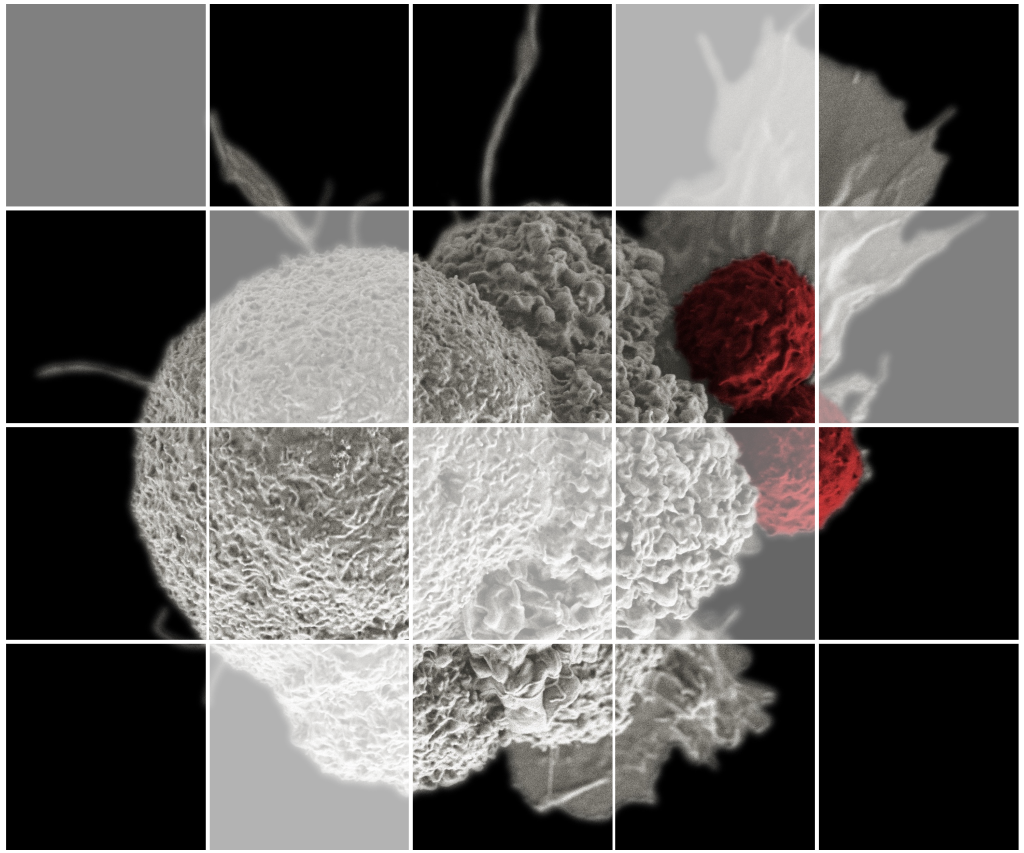
Hipolit's Biotech Breakdown:

Introduction to Cellular Immunotherapy



Hipolit Cichocki 2022.04
Dragon Gate Investment Partners LLC

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Table of Contents

The Cancer Problem

Cancer is One of the Top Three Leading Causes of Death

Worldwide, the estimated new cancer cases and deaths in 2020 were 19.3 million and 10 million. In 2040, the burden is projected increase to 28.4 million cases.

Cause of Death in the U.S. 2019	Total number of deaths	Percentage of total deaths
Heart disease	659041	23.1%
Cancer	599601	21.0%
Accidents (unintentional injuries)	173040	6.1%
Chronic lower respiratory diseases	156979	5.5%
Cerebrovascular diseases	150005	5.3%
Alzheimer's disease	121499	4.3%
Diabetes	87647	3.1%
Nephritis, nephrotic syndrome, and nephrosis (kidney disease)	51565	1.8%
Influenza and pneumonia	49783	1.7%
Intentional self-harm (suicide)	47511	1.7%

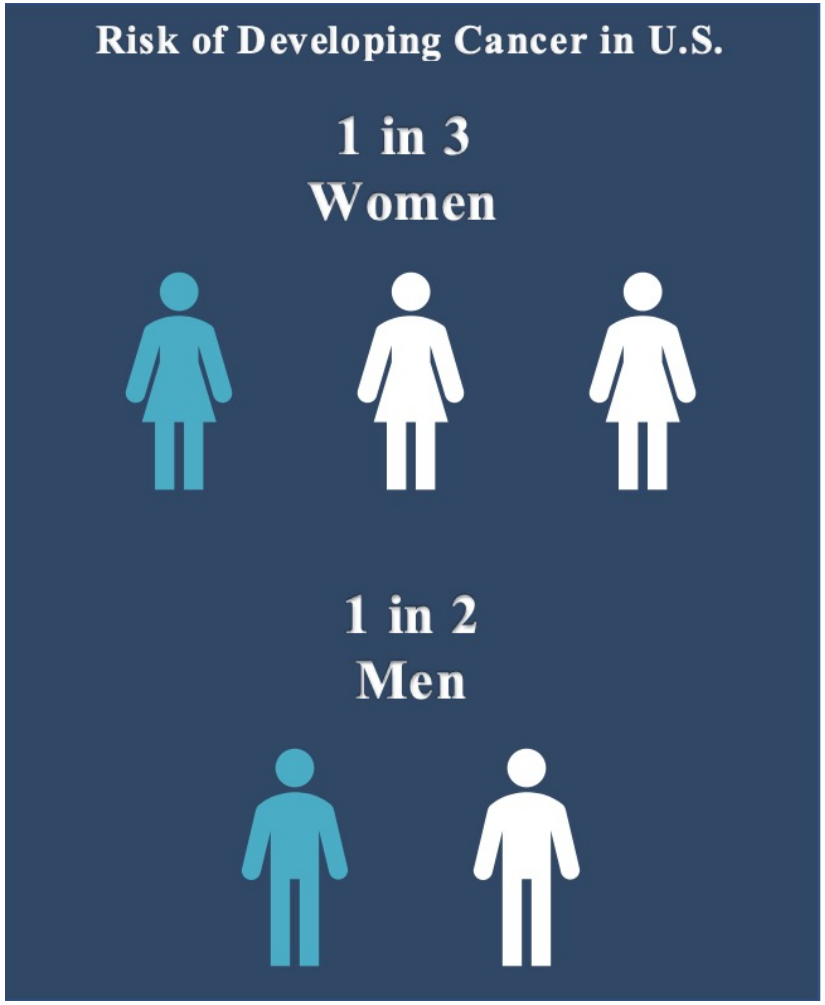
Cause of Death in the U.S. 2020	Total number of deaths	Percentage of total deaths
Heart disease	696962	20.6%
Cancer	602350	17.8%
COVID-19	350831	10.5%
Accidents (unintentional injuries)	200955	5.9%
Stroke (cerebrovascular diseases)	160234	4.7%
Chronic lower respiratory diseases	152657	4.5%
Alzheimer's disease	134242	4.0%
Diabetes	102188	3.0%
Influenza and pneumonia	53544	1.6%
Nephritis, nephrotic syndrome, and nephrosis (kidney disease)	52547	1.6%

Cause of Death in the U.S. 2021	Total number of deaths	Percentage of total deaths
Heart disease	689807	20.0%
Cancer	603150	17.5%
COVID-19	415517	12.0%
Stroke (cerebrovascular diseases)	162140	4.7%
Accidents (unintentional injuries)	148914	4.3%
Chronic lower respiratory diseases	141399	4.1%
Alzheimer's disease	118937	3.4%
Diabetes	102359	3.0%
Drug Overdose	70895	2.1%
Nephritis, nephrotic syndrome, and nephrosis (kidney disease)	54013	1.6%

Source: "The biggest causes of death in 2020", https://www.medicalnewstoday.com/articles/death-statistics-by-cause-2020. Accessed Feb. 16..; "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries", https://acsjournals.onlinelibrary.wiley.com/doi/full/10.3322/caac.21660. Accessed Feb. 8..; "Deaths Finanal Data for 2019", https://www.cdc.gov/nchs/data/nvsr/nvsr70/nvsr70-08-508.pdf. Accessed Mar. 19.; "Monthly Provisional Counts of Deaths by Select Causes, 2020-2022", https://data.cdc.gov/NCHS/Monthly-Provisional-Counts-of-Deaths-by-Select-Cau/9dzk-mvmi . Accessed Mar. 19.

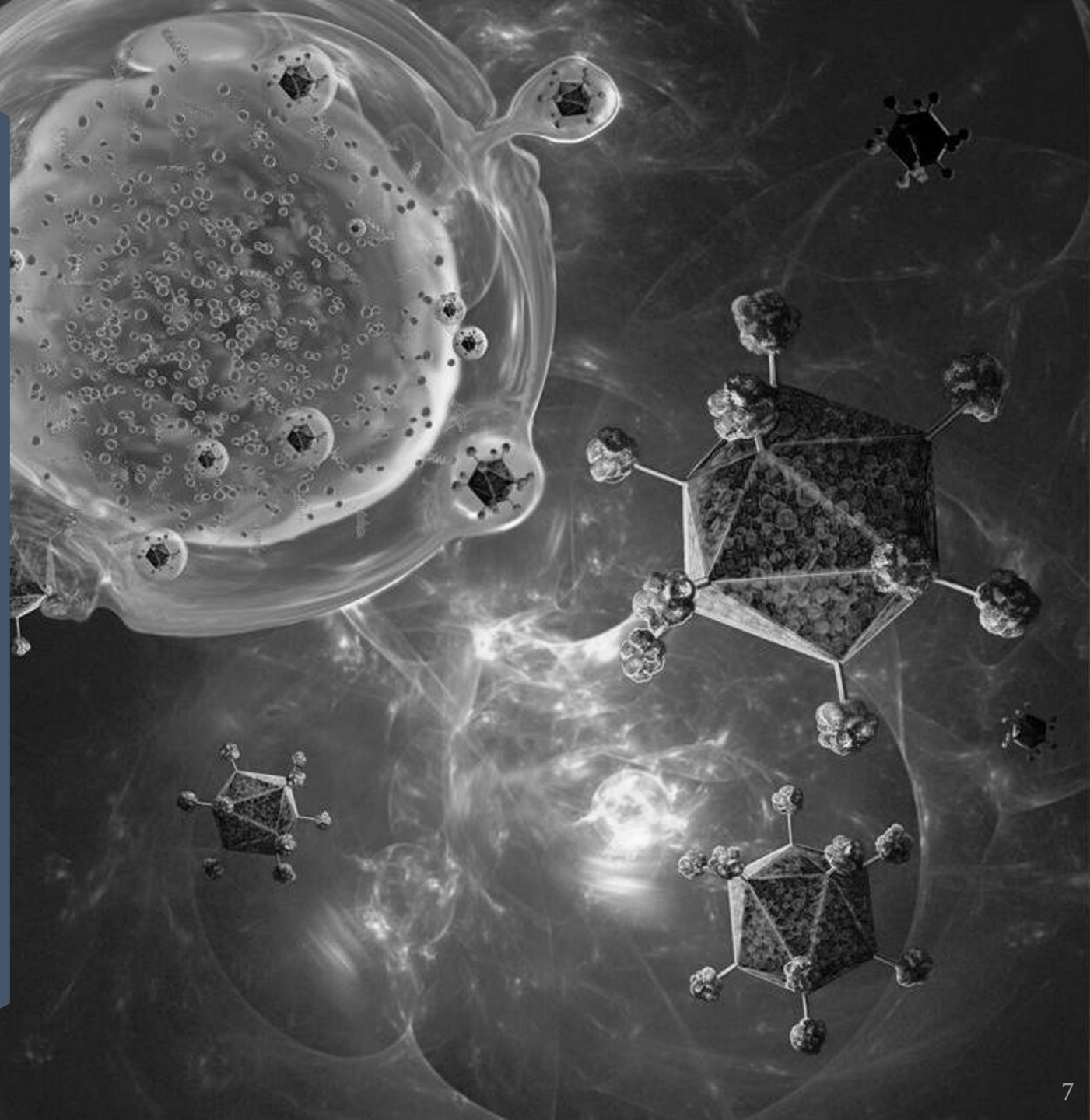
Probability of Developing Cancer

In the **United States**, the **risk of developing cancer** is **1 in 2** for **men** and **1 in 3** for **women**. The **probability** of **dying** from **cancer** was estimated to be **1 in 5**.



Source: "Lifetime Risk of Developing or Dying From Cancer", https://www.cancer.org/cancer/cancer-basics/lifetime-probability-of-developing-or-dying-from-cancer.html. Accessed Feb. 16.; "Cell Therapy Market Size to Reach USD 48,115.40 Million by 2027 at a CAGR of 25.6% | Valuates Reports", https://www.prnewswire.com/news-releases/cell-therapy-market-size-to-reach-usd-48-115-40-million-by-2027-at-a-cagr-of-25-6--valuates-reports-301402082.html. Accessed Feb. 10.

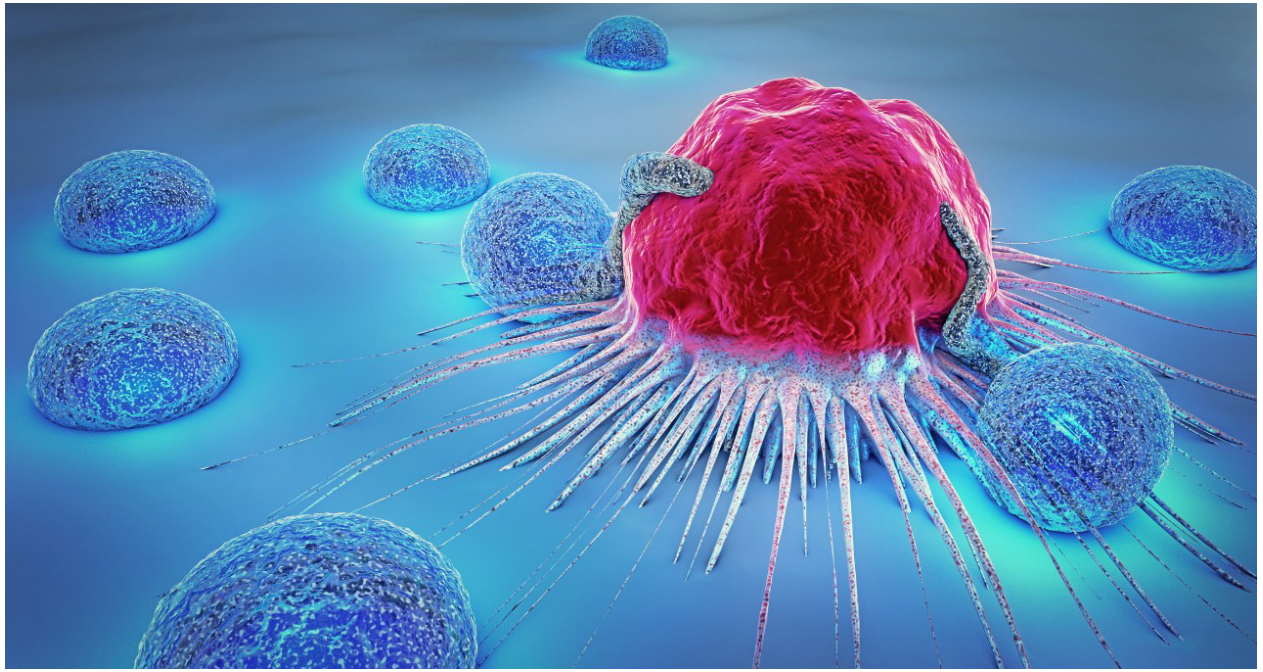
What is Cellular Immunotherapy?



Immunotherapy

Immunotherapy, or **immuno-oncology** is a form of treatment that **uses the body's own immune system to prevent, control, and eliminate cancer**.

Immunotherapy can: educate the immune system to recognize and attack cancer cells, boost immune cells to help them eliminate cancer, and provide the body with additional components to enhance the immune response.



Source: Health insure savvy.

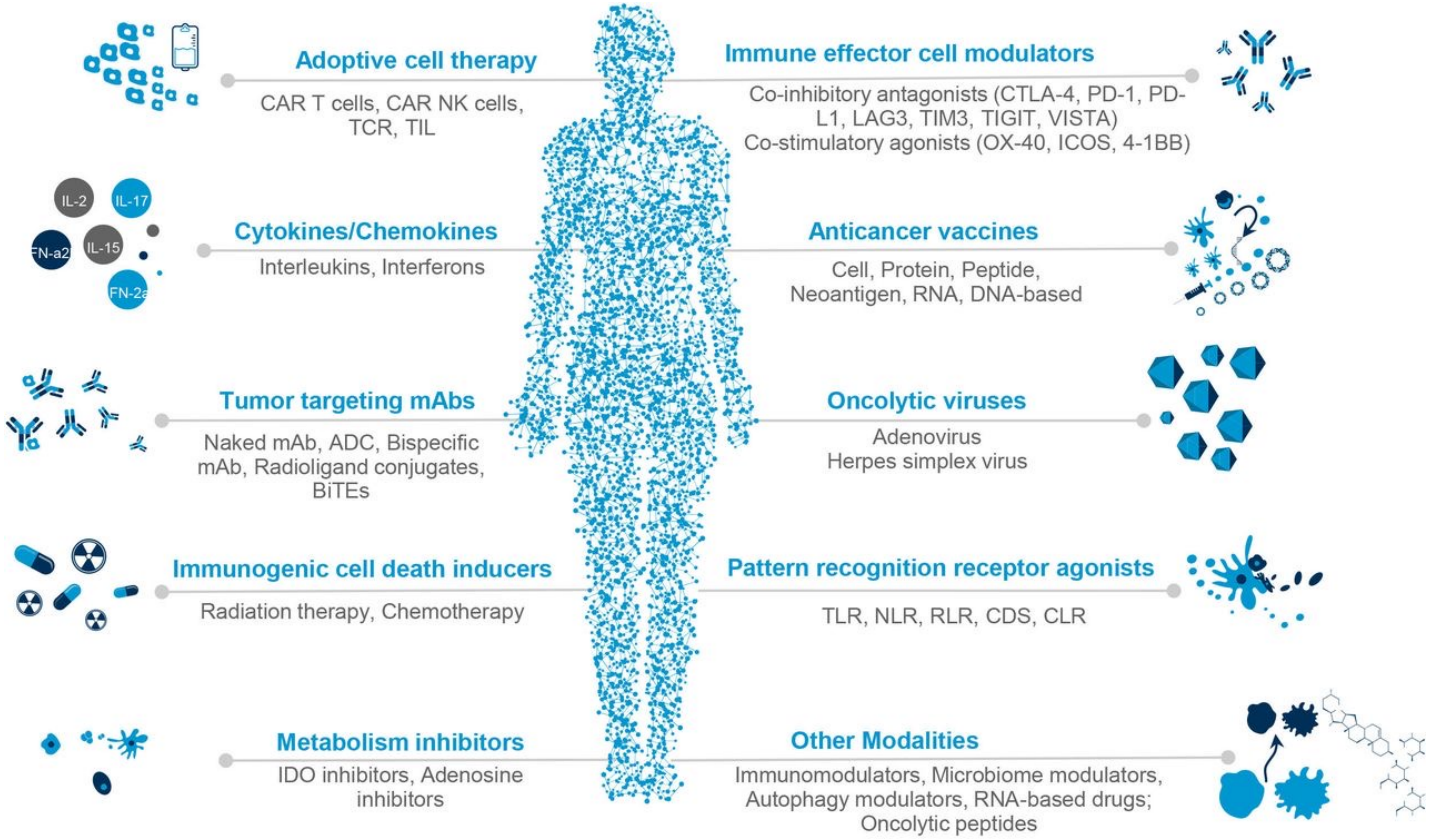
Source: "What is Immunotherapy?", https://www.cancerresearch.org/en-us/immunotherapy/what-is-immunotherapy. Accessed Feb. 7.

Immunotherapy Examples

Immunotherapy is a form of biotherapy or biological response therapy because it uses materials from living organisms to fight disease.

Some immunotherapies involve genetic engineering to enhance immune cells' cancer fighting abilities, also known as gene therapies.

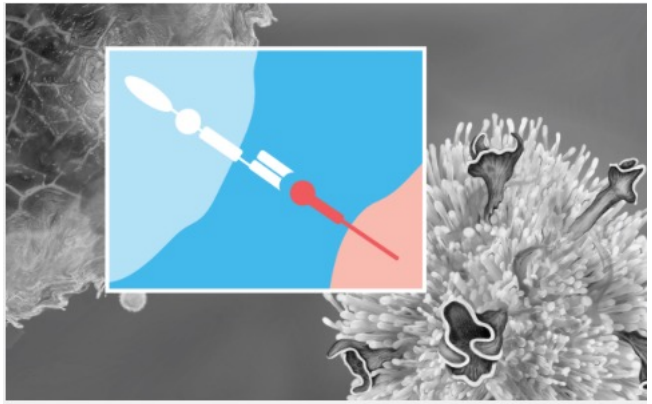
Many immunotherapies can be used in combination with other treatments such as surgery, chemo, radiation, or targeted therapies. This improves effectiveness.



Source: Journal for ImmunoTherapy of Cancer.

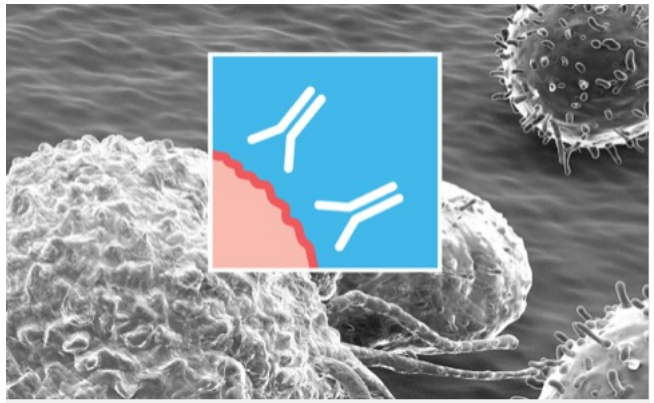
Source: "What is Immunotherapy?", https://www.cancerresearch.org/en-us/immunotherapy/what-is-immunotherapy. Accessed Feb. 7.

Immunotherapy: A Few Promising Treatments



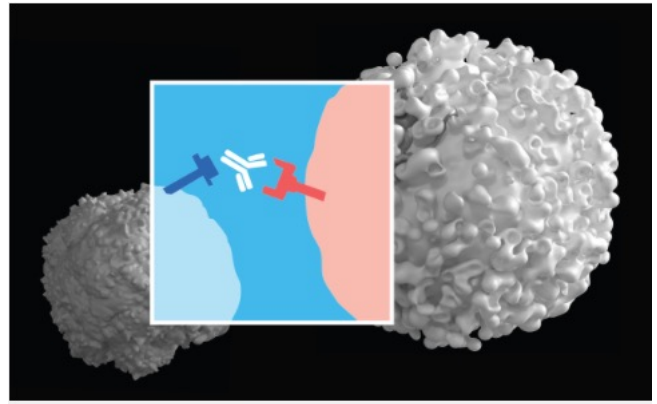
Adoptive Cell Therapy

Adoptive cell therapy reactivates, enhances, and expands naturally occurring, cancer-fighting immune cells before re-infusing them into patients.



Targeted Antibodies

Targeted antibodies can disrupt cancer cell activity and alert the immune system to attack.



Immunomodulators

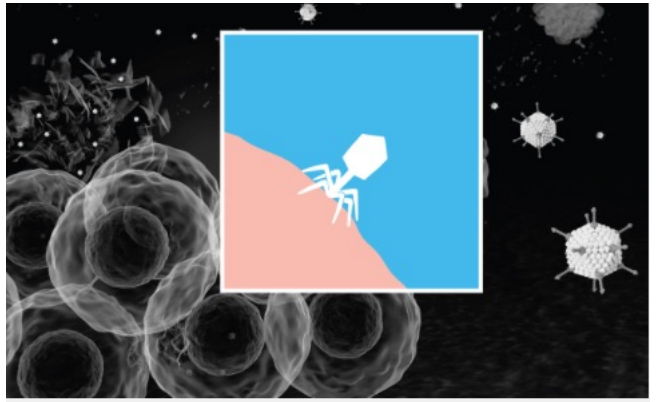
Immunomodulators manipulate the “gas pedals” and “brakes” of the immune system to fight cancer.

Source: “Immunotherapy Treatment Types”, https://www.cancerresearch.org/en-us/immunotherapy/treatment-types. Accessed Feb. 7.

Immunotherapy: A Few Promising Treatments Continued

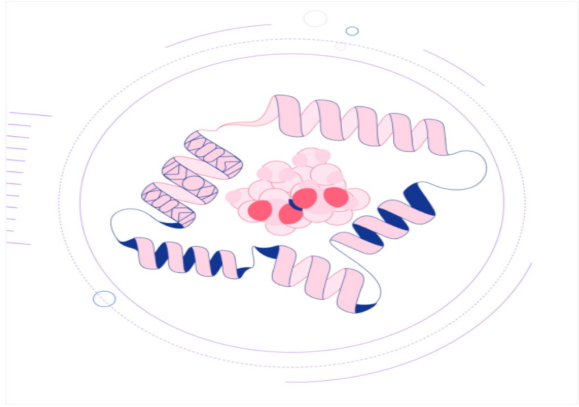
Cancer Vaccines

Two cancer vaccines, as described by, Cancer Research Institute, are preventative which can protect against cancer development or therapeutic which can stimulate immune responses against tumors.



Oncolytic Virus Therapy

Oncolytic virus therapy uses modified viruses that can infect and destroy tumors



AlphaFold 2

AlphaFold is system created by DeepMind utilizing AI that confidently predicts accurate structures for most proteins - and knows when it is wrong.

Source: "Immunotherapy Treatment Types", https://www.cancerresearch.org/en-us/immunotherapy/treatment-types. Accessed Feb. 7.; "AlphaFold2", https://predictioncenter.org/casp14/doc/presentations/2020_12_01_TS_predictor_AlphaFold2.pdf. Accessed Mar. 22.

Adoptive Cell Therapy

Cellular immunotherapy also known as adoptive cell therapy, **uses the body's own immune cells to fight cancer**. This can involve direct isolation or simple expansion of these cells.

