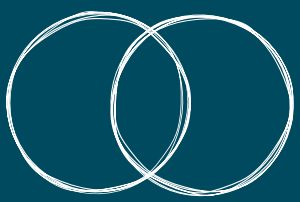
CAR T
accelerating adoption through collaboration



the cancer collaborative | le collaboratoire cancer

about this report

CAR T. accelerating adoption through collaboration was written by the cancer collaborative and it examines the challenges and opportunities of bringing disruptive technologies like CAR T to canada and the opportunity of bringing stakeholders together to bring therapies to the patients who need them. the framework of this paper was built through a discovery discussion held in november 2018 and through subsequent interviews and literary reviews.

our thanks to the participants of the discovery discussion which included;
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about colab

the cancer collaborative's mission is to bridge science, policy and advocacy to proactively identify the challenges and opportunities within oncology, prioritize them and work together to make action-oriented changes on how cancer care is delivered in canada. meeting the challenges of today's cancer ecosystem with innovation and collaboration to create meaningful impact for patients and system readiness through multi-stakeholder engagement.

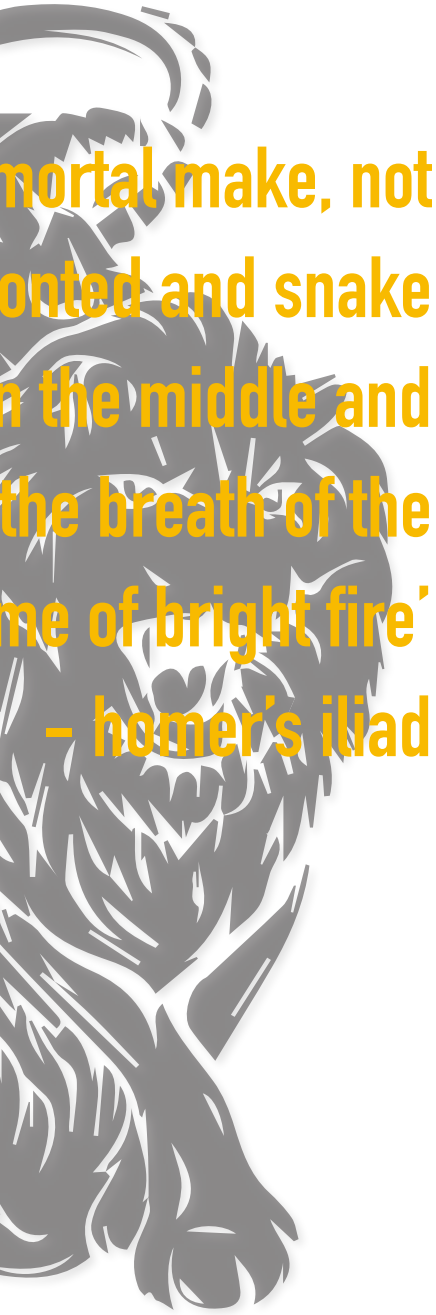
bridging science policy and advocacy

introduction

according to greek mythology, chimera was a monstrous fire breathing hybrid creature composed of the parts of three animals and usually depicted as a combination of a lion, a goat, and a serpent. in biology, a chimera means an organism composed of genetically different cells, or a hybrid protein made by splicing several different pieces of genetic code together.

chimeric antigen receptors or CARs refer to genetically engineered molecules manufactured in a laboratory, inserted into the genetic material of immune T cells that have been removed from the patient's body, and then expressed as proteins on the T cell surface. CARs are designed to give T cells, a type of white blood cell, highly specific homing abilities so that when they are returned to the patient, the T cells can more easily recognize and attack cancer cells throughout the body.

the term chimeric has been given to the genetically engineered antigen receptors because they are artificial [not because they are dangerous].



executive summary

delivering innovative cancer medicines in a modern healthcare system is a daunting challenge for canadians- with an ageing population, budget constrained health systems, and more breakthroughs and innovations make their way into the canadian landscape into an infrastructure that has neither the capacity nor the resources to support their arrival in a timely manner.

the introduction of CAR T cell therapy brings with it an enormous amount of complexity for our systems. building strong partnerships to establish canada's viability as a healthcare innovator, as a partner in delivering exceptional patient care, and a pioneer in healthcare policy that engages with stakeholders throughout the process is at a critical standpoint.

supporting broad access without limiting innovation and a multidisciplinary approach that can be adaptable as new technologies continue to be introduced while also ensuring that patients have access to these medicines, therapies and technologies is essential to delivering optimal care. and we must work together to accelerate adoption of CAR T today and to deliver the medicines of tomorrow.

CONTENT

CAR T-CELL THERAPY

what is CAR-T?

CAR T as a living drug - this emerging form of immunotherapy uses a patient's own re-engineered cells to attack cancer, an innovative, personalized treatment that is patient specific. in the process of manufacturing CAR T cell therapy, a patient's T cells, the white blood cells that are key to immune function, are removed and then modified in a lab. once these cells have been re-engineered the T cells are infused back into the patient's body. theses cells are designed to recognize and attack specific proteins or antigens [current CAR T targets CD19] on tumour cells. once infused into the patient's bloodstream the cells continue to multiply, kill malignant cells, then remain on guard to survey the tissues and fight any recurrence.

CAR T cells are a one time infusion. And although the process may take several weeks from the collection of T cells to the manufacturing, re-infusion and subsequent monitoring for adverse side effects, CAR T has permanent immunological memory and is designed to have long lasting effects. once they are infused they remain in your body- thus a living drug.

'a new and unique new way to treat cancer, CAR T-cell therapy is poised to transform the outlook for children and adults with certain otherwise incurable cancers' **ASCO [advance of the year statement]**

there are two currently approved CD19 targeted CAR T cell therapies in canada, tisagenlecleucel [kymriah] and axicabtagene ciloleucel [yescarta]. clinicaltrials.gov has over 800 studies related to chimeric antigen receptor therapy, with different targets, expanded indications including solid tumours and non cancerous disease, studies to test the effectiveness in earlier lines of therapy, in combination with other therapies, and with different antigens following CD19 directed CAR T cell therapy. [1]

tisagenlecleucel [kymriah] is approved for the treatment of B cell acute lymphoblastic leukemia [ALL] who are refractory or have relapsed after allogenic stem cell transplant [SCT], are otherwise ineligible for SCT, or have experienced second or later relapse in paediatric and young adult patients 3 to 25 years of age; and for the treatment of adult patients with relapsed or refractory [r/r] large B cell lymphoma after two or more lines of systemic therapy including diffuse large B cell lymphoma [DLBCL] not otherwise specified, high grade B cell lymphoma and DLBCL arising from follicular lymphoma.

axicabtagene ciloleucel [yescarta] is approved for the treatment of adult patients with relapsed or refractory [r/r] large B cell lymphoma after two or more lines of systemic therapy, including diffuse large B cell lymphoma [DLBCL] not otherwise specified, primary mediastinal large B cell lymphoma, high grade B cell lymphoma, and DLBCL arising from follicular lymphoma [transformed follicular lymphoma- TFL].

