Avelumab + axitinib vs sunitinib in advanced renal cell carcinoma (aRCC): final analysis of patient-reported outcomes (PROs) and quality-adjusted time without symptoms or toxicity (Q-TWiST)

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JAVELIN Renal 101

BACKGROUND

- In the JAVELIN Renal 101 phase 3 trial, 1L treatment with avelumab + axitinib resulted in significantly longer progression-free survival (PFS) and higher objective response rate (ORR) vs sunitinib in patients with aRCC[1-4]
  - After ≥68 months of follow-up in the overall population, median PFS was 13.9 vs 8.5 months, respectively (stratified hazard ratio [HR], 0.66 [95% CI, 0.566-0.769]; 1-sided p≤0.0001)[4]
  - ORR was 59.7% vs 32.0%, respectively (odds ratio, 3.226 [95% CI, 2.406-4.279]; 1-sided p<0.0001)[4]
- Overall survival (OS) analyses favored avelumab + axitinib vs sunitinib, but differences did not reach statistical significance[1-4]
  - Median OS was 44.8 vs 38.9 months, respectively (stratified HR, 0.88 [95% CI, 0.749-1.039]; 1-sided p=0.0669)[4]
- Long-term follow-up from JAVELIN Renal 101 confirmed the manageable safety profile of avelumab + axitinib[4]
- In phase 3 trials, assessment of PROs is needed to confirm that any efficacy benefits are not associated with a negative impact on health-related quality of life
- Q-TWiST is an integrated measure that incorporates efficacy (ie, OS and PFS), safety (ie, toxicity), and utility estimates (ie, overall health status) into a single value to evaluate quality and quantity of observed survival time[5]
  - The Q-TWiST value measures survival time spent without toxicities or symptoms of disease progression ("quality" survival)
  - When comparing treatments, an increase in Q-TWiST represents a net benefit
- We report long-term PRO data (secondary endpoint) and a post hoc Q-TWiST analysis from the JAVELIN Renal 101 trial

METHODS

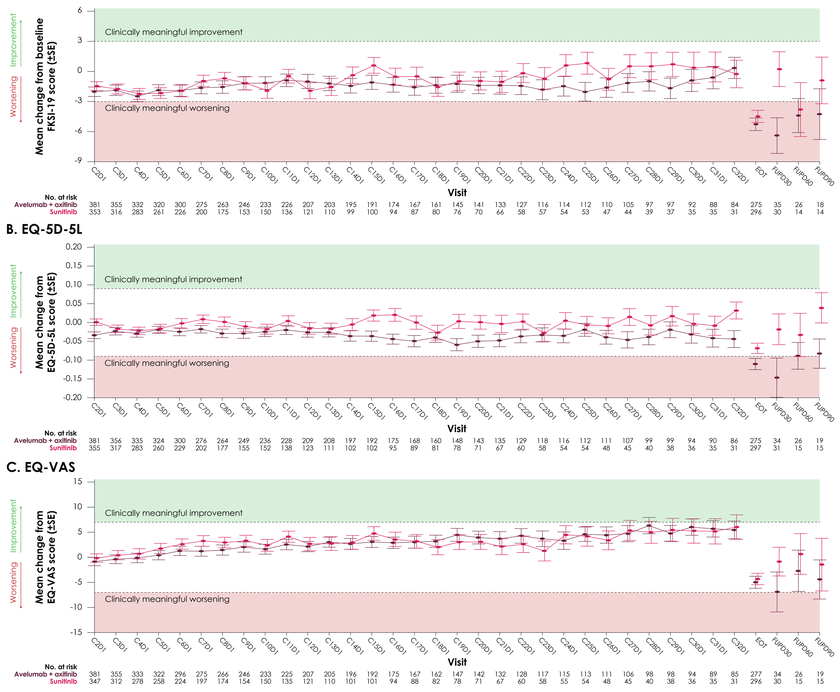
- In the JAVELIN Renal 101 (NCT02684006) trial, patients with aRCC were randomized 1:1 to receive 1L avelumab + axitinib or sunitinib
  - The independent primary endpoints were PFS and OS in patients with PD-L1+ tumors
  - Safety and PROs were secondary endpoints
  - In this analysis reported with long-term follow-up, PFS analyses are based on investigator assessment
- PROs were assessed at each visit using 2 validated instruments: Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index – 19 Item Version (FKSI-19) and EuroQol 5-Dimension 5-level (EQ-5D-5L). Both instruments were administered at the beginning of each 6-week cycle, at end of treatment/withdrawal, and at 30, 60, and 90 days after end of treatment
  - FKSI-19 is an RCC-specific questionnaire about symptoms and quality of life during the previous 7 days
  - The EQ-5D-5L assesses general health status based on mobility, self-care, usual activities, pain/discomfort, and anxiety/depression on the day of assessment; in addition, for the EQ-visual analog scale, patients score their health status from 0 and 100, corresponding to the worst and best imaginable health states, respectively
  - For both instruments, higher scores indicate better quality of life or reduced symptom burden
- In a post hoc exploratory analysis of Q-TWiST, OS in each arm was partitioned into 3 health states during the analysis period (72 months from randomization):
  - Time with all-cause grade 3/4 toxicity prior to progression (TOX)
  - Time without toxicity or symptoms of disease progression (TWiST)
  - Time after progression (relapse; REL)
- Q-TWiST was calculated by summing restricted mean time in each health state after adjustment for utility weights based on EQ-5D-5L index scores
  - Mean between-treatment differences for each health state were calculated
  - Bootstrap methods were used to estimate CIs for means and difference between means

