Journal of Advanced Scientific Research

Available online through https://sciensage.info

ISSN

0976-9595

Review Article

A Review on Systematic Treatment of Clear Cell Renal Cell Carcinoma Using Nivolumab and Cabozantinib

Tadikonda Rama Rao*, Jadhav Bharath

Department of Pharmaceutical Analysis, CMR College of Pharmacy, Hyderabad, Telangana, India.

Corresponding author: tadikondarao7@gmail.com

Received: 24-06-2024; Accepted: 17-08-2024; Published: 30-09-2024

© Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License

https://doi.org/10.55218/JASR.2024150901

ABSTRACT

Since the introduction of anti-angiogenic and targeted therapies a decade ago, the management of advanced clear-cell renal cell carcinoma has seen significant advancements. Currently, the standard of care for colorectal cancer includes combinations of tyrosine kinase inhibitors (TKIs) and immunotherapy regimens like cabozantinib and nivolumab. The first-line treatment for RCC involves the combination of the anti-PD-1 monoclonal antibody nivolumab (OPDIVO®) and the multi-targeted TKI cabozantinib (Cabometyx®). Throughout the trial, the combination of cabozantinib and nivolumab consistently led to an enhanced health-related quality of life. Cabozantinib is used in the treatment of kidney cancer, hepatocellular carcinoma, and renal cell carcinoma. Nivolumab is typically employed when anti-angiogenic therapy proves ineffective. The combination of cabozantinib plus nivolumab, involving medications like sunitinib, ipilimumab, lenvatinib, and axtinib, is primarily utilized for its efficacy and survival benefits. The present review describes cabozantinib and nivolumab which are used for cancer treatment. This review helps people who are suffering from clear cell renal cell carcinoma.

Keywords: Clear cell renal cell carcinoma, Immunotherapy, Tumours, Antibodies.

INTRODUCTION

In the United States and Europe, kidney cancer affects approximately 64,000 and 115,000 individuals annually, respectively. This disease represents over 5% of all new cancer cases and results in around 15,000 and 49,000 deaths each year in the US and Europe, respectively.[1] Clear cell renal cell carcinoma (ccRCC) is the most common form of kidney cancer, originating from renal epithelium. Updates have been made to the pathology classification of kidney tumors, with the main subtypes of ccRCC being chromophobe tumors, papillary (types I and II), and clear cell tumors.[2] Around 25 to 30% of ccRCC patients are diagnosed when the cancer has already spread locally or internationally. Following successful treatment of a localized tumor, approximately one-third of ccRCC cases will experience continued growth. In the past, cytokines played a significant role in the treatment of advanced ccRCC despite their notable side effects. These medications yielded a response rate of 10 to 15% and a median overall survival of 10 to 12 months.[3] Over the last decade, several targeted therapies have been developed simultaneously, leading to significant improvements in treatment outcomes due to advancements in our understanding of the molecular biology of ccRCC. Currently, patients with advanced ccRCC have a 50% chance of surviving for more than two years after diagnosis.

Molecular Biology

Clear cell renal cell carcinoma

In 95 and 5% of cases, respectively, clear cell RCC (ccRCC) is more likely to occur sporadically than as part of a hereditary familial condition.[4] Mutations in the VHL gene cause the Von Hippel-Lindau (VHL) syndrome. This syndrome is associated with an increased risk of medical conditions such as hemangioblastomas, retina angiomas, and ccRCC (40–60% of cases). The aberrant function of the VHL gene, either through mutations or post-transcriptional modifications, is linked to up to 90% of sporadic ccRCC.[5] Understanding this molecular pathway has paved the way for the development of personalized medicines for patients with colorectal cancer. The protein [pVHL], encoded by the VHL gene, controls the expression level of the transcription factor hypoxia-inducible factor (HIF). HIF regulates the cell's response to oxygen availability. In a normoxic environment, HIF interacts with pVHL, leading to its degradation. Conversely, low oxygen levels or pVHL deficiencies result in HIF accumulation and the transcription of genes involved in cellular adaptation to hypoxia. The activation of vascular endothelial growth factor (VEGF), transforming growth factor (TGF) alpha and beta, and platelet-derived growth factor (PDGF) promotes angiogenesis, cell proliferation, and glycolysis.[6] Novel targeted treatments for

advanced colorectal cancer have been approved by targeting these proteins and their appropriate receptors. The Cancer Genome Atlas (TCGA) project's analysis of over 400 ccRCC samples also supported these findings. The most significant genetic changes in this tumor sub-type were related to cellular oxygen sensing, including VHL and its pathway constituents. Additionally, common mutations were found in other chromatin-modulating genes, such as SETD2, KDM5C, PBRM1, and BAP1. Aggressive tumors showed up-regulation of genes involved in fatty acid synthesis and glycolysis, while nearly a third of cases had mutations in the PI3K/AKT/mTOR signaling pathway, which regulates genes involved in the Krebs cycle. These findings, combined with gene expression data, are likely to contribute to a future classification system that will aid in matching tumors with the most effective treatment options.[7,8]

