What's Next for the Treatment of ccRCC? HIF-2alpha Inhibitors: Angiogenesis, Tumorigenesis, and Emerging Agents

Supported by an educational grant from Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

Xin Gao, MD

Assistant Professor of Medicine, Harvard Medical School

Genitourinary Cancers Program

Developmental Therapeutics/Phase 1 Investigational Program

Massachusetts General Hospital Cancer Center

Boston, MA

Eric Jonasch, MD

Professor of Genitourinary Medical Oncology

Division of Cancer Medicine

The University of Texas MD Anderson Cancer Center

Houston, TX

CME OUTFITTERS

Learning Objective 1

Recognize the function of critical components of the VHL-HIF-2α-VEGF axis regulating angiogenesis in cancer

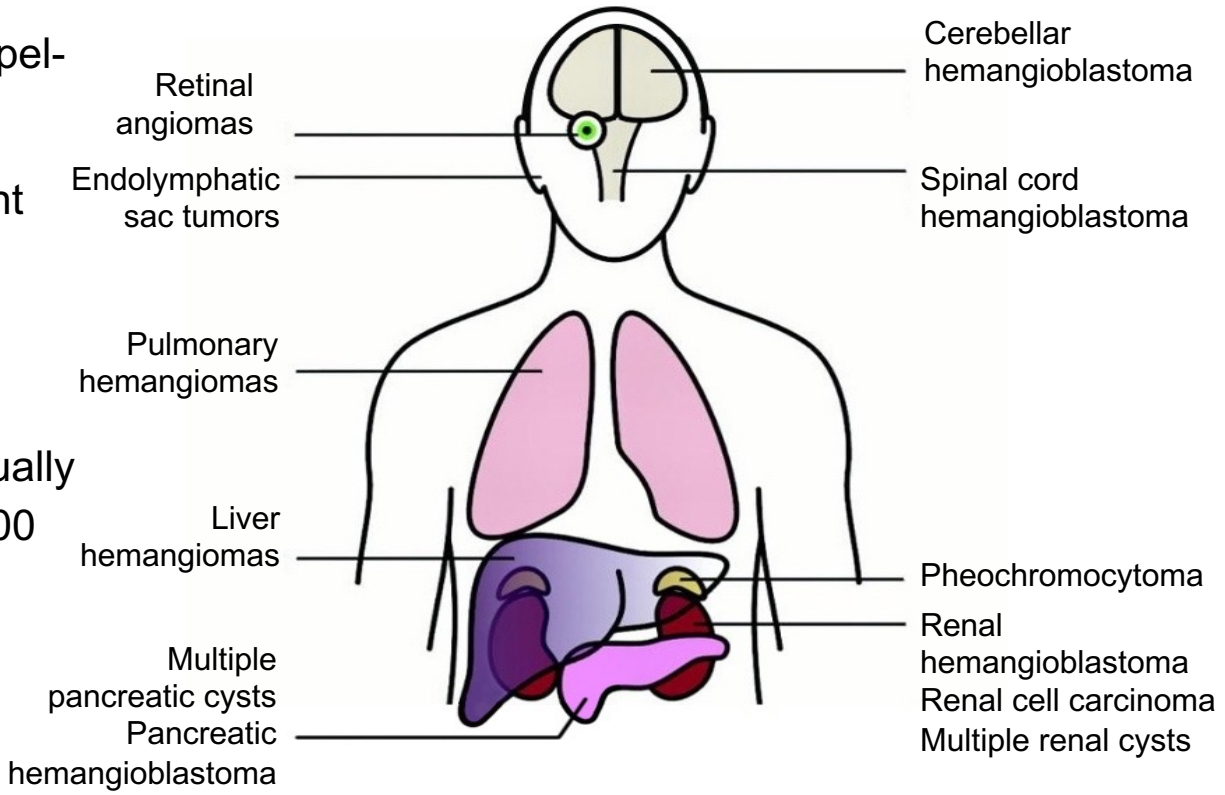
CME OUTFITTERS

Learning Objective 2

Identify the potential value of HIF-2α inhibitors in the treatment of ccRCC

VHL Disease Manifestations, Prognosis, and Standards of Care

- Autosomal dominant disease associated with loss of Von Hippel-Lindau (VHL) protein function
- Characterized by the growth of cysts and/or benign or malignant tumors in multiple organs
- Hemangioblastomas occur in ~ 50% of patients
- Average age of onset: 26 years
- Males and females affected equally
- Prevalence: 1/30,000 to 1/50,000 (6,000-7,000 patients in United States)
- Renal cell carcinoma (RCC) occurs in 40% to 70% of patients

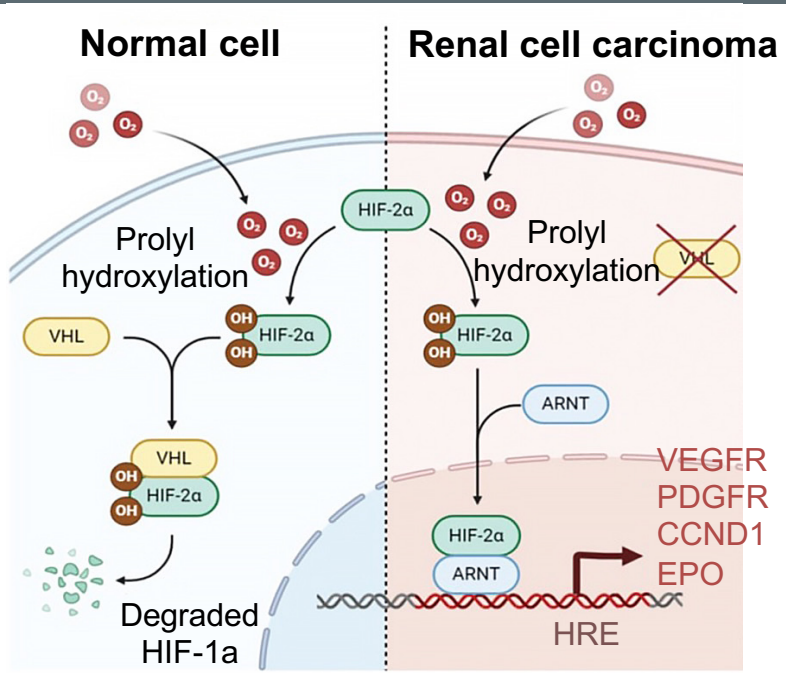


1. Mikhail M, Sing A. StatPearls. 2021. https://www.statpearls.com/ArticleLibrary/viewarticle/31268. Accessed October 27, 2021.

CME OUTFITTERS

VHL/HIF Axis Aberrations Drive Cellular and Microenvironmental Changes

- Loss/inactivation of tumor suppressor *VHL* results in VHL disease[1]
  - Hallmark of ccRCC, occurring in > 90% of cases
- VHL is substrate recognition component of E3 ligase complex that ubiquitylates hypoxia-inducible factors (HIF)-1α and HIF-2α[1]
- Loss of *VHL* results in aberrant HIF signaling, despite adequate oxygenated tissue microenvironment, leading to activation of HIF targets that regulate angiogenesis, glycolysis, and apoptosis[1]
- Response rates low with current VHL renal cancer therapy
  - Sunitinib: 33% PR, 56% SD[2]
    - 0% response rate in hemangioblastomas
  - Pazopanib: 3% CR, 49% PR[3]
    - 4% response rate in hemangioblastomas



Treatment options for VHL syndrome-associated RCC are limited

ARNT = Aryl Hydrocarbon receptor-nuclear translocator. CCND1 = Cyclin D1. ccRCC = Clear cell renal cell carcinoma. CR = Complete response. EPO = Erythropoietin. HRE = Hypoxia response element. O_2 = Oxygen. OH = Hydroxide. PDGFR = Platelet-derived growth factor. PR = Partial response. SD = Stable disease. VEGFR = Vascular endothelial growth factor receptor.

1. Hasanov E, Jonasch E. *Expert Opin Investig Drugs*. 2021;30(5):495-504. 2. Jonasch E, et al. *Ann Oncol*. 2011;22(12):2661-2666.
3. Jonasch E, et al. *Lancet Oncol*. 2018;19(10):1351-1359.

