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CheckMate 214 trial: Immune checkpoint regulators for advanced renal cell carcinoma

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SUMMARY

The follow-up of the CheckMate 214 trial 214 trial, which is a multicenter, Phase III, randomized controlled trial in adults with previously untreated advanced or metastatic clear cell renal cell carcinoma (RCC), has recently been published in *The Lancet*.[1] 1096 subjects, selected on the basis of the International Metastatic RCC Database Consortium (IMDC) criteria, were randomly assigned (1:1) into nivolumab (3 mg/kg intravenous [IV]) plus ipilimumab (1 mg/kg IV) every 3 weeks for 4 doses, followed by nivolumab (3 mg/kg IV) every 2 weeks, or sunitinib (50 mg orally) once daily for 4 weeks (6-week cycle). There were 425 intermediate/poor-risk patients and 125 good-risk patients in the combination arm as against 422 and 124, respectively, in the sunitinib arm. At a median follow-up of 25.2 months, the 18-month overall survival (OS) rate was 75% (95% confidence interval [CI] = 70–78) with nivolumab plus ipilimumab and 60% (95% CI = 55–65) with sunitinib.[2] The median OS was not reached for the nivolumab and ipilimumab arm versus 26.0 months for sunitinib ($P < 0.001$). The objective response rate (ORR) was 42% versus 27% ($P < 0.001$), and the complete response rate was 9% versus 1%. The median progression-free survival (PFS) was 11.6 months and 8.4 months, respectively (hazard ratio [HR] for disease progression or death - 0.82; $P = 0.03$, not significant per the prespecified 0.009 threshold). At a median of 32.4 months, in intermediate- and poor-risk patients, nivolumab plus ipilimumab continued to be superior in terms of OS (median not reached vs. 26·6 m HR = 0·66 [0.54–0.80], $P < 0·0001$), PFS (median 8·2 m vs. 8·3 m HR = 0·77 [0.65–0.90], $P = 0·0014$), and the proportion of patients achieving an investigator-assessed objective response (42% vs. 29%; $P = 0·0001$). In intention-to-treat (ITT) analysis, the median OS was not reached for combination versus 37.9 m for sunitinib (HR = 0.71 [95% CI = 0.59–0.86], $P = 0·0003$), median PFS was 9.7 m versus 9.7 m (HR 0·85 [95% CI = 0.73–0.98], $P = 0·027$), and investigator-assessed ORR was higher for combination therapy (41% vs. 34%; $P = 0·015$). A similar number of patients had adverse events of any grade in both groups (513 [94%] of 547 patients in combination group vs. 521 [97%] of 535 patients in the sunitinib group). Fewer Grade 3 or 4 events occurred with nivolumab plus ipilimumab than with sunitinib (255/547 [47%] vs. 342/535 [64%]). The most recent presentation of this trial at the American Society of Clinical Oncology (ASCO) GU 2020 symposium shows the continued benefit of combination arm over sunitinib in terms of OS, PFS, and ORR.[3]

COMMENTARY

The past decade has seen a rapid development of novel therapies for advanced RCC, starting from tyrosine kinase inhibitors (TKIs) to mechanistic target of rapamycin inhibitors and finally immune checkpoint regulators. The various trials and their salient points are summarized in Table 1. Based on multiple randomized control trials, pazopanib and sunitinib had shown benefit over placebo and interferon alpha, respectively, across all risk groups of metastatic RCC.[4,5,10] The COMPARZ trial did not show any difference between pazopanib and sunitinib in terms of PFS and OS.[6,11] In another retrospective study using the IMDC criteria, similar results were obtained in terms of PFS, ORR, and OS using the two drugs in the first-line setting.[12] On the basis of the above trials, the NCCN continues to recommend sunitinib and pazopanib as two of the preferred regimens in good-risk metastatic RCC and as other recommended regimens in intermediate- and poor-risk metastatic RCC. The KEYNOTE trial was a Phase III, open-label randomized trial in which patients across all risk groups received either combination of axitinib and pembrolizumab or sunitinib as the first-line therapy.[9] Combination therapy showed increased median PFS (5.1 months in the pembrolizumab plus axitinib group and 11.1 months in the sunitinib group [HR for disease progression or death = 0.69; 95% CI = 0.57–0.84; $P < 0.001$]). The ORR was 59.3% (95% CI = 54.5–63.9) in the pembrolizumab plus axitinib group and 35.7% (95% CI = 31.1–40.4) in the sunitinib group ($P < 0.001$). The benefit of combination therapy was observed across all IMDC risk groups irrespective of PDL-1 expression. Currently, therapy using the above combination is a Category 1

Table 1: Summary of important trials in therapy of metastatic renal cell carcinoma

