Tivozanib Plus Nivolumab vs Tivozanib Monotherapy in Patients With Metastatic Renal Cell Carcinoma Following an Immune Checkpoint Inhibitor: Results of the Phase 3 TiNivo-2 Study

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Declaration of Interests

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  - Institutional patents filed on molecular alterations and immunotherapy response/toxicity, and ctDNA
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Background

- Immune checkpoint inhibitors (ICIs) are the cornerstone of the first-line treatment of advanced mRCC[1-4]
- The optimal sequence in patients whose disease has progressed after treatment with ICIs is uncertain, leaving several unanswered questions:
  - Can ICI rechallenge improve clinical outcomes?
  - Can outcomes be impacted if non-ICIs were used before ICI rechallenge (ICI break)?
  - Are there any differences between anti–PD-1 or anti–PD-L1 therapies in the rechallenge setting?
- Evidence supports the value of VEGFR TKI use, including tivozanib, in patients previously treated with ICI-based regimens[5,6]
- Tivozanib was evaluated in combination with nivolumab in the phase 1/2 TiNivo study, showing promising antitumor efficacy with an expected adverse event profile in patients with mRCC[7]
- To further explore retreatment with ICI, we conducted the phase 3 TiNivo-2 study of tivozanib in combination with nivolumab (anti–PD-1) compared with tivozanib in patients with mRCC following progression on prior ICI

mRCC, metastatic renal cell carcinoma; PD-1, programmed cell death 1 protein; PD-L1, programmed cell death 1 ligand 1; VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor.

1. Choueiri TK, et al. *N Engl J Med*. 2017;367(4):354-366. 2. Choueiri TK, et al. *J Natl Cancer Inst*. 2021;113(3):234-243. 3. Braun DA, et al. *Nat Rev Clin Oncol*. 2021;18(4):199-214. 4. Ravi P, et al. *Cancer J*. 2020;26(5):464-470. 5. Pal SK, et al. *Lancet*. 2023;402:185-195. 6. Rini BI, et al. *Lancet Oncol*. 2020;21:95-104. 7. Albiges L, et al. *Ann Oncol*. 2021;32:97-102.

TiNivo-2: Phase 3 Study Design

Locally advanced or metastatic clear cell RCC after progression on 1 or 2 lines of therapy, one of which was an ICI:

- Progression during or following ≥6 weeks of treatment with an ICI
- Time from immediate prior line of therapy to randomization ≤6 months
- Measurable disease (RECIST v1.1)
- ECOG PS: 0 or 1

N=343

R
1:1

Tivozanib
0.89 mg PO, D1-21
Nivolumab
480 mg IV, D1
n=171

Tivozanib
1.34 mg PO, D1-21
n=172

28-day cycles[a]

Endpoints

Primary
- PFS by IRR

Secondary
- OS
- PFS by INV
- ORR
- DOR
- Safety/tolerability

Stratification Factors
- IMDC risk category
- Prior therapy (ICI as most recent therapy or not)

Statistical Analysis
- 220 PFS events, statistically powered to detected an improvement of 4 months in PFS (HR=0.67)
- Stratified log-rank test with a two-sided 5% significance level

Key Considerations
- Reduced dose of tivozanib in combination arm was agreed with regulatory authorities due to potential risk of higher rate of grade 3/4 hypertension
- Prior therapy (ICI as most recent therapy or not)
  - Test if ICI break impacts outcome (to resensitize the immune system to ICI therapy)

[a] Treatment was continued until progression or unacceptable toxicity; nivolumab was 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 mRCC Database Consortium; INV, investigator; IRR, independent radiology review; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; R, randomization; RCC, renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors.

