CDDF
Cancer Drug Development Forum

MEETING REPORT

CDDF Multi-Stakeholder Workshop

Gene and cell therapies in Oncology Drug Development

29-30 November 2021

Online Workshop

Prepared by the CDDF

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Learning Objectives

- To understand the current landscape of Gene & Cell Therapy (GCT) in oncology, with focus on advances in drug development
- To explore regulatory aspects, challenges and pathways now, and in the future for the development and approval of innovative GCTs
- To understand the patient perspectives and challenges with GCTs
- To explore the future perspectives related to GCT in oncology

SESSION 1: WHO IS THE GENE AND CELL CANCER-KILLER: DEEP DIVE ON THE GENE AND CELL SCIENTIFIC APPROACHES IN ONCOLOGY

TCR and CAR modified T cells as Cancer Immunotherapy- an overview

Emma Morris (University College London, UK)

T cells are part of the immune system. Their function (killing activity) is triggered by signaling through the heterodimeric protein T-cell surface receptor (TCD). This receptor is held in place by a scaffolding arrangement (components of the CD3 complex). The TCR is able to recognize and bind to a combination of a (9-13 amino acids) peptide find in the groove of a molecule MHC, one of the tissue type proteins which is expressed on the surface of all nucleated body cells, including tumor cells.

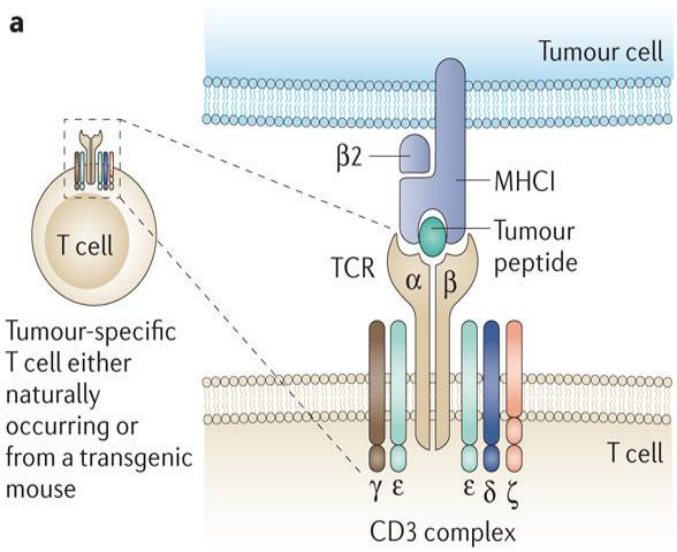

Figure 1. Source: Kershaw MH et al. Nat Rev Cancer. 2013.

Binding to the receptor leads to a signal to the T-cell and activates it. All leading to a clonal expansion of T-cell that all express the same receptor. These can differentiate, and secrete cytokines as well as release enzymes called granzyme and perforin, that lead to target cell kill. T cell memory persists in the body for the rest of the hosts live.

So, if these T cell can be manipulated to recognize cancer cells, they can become an army against the cancer involved, that persists long-term. This manipulation is performed extra-corporal, after collecting T-cells from the blood of a patient. in a laboratory, after the engineering in of the cancer cell proteins, the cells can be cultured and expanded, and then reinfused into the patient. Once in the body, the cells travel to the tumor site, recognize the tumor cells, and kill them.

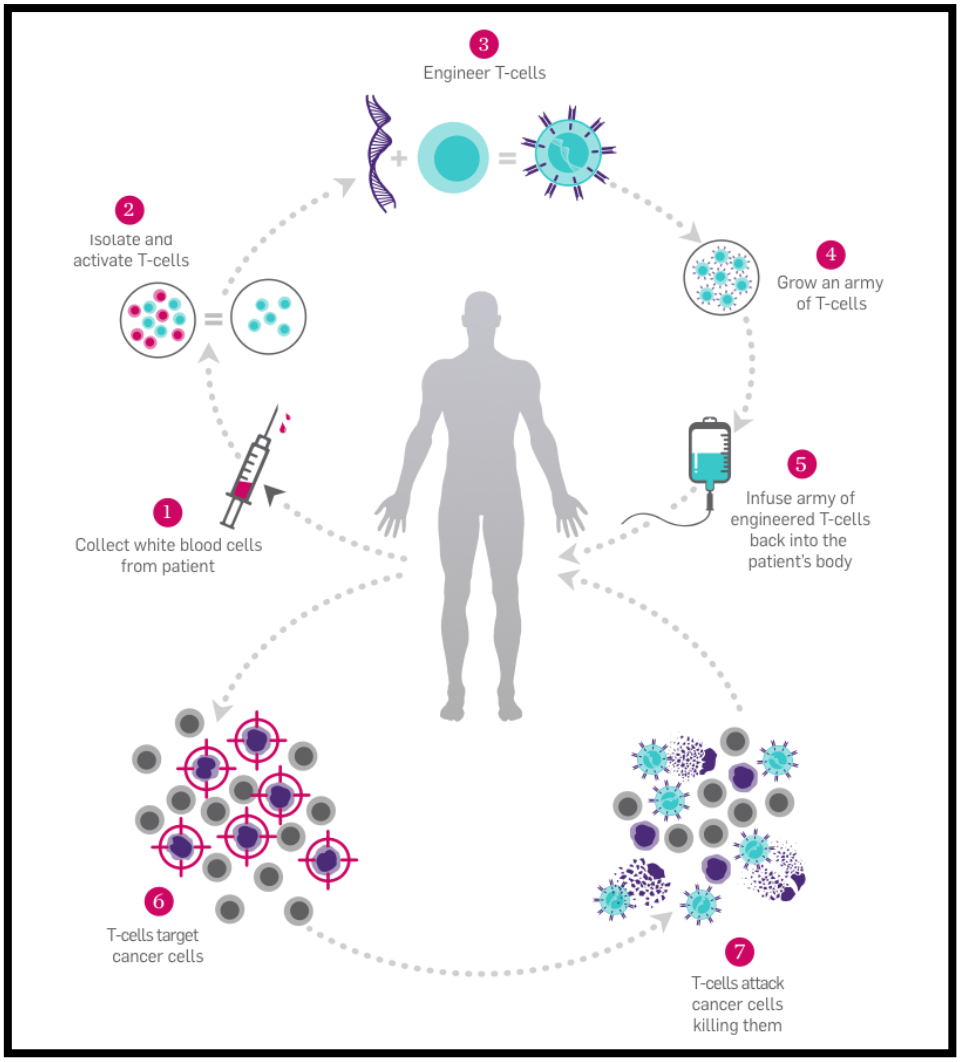

Figure 2. Source of T cells: Autologous; Allogeneic (eg HSCT donor); Third party; iPSC-derived. Source: Emma Morris' slides

There are various laboratory procedures applied in T cell engineering:

- a plasmid which encodes the DNA for the receptor that we are introducing to the T-cells;
- use of infected packaging cells that are able to make a recombinant disabled virus, which can't cause an infections but are able to enter immune cells when one cultures the patient's blood cells with the virus extra-corporal;
- after this transduction procedure, when the genes that are encoded for in the recombinant virus, are integrated into the host T-cell DNA and nucleus, this gives the instruction to the cell to make the protein and the receptor is expressed on the surface of all of these T-cells.

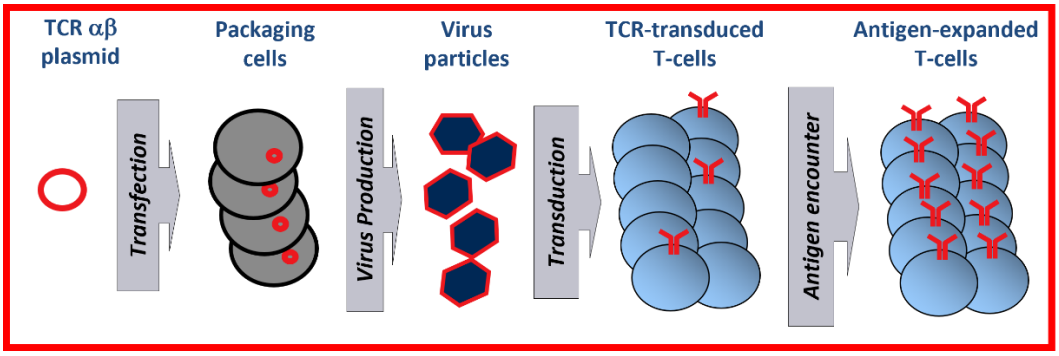

Figure 3. Source of T cells: Autologous; Allogeneic (eg HSCT donor); Third party; iPSC-derived. Source: Emma Morris' slides

This allows us to generate large numbers of Ag-specific T cells of known avidity and specificity, to augment T cell function, to enhance in vivo persistence, to alter homing in vivo, and we can insert genes that identify suicide switches or safety features that allow to switch off the T-cells should they become overly activated.

The most commonly genetically engineered T-cells in clinical use are the chimeric Antigen Receptor (CAR) T-cells. There are different kinds of receptors that can be introduced into the T-cell. These receptors are based on the fragments of an antibody. This has the advantage that antibodies recognize antigens on the surface of cells that have not been processed and presented by MHC. This means that T-cells expressing a CAR, can be used in any patient regardless of their tissue type. Scientists have had to engineer the cellular signaling domains, to allow the chimeric antigen receptor (CAR), when it engages with the target antigen, to trigger a response in the T-cell.

