



Novel immunotherapy in metastatic renal cell carcinoma

Yang Hyun Cho, Myung Soo Kim, Ho Seok Chung, Eu Chang Hwang

Department of Urology, Chonnam National University Medical School, Gwangju, Korea

Despite the rapid development of therapeutic modalities for metastatic renal cell carcinoma (mRCC) over the past decade to include a number of targeted antiangiogenic therapies and traditional immunotherapy, such as high-dose interleukin-2 and interferon- α , mRCC continues to be associated with poor prognosis. Currently, several novel immunotherapy agents, such as cancer vaccines, adoptive cell therapy, and checkpoint inhibitors, such as programmed cell death-1 (PD-1 present on T cells), one of its ligands (PD-L1 present on antigen-presenting cells and tumor cells), and cytotoxic T-lymphocyte-associated protein-4 pathways, are being studied in mRCC and are showing promise as important steps in the management of this disease. This review summarizes the current landscape of standard and emerging immune therapeutics and other modalities for mRCC.

Keywords: Immune checkpoint inhibitors; Immunotherapy; Renal cell carcinoma; Vaccines

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Renal cell cancer (RCC) is not an uncommon malignancy, with an estimated worldwide annual incidence of about 270,000 new cases; approximately 25% to 30% of cases are metastatic at diagnosis [1,2] and 20% to 30% of patients who undergo surgical management for local RCC show relapse [3]. RCC is different from other variable epithelial tumors in that it is inherently resistant to cytotoxic chemotherapy and effective systemic therapeutics did not exist for a long period of time. Despite efficacy of high-dose interleukin-2 (IL-2) and interferon- α (IFN- α) for metastatic RCC (mRCC), the 5-year survival rate was only 10% [4,5]. In the past decade, several agents targeting antiangiogenesis and signal transduction pathways such as sunitinib, pazopanib, temsirolimus, everolimus, and axitinib have replaced the

use of cytokines after showing improved clinical benefit and survival, with a median survival to approximately 40 months and a progression-free survival of up to 27 months in randomized prospective clinical trials [6-8].

However, antiangiogenic therapeutics, which mainly target the vascular endothelial growth factor pathway and mammalian target of rapamycin pathways rarely cause durable tumor regressions and most patients will eventually experience disease progression. Currently, the rapidly evolving field of immuno-oncology is yielding novel immunotherapeutic agents. Cancer vaccines, adoptive T-cell therapy, and checkpoint inhibitors are some of the strategies being used in mRCC patients. This review will focus on a brief overview of the current treatment of mRCC using immunotherapy.

Received: 27 March, 2017 • **Accepted:** 24 April, 2017

Corresponding Author: Eu Chang Hwang

Department of Urology, Chonnam National University Hwasun Hospital, 160 Baekseo-ro, Dong-gu, Gwangju 61469, Korea
TEL: +82-61-379-7745, FAX: +82-61-379-7750, E-mail: urohwan@gmail.com

TRADITIONAL IMMUNOTHERAPY FOR mRCC

The fields of immuno-oncology have been connected since the late 19th century when the American bone surgeon and cancer researcher, William Coley, showed that an injection of killed bacteria into sites of sarcoma could bring out tumor shrinkage [9]. Following that, Chen and Mellman [10] reported that an adaptive immune response requires presentation and education about its targets, and cancer cell turnover and its associated apoptosis of cells lead to the release of tumor-associated antigens, which are then captured by antigen presenting cells, called the dendritic cells. Dendritic cells migrate to secondary lymphoid organs where effector T cells are being educated and activated. They then infiltrate tumors and recognize and induce the apoptosis of cancer cells expressing specific tumor-associated antigens or mutated proteins [10].

RCC has long been recognized as an immunologically sensitive tumor, with its select successes with IFN- α and high dose IL-2 treatment. IL-2 is a potent stimulator of T-cell proliferation and differentiation, while INF- α has antiangiogenic effects, promoting antigen presentation and dendritic cell maturation. However, their precise mechanism of action is not well known. The efficacy of IFN- α for mRCC patients were first reported in 1989 [11]. Subsequent phase III studies of IFN- α showed a 15% response rate and an increase in overall survival from 3 to 7 months [12]. However, most responses to IFN- α were of limited duration and only a small number of patients showed complete responses. In addition, long-term use of IFN- α was difficult due to side effects such as flulike symptoms and liver toxicity. High dose IL-2 was approved in 1992 for treatment of mRCC based on an objective response rate between 10 and 20%; many of the responses were durable [13]. High dose IL-2 showed partial responses in 13% and complete responses in 7%. After treatment, the response lasted for up to 91 months. Despite the response to high dose IL-2, there is a limitation of significant toxicity that can demonstrate in multiple organ systems, most significantly the heart, lungs, kidneys, and central nervous system.