1. ClinicalTrials.gov. Accessed May 20, 2024. https://clinicaltrials.gov/study/NCT04987203

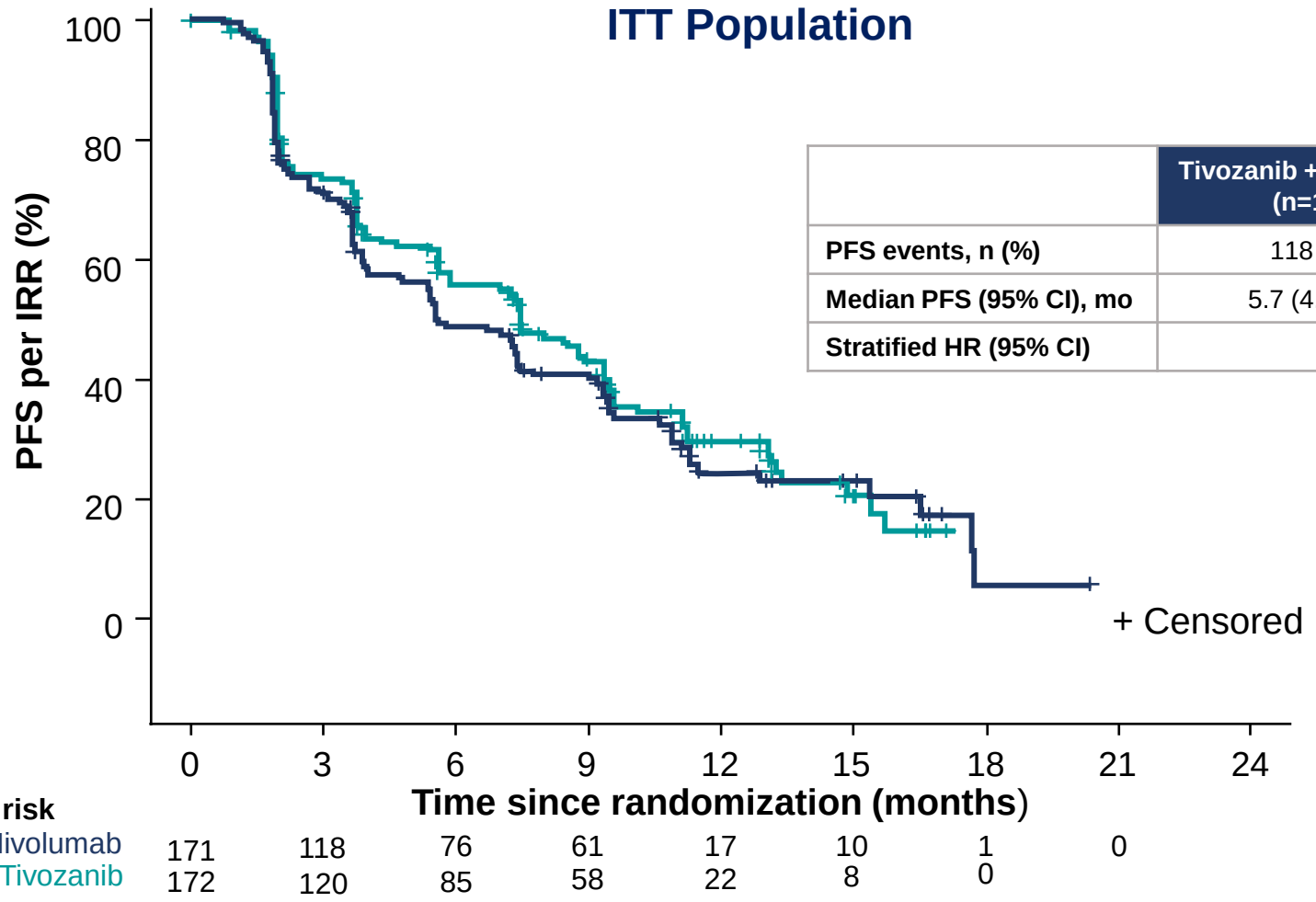
Baseline Demographics and Disease Characteristics

Characteristic	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
Age, years		
Median (range)	64 (37-87)	63 (33-82)
Sex, n (%)		
Female	46 (27)	38 (22)
Male	125 (73)	134 (78)
Race, n (%)		
White	112 (65)	107 (62)
Asian	1 (<1)	0
Black or African American	2 (1)	8 (5)
Not reported	56 (33)	57 (33)
ECOG PS, n (%)		
0	76 (44)	85 (49)
1	94 (55)	87 (51)
Missing	1 (<1)	0

Characteristic	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
IMDC risk category, n (%)		
Favorable	30 (18)	31 (18)
Intermediate	114 (67)	113 (66)
Poor	27 (16)	28 (16)
Prior lines of therapy, n (%)		
1	111 (65)	105 (61)
2	60 (35)	67 (39)
Most recent therapy, n (%)		
ICI	122 (71)	122 (71)
Non-ICI	49 (29)	50 (29)
Prior VEGFR-TKI use, n (%)		
0	53 (31)	53 (31)
1	96 (56)	101 (58)
2	22 (13)	18 (11)

ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; IMDC, International mRCC Database Consortium; VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor.

Primary Analysis of Centrally Reviewed PFS (primary endpoint)



	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
PFS events, n (%)	118 (69)	112 (65)
Median PFS (95% CI), mo	5.7 (4.0-7.4)	7.4 (5.6-9.2)
Stratified HR (95% CI)	1.10 (0.84-1.43); p=0.49	

