Improving outcomes for patients with advanced RCC: What is the role of emerging combination therapies in the first-line setting?

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What is the rationale for use of combination therapies in advanced RCC?

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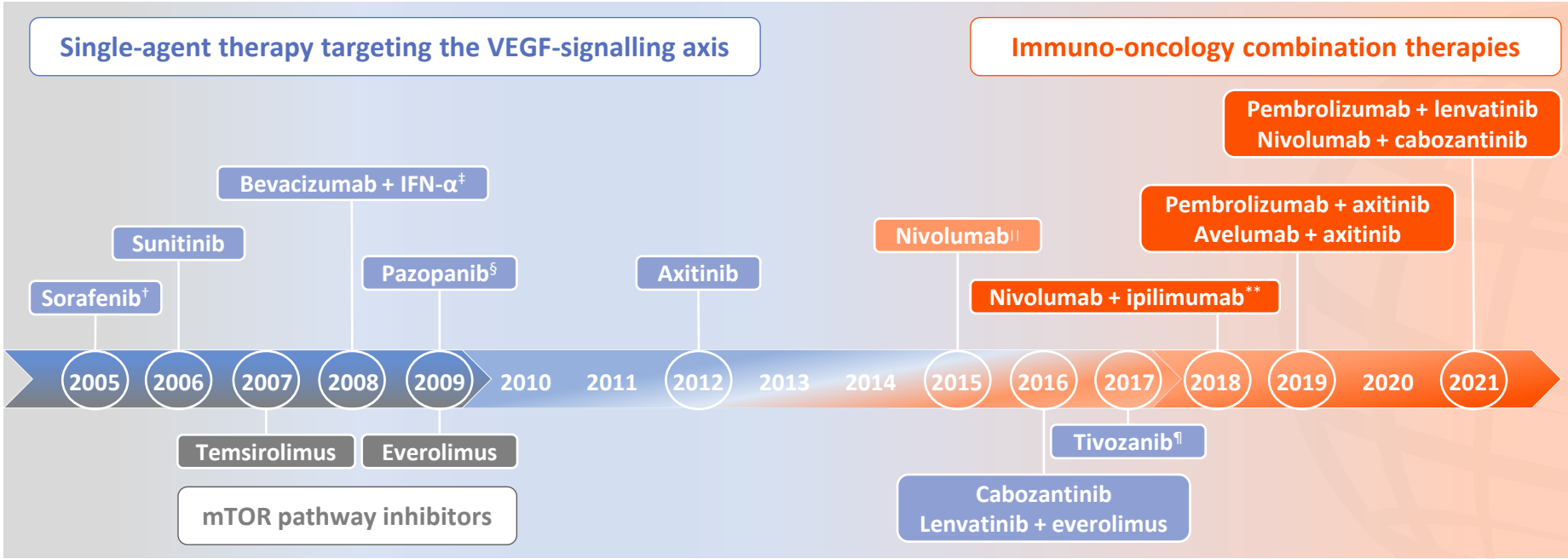
An overview of the therapeutic landscape for RCC[1]*



Median overall survival in advanced RCC has progressively increased;[1] combination therapies could lead to further improvements in the treatment of patients with advanced RCC[2]

*First approval date (either EMA or FDA) indicated; differences between two regions are footnoted; †EMA, 2006; ‡FDA, 2009; §EMA, 2010; ||EMA, 2016; ¶FDA, 2021; **EMA, 2019.
EMA, European Medicines Agency; FDA, US Food and Drug Administration; IFN, interferon; mTOR, mammalian target of rapamycin; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.
Adapted from 1. Hsieh JJ, et al. *Nat Rev Dis Primers*. 2017;3:17009; 2. Yang DC, Chen C-H. *Semin Nephrol*. 2020;40:86–97.
FDA. History of approval for all drugs. Available at: www.fda.gov/drugs; EMA. History of approval for all drugs. Available at www.ema.europa.eu (accessed 8 July 2022).

