KEYTRUDA® (pembrolizumab) LENVATINIB Eisai

Focus on possibilities

FOR TREATING YOUR PATIENTS WITH ADVANCED RCC

KEYTRUDA® (pembrolizumab), in combination with **LENVATINIB Eisai***, is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).[1,2]

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/ (**please note that the MHRA Yellow Card link will redirect you to an external website, for which MSD does not review or control the content**) or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Merck Sharp & Dohme (UK) Limited (Tel: 020 8154 8000).

Prescribing Information for KEYTRUDA and LENVATINIB can be accessed via the 'PI' button at the bottom of this page and throughout.

*LENVATINIB Eisai will be referred to as LENVATINIB across this document.

Please consult the KEYTRUDA and LENVATINIB Summary of Product Characteristics and the KEYTRUDA Risk Management Materials for further information before making any prescribing decisions.

Job code: GB-KLR-00357 Date of preparation: May 2025

Kim and Jack both have advanced RCC

Kim

- 72 years old, initially presented with abdominal discomfort and unexplained weight loss
- Performance status: 0–1
- Diagnosed with Stage IV advanced RCC, clear cell histology
  - 7.5 cm left renal mass and multiple liver metastases
  - Anaemia and slightly elevated liver enzymes
  - Renal function: Creatinine ≤1.5 × ULN
- IMDC: Intermediate risk

What treatment goals would you prioritise for Kim?

PATIENT OUTCOMES	YOUR ORDER OF PRIORITY
PFS	PFS
ORR	ORR
OS	
TTR	
DOR	
HRQoL	
AEs	

Patient cases are fictional and for illustrative purposes only.

AE, adverse event; DOR, duration of response; HRQoL, health-related quality of life; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; ULN, upper limit of normal; TTR, time to respond.

Kim and Jack both have advanced RCC

Jack

- 68 years old, former smoker with high cholesterol. Previous history of right total nephrectomy to treat RCC. Initially complained of lower back pain
- Performance status: 0–1
- Diagnosed with Stage IV metastatic RCC, clear cell histology
  - 14 cm mass in left kidney with growth into the Gerota's fascia, lymph node involvement and multiple pulmonary lesions
  - Lung and bone metastases
- IMDC: Poor risk

What treatment goals would you prioritise for Jack?

PATIENT OUTCOMES	YOUR ORDER OF PRIORITY
PFS	PFS
ORR	ORR
OS	
TTR	
DOR	
HRQoL	
AEs	

Patient cases are fictional and for illustrative purposes only.

AE, adverse event; DOR, duration of response; HRQoL, health-related quality of life; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; ULN, upper limit of normal; TTR, time to respond.

What do patients prioritise when considering treatment options?

Of the 1062 patients who participated in the 2022 KCCure online survey aimed at gathering perspectives on systemic therapy in RCC, 399 had metastatic disease[a,3]

According to the patient survey, the three most important outcomes for mRCC treatment selection, ranked on a scale of 1 to 8 were:[3]

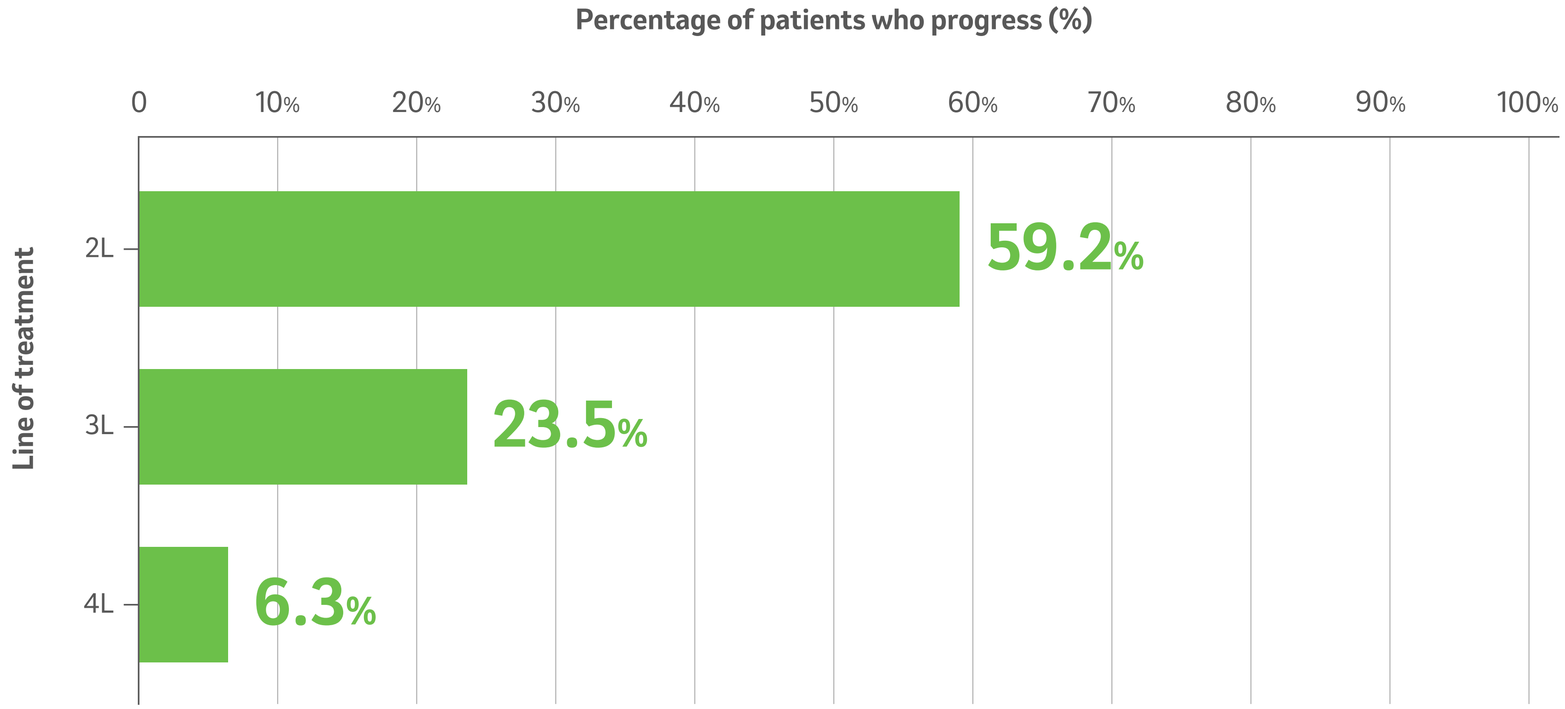
1. **Complete response[b] (6.6)**
2. **Durability of response (5.1)**
3. **Improved quality of life (5.0)**

[a]Data collected between July 2022–September 2022. 80% of patients were receiving or had received systemic therapy. 52% of patients were female with a median age of 57 years (range 28–86). 89% identified as white and 86% living in the United States; [b]Defined as elimination of all evidence of disease.

KCC, Kidney Cancer Research Alliance; RCC, renal cell carcinoma.

Percentage of patients on subsequent lines of treatment: UK audit (2018–2021)[a,4]

(retrospective analysis)



Adapted from Frazer R, et al. ESMO Real World Data and Digital Oncology. 2024.[4]

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Choosing an effective treatment at 1L for patients with advanced RCC is critical

[a]A retrospective analysis of patients treated between January 2018 to June 2021. Data was collected from 17 UK sites including 1319 patients (male: n=937; female: n=382) who received first line systemic treatment for metastatic RCC. IMDC prognostic groups were: favourable (n=294, 22.3%), intermediate (n=695, 52.7%) and poor risk (n=321, 24.3%).[4]

1L, first-line; 2L, second-line; 3L, third line; 4L, fourth line; IMDC, International Metastatic RCC Database Consortium; RCC, renal cell carcinoma; UK, United Kingdom.

Focus on possibilities for treating your patients with **KEYTRUDA** in combination with **LENVATINIB**

- **KEYTRUDA**, in combination with **LENVATINIB**, is indicated for the 1L treatment of adult patients with advanced RCC[1,2]

A dual MOA that targets two different disease pathways >

- **KEYTRUDA + LENVATINIB** is recommended as an option by the ESMO guidelines for the treatment of eligible patients with advanced non-clear cell and clear-cell RCC[5]

ESMO guidelines treatment algorithms >

1L, first-line; ESMO, European Society for Medical Oncology; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MOA, mechanism of action; RCC, renal cell carcinoma.

The efficacy and safety of KEYTRUDA + LENVATINIB vs sunitinib monotherapy were investigated in the CLEAR trial[12]

A randomised, multicentre, open-label, phase 3 trial evaluating the efficacy and safety of KEYTRUDA + LENVATINIB in patients with advanced RCC in the 1L setting (N=1069)

Key eligibility criteria

- Previously untreated advanced RCC with a clear cell component in the 1L setting
- At least one measurable lesion according to RECIST v1.1
- KPS of ≥70
- Adequately controlled blood pressure, with or without medications

Key exclusion criteria

- Active autoimmune disease
- A medical condition that required immunosuppression

Stratification factors

- Geographical region
  - North America and Western Europe vs rest of the world
- Prognostic risk group
  - Favourable vs intermediate vs poor

R
1:1:1
N=1069

n=355 → **KEYTRUDA** 200 mg IV Q3W; up to 24 months
LENVATINIB 20 mg PO QD for each 21-day cycle; up to and beyond 24 months

n=357 → **Sunitinib** 50 mg PO QD; 4 weeks on and 2 weeks off

n=357 → **LENVATINIB** 18 mg PO QD and everolimus 5 mg PO QD

Treatment continued until unacceptable toxicity or disease progression as determined by the investigator and confirmed by an independent review committee using RECIST v1.1

KEYTRUDA with **LENVATINIB** was permitted beyond RECIST-defined disease progression

Following discontinuation of the study drug, patients could receive subsequent 2L therapy

Assessment of tumour status was performed at screening and Q8W thereafter

Primary endpoint
- PFS per independent review committee

Secondary endpoints
- ORR per independent review committee; OS per independent review committee; safety

Adapted from Motzer R et al. *N Engl J Med*. 2021.[12]

1L use of LENVATINIB in combination with everolimus is not approved in the UK in patients with advanced RCC. This treatment arm has been included for transparency. Clinical data shown are from the KEYTRUDA + LENVATINIB vs sunitinib arms only.[1,2]

Full eligibility and exclusion criteria are described in the trial protocol.

1L, first-line; 2L, second-line; IV, intravenous; KPS, karnofsky performance status; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; Q3W, every 3 weeks; Q8W, every 8 weeks; QD, once daily; R, randomisation; RCC, renal cell carcinoma; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Patient baseline demographics and disease characteristics[12]

Characteristic[a]	KEYTRUDA + LENVATINIB (n=355)	Sunitinib (n=357)
Median age (range), years	64 (34–88)	61 (29–82)
Aged <65 years, n (%)	194 (54.6)	225 (63.0)
Sex, n (%)		
Male	255 (71.8)	275 (77.0)
Female	100 (28.2)	82 (23.0)
Geographical region, n (%)		
Western Europe or North America	198 (55.8)	199 (55.7)
Rest of the world	157 (44.2)	158 (44.3)
KPS, n (%)[b]		
100–90	295 (83.1)	294 (82.4)
80–70	60 (16.9)	62 (17.4)
MSKCC prognostic risk group, n (%)		
Favourable	96 (27.0)	97 (27.2)
Intermediate	227 (63.9)	228 (63.9)
Poor	32 (9.0)	32 (9.0)
IMDC prognostic risk group, n (%)		
Favourable	110 (31.0)	124 (34.7)
Intermediate	210 (59.2)	192 (53.8)
Poor	33 (9.3)	37 (10.4)
Could not be evaluated	2 (0.6)	4 (1.1)

Characteristic[a]	KEYTRUDA + LENVATINIB (n=355)	Sunitinib (n=357)
Sarcomatoid features, n (%)	28 (7.9)	21 (5.9)
PD-L1 combined positive score, n (%)		
≥1	107 (30.1)	119 (33.3)
<1	112 (31.5)	103 (28.9)
Not available	136 (38.3)	135 (37.8)
Number of metastatic organs or sites, n (%)[c]		
1	97 (27.3)	108 (30.3)
≥2	254 (71.5)	246 (68.9)
Site of metastasis, n (%)[d]		
Lung	249 (70.1)	239 (66.9)
Lymph node	170 (47.9)	159 (44.5)
Bone	85 (23.9)	97 (27.2)
Liver	60 (16.9)	61 (17.1)
Previous nephrectomy, n (%)	262 (73.8)	275 (77.0)

Adapted from Motzer R et al. *N Engl J Med*. 2021.[12]

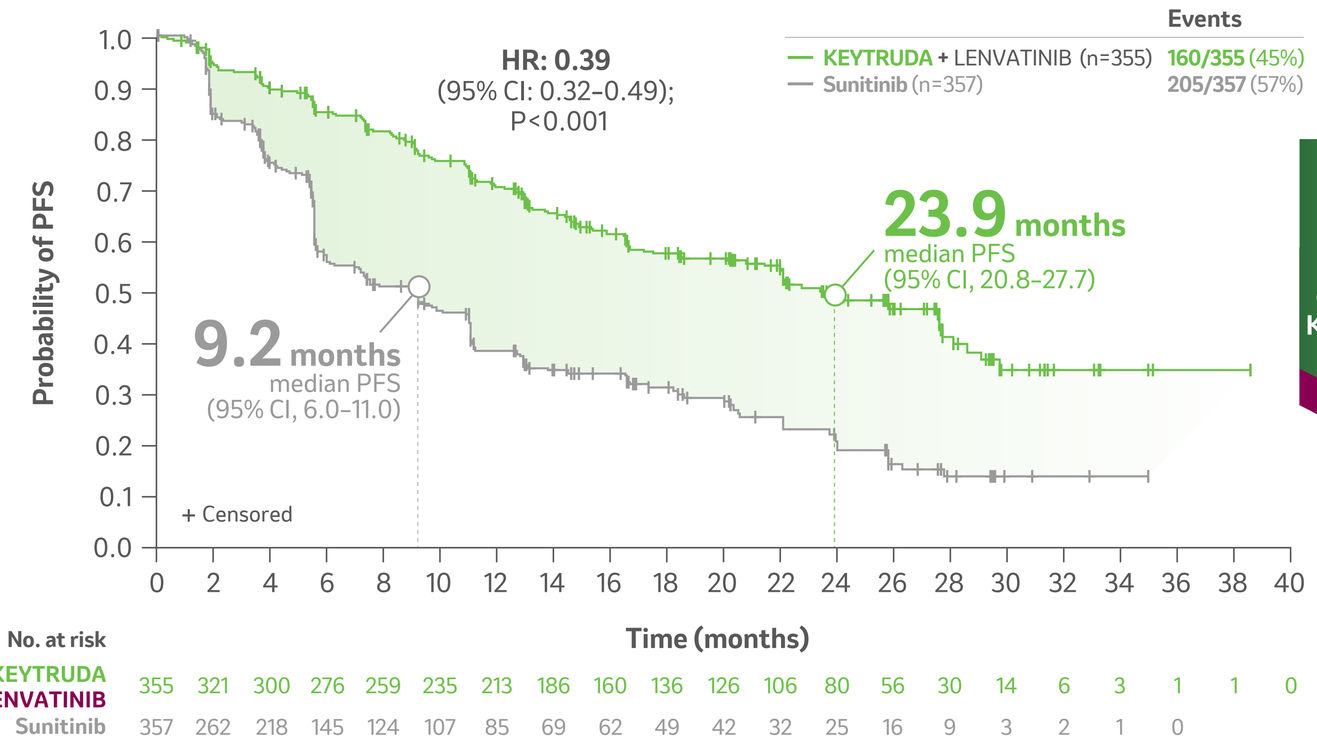
[a]One patient in the KEYTRUDA + LENVATINIB group had carcinoma without a clear cell component; [b]KPS was missing for one patient in the sunitinib group; [c]Kidney was not included in the number of metastatic organs or sites; [d]Four common sites of metastasis are shown. Patients may have had metastasis at more than one site.

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, karnofsky performance status; MSKCC, Memorial Sloan Kettering Cancer Center; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand-1; PFS, progression-free survival.

Primary endpoint – **KEYTRUDA** + **LENVATINIB** more than doubled median PFS vs sunitinib[a,12]

PFS was significantly longer in the **KEYTRUDA** + **LENVATINIB** group compared with the sunitinib group

Kaplan-Meier analysis of PFS: Superior PFS vs sunitinib



	Events
KEYTRUDA + LENVATINIB (n=355)	**160/355** (45%)
Sunitinib (n=357)	**205/357** (57%)

61% reduction in risk of disease progression with **KEYTRUDA** + LENVATINIB vs sunitinib

No. at risk																					
KEYTRUDA + **LENVATINIB**	355	321	300	276	259	235	213	186	160	136	126	106	80	56	30	14	6	3	1	1	0
Sunitinib	357	262	218	145	124	107	85	69	62	49	42	32	25	16	9	3	2	1	0		

Adapted from Motzer R et al. *N Engl J Med*. 2021.[12]

Analysis cutoff date: 28 August 2020. Median follow-up: 26.6 months.

[a]Assessed using RECIST v1.1 by an independent review committee.

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

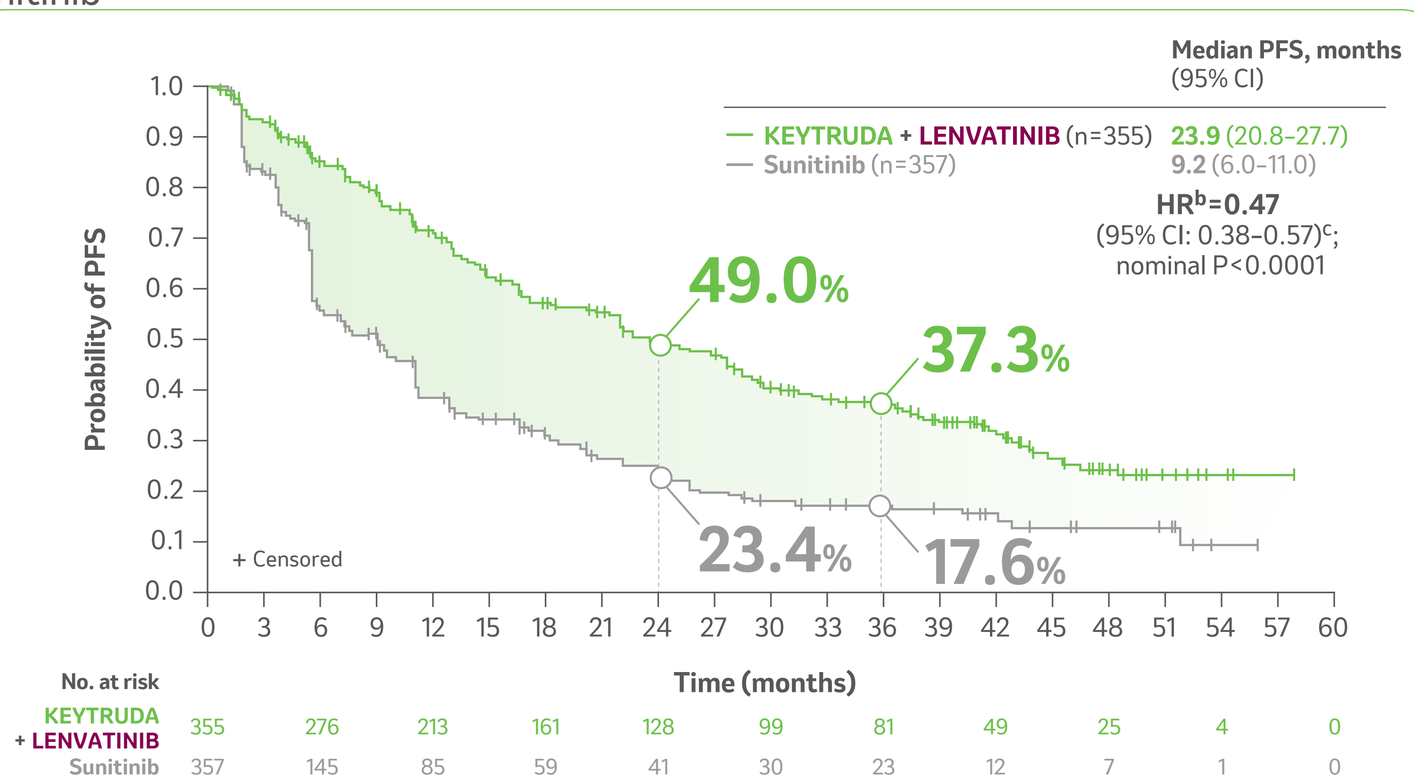
Subgroup analysis ›

Tumour responses in subgroups of interest ›

What could this mean for your patients like Kim and Jack? ›

Exploratory analysis – Kaplan-Meier estimates of PFS remained consistent with primary analysis at 39.2 months median follow-up[a,14]

Median (IQR) follow-up for PFS: 39.2 (22.1–48.5) months with **KEYTRUDA** + **LENVATINIB** and 20.6 (5.5–41.2) months with sunitinib



Adapted from Motzer R et al. ASCO 2023.[14]

LIMITATION: No formal statistical testing was performed for this analysis, and, therefore, no conclusions can be drawn.

IMDC subgroup analysis ›

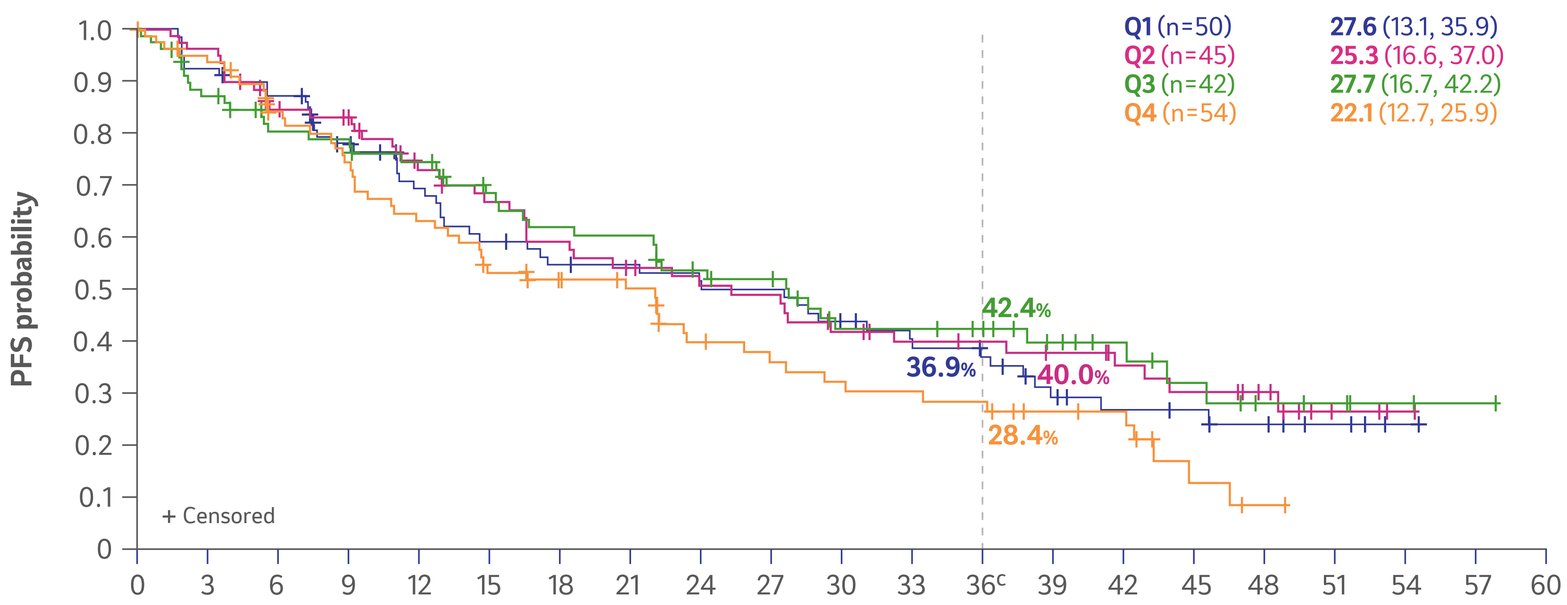
Analysis cutoff date: 31 July 2022.

[a]Assessed using RECIST v1.1 by an independent review committee; [b]Hazard ratio based on a Cox proportional hazards model including treatment group as factor. Efron method used for ties and stratified by geographic region and MSKCC prognostic groups by IxRS factors; [c]The 95% CIs are estimated with a generalised Brookmeyer and Crowley method.