CD19 CART cells used in ALL, were the initial real game changer in the field of T-cell immunotherapy.

In addition to CAR-T cells, many are developing TCR-gene modified T-cell. In this case one isolates the genes that encode the Alpha-Beta T cell receptor that has been identified in a T-cell that recognizes a tumor cell very specifically. By delivering the genes for the alpha-beta chain of the TCR one can introduce these to the patient's T-cell, and generate a T-cell that has the patient's own T-cell receptor, but also a therapeutic T-cell receptor that is specific for a target antigen. TCR-gene modified T-cells are HLA-restricted (so they can't be used for everyone), they recognize low density intracellular peptides which is important since most tumor antigens are derived from intracellular proteins. They are able to recognize single amino acid point mutations. This way the complete patient specific cancer mutagenome can potentially be detected by the T-cell.

There is a risk of mispairing of the introduced therapeutic T-cell receptor, with the endogenous T-cell receptor. There are a number of different strategies developed in the lab to reduce TCR mispairing, while at the same time improving the function of TCR -gene modified T-cells, a.o. by modifying some amino acids in the TCR itself.

Cancer killer profile: T cell fitness, autologous or allogeneic T cell, T cell or NK?

Jan Frič (Institute of Hematology and Blood Transfusion, CZ)

The lecture focused on hematological malignancies.

Currently the majority of clinical trials on T-cell therapies in hematological malignancies are involving application of CAR-T cells and NK cells.

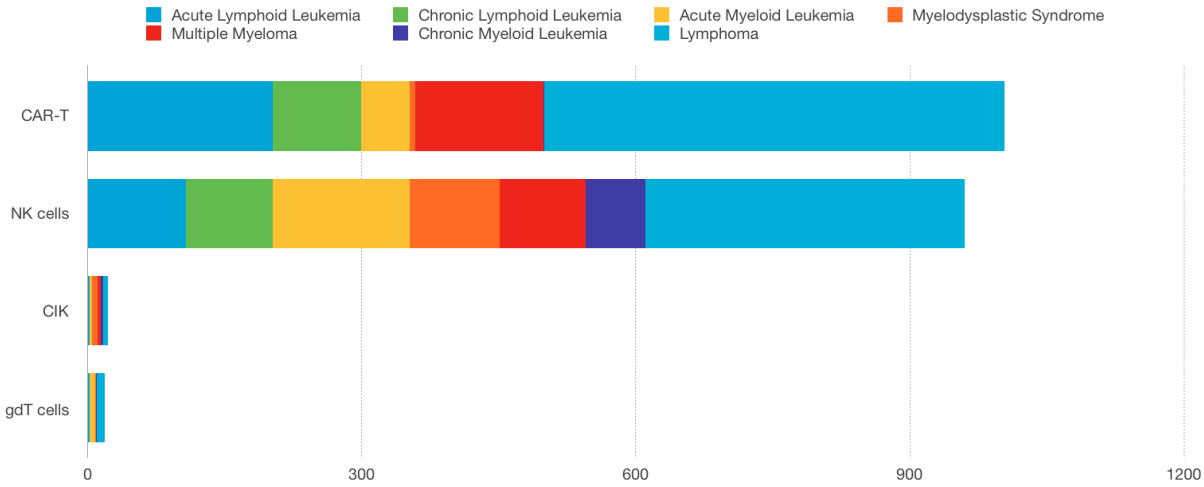

Figure 4. Overview of current clinical trials using cellular immunotherapies to haematological malignancies. Source: .clinicaltrials.gov

The largest number of trials are performed in patients with malignant lymphomas.

In AML it is yet unclear what the most important epitopes are, that should be targeted. There is a wide range of targets that can be, and are explored, and at least 14 are currently studied clinically.

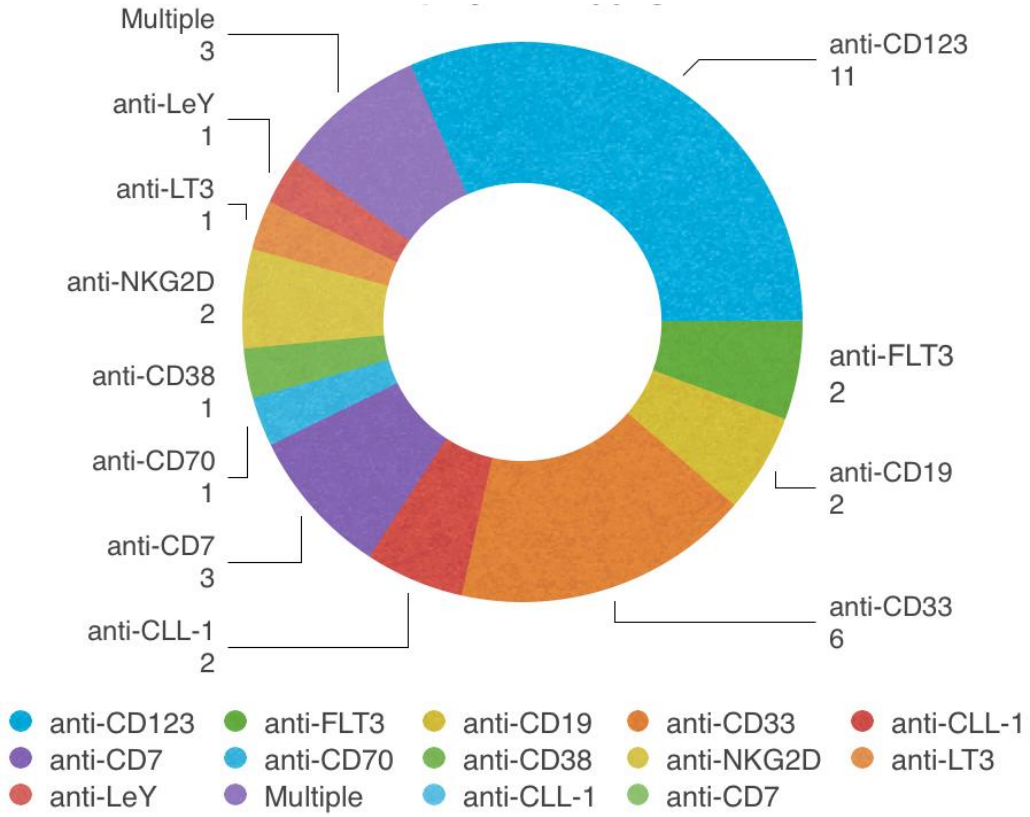

Figure 5. Cellular immunotherapy of AML with CAR-T cells. Source: .clinicaltrials.gov

There are important differences between the candidate cell types that can be used, and these can be summarized as follows:

	CART-T cells	NK or CAR-NK cells
Source	Autologous T cells	Allogeneic or haplo-identical (PBMCs, UCB, iPSCs, hESCs, HPCs, NK cell lines
Transduction efficiency	High	low
In vivo persistence	↑↑	↓↓
Safety	↑	↑↑↑
Efficacy	↑ (CAR)	↑↑↑ (CAR and innate mechanisms)
Status	Several commercial products	Numerous clinical trials

Table 1. Comparison NK cells and CAR-T cells. Source: Jan Frič's slides

An advantage of using NK-cells, is that they can be derived from a high variety of sources, including healthy donor's peripheral blood mononuclear cells, core blood, placental blood, induced pluripotent stem cells (iPSC), embryonic stem cells (hESC), and even NK-cell derived cell lines. There is still enormous variety in conditioning, indicated that the book on this has not yet been closed.

There is quite some research ongoing on the metabolic status as part of NK cell fitness after adoptive transfer. In this transfer, the environment in which these cells are functioning, is completely altered, while moving from in-vitro to in-vivo. Interference with the metabolic status of the cells before transfer, and increase NK cell fitness.

Tumor and immunological environment influences in hematological and solid tumors: Engineering techniques or drug combination?

Victor Moreno (START Madrid-FJD, ES)

There has been an immense increase in clinical trials in immunoncology in recent years.

After successes in hematological tumor types, there are now also a few in solid tumors.

There are many challenges for CAR-T cell therapies, which include CAR production failures, problems with antigen modulation, CAR related toxicities, an issues such as sanctuaries like the central nervous system.

T cell extrinsic- and intrinsic factors limit the exposure at the site of action, as well as the ability to sustain pharmacological activity. While the latter may be best addressed by optimizing CAR design, and the manufacturing process, the first might best be addressed by combination therapies or by modifying the CAR-T cells to secrete immune-modulators.

Several ways have been studied to improve CAR-T activity. Either intrinsic or extrinsic. First the intrinsic factors.

ITAMs (immunoreceptor tyrosine-based activation motifs) are critical for the intracellular activation of the TCR. They are located in the different cellular subunits of CD3. Silencing one or two of those domains of ITAMs has markedly different results on the potency of CD19/28

CAR-T cells, with improved tumor control in mice. Clinically this 2nd generation has to be tested, and preparations are underway.

Signaling is not only regulated by ITAMs. The cytoplasmatic tail of CD3ξ binds to the plasma membrane through Basic Residue rich Sequences (or BRS) and dissociation from the membrane is required for intracellular phosphorylation of Lck, after antigen presentation and recognition.

