particular interest. When the French National Authority for Health invites ELLyE to contribute to the assessments of lymphoma drugs, they contact investigators of ongoing Phase III trials and managers of early access programmes for the drug under evaluation, and ask them to invite treated patients to fill the standard French National Health Authority for Health's patient contribution questionnaire.

In addition to generating their own data, patient organisations should investigate ways to work with registries and research networks to access CAR-T patient-based evidence.

5. Increasing the number of publications on patient-generated evidence should be a goal common to all stakeholders.

Patient organisations should, as much as possible, be constant about publishing the data they generate, as it is critical patient organisations be perceived as a robust source of evidence at the same level of other sources of evidence. The involvement of experts to validate patient-generated data would support this goal. Until patient organisations' publishing capacities are increased, it is also important to acknowledge the importance of unpublished data gathered by patient groups, which is still valid.

6. The selection of PROMs and the collection of other patient-based evidence should be made with the early involvement of patients.

Industry and European HTA bodies should engage early and consistently with patient stakeholders (patient advocates, patient representatives, or patients with lived experience and knowledge of drug development and trial design) throughout the lifecycle at any point when a significant decision is made. There is a need for more transparency along the treatment pathway. Patient organisations need to be consulted on the design of clinical trials and on the way in which the impact on QoL will be measured and collected within the framework of this clinical trial.

7. Agreement is required on how best to use existing PRO questionnaires or how PRO questionnaires should be adapted to the CAR-T cell therapy patient experience. The need for a caregiver questionnaire should be explored. The fact they may complete a PRO questionnaire on behalf of a patient during the acute phase of CAR-T cell therapy should also be discussed.

There is a need for PRO collection to be adapted to innovative therapies, such as CAR-T cell therapies, which bring new, specific side-effects and problems. To avoid "questionnaire fatigue" especially in the acute phase, optimising our use of existing PRO questionnaires or designing optimal questionnaires that are reliable and pose minimal burden to patients is important. Due to the feasibility for patients to answer PRO questionnaires in the acute phase, it is critical to capture auxiliary data via caregivers and/or nurses to supplement PROs at missing time points. Additionally, there is growing interest in measuring caregivers' HRQoL, thanks to which better support for caregivers and patients can be provided.[10]

8. Clear guidelines on the frequency of PRO administration should be set and adapted to capture and characterise short-term as well as long-term safety with CAR-T cell therapy.

The literature suggests to routinely capture PROs at baseline, i.e., at the initiation of a clinical trial, to identify pre-existing deficits in HRQoL (such as high psychosocial distress, poor physical functioning, or high symptom burden). PRO questionnaires should then be administered at least weekly during the first month,[37] using PRO questionnaires with short recall memory questions, as acute toxicities are expected during that period.[7] PRO assessments should then be measured monthly up to one year, and yearly thereafter, to identify potential late effects such as residual cognitive deficit, auto-immune manifestations, and also long-term physical and psychological effects.[11, 12, 45] Clear guidelines to ensure consistency in clinical trials and clinical practice should also be issued, alongside agreement on the PRO questionnaires that are best used to do this.

9. All sponsors should ensure that clinical trial personnel be trained on PRO administration and how to optimise data compliance in real time to limit the generation of significant missing data.

The barriers to implementation of PRO questionnaires have been broadly divided into two categories: logistical and technological issues. It requires engagement of physician and ancillary staff along with a smooth operational workflow. Designing a strategy for handling missing data is crucial.[11]

10. All stakeholders should invest more efforts and resources in RWD collection either via managed entry agreements or through patient registries.

Health authorities and clinicians should develop guidance and arrangements, such as the EBMT CAR-T registry, for consistent and continuous RWD collection to improve CAR-T cell therapy delivery and ultimately clinical and patient outcomes. RWD should always include PROs.

Countries like Italy could also expand the current purpose of their existing patient registries beyond that of cost control via managed entry agreements. To that end, the industry should be more systematic in collecting clinical data, including PROs, as part of their managed entry agreement with the Italian national health system.

European clinicians are encouraged to follow the example of their Austrian counterparts, who continuously monitor their clinical practice with a view to optimise the delivery of CAR-T cell therapies. According to a patient organisation interviewed for this study, the outcomes in Austria are notably better than in any other country in Europe.

