Editorial

Immunotherapy in renal cell cancer: the more the merrier?

Jorge Camarero[1], Sol Ruiz[2]

[1]Pharmacology and Clinical Assessment Division, [2]Biotechnology and Advanced Therapies, Spanish Medicines Agency, Campezo 1 - Edificio 8, 28022 - Madrid, Spain

Correspondence to: Jorge Camarero. Pharmacology and Clinical Assessment Division, Spanish Medicines Agency, Campezo 1 - Edificio 8, 28022 - Madrid, Spain. Email: jcamarero@aemps.es.

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Renal cell carcinoma (RCC) is the most common primary malignancy affecting the kidney and considered a disease refractory to systemic therapy beyond cytokine therapy (the use of interferon alfa and interleukin 2 was limited when targeted therapies became available) (1). Currently, eight drugs are approved in the European Union (EU) for the treatment of advanced RCC, including IL-2, IFN-α, sorafenib, sunitinib, everolimus, temsirolimus, bevacizumab in combination with IFN-α, and pazopanib.

Despite the increasing availability of treatment options, a number of clinical trials are ongoing to identify and develop new therapeutic alternatives. Active immunotherapy has become an attractive option for the treatment of different types of cancer (2).

Due to the immunogenic nature of RCC, immunotherapy approaches are being developed but a number of factors have hampered their development, such as lack of defined antigens, selection of optimal dose and schedule, tumor escape from immune recognition (including loss or downregulation of HLA class I antigens) or tumor mediated suppression of immunity (involving regulatory T cells -Tregs-), increased oxidative stress, or recruitment of myeloid-derived suppressor cells (3). Indeed Steffen Walter and coauthors (4) have tried to target and investigate several of these mechanisms with a new immunotherapy for patients with RCC. Interestingly, their study has also pursued the identification of predictive biomarkers of immune response and efficacy of the "cancer vaccine".

Immune recognition of tumor-associated antigens by self-HLA (human leukocyte antigen) class I-restricted CD8+ cells is a key feature in detection and destruction of tumor cells. This is the main rationale Steffen Walter *et al*. have used for their approach, i.e. selection of HLA class I tumor-associated multiple peptides (TUMAPs) to try to stimulate an effective immune response against the tumor. The success of this treatment would require a normal expression of HLA class I genes (5) and, therefore, any regulatory or irreversible/structural defects underlying HLA class I loss may be a potential limitation for this approach. The second aim of the study was to identify an agent that reduced the number of Tregs in order to improve the clinical benefit of the vaccine. The role of Treg cells in cancer development and progression is not clear. Tregs may facilitate immune evasion through suppression on anti-tumor immune responses resulting in tumor growth (6). This is another basis for the rationale for IMA901 development. However, recent data indicate that the role of Tregs in other types of cancer, such as colorectal carcinoma, may be beneficial for the host by suppressing bacteria driven inflammation which, in the end, would promote carcinogenesis. Therefore, Tregs appear to play a dual role in cancer, sometimes being associated with a poor prognosis and others with more favourable prospects (7).

As a third aim the authors have also addressed a very interesting objective for this immunotherapy product, i.e. identification of biomarkers for a good clinical response.

From a point of view of product design, the advantages of this product are its simplicity and quite straightforward characterization as this is a mixture of 10 synthetic peptides. From the results published, the authors are presenting outcomes from a phase I and a phase II studies. For the phase I trial, 28 HLA-A*02+ subjects with RCC were recruited, 15 of them were treated with IMA901 as first line therapy, whereas 13 out of 28 had been previously treated up to three lines of treatment; 11 subjects achieved stable disease and one patient had a partial response.

In the phase II trial of Walter *et al*. 68 patients with metastatic RCC previously treated were randomised

1:1 to receive either cyclophosphamide (Cy; one single infusion administrated as an immunomodulator) together with IMA901 and GM-CSF or only IMA901 plus GM-CSF. Patients were stratified according to risk factors from Memorial Sloan-Kettering Cancer Center, (MSKCC) favourable or intermediate risk and previous treatment [cytokine or tyrosine kinase inhibitor (TKI)]. The primary endpoint was Disease Control Rate (DCR; percentage of subjects with complete or partial response or stable disease according to RECIST) after 6 months. Main secondary endpoints were Progression Free Survival (PFS), Overall Survival (OS), immunogenicity and safety. Results from this study showed a better DCR for those patients previously treated with cytokines than those receiving TKIs (31% *vs*. 14%). Focusing on the PFS and OS outcomes, no differences were observed between the two groups of study in terms of PFS, though OS was increased in the Cy+ arm [23.5 months for Cy+ compared with 14.8 months for Cy-, hazard ratio (HR) =0.57, P=0.090]. Several subgroup post-hoc analyses were carried out, showing positive results in immune responders. Of note, the median OS was not reached after 33.1 months in those patients previously treated with cytokines.

All these results seem to be pointing out to a promising treatment in metastatic RCC, although the design and sample size hamper the ability to draw firm conclusions. Indeed, results from the primary endpoint in both arms of the phase II study are unknown. Data from PFS did not show any differences between groups, and OS outcomes only appear to be outstanding in the subgroup which received previous cytokine treatment. In this way, subjects treated with cytokines could obtain a higher benefit of being treated with the cancer vaccine IMA901, whereas those patients with a TKIs front line treatment would not obtain better benefit than patients under either sorafenib or everolimus administration in second line. In fact, the median PFS for everolimus has been reported close to 4 months (RECORD-1 study) (8), albeit most of the patients in this study were heavily pre-treated; in other words, most likely patients with poorer prognosis. This apparent lower activity of the immunotherapy treatment in the TKIs pre-treated patients may indicate an unknown cross resistance mechanism, which could eventually reduce the clinical applicability for patients in second line, since the first line therapy currently used is based on TKIs and not on cytokines.

In addition, the analyses of the results, mainly PFS and OS, were carried out in the per protocol population (PP) (31 and 33 patients *vs*. 68 subjects for the ITT population). This latter caveat, methodologically speaking, goes further into subgroup analysis, with sample sizes of 17, 13, 22 or 9 patients. Interestingly, no results are shown regarding the other stratification factor, risk factor according to the MSKCC.

Taken together, these results should be considered as hypothesis generating and indeed a phase III trial is ongoing to investigate whether IMA901 can prolong OS in patients with metastatic and/or locally advanced RCC when added to standard first-line therapy with sunitinib.

In summary, the benefits of this new immunotherapy treatment seem to indicate that life expectancy for patients with metastatic and/or locally advanced RCC could be increased. However, the outcome appears to be solely outstanding in the subset of patients previously treated with cytokines, which is not deemed the standard first line therapy anymore. Despite this fact, a phase III trial will test IMA901 in combination with sunitinib, assessing OS as a primary endpoint, which is encouraging, since, as a whole, when oncologists prescribe a treatment without any expectations for full recovery, the control of the symptoms and patients' overall quality of life are the goal of the treatment. Certainly, these premises are usually sought in terms of PFS, especially from a regulatory view. However, the ongoing phase III study is ambitious and challenging, given that only temsirolimus (9) has demonstrated an increase in OS in first line for RCC patients.

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Footnote

Conflict of Interest: The authors have no conflicts of interest to declare.

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