Safety, pharmacokinetics, and antitumor activity findings from a phase 1b, open-label, dose-escalation and expansion study investigating RAF dimer inhibitor lifirafenib in combination with MEK inhibitor mirdametinib in patients with advanced or refractory solid tumors

Authors:

Benjamin Solomon,[1] Bo Gao,[2] Vivek Subbiah,[3] Michael Millward,[4] Lee Rosen,[5] Jayesh Desai,[1] Eric I Sbar,[6] Neal Collins,[7] Thuy Hoang,[6] Xi Song,[6] Wenlin Shao,[6] Jaspreet Jaggi,[7] Badreddin Edris,[6] Paraneedharan Ramachandran,[7] Lusong Luo,[7] Michael Friedlander[8]

Institutions:

1. Peter MacCallum Cancer Centre, East Melbourne, Australia
2. Blacktown Cancer and Hematology Centre, Sydney, Australia
3. MD Anderson, Houston, TX, USA
4. Linear Clinical Research, Perth, Australia
5. UCLA, Santa Monica, CA, USA
6. SpringWorks Therapeutics, Inc., Stamford, CT, USA
7. BeiGene, San Mateo, CA, USA
8. Prince of Wales Clinical School UNSW and Prince of Wales Hospital, Sydney, Australia

Abstract:

Background: RAF dimer inhibition can suppress RAF-dependent MEK reactivation leading to sustained MAPK pathway inhibition. RAF dimer inhibitor lifirafenib (L) synergized with MEK inhibitor mirdametinib (M) in *RAS*-mutated cancer models. In this ongoing Phase 1b study of L+M in patients (pts) with advanced/refractory solid tumors harboring MAPK pathway aberrations, we investigate preliminary safety, PK, and efficacy.

Methods: Pts were enrolled by a 3+3 design and treated with L (15-20 mg QD) + M (2-4 mg QD or BID) across 9 dose levels (DLs). Primary objectives were to evaluate safety/tolerability, estimate MTD, and identify recommended Phase 2 dose (RP2D). Tumor responses were investigator assessed using RECIST v1.1. AEs were graded per NCI CTCAE v5.0.

Results: Table 1 presents demographic, efficacy, and safety results as of 01 Sep 2022. Objective responses (all PRs) were achieved in 15/54 (27.8%) efficacy-evaluable pts, including 10/17 low-grade serous ovarian cancer (LGSOC) (58.8%; median exposure

~23 mo), 2 NSCLC (1 *NRAS Q61K*, 1 *BRAF-V600E*), 2 endometrial cancer (1 *BRAF ZC3HAv1* fusion, 1 *KRAS G12A*), and 1 LG serous adenocarcinoma of Mullerian origin (*KRAS G12V*). For L and M, plasma maximum drug concentration (C_{max}) and exposure (AUC) were comparable to that of each compound at the same DL in monotherapy studies, suggesting low likelihood of drug-drug interaction. L+M was generally well tolerated, with limited DLTs and discontinuations. There were 2 deaths due to TEAEs considered unrelated to L+M. The MTD/RP2D were not yet determined.

Conclusions: L+M demonstrated a favorable safety profile and showed antitumor activity in pts with various *KRAS*, *NRAS*, and *BRAF* mutations across several solid tumor types, including LGSOC, NSCLC, and endometrial cancer. The combination warrants further clinical investigation.

Table 1

Demographics (N=56)			
Age (y), median (range)	59.5 (29-78)		
ECOG PS 0/1, n (%)	56 (100.0)		
Prior lines of therapy, median (range)	1 (1-6)		
Efficacy Set (N=54), n (%)			
	LGSOC (n=17)	Other than LGSOC (n=37)	All malignancies (n=54)
ORR	10 (58.8)	5 (13.5)	15 (27.8)
PR	10 (58.8)	5 (13.5)	15 (27.8)
SD	6 (35.3)	18 (48.6)	24 (44.4)
DCR (CR+PR+SD)	16 (94.1)	23 (62.2)	39 (72.2)
Safety Set (N=56), n (%)			
TEAE[a]	55 (98.2)		
SAE	23 (41.1)		
Grade 3 TEAE	24 (42.9)		
TEAE leading to treatment discontinuation	3 (5.4)		
DLT	6 (10.7)		

CR, complete response; DCR, disease control rate; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; LGSOC, low-grade serous ovarian cancer; ORR, objective response rate; PR, partial response; SAE, serious adverse event; SD, stable disease; TEAE, treatment-emergent adverse event.
[a] Commonly reported (>40%): fatigue (55.4%), dermatitis acneiform (46.4%), and diarrhea (44.6%).