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Combinations in the first-line treatment of patients with advanced/metastatic renal cell cancer: regulatory aspects

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ABSTRACT

The therapeutic landscape in the treatment of advanced/metastatic renal cell cancer has evolved over the last 2 years with the advent of immune checkpoint inhibitors. In 2018 and 2019, marketing authorisations valid throughout the European Union were issued for nivolumab and ipilimumab dual checkpoint inhibition and pembrolizumab or avelumab in combination with the tyrosine kinase inhibitor axitinib. These applications presented numerous regulatory challenges.

In this paper, we summarise the main regulatory considerations, originating from the assessment of the dossiers submitted from the applicants for the three combinations. The regulatory issues are grouped in four sections: clinical pharmacology, efficacy, biomarkers and safety. In each section, we describe the issues raised during the regulatory evaluation performed by the Committee for Medicinal Products for Human Use (CHMP) assessors. The CHMP assessments determine whether the medicines concerned meet the necessary quality, safety and efficacy requirements, and whether the benefit–risk balance is positive.

In summary, although the overall benefit–risk was considered positive for the three combinations, the immaturity of the outcome data and the absence of long-term safety data remain issues to be addressed. Postauthorisation efficacy studies have been required to confirm the effects of the new combinations.

INTRODUCTION

Between November 2018 and July 2019, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency recommended a number of approvals for use in combination in first-line (1L) treatment of renal cancer. The first was for nivolumab and ipilimumab (based on trial CA209214), followed by pembrolizumab and axitinib (KEYNOTE-426), and avelumab and axitinib (JAVELIN Renal 101). The marketing authorisation applications were based on pivotal studies, which were randomised, open-label phase III studies comparing the efficacy of the combinations versus sunitinib in 1L treatment of patients with advanced/metastatic renal cell cancer (mRCC).

The CHMP assessments are based on scientific criteria and determine whether the medicines concerned meet the necessary quality, safety and efficacy requirements, and whether the benefit–risk balance is positive (box 1). From a regulatory perspective, the incorporation of new agents in combination therapies presents challenges since it is necessary to establish the efficacy and benefit–risk balance of each agent in the combination. Also, in the past decade, more attention has been paid to the possible role of biomarkers as predictive factors. Identification of such biomarkers during early development is encouraged by regulatory guidance, but it is often limited by inadequate understanding and complexity of tumour biology and by non-specificity of the drug. Identifying a target and classifying patients according to the presence of that target can greatly speed up drug development (box 2).

In this paper, we describe the regulatory aspects of the approval processes of the new combinations of vascular endothelial growth factor receptor (VEGFR) inhibitors and immune checkpoint inhibitors, and of dual programmed cell death protein 1 (PD-1)/cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibition. The regulatory issues are discussed in four sections: biomarkers, clinical pharmacology, safety and efficacy. In the different sections reported in this report, the major issues pointed out by the CHMP assessors are discussed, including the role of programmed death-ligand 1 (PD-L1) as a biomarker.

CURRENT TREATMENT LANDSCAPE IN RENAL CELL CANCER (RCC)

RCC represents the sixth most common cancer in men and the eighth most common in women, accounting for 3%–4% of all

Box 1 Regulatory requirements for approval: benefit–risk balance definitions

The balance of benefits and risks occupies a central place in licencing and approval decisions. In the European pharmaceutical legislation, it is defined as an evaluation of the positive therapeutic effects in relation to any risks as regards patients' health or public health, or any risks to the environment (Directive 2001/83/EC, 2001[20]). An approval shall not be granted if the benefit–risk balance is not considered to be favourable. When assessing the evidence, regulators need to strike a balance between early access for patients affected by conditions with high unmet medical need versus having as complete information as possible on the benefits and risks. Due to the large unmet need associated with most cancer indications, more emphasis has often been on efficacy rather than safety, reflecting high acceptance of risks by patients when there are no effective standard treatments or their efficacy is known to be very limited. Regulatory approval is based on objective evidence of efficacy, safety and pharmaceutical quality, to the exclusion of economic considerations, the latter being the responsibility of health technology assessment organisations and payers based on relative effectiveness and cost-effectiveness.[20 21]

adult malignancies.[1] The percentage of new cases across Europe in 2018 was 3.8%.[2] The estimated new cases in the USA in 2019 was more than 70 000, and 14 000 deaths were expected.[3]

The clinical therapeutic scenario was radically changed in the last decade with the availability of targeted agents and, more recently, with the advent of immune checkpoint inhibitors.

