Summary of Kidney Cancer Highlights from ASCO GU 2022

This year’s American Society of Clinical Oncology Genitourinary (ASCO GU) Symposium was held both virtually and face-to-face from 17-19 February 2022. The presentations are available to view on the ASCO website. The International Kidney Cancer Coalition (IKCC) reviewed the virtual scientific programme to keep abreast of the latest advances in the care and treatment of patients with kidney cancer.

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.

How do patients experience kidney cancer diagnosis and treatment across the world?

The number of patients suffering kidney cancer is rising around the world, increasing the burden on patients, their families and healthcare systems. Little is known about how kidney cancer treatment and patient experience varies between countries. This was a poster presentation of the second biennial worldwide International Kidney Cancer Coalition (IKCC) Global Patient Survey of diagnosis, management, and burden of kidney cancer.

The aim of the survey was to improve understanding and contribute to reducing the burden of kidney cancer. Patients and caregivers completed a 35-question survey to identify differences between countries in patient education, experience and awareness, access to care and clinical trials, best practices, quality of life, and unmet psychosocial needs. The survey was distributed in 13 languages via IKCC’s 46 Affiliate Organisations and social media.

Over 2,000 patients from 41 countries responded to the survey. The data were independently analysed. The full global report is available on the IKCC website. In terms of diagnosis, nearly half (48%) had been offered a biopsy to help with diagnosis and better understanding of their cancer, with only 3% refusing; 47% would be willing to undergo biopsy in the future.

In terms of treatment, many patients didn’t understand their prognosis; 42% of patients reported that the likelihood of surviving their cancer beyond 5 years was not explained. Patients aged 65 and older experienced more barriers to quality care, understood their disease less well, and waited longer for a diagnosis.

About half (49%) of patients felt they were not involved ‘as much as they wanted to be’ in planning their treatment. In addition, 56% of patients experienced barriers to treatment. Clinical trials were not discussed with many patients (41%); only one-third (31%) were invited to take part in a clinical trial.

In terms of self-care and quality of life, 45% of patients said they were not physically active enough, and half (50%) ‘very often’ or ‘always’ experienced anxiety about their cancer. More than half of patients (55%) ‘very often’ or ‘always’ experienced fear of recurrence and 52% talked to their doctor/healthcare professional about their concerns. In a quarter of patients (26%), financial issues ‘very often’ or ‘always’ resulted in stress.
The IKCC and its global Affiliate Organisations will be using these results to ensure that the patient’s voices are heard. Individual countries can use their reports to advance their understanding of patient experiences and to support improvements in local care.

Can immunotherapy help patients who have surgery for high-risk kidney cancer?

Surgery to remove one kidney (also called nephrectomy) is the standard of care for large (high-risk) kidney cancers that have not spread outside the kidney. The cancer can come back (recurrence) after nephrectomy in some patients. Taking additional treatment after surgery as ‘insurance’ against the cancer coming back is called ‘adjuvant therapy’.

There is no standard adjuvant treatment for high-risk early kidney cancer. In the past, tablets that block cancer blood supply (vascular endothelial growth factor (VEGF) tyrosine kinase inhibitors (TKIs)) have been tested as adjuvant therapies for kidney cancer, but the benefit for patients has been small and inconsistent.

Immunotherapy (with medicines called antibodies taken by an intravenous drip) is a newer kind of treatment for many types of cancer. Immunotherapy is now used in many countries for advanced kidney cancer that has spread outside the kidney. Several clinical trials are in progress to discover if giving immunotherapy to patients who underwent nephrectomy for high-risk early kidney cancer, can prevent the cancer from coming back in other parts of the body.

The KEYNOTE-564 clinical trial used an immunotherapy drug called pembrolizumab as an adjuvant therapy for these patients. Very large tumours, spread of the cancer into veins or local lymph nodes, aggressive features under the microscope, or some combination of these is considered high-risk kidney cancer. Patients with similar features were randomly allocated to two separate groups to take either pembrolizumab or placebo for one year. Patients were monitored for return of their cancer and for the effects of treatment.

