947P

TiNivo: Tivozanib Combined With Nivolumab Results in Prolonged Progression-Free Survival in Patients With Metastatic Renal Cell Carcinoma (mRCC) – Final Results

Philippe Barthelemy,[1] Bernard J. Escudier,[2] Alain Ravaud,[3] Sylvie Negrier,[4] Michael N. Needle,[5] Laurence Albiges[6]

[1]Medical Oncology, C.H.U. Strasbourg-Nouvel Hôpital Civil, Strasbourg, France; [2]GU Oncology, Institut Gustave Roussy, Villejuif, France; [3]Medical Oncology, C.H.U. Bordeaux Hôpital St. André, Bordeaux, France; [4]Medical Oncology, Centre Léon Bérard, Lyon, France; [5]AVEO Pharmaceuticals Inc, Cambridge, MA, USA; [6]Medical Oncology, Institut Gustave Roussy, Villejuif, France

Introduction

- Metastatic renal cell carcinoma (mRCC) treatment has been revolutionized over the past decade with antiangiogenic tyrosine kinase inhibitors (TKIs) and immunotherapy[1]
- Vascular endothelial growth factor receptor (VEGFR) inhibitory agents have become standard-of-care treatment for mRCC[2]
- Tivozanib, a highly potent and selective VEGFR TKI with a long half-life, is approved by the European Commission for the first-line treatment of adult patients with mRCC[3-7]
  - Due to the high selectivity leading to minimal off-target toxicities, tivozanib has a favorable adverse event (AE) profile
- The AE profile of tivozanib makes it an ideal candidate for combination therapy with nivolumab, a programmed cell death protein-1 (PD-1) immune checkpoint inhibitor
- A mechanism of synergy between VEGFR and PD-1 inhibition exists, as VEGFR TKIs have been shown to modulate antitumor immunity[8]
  - Tivozanib enhances PD-1 activity through regulatory T-cell reduction[9]
- Nivolumab has been associated with improved overall survival in patients with mRCC treated past the first line and is approved for previously treated patients with mRCC[7]
- We previously demonstrated promising efficacy for tivozanib in combination with nivolumab in the phase 1b/2 TiNivo trial (NCT03136627),[10] and now present the final results for the full maximum tolerated dose (MTD) cohort

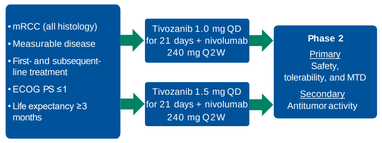
Study Objectives

- Determine the safety and tolerability of tivozanib in combination with nivolumab in patients with mRCC
- Assess antineoplastic activity of tivozanib and nivolumab in combination in patients with mRCC

Methods

- TiNivo is a phase 1b/2, open-label, multicenter, dose-escalation study of tivozanib in combination with nivolumab in patients with mRCC (**Figure 1**)

Figure 1. TiNivo study design



ECOG PS, Eastern Cooperative Oncology Group performance status; Q2W, every 2 weeks; QD, once daily.

- Key inclusion criteria include the following:
  - Patients aged ≥18 years
  - Histologically documented RCC with a clear cell component (phase 2 cohort)
  - mRCC with measurable or evaluable disease by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
  - No prior exposure to tivozanib or nivolumab
  - ECOG PS ≤1
  - Life expectancy ≥3 months
- Phase 1b consisted of 6 patients
  - Tivozanib 1.0 mg QD + nivolumab 240 mg Q2W (n=3) and tivozanib 1.5 mg QD + nivolumab 240 mg Q2W (n=3)
  - No patient experienced a dose-limiting toxicity (DLT) in cycle 1, and MTD was determined to be full-dose tivozanib (1.5 mg QD + nivolumab 240 mg Q2W)
- Following MTD determination, a phase 2 expansion cohort of MTD-enrolled patients (n=22) was added to further evaluate safety, tolerability, and efficacy
- Assessments were as follows:
  - Toxicity was graded via National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03
  - Response assessment using RECIST v1.1 with computed tomography and/or magnetic resonance imaging scans was performed every 2 cycles (8 weeks)
  - Overall objective response rate (ORR), progression-free survival, and duration of disease stabilization were calculated

Results

- A total of 25 patients received the MTD of tivozanib 1.5 mg QD plus nivolumab 240 mg Q2W (3 patients from phase 1b and 22 from phase 2)
- Baseline patient characteristics for all 25 patients are described in **Table 1**
- 17 patients discontinued treatment; most commonly due to progressive disease (41% for tivozanib and 47% for nivolumab)

