International Bar Association
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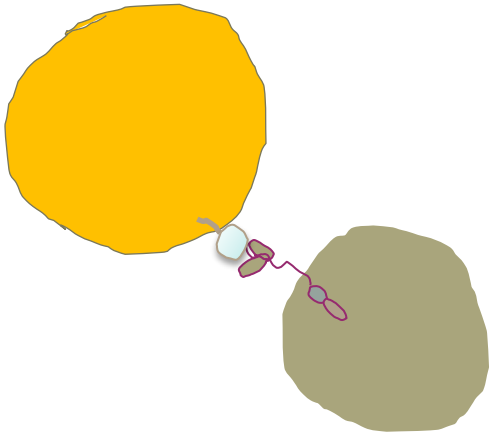
Global Regulatory Challenges of CAR T-Cell Therapies

Webinar
IBA Healthcare & Life Sciences Law Committee
8 February 2022

CAR T cells as innovative immunotherapy in cancer



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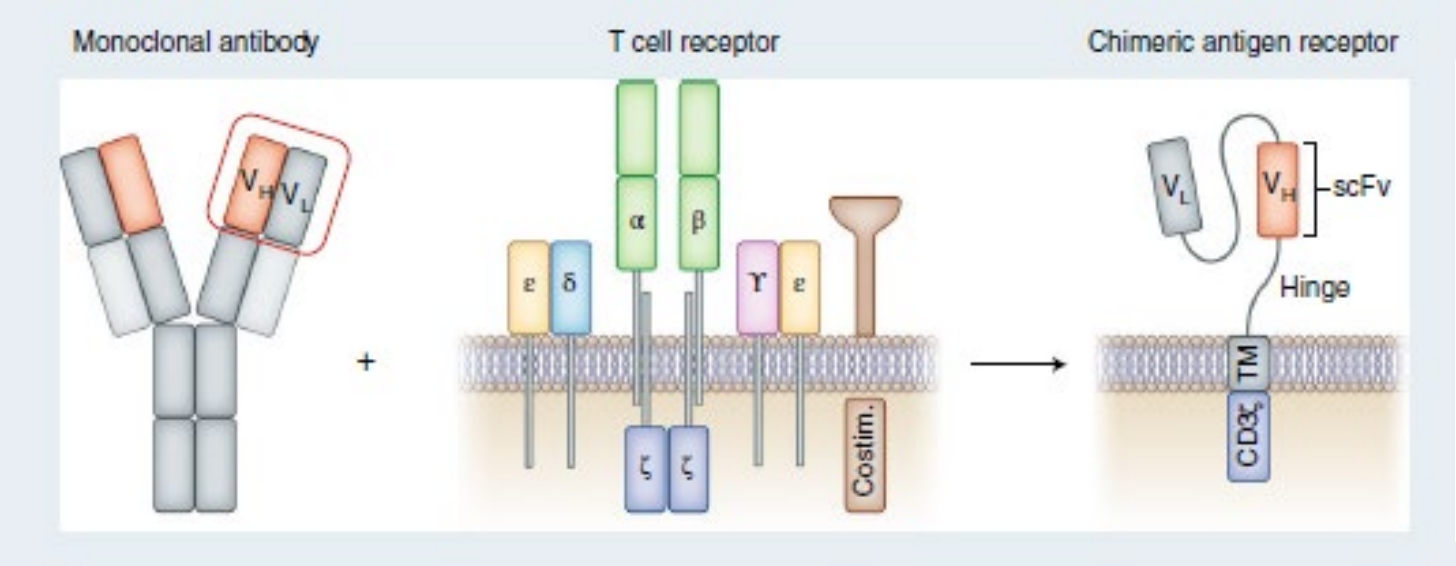
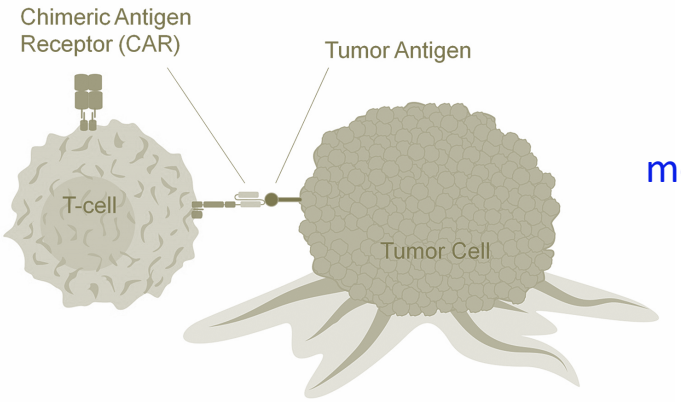
Monza, Italy