Trial name	Years	IMDC risk group	Agent used	Result	HR
Sternberg *et al*.[4]	2010	-	Pazopanib versus placebo	Increased PFS in pazopanib arm	
Motzer *et al*.[5]	2009	All risk groups	Sunitinib versus IFN alpha	OS 26.4 versus 21.8-month favoring sunitinib	HR=0.821, *P*=0.051
COMPARZ[6]	2013	-	Pazopanib versus sunitinib	PFS 8.4 versus 9.5 months Similar OS	HR=1.05 (0.90-1.22) HR=0.91 (0.76-1.08)
PISCES[7]	2014	-	Crossover study - Pazopanib followed by sunitinib	Significant patient preference for pazopanib	
CABOSUN[8]	2017	Intermediate and poor risk	Cabozantinib versus sunitinib	PFS 8.2 versus 5.6-month favoring cabozantinib	HR=0.66 (0.46-0.95), *P*=0.012
CheckMate 214[2]	2018	Good, Intermediate, and poor risk	Nivolumab + ipilimumab versus sunitinib	OS not reached versus 26-month favoring combination therapy ORR 42% versus 27% PFS 11.6 versus 8.4-month favoring combination	HR=0.63, *P*<0.001 *P*<0.001 HR=0.82, *P*=0.03 (NS)
KEYNOTE 426[9]	2019	Good, intermediate, and poor risk	Pembrolizumab + axitinib versus sunitinib	PFS 15.1 versus 11.1-month favoring combination therapy	HR=0.69 (0.57-0.84), *P*<0.001
CheckMate 214[1] (extended follow-up)	2019	Good, intermediate, and poor risk	Nivolumab + ipilimumab versus sunitinib	OS not reached versus 37.9-monthfavoring combination therapy ORR 41% versus 34% PFS 9.7 versus 9.7 months	HR=0.71 (0.59-0.86), *P*<0.001 *P*=0.015 HR=0.85 (0.73-0.98), *P*=0.027

PFS=Progression-free survival, OS=Overall survival, HR=Hazards ratio, ORR=Objective response rate, IMDC=International Metastatic RCC Database Consortium, IFN=Interferon, RCC=Renal cell carcinoma

recommendation as the first-line therapy of metastatic RCC in all IMDC risk groups.

More than three quarters of all patients with advanced RCC present with intermediate- or poor-risk disease. The CheckMate trial replicates this distribution as 77% of patients in the study were either in the intermediate-risk group or poor-risk group. The baseline tumor PD-L1 expression was lower, and the incidence of previous nephrectomy was higher in both treatment groups in favorable-risk patients than in the intermediate-risk or poor-risk group and the ITT population. In the intermediate- and poor-risk groups, the combination of ipilimumab and nivolumab showed significantly better results in terms of OS rates and ORR. The PFS was numerically better for combination therapy but did not meet the prespecified *P* value for statistical significance. With extended follow-up, a significant benefit was maintained for the ipilimumab and nivolumab combination versus sunitinib in the intermediate- and poor-risk groups and also the ITT population in terms of OS and PFS. It is important to mention here that the numerically better PFS, in the combination arm, which was not statistically significant at the initial analysis became significant on extended follow-up. This was observed because the PFS curves for the two groups began to separate only after around 9 months, and the 30-month PFS probability was 28% (95% CI = 23–33) in the nivolumab plus ipilimumab group versus 12% (8–16) in the sunitinib group. In the ITT population, the curves began to separate at 12 months, and 65% of those in the combination arm versus 71% of those in sunitinib arm had a progression event. A plateau emerged at 30 months with nivolumab plus ipilimumab treatment. Thirty-month PFS probability was 28% (95% CI = 24–32) with nivolumab plus ipilimumab versus 18% (14–22) with sunitinib. The ORR was higher in the combination therapy group with a larger proportion of complete response and durable response. For good-risk patients, initial analysis showed better PFS and ORR for sunitinib compared with combination therapy with ipilimumab and nivolumab.[2] However, the OS rates were not significantly higher. With longer follow-up, the difference between the two groups regarding OS in the good-risk group decreased, and the median OS was not reached in either group.[1] As of now, these survival data seem rather immature, and longer follow-up is necessary to know the real risk versus benefit ratio for nivolumab and ipilimumab versus sunitinib in this risk group. When comparing the toxicity profiles, common dose-related Grade 3–4 complications with combination therapy arose early and resolved within 4–6 months. Most of the side effects arose within 30 days of the last dose and were generally low grade or easily manageable. In contrast, in the sunitinib group, both early and chronic toxicities were detected even with dose adjustments. A patient-reported outcome analysis of the CheckMate 214 trial showed improved and maintained quality of life for nivolumab and ipilimumab groups compared to the sunitinib group. The most recent update from the Checkmate 214 trial comes from the ASCO GU 2020 symposium at San Francisco in February 2020 where data on OS and review of response were presented.[3] At the longest follow-up of a median 49 months, the OS and PFS benefit continued to be significantly better for the combination arm at 47.0 versus 26.6 months and 12.0 versus 8.3 months, respectively and 42 month rates of 52% versus 39% and 35% versus 19%, respectively. ORRs of 42% and 26% (10 vs. 1% complete responses) for combination versus sunitinib, respectively, were observed. This favorable

trend for combination therapy was also seen in the ITT population, except for PFS which plateaued after 30 months at 35% in both ITT and primary efficacy populations. In 249 good-risk patients, an exploratory analysis showed no significant difference between the groups with regard to OS. Both PFS and ORR were significantly poorer with the combination than sunitinib, with median PFS times of 17.8 versus 27.7 months and ORRs of 29% versus 54%. Combination therapy, however, had a higher complete response at 13% versus 6% for sunitinib.

On the basis of the initial analysis of the CheckMate data, combination therapy with nivolumab and ipilimumab is recommended as the first-line therapy for intermediate- or poor-risk RCC. The extended analysis only serves to confirm the continuing benefit of this treatment and also hints at the increased efficacy versus TKI even with good-risk patients on the ITT analysis. The approval of pembrolizumab and axitinib for the same purpose along with ipilimumab and nivolumab has brought about a paradigm shift in the landscape of treatment of metastatic RCC, which was hitherto dominated by TKIs. With longer follow-up data, these agents may soon become the treatment of choice across all risk groups.

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