CI, confidence interval; HR, hazard ratio; IQR, interquartile range; IxRS, interactive voice/web response system; MSKCC, Memorial Sloan Kettering Cancer Center; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Exploratory analysis – PFS by tumour size subgroup[a,15]

Median (IQR) follow-up for PFS: 39.2 (22.1–48.5) months with **KEYTRUDA** + **LENVATINIB**



Patients at risk, n

Q1 (≤34.72 mm)	81	73	68	56	48	41	36	35	32	32	27	23	21	14	11	10	8	4	1	0	0
Q2 (>34.72 to ≤60.06 mm)	80	75	63	60	48	43	37	33	29	28	23	20	19	17	14	12	9	3	1	0	0
Q3 (>60.06 to ≤108.56 mm)	81	67	58	57	50	42	38	37	31	29	21	21	19	14	11	8	5	4	2	1	0
Q4 (>108.56 mm)	80	71	60	53	45	37	33	30	22	19	17	16	15	11	10	3	1	0	0	0	0

Adapted from Grünwald V et al. ASCO GU 2024.[15]

LIMITATION:
This study was not powered to detect differences in the treatment effect between these subgroups. Results from exploratory analyses should be interpreted with caution due to modest patient numbers and potential imbalances in baseline characteristics between subgroups.

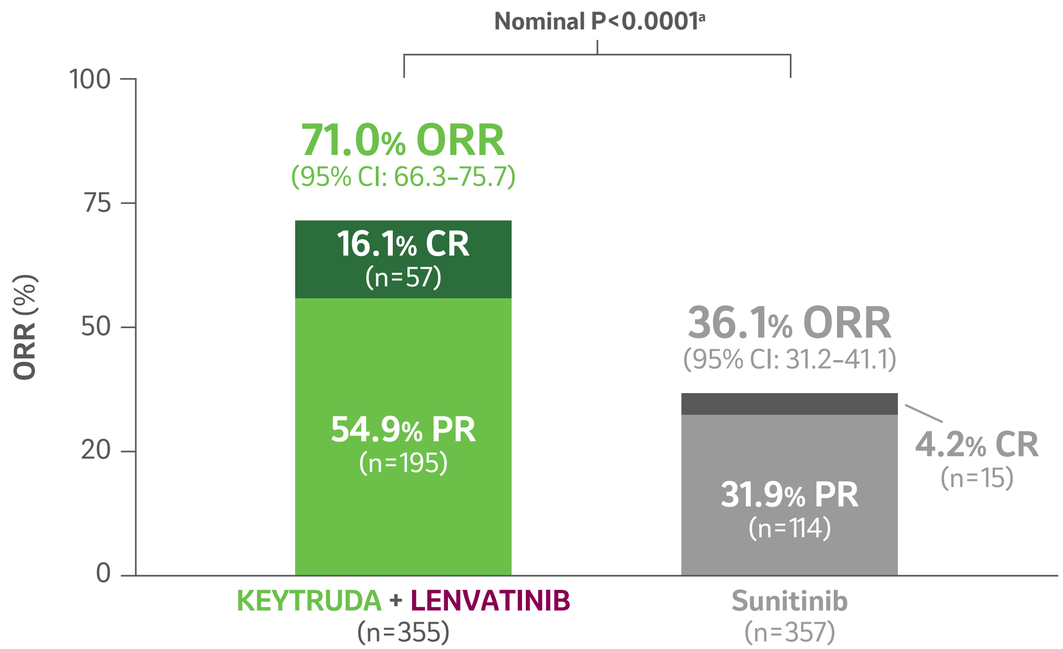
Patient characteristics ›

Data cutoff date: 31 July 2022.
[a]Assessed by independent imagine review per RECIST v1.1; [b]Medians were estimated by Kaplan-Meier method. The 95% CIs are estimated with a generalised Brookmeyer and Crowley method; [c]Survival rate at 36 months were calculated using Kaplan-Meier product-limit method.

CI, confidence interval; IQR, interquartile range; PFS, progression-free survival; Q, Quartile; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Secondary endpoint – 71% ORR with KEYTRUDA + LENVATINIB vs 36% with sunitinib[a,1,2,12]

Median follow-up: 26.6 months



Adapted from Motzer R et al. *N Engl J Med*. 2021.[12]

- Progressive disease was observed in 5.4% of patients who received KEYTRUDA + LENVATINIB vs 14% of patients with sunitinib[12]
- Stable disease was observed in 19.2% of patients who received KEYTRUDA + LENVATINIB vs 38.1% of patients with sunitinib[12]
- The median time to first response for KEYTRUDA + LENVATINIB compared with sunitinib was 1.94 (1.41–20.14) and 1.99 (1.51–16.56) months, respectively[a,12]
- The median duration of response for KEYTRUDA + LENVATINIB compared with sunitinib was 25.8 (22.1–27.9) and 14.6 (9.4–16.7) months, respectively[b,12]

Tumour responses in subgroups of interest ›

DOR ›

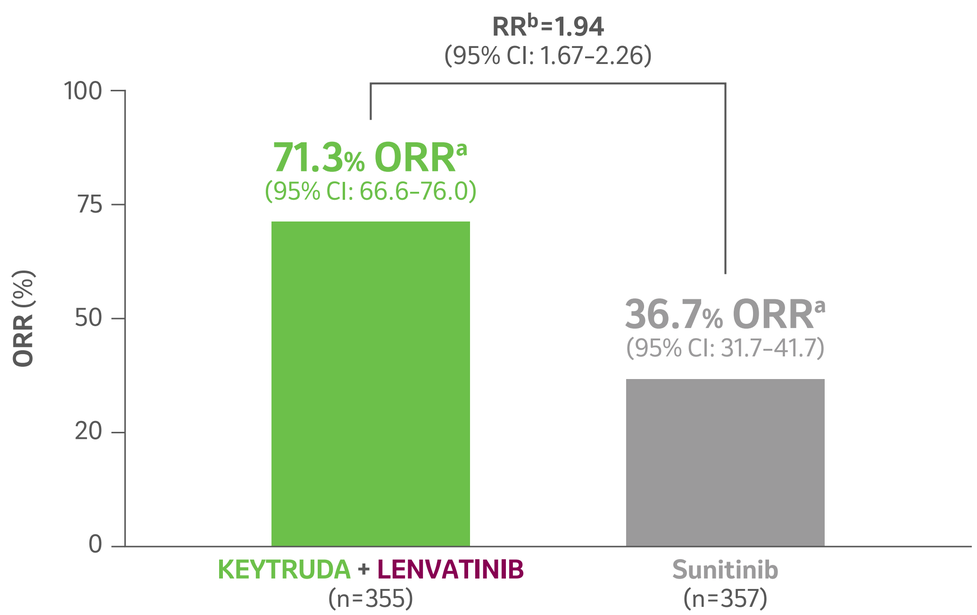
Analysis cutoff date: 28 August 2020.

[a]Assessed using RECIST v1.1; [b]Nominal P-value. At the Interim Analysis 2 prespecified final analysis of ORR (median follow-up time of 17.3 months), statistically significant superiority was achieved for ORR comparing KEYTRUDA + LENVATINIB with sunitinib (odds ratio: 3.84 [95% CI: 2.81, 5.26], nominal P-value <0.0001).

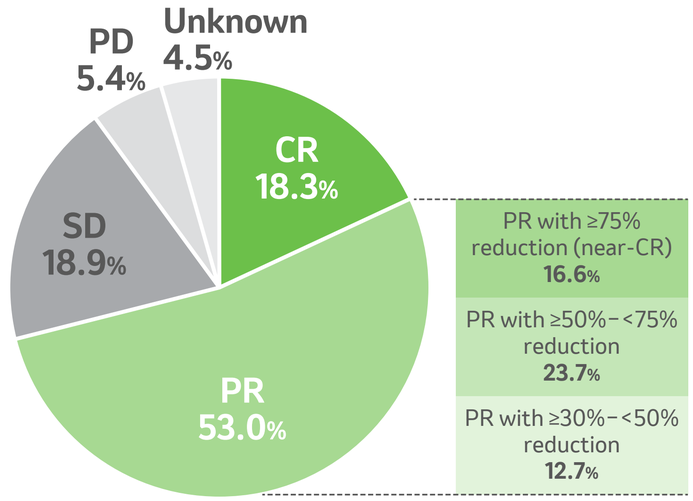
CI, confidence interval; CR, complete response; DOR, duration of response; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Exploratory analysis – ORR remained consistent with primary analysis at 49.8 months median follow-up[a,14]

Median (IQR) follow-up: 49.8 (41.4–53.1) months with **KEYTRUDA + LENVATINIB** and 49.4 (41.6–52.8) months with sunitinib



Best overall response[c] with **KEYTRUDA + LENVATINIB**



Adapted from Motzer R et al. ASCO 2023.[14]

DOR results ›

Change in target lesion size ›

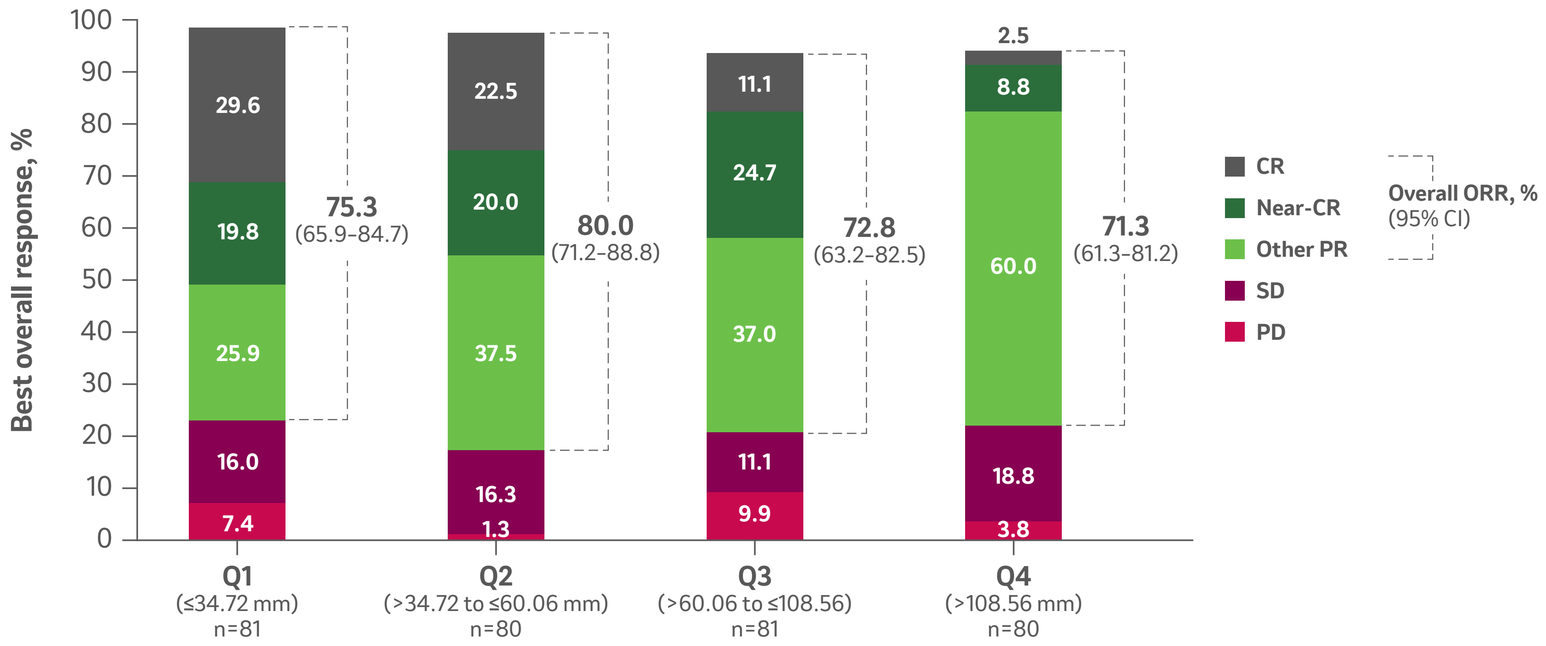
LIMITATION: No formal statistical analysis was performed for this analysis; therefore, no conclusions can be drawn.

Analysis cutoff date: 31 July 2022. When median follow-up time was not specified for an endpoint, median follow-up for OS is presented in the slide.
[a]As determined by independent review committee using RECIST v1.1; [b]RR was calculated using the Cochran-Mantel-Haenzel methods stratified by IxRS factors, and the 95% CIs were calculated using the method of normal approximation; [c]Best overall response categories (SD, PD, CR, PR or unknown) were determined based on RECIST v1.1 at the time of analysis. SD must occur ≥49 days after randomization. If a patient best overall response was non-CR/non-PD, it was grouped with the SD category.[12]

CI, confidence interval; CR, complete response; DOR, duration of response; IQR, interquartile range; ORR, objective response rate; OS, overall survival; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RR, relative risk; SD, stable disease.

Exploratory analysis – Best overall response by baseline tumour size[a,15]

Median (IQR) follow-up: 49.8 (41.4–53.1) months with **KEYTRUDA + LENVATINIB**



Adapted from Grünwald V et al. ASCO GU 2023.[15]

LIMITATION: This study was not powered to detect differences in the treatment effect between these subgroups. Results from exploratory analyses should be interpreted with caution due to modest patient numbers and potential imbalances in baseline characteristics between subgroups.

Patient characteristics ›

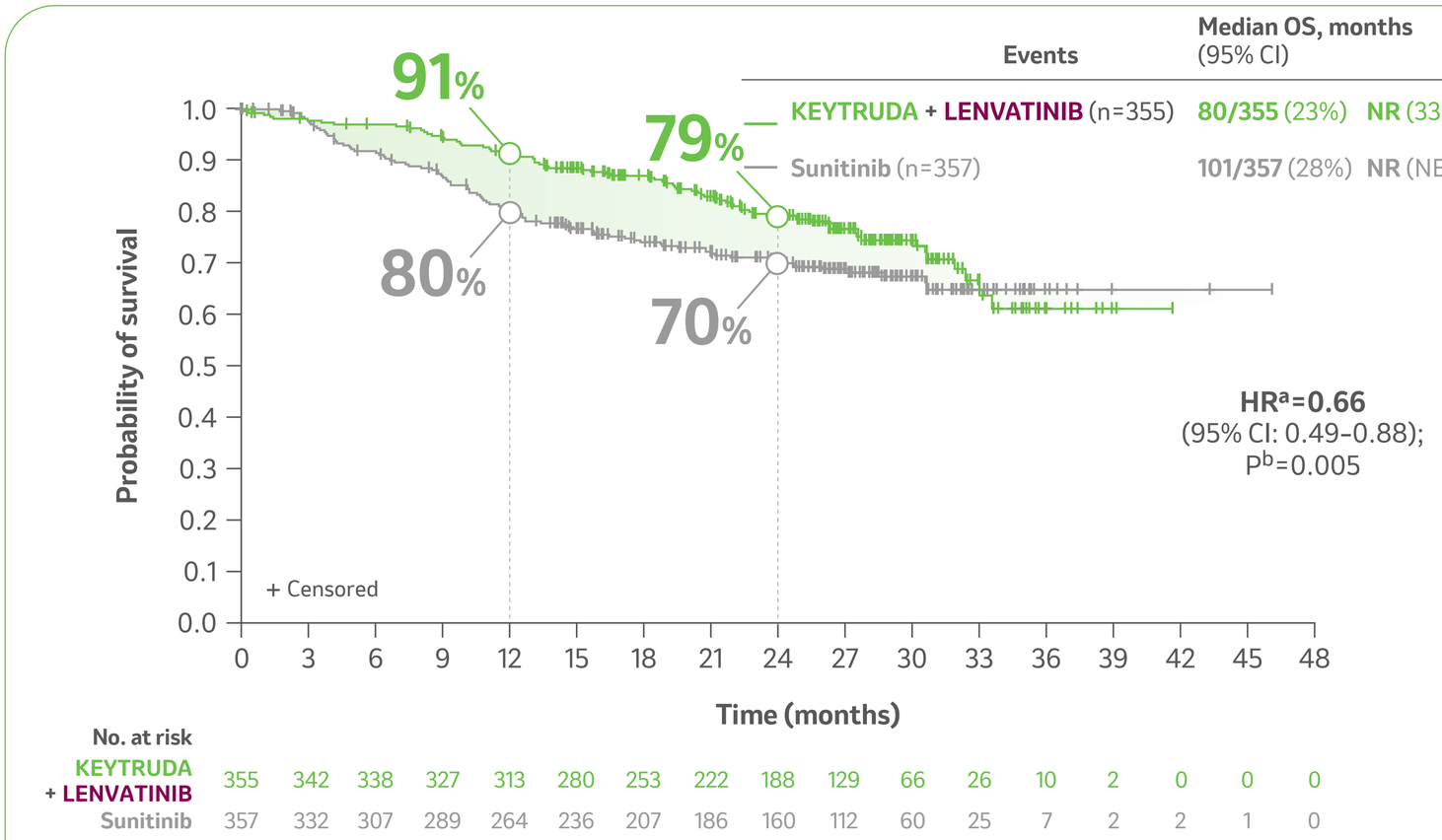
Analysis cutoff date: 31 July 2022.

Includes patients with baseline target lesion assessments, 95% CIs were calculated using asymptotic normal distribution. 'Near-CR' refers to individuals who presented a PR with a maximum tumour reduction of ≥75%. 'Other PR' refers to PRs with maximum tumour shrinkage <75%. The proportion of patients with unknown/not evaluable responses were: Q1=1.2%, Q2=2.5%, Q3=6.2%, Q4=6.3%. Percentages are based on the total number of patients in the full analysis set within the KEYTRUDA + LENVATINIB group. Percentages may not total 100 due to rounding; [a]Includes patients with baseline target lesion assessments by independent imaging review per RECIST v1.1.

CI, confidence interval; CR, complete response; IQR, interquartile range; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; Q, quartile.

Secondary endpoint – OS was superior with KEYTRUDA + LENVATINIB vs sunitinib[12]

Median follow-up: 26.6 months



Adapted from Motzer R et al. *N Engl J Med*. 2021.[12]

- **KEYTRUDA + LENVATINIB** demonstrated superior OS vs sunitinib: Reduced the risk of death by 34% (HR:[a] 0.66; 95% CI: 0.49–0.88; P=0.005[b])
- Median OS: NR in both arms
- OS may be confounded by the difference in subsequent therapies

Subgroup analysis ›

Tumour responses in subgroups of interest ›

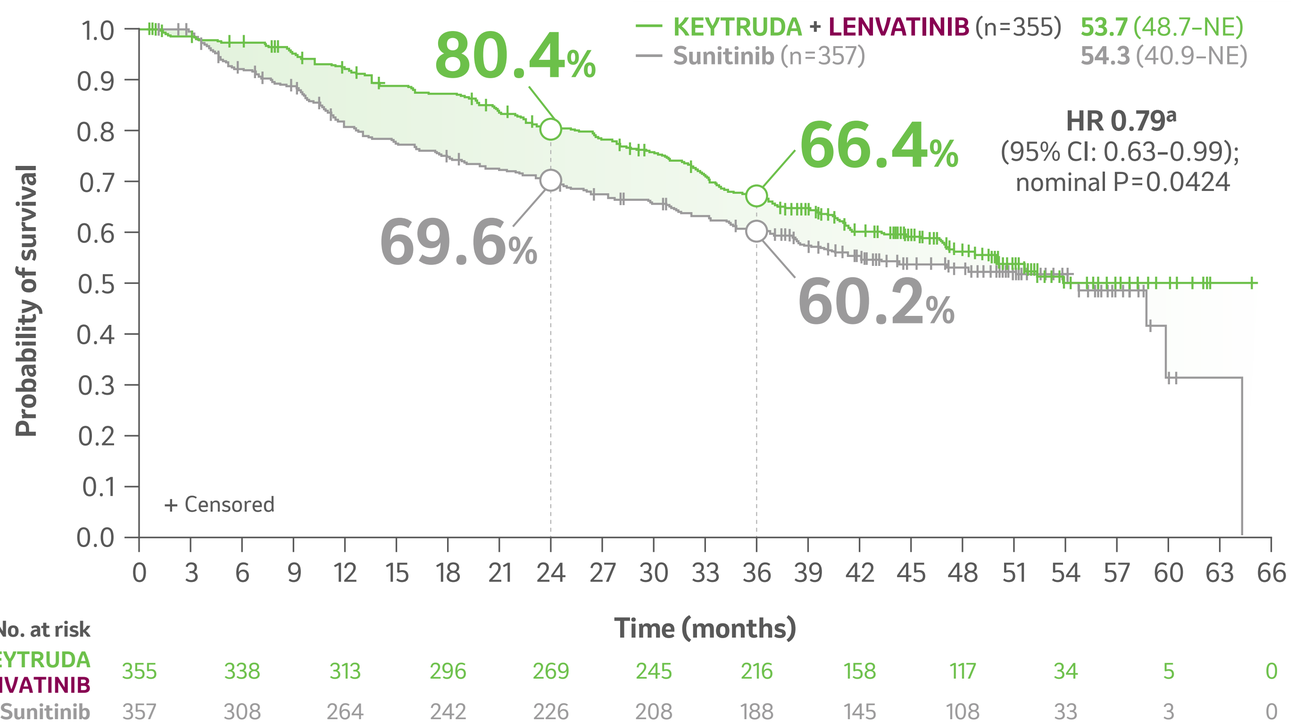
What could this mean for your patients like Kim and Jack? ›

Analysis cutoff date: 28 August 2020.
[a]Based on the stratified Cox proportional-hazards model; [b]Two-sided p-value based on stratified log-rank test.

CI, confidence interval; HR, hazard ratio; IQR, interquartile range; NE, not estimable; NR, not reached; OS, overall survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Exploratory analysis – KEYTRUDA + LENVATINIB OS at 49.8 months median follow-up[14]

Median (IQR) follow-up for OS: 49.8 (41.4–53.1) months with KEYTRUDA + LENVATINIB and 49.4 (41.6–52.8) months with sunitinib



Adapted from Motzer R et al. ASCO 2023.[14]

- The OS analysis was not adjusted to account for subsequent therapies: 54.6% of patients in the sunitinib arm subsequently received a PD-1/PD-L1 checkpoint inhibitor vs 15.8% in the KEYTRUDA + LENVATINIB arm

LIMITATION: This was a protocol-pre-specified analysis. No formal statistical testing was performed for this analysis, and, therefore, no conclusions can be drawn. OS results after 36 months of follow-up should be interpreted with caution due to the number of censored patients.

