


Focus On Possibilities

For Treating Your
Patients with Advanced RCC



KEYTRUDA® (pembrolizumab), in combination with **KISPLYX® (lenvatinib)**, is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

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 KISPLYX can be accessed via the 'PI' buttons at the bottom of this page and throughout. The KEYTRUDA Summary of Product Characteristics can be accessed by clicking the following links: [Great Britain](#); [Northern Ireland](#). The KISPLYX Summary of Product Characteristics can be accessed by clicking the following links: [Great Britain](#); [Northern Ireland](#). Please consult the Summary of Product Characteristics and Risk Management Materials for further information before making any prescribing decisions.

Job code: GB-KLR-00237

Date of preparation: April 2024



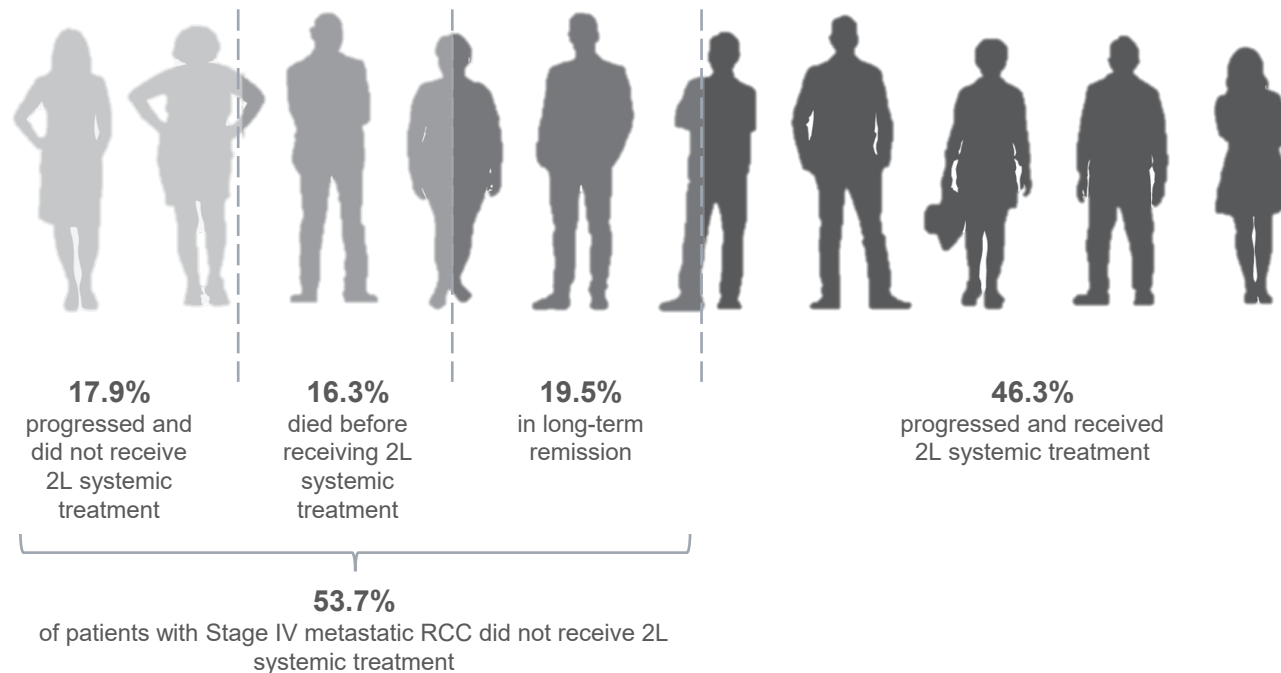
KEYTRUDA
KISPLYX

[GB PI](#) [NI PI](#)
[GB and NI PI](#)



2L systemic treatment in patients with metastatic RCC¹

In a survey of 103 physicians who treated 4509 patients monthly in five European countries in 2020,^a more than 50% of patients with Stage IV metastatic RCC did not receive 2L systemic treatment

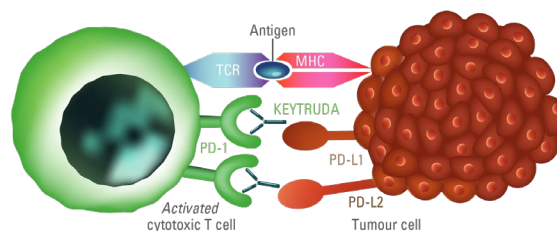


Adapted from Kantar Health 2020¹

^aFrance, Germany, Italy, Spain, UK.
2L, second-line; RCC, renal cell carcinoma.

KEYTRUDA + KISPLYX has a dual MOA inhibiting two disease pathways

KEYTRUDA mode of action

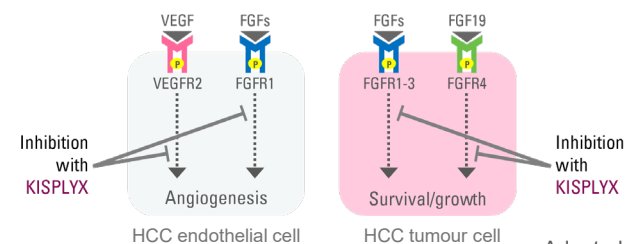


Adapted from Pardoll DM 2012²

The immune-stimulatory effect of **KEYTRUDA** (anti-PD-1)^{2,3}



KISPLYX mode of action



Adapted from Kudo M 2018⁴

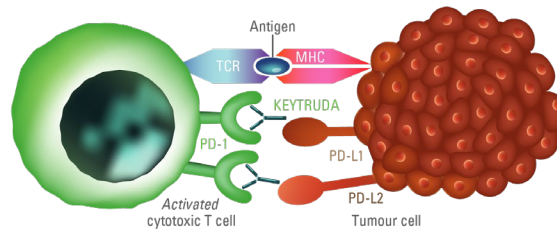
The anti-angiogenic effect of **KISPLYX** (anti-VEGFR/FGFR)^{4,5}



FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; KIT, proto-oncogene c-KIT; MHC, major histocompatibility complex; MOA, mode of action; PD-1, programmed death receptor-1; PDGFR, platelet-derived growth factor receptor; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; RET, proto-oncogene RET; RTK, receptor tyrosine kinase; TCR, T-cell receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

KEYTRUDA + KISPLYX has a dual MOA inhibiting two disease pathways

KEYTRUDA mode of action

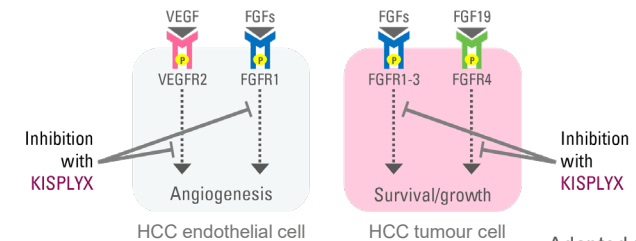


Adapted from Pardoll DM 2012²

The immune-stimulatory effect of KEYTRUDA (anti-PD-1)^{2,3}

- **KEYTRUDA** is a selective, humanised, monoclonal antibody designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2³
- By inhibiting PD-1 receptor binding, **KEYTRUDA reactivates tumour-specific cytotoxic T lymphocytes** in the tumour microenvironment, resulting in **anti-tumour immunity**³

KISPLYX mode of action



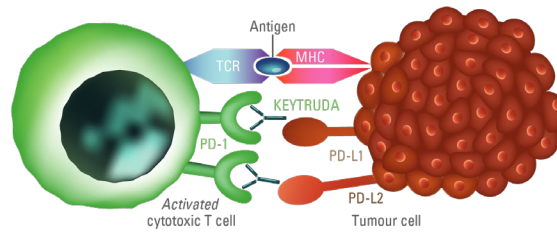
Adapted from Kudo M 2018⁴

The anti-angiogenic effect of KISPLYX (anti-VEGFR/FGFR)^{4,5}

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KEYTRUDA + KISPLYX has a dual MOA inhibiting two disease pathways

KEYTRUDA mode of action

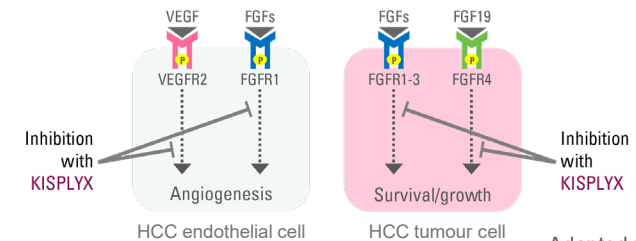


Adapted from Pardoll DM 2012²

The immune-stimulatory effect of **KEYTRUDA** (anti-PD-1)^{2,3}



KISPLYX mode of action



Adapted from Kudo M 2018⁴

The anti-angiogenic effect of **KISPLYX** (anti-VEGFR/FGFR)^{4,5}



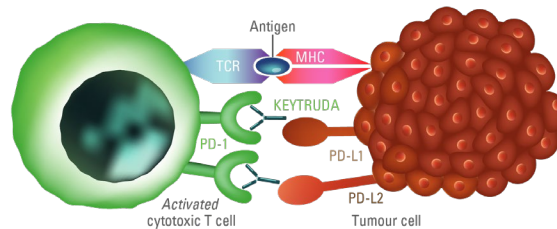
- KISPLYX** is a RTK inhibitor that selectively inhibits the kinase activities of VEGF receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), in addition to other proangiogenic and oncogenic pathway-related RTKs including FGF receptors FGFR1, 2, 3, and 4; the PDGF receptor, PDGFRα; KIT; and RET^{4,5}



FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; KIT, proto-oncogene c-KIT; MHC, major histocompatibility complex; MOA, mode of action; PD-1, programmed death receptor-1; PDGFR, platelet-derived growth factor receptor; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; RET, proto-oncogene RET; RTK, receptor tyrosine kinase; TCR, T-cell receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

KEYTRUDA + KISPLYX has a dual MOA inhibiting two disease pathways

KEYTRUDA mode of action

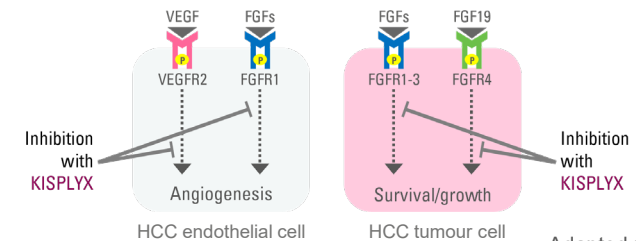


Adapted from Pardoll DM 2012²

The immune-stimulatory effect of KEYTRUDA (anti-PD-1)^{2,3}

- **KEYTRUDA** is a selective, humanised, monoclonal antibody designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2³
- By inhibiting PD-1 receptor binding, **KEYTRUDA reactivates tumour-specific cytotoxic T lymphocytes** in the tumour microenvironment, resulting in **anti-tumour immunity**³

