

Advanced Therapies Sector Overview

Gene Therapy for Rare Disorders Europe 2019

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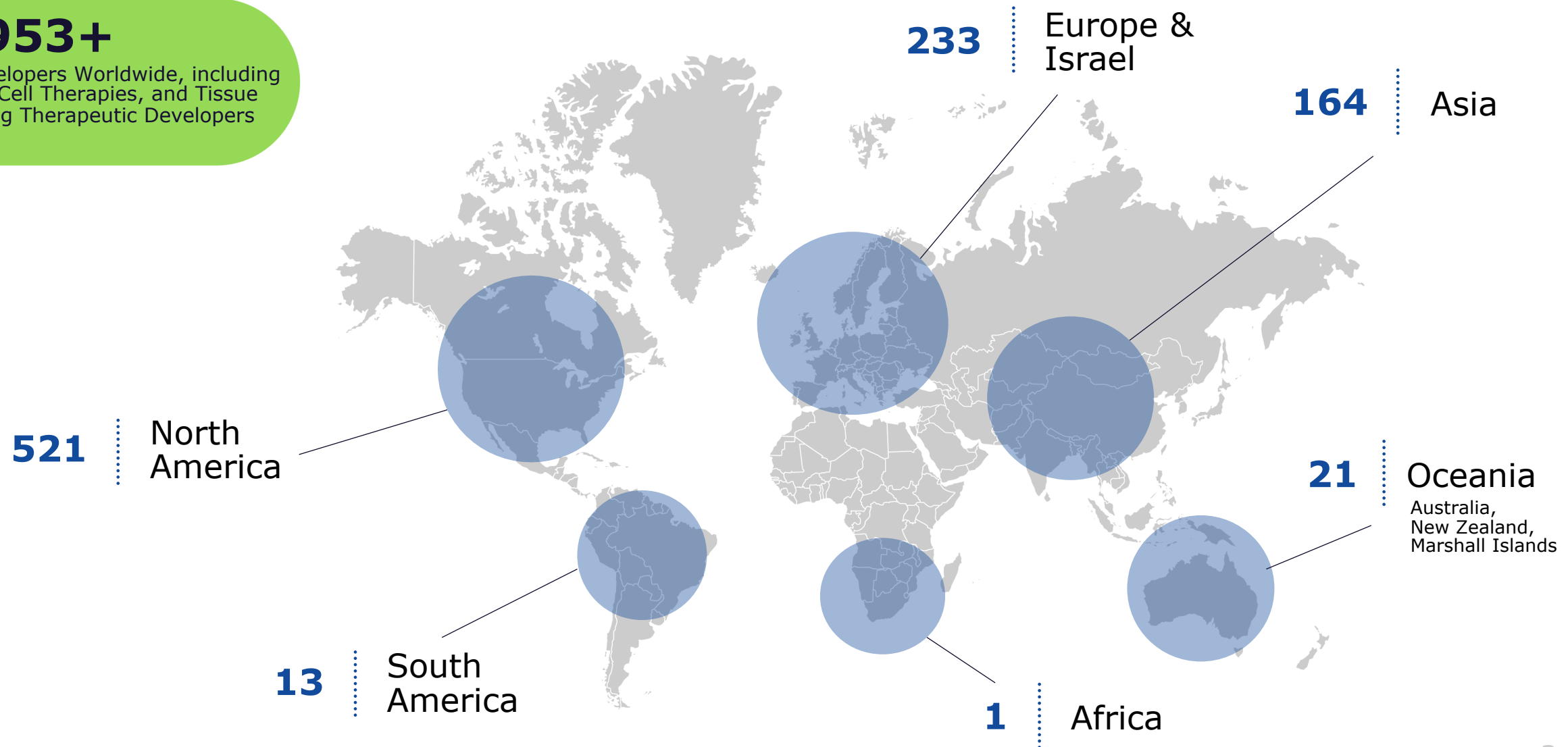
About ARM

