Pharmacodynamic Characterization of BGB-24714, a Second Mitochondrial-Derived Activator of Caspases (SMAC) Mimetic, in a First-in-Human Study in Solid Tumors

CT121

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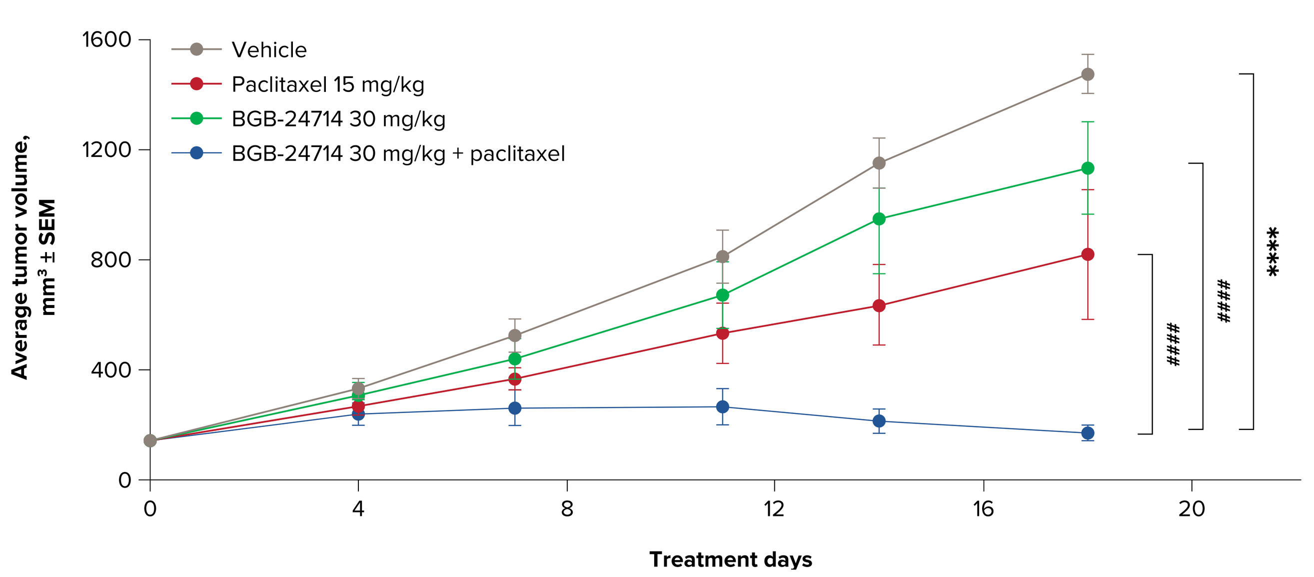
CONCLUSIONS

- Preclinical translational PD studies established cIAP1 degradation as a robust biomarker for PD characterization for BGB-24714, suggesting that rapid and durable cIAP1 degradation is required to achieve optimal antitumor efficacy
- Phase 1 clinical PD biomarker data confirmed that:
  - BGB-24714 triggers potent, rapid, and sustained on-target engagement in a dose-dependent manner
  - BGB-24714 induced dose-dependent apoptosis, consistent with its SMAC mimetic mechanism of action
  - Dose-dependent elevations in cytokines and chemokines were observed, supporting robust downstream immune-inflammatory pathway activation, confirming PD activity beyond proximal target modulation at high dose levels
- Taken together, these translational and clinical PD results substantiate the on-mechanism biological activity of BGB-24714 in patients with solid tumors

INTRODUCTION

- Inhibitor of apoptosis proteins (IAPs) are a family of anti-apoptotic proteins that suppress programmed cell death and are frequently overexpressed in cancer, contributing to tumor survival, drug resistance, and poor prognosis. Inhibition of IAPs restores apoptotic sensitivity and activates the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, leading to induction of inflammatory cytokines and chemokines
- Second mitochondrial-derived activator of caspases (SMACs), when released from mitochondria, naturally antagonize IAPs. As such, SMAC mimetics represent an attractive target for therapeutic intervention
- BGB-24714 is a potent and selective SMAC mimetic that binds and inhibits IAPs, demonstrating robust antitumor activity across multiple xenograft models (**Figure 1**)[1]

Figure 1. BGB-24714 demonstrated synergized antitumor activity in the HCC1806 (TNBC) xenograft model when used in combination with paclitaxel[1]



