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ARTICLE

Outcomes-based reimbursement for gene therapies in practice: the experience of recently launched CAR-T cell therapies in major European countries

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ABSTRACT

Background: The experience of Kymriah® and Yescarta® provides real-world examples of how health-care systems approach and manage the reimbursement of one-off, high-cost, cell, and gene therapies, and the decision uncertainty and affordability challenges they present.

Objective: To provide an overview of the reimbursement schemes used for Kymriah® and Yescarta® in France, Germany, Italy, Spain, and the UK (EU5) as per the final quarter of 2019; to identify challenges and derive learnings for future product launches.

Methodology: Secondary research, complemented by primary research with key market access stakeholders.

Findings: Kymriah® and Yescarta® have relatively uniform list prices across the EU5, and are reimbursed according to their marketing authorisations. In France and the UK, reimbursement is on the condition of collecting additional data (at the cohort level) and subject to future reassessments; elsewhere, rebates (Germany) or staged payments (Italy and Spain) are linked to individual patient outcomes.

Conclusions: The experience of Kymriah® and Yescarta® shows an increased appetite for outcomes-based reimbursement (OBR) in the EU5, with notably novel approaches applied in Italy and Spain (outcomes-based staged payments). Thus, real-world evidence (RWE) has become an increasingly powerful lever for demonstrating the value of health benefits in the clinical setting.

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Introduction and background

In August 2018, the European Commission granted marketing authorisation (MA) for two novel and potentially transformative cancer treatments, the chimeric antigen receptor T (CAR-T) cell therapies, Kymriah® (tisagenlecleucel) and Yescarta® (axicabtagene ciloleucel) [1,2]. Kymriah® is approved for two indications: 1) Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse; 2) adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy [1,3]. Yescarta® is approved for adult patients with relapsed or refractory DLBCL, or primary mediastinal large B-cell lymphoma (PMBCL) after two or more lines of systemic therapy [2,4].

2019 was a milestone year for these CAR-T cell therapies, as the products' manufacturers Novartis (Kymriah®) and Gilead (Yescarta®) managed to successfully obtain reimbursement in many key countries. The launches of these products were highly anticipated by patients, medical professionals, healthcare system stakeholders such as Health Technology Assessment (HTA) bodies and payers, as well as by the wider pharmaceutical industry. This anticipation was driven by several factors, however, from the perspective of HTA bodies, a particular consideration is the uncertainty around the real-world value of these therapies, given the potentially lifelong health benefit supported by shorter-term data at launch, combined with target prices in the hundreds of thousands of euros/pounds. This decision uncertainty raises several questions for HTA bodies and health-care payers, e.g., What price level is justifiable? What assessment methodology is appropriate? What method of payment makes the most sense for one-off therapies with potentially life-long benefits?

Many reports have been published on these topics in anticipation of the first CAR-T launches [5–9], among which a particularly interesting example is that of the "mock" technology appraisal exercise by the National Institute for Health and Care Excellence (NICE) in England. This HTA exercise for a hypothetical CAR-T cell therapy in ALL, aimed 'to provide insights into methodology issues connected with regenerative

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medicine product characteristics, pricing, and funding models and evidence maturity' [6]. A year on from obtaining MA, these two CAR-T cell therapies have been through HTAs and reimbursement negotiations in many European countries, and can now be considered as real-world examples to illustrate healthcare system stakeholders' approach to managing the data uncertainty and addressing the affordability challenges of these innovative therapies.

Objectives

The objectives of this article are to provide an overview of the reimbursement and funding schemes used for Kymriah® and Yescarta® in the five major European markets (EU5), i.e., France, Germany, Italy, Spain, and the UK (UK; England and Scotland more specifically), as per the final quarter of 2019, identify challenges and derive learnings about how other Advanced Therapy Medicinal Products (ATMPs) may be adopted in the future.

Methodology

We applied a targeted evidence review of secondary sources available in the public domain, with preference being given to materials from official bodies, e.g., HTA bodies, health authorities, regulatory agencies, and other healthcare system stakeholders. For each country, the following information was collected:

- The list price,
- The type of reimbursement scheme used,
- Any data uncertainty mitigation measures used,
- Particulars around the funding route where relevant,
- In addition, the wider adoption requirements associated with this type of therapies were considered with a focus on activities around health service preparedness and readiness.