KISPLYX mode of action



Adapted from Kudo M 2018⁴

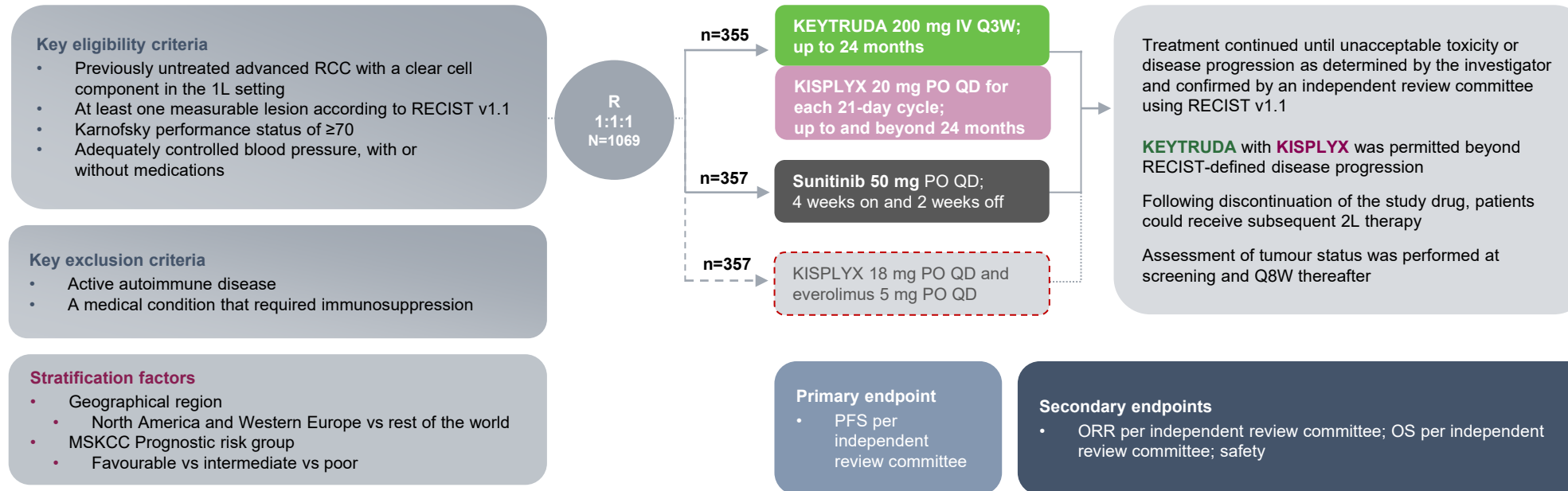
The anti-angiogenic effect of KISPLYX (anti-VEGFR/FGFR)^{4,5}

- **KISPLYX** is a RTK inhibitor that selectively inhibits the kinase activities of 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^{4,5}

FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; KIT, proto-oncogene c-KIT; MHC, major histocompatibility complex; MOA, mode of action; PD-1, programmed death receptor-1; PDGFR, platelet-derived growth factor receptor; PD-L1, programmed death ligand-1; PD-L2, programmed death ligand-2; RET, proto-oncogene RET; RTK, receptor tyrosine kinase; TCR, T-cell receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

The efficacy and safety of **KEYTRUDA** + **KISPLYX** vs sunitinib monotherapy were investigated in the CLEAR trial⁶

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



Adapted from Motzer R et al. 2021⁶

1L use of KISPLYX 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 + KISPLYX vs sunitinib arms only.^{3,5}

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

1L, first-line; 2L, second-line; DOR, duration of response; IV, intravenous; 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 characteristics⁶

Characteristic ^a	KEYTRUDA + KISPLYX (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)
Karnofsky performance status, 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)

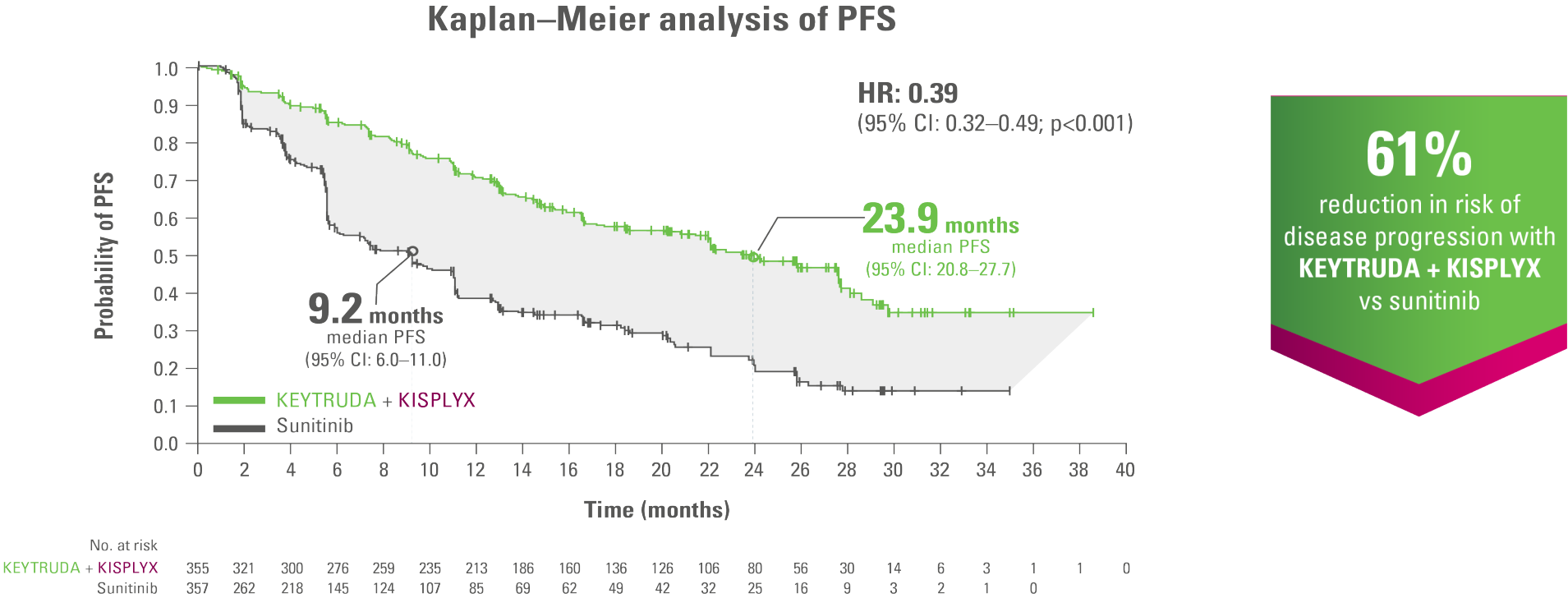
Characteristic ^a	KEYTRUDA + KISPLYX (n=355)	Sunitinib (n=357)
Sarcomatoid features, n (%)	28 (7.9)	21 (5.9)
PD-L1 combined positive score, n (%)		
≥1	107 (30.1)	119 (33.3)
<1	112 (31.5)	103 (28.9)
Not available	136 (38.3)	135 (37.8)
Number of metastatic organs or sites, n (%) ^c		
1	97 (27.3)	108 (30.3)
≥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. 2021⁶

^aOne patient in the KEYTRUDA + KISPLYX group had carcinoma without a clear cell component; ^bKarnofsky performance status was missing for one patient in the sunitinib group; ^cKidney was not included in the number of metastatic organs or sites; ^dFour common sites of metastasis are shown. Patients may have had metastasis at more than one site. IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; PD-L1, programmed death ligand-1.

Primary endpoint — **KEYTRUDA** + **KISPLYX** more than doubled median PFS vs sunitinib^{a,6}

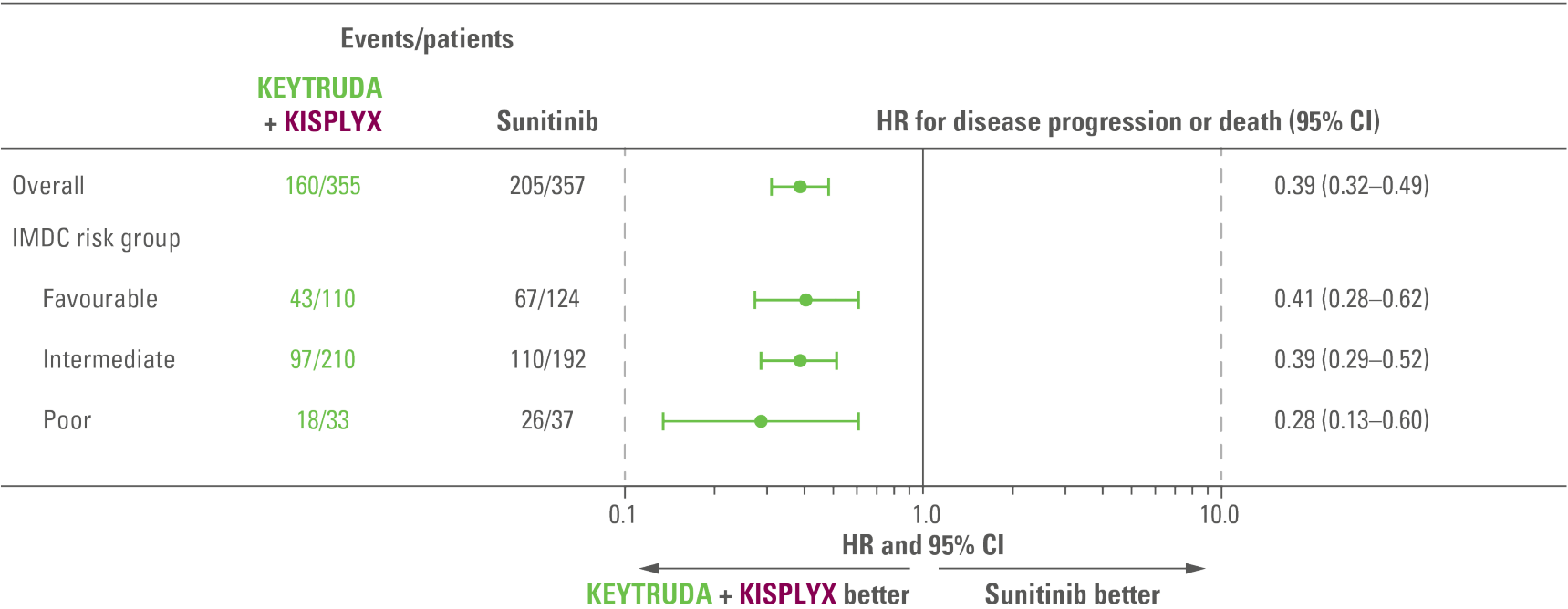
PFS was significantly longer in the **KEYTRUDA** + **KISPLYX** group compared with the sunitinib group



Adapted from Motzer R et al. 2021⁶

Analysis cutoff date: 28 August 2020. Median follow-up: 26.6 months.
^aAssessed using RECIST v1.1 by an independent review committee.
CI, confidence interval; HR, hazard ratio; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Subgroup analysis — PFS in IMDC risk groups^{a,6}



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.
^aPatients 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; PFS, progression-free survival..