VACCINES

Studies on vaccine therapies in mRCC are ongoing.

1. AGS-003

AGS-003 is a dendritic cell immuno-therapeutic vaccine constructed from autologous blood dendritic cells and

generated through electroporation of tumor-derived RNA and CD40 ligands into host immune cells, which was tested in combination with sunitinib [14-18]. Treatment is given by intradermal injection, and the tumor RNA-loaded mature dendritic cells present unique patient-specific tumor antigens via the major histocompatibility complex class I to T cells in tumor-draining lymph nodes. Furthermore, CD40 ligation promotes CD8 positive T-cell recruitment through regional production of IL-12. The phase II study of AGS-003 enrolled 21 patients with an intermediate or poor prognostic risk category of metastatic clear cells [16]. Patients were treated with 1 cycle of sunitinib (4 weeks on, 2 weeks off), followed by concomitant AGS-003 immunotherapy every 3 weeks for 5 doses and then every 12 weeks until tumor progression or the end of the study. Nine patients had a partial response, and four had stable disease. Median progression-free survival and overall survival were 11.2 months and 30.2 months, respectively, and 5 patients lived more than 5 years. Of 21 patients, 13 (62%) achieved a clinical benefit (9 with a partial response and 4 with stable disease). Treatment with AGS-003 was well tolerated, with injection site reactions as the primary adverse event. Remarkably, overall survival was more than 5 years in 5 patients (24%), with 2 patients achieving durable responses for more than 5 years. Based on these promising results, a randomized multicenter phase III ADAPT trial is now ongoing, to determine where there is an overall survival benefit between AGS-003 plus sunitinib in comparison to sunitinib alone in mRCC patients undergoing debulking nephrectomy (NCT01582672) [19].

2. IMA901

IMA901 is a therapeutic vaccine developed from multiple naturally presented tumor-associated peptides (TUMAP) [20-24]. A phase II clinical study investigated the effect of systemic treatment with IMA901 plus granulocyte macrophage-colony stimulating factor with or without cyclophosphamide as an additional immune-modulator before the first vaccination. The disease control rate at 6 months was 31% in the postcytokine group, and 14% at 6 months in the posttyrosine kinase inhibitors [22]. The majority of adverse events reported were local injection site reactions. A multicenter, open-label, randomized, phase III IMPRINT study comparing sunitinib with or without this vaccine for mRCC was recently completed. Unfortunately, the overall survival was not ameliorated with IMA901 plus sunitinib versus sunitinib alone [24].

3. Modified vaccinia Ankara (MVA-5T4; TroVax)

The 5T4 oncofetal antigen is rarely detected in normal

adult tissues but is expressed at high levels by the placenta and by a range of human carcinomas including kidney, colorectal, prostate, ovary, and breast. MVA-5T4 was engineered to stimulate the immune system to destroy cells expressing the 5T4 antigen. About 90% of renal cell tumors overexpress the tumor antigen 5T4 [25-28]. A randomized, double-blind, placebo-controlled phase III study (TRIST trial) assessed overall survival and safety in patients with metastatic clear cell RCC [28]. Patients were randomized to MVA-5T4 (n=365) or placebo (n=368) in combination with sunitinib, IL-2, or IFN- α . No significant difference in overall survival was apparent between the two treatment arms (median 20.1 months MVA-5T4 versus 19.2 months placebo; p=0.55). The adverse events profile was also similar between the treatment arms.

4. Autologous tumor cell lysate (Reniale)

Principally, autologous tumor cell lysate vaccine stimulates antigen-presenting cells, such as dendritic cells, and these cells stimulate a cytotoxic T lymphocyte response towards tumor associated antigens expressed by RCC, mediating tumor cell destruction [29-31]. Autologous tumor cell lysate vaccine improved progression-free survival in a phase III study of patients with organ confined RCC [32]. The 10-year follow-up analysis revealed that overall survival was comparable between the vaccine group and control patients. However, in subgroup analysis, pT3 RCC patients had overall survival benefit by Reniale (Liponova AG, Hannover, Germany). Additional current studies on non-protein antigens have been limited.

