Belzutifan (MK-6482) for Von Hippel-Lindau Disease–Associated Renal Cell Carcinoma

Eric Jonasch M.D,[1] Frede Donskov M.D.,[2] Othon Iliopoulos M.D.,[3] W. Kimryn Rathmell M.D., Ph.D.,[4] Vivek K. Narayan M.D,[5] Benjamin L. Maughan M.D.,[6] Stephane Oudard M.D.,[7] Tobias Else M.D.,[8] Jodi K. Maranchie M.D.,[9] Sarah J. Welsh M.D.,[10] Sanjay Thamake Ph.D..,[11] Eric K. Park M.D.,[11] Rodolfo F. Perini M.D.,[11] W. Marston Linehan M.D.,[12] and Ramaprasad Srinivasan, M.D., Ph.D.[12]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Aarhus University Hospital, Aarhus, Denmark; [3]Massachusetts General Hospital Cancer Center and Harvard Medical School, Boston, MA, USA; [4]Vanderbilt University Medical Center, Nashville, TN, USA; [5]University of Pennsylvania, Philadelphia, PA, USA; [6]University of Utah, Salt Lake City, UT, USA; [7]Hôpital Européen Georges-Pompidou, University of Paris, Paris, France; [8]University of Michigan, Ann Arbor, MI, USA; [9]University of Pittsburgh, Pittsburgh, PA, USA; [10]Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; [11]Merck & Co., Inc., Kenilworth, NJ, USA; [12]Center for Cancer Research, National Cancer Institute, Bethesda, MD, USA

Corresponding author:

Ramaprasad Srinivasan, M.D., Ph.D.
Investigator and Head, Molecular Cancer Section
Center for Cancer Research
National Cancer Institute
Bldg 10, Room 2W-5940
10 Center Drive
Bethesda, MD 20892
Office: 240-760-6251

Parts of this paper were presented at ASCO 2020 (American Society of Clinical Oncology) Virtual Scientific Program; May 29-31, 2020 and ESMO 2020 (European Society of Medical Oncology) Virtual Congress; October 16-18, 2020

ABSTRACT

Background

Patients with von Hippel-Lindau (VHL) disease have a high lifetime incidence of renal cell carcinoma due to *VHL* gene inactivation and constitutive activation of the hypoxia-inducible factor transcription factor. No systemic agents are approved for VHL disease–associated renal cell carcinoma.

Methods

This open-label, single-arm, phase 2 study was conducted to investigate the efficacy and safety of the hypoxia-inducible factor 2α inhibitor belzutifan (MK-6482, previously PT2977), 120 mg orally daily, in patients with VHL disease–associated renal cell carcinoma. Primary endpoint was objective response rate per Response Evaluation Criteria in Solid Tumors, version 1.1, by independent central review. Non–renal cell carcinoma lesion response rates and safety were also assessed.

Results

As of June 1, 2020, with a median follow-up of 68.7 weeks (range, 18.3 to 104.7), 56 of 61 patients (92%) enrolled continued to receive belzutifan. Confirmed objective response rate was 36% (95% confidence interval, 24% to 49%) with a disease control rate of 98% (95% confidence interval, 93% to 100%). Responses were seen in patients with pancreatic lesions (39/61; 64%), and central nervous system hemangioblastomas (16/50; 32%). Eleven of 16 (69%) evaluable patients showed retinal hemangioblastoma improvement. The most common adverse events were anemia (90%) and fatigue (61%). Five patients discontinued treatment (patient decision [n=3], treatment-related adverse event [n=1; grade 1 dizziness], and death [n=1; acute fentanyl toxicity]).

Conclusions

Belzutifan was well tolerated and demonstrated promising activity in VHL disease–associated renal cell carcinoma and in non–renal tumors. (Funded by Merck & Co., Inc., Kenilworth, NJ, USA; ClinicalTrials.gov number, NCT03401788).

INTRODUCTION

Von Hippel-Lindau (VHL) disease is a rare autosomal dominant hereditary disorder caused by germline pathogenic variants in the *VHL* gene, affecting approximately one in every 27,300 to 39,000 live births.[1,2] The condition is associated with benign and malignant tumors, including clear cell renal cell carcinoma, pancreatic neuroendocrine tumors, and central nervous system and retinal hemangioblastomas.[1,2]

Approximately 70% of patients with VHL disease develop renal cell carcinoma during their lifetime.[3] Although clinical judgment is exercised in assessing risk-benefit for surgery, nephron-sparing surgery is recommended for tumors greater than or equal to 3 centimeters in diameter, or for those demonstrating rapid growth, to decrease the risk of metastatic disease.[1,4,5] Patients typically undergo several surgical procedures during their lifetime for resection of renal tumors as well as other VHL-associated tumors.[6] To help preserve renal function, early surgical intervention for tumors less than 3 centimeters in diameter is generally not recommended.[3] Systemic therapy could benefit patients with VHL disease-related renal cell carcinomas by preventing tumor growth beyond 3 centimeters in diameter, thereby reducing the need for surgery, and decreasing risk of consequent renal insufficiency and/or metastases. Systemic therapy could provide similar benefits for other VHL disease manifestations.

