Renal Cell Carcinoma

Clinical Updates from Madrid

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Belzutifan for RCC

- Belzutifan is an oral HIF inhibitor approved to treat patients with VHL-associated RCC and other tumors, who do not require immediate surgery

Phase 2 Study Leading to Approval for VHL-Associated RCC

	NCT03401788[1]
Phase	2 (single arm)
Intervention	Belzutifan 120 mg PO QD
Patient population	RCC associated with VHL disease (N = 61)
Median follow-up	21.8 months
Primary endpoint	ORR
ORR	49%
trAEs	33% (grade ≥3); 15% (grade 3)

Belzutifan for Sporadic ccRCC

	LITESPARK-001[2] (NCT02974738)
Phase	1/2 (single arm)
Intervention	Belzutifan
Patient population	Advanced, previously treated ccRCC (n = 55)
MTD	Not reached up to 240 mg per day
RP2D	120 mg QD
Median follow up	28 months
ORR	25% (favorable risk, 31%; intermediate/poor risk, 24%)
DCR	80%
Median DOR	NR
Median PFS	14.5 months
trAE (grade ≥3)	19%

- Not FDA-approved for use in sporadic ccRCC
- Included in NCCN guidelines as "useful in certain circumstances" for subsequent therapy in ccRCC, regardless of patient's prior immunotherapy status (category 2B)[3]

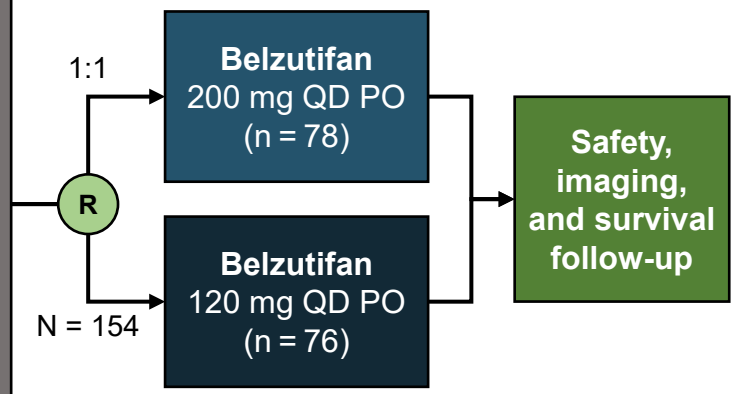
ccRCC, clear cell renal cell carcinoma; DCR, disease control rate; DOR, duration of response; FDA, US Food and Drug Administration; HIF, hypoxia-inducible factor; MTD, maximum tolerable dose; NCCN, National Comprehensive Cancer Network; NR, not reached; ORR, overall response rate; PFS, progression-free survival; PO, by mouth; QD, once daily; RCC, renal cell carcinoma; RP2D, recommended phase 2 dose; trAE, treatment-related adverse events; VHL, von Hippel-Lindau.

1. Jonasch E, et al. *N Engl J Med*. 2021;385:2036-2046. 2. Choueiri TK, et al. *Nat Med*. 2021;27(5):802-805. 3. NCCN. Kidney cancer. V1.2024. June 21, 2023.

1881O, Safety and Efficacy of 2 Doses of Belzutifan in Patients With Advanced RCC: Results of the Randomized, Phase 2 LITESPARK-013 Study

Key eligibility criteria
- Histologically confirmed advanced/metastatic RCC with clear cell component
- Measurable disease per RECIST v1.1
- Received ≤3 prior systemic therapies for advanced/metastatic disease
- Received only 1 prior anti–PD-(L)1 therapy

Stratification factors
- IMDC prognostic scores (0 vs 1-2 vs 3-6)
- Number of prior TKI regimens for advanced RCC (0 vs 1 vs 2-3)



Endpoints
- Primary: ORR (per RECIST v1.1 by BICR)
- Secondary: PFS and DOR (per RECIST v1.1 by BICR), OS, and safety

Tumor assessments
- At week 9, then every 8 weeks through week 49, and then every 12 weeks thereafter

