Dual ICI vs ICI/TKI for 1L mRCC: The Case for ICI/TKI

MaTOS GU

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Case Presentation

- 48 year old man presents to the medical oncology clinic 3 months after a radical nephrectomy which showed pT3bN1 disease
- Scans now show ascites, pleural effusion, peritoneal implants, nodules in nephrectomy bed, R adrenal nodule
- Requiring weekly paracentesis and having significant flank pain

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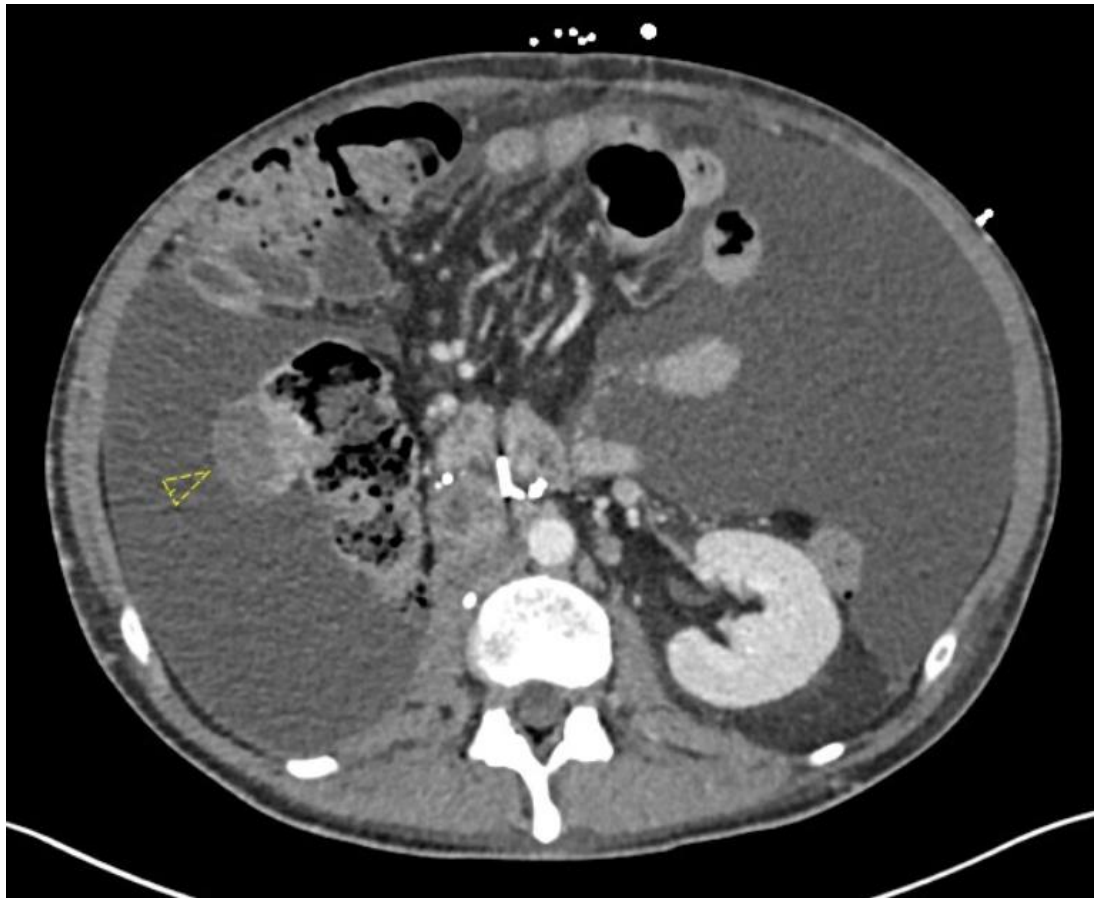


What first line therapy will provide the most benefit for this symptomatic patient with rapid progression?

