Patient-Reported Outcomes (PROs) for Tivozanib + Nivolumab (Tivo-Nivo) vs. Tivozanib (Tivo) Monotherapy in Patients With Renal Cell Carcinoma (RCC) Following an Immune Checkpoint Inhibitor (ICI): Results of the Phase 3 TiNivo-2 Study

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Background

- Tivo is a potent and highly selective oral vascular endothelial growth factor (VEGF) tyrosine kinase inhibitor (TKI) designed to optimize VEGF blockade and minimize off-target toxicities. Tivo is approved by the US Food and Drug Administration (FDA) for treatment of patients with relapsed/refractory RCC following ≥2 prior systemic therapies[1]
- Nivo is an anti-programmed death ligand antibody approved by the FDA for various tumor types, including RCC[2]
- TiNivo-2 was the first randomized, Phase 3 trial to assess the efficacy and safety of a PD-1 inhibitor combination following disease progression on or after prior PD-1/PD-L1 therapy[3]
- In the intent-to-treat (ITT) population, the median progression-free survival (mPFS) was:
- 7.4 months (95% CI: 5.6–9.2) with Tivo alone vs 5.7 months (95% CI: 4.0–7.4) with Tivo + Nivo
- Hazard ratio (HR): 1.10 (95% CI: 0.84–1.43; P = .49)
- While the study did not meet its primary endpoint of demonstrating a benefit of adding Nivo to Tivo versus Tivo alone after prior ICI exposure, clinically meaningful outcomes were observed with Tivo as a second-line (2L) and third-line (3L) treatment following ICI therapy
- Fewer treatment-emergent adverse events (TEAEs) were observed in the Tivo + Nivo arm compared to Tivo alone
- Here we present an exploratory analysis evaluating patient reported outcomes (PROs) from the TiNivo-2 study

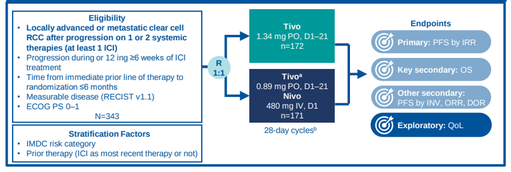
Study Objective

- To evaluate an exploratory endpoint of patient-reported outcomes(PRO) data in the TiNivo-2 study. The Functional Assessment of Cancer Therapy Kidney Cancer Symptom Index-Disease-Related Symptoms (FKSI -DRS)[5,6] and European Organization for Research and Treatment of Cancer (EORTC) QLQ C30[7] questionnaires were administered at baseline (BL), day 1 of each cycle, and at the end of treatment
- **Statistical Analysis Method**
- PRO Analysis population:
  - The PRO-evaluable set was defined as all randomized patients with a BL and 1 post-BL assessment
  - Summary statistics are provided based on the observed case

Methods

Study Design

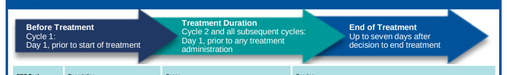
Figure 1. TiNivo-2 Phase 3 Study



[a]Reduced Tivo dose in combination arm was agreed with regulatory authorities due to potential risk of higher rate of grade 3/4 hypertension; b Treatment continued until progression or unacceptable toxicity; Nivo discontinued in all patients after 2 years of treatment.

D, day; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; INV, investigator; IRR, independent radiology review; IV, intravenous; Nivo, nivolumab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, orally; QoL, quality of life; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; Tivo, tivozanib.

Figure 2. PRO Assessment Schedule



PRO Tool	Description	Scope	Scoring
FKSI- DRS	9 questions on QoL associated with advanced kidney cancer	Lack of energy, pain, weight loss, bone pain, fatigue, dyspnea, cough, fever, hematuria	Range of summed score 0–36 Higher total score means fewer symptoms
EORTC QLQ-30	30 questions on oncology clinical trial participants general well-being and QoL	Symptoms, physical, emotional, social, and functional well-being	Range of summed score for all scales 0–100 5 multiple-item scales (functional, symptom, QoL) 6 single-item scales Higher functional score means better function; higher symptom score means more severe symptoms

EORTC QLQ-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; FKSI- DRS, Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; QoL, quality of life