NOTE* ALL accounts for 80% of leukaemia cases in children. it is estimated that 240 children per year will be diagnosed with ALL in canada with conventional therapies. although the cure rate is fairly high [80% to 85%]; about one in four patients will relapse.[2] relapsed ALL is the leading cause of death from childhood cancer.

diffuse large B cell lymphoma is the most common non hodgkin lymphoma. each year it is estimated that 10.000 adults are diagnosed with DLBCL. approximately 50% of patients are cured with first line chemotherapy and 10% with second line therapy [chemotherapy, stem cell transplant or newer therapies available through clinical trials]. 30-50% of these patients experience relapse and 10% have refractory disease, meaning their disease does not respond well to treatment. if left untreated, the life expectancy of patients with r/r DLBCL is three to four months. r/r ALL or r/r DLBCL patients have typically exhausted all curative therapies and are managed with end of life care. this population represents an unmet clinical need.[3]

CAR-T highlights

chimeric antigen receptor [CAR] T-cell therapy has dramatically shifted the landscape of treatment for lymphoid malignancies, especially diffuse large b cell lymphoma [DLBCL] and acute lymphoblastic leukaemia [ALL].

non hodgkin lymphoma is the most common hematologic malignancy in canadian adults. diffuse large b-cell lymphoma [DLBCL] is the most common lymphoma subtype, followed by follicular lymphoma. [4]

DLBCL standard of care therapies are effective, however approximately 30-50% of cases relapse or progress and the outcomes in patients who relapse or are refractory are exceedingly poor. [5]

in follicular lymphoma [FL], the overall survival rate is 72-77% with median survival just under ten years. patients with relapse or refractory FL have a poorer prognosis. nearly 20% of patients will not require therapy following the first 10 years of diagnosis, most will however experience progressive disease and need treatment. [6] [7]

more than 80% of paediatric patients with ALL, the most common childhood cancer, will be cured with intensive chemotherapy.[8] but for patients whose cancer returns after chemotherapy or stem cell transplant, the treatment options are limited.

CAR T-cell therapy has shown some very promising results in the treatment of blood cancers, including complete responses [CR] in approximately 40-60% of aggressive lymphomas and 60-80% in ALL. [9]

the unprecedented activity for CD19 directed CARs in DLBCL and ALL has created new hope for personalized cures.

ELIANA trial. this pivotal study demonstrated 60% complete response [CR] and 81% overall response rate [ORR] in 75 children and young adults with ALL. responses were durable, with a reported 80% six month relapse free survival [RFS] rate. sustained remissions were found to be associated with prolonged detection of CAR T cells in peripheral blood samples [median of 168 days] and persistent B cell aplasia. treatment related toxicities were frequent, with 73% of patients experiencing severe [grade III or higher] adverse events [AEs], including 47% developing severe cytokine release syndrome [CRS]. [10]

ZUMA1 trial. in 101 patients with refractory aggressive lymphomas, there was an 83% ORR and a 58% CR rate with 39% having ongoing responses at median follow up of 27.1 months. in contrast to tisagenlecleucel, there was a higher reported incidence of severe neurotoxicity [32%] and less CRS [11%]. response to therapy appeared to be independent of traditionally poor prognostic disease histologies, such as activated B cell [ABC] like, double expresser, or high grade lymphomas. [11]

JULIET trial. in 93 patients with DLBCL, 40% of patients achieved a CR, which in all cases remained durable at median follow up of 29.3 months. the toxicity profi le was similar to that seen in ALL patients from the ELIANA trial, with less neurotoxicity [12% grade 3 or higher] than CRS [22% grade 3 or higher]. an exploratory analysis showed no correlation between pre-infusion tumour CD19 expression levels and response. [12]

CAR T has opened up new options for patients who were otherwise untreatable. patients who participated in these studies were unresponsive to previous lines of therapy or had relapsed multiple times after receiving standard of care [chemotherapy and/or bone marrow transplant]. while clinicians hesitate to use the word cure, CAR T offers a potentially curative treatment for paediatric ALL.

while it has shown important response rates, CAR T cell therapy is associated with unique and potentially severe toxicities, most notably cytokine release syndrome [CRS] and neurotoxicity. some toxicities from CAR T cell therapy occur within hours of administration, yet CRS can generally appear within 1 to 14 days after infusion.

as we look to the future, important next steps for CAR T will be expanding its role to new disease types including solid tumours.

since the initial food and drug administration [FDA] approval of anti CD19 CARs for acute lymphoblastic leukaemia [ALL] in august 2017, there have been two additional approvals within the span of one year, and there are likely several more on the horizon.

canadian context. tisagenlecleucel [kymriah] received health canada notice of compliance [NOC] in september 2018 and CADTH and INESSS recommended the provision of tisangenleulecel in canada and québec, for DLBCL and pALL with conditions, including a reduction in price in january 2019. axicabtagene ciloleucel [yescarta] received NOC in february 2019 and CADTH and INESSS recommendations in august 2019 with conditions of a reduction in price.

in april 2018, the canadian agency for drugs and technologies in health [CADTH] decided to review the first CAR T therapies under their process for medical devices and clinical interventions rather than through the pan-canadian oncology drug review [pCODR], which

typically reviews pharmacological therapies in oncology. the decision to assess CAR T therapies through the medical device review, rather than through pCODR, was made from feedback received from federal, provincial, and territorial ministries of health [MoH], and the canadian association of provincial cancer agencies. this approach is consistent with the assessment process by the institut national d'excellence en santé et en services sociaux [INESSS] in québec. [13] CADTH released two summary reports in august and september, outlining their protocol for a health technology and optimal use assessment of tisagenlecleucel for pALL and DLBCL. since the initial approval of tisagenlecleucel, CADTH has since then announced that future CAR T therapies, including axicabtagene ciloleucel will be reviewed through pCODR. INESSS has not made an announcement of a change to their process.[14] INESSS has however announced that given the incertitude of the longer term efficacy and safety of CAR T, real world evidence will be collected with a plan to re-evaluate within three years to confirm the results with greater certainty.[15]

given this uncertainty surrounding CAR T, both regulatory and health technology assessment agencies across canada have revamped their appraisal methods, creating strong collaborations between regulatory and HTA organizations, as well as within the two HTA agencies in canada, CADTH and INESSS, who worked in close collaboration to review CAR T.

