

Recurrent pancreatic cancer treated with N-803 and PD-L1 t-haNK followed by an EGFR-targeted nanocell drug conjugate

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Abstract

Multimodal temporal therapy orchestrated to leverage immunotherapy, tumor-targeted chemotherapy, and natural killer (NK) cell therapy may provide an opportunity to induce immunogenic cell death for tumor response and increased survival in patients with recurrent cancer. The interleukin-15 (IL-15) superagonist N-803, an enhancer of NK cells, CD4 + T cells, cytotoxic CD8 + T cells, and memory T-cell activity, combined with off-the-shelf PD-L1-targeted high-affinity NK (PD-L1 t-haNK) cells represent novel immunotherapies designed to overcome an immunosuppressive tumor microenvironment (TME). The epidermal growth factor receptor-targeted antibody-nanocell conjugate E-EDV-D682 provides tumor-targeted chemotherapy in the form of its anthracycline metabolite PNU159682 (nemorubicin) cargo and is currently being studied in combination with immunomodulatory EDVs delivering the adjuvant α -galactosyl ceramide (GC). Here, we report the compassionate use treatment of this combination in a patient with recurrent, metastatic pancreatic cancer (mPC) after 3 lines of therapy. Under the initial single-patient Investigational New Drug (sIND) protocol, the patient received N-803, PD-L1 t-haNK cells, and the albumin doxorubicin conjugate aldodoxorubicin for ~27 months. The patient's disease became stable on this regimen, and a transient complete response was observed by ~14 months of therapy. Due to progression, a second sIND protocol was designed whereby the patient received E-EDV-D682 plus EDV-GC for more than 24 months, which resulted in stable disease and the patient's continued survival at the time this report was written. The patient's extended survival despite the dire prognosis associated with recurrent mPC points to the merits of this temporal combination regimen in overcoming immuno-chemo resistance with enhanced immune activity required for tumor response and extended survival.

Key words: metastatic pancreatic cancer; PD-L1 t-haNK; N-803; E-EDV-D682; EDV- α -galactosyl ceramide.

Implications for practice

A patient with recurrent, metastatic pancreatic cancer after 3 lines of therapy achieved stable disease and then a transient complete response to compassionate-use treatment with the IL-15 superagonist N-803 combined with PD-L1-targeted high-affinity NK cells and the albumin doxorubicin conjugate aldodoxorubicin. Subsequent compassionate use of the EGFR-targeted antibody-nanocell conjugate E-EDV-D682 resulted in stable disease and the patient's continued survival. The patient's extended survival despite her dire prognosis points to the merits of these temporal combination therapeutic regimens in overcoming immuno-chemo resistance with the enhanced immune activity required for tumor response and extended survival.

Introduction

Pancreatic cancer (PC) is the 4th leading cause of cancer-related death worldwide and typically has a poor prognosis, with a 5-year survival rate of 5%, and a life expectancy of ~3–6 months for patients with metastatic pancreatic cancer (mPC).¹

The National Comprehensive Cancer Network (NCCN) recommends FOLFIRINOX or nab-paclitaxel (Abraxane) plus gemcitabine as 1st-line therapy and gemcitabine mono- or combination therapy as 2nd-line therapy. Options for

additional therapy are capecitabine or fluoropyrimidine plus oxaliplatin.^{2–4} There is no standard of care (SoC) for 3rd-line therapy, although modest benefit has been reported for tegafur-gimeracil-oteracil potassium or nano-liposomal irinotecan plus 5-FU/leucovorin.^{5,6}

Options for patients with pancreatic cancer who have persistent disease after 3 lines of therapy are few, and palliative care is often the only choice.