- **International advocacy organization**
 - Dedicated to realizing the promise of safe and effective regenerative medicines for patients around the world
 - Cell and gene therapy, tissue engineering
- **350+ members**
 - Small and large companies, non-profit research institutions, patient organizations, and other sector stakeholders
 - Across 25 countries
- **Priorities:**
 - Clear, predictable, and harmonized **regulatory** pathways
 - Enabling market access and value-based **reimbursement** policies
 - Addressing industrialization and **manufacturing** hurdles
 - Conducting key stakeholder outreach, **communication**, and education
 - Facilitating sustainable access to **capital**

Current Global Sector Landscape

953+

ATMP Developers Worldwide, including
Gene and Cell Therapies, and Tissue
Engineering Therapeutic Developers



Current Global Sector Landscape

454+

Gene Therapy & Gene-based Medicine
Companies Worldwide

249

North
America

2

South
America

106

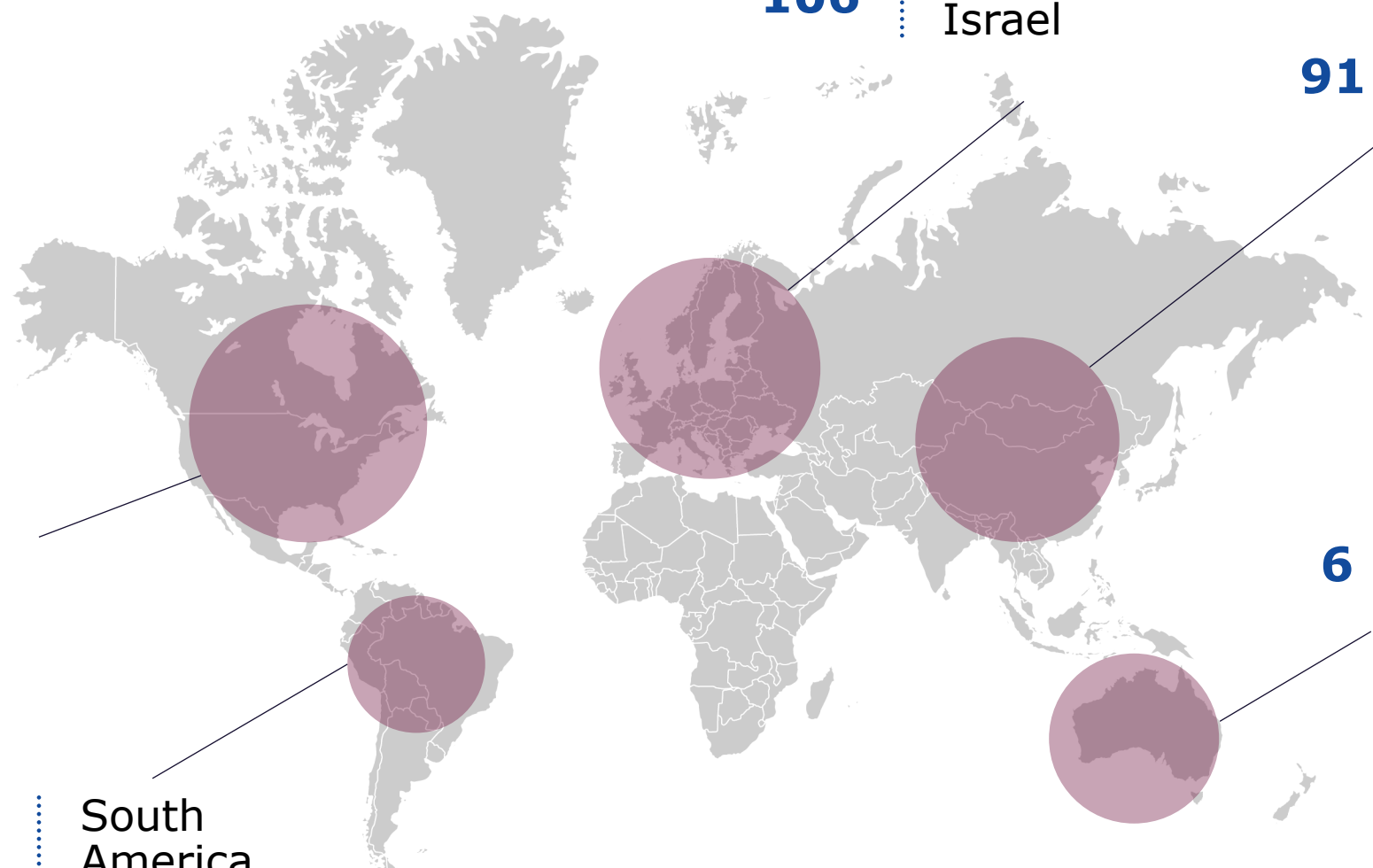
Europe &
Israel

91

Asia

6

Oceania
Australia,
New Zealand,
Marshall Islands



Current Global Sector Landscape

205

Gene Therapy & Gene-Based Medicine
Companies Active in Rare Disease

102

North
America

47

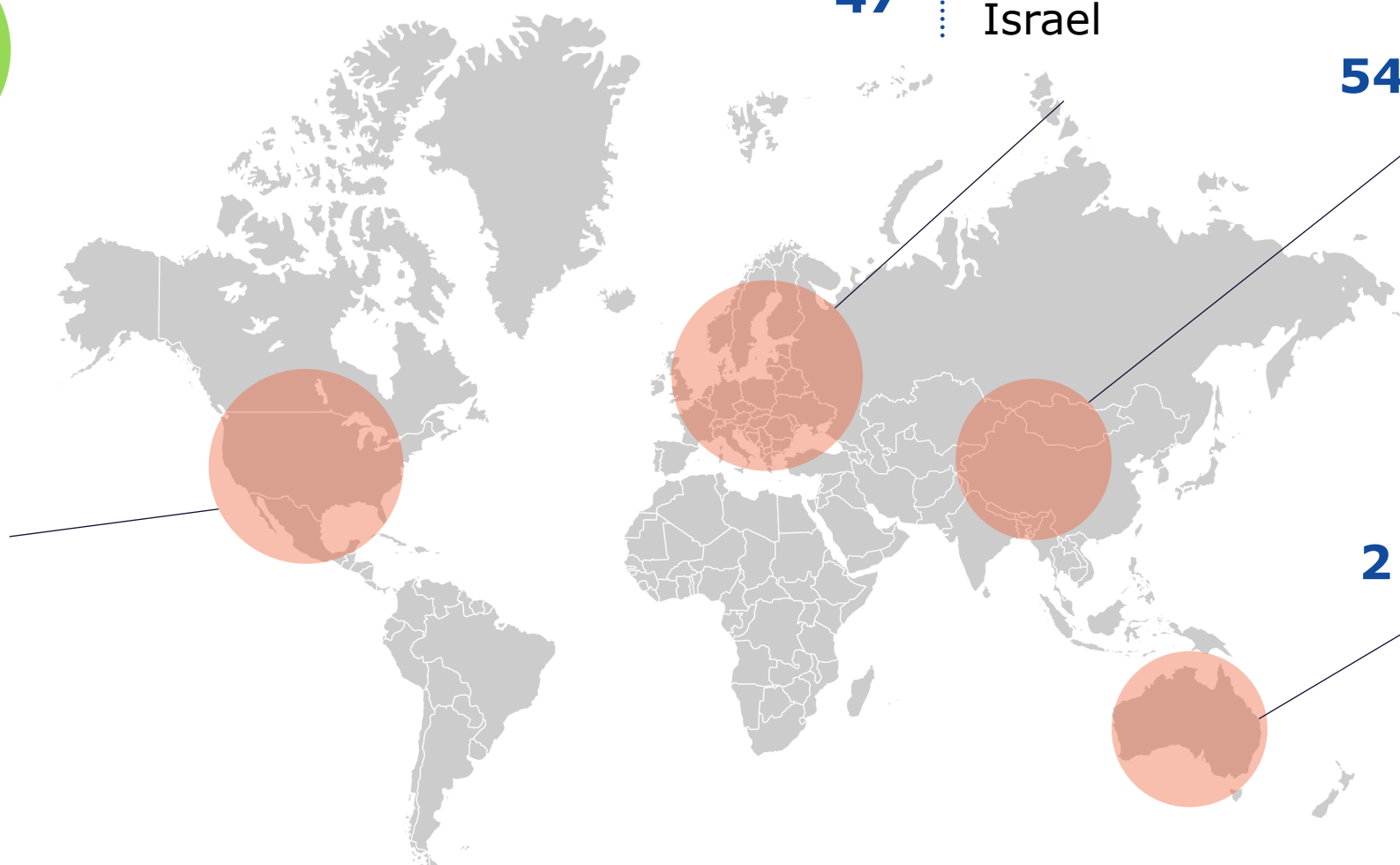
Europe &
