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First-in-human study of TU2218, TGFβRI and VEGFR2 dual inhibitor in patients with advanced solid tumors

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STUDY RATIONALE

TU2218 has been developed for the treatment in patients with advanced solid tumors. In vitro and in vivo studies have shown that TU2218 reduced the growth and migration/invasion of tumor cells and has synergistical antitumor effects in combination with anti-programmed cell death-1 (anti-PD-1) and anti-programmed cell death-1 ligand-1 (anti-PD-L1) antibodies.

The purpose of this first-in-human study is to assess the safety, tolerability and pharmacokinetics (PK) of TU2218 administered alone in a 2 weeks on treatment followed by 1 week of rest (2 weeks on/1 week off) regimen to determine the recommended Phase 2 dose (RP2D).

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 the tumor-microenvironment (TME), contributing to the immunosuppressive. Especially, immune tolerance by TGF-β and VEGF is inextricably related with poor outcomes of anti-PD-L1 therapy. Hence, a novel therapeutic agent targeting TGF-β and VEGF signaling pathway concurrently can be a good option for ICI-resistant patients.

Table 1 TU2218 Cellular Activity

Drug	Enzyme activity(IC_{50} nM)		Cellular activity(IC_{50} nM)	
	ALK5	VEGFR2	ALK5	VEGFR2
TU2218	1.2	4.9	101	52.5

Table 1 Cellular activity was determined by the IC_{50} value for phosphorylation of SMAD2 and VEGFR2 with stimulation of TGF-β and VEGF, respectively.

In cancer, TGF-β functions as a tumor promoter by activating the SMAD4-independent signaling pathway, promoting cell motility, invasion, epithelial-to-mesenchymal transition, and metastasis and decreasing antitumor immune responses particularly during the advanced stage. TGF-β signaling seemingly plays a critical role on cancer stem cells, cancer-associated fibroblasts, and immune cells that contribute to the overall process of metastatic dissemination.[1,2,3] Therefore, TGF-β signaling is a promising target for treatment of cancers, and inhibitors of ALK5 have the potential to decrease cancer cell progression by blocking TGF-β signaling.

Figure 1

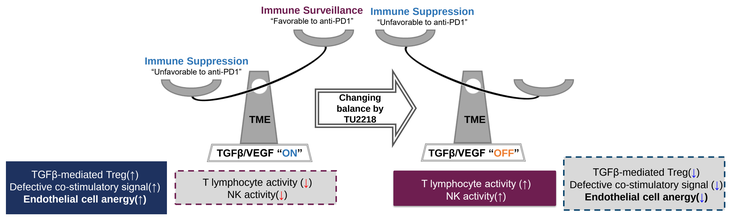

Figure 1: Expected Mode of Action of TU2218, Immune evasion mechanism in TGFβ/VEGF enriched context vs. Immune response to tumor-immune microenvironment by TU2218, Changing the immune balance toward favorable status to anti-PD1 antibody drugs.

Figure 2

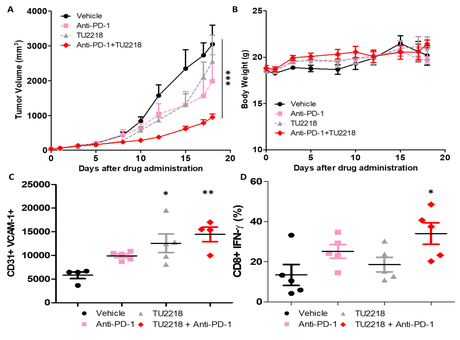

Figure 2: Antitumor activity of combination with TU2218 and anti-PD1 antibody in B16F10 syngeneic mouse model.

A. Tumor volume at indicated time points. Data are shown as mean + SEM. *** p ≤ 0.001 vs vehicle (Two-way ANOVA).
B. mean body weight + SEM for each treatment group.
C. Fluorescence intensity of CD31+VCAM1+ cell in tumors. * p ≤ 0.05, **: p ≤ 0.01 vs. vehicle (One-way ANOVA, Tukey)
D. Percent of CD8+IFNγ+ T cells in tumors. * p ≤ 0.05 vs. vehicle (One-way ANOVA, Tukey)

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References
1. Neuzillet C, Tijeras-Raballand A, Cohen R, et al. Targeting the TGFβ pathway for cancer therapy. Pharmacol Ther. 2015;147:22-31.
2. Massagué J. TGFβ signalling in context. Nat Rev Mol Cell Biol. 2012;13(10):616-30.
3. Massagué J. TGFbeta in Cancer. Cell. 2008;134(2):215-30.