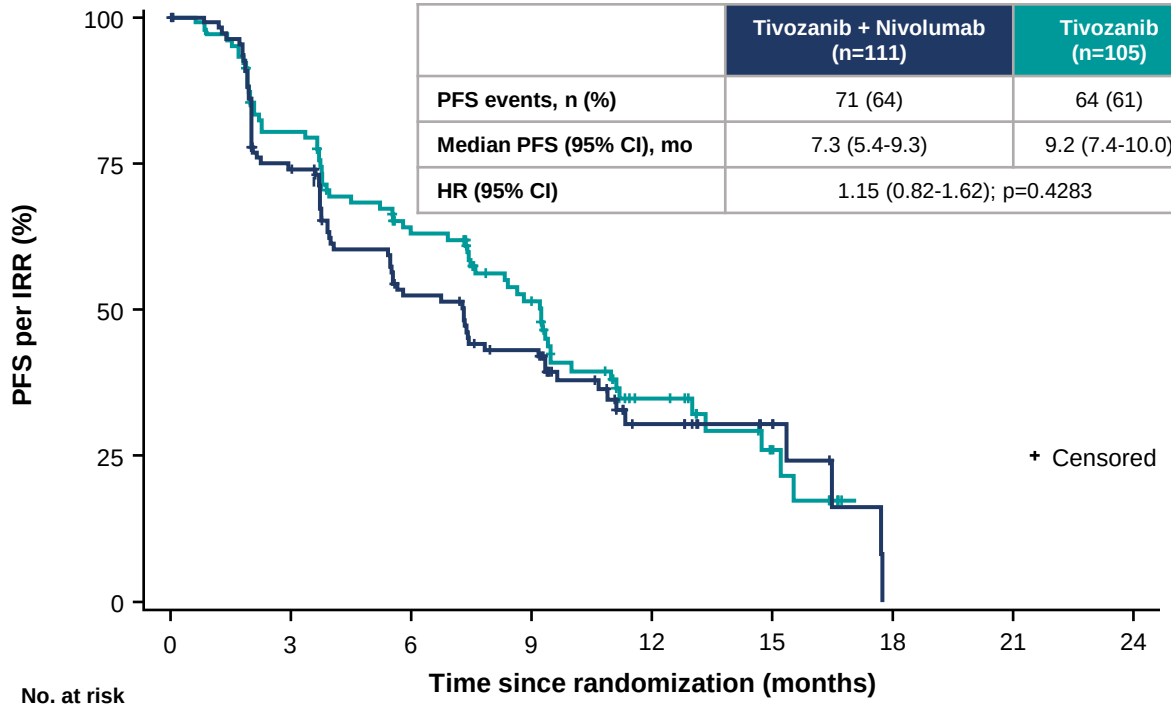
Median follow-up was 11.8 months in the tivozanib + nivolumab cohort and 12.5 months in the tivozanib monotherapy arm

HR, hazard ratio; IRR, independent radiology review; ITT, intent to treat; PFS, progression-free survival.

Centrally Reviewed PFS by Line of Therapy

Second-Line Therapy

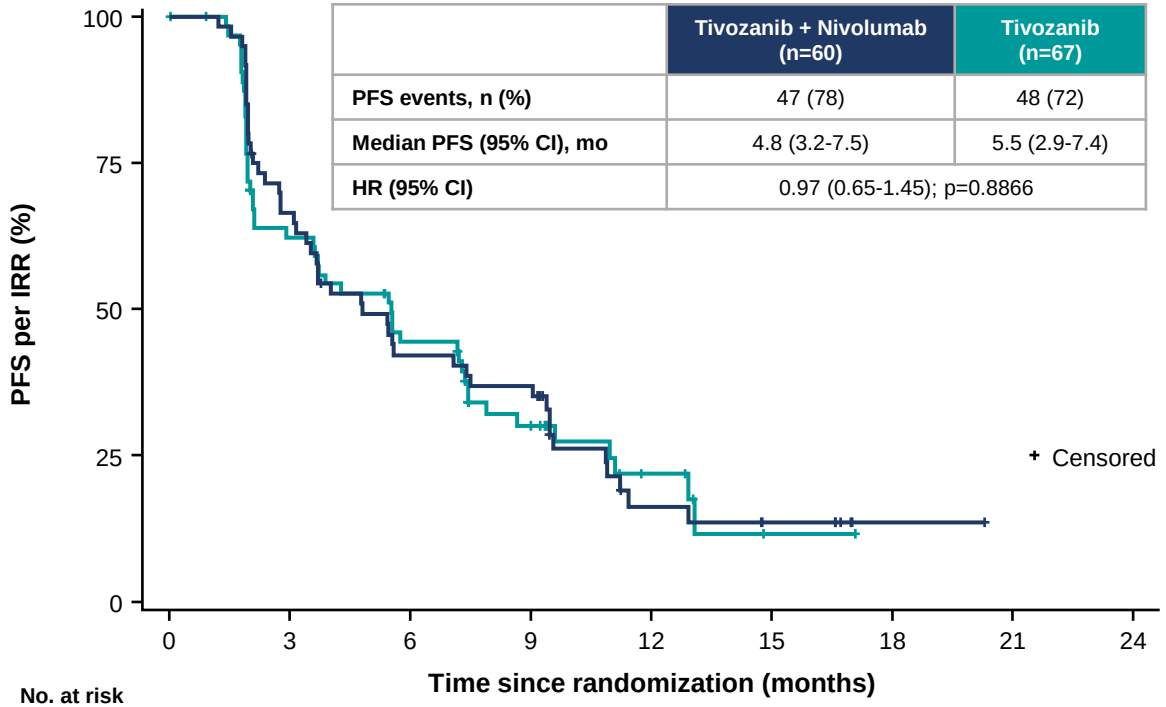
	Tivozanib + Nivolumab (n=111)	Tivozanib (n=105)
PFS events, n (%)	71 (64)	64 (61)
Median PFS (95% CI), mo	7.3 (5.4-9.3)	9.2 (7.4-10.0)
HR (95% CI)	1.15 (0.82-1.62); p=0.4283	



