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Brief Correspondence

Impact of Prior Cytoreductive Nephrectomy on Efficacy in Patients with Synchronous Metastatic Renal Cell Carcinoma Treated with Avelumab plus Axitinib or Sunitinib: Post Hoc Analysis from the JAVELIN Renal 101 Phase 3 Trial

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Abstract

Data on the effects of prior cytoreductive nephrectomy (CN) in patients with renal cell carcinoma (RCC) with synchronous metastases (M1 disease) before immune checkpoint inhibitor (ICI) treatment are limited. In this post hoc analysis of treatment-naive patients with advanced RCC from the phase 3 JAVELIN Renal 101 trial, we assessed efficacy outcomes in the avelumab + axitinib and sunitinib arms in patients who were initially diagnosed with M1 disease (n = 412) grouped by prior CN (yes vs no). Progression-free survival (PFS) and overall survival (OS) were analyzed using multivariable Cox regression, and objective response rates (ORRs) were analyzed using logistic regression. After adjusting for imbalances in baseline variables, the hazard ratio (HR) for PFS in the prior CN versus no prior CN subgroup was 0.79 (95% confidence interval [CI] 0.53–1.16) in the avelumab + axitinib arm, and 1.15 (95% CI 0.77–1.70) in the sunitinib arm. The corresponding HRs for OS were 0.59 (95% CI 0.38–0.93) and 0.86 (95% CI, 0.55–1.34), and the odds ratios for ORR were 2.67 (95% CI 1.32–5.41) and 2.02 (95% CI 0.82–4.94), respectively. Prospective studies of the potential benefits of CN and its appropriate timing in patients receiving first-line treatment with ICI-containing combinations are warranted.

Patient summary: This study looked at patients with kidney cancer whose disease had already spread outside the kidneys when it was first detected. We found that patients whose kidney had been removed before starting treatment with avelumab + axitinib

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had better outcomes than those whose kidney had not been removed. For patients treated with sunitinib, the results were more similar between the groups with and without prior kidney removal. However, statistical tests did not find any significant differences.
The JAVELIN Renal 101 trial is registered on ClinicalTrials.gov as NCT02684006.

Renal cell carcinoma (RCC) accounts for approximately 80% of all kidney cancers [1]. Patients with metastatic (M1) RCC (mRCC) at diagnosis, which is termed synchronous metastasis and represents approximately one-third of RCC cases, have poor prognosis, with a 5-yr survival rate of 12–15% [1–5]. Cytoreductive nephrectomy (CN) has been a standard of care in mRCC for 20 yr [6,7]. It has been shown that the combination of CN + interferon significantly improves overall survival (OS) versus interferon therapy alone in patients with mRCC [8]. However, in the CARMENA phase 3 trial, OS with sunitinib (multitargeted tyrosine kinase inhibitor) treatment alone was noninferior to CN followed by sunitinib [7]. In addition, in the SURTIME phase 3 trial, no significant difference in progression-free survival (PFS) was observed with sunitinib administered before deferred nephrectomy versus CN followed by sunitinib [9]. Therefore, the effect of CN remains controversial. In a systematic review and meta-analysis, contemporary immune checkpoint inhibitor (ICI)-based combination treatment was associated with a clinical benefit versus sunitinib, regardless of prior nephrectomy performed at any time [10]. To the best of our knowledge, no analysis of patients initially diagnosed with stage IV RCC with M1 disease who underwent CN followed by first-line ICI-containing combination treatment has been reported.

In the phase 3 JAVELIN Renal 101 trial (NCT02684006), first-line avelumab (anti–PD-L1 antibody) + axitinib (VEGFR inhibitor) significantly prolonged PFS versus sunitinib in patients with advanced RCC [11,12], leading to regulatory approvals worldwide. In this post hoc analysis, we investigated the effect of prior CN on efficacy outcomes in patients from JAVELIN Renal 101 who were initially diagnosed with M1 disease.

The JAVELIN Renal 101 study design has been published previously [11,12]. In brief, patients with untreated advanced RCC were randomized 1:1 to receive either avelumab 10 mg/kg every 2 wk + axitinib 5 mg twice daily, or sunitinib 50 mg once daily for 4 wk (6-wk cycle). In post hoc analyses, efficacy outcomes were assessed in subgroups of patients in the avelumab + axitinib and sunitinib arms who presented with M1 disease at diagnosis who were grouped by receipt of prior CN (yes vs no). Data from the third interim analysis were analyzed (data cutoff April 28, 2020; minimum follow-up duration 28 mo). Hazard ratios (HRs) for PFS according to investigator assessment using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and for OS were calculated using multivariable Cox regression analysis. Odds ratios for the objective response rate (ORR; confirmed complete or partial response; investigator assessment per RECIST 1.1) were calculated using logistic regression. For the multivariable Cox and logistic regression analyses, baseline characteristics included in the model were: age, Eastern Cooperative Oncology Group (ECOG) performance status, International Metastatic RCC Database Consortium risk group, geographic region, and PD-L1 status. The number of tumor sites and the tumor burden were not analyzed, which is a limitation of the analyses reported. The trial was not designed or powered to assess statistical significance for any observations in these post hoc analyses.

