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Phase 2 study of belzutifan plus cabozantinib for previously treated advanced renal cell carcinoma: Update from cohort 2 of LITESPARK-003

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Background

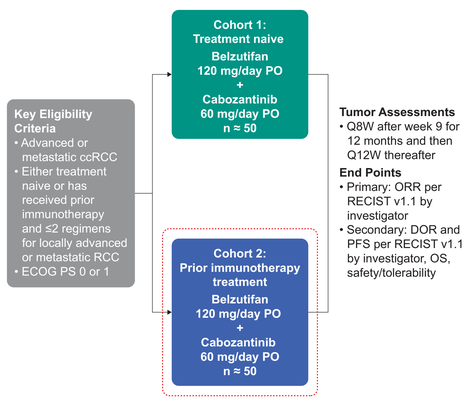
- Hypoxia and inactivation of the von Hippel-Lindau (*VHL*) gene leads to the overexpression of hypoxia-inducible factors (HIFs), which drive the expression of multiple oncogenes, including vascular endothelial growth factor (*VEGF*)[1,2]
  - *VHL* is inactivated in 90% of clear cell renal cell carcinoma (ccRCC) tumors[2]
- Belzutifan, a potent, selective, small-molecule HIF-2α inhibitor, has demonstrated antitumor activity as monotherapy in a phase 1 study of patients with heavily pretreated ccRCC and is approved for VHL disease–associated RCC not requiring immediate surgery[3,4]
- Cabozantinib, a multikinase inhibitor that targets the VEGF receptor (VEGFR), is approved for treatment of advanced RCC[5]
  - VEGF blockade leads to tumor hypoxia and HIF activation[6]
- Targeting both the HIF-2α and VEGF pathways may improve outcomes for patients with advanced ccRCC
- Cohort 2 of the ongoing, open-label, phase 2 LITESPARK-003 study (NCT03634540) was evaluated for efficacy and safety of belzutifan + cabozantinib in patients with advanced ccRCC who were previously treated with immunotherapy

Objective

- To evaluate the efficacy and safety of belzutifan + cabozantinib for the treatment of patients with advanced RCC previously treated with immunotherapy after a median 2 years of follow-up

Methods

Figure 1. Study design



DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q8W, every 8 weeks; Q12W, every 12 weeks.

Statistical analyses

- Efficacy and safety end points were analyzed in all patients who received ≥1 dose of study treatment
- The Kaplan-Meier method was used to estimate DOR, PFS, and OS
- The 95% CIs for ORR were estimated using the Clopper-Pearson method
- The database cutoff date was February 1, 2022

Results

- As of February 1, 2022, treatment was ongoing in 10 of 52 patients (19%)
  - Median time from first dose to database cutoff date was 24.6 months (range, 17.9-39.8)
  - Treatment discontinuation was primarily because of disease progression (n = 27 [52%]) and adverse events (n = 7 [13%])

Table 1. Baseline demographics and clinical characteristics

Characteristic	N = 52
Age, median (range), years	63.0 (43-79)
Men/women	38 (73)/14 (27)
ECOG PS 0/1	23 (44)/29 (56)
IMDC risk favorable/intermediate or poor	11 (21)/41 (79)
Number of prior lines of anticancer therapy 1/2	29 (56)/23 (44)
Immunotherapy only[a]/immunotherapy + anti-VEGF/VEGFR therapy[b]	28 (54)/24 (46)

Values are n (%) unless otherwise specified.

CTLA-4, cytotoxic T-lymphocyte–associated protein 4; IMDC, International Metastatic RCC Database Consortium.

[a]Treatment with a PD-1/L1 inhibitor alone or in combination with a CTLA-4 inhibitor (n = 23), and immunotherapy + additional nonimmunotherapy/non-VEGF/VEGFR inhibitor therapy (n = 5).

[b]PD-1/L1 inhibitor and anti-VEGF/VEGFR therapy in combination or in sequence (n = 21) and PD-1/L1 inhibitor and anti-VEGF/VEGFR therapy in combination or in sequence + additional nonimmunotherapy/non-VEGF/VEGFR inhibitor therapy (n = 3).

