ARTICLE | PRODUCT DEVELOPMENT

GDF15 emerges as cachexia's lead target, with Pfizer and CatalYm in Phase II/III

The cytokine sits at the intersection of tumor immune evasion and muscle wasting, offering drug developers a rare chance to address both at once

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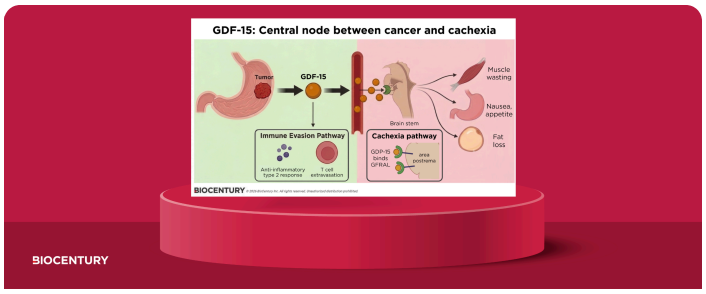


For the first time, cancer-associated cachexia — a wasting syndrome that drives a substantial share of cancer deaths and has no approved treatments — is the target of registrational clinical trials, with most activity centered on a single protein: GDF15.

In the last six months, Pfizer Inc. (NYSE:PFE) and Catalym GmbH have moved the two most advanced GDF15 antibodies, ponsegromab and visugromab, into Phase II/III studies in advanced cancers. They lead a field of at least 10 clinical programs — five targeting the GDF15 signaling axis — with some pushing into earlier-line patients to head off cachexia before it sets in.

The convergence reflects a target uniquely positioned at the intersection of tumor immune evasion and muscle wasting — and a syndrome that, despite its toll, has long been overlooked.

Cachexia is marked by involuntary weight loss and a breakdown of homeostatic control over protein and energy balance, and it disproportionately strikes patients with hard-to-treat cancers — pancreatic, esophageal, gastric, lung, colorectal and hepatic — where it shortens survival and forces dose reductions and treatment interruptions.

Unlike typical weight loss, it cannot be reversed by eating more, and it feeds a cycle in which tumor signaling worsens wasting, and wasting worsens tumor progression.

"Depending on the particular type of cancer, up to 70% of patients can be cachectic. There are a lot of patients with not just hugely diminished quality of life, but it also reduces treatment tolerance," CatalYm CEO Scott Clarke told BioCentury.

Progress has been slow in part because cachexia often occurs in advanced cancer, where subjecting patients to additional testing or follow-up may not be feasible.

GDF15 is the primary bet — though not the only one — that has changed that.

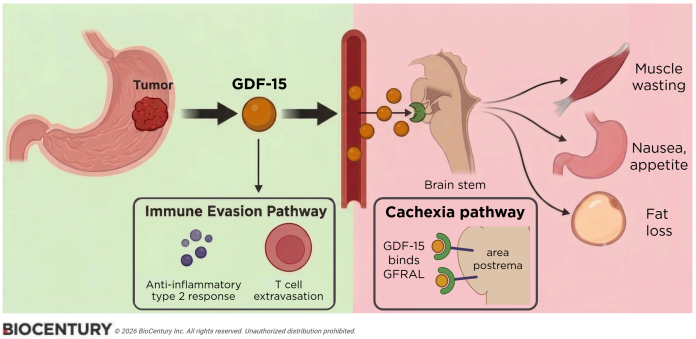
GDF15: cancer-cachexia double hitter

Despite its discovery almost 30 years ago, GDF15's role as a central node between appetite regulation in cachexia and immune evasion in cancer has only recently been understood.

GDF15 was first identified as critical for fetal-maternal immune tolerance — a dampening of the maternal immune response to a genetically foreign fetus. Tumors can co-opt that mechanism in their bid to evade the immune system.

GDF15-high tumors show reduced effector T cell adhesion and transmigration into the tumor microenvironment in preclinical models, suggesting the cytokine acts as a barrier to immune infiltration. The mechanism remains incompletely worked out — no cognate receptor has been identified on T cells or the endothelium that would offer a clean, local druggable handle — which is why current programs target the circulating ligand.

GDF-15: Central node between cancer and cachexia



The cachexia arm of the story is mechanistically tidier. Elevated GDF15 binds GFRAL, a receptor expressed almost exclusively on brainstem neurons in the area postrema, triggering appetite suppression, nausea and the metabolic shifts that drive weight loss. That anatomical specificity is what makes GFRAL itself a tractable target for cachexia — and what may limit it to cachexia.

