Volume 5, Issue 8

CELL & GENE THERAPY INSIGHTS

SPOTLIGHT ON:

Market & Patient Access

Guest Edited by Lee Buckler, RepliCel Life Sciences Inc

CELL & GENE THERAPY INSIGHTS

Volume 5, Issue 8

ISSUE SPOTLIGHT:

Market & Patient Access

Guest Edited by Lee Buckler, RepliCel Life Sciences Inc

CELL & GENE THERAPY INSIGHTS

MARKET & PATIENT ACCESS

SPOTLIGHT

COMMENTARY

Breakthrough therapies, breakthrough economics in the era of cure

Stephanie Farnia, Lisa Mostovoy, Carole Redding Flamm & Naomi Aronson

Cellular immunotherapies and gene replacement therapies herald new therapeutic categories and renewed discussion of how transformative therapies should be integrated into the US healthcare system. All stakeholders will need to participate in processes focused on long-term healthcare system stewardship.

Cell & Gene Therapy Insights 2019; 5(8), 931–936

DOI: 10.18609/cgti.2019.086

INTRODUCTION

As new cellular immunotherapies and gene replacement therapies are approved, a renewed discussion has emerged concerning how transformative therapies should be integrated into the US healthcare system. The 2017 approval of Novartis' tisagenlecleucel (Kymriah®), a chimeric antigen receptor T-cell (CAR-T) therapy, was followed quickly by the approvals of axicabtagene ciloleucel (Yescarta®), another CAR-T product, voretigene neparvovec-rzyl (Luxturna®), an ocular gene therapy, and onasemnogene abeparvovec-xioi (Zolgensma®), a gene therapy for spinal muscular atrophy. Rapid market entry will continue, with 40–60 product approvals anticipated by 2030 [1]. Payers, clinicians, and patients alike desire that cellular immunotherapy and gene therapy products will be successful and that individuals afflicted with life-altering and fatal illnesses will have the potential for cure. However, economic pragmatism demands that we maintain the affordability of health care for all – a challenge that will grow as these therapies become more available.

AFFORDABILITY

To understand the impact of these therapies on affordability, both the macro and micro levels of the healthcare system must be considered. Early products set a benchmark on pricing: $373,000 to $475,000 for the two approved CAR-T products, based on indication, and $425,000 per eye for Luxturna® [2]. Novartis recently announced a price of $2.125 million for its one-time therapy, Zolgensma® – and other companies in the blood disorder and pediatric neuromuscular disease spaces have indicated similar expectations [3,4].

Widespread perception about these therapies is that they are affordable at any price because of the exceptionally small number of eligible individuals. While it is true that the first gene therapies to market are indicated for ultra-rare/ultra-orphan diseases – with predicted incidence populations fewer than 10,000 and less than 500 in some cases – the limited numbers associated with the initial approvals and indications are simply the first phase of the market. A primary factor in expanding commercial use will be an initial surge to treat waiting prevalent populations. A second wave of expansion will come from a pipeline of therapies intended for larger populations. In publicly available investor presentations, several companies have stated their plans for post-approval broadening of indications to more common disease subtypes. In some therapeutic scenarios, such as autologous T-cell receptor therapy for non-small cell lung cancer, even the initial approval indication could mean that several hundred thousand individuals per year would be eligible for treatment. The cumulative effect of the stacking of individual rare diseases needs to be recognized by all stakeholders, particularly as precision medicine continues to reveal molecular subtypes of the more common disease states.

Despite high prices and a predicted expanding patient population, a perception that there will be a negligible impact on affordability as costs are spread across the insured population persists. However, the US healthcare system does not operate as an aggregate. The US has a multi-payer system with a wide variety of government and private health insurance companies and organizations, all of whom serve a diverse array of purchaser accounts and individuals. As such, the system is stratified into numerous smaller risk-taking entities. Each purchaser will represent a different cohort of member lives and correspondingly faces different risks of each rare disease type among their membership as a result of population demographics such as age, ethnicity, or the presence of genetic traits clustered within families. Moreover, the rapid diffusion of employers choosing self-funded insurance has altered the size of insured populations and the distribution of risk among insured groups. Over 90% of companies with more than 1000 employees are self-funded, and 61% of individuals employed by a firm of any size receive their healthcare through self-funding [5].

New financial mechanisms are in development to accommodate the transfer of high dollar amounts, but these plans do not change the fact that today's first-dollar payers are frequently individual employer accounts. While stop-loss insurance may limit an account's total

DOI: 10.18609/cgti.2019.086

initial spend, affordable stop-loss may prove elusive after several high-cost claims. Correspondingly, the affected patients and their families bear a substantial financial burden – often paying the maximum of all cost-sharing provisions while facing additional out-of-pocket costs. Thus, the idea that rare disease spend will be spread out over the entire population does not hold operationally true. The distribution of cost for each treatment case falls on a single payer and the financial structure that payer has put in place to handle high-cost claims, not the system as a whole. Even the Centers for Medicare and Medicaid Services (CMS) are not structured to spread costs in such a manner, given the subdivisions of Medicare into Fee-for-Service and Medicare Advantage and the dissimilarity between state Medicaid populations and budgets.

The perception that insurers will bear the cost of these therapies also misunderstands a fundamental mechanism of employer-sponsored health care coverage. In an employer-sponsored system, insurance is a component of wages and salaries, and premiums are ultimately pulled from the pool of funds available for total compensation. The Medical Expenditure Panel Survey (2017) noted the average employed individual spends more than 6.9% of their income on health care premiums and another 4.8% on deductibles associated with their health insurance coverage, not accounting for additional payments before reaching a maximum out-of-pocket policy limit or non-covered costs [6]. Increases in premiums alone, not including other healthcare spending, grew at twice the pace of both wage growth and inflation over the last 11 years [7]. Thus, all organizations that manage health care benefits have a fiduciary responsibility to be prudent with the allocated capital and to ensure there are adequate resources for the services incurred. Fiduciaries place a high priority on maintaining access to care through affordable premiums, which they accomplish through making informed decisions about which services are covered, how payment policies will be negotiated and how best to deliver complex, high-cost services through specialty networks and benefit design.

ADAPTABILITY

Developers are seeking an innovator's premium and are requesting adaptation of payer systems, citing that current systems are not amenable to paying for high-cost therapies. Developers propose that payers should collaborate in new ways to support access to transformative therapies, including the use of annual payment annuities or performance-based refund models relying on collaborative data resources, as well as portability vehicles that would allow outcomes-based agreements to follow patients as they move between payers.

While the entire health care system may benefit from changes in regulatory policy and payment mechanisms, such a focus represents only one aspect of system innovation. Historically, the diffusion of technological innovation was possible due to a reduction in the cost of such innovations and should remain a focus today. To promote efficient pricing models, developers also need to address the drivers of the cost of goods for cellular immunotherapies and gene therapies.

Lean processes, collaborative structures, and innovative partnerships all have the potential to reduce the costs of goods sold.

EVIDENCE GENERATION

The substantial financial commitment to gene therapies and cellular immunotherapies should be accompanied by a societal commitment to an ongoing learning system. All stakeholders need additional information to answer questions about how these new therapies perform in clinical use. The concerns around effectiveness, safety, durability, appropriate use, and quality improvement can be addressed through pharmacovigilance tracking, registries, and extensive health economics analyses. Building systems to collect and analyze long-term treatment effects, best fit populations, and outcomes of interest to all stakeholders should be a primary focus of collaboration. The collection and sharing of clinical outcomes will be a critical area of work for all parties involved with the provision of gene therapies and cellular immunotherapies. All stakeholders will be interested in whether the projected clinical outcomes and reductions in healthcare utilization are borne out over time. Developers would be well-served to participate in the process of proving out their estimations with supporting long-term follow-up.

Data on patient and caregiver experience and quality of life are also of interest. The Centers for Medicare & Medicaid Services (CMS) proposed the required collection of patient-reported quality of life at set intervals post-treatment for any CAR-T product provided to a Medicare beneficiary as part of its National Coverage Analysis Proposed Decision for Chimeric Antigen Receptor T-Cell Therapy [8,9]. Developers and clinicians should consider this proposal from CMS as an early precedent of the kinds of additional data payers may request, even if not part of the US Food and Drug Administration's (FDA) pharmacovigilance requirements.

The creation of evidence generation platforms that support multiple stakeholder use will advance the field. Ideally, these therapies would be tracked across the disease state by an independent organization that is both informed by and accessible to clinician researchers and external organizations. Gaining a comprehensive data set for a clinically related set of therapies of the pathways patients take during their disease course, and perhaps one that can be married to payer utilization data, is far preferred as a multi-stakeholder resource over a proprietary single therapy registry. The Blue Cross and Blue Shield Association (BCBSA) promotes the collection of relevant clinical outcomes within provider designation programs such as the Blue Distinction Centers. We encourage developers to seek collaborations by engaging the relevant clinical and patient communities and existing registry stewards as part of this endeavor.

An exemplar of data tracking is the Center for International Blood and Marrow Transplant Research (CIBMTR), an outcomes database which has the ability to track individuals as they experience multiple interventions during their treatment course. In 2016, the CIBMTR expanded its focus from hematopoietic cell transplantation to include cellular immunotherapies like CAR-T. CIBMTR data are accessible to any

DOI: 10.18609/cgti.2019.086

qualified stakeholder through a request process and multiple clinician advisory committees determine collaborative research projects. The CIBMTR was awarded the first National Cancer Institute Moonshot Initiative contract for the Cellular Immunotherapy Data Resource in 2018 as a result [10]. The CIBMTR serves as a resource for developers to address their Food and Drug Administration post-market surveillance requirements and. is also expected to serve as the resource for protocols that will meet the CMS coverage with evidence development study requirements.

We acknowledge that the development of this type of data resource may be perceived as an additional burden to be carried by those who are first to market, but we feel strongly that the combination of price and unique scientific mechanisms associated with these therapies warrant an enhanced level of monitoring and analysis. Collaboration among stakeholders to determine what matters – and to whom – will be important to establish core outcome measures and to find common ground in the pursuit of continuous learning through evidence generation.

TALK TO US

The Blue Cross and Blue Shield Association (BCBSA) invites gene therapy and cellular immunotherapy developers to talk with us well in advance of anticipated FDA approval. The BCBSA is a national association of 36 independent, community-based and locally operated Blue Cross Blue Shield companies. Operating since 1929, the Blue Cross and Blue Shield companies cumulatively have more than 106 million members in all 50 states, Washington, DC, and Puerto Rico.

Each of the anticipated new therapies will carry a unique combination of clinical targets, mechanisms of action, episodes of care, potential toxicities, care-team profiles and sites of care. Early communication will provide BCBSA and BCBS companies with lead time to address the education and implementation considerations, with a focus on the impact to members in the care system. While it is outside the bounds of this piece, BCBSA can have more detailed conversations about evidence generation and review processes, as well as the development of BCBS company resources that may assist in establishing post-launch communication between developers and BCBS stakeholders. The success of transformative therapies will depend on more than science – it will require deliberate system stewardship among all health care stakeholders.

FINANCIAL & COMPETING INTERESTS DISCLOSURE

The authors have no relevant financial involvement with an organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock options or ownership, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

REFERENCES

1. MIT NEWDIGS. FoCUS Projects. New Drug Development Paradigms Initiatives: https://newdigs.mit.edu/sites/default/files/FoCUS%20Research%20Brief%202018F210v027.pdf
2. Berkrot B. Spark's price for Luxturna blindness gene therapy too high: ICER. Reuters: https://www.reuters.com/article/us-spark-icer/sparks-price-for-luxturna-blindness-gene-therapy-too-high-icer-idUSKBN1F1298
3. Novartis. Novartis R&D and Investor Update: https://www.novartis.com/investors
4. Bluebirdbio. Forward-Looking Statements: http://investor.bluebirdbio.com/static-files/942436fc-fc3a-4d9e-9429-7df393f6494c
5. 2018 Employer Health Benefits Survey. Henry J Kaiser Family Foundation: https://www.kff.org/report-section/2018-employer-health-benefits-survey-section-10-plan-funding
6. Collins SR and Radley DC. The Cost of Employer Insurance is a growing burden for middle-income families. The Commonwealth fund: https://www.commonwealthfund.org/publications/issue-briefs/2018/dec/cost-employer-insurance-growing-burden-middle-income-families
7. 2018 Employer Health Benefits Survey. Henry J Kaiser Family Foundation: https://www.kff.org/health-costs/report/2018-employer-health-benefits-survey
8. Proposed Decision Memo for Chimeric Antigen Receptor (CAR) T-cell Therapy for Cancers (CAG-00451N). Centers for Medicare & Medicaid Services: https://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=291&bc=AAAAAAAAAACAA&
9. Center for International Blood & Marrow Transplant Research: https://www.cibmtr.org/Pages/index.aspx
10. Tracking Long-Term Safety, Efficacy of Cell Therapy. J Clin Pathways. Interview: https://www.journalofclinicalpathways.com/news/cibmtr-partners-kite-track-long-term-safety-efficacy-cell-therapy

AFFILIATIONS

Stephanie Farnia
Author for correspondence:
Blue Cross Blue Shield Association, 225 Michigan Ave, Chicago, IL 60601, USA
stephanie.farnia@bcbsa.com

Lisa Mostovoy
Blue Cross Blue Shield Association, 225 Michigan Ave, Chicago, IL 60601, USA

Carole Redding Flamm
Blue Cross Blue Shield Association, 225 Michigan Ave, Chicago, IL 60601, USA

Naomi Aronson
Blue Cross Blue Shield Association, 225 Michigan Ave, Chicago, IL 60601, USA

DOI: 10.18609/cgti.2019.086

CELL & GENE THERAPY INSIGHTS

MARKET & PATIENT ACCESS

SPOTLIGHT

COMMENTARY

Health Technology Assessment of Gene Therapies in Europe and the USA: Analysis and Future Considerations

Tingting Qiu, Eve Hanna, Monique Dabbous, Borisov Borislav & Mondher Toumi

Gene therapies constitute a new concept of transformative therapies, administered once in a lifetime. The value assessment of these innovative therapies constitutes a challenge for health technology assessment (HTA) bodies. The HTA reports for all seven gene therapies that have to date been granted a market authorization in the European Union (EU) and/or the United States (US) were examined to understand the rationale behind their assessment outcomes and to explore the differences in value assessment across US, England, Scotland, France and Germany. In England, Imlygic® was accepted for use with the manufacturer agreeing to the application of a discount to the list price under a patient access scheme (PAS), while Strimvelis® was recommended due to its cost–effectiveness estimate being considered as reasonable under the highly specialized technology (HST) evaluation. KYMRIAH® and Yescarta® were approved for use within the Cancer Drugs Fund (CDF) in England, conditionally, as long as managed access agreements are upheld. In France, KYMRIAH®, Yescarta®, and Luxturna® were considered as having important actual clinical benefit. In France, GLYBERA® was considered to have 'insufficient' benefit due to its unsustainable and heterogeneous treatment effects. In Germany, the extent of the added benefit of GLYBERA®, KYMRIAH®, and Yescarta® was evaluated as 'non-quantifiable' as the submitted evidence made reliable, comparative assessments difficult. In Germany, Imlygic® was assessed to have no added benefit due to the selection of inappropriate comparators. In Scotland, KYMRIAH® was

accepted for B-cell acute lymphoblastic leukemia treatment with a PAS, while Yescarta® and KYMRIAH® for diffuse large B-cell lymphoma were rejected due to unjustified cost–effectiveness estimates. In the USA, KYMRIAH®, Yescarta®, Luxturna®, and Zolgensma® were evaluated as having substantial net health benefits, however, a high certainty of conclusion for the assessment of Zolgensma® was established. Although the limitations in pivotal studies resulted in substantial uncertainties regarding long-term treatment benefit, there was still a possibility for gene therapies to gain acceptance from HTA bodies. Most importantly, further evidence collection becomes the critical key, not only to reduce the uncertainty in reimbursement decisions, but also to increase the public's confidence in the use of gene therapies.

Cell & Gene Therapy Insights 2019; 5(8), 1043–1059

DOI: 10.18609/cgti.2019.112

INTRODUCTION

Advanced therapy medicinal products (ATMPs) have transformed the disease treatment paradigm, not only alleviating disease symptoms but targeting the primary cause of diseases and curing them through single or short/limited term therapy administration [1]. Regulators have introduced a series of proactive strategies to accelerate the market approval of ATMPs through the adoption of flexible evidence assessment approaches and the implementation of expedited programs [2].

Despite an expanding number of ATMPs with regulatory approval (Table 1), addressing the uncertainties around the value and its impact on pricing and reimbursement decisions of ATMPs remains challenging [3]. ATMPs are generally considered to be costly, partly as a result of the high cost of development, manufacturing, and clinical administration. The coverage decisions are commonly driven by value assessment conducted by Health Technology Assessment (HTA) bodies, which tend to hold a more conservative attitude towards the appreciation of ATMPs as only scarce evidence is available to determine their long-term clinical benefit [4]. Furthermore, it is important to note that payers in the different countries have different perspectives on value appreciation and willingness-to-pay for certain values [5]. Such inconsistences in value appreciation will probably lead to disparity in reimbursement and pricing decisions.

This discussion paper aims to review HTA reports for gene therapies in 5 countries, including the USA, the United Kingdom (England and Scotland), France, and Germany (Table 2). The HTA reports were retrieved from the Institute for Clinical and Economic Review (ICER) [6] in the USA, the National Institute for Health and Care Excellence (NICE) [7] in England in the UK, the French National Authority for Health (HAS) [8] in France, the Federal Joint Committee (G-BA) [9] in Germany, and the Scottish Medicine Consortium (SMC) [10] in Scotland. Furthermore, this paper examines

TABLE 1

Gene therapy with market authorization in European Union and the USA.

Approved country	Brand name	Active substance	Indication	Date of market authorization	Market authorization pathway	Status
EU	GLYBERA®	Alipogene tiparvovec	Familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions	25/10/2012	Approval under exceptional circumstance	Withdrawn (28/10/2017)
EU	Imlygic®	Talimogene laherparepvec	Unresectable metastatic melanoma	16/12/2015	Standard approval	Authorized
EU	Strimvelis®	Autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cdna sequence	Severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID)	26/05/2016	Standard approval	Authorized
USA, EU	KYMRIAH®	Tisangenlecleucel	▸Relapsed or refractory B-cell acute lymphoblastic leukaemia (ALL)	USA: 30/08/2017 EU: 22/08/2018	USA: priority review, breakthrough designation (BTD)	Authorized
			▸Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)	USA: 13/04/2018 EU: 22/08/2018	EU: priority medicine (PRIME)	
USA, EU	Yescarta®	Axicabtagene ciloleucel	DLBCL and primary mediastinal B-cell lymphoma after two or more systemic therapies	USA: 18/10/2017 EU: 23/08/2018	USA: priority review, BTD EU: PRIME	Authorized
USA, EU	Luxturna®	Voretigene neparvovec	Biallelic RPE65 mutation-associated retinal dystrophy	USA: 19/12/2017 EU: 22/11/2018	USA: priority review, BTD	Authorized
USA	Zolgensma®	Onasemnogene abeparvovec-xioi	Pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (*SMN1*) gene	24/05/2019	USA: priority review, BTD	Authorized

TABLE 2

HTA decisions for Gene therapy approved in Europe and the USA.

Brand name	Health technology assessment decisions in each country				
	France	Germany	England	Scotland	USA
GLYBERA®	Not recommended (SMR*: insufficient)	Recommended (Added benefit: proven; Extent of added benefit: non-qualifiable)	NA	NA	NA
Imlygic®	NA	Recommended (Added benefit: no; Extent of added benefit: no)	Recommended with patient access scheme	Not recommended: in the absence of submission of MA holder	NA
Strimvelis®	NA	NA	Recommended	NA	NA
KYMRIAH®	Recommended for hospital use for both indications. ▸B-cell ALL (SMR: important, ASMR: III); ▸DLBCL (SMR: important, ASMR: IV)	Recommended for both indications. (Added benefit: proven Extent of added benefit: non-unqualifiable)	Recommended for use within CDF for both indications, along with market access agreement	▸B-cell ALL: recommended with patient access scheme ▸DLBCL: not recommended	▸At least a small net health benefit ▸ICER met the cost–teffectiveness threshold
Yescarta®	Recommended for hospital use for both indications (SMR: important, ASMR: III)	Recommended for both indication (Added benefit: proven; Extent of added benefit: non-qualifiable)	Recommended for use within CDF for both indications, along with market access agreement	Not recommended for neither indications	▸At least a small net health benefit ▸ICER met the cost–effectiveness threshold
Luxturna®	Recommended for hospital use (SMR: important; ASMR: II)	Ongoing	Ongoing	Ongoing	▸At least a small net health benefit ▸ICER higher than the cost–effectiveness threshold
Zolgensma®	NA	NA	NA	NA	▸High possibility to have a substantial net health benefit. ▸ICER higher than the cost–effectiveness threshold

ASMR: The Improvement of Medical Benefit; ALL: Acute lymphoblastic leukemia; CDF: Cancer Drugs Fund; DLBCL: Diffuse large B-cell lymphoma; ICER: Incremental Cost-Effectiveness Ratio; NA: Not Applicable; SMR: The Medical Benefit.

DOI: DOI: 10.18609/cgti.2019.112 Cell & Gene Therapy Insights - ISSN: 2059-7800

and discusses the differences in value appreciation processes across these five countries to explore the impact of these factors on the reimbursement decision-making for gene therapies.

HEALTH TECHNOLOGY ASSESSMENT FOR SEVEN GENE THERAPIES

GLYBERA® (alipogene tiparvovec)

GLYBERA®, for the treatment of adult patients with familial lipoprotein lipase (LPL) deficiency who have severe or multiple pancreatic crises despite a low-fat diet, was reviewed by the HAS in France and by the G-BA in Germany. GLYBERA® was withdrawn from EU on 28 October 2017 since the MA holder decided not to apply for a renewal of MA.

France: HAS

The HAS stated that the actual benefit of GLYBERA® was insufficient (SMR: insufficient) to be recommended in the list of reimbursable products for the following reasons: 1) moderate effect on the blood triglyceride level was not maintained beyond one year, and the patient responses to treatment were heterogeneous; 2) no proof that GLYBERA® had an impact in the prevention of pancreatitis; 3) uncertainties about its short- and medium-term safety due to its complex mode of administration. Taking the limitations in methodology (open, before/after, small patient number, questionable primary efficacy endpoint) into account, the benefit of GLYBERA® could not be established [11].

Germany: G-BA

The G-BA evaluated the extent of added benefit of GLYBERA® as 'non-quantifiable' because the data provided by manufacturers did not permit a reliable assessment. The G-BA pointed out that the pivotal studies had a high risk of bias in study design and outcomes. The study populations and dosage regime only partially complied with approved label. In line with the European Medicines Agency's request for the establishment of a patient registry and further data collection regarding its efficacy and safety, the G-BA's decision was only valid for one year, at which time the re-evaluation of GLYBERA® would begin based on the new evidence collected [12].

IMLYGIC® (TALIMOGENE LAHERPAREPVEC)

Imlygic® for the treatment of unresectable, regionally or distantly metastatic melanoma has been evaluated in England and Germany. NICE considered it to be cost-effective when compared with available treatments other than immunotherapies, while the G-BA assessed Imlygic® to have no added benefit due to the use of an inappropriate comparator from the G-BA perspective.