To complement the evidence review, we engaged in primary research with one key market access stakeholder for CAR-T cell therapy adoption in each of the EU5 countries. In addition, we have drawn on the experience and insights derived through our employing organisations' activities in the space of cell and gene therapies including A. Primary research conducted for the development of the Alliance for Regenerative Medicines (ARM) report on timely access to cell and gene therapies [8]. B. Through the Cell and Gene Therapy Catapult's coordinating role of the Advanced Therapy Treatment Centers in the UK, including regular updates from commissioners and Key Opinion Leader (KOL) clinicians on the adoption status with particular emphasis on clinical infrastructure requirements and challenges.

Findings

Both Kymriah® and Yescarta® have successfully obtained reimbursement in their labelled indications across the EU5, at relatively uniform list prices, as detailed in Table 1.

It should be noted that the prices detailed here reflect the list prices, and do not (necessarily) reflect the actual amount paid once rebates, discounts, or performance-based payment mechanisms have been accounted for. In the below, we provide more detail on the particulars of how the two CAR-T cell therapies are reimbursed across the EU5.

France

In France, both Kymriah® and Yescarta® were made available to French patients prior to their European MA through the early access program 'Temporary Authorisation for Use' (*Autorisation Temporaire d'Utilisation*, [ATU]) [10]. The ATU route provides reimbursed access before MA approval to therapies that hold particular therapeutic promise and are not currently available through clinical trials in France [11]. After MA, the drug is reimbursed as 'post-ATU' until reimbursement and pricing decisions are finalised. During the ATU/post-ATU period, the manufacturers set the drug price freely, however, the pricing committee sets a maximum price per unit (*indémnité maximale*)[1] [12]. In addition, drugs with annual pre-tax revenue exceeding €30 million under the ATU/post-ATU period are subject to spending caps, above which manufacturers are liable to pay rebates [13].

The ATU scheme is used as a vehicle to collect real-world data on safety, efficacy, and the clinical practice [14], and this information is used in addition to the clinical data from pivotal trials, to inform the subsequent HTA and reimbursement determination at the time of MA. In the case of Kymriah® and Yescarta®, the data collected through the ATU scheme was limited,

[1]Also, if the negotiated price, following MA and completion of the pricing and reimbursement process, is lower than the ATU price, manufacturers are required to pay back the total revenue difference between the ATU price and the actual post-launch reimbursed price.

Table 1. Summary overview of list prices, reimbursement schemes and key outcomes associated with the reimbursement of CAR-T cell therapies in EU5.

	France	Germany	Italy	Spain	UK
Reimbursement scheme	Coverage with evidence development	Outcomes-based rebates	Outcomes-based staged payments	Outcomes-based staged payments	Coverage with evidence development
Detail	Annual reassessments based on longer-term follow-up data from pivotal trials, and post-launch data collection from use in French patients	Rebates linked to individual patient outcomes	Payments in three instalments linked to individual patient outcomes	Payments in two instalments linked to individual patient outcomes	Future price reassessment based on longer-term follow-up data from pivotal trials, and post-launch data from use in UK patients
Key outcomes considered	Several (survival, remission status, disease progression, adverse events)	Survival	Specifics not disclosed	Complete response Survival	Survival Post-treatment requirement for stem cell transplantation and/or use of immunoglobulins
List price	Kymriah: €320,000 [78]* Yescarta: €327,000 [79]	Kymriah: €320,000 [29] Yescarta: €327,000 [27]	Kymriah: €300,000 [36] Yescarta: €327,000 [37]	Kymriah: €320,000 [80] Yescarta: €327,000 [81]	Kymriah: £282,000 [48,52] (~€319,000**) Yescarta: £280,451 [55] (~€317,000**)

*Kymriah post-ATU maximum price.
** Using average annual exchange rate for 2018: £1 = €1.1305 [82].

e.g., only 17 patients received Kymriah® under the ATU scheme [15].