ADOPTIVE CELL THERAPY

Adoptive cell therapy, as an encouraging method of immunotherapy, harnesses the cells that can be expanded *in vitro* and have intrinsic antitumor activity to eliminate malignant cells. Examples include tumor antigen specific cytotoxic T lymphocytes (CTL), lymphokine-activated killer cells, tumor-infiltrating lymphocytes, and cytokine-induced killer cells [33-39]. Adoptive cell therapy for mRCC was reported in 1990 and since then many clinical trials of this therapy in mRCC patients have been completed. A number of studies of adoptive cell therapy for mRCC patients have shown the median survival is only 10.2 months and the 5-year survival rate is less than 15% [39]. However, the worth of adoptive cell therapy for mRCC is still unclear, especially for tumor regression and prolonging survival.

IMMUNE CHECKPOINT INHIBITORS

Immune checkpoint inhibitors are being investigated in the majority of solid and hematologic malignancies, and are already approved or under development. Immune checkpoint proteins on CTL cut off costimulatory signals at various stages of immune activation after ligand binding and this gives rise to T-cell anergy and immune suppression. Cutting off these immune checkpoint proteins appears to improve the capability of CTL to mount and maintain an effective T cell response [40-42]. Immune checkpoint inhibitors under investigation include the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitors, ipilimumab (YERVOY; Bristol-Myers Squibb, New York, NY, USA) and tremelimumab; the programmed cell death protein 1 (PD-1) inhibitors, nivolumab (OPDIVO; Bristol-Myers Squibb, New York, NY, USA, which is US Food and Drug Administration [FDA], approved), pembrolizumab (KEYTRUDA; Merck & Co., Inc., Kenilworth, New Jersey, USA), and pidilizumab; and the programmed cell death protein ligand 1 (PD-L1) inhibitors atezolizumab (TECENTRIQ; Roche, Basel, Swiss), BMS-936559, durvalumab, and avelumab [43] (Table 1).

1. CTLA-4 inhibitors

The immune system is modulated by a series of stimulatory and inhibitory signals that coordinate to show an appropriate response to a pathogenic threat. CTLA-4 is an immune checkpoint on the surface of cytotoxic T cells that counteracts the action of costimulatory receptor CD28 and plays a crucial role in the immune response. Ipilimumab, a human IgG that binds to and blocks CTLA4, was the first drug that was shown to produce a survival benefit in metastatic melanoma [44,45] and it received FDA approval for the treatment of advanced melanoma in 2011. In a phase II study of ipilimumab for mRCC, 5 of 40 responses were noted in the higher dose group (3 mg/kg every 3 weeks) compared to 1 of 21 responses in the lower dose group (3 mg/kg followed by 1 mg/kg every 3 weeks). Adverse events and tumor regression were more frequently observed in the higher dose group [46]. However, phase III trials investigating ipilimumab alone has not yet been studied.

2. PD-1 inhibitors

Programmed cell death-1 (PD-1) (CD279) is a cell surface receptor that consists of the Ig category and is expressed on activated effector T cells as well as natural killer cells and B cells. PD-1 interact with 2 ligands, PD-L1 and PD-L2, which are manifested in various cell types, including tumor cells [43,47,48]. A clinical study demonstrated that

Table 1. Ongoing clinical trials involving PD-1 and PD-L1 inhibitor use for treatment of metastatic renal cell carcinoma (phase II or III trials)

