Gene, Cell, + RNA Therapy Landscape Report

Q4 2023 Quarterly Data Report

About the authors

The American Society of Gene & Cell Therapy (ASGCT) is the primary professional membership organization for scientists, physicians, patient advocates, and other professionals with interest in gene and cell therapy.

Our members work in a wide range of settings including universities, hospitals, government agencies, foundations, biotechnology, and pharmaceutical companies. ASGCT advances knowledge, awareness, and education leading to the discovery and clinical application of gene and cell therapies to alleviate human disease to benefit patients and society.

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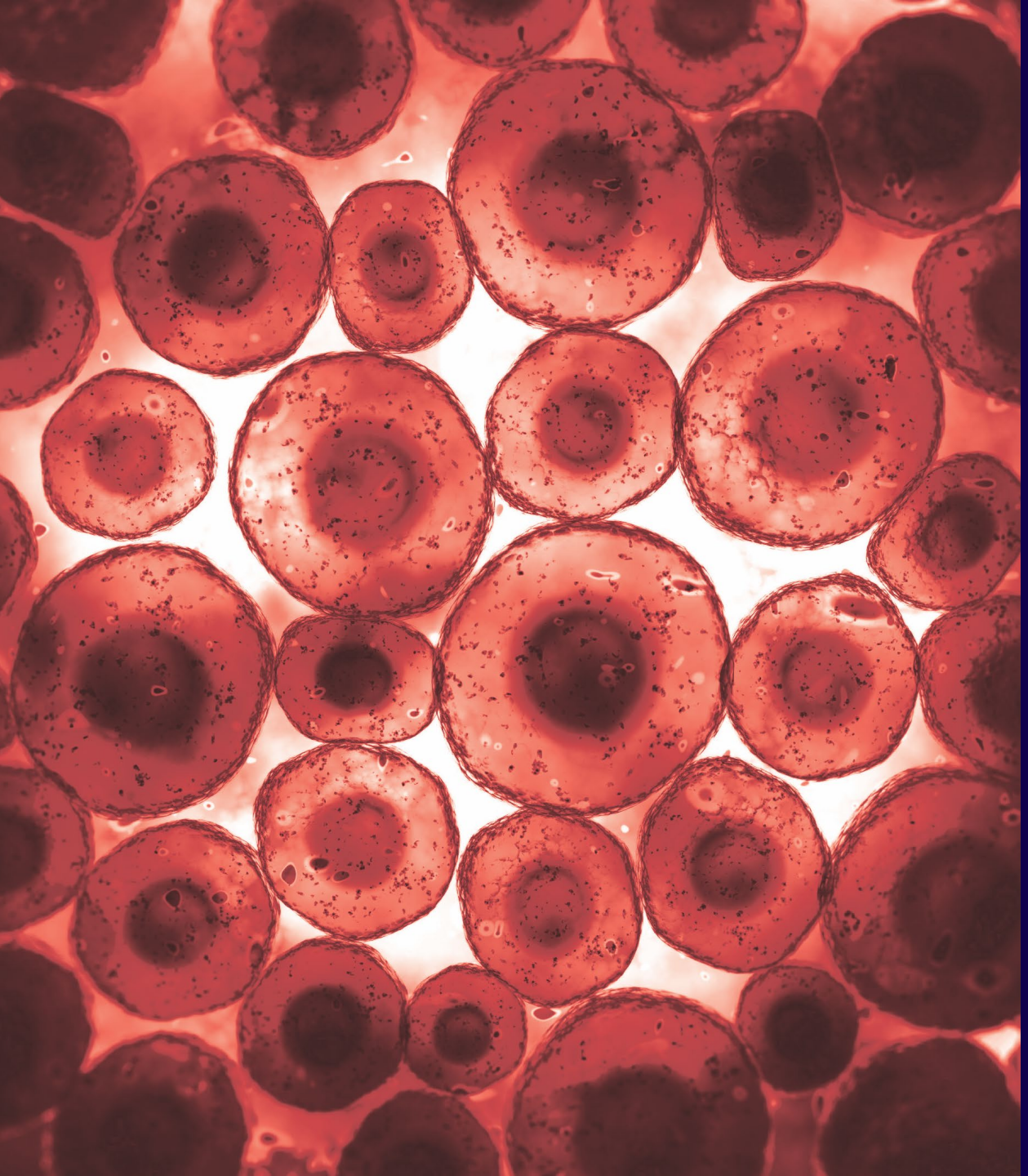


Table of contents

American Society of Gene + Cell Therapy

Introduction

Welcome to the final quarterly report of 2023 from ASGCT and Citeline! Q4 was notable for two gene therapies—Casgevy and Lyfgenia—being approved in the U.S. to treat sickle cell disease. Casgevy also represents the first-ever approval for a CRISPR-based therapeutic in the United States. Two RNA therapies were also approved in the U.S. in Q4; Wainua was approved for transthyretin-related hereditary amyloidosis and Rivfloza was approved for hyperoxaluria.

In Q4, the number of gene therapies in Phase III clinical trials grew by 10%, which was the first quarterly increase of that type since Q3 2022. Across the pipeline in 2023, RNA therapies had the largest number of approvals at eight, including five approvals for COVID-19 vaccines.

Dealmaking and funding have entered an inverse pattern; while just 93 transactions were completed in Q4 (the lowest in 2023 and a 19% decrease from Q3), overall funding nearly doubled from the quarter prior with $683 million raised from 12 financings in Q4.

Key takeaways from Q4 2023

Across 2023, the pipeline (preclinical to pre-registration) of gene, cell, and RNA therapies has grown by 6%

- This is a similar growth rate as in 2022, which saw the pipeline increase by 7% over 2021
- In a continuing trend across the past year, oncology and rare disease indications have consistently been the top areas of pipeline development for both gene therapies and non-genetically modified cell therapies
- For RNA therapies, however, 2023 saw anti-infective indications overtaking oncology to become the second most common area of pipeline development, behind rare diseases

RNA therapies saw the greatest number of approvals across the gene, cell, and RNA therapy landscape in 2023, with eight first-time approvals

- Five of these new RNA therapy approvals were for COVID-19 vaccines
- Q4 2023 specifically was a notable quarter, seeing three new gene and three new RNA therapies being approved

Dealmaking continued to decline for advanced molecular therapy companies

- A total of 93 transactions completed represented a 19% decrease from Q3 2023, as well as the lowest quarterly amount in all of 2023
- Acquisitions were a bright spot, increasing quarter over quarter with 10 in Q4, led by AstraZeneca's $1.2bn purchase of autologous and allogeneic cell developer Gracell
- Start-up financing volume continued to trend downward, amounting to 12 transactions in Q4, a 29% decrease from the previous quarter; but total financing value rebounded, almost doubling to $683m

Key highlights in Q4 2023

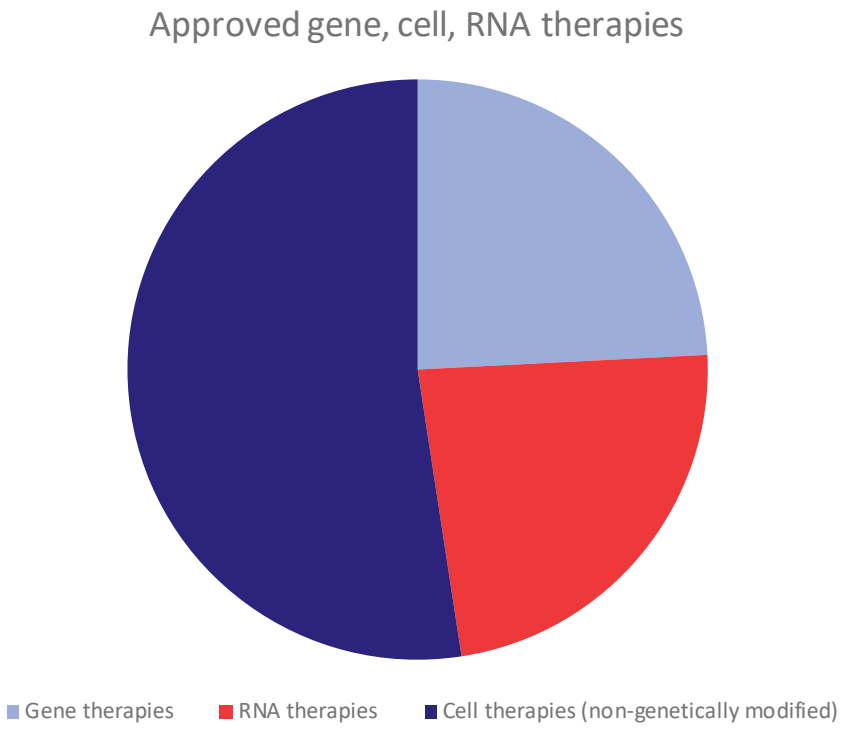
Q4 2023

American Society of Gene + Cell Therapy

Approved gene, cell, and RNA therapies

Globally, for clinical use:

- 30 gene therapies have been approved (including genetically modified cell therapies)
  - In Q4 2023, **Casgevy** was approved in the US for sickle cell disease and in the UK for both sickle cell disease and transfusion-dependent β-thalassemia, **inaticabtagene autoleucel** was approved in China for acute lymphocytic leukemia, and **Lyfgenia** was approved in the US for sickle cell disease
- 29 RNA therapies have been approved
  - In Q4 2023, **Wainua** was approved in the US for transthyretin-related hereditary amyloidosis, **Rivfloza** was approved in the US for hyperoxaluria, and **SYS-6006.32** was granted emergency use in China for COVID-19 prophylaxis
- 65 non-genetically modified cell therapies have been approved



Source: Pharmaprojects | Citeline, January 2024

Approved gene therapies as of Q4 2023 (1/3)

Product name	Generic name	Year first approved	Disease(s)	Locations approved	Originator company
Gendicine	recombinant p53 gene	2004	Head and neck cancer	China	Shenzhen SiBiono GeneTech
Oncorine	E1B/E3 deficient adenovirus	2005	Head and neck cancer; nasopharyngeal cancer	China	Shanghai Sunway Biotech
Rexin-G	mutant cyclin-G1 gene	2006	Solid tumors	Philippines	Epeius Biotechnologies
Neovasculgen	vascular endothelial growth factor gene	2011	Peripheral vascular disease; limb ischemia	Russian Federation, Ukraine	Human Stem Cells Institute
Imlygic	talimogene laherparepvec	2015	Melanoma	US, EU, UK, Australia	Amgen
Strimvelis	autologous CD34+ enriched cells	2016	Adenosine deaminase deficiency	EU, UK	Orchard Therapeutics
Kymriah	tisagenlecleucel-t	2017	Acute lymphocytic leukemia; diffuse large B-cell lymphoma; follicular lymphoma	US, EU, UK, Japan, Australia, Canada, South Korea, Switzerland	Novartis
Luxturna	voretigene neparvovec	2017	Leber's congenital amaurosis; retinitis pigmentosa	US, EU, UK, Australia, Canada, South Korea, Japan	Spark Therapeutics (Roche)
Yescarta	axicabtagene ciloleucel	2017	Diffuse large B-cell lymphoma; non-Hodgkin's lymphoma; follicular lymphoma	US, EU, UK, Japan, Canada, China, Australia	Kite Pharma (Gilead)
Collategene	beperminogene perplasmid	2019	Critical limb ischemia	Japan	AnGes
Zolgensma	onasemnogene abeparvovec	2019	Spinal muscular atrophy	US, EU, UK, Japan, Australia, Canada, Brazil, Israel, Taiwan, South Korea	Novartis
Zynteglo	betibeglogene autotemcel	2019	Transfusion-dependent beta thalassemia	US	bluebird bio

Source: Pharmaprojects | Citeline, January 2024

Text highlighted in yellow represents new approvals during Q4 2023

Approved gene therapies as of Q4 2023 (2/3)

Product name	Generic name	Year first approved	Disease(s)	Locations approved	Originator company
Tecartus	brexucabtagene autoleucel	2020	Mantle cell lymphoma; acute lymphocytic leukemia	US, EU, UK, Australia	Kite Pharma (Gilead)
Libmeldy	atidarsagene autotemcel	2020	Metachromatic leukodystrophy	EU, UK, Switzerland	Orchard Therapeutics
Breyanzi	lisocabtagene maraleucel	2021	Diffuse large B-cell lymphoma; follicular lymphoma	US, Japan, EU, Switzerland, UK, Canada	Celgene (Bristol Myers Squibb)
Abecma	idecabtagene vicleucel	2021	Multiple myeloma	US, Canada, EU, UK, Japan, Israel, Switzerland	bluebird bio
Delytact	teserpaturev	2021	Malignant glioma	Japan	Daiichi Sankyo
Relma-cel	relmacabtagene autoleucel	2021	Diffuse large B-cell lymphoma; folli cular lymphoma	China	JW Therapeutics
Skysona	elivaldogene autotemcel	2021	Early cerebral adrenoleukodystrophy (CALD)	US	bluebird bio
Carvykti	ciltacabtagene autoleucel	2022	Multiple myeloma	US, EU, UK, Japan, Australia, China	Legend Biotech
Upstaza	eladocagene exuparvovec	2022	Aromatic L-amino acid decarboxyla se (AADC) deficiency	EU, UK	PTC Therapeutics
Roctavian	valoctocogene roxaparvovec	2022	Hemophilia A	EU, UK, US	BioMarin
Hemgenix	etranacogene dezaparvovec	2022	Hemophilia B	US, EU, UK, Canada	uniQure
Adstiladrin	nadofaragene firadenovec	2022	Bladder cancer	US	Merck & Co
Elevidys	delandistrogene moxeparvovec	2023	Duchenne muscular dystrophy	US	Sarepta Therapeutics
Vyjuvek	beremagene geperpavec	2023	Dystrophic epidermolysis bullosa	US	Krystal Biotech
Fucaso	equecabtagene autoleucel	2023	Multiple myeloma	China	Nanjing IASO Biotechnology
Casgevy	exagamglogene autotemcel	2023	Sickle cell anemia; thalassemia	US, UK	CRISPR Therapeutics