11. More transparency on data submitted, debates and how evidence is used to inform assessments decision-making of CAR-T cell therapies is needed to ensure clinically meaningful and patient relevant decisions.

Per a signed confidentiality agreement, regulators and HTA bodies should give patient organisations access to all or part of the manufacturer dossier and invite them to attend the entirety of hearings and debates.

It is important to understand when patient-based evidence was provided and how it was used in decision making. Such information would help inform sponsors and patient groups to collect and submit input likely to be most valuable and relevant to decision-makers. A report published by the FDA revealed that 30% of the 176 regulatory approvals issued between June 2017 and June 2020 mentioned patient experience data in the labelling. Applicants commented that the evidentiary standards for including patient-based evidence in labelling are unclear and that patient-based evidence does not often appear in labelling, except in some instances where specific PROs or other COAs contributed to product approval.[13] As for the European regulatory approvals of CAR-T cell therapies, patient-based evidence has so far been reported in EPAR assessment reports, but not in the EPAR product information document (see Table 1).

Patient organisations call for regulators and HTA bodies to tell them the strengths and weaknesses of their contributions, so that they best use their time and experiential knowledge to support future decision-making.

12. More patient preference data is needed to understand how patients make decisions on the benefits and risks of treatments.

Patient preference data should not only be collected in earlier treatment lines; it is also critical to characterise what heavily pre-treated patients want. Coordination of this type of patient data, agreeing the questions that need answering and prioritising within disease areas is important to ensure a strategic approach. This can potentially be led by the patient community in collaboration with other stakeholders.

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APPENDICES

APPENDIX 1: GLOSSARY

- **Cytokine release syndrome (CRS):** a systemic inflammatory condition that appears as a flu-like illness and includes symptoms such as fever, fatigue, nausea, headache, dyspnea, tachycardia, and in severe cases, seizures or death.
- **Neurotoxicity:** also known as immune effector cell-associated neurotoxicity syndrome (ICANS), may appear as confusion, lethargy, headache, agitation, and in rare but severe cases, seizures death
- **PedsQL :** a standardised, generic assessment of health-related perceptions of QoL in paediatric patients. The PedsQL consists of emotional, social, and school functioning subscale scores (five items each); physical (eight items) and psychosocial health summary scores; and a total score (sum of all the items over the number of items answered on all the scales). All PedsQL scores range from 0 to 100, with higher scores indicating better QoL.
- **DESCAR-T registry:** French national registry for patients with hematological malignancies, eligible for CAR-T cell therapy

APPENDIX 2: LITERATURE SEARCH

To identify relevant literature in PubMed, a 'PICOS' strategy was used, with clear definitions of the study population of interest (P), interventions of interest (I), comparators of interest (C), outcomes of interest (O), and study design of interest (S) – see Table 1. The PubMed search strategy that was conducted is presented in Table 2.

Table 1. Literature Review Scope - Inclusion and Exclusion Criteria

PICOS	Inclusion criteria	Exclusion criteria
P - Populations of interest	❑ Patients with myeloma, lymphoma or AML ❑ Special attention will be given to patients with myeloma	❑ Not population of interest
I & C - Interventions and comparators of interest	❑ Collection of patient-based evidence for CAR T cell therapies during or after a clinical trial	❑ Not the intervention of interest
O - Outcomes of interest	❑ Patient-reported outcomes ❑ Real-world evidence, real-world data, Quality of life, health-related quality of life ❑ Patient experience	❑ Efficacy ❑ Safety and management of side effects ❑ Manufacturing
S - Study design of interest	❑ Studies reporting the outcomes of interest	❑ Studies not reporting the outcomes of interest