At the time of the assessment of the 1L combinations, in the European Union (EU), the following agents targeting the vascular endothelial growth factor (VEGF)/VEGFR signalling pathway have been approved for the 1L treatment of advanced RCC: sunitinib, pazopanib, bevacizumab and interferon alpha, tivozanib and cabozantinib (in patients who are intermediate and poor risk).[4–10] In addition to agents that target VEGFR and VEGF, other approved agents for advanced RCC include the mammalian target of rapamycin (mTOR) inhibitor temsirolimus, for patients considered to be poor risk (per the MSKCC risk category) in the 1L setting.[11] Nivolumab had been approved in the EU for the second-line setting, or more, after demonstrating a statistically significant and clinically meaningful improvement in overall survival (OS) compared with everolimus in patients who had received one or two prior antiangiogenic agents.[12]

Box 2 Biomarkers in the development of targeted therapies to optimise benefit–risk balance

The European Medicine Agency (EMA) has recommended using predictive biomarkers throughout the phases of clinical drug development of oncology drugs. A number of approved products currently contain relevant pharmacogenomics information for patient selection. Nevertheless, biomarker identification and validation remain challenging. The EMA has adopted a flexible approach advocating rigorous biomarker validation methods whenever possible while also considering results from exploratory analyses, in particular, if these can be supported with corroborative evidence, such as improved knowledge of the role of the biomarker in the natural history of the disease and evidence from other trials.[22]

DOSE SELECTION

Nivolumab/ipilimumab

The dose finding of nivolumab in combination with ipilimumab was based on the phase I study CA209016 comparing several nivolumab combinations, including 1+3, 3+1 and 3+3 mg/kg nivolumab+ipilimumab induction phase, respectively, followed by a nivolumab monotherapy maintenance phase, in previously treated or untreated advanced or mRCC. The 3+3 mg/kg regimen, resulted in dose-limiting toxicities that exceeded the maximum tolerated dose (MTD). More subjects discontinued treatment due to drug-related adverse events (AEs) in the 1+3 mg/kg nivolumab+ipilimumab cohort compared with the 3+1 mg/kg cohort (27.7% vs 10.6%, respectively). The objective response rate was comparable between cohorts. On this basis, the selected dose for the phase III study CA209214 was 3 mg/kg nivolumab+1 mg/kg ipilimumab administered intravenously every 3 weeks (Q3W) for the first four doses, followed by a nivolumab monotherapy phase.

During the assessment questions were raised on whether the selected dose for the first four doses of 3 mg/kg nivolumab+1 mg/kg ipilimumab in renal cancer was different from the combination dose in melanoma, namely, 1 mg/kg nivolumab+3 mg/kg ipilimumab. The assessment of safety in the phase I study was complicated by the small numbers in each cohort, variable demographics and prior treatments. This added to the questions regarding the chosen dose of ipilimumab and its contribution to the clinical benefit in patients with RCC (see the section Assessing the role of each drug in the combination).

Pembrolizumb/axitinib

Study A4061079 was a phase Ib, open label, single-arm, multicentre, multiple-dose, safety, efficacy, pharmacokinetics (PK) and pharmacodynamics study of axitinib in combination with pembrolizumab in adult patients with previously untreated advanced RCC.[13] The axitinib starting dose was 5 mg bis in die (two times per day) with or without food, that is, the dose approved for the indication of second-line treatment of adults with advanced RCC. The pembrolizumab starting dose was 2 mg/kg, to be administered Q3W. The study design did not allow testing higher doses. The study estimated MTD at the starting dose level. The safety profile of either study drug was consistent with the known safety profile when used as single agent. Based on separate analyses of cumulative evidence from PK, safety and efficacy data from previously submitted studies across different indications, exposures for 200 mg Q3W were shown to lie within those obtained with the 2 mg/kg Q3W. Thus, the study KEYNOTE-426

was designed with a pembrolizumab dose of 200 mg Q3W. The assessment concurred that PK simulations and observed data confirmed that exposures with the dose of 200 mg Q3W substantially overlapped with those obtained with the 2 mg/kg Q3W dose.

