Combination of PI3K inhibitor BAY 1082439 with radium-223 is a promising treatment of cancer with bone metastases

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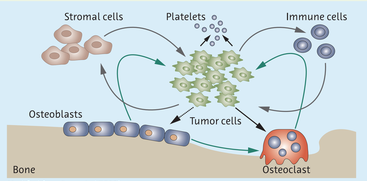
INTRODUCTION

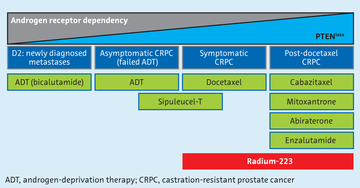
- About 80% of patients with advanced prostate, breast, and lung cancer develop bone metastases, which cause significant morbidity including chronic pain and pathological fractures
- Patients with bone metastases have a poor prognosis, and currently there is no curative treatment due to the unique biological micro-environments of bone where a wide range of growth factors promote tumor cell survival and tumor cells stimulate bone remodeling (Figure 1)[1]



Modified from Suva et al 2011[1]

Figure 1. Interactions between tumor cells, bone marrow components, and resident bone cells result in the inappropriate bone formation and bone resorption characteristic of bone metastasis diseases

- Radium-223 dichloride (radium-223) is a novel therapy which selectively targets bone and kills metastatic cancer cells by the emission of alpha particles[2] (Figure 2). Radium-223 was recently approved for the treatment of castration-resistant prostate cancer with bone metastases
- Activation of PI3K (e.g. PTEN-loss, membrane receptor activation) plays an important role in cancer cell proliferation, survival, and metastasis. PI3K also mediates critical signaling pathways involving tumor and stromal cell interactions, including cancer-induced bone turnover and osteolysis
- BAY 1082439 is a highly selective and potent PI3K inhibitor with balanced activity against PI3Kα and PI3Kβ isoforms, and is currently being evaluated in a Phase I clinical trial[3] (ClinicalTrials.gov identifier NCT01728311) (Table 1)



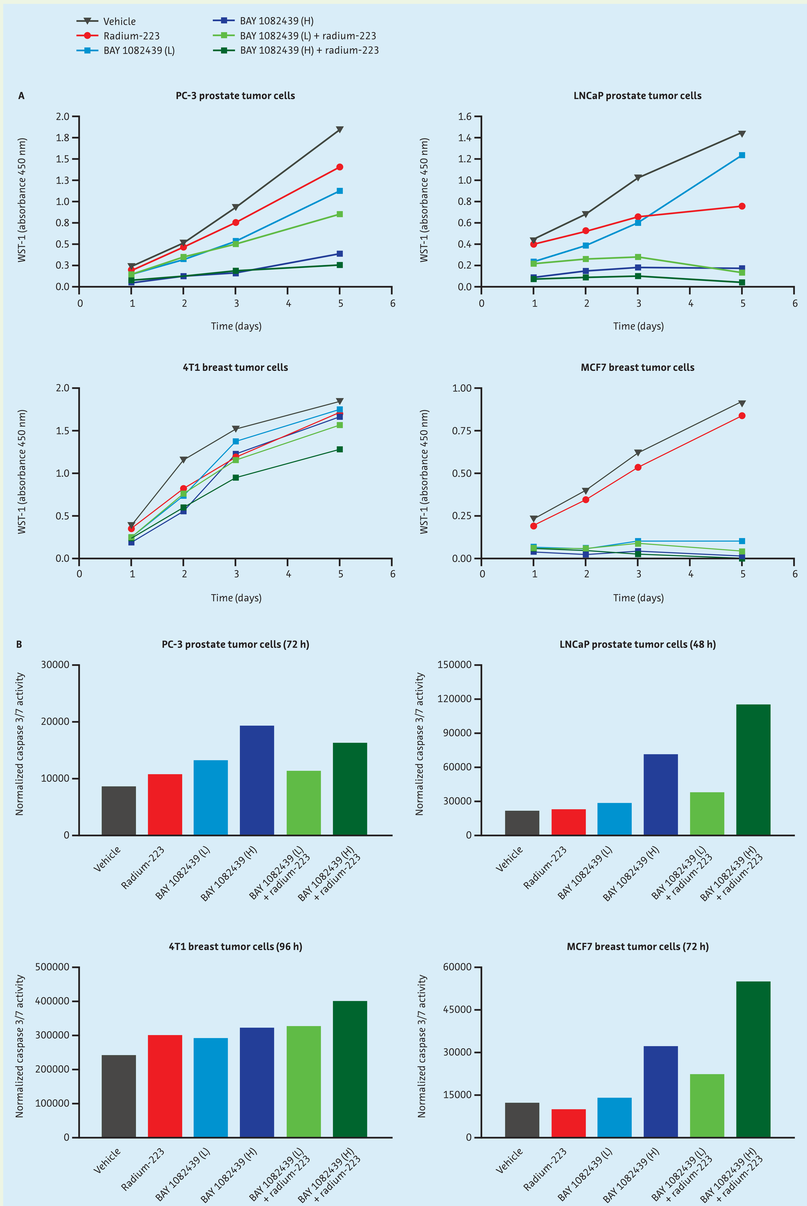
ADT, androgen-deprivation therapy; CRPC, castration-resistant prostate cancer

