Thanks a lot for the feedback.

Comment:

This study systematic reviewed the progress made with EUS-guided injectable therapies in the treatment of PDAC. The results showed that current data demonstrate that EUS-guided injectable therapies are safe for the treatment of PDAC. Further studies, especially RCT studies, are required to confirm the adverse events and potential efficacy. It is best to include a list of main adverse events (AEs) and clinical efficacy in Table 1.

Response:

We have made the necessary revision and included the outcome parameters of adverse events, tumor response, and survival in table 1 of the manuscript as follows-

TABLE 1: Characteristics of published clinical studies using EUS-FNI for PDAC

Ref.	Disease	Country	No. of subjects, no. of groups	Study type	EUS-FNI injectable agent	Type of therapy	Adverse events (AEs)	Tumor response	Median survival
Chang et al [17] 2000	unresectable PDAC	USA	8, single arm	Phase I	Allogeneic mixed lymphocyte culture	Immunotherapy	DLT-0	Partial remission 25%, minor response 12.5%	13.2 mo (OS)
Irisawa et al [22] 2007	unresectable PDAC refractory to gemcitabine	Japan	7, single arm	Pilot clinical study	DCs	Immunotherapy	AEs-0	Mixed response 28.6%, stable disease 28.6%	9.9 mo (OS)
Hirooka et al [23] 2009	LAPC	Japan	5, single arm	Phase I	OK-432-pulsed DCs	Immunotherapy	Grade 3 or 4 AEs-0	Effective response 60% (partial remission 20%, stable disease 40%)	15.9 mo (OS)

Endo et al [25] 2012	resectable PDAC	Japan	24, two arms	Phase I	iDCs and OK-4 32	Immunotherapy	Grade 3 AEs-1	NA	No difference
Hirooka et al [26] 2017	LAPC	Japan	15, single arm	Phase I/II	Zoledronate-pulsed DCs	Immunotherapy	DLT-0 (grade 3 AEs-4)	Stable disease 46.7%	11.5 mo (OS)
Levy et al [28] 2017	unresectable PDAC	USA	36, single arm	Prospective non-randomized	Gemcitabine	Chemotherapy	AEs-0	Partial response 25%, stable disease 57%	10.4 mo (OS)
Hecht et al [32] 2003	unresectable PDAC without liver metastasis	USA	21, single arm	Phase I/II	ONYX-015	Viral therapy	AEs-8 (four related to the virus and four to the injection technique)	Partial response 10%, stable disease 38%	7.5 mo (OS)
Hecht et al [9] 2012	LAPC	USA	50, single arm	Phase I/II	TNFerade Biologic	Viral therapy	DLT-3	Complete response 2%, partial response 6%, minor response 8%, stable disease 24%	297 d (OS)
Herman et al [34] 2013	LAPC	USA	304, two arms	Randomized phase III	TNFerade Biologic	Viral therapy	No difference in grade 3 to 4 AEs	No difference	10.0 mo (OS) for both arms
Hirooka et al [36] 2018	LAPC	Japan	12, single arm	Phase I	HF-10	Viral therapy	DLT-0, Serious AEs-2, Grade 3 AEs-5	Effective response 78%	5.5 mo (OS)

Lee et al [51] 2020	LAPC	South Korea	9, single arm	Phase I	Ad5-DS	Viral therapy	DLT-0	Overall response 11%, disease control rate 100%	11.4 mo (PFS)
Nishimura et al [40] 2018	unresectable PDAC	Japan	6, single arm	Prospective non-randomized	STNM01	RNA oligonucleotide	AEs-0	NA	5.8 mo (OS)
N Hanna et al [42] 2012	unresectable PDAC	USA, Israel	6, single arm	Phase I/IIA	BC-819	DNA plasmid	DLT-1	Overall response 33.3% and 66.7% in the two dose cohorts respectively	100% and 66.7% (six-month survival) in the two dose cohorts

PDAC: pancreatic ductal adenocarcinoma; LAPC: Locally advanced pancreatic cancer; iDC: Immature dendritic cell; DLT: Dose-limiting toxicity; OS: Overall survival; PFS: Progression-free survival

Dear Editor Thank you for your comment 1. We made the necessary modifications and revised the reference list accordingly- We request to seek an exception for the following four references which are from the same journal but are original studies that met the inclusion criteria for our systematic review. Removing any of these would affect the integrity of our study. These are (numbered from the latest reference list) 9 Hecht JR, Farrell JJ, Senzer N, Nemunaitis J, Rosemurgy A, Chung T, Hanna N, Chang KJ, Javle M, Posner M, Waxman I, Reid A, Erickson R, Canto M, Chak A, Blatner G, Kovacevic M, Thornton M. EUS or percutaneously guided intratumoral TNFerade biologic with 5-fluorouracil and radiotherapy for first-line treatment of locally advanced pancreatic cancer: a phase I/II study. Gastrointest Endosc 2012; 75: 332-338 [PMID: 22248601 DOI: 10.1016/j.gie.2011.10.007] 27 Levy MJ, Alberts SR, Bamlet WR, Burch PA, Farnell MB, Gleeson FC, Haddock MG, Kendrick ML, Oberg AL, Petersen GM, Takahashi N, Chari ST. EUS-guided fine-needle injection of gemcitabine for locally advanced and metastatic pancreatic cancer. Gastrointest Endosc 2017; 86: 161-169 [PMID: 27889543 DOI: 10.1016/j.gie.2016.11.014] 36 Lee JC, Shin DW, Park H, Kim J, Youn Y, Kim JH, Kim J, Hwang JH. Tolerability and safety of EUS-injected adenovirus-mediated double-suicide gene therapy with chemotherapy in locally advanced pancreatic cancer: a phase 1 trial. Gastrointest Endosc 2020; 92: 1044-1052.e1 [PMID: 32084409 DOI: 10.1016/j.gie.2020.02.012] 40 Nishimura M, Matsukawa M, Fujii Y, Matsuda Y, Arai T, Ochiai Y, Itoi T, Yahagi N. Effects of EUS-guided intratumoral injection of oligonucleotide STNM01 on tumor growth,

histology, and overall survival in patients with unresectable pancreatic cancer. Gastrointest Endosc 2018; 87: 1126-1131 [PMID: 29122598 DOI: 10.1016/j.gie.2017.10.030] 2. The tables have been added to the Auto-edited file as attached. Thank you

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