Highlights in Non-Prostate Genitourinary Tumors at ESMO 2021: Revolutionizing Management Options for Better Therapy

DOI: 10.36000/HBT.OH.2021.10.059
Cathomas R. Highlights in Non-Prostate Genitourinary Tumors at ESMO 2021: Revolutionizing Management Options for Better Therapy. *healthbook TIMES Onco Hema.* 2021;(10):34–35.

PD Dr Richard Cathomas
Division of Oncology and Internal Medicine
Cantonal Hospital of Graubünden
Chur, Switzerland

Changes in treatment scheduling may lead to clinical benefit in patients with metastatic renal cell carcinoma

STAR is a UK phase II/III multicenter, randomized controlled trial designed to determine if a tyrosine kinase inhibitor (TKI) drug-free interval strategy (DFIS) was non-inferior to a conventional continuation strategy (CCS) in the first-line treatment of advanced renal cell carcinoma (RCC).[1] A total of 920 patients were randomized 1:1 to DFIS or CCS. After 24 weeks of sunitinib or pazopanib treatment, DFIS patients took a treatment break, until disease progression, with additional breaks dependent on disease response and patient/clinician choice. In a proof of concept trial, a phase II study of intermittent sunitinib in previously untreated patients with metastatic RCC demonstrated no evidence of excessive tumor growth at discontinuation and presented encouraging survival outcomes.[2]

The primary endpoint was overall survival (OS) and it must demonstrate predefined noninferiority (≤7.5%) in intention-to-treat (ITT) and per-protocol (PP) population.[1] The trial met its endpoint in the ITT population (HR: 0.97 [95% CI: 0.83–1.12]) but not in PP population (HR: 0.94 [95% CI: 0.80–1.09]). In addition, patients on the intermittent schedule did not have a negative impact on their quality of life and therefore did not experience symptomatic progression. Furthermore, a substantial financial saving was also observed for patients receiving the intermittent schedule. Although first-line single-agent TKIs are no longer the standard of care for patients in this setting, this study suggests that changes to TKI management may be of clinical significance.

The phase II PRISM trial evaluated nivolumab in combination with alternatively scheduled ipilimumab in the first-line treatment of patients with advanced RCC.[3] A total of 192 patients were randomized 1:2 to receive 4 doses of ipilimumab once every 3 weeks (conventional) or once every 12 weeks (modified ipilimumab), in combination with nivolumab, until disease progression or unacceptable toxicity. The primary endpoint was the proportion of patients with a grade 3–4 treatment-related adverse event (TRAE) within 12 months of initiating the treatment, while the secondary endpoint included progression-free survival (PFS) at 12 months and objective response rate (ORR). The trial met its primary endpoint as TRAEs were significantly lower amongst patients receiving modified ipilimumab compared with conventional ipilimumab (32.8% v 53.1%; odds ratio: 0.43 [90% CI: 0.25–0.72]; p=0.0075), corresponding to a reduction of grade 3–4 adverse events (AEs) by 20.3%. This reduction was mostly in arthralgia (1.6% vs 7.8%), colitis (3.9% vs 6.3%), increased creatinine (0% vs 1.6%) and increased lipase (1.6% vs 9.4%). While this study was not sufficiently powered to compare the efficacy, the PFS for patients with intermediate and poor-risk of experiencing an AE are similar, and the same is true for OS. This study highlights that the benefit of TKIs may differ according to their treatment schedule. The benefit for the patients is a decrease in toxicity, leading to an improved quality of life. Patient adherence may also improve, which could impact the efficacy of the treatment. In conclusion, further studies are warranted into schedule changes of novel drug combinations in the first-line treatment of advanced RCC.

Next steps to improve management of patients with urothelial carcinoma

The phase II NORSE trial investigated the efficacy and safety of erdafitinib, a fibroblast growth factor receptor (FGFR) inhibitor or erdafitinib plus cetrelimab, a programmed cell death protein 1 (PD-1) inhibitor in patients with metastatic or locally advanced urothelial carcinoma and FGFR alterations.[4] The trial enrolled adult patients with no prior systemic therapy and were selected for *FGFR2* or *FGFR3* mutations (or fusions). Patients were then randomized 1:1 to receive either erdafitinib alone or erdafitinib plus cetrelimab. The primary endpoints were investigator-assessed overall response rate (ORR) and safety. The secondary included disease control rate (DCR), time to response (TTR), and duration of response (DOR). In the erdafitinib monotherapy group, an ORR of 33% was reported compared with 68% in the cetrelimab/erdafitinib dual therapy group. In addition, 6% of the patients attained complete remission (CR) in the monotherapy group versus 21% in the dual therapy group. Regarding side effects, FGFR inhibitors can lead to hyperphosphatemia,[5] while PD-1 inhibitors may cause colitis and diarrhea.[6] In conclusion, it appears worthwhile to further investigate this treatment regimen, given its promising efficacy.

