Excellent CBR and Prolonged PFS in Non-Squamous NSCLC with Oral CA-170, a Dual Inhibitor of VISTA and PD-L1

V. Radhakrishnan[1], S. Banavali[2], S. Gupta[3], A. Kumar[4], C. Deshmukh[5], S. Nag[6], S. Beniwal[7], M. Gopichand[8], R. Naik[9], K. Lakshmaiah[10], D. Mandavia[4*], M. Ramachandra[4], K. Prabhash[2]

[1]Tata Medical Centre, Kolkata, India, [2]Tata Memorial Hospital, Mumbai, India, [3]Advanced Centre for Treatment, Research and Education in Cancer (ACTREC), Navi Mumbai, [4]Aurigene Discovery Technologies Limited, Bangalore, India, [5]Deenanath Mangeshkar Hospital & Research Centre, Pune, India, [6]Jehangir Hospital, Pune, India, [7]Acharya Tulsi Regional Cancer Treatment & Research Institute, Bikaner, India, [8]City Cancer Center, Vijayawada, India, [9]HCG Bangalore Institute of Oncology Specialty Centre, Bangalore, India, [10]Srinivasam Cancer Care Multispeciality Hospital, Bangalore, India.

Poster ID: 1209P

Introduction

V-domain Ig suppressor of T-cell activation (VISTA) and Programmed-death ligand -1 (PD-L1) are independent immune checkpoints implicated in various malignancies. Preclinical studies have demonstrated that dual blockade of these pathways is synergistic. CA-170 is a first-in-class oral small molecule that directly targets both VISTA and PD-1/PD-L1 pathways and has shown anti-tumor activity in multiple preclinical models. A Phase 1 dose escalation study (Clinicaltrials.gov NCT02812875)[1] has shown acceptable safety of CA-170 with dose escalated up to 1200 mg BID.

Methods

The Phase II trial is a multi-tumor study and enrolled patients with Head & Neck Squamous Cell Cancer [HNSCC], squamous [Sq.] and non-squamous [Non-Sq.] Non-Small Cell Lung Cancer [NSCLC], MSI-H positive solid tumors and Classical Hodgkin Lymphoma [CHL]). Two dosages (400 mg versus 800 mg) of CA-170 were investigated. [Clinical Trials Registry of India (CTRI) registration no. - CTRI/2017/12/011026]

Key eligibility criteria include: age ≥ 18 years, ECOG ≤1, adequate organ function, no previous exposure to immuno-oncology agents, and 1-3 prior lines of systemic therapy. Primary endpoint is Response Rates by RECIST 1.1 for solid tumors and by IWG Revised Response Criteria for Classical Hodgkin Lymphoma[2,3]. Additional endpoints include response rates by immune-related Response Criteria (irRC)[4] for solid tumors, Clinical benefit Rate (CBR), as well as safety and Pharmacokinetics. CA-170 was given once daily till progression of the disease or intolerable toxicities. Patients with solid tumors were followed with contrast enhanced CT scans and those with CHL with PET/CT.

Results

Enrolment started in February 2018 and completed in September 2018, with a total enrolment of 62 patients, across all five tumor types. The tumor type distribution is provided in Table 1. This poster provides CBR rates from all tumor types, but focused on non-squamous NSCLC for additional efficacy outcomes. The baseline demographics of non-squamous NSCLC patients are provided in Table 2.

Table 1: Tumor distribution

Tumor Type	400 mg (N = 30)	800 mg (N = 32)	Total (N = 62)
HNSCC	10	10	20
Non-Sq. NSCLC	10	7	17
Sq. NSCLC	3	4	7
MSI-H positive solid tumors	1	4	5
Classical HL	6	7	13

Table 2: Baseline Demographics in Non-Sq. NSCLC

Tumor type		Non-Sq. NSCLC 400 mg (N = 10)	Non-Sq. NSCLC 800 mg (N = 7)	Total (N = 17)
Age, Median (range) in years		58.5 (44-76)	56 (46-70)	56 (44-76)
Males, n (%)		9 (90)	4 (57.1)	13 (76.5)
ECOG status 0, n (%)		5 (50)	0	5 (29.4)
ECOG status 1, n (%)		5 (50)	7 (100)	12 (70.6)
Previous lines of therapy	1, n (%)	5 (50)	2 (28.6)	7 (41.2)
	2, n (%)	4 (40)	4 (57.1)	8 (47.1)
	3, n (%)	1 (10)	1 (14.3)	2 (11.8)
Median duration of disease before enrollment (months)		13	18	15

Correspondence

*Dr. Divyesh Mandavia, MD.
Medical Lead – Clinical Development
Aurigene Discovery Technologies Limited
Email: divyesh_m@aurigene.com
Phone: +91- 80-71025588; Website: www.aurigene.com

