First Line Immunotherapy-Based Combination Therapy in Metastatic Clear-Cell Renal Carcinoma

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SUMMARY: The treatment options for metastatic renal cell carcinoma have evolved significantly over recent years. The new standard of care is to combine anti PD-1/PDL1 with another agent. Still, despite the participation of Irish patients in clinical trials which has led to the approval of these treatment options, proven efficacy of these therapeutic agents, participation of Irish expertise in supporting and publishing the trials results, and FDA approval of this combination, the Irish National Cancer Control Program (NCCP) has not agreed to fund it yet. The current practice in Ireland is to start first line treatment with tyrosine kinase inhibitors (TKIs). We can easily access immunotherapy as second line therapeutic option.

Renal cancer is the second most common cancer arising from the urinary system and the seventh common cancer type among both genders. In 2015, about 584 new cases were diagnosed with renal cell carcinoma in Ireland with only a 12.59% cure rate. Nephrectomy is the main treatment for localized disease and there is no role for adjuvant treatment post nephrectomy as shown by several clinical trials. This is either because of no clinical benefit as per a recently published trial that showed no benefit for adjuvant pazopanib over placebo[1] or due to higher toxicity when sunitinib was used in high risk population post nephrectomy.[2] Clear-cell type is the most common histological type and account for about 75% of renal carcinoma. Other non-clear cell subtypes include papillary, medullary, collecting duct, sarcomatoid, chromophobe and unclassified histology. According to the National Cancer Registry Ireland, about 20% of patients presented with distant metastatic disease at the diagnosis. The most common metastatic sites are in the lungs, distant lymph nodes, liver, and bones.[3]

The treatment options for metastatic renal cell carcinoma (mRCC) have evolved significantly over the recent years. The evolution in understanding the biological pathways and the molecular pathogenesis of renal cell carcinoma result in development of different therapeutic agents targeting different biological pathways. This includes vascular endothelial growth factor pathway (VEGF), inhibitors of the mammalian target of the rapamycin (mTOR) pathway and checkpoint inhibitors.[4] Numerous clinical trials have shown excellent clinical efficacy with a higher response rate by targeting more than one of these pathways at the same time.[5] This can be done by using combination of anti PD1/PD-L1 with either ipilimumab (a cytotoxic T-lymphocyte-associated protein 4, CTLA-4 inhibitor) or anti-angiogenesis agent.[5]

Selecting the best therapeutic option among the large number of approved treatments is crucial. This decision should be made based on patient characteristics, physician experiences and most importantly the availability of these drugs.

In this review, we present summary of the newly internationally approved immunotherapy-based combination for management of metastatic renal cell carcinoma. We will discuss their clinical efficacy, Irish participation in clinical trials involving these agents and it's availability in Ireland. Our focus will be on drugs used for management of clear-cell type of renal cell carcinoma (summarised in Table 1).

Combination therapies

1. Nivolumab in combination with Ipilimumab versus Sunitinib, Checkmate 214.

Checkmate 214 is a phase III randomized open-label, multicentre trial, comparing nivolumab (3mg/kg) plus ipilimumab (1mg/kg) with sunitinib monotherapy (50mg daily for 4 weeks on and 2 weeks off) in treatment of previously untreated metastatic renal cell carcinoma. 1096 patients were randomised to 550 patients who received nivolumab+ ipilimumab and 546 patients received sunitinib. 425 and 422 patients respectively were intermediate or poor-risk based on the International Metastatic Renal-Cell Carcinoma Database Consortium (IMDC).[6]

The median OS was not reached in nivolumab+ ipilimumab group versus 25.9 months in patients who received sunitinib (hazard ratio for death, 0.63; $p < 0.001$). Progression free survival (PFS) and overall response rates (ORR) were 11.6 versus 8.4 months and 42% versus 27%, respectively. PFS and ORR were better in the sunitinib group with IMDC favourable risk patients. PDL-1 status was not predictive of treatment response. Treatment related grade 3 or 4 toxicity were 46% and 63% in patients who received combination therapy compared to sunitinib monotherapy.[6]

