ZM-8803, a Potent and Selective SOS1::KRAS Inhibitor, is Effective in KRAS-Addicted Cancer

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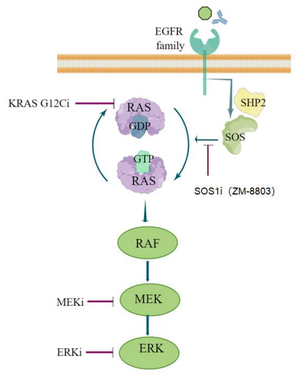
Introduction

- Dysregulated MAPK signaling is implicated in multiple malignancies, such as RAS overactivation by mutation or/and upstream cues
- SOS1/2 plays a key role in catalyzing the transformation of KRAS from inactive (GDP) to active (GTP-bound) form
- Although $KRAS^{G12C}$ inhibition has demonstrated significant clinical benefits, resistance and disease progression occur in most patients
- Furthermore, $KRAS^{G12D}$ and $KRAS^{G12V}$ are more prevalent than $KRAS^{G12C}$, a pan-KRAS inhibitor would be of great clinical value
- Targeting different steps in MAPK pathway (vertical inhibition) has been well verified, for example, BRAF plus MEK inhibitor
- Here, we report a SOS1 inhibitor ZM-8803, as a pan-KRAS inhibitor exhibiting a robust efficacy on anti-multiple *kras* mutant tumor cells growth *in vitro* and *in vivo*



Reference:

1, *Expert Opin Ther Targets*. 2012;16:103-119.
2, *Mol Cancer Ther* (2018) 17 (1): 3–16.
3, https://doi.org/ 10.1200/EDBK_351333.

Results

In vitro profile of SOS1 inhibitor, ZM-8803

Profile		ZM-8803
Binding IC_{50} (nM)	KRAS G12D/SOS1	3.8
	KRAS WT/SOS1	3.5
	KRAS G12C/SOS2	>10000
Target engagement pERK IC_{50} (nM)	H358-SOS2 KO	9.0
Anti-proliferation 3D IC_{50} (nM)	H358-SOS2 KO	28.42
Selectivity A375(non-KRAS addicted) IC_{50} (nM)		>1000
CYP inhibition IC_{50} (μM) (CYP2C9/CYP2D6/CYP3A4-M/CYP3A4-T)		>30/>30/>30/27.9
hERG inhibition IC_{50} (μM)		>30
Kinase panel (207 targets), inhibition		<40% @ 10μM
Safety panel (SAFERYscan) RC_{50} (μM)		>10 (43 targets); 4~10 (4 targets)

ZM-8803 is a selective SOS1 inhibitor with high potency on MAPK signal pathway inhibition and anti- *kras* mutant cells proliferation

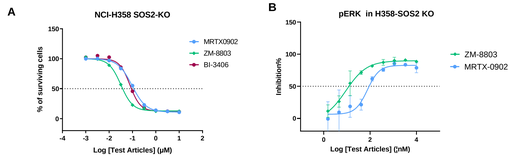


Figure 1. Cellular efficacies were determined in a *kras* mutant cell line with SOS2 knock out. A, Inhibition of cell proliferation by ZM-8803 in 3-D proliferation assays; B, Inhibition of pERK activity after 1 hour ZM-8803 treatment in 2-D assay quantified by HTRF.

In vitro sensitivity of a panel of cell lines

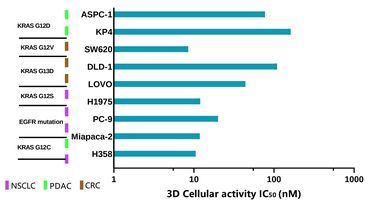


Figure2. Inhibition of cell proliferation by ZM-8803 in a cancer cell line panel in 3-D proliferation assays. Cells were treated with ZM-8803 for 7 days, the viabilities were measured by 3-D CellTiter-Glo

ZM-8803 suppresses tumor growth in xenograft models of KRAS-driven cancers

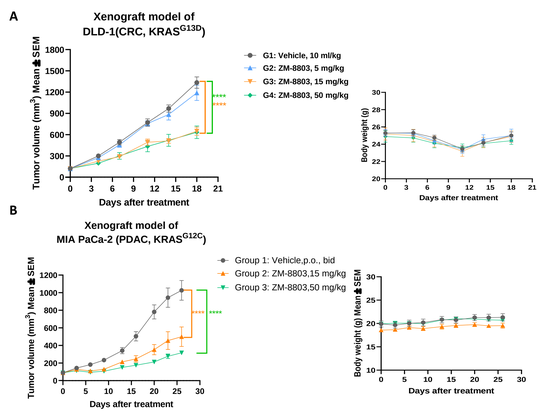


Figure3. ZM-8803 suppressed tumor growth. A, Antitumor effect in the DLD-1 xenograft model. B. Effect was also evaluated in a MIA PaCa-2 xenograft model . The results showed a well dose-dependent response. The tumor volumes were analyzed by two-way ANOVA followed by Tukey's multiple comparisons test. *: P<0.05, **: P<0.01, ***: P<0.001,****: P<0.0001.