IMDC subgroup analysis ›

Final OS adjusted for subsequent anticancer medications ›

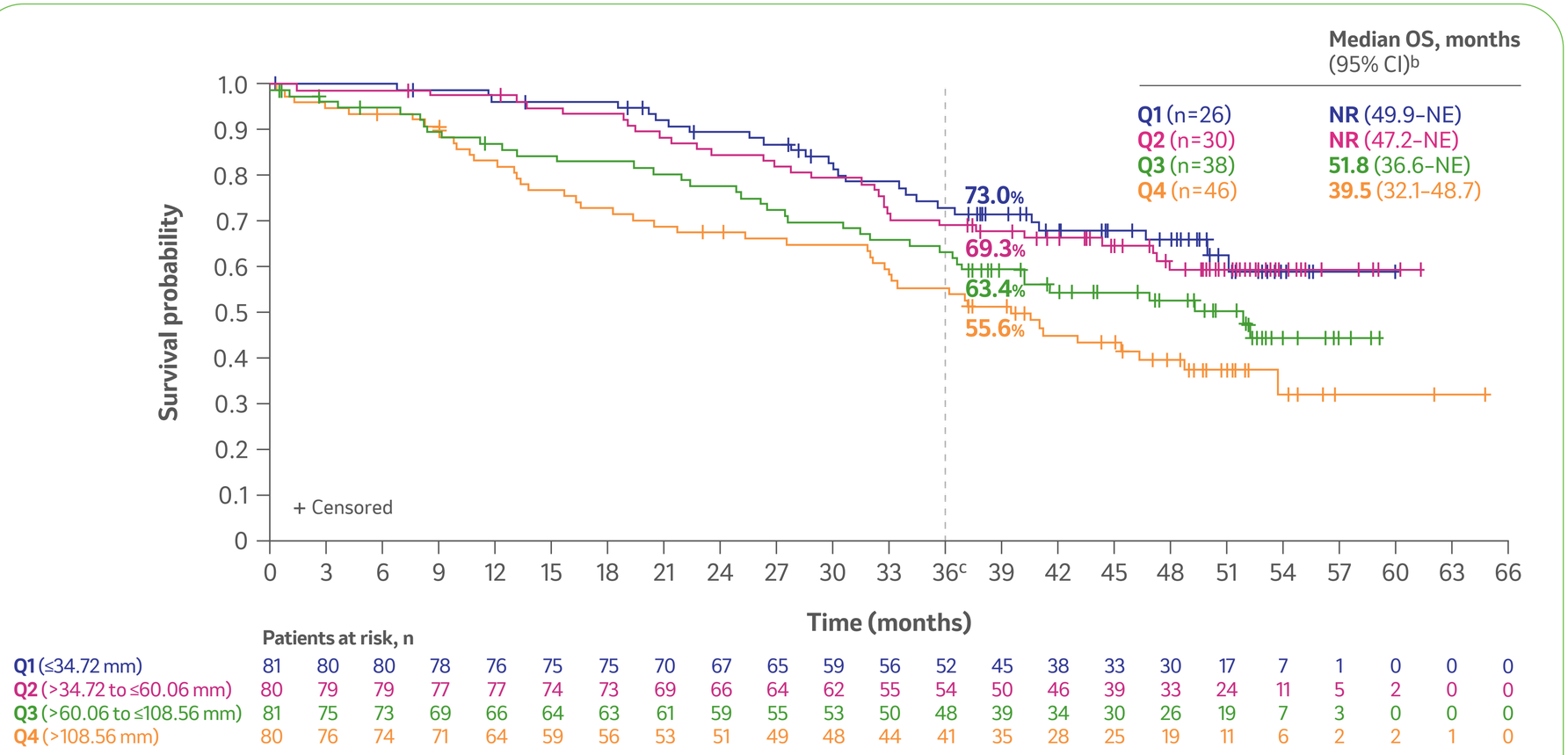
Final OS analysis by best overall response medications ›

Analysis cutoff date: 31 July 2022. A total of 308 target events had occurred, of which 149 were with KEYTRUDA + LENVATINIB and 159 with sunitinib.
[a]Hazard ratio and 2-sided 95% CI for KEYTRUDA + LENVATINIB vs sunitinib were estimated by a stratified Cox Proportional Hazards Model with Efron's method for ties, stratified by geographic region and MSKCC prognostic groups.

CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IQR, interquartile range; MSKCC, Memorial Sloan Kettering Cancer Center; NE, not estimable; OS, overall survival; PD-1, programmed death receptor-1; PD-L1, programmed death ligand-1.

Exploratory analysis – Overall survival by tumour size subgroup[a,15]

Median (IQR) follow-up: 49.8 (41.4–53.1) months with **KEYTRUDA + LENVATINIB**



Adapted from Grünwald V et al. ASCO 2024.[15]

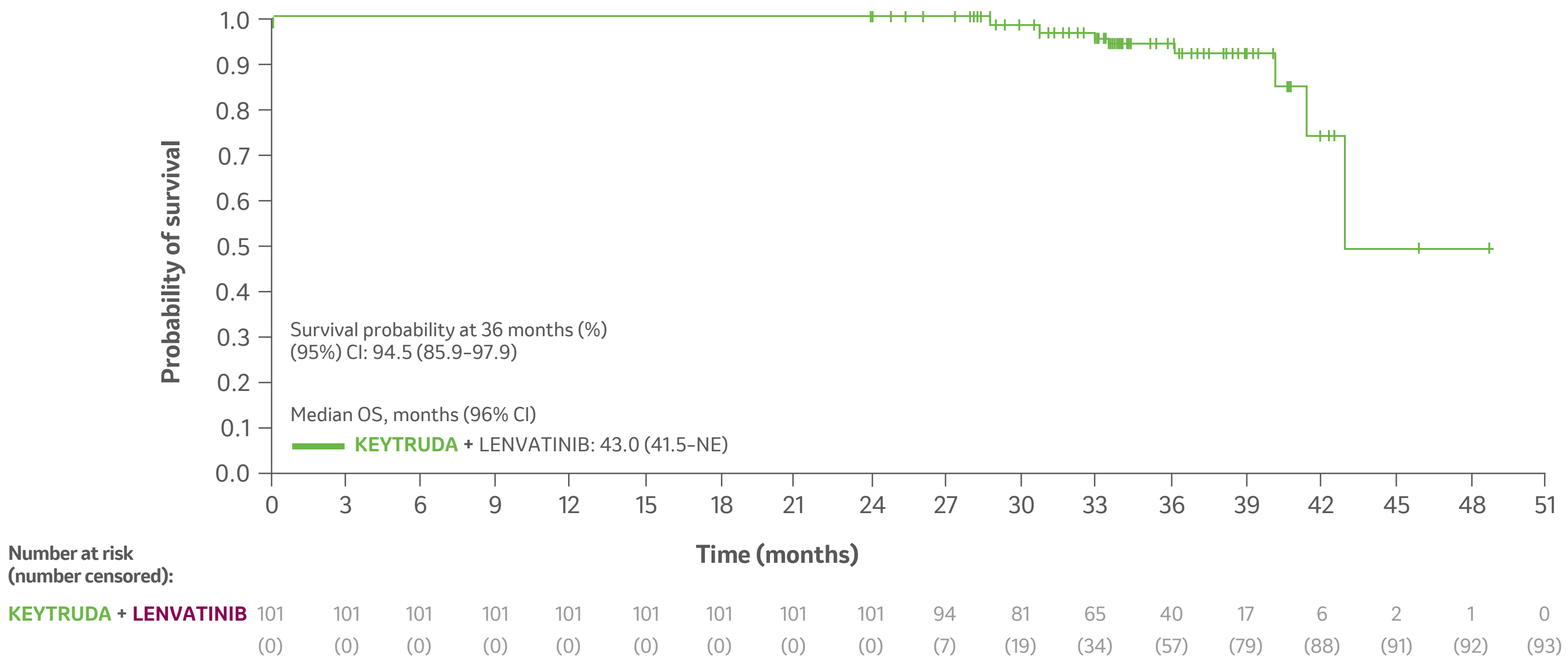
LIMITATION:
This trial was not powered to detect differences between subgroups. No formal statistical testing was planned for this exploratory analysis and, therefore, no conclusions can be drawn.

Patient characteristics ›

Data cutoff date: 31 July 2022.
[a]Assessed by independent imagine review per RECIST v1.1; [b]Medians were estimated by Kaplan-Meier method and the 95% CIs were estimated with a generalised Brookmeyer and Crowley method; [c]Survival rate at 36 months were calculated using Kaplan-Meier product-limit method.

CI, confidence interval; IQR, interquartile range; NE, not estimable; NR, not reached; OS, overall survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; Q, quartile.

Exploratory analysis — OS in patients who completed 2 years of KEYTRUDA and continued on LENVATINIB monotherapy[16]



Adapted from Choueiri et al. *Lancet Oncol.* 2023[16]

- 94.5% of patients who completed 2 years of KEYTRUDA and continued with LENVATINIB alone demonstrated a 36 months OS rate (95% CI 85.9–97.9; n=101)[a]
- Of the 101 patients, 65 had IMDC intermediate/poor-risk disease and 36 had favourable-risk disease

LIMITATION: Results from this exploratory analyses should be interpreted with caution due to modest patient numbers and potential imbalances in baseline characteristics between subgroups.

Analysis cut-off date: 31 March 2021. [a]Medians are estimated by Kaplan–Meier method.

CI, confidence interval; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; NE, not estimable; OS, overall survival

Secondary endpoint – AE summary for KEYTRUDA + LENVATINIB compared with sunitinib[a,12]

Event	KEYTRUDA + LENVATINIB (n=352)	Sunitinib (n=340)
Median duration of treatment, months (range)	17.0 (0.1–39.1)	7.8 (0.1–37.0)
AE of any grade, n (%)	351 (99.7)	335 (98.5)
Grade ≥3 AE, n (%)	290 (82.4)	244 (71.8)
Death during treatment (Grade 5 AE), n (%)[b]	15 (4.3)	11 (3.2)
Discontinuation due to any-grade AE, %	37.2	14.4
KEYTRUDA only, %	28.7	–
LENVATINIB only, %	25.6	–
Both drugs, %	13.4	–
Dose reduction due to any-grade AE, %[c]	68.8[c]	50.3
Interruption of treatment due to any-grade AE, %	78.4	53.8

Adapted from Motzer R et al. *N Engl J Med*. 2021.[12]

This list is not exhaustive. For full safety information please refer to the individual product SmPCs

AEs (primary analysis) >

TEAEs (primary analysis) >

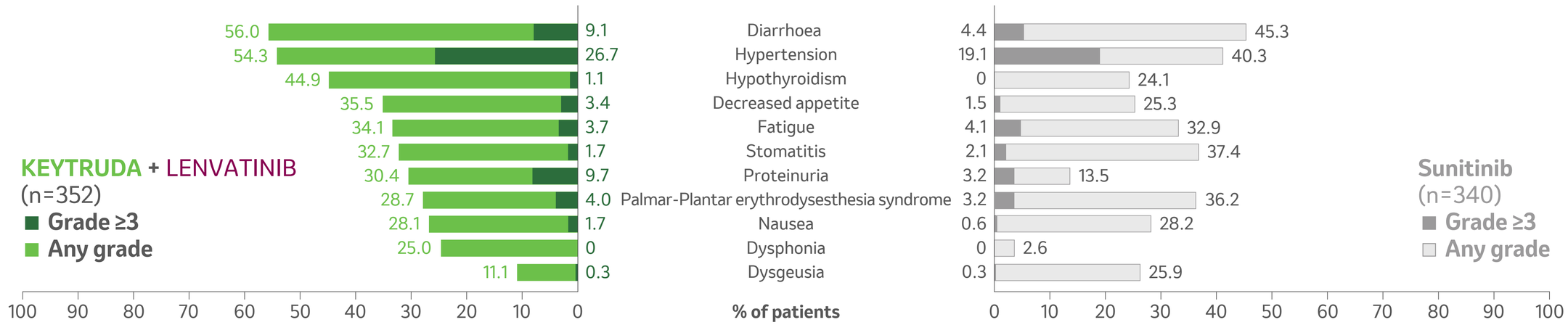
Analysis cutoff date: 28 August 2020.

[a]Safety assessment was based on an as-treated principle and consisted of monitoring and recording all AEs and serious AEs using the Common Terminology Criteria for AEs, version 4.03, in the group of patients who received at least one dose of the study drug; [b]Of the 15 patients in the KEYTRUDA + LENVATINIB group who had grade 5 AEs during treatment, 11 had fatal AEs not attributed to disease progression (acute renal failure, uncontrolled hypertension, complications from myasthenic syndrome, complications from autoimmune hepatitis, cardiac arrest, and death–cause not specified in 1 patient each; haemorrhagic events in 2 patients; and sepsis in 3 patients). Among the 11 patients in the sunitinib group with grade 5 AEs during treatment, fatal AEs not attributed to disease progression occurred in 2 patients (respiratory failure and acute kidney injury in 1 patient and death–cause not specified in 1 patient); [c]Dose reduction in LENVATINIB only. Dose reductions for KEYTRUDA are not recommended.

AE, adverse event; TEAE, treatment-emergent adverse event.

Exploratory analysis – TRAEs in ≥25% of patients in any treatment group[14]

Median (IQR) follow-up: 49.8 (41.4–53.1) months with **KEYTRUDA + LENVATINIB** and 49.4 (41.6–52.8) months with sunitinib



	KEYTRUDA + LENVATINIB (n=352)	Sunitinib (n=340)
Any grade TEAEs (%)	96.9	92.1
Grade ≥3 TEAEs (%)	74.1	60.3
Deaths	1.1	0.3
Median duration of treatment, months (IQR)	22.6 (9.4–37.1)	7.8 (3.7–19.4)

Adapted from Motzer R et al. ASCO 2023.[14]

- There were no new safety signals identified at the final pre-specified analysis

LIMITATION: This was a protocol pre-specified analysis. No formal statistical testing was performed for this analysis, and, therefore, no conclusions can be drawn.

Analysis cutoff date: 31 July 2022. When median follow-up time was not specified for an endpoint, median follow-up for OS is presented in the slide.

IQR, interquartile range; OS, overall survival; TEAE, treatment-emergent adverse event; TRAE, treatment related adverse event.

HRQoL – patient reported outcomes[a,17]

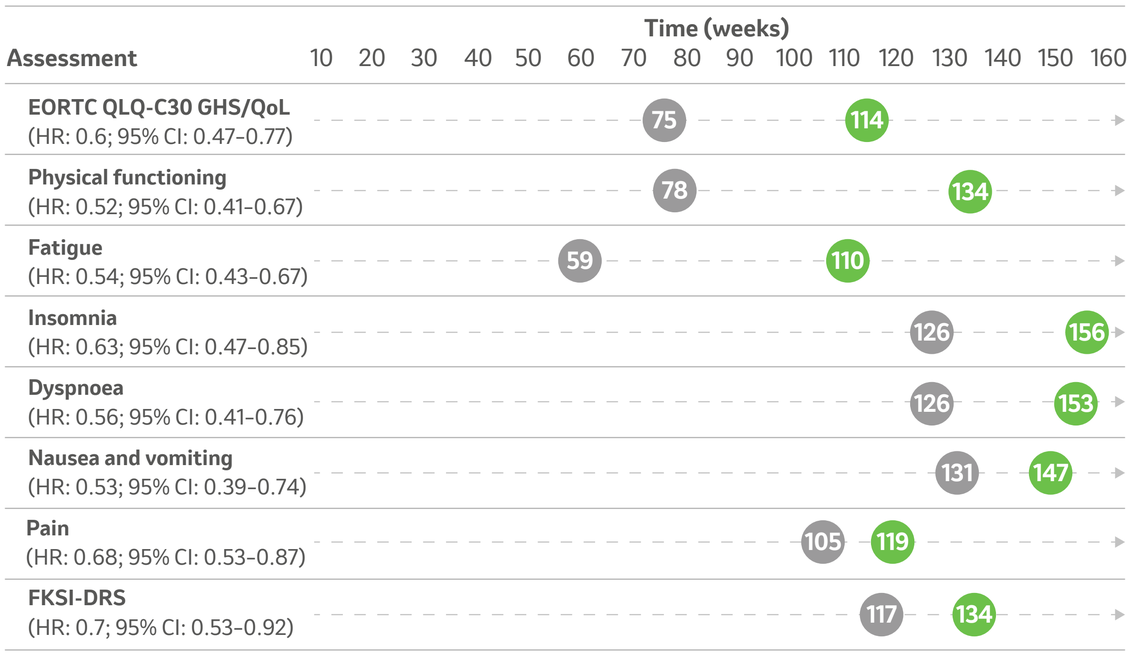
Median (IQR) follow-up: 12.9 (5.6–22.3) months with **KEYTRUDA** + **LENVATINIB** and with sunitinib

KEYTRUDA + **LENVATINIB** showed a **more than 12-week delay** in median time to worsening in GHS, physical functioning, and patient reported symptoms with no subsequent recovery vs sunitinib[b]

>12-week

delay in median time to worsening symptoms vs sunitinib group

Time to definitive deterioration in selected HRQoL scales for KEYTRUDA + LENVATINIB vs sunitinib



Adapted from Motzer R et al. *Lancet Oncol*. 2022.[16]

LIMITATION: These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

Analysis cutoff date: 24 July 2019.

[a]Patient-reported outcomes (PROs) were assessed using the EORTC QLQ-C30 and the FKSI-DRS; [b]Measured from baseline to a mean follow-up time of 46 weeks.

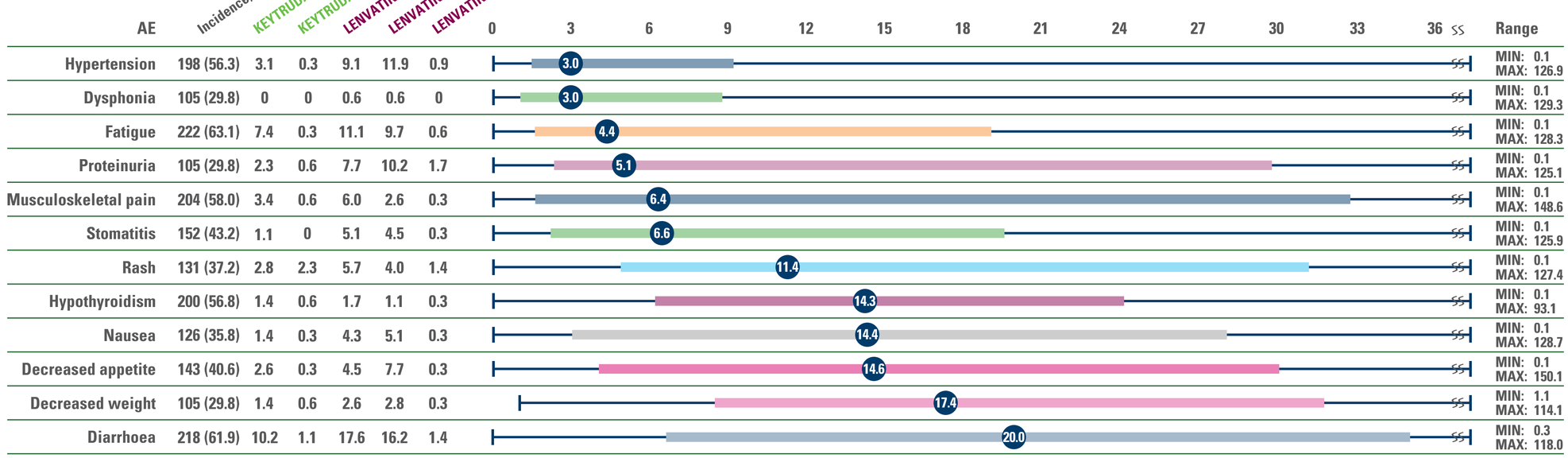
CI, confidence interval; EQ-5D-3L, European Quality of Life 5 Dimensions 3 Levels; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; FKSI-DRS, Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index – Disease Related Symptoms; GHS, Global Health Status; HR, hazard ratio; HRQoL, health-related quality of life; IQR, interquartile range; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; VAS, visual analogue scale.

Exploratory analysis — Median time to first onset of key AEs* (all grades) and dose management for KEYTRUDA + LENVATINIB[a,18]

Median follow-up: 26.6 months with KEYTRUDA + LENVATINIB and with sunitinib

Median time to first onset of key AEs was between 3 and 20 weeks in the CLEAR trial

AE	Incidence, n (%)	KEYTRUDA dose interruption %	KEYTRUDA discontinuation %	LENVATINIB dose interruption %	LENVATINIB dose reduction %	LENVATINIB discontinuation %	Range
Hypertension	198 (56.3)	3.1	0.3	9.1	11.9	0.9	MIN: 0.1 MAX: 126.9
Dysphonia	105 (29.8)	0	0	0.6	0.6	0	MIN: 0.1 MAX: 129.3
Fatigue	222 (63.1)	7.4	0.3	11.1	9.7	0.6	MIN: 0.1 MAX: 128.3
Proteinuria	105 (29.8)	2.3	0.6	7.7	10.2	1.7	MIN: 0.1 MAX: 125.1
Musculoskeletal pain	204 (58.0)	3.4	0.6	6.0	2.6	0.3	MIN: 0.1 MAX: 148.6
Stomatitis	152 (43.2)	1.1	0	5.1	4.5	0.3	MIN: 0.1 MAX: 125.9
Rash	131 (37.2)	2.8	2.3	5.7	4.0	1.4	MIN: 0.1 MAX: 127.4
Hypothyroidism	200 (56.8)	1.4	0.6	1.7	1.1	0.3	MIN: 0.1 MAX: 93.1
Nausea	126 (35.8)	1.4	0.3	4.3	5.1	0.3	MIN: 0.1 MAX: 128.7
Decreased appetite	143 (40.6)	2.6	0.3	4.5	7.7	0.3	MIN: 0.1 MAX: 150.1
Decreased weight	105 (29.8)	1.4	0.6	2.6	2.8	0.3	MIN: 1.1 MAX: 114.1
Diarrhoea	218 (61.9)	10.2	1.1	17.6	16.2	1.4	MIN: 0.3 MAX: 118.0



Adapted from Motzer R et al. *The Oncologist*. 2023.[18]

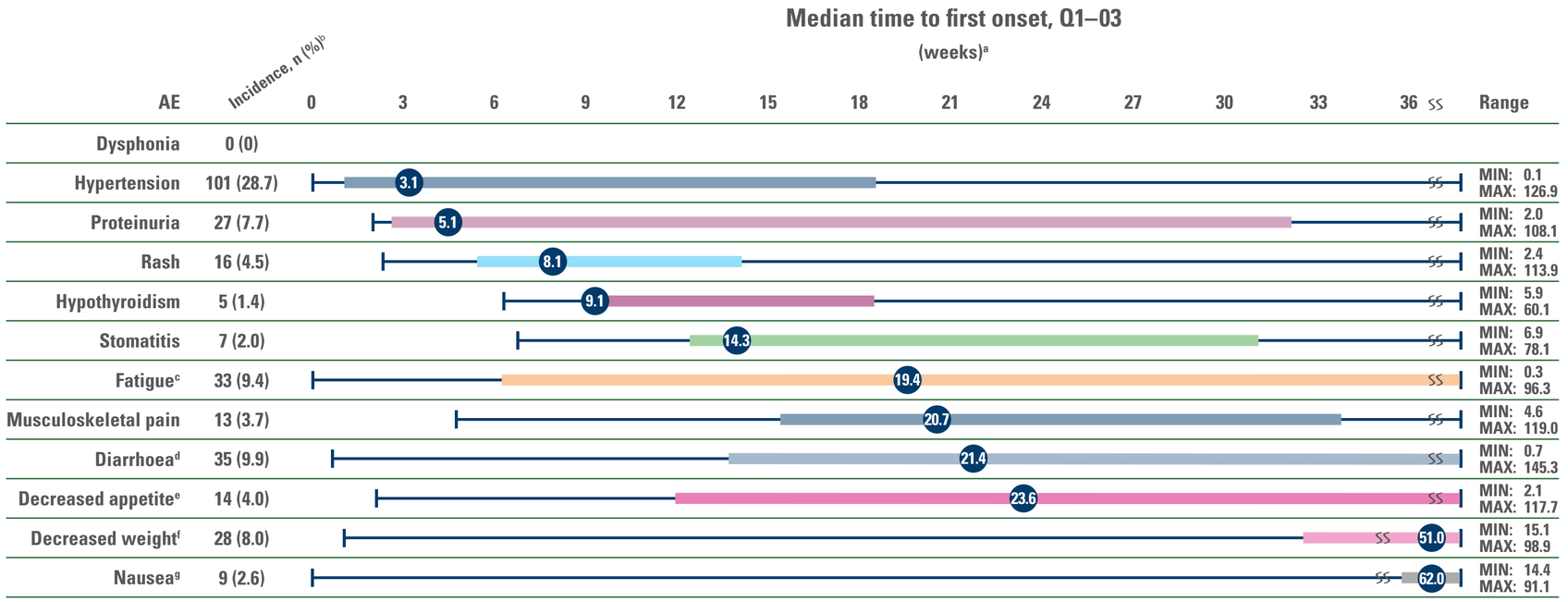
LIMITATION: This was a post-hoc exploratory analysis based on data from the CLEAR trial. No formal statistical testing was planned for this exploratory analysis and, therefore, no conclusions can be drawn.

[a]Median time to first onset in patients who experienced the AE. *Key AEs: AEs with incidence ≥30% in the KEYTRUDA + LENVATINIB group that occurred either while receiving treatment or within the protocol-defined follow-up period of 30 days after the patient's last dose. The safety population included all patients who received at least one dose of any study drug and percentages presented in the figure were based on the safety population of the pembrolizumab + LENVATINIB group (n=352). Coloured boxes represent Q1–Q3 and lines represent the range.

AE, adverse events; max, maximum; min, minimum; Q, Quartile.

Exploratory analysis — Median time to first onset of Grade ≥3 AEs in patients treated with KEYTRUDA + LENVATINIB[a,18]

Median follow-up: 26.6 months with KEYTRUDA + LENVATINIB and with sunitinib



Adapted from Motzer R et al. *The Oncologist*. 2023.[18]

LIMITATION: This was a post-hoc exploratory analysis based on data from the CLEAR trial. No formal statistical testing was planned for this exploratory analysis and, therefore, no conclusions can be drawn.

