ORIGINAL ARTICLE

# Belzutifan for Advanced Pheochromocytoma or Paraganglioma

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## ABSTRACT

### BACKGROUND

Pheochromocytoma and paraganglioma are neoplasms originating in the adrenal medulla and extraadrenal paraganglia, respectively. Most cases of metastatic pheochromocytoma and paraganglioma are driven by dysregulation of the hypoxia-inducible factor 2$\alpha$ (HIF-2$\alpha$) pathway. Belzutifan is a HIF-2$\alpha$ inhibitor that may provide antitumor activity in patients with advanced pheochromocytoma or paraganglioma.

### METHODS

We conducted a phase 2, international, single-group trial involving 72 participants with locally advanced or metastatic pheochromocytoma or paraganglioma that was not amenable to surgery or curative-intent treatment. Participants received belzutifan at a dose of 120 mg once daily until the occurrence of progression, unacceptable toxic effects, or withdrawal from the trial. The primary end point was confirmed objective response (complete or partial response) as assessed by blinded independent central review. Secondary and other key end points included the duration of response, disease control, progression-free survival as assessed by blinded independent central review, overall survival, safety, and a reduction from baseline in antihypertensive medication.

### RESULTS

At a median follow-up of 30.2 months (range, 23.3 to 37.6), the percentage of participants with a confirmed objective response was 26% (95% confidence interval [CI], 17 to 38) and the percentage of participants with disease control was 85% (95% CI, 74 to 92). The median duration of response was 20.4 months (95% CI, 8.3 to not reached), with a median duration of progression-free survival of 22.3 months (95% CI, 13.8 to not reached). Overall survival was 76% at 24 months. Among the 60 participants who were receiving antihypertensive medications, 19 (32%) had a reduction of at least 50% in the total daily dose of at least one antihypertensive medication for at least 6 months after starting treatment with belzutifan. Treatment-related adverse events occurred in 71 participants (99%); anemia of grade 3 was noted in 22% of the participants. Eight participants (11%) had treatment-related serious adverse events.

### CONCLUSIONS

Belzutifan showed antitumor activity with durable responses in participants with advanced pheochromocytoma or paraganglioma. (Funded by Merck Sharp and Dohme, a subsidiary of Merck [Rahway, NJ]; LITESPARK-015 ClinicalTrials.gov number, NCT04924075.)

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*A complete list of investigators who participated in the LITESPARK-015 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Pheochromocytoma and paraganglioma are rare neoplasms originating in the adrenal medulla and the extraadrenal sympathetic or parasympathetic paraganglia, respectively.[1] The incidence of pheochromocytoma and paraganglioma is approximately 6 cases per 1 million person-years, with approximately 10% of cases diagnosed in childhood.[2,3] Predicting the metastatic potential of pheochromocytoma and paraganglioma is challenging owing to a lack of reliable histologic, biochemical, molecular, or genetic markers.[4] Approximately 25% of patients with pheochromocytoma or paraganglioma will eventually have metastastatic disease.[5] Metastatic pheochromocytoma or paraganglioma is associated with lower survival than nonmetastatic disease and a high degree of complications owing to tumor burden, disease progression, and excessive secretion of catecholamines, which leads to cardiovascular and gastrointestinal illness.[5,6] The 5-year survival among patients with metastatic pheochromocytoma or paraganglioma is approximately 60%.[5,7] Currently, there is no standard treatment for unresectable, metastatic pheochromocytoma or paraganglioma. Alternative treatments include peptide-receptor radionuclide therapy (lutetium Lu 177 dotatate), somatostatin-receptor analogues, chemotherapy (a combination of cyclophosphamide, vincristine, dacarbazine, and temozolomide), and tyrosine kinase inhibitors.[6] Recently, production of the only treatment approved by the Food and Drug Administration (FDA) for pheochromocytoma and paraganglioma — high-specific-activity $^{131}$I-labeled metaiodobenzylguanidine — was discontinued.[8]

Dysregulation of the hypoxia-inducible factor 2$\alpha$ (HIF-2$\alpha$) pathway is one of the key oncogenic drivers of metastatic pheochromocytoma and paraganglioma. Germline pathogenic variants affecting genes encoding key Krebs cycle enzymes — such as the succinate dehydrogenase subunits (*SDHA*, *SDHB*, *SDHC*, and *SDHD*), *SDHAF2*, fumarate hydratase, and *MDH2* — or affecting components of the hypoxia signaling pathway (*VHL*, *EGLN1*, *EGLN2*, and *HIF2A* [also known as *EPAS1*]) can result in pseudohypoxia and stabilization of HIF-2$\alpha$. Stable HIF-2$\alpha$ leads to downstream activation of multiple genes that promote tumorigenesis, cell survival, metastasis, and angiogenesis.[9,10] Most cases of metastatic pheochromocytoma and paraganglioma are characterized by pseudohypoxia, and up to 50% are associated with an *SDHB* germline pathogenic variant.[11] In addition, many pheochromocytomas and paragangliomas that are not associated with the previously described germline pathogenic variants exhibit a similar molecular phenotype of pseudohypoxia.[12,13]

