Abtract
70181

A novel CSF1R/c-kit dual antagonist eliminates tumor associated macrophage without elevating intratumoral MDSC level

Ji Wang[1※], Zhiyong Yu[1], Qingchong Qiu[1], Wei Pang[1], Keke Chen[1], Cindy Cheng[1], Shifeng Liu[1]
[1]Aldai Nortye Biopharma Ltd., Hangzhou, China ※ ji.wang@adlainortye.com

A novel CSF1R/c-kit dual antagonist eliminates tumor associated macrophage without elevating intratumoral MDSC level

Background

In the tumor microenvironment (TME), CSF1R (receptor of colony-stimulating factor 1) signaling by its ligand CSF1 is necessary for differentiation and survival of tumor associated macrophage (TAM). TAM promotes tumor cell migration, invasion and metastasis. CSF1R blockade is believed to be a strategy to rebuild TME.

However, specifically blocking the CSF1R pathway has been reported to increase myeloid-derived suppress-ing cells (MDSC) in tumor tissue [1][2]. Intratumoral MDSC suppresses T cells in an antigen nonspecific manner, and higher level of MDSC in tumor tissue may lead to immune suppressive TME and neutralize anti-tumor effect of CSF1R inhibitors. Here, we will report a CSF1R antagonist, AN9015. AN9015, with CSF1R and c-kit dual antagonizing activity, could eliminate TAM without elevating intratumoral MDSC level and provide robust anti-cancer efficacy.

In vitro profile

AN9015 is a highly selective CSF1R antagonist with inhibitory activity towards c-kit kinase.

Kinase activity	AN9015 IC50 (nM)
CSF1R	2.0
c-kit	9.5
PDGFRα	40
PDGFRβ	783
FLT3	>1000

Kinase selectivity of AN9015 was profiled by DiscoverX KINOMEscan kinase panel, which in-cludes 450 human kinases and mutants (Fig.1). 31 new kinases were identified. After the removal of mutant kinases, 16 remained. 9 of the 16 kinases were confirmed with kinase inhibitory assays. AN9015 showed IC50 of <40 nM towards BRK in addition to CSF1R, c-kit and PDGFRα.

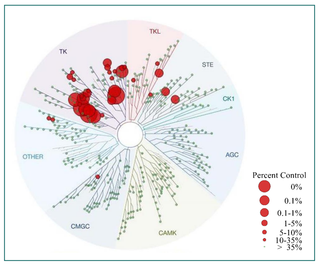


Figure 1 Kinase selectivity of AN9015 profiled by DiscoverX KINOMEscan kinase panel

IL-34, another ligand of CSF1R, has been reported to drive chemo-resistance[3]. Translational studies disclosed an association of IL-34 with multiple cancer types [4][5]. AN9015 inhibits not only CSF1 but also IL-34 induced CSF1R activation in THP-1 cells with similar potency.

Effect of AN9015 on CSF1R activation

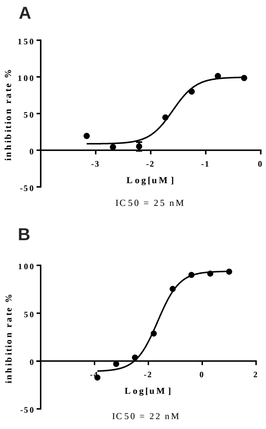


Figure 2 Effect of AN9015 on CSF1R activation in THP1 cells. (A) CSF1 induced CSF1R activation (B) IL34 induced CSF1R activation.

ADME and safety profile

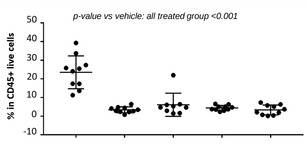
AN9015 has an excellent ADME and safety profile.

Compd ID	AN9015
Microsomal Stability	**Moderate in m/r/d/h**
CYP IC_{50} μM	**> 10**
Hepatocyte MID	**Good profile**
Mouse PK	**Good profile**
hERG (μM)	**> 30**

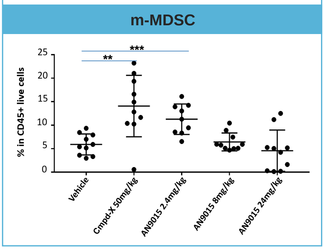
Anti-tumor efficacy

In the MC38 tumor model, AN9015 and cmpd-X, a clinical stage CSF1R inhibitor, were dosed orally for 10 days. Tumor tissues were collected for FACS analysis. Fig.3 demonstrates AN9015 could eliminate the CD206+ macro-phage without elevating MDSC. Upon AN9015 treatment, more T cells infiltrated the tumor tissue.