Other methods genetically engineer the cells to enhance cancer fighting ability. The **Immune system possesses the capability to detect and eliminate infected, damaged, and cancerous cells**. Killer T cells and other immunotherapies bind to markers, also known as antigens, on the surface of cancer cells.

Treatment options are considered for both solo and combination treatment plans. Adoptive therapies are continually being improved and constantly evolve.

Side effects vary based on treatment, location, and type of cancer. Overreactive immune response can lead to excessive inflammation via cytokine storm. Neurotoxicity can occur from inflammation in brain. Side effects can be mild to moderate and can be potentially life- threatening. In most cases side effects can be safely managed when recognized and addressed early. Immunotherapies using T cells are becoming a huge trend in cancer treatment, especially CAR T.

Source: "Adoptive Cell Therapy", https://www.cancerresearch.org/immunotherapy/treatment-types/adoptive-cell-therapy. Accessed Feb. 7.

Cancer Immunotherapy and Cell Therapy Market

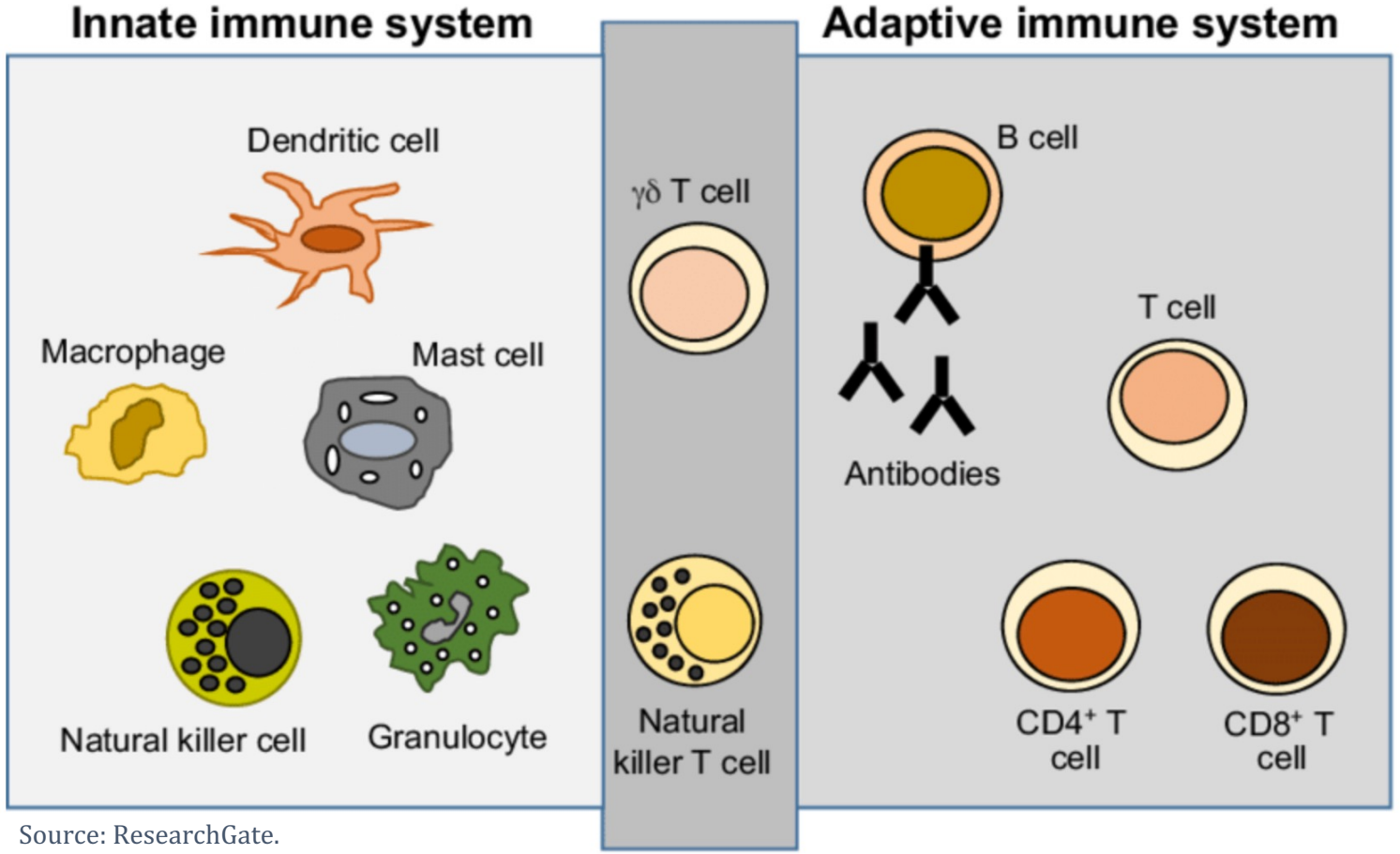
Immunotherapy: The cancer immune therapy is projected to surpass $310B by 2031. In 2021 the market was valued at $119.4B

Cell Therapy: The cell therapy market was approximately $7.75B and expected to grow at a CAGR of 25.6%, reaching approximately $48.1B by 2027. This market includes therapies for malignancies, musculoskeletal disorders, autoimmune disorders, dermatology, and others.

Source: "Cancer Immunotherapy Market", https://www.factmr.com/report/4367/cancer-immunotherapy-market. Accessed Feb. 9.; "Cell Therapy Market Size to Reach USD 48,115.40 Million by 2027 at a CAGR of 25.6% | Valuates Reports", https://www.prnewswire.com/news-releases/cell-therapy-market-size-to-reach-usd-48-115-40-million-by-2027-at-a-cagr-of-25-6--valuates-reports-301402082.html. Accessed Feb. 9.

Immune System

- **The Immune system comprised of two parts, innate and adaptive.** Innate and adaptive immunity work closely together and take on different tasks.



Source: ResearchGate.

Source: "The innate and adaptive immune systems", https://www.ncbi.nlm.nih.gov/books/NBK279396/. Accessed Feb. 16.

Innate Immunity

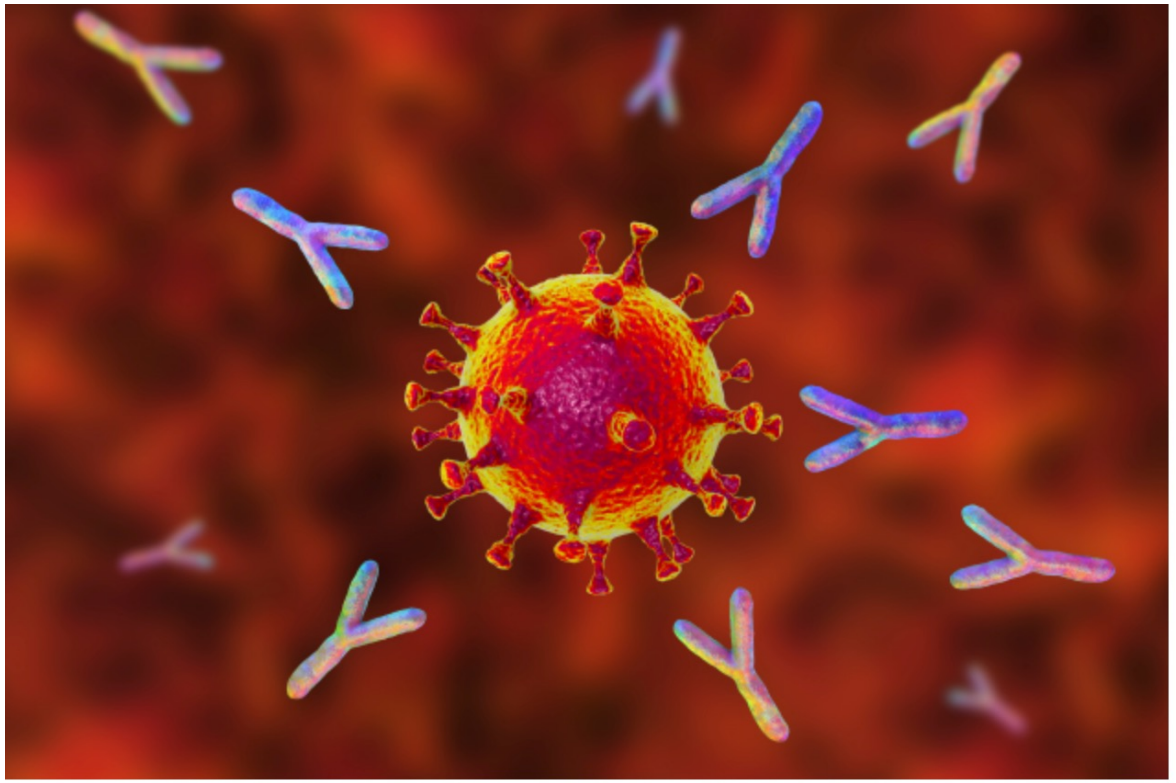
- **Innate Immunity is the first line of defense against germs entering the body.**
  - Innate immunity consists of skin, mucous membranes, immune cells, and proteins. When germs pass skin and mucous membranes, special immune cells and proteins activate.
- **Innate immunity responds the same way to all germs and foreign substances, known as nonspecific. It only has limited power to stop germs from spreading.**
- **Examples of Activation**
  - When skin infected, immune cells release substances to make blood vessels wider and more permeable leading to area around infection to be inflamed. Scavenger cells (phagocytes) can stop bacteria and viruses right away.
  - Several proteins (enzymes) activate like a chain reaction, allowing immune response to escalate quickly. Tasks include marking germs as targets for scavenger cells, attracting other immune cells from blood stream, destroy bacterial cell walls to kill them, and fight viruses by destroying viral envelope or cells that have been infected by virus.

Source: SkinKraft.

Source: "The innate and adaptive immune systems", https://www.ncbi.nlm.nih.gov/books/NBK279396/. Accessed Feb. 16.

Adaptive Immunity

- **Adaptive immunity takes over if innate cannot destroy the germs**.
- It targets the germ causing infection by first identifying it. This makes adaptive response slower but more accurate than innate immune response. One advantage adaptive immunity is remembering germs, leading to quicker adaptive response if the known germ is encountered.
- **It consists of T lymphocytes, B lymphocytes, and antibodies.**



Source: CDC.

Source: "The innate and adaptive immune systems", https://www.ncbi.nlm.nih.gov/books/NBK279396/. Accessed Feb. 16.

Introduction to T Cells & B Cells

Lymphocytes can be further differentiated into B cells, T cells, and natural killer cells.

While natural killer cells recognize general signals of immune stress such as inflammation, B and T cells recognize foreign antigens specifically via hypervariable B cell and T cell receptors (BCRs and TCRs).

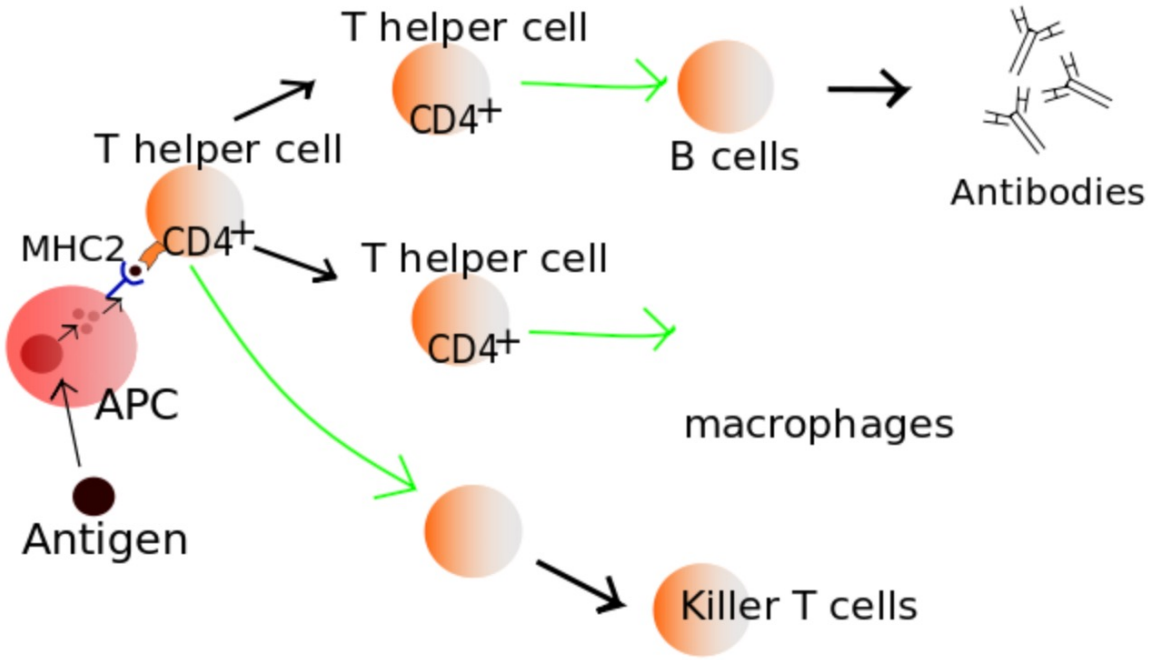
B cells recognize free, unprocessed antigens.

T cells recognize antigens within a complex of cell surface proteins called the major histocompatibility complex (**MHC**) on the surface of antigen-presenting cells (APCs).

Source: "B cell and T cell structure and function", https://irepertoire.com/t-cell-and-b-cell-overview/. Accessed Feb. 16.

T Cells: Three Main Jobs

- T Cells **use chemical messengers** to activate other immune system cells in order **to start the adaptive immune system** (T helper cells).
- T cells can **detect cells infected by viruses or tumorous cells and destroy them** (cytotoxic T cells).
- Some T helper cells become **memory T cells** after the infection has been defeated. They can "**remember" which germs were defeated** and are then ready to activate the adapted immune system quickly if there is another infection.

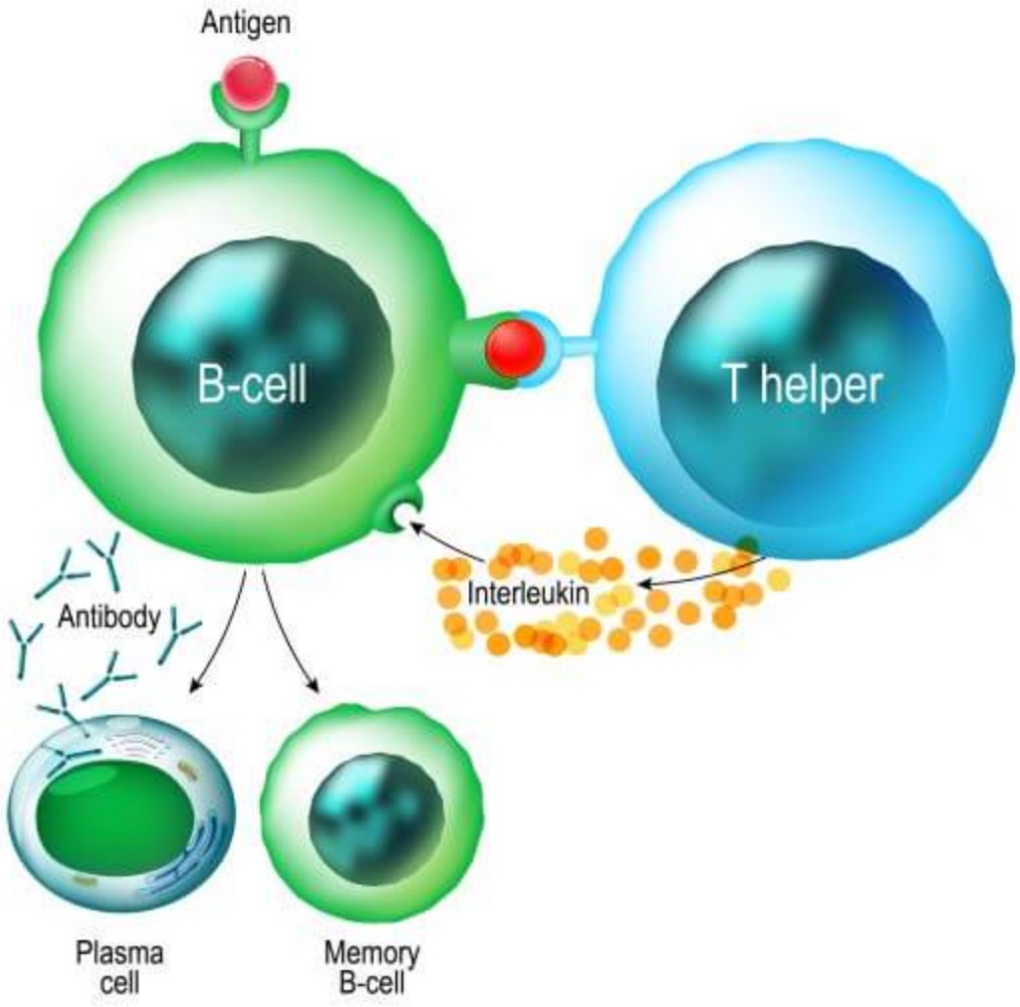


Source: Wikimedia Commons

Source: "B cell and T cell structure and function", https://irepertoire.com/t-cell-and-b-cell-overview/. Accessed Feb. 16.

B Cells

- **B cell activated through T cell dependent or T cell independent activation**.
  - In dependent, they absorb antigen on surface using MHC.
  - **Helper T** can recognize antigens via MHC and activate B cells.
  - In independent B cell must encounter antigen and receive danger signal.
- **Activated B cell can either become memory B or effector B.**
  - **Effector B cells, or plasma cells produce antibodies** that tag or alarms to target invading agents for destruction by other immune agents such as macrophage.
  - **Memory B help immune system to have a quicker response to same agent in the future.**

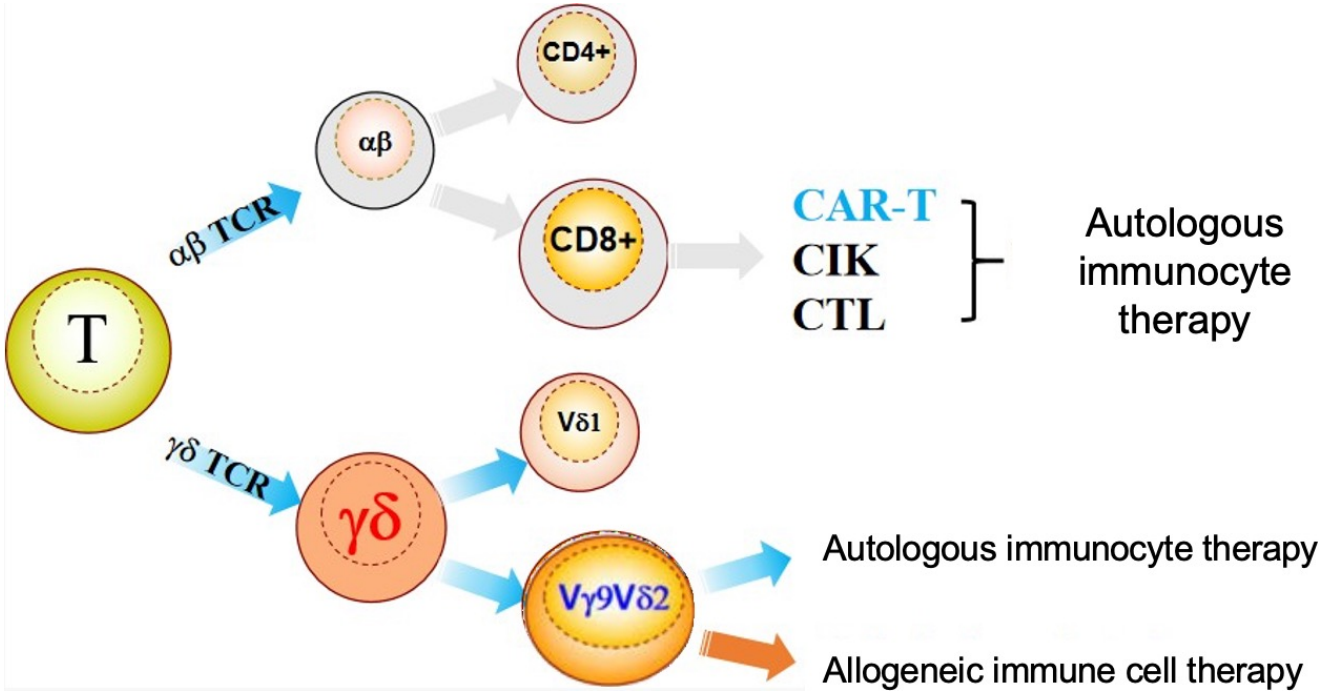


Source: Biology Dictionary

Source: "B cell and T cell structure and function", https://irepertoire.com/t-cell-and-b-cell-overview/. Accessed Feb. 16.

γδ T Cells

- **γδ T cells account for 1-5% of overall T cell population and have been described as link between adaptive and innate.**
  - These cells can undergo V-(D)-J segment rearrangement for adaptive, antigen specific response.
- **Direct activation possible** via recognition of pathogen associated or danger molecule patterns, particularly natural phospho-antigens
  - Via gamma delta TCR or non TCR proteins, acting independently or together to activate gamma delta t effector functions
- Like helper T, gamma delta T secrete particular effector cytokines in a subtype-and context-specific manner, however, unlike alpha beta T cells, most delta gamma T cells lack CD4 and CD8 and share several markers associated with NK cells or APC's such as Fc gamma RIII/CD16 and Toll-like receptors.



Source: Beroni Group

Source: "gamma delta T Cells", https://www.rndsystems.com/research-area/gamma-delta-t-cells, Accessed Feb. 16.

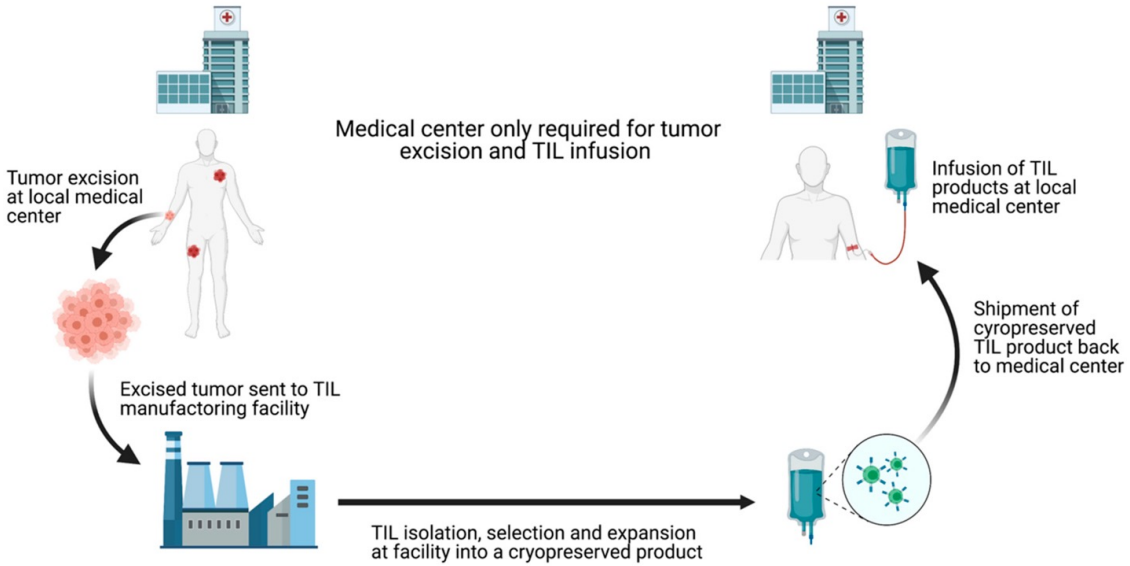
Types of Cellular Immunotherapies

Cellular Immunotherapies

- Tumor-Infiltrating Lymphocyte (TIL) Therapy
- Engineered T Cell Receptor (TCR) Therapy
- Chimeric Antigen Receptor (CAR) T Cell Therapy
- Natural Killer (NK) Cell Therapy
- Gamma Delta T (γδ T) Cell Therapy

Tumor-Infiltrating Lymphocyte (TIL) Therapy

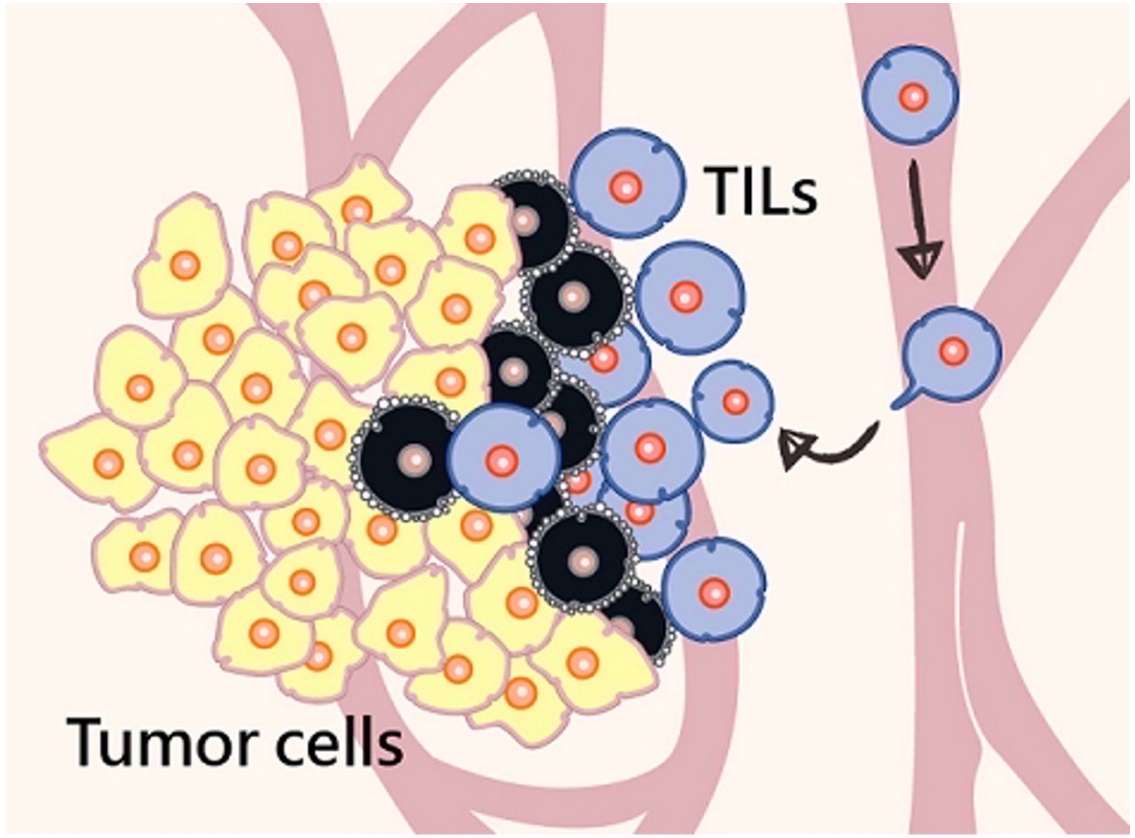
- **The process to create** tumor-infiltrating lymphocyte (**TIL**) therapy **takes naturally occurring T cells that have infiltrated a patients' tumors and activates and expands them**. A large dose of **these activated T cells is infused into the patient where they seek and destroy tumors**.
- **Advantages** include an additional line of treatment when other options are exhausted, in some cases TIL therapy may offer complete and lasting control of cancer, and it's a one-time therapy.
- **Disadvantages** include it is expensive, labor intensive to create, and may require long hospital stays (up to a few weeks). It is also challenging to receive with approval process and it's a last attempt at tumor control.