Text highlighted in yellow represents new approvals during Q4 2023

Approved gene therapies as of Q4 2023 (3/3)

Product name	Generic name	Year first approved	Disease(s)	Locations approved	Originator company
inaticabtagene autoleucel	inaticabtagene autoleucel	2023	Acute lymphocytic leukemia	China	Juventas Cell Therapy
Lyfgenia	lovotibeglogene autotemcel	2023	Sickle cell anemia	US	bluebird bio

Source: Pharmaprojects | Citeline, January 2024

Text highlighted in yellow represents new approvals during Q4 2023

Approved RNA therapies as of Q4 2023 (1/3)

Product name	Generic name	Year first approved	Disease(s)	Locations approved*	Originator company
Kynamro	mipomersen sodium	2013	Homozygous familial hypercholesterolemia	US, Mexico, Argentina, South Korea	Ionis Pharmaceuticals
Exondys 51	eteplirsen	2016	Dystrophy, Duchenne muscular	US	Sarepta Therapeutics
Spinraza	nusinersen	2016	Muscular atrophy, spinal	US, EU, UK, Canada, Japan, Brazil, Switzerland, Australia, South Korea, China, Argentina, Colombia, Taiwan, Turkey, Hong Kong, Israel	Ionis Pharmaceuticals
Ampligen	rintatolimod	2016	Chronic fatigue syndrome	Argentina	AIM ImmunoTech
Tegsedi	inotersen	2018	Amyloidosis, transthyretin-related hereditary	EU, UK, Canada, US, Brazil	Ionis Pharmaceuticals
Onpattro	patisiran	2018	Amyloidosis, transthyretin-related hereditary	US, EU, UK, Japan, Canada, Switzerland, Brazil, Taiwan, Israel, Turkey, Australia	Alnylam
Vyondys 53	golodirsen	2019	Dystrophy, Duchenne muscular	US	Sarepta Therapeutics
Waylivra	volanesorsen	2019	Hypertriglyceridemia; lipoprotein lipase deficiency	EU, UK, Brazil, Canada	Ionis Pharmaceuticals
Comirnaty	tozinameran	2020	Infection, coronavirus, novel coronavirus prophylaxis	UK, Bahrain, Israel, Canada, US, Rwanda, Serbia, United Arab Emirates, Macao, Taiwan, Mexico, Kuwait, Singapore, Saudi Arabia, Chile, Switzerland, EU, Ghana, Colombia, Philippines, Indonesia, Australia, Hong Kong, Peru, South Korea, New Zealand, Japan, Brazil, Sri Lanka, Vietnam, South Africa, Thailand, Oman, Egypt, Malaysia	BioNTech
Moderna COVID-19 vaccine	COVID-19 vaccine, Moderna	2020	Infection, coronavirus, novel coronavirus prophylaxis	US, Canada, Israel, EU, Switzerland, Singapore, Qatar, Vietnam, UK, Philippines, Thailand, Japan, South Korea, Brunei, Paraguay, Taiwan, Botswana, India, Indonesia, Saudi Arabia, Mexico, Australia, Nigeria, Colombia	Moderna Therapeutics

Source: Pharmaprojects | Citeline, January 2024

Text highlighted in yellow represents new approvals during Q4 2023

Approved RNA therapies as of Q4 2023 (2/3)

Product name	Generic name	Year first approved	Disease(s)	Locations approved*	Originator company
Givlaari	givosiran	2020	Porphyria	US, EU, UK, Canada, Switzerland, Brazil, Israel, Japan	Alnylam
Oxlumo	lumasiran	2020	Hyperoxaluria	EU, UK, US, Brazil	Alnylam
Viltepso	viltolarsen	2020	Dystrophy, Duchenne muscular	US, Japan	NS Pharma
Leqvio	inclisiran	2020	Atherosclerosis; heterozygous familial hypercholesterolemia; hypercholesterolemia	EU, UK, Australia, Canada, Israel, US, Saudi Arabia, Japan, China	Alnylam
Amondys 45	casimersen	2021	Dystrophy, Duchenne muscular	US	Sarepta Therapeutics
Nulibry	fosdenopterin	2021	Molybdenum cofactor deficiency	US, EU, UK, Israel	Orphatec
Gennova COVID-19 vaccine	COVID-19 vaccine, Gennova Biopharmaceuticals	2022	Infection, coronavirus, novel coronavirus prophylaxis	India	Gennova Biopharmaceuticals
Amvuttra	vutrisiran	2022	Amyloidosis, transthyretin-related hereditary	US, EU, UK	Alnylam
Moderna Spikevax Bivalent Original/Omicron vaccine	COVID-19 bivalent original/Omicron vaccine, Moderna	2022	Infection, coronavirus, novel coronavirus prophylaxis	UK, Canada, Taiwan, Switzerland, Japan, EU, Australia, South Korea, Singapore, US	Moderna Therapeutics
ARCoV	COVID-19 vaccine, Suzhou Abogen Biosciences	2022	Infection, coronavirus, novel coronavirus prophylaxis	Indonesia	Suzhou Abogen Biosciences
Pfizer & BioNTech's Omicron BA.4/BA.5-adapted bivalent booster vaccine	Omicron BA.4/BA.5-adapted bivalent booster vaccine	2022	Infection, coronavirus, novel coronavirus prophylaxis	US, UK	BioNTech
CSPC Pharmaceutical COVID-19 vaccine	COVID-19 vaccine, CSPC Pharmaceutical	2023	Infection, coronavirus, novel coronavirus prophylaxis	China	CSPC Pharmaceutical
Sinocelltech COVID-19 vaccine	COVID-19 alpha/beta/delta/Omicron variants S-trimer quadrivalent recombinant protein vaccine	2023	Infection, coronavirus, novel coronavirus prophylaxis	China, UAE, US	Sinocelltech

Source: Pharmaprojects | Citeline, January 2024

Text highlighted in yellow represents new approvals during Q4 2023

Approved RNA therapies as of Q4 2023 (3/3)

Product name	Generic name	Year first approved	Disease(s)	Locations approved*	Originator company
Qalsody	tofersen	2023	Amyotrophic lateral sclerosis	US	Ionis Pharmaceuticals
ARCT-154	COVID-19 mRNA vaccine, Arcturus	2023	Infection, coronavirus, novel coronavirus prophylaxis	Japan	Arcturus Therapeutics
Daichirona	COVID-19 vaccine, Daiichi Sankyo	2023	Infection, coronavirus, novel coronavirus prophylaxis	Japan	Daiichi Sankyo
Wainua	eplontersen	2023	Transthyretin-related hereditary amyloidosis	US	Ionis Pharmaceuticals
Rivfloza	nedosiran	2023	Hyperoxaluria	US	Dicerna Pharmaceuticals
SYS-6006.32	Bivalent COVID-19 mRNA vaccine, CSPC Pharmaceutical	2023	Infection, coronavirus, novel coronavirus prophylaxis	China	CSPC Pharmaceutical

*For COVID-19 vaccines, this includes emergency use authorization and full approvals

Note that molnupiravir was previously included in this list; however, it has now been removed as it is no longer considered to fall under the category of RNA therapeutics

Source: Pharmaprojects | Citeline, January 2024

Text highlighted in yellow represents new approvals during Q4 2023

Key highlights in Q4 2023

Noteworthy events that happened in Q4 2023

Drug	Event Type	Indication	Molecule	Event Date
Kresladi	Priority Review	Autoimmune disorders	Viral Gene Therapy	02 October 2023
Rivfloza	Approval (US)	Hyperoxaluria	siRNA/RNAi	02 October 2023
NTLA-2002	PRIME Designation (Europe)	Hereditary angioedema (HAE)	Non-Viral Gene Therapy	13 October 2023
DOC1021	Fast Track Status	Brain cancer - malignant glioma; AA and glioblastoma (GBM)	Cellular	17 October 2023
ANPD001	Fast Track Status	Parkinson's disease (PD)	Cellular	19 October 2023
Leqvio	Approval (Japan and China)	Dyslipidemia/hypercholesterolemia	siRNA/RNAi	24 October 2023
IMA203	Regenerative Medicine Advanced Therapy (RMAT) Designation	Solid tumors	Cellular	24 October 2023
HG-204	Orphan Drug Designation (US)	Metabolic - general	Other Nucleic Acid	30 October 2023
Wainua	European Filing Accepted	Polyneuropathy of hereditary transthyretin-mediated amyloidosis	Antisense	02 November 2023
Vyjuvek	MAA Submission (Europe)	Epidermolysis bullosa	Viral Gene Therapy	06 November 2023
AVB-101	Fast Track Status	Frontotemporal dementia (FTD)	Viral Gene Therapy	06 November 2023
Inaticabtagene autoleucel	Approval (China)	Acute lymphoblastic leukemia (ALL)	Cellular	08 November 2023
Wainua	Orphan Drug Designation (Europe)	Polyneuropathy of hereditary transthyretin-mediated amyloidosis	Antisense	09 November 2023
NTLA-2002	Orphan Drug Designation (Europe)	Hereditary angioedema (HAE)	Non-viral Gene Therapy	14 November 2023
ATSN-101	Regenerative Medicine Advanced Therapy (RMAT) Designation	Leber's congenital amaurosis (ophthalmology)	Viral Gene Therapy	14 November 2023
Elsunersen	PRIME Designation (Europe)	Seizure disorders (epilepsy)	Antisense	16 November 2023
Casgevy	Conditional Marketing Authorization (UK)	Sickle cell anemia and thalassemia	Non-viral Gene Therapy	16 November 2023
LUNAR-CF	Orphan Drug Designation (US)	Cystic fibrosis (CF)	siRNA/RNAi	21 November 2023
EB-101	Priority Review	Epidermolysis bullosa	Viral Gene Therapy	27 November 2023
OTL-203	Fast Track Status	Mucopolysaccharidosis I (MPS I; hurler syndrome)	Non-viral Gene Therapy	30 November 2023
NXL-004	Orphan Drug Designation (US)	Brain cancer - malignant Glioma; AA and glioblastoma (GBM)	Viral Gene Therapy	06 December 2023
Lyfgenia	Approval (US)	Sickle cell anemia	Viral Gene Therapy	08 December 2023
Casgevy	Approval (US)	Sickle cell anemia	Non-viral Gene Therapy	08 December 2023
AOC 1044	Orphan Drug Designation (Europe)	Duchenne muscular dystrophy (DMD)	siRNA/RNAi	13 December 2023
OCU400	Regenerative Medicine Advanced Therapy (RMAT) Designation	Retinitis pigmentosa (RP) (ophthalmology)	Viral Gene Therapy	19 December 2023
Vyjuvek	Orphan Drug Designation (Japan)	Epidermolysis bullosa	Viral Gene Therapy	19 December 2023
Wainua	Approval (US)	Polyneuropathy of hereditary transthyretin-mediated amyloidosis	Antisense	21 December 2023
NS-089/NCNP-02	Orphan Drug Designation (Europe)	Duchenne muscular dystrophy (DMD)	Antisense	21 December 2023
OCU400	Meeting with FDA	Retinitis Pigmentosa (RP) (ophthalmology)	Viral Gene Therapy	21 December 2023
DCVax-L	Filing for Approval (UK)	Brain Cancer - malignant glioma; AA and glioblastoma (GBM)	Cellular	21 December 2023

Source: Biomedtracker | Citeline, January 2024

Pipeline overview

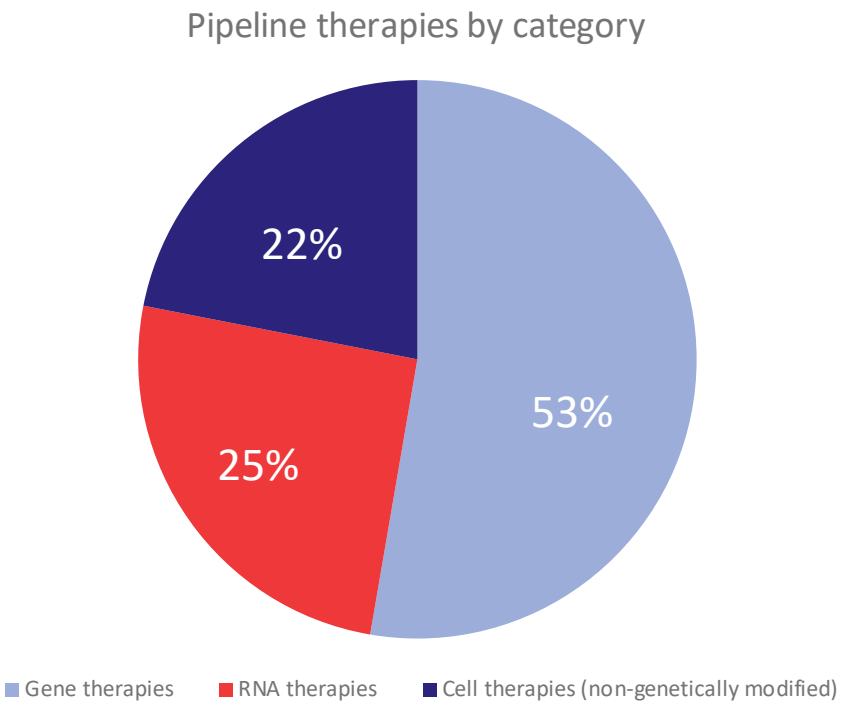
Q4 2023

American Society of Gene + Cell Therapy

Pipeline of gene, cell, and RNA therapies

3,951 therapies are in development, ranging from preclinical through pre-registration