Belzutifan is a HIF-2$\alpha$ inhibitor that is currently approved for use in adults with von Hippel–Lindau (VHL) disease–associated renal-cell carcinoma, pancreatic neuroendocrine tumors, or hemangioblastomas of the central nervous system, in whom immediate surgery is not clinically indicated.[14] This approval was supported by the results of the LITESPARK-004 trial, in which the objective response with belzutifan was 49% among participants with VHL disease–associated renal cell carcinoma, 83% among those with pancreatic neuroendocrine tumors, and 63% among those with central nervous system hemangioblastomas.[14]

Belzutifan is also approved in the United States for the treatment of advanced renal cell carcinoma after previous treatment with a programmed cell death protein 1 or programmed death ligand 1 inhibitor and vascular endothelial growth factor (VEGF) receptor–tyrosine kinase inhibitor therapy on the basis of the results of the LITESPARK-005 trial.[14,15] Progression-free survival was 47% at 6 months, 33% at 12 months, and 24% at 18 months in the belzutifan group as compared with 43%, 17%, and 8.3%, respectively, in the everolimus group.[15] Because belzutifan targets HIF-2$\alpha$, a key oncogenic driver of pheochromocytoma and paraganglioma, the efficacy and safety of belzutifan were subsequently evaluated in patients with pheochromocytoma or paraganglioma.[16,17]

Here, we present the results of the phase 2 LITESPARK-015 trial of belzutifan involving participants with advanced pheochromocytoma or paraganglioma.

## METHODS

### PARTICIPANTS

In the LITESPARK-015 trial, eligible participants were at least 12 years of age, had a documented histopathological diagnosis of pheochromocytoma or paraganglioma that was locally advanced or metastatic and was not amenable to surgery or curative-intent treatment, and had measurable disease as assessed by blinded independent central review according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Participants had to have adequately controlled blood pressure, which was defined as a blood

pressure of 150/90 mm Hg or less (≤135/85 mm Hg for adolescents), with no change in antihypertensive medications (for participants with hypertension) for at least 2 weeks before the start of the trial treatment; disease progression within 12 months before screening; an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale, with higher scores indicating greater disability); and adequate organ function. Participants were ineligible if they had received a metaiodobenzylguanidine or another radiopharmaceutical agent within 12 weeks before screening, if they had received previous systemic therapy (such as chemotherapy or targeted therapy) within 4 weeks before the start of the trial treatment, or if they had received previous treatment with a HIF-2$\alpha$ inhibitor.

### TRIAL DESIGN AND TREATMENT

In this phase 2, international, multicenter, open-label, single-group, multicohort trial, eligible participants received belzutifan orally at a dose of 120 mg once daily until the occurrence of progression, unacceptable toxic effects, or withdrawal from the trial by the participant or investigator. The dose of belzutifan could be decreased to 80 mg once daily, and then to 40 mg once daily, to manage unacceptable toxic effects. Treatment beyond the occurrence of radiologic progression was permitted in accordance with the protocol (available with the full text of this article at NEJM.org) for clinical benefit if the participant's condition was clinically stable.

### END POINTS

The primary end point was objective response, which was defined as a confirmed complete or partial response as assessed by blinded independent central review according to RECIST, version 1.1. Secondary end points were the duration of response, which was defined as the time from the first documented evidence of a complete or partial response until the first documented occurrence of disease progression or death; disease control, which was defined as a best confirmed response of complete or partial response or stable disease; progression-free survival, which was evaluated in an analysis of the time from the first dose of the trial medication to the first documented occurrence of disease progression as assessed by blinded independent central review according to RECIST, version 1.1, or death; overall survival, which was evaluated in an analysis of the time from the first dose of the trial medication to the occurrence of death from any cause; and safety. Key exploratory end points were a reduction from baseline in the total daily dose of antihypertensive medication and quality of life. A prespecified subgroup analysis of the primary end point included the following subgroup categories: age, sex, presence of *SDHB*-related tumor predisposition syndrome, number of previous lines of systemic therapy, previous treatment with a VEGF receptor–tyrosine kinase inhibitor, and previous treatment with a radiopharmaceutical agent.