Drug	Line	NCT number ^a	Study name
PD-1 inhibitor			
Nivolumab (OPDIVO®)	2nd	NCT02596035	A Safety Trial of Nivolumab in Patients With Advanced or Metastatic Renal Cell Carcinoma
Nivolumab (OPDIVO®)	1st	NCT02446860	A Study of Anti-PD1 (Nivolumab) Therapy as Pre- and Post-operative Therapy in Metastatic Renal Cell Cancer (ADAPTeR)
Nivolumab (OPDIVO®) + Ipilimumab (YERVOY®)	1st	NCT02231749	Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma (CheckMate 214)
Pembrolizumab (KEYTRUDA®)	1st	NCT02014636	Safety and Efficacy Study of Pazopanib and MK 3475 in Advanced Renal Cell Carcinoma (RCC; KEYNOTE-018)
Pembrolizumab (KEYTRUDA®)	1st/2nd	NCT02348008	Phase Ib and Phase II Studies of Anti-PD-1 Antibody MK-3475 in Combination With Bevacizumab for the Treatment of Metastatic Renal Cell Carcinoma: Big Ten Cancer Research Consortium GU14-003
Pembrolizumab (KEYTRUDA®)	1st/2nd	NCT02619253	A Phase I/Ib, Open Label, Dose Finding Study to Evaluate Safety, Pharmacodynamics and Efficacy of Pembrolizumab (MK-3475) in Combination With Vorinostat in Patients With Advanced Renal or Urothelial Cell Carcinoma
PDL-1 inhibitor			
Atezolizumab (TECENTRIQ®)	1st	NCT02420821	A Study of Atezolizumab in Combination With Bevacizumab Versus Sunitinib in Participants With Untreated Advanced Renal Cell Carcinoma [IMmotion151]
Atezolizumab (TECENTRIQ®)	1st	NCT01984242	A Phase II, Randomized Study of Atezolizumab (Anti PD-L1 Antibody) Administered as Monotherapy or in Combination With Bevacizumab Versus Sunitinib in Participants With Untreated Advanced Renal Cell Carcinoma
Avelumab	1st	NCT02684006	A Study of Avelumab With Axitinib Versus Sunitinib In Advanced Renal Cell Cancer (JAVELIN Renal 101)

^ahttps://clinicaltrials.gov/.

PD-1/PD-L1 interaction is an important regulator of tumor immune tolerance and tumor growth in RCC. Thompson et al. performed immunostaining on formalin-fixed paraffin-embedded tissue samples and showed that tumor cell PD-L1 membranous expression was seen in 24% of samples and was strongly associated with cancer-specific death (risk ratio 3.92; p<0.001) in RCC patients [48,49]. In another study, PD-L1 expression was detected by immunostaining in RCC patients with fresh frozen tissue available, and PD-L1 expression by tumor cells (>10%), on infiltrating lymphocytes (>50%), or the composite of both makers was strongly associated with poor prognosis [48,50].

Several clinical trials of the anti-PD-1 antibody (nivolumab) have been performed for RCC. Nivolumab (OPDIVO) is a human IgG4 PD-1 inhibitor antibody that selectively blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2. In a phase I study that included 34 patients with mRCC, nivolumab demonstrated objective responses and a controlled safety profile; no maximum-tolerated dose was identified (0.1 to 10 mg/kg every 3 weeks) [51]. A phase II study, enrolled 168 patients with clear cell mRCC that had received at least one previous treatment (targeted agents or cytokines). Nivolumab was given at 0.3, 2, or 10 mg/kg every 3 weeks resulted in 20%–22% objective response rates of patients with a progression free survival of 2.7–4.2 months and an overall survival of 18.2–25.5 months. The most common treatment-related adverse event was fatigue (24%, 22%, and 35%, respectively) [52].

In the pivotal open-label, randomized phase III study (Check Mate 025), 821 patients with clear cell mRCC were treated with nivolumab (3 mg/kg every 2 weeks) and it reduced the hazard ratio for death (hazard ratio, 0.73; 95% confidence interval, 0.57–0.93; p=0.002) compared with everolimus (10 mg orally every day), representing a 5.4-month improvement in median overall survival (25 months and 19.6 months, respectively). The objective response rate among patients treated with nivolumab was 25% vs. 5% in the everolimus group (p<0.001). However, the median progression-free survival was similar between groups. The exact mechanism behind the discrepancy between progression-free survival and overall survival is not clear; the authors postulated that there might be a potential delayed benefit in progression-free survival with nivolumab. The clinical benefit provided by nivolumab was independent from PD-L1 expression. Grade 3 or 4 adverse events were also lower with nivolumab compared with everolimus (19% and 37%, respectively) [53]. Recently, nivolumab was approved by the US FDA and the European Medicines Agency as a second line therapy for clear cell mRCC.

