Essential Peer-Reviewed Reading

The peer-reviewed articles summarized in this section were selected by the Editor-in-Chief, Robert A. Figlin, MD, for their timeliness, importance, relevance, and potential impact on clinical practice or translational research.

Recent eUpdate to the ESMO Clinical Practice Guidelines on renal cell carcinoma on cabozantinib and nivolumab for first-line clear cell renal cancer: Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Powles T, on behalf of theESMO Guidelines Committee. DOI:https://doi.org/10.1016/j.annonc.2020.11.016

Summary: This eUpdate outlines updated treatment recommendations for first-line ccRCC. The changes are based on recent data for the combination of cabozantinib and nivolumab. This is based on data from the CheckMate 9ER study, which is one of a number of practice-changing studies comparing PD-1 inhibitors plus VEGF TKIs vs sunitinib in the front-line setting. Results showed that the study met the primary endpoint of PFS, with a median of 16.6 months for the combination vs 8.3 months for sunitinib ($P < 0.0001$). There was also a significant overall survival advantage for cabozantinib and nivolumab at interim analysis (18.1 months median follow-up) [hazard ratio (HR) 0.60; 95% confidence interval (CI) 0.40-0.89; $P < 0.001$]. Reponses rates also significantly favoured the combination (56% versus 27% and HR 0.51, 95% CI 0.41-0.64, respectively). No new adverse event (AE) signals were identified and AE profiles were in line with expectation.

Results of a multicenter, phase 2 study of nivolumab and ipilimumab for patients with advanced rare genitourinary malignancies. McGregor et al. J Immunother Cancer. 2021; 127(6), 840-849.

Results: Fifty-five patients were enrolled at 6 institutions between April 2018 and July 2019 in 3 cohorts: BUTCVH (n = 19), adrenal tumors (n = 18), and other tumors (n = 18). The median follow-up was 9.9 months (range, 1 to 21 months). Twenty-eight patients (51%) received 4 doses of nivolumab and ipilimumab; 25 patients received nivolumab maintenance for a median of 4 cycles (range, 1-18 cycles). The ORR for the entire study was 16% (80% confidence interval, 10%-25%); the ORR in the BUTCVH cohort, including 2 complete responses, was 37%, and it was 6% in the other 2 cohorts. Twenty-two patients (40%) developed treatment-related grade 3 or higher toxicities; 24% (n = 13) required high-dose steroids (≥40 mg of prednisone or the equivalent). Grade 5 events occurred in 3 patients; 1 death was treatment related.

Conclusions: Nivolumab and ipilimumab resulted in objective responses in a subset of patients with rare genitourinary malignancies, especially those with BUTCVH. An additional cohort exploring their activity in genitourinary tumors with neuroendocrine differentiation is ongoing.

Efficacy and Safety of Atezolizumab Plus Bevacizumab Following Disease Progression on Atezolizumab or Sunitinib Monotherapy in Patients with Metastatic Renal Cell Carcinoma in IMmotion150: A Randomized Phase 2 Clinical Trial. Powles T et al. Eur Urol. 2021. S0302-2838(21)00003-8.

Abstract: Objective: To evaluate the efficacy and safety of atezolizumab + bevacizumab following disease progression on atezolizumab or sunitinib monotherapy in patients with mRCC.

Results: Fifty-nine patients in the atezolizumab arm and 78 in the sunitinib arm were eligible, and 103 initiated second-line atezolizumab + bevacizumab (atezolizumab arm, n = 44; sunitinib arm, n = 59). ORR (95% confidence interval [CI]) was 27% (19-37%). The median PFS (95% CI) from the start of second line was 8.7 (5.6-13.7) mo. The median event follow-up duration was 19.4 (12.9-21.9) mo among the 25 patients without a PFS event. Eighty-six (83%) patients had treatment-related adverse events; 31 of 103 (30%) had grade 3/4 events. Limitations were the small sample size and selection for progressors.

Conclusions: The atezolizumab + bevacizumab combination had activity and was tolerable in patients with progression on atezolizumab or sunitinib. Further studies are needed to investigate sequencing strategies in mRCC.

Combination antiangiogenic tyrosine kinase inhibition and anti-PD1 immunotherapy in metastatic renal cell carcinoma: A retrospective analysis of safety, tolerance, and clinical outcomes

Methods: We conducted a retrospective analysis of mRCC patients who received combination TKI-IO post-first-line therapy between November 2015 and January 2019 at MD Anderson Cancer Center and Duke Cancer Institute. Chart review detailed patient characteristics, treatments, toxicity, and survival. Independent radiologists, blinded to clinical data, assessed best radiographic response using RECIST v1.1.

