This promotional resource has been developed by MSD for UK healthcare professionals.

KEYTRUDA® (pembrolizumab) + KISPLYX® (lenvatinib):

Data in the first-line setting in patients with advanced non-clear cell renal cell carcinoma

KEYNOTE-B61: First-line KEYTRUDA plus KISPLYX for non–clear cell renal carcinomas (nccRCC): Phase 2 KEYNOTE-B61 study[1]

KEYTRUDA, in combination with **KISPLYX**, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).[a,2,3]

[a]**KEYTRUDA** should be continued for 2 years, or until disease progression or unacceptable toxicity whichever comes first. **KISPLYX** should be continued until disease progression or unacceptable toxicity.[2–4]

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk or search for the 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; email: pv.uk@msd.com).

KEYTRUDA prescribing information can be accessed by clicking the following link: Great Britain and Northern Ireland
KISPLYX prescribing information can be accessed by clicking the following links: Great Britain and Northern Ireland.
Please consult the Summary of Product Characteristics and the risk minimisation materials for further information before making any prescribing decisions.
This resource is intended to be viewed online and not to be printed.

MSD Eisai

KEYTRUDA® (pembrolizumab) KISPLYX® (lenvatinib) capsules

GB-KLR-00313 | Date of preparation: January 2025

KEYNOTE-B61 trial: A single-arm, multicenter, Phase 2 trial in 158 patients with advanced non-clear cell renal cell carcinoma[1,4]

Studied in the first-line setting across IMDC risk groups and histological subtypes in patients with advanced non-clear cell renal cell carcinoma[1,4]

Key inclusion criteria:

- Age ≥18 years old
- Histologically confirmed diagnosis of stage IV non-clear cell RCC (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)

KISPLYX 20 mg orally once daily; KISPLYX could be continued beyond 2 years

Treatment continued until disease progression or unacceptable toxicity.

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.[a]

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

Selected secondary endpoints:

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

Figure adapted from Voss M et al. 2024.[1]

[a]According to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The first analysis was conducted at a median follow-up of 14.9 months (IQR: 11.1–17.4)[4]

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

- Broad antitumour activity was observed in the first analysis for **KEYTRUDA** in combination with **KISPLYX** in patients with non-clear renal cell carcinoma
  - A total of 49% of patients (n=78; 95% CI, 41–57) had confirmed ORR, with approximately 75% of the responders showing a duration of response ≥12 months
  - Confirmed ORR was observed across all investigated non-clear cell carcinoma histologic subtypes, comprising papillary (54%; 50/93), chromophobe (28%; 8/29), unclassified (52%; 11/21), translocation (67%; 4/6) and others (56%; 5/9)
  - As of data cutoff, 62 (39%) patients experienced a PFS event and median PFS was 18 months (95% CI, 14–not reached). A total of 35 (22%) patients had died, and median OS was not reached (95% CI, not reached–not reached)
    - Estimated 12-month rates for PFS and OS were 63% (95% CI, 54–70) and 82% (95% CI, 75–88), respectively
- The safety profile of KEYTRUDA in combination with KISPLYX was similar to that observed in previous studies
  - Grade 3–4 treatment-related AEs occurred in 81/158 (51%) patients
  - Serious treatment-related AEs occurred in 31/158 (20%) patients and no deaths were considered related to the treatment by the investigators

AE = adverse event; **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; **IQR**, interquartile range; **KPS** = Karnofsky performance status; **MRI** = magnetic resonance imaging; **ORR** = objective response rate; **OS** = overall survival; **PFS** = progression-free survival; **RCC** = renal cell carcinoma; **RECIST v1.1** = Response Evaluation Criteria in Solid Tumors v1.1.

KEYNOTE-B61 trial: Baseline characteristics in patients with advanced non-clear cell renal cell carcinoma[1,4]

	KEYTRUDA + KISPLYX (N=158) n (%), unless otherwise specified
Age, years	
Median (IQR)	60 (52–69)
Mean (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)
Missing	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)

	KEYTRUDA + KISPLYX (N=158) n (%), unless otherwise specified (*continued*)
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)
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)

[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]Karnofsky performance status scores 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–stained cells (tumour cells, lymphocytes and macrophages) divided by the total number of viable tumour cells, multiplied by 100.

Table adapted from Albiges L et al. 2023.[4]

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; **SD** = standard deviation.