Source: MDPI.

Source: "Adoptive Cell Therapy TIL, TCR, CAR T, AND NK CELL THERAPIES", https://www.cancerresearch.org/en-us/immunotherapy/treatment-types/adoptive-cell-therapy#til. Accessed Feb. 8.; "Tumor-Infiltrating Lymphocyte Therapy", https://www.verywellhealth.com/tumor-infiltrating-lymphocyte-therapy-5079767. Accessed Feb. 8.

Tumor-Infiltrating Lymphocyte (TIL) Therapy Continued



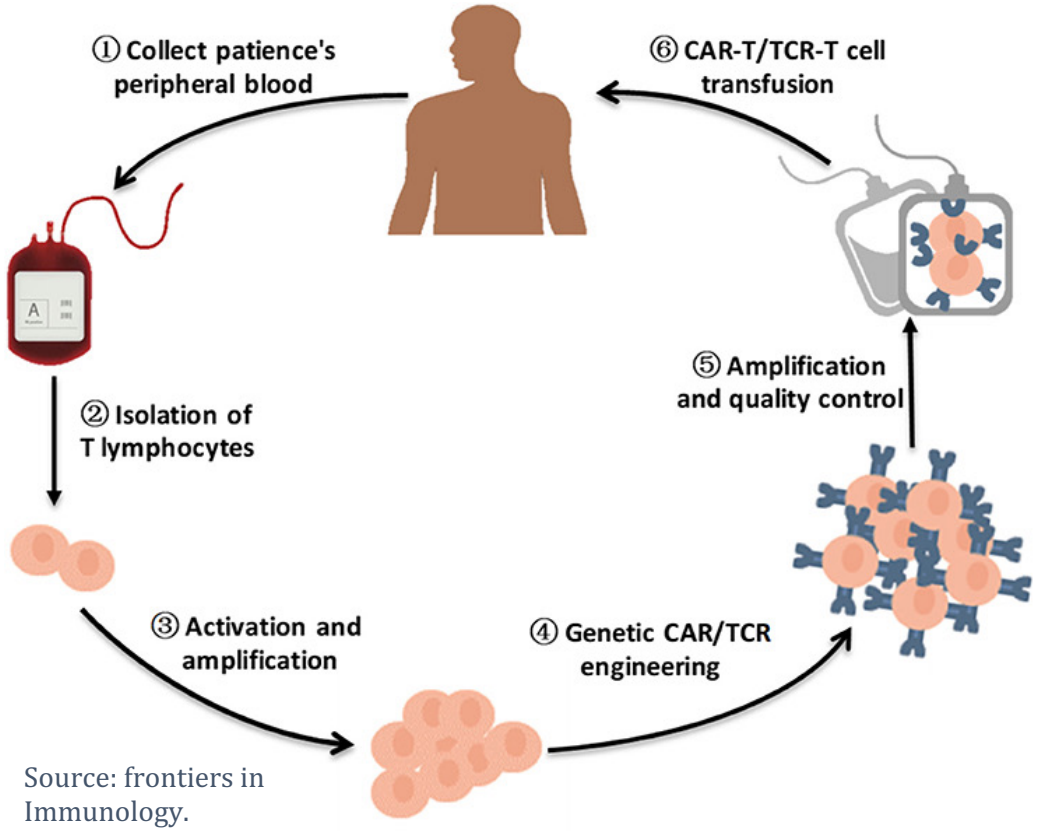
Source: Arigo Bi.

- **TIL therapy appears to have a good safety profile**. Often side effects emerge from the co-treatments such as chemo. High grade toxicity is very rare with treatment and difficult to tell apart from residual IL-2.
- The fastest **production time** is 22 days by Iovance, while others report 6-8 weeks minimum and significantly longer for tumor-specific or tumor-neoantigen-specifics
- **Most common symptoms include** short term fever, chills, and shortness of breath. Later symptoms may include autoimmune conditions, but it is unknown if TIL therapy is related.

Source: "Cell Therapy With TILs: Training and Taming T Cells to Fight Cancer", https://www.frontiersin.org/articles/10.3389/fimmu.2021.690499/full. Accessed Feb. 8.; "Tumor-Infiltrating Lymphocyte Therapy", https://www.verywellhealth.com/tumor-infiltrating-lymphocyte-therapy-5079767. Accessed Feb. 8.

Engineered T Cell Receptor (TCR) Therapy

- Some patients don't have T cells that have recognized a tumor, while other patient T cells may not be able to be activated and expanded sufficiently to reject tumors.
- **T cells are taken from patients and instead of activation and expansion, they're equipped with a T cell receptor that allows targeting of specific cancer antigens.** This process allows for further personalization of treatment by allowing doctors to select target and type of T cell.
- **One benefit** is this therapy is **more versatile and can treat more cancers when compared to CAR T**. This treatment faces the same issues as CAR T in terms of difficulty and expenses of cell separation. CAR T is a form of TCR but the main difference is the programed receptors. TCR relies on MHC to mark cancer with recognizable antigens.

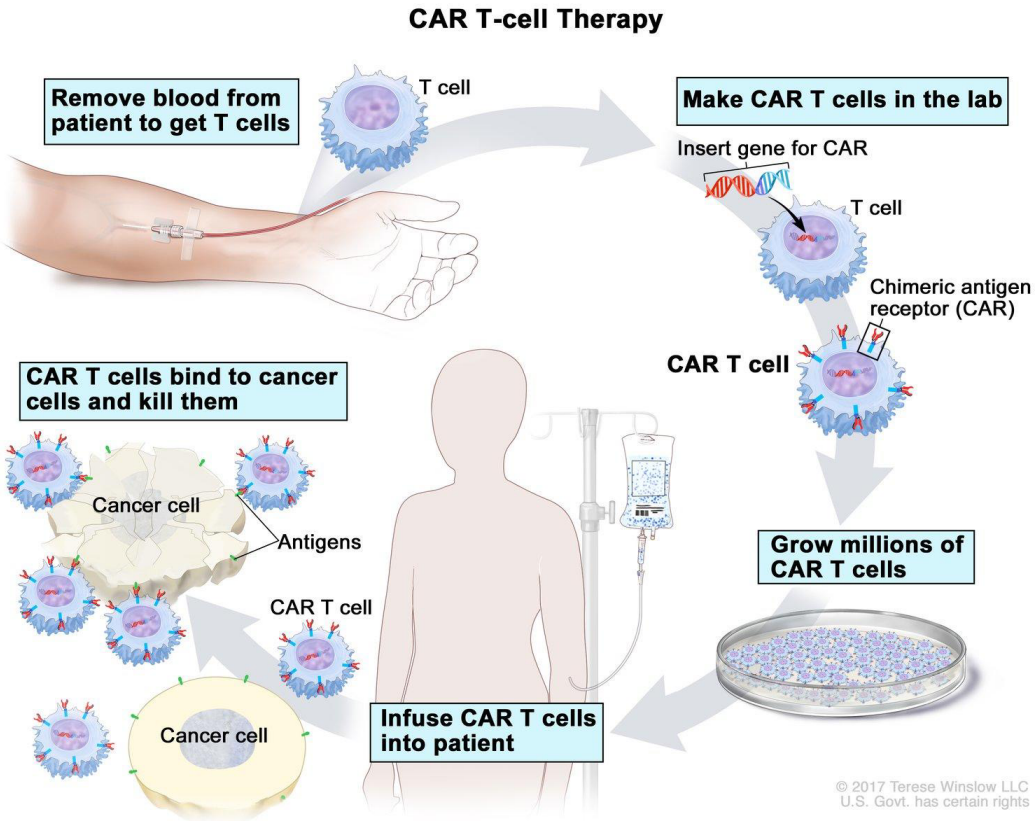


Source: frontiers in Immunology.

Source : "Adoptive Cell Therapy TIL, TCR, CAR T, AND NK CELL THERAPIES", https://www.cancerresearch.org/en-us/immunotherapy/treatment-types/adoptive-cell-therapy#til. Accessed Feb. 8.; "TCR Vs. Car-T: What is CAR -T Cell, TCR Therapy, and What are They Used For?", https://www.akadeum.com/blog/car-t-cell-therapy-vs-tcr/. Accessed Feb. 8.

Chimeric Antigen Receptor (CAR) T Cell Therapy

- **CAR T cells are created by inserting synthetic receptor into T cells**. This provides the **advantage of binding to cancer even if antigens aren't present on the surface of tumor cells via MHC proteins** (major histocompatibility complex). This advantage makes more cancer vulnerable to attack.
- CAR T can only recognize antigens naturally expressed on surface of cancer cells, so TCR therapy offers a larger range of potential antigen targets.
- **CAR T is a form of TCR therapy**, but CAR receptors target naturally occurring antigens. While **CAR T treats fewer cancers but has the potential to help with many more variations**. CAR T is costly and time consuming to produce.

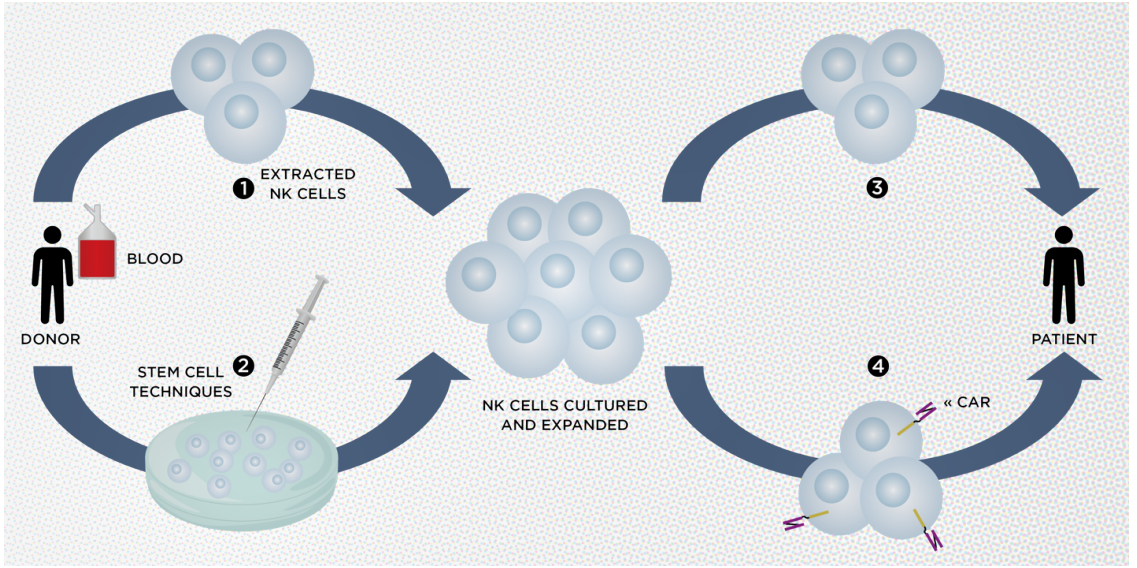


Source: National Cancer Institute.

Source : "Adoptive Cell Therapy TIL, TCR, CAR T, AND NK CELL THERAPIES", https://www.cancerresearch.org/en-us/immunotherapy/treatment-types/adoptive-cell-therapy#til. Accessed Feb. 8.; "TCR Vs. Car-T: What is CAR -T Cell, TCR Therapy, and What are They Used For?", https://www.akadeum.com/blog/car-t-cell-therapy-vs-tcr/. Accessed Feb. 8.

Natural Killer (NK) Cell Therapy

- Natural killer cell therapy uses **natural killer cells to combat cancer**. NK is part of immune system and attack germs and malignant cells.
- **NK cell therapy is not tailored to specific antigen**. NK cell therapy an destroy any abnormal cell but the cells are short lived.
- **To increase efficacy cells are enhanced to improve stamina and longevity, along with some are enhanced with CARS**.
- Advantages include no need to be genetically engineered to recognize cancer, faster to prepare, option for chemo resistant acute myeloid leukemia, limited side effects.

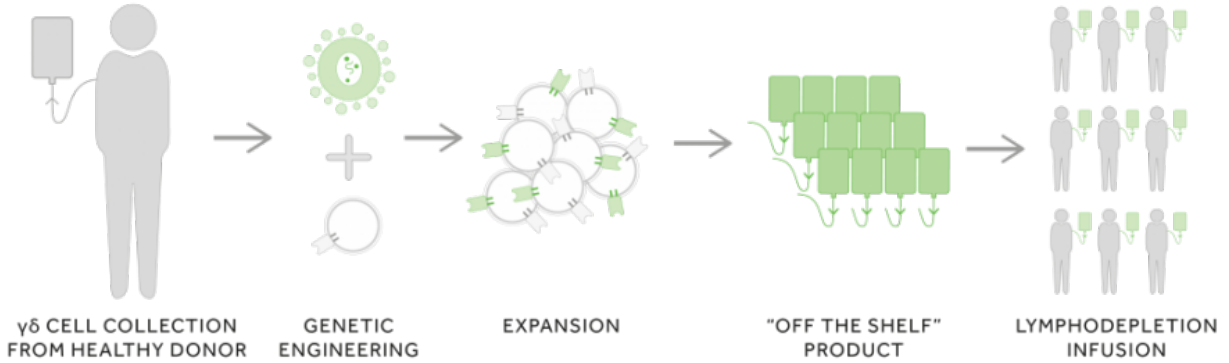


Source: The Scientist.

Source: "Natural Killer Cell Therapy", https://siteman.wustl.edu/treatment/specialized-programs/stem-cell-transplant-and-cellular-therapies-center/natural-killer-cell-therapy/, Accessed Feb. 7.

Gamma Delta T (γδ T) Cell Therapy

- **Gamma Delta T** is a new wave of immunotherapy that **has the potential to treat cancer with stronger responses and fewer side effects**. It is a **rare type of T-cell that accounts for about 5% of T-cells in body**. CAR T can come with strong and potentially deadly side effects and limited solid tumor targeting
- **Gamma delta T is part of the innate immune response, essentially pre-programed to locate and destroy cells stressed by cancer associated transformation**. Unmodified alpha beta T cells do not possess this capability. Gamma delta T cells offer a quick response in the body's immune system

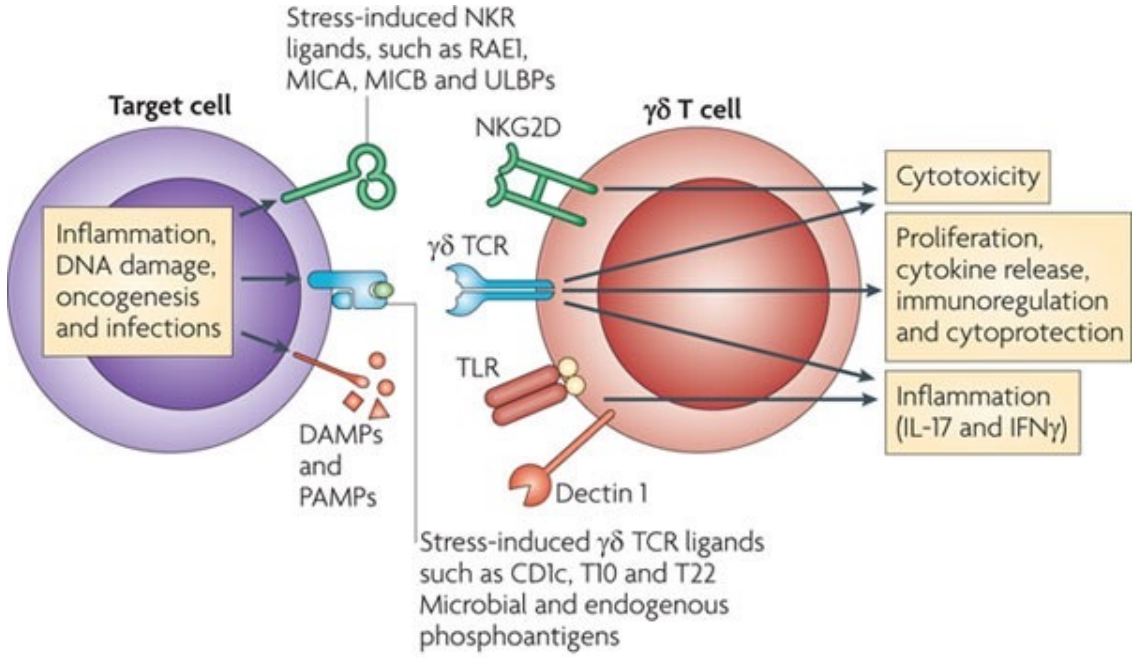


Source: Immatics.

Source:"Gamma Delta T Cells: A New Hope Against Cancer", https://www.labiotech.eu/in-depth/gamma-delta-t-cells-cancer/. Accessed Feb. 10.

Gamma Delta T Cell Therapy Continued

- Companies are researching ways to modify these gamma delta t cells in order to super charge the innate response.
- **One benefit of this is that these only target cells that have undergone cancer transformation**. This allows for large doses without the consequence of healthy cells being targeted.
- These cells **don't require donor compatibility to recognize the cancer antigen, which could lead to off the shelf treatment option**, potentially making this treatment faster to receive and more affordable.
- Gamma delta T cells can recognize antigens other than peptides, expanding the range of targets that can be used to kill a tumor.



Source: Nature Reviews Immunology.

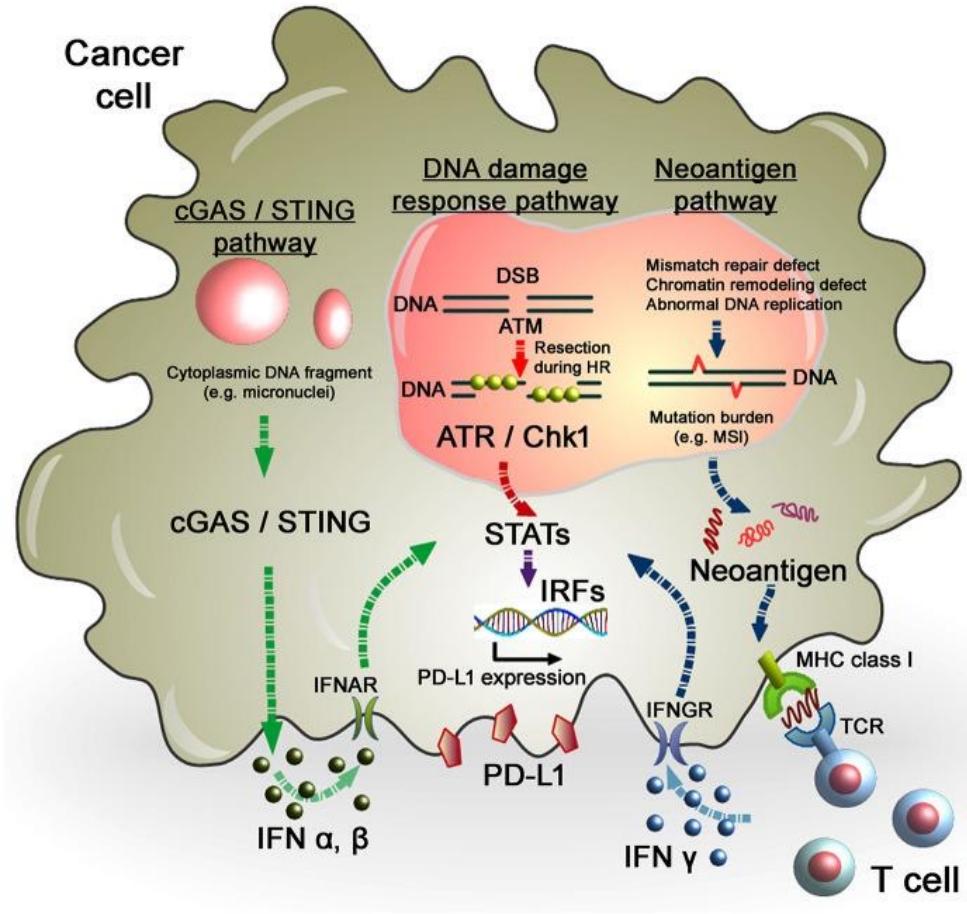
Source:"Gamma Delta T Cells: A New Hope Against Cancer", https://www.labiotech.eu/in-depth/gamma-delta-t-cells-cancer/. Accessed Feb. 10.

Interesting γδ T Research

STING and DMXAA

- STING is a pattern recognition receptor (PRR), which is expressed in a variety of endothelial, epithelial, and hematopoietic stem cells.
  - It is an interferon gene activator and is considered a linker molecule that plays an important role in antiviral immunity.
  - Studies have shown STING causes the release and production of cytokines that cause inflammation progression and tumor growth.
  - APCs phagocytose dead tumor cells, causing STING-dependent cytokines to be produced in phagocytes, facilitating cross presentation and anti-tumor CTL response.
  - Sting agonists have shown strong anti-tumor activity.

- In 2012, DMXAA (5,6-Dimethylxanthene-4-acetic acid) was first shown to be an agonist of the murine interferon gene-stimulating protein STING.
  - This activation of the STING pathway was shown to induce M2 macrophages to produce type I interferons, enhancing the antiviral effect at the level of innate immunity.



Source: Beroni Group

Source: "Clinical exploration and industrial transformation of allogeneic γδ T cells against solid tumors ", Beroni Group PPT Accessed Apr. 18.

Gamma Delta T Anti Tumor Response Enhanced by STING

Background

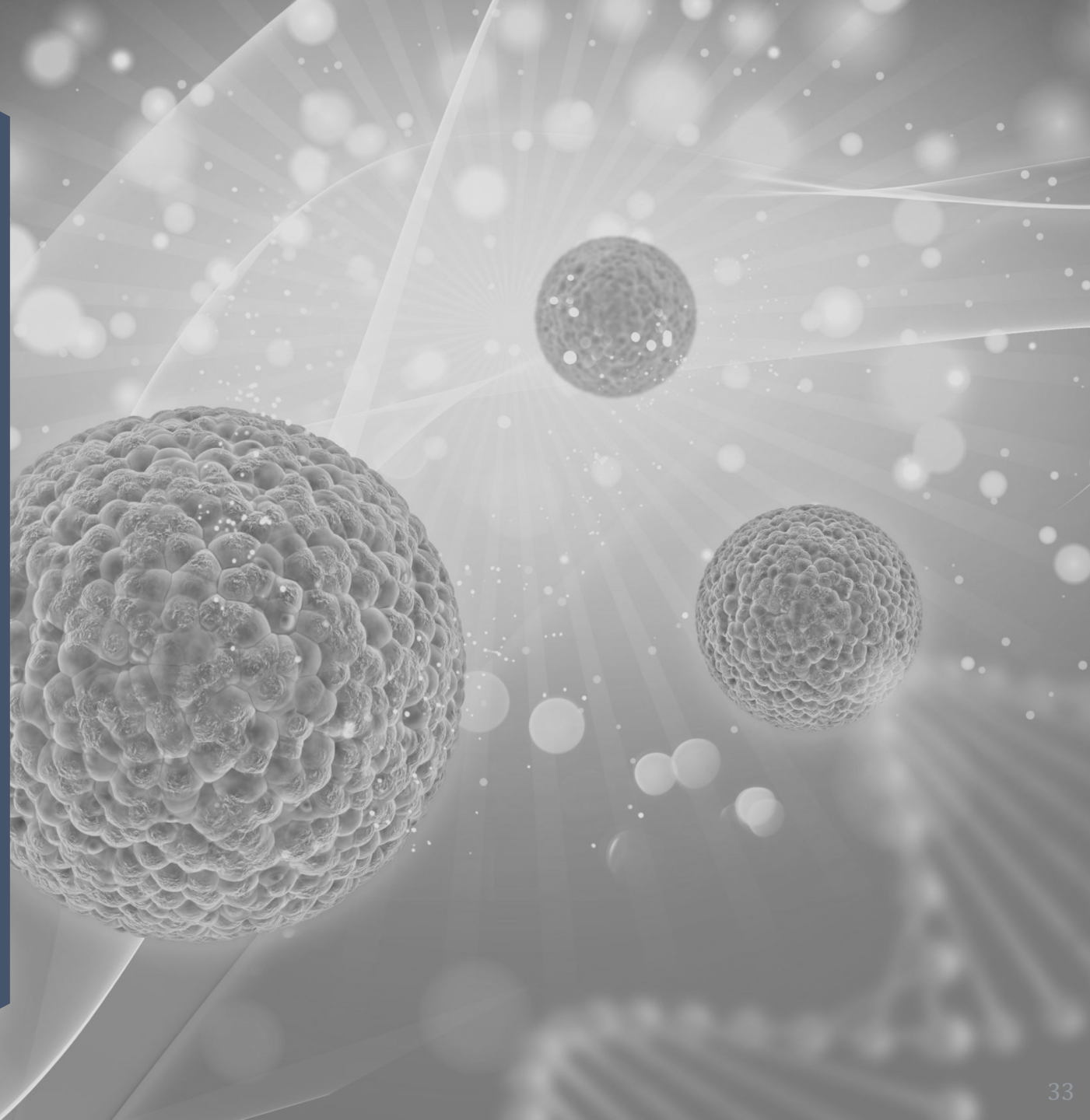
- Pre-experiments found that STING activators could target γδ T cells to enhance their anti-tumor ability, a process dependent on the upregulation of IFN-γ in γδ T cells induced by STING activation, rather than the classical STING-IFN-α/β pathway.
- This study will confirm that STING activator can target and activate γδ T cells to enhance tumor killing ability, and further clarify the downstream molecular mechanism and whether other new signaling pathways can be found.

