EXECUTIVE INSIGHTS

Looking Ahead in Biopharma: 2024

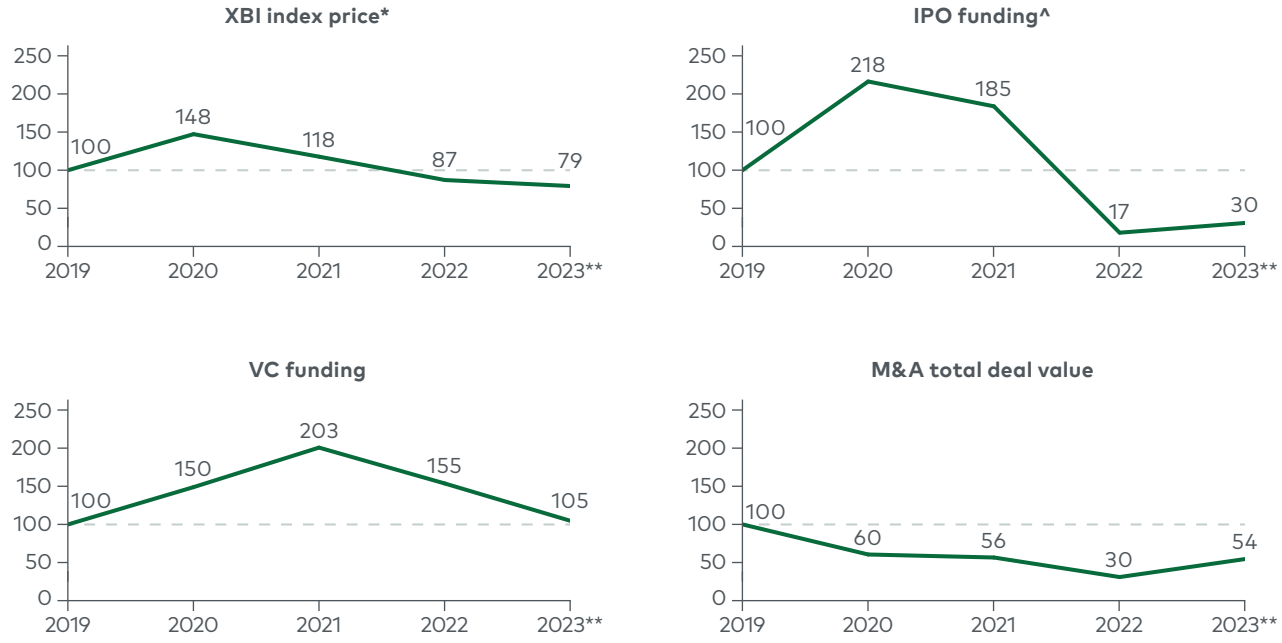
2024 finds the biopharma industry in a transitional period. After one full post-pandemic year, the market contraction has persisted, and companies are also preparing to face near-term revenue cliffs brought on by patent expirations and recently introduced drug pricing caps on the most successful Medicare products. Despite these headwinds, venture capital funding has stayed consistently above pre-pandemic levels. Many innovations are on the horizon, such as advanced therapeutic modalities in the pipeline, generative artificial intelligence (AI) in drug discovery, and omnichannel engagement augmenting traditional field forces. In this *Executive Insights*, L.E.K. Consulting's biopharma practice discusses five developments that we are monitoring as we look ahead to 2024.

1. Biopharma market correction will continue to impact financing and M&A

As 2024 begins, biotech companies continue to grapple with a market contraction. Financing channels appear to have largely stabilized year over year — although most are still significantly down from pandemic highs and even pre-pandemic baseline (see Figure 1). Cost of capital remains high. Larger biopharma firms are searching for compelling dealmaking opportunities, but there are fewer obvious gems than in prior years. Here are the top financing and M&A themes we are watching:

Figure 1

US Biopharma financing and M&A value metrics relative to 2019 (2019-23, percentage)



