Genitourinary (Non-Prostate) Cancers: 2021 ASCO Annual Meeting Highlights for the Advanced Practitioner

Following coverage from *The ASCO Post*, **Emily Lemke, DNP, AGPCNP-BC, AOCNP®,** of Medical College of Wisconsin Cancer Center, comments on an adjuvant trial of a checkpoint inhibitor for clear cell renal cell carcinoma (RCC), real-world data comparing first-line platinum regimens for patients with metastatic urothelial carcinoma, and combination regimens for RCC.

Abstract LBA5

KEYNOTE-564: Adjuvant Pembrolizumab Extends Disease-Free Survival in High-Risk Renal Cell Carcinoma

By Alice Goodman

Visit https://meetinglibrary.asco.org/record/196683/abstract to read the full abstract and view author disclosures.

Adjuvant pembrolizumab following surgery significantly improved disease-free survival compared with placebo among patients with high-risk clear cell renal cell carcinoma (RCC), according to the international phase III KEYNOTE-564 study presented at the Plenary session during the 2021 ASCO Annual Meeting.[1] The addition of the immune checkpoint inhibitor as adjuvant therapy led to a 32% reduction in the risk of disease recurrence or death compared with placebo.

"KEYNOTE-564 is the first phase III study to show an improvement in disease-free survival with adjuvant immunotherapy in patients with high-risk, fully resected clear cell RCC, the most common type of kidney cancer. The improvement in disease-free survival was statistically significant and clinically meaningful. KEYNOTE-564's disease-free survival supports pembrolizumab as a potential new standard of care in renal cell carcinoma," said lead author Toni K. Choueiri, MD, of Dana-Farber Cancer Hospital, Boston.

Background

Renal cell carcinoma is common in both men and women, responsible for 175,000 deaths worldwide in 2018. At diagnosis, most patients present with localized disease, but up to 40% will develop metastatic disease after surgery.

Partial or radical nephrectomy to remove the tumor is commonly used to treat RCC. Patients with intermediate- to high-risk advanced disease are at risk for relapse, and there are no standard treatment options after surgery to prevent relapse.

"Despite surgery, recurrence is common in clear cell RCC, and should it recur, there are limited curative treatments for patients. Given the success of pembrolizumab in the KEYNOTE-564 trial, this population may soon have a new standard of care," said ASCO Chief Medical Officer and Executive Vice President Julie R. Gralow, MD, FACP,

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FASCO, at a premeeting press conference where these findings were previewed.

Study Details

The randomized, double-blind, multicenter KEYNOTE-564 trial enrolled 994 patients with histologically confirmed high-risk clear cell RCC who had undergone nephrectomy at least 12 weeks prior to randomization. Patients had no prior systemic therapy. They were randomly assigned 1:1 to receive adjuvant pembrolizumab at 200 mg every 3 weeks for up to 17 cycles (about 1 year) or placebo. The primary endpoint was disease-free survival per investigator's assessment; overall survival and safety were secondary endpoints.

Key Findings

At a median follow-up of 24 months, the primary endpoint was met. Median disease-free survival was not reached in either treatment arm. Pembrolizumab reduced the risk of recurrence or death by 32% compared with placebo, and this difference was statistically significant (P = .0010). The 12-month disease-free survival was 85.7% with pembrolizumab vs 76.2% with placebo. At month 24, the rate of disease-free survival was 77.3% vs 68.1%, respectively.

"There was about a 10% absolute difference [in disease-free survival] between both arms at 12 months and 24 months," Dr. Choueiri told listeners.

Survival data are premature, but at month 24, 96.6% of the pembrolizumab group were alive vs 93.5% of the placebo group, representing a 46% reduction with pembrolizumab. There were 18 deaths in the pembrolizumab group vs 33 in the placebo group. Additional follow-up is planned.

Toxicity

"Safety results were in line with expectations, and there were no new safety signals with pembrolizumab," Dr. Choueiri said.