CME OUTFITTERS

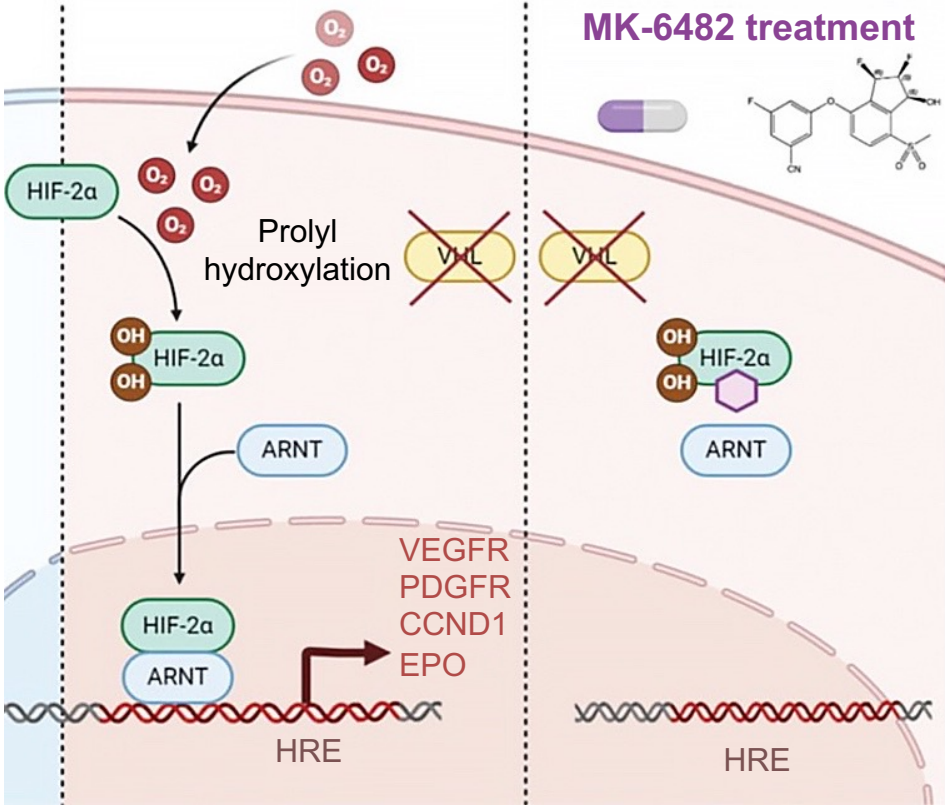
Case Study 1

- 35-year-old woman
- Family history VHL disease
- Creatinine: 1.6 mg/dL
- Established retinal hemangioblastomas, small pancreatic neuroendocrine tumor, multifocal RCC with the largest measurement of 2.5 cm
- Prior surgery for RCC
- Comes to find out about non-surgical options

cm = Centimeters. mg/dL – milligrams per deciliter.

Belzutifan Mechanism of Action

- MK-6482 (belzutifan)
  - Small molecule, second generation inhibitor of HIF2α and HIF1β/ARNT dimerization[1]
  - PT2385 was first-generation HIF2α inhibitor
  - PT2385 provided an ORR of 14%, but suffered from excessive glucuronidation metabolism[2]
- Belzutifan more potently inhibits VEGFA secretion, in vitro: EC_{50} = 13 ng/mL (vs. 95 ng/mL, PT2385)[3]
  - Reduced lipophilicity
  - Reduced binding to plasma protein



EC_{50} = Half maximal effective concentrations. ng/mL = Nanograms per milliliter. ORR = Overall response rate. VEGFA = Vascular endothelial growth factor A.

1. Hasanov E, Jonasch E. *Expert Opin Investig Drugs.* 2021;30(5):495-504. 2. Courtney KD, et al. *J Clin Oncol.* 2018;36(9):867-874. 3. Xu R, et al. *J Med Chem.* 2019;62(15):6876-6893.

CME OUTFITTERS

MK-6482-004: Study Design

Key Eligibility Criteria (N = 61)

- Age ≥ 18 years
- **Diagnosis of VHL disease based on germline alteration**
- ≥ 1 measurable RCC tumor
- No prior systemic anticancer therapy
- No metastatic disease
- ECOG PS 0-1

Belzutifan 120 mg PO QD

Tumor evaluation performed at screening and Q12W thereafter

Primary End Point

- ORR in VHL-associated RCC tumors per RECIST v1.1 by IRC

Secondary End Points

- ORR in non-RCC neoplasms
- DoR in RCC and non-RCC neoplasms
- Safety

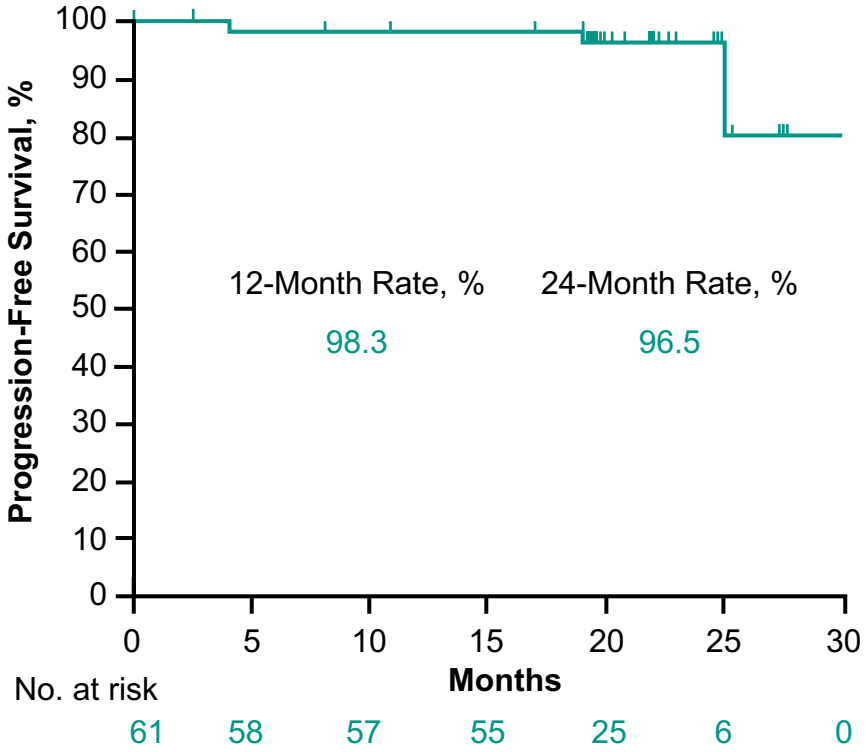
DoR = Duration of response. ECOG PS = Eastern Cooperative Oncology Group performance status. IRC = Independent review committee. mg = Milligrams. PO = Orally. Q12W = Every 12 weeks. QD = Once a day. RECIST v1.1 = Response evaluation criteria in solid tumours version 1.1.
Srinivasan R, et al. *J Clin Oncol*. 2021;39(15_suppl):4555.