Table 2. Literature Review - Search Strategy for PubMed

Search N°	ID	Search terms
P – Populations of interest: hematologic cancers / AML / MM /Lymphoma	1	(("hematologic cancer"[Title/Abstract]) OR ("Neoplasms, hematological"[MeSH Terms]) OR ("hematological malignancies"[Title/Abstract]) OR ("hematological cancer"[Title/Abstract]) OR ("Multiple myeloma"[MeSH Terms]) OR ("Myeloma"[Title/Abstract] OR ("lymphoma"[Title/Abstract]) OR ("lymphoma"[MeSH Terms]) OR ("leukemia"[Title/Abstract]) OR ("leukemia"[MeSH Terms]))
I & C - Interventions and comparators of interest: CAR-T	2	(("Antigen Receptor, T-Cell"[MeSH Terms]) OR ("chimeric antigen receptor"[Title/Abstract]) OR ("immunotherapy, adoptive"[MeSH Terms]) OR ("CAR T"[Title/Abstract]) OR ("CAR-T"[Title/Abstract]) OR ("immunotherapy, adoptive"[MeSH Terms]) OR ("CARVYKTI"[Title/Abstract]) OR ("ciltacabtagene autoleucel"[Title/Abstract]) OR ("cilta-cel"[Title/Abstract]) OR ("tisagenlecleucel"[Title/Abstract]) OR ("tisa-cel"[Title/Abstract]) OR ("Kymriah"[Title/Abstract]) OR ("axicabtagene ciloleucel"[Title/Abstract]) OR ("axi-cel"[Title/Abstract]) OR ("Yescarta"[Title/Abstract]) OR ("Idecabtagene vicleucel"[Title/Abstract]) OR ("Ide-cel"[Title/Abstract]) OR ("Abecma"[Title/Abstract]) OR ("brexucabtagene autoleucel"[Title/Abstract]) OR ("brexu-cel"[Title/Abstract]) OR ("Tecartus"[Title/Abstract]) OR ("lisocabtagene maraleucel"[Title/Abstract]) OR ("liso-cel"[Title/Abstract]) OR ("BREYANZI"[Title/Abstract]))
O - Outcomes of interest: regulatory approval or reimbursement process	3	(("drug approval"[MeSH Terms]) OR ("european medicines agency"[Title/Abstract]) OR ("EMA"[Title/Abstract]) OR ("Medicines and Healthcare products Regulatory Agency"[Title/Abstract]) OR ("MHRA"[Title/Abstract])) OR (("Costs and Cost Analysis"[MeSH Terms]) OR ("Cell- and Tissue-Based Therapy/economics"[MeSH Terms]) OR ("Models, Econometric"[MeSH Terms]) OR ("Cost-Benefit Analysis"[MeSH Terms]) OR ("health technology assessment"[Title/Abstract]) OR ("insurance, health, reimbursement"[MeSH Terms]) OR ("Insurance Coverage"[MeSH Terms]) OR ("National Institute for Health and Care Excellence"[Title/Abstract]) OR ("Scottish Medicines Consortium"[Title/Abstract]) OR ("Haute Autorité de Santé" [Title/Abstract]) OR ("French National Authority for Health "[Title/Abstract]) OR ("Institute for Quality and Efficiency in Health Care" [Title/Abstract]) OR ("Federal Joint Committee"[Title/Abstract]) OR "G-BA"(Title/Abstract]) OR ("Italian Medicines Agency"[Title/Abstract]) OR ("Dutch National Health Care Institute" [Title/Abstract]) OR (" Spanish Agency of Medicines and Medical Devices" [Title/Abstract]) OR ("Swedish Dental and Pharmaceutical Benefits Agency" [Title/Abstract]))
O - Outcomes of interest: Patient-based evidence	4	(("Patient-Reported Outcome Measures"[MeSH Terms]) OR ("Quality of Life"[MeSH Terms]) OR ("Quality of Life"[Title/Abstract]) OR ("Patient-reported"[Title/abstract]) OR ("Patient-reported outcomes"[Title/Abstract]) OR ("patient experience"[Title/Abstract]) OR ("Patient evidence"[Title/Abstract]) OR ("Patient-based evidence"[Title/Abstract]) OR ("Patient experience"[Title/Abstract]) OR ("Real-life data"[Title/Abstract]) OR ("real-life evidence"[Title/Abstract]))
S - Study design of interest:	-	No specifics
Search script	**1 AND 2 AND (3 OR 4)**	

To refine the search, the PubMed search was limited to free full text publications released between July 1, 2017 and July 1, 2022 in English language. The initial search yielded 71 results. Based on the inclusion and exclusion criteria, a short-list of 14 papers was obtained:

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- (Ref 10). Laetsch TW, Myers GD, Baruchel A, Dietz AC, Pulsipher MA, Bittencourt H, Buechner J, De Moerloose B, Davis KL, Nemecek E, Driscoll T, Mechinaud F, Boissel N, Rives S, Bader P, Peters C, Sabnis HS, Grupp SA, Yanik GA, Hiramatsu H, Stefanski HE, Rasouliyan L, Yi L, Shah S, Zhang J, Harris AC. Patient-reported quality of life after tisagenlecleucel infusion in children and young adults with relapsed or refractory B-cell acute lymphoblastic leukaemia: a global, single-arm, phase 2 trial. Lancet Oncol. 2019 Dec;20(12):1710-1718. doi: 10.1016/S1470-2045(19)30493-0. Epub 2019 Oct 9. PMID: 31606419; PMCID: PMC7480957.
- (Ref 14). Delforge M, Shah N, Miguel JSF, Braverman J, Dhanda DS, Shi L, Guo S, Yu P, Liao W, Campbell TB, Munshi NC. Health-related quality of life with idecabtagene vicleucel in relapsed and refractory multiple myeloma. Blood Adv. 2022 Feb 22;6(4):1309-1318. doi:
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- (Ref 19). Cheng R, Scippa K, Locke FL, Snider JT, Jim H. Patient Perspectives on Health-Related Quality of Life in Diffuse Large B-Cell Lymphoma Treated with Car T-Cell Therapy: A Qualitative Study. Oncol Ther. 2022 Jun;10(1):123-141. doi: 10.1007/s40487-021-00174-0. Epub 2021 Nov 15. PMID: 34778941; PMCID: PMC8590924.
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Finally, a search for 'quality of life', 'patient evidence', 'patient-based evidence', 'patient-reported outcomes', and real-world evidence was performed in publicly available health technology assessment agencies' appraisal decisions of CAR-T cell therapies in blood cancer. Agencies of interest included:

- The National Institute for Health and Clinical Excellence (NICE)
- The Scottish Medicines Consortium (SMC)
- The French National Authority for Health (HAS)
- The German Federal Joint Committee (G-BA)
- The German Institute for Quality and Efficiency in Health Care (IQWiG)
- The Spanish Agency of Medicines and Medical Devices (AEMPS)
- The Italian Medicines Agency (AIFA)
- The Canadian Agency for Drugs & Technologies in Health (CADTH)

APPENDIX 3: INTERVIEW QUESTIONS

Myeloma Patient Europe gives special thanks to the European Medicines Agency, the National Institute for Clinical Excellence (NICE), Lymphoma Coalition, Ensemble Leucémie Lymphome Espoir (ELLyE), AF3M, Leukemia Care UK, Novartis, Janssen and Intexo Società Benefit for their insight and contribution to this project.

1. What is your involvement in the regulatory and reimbursement approval of CAR-T?
2. In your opinion, what types of patient-based evidence need to be generated to support regulatory and reimbursement approvals of CAR-T

(Please note that patient-based evidence can be based on patients' experiences, perspectives, perceptions, needs, preferences or attitudes about their care and health)?

3. **When should patient-based evidence on CAR-T cell therapies be generated and by whom?**
    - ***Prompts and follow-up questions:***
        - Which phase in clinical development (phase I-III and post marketing authorisations)
        - Role of industry, patient groups and academic researchers
        - How do we encourage and facilitate the collection of this type of data?
4. **Are the current PRO questionnaires adequate to capture the quality-of-life impact of CAR-T cell therapies? What works well? What could be improved?**
5. **In the assessment of CAR-T cell therapies, from your experience, what sort of patient-based evidence has been submitted to assist decision-making (regulatory, early access or reimbursement)?**
    - ***Prompts and follow up questions:***
        - Patient report outcome data on quality of life
        - What side-effects are important in CAR-T and how do you gather evidence to demonstrate the impact?
        - Quantitative vs. qualitative
        - The role of patient preference data
        - How robust does the patient-based evidence need to be?
        - How was this data presented to be meaningful?
6. **How has patient-based evidence been considered in the decision-making on CAR-T cell therapies?**
7. **What recommendations would you make to different stakeholders in generating patient-based evidence on CAR-T cell therapies to support approval?**

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