Papillary Tumors

Two distinct types of primary papillary RCC (pRCC), type 1 and type 2, have been identified as having different biological characteristics, as well as clinical and pathological diversity. Type 1 pRCC is often linked to alterations in the MET pathway, while type 2 pRCC is defined by SETD2 mutations, TFE3 fusions, CDKN2A silencing, and activation of the NRF2-ARE pathway. Some tumors within this category exhibit a CpG island methylator phenotype (CIMP), which is associated with a poor prognosis and FH mutations. The TCGA project suggests that type 2 pRCC can be further categorized into sub-types IIa, IIb, and CIMP profiles based on molecular and phenotypic features.

Papillary Type I Renal Cell Carcinoma

An increased risk of bilateral type I papillary RCC is associated with an inherited condition called hereditary papillary RCC syndrome (HPRC). The cause of HPRC is an activating mutation in the MET gene located on chromosome 7. Research on peripapillary RCC type I (pRCC)[9] indicates that even in sporadic forms, up to 81% of patients have altered MET due to a mutation, splice variant, gene fusion, or high copy number of chromosome 7. The gene MET (HGF) encodes the trans membranal receptor for hepatocyte growth factor (HGF). HGF binds to its receptor, stimulating cellular pathways for proliferation and triggering second messenger molecules like GRB2, GAB1, or PI3K. Despite HGF binding, the activating mutation of MET leads to persistent stimulation of its receptor. However, additional oncogenic events within the cell are required for the development of papillary RCC tumors.[10] This supports the rationale for a treatment strategy targeting MET and its regulators in RCC, especially in papillary type I tumors.[11]

Papillary Type II Renal Cell Carcinoma

Papillary type II RCC is often associated with the Hereditary Leiomyomata's RCC (HLRCC) syndrome, which is characterized by the presence of cutaneous and uterine leiomyomas and an aggressive form of kidney cancer.[12] The HLRCC condition is caused by a mutation in the fumarate hydratase gene, which leads to a decrease in intracellular levels of fumarate, an important component of the Krebs cycle. In the absence of functional fumarate hydratase, fumarate accumulates and inhibits the breakdown of HIF through hydroxylation. The complexity of this tumor subtype has been revealed through genomic analysis of its sporadic forms using the TCGA.

Chromophobe Renal Cell Carcinoma

The gene called homonyms, situated on the short arm of chromosome 17, possesses an inherited, inactivating mutation that leads to the familial syndrome called Birt-Hogg-Dube (BHD). Various types of renal tumors, including hybrid oncocytic neoplasm (50%), chromophobe RCC [chRCC] (33%), ccRCC (10%), and oncocytoma (7%), are associated with an elevated risk of this condition.[13] Fibrofolliculomas, which are benign hair follicle tumors, are present in 85% of cases of this syndrome. These tumors are diagnosed as pulmonary cysts and are highly likely to be connected to spontaneous pneumothorax in over 85% of individuals affected by BHD syndrome. Approximately 90% of family members of BHD patients carry the underlying germline mutation of the BHD gene.[14]

Therapies in RCC

Approved drugs

The primary objective in treating metastatic RCC (mRCC) is to target angiogenesis. To achieve this, therapeutic strategies involve the utilization of tyrosine kinase inhibitors to hinder the vascular endothelial growth factor receptor (VEGFR) and monoclonal antibodies to obstruct VEGF (Fig. 1). Recent advancements in research have resulted in the development of several anticancer drugs that combine both effects. List of drugs used for cancer treatment as shown in Table 1.