CME OUTFITTERS

MK-6482-004: ORR and PFS

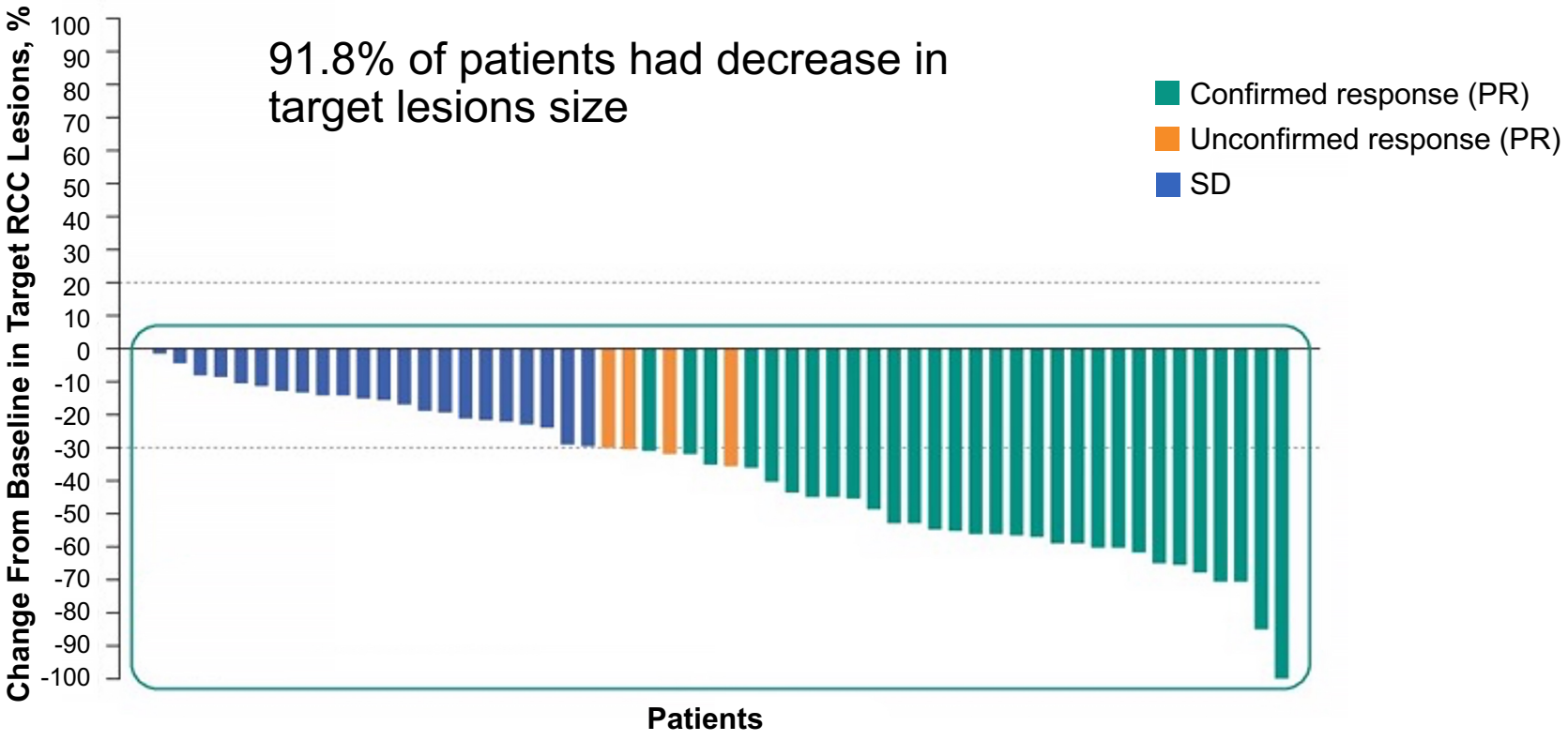
- Median time from enrollment to database cutoff: 21.8 months

	Efficacy population (N = 61)
ORR (95% CI)	49.2% (36.1%-62.3%)
CR	0%
PR	49.2%
SD	49.2%
Unconfirmed PR	6.6%
PD	0%
Not evaluable	1.6%



CI = confidence interval. PD = Progressive disease. PFS = Progression Free Survival.
Srinivasan R, et al. *J Clin Oncol*. 2021;39(15_suppl):4555.

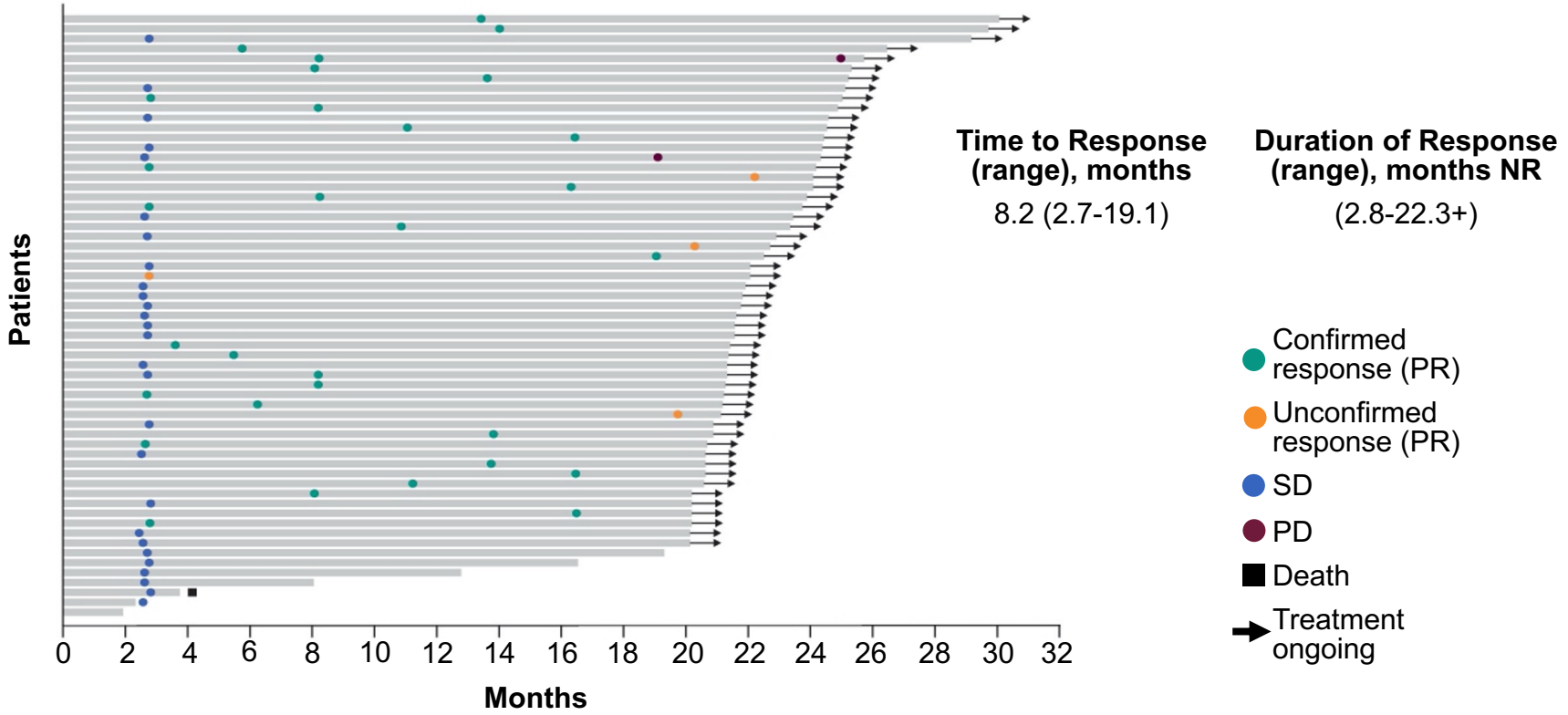
MK-6482-004: Change in Target Lesion Size



NR = Not reported.

Srinivasan R, et al. *J Clin Oncol*. 2021;39(15_suppl):4555.

