

Alliance for
Regenerative
Medicine

Regenerative Medicine
& Oncology

June 2019



The Alliance for Regenerative Medicine (ARM) is the preeminent global advocate for regenerative and advanced therapies. ARM fosters research, development, investment, and commercialization of transformational treatments and cures for patients worldwide.

By leveraging the expertise of its membership, ARM empowers multiple stakeholders to promote legislative, regulatory, and public understanding of, and support for, this expanding field.

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Regenerative Medicine & Oncology



18+ million people are diagnosed with cancer each year, with more than 9 million deaths attributed to cancer annually.

There are currently seven approved RM / AT products and 132 products in active development in oncology, including 23 in Phase III.



There 416+ companies worldwide active in developing regenerative medicine therapies for oncology, including 191 clinical-stage companies.



Cancer is among the leading causes of death worldwide, accounting for approximately 16 percent of deaths in 2016.¹ Though many people associate cancer with the growth of solid tumors, certain types of cancer – including hematological malignancies, or cancers of the blood—typically do not form these types of tumors. In these cases, the excessive cell growth caused by the cancer is referred to as a “liquid tumor.”

In recent decades, the standard of care for cancers has typically included a combination of surgery, radiation, and chemotherapy. The effectiveness of these treatments varies widely in response to a number of factors, though survival rates have increased and relapse rates have decreased for most cancers over the past several decades. However, the scientific and medical communities have recognized there is a significant unmet need for more effective cancer therapies, particularly for patients who have advanced cancers and have not responded to traditional treatments.

In particular, researchers are devoting significant resources to develop regenerative medicines and advanced therapies (RM/AT) to treat cancers. These therapies, which include gene therapies, cell therapies, and tissue-engineered products, are intended to treat the underlying cause of disease. They have the potential to provide profound and durable responses – often with just a single treatment – for patients with a wide variety of serious diseases and disorders. Cell-based immunoncology (I-O), a type of regenerative medicine which harnesses the body’s own immune system to treat cancer, is a particularly active field, constituting approximately 60% of regenerative medicine clinical trials in the treatment of cancer.

¹ World Health Organization, 2018

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Methods to treat cancer using cell-based immuno-oncology approaches include:

CAR-T Cell Therapies: CAR-T is a process by which a patient's T cells are removed and genetically engineered to produce Chimeric Antigen Receptors (CARs). These antibody-like synthetic receptors enable the T cells to recognize directly proteins, or antigens, located on tumor cells and target them for destruction.

In 2017, the FDA approved the first two CAR-T therapies in the field of oncology: Novartis's Kymriah, approved in August 2017 and Kite/Gilead's Yescarta, approved in October 2017.

CAR Macrophage Therapies: Macrophages are part of the innate immune system and can be drawn to both liquid and solid tumors. In solid tumors, macrophages can modify the tumor microenvironment and maintain an anti-tumor phenotype even in the presence of immunosuppressive factors. Macrophages can also be genetically engineered to produce CARs. These engineered macrophages recognize, engulf, and destroy tumor cells, recruiting other immune cells using antigens from the tumor cells.

Gamma Delta T-Cell Therapies: Gamma delta T Cells are a small subpopulation of lymphocytes, which have been shown to have anti-cancer activity. Gamma delta T cells, like Natural Killer cells, are able to recognize tumors without any prior activation. Gamma delta T cells do not require human leukocyte antigen (HLA) matching between the donor and recipient and therefore are being studied for allogeneic use.



iPSC-Derived T-Cell Therapies: Induced pluripotent stem cells (iPSCs) are being studied as raw material for both autologous and allogeneic universal therapies. iPSCs modified to present a universal donor phenotype can be expanded to form large cell banks with broad immuno-compatibility to treat a potentially limitless number of patients. iPSC cells may then be differentiated into other cell types such as T cells and genetically engineered to target cancer cells (allogeneic CAR-T or TCR therapies).

