

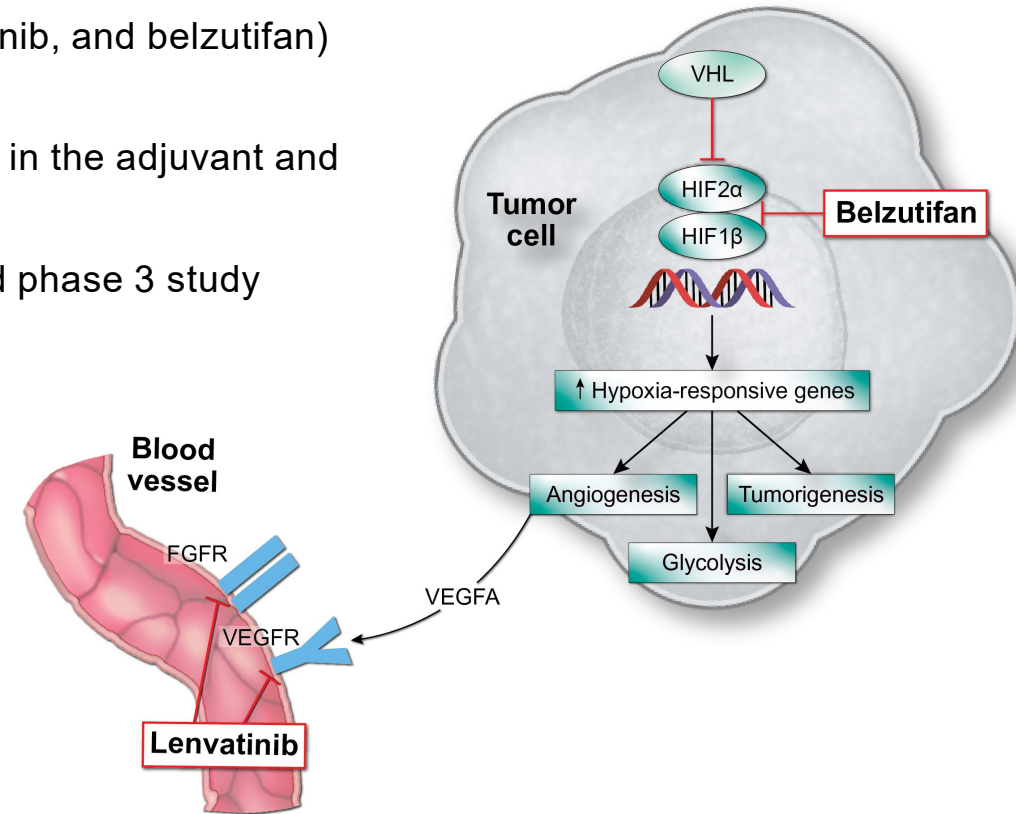
Belzutifan Plus Lenvatinib Versus Cabozantinib for Advanced Renal Cell Carcinoma After Anti-PD-(L)1 Therapy: Open-Label Phase 3 LITESPARK-011 Study

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Background

- No clear standard of care for patients with advanced RCC after disease progression following anti-PD-(L)1 therapy^{1,2}
 - Targeted therapies (cabozantinib, lenvatinib + everolimus, axitinib, tivozanib, and belzutifan) are frequently used
 - Most were established before anti-PD-(L)1 agents were standard of care in the adjuvant and advanced RCC settings
 - None have been compared to contemporary VEGFR-TKI in a randomized phase 3 study
- Belzutifan is the first-in-class HIF-2α inhibitor approved for patients with advanced RCC following both anti-PD-(L)1 and VEGFR-TKI therapy
- Lenvatinib is a potent VEGFR-TKI approved as 1L therapy in combination with pembrolizumab and in the post-VEGFR-TKI setting in combination with everolimus in RCC
- Orthogonal inhibition of angiogenesis pathways with a HIF-2α inhibitor and a VEGFR-TKI may improve upon the efficacy of a VEGFR-TKI alone
- The phase 3 LITESPARK-011 study investigated belzutifan + lenvatinib vs cabozantinib in participants with advanced clear cell RCC following anti-PD-(L)1 therapy



LITESPARK-011 Study (NCT04586231)

Key Eligibility Criteria

- Unresectable, locally advanced or metastatic clear cell RCC
- Karnofsky Performance Status score $\geq 70\%$
- ≤ 2 prior systemic regimens
- Progression on/after anti-PD-(L)1 mAb as 1L or 2L therapy or progression ≤ 6 months of the last dose of adjuvant anti-PD-(L)1 mAb
- Prior VEGFR-TKI was permitted

R
1:1

N = 371

**Belzutifan 120 mg orally QD
+
Lenvatinib 20 mg orally QD**

N = 376

Cabozantinib 60 mg orally QD

Stratification Factors

- IMDC prognostic score:^a 0 vs. 1-2 vs. 3-6
- Line of treatment for prior anti-PD-(L)1: 1L, adjuvant, neoadjuvant-adjuvant vs. 2L
- Geographic region: North America vs. western Europe vs. rest of world

Dual Primary Endpoints:

- PFS per RECIST 1.1 by BICR
- OS

Key Secondary Endpoint:

- ORR per RECIST 1.1 by BICR

Other Secondary Endpoints Include:

- DOR per RECIST 1.1 by BICR
- Safety
- Time to deterioration in patient-reported outcomes

BICR, blinded independent central review; QD, daily.