ClinicalTrials.gov ID: NCT04489771

	Belzutifan 200 mg (n = 78)	Belzutifan 120 mg (n = 76)
ORR (CR + PR), n (%)	18 (23.1%)	18 (23.7%)
	Estimated difference (95% CI), -0.5 (-14.0 to 12.9); one-sided *P* = .5312	
DCR (CR + PR + SD), n (%)	61 (78.2%)	57 (75.0%)
Best response, n (%)		
CR	4 (5.1%)	0
PR	14 (17.9%)	18 (23.7%)
SD	43 (55.1%)	39 (51.3%)
PD	12 (15.4%)	15 (19.7%)
No assessment	5 (6.4%)	4 (5.3%)
PFS, HR (95% CI)	0.94 (0.63-1.40)	
OS, HR (95% CI)	1.11 (0.65-1.90)	
trAE (any grade)	92%	92%
trAE (grade 3/4)	46%	46%
trAE-related interruption	21%	13%
trAE-related reduction	28%	24%
trAE-related discontinuation	9%	3%

BICR, blinded independent central review; CR, complete response; DCR, disease control rate; DOR, duration of response; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ORR, overall response rate; OS, overall survival; PD, progressive disease; PD-(L)1, programmed cell death protein 1 or its ligand; PFS, progression-free survival; PO, by mouth; PR, partial response; QD, once daily; R, randomization; RCC, renal cell carcinoma; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease; TKI, tyrosine kinase inhibitor; trAE, treatment-related adverse event.

1. Agarwal N, et al. ESMO 2023. Abstract 1881O.

Summary of 1L Combination Regimens for Treatment-Naive, Advanced RCC

Trial	CheckMate 214[1-3,a] NCT02231749	KEYNOTE-426[4-6] NCT02853331	CheckMate 9ER[7-11] NCT03141177	CLEAR[12-16] NCT02811861
Phase	3	3	3	3
Intervention	Ipilimumab + nivolumab vs sunitinib	Axitinib + pembrolizumab vs sunitinib	Cabozantinib + nivolumab vs sunitinib	Lenvatinib + pembrolizumab vs sunitinib
N	1096	861	651	712
FDA approval	2018, 1L for int/poor risk	2019, 1L	2021, 1L	2021, 1L
Risk (fav/int/poor)[b]	23%/61%/17%	32%/55%/13%	23%/58%/19%	31%/58%/9%
Median follow-up	67.7 months	67.2 months	44.0 months	33.7 months
Median OS (ITT)	55.7 vs 38.4 months HR (95% CI), 0.72 (0.62-0.85)	41.9 vs 37.1 months HR (95% CI), 0.84 (0.71-0.99)[c]	49.5 vs 35.5 months HR (95% CI), 70 (0.56-0.87)	NR vs NR HR (95% CI), 0.72 (0.55-0.93)
Median PFS (ITT)	12.3 vs 12.3 months HR (95% CI), 0.86 (0.73-1.01)	15.7 vs 11.1 months HR (95% CI), 0.69 (0.59-0.81)[c]	16.6 vs 8.4 months HR (95% CI), 0.59 (0.49-0.71)[c]	23.3 vs 9.2 months HR (95% CI), 0.42 (0.34-0.52)[c]
ORR (ITT)	39% vs 32%[a]	60% vs 40%	56% vs 28%	71% vs 36%
CR (ITT)	12% vs 3%	12% vs 4%	13% vs 5%	17% vs 4%
PD (ITT)	18% vs 14%	12% vs 17%	6% vs 14% (33-month follow-up)	5% vs 14%
trAE (grade ≥3)	48% vs 64% (grade 3-4)	68% vs 64%	67% vs 55%	72% vs 73%

[a]Primary endpoints of CheckMate 214 included OS (HR, 0.65; 95% CI, 0.54-0.78), PFS per IRRC (HR, 0.74; 95% CI, 0.62-0.88), and ORR per IRRC (41.9% vs 26.8%; $P < .0001$) in int/poor-risk population. [b]IMDC prognostic risk. [c]Primary endpoint.