The results of this clinical trial have been previously reported and published. In the first report, treatment with adjuvant pembrolizumab reduced the relative risk of the cancer returning by about one third (32%) after 2 years, but in absolute terms 22% of patients experienced the cancer coming back after pembrolizumab versus 33% on placebo. This means about nine patients would have to take one year of pembrolizumab treatment to stop the cancer coming back in only one person. For the other eight out of the nine patients, they would either not have experienced the cancer coming back anyway (seven would have been cured by the surgery alone), or they would have seen the cancer come back despite taking pembrolizumab (one patient).

The researchers followed this group of patients for a further 6 months and this next look at the data was presented at ASCO GU 2022. The proportion of patients who experienced the cancer coming back in both groups did not change with the longer follow-up. Also, the number of patients experiencing side effects from pembrolizumab remained unchanged and remained higher compared with patients on placebo. Serious or life-threatening side effects for patients taking pembrolizumab at 2 years and 2.5 years (8.6% versus 8.8%, respectively) compared with 0.6% for patients on placebo at both time points.

The most important question about adjuvant immunotherapy remains unanswered; however, does immediate treatment with pembrolizumab after surgery for high-risk early kidney cancer help patients live longer? Does it stop patients from dying earlier? It is still too early to see if there is a benefit in overall survival time. In the meantime, clinicians and patients need to make individual informed choices about the use of adjuvant pembrolizumab.

Quality of life of the patients on the KEYNOTE-564 trial was also looked at. There was a small deterioration of quality of life for patients treated with pembrolizumab compared to placebo, which the researchers did not consider statistically significant. Importantly, quality of life remained stable over time. Patients reported that pembrolizumab was tolerable from a patient perspective. The quality of life was not compared versus a group of patients that did not take placebo intravenous infusions, however.
While the updated analysis of KEYNOTE-564 shows that adjuvant pembrolizumab can reduce the chance of the cancer coming back on scans for patients with kidney cancer with a high risk of recurrence, there remains no evidence to date that it helps people live longer.

There remain many caveats on taking adjuvant pembrolizumab, and patients should consider their situation carefully with their doctor to balance potential treatment benefit and risk. Not all patients are the same, everyone’s cancer is different, and there is no blood test or scan that can yet predict which person is most at risk for the cancer coming back. Without a test to predict which patients might benefit from treatment or who might suffer serious side effects, overtreatment is likely to occur.

Clinicians should take special care to inform patients about the potentially serious side effects of pembrolizumab, particularly since the quality-of-life studies do not capture chronic side effects which can affect up to 40% of patients taking immunotherapy. Potential serious side effects of pembrolizumab must be considered carefully.

**What treatments are right for each person with advanced kidney cancer?**

When kidney cancer spreads to other parts of the body, we call this ‘metastatic’ or advanced kidney cancer. Medicines that block cancer blood supply (VEGF TKI tablets) or intravenous immunotherapy drugs like those described above are often used where available to help patients live better and longer. But sometimes other treatments are also useful, like radiation treatment in some patients, and even surgery.

Nephrectomy is sometimes recommended even when the cancer has spread, with an aim to reduce the total amount of cancer in the body (tumour burden), and reduce or prevent symptoms like pain or bleeding from the cancer in the kidney, which are important considerations for patients with advanced kidney cancer. It is speculated that cancer that remains in the kidney continues to somehow support and promote cancer cells that have spread to other parts of the body, whether this is by providing growth signals or by suppressing the immune system.

Based on these considerations and possibilities, doctors may recommend nephrectomy to some patients with kidney cancer, even though the kidney cancer has already spread. This remains experimental; a study presented at a previous ASCO GU conference (the CARMENA study) did not show any benefit for nephrectomy before starting VEGF TKI tablet treatment. However, in recent years, immunotherapy has taken over as the preferred first treatment for advanced kidney cancer, so doctors are starting to ask this question again. Two studies presented at the ASCO GU Symposium looked at the use of nephrectomy followed by immunotherapy combinations in patients with advanced kidney cancer.

**Nephrectomy followed by combination immunotherapy for patients with lung metastases**

This real-world study included the experiences of 1084 patients with advanced kidney cancer, some of whom had previous surgery for kidney cancer and the cancer had come back, and some were found to have advanced kidney cancer and then had a nephrectomy followed by treatment with an immunotherapy combination (either two immunotherapy antibodies, or an immunotherapy infusion plus a VEGF TKI tablet). Some patients had lung metastases (the kidney cancer had spread to the lungs) and perhaps also to other organs. Most patients (84%) were deemed high-risk in that they had unfavourable features of their cancer, and it would be expected that the advanced kidney cancer would grow and cause symptoms almost immediately.