While immunotherapy has been found to be effective in the treatment of many types of cancer, PC is generally resistant to

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checkpoint inhibitor monotherapy likely due to impairments in T-cell function and an immunosuppressive tumor microenvironment (TME).⁷⁻¹⁰

The investigational biologic N-803, an Fc-conjugated interleukin-15 superagonist, may overcome therapeutic resistance. N-803 has been shown to enhance natural killer (NK), CD4 + T, and CD8 + killer T-cell activation, leading to the generation of memory T cells and durable complete responses when used in combination with other therapies.¹¹⁻¹³ Examples of N-803 efficacy in combination therapy include the achievement of durable complete responses in all patients in a phase 1b trial of N-803 plus bacillus Calmette-Guerin (BCG) in BCG-naïve non-muscle invasive bladder cancer (NMIBC)¹⁴ and in a phase 2/3 trial of the combination in BCG-unresponsive NMIBC.¹⁵ Based findings in the latter study, the US FDA recently approved the combination for the treatment of bladder carcinoma *in situ* with or without Ta/T1 papillary disease.^{15,16}

To further circumvent immunosuppression, N-803 may be used in combination with investigational programmed death receptor ligand 1-targeted high-affinity natural killer (PD-L1 t-haNK) cells which have demonstrated activity against immunosuppressive myeloid-derived suppressor cells (MDSCs),^{17,18} and/or the investigational chemotherapy aldorubicin—doxorubicin with an acid-sensitive linker—that has enhanced activity at the tumor site.¹⁹ Investigational vaccines targeting tumor-associated antigens (TAAs) such as carcinogenic embryonic antigen or CEA (ETBX-051) and/or mucin-1 or MUC1 (ETBX-061) may also enhance responses by inducing antigen-specific T cells targeting tumor cells.^{20,21}

While the investigational agents N-803, aldorubicin, PD-L1 t-haNK, ETBX-051, and -061 have not yet been approved by the US FDA for use in pancreatic cancer, they have been studied in multiple phase I/II QUILT (Quantum Integrative Lifelong Trial) clinical studies to explore safety and early signals of efficacy across multiple tumor types, including pancreatic cancer.²²⁻²⁵ To date, over 300 subjects have participated in the QUILT trials wherein the combination immunotherapy was well-tolerated with evidence of complete responses in late-stage tumors (BCG-unresponsive non-muscle invasive bladder, triple-negative breast, pancreatic, and head/neck cancer, as well as Merkel cell carcinoma),^{26,27} supporting Institutional Review Board (IRB) approvals for their use in the present case.

An additional therapeutic approach leverages both the advantages of tumor-targeting and the stimulation of an immune response. The novel Antibody Nanocell Drug Conjugate (ANDC) E-EDV-D682 packages PNU159682, the potent secondary metabolite of the anthracycline nemo-rubicin,²⁸ and delivers it via the epidermal growth factor receptor (EGFR)-targeted nanocellular vector E-EDV. EDVs (EnGeneIC Dream Vectors) are bacterially-derived nanocells that can deliver cargos such as chemo- or immuno-therapies selectively to the tumor due to the tumor-associated leaky vasculature.²⁹⁻³¹ To further increase efficacy, EDVs carrying an immunomodulatory adjuvant α -galactosyl ceramide cargo (EDV-GC) may be used in combination with E-EDV-D68.³²

E-EDV-D682 plus EDV-GC therapy is being studied in clinical trials for mPC and has been demonstrated to be well-tolerated with no dose-limiting toxicities (DLTs), and no drug-related severe adverse event (SAEs); further, early efficacy signals suggest the ability of the drug combination to elicit partial responses (PR) or stable disease (SD) in patients

who have exhausted treatment options.^{29,33} These findings informed the approval by the IRB for the use of E-EDV-D682/GC in the present case.

The sources of the investigational agents, their mechanism of action, and roles in therapy are listed in Table 1.

Case report

Herein, we present a case report for a patient who had received 3 lines of therapy for recurrent mPC and who then underwent compassionate-use, single-patient Investigational New Drug (spIND) treatment initially with a combination of N-803, PD-L1 t-haNK, and aldorubicin; followed by ongoing treatment with E-EDV-D682 plus EDV-GC. The patient was provided spIND care at the Chan Soon-Shiong Institute for Medicine (CSSIFM) in El Segundo, California in partnership with Hoag Hospital.

