WHO IS WINNING IN INNOVATION AND HOW ARE THEY BALANCING RISK?

EXAMINING THE INNOVATION-TO-RISK BALANCE AMONG THE PHARMACEUTICAL INDUSTRY'S TOP COMPANIES

In our previous post, we evaluated the pharmaceutical industry's leading companies in terms of overall R&D pipeline strength, resulting in Roche, AstraZeneca, Bristol-Myers Squibb (BMS), Eli Lilly and Boehringer Ingelheim (BI) occupying the top five spots.

The rankings were generated using LENZ, our industry pipeline portfolio analysis tool, which pulls data directly from BEAM, our clinical trial tracking and reporting database, which is updated daily with the most current clinical trial data from across the globe. We then applied our proprietary value index and our machine-learning based probability-of-success (POS) model to arrive at a probability of technical and regulatory success (PTRS) estimate for each company's **entire** clinical-trial portfolio.

This month, we used these same tools to examine how well the top companies are balancing their investments in the proportion of innovative (novel treatments), potentially blockbuster treatments against the overall risk inherent across their portfolio. This two by two visualizes the results:

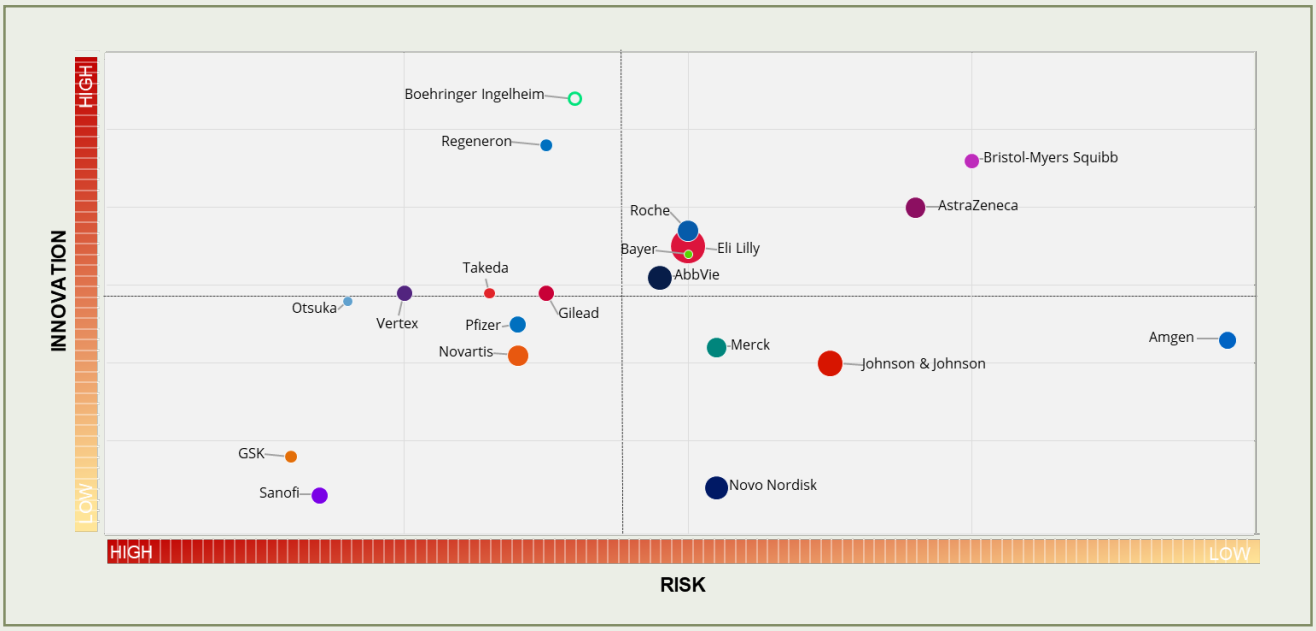

Figure 1: Innovation vs. pipeline risk where innovation is measured by the proportion of novel treatments in each company's pipeline and risk is measured at the portfolio level by total portfolio risk-adjusted value/non risk-adjusted value. Bubble sizes based on company value estimated for private companies and market cap for public companies.

In Figure 1, the upper-right quadrant represents the ideal balance for pharmaceutical companies: high innovation coupled with low risk. BMS, AstraZeneca and Roche occupy this coveted position, due in large part to their strategically diversified pipelines, which effectively offset their riskier pursuits. The companies in the upper left quadrant, including BI and Regeneron, are also pursuing novel treatments, but they lack the safer bets needed to offset riskier investments.

In the lower-right quadrant are companies that currently have a more conservative pipeline, with fewer novel treatments coupled with predictably lower risk. Companies in the lower left quadrant are in the least favorable position—carrying substantial risk without the corresponding potential for high reward.