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Guideline recommendations: First-line advanced RCC

Preferred

NCCN (2022)[1,*]

Favourable/intermediate or poor risk[†]
- Axitinib + pembrolizumab
- Cabozantinib + nivolumab
- Lenvatinib + pembrolizumab

Intermediate or poor risk[†]
- Ipilimumab + nivolumab
- Cabozantinib

Recommended

ESMO (2021)[2,3,*]

IMDC favourable/intermediate or poor risk
- Lenvatinib + pembrolizumab
- Axitinib + pembrolizumab
- Cabozantinib + nivolumab

IMDC intermediate or poor risk
- Ipilimumab + nivolumab

Other regimens

Favourable risk[†]
- Cabozantinib
- Ipilimumab + nivolumab

Favourable/intermediate or poor risk[†]
- Axitinib + avelumab
- Pazopanib
- Sunitinib

Alternative[‡]

IMDC favourable risk
- Sunitinib
- Pazopanib
- Tivozanib

IMDC intermediate/poor risk
- Sunitinib
- Pazopanib
- Cabozantinib

*Order of agents is as per guidelines; †IMDC criteria or MSKCC prognostic model; ‡Where recommended treatment is not available or is contraindicated.
ESMO, European Society for Medical Oncology; IMDC, International Metastatic RCC Database Consortium; MSKCC, Memorial Sloan Kettering Cancer Center; NCCN, The National Comprehensive Cancer Network; RCC; clear cell renal cell carcinoma.

1. Motzer RJ, et al. *J Natl Compr Canc Netw.* 2022;20:71–90; 2. Powles T, et al. *Ann Oncol*. 2021;1511–9; 3. Powles T, et al. *Ann Oncol*. 2021; 32:422–3.

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Combination therapies in first-line advanced RCC: What do the latest clinical data tell us?

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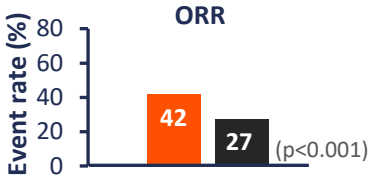
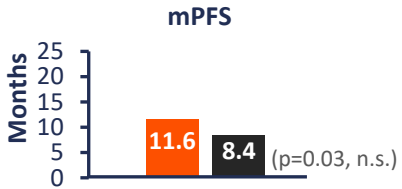
Key efficacy and safety data from pivotal trials (1/2)

CheckMate 214[1] (N=1,096)

Nivolumab + ipilimumab
vs sunitinib
(mFU: 25.2 mo)

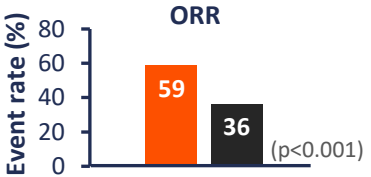


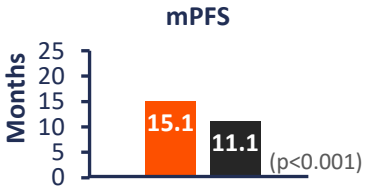


mOS (mFU, 55 mo):
NR vs 38.4 mo[2]
TRAEs (grade ≥3): 46% vs 63%

KEYNOTE-426[3] (N=861)

Axitinib + pembrolizumab
vs sunitinib
(mFU: 12.8 mo)

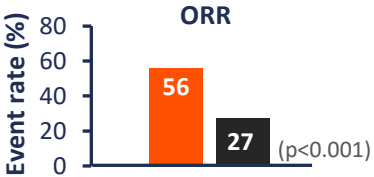


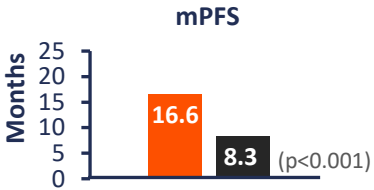


mOS (mFU, 30.6 mo):
NR vs 36 mo[4]
TRAEs (grade ≥3): 63% vs 58%

CheckMate 9ER[5] (N=651)

Cabozantinib + nivolumab
vs sunitinib
(mFU: 18.1 mo)

