CSF-1R inhibitor (C019199) enhances antitumor effect in combination with anti-PD-1 therapy on murine breast cancer models

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Background

Colony-stimulating factor-1 (CSF-1) is the primary regulator of mononuclear phagocytic cells. CSF-1 plays an important role in recruiting macrophages to tumor environment. Overexpression of CSF-1 and its ligand, colony-stimulating factor-1 receptor (CSF-1R), have been reported to be associated with the development of various types of cancers, such as breast, ovarian, and colorectal cancer. This study aims to investigate the treatment effects of a new CSF-1R inhibitor named C019199 in murine breast cancer (BC) models when administered alone or in combination with anti-PD-1 antibody.

Methods

Inhibition of CSF-1R was investigated in the murine BMDMs (bone marrow derived macrophages) for cell-based assay. Furthermore, the immunocompetent Balb/c mice were subcutaneously implanted 4T1 breast cancer cells in the right flank. Mice were randomized into groups of 9 and treated with C019199 (orally, 30mg, 60mg or 120mg/kg/d), either alone or in combination with anti-mouse PD-1 antibody (intraperitoneally, 10mg/kg). 1 of 9 groups was treated with single-agent Docetaxel (intraperitoneally, 10mg/kg). The animal body weight and tumor growth were monitored twice a week. Results were analyzed by 2-way ANOVA with Bonferroni's test.

Results

1.C019199 inhibited the murine colony-stimulating factor-1 receptor (CSF-1R) with an IC50 of about 8.0nM in cell-based assay (**Table 1**). 2. C019199 inhibited tumor growth in murine BC models. The combination of C019199 and anti-PD-1 had better synergistic antitumor efficacy than single-agent. Balb/c mice implanted 4T1 cells were treated with C019199 alone or combined with anti-PD1 for 14 days (**Figure 1**). The antitumor efficacy and treatment details (**Table 2**) were detected.

Table 1. The IC50 concentrations of C019199 in BMDMs (bone marrow derived macrophages).
SD, standard deviation.

Cells	IC50 (nM)
	BMDMs
1st trial	8.125
2nd trial	7.099
3rd trial	7.762
4th trial	8.980
Mean ± SD	7.9915±0.7840

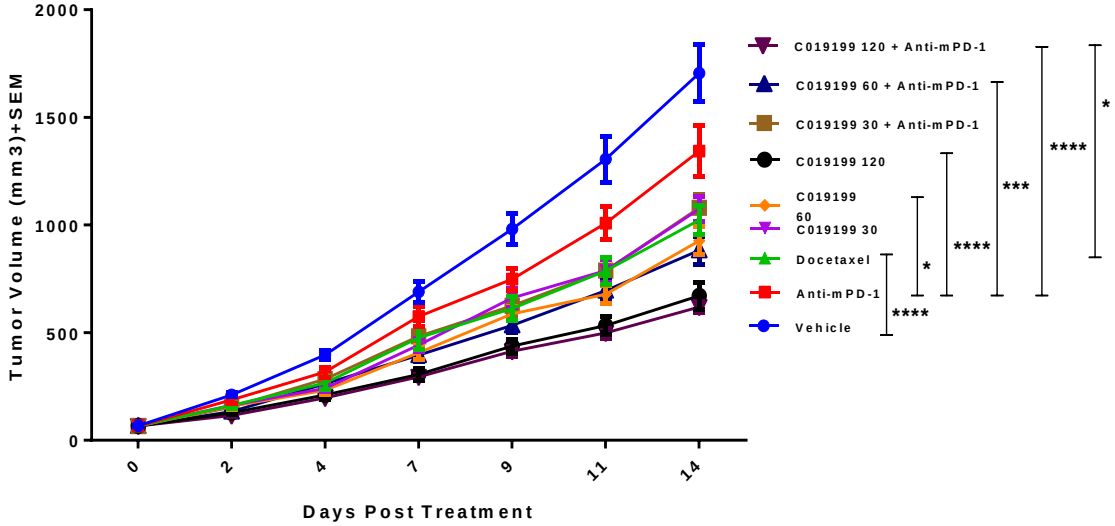

Figure 1. C019199 inhibited tumor growth in murine breast cancer models.
*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001. C019199-X, C019199 with number reflecting dose in mg/kg/day; SEM, standard error of mean.

Table 2. The antitumor efficacy and treatment details. NA, not applicable; PO, orally; IP, intraperitoneally; QD, once daily; T/C, treated/control tumor weight; SEM, standard error of mean.

Treatment	Dose (mg/kg)	Administration regimen and route	Rate% of average body weight change Day 14 vs Day 0	T/C (%) Day 14	Number of dead animal
Vehicle	NA	PO, QD x 14	13.76%	N/A	0
Anti-mPD-1	10	IP, Day 0, 3, 7, 10	16.43%	76.71%	1
Docetaxel	10	IV, Day 0, 7	4.21%	59.17%	0
C019199	30	PO, QD x 14	11.01%	62.46%	0
C019199	60	PO, QD x 14	7.97%	53.65%	0
C019199	120	PO, QD x 14	2.18%	38.51%	0
Anti-mPD-1	10	IP, Day 0, 3, 7, 10	13.25%	62.77%	0
C019199	30	PO, QD x 14			
Anti-mPD-1	10	IP, Day 0, 3, 7, 10	10.50%	47.66%	0
C019199	60	PO, QD x 14			
Anti-mPD-1	10	IP, Day 0, 3, 7, 10	4.85%	36.42%	0
C019199	120	PO, QD x 14			

Conclusions

C019199 is a new tyrosine kinase inhibitor of CSF-1R. Single-agent C019199 showed dose-dependently inhibition in murine 4T1 BC tumors. C019199 combined with anti-PD-1 had better antitumor efficacy than C019199 alone. Assessed by animal body weight, such combination therapy was well tolerated. The mechanisms of C019199-mediated immunomodulatory effects in combination with anti-PD-1 need further exploration.

Disclosure

All authors have declared no conflicts of interest.

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