TU2218 (TGFβRI/VEGFR2 dual inhibitor) maximizes the benefit of cancer immunotherapies

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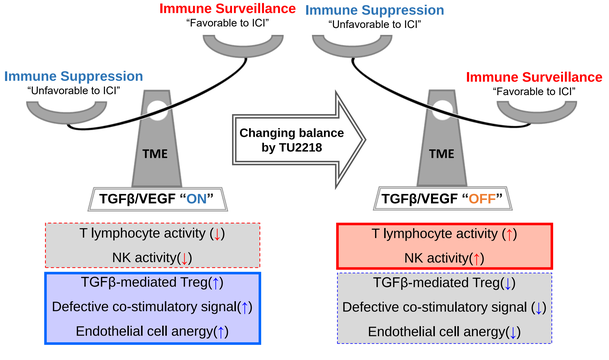
Abstract

Approved anti-PD-1 antibodies play a pivotal role in driving innovative clinical outcomes through combination with cytotoxic agents, targeted therapies, or other immune checkpoint inhibitors in various cancers. Anti-PD-1 antibody-based combination therapies have led to a paradigm shift in cancer treatment from cytotoxic agents or targeted therapy to immunotherapy. Considering this change in the regimen, the clinical development of TU2218 aims to accelerate approval and clinical application by improving the efficacy and safety of clinically proven combination therapies. TU2218 is characterized by the following four mechanisms of action: 1) improvement of T lymphocyte activity, 2) suppression of Treg, 3) improvement of costimulatory signal defects, and 4) overcoming endothelial cell anergy. Based on the mechanisms of action, TU2218 is expected to show significant clinical effects when combined with immune checkpoint inhibitors by lowering the intensity of immune evasion and changing more favorably to immune checkpoint inhibitors. To test the feasibility of various combination options based on TU2218, *in vivo* efficacy studies were conducted in 4T1, MC38, and CT26 syngeneic tumor models. In the 4T1 of TNBC type, a level of tumor reduction was significant to p<0.001 on TU2218 and anti-PD-1 antibody combination group compared to vehicle, whereas anti-PD-1 antibody alone or anti-PD-1 antibody and paclitaxel combination group was not significant. Combination therapy with anti-CTLA4 antibody and anti-PD-1 antibody has been approved for some cancers but has therapeutic limitations due to safety issues such as immune-related toxicity and needs improvement. In the MC38, the effectiveness of a dose-sparing strategy of anti-CTLA4 antibody was evaluated by adding TU2218 to the anti-CTLA4 antibody and anti-PD-1 antibody combination regimen to improve safety concerns. In the anti-CTLA4 antibody sparing group, co-administration of TU2218 maintained the anti-tumor activity despite reducing 90% or 60% of the original anti-CTLA4 antibody dose. In effect, the difference in anti-tumor activity between the group with a reduced dose of anti-CTLA4 antibody and the group without was not statistically significant. In CT26, the efficacy of Lenvatinib and anti-PD-1 antibody combination therapy was compared with the combination of Lenvatinib, anti-PD-1 antibody, and TU2218. The efficacy of the Lenvatinib, anti-PD-1 antibody, and TU2218 combination group was superior to that of TGI 99% and CR 67% than the Lenvatinib and anti-PD-1 antibody combination group of TGI 76% and CR 17%. Moreover, a statistical difference in anti-tumor activity between the two groups was significant at p<0.001. Collectively, the combination therapies using TU2218 not only improved efficacy but also showed high safety profiles without weight loss or any toxicity signs, supporting the feasibility of the combination strategy of TU2218.

Expected MoA of TU2218



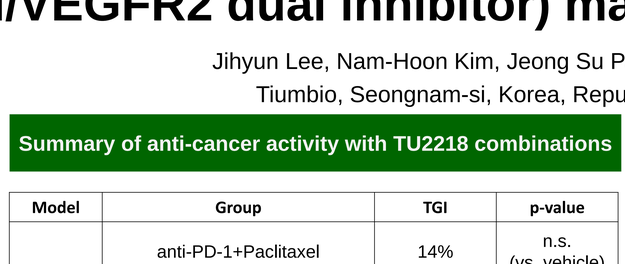
Immune evasion mechanism in TGFβ/VEGF enriched context vs. Immune response to tumor-immune microenvironment by TU2218, Changing the immune balance toward favorable status to immune checkpoint inhibitor (ICI).