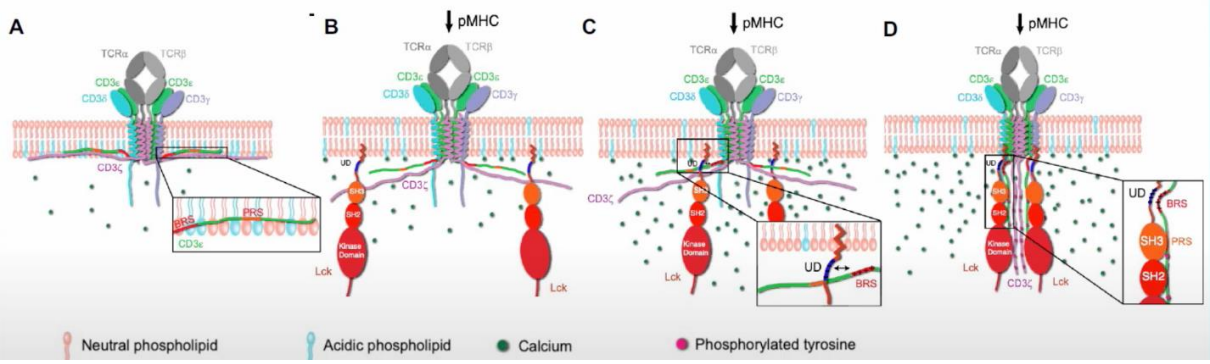

Figure 6. Source: Li et al. (2017), PNAS, 114(29):ES891-ES899

These mechanisms open options to further engineer the CARs, to improve activation and persistence.

Exhaustion of CARs is associated with increased chromatin accessibility of Activator Protein-1 (AP-1, bZIP) transcription factor motifs. This induces a defect in IL-2 production, and expression of typical exhaustion markers. By engineering CAR T-cells to overexpress c-Jun, a canonical AP-1 factor, cells showed an increased functional capacity, a diminished terminal differentiation and improved antitumor potency in vivo.

A further evolution into the 3rd generation of CARs is the incorporation of the 2 co-stimulatory domains (CD28 and 4-1BB) that confer different characteristics (involving expansion speed, peak time, exhaustion and persistence) to the CAR. This is currently being tested in the clinic and early data suggest an improved safety profile and longer CAR-T persistence.

An example of a 4th generation CARs are TRUCKs (T-cell Redirected for Universal Cytokine Killing) in which a domain is inserted to secrete pre-inflammatory cytokines, or armed with a suicide gene that can be activated in case of occurrence of a cytokine release syndrome (CSR).

Finally, there is the potential to produce universal off-the-shelf cells. Next to modulating intrinsic factors, there is the option to modulate extrinsic factors.

Antigen loss or modulation is one of the major mechanisms of resistance to T cell therapy. For this reason multi-antigen CAR T-cells are being tested, for instance involving both CD19 and CD 20 or 22. Such dual targeting can have different applications, a.o. a focus on improvement of safety. Also, conditional CAR expression to a second antigen in the presence of the first antigen, can improve T-cell specificity.

T-cell persistence can also be improved by combinatorial approaches.

In response to interferon-γ, tumor cells upregulate programmed death-ligand 1 (PD-L-1), which interacts with programmed cell death protein 1 (PD-1) on the surface of exhausted CAR T-cells. By using CAR T-cell in combination with Checkpoint inhibitors, a reactivation of CAR T-cell activity can be achieved. Another way is by engineering the CAR T-cells to achieve the

same effect, for which 4 different approaches are currently explored. This is now also being explored in clinical trials.

Another combinatorial approach is the use of oncolytic adenoviruses. Such viruses can be loaded with specific genes, that become expressed by the cancer cell after infection. This can be used to enable the cancer cells to directly stimulate T-cells to induce activation.

Finally solid tumors pose physical barriers to tumor homing and penetration by CAR T-cells. There are 2 ways to block this. First, by expression of chemokine receptors, or by targeting stromal barriers by fibroblast activating protein (FAP) targeted or heparinase secreting CAR T-cells

Panel Discussion

QUESTION: What are the pros and cons of autologous and allogeneic off-the-shelf CAR T-cells?

ANSWER: The safest product at the moment is an autologous T cell product. Allogeneic T-cells can partly also be allo-reactive, causing tissue damage and inflammation, and possibility leading to rejection. So patients own cells have highest likelihood for success. But they are expensive, since there will be a single use by definition. The art will be to develop something that can be used in multiple patients. For instance by using gene-editing techniques that knock-out the endogenous T-cell receptor within the allogeneic T-cells, which removes the driver of the allogeneic reactivity.

QUESTION: CAR T-cells are indicated to be MHC independent. So, why are CART cells only administered autologously (to the specific donor)?. Is that because of specificity to patient specific tumor antigens?

ANSWER: This is partly covered in the above answer. The use of TCR engineered T-cells, which are very much patient specific because they target neo-antigens in the patient's tumor, so in recent trials tumors are being sequenced to identify neo-antigens and subsequently engineer TCRs to target those neo-antigens, and they can be used in an autologous setting.

QUESTION: Antigen escape and T-cell exhaustion can be a challenge. Could TCR-modified T-cells be engineered in a way that circumvents these challenges?

ANSWER: It is considered less likely that such modifications would actually provide a benefit. Other techniques that have been pursued to increase T-cell fitness, such as using stem-like T-cells, may hold greater promise.

QUESTION: Could you elaborate on the relation between the amount, not just the presence, of neoantigen, being actively MHC presented to activate the T cells? What are the combinations with T cell transfer available able to increase this trafficking/presentation

ANSWER: The reason that many researchers are particularly interested in posturing TCR-gene modified T-cells is that the receptor can uniquely recognize extremely low-densities of target antigens in a way that antigen receptors can't. But providing exact numbers on amounts is currently not feasible.

QUESTION: If one would assess the ability of ex-vivo modification of the NK cells compared to T cells, would you seen differences in the generation of genetically modified NK cells.

ANSWER: This is a remaining challenge. NK cells are more difficult to modify.

QUESTION: What would be the most viable source of NK cells going forward? When can we expect use in patients?

ANSWER: The best source is still an open question. Most current studies are therefor still using PDMC's as the easy source.

QUESTION: How are we progressing in the concerns on safety in solid tumors?

ANSWER: Several approaches with co-medications have been tested to reduce the toxicities, but likely the largest advances will come from engineering the T-cell to include the safety-switches that are already being incorporated, or the dual targeting. The first will be the easiest to achieve**.**

QUESTION: What do you think of adding the whole intracellular TCR square?

ANSWER: This is now tested in in-vitro experiments, for instance using different components of the CD3 complex.

QUESTION: What is the appropriate point in time for routine bio-banking of T-cells? Should this be in an early stage of the disease, or at a stage of disease when there is minimal tumor bulk?

ANSWER: Senescence is rather individual, so it is currently very difficult to predict the influence of senescent T-cells. One should also take the issue of exhaustion into account. And this could for instance be used in combinations with checkpoint-inhibitors.

SESSION 2: HOW TO DEVELOP A GENE AND CELL CANCER KILLER: THE CLINICAL TRIALS

From clinical trials to marketing authorization of advanced therapies.

Martina Schuessler-Lenz (EMA CAT chair, Paul Ehrlich Institute, DE)

The presentation focuses on CART-cells and genetically modified T-cells. They fall under the EU Regulatory Frame No 1394/2007. These products are authorized via the centralized procedure at the EMA. Principles of existing legislations apply for Quality, Safety and Efficacy. They are assessed by the specialized Committee for Advanced Therapies (CAT). The life cycle of these products is essentially not different from the one of medicines.

The new Clinical Trial Application regulation 536/2014 will apply from Feb. 1, 2022 onward. It involves a harmonized procedure with a single application towards a EU portal that is located at the EMA. There will be a coordinated multinational assessment, with a rapporteur. EU member states do retain authorization and oversight. There will be shortened time lines for sponsors to address questions (12 days).

CAR T-cell development will face regulatory challenges on patient derived starting materials (central vs de-central manufacturing, supply chain logistics, importation from 3rd countries), patient related variables (T cell fitness, bridging treatment during manufacturing), single administration or re-treatment (benefit vs serious safety issues), long-term insertional mutagenesis data, trial design issues, the need for specialized sites, consequences of high costs and patient access.

There are many antigen targets of CART cells and TCR modified cells that are used in current clinical development. The majority of clinical studies are being performed in China and the USA, and only a small fraction is done in the EU. Most trials are still early phase trials.

The EU marketing authorization process involves CAT and CHMP.

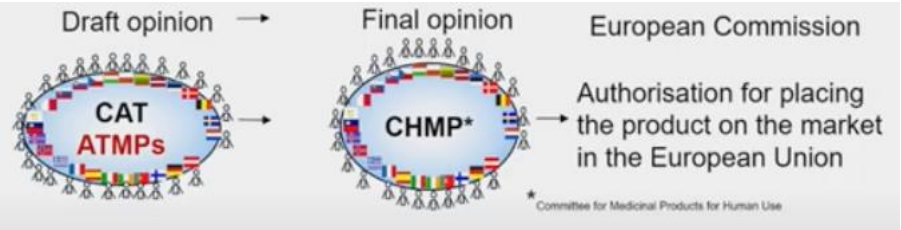

Figure 7. The EU Marketing Authorisation Process. Source: Martina Schuessler-Lenz's slides

Up to now 19 ATMPs have been approved(2009- 2021) including 4 CART products, focusing on (relapsed or refractory) multiple myeloma, various types of Non-Hodgkin's Lymphomas, and ALL. There was a subsequent major difference in time to access between EU countries (127 – 823 days), which CAT considers of concern in view of equal rights of patients within the EU. CAT and EMA have therefore started an initiative to improve post-authorization patient access on ATMP's, based on post-authorization use of real world registry based data collections and reporting. It also includes an increased exchange and collaboration with HTA's, involving joint scientific advice for ATMP's.