Adapted from Motzer R et al. 2021⁶



KEYTRUDA
KISPLYX

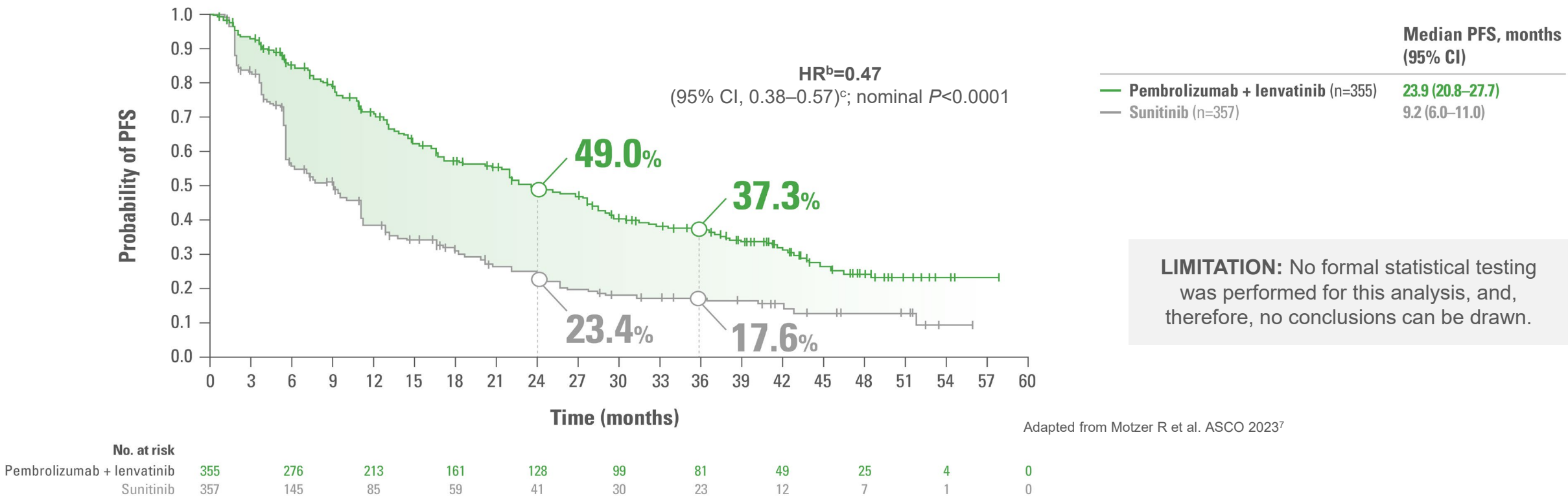
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Exploratory analysis — KEYTRUDA + KISPLYX PFS consistent with primary analysis at 39.2 months median follow up^{a,7}

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



Analysis cutoff date: 31 July 2022.
^aAssessed using RECIST v1.1 by an independent review committee; ^bHR 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; ^cThe 95% CIs are estimated with a generalised Brookmeyer and Crowley method. IQR, interquartile range; IxRS, Interactive Voice/Web Response System.

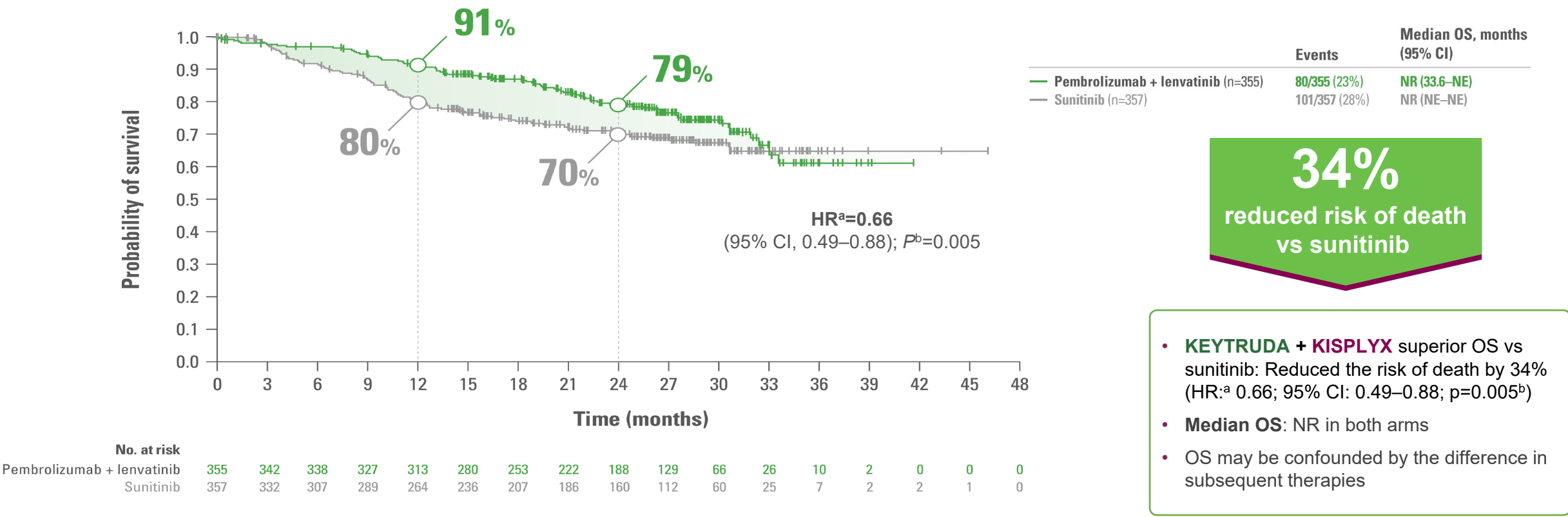


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Secondary endpoint — Superior OS with **KEYTRUDA** + **KISPLYX** vs sunitinib⁶



Analysis cutoff date: 28 August 2020. Median follow up: 26.6 months.
^aBased on the stratified Cox proportional-hazards model; ^bTwo-sided *p*-value based on stratified log-rank test.
CI, confidence interval; HR, hazard ratio; NE, not estimable; NR, not reached; OS, overall survival.

Adapted from Motzer R et al. 2021⁶



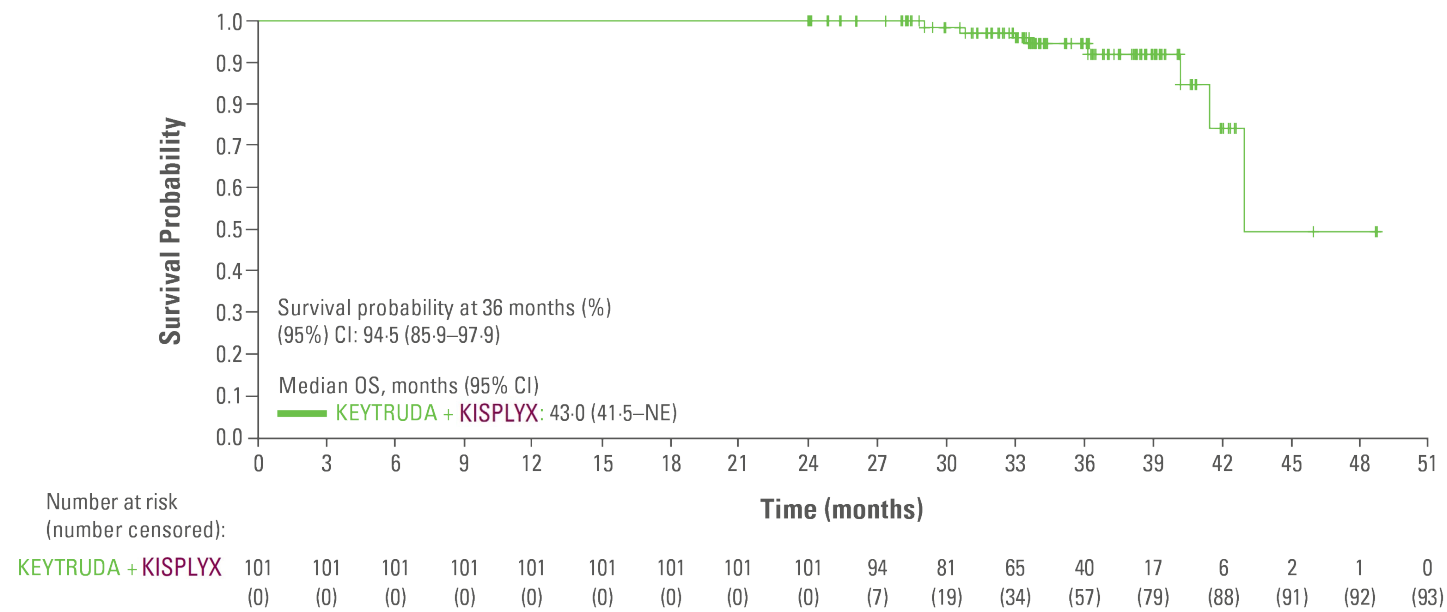
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Exploratory analysis - OS in patients who completed 2 years of **KEYTRUDA** and continued on **KISPLYX** monotherapy⁸



- Of patients who completed 2 years of **KEYTRUDA** and continued with **KISPLYX** monotherapy (101/355 patients), exploratory OS rate was 94.5% at 36 months based on Kaplan–Meier estimate
 - Of the 101 patients, 65 had IMDC intermediate/poor-risk disease and 36 had favourable-risk disease

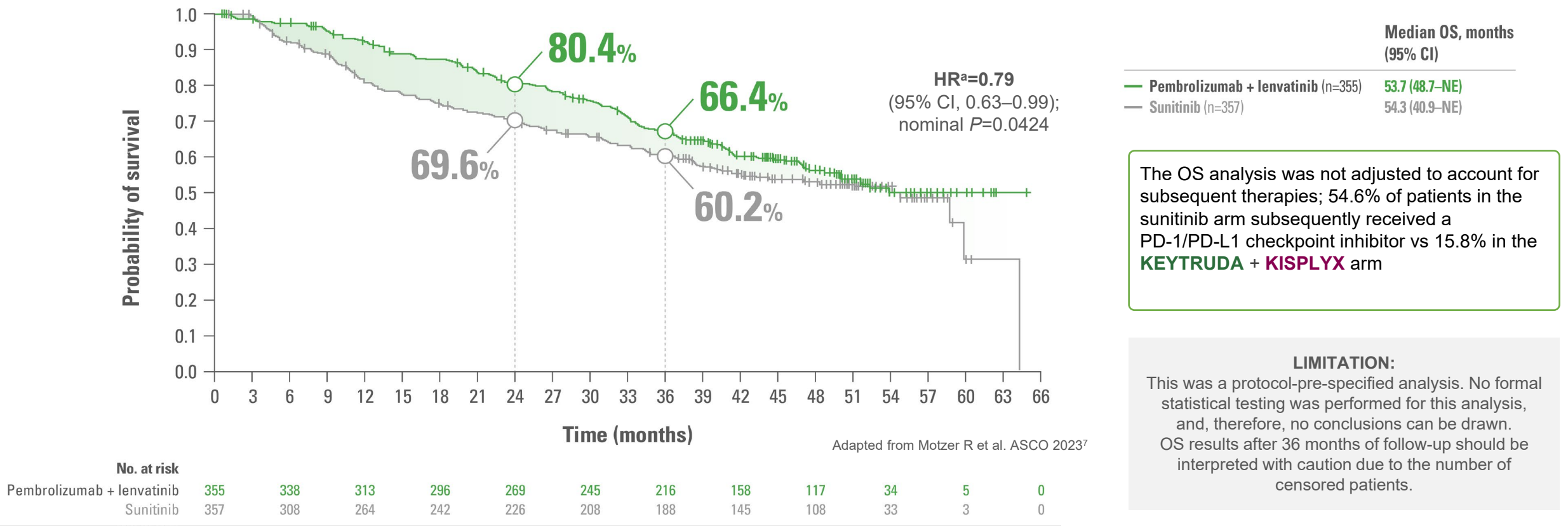
Results from exploratory analyses should be interpreted with caution due to modest patient numbers and potential imbalances in baseline characteristics between subgroups

Adapted from Choueiri et al. 2023⁸

Analysis cut-off date: 31 March 2021.
CI, confidence interval; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; NE, not estimable; OS, overall survival

Exploratory analysis — KEYTRUDA + KISPLYX OS at 49.8 months median follow up⁷

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



Analysis cutoff date: 31 July 2022. A total of 308 target OS events had occurred, of which 149 were with pembrolizumab + lenvatinib and 159 with sunitinib. ^aHR and 2-sided 95% CI for lenvatinib + pembrolizumab 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.