The VHL protein acts as an E3 ubiquitin ligase and ubiquitylates the α subunit of hypoxia-inducible factor (HIF) in an oxygen-dependent fashion, resulting in proteolysis of HIF.[7,8] Pathogenic *VHL* variants reduce VHL protein activity, resulting in stabilization of HIF subunits and the subsequent constitutive activation of HIF-mediated transcriptional pathways, independent of oxygen concentrations.[7] In particular, HIF-mediated transcription facilitates gene expression of vascular endothelial growth factor, cyclin D1, glucose transporter 1, and

erythropoietin. These factors normally function to counteract the effects of hypoxia by promoting vascularization, enhancing glucose utilization, and increasing red blood cell production through transcriptional signals.[7]

Constitutive activation of the HIF transcription factor is responsible for the hypervascularization in VHL disease-associated renal cell carcinoma.[1,7] Accordingly, vascular endothelial growth factor (VEGF)–targeted therapy has been evaluated in this disease setting.[5,8-13]
Preclinical data indicate that HIF-2α subunit antagonists, which block HIF pathway activation at its most proximal source, may have a greater inhibitory effect on tumor growth of clear cell renal cell carcinoma than VEGF-targeted therapies.[14,15] HIF-2α overexpression is ubiquitous in VHL disease-associated renal cell carcinoma and is associated with sensitivity to HIF-2α inhibitor therapy in xenograft models[14] Preliminary data from phase 1 studies of patients with advanced clear cell renal cell carcinoma indicate potential efficacy of HIF-2α blockade in patients with sporadic clear cell renal cell carcinoma.[14,16,17]

Belzutifan (MK-6482, previously PT2977) is a second-generation small molecule HIF-2α inhibitor, offering improved pharmacologic properties compared with the first-generation compound MK-3795 (PT2385), and has demonstrated efficacy and safety in a phase 1 study in patients with advanced clear cell renal cell carcinoma.[17,18] Given the role of VHL inactivation and the resulting HIF-2α activation in VHL disease–associated tumorigenesis, the objective of this study was to assess the efficacy and safety of belzutifan in patients with VHL disease–associated renal cell carcinoma.

METHODS

Patients

Eligible patients were aged ≥18 years with a diagnosis of VHL disease based on a germline *VHL* alteration and at least one measurable renal cell carcinoma tumor (at least 10 millimeters by computed tomography or magnetic resonance imaging) per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1), no renal cell carcinoma tumors greater than 3 centimeters necessitating immediate surgical intervention or evidence of metastatic disease, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Complete eligibility criteria are available in the protocol (see **Supplementary Material**).

Study Design and Treatment

This open-label, single-arm, phase 2 study (NCT03401788) enrolled patients from 11 centers in the United States, Denmark, France, and the United Kingdom between May 31, 2018, and March 29, 2019. Patients self-administered belzutifan 120 mg orally once daily (three 40-mg tablets) unless unacceptable treatment-related toxic effects or disease progression occurred. The primary objective was to evaluate the objective response rate (complete response + partial response) of VHL disease–associated renal cell carcinoma to belzutifan, per RECIST v1.1. Secondary end points were duration of response, time to response, disease control rate (complete response + partial response + stable disease), and renal cell carcinoma progression-free survival. The efficacy of belzutifan in treating VHL disease–associated non–renal cell carcinoma lesions (including retinal and central nervous system hemangioblastomas and pancreatic lesions [serious cystadenomas and pancreatic neuroendocrine tumors]), safety, and tolerability were also assessed as secondary endpoints.

Assessments

Safety endpoints were assessed throughout the study, including the recording of adverse events, laboratory parameters, vital signs, physical examinations, and electrocardiography. Adverse events were coded using Medical Dictionary for Regulatory Activities, version 23.0,

terminology. Severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Tumor imaging by computed tomography or magnetic resonance imaging was performed at baseline, within 7 days before the week 13 visit, and every 12 weeks thereafter for renal tumors. Tumor assessments of VHL disease-associated renal cell carcinoma target tumors were collected and evaluated by independent central radiology review at two or more times before screening imaging, when available, to understand growth kinetics before treatment. For non–renal cell carcinoma lesions, radiology imaging and ophthalmic evaluations (dilated fundus examination, color fundus photography, and best-corrected visual acuity measurement) were performed at baseline, and only performed during the study treatment period if there were documented lesions at baseline. Tumor assessments of solid lesions are described in the Supplement.

Statistical Analysis

The data cutoff date was June 1, 2020. The full statistical analysis plan is available in the supplemental material. A planned sample size of approximately 50 patients was expected to provide 80% power to detect a statistically significant difference (one-sided α=0.05) between an objective response rate of 30% versus the null hypothesis of an objective response rate of 15%. Confidence intervals for objective response rate were calculated using the two-sided Clopper-Pearson method.