clinical trials for other CAR T cell therapies are available throughout canada and institutionally directed, government funded programs for CAR T therapies, including BioCanRx and hôpital maisonneuve rosemont [HMR].

institutional and off the shelf CAR T
the success of cellular therapies will depend on its ability to meet global demand as well as expanding the eligible patient population- to do so a controlled, robust and reproducible manufacturing platform for the production of autologous CAR T cells is necessary.

because CAR T does not fit the standard biopharma model, based on using a 'master' cell to generate made to order therapies at a large scale, the challenge for the wide application of CAR T will be a reproducible manufacturing process' of high quality, clinical grade CAR T cell products while maintaining product quality and clinical equivalence.

clinical sites in canada must meet FACT accreditation criteria in order to provide CAR T. discussions to identify and establish standardization of good manufacturing practices [GMP] for institutional or off the shelf CAR T will be required to ensure the safety, efficacy and capacity of the product as well as the clinical site.

as well as unidentified GMP standards for institutional or off the shelf CAR T, questions remain regarding requirements for establishing a regulatory and reimbursement process for institutional and off the shelf CAR T.

value of CAR T

fundamental questions exist about paying for new therapies, what payors value, what patients and physicians value, and paying for outcomes rather than drugs. there needs to be a differentiation between the price of a drug [how much a payer is charged for the therapy], the cost [how much it takes to develop and manufacture that medicine or therapy), and its value [the actual benefit that a patient receives from a drug or procedure]. demonstrating value to the healthcare ecosystem and specifically to patients will depend on multiple factors, including level of innovation, durable clinical benefit, treatable patient population size, impact on health systems but most importantly on accessibility.

CAR T cell therapies have instituted a new era of effective cancer therapies for patients. these one time infusions have fulfilled an important unmet need for relapsed and refractory diffuse large B cell lymphoma and have the potential to replace allogenic stem cell transplant in select patients.

CAR T has challenged how stakeholders will determine value, and this is further compounded by the uncertainty and long term outcomes of the treatment. in order to determine the value, an understanding of the long term efficacy and safety of CAR T, how they compare to standard of care and where they fit in the treatment pathway and optimization of patient selection will need to be determined.

although clinically effective, calculated value to patients or social value decreases with delays to access as currently experienced in canada and will be further reduced by treatment delays for patients who must travel to receive treatment. in a study by the american journal of managed care, patients with pALL lost 9.8%, 36.2% and 67.3% of social value, respectively with 1, 2 or 6 months of treatment delays. patients with DLBCL lost 4.2%, 11.5% and 46% of social value with the same treatment delays.[16]

in canada, the first CAR T was approved by health canada in september 2018 and received CADTH and INESSS recommendations in january 2019 but as of december 2019, CAR T is still not available to patients [not including québec, an agreement between the government and manufacturer was reached in october 2019], meaning that patients have been faced with a current eleven month delay.

facilitating timely patient access will play a key factor in determining the value of CAR T. for patients receiving CAR T as a last ditch effort, delaying treatment comes at a high cost.

payment mechanisms as innovative as the therapy itself, adequate investment in and capacity in infrastructure, scalability, and policy reform are urgently needed to increase patient access and maximize the value of CAR T in the short and long term.

policy issues and pressing questions

despite regulatory and health technology assessment [HTA] approvals, challenges continue to hinder patients from receiving these life saving treatments and companies from providing them in a robust manner, including clinical, access and reimbursement hurdles.

and while the value of CAR T has been demonstrated, in canada and globally, underlying questions associated to cost effectiveness, uncertainty and affordability must be addressed. these expected barriers will hinder access to the first CAR T cell therapies.

the budgetary impact of these therapies remains the main limiting factor - at the time of writing of this report cancer care ontario [CCO] has still not concluded negotiations with the manufacturer for pricing on the first approved CAR T [approved in september 2018 by health canada].

the cost of these one time treatments inevitably poses challenges for already budget constrained reimbursement authorities across canada, representing a major barrier to ensuring ethical and equitable patient access. in a study published by the american journal of managed care, researchers suggested that improved payment mechanisms, as well as adequate capital and payment policy reform are urgently needed to increase patient access and maximize the value of CAR T therapy.[17] models for addressing the unique challenges of reimbursement of CAR T exist, and an appropriate funding mechanism or multiple options must be considered in order to enable innovation in canada, improve access to cancer care and patient outcomes.

payors and providers have expressed concern that they could pay high up front costs for therapies that do not yet have evidence to support the projected long

term benefits and for which the value cannot yet be fully characterized.

expanding inequitably access issues are the few clinical sites available to offer this specialized therapy. the first CAR T cell therapy, once a letter of intent [LOI] and provincial listing agreement [PLA] have been reached, will only be available in two provinces [QC and ON]. policies and funding plans that take into consideration associated costs beyond treatment, including travel, housing, and translation, through a harmonized, national approach will be essential in minimizing disparities in access. other needs in addressing disparities in access will be the expansion of future sites- preparation of clinical sites with active engagement from industry, healthcare professionals [HCPs] and governments will be necessary to enhance access for patients and reduce costs. more centres will allow patients to stay closer to home, reduce delays to treatment time, make more patients eligible while increasing sustainability and cost effectiveness for healthcare systems. site prioritization through government, payor, manufacturer and healthcare professional [HCP] intervention will be important to address in order to broaden the accessibility of CAR T, avoiding delays and in expanding clinical trial sites.

beyond treatment costs, administrative, as well as follow up and subsequent care costs will be barriers to sustainability and access for patients and systems. patient assistance programs provided by manufacturers in collaboration with provincial governments, to help cover potential and considerable out of pocket costs for the patients must be planned to help alleviate some of the financial barriers for patients. these programs should be discussed and agreed upon between manufacturer and government and should be implemented to fill the gap to reduce the financial burden for patients.

another major concern, is the lack of infrastructure and resources to achieve equitable access. institutional infrastructure for CAR T cell therapy is essential to meet the complex medical, logistic, training, and regulatory requirements of the treatment and inter-professional teams are necessary to effectively deliver this treatment to patients.