Median time from first dose to data cutoff: 22.8 months (range: 16.6–27.6)

50.6% (80/158) of patients (95% CI, 42.6–58.7) with advanced nonclear cell renal cell carcinoma receiving **KEYTRUDA + KISPLYX** had a confirmed ORR[1]

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

Objective response rate with KEYTRUDA + KISPLYX in the KEYNOTE-B61 trial[a,1]

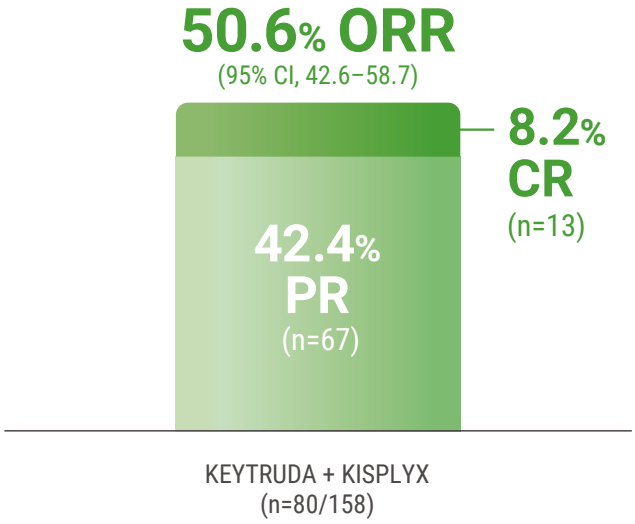


Figure adapted from Voss M et al. 2024.[1]

Confirmed ORR with KEYTRUDA + KISPLYX by histology in the updated analysis for KEYNOTE-B61 (N=158)[b,1]

Confirmed ORR was observed with KEYTRUDA + KISPLYX across multiple histologic subtypes.

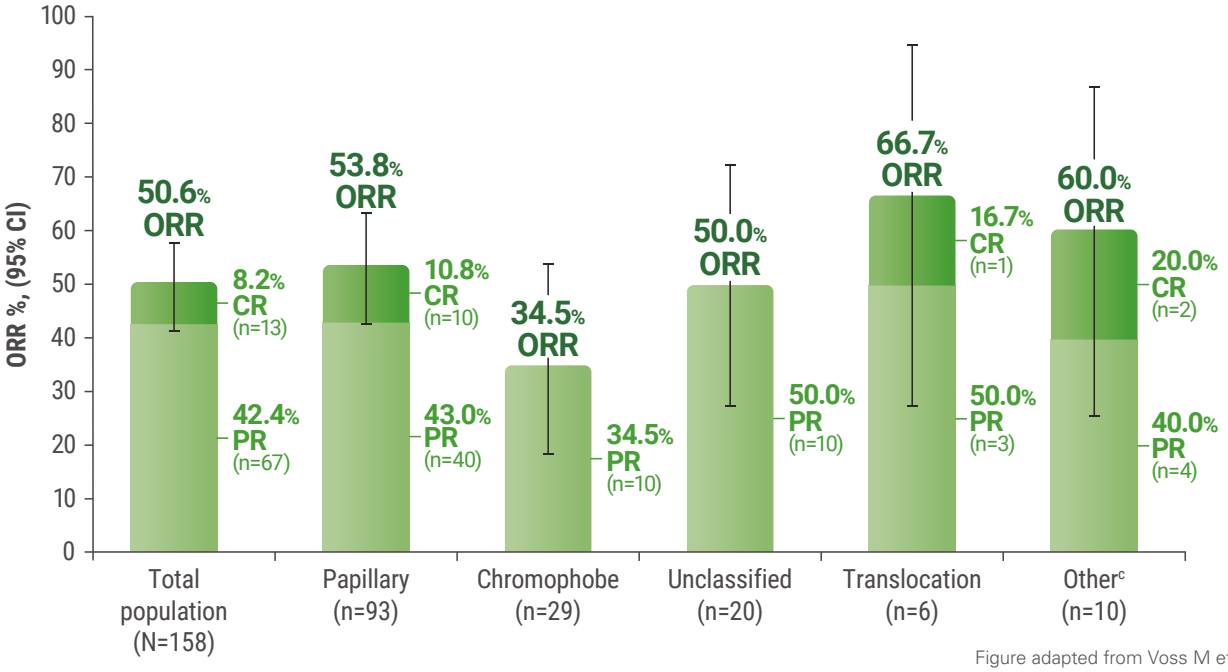


Figure adapted from Voss M et al. 2024.[1]

[a]Best overall response per adjusted RECIST v1.1 by independent central review. [b]Assessed per RECIST v1.1 by BICR. [c]Includes medullary and other histologic subtypes.