[a]Median time to first onset in patients who experienced the Grade ≥3 adverse reaction. Coloured boxes represent Q1–Q3. Lines represent the range; [b]Any grade. Percentages are based on the safety population of the KEYTRUDA + LENVATINIB group (n=352). The safety population included all patients who received at least one dose of any study drug; [c]Q1=7.86, Q3=42.29; [d]Q1=13.29, Q3=56.71; [e]Q1=10.14, Q3=69.14; [f]Q1=34.00, Q3=64.71; [g]Q1=42.57, Q3=74.00.

AE, adverse events; max, maximum; min, minimum; Q, Quartile.

KEYNOTE-B61 trial: A single-arm, multicentre, phase 2 trial in 158 patients with advanced non-clear cell RCC[19]

Studied in the 1L setting across IMDC risk groups and histological subtypes in patients with advanced non-clear cell RCC

Key eligibility criteria

- Age ≥18 years old
- Histologically confirmed diagnosis of stage IV nccRCC (locally assessed as per the AJCC 8th edition criteria)
- No prior systemic therapy for advanced disease
- Measurable disease per RECIST v1.1
- Archival or newly acquired tumour tissue sample
- KPS ≥70%

Key exclusion criteria

- Collecting duct histology
- Clinically significant cardiovascular disease within 12 months of treatment initiation
- Known active CNS metastases or carcinomatous meningitis, or both

N=158

KEYTRUDA 400 mg
Intravenously every 6 weeks for ≤18 cycles (~2 years)

+

LENVATINIB 20 mg
Orally once daily; LENVATINIB could be continued beyond 2 years

Treatment continued until disease progression or unacceptable toxicity.[a]

Tumour imaging by CT or MRI was done at baseline, at 12 weeks, then every 6 weeks until week 54, and then every 12 weeks thereafter.[b]

Tumour response was assessed per adjusted RECIST v1.1 by independent central review.

Primary endpoint

- ORR as per adjusted RECIST v1.1 assessed by independent central review

Secondary endpoints

- DOR and PFS as per adjusted RECIST v1.1 assessed by independent central review and OS

Adapted from Albiges L et al. *Lancet Oncol*. 2023.[19]

LIMITATION: No statistical testing was conducted in this single-arm, phase 2 trial and, therefore, no conclusions can be drawn.

[a]Treatment was permitted beyond RECIST-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit; [b]According to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

1L, first line; AJCC, American Joint Committee on Cancer; CNS, central nervous system; CT, computed tomography; DOR, duration of response; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; KPS, Karnofsky performance status; MRI, magnetic resonance imaging; PFS, progression-free survival; nccRCC, non-clear cell renal cell carcinoma; ORR, objective response rate; OS, overall survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RCC, renal cell carcinoma.

KEYNOTE-B61 trial: Baseline characteristics in patients with advanced non-clear cell RCC[19]

KEYTRUDA + LENVATINIB (N=158) n (%)

Age, years	
Median (IQR)	60 (52–69)
Median (SD)	59.4 (12.8)
≥65 years	60 (38%)
Sex	
Female	46 (29%)
Male	112 (71%)
Race	
White	128 (81%)
Asian	12 (8%)
Black or African American	3 (2%)
Unknown	15 (9%)
Geographical region	
North America	22 (14%)
Europe	59 (37%)
Rest of the world	77 (49%)
IMDC risk category[a]	
Favourable	70 (44%)
Intermediate	75 (47%)
Poor	13 (8%)

KPS, %[b]	
90 or 100	124 (78%)
70 or 80	34 (22%)
Presence of sarcomatoid features[c]	
Yes	19 (12%)
No	96 (61%)
Unknown	10 (6%)
Not applicable	33 (21%)
PD-L1 status[d]	
CPS ≥1	93 (59%)
CPS <1	50 (32%)
Unknown	15 (9%)
Histology[d]	
Papillary	93 (59%)
Chromophobe	29 (18%)
Unclassified	21 (13%)
Translocation	6 (4%)
Other	9 (6%)

Previous nephrectomy	
Yes	93 (59%)
No	65 (41%)
Number of organs involved at screening	
1	28 (18%)
≥2	130 (82%)
Site of metastases at screening	
Lymph node	102 (65%)
Lung	54 (34%)
Bone	49 (31%)
Liver	31 (20%)
Abdominal cavity	20 (13%)

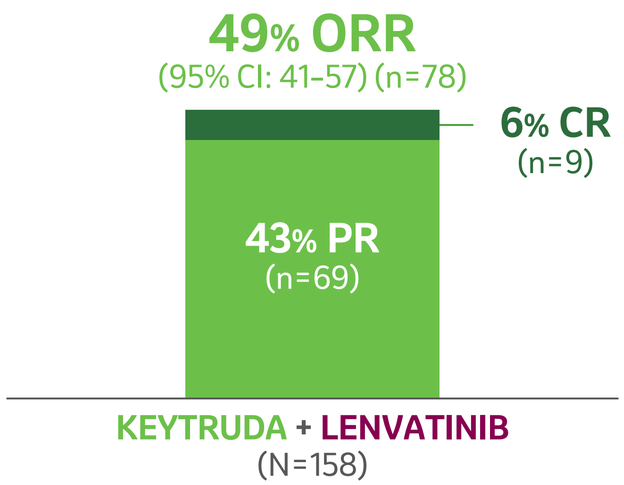
Adapted from Albiges L et al. *Lancet Oncol*. 2023.[19]

[a]An IMDC category of 0 indicates favourable risk, a score of 1 or 2 indicates intermediate risk, and a score of 3 to 6 indicates poor risk; [b]KPS range from 0 to 100%, with lower scores indicating greater disability; [c]As determined by investigator review; [d]CPS was calculated as the number of PD-L1–staining cells (tumour cells, lymphocytes, and macrophages) divided by the total number of viable tumour cells, multiplied by 100.
CPS, combined positive score; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IQR, interquartile range; KPS, karnofsky performance status; PD-L1, programmed death ligand-1; RCC, renal cell carcinoma; SD, standard deviation.

KEYNOTE-B61 trial: Primary endpoint – Objective response rate (primary analysis)[19]

Median (IQR) follow-up: 14.9 (11.1–17.4) months

Objective response rate with KEYTRUDA + LENVATINIB in the KEYNOTE-B61 trial[a,b]



Adapted from Albiges L, et al. *Lancet Oncol*. 2023.[19]

- 49% of patients with advanced non-clear cell RCC that received **KEYTRUDA + LENVATINIB** had a confirmed ORR

LIMITATION: No statistical testing was conducted in this single-arm, phase 2 trial and, therefore, no conclusions can be drawn.

Confirmed best overall response summary ›

[a]Best overall response per adjusted RECIST v1.1 by independent central review; [b]Confirmed CR and PR for at least 6 months.

CI, confidence interval; CR, complete response; IQR, interquartile range; ORR, objective response rate; PR, partial response; RCC, renal cell carcinoma; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

KEYNOTE-B61 trial: Extended follow-up – Confirmed best response[20]

Median (IQR) follow-up: 22.8 (16.6–27.6) months

Characteristic	KEYTRUDA + LENVATINIB (N=158)
Objective response rate, % (95% CI)	50.6 (42.6–58.7)
Disease control rate,[a] % (95% CI)	82.3 (75.4–87.9)
Clinical benefit rate,[b] % (95% CI)	71.5 (63.8–78.4)
Best overall response, n (%)	
CR	13 (8.2%)
PR	67 (42.4%)
SD	50 (31.6%)
SD ≥6 months	33 (20.9%)
PD	17 (10.8%)
Not evaluable[c]/Not assessed	11 (7.0%)

Adapted from Voss M, et al. ASCO GU 2024.[20]

LIMITATION: No statistical testing was conducted in this single-arm, phase 2 trial and, therefore, no conclusions can be drawn.

Page 1 of 2

Change in target lesion size by histology ›

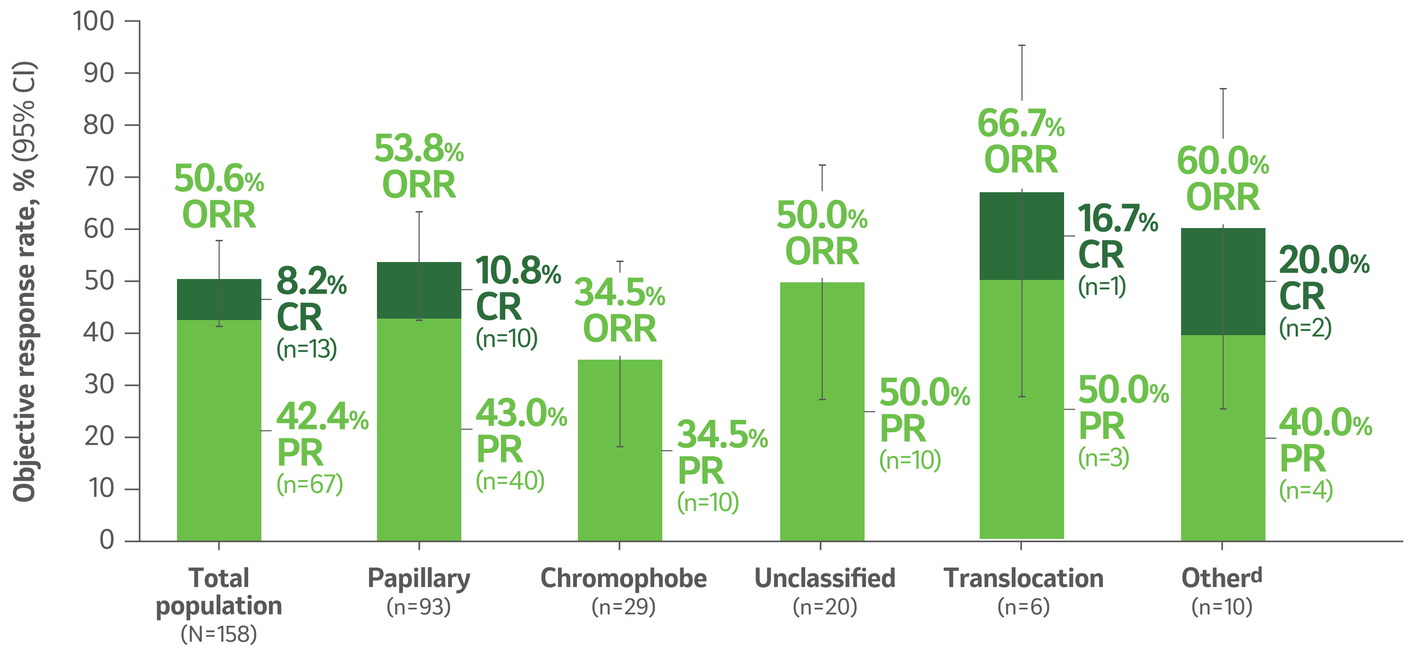
[a]Confirmed CR, PR, or SD of any duration; [b]Confirmed CR, PR, or SD for ≥6 months; [c]Postbaseline assessment, not evaluable or postbaseline assessment available. [d]Includes medullary and other histology subtypes.

CI, confidence interval; CR, complete response; IQR, interquartile range; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

KEYNOTE-B61 trial: Extended follow-up – Confirmed best response[20]

Median (IQR) follow-up: 22.8 (16.6–27.6) months

Confirmed ORR by histology per RECIST v1.1



Adapted from Voss M, et al. ASCO GU 2024.[20]

LIMITATION: No statistical testing was conducted in this single-arm, phase 2 trial and, therefore, no conclusions can be drawn.

Page 2 of 2

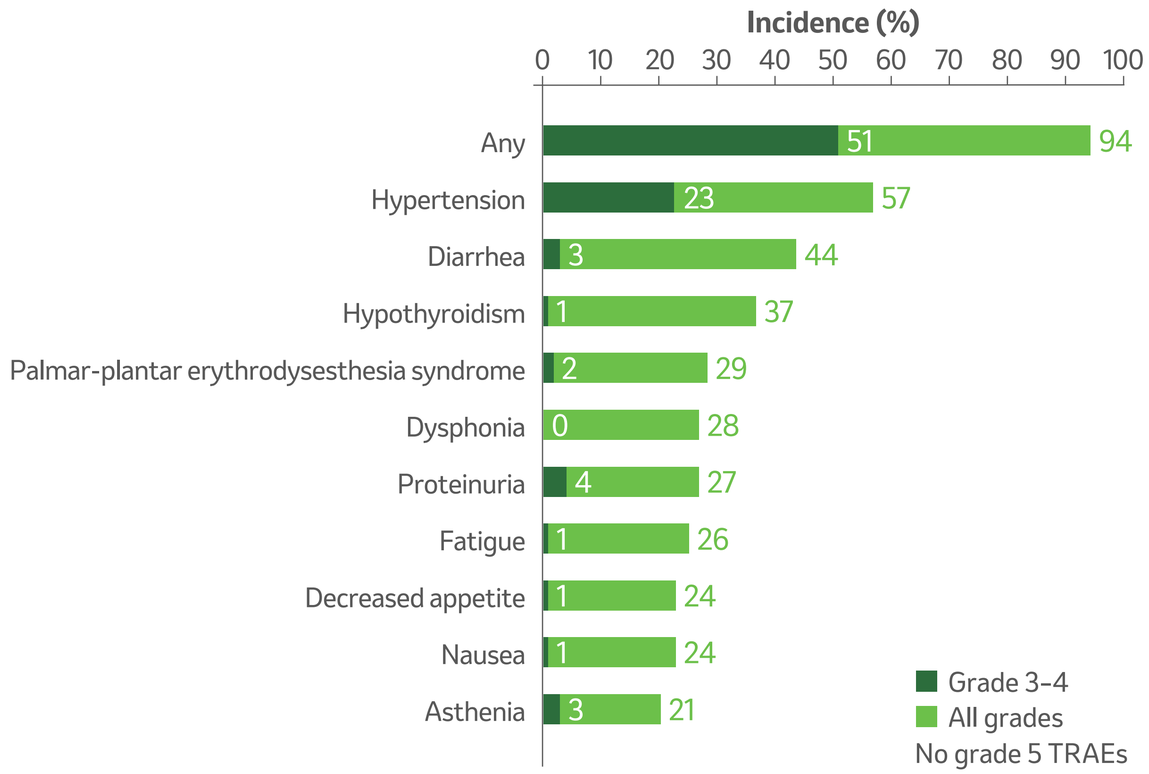
Change in target lesion size by histology ›

[a]Confirmed CR, PR, or SD of any duration; [b]Confirmed CR, PR, or SD for ≥6 months; [c]Postbaseline assessment, not evaluable or postbaseline assessment available. [d]Includes medullary and other histology subtypes.

CI, confidence interval; CR, complete response; IQR, interquartile range; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

KEYNOTE-B61 trial: AE summary (primary analysis)[19]

TRAEs that occurred in ≥20% of patients receiving KEYTRUDA + LENVATINIB in the KEYNOTE-B61 trial (N=158)[a]



Adapted from Albiges L, et al. *Lancet Oncol*. 2023.[19]

- Serious TRAEs occurred in 31/158 patients (20%)
- AEs led to dose reduction of **LENVATINIB** in 54/158 patients (34%) and dose interruption in 114/158 patients (72%)
- Due to any-cause AEs, **LENVATINIB** was discontinued in 22/158 patients (14%); **KEYTRUDA** was discontinued in 24/158 patients (15%); and both **KEYTRUDA** and **LENVATINIB** were discontinued in 11/158 patients (7%)
- AEs led to death in 8/158 (5%) of patients, no deaths were considered related to the treatment by investigators

This list is not exhaustive. For full safety information please refer to the individual product SmPCs.

[a]AEs occurring within 30 days of the last treatment dose led to discontinuation of KEYTRUDA or LENVATINIB, or both, in 31/158 patients (20%).

AE, adverse event; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SmPC, Summary of Product Characteristics; TRAE, treatment-related adverse event.

KEYNOTE B61 trial: AE summary (extended follow-up)[20]

KEYTRUDA + LENVATINIB (N=158) n (%)

Any AE	157 (99.4)
Grade 3–5	112 (70.9)
Any treatment discontinuation	42 (26.6)
KEYTRUDA discontinuation	33 (20.9)
LENVATINIB discontinuation	31 (19.6)
Both KEYTRUDA and LENVATINIB discontinuation	15 (9.5)
Serious AEs	67 (42.4)
Resulted in death	9 (5.7)
Any treatment-related AE	151 (95.6)
Grade 3 or 4	92 (58.2)

Any treatment discontinuation	34 (21.5)
KEYTRUDA discontinuation	24 (15.2)
LENVATINIB discontinuation	20 (12.7)
Both KEYTRUDA and LENVATINIB discontinuation	7 (4.4)
Serious AEs	39 (24.7%)
Resulted in death	0 (0%)
Immune-mediated AEs	92 (58.2)
Grade 3–5	15 (9.5)
Required systemic corticosteroids	22 (13.9)
High starting dose	11 (7.0)
Low starting dose	11 (7.0)

Adapted from Voss M, et al. ASCO GU 2024.[20]

TRAE (extended follow-up) ›

[a]Based on a list of preferred terms intended to capture known risks of KEYTRUDA and were considered regardless of attribution to study treatment by the investigator; [b]Defined as ≥40 mg/day prednisone or equivalent; [c]Defined as <40 mg/day prednisone or equivalent.

AE, adverse event; TRAE, treatment-related adverse event.

KEYTRUDA + LENVATINIB are administered via IV infusion and oral capsules, respectively

KEYTRUDA offers flexibility of dosing[1]

Administered as an IV infusion

Over 30 minutes

200 mg Q3W or 400 mg Q6W

- The 200 mg Q3W (once every 3 weeks) regimen has been assessed in phase 2 and 3 registration studies across a multitude of indications of **KEYTRUDA**. An exposure-response evaluation, using modelling and simulation, led to the approval of the 400 mg Q6W (once every 6 weeks) dosing for monotherapy and combination therapy.

What does flexibility mean to you and your patients?

LENVATINIB[2]

20 mg orally QD at the same time each day

Administered with or without food

Swallowed whole with water. For patients unable to swallow capsules, please refer to the SmPC for alternative methods of preparation

For patients with severe hepatic or renal impairment, a starting dose of 10 mg should be used

- Continue treatment with **LENVATINIB** for as long as there is clinical benefit or until unacceptable toxicity occurs
- For AEs thought to be related to **LENVATINIB**, upon resolution/improvement of an AE to Grade 0–1 or baseline, treatment should be resumed at a reduced dose of **LENVATINIB**
  - Please refer to the **LENVATINIB** SmPC for the management of AEs
- Please refer to the following slide for information on dose modifications in combination with **KEYTRUDA**

Please refer to the KEYTRUDA + LENVATINIB individual product SmPC for full dosing information.

Dose modification ›

AE, adverse event; IV, intravenous; QD, once daily; Q3W, every three weeks; Q6W, every six weeks; SmPC, Summary of Product Characteristics.

KEYTRUDA + LENVATINIB: Outcomes in 1L advanced clear cell RCC[12]

Median follow-up: 26.6 months

PFS

Superior PFS (primary endpoint):

- A 61% reduction in the risk of progression or death for **KEYTRUDA + LENVATINIB** vs sunitinib (HR=0.39, [95% CI: 0.32–0.49]; P<0.0001)[a]

OS

Superior OS (secondary endpoint):

- A 34% reduction in risk of death for **KEYTRUDA + LENVATINIB** vs sunitinib (HR=0.66, [95% CI: 0.49–0.88]; P=0.005)[a]

Superior ORR (nominal significance):

- ORR was 71.0% with **KEYTRUDA + LENVATINIB** vs 36.1% with sunitinib (P<0.0001 at a median follow-up of 17.3 months)[b]
  - **CR:** 16.1% with **KEYTRUDA + LENVATINIB** vs 4.2% with sunitinib

Safety:

- The safety profile of **KEYTRUDA + LENVATINIB** was consistent with the profiles for the individual drugs and the combination that had been previously reported

[a]Analysis cutoff date: 28 August 2020 and median follow-up: 26.6 months for KEYTRUDA + LENVATINIB and sunitinib;[12] [b]At the Interim Analysis 2, prespecified final analysis of ORR (median follow-up time of 17.3 months), statistically significant superiority was achieved for ORR comparing KEYTRUDA + LENVATINIB with sunitinib (odds ratio: 3.84 [95% CI: 2.81, 5.26], P<0.0001).[1,2]

1L, first-line; CI, confidence interval; CR, complete response; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma.

KEYTRUDA + LENVATINIB: Outcomes in 1L advanced clear cell RCC[14,15]

Prespecified final analysis (exploratory data; no conclusions can be drawn):[a,14]

Exploratory analysis outcome:

- The pre-specified final OS analysis presented **KEYTRUDA + LENVATINIB** as a standard of care in 1L advanced RCC

PFS:

- Median PFS was 23.9 months with **KEYTRUDA + LENVATINIB** and 9.2 months with sunitinib (HR=0.47, [95% CI: 0.38–0.57]); nominal P<0.0001)

OS:

- Median OS was 53.7 months with **KEYTRUDA + LENVATINIB** and 54.3 months with sunitinib (HR=0.79, [95% CI: 0.63–0.99]); nominal P=0.0424)

ORR and DOR:

- ORR was 71.3% with **KEYTRUDA + LENVATINIB** and 36.7% with sunitinib (RR=1.94, [95% CI: 1.67–2.26])
  - CR was 18.3% with **KEYTRUDA + LENVATINIB** and 4.8% with sunitinib
  - Median DOR was 26.7 months with **KEYTRUDA + LENVATINIB** and 14.7 months with sunitinib (HR=0.57, [95% CI: 0.43–0.76])

Safety:

- No new safety signals were identified at the final prespecified analysis

Subgroup analyses of efficacy outcomes:[15]

Baseline tumour size:

- With extended follow-up (median ~4 years) of the CLEAR study, PFS, OS and ORR outcomes with **KEYTRUDA + LENVATINIB** were observed across patients with advanced RCC, irrespective of baseline tumour size

[a] Analysis cutoff date: 31 July 2022.

1L, first-line; CI, confidence interval; CR, complete response; DOR, duration of response; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; RR, relative risk.

KEYTRUDA + LENVATINIB: Outcomes in 1L advanced non-clear cell RCC[19,20]

ORR:

- 49% of patients receiving **KEYTRUDA + LENVATINIB** had a confirmed ORR (95% CI: 41–57) at the original analysis. ORR was also generally consistent across histology subgroups
  - At the extended follow-up, **KEYTRUDA + LENVATINIB** continued to show antitumour activity in patients with advanced non-clear cell RCC with a confirmed objective response rate of 50.6% (95% CI: 42.6–58.7)

Safety:

- The safety profile was consistent with the known profile of each agent alone and with the safety profile previously observed when the agents were used together. Serious TRAEs occurred in 20% of patients
  - At the extended follow-up, **KEYTRUDA + LENVATINIB** continued to demonstrate a generally manageable safety profile with grade 3 or 4 TRAEs occurring in 58.2% of patients; no deaths due to TRAEs occurred

LIMITATION: The main limitation of this study was that no statistical testing was conducted in this single-arm, phase 2 trial and, therefore, any conclusions should be drawn with caution.

1L, first-line; CI, confidence interval; ORR, objective response rate; RCC, renal cell carcinoma; TRAE, treatment-related adverse event.

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Job code: GB-KLR-00357 **Date of preparation:** May 2025

Exploratory analysis – Patient characteristics by tumour size in the **KEYTRUDA** + **LENVATINIB** arm of the CLEAR trial[15]

Characteristic	Baseline sums of diameters of target lesions[a] (N=355)			
	Q1 81 patients (22.8%)	**Q2** 80 patients (22.5%)	**Q3** 81 patients (22.8%)	**Q4** 80 patients (22.5%)
	Defined as ≤34.72 mm	**Defined as >34.72 mm to ≤60.06 mm**	**Defined as >60.06 mm to ≤108.56 mm**	**Defined as >108.56 mm**
Age, median (range), years	63.0 (34–78)	64.0 (36–84)	64.0 (39–80)	64.5 (38–88)
IMDC risk group,[b] % Favourable / Intermediate + Poor / Not evaluable	40.7 / 58.0 / 1.2	30.0 / 68.8 / 1.3	34.6 / 65.4 / 0	6.3 / 93.8 / 0
Sarcomatoid features, %	9.9	8.8	4.9	6.3
PD-L1 expression,[c] % ≥1 / <1 / Not available	25.9 / 32.1 / 42.0	37.5 / 28.8 / 33.8	37.0 / 34.6 / 28.4	23.8 / 33.8 / 42.5
Prior nephrectomy, %	87.7	88.8	76.5	38.8

Adapted from Grünwald V et al. ASCO GU 2024.[15]

Percentages may not total 100 due to rounding. One patient in the KEYTRUDA + LENVATINIB group had carcinoma without a clear-cell component.
[a]Includes patients with baseline target lesion assessments by independent imaging review per RECIST v1.1. [b]MSKCC scores: 0 indicates favourable risk, 1 or 2 intermediate risk, and 3 or higher poor risk. [b]IMDC scores: 0 indicates favourable risk, 1 or 2 intermediate risk, and 3 to 6 poor risk. IMDC risk group was not a stratification factor and relevant data were derived programmatically; [c]PD-L1 expression was assess with the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies) and reported as the combined positive score (number of PD-L1-staining cells [tumour cells, lymphocytes, and macrophages] divided by the total number of viable tumour cells), then multiplied by 100.