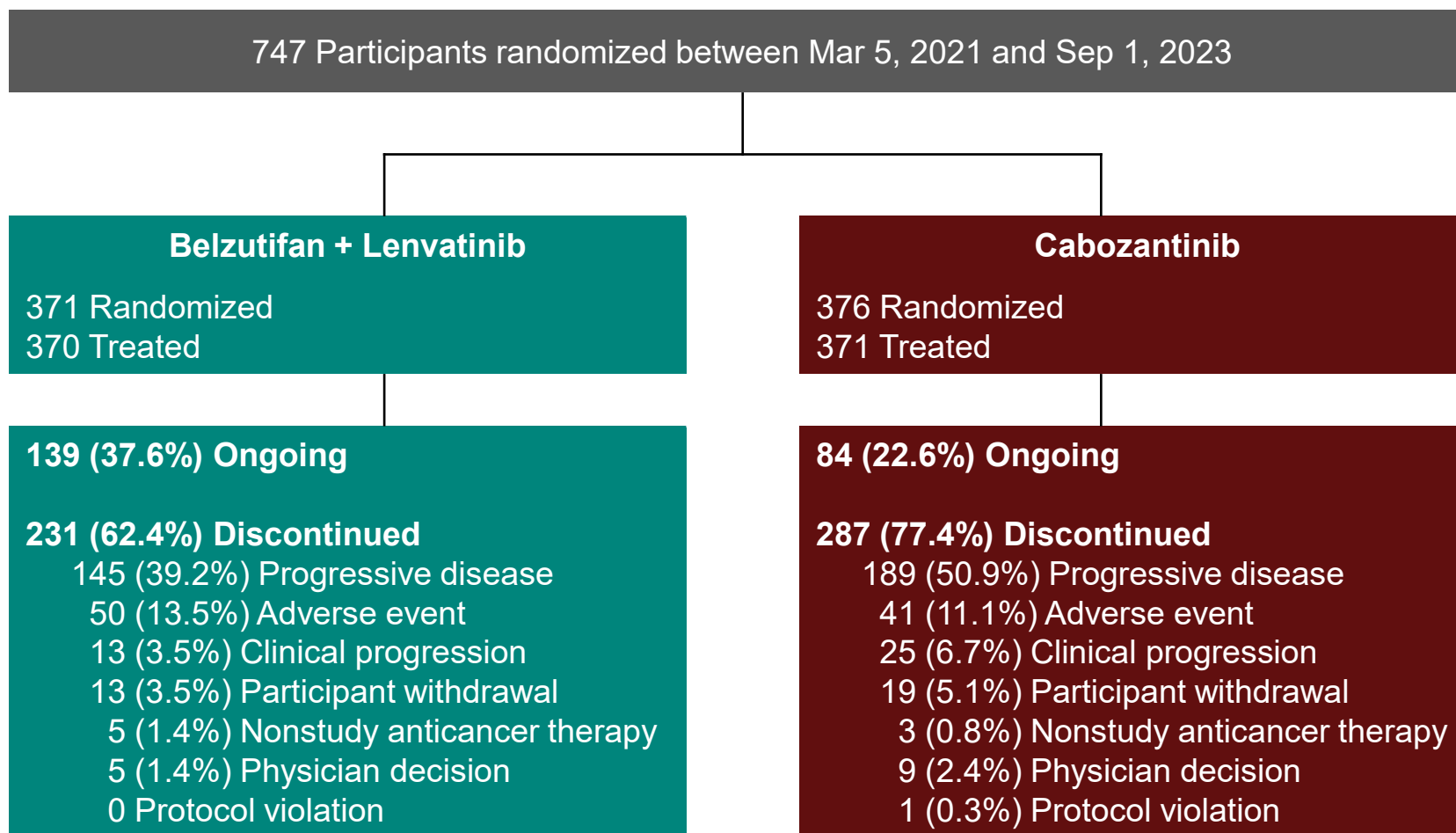
^aBased on the number of present risk factors (KPS score $< 80\%$; time from diagnosis to 1L treatment < 1 year; low hemoglobin; high corrected serum calcium; high neutrophils; high levels of platelets) according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC).

Statistical Considerations

- Initially assigned $\alpha=0.005$ (1-sided) to PFS, $\alpha=0.019$ (1-sided) to OS, and $\alpha=0.001$ (1-sided) to the key secondary hypothesis of ORR
 - Type I error rate controlled at $\alpha=2.5\%$ (1-sided) with the graphical method of Maurer and Bretz
- The study was considered positive if either of the dual primary endpoints was met
- PFS, OS HRs and 95% CIs estimated by stratified Cox regression model; between-arm differences assessed with stratified log-rank test
- ORR (95% CI) estimated with exact binomial method by Clopper and Pearson; between-arm difference by stratified Miettinen and Nurminen's method with strata weighted by sample size

	Planned analysis	Timing	Data cutoff date
First interim analysis (IA1)	- Interim PFS, OS - Final ORR	- After ~427 PFS events ≥ 9 mo after last participant randomized	June 26, 2024
Second interim analysis (IA2)	- Final PFS - Interim OS	- After ~534 PFS events ≥ 17 mo after last participant randomized	April 9, 2025

Participant Disposition



Median time from randomization to data cutoff date (IA2, April 9, 2025): **29.0 months (range, 19.3–49.2)**