Quality-of-life end points included stable status or improvement or deterioration in scores on the global health status and quality-of-life domains and in the physical functioning domain on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) and the change from baseline in the domain scores on the EORTC QLQ-C30 and the scores on the EuroQol Group 5-Dimension 5-Level (EQ-5D-5L) visual analogue scale (VAS).[18] Additional details regarding the quality-of-life end points are included in the Supplementary Appendix, available at NEJM.org.

### ASSESSMENTS

Tumor assessments were performed every 8 weeks during the first year of the trial and every 12 weeks thereafter until the occurrence of disease progression, the start of new anticancer treatment, or withdrawal from the trial. Imaging (computed tomography or magnetic resonance imaging) was performed locally; the images were then transmitted for assessment by blinded independent central review according to RECIST, version 1.1. Adverse events were monitored throughout the trial, beginning after the administration of the trial treatment, and for 30 days (90 days if serious adverse events had occurred) after treatment discontinuation and were graded by the investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5. Follow-up assessments for survival status occurred every 12 weeks after the participants completed the trial treatment or discontinued treatment. For the assessment of antihypertensive medication, the total daily dose of each antihypertensive medication taken was documented at baseline and at each visit after the start of

the trial treatment among participants receiving antihypertensive medication; discontinuation and initiation of antihypertensive medication were also assessed during follow-up. For the quality-of-life assessments, the EORTC QLQ-C30 and the EQ-5D-5L questionnaire were completed by the participants. Body weight was also recorded during the trial.

### TRIAL OVERSIGHT

The trial design was a collaboration between academic investigators and the sponsor (Merck Sharp and Dohme, a subsidiary of Merck [Rahway, NJ]). All the participants provided written informed consent. The trial was conducted in accordance with the principles of the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice guidelines, and local regulations. The protocol and its amendments were approved by the appropriate institutional review board or ethics committee at each participating institution. All the authors participated in collecting or interpreting the data and in writing or reviewing and editing earlier versions of the manuscript. All the authors had access to the data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Statisticians employed by the sponsor and included as authors performed the data analysis. A medical writer employed by the sponsor assisted with the preparation of the first draft of the manuscript and provided editorial support on other early drafts of the manuscript.

### STATISTICAL ANALYSIS

The data-cutoff date was October 23, 2024. Interim analyses could be performed after approximately 6 months of follow-up or longer. No hypothesis testing was done, given the rarity of the disease and the fact that there was no clearly defined threshold to compare in this single-group trial. The sample-size calculation was therefore based on the level of precision of the estimated percentage of participants with an objective response; the 95% confidence intervals for objective response estimates of 10%, 20%, and 30% for a target sample size of 70 participants are provided in the Supplementary Appendix. Efficacy and safety were assessed in all the participants in the as-treated population, which was defined as all the participants who received at least one dose of the trial treatment. For the analysis of objective response, point estimates and 95% confidence intervals, calculated with the use of the exact Clopper–Pearson method, were provided. Duration of response, progression-free survival, and overall survival were evaluated with the use of the Kaplan–Meier method. SAS software, version 9.4 (SAS Institute), was used for all the statistical analyses.

## RESULTS

### PARTICIPANTS AND TREATMENT

From September 7, 2021, to November 14, 2022, a total of 72 participants with advanced pheochromocytoma or paraganglioma were enrolled at 31 sites in 12 countries (Fig. S1 in the Supplementary Appendix). The median age of the participants was 51.5 years; no participants were younger than 18 years of age. Overall, 28 participants (39%) had a history of hereditary paraganglioma syndrome, with *SDHB*-related tumor predisposition syndrome being the most common (in 33% of the participants). A total of 60 participants (83%) had hypertension (Table 1). The median duration of follow-up from the first dose of the trial treatment to the time of data cutoff was 30.2 months (range, 23.3 to 37.6). Overall, 41 participants (57%) discontinued the trial treatment, primarily owing to progressive disease (in 34 participants [47%]). Three participants (4%) discontinued treatment because of clinical progression, and 2 participants (3%) discontinued treatment owing to adverse events. A total of 31 participants (43%) continued to receive the trial treatment as of the data-cutoff date.