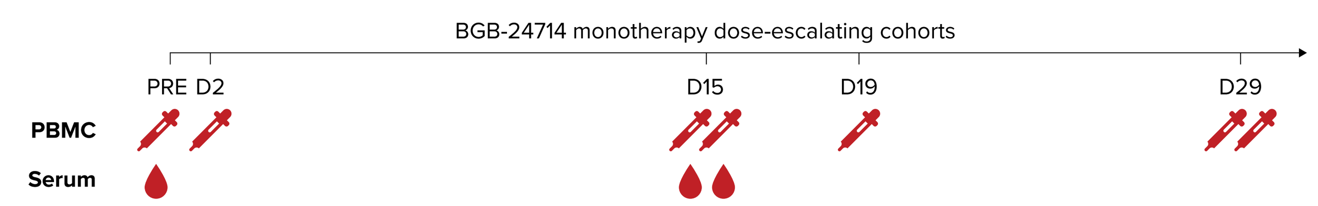
****P<.0001 versus vehicle group using ANOVA analysis with Dunnett's multiple comparison test. ####P<.0001 versus single treatment group assessed by the EOHSA test.
Abbreviations: ANOVA, analysis of variance; EOHSA, excess over highest single agent; SEM, standard error of the mean; TNBC, triple-negative breast cancer.

- BGB-24714 has been clinically evaluated in a first-in-human phase 1 study in patients with advanced or metastatic solid tumors (NCT05381909)
- We present here the first translational pharmacodynamic (PD) evaluation of BGB-24714 monotherapy in patients with solid tumors; clinical safety and efficacy outcomes are reported separately (Poster CT120)[2]

METHODS

- PD biomarkers were developed and validated in human breast cancer xenograft models to assess target engagement and downstream pathway modulation
- In the monotherapy dose-escalation cohorts of the BGB-24714 first-in-human study, target engagement PD markers such as cellular IAP1 (cIAP1) levels in peripheral blood mononuclear cells (PBMCs), circulating markers of apoptosis such as caspase-cleaved cytokeratin-18 (ccCK18), and inflammatory signaling markers such as cytokine/chemokine profiles were assessed in central laboratories according to the schedule in **Figure 2**

Figure 2. Blood-sampling schedule in the phase 1 first-in-human trial



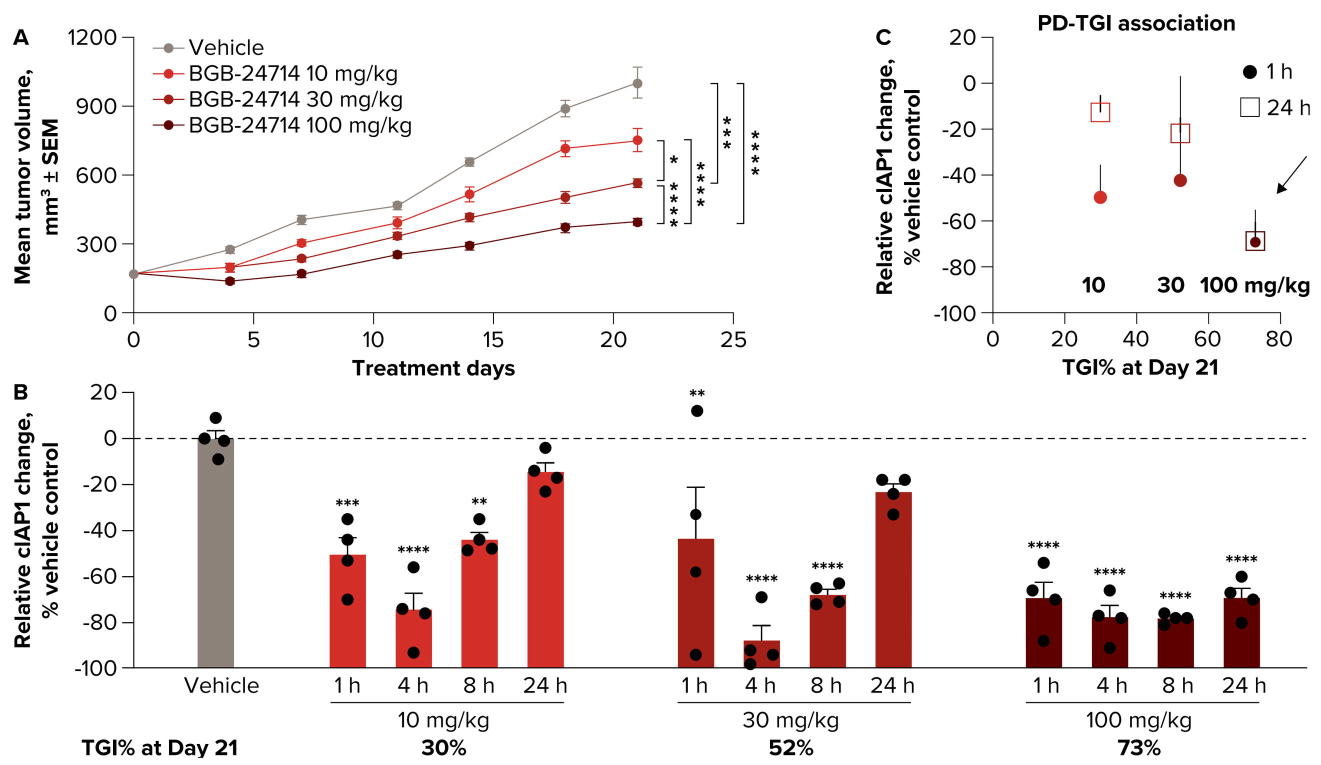
Abbreviations: D, day; PRE, pre-dose of D1.

