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Abstract A41: Sustained intratumoral activation of MM-398 results in superior activity over irinotecan demonstrated by using a systems pharmacology approach. **FREE**

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Abstract

MM-398 is a stable nanotherapeutic encapsulation of the prodrug irinotecan with an extended plasma half-life and higher intratumoral deposition compared with free-irinotecan. MM-398 is currently in multiple clinical trials, including a phase 3 trial for patients with advanced gemcitabine-resistant pancreatic cancer (NAPOLI-1). Pancreatic cancer has been described as being notoriously difficult to treat, potentially due to inadequate drug penetration through the dense stroma, or because the hypoxic tumor microenvironment suppresses cytotoxic activity. We sought to better understand how MM-398, a relatively large (100nm) liposomal nanotherapeutic, could potentially treat pancreatic cancer by determining the relative roles of systemic vs. local tumor activation of irinotecan in contributing to the activity of MM-398.

Using a systems pharmacology approach, we developed a mechanistic pharmacokinetic (PK) model of MM-398 and free-irinotecan to predict both plasma and intratumoral levels of irinotecan and SN-38. The model was trained with PK and biodistribution data from mice bearing HT-29 xenografts, which were administered intravenously with varying doses of MM-398 or free-irinotecan. Model simulations predicted that MM-398 resulted in equivalent SN-38 exposure (area under curve, AUC) in tumor at a five-fold lower dose than free-irinotecan. However, an in vivo animal activity study showed that 15-fold lower dose of MM-398 was sufficient to yield equal growth inhibition of HT-29 xenografts, which reveals the limit of relating simple AUC based exposure to in vivo tumor response.

While intratumoral SN-38 exposure from free-irinotecan was limited to the first 48 hours after dosing, MM-398 maintained high levels of SN-38 throughout the week long time window. Further

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analysis of the exposure- response identified that the duration of intratumoral SN-38 levels above the threshold was a valid predictive marker for xenograft tumor response.

Identifying the source of intratumoral SN38 is confounded by the fact that the mouse species has an additional carboxylesterase (CES) that can convert irinotecan to SN38 in serum. The serum SN-38/irinotecan ratio in mice is ten-fold higher than that observed in humans. In order to translate this preclinical observation into the clinic, it is critical to identify the role of mouse- specific serum CES on intratumoral SN-38 exposure. Thus, we performed a PK study with knockout mice lacking the *Ces1c* gene, which encodes serum CES, and then retrained our mechanistic PK model. Serum SN-38 levels in the *Ces1c* knockout mice were measurably decreased by ~85% in the central compartment. In contrast, simulating the effect of knock-out of either serum CES or tumor CES, predicts that the duration of intratumoral residence of SN-38 is significantly affected by tumor CES, rather than serum CES. This suggests that local activation to SN-38 by tumor CES as the main driver for SN-38 tumor residence, which in turn drives response.

In summary, we applied a systems pharmacology approach to identify the importance of tumor CES (local SN-38 generation) as one of the determinants of MM-398 response. Liposomal encapsulation of irinotecan dramatically alters the pharmacokinetic profile of SN-38 in the tumor, as well as tumor response, by maintaining SN-38 levels above the response threshold. Local, sustained activity of this active irinotecan metabolite could result in prolonged cytotoxic and tumor microenvironment modifications with beneficial effects on treatment of pancreatic cancer and other solid tumors.

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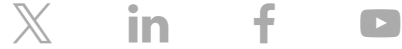
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