INNOVATIVE GENE AND CELL THERAPIES – MARKET ACCESS AND REIMBURSEMENT DECISIONS IN THE EU5: AVAILABILITY OR NOT, THAT IS THE QUESTION…

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OBJECTIVE:

- Since 2015, innovative gene and cell therapies (Alofisel®, Kymriah®, Holoclar®, Imlygic®, Spherox®, Strimvelis®, Yescarta®, Zalmoxis®, Luxturna® and Zynteglo®) have been granted marketing authorization by the European Commission. The aim is to compare pathways to market access for such therapies.

METHODS:

- A targeted literature research on official reimbursement / health technology assessment agencies websites, complemented with local market access expert interviews, were conducted in spring 2019.
- Table 1 depicts approved cell and gene therapies by the EMA.

Table 1: Approved cell and gene therapies in the EU-5 countries (as of 24 October 2019)

Brand name	Active substance	Indication	CHMP	France	Germany	Italy	Spain	UK/England*
Alofisel®	darvadstrocel	complex anal fistulas in adults with Crohn's disease	15/12/2017	positive reimbursement decision / price in negotiation / available through post ATU program	currently under price negotiation but reimbursed	not reimbursed (class C)	reimbursed; payment by results	not recommended
Kymriah®	tisagenlecleucel	B-cell acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL)	29/06/2018	positive reimbursement decision / price in negotiation / available through post ATU program	reimbursed, pay-for-performance	reimbursed; payment by results (ALL); obligatory discount (DLBCL)	reimbursed; payment by results	reimbursed via cancer drugs fund
Holoclar®	ex vivo expanded autologous human corneal epithelial cells containing stem cells	imbal stem-cell deficiency caused by chemical ocular burns	19/12/2014	positive reimbursement decision / funding by hospitals	not assessed; not reimbursed	reimbursed; payment by results	commercialized, but not reimbursed by the NHS	reimbursed via NICE's Single Technology Appraisal pathway with some restrictions using Patient Access Scheme (Simple Discount)
Imlygic®	talimogene laherparepvec	unresectable malignant melanoma	23/10/2015	no evaluation by HAS	handled as procedure - not AMNOG assessed	not commercialized	authorized, not commercialized yet	reimbursed via NICE's Single Technology Appraisal pathway using Patient Access Scheme (Simple Discount)
Spherox®	spheroids of human autologous matrix-associated chondrocytes	articular cartilage defects	24/07/2017	no evaluation by HAS	not commercialized	not commercialized	not authorized, not commercialized	reimbursed via NICE's Single Technology Appraisal pathway with some restrictions
Strimvelis®	autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence	combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID)	01/04/2016	no evaluation by HAS	unknown	reimbursed; payment by results	not authorized, not commercialized	gained full recommendation within its marketing authorisation via NICE's Highly Specialised Technology process
Yescarta®	axicabtagene ciloleucel	diffuse large B-cell lymphoma (DLBCL);primary mediastinal large B-cell lymphoma (PMBCL)	29/06/2018	reimbursed; price set at € 327.000 € for one injection with efficacy conditions in real life	reimbursed - G-BA assessed	P&R procedure not yet completed	reimbursed; payment by results	reimbursed via Cancer Drugs Fund
Zalmoxis®	allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2)	add-on treatment in adults who have received an haploidentical transplant	24/06/2016	negative reimbursement decision	reimbursed - G-BA assessed	reimbursed; flat price per patient	authorized, not commercialized yet	NICE has not yet reviewed
Luxturna®	voretigene neparvovec	loss of vision due to inherited retinal dystrophy	21/09/2018	positive reimbursement decision / price in negotiation / available through post ATU program	reimbursed - currently under G-BA assessment	P&R procedure not yet competed	authorized, not commercialized yet	reimbursed via NICE's Highly Specialised Technology Appraisal pathway using Patient Access Scheme (Simple Discount)
Zynteglo®	autulogous CD34+ cells encoding beta A-T87Q-globin gene	transfusion dependent beta-thalassaemia	28/03/2019	ongoing evaluation for reimbursement	not (yet) commercialized	no info available yet	not authorized, not commercialized	currently being appraised by NICE

* The UK data excludes Scotland.