*Pre-2023 XBI index prices as of year-end
**2023 values are updated as of 12/15/2023 for VC funding (from Pitchbook) and 11/30/2023 for other metrics (from S&P's Capital IQ) and may therefore underestimate final annual funding values
^2023 excludes Kenvue IPO, with total fundraising of ~$3.8 billion
Note: IPO=initial public offering; VC=venture capital; XBI=SPDR S&P Biotech; U.S. IPOs and M&A deals include both announced and closed transactions selected in S&P's Capital IQ from industry classifications including Pharmaceuticals, Biotechnology and Life Sciences OR Biotechnology OR Pharmaceuticals OR Pharmaceutical Products OR Pharmaceutical Research and Development; PitchBook data has not been reviewed by PitchBook analysts
Source: PitchBook (VC funding); S&P's Capital IQ (XBI index price, IPO funding, M&A total deal value)

- **The biotech capital market is starting 2024 in a significant correction period, and it is uncertain how long it will last.** Valuations are down significantly: The S&P Biotech index (XBI) is down over 55% since its 2021 peak, while the broader S&P 500 (SPY) gained over 15%.[1] History suggests that biopharma can take many years to recover from recession. For example, after a local peak in 2001, the Nasdaq Biotechnology Index fell by approximately 60% over the next four quarters and took nearly 10 years to recover. Biopharma companies should prepare for a sustained recession environment,[2] as a near-term recovery is by no means certain.

- **Biotechs with compelling clinical data may still obtain financing, albeit with lower valuations than in 2020-21.** Annual venture capital funding has remained strong, and while 2023 is well below pandemic highs, funding has kept above robust pre-pandemic levels.[3] Despite this, post-pandemic financing rounds have reportedly[4] taken longer to close than in prior years and with greater data expectations.

  Private equity firms are also increasingly testing the waters of biotechnology in partnership with venture firms, as recently demonstrated by KKR's investment in Catalio Capital

Management, and represent another source of private funding.[5] Volume and value of biotech initial public offerings remained well below pre-pandemic levels throughout 2022 and 2023.[6] Investors have higher expectations for clinical data than in prior years, and valuations are still well below pandemic highs.[7] Companies unable to access preferred forms of financing may need to find alternative sources (e.g., private investment in public equity financing, debt financing, royalty monetization), although high interest rates make debt financing less attractive. Ultimately, many biotechs may look to the M&A market for their next value inflection point.

- **While conditions are right for smaller-scale biotech acquisitions, fewer viable acquisition targets exist.** The top 16 biopharmas had over $500 billion in collective M&A firepower as of November 2023 (based on maintaining a certain net debt-to-EBITDA ratio).[8] Many players are keenly interested in dealmaking to offset forthcoming loss of exclusivity and Inflation Reduction Act (IRA) impacts on midterm revenue growth, but there is a limited supply of relevant M&A targets left given the recent wave of acquisitions. Fewer attractive M&A targets exist now than in 2020-21.
- **Biopharma may turn to larger, scale-multiplying M&A to weather the impacts of patent cliffs and the IRA.** Many large pharma companies are facing significant revenue gaps in the coming years. The spread in market cap between the largest and smallest top 15 pharma companies is wider than historical norms, making it increasingly difficult for some to compete at scale. These factors could prompt a wave of consolidation in the industry.

Based on these themes, both small and large biopharma companies may need to explore creative financing and M&A strategies this year to unlock the next stage of value creation.

2. Impacts of new drug pricing legislation will continue to unfold

2024 could prove to be another active year for drug pricing legislation as we monitor the impacts of the IRA's continued rollout, numerous lawsuits from the pharma industry related to the IRA, a presidential election and strong momentum toward pharmacy benefit manager (PBM) reform. Here are the key drug pricing policy and legislation updates to look for in 2024:

- **The publication by Sept. 1st, 2024, of maximum fair prices (MFPs) for the first 10 drugs selected for Medicare drug price negotiations will give the industry more insight into the magnitude of price reductions.** While the IRA mandates specific ceilings for MFPs relative to current pricing, no price "floor" is specified, creating potential for even more severe discounting at the discretion of the Centers for Medicare & Medicaid Services (CMS). Stakeholders across the industry will be closely watching for the initial MFP publication

in Q3 to understand the degree to which CMS will exercise the option to negotiate greater-than-mandated discounts. Further details on the specific rationale and analyses used by CMS to support MFP price-setting are not slated to be published by CMS until March 2025, but some initial insights on key drivers may be available from the biopharmas themselves before the end of 2024.