- 2,111 gene therapies (including genetically modified cell therapies such as CAR T-cell therapies) are in development, accounting for 53% of gene, cell, and RNA therapies
- 878 non-genetically modified cell therapies are in development, accounting for 22% of gene, cell, and RNA therapies



Source: Pharmaprojects | Citeline, January 2024

American Society of Gene + Cell Therapy

Gene therapy pipeline

Gene therapy and genetically modified cell therapies

Q4 2023

American Society of Gene + Cell Therapy

Gene therapy pipeline: quarterly comparison

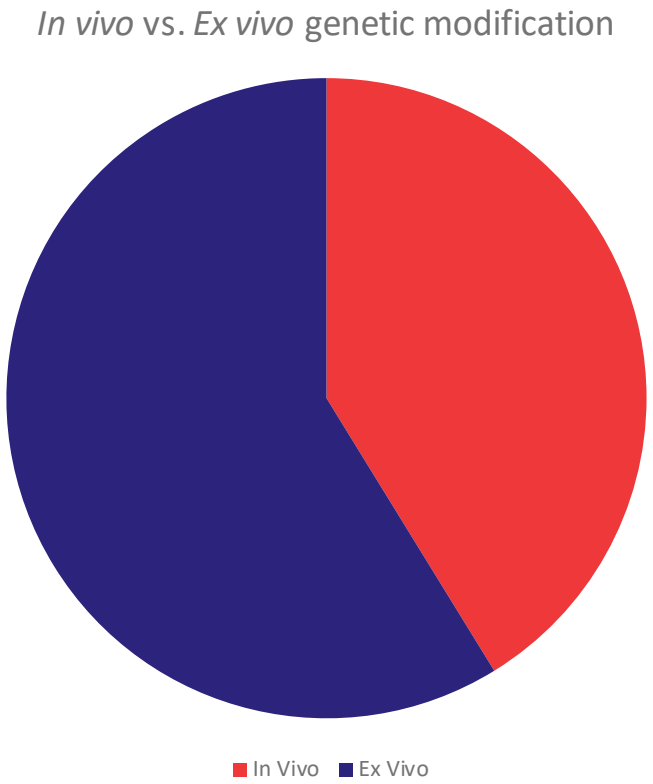
- For the first time since Q3 2022, the number of gene therapies in Phase III increased from the previous quarter, growing by 10% in Q4 2023
- Autolus filed for approval in the US for its CAR-T program, obe-cel, for the treatment of acute lymphocytic leukemia
- Adaptimmune Therapeutics filed for approval in the US for its engineered T-cell therapy, afami-cel, for the treatment of synovial sarcoma
- Therapies currently in pre-registration:
  - In China
    - zevor-cel (CARsgen Therapeutics)
  - In the EU and US
    - fidanacogene elaparvovec (Pfizer)
  - In the US
    - RP-L201 (Rocket Pharmaceuticals)
    - EB-101 (Abeona Therapeutics)
    - afami-cel (Adaptimmune Therapeutics)
    - obe-cel (Autolus Therapeutics)

Global Status	Q4 2022	Q1 2023	Q2 2023	Q3 2023	Q4 2023
Preclinical	1,515	1,493	1,539	1,522	1,528
Phase I	254	245	240	256	270
Phase II	248	247	260	267	274
Phase III	30	30	30	30	33
Pre-registration	6	7	6	7	6
Total	**2,053**	**2,022**	**2,075**	**2,082**	**2,111**

Source: Pharmaprojects | Citeline, January 2024

Genetic modification: *In vivo* vs. *Ex vivo*

- *Ex vivo* genetic modification is more widely used for gene therapies in pipeline development
- In Q4 2023, *in vivo* delivery techniques were used in 41% of gene therapies

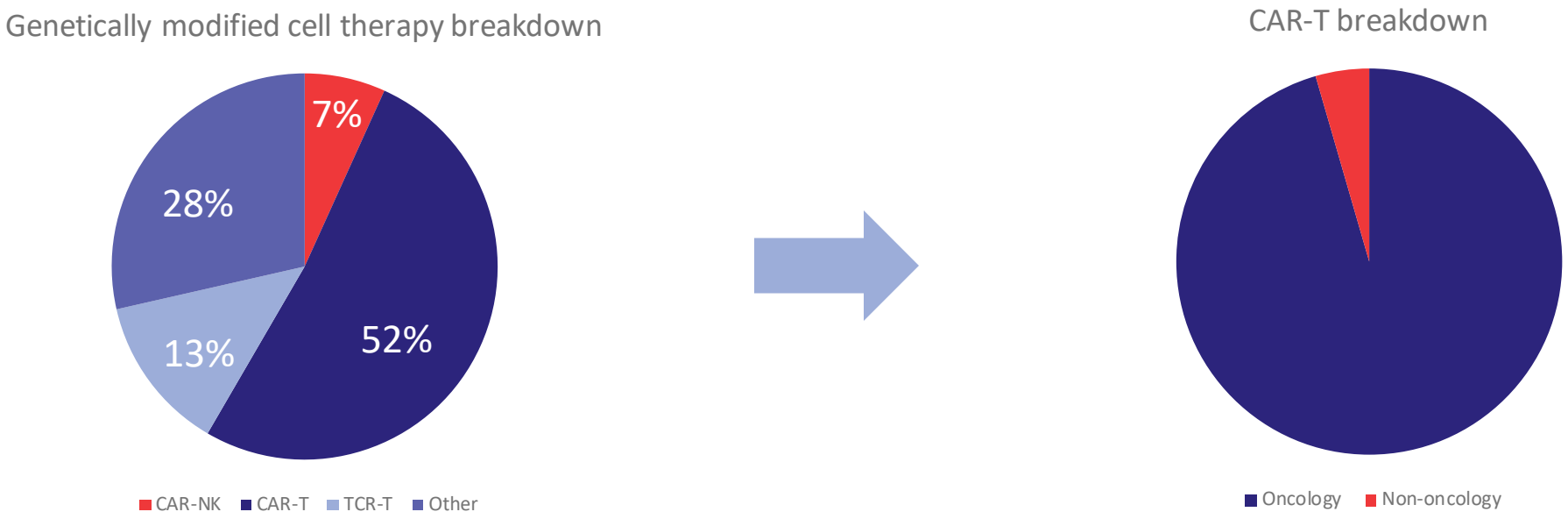


Source: Cell and Gene Therapy dashboard | Citeline, January 2024

American Society of Gene + Cell Therapy

Gene therapy breakdown: CAR-Ts continue to dominate the pipeline

- CAR-T cell therapies remained the most common technology used in the pipeline of genetically modified cell therapies (preclinical through to pre-registration), representing 52%, followed by the "other" category at 28%, which includes a list of less commonly used technologies including TCR-NK, CAR-M, and TAC-T
- 97% of CAR-T cell therapies were in development for cancer indications. The remaining non-oncology indications included scleroderma, HIV/AIDS, and autoimmune disease (unspecified)



Source: Cell and Gene Therapy dashboard | Citeline, January 2024

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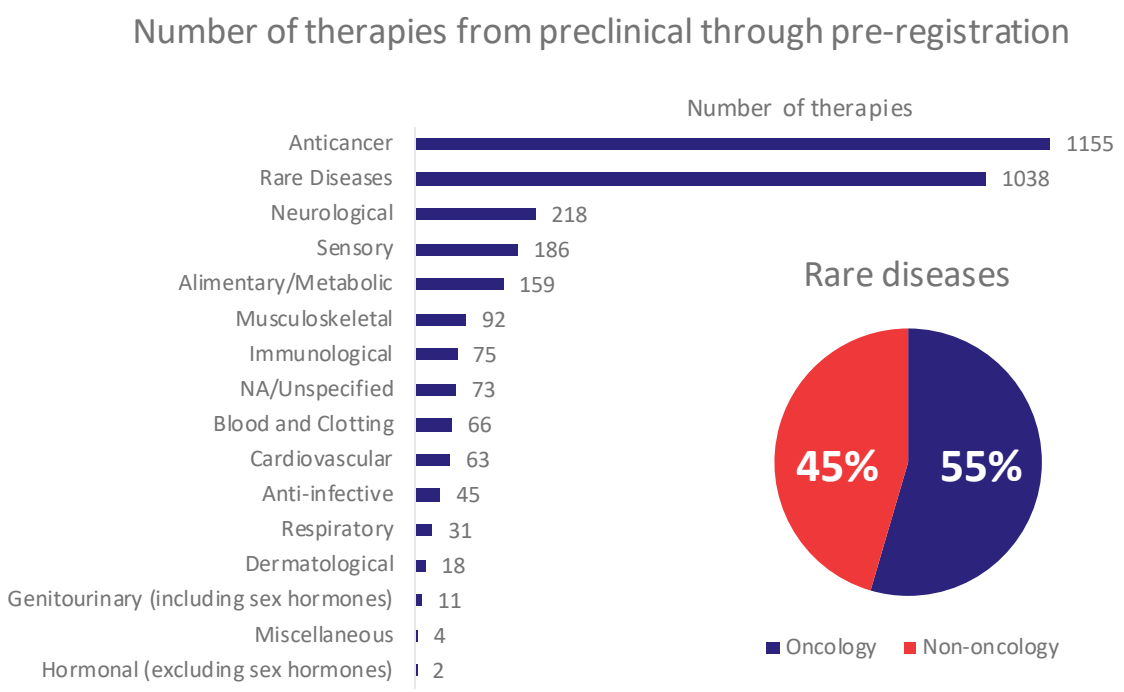
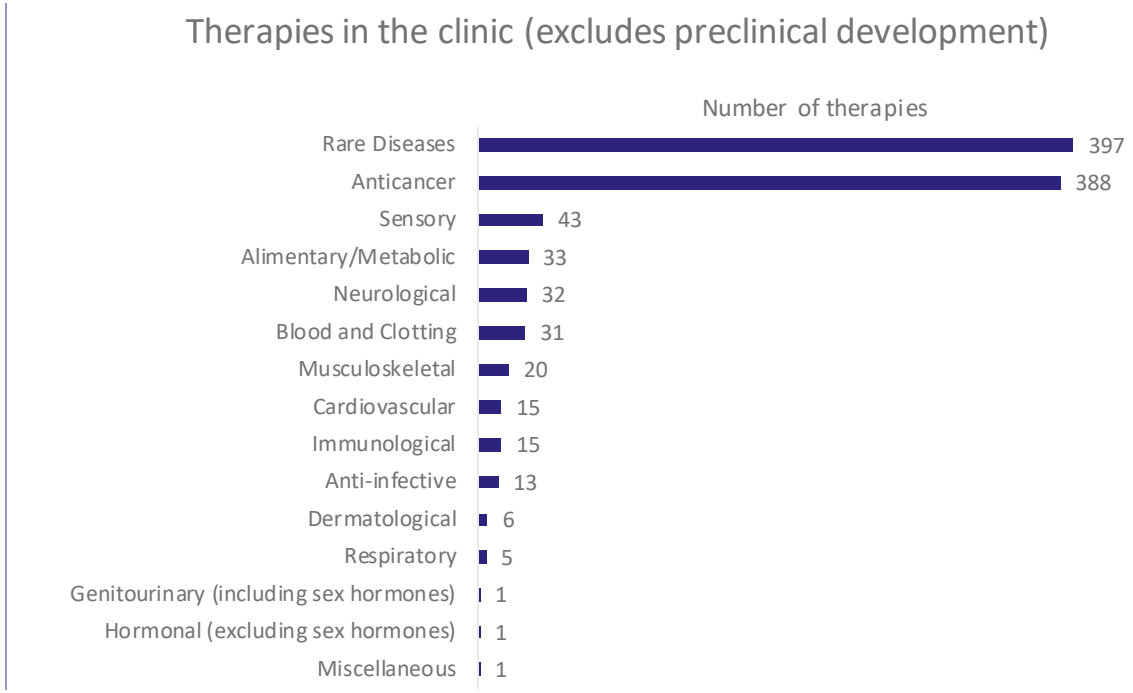
Gene therapy pipeline: most commonly targeted therapeutic areas

- Oncology and rare diseases remained the top areas of gene therapy development in both the overall pipeline (preclinical to pre-registration) and in the clinic (Phase I to pre-registration)
- Development for rare diseases most commonly occurred in oncology, representing a majority of 55% compared to non-oncology rare disease gene therapy pipeline development