Avelumab/axitinib

The dose selection was initially based on a phase Ib study to evaluate safety, PK and pharmacodynamics of avelumab in combination with axitinib in patients with previously untreated advanced RCC (JAVELIN Renal 100). At the end of the dose-finding phase, the MTD established for the combination was avelumab 10 mg/kg every 2 weeks (Q2W) and axitinib 5 mg two times per day, and this was the dose used in the pivotal phase III trial (JAVELIN Renal 101).[14]

The submission contained a change of avelumab posology from 10 mg/kg Q2W (weight-based) to a flat dose of 800 mg Q2W, both for the newly proposed indication for RCC and the already existing indication of Merkel cell carcinoma. The flat dose was proposed mainly based on PK modelling and the simulated comparison between the expected exposure range given the 10 mg/kg Q2W dosing regimen to the 800 mg Q2W flat-dose regimen. Supporting efficacy data were derived from the phase Ib study in which the overall response rate (ORR) was 60%, and the disease control rate was 78%. The exposure-efficacy analyses used data from 434 patients from the pivotal study.

Overall, the approach was endorsed and ensured that the newly proposed flat-dose regimen resulted in a similar exposure range as the 10 mg/kg dosing regimen, given the assumption that the avelumab safety and efficacy profile remained the same.

Clinical efficacy and role of biomarkers

Study design

Study designs and selection criteria were similar across pivotal trials of all three developments. In all three randomised controlled trials, patients had to have histologically or cytologically proven carcinoma of the kidney with unresectable locally advanced or metastatic disease. Patients were included irrespective of prognostic risk groups or tumour PD-L1 expression. The main exclusion criteria were history of active central nervous system metastases, autoimmune diseases, current or previous use of glucocorticoids or other immunosuppressants prior to randomisation, and prior treatment for advanced or metastatic disease.

In the nivolumab/ipilimumab study CA209214, the main analysis population was the intermediate/poor risk group, based on three coprimary endpoints OS, progression-free survival (PFS) and ORR. The overall alpha for this study was 0.05, which was split with 0.001 to evaluate ORR, 0.009 to evaluate PFS and 0.04 to evaluate OS.

The primary endpoints were PFS and OS for pembrolizumab trial KEYNOTE-426. The main analysis population was not limited by the International Metastatic RCC Database Consortium (IMDC) risk group. The overall alpha for this study was 0.05, which was split with 0.2% (one-sided) for PFS and 2.3% (one-sided) for OS.

In the avelumab+axitinib JAVELIN Renal 101 trial, PFS and OS were primary endpoints for PD-L1-positive population. PD-L1-positive tumours were defined as those tumours with PD-L1 staining of any intensity in tumour-associated immune cells covering ≥1% of tumour area by Ventana PD-L1 (SP263). The overall alpha for this study was 0.05, which was split with 0.4% (one-sided) for PFS and 2.1% (one-sided) for OS.

Clinical efficacy results

All trials observed a statistically significant difference in at least one of their primary clinical efficacy endpoints. A statistically significant difference in OS was observed for nivolumab+ipilimumab and pembrolizumab+axitinib combinations compared with the sunitinib control group. A statistically significant difference in PFS was observed in the avelumab+axitinib and pembrolizumab+axitinib trials. The results are summarised in tables 1–3.

Pd-L1 expression and efficacy outcome: exploratory data

In the nivolumab+ipilimumab combination, the analysis of the predictive relationship of PD-L1 tumour expression for OS was similar in all PD-L1 evaluable subjects with PD-L1 tumour expression of ≥1% compared with those with PD-L1 tumour expression of <1% in the nivolumab+ipilimumab group (HR 0.93, 95%CI 0.62 to 1.39).

In the pembrolizumab+axitinib combination, superior efficacy of the combination over sunitinib therapy has been observed regardless PD-L1 expression.

In the Javelin Renal 101 trial studying the avelumab/axitinib combination, the difference in PFS was observed in patients with positive PD-L1 expression (primary analysis) as well as irrespective of PD-L1 expression (secondary analysis).