Of 898 patients who had enough scans to follow possible change in tumour burden, 4% had a complete response to treatment and their cancer was undetectable after nephrectomy with the immunotherapy combination. For 38%, their cancer got smaller after treatment but didn’t disappear completely (a partial response). For 35%, the tumours remained stable for some time, but for 23%, their cancer got worse (progressed) following nephrectomy and the immunotherapy combination. The long-term survival for patients taking immunotherapy treatment seems to be longer than for patients taking VEGF TKI tablets. Most patients who experienced a complete response were still alive and the average overall survival time for these patients
cannot yet be calculated. For those who had a partial response it was 56 months, 48 months for those with stable disease but only 13 months for those whose cancer immediately progressed.

These numbers compare with past reports of using immunotherapy alone, so this real-world study provides some support for the idea that patients with kidney cancer lung metastases who have had a nephrectomy are more likely to respond to treatment with immunotherapy combinations. The study also suggested that patients with less aggressive kidney cancer were more likely to benefit from nephrectomy followed by immunotherapy combinations than those with high-risk disease. Other factors, such as sex, age, sarcomatoid histology, smoking status, and presence of liver or brain metastases, did not significantly affect the response to treatment. Additional analyses are planned to look at the effect of other clinical factors on survival. This information is suggestive but does not prove that patients should have a nephrectomy operation before starting immunotherapy treatment. A new clinical trial is needed to test that idea.

What should patients do when kidney cancer starts to spread into veins?

Many patients with early kidney cancer have a mass found in their kidney, but in around 10-20%, the cancer extends into the veins that connect the kidney to the main vein in the back of the abdomen, called the inferior vena cava. When cancer is growing inside the vein this is called a tumour thrombus. The outlook for these patients is complicated. Nephrectomy to remove the kidney and sometimes also some of the veins was the standard of care for patients with kidney cancer tumour thrombus. However, since the introduction of more effective medicines for kidney cancer, such as VEGF TKIs and immunotherapy, the options for treatment are less clear. Should these patients be given a nephrectomy followed by medication, or medication without nephrectomy?

Previous studies of patients with newly diagnosed advanced kidney cancer showed two important findings: First, patients with a tumour thrombus had similar outcomes after treatment with targeted therapy or immunotherapy to patients without a tumour thrombus. Second, nephrectomy, in addition to medication, seemed to lengthen survival times in these patients.

This study investigated these findings further. The study included 226 patients. Of the patients with a tumour thrombus (28%), nearly three quarters (72%) had a nephrectomy followed by medication (usually a VEGF TKI), while the remainder were treated with medication only. The patients were all treated before immunotherapy had become available.

When only VEGF TKI tablet medication was used to manage the disease without a nephrectomy, there was no difference in average survival times for patients with or without tumour thrombus. However, those patients with a tumour thrombus who had a nephrectomy followed by medication survived significantly longer compared with those who did not (29.4 versus 12.1 months).

Due to the small numbers of patients in this study, it cannot be used to change routine clinical practice. Also, those patients who did not have a nephrectomy were only treated with a VEGF TKI, not immunotherapy. It will be interesting to see if the benefit of nephrectomy to remove tumour thrombus is maintained in patients treated with the new immunotherapy combinations. It will also be interesting to see whether a nephrectomy is needed in those patients with a tumour thrombus who have a good response to immunotherapy combinations.

Future work will involve looking at helping patients choose better sequences and combinations of treatment, and the effectiveness of immunotherapy combinations in patients with a tumour thrombus, and to identify features on scans that might predict the response of the thrombus to treatment.

What is the best treatment if kidney cancer spreads to the pancreas?