Baseline Characteristics

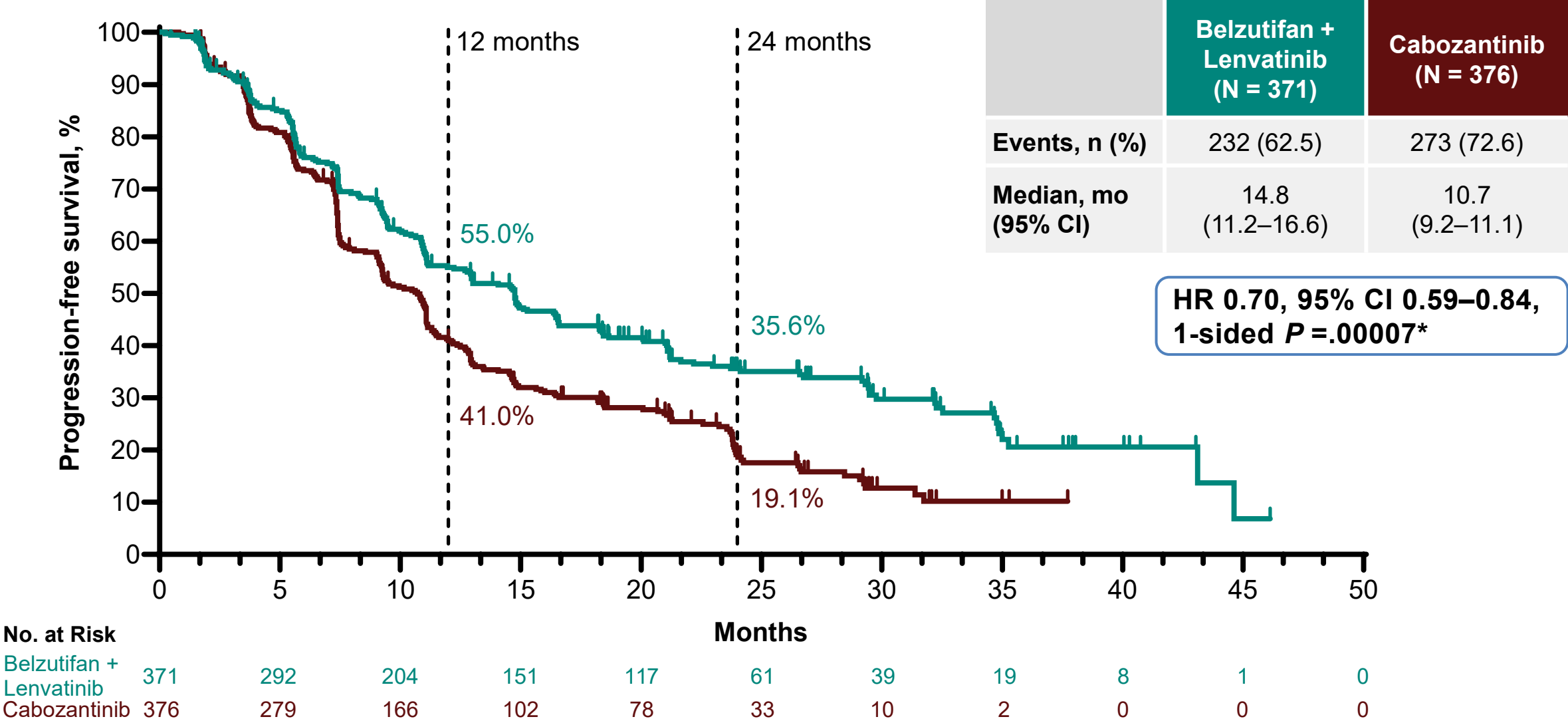
Characteristic, n (%)	Belzutifan + Lenvatinib (N = 371)	Cabozantinib (N = 376)
Median age (range), years	63.0 (30–85)	62.5 (30–86)
Sex		
Male	273 (73.6)	292 (77.7)
Female	98 (26.4)	84 (22.3)
KPS score		
90 or 100	276 (74.4)	277 (73.7)
70 or 80	95 (25.6)	99 (26.3)
Geographic region		
North America	64 (17.3)	63 (16.8)
Western Europe	221 (59.6)	216 (57.4)
Rest of world	86 (23.2)	97 (25.8)
IMDC prognostic risk categories		
Favorable (score 0)	84 (22.6)	95 (25.3)
Intermediate (score 1-2)	226 (60.9)	215 (57.2)
Poor (score 3-6)	61 (16.4)	66 (17.6)
Prior lines of therapy		
Adjuvant only	15 (4.0)	18 (4.8)
1	252 (67.9)	251 (66.8)
2	100 (27.0)	107 (28.5)
3	4 (1.1)	0
Number of prior VEGFR-TKIs		
0	158 (42.6)	165 (43.9)
1	203 (54.7)	205 (54.5)
2	10 (2.7)	6 (1.6)

Summary of Overall IA1 and IA2 Results

	IA1 (26 June 2024)		IA2 (9 April 2025)	
	Belzutifan + Lenvatinib (N = 371)	Cabozantinib (N = 376)	Belzutifan + Lenvatinib (N = 371)	Cabozantinib (N = 376)
Median PFS (95% CI), mo	14.6 (11.1–16.6)	10.6 (9.2–11.1)	14.8 (11.2–16.6)	10.7 (9.2–11.1)
HR (95% CI)	0.74 (0.61–0.89)		0.70 (0.59–0.84)	
P value (1-sided)	.00095*		.00007*	
Median OS (95% CI), mo	NR (26.5–NR)	27.4 (23.6–31.4)	34.9 (27.5–NR)	27.6 (24.0–31.4)
HR (95% CI)	0.90 (0.70–1.15)		0.85 (0.68–1.05)	
P value (1-sided)	.19322		.06075	
ORR, % (95% CI)	52.6 (47.3–57.7)	39.6 (34.6–44.8)	52.6 (47.3–57.7)	40.2 (35.2–45.3)
P value (1-sided)	.0002*		NA	