Efficacy Evaluation

Efficacy evaluation is done in "Evaluable Population" - defined as patients who have had at least one follow up scan during the study or were withdrawn due to clinical progression before the initial follow up scan without any major protocol deviation. A total of 56 patients constitute "Evaluable Population" as 2 Non-Sq. NSCLC patients (at 400 mg) were found ineligible by central radiologist after randomization and 4 patients (3 HNSCC and 1 Non-Sq. NSCLC) were withdrawn before the first post-baseline scan without clinical progression. Table 3 provides Clinical Benefit Rate for all the tumor types. Additional detailed efficacy evaluation for all the tumor types was presented at Society for Immunotherapy of Cancer (SITC) 2018 conference.[5] Current poster will focus only on Non-Sq. NSCLC efficacy data. Figure 1 provides best percent change from baseline according to RECIST 1.1[2] from Non-Sq. NSCLC patients.

Table 3: Best Response CBR by RECIST 1.1 in solid tumors[2] and by IWG Revised Response Criteria for CHL[3]

Tumor type	HNSCC (N=17)	Non-Sq. NSCLC (N=14)	Sq. NSCLC (N=7)	MSI-H positive solid tumors (N=5)	Hodgkin Lymphoma (N=13)	Total (N=56)
CBR at 400 mg; n/N (%)	4/10 (40)	7/8 (87.5)	2/3 (66.6)	0/1 (0)	4/6 (66.7)	**17/28 (60.7)**
CBR at 800 mg; n/N (%)	3/7 (42.9)	3/6 (50)	1/4 (25)	2/4 (50)	3/7 (42.9)	**12/28 (42.9)**
CBR (Total); n/N (%)	7/17 (41.2)	10/14 (71.4)	3/7 (42.8)	2/5 (40)	7/13 (53.8)	**29/56 (51.8)**

Overall CBR is 51.8% - with a strong trend towards superior benefit at lower dosage. The tendency of improved CBR is seen across all tumor types, except MSI-H where the sample size is smallest (5), and only one (1) patient was randomized to the lower dose (400 mg). The rates of CBR with 400 mg dosage is similar to the rates achieved with PD-1/PD-L1 antibodies[6]

Figure 1: Best percent change from baseline in Sum of Diameters (SoD) in Target lesions by RECIST 1.1 criteria[2] in Non-Sq. NSCLC patients

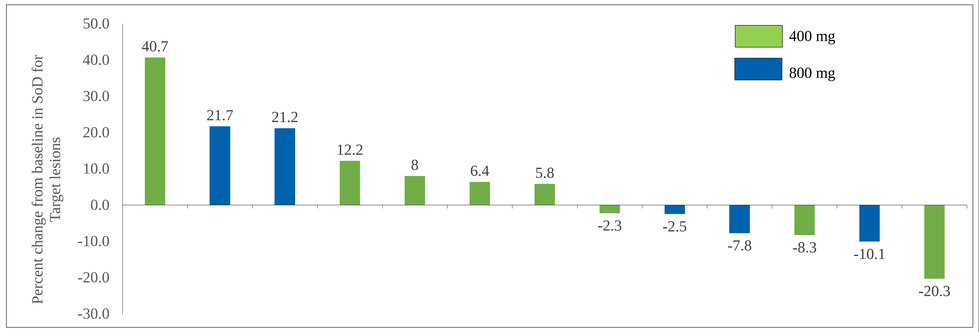

Figure 2 shows Kaplan Meir curve for Progression-Free Survival (PFS) in Non-Sq. NSCLC patients. The median PFS at 400 mg and 800 mg were 19.6 weeks (~4.6 months) and 12 weeks (~2.8 months), respectively.

Figure 2: Progression Free Survival with CA-170 in Non-Sq. NSLCLC patients

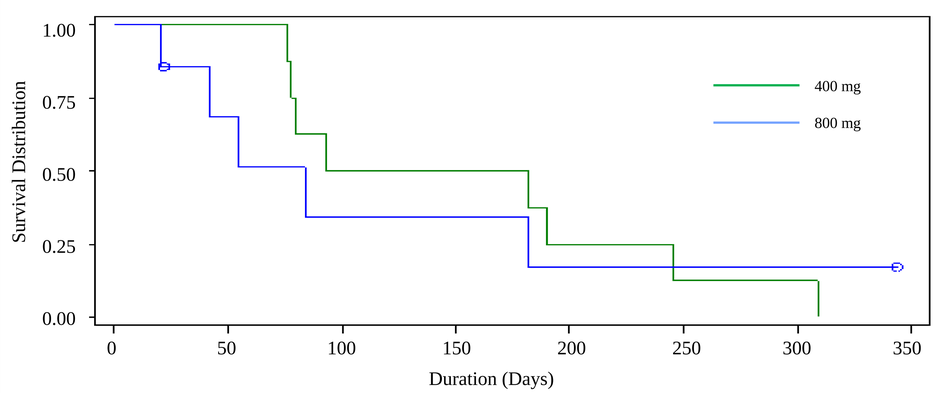

Table 4 shows cross-study comparative efficacy of CA-170 (400 mg) in non-squamous NSCLC with various anti-PD-1/PD-L1 antibodies, as well as docetaxel and Best Supportive Care (BSC) in 2nd /3rd line NSCLC patients. PFS with 400 mg CA-170 appears similar or better than other agents and clearly superior to BSC.