The patient, who at the time of this report shows no signs of disease progression, is a 65-year-old female originally diagnosed with locally-advanced PC approximately 5 years ago. She had reported abdominal pain and magnetic resonance cholangiopancreatography (MRCP) revealed a 3.2 cm mass at the head of the pancreas with dilatation of the common bile duct (CBD); CT of the abdomen and pelvis revealed a 4.1 × 3.3 cm mass with associated biliary dilatation. Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) × 3 suggested a neuroendocrine tumor (later determined by pathology to be pancreatic adenocarcinoma) and enlarged lymph nodes were noted. In the same month as her diagnosis, endoscopic retrograde CP (ERCP) was performed with placement of a CBD stent, and pathology confirmed PC. Soon after, she suffered cholangitis and cholecystitis, and underwent CT-guided placement of a cholecystostomy tube.

STRATA genome sequencing of the biopsy characterized the tissue as microsatellite stable (MSS), Tumor Mutational Burden (TMB) low, PD-L1-low, and STRATA immune signature low.³⁴ No genomic alterations were detected.

As 1st-line therapy, she received 8 cycles of neo-adjuvant FOLFIRINOX over 4 months starting 1 month after diagnosis. During that time, there was an occasion when she was admitted for ascending cholangitis.

As 2nd-line therapy, she received radiation with capecitabine (Xeloda) in 28 treatments over a month starting 1 month after completion of FOLFIRINOX therapy.

Three months later, she was scheduled for planned surgical resection of the primary tumor (Whipple procedure), but diagnostic laparoscopy demonstrated metastatic disease in the liver that did not appear on CT or PET scans. A biopsy of the liver metastasis confirmed mPC and the surgery was aborted.

As 3rd-line therapy, she began treatment with gemcitabine and nab-paclitaxel immediately after the confirmation of mPC. A PET CT 2 months later showed increased uptake in the pancreatic head, suggesting a lack of response to therapy.

PD-L1 t-haNK, N-803, and aldorubicin spIND therapy

Having exhausted 3 lines of SoC therapy, a compassionate-use treatment plan was designed and approved for this patient comprising the immune-cell activating interleukin-15 superagonist N-803, allogenic PD-L1-targeted high-affinity natural killer cells (PD-L1 t-haNK) and the linker-conjugated

Table 1. Investigational* agent description, mechanisms of action, and role in treatment

Agent	Description	Source	Mechanism(s) of action	Role	Tumor cell cytotoxicity	Release of TAAs	Coordinate ICD signals	Mitigate immuno-suppression	Enhance immune responses	Condition dendritic and T cells	Maintain immune responses
PDL-1 t-haNK	Programmed death receptor ligand 1 targeted high-affinity natural killer cells	ImmunityBio, Inc.	Increases NK cell anti-tumor function						✓		✓
N-803	Nogapendekin alfa inbakicept interleukin-15 superagonist	ImmunityBio, Inc.	Increase NK and T-cell proliferation and activation						✓	✓	✓
Aldoxorubicin	Acid-sensitive linker conjugated doxorubicin	ImmunityBio, Inc.	Inhibits DNA repair, generates cytotoxic free radical	✓		✓	✓				
ETBX-051, 061	Adenovirus-vectored tumor antigen vaccines; 051 - brachyury, 061 - MUC1	Etubics**	Leads to killing of tumor cells that express brachyury or MUC1							✓	
E-EDV-D682	Epidermal growth factor receptor (EGFR)/V)-EnGeneIC Delivery Vehicle (EDV) nanovesicle-delivered PNU-159682	EnGeneIC***	Anthracycline, inhibits DNA synthesis	✓		✓	✓	✓	✓		
EDV-GC	EDV-delivered α -galactosyl ceramide	EnGeneIC***	Adjuvant immune enhancer					✓	✓		✓

*Investigational agents are not yet approved for the target indication (here, pancreatic cancer); **Etubics is wholly owned by ImmunityBio, Inc.; ***EnGeneIC EDV products licensed by ImmunityBio, Inc..
Abbreviations: 5-FU, 5-fluorouracil; ICD, Immunogenic cell death; TAAs, tumor-associated antigens.
TME, Tumor microenvironment

doxorubicin compound, aldodoxorubicin. This investigational therapy was alternated with gemcitabine plus nab-paclitaxel.