A summary of the results is reported in the table 4.

CLINICAL SAFETY

Burden of toxicities

Overall toxicities were mostly consistent with what is known of studied immune checkpoint inhibitors and axitinib monotherapy with some exceptions. An increased frequency of all AE categories, and a higher risk of drug-related serious adverse events and for all types of AEs leading to drug discontinuation, were observed (tables 1–3).

Death as a result of study drug toxicity (as declared by the investigator) occurred in seven patients (1.3%) in the nivolumab/ipilimumab arm vs four patients (0.7%) in the sunitinib arm. Deaths attributed to 'other reasons' occurred in 22 patients in the ipilimumab/nivolumab arm vs 13 patients in the sunitinib arm. This imbalance was driven primarily by a higher frequency of infection-related deaths and cardiovascular event-related deaths in the ipilimumab/nivolumab group.

Table 1 Main efficacy endpoints and summary of safety, study CA209214 for the intermediate/poor risk population

Efficacy endpoint	Nivolumab ipilimumab (n=423)	Sunitinib (n=416)
OS		
Number of death events, n (%)	166 (39)	209 (49)
Median OS (months) (95% CI)	NE (28.2, NE)	25.9 (22.1, NE)
Stratified HR (99.8% CI)	HR 0.63 (0.44 to 0.89)	
Stratified log-rank test, two-sided p value	<0.0001	
PFS*		
Number of death events, n (%)	228 (53.6%)	228 (54.0%)
Median PFS (months) (95% CI)	11.6 (8.71 to 15.51)	8.4 (7.03 to 10.81)
Stratified HR (99.1% CI)	HR 0.82 (0.64,1.05)	
Stratified log-rank test, two-sided p value	0.0331	
ORR* (CR+PR) (%) (95% CI)	41.6 (36.9 to 46.5)	26.5 (22.4,31.0)
Stratified DerSimonian-Laird test p value	<0.0001	
Safety (%)		
Drug-related AEs, grades 3–4	45.7	62.6
SAEs	55.8	39.8
Drug discontinuation to drug-related SAEs	21.6	11.8
IRRs	5.8	2.2
Relative dose intensity (%)		
90% to ≥110% of the planned dose intensity	87.5 (nivolumab) 80.3 (ipilimumab)	58.5

Stratification factors International Metastatic RCC Database Consortium risk group: favourable versus intermediate versus poor risk groups and geographical region: USA versus Canada/Western Europe/Northern Europe versus 'rest of the world'.
*Assessed by IRRC using RECIST V.1.1.
AE, adverse event; CI, Confidence Interval; CR, complete response; HR, hazard ratio; IRR, infusion-related reaction; IRRC, independent radiological review committee; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival ; PR, partial response; SAE, serious adverse event.

A higher frequency of cardiac arrythmias/atrial fibrillation and hepatic events was observed in the pembrolizumab/axitinib arm compared with sunitinib.

The association between antidrug antibodies (ADAs) and safety was also assessed. Treatment emergent ADA status was not found to alter the PK, efficacy and safety of the combination regimens.

The immune-related AE profile observed with avelumab/axitinib appeared to be generally consistent with what was observed with avelumab alone, with the exception of thyroid disorders, hepatitis and fatal cases of myocarditis and pancreatitis.

Hypersensitivity and infusion-related reactions (IRRs)

Hypersensitivity and IRRs (all-causality, any grade) were reported in 29 (5.3%) subjects in the nivolumab+ipilimumab group and 12 (2.2%) subjects in the sunitinib group. None of the events led to permanent discontinuation of nivolumab+ipilimumab. The median time to onset was 3.14 weeks.

Drug hypersensitivity, anaphylactic reaction and anaphylactoid reaction were observed in 1.2% of patients treated with the pembrolizumab/axitinib combination vs 0.5% for the standard sunitinib arm.

In the avelumab/axitinib population, premedication with an antihistamine and paracetamol administered 30–60 min prior to each dose of avelumab was mandatory, and 28.4% of the patients had events identified as IRRs. There was no grade 4 or fatal IRRs and most AEs were of low grade. The first IRR occurred in the majority of patients at infusion 1 (21.1%) or infusion 2 (7.5%).

