Translational Research of PT-112, a Clinical Agent in Advanced Phase I Development: Evident Bone Tropism, Synergy *In Vitro* with Bortezomib and Lenalidomide, and Potent Efficacy in the Vk*MYC Mouse Model of Multiple Myeloma

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Abstract #1797

Introduction

PT-112 is a first-in-class platinum-pyrophosphate agent under advanced Phase I development in solid tumors. PT-112 was rationally designed to circumvent the toxicity and mechanisms of resistance associated with conventional chemotherapy. In previous preclinical models using PT-112, multiple cell signaling effects have been observed: p16 mediated G1/S cell cycle arrest; MDM2/p53 expression modulation; extrinsic apoptosis initiation; and signals indicative of immunogenic cell death (Ames et al., Eur. J. Cancer 2016). In addition, the ongoing first-in-human PT-112-101 Phase I trial in solid tumors has demonstrated a positive therapeutic index, with a range of biological activity observed at well-tolerated dose levels and a lack of severe hematotoxicity (Karp et al., *J. Clin. Oncol.* 2017). Due to the pyrophosphate present in PT-112, we hypothesized that PT-112 should localize to bone tissue, and be efficacious against bone marrow malignancies such as multiple myeloma (MM). Biodistribution was measured via laser ablation inductively-coupled plasma mass spectrometry (LA-ICP-MS), along with translational experimentation in the orthotopic Vk*MYC mouse model of MM. In addition, an assessment of synergy was conducted *in vitro* in combination with standard of care (SoC) agents such as bortezomib (BOR) and lenalidomide (LEN).

Methods

Biodistribution: After a single dose with 90 mg/kg PT-112 (a dose both active and well-tolerated in mouse models and, when converted, human patients) or vehicle control via tail vein injection, mice were euthanized 45min or 3h post-dose and snap frozen. Slides were prepared and LA-ICP-MS was used to measure and image the presence and concentration of platinum (Pt) in full sagittal plane cross sections and in individual organs and tissues at higher spatial resolution.

In vivo: *De novo* Vk*MYC mice with established MM were treated with either 100 mg/kg PT-112 twice weekly (n=2) or 67 mg/kg (n=1) thrice weekly via intraperitoneal injection. In parallel experiments, mice engrafted with the BOR resistant Vk12598 transplantable line received vehicle (n=11) or PT-112 at 62.5 mg/kg (n=12) twice/week. Separately, mice engrafted with the multidrug resistant Vk12653 line were treated with vehicle (n=10) or PT-112 at 62.5 mg/kg (n=10). In all cases treatment duration was two weeks and M-spike levels were monitored during treatment and for several weeks after.

In vitro: Cell viability and IC50 values in MM1R and RPMI-8226 suspension cells were measured after treatment with PT-112, LEN, BOR, or PT-112-containing combinations thereof.

Results

Biodistribution Imaging

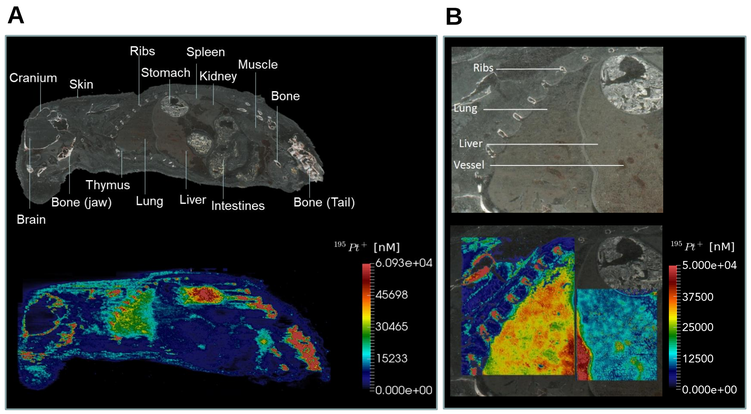

Figure 1. (A) Mouse whole-body and (B) thoracic optical image (top) and biodistribution of PT-112-derived Pt (bottom) at T=45min post dosing by LA-ICP-MS. Spatial resolutions for the whole-body, lung, and liver sections were 150µm, 50µm, and 40µm, respectively. PT-112 was detected in several different organs and tissues, such as the kidney, lung and liver, with particularly high concentrations (shown in red) found in a variety of bone tissue including the jaw, cranium, spine, ribs, leg and tail.