IHC, immunohistochemistry; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; PD-L1, programmed death ligand-1; Q, Quartile; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

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Exploratory subgroup analysis – Tumour responses across subgroups of interest[13]

Liver metastases

	Yes			No		
	KEYTRUDA + LENVATINIB (n=60)	Sunitinib (n=61)	Hazard ratio (95% CI)	KEYTRUDA + LENVATINIB (n=295)	Sunitinib (n=296)	Hazard ratio (95% CI)
Median PFS[a] (months)	16.6	5.6	0.43 (0.25–0.75)	25.9	9.4	0.37 (0.29–0.47)
Median OS[a] (months)	33.6	NE	0.52 (0.27–0.99)	NE	NE	0.66 (0.47–0.93)
ORR (%)	66.7	34.4	NE	71.9	36.5	NE

Adapted from Grünwald V et al. *Front Oncol*. 2023.[13]

LIMITATION: This study was not powered to detect differences in the treatment effect between these subgroups. Results from exploratory analyses should be interpreted with caution due to modest patient numbers and potential imbalances in baseline characteristics between subgroups.

Analysis cutoff date: 28 August 2020. Median follow up: 26.6 months.
[a] Assessed using RECIST v1.1.

NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Exploratory subgroup analysis – Tumour responses across subgroups of interest[13]

Bone metastases

	Yes			No		
	KEYTRUDA + LENVATINIB (n=85)	Sunitinib (n=97)	Hazard ratio (95% CI)	KEYTRUDA + LENVATINIB (n=270)	Sunitinib (n=260)	Hazard ratio (95% CI)
Median PFS[a] (months)	24.3	5.6	0.33 (0.21–0.52)	23.4	9.7	0.42 (0.33–0.54)
Median OS[a] (months)	NE	24.8	0.50 (0.30–0.83)	NE	NE	0.79 (0.54–1.14)
ORR (%)	64.7	22.7	NE	73.0	41.2	NE

Adapted from Grünwald V et al. *Front Oncol*. 2023.[13]

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Exploratory subgroup analysis – Tumour responses across subgroups of interest[13]

Lung metastases

	Yes			No		
	KEYTRUDA + LENVATINIB (n=249)	Sunitinib (n=239)	Hazard ratio (95% CI)	KEYTRUDA + LENVATINIB (n=106)	Sunitinib (n=118)	Hazard ratio (95% CI)
Median PFS[a] (months)	24.0	6.3	0.32 (0.25–0.41)	22.1	17.3	0.65 (0.43–0.98)
Median OS[a] (months)	NE	NE	0.57 (0.40–0.80)	33.6	NE	0.84 (0.47–1.49)
ORR (%)	74.7	36.4	NE	62.3	35.6	NE

Adapted from Grünwald V et al. *Front Oncol*. 2023.[13]

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Exploratory subgroup analysis – Tumour responses across subgroups of interest[13]

Sarcomatoid features

	Yes			No		
	KEYTRUDA + LENVATINIB (n=28)	Sunitinib (n=21)	Hazard ratio (95% CI)	KEYTRUDA + LENVATINIB (n=327)	Sunitinib (n=336)	Hazard ratio (95% CI)
Median PFS[a] (months)	11.1	5.5	0.39 (0.18–0.84)	24.3	9.4	0.38 (0.31–0.48)
Median OS[a] (months)	NE	NE	0.91 (0.32–2.58)	NE	NE	0.64 (0.47–0.87)
ORR (%)	60.7	23.8	NE	71.9	36.9	NE

Adapted from Grünwald V et al. *Front Oncol*. 2023.[13]

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Exploratory subgroup analysis – Tumour responses across subgroups of interest[13]

Previous nephrectomy

	Yes			No		
	KEYTRUDA + LENVATINIB (n=262)	Sunitinib (n=275)	Hazard ratio (95% CI)	KEYTRUDA + LENVATINIB (n=93)	Sunitinib (n=82)	Hazard ratio (95% CI)
Median PFS[a] (months)	27.7	9.4	0.37 (0.28–0.47)	15.3	7.5	0.44 (0.28–0.68)
Median OS[a] (months)	NE	NE	0.71 (0.49–1.03)	33.1	24.0	0.52 (0.31–0.86)
ORR (%)	73.7	40.0	NE	63.4	23.2	NE

Adapted from Grünwald V et al. *Front Oncol*. 2023.[13]

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Exploratory subgroup analysis – Tumour responses across subgroups of interest[13]

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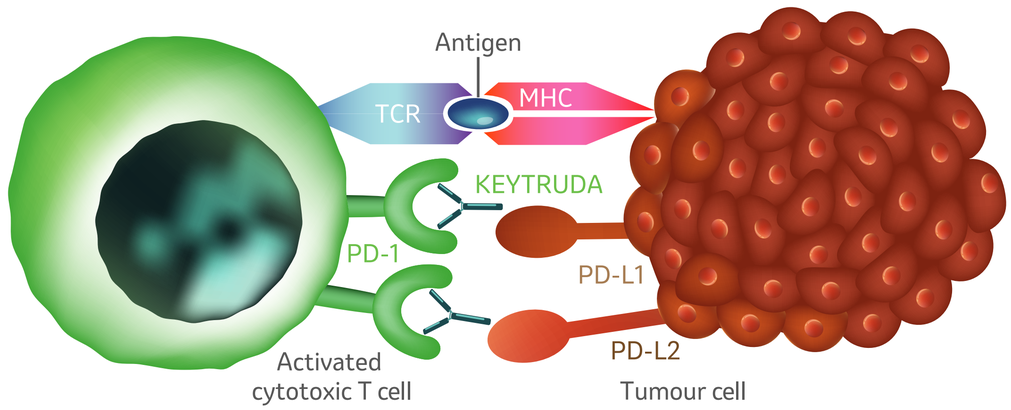
KEYTRUDA in combination with **LENVATINIB** targets two different disease pathways[6–9]

KEYTRUDA mode of action



Adapted from Pardoll DM. *Nat Rev Cancer*. 2012.[10]

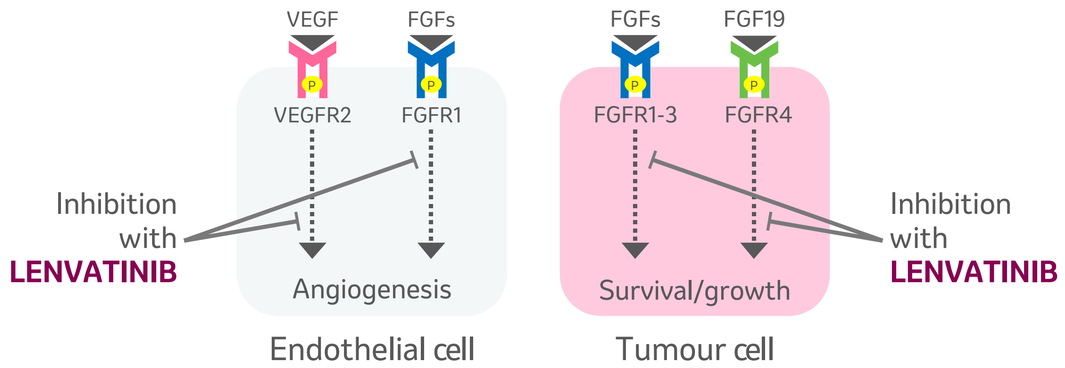
The immune-stimulatory effect of **KEYTRUDA** (anti-PD-1)[1,10]

- **KEYTRUDA** is a selective, humanised, monoclonal antibody designed to block the interaction between PD-1, PD-L1 and PD-L2[1]
- By inhibiting PD-1 receptor binding, **KEYTRUDA** **reactivates tumour-specific cytotoxic T lymphocytes** in the tumour microenvironment, resulting in **anti-tumour immunity**[1]

FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FLT, Fms-related tyrosine kinase; KDR, kinase insert domain; KIT, proto-oncogene c-KIT; MHC, major histocompatibility complex; PD-1, programmed death receptor-1; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; RCC, renal cell carcinoma; RET, rearranged during transfection; RTK, receptor tyrosine kinase; TCR, T-cell receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

KEYTRUDA in combination with **LENVATINIB** targets two different disease pathways[6–9]

LENVATINIB mode of action



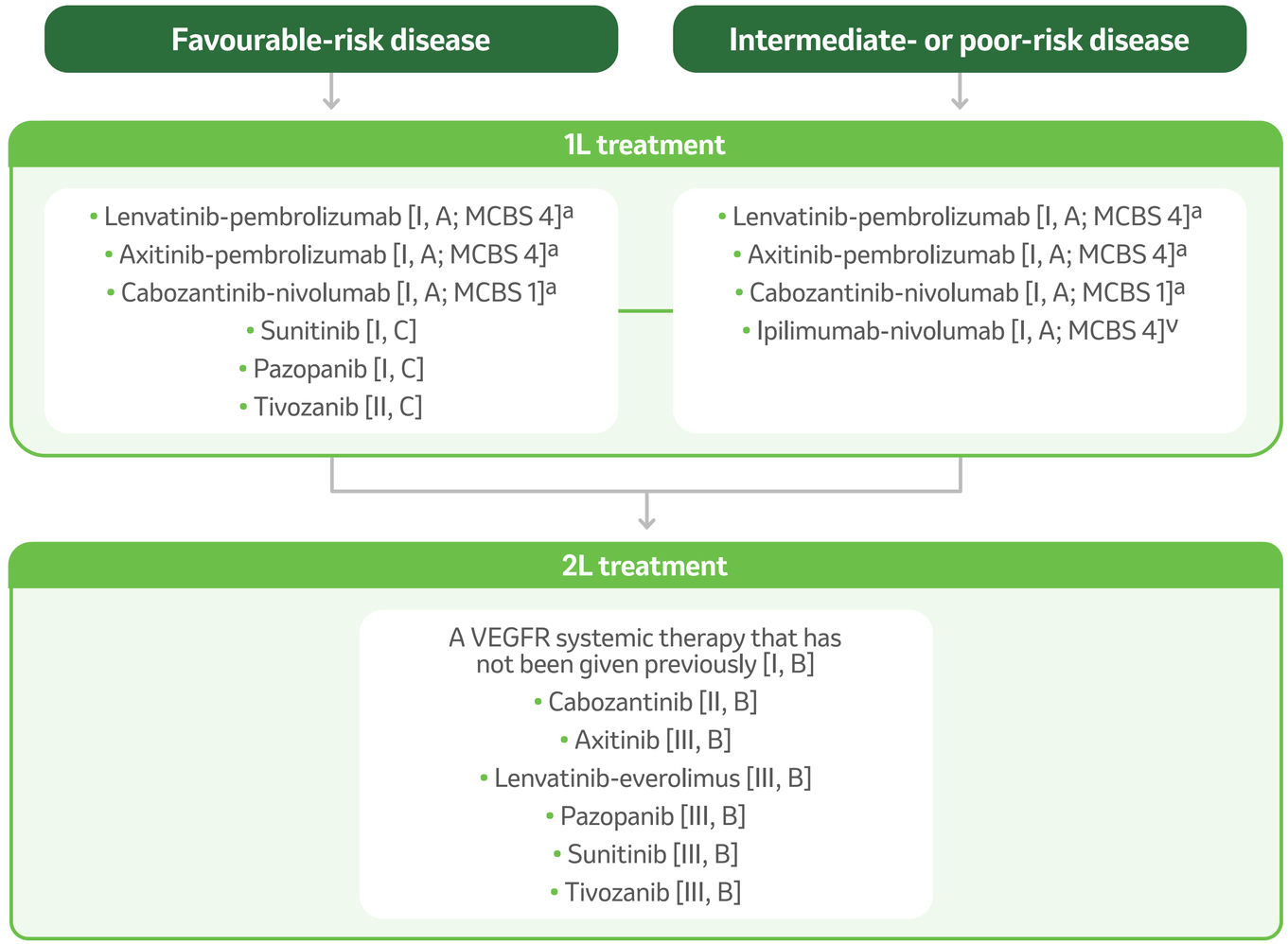
Adapted from Kudo M. *Liver Cancer*. 2018.[12]

The anti-angiogenic effect of **LENVATINIB** (anti-VEGFR/FGFR)[2,11]

- **LENVATINIB** is a receptor tyrosine kinase inhibitor that **selectively inhibits the kinase activities** of the **VEGF** receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including FGF receptors (FGFR1, 2, 3, and 4); the PDGF receptor (PDGFRα); KIT; and RET[2,11]

FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FLT, Fms-related tyrosine kinase; KDR, kinase insert domain; KIT, proto-oncogene c-KIT; MHC, major histocompatibility complex; PD-1, programmed death receptor-1; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; RCC, renal cell carcinoma; RET, rearranged during transfection; RTK, receptor tyrosine kinase; TCR, T-cell receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Advanced and metastatic ccRCC[5]



According to the ESMO 2024 guidelines, cabozantinib monotherapy is the preferred 2L option when it has not been used in the 1L setting.[5]

Adapted from Powles T, et al. *Ann Oncol*. 2024.[5]

Note that therapies not approved in the UK have been removed from the treatment algorithm.

[a]ESMO-MCBS v1.1 was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).

ccRCC, clear-cell renal cell carcinoma; chT; chemotherapy; ESMO, European Society for Medical Oncology; MCBS; Magnitude of Clinical Benefit Scale; VEGFR; vascular endothelial growth factor receptor.

Advanced and metastatic pRCC[5]

1L treatment

Preferred:

- Cabozantinib [II, B]

Alternative single-agent options:

- Sunitinib [II, B]

Alternatives to single-agent therapy:

- Lenvatinib-pembrolizumab [III, B]
- Cabozantinib -nivolumab [III, B]

2L treatment

A systemic therapy that has not been given previously [IV, C]

- Cabozantinib [IV, C]
- Sunitinib [IV, C]
- Everolimus [IV, C]

Adapted from Powles T, et al. *Ann Oncol*. 2024.[5]

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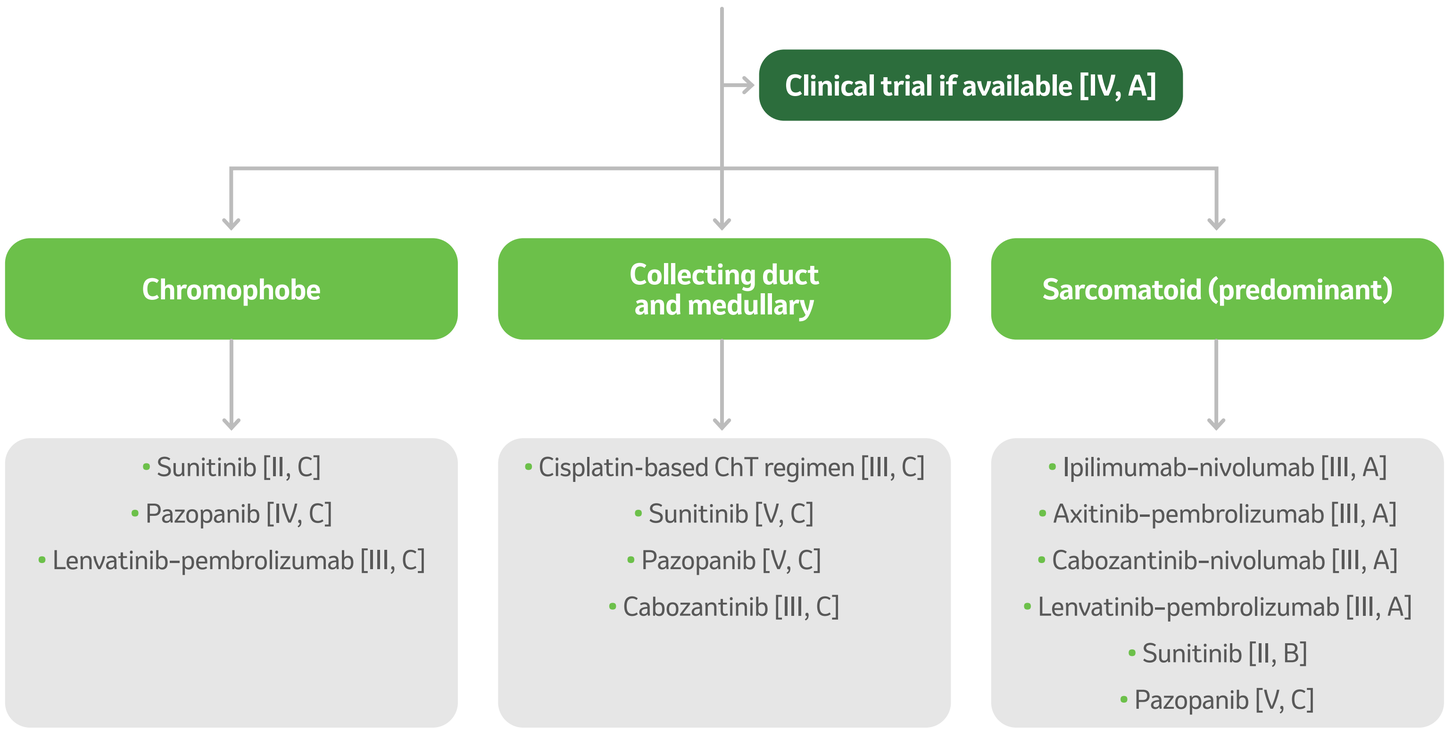
ccRCC, clear-cell renal cell carcinoma; chT; chemotherapy; ESMO, European Society for Medical Oncology; MCBS; Magnitude of Clinical Benefit Scale; VEGFR; vascular endothelial growth factor receptor.

Advanced and metastatic non-clear-cell and non-papillary RCC[5]



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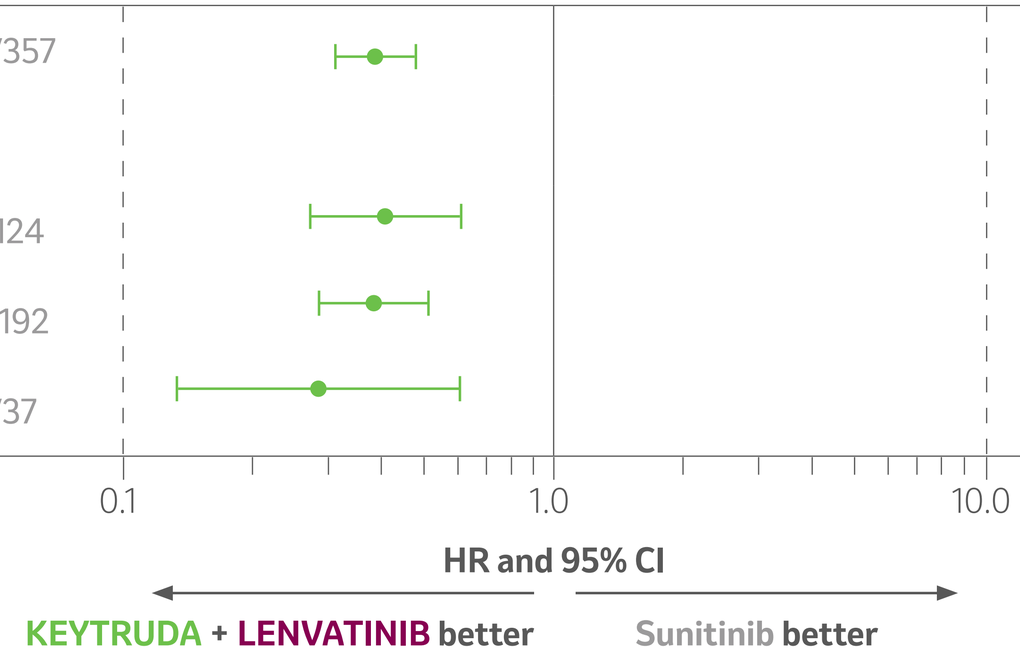
ccRCC, clear-cell renal cell carcinoma; chT; chemotherapy; ESMO, European Society for Medical Oncology; MCBS; Magnitude of Clinical Benefit Scale; VEGFR; vascular endothelial growth factor receptor.

Primary analysis – PFS by IMDC risk groups (exploratory subgroup analysis)[a,12]

	Events/Patients		HR for disease progression or death (95% CI)
	KEYTRUDA + LENVATINIB	Sunitinib	
Overall	160/355	205/357	0.39 (0.32–0.49)
IMDC risk group			
Favourable	43/110	67/124	0.41 (0.28–0.62)
Intermediate	97/210	110/192	0.39 (0.29–0.52)
Poor	18/33	26/37	0.28 (0.13–0.60)



Adapted from Motzer R et al. *N Engl J Med*. 2021.[12]

LIMITATION: This study was not powered to detect differences in the treatment effect between these subgroups. Results from exploratory analyses should be interpreted with caution due to modest patient numbers and potential imbalances in baseline characteristics between subgroups.

Analysis cutoff date: 28 August 2020. Median follow up: 26.6 months.
[a]Patients were stratified by MSKCC risk group but not by IMDC risk group.

CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Centre; PFS, progression-free survival.

Exploratory subgroup analysis – Tumour responses across subgroups of interest[13]

Liver metastases

	Yes			No		
	KEYTRUDA + LENVATINIB (n=60)	Sunitinib (n=61)	Hazard ratio (95% CI)	KEYTRUDA + LENVATINIB (n=295)	Sunitinib (n=296)	Hazard ratio (95% CI)
Median PFS[a] (months)	16.6	5.6	0.43 (0.25–0.75)	25.9	9.4	0.37 (0.29–0.47)
Median OS[a] (months)	33.6	NE	0.52 (0.27–0.99)	NE	NE	0.66 (0.47–0.93)
ORR (%)	66.7	34.4	NE	71.9	36.5	NE

Adapted from Grünwald V et al. *Front Oncol*. 2023.[13]

LIMITATION: This study was not powered to detect differences in the treatment effect between these subgroups. Results from exploratory analyses should be interpreted with caution due to modest patient numbers and potential imbalances in baseline characteristics between subgroups.

Analysis cutoff date: 28 August 2020. Median follow up: 26.6 months.
[a] Assessed using RECIST v1.1.

NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Exploratory subgroup analysis – Tumour responses across subgroups of interest[13]

Bone metastases

	Yes			No		
	KEYTRUDA + LENVATINIB (n=85)	Sunitinib (n=97)	Hazard ratio (95% CI)	KEYTRUDA + LENVATINIB (n=270)	Sunitinib (n=260)	Hazard ratio (95% CI)
Median PFS[a] (months)	24.3	5.6	0.33 (0.21–0.52)	23.4	9.7	0.42 (0.33–0.54)
Median OS[a] (months)	NE	24.8	0.50 (0.30–0.83)	NE	NE	0.79 (0.54–1.14)
ORR (%)	64.7	22.7	NE	73.0	41.2	NE

Adapted from Grünwald V et al. *Front Oncol*. 2023.[13]

LIMITATION: This study was not powered to detect differences in the treatment effect between these subgroups. Results from exploratory analyses should be interpreted with caution due to modest patient numbers and potential imbalances in baseline characteristics between subgroups.

Analysis cutoff date: 28 August 2020. Median follow up: 26.6 months.
[a] Assessed using RECIST v1.1.

NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Exploratory subgroup analysis – Tumour responses across subgroups of interest[13]

Lung metastases

	Yes			No		
	KEYTRUDA + LENVATINIB (n=249)	**Sunitinib** (n=239)	**Hazard ratio** (95% CI)	**KEYTRUDA + LENVATINIB** (n=106)	**Sunitinib** (n=118)	**Hazard ratio** (95% CI)
Median PFS[a] (months)	24.0	6.3	0.32 (0.25–0.41)	22.1	17.3	0.65 (0.43–0.98)
Median OS[a] (months)	NE	NE	0.57 (0.40–0.80)	33.6	NE	0.84 (0.47–1.49)
ORR (%)	74.7	36.4	NE	62.3	35.6	NE

Adapted from Grünwald V et al. *Front Oncol*. 2023.[13]

LIMITATION: This study was not powered to detect differences in the treatment effect between these subgroups. Results from exploratory analyses should be interpreted with caution due to modest patient numbers and potential imbalances in baseline characteristics between subgroups.