Results: We identified 48 mRCC patients for inclusion: median age 65 years, 75.0% clear cell histology, 68.8% IMDC intermediate risk, and median two prior systemic therapies. TKI-IO combinations included nivolumab-cabozantinib (N +C; 24 patients), nivolumab-pazopanib (N+P; 13), nivolumab-axitinib (6), nivolumab-lenvatinib (2), and nivolumab-ipilimumab-cabozantinib (3). The median progression-free survival was 11.6 months and the median overall survival was not reached. Response data were available in 45 patients: complete response (CR; n = 3, 6.7%), partial response (PR; 20, 44.4%), stable disease (SD; 19, 42.2%), and progressive disease (3, 6.7%). Overall response rate was 51% and disease control rate (CR+PR+SD) was 93%. Only one patient had a grade ≥3 adverse event.

Conclusion: To our knowledge, this is the first case series reporting off-label use of combination TKI-IO for mRCC. TKI-IO combinations, particularly N+P and N+C, are well tolerated and efficacious. Although further prospective research is essential, slow disease progression on IO or TKI monotherapy may be safely controlled with addition of either TKI or IO.

Outcomes of Patients with Metastatic Renal Cell Carcinoma Treated with Targeted Therapy After Immuno-oncology Checkpoint Inhibitors. Graham J. Eur Urol Oncol. 2021; 4(1), 102-111.

Objective: To describe treatment sequence and assess clinical effectiveness of targeted therapy for mRCC patients who received prior IO therapy. Design: A retrospective, longitudinal cohort study using data from eight international cancer centers was conducted. Patients with mRCC were ≥18 yr old, received IO therapy in any line, and initiated targeted therapy following IO therapy discontinuation. Patients were treated with vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR-TKIs) or mammalian target of rapamycin inhibitors (mTORIs). Outcomes were time to treatment discontinuation (TTD), overall survival (OS), and objective response rate (ORR). Crude and adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) were estimated using Cox proportional hazard models.

Results: Among 314 patients, 276 (87.9%) and 38 (12.1%) were treated with VEGFR-TKI and mTORI therapy, respectively. The most common tyrosine kinase inhibitor treatments were axitinib, cabozantinib, and sunitinib following IO therapy. In adjusted models, patients treated with VEGFR-TKI versus mTORI therapy had lower hazard of TTD after IO treatment (aHR = 0.46; 95% CI: 0.30–0.71; $p < 0.01$). One-year OS probability (65% vs 47%, $p < 0.01$) and proportion of ORR (29.8% vs 3.6%, $p < 0.01$) were significantly greater for patients treated with VEGFR-TKIs versus those treated with mTORIs.

Conclusions: Targeted therapy has clinical activity following IO treatment. Patients who received VEGFR-TKIs versus mTORIs following IO therapy had improved clinical outcomes. These findings may help inform treatment guidelines and clinical practice for patients post-IO therapy.

Real-world evidence of cabozantinib in patients with metastatic renal cell carcinoma: Results from the CABOREAL Early Access Program. Albiges L. Eur J Cancer . 2021 Jan;142:102-111.

Patients and methods: This multicentre (n = 26), observational, retrospective study enrolled patients with mRCC who had received ≥1 dose of cabozantinib. Overall survival (OS) was estimated using the Ka-

plan-Meier method; subgroups were compared using the log-rank test. A multiple Cox regression model assessed predictive factors of OS after cabozantinib initiation.

Results: Four hundred and ten recruited patients started treatment between September 2016 and February 2018: the Eastern Cooperative Oncology Group Performance Status ≥2, 39.3%; poor International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) risk, 31.7%; 0-1, 2 and ≥3 previous treatment lines, 25.3%, 33.4% and 41.2%, respectively; bone metastases, 55.9%; brain metastases, 16.8%. Median (min-max) follow-up was 14.4 (0-30) months. Overall, 57.0% of patients had a dose reduction, 15.6% an alternative dose schedule. The median average daily dose was 40.0 mg. Median (quartile [Q]1-Q3) treatment duration was 7.6 (0.1-29.1) months, median OS was 14.4 months, and the 12-month OS rate was 56.5% (95% confidence interval: 51.5-61.2). Most patients (54.4%) received subsequent treatment. Predictive factors associated with longer OS were body mass index ≥25 kg/m2 (p = 0.0021), prior nephrectomy (p = 0.0109), favourable or intermediate IMDC risk (p < 0.0001) and cabozantinib initiation at 60 mg/day (p = 0.0486).

Conclusion: In the largest real-world study to date, cabozantinib was effective in unselected, heavily pretreated patients with mRCC. Initiation at 60 mg/day was associated with improved outcomes. CLINICALTRIALS: NCT03744585.

Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. Motzer R et al. N Engl J Med. 2021 Feb 13. doi: 10.1056/NEJMoa2035716.