Missing information and pharmacovigilance activities

Missing information, common to the combinations, concern the use in patients with moderate or severe hepatic impairment, severe renal impairment, active systemic autoimmune disease, with HIV or hepatitis B or hepatitis C, previous hypersensitivity to another monoclonal antibody, long-term safety, reproductive and lactation data, potential pharmacodynamic interaction with systemic immunosuppressants in patients with organ transplants and safety in paediatric patients. Postauthorisation efficacy studies have been required to address these aspects.

Table 2 Main efficacy endpoints and summary of safety, study KEYNOTE-426

Efficacy endpoint	Pembrolizumab axitinib (n=432)	Sunitinib (n=429)
Overall survival		
Number of death events, n (%)	59 (14)	97 (23)
Median overall survival (months) (95% CI)	NR	NR
Stratified HR (95% CI)	0.59 (0.38 to 0.74)	
Stratified log-rank test, p value	0.00005	
PFS*		
Number of events, n (%)	183 (42)	213 (50)
Median PFS (months) (95% CI)	15.1 (12.6 to 17.7)	11.0 (8.7 to 12.5)
Stratified HR (95% CI)	0.69 (0.56 to 0.84)	
Stratified log-rank test, p value	0.00012	
ORR (CR+PR) (%) (95% CI)	59 (54 to 64)	36 (31 to 40)
Stratified method of Miettinen and Nurminen test p value¶[12]	<0.0001	
Safety (%)		
Grade 3–5 AEs	75.8	70.6
SAEs	40.3	31.3
Drug-related hepatic AEs	34.3	20.7
Drug discontinuation due to hepatic AEs	13.3	0.5
Drug discontinuation to drug-related SAEs	17	9.9
IRRs	1.7	0.5
Proportion of subjects with exposures to drugs (%)		
>6/>12 months	77.9/40.3	63.5/25.4

Stratification factors, International Metastatic RCC Database Consortium risk group: favourable versus intermediate versus poor risk groups and geographical region: North America versus Western Europe versus 'rest of the world'.
*Assessed by Blinded Independent Central Review using RECIST V.1.1.
AE, adverse event; CR, complete response; IRR, infusion-related reaction; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SAE, serious adverse event.

Nivolumab/ipilimumab

A postauthorisation efficacy study was requested to elucidate further the contribution of ipilimumab to the efficacy and toxicity of the combination regimen of nivolumab+ipilimumab. The applicant should carry out a randomised clinical study comparing the efficacy and safety of the combination of nivolumab+ipilimumab to nivolumab monotherapy in previously untreated adult patients with intermediate/poor risk advanced renal cell carcinoma, and with an appropriate spectrum of PD-L1 expression levels.

Pembrolizumab/axitinib

The immaturity of efficacy data that did not allow to draw any sound conclusion with regard to the IMDC favourable risk group (HR 0.94, 95% CI 0.43 to 2.07). The OS Kaplan-Meier (KM) curves in this subgroup were superimposable at the time of analysis. The final clinical study report (CSR) was required to be provided postapproval.

Avelumab/axitinib

Long-term safety data were not available at the time of assessment. This will be addressed through further monitoring and characterisation of long-term avelumab treatment in the ongoing clinical trials.

ASSESSING THE ROLE OF EACH DRUG IN THE COMBINATION

From a regulatory perspective, the incorporation of new agents in combination therapies presents challenges since it is important to establish the efficacy and benefit–risk balance of each agent in the combination. Thus, the ideal study design for two novel agents A and B to be used in combination and a control arm C would be A versus B versus AB versus C. However, studies powered for so many comparisons are often prohibitively large. Thus, if there is sufficient evidence to show efficacy, or lack of efficacy, for any of the individual components of the combination used as monotherapies, sometimes these can be omitted from the study design. This type of study does not include one or more monotherapy groups, but this should be justified based on available clinical and/or non-clinical data. The trials discussed in this article have been conducted testing a new AB combination against the standard of care C, raising questions about the justification for excluding monotherapy groups for the different combinations.