BICR = blinded independent central review; **CI** = confidence interval; **CR** = complete response; **ORR** = objective response rate; **PR** = partial response; **RECIST v1.1** = Response Evaluation Criteria in Solid Tumors v1.1.

Median time from first dose to data cutoff: 22.8 months (range: 16.6–27.6)

Median DOR was 19.5 months (range: 1.5–23.5) with **KEYTRUDA + KISPLYX**[1]

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

Kaplan–Meier estimates of DOR with KEYTRUDA + KISPLYX in patients with a confirmed objective response in the KEYNOTE-B61 trial (n=80)[b,1]

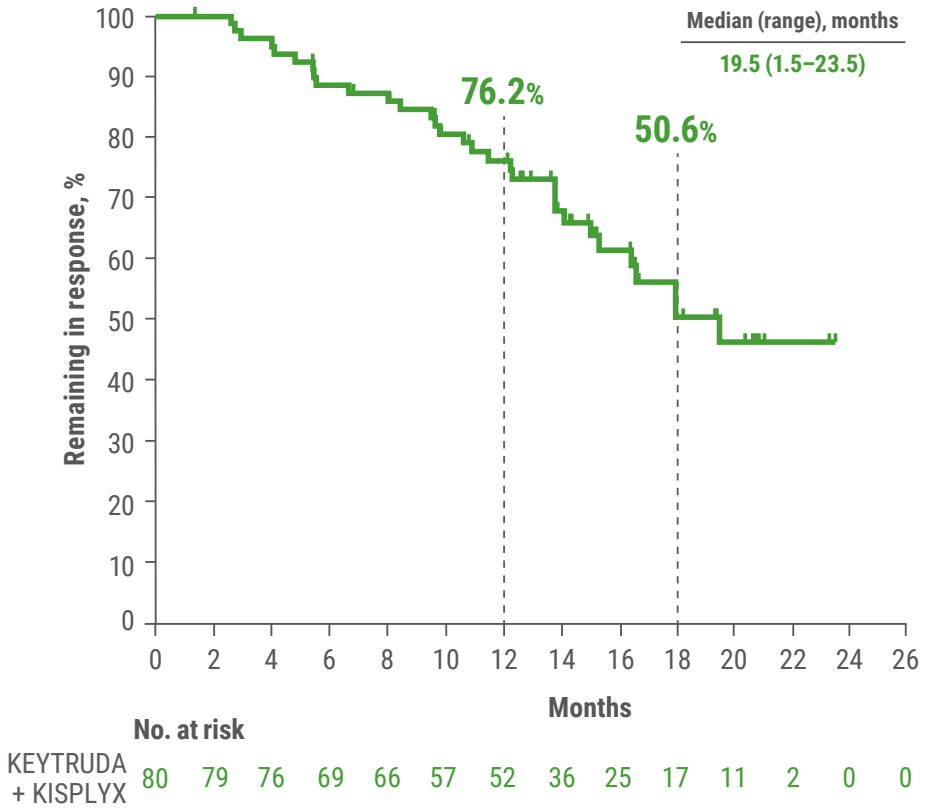


Figure adapted from Voss M et al. 2024.[1]

[a]The non-parametric Kaplan–Meier method was used to estimate DOR, PFS, and OS.

CI = confidence interval; **DOR** = duration of response; **NR** = not reached; **OS** = overall survival; **PFS** = progression-free survival.