Table 1. Baseline patient characteristics in all enrolled patients

	Patients (N=25)
Median age, y (range)	64 (37-75)
Sex, n (%)	
Male	19 (76)
Female	6 (24)
Prior therapy, n (%)	
0	12 (48)
1	11 (44)
2+	2 (8)
ECOG PS, n (%)	
0	15 (60)
1	10 (40)
IMDC, n (%)	
Favorable	7 (28)
Intermediate	17 (68)
Poor	1 (4)

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

Safety

- 20 patients (80%) experienced ≥1 treatment-related grade 3/4 AE (**Table 2**)
  - However, excluding uncomplicated hypertension, the rate of treatment-related grade 3/4 AEs was 64%

Table 2. Treatment-related AEs of all grades (AEs in≥ 30% of patients) and grade 3/4 (all AEs)

	All grades	Grade 3/4
	Patients (N=25)	
Total, n (%)	25 (100)	20 (80)
Gastrointestinal disorders, n (%)	17 (68)	0
Diarrhea	11 (44)	0
Stomatitis	10 (40)	0
General disorders, n (%)	19 (76)	3 (12)
Asthenia	15 (60)	0
Fatigue	4 (16)	2 (8)
Systemic inflammatory response syndrome	1 (4)	1 (4)
Skin and subcutaneous disorders, n (%)	17 (68)	3 (12)
Pruritus	11 (44)	0
Dry skin	8 (32)	0
Palmar-plantar erythrodysesthesia syndrome	9 (36)	2 (8)
Rash	4 (16)	1 (4)
Musculoskeletal disorders, n (%)	16 (64)	1 (4)
Arthralgia	11 (44)	0
Myalgia	8 (32)	0
Pain in extremity	2 (8)	1 (4)
Vascular disorders, n (%)	16 (64)	13 (52)
Hypertension	17 (68)	13 (52)
Malignant hypertension	2 (8)	2 (8)
Cardiac disorders, n (%)	2 (8)	1 (4)
Acute coronary syndrome	1 (4)	1 (4)
Prolonged electrocardiogram QT	1 (4)	1 (4)
Respiratory disorders, n (%)	13 (52)	0
Dysphonia	11 (44)	0
Investigations, n (%)	13 (52)	8 (32)
Increased amylase	2 (8)	2 (8)
Increased ALT	4 (16)	1 (4)
Increased AST	4 (16)	1 (4)
Increased blood alkaline phosphatase	1 (4)	1 (4)
Increased gamma-glutamyl transferase	1 (4)	1 (4)
Increased lipase	1 (4)	1 (4)
Metabolism and nutritional disorders, n (%)	12 (48)	0
Decreased appetite	10 (40)	0
Nervous system disorders, n (%)	8 (32)	2 (8)
Cerebrovascular accident	1 (4)	1 (4)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Efficacy

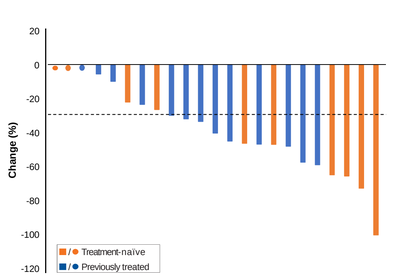
- **ORR was 56%**, and **disease control rate was 96%** (**Table 3**)
  - Median time to best response was 7.9 weeks
  - ORR was comparable in treatment-naïve and previously treated patients
- In total, 16 patients (64%) had tumor shrinkage ≥25% (**Figure 2**)
- To date, 8 patients remain on treatment (**Figure 3**)

Table 3. Response to treatment in patients receiving the full treatment dose with≥ 2 treatment scans

Best overall response, n (%)	All patients (N=25)	Treatment naïve (n=12)	Previously treated (n=13)
CR	1 (4)	1 (8)	0
PR	13[a] (52)	5 (42)	8[a] (62)
SD	10 (40)	5 (42)	5 (38)
PD	1 (4)	1 (8)	0
ORR (CR + PR)	**14/25 (56)**	**6/12 (50)**	**8/13 (62)**
Disease control rate (CR + PR + SD)	**24/25 (96)**	**11/12 (92)**	**13 (100)**

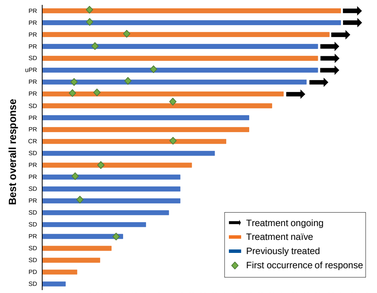
[a]One partial response was unconfirmed.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Figure 2. Change in tumor size by prior treatment[a,b]



[a]One patient had progressive disease as best response due to appearance of new lesions in the first scan.
[b]One patient had a lymph node measurement of 9 mm not taken into account on the reduction presented.