The Transparency Committee (TC) published its assessments of Kymriah® and Yescarta® in December 2018 [15,16]:

- The TC considered Yescarta® to have an *important* actual clinical benefit (*service médical rendu* [SMR]) and a *moderate* improvement in added benefit over available therapies (*amélioration du service médical rendu* [ASMR]: III) in both labelled indications. This assessment was made primarily by relying on the results of the ZUMA-1 study, in which Yescarta® showed potential clinical benefits in complete response rate and 18-month survival rate.
- The TC considered Kymriah® to have an *important* actual clinical benefit (SMR: important) and a *moderate* improvement in added benefit over available therapies (ASMR: III) for the treatment of B-cell ALL, based on high rates of complete remission. In DLBCL, the TC assessed Kymriah® as having an *important* actual clinical benefit (SMR: important), however, a *minor* improvement in added benefit over the comparator therapies (ASMR: IV). The primary data sources for the assessments were the clinical trial JULIET and Schuster in DLBCL, and ELIANA, and ENSIGN in ALL.

For both CAR-T cell therapies, the TC requested that further long-term data should be collected to address the uncertainties regarding the long-term efficacy, safety, and complexity of the treatment process. Consequently, the TC recommended that Kymriah® and Yescarta® be reimbursed on the condition that a CAR-T-specific registry be established to collect further data from French patients to enable a reassessment of the health benefit observed in the real world [17]. Key outcomes that are to be collected include survival, remission status, disease progression and adverse events, and these are to be recorded at 28 days, 100 days, 6 months and every subsequent 6 months after injection, and reported by hospitals on a quarterly basis [18]. Data collection is facilitated through the Lymphoma Academic Research Organisation (LYSARC) data platform [19].

In addition, the French health authority (HAS) considers CAR-T cell therapies as a new class with promising potential that needs to be confirmed. Therefore, and due to the high uncertainty around the real-world effectiveness and the ancillary implications of delivering the CAR-T cell therapies (e.g., cost of hospitalisation, etc.), HAS will undertake annual HTAs, reassessing the improvement in clinical benefit (ASMR) using the data collected in the registry, as well as any new data available from the follow-up of the pivotal trials [20].

In July 2019, Yescarta® transited from post-ATU funding to funding through the supplementary list of costly medicines (*liste en sus)*, meaning treating hospitals can access supplementary funding (outside the standard Diagnosis Related Group [DRG] funding codes used for French hospitals) [21,22]. This funding route is restricted to therapies that have been assessed by TC to have an improvement in health benefit that is moderate (ASMR III), important (ASMR II) or major (ASMR I), and Yescarta® received an ASMR III [16], making it eligible for inclusion in the *liste en sus*.

Kymriah® has not yet been included in the *liste en sus*, but is still funded through the post-ATU arrangement, however, as Kymriah® was granted an ASMR III in the ALL indication [23], it would be assumed as a candidate for the *liste en sus*. It is worth noting that from the point of view of patient access, the post-ATU arrangement in France means that reimbursed access is facilitated while the HTA and price negotiations are concluded. In addition, the fact that it received an ASMR IV in DLBCL [15] should not preclude Kymriah® from inclusion on the *liste en sus*, as it is possible to list therapies solely in the indications that meet this criterion (and exclude the others) [24].

Germany

New drugs launching in Germany are priced freely for the first 12 months after launch, during which an HTA is undertaken and a reimbursement recommendation made by the Federal Joint Committee (G-BA). This HTA is used in the subsequent (ceiling) price negotiation with the National Association of Statutory Health Insurance Funds (GKV Spitzenverband), the umbrella organisation for the 109 German health insurers (as per January 2019) [25,26]. Innovative pricing and reimbursement mechanisms such as OBR have historically not been widely used in Germany, however, the launches of Kymriah® and Yescarta® illustrate some development on this front. Both Novartis and Gilead made interim arrangements for outcomes-based rebates for Kymriah® and Yescarta® during the initial 12-month period of free pricing (with the possibility for renewal). These OBR schemes were agreed with several health insurers including two umbrella groups of insurers. Those two umbrella groups are VDEK (an organisation of six health insurance funds) (TK, Barmer, DAK-Gesundheit, KKH, HKK, and HEK), and GWQ ServicePlus (an organisation representing several medium-sized insurers). The agreements made with these different health insurers cover a total of more than 41 million people [27], which is nearly 60% of the 70 million Germans who are insured through statutory health insurance [26], making for a substantial share of the market.

