ARTICLE NAVIGATION

THERAPY | APRIL 03 2014

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

Jaeyeon Kim; Eliel Bayever; Peter Laivins; Clet Niyikiza; Ulrik Nielsen; Jonathan Fitzgerald; Ashish Kalra; Milind Chalishazar; Stephan Klinz; Nancy Paz; Bart Hendriks; Daryl Drummond; Dmitri Kirpotin; Victor Moyo

Check for updates

+ Author & Article Information

Cancer Res (2012) 72 (14_Supplement): A41.

https://doi.org/10.1158/1538-7445.PANCA2012-A41

Split-Screen Share Tools Versions

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 gemcitabineresistant 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

Skip to Main Content

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.

Citation Format: Jaeyeon Kim, Eliel Bayever, Peter Laivins, Clet Niyikiza, Ulrik Nielsen, Jonathan Fitzgerald, Ashish Kalra, Milind Chalishazar, Stephan Klinz, Nancy Paz, Bart Hendriks, Daryl Drummond, Dmitri Kirpotin, Victor Moyo. Sustained intratumoral activation of MM-398 results in superior activity over irinotecan demonstrated by using a systems pharmacology approach. [abstract]. In: Proceedings of the AACR Special Conference on Pancreatic Cancer: Progress and Challenges; Jun 18-21, 2012; Lake Tahoe, NV. Philadelphia (PA): AACR; Cancer Res 2012;72(12 Suppl):Abstract nr A41.

View Metrics

Citing Articles Via

Google Scholar

Email Alerts

Article Activity Alert

eTOC Alert

Breaking

Amivantamab–Lazertinib Combo Bests Osimertinib's OS

DFCI Initiative to Study RAS-Driven Cancers

Surgeon General Issues Advisory on Alcohol–Cancer Link

View more recent articles ›

Latest News

Keto Diet Key to Fueling CARs?

ADC for Lymphoma Elicits Near-Perfect Response Rate

Novel Degrader Shows Anti–Lymphoma and Myeloma Activity

View more recent articles ›

Research Watch

Tumor Suppressor Gene Zygosity Can Predict Therapeutic Response in Cancer

Patient-Specific Hematologic Setpoints Inform Diagnosis and Prognosis

GDF-15 Blockade Overcomes Resistance to Immune Checkpoint Inhibition

View more recent articles ›

Online ISSN 1538-7445 **Print ISSN** 0008-5472