Gene, Cell, & RNA Therapy Landscape

Q4 2022 Quarterly Data Report

American Society
of Gene + Cell Therapy

CITELINE
formerly Pharma Intelligence

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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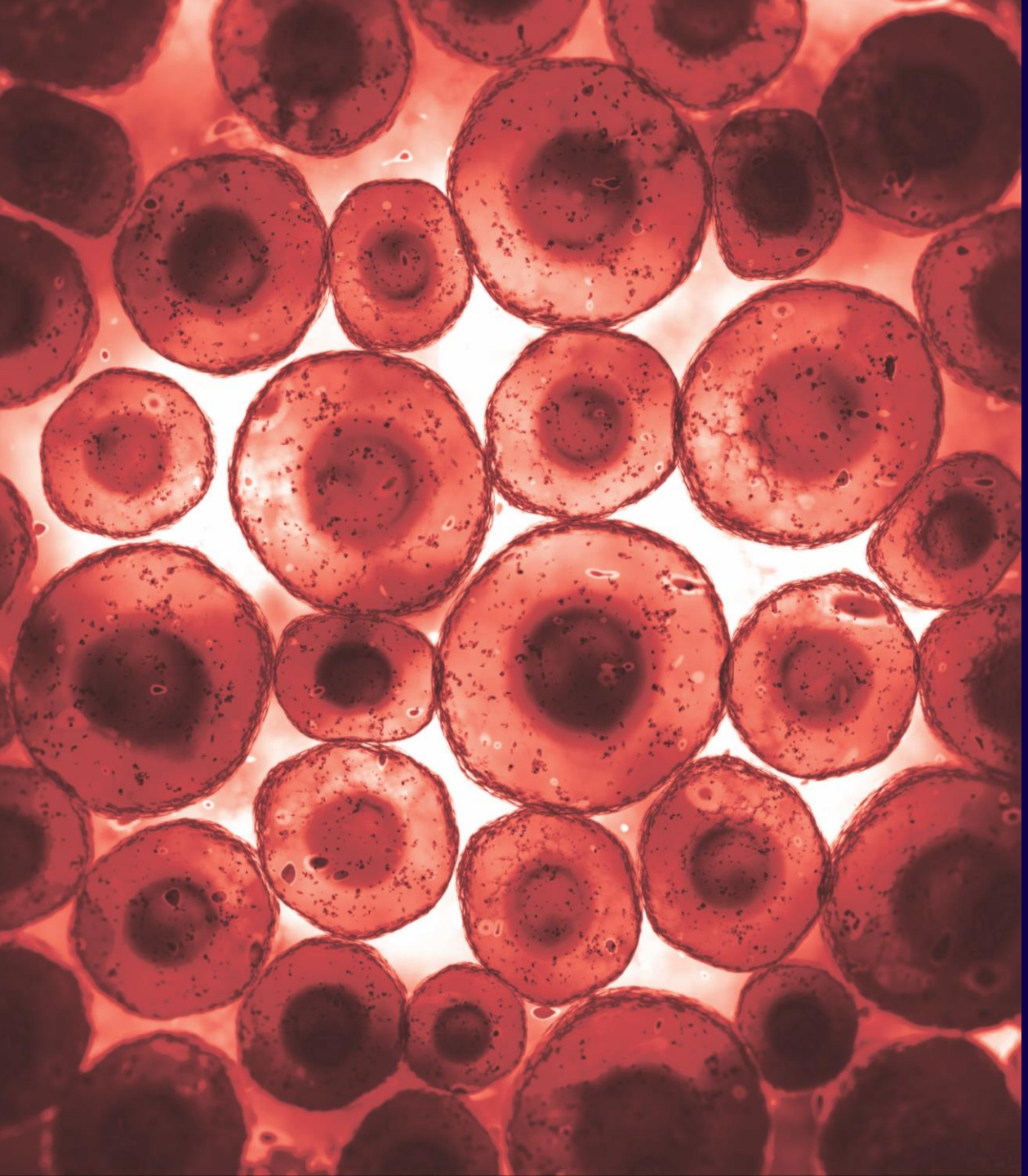
Our global teams of analysts, journalists and consultants keep their fingers on the pulse of the pharmaceutical, biomedical and medtech industries, covering it all with expert insights: key diseases, clinical trials, drug R&D and approvals, market forecasts and more. For more information on one of the world's most trusted life science partners, visit Citeline.



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Introduction

Welcome to the latest quarterly report from ASGCT and Citeline! During the fourth quarter of 2022, gene therapies Hemgenix and Adstiladrin were approved in the US for hemophilia B and bladder cancer, respectively, bringing the total number of globally approved gene therapies to 24. Among those, Relma-cel was approved to treat follicular lymphoma, a second disease, in China. In the EU, cell therapy Ebvallo was approved for Epstein-Barr virus-positive post-transplant lymphoproliferative disease. Additionally in Q4, 21 RNA therapies were approved.

In 2022, the gene, cell, and RNA therapy pipeline from preclinical to pre-registration grew by 7%, bringing the total number of therapies in development to 3,726. More than half (55%) of those are gene therapies, including genetically modified therapies like CAR T-cell therapies. The remainder are non-genetically modified cell therapies (22%) and RNA therapies (23%). In the gene therapy pipeline, oncology and rare diseases remain the top areas of development overall and in the clinic. Oncology and rare diseases are also the top areas of development in the overall pipeline of non-genetically modified cell therapies. Rare diseases and anti-infective therapies remain the top two targeted areas by RNA therapies.

The fourth quarter saw a slight decrease in dealmaking to 106 deals signed, down from 110 in Q3. There were 10 Series A or seed financing rounds completed in Q4 totaling $310.3 million, down from 19 rounds totaling $569.3 million in the third quarter.

Key takeaways from Q4 2022

Across 2022, the pipeline (preclinical to pre-registration) of gene, cell, and RNA therapies has grown by 7%

- The gene therapy pipeline itself grew by 6%, and 2022 saw five gene therapies approved for the first time, two of which are indicated for hemophilia. Oncology and rare diseases remain the most commonly targeted indications by gene therapies both across the pipeline and in the clinic
- The RNA pipeline grew the most throughout 2022, increasing by 17%

Q4 2022 specifically saw three new approvals

- Two new gene therapy approvals in the US: etranacogene dezaparvovec (Hemgenix) for hemophilia B, and nadofaragene firadenovec (Adstiladrin) for bladder cancer
- A cell therapy, tabelecleucel (Ebvallo), was also approved for Epstein-Barr virus-positive post-transplant lymphoproliferative disease in the EU

Dealmaking and financing by advanced molecular companies was down in Q4

- The total number of deals signed by advanced molecular companies saw a decrease of 27% in the final quarter of 2022 compared with Q3; one bright spot, however, was a large uptick in acquisitions, which have doubled in the last year
- Start-up financing also declined in Q4, with only 10 companies raising Series A or seed rounds, for an aggregate $310.3 million
- Top fundraiser iECURE, an in vivo gene editing company, brought in $65 million from Novo Holdings and LYFE Capital to support development in loss-of-function liver disorders

Key highlights in Q4 2022

Q4 2022

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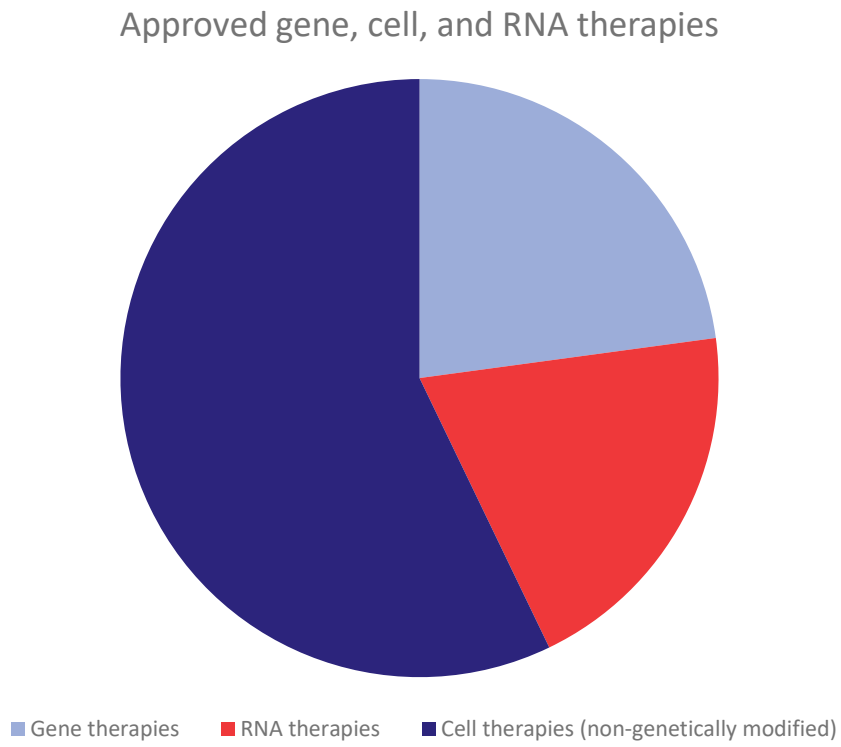
Approved gene, cell, and RNA therapies

Globally, for clinical use:

- 24 gene therapies are approved (including genetically modified cell therapies)
  - In Q4 2022, there were two new gene therapy approvals: etranacogene dezaparvovec (Hemgenix) for hemophilia B, and nadofaragene firadenovec (Adstiladrin) for bladder cancer, both in the US
- 21 RNA therapies are approved
- 60 non-genetically modified cell therapies are approved
  - In Q4 2022, tabelecleucel (Ebvallo) was approved for Epstein-Barr virus-positive post-transplant lymphoproliferative disease in the EU



Source: Pharmaprojects | Citeline, January 2023

Approved gene therapies as of Q4 2022 (1/2)

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	Spark Therapeutics (Roche)
Yescarta	axicabtagene ciloleucel	2017	Diffuse large B-cell lymphoma; non-Hodgkin's lymphoma; follicular lymphoma	US, EU, UK, Japan, Canada, China	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 2023

Text highlighted in yellow represents new approvals during Q4 2022

Approved gene therapies as of Q4 2022 (2/2)

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	Kite Pharma (Gilead)
Libmeldy	atidarsagene autotemcel	2020	Metachromatic leukodystrophy	EU, UK	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	bluebird bio
Delytact	teserpaturev	2021	Malignant glioma	Japan	Daiichi Sankyo
Relma-cel	relmacabtagene autoleucel	2021	Diffuse large B-cell lymphoma; follicular 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	Legend Biotech
Upstaza	eladocagene exuparvovec	2022	Aromatic L-amino acid decarboxylase (AADC) deficiency	EU, UK	PTC Therapeutics
Roctavian	valoctocogene roxaparvovec	2022	Hemophilia A	EU, UK	BioMarin
Hemgenix	etranacogene dezaparvovec	2022	Hemophilia B	US	uniQure
Adstiladrin	nadofaragene firadenovec	2022	Bladder cancer	US	Merck & Co