Findings

1. The STING activator DMXAA enhances mRNA expression levels of interferon-gamma (IFN-γ) produced by γδ T cells.
2. The STING activator DMXAA does not induce apoptosis within the effective time.
3. The STING activator DMXAA upregulates IFN-γ protein expression in γδ T cells.
4. The STING activator DMXAA enhances γδ T cell-mediated tumor killing by upregulating IFN-γ.
5. DMXAA up-regulates the expression of IFN-γ in γδ T cells by Eomes.

Source: “Clinical exploration and industrial transformation of allogeneic γδ T cells against solid tumors ”, Beroni Group PPT Accessed Apr. 18.

Future of Cellular Immunotherapy



Cellular Immunotherapy Future Outlook

Cancer immunotherapy has emerged as a promising therapeutic alternative, but cellular immunotherapy still faces many challenges.

Solid tumors create an immunosuppressive environment, and they have immune escape mechanisms increasing the difficulty of treatment.

Further research, individualized approaches and strategies to combine treatments, will be needed to help response rates in the future.

T cell immunotherapy is a rapidly evolving area in cancer treatment. In the future T cell immunotherapy is expected to be further established as part of the standard therapy arsenal for solid cancer.

With AlphaFold 2 hailed for solving a 50-year-old protein folding problem, there is a treasure trove of data now waiting to be transformed into future advances.

Source: "Facing the future: challenges and opportunities in adoptive T cell therapy in cancer", https://www.tandfonline.com/doi/full/10.1080/14712598.2019.1608179. Accessed Feb. 10.; "Putting the power of AlphaFold into the world's hands", https://www.deepmind.com/blog/putting-the-power-of-alphafold-into-the-worlds-hands. Accessed Mar. 22.

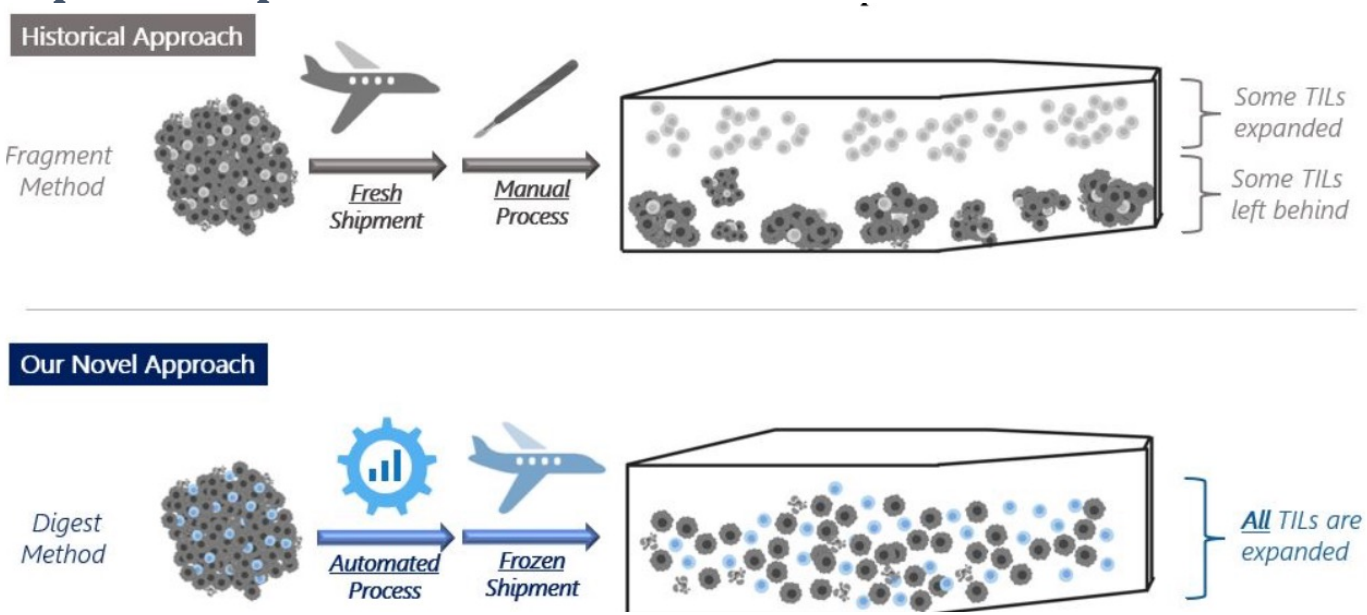
Notable Players in Cellular Immunotherapy

Tumor Infiltrating Lymphocytes (TIL) Therapy

Instil Bio Inc	Slide 37
Iovance Biotherapeutics, Inc	Slide 39
Achilles Therapeutics, plc	Slide 41

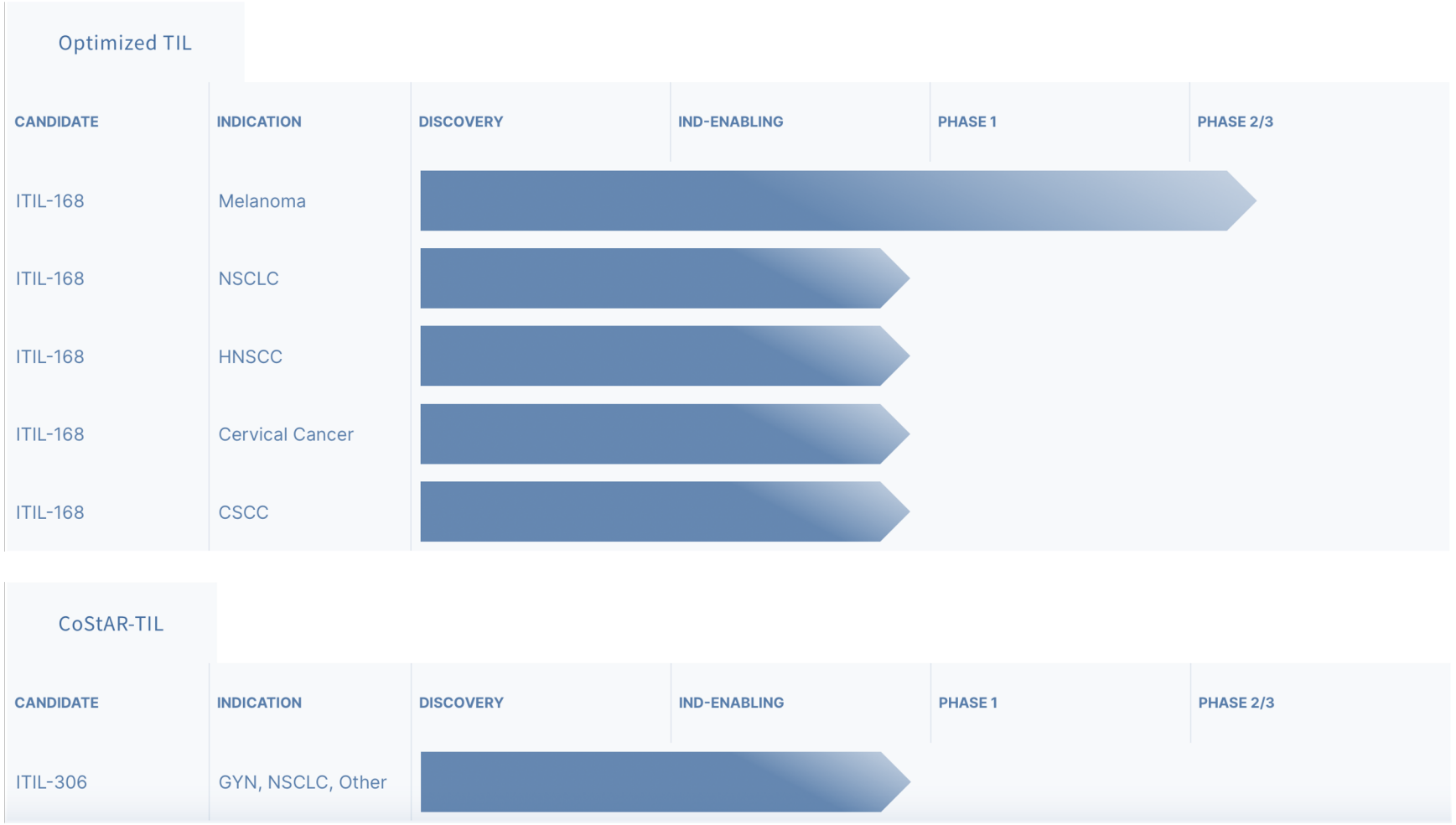
Instil Bio Inc (NasdaqGS: TIL)

- **Novel TIL manufacturing process**
  - **Three distinct stages**: **tumor processing**- includes tissue harvesting and cryopreservation, **TIL generation**- includes outgrowth and rapid expansion phases, **final product processing**- includes formulation and cryopreservation
  - **Some potential advantages-** scheduling flexibility for physicians and patients, increased shelf life, more opportunities for optimization, enhanced cell viability and potency, more TILs from digested tumor tissue
- **Company-operated in-house manufacturing facilities**
- **Robust clinical development experience with TILs**



Source: "SEC Form 10-K", https://www.sec.gov/ix?doc=/Archives/edgar/data/1789769/000178976922000008/til-20211231.htm#i8d9457f14008434d980b5193fed1ca7f_13. Accessed Mar. 21.

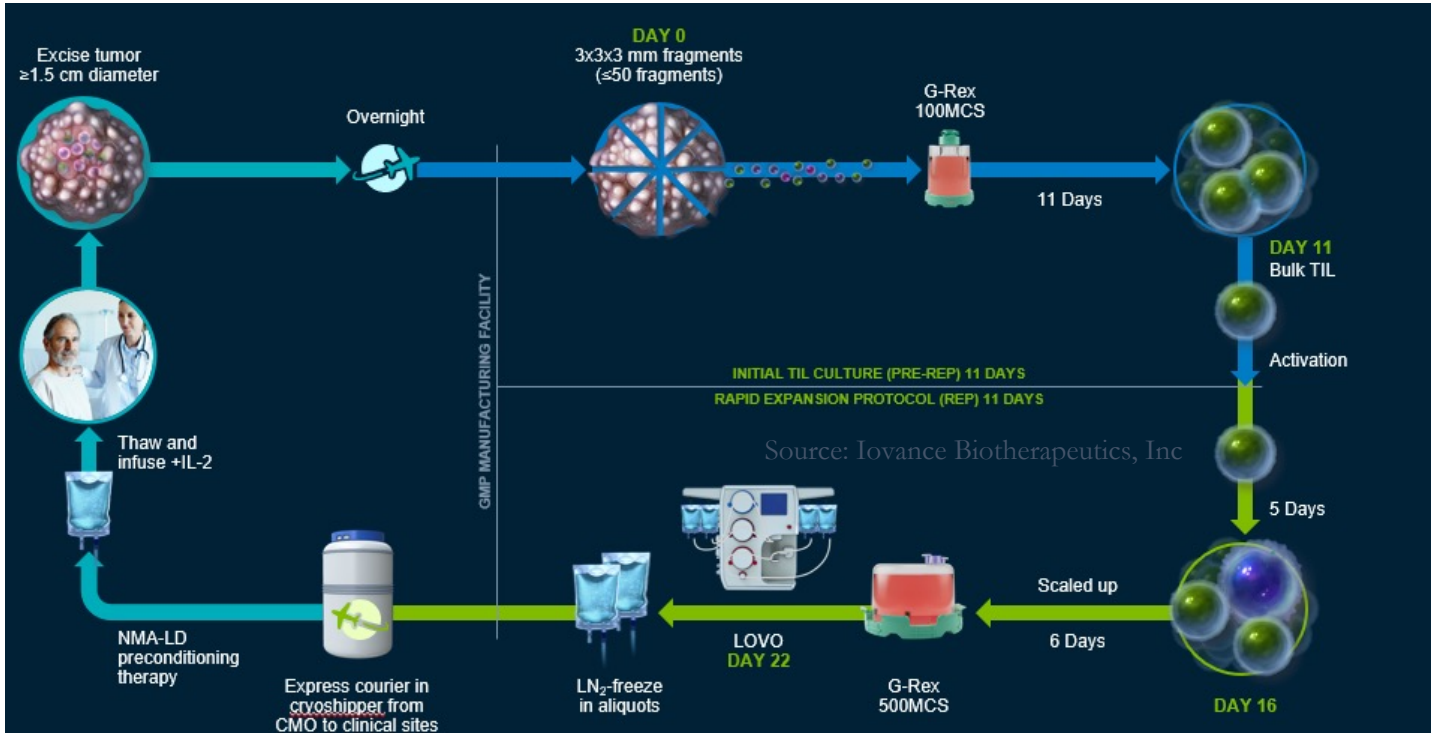
Instil Bio Inc (NasdaqGS: TIL) Pipeline



Source: "Pipeline", https://instilbio.com/pipeline/. Accessed Mar. 21.

Iovance Biotherapeutics, Inc (NasdaqGM: IOVA)

- Iovance deploys **billions of personalized patient-specific polyclonal TIL cells** to recognize and target a multitude of nonoverlapping neoantigens in patients with solid tumors.
- **22-day proprietary manufacturing process**, manufacturing success rate of 90%+, 500+ patients treated with Iovance TIL



Source: "Iovance Biotherapeutics 40th Annual J.P. Morgan Healthcare Conference", https://ir.iovance.com/static-files/3f991737-1354-441b-9ba2-e4231f1fb3d5, Accessed Mar. 2.; "Iovance Cell Therapy Center: iCTC", https://ir.iovance.com/static-files/0d89980d-9b77-4fd0-ad05-bcbf2d5776aa, Accessed Mar. 2.

Iovance Biotherapeutics, Inc (NasdaqGM: IOVA) Clinical Pipeline

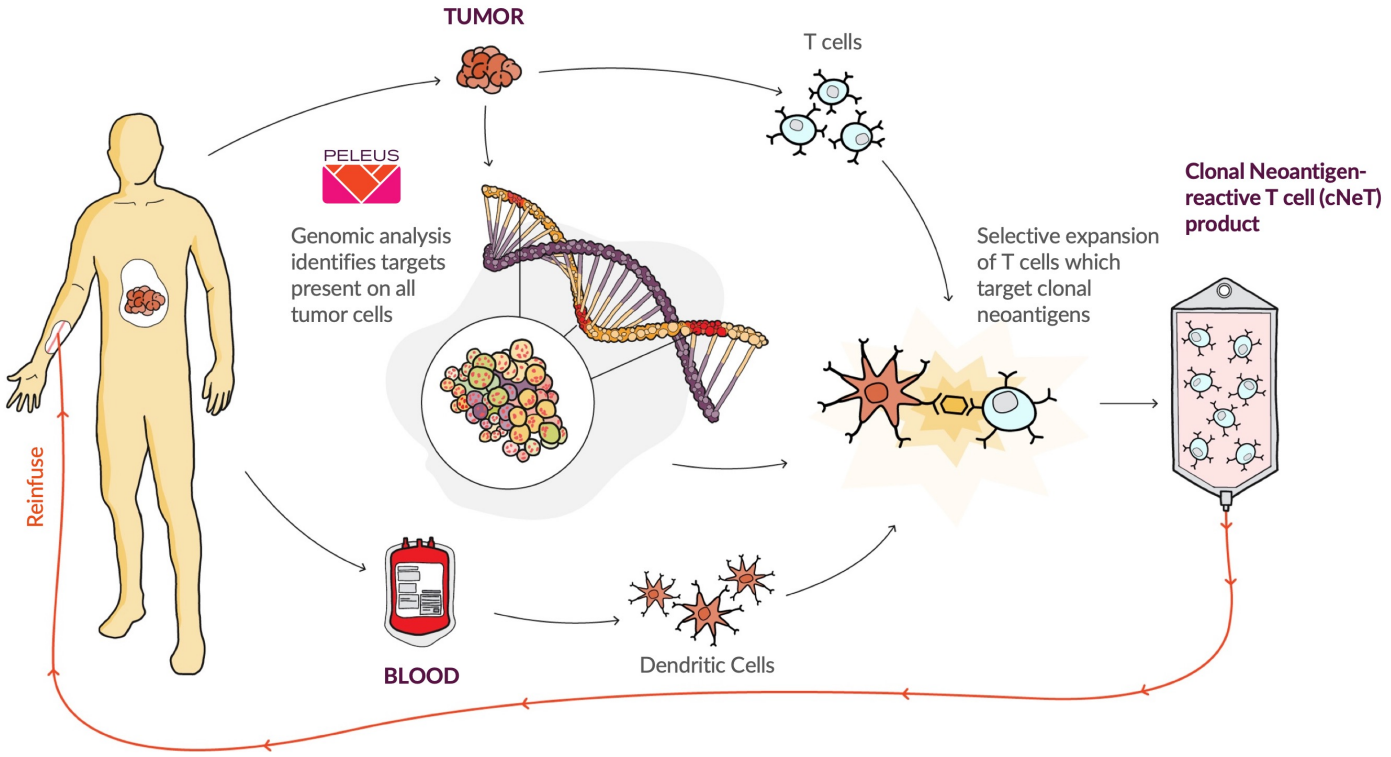
	Product Candidate	Indication(s)	IND-Enabling	Phase 1	Phase 2	Pivotal
TIL	Lifileucel/LN-144	Melanoma (post-anti-PD-1)	C-144-01 Study, Cohorts 2 & 4			FDA RMAT designation
	Lifileucel	Cervical cancer (post-chemo; post-chemo & post-anti-PD-1)	C-145-04 Study, Cohorts 1 & 2			FDA BTD
	LN-145	NSCLC (2L post-chemo & post-anti-PD-1)	IOV-LUN-202 Study, Cohorts 1 & 2			
	LN-145	NSCLC (2-4L incl. post-anti-PD-1)	IOV-COM-202 Study, Cohort 3B			
	LN-145	HNSCC (post-anti-PD-1)	C-145-03 Study, Cohort 2			
TIL Combinations	Lifileucel + pembro	Melanoma (anti-PD-1 naïve)	IOV-COM-202 Study, Cohort 1A			
	Lifileucel + pembro	Cervical cancer (1L, chemo & anti-PD-1 naïve)	C-145-04 Study, Cohort 3			
	LN-145 + pembro	NSCLC (anti-PD-1 naïve)	IOV-COM-202 Study, Cohort 3A			
	LN-145 + ipi/nivo	NSCLC (post-anti-PD-1)	IOV-COM-202 Study, Cohort 3C			
	LN-145 + pembro	HNSCC (anti-PD-1 naive)	IOV-COM-202 Study, Cohort 2A			
PD-1 Selected TIL	LN-145-S1	Melanoma (post-anti-PD-1)	IOV-COM-202 Study, Cohort 1B			
	LN-145-S1	HNSCC (post-anti-PD-1)	C-145-03 Study, Cohort 4			
Third Generation (Gen 3) TIL 16-day manufacturing	LN-145 Gen 3 + core biopsy	NSCLC (2L post-chemo & post-anti-PD-1)	IOV-LUN-202 Study, Cohort 3			
	LN-144 Gen 3	Melanoma (post-anti-PD-1)	IOV-COM-202 Study, Cohort 1C			
	LN-145 Gen 3	HNSCC (post-anti-PD-1)	C-145-03 Study, Cohort 3			
PBL Therapy	IOV-2001	CLL/SLL (post-BTKi)	IOV-CLL-01 Study			
PD-1 Inactivated TIL	IOV-4001	Multiple				
IL-2 Analog	IOV-3001	Multiple				

Abbreviations: BTD=breakthrough therapy designation; BTKi=Bruton's tyrosine kinase inhibitor; CLL/SLL=chronic lymphocytic leukemia and small lymphocytic lymphoma; HNSCC=head and neck squamous cell carcinoma; IL-2=interleukin 2; ipi/nivo=ipiliumumabn/nivolumab; NSCLC=non-small cell lung cancer; PBL=peripheral blood lymphocytes; RMAT=Regenerative Medicines Advanced Therapy; TIL=tumor infiltrating lymphocytes

Source: "Clinical Pipeline", https://www.iovance.com/clinical/pipeline/. Accessed Mar. 2.

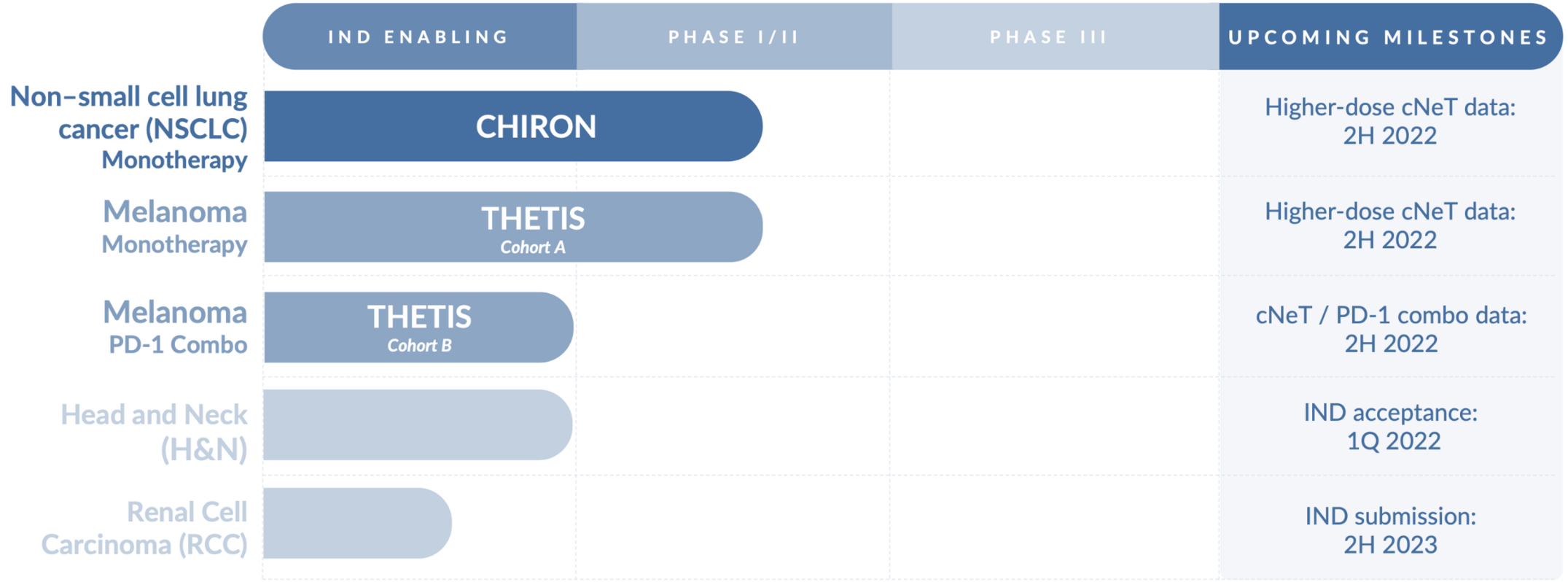
Achilles Therapeutics, plc (NasdaqGS: ACHL)

- **Targeting Personalized Clonal Neoantigens, Present on all Tumor Cells**
- Tumor eradicating potential designed to overcome limitations of current therapies
- Industry-leading clonal neoantigen discovery **using real world patient data** (**TRACERx**) and a **proprietary bioinformatics tool (PELEUS®)** to enable precision T cell targeting



Source: "Achilles Therapeutics AI-Powered Precision TIL Therapy", https://ir.achillestx.com/static-files/9979c84e-4ee4-40e8-a7ed-07fb97c6ed3f, Accessed Mar. 2.

Achilles Therapeutics, plc (NasdaqGS: ACHL) Clinical Pipeline

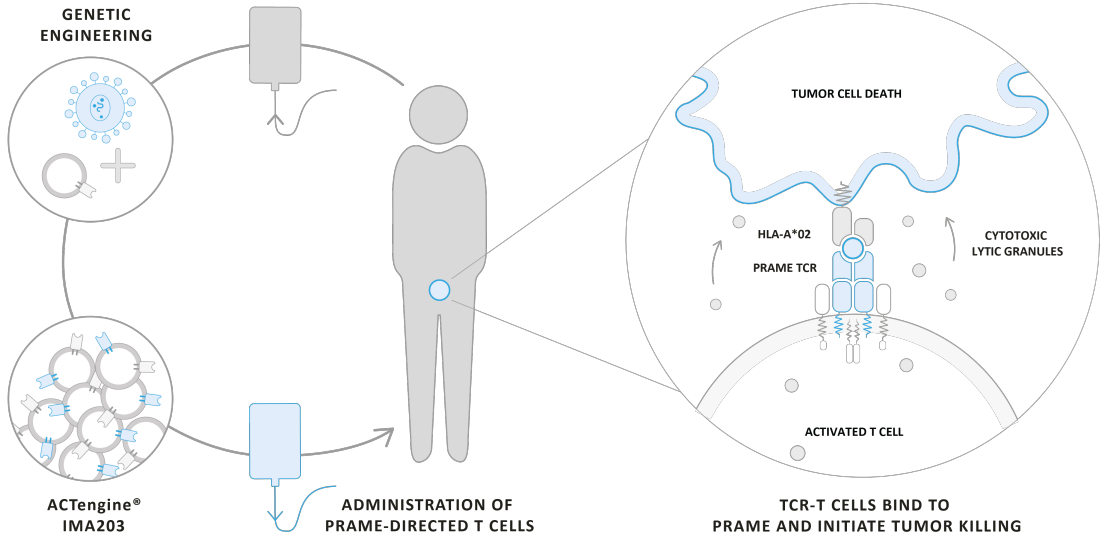


Source: "Achilles Therapeutics AI-Powered Precision TIL Therapy", https://ir.achillestx.com/static-files/9979c84e-4ee4-40e8-a7ed-07fb97c6ed3f, Accessed Mar. 2.