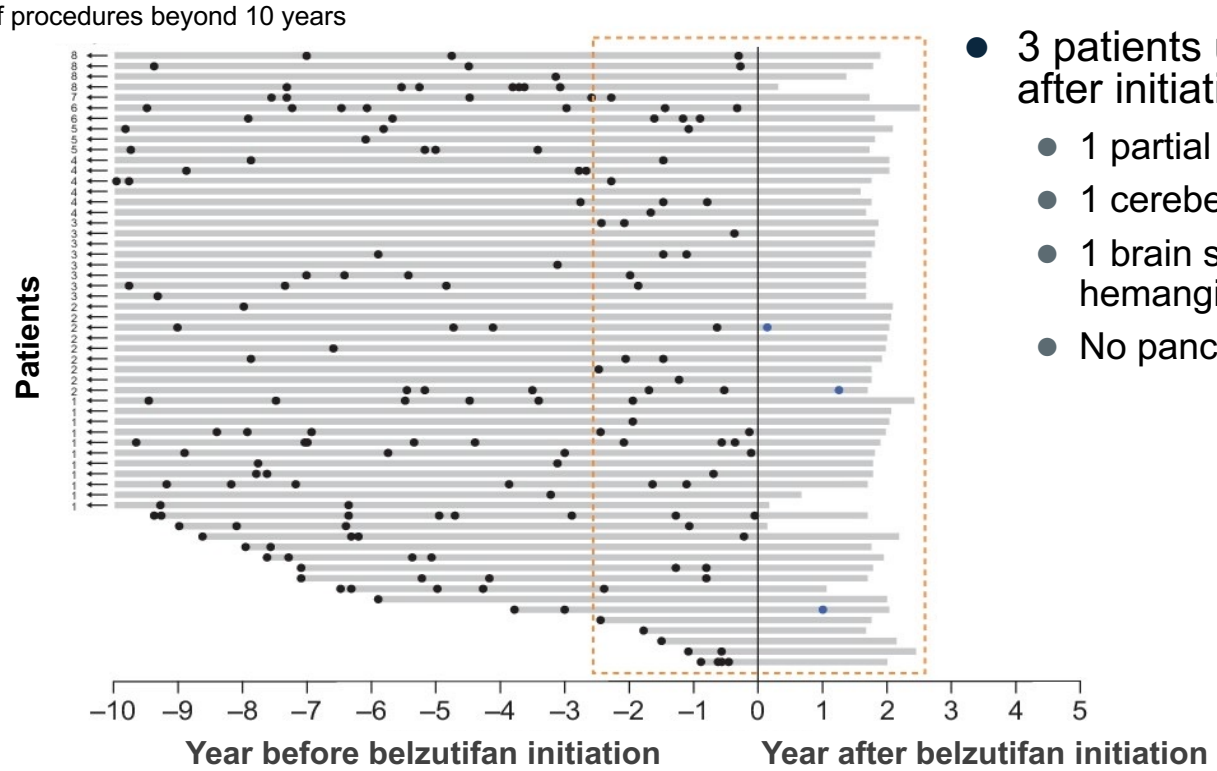
MK-6482-004: Duration of Response



NR = Not reported.

Srinivasan R, et al. *J Clin Oncol*. 2021;39(15_suppl):4555.

MK-6482-004: Frequency of Tumor Reduction Procedures Before and After Belzutifan Initiation



- 3 patients underwent a procedure after initiation of belzutifan
  - 1 partial nephrectomy
  - 1 cerebellar radiation
  - 1 brain surgery (CNS hemangioblastoma)
  - No pancreatic surgeries

- Procedure after study enrollment
- Procedure before study enrollment
- Patient had ≥ 1 procedure beyond 10 years before study enrollment

Procedures included adrenalectomy, craniotomy, cryoablation, cryotherapy, eye removal, intradural resection, laser ablation, laser surgery, laminectomy, laser photocoagulation, pancreatectomy, partial nephrectomy, radiation therapy, radiofrequency ablation, retinal surgery, total nephrectomy, tumor enucleation, and ventriculoperitoneal shunt placement.

Srinivasan R, et al. *J Clin Oncol*. 2021;39(15_suppl):4555.

CME OUTFITTERS

MK-6482-004: Efficacy Against Pancreatic Lesions and CNS and Retinal Hemangioblastomas

Response in Pancreatic Lesions and CNS Hemangioblastomas by IRC

Parameter	Pancreatic lesions n = 61	Pancreatic neuroendocrine tumors, n = 22	CNS hemangioblastomas, n = 50
ORR, (95% CI)	77.0% (64.5%-86.8%)	90.9% (70.8%-98.9%)	30.0% (17.9%-44.6%)
CR	9.8%	13.6%	6.0%
PR	67.2%	77.3%	24.0%
SD	21.3%	9.1%	62.0%
PD	0%	0%	4.0%
Not evaluable	1.6%	0%	4.0%

Response in Patients with Retinal Hemangioblastomas

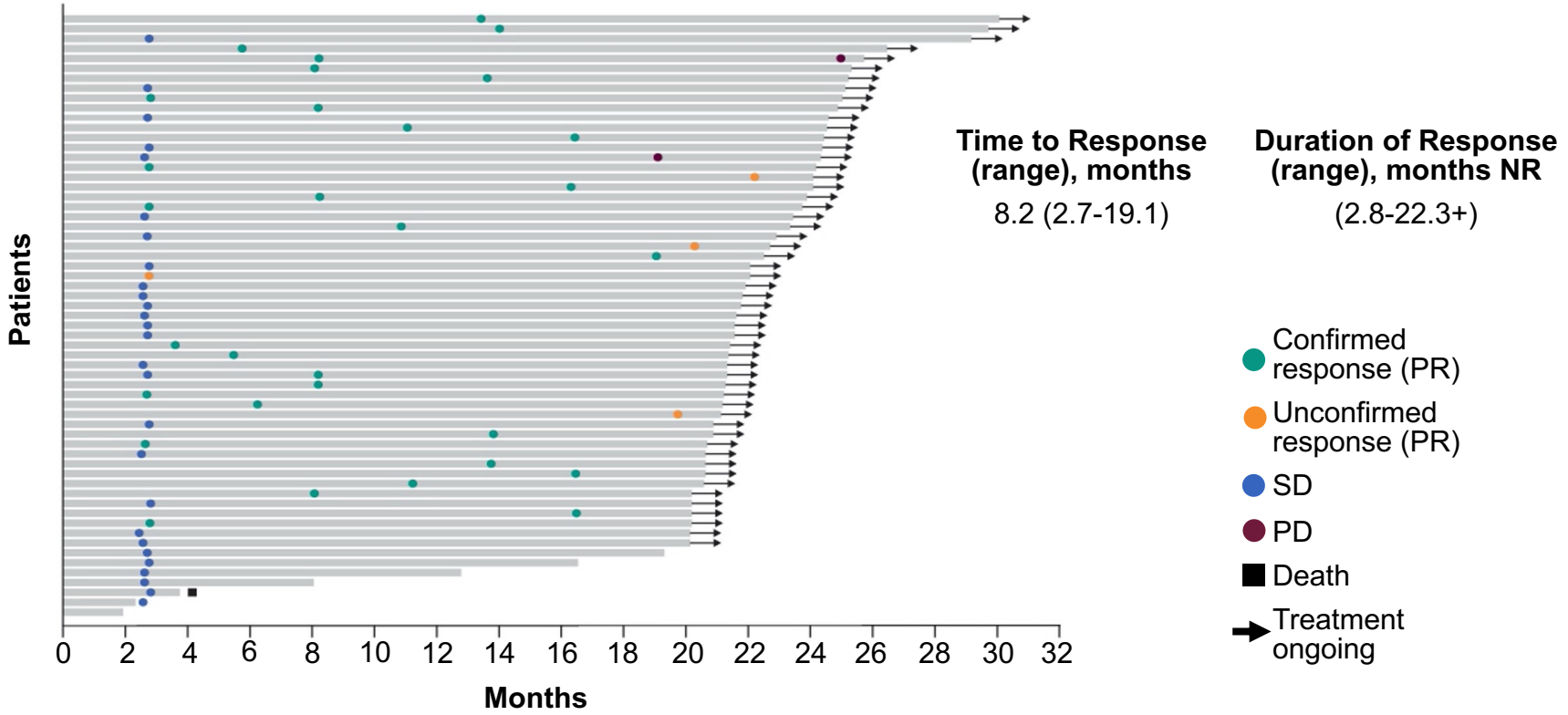
Best response, n (%)	Retinal lesions, n = 16
Improved + stable	16 (100%)
Improved	11 (68.8%)
Stable	5 (31.3%)
Progressed	0 (0%)
Not evaluable	0 (0%)

CNS = Central nervous system.

Srinivasan R, et al. *J Clin Oncol*. 2021;39(15_suppl):4555.

CME OUTFITTERS

MK-6482-004: Duration of Response



Srinivasan R, et al. *J Clin Oncol*. 2021;39(15_suppl):4555.

MK-6482-004: Safety Overview

Adverse event (AE), n (%)	Safety Population N = 61
Any-grade AE	61 (100%)
Any-grade Treatment-related(TR) AE	61 (100%)
Grade 3-5 AE	20 (32.8%)
Grade 3 TRAE	9 (14.8%)
Grade 4-5 TRAE	0 (0%)
AE leading to treatment discontinuation	2 (3.3%)[a]
TRAE leading to treatment discontinuation	1 (1.6%)[b]
Death	1 (1.6%)[c]
Death due to TRAE	0 (0%)

[a] Patient death recorded as an AE. [b] Patient discontinued because of Grade 1 dizziness. [c] Grade 5 AE (not treatment-related) caused by acute fentanyl toxic effects.