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Natural Killer (NK) Therapies: NK cells are a type of lymphocyte involved in the detection and destruction of tumors and virally infected cells. They are part of the innate immune system and therefore can target tumors without prior activation. Cell therapy methods allow researchers to modify NK cells to make them more effective at targeting specific cancer cells. Because human leukocyte antigen matching is less of a concern with NK cells than with T cells, NK cells are also a prime target for allogeneic or universal therapies.

T-Cell Receptor (TCRs) Therapy: Like CAR-T therapies, therapies that utilize TCRs begin by harvesting a patient's T cells and genetically engineering them, in the case to create specialized T Cell Receptors. These TCRs are engineered to activate in the presence of an internal antigen that must be presented as a peptide complex on the surface of cancer cells, enhancing the body's adaptive immune response. The immune system will then work together to rid the body of the foreign antigen.

Tumor-Infiltrating Lymphocytes (TILs) & Marrow-Infiltrating Lymphocytes (MILs): Tumor-infiltrating lymphocytes are a type of white blood cell that works to destroy tumors in the body by infiltrating them. Scientists have discovered the ability to modify these cells to make them more effective in the destruction of tumors. This enhancement in function is currently being investigated in clinical trials for metastatic melanoma, HPV, and non-small cell lung cancer. Marrow-infiltrating lymphocytes are T cells located within the bone marrow. Like TILs, they can be modified to make them more effective in the destruction of tumors. Current clinical trials use these immune cells as a form of treatment for patients with myeloma and relapsed diseases.

Other regenerative medicine approaches to treat cancer include:

Gene Therapy: Gene delivery or gene editing methods can be used to introduce a gene to cancer cells or surrounding tissues to cause cell death or slow the growth of tumors.

Cell Therapy: Cell therapies may be utilized in a number of cancer treatments. Many cell therapies are currently in clinical trials to improve the outcomes of patients with hematological malignancies who need to receive hematopoietic stem cell transplant, also known as a bone marrow transplant.

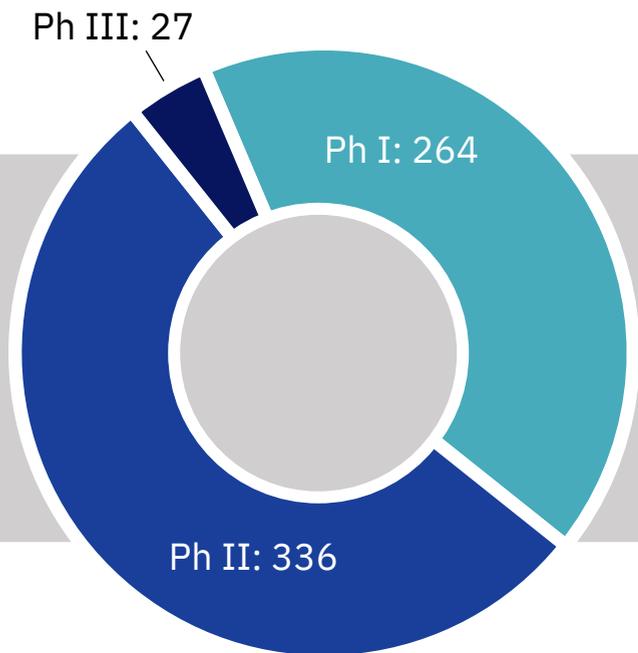
Oncolytic Viruses: An oncolytic virus is a type of virus that preferentially infects and breaks down cancer cells. Most current oncolytic viruses are engineered for tumor selectivity, although there are naturally occurring examples. Amgen's Imlygic/T-VEC was the first oncolytic herpes virus (created by genetically modifying herpes simplex virus) approved for use by the US FDA and by the EMA in the EU in 2015 for the treatment of advanced inoperable melanoma.