Other PD-1 inhibitors, such as pembrolizumab (KEYTRUDA, IgG4 monoclonal antibody) and pidilizumab (IgG1 monoclonal antibody), are currently undergoing clinical trials, the majority of which are combination trials. Pembrolizumab, approved for advanced melanoma and non-small-cell lung carcinoma, is currently being tested in two randomized phase II trials with mRCC patients [54]. There are several ongoing trials evaluating pembrolizumab in combination with other drugs.

3. Anti-PD-L1 antibodies

Based on the promising results of PD-1 inhibitors for the management of mRCC inspired more interest in the inhibition of the ligands of PD-1, namely PD-L1. PD-L1 is expressed on several cell types, including resting T cells, B cells, macrophages, dendritic cells, vascular endothelial cells, and pancreatic islet cells; PD-L2 is expressed only on macrophages and dendritic cells. PD-L1 and PD L2 inhibit T-cell proliferation and adhesion, as well as cytokine production [14,47,55]. Atezolizumab (TECENTRIQ), a PD-L1 antibody, has demonstrated encouraging results in a multicenter phase I monotherapy trial in 17 mRCC patients. The objective response rate was 12% and responses lasted 4 to 17 months. Seven mRCC patients (41%) had stable disease for at least 24 weeks [47]. In another recent study to evaluate the safety and clinical activity of atezolizumab, clear cell mRCC patients were evaluable for median overall survival, median progression free survival, and objective response rate (28.9 months, 5.6 months and 15%, respectively) [56].

BMS-936559 binds human PD-L1 with high affinity and blocks PD-L1 binding to both PD-1 and B7.1. In a phase I study, 207 patients with different tumors were treated with BMS936559, including clear cell mRCC, showed 6%–17% of overall response rates with 2 of 17 patients having an objective response. The treatment was well tolerated; grade 3 or 4 adverse events were observed in 9% of patients [57].

Other PD-L1 inhibitors, durvalumab and avelumab, are currently undergoing clinical trials.

COMBINATION STRATEGIES

Previously mentioned dynamic nature of the immune tumor response and intricacy of the regulation of various immune checkpoints, there is a reason to assist combination immunotherapy strategies to maximize clinical benefit. Therefore, a number of combination strategies such as PD-1/PD-L1 blockade, PD-1 inhibitor with antiangiogenesis inhibitors, PD-1 inhibitor with other immunotherapeutic agents and combination with radiotherapy are currently

ongoing clinical trial investigation for mRCC patients. Several recently accomplished trials and ongoing randomized phase III clinical trials are analyzing various treatments to determine whether there is a most favorable sequence of targeted agents and if combination strategy with targeted therapeutic agents benefits mRCC patients. However, the combination of immunotherapeutic agents does have considerable toxicities such as gastrointestinal, hepatic toxicities and careful patient selection be guaranteed [58,59]. Therefore, as we develop novel immunotherapeutics and reasonable rational combinations, much more study should be performed.

CYTOREDUCTIVE NEPHRECTOMY

Elimination of the primary tumor (debulking or cytoreductive nephrectomy) should be performed in all renal cell carcinoma patients where is clinically feasible and justifiable before starting systemic therapy. Randomized many clinical trials showed that renal cell carcinoma patients who receive a cytoreductive nephrectomy treated with IFN- α and immunotherapy had survival benefit compared with those with a not resected primary tumors [60,61]. In the era of immunotherapeutics, the role of cytoreductive nephrectomy is not apparently definite. Currently, 2 prospective randomized phase III studies (CARMENA; NCT00930033 and EORTC 30073) is now in progress and awaiting the results. Even, in the era of novel immunotherapeutic agents, cytoreductive nephrectomy or metastatectomy would still have some roles in highly selected clinically feasible mRCC patients [62].

CONCLUSIONS

New perceptions in cancer immunology have led to the development of new immune modulatory agents. From this perspective, the treatment of mRCC continues to evolve faster than ever before and new targeted agents have been developed with treatment regimens that continue to be optimized. Results from recent clinical trials with immunotherapeutic agents suggest that immunotherapy, such as monotherapy or in combination with other agents, with these agents is capable of producing durable responses and significant overall survival improvement. Thus, in the future, immunotherapy alone or together with other treatments, will likely cause a paradigm shift in the clinical management of mRCC patients. Moreover, further studies are warranted to identify biomarkers that reliably predict treatment benefit from these new therapies.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

- Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2015. Toronto (ON): Canadian Cancer Society; 2015.
- Ljungberg B, Campbell SC, Choi HY, Jacqmin D, Lee JE, Weikert S, et al. Corrigendum to "The epidemiology of renal cell carcinoma" [Eur Urol 2011;60:615-21]. *Eur Urol* 2011;60:1317.
- Athar U, Gentile TC. Treatment options for metastatic renal cell carcinoma: a review. *Can J Urol* 2008;15:3954-66.
- Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. *Cancer Treat Rev* 2008;34:193-205.
- Rosenberg SA, Lotze MT, Muul LM, Chang AE, Avis FP, Leitman S, et al. A progress report on the treatment of 157 patients with advanced cancer using lymphokine-activated killer cells and interleukin-2 or high-dose interleukin-2 alone. *N Engl J Med* 1987;316:889-97.
- Escudier B, Goupil MG, Massard C, Fizazi K. Sequential therapy in renal cell carcinoma. *Cancer* 2009;115(10 Suppl):2321-6.
- Sun M, Lughezzani G, Perrotte P, Karakiewicz PI. Treatment of metastatic renal cell carcinoma. *Nat Rev Urol* 2010;7:327-38.
- Hutson TE. Targeted therapies for the treatment of metastatic renal cell carcinoma: clinical evidence. *Oncologist* 2011;16 Suppl 2:14-22.
- Decker WK, Safdar A. Bioimmunoadjuvants for the treatment of neoplastic and infectious disease: Coley's legacy revisited. *Cytokine Growth Factor Rev* 2009;20:271-81.
- Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity* 2013;39:1-10.
- Oliver RT, Nethersell AB, Bottomley JM. Unexplained spontaneous regression and alpha-interferon as treatment for metastatic renal carcinoma. *Br J Urol* 1989;63:128-31.
- Fossà SD. Interferon in metastatic renal cell carcinoma. *Semin Oncol* 2000;27:187-93.
- Floros T, Tarhini AA. Anticancer cytokines: biology and clinical effects of interferon- α 2, interleukin (IL)-2, IL-15, IL-21, and IL-12. *Semin Oncol* 2015;42:539-48.
- Combe P, de Guillebon E, Thibault C, Granier C, Tartour E, Oudard S. Trial watch: therapeutic vaccines in metastatic renal cell carcinoma. *Oncoimmunology* 2015;4:e1001236.
- Figlin RA. Personalized immunotherapy (AGS-003) when combined with sunitinib for the treatment of metastatic renal cell carcinoma. *Expert Opin Biol Ther* 2015;15:1241-8.
- Amin A, Dudek AZ, Logan TE, Lance RS, Holzbeierlein JM, Knox JJ, et al. Survival with AGS-003, an autologous dendritic cell-based immunotherapy, in combination with sunitinib in unfavorable risk patients with advanced renal cell carcinoma (RCC): Phase 2 study results. *J Immunother Cancer* 2015;3:14.
- Bedke J, Stenzl A. Immunotherapeutic strategies for the treatment of renal cell carcinoma: where are we now? *Expert Rev Anticancer Ther* 2013;13:1399-408.
- Pal SK, Hu A, Figlin RA. A new age for vaccine therapy in renal cell carcinoma. *Cancer J* 2013;19:365-70.
- ClinicalTrials.gov. Phase 3 trial of autologous dendritic cell immunotherapy (AGS-003) plus standard treatment of advanced renal cell carcinoma (RCC). ClinicalTrials.gov Identifier: NCT01582672 [Internet]. Bethesda (MD): U.S. National Library of Medicine, U.S. National Institutes of Health, U.S. Department of Health and Human Services; c2017 [cited 2017 Mar 2]. Available from: <https://clinicaltrials.gov/ct2/show/NCT01582672>
- Bedke J, Stenzl A. IMA901: a peptide vaccine in renal cell carcinoma. *Expert Opin Investig Drugs* 2013;22:1329-36.
- Kirner A, Mayer-Mokler A, Reinhardt C. IMA901: a multi-peptide cancer vaccine for treatment of renal cell cancer. *Hum Vaccin Immunother* 2014;10:3179-89.
- Walter S, Weinschenk T, Stenzl A, Zdrojowy R, Pluzanska A, Szczylik C, et al. Multi-peptide immune response to cancer vaccine IMA901 after single-dose cyclophosphamide associates with longer patient survival. *Nat Med* 2012;18:1254-61.
- Finke JH, Rini B, Ireland J, Rayman P, Richmond A, Golshayan A, et al. Sunitinib reverses type-1 immune suppression and decreases T-regulatory cells in renal cell carcinoma patients. *Clin Cancer Res* 2008;14:6674-82.
- Rini BI, Stenzl A, Zdrojowy R, Kogan M, Shkolnik M, Oudard S, et al. IMA901, a multi-peptide cancer vaccine, plus sunitinib versus sunitinib alone, as first-line therapy for advanced or metastatic renal cell carcinoma (IMPRINT): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet Oncol* 2016;17:1599-611.
- Amato RJ. 5T4-modified vaccinia Ankara: progress in tumor-associated antigen-based immunotherapy. *Expert Opin Biol Ther* 2010;10:281-7.
- Amato RJ, Shingler W, Goonewardena M, de Belin J, Naylor S, Jac J, et al. Vaccination of renal cell cancer patients with modified vaccinia Ankara delivering the tumor antigen 5T4 (TroVax) alone or administered in combination with interferon-alpha (IFN-alpha): a phase 2 trial. *J Immunother* 2009;32:765-72.
- Kaufman HL, Taback B, Sherman W, Kim DW, Shingler WH, Moroziewicz D, et al. Phase II trial of Modified Vaccinia Ankara (MVA) virus expressing 5T4 and high dose Interleukin-2 (IL-2) in patients with metastatic renal cell carcinoma. *J Transl*

