Final Results of a Phase 1b/2 Study of Tivozanib in Combination With Durvalumab in Patients With Advanced Hepatocellular Carcinoma in Both Previously Untreated Patients and Patients Progressing on Atezolizumab and Bevacizumab

Daneng Li[1*], Farshid Dayyani[2], Devalingam Mahalingam[3], Julie Rowe[4], Thomas Abrams[5], Vijay Kasturi[6], Renuka Iyer[7]

**Presenting author.*

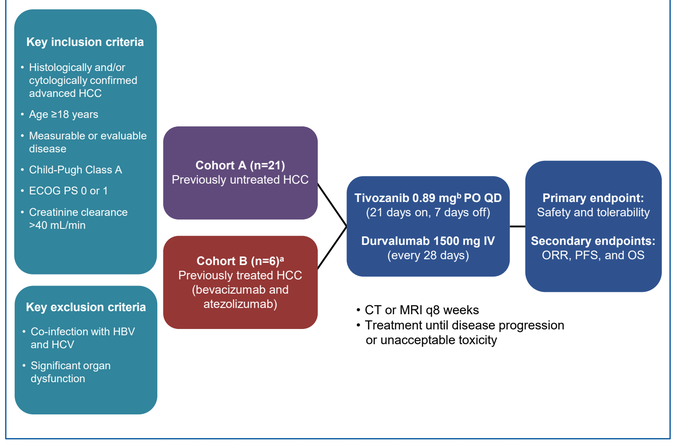
[1]City of Hope Comprehensive Cancer Center, Duarte, CA [2]UC Irvine Chao Family Comprehensive Cancer Center, Orange, CA [3]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL [4]University of Texas Health Science Center at Houston, Houston, TX [5]Dana-Farber Cancer Institute, Boston, MA [6]AVEO Oncology, Boston, MA [7]Roswell Park Comprehensive Cancer Center, Buffalo, NY

Tivozanib and Durvalumab Combination in HCC

- The combination of atezolizumab, a monoclonal anti–programmed death-ligand 1 (PD-L1) antibody, and bevacizumab, a vascular endothelial growth factor (VEGF)-A monoclonal antibody, has improved the standard of care over sorafenib in advanced hepatocellular cancer (HCC) with a median PFS of 6.8 months and a 1-year overall survival of 67.2%.[1] Serious toxicities were noted in 38% of patients who received the combination[1]
- Tivozanib, a potent and selective VEGFR 1, 2 and 3 tyrosine kinase inhibitor (TKI), and durvalumab, an anti–PD-L1 antibody, have each demonstrated single agent activity in HCC[2,3]
- Tivozanib can also reduce frequencies of FOXP3$^+$ regulatory T cells, myeloid-derived suppressor cells and exhausted T cells,[4] thus potentially facilitating immune-mediated responses
- Durvalumab blocks the interaction of programmed death ligand 1 with the immune checkpoint receptor PD-1, thus facilitating cytotoxic T cell proliferation[3]
- The selectivity and favorable tolerability of the VEGFR TKI tivozanib[2] may allow it to be used more readily as a combination therapy with an immune checkpoint inhibitor, potentially leading to improved safety and efficacy in HCC
- DEDUCTIVE (NCT03970616) is a Phase 1b/2, multicenter, open-label study to assess the safety and efficacy of tivozanib with durvalumab in patients with advanced HCC previously untreated or bevacizumab- and atezolizumab-pretreated advanced HCC
  - Preliminary results showed this combination was well tolerated with comparable efficacy to other immune checkpoint and anti-VEGF containing regimens in patients with previously untreated HCC[5]
  - Results from patients with previously untreated HCC (cohort A) and bevacizumab and atezolizumab pretreated HCC (cohort B) are presented here

Study Design and Methods

DEDUCTIVE Study (NCT03970616) Design



CT, computerized tomography; ECOG, Easter Cooperative Oncology Group; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IV, intravenous; MRI, magnetic resonance imaging; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, oral administration; PS, performance status; QD, once daily.

[a] Twenty patients were planned to be recruited in cohort B. Actual recruitment was 6 patients; [b] Equivalent to 1 mg tivozanib hydrochloride salt.

- Median follow-up was 13.4 and 5.5 months for cohorts A and B, respectively
- Median number of treatment cycles started was 8 and 4 for cohorts A and B, respectively

Baseline Characteristics	All patients (N=27)
Median age (range), years	67 (40-82)
Sex, n (%)	
Male	24 (88.9)
Female	3 (11.1)
Race, n (%)	
White	16 (59.3)
Black/African American	2 (7.4)
Asian	7 (25.9)
Native Hawaiian or Other Pacific Islander	1 (3.7)
Other	1 (3.7)
ECOG PS, n (%)	
0	11 (40.7)
1	16 (59.3)

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Safety and Tolerability

Adverse Events (AE), n (%)	All patients (N=27)
Any-grade TEAE	26 (96.3)
Grade ≥3 TEAE	15 (55.6)
Serious TEAE	10 (37.0)
TEAE leading to death	2 (7.4)
Any-grade TRAE	25 (92.6)
Grade ≥3 TRAE	8 (29.6)
Serious TRAE	3 (11.1)
TRAE leading to death	1 (3.7)

Data cutoff: November 28, 2022.

TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

TRAEs in ≥10% of Patients, n (%)	Any Grade (N=27)	Grade ≥3 (N=27)
Diarrhea	8 (29.6)	2 (7.4)
Hypothyroidism	8 (29.6)	0
Hypertension	7 (25.9)	2 (7.4)
Fatigue	6 (22.2)	0
Nausea	5 (18.5)	0
Dysphonia	4 (14.8)	0
Palmar-plantar ertythrodysesthesia	4 (14.8)	0
Increased AST	3 (11.1)	1 (3.7)
Arthralgia	3 (11.1)	0
Rash	3 (11.1)	0

Data cutoff: November 28, 2022.

AST, aspartate aminotransferase; TRAE, treatment-related adverse event.

Results

- 3 patients experienced serious TRAEs: 1 pneumonitis, 1 with gastrointestinal hemorrhage and anemia, and 1 with diarrhea and hepatic failure
  - There were no grade 4 TRAEs; 1 patient experienced a grade 5 TRAE (hepatic failure) leading to death
- The most common (≥15%) grade 1 and 2 TRAEs were diarrhea, hypothyroidism, hypertension, fatigue, and nausea
  - There were no grade 4 or 5 hypertension TRAEs; 2 patients (7.4%) experienced a grade 3 hypertension TRAE
- Dose modifications occurred in 18 patients (8.0%) and 4 patients (16.7%) in cohort A and B, respectively

Efficacy

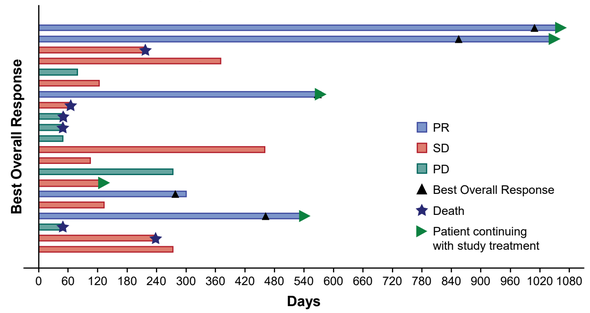
Efficacy Endpoint	Cohort A (n=21)	Cohort B (n=6)
ORR, n (%)[a]	5 (23.8)[b]	0
CR	0	0
PR	5 (23.8)[b]	0
SD[c]	10 (47.6)	4 (66.7)
PD	6 (28.6)	1 (16.7)
Median DOR (95% CI), days[d]	NE (NE-NE)	NE (NE-NE)
Median DSD (95% CI), days[d,e]	56 (51-59)	54 (50-NE)
Median PFS (95% CI), days[d]	113 (54-NE)	109.5 (57-NE)
Median OS (95% CI), days[d]	647 (331-NE)	NE (134-NE)

Data cutoff: November 28, 2022.

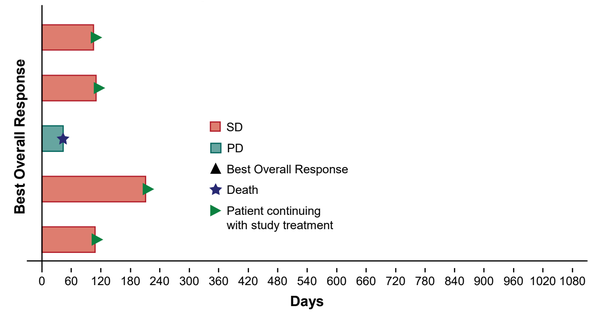
CR, complete response; DOR, duration of response; DSD, duration of stable disease; NE, not estimable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

[a] ORR defined as proportion of patients who experienced a CR or PR; [b] Confirmed response; [c] Follow-up measurements must have met the SD criteria at least once after study entry at a minimal interval of 4 weeks. Assessments are based on RECIST v 1.1; [d] Kaplan-Meier estimates; [e] DSD defined as the time from treatment initiation until time of objectively documented stable disease + 1 day.

Best Overall Response and Treatment Duration in Cohort A



Best Overall Response and Treatment Duration in Cohort B



Data cutoff: November 28, 2022.

PD, progressive disease; PR, partial response; SD, stable disease.

Conclusions

- **The safety profile of the tivozanib and durvalumab combination was consistent with the known safety profile for tivozanib and durvalumab, and was considered acceptable for a patient population with limited treatment options.**
- **Preliminary evidence of antitumor activity was observed for tivozanib in combination with durvalumab**
  - **Final efficacy results for cohort A demonstrate an ORR of 24%, a median PFS of 113 days, and a median OS of 647 days. Final efficacy results for cohort B demonstrate an ORR of 0% and a median PFS of 110 days**

References

1. Finn R, et al. *N Engl J Med*. 2020;382:1894-1905.
2. Fountzilas C, et al. *Br J Cancer*. 2020;122(7):963-70.
3. Wainberg ZA, et al. *J Clin Oncol*. 2017;35(15_suppl):4071.
4. Kalathil SG, et al. *Oncoimmunology*. 2020;9(1):1824863.
5. Iyer RV, et al. *J Clin Oncol*. 2022; 40:4_suppl:462.

Acknowledgments

This study was sponsored by AVEO Oncology and AstraZeneca. Medical writing and editorial assistance was provided by Jamie Story of SciMentum, Inc, a Nucleus Holdings Ltd company, and was funded by AVEO Oncology.

Presented at the American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium; January 19-21, 2023; San Francisco, CA, USA

E-mail:
vkasturi@aveooncology.com