

Efficacy of MDX-124, a novel anti-annexin-A1 antibody, in preclinical models of pancreatic cancer

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BACKGROUND

Annexin-A1 (ANXA1) is secreted in response to several physiological stimuli where it activates formyl peptide receptors (FPR1/2) triggering multiple oncogenic processes. High ANXA1 expression in pancreatic cancer patients is associated with poor overall survival¹, and influences cancer progression², drug sensitivity³, migration and invasion⁴. MDX-124 is a novel humanized antibody targeting ANXA1 and we have previously presented data demonstrating its significant anti-proliferative activity. Here we present further data showing the efficacy of MDX-124 in several preclinical models of pancreatic cancer.

METHODS

Cell Cycle Analysis: MIA PaCa-2 cells (1x10⁶) incubated for 24 h with MDX-124 (10 μ M). Cells harvested and labeled with Cytophase violet dye (8 μ M) before incubation at 37 °C for 30 min. Flow cytometry was conducted using a CytoFLEX LX (Beckman Coulter) and analyzed with FlowJo™ (BD Life Sciences) to determine percentage of cells in each phase of cell cycle (G1, S and G2).

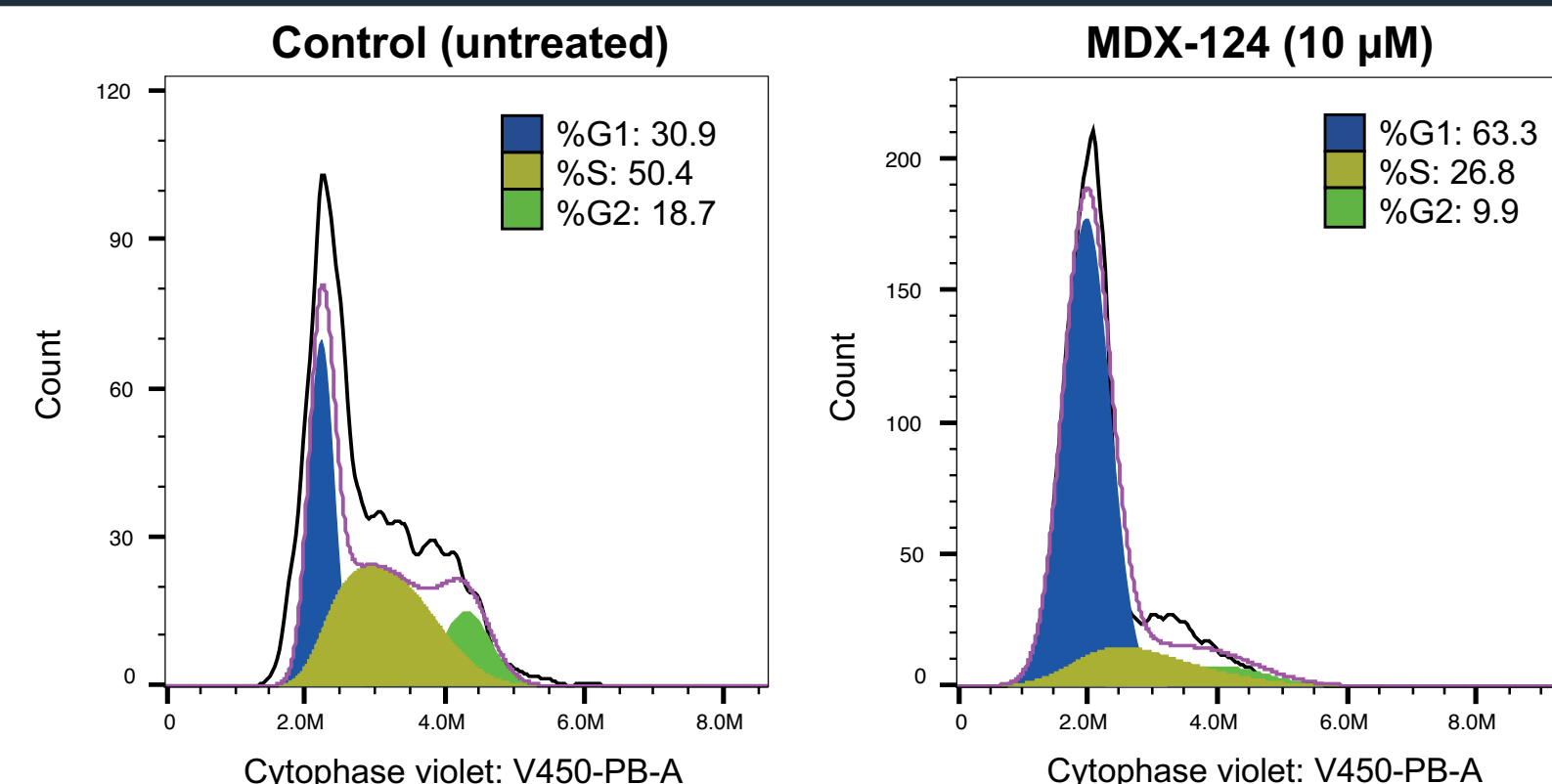
Cell Viability: MIA PaCa-2 and PANC-1 cells (1x10⁵) incubated for 72 h with IgG isotype control (0-10 μ M), MDX-124 (0-10 μ M), MDX-124 + IC₅₀ 5-FU (100 μ M) or IC₅₀ gemcitabine (20 μ M). Cell viability was measured via MTT assay. Statistical significance was calculated using an unpaired t-test (GraphPad Prism 9.0), where **p<0.01 and ****p<0.0001 (MDX-124 vs MDX-124 + 5-FU or gemcitabine) or °p<0.05, °°p<0.01 and °°°p<0.0001 (MDX-124 vs IgG isotype control).