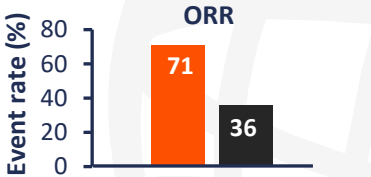


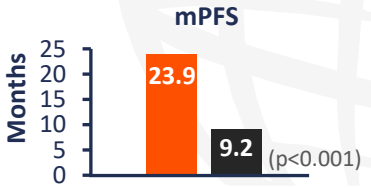


mOS (mFU, 32.9 mo):
37.7 vs 34.3 mo[6]
TRAEs (grade ≥3): 61% vs 51%

CLEAR[7] (n=712)

Lenvatinib + pembrolizumab
vs sunitinib
(mFU: 26.6 mo)





mOS (mFU, 26.6 mo):
NR, either group
AEs (grade ≥3): 82% vs 72%

AE, adverse event; FU, follow-up; m, median; mo, month; NR, not reached; n.s., non-significant; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TRAE, treatment-related adverse event.

1. Motzer RJ, et al. *N Engl J Med*. 2018;378:1277–90; 2. Albiges L. et al. *ESMO Open*. 2020;5:e001079. 3. Rini BI, et al. *N Engl J Med.* 2019;380:1116–27; 4. Powles T, et al. *Lancet Oncol*. 2020;21:1563–73; 5. Choueiri TK, et al. *N Engl J Med.* 2021;384:829–41; 6. Powles T, et al. *J Clin Oncol*. 2022;40(Suppl. 6):350; 7. Motzer RJ, et al. *N Engl J Med*. 2021;384:1289–300.

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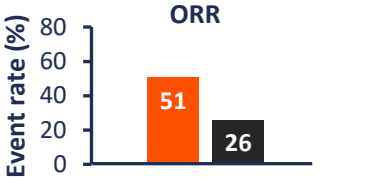
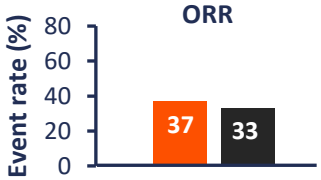
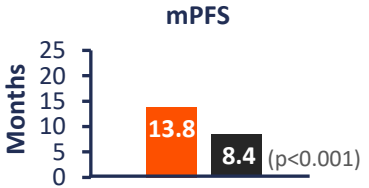
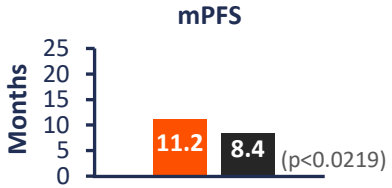
Key efficacy and safety data from pivotal trials (2/2)

JAVELIN Renal 101[1] (N=886)	IMmotion151[2] (N=915)
Axitinib + avelumab vs sunitinib (mFU: 10.8 vs 8.6 mo)	**Atezolizumab + bevacizumab vs sunitinib** (mFU: 15.0 mo)
	
	
mOS: NE, either group **AEs** (grade ≥3): 71% vs 72%	**mOS** (mFU, 24 mo): 33.6 vs 34.9 mo **TRAEs** (grade ≥3): 40% vs 54%

AE, adverse event; FU, follow-up; m, median; mo, month; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TRAE, treatment-related adverse event.

1. Motzer RJ, et al. *N Engl J Med*. 2019;380:1103–15; 2. Rini BI, et al. *Lancet*. 2019;393:2404–15.

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Recent updates: ASCO 2022

KEYNOTE-426[1] Axitinib + pembrolizumab*	PFS2† at 43 months was longer with axitinib + pembrolizumab versus sunitinib, regardless of IMDC risk
CheckMate 214[2] Nivolumab + ipilimumab*	Baseline HRQoL scores are a potential predictor for survival in advanced RCC
CheckMate 9ER[3] Cabozantinib + nivolumab*	Depth of response‡ was generally associated with improved PFS and OS

*Versus sunitinib; †Time from randomisation to objective tumour progression on next-line treatment or death from any cause; ‡Patients alive at the 6-month landmark.
ASCO, American Society of Clinical Oncology; HRQoL, health-related quality of life; IMDC, International Metastatic RCC Database Consortium; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma.
1. Powles T, et al. Presented at ASCO, Chicago, 3–7 June 2022:abstract 4513; 2. Cella D, et al. Presented at ASCO, Chicago, 3–7 June 2022:abstract 4502;
3. Suàrez C, et al. Presented at ASCO, Chicago, 3–7 June 2022:abstract 4501.