The US Food and Drug Administration (FDA) and the National Comprehensive Cancer Network (NCCN) approved the combination therapy with nivolumab plus ipilimumab for patients with intermediate and poor risk metastatic renal cell carcinoma as a first line treatment option, (7). Despite the participation of Irish patients in this trial, this combination of nivolumab+ ipilimumab is not approved for reimbursement by the Irish Oncology Drug Management System (ODMS) and Community Drug Schemes (CDS).[8]

2. Pembrolizumab in combination with Axitinib.

KEYNOTE-426 is a phase III randomized open-label, multicentre trial, comparing pembrolizumab (200mg every 3 weeks) in combination with axitinib (5mg twice a day orally) with sunitinib monotherapy in treatment naïve metastatic renal cell carcinoma. 861 patients were randomized to receive pembrolizumab + axitinib or sunitinib monotherapy irrespective of their IMDC risk group.

The median OS was not reached in pembrolizumab + axitinib group, while the risk of death was 47% lower in the combination group compared to the sunitinib monotherapy arm. PFS was 15.1 months versus 11.1 months; $P < 0.001$ in the combination group when compared to sunitinib group. ORR was 59.3% versus 35.7%, respectively.

FDA and NCCN approved the combination therapy with pembrolizumab and axitinib for treatment naïve metastatic renal cell carcinoma irrespective of IMDC risk or PDL-1 status. Irish patient participated in this trial and one of the Irish expertise, Prof R. McDermott, was a co-author of the main article published in the New England Journal of Medicine supporting this trial result.[9] Hoverer, this combination of is not approved for reimbursement by the Irish National Cancer Control Program (NCCP).[10]

3. Avelumab in combination with Axitinib.

JAVELIN Renal 101 is a phase III randomized open-label, multicentre trial, comparing avelumab (10mg/Kg IV every 2 weeks) in combination with axitinib (5mg twice a day orally) with sunitinib in first line setting metastatic renal cell carcinoma. 886 patients were randomized to receive avelumab + axitinib or sunitinib.

The OS benefit was much less conclusive (HR = 0.78; 95% CI, 0.55–1.08; $p = 0.14$). PFS was 13.8 versus 8.2 months in overall population in combination group when compared to sunitinib group. ORR were 51.4 % versus 25.7 %, respectively. Grade 3 or higher adverse events were seen in 71.2 and 71.5% in the combination group and sunitinib monotherapy group, respectively.

FDA and NCCN approved the combination therapy with avelumab and axitinib as first line option for treatment naïve metastatic renal cell carcinoma across all IMDC risk subgroups. This treatment option was not on NCCP cancer treatment website yet.

These immunotherapy-Based Combination therapeutic options are incorporated in the treatment algorithm of first line clear-cell metastatic renal cell carcinoma at international level including NCCN, European society of medical oncology (ESMO) and American Society of Clinical Oncology (ASCO),(see Table 2 for NCCN guideline).

Table 1: OS, overall survival; PFS, Progression free survival; ORR, overall response rates; FDA, US Food and Drug Administration; NCCN, the National Comprehensive Cancer Network; NR, not reached; NCCP, National Cancer Control Program(NCCP); N/A, not available;

