

MM-398 Achieves Primary Endpoint of Overall Survival in Phase III Study in Patients with Gemcitabine Refractory Metastatic Pancreatic Cancer

Muhammad Wasif Saif

Tufts University School of Medicine. Boston, MA, USA

MM-398 (irinotecan liposome injection), also known as “nal-IRI”, is a nanoliposomal encapsulation of irinotecan, a topoisomerase-I poison. On May 1st, 2014, Merrimack Pharmaceuticals, Inc. (Cambridge, MA, USA) announced that the combination of MM-398 with 5-fluorouracil (5-FU) and leucovorin achieved an overall survival of 6.1 months, a 1.9 month improvement over the 4.2 month survival demonstrated by the control arm of 5-FU and leucovorin alone [1]. The primary log-rank analysis of overall survival was statistically significant (P=0.012) with a corresponding hazard ratio of 0.67. A statistically significant advantage for progression free survival was also observed in the combination arm. These results were based on a randomized large phase III study called the NAPOLI-1 study. This study treated patients with metastatic pancreatic cancer who previously received gemcitabine-based therapy. The most common Grade ≥ 3 toxicities seen were neutropenia (14.5%), fatigue (13.7%), diarrhea (12.8%) and vomiting (11.1%).

The results of the NAPOLI-1 study are exciting, as currently FDA has approved no regimen for second-line treatment of pancreatic cancer. While it offers a new regime for our patients, the study also brings new questions such as:

1. Reformulation of an old drug can produce different results. This is in consistency with the results of nab-paclitaxel and gemcitabine study, which tested a new form of paclitaxel and produced positive outcome [2].

2. Now that we have combination of 5-fluorouracil, oxaliplatin, irinotecan, leucovorin (FOLFIRINOX) as an option for first-line treatment too, how will this regimen fit in the algorithm of the treatment? [3, 4]

3. It seems logical to test this drug/regimen further: will it be worth replacing irinotecan in FOLFIRINOX with MM-398. However, bone marrow toxicity has to be borne in mind.

However, keeping the history of drug testing for pancreatic cancer, it is clearly a groundbreaking study in the gemcitabine-refractory setting. Previously only one study by the Charité Onkologie Clinical (CONKO) tested combination of oxaliplatin, folinic acid and 5-fluorouracil (OFF) regimen *versus* best supportive care (BSC) [5]. Moreover, this also underlines the proof of concept development of drugs such as MM-398, a nanoliposomal drug. These results also enhance the importance of clinical studies in order to improve the outcome in this deadly disease.

This study has been approved for oral presentation at the European Society for Medical Oncology World Conference on Gastrointestinal Cancer to be held in Barcelona, Spain on June 25-28, 2014.

Keywords Carcinoma; Drug Therapy; Gemcitabine; Neoplasm Metastasis; Pancreas; Pancreatic Neoplasms; Therapeutics

Abbreviations FOLFIRINOX: 5-fluorouracil, oxaliplatin, irinotecan, leucovorin

Correspondence Muhammad Wasif Saif

Department of Medicine and Cancer Center, Tufts Medical Center, 800 Washington Street Box 245, Boston, MA 02111; USA

Phone: +1-617.636.5627, Fax: +1-617.636.8535

E-mail: wsaif@tuftsmedicalcenter.org

Conflict of Interest

The author has no potential conflicts of interest

References

1. <http://www.marketwatch.com/story/merrimack-pharmaceuticals-announces-mm-398-achieves-primary-endpoint-of-overall-survival-in-phase-3-trial-in-post->

gemcitabine-metastatic-pancreatic-cancer-2014-05-01 (last assessed May 06, 2014)

2. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013 Oct 16.

3. Conroy T, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011 May 12; 364(19):1817-25.

4. Saif MW, Chabot J. Chemotherapy: Metastatic pancreatic cancer: is FOLFIRINOX the new standard? *Nat Rev Clin Oncol* 2011 Jul 5; 8(8):452-3.

5. Pelzer U, Schwaner I, Stieler J, Adler M, Seraphin J, Dörken B, et al. Best supportive care (BSC) versus oxaliplatin, folinic acid and 5-fluorouracil (OFF) plus BSC in patients for second-line advanced pancreatic cancer: a phase III-study from the German CONKO-study group. *Eur J Cancer*. 2011; 47: 1676-81.