The United Kingdom: England: NICE

Not the same as the indication approved by EMA, NICE

DOI: 10.18609/cgti.2019.112

recommended that the use of Imlygic® should be restricted to adult patients whose diseases were not suitable for immunotherapies. As agreed in the patient access scheme, the manufacturing company must apply a discount to Imlygic®'s list price. Imlygic® was proven to have a significant improvement in overall survival and complete response compared with an ineffective treatment (GM-CSF). However, a reliable assessment for the effectiveness of Imlygic® against currently used immunotherapies (such as ipilimumab) was difficult due to a lack of evidence. This made the ICER appreciation for Imlygic® versus immunotherapies impossible. Nevertheless, NICE considered Imlygic® to be cost-effective compared to dacarbazine and the best supportive care [13].

Germany: G-BA

The G-BA distinguished between three treatment populations: 1) treated naïve adults with BRAF V600 mutant tumor, 2) treated naïve adults with BFAR V600 wild type tumor; and 3) pre-treated adults. The German HTA body also specified a different, appropriate comparator therapy for each treatment population. The manufacturer-selected comparator, GM-CSF, did not concur with any of the research questions and was not approved for the treatment of melanoma. The Institute for Quality and Efficiency in Health Care (IQWIG), which advises the G-BA, considered that no studies allowing for an indirect comparison with the appropriate comparator therapy were presented. As no suitable data from which an added benefit could be derived was available, an added benefit of Imlygic® was not proven [14].

STRIMVELIS®

Strimvelis® for the treatment of severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID) has been evaluated in England only. Additionally, Italy, as the only country with a licensed manufacturing center for Strimvelis®, also agreed to reimburse it with a pay for performance deal.

England: NICE

NICE has recommended Strimvelis® as an option for the treatment of severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID). Strimvelis® was considered as a highly specialized technology (HST) due to the ultra-rare nature of its target disease and its innovative mechanism of action. Despite the uncertainty in small patient number and uncontrolled study design, NICE determined that Strimvelis® showed clinical benefits in improving survival and reconstituting the patients' immune system. Moreover, its advantages over hematopoietic stem cell transplantation (HSCT) in terms of lower risk of post-treatment mortality and the lack of graft-versus-host disease (GvHD) were also appreciated. NICE believed that Strimvelis® had an ICER lower than the cost–effectiveness threshold (£100,000 per QALY gained) that is commonly considered as acceptable as a HST, even when several health-related benefits and wider benefits of Strimvelis® were not captured in the economic analysis [15].

KYMRIAH® (Tisagenlecleucel)

KYMRIAH®, indicated for the treatment of B-cell acute lymphoblastic leukaemia (ALL) and for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL), has been evaluated in five countries (UK, France, Germany, Scotland, and the USA). It is reimbursed for both indications in four countries (England, France, Germany, and the USA). In Scotland, KYMRIAH®, was reimbursed for the treatment of B-cell ALL, yet failed to be accepted for the treatment of DLBCL.

The United Kingdom: England: NICE

NICE recommended KYMRIAH® for both indications in the treatment of B-cell ALL and DLBCL, with funding from the Cancer Drugs Fund (CDF) via a managed entry agreement detailing the conditions of the recommendation [16,17]. The CDF provides interim funding for promising new cancer treatments in order to facilitate patient access, primarily where NHS, based on NICE recommendation, is unwilling and/or unable to fund [18]. The cost–effectiveness estimate for KYMRIAH® was higher than the threshold which NICE normally considers as acceptable. Therefore, KYMRIAH® was not recommended for routine use in England. Additional data will be collected from ongoing clinical trials (ELIANA study for B-cell ALL patients and JULIET study for DLBCL patients) and from UK routine, population-wide public health databases to address uncertainties surrounding: 1) more mature data to support its curative nature; 2) rate of subsequent stem cell transplant (in case of B-cell ALL); 3) the number of patients who will need intravenous immunoglobulin treatment and the treatment duration. NICE will begin a review of the current guideline once the additional data becomes available.

The United Kingdom: Scotland: SMC

The SMC recognized KYMRIAH®'s higher overall remission rate compared with historical controls in the treatment of B-cell ALL indicated in the pivotal ELIANA study, and agreed to accept greater uncertainty in the economic analysis of an ultra-orphan drug. KYMRIAH® was accepted for reimbursement in B-cell ALL treatment with the implementation of Patient Access Scheme (PAS) to improve its cost–effectiveness. Additionally, opinions from the Patient and Clinical Engagement (PACE) process were also taken into account. They concluded that, as a potentially life-extending and even curative treatment, KYMRIAH® could help reduce the emotional burden and improve overall quality of life for B-cell ALL patients [19]. However, KYMRIAH® was not recommended for DLBCL because the treatment cost in relation to its health benefits was not sufficiently justified, in addition to a lack of robust economic analysis [20].

France: HAS

The HAS has considered KYMRIAH® to have a high actual clinical benefit (SMR: important) and a moderate clinical added benefit (ASMR: III) for the treatment of

DOI: 10.18609/cgti.2019.112

B-cell ALL based on the evidence that high rates of complete remission were achieved in both the ELIANA and ENSIGN studies (approximately 67% in the intention to treat population) [21]. The HAS also assessed KYMRIAH® as having a high actual clinical benefit (SMR: important) and a minor clinical added value (ASMR: IV) for the treatment of DLBCL [22]. HAS suggested that the precise quantification of clinical benefits was difficult due to the lack of comparative studies versus existing treatments. Uncertainties remained in the persistence of efficacy, long-term safety and the impact of complex treatment process on actual efficacy. Health authorities at HAS further pointed out that the administration of KYMRIAH® should only be limited to a small number of qualified healthcare institutions.

Germany: G-BA

The added benefit of KYMRIAH® in both B-cell ALL and DLBCL was considered to be already proven due to its orphan drug status within German regulation in early benefit assessment. The G-BA evaluated the extent of additional benefit of KYMRIAH® for the treatment of B-cell ALL and DLBCL as 'non-quantifiable' due to data scarcity and the uncertainty in short follow-up duration, incomplete patient recruitment, the impact of bridging therapy (chemotherapy received before KYMRIAH® treatment), and the indirect comparison with historical evidence [23,24].

USA: ICER

ICER stated that the uncertainty in a non-comparative study with small patient size and short follow-up made it difficult to evaluate the magnitude of health benefit compared to other therapies. However, considering KYMRIAH®'s superior efficacy and manageable adverse effects, ICER did recognize that it at least offered a small net health benefit compared with current salvage chemotherapy in both B-cell ALL and DLBCL patients. KYMRIAH® was, therefore, considered to provide clinical benefits in terms of the improvement of Quality-Adjusted Life-Years (QALYs) and the survival rate versus the comparator, and meeting the commonly cited cost–effectiveness threshold in the USA ($150,000 per QALY) [25].

YESCARTA® (AXICABTAGENE CILOLEUCEL)

Yescarta® for the treatment of diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) has been evaluated in 5 countries (UK – England, UK – Scotland, France, Germany, and the USA).

England: NICE

NICE recommended Yescarta® for use within the CDF along with a managed access agreement outlining the conditions of the recommendation. Yescarta® met NICE's requirements for a life-extending treatment at the end of life. NICE recognized its clinical benefits shown in increasing patients' survival (overall or progression-free) and response rates. However, the exact magnitude of Yescarta®'s benefit was unknown due to the limitation regarding short follow-up duration

and the non-comparative design of pivotal study. NICE requested that further data be collected from ongoing clinical trial (ZUMA-1) in order to reduce the uncertainty in survival (overall and progression-free) and immunoglobulin use until February 2022. Once this data is obtained and made available, NICE will re-evaluate whether it should be recommended for use and update the current guidance accordingly [26].

France: HAS

HAS considered Yescarta® had a high actual clinical benefit (SMR: important) and a moderate clinical added benefit (ASMR: III) for both indications [27], unlike KYMRIAH®. This assessment was made primarily relying on the results of ZUMA-1 study, in which Yescarta® showed potential clinical benefits in complete response rate and 18-month survival rate. However, HAS requested that further data be collected and provided to address the uncertainties regarding the efficacy, safety, and complexity of the treatment process. Yescarta®'s use should be restricted to a small number of specifically qualified centers.

Germany: G-BA

The added benefit of Yescarta® was considered as proven due to its orphan drug status, while the extent of added benefit of Yescarta® was evaluated as 'non-quantifiable'. As suggested in the SCHOLAR-1 study, the G-BA acknowledged that Yescarta® had a potential advantage in improving the overall survival for both DLBCL and PMBCL patients. Considering the disease severity and poor prognosis, the improvement in overall survival could be of high meaning. However, due to the limitation regarding indirect historical comparison and further uncertainty in the ZUMA-1 study, the comparative assessment for other outcomes on morbidity, adverse effects, and quality of life was not possible. The decision made by the G-BA will remain valid until the 15th of May, 2022, at which time the G-BA will update the benefit assessment of Yescarta® based on new evidence, which could be generated from an ongoing clinical trial (such as the 60-month data of the ZUMA-1 study) or prospective comparative studies beyond the pivotal trial [28].

Scotland: SMC

Despite the advice from PACE process that Yescarta® could potentially achieve a durable response and be a life-extending treatment option, the SMC did not recommend its use in Scotland. It was not accepted as the SMC considered that the limitations in ZUMA-1 study (study design and no subgroup analysis) and SCHOLAR-1 (bridging chemotherapy, population heterogeneity and no baseline data) caused uncertainty in Yescarta®'s long-term benefits. Although the SMC agreed to accept more uncertainty in the economic analysis of ultra-orphan medicines, they claimed that Yescarta®'s cost in relation to its long-term benefits was not sufficiently justified [29].

The USA: ICER

ICER evaluated that the net health benefit of Yescarta® might be substantial as it showed clinical advantages

DOI: 10.18609/cgti.2019.112

in terms of complete remission rate, disease-free survival, and overall survival compared with other therapies. While the certainty for this conclusion was low due to limitations of non-comparative trial with small size and short follow-up, Yescarta®'s clinical benefits contributed to a cost–effectiveness estimate that met the commonly cited cost–effectiveness threshold in the USA [25].

LUXTURNA® (VORETIGENE NEPARVOVEC)

Luxturna® for the treatment of inherited retinal dystrophies caused by RPE65 gene mutations has been evaluated in France and the USA. The assessment in the UK, Germany, and Scotland is currently ongoing and expected to be published in late 2019 or early 2020.

France: HAS

The HAS considered Luxturna® to have a high actual clinical benefit (SMR: important) and an important clinical added benefit (ASMR: II). This assessment was made based on its proven efficacy in a pivotal Phase 3 study. Moreover, disease severity, rarity, and the unavailability of alternative treatments for the target disease were also key factors for this positive recommendation. HAS requires that the treatment be limited to specialized institutions, with treatment decisions made by multidisciplinary consultation meetings and based on a set of medical examinations. Follow-up studies to collect data on patient characteristics, treatment patterns, conditions of use, long-term efficacy, safety, and impact on quality of life must also be conducted. The HAS will re-evaluate the drug benefit once the 5 years of data collection has been completed [30].

USA: ICER

ICER evaluated Luxturna® to have significantly improved health outcomes compared to the standard of care (SoC), while potential harms related to surgical aspects of administration were also considered. Therefore, Luxturna® was found to provide, at least, a small net health benefit. The high cost made it unlikely to be a cost-effective intervention at the commonly used cost–effectiveness threshold in the USA [31]. However, inclusion of the indirect and non-medical costs would decrease the total incremental cost and, therefore, the corresponding cost–effectiveness ratio. ICER recognized uncertainty around the relevance of the primary endpoint in the real-world setting, as well as its long-term effect on retinal degeneration.

ZOLGENSMA® (ONASEMNOGENE ABEPARVOVEC)

Zolgensma® for the treatment of spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron (SMN) 1 gene has been evaluated by ICER in April 2019. This evaluation was updated on May 24th, 2019 to align with the Food and Drug Administration (FDA) approval.

USA: ICER

Zolgensma® was found to improve motor function, survival, and reduce

the needs for permanent ventilator support. Despite the limitation of a single-arm, open label study with small patient number, ICER had high certainty that Zolgensma® would provide a substantial net health benefit [32]. The value-based price benchmark of Zolgensma® would be $1.1–1.9 million in order to meet the commonly cited cost–effectiveness threshold ($100,000–150,000) from the QALY perspective, but a higher price ($1.2–2.1 million) could be possible to achieve if the alternative threshold for cost per Life-Year (LY) gained was used. The limitation in study design raised concerns in the generalizability of results to a broader population as well as the possibility in treatment effect overestimation as seen in single arm trials.

CONCLUSION: DISCREPANCY IN THE HEALTH TECHNOLOGY ASSESSMENT OF GENE THERAPY

Gene therapies have usually been approved based on short-term clinical data derived from non-comparative, open-labelled studies with short follow-up durations and small patient populations. Such limitations in pivotal clinical trials methodology have led to uncertainties regarding gene therapies' long-term efficacy and safety and furthermore, have made the precise assessment of gene therapy' benefit and cost–effectiveness challenging.

Value appreciation

In general, value appreciation constituted one of the most important factors for the reimbursement decisions (Table 3), while different countries showed varying perspectives on the weights allocated to each attribute [33].

France emphasized clinical effectiveness, disease severity and rarity as well as the unmet medical needs of the disease area and patients, as can be seen in the fact that all recommended gene therapies (KYMRIAH®, Yescarta®, and Luxturna®) were evaluated as having 'important' actual clinical benefit.

Germany underlined the comparative benefits against available treatments. Therefore, the limitations of indirect historical comparison were mentioned as one of the important reasons for the unavailability of accurate benefit assessments for GLYBERA, KYMRIAH® and Yescarta®. Not surprisingly, Imlygic® was evaluated with no added benefit due to the inappropriateness of comparator from G-BA perspective.

In the UK (England and Scotland), as in the USA, great importance is attached to cost–effectiveness analysis. NICE defined a higher ICER threshold for ultra-orphan drugs evaluated under the HST pathway. The SMC introduced a new approach for the assessment of ultra-orphan drugs, in which a higher uncertainty in economic analysis could be acceptable. This was the case with Strimvelis® for ADA-SCID treatment in England, as well as KYMRIAH® for B-cell ALL treatment in Scotland.

Reimbursement & affordability strategies

Along with the disparity in value assessment, different strategies were adopted in each country to achieve prompt market access to innovative

DOI: 10.18609/cgti.2019.112

TABLE 3

The uncertainty in available evidence identified by HTA body.

Branch name	Uncertainty existed in the submitted evidence
GLYBERA®	▸ HAS: short and medium-term safety accompanying with the complex administration process ▸ G-BA: bias resulted from included population and dosage regime in pivotal studies
Imlygic®	▸ NICE: comparative effectiveness against currently used immunotherapies ▸ G-BA: comparators were not relevant to research questions and not approved for use in same indication
Strimvelis®	▸ NICE: limited evidence for comparator
KYMRIAH®	▸ HAS: long-term efficacy and safety; impact of complex administration process ▸ G-BA: incomplete patient recruitment, the influence of bridging therapy and historical comparison ▸ SMC: the justification of cost in relation to the health benefit
Yescarta®	▸ HAS: long-term efficacy and safety; impact of complex administration process ▸ G-BA: the effect on morbidity, adverse effects and quality of life compared to other therapies ▸ SMC: questionable study design (no subgroup analysis, population heterogeneity and lack of baseline data) ▸ NICE: the exact magnitude of treatment benefit on survival rate and immunoglobulin use
Luxturna®	▸ HAS: long-term efficacy, safety and impact on quality of life ▸ ICER: the validity of primary endpoint, and effect on retinal degeneration
Zolgensma®	▸ ICER: the generalizability of results; the possibility of effect exaggeration

G-BA: the Federal Joint Committee; HAS: Haute Autorité de Santé; ICER: The Institute for Clinical and Economic Review; NICE: The National Institute for Health and Care Excellence; SMC: The Scottish Medicines Consortium.

gene therapy without impairing healthcare affordability by including costly yet effective treatments in the reimbursement list [34].

In England, all gene therapies except Strimvelis® were recommended for use in combination with a commercial PAS in order to improve the cost–effectiveness profiles. Additionally, despite negative recommendations for routine use in England, two chimeric antigen receptor T cell therapies, KYMRIAH® and Yescarta®, were accepted for interim use in the CDF during further data collection period.

In France, all reimbursed gene therapies were restricted to be administered in qualified healthcare institutions. Moreover, the prescription decision for Luxturna® must be examined by a multi-discipline expert panel, and the HAS will re-evaluate Luxturna®'s benefit after five years based on new evidence.

In Germany, the G-BA holds a conservative attitude in the assessment of extent of added benefit, which is reflected in the fact that all gene therapies (except for Imlygic®) were considered to have 'non-quantifiable' added benefit. Additionally, all the assessments were valid for a limited time, with re-evaluation beginning after additional data collection is completed.

TABLE 4

The description of pivotal studies for seven gene therapies.

Study design	Patient size	Primary endpoints	Register number in clinicaltrail.gov
KYMRIAH®			
- For B-cell ALL			
▶ ELIANA study: Phase 2, single-arm, open-label	81	Overall remission rate per IRC assessment	NCT02435849
▶ ENSIGN study: Phase 2, single-arm, open-label	64	Overall remission rate 1) per IRC assessment 2) per local Investigator assessment	NCT02228096
- For DLBCL			
▶ JULIET study: Phase 2, single-arm, open-label	167	Overall response rate	NCT02445248
Luxturna®			
▶ Study 301: Phase 3, randomized control, open-label study; control group: patients receiving no intervention	31	Multi-luminance Mobility Testing (MLMT), Bilateral	NCT00999609
Zolgensma®			
▶ CL-101 study: Phase 1, single-arm, two cohorts, open-label	15	Number of Participants 1) experienced one grade III or higher unanticipated, treatment-related toxicity; 2) requirement of ≥16-hour respiratory assistance per day ≥2 weeks; 3) CHOP-INTEND score	NCT02122952
▶ STR1VE study: ongoing Phase 3 study: single-arm, open-label	20	1) The proportion of patients achieving the milestone of sitting without support for at least 30 seconds at 18 months of age 2) survival at 14 months of age	NCT03306277
▶ START study: observational, long-term follow up study up to 5 years	15	Long-term safety	NCT03421977
Imlygic®			
▶ OPTiM Study (Study 005/05): Phase 3, randomized, controlled, open-label study; Control group: GM-CSF	437	Durable response rate (defined as the rate of objective response, complete or partial)	NCT00769704

ALL: Acute Lymphocytic Leukemia; CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; DLBCL: Diffuse Large B-cell Lymphoma; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; IRC: Independent Review Committee.

DOI: 10.18609/cgti.2019.112

TABLE 4 CONTINUED

The description of pivotal studies for seven gene therapies.

Study design	Patient size	Primary endpoints	Register number in clinicaltrail.gov
Strimvelis®			
▸ Study AD1115611: Phase 1/2, single-arm, open label	12	Survival rate up to 1 year	NCT00598481
Yescarta®			
▸ ZUMA-1 study: Phase 1/2, single-arm, open label	118	Percentage of participants experiencing adverse events; overall response rate	NCT02348216
▸ SCHOLAR-1 study: multi-cohort, retrospective, pooled analysis data from two randomised controlled studies and two retrospective databases; Control group: salvage chemotherapies	636	Response rate, complete response and overall survival	Not available
GLYBERA®			
▸ CT-AMT-010-01 study: single-arm, open-label, dose-escalating study	8	Reduction of fasting triglyceride (TG) concentrations; toxicity	Not available
▸ CT-AMT-011-01 study: single-arm, open-label, dose-escalating study	14	Reduction of fasting triglyceride (TG) concentrations; toxicity	NCT01109498
▸ CT-AMT-011-02 study: single-arm, open-label study	5	Reduction of fasting triglyceride (TG) concentrations; toxicity	NCT00891306

ALL: Acute Lymphocytic Leukemia; CHOP-INTEND: Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; DLBCL: Diffuse Large B-cell Lymphoma; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; IRC: Independent Review Committee.

In Scotland, the SMC took more precautions in the reimbursement of gene therapies with unjustified cost–effectiveness, which resulted in negative recommendations in DLBCL for Yescarta® and KYMRIAH®. Although additional factors including disease rarity, opinions from other stakeholders (such as patient advocacy organizations) and the implementation of a PAS were also considered, economic analysis remained the key determinant for reimbursement decision-making.

Clinical trials methodology & further data collection requirements

Apart from the commonly cited study limitations (single-arm,

open label, small patient number, and short follow-up) in pivotal studies, some additional weaknesses in study methodologies were also noticed in certain countries. For example, the SMC indicated concerns for population heterogeneity in the SCHOLAR-1 study, while ICER doubted whether the primary endpoint used in the Phase 3 study for Zolgensma® would be well correlated with outcomes in real-world setting (Table 3). This indicated payers' insights on areas for improvement in clinical trial design and what evidence will still be required in the future to minimize uncertainties. However, there were differences with regards to the uncertainty that most concerned the payers across the countries included in this study. This suggests that further data collection must take into consideration the different evidence requirements on a country-by-country basis, thus, the administration burden for manufacturers may not be negligible [35].

TRANSLATION INSIGHTS

Substantial limitations in the study methodology have raised concerns regarding the long-term efficacy and safety for most gene therapies. Various approaches were used by different HTA bodies to minimize the potential risk of accepting costly gene therapies with uncertain outcomes or severe impact on the reimbursement list. England was able to use side pathways to reimburse such products, via the HSTC and the CDF. Germany has relied on a law that systematically grants added benefit for orphan designated products. France has shown an unusually generous attitude towards gene therapies. Scotland has used modifiers for orphan drugs to boost the access of gene therapies.

One way or another, all countries have considered a reassessment as more data is collected in the real world to inform future decisions in continuing to maintain the reimbursement of these gene therapies. One must acknowledge that despite the evidence presented by gene therapy manufacturers not matching the standard requirements of HTA agencies - having no comparative studies with single arm trials, short term durations, and surrogate endpoints in some cases (Table 4) – to date, most gene therapies have successfully gained reimbursement. It is doubtful these therapies would have been as successful in achieving these favorable results had they not been gene therapies.

It is unclear how long such favorable attitude towards these gene therapies will endure. However, it is sending a strong positive signal to manufacturers that payers are open to such innovation and face some informal resistance to refuse access to gene therapies.

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

DOI: 10.18609/cgti.2019.112

Disclosure and potential conflicts of interest: *Dr. Hanna reports personal fees from Creativ-ceutical, outside the submitted work. The authors declare that they have no other conflicts of interest.*

Funding declaration: *The authors received no financial support for the research, authorship and/or publication of this article.*

ARTICLE & COPYRIGHT INFORMATION

Article source: *Invited*

Revised manuscript received: *Jul 4 2019*; *Publication date: Sep 2 2019*.