Summary of anti-cancer activity with TU2218 combinations

Model	Group	TGI	p-value
4T1	anti-PD-1+Paclitaxel	14%	n.s. (vs. vehicle)
	TU2218+anti-PD-1	62%	p<0.001 (vs.vehicle)
MC38	anti-PD-1+anti-CTLA4 10mg/kg	70%	n.s.
	TU2218+anti-PD-1+anti-CTLA4 1mg/kg	84%	
	TU2218+anti-PD-1+anti-CTLA4 3mg/kg	84%	
CT26	Lenvatinib+anti-PD-1	76%	p<0.001
	TU2218+Lenvatinib+anti-PD-1	99%	

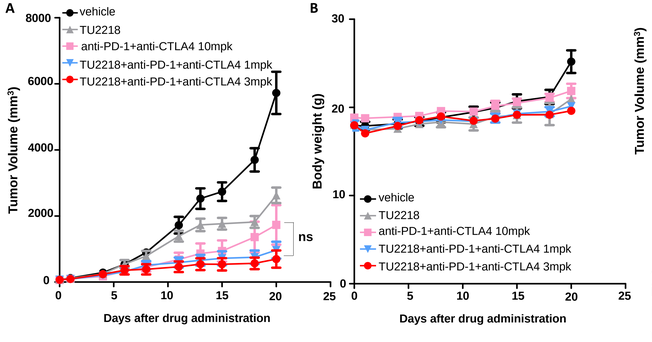
Antitumor activity of various combination regimens based on TU2218 in 4T1, MC38, and CT26 syngeneic mouse tumor models. Efficacy is shown as tumor growth inhibition(%TGI) and stastical p-value (two-way ANOVA) n.s. p > 0.05.

Combination with TU2218 and anti-PD-1 is superior than anti-PD-1 plus Paclitaxel regimen



Antitumor activities in 4T1 syngeneic mouse tumor models. **A**, Tumor volume at indicated time points. Data are shown as mean ± SEM. *** p ≤ 0.001 vs. vehicle or TU2218 (two-way ANOVA). **B**, Mean body weight + SEM for each treatment group.

Combination with TU2218, anti-PD-1 and anti-CTLA4 is superior than anti-PD-1 plus anti-CTLA4 regimen



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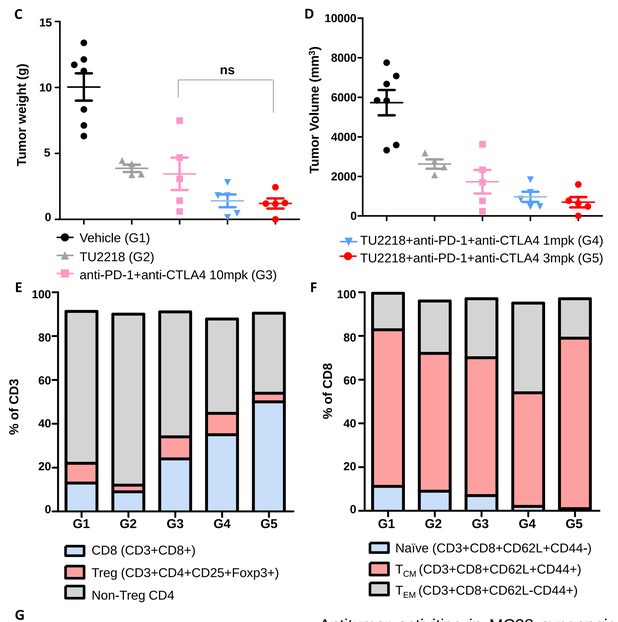
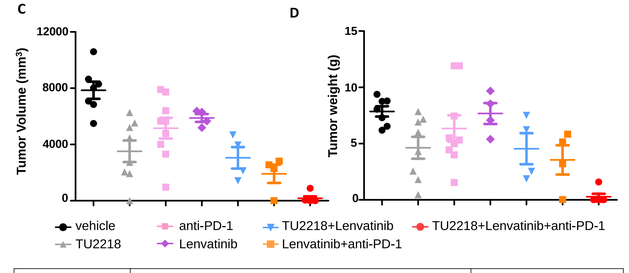