NCCN guidelines include ICI/ICI and ICI/TKI

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Kidney Cancer

PRINCIPLES OF SYSTEMIC THERAPY FOR STAGE IV (M1 OR UNRESECTABLE T4, M0) OR RELAPSED DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	**Preferred Regimens**	**Other Recommended Regimens**	**Useful in Certain Circumstances**
Favorable[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b,c] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Ipilimumab + nivolumab[b,d]	• Axitinib + avelumab[b] • Cabozantinib (category 2B) • Pazopanib • Sunitinib	• Active surveillance[1,2,3] • Axitinib (category 2B)
Poor/ intermediate[a]	• Axitinib + pembrolizumab[b] (category 1) • Cabozantinib + nivolumab[b,c] (category 1) • Ipilimumab + nivolumab[b,d] (category 1) • Lenvatinib + pembrolizumab[b] (category 1) • Cabozantinib	• Axitinib + avelumab[b] • Pazopanib • Sunitinib	• Axitinib (category 2B)

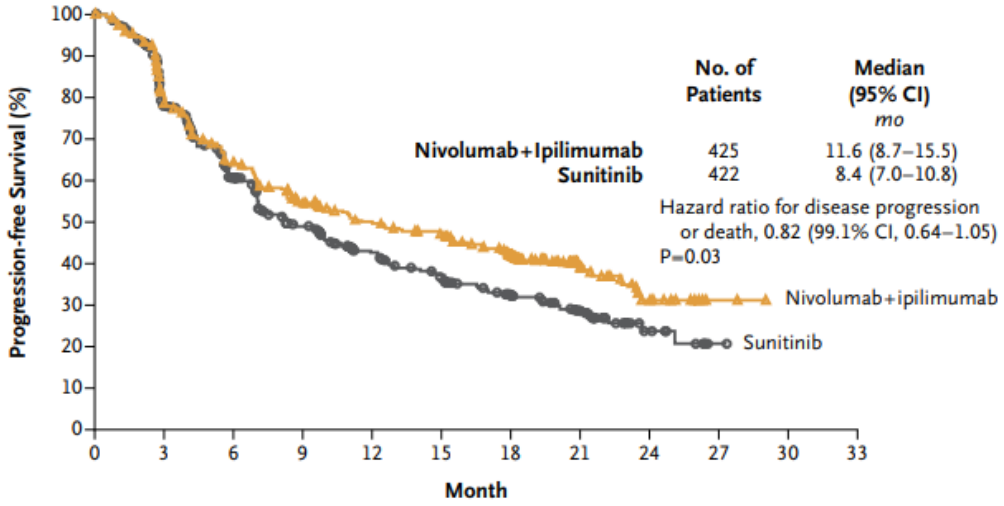
NCCN.org

ICI based combinations for Stage IV ccRCC

	CheckMate 214 Ipi/nivo v sunitinib	KEYNOTE-426 Pembro+axi v sunitinib	CheckMate 9ER Nivo+cabo v sunitinib	CLEAR Pembro+lenva v sunitinib
mPFS (months) HR	**12.3** vs 12.3 0.86 (0.73–1.01)	**16** vs 11 0.68 (0.58–0.80)	**16.4** vs 8.4 0.58 (0.49–0.7)	**23.9** vs 9.2 0.39 (0.32-0.49)
mOS (months) HR	**55.7** v 38.4 **0.72** (0.62-0.85)	**46** vs 40 **0.73** (0.6–0.88)	**46.5** vs 36 **0.77** (0.63-0.95)	**53.7** vs 54.3 **0.79** (0.63-0.99)
Prognostic Risk % Favorable Intermediate Poor	 23 61 17	 32 55 13	 23 58 19	 31 59 9
>= Grade 3 TRAE	46 vs 63	68 vs 64	61 vs 51	72 vs 59

Motzer et al. NEJM 2018. PMID: 29562145
Rini et al. NEJM 2019. PMID: 30779529
Choueiri et al. NEJM 2021. PMID: 33657295
Motzer et al. JCO 2024. PMID: 38227898