- **Ongoing litigation and the presidential election could also shape the future of the IRA's drug pricing provisions.** Several drugmakers and PhRMA have filed lawsuits challenging the constitutionality of the IRA's Medicare price negotiation provisions. Given the unprecedented nature of the pricing negotiations, there is a significant likelihood that these cases will face multiple levels of judicial review and appeal, including potential review by the Supreme Court. Final judicial resolution before the end of 2024 is unlikely, and near-term injunctions to stop price negotiations are not anticipated since MFP pricing will not take effect until 2026.

  Drug pricing and the legislative future of IRA-mandated pricing negotiations are likely to be a significant area of debate during 2024's presidential election. Legislative amendment to the IRA is unlikely in 2024 while Democrats retain the presidency and the Senate. Republicans voted unanimously against passage of the IRA in 2022, and if they were to take control of Congress in 2025, they may pursue a repeal of some or all drug price provisions.[9] However, Republican presidential nominee front-runner Donald Trump has taken a strong stance on lowering drug prices and supported Medicare price negotiations in his 2016 candidacy, so it remains to be seen whether such a repeal would be passed even with a Republican president.[10,11]

- **Key PBM legislation in the pipeline pushes for transparency, with bipartisan support.** The next major policy priority aimed at reducing drug prices is PBM reform, with strong legislative momentum in 2023 after years of discussion on the topic. The House and Senate have proposed several bills calling for various degrees of transparency around PBM compensation, and restrictions on spread pricing, pass-through rebates and pharmacy clawbacks. The House has already passed their bill, called the "Lower Costs, More Transparency Act," which may be amended based on the language of the similar bills proposed in the Senate before the Senate votes.

  Broadly speaking, we expect the proposed legislation would exert downward pressure on the gross-to-net bubble if spread pricing were to be banned and/or PBM compensation were to be delinked from size of negotiated rebates. Further compensation transparency should also serve to better align PBM incentives with reducing healthcare costs, although transparency terms vary from routine full public disclosure of all drug prices net of rebates

and other discounts (in the House's bill)[12] to periodic reporting to plan sponsors and the Department of Health and Human Services only (in the Senate's Modernizing and Ensuring PBM Accountability Act).[13]

- **Beyond the U.S., biopharma leaders will need to begin planning for changes on the horizon in the EU as well.**[14] The EUnetHTA 21 regulation will make EU-wide joint clinical health technology assessments mandatory beginning in 2025 for advanced therapeutics and oncology products and by 2030 for all other drug products. This shift in clinical assessments from national to EU-wide level will present a short-term burden for pharma, requiring additional market access resources. However, the regulation could prove to be a long-term opportunity, as centralization of clinical assessments could mean earlier initiation of pricing and reimbursement negotiation with EU countries.