Cabozantinib

Preclinical investigations have revealed the potential anti-tumor effects of cabozantinib, an oral TKI targeting MET, VEGFR2, AXL, and RET. Phase I and II trials have shown promising results, with a 28% PR and a median PFS of approximately 15 months.[16] The main adverse events reported were hyponatremia, hypophosphatemia, fatigue, diarrhea, and hypertension.[17] Cabozantinib's clinical trials focused on patients who had progressed after prior treatments. In the METEOR phase III trial, patients with RCC resistant to anti-angiogenics were randomly assigned to receive either cabozantinib (60 mg daily) or everolimus (10 mg daily) (Fig. 2). The cabozantinib arm showed a longer median PFS (7.4 *versus* 3.8 months; HR 0.58; 95% CI 0.45–0.75) and a higher ORR (21% *versus* 5%). An interim analysis also indicated a higher median OS in the cabozantinib group (HR

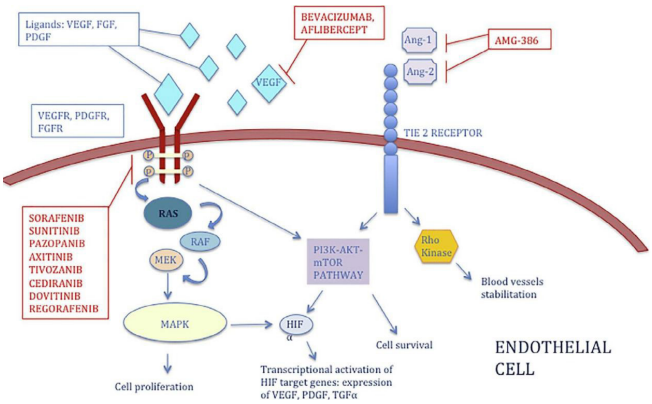

Fig. 1: Angiogenesis pathway and targeted therapies in RCC[15]

0.67; 95% CI 0.51–0.89) with manageable side effects. Cabozantinib was approved by the FDA and EMA in 2016 for treating advanced RCC resistant to anti-angiogenics at a dosage of 60 mg per day.[18] The phase II CABOSUN trial demonstrated a superior median PFS with cabozantinib compared to sunitinib in patients with intermediate or poor prognosis mRCC (8.2 *versus* 5.6 months; one-sided $p = 0.012$; adjusted hazard ratio, 0.66; 95% CI, 0.46–0.95) along with a better ORR (46 *versus* 18%). Grade 3–4 AEs were reported in 67% of patients on cabozantinib and 68% on sunitinib.

Adverse reactions such as hematological toxicity, fatigue, hypertension, diarrhea, and Palmer-plantar erythrodysesthesia were documented. Based on the data, there is a chance that this compound may be utilized as a primary treatment option in the future.[19]

Medical Uses

There are two methods of utilizing cabozantinib. Cometriq, available in capsule form, is employed for the treatment of medullary thyroid cancer.[20,21] On the other hand, cabometyx, in tablet form, is utilized to address differentiated thyroid carcinoma, hepatocellular carcinoma, and renal cell carcinoma.[22-24]

Contraindications

Cabozantinib has not undergone testing on pregnant women, but it has been found to be harmful to rodent fetuses. Therefore, women who are taking this medication or planning to conceive while on it should take precautions to avoid pregnancy. The potential transfer of cabozantinib through breast milk is still uncertain, as there is no information available regarding its excretion in breast milk.[21,23]

Adverse Effects

The following adverse effects were observed

Formation of blood clots, cardiac events or cerebrovascular accidents, elevated blood pressure, hypertensive emergency osteonecrosis of the jaw, profuse diarrhea, vertigo, impaired vision, convulsions, presence of protein in urine, decreased appetite, migraine, vertigo, hypocalcemia reduced thyroid hormone levels.[20-24]

Immunotherapy

Active immunotherapy: Anti-PD1

The development of targeted therapies has revolutionized the treatment approach for renal cell carcinoma (RCC) in recent years. However, it is important to note that VEGF/VEGFR and mTOR inhibitors may not always yield favorable outcomes for patients. Despite their potential benefits, these agents can fail to produce durable responses and resistance can emerge, either as primary refractory or after an initial period of improvement. Considering this, researchers have explored alternative strategies, such as stimulating the immune system through medications that target checkpoint pathways like programmed cell death 1 (PD1) and programmed cell death ligand 1 (PDL1).[25]