No. at risk							
Tivozanib + Nivolumab	111	79	52	40	11	6	0
Tivozanib	105	81	58	43	16	7	0

Third-Line Therapy

	Tivozanib + Nivolumab (n=60)	Tivozanib (n=67)
PFS events, n (%)	47 (78)	48 (72)
Median PFS (95% CI), mo	4.8 (3.2-7.5)	5.5 (2.9-7.4)
HR (95% CI)	0.97 (0.65-1.45); p=0.8866	



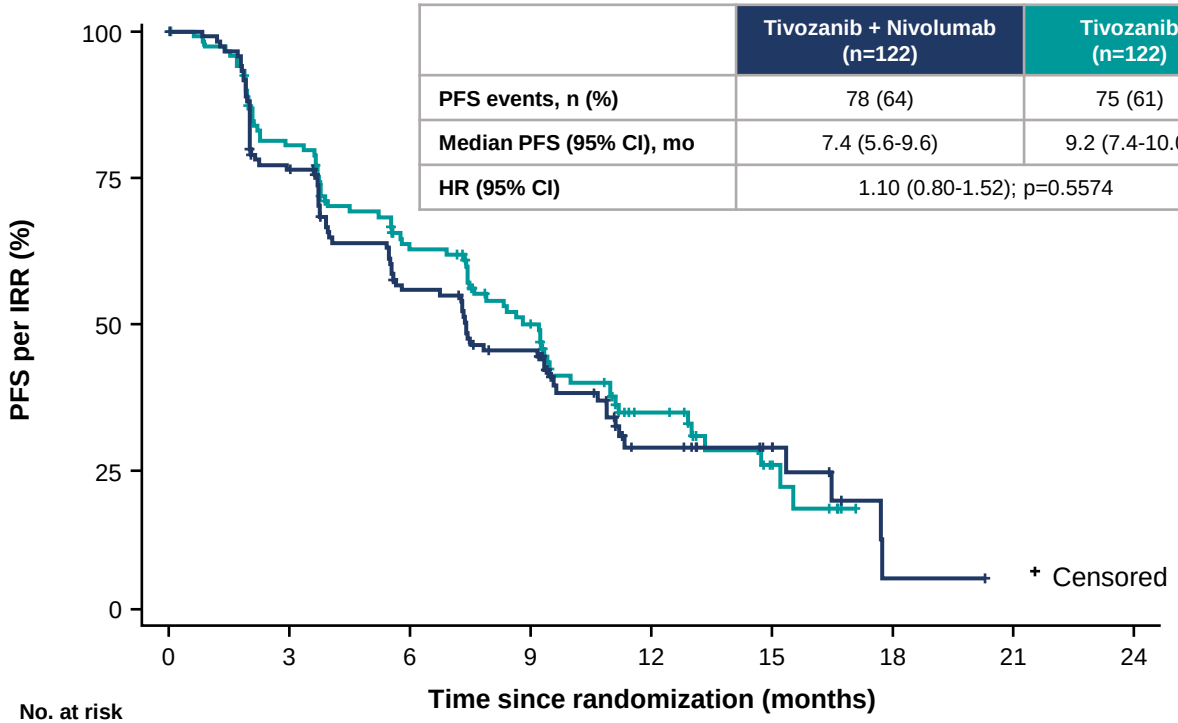
No. at risk								
Tivozanib + Nivolumab	60	39	24	21	6	4	1	0
Tivozanib	67	39	27	15	6	1	0	

HR, hazard ratio; IRR, independent radiology review; PFS, progression-free survival.

