ZS's assessment of the cell and gene therapy pipeline

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The field of cell and gene therapy (C&GT) represents a heterogenous set of therapy types that includes many modalities and technologies. Building successful C&GT development and commercialization strategies requires an understanding of the major market trends, how the therapy types are distributed across the clinical landscape and why some therapies are preferred over others based on their scientific rationale.

ZS regularly covers the C&GT landscape and highlights key insights. Here are three key trends on therapies in development and trials to date.

FIGURE 1: Efficacy and safety data for autologous vs. allogeneic cell therapies in development

Autologous cell therapies

Indication	Effiicacy(%)		Safety and Adverse Events (%)	
	Overall Survival (OS) and Progression-Free Survival (PFS) (in months)	Overall Response Rate (Complete Response Rate)	Cytokine Release Syndrome (Gr3+)	Neurotoxicity (Gr3+)
Autologous CAR-Ts				
Large B-Cell Lymphoma (LBCL) n=361 eff, n=475 safety	-	50–73 (32–54)	46–94 (4–23)	35–87 (12–31)
Mantle Cell Lymphoma (MCL) n=68	-	93 (67)	91 (18)	81 (37)
Acute Lymphoblastic Leukemia (ALL) n=134	-	NA (71–83)	79 (24–49)	72 (25–1)
Multiple Myeloma (MM) n=271	18.8 PFS	67–100 (28–79)	85–95 (4–9)	21–28 (4–10)
Follicular Lymphoma (FL) n=94		86 (66)	49 (0)	9 (1)
Chronic Lymphocytic Leukemia (CLL) n=23	18 PFS	82 (45)	-	-
Pancreatic Cancer n=5	4.3 PFS	-	Only qualitative data**	None*

Allogeneic cell therapies

Indication	Effiicacy(%)		Safety and Adverse Events (%)	
	Overall Survival (OS) and Progression-Free Survival (PFS)	Overall Response Rate (Complete Response Rate)	Cytokine Release Syndrome (Gr3+)	Neurotoxicity (Gr3+)
Allogeneic CAR-Ts				
Large B-Cell Lymphoma (LBCL) n=20 eff, 24 safety	-	56–64 (46–56)	15–27^ (8)	-
Follicular Lymphoma (FL) n=21	-	81 (52)	27^ (0)	-
Non-Hodgkin Lymphoma (NHL) n=27	-	36–69 (36–38)##	30^(0)	10^^(0)
Acute Lymphoblastic Leukemia (ALL) n=17	-	36–83## (36–83)***	100 (0)	None*
Multiple Myeloma (MM) n=15	-	~33.3##	24^(0)	None*
Acute Myelogenous Leukemia (AML) n=3	-	100 (33)	66^^(0)	-
Allogeneic NK cells				
Diffuse Large B-Cell Lymphoma (DLBCL) n=10	66% (at 12 months OS)	(50)	22^^(0)	None*
Non-Hodgkin Lymphoma (NHL) n=6	-	66	None*	None*
Chronic Lymphocytic Leukemia (CLL) n=5	-	80	None*	None*
Follicular Lymphoma (FL) n=7	66% (at 12 months OS)	(100)	None*	None*
Acute Myelogenous Leukemia (AML) n=17, n=13 eff	7.5 months OS	79 (50)	None*	None*
Multiple Myeloma (MM) (n=48)	-	(44–65)	None*	None*
B-Cell Lymphoma (BCL) n=20	-	66–71 (50)	14^(0)	None*

FIGURE 1 FOOTNOTES

Note: Removed indications wherever clinical data was not available, i.e., Melanoma (autologous TCR-T), Chronic Lymphocytic Leukemia (allogeneic CAR-T), Leukemia and cytomegalovirus (CMV) infection (allogeneic TCR-T), Non-Small Cell Lung Cancer (allogeneic dendritic cell), Solid Tumor, Brain Cancer and Multiple Myeloma (allogeneic NK cells).

