BGB-24714, a novel oral IAP antagonist, displayed significant anti-tumor activities in preclinical models as a monotherapy and in combination with paclitaxel

Jie Li, Nan Hu, Yilu Zhang, Xiaolong Yang, Minjuan Deng, Wenfeng Gong, Longbo Yin, Yong Liu, Yajuan Gao, Wei Wei, Xing Wang, Xinyi Liang, Yanwen Ma, Xuxing Sang, Chang Liu, Jingyuan Wang, Qianqian Lu, Fengtao Song, Xi Yuan, Yanzhou Zhang, Yibing Wang, Jing Li, Wei Jin, Xuesong Liu, Xiaomin Song*
Authors' Affiliations: BeiGene Global Research, Beijing 102206, P.R. China; *Correspondence: xiaomin.song@beigene.com

Abstract

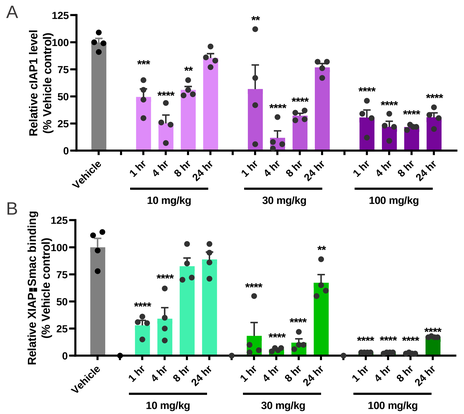
Evasion of apoptosis is identified as one of the essential hallmarks of cancer and upregulation of inhibitor of apoptosis proteins (IAPs) is one of the mechanisms by which tumor cells evade apoptosis. An oral SMAC mimetic and antagonist of cellular IAP1 (cIAP1) and X-linked IAP (XIAP), BGB-24714, is currently investigated in a phase 1a/1b oncology trial in patients with advanced or metastatic solid tumors (NCT05381909). Here, we evaluated the anti-tumor activity of BGB-24714 as a single agent or in combination with paclitaxel in preclinical models.

BGB-24714 effectively inhibited cIAP1 by inducing its degradation in MDA-MB-231 cells. It also potently antagonized the inhibitory interaction of XIAP with caspase-9 and induced caspase-9 autoactivation in MDA-MB-231 cells. In a panel of 25 breast cancer cell lines treated with TNFα, BGB-24714 potently inhibited the in vitro proliferation of 5 breast cancer cells with EC50 < 100 nM. In pharmacodynamics studies, single dose administration of BGB-24714 significantly induced degradation of cIAP1 and antagonism of the XIAP: Smac interaction in the MDA-MB-231 xenograft model in a dose dependent manner. Using the same model, BGB-24714 exhibited dose-dependent anti-tumor activities as a single agent. Furthermore, BGB-24714 demonstrated synergized anti-tumor activity in HCC1806 xenograft model when used in combination with paclitaxel. In intermittent dosing study, BGB-24714 with the intermittent dosing schedule demonstrated significant anti-tumor activity, although the activity is slightly less effective than the continuous dosing schedule.

In summary, BGB-24714, as a novel oral IAP antagonist, showing significant anti-tumor activities in preclinical models, which is promising and warrants the testing of the compound in human.

Pharmacodynamic Activity in Mouse

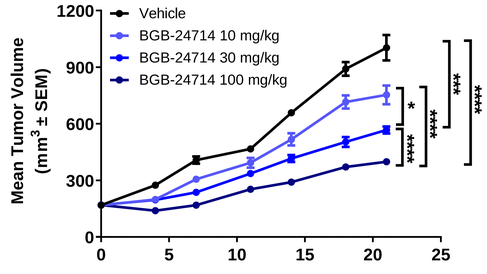
The pharmacokinetics and pharmacodynamics of BGB-24714 were evaluated in the MDA-MB-231 xenograft model in NCG mice. Tumor-bearing animals were treated with a single dose of BGB-24714. Protein levels of cIAP1 (A) and binding of XIAP:Smac (B) in the tumor tissue were determined using the MSD assay.



- Single dose treatment of BGB-24714 resulted in dose dependent degradation of cIAP1 (Figure A)
- Single dose treatment of BGB-24714 leads to dose dependent antagonism of XIAP:Smac binding in tumor tissues (Figure B).

Monotherapy in MDA-MB-231 Model

MDA-MB-231 cells were implanted into NCG mice. BGB-24714 was orally administrated daily at 10, 30, or 100 mg/kg for 21 days.

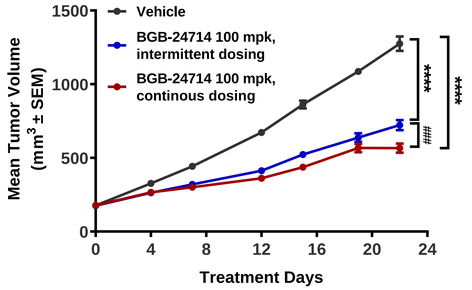


Compound	n	Dose (mg/kg)	TGI (%) (Day 21)	Mean tumor volume on Day 21 (mm^3)
Vehicle	8	NA	NA	1003.1
BGB-24714	8	10 QD	30	753.2
BGB-24714	8	30 QD	52	567.0
BGB-24714	8	100 QD	73	398.8

BGB-24714 demonstrated dose-dependent tumor growth inhibition on Day 21, and the tumor growth inhibition (TGI) rates were 30%, 52%, and 73% in 10, 30, and 100 mg/kg treatment groups, respectively.