The synergistic effects are demonstrated for ZM-8803 combined with additional MAPK pathway inhibitors

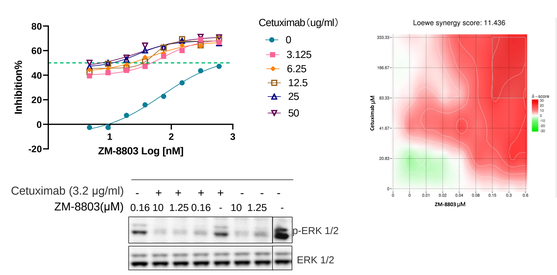


Figure4. The anti-proliferation efficacy of ZM-8803 was enhanced when combined with cetuximab in 3-D proliferation assay. The average synergy score was 11.4 calculated by SynergyFinder (http://www.synergyfinder.org/). Meanwhile, pERK levels decrease were enhanced for combination compared to single drug treatment. DLD-1 cells were treated with multiple doses of ZM-8803 and/or cetuximab for 7 days, and cell viabilities were determined by 3-D CTG. pERK levels in DLD-1 cells after 4h compounds treatment were analyzed by WB.

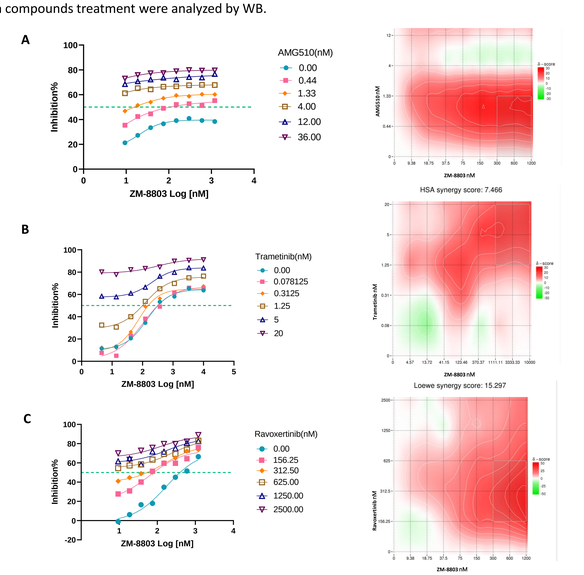


Figure5. Synergistic effects were evaluated for ZM-8803 combined with AMG510 (A), Trametinib (B), or Ravexertinib (C). Mia PaCa-2 cell were treated with a linearly diluted ZM-8803 and / or AMG510 for 7 days, cell viabilities were determined by 3-D CTG, and the synergy effects were analyzed by SynergyFinder. The combination of ZM-8803 with Trametinib or ZM-8803 with Ravoxertinib were tested in DLD-1 model with the similar assay condition.

Dual MAPK signal pathway inhibitors combination as effective strategy to treat *kras*-mutant tumors

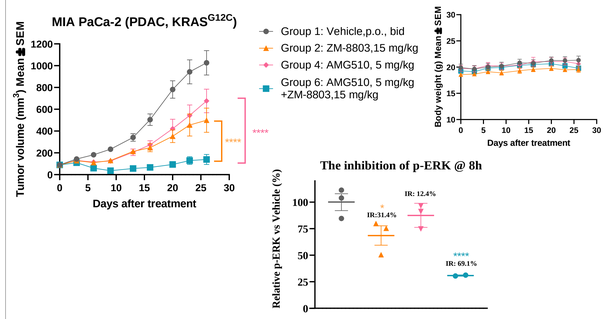


Figure6. Combined ZM-8803 and AMG510 efficiently suppressed tumor growth in MIA PaCa-2 bearing mice . And the correlated PD effect was also demonstrated through the decrease of pERK level. The tumor volumes were analyzed by two-way ANOVA followed by Tukey's multiple comparisons test. *: P<0.05, **: P<0.01, ***: P<0.001,****: P<0.0001.

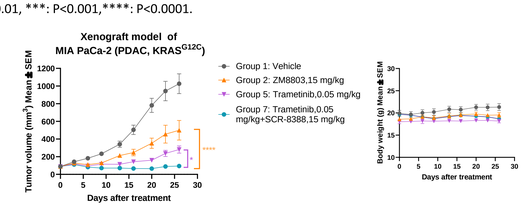


Figure7. Combined ZM-8803 and Trametinib efficiently suppressed tumor growth in in MIA PaCa-2 bearing mice. The tumor volumes were analyzed by two-way ANOVA followed by Tukey's multiple comparisons test. *: P<0.05, **: P<0.01, ***: P<0.001,****: P<0.0001.

Summary

- A SOS1 selective inhibitor, ZM08803, as a pan-KRAS inhibitor, efficaciously inhibits several *kras*-mutant oncoprotein activities , and exhibits high potency in suppressing multiple *kras*-mutant tumor cells growth
- Oral administration of ZM-8803 effectively suppresses tumor growth in xenograft models of KRAS-driven cancer
- It was well demonstrated that ZM-8803 could block MAPK signal pathway and exhibited synergistic effects in combination with additional MAPK pathway inhibitors, indicating dual MAPK signal inhibitors is an effective strategy to treat *kras*-mutant tumor
- ZM-8803 will proceed to IND application soon