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ARM members with disclosed preclinical or clinical oncology-focused regenerative medicine therapies include:

- 4D Molecular Therapeutics
- Abeona Therapeutic
- Adaptimmune Therapeutics
- Adicet Bio
- Adverum Biotechnologies
- Aegle Therapeutics
- AGTC
- American Gene Technologies
- Amicus Therapeutics
- Angiocrine Bioscience
- Astellas Pharma
- Asterias Biotherapeutics
- Atara Biotherapeutics
- Athersys
- Audentes Therapeutics
- Autolus Therapeutics
- AveXis
- AVROBIO
- Axovant Gene Therapies
- Bellicum Pharmaceuticals
- Benitec Biopharma
- BioCardia
- Biostage
- BioTime
- bluebird bio
- Brainstorm Cell Therapeutics
- Caladrius Biosciences
- Capricor Therapeutics
- Carisma Therapeutics
- Casebia Therapeutics
- Celgene Corporation
- Celixir
- Cell Medica
- Collect Biotechnology
- Cellerant Therapeutics
- Cells for Cells
- Cellular Biomedicine Group
- Cevec Pharmaceuticals
- CRISPR Therapeutics
- Cynata Therapeutics Limited
- Editas Medicine
- ExCellThera
- Excision BioTherapeutics
- Fate Therapeutics
- Fibrocell
- Gamida Cell
- GammaDelta Therapeutics
- Generation Bio
- Genethon
- Genprex
- GenSight Biologics
- Gilead Sciences
- GlaxoSmithKline
- Healios KK
- Histogen
- Hitachi Chemical Advanced Therapeutics Solutions
- Homology Medicines
- Immusoft Corporation
- Intellia Therapeutics
- Iovance Biotherapeutics
- Johnson & Johnson
- Juventas Therapeutics
- Kite Pharma
- Krystal Biotech
- Legend Biotech Corporation
- Lentigen Technology
- LogicBio Therapeutics
- Lysogene
- Magenta Therapeutics
- Masthercell
- MaxCyte
- Medeor Therapeutics
- MEDIPOST
- MeiraGTx
- Mesoblast Limited
- MiMedx Group
- Minerva Biotechnologies
- MolMed
- Mustang Bio
- Myonex Therapeutics
- Neuralstem
- NexImmune
- Nightstar Therapeutics
- Nohla Therapeutics
- Novadip Biosciences
- Novartis
- Opsi Therapeutics
- Organesis
- Orthocell
- Oxford BioMedica
- PDC line Pharma
- Pfizer
- Pluristem Therapeutics
- Poseida Therapeutics
- Precision BioSciences
- PROMETHERA Biosciences
- PTC Therapeutics
- Regenerex
- Regeneus
- REGENXBIO
- Rocket Pharmaceuticals
- SanBio
- Sangamo Therapeutics
- Sanofi Genzyme
- Sarepta Therapeutics
- Semma Therapeutics
- Sentien Biotechnologies
- Sernova Corp
- Shire
- Sigilon Therapeutics
- Spark Therapeutics
- Terumo BCT
- Tessa Therapeutics
- Thermo Fisher Scientific
- Tmunity Therapeutics
- TxCell
- Ultragenyx Pharmaceutical
- uniQure
- Vivet Therapeutics
- Voyager Therapeutics
- WindMIL Therapeutics
- Zelluna Immunotherapy