The VESPER trial was a practice-changing, phase III study conducted in France that investigated the use of neoadjuvant or adjuvant chemotherapy in patients with nonmetastatic muscle-invasive bladder cancer (MIBC).[7] Patients were randomly assigned to two different chemotherapy regimens: either four cycles of cisplatin gemcitabine (GM/CS) or six cycles of dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (dd-MVAC) repeated every two weeks (with granulocyte-colony stimulating factor [G-CSF] support) before surgery (neoadjuvant group) or after surgery (adjuvant group). The majority of the patients (88%) in the trial received neoadjuvant treatment and 60% of these patients received the planned six cycles in the dd-MVAC arm. The pathological response rate was better in the dd-MVAC group with 42%, compared with 36% for the GM/CIS group. Interestingly, the side effect profile between the two groups was similar; however, the dose-dense MVAC group was supported with G-CSF treatment. Compared with other phase II trials, the complete pathological response rate of 42% in the VESPER trial is among the highest rate achieved. The primary endpoint of PFS was not met for the whole trial population since the adjuvant patients did not benefit as much from dd- MVAC. However, for the neoadjuvant chemotherapy patients, there is a clear and significant difference in favor of dd-MVAC. Taken together, dd-MVAC cisplatin-based chemotherapy should be considered as a new standard of care for fit patients.

Swiss study reports promising new results in the treatment of testis cancer

The trial SAKK 01/10 of the Swiss Group for Clinical Cancer Research (SAKK) is a multicenter, single-arm, phase II study in patients with lymph node metastatic seminoma clinical (CS) stage IIA/B.[8] Standard treatment options for this patient population are either extensive "dog-leg" para-aortic/pelvic radiotherapy (RT) or 3-4 cycles of cisplatin-based combination chemotherapy (ChT). Out of a total of 120 patients who were included in the trial, 116 eligible patients received one cycle of carboplatin AUC7 followed by involved-node radiotherapy after three weeks. The primary endpoint was PFS at three years. With a target PFS at 3 years of 95%, 120 patients were required to show that the lower limit of a two-sided 90% confidence interval is >90%. At a median follow-up of 4.5 years, the three-year overall PFS rate was 93.7% (90% CI: 88.5%–96.6%), with only seven patients relapsing, one of whom with seminoma stage IIA and six patients with seminoma stage IIB. In fact, the failure of the trial to meet its primary endpoint of lower level of confidence interval of 90% was due to the death of a patient by causes unrelated to seminoma. In terms of safety, the de-escalated treatment regimen was very well tolerated with few acute toxicity events. Furthermore, the median planning target volume for radiotherapy was reduced by 75% compared with the standard of care. In summary, the efficacy of the de-escalated treatment regimen is similar to the standard of care options with polychemotherapy or extensive "dog-leg" RT. It appears to be an effective and well-tolerated treatment option for patients in this setting and a follow-up trial is already ongoing in Switzerland and Germany.

1. Brown JE, Royle KL, Ralph C, et al. LBA28 STAR: A randomised multi-stage phase II/III trial of standard first-line therapy (sunitinib or pazopanib) comparing temporary cessation with allowing continuation, in the treatment of locally advanced and/or metastatic renal Cancer (RCC). *Ann Oncol.* 2021;32(suppl_5):S1303-S1304. doi:10.1016/j.annonc.2021.08.2104
2. Ornstein MC, Wood LS, Elson P, et al. A Phase II Study of Intermittent Sunitinib in Previously Untreated Patients With Metastatic Renal Cell Carcinoma. *J Clin Oncol.* 2017;35(16):1764-1769. doi:10.1200/JCO.2016.71.1184
3. Vasudev NS, Ainsworth G, Brown S, et al. LBA29 Nivolumab in combination with alternatively scheduled ipilimumab in first-line treatment of patients with advanced renal cell carcinoma: A randomized phase II trial (PRISM). *Ann Oncol.* 2021;32(suppl_5):S1304-S1305. doi:10.1016/j.annonc.2021.08.2105
4. Powles TB, Chistyakov V, Beliakouski V, et al. LBA27 Erdafitinib (ERDA) or ERDA plus cetrelimab (CET) for patients with metastatic or locally advanced urothelial carcinoma (mUC) and Fibroblast Growth Factor Receptor alterations (FGFRa): First phase (Ph) II results from the NORSE study. *Ann Oncol.* 2021;32(suppl_5):S1303. doi:10.1016/j.annonc.2021.08.2103
5. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol.* 2020;21(5):671-684. doi:10.1016/S1470-2045(20)30109-1
6. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer. *N Engl J Med.* 2015;372(21):2018-2028. doi:10.1056/NEJMoa1501824
7. Pfister C, Gravis G, Fléchon A, et al. Randomized Phase III Trial of Dose-dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin, or Gemcitabine and Cisplatin as Perioperative Chemotherapy for Patients with Muscle-invasive Bladder Cancer. Analysis of the GETUG/AFU V05 VESPER Trial Secondary Endpoints: Chemotherapy Toxicity and Pathological Responses. *Eur Urol.* 2021;79(2):214-221. doi:10.1016/j.eururo.2020.08.024
8. Papachristofilou A, Bedke J, Hayoz S, et al. LBA30 Single-dose carboplatin followed by involved-node radiotherapy as curative treatment for seminoma stage IIA/B: Efficacy results from the international multicenter phase II trial SAKK 01/10. *Ann Oncol.* 2021;32(suppl_5):S1305. doi:10.1016/j.annonc.2021.08.2106