Renal Cell Carcinoma Highlights from ASCO GU 2021: Key Updates

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DOI: 10.36000/HBT.OH.2021.08.040

Vogl U. Renal Cell Carcinoma Highlights from ASCO GU 2021: Key Updates.
healthbook TIMES Onco Hema. 2021; (8): 78–80.

Lenvatinib plus pembrolizumab is a potential first-line treatment for patients with advanced RCC

At the ASCO GU 2021, Prof. Robert Motzer presented the results of the large phase III CLEAR trial, which investigated frontline lenvatinib, a potent multi-receptor tyrosine kinase inhibitor (TKI)¹, plus pembrolizumab or everolimus in patients with advanced renal cell carcinoma (RCC).^{2,3} In this 3-arm study, 1,069 treatment-naïve patients were randomized to receive either lenvatinib (20 mg daily) plus pembrolizumab (200 mg every 3 weeks), lenvatinib (18 mg daily) plus everolimus (5 mg daily) or sunitinib (50 mg daily; 4 weeks on/2 weeks off). Most patients had prior nephrectomy and about 7% had sarcomatoid features. At data cut-off, an encouraging progression-free survival (PFS) of 23.9 months was observed with lenvatinib plus pembrolizumab, which is the longest PFS ever reported in the first-line trial in metastatic RCC. Although the median PFS was also improved with the approved combination of lenvatinib plus everolimus (14.7 months vs 9.2 months with sunitinib), a significant overall survival (OS) benefit was observed only with lenvatinib plus pembrolizumab versus sunitinib (HR: 0.66 [95% CI: 0.49–0.88]; $p=0.005$). Patients treated with the combination of lenvatinib and pembrolizumab also achieved an impressive

confirmed objective response rate (ORR), with a clinical benefit rate of 94.6% and a complete response (CR) rate of 16.1%. In terms of safety, there was a higher incidence of grade ≥ 3 toxicity and dose reduction in both lenvatinib-based arms versus the sunitinib arm. Lenvatinib plus pembrolizumab induced diarrhea in 54.5% and hypertension in 52.3% of patients, while hypothyroidism occurred in 42.6% of patients. In conclusion, lenvatinib plus pembrolizumab is a novel combination in the treatment armamentarium of previously untreated clear cell (cc) RCC. However, before integrating this regimen into daily clinical practice, the awaiting approval and treatment guidelines are required.

Cabozantinib is a new standard for metastatic papillary RCC

Papillary RCC, which accounts for 15–20% of cases of RCC, is often associated with *MET* mutations.⁴ At ASCO GU 2021, Dr Sumanta Pal presented the findings from the 4-arm, phase II SWOG 1500 trial, which assessed sunitinib, a current standard of care, versus putative *MET* kinase inhibitors in patients with papillary RCC. Patients with a histologically confirmed diagnosis of papillary RCC who received ≤ 1 prior line of treatment were randomized to receive either sunitinib ($n=46$), cabozantinib

(n=44), crizotinib (n=28) or savolitinib (n=29). Most of the patients had type II papillary RCC and about 7% of patients received prior systemic therapy. At data cut-off, cabozantinib significantly prolonged PFS compared with sunitinib (HR: 0.60 [95% CI: 0.37–0.97]; $p=0.019$). Confirmed ORR was 23% with cabozantinib and 4% with sunitinib ($p=0.010$), with partial responses of 18% and 4%, respectively. Regarding the other two MET kinase inhibitors, the prespecified futility analysis led to the closure of the crizotinib and savolitinib arms. Based on these results, cabozantinib is a new standard for metastatic papillary RCC.

Belzutifan alone or in combination with cabozantinib in pretreated patients with advanced RCC

MK-6482 (belzutifan) is a potent, selective, small-molecule hypoxia-inducible factor (HIF)-2 α inhibitor, which demonstrated promising efficacy and tolerability in patients with Von Hippel-Lindau disease (VHL)-associated clear cell (cc) RCC.⁵ At ASCO GU 2021, the results of a phase I/II study assessing the efficacy of belzutifan in 55 patients with advanced ccRCC were presented.⁶ The median age was 62 years and 80% were male. Patients were treated with a median of 3 prior systemic therapies (range: 1–9); mostly with anti-programmed cell death protein 1 (PD-1) and anti-vascular endothelial growth factor (VEGF)/VEGF receptor agents. The response rate was about 25% in the overall population and 24% among patients with IMDC intermediate/poor group (n=42). The disease control rate was 80%, while 64% of patients had a reduction in target lesion size. An impressive median PFS of 14.5 months was achieved in this heavily-pretreated patient population.

