On behalf of Merrimack Pharmaceuticals, I respectfully request the recently updated NCCN Pancreatic Adenocarcinoma Guideline version 1.2016 Panel to review the enclosed data regarding the use of irinotecan liposome injection (ONIVYDE®) as a treatment option for patients with metastatic adenocarcinoma of the pancreas whose disease has progressed following gemcitabine-based therapy.

**Specific changes:**

1. Consideration of a footnote or call out noting that liposomal irinotecan with 5-FU and leucovorin is a reasonable option for patients with KPS $\geq$ 70 in the post-gemcitabine setting
2. Clarification around the use of liposomal irinotecan with 5-FU and leucovorin after prior fluoropyrimidine-based therapy
3. Consideration for inclusion of liposomal irinotecan with 5-FU and leucovorin as first-line metastatic therapy after gemcitabine-based therapy in the adjuvant, neoadjuvant, or locally advanced setting

**FDA Clearance:** ONIVYDE is FDA-approved for use in combination with fluorouracil and leucovorin for the treatment of patients with metastatic adenocarcinoma of the pancreas whose disease has progressed following gemcitabine-based therapy.¹

**Rationale:**

1. In the proposed guidelines (version 1.2016), liposomal irinotecan is noted for use in patients with good performance status, defined as ECOG 0-1 with good pain management, patent biliary stent, and adequate nutritional intake (see footnote ‘u’ in PANC-9). The protocol for NAPOLI-1, the registration trial for liposomal irinotecan,² included patients with a KPS $\geq$ 70. We ask that you consider adding a footnote noting that liposomal irinotecan with 5-FU and leucovorin is reasonable for this patient population, as was done for gemcitabine with albumin-bound paclitaxel (see footnote ‘v’ in PANC-9).
2. In the proposed guidelines (see PANC-9), it appears as if liposomal irinotecan with 5-FU and leucovorin are not recommended after prior treatment with fluoropyrimidine-based therapy. To be eligible for NAPOLI-1, patients were required to have received gemcitabine therapy, but also may have had multiple other therapies. Prior therapy with
5-FU-based therapy was not an exclusion criterion—in fact, 43% (50/117) of patients in the arm that received liposomal irinotecan with 5-FU and leucovorin had received prior 5-FU-based therapy (Hazard Ratio [95%CI], 0.52 [0.31–0.86]).

3. While NAPOLI-1 included patients who progressed after gemcitabine-based therapy in the metastatic setting, it also included patients whose disease progressed after previous gemcitabine-based therapy given in a neoadjuvant, adjuvant (only if distant metastases occurred within 6 months of completing adjuvant therapy) or locally advanced setting. A total of 13% (15/117) of patients who received liposomal irinotecan with 5-FU were included in this group (Hazard Ratio [95%CI], 0.68 [0.28–1.64]).

The following prescribing information and article are submitted in support of these proposed changes. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors for some of these publications.

1. ONIVYDE® (irinotecan liposome injection) [Prescribing Information]. Cambridge, MA: Merrimack Pharmaceuticals, Inc. 2015.

Should you have any questions regarding the content of this letter, please do not hesitate to contact us.

Sincerely,

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