3. Early impact of AI transformation and operational improvements may be realized

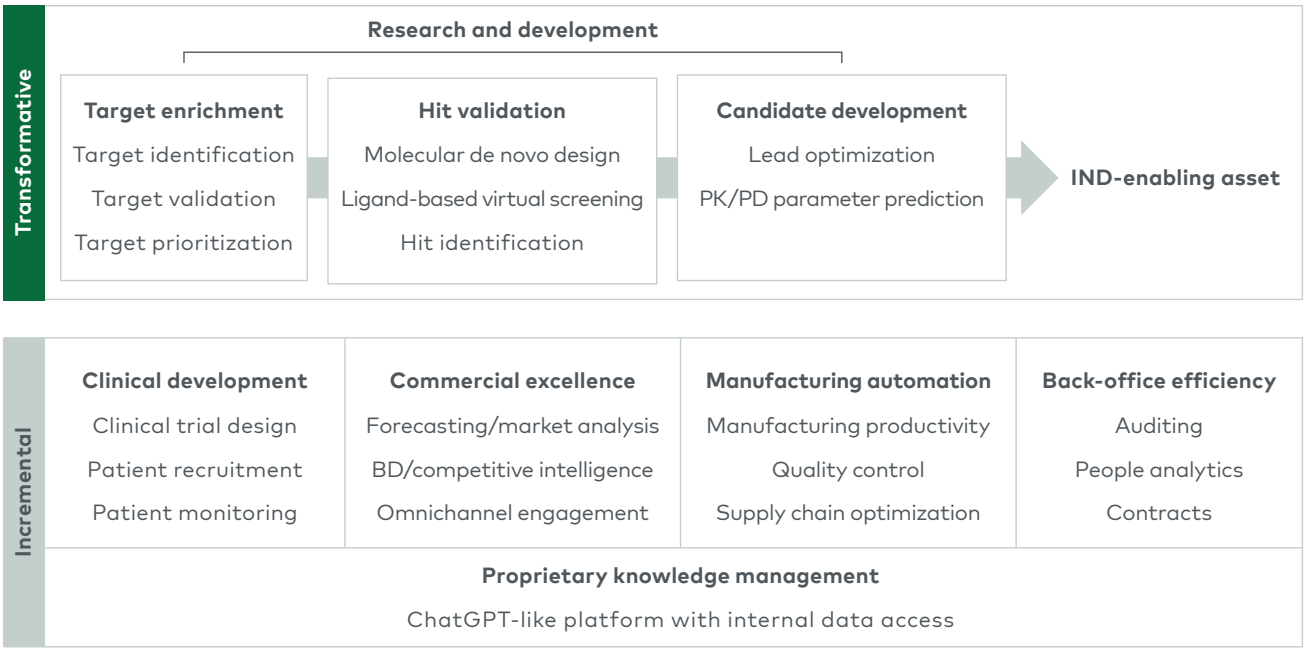
2024 should bring both transformational developments and incremental/operational improvements as a result of AI (see Figure 2). Both machine learning (ML)/big data and generative AI, the latest AI computing approach involving the generation of novel content based on training data and context prompting, will be key drivers of efficiency in drug discovery and beyond:

- **The transformative potential of AI-driven drug discovery will be tested in some of the first clinical efficacy readouts.** Generative AI and ML will aid in expanding the repertoire of potential drug candidates and accelerate the elimination of less promising ones, hastening progression to clinical trials. In this area specifically, generative AI complements current high-throughput drug discovery's cycle of deductive and inductive reasoning well and is a natural fit for early adoption. Advances here are particularly important for emerging biotech firms, whose value can hinge on just one or a few early research and development breakthroughs. 2024 will see several clinical readouts from assets whose discovery was heavily influenced by AI, such as InSilico Medicine's phase 2 data for INS018_055 in idiopathic pulmonary fibrosis[15] and Relay Therapeutics' phase 2 clinical and regulatory update for tumor-agnostic lirafugratinib (RLY-4008).[16]

- **Beyond drug discovery, biopharmas will be looking for ways to drive incremental improvements through AI**, with examples such as improving clinical trial design and participant recruitment, streamlining manufacturing and supply chain processes, simplifying competitive intelligence, and enhancing the development and coordination of sales and marketing materials. Bristol Myers Squibb (BMS) has already applied GPT-4 to clinical trial protocol design, while Takeda has explored applications of AI/ML in patient monitoring.[17] Additional operational

enhancements and pilot programs in biopharma will likely be announced this year. While evidence of generative AI's operational impacts in biopharma will be more challenging to discern, efficiency impacts will drive incremental improvements throughout the organization.

Figure 2
Potential use cases for generative AI computing in biopharma (nonexhaustive)



Note: AI=artificial intelligence; PK/PD=pharmacokinetics/pharmacodynamics; IND=investigational new drug; BD=business development
Source: Company websites; press releases

- **Beyond R&D, early AI implementation is likely to shine a light on digital strategy and data management processes and systems.** Generative AI is only as useful as its training data, as shown by early large language models only being able to provide information up to certain date cutoffs. The most powerful corporate AI systems will have comprehensive access to both internet data in the public domain and internal/proprietary data. Moderna is one company at the forefront, having implemented an internal large language model with access to company databases mere weeks after the publicization of ChatGPT.[18] 2024 is expected to bring many more such announcements of internal tools and programs to pilot the utility of AI. Biopharma companies' readiness to effectively implement AI will depend on the richness and accessibility of their proprietary data.