Efficacy

Table 2. ORR in IMDC subgroups

	All patients N = 52	IMDC risk category	
		Favorable n = 11	Intermediate/poor n = 41
ORR, % (95% CI)	31 (18.7-45.1)	27 (6.0-61.0)	32 (18.1-48.1)
Best overall response			
CR	1 (2)	0 (0)	1 (2)
PR	15 (29)	3 (27)	12 (29)
SD	32 (62)	8 (73)	24 (59)
PD	3 (6)	0 (0)	3 (7)
Not available	1 (2)	0 (0)	1 (2)

Values are n (%) unless otherwise specified.

CR complete response; PD, progressive disease; PR, partial response; SD, stable disease.

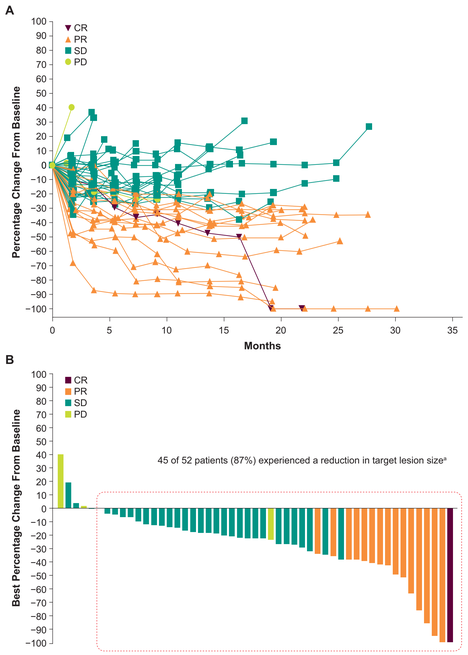
Table 3. ORR by prior anticancer therapy

	All patients N = 52	Prior anticancer therapy		Line of prior anticancer therapy	
		Immunotherapy only[a] n = 28	Immunotherapy/ anti-VEGF therapy[b] n = 24	1 line of prior therapy n = 29	2 lines of prior therapy n = 23
ORR, % (95% CI)	31 (18.7-45.1)	32 (15.9-52.4)	29 (12.6-51.1)	31 (15.3-50.8)	30 (13.2-52.9)
Best overall response					
CR	1 (2)	1 (4)	0 (0)	1 (3)	0 (0)
PR	15 (29)	8 (29)	7 (29)	8 (28)	7 (30)
SD	32 (62)	17 (61)	15 (63)	18 (62)	14 (61)
PD	3 (6)	1 (4)	2 (8)	2 (7)	1 (4)
Not available	1 (2)	1 (4)	0 (0)	0 (0)	1 (4)

Values are n (%) unless otherwise specified.

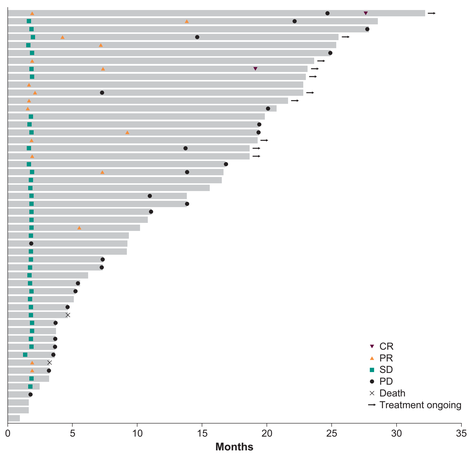
[a]Treatment with a PD-1/L1 inhibitor alone or in combination with a CTLA-4 inhibitor, and immunotherapy + additional nonimmunotherapy/non-VEGF/VEGFR inhibitor therapy.
[b]PD-1/L1 inhibitor and anti-VEGF/VEGFR therapy in combination or in sequence and PD-1/L1 inhibitor and anti-VEGF/VEGFR therapy in combination or in sequence + additional nonimmunotherapy/non-VEGF/VEGFR inhibitor therapy.