FDA Approval Pathways for Innovative Cell and Gene Cancer Therapies

Adnan Jaigirdar (FDA, USA)

FDA has various centers responsible for review of medical products, and the regulatory review of CAR-T and other cellular and gene therapies are overseen by the Office of Tissues and Advanced Therapies (OTAT) within the Center for Biologics Evaluation and Research (CBER). The Oncology Center of Excellence (OCE) fosters unified interactions between FDA Centers for the clinical review of oncology therapies

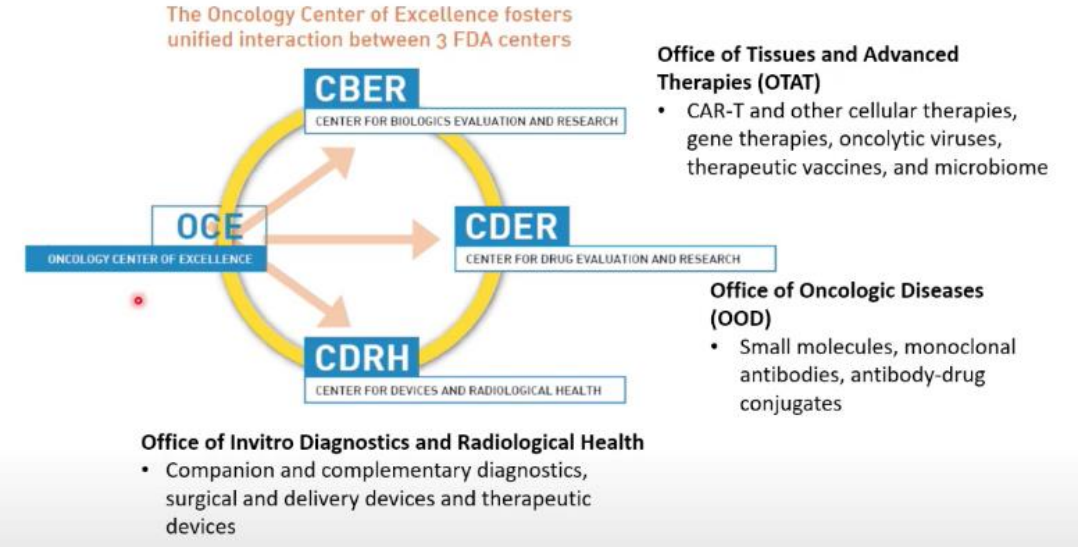

Figure 8. FDA Regulation of Oncology Products. Source: www.fda.gov

There has been an exponential growth in IND applications for gene therapy products in the last 10 years. The genetically engineered cell therapies approved by CBER over the past few years in cancer, involve CAR-T cells. A unique feature of all cellular therapies under consideration or in development is that they require complex manufacturing.

Considerations to take into account for studies for cell and gene therapies, include:

- For genetically engineered CAR-T cellular therapies
  - The potential of secondary malignancy
  - Off-target effects, potentially causing adverse reactions
- For Gene Therapies
  - The possibility of immune responses to the vectors and/or transgenes
  - Insertional mutagenesis leading to secondary malignancy
- Invasive procedures may be required
  - That could have associated procedural risks
- Cells or genes may persist for extended periods of time or produce sustained effect
  - Leading to intensified or prolonged adverse reactions
  - And making it challenging to establish a standardized approach for defining and capturing toxicities, such as cytokine release syndrome (CRS)

With respect to study design, in areas of unmet need, single-arm studies may serve as the basis for accelerated approval based on cancer response. However, if the products are used in a combinatorial fashion with other therapies, assessing the contribution of effect of each agent may be challenging in single-arm studies. Additionally, if assays for specific targets are

needed for safe and effective use of cancer therapy, a companion diagnostic will need to be considered, for which a study risk evaluation would be required.

With regards to endpoints, clinical trials for cell- and gene therapies have similar considerations as trials for other therapeutic agents.

For first-in-human (FIH) studies, the starting dose is based on pharmacology/toxicology data and available prior human experience with similar constructs. Dose escalation strategies need to take *in vivo* cell expansion into account, and FDA typically recommends that doses are escalated in have half-log increments between cohorts.

Additionally, as on-target off tumor or off target toxicities may occur, the study protocol should include an adequate algorithm for toxicity assessment and detailed management. Safety monitoring is paramount and should also include long-term follow-up monitoring (FDA Guidance: Long Term Follow-up After Administration of Human Gene Therapy Products (2020), https://www.fda.gov/media/113768/download) .

Throughout product development, FDA offers multiple opportunities for meetings with the sponsors:

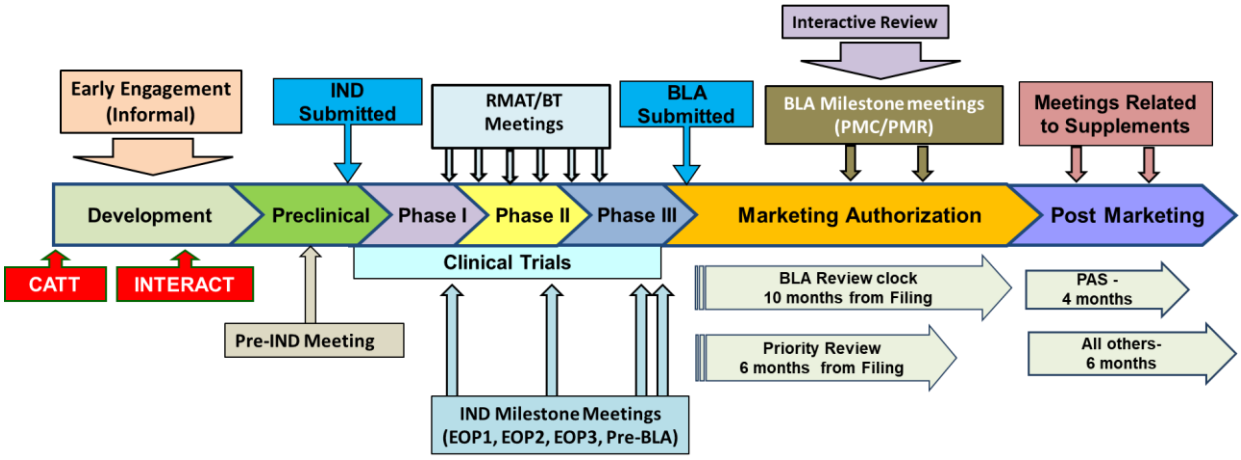

Figure 9. Interaction with CBER/OTAT. Source: Adnan Jaigirdar's slides

For the various FDA guidances that are now available for gene- and cell therapies, please visit https://www.fda.gove/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances

Clinical trials with cell therapies – challenges and opportunities. The industry perspective

Laura Pearce (GSK, USA)

The growth in development of cell therapies for cancer has already been addressed.

Lete-cel, is a 1st generation T cell therapy, consisting of CD4 and CD8 positive T cells that have been genetically modified to express a T-cell receptor that recognizes NY-ESO-1 and HLA-A*02 on a cancer cell, with greater binding affinity than naturally occurring T-cells. NY-ESO-1 is expressed in various solid tumors. Lete-cel has shown relevant activity in Synovial Sarcoma. As outlined in other lectures, Lete-cel is a TCR that is individual patient specific, so a truly "personalized therapy". Lete-cel will serve as example to discuss industry perspectives in the development of similar types of cell therapies.

Screening of patients is critically tied to the assay and the screening method and approaches. And should be performed in a way that avoids treatment delays as much as possible. The rareness of the population could cause attrition issues and screening exhaustion.

Manufacturing of the GMP materials requires a balancing of capacity and the speed of manufacture, as well as maintenance of an adequate supply chain. And given irregular patient enrollment rates a careful coordination and communication is needed.

From an operational perspective cell therapy trials have a greater resource demand. Site identification and assessment of site footprint are key.