Nivolumab

BMS-936558, also known as nivolumab, is a fully human IgG4 antibody targeting PD1. In a phase I clinical trial, a previously treated RCC patient experienced a lasting partial response after just three nivolumab infusions, lasting over eighteen months. Pneumonitis, a respiratory condition, was among the grade 3 to 4 toxicities affecting 14% of patients, leading to fatal outcomes in 3 cases.[26] These findings drove the clinical development of nivolumab in mRCC. In the CheckMate 025 phase III trial, 821 mRCC patients who had received one or two lines of anti-angiogenic therapy were randomized to receive nivolumab 3 mg/kg, i.e., every two weeks or 10 mg of everolimus orally daily.[27] The experimental arm showed a response rate of 25% *versus* 5% and a median OS of 25 months versus 19 months (HR 0.73; $p = 0.002$), indicating better clinical outcomes. Grade 3 to 4 toxicities were reported in 19 and 37% of patients, respectively. Further analysis highlighted concerns about pseudo-progression under immunotherapy, suggesting clinical benefits from nivolumab even without radiological progression.[28] Nivolumab was approved by the FDA in November 2015 and by the EMA in February 2016 for treating RCC post-TKI therapy progression.

Medical Uses

Nivolumab is administered as a primary treatment option for inoperable or metastatic melanoma, in combination with ipilimumab, if the cancer lacks a BRAF mutation.[29] However, if the cancer does possess a BRAF mutation, nivolumab is utilized as a secondary treatment following ipilimumab therapy alongside a BRAF inhibitor.[29,30] Additionally, nivolumab is employed in the management of small cell lung cancer and metastatic squamous non-small cell lung cancer that continues to progress despite platinum-based medications.[29,31] Furthermore, it serves as an alternative treatment approach for renal cell carcinoma in cases where anti-angiogenic therapy has proven ineffective.[29]

Side Effects

The following adverse effects were observed

Immune-mediated inflammation of the lungs, colon, liver, and kidneys. Type 1diabetes may develop cough, upper respiratory tract infections, peripheral edema, rash, and itchy skin, ventricular arrhythmia, iridocyclitis (eye inflammation), vitiligo and psoriasis, chest pain, shortness of breath, muscle and joint pain, decreased appetite, abdominal pain, and constipation.[29,32]

Mechanism of Action

By targeting specific cancer cells, T lymphocytes provide protection against cancer within the body. However, cancer cells produce

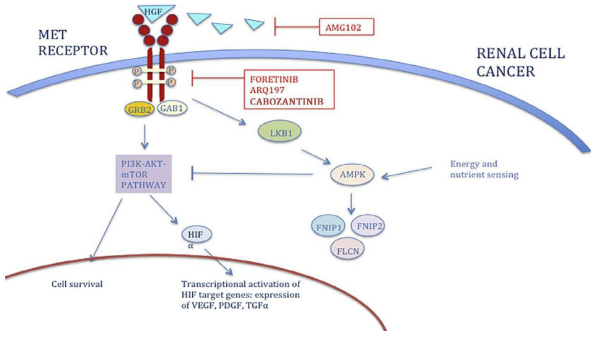

Fig. 2: MET pathway and targeted therapies in RCC[15]

Table 1: List of drugs used for cancer treatment

S. No.	*Drug*	*Efficacy (%)*	*Survival*	*Adverse effects*	*Cost*
1.	Nivolumab & cabozantinib	50 & 95	18.1 months for overall survival	Fatigue, nausea, diarrhea, vomiting, high blood pressure, decreased appetite, taste change, low blood platelets,	Nivolumab 100 mg -Rs. 83,000 Cabozantinib 40 mg- Rs. 14,000
2.	Ipilimumab	60	12-month overall survival rate	Fatigue, diarrhea, skin rash	Ipilimumab 50 mg- Rs. 1,48,000
3.	Axtinib	85.7	15.7 months overall survival rate	Decrease in appetite, weight loss, nausea, vomiting, constipation	Axtinib 5mg- RS. 42,999
4.	Lenvatinib	86.0	12.1 months overall survival rate	Musculoskeletal pain, hypertension, stomatitis, decreased appetite, rash, nausea, and proteinuria.	Lenvatinib 10 mg- RS. 25,000

proteins to resist T cells. Nivolumab blocks these protective proteins, allowing the T cells to effectively eliminate the cancer cells. An immune checkpoint blockade is depicted to illustrate this process.[33,34]