General structure of CAR molecules

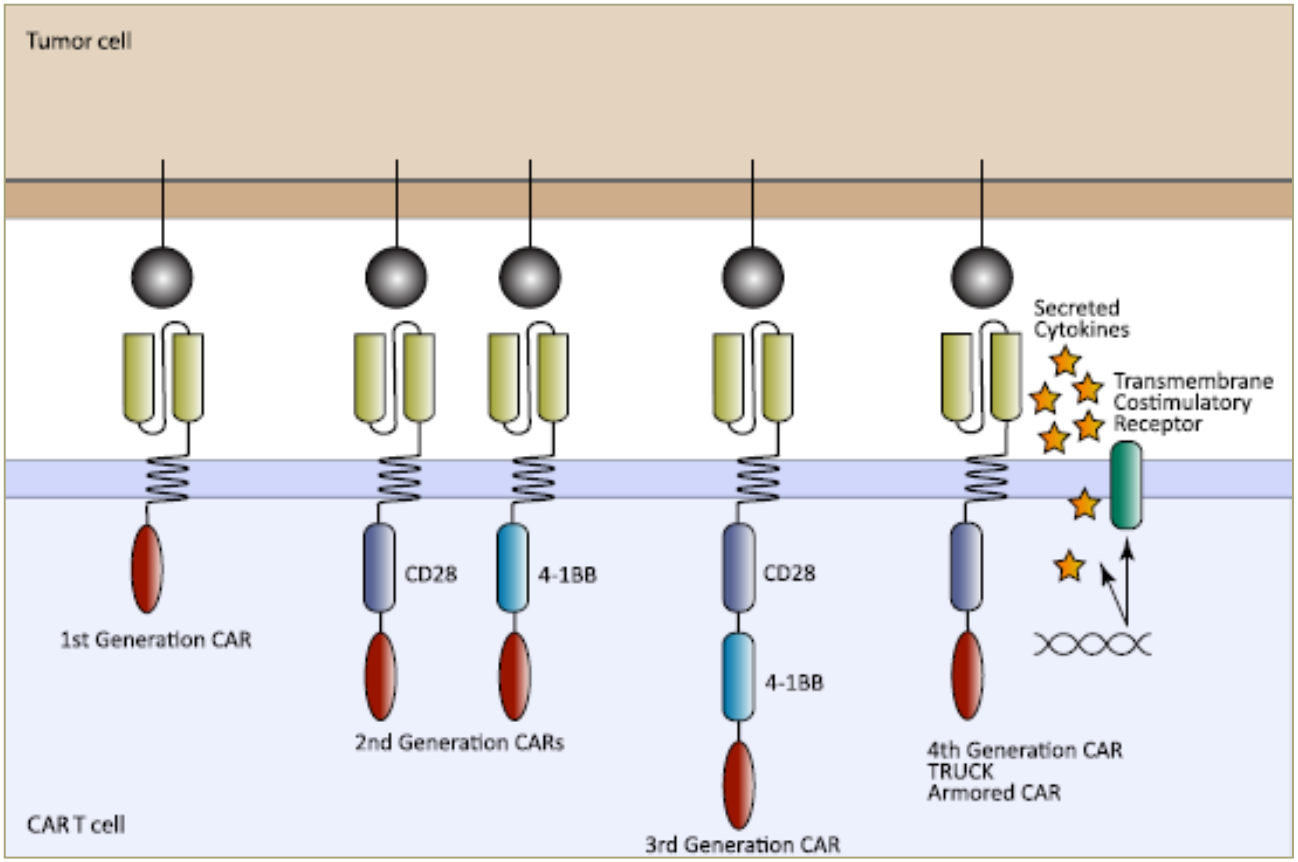


RG Majzner and CL Mackall, Nature Medicine 2019



modified from Albert H., *Gen Vol,* 36 (21)

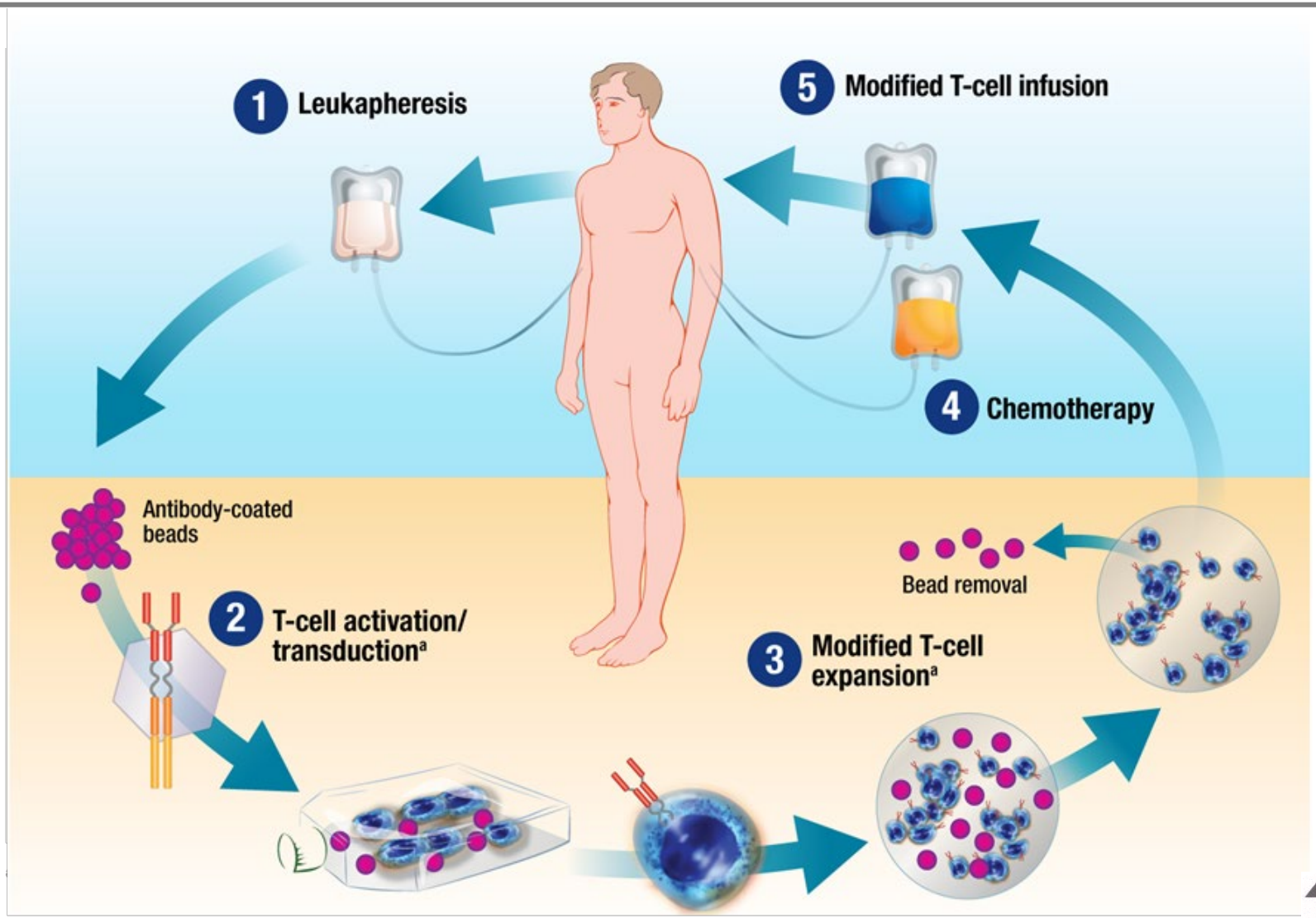
Different CAR T molecules



Cytotoxicity ↑	Cytotoxicity ↑	Cytotoxicity ↑↑
	Proliferation ↑	Proliferation ↑↑
	Cytokine secretion ↑	Cytokine secretion ↑↑
	Resistance ↑	Resistance ↑↑
	In vivo persistance ↑	In vivo persistance ↑↑

