A Phase 1b/2 Study of Tivozanib in Combination with Durvalumab in Subjects with Advanced Hepatocellular Carcinoma (DEDUCTIVE): Efficacy Results in Previously Untreated Patients

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

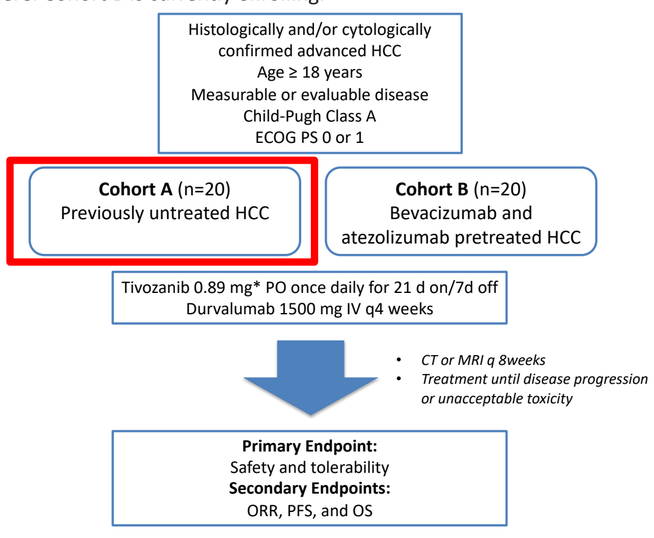
[1]Roswell Park Comprehensive Cancer Center, Buffalo, NY [2]City of Hope Comprehensive Cancer Center, Duarte, CA [3]UC Irvine Health, Orange, CA [4]University of Texas School of Health Sciences at Houston, Houston, TX [5]University of Texas Southwestern Medical Center, Dallas, TX [6]AVEO Oncology, Boston, MA [7]Dana-Farber Cancer Institute, Boston, MA

Rationale for Tivozanib and Durvalumab in HCC

- The combination of atezolizumab, an anti-PD-L1 antibody, and bevacizumab, a 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%. Serious toxic effects were noted in 38% of patients who received the combination.[1]
- Tivozanib, a potent and selective VEGFR 1, 2 and 3 TKI, and durvalumab, an anti-PD-L1 antibody, have both demonstrated single agent activity in HCC.[2,3]
- Tivozanib has been shown to reduce production of regulatory 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 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.

Study Design and Methods:

- Results from Cohort A, subjects with previously untreated HCC, are presented here. Cohort B is currently enrolling.



*equivalent to 1 mg tivozanib hydrochloride salt

Results: Cohort A

Baseline Clinical Characteristics	All patients N = 20
Age, median (range), years	68.5 (40-82)
Sex, (%) Male Female	 17 (85) 3 (15)
Race, (%) White Black Asian Other	 13 (65) 0 5 (25) 1 (5)
ECOG PS, n (%) 0 1	 8 (40) 12 (60)
Baseline BMI, median (range)	27.2 (21.8-37.9)

Safety and Tolerability

Adverse Events (AE), n (%)	All Patients N=20
Any-grade treatment-related (TR)AE	16 (80)
Grade 3-5 TRAE	3 (15)
Any-grade treatment-emergent (TE)AE	19 (95)
Grade 3-5 TEAE Grade 4 Grade 5	11 (55) 1 (5)* 1 (5)*
TEAE leading to Death	1 (5)

*hepaticencephalopatly

TRAE in ≥ 10%, n (%)	Any Grade (n=20)	Grade ≥3 (n=20)
Hypertension	7 (35)	2 (10)
Fatigue	4 (20)	0
Diarrhea	4 (20)	0
Nausea	4 (20)	0
Hypothyroidism	4 (20)	0
LFT elevation (AST, ALT and/or ALP)	4 (20)	0
Dysphonia	3 (15)	0
Arthralgia	2 (10)	0
Palmar-plantar ertythrodysesthesia	2 (10)	0

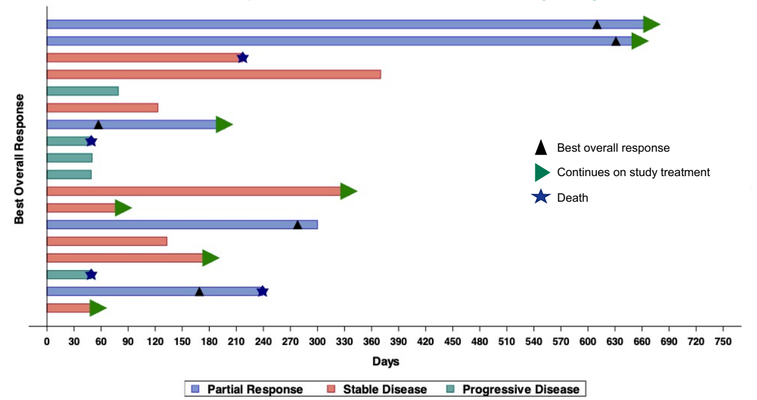
- Grade 3 TRAEs occurred in n=3 patients (2 hypertension [HTN], 1 GI hemorrhage). There were no Grade 4 or 5 TRAEs.
- The most common Grade 1 and 2 TRAEs were HTN, fatigue, diarrhea, nausea and hypothyroidism.

Efficacy

Efficacy Endpoint	Evaluable Patients N = 18*
Overall Response Rate, n (%) CR PR	**5 (27.8)** 0 5 (27.8)
Stable Disease [SD], n (%)	8 (40)
Progressive Disease, n (%)	5 (27.8)
Disease Control Rate (CR+PR+SD), n (%)	13 (67.8)
Duration of Overall Response (DOR), median (95% CI)	NE (2.6–NE)
Progression-free Survival (PFS), median (95% CI)	7.3 mos (1.8–NE)
Overall Survival (OS), median (95% CI)	13.4 mos (8.2–NE)
1-year OS, %	76

*Data cut-off Dec 8, 2021, n=18 patients evaluable for response, n=2 patients not yet reached first scan censored for PFS and OS
NE, not estimable

Best Overall Response and Treatment Duration by Subject



Conclusions

The combination of tivozanib and durvalumab in previously untreated advanced HCC was well tolerated, and the observed safety profile was consistent with the known profile of both agents. Initial efficacy results demonstrate a median PFS of 7.3 months and a 1-year OS of 76%.

References and Acknowledgements

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