Centrally Reviewed PFS by Most Recent Line of Therapy

ICI as Most Recent Therapy

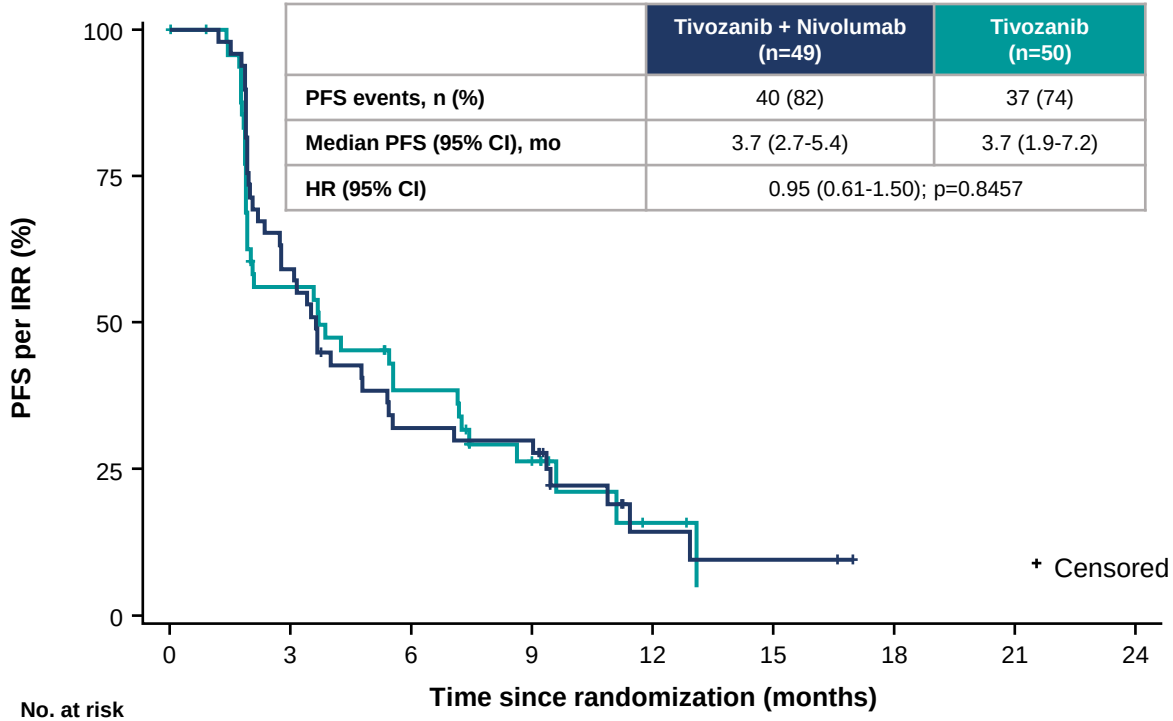
	Tivozanib + Nivolumab (n=122)	Tivozanib (n=122)
PFS events, n (%)	78 (64)	75 (61)
Median PFS (95% CI), mo	7.4 (5.6-9.6)	9.2 (7.4-10.0)
HR (95% CI)	1.10 (0.80-1.52); p=0.5574	



No. at risk								
Tivozanib + Nivolumab	122	89	61	47	14	8	1	0
Tivozanib	122	94	68	49	20	8	0	

Non-ICI as Most Recent Therapy

	Tivozanib + Nivolumab (n=49)	Tivozanib (n=50)
PFS events, n (%)	40 (82)	37 (74)
Median PFS (95% CI), mo	3.7 (2.7-5.4)	3.7 (1.9-7.2)
HR (95% CI)	0.95 (0.61-1.50); p=0.8457	

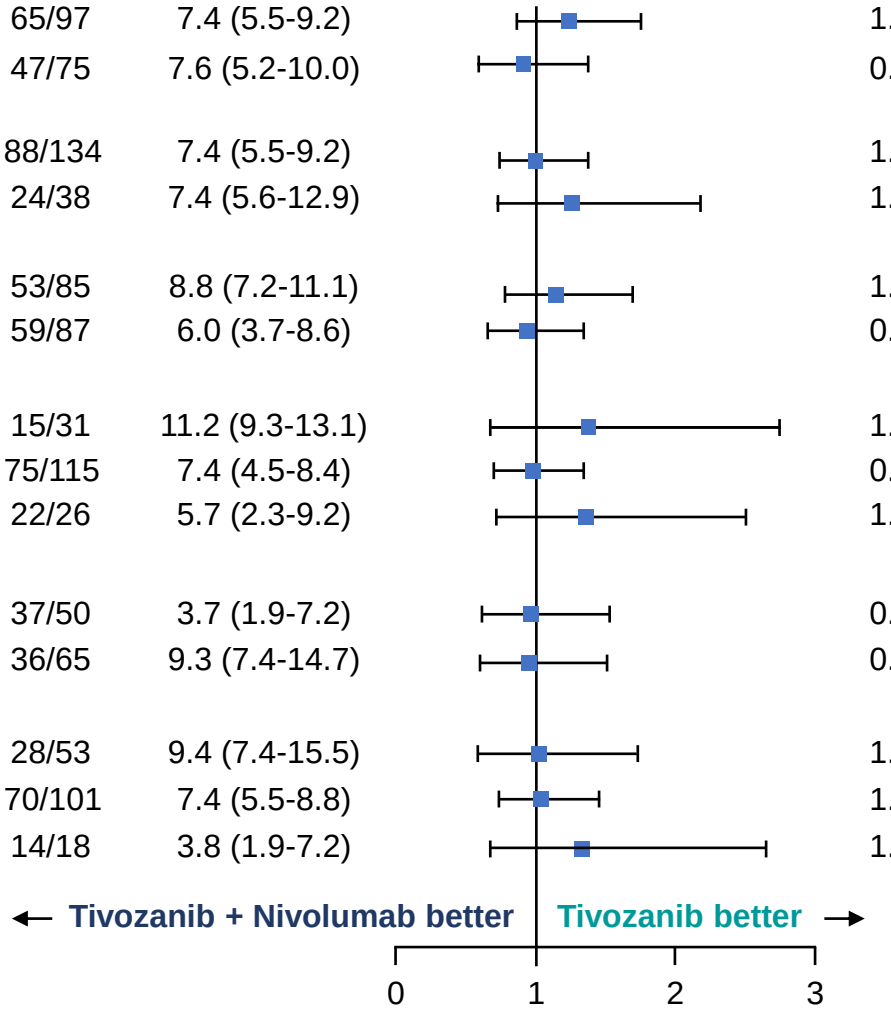


No. at risk								
Tivozanib + Nivolumab	49	29	15	14	3	2	0	
Tivozanib	50	26	17	9	2	0		

