Combined immunotherapy and VEGF-targeted therapy for metastatic ccRCC

Background

Clear cell renal cell carcinoma (ccRCC) is a common type of kidney cancer.[1] The current treatment guidelines for metastatic ccRCC have shifted from single-agent vascular endothelial growth factor receptor - tyrosine kinase inhibitors (VEGFR-TKIs) therapies such as sunitinib or axitinib to combination therapies with immune checkpoint inhibitors (ICIs). For advanced ccRCC patients, a combination of ICIs is now available that includes CTLA4 (cytotoxic T lymphocyte antigen 4) inhibitors (e.g., ipilimumab) as well as agents that block the PD-1 (Programmed Death-1) signaling pathway in peripheral tissues (e.g., nivolumab and pembrolizumab).[2] Several phase 3 clinical trials have evaluated the efficacy and safety of VEGFR-TKIs when combined with ICIs.[3,4] KEYNOTE-426 (NCT02853331) compared pembrolizumab plus axitinib to sunsitib, the benchmark control.[5]

Methodology

KEYNOTE-426 was a phase 3, open-label and multicenter trial involving 861 patients (median age, 62 years; 73% men) with Karnofsky performance scores of at least 70%. Throughout the study, patients were randomly assigned (1:1) to receive pembrolizumab (200 mg, intravenously given every 21 days) plus axitinib (5 mg, orally and twice daily) or sunitinib (50 mg, orally and once daily) in cycles of 4-weeks-on and 2-weeks-off for six weeks. The co-primary endpoints were overall survival and progression-free survival in the intention-to-treat population, and the secondary endpoint was objective response rates.

Results

After a median follow-up of 12.8 months, the pembrolizumab-axitinib (P+A) group outperformed sunitinib regarding overall survival. Pembrolizumab-axitinib combination, compared with sunitinib, resulted in a hazard ratio of 0.53 (95% confidence interval [CI], 0.38 to 0.74; P<0.0001), translating into a 47% reduction in risk of death. The hazard ratio for disease progression is 0.69 (95% CI, 0.57 to 0.84; P<0.001), translating to a 31% lower risk of disease progression or death. In the (P+A) group, the median progression-free survival was 15.1 months, while in the sunitinib group, it was 11.1 months. The objective response rate was 23.6% higher than in the sunitinib group (95% CI, P<0.001). All dual endpoints have been met according to RECIST, version 1.1, as determined by a blinded, independent central review. Pembrolizumab–axitinib and sunitinib groups reported 75.8% and 70.6% of grade 3 or higher adverse events, respectively. Diarrhea and hypertension were the most common adverse events of any cause in both groups. Regarding toxicity, the hepatic toxic effects of Pembrolizumab-axitinib require further examination, but the combination is a well-tolerated regimen.

Clinical implications

Pembrolizumab plus axitinib is the first combination of immuno-oncology, and VEGFR-TKIs approved by the FDA for treating advanced ccRCC. Several phase 3 trials compared sunitinib with other ICIs and VEGFR-TKIs, demonstrating the efficacy and safety of this approach. A key finding is that pembrolizumab and axitinib have synergistic antiangiogenic and immunotherapeutic effects. Compared to patients receiving only sunitinib therapy, the combined therapy of the (P+A) group demonstrated significantly longer overall survival, progression-free survival, and objective response rates. KEYNOTE-426 provided robust data that led to practice-changing guidelines and introduced the first standard of care for treating advanced ccRCC using VGFR-TKIs and ICIs.

Table 1: Summary of the patient population, efficacy, and Safety of Phase 3 trial KEYNOTE-426

Variable	Pembrolizumab + Axitinib (n=432)	Sunsitib (n=429)
Patient population		
IMDC risk category		
Favorable	31.9%	31%
Intermediate	55.1%	57%
Poor	13%	12%
PD-L1 positive § (ITT) ≥1%	59.3%	62%
Median time to response (range)*, ¶ (Months)	2.8 (1.5 to 16.6)	2.9 (2.1 to 15.1)
The median duration of response *, ¥ (Months)	23.6	15.3
Median Follow-up (Months)*	12.8	
Primary endpoint	OS and PFS in the ITT population	
Efficacy		
OS (95% CI; P<0.0001) IMDC All risk	89.9%	78.3%
OS (ITT) (95% CI; P<0.0001) Hazard Ratio (range)	0.53 (0.38 to 0.74)	
PFS (Median Months; ITT)	15.1	11.1
PFS (95% CI; P<0.001) Hazard Ratio (range)	0.69 (0.57 to 0.84)	
ORR% *, ł (95% CI; P<0.001)	59.3%	35.7%
CR% *, ł	5.8%	1.9%
Safety		
Adverse event of any case%	98.4%	99.5%
Grade 3 or Higher%	75.8%	70.6%
Grade 3 or higher/Treatment-related %	62.9%	58.1%
Discontinuation rate%	30.5%	13.9%
Deaths £	4 (0.9)	6(1.4)

CI= Confidence interval; IMDC= International Metastatic Renal Cell Carcinoma Database Consortium; ITT= Intent to treat; ORR=Objective response rate; PD-L1= Programmed death ligand 1; PFS= Progression-free survival; CR= Complete response; OS= Overall survival

* A blinded, independent central review of radiologic images was conducted to assess the response in accordance with Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Because of rounding, percentages may not equal 100

Ł Based on the Miettinen and Nurminen method, this estimate was stratified by IMDC risk groups (favorable, intermediate, or poor) as well as geographical regions (North America, Western Europe, or the rest of the world).).

¶ We calculated the median response time only for those patients who responded completely or partially.

¥ We calculated the median duration of response using Kaplan-Meier methods and data from patients who completed or partially completed the study.

§ To determine the combined positive score of programmed death ligand 1 (PD-L1), the number of cells expressing PD-L1 (cancer cells, lymphocytes, and macrophages) was divided by the total number of cancer cells multiplied by 100. To analyze the PD-L1 combined positive score subgroup, patients expressing PD-L1 but unable to be evaluated were excluded.

£ The data is obtained using updated trial results.

References:

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