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Critical Analysis of the Study of Nivolumab with Cabozantinib Versus Sunitinib in Previously Untreated Patients with Advanced or Metastatic Kidney Cancer (CheckMate 9ER)

Adrian Hunis MD *, Melisa Hunis MD[1]

Corresponding Author: Adrian Hunis MD**,** School of Medicine, Buenos Aires University (UBA)**,** School of Medicine, Maimonides University (UMAI), Oncología Integral Belgrano (Buenos Aires, Argentina), Buenos Aires, Argentina.

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Abstract

CheckMate-9ER is a phase III, randomized, open label study evaluating patients with previously untreated advanced renal cell carcinoma (CRC).

Introduction

Renal cell carcinoma (RCC), also called renal cell cancer or renal cell adenocarcinoma is a common type of kidney cancer. Renal cell carcinomas account for about 90 percent of all kidney cancers. (1)

RCC usually begins as a tumor growing in one of your kidneys. It can also develop in both kidneys. The disease is more common in men than women.

How does it spread?

If a cancerous tumor is discovered in one kidney, the usual treatment is to surgically remove part or all of the affected kidney.

If the tumor is not removed, it's more likely that cancer will spread to either your lymph nodes or other organs (metastasis)

In the case of RCC, the tumor can invade a large vein leading out of the kidney. It can also spread to the lymph system and other organs. The lungs are especially vulnerable.

TNM staging and the stages of kidney cancer

Kidney cancer is described in stages that the American Joint Committee on Cancer developed. The system is better known as the TNM system.

- **"T"** refers to the tumor. Doctors assign a "T" with a number that's based on the size and growth of the tumor.
- **"N"** describes whether cancer has spread to any nodes in the lymph system.
- **"M"** means cancer has metastasized.

Based on the characteristics above, doctors assign RCC a stage. The stage is based on the size of the tumor and the spread of cancer.

There are four stages:

- **Stages 1 and 2** describe cancers in which the tumor is still in the kidney. Stage 2 means that the tumor is larger than seven centimeters across.
- **Stages 3 and 4** mean cancer has either spread into a major vein or nearby tissue or to lymph nodes.
- **Stage 4** is the most advanced form of the disease. Stage 4 means that cancer has spread to the adrenal gland or has spread to distant lymph nodes or other organs. Because the adrenal gland is attached to the kidney, cancer often spreads there first.

What's the outlook?

Five-year survival rates for kidney cancer are based on the percentage of people who live at least 5 years with the disease after it's been diagnosed.

The American Cancer Society (ACS) reports the percentage of people living 5 years or more after diagnosis according to three stages based on data from the National Cancer Institute.

These stages are:

- localized (cancer has not spread beyond the kidney)
- regional (cancer has spread nearby)
- distant (cancer has spread to distant parts of the body)

According to the ACS, the RCC survival rates based on these three stages are:

- **localized:** 93 percent
- **regional:** 70 percent
- **distant:** 12 percent

What are the treatment options?

The type of treatment you receive largely depends on the stage of your cancer. Stage 1 RCC may be treated with surgery.

However, by the time cancer has advanced to stage 4, surgery may not be an option.

If the tumor and metastasis can be isolated, surgical removal of the cancerous tissue and/or treatment of the metastatic tumor by removal or other procedures such as stereotactic body radiation therapy or thermal ablation may still be possible.

If you have stage 4 RCC, your doctor will consider the location and spread of your cancer and your overall health to determine your eligibility for surgery.

If surgery isn't a realistic option to treat stage 4 RCC, your doctor may recommend systemic therapies using a combination of drugs.

A sample of your tumor, called a biopsy, may be obtained to help determine the best therapy for your specific type of cancer. Treatment may depend on whether you have clear cell or non-clear cell RCC.

Targeted therapy and immunotherapy, including tyrosine kinase inhibitors and anti-PD-1 monoclonal antibodies, can be used to treat stage 4 RCC. A specific drug may be given alone or in combination with another drug.

Treatments may include:

- axitinib + pembrolizumab
- pazopanib
- sunitinib
- ipilimumab + nivolumab
- cabozantinib

In 2011, our working group published in ASCO, personal experience with classical and conventional therapies (hormone therapy, chemotherapy, interferon, interleukin, etc.) versus the new target therapies (TT) whose summary we attach: Kidney cancer:

"Experience of Centro Oncologico Buenos Aires (COBA) with immunotherapy (It) and targeted therapies (TT)" *(2)*

