J Cancer Immunol. 2026;8(1):42–46.

Journal of Cancer Immunology Commentary

A Promising Synergy: R-Ketorolac and GDF-15 Inhibitors to Overcome the Limitations of Monotherapy in Cancer Cachexia

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Received date: March 24, 2026, **Accepted date:** May 12, 2026

Citation: Zhang L. A Promising Synergy: R-Ketorolac and GDF-15 Inhibitors to Overcome the Limitations of Monotherapy in Cancer Cachexia. J Cancer Immunol. 2026;8(1):42–46.

Commentary

Cancer cachexia remains one of the most devastating and under-treated complications of advanced malignancy. This multifactorial syndrome—characterized by severe weight loss, muscle wasting, adipose tissue depletion, anorexia, and systemic inflammation—afflicts up to 80% of patients with certain cancers (such as pancreatic) and directly contributes to reduced quality of life, poorer treatment tolerance, and increased mortality [1]. Cancer cachexia not only contributes directly to mortality—accounting for up to 30% of cancer deaths—but also profoundly impairs treatment tolerance, often leading to chemotherapy dose reductions, delays, or discontinuation, thereby indirectly worsening oncological outcomes.

It is a complex syndrome involving changes in the body's immune and inflammatory states, systemic neuroendocrine stress, a tumor-initiated response, and downstream systemic metabolic imbalances affecting multiple organs [2]. Despite its clinical importance and the development of agents directed at neuroendocrine and metabolic pathways, there are currently no therapies yet approved by the U.S. Food and Drug Administration for the treatment of cancer cachexia (although anamorelin [Adlumiz] is approved in Japan for cancer cachexia in selected tumor types), leaving clinicians with limited options beyond nutritional support and symptomatic management.

GDF-15 as a Central but Incomplete Target

Recent advances have highlighted growth differentiation factor 15 (GDF-15) as a central mediator of cancer-associated cachexia. This stress-induced cytokine, often elevated in cancer, acts primarily through its receptor GFRAL in the brainstem to suppress appetite, induce nausea, promote lipolysis and muscle atrophy, and disrupt energy homeostasis [3]. Clinical proof-of-concept for therapeutic inhibition of the GDF-15/GFRAL axis has been provided by the monoclonal antibody ponsegromab (Pfizer), which binds and neutralizes circulating GDF-15.

Promising clinical data with GDF-15 inhibitors—such as ponsegromab—have demonstrated meaningful benefits: weight gain, improved appetite, increased physical activity, and reduced cachexia symptoms in patients with elevated GDF-15 levels. In a Phase 2 randomized, double-blind trial, ponsegromab (at doses up to 400 mg every 4 weeks) led to body weight increases of up to 5.61% over 12 weeks compared to placebo, alongside improvements in appetite, physical function, skeletal muscle index, and other cachexia symptoms, with a favorable safety profile [4]. Although this represents a meaningful clinical signal, the modest absolute weight gain observed in severely cachectic patients underscores the limitations of targeting the neuroendocrine axis alone, and highlights the need to also address the inflammatory and immune components of cachexia as well. Beyond its central neuroendocrine effects, GDF-15 has also been shown to suppress T-cell trafficking to the tumor microenvironment through LFA-1–dependent, integrin-mediated mechanisms. Ponsegromab has since advanced to a Phase 3 evaluation (GOFURTHER; NCT06134973), and additional anti-GDF-15 agents are in clinical development, underscoring the growing translational momentum of this therapeutic approach.

However, cancer cachexia arises from a complex interplay of tumor- and host-derived factors that extend beyond GDF-15–mediated neuroendocrine signaling. Chronic systemic inflammation—driven by cytokines such as interleukin-6 (IL-6), IL-8, TNF-α, and others—fuels cytokine dysregulation, immune cell disturbances such as T-lymphopenia, metabolic

shifts toward catabolism, and direct wasting of skeletal muscle and adipose tissue. These inflammatory mediators can operate upstream of, or in parallel with, GDF-15, and likely contribute substantially to the persistence and severity of cachexia even when neuroendocrine pathways are blocked [5].