Table 3 Main efficacy endpoints and summary of safety, study JAVELIN Renal 101

Efficacy endpoint	Avelumab axitinib (n=442)	Sunitinib (n=444)
Overall survival*		
Number of death events, n (%)	109 (25.7)	129 (29.1)
Median overall survival (months) (95% CI)	NR (30, NE)	NE (27.4, NE)
Stratified HR (95% CI)	0.8 (0.616 to 1.027)	
Stratified log-rank test, one-sided p value	0.0392	
PFS*		
Number of events, n (%)	229 (52)	258 (58)
Median PFS (months) (95% CI)	13.3 (11.1 to 15.3)	8.0 (6.7 to 9.8)
Stratified HR (95% CI)	0.69 (0.57 to 0.83)	
Stratified log-rank test, one-sided p value	<0.0001	
ORR* (CR+PR) (%) (95% CI)	232 (52.5) (47.7 to 57.2)	121 (27.3) (23.2 to 31.6)
Stratified method, Clopper–Pearson OR	OR 2.996 (2.230 to 3.998)	
Safety (%)		
irAEs	38.9	5.0
TEAEs	99.6	99.3
Grade>3 TEAEs	71.6	71.5
STEAEs	35.4	28.7
Drug discontinuation to drug-related TEAEs	14.9	3.3
IRRs	28.4	0
Dose intensity (%)		
Relative dose intensity	92.3	88.4

Stratification factors ECOG PS 0 vs 1 and region (USA vs Canada/Western Europe vs the rest of the world).
*Assessed by Blinded Independent Central Review using RECIST V.1.1, irrespective of programmed death ligand 1 expression.
AE, adverse event; CR, complete response; ECOG, Eastern Cooperative Oncology Group; irAE, immune-related adverse event; IRR, infusion-related reaction; NE, non evaluable; ORR, overall response rate; PFS, progression-free survival ; PR, partial response; STEAE, serious treatment emergent adverse event; TEAE, treatment emergent adverse event.

Nivolumab and ipilimumab

The main uncertainty that remained at the time of assessment was the exact contribution of ipilimumab to the efficacy of the combination therapy nivolumab/ipilimumab. Nivolumab has previously been shown to be active in the target population and is approved for the treatment of advanced RCC after prior therapy in adults. In contrast, the benefits of ipilimumab treatment in the target population are insufficiently characterised. The pivotal study did not compare efficacy of the combination therapy with either nivolumab monotherapy or ipilimumab monotherapy, and the dose–response relationship of ipilimumab in RCC was not well characterised. Also, in the phase I/II studies, the effect of the combination therapy was not investigated in comparison with either nivolumab or ipilimumab monotherapy, although a direct comparison was made between 1 mg/kg ipilimumab+3 mg/kg nivolumab and 3 mg/kg ipilimumab+1 mg/kg nivolumab.

The lack of knowledge of the quantitative contribution of ipilimumab to efficacy of the combination treatment was considered an important issue, especially because it was evident that addition of ipilimumab led to substantial additional toxicity. It was not clear whether 1 mg/kg ipilimumab was an effective dose contributing to clinical benefit in RCC (nor in other cancers). Dosing schedules containing only 1 mg/kg ipilimumab had not been tested in patients with RCC (only a study in which patients received first a 3 mg/kg loading dose followed by doses of 1 mg/kg, in which 1/21 patients had a partial response). As a result, the dose–response relationship of ipilimumab in RCC had been poorly characterised, and it could not be concluded that 1 mg/kg ipilimumab contributed to a relevant extent to efficacy of the combination treatment.

A Scientific Advisory Group (SAG) meeting was requested by CHMP to clarify some issues. The expert panel stated that the trial was not designed to assess the additive effect of ipilimumab or nivolumab to the combination. Thus, robust clinical evidence to assess the individual contribution of each agent was lacking. However, relevant activity of the combination had been established in melanoma for ipilimumab monotherapy and especially for the combination with nivolumab. With reference to scientific rationale, CTLA-4 being the drug target for ipilimumab and PD-1, being target for nivolumab, these monoclonal antibodies have separate immunological 'break functions', indicating the potential value by combining

