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**MET Target Inhibition-Guided Efficacy in Preclinical Models**

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**INTRODUCTION**

A wide variety of drug efficacy for the multiple agents currently in clinical development targeting MET-driven cancers would be useful for the selection of optimal treatment options. Previously, we utilized selected MET pharmacometric (PD) assays to compare the time-course of phosphoMET (pMET) suppression for five MET inhibitors (ASCO 2012). Those agents included an active MET inhibition ( Foretinib), two MET inhibitors (otlinetib – Kinase inhibitor; AMG 232 – small molecule inhibitor), and two MET antibodies (XL880 and XL184). We have shown that each agent was able to reduce tumor and cell lines. Our results validated two important thresholds: 1) tumor drug levels > 90% suppression of pMET levels in tumor tissue and 2) tumor regression in tumor models. We also provided a direct link between a threshold MET suppression and tumor regression in vivo.

**RESULTS**

**Changes in intact MET levels in response to MET inhibitors**

Changes in intact MET levels after single dose treatment were measured by Bio-Plex ELISA. The inhibition of intact MET was dose dependent for all MET inhibitors. The most potent inhibitor was XL880 followed by EMD1214063. EMD1214063 showed >90% inhibition of intact MET in tumor tissue. All three MET inhibitors showed >90% inhibition of intact MET in tumor tissue at day 8 (Fig. 4).

**Summary of suppression of MET and signaling molecules involved in MET pathway**

**REFERENCES & ACKNOWLEDGMENTS**

**SUMMARY AND CONCLUSIONS**

This study provided a head to head comparison of intact MET inhibitors (XL880, IL108, EMD121463) at doses and schedules evaluated to produce equivalent suppression of pMET levels in tumors. A fourth MET inhibitor, AMG232, was excluded from this study because it failed to show pMET suppression in our preclinical studies (Srivastava et al., ASCO 2013). The absolute tumor levels of MET inhibitors required to achieve >90% suppression of pMET levels is in the range of 2–7 μg/mL. A higher tumor exposure for EMD121463 was targeted because we observed a normal in PD response at 10 μg/mL in tumor tissue. All three MET inhibitors showed >90% inhibition of pMET levels in tumor tissue at doses tested in this study.

Our data showed that all three MET inhibitors showed an 80–90% reduction in intact MET levels compared to placebo by >90% inhibition of pMET levels in tumor tissue. Our results validate two important thresholds: 1) tumor drug exposure required to achieve a defined MET suppression, and 2) MET suppression that achieves tumor regression. Thus, our data also provide a direct link between a threshold MET suppression and tumor regression in vivo.

Our data strongly support the use of the MET PD assays to guide drug design decisions. The development of a response-guided dosing strategy in vivo, using the MET response-guided dosing was demonstrated in achieving the desired efficacy in a lower dose for XL880 and EMD121463 than efficacy doses described previously.26-28 A limitation of our study is that we tested the single pMET suppression threshold of pMET in a model that could be sensitive to MET inhibitors. It remains to be seen if similar efficacy can be achieved at lower pMET suppression thresholds in vivo, where pMET suppression is much lower.