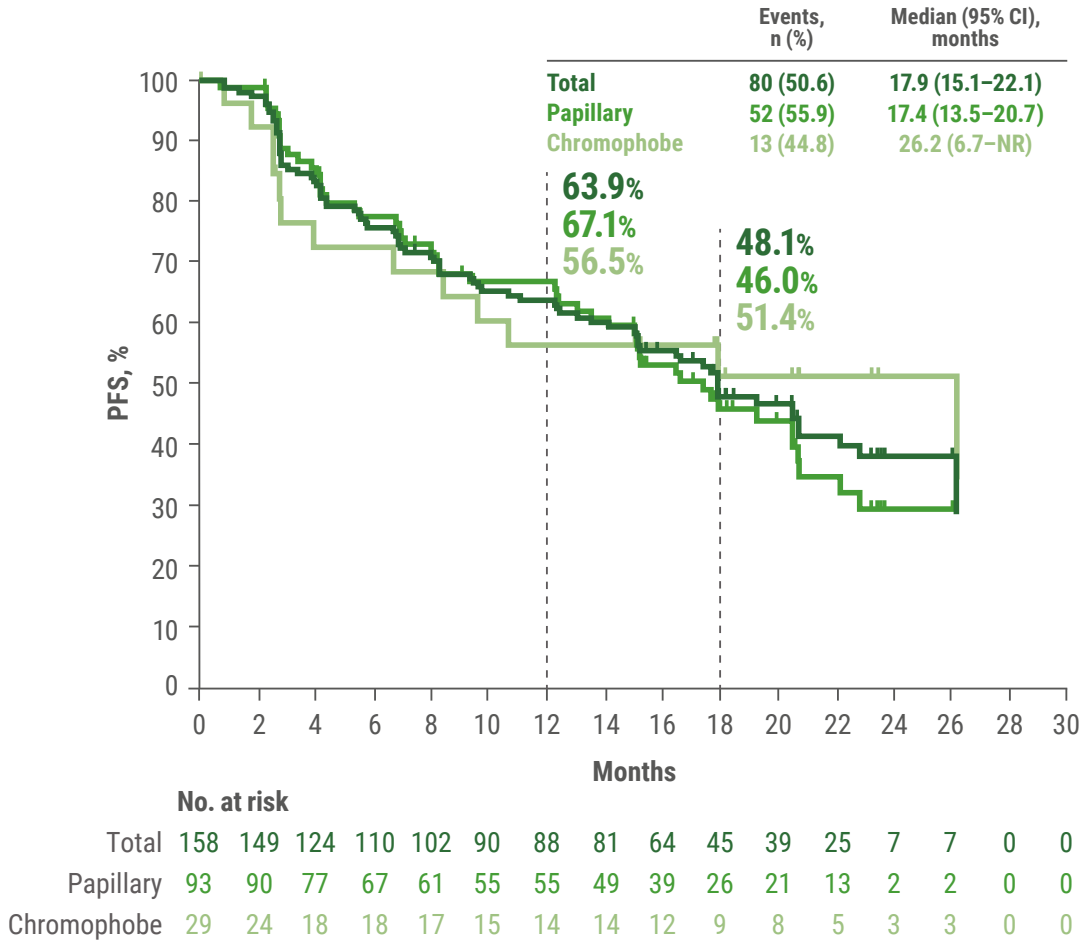
Median time from first dose to data cutoff: 22.8 months (range: 16.6–27.6)

Median PFS was 17.9 months (95% CI, 15.1–22.1) with **KEYTRUDA + KISPLYX**[1]

- Number of events in the total population: 80/158 (50.6%)[1]

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

Kaplan–Meier estimates of PFS with KEYTRUDA + KISPLYX in the total population (N=158), papillary histology subgroup, and chromophobe histology subgroup[a,b,1]



No. at risk

Total	158	149	124	110	102	90	88	81	64	45	39	25	7	7	0	0
Papillary	93	90	77	67	61	55	55	49	39	26	21	13	2	2	0	0
Chromophobe	29	24	18	18	17	15	14	14	12	9	8	5	3	3	0	0

Figure adapted from Voss M et al. 2024.[1]

[a]The non-parametric Kaplan–Meier method was used to estimate DOR, PFS and OS.
[b]Tumour assessments were based on RECIST v1.1 assessed by independent central review; data cutoff date = 5 July 2023.

CI = confidence interval; **DOR** = duration of response; **OS** = overall survival; **PFS** = progression-free survival; **RECIST v1.1** = Response Evaluation Criteria in Solid Tumors v1.1.

