Advancing Care in Non-Clear Cell RCC: Optimizing ICI and TKIs

Key Clinical Trial Data:
Current and Emerging Therapeutic Approaches for nccRCC

Learning Objectives

- Improved ability to compare and contrast clinical trial data on current and emerging uses of ICIs, TKIs, and combination ICI/TKI therapy for nccRCC
- Increased knowledge and skills in understanding the clinical profiles of ICI- and TKI-based therapies for nccRCC

Clinical Trial Outcomes Favor TKI + ICI Regimens for nccRCC and Papillary RCC

Across nccRCC subtypes, patient outcomes are better with TKI + ICI regimens than with other regimens

	Trial Design	Treatment in nccRCC	ORR
mTORi vs. TKI	Phase 2, randomized *ASPEN*[1]	Everolimus (n = 57) Sunitinib (n = 51)	9% 18%
	Phase 2, randomized *ESPN*[2]	Everolimus (n = 35) Sunitinib (n = 33)	3% 9%
mTORi + TKI	Phase 2, single arm[3]	Everolimus + lenvatinib (n = 31)	26%
mTORi + VEGFi	Phase 2, single arm[4]	Everolimus + bevacizumab (n = 34)	29%
ICI	Phase 2, single arm *KEYNOTE-427*[5]	Pembrolizumab (n = 165)	27%
TKI + ICI	Phase 2, single arm[6, 7]	Cabozantinib + nivolumab (n = 40)	48%
	Phase 2, single arm *KEYNOTE-B61*[8]	Lenvatinib + pembrolizumab (n = 158)	49%
	Phase 2, single arm[9, 10]	Cabozantinib + nivolumab + ipilimumab (n = 39)	21%
ICI + ICI	Phase 3b/4, single arm[11]	Nivolumab + ipilimumab (n = 46)	20%
	Phase 2, randomized *SUNNIFORECAST*[12]	Nivolumab + ipilimumab (n = 125) Standard of care (n = 122)	33% 20%
Other combinations	Retrospective *ORACLE*[13]	Nivolumab + ipilimumab (n = 124) ICI + VEGFi (n = 81) VEGFi + mTORi (n = 28)	26% 31% 20%

ICI, immune checkpoint inhibitor; mTORi, mammalian target of rapamycin inhibitor; ORR, objective response rate; TKI, tyrosine kinase inhibitor; VEGFi, vascular endothelial growth factor inhibitor

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For papillary RCC, ORRs are higher with TKI + ICI combinations (47%-54%) than with other regimens (0%-35%)

	Trial Design	Treatment in Papillary RCC	ORR
TKI	Phase 2, randomized[14]	Cabozantinib (n = 44) Sunitinib (n = 46)	23% 4%
	Phase 2, single arm[15]	Savolitinib (n = 109)	7%
mTORi vs. TKI	Phase 2, randomized *ASPEN*[1]	Everolimus (n = 37) Sunitinib (n = 33)	5% 24%
	Phase 2, randomized *ESPN*[2]	Everolimus (n = 13) Sunitinib (n = 14)	0% 7%
mTORi + TKI	Phase 2, single arm[1]	Everolimus + lenvatinib (n = 20)	15%
mTORi + VEGFi	Phase 2, single arm[4]	Everolimus + bevacizumab (n = 4)	25%
TKI + VEGFi	Phase 2, single arm[16]	Erlotinib + bevacizumab (n = 40)	35%
ICI	Phase 2, single arm *KEYNOTE-427*[5]	Pembrolizumab (n = 118)	29%
TKI + ICI	Phase 2, single arm[6, 7]	Cabozantinib + nivolumab (n = 32)	47%
	Phase 2, single arm *KEYNOTE-B61*[8]	Lenvatinib + pembrolizumab (n = 93)	47%
	Phase 2, single arm[9]	Cabozantinib + nivolumab + ipilimumab (n = 19)	32%
ICI + ICI	Phase 3b/4, single arm[11]	Nivolumab + ipilimumab (n = 18)	28%
Other combinations	Retrospective *ORACLE*[13]	Nivolumab + ipilimumab ICI + VEGFi VEGFi + mTORi	15% 28% 0