Source: Pharmaprojects | Citeline, January 2023

Text highlighted in yellow represents new approvals during Q4 2022

Approved RNA therapies as of Q4 2022 (1/2)

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	Alnylam
Vyondys 53	golodirsen	2019	Dystrophy, Duchenne muscular	US	Sarepta Therapeutics
Waylivra	volanesorsen	2019	Hypertriglyceridemia; Lipoprotein lipase deficiency	EU, UK, Brazil	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

*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 2023

Text highlighted in yellow represents new approvals during Q4 2022

Approved RNA therapies as of Q4 2022 (2/2)

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	Alnylam
Amondys 45	casimersen	2021	Dystrophy, Duchenne muscular	US	Sarepta Therapeutics
Nulibry	fosdenopterin	2021	Molybdenum cofactor deficiency	US, EU, 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

*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 2023

Text highlighted in yellow represents new approvals during Q4 2022

Key highlights in Q4 2022

Noteworthy events that happened in Q4 2022

Drug	Event Type	Indication	Molecule	Event Date
ET140203	Orphan Drug Designation (U.S.)	Hepatocellular (Liver) Cancer (HCC) (Including Secondary Metastases)	Cellular	7 October 2022
OTOF-GT	Orphan Drug Designation (Europe)	Hearing Loss - General	Viral Gene Therapy	11 October 2022
Roctavian	NDA/BLA Accepted	Hemophilia A	Viral Gene Therapy	12 October 2022
AVR-RD-02	Innovative Licensing and Access Pathway (ILAP) (U.K.)	Gaucher's Disease	Cellular	18 October 2022
CT053	Filing for Approval (China)	Multiple Myeloma (MM)	Cellular	18 October 2022
LX1004	Orphan Drug Designation (Europe)	Neuronal Ceroid Lipofuscinosis (NCL)	Other Nucleic Acid	18 October 2022
AVR-RD-02	Rare Pediatric Disease (RPD) Designation	Gaucher's Disease	Cellular	27 October 2022
EndolucinBeta	Fast Track Status	Neuroendocrine Tumors (NET)	Other Nucleic Acid	27 October 2022
DYNE-251	Fast Track Status	Duchenne Muscular Dystrophy (DMD)	Antisense	31 October 2022
OTX-2002	Orphan Drug Designation (U.S.)	Hepatocellular (Liver) Cancer (HCC) (Including Secondary Metastases)	mRNA (messenger RNA)	31 October 2022
OTOF-GT	Rare Pediatric Disease (RPD) Designation	Hearing Loss - General	Viral Gene Therapy	7 November 2022
ALETA-001	Innovative Licensing and Access Pathway (ILAP) (U.K.)	Hematologic Cancer	Cellular	7 November 2022
Upstaza	Approval (U.K.)	Neurology - Other	Viral Gene Therapy	17 November 2022
Hemgenix	Approval (U.S.)	Hemophilia B	Viral Gene Therapy	22 November 2022
SRP-9001	Priority Review	Duchenne Muscular Dystrophy (DMD)	Viral Gene Therapy	28 November 2022
OTOF-GT	Orphan Drug Designation (U.S.)	Hearing Loss - General	Viral Gene Therapy	29 November 2022
CB-010	Fast Track Status	Non-Hodgkin's Lymphoma (NHL)	Cellular	29 November 2022
IONIS-SOD1Rx	European Filing Accepted	Amyotrophic Lateral Sclerosis (ALS)	Antisense	5 December 2022
Vyjuvek	MAA Submission (Europe)	Epidermolysis Bullosa	Viral Gene Therapy	14 December 2022
Hemgenix	CHMP (European Panel) Results (Positive)	Hemophilia B	Viral Gene Therapy	15 December 2022
realSKIN	Regenerative Medicine Advanced Therapy (RMAT) Designation	Burn Injury	Cellular	15 December 2022
OCU400	Orphan Drug Designation (U.S.)	Retinitis Pigmentosa (RP) (Ophthalmology)	Viral Gene Therapy	15 December 2022
Adstiladrin	Approval (U.S.)	Bladder Cancer	Viral Gene Therapy	16 December 2022
Ebvallo	Approval (Europe)	Epstein-Barr Virus-Positive Post-Transplant Lymphoproliferative Disease	Cellular	19 December 2022

Source: Biomedtracker | Citeline, January 2023

Pipeline overview

Q4 2022

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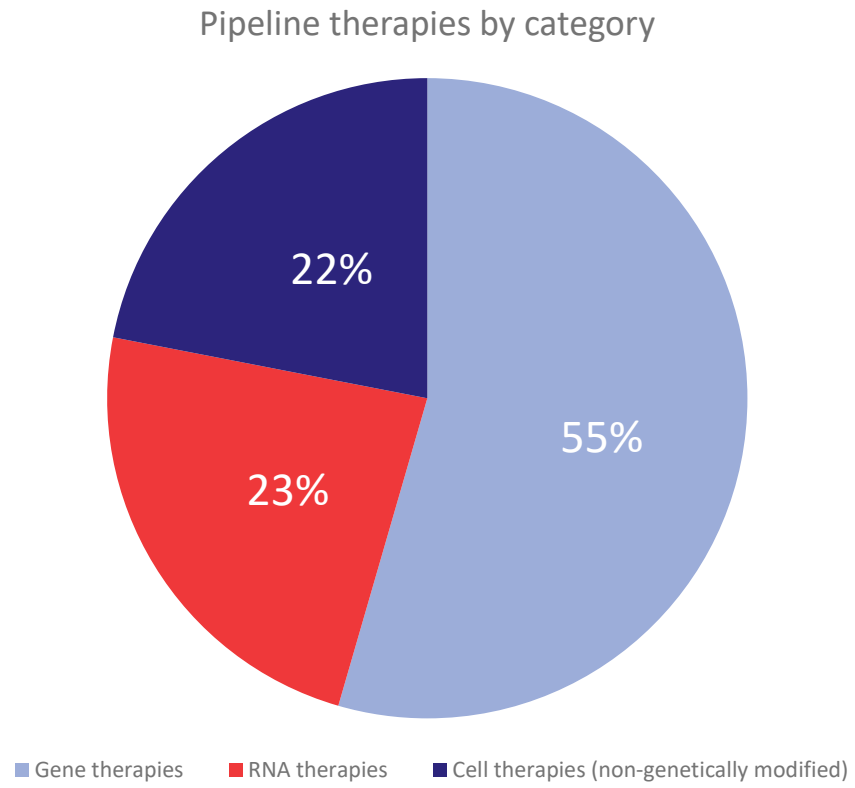
Pipeline of gene, cell, and RNA therapies

3,726 therapies are in development, ranging from preclinical through pre-registration

- 2,053 gene therapies (including genetically modified cell therapies such as CAR T-cell therapies) are in development, accounting for 55% of gene, cell, and RNA therapies
- 827 non-genetically modified cell therapies are in development, accounting for 22% of gene, cell, and RNA therapies



Source: Pharmaprojects| Citeline, January 2023

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Gene therapy pipeline

Gene therapy and genetically modified cell therapies

Q4 2022

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Gene therapy pipeline: Quarterly comparison

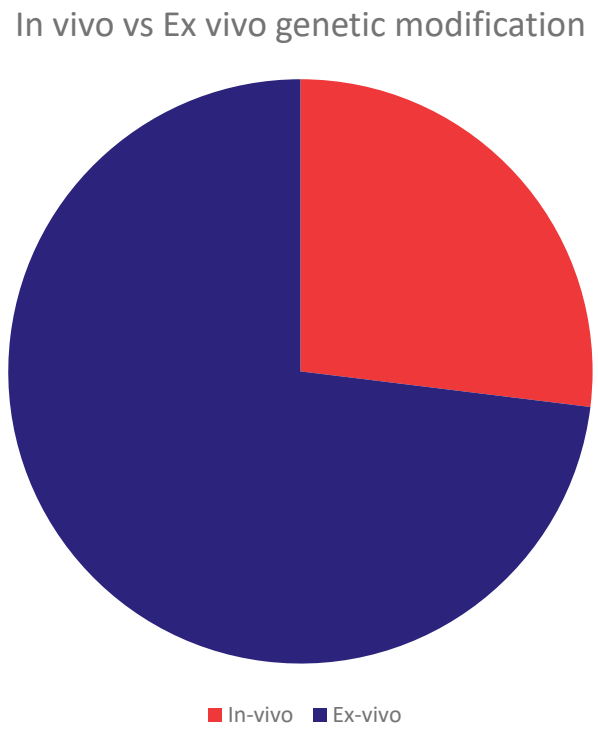
- Unlike last quarter, the number of drugs in Phase I, Phase II, and Phase III have all decreased since the previous quarter
- Although two drugs which were at a global status of pre-registration in Q3 2022 are now approved, two new gene therapies filed for approval in Q4. Therapies currently in pre-registration comprise:
  - lenadogene nolparvovec (Genethon, GenSight Biologics)
    - In the EU and UK
  - beremagene geperpavec (Krystal Biotech)
    - In the US, EU, and UK
  - equecabtagene autoleucel (Nanjing IASO Biotherapeutics, Innovent)
    - In China
  - delandistrogene moxeparvovec (Sarepta Therapeutics)
    - In the US
  - zevor-cel (CARsgen Therapeutics)
    - In China
  - inaticabtagene autoleucel (CASI Pharmaceuticals, Juventas Cell Therapy)
    - In China

Global Status	Q4 2021	Q1 2022	Q2 2022	Q3 2022	Q4 2022
Preclinical	1,412	1,451	1,482	1,480	1,515
Phase I	248	248	258	264	254
Phase II	244	250	248	249	248
Phase III	32	31	28	32	30
Pre-registration	5	6	8	6	6
Total	**1,941**	**1,986**	**2,024**	**2,031**	**2,053**

Source: Pharmaprojects| Citeline, January 2023

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

- *Ex vivo* genetic modification is more widely used for gene therapies in pipeline development
- In Q4 2022, *in vivo* delivery techniques were used in 27% of gene therapies, the same proportion as throughout 2022 and in Q4 2021



Source: Cell and Gene Therapy dashboard | Citeline, January 2023

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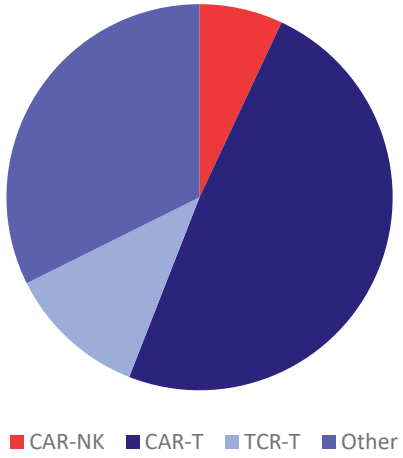
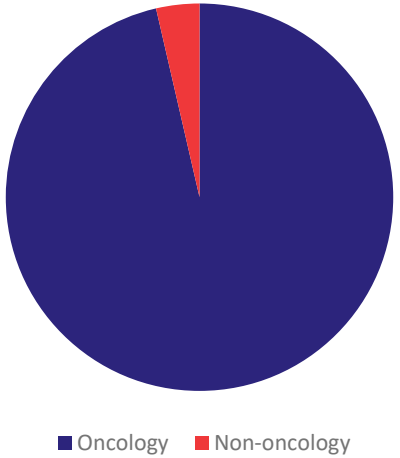
Gene therapy breakdown: CAR-Ts continue to dominate pipeline