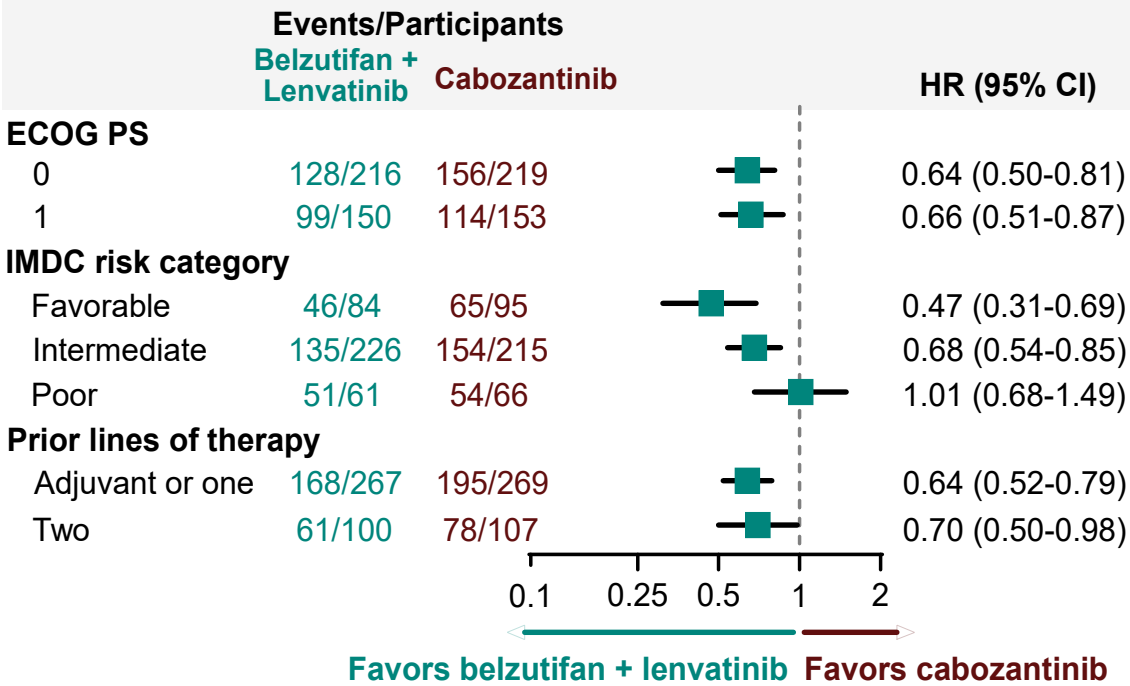
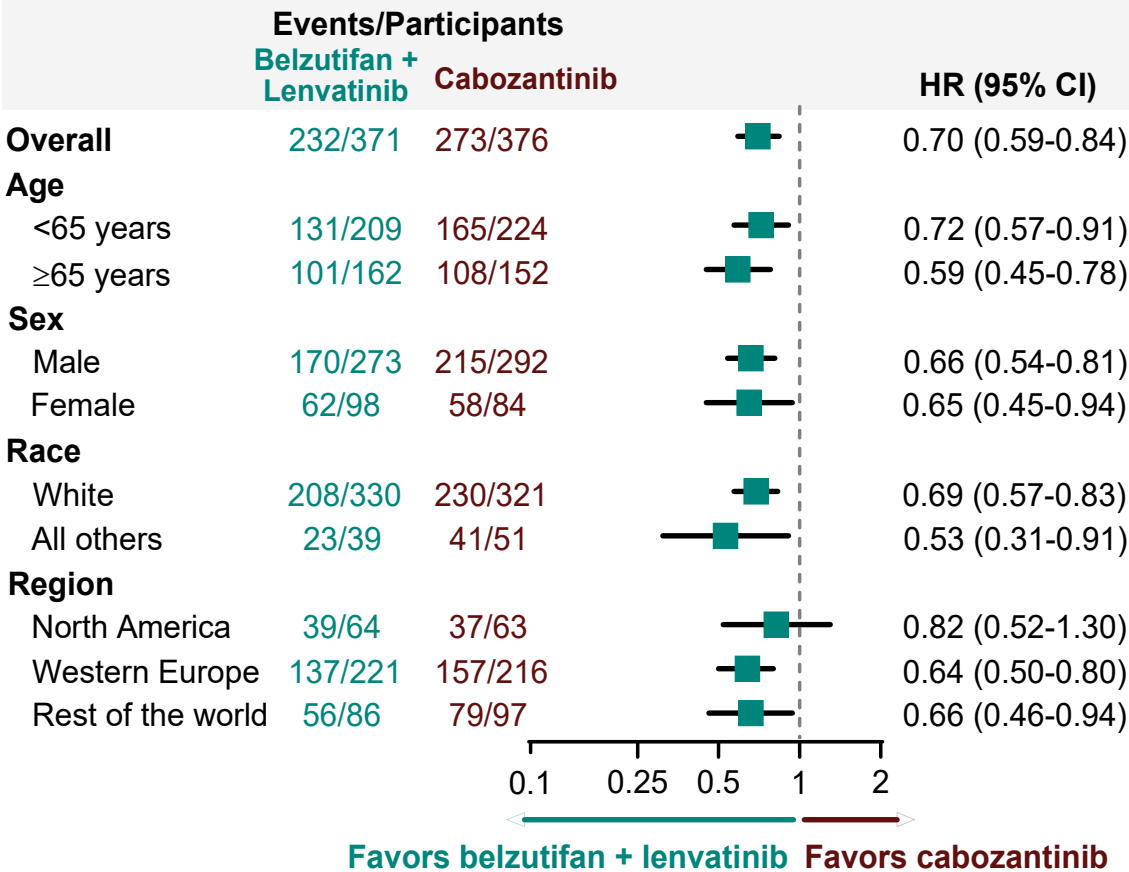
* denotes statistical significance; 1-sided boundary for PFS at IA1 =.0017 and IA2 =.0047; 1-sided boundary for ORR =.001.