study	Study arms	Patients cohort/ IMDC	Median OS	Median PFS	ORR	Grade 3 and 4 toxicity	FDA approval	NCCN approval	NCCP approval
Checkmate 214	Nivolumab + ipilimumab vs. sunitinib	Intermediate and poor risk	NR vs. 25.9 HR = 0.63; p < 0.001	11.6 vs. 8.4 (HR = 0.82; p = 0.0331)	42% vs. 27%	46% vs. 63%	16.04.2018	Approved	Reimbursement not approved **despite Irish patients participation in this trial.**
KEYNOTE-426	Pembrolizumab + axitinib vs sunitinib	N/A	NR, HR 0.53; p < 0.0001 12-mo OS: 90% vs. 78%	15.1 vs. 11.1 (HR 0.69; p = 0.0001)	59.3% vs. 35.7%	62.9% vs. 58.1%	19.04.2019	Approved	Reimbursement not approved **despite Irish patients participation in this trial.**
JAVELIN Renal 101	Avelumab + axitinib vs sunitinib	All	NR, HR 0.78; 12-mo OS: 86% vs. 83% p = 0.14)	13.8 vs 8.4 (HR 0.69; p < 0.0001)	51.4% vs. 25.7 %	71.2% vs. 71.5%	14.05.2019	Approved	N/A

Risk-group	Preferred regimens	Other options
Favourable risk	pembrolizumab + Axitinib Pazopanib Sunitinib	Nivolumab + Ipilimumab Avelumab + Axitinib Cabozantinib
Poor/Intermediate risk	Nivolumab + Ipilimumab pembrolizumab + Axitinib Cabozantinib	Avelumab + Axitinib Pazopanib Sunitinib

Table 2: NCCN: First line therapy for Clear-cell histology mRCC

References

1. Motzer RJ, Haas NB, Donskov F, Gross-Goupil M, Varlamov S, Kopyltsov E, et al. Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with localized or locally advanced renal cell carcinoma. J Clin Oncol. 2017;35(35):3916–23.

2. Ravaud A, Motzer RJ, Pandha HS, George DJ, Pantuck AJ, Patel A, et al. Adjuvant sunitinib in high-risk renal-cell carcinoma after nephrectomy. N Engl J Med. 2016;375(23):2246–54.

3. Nieder C, Dalhaug A, Pawinski AR. Management of patients with metastatic renal cell cancer and bone metastases. In Vivo (Brooklyn). 2020;34(2):675–8.

4. Garje R, An J, Greco A, Vaddepally RK, Zakharia Y. The future of immunotherapy-based combination therapy in metastatic renal cell carcinoma. Cancers (Basel). 2020;12(1):1–13.

5. Hindié E. Optimising first-line treatment for metastatic renal cell carcinoma. Lancet. 2020;395(10219):e6.

6. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus Ipilimumab versus Sunitinib in advanced renal-cell carcinoma. N Engl J Med. 2018;378(14):1277–90.

7. Abouassaly R, Campbell SC. Kidney cancer. Geriatr Urol. 2013;309–23.

8. Regimen NC. NCCP Chemotherapy Regimen Nivolumab 3mg / kg with Ipilimumab 1mg / kg Therapy. 2021;1–11.

9. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019;380(12):1116–27.

10. Regimen NC. NCCP Chemotherapy Regimen Pembrolizumab 200mg and Axitinib Therapy. 2021;1–12.

11. National Cancer Registry Ireland Kidney cancer statistics https://www.ncri.ie/sites/ncri/files/factsheets/Factsheet%20kideny.pdf

12. Renal cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up https://www.esmo.org/guidelines/genitourinary-cancers/Renal-cancer

13. Cancer Trials Ireland, Trials in follow up www.cancertrials.ie/trials-in-follow-up/

14. Choueiri, T.K.; Larkin, J.; Oya, M.; Thistlethwaite, F.; Martignoni, M.; Nathan, P.; Powles, T.; McDermott, D.; Robbins, P.B.; Chism, D.D.; et al. Preliminary results for avelumab plus axitinib as first-line therapy in patients with advanced clear-cell renal-cell carcinoma (JAVELIN Renal 100): An open-label, dose-finding and dose-expansion, phase 1b trial. Lancet Oncol. 2018, 19, 451–460.

15. www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-nivolumab-plus-ipilimumab-combination-intermediate-or-poor-risk-advanced-renal-cell