COMPANY	INNOVATION RANK	RISK RANK	AVERAGE PHASE 3 POS (TOP NOVEL TREATMENTS)
BOEHRINGER INGELHEIM	1	11	45%
REGENERON	2	13	58%
BRISTOL-MYERS SQUIBB	3	2	50%
ASTRAZENECA	4	3	73%
ROCHE	5	7	72%

BMS and BI are investing in more novel targets, while AstraZeneca and Regeneron focus more on expanding existing mechanisms for treatment. This strategic difference is reflected in trial performance: the average Phase 3 POS of the top novel treatments for BMS and BI is somewhat lower than that of AstraZeneca, Regeneron or Roche.

A CLOSER LOOK AT INNOVATION WINNERS

The ability of a company to translate innovation into near-term value rests heavily on its most mature assets, so we took a closer look at the top five innovators' respective Phase 3 programs, which represent the most significant near-term revenue drivers and risk factors. Each trial was given a POS score calculated using our advanced, machine learning-based forecasting model.

Boehringer Ingelheim

BI's nerandomilast idiopathic pulmonary fibrosis (IPF) trial (NCT05321069) was successful, and the drug received FDA approval on October 7. This marks the first new therapy for IPF in over a decade, significantly strengthening BI's presence in rare lung diseases and providing an immediate, high-value win in a novel therapeutic area. Conversely, the termination of the brigimadlin program demonstrates the inherent risk in BI's strategy of pursuing truly novel cancer mechanisms, which contributed to its lower average Phase 3 POS.

BI is also making a play in the burgeoning cardio-metabolic market with survodutide, a GLP-1/glucagon dual agonist. While the GLP-1 class is widely recognized for its efficacy in obesity, BI is strategically pursuing the related and high-value indication of metabolic dysfunction-associated steatohepatitis (MASH). This dual-agonist approach in MASH demonstrates BI's capacity to blend an existing class mechanism (GLP-1) with a novel therapeutic focus (MASH) to drive long-term value, a strategy that was validated when survodutide received FDA Breakthrough Therapy designation in August 2024 for MASH.

ASSET	INDICATION(S)	SUPPORTING TRIALS	POS
NERANDOMILAST PDE4B INHIBITOR (NOVEL)	INTERSTITIAL LUNG DISEASES	NCT05321082	69%
	IDIOPATHIC PULMONARY FIBROSIS	NCT05321069	SUCCESS
SURVODUTIDE GLP-1 AGONIST (NOT NOVEL)	METABOLIC DYSFUNCTION-ASSOCIATED STEATOHEPATITIS (MASH)	NCT06632457	61%
	LIVER CIRRHOSIS	NCT06632444	61%
	OBESITY	NCT06077864	36%

Regeneron

Regeneron is advancing a major oncology portfolio with fianlimab and odronextamab, both of which are novel immune-oncology mechanisms that address difficult-to-treat cancers. Fianlimab is an investigational anti-LAG-3 monoclonal antibody and is currently being evaluated in multiple active Phase 3 trials for melanoma and other cancers.

Odronextamab is approved by the European Medicines Agency for the treatment of patients with relapsed/refractory follicular lymphoma who have received at least 2 prior lines of systemic therapy; however, its safety and efficacy remain under evaluation by the FDA. In the meantime, a large-scale Phase 3 clinical trial program is underway to evaluate whether odronextamab can be successfully used in earlier stages of a patient's treatment, potentially offering a powerful new option sooner in the disease course.

ASSET	INDICATION(S)	SUPPORTING TRIALS	POS
FIANLIMAB LAG3 ANTAGONIST (NOT NOVEL)	MELANOMA	NCT05352672 NCT05608291	36% 79%
	NON-SMALL CELL LUNG CANCER (NSCLC)	NCT05785767 NCT05800015	52% 52%
ODRONEXTAMAB CD20 ANTAGONIST | CD3 INHIBITOR (NOT NOVEL)	FOLLICULAR LYMPHOMA	NCT06097364 NCT06091254	44% 62%
	B-CELL LYMPHOMA	NCT03888105 NCT06091865	12% 80%

BMS

While BMS's risk for innovative trials is similar to BI's, its overall risk profile looks more attractive, likely due to the portfolio balancing effects of its other line extension treatments. BMS is one of the few companies targeting the much needed, yet still unproven, neurodegenerative and neuropsychiatric spaces. Its M1/M4 agonist KarXT, now known as Cobenfy, failed to meet its Phase 3 primary endpoint, showing no significant improvement in symptoms compared to placebo. Despite the setback, BMS is pursuing other indications for the drug.

Besides neuro, BMS is also hoping to continue its success in immuno-oncology/CAR-T with arlocabtagene autoleucel. The admilparant IPF trial has a respectable 48% POS—despite the fact that BI's nerandomilast has already been submitted for approval.