*Analysis by strata.
HR, hazard ratio; ICI, immune checkpoint inhibitor; IRR, independent radiology review; PFS, progression-free survival

Centrally Reviewed PFS by Subgroups

Category	Tivozanib + Nivolumab Event/N	Tivozanib + Nivolumab Median PFS (95% CI), months	Tivozanib Event/N	Tivozanib Median PFS (95% CI), months	PFS HR (95% CI)
Age					
<65 years	68/89	4.8 (3.7-7.3)	65/97	7.4 (5.5-9.2)	1.25 (0.89-1.76)
≥65 years	50/82	9.2 (5.5-9.6)	47/75	7.6 (5.2-10.0)	0.92 (0.61-1.37)
Sex					
Male	86/125	5.6 (3.9-7.5)	88/134	7.4 (5.5-9.2)	1.01 (0.75-1.36)
Female	32/46	6.7 (3.7-10.9)	24/38	7.4 (5.6-12.9)	1.27 (0.75-2.16)
ECOG PS					
0	52/76	7.3 (4.0-9.4)	53/85	8.8 (7.2-11.1)	1.15 (0.78-1.69)
1	66/94	5.5 (3.7-9.0)	59/87	6.0 (3.7-8.6)	0.95 (0.67-1.36)
IMDC risk category					
Favorable	18/30	9.3 (4.0-11.4)	15/31	11.2 (9.3-13.1)	1.37 (0.69-2.73)
Intermediate	78/114	5.7 (4.0-9.4)	75/115	7.4 (4.5-8.4)	0.99 (0.72-1.36)
Poor	22/27	3.7 (2.7-7.4)	22/26	5.7 (2.3-9.2)	1.35 (0.73-2.50)
VEGFR-TKI use in most recent line					
Yes	37/45	3.4 (2.2-4.8)	37/50	3.7 (1.9-7.2)	0.96 (0.61-1.52)
No	37/66	9.6 (7.5-11.2)	36/65	9.3 (7.4-14.7)	0.95 (0.60-1.51)
No. of previous VEGFR-TKIs (any prior line)					
0	29/53	9.6 (7.4-15.3)	28/53	9.4 (7.4-15.5)	1.03 (0.61-1.74)
1	69/96	5.4 (3.7-6.7)	70/101	7.4 (5.5-8.8)	1.04 (0.74-1.45)
2	20/22	3.1 (2.1-4.0)	14/18	3.8 (1.9-7.2)	1.33 (0.67-2.65)



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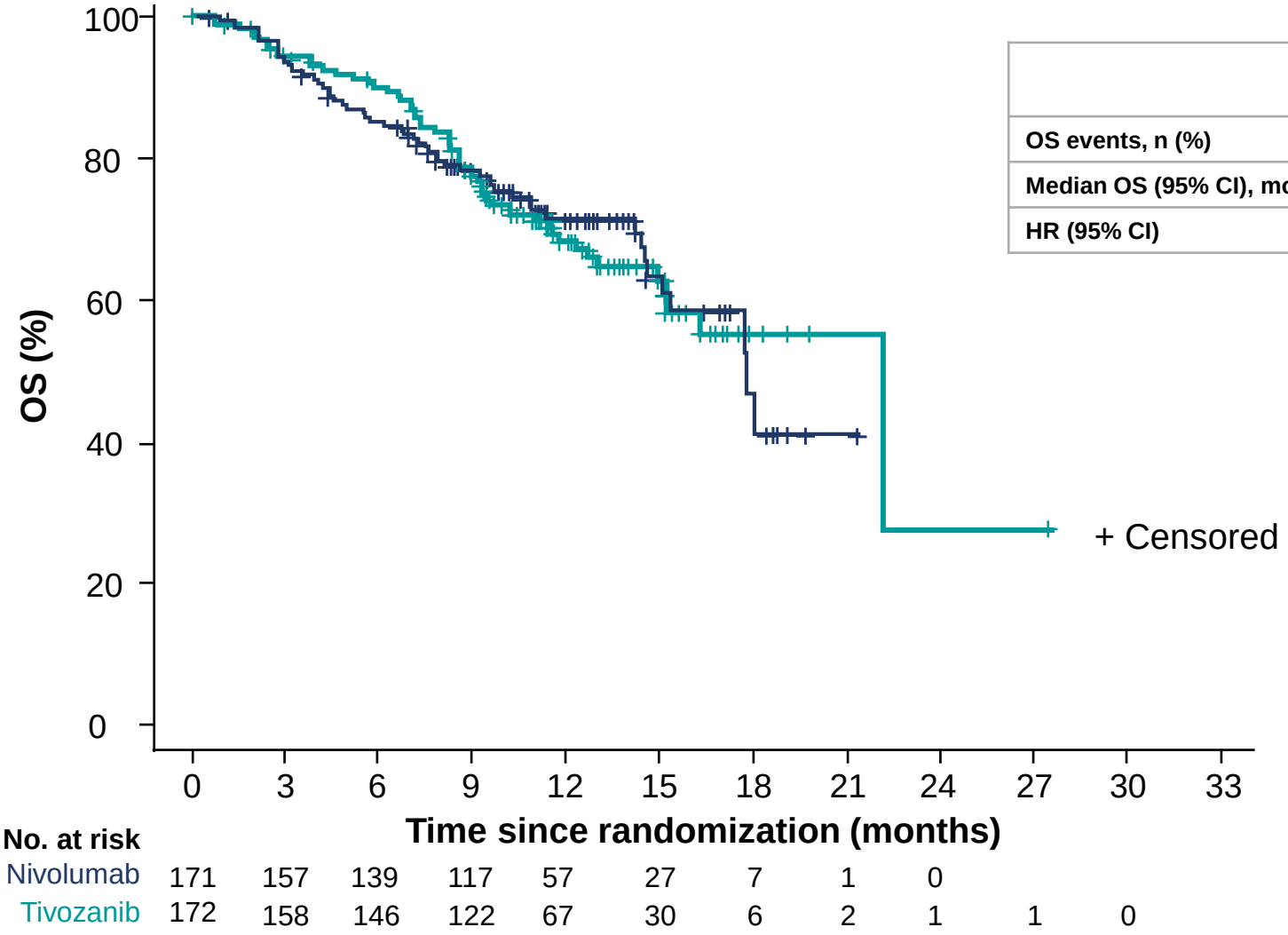
ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ICI, immune checkpoint inhibitor; IMDC, International mRCC Database Consortium; IRR, independent radiology review; PFS, progression-free survival; VEGFR-TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor.