Study design and regulatory issues are relevant (see above)

The traditional approach in development requires a study team, and an IND for each individual study. Which requires a lot of resources. In the "Parent-Child" protocol development Strategy, multiple technologies can be developed in a faster and more cost-efficient way

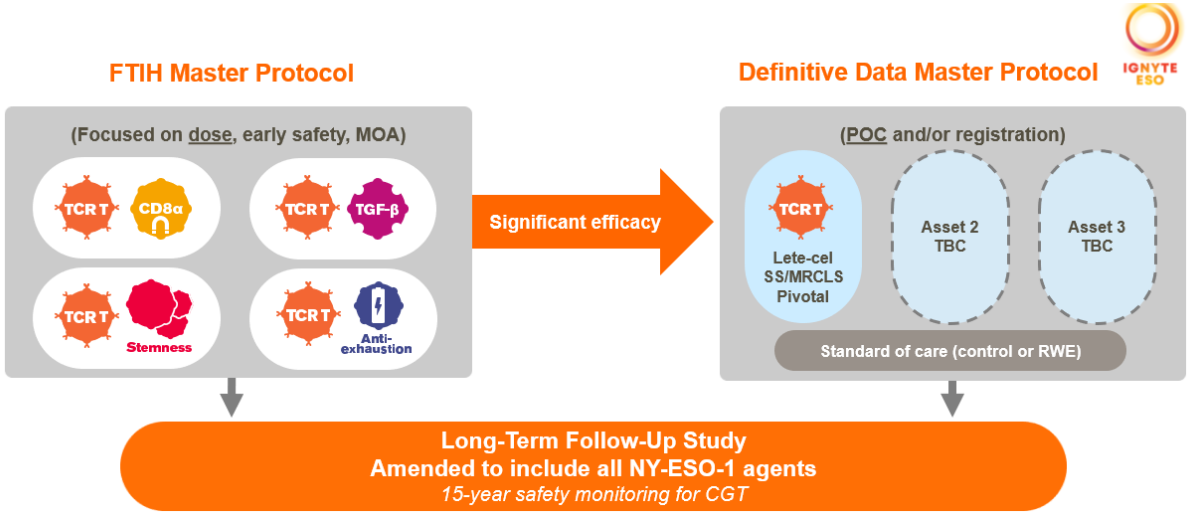

Figure 10. Parent-Child Development Strategy. Two Master Protocols + One LTFU Study. Source: Laura Pearce's slides

In this example the FTIH on the left is a platform protocol, consisting of a core and multiple independent sub-studies focused on dose, early safety and multiple mechanisms of action. On the right is the definitive Data Master Protocol, that has the same structure, but focused on proof of concept and/or registration. The 3rd, on the bottom, is a single long-term follow-up study, to which all patients from all sub-studies, and all agents, transfer following end of the treatment study for the patient. This approach provides an ideal framework for cell therapy development.

In practical terms it allows parallel examinations of multiple assets in a single master protocol with cross-referenced IND's. The parent IND contains all relevant information and each "child" is related to the "parent". The child IND adds to specific engineering, manufacturing changes, and cross-references to parent IND.

Challenges and learnings in conducting clinical trials with gene and cell therapies – The investigator perspective

Michael Hudecek – University of Wurzburg, Wurzburg, DE

Currently there 18 academic trials with CAR-T cells that are being performed in Europe.

The CARAMBA phase I-II trial is presented as an example of such an academic trial. This trial is financed by a grant from the EU Horizon 2020 program. The CAR-T cell product is directed at SLAMF7, and the study runs in multiple myeloma. The SLAMF7 antigen has the advantage of a homogeneous expression, that is sufficiently high in all patients, and not shredded.

The Caramba project involves 6 European countries, and is supported by Myeloma Patients Europe (MPE), which creates a patient-centered focus. Lots of required specific expertise is provided by specific partners in the consortium.

It took only 3 years from the reporting of the preclinical data, to the entry of the first patient into the clinical study. There was a staggered approach in IND submissions in countries involved, which allowed a learning process from country to country. A fresh, non-cryopreserved, cell product is used in the study, with a limited manufacturing time (total 16 days) between leukapheresis and CAR-T infusion.

The study has now completed dose level 1, and CRS has been observed, as well as reduction in MM markers, which suggests initial treatment activity.

CARAMBA clearly shows that a purely academic cell therapy trial is feasible.

A novel multi-stakeholder project in the Innovative Medicines Initiative is T2Evolve. It focuses on Accelerating the development and increasing access to CAR and TCR-engineered T cell therapy.

Panel Discussion

- Hans Scheurer, representing Myeloma Patients Europe (MPE, joins the panel, and stresses the importance of involving patients in development issues, and of making the trial design patient friendly
- Carin Uyl-de Groot, professor of Health Technology Assessment at Erasmus University Rotterdam, also joins and reminds that HTA looks at costs and consequences, and the level of evidence important is essential and unfortunately frequently lacking. In addition the long term consequences of cell therapies are yet unclear, which can be an issue for HTA.
- In the polls preceding the discussion the workshop attendees indicate that there is absolutely a role for Randomized Phase 3 trials in the marketing approval process, but at the same time 92% of the audience indicates that Registry data should be usable as comparator, for the same approval purpose.

QUESTION: Is there cooperation among regulatory agencies worldwide?

ANSWER: Yes, the various regulatory agencies have regularly scheduled collaborative discussions. Additionally, there is opportunity for parallel scientific advice from both the EMA and FDA.

FDA comment:

- Overall, global treatment landscape should be taken in perspective when approving therapies
- Engagement with regulatory agencies worldwide is crucial
- FDA conducts regularly (scheduled) meetings with other agencies
- A harmonized approach to review is important

EMA comment:

- Already lot of convergence, albeit not yet 100%
- Issue of member state involvement/autonomy

QUESTION: Can you dwell on the importance of RCT's in the development of cell therapies?

ANSWERS:

- **FDA:** RCTs remain the mainstay of licensure for oncology therapies. However, in relapsed/refractory disease, particularly where robust clinically meaningful treatment effects are observed, single-arm trials may be sufficient to support licensure. However, the study design for a particular cell therapy will depend on a variety of factors to include the condition, patient population, available therapies, prior lines of therapy, etc. The appropriate study design and potential regulatory approval pathways require a close discussion with the FDA review division(s). In such thorough discussions, lack of equipoise may need to be taken into account to facilitate patient access to such therapies. Adaptive designs could also be very helpful to accumulate adequate safety and efficacy data.
- **EMA** takes advantage of an external control arm to assess if the treatment effect from a single arm trial is indeed compelling and to contextualize the single arm clinical trial results. EMA also considers if a RCT would be feasible and if longer follow-up data are important for optimal assessment. Such information can be insisted on, and obtained post-approval, if approvals are conditional but also in case of full marketing authorisations. Approval based on real world data is not foreseeable in the near future.
- FDA may consider real world data if collected in a prespecified manner to provide comparator data for single-arm trials, but would require discussions with the FDA for applicability and appropriateness.
- Within EMA the use of RWD is currently discussed in the review of the pharmaceutical legislation

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QUESTION: What do the patients and the HTA experts expect from clinical trial development involving gene- and cell therapies?

ANSWERS:

- From the **patient perspective**, one of the key elements of a trial is that patients should be able to unambiguously understand the patient information sheet, on trial consequences and the impact on daily life.
- From **HTA perspective** the use of PROMS (patient reported outcomes) is very helpful. It will also be very important to have some kind of control group data and a prospective trial will be better standardizable and controllable. RWD Could then provide additive relevant information.

QUESTION: Could you further expand on the strategy for the Parent-Child concept?

ANSWER: The intent is focused on how to conduct clinical trials more efficiently. And on how we can avoid to rebuild required infrastructures every time. Also to make it easier for sites and involved committees to assess the protocols. It is important to realize that, from a regulatory perspective, manufacturing will create issues once multiple manufacturing sites are involved.

QUESTION: From the poll, HARMONIZATION is the winner word. Does the panel see any other advantages of harmonization.

ANSWER: The key variable is the cell product. In terms of monitoring there is much more we can learn if there would be standards.

SESSION 3: HOW TO BRING A GENE AND CELL CANCER KILLER TO PATIENTS: HOW TO IMPROVE PATIENT ACCESS

From marketing authorization to patient access – The rollout from the industry perspective

Bernd Eschgfaeller (Novartis, CH)

The lecture described Novartis journey in the development of CAR-T cell therapy, that started from a collaboration with the University of Pennsylvania in 2012, and had its first regulatory success in August 2017 with the FDA approval of tisagenlecleucel for the treatment of B-cell precursor ALL.

The experience obtained throughout the process has taught that it is key to have a sophisticated manufacturing process in place. This is an individual patient based process, which provide unique challenges, with quite variable pressures on demands. The process that has been build, now enables to actually bring CART back to 98% of involved patients.

The details of CAR-T production have been described above.

There are 3 components there are important for Tisagenlecleucel:

1. The cryopreservation that is utilized in manufacturing. This provides apheresis scheduling flexibility, and also gives durability while in transit in case of unforeseen transport delays. Finally it enables to preserve cell quality for a long time.
2. The 4-1BB costimulatory domain enhances the cellular expansion and persistence
3. The truly global involvement of study sites, allowed relatively rapid study performance in 2 distinct indications (ALL and DLBCL).

It is also important to take into account the fact that both EMA and FDA require to qualify treatment centers (JACIE accreditation), since for autologous therapies, centers have the dual role of supplier and customer.

After marketing approval, it is also important to have a broad geographic footprint for worldwide patient access to CART. Novartis ensured wide reimbursement thanks to collaborative and innovative approaches, that included:

- One-time payment
- Price volume agreements
- Installment payments
- Value based agreements based on outcome
- Price by indication

It is thus a truly global undertaking to bring CART to every patient in need. 7 manufacturing facilities across the world also indicate continuous commitment.

All of what has been created allows development into a platform for various new CAR-T therapies.

How to improve access to cell and gene therapies. A patient organisation perspective

Kate Morgan (Myeloma Patients Europe, UK)

One CAR-T product has been approved by FDA and EMA, and is now undergoing HTA assessment in Europe. Several others are in the pipeline. Most studies up to now are small single arm studies, so the uncertainty related to clinical data will likely cause serious issues in

the HTA pathway. In addition the fact that major costs would be added at the end of a patient life-journey, may be limiting factors for acceptance by HTA.

First, we need to better understand and articulate the patient impact and burden of cell and gene therapies rot regulators and reimbursement decision-makers to support access. The safety aspects of the treatment are considerable and may negatively affect Quality of Life. A problem may be that existing patient reported outcome (PRO) tools for measuring quality of life in cancer, are not fit for purpose in cell and gene therapies. There is little consensus on which existing tools to best use, and when and how. So, it will be important to develop a new to tool to supplement better data.