Modified from E. Maryamchik et al, Cytometry B, Clinical Cytometry 2020

CAR T: the process of preparation



[a] Cellular reprogramming and ex vivo expansion are conducted at a cell processing facility.

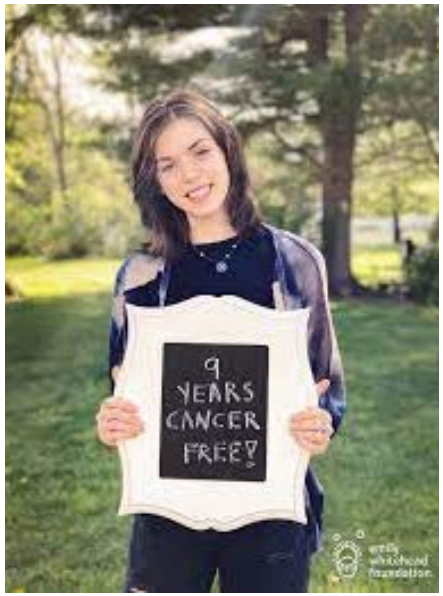
Commercial CAR T products and their indication and availability worldwide

Active substance	Name	Indications	Manufacturer	Approvals	Target	Costimulator domain
tisagenlecleucel	Kymriah	Pediatric and young adult R/R acute lymphoblastic leukemia; Adult R/R DLBCL	Novartis	FDA, EMA, Health Canada, Swissmedic, Japan's MHLW, Singapore's HSA, Australian TGA, UK's NICE	CD19	CD137
axicabtagene ciloleucel	Yescarta	R/R large B-cell lymphoma (DLBCL, PMBCL, high grade B-cell lymphoma, DLBCL arising from FL)	Kite Pharma	FDA, EMA, Health Canada, Swissmedic, Japan's MHLW, China's NMPA, Australian TGA, UK's NICE	CD19	CD28
brexucabtagene autoleucel	Tecartus	Mantle cell lymphoma	Kite Pharma	FDA, EMA, Swissmedic, UK's NICE	BCMA	CD28
lisocabtagene maraleuecel	Breyanzi	R/R large B-cell lymphoma	BMS and Juno Therapeutics	FDA, Japan's MHLW	CD19	CD137
idecabtagene vicleucel	Abecma	Multiple myeloma	BMS and Bluebird Bio	FDA, EMA, Health Canada, Swissmedic, Japan	BCMA	CD137
relmacabtagene autoleucel	Carteyva	R/R large B-cell lymphoma	JW Therapeutics	China's NMPA	CD19	CD137

MHLW Ministry of Health, Labor and Welfare; HAS Health Sciences Authority; TGA: Therapeutic Goods Administration; NMPA: National Medical Products Administration; NICE The National Institute for Health and Care Excellence

Tisangelecleucel: CAR-T living cells; impressive efficacy in patients with very poor prognosis

Single infusion



Unexpected and fast to get results in ALL patients without therapeutic alternatives

"living" cell therapy vs chemotherapy

CAR T cell-based gene therapies have been able to provide unprecedented remission rates and have demonstrated success where other therapies have failed.

- Grupp SL et *al. NEJM* (2013); 368(16):1509-1518;
- Maude SL et *al. NEJM* (2018); 378(5):439-448;
- Park JH et *al. NEJM* (2018); 378(5):449-459;
- Gardner R et *al. Blood* (2017); 129(25):3322-3331

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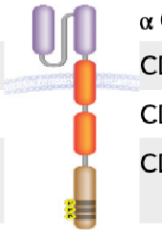
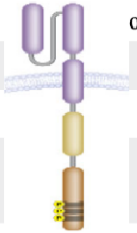
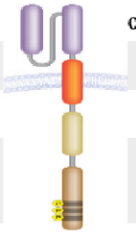
CAR T in non-Hodgkin Lymphoma (NHL)

	Axicabtagene ciloleucel ZUMA-1[4]	Tisagenlecleucel JULIET[2,10,11]	Lisocabtagene maraleucel TRANSCEND[6]
CAR	 α CD19	 α CD19	 α CD19
Transmembrane domain	CD28	CD8	CD28
Co-stimulatory domain	CD28	4-1BB	4-1BB
T-cell activation domain	CD3ζ	CD3ζ	CD3ζ
Leukapheresis	Fresh product direct to manufacturing (within US)	Cryopreserved product (could be stored before manufacturing)	Fresh product direct to manufacturing (within US)
Conditioning therapy	Cyclophosphamide-fludarabine (500 mg/m^2, 30 mg/m^2 daily × 3 days)	Cyclophosphamide-fludarabine (250 mg/m^2, 25 mg/m^2 daily × 3 days) or Bendamustine (90 mg/m^2 daily × 2 days)[a]	Cyclophosphamide-fludarabine (300 mg/m^2, 30 mg/m^2 daily × 3 days)
CAR-T cell target dose	2 × 10^6/kg; max dose was 2 × 10^8/kg	0.1 × 10^8 to 6 × 10^8 flat dose	0.5 × 10^8 to 1.5 × 10^8 each of CD4+ and CD8+ CAR-T cells at 1:1 dose ratio
CNS disease	No history of, or active, CNS disease allowed	No active CNS disease allowed	Secondary CNS allowed