Srinivasan R, et al. *J Clin Oncol*. 2021;39(15_suppl):4555.

CME OUTFITTERS

MK-6482-004: Frequency of AEs

AE, n (%)	Safety population N = 61			
	Any grade	Grade 1-2	Grade 3[a]	Grade 4-5[b,c]
Anemia[d]	55 (90.2)	50 (82.0)	5 (8.2)	0 (0)
Fatigue	40 (65.6)	37 (60.7)	3 (4.9)	0 (0)
Headache	25 (41.0)	25 (41.0)	0 (0)	0 (0)
Dizziness	24 (39.3)	24 (39.3)	0(0)	0 (0)
Nausea	21 (34.4)	21 (34.4)	0 (0)	0 (0)
Dyspnea	14 (23.0)	13 (21.3)	1 (1.6)	0 (0)
Arthralgia	12 (19.7)	12 (19.7)	0 (0)	0 (0)
Constipation	12 (19.7)	12 (19.7)	0 (0)	0 (0)
Myalgia	12 (19.7)	11 (18.0)	1 (1.6)	0 (0)
Upper respiratory tract infection	11 (18.0)	11 (18.0)	0 (0)	0 (0)
ALT increased	10 (16.4)	10 (16.4)	0 (0)	0 (0)
Hypertension	10 (16.4)	5 (8.2)	5 (8.2)	0 (0)
Vision blurred	10 (16.4)	10 (16.4)	0 (0)	0 (0)

ALT = Alanine aminotransferase. [a] 1 patient reported asymptomatic Grade 3 hypoxia that did not necessitate treatment. [b] 1 patient had retinal detachment (Grade 4; not treatment-related). [c] Grade 5 AE (not treatment-related) caused by acute fentanyl toxic effects. [d] 4 patients with Grade ≥2 anemia received blood transfusions and 12 patients received erythropoietin-stimulating agents (ESA) (3 patients received an ESA and a blood transfusion).

Srinivasan R, et al. *J Clin Oncol*. 2021;39(15_suppl):4555.

CME OUTFITTERS

Belzutifan Side Effect Management

- Promptly identifying and managing side effects improves therapy adherence and outcomes[1]
- Anemia: monitor blood counts, transfuse patients as clinically indicated[2]
  - Do not administer ESAs for treatment of anemia.
- Hypoxia: monitor oxygen saturation, maintain pulse oximeter ≥ 88% or PaO_2 > 55 mmHg[2]
- Poor metabolizers of dual UGT2B17 and CYP2C19 may experience increased exposure[2]

mmHg = Millimeters of mercury. PaO_s = Partial pressure of oxygen.

1. Krikorian SA, Shamim K. *Am J Lifestyle Med*. 2013;7(3):206-222. 2. WELIREG® (belzutifan) tablet. Whitehouse Station, NJ: Merck Sharp & Dohme Corp; Revised 8, 2021. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=13e15ee0-d679-4fa9-9430-e2e2170474da. Accessed October 22, 2021.

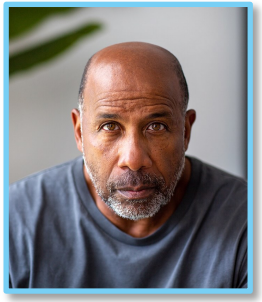
CME OUTFITTERS

Case Study 1

- 35-year-old woman
- Family history VHL disease
- Creatinine: 1.6 mg/dL
- Established retinal hemangioblastomas, small pancreatic neuroendocrine tumor, multifocal RCC with the largest measurement of 2.5 cm
- Prior surgery for RCC
- What is this patient's best option?

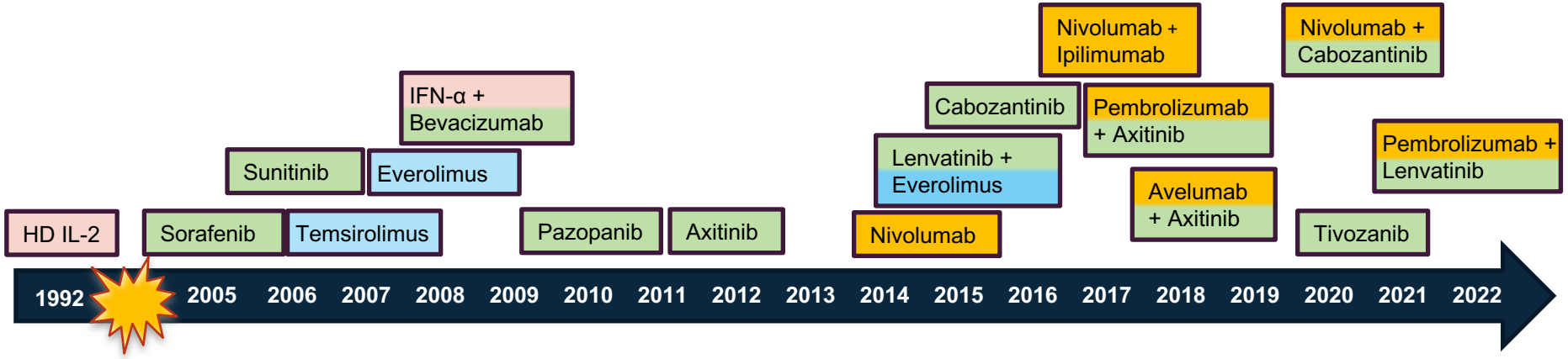
ICI = Immune checkpoint inhibitor.

Case Study 2



- 60-year-old Black male
- Intermediate risk ccRCC
- Surgery (complete resection, 18 months to metastasis)
- 1st-line pembrolizumab/axitinib (CR, 10 months duration)
- 2nd-line cabozantinib (SD, 4 months)
- Now at 2nd recurrence, would like to discuss treatment options

Medical Therapies for Metastatic RCC



Legend

- Cytokine immunotherapy
- Anti-angiogenic therapy (tyrosine kinase inhibitor, TKI)
- mTOR inhibitor
- Immune checkpoint inhibitor

- RCC therapy space is crowded with multiple entries in 4 classes of agents
- As combination therapies move to first-line, development of therapies targeting novel pathways/mechanisms become even more important

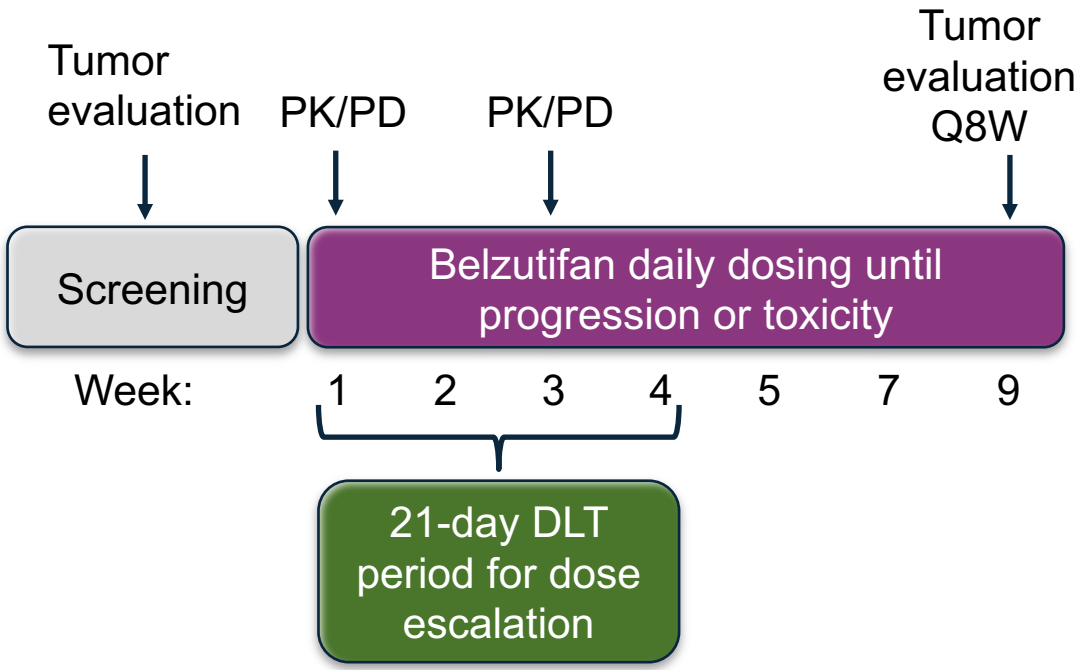
HD IL-2 = High-does Interleukin-2. IFN-α = Interferon-alpha. mTOR = Mechanistic target of rapamycin.