France

- Six of these innovative therapies were assessed by the transparency committee: five obtained a positive reimbursement decision (Yescarta®, Kymriah®, Luxturna®, Holoclar®, Alofisel®). Yescarta price is set up at € 327 000 for one injection (but not published at this time), others are under negotiations. Kymriah®, Yescarta® and Luxturna® are available through ATU/post-ATU process and Holoclar® which can be funded by hospitals. Zinteglo® evaluation for reimbursement is ongoing.
- In December 2018, the transparency committee gave a favorable opinion for the reimbursement of Yescarta® and Kymriah® (Substantial medical benefit) and:
  - o Yescarta® obtained an ASMR III (medicine considered as innovative) for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma, after two or more lines of systemic therapy. [1]
  - o Kymriah® obtained two differentiated ASMRs:
    - o III for the treatment of paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) being refractory, in relapse post transplant or in second or later relapse.[2]
    - o IV for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.[3]
- The CEESP (Economic and Public Health Assessment Committee) gave also their opinion about the cost-effectiveness methodology:
  - o The ICER of Kymriah® was not deemed to be evaluable due to major critiques about the extrapolation of survival data.[4]
  - o The ICER of Yescarta® was evaluated to be € 114 509 per QALY.[5]

In July 2019, a price agreement regarding Yescarta® was achieved. Kymriah® price negotiations are still on-going.

- On 28 march 2019, a ministerial order was adopted limiting the use of autologous CAR-T cells to a limited number of qualified health centres following the favourable opinion of the HAS, which recommended the implementation of a national tool for monitoring patients treated with innovative therapy in France.
- The ministerial order also specifies that the health insurance coverage is conditioned on:
  - o The transmission, for all eligible patients, of exhaustive data.
  - o The compliance by the concerned centres with the indications, conditions and procedures for prescription, use and information.
- This health insurance coverage will probably be global, which means that it will cover all the costs associated to the disease (including the follow-up and support).

Germany

- As shown in Table 2, 6 out of 10 therapies were assessed within the AMNOG process. Core reason for a non-assessment was the decision to treat such therapies as a procedure for the inpatient usage. Kymriah® was the first ever therapy in Germany on which a pay-for-performance deal was agreed.
- Novartis and GWQ (a group of 63 German insurers - BKKs) have agreed to pilot a deal that will see Novartis pay back some of the cost of its CAR-T therapy Kymriah® if survival outcomes are not met.
- The agreement stipulates that Novartis will repay part of the treatment cost to the Statutory Health Insurance if a patient dies because of their disease within a defined period of time. The deal applies to both approved indications for Kymriah®.
- The agreement will apply for the first year that Kymriah® is on the market, until the GKV (association of health insurers) decides on a final price for the treatment.

Italy

- Four drugs successfully completed P&R negotiations with AIFA (Kymriah®, Holoclar®, Strimvelis®, and Zalmoxis®), one drug (Alofisel®) was allocated to class C (i.e. not reimbursed), and others have not completed a negotiation process. The final decision on Yescarta®, which is currently in pricing negotiations with AIFA's Pricing and Reimbursement Committee (CPR), is pending.
- Two drugs (Alofisel® and Zalmoxis®) were classified by AIFA as non-innovative and other two drugs (Strimvelis® and Kymriah®) were recognized as innovative: Strimvelis® although the validity period of this decision has recently expired, and Kymriah®. Worthy to note that for Kymriah® the duration period of the so-called innovation status would last for 12 months while usually this period is 36 months long.

Table 3 depicts the key milestones of the P&R process in Italy for the 10 considered drugs and their corresponding reimbursement status.