Figure 3. Response and treatment duration



uPR=unconfirmed partial response.

- In all 25 patients, median progression-free survival was 18.9 months (95% confidence interval [CI] 16.4, not reached [NR]) (**Figure 4**)
  - In treatment-naïve patients, median progression-free survival was 18.9 months (95% CI 4.7, NR) (**Figure 5**)
  - In previously treated patients, median progression-free survival had not been reached (95% CI 11.0, NR) (**Figure 5**)

Figure 4. Progression-free survival in all patients

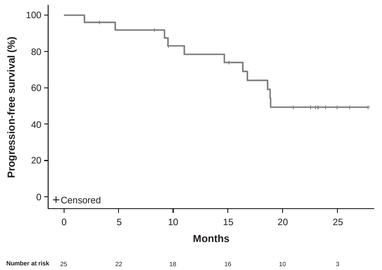
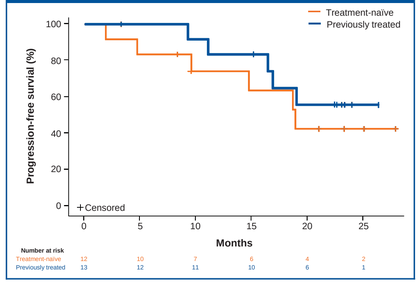


Figure 5. Progression-free survival by prior therapy



Conclusions

- In TiNivo, the tivozanib and nivolumab combination regimen showed promising antitumor efficacy, with a median progression-free survival of 18.9 months and most patients demonstrating disease control for ≥60 weeks
  - A high rate of disease control was observed, including a patient with a complete response
- The combination regimen was found to be comparable to other VEGFR TKI combinations
- A favorable AE profile with minimal off-target effects was noted, likely due to the high specificity of tivozanib
  - The most common grade 3/4 AE was uncomplicated hypertension, an on-target effect
  - Notably, grade 3/4 fatigue, diarrhea, and elevations of hepatic enzymes were low, as predicted by single-agent experience with tivozanib
  - A low discontinuation rate and a small number of dose reductions due to AEs were observed
- At the time of this final analysis, 8 patients remain on treatment
- Plans are underway for an additional randomized trial

References

1. National Cancer Institute. https://seer.cancer.gov/statfacts/html/kidrp.html. Accessed October 3, 2018.
2. Ohm JE, et al. *Immunol Res.* 2001;23(2-3):263-272.
3. Nakamura K, et al. *Cancer Res.* 2006;66(18):9134-9142.
4. Eskens FA, et al. *Clin Cancer Res.* 2011;17(22):7156-7163.
5. Haberkorn BCM, et al. *Future Oncol.* 2013;9(1):13-20.
6. Berge EM, et al. *Drugs Today (Barc).* 2013;49(5):303-315.
7. Motzer R, et al. *N Engl J Med.* 2015;373(19):1803-1813.
8. Gunturi A, et al. *Curr Treat Options Oncol.* 2014;15(1):137-146.
9. Pawlowski N, et al. Presented at the AACR 104th Annual Meeting; April 6-10, 2013. Poster 3971.
10. Barthelemy P, et al. Presented at the ESMO 2018 Congress; October 29-23, 2018. Poster 878.

Acknowledgments

This study was sponsored by AVEO Oncology. Nivolumab was provided by Bristol-Myers Squibb. Editorial assistance was provided by Scientific Connexions, an Ashfield Company, and was funded by AVEO Oncology and EUSA Pharma.

Dr. Barthelemy reports receiving advisory board/consulting fees from Bristol-Myers Squibb, Pfizer, Ipsen, Novartis, Roche, MSD, Janssen-Cilag, and Sanofi, as well as honoraria from Astellas.

PRESENTED AT THE EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY (ESMO) 2019 CONGRESS; SEPTEMBER 27—OCTOBER 1, 2019; BARCELONA, SPAIN

Email: philippe.barthelemy@chru-strasbourg.fr