KEYTRUDA
KISPLYX

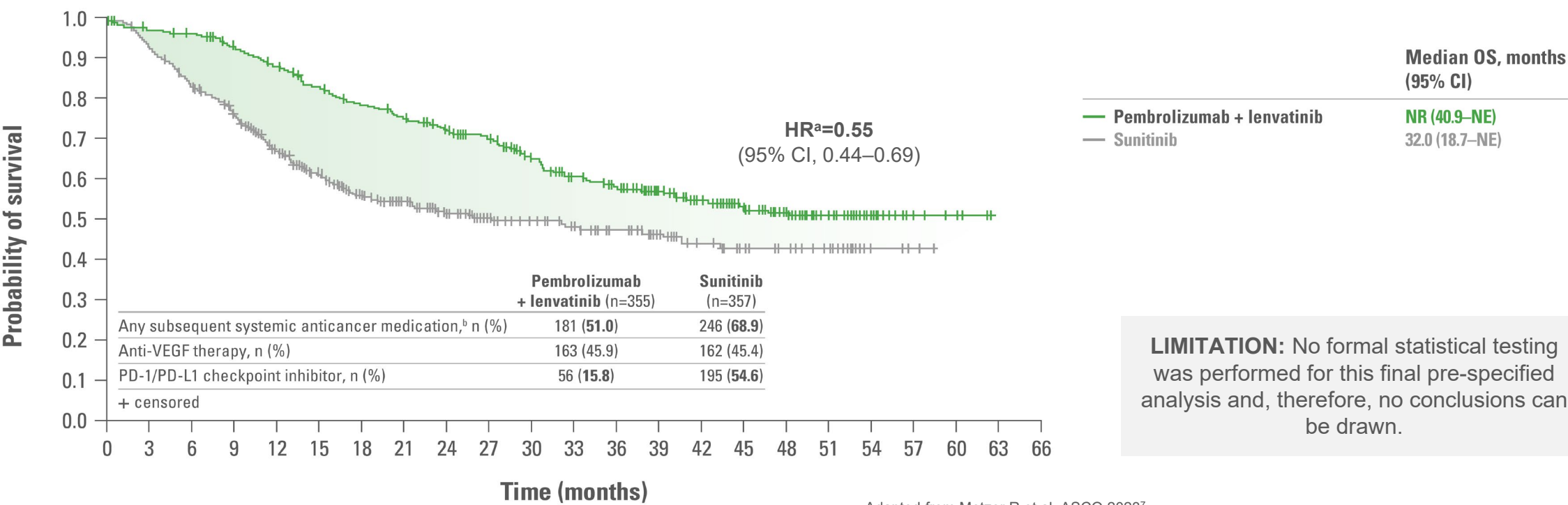
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Exploratory analysis — Final OS analysis adjusted for subsequent anticancer medications⁷

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



No. at risk												
Pembrolizumab + lenvatinib	355	336	303	266	240	193	159	107	68	19	3	0
Sunitinib	357	282	212	140	100	72	56	37	26	4	0	0

Analysis cutoff date: 31 July 2022. ^aA 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; ^bDuring survival follow-up.



KEYTRUDA
KISPLYX

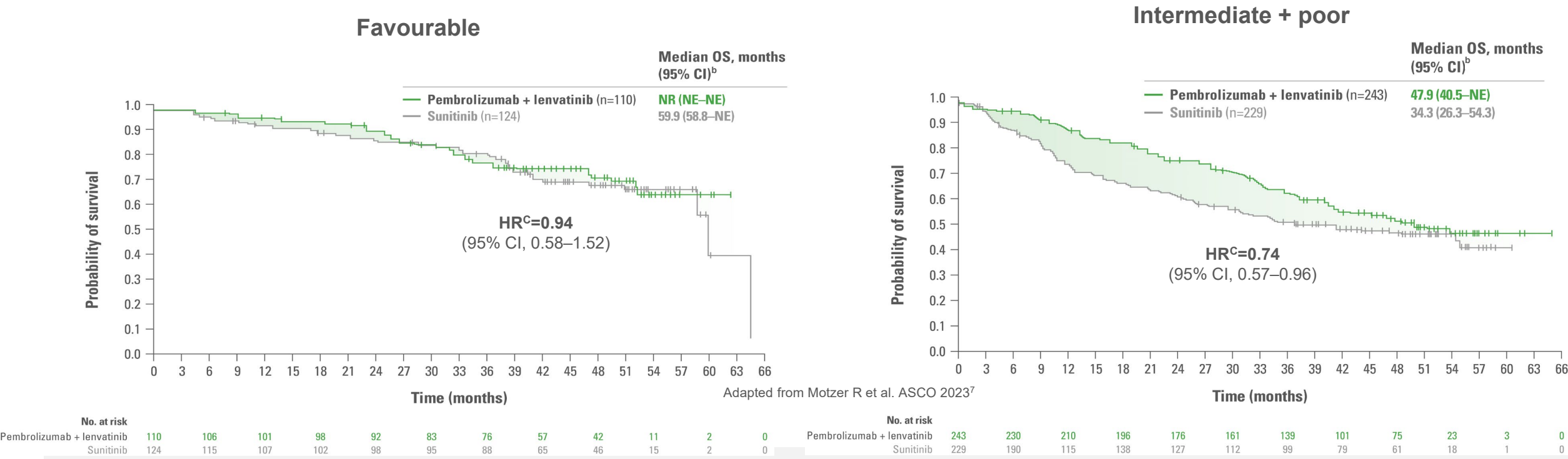
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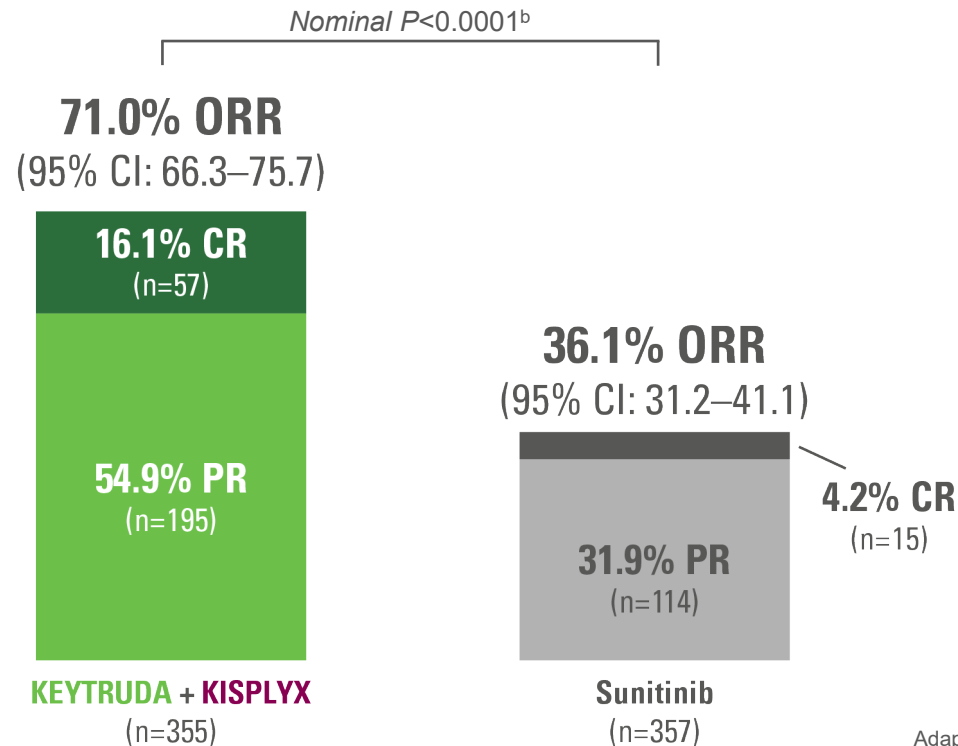
Exploratory analysis — Kaplan-Meier estimates of OS by IMDC risk subgroup^{a,7}

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



Secondary endpoint — ORR^a nearly double with **KEYTRUDA + KISPLYX** vs sunitinib^{3,5,6}

Superior ORR vs sunitinib



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

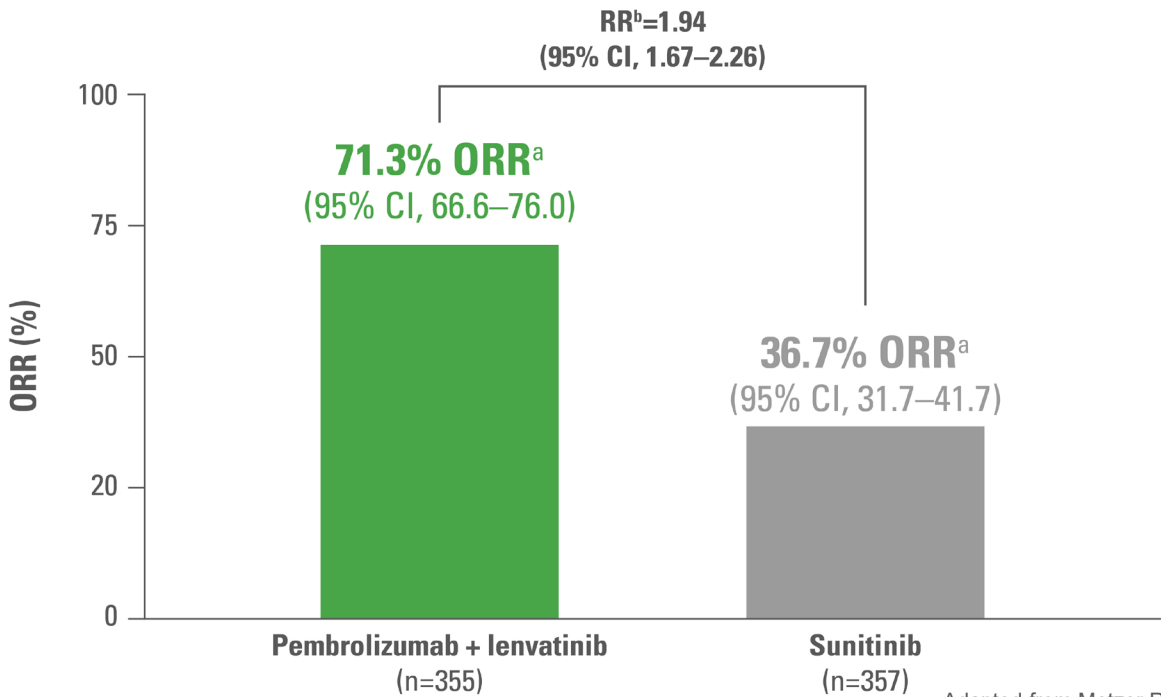
Adapted from Motzer R et al. 2021⁶

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

^aAssessed using RECIST v1.1; ^bNominal 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 + KISPLYX with sunitinib (odds ratio: 3.84 [95% CI: 2.81, 5.26], nominal P-value < 0.0001);^{7,9} CI, confidence interval; CR, complete response; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