Efficacy was assessed in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of belzutifan. Efficacy and safety outcomes were summarized descriptively.

Trial Oversight

This ongoing study is sponsored by Merck & Co., Inc., Kenilworth, NJ, USA, and was designed by sponsor representatives in collaboration with academic advisors. The protocol and its amendments were approved by the appropriate institutional review board or independent ethics committee at each center, and the trial was conducted per Good Clinical Practice guidelines and the declaration of Helsinki. All patients provided written informed consent. Data were collected by study investigators and site personnel. The authors and sponsor representatives were responsible for the analysis and interpretation of the data. All authors had access to the study data, reviewed and edited this manuscript, and approved the submitted draft. The authors vouch for the completeness and accuracy of the reported data, and attest that the trial was conducted per protocol. Medical writing and/or editorial assistance was provided by ApotheCom (Yardley, PA, USA) and funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

RESULTS

Patient Characteristics

In total, 61 patients were enrolled in this study. Median patient age was 41 years (range, 19 to 66), 32 (52%) were male, and 50 (82%) had an Eastern Cooperative Group performance status of 0 (Table 1). Fifty-nine (97%) patients had at least one prior tumor reduction procedure (e.g., partial nephrectomy, craniotomy, cryoablation). Forty-seven of 61 (77%) patients had procedures for renal tumors; 74% (45 of 61) had undergone a partial or radical nephrectomy. At baseline, patients had a median of 2.0 (range, 1.0 to 5.0) renal cell carcinoma target tumors, 1.0 (range, 1.0 to 3.0) pancreatic target lesions, and 1.5 (range, 1.0 to 5.0) central nervous system target hemangioblastomas. All patients had localized renal cell carcinoma and pancreatic lesions (20 [33%] had pancreatic neuroendocrine tumors), 50 (82%) had central nervous system

hemangioblastomas, and 16 (26%) had retinal hemangioblastomas that were evaluable by independent central review.

Efficacy in Renal Cell Carcinoma

As of June 1, 2020, the median follow up, defined as time from first dose to the date of death or database cutoff date, was 68.7 weeks (range, 18.3 to 104.7). Median exposure was 68.0 weeks (range, 8.4 to 104.7). Fifty-six patients (92%) remained on treatment with belzutifan with a minimum of 60 weeks follow-up

The objective response rate in renal cell carcinomas was 36% (22 of 61 patients) (95% confidence interval, 24% to 49%; all partial responses) (Table 2). An additional seven (11%) unconfirmed partial responses (documented at a single time point and pending confirmation at data cutoff) were also reported. The disease control rate was 98% (95% confidence interval, 91% to 100%). A reduction in the sum of all target lesion diameters was observed in 56 patients (92%) (Fig. 1A). Most patients had growing lesions prior to treatment, followed by an observed reduction in the sum of largest tumor diameters after treatment initiation (Fig. 1B). One-year progression-free survival was 98% (95% confidence interval, 89% to 100%). Median progression-free survival was not reached (Supplementary Fig. S1).

The linear growth rate for target tumors before treatment was calculated for patients who underwent at least three pretreatment imaging assessments, including the screening scan. Linear growth rate after treatment was calculated for patients with a screening and at least two imaging assessments on treatment. Fifty-seven patients met the pretreatment criteria, 58 met the on treatment criteria, and 54 met pretreatment and on treatment criteria. At the patient level, the median linear growth rate pretreatment was +3.6 millimeters per year (range, −3.4 to +33.1) versus −4.5 millimeters per year (range, −12.8 to +5.1) on treatment (Fig. 1B). Evaluable

patients with a partial response (n=22) had a median linear growth rate of +4.1 millimeters per year (range, −3.1 to +33.1) pretreatment versus −7.3 millimeters per year (range, −12.8 to −4.1) on treatment. For evaluable patients with stable disease, the median linear growth rate was +3.6 millimeters per year (range, −3.5 to +10.1) in 35 patients before treatment and was −2.7 millimeters per year (range, −10.0 to +5.1) in 36 patients on treatment.

At the lesion level, the median linear growth rate was +3.3 millimeters per year (range, −9.2 to +50.2) in 109 lesions before treatment and was −4.6 millimeters per year (range, −24.8 to +5.9) in 104 lesions during treatment.

Median time to response was 31.1 weeks (range, 11.6 to 61.0) (Fig. 1C), and median duration of response was not reached (range, 11.9 to 62.3 weeks) (Supplementary Fig. S2). All 22 partial responses were ongoing at data cutoff. Thirty-four (56%) patients were continuing treatment in the absence of a confirmed response, including all patients who had an unconfirmed partial response. As of the data cutoff, two patients required a tumor reduction procedure (partial nephrectomy [n=1] and cerebellar radiation [n=1]). No patient required pancreatic surgery, and one patient received a vitrectomy for retinal detachment, which was not considered related to active disease by study investigators. In contrast, the median number of procedures per year was 18 (range, 7-28) in the 10 years before treatment (Fig. 1D).