Results

Table 1. PRO Questionnaire Completion and Compliance Rates

Metric, n/N (%)	Time point	Tivo	Tivo-Nivo
FKSI-DRS			
Completion	Baseline	165/171 (96.5)	164/172 (95.3)
	Week 24	91/171 (53.2)	97/172 (56.4)
Compliance	Baseline	165/171 (96.5)	164/172 (95.3)
	Week 24	91/98 (92.9)	97/106 (91.5)
EORTC QLQ-c30			
Completion	Baseline	161/171 (94.2)	165/171 (96.5)
	Week 24	92/171 (53.8)	91/171 (53.2)
Compliance	Baseline	161/171 (94.2)	165/171 (96.5)
	Week 24	92/98 (93.9)	91/98 (92.9)

EORTC QLQ-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; FKSI- DRS, Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; NIVO, nivolumab; PRO, patient-reported outcomes; TIVO, tivozanib.

Completion rate at each point was calculated as the proportion of participants from the ITT population that completed the PRO questionnaire at the assessment timepoint

Compliance rate was calculated as the proportion of remaining trial participants who completed the PRO questionnaire at the assessment time point

Figure 3. Centrally Reviewed PFS by Line of Therapy[4]

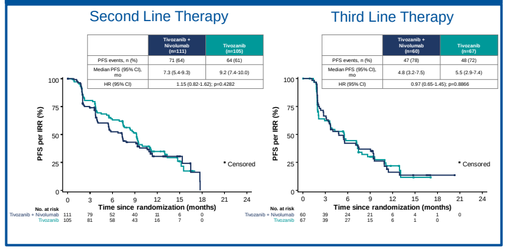
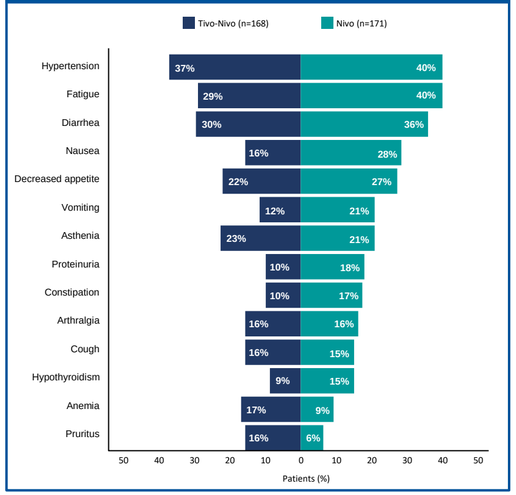


Figure 4. Treatment Emergent Adverse Events (TEAE) Occurring in ≥15% of Patients in Either Arm



- The type and frequency of safety events in the tivozanib monotherapy group in this study were consistent with its known safety profile, confirming Tivozanib tolerability
- For certain TEAEs, such as fatigue, nausea, vomiting, proteinuria and hypothyroidism, the combination group showed lower numerical rates. However, this was not the case for anemia, pruritus, which showed the reverse. The lower dose in the combination potentially explains the lower rate of TEAEs associated with VEGF-TKIs.

Table 2. Change Of FKSI-DRS And EORTC-QLQ-C30 Score At Week 24

PRO variables	Tivo + Nivo			Tivo		
	ITT	2L	3L	ITT	2L	3L
FKSI-DRS BL mean (SD)	28.8 (5.6)	29.5 (4.9)	27.6 (6.5)	29.3 (5.3)	29.1(5.5)	29.5 (5.0)
Week 24 mean (SD)	29.9 (4.9)	30.1 (4.7)	29.5 (5.4)	29.4 (5.3)	29.3 (4.8)	29.6 (6.3)
EORTC-QLQ-C30 BL mean (SD)	63.4 (23.4)	65.0 (21.8)	60.5 (26.1)	66.2 (21.4)	67.1 (21.9)	64.9 (20.7)
Week 24 mean (SD)	68.7 (17.4)	68.7 (16.1)	68.6 (20.6)	64.8 (21.1)	64.6 (20.7)	65.1 (22.4)

Figure 5. Changes in FKSI-DRS and EORTC QLQ-c30

FKSI-DRS and EORTC QLQ-c30 summary scores showed that there was no significant change in symptom scores over time in both treatment groups