REFERENCES

1. Buzhor E, Lenshansky L, Blumenthal J *et al.* Cell-based therapy approaches: the hope for incurable diseases. *Regen. Med.* 2014; 9: 649–72.
2. Jokura Y, Yano K, Yamato M. Comparison of the new Japanese legislation for expedited approval of regenerative medicine products with the existing systems in the USA and European Union. *J. Tissue Eng. Regen. Med.* 2018; 12: e1056–e1062.
3. Davies BM, Smith J, Rikabi S et al. A quantitative, multi-national and multi-stakeholder assessment of barriers to the adoption of cell therapies. *J. Tissue Eng.* 2017; 8: 2041731417724413.
4. Bubela T, McCabe.C., Archibald P *et al.* Bringing regenerative medicines to the clinic: the future for regulation and reimbursement. *Regen. Med.* 2015; 10: 897–911.
5. Denis A, Mergaert L, Fostier C, Cleemput I, Simoens S. A comparative study of European rare disease and orphan drug markets. *Health Policy* 2010; 97: 173–9.
6. Institute for Clinical and Economic Review (ICER): https://icer-review.org/
7. National Institute for Health and Care Excellence (NICE): https://www.nice.org.uk/
8. French National Authority for Health (HAS): https://www.has-sante.fr/portail/jcms/r_1455081/en/home-page?portal=r_1455081
9. Federal Joint Committee (G-BA): https://www.g-ba.de/english/structure/
10. Scottish Medicine Consortium (SMC): https://www.scottishmedicines.org.uk/
11. GLYBERA (alipogène tiparvovec), thérapie génique (Haute Autorité de Santé, HAS): https://www.has sante.fr/portail/upload/docs/evamed/CT-14224_GLYBERA_PIC_INS_Avis3_CT14224.pdf
12. zum Beschluss des Gemeinsamen Bundesausschusses über einen Antrag auf Verlängerung der Befristung der Geltungsdauer eines Beschlusses über die Nutzenbewertung nach § 35a SGB V – Alipogentiparvovec (Gemeinsamer Bundesausschuss, GBA): https://www.g-ba.de/downloads/40-268-4392/2017-05-18_AM-RL-XII_Alipogentiparvovec_Fristverlaengerung_D-138_TrG.pdf
13. Talimogene laherparepvec for treating unresectable metastatic melanoma (The National Institute for Health and Care Excellence, NICE): https://www.nice.org.uk/guidance/ta410/documents/final-appraisal-determination-document
14. zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Talimogen laherparepvec (Gemeinsamer Bundesausschuss, GBA): https://www.g-ba.de/downloads/40-268-4103/2016-12-15_AM-RL-XII_Talimogen-laherparepvec_D-237_TrG.pdf

15. Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency (The National Institute for Health and Care Excellence, NICE): https://www.nice.org.uk/guidance/hst7/resources/strimvelis-for-treating-adenosine-deaminase-deficiencysevere-combined-immunodeficiency-pdf-1394905926085

16. Tisagenlecleucel for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in people aged up to 25 years(The National Institute for Health and Care Excellence, NICE): https://www.nice.org.uk/guidance/ta554/resources/tisagenlecleucel-for-treating-relapsed-or-refractory-bcell-acute-lymphoblastic-leukaemia-in-people-aged-up-to-25-years-pdf-82607021872837

17. Tisagenlecleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic therapies(The National Institute for Health and Care Excellence, NICE): https://www.nice.org.uk/guidance/ta567/resources/tisagenlecleucel-for-treating-relapsed-or-refractory-diffuse-large-bcell-lymphoma-after-2-or-more-systemic-therapies-pdf-82607087377861

18. NHS England-Cancer Drug Fund: https://www.england.nhs.uk/cancer/cdf/

19. tisagenlecleucel 1.2 x 106 – 6 x 108 cells dispersion for infusion (KYMRIAH®)(The Scottish Medicines Consortium, SMC): https://www.scottishmedicines.org.uk/media/4132/tisagenlecleucel-KYMRIAH-final-jan-2019-for-website.pdf

20. tisagenlecleucel 1.2 x 106 to 6 x 108 cells dispersion for infusion (KYMRIAH®)(The Scottish Medicines Consortium, SMC): https://www.scottishmedicines.org.uk/media/4228/tisagenlecleucel-kymriah-final-feb-2019-amended-7319-for-website.pdf

21. KYMRIAH (tisagenlecleucel), CAR T anti-CD19 (LAL)(Haute Autorité de Santé, HAS): https://www.has-sante.fr/portail/upload/docs/application/pdf/2018-12/kymriah_lal_pic_ins_avis3_ct17202.pdf

22. KYMRIAH (tisagenlecleucel), CAR T anti-CD19 (LDGCB) (Haute Autorité de Santé, HAS): https://www.has-sante.fr/portail/upload/docs/application/pdf/2018-12/kymriah_ldgcb_pic_ins_avis3_ct17238.pdf

23. zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Tisagenlecleucel (akute lymphatische B-ZellLeukämie) (Gemeinsamer Bundesausschuss, GBA): https://www.g-ba.de/downloads/40-268-5623/2019-03-07_AM-RL-XII_Tisagenlecleucel-ALL_D-376_TrG.pdf

24. zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Tisagenlecleucel (diffus großzelliges B-ZellLymphom) (Gemeinsamer Bundesausschuss, GBA):https://www.g-ba.de/downloads/40-268-5622/2019-03-07_AM-RL-XII_Tisagenlecleucel-DLBCL_D-375_TrG.pdf

25. Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value(The Institute for Clinical and Economic Review, ICER): https://icer-review.org/wp-content/uploads/2017/07/ICER_CAR_T_Final_Evidence_Report_032318.pdf

26. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies (The National Institute for Health and Care Excellence, NICE): https://www.nice.org.uk/guidance/ta559/resources/axicabtagene-ciloleucel-for-treating-diffuse-large-bcell-lymphoma-and-primary-mediastinal-large-bcell-lymphoma-after-2-or-more-systemic-therapies-pdf-82607030270917

27. YESCARTA (axicabtagene ciloleucel), CAR T anti-CD19(Haute Autorité de Santé, HAS): https://www.has-sante.fr/portail/upload/docs/application/pdf/2018-12/yescarta_pic_ins_avis3_ct17214.pdf

28. zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V Axicabtagen-Ciloleucel (Gemeinsamer Bundesausschuss, GBA): https://www.g-ba.de/downloads/40-268-5741/2019-05-02_AM-RL-XII_Axicabtagen-Ciloleucel_D-406_D-416_TrG.pdf

29. axicabtagene ciloleucel 0.4 – 2 x 108 cells dispersion for infusion dispersion for infusion (Yescarta®)(The Scottish Medicines Consortium, SMC): https://www.scottishmedicines.org.uk/media/4121/axicabtagene-ciloleucel-yescarta-final-nov2018-for-website.pdf

30. LUXTURNA (voretigene neparvovec), thérapie génique (Haute Autorité de Santé, HAS): https://www.has-sante.fr/portail/upload/docs/evamed/

DOI: 10.18609/cgti.2019.112

CT-17535_LUXTURNA_PIC_INS_Avis2_CT17535.pdf

31. Voretigene Neparvovec for Biallelic RPE65- Mediated Retinal Disease: Effectiveness and Value (The Institute for Clinical and Economic Review, ICER): https://icer-review.org/wp-content/uploads/2017/06/MWCEPAC_VORETIGENE_FINAL_EVIDENCE_REPORT_02142018.pdf

32. Spinraza® and Zolgensma® for Spinal Muscular Atrophy: Effectiveness and Value (The Institute for Clinical and Economic Review, ICER): https://icer-review.org/wp-content/uploads/2018/07/ICER_SMA_Final_Evidence_Report_052419.pdf

33. Rémuzat C, Mzoughi O, Rodrigues J, Korchagina D, Toumi M. HTA Assessment Comparison Of Orphan Drugs In France And Germany. *Value Health* 2014; 17: A236–A237.

34. Jorgensen J, Mungapen L, Kefalas P, Data collection infrastructure for patient outcomes in the UK - opportunities and challenges for cell and gene therapies launching. *J. Mark. Access Health Policy* 2019; 7: 1573164.

35. Kaemmerer WF. How will the field of gene therapy survive its success? *Bioeng. Transl. Med.* 2018; 3: 166–77.

AFFILIATIONS

Tingting Qiu
Aix Marseille University, Public Health Department, 27, bd Jean Moulin, 13385 Marseille Cedex 05, France

Eve Hanna
Creativ-Ceutical, 215, rue du Faubourg St-Honoré, 75008 Paris, France

Monique Dabbous
Aix Marseille University, Public Health Department, 27, bd Jean Moulin, 13385 Marseille Cedex 05, France

Borislav Borissov
Prescriptia 28, Hristo Botev Blvd, Sofia, Bulgaria

Mondher Toumi
Author for correspondence
Aix Marseille University, Public Health Department, 27, bd Jean Moulin, 13385 Marseille Cedex 05, France
mondher.toumi@univ-amu.fr

CELL & GENE THERAPY INSIGHTS

MARKET & PATIENT ACCESS

SPOTLIGHT

COMMENTARY

Genetic-based therapies: looking ahead to ensuring access to a cure for cystic fibrosis

Lisa B Feng, Jacqueline V Erdo & Mary B Dwight

Recent scientific advancements have accelerated research for a cure for cystic fibrosis (CF). Research is underway for genetic-based therapies such as gene therapy, gene editing, and RNA therapy. However, great optimism is countered by concerns about how and if patients will have access to a future cure. As health care decisionmakers look to solutions for paying for and ensuring access to curative therapies, they should: integrate patient preferences into new payment mechanisms for a cure; design insurance benefits to incentivize highly effective therapies; and ensure equity.

Submitted for Peer Review: XXX ▶ **Published:** XXX

Cell & Gene Therapy Insights 2019; 5(8), 573–576

DOI: 10.18609/cgti.2019.066

Recent scientific advancements, notably the development of the CRISPR Cas9 gene editing technology, have accelerated research for a cure for cystic fibrosis (CF). Cystic fibrosis is a recessive, genetic disease that affects approximately 35,000 people in the United States [1]. The disease is caused by mutations of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that encodes the CFTR protein which regulates chloride flow in epithelial cell surfaces. There are over 1,700 documented variants of the *CFTR* gene and nearly 350 known to cause CF [2]. These mutations lead to reduced or absent CFTR protein, resulting in the accumulation of thick and sticky mucus in affected organs, including the lungs, gastrointestinal tract, nasal airways, and pancreas [3]. Progressive airway

destruction characterized by loss of lung function is the predominant cause of death [4].

Health outcomes for cystic fibrosis have greatly improved due to more effective treatments and a comprehensive multidisciplinary care model, however, genetic-based therapies are required to deliver a cure – ultimately, a treatment that will permanently correct the defect in the *CFTR* gene. While the long-term goal of a cure is for children with CF to never experience symptoms of the disease, many living with CF may have to manage the symptoms and complications associated with advanced disease even if they receive a genetic fix.

As the world's largest funder of CF research and advocate for people with CF, we believe innovation should be rewarded. Bringing a cure to market, from the basic science lab through the Food and Drug Administration, takes tremendous time and financial resources. This investment is worthwhile, and we will work relentlessly to fulfill this dream for the CF community, which has invested decades to increase awareness, participate in research, improve care, and raise funds to support the search for a cure.

The Cystic Fibrosis Foundation (CFF) is committed to exploring all appropriate approaches for genetic-based therapies to restore CFTR for all people with CF, including gene therapy, gene editing, and RNA therapy. This process is rife with scientific challenges, but incremental successes have bolstered our confidence and hope that a safe and effective cure is possible. The great optimism for the discovery of a cure, however, is dampened by concerns about how and if patients would have access to these therapies once they are available. Recent cures in other rare diseases, including hereditary blindness and spinal muscular atrophy, loom at a million dollars or more per patient.

As we anticipate the scientific promise of a cure for many more diseases, we know that today's healthcare system is not designed to absorb and withstand an influx of demand for multi-million-dollar treatments. Public payers like Medicare and state Medicaid programs who cover some of the nation's most vulnerable will be challenged to handle large one-time payments for cures. Similarly, self-insured employers who manage risk among employees will have to make the difficult decision about whether to offer expensive cures at all.

Innovation must be accessible. Looking to the future, it is incumbent upon all healthcare stakeholders — drug manufacturers, policy makers, public and private payers, think tanks, advocates, and others — to prepare for a scenario where thousands of people with serious diseases may qualify for a high-cost cure.

More specifically, the treatment must be covered by insurance. This is the basic requirement for access for those who are insured. Further, the criteria for coverage should be clinically appropriate with minimally necessary documentation requirements for patients and clinicians. Additionally, acquiring the therapy should not cause undue financial burden to the patient. Today, patients experience significant financial burden; insurance benefits are not designed to enable affordable access for people living

DOI: 10.18609/cgti.2019.066

with chronic illnesses like CF to the care they need. This promising new era of curative therapies presents the opportunity to find innovative ways to pay for these treatments so that patients don't face the impossible question of whether or not they can afford a cure. There is some exciting work on payment and access already underway. We recommend healthcare decision-makers focus on the following issues as they consider policy solutions for ensuring access to a cure for CF.

- Integrate patient preferences into new payment mechanisms for a cure: as the system moves toward structuring payments to be made over time and tying them to demonstrated benefits of the drug, known as outcomes-based contracts, knowing what is meaningful to patients is paramount. Manufacturers and payers who agree upon pre-determined performance milestones should consider clinical and patient-reported measures. There must be more research and expertise in this area. Efforts to achieve multi-stakeholder consensus that includes patient advocacy organizations like the Cystic Fibrosis Foundation would help ensure alignment on this new approach;

- Design insurance benefits to incentivize highly effective therapies: concurrent with efforts to find alternative ways for payers to pay for high-cost gene therapies, payers should also develop coverage schemes that enable access for beneficiaries. High deductible health plans, or other plan designs that require high cost sharing from enrollees, would make a cure unaffordable for many patients. New coverage schemes must enable and encourage access to highly effective therapies, including a cure;

- Ensure equity: all people with cystic fibrosis should have the same opportunity to achieve optimal health, regardless of who they are or where they live. Socioeconomic status and type of insurance should not prevent access to a cure. Any policy solutions to pay for cures must prevent a gap between those who can and cannot access the treatments.

Many lessons will be learned in the coming years as cures are discovered and available. Healthcare leaders have the difficult yet exciting task of evolving our system into one that allows for swift access to cures for life-threatening diseases like cystic fibrosis in a way that rewards innovators without bankrupting payers and patients. At a time when we can plausibly imagine a cure for cystic fibrosis, we must pursue financing models that ensure all people can afford to access such a treatment as vigorously as we pursue the science. People's lives depend on it.

FINANCIAL & COMPETING INTERESTS DISCLOSURE

The authors have no relevant financial involvement with an organization or

entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock options or ownership, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

REFERENCES

1. Knapp EA, Fink AK, Goss CH *et al.* The Cystic Fibrosis Foundation Patient Registry: design and methods of a national observational disease registry. *Ann. Am. Thorac. Soc.* 2016; 13: 1173–9.
2. CFTR2: https://www.cftr2.org/mutations_history
3. Cohen TS, Prince A. Cystic fibrosis: a mucosal immunodeficiency syndrome. *Nat. Med.* 2012; 18: 509–19.
4. Ong T, Ramsey BW. Modifying disease in cystic fibrosis: current and future therapies on the horizon. *Curr. Opin. Pulm. Med.* 2013; 19: 645–51.

AFFILIATIONS

Lisa B Feng, DrPH
Cystic Fibrosis Foundation, USA

Jacqueline Erdo, MPH
Cystic Fibrosis Foundation, USA

Mary B Dwight
Cystic Fibrosis Foundation, USA

DOI: 10.18609/cgti.2019.066

CELL & GENE THERAPY INSIGHTS

MARKET & PATIENT ACCESS

SPOTLIGHT

INTERVIEW

Staying ahead of the curve: NICE's approach to HTA of novel fields of biotech innovation

NICK CRABB had a 20-year career in analytical science, process technology and general management in the chemical, pharmaceutical and contract laboratory industries prior to joining NICE in 2010 as the associate director responsible for establishing and managing the Diagnostics Assessment Programme. In 2014 Nick was appointed to his current role where he oversees NICE Scientific Advice, the Science Policy and Research programme and NICE's input to the European Network for Health Technology Assessment (EUnetHTA). Nick has broad scientific and policy interests relating to the evaluation of technologies and interventions to support the development of clinical, public health and social care guidance. His experience includes consideration of HTA issues arising from the availability of novel new products such as cell and gene therapies and work on methods issues relating to the evaluation of antimicrobials. Nick was also the co-chair of the evaluation and commissioning subgroup of the UK regenerative medicine expert group and led NICE's contribution to a project on the assessment and appraisal of regenerative medicines that reported in 2016.

Cell & Gene Therapy Insights 2019; 5(8), 919–924

DOI: 10.18609/cgti.2019.102

Q Can you summarize your current role at NICE for us – what are your chief activities and priorities?

NC: As Programme Director for Scientific Affairs at NICE, I oversee the NICE Scientific Advice service and the Science Policy and Research programme. I also lead on NICE's input to the European Network for Health Technology Assessment (EUnetHTA).

I have broad scientific and policy interests relating to evaluation of technologies and interventions to support the development of clinical, public health and social care guidance.

"...there's a lot of work going on around reviewing and updating our methods for HTA..."

My personal experience includes consideration of HTA issues arising from the availability of novel products such as cell and gene therapies. Currently, one of my main areas of interest is around methods relating to the evaluation of antimicrobials, where there's a lot of complexity for a number of reasons.

In terms of experience relevant to the cell and gene therapy area, I was a co-chair of the evaluation and commissioning subgroup of the UK regenerative medicine expert group. I also led NICE's contribution to a project on the assessment and appraisal of regenerative medicines, which was undertaken in collaboration with the University of York. That work reported in 2016.

Q NICE has for quite a while been seen as a trailblazer among HTAs in terms of how it assesses novel therapeutic modalities – how are the organization's approaches and processes continuing to evolve around emerging, increasingly commercial fields such as cell and gene therapy?

NC: We work to make sure that our methods are fit for purpose across the full range of health technologies and therapeutic areas – the point of HTA is to be able to look at different technologies and therapeutic areas on a level playing field, and that's really what we try to do. It would therefore be inappropriate to develop specific evaluation methods for cell and gene therapies, for example. There are all sorts of challenges in HTA and many of those challenges relate to cell and gene therapies in the same way as they relate to other products.

That said, one thing we did do to try to stay ahead of the curve with cell and gene therapy was the aforementioned study with the University of York. There are two reports available from that project: a very substantial, excellent technical report from the University of York, and a shorter summary report, published by NICE, that hopefully captures the key issues fairly efficiently.

The project was designed to test whether the NICE health technology assessment methods and processes are fit for purpose for regenerative

DOI: 10.18609/cgti.2019.102

medicines and cell therapies. Part of the project concerned the appraisal of a hypothetical CAR T cell therapy.

A key conclusion was that the NICE appraisal methods and decision framework are applicable to such products, so a fundamentally new approach is not indicated. There are, nonetheless, a range of challenges around the HTA of potential cures and being mindful of these is important in optimizing methods on an ongoing basis.

Since this report, NICE has published guidance on six products that are either cell or gene therapies and in every case, there have been positive recommendations to use the products:

- Holoclar for treating limbal stem cell deficiency after eye burns (TA 467, August 2017, https://www.nice.org.uk/guidance/ta467)
- Autologous chondrocyte implantation for treating symptomatic articular cartilage defects of the knee (TA477, October 2017, https://www.nice.org.uk/guidance/ta477)
- Strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency (HST7, February 2018, https://www.nice.org.uk/guidance/hst7)
- Autologous chondrocyte implantation with chondrosphere for treating articular cartilage defects (ID851, publication expected April 2018, https://www.nice.org.uk/guidance/indevelopment/gid-ta10162)
- Tisagenlecleucel-T for previously treated B-cell acute lymphoblastic leukemia in people aged up to 25 years, (TA554, https://www.nice.org.uk/guidance/TA554)
- Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma after 2 or more systemic therapies, TA559, https://www.nice.org.uk/guidance/TA559)

Essentially, there's a lot of work going on around reviewing and updating our methods for HTA and obviously, any learnings from cell and gene therapies will be part of that. But again, we don't believe we need a fundamentally different framework to deal with these products.

Q Value-based pricing and reimbursement continues to grow as a theme for this field worldwide as more premium-priced, potentially curative therapeutics reach the market – how and where is NICE getting involved in the effort to develop novel models and practices in this regard?

NC: Again, based on our experience to date, we believe that our current methods and framework are essentially fit for purpose, but we are of course committed to ensuring our methods do remain so, and also to adopting best practices as the science develops further.

We actively contribute to the development of improved methods through our Science Policy and Research program. We do this in a number of ways – for example, we help ensure research is undertaken in areas that are specific requirements for NICE, and we also participate in a range of Innovative Medicines Initiative (IMI) projects where we're collaborating with various European partners.

So, we are very actively involved in understanding what the challenges are for HTA across all therapy areas and all technology types, and we're doing our best to stay ahead of those challenges.

One of the key issues around cell and gene therapies – or indeed, any product that seems to offer a potential cure – is the fact that at the point of regulatory approval and launch, very little is really known about the long-term health impact. It may be clear that these products are very promising and that they represent major advances on current therapies, but it's going to take several years of follow-up before the true magnitude of those benefits is properly understood. That makes it very difficult to estimate the full health benefits and cost–effectiveness at the point of launch.

I think that's the crux of the issue here. It is actually a very common problem in HTA, but it does become particularly important where a product offers prolonged benefit or a potential cure. In addition to considering evaluation methods issues, there is an important role for managed access arrangements. This is an area where NICE collaborates closely with NHS England – through the Cancer Drugs Fund, for example – to facilitate timely patient access to promising products while the long-term health impact evidence is still emerging. Similarly, there are a number of examples of the use of managed access arrangements in our highly specialized technologies (HST) program.

Q Are there any other particular current or planned initiatives in which NICE is involved that are of relevance to the cell and gene therapy field?

NC: Yes. I think the main one is a part of our normal, periodic updating of the Technology Appraisals methods guide, which is all about ensuring the latest developments in health technologies and their methods of assessment are being taken into account. NICE will be undertaking a

DOI: 10.18609/cgti.2019.102

full update in 2019, which will include methods and policy developments across all health technology types and therapeutic areas.

> "...the managed access approach we've been talking about is becoming increasingly important..."

Meanwhile in the USA, ICER is currently undertaking a project on Valuing Cures. ICER invited NICE to contribute to this project. We value opportunities to develop and share best practice with international collaborators and were pleased to accept the invitation. We've had some very interesting discussions to date.

Q By this time next year, we are likely to see multiple cell and gene therapy products aimed at the same specific targets and indications competing on the market – how might this impact NICE's assessment of such technologies, particularly those that might be second, third, fourth to market?

NC: Again, I think this is an area which in principle isn't any different to any other therapeutic area or technology area. Essentially, when NICE evaluates any health technology, we assess the incremental benefits and incremental costs compared to the current standard of care, which we call the comparator.

Where a cell or gene therapy has become established as the standard of care, a new competing cell or gene therapy would be assessed against the established product. A competing product could be found to be cost effective either through evidence of superior clinical performance (improved length and/or quality of life), or through evidence of comparable clinical performance at a lower cost.

Q Lastly, can you share NICE's vision moving forward in terms of emerging technology areas such as cell and gene therapy?

NC: Firstly, we're doing a lot of horizon scanning and not just for specific technologies, but for potential issues, and things that might challenge the methods and decision framework paradigms that we have, so that we can get ahead of them.