In the case of VDEK, both Novartis and Gilead have reportedly signed outcomes-based agreements, whereby the companies will provide rebates to the health insurers for patients dying after treatment with Kymriah® or Yescarta® [27]. In the case of GWQ ServicePlus, Novartis will similarly provide rebates for patients who die within a (not disclosed) time period after treatment with Kymriah® [28]. The time horizon for measuring survival, and the magnitude of the rebate are not available in the public domain, but our primary research indicates that these are in the region of 12 months and less than 50%, respectively.

The national price negotiation for Kymriah® was successfully completed on 15 September 2019 [29], and on 3 December 2019 for Yescarta® [30]. The prices negotiated with the GKV-Spitzenverband are lower than the freely set price applied during the first 12 months on the market, however, the exact price levels are not available in the public domain; primary research indicates that Novartis and Gilead may pursue simple discount agreements once the period of the OBR schemes is up. In the case of Yescarta®'s agreement with VDEK this is after two years, from the first half 2019 (exact timing not disclosed) [27], and for Kymriah® with GWQ ServicePlus, after 1 year from March 2019 [28].

The German system allows for additional funding for hospitals that adopt new and more costly therapies, which are not appropriately covered by existing DRG tariffs. Hospitals wanting to use new and more costly therapies can apply to the Institute for Hospital Remuneration (InEk) for a *Neue Untersuchungs- und Behandlungsmethoden* (NUB) status for the new therapy, which (if granted) allows hospitals to negotiate additional fees with insurers. The deadline for NUB applications is annual at 31 October [31], and for 2019, a NUB code 114 was established for the 'administration of CAR T cells for the treatment of hematological diseases' (NUB status 1) [32], which helps reduce an important hurdle to patient access for both CAR-T cell therapies, through a formalised path to negotiating additional funding. The NUB tariffs paid by insurers to hospitals pertain to the medicinal product alone, and does not cover other associated costs, e.g., apheresis, administration, managing toxicities, etc. If additional funding arrangements are not made, these associated costs need to be covered using existing DRG tariffs, however, the existing DRG tariffs are considered insufficient to cover all of these costs. This has been perceived as a key concern for hospitals considering to adopt the CAR-Ts, and may have a curbing effect on uptake.

Italy

In 2005, the Italian Medicines Agency's (AIFA) established a designated data collection infrastructure, the AIFA registry, which tracks the eligibility of patients in the treatment

pathway, with the aim to guarantee the appropriateness of use of pharmaceutical products, according to their approved indications [33]. The AIFA registry also serves as a vehicle for OBR, and since 2005, OBR schemes have been prolific, particularly in oncology, however, most schemes are based on retrospective rebates or providing a certain number of cycles for free (and the National Health Service [NHS] will then pay for subsequent cycles for responding patients) [34].

The launch of Kymriah® and Yescarta® saw AIFA break the traditional mould by introducing a staged payment scheme for both therapies, whereby payments (adjusted for a confidential discount on the list price) will be made in instalments, as long as the agreed outcome(s) has been achieved and sustained [35–38]. In the case of Kymriah®, Novartis will be paid at three time points (assuming that the patient sustains the agreed health benefit): The first at the time of infusion, the second after six months, and the third after 12 months [36]. Similarly, for Yescarta®, Gilead will be paid in three instalments, however, there is a key difference in how the payments for Yescarta® are structured as compared to Kymriah®: The first payment for Yescarta® is scheduled at 180 days after infusion, the second payment at 270 days, and the final payment at 365 days [37]. Under these circumstances, Gilead may not receive any payments for patients who do not make it to the 180-day mark, which suggests that Gilead may absorb more risk in its scheme for Yescarta® than Novartis under its scheme for Kymriah® (however it is likely that this is also impacted by AIFA's deliberations on how uncertainty in supporting evidence differs between the two CAR-T cell therapies and across their target indications). These contractual arrangements are valid for 18 months for both products (from 7 August 2019 for Kymriah®, and from 4 November 2019 for Yescarta®) [36,37].

AIFA's HTAs concluded that both products are 'innovative', which means that they are automatically included on the regional formularies, and funded through the national innovation fund [36,37], thereby reducing the regional hurdles to adoption. For both Kymriah® and Yescarta®, data collection is facilitated through AIFA's national registry and using its web-based tool for data collection [36,37].

