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NCCN Guidelines Panel: Pancreatic Adenocarcinoma

I would like to formally request for the NCCN Pancreatic Adenocarcinoma Panel to review the referenced articles and associated data detailing the survival benefit of irreversible electroporation as an accepted mode of treatment for locally advanced pancreatic adenocarcinoma (LAPC).

#### Specific Changes

Irreversible electroporation, as is currently omitted from the Guidelines as an accepted approach to treatment, should be recommended as an effective form of therapy to patients who have previously undergone unsuccessful chemo/radiotherapy for the down staging of unresectable LAPC.

#### FDA Clearance

The NanoKnife System has received FDA clearance for the surgical ablation of soft tissue. It has no clearance for the therapy or treatment of any specific disease or condition, such as LAPC.

#### Rationale

LAPC is the fourth leading cause of cancer mortality in the United States<sup>1</sup>. Because preliminary symptoms can be silent, those afflicted often go undiagnosed for long periods, and by the time the disease is diagnosed it is considered unresectable in the majority of patients (~85%)<sup>2,3</sup>. Standard treatments, such as chemotherapy and/or radiation, have been used to treat pancreatic cancer and yield quantifiable benefits. In a study by Yoo et al examining the efficacy of FOLFIRI and FOLFOX in the treatment of gemcitabine-refractory pancreatic cancer, median overall survival (O.S.) was found to be 3.8 and 3.4 months respectively<sup>4</sup>. However, a study by Hammel et al involving 449 patients found there was no significant difference in O.S. between chemoradiotherapy compared with chemotherapy alone, nor between gemcitabine and gemcitabine paired with erlotinib<sup>5</sup>.

Irreversible electroporation (IRE) is a non-thermal technique that utilizes electric pulses to induce the formation of nanopores in the cellular membrane. The formation of these nanopores destabilizes the phospholipid bilayer leading to cell death similar to apoptosis. This mechanism of action provides notable safety benefits; as the procedure does not rely on thermal energy, there is no heat-related damage done to surrounding tissues or critical structures nor does the heat sink effect limiting efficacy. This targeted tissue destruction preserves critical structures and surrounding healthy tissue

IRE is associated with high survival rates and low recurrence, including in patients who are unable to proceed with aforementioned standard treatments. In a study by Martin et al<sup>6</sup> involving 200 Stage III LAPC patients treated with IRE, 37% of patients sustained complications with a mean grade of 2 (range

1-5), and only 3% have experienced local recurrence. O.S. was 24.9 months (range 4.9-85 months). A study conducted by Kwon<sup>7</sup> et al involving 48 patients found a similarly low recurrence rate (6%) with only 11% of patients presenting with complications. O.S. was 22.4 months. IRE is well tolerated and patients often do not have to undergo repeat treatments. Complications are generally transient and mild, and include infection, thrombosis, pancreatitis, and bleeding<sup>8</sup>. The following peer-reviewed publications are submitted to support this proposed change.

Sincerely,

Kathleen Pietrovito

Director, Medical Affairs and Clinical Operations

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods, and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015 Mar; 136(5) E359-86.
2. Habermehl D, Brecht IC, Bergmann F, et al. Chemoradiation in patients with isolated recurrent pancreatic cancer – therapeutical efficacy and probability of re-resection. *Radiat Oncol*. 2013 Jan; 8: 27.
3. Bria E, Milella M, Gelibter A, et al. Gemcitabine-based combinations for inoperable pancreatic cancer: have we made real progress? A meta-analysis of 20 phase 3 trials. *Cancer*. 2007 Aug; 110(3): 525-33.
4. Moir J, White SA, French JJ, et al. Systematic review of irreversible electroporation in the treatment of advanced pancreatic cancer. *Eur J Surg Oncol*. 2014 Dec; 40(12): 1598-604.
5. Martin RC 2<sup>nd</sup>, Kwon D, Chalikonda S, et al. Treatment of 200 locally advanced (Stage III) pancreatic carcinoma patients with irreversible electroporation: safety and efficacy. *Ann Surg*. 2012 Sept; 262(3): 486-4.
6. Mansson C, Brahmstaedt R, Nilsson A, et al. Percutaneous irreversible electroporation for treatment of locally advanced pancreatic cancer following chemotherapy or radiochemotherapy. *Eur J Surg Oncol*. 2016 Feb; pii: S0748-7983(16)00094-9.
7. Paiella S, Butturini G, Frigerio I, et al. Safety and feasibility of Irreversible Electroporation (IRE) in patients with locally advanced pancreatic cancer: results of a prospective study. *Dig Surg*. 2015; 32(2): 90-7.

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<sup>1</sup> Desai NV, Sliesoraitis S, Hughes SJ, et al. Multidisciplinary neoadjuvant management for potentially curable pancreatic cancer. *Cancer Med*. 2015;4(8):1224-39.

<sup>2</sup> Habermehl D, Brecht IC, Bergmann F, et al. Chemoradiation in patients with isolated recurrent pancreatic cancer – therapeutical efficacy and probability of re-resection. *Radiat Oncol*. 2013 Jan; 8: 27

<sup>3</sup> Ni X, Yang J, Li M. Imaging-guided curative surgical resection of pancreatic cancer in a xenograft mouse model. *Cancer Lett*. 2012 Nov; 324(2): 179-85

<sup>4</sup> Yoo C, Hwang JY, Kim JE, et al. A randomised phase II study of modified FOLFIRI.3 vs modified FOLFOX as second-line therapy in patients with gemcitabine-refractory advanced pancreatic cancer. *Br J Cancer*. 2009;101(10):1658-63.

<sup>5</sup> Hammel P, Huguet F, Van laethem JL, et al. Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib: The LAP07 Randomized Clinical Trial. *JAMA*. 2016;315(17):1844-53.

<sup>6</sup> Martin RC 2<sup>nd</sup>, Kwon D, Chalikonda S, et al. Treatment of 200 locally advanced (Stage III) pancreatic carcinoma patients with irreversible electroporation: safety and efficacy. *Ann Surg*. 2012 Sept; 262(3): 486-4

<sup>7</sup> Kwon D, McFarland K, Velanovich V, et al. Borderline and locally advanced pancreatic adenocarcinoma margin accentuation with intraoperative irreversible electroporation. *Surgery*. 2014;156(4):910-20

<sup>8</sup> Martin RC 2<sup>nd</sup>, McFarland K, Ellis S, Velanovich V. Irreversible electroporation in locally advanced pancreatic cancer: potential improved overall survival. *Ann Surg Oncol*. 2013; Suppl 3:S443-9.