Summary of Kidney Cancer Highlights from ASCO 2024

This year's American Society of Clinical Oncology (ASCO) Annual Meeting was held from 1-5 June 2024, in Chicago, USA. The presentations are available to view on the ASCO website. Some affiliates of the International Kidney Cancer Coalition (IKCC) went to the meeting to keep up to date with the care and treatment of patients with kidney cancer. A brief "Take home messages" section is followed by more in-depth review of selected abstracts.

Please note: The following summary was prepared for the benefit of patient advocates and patient organisations around the world who focus on kidney cancer. While this summary has been medically reviewed, the information contained herein is based upon public data shared at this meeting and is not intended to be exhaustive or act as medical advice. Patients should speak to their doctor about their own care and treatment.

Take home messages

There were several interesting presentations about biomarkers for kidney cancer at ASCO this year. The presentations analysed biomarkers from tumour and blood samples taken from patients in the CLEAR, KEYNOTE-426 and IMmotion101 studies. There was also a presentation about a biomarker for the early detection of kidney cancer.

In **abstract 4504**, none of the biomarkers that were evaluated proved to be predictive of a better response to treatment with pembrolizumab plus lenvatinib. However, the combination therapy was superior to treatment with sunitinib regardless of biomarker expression.

In **abstract 4505**, researchers found that high levels of an inflammatory biomarker in the tumour, $Tcell_{inf}GEP$, were associated with better outcomes in patients treated with pembrolizumab and axitinib. However, regardless of biomarker status, patients did better on pembrolizumab plus axitinib when compared to sunitinib, and this biomarker does not help us choose between regimens.

Importance: The results from these trials help researchers identify biomarkers that could predict better outcomes, and even help in decisions about treatments for each individual patient. However, based on these results, the combination therapy remains superior to sunitinib, regardless of biomarker expression, and more work needs to be done to refine these biomarker strategies.

In **abstract 4506**, researchers suggested that elevated KIM-1 may be a biomarker to identify patients with higher risk of recurrence of kidney cancer, and to select for patients that will

benefit from adjuvant treatment with atezolizumab. **Importance:** the goal of adjuvant therapy is to prevent disease recurrence; however, some patients will be cured with surgery alone. Biomarkers, such as KIM-1, could aid in the identification of patients that are at higher risk of recurrence and will benefit of additional treatment.

In **abstract 4526**, CA-62 proved to be a useful biomarker for early detection of kidney cancer. However, because it is not a specific biomarker for kidney cancer, the use of other biomarkers, in addition to CA-62, could become a strategy for kidney cancer screening.

In **abstract 4532**, an injectable form of nivolumab (subcutaneous nivolumab) was compared to nivolumab that is given by infusion into a vein (intravenous nivolumab). Subcutaneous nivolumab was shown to be as good as intravenous nivolumab. The safety of the subcutaneous nivolumab was comparable to that of intravenous nivolumab; immune-related side effects were manageable, and patients reported minimal bother by treatment side effects. **Importance:** These results support the use of subcutaneous nivolumab as an option for improving patient experience and is preferred by patients.

In **abstract 4508**, long-term survival data was presented for the avelumab plus axitinib combination compared to sunitinib in untreated patients with advanced kidney cancer. The avelumab plus axitinib combination did not significantly improve overall survival. **Importance:** These results confirm the approach of combining TKIs with immunotherapy for the treatment of advanced kidney cancer with long-term effectiveness and manageable side effects.

In **abstract 4512**, the analysis showed that combination therapies improved clinical outcomes for patients with metastatic chromophobe RCC compared to single therapies. **Importance:** The researchers are continuing this work and collaborating with other centres to increase the number of patients with metastatic chromophobe RCC in this study to collect further data and compare outcomes with other treatments.

In **abstract TPS4611**, a new VEGFR TKI called zanzalintinib was shown to be safe and effective in patients with metastatic clear cell RCC in a phase 1 study. This abstract describes a phase 3 randomised global study of zanzalintinib plus nivolumab in patients with advanced/metastatic non-clear cell RCC. **Importance:** The STELLAR-304 study is currently recruiting patients in Europe, North and South America, and the Asia Pacific region.

Abstract TPS610 describes a study with a new treatment for untreated metastatic kidney cancer, ^{177}Lu girentuximab. Girentuximab is an antibody that is used to deliver radioactive lutetium (^{177}Lu) directly to the cancer cells. Once in the cell, the radiation leads to DNA damage and cell death. This study hopes to show that damage to the tumour cell DNA caused by ^{177}Lu girentuximab will activate the T cells of the immune system to attack the cancer cells. **Importance:** The study is about to start recruiting patients at MD Anderson Cancer Centre, Houston, Texas, USA.

