Treatment for renal cell carcinoma (RCC) is undergoing landscape changes in recent years with introduction of immune check point inhibitors and combination regimens. Sunitinib and pazopanib are vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs). They have been the standard of care for the first line treatment of advanced RCC over a decade (1-3). Axitinib, sorafenib; the anti-VEGF monoclonal antibody bevacizumab; and the mammalian target of rapamycin (mTOR) inhibitors everolimus were often used in the second line or refractory setting with only 15–25% response rate, significant toxicities and limited time for progression free survival (PFS) and overall survival (OS) (4-6). Avelumab plus axitinib combination is just approved for first-line treatment of patients with advanced RCC on May 14, 2019. This breakthrough offers RCC patients with another new treatment option and better outcome based on the result from a phase III, randomized, multicenter, open-label JAVELIN Renal 101 trial (NCT02684006).

RCC is known to be immune sensitive with a record of interferon-alpha (IFN-α) and high-dose interleukin (IL)-2 therapies as the standards of care till VEGFR TKIs in 2007. High-dose IL-2 is still used in selective advanced RCC patients due to around 7% complete response and durable response (7). Immune checkpoint inhibitors such as anti-programmed cell death protein-1 (PD-1) and anti-programmed death-ligand 1 (PD-L1) monoclonal antibodies have made breakthroughs in multiple malignancies in recent years (8-11). Avelumab is a fully human mAb of the immunoglobulin (Ig) G1 isotype that specifically targets and blocks PD-L1. It has been approved for Merkel cell carcinoma and advanced urothelial carcinoma by FDA with multiple studies ongoing with a wide variety of malignancies as a single agent or in combination with treatment modalities (12-14). Immunotherapy with PD-1 inhibition has already proven to be effective in the second line and refractory setting with another PD-1 inhibitor nivolumab after VEGFR TKIs (15). The combination of nivolumab with an antibody to cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) ipilimumab demonstrated acceptable safety and improved PFS and OS in intermediate or poor risk, previously untreated advanced RCC compared to sunitinib (16). Axitinib is an oral inhibitor of VEGF receptor and it was approved for advanced RCC after failure of sunitinib. A phase III clinical trial demonstrated axitinib significantly longer PFS compared with sorafenib for second-line therapy of advanced RCC. PFS was 6-7 months with axitinib compared to 4-7 months with sorafenib [hazard ratio (HR) 0.665; 95% CI: 0.544–0.812; one-sided P=0.0001] (4). Given the safety profile of lower risk of hepatic toxicities comparing to sunitinib and pazopanib, axitinib was chosen by the study group. Combining PD-L1 inhibitor avelumab with VEGFR TKI axitinib with the hope to increase response rate, prolong PFS and OS, and potential achieve durable response led to JAVELIN Renal 101 trial.

Eight hundred and eighty-six patients’ treatment naïve
advanced clear cell RCC regardless of tumor PD-L1 expression were randomized to receive either avelumab 10 mg/kg intravenous infusion every 2 weeks in combination with axitinib 5 mg twice daily orally or sunitinib 50 mg once daily orally for 4 weeks followed by 2 weeks off until radiographic progression or unacceptable toxicity. The primary outcomes were PFS, and OS in patients with PD-L1-positive tumors. Five hundred and sixty patients with PD-L1-positive tumors (63.2%) demonstrated a statistically significant improvement in PFS with 13.8 months in the avelumab plus axitinib combination cohort compared to 7.2 months in sunitinib (HR 0.61; 95% CI: 0.47–0.79; P<0.0001) (17). Median PFS in the total population was also positive 13.8 vs. 8.4 months respectively (HR 0.69; 95% CI: 0.56–0.84; P<0.001) (17). With a median OS follow-up of 19 months, OS data were immature with 27% deaths in the intent-to-treat population. Among the patients with PD-L1-positive tumors, the response rate was 55.2% in avelumab plus axitinib cohort compared to 25.5% in sunitinib cohort; complete response rate were 4.4% vs. 2.1 % respectively (17). PFS and OS favored combination in all subgroups assessed regardless of PD-L1 status and all Memorial Sloan Kettering Cancer Center (MSKCC) and International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic risk groups. The frequency and severity of adverse events with the combination of avelumab plus axitinib were similar compared to sunitinib group, with 99.5% vs. 99.3% for any adverse event, 71.2% vs. 71.5% for grade 3 or higher in the respective groups (17). Avelumab plus axitinib as first-line treatment for advanced RCC is approved on May 14, 2019 based on the efficacy and safety profile from JAVELIN Renal 101 trial.