Spain

The main drivers of pricing in Spain have traditionally been international and domestic reference-pricing [39], with few examples of OBR, however, recent efforts appear to pave the way for an increased use of value-based pricing of pharmaceuticals. More specifically, the Spanish Ministry of Health (MoH) introduced a new data collection and management system for the Spanish NHS called Valtermed (an abbreviation for *Sistema de Información para determinar el **Val**or **Ter**apéutico en la Práctica Clínica Real de los **Med**icamentos de Alto Impacto Sanitario y Económico en el SNS*[2]) [40]. The Valtermed registry system is designed to collect real-world clinical data through a web-based tool to reduce the uncertainty associated with new therapies and the benefit observed in clinical practice [41]. The system was piloted through the first three quarters of 2019, and was set to launch officially on 4 November 2019 [42]. A subsequent phase of the Valtermed system is envisioned to include greater integration with other NHS data sources, as well as the possibility for patients to enter quality of life (QoL) data to inform cost-effectiveness analyses [40].

Kymriah® and Yescarta® were two of the subject therapies used to pilot and validate the Valtermed system for roll-out in November [43]. Kymriah® is reimbursed in the Spanish NHS through two outcomes-based, staged payments based on data collected through the Valtermed system: one at the time of treatment (reported to be 52% of the total €320,000 [44]), and a second payment at 18 months [45] (reportedly the remaining 48% [44]), provided that the patient has achieved and sustained a complete response to the treatment. Yescarta® was approved for reimbursement in July 2019, and follows a similar approach to Kymriah®, however, with payments linked to survival as collected through Valtermed: reportedly a first payment of €118,000, and a second payment of €209,000 [46].

The UK (UK)

England

In England, both Kymriah® and Yescarta® are reimbursed in their EMA approved indications through the Cancer Drugs Fund (CDF), which is a cancer-specific funding source that enables access to drugs for which there is plausible potential that they would satisfy the criteria for routine commissioning, but where there is significant clinical uncertainty. NICE considered that the two products could not be recommended for routine use due to high uncertainty and limitations in clinical data, however, approved patient access through the CDF on the condition of gathering more evidence on the real-world effectiveness (i.e., coverage with evidence development) [47]. NICE was the first HTA body

[2]Which translates loosely to 'Information System to determine the Therapeutic Value of High Health and Economic Impact Drugs for the NHS in Real Clinical Practice'.

in EU5 to issue a favourable reimbursement recommendation for a CAR-T cell therapy, Kymriah®, which secured reimbursement in ALL through the CDF less than 10 days after obtaining MA [48]. Subsequently, Kymriah®'s DLBCL indication and Yescarta®'s two indications received positive NICE recommendations, and were approved for reimbursement through the CDF as well, all on the condition of confidential discounts and a requirement to collect and submit additional data for the purposes of a future price reassessment [49–51].

The primary data sources that are to inform the price reassessment for Kymriah® and Yescarta® (in 2023) are the follow-up data from the ongoing trials [49,51]. For Kymriah®, a key uncertainty for NICE is around overall survival and the proportion of patients who go on to have a stem cell transplant or require intravenous immunoglobulin after treatment [49,50]. The primary data sources for the reassessment are the ongoing clinical trials (JULIET and Schuster in DLBCL, and ELIANA, ENSIGN and B2101J in ALL) [49,50]. For Yescarta®, a key uncertainty for NICE is with regards to the choice of overall survival extrapolation in the cost-utility analysis, and the resulting uncertainty around the incremental cost-effectiveness ratio (ICER). Similarly as for Kymriah®, the primary source of data collection for Yescarta® is the follow-up from the ZUMA-1 pivotal trial [51].

Additionally, real-world evidence (RWE) will be collected for both CAR-T cell therapies through the Systemic Anti-Cancer Therapy (SACT) dataset and Bluteq (both standard requirements for treatments funded through the CDF), as well as through other Public Health England (PHE) datasets, and possibly the British Society of Blood and Marrow Transplantation registry (for Kymriah® in ALL) [49,51]. This combination of data sources will allow NICE and NHS England to more firmly establish the long-term efficacy (through the trial follow-up data) as well as the (shorter-term) real-world effectiveness in the English setting.

Scotland

In January 2019, Kymriah® was recommended for reimbursement in ALL by the Scottish Medicines Consortium (SMC) under its ultra-orphan and end of life process, on the condition of a confidential discount [52]. After an initial rejection (because the 'justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the submitting company did not present a sufficiently robust economic analysis' [53]), it was recommended for reimbursement also in DLBCL in August 2019 [54]. Yescarta® was initially not recommended for reimbursement in Scotland (due to uncertainty around the treatment's long-term benefits), however, in October 2019, it succeeded in both DLBCL and PMBCL, also under the ultra-orphan and end of life process [55].

