

A Phase I Study of Immune Checkpoint Inhibition (anti-CTLA4 and anti-PD-L1) in Combination with Radiation Therapy in Patients with Locally Advanced Unresectable Pancreatic Cancer

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Abstract

Background: No clear consensus exists on the best treatment for unresectable locally advanced pancreatic cancer. Programmed death ligand-1 (PD-L1) inhibitors and cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitors, especially in combination, have been shown to increase survival in a variety of cancers. Preclinical data indicates potential synergy between immunotherapy, such as PD-L1 and CTLA-4 inhibitors, with radiation therapy. Specifically, in combination with Stereotactic Body Radiation Therapy (SBRT), immunotherapy may provide an effective treatment modality for this difficult-to-treat patient population.

Aim: To determine the safety and recommended phase 2 dose (RP2D) of SBRT in combination with either (A) Durvalumab (MEDI4736) alone, (B) Tremelimumab alone or (C) the combination of Durvalumab (MEDI4736) and Tremelimumab for patients with unresectable locally advanced adenocarcinoma.

Methods: A multi-institutional phase Ib trial of radiation therapy in combination with immune checkpoint inhibition (anti-CTLA4 alone, anti-PD-L1 alone, or anti-CTLA4 with anti-PDL1) in patients with unresectable locally advanced pancreatic cancer.

Cohort A: SBRT plus Durvalumab (MEDI4736): 1 dose escalation

Cohort B: SBRT plus Tremelimumab: 1 dose escalation

Cohort C: SBRT plus Durvalumab (MEDI4736) in combination with Tremelimumab: For Durvalumab (MEDI4736), there will be either 1 dose escalation (if RP2D of Cohort A is >750mg) or no dose escalation (if RP2D of Cohort A is 750mg). For Tremelimumab, there will be flat dosing of 75 mg, no dose escalation. Each cohort will have a standard 3 + 3 dose escalation design. SBRT will be administered at the standard dose of 6.6 Gy daily for 5 days in each cohort.

Results: Due to slow accrual, the study was terminated after 4 subjects were enrolled. Treatment was well-tolerated; no patients discontinued treatment due to adverse events. Adverse events were those commonly seen with immunotherapy, including LFT abnormalities, maculopapular rash, and diarrhea. Pulmonary embolism and duodenal ulcer leading to hemorrhage developed in two different patients, neither of which was related to treatment.

Conclusion: The combination of SBRT with either Durvalumab (MEDI4736) or Tremelimumab appears to be safe and tolerable in four patients with unresectable locally advanced pancreatic adenocarcinoma. Further studies are required to further explore the safety and clinical benefit of this treatment regimen.

Keywords: Pancreatic cancer • Immune checkpoint inhibitor • Immunotherapy • Durvalumab • Tremelimumab • Stereotactic body radiation therapy

Coretip

This study investigated the combination of novel immunotherapy and radiation therapy in locally advanced pancreatic cancer without metastasis, providing early safety data. Although only four patients were enrolled, this

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approach appears to be safe and tolerable, and thus is a novel strategy that warrants further investigation. We review other clinical trials in this area of important study.

Article Highlights

Research background

Programmed death ligand-1 (PD-L1) inhibitors and anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitors, especially in combination, have been shown to increase survival in a variety of cancers. In combination with Stereotactic Body Radiation Therapy (SBRT), they may provide an effective treatment modality for the difficult-to-treat patient population.

Research motivation

Immune priming has been shown to work well in pancreatic cancer when

applied to serial vaccine therapy, and may also hold true for hypofractionated radiation therapy (RT). Several studies have noted an increase in peripheral antitumor immunity following irradiation. This effect appears to be potentiated by immunotherapy such as anti-CTLA-4 and anti-PD-L1. Therefore, the combination of hypofractionated RT and immunotherapy could be a promising strategy in the treatment of nonimmunogenic tumors including pancreatic cancer.

Research objectives

To determine the safety and recommended phase 2 dose (RP2D) of SBRT in combination with either (A) Durvalumab (MEDI4736) alone, (B) Tremelimumab alone or (C) the combination of Durvalumab (MEDI4736) and Tremelimumab for patients with unresectable locally advanced pancreatic adenocarcinoma.

Research methods

Cohort A- Stereotactic Body Radiation Therapy (SBRT) plus Durvalumab (MEDI4736): 1 dose escalation, Cohort B- SBRT plus Tremelimumab: 1 dose escalation, Cohort C- SBRT plus Durvalumab (MEDI4736) in combination with Tremelimumab: For Durvalumab (MEDI4736), there will be either 1 dose escalation (if RP2D of Cohort A is >750 mg) or no dose escalation (if RP2D of Cohort A is 750 mg). For Tremelimumab, there will be flat dosing of 75 mg, no dose escalation. Each cohort will have a standard 3+3 dose escalation design. SBRT will be administered at the standard dose of 6.6 Gy daily for 5 days in each cohort.