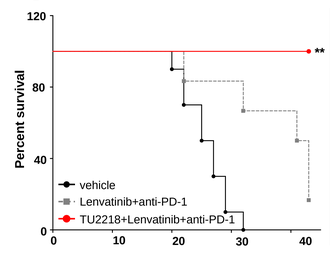
Antitumor activities in MC38 syngeneic mouse tumor models **A**, Tumor volume at indicated time points. Data are shown as mean ± SEM. ns p > 0.05 vs. anti-PD-1+anti-CTLA4 antibody (two-way ANOVA). **B**, Mean body weight ± SEM for each treatment group. **C**,**D**, Individual tumor weight, volume at the endpoint. **E**, Frequency of CD8, Treg, and non-Treg CD4 of CD3 in tumor. **F**, Frequency of immune memory T cell subsets of CD8 in tumor **G,** Individual tumor image at the endpoint

Combination with TU2218, Lenvatinib and anti-PD-1 is superior than Lenvatinib plus anti-PD-1 regimen



Model	Group	CR
CT26	Lenvatinib+anti-PD-1	17% (1/6)
	TU2218+Lenvatinib+anti-PD-1	67% (4/6)

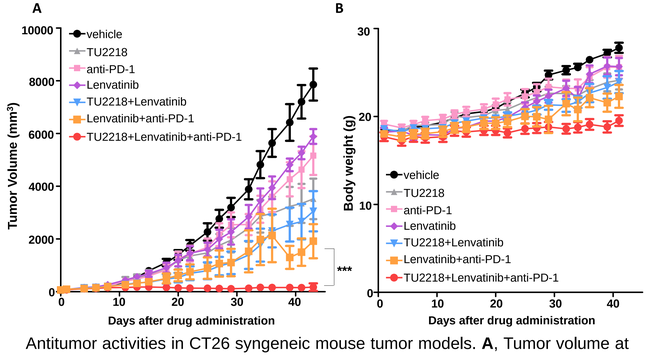
C, Individual tumor volume at the endpoint. **D**, Individual tumor weight at the endpoint. Table represents a complete remission (CR) ratio of indicated combination therapy at endpoint.



Group	Survival	Median survival (days)	P-value
Vehicle	0% (0/10)	26	-
Lenvatinib +anti-PD-1	17% (1/6)	42	p<0.01
TU2218 +Lenvatinib +anti-PD-1	100% (6/6)	N.D	

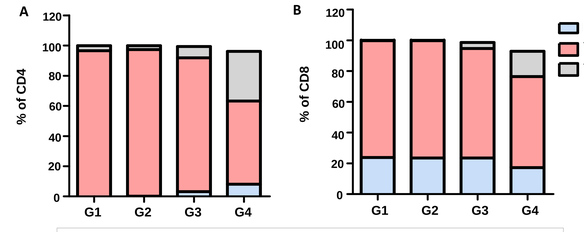
E, Survival curve of CT26 tumor-bearing mice with combination therapy at indicated timepoint. Individuals with tumor size over 2000mm^3 were counted as death. N.D : not determined.**: p<0.01 vs. Lenvatinib+anti-PD-1 (Log-rank)

Combination with TU2218, Lenvatinib and anti-PD-1 is superior than Lenvatinib plus anti-PD-1 regimen



Antitumor activities in CT26 syngeneic mouse tumor models. **A**, Tumor volume at indicated time points. Data are shown as mean ± SEM. *** p < 0.001 vs. Lenvatinib anti-PD1 (two-way ANOVA). **B**, Mean body weight ± SEM for each treatment group.

Increase of effector memory T cells in combination with TU2218, Lenvatinib and anti-PD-1



G1 : vehicle **G3 :** Lenvatinib+anti-PD-1
G2 : TU2218+Lenvatinib **G4 :** TU2218+Lenvatinib+anti-PD-1

Immune memory population in spleen with indicated combination regimen in CT26-bearing mouse . Frequency of naïve, central memory T cell(T_{CM}), effector memory T cell(T_{EM}) subsets of CD4 **(A)**, and CD8 **(B)**

Conclusions

- Various combination options based on TU2218 showed superior efficacy over approved combination regimens.
- Clinical study combining TU2218 and Pembrolizumab for HNSCC, BTC, and CRC patients is planned in 2024(NCT05204862).