- CAR T-cell therapies remain the most common technology used in the pipeline of genetically modified cell therapies (preclinical through to pre-registration), representing 49%, followed by the “other” category at 32%, which includes a list of less commonly used technologies including TCR-NK, CAR-M, and TAC-T
- 97% of CAR T-cell therapies are in development for cancer indications. The remaining non-oncology indications include scleroderma, HIV/AIDS, and autoimmune disease (unspecified)

Genetically modified cell therapy breakdown



CAR-T breakdown

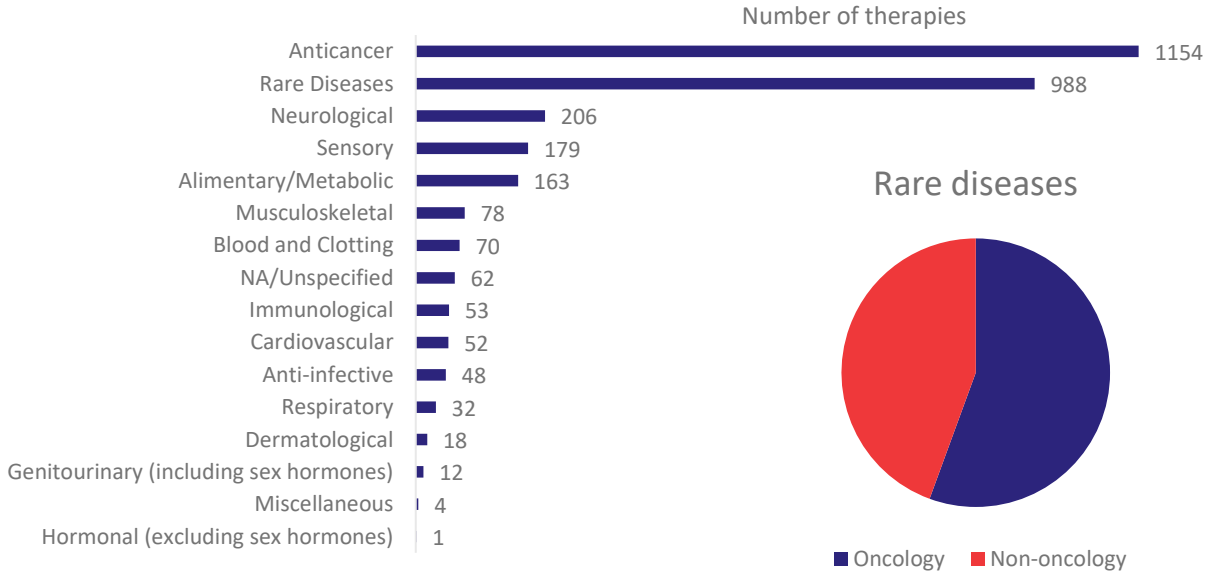


Source: Cell and Gene Therapy dashboard | Citeline, January 2023

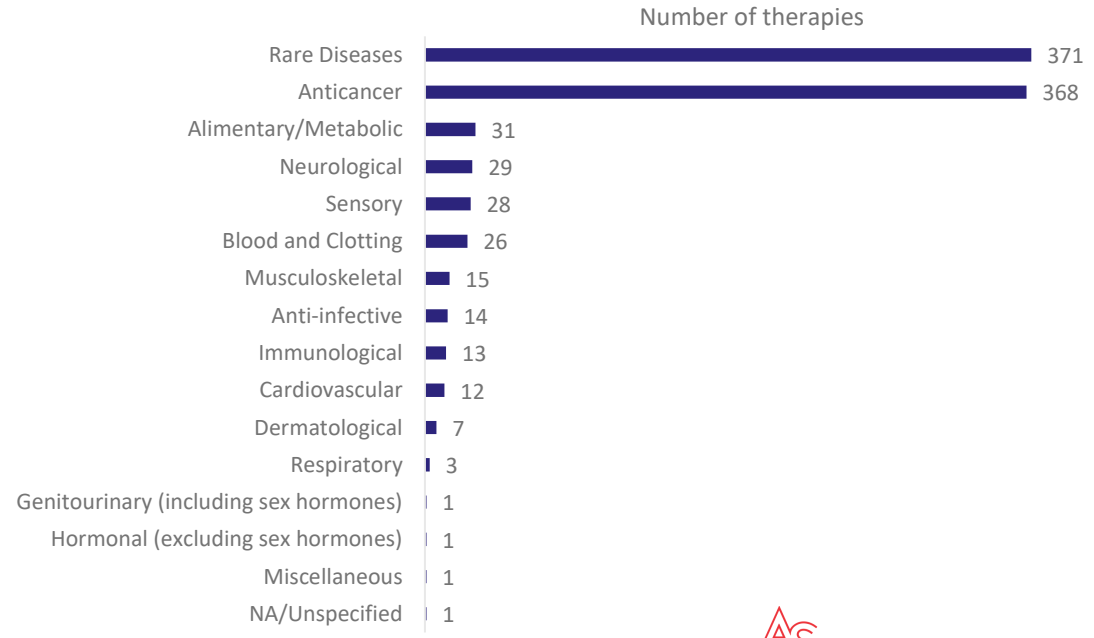
Gene therapy pipeline: Most commonly targeted therapeutic areas

- Oncology and rare diseases remain 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 occurs in oncology, representing a majority of 56% compared to non-oncology rare disease gene therapy pipeline development

Number of therapies from preclinical through pre-registration



Therapies in the clinic (excludes preclinical development)



Source: Pharmaprojects| Citeline, January 2023

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

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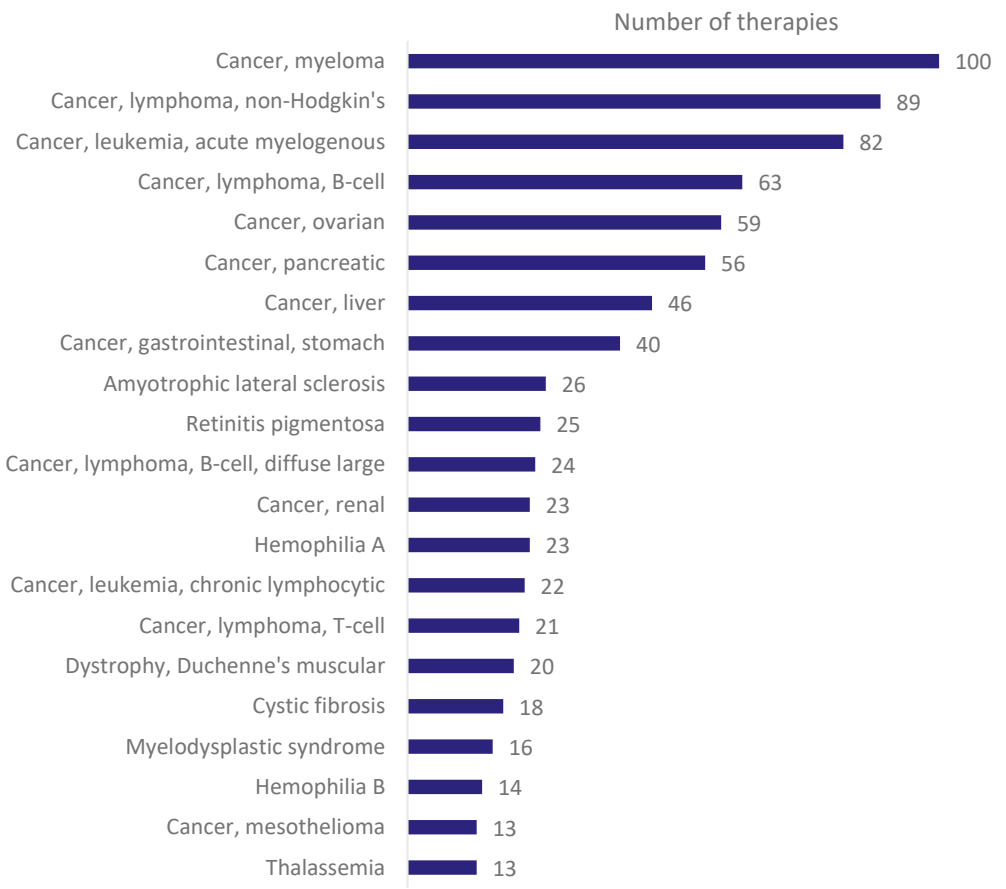
Gene therapy pipeline: Most common rare diseases targeted

- For the 988 pipeline (preclinical to pre-registration) gene therapies which are being developed for rare diseases, eight out of the top 10 rare diseases are oncological, as seen all throughout 2022
- In the same order as the previous five quarters, the top five rare diseases for which gene therapies are being developed are:
  1. Myeloma
  2. Non-Hodgkin’s lymphoma
  3. Acute myelogenous leukemia
  4. B-cell lymphoma
  5. Ovarian cancer



Source: Pharmaprojects| Citeline, January 2023

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

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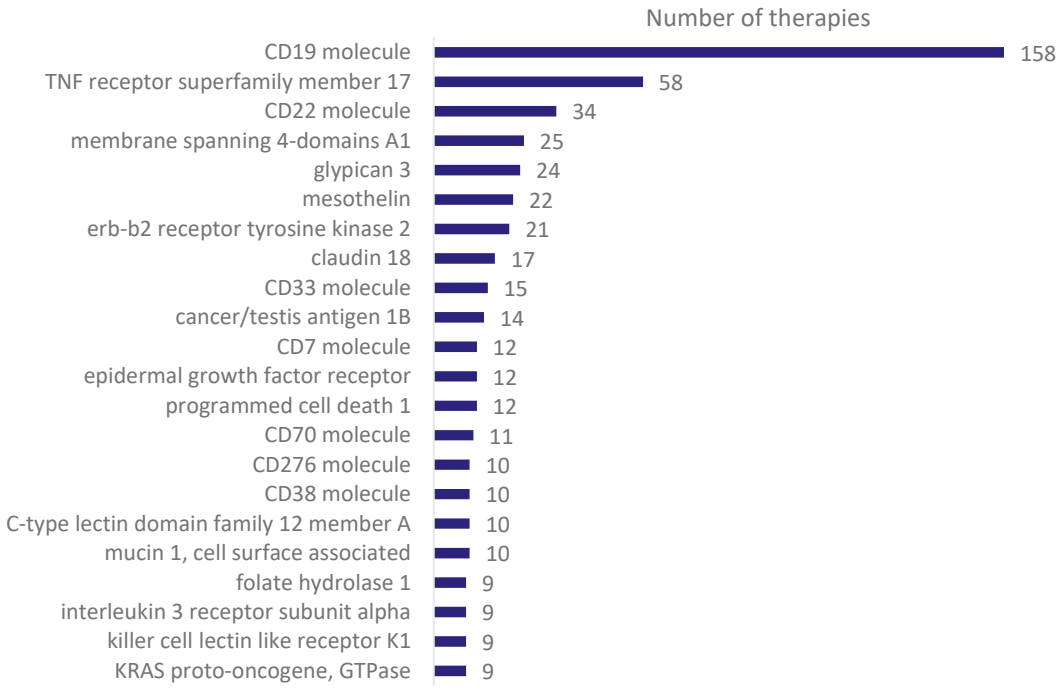
Gene therapy pipeline: Most common targets