CAR T is an area that needs careful collaboration between payors and clinicians to come up with guidelines. because resources are limited, eligibility criteria may exclude more patients than it includes and funding agencies may be even more selective. ultimately, selection criteria should allow clinicians to determine the best patients for these therapies. legal and ethical considerations that protect the rights and interests of the patients, including timely treatment opportunities, ensuring equitable access both financially and geographically and the management of patient expectations, especially as these therapies move from last ditch efforts to first line therapies must also be considered and implemented.

the process of making CAR T cells, although now well established, is extremely intricate and the complexity of this treatment has limited the treatments availability. the global capacity for manufacturers to produce CAR T in one manufacturing lab as clinical centres increase and more patients become eligible to receive treatment will need to be re-evaluated in order to ensure that delays do not occur due to manufacturing processes. and the manufacturing and delivery of CAR T must be improved to broaden the eligible patient population and reduce costs. as CAR T cell therapy use expands, the necessity to reproduce it on a larger scale to be available to more patients through a simplified process, with quicker turn around, will increase the eligibility criteria, making it available to more patients, and more cost effectively.

in order to build the capacity for this, strong partnerships and investment by government and industry will be required.

important considerations must also be placed on second infusions for patients who do not respond to first generation CAR T cell therapy, including second infusion with CD19 directed CAR T cell therapy or other antigens now being researched and the legal considerations associated with the collection of human cells.

novel immunocellular therapies such as CAR T require more complex patient specific manufacturing, administration and monitoring than traditional cancer therapies, presenting a number of challenges for healthcare systems that are currently not set up to provide such complex and transformative technologies. the complexity of the manufacturing process of autologous CAR T cells requires leukapheresis, followed by the extraction of patients' T cells, transportation to the manufacturing facility, genetic engineering to incorporate CARs, and transportation of the finished product back to the treatment centre and finally administration to the patient, will require significant investment in current healthcare frameworks [including financial, organization and policy frameworks] in order to adjust to the changing landscape. this pace of change requires new approaches in healthcare delivery, organization, funding and collaboration- rethinking strategies that address the nimble and flexible integration of therapies that challenge current healthcare delivery into the existing framework without disrupting patient outcomes. these strategies must also consider eliminating silos to create multidisciplinary workflow amongst stakeholders, that deliveries quality cancer care. failing to address these issues upfront could result in limited or restricted patient access and can hinder future innovation in canada.

because of the high budget impact of CAR T on the healthcare system determining the value [through health economic analyses and data collection],

transparent patient criteria and guidelines, use of molecular testing to identify appropriate patients, decreasing delays to access will also be of important consideration.

the difficulty of balancing paying for innovation within constrained healthcare budgets has been a major concern for canada, and the emergence of cell and gene therapies has only exacerbated that conundrum. the launch of the first two CAR T cell therapies will likely prove to be useful case studies for how HTA, payors and governments will respond to this new reality. current challenges associated with pricing and reimbursement of CAR T cell therapy could be further heightened as additional indications for CAR T are granted approval and the patient population eligible for the treatment modality increases. therefore the development of workable payment models for these therapies now, is a critical issue in healthcare and will become increasingly time sensitive as more gene and cell therapies advance. towards commercialization.

payment models as innovative as the treatments themselves are necessary, but are provincial governments in canada willing to adopt these outcomes based payment approaches to address the high upfront costs. the complexity of value based agreements may deter governments from considering such an approach, however, there are ways to achieve risk sharing and predictability without the complexity.

another consideration for manufacturers will be to re-evaluate their applications to HTA to reflect this changing landscape as HTA agencies continue to refine and innovate their evaluation processes.

alternative funding models

current reimbursement models in general do not accommodate many of the unique factors that are common among gene and cell therapies, including smaller patient populations, shorter treatment windows, potentially curative efficacy, high up front costs, lack of long term efficacy and safety data, and costs associated with complex administration, dosing, and patient monitoring requirements. these types of agreements or funding models allow payors to better balance paying for innovation within their budgets. however, refining or even fundamentally restructuring value demonstration and pricing strategies to support these therapies, and new models may need to be implemented.

globally, payors and industry are looking at several innovative payment options, including models based on clinical outcomes, annuity payments, and expanded risk pools.

a sample of potential funding models

value based agreements

in these models, products must meet predetermined target outcomes at preset time periods to earn reimbursement. if endpoints are not met, products are not reimbursed by payors.

amortized payment models

these models can be adapted to individual therapies by adjusting which stakeholder will absorb different levels of risk. this approach is one of the most popular models under consideration for gene therapies and could help soften the near term impact on healthcare budgets while providing sufficient returns for innovators.

carve outs and risk pools

cell and gene therapies may also become more affordable through disease area carve out plans or by expanding risk pools. carve out plans typically involve one payor [or care provider] that excludes specific diseases while another provider supplies coverage for those excluded diseases. this approach often leads to the creation of payors or vendors with deep clinical expertise in specific therapeutic areas that are well positioned to consider unique payment structures while establishing specialized legal protections for sensitive data. many payors have implemented carve out policies for high-cost services such as organ transplantation and mental health.

with expanded risk pools, a combination of public and private funding from stakeholders such as charitable foundations could help keep premiums and cost sharing at relatively manageable levels. this model could require private payors, employers, and governments to allocate a portion of healthcare budgets to a dedicated fund for gene and cell therapies. funds would be withdrawn and paid out if the cost of therapy exceeds a predetermined threshold. in canada, a nonprofit called the canadian drug insurance pooling corporation manages this type of risk pool, in which employer group plans agree to spread the burden of high cost therapies, including gene and cell therapies, across multiple payors. in the UK, the cancer drug fund is an example of a separate, centrally coordinated, government sponsored funding mechanism.

as we look to reduce cost and improve efficiency of CAR T cell therapy through continuous improvements a consideration of the regulatory and reimbursement framework that optimizes CAR T to make it affordable and reach more patients is necessary. as payors, manufacturers, patients, healthcare professionals and canadians we need to consider how much we are willing to invest in innovative therapies that work in some patients now, or continue to spend on ineffective therapies only to pay for innovation down the line. [18]

payor landscape

USA

in the USA, novartis has implemented indication specific pricing for kymriah- 475.000$ for B cell ALL and 373.000$ for DLBCL. yescarta's US list price is 373.000$ for DLBCL and PMBCL.

europe

in europe and canada, pricing strategies for kymriah and yescarta will be critical for securing optimal access and reimbursement from national authorities.