Analysis cutoff date: 28 August 2020. Median follow up: 26.6 months.
[a]Assessed using RECIST v1.1.

NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Exploratory subgroup analysis – Tumour responses across subgroups of interest[13]

Sarcomatoid features

	Yes			No		
	KEYTRUDA + LENVATINIB (n=28)	Sunitinib (n=21)	Hazard ratio (95% CI)	KEYTRUDA + LENVATINIB (n=327)	Sunitinib (n=336)	Hazard ratio (95% CI)
Median PFS[a] (months)	11.1	5.5	0.39 (0.18–0.84)	24.3	9.4	0.38 (0.31–0.48)
Median OS[a] (months)	NE	NE	0.91 (0.32–2.58)	NE	NE	0.64 (0.47–0.87)
ORR (%)	60.7	23.8	NE	71.9	36.9	NE

Adapted from Grünwald V et al. *Front Oncol*. 2023.[13]

LIMITATION: This study was not powered to detect differences in the treatment effect between these subgroups. Results from exploratory analyses should be interpreted with caution due to modest patient numbers and potential imbalances in baseline characteristics between subgroups.

Analysis cutoff date: 28 August 2020. Median follow up: 26.6 months.
[a] Assessed using RECIST v1.1.

NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Exploratory subgroup analysis – Tumour responses across subgroups of interest[13]

Previous nephrectomy

	Yes			No		
	KEYTRUDA + LENVATINIB (n=262)	Sunitinib (n=275)	Hazard ratio (95% CI)	KEYTRUDA + LENVATINIB (n=93)	Sunitinib (n=82)	Hazard ratio (95% CI)
Median PFS[a] (months)	27.7	9.4	0.37 (0.28–0.47)	15.3	7.5	0.44 (0.28–0.68)
Median OS[a] (months)	NE	NE	0.71 (0.49–1.03)	33.1	24.0	0.52 (0.31–0.86)
ORR (%)	73.7	40.0	NE	63.4	23.2	NE

Adapted from Grünwald V et al. *Front Oncol*. 2023.[13]

LIMITATION: This study was not powered to detect differences in the treatment effect between these subgroups. Results from exploratory analyses should be interpreted with caution due to modest patient numbers and potential imbalances in baseline characteristics between subgroups.

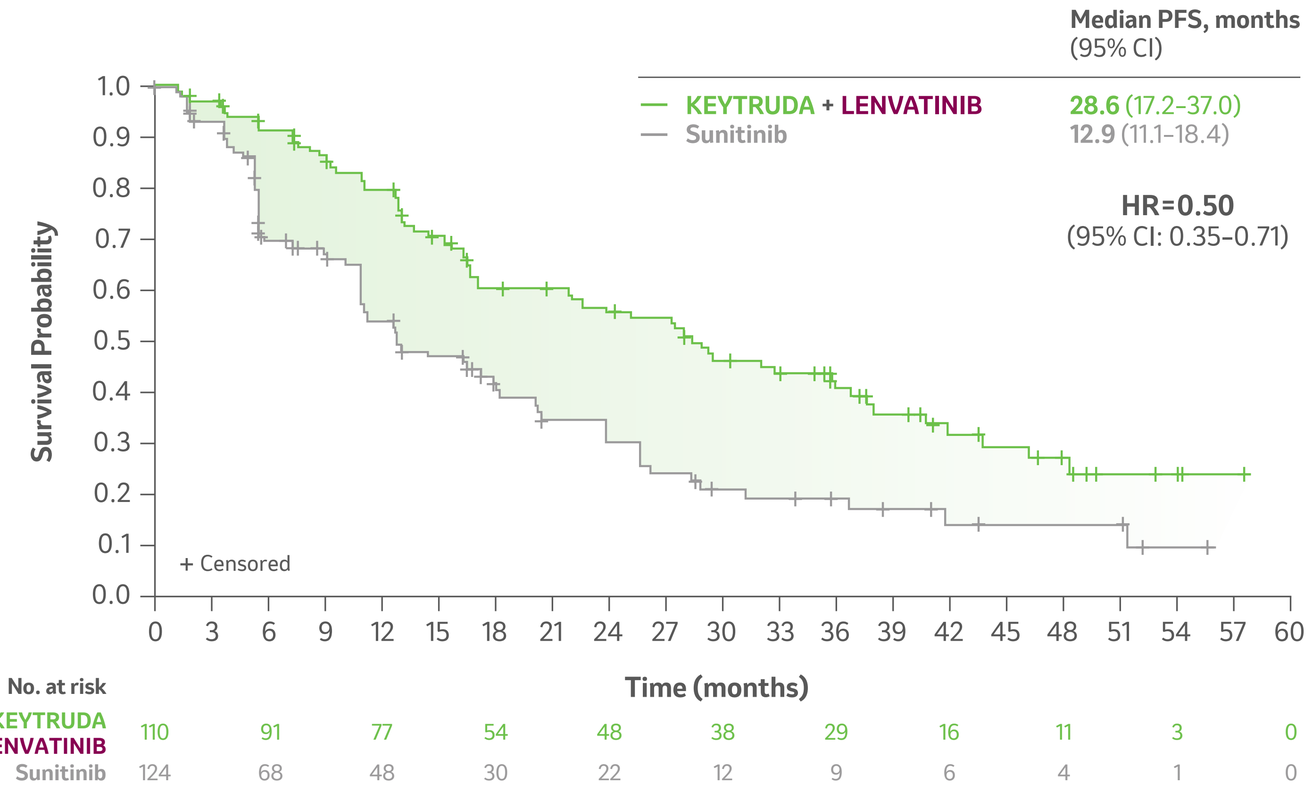
Analysis cutoff date: 28 August 2020. Median follow up: 26.6 months.
[a] Assessed using RECIST v1.1.

NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Exploratory analysis – Kaplan-Meier estimates of PFS by IMDC risk subgroup[a,14]

Median (IQR) follow-up for PFS: 39.2 (22.1–48.5) months with **KEYTRUDA** + **LENVATINIB** and 20.6 (5.5–41.2) months with sunitinib

Favourable risk group



Adapted from Motzer R et al. ASCO 2023.[14]

LIMITATION: This trial was not powered to detect differences between subgroups. No formal statistical testing was planned for this exploratory analysis and, therefore, no conclusions can be drawn.

Analysis cutoff date: 31 July 2022.

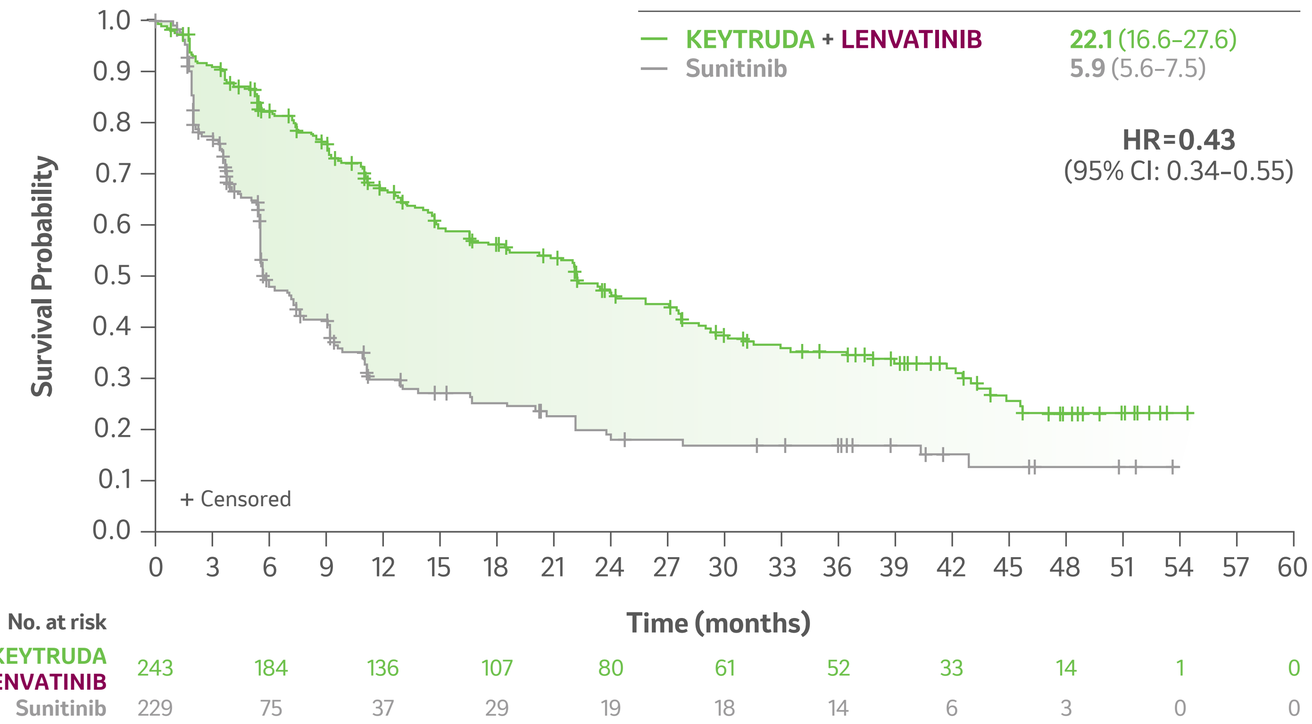
[a]IMDC risk group was not a stratification factor and relevant data were derived programmatically; [b]Medians were estimated by Kaplan-Meier method and 95% CIs were estimated with a generalised Brookmeyer and Crowley method; [c]HR was based on a Cox regression model with treatment as a factor and with Efron's method used for correction of tied events.

CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IQR, interquartile range; PFS, progression-free survival.

Exploratory analysis – Kaplan-Meier estimates of PFS by IMDC risk subgroup[a,14]

Median (IQR) follow-up for PFS: 39.2 (22.1–48.5) months with **KEYTRUDA + LENVATINIB** and 20.6 (5.5–41.2) months with sunitinib

Intermediate + Poor risk group



Adapted from Motzer R et al. ASCO 2023.[14]

LIMITATION: This trial was not powered to detect differences between subgroups. No formal statistical testing was planned for this exploratory analysis and, therefore, no conclusions can be drawn.

Analysis cutoff date: 31 July 2022.

[a]IMDC risk group was not a stratification factor and relevant data were derived programmatically; [b]Medians were estimated by Kaplan-Meier method and 95% CIs were estimated with a generalised Brookmeyer and Crowley method; [c]HR was based on a Cox regression model with treatment as a factor and with Efron's method used for correction of tied events.

CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IQR, interquartile range; PFS, progression-free survival.

Exploratory analysis – Patient characteristics by tumour size in the **KEYTRUDA** + **LENVATINIB** arm of the CLEAR trial[15]

Characteristic	Baseline sums of diameters of target lesions[a] (N=355)			
	Q1 81 patients (22.8%)	**Q2** 80 patients (22.5%)	**Q3** 81 patients (22.8%)	**Q4** 80 patients (22.5%)
	Defined as ≤34.72 mm	**Defined as >34.72 mm to ≤60.06 mm**	**Defined as >60.06 mm to ≤108.56 mm**	**Defined as >108.56 mm**
Age, median (range), years	63.0 (34–78)	64.0 (36–84)	64.0 (39–80)	64.5 (38–88)
IMDC risk group,[b] % Favourable / Intermediate + Poor / Not evaluable	40.7 / 58.0 / 1.2	30.0 / 68.8 / 1.3	34.6 / 65.4 / 0	6.3 / 93.8 / 0
Sarcomatoid features, %	9.9	8.8	4.9	6.3
PD-L1 expression,[c] % ≥1 / <1 / Not available	25.9 / 32.1 / 42.0	37.5 / 28.8 / 33.8	37.0 / 34.6 / 28.4	23.8 / 33.8 / 42.5
Prior nephrectomy, %	87.7	88.8	76.5	38.8

Adapted from Grünwald V et al. ASCO GU 2024.[15]

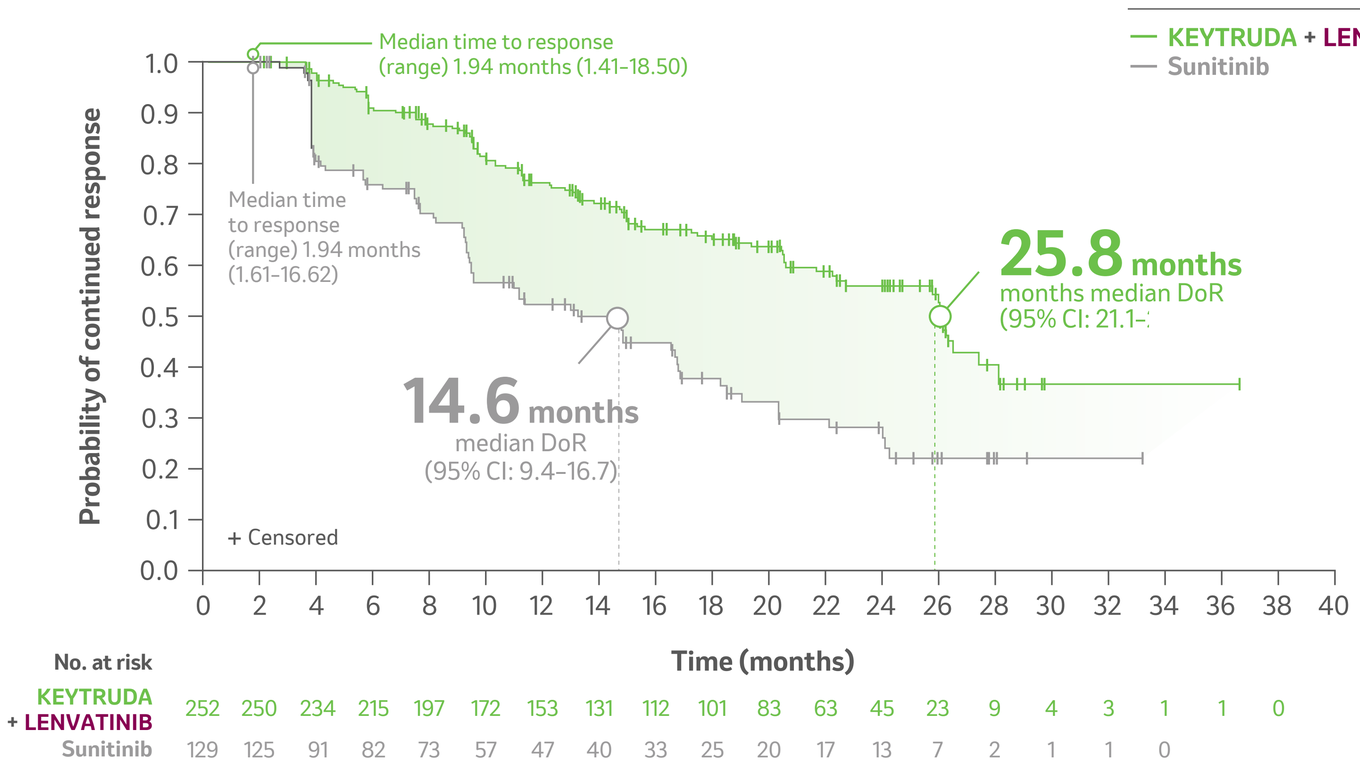
Percentages may not total 100 due to rounding. One patient in the KEYTRUDA + LENVATINIB group had carcinoma without a clear-cell component.
[a]Includes patients with baseline target lesion assessments by independent imaging review per RECIST v1.1. [b]MSKCC scores: 0 indicates favourable risk, 1 or 2 intermediate risk, and 3 or higher poor risk. [b]IMDC scores: 0 indicates favourable risk, 1 or 2 intermediate risk, and 3 to 6 poor risk. IMDC risk group was not a stratification factor and relevant data were derived programmatically; [c]PD-L1 expression was assess with the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies) and reported as the combined positive score (number of PD-L1-staining cells [tumour cells, lymphocytes, and macrophages] divided by the total number of viable tumour cells), then multiplied by 100.

IHC, immunohistochemistry; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; PD-L1, programmed death ligand-1; Q, Quartile; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Primary analysis – Median DOR was 25.8 months for **KEYTRUDA** + **LENVATINIB** versus 14.6 months for sunitinib[a,12]

Median follow-up: 26.6 months

Kaplan-Meier analysis of DoR



Adapted from Motzer et al. *N Engl J Med*. 2021.[12]

- Median time to response (range) in the **KEYTRUDA** + **LENVATINIB** arm was 1.94 (1.41–18.50) months and 1.94 (1.61–16.62) months in the sunitinib arm

LIMITATION: Exploratory analysis, no formal statistical testing was performed for this analysis, and, therefore, no conclusions can be drawn.

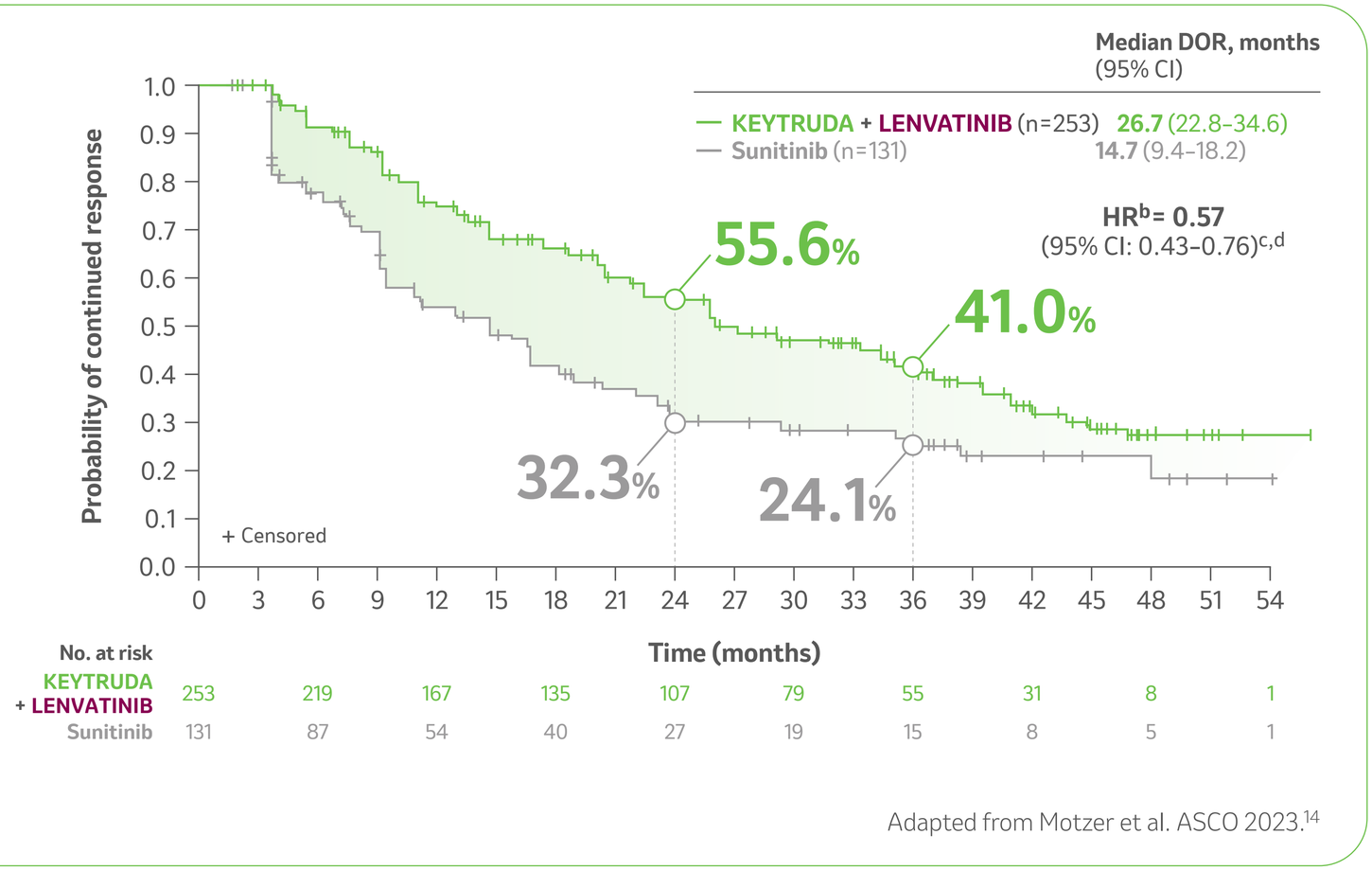
Analysis cut-off date: 28 August 2020.

[a]Responses were assessed by an independent review committee using RECIST v1.1.

CI, confidence interval; DOR, duration of response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Exploratory analysis – Duration of response (DOR)[a,14]

Median (IQR) follow-up: 49.8 (41.4–53.1) months with **KEYTRUDA + LENVATINIB** and 49.4 (41.6–52.8) months with sunitinib



Adapted from Motzer et al. ASCO 2023.[14]

- In the **KEYTRUDA + LENVATINIB** group, median DOR (95% CI) for CR was 43.7 (39.2–NE) months
- Median DOR (95% CI) for near-CR[e] with **KEYTRUDA + LENVATINIB** was 30.5 (22.4–NE) months

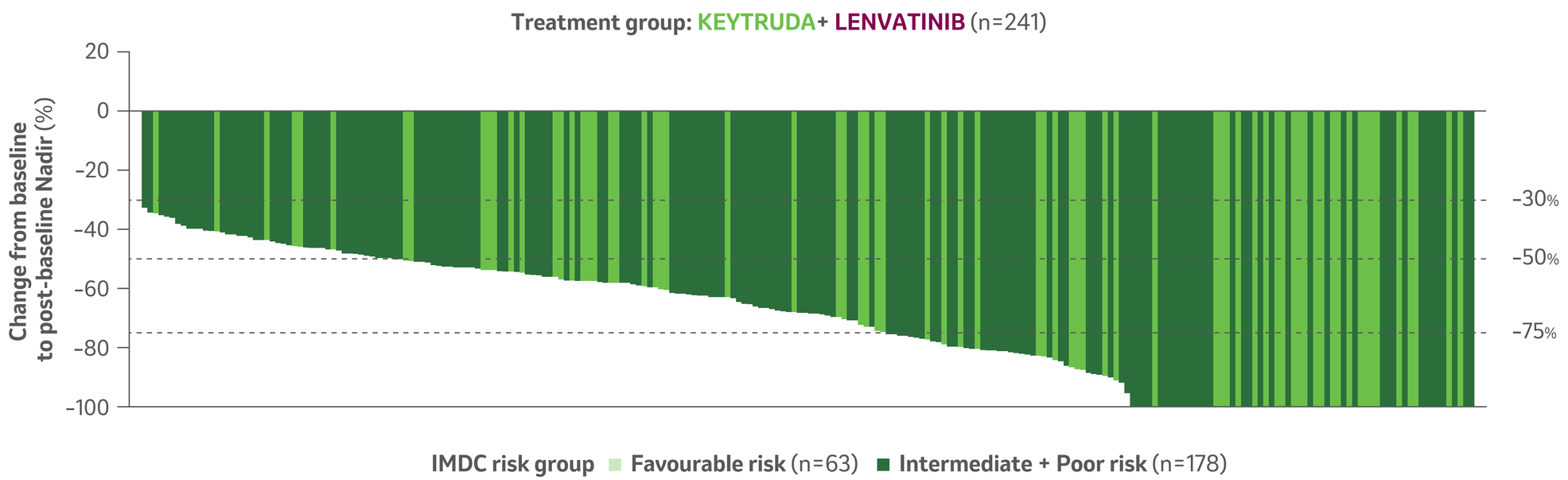
LIMITATION: This analysis was a protocol pre-specified descriptive analysis. No formal statistical analysis was performed for this analysis; therefore, no conclusions can be drawn.

Analysis cutoff date: 31 July 2022. When median follow-up time was not specified for an endpoint, median follow-up for OS is presented in the slide.
[a]As determined by independent review committee using RECIST v1.1; [b]HR is based on a Cox Proportional Hazards Model including treatment group as a factor. Efron method is used for ties and stratified by geographic region and MSKCC prognostic groups by IxRS; [c]The 95% CIs were estimated using the method of normal approximation; [d]The 95% CIs are estimated with a generalised Brookmeyer and Crowley method; [e]Near-CR refers to individuals who presented a PR with a maximum tumour reduction of ≥75%.