The Scottish ultra-orphan process provides reimbursement for a period of up to three years on the condition that further clinical effectiveness data are gathered. After this period, the company will be asked to provide an updated submission for reassessment and SMC will make a decision on routine use of the medicine in NHS Scotland [56].

Discussion

After years of anticipation and theoretical discussion, the launches of Kymriah® and Yescarta® provide concrete, practical examples of how different healthcare systems have approached and managed the decision uncertainty associated with these therapies. The recent experience with these products shows an increased appetite for OBR in the EU5, notably with novel approaches to reimbursement being applied in Germany, Italy, and Spain.

Germany has historically been on the fence in terms of OBR, but Kymriah® and Yescarta® were adopted using outcomes-based rebate schemes covering around half of the (total) German population. These schemes are thought to serve primarily as a means to drive adoption during the 12-month period of free pricing (while the national price negotiations are undertaken), and primary research indicates that manufacturers are assumed to prefer simple discounts once the OBR scheme period is up. It is worth noting, however, that GWQ ServicePlus (one of the groups of health insurers that engaged in the outcomes-based rebate for Kymriah®) also adopted a pay-for-performance contract for multiple sclerosis therapy in 2018[3] [57,58]. This indicates an increase in the acceptability of innovative reimbursement schemes amongst German payers in circumstances where traditional frameworks present limitations in managing uncertainty.

The experience in Italy and Spain provides arguably the most novel examples of OBR with the staged payments tied to patient outcomes used for both CAR-T cell therapies. To our knowledge, these are the first examples of national reimbursement schemes involving outcomes-based staged payments in the EU5. The implementation of these schemes show that there is willingness both on the part of manufacturers and NHS decision-makers to move beyond the more traditional reimbursement schemes (e.g., simple discounts) to

[3]Merck Serono will pay for subsequent treatments for patients who failed treatment with their drug Mavenclad®.

payments conditional on treatment success, whose benefits we have advocated in previous work [59–61].

In terms of the outcomes used to inform the reimbursement schemes, survival is key for both Kymriah® and Yescarta® in Germany and for Yescarta® in Spain, while a complete response is used for Kymriah® in Spain. In Italy, the outcomes used to trigger the payments are not disclosed, however, linkage to survival or complete response/complete remission seems likely also here. A further interesting development in Spain is the ambition to include patient-reported QoL measures into the Valtermed system (potentially from 2020) to enable cost-utility analyses (CUAs) from the Spanish perspective. This marks a departure from the stance taken by the Spanish Ministry of Health in 2017, where they rejected the use of CUAs and Quality-Adjusted Life Years (QALYs) for pricing assessments [62,63].

The developments in Italy and Spain also illustrate that it is possible to overcome the (annual) budget cycle focus often taken by health-care payers and manufacturers. The time horizons of the Italian and Spanish OBR schemes (12 and 18 months, respectively) mean that payments are deferred into the next financial year (at least), and in the case of Spain, potentially up to two financial years into the future (depending on when in the financial year the infusion takes place), which makes financial forecasting more challenging for both NHS and industry stakeholders. It is not possible to say for certain what strategies enabled these stakeholders to overcome these hurdles, but in both countries a close collaboration between industry and NHS stakeholders preceded the product launches [35,43,45,64]. In the case of Spain, there appears to have been a considerable drive and political will from central healthcare authorities to dramatically overhaul the pharmaceutical system, as illustrated by the fact that Valtermed was implemented over the course of only a year, since it was confirmed in September 2018 [42]. Early engagement with NHS stakeholders is key across the EU5, and this is exemplified further by the NHS Commercial Framework for Medicines currently under consultation in England. Among its core objectives is to 'drive earlier and more purposeful engagement between the pharmaceutical industry, NHS England and NICE', and to 'facilitate timelier and more streamlined discussions about value, affordability, and transactability so technology appraisal decisions, and ultimately patient access, are not unnecessarily delayed, to ensuring early and fast access to new medicines' [65]. ATMP manufacturers should take note of these developments, and engage with relevant market access stakeholders from an early stage to minimise hurdles to access.