Source: Pharmaprojects | Citeline, January 2024

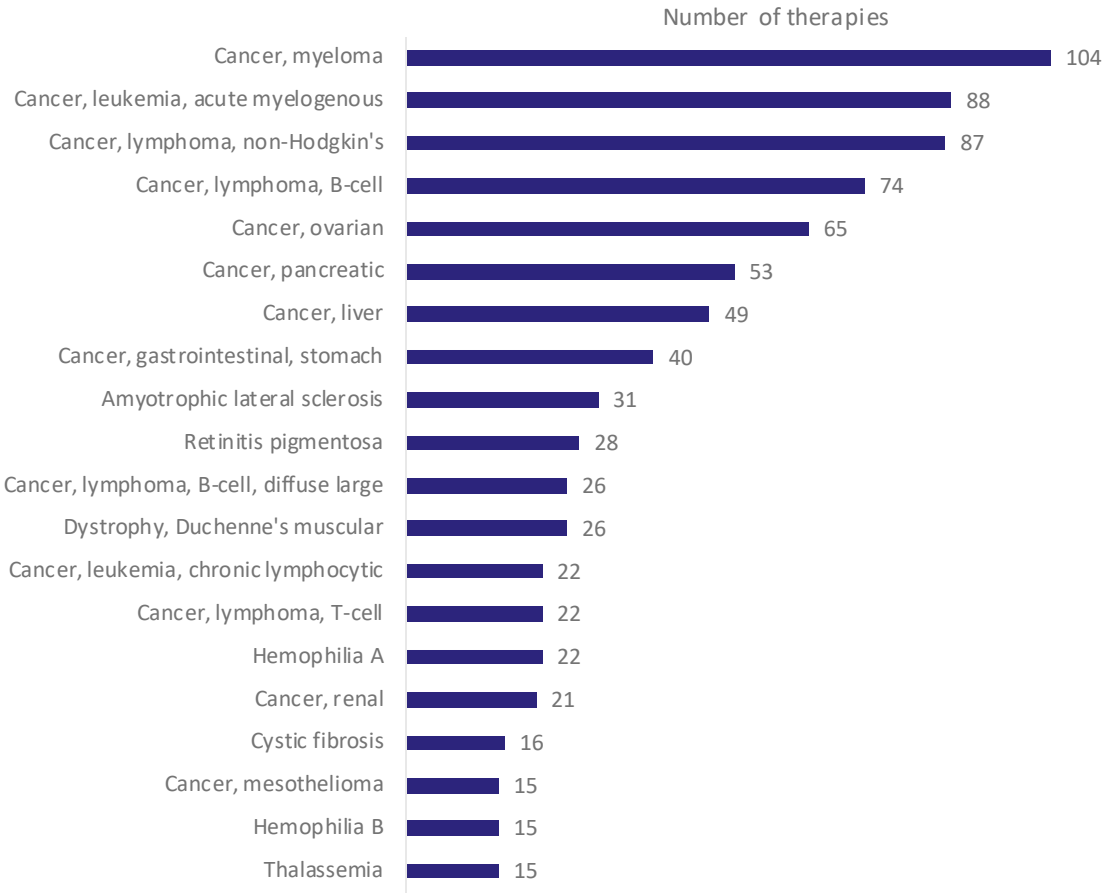
Note: Figures based on indications in pipeline development only for each therapy

American Society of Gene + Cell Therapy

Gene therapy pipeline: most common rare diseases targeted

- For the 1,038 pipeline (preclinical to pre-registration) gene therapies being developed for rare diseases, eight out of the top 10 rare diseases were oncological, a trend seen throughout 2022 and 2023
- With development in acute myelogenous leukemia overtaking development in non-Hodgkin's lymphoma for the first time in the past nine quarters, the top five rare diseases for which gene therapies are being developed are:

1. Myeloma
2. Acute myelogenous leukemia
3. Non-Hodgkin's lymphoma
4. B-cell lymphoma
5. Ovarian cancer



Source: Pharmaprojects | Citeline, January 2024

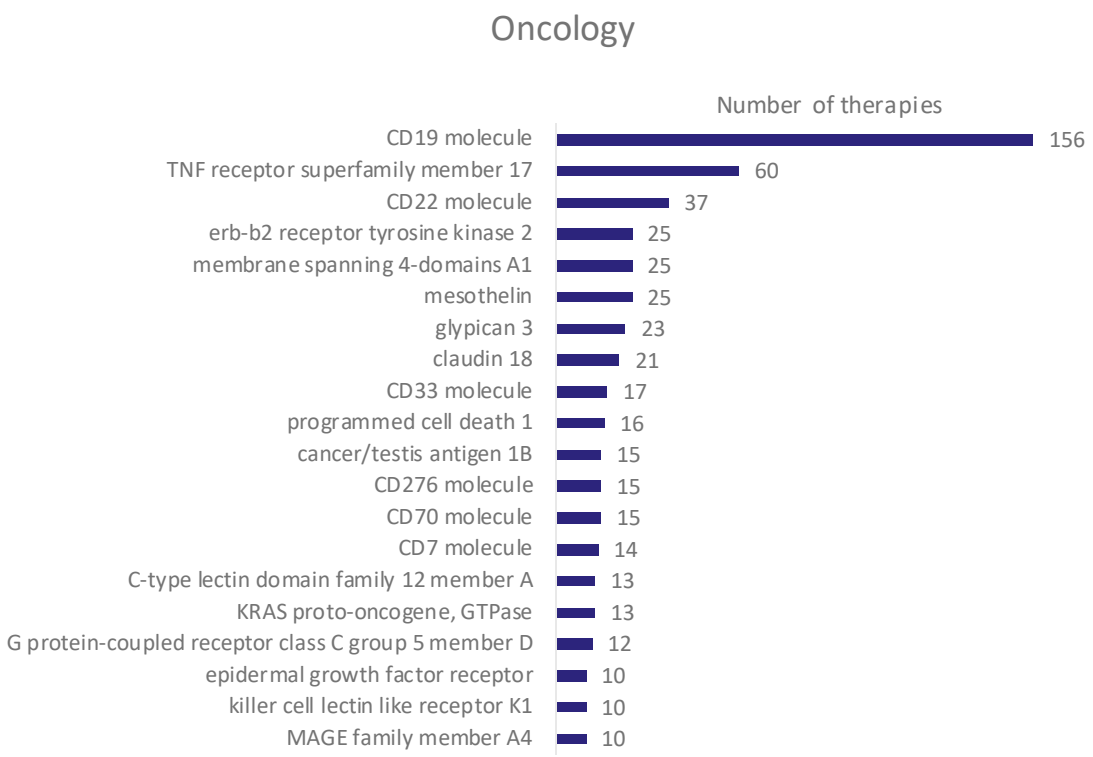
Note: Figures based on indications in pipeline development only for each therapy

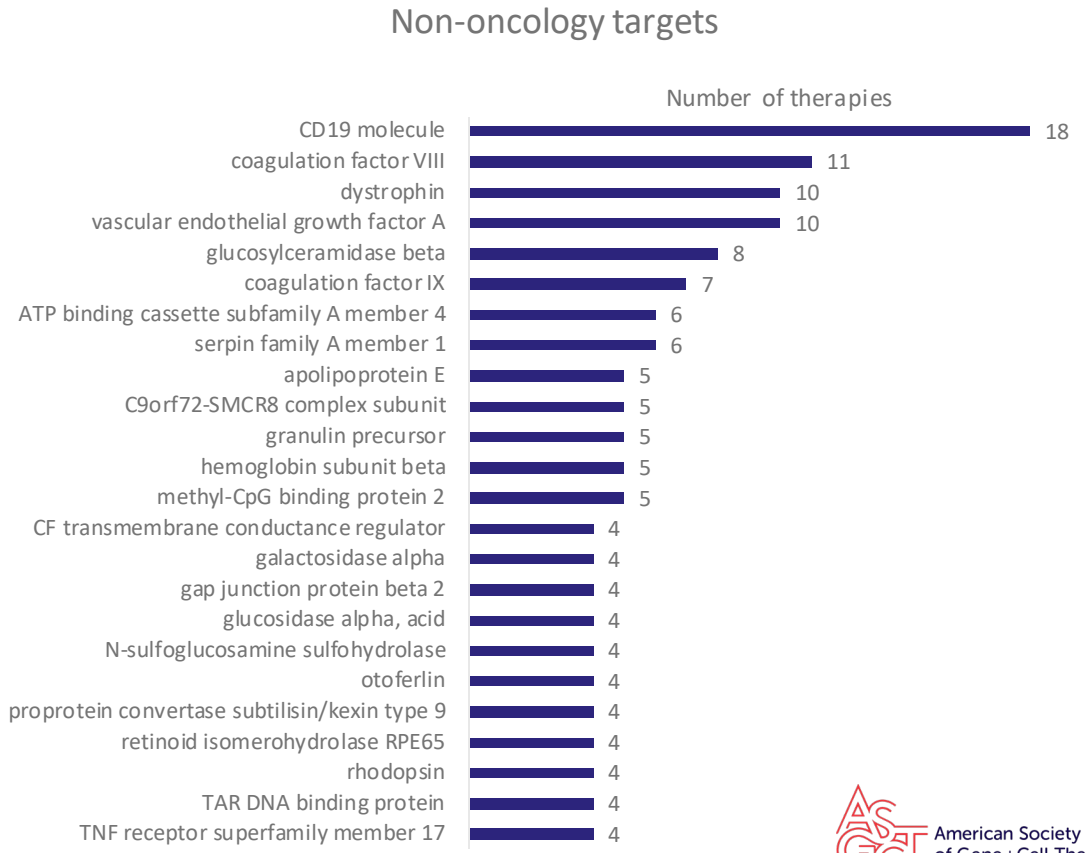
American Society of Gene + Cell Therapy

Gene therapy pipeline: most common targets

Of the gene therapies in preclinical trials through pre-registration for which targets were disclosed:

- CD19, B-cell maturation antigen (BCMA), also known as TNF receptor superfamily member 17, and CD22 molecule continued to be the top three most common targets for oncology indications
- CD19 molecule was the most common target for non-oncology indications, while coagulation factor VIII remained the second most common in Q4 2023, as seen in the previous quarter



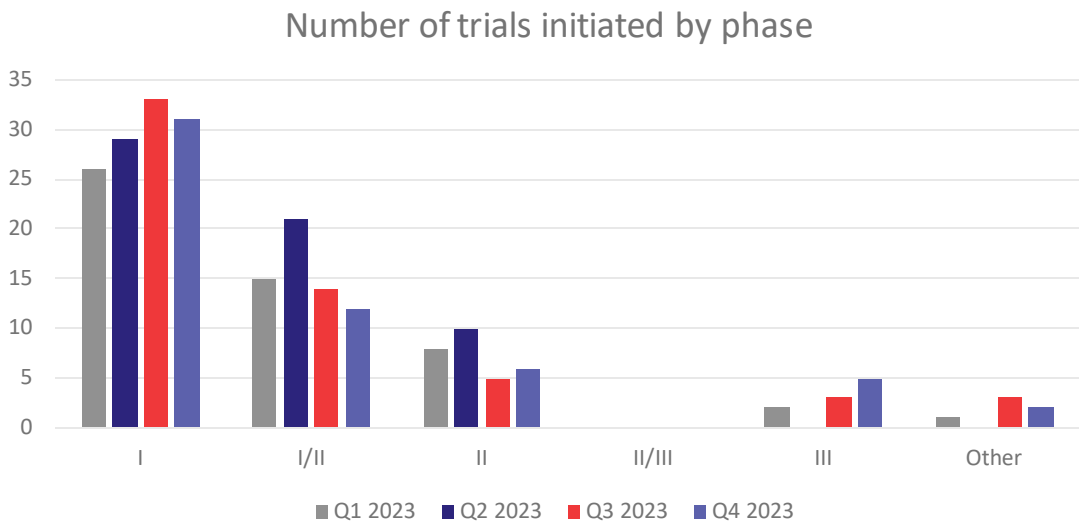


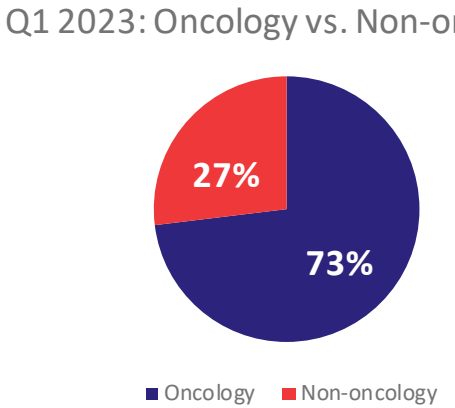
Source: Pharmaprojects | Citeline, January 2024

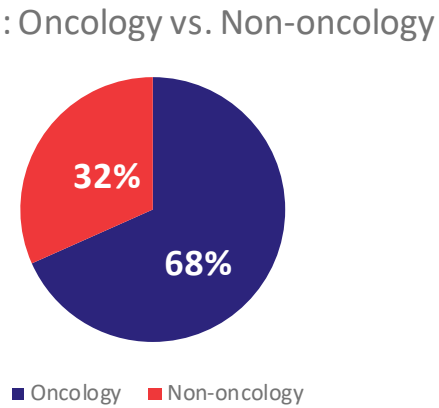
American Society of Gene + Cell Therapy

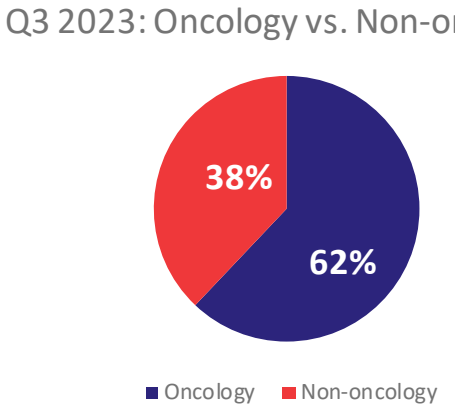
Gene therapy clinical trial activity

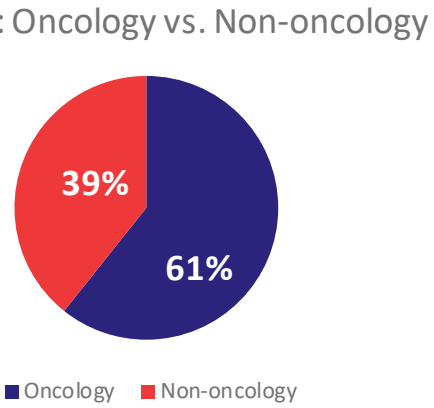
- The proportion of gene therapy trials for non-oncology indications has increased by one percentage point since the previous quarter, to 39%, continuing the trend of an increasing proportion of non-oncology gene therapy trials initiating each quarter since Q4 2022
- 56 gene therapy trials were initiated in Q4 2023