Summaries

Potential biomarkers for advanced kidney cancer

A biomarker is something that can be measured in the blood, urine or body tissue to indicate a biological state, disease or condition. In cancer, a biomarker could be protein circulating in the blood, a protein expressed in the tumour cell or a gene mutation. Biomarkers have multiple functions, they could help diagnose the disease, predict its response to therapy and could give information about the prognosis of a patient.

Currently, the prediction of outcomes for patients with kidney cancer is based on the stage, grade, subtype, and overall health of the patient. Reliable biomarkers for predicting the response of individual patients to kidney cancer treatments and the outcomes of the disease are an unmet need. The identification of biomarker could help doctors personalise treatment to individual patients to maximise benefits and improve outcomes.

There were several interesting presentations about biomarkers for kidney cancer at ASCO this year. Two of the key presentations aimed to find a biomarker that could predict the response to therapy in advanced or metastatic kidney cancer (CLEAR, KEYNOTE-426 trials). Another study, IMmotion101, focused on finding biomarkers that predict disease recurrence in patients that underwent a curative surgery for their kidney cancer. Finally, in another trial (abstract 4526) researchers are trying to identify a biomarker that could aid in early detection of kidney cancer.

In the CLEAR study (abstract 4504), researchers were looking for biomarkers in tumour samples taken from patients with advanced kidney cancer that received treatment with either the pembrolizumab plus lenvatinib combination or sunitinib in the first-line setting. They looked at several biomarkers, including proteins found in the outer layer of the cell (PD-L1) and in the genes of the tumour cells, especially genes that participate in cancer growth, in development of new blood vessels (angiogenesis) and those that participate in the spread of the tumour beyond the kidney. In addition, five genes were studied (*VHL, PBRM1, ESTD2, BAP1 and KDM5C*). For all of these biomarkers, patients treated with lenvatinib plus pembrolizumab showed a longer time to when the treatment stopped working and the cancer started growing again (improved progression-free survival). Overall, none of these biomarkers were useful to predict a better response with the combination therapy, and regardless of which biomarker was looked at, all patients showed longer progression free survival if treated with the combination of lenvatinib plus pembrolizumab.

In the KEYNOTE-426 study (abstract 4505), the researchers looked for biomarkers of response to treatment with pembrolizumab plus axitinib or sunitinib in tumour samples taken from patients with previously untreated advanced kidney cancer. They looked for biomarkers called T cell-inflamed gene signature ($Tcell_{inf}$GEP), angiogenesis gene signature (RNAseq,) and PD-L1. They found a strong relationship between $Tcell_{inf}$GEP, a marker that is associated with an inflamed tumour state, and patient outcomes in patients that received treatment with pembrolizumab and axitinib; those with high levels of $Tcell_{inf}$GEP had better response rates, progression free survival and overall survival than those with low levels. Conversely, in patients who received sunitinib, the angiogenesis gene signature was

associated with a better response rate, progression free survival and overall survival. Importantly, regardless of gene signature expression, patients who received axitinib and pembrolizumab showed better outcomes than those who received sunitinib, so in the end these biomarkers don't help us choose between these regimens.

Potential biomarkers for early-stage kidney cancer

The IMmotion101 study (abstract 4506) is a trial that looked at the effectiveness of atezolizumab with the intention to reduce the risk of kidney cancer coming back after a nephrectomy. The study did not reduce the risk of cancer coming back. In this later analysis the researchers were looking for a biomarker that could identify those patients at higher risk of recurrence and help them predict which patients could benefit from atezolizumab. They identified a protein called kidney injury molecule-1 (KIM-1) as a potential biomarker. In the results, they noticed that patients that had high blood levels of the protein after nephrectomy were at higher risk of recurring. Additionally, patients with higher baseline KIM-1 levels demonstrated benefit from adjuvant atezolizumab, with longer progression free survival when compared to placebo. The researchers concluded that KIM-1 may be a biomarker for recurrence of kidney cancer and could help in selecting patients that will benefit from further therapy after surgery. More research is needed to confirm the role of KIM-1 as a biomarker of poor prognosis in localised kidney cancer.

Although kidney cancer is the fourteenth most common cancer worldwide, and the incidence of kidney cancer is increasing, there remains an unmet need for an effective biomarker for early detection of the disease. This study (abstract 4526) reports on carcinoma-specific transmembrane N-glycoprotein or CA-62, a potential biomarker for the detection of early-stage kidney cancer. CA-62 showed high sensitivity (94.3%) for the detection of early-stage kidney cancer. However, because CA-62 is not specific for kidney cancer, a combination of CA-62 plus other biomarkers, such as the transmembrane glycoprotein (CD-105) and various growth factor proteins, could become a useful strategy for kidney cancer screening.