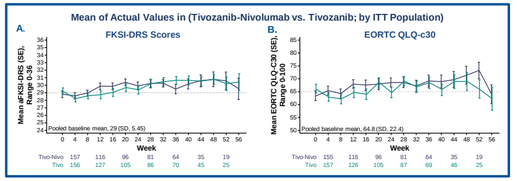


Figure 6. Changes in FKSI-DRS Score in the 2L and 3L Setting

- Patients receiving treatment in the second- or third-line setting showed a similar trend
- Symptom scores-maintained over time

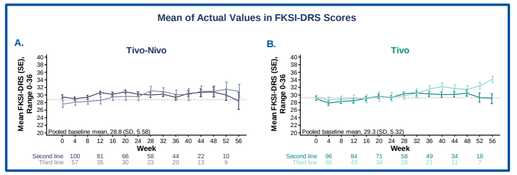


Figure 6. Changes in EORTC QLQ-C30 Score in the 2L and 3L Setting

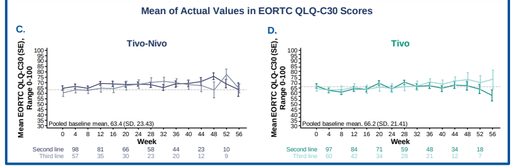
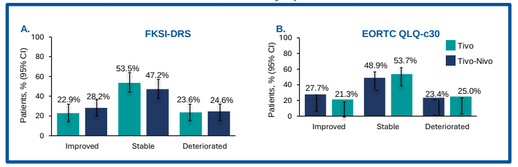


Figure 7. Patients With Improved, Stable Or Deteriorated QoL Scores

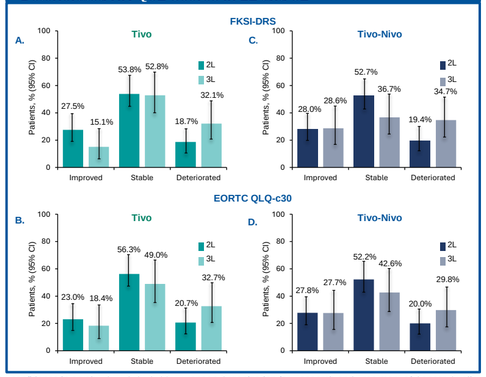
- FKSI-DRS and EORTC QLQ-c30 questionnaires reported consistent trends and proportions of patients with improved, stable, or deteriorated symptoms (Figure 7A, 7B)
- Approximately 75% of all patients reported improved or stable kidney cancer and cancer-treatment related symptoms in both treatment arms



CI, confidence interval; EORTC QLQ-30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; FKSI- DRS, Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; Nivo, nivolumab; Tivo, tivozanib.

- The overall proportions of patients with stable or deteriorated symptoms was consistent with both questionnaires and treatment arms (Figure 8A-D)
- In the TIVO arm, patients receiving 2L treatment showed a trend towards numerically greater improvement in FKSI-DRS and EORTC QLQ-C30 scores compared to those receiving 3L treatment. Additionally, the proportion of patients experiencing deterioration was smaller in the 2L group than in the 3L group

Figure 8. Proportion of Patients with Stable, Improved or Deteriorated HR-QoL Scores in 2L and 3L



CI, confidence interval; EORTC QLQ-30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire - Core 30; FKSI- DRS, Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease-Related Symptoms; Nivo, nivolumab; Tivo, tivozanib.

Definitions	
Improved	A clinically meaningful increase in scores (≥3 points[1]) from baseline at any time during the study, confirmed by a clinically meaningful increase in score at the next consecutive visit
Stable	When not meeting criteria for improvement, a change in score of <3 points[1] that is confirmed at the next consecutive visit
Deteriorated	A clinically meaningful decrease in score(≥3 points[1]) from baseline at any time during the study

Conclusions

- There were no differences in the PRO outcomes between the combination therapy and monotherapy arms. PRO data suggested that Tivo maintained the FKSI-DRS and EORTC QLQ-C30 mean scores over time
- In the Tivo arm, improvement in FKSI-DRS and EORTC QLQ-C30 scores was numerically greater in patients receiving 2L treatment than 3L treatment (FKSI-DRS: 2L 27.5% vs 3L 15.1%, EORTC QLQ-c30: 2L 23.0% vs 3L 18.4%), while the fewer patients reported deterioration in the 2L than in the 3L (FKSI-DRS: 2L 18.7% vs 3L 32.1%, EORTC QLQ-c30: 2L 20.7% vs 3L 32.7%).

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