4. New technologies will evolve customer engagement with a 'digital too' approach

Commercial leaders have made significant investments in digital tools and data in recent years, and the focus in 2024 is on upskilling teams and getting the most out of these investments. While virtual approaches are here to stay, sales representatives have returned to face-to-face

interactions, which represented 78% of global channel mix from January through September 2023.[19] In-person engagement will continue to be critical for key interactions like initial launch support, new data readouts and life cycle updates. These dynamics suggest the next evolution of the biopharma customer engagement model is better characterized as a "digital too" rather than "digital first" strategy. Continued digital evolution of the biopharma engagement model is most evident in three areas:

- **The modern field representative must be digitally savvy, coordinating engagement across physical and virtual channels based on customer preferences.** The role of the field representative is evolving, with responsibilities that increasingly require digital expertise, the ability to discern optimal engagement channels, and tailored in-person interactions based on data and analytics. Representatives must adapt their approach in the field based on in-person cues, assessment of available data, and decision-making tools such as Salesforce and Veeva.

  Forward-thinking companies are already developing digital profiles of doctors and other key customers, and others soon need to follow in order to deliver sufficient value to customers and avoid overspending on a mass-marketing model that is not adjusted for customer preferences. This upskilling requirement is not isolated to large biopharmas in leading franchises. A leading orphan disease biotech company is building digital channel proficiency into sales representative phenotype development and recruiting. Future training modules will include both next-best action and the role of the rep in self-generated data to shape the customer experience.

- **Personalized marketing and other new technologies enable shorter cycle times for brand and content planning.** This speed is enabled by upskilling internal teams' data and analytics capabilities and focusing on single customer views (SCVs), where messages are customized according to individual physician signals for priority topics, necessary context and preferred channels. Technologies like next-best action marketing (using SCV data and predictive analytics to determine next-best action to drive customer engagement and ultimately sales), zero-party data and analytics (analytics of information shared directly and voluntarily by the customer), and generative AI are enabling commercial organizations to better listen to the customer and deliver targeted communications.

  Novartis is one pharmaceutical leader that has embraced SCVs to power its marketing decision engine, developing nuanced profiles of target audiences and delivering channel-specific marketing based on modular assets.[20] Commercial leaders will need to thoughtfully integrate these various new tools and marketing strategies with decentralized customer bases and field forces.

- **More targeted sales and marketing deployment could drive spending efficiency** as it allows companies to depart from the mass-marketing approaches of the past and move toward an era of precision marketing. As SCVs are aggregated into customer archetypes, prescribers and consumers can be targeted through messages and channels that better meet their needs. Such approaches may present a lower-cost alternative to, for example, traditional TV-based advertising with vast audiences and a small proportion of intended recipients.

To harness these opportunities, companies should assess their organizational readiness to evolve the digitalization of commercial activities. Key capabilities needed include:

- Improved ability of business insights and analytics functions to access, clean, integrate and draw conclusions from large datasets
- Optimized medical-legal-regulatory review processes, which need to be faster and manage more content
- Deployment of tools to support in-the-field decision-making

Companies that have made significant investments in customer experience, content personalization and a next-best action model are moving into "version 2.0" of internal capability development along the people/process axis. Leading biopharmas are moving away from a strict center of excellence model and are beginning to internalize cross-functional development and delivery teams to take advantage of existing digital platform capabilities. Learning by conducting agile team test-and-learn pilots has proven the most effective way to transform organizations without disrupting valuable in-line brand operations. By embracing a "digital too" mentality, biopharmas and their customer-facing teams can more effectively listen to and engage with customers on the topics they are interested in, through the channels they prefer, at the right time.

5. The advanced therapeutic modality pipeline will face important clinical and commercial milestones

As the advanced modality pipeline expands and the number of marketed therapies increases, many important clinical and commercial developments are expected to emerge.

- **Advances are on the horizon for cell therapy in oncology and beyond.** In solid tumors, key TCR-T (T cell receptor-engineered)[21] and NK (natural killer) cell[22] therapies will have phase 2 readouts this year. CD22 proteins are being trialed in patients with large B cell lymphoma (LBCL) who are refractory to CD19-directed CAR-T therapy.[23]

  On the allogeneic front, phase 3 topline data is expected from Allovir's posoleucel[24] to restore T-cell immunity after allogeneic hematopoietic stem cell transplantation, and both

Imugene and Allogene are expected to have CAR-T assets entering registrational trials in LBCL.[25,26] Within immunology, more data will likely emerge from companies like Cabaletta Bio (phase 1/2 topline data expected in 1H), Novartis (phase 2 data update in 2H), BMS and others on the performance of CAR-Ts in autoimmune conditions, with 30+ companies pursuing development in the space.[27] However, preliminary reports of secondary T-cell malignancies after CD19 or B-cell maturation antigen (BCMA) CAR-T infusion may hinder the risk/benefit profile for the therapies, particularly in immunology, depending on their frequency.[28] The potential for secondary malignancy after autologous CAR-T treatment highlights the need for new technologies that perform fewer random insertions.