In another phase II study, belzutifan (120 mg daily) in combination

with cabozantinib (60 mg daily) was investigated in 52 patients with advanced or metastatic ccRCC who had received prior immunotherapy treatment.⁷ In the efficacy population (n=41), the response rate was 22%, which was similar to the phase I/II study on belzutifan monotherapy.⁶ The disease control rate with belzutifan plus cabozantinib was remarkable, with 90% of patients responding and only 7% having a progressive disease (PD).⁷ The median PFS was 60 months. In terms of safety, most patients developed anemia, with 12% of patients experiencing grade 3 anemia. This adverse event (AE) was manageable, and no treatment interruption occurred due to anemia. Furthermore, treatment-related hypoxia was rare and occurred in approximately 4% of patients.

At our center at the IOSI in Ticino, we are currently enrolling patients for a phase III study investigating belzutifan in combination with lenvatinib versus cabozantinib as a second- or third-line treatment for ccRCC patients who progressed after immunotherapy with a checkpoint inhibitor.⁸ In the near future, other centers in Switzerland will be included in this study for which I encourage everyone to recruit patients.

Real-world evidence: First-line immuno-oncology combination therapies in metastatic RCC

At ASCO GU 2021, Dr Chun Loo Gan presented the real-world data from the International Metastatic RCC Database Consortium (IMDC), which assessed clinical outcomes of ipilimumab plus nivolumab and immuno-oncology (IO) plus VEGF inhibitor combinations in patients with metastatic RCC.⁹ In this study, 571 patients were treated with ipilimumab plus nivolumab and 152 patients with different IO-VEGF combinations, mainly with

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pembrolizumab plus axitinib. About 8% of the ipilimumab plus nivolumab-treated and 2% of the IO-VEGF-treated patients had brain metastases, while 59% and 75% of patients, respectively, had nephrectomy. Among patients in the IMDC intermediate/poor group, there was an ORR of 37% with ipilimumab plus nivolumab and 59% with IO-VEGF regimens, with rates of partial remission of 33% and 55% and PD of 31% and 15%, respectively. These results indicate that most of the patients benefit from currently available first-line treatment combinations, with a high likelihood of a response to treatment. Data further showed no significant difference in median OS (HR: 0.92 [95% CI: 0.61–1.40]; $p=0.71$) and the time to next treatment ($p=0.11$) between the two treatment groups. Regarding safety, similar rates of AEs were observed with both treatment regimens. Of note, those patients who developed immune-related AEs had better OS outcomes, which is consistent with the experience in clinical practice. The study also did not identify clinical predictive factors for treatment selections, suggesting both treatment combinations as reasonable first-line strategies.

Frontline treatment options for ccRCC: Current guidelines and the future

In the current ESMO guidelines, first-line treatment options include pembrolizumab plus axitinib among all ccRCC patients and ipilimumab plus nivolumab among those with intermediate- and poor-risk disease; both therapies are approved by Swissmedic.¹⁰ A recent update also integrated cabozantinib plus nivolumab for the treatment of ccRCC regardless of risk status, but this combination has not yet been authorized in Switzerland. Based on data presented at ASCO GU 2021, the pembrolizumab and lenvatinib doublet is also a viable treatment combination in the RCC setting.

Currently, there are several ongoing clinical trials investigating further first-line treatment options for ccRCC. The phase III PDIGREE trial is an innovative study with a tailored immunotherapy approach assessing the combination of nivolumab plus ipilimumab, followed by nivolumab monotherapy in case of complete response and cabozantinib alone or cabozantinib plus nivolumab in case of partial response or PD, respectively.¹¹ Another trial utilizing a tailored immunotherapy approach is the phase II TITAN RCC study investigating nivolumab, followed by nivolumab plus ipilimumab in patients with PD.¹² In the neoadjuvant setting, a phase II study is currently evaluating cytoreductive surgery plus nivolumab and

cabozantinib in patients with metastatic RCC.¹³ Furthermore, the COSMIC313 trial aimed to test ipilimumab plus nivolumab with or without cabozantinib in treatment-naïve RCC patients¹⁴, while another phase III study will evaluate belzutifan versus everolimus in patients with ccRCC who progressed after prior PD-1/L1 and VEGF-targeted therapies.

In conclusion, there are still many unanswered questions in terms of treatment selection and treatment optimization. Currently, there are four available first-line therapy options and treatment selection should be based on the patients' preferences and safety profiles of different combination strategies. Furthermore, in the intermediate/poor-risk group, there is uncertainty whether those patients should be treated with immunotherapy with or without a TKI. Another open question is whether treatment should be discontinued after optimal response, which also includes the issue of financial toxicity. Finally, the challenges of treatment reduction with adaptive strategies and subsequent treatment options after immunotherapy is an area that needs to be resolved in the future.

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