Primary Endpoint: PFS per RECIST 1.1 by BICR

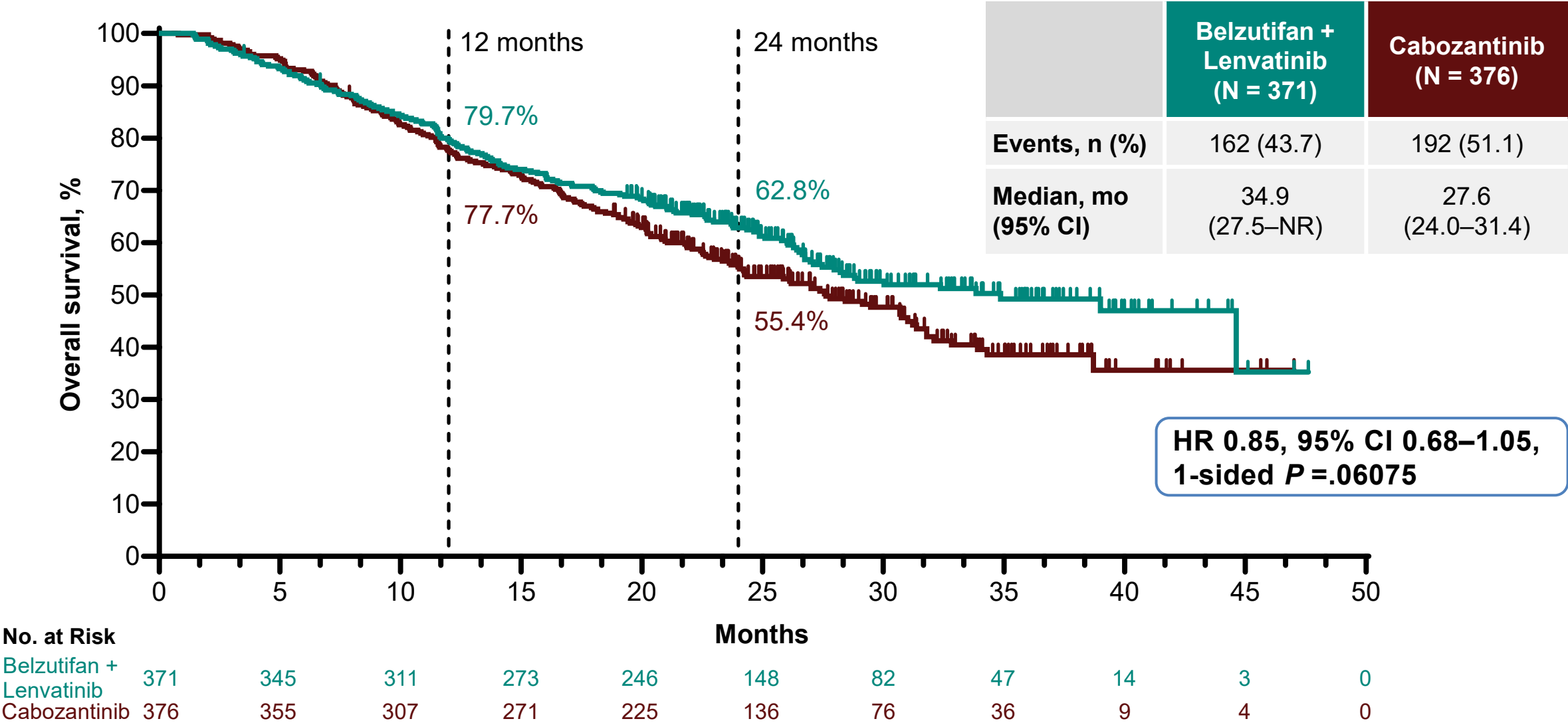


* denotes statistical significance (1-sided boundary 0.0047).