Westin JR et al.: Am J Hematol 2021 96, 1295-1312

CAR-T marketed (1.0): main issues

Despite the breakthrough nature of the clinical data, these first-wave CAR-T 1.0 therapies are struggling to find commercial success, due to factors including:

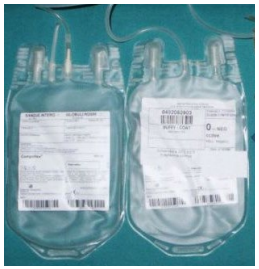
- **Cost of the approved products**, coupled with payment and reimbursement challenges in ALL and DLC Lymphoma indications **(Value-Based Pricing)**
- Burdensome training and **accreditation processes**
- **Toxicity concerns** with administering and receiving the therapy, for patients **requiring hospitalization in intensive care**
- **Autologous manufacturing production issues:**
  - **"made on-demand"** therapy with a **high cost for manufacturers**.
  - manufacturing process **difficult to scale** effectively
- **Production Capability**
- **Logistic challenges** with regard to patients successfully receiving the therapy in approved centers of excellence, and **a waiting period of at least four weeks**

A pragmatic approach to ATMP/GTMP development: Clinicians-led *vs* Company-led

Clinicians-led therapies/procedures

Company-led therapies

GTMPs



Autologous (or Allogeneic)
for
'one to one' therapies

off-the shelf

Allogeneic
for
'one to many' therapies

Decentralised manufacturing
(within a hospital unit)

OR

Centralised manufacturing

Closer to a "transplantation" concept

Closer to traditional pharmaceuticals/biologics products

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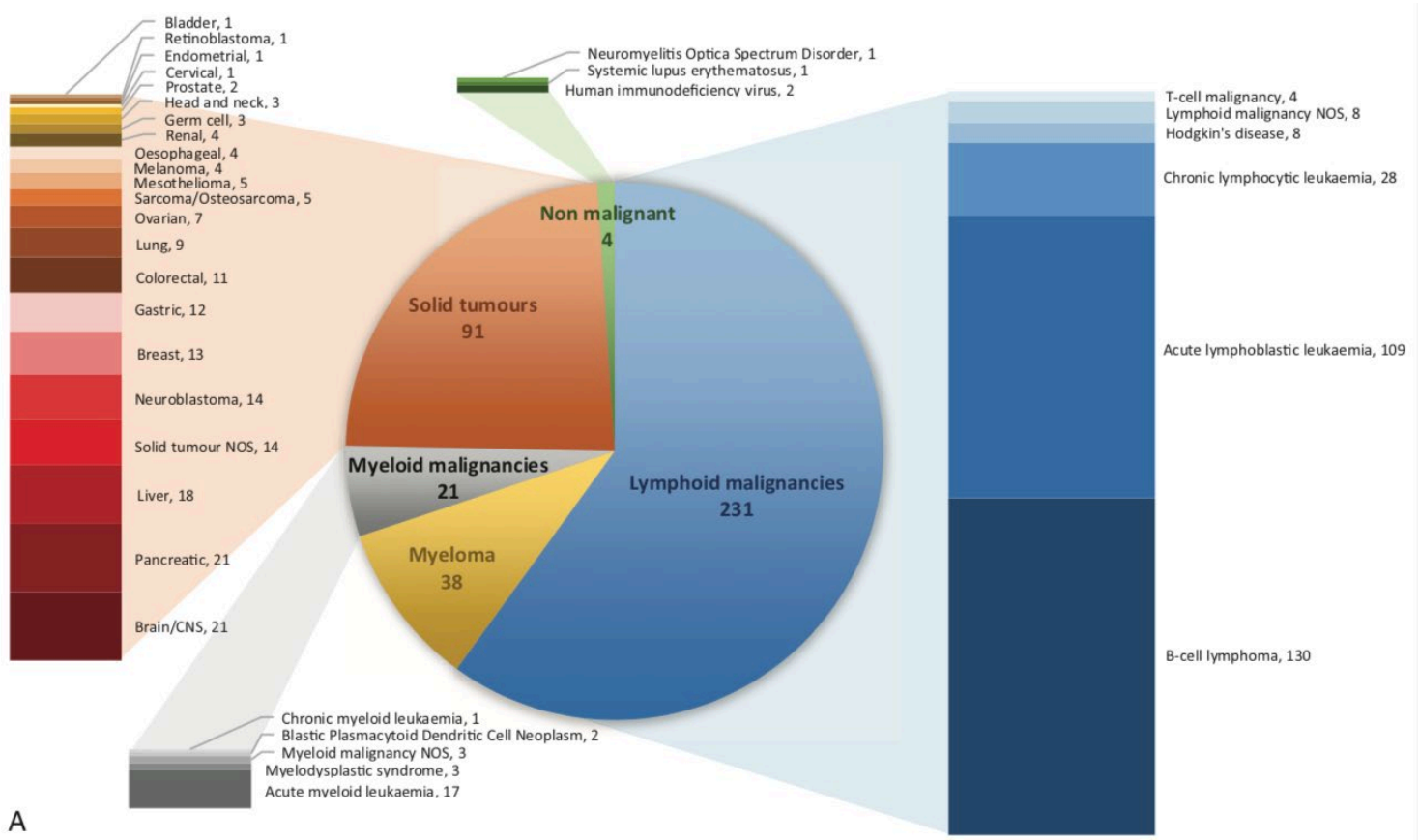
An analysis of CAR-T trials registered at clinicaltrials.gov.



The majority of clinical trials using CAR-T cells **are early phase studies in B cell malignancies**. Trial activity increased dramatically in 2016 and continues **at a rate of nearly 100 new trial registrations each year**. **The most common target is CD19**, In the United States alone, well over 1000 patients have now received CAR-T cells, and several studies have opened looking at the long-term effects in responders.