METHOD

Figure 3

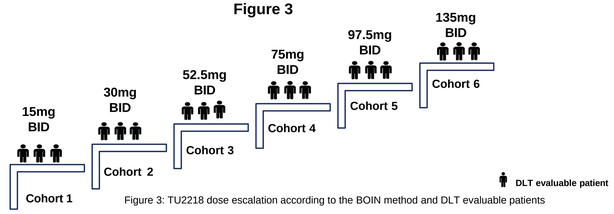

Figure 3: TU2218 dose escalation according to the BOIN method and DLT evaluable patients

- This non-randomized, multinational, open-label study has been evaluating the safety, tolerability, PK, and preliminary efficacy of TU2218 mono-therapy in advanced solid tumors.
- The eligible patients were aged ≥ 18 years, ECOG (0 or 1), and had measurable tumors per RECIST 1.1.
- 6 dose levels of TU2218 (30, 60, 105, 150, 195, 270 mg/day) were administrated for 2 weeks on and 1 week off in a 3-week cycles. The dose escalations as determined by the Safety Review Committee, were made according to the Bayesian Optimal Interval Designs (BOIN) method to determine the MTD and optimal biological effective dose of TU2218.
- The starting dose of TU2218 given with pembrolizumab was determined after yielding TRAEs of at least Grade 2 in severity during monotherapy.

Table 2 Patient demographics and Baseline Characteristics

Cohort	1	2	3	4	5	6	Total
Dose (BID)	15 mg	30 mg	52.5 mg	75 mg	97.5 mg	135 mg	
Age (years)							
N (%)	3	4	4	3	3	5	22
Mean (SD)	52.7 (4.16)	61.5 (15.86)	67.3 (10.72)	66.7 (9.24)	59.0 (19.70)	63.4 (7.33)	62.1 (11.49)
Median	54.0	61.0	70.0	72.0	65.0	62.0	63.5
Min, Max	48, 56	46, 78	52, 77	56, 72	37, 75	56, 72	37, 78
Sex							
N (%)	3	4	4	3	3	5	22
Male	0	2 (50.0)	1 (25.0)	1 (33.3)	1 (33.3)	3 (60.0)	8 (36.4)
Female	3 (100)	2 (50.0)	3 (75.0)	2 (66.7)	2 (66.7)	2 (40.0)	14 (63.6)
Race							
N (%)	3	4	4	3	3	5	22
White	3 (100)	3 (75.0)	0	1 (33.3)	0	0	7 (31.8)
Asian	0	1 (25.0)	4 (100)	2 (66.7)	3 (100)	5 (100)	15 (68.2)
Cancer Site/Organ of initial diagnosis							
N (%)	3	4	4	3	3	5	22
Pancreas	0	1(25.0)	2(50.0)	1(33.3)	1(33.3)	2(40.0)	7(31.8)
Liver	0	0	0	1(33.3)	0	1(20.0)	4(18.2)
Biliary Tract	0	0	1(25.0)	0	0	1(20.0)	2(9.1)
Colon	0	1(25.0)	0	0	0	1(20.0)	2(9.1)
Ovary	1(33.3)	0	0	1(33.3)	0	0	2(9.1)
Cervix Uteri	1(33.3)	0	0	0	0	0	1(4.5)
Rectum	0	0	0	0	1(33.3)	0	1(4.5)
Ampulla of Vater	0	0	1(25.0)	0	1(33.3)	0	2(9.1)
Sarcoma	1(33.3)	1(25.0)	0	0	0	0	2(9.1)
Melanoma	0	1(25.0)	0	0	0	0	1(4.5)
Time Since Initial Cancer diagnosis (Months)							
N (%)	3	4	4	3	3	5	22
Median (range)	27.9 (20-31)	58.6 (39-78)	31.2 (12-37)	22.6 (13-256)	25.8 (15-82)	31.9 (10-37)	31.3 (10-256)

Table 2: Patients demographics and baseline characteristics

RESULTS

- No TRAEs of Grade 3 or higher were reported while all Grade 2 TRAEs were tolerable in TU2218 monotherapy.
- MTD was not identified during the DLT period of 135mg BID dosing.
- Systemic exposure to TU2218 increased over-proportionally with the dose-escalation.
- The starting dose of next Phase 1b study of TU2218 in combination with pembrolizumab was recommended 52.5mg BID and will be subsequently increased.

NCT Number: NCT05204862 Phase 1a trial TU2218 Alone / NCT05784688 Phase 1b trial TU2218 in combination with pembrolizumab
Acknowledgement: Study sponsored by TiumBio Co., Ltd.