1L, first line; CR, complete response; fav, favorable; FDA, US Food and Drug Administration; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; int, intermediate; IRRC, independent radiology review committee; ITT, intent to treat; NR, not reached; ORR, overall response rate; OS, overall survival; PD, disease progression; PFS, progression-free survival; RCC, renal cell carcinoma; trAE, treatment-related adverse event.

1. Motzer RJ, et al. *Cancer*. 2022;128:2085-2097. 2. Motzer RJ, et al. ESMO 2021. Abstract 661P. 3. Albiges L, et al. *ESMO Open.* 2020;5:e0001079. 4. Rini BI, et al. ASCO 2023. Abstract LBA4501. 5. Rini BI, et al. ASCO 2021. Abstract 4500. 6. Powles T, et al. *Lancet Oncol*. 2020;21:1563-1573. 7. Burotto M, et al. ASCO GU 2023. Abstract 603. 8. Powles T, et al. GU Cancers Symposium 2022. Abstract 350. 9. Motzer RJ, et al. *Lancet Oncol*. 2022;23:888-898. 10. Choueiri TK, et al. *N Engl J Med.* 2021;384:829-41. 11. Apolo A, et al. ASCO 2021. Abstract 4553. 12. Choueiri TK, et al. *Lancet Oncol*. 2023;24:228-238. 13. Porta CG, et al. ESMO 2022. Abstract 1449MO. 14. Motzer RJ, et al. *N Engl J Med*. 2021;384:1289-1300. 15. Grünwald V, et al. ASCO 2021. Abstract 4560. 16. Choueiri TK, et al. KCRS21. Oral Abstract.

LBA87, Phase 2 LITESPARK-003 Study of Belzutifan in Combination With Cabozantinib for Advanced ccRCC—Cohort 1, First-line Therapy

Key eligibility criteria
- Advanced or metastatic ccRCC
- Being treatment naive **or** having previously received immunotherapy and ≤2 regimens for locally advanced or metastatic RCC
- ECOG PS 0 or 1
- All IMDC risk categories (favorable, intermediate, or poor) allowed

Cohort 1 (treatment naive)
Belzutifan 120 mg/d PO + cabozantinib 60 mg/d PO
(n ≈ 50)

Cohort 2 (prior immunotherapy with or without prior targeted therapy)
Belzutifan 120 mg/d PO + cabozantinib 60 mg/d PO
(n ≈ 50)

Tumor assessments
- Every 8 weeks after week 9 for 12 months and then every 12 weeks thereafter

Endpoints
- Primary: ORR
- Secondary: PFS, TTR, DOR, OS, safety/tolerability, pharmacokinetics/ pharmacodynamics

Safety and tolerability were evaluated in the first 6 participants enrolled, irrespective of cohort.
- If tolerability was established, enrollment continued
- If tolerability was not established, dose was reviewed

ClinicalTrials.gov ID: NCT03634540

Cohort 1, First-line Therapy
(median follow-up[a], 24.3 months)

	All (n = 50)	IMDC risk group	
		Favorable (n = 28)	Intermediate or poor (n = 22)
ORR	59%	70%	79%
CR	5%	8%	11%
PR	55%	62%	68%
SD	36%	28%	21%
PD	5%	2%	0
Median DOR	28.6 months		
Median PFS	30.3 months		
Median OS	NR		
trAEs (grades 3-5)	46%		

Data cutoff: May 15, 2023.

[a]Follow-up = the time from the first dose to the database cutoff date.

ccRCC, clear cell renal cell carcinoma; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; PO, by mouth; PR, partial response; RCC, renal cell carcinoma; SD, stable disease; trAE, treatment-related adverse event; TTR, time to response.