Figure 2. Approved therapies for the treatment of prostate cancer

Table 1. Pharmacological profile of PI3Kα/β balanced inhibitor BAY 1082439

Biochemical activity	**IC_{50} (nM)**
PI3Kα	4.9
PI3Kβ	15.0
PI3Kγ	51.0
PI3Kδ	1.0
Inhibition of cellular p-AKT	**IC_{50} (nM)**
KPL-4 (PIK3CA^{mut})	6.0
LNCaP (PTEN^{del})	12.5
MCF10A (PIK3CA^{mut})	23.6
MCF10A (PTEN^{del})	22.6
Tumor cell proliferation	**IC_{50} (nM)**
KPL-4 (PIK3CA^{mut})	52.0
LNCaP (PTEN^{del})	134.0

In vitro assessment of BAY 1082439



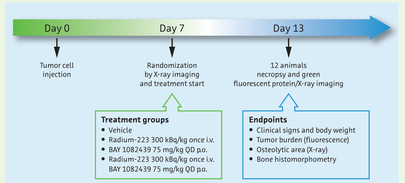
(A) Effects on tumor cell growth. (B) Effects on apoptosis induction
The effects on cell proliferation were studied using a WST-1-based proliferation assay on days 1, 2, 3, and 5. The effects on apoptosis were studied by measuring caspase 3/7 activity on the indicated day. Caspase 3/7 activity was normalized to the value obtained with the WST-1 assay in the parallel plates. The following drug concentrations were used: BAY 1082439 (H) = 5000 nM; BAY 1082439 (L) = 250 nM for MCF7 and LNCaP cells and 500 nM for 4T1 and PC-3 cells; radium-223 = 1600 Bq/mL

Figure 3. *In vitro* anti-tumor effects of BAY 1082439 and radium-223 as single agents and in combination

RESULTS

- BAY 1082439 and radium-223 showed additive to synergistic direct anti-proliferative activity in 4T1 and PC-3 hormone-independent breast and prostate tumor cell lines (Figure 3A)
- They also showed pronounced synergistic effects on apoptosis induction in hormone-dependent MCF7 and LNCaP cell lines *in vitro* (Figure 3B)

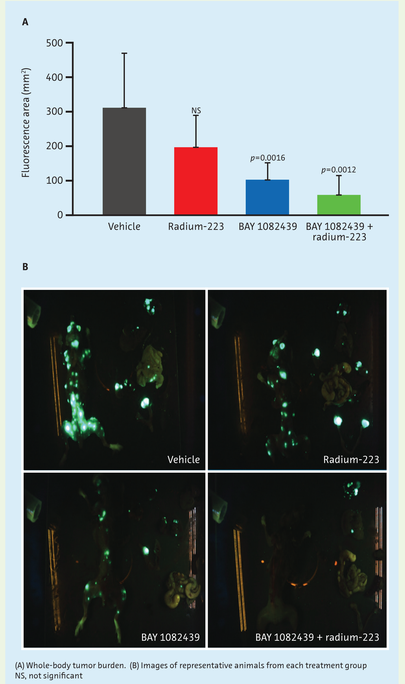
In vivo assessment of BAY 1082439



Intracardiac inoculation of 4T1-GFP breast cancer cells was on day 0. Osteolytic lesions and whole-body tumor burden were measured by X-ray and fluorescence imaging. Body weight was measured 3 times a week
QD, once daily

Figure 4. *In vivo* study design

- BAY 1082439 showed statistically significantly stronger reduction of whole-body tumor burden compared with radium-223 alone (Figure 5)
- Synergistic combination of BAY 1082439 with radium-223 further reduced tumor burden from 37% to 16% and led to complete inhibition of tumor growth in bone marrow (Figure 5)



