

The Pentarin Miniaturized Drug Conjugate PEN-221 Targets the Potent Cytotoxic DM1 to Somatostatin Receptor 2 Expressing Cancers

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Background: The selective targeting of potent therapeutics to cancer cells has shown promise in delivering patient benefit while limiting the exposure to and toxicity in normal tissues. Most attention has been given to antibody drug conjugates (ADCs) with a handful of new drug approvals and many molecules in clinical development. Despite long plasma half-lives, the size large of ADCs (150 kDa) is known to limit tumor exposure due to the slow penetration of solid tumor tissue leading to inefficient delivery of the cytotoxic payload. Further, the payload on many ADCs is released while in the plasma, resulting in the delivery of the antibody alone and loss of therapeutic activity. In contrast, Pentarins are miniaturized drug conjugates of ~5 kDa that rapidly penetrate deep into solid tumor tissue to specifically deliver potent payloads to tumor cells.

Methods: Somatostatin receptor 2 (SSTR2) is over expressed in multiple types of neuroendocrine cancers including gastroenteropancreatic, lung and thymus neuroendocrine tumors and small cell lung cancer. Tumor expression of SSTR2 can be detected with approved imaging agents such as ¹¹¹In-pentetreotide and ⁶⁸Ga-DOTATATE making it possible to identify patients to treat with SSTR2 targeting agents.

Results: PEN-221 is a highly potent and selective Pentarin consisting of a peptide somatostatin analog conjugated to the potent microtubule binding cytotoxic DM1 through a cleavable linker. The affinity of PEN-221 for SSTR2 matches the affinity of somatostatin 14. Upon binding, PEN-221 stimulates SSTR2 internalization, delivering and capturing the Pentarin in SSTR2 expressing tumor cells. The biological consequences of DM1 release from PEN-221 includes the induction of apoptosis as characterized by increased levels of cleaved caspase-3. In multiple SSTR2-expressing human tumor mouse xenograft models, these effects result in complete and sustained tumor regressions.

Conclusion: PEN-221 is the first Pentarin heading towards human clinical studies in patients with SSTR2 expressing tumors.