Efficacy in Non–Renal Cell Carcinoma Lesions

A confirmed response was observed in 39 of 61 patients (64%) with pancreatic lesions, which included 4 (7%) complete responses. This included 20 patients with a pancreatic neuroendocrine tumor, of whom 16 (80%) had a confirmed response (one complete response [5%]). In patients with central nervous system hemangioblastomas, 16 of 50 (32%) patients had a confirmed response (one complete response [2%]). Median time to response was 35.0 weeks (range, 10.7 to 59.7) for all pancreatic lesions, 23.9 weeks (range, 10.7 to 47.7) for pancreatic

neuroendocrine tumors, and 13.2 weeks (range, 9.9 to 59.6) for central nervous system hemangioblastomas. Median duration of response was not reached (range, 11.1+ to 71.0+) in patients with pancreatic lesions, not reached (range, 12.3+ to 71.0+ weeks) in patients with pancreatic neuroendocrine tumors, and not reached (range, 11.6+ to 72.4+ weeks) in patients with central nervous system hemangioblastomas. Of 16 patients with evaluable retinal hemangioblastomas at baseline, 11 (69%) showed improvement per independent review committee. In those 16 patients, 29 eyes were followed for retinal hemangioblastomas: 16 (55%) showed improvement, 12 (41%) remained stable, and one (3.4%) was not evaluated.

Safety

All 61 patients reported at least one adverse event. Treatment-related adverse events were reported by 60 patients (98%). The most common all-cause adverse events were anemia, fatigue, headache, and dizziness (Table 3). Dosing was interrupted for 44 patients (72%). Dose was reduced in eight patients (13%) because of adverse events. Five patients discontinued treatment (n=3 patient decision, n=1 treatment-related adverse event [grade 1 dizziness], n=1 death due to acute fentanyl toxicity). The median duration of treatment for these five patients was 16.4 weeks (range, 3.4 to 55.7).

Adverse events were generally mild or moderate. All-cause grade 3 to 5 adverse events were reported in 15 patients (25%). Grade 3 events were considered treatment-related in eight patients (13%). Only one grade 4 adverse event occurred (2%; retinal detachment) and was considered unrelated to treatment. No patients died of a treatment-related adverse event. One death (acute fentanyl toxic effects) was considered unrelated to the study drug.

All patients experienced a decrease of at least 1.9 grams per deciliter in hemoglobin levels during the first 13 weeks of treatment before stabilization (Fig. 2). Four patients (7%) received blood transfusions because of a grade 3 hemoglobin level decrease. Nine patients (15%)

received exogenous erythropoietin; three of these patients (5%) received a blood transfusion and exogenous erythropoietin. One patient (2%) had grade 3 transient hypoxia, which was resolved with dose interruption for 1 week followed by dose reduction to 80 mg. This patient did not require supplemental oxygen or other treatment.

DISCUSSION

VHL-associated tumors are currently managed with surgical resection or ablation, with the intent of reducing the risk of metastatic disease and/or controlling local or systemic sequelae. Since patients with VHL disease are at lifelong risk for developing tumors in affected organs, most of them undergo several surgical procedures in their lifetime, with considerable attendant morbidity. An effective systemic alternative might reduce the surgical burden in patients with VHL disease and represents a novel approach to the management of organ confined, VHL-associated tumors.

Belzutifan is a novel pharmacologic agent targeting HIF-2α. In this study, belzutifan was active against renal cell carcinomas in patients with VHL disease, with a confirmed objective response rate of 36%, with an additional seven patients demonstrating a partial response that is yet to be confirmed; most patients experienced a reduction in renal tumor size. These data indicate that belzutifan is an active treatment for patients with VHL disease associated renal cell carcinoma.

Extrarenal manifestations are also associated with substantial morbidity and mortality in patients with VHL disease,[6] and effective systemic therapy could decrease the frequency of surgical intervention for these lesions. In this study, 30% of patients with central nervous system hemangioblastomas demonstrated response after treatment with belzutifan, as did 80% of patients with pancreatic neuroendocrine tumors, indicating clear signs of activity in these VHL disease manifestations. Since tumor size is a primary determinant of the need for surgical intervention, reductions in tumor size will likely result in fewer indications for surgery. As

observed in this study, patients often required multiple surgical/ablative procedures prior to treatment with belzutifan. Following treatment initiation, only two patients required an antitumor procedure for a VHL-associated tumor. Belzutifan may therefore serve an integral role in the management of patients with VHL disease by functioning to delay or obviate the need for serial surgeries that are associated with significant morbidity.

The safety and tolerability profile of belzutifan was favorable: only one patient (2%) discontinued treatment because of a treatment-related adverse event (dizziness). Adverse events were consistent with expectations for a HIF-2α inhibitor given the integral role of HIF-2α in erythropoietin production and erythropoiesis.[19-21] Anemia, considered an on-target effect of HIF-2α inhibition, was the most common adverse event, but the number of patients requiring transfusion or growth factor support was low. Hemoglobin levels also stabilized, typically without intervention, after an initial decrease. Hypoxia has previously been reported in patients with advanced renal cell carcinoma who received belzutifan[17]; however, in the current study, only one transient hypoxia event was reported.