Israel

54

Asia

2

Oceania
Australia,
New Zealand,
Marshall Islands



- **Viral vectors:** retroviruses, adenoviruses, herpes simplex, vaccinia, and adeno-associated virus (AAV)
- **Non-viral vectors:** nanoparticles, nanospheres, transposons, electroporation, and others
- **Genetically modified cell therapies:** chimeric antigen receptors (CAR) T cell therapies, T cell receptor (TCR) therapies, natural killer (NK) cell therapies, tumor infiltrating lymphocytes (TILs), marrow derived lymphocytes (MILs), gammadelta T cells, and dendritic vaccines.
- **Genome editing:** meganucleases, homing endonucleases; zinc finger nucleases (ZFNs); transcription activator-like effector-based nucleases (TALEN); nucleases such as Cas9 and Cas12a that derive from the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR/Cas); homologous recombination of adeno-associated virus (AAV)-derived sequences.
- **Next-gen expression constructs:** novel capsids; innovative regulatory elements, including synthetic promoters that enable specificity, strength, and improve capacity; inducible elements to regulate gene expression temporally or in response to external stimuli: molecular kill switches to improve safety; etc.

Clinical Environment



Patient Impact of Recently Approved Products

Therapy Name	Product Developer	Response
Kymriah	Novartis	<ul style="list-style-type: none">• 40% of patients with R/R DLBCL treated experienced a complete response• 60% of patients with R/R B-Cell ALL treated experienced a complete response
Yescarta	Kite Pharma, a Gilead company	<ul style="list-style-type: none">• 58% of patients with R/R B-Cell NHL treated experienced a complete response
LUXTURN A	Spark Therapeutics	<ul style="list-style-type: none">• 55% of patients inherited retinal disease due to mutations in both copies of the RPE65 gene showed an improvement of 2+ light levels darker after treatment
Zynteglo	bluebird bio	<ul style="list-style-type: none">• 75% of patients with TDT without $\beta 0/\beta 0$ genotype treated achieved transfusion independence



There is a steady growth of clinical trials in [the ATMP] domain. We expect to be at 10 to 20 approvals or submissions each year within the next five years.

-- Dr. Guido Rasi, Executive Director, EMA





Gene Therapy for Rare Disease

Zolgensma (AveXis / Novartis)

- Spinal muscular atrophy type 1
- Decision expected: end 2019

Valrox (BioMarin)

- Hemophilia A
- Expects to file: Q4 2019

GS010 (GenSight Biologics)

- Leber hereditary optic neuropathy
- Expects to file: H2 2020

AT132 (Audentes Therapeutics)

