of death, as observed in retrospective analyses.[1] Our trial included only persons with a plasma potassium level of no more than 4.3 mmol per liter and an eGFR of at least 30 ml per minute per 1.73 m^2, and we did not observe any apparent interaction for the primary end point between participants with renal failure and those without.

Hurtado-Torres addresses an interesting aspect of increases in plasma magnesium levels during mineralocorticoid receptor antagonist treatment. We agree that parallel changes in plasma magnesium levels may have contributed to the positive outcomes. However, a positive outcome was also observed in participants in whom the plasma potassium level reached the target range without mineralocorticoid receptor antagonist treatment.

Abramov and Garg discuss effects of increased plasma potassium levels in participants who had heart failure or were receiving a mineralocorticoid receptor antagonist at baseline. No significant interaction was apparent between participants with a left ventricular ejection fraction of 40% or less and those with a value greater than 40%, between those with heart failure and those without (New York Heart Association class I vs. class II, III, or IV), or between those who were receiving a mineralocorticoid receptor antagonist at baseline and those who were not (Fig. 2 of our article). We agree that discontinuation of treatment with kaliuretic diuretics should be considered if possible[2] and that the suggested potassium stewardship should be applied regardless of the presence of heart failure and also in persons being treated with a mineralocorticoid receptor antagonist, if the patient's plasma potassium level is 4.3 mmol per liter or less.

Yuan and colleagues comment on the potential that effects other than an increase in the plasma potassium level may have contributed to the outcomes observed in our trial. No difference was seen between the 409 participants who received mineralocorticoid receptor antagonists at the end of the adjustment period and the 191 participants who were not treated with a mineralocorticoid receptor antagonist, which indicates an effect on the outcomes because of the plasma potassium increase per se. No significant interaction was apparent between participants with a baseline plasma potassium level above 4 mmol per liter and those with a level of 4 mmol per liter or lower (Fig. 2 of our article).

Ingwiller expresses concern about steps in the measurement of plasma potassium, given that various errors may falsely increase the level. Measurements of plasma potassium followed standard clinical procedures in all the participants in both trial groups. Thus, any potential error should have affected levels in both groups. Plasma potassium levels were stable at baseline, and measurements showed that levels differed between the two groups after adjustment of treatment in the high-normal potassium group was implemented. Thus, in that respect, the POTCAST trial had a pragmatic approach to facilitate clinical implementation of the results.[3]

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Since publication of the article, the authors report no further potential conflict of interest.

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Belzutifan for Advanced Pheochromocytoma or Paraganglioma

TO THE EDITOR: Jimenez et al. (Nov. 20 issue)[1] report that the hypoxia-inducible factor 2α (HIF-2α) inhibitor belzutifan resulted in an objective response in 26% of participants and disease control in 85% of participants with advanced pheochromocytoma or paraganglioma, with a median progression-free survival of 22.3 months. Prospective data on peptide receptor radionuclide therapy are encouraging. In the series by Severi et al. involving 46 patients with metastatic somatostatin receptor–positive pheochromocytoma or paraganglioma, treatment with ^{90}Y-DOTATOC or ^{177}Lu-DOTATATE resulted in disease control in 80% and prolonged progression-free survival and

overall survival, with limited renal and bone marrow toxic effects.[2] Similarly, the National Institutes of Health phase 2, two-stage study of ^{177}Lu-DOTATATE in 36 patients with progressive pheochromocytoma or paraganglioma showed a 6-month progression-free survival of 86%, a median progression-free survival of 19.9 months, and a median overall survival of 51.7 months, with acceptable hematologic toxicity but catecholamine crises in 17% of patients.[3]

These data suggest that peptide receptor radionuclide therapy can provide disease control similar to that of belzutifan and should remain a cornerstone for slowly progressive, somatostatin receptor–positive disease. Belzutifan may be best used after or in place of radionuclide therapy, particularly when objective response is desired or ^{68}Ga-DOTATOC positron-emission tomography–computed tomography is negative.[2-5] Prospective studies comparing or sequencing peptide receptor radionuclide therapy and HIF-2α inhibition are warranted.

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TO THE EDITOR: In our experience (in research funded in part by the National Institute of Diabetes and Digestive and Kidney Diseases and the Eunice Kennedy Shriver National Institute of Child Health and Human Development), belzutifan produced a rapid biochemical and cardiovascular response, with normalization of blood pressure and catecholamine levels within 3 to 6 hours, potentially driven by suppression of tyrosine hydroxylase expression or phosphorylation and by catecholamine release.[1] We wonder whether Jimenez et al. observed similar rapid hemodynamic improvement.