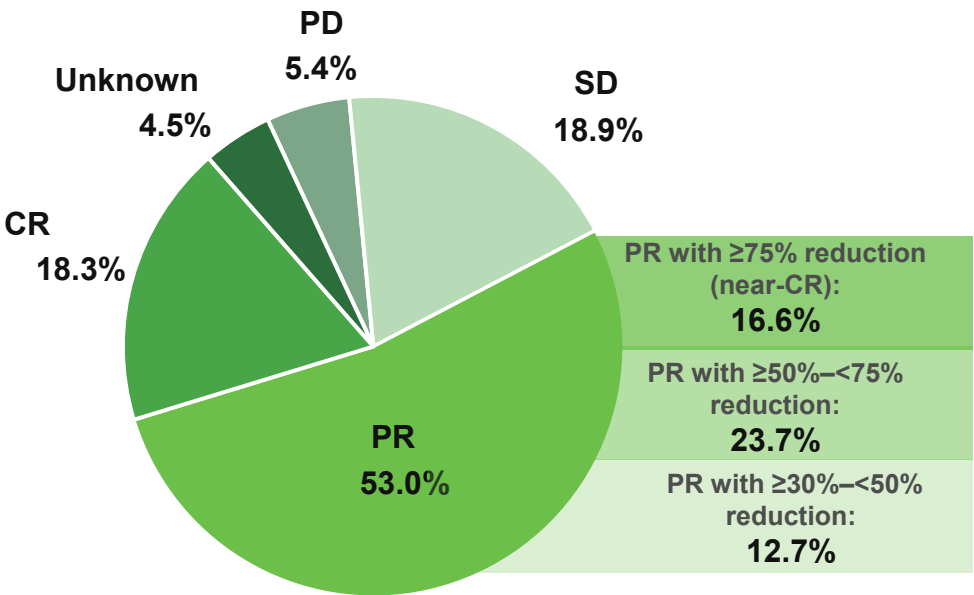
Exploratory analysis — ORR consistent with primary analysis at 49.8 months median follow up^{a,7}

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



Adapted from Motzer R et al. ASCO 2023⁷

Best overall response^c with KEYTRUDA + KISPLYX



Adapted from Motzer R et al. ASCO 2023⁷

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. ^aAs determined by independent review committee using RECIST v1.1; ^bRR, Relative Risk was calculated using the Cochran-Mantel-Haenzel methods stratified by IxRS factors, and the 95% CIs were calculated using the method of normal approximation; ^cBest 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.¹⁰ RR, relative risk.



KEYTRUDA
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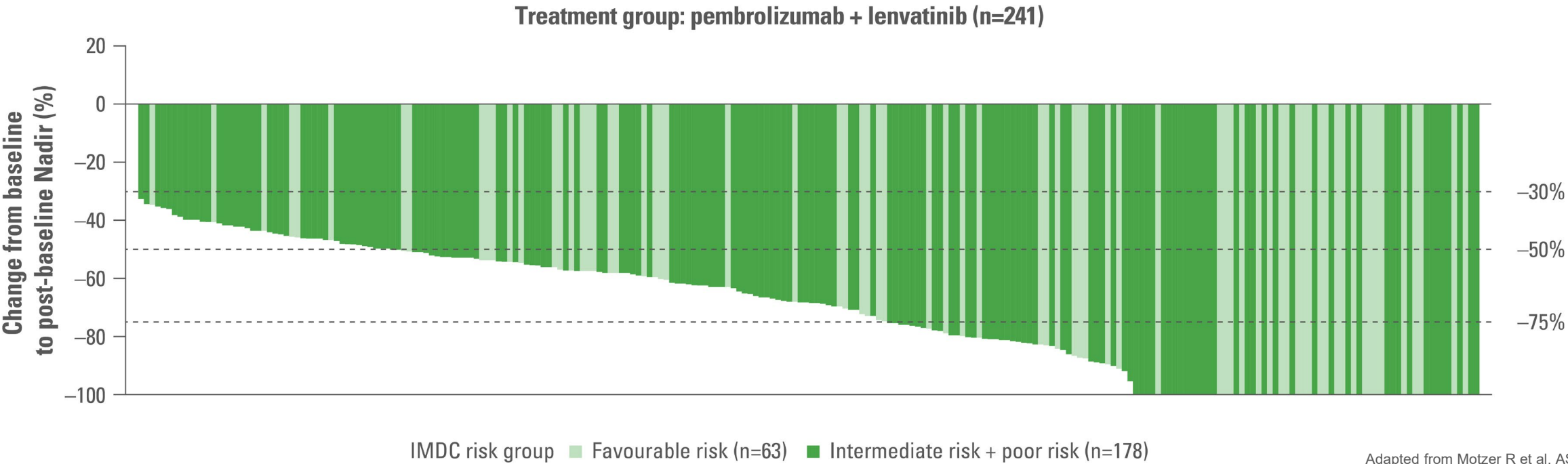
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Prespecified final analysis

Exploratory analysis — Change in target lesion size^a in patients who responded to treatment with **KEYTRUDA** + **KISPLYX**⁷

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

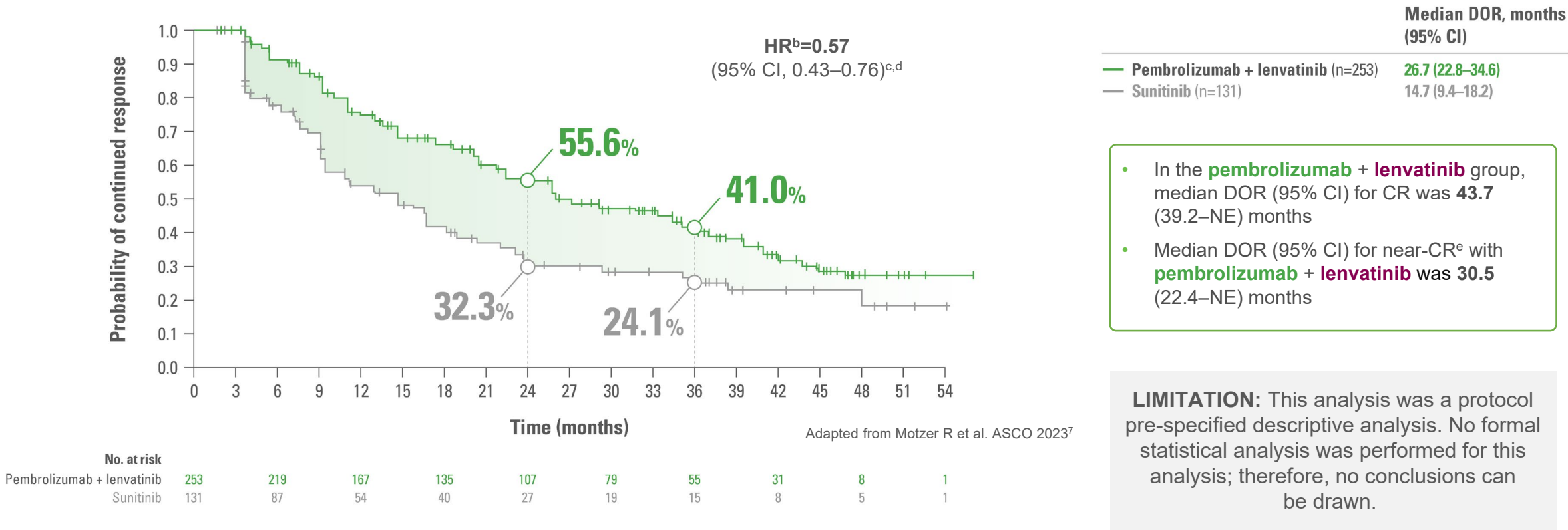


LIMITATION: No formal statistical analysis was performed for this analysis; therefore, no conclusions can be drawn.

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.
^aChanges 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.

Exploratory analysis — Duration of response (DOR)^{a,7}

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



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.
^aAs determined by independent review committee using RECIST v1.1; ^bHR 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; ^cThe 95% CIs were estimated using the method of normal approximation; ^dThe 95% CIs are estimated with a generalised Brookmeyer and Crowley method; ^eNear-CR refers to individuals who presented a PR with a maximum tumour reduction of ≥75%. NE, not estimable.



KEYTRUDA
KISPLYX

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NI PI



Subgroup analysis — Tumour responses across subgroups of interest⁹

Median follow-up: 26.6 months with KEYTRUDA + KISPLYX and with sunitinib²

Parameter	Sarcomatoid features				Bone metastases			
	Yes		No		Yes		No	
	Pembrolizumab + lenvatinib (n=28)	Sunitinib (n=21)	Pembrolizumab + lenvatinib (n=327)	Sunitinib (n=336)	Pembrolizumab + lenvatinib (n=85)	Sunitinib (n=97)	Pembrolizumab + lenvatinib (n=270)	Sunitinib (n=260)
ORR, ^a n (%)	17 (60.7)	5 (23.8)	235 (71.9)	124 (36.9)	55 (64.7)	22 (22.7)	197 (73.0)	107 (41.2)

Parameter	Liver metastases				Previous nephrectomy			
	Yes		No		Yes		No	
	Pembrolizumab + lenvatinib (n=60)	Sunitinib (n=61)	Pembrolizumab + lenvatinib (n=295)	Sunitinib (n=296)	Pembrolizumab + lenvatinib (n=262)	Sunitinib (n=275)	Pembrolizumab + lenvatinib (n=93)	Sunitinib (n=82)
ORR, ^a n (%)	40 (66.7)	21 (34.4)	212 (71.9)	108 (36.5)	193 (73.7)	110 (40.0)	59 (63.4)	19 (23.2)

Parameter	Lung metastases			
	Yes		No	
	Pembrolizumab + lenvatinib (n=249)	Sunitinib (n=239)	Pembrolizumab + lenvatinib (n=106)	Sunitinib (n=118)
ORR, ^a n (%)	186 (74.7)	87 (36.4)	66 (62.3)	42 (35.6)

Adapted from Grünwald V et al 2023⁹

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

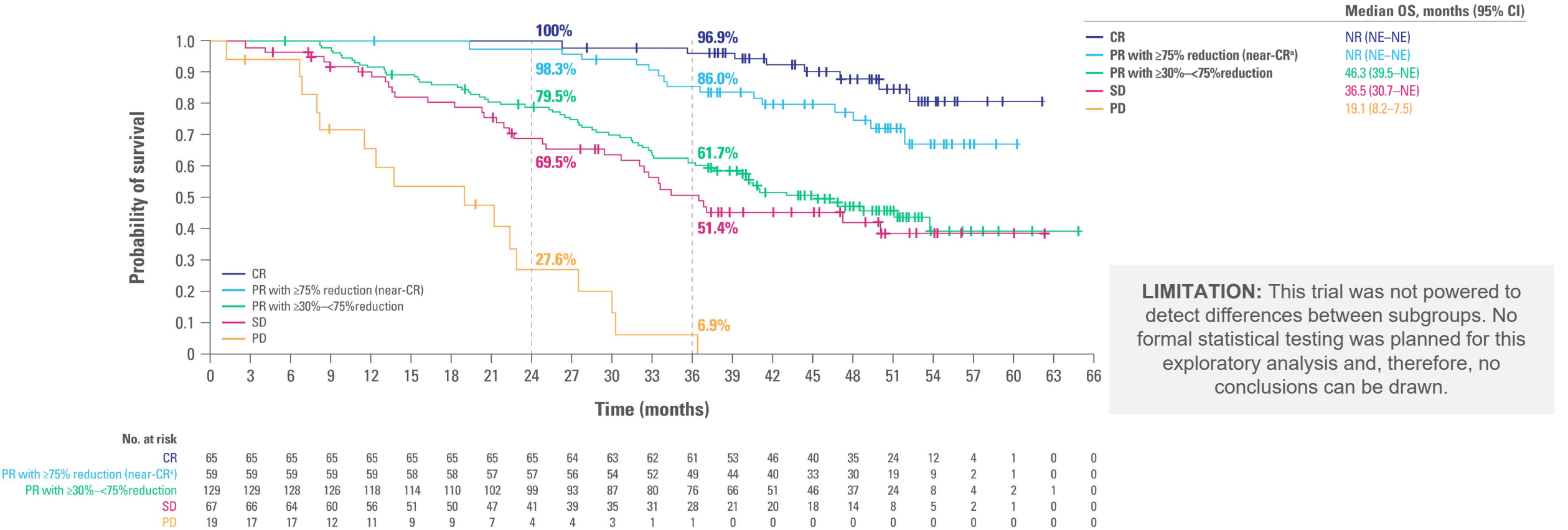
Analysis cutoff date: 28 August 2020.^aAssessed using RECIST v1.1. CI, confidence interval; ORR, objective response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.