1. Choueiri TK, et al. ESMO 2023. Abstract LBA87.

1882O, RENOTORCH: Toripalimab Combined With Axitinib Versus Sunitinib in 1L Treatment of Advanced RCC—a Randomized, Open-Label, Phase 3 Study

Key eligibility criteria
- Unresectable or metastatic ccRCC with or without sarcomatoid components
- No previous systemic antitumor therapy
- Intermediate/poor risk per IMDC criteria
- ECOG PS 0 or 1
- ≥1 measurable lesion per RECIST v1.1

Stratification factors
- IMDC risk group (intermediate vs poor)

1:1 randomization (R)

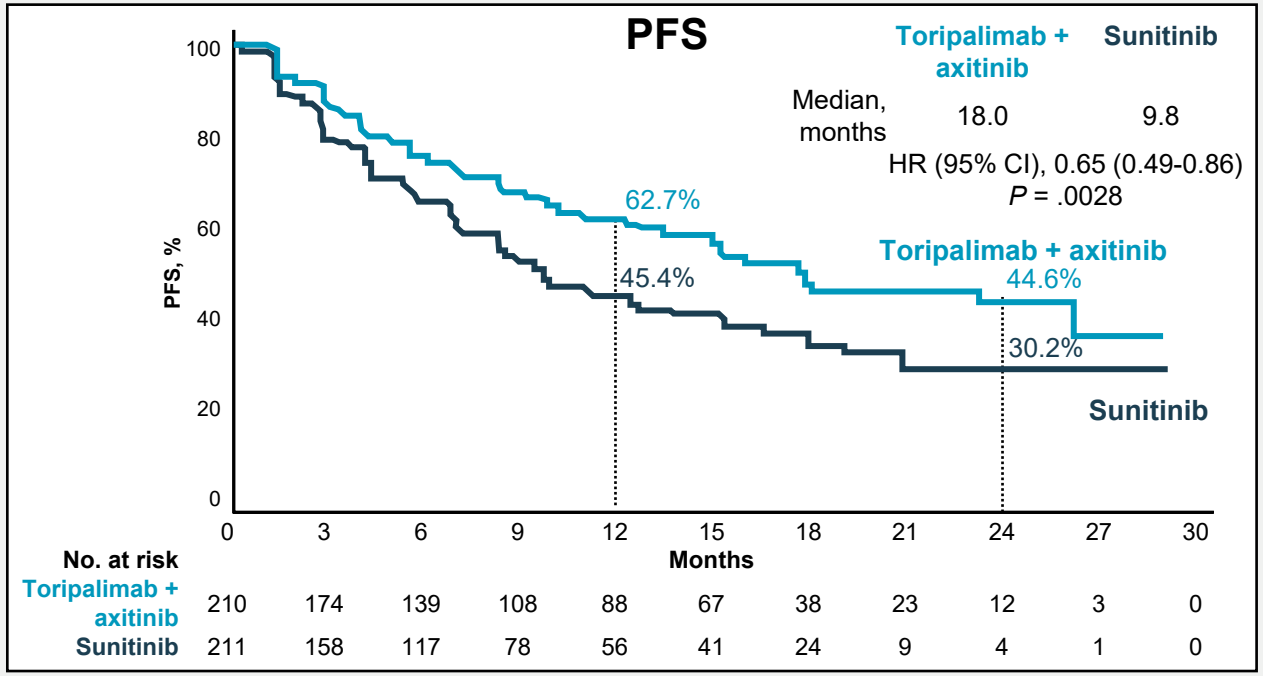
- Toripalimab 240 mg Q3W + axitinib 5 mg BID
- Sunitinib 50 mg QD for 4 weeks (6-week cycle) or 2 weeks (3-week cycle)

Treatment until disease progression or intolerable toxicity

Median follow-up, 14.6 months

Endpoints
- Primary: PFS by BICR per RECIST v1.1
- Secondary: ORR, OS, PFS per investigator, DOR, DCR, 1- and 2-year OS rates, and safety

ClinicalTrials.gov ID: NCT04394975



Safety Summary

	Toripalimab + axitinib (n = 208)	Sunitinib (n = 210)
Any TEAE (grade ≥3)	71%	67%
TEAE-related interruption	69%	43%
TEAE-related discontinuation	14%	8%

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Toripalimab plus axitinib versus sunitinib as first-line treatment for advanced renal cell carcinoma: RENOTORCH, a randomized, open-label, phase III study

1L, first line; BICR, blinded independent central review; BID, twice daily; ccRCC, clear cell renal cell carcinoma; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; QD, once daily; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; TEAE, treatment-emergent adverse event.