Of 886 patients with advanced RCC enrolled in the trial, 412 were initially diagnosed with M1 disease and were included in this analysis. In the avelumab + axitinib and sunitinib arms, 126 and 147 patients had undergone prior CN, and 72 and 67 patients had not undergone prior CN, respectively. While baseline characteristics in the subgroups were similar between the treatment arms, imbalances were observed between subgroups with or without prior CN (Table 1). Specifically, the proportions of patients aged >65 yr, with ECOG performance status $\geq$1, or with a poor risk score were numerically higher in the subgroups without prior CN than in the subgroups with prior CN; however, a numerically lower proportion of patients without prior CN had a PD-L1-positive tumor.

After adjusting for imbalances in the baseline characteristics listed in Table 1, the HR for progression or death in the avelumab + axitinib arm in the prior CN subgroup versus the subgroup without prior CN was 0.79 (95% confidence interval [CI] 0.53–1.16). In the sunitinib arm, the adjusted HR for progression or death in the prior CN subgroup versus the subgroup without prior CN was 1.15 (95% CI 0.77–1.70). In addition, the adjusted HR for death in the prior CN subgroup versus the subgroup without prior CN was 0.59 (95% CI 0.38–0.93) in the avelumab + axitinib arm and 0.86 (95% CI 0.55–1.34) in the sunitinib arm. The odds ratio for response in the prior CN subgroup versus the subgroup without prior CN was 2.67 (95% CI 1.32–5.41) in the avelumab + axitinib arm and 2.02 (95% CI 0.82–4.94) in the sunitinib arm.

Although CN is recommended in selected patients with good performance status [1,6], its role in patients who receive currently available drug therapies is controversial. In this post hoc analysis of patients who presented with newly diagnosed metastatic disease, analyses of efficacy in terms of PFS, OS, and ORR outcomes suggested a more beneficial effect of prior CN in those who had received avelumab + axitinib; this was not observed in the sunitinib arm. However, interaction tests between treatment and prior CN were not significant for PFS, OS, or ORR ($p > 0.05$), suggesting no significant efficacy difference between the two treatment arms according to prior CN (Tables 2–4).

Table 1 – Baseline characteristics of patients who had M1 disease at initial diagnosis of renal cell carcinoma

Parameter	Avelumab + axitinib arm, *n* (%)		Sunitinib arm, *n* (%)	
	Prior CN (*n* = 126)	No prior CN (*n* = 72)	Prior CN (*n* = 147)	No prior CN (*n* = 67)
Age <65 yr	86 (68)	46 (64)	100 (68)	34 (51)
Sex				
Male	91 (72)	51 (71)	115 (78)	46 (68)
ECOG PS				
0	80 (64)	32 (44)	85 (58)	31 (46)
1	46 (37)	40 (56)	62 (42)	35 (52)
2	0	0	0	1 (1.5)
IMDC prognostic risk group				
Favorable	8 (6.3)	2 (2.8)	7 (4.8)	0
Intermediate	96 (76)	41 (57)	116 (79)	40 (60)
Poor	22 (18)	29 (40)	23 (16)	27 (40)
Unknown	0	0	1 (0.7)	0
MSKCC prognostic risk group				
Favorable	8 (6.3)	2 (2.8)	10 (6.8)	0
Intermediate	103 (82)	43 (60)	121 (82)	47 (70)
Poor	14 (11)	27 (38)	15 (10)	20 (30)
Unknown	1 (0.8)	0	1 (0.7)	0
Geographic region				
Europe	47 (37)	25 (35)	62 (42)	36 (54)
North America	45 (36)	22 (31)	45 (31)	15 (22)
Asia	21 (17)	19 (26)	25 (17)	11 (16)
Rest of the world	13 (10)	6 (8)	15 (10)	5 (7.5)
PD-L1 status				
Positive	96 (76)	29 (40)	114 (77)	26 (39)
Negative	26 (21)	30 (42)	27 (18)	29 (43)
Unknown	4 (3.2)	13 (18)	6 (4.1)	12 (18)

CN = cytoreductive nephrectomy; ECOG PS = Eastern Cooperative Oncology Group performance status; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; M1 = metastatic; MSKCC = Memorial Sloan Kettering Cancer Center.