"Both GDF15 and GFRAL are legitimate targets for cachexia, either by antagonizing the receptor or neutralizing GDF15," said Clarke. But he added that "it doesn't seem antagonizing the receptor will have a significant effect in oncology."

GFRAL-targeting NGM120 from NGM Biopharmaceuticals Inc. illustrates that trade-off. The molecule failed to show convincing antitumor activity in a Phase I study in metastatic castration-resistant prostate cancer, and the company has since redirected the asset into a Phase II trial in colorectal cancer patients with cachexia, with change in body weight as the primary endpoint. Data are expected next year.

At least one other company has a GFRAL-targeting candidate in the clinic. JMT203 from Shanghai JMT Bio, a wholly owned subsidiary of CSPC Pharmaceutical Group Ltd. (HKEX:1093), is in Phase I testing.

GDF15's role in both pathways — and the fact that cancer cachexia is the indication where biology, unmet need and patient enrichment via serum GDF15 levels all align — explains why cancer-associated cachexia has become the lead indication for most companies pursuing the target, with non-cancer cachexia programs largely pointed at other pathways.

GDF15 in the clinic

Pfizer and CatalYm are the clear front-runners in the GDF15 race. In the past six months, both companies moved their GDF15-targeting antibodies into Phase II/III trials in advanced cancers with cachexia endpoints, and earlier-stage data from each program has shown improvements in cachectic symptoms. CatalYm's visugromab is also being tested in combination with anti-PD-1 therapy for effects on tumor progression.

Pfizer's Phase II PROACC-1 trial enrolled 187 patients with non-small cell lung, pancreatic, or colorectal cancer and elevated serum GDF15. Those treated with ponsegromab had significantly greater weight gain versus placebo at 12 weeks, with a 2.81 kg median difference in the highest-dose group.

In CatalYm's Phase I/II GDFATHER study, patients with cachexia gained a mean of 2.3% body weight on visugromab plus anti-PD-1 therapy by cycle 5, compared with a mean 6.5% weight loss in the six months before enrollment. Patients without baseline cachexia showed no significant weight change, suggesting the therapy reverses pathological wasting rather than causing indiscriminate weight gain.

The significance of weight gain alone remains hard to interpret. Phase III trials of both therapies will also measure functional endpoints to show whether patients are gaining strength alongside weight and appetite.

Based on evidence that high GDF15 levels can make tumors unresponsive to checkpoint inhibition, CatalYm also assessed whether visugromab plus anti-PD-1 therapy could induce responses in late-line patients whose cancers had relapsed or were refractory to prior anti-PD-1 treatment.

The combination led to an ORR of 19%, with two partial and two complete responses (PR/CR) in non-squamous non-small lung cancer; an 18.5% ORR in urothelial cancer, with 4 PR and 1 CR; and a 20% ORR in hepatocellular cancer, with 3 PR and 1 CR per RECIST 1.1.

CatalYm is moving the combo into earlier lines of therapy in a bid to prevent resistance.

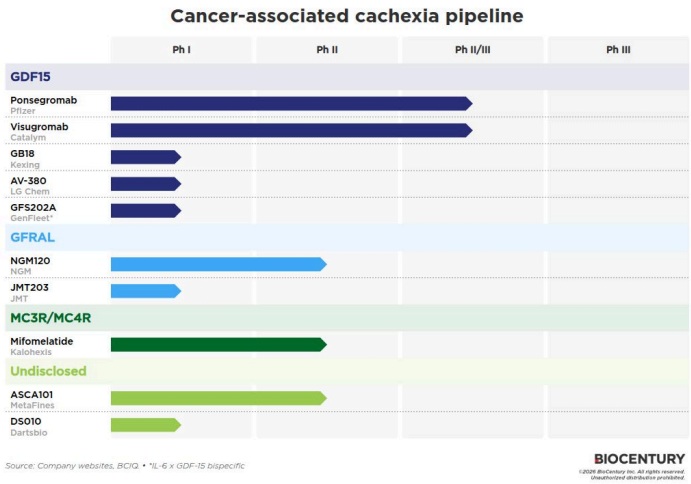
Ponsegromab and visugromab differ in antibody design in a way that is consistent with their different clinical strategies: ponsegromab uses the more common IgG1 scaffold, while visugromab is built on an IgG4 backbone, the same subclass used for leading anti-PD-1 mAbs. IgG4 has reduced Fc receptor binding and complement activation relative to IgG1, features that could be advantageous in checkpoint blockade combinations.

