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Targeted alpha therapy with PSMA-TTC: Preclinical activity at different dosing schedules and total antibody doses in prostate cancer xenograft models

Targeted alpha therapy (TAT) agents deliver high linear energy transfer (LET) alpha-radiation selectively to tumors. The first TAT approved is radium-223 which prolongs overall survival in metastatic castration resistant prostate cancer (mCRPC) patients with symptomatic bone metastasis. The PSMA targeted thorium-227 conjugate PSMA-TTC represents another TAT approach in mCRPC. It consists of a fully human PSMA IgG antibody covalently linked to the chelator moiety (3,2 HOPO). This antibody-chelator conjugate is radiolabeled with thorium-227, which decays with a half-life of 18.7 days to radium-223 via alpha-particle emission. Anti-tumor activity of PSMA-TTC in cell line and patient derived prostate cancer xenograft models has been shown previously.

Here we describe the impact of different total antibody doses applied on tumor targeting and anti-tumor activity of PSMA-TTC in the prostate cancer xenograft models 22Rv1 and LNCap, which harbor moderate or high PSMA target levels, respectively. Additionally, anti-tumor activity was assessed at different dosing schedules, applying the same radioactivity dose as single bolus or multiple dosing at weekly or biweekly schedules.

At the thorium-227 dose of 500 kBq/kg, the anti-tumor activity of PSMA-TTC was comparable at total antibody doses ranging from 0.14 to 1.5 mg/kg; while a substantial decrease in anti-tumor activity was observed at 5 mg/kg. Additionally the efficacy of PSMA-TTC at total antibody doses of 0.43 and 1.5 mg/kg was not affected by pretreatement of the unlabeled antibody-conjugate 5 days before treatment with PSMA-TTC at equivalent total antibody doses. In the preclinical models, comparable anti-tumor efficacy was observed at a cumulative radioactivity dose of 500 kB/kg, irrespective of whether the drug was administered as single or multiple doses at weekly or biweekly schedules.

In summary, PSMA-TTC shows strong anti-tumor activity within a range of different total antibody doses and dosing schedules in preclinical prostate cancer models. These data warrant further clinical investigation of this targeted alpha agent.

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Bayer AG

Email Address

stefanie.hammer@bayer.com

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Primary authors: Dr ZITZMANN-KOLBE, Sabine (Bayer AG, Pharmaceuticals Division); Dr HAMMER, Stefanie (Bayer AG, Pharmaceuticals Division)

Co-authors: Dr LARSEN, Aasmund (BAYER AS); Dr CUTHBERTSON, Alan (Bayer AS); Mrs ELLINGSEN, Christine (Bayer AS); Dr GRANT, Derek (Bayer AS); Dr MUMBERG, Dominik (Bayer AG, Pharmaceuticals Division); Dr HENNEKES, Hartwig (Bayer AG, Pharmaceuticals Division); Dr KARLSSON, Jenny (Bayer AS); Dr RYAN, Olav B (Bayer AS); Dr VON AHSEN, Oliver (Bayer AG, Pharmaceuticals Division); Mr BJERKE, Roger M (Bayer AS); Dr HAGEMANN, Urs B (Bayer AG, Pharmaceuticals Division)

Presenter: Dr ZITZMANN-KOLBE, Sabine (Bayer AG, Pharmaceuticals Division)