In both England and France, Kymriah® and Yescarta® were reimbursed using Coverage with Evidence Development (CED) schemes where the future price and reimbursement reassessment will be based on a combination of both longer-term follow-up from the ongoing trials, and real-world data from the national clinical practice. In England, it is not uncommon for new cancer medicines with uncertainty around their cost-effectiveness to be reimbursed through the CDF on the condition of additional data collection to inform a price reassessment (for Kymriah® and Yescarta® this reassessment is to take place after five years). The CDF provides a CED-type of reimbursement, which is an effective means to minimise delays in patient access, however, this arrangement is available only to cancer medicines. This means that the situation in terms of time between MA and reimbursement recommendation might have been different if the two CAR-T cell therapies were targeting other therapy areas. However, it should be noted that therapies targeting smaller patient populations than those targeted by Kymriah® and Yescarta® may be assessed under the Highly Specialised Technology evaluation pathway, for which higher ICER thresholds are accepted by NICE [66]. This provides an opportunity for innovative therapies to secure routine commissioning even at higher levels of data uncertainty.

In France, Kymriah® and Yescarta® were also reimbursed through CED for an initial period while additional data is collected through the LYSARC platform. Typically, the price of a new drug is reassessed after five years, however, price revision may take place upon the request of manufacturers or the pricing committee based on substantive changes that warrant an earlier reassessment, e.g., new data becomes available, the ASMR is changed, considerable changes in EU prices, or the launch of a follow-on indication [67]. However, in the case of the CAR-T cell therapies, the French health authority (HAS) considered the data uncertainty to be such that additional data from use in French patients must be submitted annually to inform reassessments of the SMR and ASMR. Any changes in the ASMR score will then be used to inform a reassessment of the price.

In both England and France, future health technology reassessments are based on cohort data from a combination of follow-up from the pivotal trials, as well as RWE from use in clinical practice in either country. The follow-up data collected in the ongoing studies reduce uncertainty around the long-term benefit, while the RWE collected in French and English patients provides data on how the CAR-T cell therapies perform in the real-world patients, however, this data will be skewed more towards the short-term effectiveness, rather than the longer-term sustainability of effect.

This contrasts the schemes operated in Germany, Italy, and Spain, where the rebates or milestone payments are based on individual patient data (collected in the real-world setting), rather than cohort data. In the previous work, we have shown how cohort schemes can be less costly to implement than those based on individual patient data [68], however, in a situation where the therapies underperform, payers in Germany, Italy, and Spain are unlikely to overpay (as payments are tied to individual patient outcomes), while payers in France and the UK will risk overpaying, as reimbursement has been granted for the initial period before the price is reassessed.

Collection of RWE is a powerful lever for all innovative products to demonstrate the health benefit in the clinical setting, and its importance seems to be gaining recognition (as exemplified, e.g.,, by the recent implementation of Valtermed in Spain). However, there are different approaches that can be followed in order to collect, manage, and/or utilise such data. The AIFA and Valtermed registries used in Italy and Spain are examples of data collection infrastructures that are national, and disease/indication-agnostic, however, where the entry of clinical data essentially is a duplication of data already collected elsewhere. Another option is to utilise data already routinely collected in existing standalone structures such as the SACT dataset in England, however, the data collected in this one structure may not provide the clinical outcomes needed for the purposes of informing OBR schemes (as we have shown in the previous work [68]). Another approach is to draw on a more comprehensive range of data by integrating different existing data sources used routinely, an example of which is that of the National Cancer Registration and Analysis Service (NCRAS) operated by PHE in the UK to support cancer epidemiology, public health, service monitoring, and research [69]. It is our belief that a centralised, disease-agnostic platform that utilises data from the sources where it is collected in routine practice would be the most beneficial solution in terms of facilitating OBR while avoiding duplication of efforts; this can be supplemented by improving data collection processes to address data gaps in existing sources.