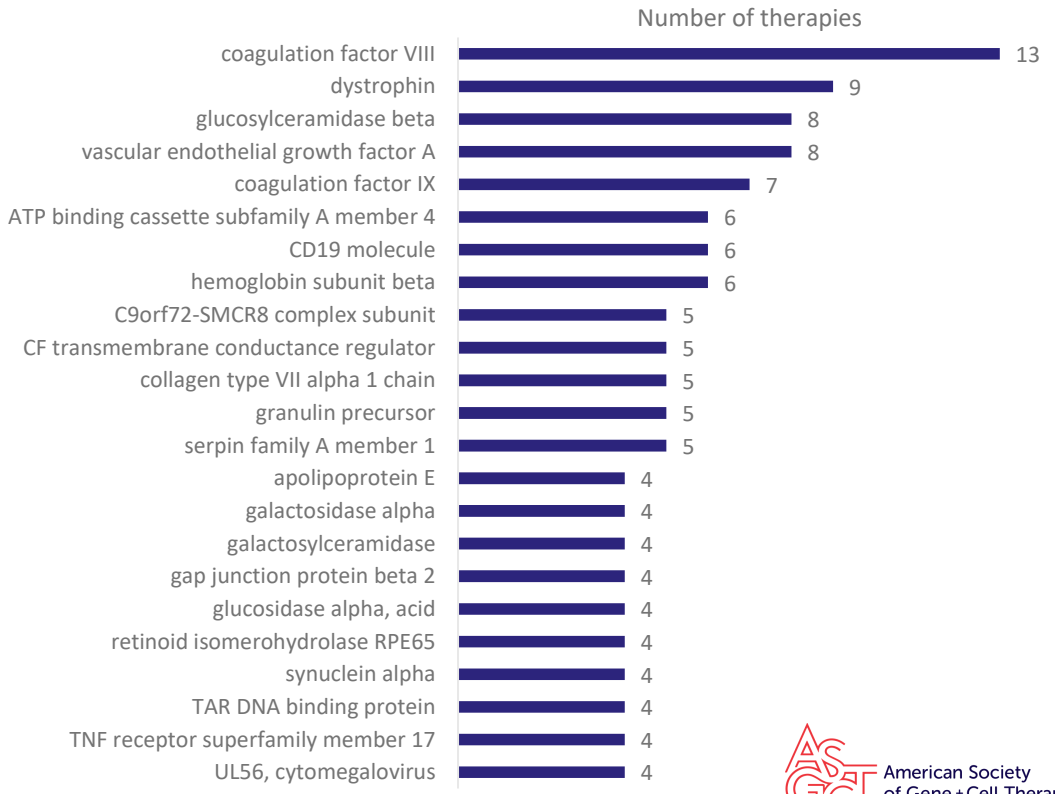
Of the gene therapies in preclinical trials through pre-registration for which targets are disclosed:

- CD19, B-cell maturation antigen (BCMA), also known as TNF receptor superfamily member 17, and CD22 molecule continue to be the top three most common targets for oncology indications
- Coagulation factor VIII remains the most common target for non-oncology indications, while dystrophin replaces coagulation factor IX as the second most common

Oncology targets



Non-oncology targets



Source: Pharmaprojects| Citeline, January 2023

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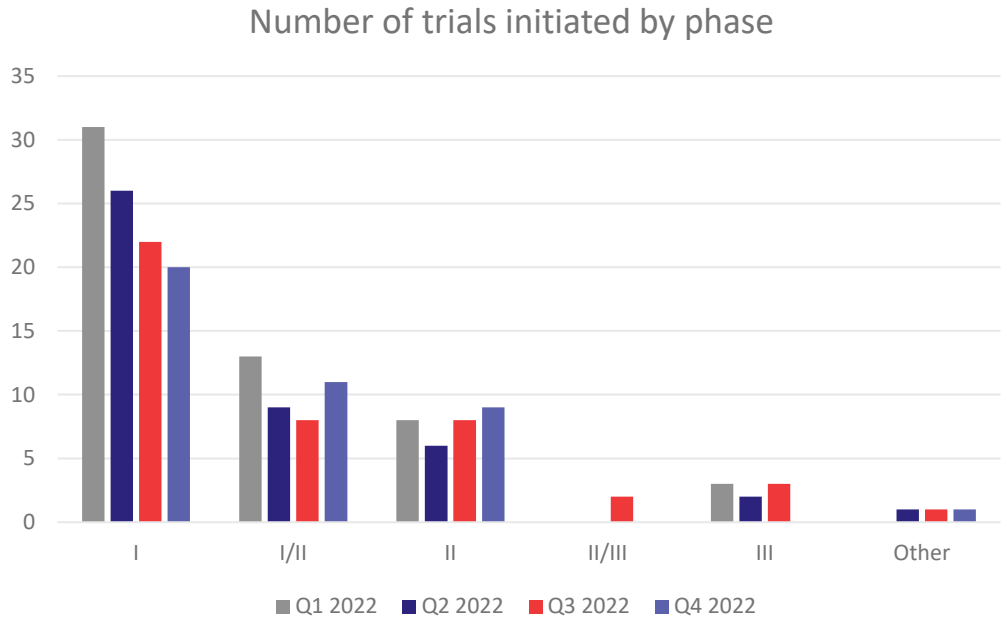
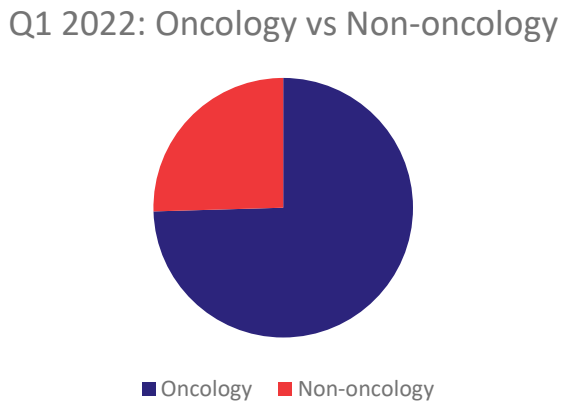
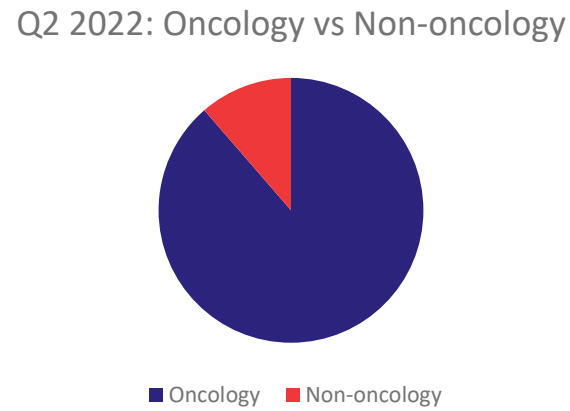
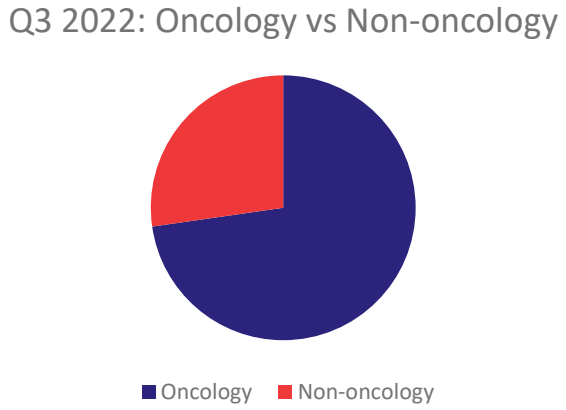
Gene therapy clinical trial activity

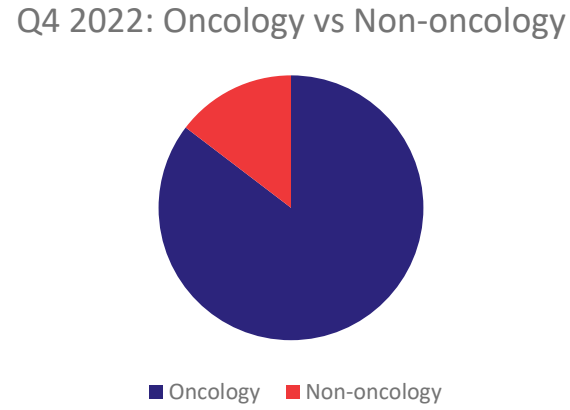
- 41 trials were initiated in Q4 2022 for gene therapies
- The proportion of gene therapy trials for non-oncology indications has decreased by 12 percentage points since the previous quarter, to 15%











Source: Trialtrove| Citeline, January 2023

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Non-genetically modified cell therapy pipeline

Q4 2022

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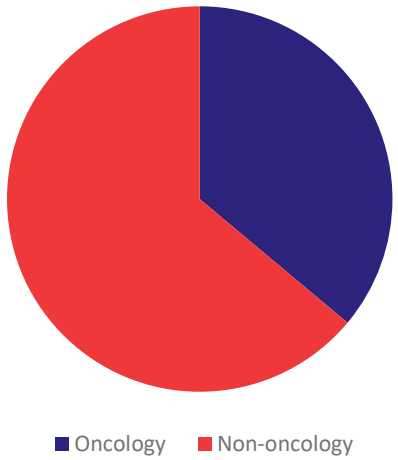
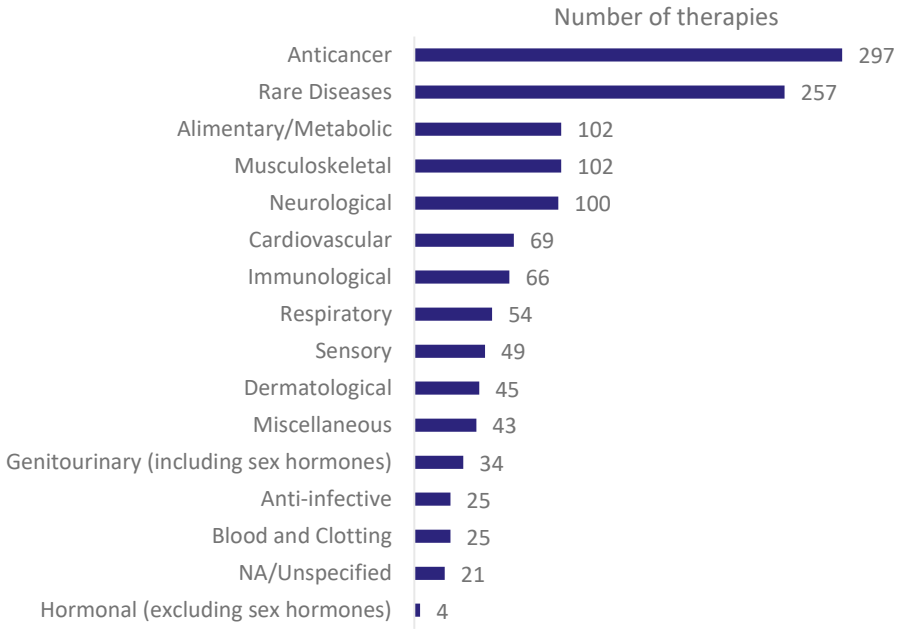
Non-genetically modified cell therapy pipeline: Most common therapeutic areas targeted