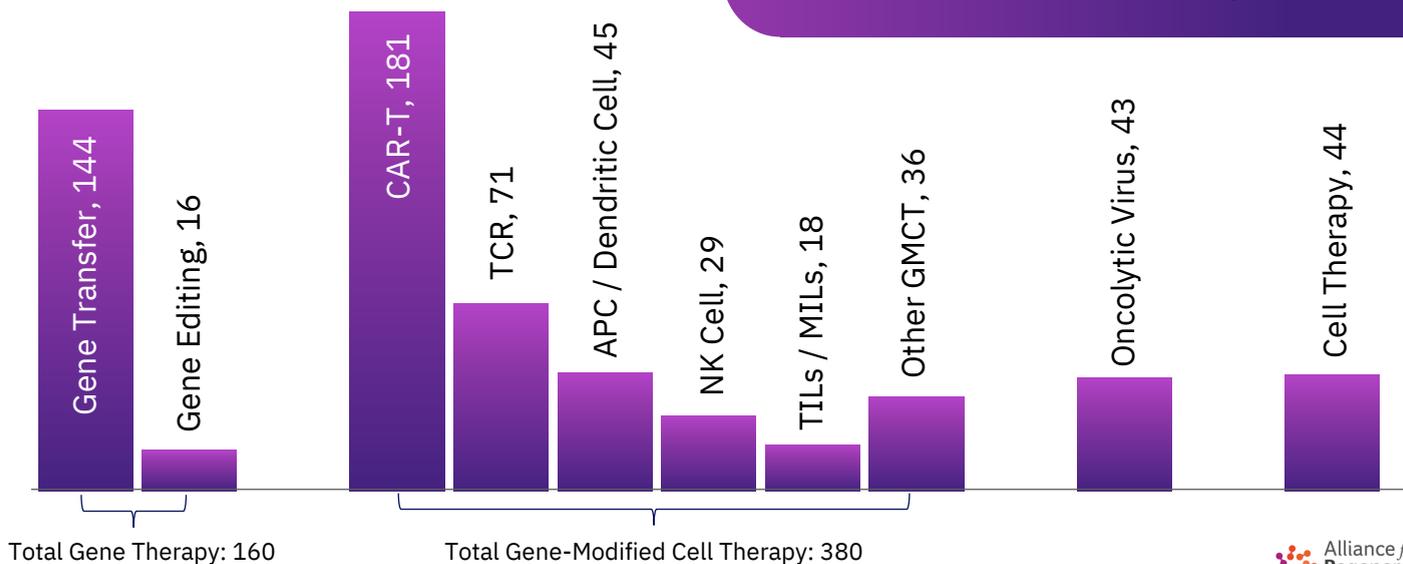
Clinical Trials in Oncology



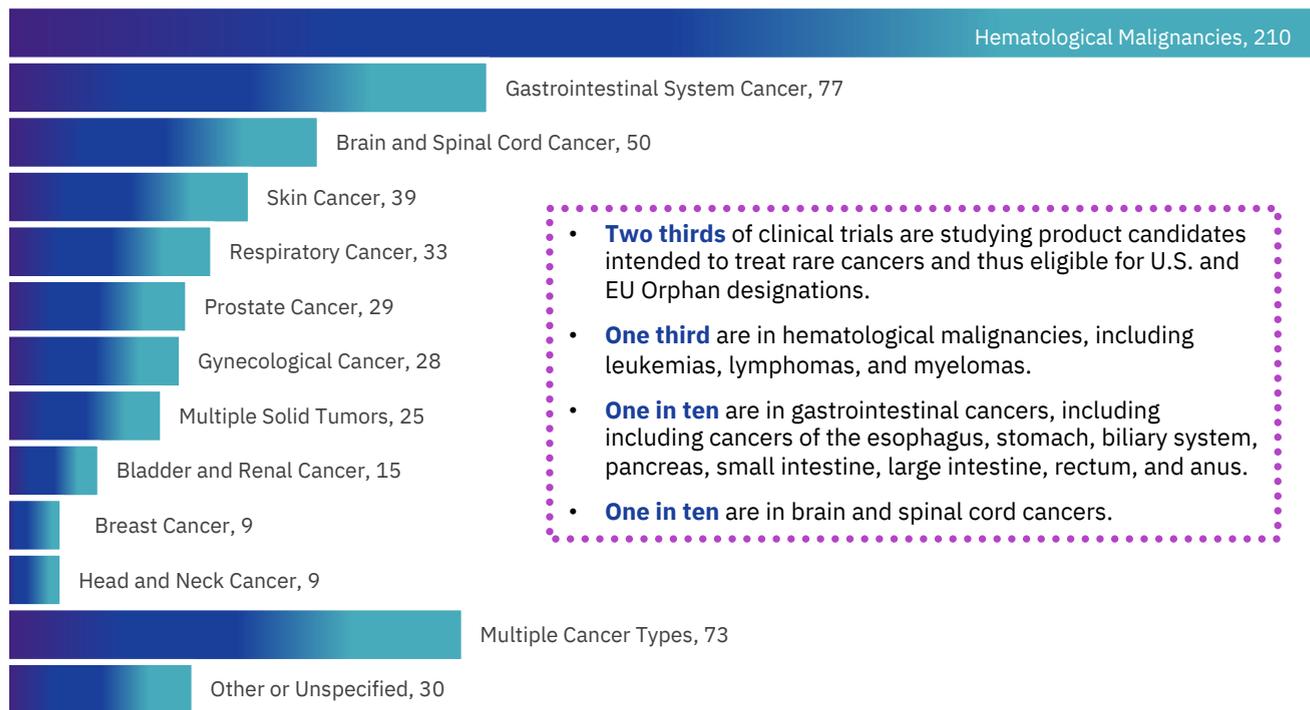
ARM currently tracks info from

627
clinical trials
in oncology

Clinical Trials by Technology



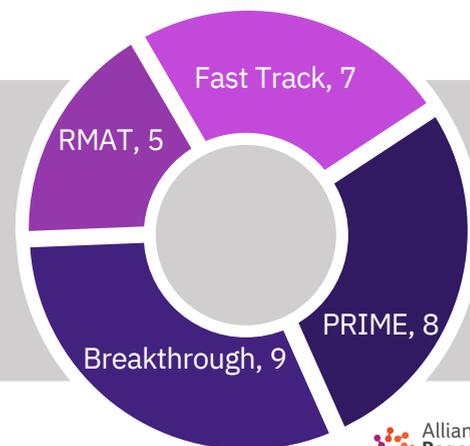
Clinical Trials by Indication



- **Two thirds** of clinical trials are studying product candidates intended to treat rare cancers and thus eligible for U.S. and EU Orphan designations.
- **One third** are in hematological malignancies, including leukemias, lymphomas, and myelomas.
- **One in ten** are in gastrointestinal cancers, including including cancers of the esophagus, stomach, biliary system, pancreas, small intestine, large intestine, rectum, and anus.
- **One in ten** are in brain and spinal cord cancers.