Treatment with ICI/TKI shows earlier trend toward benefit compared to sunitinib



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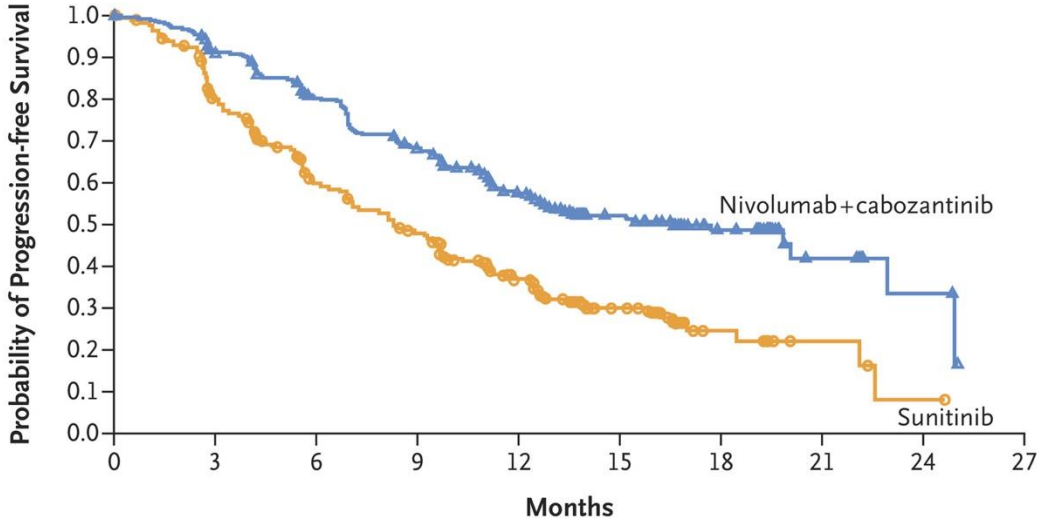

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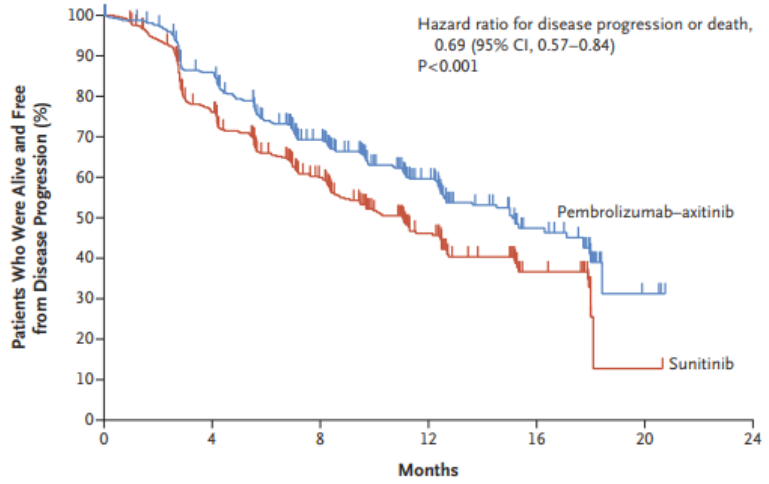

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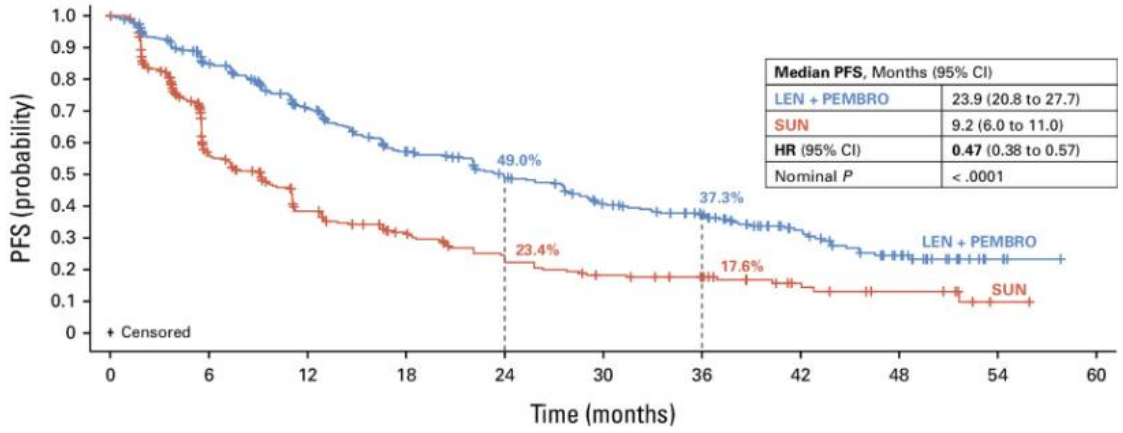