Table 4 PD-L1 expression and efficacy outcome

Endpoint	Analysis set	Cut-off PD-L1	Trial, experimental drugs (IMDC subgroups) PD-L1 positive patients (%) experimental versus sunitinib CA209214 Nivolumab/ipilimumab (intermediate/high)	KEYNOTE-426 Pembrolizumab (all risk group)	JAVELIN renal 101 Avelumab (all risk group)
			284 (66.8)/278 (65.9)	243 (56.3)/254 (59.2)	270 (61.6)/290 (59.3)
OS HR (95% CI)	ITT		0.63 (0.44 to 0.89)	0.59 (0.45 to 0.78)	0.80 (0.616 to 1.027)
	PD-L1	<1%	0.73 (0.56 to 0.96)	0.54 (0.32 to 0.90)	0.79 (0.484 to 1.277)
		>1%	0.45 (0.29 to 0.71)	0.63 (0.44 to 0.91)	0.83 (0.596 to 1.151)
PFS HR (95% CI)	ITT		0.82 (0.64 to 1.05)	0.69 (0.56 to 0.84)	0.69 (0.57 to 0.83)
	PD-L1	<1%	1.06 (0.87 to 1.36)	0.85 (0.61 to 1.17)	0.87 (0.622 to 1.220)
		>1%	0.47 (0.34 to 0.64)	0.61 (0.48 to 0.79)	0.62 (0.49 to 0.777)
ORR % (95% CI) Experimental arm versus comparator	ITT		41.6 vs 26.5 (36.9 to 46.5)–(22.4 to31.0)	59.3 vs 35.7 (54.5 to 63.9)–(31.1 to 40.4)	52.5 vs 27.3 (47.7 to 57.2)–(23.2 to 31.6)
	PD-L1	<1%	37.3 vs 28.4 (31.7 to 43.2)–(23.2 to 34.1)	56.3 vs NR (48.4 to 63.9)	49,2 vs 29.2 (40.4 to 58.1)–(21.2 to 38.2)
		>1%	58 vs 21.9 (47.7 to 67.8)–(14.7 to 30.6)	60.5 vs NR (54.0 to 66.7)	55.9 vs 27.2 (49.8 to 61.9)–(22.2 to 32.8)

Test used for tumour PD-L1 expression (≥1% vs <1%): study CA209214: Dako PD-L1 IHC 28–8 pharmDx test; study KEYNOTE-426: PD-L1 IHC 22C3 pharmDx assay; study JAVELIN Renal 101: Ventana PD-L1 (SP263) assay (Ventana Medical Systems).
IMDC, International Metastatic RCC Database Consortium; ITT, intent to treat; NR, not reported; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

them. The drugs have in addition partly different side-effect profiles. In conclusion, mechanistic arguments and extrapolation supported a role for ipilimumab in combination with nivolumab in the studied posology in mRCC. The primary analysis population (intermediate/poor risk) in study CA209214 represented a population with a high unmet medical need (median OS for favourable risk patients was 43 months, but that for intermediate risk was 23 months and that for poor risk was 8 months). While agents currently approved for treatment of 1L advanced RCC have demonstrated statistically significant benefits in terms of PFS, no agent in this population has been approved based on OS benefit. In addition, no agent has demonstrated superiority to sunitinib based on a phase III study over the past 10 years. Overall, the CHMP agreed with the advice from the SAG, fully acknowledging the limitations of cross-tumour extrapolations and the weakness in the evidence submitted. Two trials, presented at the American Society of Clinical Oncology 2020 meeting, focused on the contribution of ipilimumab in patients with advanced RCC not responding or progressing on nivolumab monotherapy. Additional responses have been observed with the salvage strategy, which included ipilimumab, but the response rates were not as high as observed with upfront dual checkpoint inhibition. These data support the contribution of ipilimumab given upfront in combination with nivolumab.[15 16]

Pembrolizumab in combination with axitinib

The combination of pembrolizumab/axitinib demonstrated superiority versus sunitinib with a statistically significant benefit observed for PFS and OS in patients with advanced RCC, supported by an advantage in terms of ORR. The lack of monotherapy experimental arms in study KEYNOTE-426 hampered quantitative assessment of the contribution of each component of the combination treatment. Even though exploratory data showed higher ORR with the combination compared with both pembrolizumab and axitinib alone, only indirect comparison is available. The data regarding axitinib and pembrolizumab activity as monotherapy derived from the phase III study A4061051 and the phase II Keynote-427 in which mPFS were 10 and 7 months, respectively, and ORRs were 32% and 36%, respectively. The uncertainty of the role of each drug is particularly relevant for pembrolizumab, since conventional response evaluation