Prespecified final analysis

Exploratory analysis — Final OS analysis by best overall response in patients treated with KEYTRUDA + KISPLYX⁷

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



Analysis cutoff date: 31 July 2022. ^aNear-CR refers to individuals who presented a PR with a maximum tumour reduction of ≥75%. Adapted from Motzer R et al. ASCO 2023⁷



KEYTRUDA
KISPLYX

GB PI NI PI

GB and NI PI



Secondary endpoint — AE summary for **KEYTRUDA** + **KISPLYX** compared with sunitinib^{a,6}

	KEYTRUDA + KISPLYX (n=352)	Sunitinib (n=340)
Median duration of treatment, months (range)	17.0 (0.1–39.1)	7.8 (0.1–37.0)
AEs of any grade, any cause, %	99.7	98.5
Grade ≥3	82.4	71.8
Death during treatment (Grade 5 AE) ^b	4.3	3.2
Patients with any grade TEAEs leading to discontinuation vs sunitinib, %		
Pembrolizumab , lenvatinib , or both drugs	37.2	14.4
Pembrolizumab	28.7	
Lenvatinib	25.6	
Pembrolizumab + lenvatinib	13.4	
Patients with any grade TEAEs leading to dose interruption (pembrolizumab , lenvatinib , or both drugs) vs sunitinib, %	78.4	53.8
Patients with any grade TEAEs leading to dose reduction (for lenvatinib ONLY) vs sunitinib ^c , %	68.8	50.3

Analysis cutoff date: 28 August 2020. ^aSafety 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; ^bOf the 15 patients in the KEYTRUDA + KISPLYX 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); ^cDose reduction in KISPLYX only. Dose reductions for KEYTRUDA are not recommended. AE, adverse event; TEAE, treatment-emergent adverse event.



KEYTRUDA
KISPLYX

GB PI

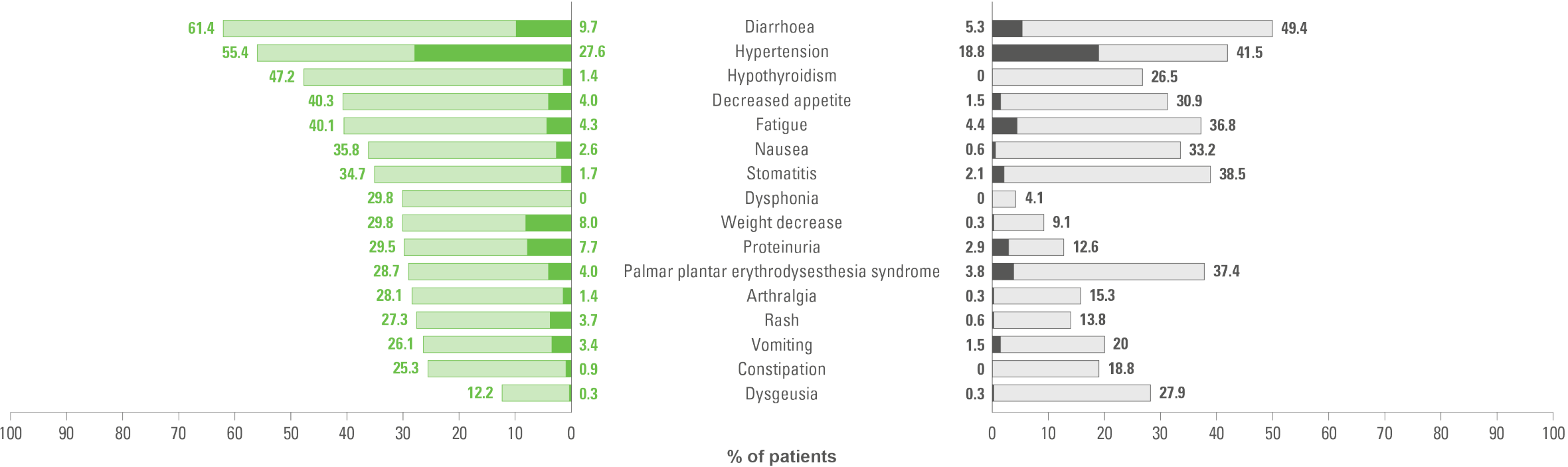
NI PI

GB and NI PI



CLEAR study primary analysis

Secondary endpoint — AEs of any cause that emerged or worsened during treatment in ≥25% of patients in either treatment group^{a,6}



KEYTRUDA + KISPLYX (n=352) ■ Grade ≥3 ■ Any grade

Sunitinib (n=340) ■ Grade ≥3 ■ Any grade

Adapted from Motzer R et al. 2021⁶

Analysis cutoff date: 28 August 2020.
^aSafety 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.



KEYTRUDA
KISPLYX

[GB PI](#) [NI PI](#)

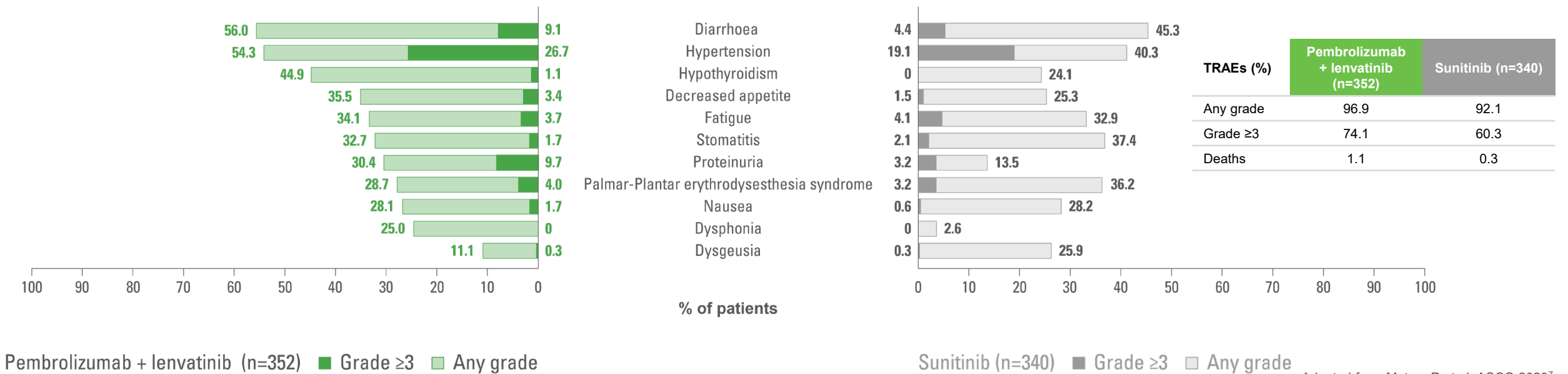
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Prespecified final analysis

Exploratory analysis — TRAEs in ≥25% of patients in any treatment group⁷

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



- There were no new safety signals identified at 49.8 months median follow up

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. The median duration of treatment (IQR) was 22.6 (9.4–37.1) months with pembrolizumab + lenvatinib and 7.8 (3.7–19.4) months with sunitinib.



Secondary endpoint — summary of TEAEs of interest for KEYTRUDA^{a,6}

Click for TEAEs of interest for KISPLYX

TEAE	KEYTRUDA + KISPLYX (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)
Encephelitis	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)

TEAE	KEYTRUDA + KISPLYX (n=352)		Sunitinib (n=340)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
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. 2021⁶

Analysis cutoff date: 28 August 2020.
^aNo cases of Guillain-Barré syndrome, myelitis, or sarcoidosis were reported in any group.
AE, adverse event, TEAE, treatment-emergent adverse event.



KEYTRUDA

KISPLYX

GB PI

GB and NI PI

NI PI



Secondary endpoint — summary of clinically significant TEAEs for KISPLYX⁶

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Click for TEAEs of interest for KEYTRUDA

TEAE	KEYTRUDA + KISPLYX (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)

TEAE	KEYTRUDA + KISPLYX (n=352)		Sunitinib (n=340)	
	Any grade	Grade ≥3	Any grade	Grade ≥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. 2021⁶

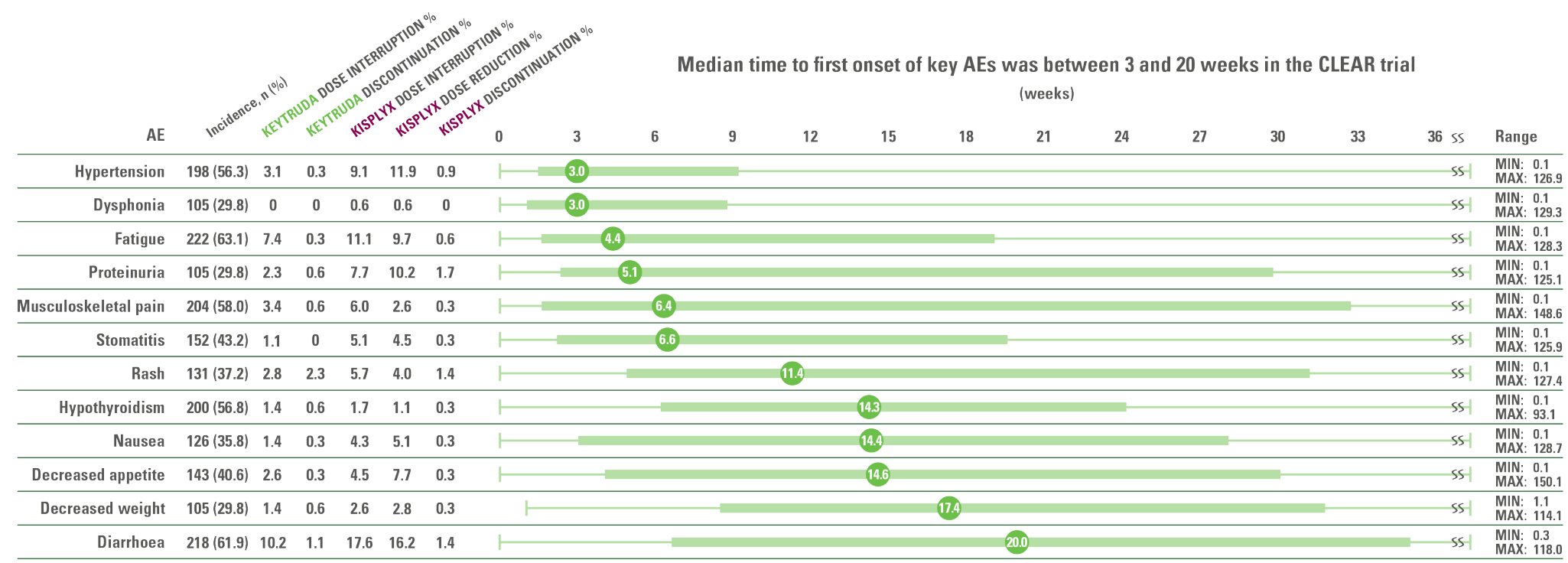
Analysis cutoff date: 28 August 2020.