Table 3: Overview of key P & R milestones for cell and gene therapies approved by the EMA in Italy[7] (as of 24 October 2019)

Brand name	CHMP Opinion	Marketing authorization	CTS opinion	CPR opinion	IOJ publication	P&R status
Alofisel®	15/12/2017	23/03/2018	Jul-18	decision taken by CTS	08/10/2018	not reimbursed
Holoclar®	19/12/2014	17/02/2015	Sep-16	Oct-16	24/02/2017	reimbursed
Imlygic®	23/10/2015	16/12/2015	NA	NA	NA	NA
Kymriah®	29/06/2018	23/08/2018	Mar-19	Jul-19	12/08/2019	reimbursed
Luxturna®	21/09/2018	22/11/2018	ongoing	NA	NA	NA
Spherox®	18/05/2017	10/07/2017	NA	NA	NA	NA
Stimvelis®	01/04/2016	24/06/2016	May-16	Jun-16	01/08/2016	reimbursed
Yescarta®	29/06/2018	23/08/2018	Mar-19	ongoing	NA	NA
Zalmoxis®	24/06/2016	18/08/2016	Sep-17	Nov-17	14/02/2018	reimbursed
Zynteglo®	28/03/2019	29/05/2019	ongoing	NA	NA	NA

CTS = AIFA's Technical and Scientific Commission; CPR – AIFA's Pricing and Reimbursement Committee; IOJ – Italian Official Journal with P&R resolutions; NA = data not available

Important allocation decisions relevant for cell and gene therapies were made by the Italian Parliament in 2019:

- In December 2018 the Chamber of Deputies commissioned the Government to take a series of initiatives aimed to achieve:
  - o The definition of a high scientific level project group in charge of presenting a feasibility project on CAR-T (the so-called «Progetto Italia CAR-T Cells»);
  - o The feasibility study that is aimed to develop pre-clinical pathways for the treatment of tumours with Chimeric Antigen Receptor T-cells by a strong network of public and private institutions.
- On April 2019, the Italian Parliament allocated 5 Mio. Euros for a research project related to the new CAR-T technologies, on top of other 5 Mio. (10 Mio. in total) allocated for the same purpose by the Financial law 2019 (Law 136/2018).

Spain

- Three therapies are reimbursed (Kymriah®, Yescarta® and Alofisel®; all of them with a payment by results agreement), one is commercialised but not reimbursed (Holoclar®); and the others are not commercialized.[8,9] The three therapies that are reimbursed have been evaluated using Valtermed.[12]

Important considerations must be taken into account with regard to gene and cell therapies in Spain:

- Kymriah's P&R decision was relatively fast compared to that of other orphan drugs (<4 months after EMA approval).
  - o Positioning as per indication (both indications)
  - o Confidential risk-sharing agreement based on clinical outcomes
- A few centers have been accredited and protocols have been developed.
- Access to CAR-T drugs must follow the guidelines established in the "PLAN DE ABORDAJE DE LAS TERAPIAS AVANZADAS EN EL SISTEMA NACIONAL DE SALUD: MEDICAMENTOS CAR" [10], included in it are besides other aspects:
  - o The creation of a network of reference centers for the use and administration of CAR-T therapies in Spain.
  - o The conditions to be fulfilled by the centers for manufacturing CAR-T in Spain.

United Kingdom

- 7 out of 10 drugs are reimbursed to date. The UK data excludes Scotland as they have their own HTA system. Only one of these, Strimvelis®, was reimbursed at its full list price, in line with its market authorisation. Spherox®was reimbursed via NICE's Single Technology Appraisal (STA) pathway with some restrictions. The two CAR-Ts were reimbursed via NHS England's Cancer Drugs Fund. Meanwhile, two drugs (Holoclar® and Imlygic®) were recommended using a simple discount Patient Access Scheme (PAS) via NICE's STA pathway. Luxturna® was recommended using a PAS via NICE's Highly Specialised Technology pathway. Zalmoxis® and Zynteglo® have not yet been appraised by NICE. Alofisel® was not recommended by NICE.