Compared with antiangiogenic agents, which are associated with cardiovascular adverse events, hematologic disturbances, hepatotoxicity, diarrhea, and metabolic disturbances, HIF-2α inhibition may offer a more favorable safety profile.[9,10,12] Studies evaluating the tyrosine kinase inhibitors dovitinib (n=6)[11] and sunitinib (n=15 and n=5)[12,13] in patients with VHL disease showed modest efficacy at best and were limited by treatment-related toxic effects and a low number of patients enrolled. Results of a phase 2 study of pazopanib in patients with VHL disease showed an objective response rate of 42% (13/31; all partial responses) across kidney, pancreas, and central nervous system lesions, but 23% (7/31) of patients discontinued because of adverse events, including four patients who experienced grade 3 to 4 increases in liver transaminase levels.[10] Furthermore, only ten of 31 (32%) patients who received pazopanib were able to tolerate a full dose of 800 mg, and 16 patients (52%) remained on treatment after 24 weeks. In

comparison, 56 of 61 (92%) patients in this study remained on treatment at the time of data cutoff, and most patients (87%; 53 of 61) did not require a dose reduction because of adverse events.

The interpretation of outcomes in this study is limited by the lack of a comparator group and a modest sample size; however, this study is the largest in this rare patient population. Furthermore, there is currently no effective non-surgical treatment for VHL disease, which poses ethical challenges for a randomized control trial. The observation that patients receiving treatment with belzutifan required fewer interventions compared with the number of interventions needed before treatment suggests the potential for clinical benefit, though additional follow up is required to determine long-term outcomes for patients with VHL disease–associated renal cell carcinoma and other disease manifestations.

In conclusion, belzutifan has a favorable safety profile and has demonstrated activity in patients with VHL disease–associated renal cell carcinoma, pancreatic neuroendocrine tumors, and hemangioblastomas by targeting the underlying pathophysiology of the disease.

ACKNOWLEDGMENTS

Medical writing and/or editorial assistance was provided by Robert Steger, PhD, and Matthew Grzywacz, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme Corp., a wholly owned subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Funding for this research was provided by Merck & Co., Inc., Kenilworth, NJ, USA.

DISCLOSURES

Frede Donskov has received grants from Pfizer, Ipsen, and Merck & Co., Inc.

Tobias Else has received funding for an institutional contracted study.

Benjamin Maughan has received research funding from Bristol-Myers Squibb, Clovis, Exelixis, and Bavarian-Nordic and participated in advisory boards for Peloton Therapeutics, Inc., a wholly owned subsidiary of Merck & Co., Inc., Janssen, Astellas, Bristol-Myers Squibb, Clovis, Tempus, Merck & Co., Inc., Bayer, and Exelixis, and has received personal fees from Foundation Medicine.

Vivek Narayan has received research funding from Merck & Co., Inc., Pfizer, Bristol-Myers Squibb, GlaxoSmithKline, and Janssen and has received personal fees from Pfizer, AstraZeneca, EMD Serono, Modra Pharmaceuticals, and Janssen.

Eric Park is an employee of and has stock ownership in Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

Stephane Oudard has received honoraria from Astellas, Bayer, Bristol-Myers Squibb, Eisai, Ipsen, Janssen, Merck & Co., Inc., Novartis, Pfizer, Roche/Genentech, Sanofi; has been a consultant to Astellas, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eisai, Ipsen, Janssen, Merck & Co., Inc., SD Oncology, Novartis, Pfizer, Roche, and Sanofi; has received research funding from Ipsen and Sanofi; and has received travel, accommodations, and expenses from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Eisai, Merck & Co., Inc., MSD Oncology, Novartis, and Roche.

W. Kimryn Rathmell has received research funding from Incyte, Calithera, Pfizer, Bristol-Myers Squib, and Peloton Therapeutics, Inc., a wholly owned subsidiary of Merck & Co., Inc.

Sanjay Thamake is an employee of and has stock ownership in Peloton Therapeutics, Inc., a wholly owned subsidiary of Merck & Co., Inc.

Ramaprasad Srinivasan is a federal government employee working in the National Cancer Institute, has received funding from Peloton Therapeutics, Inc., a wholly owned subsidiary of

Merck & Co., Inc and Calithera Biosciences to partly defray the costs of clinical trial conduct provided to my institution via a CRADA.

Rodolfo F. Perini is an employee of and has stock ownership in Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

Eric Jonasch has received research funding from Merck & Co., Inc., Pfizer, Novartis and Exelixis and personal fees from Merck & Co., Inc., Eisai, Pfizer, and Novartis, and Ipsen.

W Marston Linehan, Sara Welsh, Jodi Maranchie, and Othon Iliopoulos have no relationships to disclose.

Author Contributions

Frede Donskov contributed to the acquisition of data and interpretation of results, provision of study patients, drafting and revising of the manuscript, and provided final approval to submit the manuscript for publication.