For example, some cancer drugs are now being developed with an expectation of a site-agnostic indication – there are already licensed products in the USA and potentially some coming through the system in Europe.

That's very challenging to our normal methods, partly as most of the comparator evidence will not be in a site-agnostic sense but will be related to specific anatomical tumor sites.

So that's an area we've picked up as a potentially big issue and we're commissioning research to help us understand how to deal with those sort of products as and when they start coming through to market. If we were to come across similar issues or learning points with cell and gene therapies in future, then that's the type of approach we would take – we always try to understand what technologies are coming through, and the challenges they will pose to our evaluation methods and decision framework.

There are other, related UK initiatives in the technology space – for example, the Accelerated Access Collaborative (AAC), which has a very senior-level Board, including the NICE Chief Executive, covering the whole spectrum of the health innovation pipeline in the UK. The AAC is playing a key role in identifying technologies for fast-tracking through the UK system.

Ultimately, the mission of the health technology assessment side of NICE remains trying to facilitate timely patient access to health technologies that have the potential to really help them – and doing that in a financially sustainable way, of course. I do think the managed access approach we've been talking about is becoming increasingly important in achieving that financial sustainability, particularly given that there remain big questions over the true, long-term patient outcome benefits of these products.

AFFILIATION

Nick Crabb
Programme Director, Science Advice and Research, National Institute for Health and Care Excellence (NICE)

DOI: 10.18609/cgti.2019.102

CELL & GENE THERAPY INSIGHTS

MARKET & PATIENT ACCESS

SPOTLIGHT

INTERVIEW

Interview title text

JANET LYNCH LAMBERT joined ARM in 2017 as the organization's first CEO. With more than 25 years in public and private sector management, Janet is an experienced government relations and business professional with an extensive record of accomplishment. Janet most recently served as the Acting Head of Engagement for the All of Us Research Program at the National Institutes of Health and as head of the Outreach Office in the Office of the NIH Director. Prior to joining NIH, she was Vice President of Government Relations and head of the Washington office of Life Technologies, aiding the company in its growth from $300 million in annual sales to more than $3 billion.

Prior to Life Technologies, Janet held leadership positions in government relations, marketing and business development at large and small life science organizations, including GE and InforMax. Her experience also includes legislative and staff leadership positions in the U.S. Senate and House of Representatives.

Janet received her MBA in International Business from Georgetown University and her B.A. in Political Science from Stanford University. She lives in the Washington, D.C. area with her husband and two daughters.

Cell & Gene Therapy Insights 2019; 5(8), 975–981

DOI: 10.18609/cgti.2019.106

Q It has been a momentous past 2–3 years for cell and gene therapy in terms of advancing towards becoming a fully commercial sector – how have ARM's specific activities and priorities evolved over this period in line with this progress?

JLL: You're absolutely right – it's been a phenomenal couple of years for the cell and gene therapy sector. I like to say we've moved

from a world of very exciting promise to a world of fantastic reality. Of greatest significance has been the arrival on the market in the USA of the first approved gene therapies and gene-modified cell therapies.

I would pick out two major changes to ARM's priorities over this period. Firstly, we have really started to focus on the commercial challenges that face the sector now we have products on the market in the USA and Europe. Secondly, we have sought to expand our reach and our work in Europe where clearly the sector is growing rapidly, and where we have had less of a presence in the past compared to the USA.

Q Can you tell us more about ARMs ongoing and planned future activities in the realm of value demonstration and pricing of novel cell and gene therapies?

JLL: The issue of value and pricing for these therapies is top of mind for many policymakers and payers, and our work in this domain has been quite robust.

ARM has laid the groundwork to articulate what's special about this category of medicine and to identify what some potential novel payment structures might be. We've done significant work to explain why these therapies require a different kind of payment model – why the traditional payment system doesn't work well for therapies that are likely to be a one-time administration and in some cases curative, or at a minimum, more durable than the therapies for which the payment system was originally designed.

We're now actively involved with legislators, policymakers, and payers to try to implement these novel payment structures. First and foremost, that involves establishing a system that enables payment over time and which allows for payment to be linked to performance.

ARM also has an affiliated foundation called the ARM Foundation for Cell and Gene Medicine, which was launched in January 2018. One of the core projects of the Foundation is developing a health economic impact model specific to advanced therapies. They have examined some of the leading value models that are being used by HTAs around the world, and are addressing what's lacking in them when it comes to cell and gene therapy. That project is now underway, with many ARM members involved. We hope it will produce the first iteration of an updated value model late this year or early in 2020.

Q Pricing of cell and gene therapy products is clearly quite a contentious topic at the moment, with some

DOI: 10.18609/cgti.2019.106

seemingly wide differences of opinion between the various stakeholders involved – what would be your advice to cell and gene therapy developers currently making their way into and through the clinic in terms of how to prepare for the potentially tough negotiations ahead?

JLL: The advice I would give them is what we hear from the payers themselves, which is engage early and often. And I do think companies are doing a good job of this, in general.

Payers are tasked with considering the therapeutic impact of a product and the relevant population that will be addressed, and any kind of costs that will be avoided. They also must establish what exactly a performance metric might look like, if such a metric can be easily tested and relied upon, and reach agreement with the developer on what constitutes a good clinical marker of success. However, all these considerations can take quite a bit of time, so the industry has to get engaged with both commercial and government payers pretty early on.

We've also heard from commercial payers in particular that even where there is a desire to implement these kinds of pay-per-performance/payment-over-time models, the operational part of the process is often the hardest. It's not the theoretical agreement about whether or not it's a good idea to do it, but the simple fact that it hasn't been done very much before, that every case is specific, that there are many different departments involved, and that sometimes, the practical realities of running any business can be thorny and can take a little bit of time to work out.

In summary, I think cell and gene therapy companies would be well advised to do the analytical work behind any value they want to ascribe to their product and then join a conversation with the payers early on.

On this point, ARM has been working with the National Association of Managed Care Physicians (NAMCP), which is a group of chief medical officers from managed care health plans in the USA. We are working with the NAMCP to put together a guide for how a developer should approach the managed care payors. There will be a series of workshops on this which will lead up to a report – that will be out in early 2020.

Q Can you expand on the challenges facing the healthcare sector when it comes to identifying and implementing an optimal innovative reimbursement model for single dose, potentially curative therapeutics?

"Right now, we're tracking more than 900 therapeutic developers … working in cell and gene therapy and other regenerative medicines."

JLL: I think what we're finding is that every market has its own particular dynamics: between European countries and the USA, for example, as well as differences between the commercial and public environments.

There's a growing consensus on the public payer side in the USA that some legislative clarity as a minimum would be helpful – and there may need to be some refinement of the regulatory and legal language.

In the USA, we currently have price reporting requirements for Medicare and Medicaid that constrain the ability for a company and the government to enter into a pay-per-performance agreement. In simple terms, there are requirements around a provision known as 'Best Price' – that you have to offer to government the best price that you would offer to anyone else. However, you may have a pay-for-performance agreement in place and if a patient doesn't respond to treatment, that patient pays zero. Suddenly, zero becomes the best price. Obviously, nobody wants that – that wouldn't be a very workable scenario. Therefore, we need to find a way around the 'Best Price' problem.

There's also something in the USA called the 'Anti-Kickback Statute,' which was designed to make sure physicians weren't incentivized to prescribe a particular product by means of getting money back. This creates some complexity and potential problems where a pay-per-performance model might have a rebate attached to it – for instance, you may pay upfront for the therapy but then receive a refund if the therapy fails to work in a given patient.

There's quite a lot of activity around this issue in the US Congress right now, trying to identify if there is a legislative fix that would allow CMS to enter into these more novel reimbursement models. There are also other ideas that are less well fleshed out and less legislative in nature. For example, approaches like reinsurance or risk pools to compensate for the fact that in certain geographies, including the USA, citizens change health plans all the time. How then do you keep a small insurer who might pay upfront for someone's lifetime benefit from being harmed when that patient leaves after one year to go to another plan? There's a lot of work going on in that area, too, although there's a little less specificity attached to the solution, as yet.

Q What further steps does the sector need to take on the patient access side of things to ensure that

DOI: 10.18609/cgti.2019.106

approved cell and gene therapy products do reach those who need them most?

JLL: There are all kinds of needs on the patient side of cell and gene therapy. I mention the ARM Foundation again here because one of the reasons we launched it was the huge need for patient and caregiver education around cell and gene therapy, whether that was patients having the potential to enroll in a clinical trial or facing a choice about a commercial product. This is fairly complex information – not something the average person knows a lot about until they're in a situation that they never wanted to be in – and so we feel that providing that information in an accessible way is essential.

In terms of patient access, obviously ARM's efforts are around trying to make sure the insurance systems that exist, either in a national health system like that in the UK or in the more varied system in the USA, cover these therapies in a way that makes them accessible to patients. That's really our core goal.

There are other efforts underway to try to tackle different aspects of the pricing debate, but I think we're still at step one: ensuring these products can effectively be covered by insurance in a way that makes it possible for whichever healthcare system to absorb them into its structure. And in the cases where patients may have some part of the responsibility for the payment, we must also ensure that those patients will be able to afford it, and this won't hinder access or treatment.

Q Where do you see the greatest need for new technological innovation to help the cell and gene therapy sector continue its journey towards a commercially successful future?

JLL: There's a great need for innovation in the manufacturing of cell and gene therapies, and also in logistics. The infrastructure for, say, modified cell therapy is pretty different to what's been required for other types of therapies or products in the past. A lot of companies are working to fill that gap.

"...we have really started to focus on the commercial challenges that face the sector..."

We've found that the expedited approval pathways that exist around the world for cell and gene therapies have been really effective at moving products through a rigorous but also rapid approval process. What the

"We're getting to the point where there's going to be 10 to 20 approvals every single year for cell and gene therapy, and that's just in the USA."

sector now faces are mainly manufacturing issues around either regulators' requirements or scalability.

The technologies are many, of course. There's everything from delivery technologies (are there alternatives to the vectors we're currently using?) to various kinds of assays (what's the right potency assay? Are we measuring the right thing from a regulatory point of view that really has the most clinical relevance? And are the tools we have to measure those things really where we want them to be?)

ARM's established a number of initiatives to address these uncertainties. Firstly, we incubated and launched something called the Standards Coordinating Body (SCB) which is now a standalone, non-profit organisation currently supported by the US FDA and other organizations. It is designed to identify where there are standards needs in cell and gene therapy and to then to help develop and advance them.

We're also doing a lot of work in manufacturing in terms of trying to develop a book of knowledge, if you will, around a hypothetical gene therapy 'case study' – in this case, an AAV gene therapy. A number of ARM's member organizations are volunteering their time to take on drafting chapters of this book of knowledge in order to try to summarize what are the key known best practices in AAV gene therapy manufacturing. As you can appreciate, the growth of this sector is so rapid and there aren't that many experts – a lot of the people working in cell and gene therapy manufacturing have transitioned from other technology areas. With this book of knowledge, we're trying to help bring these new arrivals up to speed faster and reduce the amount of trial and error that is only natural when people first enter this field.

Lastly, we've had a series of conversations with regulators – specifically, around some of the areas where guidance is either not clear or not appropriate for modern gene and cell therapy CMC. We've also driven the agenda for harmonization where there are currently different approaches relating to certain aspects of cell and gene therapy manufacturing – between the USA and Europe, for example.

Q Finally, can you summarize for us ARM's vision for the future of commercial cell and gene therapy?

JLL: We track the sector pretty closely using source data from our data partner, Informa, and continually curate our own

DOI: 10.18609/cgti.2019.106

ARM-specific global database of regenerative medicine companies. Right now, we're tracking more than 900 therapeutic developers around the world working in cell and gene therapy and other regenerative medicines. We're tracking more than 1,000 clinical trials. And investment in the sector, which we also track, has been very robust for the last several years.

What's clearly evident from all this data – and our vision for the future – is that we are rapidly approaching a world where it's no longer going to be 'ones and twos' – one product making it to market each year in the USA, a couple a year in Europe… and so on. We're getting to the point where there's going to be 10 to 20 approvals every single year for cell and gene therapy, and that's just in the USA. We'll also have institutions that are very well practiced in the delivery of these novel therapies. We'll start to see them expand beyond a limited number of clinical centers and we'll begin to see the benefits of these therapies across many different kinds of people and lots of different indications.

We're at the curve of the hockey stick – cell and gene therapy will in very short order start having a profound and widespread impact on patients and families across a whole variety of diseases. And we're obviously super excited about that!

AFFILIATION

Janet Lynch Lambert
CEO,
Alliance for Regenerative Medicine

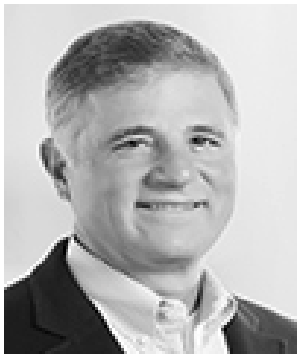
CELL & GENE THERAPY INSIGHTS

MARKET & PATIENT ACCESS

SPOTLIGHT

INTERVIEW

Future trends in commercial cell and gene therapy: the investor's perspective



GREGORY BONFIGLIO is the Founder and Managing Partner of Proteus, LLC – an investment and advisory firm focused solely on Regenerative Medicine. Formed in 2006, Proteus provides fund management and consulting services to the regenerative medicine industry. Proteus works with cell and gene therapy companies across all stages of development from early stage entities to large public companies, as well as governmental organizations pursuing RM initiatives. Mr Bonfiglio serves on the Board of Healios KK, one of the largest publicly traded RM companies in Japan. He is on the Investment Committee of the Centre for Commercialization of Regenerative Medicine (RM Translation Center in Toronto, Canada). He is on the Advisory Board of BioBridge Global (RM Translation Center in San Antonio, Texas). He is on the ISSCR Finance Committee. Mr Bonfiglio was an early investor in the RM field, and he continues to be actively involved in the space. He has over 35 years' experience working with technology companies. He received his BA in Mathematics (magna cum laude) from Michigan State University in 1975, and his JD (magna cum laude) from the University of Michigan Law School in 1981.

Cell & Gene Therapy Insights 2019; 5(8), 1081–1089

DOI: 10.18609/cgti.2019.116

Q What are your chief considerations when you evaluate a potential company or technology? And have these criteria changed at all over recent years?

GB: Our diligence criteria for investments are similar to other folks in the biotech space. The top few criteria are always technology,

"For us, technology is the driver. First and foremost, we're interested in identifying technologies that will drive sea changes in the field. Typically, we're not looking at technologies that would make an incremental improvement over an existing technology, but something that will fundamentally change the approach."

regulatory pathway, team, intellectual property portfolio and then commercialisation considerations. For us, technology is the driver. For us, technology is the driver. First and foremost, we're interested in identifying technologies that will drive sea changes in the field. Typically, we're not looking at technologies that would make an incremental improvement over an existing technology, but something that will fundamentally change the approach.The promise of regenerative medicine, cell and gene therapies, has always been that they would fundamentally alter the approach to healthcare. The good news is that in the last 10 years, that promise has been realised.

One of the other key criteria for us is looking at the regulatory strategy and path. How long will it take to get approval? How rapidly can a company build human data demonstrating their technology works? One of the hallmarks of investing these days is the ability to get early data to get a go/no-go decision sooner rather than later. Fundamentally, valuation in biotech is a relatively straightforward process. Value is built in biotech by moving your technology through the regulatory path. What that means, at a very fundamental level, is demonstrating in humans that your technology works and provides significant therapeutic value. Human data is the key driver of value in biotech companies across the board; certainly in cell and gene therapies.

We also look at the intellectual property portfolio. We want to make sure the company is capable of protecting its IP so that if we put money into developing a technology, there will be an opportunity to commercialise that technology without folks coming in and copying it.

"Human data is the key driver of value in biotech companies across the board; certainly in cell and gene therapies."

We also look at the management team, of course. That's important because these are fundamentally business decisions. As much as technology plays a dominant role, you still have to execute on the business plan.

DOI: 10.18609/cgti.2019.116

Then last, but certainly not least, is the ability to commercialise technology and move from your clinical programme into a successful commercial launch. That means having a manufacturing strategy that allows you to optimise your manufacturing process and the ability to go from a process in which you're producing relatively small volumes into full scale commercial manufacturing. This is an important issue, as manufacturing challenges have proven to be a real problem for a number of companies. Going back 10-15 years, Advanced Tissue Sciences raised a ton of money, went public, had a big valuation, then found they couldn't manufacture their product. Dendreon is another company that had immunotherapy technology, raised a ton of money, had a big valuation, but ultimately could not manufacture their product on a cost-efficient, commercially viable basis.

We're very pleased to see the dramatic results coming out of clinical trials but this hasn't changed our diligence criteria or investment criteria. We have focused more than we have in the past on manufacturing. If you look at where we are now in terms of clinical phases, there's a significant amount of activity now in late-stage clinical trials. Companies garnering big valuations and significant investment dollars are now in late phase 2 or in phase 3. Manufacturing has become a much more significant issue for us in our diligence than in the past. There is a significant shortfall in underlying manufacturing capability, both at the cell level and even more acutely, at the viral level. My understanding that the time delay to get a viral vector produced is in the order of 12-18 months, such that production of the vector ends up being a rate limiting step, whether you're working on a pure gene therapy or an engineered cell like a CART.

Q Will the recent trend for very high levels of private investment and public company valuations in cell and gene therapy be maintained, or even grow further?

GB: I think it will continue. The valuations are very high by historic terms for biotech, but the clinical data justify that, quite honestly. Immunotherapy is the technology area that has really garnered the attention and started this wave of new investment in the field, largely because they were demonstrating really dramatic results in their clinical studies. Some immunotherapies have been showing 70, 80, 90% response rates in their trials – and that's previously unheard of.

The field as a whole is maturing. As I mentioned earlier, we're seeing many more technologies in late-stage clinical development and on the verge of commercial launch. Again, these are companies bringing forward

"If you want to attract these large rounds of financing and hope to get a large number in your IPO, you're going to have to demonstrate at least 60, 70, 80% response rate in your clinical trials. Valuation numbers are up, but so are expectations."

technologies that fundamentally change the approach to treatment of disease. They're looking to cure the disease, not simply manage it, and they're showing dramatic results.

If you believe, as I do, that value is created in biotech by demonstrating your product has therapeutic value, the greater that therapeutic effect, the more significant the value of the company should be. The sooner you can demonstrate that therapeutic effect, the more investor interest you will attract. As a result, we've seen some very high valuations in the field following release of robust clinical data. Then, on the gene therapy side, we've seen people come in for monogenic disorders, such as lysosomal storage disorders, correct a single gene defect and demonstrate that it can effectively cure the patient of the disease. So, I'm not surprised that we've got these large valuations.

Another factor in the rate of investment is that there's been a huge flood of money into the field. It seems like almost every year we're hitting new heights in this regard.

On the other side of the coin, you're also seeing that the field itself has matured on the infrastructure side. Manufacturing is still a challenge, but there's a significant amount of manufacturing infrastructure in place now that did not exist 10 years ago and more is being built all the time. All these things come together to generate investor enthusiasm and explain the large valuations that are coming into play.

Do I expect that to continue? I expect it to continue for companies that are able to demonstrate that they can provide that significant therapeutic value. The good news is you're getting big valuations and lots of money is coming in through venture and public markets. But along with that, the bar has been raised significantly for companies wanting to come into the field. If you want to attract these large rounds of financing and hope to get a large number in your IPO, you're going to have to demonstrate at least 60, 70, 80% response rate in your clinical trials. Valuation numbers are up, but so are expectations. If you look at what happened to some of the companies that went public and then met difficulties in their clinical programme – not necessarily that the programme failed, but that it didn't meet lofty expectations – their stock got crushed. That's not a new phenomenon – historically in biotech, if you don't do well in clinical trials, your stock gets crushed. But the standards in terms of what it takes to succeed are now higher.

DOI: 10.18609/cgti.2019.116

Q Regarding the rare disease space in particular, how does one justify high biotech valuations and how do you expect that scenario to play out?

GB: It's a somewhat new phenomenon in the field that rare disease and ultra-rare disease models are garnering a lot of investor interest and valuations. Why do people go after rare and ultra-rare disease? It's a variation in theme on the orphan drug strategy that's been applied by pharma and biotech for many years. The notion is if you're looking at an orphan disease or a rare or ultra-rare disease, you are able to get into your clinical trials and generate data more rapidly – the clinical path to approval is accelerated.

The reason people have gone into those indications, particularly in gene therapy, is there is this convergence of two models that can produce dramatic results on a relatively easy path. What you're seeing in the rare and ultra-rare disease area, at least on the gene therapy side, is companies looking at monogenic disorders. These are single gene defects that can be cured with a single gene manipulation. I'm not trying to underestimate or minimise the challenges facing these companies in any way, or their underlying technology, but they're 'easy' because you only have to modify one gene. The other thing is, once you modify that gene, it's binary: it either works or it doesn't, so you tend to get your results relatively quickly.

Owing to the fact that the diseases are ultra-rare and orphan, because there aren't other treatments available for them, the regulatory path is fairly straightforward. The FDA, EMA and other agencies around the world are providing straightforward paths into trials and approval pathways that are much shorter than if you're looking at other disease models.

That explains why people are going into it. Does it explain the lofty valuations attached to these companies? I'm not sure it does entirely. I think there will be some reality testing once we have a few more companies approved and in full commercial launch, where they're being measured by the amount of revenue they generate rather than success in clinical trials. There

"...for the near term you'll continue to see the valuations maintained. Once you get into full commercial launch and are trying to treat patients, and the company's valuation is measured by the economics and not the clinical programme, you may see a readjustment of the valuation."

will have to be some very lofty reimbursement codes for these technologies in order to justify the significant expense that went into developing them, and I wonder whether the system can support those kinds of codes.

I think for the near term you'll continue to see the valuations maintained. Once you get into full commercial launch and are trying to treat patients, and the company's valuation is measured by the economics and not the clinical programme, you may see a readjustment of the valuation.

Q Which specific disease and technology areas will come to the fore in commercial terms and drive the field forward over the short- to mid-term?

GB: We're going to continue seeing the majority of clinical trials in gene therapy or gene modified cells – CAR-T or other engineered cells. The third category would be primary cells. Tissue engineering has relatively few clinical trials underway. The majority of therapeutics being developed 5 years from now will be engineered cells of some kind. The technology is too compelling for it not to go this way. If you can engineer a mesenchymal cell and optimise its anti-inflammatory effects, why wouldn't you do that and have the cell provide 5 or 10 times more therapeutic value?

We will also see continued growth in gene therapy. Gene insertion technologies, such as CRISPR and others, are getting better – there appears to be a whole new generation of gene insertion technologies coming that will enable more gene therapies and solve some of the problems we have with viral vectors. I think we're going to see some growth and activity that might replace viral vectors, and that will continue to enable gene therapies and engineered cells.

At some point, genetic engineering of cells will reach a level of sophistication where the sector can begin to take on more complex diseases. I wish I could give you a timeframe for that, but I can't. It will happen eventually, but in the near term, you'll see activity continue to expand in monogenic disorders and the number of disorders being addressed will continue to increase. What will happen is we'll end up with people bringing forward new insertion technologies and more targeted technologies to minimise some of the off-target effects and toxicity related to viral vectors in general.