- No data available

* No cases reported

** Qualitative data was available that stated only Grade 1 or 2 cytokine release syndrome (CRS) was observed.

*** Cytokine release syndrome for CTA-101, overall response rate (ORR), was not reported for this molecule.

Cross-dosed

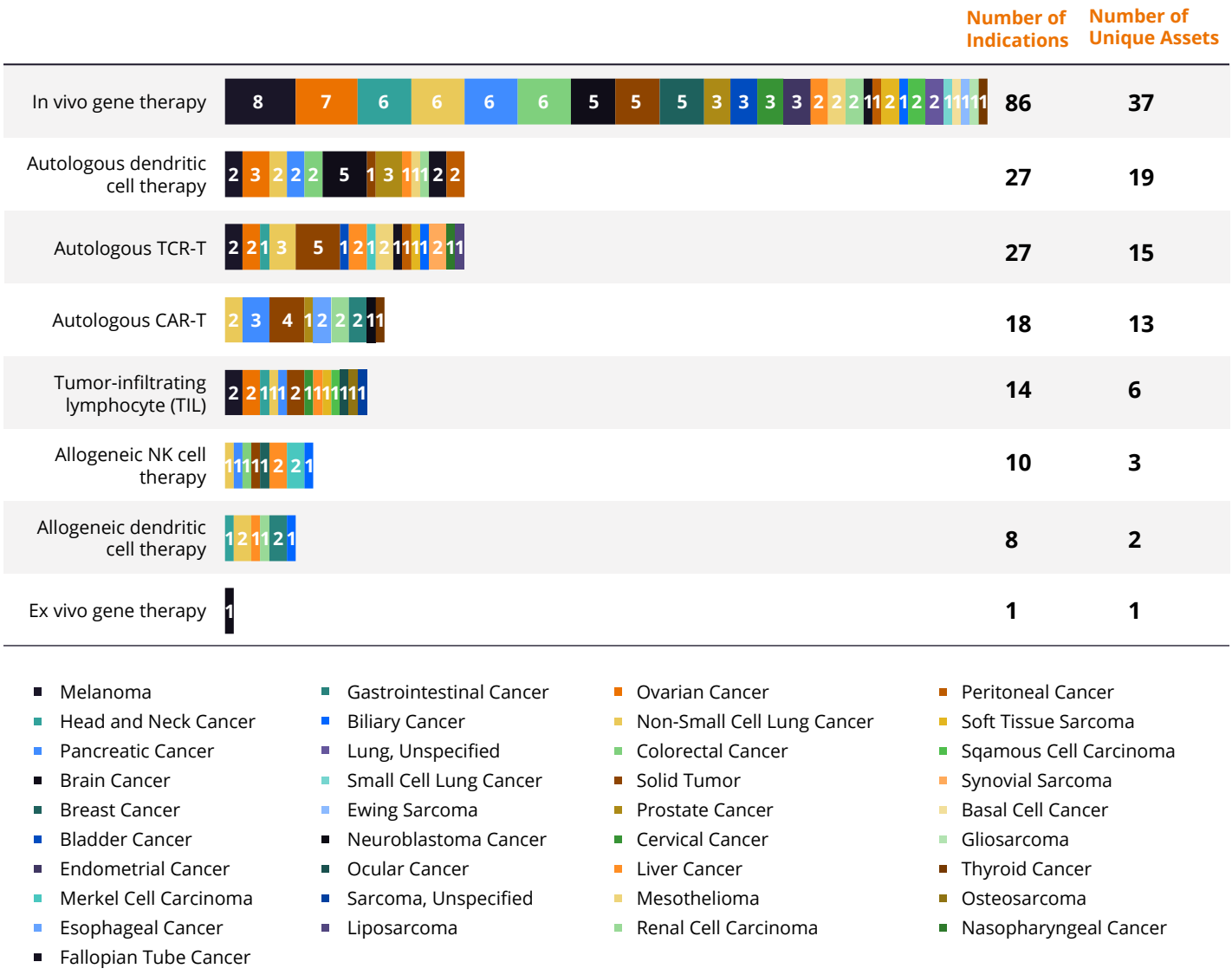
^ Grade 1 or 2 cytokine release syndrome (CRS) was observed.

^^ Grade 1 cytokine release syndrome (CRS) was observed.

Allogeneic NKs have the potential to displace current cell therapies in oncology

Although they are still early in development, the responses seen from allogeneic NK cells appear comparable in terms of response rate but demonstrate the added benefit of dramatically reduced toxicity. NKs do not need to worry about knocking out additional genes to avoid graft versus host disease (GvHD) when being developed for allogeneic administration, due to the major histocompatibility complex (MHC) independent mechanisms of NK cells and their limited lifespan in circulation relative to T-cells. Additionally, NKs release a set of secreted cytokines distinct from the set induced by CAR-T cells that are highly associated with cytokine release syndrome (CRS) and neurotoxicity (NT). For example, NKs do not generally excrete IL-6 as one of their primary cytokines, once activated.