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Time to response and response rates vary

	Ipi/Nivo	Pembro/Axi	Cabo/nivo	Len/pembro
Complete Response (%)	9	5.8	8.0	10.1
Partial Response (%)	32	53.5	47.7	58.6
ORR	42	59.3	55.7	68.7
Median Time to First Response (range)	2.8 (0.9-11.3)	2.8 months (1.5-16.6)	2.8 months (1.0-19.4)	1.94 months (1.41-20.14)
Primary progressive disease	17.6	11.6	6.5	5.4

Motzer et al. NEJM 2018. PMID: 29562145
Rini et al. NEJM 2019. PMID: 30779529
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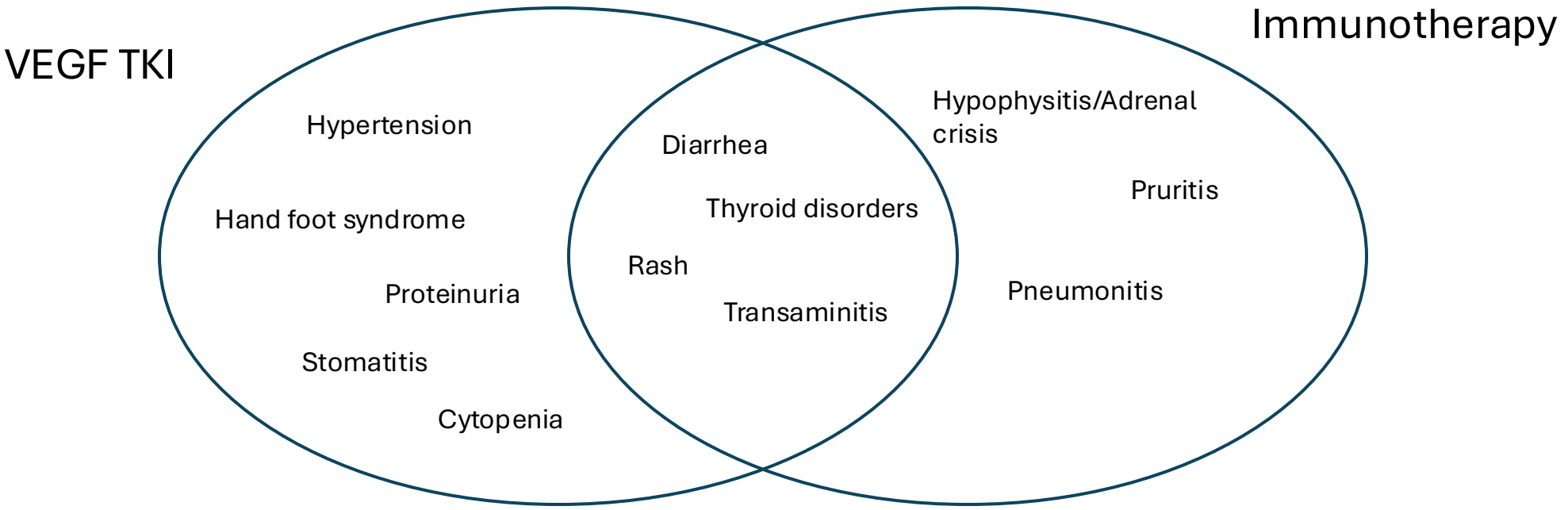
Toxicities with TKI treatments are predictable