RESULTS

Preclinical PD and Antitumor Activity Association

- BGB-24714 demonstrated dose-dependent antitumor activity in a human breast cancer xenograft model (**Figure 3**)
- The dose-dependent antitumor activity was accompanied by rapid and sustained degradation of cIAP1, with maximal effects at 100 mg/kg
- cIAP1 inhibition was observed within 1 hour post-dose and persisted for at least 24 hours at 100 mg/kg

Figure 3.

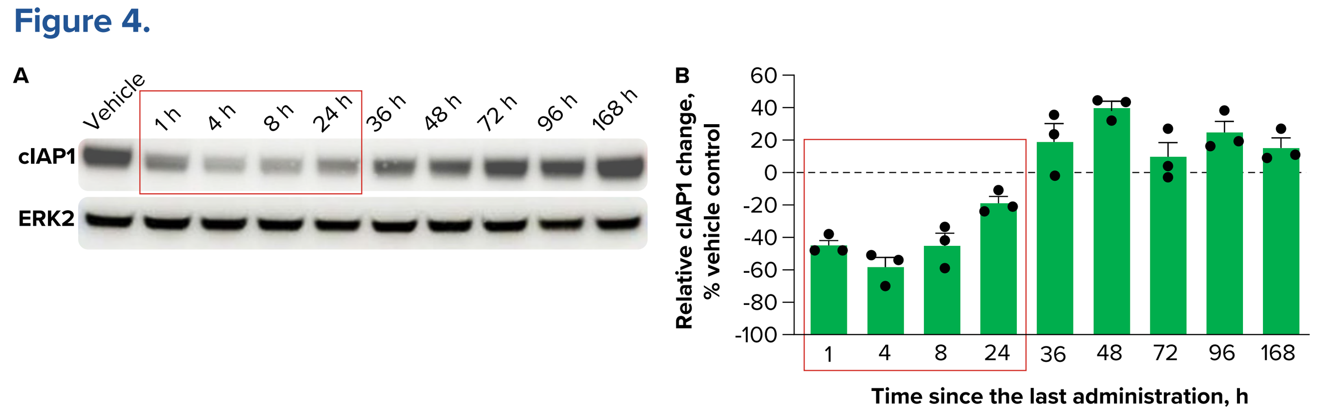


(A) BGB-24714 was administered at 10, 30, or 100 mg/kg for 21 days. TGI was measured at the end of study.
(B) PDs were evaluated after a single dose of BGB-24714. Protein levels of cIAP1 in the tumor tissue were determined using an MSD assay.
(C) Comparison of cIAP1 changes at 1 h and 24 h with TGI% at Day 21.
*P<.05, **P<.01, ***P<.001, ****P<.0001 versus vehicle control using ANOVA analysis with Dunnett's multiple comparison test.
Abbreviations: h, hour; MSD, Meso Scale Discovery; TGI, tumor growth inhibition.