PFS by BICR in Key Subgroups

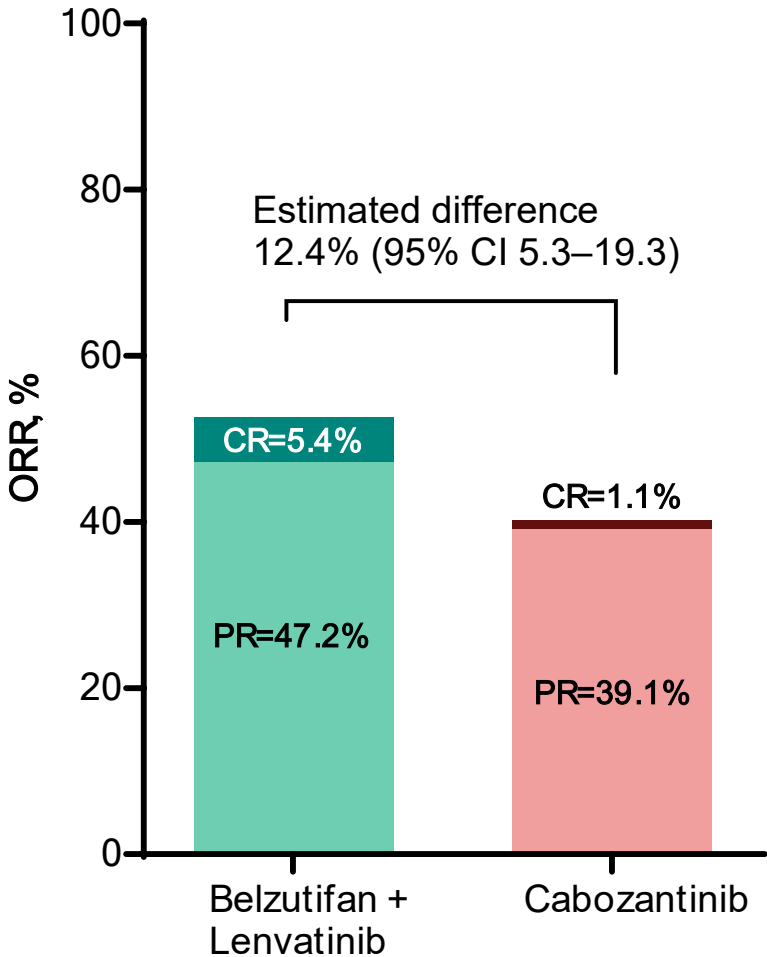


Primary Endpoint: OS



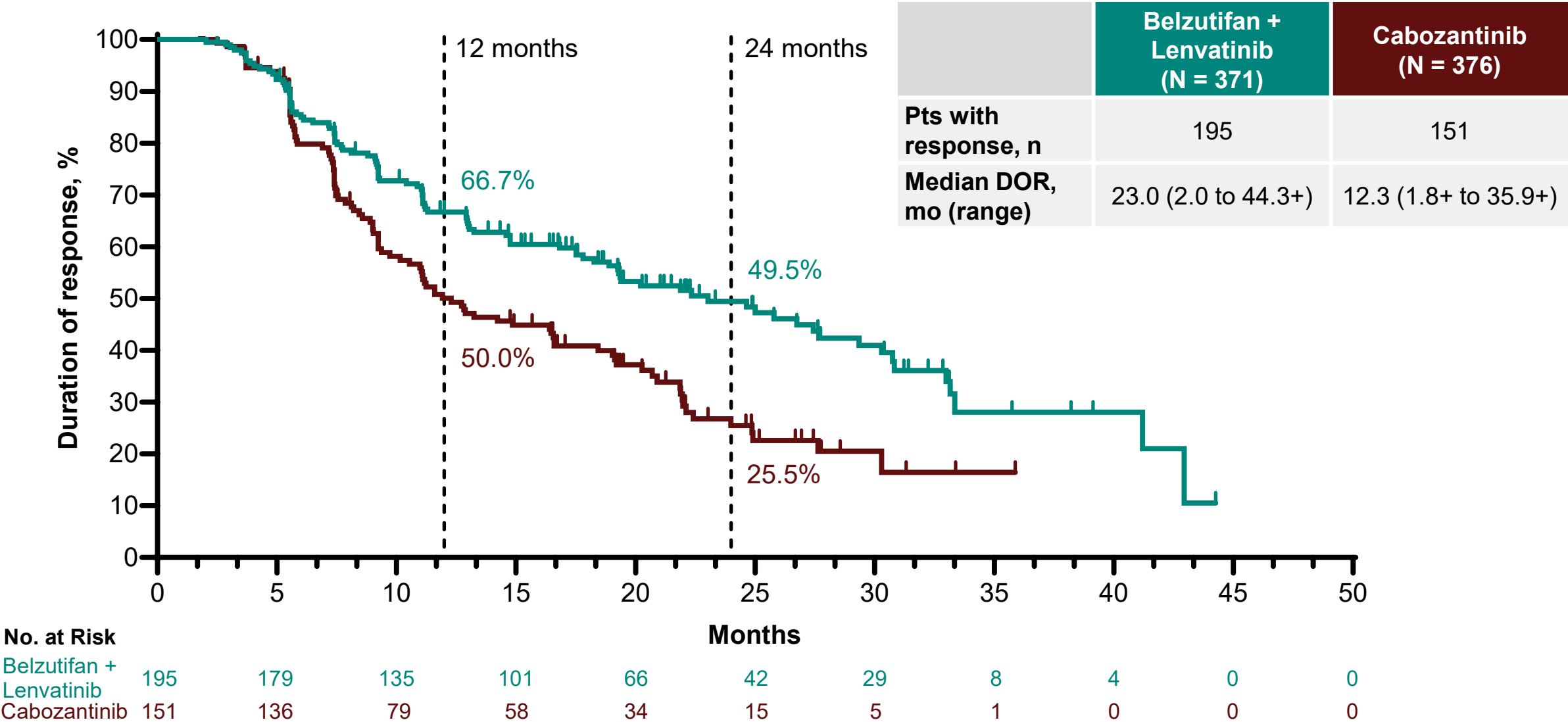
Key Secondary Endpoint: ORR per RECIST 1.1 by BICR

	Belzutifan + Lenvatinib (N = 371)	Cabozantinib (N = 376)
ORR, % (95% CI)	52.6 (47.3–57.7)	40.2 (35.2–45.3)
Estimated difference, % (95% CI)	12.4 (5.3–19.3) ^a	
Best overall response		
CR	20 (5.4)	4 (1.1)
PR	175 (47.2)	147 (39.1)
SD	143 (38.5)	186 (49.5)
PD	21 (5.7)	22 (5.9)
Not evaluable ^b	4 (1.1)	7 (1.9)
No assessment ^c	8 (2.2)	10 (2.7)



^aORR not tested again at IA2, and was statistically significant at IA1 (52.6% vs 39.6%; 1-sided *P*=.0002).
^bIncluding pts with insufficient data for response assessment or no evidence of disease by BICR per RECIST 1.1.
^cIncluding pts without post-baseline assessment by the data cutoff date.