Longer term, we will start to see some dramatic results in cancer. Right now, we have seen dramatic results in hematologic malignancies, but it has been more challenging to bring these immunotherapies in to solid tumours. I do think we're beginning to see some progress being made there, though, and that will continue.

DOI: 10.18609/cgti.2019.116

Q What specific trends do you expect to see in geographical terms moving forward, given the tremendous market potential in regions beyond North America and Europe?

"We're seeing the Asian market emerge as a legitimate, reliable player in the field – both in terms of the fundamental ability to do clinical trials there, but also because there are large patient populations..."

GB: This is one of the more interesting developments in the field in the last 24 months. What has happened is that Asia has emerged as a key player in the cell and gene therapy field – not simply because carrying out a clinical trial in China may be cheaper and faster, but because there has now emerged a whole group of investors. The momentum started to build in Asia when the Japanese PMDA introduced their new regulations around regenerative medicine technologies. They were the first legitimate jurisdiction to adopt a regulatory framework that accelerated the approval process specifically for cell and gene therapies. Because that happened in Japan, and not in the United States or Europe, that started people looking at the Asian market. It also garnered some investment activity and money flowing into Japanese companies, or other companies utilising the PMDA's accelerated process to bring their products to market.

China is growing as an economic force worldwide, but there have been concerns about IP protection, the legitimacy of their regulatory programmes and around the infrastructure in China. The Chinese Government has adopted some progressive and aggressive programmes to develop the biotech infrastructure, and it's now starting to bear fruit. In 2017 there were almost 40 billion dollars raised in biotech funds focused on China. That was almost a threefold growth over the 2 years prior. In terms of venture investment in Chinese biotech, in 2017 there was almost US$12 billion invested – that's 5 times the amount invested in 2016. And in 2018, that trend continued, according to PwC data.

We're seeing the Asian market emerge as a legitimate, reliable player in the field – both in terms of the fundamental ability to do clinical trials there, but also because there are large patient populations, so being able to enrol patients in trials is not as much of a challenge as it can be in the West. Now you have infrastructure being built and funding being provided. Those are the pillars on which biotech is built. North America had been the centre of power for healthcare, and for biotech in particular, for 40-50 years, but I think the Asian market is emerging as a legitimate challenger in

the field with internal, indigenous funding, technology and infrastructure – both clinical and manufacturing infrastructure – that will allow people to bring their technologies forward.

Q Finally, can you highlight some of the most critical specific elements of the 'begin with the end in mind' mantra, as far as investors are concerned?

GB: The notion of beginning with the end in mind actually applies with the greatest force in IT. The problems emerging companies face in IT are largely engineering problems, not fundamental science. If you have a clear vision of where you want to go and enough dollars, you can always engineer your way out of a problem or to a solution. In biotech, clinical trials are in essence a scientific endeavour. You're still testing the science, still testing the technology, and often you are making advances in the underlying science while bringing your technology forward. It's not an engineering challenge through the clinical trials phases, but once you launch, it does become an engineering challenge.

So I'm not sure that maxim applies as much to biotech as a whole, but the comments I made earlier around manufacturing do apply with tremendous force here. Given the maturation of the field, the amount of money being invested and where we are in terms of clinical trials, manufacturing and the ability to successfully launch on a commercial scale has now become a very, very important issue.

Traditionally, when you're in phase 1 or 2, you're typically at least 3-5 years from a commercial launch and historically, management teams in those companies haven't spent a huge amount of time on manufacturing issues at that stage. But today, with the way things are moving much more rapidly, I think it is incumbent on any biotech company management team to have mapped out and tested its manufacturing strategy by that stage. You need to identify your manufacturing partners, decide whether you'll do it on your own or outsource, and optimise your manufacturing process.

The sooner you can address those issues and optimise your manufacturing process, the better off you will be. To succeed, cell and gene therapy companies need to think long and hard about their manufacturing strategy and do it sooner rather than later.

AFFILIATION

Gregory Bonfiglio,
Founder & Managing Partner,
Proteus, LLC

DOI: 10.18609/cgti.2019.116

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *The authors declare that they have no conflicts of interest.*

Funding declaration: *The authors received no financial support for the research, authorship and/or publication of this article.*

ARTICLE & COPYRIGHT INFORMATION

Article source: Invited.

Interview conducted: Dec 6 2018; Publication date: Sep 2 2019.

CELL & GENE THERAPY INSIGHTS

MARKET & PATIENT ACCESS

SPOTLIGHT

COMMENTARY

The diversity in regenerative medicines regulations in Europe, USA and Japan

Tingting Qiu, Monique Dabbous, Lylia Chachoua, Claude Dussart & Mondher Toumi

Substantial efforts have been made to increase harmonization across regulatory authorities for the regulation of regenerative medicines (RMs), yet variations still exist in market authorization (MA) processes with regards to terminology, product classification, and evidence requirements. Regulatory and MA processes were examined in the EU, the USA and Japan. RMs are evaluated under similar regulatory frameworks as either traditional medicines or biologicals by the Food and Drug Administration in the USA, with a risk-based approach acknowledging the RM's specificities. In the EU, RMs are regulated under the centralized procedure by European Medicines Agency (EMA), with an additional step that a draft opinion is prepared by Committee for Advanced Therapies (CAT) prior to a final MA opinion from Committee for Medicinal Products for Human Use (CHMP). The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan has shifted the regulatory paradigm of RMs with a time-limited, conditional MA pathway to accelerate patient access and increase global competitiveness. Opponents argue that such a system may be too permissive in potentially exposing vulnerable patients to treatments with questionable efficacy and safety. The FDA and EMA have shown more willingness to accept real world evidence (RWE) to support MA applications. RWE was more commonly used in post-market surveillance by the PMDA in the past, but efforts are underway to explore the possibility of using patient registry data for MA application. To avoid the use of unauthorized RMs, the FDA has temporarily established the Tissue Reference Group (TRG) Rapid Inquiry Program (TRIP) to support sponsors in the regulation of specific RMs, along with the release of final guidelines to

explain the principle of 'minimal manipulation and homologous use'. The PMDA requires a specific expert committee review for RMs (including autologous RMs for homologous use) administered in medical practices and research based on effects on human health. The 'hospital exemption' rule in the EMA still needs more clarification to ensure its harmonious implementation across different Member States. Expedited approval programs in three jurisdictions showed disparities in eligibility criteria, application timelines and incentives provided to sponsors.

Cell & Gene Therapy Insights 2019; 5(8), 1031–1042

DOI: 10.18609/cgti.2019.111

REGULATION AND MARKETING AUTHORIZATION OF REGENERATIVE MEDICINES

Regulatory authorities worldwide have made substantial efforts to facilitate the market approval of RMs through the establishment of specific RM legislations incorporating scientific support, expedited approval programs, and flexible evidence assessment approaches. Regulation (EC) no 1394/2007 was released by European Medicines Agency (EMA) in November 2007 as a specific legislative act to regulate relevant activities related to Advanced Therapy Medicinal Products (ATMPs) from the drug development phase to the post-market surveillance [1]. Afterwards, Japan's revised Pharmaceutical and Medical Device Act (PMD Act) was enacted in November 2013, in which RMs were defined as a new category that were subject to a separate regulatory pathway [2]. The US Food and Drug Administration (FDA) announced a comprehensive RMs policy framework in November 2017, which outlined a suite of guideline documents for the development and oversight of RMs [3].

The differences in the market authorization (MA) processes of RMs in the EU, the USA and Japan are the focus of this paper's examination.

DIFFERENCES IN THE REGULATION FRAMEWORK OF REGENERATIVE MEDICINES

Definition of regenerative medicines

From the perspective of definition, unrelated allogeneic hematopoietic stem/progenitor cell therapies from placental/umbilical cord blood that are minimally manipulated are regulated as biologics in the USA – therefore, a MA must be obtained before a product can be commercialized. However, these therapies are not regulated as medicinal products (biologics or traditional medicines) in the EU and Japan, where no requirements for MA are imposed [5].

The regulation by the EMA of ATMPs classifies products in three categories [6]:

1. Gene Therapy Medicinal Product (GTMP);
2. Tissue Engineered Products (TEP); and
3. Somatic Cell Therapy Medicinal Products (CTMP)

Based on the EMA regulation, an *ex vivo* gene therapy would be classified as a GTMP even though the final therapeutic product would be cell-based like CTMPs. For example, the chimeric antigen receptor (CAR) T cell therapy, Kymriah®, falls within the category of a gene therapy for the EMA, while it was approved as a somatic cell processing product by the PMDA. Another example is MACI®, which was approved as a tissue engineered product by the EMA, while it was classified as a cellular therapy by the FDA.

To better support manufacturers on regulation issues, scientific recommendations can be sought from the EMA and the FDA to determine whether applicants in development meet the definition of RMs, product category, and which regulations will be applied to their specific products through ATMP classification procedure [7] and Tissue Reference Group (TRG)-Rapid Inquiry Program (TRIP) [8].

Market authorization pathway

Despite showing more willingness to accept uncertainty and develop adaptive pathways to accelerate the market access of RMs, authorities differed in balancing the flexibility and stringency in the evidence assessment process (Table 1).

In EMA, ATMPs are regulated under centralized MA procedure, where manufacturers send a single MA application to Committee for Advance Therapies (CAT) for the assessment of quality, efficacy and safety. CAT bears the responsibility of preparing a draft opinion on MA application before Committee for Medicinal Products for Human Use (CHMP) adopts a final MA opinion. Products that have positive benefit-risk profile and hold promise to fulfill unmet medical needs, would be eligible for conditional MA, while MA holders must complete the scientific obligations to collect comprehensive data before a standard MA could be granted. Unlike conditional MA, authorization under exceptional circumstances can be granted when the applicants are unable to provide confirmatory data even after MA because of disease rarity or unethical consideration.

In PMDA, RMs are regulated under a unique, fast-track approval pathway separated from all the other product categories by the regulator. There have been some controversies suggesting that such accelerated approval systems may be too permissive in the premature approval of RMs, which has raised concerns around whether the product's long-term efficacy would be as promising as claimed [10]. For example, the PMDA's conditional approval of HeartSheet® for heart disease and Stemirac® for spinal cord injury were criticized as too risky, as only non-controlled studies with small patient populations were available to support their efficacy.

In the FDA, a similar conditional approval pathway to the one established by the PMDA was put in place in March of 2016. Known as the REGROW Act, it eliminated

TABLE 1

The legislation and market authorization procedure of regenerative medicines in Europe, the USA and Japan.

Country	Legislation	Definition of regenerative medicines	Market authorization procedure	Products exempted from MA regulation
Europe	Regulation (EC) No 1394/2007 (2007)	▸Advanced therapy medicinal products (ATMP): Medicines for human use that are based on genes, tissues or cells ▸Gene therapy medicines: these contain genes that lead to a therapeutic, prophylactic or diagnostic effect ▸Somatic-cell therapy medicines: these contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body ▸Tissue-engineered medicines: these contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue	▸Centralized market authorization procedure: ▸Pharmaceutical companies submitted a single market authorization application to Committee for Advanced Therapy (CAT) for the primary evaluation and draft recommendation to Committee for Medicinal Products for Human Use (CHMP), followed by CHMP generated final opinion and transmitted to European Commission for MA decision ▸Under the same oversight framework as other medicines, but requirements for evidence assessment could be more flexible ▸Risk-based approach was recommended for MA application dossier to identify the risk factors regarding the quality, safety and efficacy of ATMPs, along with determining the extent of evidence to be included in the MAA	▸Eligible ATMPs satisfy the criterial for the 'hospital exemption' (HE) rules: prepared on a non-routine basis according to specific quality standards, and utilized within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient ▸The use of HE products needs to be authorized by the national competent authorities (NCAs). In principle, ATMPs under the HE scheme should be of equivalent quality to ATMPs developed for commercialization, but the implementation of quality requirements varied among different Member State
USA	▸Public Health Service (PHS) Act (1944) ▸Federal Food Drug and Cosmetic (FD&C) Act (1938) ▸Title 21 of the Code of Federal Regulation (CFR) part 1271	▸Cellular and Tissue-based products (HCT/Ps) are defined as articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient ▸Regenerative medicines was defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products	▸Tiered, risk-based approach was used to regulate the HCT/Ps based on public health and regulatory concerns (such as the transmission of communicable diseases) ▸HCT/Ps not meeting the definition of 'Section 361' product will be regulated as drugs, medical devices, or biological products under Section 351 of PHS Act and FD&C Act, thus pre-market approval was needed	▸'Section 361' HCT/Ps: products that are minimally manipulated, intended for homologous use, non-combined products, and not associated with systematic effects and not dependent upon the metabolic activity of living cells for its primary functions ▸'Section 361' HCT/Ps will be subject solely to the regulation under Section 361 of PHS Act and 21 CFR Part 1271
Japan	▸Pharmaceutical and Medical Device Act (PMD Act) (approved in Nov 2013) ▸Act on the Safety of Regenerative Medicine (RM Act) (approved in Nov 2013)	▸Regenerative medicine: (1) Processed human or animal cells intended for either: (a) the reconstruction repair, or formation of the structure or function of the human (or animal) body; (b) the treatment or prevention of human (or animal) diseases (2) Articles intended for the treatment of disease in humans(or animals) and are transgened to express in human (or animal) cells	▸Regenerative medicine was defined as a new category of products separate from conventional pharmaceutical medicine and medical device ▸Conditional, time-limited approval for a maximum of 7 years for RM demonstrating likely efficacy and confirmed safety evidence in the preliminary clinical trial ▸Secondary MA application is obligated to assess whether the actual performance of regenerative medicines satisfy the requirements of full market authorization based on post-market evidence collected in the period of conditional MA	▸Unprocessed products, including 1) separation and cutting of tissues; 2) isolation of specific cells; 3) treatment with antibiotics; 4) washing; 5) sterilization by gamma ray; 6) freezing; 7) thawing, and/or other procedures that do not use cells for the purpose of gaining different structures and functions from the original cells ▸For RMs administrated in daily practice and clinical research, they will be classified into three categories: Class 1 (high risk products requiring CSCRM review and MHLW approval), Class 2 (medium risk products requiring CSCRM review), Class 3 (low risk products requiring CCRM review)

CCRM: Certified Committee for Regenerative Medicine; CSCRM: Certified Special Committee for Regenerative Medicine; EC: European Commission; MA: Market Authorization; MHLW: Ministry of Health, Labor and welfare.

the requirement for Phase 3 studies. Ultimately, the REGROW Act was rejected due to strong objection from the academic community that it compromised the FDA's oversight standards and allowed for potentially ineffective or even dangerous drugs onto the market. Instead, an accelerated approval pathway (Regenerative Medicine Advanced Therapy (RMAT) designation) was introduced under 21st Century Cures Legislation, which has allowed more flexibility in data requirements and ensures that regulatory stringency has been upheld at the same time [11].

The acceptance of real-world evidence in market authorization application

The FDA holds a favorable attitude towards the use of real world evidence (RWE) (i.e., electronic health records, medical claims, patient registries and/or mobile devices) as part of a regulatory submission of RMs, with a separate section of "Modern Trial Design and Evidence Development" included in the US 21st Century Cure Act [12].

The EMA piloted an adaptive pathway for innovative medicines from March 2014 to August 2016. It was built on the existing conditional market authorization pathway and based on three principles: 1) iterative approval and coverage; 2) reliance on RWE to supplement clinical trial data; and 3) early involvement of other stakeholders including patients and health technology assessment (HTA) bodies. It underlined the importance of RWE for early approval and coverage decision-making as long as the rationale for the use of non-RCT study could be justified [13].

In the PMDA, RWE is more widely used for post-market clinical data collection or safety surveillance. There are no official RWE documents clarifying its definition or scope of application available. In April 2019, the PMDA initiated public consultation around the appropriateness of using patient registries in evaluating the efficacy and safety for MA applications when randomized controlled trials were difficult to conduct [14].

Regulation exemption

Eligibility criteria for regulation exemption suggests some differences between the EU, the USA and Japan. Except for the common requirements for minimal manipulation and homologous use, the FDA has emphasized that exempted products must be non-combination products, free of systemic effects, and independent from the metabolic activity for their primary function [15]. The FDA's 'Regulatory Consideration for Minimal Manipulation and Homologous Use' was issued in November 2017, in order to support sponsors in assessing the qualification of regulation exemption of their product and to protect vulnerable patients from unlicensed treatments.

Hospital exemption (HE) regulation by the EMA highlights the custom-made ATMPs use in a hospital setting for a specific patient under the responsibility of individual physicians within the Member State where they are manufactured and used. However, the divergence in interpretation of HE definition at the national level has caused

confusion for developers in navigating each EU member state's framework. This also has the potential to pose a threat to profitability of MA holders who have made enormous investments in commercial product development [16].

In Japan, the 'Act on the Safety of Regenerative Medicine' of 2014 stipulated that all processed cells used in medical practice and research must be classified into three categories (Class I-high risk, Class II-medium risk and Class III-low risk) based on the degree of the product's effect on human health. All protocols must be approved by specific ethical and scientific committees, while additional requirements of the Minister of Health, Labour and Welfare (MHLW) inspection for Class III RMs must also be fulfilled [17]. Furthermore, in response to the call for the strengthening in regulation and increased transparency of RM use in private clinics, MHLW has required that more treatment details must be disclosed by private entities, such as institution name, procedure description, and a detailed protocol link on the MHLW website [18].

Expedited approval program

Although all expedited drug designation programs share common goals to facilitate the approval of innovative therapies, they show differences in terms of eligibility criteria, application timeline, decision publication, and incentives offered (Table 2).

Unlike priority medicine (PRIME) designation in Europe and SAKIGAKE designation in Japan, RMAT designation by the US FDA is exclusively applicable to RMs indicated for life-threatening diseases with high unmet clinical needs, where no requirement for therapeutic superiority over existing treatments is imposed. Requests for RMAT designation must be made concurrently with the submission of an Investigational New Drug (IND) application, or as an amendment to an existing IND. The FDA will notify the sponsor about the final decision no later than 60 calendar days after the receipt of the designation request. However, no official list of RMAT approvals has yet been made available [19]. 33 products (5 withdrawn) received RMAT designation as of March 2019.

PRIME designation underlines the potential to benefit patients with unmet medical needs on the basis of preliminary clinical data. Academic or small and medium-sized enterprises (SMEs) are allowed to apply earlier based on compelling non-clinical data or tolerability data. The EMA proposed 11 deadlines for PRIME designation submission in 2019, and updated the list for granted products on a monthly basis [20]. 53 products have received PRIME designation as of May 2019, among which 23 (43.40%) have been RMs.

SAKIGAKE designation encourages innovation and promotes the approval of the product in Japan ahead of other countries. Announcements for the commencement of SAKIGAKE designation application and approval is released annually [21]. After four rounds of application until May 2019, 43 products have received SAKIGAKE designation. Among these, 11 were RMs.

Drugs with SAKIGAKE designation may also benefit from prioritized consultation and prioritized

DOI: 10.18609/cgti.2019.111

TABLE 2

The comparison of expedite programs in Europe, the USA and Japan.

		Eligible criteria	Advantages	RMs approved under each system (Approval date)
Europe	Conditional market authorization	▸ Positive risk–benefit balance ▸ Unmet clinical needs will be fulfilled ▸ It's likely to provide comprehensive data after MA ▸ Benefit of immediate availability outweigh the risk of lees comprehensive data	▸ Accelerated approval on condition that scientific obligation must be fulfilled to collect confirmatory data ▸ Converted into standard market authorization once comprehensive data was collected	Zalmoxis® (18/08/2016) Holoclar® (17/02/2015)
	Approval under exceptional circumstance (EC)	Applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use due to 1) disease rarity or 2) ethical reasons		Glybera® (25/10/2012) Withdrawal from market
	Accelerated assessment	▸ Expected to be of major public health interest ▸ Particularly from therapeutic innovation perspective	Reduce CHMP review timeframe to 150 days compared to 210 days under standard review	None
	Priority medicine (PRIME) designation	▸ Offer a major therapeutic advantage over existing treatments ▸ Benefit patients without treatment options ▸ Show its potential to benefit patients with unmet medical needs based on early clinical data	▸ Appoint a rapporteur from CHMP or CAT ▸ Intensive guidelines on the overall development plan and regulatory strategies ▸ Scientific advice at key development milestones, involving additional stakeholders, such as HTA body ▸ Potential for accelerated assessment	Kymriah® (22/08/2018) Yesccarta® (23/08/2018) Zynteglo® (29/05/2019)
USA	Fast track	▸ Indicated for serious conditions ▸ Fill an unmet medical need defined as providing a therapy where none exists or providing a therapy which may be potentially better than available therapy (such as superior effectiveness or avoiding serious side effects)	▸ More frequent meetings with FDA to discuss the drug's development plan and data collection ▸ More frequent written communication from FDA to discuss the clinical trials design and use of biomarkers ▸ Rolling review	Hemacord® (10/11/2011), Imlygic® (27/10/2015) Provenge® (29/04/2010)
	Accelerated approval	▸ Drugs for serious conditions that filled an unmet medical needs	Allow faster drug approval based on 1) surrogate (such as a laboratory measurement, radiographic image) or 2) an intermediate clinical endpoint (a measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit)	Carticel® (22/08/1997)
	Priority review	▸ Drugs that have significant improvements in following aspects: 1) increased effectiveness; 2) elimination or significantly reduce the drug adverse effects; 3) enhancement in patient compliance; 4) better safety or effectiveness in a new subpopulation	Reduce the FDA review time to 6 months compared to 10 months under standard review	Kymriah® (30/08/2017), Luxturna® (18/12/2017), Yescarta® (18/10/2017), Zolgensma® (24/05/2019)
	Breakthrough designation	▸ Intend to treat a serious condition ▸ Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint	▸ All Fast Track designation features ▸ Intensive guidance on an efficient drug development program, beginning as early as Phase 1 ▸ Organizational commitment involving senior managers	Kymriah® (30/08/2017), Luxturna® (18/12/2017), Yescarta® (18/10/2017) Zolgensma® (24/05/2019)
	Regenerative medicine Advance therapy (RMAT) designation	▸ Regenerative medicines that are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition ▸ Preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition	▸ Intensive guidelines on drug development as early as Phase 1; ▸ Early interaction to discuss potential surrogate or intermediate endpoints; ▸ Organizational commitment involving as senior managers; ▸ Statute addresses potential ways to support accelerated approval and satisfy post-approval requirements	Not available

CAT: Committee for Advanced Therapies; CHMP: Committee for Medicinal Products for Human Use; FDA: US FOOD & DRUG ADMINISTRATION; HTA: HEALTH TECHNOLOGY ASSESSMENT; MA: Market Authorization; PMDA: Pharmaceuticals and Medical Devices Agency.

DOI: DOI: 10.18609/cgti.2019.111 Cell & Gene Therapy Insights - ISSN: 2059-7800

TABLE 2 CONTINUED.

The comparison of expedite programs in Europe, the USA and Japan.