A new injectable form of nivolumab

Nivolumab, an immune-stimulating therapy, improves outcomes for people with many different cancers. Nivolumab is given as an intravenous infusion through a vein in the arm over 30 to 60 minutes every 2-4 weeks. Patients need to visit a hospital or clinic to have their infusion. This affects their quality of life as well as their finances, since patients may need to take time off work, travel long distances to regional cancer centres, organise childcare, or have a partner travel with them for treatment. A form of immunotherapy that can be injected at a local clinic could reduce these burdens on the patient and their family.

The CheckMate-67T study (abstract 4532) looked at a form of nivolumab that can be injected under the skin (subcutaneous nivolumab) and compared it to nivolumab that is given intravenously in patients with advanced kidney cancer that had progressed to one or more previous treatments. The researchers found that the subcutaneous nivolumab was as effective as intravenous nivolumab, but with a much shorter injection time (less than 5 minutes). The safety of the subcutaneous nivolumab was compared to that of the

intravenous nivolumab by monitoring and managing the adverse events. Patient reported outcomes were also assessed.

The side effects to subcutaneous nivolumab were the same or less than intravenous nivolumab, and most of these events were mild and manageable. The proportion of patients with local injection site reactions was slightly higher with subcutaneous injection (8 in 100 patients) compared to intravenous infusion (2 in 100 patients). All were mild-moderate and did not need treatment. Most patients in both treatment groups reported minimal bother from treatment side effects.

With these results, the researchers concluded that the use of subcutaneous nivolumab is safe, with adverse events that are comparable to intravenous nivolumab, with the upside of improving patient experience while receiving treatment.

Updates on efficacy of combination treatment for advanced/metastatic kidney cancer

Advanced/metastatic kidney cancer is often treated with a combination of medicines; either two infusions of immunotherapy (nivolumab and ipilimumab) or immunotherapy (avelumab, pembrolizumab or nivolumab) plus a vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitor (TKI) tablet (axitinib, lenvatinib, or cabozantinib).

Combination therapies are standard of care for the treatment for advanced kidney cancer. However, the question remains; Are all combination therapies effective for treating advanced kidney cancer?

In the JAVELIN Renal 101 phase 3 study (abstract 4508), treatment with a combination of avelumab plus axitinib was compared to sunitinib as a first treatment for people with advanced kidney cancer. The study has already shown that avelumab plus axitinib significantly increases the time to when the treatment stops working and the cancer starts growing again (progression-free survival) compared to sunitinib, as well as an improved response to treatment and tolerable side effects. The final overall survival results were presented at ASCO 2024.

There were nearly 900 patients in this study. Patients were followed-up for an average of just over 7 years. After this time, researchers found that the average survival time was 3 years and 9 months with the combination therapy compared to 3 years and 3 months with sunitinib. This 6-month difference did not reach statistical significance as per study design.

The lack of overall survival benefit does question whether PD-L1 inhibitors, such as avelumab, are not as effective as PD-1 inhibitors, such as pembrolizumab for kidney cancer.

Improving treatment for rare kidney cancer subtypes

Non-clear cell kidney cancer comprises about 20-25% of all kidney cancer diagnoses, and includes subtypes such as papillary, chromophobe, translocation and unclassified renal cell carcinoma. Non-clear cell kidney cancer usually has worse survival than clear cell kidney

cancer. Identification of an effective treatment for advanced non-clear cell kidney cancer remains an unmet need.

Chromophobe renal cell carcinoma (ChRCC) represents about 5-10% of all kidney cancer. Because it is a rare cancer, there is limited information to guide treatment options for metastatic chromophobe RCC. Phase 2 clinical trials have shown that VEGFR TKIs, such as sunitinib and pazopanib, and mTOR inhibitors, such as everolimus have similar effectiveness for chromophobe RCC compared to the more common clear cell kidney cancer. However, immunotherapy seems to be less effective for chromophobe RCC. Larger studies are needed to confirm this finding.

A retrospective study (abstract 4512) looked at information on frontline treatment of 99 patients with metastatic chromophobe RCC from three centres. Patients were categorised into four treatment groups: 1) immunotherapy plus TKI (e.g., lenvatinib plus pembrolizumab) 2) immunotherapy (alone or a combination of immunotherapies, e.g., nivolumab plus ipilimumab) 3) targeted therapy combinations (e.g., lenvatinib plus everolimus) and 4) targeted therapy alone (e.g., sunitinib).

This analysis showed improved clinical outcomes for patients with metastatic chromophobe RCC with combination therapies compared to single therapies. Patients on combination therapies had a longer time to treatment failure and a longer overall survival compared to single therapies. The researchers are continuing with this work and collaborating with other centres to increase the number of patients with metastatic chromophobe RCC in this study and collect further data to compare outcomes with other treatments.