National Comprehensive Cancer Network (NCCN). *NCCN clinical practice guidelines in oncology (NCCN Guidelines®), kidney cancer, version 2.2022.* NCCN Website. 2021.https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed October 27, 2021.

CME OUTFITTERS

MK-6482-001: Study Design

- Phase 1/2
- ccRCC second-line and above
- Belzutifan monotherapy
- RP2D: 120 mg daily
- 55 patients enrolled with previously treated ccRCC
  - 44 (80%) discontinued (33 [60%] due disease progression)
- Median (range) follow up: 27.7 (24.8-34.3) months



DLT = Dose-limiting toxicities. PK/PD = Pharmacokinetic/pharmacodynamic. Q8W = Every 8 weeks. RP2D = Recommended Phase 2 dose.
Choueiri TK, et al. *Nat Med*. 2021;27(5):802-805.

MK-6482-001: Patient Characteristics

Characteristics	All Patients N = 55
Age, Median (range), years	62 (39-75)
Sex, n (%)	
Male	44 (80)
Female	11 (20)
ECOG PS, n (%)	
0	20 (36)
1	34 (62)
2	1 (2)
IMDC risk category, n (%)	
Favorable	13 (24)
Intermediate/poor	42 (76)

Characteristics	All Patients N = 55
Prior systemic therapies, median (range), n	3 (1-9)
Prior systemic therapies, n (%)	
1	8 (15)
2	13 (24)
≥ 3	34 (62)
Prior anticancer therapies, n (%)	
VEGF/VEGFR	50 (91)
Checkpoint inhibitor	44 (80)
Investigational/other	16 (29)
mTOR inhibitor	13 (24)
Cytokine	10 (18)

39 patients (71%) received both anti–PD-1 and anti-VEGF agents

IMDC = International Metastatic. RCC Database Consortium.
Choueiri TK, et al. *Nat Med*. 2021;27(5):802-805.

CME OUTFITTERS

MK-6482-001: Frequency of AEs

- 55 patients received 120 mg/d belzutifan
- 22 (40%) patients had a grade 3 TRAE
- 2 (4%) patients discontinued treatment due to TRAE (hypoxia for both)
- No grade 4-5 TRAE
- 4 patients (7%) died
  - 1 from acute kidney infection
  - 1 from cardiac arrest
  - 2 from disease progression

All cause AEs ≥ 20% (%)	Any grade	Grade 3	Grade 4
Any AE	100	60	4
Anemia	76	27	0
Fatigue	71	5	0
Dyspnea	49	5	0
Nausea	36	2	0
Cough	31	0	0
Hypoxia	31	16	0
Vomiting	29	0	0
Peripheral edema	27	0	0
Arthralgia	25	0	0
Creatinine increase	25	2	0
Headache	25	2	0
Dizziness	24	0	0
Back pain	22	2	0
Diarrhea	22	0	0
Hyperkalemia	22	2	0
Constipation	22	0	0
Dehydration	20	2	0

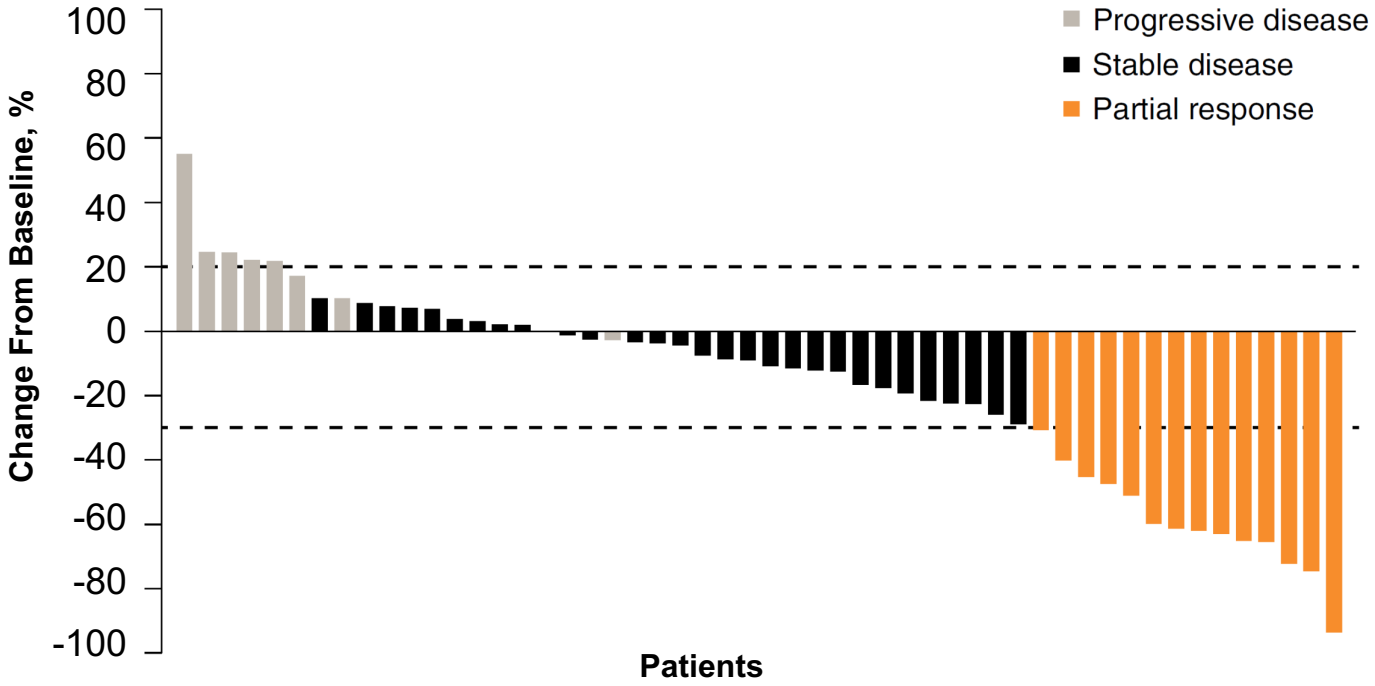
Mg/d = Milligrams per day.

Choueiri TK, et al. *Nat Med*. 2021;27(5):802-805.