ASSET	INDICATION(S)	SUPPORTING TRIALS	POS
KARXT M1 AGONIST M4 AGONIST (NOVEL)	SCHIZOPHRENIA	NCT05511363 NCT05980949 NCT06126224	42% 43% 42%
	ALZHEIMER'S DISEASE	NCT06585787	35%
ADMILPARANT LPA1 ANTAGONIST (NOVEL)	IDIOPATHIC PULMONARY FIBROSIS	NCT06003426	48%
	PROGRESSIVE PULMONARY FIBROSIS	NCT06025578	62%
ARLOCABTAGENE AUTOLEUCEL CAR-T GPRC5D (NOVEL)	MULTIPLE MYELOMA	NCT04674813 NCT06121843 NCT06297226 NCT06615479	23% 23% 12% 75%

AstraZeneca

AstraZeneca is drawing on its extensive expertise in cancer treatment to create a multi-pronged attack against high-priority tumors. Their strategy is built on advancing established pathways, such as PD-1 inhibition, but through bispecific antibodies like volrustomig and rilvegostomig, which aim to enhance efficacy by blocking two checkpoints simultaneously. The company's pipeline leverages antibody-drug conjugates (ADCs), exemplified by datopotamab deruxtecan (approved in June 2025 in NSCLC), to selectively deliver highly potent cytotoxic payloads. This approach balances the lower risk of leveraging known mechanisms with the innovation of superior delivery systems and combination targets, resulting in a robust portfolio that focuses on a range of difficult-to-treat cancers, including non-small cell lung cancer (NSCLC) and breast cancer, with trials performing above the industry average Phase 3 POS.

ASSET	INDICATION(S)	SUPPORTING TRIALS	POS
VOLRUSTOMIG PD-1 INHIBITOR	MESOTHELIOMA	NCT06097728	76%
	CERVICAL CANCER	NCT06079671	72%
	WITH METASTATIC NON-SMALL CELL LUNG CANCER (MNSCLC)	NCT05984277	68%
RILVEGOSTOMIG PD-1 INHIBITOR	BILIARY TRACT CANCER	NCT06109779	73%
	BILIARY TRACT CANCER	NCT06467357	74%
	NSCLC	NCT06357533	75%
DATOPOTAMAB DERUXTECAN TROP2-TARGETING ADC	BREAST CANCER	NCT05104866	93%
	NSCLC	NCT05687266	80%
	SOLID TUMOR CANCERS	NCT05489211	12%

Roche

Roche's approach to innovation involves pursuing novel mechanisms across a broad therapeutic spectrum, including oncology, immunology, and neuroscience, with a similar overall risk profile among its novel assets versus its line extensions. The company's top three novel assets reflect this diversified strategy and demonstrate Roche's commitment to pioneering new therapeutic classes in areas of high unmet need.

ASSET	INDICATION(S)	SUPPORTING TRIALS	POS
TIRAGOLUMAB TIGIT INHIBITOR (NOVEL)	SQUAMOUS CELL CARCINOMA (CANCER)	NCT04543617	77%
RO-7790121 TL1A INHIBITOR (NOVEL)	ULCERATIVE COLITIS	NCT06589986	74%
RO-7204239 GDF8 BINDER (NOVEL)	MUSCULAR ATROPHY, SPINAL	NCT05115110	66%

The low-innovation, high risk companies

The low innovation/high-risk quadrant generally reflects pipeline profiles in which overall value is driven by assets that are either incremental improvements on existing treatments or high-stakes bets on challenging targets that have recently failed. For GSK, the "high risk" is exemplified by the major Phase 3 failure of its novel oncology asset, cobolimab. Its promising but non-novel assets like depemokimab, which competes on convenience rather than a breakthrough mechanism of action, contribute to its low-innovation classification.

Similarly, Sanofi's positioning is influenced by the significant resources spent on, and subsequent failures of, drugs like venglustat across multiple indications. While Sanofi has assets with truly novel targets like itepekimab, the overall innovation score is diluted by a reliance on assets with non-novel mechanisms, such as riliprubart, and a pipeline that has been criticized for a lack of depth in early-stage, cutting-edge research.

Summary

Novel, game-changing treatments are essential for blockbuster returns, but the high risk inherent in these programs must be balanced to ensure a strong, sustainable pipeline. For companies in the lower half of the innovation spectrum, M&A is the fastest path to portfolio renewal. This requires aggressively acquiring high-quality, scientifically novel assets—programs with the "right" innovation-to-risk profile—to immediately elevate their pipeline position.

For companies already leading in innovation (the upper half), M&A serves a different, but equally vital, function: accelerating growth while managing the risk profile. These acquisitions target assets that further cement their leadership, diversify their high-risk bets, or provide a necessary technology platform to maintain their edge.

Ultimately, pipeline transformation hinges on a strategic rotation: focusing on the acquisition of new, scientifically novel, yet pre-commercial external programs that strategically manage risk while maximizing innovation potential. Next month, we'll delve into specific M&A strategies proven to advance innovation pipelines while effectively managing financial risk.
