Efficacy of second line (2L) treatment with Tivozanib (Tivo) as monotherapy or with Nivolumab (Nivo) in patients (pts) with metastatic renal cell carcinoma (mRCC) previously treated with an immune checkpoint inhibitor (ICI) combination of ipilimumab (Ipi)/Nivo or vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI)/ICI in the Phase 3 TiNivo-2 study

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Alex Chehrazi-Raffle[1], Robert J. Motzer[2], Katy Beckermann[3], Philippe Barthelemy[4], Roberto Iacovelli[5], Sheik Emambux[6], Javier Molina-Cerrillo[7], Benjamin Garmezy[8], Pedro C. Barata[9], Rana R. McKay[10], Hans J. Hammers[11], Daniel Yick Chin Heng[12], Bo Jin[13], Claudia Lebedinsky[13], Edgar E. Braendle[13], Bradley Alexander McGregor[14], Laurence Albiges[15], Toni K. Choueiri[16] **For more information contact: achehraziraffle@coh.org**

*[1]City of Hope Comprehensive Cancer Center, Duarte, CA; [2]Genitourinary Oncology, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY; [3]Vanderbilt University, Nashville, TN; [4]Institut de Cancérologie Strasbourg Europe, Strasbourg, France; [5]Comprehensive Cancer Center, Oncology Unit, Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy; [6]Centre Hospitalier Universitaire de Poitiers, Poitiers, France; [7]Medical Oncology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain; [8]Sarah Cannon Research Institute, Nashville, TN; [9]University Hospitals Seidman Cancer Center, Cleveland, OH; [10]Department of Medicine, University of California San Diego, San Diego, CA; [11]Department of Internal Medicine, Division of Hematology and Oncology, UT Southwestern, Dallas, TX; [12]Tom Baker Cancer Centre, University of Calgary, Calgary, AB; [13]AVEO Oncology, Boston, MA; [14]Dana-Farber Cancer Institute, Boston, MA; [15]Gustave Roussy, Paris Saclay University, Paris, France; [16]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA

Background

- Tivo is a potent and highly selective oral vascular endothelial growth factor receptor (VEGFR) 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 pts with relapsed/refractory RCC following ≥2 prior systemic therapies[1,2]
- Nivo is an anti-programmed death ligand antibody approved by the FDA for various tumor types, including RCC[3]
- 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[4]
- Pts were randomized 1:1 to receive Tivo once daily for 21/28 days at either 1.34 mg alone or at 0.89 mg with Nivo at 480 mg by IV infusion on day 1 of each 28-day cycle[4]
- 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[4]
- **Median progression-free survival (mPFS) for pts that received study treatment as[4]:**
  - **2L:** 7.3 months (95% CI 5.4–9.3) with Tivo+Nivo and 9.2 months (7.4–10.0) with Tivo monotherapy (HR 1.15, 95% CI 0.82–1.62; p=0.43)
  - **3L:** 4.8 months (95% CI 3.2–7.5) with Tivo+Nivo and 5.5 months (2.9–7.4) with Tivo monotherapy (HR 0·97, 95% CI 0.65–1.45; p=0.89)

Study Objective: To assess efficacy of Tivo as a 2L therapeutic in the context of contemporary treatment sequencing, study outcomes were evaluated in pts who failed first line (1L) Ipi/Nivo or VEGFR-TKI/ICI therapy

Methods & Statistical Analyses

- For this exploratory sub-analysis, the efficacy data of progression free survival (PFS) and objective response rate (ORR) assessed by blinded independent review committee (BIRC) were analyzed in two cohorts of pts who were not treated with adjuvant therapy and had progressed on 1L on Ipi/Nivo, or VEGFR-TKI/ICI therapy
- A summary of key demographic and baseline disease characteristics of these two pt cohorts are shown in **Table 1;** some imbalances were observed. (Complete tables are accessible by embedded QR code)
- Treatment comparisons in PFS are conducted by log rank test. The PFS medians and 95% confidence limits are provided based on the Kaplan-Meier method
- The hazard ratios and 95% confidence intervals are obtained by the Cox proportional hazards model. The estimated ORRs and respective 95% CI are summarized by treatment. Best percent changes from baseline in target lesion tumor size are also presented by treatment in the two cohorts of pts