Charrot S, Hallam S. CAR-T Cells: Future Perspectives. HemaSphere, 2019;3:2.

Conclusions

- CAR-T cells are changing the therapeutic landscape of ALL and other lymphoid neoplasia
- The number of CAR-T cell products available on the market is rapidly increasing
- New CAR-T cells are under academic development and many of them will be evaluated soon for market authorization
- More work is needed to improve the efficacy, the safety and the availability of CAR- T cells

GENE THERAPY MARKET ACCESS CHALLENGES AND SOLUTIONS ACROSS EUROPE, USA AND CANADA

MIT MANAGEMENT SLOAN SCHOOL

IBA Webinar

8 February 2022

Sissel Michelsen (University of Leuven)
Mark Trusheim (MIT)

Agenda

01 Scope & Approach

- Defining GTMPs
- Payer Decision History
- Literature Reviewed

02 Challenges

- Clinical Trial Design & Evidence
- Manufacturing
- Health Economics & Assessment
- Procedural
- Trends

03 Solutions

- Standards
- Addressing Uncertainties
- Procedure innovation
- Collaboration

GENE AND CELL THERAPIES HAVE COMPLEX DEFINITION TO MATCH THE SCIENCE

- **European regulation (EC) No 1394/200 states that GTMP products may fall under both definitions of**
  - somatic cell therapy medicinal product (sCTMP) or
  - tissue-engineered products (TEP)

- **Directive 2001/83/EC: Gene therapy medicinal product (GTMPs) is a biological medicinal product that has the following characteristics:**
  - (a) contains an active substance that contains or comprises a recombinant nucleic acid used in or administered to humans with a view to regulating, repairing, replacing, adding, or deleting a genetic sequence;
  - (b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence. Gene therapy medicinal products do not include vaccines against infectious diseases

- **EMA classifies GTMPs as Advanced Therapy Medicinal Products (ATMPs) evaluated by the Committee for Advanced Therapies (CAT)**

USA AND CANADA ALSO HAVE SPECIAL GTMP DEFINITIONS AND PROCESSES

- **USA**
  - GTMPs are called Cellular and Gene Therapy Products under the Office of Tissues and Advanced Therapies (OTAT) in the Center for Biologics Evaluation and Research (CBER)
  - The Tissue and Gene Therapies Advisory Committee (CTGTAC) can provide the FDA with advice from external experts
  - FDA Regenerative Medicine Advanced Therapy designation developed under 2016 21st Century Cures Act

- **Canada**
  - GTMPs are regulated as Advanced Therapeutic Products (ATPs) by the Biologics and Genetic Therapies Directorate of Health Canada
  - A new pathway (regulatory sandbox) for ATPs is being developed under new provisions in the Food and Drugs Act from June 2019

PAYERS USUALLY COVERING BUT DELAYS SEEN IN SOME EU COUNTRIES

EU has more authorized products than the US

Canada has few product authorizations

Payer decisions regarding GTMPs approved in Europe, the USA, and Canada[a,b,c]

GTMP	Europe						USA		Canada	
	MA date	Payer decisions (EU Big 5)					MA date	Payer	MA date	Payer
		France	Germany	UK	Italy	Spain				
Glybera®	2012	NR	R	NA	NA	NA	NA	NA	NA	NA
Imlygic®	2015	NA	NR	R	R	NA	2015	R	NA	NA
Strimvelis®	2016	NA	NA	R	R	NA	NA	NA	NA	NA
Kymriah®	2018	R	R	R	R	R	2017	R	2018	R[d,e]
Yescarta®	2018	R	R	R	R	R	2017	R	2019	E[d]
Luxturna®	2018	R	R	R	NA	NA	2017	R	NA	NA
Zynteglo®	2019	NA	R	NA	NA	NA	NA	NA	NA	NA
Zalmoxis®	2016	NR	R	NA	R	NA	NA	NA	NA	NA
Zolgensma®	2020	NA	E	NA	NA	NA	2019	R	NA	NA

[a] Data from [3,21,104,106–111]. [b] Abbreviations: E, reimbursement expected; MA, marketing authorization; NA, not applicable because application for marketing authorization or reimbursement has not been submitted or a decision has not yet been reached; NR, not reimbursed; R, reimbursed.
[c] Green, countries where product is reimbursed; Red, countries where reimbursement of product was refused; Blue, decisions are no longer effective because product is withdrawn from the market; Yellow, recommended by HTA body but not reimbursed by any payer.
[d] Recommended by national HTA body on the condition of a substantial price reduction. [e] Reimbursed in Ontario and Quebec.

van Overbeeke, Eline, et al. "Market access of gene therapies across Europe, USA, and Canada: challenges, trends, and solutions." *Drug discovery today* 26.2 (2021): 399-415.