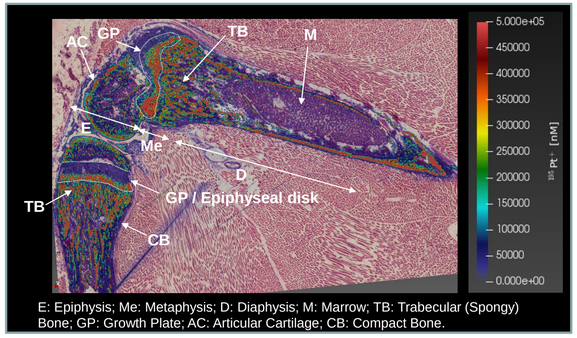

Figure 2. Distribution of PT-112-derived Pt in Femur (top) and Tibia (bottom) at T=3h post-dosing, assessed by LA-ICP-MS at 20 µm spatial resolution. PT-112 was highly concentrated in several areas, including the hypertrophic area of the growth plate (GP) and trabecular (TB) bone regions, and in the periphery of the calcified bone, generally associated with the localization of MM cells.

Activity in Predictive *in Vivo* Model

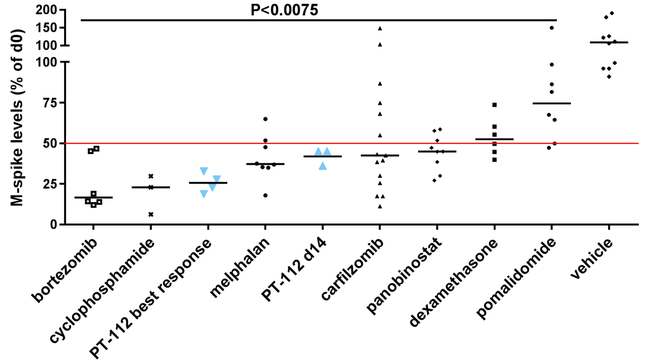

Figure 3. **PT-112 response in Vk*MYC MM mouse model.** PT-112 treatment induced a response in all of the *de novo* Vk*MYC mice with >50% reductions in M-spike at the 2-week time point, passing the statistically correlated activity threshold indicative of robust activity in human MM patients for agents tested in the model (Chesi et al., *Blood* 2012). At this point treatment was discontinued, and M-spike levels continued to decline for 1-2 weeks (see "PT-112 best response, above"), with the lowest observed M-spike at 19% of baseline 11 days after treatment discontinuation. These results were comparable or superior to those generated by treatment with approved MM SoC agents.

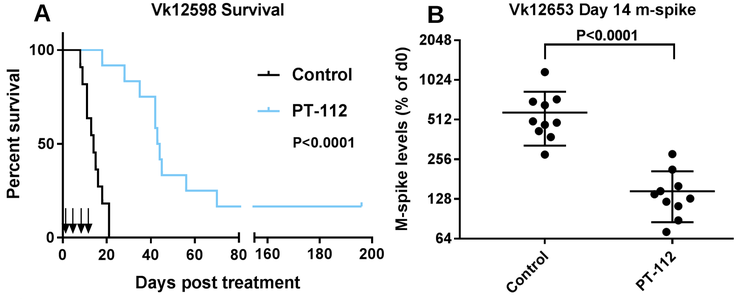

Figure 4. **PT-112 activity in transplant Vk*MYC models.** (A) Survival of mice transplanted with the BOR-resistant Vk12598 line. Arrows indicate PT-112 dosing days. Treated animals experienced a substantial survival benefit, with some durable complete responses lasting over six months. (B) M-spike response of mice transplanted with the multidrug-resistant Vk12653 line. PT-112 treatment resulted in a significant inhibition of M-spike in comparison to untreated control animals.

In Vitro Synergy with SoC

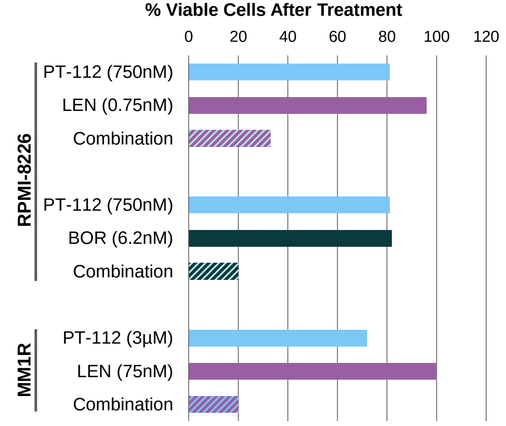

Figure 5. **Activity of PT-112-containing combinations in MM *in vitro* systems.** Combining PT-112 with LEN or BOR in the MM cell lines RPMI-8226 or dexamethason-resistant MM1R results in strong synergy. The most synergistic combinations of concentrations are shown.

Conclusions

Sophisticated biodistribution imaging techniques revealed the presence of PT-112 in several target tissues, with a demonstrably high accumulation in bone tissue. These results likely explain in part the strong efficacy observed in Vk*MYC mice. Given the predictive power of this model, the likelihood of PT-112 activity in human MM patients is high. Additionally, the potent synergy observed in *in vitro* systems provides encouraging evidence that PT-112 might combine well with SoC agents for the treatment of MM. Taken together, these data provide a strong rationale for the study of PT-112 as both a single agent and in combination in MM patients, with a further prospect for investigating the treatment of other hematological malignancies with PT-112.