		Eligible criteria	Advantages	RMs approved under each system (Approval date)
Japan	Time limited, conditional market authorization	▸ Regenerative medicines showing likely efficacy and confirmed safety in early clinical study	▸ A maximum of 7 years of market authorization on condition that further data will be collected during conditional MA period	Collategene® (20/02/2019), Stemirac® (28/12/2018), HeartSheet® (18/09/2015), JACC® (27/07/2012)
	SAKIGAKE designation	▸ Product innovativeness ▸ Target disease condition should be serious or life-threatening, or have no available curative treatments ▸ Significantly improvement in effectiveness or safety compared to existing treatments ▸ Develop the product rapidly and file an application for approval in Japan, ahead of other countries	▸ Consistent prioritized consultation ▸ Pre-application consultation ▸ Prioritized review aiming for a further reduction in the total review period to 6 months compared to 9 months in ordinal priority review and 12 months in standard review. ▸ Assigning a PMDA manager as a concierge. ▸ Extension of re-examination period ▸ Potential of 10–20% premium at drug price.	Stemirac® (28/12/2018)
	Regenerative medicine specific orphan drug designation	▸ Prevalence of the disease covered by the indication of the product concerned is less than 50,000 patients in Japan ▸ Indicated for serious disease with high medical needs	▸ Subsidy granting of direct expenses of the development and authorization of such products ▸ PMDA provide advices and consultations concerning the interpretation of designation criteria and other regulatory matters ▸ Tax credits for the direct expense required during the subsidy period of research and development stage	JACE® (29/09/2016), Temcell® HS (18/09/2015)
	Priority review	▸ Target a serious or life-threatening condition ▸ Demonstrate clinical advantages over existing therapies in terms of safety, efficacy, or patient quality of life	▸ PMDA review time reduce to 9 months compared to 12 months under standard review	JACE® (06/08/2007)

CAT: Committee for Advanced Therapies; CHMP: Committee for Medicinal Products for Human Use; FDA: US FOOD & DRUG ADMINISTRATION; HTA: HEALTH TECHNOLOGY ASSESSMENT; MA: Market Authorization; PMDA: Pharmaceuticals and Medical Devices Agency.

review, which means that the pending time for consultation is reduced to 1 month (rather than the 2 months under standard consultation) and review time is shortened to 6 months (instead of the 9 months for standard priority review). Additionally, extension of the re-examination period (8–10 years) to strengthen data protection and post-market safety measures is granted to SAKIGAKE designated drugs [22].

RMAT designation and SAKIGAKE designation allow for rolling review during which a company may submit sections of MA application as they are completed for review, rather than waiting to complete the full application for submission. However, rolling review is not automatically permitted for PRIME designated drugs [23].

Pricing and reimbursement mechanisms have been involved in expedited programs. For example, products with PRIME designation are offered the chance to interact with additional stakeholders, such as HTA bodies, in order to facilitate quicker patient access, and SAKIGAKE designated drugs have the potential to benefit from a 10–20% price premium [22].

Post-market surveillance perspective

Substantial, specific obligations for conducting further studies to confirm efficacy and safety were mandatory to obtain standard MA for products with conditional MA in the EU. Similarly, In parallel with the requirements for secondary application of RMs with time-limited, conditional approval in Japan, National Regenerative Medicine Database (NRMD) operated by the Japanese Society for Regenerative Medicine (JSRM) was established for post-market surveillance of efficacy and safety [24]. It implies that conditional approval may face the risk of withdrawal if products fail to collect confirmatory evidence or to satisfy the requirements for standard MA, although no products with conditional approval have been withdrawn from the EU market due to misconduct or delays in completing the post-market studies [25].

Although the FDA has indicated that a confirmatory Phase 4 study was required for drugs with accelerated approval, no requirements for mandatory re-evaluation or re-application after MA are imposed, thus sponsors have less motivation to complete the post-market studies as required [26].

TRANSLATION INSIGHTS

International coordination to standardize terminology, in addition to establishing a universally recognized regulatory pathway, is crucial to facilitate the approval of RMs. However, it could be challenging to establish such a uniform platform due to the fast-changing regulatory environment and different public health needs. For instance, historically, the FDA showed a prompt attitude to approving new innovative products while the EMA took a more conservative approach. However, more recently, the EMA has introduced a number of accelerated programs and has moved ahead of the FDA in terms of piloting adaptive pathways, which are considered not only from a licensing perspective but also from a market access perspective [4].

There remains hope for greater collaboration in the future. A number of international harmonization initiatives have already been established, such as the joint EMA-FDA-Health Canada Committee, allowing regulators to communicate with each other on RM matters through bi-monthly meetings [27], and the International Pharmaceutical Regulators Program's (IPRP) specific gene and cell therapy group, which includes international regulators from 12 countries and meets regularly [28].

A common scientific platform would at least secure a joint understanding of the minimum requirements for positive benefit-risk assessment and a timely marketing approval for these therapies. Harmonized regulation could provide crucial impetus for realizing international integration and increasing global competition.

AUTHORSHIP & CONFLICT OF INTEREST

Contributions: *All named authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.*

Acknowledgements: *None.*

Disclosure and potential conflicts of interest: *The authors declare that they have no conflicts of interest.*

Funding declaration: *The authors received no financial support for the research, authorship and/or publication of this article.*

ARTICLE & COPYRIGHT INFORMATION

Article source: *Invited.*

Revised manuscript received: *Jul 4 2019; Publication date: Sep 2 2019.*

REFERENCES

4. Salmikangas P, Schuessler-Lenz M, Ruiz S *et al.* Marketing Regulatory Oversight of Advanced Therapy Medicinal Products (ATMPs) in Europe: The EMA/CAT Perspective. *Adv. Exp. Med. Biol.* 2015; 871: 103–30.

5. Azuma K. Regulatory Landscape of Regenerative Medicine in Japan. *Curr. Stem Cell Rep.* 2015; 1: 118–28.

6. US FOOD AND DRUG ADMINISTRATION. Comprehensive regenerative medicine policy framework: https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regenerative-medicine-policy-framework.

7. Rosemann A, Vasen F, Bortz G. Global Diversification in Medicine Regulation: Insights from Regenerative Stem Cell Medicine. *Science as Culture.* 2018: 1–27.

8. Coppens DGM, De Bruin ML, Leufkens HGM, Hoekman J. Global Regulatory Differences for Gene- and Cell-Based Therapies: Consequences and Implications for Patient Access and Therapeutic Innovation. *Clin. Pharmacol. Ther.* 2018; 103: 120–27.

 DOI: 10.18609/cgti.2019.111

9. Halioua-Haubold CL, Peyer JG, Smith JA *et al.* Regualtion considerations of gene therapy products in US,EU and Japan. *Yale J. Biol. Med.* 2017; 90: 683–93.

10. EUROPEAN MEDICINES AGENCY. Advaced therapy classification: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/advanced-therapies/advanced-therapy-classification

11. FOOD AND DRUG ADMINISTRATION. TRG Rapid Inquiry Program (TRIP). 2019: https://www.fda.gov/vaccines-blood-biologics/trg-rapid-inquiry-program-trip

12. LEUVEN MINDGATE. TiGenix reports on regulatory path for ChondroCelect in the US 2010: https://registrations.leuvenmindgate.be/event/36/115/TiGenix_reports_on_regulatory_path_for_ChondroCelect_in_the_US/

13. NATURE. Stem cell tests must show success-Japan needs to demonstrate that a promising therapy for damaged hearts works as claimed. 2018: https://www.nature.com/articles/d41586-018-05284-w

14. Servick K. Under 21st Century Cures legislation, stem cell advocates expect regulatory shortcuts. 2016: https://www.sciencemag.org/news/2016/12/under-21st-century-cures-legislation-stem-cell-advocates-expect-regulatory-shortcuts-0

15. FOOD AND DRUG ADMINISTRATION. 21st Century Cures Act. 2018: https://www.fda.gov/regulatory-information/selected-amendments-fdc-act/21st-century-cures-act

16. Eichler HG, Baird LG, Barker R *et al.* From adaptive licensing to adaptive pathways: delivering a flexible lifespan approach to bring new drugs to patients. *Clin. Pharmacol. Ther.* 2015; 97: 234–46.

17. Maruyama Y, Kasai M, Fujiwara Y, Asano J, Jotatsu Y. Experience from Japan: conditonal and tme-limited approval, an early approval scheme for regeneratve medical products. *Cell Gene Ther. Ins.* 2019; 5: 561–8.

18. Tigerstrom B. The European ATMP 'hospital exemption': a model for North America? *Cytotherapy* 2014; 16: S50–S51.

19. Ivaskiene T, Mauricas M, Ivaska J. Hospital Exemption for Advanced Therapy Medicinal Products: Issue in Application in the European Union Member States. *Curr. Stem Cell Res. Ther.* 2017; 12: 45–51.

20. Yano K, Yamato M. Compassionate use and hospital exemption for regenerative medicine: Something wrong to apply the program for patients in a real world. *Regen. Ther.* 2018; 8: 63–4.

21. Sipp D, Okano H. Japan Strengthens Regenerative Medicine Oversight. *Cell Stem Cell.* 2018; 22: 153–6.

22. FOOD AND DRUG ADMINISTRATION. Regenerative Medicine Advanced Therapy Designation. 2017: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/regenerative-medicine-advanced-therapy-designation

23. EUROPEAN MEDICINES AGENCY. PRIME: priority medicines. 2016: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines.

24. Maruyama Y, Kasai M, Oyama K, Chikazawa K. Experiences from Japan – SAKIGAKE Designation System for Regenerative Medical Products. *Cell Gene Ther. Ins.* 2018; 4: 545–54.

25. Kondo H, Hata T, Ito K, Koike H, Kono N. The Current Status of Sakigake Designation in Japan, PRIME in the European Union, and Breakthrough Therapy Designation in the United States. *Ther. Innov. Regul. Sci.* 2017; 51: 51–4.

26. Inoue S. Regulatory Update from MHLW/PMDA. 2017: https://www.pmda.go.jp/files/000221880.pdf

27. Okada K, Sato Y, Sugiyama D, Sawa Y. Establishment of the National Consortium for Regenerative Medicine and National Regenerative Medicine Database in Japan. *Clin. Ther.* 2018; 40: 1076–83.

28. EUROPEAN MEDICINES AGENCY. Conditional-marketing-authorisation-report-ten-years-experience-european-medicines-agency: https://www.ema.europa.eu/en/documents/report/conditional-marketing-authorisation-report-ten-years-experience-european-medicines-agency_en.pdf

29. Moore TJ, Furberg CD. Development times, clinical testing, postmarket follow-up, and safety risks for the new drugs approved by the US food and drug administration: the class of 2008. *JAMA Intern. Med.* 2014; 174: 90–5.

30. EUROPEAN MEDICINES AGENCY. Cluster activities: https://www.ema.europa.eu/en/partners-networks/international-activities/cluster-activities#advanced-therapy-medicinal-products-section.

31. International Pharmaceutical Regulators Programme (IPRP). Cell therapy working group: http://www.iprp.global/working-group/cell-therapy

AFFILIATIONS

Tingting Qiu
Aix Marseille University, Public Health Department, 27, bd Jean Moulin, 13385 Marseille Cedex 05, France

Monique Dabbous
Aix Marseille University, Public Health Department, 27, bd Jean Moulin, 13385 Marseille Cedex 05, France

Lylia Chachoua
Aix Marseille University, Public Health Department, 27, bd Jean Moulin, 13385 Marseille Cedex 05, France

Claude Dussart
Université Claude Bernard, Laboratoire Parcours Santé Systémique, EA 4129, Faculté de Médecine Laennec, 7-11 rue Guillaume Paradin, 69372 Lyon Cedex 08, France

Mondher Toumi
Author for correspondence

Aix Marseille University, Public Health Department, 27, bd Jean Moulin, 13385 Marseille Cedex 05, France
mondher.toumi@univ-amu.fr

DOI: 10.18609/cgti.2019.111

CELL & GENE THERAPY INSIGHTS

MEETING PRECLINICAL DATA REQUIREMENTS FOR CELL & GENE THERAPIES

SPOTLIGHT

INTERVIEW

An outcomes-based, innovative reimbursement mechanism for curative medicines

OMAR ALI qualified as a hospital pharmacist and has exetnsive experience as an NHS formulary pharmacist reviewing cost effectiveness of medicines for access and reimbursement at regional and national level. He was a former adviser to NICE on the ERG for adoptiona and impact of new medicines. He is currently working towards a PhD in value-based agreements and innovative contracting for new medicines, last year authoring on a paper providing a methodological framework for CAR-T reimbursment based upon remission (pay for performance model) over time.

Cell & Gene Therapy Insights 2019; 5(8), 859–865

DOI: 10.18609/cgti.2019.099

Q Tell us a bit about yourself and how you came to specialize in value-based agreements.

OA: I previously worked in the UK NHS healthcare system as a hospital pharmacy payer, assessing new medicines for cost–effectiveness and utility at local/regional level for drug budget allocation. My work at NICE involved drug assessment across various panels on health technology assessment, health utility, disutility, cost–effectiveness – all the typical things NICE will look at for new health technologies assessment and evaluation. I became very interested in value-based agreements, risk sharing, and some of the innovative contracting that was going on at NICE.

I then decided to do my PhD on this subject matter at the University of Portsmouth. My PhD thesis is on value-based pricing and outcomes-based innovative contracting of new medicines and health technologies.

My first paper for this PhD was published last year and was on the subject of a methodological approach of looking at a new treatment such as a CAR T cell therapy. CAR T was really still on the horizon at that point – it hadn't actually entered the market – so it was quite timely.

"Affordability is really about opportunity cost in a situation where there is a finite budget cap..."

I co-authored the paper with Cell and Gene Therapy Catapult (part of Innovate UK, based at Guy's & St Thomas Hospital in London). It was an original piece of research to look at how an outcomes based, innovative reimbursement mechanism for a curative medicine such as CAR T, could be implemented within a single payer healthcare system, from top to bottom, including all touchpoints (clinical, administrative, personnel and capital). In essence, a comprehensive design and assessment providing a methodological approach for curative, transformative cell and gene therapies.

Our research involved everyone from the top-end at the Department of Health and NHS England down to hospital-level management, finance, clinicians and pharmacy departments. We were able to track how such a CAR T cell therapy innovative reimbursement model could be implemented and adopted, into a Western healthcare system; it was actually a methodological approach, meaning it didn't have to be the NHS, specifically. We looked at who will be doing what, what are the costs and what is the administrative burden – all with a view to providing stakeholder organizations such as payers and manufacturers with a template to help bring some of these new therapies to market. Our ongoing PhD work in the area of outcomes based innovative contracts shows that many healthcare organizations and drug manufacturers are struggling with deployment and scalability of such contracts once the architecture has been outlined. At the end of the day, the goal is to help improve access to these therapies.

Q Can you frame for us why curative therapies pose such pragmatic problems for payer organizations around the world?

OA: As we move from daily treatments to one-off cures, the main issues arising stem from three domains: cost–effectiveness, affordability and uncertainty.

DOI: 10.18609/cgti.2019.099

Cost–effectiveness helps bring about a list price model. Some of the list prices for recently approved cell and gene therapies do look eye watering at first glance, heading up to around the US$1–2 million range. Therefore, the first question is, does the cost per QALY (quality-adjusted life year) add up? In many instances it doesn't, so we immediately have a pricing issue. A complicating factor here is that different markets have different thresholds. For example, in the UK, we usually have a ceiling of around £20,000–£30,000 per QALY, but with orphan conditions it can go up to £100,000–£150,000 per QALY. However, it's a very different threshold in the US. They do use cost per QALY to a certain extent, but they almost start at the UK's upper limit – their standard therapies can often fall within the UK's orphan drugs range.

Once payers are happy with the list price (in other words, they agree there is a QALY gain with the product – it is transformative or curative) then the next question is one of affordability. Some nations have drawn a line in the sand with regard to affordability, while others haven't done so yet. The UK, for example, has introduced an affordability threshold, which sit at around £20 million in each of any of the first three years of product launch. That's actually the first time that a major Western country has said, 'look, it's not just about cost–effectiveness now, but affordability, too'. So in the UK, if you're exceeding that £20 million per year in any of your first 3 years on the market, then the payers may have to go back to the drawing board to see how can they can afford this as a therapy.

Affordability is really about opportunity cost in a situation where there is a finite budget cap: if I pay for a CAR T cell therapy, it's so expensive that I'm having to decommission treatments to be in a position to afford it. So affordability of these transformative drugs – CART and gene therapies – is also becoming an issue. Additionally, it is going to be nigh impossible for most healthcare systems to be in a position to pay for these therapies in a single instalment.

Payers are not just worried about each individual treatment, of course – they see a queue of buses, if you like, coming down the road, each holding a price tag of upwards of $1–2million USD per patient and rising! As a payer, if I have 20 'buses' claiming to cure 20 diseases and they're all priced in this new paradigm, I've got a big problem on my hands. And as we set these list prices for the first few therapies, those following them are going to fall into the same price referencing. They're all going to want these price points – even if some of them are not actually worth it, that's the value they'll claim. The sustainability of global healthcare systems will collapse under such strain – and hence the trigger for innovative reimbursement mechanisms to provide access to these treatments has never been so critical. For every unaffordable treatment, there's a patient in the wings wanting, demanding access – and demanding it now.

Thirdly, we have the uncertainty piece – for example, where a novel drug claims to offer a 20-year cure, but only has data for 2 years. The 20-year cure may actually allow for a price point in the millions of dollars, but if you've only got 2 years of data that means there are 18 years of uncertainty. This presents payers with a further problem – what if it doesn't cure? What if the disease comes back? What if we have to give another dose at some point in the future – will we have to find the money again? The ratio between the evidence duration and the lifetime cure is becoming increasingly important for trying to model uncertainty.

This triangle of cost–effectiveness, affordability and uncertainty means that these transformative medicines are generating significant tension in pricing and reimbursement systems across the globe. Stakeholders are now evolving innovative, non-traditional payment mechanisms to be able to adopt these therapies for indications where there's big unmet need and demand is high for a cure. Some of these mechanisms are finance-based, some are outcomes-based, some are a mixture of the two – all are aimed at somehow providing a sustainable reimbursement model so that healthcare systems don't go bankrupt on day one.

It is really very unfortunate – the tension in the system is a real paradox: we're finally coming up with curative therapies, but paying the price for each one will be problematic.

Q You mention your research could be applied broadly as a methodological approach. Can you give us more detail on it?

OA: We (Catapult and Verpora) undertook the research because we realized there wasn't really any publicly available original research on how such an innovative outcomes-based contract could be integrated into a traditional reimbursement model today, here and now.

We looked at a hypothetical CART product for relapsed ALL. We looked at the current NHS healthcare system and asked, 'how could it implement, from top to bottom, an outcomes-based innovative contract?' That contract was based on a premise from the work that NICE did with the University of York - that one of the models that could be adopted would be something like a mortgage repayment, where you would pay an upfront deposit, make ongoing monthly payments thereafter, and then pay a final instalment and exit the repayment plan at a given point some years later.

What we did was to examine every level of the Department of Health, NHS England, individual hospitals, and the specific departments within them that are really the adopters of the technology. We looked at how the

 DOI: 10.18609/cgti.2019.099

healthcare system as a whole could manage the upfront deposit and payment over time, dependent on the performance of the drug - how it would work, how the money would flow, who would do the work, and what it would all add up to.

"Who is going to pay for that administrative burden and then how do you base reimbursement upon it?"

Firstly, we found that most of the administrative burden is in year one. Set-up costs are quite significant – for one thing, you're paying about 1% of the total cost of CART just to implement such an innovative financial model. We did original interviews and research across a number of hospitals to generate our data and at the top line, we saw that about 60% of the entire burden of employing this model falls with hospital pharmacy. After that, it's finance, IT, and then some physician time, too.

Moving forward from that, let's take a CAR T cell therapy with a list price in excess of £250,000 as an example. There would be an upfront deposit of perhaps £150,000, and then monthly payments based on the patient's blood test results for up to 10 years – the period of the curative promise, upon which the list price is based. If this promise is broken at any point and the patient relapses, then the payments would cease – so in effect, a graduated money back guarantee would be applied.

You need an outcomes-based model that is feasible for both the manufacturer and the NHS payer so for our paper, we looked at minimal residual disease (MRD) which is as close to remission as we may get. Payment was based on a patient's blood tests, which were not to carried out any more frequently than they normally would be for surveillance of their condition – under standard of care, a patient would have chemotherapy, maybe a stem cell transplant, and then they'd go home. They would then be monitored perhaps once every quarter in year one. We were quite keen not to inflict more blood tests on our hypothetical patients than they would normally undergo. In fact, the only real difference under our model is there's a reimbursement mechanism that comes from the hospital finance department back to the manufacturer, which says, 'yes, this patient is still in remission, so here is your monthly payment for him/her, but this other patent has relapsed, so we've stopped payment there and that contract ceases'.

Q How do you see value-based agreements panning out? What do you see as the chief challenges and barriers to their implementation, and will they provide the ultimate answer to managing higher drug prices?

OA: I think we're coming to the realization that outcomes- or value-based agreements probably are not the panacea to high drug prices; but it's the start of a journey that's already shaping markets. This shift from "volume to value" in healthcare is happening in our hospitals, in our clinics, and now it's happening with medicines.

Where does the journey go? I don't think we really know at this point, but the key thing for me is we have started to shift focus from volume to value. We've started the move from buying things and processes to buying outcomes.

Healthcare systems are already quite used to paying for outcomes, even in the USA. If you think about a lot of the contracts between healthcare providers and health plans and insurers, they are based upon achieving a certain result. All that has happened is this model is now being applied to the evaluation of novel medicines, too. The high list prices have probably enabled that shift to happen more quickly.

In the USA, we're really seeing an explosion in value-based agreements now. As part of my PhD, I've been compiling a list of value-based agreements across the EU, USA and some other countries. The USA is far ahead of the others, with just under a hundred value-based agreements having been published to date. Most of these are for medicines – there are just a few for devices. Some of the medicines are transformative, as cell and gene therapies can be, but others are for everyday symptom management in chronic diseases like diabetes, heart disease, etc. When you realize that for every value-based agreement in the public domain, there are at least 7 or 8 'unpublished', so to speak, you can see just how prevalent they have already become.

"...where do you even begin that negotiation if there's no grounding? Anyone can come in at any price they like and just say, 'let's start here'."

Regarding the next steps on this journey, I think what we're seeing in the US is it's all about scalability. At the moment, value-based agreements are for individual drugs and contracts. What payer organizations and manufacturers are now saying is, 'how do I do this across numerous contracts/drugs?' That trend will see pharma and biotech companies begin to place their revenues at greater risk. It's going to mean quite a change in the whole way drug pricing occurs moving forward.

At the moment, biopharma is trying to hold on to very high list prices. This leads to value-based agreements being used to pay for outcomes rather than the product or process itself. And that means companies are going to increasingly be putting more of their stock at risk. Under a value-based agreement, companies might be putting 10 or 20% of their stock

DOI: 10.18609/cgti.2019.099

at risk – something they have never had to do before. That's clearly going to change the way that investor relations happens for these companies, how they perform on the public markets, etc.

So there's going to be a multitude of dimensions to it, but right now and in the near future, it's about scalability. Data platforms represent a key component of this. Our research showed that a lot of the upfront cost relates to how you collect the data – who collects it, and whether it is being done in a sustainable way. Because with value-based agreements, there's often going to be monitoring of outcomes that we don't normally track. Who is going to pay for that administrative burden and then how do you base reimbursement upon it?

Q One hears more and more about the growing influence of the Institute for Clinical and Economic Review (ICER). What is your view on how they go about their product valuations?