Furthermore, in our smaller cohort of patients with *EPAS1*-related pheochromocytoma or paraganglioma, a higher incidence of response to belzutifan was observed, with four of five patients (80%) having a partial response and one patient having stable disease.[2] We therefore suspect that belzutifan may be most effective in selected patients with tumors harboring *EPAS1*-activating variants and possibly other alterations directly related to HIF-2α biologic features and signaling mechanisms (e.g., variants in *VHL*, *EGLN1*, and *EGLN2*).[3] Our suspicion appears to be consistent with the subgroup analysis from the trial by Jimenez et al., which showed a numerically higher incidence of response among participants with *SDHB*-mutated tumors than among those without such tumors (38% [9 of 24 participants] vs. 25% [6 of 24]). Identifying such genetic biomarkers is essential for precision medicine today, because pooled genotype-agnostic analyses may obscure biologically driven effects. A genotype-stratified waterfall plot would be valuable to further illustrate these findings.

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The findings and conclusions presented in this letter are those of the authors and do not necessarily reflect the views of the National Institutes of Health or the U.S. Department of Health and Human Services.

No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Bongiovanni and Liverani suggest that peptide receptor radionuclide therapy can provide disease control similar to that of belzutifan and should remain a cornerstone for slowly progressive, somatostatin receptor–positive disease, and they recommend prospective studies comparing or sequencing peptide receptor radionuclide therapy and HIF-2α inhibition. The authors noted encouraging results from the phase 2 study by Lin et al. of ^{177}Lu-DOTATATE in 36 patients with progressive pheochromocytoma or paraganglioma (median progression-free survival of 19.9 months, 6-month progression-free survival of 86%, and median overall survival of 51.7 months).[1] In our trial (LITESPARK-015) of belzutifan in 72 participants with locally advanced or metastatic pheochromocytoma or paraganglioma, after a median follow-up of 30.2 months, median progression-free survival was 22.3 months, with 24-month progression-free survival of 49% and 24-month overall survival of 76%; the incidence of objective response was 26% and of disease control was 85%. Moreover, a durable response was observed with belzutifan in this patient population, with a median duration of response of 20.4 months and an estimated 64% of participants having a response at 12 months. Furthermore, belzutifan did not confer a predisposition to a catecholamine crisis.

Although we agree that other treatment options should be considered and a study directly comparing belzutifan with radionuclide therapy would be of interest, cross-study comparison of an interim analysis from a single-center study involving patients with somatostatin receptor–positive pheochromocytoma or paraganglioma to the analysis of an international trial involving unselected patients with pheochromocytoma or paraganglioma is challenging, and valid conclusions cannot be drawn. The assertion that peptide receptor radionuclide therapy should be the cornerstone of therapy is premature.

Alkaissi and Pacak highlight observation of a higher incidence of response to belzutifan among patients with *EPAS1*-related pheochromocytoma or paraganglioma in a very small case series[2] and suggest that this finding is consistent with a numerically higher incidence of response observed in a subgroup of patients with *SDHB*-mutated tumors in the LITESPARK-015 trial. We agree that identifying biomarkers of response in this field warrants further investigation. However, any subgroup analysis of our trial is hypothesis-generating, and no definitive conclusions can be drawn because these prespecified subgroups are limited in number and not powered for significance. In addition, extrapolating results from a limited case series involving a single rare mutation to other mutations in the HIF-2α pathway such as mutations in *SDHx* should be approached with caution. Belzutifan is currently being investigated in advanced solid tumors including pheochromocytoma or paraganglioma that harbor an HIF-2α–related mutation (including mutations in *EPAS1* and *SDHx*) in cohort D of our ongoing trial, which will provide prospective evidence of the effect of belzutifan on tumors that harbor HIF-2α–related mutations.

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Since publication of the article, the authors report no further potential conflict of interest.

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CORRECTIONS

Paget's Disease of the Breast (N Engl J Med 2023;388:1126-1126). The description of Panel C of the figure as depicting Paget cells was incorrect, and the panel has been removed. The article is correct at NEJM.org.

Standard or Extended Lymphadenectomy for Muscle-Invasive Bladder Cancer (N Engl J Med 2024;391:1206-1216). In the legend for Figure 2 (page 1213), the median follow-up should have been 6.1 years, rather than 6.1 months. The article is correct at NEJM.org.