Migration: MIA PaCa-2 and BxPC-3 cells (1x10⁶) pre-treated with MDX-124 (0 μ M – 50 μ M) for 1 h and transferred into 8 μ m pore transwell plates for 24 h incubation. Migrated and non-migrated cells were harvested and counted using flow cytometry (CytoFLEX). Statistical significance was calculated using a 2-way ANOVA with Tukey's multiple comparison correction (GraphPad Prism 9.0), where *p<0.05 and ****p<0.0001 (MDX-124 vs untreated control).

In-vivo Efficacy Study: C57Bl/6 mice (n = 9) inoculated orthotopically with FC124^{luc/zsGreen} (KPC-derived) pancreatic cancer cells (1x10⁶) and randomized to treatment groups after 7 days. Mice treated via i.p injection with isotype control (IgG2b) or a murine analog of MDX-124 (MDX-001) at 10 mg/kg, BIW until day 30. Incidence and burden of lung metastases were measured via bioluminescent imaging (BLI). Necrosis of primary pancreatic tumors was assessed by H&E staining and analyzed using QuPath™.

RESULTS

Figure 1. Incubation of MDX-124 with MIA PaCa-2 cells significantly decreased the proportion of cells in S-phase and increased cells in G1 phase versus untreated controls in a dose-dependent manner. This is consistent with an MDX-124 mediated increase in cell cycle arrest.



KEY FINDINGS

In preclinical models of pancreatic cancer MDX-124:

- Significantly reduced cancer cell proliferation via cell cycle arrest
- Demonstrated strong synergy with 5-FU and gemcitabine
- Significantly decreased cancer cell migration
- Reduced the incidence and burden of lung metastases
- Increased primary tumor necrosis

Medannex will generate initial clinical data in 2022 from a First-in-Human study evaluating MDX-124 in solid malignancies, including pancreatic cancer.

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RESULTS (Continued)