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

CLEAR study primary analysis

Exploratory analysis — Median time to first onset of key AEs* (all grades) and dose management for **KEYTRUDA** + **KISPLYX**^{a,10}

Median follow-up: 26.6 months with pembrolizumab + lenvatinib and with sunitinib



Adapted from Motzer R et al. 2023¹⁰

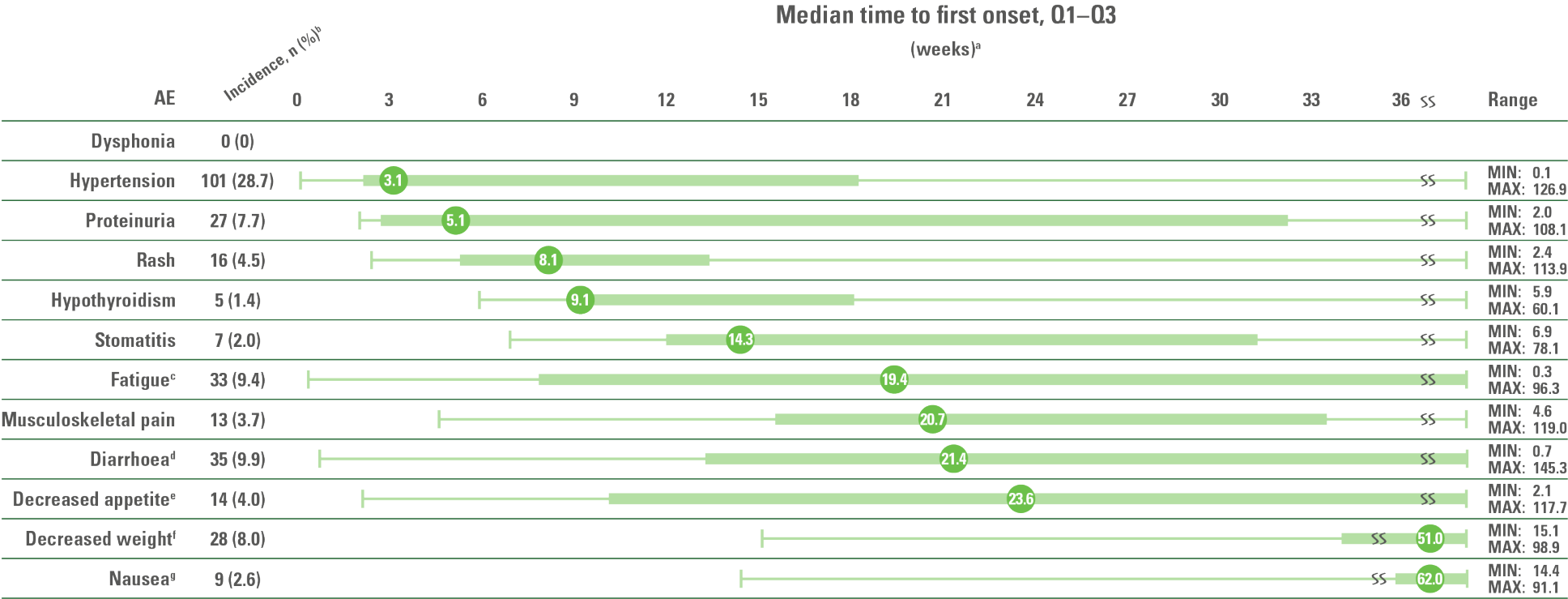
LIMITATION:
This was a post-hoc exploratory analysis based on data from the CLEAR trial. No formal statistical testing was planned for this exploratory analysis and, therefore, no conclusions can be drawn.

^aMedian time to first onset in patients who experienced the AE. *Key AEs: AEs with incidence ≥30% in the KEYTRUDA + KISPLYX 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 event; max, maximum; min, minimum; Q, Quartile.

CLEAR study primary analysis

Exploratory analysis — Median time to first onset of Grade ≥3 AEs in patients treated with
KEYTRUDA + KISPLYX^{a,10}

Median follow-up: 26.6 months with pembrolizumab + lenvatinib and with sunitinib



Adapted from Motzer R et al. 2023¹⁰

^aMedian time to first onset in patients who experienced the Grade ≥3 adverse reaction. Coloured boxes represent Q1–Q3. Lines represent the range; ^bAny grade. Percentages are based on the safety population of the KEYTRUDA + KISPLYX group (n=352). The safety population included all patients who received at least one dose of any study drug; ^cQ1=7.86, Q3=42.29; ^dQ1=13.29, Q3=56.71; ^eQ1=10.14, Q3=69.14; ^fQ1=34.00, Q3=64.71; ^gQ1=42.57, Q3=74.00. AE, adverse event; max, maximum; min, minimum; Q, Quartile

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.



KEYTRUDA
KISPLYX

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CLEAR study primary analysis

HRQoL — patient reported outcomes^{a11}

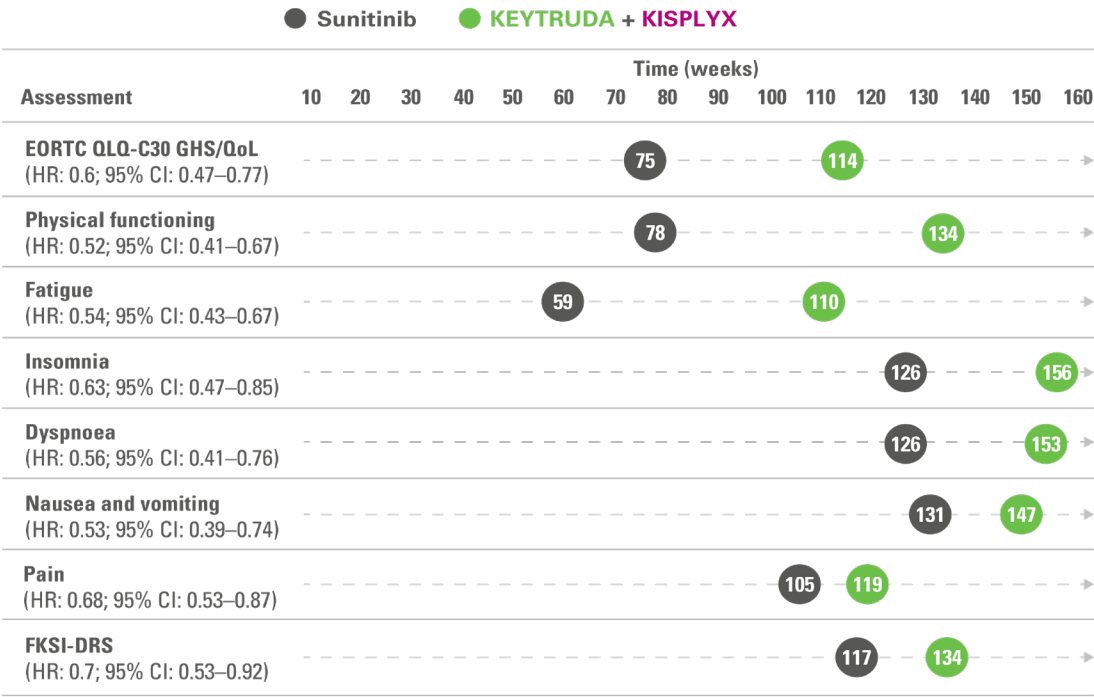
Median (IQR) follow-up: 12.9 (5.6–22.3) months with pembrolizumab + lenvatinib and with sunitinib

- KEYTRUDA + KISPLYX 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

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

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



Adapted from Motzer R et al. 2022¹¹

Analysis cutoff date: 24 July 2019.
^aPatient-reported outcomes (PROs) were assessed using the EORTC QLQ-C30 and the FKSI-DRS; ^bMeasured from baseline to a mean follow-up time of 46 weeks.
AE, adverse event; 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; QoL, quality of life; VAS, visual analogue scale.

KEYTRUDA and **KISPLYX** are administered via IV infusion and oral capsules, respectively

KEYTRUDA offers flexibility of dosing³



Administered as
an IV infusion³



Over 30
minutes³



200 mg Q3W or
400 mg Q6W³

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 therapy³

What does flexibility mean to you and your patients?

KISPLYX⁵



20 mg orally
QD at the
same time each day⁵



Administered with or
without food⁵

Swallowed whole with water.
For patients unable to
swallow capsules,
please refer to the SmPC for
alternative methods of
preparation⁵

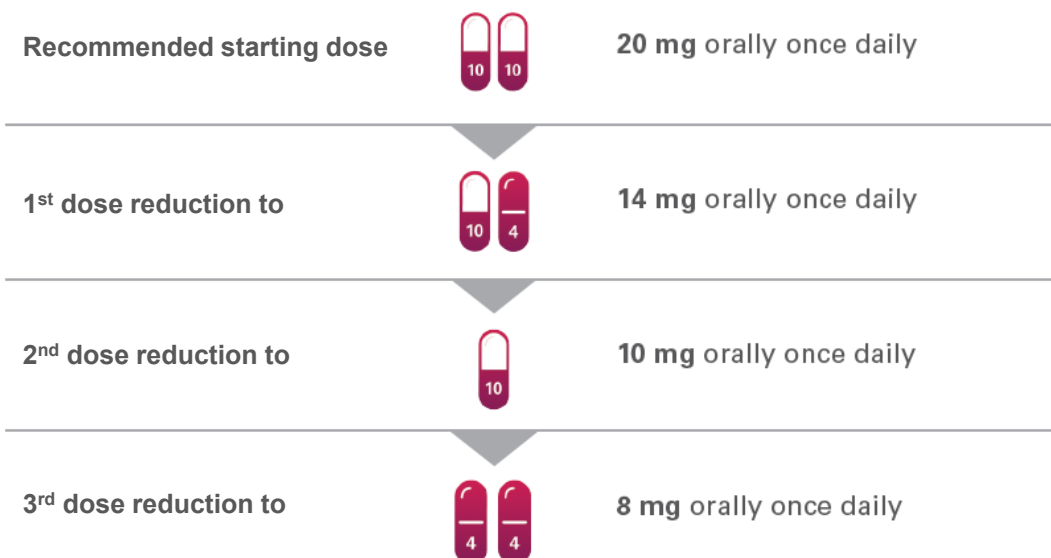
- Continue treatment with **KISPLYX** for as long as there is clinical benefit or until unacceptable toxicity occurs
- For AEs thought to be related to **KISPLYX**, upon resolution/improvement of an AE to Grade 0–1 or baseline, treatment should be resumed at a reduced dose of **KISPLYX**
 - Please refer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

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

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

- The recommended starting daily dose of **KISPLYX** is 20 mg. Dose modification can be used to manage adverse reactions as appropriate⁵
- When administering **KISPLYX** in combination with **KEYTRUDA**, interrupt, reduce or discontinue **KISPLYX** as appropriate. Withhold or discontinue **KEYTRUDA** in accordance with the instructions in the SmPC for **KEYTRUDA**. No dose reductions are recommended for **KEYTRUDA**^{3,5}

Recommended dose modification for **KISPLYX** in advanced RCC⁵



QD, once daily; RCC, renal cell carcinoma.