General considerations must be taken into account with regard to gene therapies in the UK.

- No specific mechanism to approve gene therapies/innovative therapies through the NICE HTA pathways.
- NICE's STA allows products which show plausible cost-effectiveness to enter into a Managed Access Agreement (MAA), whereby a restricted set of patients gain access to a treatment whilst more evidence is generated. This is predominantly to the benefit of orphan oncology products.
- All ATMPs will be assessed by NICE.
- NICE always considers innovation in its assessment.
- The Accelerated Access Collaborative (AAC) was set up to drive the uptake and adoption of innovation in the NHS. The AAC's remit is to offer joined-up support for innovators and set the strategy for innovation in the health system.
  - o Much of this work focuses on medical technologies and has so far excluded drugs/gene therapies.

The following additional reimbursement challenges exist in the UK:

- Budgetary planning in the UK health service is not set up for potentially curative one-time therapies, such as gene therapies.
- There is a need for innovative reimbursement mechanisms so that regulators can acknowledge the added value of disruptive technologies like gene therapies.
- Some stakeholders are calling for an outcomes-based risk sharing approach to reimbursement, which would mitigate some of the uncertainty that gene therapies with low evidence bases have at the point of approval.
- These conversations are currently being had with the health service.

CONCLUSIONS:

- There is no difference in market access processes for gene therapies in comparison to standard pathways in Europe. Innovative and sustainable pricing schemes are under discussions between payers within EU member states.

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Brand name	Active substance/INN	Indication	Therapeutic area	MA date	Reimbursement status	GBA status	Added benefit(AB)
Alofisel®	Darvadstrocel	Alofisel is indicated for the treatment of complex perianal fistulas in adult patients with nonactive/mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy. Alofisel should be used after conditioning of fistula.	Cell therapy; Crohn Disease	23/03/18	Reimbursed year one	Process completed 22-Nov-2018	Non-quantifiable
Imlygic®	Talimogene laherparepvec	Imlygic is indicated for the treatment of adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral involvement.	Gene Therapy; Melanoma	16/12/15	Reimbursed year one	Process completed 15-Dec-2016	Not proven
Kymriah®	Tisagenlecleucel	Indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.	Diffuse large B-cell lymphoma (DLBCL); Gene Therapy	23/08/18	Reimbursed year one	Process completed 07-Mar-2019	Non-quantifiable
		Indicated for the treatment of 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.	B-cell acute lymphoblastic leukemia (B-ALL); Gene Therapy	23/08/18	Reimbursed year one	Process completed 07-Mar-2019	Non-quantifiable
Luxturna®	Voretigen Neparvovec	Indicated for the treatment of adult and paediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic RPE65 mutations and who have sufficient viable retinal cells.	Gene Therapy; Leber's Congenital Amaurosis (LCA)	22/11/18	Reimbursed year one	Process completed 17-Oct-2019	Considerable
Yescarta®	Axicabtagene ciloleucel	YESCARTA is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy.	Diffuse large B-cell lymphoma (DLBCL); Gene Therapy	23/08/18	Reimbursed year one	Process completed 02-May-2019	Non-quantifiable
		Yescarta is indicated for the treatment of adult patients with primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.	Gene Therapy; Primary mediastinal B-cell lymphoma (PMBL)	23/08/18	Reimbursed year one	Process completed 02-May-2019	Non-quantifiable
Zalmoxis®	Allogeneic T cells genetically modified	Indicated as adjunctive treatment in haploidentical haematopoietic stem cell transplantation (HSCT) of adult patients with high-risk haematological malignancies.	Hematopoietic stem cell transplantation Graft versus host disease (GvHD)	18/08/16	Reimbursed year one	Process completed 05-Jul-2018	Non-quantifiable

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