1. Sheng X, et al. ESMO 2023. Abstract 1882O. 2. Yan XQ, et al. *Ann Oncol*. 2023;S0923-7534(23)04003-6.

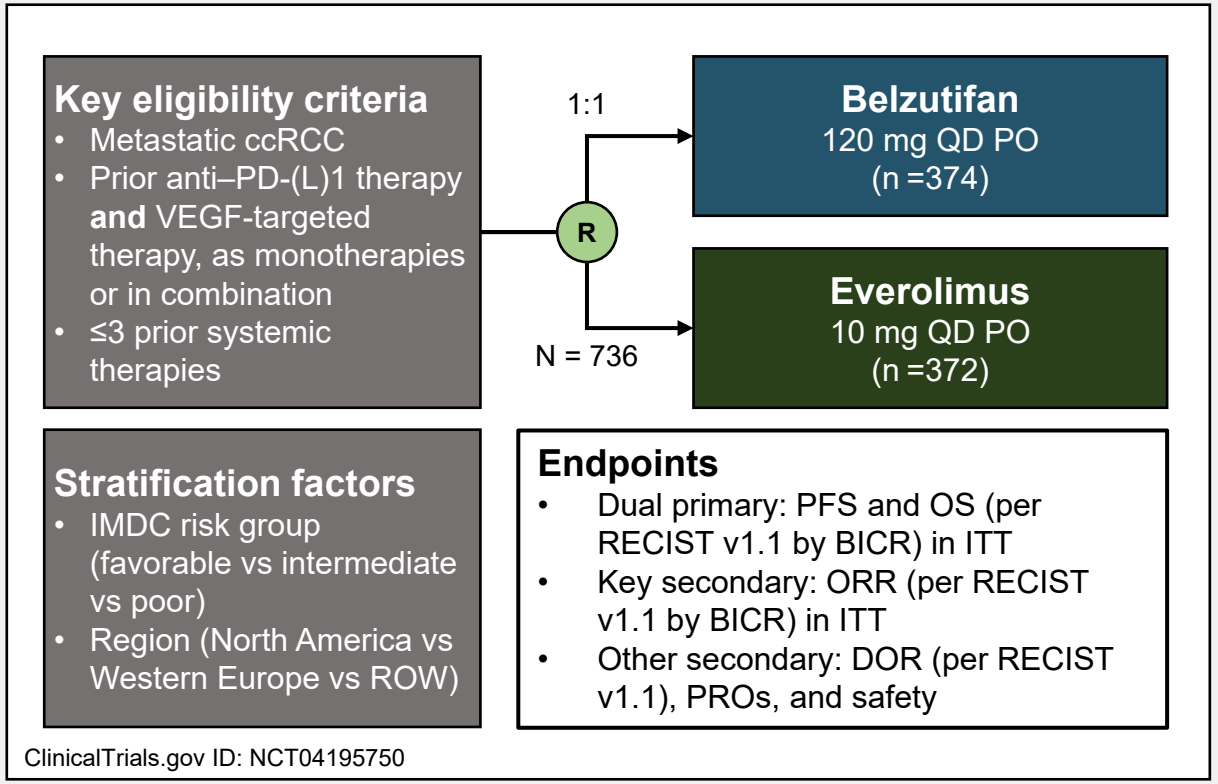
Summary of Selected Subsequent-Line Therapy Options for Advanced/Metastatic RCC