PD-1 is a protein found on activated T lymphocytes' surface. When PD-L1 or PD-L2 (programmed cell death 1 ligand 1 or 2) binds to PD-1, the T cell becomes inactive. This mechanism helps regulate the immune system to prevent an excessive response. Cancer cells often release PD-L1, which hinders T lymphocytes from attacking the tumor. Nivolumab works by preventing PD-L1 from binding to PD-1, enabling the T cells to function properly. PD-L1 is detected in 40 to 50% of melanomas and is minimally expressed in most internal organs except for placental tissue and respiratory epithelium.[35]

CONCLUSION

Numerous targeted agents have been developed, with many more currently undergoing clinical development, all in conjunction with the notable progress made in our understanding of the molecular biology and cytogenetics of RCC over the past decade. The elements associated with angiogenesis and their governing mechanisms are arguably the most extensively studied targets in RCC therapeutics, and they continue to be so. Despite these significant advancements, several crucial questions remain unanswered, including optimal patient selection, primary and secondary resistance mechanisms, and the most effective sequencing of available compounds. To maximize patient benefit and establish a sustainable system, research efforts should be directed toward addressing these needs.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin2017; 67:7–30.
2. Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO classification of tumors of the urinary system and male genital organs-Part A: renal, penile, and testicular tumors. Eur Urol 2016;70(1):93–105.
3. Coppin C, Porzsolt F, Awa A, Kumpf J, Coldman A, Wilt T. Immunotherapy for advanced renal cell cancer. Cochrane Database systematic review 20159:(12); CD001425.
4. Pavlovich CP, Schmidt LS. Searching for the hereditary causes of renal-cellcarcinoma. Nat Rev Cancer 2004 May;4(5):381–93.
5. Nickerson ML, Jaeger E, Shi Y, Durocher JA, Mahurkar S, Zaridze D, et al.Improved identification of von Hippel-Lindau gene alterations in clear cell renal tumors. Clin Cancer Res 2008;14(15):4726–34.
6. Maxwell PH, Wiesner MS, Chang GW, Clifford SC, Vaux EC, Cockman ME, et al. The tumor suppressor protein VHL targets hypoxia-inducible factors for oxygen- dependent proteolysis. Nature 1999;399(6733):271–5.
7. Cancer Genomics Atlas Research N. Comprehensive molecular characterization of clear cell renal cell carcinoma. Nature 2013;499(7456):43–9.
8. Brugarolas J. Molecular genetics of clear-cell renal cell carcinoma. J Clin Oncol 2014;32(18):1968–76.
9. Linehan WM, Spellman PT, Ricketts CJ, Creighton CJ, Fei SS, Davis C, et al. Comprehensive molecular characterization of papillary renal-cell carcinoma the cancer genome atlas research network. N Engl J Med 2016;374 (2):135–45.
10. Kovacs G, Fuzesi L, Emanual A, Kung HF. Cytogenetics of papillary renal cell tumors. Genes Chromosomes Cancer 1991;3(4):249–55.
11. Choueiri TK, Vaishampayan U, Rosenberg JE, Logan TF, Harzstark AL, Bukowski RM, et al. Phase II and biomarker study of the dual MET/VEGFR2 inhibitor foretinib in patients with papillary renal cell carcinoma. J Clin Oncol 2013;31(2):181–6.
12. Launonen V, Vierimaa O, Kiuru M, Isola J, Roth S, Pukkala E, et al. Inherited susceptibility to uterine leiomyomas and renal cell cancer. Proc Natl Acad Sci USA 2001;98(6):3387–92
13. Pavlovich CP, Walther MM, Eyler RA, Hewitt SM, Zbar B, Linehan WM, et al. Renal tumors in the Birt-Hogg-Dube syndrome. Am J Surg Pathol 2002;26 (12):1542–52.
14. Schmidt LS, Nickerson ML, Warren MB, Glenn GM, Toro JR, Merino MJ, et al.Germline BHD-mutation spectrum and phenotype analysis of a large cohort offamilies with Brit-Hogg-Dube syndrome. Am J Hum Genet 2005;76 (6):1023–33.
15. A. Sánchez-Gastaldo et al. / Cancer Treatment Reviews 60 (2017) 77–89.
16. Kurzrock R, Sherman SI, Ball DW, Forastiere AA, Cohen RB, Mehra R, et al.Activity of XL184 (Cabozantinib), an oral tyro-sine kinase inhibitor, in patients withmedullary thyroid cancer. J Clin Oncol 2011;29(19):2660–6.
17. Choueiri TK, Pal SK, McDermott DF, Morrissey S, Ferguson KC, Holland J, et al. A phase I study of cabozantinib (XL184) in patients with renal cell cancer. Ann Oncol 2014;25(8):1603–8.
18. Choueiri TK, Escudier B, Powles T, Tannir NM, Mainwaring PN, Rini BI, et al. METEOR investigators. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): results from a randomized, open-label, phase 3 trial. Lancet Oncol 2016;17(7):917–27.
19. Choueiri TK, Halabi S, Sanford BL, Hahn O, Michaelson MD, Walsh MK, et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: the alliance A031203 CABOSUN trial. J Clin Oncol 2017;35(6):591–7.
20. "Cometriq- cabozantinib kit Cometriq- cabozantinib capsule". DailyMed. 11February 2020. Retrieved 23 September 2020.
21. Cometriq 20 & 80 mg hard capsules - Summary of Product