- If a **KISPLYX** dose is missed and cannot be administered within 12 hours, skip that dose and take the next dose at the usual time of administration⁵
- Continue treatment with **KEYTRUDA** + **KISPLYX** until disease progression, unacceptable toxicity or, for **KEYTRUDA**, up to 24 months^{3,5}
- The recommended starting dose of **KISPLYX** for patients with advanced RCC and severe renal impairment is 10 mg administered orally QD⁵
- The recommended starting dose of **KISPLYX** for patients with advanced RCC and severe hepatic impairment (Child–Pugh C) is 10 mg administered orally QD⁵

Exploratory subgroup analysis of efficacy outcomes by baseline tumour size¹²

Patient characteristics

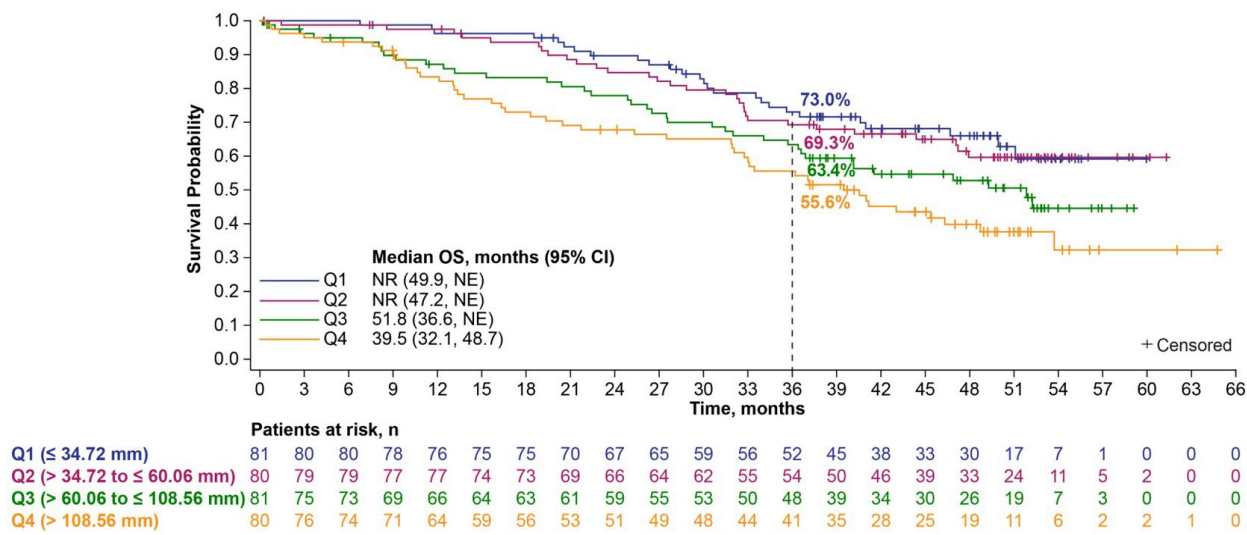
Characteristic	Baseline sums of diameters of target lesions ^a (N=355)			
	Q1 81 patients (22.8%)	Q2 80 patients (22.5%)	Q3 81 patients (22.8%)	Q4 80 patients (22.5%)
	Defined as ≤34.72 mm	Defined as >34.72 mm to ≤60.06 mm	Defined as >60.06 mm to ≤108.56 mm	Defined as >108.56 mm
Age, median (range), 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 2024¹²

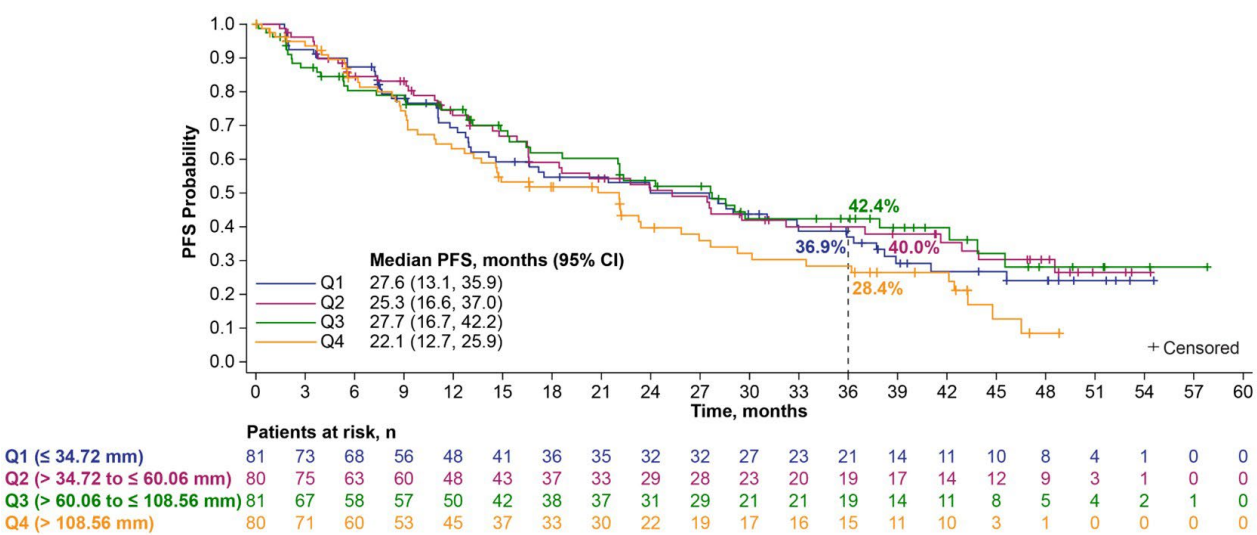
Percentages may not total 100 due to rounding. One patient in the KEYTRUDA + KISPLYX group had carcinoma without a clear-cell component.
^aIncludes patients in the full analysis set within the KEYTRUDA + KISPLYX group with baseline target lesion assessments by independent imaging review per RECIST v1.1; ^bIMDC 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; ^cPD-L1 expression was assessed with the PD-L1 immunohistochemistry 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.
IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; PD-L1, programmed death ligand-1; Q, Quartile; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Exploratory subgroup analysis¹²

OS by baseline tumour size^a



PFS by baseline tumour size^b



Adapted from Grünwald V et al. ASCO GU 2024¹²

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.

Medians were estimated by the Kaplan–Meier method, and 95% CIs were estimated with a generalised Brookmeyer and Crowley method. Survival rate at 36 months was calculated using the Kaplan–Meier product-limit method.
^aThe number of patients with OS events (deaths) were: Q1=26, Q2=30, Q3=38, Q4=46; ^bIndependent imaging review by RECIST v1.1. The number of patients with PFS events (death or progressive disease) were: Q1=50, Q2=45, Q3=42, Q4=54.
CI, confidence interval; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; Q, Quartile; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.



KEYTRUDA
KISPLYX

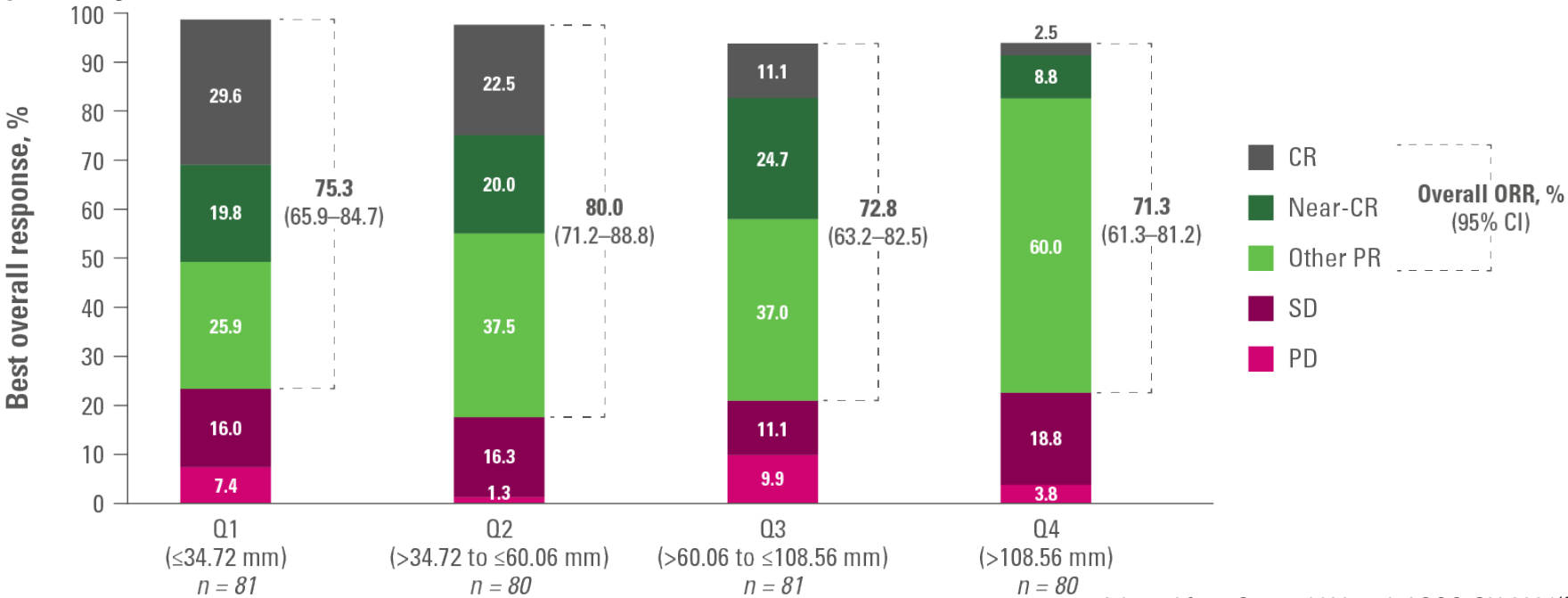
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Exploratory subgroup analysis¹²

Best overall response by baseline tumour size^a



Adapted from Grünwald V et al. ASCO GU 2024¹²

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.

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 + KISPLYX group. Percentages may not total 100 due to rounding.

^aIncludes patients with baseline target lesion assessments by independent imaging review per RECIST v1.1.

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

Pembrolizumab + lenvatinib: Outcomes in 1L advanced RCC⁶



Superior PFS:

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



Superior OS:

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



Superior ORR:

- ORR was **71.0%** with **KEYTRUDA** + **KISPLYX** vs 36.1% with sunitinib ($P<0.0001$)^b
 - CR: **16.1%** with **KEYTRUDA** + **KISPLYX** vs 4.2% with sunitinib



Safety:

- The safety profile of **KEYTRUDA** + **KISPLYX** was consistent with the profiles for the individual drugs

^aAnalysis cutoff date: 28 August 2020 and median follow-up: 26.6 months for pembrolizumab + lenvatinib and sunitinib¹⁰; ^bAt 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 pembrolizumab + lenvatinib with sunitinib (odds ratio: 3.84 [95% CI: 2.81, 5.26], $P<0.0001$).^{7,9}
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.

Pembrolizumab + lenvatinib: Outcomes in 1L advanced RCC^{7,12}



Prespecified final analysis (exploratory data; no conclusions can be drawn):

- The pre-specified final OS analysis continues to support **KEYTRUDA** + **KISPLYX** as a standard of care in 1L advanced RCC



PFS:

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



OS:

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



ORR and DOR:

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



Safety:

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



Outcome by baseline tumour size:

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

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.

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Grünwald V et al. Subgroup analyses of efficacy outcomes by baseline tumor size in the Phase 3, open-label, CLEAR trial. Slide deck (Abstract #364) presented at: American Society of Clinical Oncology (ASCO) Genitourinary (GU) Cancer Symposium; January 25–27, 2024; San Francisco, California, USA.

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KEYTRUDA
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