Like any other cancer, kidney cancer can spread to many parts of the body, but some patients have a very unusual pattern of cancer spread; it seems to only spread to organs of the body that produce hormones, like the pancreas and the thyroid gland. Patients with this limited pattern of cancer spread seem to have more slow growing cancer, and have seemed to benefit from VEGF TKI tablets, but strangely, not immunotherapy. Two posters from ASCO GU 2022 shed more light on this situation. One group of researchers compared the biology
of kidney cancers that had spread to the pancreas compared to other parts of the body, and found them to be less aggressive, but more invisible to the immune system. A second group of researchers studied the International Metastatic RCC Database Consortium (IMDC) of patients with kidney cancer from around the world. This gives more evidence to support the idea that immunotherapy combinations might not be the best option for patients with this pattern of spread, but that the combination of immunotherapy and VEGF TKI tablets together might be the best treatment.

Which combination of treatments should we choose for patients with advanced kidney cancer?

This is a very important question for patients with advanced kidney cancer, but we don’t yet know the answer.

Advanced kidney cancer is commonly treated today with a combination of either two medicines; either two infusions that unleash the immune system (immunotherapy; nivolumab and ipilimumab) or immunotherapy (avelumab, pembrolizumab or nivolumab) plus a VEGF TKI tablet (axitinib, lenvatinib or cabozantinib). Many other similar combinations have been tested and others are in development.

Combination therapies continue to be of great interest at ASCO GU 202, with the presentation of updated results from some ongoing studies. But crucially, none of these studies can help us with the critical question; which combination of treatments is best for an individual patient with advanced kidney cancer?

Does the benefit seen with cabozantinib plus nivolumab persist after longer follow-up?

Additional follow-up information from the phase III clinical trial, CheckMate-9ER, shows that cabozantinib (a VEGF TKI tablet) used together with nivolumab (an immunotherapy infusion) is still better than VEGF TKI alone at shrinking the cancer, and for survival, in patients with advanced kidney cancer who had not previously taken any treatment.

After an average follow-up time of nearly three years (33 months) the combination of cabozantinib plus nivolumab continued to show longer survival, control of the cancer, and shrinkage of the cancer on scans compared to sunitinib (a VEGF TKI tablet).

The time to when the treatment stopped working and the cancer started growing again was doubled with the combination compared to the VEGF TKI sunitinib (16.6 months versus 8.3 months, respectively). Additionally, the number of patients who responded to treatment with a complete response (no detectable cancer on the scans) or partial response (spots of cancer on the scan are smaller) was greater for the combination than for sunitinib (55.7% versus 28.4%). 12.4% of patients treated with the combination had a complete response to treatment compared to 5.2% for sunitinib.

More patients with cabozantinib plus nivolumab experience side-effects, and in general more severe side-effects but this was similar to previous studies of this combination. Over a long period of time, the quality of life as reported by patients on questionnaires was better with the combination than on sunitinib. Overall, 7.5% of patients stopped taking the combination due to side effects.

After almost 3 years follow-up, patients continued to report improved quality of life with the cabozantinib plus nivolumab combination compared to sunitinib. Quality of life was improved or maintained over time with the combination but declined for patients on sunitinib. Also, patients on the combination were 48% less likely to be bothered by treatment side effects than patients taking sunitinib.

This information doesn’t tell us if the combination of cabozantinib plus nivolumab is better than any other immunotherapy plus VEGF TKI combination, or if it is better than two immunotherapy drugs (nivolumab and ipilimumab).
Are there any differences in treatment with lenvatinib plus pembrolizumab in East Asian patients with advanced kidney cancer?

Lenvatinib plus pembrolizumab is another combination of immunotherapy plus a VEGF TKI. In the original international phase 3 clinical trial (the CLEAR study), 1069 untreated patients from countries around the world were put into 2 groups: one group were treated with lenvatinib (a VEGF TKI tablet) plus pembrolizumab (an immunotherapy infusion), the other with sunitinib (a VEGF TKI tablet). The results from this trial showed significant improvements in survival and shrinkage of the cancer for the combination compared to sunitinib.

In this presentation, the results from patients from East Asia are compared to the overall study population in the study. Of the 1069 patients in the study, 75 patients on the combination of lenvatinib plus pembrolizumab and 65 patients on sunitinib were from East Asia. Patients were from Japan and the Republic of Korea, and their health, wellbeing and the characteristics of their cancers were similar to those of the overall study population.