Tobias Else contributed to the acquisition of the data, provision of study patients, drafting and revising of the manuscript, and provided final approval to submit the manuscript for publication.

W. Marston Linehan has contributed to the conception and design of the study, acquisition and analysis of data, interpretation of the results, provision of study patients, drafting and revising of the manuscript, and provided final approval to submit the manuscript for publication.

Benjamin Maughan contributed to the analysis and acquisition of the data, interpretation of the results, drafting and revising of the manuscript, and provided final approval to submit the manuscript for publication.

Vivek Narayan contributed to the analysis and acquisition of the data, interpretation of the results, drafting and revising of the manuscript, and provided final approval to submit the manuscript for publication.

Eric Park contributed to the conception and design of the study, acquisition and analysis of data, interpretation of the results, drafting and revising of the manuscript, and provided final approval to submit the manuscript for publication.

Sarah Welsh contributed to the interpretation of results, drafting and revising of the manuscript, and provided final approval to submit the manuscript for publication.

Jodi Maranchie contributed to the acquisition of data, drafting and revising of the manuscript, and provided final approval to submit the manuscript for publication.

W. Kimryn Rathmell contributed to the conception and design of the study, acquisition of the data and interpretation of the results, drafting and revising of the manuscript, and provided final approval to submit the manuscript for publication.

Othon Iliopoulos contributed to the acquisition of the data and interpretation of the results, drafting and revising of the manuscript, and provided final approval to submit the manuscript for publication.

Stephane Oudard contributed to the acquisition of the data and interpretation of the results, drafting and revising of the manuscript, and provided final approval to submit the manuscript for publication.

Sanjay Thamake contributed to the conception of the study design, acquisition of the data and interpretation of the results, drafting and revising of the manuscript, and provided final approval to submit the manuscript for publication.

Rodolfo F. Perini contributed to the conception of the study design and data interpretation, drafting and revising of the manuscript, and provided final approval to submit the manuscript for publication.

Ramaprasad Srinivasan contributed to the conception and design of the study, acquisition and analysis of data, interpretation of the results, provision of study patients, study funding, drafting and revising of the manuscript, and provided final approval to submit the manuscript for publication.

Eric Jonasch has contributed to the conception and design of the study, acquisition and analysis of data, interpretation of the results, provision of study patients, drafting and revising of the manuscript, and provided final approval to submit the manuscript for publication.

Data Sharing Statement

Merck Sharp & Dohme Corp. (MSD), a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA is committed to providing qualified scientific researchers access to anonymized patient-level data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. The company is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The process includes submission of data requests to the MSD data-sharing website (http://engagezone.msd.com/ds_documentation.php). Data will be made available for request after product approval in the United States and European Union or after product development is discontinued. There are circumstances that may prevent MSD from sharing the requested data.

REFERENCES

1. Couch V, Lindor NM, Karnes PS, Michels VV. von Hippel-Lindau disease. Mayo Clin Proc 2000;75:265-72.

2. Binderup ML, Galanakis M, Budtz-Jørgensen E, Kosteljanetz M, Luise Bisgaard M. Prevalence, birth incidence, and penetrance of von Hippel-Lindau disease (vHL) in Denmark. Eur J Hum Genet 2017;25:301-7.

3. Maher ER, Neumann HP, Richard S. von Hippel-Lindau disease: a clinical and scientific review. European journal of human genetics : EJHG 2011;19:617-23.

4. Schmid S, Gillessen S, Binet I, et al. Management of von hippel-lindau disease: an interdisciplinary review. Oncol Res Treat 2014;37:761-71.

5. Kim E, Zschiedrich S. Renal Cell Carcinoma in von Hippel-Lindau Disease-From Tumor Genetics to Novel Therapeutic Strategies. Front Pediatr 2018;6:16.

6. Binderup ML, Jensen AM, Budtz-Jørgensen E, Bisgaard ML. Survival and causes of death in patients with von Hippel-Lindau disease. J Med Genet 2017;54:11-8.

7. Haase VH. The VHL tumor suppressor: master regulator of HIF. Curr Pharm Des 2009;15:3895-903.

8. Meléndez-Rodríguez F, Roche O, Sanchez-Prieto R, Aragones J. Hypoxia-Inducible Factor 2-Dependent Pathways Driving Von Hippel-Lindau-Deficient Renal Cancer. Front Oncol 2018;8:214.

9. NCCN Clinical Practice Guidelines in Oncology. Kidney cancer. Version 2.2020. (Accessed June 23, 2020, at https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf.)

10. Jonasch E, McCutcheon IE, Gombos DS, et al. Pazopanib in patients with von Hippel-Lindau disease: a single-arm, single-centre, phase 2 trial. Lancet Oncol 2018;19:1351-9.

11. Pilié P, Hasanov E, Matin SF, et al. Pilot study of dovitinib in patients with von Hippel-Lindau disease. Oncotarget 2018;9:23390-5.