Secondary Endpoint: DOR per RECIST 1.1 by BICR



Summary of Treatment Exposure and Safety^a

Treatment-emergent AEs	Belzutifan + Lenvatinib (N = 370)	Cabozantinib (N = 371)
Median duration of therapy, mo (range)	16.8 (0.03–46.9)	13.2 (0.4–41.9)
Pts with AE, n (%)		
Any	369 (99.7)	369 (99.5)
Grade ≥3	311 (84.1)	307 (82.7)
Serious	191 (51.6)	163 (43.9)
Led to dose reduction of:		
VEGFR-TKI	246 (66.5)	288 (77.6)
Belzutifan	125 (33.8)	NA
Led to discontinuation of:		
All study drugs	41 (11.1)	42 (11.3)
Belzutifan	62 (16.8)	NA
VEGFR-TKI	78 (21.1)	42 (11.3)

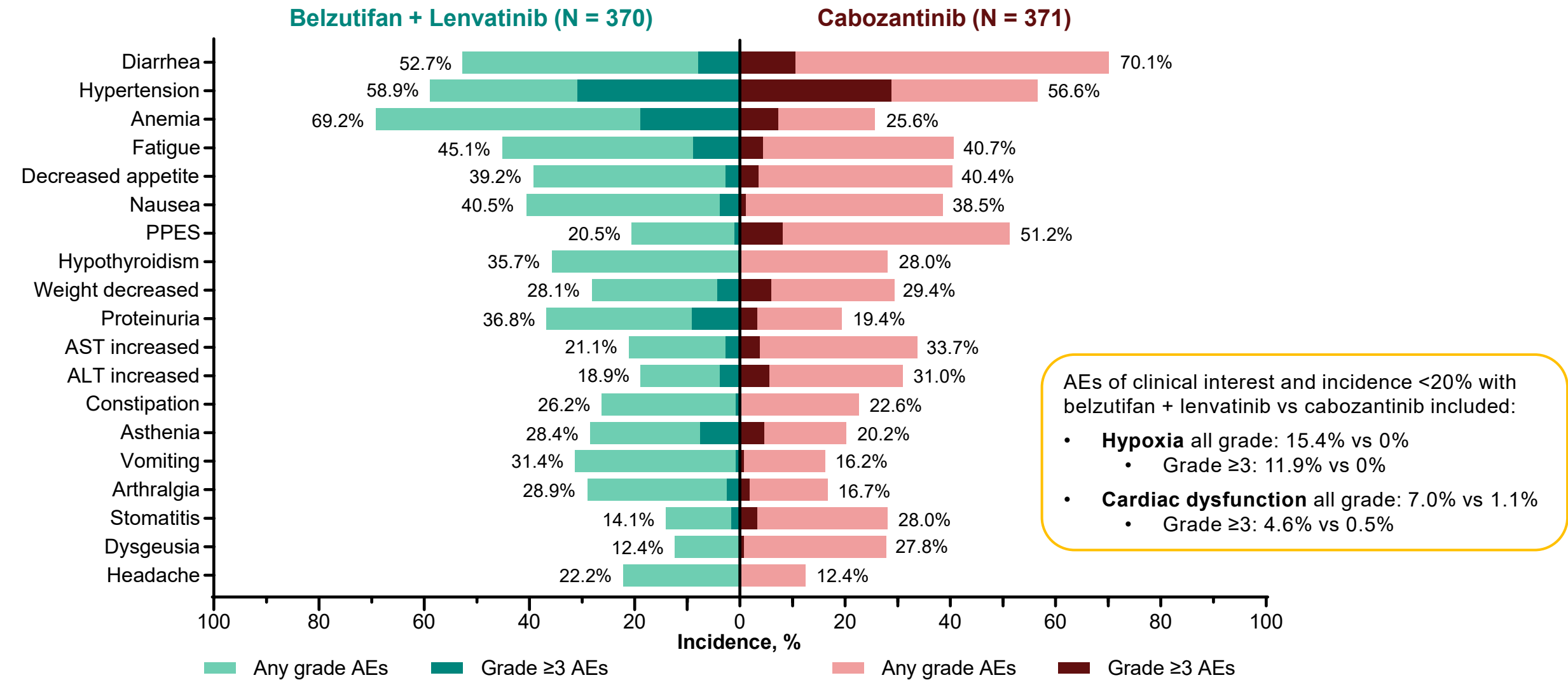
Treatment-related AEs	Belzutifan + Lenvatinib (N = 370)	Cabozantinib (N = 371)
Pts with AE, n (%)		
Any	361 (97.6)	363 (97.8)
Grade ≥3	265 (71.6)	244 (65.8)
Serious	98 (26.5)	63 (17.0)
Led to death ^b	2 (0.5)	1 (0.3)

^aReported for the as-treated population, defined as all randomized pts who received ≥1 dose of study treatment.

^bTreatment-related AEs that led to death were thrombotic microangiopathy (n=1) and pneumonitis (n=1) in the belzutifan + lenvatinib arm, and hemoptysis (n=1) in the cabozantinib arm.