Engineered T Cell (TCR) Therapy

Immatics N.V. (NasdaqCM: IMTX)

- We are unlocking immunotherapies for solid cancer patients with high unmet medical need by accessing intracellular cancer targets with TCR-based therapeutics.
- **Proprietary Target and TCR Discovery Platforms**
  - **True Target** via XPRESIDENT® Target Discovery Platform
  - **Right TCR** via XCEPTOR® TCR Discovery Platform
- **TCER®** – Next-generation Bispecific platform with the lead molecule entering the clinical development in 2022
- **ACTengine® (TCR-T)** – High Objective Response Rate during ongoing dose escalation in TCR-T Ph1a trial IMA203 to PRAME



Source: "Immatics Corporate Presentation", https://investors.immatics.com/static-files/3b9b921d-f109-447a-89cd-ab73db220caa. Accessed Mar. 1.

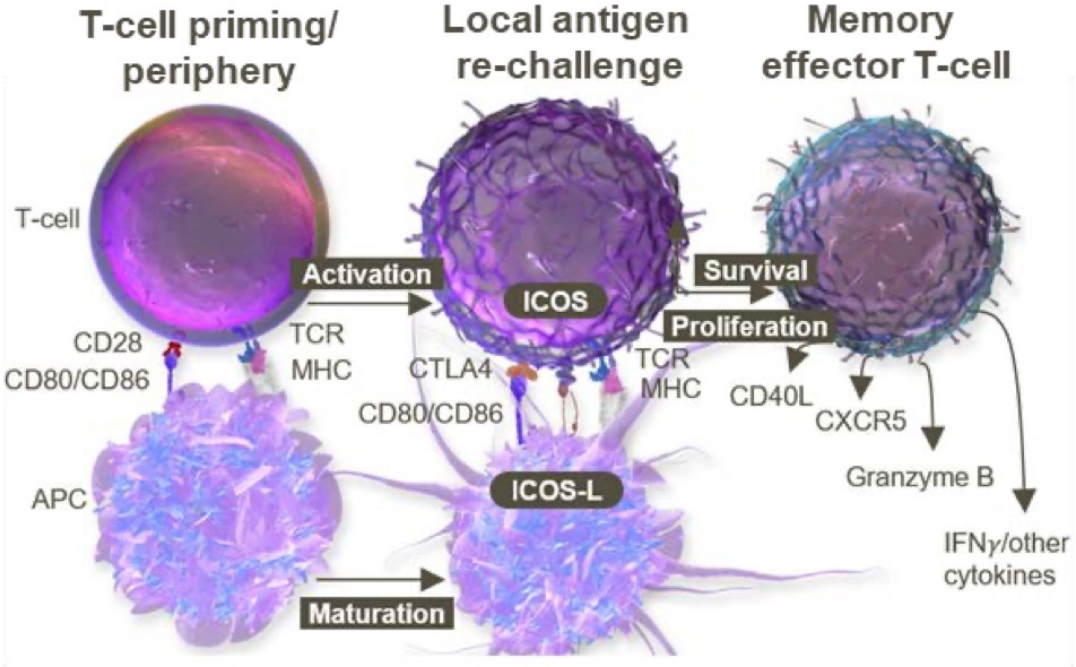
Immatics N.V. (NasdaqCM: IMTX) Clinical Pipeline

Modality	Product Candidate	Status	Preclinical	Phase 1a[1]	Phase 1b[1]	Phase 2/3
ACTengine® Autologous ACT	IMA201 (MAGEA4/8)	Proprietary				
	IMA202 (MAGEA1)	Proprietary				
	IMA203 (PRAME)	Proprietary				
	IMA203 (PRAME) + Checkpoint Inhibitor	Proprietary				
	IMA203CD8 (PRAME)	Proprietary				
	IMA204 (COL6A3)	Proprietary				
Autologous ACT	3 ACT programs (Undisclosed)	Bristol Myers Squibb				
	2 ACT programs (Undisclosed)	gsk				
Allogeneic ACT	ACTallo® IMA30x (Undisclosed)	Proprietary				
TCER® Bispecifics	IMA401 (MAGEA4/8)	Bristol Myers Squibb				
	IMA402 (PRAME)	Proprietary				
	IMA40x (Undisclosed)	Proprietary				
Bispecifics	3 Bispecific programs (Undisclosed)	Genmab				

Source: "Immatics Corporate Presentation", https://investors.immatics.com/static-files/3b9b921d-f109-447a-89cd-ab73db220caa. Accessed Mar. 1.

GlaxoSmith Kline, plc (NYSE: GSK)

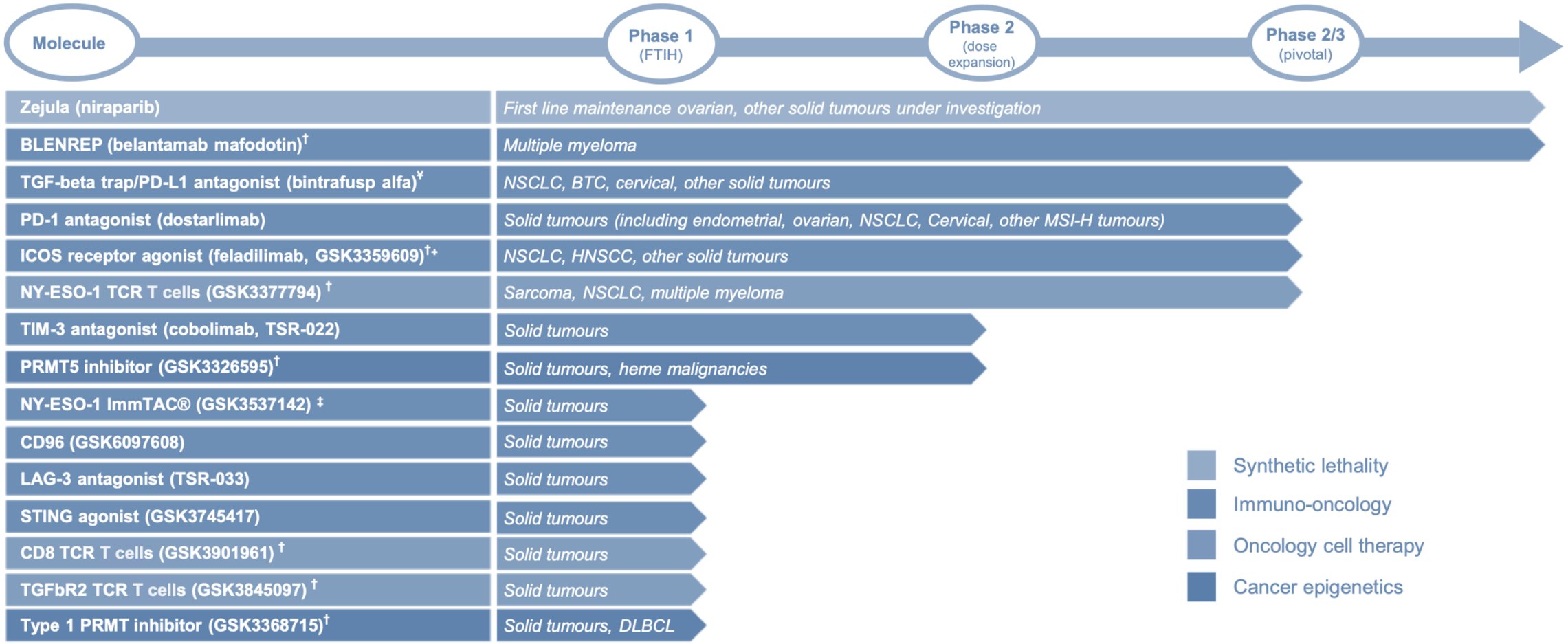
- **Innovative approach to the CD226 axis** (anti-CD96, anti-PVRIG)
  - CD226 axis plays an important role in cancer immune surveillance
- **BLENREP**: first-in-class BCMA targeted therapeutic for multiple myeloma
- **Feladilimab**, ICOS receptor agonist: several near-term catalysts anticipated
  - Novel I-O target, expected to modulate T-cell dynamics



APC, antigen-presenting cell; CXCR5, C-X-C motif chemokine receptor 5; ICOS-L, ICOS ligand; IFN-γ, interferon gamma; MHC, major histocompatibility complex

Source: "gsk JP Morgan Healthcare Conference", https://www.gsk.com/media/6528/gsk_jpm_2021_final_12012021.pdf. Accessed Mar. 1.

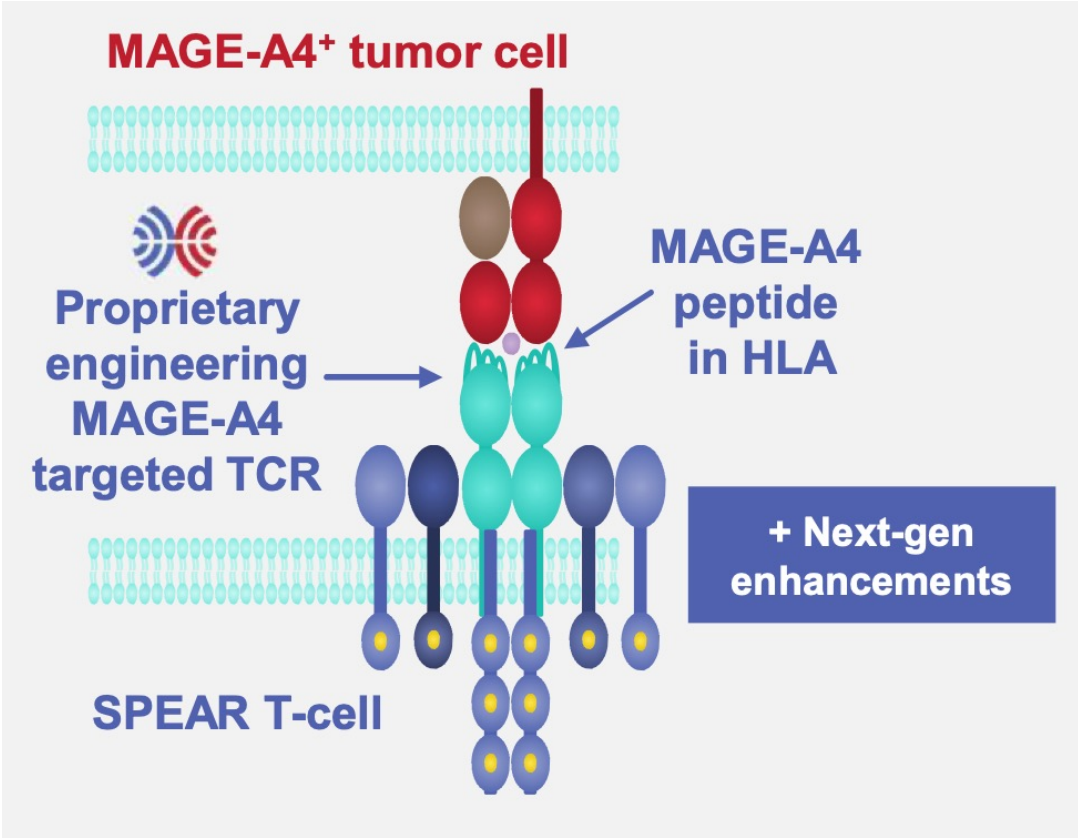
GlaxoSmith Kline, plc (NYSE: GSK) Oncology Pipeline



Source: "gsk JP Morgan Healthcare Conference", https://www.gsk.com/media/6528/gsk_jpm_2021_final_12012021.pdf. Accessed Mar. 1.

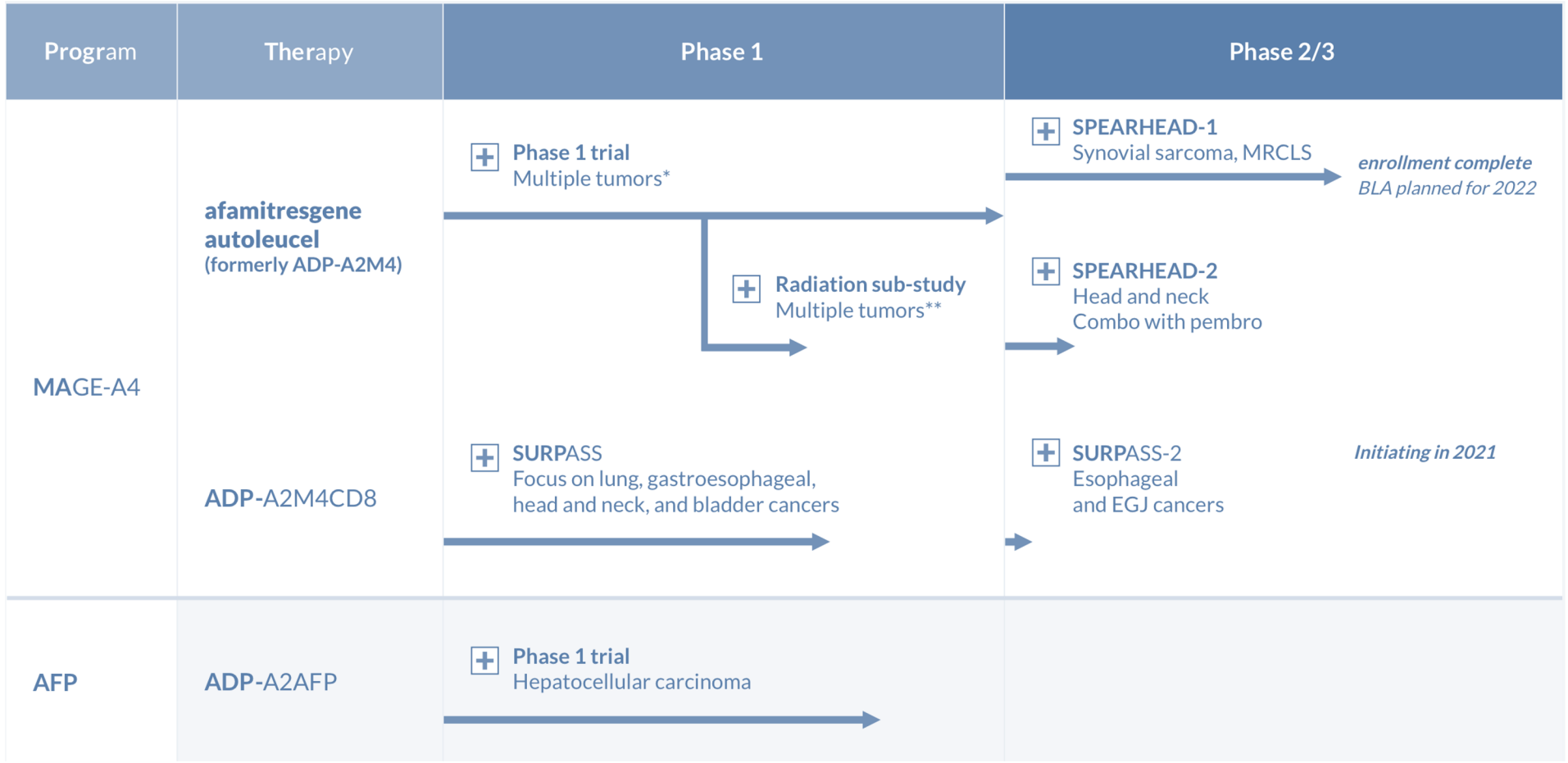
Adaptimmune Therapeutics (NasdaqGS: ADAP)

- **Our MAGE-A4 franchise is the cornerstone of our success**
  - MAGE-A4 is a validated target
- **Our fully integrated cell production expertise puts us on quick path to allogeneic scale up**
- **HiT induces strong, dose-dependent and persistent tumor regression in vivo**
- **Enhancing SPEAR T-cells to improve patient response, survival, and quality of life**



Source: "SPEAR-heading THE CANCER REVOLUTION", https://d1io3yog0oux5.cloudfront.net/_858b4ec828d6ea759f0709fa56ae7a3c/adaptimmune/db/249/3338/pdf/ADAP_19Jan2022.pdf. Accessed Mar. 1.

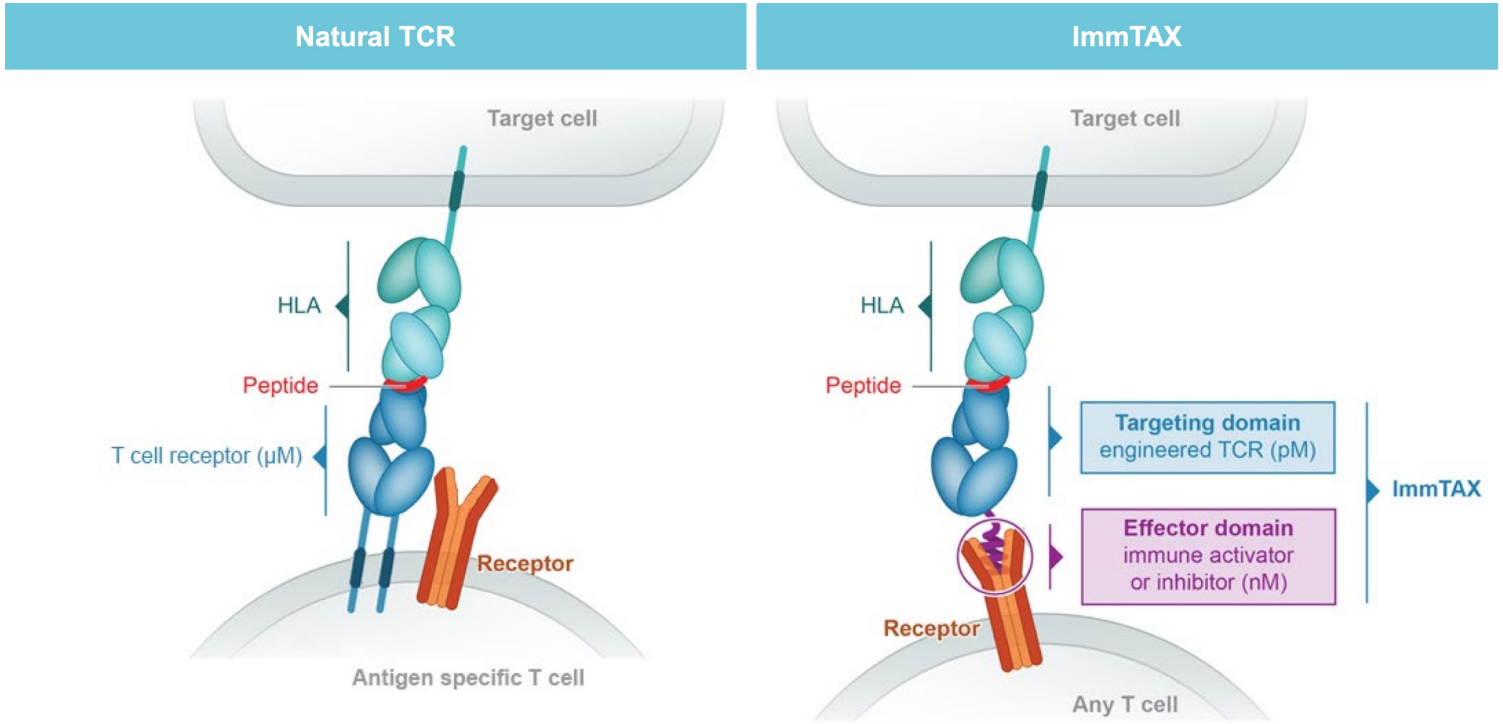
Adaptimmune Therapeutics (NasdaqGS: ADAP) Pipeline



Source: "SPEAR-heading THE CANCER REVOLUTION", https://d1io3yog0oux5.cloudfront.net/_858b4ec828d6ea759f0709fa56ae7a3c/adaptimmune/db/249/3338/pdf/ADAP_19Jan2022.pdf. Accessed Mar. 1.

Immunocore Holdings plc (NasdaqGS: IMCR)

- **KIMMTRAK®: First-in-class, off-the-shelf, bispecific TCR**
  - Targeting gp100 protein in melanoma
- **We pioneered converting membrane-bound T cell receptors**
  - Into soluble, off-the-shelf, bispecific therapeutics (ImmTAX)



Source: "IMMUNOCORE Corporate Presentation", https://ir.immunocore.com/static-files/fe1d86ba-b9e1-4546-ac42-3d5abc3f16b3. Accessed Mar. 21.

Immunocore Holdings plc (NasdaqGS: IMCR) Pipeline

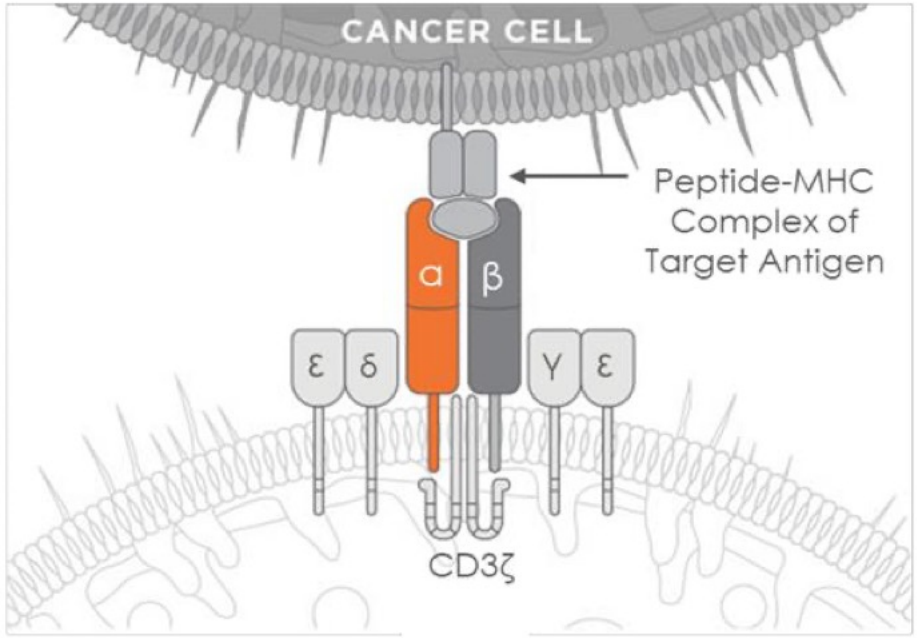
Candidate	Target	Indication	Pre-clinical	Phase 1 / 2	Phase 3	Approved	Anticipated Milestones
Oncology							
KIMMTRAK®	gp100	Uveal melanoma					✓ FDA Approval 1Q 2022 ❖ Commercial launch 1H 2022
		Cutaneous melanoma					❖ Randomized study 4Q 2022
IMC-C103C [1]	MAGE-A4	NSCLC, gastric, head & neck, ovarian, synovial sarcoma					✓ Initiated ovarian expansion ❖ Ph. 1 update 4Q 2022
IMC-F106C	PRAME	NSCLC, breast, endometrial, ovarian, SCLC, melanoma					❖ Ph. 1 initial data 3Q 2022
Candidate #4	Undisclosed	Multiple solid tumors					
Candidate #5	Undisclosed	Colorectal, gastric, pancreatic					
Infectious Diseases							
IMC-I109V	Envelope	Hepatitis B Virus (HBV)					❖ Enrolling Ph. 1
IMC-M113V [2]	Gag	Human Immunodeficiency Virus (HIV)					❖ First patient dosing 2Q 2022

Source: "IMMUNOCORE Corporate Presentation", https://ir.immunocore.com/static-files/fe1d86ba-b9e1-4546-ac42-3d5abc3f16b3. Accessed Mar. 21.

Chimeric Antigen Receptor (CAR) T Cell Therapy

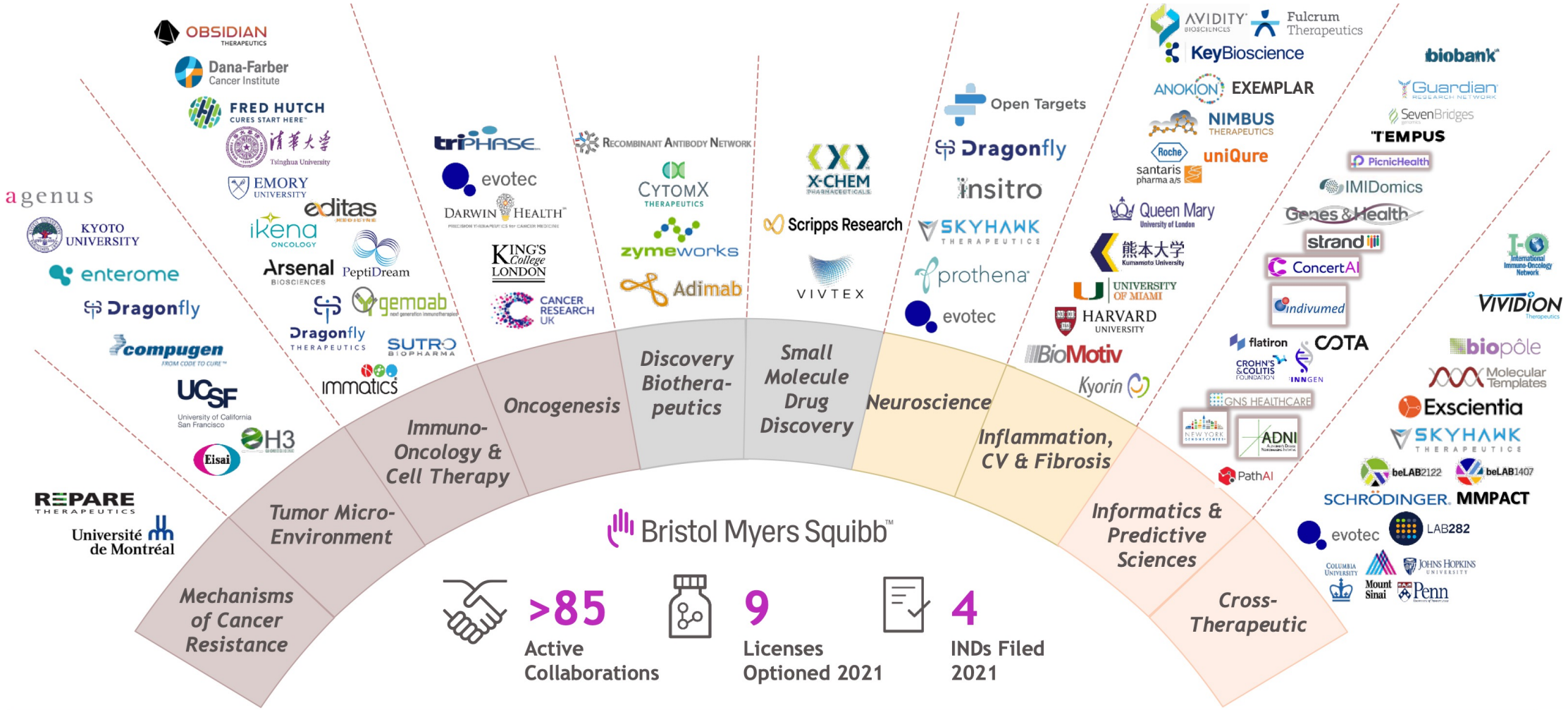
Bristol-Myers Squibb Company (NYSE: BMY)

- **Broad investment in next generation cell therapies**
  - **Dual Antigen Targeting CAR Ts-** mitigating antigen loss
  - **CAR T Armed Payload-** overcoming tumor microenvironment resistance
  - **Engineered TCR T Cells for Solid Tumors-** recognizes intracellular targets
  - **Allogeneic CAR T Cells-** off the shelf alternative



Source: "Bristol Myers Squibb Investor Event", https://s21.q4cdn.com/104148044/files/doc_presentations/2021/2021-BMS-Investor-Event-Presentation.pdf Accessed Mar. 21.