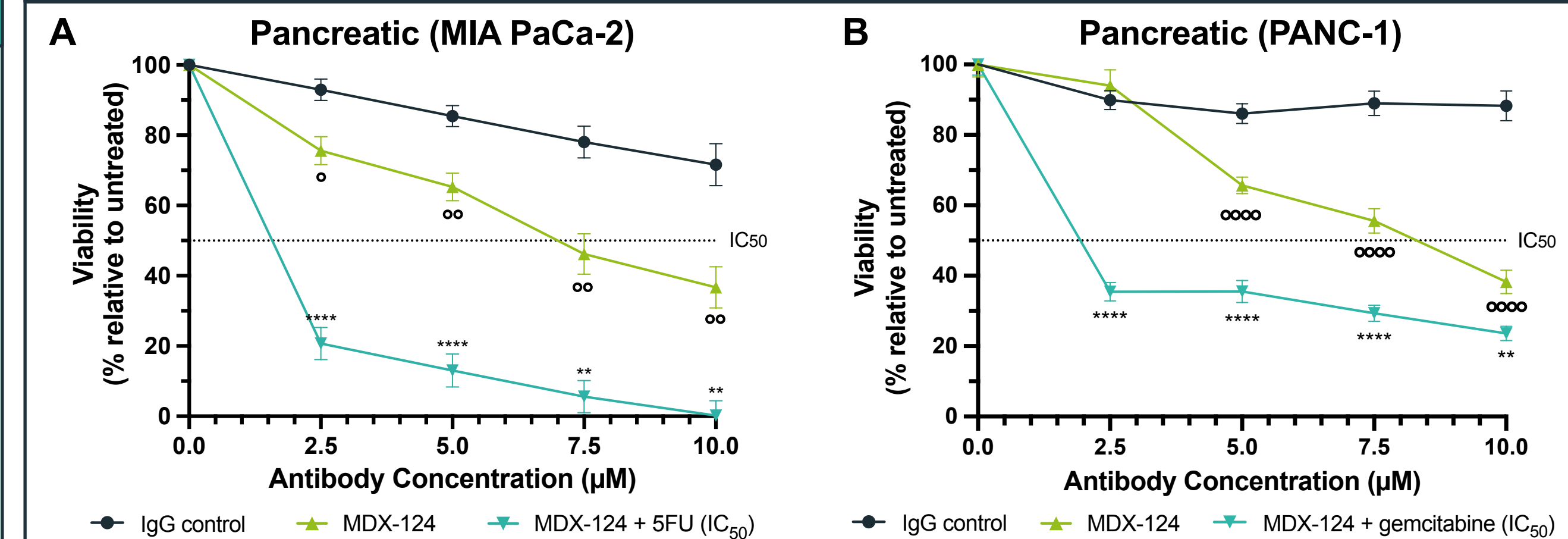


Figure 2. MIA PaCa-2 and PANC-1 cell viability was significantly reduced after incubation with MDX-124 alone versus an IgG isotype control. Strong synergistic activity observed when MDX-124 was combined with (A) 5-FU or (B) gemcitabine.