Trial	AXIS[1,2] NCT00678392	METEOR[3] NCT01865747	Study 205[4] NCT01136733	TIVO-3[5,6] NCT02627963
Phase	3	3	2	3
Intervention	Axitinib vs sorafenib	Cabozantinib vs everolimus	Lenvatinib + everolimus vs lenvatinib or everolimus	Tivozanib vs sorafenib
Patient population	ccRCC with PD despite 1L sunitinib, bevacizumab + IFN-alfa, temsirolimus, or cytokines (N = 723)	TKI-refractory, ccRCC (71% 1 prior) (N = 658)	TKI-refractory, ccRCC (100% 1 prior) (N = 153)	TKI-refractory, ccRCC, 2-3 prior regimens (N = 350)
Median follow-up	NR	18.7 months	24.2 months	19 months
Primary endpoint	PFS (IRC)	PFS (IRC)	PFS (INV)	PFS (IRC)
ORR	19% vs 9%	17% vs 3%	43% vs 27% vs 6%	23% vs 11%
Median PFS	6.7 vs 4.7 months HR (95% CI), 0.665 (0.544-0.812); *P* < .0001	7.4 vs 3.9 months HR (95% CI), 0.51 (0.41-0.62); *P* < .0001	14.6 vs 7.4 vs 5.5 months HR (95% CI) for L+E vs E, 0.40 (0.24-0.68); *P* = .0005	5.6 vs 3.9 months HR (95% CI), 0.73 (0.56-0.94); *P* = .016
Median OS	20.1 vs 19.2 months HR (95% CI), 0.969 (0.800-1.174); *P* = .3744	21.4 vs 16.5 months HR (95% CI), 0.66 (0.53-0.83); *P* = .00026	25.5 vs 19.1 vs 15.4 months HR (95% CI) for L+E vs E, 0.51 (0.30-0.88); *P* = .024	— HR (95% CI), 0.89 (0.70-1.14) (mean follow-up, 22.8 months[6])
Toxicity	Most common grade 3/4: HTN, 16%; diarrhea, 11%; fatigue, 11%	71% (grade 3/4)	L+E: 57% (grade 3); 14% (grade 4)	Most common grade 3/4: HTN

1L, first line; ccRCC, clear cell renal cell carcinoma; E, everolimus; HR, hazard ratio; HTN, hypertension; IFN, interferon; INV, investigator; IRC, independent review committee; L, lenvatinib; NR, not reported; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

1. Rini BI, et al. *Lance*t. 2011;378:1931-1939. 2. Motzer RJ, et al. *Lancet Oncol*. 2013;14:552-562. 3. Choueiri TK, et al. *Lancet Oncol.* 2016;17:917-927. 4. Motzer RJ, et al. *Lancet Oncol*. 2015;16:1473-1482. 5. Rini BI, et al. *Lancet Oncol*. 2020;21:95-104. 6. Rini BI, et al. ASCO 2022. Abstract 4557.

LBA88, Belzutifan Versus Everolimus in Participants With Previously Treated, Advanced ccRCC: Randomized, Open-Label, Phase 3 LITESPARK-005 Study



	Interim analysis 1 (median follow-up, 18.4 months)		Interim analysis 2 (median follow-up, 25.7 months)	
	Belzutifan (n = 374)	Everolimus (n = 372)	Belzutifan (n = 374)	Everolimus (n = 372)
Median PFS	5.6 months	5.6 months	5.6 months	5.6 months
	HR (95% CI), 0.75 (0.63-0.90); *P* < .001		HR (95% CI), 0.74 (0.63-0.88)	
Median OS	21.0 months	17.2 months	21.4 months	18.1 months
	HR (95% CI), 0.87 (0.71-1.07); *P* = .096		HR (95% CI), 0.88 (0.73-1.07); *P* = .099	
ORR	21.9%	3.5%	22.7%	3.5%
	P < .00001		N/A	

- Similar rates of grade ≥3 trAEs between study arms (39%)
- Lower rates of AE-related treatment discontinuations with belzutifan (6% vs 15%)

AE, adverse event; BICR, blinded independent central review; ccRCC, clear cell renal cell carcinoma; DOR, duration of response; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ITT, intent to treat; ORR, overall response rate; OS, overall survival; PD-(L)1, programmed cell death protein 1 or its ligand; PFS, progression-free survival; PO, by mouth; PRO, patient-reported outcome; QD, once daily; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; ROW, rest of world; trAE, treatment-related adverse event; VEGF, vascular endothelial growth factor.

1. Albiges L, et al. ESMO 2023. Abstract LBA88.