Monotherapy approaches that focus solely on neuroendocrine or downstream metabolic targets—such as GDF-15 inhibition or the ghrelin receptor agonist anamorelin (Adlumiz), which is approved in Japan for cancer cachexia in selected tumor settings—may therefore leave a significant component of the upstream, cytokine-driven etiology unaddressed, limiting the overall efficacy of parallel or downstream monotherapies, particularly in patients with advanced disease. This recognition has led to growing interest in rational combination strategies [6].

R-Ketorolac: An Enantiomer-Specific Rac1/Cdc42 Inhibitor with Significant Immunomodulatory Activity

R-ketorolac (RK), the R-enantiomer of the racemic nonsteroidal anti-inflammatory drug ketorolac. The R-enantiomer has been identified as a direct modulator of the small Rho-family GTPases Cdc42 and Rac1, an activity that is distinct and separable from the cyclooxygenase (COX) inhibitory effects of the S-enantiomer.

In preclinical studies using cachexia-inducing tumor models (such as C26 colon carcinoma and CHX207), R-ketorolac dramatically ameliorated cachexia symptoms: it prevented severe body weight loss, preserved skeletal muscle (e.g., quadriceps) and adipose tissue, reversed cancer-induced T-lymphopenia, and markedly reduced circulating IL-6 levels. These effects translated to profound survival benefits—R-ketorolac alone improved survival in C26-bearing mice from 10% in untreated controls to 100% at day 10, an effect that was maintained even in the presence of the added toxicity of cyclophosphamide chemotherapy observed [7]. The benefits were T-cell dependent, as R-ketorolac showed limited efficacy in T-cell-deficient nude mice, underscoring its role in restoring immune balance rather than merely suppressing inflammation. It should be noted that nude mice, while useful for assessing T-cell dependence, harbor additional immune alterations beyond T-cell deficiency (including impaired NK cell regulation), and the C26 colon carcinoma model is highly inflammatory and may not fully recapitulate the heterogeneity of human cancer cachexia. Validation in human trials will be essential. Several additional caveats govern the translation of these preclinical findings to human disease. The C26 and CHX207 models are syngeneic murine systems that do not fully capture the genetic, immunological, and metabolic heterogeneity of human cancer cachexia across tumor types. The inflammatory milieu of the C26 model is unusually intense relative to many human tumors, potentially overstating the magnitude of benefit in less inflammatory settings. Furthermore, human cachexia is shaped by aging, comorbidities, polypharmacy, and nutritional status in ways not modeled in young inbred mice on standard chow. These limitations reinforce the importance of ongoing and planned clinical programs—including Phase 1/2a evaluation of pure R-ketorolac—as the necessary bridge from preclinical signal to human validation.

Early human data with ketorolac (racemic mixture, including the R-enantiomer) in pancreatic cancer cachexia support these findings. In a feasibility trial (NCT05336266), short-term ketorolac treatment was associated with statistically significant weight stabilization or gain (adjusted for baseline BMI), increased physical activity (e.g., steps per day), and trends toward reduced serum GDF-15 and IL-8 levels, particularly in responders who gained weight or activity [8]. Importantly, this trial employed racemic ketorolac (containing both R- and S-enantiomers), not pure R-ketorolac. The observed trends toward reduced serum GDF-15 and IL-8 levels, while consistent with data from preclinical animal models, are at present preliminary. They suggest support of the immunomodulatory hypothesis, but it awaits clinical confirmation using R-ketorolac to specifically attribute these effects to the R-enantiomer's Rac1/Cdc42 inhibitory activity.

Collectively, these data support a model in which the enantiomer-specific, allosteric inhibition of Rac1/Cdc42 by R-ketorolac attenuates tumor- and host-derived inflammatory signaling, leading to reduced systemic IL-6 and related cytokines, restoration of immune competence, and protection against catabolic tissue wasting, leading to dramatically improved survival in preclinical models. This positions R-ketorolac as a candidate small molecule to address the inflammatory and immune components of cancer cachexia.