As shown in Figure 1, 4th-line spIND therapy began within weeks of the noted lack of response to previous therapy, following a schedule of alternating therapies for ~9

months. Treatment was held in month 2 due to low ANC and in month 3 due to possible coronavirus disease exposure. Aldodoxorubicin only was held and 2 units of PRBCs were given in month 4 due to low hemoglobin. A dose of cyclophosphamide was given at 3 months, and regular

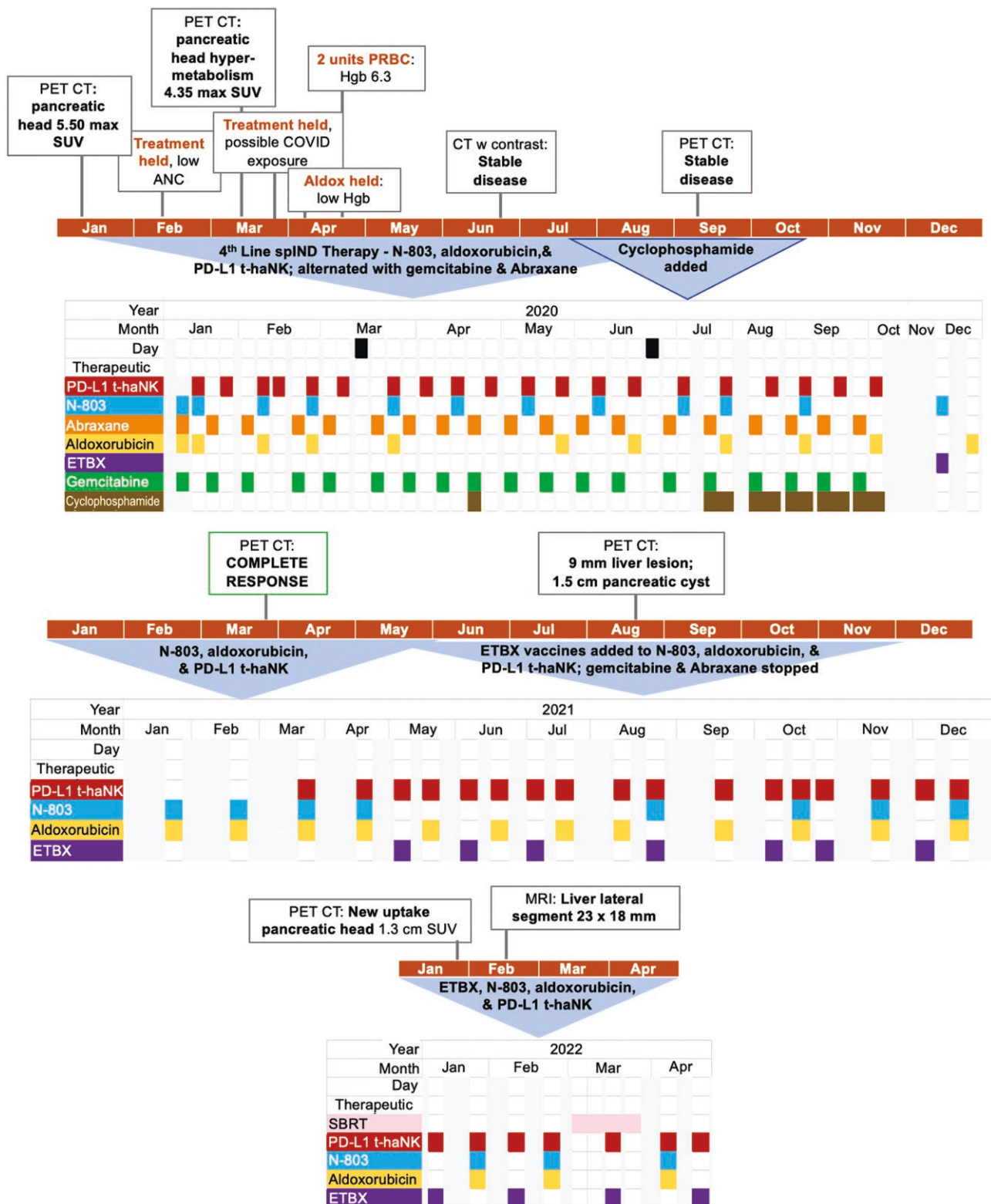


Figure 1. Initial spIND therapy with N-803, aldodoxorubicin, and PD-L1 t-haNK. The patient received the initial compassionate-use therapy as shown by year. Any adverse events, blood chemistry or other findings that affected treatment are shown in comment boxes above the timeline.

administration of cyclophosphamide 6-9 months after initiation of spIND therapy.