- Med 2009;7:2.
28. Amato RJ, Hawkins RE, Kaufman HL, Thompson JA, Tomczak P, Szczylik C, et al. Vaccination of metastatic renal cancer patients with MVA-5T4: a randomized, double-blind, placebo-controlled phase III study. *Clin Cancer Res* 2010;16:5539-47.
 29. Wittke S, Baxmann S, Fahlenkamp D, Kiessig ST. Tumor heterogeneity as a rationale for a multi-epitope approach in an autologous renal cell cancer tumor vaccine. *Onco Targets Ther* 2016;9:523-37.
 30. Matsushita H, Enomoto Y, Kume H, Nakagawa T, Fukuhara H, Suzuki M, et al. A pilot study of autologous tumor lysate-loaded dendritic cell vaccination combined with sunitinib for metastatic renal cell carcinoma. *J Immunother Cancer* 2014;2:30.
 31. Wang H, Feng F, Zhu M, Wang R, Wang X, Wu Y, et al. Therapeutic efficacy of dendritic cells pulsed by autologous tumor cell lysate in combination with CIK cells on advanced renal cell carcinoma. *Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi* 2015;31:67-71.
 32. May M, Kendel F, Hoschke B, Gilfrich C, Kiessig S, Pflanz S, et al. Adjuvant autologous tumour cell vaccination in patients with renal cell carcinoma. Overall survival analysis with a follow-up period in excess of more than 10 years. *Urologe A* 2009;48:1075-83.
 33. Rosenberg SA, Lotze MT, Muul LM, Leitman S, Chang AE, Ettinghausen SE, et al. Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. *N Engl J Med* 1985;313:1485-92.
 34. Rosenberg SA, Lotze MT, Yang JC, Topalian SL, Chang AE, Schwartzentruber DJ, et al. Prospective randomized trial of high-dose interleukin-2 alone or in conjunction with lymphokine-activated killer cells for the treatment of patients with advanced cancer. *J Natl Cancer Inst* 1993;85:622-32.
 35. Tomita Y, Katagiri A, Saito K, Imai T, Saito T, Tanikawa T, et al. Adoptive immunotherapy of patients with metastatic renal cell cancer using lymphokine-activated killer cells, interleukin-2 and cyclophosphamide: long-term results. *Int J Urol* 1998;5:16-21.
 36. Wersäll P, Mellstedt H. Increased LAK and T cell activation in responding renal cell carcinoma patients after low dose cyclophosphamide, IL-2 and alpha-IFN. *Med Oncol* 1995;12:69-77.
 37. Thompson JA, Lee DJ, Lindgren CG, Benz LA, Collins C, Shuman WP, et al. Influence of schedule of interleukin 2 administration on therapy with interleukin 2 and lymphokine activated killer cells. *Cancer Res* 1989;49:235-40.
 38. Perica K, Varela JC, Oelke M, Schneck J. Adoptive T cell immunotherapy for cancer. *Rambam Maimonides Med J* 2015;6:e0004.
 39. Tang X, Liu T, Zang X, Liu H, Wang D, Chen H, et al. Adoptive cellular immunotherapy in metastatic renal cell carcinoma: a systematic review and meta-analysis. *PLoS One* 2013;8:e62847.
 40. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;12:252-64.
 41. Webster RM. The immune checkpoint inhibitors: where are we now? *Nat Rev Drug Discov* 2014;13:883-4.
 42. Byun DJ, Wolchok JD, Rosenberg LM, Girotra M. Cancer immunotherapy - immune checkpoint blockade and associated endocrinopathies. *Nat Rev Endocrinol* 2017;13:195-207.
 43. Ghatalia P, Zibelman M, Geynisman DM, Plimack ER. Checkpoint inhibitors for the treatment of renal cell carcinoma. *Curr Treat Options Oncol* 2017;18:7.
 44. Lipson EJ, Drake CG. Ipilimumab: an anti-CTLA-4 antibody for metastatic melanoma. *Clin Cancer Res* 2011;17:6958-62.
 45. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711-23.
 46. Yang JC, Hughes M, Kammula U, Royal R, Sherry RM, Topalian SL, et al. Ipilimumab (anti-CTLA4 antibody) causes regression of metastatic renal cell cancer associated with enteritis and hypophysitis. *J Immunother* 2007;30:825-30.
 47. Weinstock M, McDermott D. Targeting PD-1/PD-L1 in the treatment of metastatic renal cell carcinoma. *Ther Adv Urol* 2015;7:365-77.
 48. Tykodi SS. PD-1 as an emerging therapeutic target in renal cell carcinoma: current evidence. *Onco Targets Ther* 2014;7:1349-59.
 49. Thompson RH, Kuntz SM, Leibovich BC, Dong H, Lohse CM, Webster WS, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. *Cancer Res* 2006;66:3381-5.
 50. Thompson RH, Gillett MD, Cheville JC, Lohse CM, Dong H, Webster WS, et al. Costimulatory B7-H1 in renal cell carcinoma patients: indicator of tumor aggressiveness and potential therapeutic target. *Proc Natl Acad Sci U S A* 2004;101:17174-9.
 51. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443-54.
 52. Motzer RJ, Rini BI, McDermott DF, Redman BG, Kuzel TM, Harrison MR, et al. Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. *J Clin Oncol* 2015;33:1430-7.
 53. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015;373:1803-13.
 54. Godwin JL, Zibelman M, Plimack ER, Geynisman DM. Immune checkpoint blockade as a novel immunotherapeutic