Overall Survival



	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
OS events, n (%)	53 (31)	57 (33)
Median OS (95% CI), mo	17.7 (15.1-NR)	22.1 (15.2-NR)
HR (95% CI)	1.00 (0.68-1.46); p=0.9868	

Overall survival data are not mature.
At data cutoff, 32% of events had occurred.

NR, not reached; OS, overall survival.

Best Overall Response per Central Review

	Tivozanib + Nivolumab (n=171)	Tivozanib (n=172)
ORR, n (%) [95% CI]	33 (19.3) [13.7-26.0]	34 (19.8) [14.1-26.5]
CR, n (%)	1 (0.6)	1 (0.6)
PR, n (%)	32 (18.7)	33 (19.2)
SD, n (%)	74 (43.3)	81 (47.1)
PD, n (%)	49 (28.7)	43 (25.0)
NE, n (%)	15 (8.8)	14 (8.1)
mDOR (95% CI), mo	15.77 (5.65-NR)	9.66 (3.71-NR)

Included are patients who presented with measurable disease according to RECIST 1.1, as assessed by central review.
CR, complete response; mDOR, median duration of response; NE, not evaluable; NR, not reached. ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Safety Summary

Adverse event	Tivozanib 0.89 mg + Nivolumab (n=168)	Tivozanib 1.34 mg (n=171)
Any-cause TEAE, n (%)	**163 (97)**	**167 (98)**
Related TEAE	137 (82)	144 (84)
Tivozanib	135 (80)	144 (84)
Nivolumab	119 (71)	0
Grade ≥3 AE, n (%)	**102 (61)**	**103 (60)**
Related	54 (32)	60 (35)
Serious AE, n (%)	**54 (32)**	**64 (37)**
Related	14 (8)	15 (9)
Death due to AE, n (%)	**7 (4)**	**5 (3)**
Related	0	1 (<1)
TEAE leading to discontinuation, n (%)	**27 (16)**	**33 (19)**
Due to tivozanib	19 (11)	33 (19)
Due to nivolumab	22 (13)	0
TEAE leading to dose interruption, n (%)	**82 (49)**	**93 (54)**
Due to tivozanib	79 (47)	93 (54)
Due to nivolumab	35 (21)	0
TEAE leading to dose reduction of tivozanib, n (%)	**18 (11)**	**38 (22)**
Median duration of treatment (range), months	**6.3 (0.0-20.7)**	**7.4 (0.1-17.9)**

AE, adverse event; TEAE, treatment-emergent adverse event.

Most Common All-Grade Adverse Events Regardless of Causality

Adverse event, n (%)[a]	Tivozanib 0.89 mg + Nivolumab (n=168)	Tivozanib 1.34 mg (n=171)
Hypertension	62 (37)	69 (40)
Fatigue	49 (29)	68 (40)
Diarrhea	51 (30)	62 (36)
Nausea	26 (16)	47 (28)
Decreased appetite	37 (22)	46 (27)
Vomiting	20 (12)	36 (21)
Asthenia	39 (23)	35 (21)
Proteinuria	16 (10)	30 (18)
Constipation	17 (10)	29 (17)
Arthralgia	26 (16)	27 (16)
Cough	26 (16)	26 (15)
Hypothyroidism	15 (9)	26 (15)
Anemia	28 (17)	16 (9)
Pruritus	26 (16)	11 (6)

[a] Treatment-emergent adverse events occurring in ≥15% of patients in either arm.