Research results

Treatment was well-tolerated, with no patients discontinuing treatment due to adverse events. Adverse events were those commonly seen with immunotherapy, including LFT abnormalities, maculopapular rash, and diarrhea. Pulmonary embolism and duodenal ulcer leading to hemorrhage developed in two different patients, neither of which was related to treatment.

Research conclusion

Anti-CTLA-4 therapy Tremelimumab and anti-PD-L1 therapy Durvalumab (MEDI4736) in combination with hypofractionated RT demonstrate a manageable toxicity profile in four patients. Further investigations are underway to validate the safety results and to evaluate efficacy.

Research perspectives

The combination of SBRT with either Durvalumab (MEDI4736) or Tremelimumab appears to be safe and tolerable in four patients with unresectable locally advanced pancreatic adenocarcinoma. Further studies are needed to assess efficacy and clinical benefit.

Introduction

Pancreatic cancer is one of the top five most common cancers in the United States with a rising incidence, in contrast to prostate, lung, and colorectal cancers, which are declining in incidence [1]. In approximately 30% of pancreatic cancer patients, the disease presents as locally advanced (LAPC) without metastases but surgically unresectable and is, therefore, incurable. For such patients, the optimal first-line treatment continues to be a subject of debate. Traditionally, patients have been treated with a combination of chemotherapy and radiation therapy (RT) based on several studies which showed improvements in overall survival (OS) and progression-free survival (PFS). In 74 patients with LAPC, a randomized controlled trial of gemcitabine/RT found improved OS when compared with gemcitabine alone, although with increased toxicity [2]. Similarly, a meta-analysis of 753 patients with LAPC who received chemo/RT demonstrated that patients who received chemo/RT achieved improved PFS compared to RT alone, with a hazard ratio of 0.63 (0.41-0.96) [3]. The RT regimen for this disease has conventionally been a prolonged course that requires 5-fluorouracil as a radiosensitizer, but a hypofractionated

course is becoming the standard of care. Stereotactic Body Radiation Therapy (SBRT) given over 5 days has been shown to be safe and effective in LAPC and has been widely adopted in the United States [4].

Programmed death ligand-1 (PD-L1) inhibitors and cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitors exemplify the success of immunotherapy, and have demonstrated remarkable clinical activity both alone and in combination in immunogenic tumors. Both anti-CTLA4 and anti-PD-L1 therapy enhance anti-tumor immunity, the former by blocking tumor-induced suppression of cytotoxic T-cells, and the latter by allowing recognition of tumor cells by the immune system [5,6]. In combination, these therapies have been shown to be even more effective than either immunotherapy alone, with a manageable toxicity profile in immunogenic cancers such as melanoma, hepatocellular carcinoma, and renal cell carcinoma [7-9]. Unfortunately, however, pancreatic cancer is known to be a non-immunogenic tumor [10]. Despite modestly positive results in a phase I study of PD-L1 inhibitor Durvalumab in patients with advanced pancreatic cancer refractory to therapy achieving tumor shrinkage achieved as early as 6 weeks, single-agent immunotherapy is generally insufficient for meaningful responses in pancreatic cancer [11,12]. For instance, no objective responses were observed in a trial of PD-L1 inhibitor monotherapy in 14 patients with pancreatic cancer [13]. Thus, there is concern that immunotherapy alone may not be sufficient to elicit a meaningful response or improve survival. Consequently, transforming pancreatic cancer into an immunogenically responsive tumor is a major focus of clinical investigation [14].

Immune priming, or sensitizing the immune system to tumor antigen, has been demonstrated in pancreatic cancer via serial vaccine therapy [15]. This immune priming effect may apply to RT as well, as several studies have documented an increase in peripheral antitumor immunity following RT in patients with pancreatic and other cancers [16-18]. There are varying hypotheses as to how RT induces immune priming, including changes in angiogenesis, as the phenomenon appears to be p53-mediated, or by producing antigens that resemble tumor antigens, as the phenomenon also appears to be T cell-mediated. Regardless of the mechanism, this immune priming effect only holds true for hypofractionated RT, and appears to be potentiated by immunotherapy such as anti-CTLA4 and anti-PD-1 [19-23]. This provided the rationale for the use of hypofractionated RT in the current study protocol, and suggests that hypofractionated RT and immunotherapy could be a promising strategy in the treatment of nonimmunogenic tumors such as pancreatic cancer. Studies using KPC pancreatic mouse models have supported this hypothesis [24]. In one study, 25 mice were divided equally into groups that received either RT alone; CTLA4 antibody +PD-1 antibody without RT; RT+ CTLA4 antibody; RT+ PD-1 antibody, or RT+ CTLA4 antibody +PD-1 antibody. The 5 mice receiving RT all died within 4 weeks, which is the usual lifespan of KPC mice without treatment. The group receiving the combination of CTLA4 antibody and PD-1 antibody had a slightly improved median survival of 6 weeks. However, once RT was combined with immunotherapy, the median survival of the mice increased dramatically. At 20 weeks, 60% and 80% of the RT+ PD-1 antibody group and the RT+ CTLA4 antibody group, respectively, were alive, and all mice in the RT+ CTLA4 antibody +PD-1 antibody were alive [25].