- X-linked myotubular myopathy
- Expects to file: H2 2020

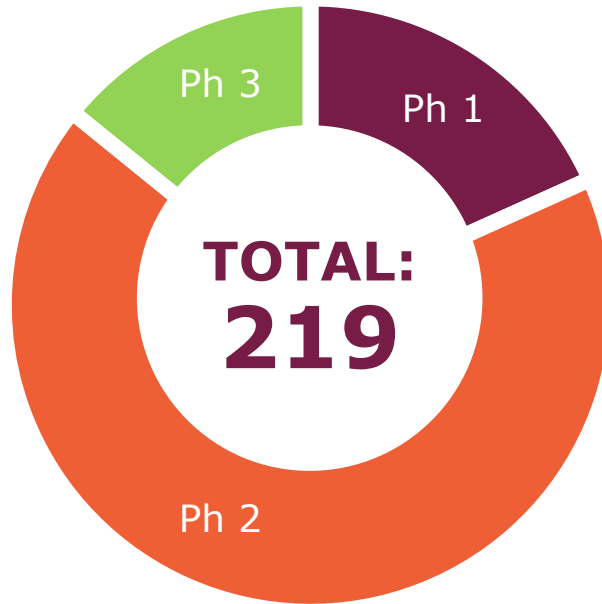
OTL-200 (Orchard Therapeutics)

- Metachromatic leukodystrophy
- Expects to file: 2020



ATMP Clinical Trials in Rare Disease

with European Trial Locations

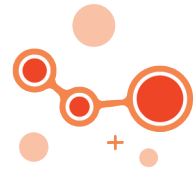


88% of ATMP trials in rare disease utilize gene therapies or gene-modified cell therapies



