Ponsegromab, GDF-15, and Cancer Cachexia.
Cachexia is initiated by a complex mixture of tumor-derived factors and proinflammatory molecules generated by cross-talk between tumor cells and associated immune cells. These factors may elicit catabolism directly in the end organs of cachexia (skeletal muscle, adipose tissue, and heart) or do so through the central nervous system. Chemotherapy spurs on cachexia by the induction of nausea and vomiting and through toxic actions on muscle and fat cells. Multiple sources contribute to rising humoral levels of growth differentiation factor 15 (GDF-15), which is expressed by tumor cells, immune cells, and organs and tissues (liver, kidney, and muscle and adipose tissue) in response to chemotherapy. Key brain regions that regulate energy balance include the brain stem, hypothalamus, and reward system. Interconnected brain-stem regions include the area postrema (AP), nucleus tractus solitarius (NTS), chemoreceptor trigger zone (CTZ), and vomiting center (VC). GDF-15 exerts its action through a specific receptor (glial cell–derived neurotrophic factor family receptor α-like [GFRAL]) expressed by neurons of the AP and NTS, intersecting with chemotherapy-induced nausea (signaled directly on the CTZ as well as from the gastrointestinal tract via the vagus nerve; the latter is not shown).