All-cause adverse events were reported in 96.3% of the pembrolizumab group vs 91.1% of the placebo group. Grade 3 to 5 adverse events occurred in 32.4% vs 17.7%, respectively. There were two deaths in the pembrolizumab arm and one in the placebo arm due to all-cause adverse events.

Treatment-related adverse events were reported in 79.1% of the pembrolizumab arm vs 53.4% of the placebo arm. Grade 3 to 5 treatment-related adverse events occurred in 18.9% vs 1.2%, respectively. No deaths due to treatment-related adverse events were reported.

Reference

1. Choueiri TK, Tomczak P, Park SH, et al: Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for patients with renal cell carcinoma: Randomized, double-blind, phase III KEYNOTE-564 study. 2021 ASCO Annual Meeting. Abstract LBA5. Presented June 6, 2021.

The Advanced Practitioner Perspective

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Despite the FDA approval for adjuvant sunitinib (Sutent) for patients with high-risk renal cell carcinoma (RCC), the excitement for adjuvant therapies has been lackluster given the absence of overall survival (OS) benefit coupled with significant toxicity. The results of KEYNOTE-564 have the potential to be practice changing given the impact on disease-free survival (DFS) and acceptable toxicity profile.

KEYNOTE-564 is a phase III, multicenter trial of pembrolizumab vs. placebo in patients with intermediate-high risk, high-risk, or M1 no evidence of disease (NED) clear cell RCC following nephrectomy. Patients were randomized to either placebo or pembrolizumab within 12 weeks following nephrectomy, and treatment was given for up to 17 cycles (roughly 1 year). The primary endpoint, DFS, was 77.3% in the pembrolizumab arm vs. 68.1% in the placebo arm at 24 months. Follow-up is planned to report on OS—a key secondary outcome.

This is the first reported adjuvant trial for clear cell RCC with a checkpoint inhibitor. The inclusion of M1 NED patients is notable and addresses an unmet need in adjuvant trials given the role of metastasectomy in M1 RCC. In the current era of immunotherapy, advanced practitioners are well versed in managing these therapies and their side effects, making this a seamless addition to day-to-day practice should FDA approval be granted. However, questions re-

main, primarily on the impact on OS, as well as how adjuvant immunotherapy might impact future immunotherapy use in the metastatic setting. Advanced practitioners should be familiar with DFS and the ideal patient population in which adjuvant therapy should be considered.

Disclosure: Dr. Lemke has no conflicts of interest to disclose.

Abstract 4535

Choice of First-Line Platinum Chemotherapy Does Not Significantly Impact Efficacy of Second-Line Immunotherapy in Advanced Urothelial Carcinoma

By The ASCO Post Staff

Visit https://meetinglibrary.asco.org/record/197294/abstract to read the full abstract and view author disclosures.

In a presentation of real-world data given during the 2021 ASCO Annual Meeting, Miron et al concluded that the choice of first-line platinum chemotherapy did not result in a significant difference in overall survival benefit among patients with advanced bladder cancer who were able to go on to receive second-line immunotherapy (Abstract 4535).

"Over the last 5 years, we have seen major advances in the treatment of advanced bladder cancer with the approval of immunotherapy in the second-line and maintenance settings after treatment with platinum chemotherapy," said Benjamin Miron, MD, a second-year hematology/oncology fellow at Fox Chase Cancer Center. "These new options give us this opportunity to reflect on the data we have in the first line and ask new research questions."

The standard of care for first-line treatment of patients with advanced bladder cancer is either cisplatin or carboplatin—both platinum-containing chemotherapy regimens.

"Carboplatin is a modified version of cisplatin, and the changes to the molecule influence both its toxicity and also efficacy based on its ability to bind DNA," Dr. Miron said. "In clinical practice, it has been shown that cisplatin is a more effective therapy for [patients with] bladder cancer, but it is also more toxic and, as a result, not all patients can tolerate cisplatin well."

