Alpharadin (Radium-223) in Bone Metastatic Prostate Cancer
From Discovery to Drug

Skeletal metastases are present in >90% of patients with castrate resistant prostate cancer (CRPC). The pronounced bone-tropism in this cancer with less frequent visceral involvement and the sclerotic phenotype of the bone metastases provide the basis for bone-targeted radionuclide therapy. Based on experiences with beta-emitting variants of bone-seeking radiopharmaceuticals (BSR), we proposed; 13 years ago, the use of the alpha-emitting BSR ^{223}Ra in it's chloride formulation. The presentation will highlight aspects of the production technology (Bruland et al., 2006), some pre-clinical observations (Henriksen et al., 2002, 2003), but focus primarily on results from clinical trials; one phase-1, two randomized phase-2 and the recently completed pivotal phase-3 ALSYMPCA-trial.

In the phase-1 dose-escalation trial dose-limiting toxicity was not reached (Nilsson et al. 2005). In the subsequent phase-2 trial patients with CRPCand bone pain needing external-beam radiotherapy were assigned to four intravenous injections of ^{223}Ra (50 kBq/kg, 33 patients) or placebo (31 patients), given every 4 weeks (Nilsson et al., 2007). Primary endpoints were change in bone-alkaline phosphatase (ALP) concentration and time to skeletal-related events (SREs). Secondary endpoints included toxic effects, time to prostate-specific-antigen (PSA) progression, and overall survival. ^{223}Ra was well tolerated with minimum myelotoxicity, and had a significant effect on bone-ALP concentrations. No patient discontinued ^{223}Ra because of treatment toxicity. Median time to PSA progression was 26 weeks (16–39) versus 8 weeks (4–12) for ^{223}Ra versus placebo, respectively. Median overall survival was 65.3 weeks for ^{223}Ra and 46.4 weeks for placebo. The hazard ratio for overall survival, adjusted for baseline covariates was 2.12 (1.13–3.98, p=0.020, Cox regression). In another phase 2 dose-response study with ^{223}Ra treatment, pain response was seen in up to 71% of CRPC pts with painful bone metastases (Nilsson 2012). In the completed phase 3 ALSYMPCA study, which included 921 CRPC pts with bone metastases (^{223}Ra, n=614; placebo, n=307), ^{223}Ra significantly improved overall survival vs placebo (median 14.0 vs 11.2 mo; HR=0.695; *P*=0.002) and was well tolerated (preliminary reviewed in: Sartor 2013; now accepted for publication).

Selected references:

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