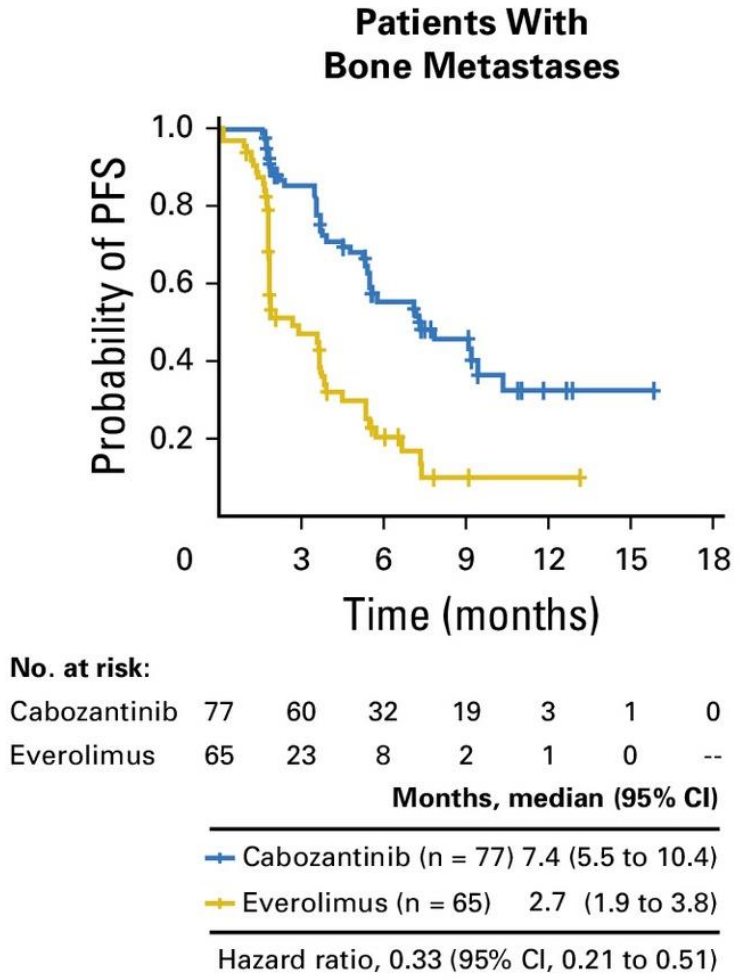
TKI toxicities can be managed with dose reduction and altered dosing schedules

Dual ICI vs ICI-TKI Combination

	Pros	Cons
ICI/ICI	• Durable responses • Treatment-free interval possible • OS advantage over TKI monotherapy	• **Potential long-term toxicity** • **Lower ORR**
ICI/TKI	• **Higher ORR** • **Rapid responses** • **Dose adjustment possible**	• Lack of durable response • Acute toxicity • Pill burden

Bone metastases may benefit from TKI

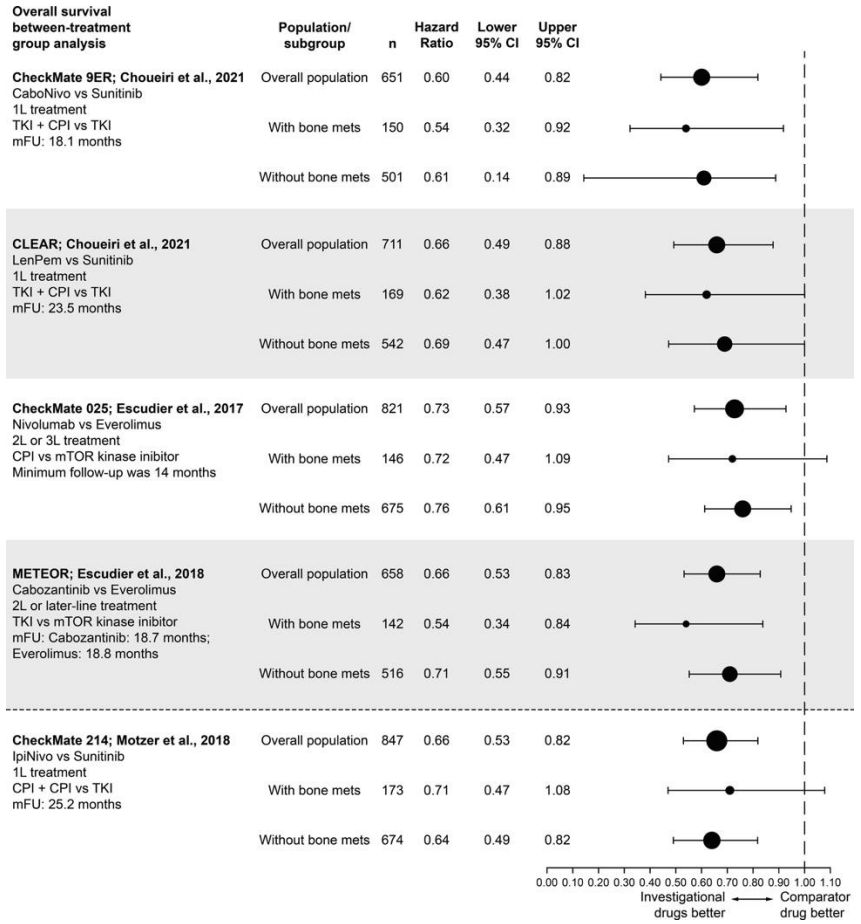
- METEOR trial compared cabozantinib and everolimus
- Subgroup analysis examined patients with bone metastases
  - PFS of 7.4 vs 2.7 months
  - OS 20.1 vs 12.1 months
  - ORR 17% vs 0%
- ASCO guidelines for mRCC:
  - cabozantinib-containing regimens may be preferred (expert opinion)