Phase 1: 40
across all tech types
in rare disease

Gene Therapy: 16
Gene-Modified Cell Therapy: 20
GT & GMCT Total: 36



Phase 2: 148
across all tech types
in rare disease

Gene Therapy: 57
Gene-Modified Cell Therapy: 74
GT & GMCT Total: 131

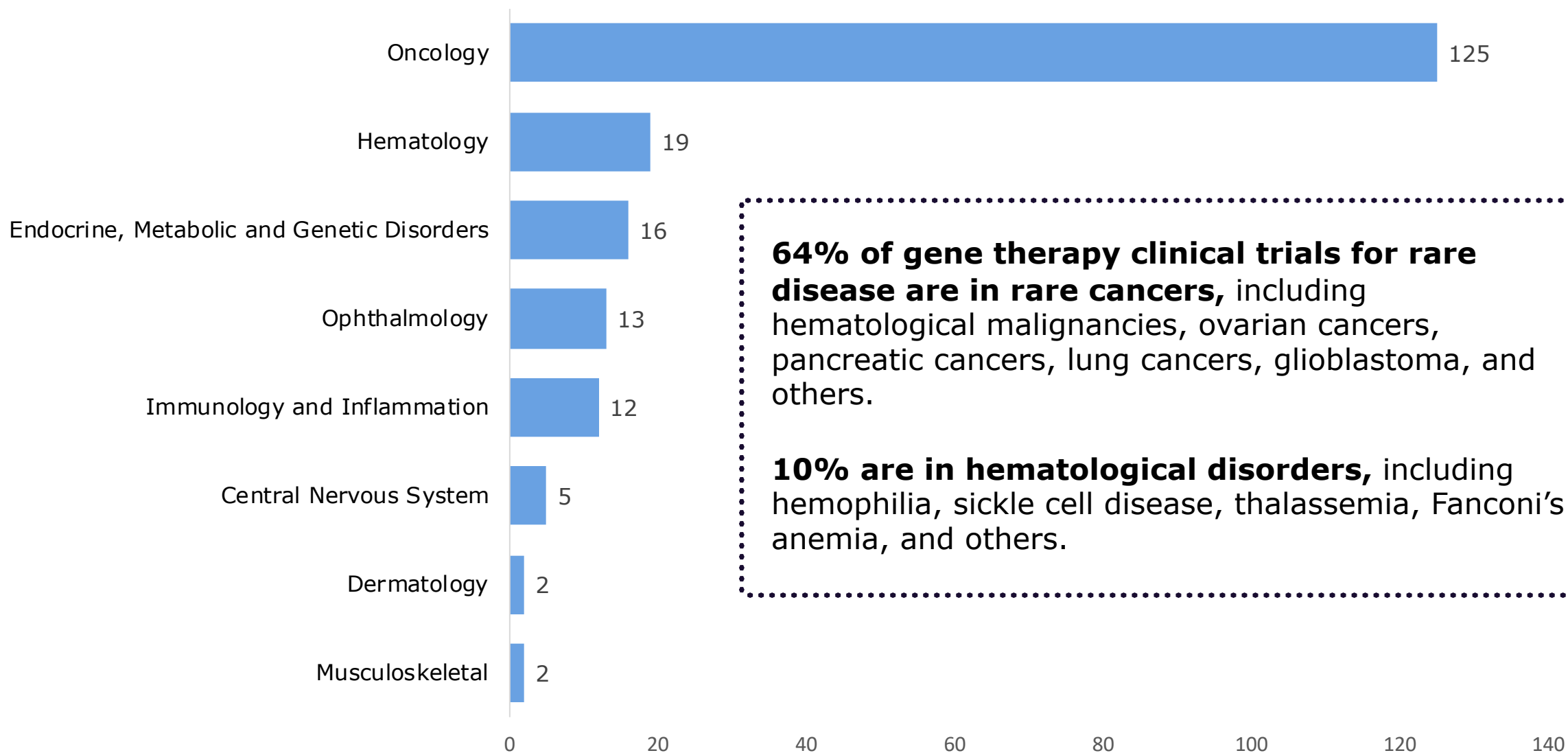


Phase 3: 31
across all tech types
in rare disease

Gene Therapy: 20
Gene-Modified Cell Therapy: 27
GT & GMCT Total: 27

Gene Therapy & Gene Modified Therapy Clinical Trials for Rare Disease

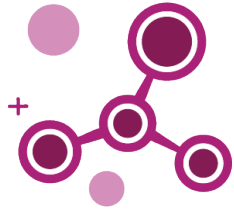
With European Trial Locations



Sector Financings

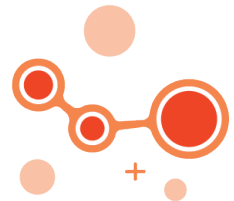
Total Global Financings Year-to-Date

YTD 2019 financings calculated as of 20 Sept 2019



**Total Global
Financings**

€6.8B
YTD 2019



**Gene-Based
Therapies**

€5.2B
YTD 2019



Gene Editing

€778M
YTD 2019

Select financings for companies headquartered in Europe:

- uniQure raises **\$225M (€204M) in follow-on offering** – 4 September
- Vertex **signs \$175M (€158M) upfront agreement** with CRISPR Tx for gene edited therapies for Duchenne Muscular Dystrophy and Myotonic Dystrophy Type 1 – 6 June
- Orchard Tx raises **\$128M (€116M) in follow-on offering** – 3 June
- Oxford Biomedica raises **\$68M (€62M) in private placement** – 28 May
- Vivet Therapeutics and Pfizer enter into **\$51M (€46M) upfront agreement** for the development of VTX-801 gene therapy for Wilson's disease – 20 March
- Axovant raises **\$40M (€36M) in public offering** of shares – 13 March

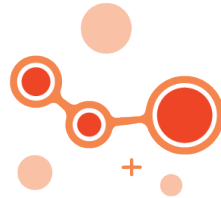
Policy & Advocacy





Regulatory Issues

CMC requirements; draft guidance; hospital exemption; international convergence of requirements



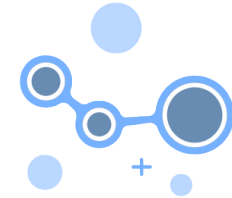
Market Access

Adapting value assessments to one time/durable/curative therapies; enabling payment over time and outcome-based contracts;



Clinical Trials

GMO requirement harmonization; trial design; improvement of timelines and process for approval of multinational trials in Europe