CT and PET CT were performed at months 5 and 8 of spIND therapy showed stable disease.

Eleven months after the initiation of spIND therapy, the investigational human adenovirus serotype 5 (hAd5) vector-based cancer vaccines ETBX-051 (targeting carcino- genic embryonic antigen; CEA) and -061 (targeting mucin-1; MUC1) were added, and treatment with gemcitabine/nab- paclitaxel ceased.

Notably, after ~14 months of spIND therapy, no abnormal metabolic activity was observed on PET CT, suggestive of a complete response (CR) (Figure 1). Subsequent PET CTs per- formed 19 and 24 months (2 years) after commencement of spIND therapy revealed the presence of a new lateral segment liver lesion likely representing progressive disease. At that time the patient required routine paracentesis due to abdom- inal ascites. The initial spIND regimen was continued for a

total of 2 years and 3 months. In the final month, the patient received radiation therapy to the liver.

E-EDV-D682 plus EDV-GC spIND therapy

Given the patient’s progression after a complete response to the initial spIND therapy, a new compassionate-use treat- ment plan based on a recently approved Investigational New Drug (IND) application for pancreatic ductal adeno- carcinoma (PDAC) of the antibody nanocell drug conjugate packaging nemorubicin, E-EDV-D682, plus the immuno- modulatory adjuvant EDV- α -galactosyl ceramide, EDV-GC, was initiated.

As shown in Figure 2, immediately after cessation of the first spIND regimen, 2 sequential doses of E-EDV-D682 plus EDV-GC were administered bi-weekly for 4 weeks (16 doses). On the treatment day, the 1st dose was followed 45 (+ 15) minutes after completion by a 2nd repeat dose. In month 2 of this regimen, a dose was held due to elevated liver function