### EFFICACY

Among the eligible participants who had been enrolled to receive belzutifan, a confirmed objective response occurred in 19 participants (26%) (all 19 had a partial response); 51 participants (71%) had a reduction from baseline in tumor size (Fig. 1A and Table 2). Overall, 42 participants (58%) had a best response of stable disease as assessed by blinded independent central review according to RECIST, version 1.1; 85% of the participants had disease control (Table 2). Most of the participants with a response had tumor reduction early on after starting the trial treatment (Fig. 1B). Objective responses were noted across prespecified subgroups (Fig. S2).

The median time to response was 11.0 months (range, 1.7 to 24.8) (Fig. 1C). The me-

**Table 1. Demographic and Disease Characteristics at Baseline.***

| Characteristic | All Participants (N=72) |
|---|---|
| Age | |
| Median (range) — yr | 51.5 (22–77) |
| ≥65 yr — no. (%) | 9 (12) |
| Male sex — no. (%) | 42 (58) |
| Geographic region — no. (%) | |
| North America | 21 (29) |
| Western Europe | 46 (64) |
| Rest of the world | 5 (7) |
| ECOG performance-status score — no. (%)† | |
| 0 | 39 (54) |
| 1 | 33 (46) |
| Previous lines of systemic therapy‡ | |
| Median no. (range) | 1 (0–5) |
| ≥1 Previous line of systemic therapy — no. of participants (%) | 54 (75) |
| Previous therapy — no. (%) | |
| Chemotherapy | 36 (50) |
| Radiopharmaceutical agent | 32 (44) |
| VEGF receptor–tyrosine kinase inhibitor | 18 (25) |
| Other anticancer therapy | 5 (7) |
| Somatostatin-receptor analogue | 10 (14) |
| History of genetic syndrome — no. (%) | |
| Yes | 28 (39) |
| *SDHD*-related tumor predisposition syndrome | 2 (3) |
| *SDHB*-related tumor predisposition syndrome | 24 (33) |
| *SDHA*-related tumor predisposition syndrome | 2 (3) |
| No | 20 (28) |
| Unknown | 24 (33) |
| Disease type — no. (%) | |
| Locally advanced | 2 (3) |
| Metastatic | 70 (97) |
| History of hypertension — no. (%) | 60 (83) |
| Diagnosis — no. (%) | |
| Pheochromocytoma | 24 (33) |
| Paraganglioma | 45 (62) |
| Both pheochromocytoma and paraganglioma | 3 (4) |
| Median tumor burden (range) — mm | 84.5 (10–261) |
| Site of disease or metastasis — no. (%) | |
| Lymph node | 48 (67) |
| Bone | 41 (57) |
| Liver | 23 (32) |
| Lung | 19 (26) |
| Peritoneum | 10 (14) |
| Other | 57 (79) |

* VEGF denotes vascular endothelial growth factor.
† Eastern Cooperative Oncology Group (ECOG) scores range from 0 to 5, with higher scores indicating greater disability.
‡ Zero indicates no previous systemic therapy or previous therapies that do not meet the definition of previous lines of systemic therapy.