A further point of importance for many ATMPs, is that securing reimbursement may not be enough in and of itself to enable timely adoption. CAR-T cell therapies like Kymriah® and Yescarta® rely on highly complex requirements in terms of the care pathway, clinical infrastructure, and skill of the clinical staff to be delivered successfully to patients [70]; meeting these requirements at the hospital level is challenging, but critical for enabling timely adoption, as well as for optimising patient outcomes. In England, following the initial designation of centres of excellence (in 2018) where Kymriah® and Yescarta® can be administered, there was a need to increase the capacity in the system to be able to treat the full eligible population; NHS England therefore had to designate additional centres later in 2019 [71]. This staggered approach to creating capacity in the clinical infrastructure has been echoed also in primary research as a potential explanation for the relatively modest uptake of the CAR-T cell therapies to date. Institutional readiness [72] is therefore a crucial component to enable timely adoption for advanced therapies after a reimbursement recommendation has been made [73] (e.g., within the statutory 90-day time window operational in England [74]). Thus, early pre-launch engagement with the NHS is needed in order to get the necessary planning and preparations underway.

Additionally, it should be noted that the outcomes of such advanced treatments hinge not only on the effectiveness of the CAR-T cell therapies themselves, but also on the appropriateness of the care pathway, and the experience of the clinical staff in delivering them (e.g., managing side effects like the potentially deadly cytokine release syndrome). The efficacy and safety observed in the clinical trial setting can best be achieved in the real world once an appropriate clinical pathway, practice and experience in delivery has been established, providing the best possible environment for treating patients. It is important that manufacturers work closely with healthcare providers to ensure the appropriate clinical infrastructure and processes are in place in preparation for the successful and timely adoption of such complex-to-deliver therapies to optimise their real-world effectiveness.

Furthermore, from the hospital perspective, the costs of treating and managing these patients (e.g., costs of apheresis, storage and handling, infusion, managing toxicities, etc.) go far beyond the acquisition cost of the CAR-T cell therapy itself. There is limited EU data on the cost of hospitalisation for patients undergoing the CAR-T cell treatments, however, US data show that the median total cost of hospitalisation per patient was $82,059 for adults and $280,276 for children [75,76]. Given the magnitude of the associated treatment costs, it is clear that hospitals could be at a financial disadvantage if appropriate funding is not in place. In England, an interim solution has been to use the tariffs normally used for bone marrow transplant patients, however, primary research indicates that this is not sufficient to cover the costs of managing these patients. In France, a specific funding code has been implemented for Kymriah® and Yescarta® that provides authorised hospitals with €15,000 to cover the costs associated with the hospitalisation of each patient receiving one

of these two CAR-T in their approved indications [77], however, it is hard to see how this can be sufficient when seen in relation to the US costs. Ensuring that there is adequate funding, like DRG tariffs or budget allocations, to cover the cost of the whole treatment pathway is therefore another important consideration for minimising delays in adoption, or slow uptake. The implementation of temporary funding arrangements while the DRG tariffs are updated is another important measure in this respect.

Industry and NHS decision-makers in the EU5 have broken new ground and may have started setting new precedents for subsequent ATMP launches with the reimbursement and adoption of the first two CAR-T cell therapies to come to market. However, it is important to note that these are only two therapies, and that one should exercise caution when trying to extrapolate too much into the future from an N of just two. E.g., the fact that both therapies were reimbursed in England through a route that is not uncommon for cancer therapies with data uncertainty at launch, may not preclude the use of OBR schemes (like the staged payments in Italy and Spain, or the rebates in Germany) for future ATMP launches. NICE and the NHS in England have expressed openness to such OBR schemes as illustrated by the exploration of 'lifetime leasing' (staged payments) in the NICE regenerative medicines study [6], as well as outlining OBR schemes in the draft NHS Commercial Framework for Medicines (for consultation) [65] as a potential route to commissioning.

Kymriah® and Yescarta® serve as relevant and interesting examples of how innovative, high-cost therapies with data uncertainty at launch, and with the potential to deliver significant patient and healthcare system benefits, can secure adoption. The developments, particularly in Germany, Italy, and Spain, suggest that the door for OBR is opening in large parts of continental Europe, which is exciting. Still, it is important to highlight that there is no 'one size fits all' solution, as different countries have different HTA methodologies and processes, and different preferences and priorities on behalf of NHS decision-makers. Each new product comes with its own unique characteristics and challenges both for manufacturers and NHS stakeholders, and each case will be handled on its own merits. Still, it is our belief that the direction of travel with regards to reimbursement for such therapies is beneficial for patients, clinical personnel, NHS stakeholders, and industry alike, and we look forward to see what the future holds for the subsequent ATMP launches.

Disclosure statement

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