Background: To review the COBA results obtained in the first-line treatment of patients (pts.) with advanced kidney cancer for the past 10 years, from January 2000 to June 2006 (It) and from July 2006 to October 2010 (sunitinib and other TT). **Methods:** A descriptive, retrospective, longitudinal, non-comparative study. **Results:** The study included 150 pts. (106 male and 44 female 71% 29% H ratio: 1.5 - M: 1). Age: 51-60 years: 66 pts. (44%), 61 - 70 years: 34 pts. (23%). Histology: clear cell: 128 pts. (85%), chromophobe 8 pts. (5%), papillary 6 pts. (4%), oncocytoma 2 pts. (2%), sarcomatoid 2 pts. (2%), urothelial 2 pts. (2%), leiomyosarcoma 2 pts. (2%). Stages: stage IV: 88 pts. (59%) metastatic sites: 48 pts. (32%) lung, 30 pts. (20%) bone, 18 pts. (12%) retroperitoneal, 16 pts. (11%) lymph node, stage III: 6 pts. (4%) Stage II: 20 pts. (13%) Stage I: 36 pts. (24%). Surgery: radical nephrectomy: 122 pts. (81%). It.: 44 pts. (30% of 150 pts.) From January 2000 to June 2006: INF-α 2 (10 MU/I three times per week): 38 pts. (86.4%); IL2: 6 pts. (13.6%). From the studies published by Motzer et al. at ASCO 2006 and later began using sunitinib as first-line treatment in July 2006. TT: 52 pts. 34.6% of the 150. From July 2006 to October 2010: sunitinib: 42 pts. (80.8%), sorafenib: 4 pts. (7.7%), temsirolimus: 6 pts. (11.5%) Stable disease: TT (16 pts. - 30%): 10 months; It. (10 pts. - 22.7%): 5.5 months. Sunitinib toxicity: fatigue: 42 pts. (100%) arterial hypertension: 6 pts. (14%), hand-foot syndrome: 4 pts. (9%), mucositis: 2 pts. (5%). **Conclusions:** Treatment with TT proved useful in

controlling metastatic renal disease, achieving a statistically significant result of stable disease compared to that obtained with immunotherapy (10 vs. 5.5 months - p <0.001).

Recently (January 25, 2021) the FDA approved the following protocol, accepted as the first line of treatment.

The FDA just approved 1st line nivolumab + cabozantinib in advanced kidney cancer.

The approval was based on the phase III CheckMate-9ER study, which compared nivolumab in combination with cabozantinib versus sunitinib in patients with advanced renal cell cancer.

About the CheckMate -9ER study

CheckMate-9ER is a phase III, randomized, open-label study evaluating patients with previously untreated advanced renal cell carcinoma (CRC).

A total of 651 patients (22% favorable risk, 58% intermediate risk, 20% poor risk) were randomized to receive nivolumab in combination with cabozantinib (n = 323) versus sunitinib (n = 328).

Patients were randomized to receive 240 mg of nivolumab every two weeks intravenously and 40 mg of cabozantinib orally daily or sunitinib 50 mg orally daily for the first four weeks of a six-week cycle.

Treatment with nivolumab continued until disease progression as assessed by RECIST v1.1 response or unacceptable toxicity.

The recommended dose for nivolumab and cabozantinib is 240 mg of nivolumab every two weeks or 480 mg every four weeks in combination with 40 mg of cabozantinib once daily orally without food. The recommended treatment for nivolumab is until disease progression, unacceptable toxicity, or up to two years.

Treatment with cabozantinib is until disease progression or unacceptable toxicity.

The primary endpoint was progression-free survival (PFS) as assessed by the Blinded Independent Central Review (BICR), using RECIST v1.1.

Secondary endpoints included overall survival (OS) and objective response rate which was assessed by BICR using RECIST v1.1.

In the study, patients treated with nivolumab in combination with cabozantinib lived twice as long without their tumors progressing compared to patients treated with sunitinib (median PFS was 16.6 months [95% CI 12.5-24.9] vs. median PFS of 8.3 months [95% CI: 7.0-9.7]; [HR: 0.51] [95% CI: 0.41-0.64], P <0.0001; mean follow-up 18.1 months]; range: 10.6-30.6 months).

Nivolumab in combination with cabozantinib also reduced the risk of death by 40% compared to sunitinib (HR: 0.60 [98.89% CI 0.40-0.89]; P = 0.0010; median OS was not reached for nivolumab in combination with cabozantinib and is not available for sunitinib [range: 22.6-NR months]).

Additionally, more patients responded to nivolumab in combination with cabozantinib than to sunitinib, with an ORR of 55.7% (n = 180/323) (95% CI: 50.1 to 61.2) versus 27.1% (n = 89/328) (95% CI: 22.4 to 32.3); P <0.0001, respectively. In the combination group, 8.0% (n = 26/323) of patients experienced a complete response and 47.7% (n = 154/323) experienced a partial response versus 4.6% (n = 15/328) and 22.6% (n = 74/328) of those treated with sunitinib.

Among responding patients, the mean duration of response was 20.2 months for nivolumab in combination with cabozantinib (95% CI 17.3 to NA) and 11.5 months for sunitinib (95% CI 8.3 to 18.4).

Consistent results for PFS were observed in pre-specified subgroups of risk categories from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) and PD-L1 tumor expression status.

Adverse reactions greater than grade 3 in the study were similar to nivolumab in combination with cabozantinib versus sunitinib (75% versus 71%). All-cause adverse reactions leading to discontinuation of nivolumab or cabozantinib occurred in 19.7% of patients; 6.6% for nivolumab alone, 7.5% for cabozantinib alone, and 5.6% for the combination due to the same adverse reaction at the same time.

Although it is very premature, to affirm that this combination is the new standard in advanced kidney cancer, everything seems to indicate that it would be the new first-line scheme.

References

1)Introduction to Clinical Oncology. Hunis et al. Editorial of the National University of Quilmes. Volume I and II. 2009

2)https://ascopubs.org/toc/jco/29/15_suppl Hunis et al.

3)A Study of Nivolumab Combined with Cabozantinib Compared to Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma (CheckMate 9ER) https://clinicaltrials.gov/ct2/show/NCT03141177