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

- Oncology and rare diseases remain 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, 66% are in development for non-oncology rare diseases, an increase of three percentage points from the previous three quarters of 2022





Source: Pharmaprojects| Citeline, January 2023

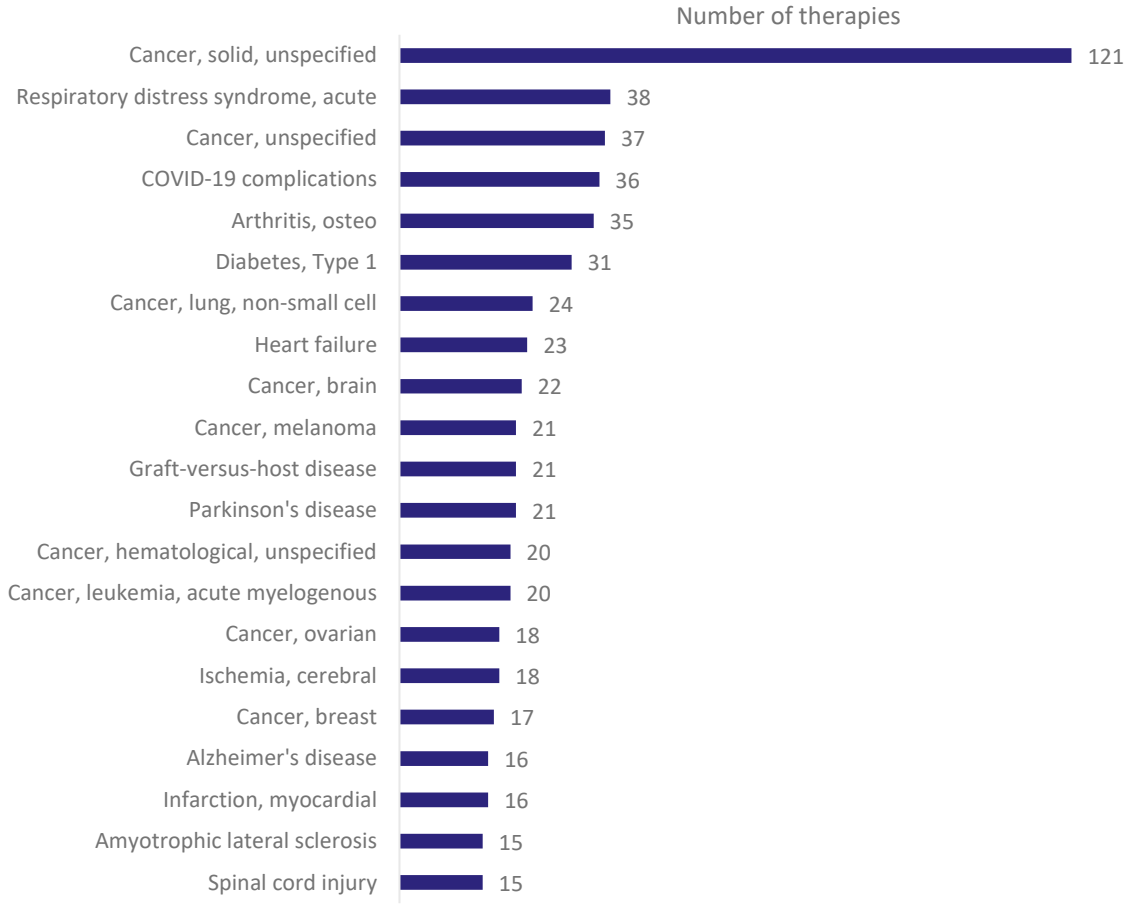
Note: figures based on indications in pipeline development only for each therapy

American Society of Gene + Cell Therapy

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

Of the therapies for which indications are specified, the top three indications remain the same as in Q4 2021 and throughout 2022:

1. Acute respiratory distress syndrome
2. COVID-19 complications
3. Osteo arthritis



Source: Pharmaprojects| Citeline, January 2023

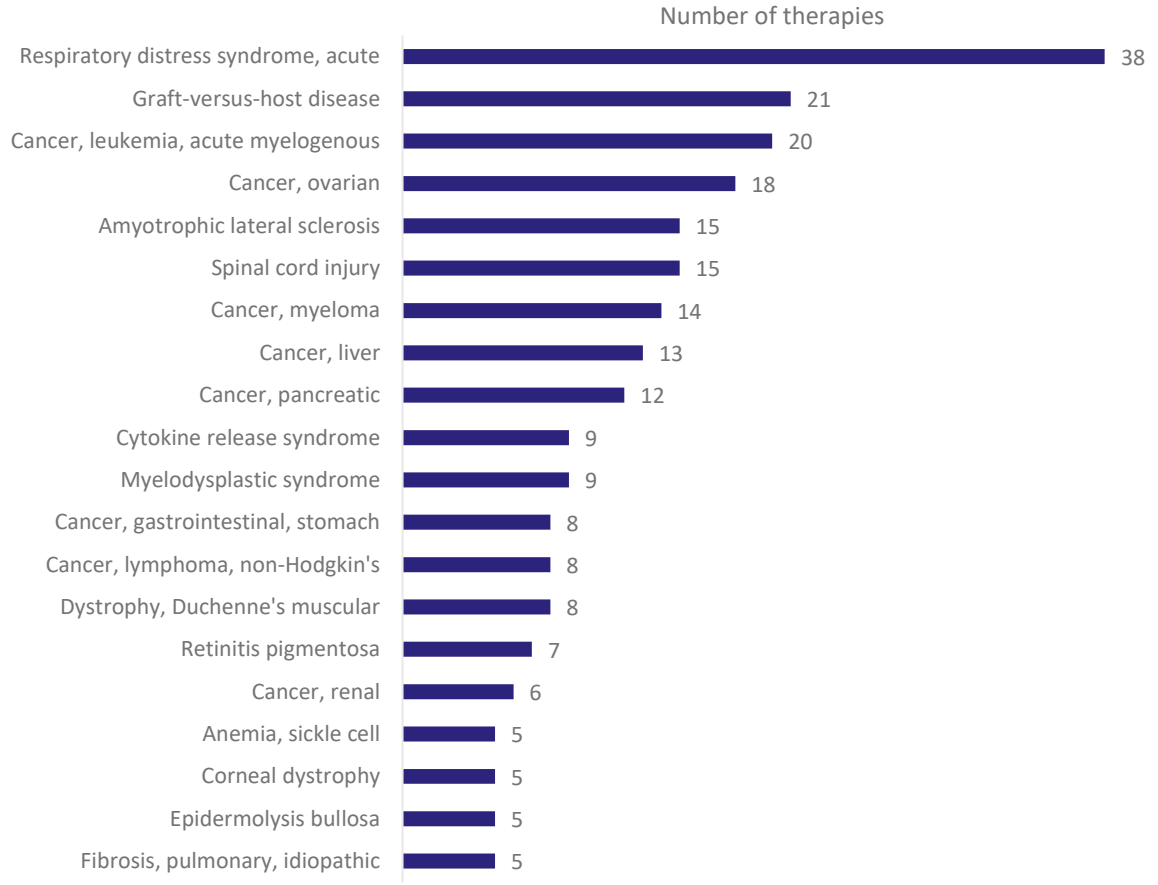
Note: figures based on indications in pipeline development only for each therapy

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 are acute myelogenous leukemia, ovarian cancer, and myeloma
- The top three non-oncology indications remain acute respiratory distress syndrome, graft-versus-host disease, and amyotrophic lateral sclerosis



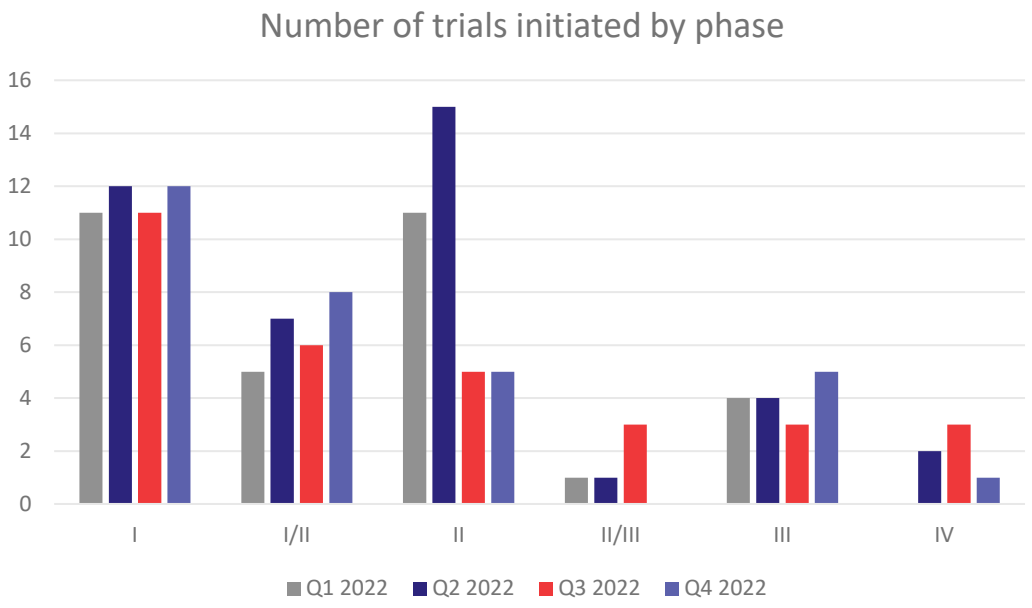
Source: Pharmaprojects| Citeline, January 2023