OA: I have seen ICER come from a somewhat rocky start and really grow in strength. I think this has happened because they're the first independent organization to provide some kind of grounding as to what a fair and reasonable price for a novel drug might be. At the end of the day, price is a negotiation – but where do you even begin that negotiation if there's no grounding? Anyone can come in at any price they like and just say, 'let's start here'.

ICER has come along and essentially used NICE methodology – they're using the QALY, for instance (which I must point out, a lot of people don't necessary buy into). ICER is the first organization that's in tune with payers, is making independent drug assessments, and is providing a grounding in terms of what's a reasonable ballpark for price. And they're gaining credibility and significant influence, I would say. Payers are referencing them every day in their P&T committees and in their coverage decisions.

As I've already mentioned, the thresholds in the USA are still much higher than in the UK, for instance, but the principle remains the same - it's about having a starting point and a limit to your discussions. I think it's well needed – in the USA in particular.

AFFILIATION

Omar Ali BSc(Hons)Pharm DipClinPharm MRPharmS ACPP,
Visiting Lecturer Value Based Pricing & Innovative Contracting of New Medicines, University of Portsmouth
and; Former Adviser for NICE Adoption & Impact Programme Reference Panel

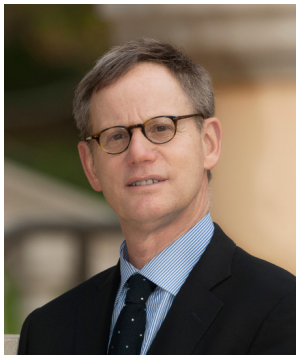
CELL & GENE THERAPY INSIGHTS

MARKET & PATIENT ACCESS

SPOTLIGHT

INTERVIEW

Market access in the era of personalized cell & gene therapy



EDWARD ABRAHAMS, Ph.D., is the President of PMC. Representing innovators, scientists, patients, providers and payers, PMC promotes the understanding and adoption of personalized medicine concepts, services and products for the benefit of patients and the health system. It has grown from its original 18 founding members in 2004 to more than 200 today.

Previously, Dr. Abrahams was the Executive Director of the Pennsylvania Biotechnology Association, where he spearheaded the successful effort that led to the Commonwealth of Pennsylvania's investment of $200 million to commercialize biotechnology in the state. Earlier, he had been Assistant Vice President for Federal Relations at the University of Pennsylvania and held a senior administrative position at Brown University.

Dr. Abrahams worked for seven years for the U.S. Congress, including as a legislative assistant to Senator Lloyd Bentsen, as an economist for the Joint Economic Committee under the chairmanship of Representative Lee Hamilton, and as a AAAS Congressional Fellow for Representative Edward J. Markey.

Cell & Gene Therapy Insights 2019; 5(8), 971–974

DOI: 10.18609/cgti.2019.105

Q Can you give us a brief history of the Personalized Medicine Coalition and describe how and why it became involved in the cell and gene therapy field?

EA: The Personalized Medicine Coalition was founded at the end of 2004, based on the assumption that science alone wasn't going to lead to the breakthroughs in personalized medicine that

would benefit patients and the healthcare system – that we needed to address issues in the space between the science and the patient. We focus on regulation, reimbursement, education and efforts to facilitate clinical adoption. The Coalition was therefore put together as a multi-stakeholder group that would address those concerns.

"The future is going to be one of targeted therapies and... ultra-personalized therapy..."

New developments in cell and gene therapy may be less than a decade old, but we recognize this as a new chapter in medicine that is truly personalized, whereby therapies are actually targeted to individuals through the re-engineering of their own cells and tissues. However, this move to a more personalized approach doesn't change the issues we are seeing about translation into clinical care. In fact, they're even more important because we're dealing with more complex technical, regulatory and reimbursement issues.

Q Can you go a bit deeper on your current specific activities that relate to the cell and gene therapy field – what are the PMC's goals for these activities?

EA: The main goal we have at the moment, especially in light of the high prices of the two CART therapies that are on the market, is to get the system to focus on the question of value rather than price. That will further encourage investment in the field and make it possible for the healthcare system to adopt these therapies once they are proven to be effective. We want to make sure that the system does not back away from deriving what could be a new definition of value based on these therapies – value based upon actually curing cancer for the first time.

Q What do you see as the chief obstacles that need to be overcome in order for patient-specific cell and gene therapy products to reach a large patient population?

EA: The first challenge is technical – simply making it work. It's not a trivial exercise to take tissue from a patient, re-engineer it, reinsert

DOI: 10.18609/cgti.2019.105

it, and make it provide a sufficient immunotherapeutic effect. Immunotherapeutic ability has been shown to work, but we've got a long way to go before many of the 1,000 or so new drugs in the clinic make it to patients on a commercial basis.

The second issue is how we regulate the field – how the FDA deals with the approval process.

The third issue is working out how we pay for these therapies.

And the fourth is training systems to help the actual adoption and implementation of these brand new technologies.

Bearing all of these things in mind, we have a real challenge to get it right based upon the new science and technology.

Q In terms of market access challenges facing the space, what do you feel are the necessary steps towards delivering pricing and reimbursement models that are fit for purpose for such novel product types?

EA: We need to understand what the extension of life – if not the actual curing of the cancer – will mean to patients, so that the high price is not considered an obstacle to development of these therapies. However, I think right now it is a barrier. This is because we're used to paying pennies for daily pills, not several hundred thousand dollars for one-time treatments that have lasting benefits. We need to re-educate or reconfigure the system to appreciate the issue of value and consider price in that context.

The optimal solution is that both public and private sector payers around the world recognize they're going to pay one way or another, and that it's better to get high value even if it incurs a large up-front cost. Then it's going to be incumbent on the companies developing these drugs, either individually or collectively, to demonstrate that value to the payers.

Right now, we know that hospitals like Brigham and Women's are providing CAR T cell therapies at a loss to themselves, but they're doing it anyway because they want to stay ahead of the curve and offer the best possible therapies to their patients. Nevertheless, that can't go on forever.

Q What is your vision for the future of cancer therapy and cancer healthcare in general?

EA: The future has been clear for a while. We know that almost all therapies in clinical trials in cancer are targeted – that is to say, they're

directed at sub-populations of patients – because firstly, that's what the FDA wants, and secondly, that's what works.

Pharmaceutical companies now understand that even if they develop products for small populations, they can still make a lot of money. The future is going to be one of targeted therapies and in addition to that, ultra-personalized therapy in the form of CART and other immunotherapies.

Q What's next on the agenda for the Personalized Medicine Coalition?

EA: There's a lot on our agenda. We are discussing what the up-to-date science is telling us, what the obstacles to translation are and if we are ready for what many people are calling a tidal wave of progress in immunotherapy. Our next conference, where we will discuss some of these issues and how we're going to deal with them, is scheduled for this November 13 and 14 at Harvard Medical School. The conference will feature some key thought leaders discussing these topics.

AFFILIATION

Ed Abrahams
President,
Personalized Medicine Coalition

DOI: 10.18609/cgti.2019.105

COMMERCIAL INSIGHT: JUL 2019

Commercial insight: cell and gene therapy

Providing a critical overview of the sector's commercial developments – M&As, licensing agreements & collaborations, financial results, IPOs and clinical/regulatory updates, with commentary from our Expert Contributors.

CELL THERAPY

Mark Curtis. Financial Portfolio Manager, Emerging Technologies, Lonza AG, Switzerland

PACT Pharma has started enrollment for a Phase 1 study investigating an autologous T-cell immunotherapy that will target patient-specific neoantigens. While we have made headway in the use of cell-based immunotherapies for blood cancers, there remains significant room for development of cell therapies that are able to eradicate solid tumors. PACT Pharma, and Neon Therapeutics, another biotech taking a personalized neoantigen approach for solid tumor applications, believe the key to solid tumor destruction is personalization of therapies at the level of each patient's unique tumor fingerprint. PACT recently announced data that validates their approach can be successfully deployed to identify patient-specific cancer mutation targets and generate T cells that are capable of targeting and eradicating cancer cells. It's early days for tailored, bioinformatics-driven technologies for oncology application but they hold great promise.

GENE THERAPY

Richard Philipson. Chief Medical Officer, Trizell Ltd, UK

Retinal degenerative diseases continue to be the focus of much attention in the biotech sector, with three groups releasing positive news this month. Children's Hospital Los Angeles has used Spark Therapeutics' voretigene neparvovec (Luxterna) to treat nine children with RPE65 mutations, with encouraging

improvements in vision; GenSight Biologics has completed enrolment into its Phase 3 trial for Leber Hereditary Optic Neuropathy ahead of schedule; and IVERIC bio has advanced its pipeline of treatments for LCA10 and Usher syndrome. Batten disease, a rare group of nervous system disorders called neuronal ceroid lipofuscinosis, also receives some attention, with positive news from Amicus Therapeutics' Phase 1/ 2 study in the CLN6 variant, and the announcement from Neurogene that it plans to initiate a natural history study in the CLN7 and CLN5 late infantile variants of the disease. Elsewhere, the announcement that Dicerna has received Breakthrough Therapy Designation for its RNAi-based therapy for the treatment of Primary Hyperoxaluria Type 1 (PH1), recognises the importance of the treatment and builds on the recent release of positive urinary oxalate data from the company's clinical trial program.

CLINICAL/REGULATORY

AMICUS' GENE THERAPY TRIAL OFFERS HOPE FOR BATTEN DISEASE PATIENTS

Amicus Therapeutics provides early update on its Phase 1/2 gene therapy trial developed to treat patients with CLN6 Batten disease, an inherited childhood neurodegenerative disorder.

Batten disease (also known as Neuronal Ceroid Lipofuscinoses, NCL) is a group of severe, inherited childhood neurodegenerative disorders caused by mutations in either soluble enzymes or membrane-associated structural proteins that result in lysosome dysfunction.

Over 400 mutations in 13 different genes have been described that cause the various forms of Batten disease and they are the most common cause of inherited neurodegeneration in children. The current trial targets Batten disease caused by mutation in the *CLN6* gene.

The hallmarks of the disease include accumulation of lysosomal residual bodies in neurons and extracerebral tissue and loss of neurons. These diseases share common pathological characteristics including motor problems, vision loss, seizures, and cognitive decline, culminating in premature death. Currently, no form of the disease can be treated or cured, with only palliative care to minimize discomfort.

Amicus' gene therapy program is licensed from the Abigail Wexner Research Institute (AWRI) at Nationwide Children's Hospital. Interim efficacy data obtained from the first eight children with CLN6 Batten disease treated with one-time AAV-CLN6 gene therapy showed meaningful impact on motor and language function. The treated children were evaluated for up to 24 months post-administration of the gene therapy. The Hamburg Motor & Language Score, an assessment of ambulation and speech, was used to evaluate the

DOI: 10.18609/cgti.2019.117

changes in motor activity and language in patients over the course of recovery. Data showed that the gene therapy rendered a positive impact on motor and language function and the disease was stabilized over the course of 2 years.

Treatment with AAV-CLN6 gene therapy was generally well tolerated. The study lacked control groups; therefore, Amicus compared the results with the performance of the siblings of patients treated in the trial. For example, one of the patients scored five out of six on the Hamburg Motor & Language scale at the time of treatment and was still at that level 24 months later. In contrast, the score of the sibling of that patient reduced from five to two over the same 24-month window. The Hamburg Motor & Language Score (0–6) separately measures performance of mobility (0–3) and speech (0–3). For each domain, a 3 represents the child's normal function and a 0 represents no ability to walk or speak, with each point decline representing significant impairment.

Amicus is hopeful with the results and intends to dose additional patients and advance talks with regulators. In parallel, Amicus will continue development of its other gene therapies, that target CLN3, CLN8 and CLN1 Batten disease.

Amicus' Chairman and CEO John F. Crowley commented:

"These interim clinical data suggest that our gene therapy in CLN6 Batten disease has the potential to halt the progression of this devastating fatal disease that untreated destroys brain function and kills children. It is remarkable that most children in this study appear to show stabilization, particularly the younger children who were able to maintain high baseline motor and language scores for up to two years. We look forward to presenting additional data throughout this year and continuing to advance our CLN6 and other Batten disease gene therapy programs that all apply the same AAV technology platform developed by Dr. Brian Kaspar and his former colleagues at Nationwide Children's. Early intervention is crucial, so we move forward with a great sense of urgency here for these children and their families."

*An interim analysis of data from Amicus Therapeutics' Batten disease Phase 1/ 2 study shows promising signs of efficacy in patients with the CLN6 variant of the disease. The AAV9-based treatment, carrying the gene for CLN6, is administered as a single, one-off dose by intrathecal catheter into the sub-arachnoid space of the lumbar thecal sac. Batten disease is an inherited lysosomal storage disease that is typically diagnosed at around 4–5 years of age and which is usually fatal by the age of 10. There are more than a dozen sub-types, of which only one has an approved treatment – BioMarin's cerliponase alfa for the CLN2 variant. Amicus estimates that there are approximately 1000 patients with the CLN6 variant worldwide who could be helped by the treatment, which has the potential to at least stabilize the disease, as measured by a six-point score that gauges mobility and speech ability. The next update from the study is expected at the Child Neurology Society's annual meeting in October, which will undoubtedly be anticipated with great interest. –**Richard Philipson***

HORIZON'S SHRNA TECHNOLOGY TO BE USED IN CELYAD'S CAR-T CLINICAL TRIAL

The US FDA has accepted Celyad's Investigational New Drug (IND) application for the autologous NKG2D based CAR-T cell therapy, CYAD-02. The news is exciting for Horizon Discovery as Celyad will be deploying Horizon's optimized SMARTvector™ shRNA technology.

Horizon is a biopharmaceutical company providing gene editing and gene modulation platforms for the global life science market. Celyad entered into exclusive license agreement with Horizon Discovery in October 2018 for the use of its shRNA technology for NKG2D-based CAR-T cell therapy.

The Phase 1 trial is scheduled to begin in early 2020 and it will be the first CAR-T cell therapy to employ the SMARTvector platform. It will evaluate the safety and clinical efficacy of CYAD-02 in patients with relapse/refractory acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS). Horizon will receive an undisclosed milestone payment for the successful IND filing.

Celyad has been investigating the use of shRNAs to support the clinical development of its CAR-T cell platform. The FDA approved IND application involves CYAD-02, a next generation CAR-T cell therapy in which shRNA is employed to suppress two genes. Celyad has pre-clinical data indicating that this improves in vivo engraftment and efficacy of CYAD-02.

Terry Pizzie, Horizon Discovery's CEO commented:

"We see great potential for shRNA technology in the optimization of next-generation cell therapies. The success of this IND filing is testament to the strength of our relationship with Celyad, and the powerful combination of Horizon's SMARTvector shRNA platform with Celyad's CAR-T expertise."

FDA PLACES CLINICAL HOLD ON UNUM'S CELL THERAPY TRIAL

FDA has placed clinical hold on Unum Therapeutics' cell therapy trial a second time after a patient experienced serious adverse event including neurotoxicity and respiratory distress.

The Phase 1 trial (ATTCK-20-2) is evaluating an engineered cell therapy, ACTR087 in combination with rituximab in patients with relapsed/refractory $CD20^+$ B cell non-Hodgkin lymphoma (r/r NHL).

ACTR087 is an autologous T cell therapy designed to bind to cancer cells and then orchestrate their destruction via mechanisms including the release of cytokines and recruitment of immune-mediated killer cells.

The clinical hold was initiated after Unum submitted a safety report

DOI: 10.18609/cgti.2019.117

to FDA about a patient in its safety expansion cohort of the trial who recently experienced serious adverse events that included grade 3 neurotoxicity and cytomegalovirus infection, and grade 4 respiratory distress.

This is the second time Unum is halting the trial because of safety issues. Earlier, one patient had died after suffering neurotoxicity related to ACTR087 and two other patients suffered cytokine release syndrome. The trial was later restarted after the FDA accepted the protocol and dosing amendments.

Patients receiving the combination therapy receive doses of lymphodepleting chemotherapy with fludarabine and cyclophosphamide beforehand to make the tumor more vulnerable to the treatment.

Unum Therapeutics uses T-cell technology to develop cellular immunotherapies for treating cancers. ACTR087 is no longer Unum's lead product candidate as it had announced last year that it was deprioritizing ACTR087 in order to advance its new ACTR construct, ACTR707. Unum had stopped enrolling patients in the Phase 1 ATTCK-20-2 trial with ACTR087 earlier this year.

FDA has agreed that patients who previously received ACTR087 and have ongoing clinical responses may continue to receive rituximab infusions, with continued monitoring for adverse events. Unum will continue to work closely with the FDA to further review these events.

Unum has four ongoing clinical programs currently in Phase 1 clinical testing, including ACTR707 used in combination with rituximab in adult patients with r/r NHL; ACTR087 used in combination with Seattle Genetics' novel antibody SEA-BCMA in r/r multiple myeloma; and ACTR707 used in combination with trastuzumab in adult patients with $HER2^+$ advanced cancer.

Unum share fell by nearly 20% in after-hours trading following the news. While ACTR087 is no longer Unum's lead lymphoma drug, the safety of the asset could still have implications for the company and the adverse events could widely impact the technology, drawing more scrutiny to the effects of engineered human immune cells.

SANGAMO'S GENE THERAPY HOLDS PROMISE IN TREATING HEMOPHILIA A

Sangamo Therapeutics together with its collaborator Pfizer has announced encouraging interim results from its ongoing Phase 1/2 study evaluating an AAV-based gene therapy approach to treat severe hemophilia A.

Data presented at the XXVII Congress of the International Society on Thrombosis and Haemostasis (ISTH), in Melbourne, Australia reported encouraging results of Sangamo's Phase 1/2 Alta gene therapy trial.

The Alta study of SB-525 is designed to evaluate the safety and kinetics of a single intravenous infusion of SB-525 in hemophilia A patients. SB-525 is a recombinant adeno-associated virus vector 6

(AAV6) encoding the complementary deoxyribonucleic acid for B domain deleted human FVIII.

The study evaluated ten patients across four ascending dosage cohorts; two patients in the first three cohorts and four patients in the highest dose (3e13 vg/kg) cohort. Patients demonstrated a dose-dependent increase in FVIII levels and dose-dependent decrease in the use of FVIII replacement therapy. Patients in the highest dose cohort achieved normal FVIII levels starting at 5–7 weeks following the therapy. The treatment was generally well tolerated.

Two patients in the 3e13 vg/kg cohort continue to have normal FVIII levels through 24 and 19 weeks of follow-up. The next two patients in this cohort are at 7 and 4 weeks of follow-up and have demonstrated FVIII activity kinetics similar to that of the previous patients in the same cohort.

Sangamo entered into a global collaboration and license agreement with Pfizer in 2017 for the SB-525 program. Later the collaboration was also extended to developing gene therapies for amyotrophic lateral sclerosis and frontotemporal lobar degeneration using Sangamo's proprietary zinc finger protein transcription-factor technology.

SB-525 received FDA's Orphan Drug and Fast Track designations and EMA's Orphan Medicinal Product designation. FDA has also recently granted regenerative medicine advanced therapy (RMAT) designation for SB-525 gene therapy to treat severe hemophilia A. RMAT designation will allow the company to interact with FDA more frequently.

Sangamo intends to dose a fifth patient in the 3e13 vg/kg cohort. Sangamo and Pfizer are working on plans to advance SB-525 to a registrational study. Pfizer will hold responsibility for late-stage development and manufacturing of the therapy, transfer of which from Sangamo to Pfizer has been initiated.

VACCINATION TRIGGERS ENGINEERED CAR-T CELLS TO ATTACK SOLID TUMORS

CAR-T cell therapies have emerged as a potent tool for hematologic malignancies and several clinical studies have shown its potential in refractory or relapsed B-cell malignancies. However, the full potential of CAR-T cell therapy in solid tumors is limited partly due to the difficulty in targeting functional engineered T cells to the tumor site.

In a recent study published in *Science*, Professor Darrell Irvine and team at Massachusetts Institute of Technology sought to address this concern using therapeutic cancer vaccines. These vaccines are designed to direct one's own immune cells to attack cancer cells. The team designed a vaccine strategy to improve the efficacy of CAR-T cells by restimulating the CAR directly within the native lymph node microenvironment. Injected 'amph-ligand' vaccines promoted synthetic antigen presentation and led to CAR-T cell activation, expansion,

DOI: 10.18609/cgti.2019.117

and increased tumor killing. The system could potentially be applied to boost any CAR-T cell.

Dr Irvine commented:

"Our hypothesis was that if you boosted those T cells through their CAR receptor in the lymph node, they would receive the right set of priming cues to make them more functional so they'd be resistant to shutdown and would still function when they got into the tumor."

To build the new vaccine, the team used an antigen that stimulates the CAR-T cells. The antigen could be either the same tumor antigen to be targeted by the T cells, or a random molecule that the researchers selected.

Results showed that the vaccines dramatically boosted CAR-T cell populations in mice. Mice given about 50,000 CAR-T cells without vaccine showed nearly no CAR-T cells in the bloodstream. But CAR-T cells comprised up to 65% of the animals' total T-cell population in animals that got the vaccine.

The combination treatment eradicated tumors including glioblastoma, breast and melanoma in 60% of mice, while CAR-T treatments alone produced no effect on those tumors. Next, the team re-challenged the mice that achieved tumor clearance with tumor cells. All tumor cells: tumor cells that were identical to the original ones and those that were slightly different, disappeared.

Findings from the study clearly demonstrate the clinical benefit of using a vaccine containing an antigen that stimulates CAR-T cells in lymph nodes, together with CAR-T therapy in treating difficult-to-treat solid tumors.

NOVEL TECHNOLOGY FOR ENHANCING THE EFFICACY OF CAR-T DRUG PRODUCT

Many patient's will go into relapse following a dose of CAR-T cells but will see their cancer relapse due to limited persistence of T cells or through antigen loss in tumor cells. To address the issue of persistence a group of researchers at MIT have developed a vaccine approach, targeted to the lymph node, an organ compartment that shelters T cells, in order to augment T-cell persistence. By administering either the protein that is targeted by the T cells, or a random protein, researchers showed that T cells persisted for longer in vivo and eradicated a variety of tumors. Elicio Therapeutics has a license to the technology and will bring it into the clinic. This is a great example of the combinatorial approaches we will need to take to eradicate solid tumors. –Mark Curtis

14 PATIENTS TREATED WITH SPARK'S VISION RESTORING RPE65 GENE THERAPY

Surgeons at the Children's Hospital Los Angeles (CHOL) have treated 14 patients with retinal degeneration using Spark Therapeutics' Luxturna™, the first FDA-approved gene therapy for a genetic condition in the USA.

Spark obtained marketing approval for LUXTURNA™ from the

US FDA in December 2017 for treating children and adults with a defective *RPE65* gene.

RPE65-mediated inherited retinal dystrophy is an inherited retinal disease (IRD) which progresses to complete blindness. Between 1,000 and 2,000 people in the USA is estimated to have vision loss due to biallelic *RPE65* mutations. The gene therapy uses adeno-associated virus vector to deliver *RPE65* gene to the affected patients.

CHLA is one of the seven hospitals approved nationwide to deliver the therapy and it has two full-time pediatric retinal surgeons on site, Drs Aaron Nagiel and Thomas C Lee. Genetic testing to verify the gene mutation and identify biallelic *RPE65* mutations is a pre-requisite before the procedure and CHLA's laboratory is certified to do the same.

