631 PHARMACOKINETICS AND PHARMACODYNAMICS STUDY OF TU2218, TGFβRI AND VEGFR2 DUAL INHIBITOR IN PATIENTS WITH ADVANCED SOLID TUMORS

[1]Hyesung Shin*, [1]Huntaek Kim, [1]Soo Jin Kim, [1]Eunsun Lee, [2]Do-Youn Oh, [3]Kyu Pyo Kim, [4]Anthony W Tolcher. *[1]TiumBio Co., Ltd, Seongnam, Gyeonggi-do, Republic of Korea; [2]Seoul National University Hospital, Seoul, Republic of Korea; [3]Asan Medical Center, Seoul, Republic of Korea; [4]NEXT Oncology, San Antonio, TX, USA*

Background TU2218 is a highly potent, oral dual inhibitor against TGFβ type I receptor (TGFβRI/ALK5) and VEGFR2. VEGF and TGF-β pathways play important roles in the function of TME, especially in immune tolerance inextricably related with poor outcomes of anti-PD-(L)1 therapy. This is a first-in-human study to investigate the safety and tolerability of TU2218 mono- and combination therapy with pembrolizumab.

Methods This non-randomized, multinational, open-label study has been evaluating the safety, tolerability, PK, PD and preliminary efficacy of TU2218 mono- and combination therapy with pembrolizumab in advanced solid tumors. The eligible patients were aged ≥ 18 years, ECOG (0 or 1), and had measurable tumors per RECIST 1.1. TU2218 monotherapy was planned at 6 dose levels (30, 60, 105, 150, 195, 270 mg/day) with 2 weeks on and 1 week off in 3-week cycles according to the BOIN method. The starting dose of TU2218 given with pembrolizumab was determined after yielding TRAEs of at least Grade 2 in severity during monotherapy using the traditional 3+3 design.

Results Seventeen patients with advanced solid tumors received 5 different dose levels of monotherapy. Major demographics, treatment-related adverse events (TRAEs) and PK parameters are summarized in table 1.

No TRAEs of Grade 3 or higher were reported while all Grade 2 TRAEs were tolerable in TU2218 monotherapy. Systemic exposure to TU2218 increased over-proportionally with the dose-escalation. TU2218 showed reduction in PD marker of TGFβ, CTGF and PAI-1 after 7 days administration (figure 1) and correlation between TU2218 exposure (AUC) and PD markers of TGFβ and CTGF ($P<0.05$). The starting dose of TU2218 in combination with pembrolizumab was 105mg/day, with subsequent incremental doses of 150mg/day and 195mg/day.