Preclinical cIAP1 Degradation Kinetics

- Similar levels and kinetics of cIAP1 degradation were observed in PBMCs (**Figure 4A**) and tumor tissue (**Figure 4B**) in mice at a clinically relevant dose

Figure 4.



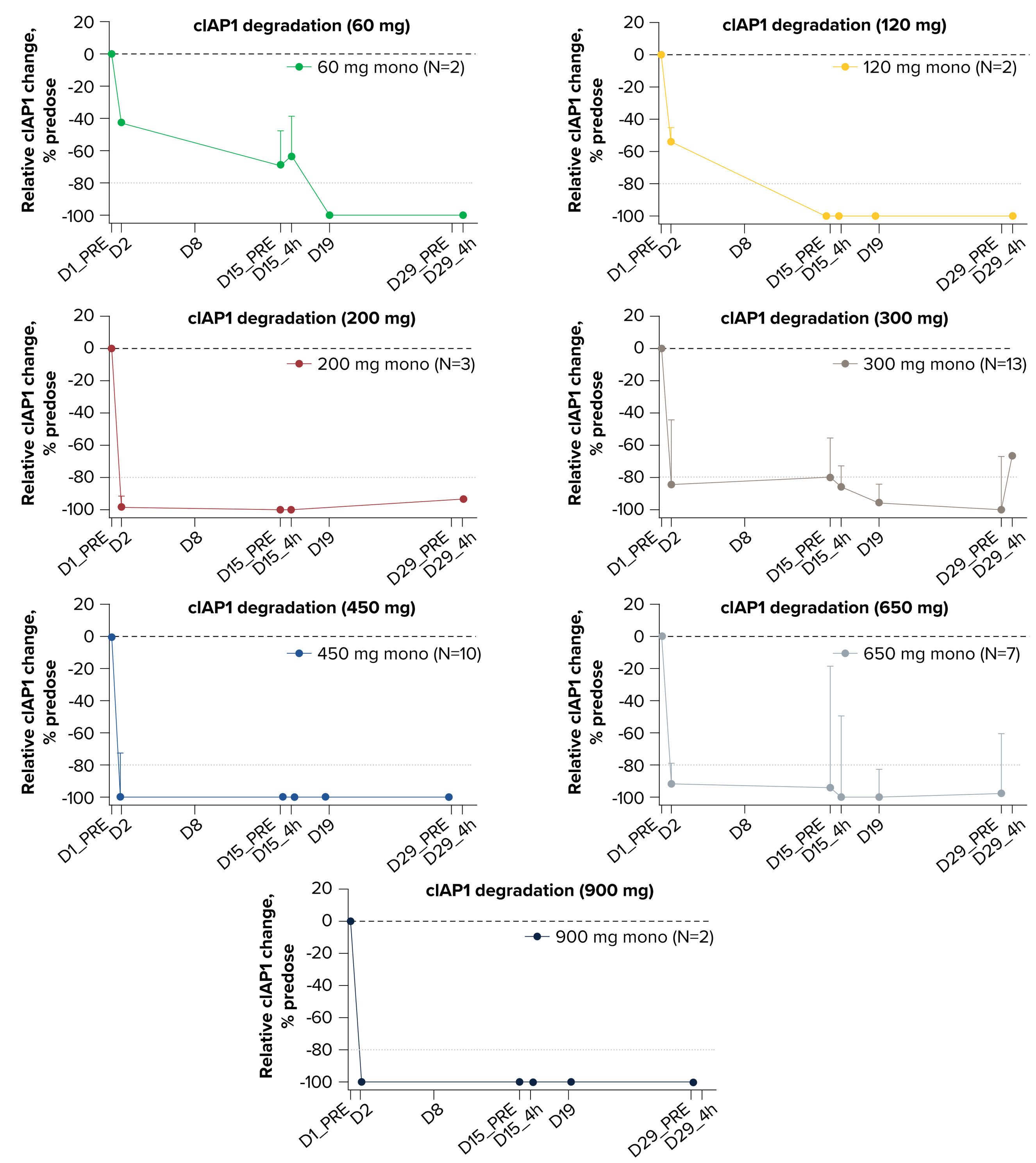
cIAP1 levels were evaluated in a human breast cancer xenograft model after single dose of BGB-24714.
(A) Peripheral cIAP1 levels in PBMCs were detected by western blot.
(B) cIAP1 levels in the tumor tissue were determined using an MSD assay.