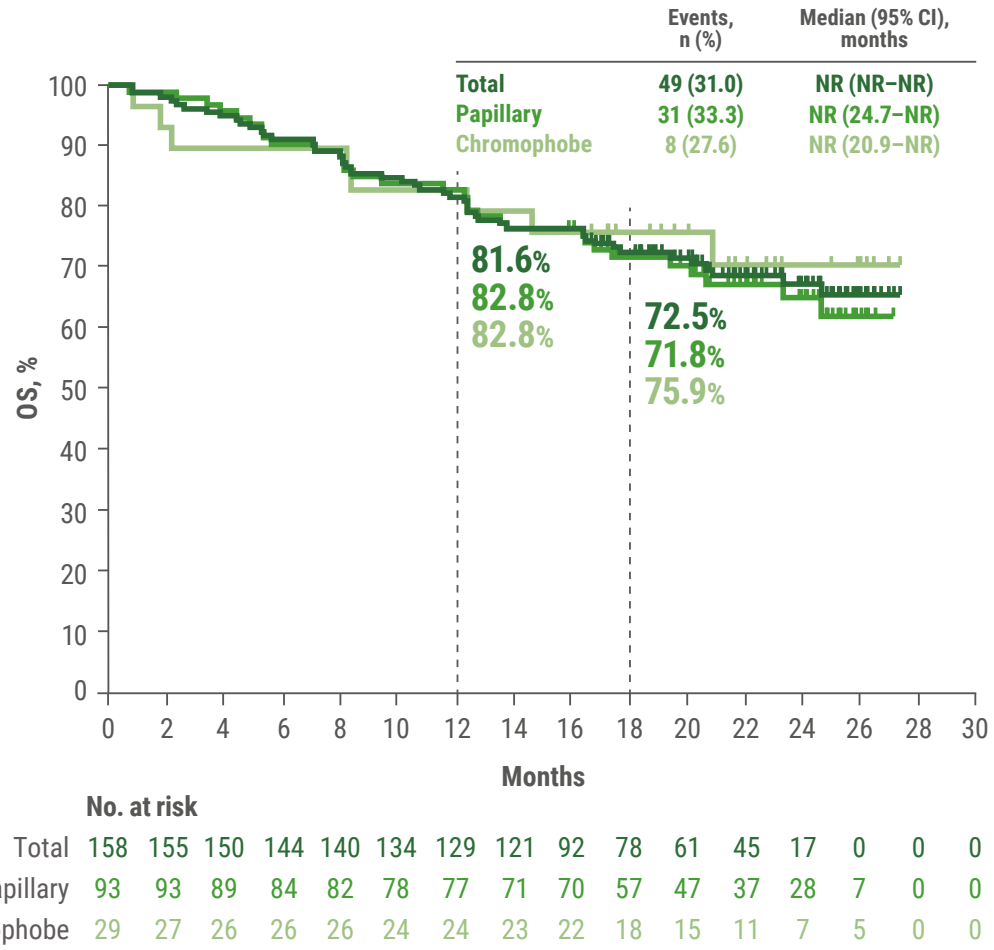
Median time from first dose to data cutoff: 22.8 months (range: 16.6–27.6)

Median OS (95% CI, NR–NR) was not reached with **KEYTRUDA + KISPLYX**[1,4]

- Number of deaths: 49/158 (31.0%)[1]

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

Kaplan–Meier estimates of OS with KEYTRUDA + KISPLYX in the total population (N=158), papillary histology subgroup, and chromophobe histology subgroup[a,1]



No. at risk

Total	158	155	150	144	140	134	129	121	92	78	61	45	17	0	0	0
Papillary	93	93	89	84	82	78	77	71	70	57	47	37	28	7	0	0
Chromophobe	29	27	26	26	26	24	24	23	22	18	15	11	7	5	0	0

Figure adapted from Voss M et al. 2024.[1]

[a]The non-parametric Kaplan–Meier method was used to estimate DOR, PFS and OS; data cutoff = 5 July 2023.

CI = confidence interval; **DOR** = duration of response; **NR** = not reached; **OS** = overall survival; **PFS** = progression-free survival.

For full safety information please consult the Summary of Product Characteristics for KEYTRUDA and for KISPLYX

Median time from first dose to data cutoff: 22.8 months (range: 16.6–27.6)

AE summary in the updated analysis for KEYNOTE-B61[1]

	KEYTRUDA + KISPLYX (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)
KISPLYX discontinuation	31 (19.6)
Both KEYTRUDA and KISPLYX 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)
KISPLYX discontinuation	20 (12.7)
Both KEYTRUDA and KISPLYX discontinuation	7 (4.4)
Serious AEs	39 (24.7)
Resulted in death	0 (0)
Immune-mediated AE[a]	92 (58.2)
Grade 3–5	15 (9.5)
Required systemic corticosteroids	22 (13.9)
High starting dose[b]	11 (7.0)
Low starting dose[c]	11 (7.0)

[a]Based on a list of preferred terms intended to capture known risks of KEYTRUDA and 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.

Table adapted from Voss M et al. 2024.[1]

AE = adverse event.

