Ponsegromab for the Treatment of Cancer Cachexia

TO THE EDITOR: Groarke et al. (Dec. 19/26 issue)[1] report on the efficacy and safety of ponsegromab for cancer-related cachexia in patients with elevated levels of growth differentiation factor 15 (GDF-15). Although this trial focused on cancer cachexia, it is noteworthy that other conditions, such as chronic kidney disease (CKD), may also be associated with cachexia and muscle wasting,[2] along with elevated GDF-15 levels. GDF-15, a stress-induced cytokine, is not only overexpressed by many tumors but is also induced in nontumor tissues (e.g., kidney and liver) and immune cells. Patients with CKD, particularly those undergoing dialysis, have GDF-15 levels approximately seven times as high as those in healthy persons.[3] Systemic inflammation, coexisting cardiac conditions, and uremia may contribute to heightened cellular stress, leading to GDF-15 production, together with impaired renal clearance. Elevated GDF-15 levels in this population strongly correlate with increased mortality.[4,5] The findings of Groarke et al. thus raise the questions of whether anorexia and nausea, which are commonly observed in patients with CKD, could be accounted for by GDF-15 levels and whether ponsegromab also holds therapeutic potential beyond cancer in patients with cachexia due to CKD.

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TO THE EDITOR: Groarke et al. found that ponsegromab increased weight and reduced cachexia symptoms such as poor appetite in patients with cancer cachexia and a median GDF-15 level of 3903 pg per milliliter (interquartile range, 2366 to 7677). Given the lack of effective interventions for anorexia of aging, a prevalent geriatric syndrome in hospitalized older adults[1] that is characterized by poor appetite or food intake (or both),[2] these findings are interesting.

We have previously found that elevated GDF-15 levels were significantly associated with both malnutrition and poor appetite in hospitalized older adults with a median GDF-15 level of 2200 pg per milliliter (interquartile range, 1450 to 3510).[3] In addition, elevated GDF-15 levels persisted after hospital admission.[4]

To assess the potential of ponsegromab in hospitalized older patients, we investigated the prevalence of patients who met the criteria for weight loss and GDF-15 level that were outlined by Groarke et al. (Table 1). We found that 49 of 269 patients (18%) met the criteria, which highlights the potential of ponsegromab in this population. Further investigation is needed to determine whether the therapeutic benefits of ponsegromab extend to other syndromes characterized by poor appetite and elevated GDF-15 levels.

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Table 1. Clinical Characteristics of 269 Hospitalized Older Adults Stratified According to Involuntary Weight Loss in the Past 3 Months.*

Characteristic	Weight Loss of ≤5% (N=212)	Weight Loss of >5% (N=57)
GDF-15 level		
Median (IQR) — pg/ml	1980 (1350–3320)	2770 (2040–4020)
<1500 pg/ml — no. (%)	68 (32)	8 (14)
≥1500 pg/ml — no (%)	144 (68)	49 (86)
Median age (IQR) — yr	77.7 (72.4–83.1)	80.2 (75.6–85.3)
Female sex — no. (%)	121 (57)	34 (60)
Body-mass index†		
Median (IQR)	25.9 (23.2–30.3)	22.8 (19.5–27.9)
<20 — no./total no. (%)	17/211 (8)	16/57 (28)
≥20 — no./total no. (%)	194/211 (92)	41/57 (72)
Cancer treatment — no. (%)	10 (5)	4 (7)
Hand-grip strength		
Median (IQR) — kg	21.2 (16.0–28.7)	18.2 (13.4–26.0)
Low strength: <27 kg in men and <16 kg in women — no./total no. (%)	81/203 (20)	34/55 (62)
SNAQ score‡		
Median (IQR)	15 (13–16)	13 (11–15)
Poor appetite: score of ≤14 — no./total no. (%)	92/208 (44)	38/56 (68)
MNA-SF score§		
Median (IQR)	11 (9–12)	6 (5–7)
Normal nutrition: score of 12–14 — no./total no. (%)	84/209 (40)	1/57 (2)
Malnutrition risk: score of 8–11 — no./total no. (%)	99/209 (47)	11/57 (19)
Malnutrition: score of 0–7 — no./total no. (%)	26/209 (12)	45/57 (79)

* Percentages may not total 100 because of rounding. GDF-15 denotes growth differentiation factor 15, and IQR interquartile range.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Scores on the Simplified Nutritional Appetite Questionnaire (SNAQ) range from 4 to 20, with higher scores indicating better appetite.
§ Scores on the Mini Nutritional Assessment–Short Form (MNA-SF) range from 0 to 14, with higher scores indicating better nutritional status.