Rathmell et al. JCO 2022. PMID: 35728020
Escudier et al. JCO 2018. PMID: 29309249

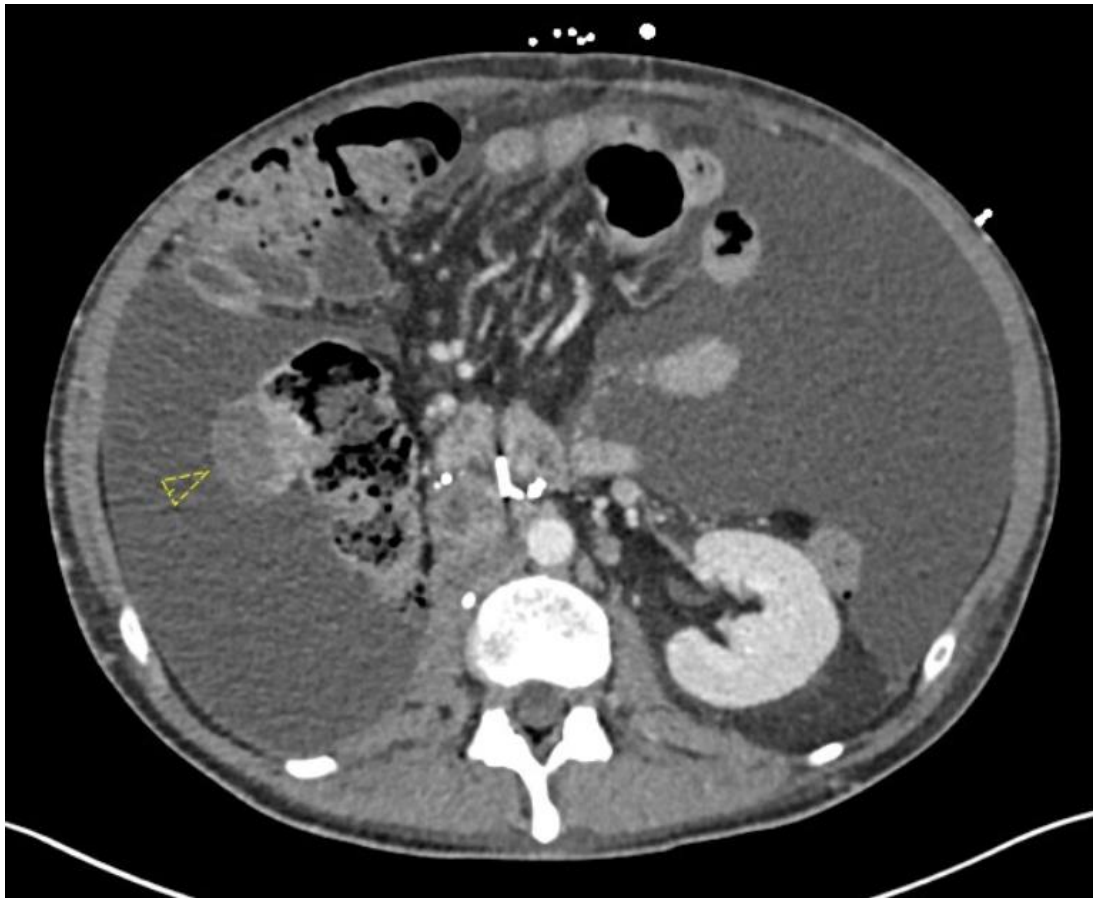
Bone metastases may benefit from TKI

- Trial data on patients with bone metastases is limited by small sample size