Given the above uncertainty, it is important to consider other forms of patient related evidence as well. Acknowledging that there will not be a one-size-fits all, patient organizations do have an obligation to develop tools and generate such evidence.

A second issue to deal with is uncertainty on effect. Outcomes based reimbursement models and Real World Evidence will have a big role to play in reimbursement. But the best way to collect such data are still subject to major debate.

The third major issue it inequalities in patient access at the pan-European level, since these are currently significant. Many EU countries are even many years behind ESMO standards, and do not have the experience and hospital capacity to provide CAR-T therapies. Such therapies are still science fiction for such countries. The inequality can easily be seen on this graphic, that shows access to relatively simple standard of care:

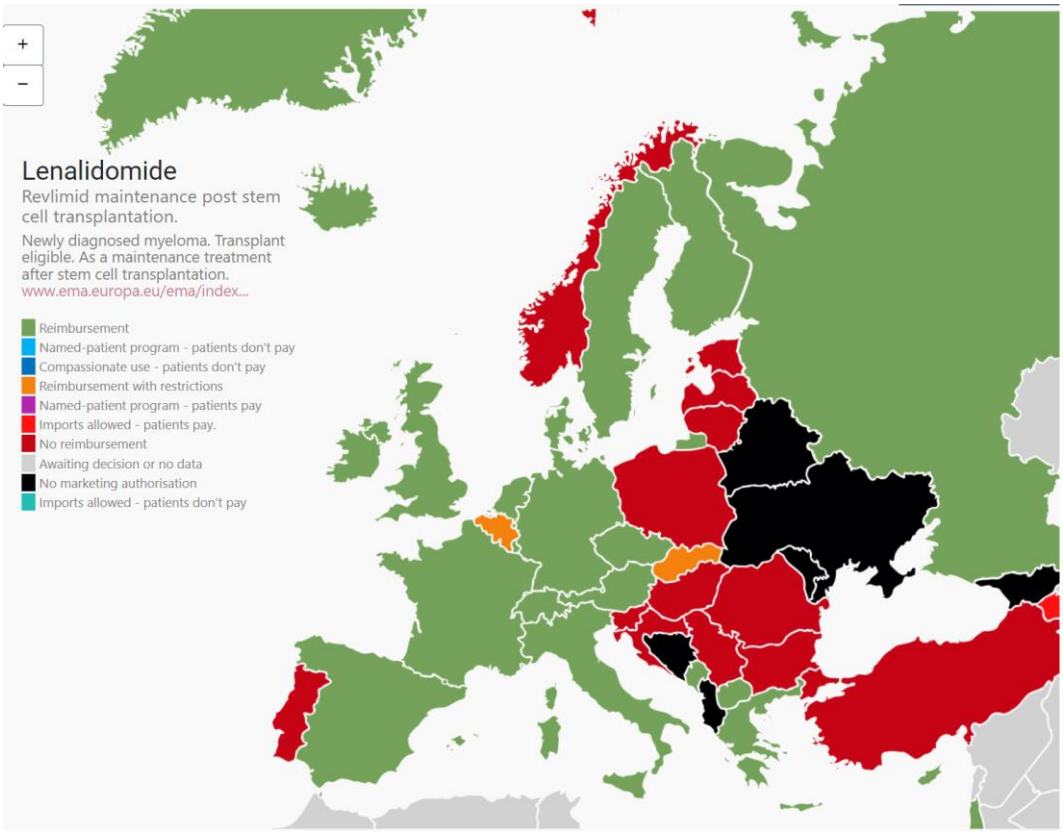

*Figure 11. Inequalities in access. Examples from the Myeloma Access Atlas: Lenalidomide. Source: www.ema.europa.eu/ema/index_*

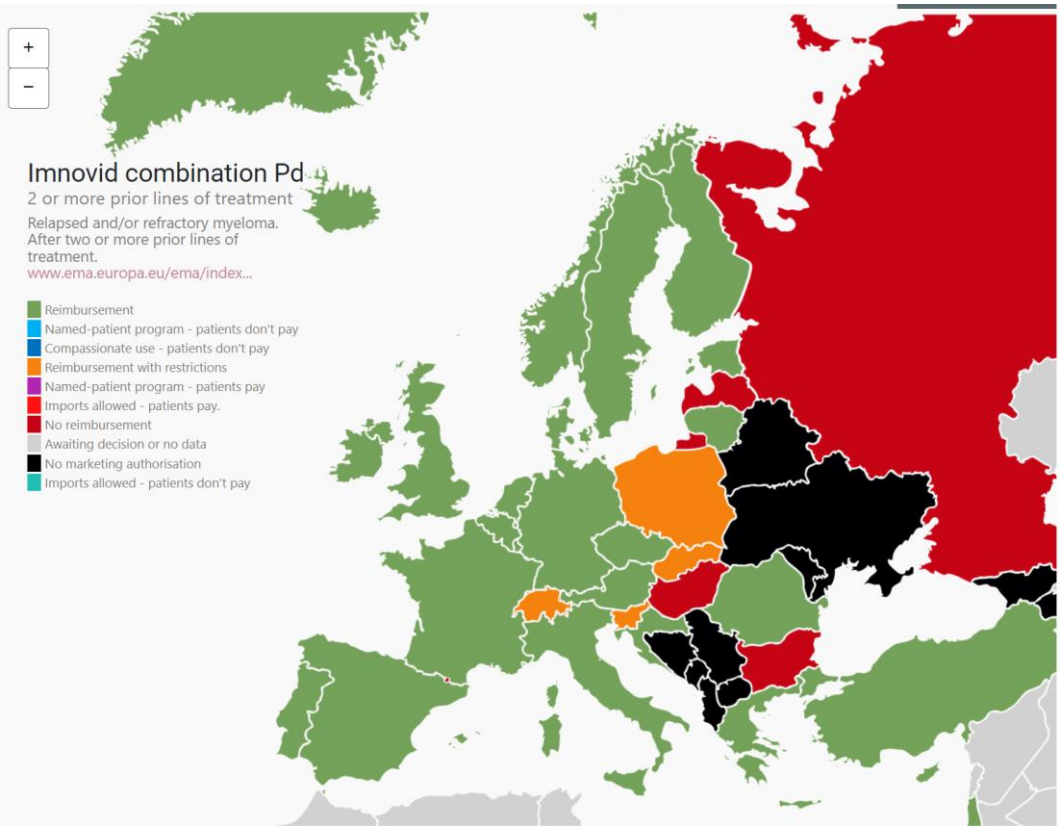

*Figure 12. Inequalities in access. Examples from the Myeloma Access Atlas: Imnovid combination Pd. Source: www.ema.europa.eu/ema/index_*

Even where national reimbursement is granted, it does not guarantee patient-access, creating a wide range of concerns for individual patients.

Potential solutions can be found in:

- Creation of local CAR-T manufacturing sites
- Academic collaborations and networks
- Appropriate triage of patients
- Addressing of scalability issues
- Awaiting data from larger trials earlier on in the pathway.

HTA and Reimbursement models in cell therapies

Carin Uyl-de Groot (Erasmus School of Health Policy and Management, NL)

Current policy goals in health care are Quality of care, Equity, and Sustainability. Quality of care should include benefit and safety, but also patient centeredness. And Equity indicates that care should be available for all, completely independent of a person's background. So, together these aims lead to 1 common goal:

Ensuring affordable and equitable access for (all) patients to effective therapies in a sustainable manner.

While there are many innovative cancer drugs, there are huge differences among EU countries, with major differences in expenditure leading to unequal access.

In this landscape, and taking into account that what is spend on one patient cannot be spend on another (so called "opportunity costs"), the per patient costs for CAR-T cell therapies that

amount € 300.000-400.000, create a challenge. They can likely not be covered within the allowed maximum yearly budget growth of 1.2%.

Health Technology Assessment (HTA) aims to analyse and balance these issues. The HTA process is multidisciplinary. The two main phases of HTA are Assessment and appraisal, as outlined in the figure.