Bristol-Myers Squibb Company (NYSE: BMY) Partnerships



Source: "Bristol Myers Squibb Investor Event", https://s21.q4cdn.com/104148044/files/doc_presentations/2021/2021-BMS-Investor-Event-Presentation.pdf Accessed Mar. 21.

Bristol-Myers Squibb Company (NYSE: BMY) Pipeline

Phase 1

- AHR Antagonist (*Ikena*)[2]
- Anti-NKG2A
- Anti-TIM3
- Anti-CCR8
- Anti-OX40
- AR LDD
- Anti-CTLA-4 NF-Probody
- motolimod
- CD3xPSCA (*GEMoaB*)[2]
- STING Agonist
- Anti-IL-8
- TIGIT Bispecific
- IL-12 Fc
- TGFβ Inhibitor

Phase 2

- Anti-CTLA-4 NF
- BET Inhibitor[1] (CC-90010)
- Anti-CTLA-4 Probody
- farletuzumab - eribulin ADC
- Anti-Fucosyl GM1
- LSD1 Inhibitor[1]
- Anti-TIGIT

Phase 3

- bempegal-desleukin
- linrodostat
- subcutaneous nivolumab
- relatlimab[1]

Marketed

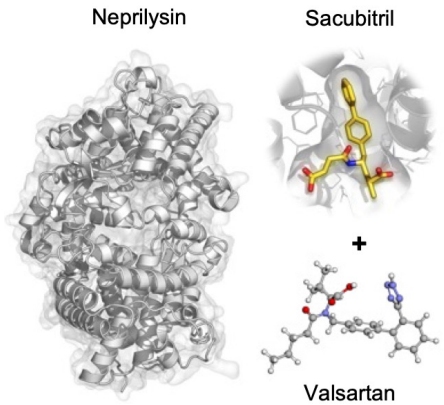
OPDIVO™ (nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

YERVOY™ (ipilimumab)
Injection for intravenous infusion

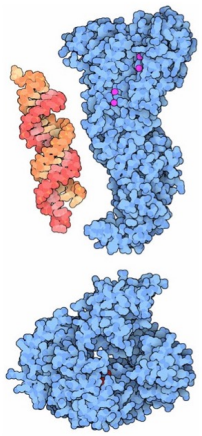
Source: "Bristol Myers Squibb Investor Event", https://s21.q4cdn.com/104148044/files/doc_presentations/2021/2021-BMS-Investor-Event-Presentation.pdf Accessed Mar. 21.

Novartis AG (NYSE: NVS)

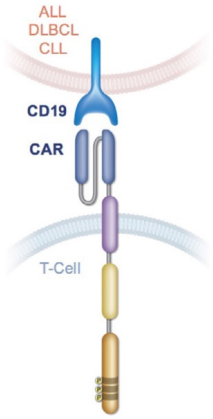
- **Over 30 NMEs in clinical development**
- Kymriah: is an **FDA approved CAR-T therapy**
- Investing in innovative combinations and advanced therapy platforms
- **NIBR deploys a technology-forward approach to unlock therapeutic opportunities across five platforms**



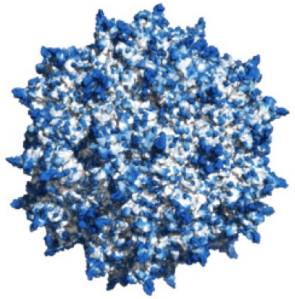
Discovery Chemistry
Entresto | HFrEF



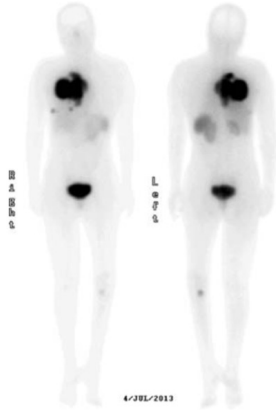
Biotherapeutics
Leqvio | CVRR



Stem-Progenitor Cell Therapy
Kymriah | B-ALL



Viral Gene Therapy
Zolgensma | SMA

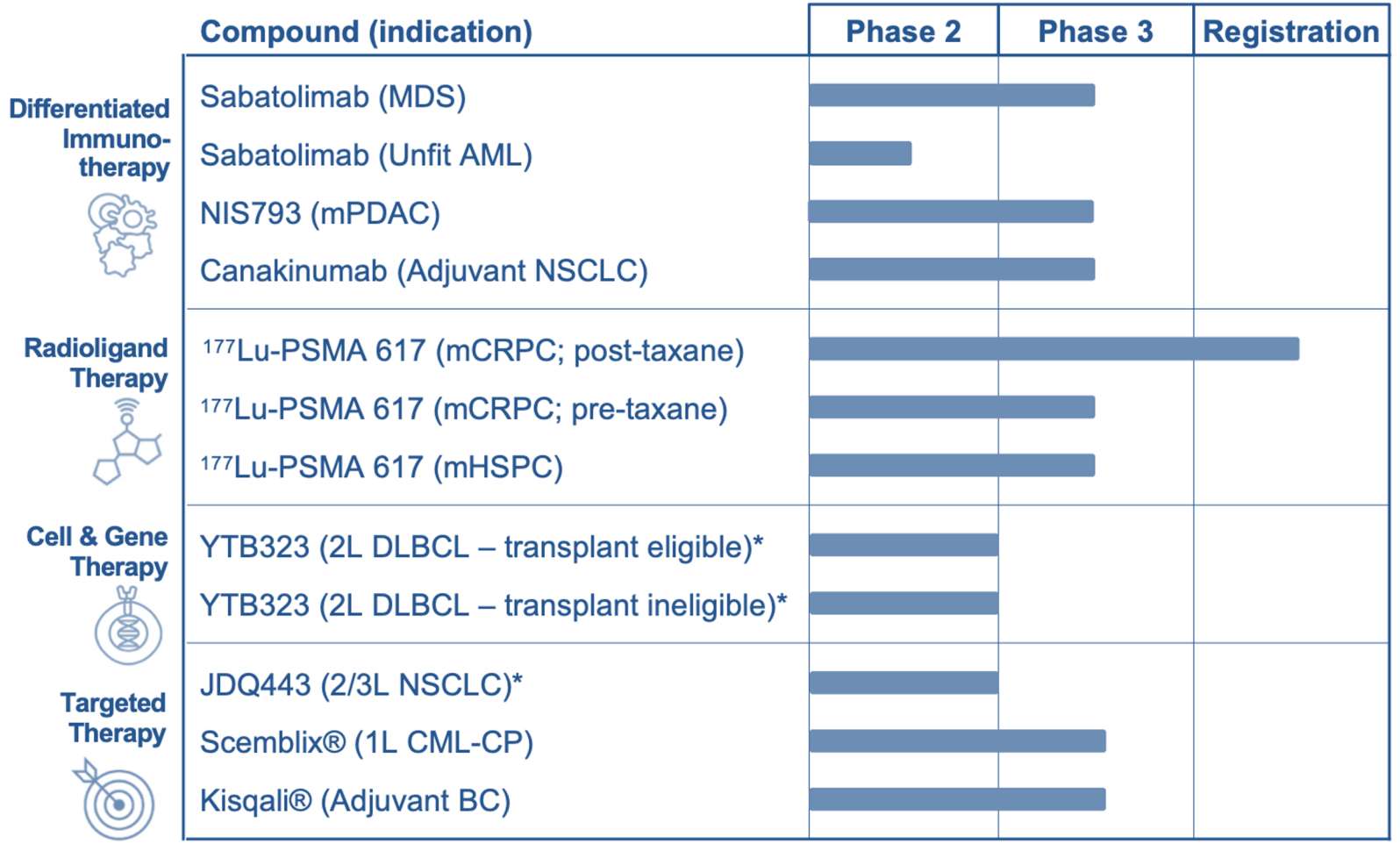


Radioligand Therapy
Lutathera | NET

Crespo-Jara A. et.al., Clinical Nuclear Medicine, 2016; PDB 2ffl, 2f8s, 1u04.

Source: "KYMRIAH (tisagenlecleucel)", https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/kymriah-tisagenlecleucel. Accessed Mar. 21.; "Novartis R&D Day December 2, 2021", https://www.novartis.com/sites/novartis_com/files/novartis-r-d-day-2021-presentation.pdf. Accessed Mar. 21.

Novartis AG (NYSE: NVS) 2022 Key Late-Stage Programs

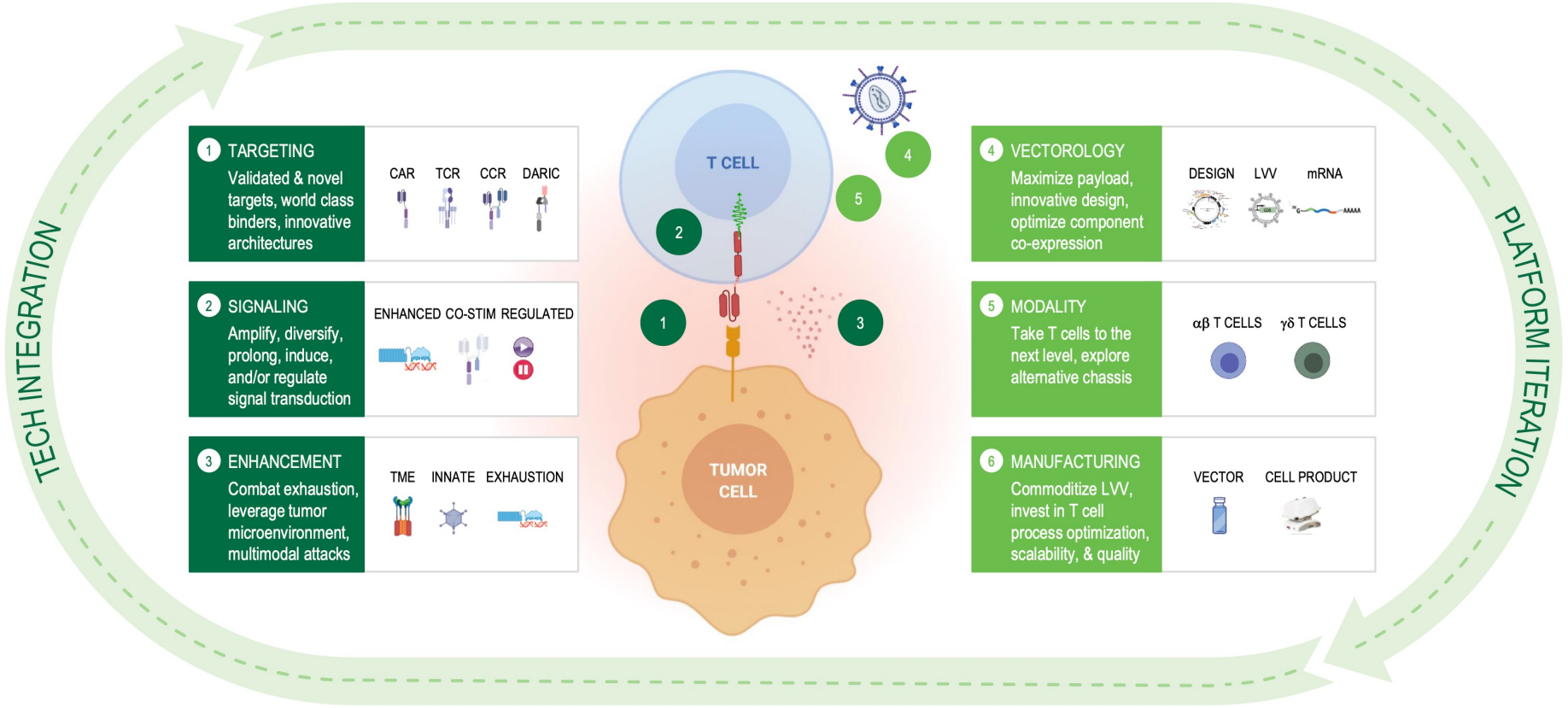


* Planned Phase 3 programs initiating in 2022

Source: "Novartis R&D Day December 2, 2021", https://www.novartis.com/sites/novartis_com/files/novartis-r-d-day-2021-presentation.pdf. Accessed Mar. 21.

2seventy bio, Inc (NasdaqGS: TSVT)

- **R&D engine built to rapidly design, test learn, & iterate.**
- **Multiple approved autologous CAR T products establish a powerful platform on which to build**



Source: "Join the Patient Mission 2022 Full Year Outlook", https://ir.2seventybio.com/static-files/c7058720-1ee9-4976-a8ac-f942e58e3ba9. Accessed Mar. 2.

2seventy bio, Inc (NasdaqGS: TSVT) Pipeline

INDICATION [DRUG]	TARGET	TECHNOLOGY	DISCOVERY STAGE R&D	IND-ENABLING PRECLINICAL STUDIES	CLINICAL STUDIES	APPROVED PRODUCTS
Multiple Myeloma [ABECMA]	BCMA	CAR T cell	BMS Partnership			Abecma
Multiple Myeloma [ABECMA]	BCMA	CAR T cell	BMS Partnership; Earlier-line Studies		Label Expansion	
AML-Pediatric [DARIC33]	CD33	Drug-Regulated CAR T cell (DARIC)	SCRI Collaboration		Phase 1 Open	
B-NHL [bbT369]	Dual B cell targets	Dual-Targeted CAR T cell Signal Enhanced Gene Edited	TSVT Owned		Phase 1 Open	
AML-Adult [DARIC33 Next-Gen]	CD33 + Undisclosed	Drug-Regulated CAR T cell Dual-Targeted Potency Enhanced	SCRI Collaboration			
Ovarian Cancer [bbT4015]	MUC16	CAR T cell Pharmacologic Enhancements	REGN Collaboration		2023 IND Submission	
Solid Tumors	MAGE-A4	TCR T cell Potency Enhanced	REGN / MEDG Collaboration		2023 IND Submission	
Solid Tumors	Multiple	CAR / TCR T cell Potency Enhanced	Multiple			
Multiple Myeloma	Multiple	Multi-Targeted CAR T cell Potency Enhanced	TSVT Owned			
Additional Indications	Undisclosed	Multiple	Multiple; Including Collab. with Novo Nordisk			

Source: "Join the Patient Mission 2022 Full Year Outlook", https://ir.2seventybio.com/static-files/c7058720-1ee9-4976-a8ac-f942e58e3ba9. Accessed Mar. 2.

Roche Holdings AG (OTCQX: RHHBY)

- **NAVIFY® Oncology Hub** *Empowering more efficient and effective clinical decisions*
- Large pipeline of oncology treatments

Phase III (11 NMEs + 40 AIs)

RG3502	Kadcyla + T	2L+ HER-2+ PD-L1+ mBC
	Kadcyla + T	HER-2+ eBC high-risk
RG6026	glofitamab + chemo	2L+ DLBCL
RG6058	tiragolumab + T + chemo	1L SCLC
	tiragolumab + T	1L PD-L1+ NSCLC
	tiragolumab + T	locally advanced esophageal cancer
	tiragolumab + T	1L esophageal cancer
	tiragolumab + T	stage III unresectable 1L NSCLC
RG6107	crovalimab	PNH
	crovalimab	aHUS
RG6114	inavolisib (mPI3K alpha inh)	1L HR+ mBC
RG6171	giredestrant (SERD)	ER+/HER2- mBC
	giredestrant (SERD)	adj ER+ BC
RG6268	Rozlytrek ROS1+	1L NSCLC
RG7440	ipatasertib + abiraterone	1L CRPC
RG7446	Tecentriq + platinum chemo	NSCLC neoadj
	Tecentriq	NMIBC, high risk
	Tecentriq	RCC adj
	Tecentriq + cabozantinib	advanced RCC
	Tecentriq + cabozantinib	2L NSCLC
	T ± chemo	SCCHN adj
	T + capecitabine or carbo/gem	1L TNBC
	T + paclitaxel	TNBC adj
	T + Avastin	HCC adj
	T ± chemo	1L mUC
	Tecentriq	SC NSCLC
	Tecentriq	ctDNA+ high-risk MIBC
	T+ lurbinectedin (TBC)	1L maintenance SCLC
RG7601	Venclexta	r/r MM t(11:14)
	Venclexta + azacitidine	1L MDS
RG7828	mosunetuzumab + lenalidomide	2L+ FL
RG7853	Alecensa	ALK+ NSCLC adj
RG3648	Xolair	food allergy
RG6354	rhPTX-2 (PRM-151	idiopathic pulmonary fibrosis
RG7159	Gazyva	lupus nephritis
	Gazyva	membranous nephropathy
	Gazyva	systemic lupus erythematosus
RG6152	Xofluza	influenza, pediatric (0-1 year)
	Xofluza	influenza direct transmission
RG1450	gantenerumab	Alzheimer's
RG1594	Ocrevus higher dose	RMS & PPMS
RG6042	tominersen	Huntington's
RG6168	Enspryng	myasthenia gravis
RG6356	delandistrogene moxeparvovec (SRP-9001)	DMD
RG7845	fenebrutinib	PPMS
RG7845	fenebrutinib	RMS
RG6321	Susvimo (PDS with ranibizumab)	DME
	Susvimo (PDS with ranibizumab)	DR
	Susvimo (PDS with ranibizumab)	wAMD, 36-week
RG7716	Vabysmo (faricimab)	BRVO
	Vabysmo (faricimab)	CRVO

T=Tecentriq

Registration US & EU (3 NMEs + 8 AIs)

RG6013	Hemlibra[3]	mild to moderate hemophilia A
RG6396	Gavreto[2]	RET+ MTC, TC
RG7446	Tecentriq[2]	NSCLC adj
RG7596	Polivy[3]	1L DLBCL
RG7828	mosunetuzumab	3 L+ FL
RG6321	Susvimo (PDS with ranibizumab)	wAMD
RG7716	Vabysmo (faricimab)[1]	DME
	Vabysmo (faricimab)[1]	wAMD
RG6152	Xofluza[3]	influenza, pediatric (1-12 years)
RG1569	Actemra[4]	COVID-19 pneumonia
RG7916	Evrysdi	SMA pediatric >2months

[1] Approved in US, filed in EU

[2] Approved in US

[3] Filed in the EU

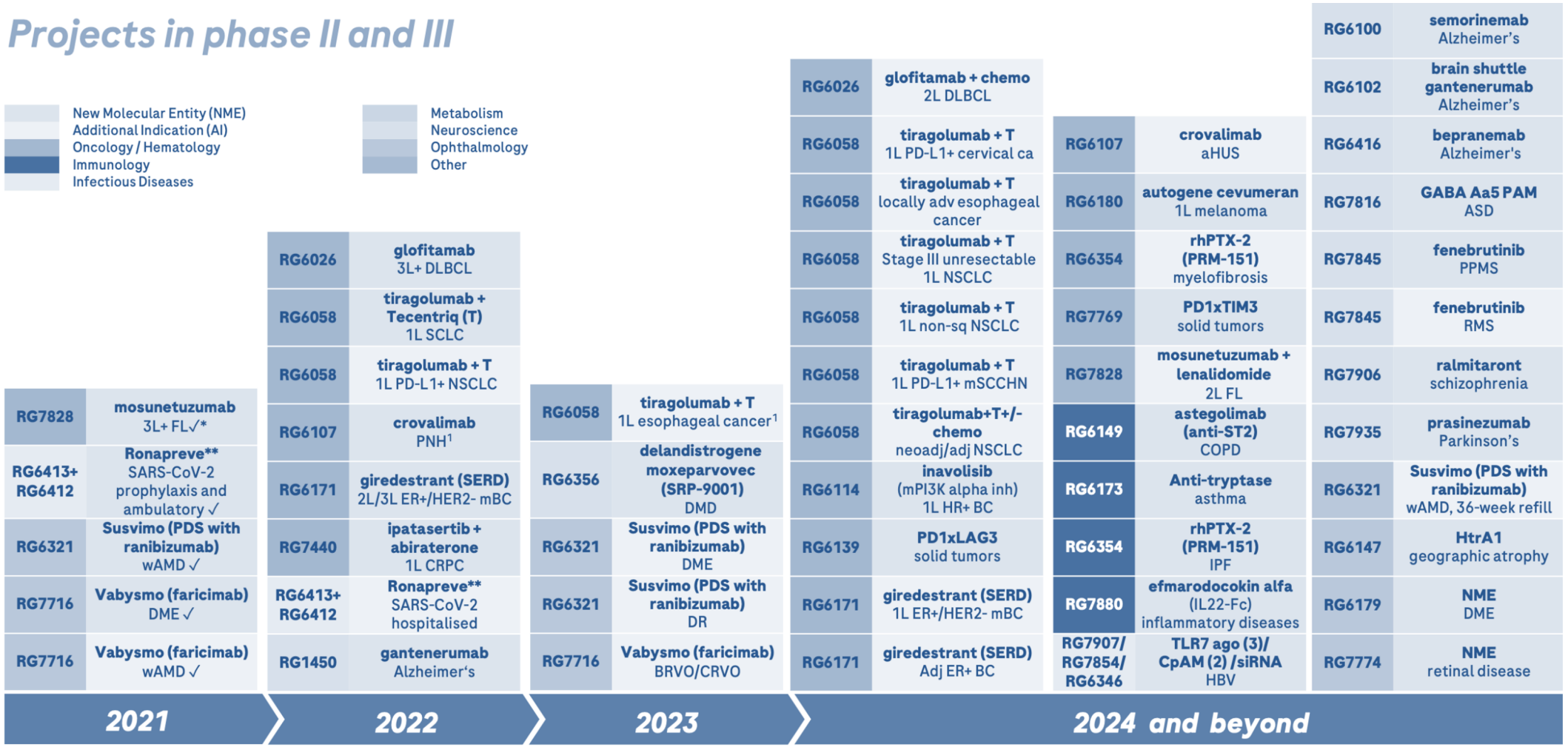
[4] Approved in EU

New Molecular Entity (NME)
Additional Indication (AI)
Oncology / Hematology
Immunology
Infectious Diseases

Metabolism
Neuroscience
Ophthalmology
Other

Source: "Roche 2021 Results", https://assets.cwp.roche.com/f/126832/x/baa445a513/irp220203-a.pdf. Accessed Mar. 15.

Roche Holdings AG (OTCQX: RHHBY) NME submissions and their additional indications



Source: "Roche 2021 Results", https://assets.cwp.roche.com/f/126832/x/baa445a513/irp220203-a.pdf. Accessed Mar. 15.

Kite A Gilead Company

YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion

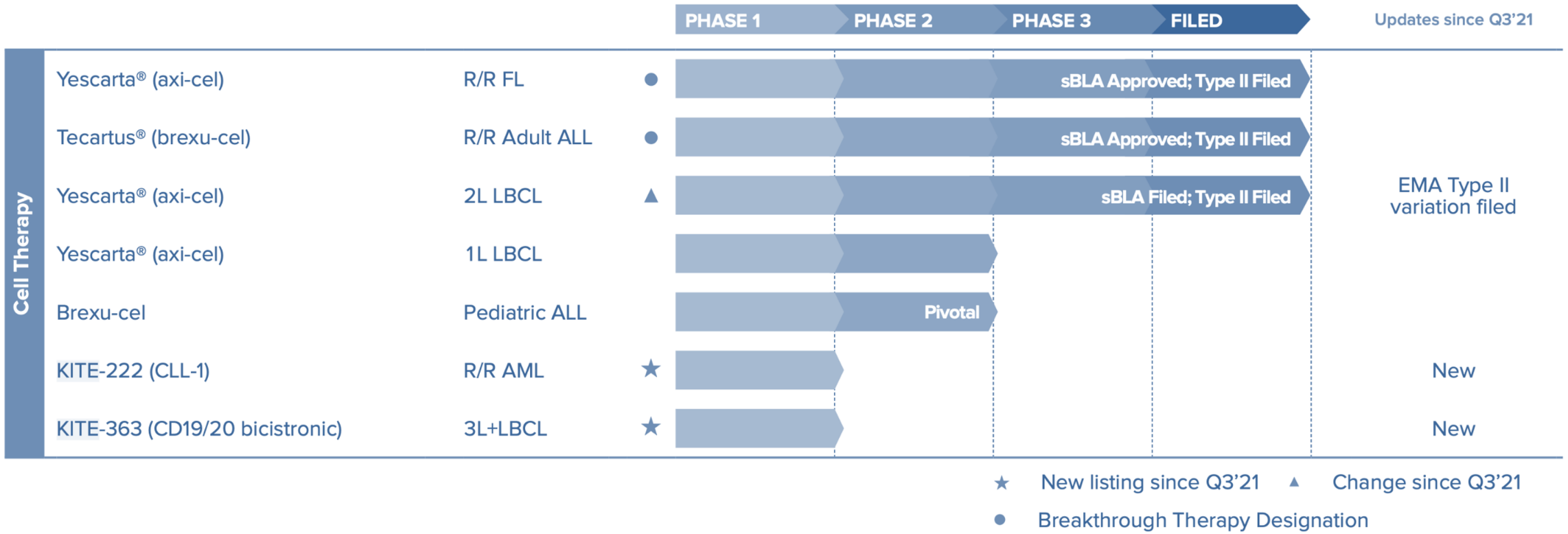
- First cell therapy approved in U.S. for 3L for Relapsed or Refractory (R/R) Large B-cell Lymphoma (LBCL) October 2017
- Accelerated approval in U.S. for 3L for R/R Follicular Lymphoma (FL) March 2021

TECARTUS® (brexucabtagene autoleucel) Suspension for IV infusion

- Accelerated approval in U.S. for R/R Mantle Cell Lymphoma (MCL) July 2020
- Conditional Marketing Authorization in EU for R/R MCL December 2020
- Approved in U.S. for Adult R/R B-cell Precursor Acute Lymphoblastic Leukemia (ALL) October 2021

Source: "Investor Resource Book February 2022", https://investors.gilead.com/static-files/158adf96-b224-4b67-9a32-7f8a30128b81. Accessed Mar. 15.