Results

Figure 1. 1L TKI/ICI Progression-Free Survival

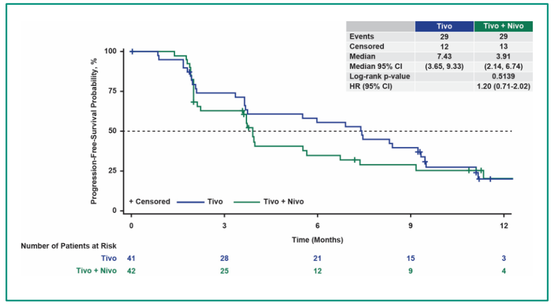


Table 2. 1L TKI/ICI Objective Response Rate, N (%)

Best Response	TKI/ICI	
	Tivo	Tivo + Nivo
CR	0	0
PR	9 (22)	4 (9.5)
SD	16 (39)	20 (47.6)
PD	9 (22)	16 (38.1)
NE/missing	7 (17.1)	2 (4.4)
ORR% [95% CI]	22 (10.6-37.6)	9.5 (2.7-22.6)

In pts who received TKI/ICI in 1L, mPFS was 7.4 months (95% CI, 3.7-9.3) with Tivo and 3.9 months (95% CI, 2.1-5.7) with Tivo+Nivo; ORR was 22.0% (95% CI, 10.6%-37.6%) with Tivo and 9.5% (95% CI, 2.7%-22.6%) with Tivo+Nivo (**Figure 1, Table 2**).

Figure 2. 1L Ipi/Nivo Progression-Free Survival

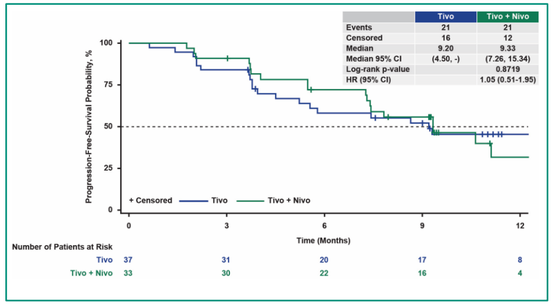


Table 3. 1L Ipi/Nivo Objective Response Rate, N (%)

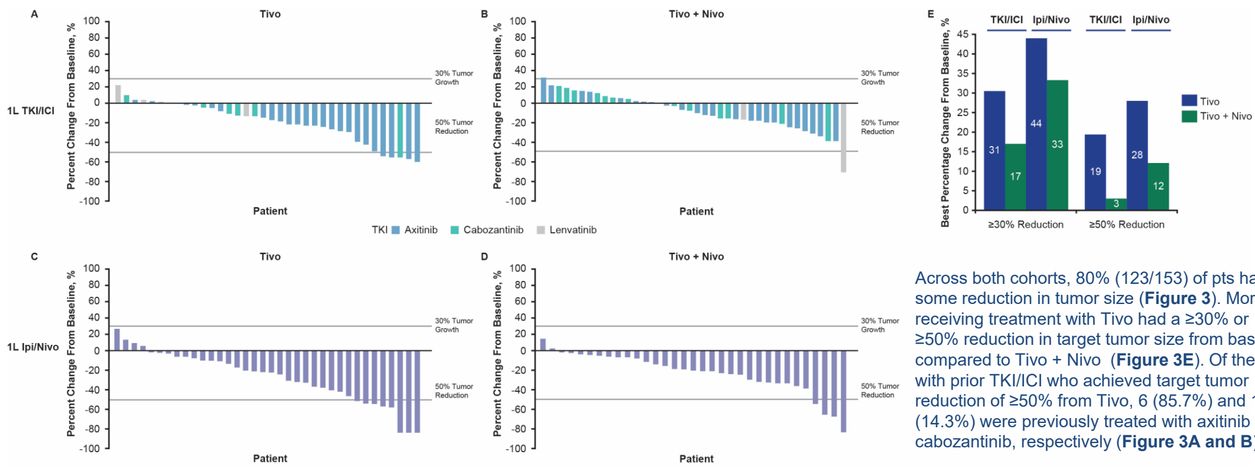
Best Response	Ipi/Nivo	
	Tivo	Tivo + Nivo
CR	0	0
PR	12 (32.4)	8 (24.2)
SD	17 (45.9)	19 (57.6)
PD	7 (18.9)	6 (18.2)
NE/missing	1 (2.7)	0
ORR% [95% CI]	32.4 (18-49.8)	24.2 (11.1-42.3)