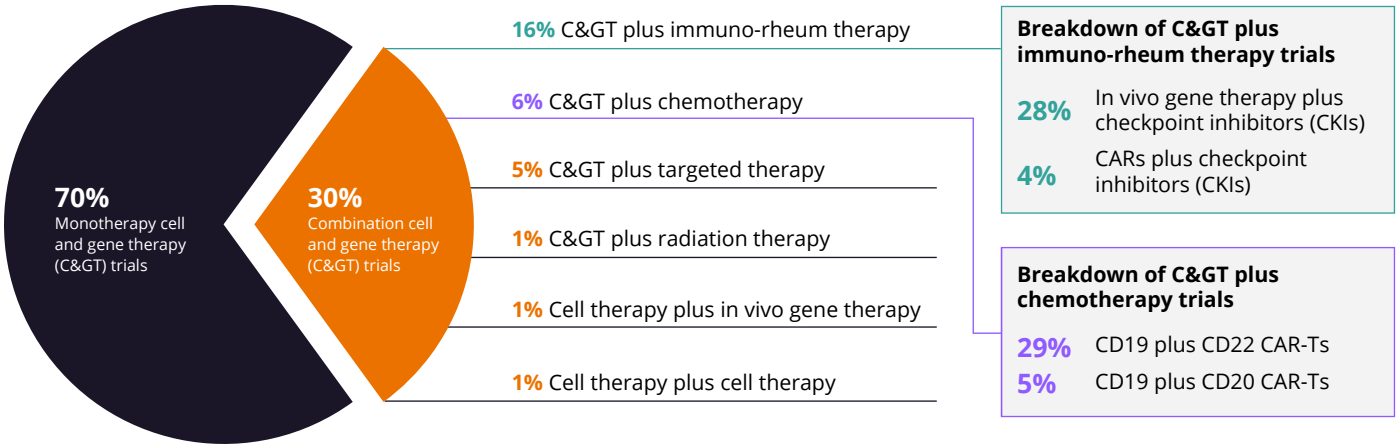
FIGURE 2: Number of indications and unique assets for cell and gene therapies in solid tumors



In vivo gene therapies may help improve the treatment of solid tumors

In vivo gene therapies (versus cell-based therapies) could be the more prominent C&GT technology used to treat solid cancers. In figure 2, we highlight the number of unique cancer targets being targeted by therapy type, disease indication, total number of indications and number of unique assets in Phase 2 or later trials. Of all the solid cancer indications being investigated by C&GTs, there are the most in vivo gene products currently in the pipeline, with 37 unique assets targeting 86 indications currently under investigation. In vivo gene therapies offer the potential to reduce the complicated logistics and long turnaround times (TATs) associated with TCR and CAR therapies, which may serve as an off-the-shelf option. Gene therapies should also be, theoretically, much less affected by the tumor immune microenvironment (TME).

FIGURE 3: Overview of mono vs. combination cell and gene therapy trials to date



While the first wave of C&GTs are single agents, the future may be combinations

C&GT combinations have the potential to revolutionize the overall oncology market. Although the majority of treatments being studied today focus on just one therapy, approximately 30% are being studied in combination with other therapies. In fact, there are nearly 350 combination trials currently in progress, including combinations of cell with gene therapies, cell therapies with each other, in vivo gene therapies with each other, and cell and C&GTs with checkpoint inhibitors. In figure 3, we break down the trial landscape to date, illustrating some of the types of combinations in these trials, which are pairing C&GTs with immuno-rheum therapies, chemotherapy, targeted therapy, radiation therapy and in vivo gene therapy—among others.

The ZS view on cell and gene therapy

ZS helps turn hope into reality by simplifying and accelerating the process of discovering, developing and delivering transformational, durable and life-changing C&GTs to patients. For more on the challenges we solve, the impact we bring our clients and our approach to the interconnected and specialized challenges in cell and gene therapy, please visit:

https://www.zs.com/industries/pharmaceuticals-biotech/cell-and-gene-therapy

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