Conclusions

- TiNivo-2 was the first randomized, phase 3 trial to evaluate the efficacy and safety of a **PD-1 inhibitor** combination following progression on or after prior treatment with PD-1/PD-L1 therapy
- The addition of nivolumab to tivozanib did not result in improved clinical outcomes in patients with mRCC whose disease progressed on or after prior ICI treatment
  - No subgroup was identified that benefited from the addition of nivolumab
- This trial confirms and expands key conclusions from CONTACT-03, and suggests that ICI rechallenge should be generally discouraged regardless of treatment sequence
- The reduced dose of tivozanib in the combination arm may have impacted the efficacy reflected by the numerically lower mPFS
- Meaningful efficacy was observed in the second-line tivozanib monotherapy arm, with a 9.2-month mPFS immediately following ICI
- These results support tivozanib monotherapy at 1.34 mg as a second-line therapy option in patients following progression on previous ICI therapy

ICI, immune checkpoint inhibitor; mPFS, median progression-free survival; mRCC, metastatic renal cell carcinoma; PD-1, programmed cell death 1 protein; PD-L1, programmed cell death 1 ligand 1.

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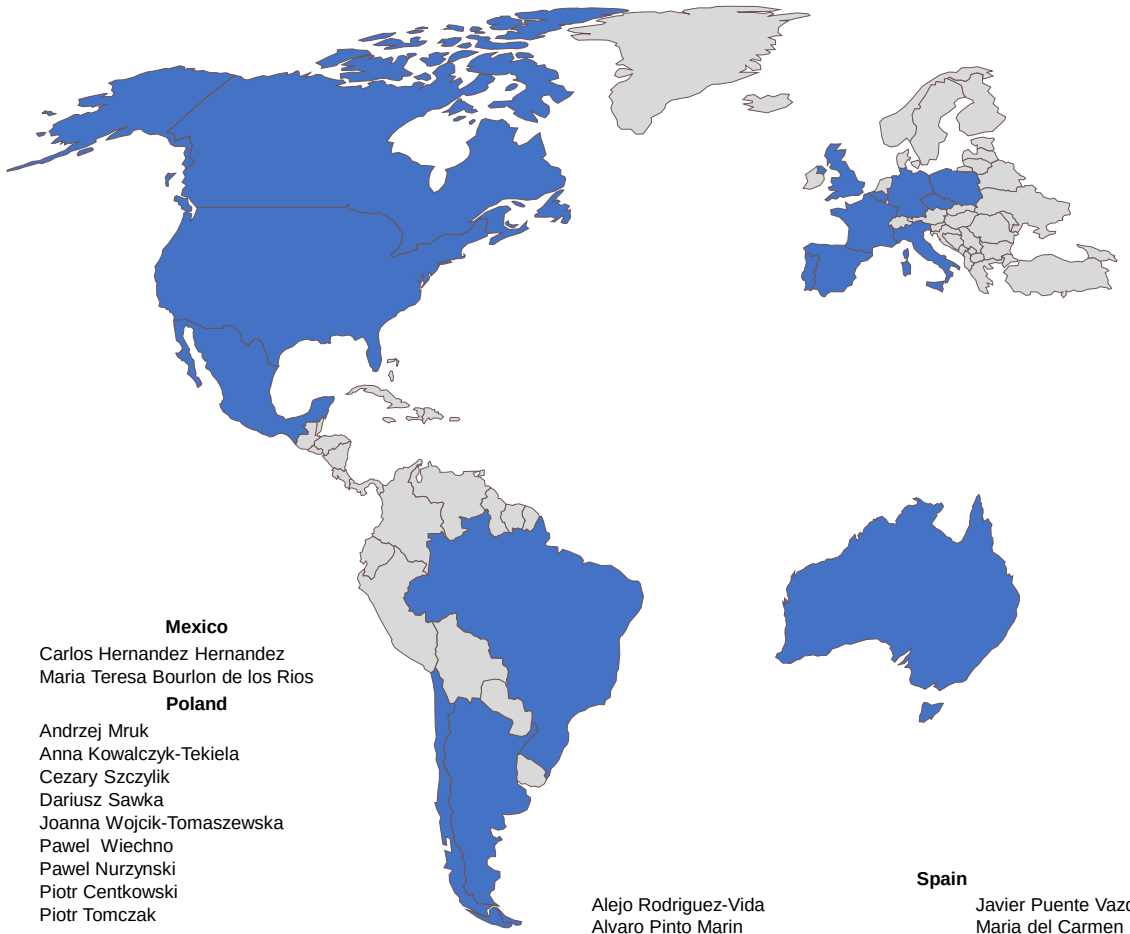

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Tivozanib plus nivolumab versus tivozanib monotherapy in patients with renal cell carcinoma following an immune checkpoint inhibitor: results of the phase 3 TiNivo-2 Study

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