Source: Trialtrove | Citeline, January 2024

American Society of Gene + Cell Therapy

Non-genetically modified cell therapy pipeline

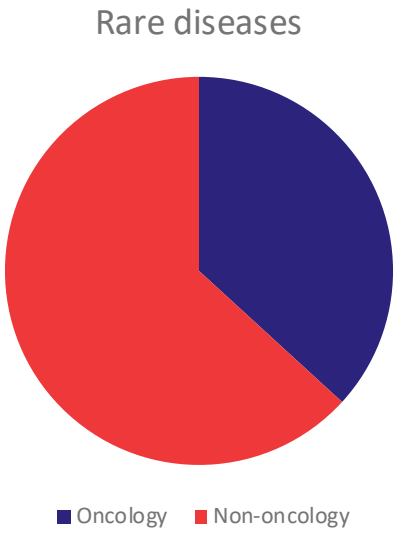
Q4 2023

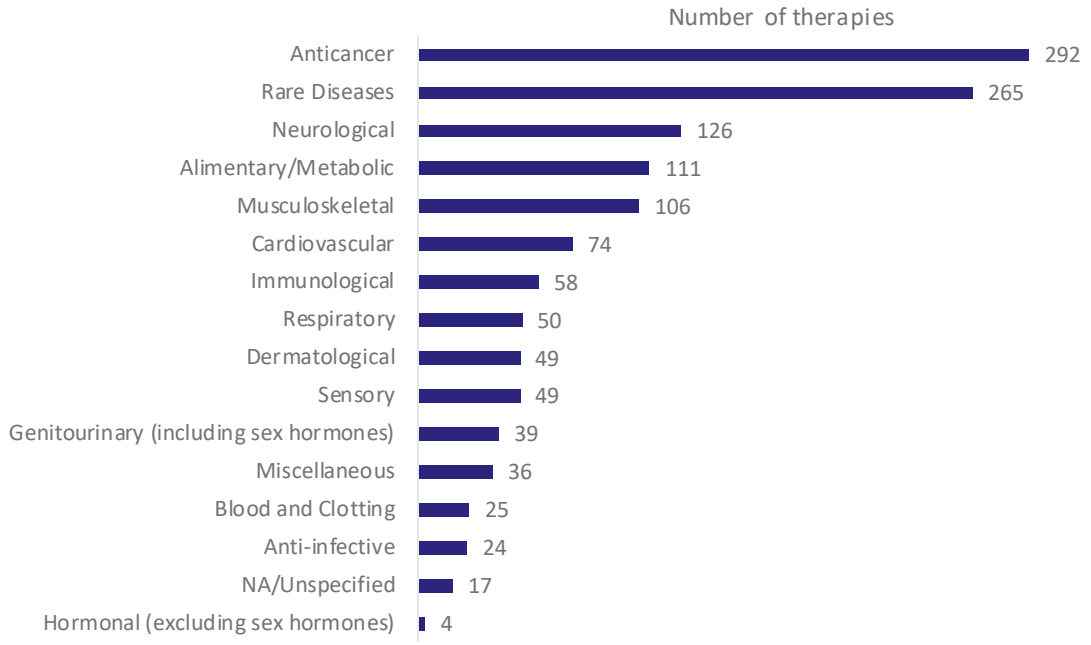
American Society of Gene + Cell Therapy

Non-genetically modified cell therapy pipeline: most common therapeutic areas targeted

Of the cell therapies in development (preclinical through pre-registration):

- Oncology and rare diseases remained the top areas of non-genetically modified cell therapy development
- Of the non-genetically modified cell therapies in preclinical to pre-registration stages for rare diseases, 64% were in development for non-oncology rare diseases, as found in the previous two quarters





Source: Pharmaprojects | Citeline, January 2024

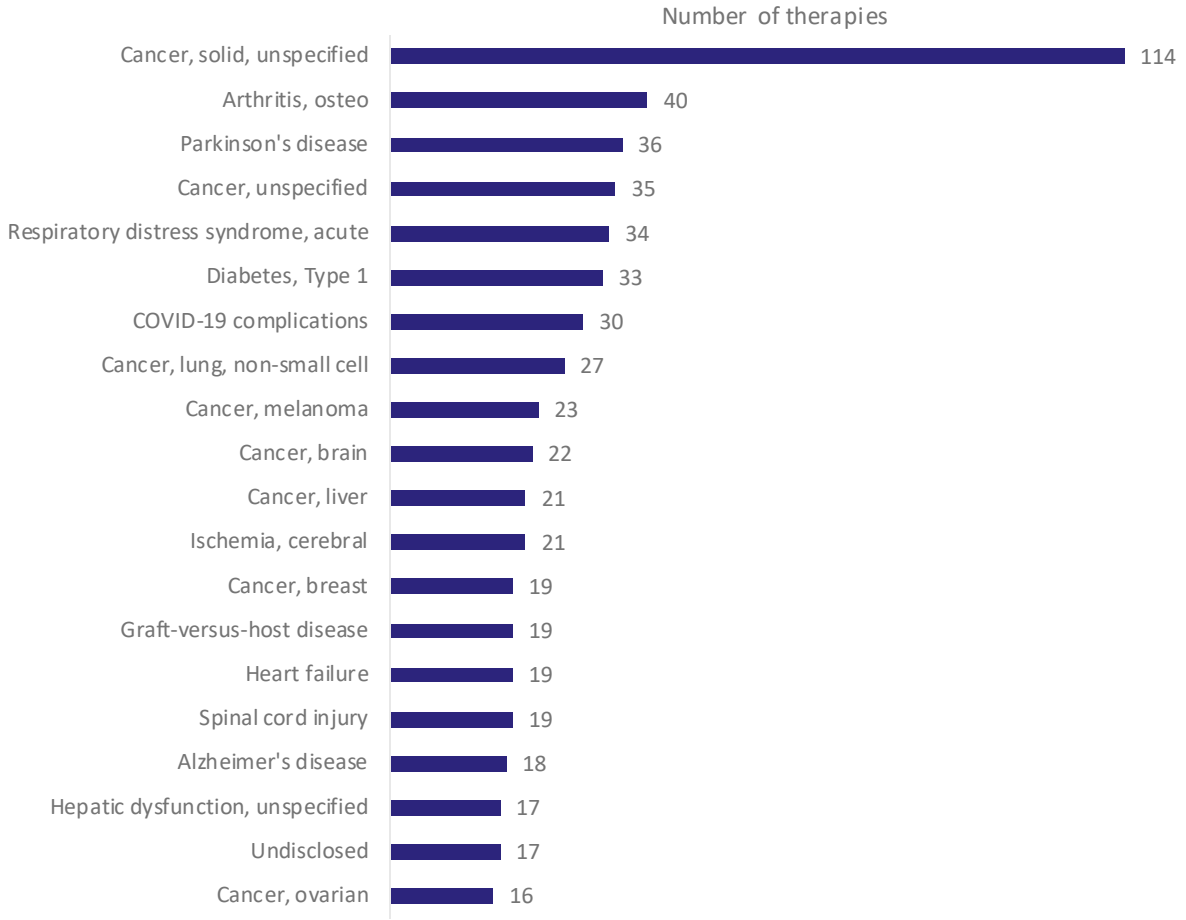
Note: Figures based on indications in pipeline development only for each therapy

American Society of Gene + Cell Therapy

Non-genetically modified cell therapy pipeline: most common diseases targeted

Of the therapies for which indications are specified, Parkinson's disease has overtaken acute respiratory distress syndrome to be the second most targeted disease:

1. Osteoarthritis
2. Parkinson's disease
3. Acute respiratory distress syndrome



Source: Pharmaprojects | Citeline, January 2024

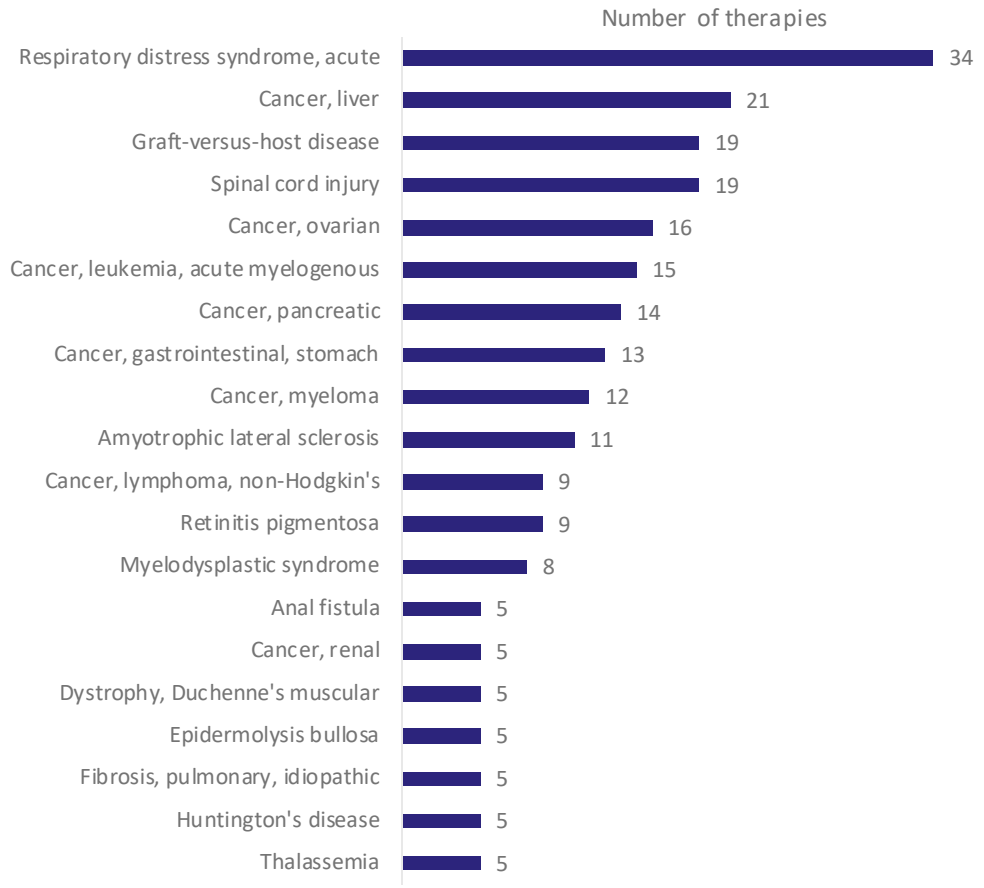
Note: Figures based on indications in pipeline development only for each therapy

American Society of Gene + Cell Therapy

Non-genetically modified cell therapy pipeline: most common rare diseases targeted

Of the therapies in development (preclinical through pre-registration) for rare diseases:

- The top three oncology indications were liver cancer, ovarian cancer, and acute myelogenous leukemia
- The top three non-oncology indications were acute respiratory distress syndrome, graft-versus-host disease, and spinal cord injury



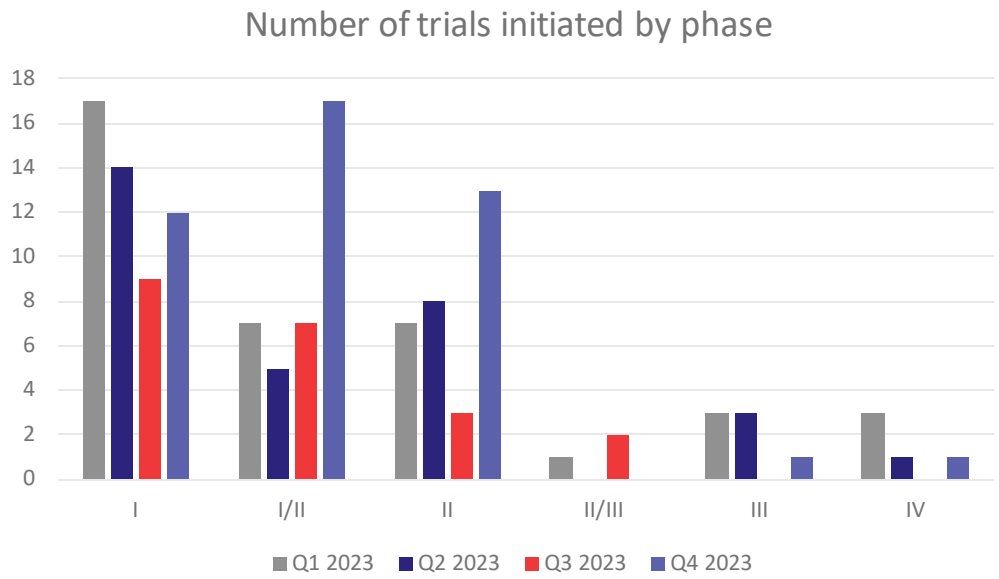
Source: Pharmaprojects| Citeline, January 2024

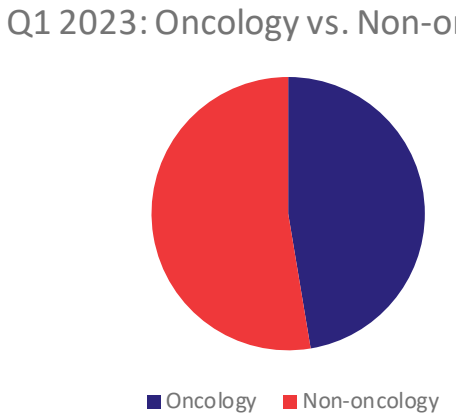
Note: Figures based on indications in pipeline development only for each therapy