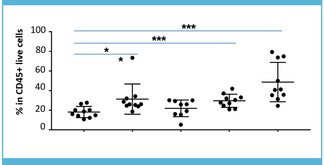
CD206+ macrophage



m-MDSC



T cell



g-MDSC

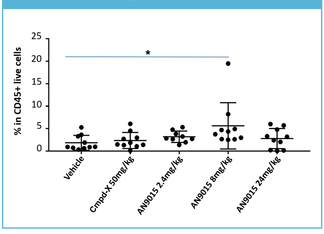


Figure 3 Effect of AN9015 on intratumoral lymphocyte subsets in MC38 tumor. *, *p<0.05;* **, *p<0.01;* ***, *p<0.001.*

To evaluate anti-tumor efficacy, AN9015 and cmpd-X were administrated orally to MC38 tumor bearing mice. Anti PD-1 Ab was injected as a combo treatment. Fig.4 indicates a single treatment of AN9015 could significantly inhibit tumor growth. When, in combo with anti-PD-1 Ab, AN9015 demonstrated superior anti-tumor efficacy.

Mouse MC38 model

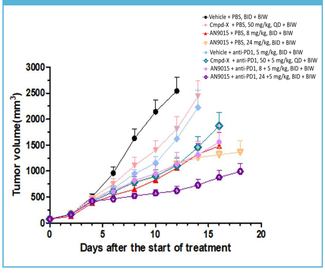


Figure 4 Anti-tumor efficacy of AN9015 in MC38 tumor bearing mice. Error bar represents SEM.

Conclusion and Discussion

AN9015，a highly potent and selective CSF1R/c-kit inhibitor with an excellent ADME and safety profile , can eliminate CD206+ macrophage without elevating intratumoral MDSC. The pharmacology profile and robust anti-tumor efficacy supports further clinical development.

References

1.Ries CH, Cannarile MA, et al. Cancer Cell, 2014, 25:846-859.
2.David IB, Nebiyu W, et al. Cancer Res., 2017, 77:abstract 1599.
3.Chow LQ, Haddad R, Gupta S, Mahipal A, Mehra R, Tahara M, et al. J. Clin. Oncol., 2016, 34:3838–45.
4.Franze E, Dinallo V, et al. Oncotarget, 2018, 9:3432-3445.
5.Baghdadi M, Endo H, et al. Sci. Rep., 2018, 8:418.

Adlai Nortye

Conflict of Interest disclosure slide for representative speakers or investigators

Research fund	☐scientific research fund ☐contract ☐donation X other ( ) ☐N/A	Sponsor	Adlai Nortye Biopharma Ltd.
Name of lead presenter	Ji Wang	Institution or company/position	Adlai Nortye Biopharma Ltd. Sr. Director

	No	If yes, please specify the name of company, organization, your status.
employee or adviser of company and/or profit-making organization	☐	Employee of Adlai Nortye Biopharma Ltd.
profit of stock	X	
patent fee	X	
lecturer fee	X	
manuscript fee	X	
research expenses from company	☐	This study is financially supported by Adlai Nortye Biopharma Ltd.
contributions or endowed chair	X	
fees of testimony, judgment, comment, etc.	X	
presents or other payment	X	
representative of organization for clinical study receiving research expenses from company	X	

Name of principal investigator	Ji Wang	Institution or company/position	Adlai Nortye Biopharma Ltd. Sr. Director

	No	If yes, please specify the name of company, organization, your status.
employee or adviser of company and/or profit-making organization	☐	Employee of Adlai Nortye Biopharma Ltd.
profit of stock	X	
patent fee	X	
lecturer fee	X	
manuscript fee	X	
research expenses from company	☐	This study is financially supported by Adlai Nortye Biopharma Ltd.
contributions or endowed chair	X	
fees of testimony, judgment, comment, etc.	X	
presents or other payment	X	
representative of organization for clinical study receiving research expenses from company	X	