12. Jonasch E, McCutcheon IE, Waguespack SG, et al. Pilot trial of sunitinib therapy in patients with von Hippel-Lindau disease. Ann Oncol 2011;22:2661-6.

13. Oudard S, Elaidi R, Brizard M, et al. Sunitinib for the treatment of benign and malignant neoplasms from von Hippel-Lindau disease: A single-arm, prospective phase II clinical study from the PREDIR group. Oncotarget 2016;7:85306-17.

14. Chen W, Hill H, Christie A, et al. Targeting renal cell carcinoma with a HIF-2 antagonist. Nature 2016;539:112-7.

15. Cho H, Du X, Rizzi JP, Liberzon E, et al. On-target efficacy of a HIF-2α antagonist in preclinical kidney cancer models. Nature. 2016;539(7627):107-11.

16. Courtney KD, Infante JR, Lam ET, et al. Phase I Dose-Escalation Trial of PT2385, a First-in-Class Hypoxia-Inducible Factor-2alpha Antagonist in Patients With Previously Treated Advanced Clear Cell Renal Cell Carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2018;36:867-74.

17. Choueiri TK, Plimack ER, Bauer TM, et al. Phase I/II study of the oral HIF-2 α inhibitor MK-6482 in patients with advanced clear cell renal cell carcinoma (RCC). J Clin Oncol 2020;38 (no. 6_suppl):611.

18. Courtney KD, Ma Y, Diaz de Leon A, et al. HIF-2 Complex Dissociation, Target Inhibition, and Acquired Resistance with PT2385, a First-in-Class HIF-2 Inhibitor, in Patients with Clear Cell Renal Cell Carcinoma. Clin Cancer Res 2020;26:793-803.

19. Rankin EB, Biju MP, Liu Q, et al. Hypoxia-inducible factor-2 (HIF-2) regulates hepatic erythropoietin in vivo. J Clin Invest 2007;117:1068-77.

20. Scortegagna M, Ding K, Zhang Q, et al. HIF-2alpha regulates murine hematopoietic development in an erythropoietin-dependent manner. Blood 2005;105:3133-40.

21. Semenza GL. Pharmacologic Targeting of Hypoxia-Inducible Factors. Annu Rev Pharmacol Toxicol 2019;59:379-403.

Table 1. Baseline Demographics and Disease Characteristics in the Safety Population.

Characteristic	All Patients (N=61)
Age, median (range) — yr	41 (19–66)
Age at time of VHL diagnosis, median (range) — yr	33 (4–66)
Age at time of VHL-associated renal cell carcinoma diagnosis, median (range) — yr	31 (16-62)
Sex — no. (%)	
Male	32 (52)
Female	29 (48)
Eastern Cooperative Oncology Group performance status — no. (%)	
0	50 (82)
1	10 (16)
2*	1 (2)
Von Hippel-Lindau disease subtype† — no. (%)	
Type 1	51 (84)
Type 2A	2 (3)
Type 2B	6 (10)
Type 2C	0
Missing	2 (3)
Prior surgery or ablative procedure — no. (%)	59 (97)
Renal cell carcinoma	47 (77)
Partial or radical nephrectomy‡	45 (74)
Ablative procedures§	19 (31)

Central nervous system surgery	47 (77)
Pancreas-related surgery	9 (15)
Number of prior procedures per patient	
0 procedures	2 (3)
1 procedure	5 (8)
2 procedures	5 (8)
3 procedures	9 (15)
≥4 procedures	40 (66)
median (range)	5 (0-15)
Non–renal cell carcinoma tumor type[‖] — no. (%)	
Pancreatic lesions[¶]	61 (100)
Pancreatic neuroendocrine tumors	20 (33)
Central nervous system hemangioblastomas	50 (82)
Retinal hemangioblastomas	16 (26)
Size of target lesions, median (range) — mm	
Renal cell carcinomas	22 (10-61)
Pancreatic lesions[¶]	19 (10-89)
Pancreatic neuroendocrine tumors	20 (10-41)
Central nervous system hemangioblastoma	16 (10-87)

[*]A waiver was requested by the investigator and approved by the institutional review board before enrollment of the patient with an Eastern Cooperative Oncology Group performance status of 2.

[†]Type 1 disease presents with retinal and central nervous system hemangioblastomas, renal cell carcinoma, pancreatic cysts, and neuroendocrine tumors and decreased risk of pheochromocytomas; Type 2A disease presents with pheochromocytomas, retinal and central

nervous system hemangioblastomas and a decreased risk of renal cell carcinoma; Type 2B disease presents with renal cell carcinoma, pheochromocytomas, and retinal and central nervous system hemangioblastomas; Type 2C disease presents with pheochromocytomas only.[3]

‡Partial or radical nephrectomy also includes renal surgery and renal tumor excision

§Ablative procedures include cryotherapy and kidney ablation.

|As evaluable by independent central review.

¶Pancreatic neuroendocrine tumors and serous cystadenomas.

Table 2. Best Objective Response per RECIST v1.1 of von Hippel-Lindau–Associated Renal Cell Carcinoma in the Efficacy Population.