RESEARCH APPROACH

95 Publications identified reporting on GTMP market access challenges

Publications mentioning issues by general areas category

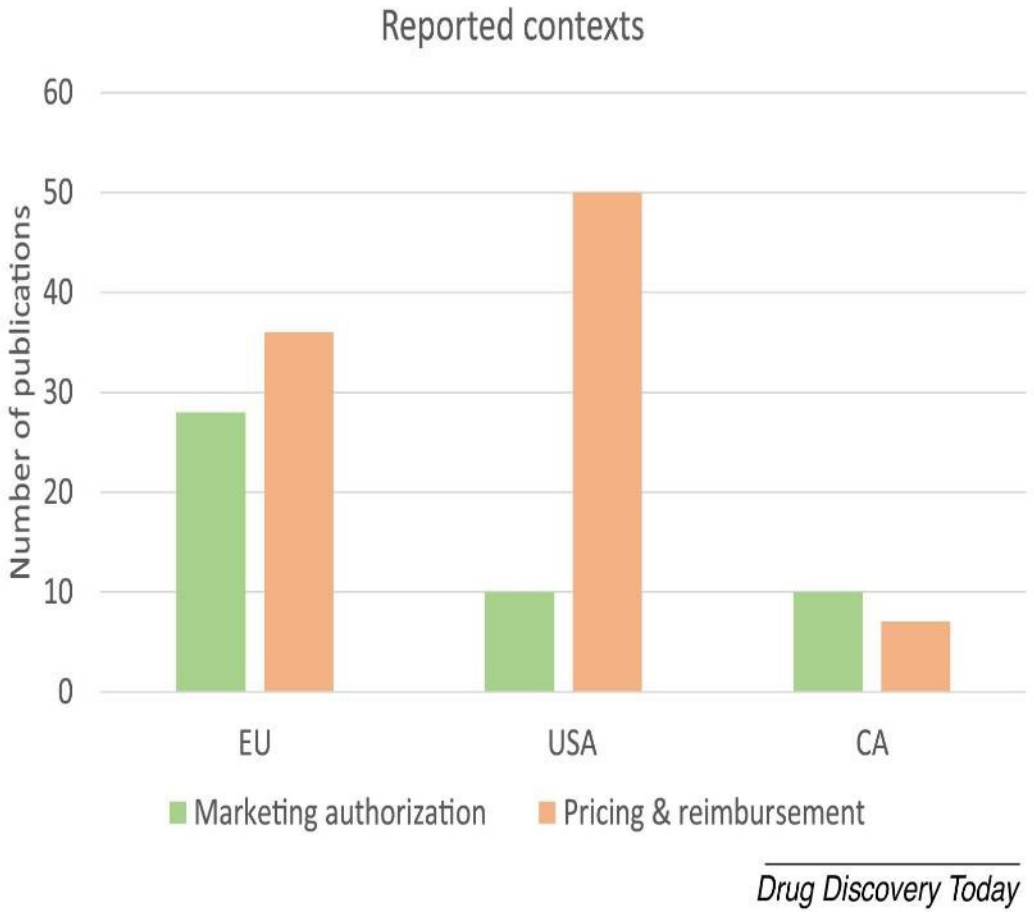
- **Manufacturing: 19 publications**
- **Clinical trial design: 50**
- **Clinical evidence: 51**
- **Health economics: 56**
- **Assessments: 26**
- **Procedures and organizations: 28**


CHALLENGES

ISSUE EMPHASIS VARIED BY REGION

EU and Canada had relatively more emphasis on regulatory market authorization

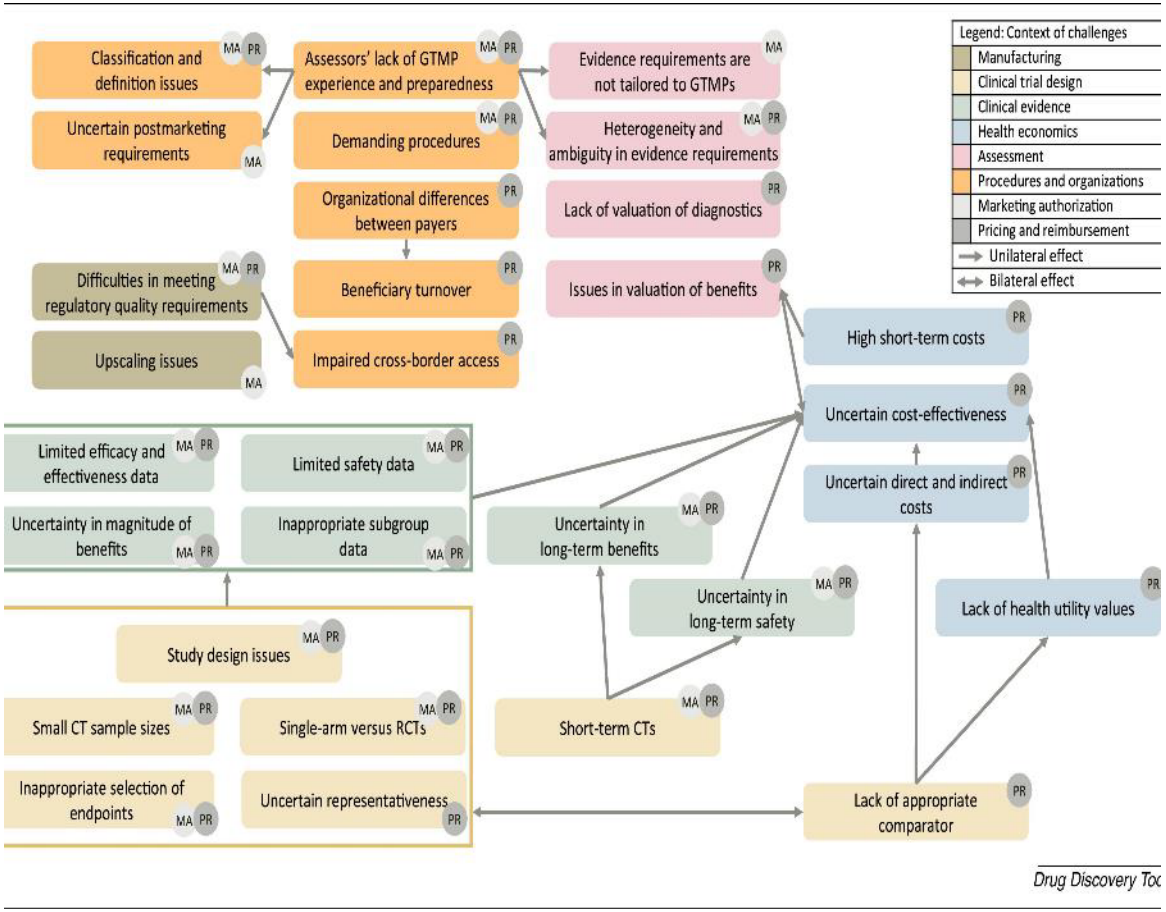
US had relatively more citations on Pricing & Reimbursement