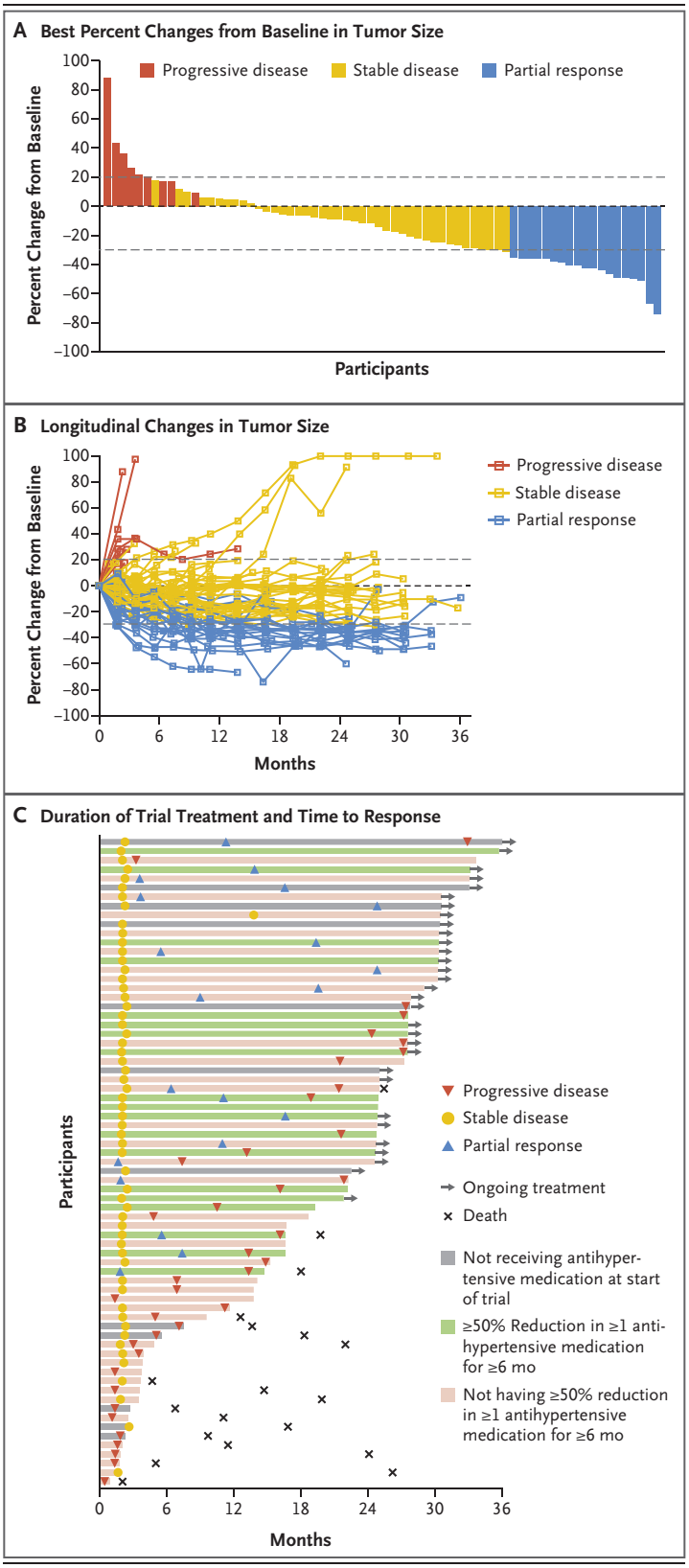


**Figure 1. Changes in Tumor Size, Duration of Treatment, and Time to Response.**

Panel A shows the best percent changes from baseline in pheochromocytoma or paraganglioma tumor size. Panel B shows longitudinal changes in the size of target pheochromocytoma or paraganglioma tumors over time. Panel C shows the duration of the trial treatment and the time to response. In Panel C, the gray bars indicate participants who were not receiving antihypertensive medication at the start of the trial. The green bars indicate participants who were receiving antihypertensive medication at the start of the trial and had a reduction of at least 50% in the total daily dose of at least one antihypertensive medication for at least 6 months. The pink bars indicate participants who were receiving antihypertensive medication at the start of the trial and did not have a reduction of at least 50% in the total daily dose of at least one antihypertensive medication for at least 6 months. One participant had no postbaseline assessment.

dian duration of response was 20.4 months (range, 5.6+ to 29.6+; the plus signs indicate an ongoing response at the time of data cutoff); the Kaplan–Meier estimate of duration of response at 12 months was 64% (Fig. 2A and Table 2). At the time of data cutoff, 39 participants (54%) had had disease progression. The median duration of progression-free survival was 22.3 months; the Kaplan–Meier estimate of progression-free survival at 24 months was 49% (Fig. 2B and Table 2). The median overall survival was not reached, with a Kaplan–Meier estimate of 76% at 24 months (Fig. 2C and Table 2).

### BLOOD-PRESSURE CONTROL, QUALITY OF LIFE, AND BODY WEIGHT

A total of 60 participants were receiving treatment with antihypertensive medication at the start of the trial. Among these participants, 20 (33%) had a reduction of at least 25% in the total daily dose of at least one antihypertensive medication for at least 6 months, and 19 (32%) had a reduction of at least 50% in the total daily dose of at least one antihypertensive medication for at least 6 months. A reduction in antihypertensive medication was noted among participants with partial responses and stable disease (Fig. 1C).

The scores on the EORTC QLQ-C30 global health status–quality of life assessment showed that 22% of the participants had improvement, 52% had a stable status, and 25% had deterioration. The scores on the EORTC QLQ-C30 physi-