Table 3 Treatment Related Adverse Events

Dose (BID) / Preferred Term	15mg N=3 n (G2)	30 mg N=4 n (G2)	52.5 mg N=4 n (G2)	75 mg N=3 n (G2)	97.5 mg N=3 n (G2)	135 mg N=5 n(G2)	Total N=22 n(≥G2)
Nausea	1 (1)	2 (1)	1 (0)	2 (1)	2 (1)	2 (0)	10 (3)
Diarrhoea	0	0	1 (0)	1 (0)	1 (0)	1 (0)	4 (0)
Vomiting	0	1 (0)	1 (0)	1 (0)	0	0	3 (0)
Constipation	2 (0)	0	0	0	0	0	2 (0)
Stomatitis	0	0	0	0	1 (1)	2(1)	3 (2)
Dyspepsia	0	0	0	0	0	1(0)	1 (0)
Lower gastrointestinal haemorrhage	0	0	0	0	1 (0)	0	1 (0)
Pruritus	0	1 (0)	1 (1)	1 (1)	3 (1)	2 (1)	8 (4)
Rash	0	0	0	0	1(0)	3 (0)	4 (0)
Rash maculo-papular	1 (0)	0	0	0	0	0	1 (0)
Asthenia	0	0	0	0	1(0)	0	1 (4.5)
Fatigue	0	1 (1)	0	0	0	0	1 (1)
Decreased appetite	0	0	0	0	1 (1)	0	1 (1)
Dehydration	0	1 (1)	0	0	0	0	1 (1)
Headache	0	0	0	1 (0)	1 (0)	3 (0)	5 (0)
Platelet count decreased	0	0	1 (1)	0	1 (0)	0	2 (1)
Arthralgia	0	0	0	0	1 (1)	0	1 (1)
Myalgia	0	0	0	0	2 (1)	0	2 (1)
Epistaxis	0	0	0	0	0	1 (0)	1 (0)
Haemoptysis	0	0	0	0	0	1 (0)	1 (0)
Oropharyngeal pain	0	0	1 (0)	0	0	0	1 (0)

Table 3: List of Treatment Related Adverse Event

PHARMACOKINETICS

Figure 4

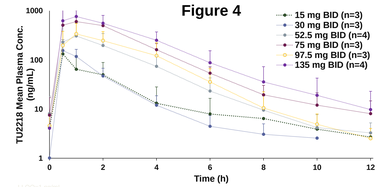

Figure 5

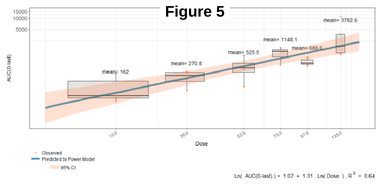

Figure 4: TU2218 Mean semi-log plasma concentration-time curves – Cycle 1 Day 8, Cohort 1 to 6
Figure 5: Power Model for $AUC_{(0\text{-last})}$ on Cycle 1 Day 1 : Across the dose range of 15 to 135 mg BID, exposure increased in a slightly greater than dose proportional manner, however there was a decrease observed in Cohort 5.

Table 4 TU2218 PK Parameters

Dose (BID)	15 mg		30 mg		52.5 mg		75 mg		97.5 mg		135 mg	
Cycle/Day	C1D1	C1D8	C1D1	C1D8	C1D1	C1D8	C1D1	C1D8	C1D1	C1D8	C1D1	C1D8
n	3	3	4	3	4	4	3	3	3	3	5	4
t_{max} (h)	1.2	1.0	0.5	0.7	1.8	1.6	2.0	1.2	2.8	2.0	1.5	0.8
C_{max} (ng/mL)	87	95	208	162	264	375	531	781	252	382	958	808
AUC_{last} (ng·h/mL)	162	200	271	257	525	819	1148	1854	689	998	3783	2426
AUC_{inf} (ng·h/mL)	217	292	273	262	654	826	1158	1891	699	1003	4145	2457
$t_{1/2}$ (h)	2.0	2.1	1.13	1.7	1.3	1.7	2.5	2.6	1.5	1.4	2.1	1.7
CL/F, CL_{ss}/F (L/h)	106	68	134	146	92	104	79	43	145	98	72	66
V_z/F (L)	194	150	195	297	168	236	246	149	327	195	170	146

Table 4: TU2218 Pharmacokinetics parameters

OVERALL CANCER RESPONSE

Table 5 Overall Cancer Response

Dose (BID)	15 mg	30 mg	52.5 mg	75 mg	97.5 mg	135 mg	
N (%)	**3**	**4**	**4**	**1**	**3**	**5**	**19**
CR - Complete Response	0	0	0	0	0	0	0
PR - Partial Response	0	0	0	0	0	0	0
SD - Stable Disease	2 (66.7)	2 (50.0)	1 (25.0)	0	0	0	5 (26.3)
PD - Progressive Disease	1 (33.3)	1 (25.0)	2 (50.0)	1 (100)	3 (100)	4 (100)	12 (63.2)
NE - Not Evaluable	0	1 (25.0)	1 (25.0)	0	0	0	2 (10.5)

Table 5: Overall Cancer Response. Percentages are based on the number of patients in efficacy analysis evaluable for each cohort .

CONCLUSION

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 pembrolizumab.