Study Details

The study examined whether the established efficacy benefit of first-line treatment with cisplatin compared with carboplatin remained significant among patients who went on to receive immunotherapy in the second-line setting.

Using data from the nationwide Flatiron Health deidentified database, they studied 780 patients diagnosed with advanced bladder cancer who were treated with either first-line cisplatin plus gemcitabine or carboplatin plus gemcitabine and went on to receive second-line immunotherapy.

"We found that survival for patients treated first with cisplatin was numerically longer than carboplatin, but the difference was not statistically significant," Dr. Miron said.

Patients who received first-line cisplatin did have a significantly longer time to receipt of second-line immunotherapy, but there was no difference in survival time on second-line therapy between the two platinum regimens.

Recently, the U.S. Food and Drug Administration approved one immunotherapy treatment as a maintenance therapy for patients whose disease is controlled by first-line platinum chemotherapy. This treatment strategy has shown an overall survival benefit and has become the standard of care in patients who are eligible. Otherwise, immunotherapy regimens are reserved in the first line for patients who are ineligible for platinum therapy or have high PD-L1 expression and are in the second line.

Studies have shown that treatment approaches combining chemotherapy and immunotherapy or using immunotherapy alone in the first line do not have a benefit compared with chemotherapy in patients with advanced disease.

Because this study was retrospective, the results should not change clinical practice. But, Dr. Miron added, "The results certainly help us quantify and better understand the magnitude of benefit of cisplatin vs carboplatin in the era of immunotherapy and potentially allow the patient and clinician to feel more comfortable about the use of carboplatin."

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Real-world data provides useful insight for advanced practitioners and physicians alike when making day-to-day clinical decisions for patients receiving standard-of-care systemic therapies. This abstract addresses a practical consideration for patients with metastatic urothelial carcinoma (mUC) who are deemed cisplatin ineligible: Is first-line carboplatin good enough? Based on this retrospective data, the answer is yes.

This data set specifically focused on patients with mUC who received first-line gemcitabine + cisplatin (gem/cis) or gemcitabine + carboplatin (gem/carbo) and then went on to receive second-line immunotherapy. Second-line immunotherapy included pembrolizumab (Keytruda), nivolumab (Opdivo), avelumab (Bavencio), atezolizumab (Tecentriq), and durvalumab (Imfinzi). Miron and colleagues conclude there is no statistically significant overall survival (OS) benefit between gem/cis and gem/carbo.

Unfortunately, results were not stratified based on the second-line immunotherapy that was selected. In the current era, some of the previously used immunotherapies have fallen out of favor with a clear preference for pembrolizumab, given its Category 1 designation. Therefore, we cannot know how second-line immunotherapy selection impacted the OS between these two groups. However, the utility of this abstract for advanced practitioners should center around the reassurance that choosing carboplatin has similar outcomes as compared to cisplatin with a potentially more favorable toxicity profile. This can help guide discussions with patients about toxicity and efficacy of both platinum regimens.

Disclosure: Dr. Lemke has no conflicts of interest to disclose.

Abstract 4551

No Survival Difference for Front-Line Combination Regimens in Intermediate- and Poor-Risk Clear Cell RCC: Real-World Outcomes

By The ASCO Post Staff

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A large retrospective study of real-world patients with renal cell carcinoma (RCC) showed similar survival outcomes for patients with intermediate- or poor-risk disease regardless of whether they were treated with the combination of axitinib plus pembrolizumab or ipilimumab plus nivolumab. These findings were presented by Zarrabi et al during the 2021 ASCO Annual Meeting (Abstract 4551).

"Clinicians can take some reassurance that both combinations provide a survival benefit, and there seems to be no harm in choosing one combination over the other based on this analysis," said Kevin Zarrabi, MD, a second-year hematology/oncology fellow at Fox Chase Cancer Center and lead author of the study.