- Suggestion of benefit for TKI inclusion in this patient population



Brown et al. Cancer Treatment Review 2024. PMID 38972135

Case: 3 months of Lenvatinib/pembrolizumab



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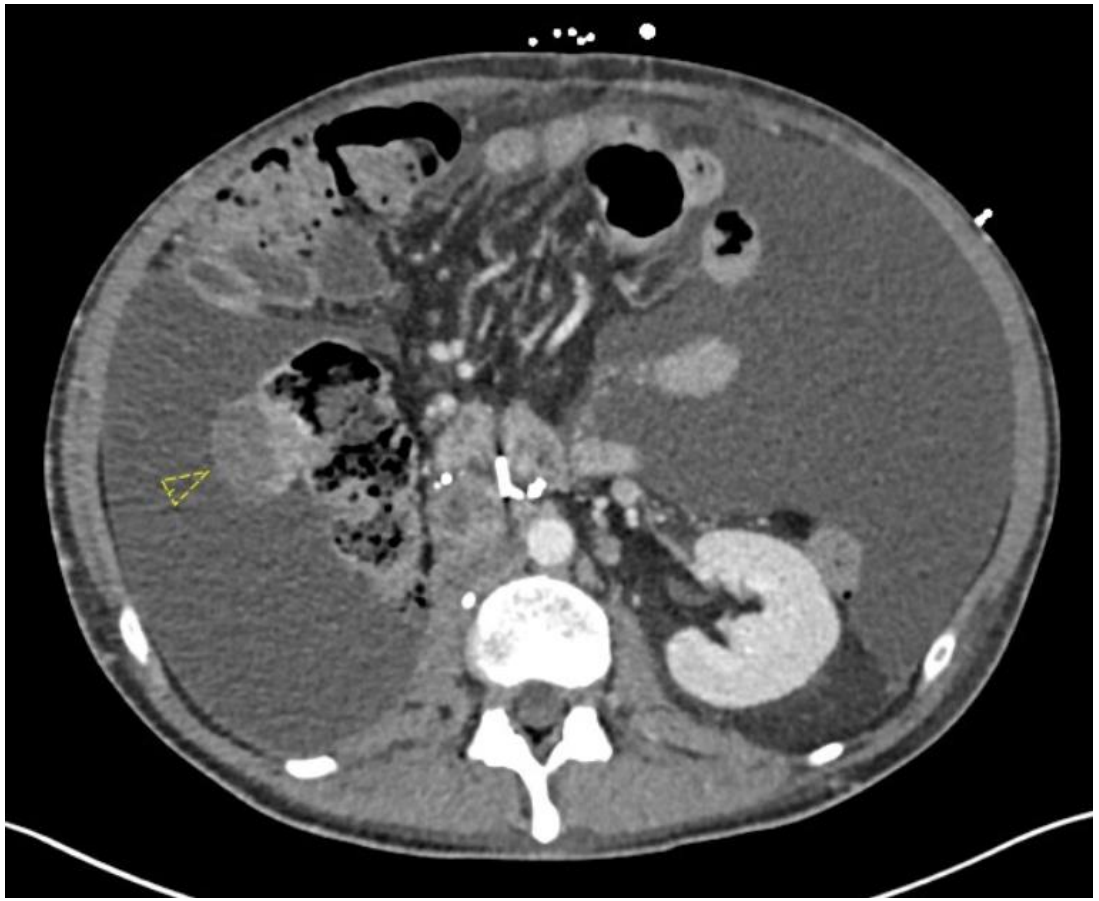