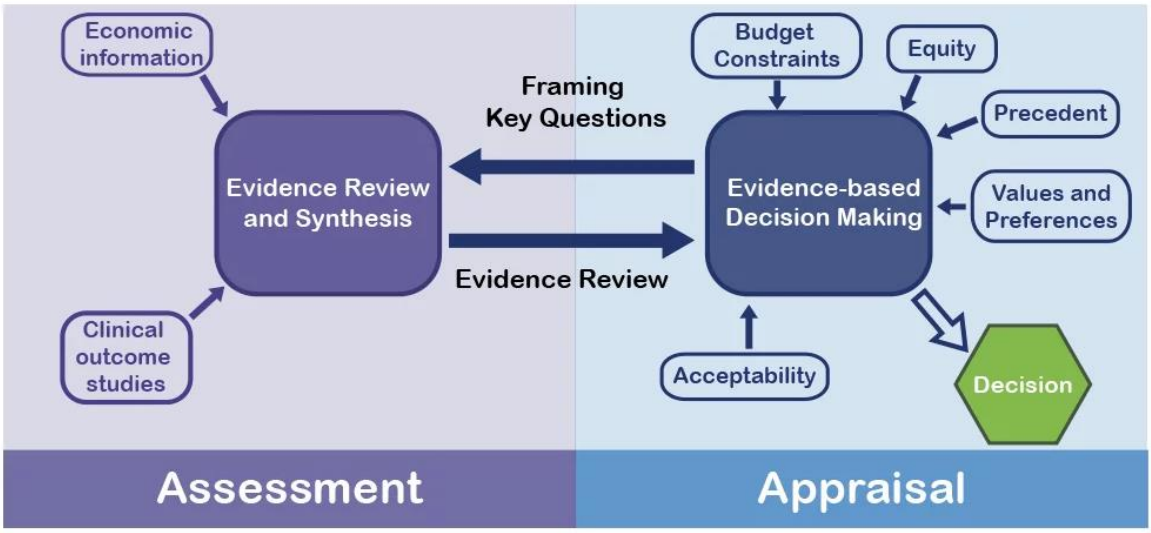

Figure 13. The two main components of HTA: Assesment and Appraisal. Source: www.eupati.eu [Adapted from Teutsch S., Berger M. (2005) "Evidence syntesis and evidence-based decision making: Related but disctinct processes." Medical Decision Making, pp 487-489]

Decision could go many ways. Each EU country decides for itself. All struggle with the problem that the current systems are not sustainable. A leading question is how to reduce spending? To address this, value based pricing has been introduced. This includes factors such as:

- Cost per QALY (with major differences between countries)
- Pay for performance (P4P), and
- Volume-price arrangements, and more recently
- Coverage with evidence development (CED)

The latter is particularly applied for drugs for which adequate large data sets are yet lacking.

Despite use of these factors, sustainability has not yet been achieved. Clearly, other measures are needed. A newly proposed pricing algorithm for fair pricing of cancer drugs was published in Nature Reviews and Clinical Oncology (2018; 15:405-406):

$$\text{Fair Cost of New Medicine} = \left[\frac{\text{R\&D costs}}{\text{nr. of patients} \times \text{years of patent left}} + \text{production costs per patient per year} \right] \times (1 + \text{profit margin})$$

Figure 14. New pricing algorithm for innovative (cancer) drugs. Source: Uyl-de Groot C., Löwenberg B., (2018); "Sustainability and affordability of cancer drugs : a novel pricing"; Nature Reviews Clinical Oncology 15, pp. 405-406

In which the profit margin should depend on clinical value as for instance determined by the ESMO Magnitude of Clinical Benefit Score (MCBS).

In a recent analysis it was shown that list prices of recently approved Cell and gene therapy products were quite similar in 6 EU countries, being in the range of € 320.000 – 350.000 per patient. The other cost components involved in each such treatment can add up to € 50.000.

A recent analysis of current and forecasted expenditure cost CART per country, illustrates the financial challenge society is facing:

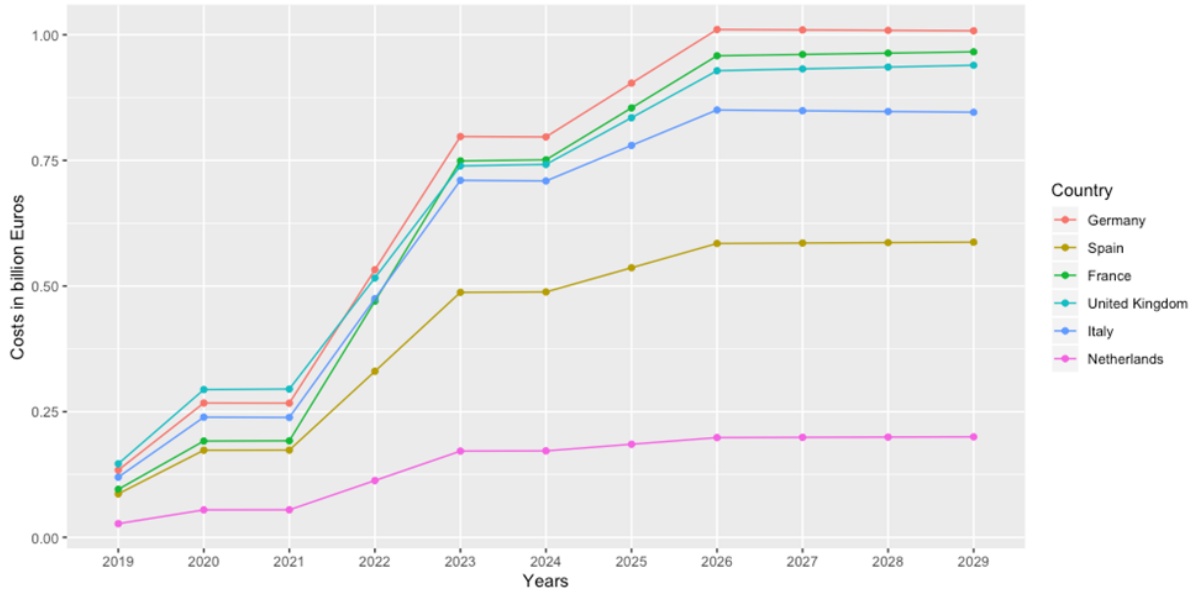

Figure 15. Expenditure forecast cost CAR-T per country (all indications). Source: Carin Uyl-de Goot's slides

This already now leads to major differences in reimbursement of CART across the EU.

The HTA process and the country specific assessment has already lead to major and basically unacceptable differences in patient access to cancer drugs within the EU (Uyl-de Groot C, et al, Cancers 2020; 12:2313-2330).

Panel Discussion

- Michael Hudecek joins the others for the panel discussion.
- Communication comes up in the pre-panel poll as the main opportunity to improve patient access to GCT. The panel confirms that there is a major need for education of and information for patients and family members, as well healthcare professionals. It is still an open question in which format this can best be provided. It is also acknowledged that it is crucial to provide optimal information to HTA authorities, to justify approval, as well as reimbursement. With balancing of safety and efficacy. Consortia such as the briefly mentioned T2Evolve can help to set standards.

QUESTION: Is there any difference within geographic reasons with respect to turn-around time?

ANSWER: Bernd Eschfaeller: There are major difference between regions concerning the time between pheresis and return of product. This is a.o. related to availability of airports, cross-border customs procedures. Novartis time line difference was 10 days at start of the studies, while it has now been reduced to 2-3 days. There is room here for improvement that will likely require harmonization. The difference in time to patient access was already exemplified in Carin's lecture for the EU. In this respect the EU does not act as a union.

QUESTION: How can we improve on communication?

ANSWER: Kate Morgan stresses that it will be important to share best practices among disease areas. Having multi-stakeholder discussions, like this workshop, will be very important to share experiences and so we learn from each other. Carin Uyl indicates that improvements in evidence generation will be key, and that product costs are remain an issue. More transparency on how prices become established will also help.

QUESTION: Is it not the case that designing a disease-specific PRO instrument is easier than using the general ones such as EORTC?

ANSWER: Most tools in current use are quite outdated. It will be important to analyze their shortcomings, and jointly look for improvements. HTA will need utility instruments, and it will be important to include these in the PRO. Which again stresses the importance of joint multi-stakeholder involvement, and make them CAR-T and/or disease specific.

QUESTION: Considering between-country inequalities: Are all physicians fully aware of these disruptive technologies? Is lack of education a source of inequalities in access?

ANSWER: Doctors are usually well aware throughout Europe. While Trial access may differ between countries, distribution of knowledge is usually smooth and of high quality. Yet, RWD show striking differences between countries, while at the same time there are hardly differences in outcomes from trials and from registries within a given country. So, there is room for improvement. Also on this aspect, multi-stakeholder meetings will be helpful.

SESSION 4: FUTURE PERSPECTIVE IN THE ECO-SYSTEM

How can a collaborative CAR-T registry advance development?

Nicolaus Kröger (EBMT President, Medical Center Hamburg-Eppendorf, DE

The EBMT (European Society for Blood and Marrow Transplantation), involves over 570 sites worldwide and is aimed to advance the field of blood and marrow transplantation and cell therapy, through science, education and advocacy. The EBMT registry contains patient clinical data on disease and management, including HSCT or cell therapy associated procedures, transplant type, donor type, stem cell source, complications, and outcome. A participating site consents to report all of its cell therapy procedures yearly. The patient itself remains owner of the data.
The registry started in the 1970's and contains data on > 600.000 procedures. It covers 90% of all yearly procedures in Europe.
The registry allows assessment as a classical registry, for benchmarking models, retrospective EBMT studies, Non - interventional cohort studies, and clinical intervention studies.
There are 10 different EBMT working parties that develop scientific proposals.
The aims to collect data are: To capture "real life" data, to collect rare and long-term adverse events, to compare clinical results of cell and gene therapies to gold standard therapies, and to increase collaborative interactions between Cell and Gene Therapy stakeholders.
A registry such as the EMBT avoids blocking of data sharing, avoids fragmentation into small data sets, contribute to standardization, and allows use by third parties such as regulatory authorities. It also enables a real-world setting assessment, in content and costs.
The EBMT has joined forces with the European Hematology Association (EHA), and created the GoCART coalition, that also incorporates all other stakeholders.

Advancing CAGT Trials: The emerging value of external comparators

Emily Bratton (IQVIA, USA)

Real World Evidence (RWE), obtained from Real World Data (RWD) can inform stakeholder decisions throughout the lifecycle of a product, and is increasingly relevant for regulatory purposes. This way natural history of disease, biomarker performance information, and a comparator treatment effect in rare diseases, can be obtained. Regulators across the globe are now beginning to recognize the potential value of such RWE, and several guidelines have meanwhile been published. For instance, FDA accepts RWE primarily in the setting of oncology and rare disease, for approvals based upon a single-arm interventional trial when a parallel control arm is unethical or not feasible, and the effect size is large. EMA has similar considerations, and considers a role for RWE when a randomized clinical trial is infeasible.