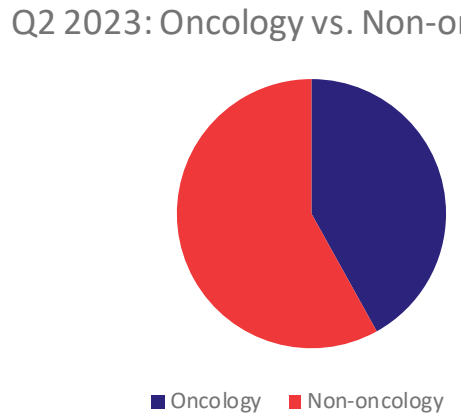
American Society of Gene + Cell Therapy

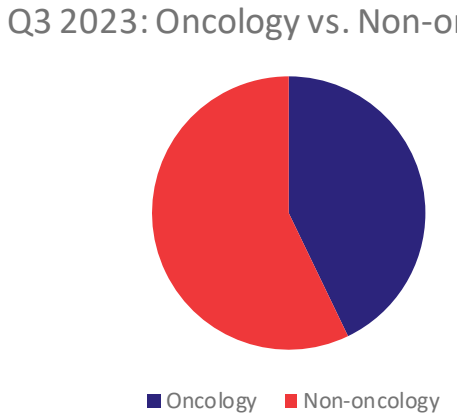
Non-genetically modified cell therapy trial activity

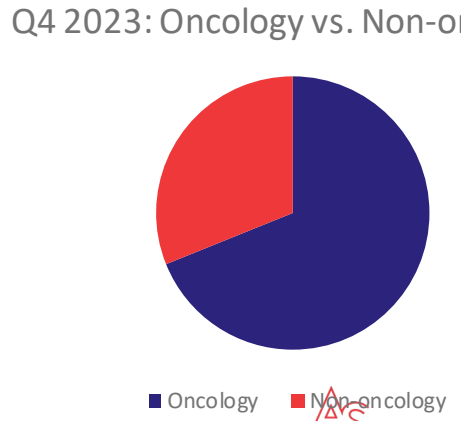
- 44 trials were initiated for non-genetically modified cell therapies in Q4 2023, more than twice the number in Q3
- Of these 44, 32% were for non-oncology indications, meaning that for the first time since Q3 2022, most newly initiated non-genetically modified cell therapy trials were for oncology indications











Source: Trialtrove| Citeline, January 2024

American Society of Gene + Cell Therapy

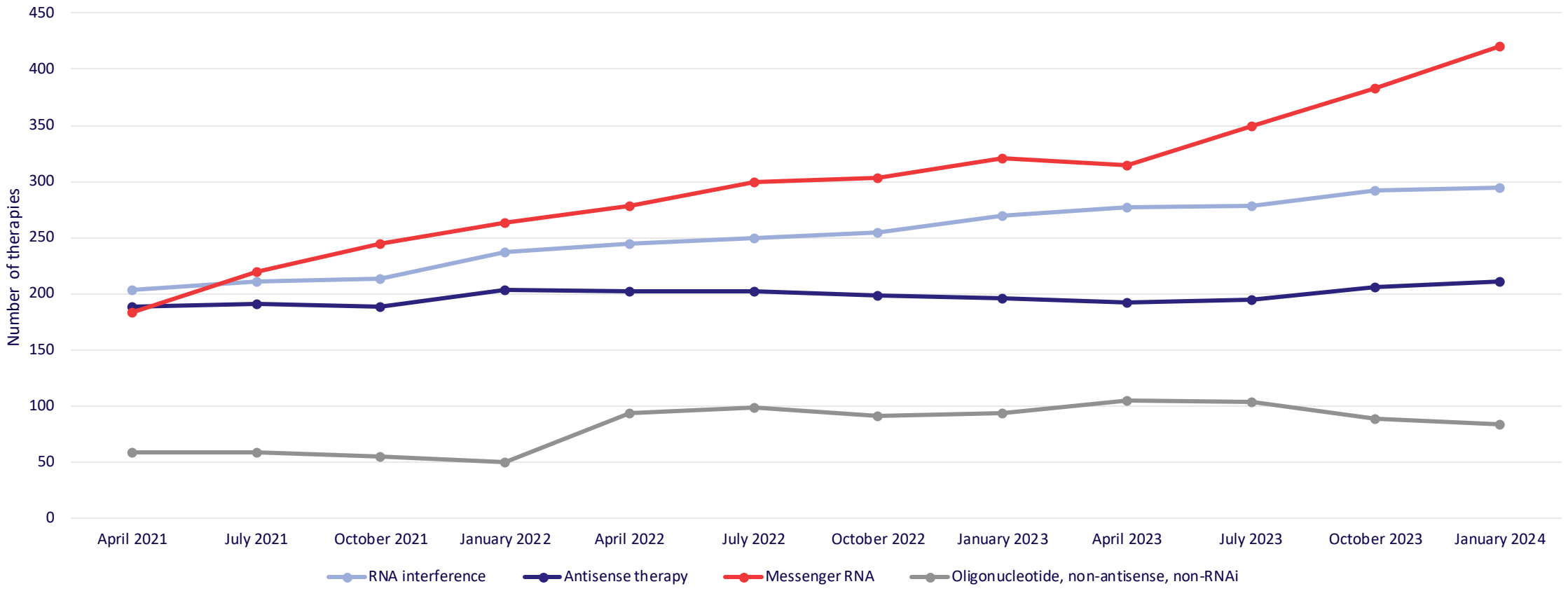
RNA therapy pipeline

Q4 2023

American Society of Gene + Cell Therapy

RNA therapy pipeline: most common modalities

- Of RNA therapies in the pipeline, messenger RNA (mRNA) and RNA interference (RNAi) continued to be the preferred RNA modalities for research

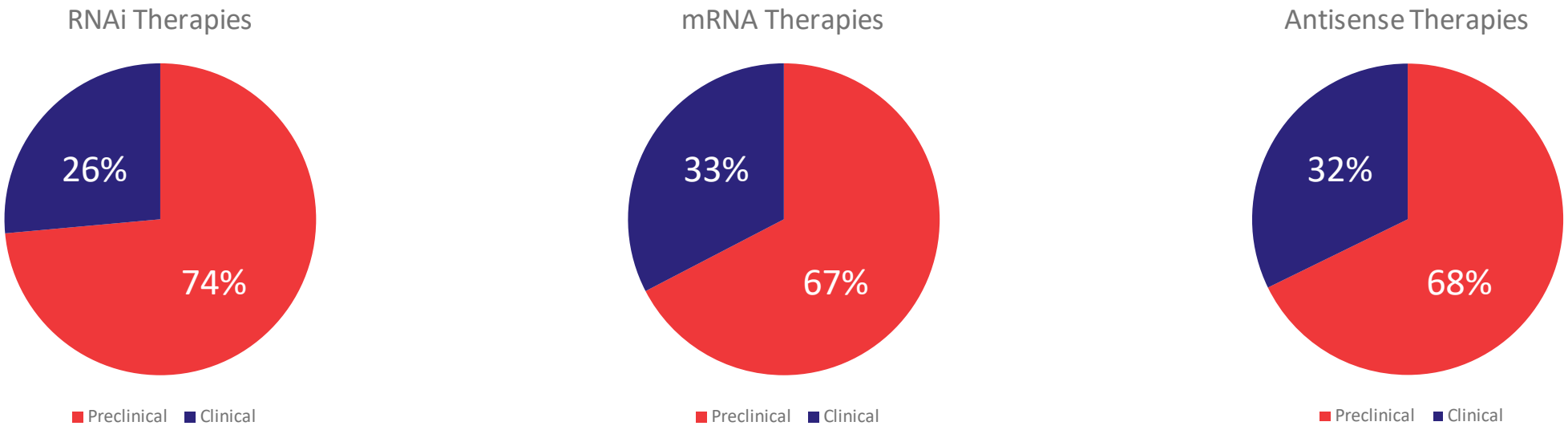


Source: Pharmaprojects | Citeline, January 2024

American Society of Gene + Cell Therapy

RNAi, mRNA, and antisense oligonucleotides: preclinical vs. clinical

- The majority of RNAi, mRNA, and antisense therapeutics in development were in the preclinical stage, representing 74%, 67%, and 68% of their respective pipelines

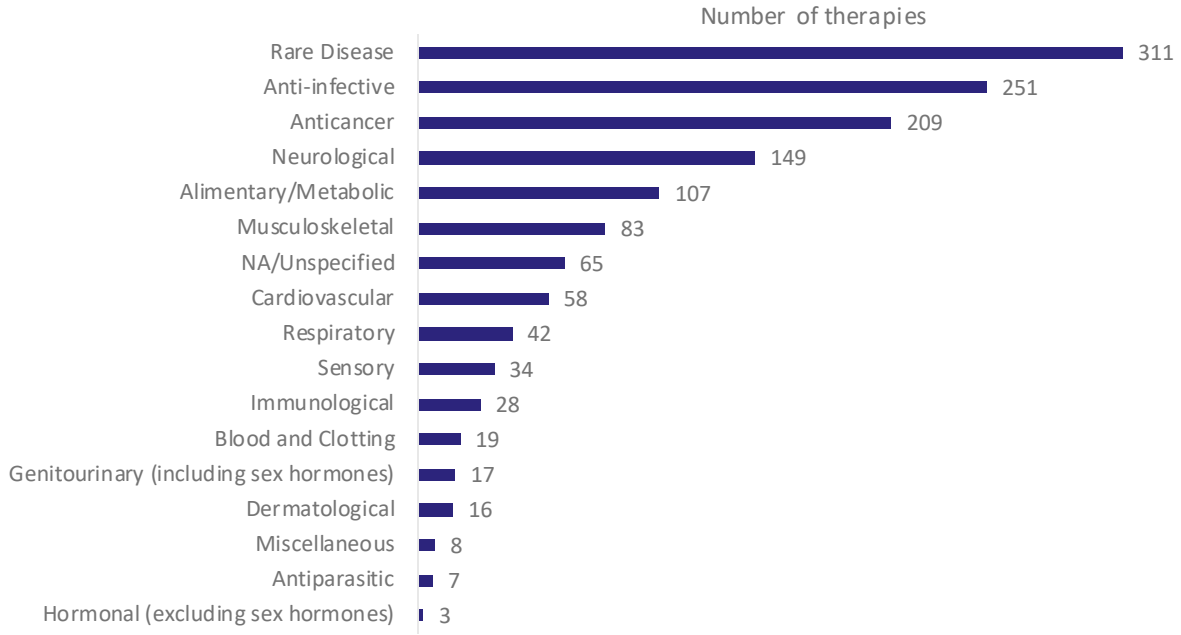


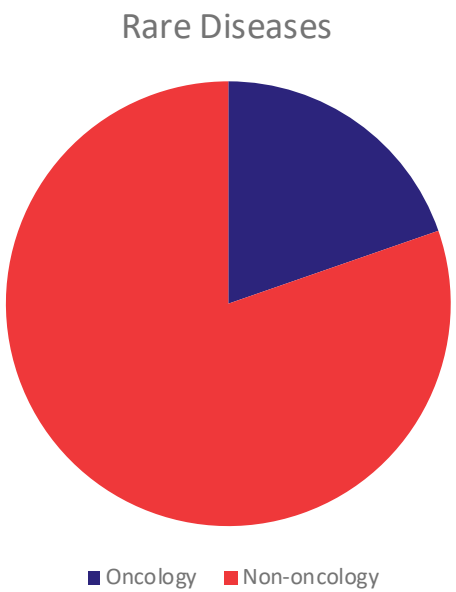
Source: Pharmaprojects | Citeline, January 2024

RNA therapies: most commonly targeted therapeutic areas

Of the 1,016 RNA therapies currently in the pipeline (from preclinical through pre-registration):

- Rare diseases remained the top targeted therapeutic area by RNA therapies, while anti-infective indications remained the second most commonly targeted, above oncology indications
- Non-oncology indications continued to be the most targeted rare diseases by RNA therapies, representing a majority of 81%





