Radium-223 dichloride exhibits dual mode-of-action inhibiting both tumor and tumor-induced bone growth in two osteoblastic prostate cancer models.

**SUMMARY**

- **RESULTS**
  - **B** Radium-223 suppresses bone metabolic activity as evidenced by decreased number of osteoblasts and osteoclasts (Fig. 2D-E) and reduced level of bone formation marker PINP (mean ± SD) reflecting new bone formation rate in mice bearing prostate cancer models.
  - **C** Relative necrotic tumor area (%): The percentage of necrotic tissue was assessed in LuCaP 58 (Ra-223) and LNCaP (Vehicle) tumors using H&E staining and ImageJ software. The necrotic area was quantified as the percentage of darkly stained tissue in each tumor section. The crosses indicate mean values, *p* < 0.05, **p** < 0.01, ***p* < 0.001, a = p < 0.1, ns = not significant.
  - **D** Total bone area (mm²): The total bone area was measured in the intra-tumoral bone matrix using image analysis software (ImageJ). The bone area was determined from the tumor sections stained with hematoxylin and eosin (H&E). The bone area was quantified as the percentage of the total area occupied by bone tissue. The crosses indicate mean values, *p* < 0.05, **p** < 0.01, ***p* < 0.001, a = p < 0.1, ns = not significant.
  - **E** PinP level: The PINP level was measured in the serum of mice bearing prostate cancer models. The PINP level was determined using ELISA. The crosses indicate mean values, *p* < 0.05, **p** < 0.01, ***p* < 0.001, a = p < 0.1, ns = not significant.
  - **F** Visceral metastases: The number of visceral metastases was assessed in mice bearing prostate cancer models. The visceral metastases were quantified as the number of metastatic nodules in the liver, lungs, and other organs. The crosses indicate mean values, *p* < 0.05, **p** < 0.01, ***p* < 0.001, a = p < 0.1, ns = not significant.

- **MODE OF ACTION**
  - **A** Visceral metastases: The number of visceral metastases was assessed in mice bearing prostate cancer models. The visceral metastases were quantified as the number of metastatic nodules in the liver, lungs, and other organs. The crosses indicate mean values, *p* < 0.05, **p** < 0.01, ***p* < 0.001, a = p < 0.1, ns = not significant.
  - **B** DNA double-strand breaks in tumor cells: The number of DNA double-strand breaks was assessed in tumor cells using histological analysis. The DNA double-strand breaks were quantified as the number of lesions per cell. The crosses indicate mean values, *p* < 0.05, **p** < 0.01, ***p* < 0.001, a = p < 0.1, ns = not significant.
  - **C** Relative necrotic tumor area (%): The percentage of necrotic tissue was assessed in LuCaP 58 (Ra-223) and LNCaP (Vehicle) tumors using H&E staining and ImageJ software. The necrotic area was quantified as the percentage of darkly stained tissue in each tumor section. The crosses indicate mean values, *p* < 0.05, **p** < 0.01, ***p* < 0.001, a = p < 0.1, ns = not significant.

- **CONCLUSIONS**
  - Radium-223 therapy exhibits a dual mode-of-action that impacts on tumor growth and on tumor-induced bone reaction, both important players in the destructive vicious cycle of osteoblastic bone metastasis in prostate cancer (Fig. 6).
  - Our findings confirm the previously reported beneficial effects of Radium-223 and strongly support further development of Radium-223 for the treatment of patients with prostate cancer.

**REFERENCES**


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**BIODISTRIBUTION**

- **A** Radium-223 inhibits disease progression (Fig. 1C-D). Radium-223 suppresses bone metabolic activity as evidenced by decreased number of osteoblasts and osteoclasts (Fig. 2D-E) and reduced level of bone formation marker PINP (Fig. 5).

- **B** Radium-223 treatment results in lower PSA levels (Fig. 3A). Radium-223 therapy demonstrates a significant reduction in PSA levels compared to the control group (Fig. 3B). The crosses indicate mean values, *p* < 0.05, **p** < 0.01, ***p* < 0.001, a = p < 0.1, ns = not significant.

- **C** Relative necrotic tumor area (%): The percentage of necrotic tissue was assessed in LuCaP 58 (Ra-223) and LNCaP (Vehicle) tumors using H&E staining and ImageJ software. The necrotic area was quantified as the percentage of darkly stained tissue in each tumor section. The crosses indicate mean values, *p* < 0.05, **p** < 0.01, ***p* < 0.001, a = p < 0.1, ns = not significant.