*in **germany**,* a country that traditionally shies away from complex managed entry agreements [MEAs] or other forms of discounts, payors actively pushed for outcomes agreements because of the high levels of uncertainty and prices associated with CAR T. [19] [20]

*in the **UK***, the national institute for care and health excellence [NICE] have consigned the drugs to the cancer drugs fund [CDF], where they will have a set amount of time [february 2020] to prove their efficacy through collected real word data before being re-evaluated for funding. despite its list price of 288,000£, it is considered to be the fastest funding approval in NICE history and this expediency was likely in part due to preparedness on the part of the U.K. payors completed a mock assessment prior to approval that demonstrated the drugs would likely be cost effective, at least in some populations. [21] and in january 2019, the voluntary pricing and access scheme [equivalent of the patent medicines prices review board] agreed to a set of commitments that would see earlier engagement to support the introduction of new medicines and greater uptake of the most clinically and cost-effective medicines that provide significant health gain. [22]

Table1: Factors influencing ability & likelihood of EU5 countries to enable access to CAR-T therapies

Country	Innovation policy		CAR-T innovation funding		Established Reg. Path based on CGT precedent		Access schemes		Overall attractiveness	Notes
	Yes	No	Yes	No	Yes	No	Yes	No		
England	✓		✓		✓		✓ ✓		High	NICE assessed the feasibility of its appraisal for regenerative medicines and considered it suitable. The NHS confirmed preparations for CAR-T therapies Patient access schemes are widely used to gain access and ensure cost effectiveness
France	✓			✓		✓	✓		Low	France has no precedent in paying for gene therapies, several private investment funds are supporting the biotech industry. In particular in oncology models like price volume agreements are common
Germany	✓		✓		✓			✓	Medium	Germany approved several CGT (cell and gene therapy) products and P4A research confirmed that the AMNOG process is appropriate for approval of innovative therapies, government innovation funds covered for early CAR-T developments
Italy	✓		✓		✓		✓ ✓ ✓		High	Italy set up measures to ensure patients can have access to inovative therapies, including the innovation fund supporting market access, however, access schemes are key. So far, Italy is the only country offering Strimvelis treatment and patients across Europe are travelling to Italy
Spain	✓		✓			✓	✓ ✓		Medium	Spain funds several biotech projects some of which in medical research, Spain was one of the first European trial sites that conducted CAR-T trials. Spain has a new model for high economic impact products supporting access to innovative products with a high unmet need

Source: Partners4Access

figure 1. Partners for Access

in ***france,*** l'autorisation temporaire d'utilisation [ATU] program gathered real world evidence on CD19 CAR T cell for patients to be used during pricing negotiations. [23] INESSS will be implementing a similar approach.

in ***italy***, CAR T therapies were approved with innovative status and therefore had instant inclusion on all formularies. it should be noted, that italy has historically used outcomes based agreements to fund high cost therapies, particularly for oncology therapies, and the agenzia italiana del farmaco [AIFA] has announced that it will reimburse CAR T using a new reimbursement model *'payment at results'*. [24]

in ***spain***, the sistema nacional de salud, [SNS] approved the reimbursement of kymriah in december 2018. national payors, working with regions, agreed on an outcomes based agreement for ALL and DLBCL that will result in a price that is sustainable for the national health system. it was also announced that a similar agreement was being negotiated with gilead for yescarta for its approved indications. SNS in collaboration with experts, regional governments and patients defined centre referral and designation criteria for CAR T therapy. [25]

recognizing the value of innovative and therapeutic advances will require canada to examine new potential funding mechanisms to deliver on innovation. the tools exist within canada to employ funding models that promote efficiency in health care delivery and to further demonstrate commitment to value and accountability without placing undue burden on patients, clinicians and systems.

managing patient expectations

the tremendous excitement surrounding CAR T from increasing awareness and success rates has inundated patients with the promise of a cure. despite the optimism, CAR T cell therapy has its downsides. it is not available to most patients, it's approval has strict limitations, and it triggers serious side effects in some patients. there is a lag time between patient selection and the actual administration or infusion of the CAR T, which can take up to nine [9] weeks. this will require that some patients receive a bridging therapy, in which time the disease may progress, meaning some patients may no longer be eligible to receive CAR T, while some others may decease during this waiting time.

translating trial results into the clinic often yields unexpected patient responses and these results may not be the same in the real world. the challenge now will be managing patient expectations as CAR T cell therapy comes to market in canada, including how patients are selected and when, and throughout their treatment process, and even once they have returned home after receiving treatment.

because of their complexity and uniqueness, raising awareness and educating on CAR T prior to the launch of the technology in canada is important. it is crucial that patients are comprehensively educated and prepared to what to expect during CAR T treatment. patients and their families should be educated about the symptoms and associated adverse events [AEs], their severity to avoid delays in seeking proper treatment. equally important in educating patients, is the possibility of not having any adverse events. in a survey conducted by bloodwise UK, patients who did not experience any adverse events felt anxiety about the effectiveness of the treatment. [26]

patients, their families and caregivers need responsible and transparent communication on the issues related to the therapy, including the possible side effects [including lack of] and their management, patient selection criteria and treatment pathways, what each province will be supporting for patients to access this therapy and possible outcomes, including relapse.

presently, CAR T cell therapy will be limited to certain certified centres across canada, and only provided to patients who meet strict eligibility criteria unlike other chemotherapeutic agents with broad access. because of this, some patients and their caregivers will be required to travel out of province, or within province to academic centres [currently only in québec and ontario] to receive treatment. this will have a significant impact on families and caregivers- not only time away from work and family, but also the substantial out of pocket costs that will be required.

additionally, patients who do not have support from a caregiver will likely not be offered the treatment.

lessons learned

CAR T is a disruptive technology that brings with it the potential for fundamental change that will require the need for health systems to work differently. adding to the complexity is the highly dynamic nature of this innovative field, using the lessons learned from the introduction of CAR T to better anticipate, respond and act with policies and processes that promote innovation while also creating efficiency and value as future cell and gene therapies come into canada.

engagement and collaboration

engage early and often with stakeholders to shape the therapy and policy environment so the therapy's value is broadly recognized.

proactively engage with all stakeholders to anticipate challenges and opportunities and determine possible solutions and recommendations

facilitate the translation of knowledge, including patient selection, treatment pathways, design and implementation to overcome barriers

preparedness

address and prioritize potential clinical, access and reimbursement challenges

create appropriate infrastructure and build capacity

develop a network that can develop the strategic direction for cell and gene therapies beyond CAR T

reduce inefficiencies and delays with unnecessary processes

prepare for transformation implementation

value and investment

determine what patients, physicians, payors value and what canada is willing to invest in

for manufacturers- quantify the value of the therapy and be prepared to offer pricing that is consistent with that value

invest now in system transformation that will be required for future technologies and innovations in healthcare

use funding models to achieve risk sharing and predictability

long term planning

thoughtful planning and phased implementation of healthcare system changes to improve quality, accessibility, efficiency, affordability and sustainability.

identify technologies and therapies that may be available in the short to long term and respond appropriately and collaboratively, with the lessons learned from this experience to implement a process that appropriately responds to the needs of all stakeholders.

leadership

game changing treatments have arrived but is canada ready to deliver them. in order to successfully deliver on the promise of CAR T the need for strong multi-stakeholder partnerships and development of best practices is necessary. governments working with industry and other stakeholders to ensure affordability, sustainability and reimbursement and working with the community to implement equitable and ethical delivery of patient care of these novel therapies.