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Key trials assessing treatment optimization

Treatment	Patients; risk	Design	Study (completion)
Triplet vs doublet combination	N=840; Intermediate or poor risk	Nivolumab + ipilimumab + cabozantinib *vs* Nivolumab + ipilimumab + placebo	**COSMIC-313** NCT03937219 (March 2025)
Combination vs monotherapy	N=437; Intermediate or poor risk	Nivolumab + ipilimumab *vs* nivolumab	**CheckMate CA209-8Y8** NCT03873402 (March 2025)
Drug sequencing	N=1,046; Intermediate or poor risk	Nivolumab + ipilimumab **followed by** nivolumab + cabozantinib *vs* Nivolumab + ipilimumab **followed by** nivolumab	**PDIGREE** NCT03793166 (September 2022)

Clinical trials are available at: ClinicalTrials.gov using the study identifier (accessed 8 July 2022).

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Side effects associated with combination therapies for first-line advanced RCC: What is best practice for management?

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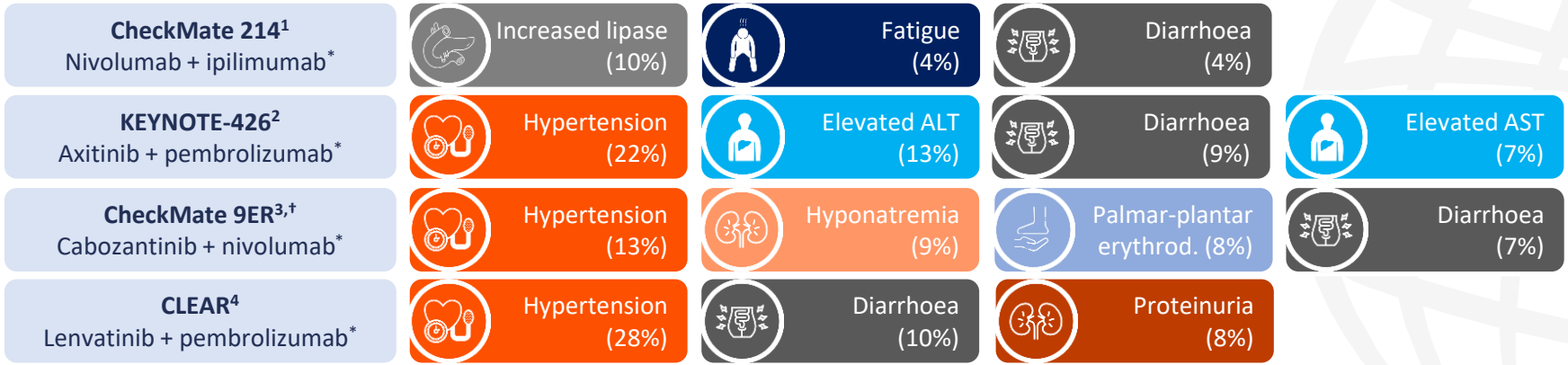
Pivotal trials: Adverse events (grade ≥3)



*Versus sunitinib; †The four highest incidences of grade ≥3 adverse events are shown. Other adverse events occuring in ≥5% of patients included hypophosphatemia (6%), increased lipase (6%), and elevated ALT (5%).
ALT, alanine aminotransferease; AST, aspartate transferase; erythrod., erythrodysesthesia.
1. Motzer RJ, et al. *N Engl J Med*. 2018;378:1277–90; 2. Rini BI, et al. *N Engl J Med*. 2019;380:1116–27; 3. Choueiri T, et al. *N Engl J Med*. 2021;384:829–41;
4. Motzer RJ, et al. *N Engl J Med*. 2021;384:1289–300.

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