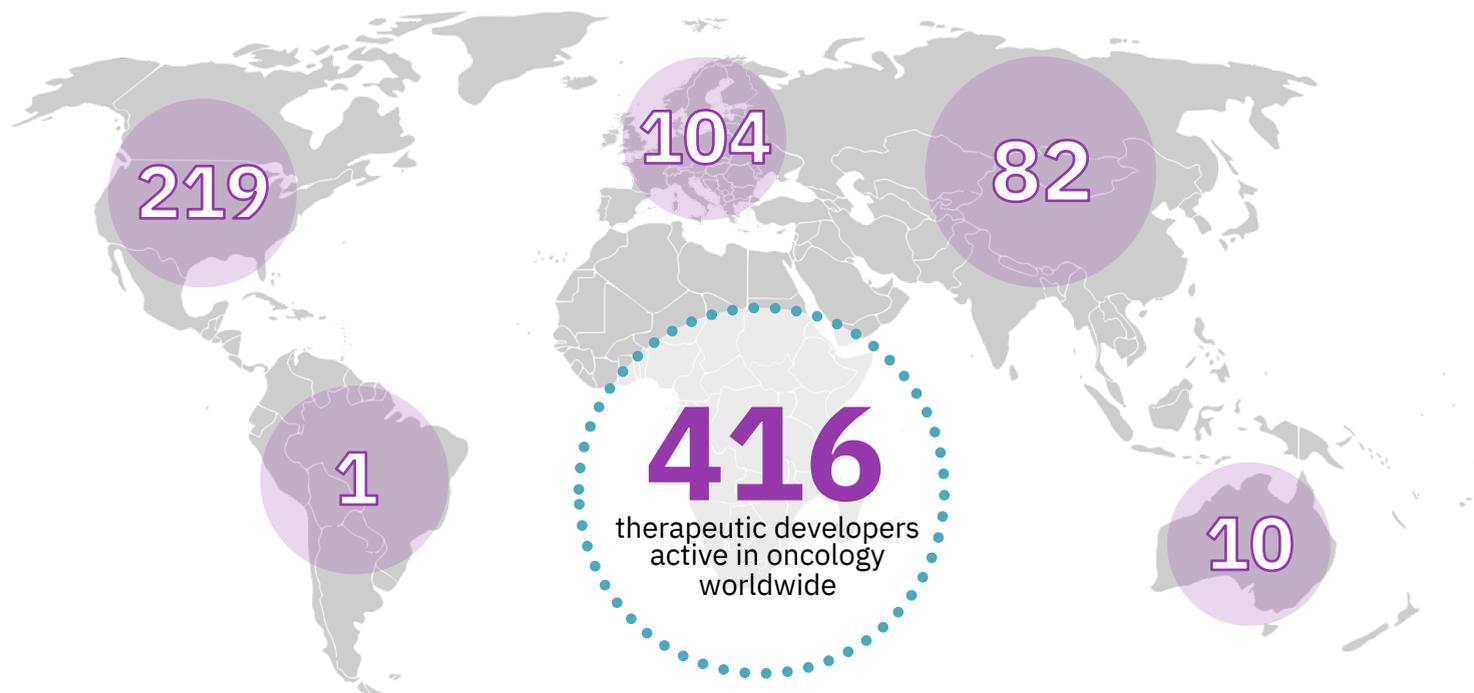
Expedited Approval Designations

Regulatory designations that provide expedited pathways to approval, including RMAT, Breakthrough, and Fast Track designations in the U.S. and PRIME designation in the EU, ensure that patients can access innovative therapies as quickly as possible.

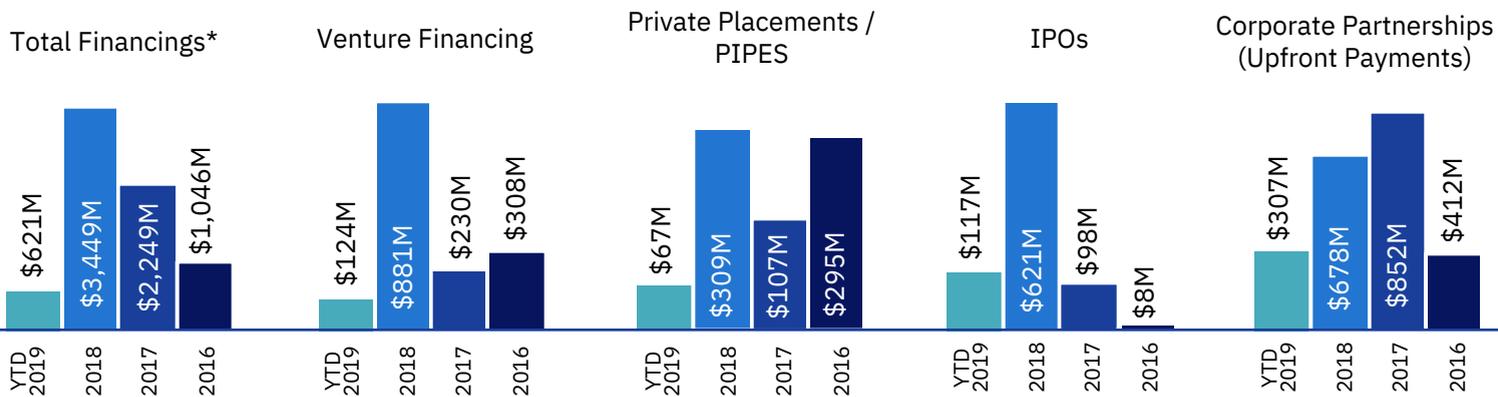


In addition to the expedited approval designations highlighted here, 136 RM/AT products in oncology have received U.S. Orphan Designation and 66 have received EMA Orphan Designation.

