AB Science: Development of masitinib, a novel tyrosine kinase inhibitor and immunotherapeutic, for the treatment of peripheral T-cell lymphoma

Presenting author*: Olivier Hermine MD, PhD

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* Olivier Hermine MD, PhD, (Institut IMAGINE, CNRS UMR 8147, Hôpital Necker, 149 - 161 rue de Sèvres, Paris, France). E-mail: ohermine@gmail.com.

Masitinib is an oral tyrosine kinase inhibitor that potently and selectively targets c-Kit and platelet-derived growth factor receptor (PDGFR). Studies in human T-cell lymphoma (TCL) have identified aberrant expression of PDGFR-alpha and that this kinase fosters peripheral TCL cell proliferation via an autocrine loop. Masitinib may therefore exert an antiproliferative and pro-apoptotic action on abnormal T-cells. Additionally, masitinib can elicit antitumor effects by acting on mast cells and macrophages. By inhibiting mast cells, masitinib reduces the release of pro-tumoral M2-polarizing cytokines as well as factors favoring metastasis and angiogenesis. Masitinib can also promote macrophage infiltration into tumors, inducing an anti-tumoral Th1 immune response.

Inhibition of cell proliferation was observed following single-agent masitinib treatment in the OSW canine TCL line, with an IC_{50} of 0.005 μM, suggesting that it could be used efficiently for the treatment of TCL. This hypothesis was substantiated via two separate independent studies, each comprised of 11 dogs with TCL. A first study reported an overall response rate (ORR) of 73%, including 3/11 dogs with complete response (CR) and 5/11 dogs with partial response (PR) after 3 months of treatment. A second study reported an ORR of 45%, including 2/11 dogs with CR and 3/11 dogs with PR after 3 months of treatment. Meta-analysis of these data (n=23) showed that masitinib treatment of canine TCL resulted in a CR in 6/23 dogs (26%) and in a PR 8/23 dogs (35%), resulting in an ORR of 61%. Naturally occurring tumors in dogs have more clinical and biological similarities to human cancers than any other animal cancer model, hence these data provide strong medical plausibility for masitinib in the treatment of human peripheral TCL.

The above *in vitro* and *in vivo* data led to initiation of a randomized, open-label, three-parallel group, phase 2 study to evaluate the combination of masitinib plus dexamethasone with or without gemcitabine in patients with relapsed or refractory peripheral TCL. A recent decision to accelerate to a phase 3 study was based on an observed survival benefit for masitinib treated patients when compared with the control arm, and an acceptable safety profile; passage to phase 3 was validated by the independent Data Safety Monitoring Board with data blinded to sponsor and investigator. Specifically, pooled data from all masitinib-treated patients in the phase 2 stage (n=34) estimated a median overall survival (OS) of 9.0 months, which compares favorably against the literature benchmark median OS of 5.5 months for documented chemotherapy in this indication.

This phase 3 study is currently open for patient recruitment in at least 14 countries and has OS as the primary endpoint. If successful, masitinib could provide a new treatment option in relapsed or refractory peripheral TCL, for which there remains an unmet medical need and no established 2nd line therapy.