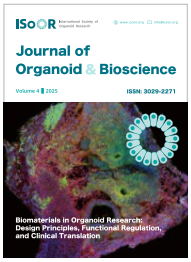
ISoOR International Society of Organoid Research

Journal of Organoid & Bioscience Volume 4 (2025), page 44-47

Journal of Organoid & Bioscience

Official Journal of ISoOR: www.jobs.isoor.org



Industry News & Perspectives

Genmab Acquires Merus for $8 Billion: The First Organoid-Discovered Clinical Asset Drives the Largest European Oncology Deal of 2025

ISoOR Insight Team

*E-mail address: info@isoor.org

COPENHAGEN & UTRECHT – September 29, 2025 – In the largest European oncology acquisition of 2025, Genmab A/S (Nasdaq: GMAB) has agreed to acquire Merus N.V. (Nasdaq: MRUS) for approximately $8 billion in cash, or $97.00 per share. The transaction instantly delivers full ownership of petosemtamab (MCLA-158), a first-in-class EGFR × LGR5 bispecific antibody that represents a historic milestone: it is the first therapeutic candidate discovered, prioritized, and advanced into Phase III clinical trials exclusively through patient-derived organoid (PDO) screening. With two FDA Breakthrough Therapy Designations already secured and Phase III trials actively enrolling globally, petosemtamab has rapidly emerged as one of the most promising investigational therapies in head-and-neck squamous cell carcinoma (HNSCC) and is projected to achieve multibillion-dollar peak sales. Breakthrough Therapy Designation is granted to expedite the development and review of drugs that show substantial improvement over existing therapies for serious conditions.

The $97.00 per-share offer carries a 41% premium to Merus' closing price of $68.89 on September 26, 2025, and a 44% premium over the 30-day volume-weighted average price of $67.42. Genmab will finance the deal through a combination of approximately $5.5 billion in newly issued non-convertible senior unsecured notes and existing cash reserves, eliminating any financing contingency. The tender offer is scheduled to commence in October 2025, with closing anticipated in the first quarter of 2026, subject to customary antitrust clearances and acceptance by at least 80% of outstanding shares (potentially reducible to 75% under Dutch law provisions).

Genmab Chief Executive Officer Jan van de Winkel described the acquisition as "a transformational step that instantly establishes a robust, wholly owned late-stage pipeline and accelerates our evolution into a fully integrated oncology company

capable of delivering multiple innovative medicines this decade." Merus Chief Executive Officer Bill Lundberg emphasized the strategic and cultural alignment, noting that both organizations have pioneered Biclonics® and common-light-chain bispecific antibody technologies for over fifteen years and share an unwavering commitment to precision oncology driven by deep biological insight.

Petosemtamab (MCLA-158): From Organoid Screen to Phase III in Under a Decade

Petosemtamab is a full-length human IgG1 bispecific antibody that simultaneously binds extracellular domains of EGFR and LGR5. LGR5, a Wnt pathway co-receptor and established marker of adult stem cells, is selectively overexpressed on cancer stem cells in colorectal, head-and-neck, esophageal, gastric, and certain lung adenocarcinomas. By co-engaging both targets, petosemtamab triggers potent internalization and lysosomal degradation of EGFR specifically on LGR5-positive malignant cells, thereby blocking two orthogonal survival pathways (independent signaling mechanisms that promote cancer cell survival; dual targeting reduces the risk of compensatory resistance mechanisms) while sparing healthy LGR5-positive stem cells in the intestine and skin – a critical differentiation from conventional EGFR inhibitors that cause dose-limiting rash and diarrhea.

The molecule originated in 2015 from a multi-year collaboration between Merus and the Institute for Research in Biomedicine (IRB Barcelona), led by Eduard Batlle. The team had established one of the world's largest living biobanks comprising more than 150 colorectal and head-and-neck cancer PDO lines that faithfully preserved tumor heterogeneity, stem cell hierarchy, and metastatic potential. Rather than screening candidates in immortalized 2D cell lines or xenografts, Merus applied high- throughput functional testing directly on three-dimensional PDOs, evaluating both tumor-killing potency and selectivity against matched healthy organoids from the same patients. From hundreds of Biclonics® candidates, MCLA-158 was selected as the sole molecule that eradicated LGR5-high tumor spheres while completely sparing normal intestinal crypt organoids – a selectivity profile that preclinical mouse models had failed to predict for prior EGFR-targeted therapies.

Preclinical validation, published in *Nature Cancer* in 2022, demonstrated that petosemtamab completely blocked organoid initiation from residual LGR5+ cells after chemotherapy, prevented liver and lung metastasis in orthotopic PDO-xenograft models, and synergized with PD-1 blockade. These findings translated rapidly into the clinic. Updated Phase 1/2 results presented at ASCForename 2025 showed a 63% confirmed objective response rate and >90% clinical benefit rate when petosemtamab was combined with pembrolizumab in first-line PD-L1-positive recurrent/metastatic HNSCC (n=43). As monotherapy in later lines, durable responses were observed in 37- 40% of cetuximab- and checkpoint-refractory patients, with median duration of response exceeding six months and a manageable safety profile dominated by infusion-related reactions largely confined to the first dose.

The strength and consistency of these data prompted the FDA to grant Breakthrough Therapy Designation twice in 2025 – first for the first-line combination and subsequently for second-line and beyond monotherapy – paving the way for accelerated development and review. Two pivotal Phase III trials are now underway (Table 1).