Kite Pipeline



Source: "Investor Resource Book February 2022", https://investors.gilead.com/static-files/158adf96-b224-4b67-9a32-7f8a30128b81. Accessed Mar. 15.

Gilead Sciences, Inc. (NasdaqGS: GILD)

Our transformative science is focused on three core areas :

- Therapies that **trigger tumor-intrinsic cell death** (e.g. Trodelvy).
- Therapies that **promote immune-mediated tumor killing** (e.g. Yescarta, magrolimab, Tecartus).
- Therapies that **remodel the tumor-permissive microenvironment** (e.g. etrumadenant).

Approved Medicines

CAR T-cell Therapies and 2L Treatment

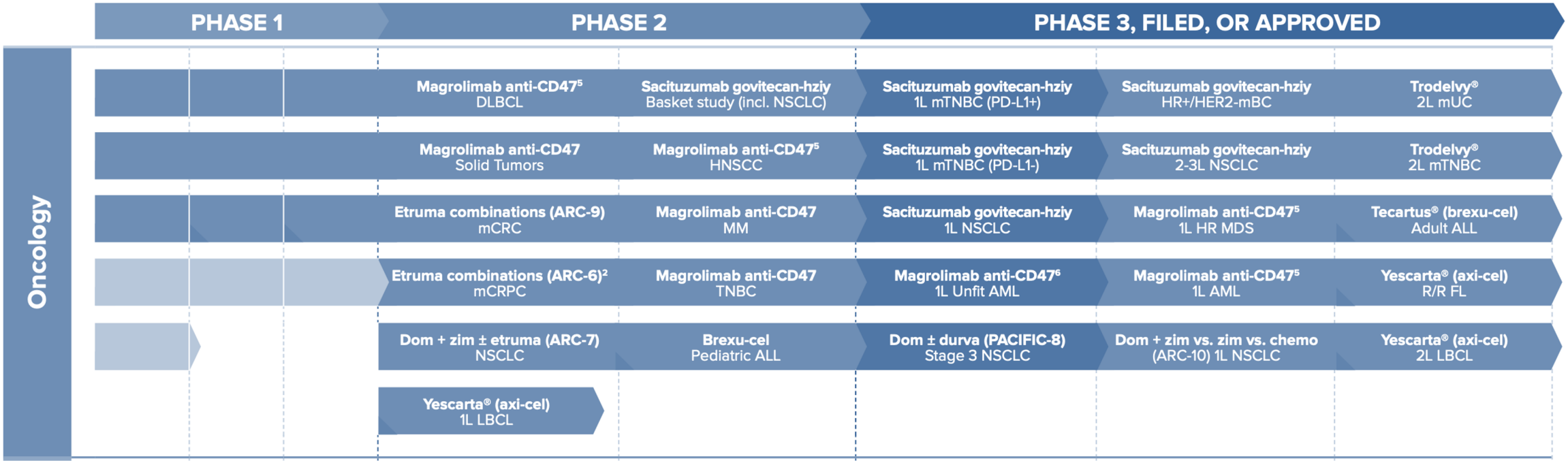
YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion

TECARTUS® (brexucabtagene autoleucel) Suspension for IV infusion

TRODELVY™ sacituzumab govitecan-hziy 180 mg for injection

Source: "Investor Resource Book February 2022", https://investors.gilead.com/static-files/158adf96-b224-4b67-9a32-7f8a30128b81. Accessed Mar. 15.

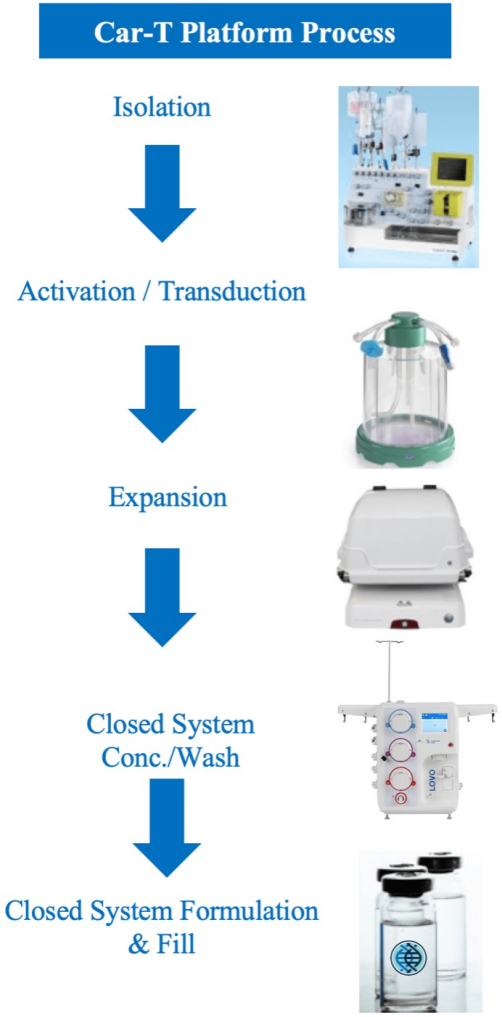
Gilead Sciences, Inc. (NasdaqGS: GILD) Oncology Pipeline



Source: "Investor Resource Book February 2022", https://investors.gilead.com/static-files/158adf96-b224-4b67-9a32-7f8a30128b81. Accessed Mar. 15.

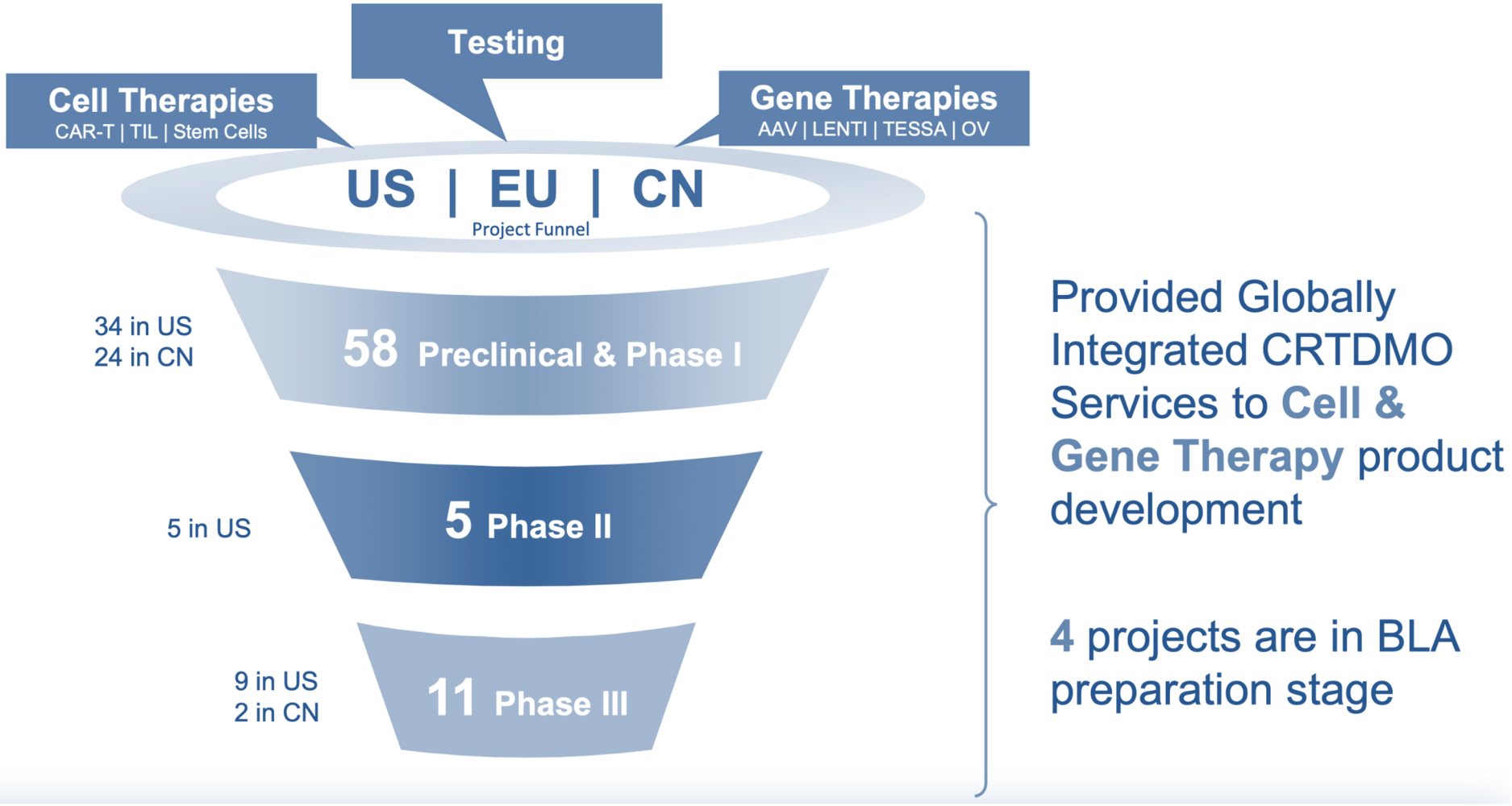
WuXi AppTec Co., Ltd. (Pink Limited Infromation:WUXAY)

- **Five Platforms**
  - WuXi Chemistry, WuXi Biology, WuXi Testing, WuXi ATU, WuXi DDSU
- **Provide cell and gene therapy CTDMO partnership**
  - Integrated development, manufacturing, and testing services can be tailored to meet client needs
- **New Facility in PA**
  - Triples current testing capacity for cell and gene therapy
  - Full testing capabilities covering assay development, biologics safety testing, viral clearance, commercial lot release assays
- **New Facility in Shanghai**
  - Offers integrated development, manufacturing, and testing services for viral vectors and cell therapies to global clients



Source: "Investor WuXi AppTec 2022 January J.P. Morgan Healthcare Conference", https://static.wuxiapptec.com/94/20220110/94b8693d84640711.pdf. Accessed Mar. 25.; "Cell and Gene Therapy CTDMO", https://advancedtherapies.com/cell-and-gene-therapy-cdmo/. Accessed Mar. 25.

WuXi AppTec (Pink Limited Infromation:WUXAY) Cell and Gene Therapy Pipeline



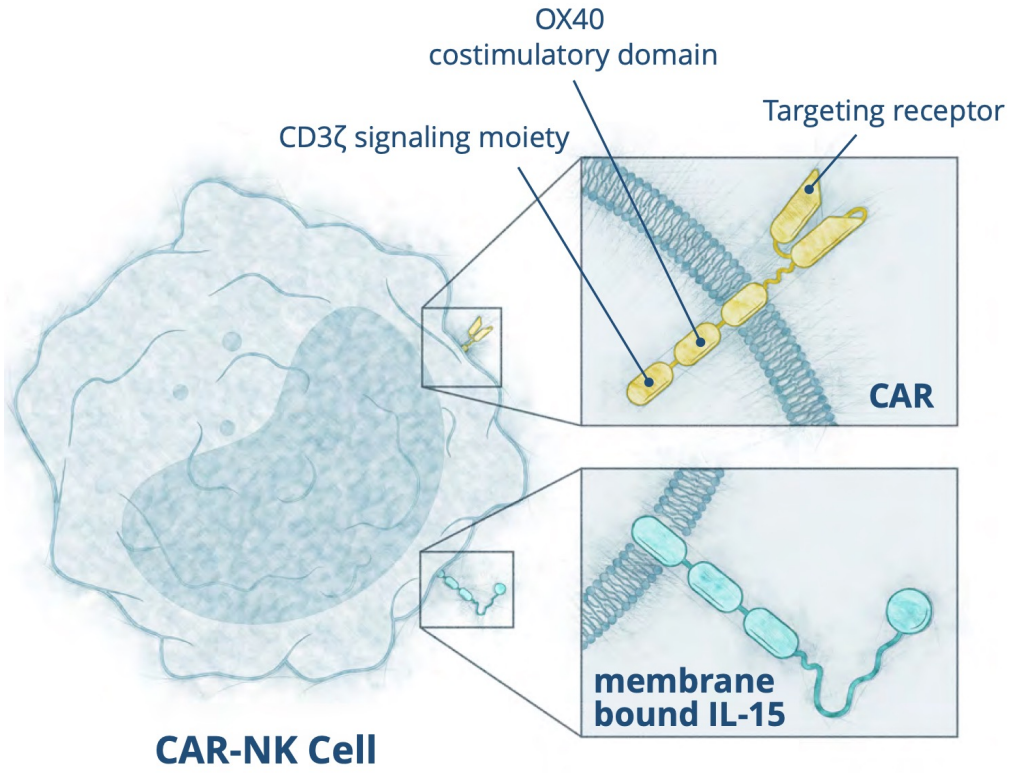
Source: "WuXi AppTec 2021 Annual Results", https://static.wuxiapptec.com/ea/20220323/eaae5248c71f3513.pdf. Accessed Mar. 25.

Natural Killer (NK) Cell Therapy

Nkarta, Inc	Slide 69
Artiva Biotherapeutics, Inc	Slide 71

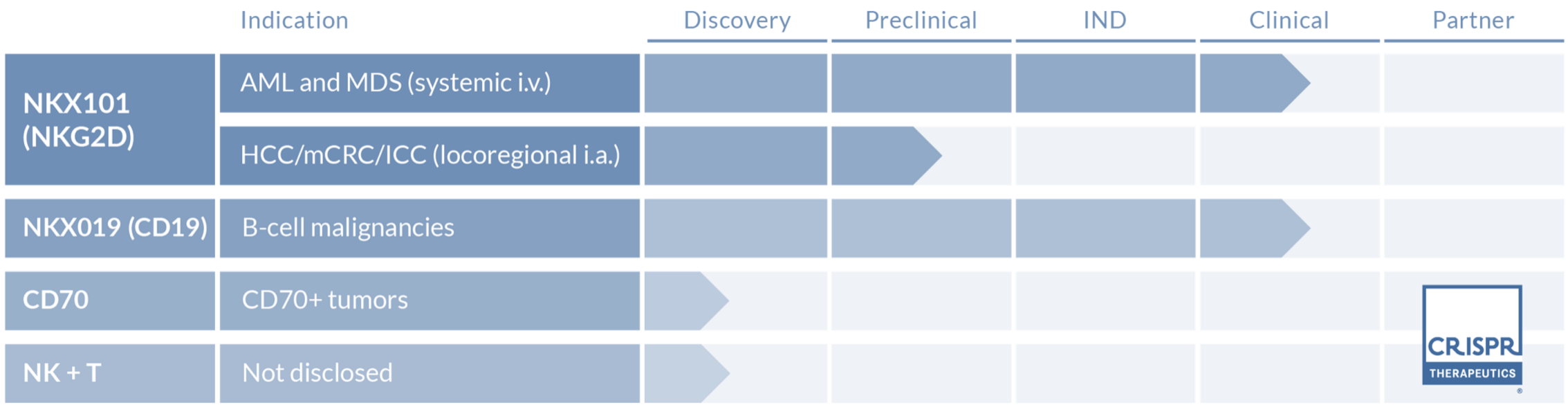
Nkarta, Inc (NasdaqGS: NKTX)

- **NK cell platform built for**
  - Blood cancers and solid tumors, allogeneic and off-the-shelf, industrialized manufacturing, and outpatient administration
- **Genome engineering capability**
  - Clinically validated **CRISPR gene editing**,
  - Ability to deploy up to 5 CRISPR/Cas9 gene edits in unlimited number of Nkarta product candidates
- **Experienced clinical development partner**
- **A Platform That Incorporates Multiple Next Generation Enhancements**
  - No requirement for cytokine support, Enhanced expansion, persistence and TME resistance via CISH deletion, armored cells with membrane-bound IL-15 for persistence



Source: "NEXT GENERATION Natural Killer Cells Engineered to Beat Cancer", https://ir.nkartatx.com/static-files/8db681b8-4ea3-452f-a3e6-3a151d8866d9. Accessed Mar. 15.

Nkarta, Inc (NasdaqGS: NKTX) Pipeline

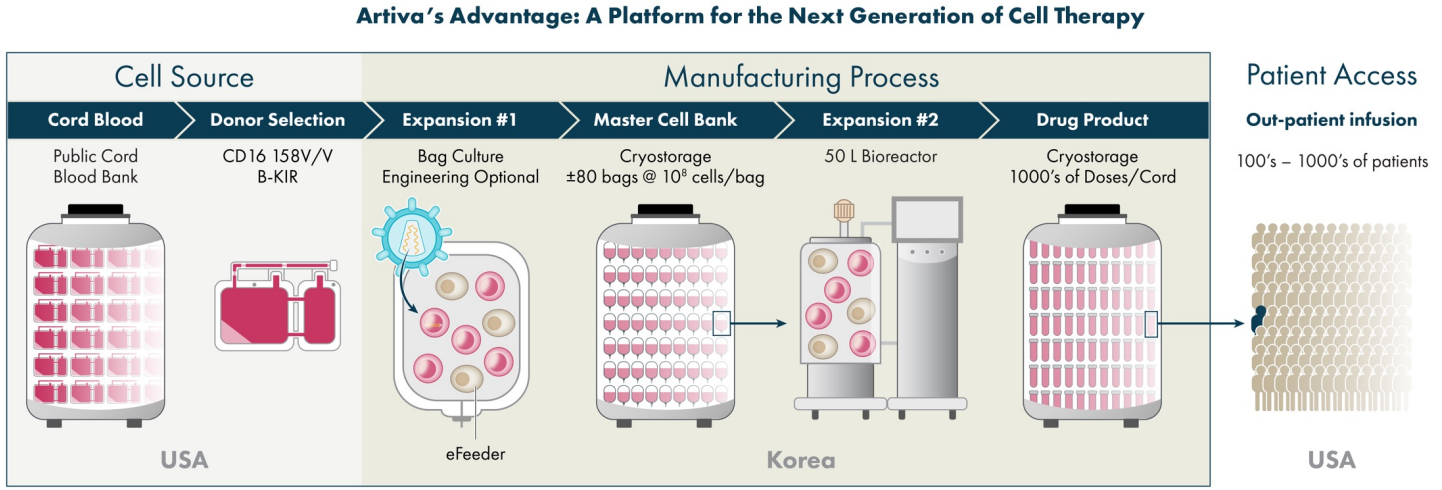


Source: Nkarta, Inc

Source: "Pipeline", https://www.nkartatx.com/pipeline/. Accessed Mar. 15.

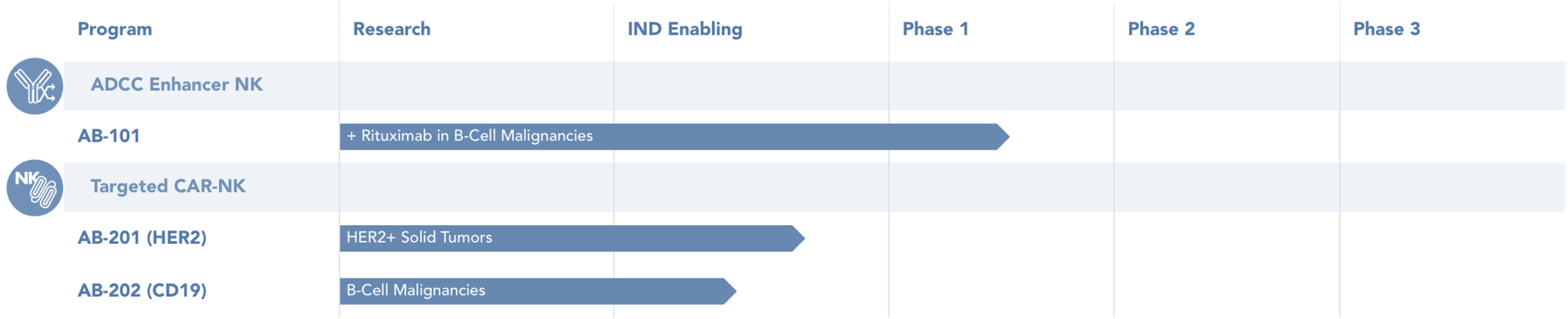
Artiva Biotherapeutics, Inc (Pre-IPO)

- **Manufacturing-First approach**
  - enabled us to produce, store and ship our product candidates and make them accessible like traditional protein biologic therapies.
- **Twofold product strategy**
  - **ADCC Enhancers** – NK cells that can enhance a patient's antibody-dependent cellular cytotoxicity (ADCC) response when undergoing monoclonal antibody therapy, increasing the therapy's anti-tumor activity.
  - **Targeted CAR-NK** – NK cells engineered to express proprietary chimeric antigen receptors (CARs) that have the potential to enhance the targeting and activity of the NK cells.
- **Proprietary Off-the-Shelf AlloNK™ Cell Therapy Platform**
- **Strategic Partnerships with MERK, Affimed, GC Cell**



Source: "AMENDMENT NO. 3 to SEC FORM S-1", https://www.sec.gov/Archives/edgar/data/0001817241/000119312522068001/d76940ds1a.htm. Accessed Mar. 15.

Artiva Biotherapeutics, Inc (Pre-IPO) Pipeline

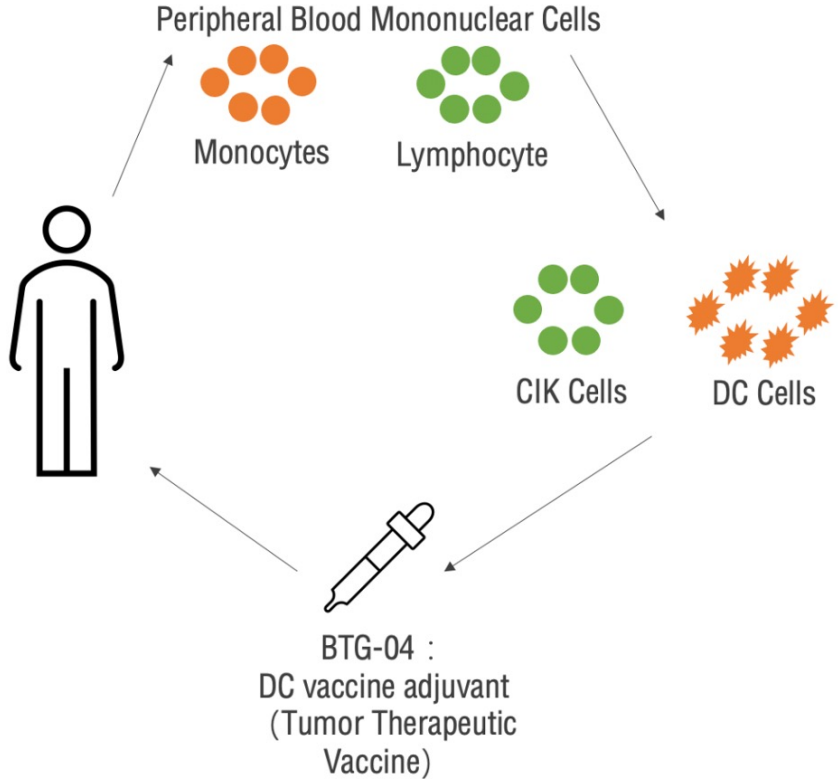


Source: "NK Cell Therapies", https://www.artivabio.com/nk-cell-therapy-pipeline/. Accessed Mar. 15.