Source: Pharmaprojects | Citeline, January 2024

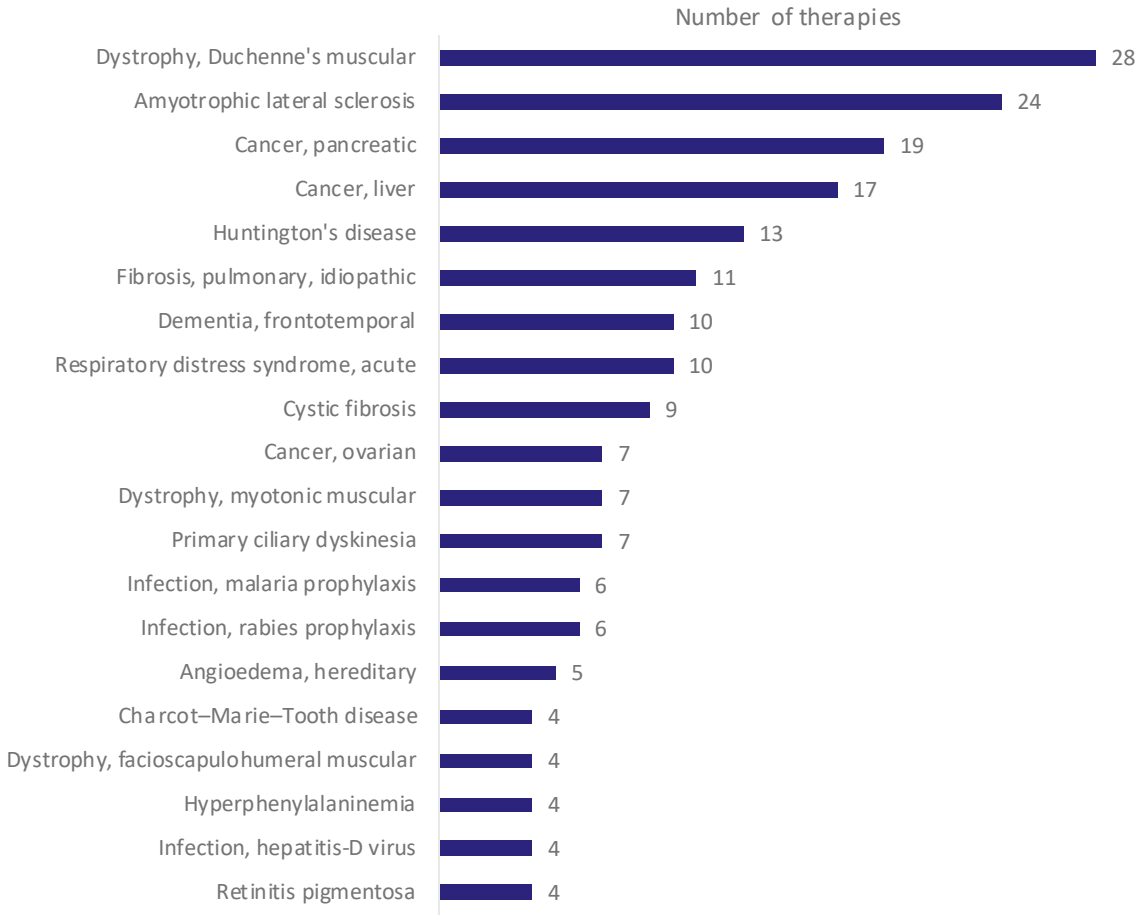
Note: Figures based on indications in pipeline development only for each therapy

American Society of Gene + Cell Therapy

RNA therapies: most common rare diseases targeted

Of the RNA therapies currently in the pipeline (from preclinical through pre-registration):

- Top specified rare oncology indications were pancreatic, liver, and ovarian cancer
- For non-oncology rare diseases, Duchenne muscular dystrophy, amyotrophic lateral sclerosis, and Huntington's disease were the most targeted indications

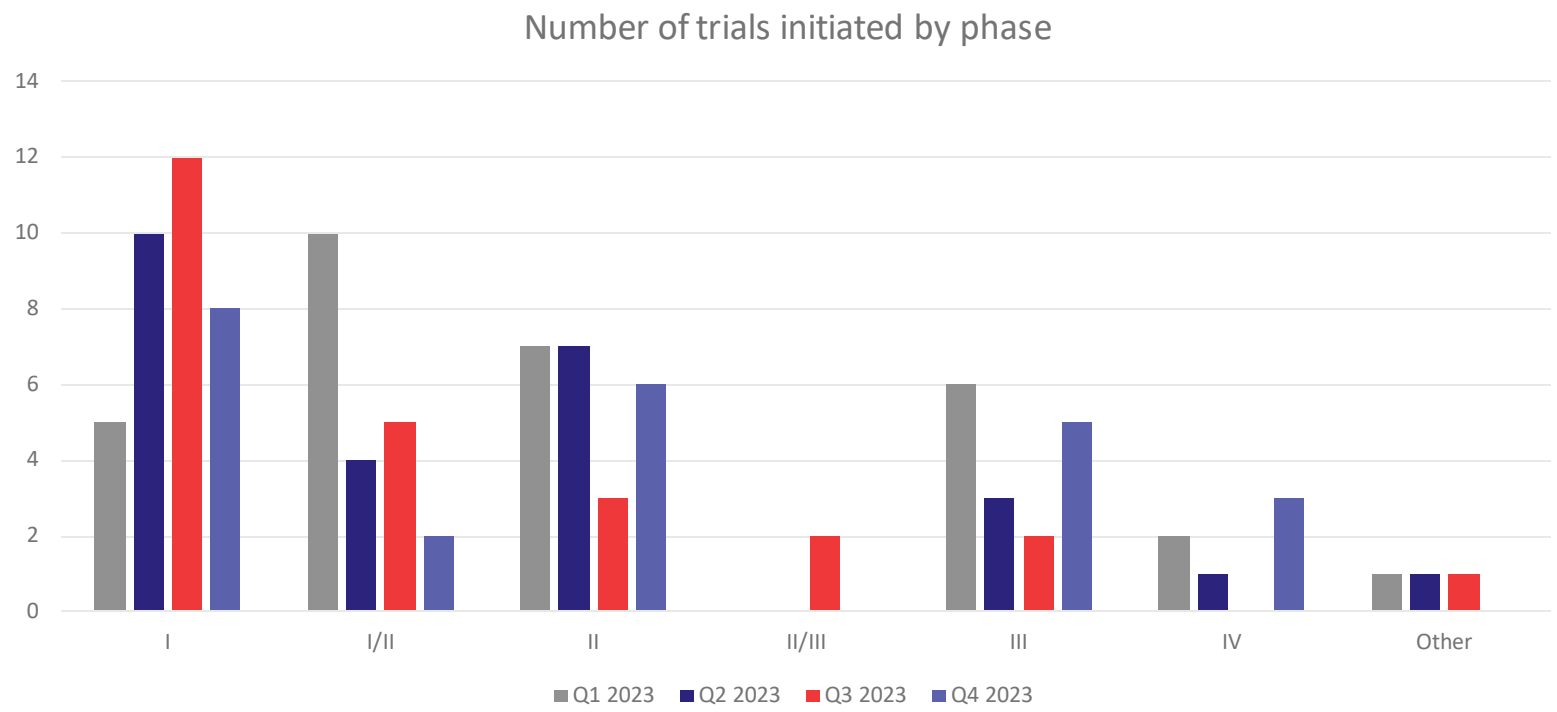


Source: Pharmaprojects | Citeline, January 2024

Note: Figures based on indications in pipeline development only for each therapy

RNA therapy pipeline: clinical trial activity

- 24 RNA trials were initiated in Q4 2023, compared to 25 in Q3 2023, 83% of which were for non-oncology indications



Source: Trialtrove | Citeline, January 2024

American Society of Gene + Cell Therapy

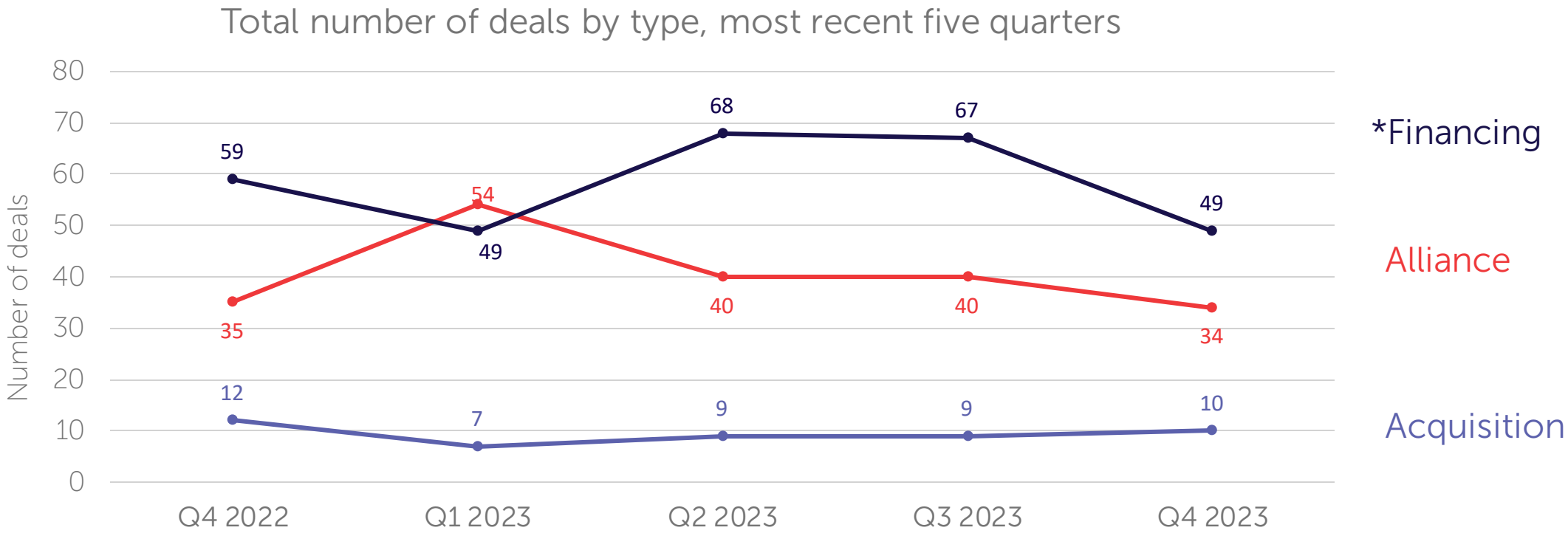
Overview of dealmaking for gene, cell, and RNA therapy companies

Q4 2023

American Society of Gene + Cell Therapy

Alliance, acquisition, and financing in gene, cell, and RNA therapy

- Advanced molecular therapy companies signed 93 transactions in Q4 2023, a 19% drop from the previous quarter's 116
- Q4 2023 also represented the lowest quarterly total in 2023, and was down 12% from the 106 agreements done in 2022's closing quarter
- The volume of financings and alliances declined, while acquisitions were up in Q4 2023, but not quite reaching the amount seen in Q4 2022



Source: Biomedtracker | Citeline, BioSciDB| Evaluate, January 2024

*Financings include public financings (IPOs and follow-ons) plus privately raised funding through venture rounds, debt offerings, or private investment in public equity

American Society of Gene + Cell Therapy

Q4 2023 acquisitions in gene, cell, and RNA therapy

- 10 acquisitions of advanced molecular therapy companies occurred in Q4 2023, up from Q3 2023's nine deals
- The biggest acquisition, announced just before the quarter's end, featured AstraZeneca acquiring autologous and allogeneic cell developer Gracell for $1.2bn
- M&A activity also included two reverse mergers — NAYA Biosciences with INVO Bioscience, and Selecta with Cartesian — and three acquisitions of CDMOs: Applied StemCell, Forge Biologics, and ABL Europe

Deal date	Deal title	Potential deal value (USD $)
2 October 2023	Clade Therapeutics Acquires Gadeta B.V.	Undisclosed
5 October 2023	Kyowa Kirin to Acquire Orchard Therapeutics	477,600,000
9 October 2023	QHP Capital Acquires Applied StemCell	Undisclosed
23 October 2023	INVO Bioscience and NAYA Biosciences Announce Definitive Agreement to Reverse Merge	Undisclosed
30 October 2023	United Therapeutics to Acquire Miromatrix Medical; Merger Closed	91,000,000
13 November 2023	Selecta Biosciences Completes Reverse Merger with Cartesian Therapeutics	Undisclosed
13 November 2023	Ajinomoto Co. to Acquire Forge Biologics	620,000,000
22 November 2023	Syncona to Acquire Freeline Therapeutics	28,300,000
4 December 2023	Oxford BioMedica Acquires CDMO ABL Europe	16,000,000
26 December 2023	AstraZeneca to Acquire Gracell	1,200,000,000

Source: Biomedtracker | Citeline, BioSciDB| Evaluate, January 2024

Start-up funding for gene, cell, and RNA therapy companies

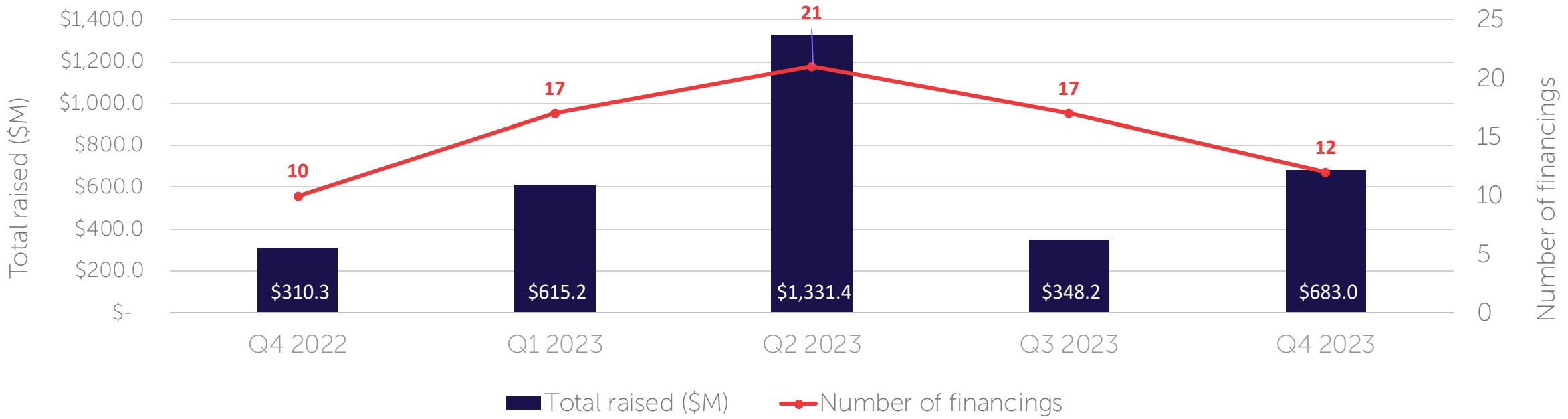
Q4 2023

American Society of Gene + Cell Therapy

Start-up financing for gene, cell, and RNA therapy companies

- Start-up financing volume continued to trend downward with 12 transactions in Q4 2023, a 29% decrease from Q3's 17, but ahead of the 10 funding rounds completed in Q4 2022
- Total financing dollars rebounded, though, almost doubling from $348.2m in Q3 2023 to $683.0m in Q4 2023
- Q4 2023's aggregate value also represented more than double the $310.3m brought in through start-up financing in Q4 2022