Rationale for Combining R-ketorolac with GDF-15 Pathway Inhibitors

The complementary biology of GDF-15/GFRAL pathway inhibition and R-ketorolac's Rac1/Cdc42-mediated, cytokine-modulating activity provides a strong rationale for combination therapy in cancer cachexia. GDF-15 inhibitors such as ponsegromab (Pfizer) primarily act at the level of central neuroendocrine control of appetite and energy balance: by neutralizing GDF-15, relieving nausea and anorexia, while supporting T cell infiltration by countering integrin-mediated suppression of T cell adhesion by GDF-15. In contrast, R-ketorolac targets upstream inflammatory and immune dysregulation by reducing IL-6–driven systemic inflammation, preserving muscle and adipose tissue mass, while correcting T-lymphopenia, and dramatically increasing survival as demonstrated in preclinical cachexia models. Importantly, GDF-15 and R-ketorolac address T-cell

dysfunction through distinct, non-overlapping mechanisms: GDF-15 blockade restores LFA-1-dependent T-cell trafficking to the tumor microenvironment (countering integrin-mediated suppression of T-cell adhesion) [9], while R-ketorolac corrects systemic T-lymphopenia driven by IL-6 and Rac1/Cdc42 dysregulation. This mechanistic complementarity at the level of immune restoration provides a particularly compelling rationale for their combined use.

A combination of R-ketorolac to normalize the immunological cytokine storm, and GDF-15 pathway antagonists to block the major axis of the tissue stress response offers the potential to address both major arms of cachexia pathophysiology simultaneously. Therefore, a combined approach that addresses these two distinct mechanisms could yield additive or synergistic benefits: more robust reversal of muscle/fat loss, better preservation of functional status, enhanced tolerance to chemotherapy/immunotherapy, and ultimately improved survival. Preclinical evidence already supports enhanced outcomes with immunomodulators in cachexia models, and the non-overlapping mechanisms (tumor-induced central neural vs. systemic immune/inflammatory) minimize redundancy while maximizing coverage of cachexia's far-reaching systemic impact (**Table 1**).

Table 1. Comparative overview of R-Ketorolac and GDF-15 inhibition as therapeutic strategies in cancer cachexia, and predicted benefits of combination therapy.

	R-Ketorolac	**GDF-15 Inhibition (e.g., Ponsegromab)**
Mechanism of Action	Allosteric inhibition of Rac1/Cdc42 GTPases; suppresses tumor- and host-derived IL-6 and related cytokines; restores immune competence via T-cell-dependent pathway	Monoclonal antibody binding and neutralization of circulating GDF-15; relieves GFRAL-mediated brainstem signaling; restores appetite and reduces nausea
Primary Target Organ/ System	Systemic immune/inflammatory axis; skeletal muscle and adipose tissue (peripheral)	Central neuroendocrine axis (area postrema/ brainstem); peripheral T-cell trafficking (LFA-1/integrin)
T-Cell Effect	Corrects systemic T-lymphopenia driven by IL-6 and Rac1/Cdc42 dysregulation (peripheral immune restoration)	Restores LFA-1-dependent T-cell trafficking to the tumor microenvironment by countering integrin-mediated suppression of T-cell adhesion
Key Preclinical Efficacy Data	C26 model: 10% → 100% survival at day 10 with R-ketorolac alone; maintained with cyclophosphamide. Prevented weight loss, preserved quadriceps and fat mass, reduced IL-6. Attenuated in T-cell-deficient nude mice.	Preclinical GDF-15 blockade reduces anorexia, weight loss, and lipolysis in tumor-bearing rodents. Emerging evidence for direct effects on skeletal muscle mitochondrial function and protein catabolism.
Clinical Evidence to Date	NCT05336266 feasibility trial (racemic ketorolac): weight stabilization/gain, increased physical activity, trends toward reduced GDF-15 and IL-8 in responders. Hypothesis-generating; R-ketorolac-specific trial not yet completed.	Phase 2 randomized, double-blind trial: ponsegromab (400 mg Q4W) produced +5.61% body weight gain over 12 weeks vs. placebo, with improvements in appetite, physical function, and skeletal muscle index.
Limitations of Monotherapy	Does not directly block GDF-15-driven anorexia or nausea; T-cell restoration may be insufficient in the presence of ongoing neuroendocrine suppression	Does not address upstream inflammatory cytokine dysregulation (IL-6, IL-8, TNF-α) or systemic T-lymphopenia; 5.61% weight gain is modest in absolute terms for severely cachectic patients
Predicted Additive Benefit of Combination	Simultaneous blockade of neuroendocrine (GDF-15/GFRAL) and inflammatory (IL-6/Rac1/Cdc42) axes; dual, non-overlapping restoration of T-cell function (trafficking + numbers); enhanced muscle and adipose preservation; improved tolerance to chemotherapy and immunotherapy; potentially extended therapeutic window of anti-GDF-15 therapy through upstream inflammatory suppression	
Key Safety Considerations	Renal and GI risks (NSAID class); COX-independent R-enantiomer may have a more favorable GI profile than racemic ketorolac, but formal safety data for R-ketorolac are to be determined; PK interaction with monoclonal antibodies not yet studied	Gastrointestinal effects (nausea, vomiting) reported in some patients; novel agent with limited long-term safety data; no known direct renal toxicity
Proposed Monitoring Strategy (Combination)	Baseline and monthly eGFR and serum creatinine; systematic GI symptom tracking (patient-reported outcome instruments); prespecified dose-modification protocols; formal PK interaction study prior to or during Phase 2	