MANY OF THE ISSUES CONNECT AND CASCADE TO IMPACT HEALTH ECONOMICS

30 market access issues identified 6 areas:

1. **Manufacturing**
2. **Clinical Trial Design**
3. **Clinical evidence**
4. **Health Economics**
5. **Assessment**
6. **Procedures and organizations**



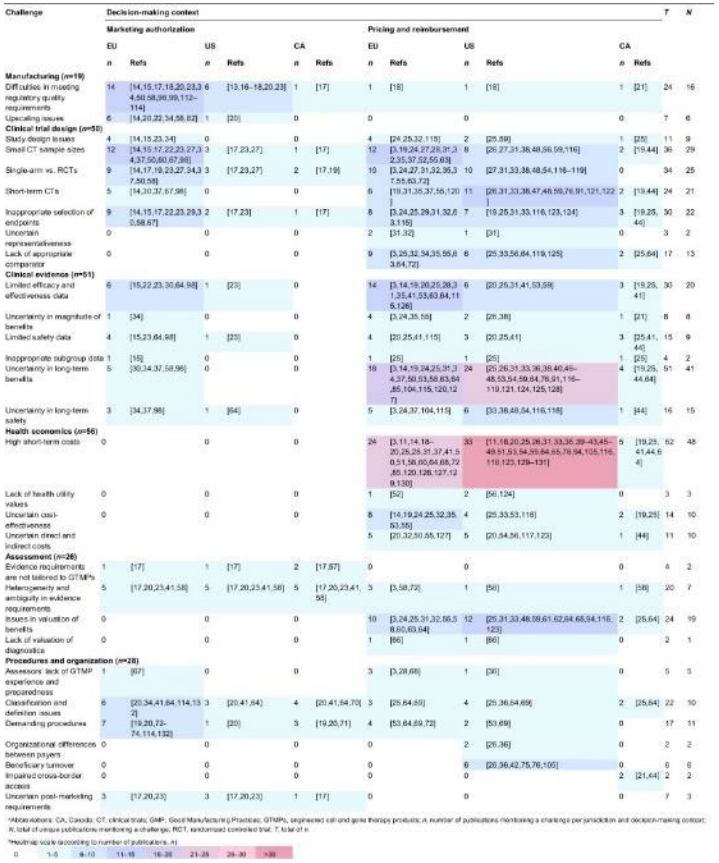
UNCERTAINTIES FROM LIMITED EVIDENCE UNDERLIE MOST HIGHLY CITED ISSUES

Most cited Pricing and Reimbursement issues

1. **High short-term costs**
2. **Uncertainty in long-term benefits**
3. **Limited efficacy and effectiveness data**
4. **Short term clinical trial designs**
5. **Small clinical trial sample sizes**
6. **Valuation of benefits**

Comparably cited Regulatory Marketing Authorization issues

1. **Meeting regulatory quality requirements**
2. **Small clinical trial sample sizes**



Challenge	Decision-making context												T	N
	Marketing authorization						Pricing and reimbursement							
	EU		US		CA		EU		US		CA			
	n	Refs	n	Refs	n	Refs	n	Refs	n	Refs	n	Refs		
Manufacturing (n=19)														
Difficulties in meeting regulatory quality requirements	14	[14,15,17,18,20,23,3 4,50,58,98,99,112–114]	6	[13,16–18,20,23]	1	[17]	1	[18]	1	[18]	1	[21]	24	16
Upscaling issues	6	[14,20,22,34,58,82]	1	[20]	0		0		0		0		7	6
Clinical trial design (n=50)														
Study design issues	4	[14,15,23,34]	0		0		4	[24,25,32,115]	2	[25,59]	1	[25]	11	9
Small CT sample sizes	12	[14,15,17,22,23,27,3 4,37,50,60,67,98]	3	[17,23,27]	1	[17]	12	[3,19,24,27,28,31,3 2,35,37,52,55,63]	8	[26,27,31,38,48,56,59,116]	2	[19,44]	36	29
Single-arm vs. RCTs	9	[14,17,19,23,27,34,3 7,50,58]	3	[17,23,27]	2	[17,19]	10	[3,24,27,31,32,35,3 7,55,63,72]	10	[27,31,33,38,48,54,116–119]	0		34	25
Short-term CTs	5	[14,30,37,67,98]	0		0		6	[19,31,35,37,55,120]	11	[26,31,33,38,47,48,59,76,91,121,122]	2	[19,44]	24	21
Inappropriate selection of endpoints	9	[14,15,17,22,23,28,3 0,58,67]	2	[17,23]	1	[17]	8	[3,24,25,29,31,32,6 3,115]	7	[19,25,31,33,116,123,124]	3	[19,25, 44]	30	22
Uncertain representativeness	0		0		0		2	[31,32]	1	[31]	0		3	2
Lack of appropriate comparator	0		0		0		9	[3,25,32,34,35,55,6 3,64,72]	6	[25,33,56,64,119,125]	2	[25,64]	17	13
Clinical evidence (n=51)														
Limited efficacy and effectiveness data	6	[15,22,23,30,64,98]	1	[23]	0		14	[3,14,19,20,25,28,3 1,35,41,53,63,64,11 5,126]	6	[20,25,31,41,53,58]	3	[19,25, 41]	30	20
Uncertainty in magnitude of benefits	1	[34]	0		0		4	[3,24,35,55]	2	[26,38]	1	[21]	8	6
Limited safety data	4	[15,23,64,98]	1	[23]	0		4	[20,25,41,115]	3	[20,25,41]	3	[25,41, 44]	15	9
Inappropriate subgroup data	1	[15]	0		0		1	[25]	1	[25]	1	[25]	4	2
Uncertainty in long-term benefits	5	[30,34,37,58,98]	0		0		18	[3,14,19,24,25,31,3 4,37,50,53,58,63,64 ,65,104,115,120,12 7]	24	[25,26,31,33,36,38,40,46–48,53,54,58,64,76,91,116–119,121,124,125,126]	4	[19,25, 44,64]	51	41
Uncertainty in long-term safety	3	[34,37,98]	1	[64]	0		5	[3,24,37,104,115]	6	[33,38,48,54,116,118]	1	[44]	16	15
Health economics (n=56)														
High short-term costs	0		0		0		24	[3,11,14,18–20,25,28,31,37,41,5 0,51,56,60,64,68,72 ,85,120,126,127,12 9,130]	33	[11,18,20,25,26,31,33,36,39–43,45–49,51,53,54,56,64,65,76,94,105,116,118,123,129–131]	5	[19,25, 41,44,6 4]	62	48
Lack of health utility values	0		0		0		1	[52]	2	[56,124]	0		3	3
Uncertain cost-effectiveness	0		0		0		8	[14,19,24,25,32,35,53,55]	4	[25,33,53,116]	2	[19,25]	14	10
Uncertain direct and indirect costs							5	[20,32,50,55,127]	5	[20,54,56,117,123]	1	[44]	11	10
Assessment (n=26)														
Evidence requirements are not tailored to GTMPs	1	[17]	1	[17]	2	[17,67]	0		0		0		4	2
Heterogeneity and ambiguity in evidence requirements	5	[17,20,23,41,58]	5	[17,20,23,41,58]	5	[17,20,23,41, 58]	3	[3,58,72]	1	[58]	1	[58]	20	7
Issues in valuation of benefits	0		0		0		10	[3,24,25,31,32,55,5 8,65,83,84]	12	[25,31,33,48,59,61,62,64,65,84,116,123]	2	[25,64]	24	19
Lack of valuation of diagnostics	0		0		0		1	[66]	1	[66]	0		2	1
Procedures and organization (n=28)														
Assessors' lack of GTMP experience and preparedness	1	[67]	0		0		3	[3,28,66]	1	[30]	0		5	5
Classification and definition issues	6	[20,34,41,64,114,13 2]	3	[20,41,64]	4	[20,41,64,70]	3	[25,64,69]	4	[25,36,64,69]	2	[25,64]	22	10
Demanding procedures	7	[19,20,72–74,114,132]	1	[20]	3	[19,20,71]	4	[53,64,69,72]	2	[53,69]	0		17	11
Organizational differences between payers	0		0		0		0		2	[26,36]	0		2	2
Beneficiary turnover	0		0		0		0		6	[26,36,42,75,76,105]	0		6	6
Impaired cross-border access	0		0		0		0		0		2	[21,44]	2	2
Uncertain post-marketing requirements	3	[17,20,23]	3	[17,20,23]	1	[17]	0		0		0		7	3