Clinical PD

Effect of cIAP Degradation

- BGB-24714 induced rapid, sustained, and dose-dependent cIAP1 degradation across monotherapy dose-escalation cohorts (**Figure 5**)
- Approximately 50% degradation was observed on Day 2 at the 60 mg dose, and near complete cIAP1 degradation was achieved by Day 2 and maintained thereafter at doses ≥200 mg

Figure 5.

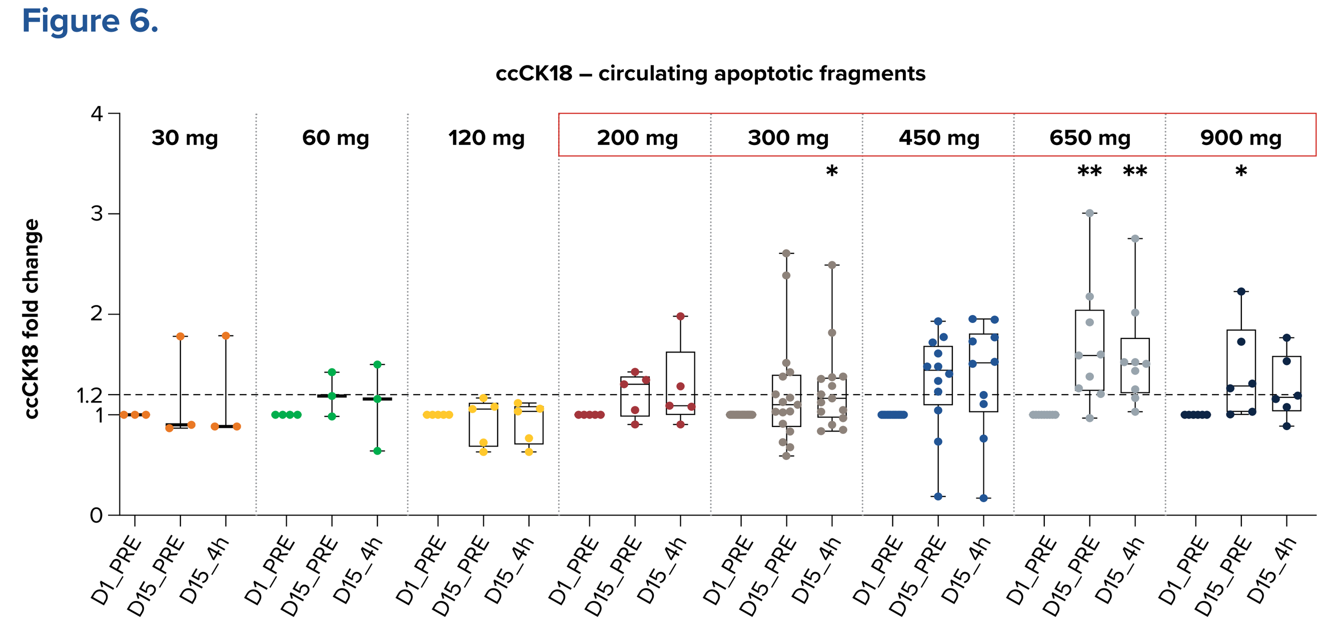


Median ± interquartile range of cIAP1 level measured in peripheral PBMC.

Effect on circulation marker of apoptosis (ccCK18)

- BGB-24714 induced a dose-dependent release in circulating ccCK18 at Day 15, indicative of apoptosis induction (**Figure 6**)
- A trend toward higher level of ccCK18 was observed at doses ≥200 mg BGB-24714

Figure 6.