This is an exciting era for RCCs. The first line treatment for RCC dramatically improved with several options available. Beyond avelumab plus axitinib approval, KEYNOTE-426 trial demonstrated level 1 evidence of PFS and OS benefit of another similar combination regimen with a PD-1 inhibitor pembrolizumab plus axitinib compared to sunitinib (survival rate 89.9% vs. 78.3%; HR for death 0.53; 95% CI: 0.38–0.74; P<0.0001; PFS 15.1 vs. 11.1 months; HR 0.69; 95% CI: 0.57–0.84; P<0.001) (18). The combination of a PD-1 inhibitor nivolumab with CTLA-4 antibody ipilimumab received approval based on OS and objective response rates improvement than with sunitinib among intermediate- and poor-risk patients in first line setting too. The median OS was not reached with nivolumab plus ipilimumab vs. 26.0 months with sunitinib (HR 0.63; P<0.001; OS 42% vs. 27%. P<0.001) (16). Cabozantinib is an oral potent inhibitor of VEGFR2, MET, and AXL and also showed to significantly increased median PFS (8.2 vs. 5.6 months) and was associated with a 34% reduction in rate of progression or death (HR 0.66; 95% CI: 0.46–0.95; one-sided P=0.012). OR was 46% (95% CI: 34–57%) for cabozantinib vs. 18% (95% CI: 10–28%) for sunitinib in a randomized phase II multicenter trial. It also gained FDA approval in patients with intermediate- or poor-risk RCC (19).

With the different options become available recently, the treatment paradigm for advanced RCCs has changed dramatically in the clinic (Table 1). How to select the treatment options in between the PD-1/PD-L1 inhibitor plus axitinib vs. PD-1 plus CTLA4? Is there still a role of sunitinib and pazopanib in the first line setting? Which patient population benefit more from cabozantinib? With the clear PFS and even OS benefit, single agent TKIs with either sunitinib or pazopanib are no longer the drug of preference for the first line use. However, the question remains whether or not immune check point inhibitor with TKI are synergistic or simply additive effect to make a sequential approach reasonable. There are no head to head comparison of the current approved combination regimens. Sunitinib has been used as the control arm for three immunotherapy combination studies. The PD-1 inhibitor and PD-L1 inhibitor did not show major difference in other studies in terms of efficacy and major toxicities so far (20). It is still an area under investigation. The combination of pembrolizumab and axitinib also already demonstrated OS benefit while avelumab and axitinib has not reach it. It is important to know the OS result when data matures with

### Table 1 FDA approval timeline for first line renal cell carcinoma

<table>
<thead>
<tr>
<th>Favorable risk</th>
<th>Intermediate/poor risk</th>
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<tbody>
<tr>
<td>Sunitinib [2006]</td>
<td>Sunitinib [2006]</td>
</tr>
<tr>
<td>Axitinib + pembrolizumab [2019]</td>
<td>Pazopanib [2009]</td>
</tr>
<tr>
<td>Axitinib + avelumab [2019]</td>
<td>Carbozantinib [2016]</td>
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longer follow up. Multiple other combination regimens are also under evaluation such as atezolizumab plus bevacizumab vs. sunitinib; lenvatinib plus everolimus vs. lenvatinib plus pembrolizumab vs. sunitinib; nivolumab plus cabozantinib vs. sunitinib etc. The approach to combination regimens will become standard of care. It will be widely used in the first line setting with more data rising in the next several years.

IMDC model is widely used for risk stratification in both clinical trial and daily practice. The efficacy for the PD-1/PD-L1 inhibitor plus axitinib is across the board of favorable, intermediate and poor risk disease. However, nivolumab plus ipilimumab only demonstrated statistically significant improvement in patients with intermediate- or poor-risk RCC. The overall response rate in the favorable risk disease patients in contrast were much higher in sunitinib vs. the combination arm instead (52% vs. 29%; P=0.0002) as well as a significantly longer PFS (25.1 vs. 15.3 months; P<0.001) (16). VEGFR inhibition seems to have an important role in the favorable risk disease group. However, one caveat is the much higher complete response rate of 9% with nivolumab plus ipilimumab compared to 5.8% and 3.4% complete response rate in the pembrolizumab and avelumab plus axitinib trials respectively (16-18). cabozantinib was also only approved for intermediate- or poor-risk RCC based on phase II clinical trial. Risk classification needs to be done with each individual newly diagnosed advanced RCC patient. It should be discussed with patient and their family. Individual patient’s preference should be taken into consideration for regimen selection.

PD-L1 expression status has been assessed in all the immunotherapy trials. The combination of avelumab and axitinib trial even selected patients with PD-L1 positive for PFS and OS analysis as primary end points. However, the three trials used different assays for their evaluations. In the exploratory analysis for nivolumab plus ipilimumab trial showed longer PFS was observed with patients with 1% or greater PD-L1 expression but not in the negative PD-L1 group, while OS and response rate (RR) was not affected by PD-L1 expression status. The benefits of pembrolizumab plus axitinib with respect to OS and PFS were observed in all subgroups examined regardless of PD-L1 expression status. PD-L1 expression as a biomarker for these immunotherapies is unsatisfactory with limitations in both daily clinical practice and hurdles in clinical trial interpretation. With the immunotherapy-based combination regimens approval one after another, the economic burden requires more attention. More effectively select patients who will benefit from these treatments is critical important. Better biomarker is an unmet need to further classify advanced RCC and more effectively predict treatment response to immunotherapy and/or VEGFR inhibitors.

In the era of cancer immunotherapy, avelumab and axitinib combination is a brand-new addition to the first line treatment options for RCC. It is not only practice changing but also advance the landscape of combination immunotherapy and target therapy.

Acknowledgments

None.

Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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