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THE AUTHORS AND A COLLEAGUE REPLY: Dufour and colleagues highlight GDF-15 elevation and cachexia in patients with CKD, in whom the GDF-15 level is an independent predictor of CKD progression and adverse outcomes. Elevated GDF-15 levels are also observed in cachexia associated with other serious chronic conditions, including pulmonary and cardiac diseases, with similar correlations to disease severity and worse prognosis.[1] In this context, our recent phase 2 study (funded by Pfizer) showing that ponsegromab-mediated GDF-15 inhibition can ameliorate the cancer cachexia phenotype begets a hypothesis that this cytokine is more than a prognostic biomarker and may represent a common therapeutic target in cachexia associated with either malignant

or nonmalignant diseases. The need for further evaluation of the broader potential for anti–GDF-15 therapies with dedicated clinical trials is highlighted by the absence of approved therapies for any cachexia indication in most countries. However, the current lack of consensus on the optimal end points needed for regulatory approval[2] and the multiple competing risks common in these populations with advanced disease are important, practical considerations for clinical trials regarding cachexia.

Nielsen and colleagues identify hospitalized older adults with anorexia and elevated GDF-15 levels as another population who may benefit from GDF-15 inhibition. Their finding that 18% of hospitalized older patients had weight loss of more than 5% and a GDF-15 level of at least 1500 pg per milliliter — the GDF-15 threshold used in our recent phase 2 study — highlights the complexities in interpreting GDF-15 levels across different patient groups and in determining GDF-15 thresholds for the selection of appropriate patients for anti–GDF-15 therapies, given that 72% of this overall cohort of hospitalized older patients had GDF-15 levels of at least 1500 pg per milliliter. Clinical interpretation of GDF-15 levels should consider multiple physiological and pathophysiological contributors, including aging,[3] and would benefit from additional disease-specific and age-stratified, longitudinal GDF-15 data derived from standardized diagnostic assays.

We agree with these proposals that therapeutic opportunities for GDF-15 inhibition probably extend beyond cancer cachexia. An evolving understanding of potential downstream effects of GDF-15 beyond the central actions on appetite and food-intake regulation, including activation of the hypothalamic–pituitary–adrenal axis[4] and tumor-derived immunosuppression,[5] will inform the true breadth of therapeutic potential.

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Dr. Sessa reports being a Pfizer employee and shareholder. Since publication of the article, Drs. Groarke and Saxena report no further potential conflict of interest.

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PCI in Patients Undergoing TAVI

TO THE EDITOR: The third Nordic Aortic Value Intervention (NOTION-3) trial reported by Lønborg et al. (Dec. 12 issue)[1] offers valuable insights into the management of coronary artery disease among patients receiving transcatheter aortic-valve implantation (TAVI) procedures, highlighting the significant reduction in a composite of death, myocardial infarction, and urgent revascularization observed with percutaneous coronary intervention (PCI). However, several factors merit further consideration to enhance the interpretation of the trial.

The timing of PCI — whether performed before, during, or after TAVI — may influence procedural risks such as vascular complications and contrast-induced nephropathy. Clarifying this factor would provide better context to understand the outcomes. In addition, although Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) scores (which reflect a comprehensive angiographic assessment of the coronary vasculature) were similar in the PCI and conservative-treatment groups, the lack of detailed data on critical lesion locations, such as in the left main coronary artery or proximal left anterior descending artery, limits generalizability. Favorable outcomes in the PCI group may have been influenced