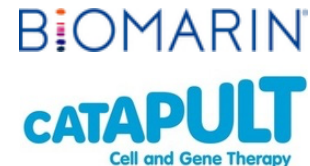
Gene Editing

ARM Published Therapeutic Developers Statement of Principles; WHO expert advisory group's global gene editing clinical trial registry

Overcoming Manufacturing Barriers

- Member workshop on comparability in cell & gene therapy development, with USP & global regulators
- *In Vivo* publication on manufacturing challenges in cell and gene therapy in June, and co-hosted a follow-up webinar in September
- Finalizing a comprehensive framework document – A-Gene – covering development, manufacture, regulatory submission, and lifecycle of gene therapies
 - Expected release in early 2020
 - Content is currently being drafted for A-Cell, a similar project focusing on cell therapies

A-Gene participants include:



EU Market Access Report

	Product	MA Status	Countries with Reimbursement
Gene Therapies	Glybera	×	Germany
	Imlygic	✓	UK (with restriction)
	Strimvelis	✓	Germany, Italy
	Kymriah	✓	France, Germany, UK, Italy
	Yescarta	✓	France, Germany, UK, Italy
Cell Therapies	Luxturna	✓	France, Germany, UK
	Zynteglo	✓	N/A
	Provenge	×	Germany
	Zalmoxis	×	Germany, Italy
	Alofisel	✓	France, Germany
	Chondrocelect	×	UK, Spain

- Europe has been a leader in scientific innovation and regulatory advancement for ATMPs in Europe
- Europe is at the forefront of ATMP commercialization
 - First gene therapy (Glybera) was approved in Europe in 2012; later removed from the market
- The region has seen commercial failures, as well as several recent approvals
- Not all of these products are available across Europe due to country-specific reimbursement challenges

As an increasing number of ATMPs receive approval in Europe, it is vital that the barriers that have delayed or precluded access to early ATMPs are addressed

Recommendation 1: Better adapt Health Technology Assessment (HTA) frameworks to ATMPs.

Recommendation 2: Favor wider application of conditional reimbursement schemes

Recommendation 3: Develop pan-European initiatives to create: Real-World-Evidence (RWE) infrastructure, new early-dialogue opportunities, and timely & effective access to cross-border healthcare for all EU patients.

Recommendation 4: Favor wider application of innovative access and funding arrangements

- We endorse investigation of therapeutic applications of **somatic cell gene editing**, under the oversight of national or regional regulatory bodies
- We support the use of **gene editing standards** to facilitate the development of safe and effective therapies (e.g. the NIST Genome Editing Consortium)
- We support the continued **evolution of national and regional regulatory frameworks** governing the development of somatic cell gene editing technologies
- Unless and until ethical and potential safety questions with respect to germline gene editing are adequately addressed, **we do not support or condone germline gene editing in human clinical trials** or for human implantation
- We believe that these are international concerns and support discussion of therapeutic gene editing issues on a **global stage**

Therapeutic Developers' Statement of Principles

Signatories:

- ✿ Audentes Therapeutics
- ✿ bluebird bio
- ✿ BlueRock Therapeutics
- ✿ Caribou Biosciences
- ✿ Casebia Therapeutics
- ✿ CRISPR Therapeutics
- ✿ Editas Medicine
- ✿ Homology Medicines
- ✿ Intellia Therapeutics
- ✿ LogicBio Therapeutics
- ✿ Pfizer Inc.
- ✿ Precision Biosciences
- ✿ Sangamo Therapeutics
- ✿ Tmunity Therapeutics

Released 27 August 2019

*The Statement of Principles remains open for additional ARM Member signatures
The full Statement is available at www.alliancerm.org*

This presentation will be available on our website and shared via Twitter at @alliancerm

Visit www.alliancerm.org to access additional resources, including:

- ✿ Quarterly sector data reports
- ✿ Upcoming near-term clinical trial milestones & data readouts
- ✿ Access to slides, graphics, and figures from ARM presentations
- ✿ Our weekly sector newsletter, a robust round-up of business, clinical, scientific, and policy news in the sector
- ✿ Commentary from experts in the field

Thank You!