As in the overall study population, the time to when the treatment stopped working and the cancer started growing again was twice as long in the combination group compared with sunitinib (average 22.1 months compared to 11.1 months, respectively). More patients in the combination group had shrinkage of their cancer compared to those on sunitinib (65.3% compared to 49.2%). The duration of cancer control was longer for the patients on the combination (20.3 months compared to 12.9 months for sunitinib). In this group of East Asian patients, 17.3% had a complete response to treatment with the lenvatinib plus pembrolizumab combination and 48% had a partial shrinkage of their cancer (compared with 7.7% and 41.5% with sunitinib, respectively). Patients from East Asia seemed to benefit at least as much as patients from elsewhere in the world.

Some side effects of the combination treatment were more common in the East Asian group of patients than in the overall study population, including hand-foot syndrome (where the skin on palms and soles of feet becomes red, sore, cracked and broken), protein in the urine (proteinuria) and decreased neutrophil (white blood cell) counts. However, the total number of side effects were similar to the overall study population and 16% of East Asian patients stopped treatment because of side effects (compared to 9.7% of patients in the overall study population).

The effectiveness and safety of the combination of lenvatinib and pembrolizumab were similar in East Asian patients with advanced kidney cancer compared to the overall study population in the CLEAR study.

How do we choose between combination treatments for untreated patients with advanced kidney cancer?

During the ASCO GU meeting, Drs Wenxin Xu MD and Toni Choueiri MD from Harvard Medical School and the Dana-Farber Cancer Institute in the US discussed how to choose between different combination treatments for patients with previously untreated advanced kidney cancer.

Combination treatments have changed how we treat patients with advanced (or metastatic) kidney cancer. The first combination was two immunotherapies, ipilimumab plus nivolumab, which improved overall survival compared with sunitinib for untreated patients with kidney cancer. This has been followed by several immunotherapy infusions plus VEGF TKI tablet combinations that also showed improved survival compared with sunitinib when given to untreated kidney cancer patients with advanced disease (axitinib plus pembrolizumab, axitinib plus avelumab, cabozantinib plus nivolumab, and lenvatinib plus pembrolizumab). Unfortunately, all these combinations were compared against what is now an historical standard of care, sunitinib, and not against each other.

These combinations of treatments have consistently been shown to improve survival for patients with advanced kidney cancer. However, not all patients need combination therapy:

- Not all patients with advanced disease need to be treated immediately. Some have slow-growing disease, small tumours, or do not have any symptoms from their disease. These patients may do well with careful
active surveillance and may benefit from time-before-taking-treatment. Some patients may undertake active surveillance for years before needing treatment.

- Some patients with only one or two metastases might benefit from treatment directed at the metastases, such as surgery to cut out a single spot that has spread, or precision targeted (stereotactic) radiotherapy, especially in those patients where the advanced cancer is not in a critical location. These patients might wish to delay the side effects from taking medication, facing instead the effects of surgery or radiation. It is important to note that researchers are unsure whether this treatment strategy improves survival compared to immediate treatment with combination therapies.

- Although patients with low-risk advanced disease respond well to combination therapies, it is not clear whether overall survival time is improved in these patients compared to sunitinib. These patients make up 20% of the overall population of patients with advanced kidney cancer. Some patients with low-risk disease do well by taking VEGF TKIs first, and immunotherapy as a second separate treatment; however, combination therapies can be considered for these patients because they might extend the time to when the cancer starts growing again.

And so, to the biggest question of all; which combination therapy should patients choose?

- The advantages of ipilimumab plus nivolumab are potential long-term survival and no VEGF TKI side effects. Nivolumab is relatively easy to tolerate, and some patients may even be able to stop treatment if they have a long-term response. The disadvantages of ipilimumab plus nivolumab are higher risk of immune-related side effects, and less rapid shrinkage of the cancer compared to the immunotherapy plus VEGF TKI combinations.

- The advantages of immunotherapy plus VEGF TKI combinations include deeper and faster cancer shrinkage and possibly a lower risk of immune-related side effects. However, there are on average more side-effects overall and potential long-term side effects from VEGF TKIs and immunotherapies.