NHS england responded with a vision to form a network for co-ordinated activity and shared learning to overcome barriers. seven [7] first wave commissioned CAR T centres were approved ahead of NICE product approvals.

the NHSE worked in close collaboration with industry partners to agree on price and process an NHSE managed access agreement was established via the cancer drug fund [until cost effectiveness can be established - data collection until february 2020]. a national CAR T panel to approve patients was implemented and 122 patients have been approved between december 2018-july 2019.

the NHSE also set up a national network of advanced therapies treatment centres [ATTC] to develop world leading infrastructure and capabilities to support the development and adoption of advanced therapy medicinal products [ATMP]. collaboratively. the goal of the ATTC network is to increase patient access to advanced therapy medicinal products on a national scale, to establish best practice for safe and effective delivery throughout the manufacturing and final preparation process, to accelerate adoption by the NHS and to develop the UK as a global leader.

the UK has capitalized on the opportunity presented by CAR T to set a precedence and become global leaders in the implementation, adoption and delivery of CAR T.

the NHSE and the ATTC network are addressing the logistical and clinical barriers to establish a stakeholder partnership, scalable infrastructure and system of best practice for transformative and effective delivery of ATMPs and ATMP trials across the NHS. [27]

canada showed leadership in the regulatory and HTA process, with health canada working in partnership with CADTH and CADTH and INESSS assessing CAR T collaboratively. CADTH also adapted their process based on feedback by payors and decision makers. and INESSS has initiated a plan to collect RWE [an innovative approach for a HTA organization]. since the process moved to pricing negotiations it has stalled, delaying access for patients and hampering canada's ability to show leadership.

flexibility, willingness to partner and political appetite is necessary if canada desires to become a player in the global CAR T and emerging cell and gene therapy field - from implementation, delivery and manufacturing. CAR T therapies, as well as other novel therapies have highlighted the need to re-evaluate current frameworks and methodologies to sufficiently evaluate emerging technologies. Including reforming processes for approval of innovative therapies, and identifying sustainable funding for innovative medicines. governments must be willing to work with industry to create innovative pricing strategies, provide training for skilled staff, expand clinical sites, develop transparent patient selection criteria and clear treatment pathways. decision makers will need to prioritize patient and public engagement in policy decisions and implement data collection to better understand the cost effectiveness of these therapies and their appropriate place in the treatment paradigm. [28] [29]

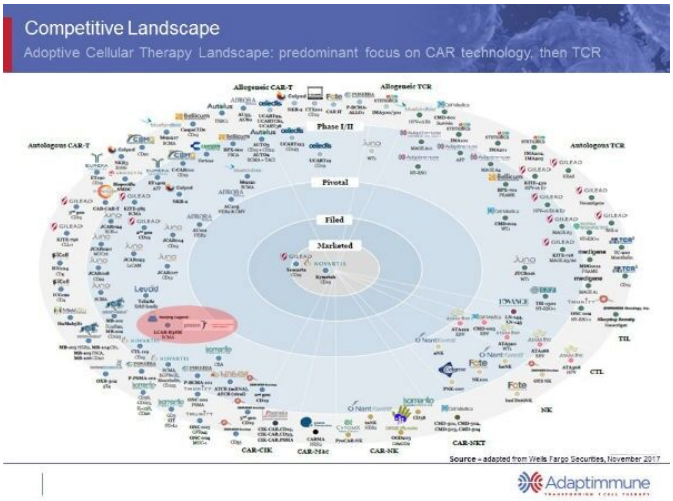
stakeholders must determine what role canada wants to play in the implementation and delivery of CAR T, as well as future cell and gene therapies and other innovative and possibly disruptive therapies and technologies and what each stakeholder's responsibility is in achieving that. a pathway that emphasizes the need for a multidisciplinary approach in the implementation, adoption and delivery of

CAR T cell therapy in canada, and which is critical to the success and leadership of CAR T.

future directions

cell and gene therapies are the fastest growing area of research, and labs around the world are now developing CAR T therapies that work on different targets and different diseases. the promising outcomes from clinical trials investigating CAR T cells across various patient populations and disease types have invigorated the field of cellular therapies. this technology enables an almost limitless variety of possible unique CAR designs. in the next few years we're going to see dramatic progress and researchers pushing the boundaries of what many people thought was possible with these adoptive cell transfer based treatments

the FDA expects 200 cell and gene therapy investigational new drug applications each year by 2020, with 15 to 20 approvals each year by 2025. [30]



innovative medicines have the potential to revolutionize the management of many cancers, but these are complex and expensive treatments with many barriers to routine adoption. strong stakeholder partnerships, working together to develop capability and scalable capacity within a robust infrastructure, will enable advanced therapies to improve healthcare at an acceptable cost that is sustainable and deliverable to a larger number of patients in a routine setting. in order to achieve this, improved patient selection, more investment from government and industry, improved treatment safety, health regulation and investment and raised public awareness is necessary.

future success requires

i. *reducing cost and manufacturing time.*
-simplification of supply chain logistics and development of off the shelf | institutional cell and gene therapies.
-improving patient selection, reducing product failure and treatment attrition.
-value based agreements and industry collaboration and innovatively priced treatment strategies.
-creating marketing competition and the development of off the shelf or institutional products.
-implementation of CAR T in earlier lines of therapy.

ii. improving treatment safety.
-standardization of safety algorithms, training of skilled staff and establishment of robust supportive care systems with industry playing a role in training. -new approaches to decrease the incidence and severity of toxicities.

iii. improving patient selection.
-a significant proportion of patients will relapse and responses seen in solid tumours have been less robust.
-a long term understanding of the efficacy and safety of CAR T therapies and how they compare with standard of care treatments and where they will fit into the treatment paradigm.
-further investigation into innovative next generation CAR designs, identification of new targets, rational combination with other therapies, selection of biomarkers and the development of companion diagnostics, improving the toxicity profile, finding the cause of resistance, as well as earlier referral will be necessary to improve patient selection. [31]

iv. RWE.

-performance based or risk sharing agreements will require coordinated data collection infrastructure because reimbursement is tied to clinical outcomes, therefore data infrastructure will need to be established.

-identifying the role and responsibility of each stakeholder.