Figure 2. (A) Percentage change in target lesion size over time and (B) best percentage change from baseline in target lesions



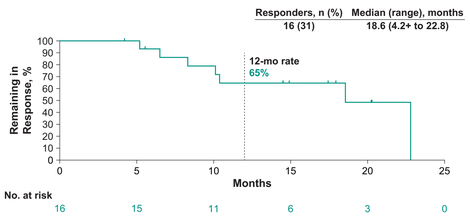
[a]1 patient with a best response of PD had SD as a target lesion response but PD as a nontarget lesion response and developed a new lesion at the first imaging assessment; 1 patient with a 100% reduction in tumor size had an initial PR, then continued treatment following PD, and then subsequently experienced a CR.

Figure 3. Duration of treatment and best overall response[a]



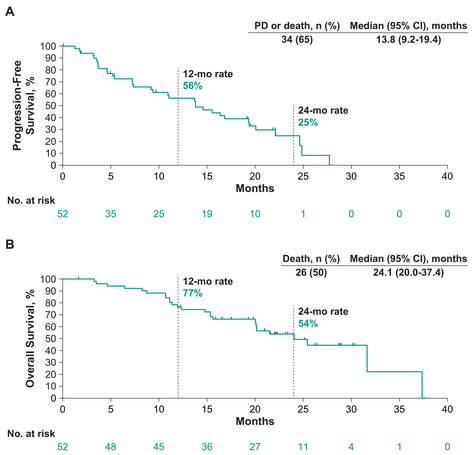
[a]1 patient who had an initial PR continued on treatment following PD and subsequently experienced a CR.

Figure 4. Kaplan-Meier assessment of DOR



+ Indicates response is ongoing.

Figure 5. Kaplan-Meier assessment of (A) PFS and (B) OS



Safety

Table 4. Treatment-related adverse events with incidence of ≥15% and corresponding grade 3-5 treatment-related adverse events

Adverse event	All patients N = 52	
	All grades	Grade 3[a,b]
Any	51 (98)	34 (65)
Anemia	44 (85)	8 (15)
Fatigue	37 (71)	6 (12)
Palmar-plantar erythrodysesthesia	28 (54)	2 (4)
Hypertension	25 (48)	14 (27)
Diarrhea	27 (52)	2 (4)
Nausea	24 (46)	1 (2)
ALT increased	20 (38)	3 (6)
AST increased	19 (37)	2 (4)
Decreased appetite	18 (35)	2 (4)
Dyspnea	10 (19)	1 (2)
Headache	10 (19)	0 (0)
Hypophosphatemia	10 (19)	2 (4)
Vomiting	10 (19)	0 (0)
Dysgeusia	9 (17)	0 (0)
Hypothyroidism	9 (17)	0 (0)
Muscle spasms	9 (17)	0 (0)
Stomatitis	9 (17)	0 (0)
Thrombocytopenia	9 (17)	0 (0)

Values are n (%).

ALT, alanine transaminase; AST, aspartate transaminase.

[a]Grade 3 hypoxia occurred in 2 patients.
[b]No grade 4 treatment-related adverse events occurred.

- 1 patient (2%) died from treatment-related respiratory failure
  - This patient had numerous comorbidities including chronic obstructive pulmonary disease, pulmonary metastasis, pleural effusion, and lymphangitic carcinomatosis

Conclusions

- With a median follow-up of 24.6 months, the results continued to show that belzutifan + cabozantinib had promising antitumor activity in patients with advanced ccRCC previously treated with immunotherapy
- Belzutifan + cabozantinib had a manageable safety profile, which was consistent with individual profiles of each agent[4,5]
  - No grade 4 treatment-related adverse events occurred, and 1 patient died from treatment-related respiratory failure
- Results from this study provide rationale for further investigation of the HIF-2α inhibitor belzutifan in combination with a tyrosine kinase inhibitor as treatment for patients with advanced ccRCC
- The phase 3 LITESPARK-011 study of belzutifan + lenvatinib versus cabozantinib is recruiting patients with advanced ccRCC who received prior immunotherapy and up to 2 prior systemic regimens

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