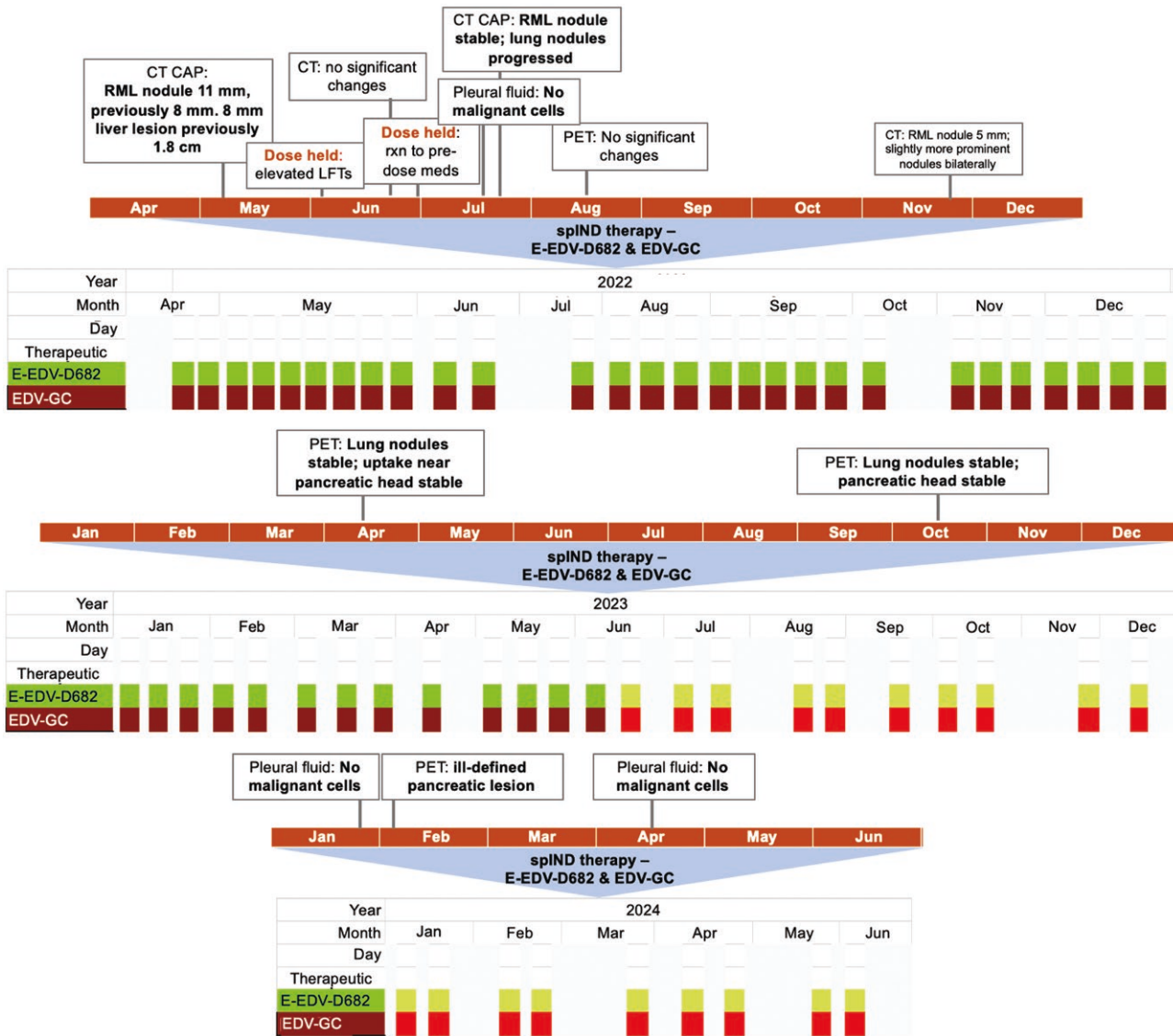


Figure 2. spIND therapy with E-EDV-D682 and EDV-GC. The patient received a second compassionate use therapy regimen as shown by year. The initial dosing regimen comprising two repeat doses is shown in darker colors and the single dosing regimen (started after approximately 14 months of therapy) in lighter colors. Any adverse events, blood chemistry, or other findings that affected treatment are shown in comment boxes above the timeline. The dosing regimen was ongoing as of June 2024.

tests (LFTs), and one was held later that month due to the patient's reaction to pre-dose medications.

Subsequent cycles consisted of a maintenance regimen of 2 repeat doses of E-EDV-D682 plus EDV-GC delivered 45 (+ 15) minutes apart starting 10 months from initiation of the second spIND regimen, followed by a regimen of a single dose of E-EDV-D682 plus EDV-GC commencing 4 months after that; for both regimens, dosing was every 2 weeks.

Noting that the patient's disease is characterized by being diffuse and not clearly defined on imaging, findings from imaging and the absence of malignant cells in pleural fluid collected frequently throughout treatment confirm a lack of disease progression and are suggestive of a response to therapy for at least an additional 12 months, at which time this report was written.

Discussion

Herein we describe the case of a patient with advanced, recurrent metastatic pancreatic cancer who—after exhausting 3 lines of standard therapy—achieved a complete response with the combination of N-803, PD-L1 t-haNK, aldorubicin, and a single dose of CEA- and MUC-based adeno (Ad5) vaccines. Following the patient's progression, she then began a new spIND regimen comprising investigational E-EDV-D682 plus adjuvant EDV-GC therapy which prevented disease progression and supported the patient's continued survival.

Standard chemotherapies—FOLFIRINOX, capecitabine, and gemcitabine—as well as radiation all have tumor cell cytotoxicity and thus elicit release of tumor-associated antigens from dying cells that coordinate immunogenic cell death (ICD) signaling.³⁵ In an immunosuppressive TME, however, the magnitude of ICD needed to elicit a response to therapy is unlikely. Nab-paclitaxel offers an opportunity to mitigate TME immunosuppression by its albumin-bound form,^{36,37} but is not always sufficient.