- **Bottlenecks in cell therapy manufacturing and supply remain a critical issue before expanding to new therapeutic areas like immunology.** Existing patients must wait up to three weeks after apheresis for autologous CAR-T manufacturing to begin at centralized centers, followed by another two to four weeks for product release.[29] Potential autologous manufacturing improvements on the horizon include fully closed and automated systems like Lonza's Cocoon, integrated manufacturing/cleanroom solutions like Cellares' Cell Shuttle, and in vivo CAR-T manufacturing, being explored by Umoja Biopharma, Orna Therapeutics and others.

- **Despite impressive scientific innovations, gene therapy developers will need to show they can translate science into commercial success.** The modality has so far struggled to keep pace with market expectations, with nine viral vector-based gene therapies on the U.S. market and only one (Zolgensma) exceeding annual worldwide sales of $500 million.[30]

  Clinical data to date has not sufficiently validated expectations of gene therapies producing durable and drug-free disease remission, with about one-third of spinal muscular atrophy patients continuing to receive other treatments after Zolgensma.[31] Despite early challenges with commercial uptake, the gene therapy pipeline is expected to expand, with milestones anticipated in transfusion-dependent beta thalassemia (Vertex/CRISPR Therapeutics' Exa-cel Prescription Drug User Fee Act (PDUFA) date on March 30),[32] hemophilia A (Pfizer/Sangamo Therapeutics' giroctocogene fitelparvovec phase 3 readout in mid-2024)[33] and B (Pfizer/Spark's fidanacogene elaparvovec PDUFA in Q2),[34] and more. It will also be important for recently launched gene therapies (e.g., lovo-cel, Roctavian, Hemgenix, Vyjuvek, Elevidys) to justify high price points with strong real-world clinical data and commercial uptake.

- **Other highly anticipated advancements include milestones in gene editing, mRNA in oncology and antibody-drug conjugates (ADCs).** Within in vivo gene editing, Intellia is expected to launch phase 2 for NTLA-2002 in hereditary angioedema in Q3,[35] on the heels of its recent phase 3 initiation of NTLA-2001 for the treatment of transthyretin amyloidosis.[36] In oncology

mRNA, Moderna and Merck continue to expand on early clinical success of the personalized mRNA cancer vaccine V940 combined with Keytruda for the treatment of high-risk melanoma with an ongoing phase 3 trial.[37] And last, renewed interest in ADCs is likely to continue after the recent $5.5-$22 billion ADC deal signed by Merck and Daiichi Sankyo,[38] alongside last year's impressive trial readouts of AstraZeneca/Daichii's Enhertu in HER2-expressing pan-tumor[39] and Astellas/Seagen's Padcev with Keytruda in advanced bladder cancer in 2023.[40]

This momentum could prompt a wave of ADC/checkpoint inhibitor dealmaking in 2024, although companies should thoroughly vet opportunities for first-in-class/first-in-indication potential. Finally, new developments can be expected with radiopharmaceuticals and bispecific antibodies after significant investment in both areas in 2023, such as Eli Lilly's $1.4 billion acquisition of Point Biopharma and BioNTech's deal with Biotheus worth up to $1 billion.[41,42]

Figure 3
Select 2024 milestones in advanced modalities (nonexhaustive)

Cell therapy

Company	Class	Asset	Indication	Ph.I	Ph.II	Ph.III	Filing	Catalyst
Bristol Myers Squibb	CD19 CAR T, auto.	Breyanzi	CLL or SLL, R/R (3L+)					PDUFA: March 14
Johnson & Johnson	BCMA CAR T, auto.	Carvykti	Multiple Myeloma, R/R, (2L+)					PDUFA: April 5
Allovir	MVS T cell, allo.	Posoleucel	AdV; BKV; CMV; EBV; HHV-6; JCV					Topline data Q3-4
Artiva	NK cell with innate cell engager	AB-101 with AFM13	Classical Hodgkin Lymphoma					Topline data Q3-4
Adaptimmune	TCR-T	ADP-A2M4CD8	Ovarian cancer, Platinum- resistant					Topline data 2024