Gamma Delta T Cell Therapy

Beroni Group Limited (OTCQX: BNIGF)

- **Next-Gen oncology drug: PENAO** has shown pre-clinical activity in a variety of cancers including ovarian, breast, and pancreatic cancer
- **Proprietary Allogenic Gamma Delta T-Cell Formula**
  - can improve the survival and tumor killing capability of Gamma Delta T-cells
  - Shown to kill cancer cells in preclinical trial
  - Preliminary clinical trial shown treatment for solid tumors is safe, no rejection, and cell factor- free storm
- **DC Vaccine Adjuvant**
  - Our technology can prepare antigen-presenting cells (APCs) with the ability to activate T cells, and use the properties of APCs to prepare pharmaceutical compositions for effective treatment of cancer and infectious diseases
- **Joint Gene Detection Lab with ThorGene**



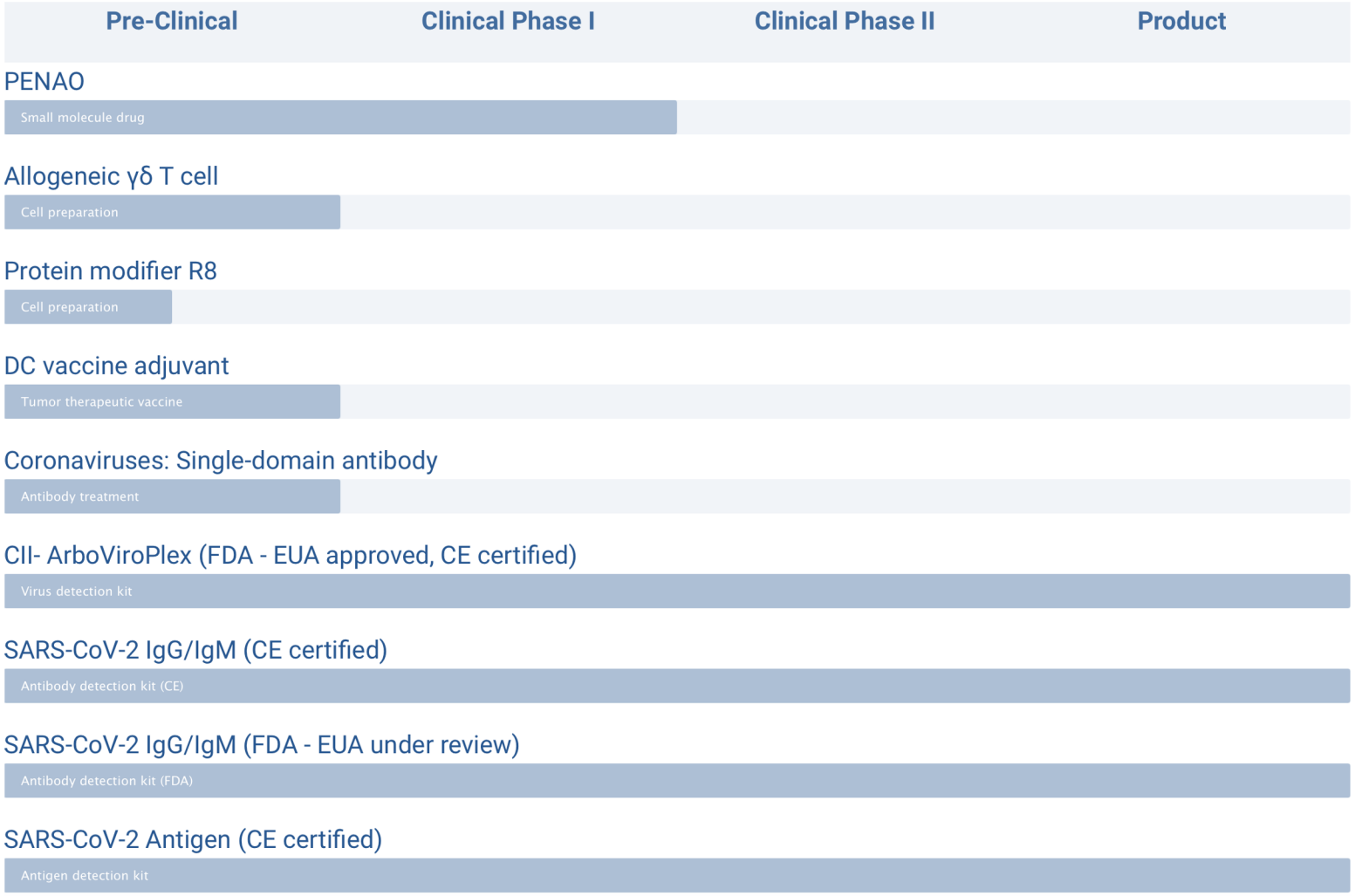
Source: "Beroni Group Ltd. A diversified global biopharmaceutical enterprise", Beroni Group PPT. Accessed Mar. 28.

Beroni Group Limited (OTCQX: BNIGF) γδ T Clinical Trial

- Clinical trials have shown gamma delta T cell therapy was safe for clinical treatment of tumors.
  - No clinical side effects were observed
  - Patients felt an improvement in quality of life
- According to clinical observations and tests, for most tumor patients, effects of therapy were significant
- γδ T cell therapy has a significant impact on the immune function of some patients and can significantly up-regulate the expression levels of cytokines such as tumor necrosis factor and interferon in patients.
- With positive trial results, the curative effect on postoperative tumor and the effect on the patient's immune function need to be followed up.

Source: "Clinical exploration and industrial transformation of allogeneic γδ T cells against solid tumors ", Beroni Group PPT. Accessed Apr. 18.

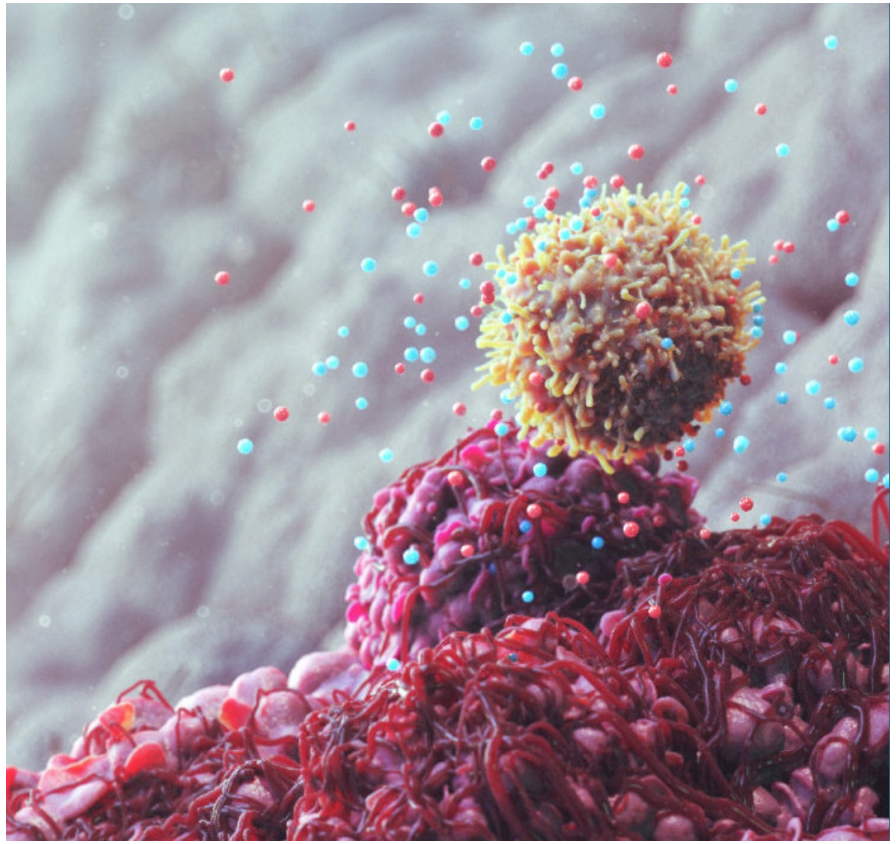
Beroni Group Limited (OTCQX: BNIGF) R&D Pipeline



Source: "RESEARCH & DEVELOPMENT", https://www.beronigroup.com/rd/. Accessed Mar. 28.

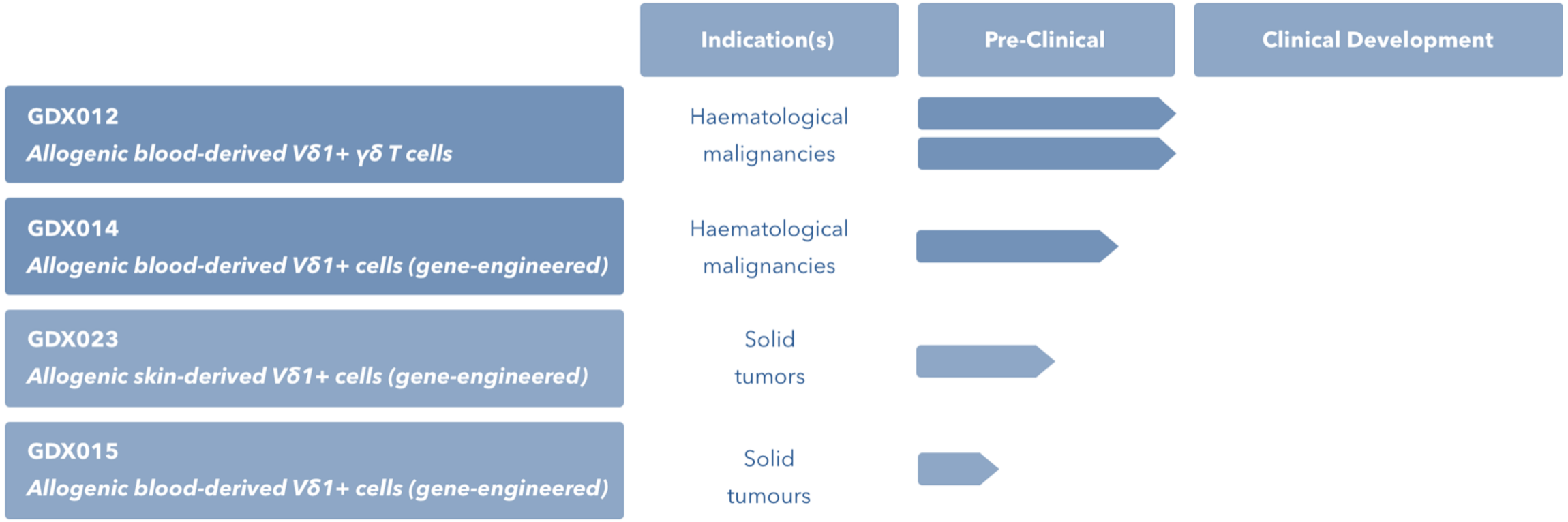
GammaDelta Therapeutics

- **Ability to expand distinct populations of Vδ1⁺ T cells from both tissue and blood** allows us to compare their properties and explore their complementary potential for treatment of various diseases.
- We are **exploring introduction of Chimeric Antigen Receptors (CAR) and other gene constructs into our Vδ1⁺ T cells to target cancers and other serious diseases.**
- **Takeda announced the exercise of option to acquire GammaDelta Therapeutics**
  - Deal expected to be finalized in Q1 of Takeda's 2022 fiscal year
- **Strategic Partners**
  - Kings College London, The Francis Crick Institute, Cancer Research Technology, Takeda



Source: "THE SCIENCE", https://gammadeltatx.com/the-science/. Accessed Mar. 21.; "PARTNERING", https://gammadeltatx.com/partnering/. Accessed Mar. 21.; "Takeda to Acquire GammaDelta Therapeutics to Accelerate Development of Allogeneic γδT Cell Therapies Addressing Solid Tumors", https://gammadeltatx.com/takeda-to-acquire-gammadelta-therapeutics-to-accelerate-development-of-allogeneic-γδt-cell-therapies-addressing-solid-tumors/. Accessed Mar. 21.

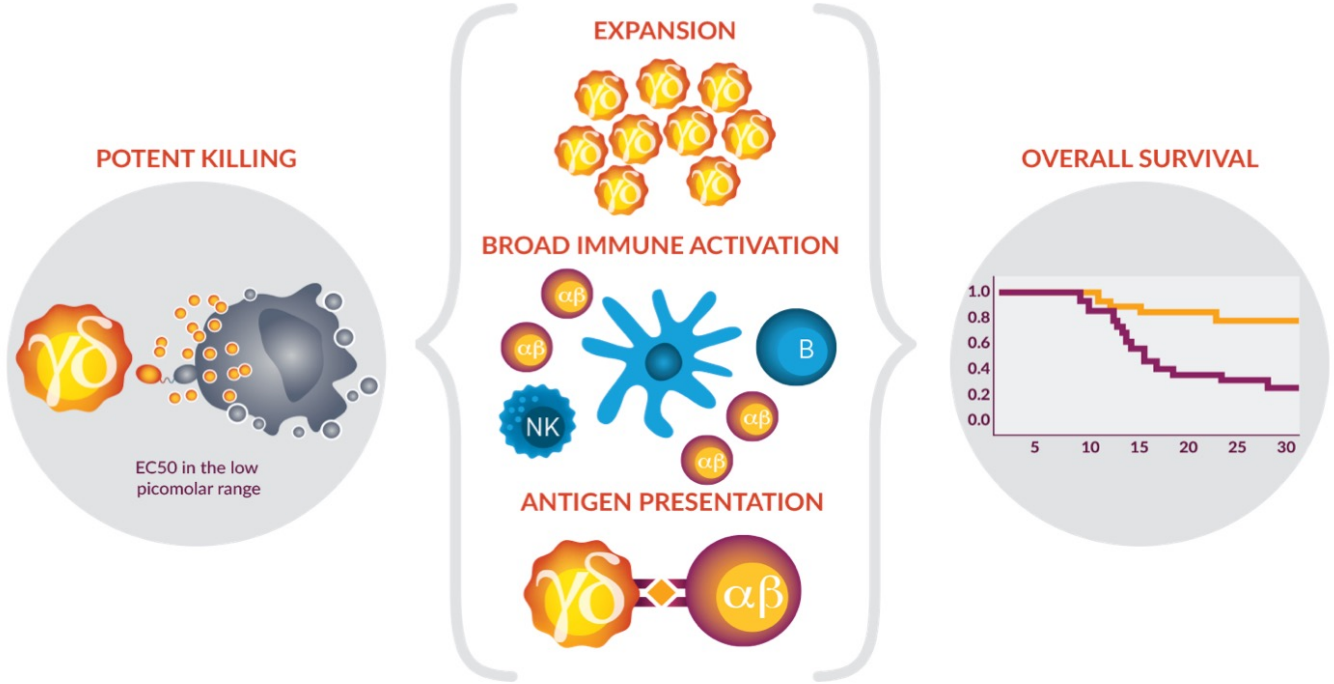
GammaDelta Therapeutics Pipeline



Source: "Our Pipeline", https://gammadeltatx.com/our-pipeline/. Accessed Mar. 17.

LAVA Therapeutics N.V. (NasdaqGS: LVTX)

- **Proprietary Platform Gammabody™**
  - platform triggers the potent and precise antitumor properties of Vg9Vd2 T cells
  - First off-the-shelf bispecific gd T cell engager platform
- **Potential to address broad patient populations with high unmet medical needs regardless of tumor mutational load**
- **Leverages unique characteristics of Vg9Vd2 T cells to provide a wider therapeutic window**



Source: "Fighting Cancer with Precision GammabodyTM Platform", https://ir.lavatherapeutics.com/static-files/6aa38edc-ee3e-40bc-8d49-c55a6008e980, Accessed Mar. 17.

LAVA Therapeutics N.V. (NasdaqGS: LVTX) Pipeline

Candidate	Antigen Target	Indication(s)	Discovery	Preclinical	Phase 1	Phase 2	Phase 3
LAVA-051	CD1d	MM CLL AML					
LAVA-1207	PSMA	mCRPC					
LAVA-1223	EGFR	Solid Tumors					
LAVA-1278	CD40	Hematologic Malignancies					
Janssen Biotech Collaboration	undisclosed						

Hematologic malignancy
Solid Tumor

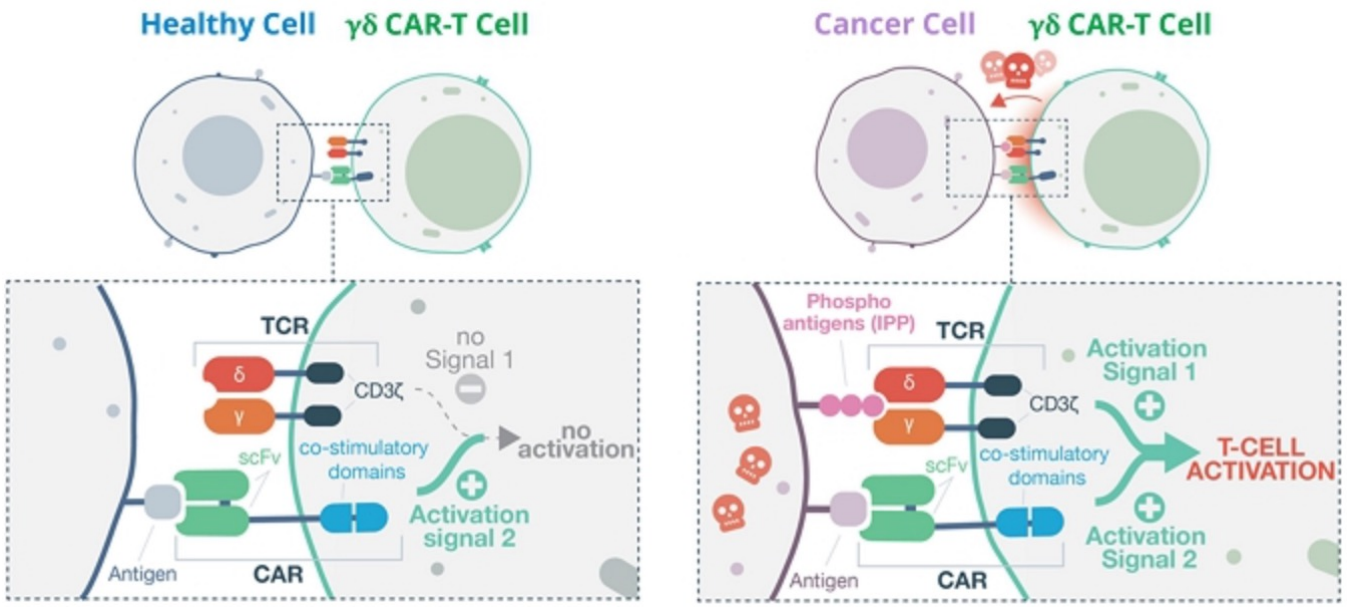
MM: multiple myeloma
CLL: chronic lymphocytic leukemia
AML: acute myeloid leukemia

PSMA: prostate-specific membrane antigen
EGFR: epidermal growth factor receptor
mCRPC: metastatic castration-resistant prostate cancer

Source: "Pipeline", https://www.lavatherapeutics.com/pipeline-programs/pipeline/, Accessed Mar. 17.

TC BioPharm (Holdings) plc (NasdaqCM: TCBP)

- **Step-wise approach to clinical development and commercialization**
  - Clinical transition from autologous GD-Ts to allogeneic GD-Ts to CAR-modified allogeneic GD-Ts
- We have built a world-class **fully integrated GMP grade specialist GD-T manufacturing cente**r in Glasgow, Scotland
  - Facility undertakes all key functions associated with our GD-T cell development, testing, quality assurance, product manufacture, clinical trial recruitment, management design, support and interaction with regulators
- **Allogeneic Cell Banks**
  - Donor GD-Ts selection based on highest therapeutic quality



Source: "AMENDMENT NO. 6 to SEC FORM F-1", https://www.sec.gov/Archives/edgar/data/0001872812/000149315222003620/formf-1a.htm. Accessed Mar. 17.

TC BioPharm (Holdings) plc (NasdaqCM: TCBP) Pipeline

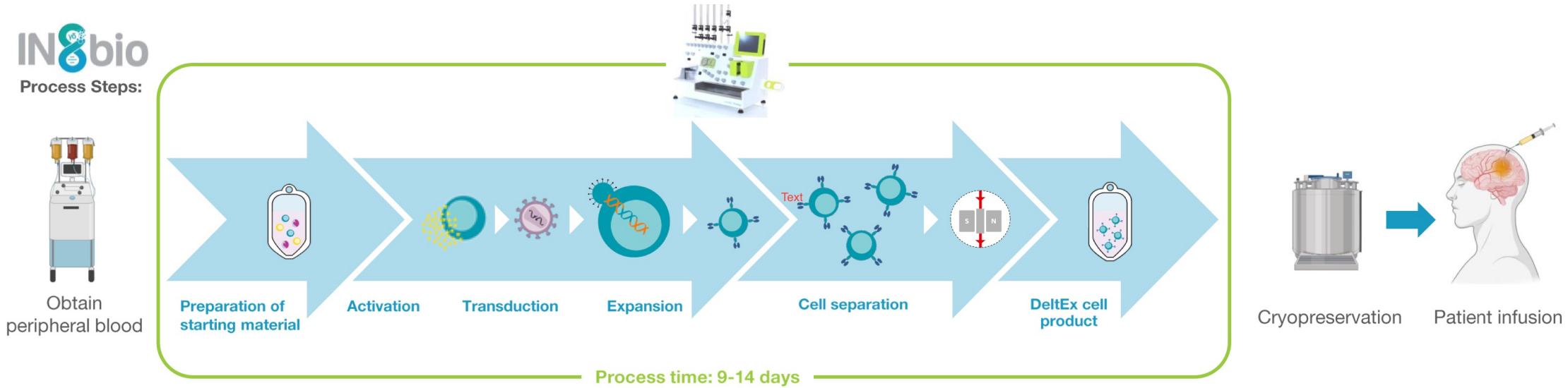
Includes focused CAR-GDT cell therapy pipeline

Program	Indication	Pre-clinical	Phase 1	Phase 2	Phase 3	Status / Upcoming Milestone
TCB001 Autologous (unmodified)	Melanoma			2a		Phase 1b/2a POC complete – evidence of tumor shrinkage (not pursuing further development)
OmnImmune (Vδ2 subtype) Allogeneic unmodified)	**AML/Haem**			2a		Phase 1b/2a complete H1 2020 – PR/CR achieved **Phase 2b into pivotal commences H1 2022** **Launch planned 2023**
ImmuniStim (Vδ2 subtype)	**Viral/Covid**		1b			**Phase 1b/2a commenced H1 2022**
TCB009 (Vδ1 subtype)	**GI Tract**					**Phase 1b/2a planned 2023 (GI-tract cancers)**
TCB005/6 (Vδ2 CAR-T)	**Solid tumors**					**Phase 1b/2a planned 2023 (B7H3/5T4)**

Source: "AMENDMENT NO. 6 to SEC FORM F-1", https://www.sec.gov/Archives/edgar/data/0001872812/000149315222003620/formf-1a.htm. Accessed Mar. 17.

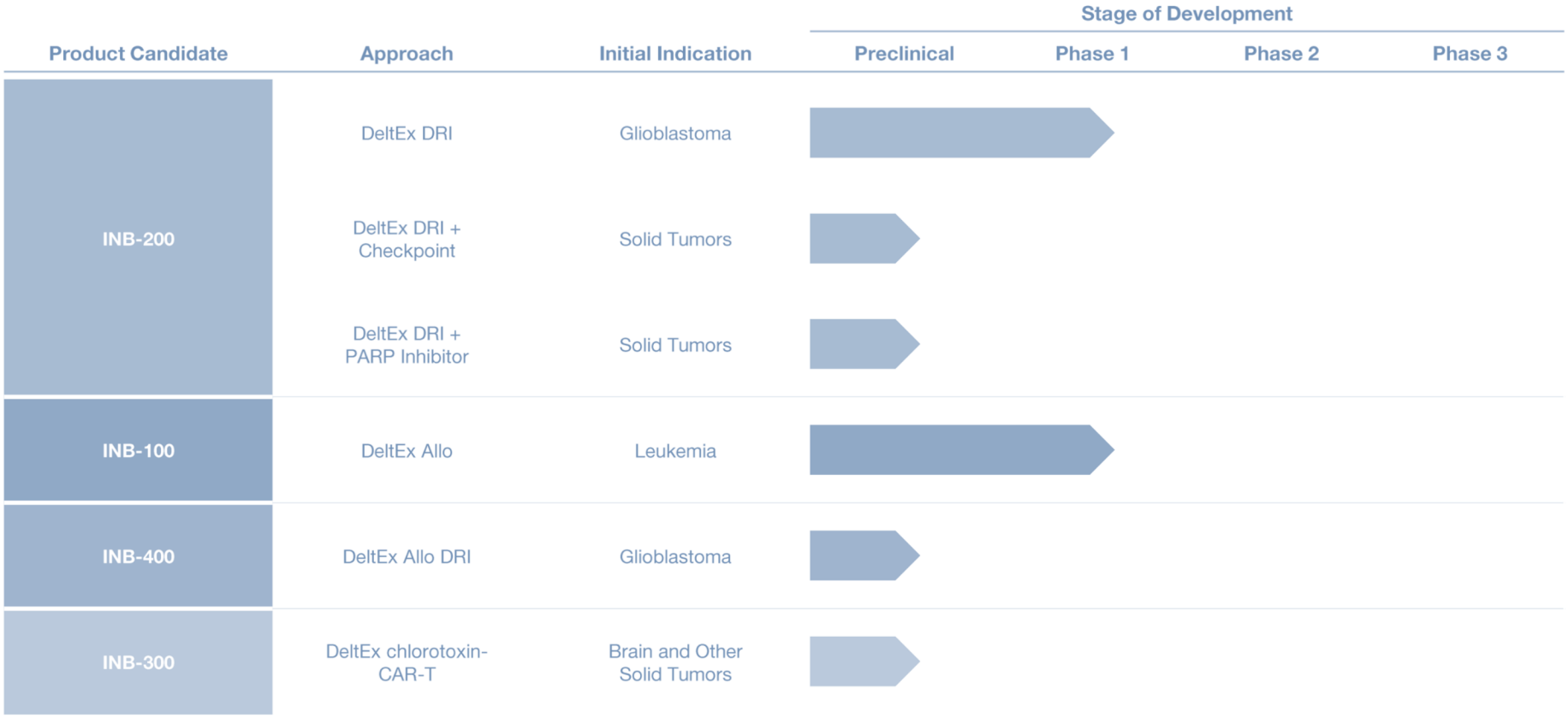
IN8bio, Inc (NasdaqGM: INAB)

- **Automated, robust and scalable cell manufacturing within the CliniMACS Prodigy®**
  - Consolidates entire manufacturing process in a single closed system to reduce risks of contamination
- **Proprietary gamma-delta T cell engineering**
  - DeltEx Drug Resistant Immunotherapy, or DRI protects cells to survive chemotherapy and maintains natural ability to recognize, engage and kill cancer cells



Source: "IN8bio A Leader in Gamma-Delta T Cells", https://investors.in8bio.com/static-files/7e194a1f-faac-4bca-a82e-0856673562f3. Accessed Mar. 17.

IN8bio, Inc (NasdaqGS: INAB) Pipeline



Source: "IN8bio A Leader in Gamma-Delta T Cells", https://investors.in8bio.com/static-files/7e194a1f-faac-4bca-a82e-0856673562f3. Accessed Mar. 17.

Thanks!

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