*Abbreviations: CA, Canada; CT, clinical trials; GMP, Good Manufacturing Practices; GTMPs, engineered cell and gene therapy products; n, number of publications mentioning a challenge per jurisdiction and decision-making context; N, total of unique publications mentioning a challenge; RCT, randomized controlled trial; T, total of n.

†Heatmap scale according to number of publications, n:

0 | 1–5 | 6–10 | 11–15 | 16–20 | 21–25 | 26–30 | >30

van Overbeeke, Eline, et al. "Market access of gene therapies across Europe, USA, and Canada: challenges, trends, and solutions." *Drug discovery today* 26.2 (2021): 399-415.

SOLUTIONS

Standards

Addressing Clinical Uncertainties

New Price Setting Procedures, Value Frameworks and Payment Models

Support, Stakeholder Interaction and Partnering

STANDARDS ARE ADVANCING

Quality Standards

- **EMA data quality certification and assessment**
- **FDA issued RMAT Designation in 2019**
- **FDA has now issued guidances for trials and REMS (2020-2021)**

Manufacturing Facilities and Upscaling

- **FDA has now issued guidance for manufacturing (2021)**
- **Move to allogeneic from autologous**
- **Equipment advances for larger scale and also for local hospital production**

ADDRESSING CLINICAL UNCERTAINTIES

- **Evidence generation harmonization among regulators, HTAs, payers and developers**
- **Use of systemic reviews, meta-analyses and RWE/registries**
- **Use of conditional market authorizations and conditional reimbursement**
- **RWE infrastructure to support the above**
  - Example: World Hemophilia Association World Bleeding Disorders Registry
  - Example: UK has >50 registries but most not suitable for conditional reimbursement

PRICE AND PAYMENT INNOVATION

- **Refining and/or balancing value-based, procedure-based and R&D-based pricing**
- **Update HTA value frameworks to account for durations, uncertainties and benefit elements as well as sharing of value among stakeholders**
- **Novel payment models: MEAs, outcomes-based contracts, annuities, risk pools, subscription/leasing, Healthcoin, Stop Loss insurance & reinsurance**

COLLABORATION ENHANCEMENTS

- **Developer interaction with regulators, HTA bodies and payers**
  - Within regions and harmonization among them
  - Joint scientific advice
  - Endpoint and required evidence alignment
- **Translational research support**
- **Specialized manufacturing and delivery platforms via public private partnerships**
- **Patient engagement for natural history, clinical and real-world research**
- **Transparency of data and evidence, perhaps with patient ownership**

NOVEL GTMP CHALLENGES INSPIRING INNOVATIVE (LEGAL) SOLUTIONS

- **GTMPs are a heterogeneous set of products for diverse conditions**
- **GTMPs experience a wide range of access challenges. Some old, some new**
  - From early development through manufacturing to pricing, reimbursement and adoption
  - The potentially durable effects especially create novel challenges
- Challenges create opportunities for solutions employing
  - Joint action among stakeholders
  - Conditional authorizations, coverage and reimbursement with RWE
  - Expanded international RWE infrastructure
  - Innovative AND efficient pricing and payment models based on value received, not value projected

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THANK YOU

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Any questions?

Webinar - *Global Regulatory Challenges of CAR T-Cell Therapies*
IBA Healthcare & Life Sciences Law Committee
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