The first patient who underwent the surgery on March 20th was an adult who suffered from Leber congenital amaurosis (LCA). Recently CHLA performed the procedure on nine children, as young as age three, and a handful of adults. While results have been less dramatic with adult patients — the inherited disease manifests itself early in childhood and gets worse over time, leading to total blindness — eyesight improvement is largely contingent on how far the condition has advanced.

Dr Nagiel commented:

"We have found that using gene therapy to treat this condition can be life-changing for children under the age of 10. While they are not going to have normal vision, we can improve it to a degree that they can do activities they couldn't do before, like playing outside at night. They gain greater visual clarity of edges on objects, so they can draw and enjoy picture books, and play with toys like puzzles and Legos."

DICERNA'S RNAI CANDIDATE RECEIVES FDA'S BREAKTHROUGH THERAPY DESIGNATION

Dicerna, a pharmaceutical company developing RNAi-based therapies, has announced that the FDA has granted Breakthrough Therapy Designation for its investigational RNAi candidate, DCR-PHXC, for treating patients with primary hyperoxaluria type 1 (PH1).

PH1 is an inborn error of metabolism and is a rare genetic disease characterized by excessive oxalate accumulation in plasma and urine, resulting in calcium oxalate crystal formation and deposition in the kidney and many other tissues. Oxalate is a natural chemical in the body that is normally eliminated as waste through the kidneys. In patients with PH, the kidneys are unable to eliminate the large amount of oxalate that is produced. The condition arises from mutations in the enzyme alanine-glyoxylate aminotransferase.

DCR-PHXC is being evaluated currently in the PHYOX™ clinical trial program. FDA's Breakthrough Therapy designation is a process designed to accelerate the development and review of drugs that are

DOI: 10.18609/cgti.2019.117

intended to treat a serious condition. The present Breakthrough Therapy Designation is based on preliminary results from the PHYOX1 Phase 1 trial of DCR-PHXC and preclinical results obtained from animal models of PH. Phase 1 trial results showed that a single dose of DCR-PHXC led to normalization or near-normalization of urinary oxalate levels in most patients and was generally well-tolerated.

In animal models, DCR-PHXC selectively silences lactate dehydrogenase A enzyme, or LDHA, in the liver, blocking the excess production of oxalate. The compound was well tolerated with no adverse effects in the liver.

DCR-PHXC uses Dicerna's GalXC™ technology which is a proprietary platform developed by Dicerna scientists to discover and develop next-generation RNAi-based therapies designed to silence disease-driving genes in the liver.

FDA also recognized its determination that PH type 2 and PH type 3 meet the criteria for a serious or life-threatening disease or condition, based on the Agency's standards. The company will continue its ongoing dialogue with the FDA regarding endpoints for studies of DCR-PHXC in patients with PH2 and PH3, as part of the PHYOX™ clinical development program.

Dr Ralf Rosskamp, Dicerna's CMO, commented:

"By granting Breakthrough Therapy Designation, the FDA recognizes both the urgent need to develop a therapy for primary hyperoxaluria type 1 and the encouraging preliminary data from the PHYOX1 clinical trial of DCR-PHXC in these patients. We look forward to continuing our dialogue with the FDA as we advance DCR-PHXC as quickly as possible as a potential therapeutic option for all persons living with primary hyperoxaluria."

KITE PLANS TO EXPAND CELL THERAPY MANUFACTURING CAPABILITIES

Kite, a Gilead company, has announced its plans to start a new manufacturing facility in Oceanside, California, to develop and manufacture viral vectors, a critical starting material in the production of its cell therapies.

The new 67,000-square-foot facility builds on Kite's existing state-of-the-art manufacturing capabilities to deliver innovative cell therapies for people with cancer, including Yescarta® (axicabtagene ciloleucel), Kite's first commercially available CAR-T cell therapy, and investigational T-cell receptor and tumor neoantigen targeting cell therapies being evaluated in solid tumors.

By pursuing its own viral vector facility, Kite intends to advance viral vector development and supply to allow for accelerated process development of current CAR-T and future pipeline therapies, while continuing to partner with external suppliers.

Kite's facility will be constructed within an existing Gilead biologics operations facility in Oceanside and will become part of Kite's growing

commercial manufacturing network that includes sites in California, Maryland and the Netherlands.

Tim Moore, Executive Vice President of Technical Operations at Kite, commented:

"The new viral vector facility in Oceanside is an example of our continued investment in achieving technical advances that will help meet the needs of people living with cancer today and in the future."

AVROBIO'S GENE THERAPY HOLDS POTENTIAL IN TREATING FABRY DISEASE

The clinical-stage biotechnology company AVROBIO has announced the first kidney biopsy result and additional interim clinical data from two of its ongoing gene therapy clinical trials for Fabry disease. To date, eight patients have been dosed in the trials – three patients in the Phase 2 FAB-201 trial and five patients in the Phase 1 FACTs trial.

Data obtained from the patients shows positive outcome and favors the therapeutic potential of lentiviral-mediated gene therapy in treating this rare disease.

Fabry disease is an X-linked, rare lysosomal storage disorder caused by a deficiency of alpha-galactosidase A enzyme with the progressive accumulation of globotriaosylceramide in vascular endothelial cells.

In AVROBIO's lentivirus-mediated gene therapy trials of AVR-RD-01 (an investigator-sponsored Phase 1 study and the AVROBIO-sponsored Phase 2 trial), patient's stem cells are extracted and genetically modified by adding a functional copy of the GLA gene coding for alpha-galactosidase A. The modified cells are then infused back into the patient via a one-time procedure. The procedure expects to achieve a sustained increase in the enzyme, with the potential to significantly improve patient outcomes and eliminate costly lifetime biweekly intravenous infusions of enzyme replacement therapy (ERT).

The investigator-sponsored Phase 1 study evaluates the safety of AVR-RD-01 in Fabry disease patients who have been treated with standard of care ERT for at least 6 months prior to receiving the gene therapy. The company-sponsored Phase 2 trial is an open-label, single-arm clinical trial evaluating the efficacy and safety of gene therapy in eight to twelve patients who have never received ERT (treatment-naive).

The primary efficacy endpoint for the Phase 2 FAB-201 trial is the change from baseline in the average number of Gb3 inclusions per peritubular capillary (PTC) as measured in a kidney biopsy 1-year post-treatment with AVR-RD-01. Gb3, or globotriaosylceramide, is a substrate (or fat) that accumulates in the cells of Fabry patients and can result in damage to multiple organs including the kidneys and heart. Data showed an 87% reduction in average number of Gb3 inclusions in first kidney biopsy taken 1-year post-treatment.

The FAB-201 and Phase 1 clinical trials are examining a number of

DOI: 10.18609/cgti.2019.117

secondary efficacy and other endpoints, including biomarkers, such as measurements in the plasma of Gb3 and lyso-Gb3 (the toxic metabolite of Gb3), AGA enzyme activity levels in leukocytes and plasma, vector copy number (VCN), as well as indicators of kidney and cardiac function. Data showed that plasma lyso-Gb3 consistently reduced 33 to 41% below baseline ERT levels in the first four Phase 1 patients. Durability observed across multiple biomarkers, sustained at more than two years for the first Phase 1 patient. The treatment was generally well tolerated and no SAEs related to AVR-RD-01 drug product were reported.

Dr Birgitte Volck, AVROBIO's President of R&D, commented:

"We are excited by the magnitude of the Gb3 reduction observed in the first patient's kidney biopsy at 12 months. This is the primary efficacy endpoint in FAB-201 and an efficacy endpoint that has previously been utilized by the FDA in evaluating and approving treatment for Fabry disease. Our prior data readouts have shown AVR-RD-01 is associated with reductions of Gb3 and lyso-Gb3 levels in the plasma, and today's data further support its potential to reduce Gb3 levels in tissue, including in the kidney. We believe the 87% Gb3 clearance in the kidney biopsy may be considered clinically relevant since Gb3 accumulation in organs of Fabry patients is associated with significant morbidity and early mortality."

AVROBIO's gene therapy for Fabry disease has demonstrated promising reductions in the key substrate of the disease – globotriaosylceramide, or Gb3 – in kidney biopsies, and also in lyso-Gb3 – the toxic metabolite of Gb3 – in plasma. Fabry disease, an X-linked condition caused by a deficiency in the enzyme alpha galactosidase which leads to accumulation of Gb3, manifests from childhood onwards with gastrointestinal pain, chronic kidney disease, cardiomyopathy, neuropathy and skin changes. The enzyme replacement therapies (ERT) Replagal (Shire) and Fabrazyme (Genzyme) remain the mainstays of treatment, now joined by Amicus's chaperone therapy Galafold (miglustat). AVROBIO's treatment may offer a more permanent "cure" – two patients in the Phase 1 trial were able to discontinue ERT; however, the treatment is not to be undertaken lightly, requiring stem cell mobilization, apheresis and partial myeloablation, prior to infusion of the lentivirus-based AVR-RD-01 (transduced autologous CD34$^+$ cell-enriched fraction). Longer term questions such as durability of benefit and risk of insertional mutagenesis remain open, but the early data certainly look encouraging. – Richard Philipson

PACT PHARMA TO TARGET CANCER NEO-ANTIGENS TO ERADICATE SOLID TUMORS

PACT Pharma, a startup company focusing on developing personalized adoptive cell therapy for treating cancers, has presented new data at a conference conducted by the American Association for Cancer

Research (AACR). The strategy is expected to provide the solution to treat solid tumors using customized adoptive cell therapy.

Cancers originate from primary tumors and the genomic mutations that initiate cancer growth and development expand in number and diversify over time to create a wide spectrum of cancer mutations called neo-antigens. These neo-antigens are unique to each cancer patient and are absent from healthy cells of the same person.

PACT Pharma intends to address cancer by specifically targeting these neo-antigens. The company is working with researchers at the University of California, Los Angeles (UCLA) to solve this problem.

The company's approach entails defining specific cancer mutations in each individual patient and then manufacturing an immune-cell therapy that targets abnormal proteins, or 'neoantigens,' produced by genes with those mutations.

The company has launched a Phase 1 study of the approach in patients with solid tumors. The procedure starts by using bioinformatics technology to identify the 'mutation blueprint' of each patient's tumor. Then the T cells in the blood of the patient will be captured. These T cells will have the ability to recognize and target the new mutations.

Researchers will then identify mutation-targeted T-cell receptors and use gene editing to attach them to T cells from the patients. The resulting product, called NeoTCR-P1, will be infused back into the patients. The company hopes to show in clinical trials that the engineered T cells will eliminate tumors that express the mutations they were designed to target.

Data presented at the AACR meeting showed that Pact's technology could identify mutations in melanoma samples from two patients who had two different kinds of neo-antigens. Then they made T cells specific to those mutations and showed they could use them to kill melanoma cells from the patients.

PACT aims to enroll 148 patients in its phase 1 trial of NeoTCR-P1, which it plans to study both as a solo treatment and as a combination with the anti-PD-1 drug Opdivo.

GENSIGHT BIOLOGICS COMPLETES ENROLLING PATIENTS IN ITS RETINAL GENE THERAPY PROGRAM

Paris-based clinical-stage biotechnology company has announced that it has completed enrolling patients in REFLECT, a Phase 3 clinical trial of GS010 for treating Leber Hereditary Optic Neuropathy (LHON). The trial is progressing ahead of schedule. Enrolling the target number of 90 subjects was originally anticipated to be completed in September 2019; instead the 98th subject enrolled in the trial was treated on July 2.

LHON is a rare genetic disorder affecting the retinal ganglion cells leading to vision loss within weeks or months. It is caused by G11778A mutation in the

DOI: 10.18609/cgti.2019.117

mitochondrial ND4 gene. GenSight's GS010 uses a mitochondrial targeting sequence proprietary technology platform which, when associated with the gene of interest, allows the platform to specifically address defects inside the mitochondria using an adeno-associated vector.

GenSight Biologics is developing gene therapies for retinal diseases and diseases of the central nervous system. REFLECT trial is a multi-center, randomized, double-masked, placebo-controlled study designed to evaluate the safety and efficacy of bilateral injections of GS010 in patients with <1 year of onset of vision loss in LHON.

The trial enrolled subjects across multiple centers in the USA, Europe and Taiwan. In the active arm, GS010 was administered as a single intravitreal injection to both eyes of each subject. In the placebo arm, GS010 was administered as a single intravitreal injection to the first affected eye, while the fellow eye received a placebo injection.

The primary endpoint for the REFLECT trial is the best corrected visual acuity change from baseline reported in LogMAR at 52 weeks post-treatment in the second affected/not yet affected eye. The first subject was treated in March 2018; topline week 52 results are expected to be available in the third quarter of 2020. GS010 has Orphan Drug Designation both in the USA and in Europe.

APIC BIO'S GENE THERAPY FOR ALS RECEIVES FDA'S ORPHAN DRUG DESIGNATION

Apic Bio, a gene therapy company developing novel treatment options for patients with rare genetic diseases, has announced that the FDA has granted orphan drug designation to APB-102, a gene therapy soon to be in clinical development for the treatment of genetic SOD1 amyotrophic lateral sclerosis (ALS).

FDA provides orphan designation to novel drugs that are intended for the treatment of rare diseases (those affecting fewer than 200,000 people in the USA). The designation provides sponsors with development and commercial incentives including seven years of market exclusivity in the USA, consultation by FDA on clinical study design, potential for expedited drug development, and certain fee exemptions and reductions.

The incidence of ALS is estimated to be 1.5 to 2.5 cases in 100,000 persons in the USA and in Europe, or up to about 30,000 new cases of ALS per year in those areas. It is estimated that 10% of all cases are thought to be inherited as a dominant trait, or otherwise known as Familial ALS (FALS.) Approximately 15 to 20% of FALS cases are caused by mutations in the gene that produces the copper zinc superoxide dismutase 1 (*SOD1*) enzyme, which leads to a progressive degeneration of motor neurons affecting movement and muscle control.

Apic Bio is a spin-off from the University of Massachusetts

Medical School (UMMS) and is based upon nearly 30 years of gene therapy research by Apic's scientific founders. Apic is developing treatment options for rare, devastating neurological and liver diseases. Its current pipeline focuses on new and effective treatments for Alpha-1 Antitrypsin Deficiency (Alpha-1, or AATD) and genetic ALS.

LICENSING AGREEMENTS & COLLABORATIONS

IVERIC BIO PARTNERS WITH UMASS MEDICAL SCHOOL

IVERIC Bio has entered into an exclusive global license agreement with the University of Massachusetts Medical School to develop and commercialize mutation independent novel AAV gene therapy product candidates for the treatment of Leber Congenital Amaurosis type 10 (LCA10) due to mutations to the *CEP290* gene, the most common type of LCA.

IVERIC bio's collaboration with UMass Medical School and its Horae Gene Therapy Center, utilizing the minigene therapy approach, has resulted in additional research data that supports the company's plans to move the program forward.

The company also announced that it is expanding its gene therapy portfolio by entering into a sponsored research agreement with UMass Medical School and an exclusive option agreement for rights to develop and commercialize novel AAV gene therapy product candidates utilizing a mutation independent minigene therapy approach for the treatment of vision loss in *USH2A*-related inherited retinal diseases (IRDs). This is a group of orphan IRDs that includes Usher syndrome type 2A and *USH2A*-associated autosomal recessive nonsyndromatic retinitis pigmentosa.

Glenn P Sblendorio, CEO and President of IVERIC bio, commented:

"Moving our LCA10 program forward and expanding our pipeline with the addition of a minigene research program for ***USH2A*** *further validates our commitment to develop innovative and life changing gene therapies for patients with orphan inherited retinal diseases. We are very excited about the progress of our collaboration with world-renowned AAV gene therapy scientists at UMass Medical School, Hemant Khanna, PhD, and Guangping Gao, PhD."*

Minigene therapy is intended to deliver smaller but functional portion of the larger gene packaged into a standard-size AAV delivery vector commonly used in ocular gene therapy. Research in this evolving area of gene therapy is led by Drs Hemant Khanna and Guangping Gao in the Horae Gene Therapy Center.

DOI: 10.18609/cgti.2019.117

PHARMACYTE & UTS COLLABORATE OVER MELLIGEN CELLS

PharmaCyte Biotech, a US-based clinical-stage company specialized in developing targeted treatments for cancer and diabetes has announced that it has entered into a new research agreement with the University of Technology Sydney (UTS) in Australia to create a new version of Melligen cells for the treatment of diabetes with the potential to express higher levels of insulin.

Melligen cells are human liver cells that have been genetically engineered to produce, store and release insulin in response to the levels of blood sugar in the body. PharmaCyte has obtained the exclusive worldwide license rights from UTS to use these cells to develop a therapy for Type 1 and insulin-dependent Type 2 diabetes.

Under the new collaboration, PharmaCyte plans to encapsulate Melligen cells using its Cell-in-a-Box® technology to protect the Melligen cells from immune system attack in the body and thus function as a 'bioartificial pancreas' for purposes of insulin production.

PharmaCyte Biotech's Cell-in-a-Box technology encloses genetically modified living cells in pinhead-sized, porous capsules. The live cells inside the capsule are nourished and thrive while the capsules are in the body and are designed against destruction by the body's immune system.

The encapsulation of living cells in the Cell-in-a-box technology is a multi-step process. First, the live cells to be encapsulated are suspended in a medium containing a polymer and sodium cellulose sulfate. This suspension is then passed through a droplet-generating machine; the resulting droplets are made to fall into a solution containing another polymer. As the two polymers interact, a membrane is formed around each droplet, which ultimately develops into a shell around the droplet. The resulting spherical capsule is 0.7–0.8mm in diameter.

The work undertaken by PharmaCyte, UTS and PharmaCyte's International Diabetes Consortium over the last two years has resulted in an opportunity to re-engineer the Melligen cells with the aim of increasing their insulin production as well as the bioactivity of the produced insulin. With this new agreement in place, the research will be done in Australia under the leadership of Professor Ann Simpson, the developer of the original Melligen cell line.

The unique properties that set the Melligen cells apart from all other available insulin-producing cell types, include their robustness, their ability to withstand an attack from cell-toxic molecules that typically lead to the destruction of insulin-producing cells and their suitability for cost-efficient pharmacological-grade large scale production. In contrast to primary beta islet cells of the pancreas, which normally produce insulin and stem-cell-derived insulin producing cells, Melligen cells are a scalable and a highly characterized cell line that can readily be expanded in a

bioreactor to generate the amounts of cells needed for cell banking, testing and production.

PharmaCyte's CEO, Kenneth L Waggoner, stated,

"We are pleased to have come to an agreement with UTS that allows us to take the Melligen cells to the next level in our development of a 'bioartificial pancreas' for the treatment of Type 1 and insulin-dependent Type 2 diabetes. If we are successful, it will bring to fruition the many years of research that have been conducted by Professor Ann Simpson and her colleagues at UTS as well as PharmaCyte in developing these remarkable insulin-producing cells."

BE THE MATCH BIOTHERAPIES® & TMUNITY COLLABORATE TO ACCELERATE NEXT-GENERATION IMMUNOTHERAPIES

Biotherapeutic company Tmunity has partnered with Be The Match BioTherapies®, an organization offering solutions for companies developing and commercializing cell and gene therapies, to accelerate patient access to life-saving cell therapies.

Tmunity will utilize Be The Match BioTherapies' industry-leading cell therapy supply chain and collection network management expertise to support clinical development of its next-generation immunotherapies. Tmunity is currently working on broadening its clinical pipeline of investigational immunotherapies to address a broad range of solid tumor and hematological cancers.

Be The Match BioTherapies will provide the expertise related to the management of cell therapy supply chain and logistics supported by the company's MatchSource® Supply Chain Software. In addition, Be The Match BioTherapies will qualify, develop and train a network of collection centers to help ensure the collection of consistent, compliant and high-quality cell starting material. To gain efficiencies in site qualification, Tmunity will receive licensed access to quality system audit results through the Quality System Audit Program (QSAP).

Tmunity's work is focused on the development of T cell-based therapies for the treatment of cancer. The company was founded on a licensing agreement with the University of Pennsylvania.

MASSACHUSETTS GENERAL HOSPITAL JOIN HANDS WITH ELEVATEBIO TO ADVANCE INNOVATIVE CELL & GENE THERAPIES

Massachusetts General Hospital (MGH) has entered into a 10-year alliance agreement with ElevateBio, a Cambridge, MA-based cell and

DOI: 10.18609/cgti.2019.117

gene therapy company. The agreement provides MGH preferred access to ElevateBio's BaseCamp research, process development and manufacturing facility in Waltham, MA for developing and manufacturing innovative cell and gene therapies developed at MGH.

Under this agreement, MGH is making an investment in ElevateBio BaseCamp, and BaseCamp's facilities and expert staff will support a range of cell- and gene-therapy programs arising from MGH's research programs and laboratories. In addition, ElevateBio and MGH will jointly identify innovative cell and gene technologies from university labs and other external sources to create therapeutics companies to advance additional cell and gene therapies from the lab to the bedside of patients suffering from severe diseases.

According to the terms of the agreement, MGH will have guaranteed access to ElevateBio's BaseCamp for multiple, simultaneous cell- and gene-therapy programs for process development and manufacturing each year. At the same time, ElevateBio and MGH may jointly form any number of companies to manufacture and develop cell- and gene-therapeutic candidates from multiple sources.

David Hallal, CEO of ElevateBio, commented:

"This 10-year alliance with MGH advances key objectives for our organization as we strive to reach more patients faster with innovative clinical-stage cell and gene therapies. We look forward to providing updates of our progress under this new collaboration in the months ahead."

CHRISTI SHAW JOINS KITE AS NEW CEO

Kite Pharma, a Gilead Company, has appointed Christie L Shaw as its new CEO and a member of Gilead's senior leadership team.

Ms. Shaw has extensive experience across the biopharmaceutical industry and has held various leadership positions in the pharma sector. She currently serves as Senior Vice President of Eli Lilly &. Co., and President of Lilly Bio-Medicines. She also serves as a board member of both Avantor, Inc. and the Biotechnology Industry Organization (BIO), and as an advisor to the Healthcare Businesswomen's Association.

Prior to joining Lilly, she served as US Country Head and President of Novartis Corp. and North American Head of Novartis Oncology. She earned a BA in Business Administration from Iowa State University and an MBA from the University of Wisconsin.

SANGAMO THERAPEUTICS APPOINTS GARY H LOEB AS EXECUTIVE VICE PRESIDENT & GENERAL COUNSEL

Genomic medicines company Sangamo Therapeutics has appointed Gary H Loeb as its Executive Vice President and General Counsel. Mr. Loeb will oversee all legal matters for Sangamo and will report to the CEO.

Mr Loeb has over 20 years of experience in biotechnology and pharmaceutical law, compliance, intellectual property, litigation, human resources, regulatory, and facilities. Before joining Sangamo, he served as General Counsel, Corporate Secretary, and Chief Compliance Officer at Achaogen, an anti-infectives company. At Achaogen, Mr Loeb was a member of the Executive Team and the first full-time in-house attorney, where he built the legal and compliance teams. Before Achaogen, Mr Loeb worked in roles of increasing responsibility at Counsyl, a genetic screening company, Amyris, Inc., and Genentech.

Written by Dr Applonia Rose, Cell and Gene Therapy Insights

DOI: 10.18609/cgti.2019.117