Volume and dollar value of Series A and seed financings for gene, cell, & RNA therapy companies, most recent five quarters



Source: Biomedtracker | Citeline, January 2024

American Society of Gene + Cell Therapy

Q4 2023 start-up financing for gene, cell, and RNA therapy companies

Deal date	Deal title	Modality type	Company location	Academic source	Potential deal value ($M)
10 October 2023	Mana.bio Raises $19.5M in Seed Financing	LNP delivery of nucleic acid	Israel/Tel Aviv	Technion Institute of Technology	19.5
24 October 2023	LyGenesis Raises $19M in Series A-2 Financing	Cell therapy	United States/ Pennsylvania/Pittsburgh	Pittsburgh Liver Research Center	19
24 October 2023	Rampart Bioscience Closes $85M Series A Financing	Gene therapy	United States/Arizona/ Phoenix	n/a - founded by two former executives from Calimmune	85
31 October 2023	Imagine Pharma Secures $32.5M Series A Round; Brings in $10M at Closing	Cell therapy	United States/ Pennsylvania/Devon	Undisclosed	32.5
13 November 2023	ViaNautis Bio Closes $25M Series A Round	mRNA, siRNA, and ASO delivery	United Kingdom/Cambridge	University College London	25
14 November 2023	VectorY Therapeutics Gets $138M in Series A Financings	Vectorized antibodies	Netherlands/Amsterdam	Undisclosed	138
15 November 2023	T-Therapeutics Raises £48M in Series A Financing	Cell therapy	United Kingdom/Cambridge	University of Cambridge	59.4
30 November 2023	Mytos Raises $19M in Series A Round	Cell manufacturing	United Kingdom/London	Imperial College London	19
5 December 2023	Cytonus Therapeutics Gets $11.7M in Series A Round	Cell delivery	United States/California/San Diego	University of California, San Diego	11.7
12 December 2023	Shinobi Therapeutics Launches with Completion of $51M Series A	Cell therapy	United States/California/San Francisco	Kyoto University; University of California, San Francisco	51
12 December 2023	Tome Biosciences Launches with Over $200M in Early Funding	Gene editing	United States/ Massachusetts/Watertown	Massachusetts Institute of Technology	213
13 December 2023	Encellin Closes $9.9M Series A Financing	Cell therapy	United States/California/San Francisco	University of California, San Francisco	9.9

Source: Biomedtracker| Citeline, January 2024

Notable Q4 2023 start-up gene, cell, and RNA therapy companies

	Company details	Academic source	Financing type/ amount raised	Lead investor(s)	Therapy areas of interest
Tome BIOSCIENCES	Programmable genomic integration, combining CRISPR/Cas9 editing with enzymes for gene insertion and writing without double-stranded breaks	Massachusetts Institute of Technology	Series A + B/$213M	Andreessen Horowitz (a16z) Bio + Health; Arch Venture Partners; GV; Longwood Fund; Polaris Partners; Bruker Corp.; Fujifilm Corp.; Alexandria Venture Investments	Liver and autoimmune diseases
VectorY THERAPEUTICS	Delivery of therapeutic antibodies to the CNS using AAV vectors	Undisclosed	Series A/$138M	EQT Life Sciences; Forbion Growth Opportunities Fund	Neurodegenerative diseases including ALS, Huntington's, and Parkinson's
RAMPARTBIO	HALO non-viral gene delivery platform	n/a - founded by two former executives from Calimmune	Series A/$85M	Forbion	Rare liver diseases and hypophosphatasia

Source: Biomedtracker | Citeline, January 2024

Upcoming catalysts

Q4 2023

American Society of Gene + Cell Therapy

Upcoming Catalysts

Below are noteworthy catalysts (forward-looking events) expected in Q1 2024

Therapy	Generic name	Disease	Catalyst	Catalyst date
SB623	vandefitemcel	Traumatic Brain Injury (TBI)	Approval Decision (Japan)	20 Jun 2023 - 31 Jan 2024
Oxlumo	lumasiran	Hyperoxaluria	Supplemental Approval (Europe)	27 Oct 2023 - 31 Jan 2024
LN-144	lifileucel	Melanoma	PDUFA/Approval Decision (U.S.)	24 Feb 2024 - 24 Feb 2024
Casgevy	exagamglogene autotemcel	Thalassemia	Conditional Marketing Authorisation (Europe)	1 Feb 2024 - 29 Feb 2024
Casgevy	exagamglogene autotemcel	Sickle Cell Anemia	Conditional Marketing Authorisation (Europe)	1 Feb 2024 - 29 Feb 2024
resamirigene bilparvovec	resamirigene bilparvovec	X-linked Myotubular Myopathy	Meeting with FDA	26 Oct 2023 - 29 Feb 2024
Abecma	idecabtagene vicleucel	Multiple Myeloma (MM)	FDA Advisory Panel Brief	20 Nov 2023 - 29 Feb 2024
Abecma	idecabtagene vicleucel	Multiple Myeloma (MM)	FDA Advisory Panel Meeting	20 Nov 2023 - 29 Feb 2024
Breyanzi	lisocabtagene maraleucel	Chronic Lymphocytic Leukemia (CLL)/Small Cell Lymphocytic Lymphoma (SLL) - NHL	PDUFA for sNDA/sBLA	14 Mar 2024 - 14 Mar 2024
OTL-200	atidarsagene autotemcel	Metachromatic Leukodystrophy	PDUFA/Approval Decision (U.S.)	18 Mar 2024 - 18 Mar 2024
Casgevy	exagamglogene autotemcel	Thalassemia	PDUFA/Approval Decision (U.S.)	20 Mar 2024 - 20 Mar 2024
Kresladi	Leukocyte Adhesion Deficiency-1 Gene Therapy	Autoimmune Disorders	PDUFA/Approval Decision (U.S.)	29 Mar 2024 - 29 Mar 2024
MC-001	HPC-Cord Blood Therapy	Ischemic Stroke	PDUFA/Approval Decision (U.S.)	28 Dec 2023 - 31 Mar 2024
Qalsody	tofersen	Amyotrophic Lateral Sclerosis (ALS)	CHMP (European Panel) Results	27 Dec 2023 - 31 Mar 2024
Imetelstat	imetelstat	Myelodysplastic Syndrome (MDS)	FDA Advisory Panel Meeting	22 Aug 2023 - 31 Mar 2024
Vyjuvek	beremagene geperpavec	Epidermolysis Bullosa	CHMP (European Panel) Results	1 Sep 2023 - 31 Mar 2024
Qalsody	tofersen	Amyotrophic Lateral Sclerosis (ALS)	Approval Decision (Europe)	1 Nov 2023 - 31 May 2024
SPK-9011	fidanacogene elaparvovec	Hemophilia B	CHMP (European Panel) Results	1 Mar 2024 - 30 Sep 2024
Breyanzi	lisocabtagene maraleucel	Indolent Non-Hodgkin's Lymphoma - iNHL	PDUFA for sNDA/sBLA	1 Jan 2024 - 31 Dec 2024

Source: Biomedtracker| Citeline, January 2024

Appendix

Methodology, sources, and glossary of key terms

Q4 2023

American Society of Gene + Cell Therapy

Methodology: sources and scope of therapies

Sources for all data come from Citeline

Pipeline and trial data

- Data derived from **Pharmaprojects and Trialtrove**
- Therapeutic classes included in report categorizations:
  - Gene therapies: gene therapy; cellular therapy, chimeric antigen receptor; cellular therapy, T-cell receptor; lytic virus
  - Cell therapies: cellular therapy, other; cellular therapy, stem cell; cellular therapy, tumor-infiltrating lymphocyte
  - RNA therapies: messenger RNA; oligonucleotide, non-antisense, non-RNAi; RNA interference; antisense therapy

Deal, financing, and catalyst data

- Data derived from **Biomedtracker**. The following industry categorizations of deals are included: gene therapy, cell therapy; antisense, oligonucleotides
- Additional alliance and acquisition deals data from **BioSciDB**, part of **Evaluate Ltd.** The following industry categorizations of deals are included: cell therapy - stem cells/factors, oligonucleotides, antisense/triple helix, gene therapy, RNAi

Glossary of Key Terms

Therapy type definitions

Gene therapy is the use of genetic material to treat or prevent disease.
For the purpose of this report, the following terms shall mean the following:

Gene therapy	Therapies containing an active ingredient synthesized following vector-mediated introduction of a genetic sequence into target cells *in-* or *ex-vivo*. Used to replace defective or missing genes (as in cystic fibrosis) as well as to introduce broadly acting genetic sequences for the treatment of multifactorial diseases (e.g., cancer). Direct administration of oligonucleotides without using vectors is covered separately in the antisense therapy class; RNA interference class; or oligonucleotide, non-antisense, non-RNAi class. Platform technologies for gene delivery are covered separately in the gene delivery vector class
Cellular therapy, chimeric antigen receptor *(falls under gene therapy in this report)*	Cellular therapy consisting of T cells that have been modified to express a chimeric antigen receptor (CAR) – this is a cell surface receptor that gives the T cells the ability to target a specific protein and fight the targeted cells
Cellular therapy, T cell receptor *(falls under gene therapy in this report)*	Cellular therapies whereby natural T cells collected for the patient are engineered to express artificial receptors (usually through viral transfections) that would target specific intracellular antigens (as peptides bound to proteins encoded by the major histocompatibility complex, MHC)
Lytic virus *(falls under gene therapy in this report)*	Therapies that have a replication-competent virus, that lyse pathogenic cells directly. These are normally genetically modified to render them harmless to normal tissues. Examples include oncolytic viruses that specifically attack cancer cells

Glossary of Key Terms

Therapy type definitions, cont.

Cell therapy includes the following therapeutic classes:

Cellular therapy, stem cell	Regenerative therapy which promotes the repair response of injured tissue using stem cells (cells from which all other specialized cells would originate)
Cellular therapy, tumor-infiltrating lymphocyte	Adoptive cellular transfer of tumor-resident T cells from tumor material, their expansion *ex vivo,* and transfer back into the same patient after a lymphodepleting preparative regimen
Cellular therapy, other	Cellular therapies that do not fall under the categories of cellular therapy, stem cell; cellular therapy, CAR; cellular therapy, TIL; cellular therapy, TCR; or the specific cellular therapy are unspecified

Glossary of Key Terms

Therapy type definitions, cont.

RNA therapy includes the following therapeutic classes:

Messenger RNA	Therapies that carry the desired mRNA code to overcome genetic mutations. The mRNA sequence will replace the defective mRNA in a patient and starts producing the desired protein
Oligonucleotide, non-antisense, non-RNAi	Synthetic therapeutic oligonucleotides which operate by a mechanism other than antisense or RNA interference (RNAi). This includes ribozymes, aptamers, decoys, CpGs, and mismatched and immunostimulant oligonucleotides. Sequences delivered using vectors (gene therapy) are covered separately in "gene therapy." Antisense and RNAi oligonucleotides are covered separately in "antisense therapy" and "RNA interference," respectively
RNA interference	Includes products which act therapeutically via an RNA interference (RNAi) mechanism, including small interfering RNAs (siRNAs). These may be synthetic oligonucleotides, or RNAi sequences may be expressed from a vector as a form of gene therapy (see "gene therapy" therapeutic class). *In vivo*, these sequences block the expression of a specific protein by forming an RNA-induced silencing complex, which then specifically binds to and degrades a complementary mRNA encoding the target protein. The use of RNAi purely as a drug discovery tool (e.g., in transgenic animal model production or in target validation) is not covered in this section
Antisense therapy	Antisense compounds under development as potential therapeutics. These may be synthetic oligonucleotides, or antisense RNA may be expressed from a vector as a form of gene therapy. They may prevent the expression of a specific protein *in vivo* by binding to and inhibiting the action of mRNA, since they have a specific oligonucleotide sequence which is complementary to the DNA or RNA sequence which codes for the protein

Glossary of Key Terms

Development status definitions

Pipeline	Drugs that are in active development
Preclinical	Not yet tested in humans
Phase I	Early trials, usually in volunteers, safety, PK, PD
Phase II	First efficacy trials in small numbers of patients
Phase III	Large-scale trials for registrational data
Pre-registration	Filing for approval made to regulatory authorities
Approved	Approval from relevant regulatory authorities for human use

Unspecified indications

Cancer, unspecified	Indications for which the specific tumor type is not specified
Cancer, hematological, unspecified	Indications for which the specific hematological cancer is not specified
Cancer, solid, unspecified	Indications for which the specific solid tumor is not specified

Deal type categories

Alliances	Co-marketing, co-promotion, disease management, joint venture, manufacturing or supply, marketing-licensing, product or technology swap, product purchase, R&D and marketing-licensing, reverse licensing, trial collaborations
Financing	Convertible debt, FOPO, IPO, nonconvertible debt, financing/other, private investment in public equity, private placement, royalty sale, special-purpose financing vehicle, spin-off
Acquisitions	Buy-out, divestiture, spin-out, full acquisition, partial acquisition, reverse acquisition

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