CME OUTFITTERS

MK-6482-001: Change in Lesion Size

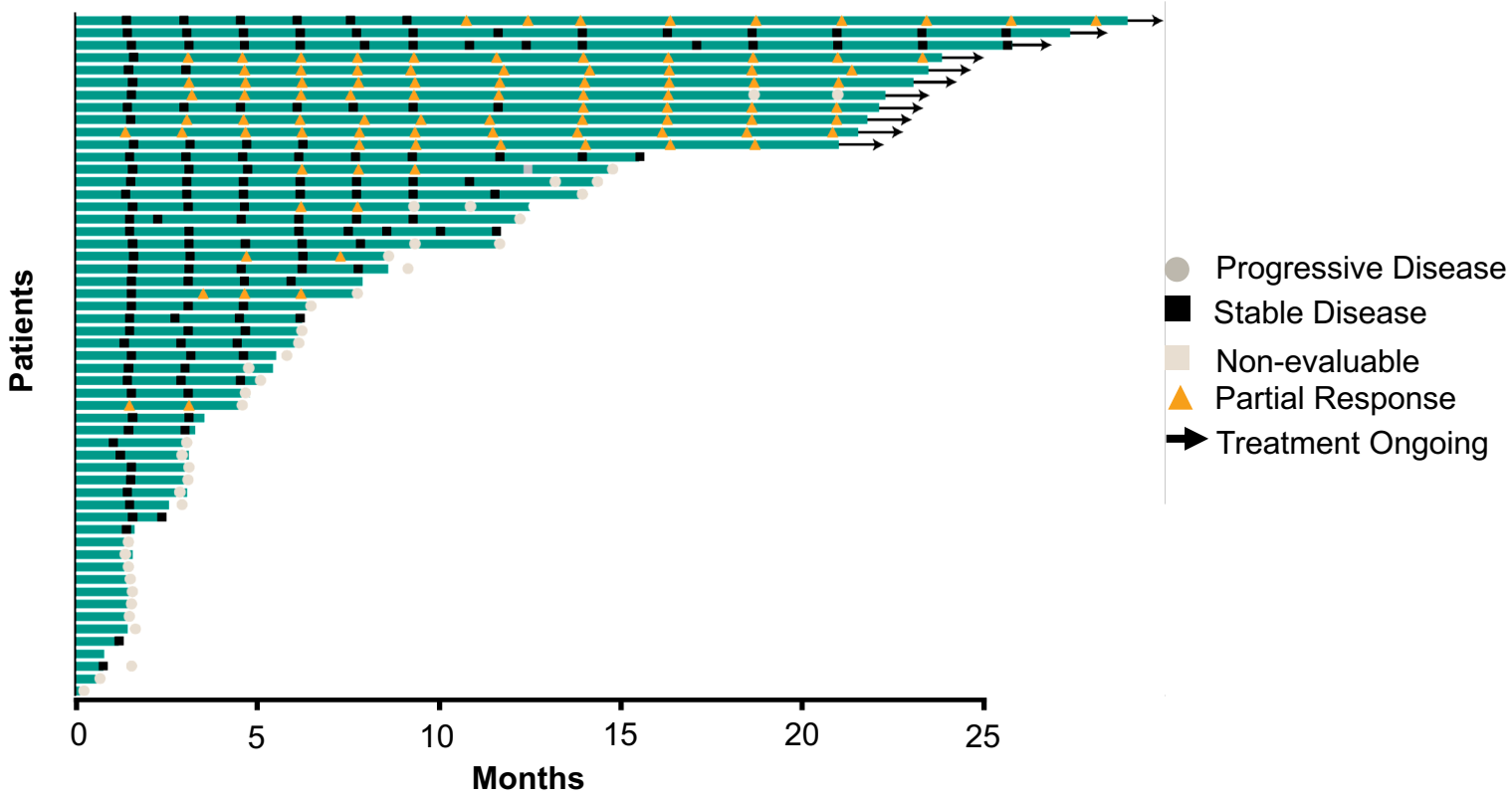
- ORR, 25% (all PR)
  - Disease control rate, 80%
- PFS, 14.5 months
  - DOR ≥ 6 months, 71%



Choueiri TK, et al. *Nat Med*. 2021;27(5):802-805.

CME OUTFITTERS

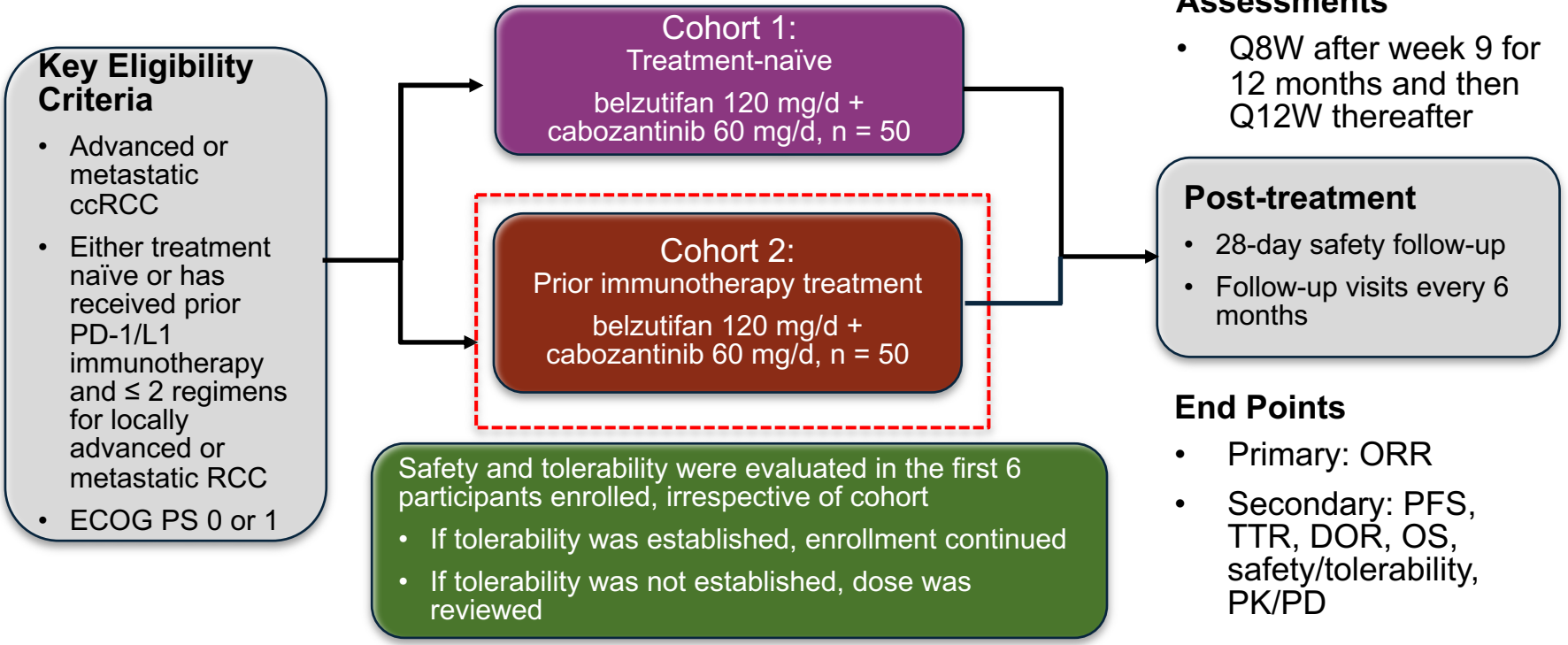
MK-6482-001: Duration of Response



Choueiri TK, et al. *Nat Med*. 2021;27(5):802-805.

MK-6482-003: Study Design

- Phase II, single arm, combination belzutifan + cabozantinib in patients with advanced or metastatic ccRCC (NCT03634540)



NCT = National clinical trial. TTR = Time to response.

Choueiri TK, et al. *J Clin Oncol*. 2021;39(6_suppl):272.

CME OUTFITTERS

MK-6482-003: Patient Characteristics

Characteristics	All Patients N = 52
Age, Median (range), years	63 (43-79)
Sex, n (%)	
Male	38 (73)
Female	14 (27)
ECOG PS, n (%)	
0	23 (44)
1	29 (56)
Prior number of lines of anticancer therapy, n (%)	
1	28 (54)
2	23 (44)