Characteristics (SmPC)". (emc). 6 October 2022. Retrieved 9 April 2023.

22. "Cabometyx- cabozantinib tablet". DailyMed. 21 July 2020. Retrieved 23 September 2020.
23. "Cabometyx 20mg, 40mg, 60mg - Summary of Product Characteristics (SmPC)". (emc). 7 October 2022. Retrieved 9 April 2023.
24. FDA approves cabozantinib for differentiated thyroid cancer". U.S. Food and Drug Administration (FDA). 22 September 2021. Retrieved 22 September 2021. This article incorporates text from this source, which is inthe public domain.
25. Keir ME, Francisco LM, Sharpe AH. PD-1 and its ligands in T-cell immunity. Curr Opin Immunol 2007;19(3):309–14.
26. Brahmer JR, Drake CG, Wollner I, Powderly JD, Picus J, Sharfman WH, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: safety, clinical activity, pharmacodynamics, and immunologic correlates. J Clin Oncol 2010;28(19):3167.
27. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Eng J Med 2015;373(19):1803–13.
28. Escudier BJ, Motzer RJ, Sharma P, Wagstaff J, Plimack ER, Hammers HJ, et al. Treatment beyond progression with nivolumab (nivo) in patients 8pts) with advanced renal cell carcinoma (aRCC) in the phase III Checkmate 025 study. J Clin Oncol 34, 2016 (suppl; abstr 4509).
29. "OPDIVO- nivolumab injection". DailyMed. 17 December 2019. Retrieved 11March 2020.
30. Johnson DB, Peng C, Sosman JA (March 2015). "Nivolumab in melanoma: latest evidence and clinical potential". Therapeutic Advances in Medical Oncology. 7 (2): 97–106. doi:10.1177/1758834014567469. PMC 4346215. PMID 25755682.
31. Sundar R, Cho BC, Brahmer JR, Soo RA (March 2015). "Nivolumab in NSCLC: latest evidence and clinical potential". Therapeutic Advances in Medical Oncology.7(2):8596. doi:10.1177/1758834014567470. PMC 4346216. PMID 257556 81.
32. de Filette J, Andreescu CE, Cools F, Bravenboer B, Velkeniers B (March 2019). "A Systematic Review and Meta-Analysis of Endocrine-Related Adverse Events Associated with Immune Checkpoint Inhibitors". Hormone and Metabolic Research. 51 (3): 145–156. doi:10.1055/a-0843-3366. PMID 30861560.
33. Pardoll DM (March 2012). "The blockade of immune checkpoints in cancer immunotherapy". Nature Reviews. Cancer.12(4):25264. doi:10.1038/nrc3239 PMC 4856023. PMID 22437870.
34. Syn NL, Teng MW, Mok TS, Soo RA (December 2017). "De-novo and acquired resistance to immune checkpoint targeting". The Lancet. Oncology. 18 (12): e731– e741. doi:10.1016/s1470-2045(17)30607-1. PMID 29208439.
35. Johnson DB, Peng C, Sosman JA (March 2015). "Nivolumab in melanoma: latest evidence and clinical potential". Therapeutic Advances in Medical Oncology. 7 (2): 97–106. doi:10.1177/1758834014567469. PMC 4346215. PMID 25755682.

HOW TO CITE THIS ARTICLE: Rao TR, Bharath J. A Review on Systematic Treatment of Clear Cell Renal Cell Carcinoma Using Nivolumab And Cabozantinib. *J Adv Sci Res*. 2024;15(9): 1-5 **DOI:** 10.55218/JASR.2024150901