**Table 2. Antitumor Activity.***

| Variable | All Participants (N=72) |
|---|---|
| Objective response — no. | 19 |
| % (95% CI) | 26 (17 to 38) |
| Complete response — no. | 0 |
| Partial response — no. (%) | 19 (26) |
| Stable disease — no. (%) | 42 (58) |
| Disease control — no. | 61 |
| % (95% CI) | 85 (74 to 92) |
| Median time to response (range) — mo | 11.0 (1.7 to 24.8) |
| Duration of response | |
| Median (95% CI) (range) — mo | 20.4 (8.3 to NR) (5.6+ to 26.6+)† |
| Kaplan–Meier estimate at 12 mo — % | 64 |
| Kaplan–Meier estimate at 24 mo — % | 28 |
| Progression-free survival | |
| Median (95% CI) — mo | 22.3 (13.8 to NR) |
| Kaplan–Meier estimate at 12 mo — % | 66 |
| Kaplan–Meier estimate at 24 mo — % | 49 |
| Overall survival | |
| Median (95% CI) — mo | NR (NR to NR) |
| Kaplan–Meier estimate at 12 mo — % | 89 |
| Kaplan–Meier estimate at 24 mo — % | 76 |

* CI denotes confidence interval, and NR not reached.
† Plus sign indicates ongoing response.

cal functioning assessment showed that 20% of the participants had improvement, 58% had a stable status, and 17% had deterioration. As compared with baseline, global health status–quality of life and physical functioning were stable or improved in a majority of the participants (Table S1).

At week 73 (the prespecified main time point at which the analyses of quality of life were performed), the percentage of participants who had completed the quality-of-life questionnaires (calculated as the number of treated participants who completed at least one item divided by the number of treated participants who were included in the analyses of patient-reported outcomes) was 64%. The percentage who were adherent to completion of the questionnaires (calculated as the number of treated participants who completed at least one item divided by the number of eligible participants who had been expected to complete the questionnaires) was 94%. Further details are provided in the Supplementary Appendix. With the exception of cognitive functioning, the empirical mean changes in the EORTC QLQ-C30 functional-scale scores from baseline to week 73 were positive, which indicated a numerical improvement. The empirical mean changes from baseline to week 73 in the EORTC QLQ-C30 symptom-scale scores were negative, which appeared to suggest a decrease for most of the scales, including important tumor-related symptoms such as pain, constipation, and loss of appetite (Fig. S3 and Table S2). A numerical improvement from baseline to week 73 in the EQ-5D-5L VAS score was observed, with an empirical mean change of 4.11 (95% confidence interval [CI], –1.88 to 10.11).

The overall mean percentage change from baseline in body weight was 2% at week 3, 6% at week 45, 8% at week 113, and 12% at week 137. These results suggested a weight gain over the course of the trial.

### SAFETY

At the time of data cutoff, the median duration of treatment with belzutifan was 23.5 months (range, 0.3 to 37.0). Overall, 71 participants (99%) had treatment-related adverse events (Table 3). Treatment-related serious adverse events occurred in 8 participants (11%). Treatment-related adverse events of grade 3 occurred in 43% of the participants, and 3% of the participants had treatment-related adverse events of grade 4. The dose of belzutifan was reduced in 10 participants (14%); in 9 of these participants (12%) the dose was reduced owing to treatment-related adverse events. Two participants (3%) discontinued belzutifan owing to treatment-related adverse events (paraparesis and increase in alanine aminotransferase). No participants died owing to adverse events. The most common treatment-related adverse events were anemia (in 88% of the participants), fatigue (in 32%), dyspnea (in 21%), hypoxia (in 14%), asthenia (in 14%), nausea (in 13%), peripheral edema (in 13%), and headache (in 11%). Of note, 1 participant (1%) had hypertensive crisis, which was not considered to be related to belzutifan.

A summary of concomitant treatment for anemia is provided in Table S3; among the 69 participants with anemia, 26% received erythropoiesis-stimulating agents, 20% received blood transfusions, and 6% received both erythropoie-