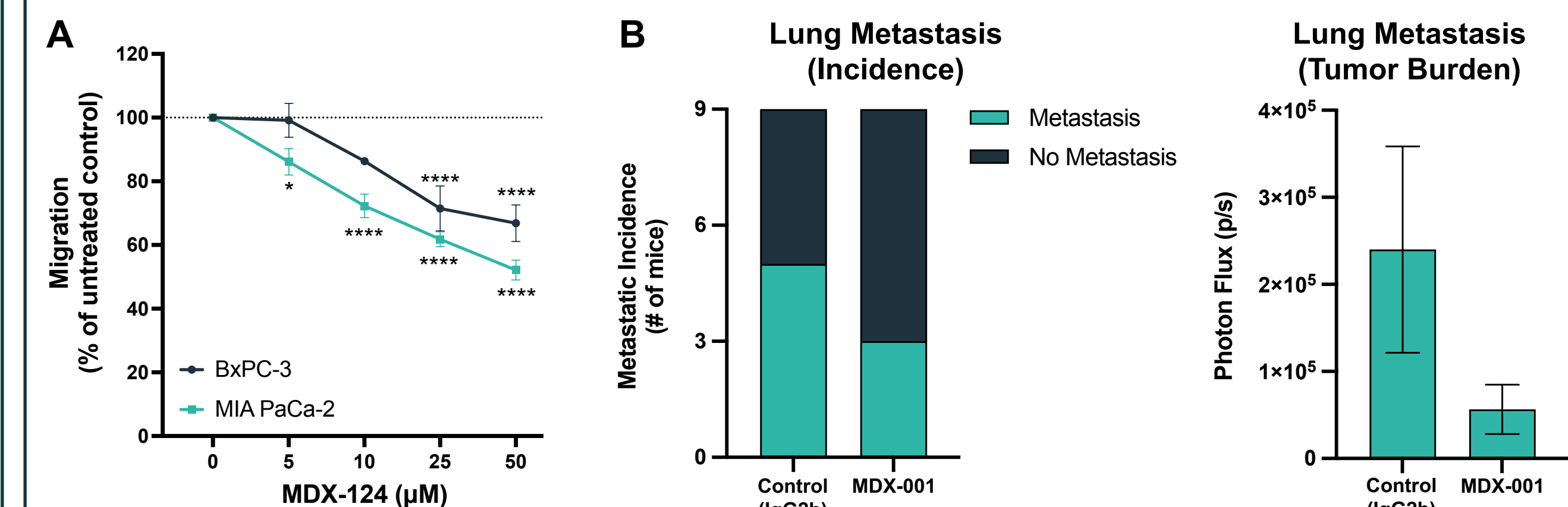


Figure 3. (A) MDX-124 significantly decreased MIA PaCa-2 and BxPC-3 cell migration versus untreated control cells. (B) The murine analog of MDX-124 (MDX-001) reduced both the incidence and tumor burden of FC124^{luc/zsGreen} lung metastases.

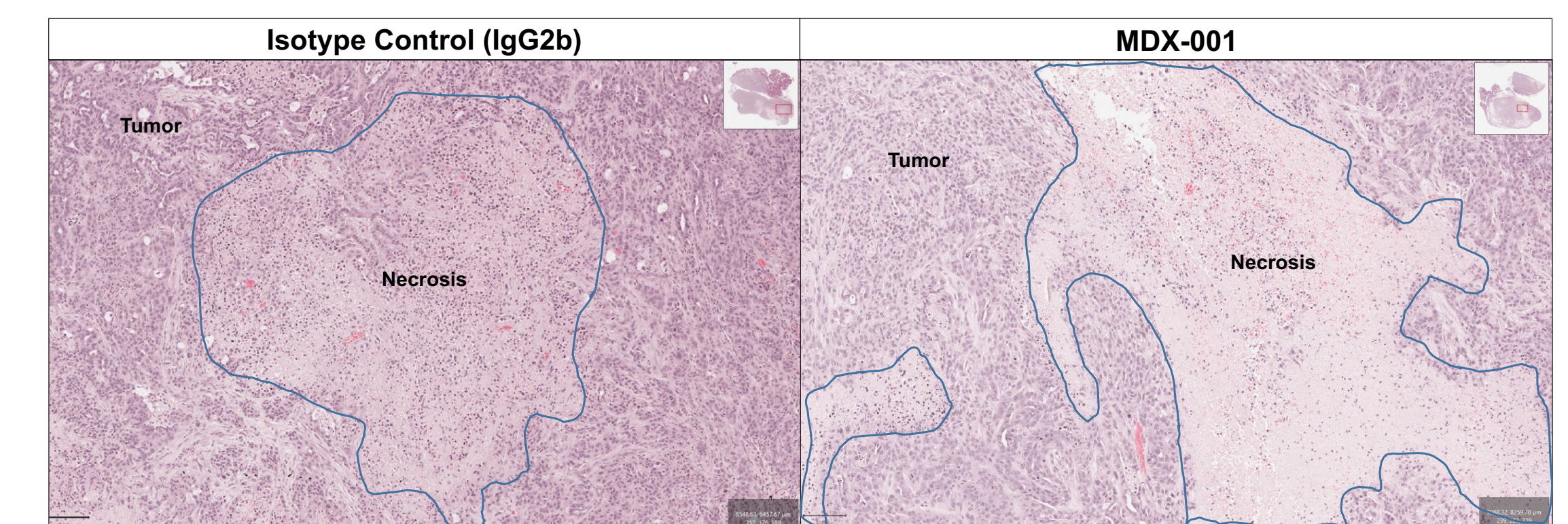


Figure 4. The murine analog of MDX-124 (MDX-001) increased FC124^{luc/zsGreen} primary tumor necrosis versus isotype control treated mice.

References:

(1) Chen et al., (2012). *Pacific J. Cancer Prev.*, **13**(9), 4707–4712. (2) Novizio et al., (2021). *Int. J. Mol. Sci.*, **22**(20), 11018. (3) Oshi et al., (2019). *Cells*, **10**(3), 1–16. (4) Belvedere et al., (2014). *BMC Cancer*, **14**(1), 1–15.

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