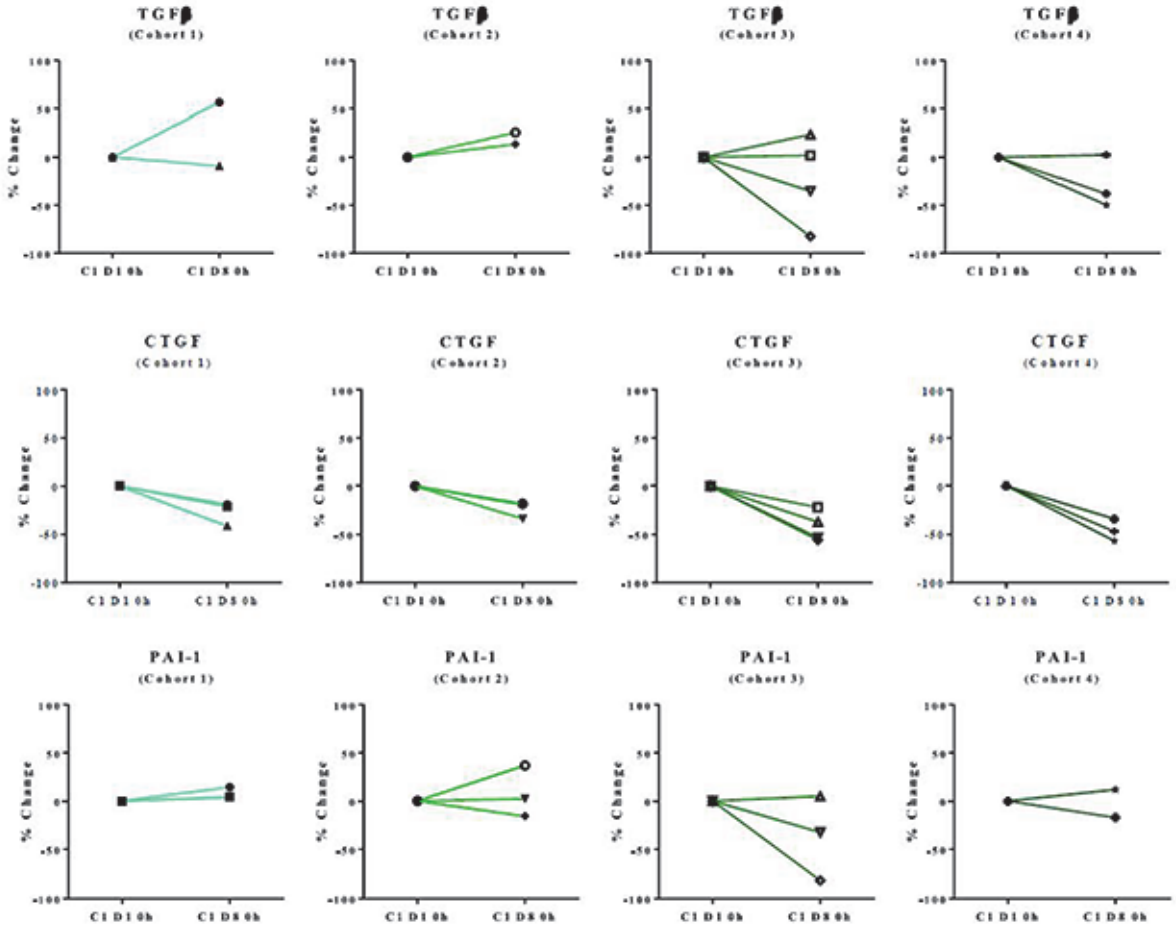
Conclusions TU2218, a first-in-class oral dual inhibitor against TGFβRI and VEGFR2, was well-tolerated in the monotherapy and will be subsequently investigated for the combination therapy with PD-L1.

Trial Registration This trial registered in clinicaltrials.gov. (NCT05204862)

Ethics Approval This study protocol, informed consent and all applicable information had been reviewed and approved by the IRB/ECs of the participating study indtitutions. (Salus IRB: Protocol Number TUC1PI-01, NXSAT21.72; Seoul National Univeraity Hospital Institutional Review Board Protocol Number TUC1PI-01, H-2203–016-1304; Institutional Review Board Asan Medical Center Protocol Number TUC1PI-01, 2022–0395)

Abstract 631 Table 1 Summary of Demographics, TRAE and PK Parameters

Cohort	1	2	3	4	5
Total Daily Dose (mg)	30	60	105	150	195
Patients (N)	3	4	4	3	3
Median age (Range)	54 (48–56)	61 (46–78)	70 (52–77)	72 (56–72)	65 (37–75)
Male/Female	0/3	2/2	1/3	1/2	1/2
TRAE, n (Grade)	0	3 (G2)	2 (G2)	1 (G2)	6 (G2)
Mean of PK Parameters					
tmax (h)	1	0.7	1.6	1.2	
Cmax (ng/mL)	95	162	374	781	1875
AUClast (ng·h/mL)	200	257	819	1854	3664
t1/2 (h)	2.1	1.7	1.7	2.6	
* For cohort 5, simulated data					



C1D1: Cycl1 1 Day 1, C1D8: Cycle 1 Day 8, TU2218 Total daily dose of Cohort 1=30mg, Cohort 2=60mg, Cohort 3=105mg, Cohort 4=150mg
TGF ; transforming growth factor- , CTGF; connective tissue growth factor, PAI-1; plasminogen activator inhibitor-1

Abstract 631 Figure 1 PD Markers of TGFβ, CTGF and PAI-1 After 7 Days Administration of TU2218

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0631