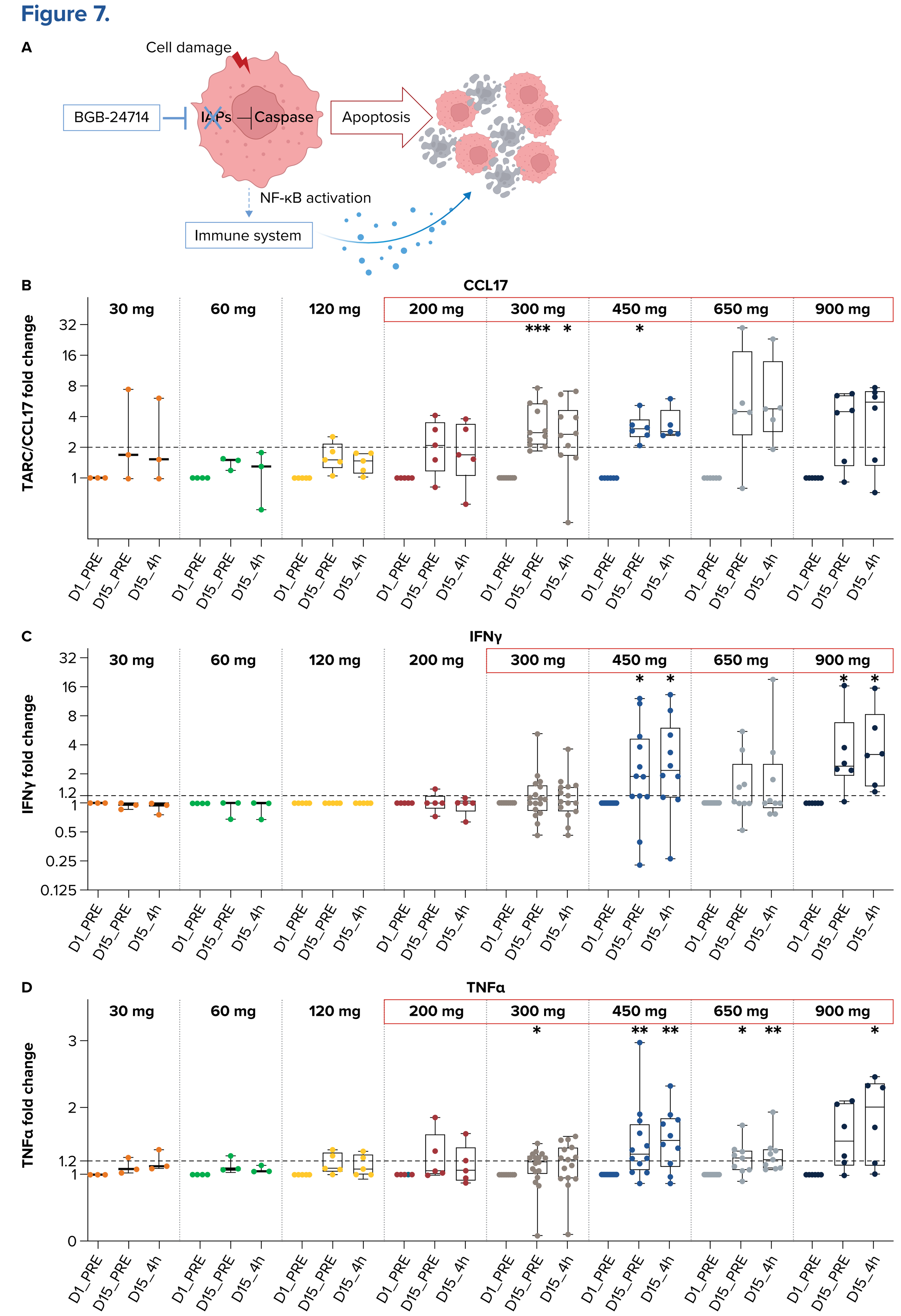


*P<.05, **P<.01 versus predose on D1 using paired samples Wilcoxon test.

Downstream Regulation on Immune-Inflammatory Modulation

- In addition to apoptosis sensitization, inhibition of IAPs leads to activation of the NF-κB pathway, and subsequently to increased production of inflammatory chemokines and cytokines (**Figure 7**)
- Dose-dependent elevations in circulating CCL17, interferon gamma (IFNγ), and tumor necrosis factor alpha (TNFα) were detected at Day 15 from doses of 200 mg or 300 mg, with a more pronounced trend at 450 mg and above, consistent with NF-κB pathway activation

Figure 7.



*P<.05, **P<.01, ***P<.001 versus predose on D1 using paired samples Wilcoxon test.

REFERENCES

1. Li J, et al. *Cancer Res.* 2023;83:Abstract nr 6158.
2. Varkaris A, et al. *Cancer Res.* 2026;AACR 2026 Poster CT120.

DISCLOSURES

FD: Employment: BeOne Medicines, Ltd.

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