-there exists a need to continue to monitor the safety and efficacy of these emergent therapies- an important consideration for new therapies. outcomes must be followed and processes and policies must be re-evaluated to meet these findings as they become available.

-what we know now is based on the information currently available, and as more data is made available our understanding will need to adjust accordingly.

v. investment from government and industry.

-to expand this exciting technology into new areas of unmet clinical need where cell and gene therapies have transformative potential investment by both industry and government is necessary.

-the development of new, cheaper and more efficient technologies to deliver cell and gene therapies to a larger number of patients at affordable costs.

-reforming process' for approval of innovative therapies.

-identifying sustainable funding for innovative medicines.

-considering the cost implications of long terms benefits or risks to health.

vi. *raising public awareness.*

-cancer charities, patient groups and governments working together to raise awareness and publicize the issues.

-publishing transparent patient selection criteria and clear treatment pathways. prioritizing patient and public engagement in policy decision, patient selection panels and development and actively involve patients in decision making that allows them to participate in decisions about their health and health systems.

vii. *delivery of clinical trials.*

-it will be incumbent on the medical field to continue to pursue academic work in this area to better identify the patients who will respond to this therapy and future uses of CAR T therapies.

-ensuring that canadians have access to clinical trials in canada.

future success will depend on reducing the cost and manufacturing time, improving product safety and patient selection in order to make these products accessible, affordable, effective and deliverable on a larger scale to a wider range of patients.

CAR T in solid tumours

cellular therapies have yet to produce reliable results in solid tumours despite extensive research. the known barriers caused by the unique challenges posed by CAR T cell therapy by solid tumours can be described in three categories, finding, entering and surviving in the tumour microenvironment. [32]

translating the success into solid tumours poses a number of challenges, not the least of which is identifying suitable targets, unlike hematologic cancers such as ALL or chronic lymphocytic leukaemia [CLL] in which tumour cells universally express B cell marker CD19, solid tumours rarely express one tumour specific antigen, the tumour microenvironment makes it difficult for T cells to infiltrate and persist in a solid mass and the heterogeneity of tumours also means that the chosen CAR won't bind to every tumour cell. [33]

CAR T in other blood cancers

chronic lymphocytic leukaemia [CLL]. treatment options for CLL including novel targeted agents and pathway inhibitors [PI] provide remarkable efficacy and response rate [RR] may be as high as 95%. despite these high response rates only 10-30% of patients achieve complete remission and approximately 50% of treated patients will relapse within 3-4years. patients who experience disease progression during therapy with PIs have limited options and shortened survival. preclinical studies of CAR T have shown consistent RRs of 75% in a subset of drug resistant patients. [34]

multiple myeloma [MM]. despite advances in MM the disease remains incurable in most patients and almost all patients with MM relapse after initial therapy. the disease is then characterized by multiple relapses and remissions, with the number of remissions dependent on the available treatment options during the first relapse, clinically relevant responses can be achieved in 40-50% of patients.

treatment of relapsed/refractory multiple myeloma [rrMM] presents a special therapeutic challenge, in second relapse and beyond the goal of treatment is to prevent organ impairment and to achieve disease control. patients who received CAR T had received at least three previous lines of therapy or were refractory. objective response rate was 85% with 45% achieving a complete response in drug resistant patients. six of the 15 patients who had a complete response have had a relapse and CAR T cells persisted up to 1 year after infusion.[35] [36] [37] [38] [39]

acute myeloid leukaemia. [AML] despite high response rates after initial chemotherapy, relapse occurs frequently, resulting in a five year survival of <30%. the treatment of AML has remained a particular challenge due to the heterogeneity of AML bearing cells rendering single antigen targeting CAR T cell therapy ineffective. compound targeting of CLL1 and CD33 [cCAR] have demonstrated profound anti-tumour activity in AML.

first in human trial demonstrates promising efficacy of cCAR therapy in treating patients with r/r AML. [40] [41]

the excitement surrounding CAR T has led to extensive and rapid clinical development targeting several antigens across many indications. there are over 400 trials listed on clinicaltrials.gov related to chimeric antigen receptor therapy.

collaboration to impact change

healthcare systems are not prepared for the logistical challenges presented by these innovative therapies- CAR T cells have demonstrated the importance of preparation and engagement with relevant stakeholders as early and as often as possible. stakeholders must learn to work together in a collaborative environment in order to bridge the gap rather than widen it so a common strategy can be developed that responds to both the priorities of patients and healthcare systems. ensuring widespread access to cell and gene therapies and other innovative technologies will require stakeholders to work together to design a healthcare system that can adjust to the change of pace and innovation currently being seen in oncology.

we need

new levels of collaboration

new levels of collaboration among governments, payors, manufacturers, nonprofits, and other stakeholders are necessary. collaboration earlier in the process to ensure appropriate implementation and accelerated adoption [working together to make a more meaningful impact for patients] including the development of national pathways and implementation roadmaps, and a reform of the healthcare system to adapt to the current landscape and realities.

ethical, equitable and consistent access

creating ethical, equitable and consistent access to patients, through clear, transparent and consistent communication amongst stakeholders and undertaking novel tactics to engage with key public | private payors, regulators, medical associations, manufacturers and patient organizations

to work closely together

working closely with payors and policymakers to ensure sufficient and appropriate reimbursement for CAR T cell therapy for paediatric and adult patients across all provinces and without [further] delays. and ensuring speed of access to new treatments through regulatory and reimbursement frameworks are not compromised

co operation

co operation between health systems and stakeholders to establish a network [to expand clinical sites, manage expectations, set guidelines, build RWE, etc.]

exchange of expertise

exchange of expertise [patient experience, health economics, registries, clinical data, clinical expansion, education, learning, supporting physicians] and a timely exchange of knowledge.

information and expertise should travel - not the patient

outcomes based approaches

as the healthcare industry shifts toward value based healthcare, it is incumbent on canada to begin to outline an approach based on outcomes.

financing and risk issues resolution

resolving complex financing and risk issues that can delay market access and reimbursement is paramount to the success of gene and cell therapies.

anticipate future therapies

anticipating future cell and gene therapies and being prepared to respond to any potential clinician and patient challenges that may arise. and a flexibility to ensure new approaches to health policy are adopted that can optimize patient access within a viable long term model of sustainability.

national alignment

create national alignment on policy and reimbursement to accessing CAR T cell therapy.

real world evidence

develop an RWE strategy that will help identify appropriate patients, where the therapy fits in the treatment paradigm, the value of the therapy, as well as long term safety and efficacy of the therapy.