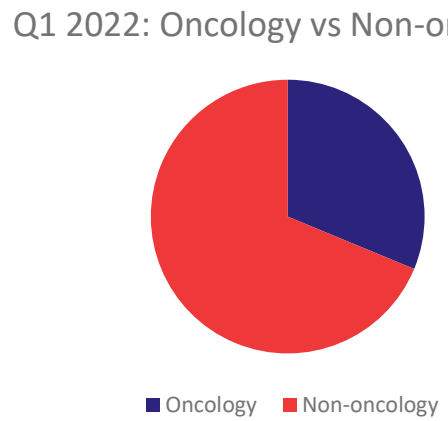
Note: figures based on indications in pipeline development only for each therapy

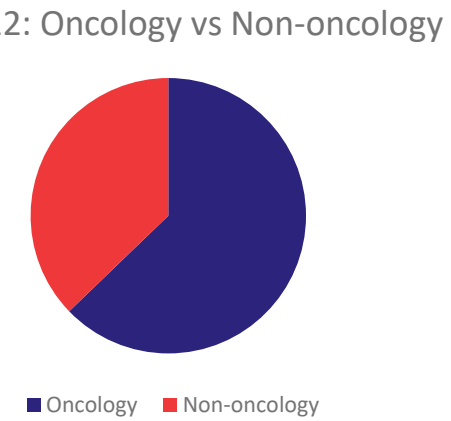
American Society of Gene + Cell Therapy

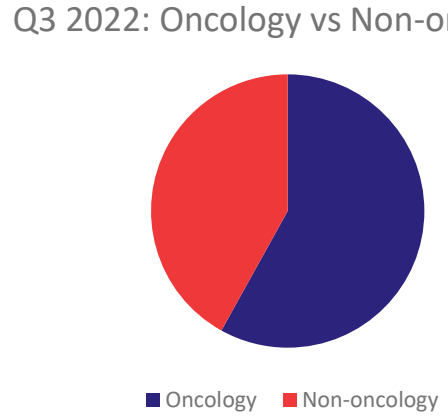
Non-genetically modified cell therapy trial activity

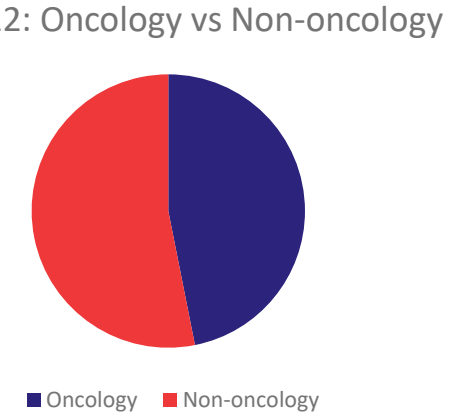
- As in Q3 2022, 31 trials were initiated for non-genetically modified cell therapies in Q4 2022
- Of these 31, 55% are for non-oncology indications, an increase of 13 percentage points from Q3 2022











Source: Trialtrove| Citeline, January 2023

American Society of Gene + Cell Therapy

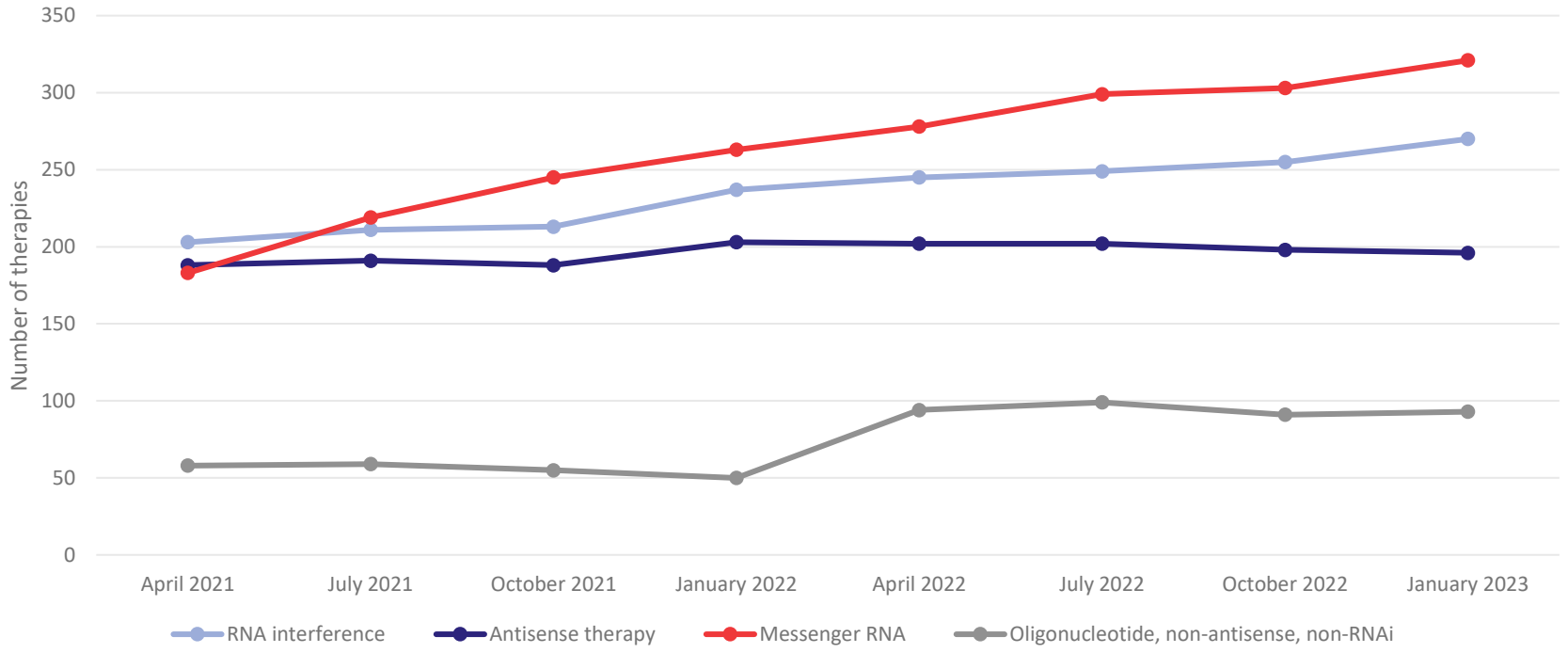
RNA therapy pipeline

Q4 2022

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) continue to be the preferred RNA modalities for research

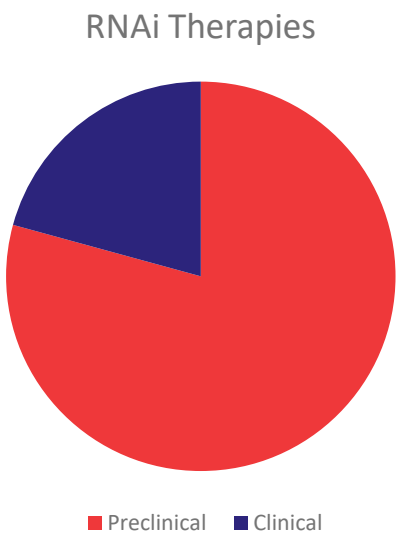


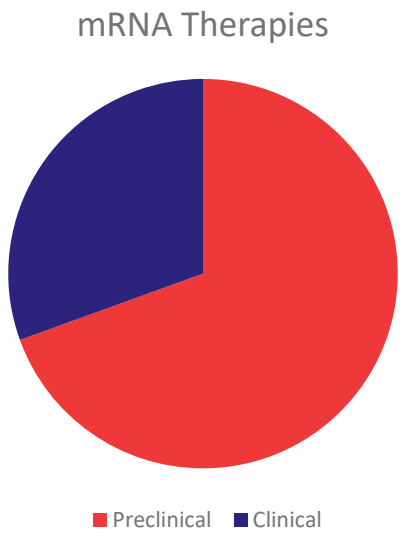
Source: Pharmaprojects| Citeline, January 2023

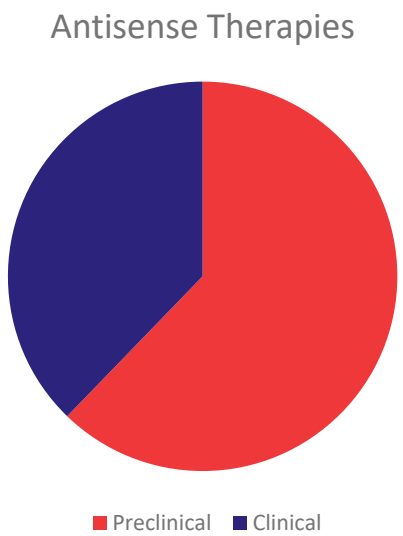
American Society of Gene + Cell Therapy

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

- The majority of RNAi, mRNA, and antisense therapeutics in development are in preclinical development, representing 79%, 69%, and 62% of their respective pipelines. These values are all slightly lower than last quarter







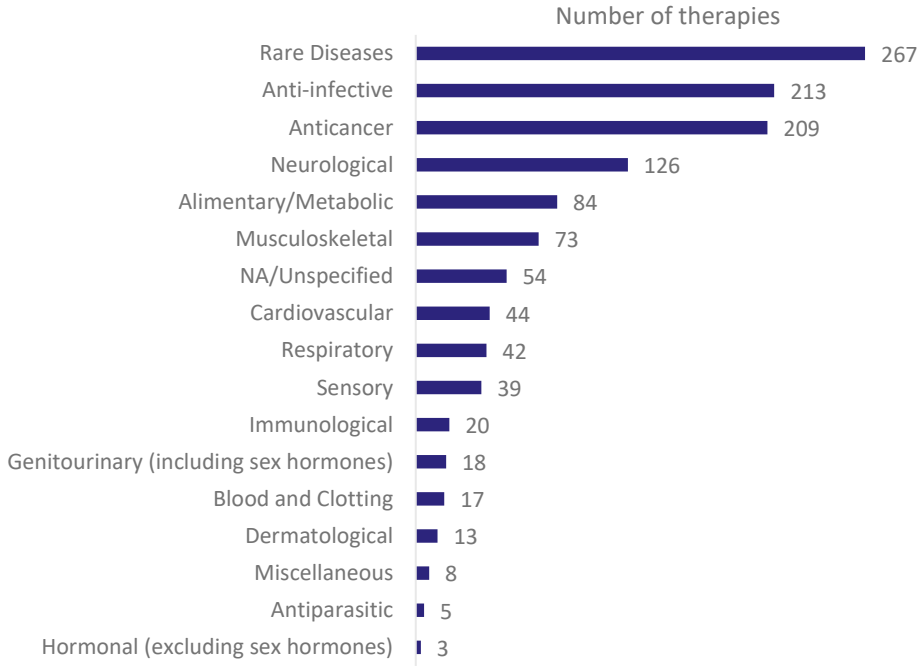
Source: Pharmaprojects| Citeline, January 2023