Global Landscape: RM/AT Developers Active in Oncology



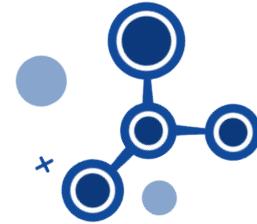
Global Regenerative Medicine Financings in Oncology



*Total financings do not include M&A activity.



Jason Slingsby
Chief Business Officer
Oxford Biomedica



Gene-modified cell therapies are becoming a commercial reality and, as the sector continues to grow, patients across the globe will benefit from access to these much-needed treatments. To address these growing needs, Oxford Biomedica has invested significantly in innovation over the last 10 years, specifically focusing on the clinical and commercial manufacture of lentiviral vectors, where we have developed proprietary vector technologies and manufacturing processes.

It's our view that the vector should not be thought of as a commodity but rather as an integral part of the overall product. While the cell manufacturing process is crucial to product activity and potential success in the clinic, and ultimately in the market place, the source, quality and embedded technology in lentiviral vectors represents a vital part of the overall gene-modified cell product. It is an exciting time to be involved in the development of such transformative technologies and we look forward to realizing the promise of this emerging field.

OXB has partnered its LentiVector platform with Novartis and is the sole commercial manufacturer of the vector for CAR-T therapy Kymriah, which is currently approved in the U.S., EU, Canada, Australia, and Japan. Beyond targeting CD19 in liquid tumors such as r/r ALL and DLBCL, we look forward to the development of CAR-T therapies targeting other antigens in liquid tumors and in more challenging solid tumor settings.

Sector Commentary

From a panel on cell therapies for solid tumors at ARM's Cell & Gene Meeting on the Med 2019:



Usman Azam
President & CEO
Tmunity Therapeutics

“No one to my knowledge has gotten to the stage where they’ve taken a TCR or CAR effectively to the clinic with a combination strategy, yet that is probably going to be the next wave of second and third generation products.”

“I think it’s going to be a painful track, it’s not going to be done overnight, it probably is going to take ten to twenty years. But I think the fundamentals in terms of synthetic biology are all coming together nicely and it’s who can combine these modalities in a safe way that gets regulators comfortable. How do you think about the CMC components of this? [...] How do regulators start to think about these combinatorial approaches? Because they are going to come sooner than we think. Is the framework in place yet for that? I’m not so sure. Say you have a base product and you add in an element – is that a new IND each time? How are you going to figure this out and speed up that process?”

“I think the beauty of this sector and this field is that we’re always pollinating and learning from each other in real time. I mean, it’s amazing when you think of where the field went from 2012 with a handful of patients that were initial CD19 proof of concepts to where the field is now. It’s only going to get better, I think, providing we’re willing to share, and I certainly feel in this sector more than others we really are willing and wanting to collaborate with others.”



Kimberly Freeman
VP, Commercial
Strategy & Planning
Adaptimmune

“I think the hurdle is the heterogeneity of all these multiple tumor types and the heterogeneity of each of the patients’ starting material, the prior therapies they’ve seen, the different modalities they’ve seen – it really impacts the outcome of these therapies. So whether or not a single antigen or the right target approach will hold true for all of the solid tumors we are exploring, I think we have yet to see that.”

“I’ve never seen this amount of collaboration, I’ve been in oncology research for 25 years. I think that whether it was monoclonal antibodies or targeted tyrosine kinase inhibitors, whatever the pathway was, there was never this amount of collaboration. [...] So I completely agree that we have to learn from each other and share the information to best move these programs forward.”



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