Table 4: ORR and PFS with various anti-cancer agents as well as BSC in 2nd /3rd line NSCLC patients

Parameter	Pembro[7]	Nivo[8]	Atezoli[9]	Durvalu[10]	Avelumab[11]	Docetaxel[7]	BSC[12]	CA-170 (400 mg)
Mechanism of action	anti-PD1	anti-PD1	anti-PD-L1	anti-PD-L1	anti-PD-L1	Chemo	No active drug	Anti-VISTA+PD-L1
Histology	Sq.+Non-Sq.	Non-Sq.	Sq.+Non-Sq.	Sq.+Non-Sq.	Sq..+Non-Sq.	Sq.+Non-Sq	Sq.+Non-Sq.	Non-Sq.
Line of therapy	2nd	2nd	2nd	1st /2nd/3rd	2nd	2nd	2nd	2nd/3rd/4th
Overall Response rate	18%	19%	14%	15.3%	12%	9%	None	No objective responses
Median PFS (in weeks)	16.7	9.9	12	7.3	12	17.3	8.0	19.6

Safety

Safety is evaluated among all 62 patients who received CA-170. Overall, CA170 has been well tolerated, with potentially Immune Related Adverse Events (irAEs) seen in 5 patients – two (2) patients with increase in TSH or worsening hypothyroidism (both at 400 mg), two (2) with skin rash (both at 400 mg) and one (1) with Grade 3 neutropenia and Grade 3 anemia (at 400 mg). Neutropenia improved quickly (in 2 weeks) with interruption of CA-170 and re-appeared after resuming CA-170. Interestingly, incidence of irAEs were noted at the lower dosage of 400 mg.

Conclusions

- CA-170 has excellent safety as an oral drug.
- CBR in non-squamous NSCLC appears remarkable (> 70%), without any objective responses, but several patients have tumor reductions.
- Higher incidence of irAEs and clinical benefit across tumor types, including non-squamous NSCLC, is observed at the lower dosage (400 mg). These are consistent with pre-clinical findings showing bell-shaped curve of immune activation likely due to activation-induced cell death with CA-170.[5]
- CA-170 at 400mg leads to highly promising PFS (19.6 weeks), when compared to other IO agents or Best Supportive Care.
- With oral route of administration, excellent safety and ease of titration with AEs, CA-170 should be investigated in maintenance setting for Stage III as well as Stage IV Non-Sq. NSCLC.

References

1. Bang YJ, et al., abstract poster 341, Phase 1 trial of CA-170, a first-in-class, orally available, small molecule immune checkpoint inhibitor (ICI) dually targeting PD-L1 and VISTA, in patients with advanced solid tumors or lymphomas. SITC 2017.
2. Eisenhauer EA, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Can. 2009;45:228-247.
3. Cheson BD, et al. International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-86.
4. Wolchok JD, et al. Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. Clin Cancer Res. 2009;15(23):7412–20.
5. Radhakrishnan et al. Phase 2 trial of CA-170, a novel oral small molecule dual inhibitor of immune checkpoints VISTA and PD-1, in patients with advanced solid tumor and Hodgkin lymphoma. SITC 2018
6. Alberto Carretero-González, et al. Analysis of response rate with ANTI PD1/PD-L1 monoclonal antibodies in advanced solid tumors: a meta-analysis of randomized clinical trials. Oncotarget 2018 Feb 2; 9(9): 8706–8715.
7. Herbst RS, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016 Apr 9;387(10027):1540-1550.
8. Borghaei H, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Oct 22;373(17):1627-39.
9. Rittmeyer A, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017 Jan 21;389(10066):255-265.
10. Antonia SJ, et al. Clinical Activity, Tolerability, and Long-term Follow-up of Durvalumab in Patients With Advanced NSCLC. J Thorac Oncol. 2019 Jun 19. pii: S1556-0864(19)30475-7
11. Barlesi F, et al. Avelumab versus docetaxel in patients with platinum-treated advanced non-small-cell lung cancer (JAVELIN Lung 200): an open-label, randomised, phase 3 study. Lancet Oncol. 2018 Nov;19(11):1468-1479.
12. Shepherd FA, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol. 2000 May;18(10):2095-103.