Common Treatment-Emergent AEs^a

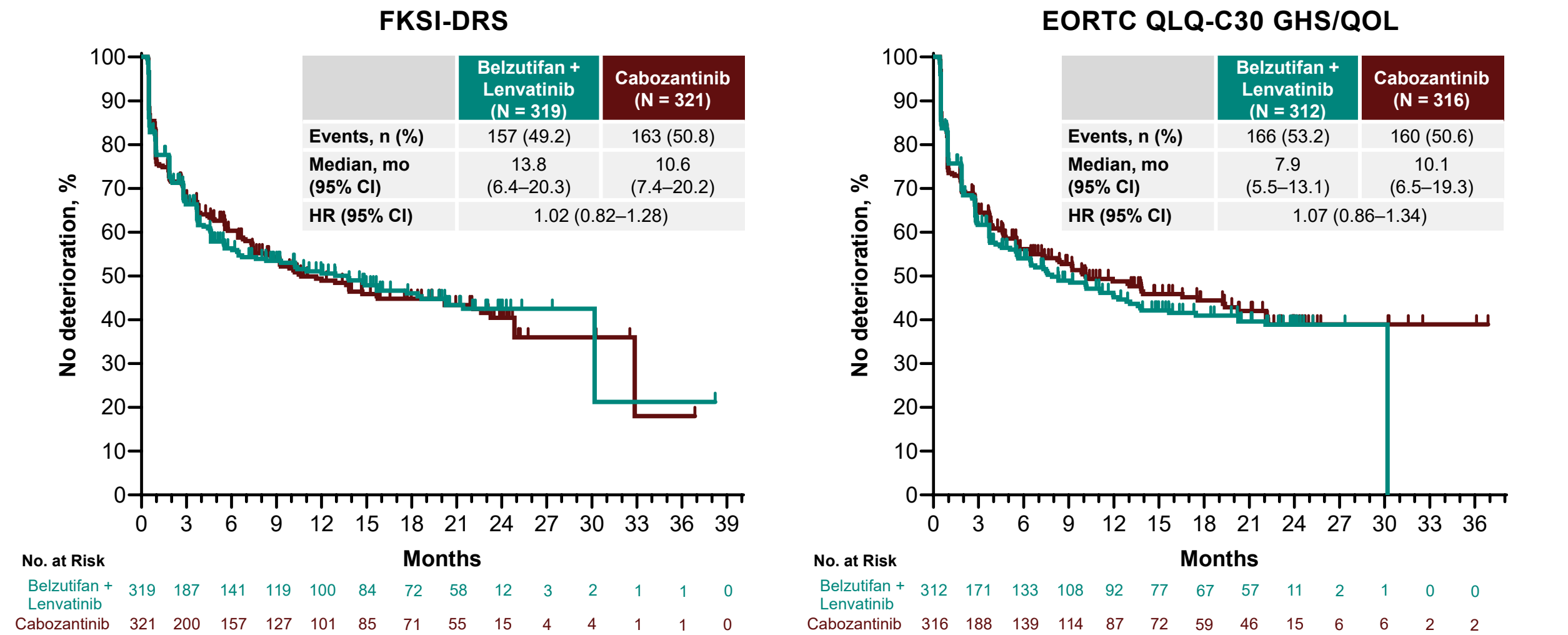
Incidence $\geq 20\%$ in Any Arm



ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPES, palmar-plantar erythrodysesthesia syndrome.

^aCollected up to 30 days after cessation of study treatment.

Exploratory Endpoint: Time to Deterioration in Patient-Reported Outcomes



Summary and Conclusions

- Belzutifan + lenvatinib demonstrated superior PFS and ORR vs cabozantinib in participants with advanced clear cell RCC following anti-PD-(L)1 therapy
- OS favored belzutifan + lenvatinib but did not reach statistical significance and will be tested further at final analysis
- The safety profile of belzutifan + lenvatinib was generally consistent with the profiles of the individual drugs
- Time to worsening in disease-specific symptoms and quality of life were similar between belzutifan + lenvatinib vs cabozantinib
- LITESPARK-011 is the first phase 3 study of a HIF-2 α inhibitor plus a VEGFR-TKI, and the first phase 3 study in RCC in the post-PD-(L)1 setting to show improved outcomes vs a contemporary VEGFR-TKI
- Belzutifan + lenvatinib addresses an unmet clinical need and represents a potential new treatment option for patients with RCC that progressed after anti-PD-(L)1 therapy

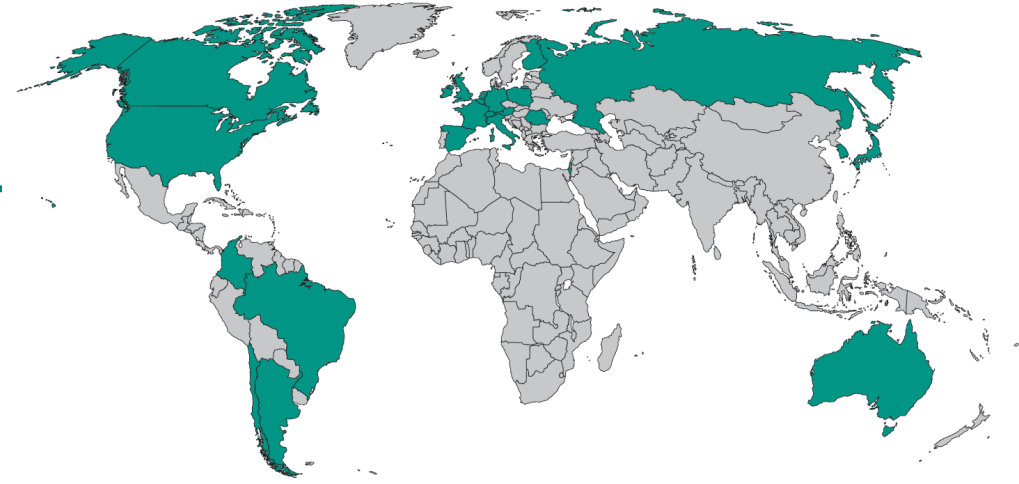
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Acknowledgments

Participants and their families

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This study was funded and conducted by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA (MSD).

MSD: The LITESPARK-011 study team, including but not limited to Ke (Cindy) Chen, Shuyan (Sabrina) Wan for statistical analysis support and oversight; Donna Vickery for study support; M. Catherine Pietanza for study support and critical review; Ina Bremer for writing assistance; Shaun Patrick Rosebeck and Jennifer Pawlowski for administrative/logistical support

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