Adjuvant Therapy for Patients with High-Risk Kidney Cancer

MUSIC Michigan Urological Surgery Improvement Collaborative | KIDNEY Kidney mass: Identifying & Defining Necessary Evaluation & Therapy

2024 NCCN guidelines: Recommend adjuvant pembrolizumab for clear cell RCC pT2G4N0, pT3/4GanyN0, pTanyGanyN1, and M1 with no evidence of disease

2021 AUA guidelines: Patients should be counseled on risks/benefits, consider adjuvant therapy and medical oncology consultation

Pembrolizumab (Keytruda) ✓

Randomized clinical trial (RCT) SUPPORTS use

Pembrolizumab inhibits the PD-1 receptor and is a checkpoint inhibitor (**CKI**). **Administered IV every 3 weeks** for 1 year (200 mg)

Significant benefit in KEYNOTE-564 (n=994)
- **Disease-free survival:** HR 0.68 (95% CI 0.53-0.87), p=0.002
- **Overall survival (OS):** HR 0.54 (95% CI 0.30-0.96), p=NA as median OS not reached

Patient reported outcomes: adverse effects were **acceptable** from the patient perspective

Adverse effects: grade ≥3 in 32% (no deaths)
- Fatigue
- Diarrhea
- Pruritis
- Arthralgia
- Hypothyroidism
- Hyperthyroidism

Inclusion criteria / approved patients: (clear cell RCC only)
- pT2 (G4 or sarcomatoid) N0
- pT3/4 Gany N0
- pTany Gany N1
- M1 with no evidence of disease

Sunitinib (Sutent) and Pazopanib (Votrient) ☹

RCTs demonstrate MIXED RESULTS for adjuvant use

Sunitinib is a tyrosine kinase inhibitor (**TKI**) and suppresses tumor angiogenesis. **Administered PO daily** on 4 week on / 2 week off schedule for 1 year (50, 37.5, 25 mg)
Inclusion criteria: pT3/4 Gany N0 or any N1 clear cell RCC

One RCT showed benefit (S-TRAC, n=615):
- **Disease-free survival (DFS):** HR 0.76 (95% CI 0.59-0.98), p=0.03; 6.8 years vs. 5.6 years
- BUT Overall survival: HR 1.01 (95% CI 0.72-1.44), p=0.94

One RCT showed no benefit (ASSURE (n=1943):
- DFS: HR 1.02 (97.5%CI 0.85-1.23), p=0.80

Patient reported outcomes: significantly worse from the patient perspective
Adverse effects: grade ≥3 in 63% (12% grade 4, no deaths)

Pazopanib: TKI administered PO (PROTECT trial, n=1538)
The **RCT showed benefit:** 800 mg was effective
- DFS: HR 0.69 (95% CI 0.51-0.94) p=0.02, but not well-tolerated; 600 mg was better tolerated, but not effective
- DFS: HR 0.86 (95% CI 0.70-1.06) p=0.16

Patient reported outcomes: significantly worse from the patient perspective; (4 treatment-related deaths)

Other agents ✕

RCTs demonstrate evidence AGAINST use as adjuvant therapy for high-risk RCC

TKI: Axitinib (ATLAS, n=724)
- DFS: HR 0.87 (95% CI 0.66-1.15), p=0.32

TKI: Sorafenib (ASSURE, n=1942; SORCE, n=1711)
- DFS: HR 0.97 (97.5% CI 0.80-1.17), p=0.72
- DFS: HR 1.01 (95% CI 0.82-1.23), p=0.95

CKI: Nivolumab (PROSPER trial, n=805)
- RFS: HR 0.97 (95% CI 0.74-1.28), 1-sided p=0.43

CKI: Atezolizumab (IMMOTION-010 trial, n=778)
- DFS: HR 0.93 (95% CI 0.75-1.15), p=0.50

CKI: Nivolumab + ipilimumab (CheckMate-914, n=816)
- DFS: HR 0.92 (95% CI 0.71-1.19), p=0.53

mAb recognizing CAIX: Girentuximab (ARISER trial, n=864)
- DFS: HR 0.97 (95% CI 0.79-1.18), p=0.74

Everolimus (Afinitor) **mTOR inhibitor administered PO** (EVEREST trial, n=1545), Recurrence free survival (RFS)
- RFS: HR 0.85 (95% CI 0.72-1.00), p=0.051. RFS was longer in the very-high-risk group (HR 0·79, 95% CI 0·65–0·97; p=0·022), but not intermediate-high-risk group (p=0.96)

Adverse effects: grade ≥3 in 46% (no deaths)