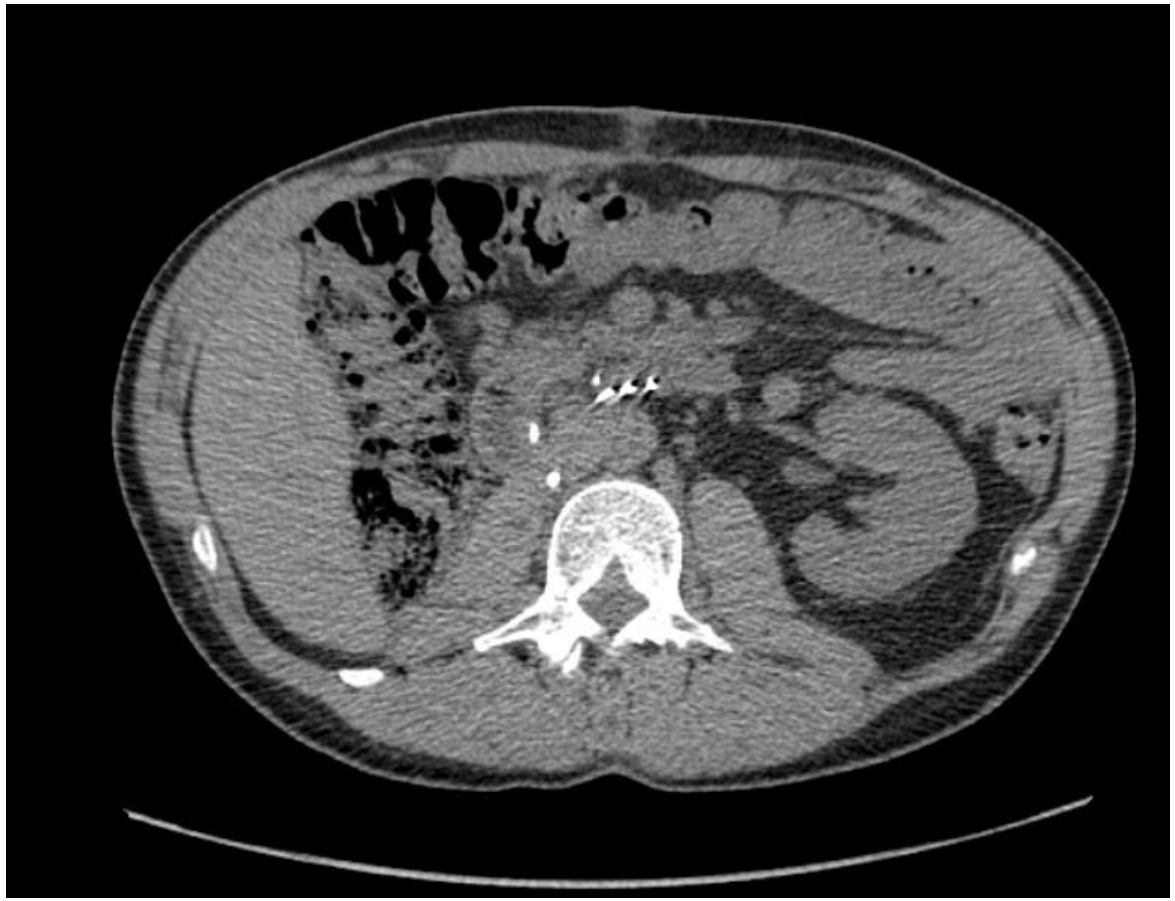

The Case for ICI/TKI

- ICI/TKI has a higher overall response rate, which for a symptomatic patient provides higher chance of symptomatic improvement
- TKI have predictable and manageable toxicities
- Subpopulations such as those with bone metastases may benefit from TKI inclusion