CI, confidence interval; CR, complete response; DOR, duration of response; HR, hazard ratio; IQR, interquartile range; IxRS, interactive voice/web response system; MSKCC, Memorial Sloan Kettering Cancer Center; NE, not estimable; OS, overall survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; PR, partial response.

Exploratory analysis – Change in target lesion size[a] in patients who responded to treatment with **KEYTRUDA** + **LENVATINIB**[14]

Median (IQR) follow-up: 49.8 (41.4–53.1) months with **KEYTRUDA** + **LENVATINIB** and 49.4 (41.6–52.8) months with sunitinib



Adapted from Motzer et al. ASCO 2023.[14]

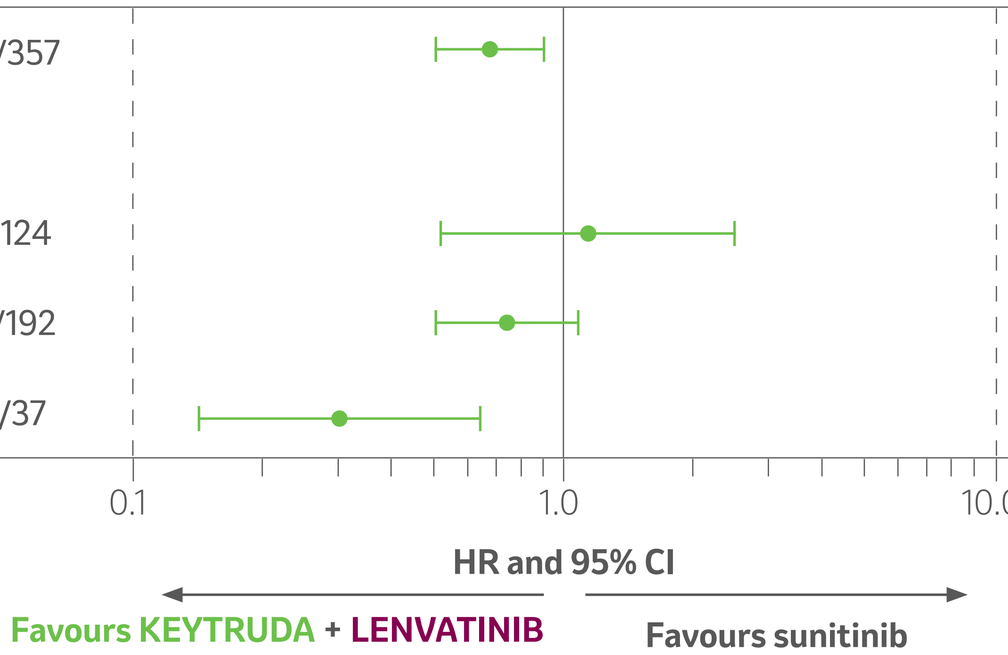
LIMITATION: No formal statistical analysis was performed for this analysis; therefore, no conclusions can be drawn.

Analysis cutoff date: 31 July 2022. When median follow-up time was not specified for an endpoint, median follow-up for OS is presented in the slide.
[a]Changes in size of the target lesion were determined as per independent review. Patients included in the analysis had both baseline and ≥1 post-baseline target lesion assessment.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IQR, interquartile range; OS, overall survival.

Primary analysis – OS by IMDC risk groups (subgroup analysis)[a,12]

Median follow-up: 26.6 months

	Events/Patients		
	KEYTRUDA + LENVATINIB	Sunitinib	**HR** (95% CI)
Overall	80/355	101/357	0.66 (0.49–0.88)
IMDC risk group			
Favourable	14/110	15/124	1.15 (0.55–2.40)
Intermediate	56/210	60/192	0.72 (0.50–1.05)
Poor	10/33	25/37	0.30 (0.14–0.64)



Adapted from Motzer R et al. *N Engl J Med*. 2021.[12]

LIMITATION: This study was not powered to detect differences in the treatment effect between these subgroups. Results from exploratory analyses should be interpreted with caution due to modest patient numbers and potential imbalances in baseline characteristics between subgroups.

Analysis cutoff date: 28 August 2020.

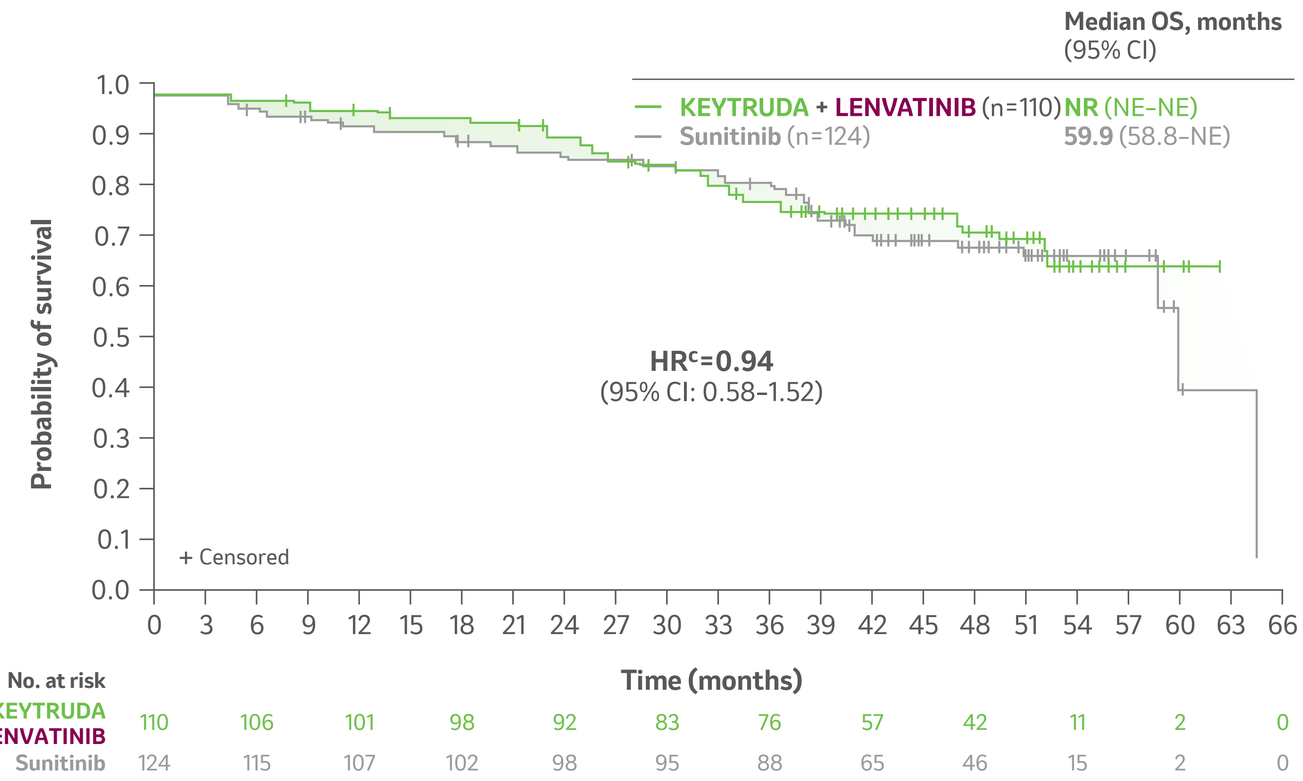
[a] Patients were stratified by MSKCC risk group but not by IMDC risk group.

CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival.

Exploratory analysis – Kaplan-Meier estimates of OS by IMDC risk subgroup[a,14]

Median (IQR) follow-up for OS: 49.8 (41.4–53.1) months with **KEYTRUDA** + **LENVATINIB** and 49.4 (41.6–52.8) months with sunitinib

Favourable risk group



No. at risk												
KEYTRUDA + LENVATINIB	110	106	101	98	92	83	76	57	42	11	2	0
Sunitinib	124	115	107	102	98	95	88	65	46	15	2	0

Adapted from Motzer R et al. ASCO 2023.[14]

LIMITATION: This trial was not powered to detect differences between subgroups. No formal statistical testing was planned for this exploratory analysis and, therefore, no conclusions can be drawn.

Analysis cutoff date: 31 July 2022.

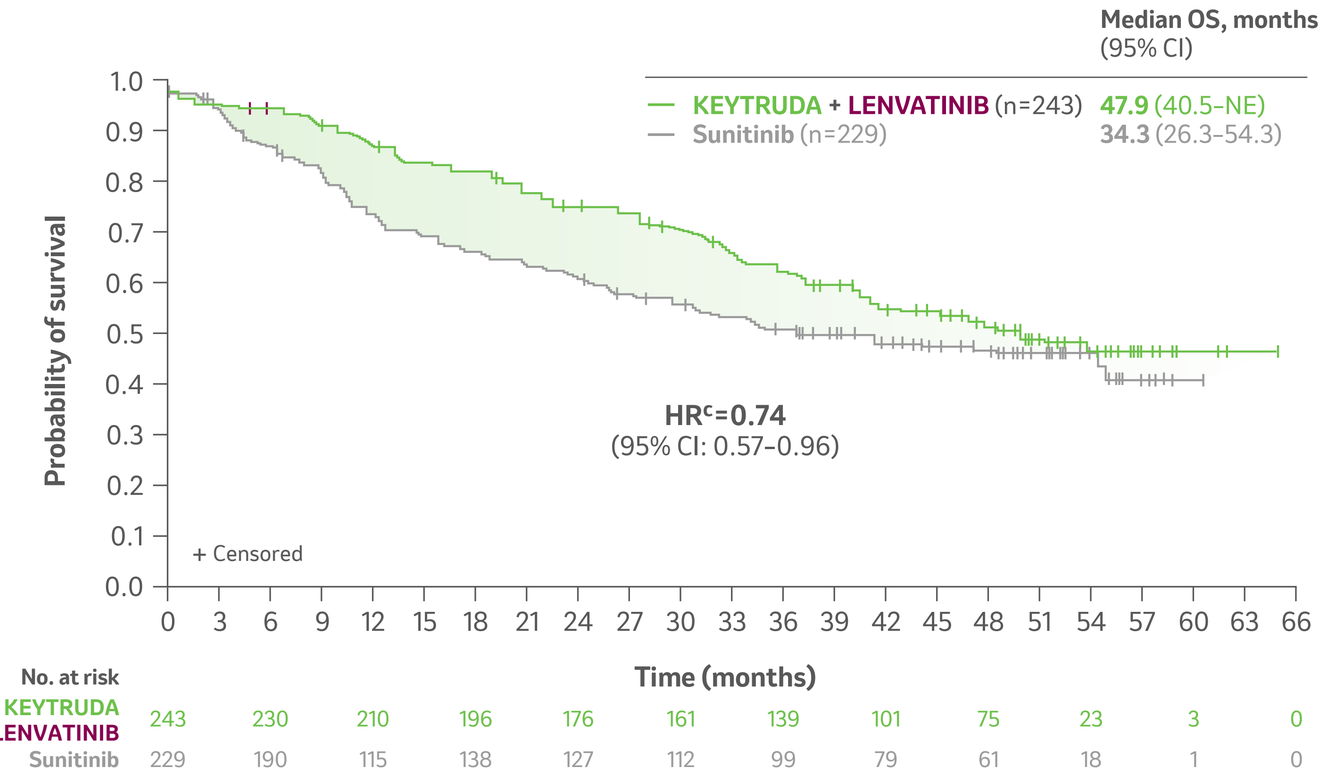
[a]IMDC risk group was not a stratification factor and relevant data were derived programmatically; [b]Medians were estimated by the Kaplan-Meier method and 95% CIs were estimated with a generalised Brookmeyer and Crowley method; [c]Hazard ratio was based on a Cox regression model with treatment as a factor and with Efron's method used for correction of tied events.

CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IQR, interquartile range; NE, not estimable; NR, not reached; OS, overall survival.

Exploratory analysis – Kaplan-Meier estimates of OS by IMDC risk subgroup[a,14]

Median (IQR) follow-up for OS: 49.8 (41.4–53.1) months with **KEYTRUDA** + **LENVATINIB** and 49.4 (41.6–52.8) months with sunitinib

Intermediate + Poor risk group



Adapted from Motzer R et al. ASCO 2023.[14]

LIMITATION: This trial was not powered to detect differences between subgroups. No formal statistical testing was planned for this exploratory analysis and, therefore, no conclusions can be drawn.

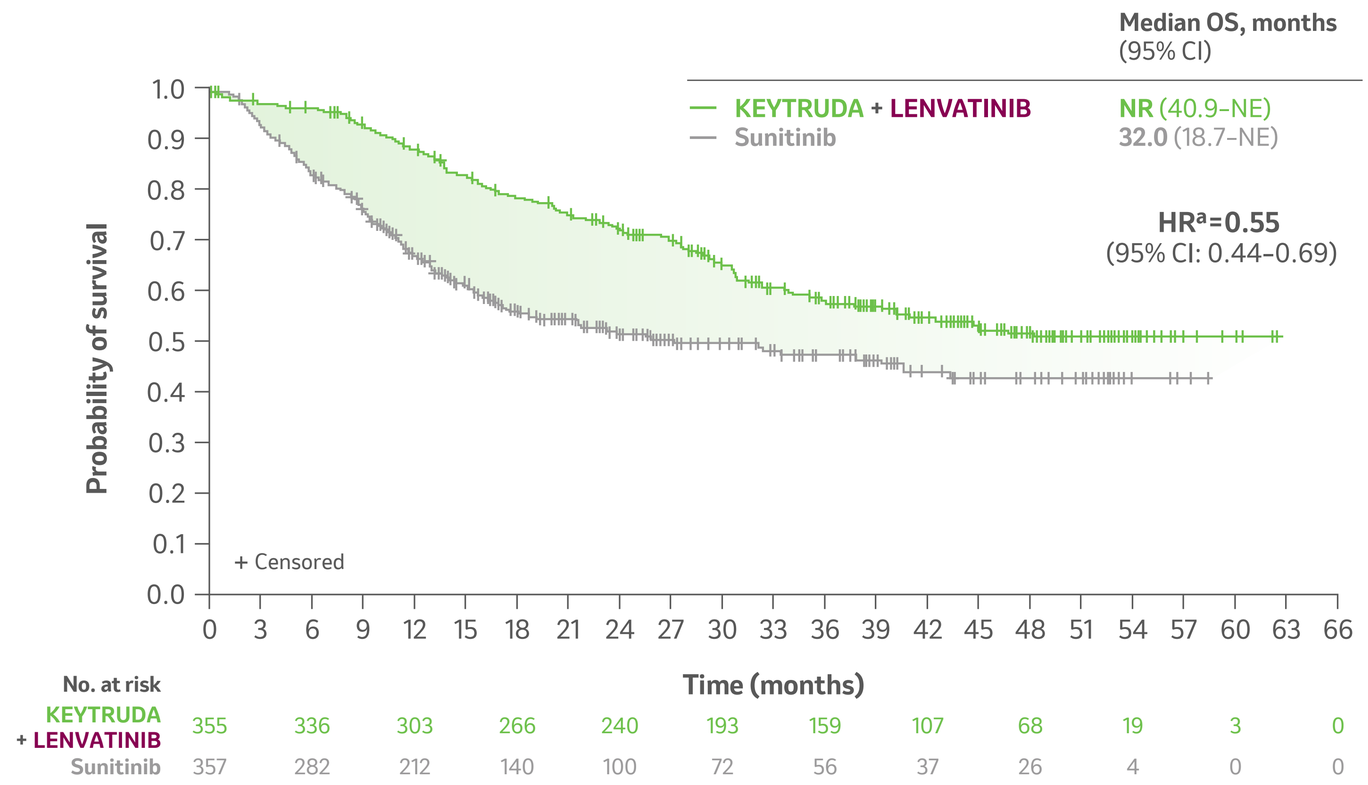
Analysis cutoff date: 31 July 2022.

[a]IMDC risk group was not a stratification factor and relevant data were derived programmatically; [b]Medians were estimated by the Kaplan-Meier method and 95% CIs were estimated with a generalised Brookmeyer and Crowley method; [c]Hazard ratio was based on a Cox regression model with treatment as a factor and with Efron's method used for correction of tied events.

CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IQR, interquartile range; NE, not estimable; NR, not reached; OS, overall survival.

Exploratory analysis – Final OS analysis adjusted for subsequent anticancer medications[14]

Median (IQR) follow-up for OS: 49.8 (41.4–53.1) months with **KEYTRUDA + LENVATINIB** and 49.4 (41.6–52.8) months with sunitinib



Adapted from Motzer R et al. ASCO 2023.[14]

	KEYTRUDA + LENVATINIB (n=355)	Sunitinib (n=357)
Any subsequent systemic anticancer medication,[b] n (%)	181 (51.0)	246 (68.9)
Anti-VEGF therapy, n (%)	163 (45.9)	162 (45.4)
PD-1/PD-L1 checkpoint inhibitor, n (%)	56 (15.8)	195 (54.6)

LIMITATION: No formal statistical testing was performed for this final prespecified analysis, and, therefore, no conclusions can be drawn.

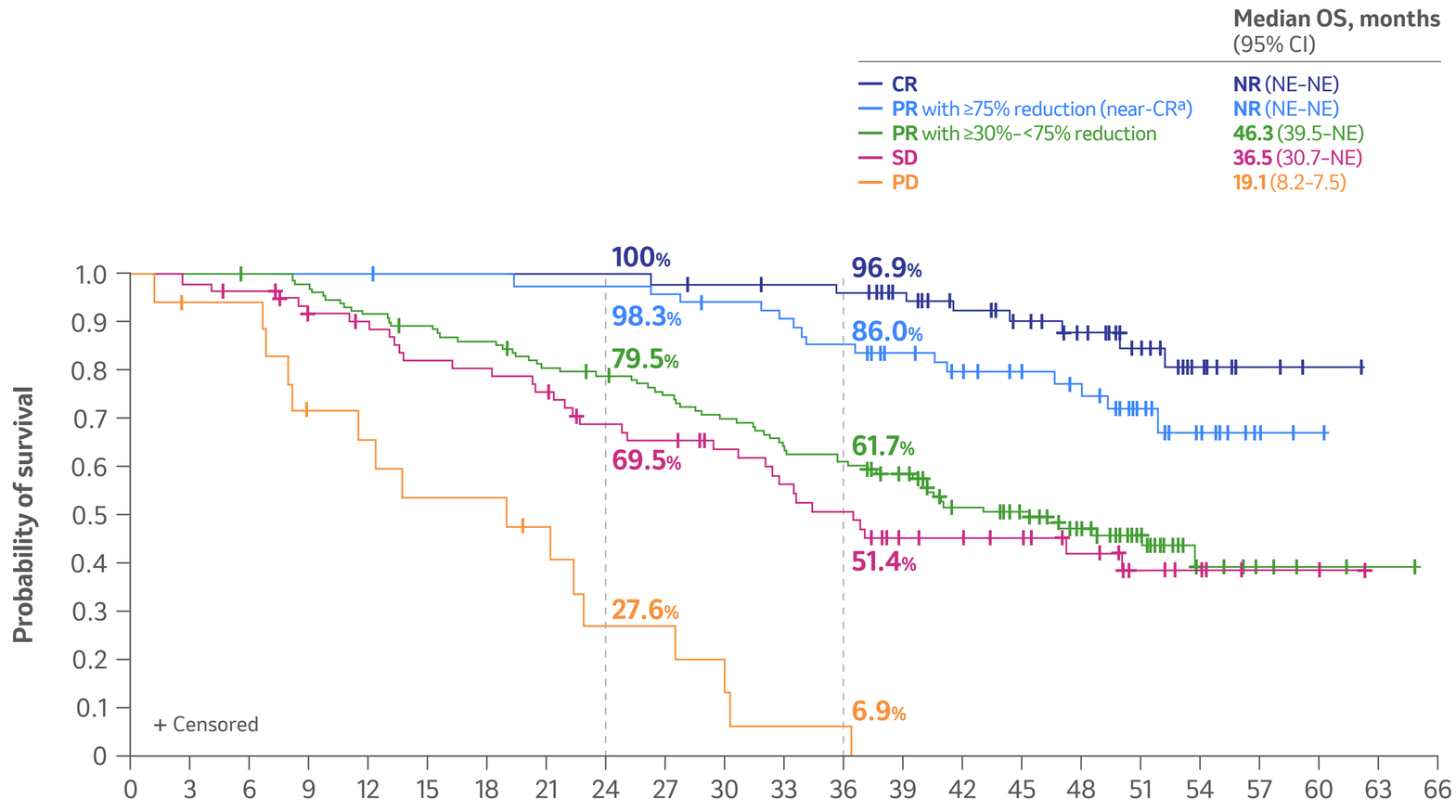
Analysis cutoff date: 31 July 2022.

[a]A 2-stage estimation method was used for the post-hoc analysis of OS to adjust for the impact of imbalance in subsequent anticancer medications between treatment groups; [b]During survival follow-up.

CI, confidence interval; HR, hazard ratio; IQR, interquartile range; NE, not estimable; NR, not reached; OS, overall survival; PD-1, programmed death receptor-1; PD-L1, programmed death ligand-1; VEGF, vascular endothelial growth factor.

Exploratory analysis – Final OS analysis by best overall response in patients treated with **KEYTRUDA** + **LENVATINIB**[14]

Median (IQR) follow-up for OS: 49.8 (41.4–53.1) months with **KEYTRUDA** + **LENVATINIB** and 49.4 (41.6–52.8) months with sunitinib



No. at risk																							
CR	65	65	65	65	65	65	65	65	65	64	63	62	61	53	46	40	35	24	12	4	1	0	0
PR with ≥75% reduction (near-CR[a])	59	59	59	59	59	58	58	57	57	56	54	52	49	44	40	33	30	19	9	2	1	0	0
PR with ≥30%–<75% reduction	129	129	128	126	118	114	110	102	99	93	87	80	76	66	51	46	37	24	8	4	2	1	0
SD	67	66	64	60	56	51	50	47	41	39	35	31	28	21	20	18	14	8	5	2	1	0	0
PD	19	17	17	12	11	9	9	7	4	4	3	1	1	0	0	0	0	0	0	0	0	0	0

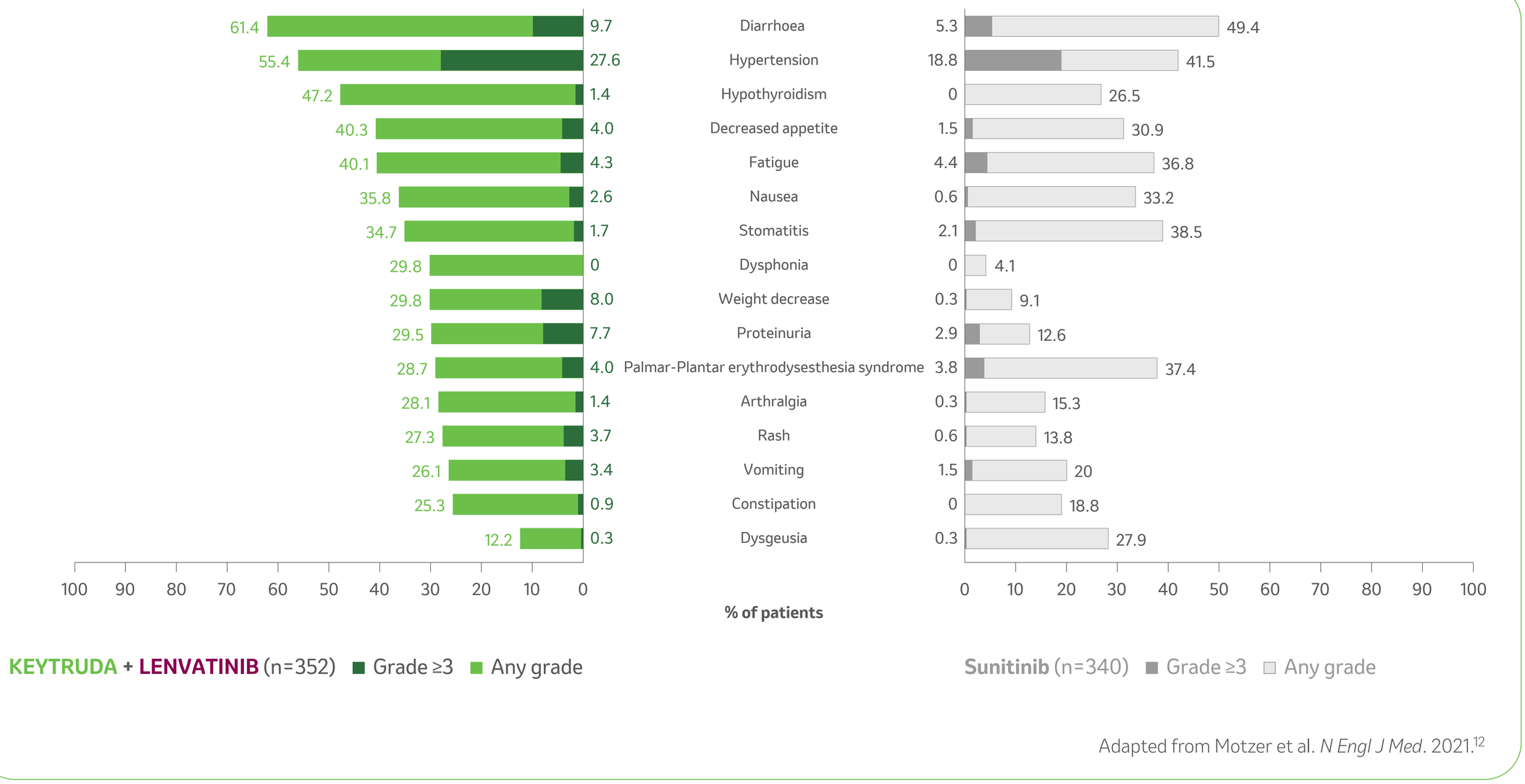
Adapted from Motzer R et al. ASCO 2023.[14]

LIMITATION:
This trial was not powered to detect differences between subgroups. No formal statistical testing was performed for this final prespecified analysis and, therefore, no conclusions can be drawn.

