The aim of this study was to deepen our understanding of the ATRi BAY 1895344 and Ra-223 combination. We have previously reported that combination therapy with the ATRi BAY 1895344 and Ra-223 showed synergistic anti-tumor efficacy in intratibial LNCaP xenograft models in mice.2 The ataxia telangiectasia and Rad3-related (ATR) kinase plays a central role in the DNA damage response and the ATRi BAY 1895344 in combination with Ra-223 shows anti-tumor efficacy with doses decreasing the number of osteoclasts.3 In a mouse model of osteolytic breast cancer bone metastasis, Ra-223 reduced the development of osteoblastic lesions and improved survival by inducing DNA double strand breaks in tumor cells and by decreasing the number of osteoclasts.2

The ATRi BAY 1895344 in combination with Ra-223 reduces the development of osteoblastic lesions and improves survival by inducing DNA double strand breaks in tumor cells and by decreasing the number of osteoclasts.2

The highest anti-tumor efficacy with BAY 1895344 and Ra-223 combination was achieved with 20 mg/kg BAY 1895344 administered once daily for 2 days on/5 days off and with a 40 mg/kg dose administered once daily for 1 day on/6 days off. BAY 1895344 in combination with Ra-223 shows anti-tumor efficacy with doses decreasing the number of osteoclasts.

In a mouse model of osteolytic breast cancer bone metastasis, Ra-223 reduced the development of osteoblastic lesions and improved survival by inducing DNA double strand breaks in tumor cells and by decreasing the number of osteoclasts.2

The ATRi BAY 1895344 in combination with Ra-223 shows synergistic anti-tumor efficacy when BAY 1895344 treatment starts 24 h after Ra-223 administration.

The in vivo anti-tumor efficacy of different doses of BAY 1895344 in combination with Ra-223 as determined by the number of foci in LNCaP tumor-bearing bone compared to respective monotherapies. * P < 0.05 vs vehicle; # P < 0.05 vs Ra-223 (one-way ANOVA on ranks followed by Dunnett's test for multiple comparisons).

The ATRi BAY 1895344 in combination with Ra-223 increases DNA damage in tumor cells in the LNCaP mCRPC model. BAY 1895344 in combination with Ra-223 showed an enhanced effect on DNA damage induction and toxicity, as indicated by an increased level of γH2AX foci in LNCaP tumor-bearing bone compared to respective monotherapies.

Synergistic in vivo activity of the ATR inhibitor BAY 1895344 in combination with the targeted alpha therapy radium-223 dichloride in a preclinical tumor model mimicking bone metastatic castration-resistant prostate cancer (mCRPC)

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