The two also differ in dosing: visugromab every two weeks, ponsegromab every four.

Pfizer started its Phase IIb/III trial in metastatic pancreatic cancer patients with cachexia in October, testing ponsegromab against placebo on top of first-line chemotherapy and measuring cachexia-related outcomes including body weight, physical activity, skeletal muscle and adipose tissue area.

CatalYm started its Phase II/III VINCIT cachexia trial in April, while also advancing separate Phase IIb trials of visugromab combinations in NSCLC, HCC and other solid tumors.

At least three other companies have GDF15-targeting programs in Phase I testing.



The most advanced of these is IgG1 mAb AV-380 from LG Chem Ltd. (KRX:051910), which has completed a Phase I study in healthy volunteers and is in a Phase Ib dose-escalation study in cancer patients with cachexia.

The other two are differentiated by modality: GFS202A from GenFleet Therapeutics (Shanghai) Inc. (HKEX:2595) is a bispecific antibody targeting GDF15 and IL-6; and GB18 from Kexing Biopharm Co. Ltd. (Shanghai:688136) is an Fc-fused GDF15 nanobody.

IL-6 may have its own role in cachexia — elevated IL-6 levels correlate with weight loss and muscle atrophy in cancer patients, and the cytokine drives systemic inflammation and peripheral muscle breakdown. That mechanism is distinct from GDF15's metabolic pathway, which is the rationale for hitting both targets at once.

According to GenFleet, preclinical studies of GFS202A show dose-dependent increases in body weight, lean body mass, and adipose tissue with inflammatory suppression similar to ponsegromab.

GenFleet is running a Phase I trial of GFS202A in cancer cachexia in China. The company has expressed interest in expanding to other chronic diseases involving cachexia, such as heart failure, chronic obstructive pulmonary disease, and chronic nephritis.

Kexing's GDF15-targeting GB18 uses a camelid-derived single-domain antibody scaffold that is much smaller than a typical IgG and is designed for better tissue penetration and simpler manufacturing.

In preclinical studies, GB18 produced comparable weight recovery to Pfizer's ponsegromab and greater improvements in ambulatory activity, according to a paper in *mAbs*.

Targets beyond GDF15 signaling

The pipeline beyond GDF15 and GFRAL is thinner, but a handful of programs are pursuing alternative mechanisms.

Kalohexis LLC is pursuing MC3R/MC4R, hypothalamic receptors in the melanocortin pathway that regulate appetite, energy expenditure, and nutrient storage. The company's mifomelatide is a synthetic cyclic peptide dual agonist designed to penetrate the blood-brain barrier and counteract the overactive weight-regulation signaling driven by tumor inflammation. The melanocortin pathway also overlaps downstream with GDF15 signaling in the brainstem, raising the same question of additive targeting potential that comes up with the IL-6 bispecifics. Mifomelatide entered a Phase II trial last year in newly diagnosed colorectal cancer patients with cachexia.

Kalohexis' program illustrates the potential for cachexia-linked targets to be useful alongside current obesity treatments, an indication the company is also exploring. While cachexia is distinct from traditional weight loss, some of the mechanisms may overlap with potential repurposing of future cachectic drugs to help prevent the breakdown of muscle that coincides with fat loss during a caloric deficit, a common side effect of current GLP-1-induced weight loss.

At least two companies that have therapies in the clinic for cachexia — MetaFines Co. Ltd. and Dartsbio Pharmaceuticals Ltd. — have not disclosed how their molecules work. MetaFines' Phase II program, ASCA101, is described as a mitochondria-modulating small molecule. Dartsbio's DS010 is in a Phase I/II dose-escalation study in cancer cachexia.

Beyond the dedicated pipeline, olanzapine — a generic atypical antipsychotic long used off label for cancer cachexia — continues to be tested in academic trials. A recently published Phase III trial at Cairo University showed olanzapine produced more weight gain than placebo in patients with advanced cancers, though it was also associated with declines in handgrip strength. A Mahidol University-sponsored Phase III trial is underway in cancer cachexia.