RESULTS

PROs

- At data cutoff (August 31, 2023), median follow-up was 73.7 months in the avelumab + axitinib arm (N=442) and 73.6 months in the sunitinib arm (N=444)
  - Minimum follow-up was 68 months in both arms
- In both arms, completion rates for both PRO instruments among evaluable patients were >90% at all time points during treatment
- Overall, PRO scores in both arms remained stable throughout treatment, and no clinically important changes from baseline were reported (**Figure 1**)
  - A limitation of these analyses is that PROs were assessed every 6 weeks, which represented "off-treatment" weeks in the sunitinib arm; thus, PRO results may not represent the average symptom burden during sunitinib treatment[6]

Figure 1. PRO scores over time in the overall population



C, cycle; **D**, day; **EOT**, end of treatment; **EQ-5D-5L**, EuroQol 5-Dimension 5-level; **EQ-VAS**, EuroQol visual analog scale; **FKSI-19**, Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index – 19 Item Version; **FUPD30**, follow-up day 30; **FUPD60**, follow-up day 60; **FUPD90**, follow-up day 90; **PRO**, patient-reported outcome.

Q-TWIST

- Time spent in TOX and TWiST were longer with avelumab + axitinib vs sunitinib (**Figure 2** and **Table 1**)
- Time in REL was shorter with avelumab + axitinib vs sunitinib because patients in the avelumab + axitinib arm spent more time in a progression-free state
- Avelumab + axitinib treatment resulted in a 3.20-month gain in mean Q-TWiST vs sunitinib (**Table 1**), representing a 10.9% relative improvement (established clinically important difference, ≥10%)[7]

Figure 2. Q-TWiST analysis: survival plots partitioned by REL, TWiST, and TOX for the avelumab + axitinib and sunitinib arms based on Kaplan-Meier analysis

In both graphs, the OS curve (top line) is partitioned by curves for PFS (middle line) and TOX (bottom line). The area between the curves illustrates the time in each of the 3 health states in the Q-TWiST analysis: REL, TWiST, and TOX. **OS**, overall survival; **PFS**, progression-free survival; **Q-TWiST**, quality-adjusted time without symptoms or toxicity; **REL**, time after progression (relapse); **TOX**, time with grade 3/4 toxicity prior to progression; **TWiST**, time without toxicity or symptoms of disease progression.

Table 1. Restricted mean durations of health states and Q-TWiST by treatment arm

Mean (95% CI), months	Avelumab + axitinib (N=442)	Sunitinib (N=444)	Difference
OS	43.70 (41.25-46.01)	40.85 (38.35-43.31)	2.86 (−0.91 to 6.12)
PFS	22.86 (20.62-25.04)	15.53 (13.66-17.43)	7.34 (4.07-10.18)
TOX	5.70 (4.28-7.16)	3.53 (2.68-4.42)	2.18 (0.69-3.83)
TWiST	17.16 (15.18-19.22)	12.00 (10.50-13.67)	5.16 (2.39-7.73)
REL	20.84 (18.68-22.94)	25.32 (23.00-27.78)	−4.48 (−7.78 to −1.35)
Q-TWiST	32.57 (30.72-34.28)	29.37 (27.60-31.16)	3.20 (0.43-5.62)

OS, overall survival; **PFS**, progression-free survival; **Q-TWiST**, quality-adjusted time without symptoms or toxicity; **REL**, time after progression (relapse); **TOX**, time with grade 3/4 toxicity prior to progression; **TWiST**, time without toxicity or symptoms of disease progression.

CONCLUSIONS

- **Long-term analyses of PROs in the JAVELIN Renal 101 trial (≥68 months of follow-up in all patients) showed that first-line (1L) treatment with avelumab + axitinib or sunitinib monotherapy was associated with stable PROs in patients with aRCC**
  - **These results show that adding avelumab to the tyrosine kinase inhibitor treatment had no negative impact on health-related quality of life**
- **In a post hoc analysis, avelumab + axitinib treatment resulted in longer Q-TWiST vs sunitinib treatment (10.9% relative improvement), indicating an increase in quality-adjusted survival time**
  - **The improvement in Q-TWiST exceeded the established threshold that indicates a clinically relevant benefit (≥10%)**
  - **The Q-TWiST improvement reflects the efficacy benefits of avelumab + axitinib vs sunitinib in the context of safety and health-related quality of life profiles**
- **Overall, these results support the use of avelumab + axitinib as a 1L treatment for patients with aRCC**

PLAIN LANGUAGE SUMMARY

- **In the JAVELIN Renal 101 study, people with advanced renal cell cancer treated with avelumab + axitinib lived longer without their cancer getting worse than people treated with sunitinib**
- **In this analysis, researchers looked at the effects of avelumab + axitinib and sunitinib treatment on a person's quality of life**
  - **Quality of life is a measure of well-being, which includes how a person feels about their physical health, emotional well-being, ability to be active, and other factors affecting everyday life**
  - **Both avelumab + axitinib and sunitinib treatment were found to maintain quality of life**
- **Researchers also looked at how long people lived without cancer symptoms or severe side effects to assess the "quality" of survival with avelumab + axitinib or sunitinib treatment**
  - **Results showed that people lived longer without cancer symptoms or severe side effects with avelumab + axitinib compared to sunitinib treatment**
- **Overall, these findings provide more support for using avelumab + axitinib as a treatment for people with advanced renal cell cancer**

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