Analysis cutoff date: 31 July 2022.
[a]Near-CR refers to individuals who presented a PR with a maximum tumour reduction of ≥75%.

CI, confidence interval; CR, complete response; IQR, interquartile range; NE, not estimable; NR, not reached; OS, overall survival; PD, progressive disease; PR, partial response; SD, stable disease.

Secondary endpoint – AEs of any cause that emerged or worsened during treatment in ≥25% of patients in either treatment group[a,12]



Adapted from Motzer et al. *N Engl J Med*. 2021.[12]

Analysis cutoff date: 28 August 2020.

[a]Safety assessment was based on an as-treated principle and consisted of monitoring and recording all AEs and serious AEs using the Common Terminology Criteria for AEs, version 4.03, in the group of patients who received at least one dose of the study drug. Hypothyroidism is an AE of interest associated with KEYTRUDA.

AE, adverse event.

Secondary endpoint – summary of TEAEs of interest for KEYTRUDA[a,12]

TEAE, n (%)	KEYTRUDA + LENVATINIB (n=352)		Sunitinib (n=340)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	214 (60.8)	52 (14.8)	105 (30.9)	4 (1.2)
Adrenal insufficiency	18 (5.1)	4 (1.1)	0 (0.0)	0 (0.0)
Colitis	9 (2.6)	4 (1.1)	2 (0.6)	0 (0.0)
Encephalitis	2 (0.6)	2 (0.6)	0 (0.0)	0 (0.0)
Hepatitis	7 (2.0)	5 (1.4)	0 (0.0)	0 (0.0)
Hyperthyroidism	28 (8.0)	0 (0.0)	12 (3.5)	0 (0.0)
Hypophysitis	3 (0.9)	2 (0.6)	0 (0.0)	0 (0.0)
Hypothyroidism	166 (47.2)	5 (1.4)	90 (26.5)	0 (0.0)
Infusion reactions	5 (1.4)	1 (0.3)	2 (0.6)	0 (0.0)
Myasthenic syndrome	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Myocarditis	4 (1.1)	3 (0.9)	0 (0.0)	0 (0.0)
Myositis	3 (0.9)	2 (0.6)	0 (0.0)	0 (0.0)
Nephritis	6 (1.7)	4 (1.1)	0 (0.0)	0 (0.0)
Pancreatitis	10 (2.8)	6 (1.7)	2 (0.6)	1 (0.3)
Pneumonitis	19 (5.4)	7 (2.0)	0 (0.0)	0 (0.0)
Severe skin reactions	18 (5.1)	18 (5.1)	5 (1.5)	3 (0.9)
Thyroiditis	2 (0.6)	0 (0.0)	2 (0.6)	0 (0.0)
Type 1 diabetes mellitus	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)
Uveitis	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)

Adapted from Motzer et al. *N Engl J Med*. 2021.[12]

Click for clinically significant TEAEs of interest for LENVATINIB

Analysis cutoff date: 28 August 2020.
[a]No cases of Guillain-Barré syndrome, myelitis, or sarcoidosis were reported in any group.
TEAE, treatment-emergent adverse event.

Secondary endpoint – summary of clinically significant TEAEs for **LENVATINIB**[12]

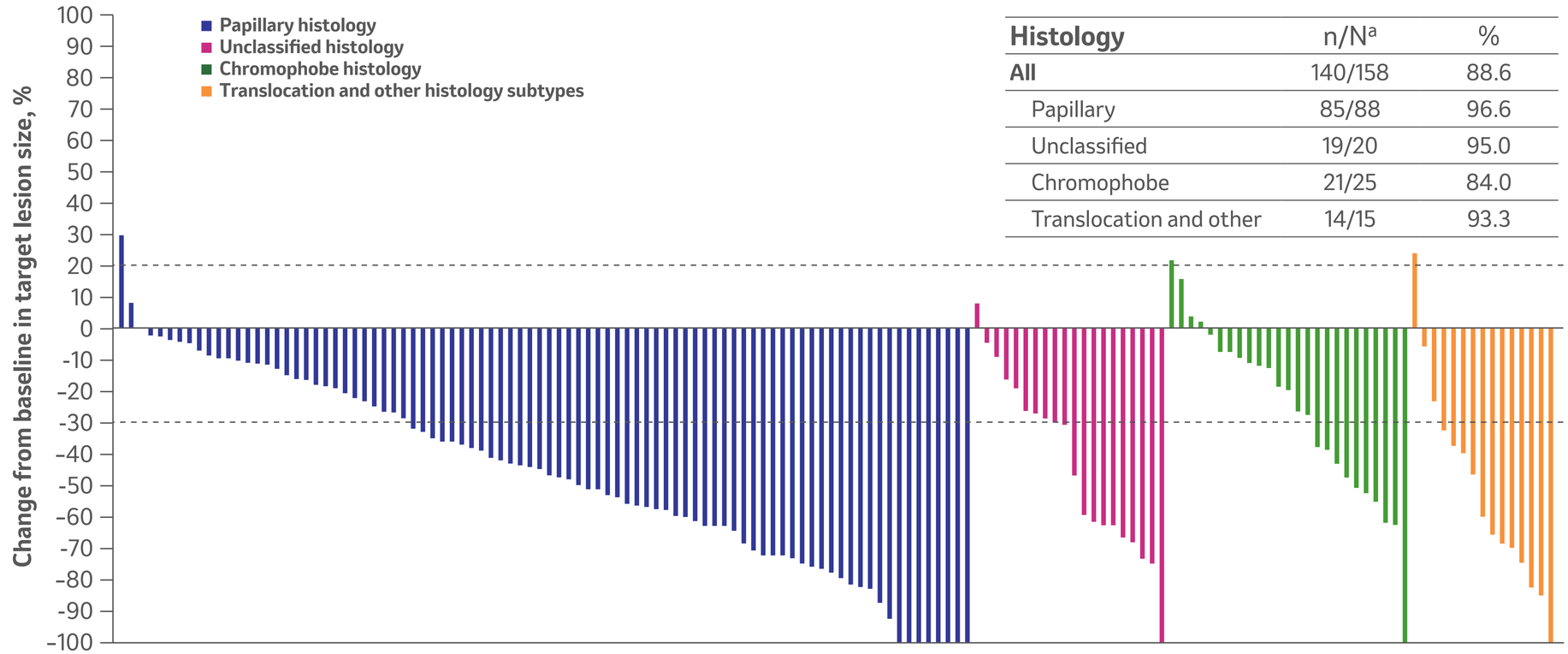
Click for TEAEs of interest for **KEYTRUDA**

TEAE, n (%)	KEYTRUDA + LENVATINIB (n=352)		Sunitinib (n=340)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Any	331 (94.0)	188 (53.4)	289 (85.0)	118 (34.7)
Arterial thromboembolic events	19 (5.4)	13 (3.7)	7 (2.1)	2 (0.6)
Cardiac dysfunction	9 (2.6)	6 (1.7)	7 (2.1)	4 (1.2)
Fistula formation	2 (0.6)	0 (0.0)	2 (0.6)	1 (0.3)
Gastrointestinal perforation	5 (1.4)	4 (1.1)	3 (0.9)	1 (0.3)
Haemorrhage	96 (27.3)	18 (5.1)	90 (26.5)	13 (3.8)
Hepatotoxicity	96 (27.3)	35 (9.9)	82 (24.1)	18 (5.3)
Hypertension	198 (56.3)	101 (28.7)	145 (42.6)	66 (19.4)
Hypocalcaemia	5 (1.4)	1 (0.3)	9 (2.6)	1 (0.3)
Hypothyroidism	200 (56.8)	5 (1.4)	109 (32.1)	0 (0.0)
Palmar–Plantar erythrodysesthesia syndrome	104 (29.5)	14 (4.0)	129 (37.9)	13 (3.8)
Posterior reversible encephalopathy syndrome	2 (0.6)	2 (0.6)	1 (0.3)	0 (0.0)
Proteinuria	104 (29.5)	27 (7.7)	43 (12.6)	10 (2.9)
QT prolongation	23 (6.5)	10 (2.8)	13 (3.8)	4 (1.2)
Renal events	78 (22.2)	20 (5.7)	60 (17.6)	8 (2.4)

Adapted from Motzer et al. *N Engl J Med*. 2021.[12]

Analysis cutoff date: 28 August 2020.
TEAE, treatment-emergent adverse event.

KEYNOTE-B61 trial: Exploratory analysis – Best percentage change from baseline in target lesion size by histology[20]



Any reduction in tumour burden

Histology	n/N[a]	%
All	140/158	88.6
Papillary	85/88	96.6
Unclassified	19/20	95.0
Chromophobe	21/25	84.0
Translocation and other	14/15	93.3

Adapted from Voss M, et al. ASCO GU 2024.[20]

LIMITATION: No statistical testing was conducted in this single-arm, phase 2 trial and, therefore, no conclusions can be drawn.

Assessed using RECIST v1.1 by independent central review; [a]A total of 148 patients had a baseline and ≥1 postbaseline assessment.
RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

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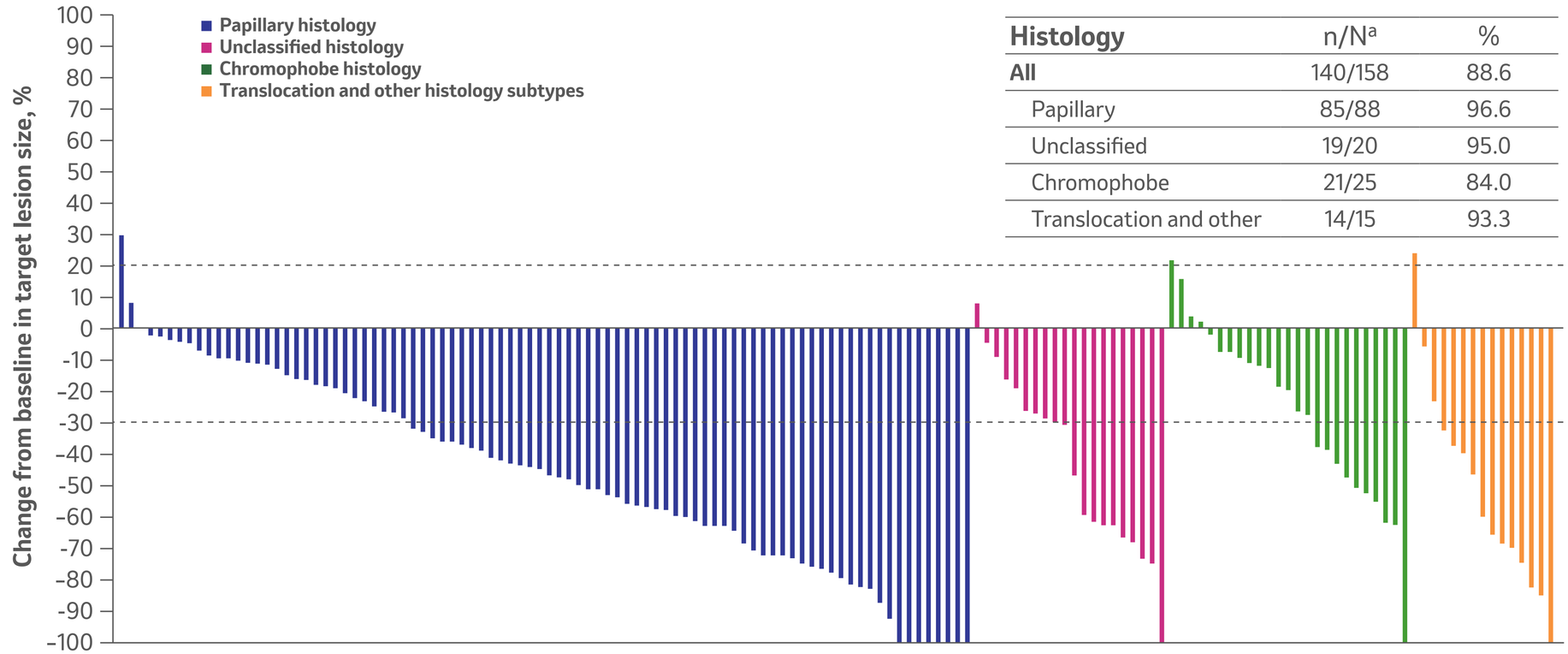

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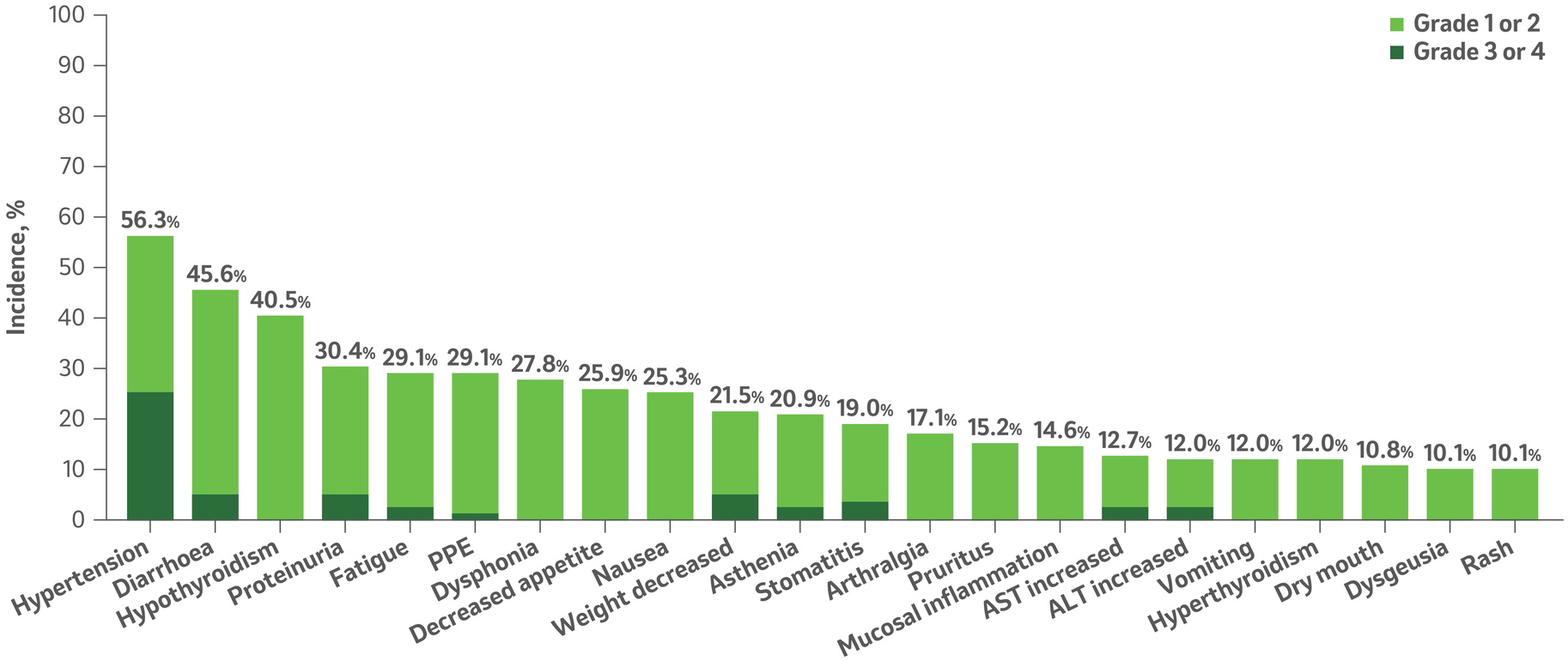
KEYNOTE-B61 trial: TRAEs that occurred in ≥10% of patients (extended follow-up)[20]



Adapted from Voss M, et al. ASCO GU 2024.[20]

Terms were determined by the investigator per Medical Dictionary for Regulatory Activities version 26.0 terminology. No grade 5 events occurred.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPE, palmar-plantar erythrodysaesthesia; TRAE, treatment-related adverse event.

Dose modification for **LENVATINIB** in combination with **KEYTRUDA**

- The recommended starting daily dose of **LENVATINIB** is 20 mg. Dose modification can be used to manage adverse reactions as appropriate[2]
- When administering **LENVATINIB** in combination with **KEYTRUDA**, interrupt, reduce or discontinue **LENVATINIB** as appropriate. Withhold or discontinue **KEYTRUDA** in accordance with the instructions in the SmPC for **KEYTRUDA**. No dose reductions are recommended for **KEYTRUDA**.[1,2]

Recommended dose modification for **LENVATINIB** in advanced RCC[2]

Recommended starting dose	10 10	**20 mg** orally once daily
1st dose reduction to	10 4	**14 mg** orally once daily
2nd dose reduction to	10	**10 mg** orally once daily
3rd dose reduction to	4 4	**8mg** orally once daily

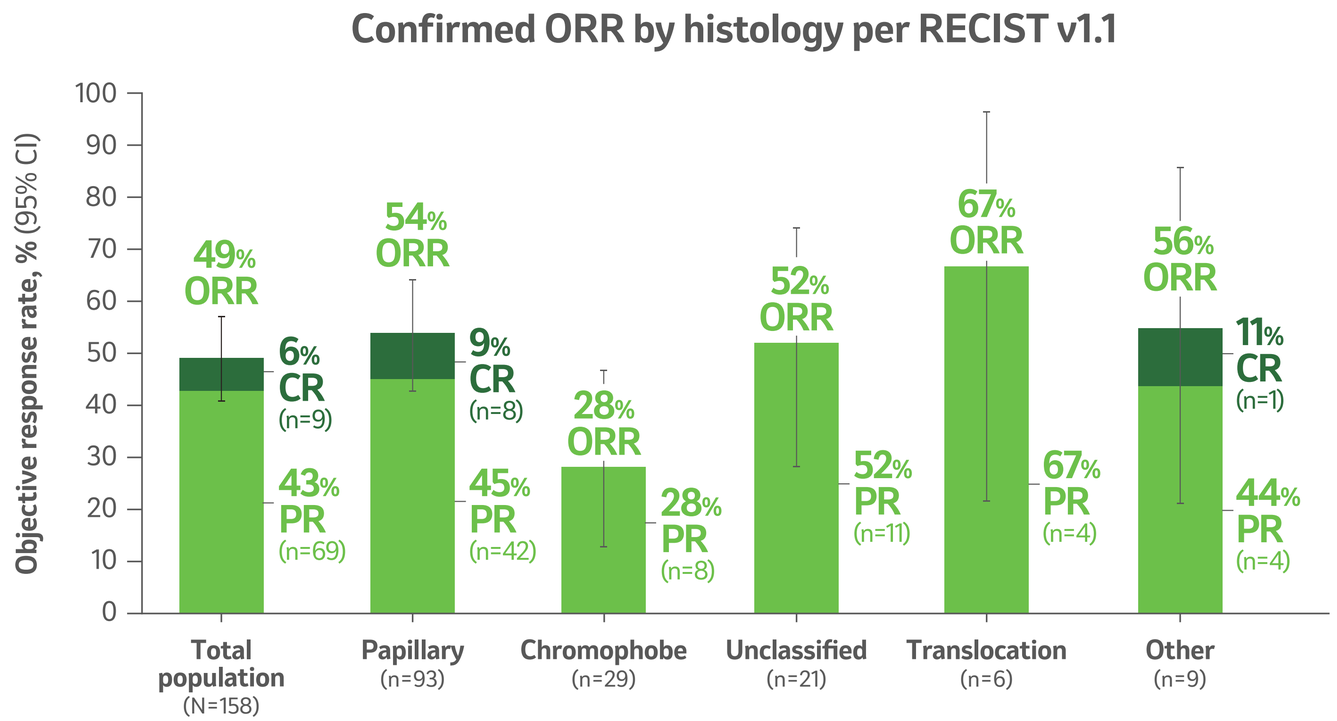
- If a **LENVATINIB** dose is missed and cannot be administered within 12 hours, skip that dose and take the next dose at the usual time of administration[2]
- Continue treatment with **KEYTRUDA** + **LENVATINIB** until disease progression, unacceptable toxicity or, for **KEYTRUDA**, up to 24 months[1,2]
- The recommended starting dose of **LENVATINIB** for patients with advanced RCC and severe renal impairment is 10 mg administered orally QD[2]
- The recommended starting dose of **LENVATINIB** for patients with advanced RCC and severe hepatic impairment (Child-Pugh C) is 10 mg administered orally QD[2]

Please refer to the KEYTRUDA + LENVATINIB individual product SmPC for full dosing information.

QD, once daily; RCC, renal cell carcinoma; SmPC, Summary of Product Characteristics.

KEYNOTE-B61 trial: Confirmed best overall response (primary analysis)[19]

Characteristic	KEYTRUDA + LENVATINIB (N=158)
Confirmed objective response	78 (49%) [95% CI: 41–57]
Confirmed disease control[a]	130 (82%) [95% CI: 75–88]
Confirmed clinical benefit[b]	113 (72%) [95% CI: 64–78]
Best overall response	
Confirmed CR	9 (6%)
Confirmed PR	69 (43%)
SD	52 (33%)
PD	17 (11%)
Not evaluable[c]	1 (1%)
Not assessed[d]	10 (6%)



Adapted from Albiges L et al. *Lancet Oncol*. 2023.[19]

LIMITATION: No statistical testing was conducted in this single-arm, phase 2 trial and, therefore, no conclusions can be drawn.

[a]Confirmed CR, PR, or SD of any duration; [b]Confirmed CR, PR, or SD for ≥6 months; [c]Postbaseline assessment, not evaluable; [d]No post-baseline assessment available.

CI, confidence interval; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

Kim and Jack both have advanced RCC

Kim

- 72 years old, initially presented with abdominal discomfort and unexplained weight loss
- Performance status: 0–1
- Diagnosed with Stage IV advanced RCC, clear cell histology
  - 7.5 cm left renal mass and multiple liver metastases
  - Anaemia and slightly elevated liver enzymes
  - Renal function: Creatinine ≤1.5 × ULN
- IMDC: Intermediate risk

What treatment goals would you prioritise for Kim?

PATIENT OUTCOMES	YOUR ORDER OF PRIORITY
PFS	PFS
ORR	ORR
OS	
TTR	
DOR	
HRQoL	
AEs	

Patient cases are fictional and for illustrative purposes only.

AE, adverse event; DOR, duration of response; HRQoL, health-related quality of life; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; ULN, upper limit of normal; TTR, time to respond.

Kim and Jack both have advanced RCC

Jack

- 68 years old, former smoker with high cholesterol. Previous history of right total nephrectomy to treat RCC. Initially complained of lower back pain
- Performance status: 0–1
- Diagnosed with Stage IV metastatic RCC, clear cell histology
  - 14 cm mass in left kidney with growth into the Gerota's fascia, lymph node involvement and multiple pulmonary lesions
  - Lung and bone metastases
- IMDC: Poor risk

What treatment goals would you prioritise for Jack?

PATIENT OUTCOMES	YOUR ORDER OF PRIORITY
PFS	PFS
ORR	ORR
OS	
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PFS	PFS
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