Intermittent Dosing in MDA-MB-231 Model

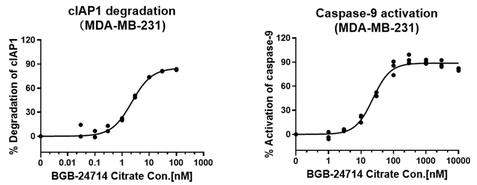
MDA-MB-231 cells were implanted into NCG mice. Tumor-bearing animals were treated with BGB-24714 (100 mg/kg) for continuous dosing or intermittent dosing.



Treatment	n	Dose (mg/kg)	TGI (%) (Day 22)	Mean tumor volume on Day 22 (mm^3)
Vehicle	8	NA	NA	1275.0
BGB-24714	8	100 QD, intermittent dosing	50	723.0
BGB-24714	8	100 QD, continuous dosing	65	561.9

The intermittent dose schedule at 100 mg/kg achieved significant tumor growth inhibition, which was 50% on Day 22, slightly lower than the inhibition rate (65%) in the continuous dosing group.

Effect on cIAP1 Degradation and Caspase-9 Activation

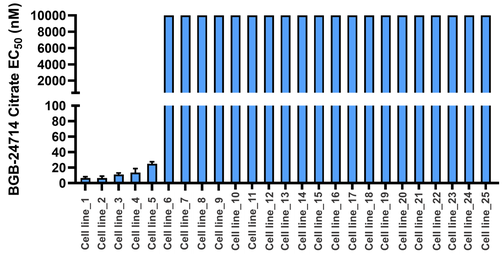


Cell lines	IAPs	EC_{50} (nM) (Mean ± SD)	E_{max} (%) (Mean ± SD)	n
MDA-MB-231	cIAP1	2.5 ± 0.15	85 ± 2.7	3
MDA-MB-231	XIAP	23 ± 1.0	92 ± 6.7	3

- BGB-24714 effectively inhibited cIAP1 by inducing its degradation in MDA-MB-231 cells, with an EC50 of 2.5 nM.
- BGB-24714 potently antagonized the inhibitory interaction of XIAP with caspase-9 and induced caspase-9 autoactivation in MDA-MB-231 cells, with an EC50 of 23 nM.

Anti-proliferation in a Panel of Breast Cancer Cells

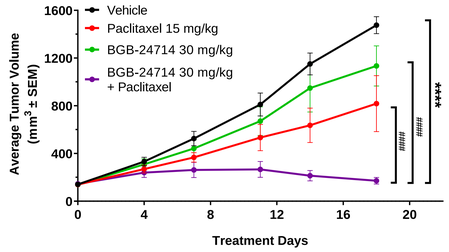
The effect of BGB-24714 on cell proliferation was assessed in a panel of 25 breast cancer cell lines. The activity of compounds was determined using CellTiter-Glo luminescent cell viability assay.



Cells were seeded into 96-well plates in 0.02 ng/mL TNFα containing medium and were treated with a titration of compounds for 72 hrs. BGB-24714 potently inhibited the *in vitro* proliferation of 5 of the 25 breast cancer cells with EC50 < 100 nM.

Combination with Paclitaxel

HCC1806 cells were subcutaneously implanted into BALB/c nude mice. Mice were treated with BGB-24714 (30 mg/kg, orally, once daily), paclitaxel (15 mg/kg, intraperitoneally, twice weekly) or the combination of both agents for 18 days.



- Mice receiving the combination of BGB 24714 with paclitaxel showed significantly induced tumor growth inhibition, the TGI is 98% on Day 18.
- The combination of BGB-24714 with paclitaxel exhibited synergized antitumor activity compared to paclitaxel alone.

Conclusions

- BGB-24714 effectively inhibited cIAP1 by inducing its degradation in MDA-MB-231 cells
- BGB-24714 potently antagonized the inhibitory interaction of XIAP with caspase-9 and induced caspase-9 autoactivation in MDA-MB-231 cells
- BGB-24714 potently inhibited the *in vitro* proliferation of 5 (out of 25) breast cancer cells treated with TNFα
- Single dose administration of BGB-24714 significantly induced degradation of cIAP1 and antagonism of the XIAP:Smac interaction in the MDA-MB-231 xenograft model in a dose dependent manner
- BGB-24714 exhibited dose-dependent anti-tumor activity as a single agent in MDA-MB-231 xenograft model
- BGB-24714 at 30 mg/kg demonstrated synergized anti-tumor activity in HCC1806 xenograft model when used in combination with paclitaxel
- In intermittent dosing study, BGB-24714 with the intermittent dosing schedule demonstrated significant anti-tumor activity, although the activity is slightly less effective than the continuous dosing schedule.

AACR 2023, #6158