Abbreviations: GDF-15: Growth Differentiation Factor 15; GFRAL: GDNF Family Receptor Alpha-Like; IL-6: Interleukin-6; IL-8: Interleukin-8; TNF-α: Tumor Necrosis Factor-Alpha; LFA-1: Lymphocyte Function-Associated Antigen 1; COX: Cyclooxygenase; eGFR: Estimated Glomerular Filtration Rate; GI: Gastrointestinal; PK: Pharmacokinetic; Q4W: Every 4 Weeks.

Preclinical data indicate that R-ketorolac can alleviate cachexia and prolong survival even in the presence of chemotherapy, suggesting that its incorporation into combination regimens is feasible from a safety and efficacy perspective. Interestingly, despite the scientific association of the Rac1/Cdc42 pathway with several tumor cell functions, no direct impact on the tumor is observed [10]. Building on the Phase 2 clinical signal of ponsegromab in improving weight, muscle mass, and activity in patients with GDF-15–driven cachexia, a next logical step is to evaluate whether adding R-ketorolac to GDF-15 blockade can produce additive or synergistic benefits across key cachexia and treatment-tolerance endpoints. While ponsegromab produced a statistically significant 5.61% body weight gain over 12 weeks in its Phase 2 trial, the hypothesis underlying this combination strategy is that simultaneously addressing the inflammatory and immune axis with R-ketorolac will yield additional weight gain, and meaningfully greater improvement in lean body mass, functional endpoints, cytokine profile, and survival compared with GDF-15 inhibition alone. This hypothesis requires prospective testing in an appropriately powered randomized trial. No formal pharmacokinetic interaction between R-ketorolac and anti-GDF-15 monoclonal antibodies has been identified, given their fundamentally different ADME profiles; however, potential pharmacodynamic cross-pathway interactions—including whether R-ketorolac alters circulating GDF-15 levels—remain an important open question addressed further in Future Directions.

Proposed Future Directions

The idea of combining therapies to treat the multiple systemic symptoms of cachexia, which, for simplicity, we broadly categorize as immunomodulatory, neuroendocrine, and metabolic, is not new [11]. However, based on the mechanistic and preclinical evidence summarized above, we propose that R-ketorolac (principally immunomodulatory), in combination with an anti-GDF-15 antibody (several of which are already in clinical development) or a GFRAL inhibitor (principally neuroendocrine), represents a rational next-generation therapeutic strategy for cancer-associated cachexia.