Table 1. Ongoing Phase III trials of petosemtamab

Trial	Indication	Design	Primary Endpoints	Target Enrollment
PETTONC-1	1L PD-L1+r/m HNSCC	Petosemtamab + pembrolizumab vs. pembrolizumab + platinum/5-FU	ORR, PFS	>400
PETTONC-2	2L/3L HNSCC	Petosemtamab monotherapy vs. investigator's choice	ORR, OS	>300

Top-line readouts are expected in 2026, positioning petosemtamab for potential regulatory submissions in 2027 and first commercial launch in 2027–2028 across multiple indications.

Why Organoids Proved Decisive in De-Risking the Program

Traditional discovery paradigms that rely on engineered cell lines or patient-derived xenografts routinely overestimate efficacy and underestimate toxicity because they fail to recapitulate native stem cell niches and tumor–stroma interactions. The Merus–IRB Barcelona PDO platform circumvented these limitations by preserving the exact cellular hierarchy and mutational landscape of individual patients. Screening in matched tumor-versus-normal organoids provided an unprecedented early readout of therapeutic window, eliminating dozens of otherwise promising EGFR-targeted molecules that proved toxic to healthy tissue. This rigorous human-first selection process is widely credited with petosemtamab's remarkably clean safety profile and high response rates in molecularly unselected, real-world populations – outcomes that have historically eluded the EGFR class, and demonstrates the potential of PDOs to reduce attrition in oncology drug development by several years.

Broader Industry Validation and Perfect Regulatory Timing

The acquisition occurred just four days after the NIH officially launched the Standardized Organoid Modeling (SOM) Center at the Frederick National Laboratory on September 25, 2025, with an initial $87 million commitment to develop reproducible, regulatory-grade organoid standards for major organ systems. The SOM Center directly implements NIH directive NOT-OD-26-004 (July 2025), which mandates prioritization of human-based New Approach Methodologies over animal testing, and dovetails with the FDA Modernization Act 2.0 framework that now explicitly accepts organoids and microphysiological systems as standalone nonclinical evidence packages. Regulatory frameworks are increasingly recognizing human-based models such as organoids as valid nonclinical evidence, with the FDA actively supporting the use of New Approach Methodologies (NAMs) to reduce reliance on animal testing, which may set new precedents for global clinical trial design, particularly in oncology [FDA, 2025; Zushin et al., 2023].

Genmab's decision to pay an $8 billion premium for a pipeline anchored by an organoid-originated asset sends an unequivocal message: large-cap biopharma now views mature organoid platforms as commercially derisked engines capable of delivering blockbuster oncology medicines faster, more predictively, and more ethically than legacy preclinical models.

Financial and Strategic Implications

Wall Street analysts currently project peak annual sales for petosemtamab in excess of $4 – 6 billion across HNSCC, colorectal, and esophageal indications, with significant additional upside from earlier lines and combination regimens. The

transaction also adds three earlier-stage wholly owned programs (MCLA-145, MCLA-129, MCLA-138), instantly expanding Genmab's late-stage portfolio from two partnered assets to seven wholly owned or co-commercialized programs. The deal is expected to be accretive to EBITDA by 2029 and reinforces the resurgence of high-value oncology M&A following a prolonged drought.

Future Outlook

When petosemtamab reaches the market – potentially as early as 2027 – it will mark the first blockbuster oncology therapy whose discovery, candidate selection, and preclinical validation were driven end-to-end by living human organoid models. This precedent is poised to catalyze massive investment into next-generation organoid biobanks, vascularized and immune-competent systems, multi-organ chips, and AIaugmented phenotypic screening. For organoid researchers worldwide, the Genmab–Merus transaction validates PDO biobanks as indispensable tools for the design of tomorrow's precision medicines.

References

[1] Weeber, F., Ooft, S. N., Dijkstra, K. K., & Voest, E. E. Tumor organoids as a pre-clinical cancer model for drug discovery. Cell Chem. Biol. 24, 1092–1100 (2017). https://doi.org/10.1016/j.chembiol.2017.06.012

[2] Genmab A/S. Genmab announces agreement to acquire Merus. Press Release, September 29, 2025. Available at: *https://ir.genmab.com/newsreleases/news-release-details/genmab-acquire-merus-expanding-late-stagepipeline-and*

[3] Merus N.V. Investor presentation: Acquisition by Genmab. September 29, 2025. Available at: *https://ir.merus.nl/events-presentations*

[4] NIH. NOT-OD-26-004: Information for the NIH Extramural Community During the Lapse of Federal Government Funding. October 1, 2025. Available at: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-26-004.html

[5] U.S. Congress. Food and Drug Omnibus Reform Act of 2022 (Sec. 3209:Animal-Testing Alternatives). Division FF, Title III, Subtitle B, Chapter 1,Consolidated Appropriations Act, 2023 (Public Law 117-328). December 29, 2022. Available at: https://www.congress.gov/bill/117th-congress/housebill/2617/text

[6] U.S. Food & Drug Administration. Advancing New Alternative Methods at FDA (FDORA). 2025. FDA.Available at: https://www.fda.gov/media/170186/download

[7] Zushin, P.-J. H., Mukherjee, S., & Wu, J. C. FDA Modernization Act 2.0: transitioning beyond animal models with human cells, organoids, and AI/MLbased approaches. J Clin Invest. 2023;133(21):e175824. https://doi.org/10.1172/JCI175824

[8] U.S. Food & Drug Administration. FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs. Press Release, April 10, 2025. Available at: https://www.fda.gov/newsevents/press-announcements/fda-announces-plan-phase-out-animal-testingrequirement-monoclonal-antibodies-and-other-drugs

Disclosure The author declares no competing financial interests.