- strategy for renal cell carcinoma: a review of clinical trials. *Discov Med* 2014;18:341-50.
55. Gunturi A, McDermott DF. Potential of new therapies like anti-PD1 in kidney cancer. *Curr Treat Options Oncol* 2014;15:137-46.
 56. McDermott DF, Sosman JA, Sznol M, Massard C, Gordon MS, Hamid O, et al. Atezolizumab, an anti-programmed death-ligand 1 antibody, in metastatic renal cell carcinoma: long-term safety, clinical activity, and immune correlates from a phase Ia study. *J Clin Oncol* 2016;34:833-42.
 57. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012;366:2455-65.
 58. Pal SK, Vogelzang NJ. Sequential treatment strategies and combination therapy regimens in metastatic renal cell carcinoma. *Clin Adv Hematol Oncol* 2013;11:146-55.
 59. Buonerba C, Di Lorenzo G, Sonpavde G. Combination therapy for metastatic renal cell carcinoma. *Ann Transl Med* 2016;4:100.
 60. Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R; European Organisation for Research and Treatment of Cancer (EORTC) Genitourinary Group. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomised trial. *Lancet* 2001;358:966-70.
 61. Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H, Crawford ED. Cytoreductive nephrectomy in patients with metastatic renal cancer: a combined analysis. *J Urol* 2004;171:1071-6.
 62. Aslam MZ, Matthews PN. Cytoreductive nephrectomy for metastatic renal cell carcinoma: a review of the historical literature and its role in the era of targeted molecular therapy. *ISRN Urol* 2014;2014:717295.