Results: A total of 1069 patients were randomly assigned to receive lenvatinib plus pembrolizumab (355 patients), lenvatinib plus everolimus (357), or sunitinib (357). Progression-free survival was longer with lenvatinib plus pembrolizumab than with sunitinib (median, 23.9 vs. 9.2 months; hazard ratio for disease progression or death, 0.39; 95% confidence interval [CI], 0.32 to 0.49; P<0.001) and was longer with lenvatinib plus everolimus than with sunitinib (median, 14.7 vs. 9.2 months; hazard ratio, 0.65; 95% CI, 0.53 to 0.80; P<0.001). Overall survival was longer with lenvatinib plus pembrolizumab than with sunitinib (hazard ratio for death, 0.66; 95% CI, 0.49 to 0.88; P = 0.005) but was not longer with lenvatinib plus everolimus than with sunitinib (hazard ratio, 1.15; 95% CI, 0.88 to 1.50; P = 0.30). Grade 3 or higher adverse events emerged or worsened during treatment in 82.4% of the patients who received lenvatinib plus pembrolizumab, 83.1% of those who received lenvatinib plus everolimus, and 71.8% of those who received sunitinib. Grade 3 or higher adverse events occurring in at least 10% of the patients in any group included hypertension, diarrhea, and elevated lipase levels.

Conclusions: Lenvatinib plus pembrolizumab was associated with significantly longer progression-free survival and overall survival than sunitinib. CLEAR ClinicalTrials.gov number, NCT02811861.

Open-Label, Single-Arm, Phase II Study of Pembrolizumab Monotherapy as First-Line Therapy in Patients With Advanced Non-Clear Cell Renal Cell Carcinoma. McDermott D et al. J Clin Oncol. 2021; 39(9):1029-1039.

Results: Among enrolled patients (N = 165), 71.5% had confirmed papillary, 12.7% had chromophobe, and 15.8% had unclassified RCC histology. Most patients (67.9%) had intermediate or poor International Metastatic RCC Database Consortium risk status and tumors with programmed death ligand 1 (PD-L1) combined positive score (CPS) ≥ 1 (61.8%). The median time from enrollment to database cutoff was 31.5 months (range, 22.7-38.8). In all patients, the ORR was 26.7%. The median duration of response was 29.0 months; 59.7% of responses lasted ≥ 12 months. The ORR by CPS ≥ 1 and CPS < 1 status was 35.3% and 12.1%, respectively. The ORR by histology was 28.8% for papillary, 9.5% for chromophobe, and 30.8% for unclassified. Overall, the median progression-free survival was 4.2 months (95% CI, 2.9 to 5.6); the 24-month rate was 18.6%. The median overall survival was 28.9 months (95% CI, 24.3 months to not reached); the 24-month rate was 58.4%. Overall, 69.7% of patients reported treatment-related adverse events, most commonly pruritus (20.0%) and hypothyroidism (14.5%). Two deaths were treatment related (pneumonitis and cardiac arrest).

Conclusion: First-line pembrolizumab monotherapy showed promising antitumor activity in nccRCC. The safety profile was similar to that observed in other tumor types.

KCJ MEDICAL INTELLIGENCE

Newsworthy, Late-breaking Information From Web-based Sources, Professional Societies, and Government Agencies

FDA Approves Tivozanib as First Therapy for a Relapsed/Refractory Advanced RCC Subgroup

The first therapy for adults with relapsed or refractory advanced renal cell carcinoma who have received two or more prior systemic therapies has been granted approval by the FDA. This US FDA approval was granted based on the data from the phase 2 TIVO-3 clinical trial (NCT02627963). TIVO-3 is a controlled, multicenter, open-label, phase III trial of 350 patients with highly refractory metastatic RCC who had failed ≥2 prior regimens, including VEGF TKI treatment.

Lead investigator Dr. Brian Rini of this trial (NCT02627963) along with other senior investigator Dr. Thomas Hutson discussed the TIVO-3 outcomes and prospect of tivozanib for combinatorial therapy with other IO agents (See Page 4: *Roundtable Discussion* in this issue).

Results that the hazard ratio for overall survival (OS) with tivozanib versus sorafenib was 0.97 (95% CI, 0.75-1.24; P =.78). The median OS in the tivozanib arm was 16.4 months (95% CI, 13.4-22.2) and 19.2 months in the sorafenib arm (95% CI, 15.0-24.2). The study included a subgroup of patients who received previous checkpoint inhibitor and VEGF inhibitor therapy, and in this population, the HR for death was 0.55 and was 0.57 for those who received 2 prior checkpoint or VEGF inhibitors. In terms of response, tivozanib led to an 18% (95% CI: 12%-24%) overall response rate compared with 8% (95% CI: 4%-13%) in the sorafenib arm. Tivozanib appeared to have a favorable safety profile during the study. Treatment-related adverse events (TRAEs) were observed in 84% compared with 94% of the sorafenib arm. Serious TRAEs were observed in 11% of the patients who received tivozanib compared with 10% of those treated with sorafenib.

Reference: 1. Rini BI, Pal SK, Escudier BJ, Atkins MB, Hutson TE, Porta C, Verzoni E, Needle MN, McDermott DF. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study. Lancet Oncol. 2020 Jan;21(1):95-104. PMID: 31810797.