An effective treatment for non-clear cell kidney cancer remains an unmet clinical need. There have been few randomised controlled studies for patients with non-clear cell kidney cancer, and new treatment options are needed. Current treatments include sunitinib, a VEGFR TKI tablet. To date, no treatment has shown a significant improvement in overall survival times compared to sunitinib in any non-clear cell kidney cancer subtype. Immunotherapies alone have shown only small improvements in response to treatment, but combinations of immunotherapies plus VEGFR TKIs have been more promising in phase 2 studies.

Zanzalintinib is a new VEGFR TKI that targets several protein receptors on the cancer cells that are involved in the growth of a new blood supply to the tumour (angiogenesis), the spread of the cancer (metastasis), and suppression of the immune system. Zanzalintinib has shown anti-cancer activity and stimulation of the immune system in animals when used alone or in combination with immunotherapy.

In the phase 1 STELLAR-001 study, zanzalintinib showed promising anti-cancer activity by reducing the tumour size in nearly 4 out of 10 patients and controlling the tumour growth in nearly 9 out of 10 previously treated patients with advanced clear cell kidney cancer. Zanzalintinib also had manageable side effects.

STELLAR-304 (abstract TPS4611) is a phase 3, randomised global study looking to enrol patients with papillary, unclassified or translocation kidney cancer (including sarcomatoid kidney cancer). Patients with chromophobe, renal medullary carcinoma or collecting duct

subtypes are excluded from the study. Patients should be untreated for advanced/metastatic non-clear cell kidney cancer, but one adjuvant treatment (including immunotherapy, but excluding sunitinib) is allowed. Patients are randomised 2:1 to be treated with zanzalintinib plus nivolumab or sunitinib alone. The primary endpoints of the study are the time to when the treatment stops working and the cancer starts growing again (progression-free survival) and response to treatment. The secondary endpoint is overall survival time. Side effects will also be assessed.

STELLAR-304 is currently recruiting patients in Europe, North and South America, and the Asia Pacific region.

Potential new treatments for advanced kidney cancer

So far, the best first line treatment for patients with advanced kidney cancer is a combination of immunotherapy and VEGFR TKI (e.g., nivolumab plus cabozantinib) or a combination of immunotherapies (e.g., nivolumab plus ipilimumab). With these combination therapies the outcomes of patients with advanced kidney cancer have improved significantly.

Furthermore, there is a percentage of patients that achieve a complete response, meaning that in some patients there is a complete shrinkage of all metastases. In the case of nivolumab plus cabozantinib approximately 9% of the patients achieve a complete response. Further therapies are being looked at to see if a higher percentage of patients could achieve a complete tumour response.

During a session on clinical trials in progress, Dr Jonasch discussed the design of a phase 1b/2 trial looking at a combination of a new treatment called ^{177}Lu girentuximab in combination with cabozantinib and nivolumab in previously untreated patients with advanced kidney cancer (abstract TPS610).

Studies have shown that radiation treatment improves the action of immunotherapy. However, it is not always possible to treat all metastases with radiation.

Girentuximab is an antibody that attaches to an enzyme called carbonic anhydrase IX (CAIX). This enzyme is found in most cells of clear cell kidney cancer. ^{177}Lu girentuximab is a product made from combining a radioactive molecule called lutetium (Lu 177) with girentuximab. When given to humans, ^{177}Lu girentuximab binds to carbonic anhydrase IX in kidney cancer tumours and delivers the radioactive lutetium directly to the cancer cells. Once in the cell, the radiation leads to DNA damage and cell death. ^{177}Lu girentuximab has been tested in metastatic clear cell kidney cancer and has been shown to be safe and effective in stabilising disease in 57% of patients.

This study hopes to show that damage to the tumour cell DNA caused by ^{177}Lu girentuximab will activate the T cells of the immune system to attack the cancer cells. This could help make the effect of immunotherapy stronger and increase complete response to treatment.

The study aims to recruit up to 100 patients with untreated metastatic kidney cancer to look

at the safety and complete response to a combination ^{177}Lu girentuximab plus nivolumab and cabozantinib. ^{177}Lu-girentuximab will be given every 12 weeks for up to 3 cycles. And nivolumab plus cabozantinib will be added at week 5.

Patients will have PET scans and biopsies throughout the study to look at the effects of the treatment on T cells and the immune system. The investigators will also be looking at the response of patients to treatment, the time to when the treatment stops working and the cancer starts growing again, the duration of response to treatment, the benefit to patients and overall survival time. The study is about to start recruiting patients at MD Anderson Cancer Centre, Houston, Texas, USA.

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