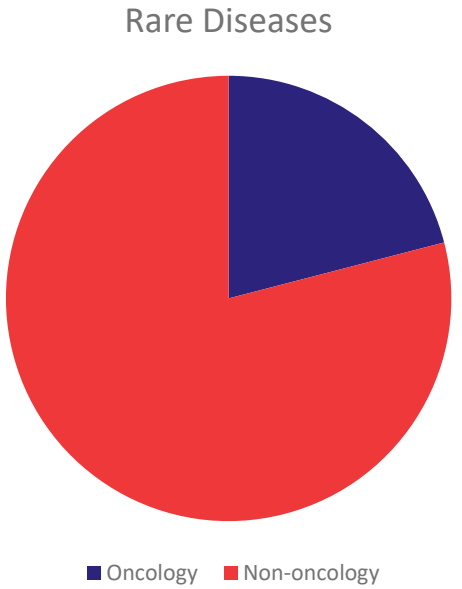
American Society of Gene + Cell Therapy

RNA therapies: Most commonly targeted therapeutic areas

Of the 888 RNA therapies currently in the pipeline (from preclinical through pre-registration):

- Rare diseases and anti-infective therapies remain the top two targeted therapeutic areas by RNA therapies
- Non-oncology indications continue to be the most targeted rare diseases by RNA therapies, representing a majority of 81%





Source: Pharmaprojects| Citeline, January 2023

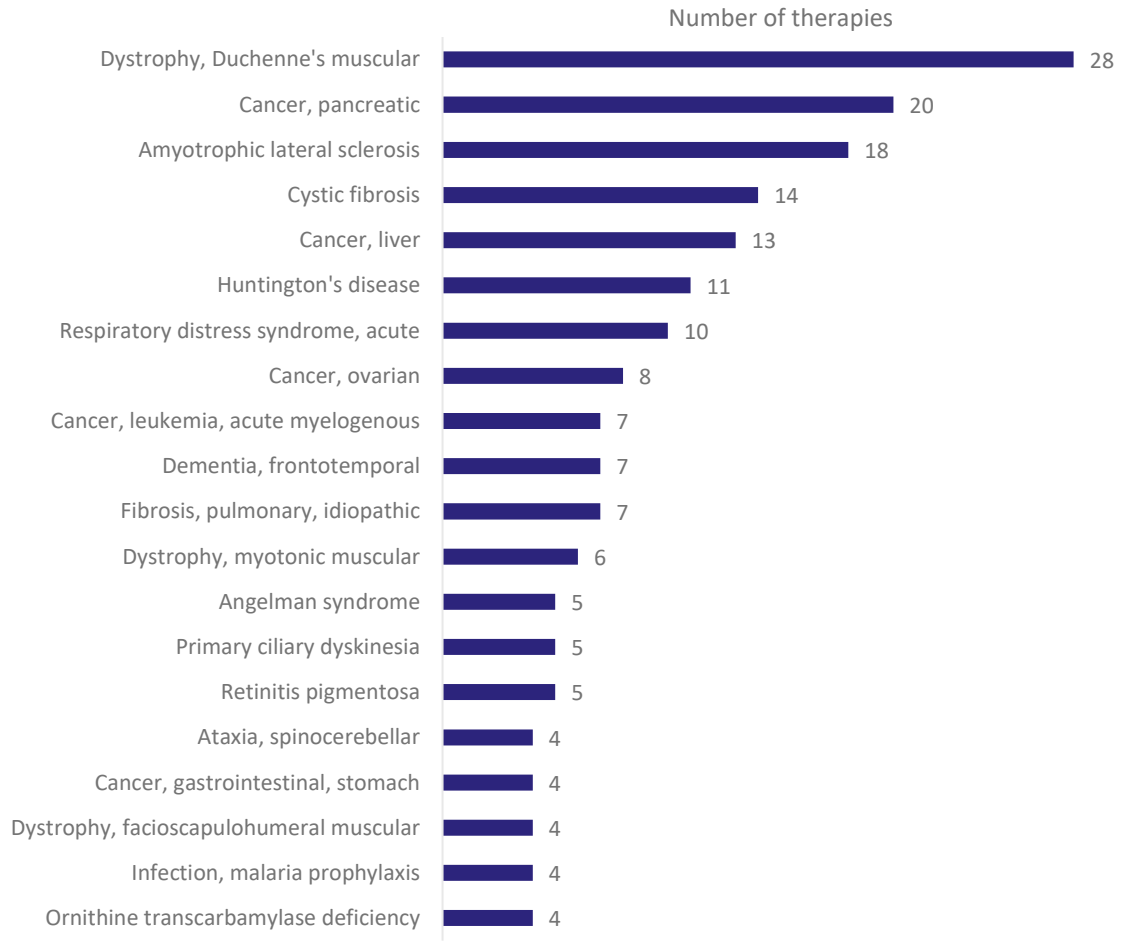
Note: figures based on indications in pipeline development only for each therapy

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 are pancreatic, liver, and ovarian cancer
- For non-oncology rare diseases, Duchenne's muscular dystrophy, amyotrophic lateral sclerosis, and cystic fibrosis are the most commonly targeted indications

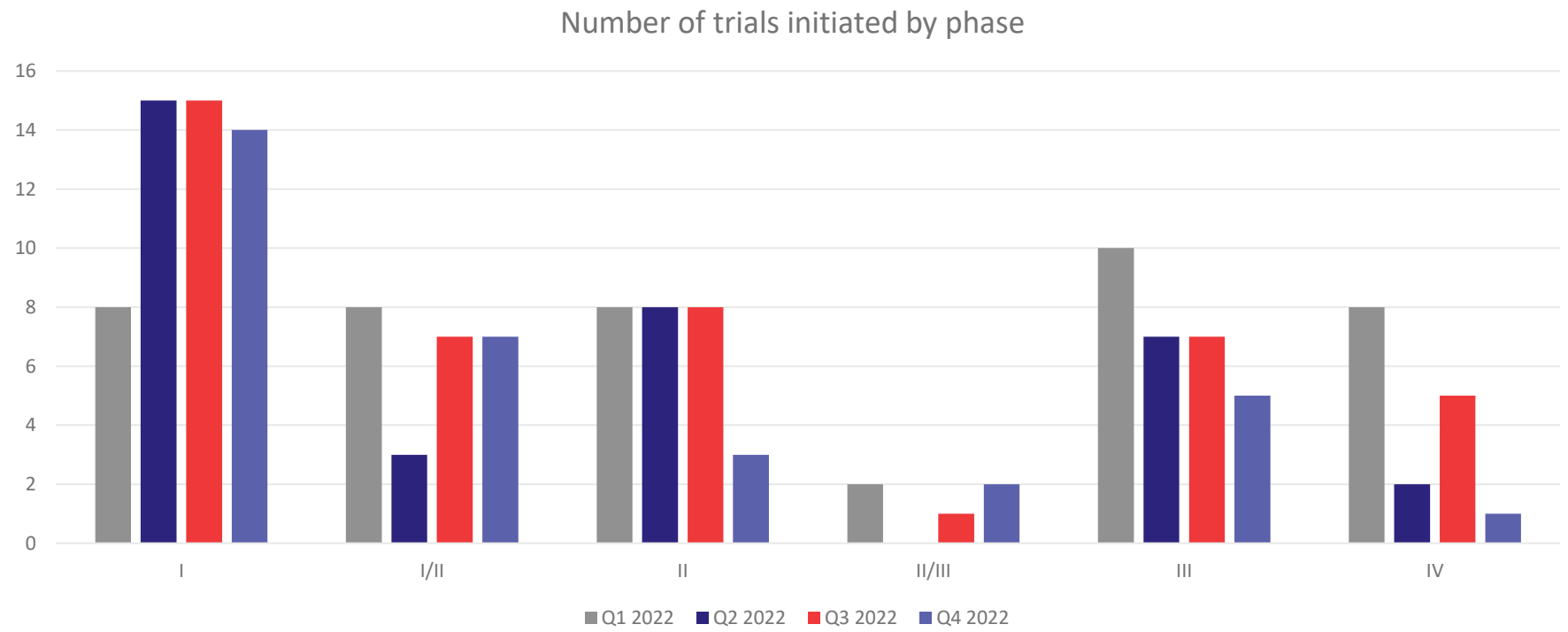


Source: Pharmaprojects| Citeline, January 2023

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

RNA therapy pipeline: Clinical trial activity

- 32 RNA trials were initiated in Q4 2022, compared to 43 in Q3 2022, 94% of which were for non-oncology indications



Source: Trialtrove| Citeline, January 2023

American Society of Gene + Cell Therapy

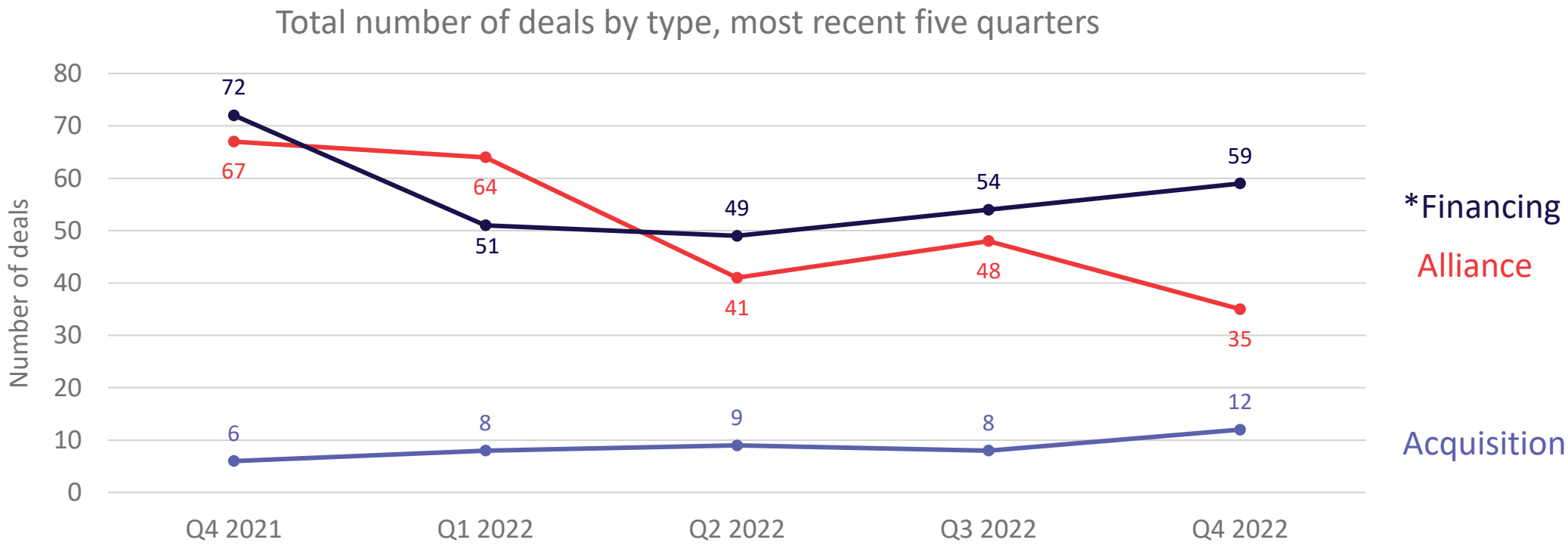
Overview of dealmaking for gene, cell, and RNA therapy companies