Front-Line Treatment for RCC

Front-line treatment for patients with metastatic clear cell RCC has changed rapidly in the last few years, first with the approval of targeted agents like sunitinib and everolimus, and later with the approval of combination axitinib plus pembrolizumab and ipilimumab plus nivolumab, Dr. Zarrabi said.

"Both of the newer combination regimens showed marked advances in progression-free survival in patients with kidney cancer and were considered giant leaps forward," he explained. "With no prospective data comparing the regimens, questions remained about which is the better option for these patients."

Axitinib/Pembrolizumab vs Ipilimumab/Nivolumab

To evaluate that question, Dr. Zarrabi and colleagues used data from 821 patients with metastatic clear cell RCC treated with either axitinib plus pembrolizumab (n = 259) or ipilimumab plus nivolumab (n = 562) taken from the nationwide Flatiron Health electronic health records–de-

rived, de-identified database. All patients in the study had International Metastatic RCC Database Consortium (IMDC) intermediate- or poor-risk disease.

"By looking at real-world patients, we are looking at the actual outcomes in patients across the country treated at academic or community practices," Dr. Zarrabi said. "This provides an advantage because clinical trials often have strict inclusion or exclusion criteria and do not account for many patients that we encounter in the general population."

At 12 months' follow-up, there was no significant difference in survival between patients treated with either combination regimen. The median overall survival was not reached for axitinib plus pembrolizumab and was 22 months for ipilimumab plus nivolumab. The 12-month survival was 68.5% for patients treated with axitinib/pembrolizumab and 65.8% for patients treated with ipilimumab/nivolumab.

"This large, real-world retrospective analysis—with the caveat of limited follow-up—shows that both therapies are appropriate for [International Metastatic RCC Database Consortium] intermediate- and poor-risk disease, and appear to confer similar survival," said Daniel M. Geynisman, MD, Associate Professor in the Department of Hematology/Oncology at Fox Chase and senior author of the study. "Therefore, clinicians should take into account multiple clinical factors when making treatment decisions for these patients."

Clinicians may choose one regimen over another due to patient comorbidities, familiarity with study data, or comfort with administering the drugs, Dr. Zarrabi said.

Dr. Geynisman noted that one key remaining question will be how these outcomes evolve over time and whether they remain similar for both regimens, and the team will be looking at that with longer term follow-up data.

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After many years of tyrosine kinase inhibitor (TKI) monotherapy reigning as the standard of care for front-line metastatic clear cell renal cell carcinoma (mccRCC), combination therapy with both immunotherapy doublets and TKI/immunotherapy combinations has changed the landscape of mccRCC. Given the multiple FDA approvals for combination therapies, all backed with compelling data as compared to single-agent TKIs, clinicians are faced with the million-dollar question in the current era: Which first-line combination therapy is best?

Zarrabi and colleagues report on retrospective, real-world outcomes for patients with mccRCC receiving front-line axitinib (Inlyta) + pembrolizumab (axi/pembro) vs. front-line nivolumab + ipilimumab (nivo/ipi). This retrospective data set included a total of 821 patients with the primary endpoints of overall survival (OS) and real-world progression-free survival (rwPFS). Twelve-month survival was reported to be 68.5% for axi/pembro and 65.8% for nivo/ipi; this was not statistically different irrespective of International Metastatic RCC Database Consortium (IMDC) risk category. Twelve-month rwPFS was reported to be 41.4% for axi/pembro and 39.7% for nivo/ipi.

This real-world data set does not answer which regimen is superior, and longer follow-up is needed to report any significant survival differences. With multiple TKI/immunotherapy regimens available in the front-line space, more studies are needed to clarify which regimen is ideal. In future reporting, advanced practitioners should pay special attention to outcomes such as complete response and toxicity. Other key population characteristics to be mindful of in real-world data sets include IMDC risk score, percentage of patients with prior nephrectomy, and metastatic burden.

Disclosure: Dr. Lemke has no conflicts of interest to disclose.