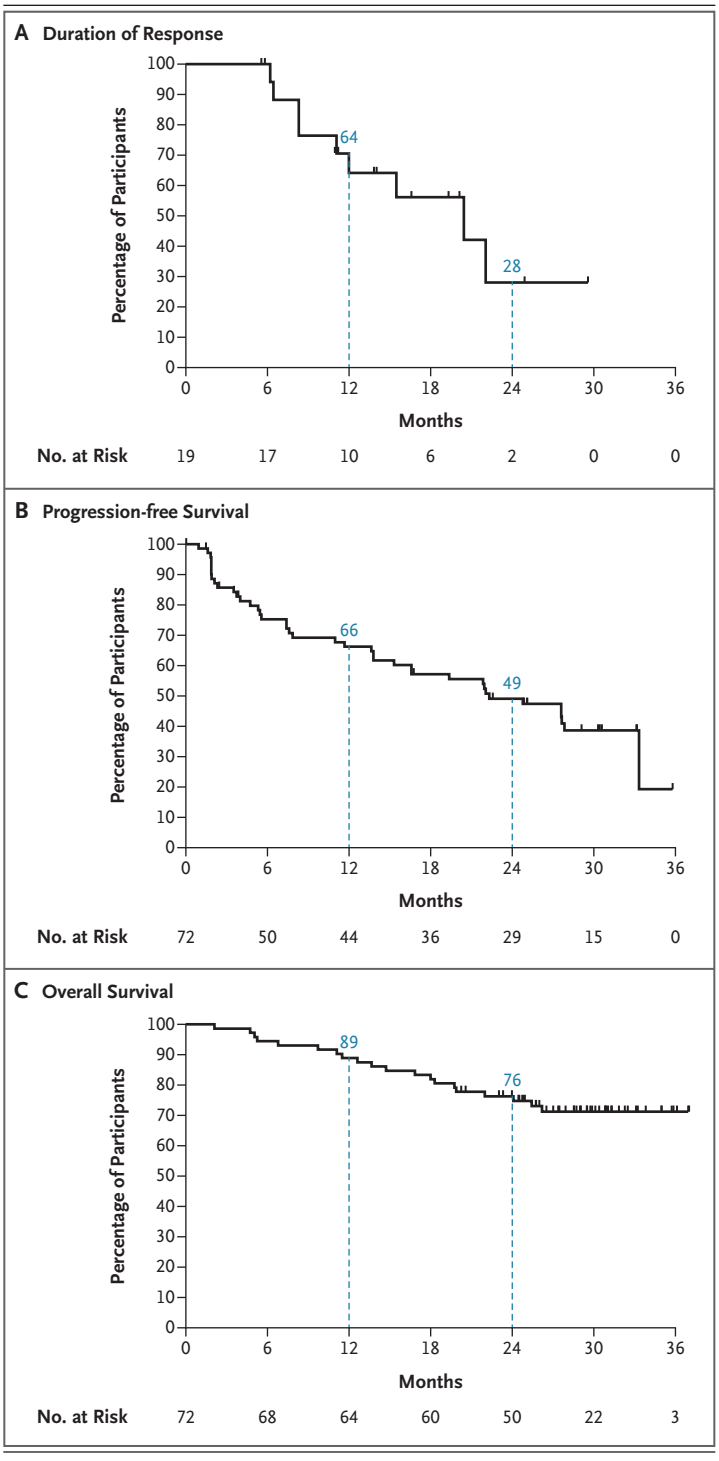


**Figure 2. Duration of Response, Progression-free Survival, and Overall Survival.**

Shown are Kaplan–Meier estimates of duration of response as assessed by blinded independent central review according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (Panel A); progression-free survival as assessed by blinded independent central review according to RECIST, version 1.1 (Panel B); and overall survival (Panel C). Tick marks indicate censored data.

sis-stimulating agents and blood transfusions. Hypoxia was resolved in 9 of 10 affected participants at the time of data cutoff and was readily manageable with standard care, including supplemental oxygen, which was used in 7 of the participants.

## DISCUSSION

Patients with pheochromocytoma or paraganglioma face substantial health challenges associated with tumor burden, cardiovascular complications related to hypertension, and gastrointestinal symptoms such as constipation due to catecholamine excess.[19,20] Treatment options for pheochromocytoma and paraganglioma are limited, primarily owing to the paucity of data from small-scale clinical trials, concerns about toxic effects, and the fact that benefits are short-term.[21-24]

HIF-2$\alpha$ has been identified as a key driver of metastatic pheochromocytoma and paraganglioma.[25] In the LITESPARK-015 trial, we assessed the efficacy of belzutifan, a selective HIF-2$\alpha$ inhibitor, for the treatment of pheochromocytoma and paraganglioma. The results showed an objective response of 26% among participants with advanced pheochromocytoma or paraganglioma. In addition, 58% of the participants had stable disease, resulting in an incidence of overall disease control of approximately 85%. Responses were durable, with a median duration of 20.4 months, and 64% of the participants with a response maintained their response for at least 12 months. The median duration of progression-free survival was 22.3 months, and the median overall survival was not reached.