Table 2 – Multivariable Cox regression analysis of progression-free survival (investigator assessment per RECIST 1.1) in patients who had M1 disease at initial diagnosis of renal cell carcinoma, including an interaction term for prior CN*treatment

Variable	Parameter estimate	SE	*p* value[a]
Prior CN (yes vs no)	0.14	0.20	0.5
Treatment (avelumab + axitinib vs sunitinib)	−0.19	0.23	0.4
Age (≥65 vs <65 yr)	−0.24	0.13	0.06
Geographic region (vs Asia)			
North America	0.52	0.18	<0.01
Europe	0.17	0.18	0.3
Rest of the world	0.13	0.25	0.6
ECOG PS (vs 0)			
1	0.20	0.13	0.1
2	4.54	1.24	<0.01
IMDC prognostic risk group (vs favorable)			
Intermediate	0.50	0.32	0.1
Poor	0.89	0.34	<0.01
PD-L1 status (positive vs negative)	0.13	0.14	0.4
Prior CN*treatment interaction	−0.38	0.27	0.2
Prior CN vs no prior CN	**HR (95% CI)**		
Avelumab + axitinib	0.79 (0.53–1.16)		
Sunitinib	1.15 (0.77–1.70)		

CN = cytoreductive nephrectomy; ECOG PS = Eastern Cooperative Oncology Group performance status; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; RECIST = Response Evaluation Criteria in Solid Tumors; SE = standard error; HR = hazard ratio; CI = confidence interval.
[a] Two-sided.

Table 3 – Multivariable Cox regression analysis of overall survival for patients who had M1 disease at initial diagnosis of renal cell carcinoma, including an interaction term for prior CN*treatment

Variable	Parameter estimate	SE	*p* value[a]
Prior CN (yes vs no)	−0.15	0.23	0.5
Treatment (avelumab + axitinib vs sunitinib)	−0.04	0.25	0.9
Age (≥65 vs <65 yr)	−0.13	0.15	0.4
Geographic region (vs Asia)			
North America	0.45	0.23	0.05
Europe	0.34	0.23	0.1
Rest of the world	0.11	0.33	0.7
ECOG PS (vs 0)			
1	0.53	0.15	<0.01
2	5.36	1.43	<0.01
IMDC prognostic risk group (vs favorable)			
Intermediate	0.83	0.51	0.1
Poor	1.34	0.52	0.01
PD-L1 status (positive vs negative)	0.19	0.17	0.3
Prior CN*treatment interaction	−0.37	0.31	0.2
Prior CN vs no prior CN	**HR (95% CI)**		
Avelumab + axitinib	0.59 (0.38–0.93)		
Sunitinib	0.86 (0.55–1.34)		

CN = cytoreductive nephrectomy; ECOG PS = Eastern Cooperative Oncology Group performance status; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; SE = standard error; HR = hazard ratio; CI = confidence interval.
[a] Two-sided.

No firm conclusions can be drawn given the post hoc nature of the analyses. Prospective studies and analyses from trials of other first-line treatment options are needed to further evaluate the added value of CN and its appropriate timing in patients receiving ICI-containing combinations. In particular, the PROBE/Southwest Oncology Group S1931 trial (NCT04510597) will compare outcomes with immunotherapy-based combination therapy in patients

Table 4 – Logistic regression analysis of objective response (investigator assessment per RECIST 1.1) in patients who had M1 disease at initial diagnosis of renal cell carcinoma, including an interaction term for prior CN*treatment

Variable	Parameter estimate	SE	*p* value[a]
Prior CN (yes vs no)	0.70	0.46	0.1
Treatment (avelumab + axitinib vs sunitinib)	1.35	0.50	<0.01
Age (≥65 vs <65 yr)	0.28	0.25	0.3
Geographic region (vs Asia)			
North America	−1.05	0.35	<0.01
Europe	−0.94	0.33	<0.01
Rest of the world	−0.80	0.46	0.08
ECOG PS (vs 0)			
1	−0.23	0.25	0.4
2	−10.51	759.71	1
IMDC prognostic risk group (vs favorable)			
Intermediate	−0.20	0.56	0.7
Poor	−1.15	0.62	0.06
PD-L1 status (positive vs negative)	−0.03	0.28	0.9
Prior CN*treatment interaction	0.28	0.56	0.6
Prior CN vs no prior CN	**HR (95% CI)**		
Avelumab + axitinib	2.67 (1.32–5.41)		
Sunitinib	2.02 (0.82–4.94)		

CN = cytoreductive nephrectomy; ECOG PS = Eastern Cooperative Oncology Group performance status; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; RECIST = Response Evaluation Criteria in Solid Tumors; SE = standard error; HR = hazard ratio; CI = confidence interval.
[a] Two-sided.

with or without prior radical or partial nephrectomy for metastatic RCC.

Overall, our findings suggest that prospective studies to investigate the potential benefits of prior CN in patients who receive first-line treatment with ICI-containing combinations are warranted.

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Study concept and design: Grimm, di Pietro, Mariani, Wang, Thomaidou.
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