Q4 2022

American Society of Gene + Cell Therapy

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

- Advanced molecular therapy companies signed a total of 106 deals in Q4 2022, a slight decrease from the 110 in Q3, and 27% fewer than the 145 deals signed in the same quarter of 2021
- Acquisitions have seen a large uptick, doubling in Q4 2022 to 12 transactions compared with six in the final quarter of 2021; financings have also continued to trend upward
- Alliance counts continue to decrease, with the lowest quarterly number of partnerships in the most recent five quarters



Source: Biomedtracker| Citeline, January 2023

*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 2022 acquisitions in gene, cell, and RNA therapy

- Myovant, whose pipeline includes the oligopeptide kisspeptin-1 receptor agonist MVT-602 for infertility, was fully acquired by Sumitovant for $1.7 billion
- Three privately held advanced molecular companies – Estrella Biopharma, Liminatus Pharma, and GRI Bio – completed reverse mergers with public shell entities, taking over the public listings to access public markets

Deal Date	Deal Title	Potential Deal Value (US $)
3 October 2022	Estrella Biopharma to Become Publicly Traded Via Merger with TradeUP Acquisition Corp	Undisclosed
3 October 2022	Alexion to Acquire LogicBio Therapeutics; Acquisition Complete	68,232,857
18 October 2022	Lilly to Acquire Akouos to Discover and Develop Treatments for Hearing Loss; Acquisition Complete	610,000,000
23 October 2022	Syncona to Acquire Applied Genetic Technologies for $73.5M; Acquisition Complete	73,500,000
24 October 2022	Sumitovant Enters Definitive Agreement to Acquire All Outstanding Shares of Myovant Sciences Not Already Owned for $1.7B	1,700,000,000
7 November 2022	Viatris to Acquire Oyster Point Pharma	Undisclosed
15 November 2022	Ascend Gene and Cell Therapies Acquired Freeline's CMC-Focused Subsidiary in Germany	25,000,000
16 November 2022	Kriya Acquires Redpin Therapeutics	Undisclosed
29 November 2022	AstraZeneca to Acquire Neogene Therapeutics	320,000,000
30 November 2022	Liminatus Pharma to go Public Through Reverse Merger with Iris Acquisition	Undisclosed
13 December 2022	GRI Bio to Become Publicly Listed via Reverse Merger with Vallon Pharmaceuticals	Undisclosed
20 December 2022	Kite to Acquire Tmunity Therapeutics to Pursue Next-Generation CAR T-Cell Therapy Advancements in Cancer	Undisclosed

Source: Biomedtracker| Citeline, January 2023

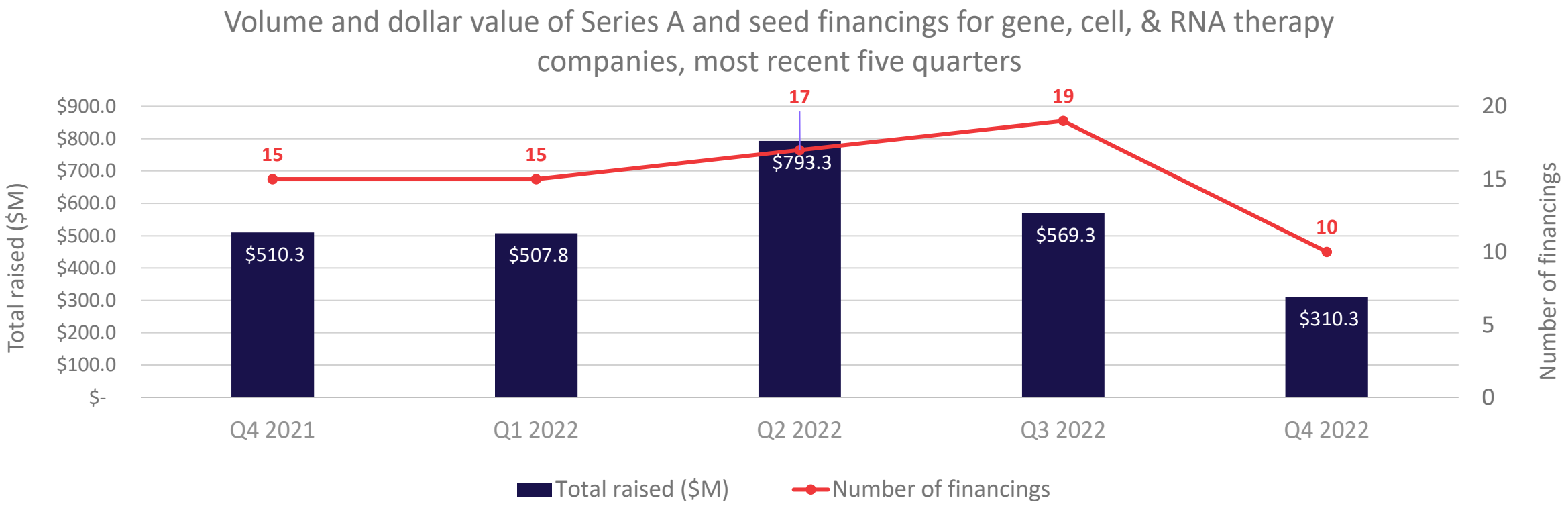
Start-up funding for gene, cell, and RNA therapy companies

Q4 2022

American Society of Gene + Cell Therapy

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

- 2022 ended with a decline in volume and value of start-up financings, with 10 Series A or seed rounds completed in Q4 (a 47% decrease vs Q3), totaling $310.3 million, which was down 46%
- The final quarter of 2022 was also down from the same quarter in 2021, with five fewer start-up financings done, and $200 million less in financing



Source: Biomedtracker| Citeline, January 2023

American Society of Gene + Cell Therapy

Q4 2022 start-up financing for gene, cell, and RNA therapy companies

Deal Date	Deal Title	Modality Type	Company Location	Academic Source	Potential Deal Value (US, $M)
10 October 2022	Ochre Bio Raises $30M in Series A Financing	siRNA	United Kingdom, Oxford	Undisclosed	30
11 October 2022	Trailhead Biosystems Raises $10M in Series A2 Financing	Cell therapy	United States, Ohio, Cleveland	Early work in collaboration with Advanced Regenerative Manufacturing Institute (ARMI)	10
12 October 2022	Ascidian Therapeutics Raises $50M in Series A Financing	RNA trans-splicing	United States, Massachusetts, Boston	Undisclosed	50
13 October 2022	Carmine Therapeutics Announces First Close of Series A Funding	Non-viral gene therapy	United States, Massachusetts, Cambridge	National University of Singapore; Massachusetts Institute of Technology	Undisclosed
19 October 2022	PIC Therapeutics Completes $35M Series A Financing	RNA translation modulation	United States, Massachusetts, Boston	Harvard University; McGill University	35
26 October 2022	VacV Biotherapeutics Emerges from Stealth to Advance Immunotherapies for Cancer	Oncolytic viral therapy	United Kingdom, London	Barts Cancer Institute at Queen Mary University of London	3
9 November 2022	Avstera Therapeutics Closes $4.55M Seed Round	Cell therapy and mRNA vaccine	United States, Pennsylvania, Malvern	Georgetown University; George Washington University; University of Pennsylvania	4.55
29 November 2022	Rgenta Closes $52M Series A Round	Small molecule RNA modulators	United States, Massachusetts, Cambridge	University of Massachusetts Medical School	52
30 November 2022	iECURE Closes $65M Series A1 Financing	In vivo gene editing	United States, Pennsylvania, Philadelphia	University of Pennsylvania's Gene Therapy Program	65
5 December 2022	SonoThera Completes $60.75M Series A Funding	Non-viral gene therapy (ultrasound-guided)	United States, California, San Francisco	Rush University	60.75

Source: Biomedtracker| Citeline, January 2023

Notable Q4 2022 start-up gene, cell, and RNA therapy companies

	Company details	Academic source	Financing type/amount raised	Lead investor(s)	Therapy areas of interest
ECURE	In vivo gene editing (gene knock-in) using ARCUS nuclease	University of Pennsylvania's Gene Therapy Program	Series A1/$65M	Novo Holdings and LYFE Capital	Loss-of-function liver disorders (OTC, citrullinemia type 1, PKU)
SONOTHERA™	Ultrasound microbubbles technology for non-invasive and non-viral delivery of gene therapy	Rush University	Series A/$60.75M	ARCH Venture Partners	Unspecified – technology enables delivery to "wide range of organs within the body"
Rgenta	Identifying high-efficacy and high-specificity RNA target sites of disease-causing genes, and selective modulation of RNA splicing and processing	University of Massachusetts Medical School	Series A/52M	AZ-CICC Healthcare Investment Fund	Oncology and neurology

Source: Biomedtracker| Citeline, January 2023

Upcoming catalysts

Q4 2022

American Society of Gene + Cell Therapy

Upcoming Catalysts

Below are noteworthy catalysts (forward-looking events) expected in Q1 2023

Therapy	Generic Name	Disease	Catalyst	Catalyst Date
Oxlumo	lumasiran	Hyperoxaluria	Supplemental Approval Europe (PH1)	19 Dec 2022 - 31 Jan 2023
Vyjuvek	beremagene geperpavec	Epidermolysis Bullosa	PDUFA for BLA - First Review	17 Feb 2023 - 17 Feb 2023
Hemgenix	etranacogene dezaparvovec	Hemophilia B	European Approval Decision	23 Feb 2023 - 23 Feb 2023
Roctavian	valoctocogene roxaparvovec	Hemophilia A	PDUFA for BLA - Second Review	29 Sep 2022 - 31 Mar 2023
Lantidra	allogeneic Islets of Langerhans	Diabetes Mellitus, Type I	PDUFA for BLA - First Review	21 Dec 2022 - 30 Jun 2023
Lumevoq	lenadogene nolparvovec	Leber's Hereditary Optic Neuropathy (LHON) (Ophthalmology)	European Approval Decision	1 Dec 2022 - 30 Nov 2023
Abecma	idecabtagene vicleucel	Multiple Myeloma (MM)	Supplemental Approval (3-5L)	1 Jan 2023 - 31 Dec 2023
HPC-Cord Blood Therapy	Umbilical cord blood mononuclear stem cell therapy	Ischemic Stroke	PDUFA for BLA - First Review	1 Jan 2023 - 31 Dec 2023

Source: Biomedtracker| Citeline, January 2023

Appendix

Methodology, sources, and glossary of key terms

Q4 2022

American Society of Gene + Cell Therapy

Methodology: Sources and scope of therapies

Sources for all data come from Citeline (formerly Pharma Intelligence)

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

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 which 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 which 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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