management of expectations

management of patient expectations will be important as equally important will be the information provided to patients on what and whom is eligible to receive CAR T in or out of province and what provinces will reimburse and which costs will come out of pocket [removing administrative burdens for patients] and ensuring that patients are aware of their rights. [eg. cross provincial toolkit]

doing better for patients

CAR T is moving at an exponential pace and has the potential to transform cancer treatment, however, in order to deliver on the promise of CAR T, patients need to remain at the centre of efforts in healthcare- from clinical trials to decision making, through to education, awareness and advocacy and ensuring that stakeholder priorities match patient priorities. patient centricity has become an evolving trend, and as more breakthroughs and discoveries occur in personalized medicine, cancer care and healthcare is shifting from treating the cancer to treating the patient and stakeholders must respond appropriately.

doing better for patients means systems that adapt to embrace innovation and new technologies, infrastructure that determines the actual value and cost effectiveness of these therapies in the short term and long term, optimizing patient selection and ensuring that patients are getting treated earlier. because patients are heavily pretreated prior to receiving CAR T and the lag in manufacturing process [8-9 weeks] creates additional barriers to response. earlier treatment also creates cost effectiveness for healthcare systems.

manufacturing processes need to be simplified and shortened in order to reach a larger patient population with shared care models in communities to bring treatments closer to home and reduce disparities in access. improving treatment results and enhancing efficacy- we can do better than 20-30% failure rate. improving processes which can take years before the therapies become available to canadians, identifying funding models that create sustainability and affordability for healthcare systems that translates into better, and improved access for patients.

inclusion of patients and patient groups in decision making about their health and healthcare systems is the only way to really create patient centricity in healthcare.

these can only be achieved with a strong government commitment in innovation that includes a supportive framework tobring these life saving therapies to patients.

finally, have we learned from the canadian experience with CAR T and other global experiences, have we asked the right questions and have we put the appropriate processes in place. what take aways can stakeholders take from these experiences to improve upon for future innovative medicines in canada to make a meaningful impact for patients

'learning and innovation go hand in hand. the arrogance of success is to think that what you did yesterday will be sufficient for tomorrow.'

william pollard

conclusions

the recent approval of the first CAR T cell therapies in canada despite concerns about uncertainty in the data and cost, has shown a willingness from payors to embrace CAR T. a promising sign for other emerging cell and gene therapies and innovative medicines in canada.

the rapid clinical expansion and potential of cell and gene therapies can lead to a new generation of therapies targeting significant areas of unmet need. however innovative, these new technological and therapeutic approaches will be disruptive to current systems and will require entirely new approaches to treatment that will also call for new levels of thinking in pricing and drug access strategies as well as in delivery.

the realization of CARs clinical and economic potential can only be achieved by their capacity to be accessed by the patients who will benefit from them. at present, with delays in achieving access to first generation CAR T, the potential and promise of CAR T has not been achieved, nor has canada been able to capitalize on the opportunity to become leaders in the delivery of this innovative therapy. challenges and opportunities from the regulatory process to implementation and patient delivery can be overcome through current opportunities to build strong partnerships amongst stakeholders to accelerate adoption of CAR T cell in canada for first generation and subsequent cell and gene therapies while creating meaningful impact for patients. stakeholders must come together to define the ultimate role of CAR T in oncology in canada and then create the roadmap to implement this now and for future cell and gene therapies.

this is just the beginning. we are only at the cusp of what CAR T cell therapies can do for oncology, and stakeholders must be prepared to respond to this and the challenges and opportunities that come with it, identifying and eliminating inefficiencies from the healthcare system to improve delivery of these agents so more patients can have access and to position canada as a leader in healthcare innovation and development.

timeline

april 2014. tisagenlecleucel receives orphan designation by the EMA for the treatment of B cell lymphoblastic leukaemia/lymphoma.

july 2014. the FDA grants breakthrough designation status to CD19 directed CAR T cells signalling the field's scientific and clinical progress.

december 2014. orphan designation granted to axicabtagene ciloleucel by the EMA for the treatment of diffuse large B–cell lymphoma.

october 2015. orphan designation granted to axicabtagene ciloleucel for the treatment of primary mediastinal large B-cell lymphoma.

october 2016. orphan designation granted to tisagenlecleucel for the treatment of diffuse large B-cell lymphoma.

april 2017. FDA grants breakthrough designation for tisagenlecleucel for the treatment of adult patients with r/r DLBCL

august 2017. FDA approves tisagenlecleucel for the treatment of r/r acute lymphoblastic leukemia [ALL] in children and young adults

may 2017. axicabtagene ciloleucel receives priority review by the FDA

october 2017. FDA approves axicabtagene ciloleucel for the treatment of adults with certain types of large b cell lymphoma

2018. ***ASCO names CAR T cell therapy the advance of the year.***

may 2018. tisagenlecleucel receives second FDA approval for patients with large b cell lymphoma

august 2018. EMA authorization for axicabtagene ciloleucel for the treatment of follicular lymphoma and DLBCL.

august 2018. EMA authorization for tisagenlecleucel for pediatric r/r B-cell ALL

september 2018. tisagenlecleucel receives health canada approval.

september 2018. NICE approval for paediatric and young adult patients up to 25 years of age with r/r B-cell acute lymphoblastic leukaemia [adult DLBCL rejected for not being cost effective].

october 2018. NICE reverses decision and reimburses axicabtagene ciloleucel for the treatment of adults with r/r large b cell lymphoma.

january 2019. CADTH and INESSS recommend tisagenlecleucel [with conditions].

january 2019. axicabtagene ciloleucel therapy is recommended for use within the cancer drugs fund [UK] as an option for treating r/r DLBCL or primary mediastinal large B–cell lymphoma in adults after 2 or more systemic therapies.

february 2019. health canada approves axicabtagene ciloleucel for r/r large b-cell lymphoma.

august 2019. CADTH and INESSS approval [with conditions] for axicabtagene ciloleucel for the treatment of r/r large B-cell lymphoma after two or more lines of systemic therapy.

october 2019. québec announces reimbursement for tisagenlecleucel -

december 2019 no agreed PLA in canada [current wait time 11 months].

endnotes

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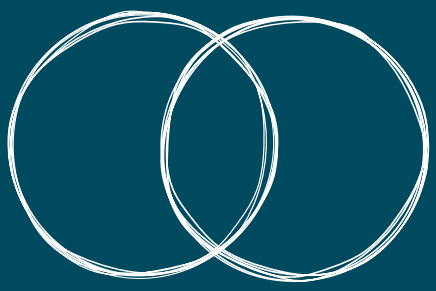
‘alone we can do do so little. together we can do so much.’

helen keller



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