	Efficacy Population (N=61)
Objective response	
No. of patients	22
% (95% CI)	36 (24-49)
Best response — no. (%)	
Complete response	0
Partial response	22 (36)
Stable disease[*]	38 (62)
Disease progression	0
Not evaluable[†]	1 (2)
Median time to response (range) – wk	31.1 (11.6-61.0)
Median duration of response (range) – wk	NR (11.9-62.3)

[*]Includes seven patients (11%) with unconfirmed partial response documented at a single time point that had not been confirmed before the data cutoff date of June 1, 2020.

[†]One patient discontinued the study before the first postbaseline tumor assessment.

NR denotes not reached, and RECIST v1.1 Response Evaluation Criteria in Solid Tumors, version 1.1.

Table 3. Incidence of All-Cause Adverse Events ≥5% in the Safety Population.

Adverse Event — no. (%)			**Safety Population (N=61)**	
Any-grade adverse event			61 (100)	
Any-grade treatment-related adverse event			60 (98)	
Grade 3 to 5 adverse event			15 (25)	
Grade 3 treatment-related adverse event			8 (13)	
Grade 4 or 5 treatment-related adverse event			0	
Treatment discontinuation due to an adverse event			2 (3)*	
Treatment discontinuation due to a treatment-related adverse event			1 (2)	
Deaths			1 (2)†	
Deaths due to a treatment-related adverse event			0	
All-cause adverse events in ≥5% of patients — no. (%)	**Any Grade**	**Grade 1**	**Grade 2**	**Grade 3‡**
Anemia	55 (90)	25 (41)	26 (43)	4 (7)
Fatigue	37 (61)	26 (43)	8 (13)	3 (5)
Headache	23 (38)	19 (31)	4 (7)	0
Dizziness	22 (36)	19 (31)	3 (5)	0

Nausea	19 (31)	14 (23)	5 (8)	0
Dyspnea	12 (20)	11 (18)	0	1 (2)
Arthralgia	11 (18)	10 (16)	1 (2)	0
Upper respiratory tract infection	11 (18)	4 (7)	7 (11)	0
Alanine aminotransferase increased	10 (16)	10 (16)	0	0
Myalgia	10 (16)	10 (16)	0	0
Vision blurred	9 (15)	5 (8)	4 (7)	0
Constipation	8 (13)	7 (11)	1 (2)	0
Hypertension	8 (13)	3 (5)	3 (5)	2 (3)
Abdominal pain	7 (11)	5 (8)	2 (3)	0
Aspartate aminotransferase increased	7 (11)	7 (11)	0	0
Weight increased	7 (11)	5 (8)	1 (2)	1 (2)
Muscle spasms	6 (10)	4 (7)	2 (3)	0
Edema peripheral	6 (10)	5 (8)	1 (2)	0
Palpitations	6 (10)	5 (8)	1 (2)	0
Vomiting	6 (10)	5 (8)	1 (2)	0
Back pain	5 (8)	3 (5)	2 (3)	0

Blood creatinine increased	5 (8)	5 (8)	0	0
Diarrhea	5 (8)	5 (8)	0	0
Disturbance in attention	5 (8)	4 (7)	1 (2)	0
Dry mouth	5 (8)	4 (7)	1 (2)	0
Dyspepsia	5 (8)	3 (5)	2 (3)	0
Urinary tract infection	5 (8)	0	5 (8)	0
Dry skin	4 (7)	4 (7)	0	0
Eye pain	4 (7)	4 (7)	0	0
Flank pain	4 (7)	3 (5)	1 (2)	0
Gastroesophageal reflux disease	4 (7)	3 (5)	1 (2)	0
Hot flush	4 (7)	4 (7)	0	0
Hypokalemia	4 (7)	2 (3)	2 (3)	0
Influenza-like illness	4 (7)	3 (5)	1 (2)	0
Pain in extremity	4 (7)	4 (7)	0	0
Visual impairment	4 (7)	4 (7)	0	0
Chest discomfort	3 (5)	3 (5)	0	0
Cough	3 (5)	3 (5)	0	0
Decreased appetite	3 (5)	3 (5)	0	0

Insomnia	3 (5)	1 (2)	2 (3)	0
Micturition urgency	3 (5)	3 (5)	0	0
Nasal congestion	3 (5)	3 (5)	0	0
Neck pain	3 (5)	3 (5)	0	0
Otitis media	3 (5)	2 (3)	1 (2)	0
Paraesthesia	3 (5)	2 (3)	1 (2)	0
Pollakiuria	3 (5)	3 (5)	0	0
Pruritus	3 (5)	2 (3)	1 (2)	0
Upper airway cough syndrome	3 (5)	2 (3)	1 (2)	0
Weight decreased	3 (5)	3 (5)	0	0
White blood cell count decreased	3 (5)	3 (5)	0	0

*Patient death recorded as an adverse event.

†Death caused by acute fentanyl toxic effects.

‡One patient reported asymptomatic grade 3 hypoxia that did not require treatment.