Of course, challenges remain. The precise interaction between R-ketorolac and GDF-15 pathways, for example, requires dedicated investigation, as does the safety of combination therapy—particularly regarding potential overlapping effects on inflammation or cytokine networks. In preparation, ongoing and future trials should prioritize biomarkers (e.g., IL-6, GDF-15 levels, immune profiles) to identify patients most likely to benefit from combination therapy and to optimize dosing regimens. We hypothesize that patients with advanced cancer cachexia who have both elevated serum GDF-15 (≥1,500 pg/mL) and elevated IL-6 (>5 pg/mL)—reflecting activation of both the neuroendocrine and inflammatory arms of cachexia pathophysiology—represent the population most likely to derive additive benefit from R-ketorolac combined with a GDF-15 inhibitor, compared to either monotherapy alone.

Such studies would also provide an opportunity to explore biomarker-driven patient selection (for example, by stratifying based on GDF-15 and IL-6 levels), to characterize pharmacodynamic interactions between GDF-15 blockade and Rac1/Cdc42 inhibition, and to refine combination regimens with concomitant chemotherapy or immunotherapy. If successful, a biomarker-driven combination strategy could help shift the therapeutic paradigm in cancer cachexia from symptomatic, largely palliative intervention toward integrated, multi-pathway regimens that mechanistically address both the inflammatory/immune and neuroendocrine/metabolic roots of the syndrome. A concrete next step would be a Phase 2b, three-arm, randomized trial in patients with pancreatic ductal adenocarcinoma and documented cachexia (≥5% weight loss over 6 months, or ≥2% with BMI <20), stratified by baseline GDF-15 and IL-6 levels, comparing: (1) R-ketorolac alone; (2) anti-GDF-15 therapy (e.g., ponsegromab) alone; and (3) anti-GDF-15 + R-ketorolac in combination. The primary endpoint would be change in body weight at 12 weeks, with key secondary endpoints including sustained diminution of circulating cachexia-promoting cytokines (IL-6, IL-8, TNF-α), lean body mass by CT, neuroendocrine response (change in circulating GDF-15), handgrip strength, 6-minute walk distance, FAACT score, and overall survival. Based on the ponsegromab Phase 2 effect size (5.61% weight gain) and hypothesizing that combination therapy achieves ≥3% additional weight gain over monotherapy, approximately 80–100 patients per arm would be required at 80% power.

Safety considerations warrant dedicated attention. Ketorolac carries known renal and gastrointestinal risks, and it is premature to assume that R-ketorolac is free of these established NSAID-class effects prior to dedicated testing. GDF-15 inhibitors may also produce gastrointestinal adverse effects (nausea, vomiting) in some patients. We therefore propose baseline and monthly renal function monitoring (eGFR, serum creatinine), systematic gastrointestinal symptom tracking using patient-reported outcome instruments and prespecified dose-modification protocols. Formal pharmacokinetic interaction studies between R-ketorolac and anti-GDF-15 monoclonal antibodies have not been conducted and are warranted prior to or during Phase 2 evaluation.

The optimal timing and sequencing of combination therapy represents a key unanswered question. Cancer cachexia evolves along a continuum, and it remains unknown whether cytokine-driven etiology or stress-induced GDF-15-driven anorexia will predominate at any given disease stage. Phase 1/2a monotherapy results with R-ketorolac will be compared and contrasted with ponsegromab data to inform sequencing decisions. Preclinical evidence suggests that anti-GDF-15 may be most effective early in disease, while R-ketorolac

demonstrates efficacy in well-established cachexia; however, this is insufficient to conclude that R-ketorolac should be reserved for later-stage disease. Indeed, early use of R-ketorolac may prolong the effective therapeutic window of anti-GDF-15 therapy by simultaneously suppressing the inflammatory drivers that perpetuate cachexia independently of the GDF-15 axis. We therefore identify the optimal timing and sequencing of combination therapy as a priority question for future study.

Finally, we explicitly acknowledge that preclinical data on whether R-ketorolac alters circulating GDF-15 levels—or whether GDF-15 inhibition in turn alters IL-6 or Rac1/Cdc42 signaling—are not currently available, and we flag this as a priority knowledge gap. The NCT05336266 feasibility trial observed trends toward GDF-15 reduction with racemic ketorolac in weight responders, which, if validated using pure R-ketorolac, would suggest a pharmacodynamic interaction that could be synergistic with direct GDF-15 neutralization; however, this remains speculative and requires dedicated investigation.

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