(A) Whole-body tumor burden. (B) Images of representative animals from each treatment group
NS, not significant

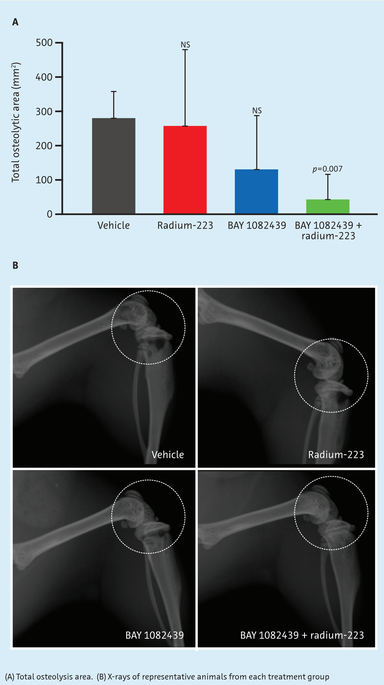
Figure 5. Inhibition of whole-body 4T1-GFP tumor burden in mice treated with BAY 1082439 and radium-223

- BAY 1082439 showed single-agent activity in inhibiting 4T1 tumor metastatic growth in soft tissues
- Synergistic effect of BAY 1082439 and radium-223 led to complete inhibition of tumor metastatic growth in kidneys and a significant reduction in metastatic growth in adrenal glands and ovaries (Table 2)

Table 2. Prevention of 4T1 tumor metastatic growth in soft tissues by BAY 1082439 and radium-223

		Treatment		
Organ	**Control**	**Radium-223**	**BAY 1082439**	**BAY 1082439 + radium-223**
Kidneys (%)	63	22	17	0
p value		**0.035**	**0.012**	**<0.001**
Adrenal glands (%)	88	94	61	43
p value		0.591	0.125	**0.019**
Ovaries (%)	81	94	56	29
p value		0.323	0.152	**0.009**

- BAY 1082439 as a single agent is active in reducing tumor-induced osteolysis measured by radiography (Figure 6)
- Strong synergy of BAY 1082439 in combination with radium-223 led to complete prevention of tumor-induced osteolysis (Figure 6)



(A) Total osteolysis area. (B) X-rays of representative animals from each treatment group

Figure 6. Inhibition of osteolysis by BAY 1082439 and radium-223 measured by radiography

- BAY 1082439 alone or in combination with radium-223 showed good tolerability, with no significant body weight loss compared with the vehicle group (Figure 7)

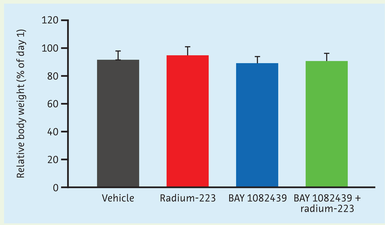


Figure 7. Tolerability assessment of BAY 1082439 and radium-223

CONCLUSIONS

- **BAY 1082439 and radium-223 showed additive to synergistic direct anti-proliferative activity and pronounced synergistic effects on apoptosis in breast and prostate tumor cell lines *in vitro***
- **BAY 1082439 significantly decreased whole-body tumor burden as a single agent, and even more effectively in combination with radium-223**
- **BAY 1082439 effectively inhibited tumor-induced osteolysis, measured by radiography, as a single agent and showed further synergistic effect in combination with radium-223**
- **BAY 1082439 decreased the frequency of soft-tissue metastases, which was even more pronounced when combined with radium-223**
- ***In vivo*, the combination of BAY 1082439 at the maximum tolerated dose and radium-223 at the efficacious dose was well tolerated**
- **In summary, our data indicate additive to synergistic effects of BAY 1082439 and radium-223 in inhibiting tumor cell proliferation, survival, total and bone marrow burden, and tumor-induced osteolysis. Hence, further clinical evaluation of this promising combination therapy for the treatment of cancers with bone metastases and alterations in the PI3K signaling pathway is warranted**

References

1. Suva LJ et al. *Nat Rev Endocrinol* 2011; 7: 208-218
2. Parker C et al. *N Engl J Med* 2013; 369: 213-223
3. Liu N et al. Poster 2799 presented at AACR Annual Meeting, Chicago, Illinois, USA, March 31 - April 4, 2012

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