[a]Across treatment arms, n = 97 patients with papillary RCC

ICI, immune checkpoint inhibitor; mTORi, mammalian target of rapamycin inhibitor; ORR, objective response rate; TKI, tyrosine kinase inhibitor; VEGFi, vascular endothelial growth factor inhibitor

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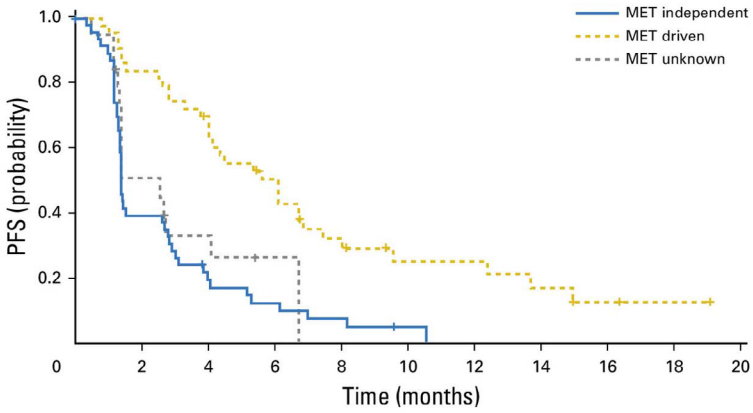
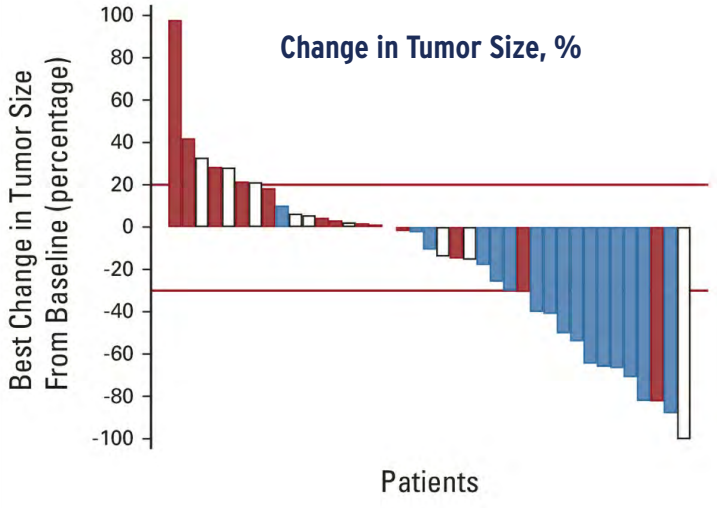


Time, months	0	1.4	2.8	4.1	5.5	6.9	8.3	9.7	11.1	12.5	13.9	15.2	16.6	18.0	19.4
No. at risk:															
MET independent	46	30	15	8	4	3	2	1	0						
MET driven	44	39	29	20	13	9	6	6	4	3	3	3	0		
MET unknown	19	13	3	2	1	0									

Regardless of treatment regimen, median PFS for papillary RCC is < 9 months and median OS is 14-22 months[15]

Treatment outcomes are consistently better for patients with MET-driven papillary RCC vs. MET-independent tumors[17]



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Key Takeaways

Clinical trial results for nccRCC subtypes

- Objective response rates were higher with TKI + ICI combinations (40%-49%) than with other regimens (3%–23%)
- Median PFS was also longer with TKI + ICI combinations (9.7-18 months) than with other regimens (4.2-9.2 months)
- Median OS varied across treatment regimens and was 28 months; not reached with TKI + ICI combinations

Clinical trial results for papillary RCC

- Objective response rates were higher with TKI + ICI combinations (47%-54%) than with other regimens (0%-35%)
- For all regimens, the median PFS is less than 9 months
- Median OS varied across treatment regimens, from 14-22 months
- Treatment outcomes are consistently better for patients with MET-driven vs. MET-independent tumors

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