Gene therapy

Company	Class	Asset	Indication	Ph.I	Ph.II	Ph.III	Filing	Catalyst
Orchard Therapeutics	LVV-transduced CD34+ enriched stem cells	Libmeldy (atidarsagene autotemcel)	Metachromatic leukodystrophy					PDUFA: March 18
Rocket Pharmaceuticals	LVV-transduced stem cells	Marnetegragene autotemcel	LAD-I					PDUFA: March 31
Vertex/CRISPR Therapeutics	CRISPR-CAS9 autologous CD34+	Exa-cel	Transfusion-Dependent Beta Thalassemia					PDUFA: March 30
Pfizer/Spark Therapeutics	Bioengineered AAV vector (AAV-Spark100)	Fidanacogene elaparvovec	Hemophilia B					PDUFA: Q2
Pfizer	AAV6 vector	Giroctocogene fitelparvovec	Hemophilia A					Topline results Q2-3

Others

Company	Class	Asset	Indication	Ph.I	Ph.II	Ph.III	Filing	Catalyst
Geron Corporation	Oligonucleotide (Telomerase inhibitor)	Imetelstat	Lower risk myelodysplastic syndrome					PDUFA: June 16 2024
AstraZeneca / Daiichi Sankyo	ADC (Humanized anti-HER2 IgG1 mAb+ topoisomerase inhibitor + tetrapeptide linker)	Enhertu	Breast cancer, HER2+ (3L+); Others*					PDUFA: Q3-4
Ionis Pharmaceuticals	LICA (PKK inhibitor)	Donidalorsen	HAE					Topline results Q1-2
Arrowhead Pharmaceuticals	RNAi (APOC3 Inhibitor)	ARO-APOC3	Familial chylomicronemia syndrome					Topline results Q1-2

Note: Milestones include U.S. PDUFA and topline trial readouts only; AAV = Adeno-associated virus; ADC = Antibody-drug conjugate; APOC3 = Apolipoprotein C-III; AdV = Adenovirus; BCMA = B-cell maturation antigen; BKV = BK Virus; CAR = Chimeric antigen receptor; CLL = Chronic lymphocytic leukemia; CMV = Cytomegalovirus; CRISPR-Cas9 = Clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9; EBV = Epstein-Barr virus; HAE = Hereditary Angioedema; HER2 = Human epidermal growth factor receptor 2; HHV-6 = Human herpesvirus 6; JCV = JC virus; LAD-I = Leukocyte adhesion de iciency type I; LICA = Ligand-Conjugated Antisense; LVV = Lentiviral vector; NK = Natural killer cell; PKK = Prekallikrein; PDUFA = Prescription drug user fee act; RNAi = Ribonucleic acid interference; R/R = Relapsed or refractory; SLL = Small lymphocytic lymphoma; sBLA = Supplemental Biologics Application; TCR-T = T cell receptor-engineered T cell; *Numerous other milestones in 2024, including Ph. III topline results for the following: HR(+), HER2(-) chemo-naïve breast cancer patients in Q1, HER2(+) 1L breast cancer in Q2+, HER2 mutant, NSCLC 1L in Q2+, HER2(+) breast cancer as neoadjuvant in Q2+, and High-risk HER2(+) breast cancer after neoadjuvant therapy Source: PharmaIntelligence Biomedtracker; American Society of Cell and Gene Therapy. "Gene, Cell, + RNA Therapy Landscape Report: Q3 2023 Quarterly Data Report." https://asgct.org/global/documents/asgct-citeline-q3-2023-report.aspx

Despite financing and legislative headwinds, the biopharmaceutical industry has continued to press on, with many innovations and achievements on the horizon this year. We look forward to helping our clients navigate these ongoing challenges and new frontiers in the coming months.

This edition of *Executive Insights* was authored by The Biopharma Practice at L.E.K., with a special thanks to Jenny Mackey and Jeff Pike.

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Endnotes

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