criteria may underestimate the long-term benefit, and it cannot be excluded that pembrolizumab monotherapy could represent a valid treatment option for at least a subgroup of patients (eg, high PD-L1 expression). The final CSR of the pivotal KEYNOTE-426 study will provide results with longer follow-up. Nevertheless, similarly to what was described for nivolumab/ipilimumab, based on the large effects having been observed in a population of high unmet medical need, the role and potential optimisation of the contribution of each agent in the combination were not a blocking issue.

Avelumab in combination with axitinib

The additive effects of axitinib/avelumab have been shown based on a substantial increase in ORR over the individual agents and were based on cross-study comparisons. In an effort to characterise the contribution of each component, data from phase I study EMR100070-001, concerning avelumab monotherapy in 62 previously untreated mRCC patients (ORR 16%), and phase III study A4061051, comparing PFS and OS of treatment-naïve patients with mRCC receiving axitinib versus sorafenib (ORR 32%), were submitted. In the absence of randomised studies with a factorial design, there was some uncertainty on the quantitative contribution of each agent, but the provided data were indicative of a substantial increase in sum pharmacodynamic activity (ORR) when avelumab and axitinib are combined. This conclusion was supported by data on other combinations of VGEF-targeting tyrosine kinase inhibitors and PD-L1 targeting agents. Thus, the additive effect was shown in a qualitative sense, but there was no precise quantification of the contribution of each agent. However, available efficacy data from the comparison of the avelumab/axitinib combination versus sunitinib were considered sufficient to justify the contribution of each agent to the overall activity of the proposed regimen.

SUMMARY AND DISCUSSION

This review was conducted to explain the regulatory considerations in the evaluation of three combinations for the 1L treatment of advanced renal cancer. All combinations were assessed to provide significant clinical benefit compared with control in large clinical trials. The results were convincing and represent a major leap forward in the treatment of this disease. However, the combination treatment comes with additional toxicity and complexity so that justification and refined understanding of the role of each element in the combination has understandably been an important issue.

In situations where the exact role of each drug combinations is not exactly known, there are essentially two choices. One would be to require conducting very large trials to test each agent as monotherapy as well as in combination. Another approach, if justified, would be to test the overall combination first and only subsequently try to distinguish the role of each element, although the task of optimising treatments postapproval will be admittedly more arduous. The latter strategy has been considered acceptable here, not without controversy, and this has been justified on the basis of the large improvement in survival or PFS in a situation of high unmet medical need, as well as indirect evidence and assumptions about the effect of the individual components. Similar examples in the past have been acceptable in similar situations in rare diseases, like temozolomide in combination with radiotherapy for high-grade glioma and histamine in combination with interleukin-2 for acute myeloid leukaemia.

Identification of biomarkers during early development is encouraged by regulatory guidance but is often limited by inadequate understanding and complexity of tumour biology and by non-specificity of the drug. Identifying a target and classifying patients according to the presence of that target can greatly speed up drug development and decrease the high attrition rate observed in late clinical stages of cancer drug development. On the other hand, failure to identify the correct target population early in development can lead to important delays in approval.[17]

The role of PD-L1 as predictive biomarker represents a topic of interest as it would possibly allow the identification of a subset of patients who could benefit most from the immune checkpoint inhibitors drugs, but the role of PD-L1 expression is still debated in RCC. PD-L1 represents a continuous marker variable and different (companion) diagnostics have been developed for every PD1/PD-L1 targeting drug generating some confusion in the interpretation of the results and the consistency of the results obtained. The PD-L1 showed a negative prognostic role when highly expressed, but PD-L1 expression could differ between primary and metastases.[18] The predictive role is controversial, although some signals of an increased efficacy in patients with a high PD-L1 level receiving a double immunotherapy combination have recently emerged.[19]

The long-term safety profile also represents an uncertainty that will require further follow-up and careful assessment to ensure patient safety. Postauthorisation efficacy studies have been required to confirm the consistency of the efficacy and safety of the new combination of pembrolizumab/axitinib and nivolumab/ipilimumab.

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