This also includes cell- and gene therapies (CAGT). Due to scientific advances, this market is rapidly growing in size and projected to involve 35 billion USD by 2026, mainly in rare indications. An external comparator can establish context for single-arm trials in such cases.

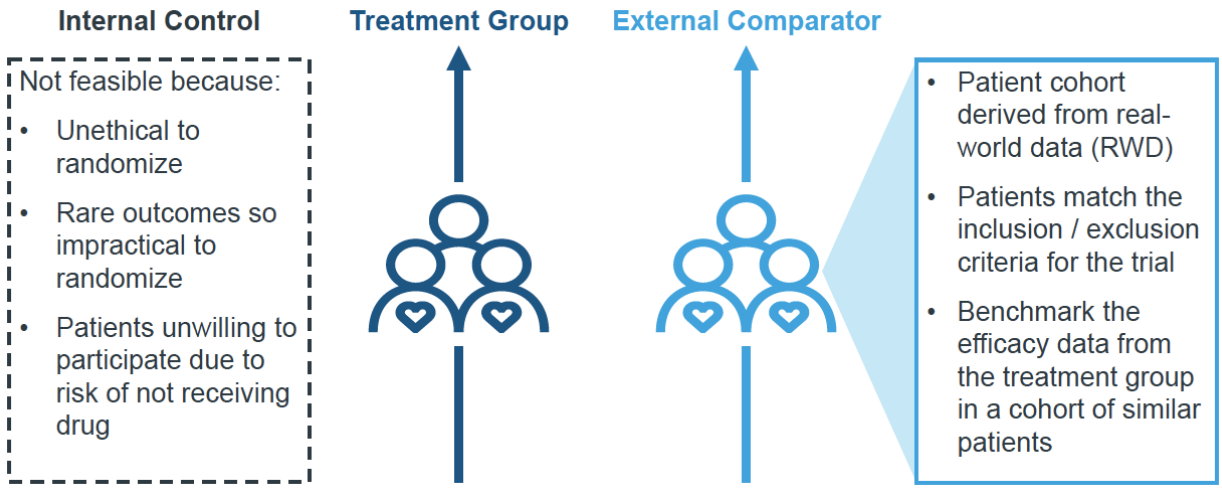

Figure 16. An external comparator can establish context for single-arm trials. Source: Emily Bratton's slides

In assessing external comparators, one should differentiate External controls (that include adjustment of data at patient-level) from Benchmark controls (exclude adjustment of data at patient-level).

There is increasing use of RWE for regulatory purposes with External controls.

From 2017-2019, we saw 11 medicines submitted to EMA and/or FDA for approval leveraging external comparators as comparative evidence. Seven of these were accepted (either via direct patient methods for comparison or aggregated benchmark analysis), and 4 were not.

EC regulatory use cases, 2017-2019

			FDA		EMA	
			Approval	Label Expansion	Conditional Approval	Approval
	Product	Indication				
Accepted by RAs	avelumab	Metastatic Merkel cell carcinoma	(2017)		(2017)	
	cerliponase alfa	Infantile batten disease	(2017)			(2017)
	axicabtagene ciloleucel	Diffuse large B-cell lymphoma				(2018)
	tisagenlecluecel	Diffuse large B-cell lymphoma				(2018)
	omegaven	Parenteral nutrition-associated cholestasis	(2018)			
	blinatumomab	B-cell precursor acute lymphoblastic leukemia in 1st / 2nd complete remission with MRD ≥ 0.1%		(2018)		(2019)
	onasemnogene abeparvovec-xioi	Spinal muscular atrophy	(2019)			
Not accepted by RAs	selinexor	Relapsed refractory multiple myeloma	(2019)			
	tazemetostat	Epithelioid sarcoma	(2019)			
	entrectinib	ROS1-positive metastatic non-small cell lung cancer	(2019)			
	erdafitinib	Adult patients with locally advanced or metastatic urothelial cancer with FGFR2/3 mutations	(2019)			

RA= Regulatory Agency
MRD = minimal residual disease

Figure 17. EC regulatory use cases, 2017-2019. Source: Emily Bratton's slides

And 1 example of use of benchmark comparators (Zolgensma for Spinal muscular atrophy). The challenges in using external comparators are various:

- Selection of patients between cohorts differ, including temporality,
- The external comparators often use different data source from patients in a clinical trial

- Variable between sources may have different meanings, quality, and completeness.

In several aspects the regulators concluded positively on the use of RWE. But likewise they also raised concerns on issues such as differences in years on receiving treatment, in selection of patients, in confounding factors, in treatment response assessment frequency.

Also at the level of payers there is interest in using RWE, with similar concerns in assessment.

Regulatory feedback for CAGT trial planning, if leveraging an external comparator design strategy, has suggested importance of planning ahead, minimizing bias and cofounding, and ensuring comparability to trial subjects and trial endpoints.

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AI (artificial intelligence) for better cell therapy

Thomas Clozel (OWKIN, France)

Important challenges of cell therapy development are to predict responders vs non-responders, identify their respective biomarkers, and create a rational of combination therapies, and predict safety. In order to appropriately address these, one always has to take the host, the tumor as well as the therapy into an integrated account.

Answering the questions related to these challenges, requires finding of, and getting access to the right data. Obviously the adequacy of those data should be beyond doubt, and they should be collected without prejudice. Only post-hoc will we be able to identify forward looking factors, and test these prospectively.

A Federated Learning (FL) system has been developed. It leaves the data within the hospital firewall. Only the algorithm travels, to be trained at different clinical sites. This also has the advantage of safeguarding patient privacy.

FL is deployed in Melloddy, the IMI consortium that includes 10 large pharmaceutical companies that are jointly developing machine learning for small molecule drug discovery.

Finally, what matters, is finding the right AI technology. For instance, it will be important to connect histology data with genomics data. The FL also has the advantage that it allows trans sectional development of biomarkers from different sources.

Using FL, it has already been possible to build predictor models for survival in mesothelioma, as well as predicting gene expression in Her2NA disease, based upon analysis of histology data.

Panel Discussion

- Martina Schuessler-Lenz (CAT/EMA) and Natacha Bolanos (Lymphoma Coalition) join the speakers and moderators for the discussion.

QUESTION: Have EMA and/or FDA already used EBMT generated data, and how can we leverage Registry data?

ANSWER: If there is a positive opinion at CAT on a GCT product, the marketing authorization includes provision for benefit and safety follow-up, for which registry data can be used. EMA does not prescribe which registry should be used, but indeed EBMT data can be, and have been used. The responsibility for providing is with the marketing authorization holder.

QUESTION: Is there acceptance by HTA authorities for the use of registry data?

ANSWER: This is yet complex for GCT, since generally there is insistence on RCT data. For HTA, generalizable data are crucial.

QUESTION: Is there a difference perceived in quality of data in the EBMT, for patients that were entered into prospective clinical trials vs. those that were treated as standard of care?

ANSWER: In general, the quality of data from trials, are better than those from real world. And the time periods and over which data have been collected and the related quality control changes, also create differences in quality of data over time. For marketing authorization the primary evidence generation builds on clinical trials. In the ATMP/GCT field, RWD have been used in all authorizations since 2018, in the pre-authorization setting, to contextualize results generated in single arm prospective studies. It will be important to also use PRO's, and improve their quality. Particularly such data will be important of the HTA. Prospective collection of structured RWD can help to improve the quality and therewith the relevance of such data.

QUESTION: Can we improve the standardization of data collection in general in the standard of care?

ANSWER: The data we have from RWD vs clinical trial data in the authorization for the first GCT products, indicate the quality of RWD on hard endpoints such as survival, can already be quite good. For PRO this is more complex, and hampered by the consequence of the EU privacy protection acts.

AI can help by "federative learning". The future will likely be in a mix of centralized registries and decentralized data, but in general standardization of data description and collection will remain crucial. As mentioned before, having multi-stakeholder consensus on what kind of data should be collected, is extremely important.

All of the above will have to be balanced against the value proposition of the product.

QUESTION: Is it conceivable that standardization will enable the creation of one unique data set that will satisfy the marketing authorization regulators as well as HTA and payers?

ANSWER: The upcoming EU HTA regulation foresees joint clinical assessments between the participating HTA's and preceding to that there is now a reinforcement of joint/parallel scientific advices between EMA/SAWP and HTA's.

QUESTION: How valuable could a comparator synthetic arm be, when it is geographically restricted? Is there any guidance on potential content of the arm?

ANSWER: There is currently not a single, one-size-fits-all, recipe. This also requires discussion on the definition of “Real World”. Missing data for instance, are part of the Real World. This links to the difference between “efficacy” and “effectiveness”. Again, it will be important to involve all stakeholders in such a discussion.

QUESTION: Would AI systems allow identification of external comparators, for the increasingly fragmented clinical trial population (due to improved diagnostic tools)?

ANSWER: Indeed AI could help solve several aspects. And get to better predictable outcomes. This can be done at many different levels.

QUESTION: Will AI become helpful in the pre-screening phase, in patient profiling?

ANSWER: Already now, it is possible to accurately predict genetic profiles, even based on simple histological patterns. AI is a good way to enrich datasets.