The clinical benefit of belzutifan with respect to tumor-related symptoms was further supported by a sustained reduction in the total daily dose of antihypertensive medication; approximately one third of the participants who had been receiving treatment with antihypertensive medication had a reduction of at least 50% in the total daily dose of at least one blood-pressure medication for at least 6 months (including discontinuation of the

**Table 3. Treatment-Related Adverse Events.***

| Adverse Event | All Participants (N=72) | |
|---|---|---|
| | Any Grade | Grade 3 or 4 |
| | *no. (%)* | |
| Any | 71 (99) | 33 (46) |
| Led to discontinuation of belzutifan | 2 (3) | |
| Led to dose reduction of belzutifan | 9 (12) | |
| Reported in >10% of participants | | |
| Anemia | 63 (88) | 16 (22) |
| Fatigue | 23 (32) | 3 (4) |
| Dyspnea | 15 (21) | 0 |
| Hypoxia | 10 (14) | 7 (10) |
| Asthenia | 10 (14) | 0 |
| Nausea | 9 (12) | 1 (1) |
| Peripheral edema | 9 (12) | 0 |
| Headache | 8 (11) | 0 |

* No participant had an adverse event that led to death (grade 5).

medication). Of note, a reduction in antihypertensive medication was seen not only among participants with objective tumor responses but also among those with stable disease — a finding that indicates clinical benefit beyond tumor shrinkage and radiologic response. The incidence of hypertension or hypertensive crisis was generally low among participants who were receiving belzutifan; in contrast, these events are common with other agents such as tyrosine kinase inhibitors, which are associated with treatment-related increases in blood pressure that can exacerbate catecholamine-induced hypertension.[26]

The analyses of participant-reported end points indicated that health-related quality of life was maintained overall and that global health status–quality of life and physical functioning were stable or improved during treatment with belzutifan in a majority of the participants. The safety profile of belzutifan was consistent with that seen in previous trials; adverse events were manageable, and the incidence of dose reduction and treatment discontinuation was low.[15,27] Treatment-related adverse events of grade 3 or 4 occurred in 46% of the participants, most of whom had grade 3 events, and no grade 5 events were reported. No new safety concerns emerged.

Given the rarity of pheochromocytoma and paraganglioma and the limited therapeutic options, these findings represent a meaningful advancement. Currently, the only treatment approved by the FDA — high-specific-activity $^{131}$I-labeled metaiodobenzylguanidine — is restricted to tumors expressing the noradrenaline transporter, and production was recently discontinued.[8,28] Data from a previous study showed some efficacy with this agent, including partial responses and reductions in antihypertensive medications, but its availability was limited.[28]

Although not approved, some treatment alternatives for pheochromocytoma and paraganglioma include chemotherapy, peptide receptor radionuclide therapy, and tyrosine kinase inhibitors.[6] Tyrosine kinase inhibitors have shown responses of 13 to 36%, with disease control ranging from 69 to 94% and a median duration of response of 12.2 months reported in one trial.[21] However, given that serious cardiovascular events such as hypertension were common in that trial and others,[21,22,24,29] the use of tyrosine kinase inhibitors poses a challenge in the treatment of patients with pheochromocytoma or paraganglioma who have catecholamine-induced hypertension for which careful monitoring is warranted.

In the randomized FIRSTMAPPP (First International Randomized Study in Malignant Progressive Pheochromocytoma and Paragangliomas) trial,[21] the use of sunitinib was evaluated in patients with metastatic pheochromocytoma or paraganglioma. Although some benefit was observed, the enrollment period of almost 7 years underscores the difficulty of conducting large randomized, controlled trials in patients with this rare disease to advance novel therapies. The FIRSTMAPPP trial provided useful insights because the use of a placebo group in the trial added context in the absence of natural history studies in patients with pheochromocytoma or paraganglioma; an objective response occurred in 8% of the participants in the placebo group (1 participant [3%] had a response that was attributed to crossover to the sunitinib group). The most common adverse events of grade 3 in the sunitinib group were asthenia and hypertension, and overall, 44% of the participants had at least one dose reduction and 14% discontinued sunitinib or placebo.[21]

In the current trial, at least one response was noted in prespecified subgroups defined accord-

ing to age, sex, previous use of tyrosine kinase inhibitors, previous treatment with a radiopharmaceutical agent, number of previous lines of systemic therapy, and a reported history of *SDHB*-related tumor predisposition syndrome. Although the single-group design limits comparative conclusions and interpretation of time-to-event data (progression-free survival and overall survival), the totality of the data shows that belzutifan is clinically active and supports the potential use of belzutifan as a novel treatment option for patients with advanced pheochromocytoma or paraganglioma. Biomarker and genetic analyses are in progress. Ongoing trials of targeted agents and new combinations of treatment are limited in patients with advanced pheochromocytoma and paraganglioma; one such trial is a phase 2 trial (ClinicalTrials.gov number, NCT04394858) of the combination of olaparib with temozolomide.[30] Pheochromocytoma and paraganglioma remain challenging conditions to manage, but emerging targeted therapies such as belzutifan show promise for improving patient outcomes.

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