In pts who received Ipi/Nivo in 1L, mPFS was 9.2 months (95% CI, 4.5-NR) with Tivo and 9.3 months (95% CI, 7.3-15.3) with Tivo+Nivo; ORR was 35.1% (95% CI, 18.0%-49.8%) with Tivo and 24.2% (95% CI, 11.1%-42.3%) with Tivo+Nivo (**Figure 2, Table 3).**

Table 1. Key Patient Baseline Demographics and Disease Characteristics

Patient Baseline Demographics and Disease Characteristics Summary		1L: ICI-TKI		1L: Ipi/Nivo	
		Tivo (N=41)	Tivo + Nivo (N=42)	Tivo (N=37)	Tivo + Nivo (N=33)
Age	Mean (SD)	64.3 (10.27)	66.0 (8.44)	59.6 (9.62)	62.1 (12.25)
	Median	64	67	59	61
	< 65 years, n (%)	21 (51.2)	16 (38.1)	27 (73.0)	19 (57.6)
	≥ 65 years, n (%)	20 (48.8)	26 (61.9)	10 (27.0)	14 (42.4)
Location of metastasis, n (%)	Adrenal Gland	6 (14.6)	12 (28.6)	7 (18.9)	5 (15.2)
	Brain	2 (4.9)	3 (7.1)	2 (5.4)	4 (12.1)
	Bone	11 (26.8)	15 (35.7)	8 (21.6)	9 (27.3)
	Colon	1 (2.4)	0	1 (2.7)	1 (3.0)
	Kidney	7 (17.1)	5 (11.9)	7 (18.9)	5 (15.2)
	Lung	28 (68.3)	27 (64.3)	30 (81.1)	22 (66.7)
	Lymph node	16 (39.0)	16 (38.1	22 (59.5)	19 (57.6)
	Liver	11 (26.8)	9 (21.4)	7 (18.9)	7 (21.2)
	Rectum	0	1 (2.4)	1 (2.7)	0
	Spine	1 (2.4)	0	0	0
	Skin/Soft tissue	6 (14.6)	2 (4.8)	4 (10.8)	4 (12.1)
	Other	14 (34.1)	12 (28.6)	6 (16.2)	12 (36.4)
	Missing	1 (2.4)	0	N/A	N/A
Prior Nephrectomy, n (%)	Complete	19 (67.9)	10 (43.5)	14 (77.8)	11 (73.3)
	Partial	5 (17.9)	11 (47.8)	2 (11.1)	3 (20.0)
	Other	4 (14.3)	2 (8.7)	2 (11.1)	1 (6.7)
	No	13 (31.7)	19 (45.2)	19 (51.4)	18 (54.5)
Sub-categories in ICI+TKI, n (%)	Avelumab/Axitinib	6 (14.6)	4 (9.5)	N/A	N/A
	Axitinib/Pembrolizumab	22 (53.7)	23 (54.8)	N/A	N/A
	Cabozantinib/Nivolumab	8 (19.5)	13 (31.0)	N/A	N/A
	Lenvatinib/Pembrolizumab	5 (12.2)	2 (4.8)	N/A	N/A

Figure 3. Percentage Change in Tumor Size From Baseline



Across both cohorts, 80% (123/153) of pts had some reduction in tumor size (**Figure 3**). More pts receiving treatment with Tivo had a ≥30% or ≥50% reduction in target tumor size from baseline compared to Tivo + Nivo (**Figure 3E**). Of the 7 pts with prior TKI/ICI who achieved target tumor reduction of ≥50% from Tivo, 6 (85.7%) and 1 (14.3%) were previously treated with axitinib and cabozantinib, respectively (**Figure 3A and B**).

Conclusions

- In this TiNivo-2 subgroup analysis, **Tivo monotherapy at 1.34 mg daily showed activity in pts who previously received a contemporary 1L mRCC regimen**
  - **Substantial tumor size reduction** was observed, after 1L Ipi/Nivo and TKI-ICI
  - **ORR ranged from 22-32%** based on 1L treatment
- There appeared to be no benefit with the addition of Nivo to Tivo in this context, akin to the results of the parent trial

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References FOTIVDA® (Tivozanib) Prescribing Information. 2024; [2]Rathmell WK, et al. J Clin Oncol. 2022; 40:2957–2995; [3]OPDIVO® (Nivolumab) Prescribing Information. 2024; [4]Choueiri TK, et al. Lancet. 2024; 404:1309–1320.

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