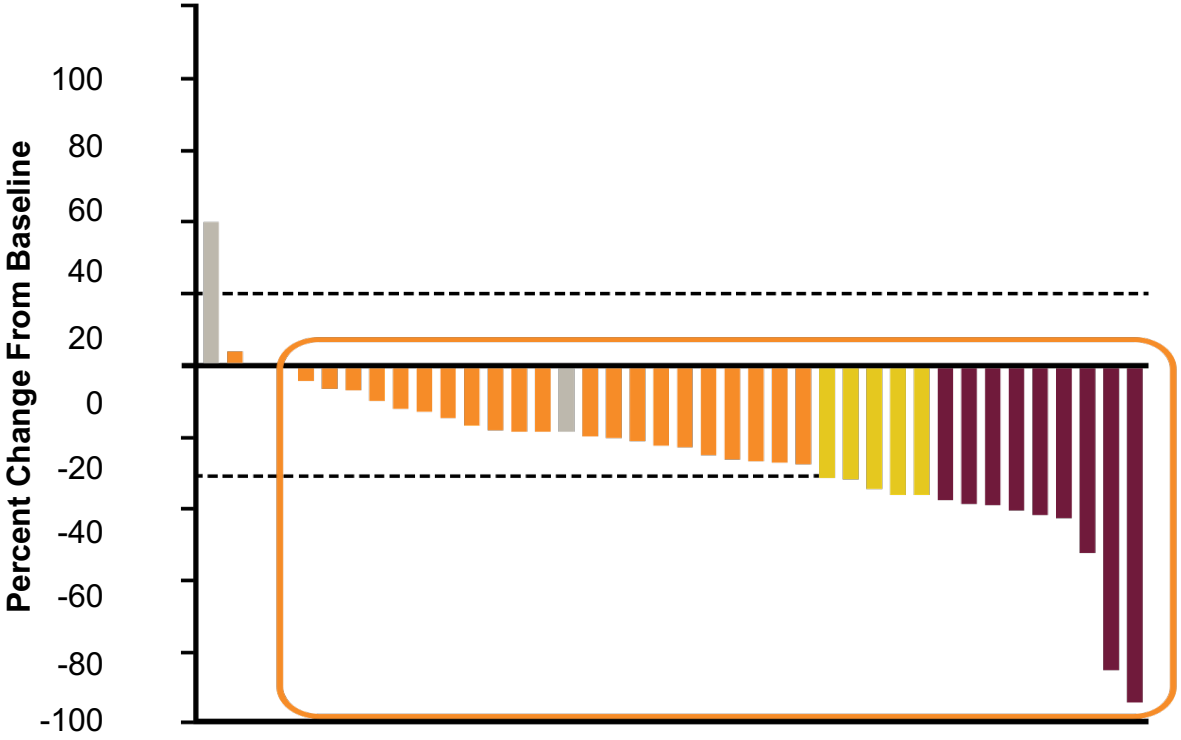
Prior Treatment, n (%)	All Patients N = 52
PD-1/L1 + CTLA4	34 (65)
PD-1/L1 and VEGF/VEGF TKI inhibitor	18 (35)
IO Combination + VEGF/VEGF TKI	0 (0)
IO followed by VEGF/VEGF TKI or VEGF/VEGF TKI followed by IO	7 (14)

CTLA4 = Cytotoxic T-lymphocyte associated protein 4. IO = Immuno-oncology.

Choueiri TK, et al. *J Clin Oncol*. 2021;39(6_suppl):272.

CME OUTFITTERS

MK-6482-003: Change in Lesion Size



36 of 41 patients (88%) experienced a reduction in target lesion size[a]

PD
SD
Unconfirmed PR[b]
Confirmed PR

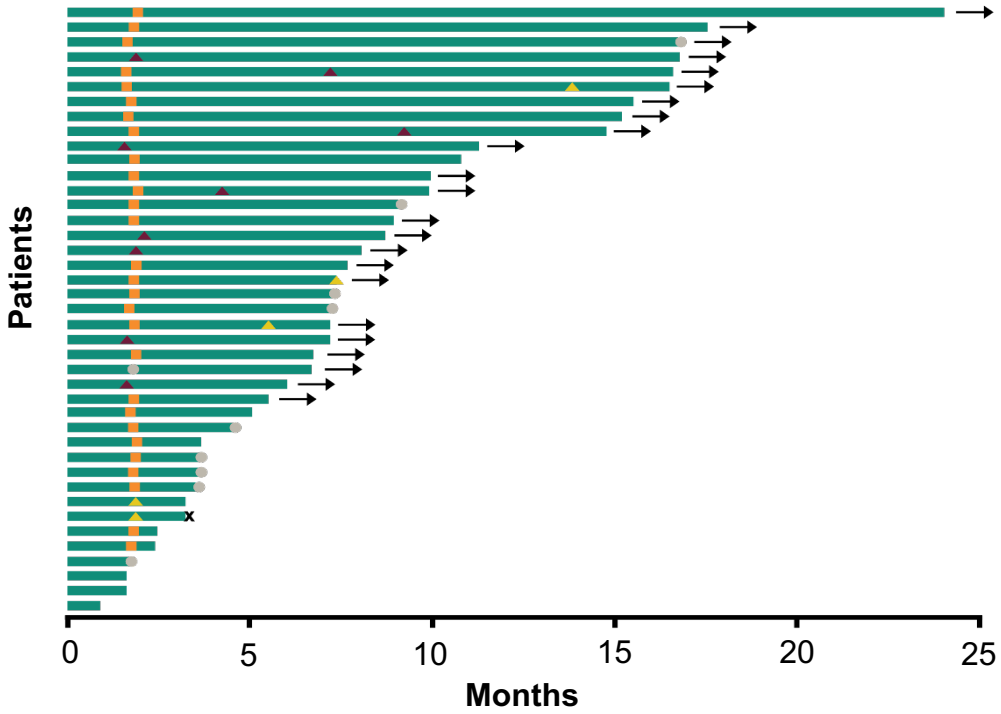
[a]One patient had a response of "not available" and was recorded as having no change from baseline value. [b]Documented at one time point, to be confirmed at a subsequent time point. Data cutoff: October 15, 2020.

Choueiri TK, et al. *J Clin Oncol*. 2021;39(6_suppl):272.

CME OUTFITTERS

MK-6482-003: Duration of Response

Time to Response & Response Duration: Efficacy Analysis Set



- Median time to response was 1.9 months (range, 1.5-9.2)
- Median DOR was not reached (range, 3.7+ to 14.8+ months)
- All confirmed responses were ongoing as of the data cutoff date

[a]Documented at one time point, to be confirmed at a subsequent time point. "+" indicates ongoing response. Data cutoff: October 15, 2020.

Choueiri TK, et al. *J Clin Oncol*. 2021;39(6_suppl):272.

CME OUTFITTERS

Belzutifan Summary

- HIF2α blockade with belzutifan demonstrated value for VHL mutated cancers, including VHL disease and ccRCC
  - FDA approval in Aug 2021 for belzutifan in VHL disease-related RCC, hemangioblastomas, and pancreatic neuroendocrine tumors
- Encouraging data are emerging in advanced sporadic ccRCC
  - Phase I monotherapy and phase II combination data show encouraging ORR, PFS, and tolerability
- Robust clinical development program underway
  - Advanced ccRCC in the second line as monotherapy
  - Combination strategies in second-line setting with VEGF, mTOR, and immune checkpoint inhibitors
  - Combination strategies in the frontline setting with VEGF and immune checkpoint inhibitors

FDA = U.S. Food and Drug Administration.

CME OUTFITTERS

Emerging HIF2α Inhibitors for ccRCC

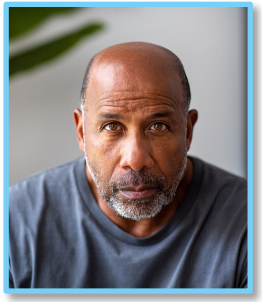
- Belzutifan (MK-6482): Diverse 1st/2nd-line program, single agent, and combinations
- DFF332: NCT04895748, phase I, single agent vs. everolimus or spartalizumab + taminadenant
- ARO-HIF2[1]:
  - NCT04169711 (AROHIF21001), phase I, single agent, interim results
  - RNA interference agent
  - 17 patients, weekly IV dosing
  - 9/17 evaluable:
    - 7/9 reduction in HIF2α expression in tumor biopsies
    - 1/7 PR, 5/7 SD
    - No anemia reported

IV = Intravenous.

1. Arrowhead Pharmaceuticals Website. 2021. https://ir.arrowheadpharma.com/node/16321/pdf. Accessed October 26, 2021.

CME OUTFITTERS

Case Study 2



- 60-year-old Black male
- Intermediate risk ccRCC
- Surgery (complete resection, 18 months to metastasis)
- 1st-line pembrolizumab/axitinib (CR, 10 months duration)
- 2nd-line cabozantinib (SD, 4 months)
- Now at 2nd recurrence

- What is this patient's best option?

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Clinicians should be aware of the data supporting the use of belzutifan in patients with VHL mutation-driven disease
- Clinicians can encourage their patients with previously treated ccRCC to participate in clinical trials that give access to emerging therapies
- Clinicians should be aware of the side effect profile of belzutifan

CME OUTFITTERS

To Receive Credit

To receive CME/CE credit for this activity, participants must complete the post-test and evaluation online.

Participants will be able to download and print their certificate immediately upon completion.

CME OUTFITTERS

Visit the

Oncology Hub

Free resources and education for
health care providers and patients

https://www.cmeoutfitters.com/oncology-education-hub/