- The patient’s general health and preferences should be considered when deciding which combination therapy to give. For example, some patients may react badly to VEGF TKIs (high blood pressure, cardiovascular disease). Some patients with low-risk disease may want the chance of a long-term response and choose ipilimumab plus nivolumab. Others with significant symptoms of the cancer may need an immediate response to treatment, in which case an immunotherapy plus VEGF TKI might be more suitable.

Currently, there are four immunotherapy plus VEGF TKI combination therapies. They all work in a similar way, and it is difficult to compare them because they have not been tested against each other in clinical trials.

Some medicines used in combination therapies have different benefits. For example, cabozantinib has slightly different spectrum of action and might help patients with non-clear cell kidney cancers. Axitinib does not last as long in the body and may be a better choice for patients who experience bad side effects to VEGF TKIs.

Combination therapies have changed the way that advanced kidney cancer patients are treated. All combinations are better than sunitinib, and the choice of which combination to use is not clear. This is made worse by the fact that none of these combinations have been compared in randomised controlled trials.

Future treatments being tested are the HIF-2α inhibitor, belzutifan, and combinations of three medications. Questions remain about whether patients who receive adjuvant immunotherapy will benefit from these combinations if they develop metastases, and whether predictive biomarkers may personalise treatment.

One important way that we can learn more about the experience of patients taking these treatments is to follow the experience of patients in the real-world taking these treatments, through further studies and registries. Ask your doctor if they are sharing your experience in these international studies.
Does immunotherapy work for patients with sarcomatoid kidney cancer?

Sarcomatoid clear cell kidney cancer is an aggressive type of kidney cancer with poor outcomes and limited treatment options. However, immunotherapy has been shown to be more effective than sunitinib in patients with high-risk sarcomatoid kidney cancer. Two poster presentations at this year’s ASCO GU Symposium look at survival outcomes in patients with advanced sarcomatoid kidney cancer treated with immunotherapy.

Is combination immunotherapy effective for sarcomatoid kidney cancer?

In this poster, long-term follow-up data from patients with high-risk sarcomatoid advanced kidney cancer in the CheckMate-214 study of nivolumab plus ipilimumab were presented. Patients had been randomly allocated to take the ipilimumab plus nivolumab combination or sunitinib. Of the 1096 patients in CheckMate-214, 139 patients with high-risk sarcomatoid kidney cancer were identified, 74 in the ipilimumab plus nivolumab group and 65 in the sunitinib group.

Patients with advanced sarcomatoid kidney cancer had better long-term survival with the immunotherapy combination compared to those taking sunitinib. More patients had shrinkage of their cancer (61% versus 23%) and more experienced a complete response to treatment (23% versus 6%) with the combination compared to sunitinib. The average overall survival time was significantly improved (49 versus 14 months), as was the time to when the treatment stopped working and the cancer started growing again (26 versus 5 months, respectively).

Although the presence of sarcomatoid features was not an original part of the CheckMate-214 study, the number of patients in each group was roughly the same, and these results support the idea that there is more benefit of an immunotherapy combination over sunitinib for the treatment of sarcomatoid kidney cancer. The results from this study are particularly impressive considering the aggressive nature of sarcomatoid kidney cancer and the poor outcomes previously experienced by patients with this form of kidney cancer.

Survival of patients with sarcomatoid kidney cancer on different treatments

This poster looked at several recent phase 3 clinical trials with immunotherapy, targeted therapy, and chemotherapy to see which treatment improved survival the most in patients with advanced sarcomatoid kidney cancer.

In total, 44 patients with advanced sarcomatoid kidney cancer were looked at. Most patients had high-risk disease (94%). Eight (18.2%) patients were treated with immunotherapy as a first treatment, the remainder (81.8%) received either targeted therapy or chemotherapy. The patients were followed for an average of 5 and a half years. The average overall survival time for all 44 patients was 15.6 months. The overall survival time for the 8 patients on immunotherapy was so long that an average has not yet been reached. Overall survival time for the patients who did not take immunotherapy was 10.3 months. The average time from when the treatment stopped working to when the cancer started growing again was 24 months for patients on immunotherapy compared to 5.4 months for patients on other treatments.

Although the numbers of patients were small, this study again supports the benefits of immunotherapy for advanced sarcomatoid kidney cancer patients in the real world. Immunotherapy or immunotherapy combinations should be considered as the standard-of-care for these patients.

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