Median time from first dose to data cutoff: 22.8 months (range: 16.6–27.6)

Treatment-related AEs in patients with advanced non-clear cell renal cell carcinoma[1]

Treatment-related AEs that occurred in ≥20% of patients receiving KEYTRUDA + KISPLYX in the updated analysis of the KEYNOTE-B61 trial (N=158)[1]

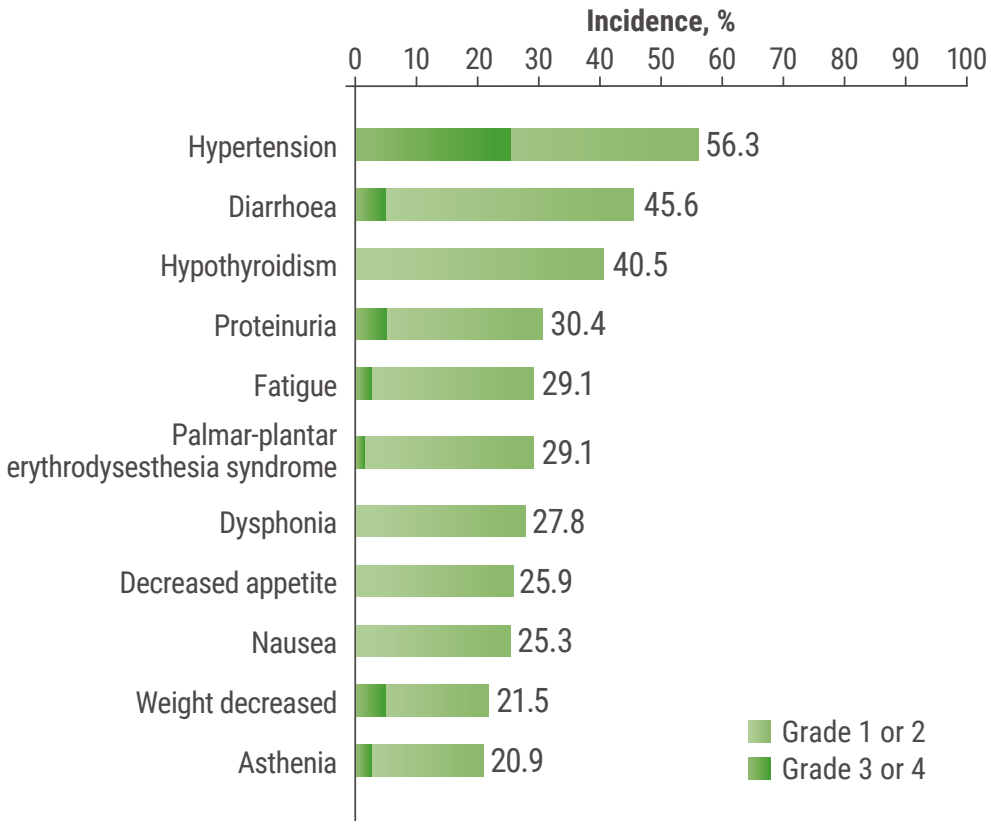


Figure adapted from Voss M et al. 2024.[1]

- Median time from the first dose to data cutoff (5 July, 2023) was 22.8 months (range: 16.6–27.6)[1]
- No Grade 5 events occurred[1]

AE = adverse event.

In the extended 22.8 months follow-up analysis, first-line **KEYTRUDA in combination with KISPLYX continued to show durable antitumour activity** in patients with advanced non-clear cell carcinoma[1]

- ORR was 50.6% in the total population and showed consistency across key histologic subtypes
- The safety profile of KEYTRUDA in combination with KISPLYX was generally manageable and consistent to that observed in previous studies
  - Grade 3 or 4 treatment-related AEs were reported in 58.2% of patient and no deaths due to treatment-related AEs occurred

AE = adverse event; **ORR** = objective response rate.

References: 1. Voss M, Gurney H, Atduev V et al. First-line pembrolizumab plus lenvatinib for non-clear cell renal cell carcinomas: Extended follow-up of the Phase 2 KEYNOTE-B61 study. Poster presented at: ASCO Genitourinary Cancers Symposium; 25–27 January, 2024; San Francisco, CA; **2.** KEYTRUDA (pembrolizumab) Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/product/2498/smpc. Accessed October 2024; **3.** KISPLYX (lenvatinib) Summary of Product Characteristics. Available at: www.medicines.org.uk/emc/product/7380/smpc. Accessed October 2024; **4.** Albiges L, Gurney H, Atduev V, et al. Pembrolizumab plus lenvatinib as first-line therapy for advanced non-clear-cell renal cell carcinoma (KEYNOTE-B61): a single-arm, multicentre, Phase 2 trial. *Lancet Oncol* 2023;24:881–891. doi:10.1016/S1470-2045(23)00276-0.