N-803, PD-L1 t-haNK, aldorubicin, and the ETBX TAA-targeted vaccines all address the problem of immunosuppression by different mechanisms: N-803 by direct activation of NK and T cells,^{38,39} PD-L1 t-haNK by the provision of an exogenous source of NK cells that not only can assist in overcoming endogenous NK insufficiency but also the expression of immunosuppressive PD-L1 and, importantly, the presence of MDSCs.^{17,18}

Aldorubicin, in a fashion similar to nab-paclitaxel, allows for a greater concentration of effective chemotherapy at the tumor site, with a reduction of off-target effects that can limit the dose or frequency of dosing with other chemotherapies.¹⁹

The vaccines have the potential to then add to responses by directing the immune system to surviving tumor cells expressing TAAs and thus conditioning dendritic and T cells to recognize these tumor cells if they recur.

The response of this patient to this first spIND regimen was not completely unexpected, as some advanced PC patients in QUILT clinical trials have been observed to respond to similar treatment regimens,^{22,24} but is nonetheless notable due to the patient's treatment history and prognosis.

The subsequent response to additional spIND therapy is also explained by the mechanisms of action of E-EDV-D682 and EDV-GC. E-EDV-D682 is targeted directly to cancer cells via an anti-EGFR antibody. Its bilayer membrane protects the drug payload, facilitating the use of the highly cytotoxic compound PNU159682, which has the potential to

overcome drug resistance. The E-EDV-D682 particle size prevents extravasation into non-target tissues, allowing delivery of higher concentrations of effective therapy to the targeted tumor with no payload-related off-target effects²⁸; efficacy is increased by co-delivery of the immuno-enhancer EDV-GC, with similarly protected cargo.²⁹ In this patient, E-EDV-D682 plus EDV-GC therapy has prevented disease progression and prolonged survival with minimal toxicities. This is in alignment with findings from a clinical trial of E-EDV-D682/GC in patients with advanced pancreatic cancer wherein partial response (PR) or stable disease (SD) was achieved at 8 weeks in 8/9 patients.^{29,33}

The EDV-based treatment regimen also benefited the patient by reducing the need for long infusion times. Currently, available treatments for mPC are highly toxic and time-intensive, often requiring patients to endure hours of infusions. For this patient, E-EDV-D682 offered a novel, targeted approach to the delivery of effective chemotherapy, with minimal toxicities and a significant reduction in infusion time, ultimately contributing to improved quality of life and resumption of regular activities.

The prolonged survival and tumor response of this patient with advanced PC provides encouraging validation that temporal/spatial orchestration of the innate and adaptive immune systems to elicit immunogenic cell death raises the possibility of converting metastatic cancer to a chronic disease. Further evidence of the efficacy of this approach is provided by the durable complete responses observed in patients with BCG-naïve and BCG-unresponsive non-muscle invasive bladder cancer.^{14,15} While N-803 (ANKTIVA) plus BCG has been approved for the treatment of BCG-unresponsive NMIBC, the investigational therapies described herein are currently only available for patients with pancreatic cancer through a compassionate use or participation in a clinical trial.

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Author contributions

Katayoun Moini, Chaitali Nangia, and Tara Seery provided patient care, contributed to spIND design, and performed data collection and analysis. Tara Seery was the principal investigator of the spIND study. Jennifer MacDiarmid and Himanshu Brahmabhatt co-invented and developed the EDV-based therapeutics and contributed to spIND design. Patrick Soon-Shiong performed data analysis, created all figures and tables, and wrote the initial draft of the manuscript. Lennie Sender supervised patient care and progress and contributed to spIND design. Patrick Soon-Shiong developed the QUILT Trial regimen, contributed to spIND design, is the inventor of Abraxane, and co-developed investigational therapeutics N-803, PD-L1 t-haNK, aldorubicin and the ETBX vaccines. All authors reviewed the manuscript and approved its submission for publication.

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Conflict of interests

K.M., T.S., C.N., P.S., L.S., and P.S.-S. are employees or management of or have a financial interest in, ImmunityBio, Inc., manufacturer of N-803, PD-L1 t-haNK cells, aldoxorubicin, ETBX-051 and ETBX-061. J.M.D. and H.B. are employees or management of EnGeneIC, manufacture of E-EDV-D682 and EDV-GC and are shareholders in the company. P.S.-S. is the inventor of Abraxane and NANT Cancer Vaccine patents.

Data availability

All data are presented in the manuscript or are available upon reasonable request.

Ethics statement

The patient provided signed, informed consent to receive the investigational therapeutics and for publication of the report.

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