In order to further assess the potential benefit of immunotherapy potentiated by RT, we examined the combination in a phase Ib study in humans. This study was designed to evaluate the combination of hypofractionated RT in combination with anti-CTLA-4 therapy Tremelimumab or with anti-PD-L1 therapy Durvalumab (MEDI4736) for the treatment of locally advanced unresectable pancreatic cancer.

Materials and Methods

Recruitment strategies

The study was posted on the NYU website and on clinicaltrials.gov. All patients were consented prior to participation in the study. This study was performed at the NYU Perlmutter Cancer Center, with subcontracting with the National Cancer Institute and Memorial Sloan Kettering Cancer Center.

The enrollment was expected to be 12 patients per site, per year, but enrollment stopped after four patients as the study sponsor discontinued funding for the trial. Enrollment lasted only five months, beginning on 7/10/2017 and ending on 12/14/2017.

Study population

Adult treatment-naïve patients with biopsy-proven pancreatic adenocarcinoma, which is not resectable and not metastatic, with measurable lesion according to RECIST 1.1 were enrolled. All patients had ECOG performance status of 0 or 1 and adequate organ and marrow function as defined below: Absolute Neutrophil Count >1,500/mcL, Platelets ≥ 100,000/mcL, Hemoglobin >9.0 g/dL, Total Bilirubin ≤ 1.5xULN, Serum Albumin ≥ 2.5 g/dL, ALT or AST up to 2.5 x ULN (if no liver metastases), or ALT or AST up to 5 x ULN (if liver metastases present), Creatinine <2x institution upper limit of normal OR Creatinine Clearance >45 mL/min/1.73 m² for patients with creatinine levels above institutional normal. Patients with active autoimmune disease or pneumonitis were excluded from the study.

Investigational agent

Durvalumab (MEDI4736) and Tremelimumab were provided by AstraZeneca PLC. SBRT is commercially available.

Study design

A multi-institutional phase Ib trial of radiation therapy in combination with immune checkpoint inhibition (anti-CTLA4 alone, anti-PD-L1 alone, or anti-CTLA4 with anti-PDL1) in patients with unresectable locally advanced pancreatic cancer.

Dose and administration

Cohort A- SBRT plus Durvalumab (MEDI4736): 1 dose escalation, Cohort B- SBRT plus Tremelimumab: 1 dose escalation, Cohort C- SBRT plus Durvalumab (MEDI4736) in combination with Tremelimumab: For Durvalumab (MEDI4736), there will be either 1 dose escalation (if Recommended Phase 2 Dose (RP2D) of Cohort A is >750 mg) or no dose escalation (if RP2D of Cohort A is 750 mg). For Tremelimumab, there will be flat dosing of 75 mg, no dose escalation. Each cohort will have a standard 3+3 dose escalation design. SBRT will be administered at the standard dose of 6.6 Gy daily for 5 days in each cohort. Following randomization to Cohorts A, B, and C, individuals in each cohort will undergo the following dosing schema (Figure 1). They will each receive SBRT 6.6 Gy x 5 days, in conjunction with Durvalumab and/or Tremelimumab dosing based on cohort. In cohort A, for Dose Level 0, Durvalumab (MEDI4736) will be administered at a dose of 1125 mg over 60 minutes on cycle 1 day 1, followed by 1125 mg over 60 minutes every 4 weeks thereafter, for a total of

48 weeks. For Dose Level -1, Durvalumab (MEDI4736) will be administered at a dose of 750 mg over 60 minutes on cycle 1 day 1, followed by 750 mg over 60 minutes every 4 weeks thereafter, for a total of 48 weeks. For Dose Level 1, Durvalumab (MEDI4736) will be administered at a dose of 1500 mg over 60 minutes on cycle 1 day 1, followed by 1500 mg over 60 minutes every 4 weeks thereafter, for a total of 48 weeks. In Cohort B, for Dose Level 0, Tremelimumab will be administered at a dose of 75 mg over 60 minutes on cycle 1 day 1, followed by 75 mg over 60 minutes every 4 weeks, for a total of 6 doses, and every 12 weeks, for an additional 2 doses. For Dose Level 1, Tremelimumab will be administered at a dose of 225 mg over 60 minutes on cycle 1 day 1, followed by 225 mg over 60 minutes every 4 weeks, for a total of 6 doses, and every 12 weeks for an additional 2 doses. In Cohort C, Tremelimumab will be administered at a dose of 75 mg over 60 minutes on cycle 1 day 1, followed by a 1-hour wait period and then administration of Durvalumab (MEDI4736) over 60 minutes (the dose of Durvalumab (MEDI4736) will be dependent on the RP2D determined in Cohort A). If there are no clinically significant concerns after the first cycle, the Durvalumab (MEDI4736) infusion may be administered immediately after the Tremelimumab infusion has finished in subsequent cycles. The combination of Tremelimumab plus Durvalumab (MEDI4736) will be administered every 4 weeks for a total of 4 doses, after which subjects will continue to receive Durvalumab (MEDI4736) monotherapy every 4 weeks. The first dose of Durvalumab (MEDI4736) monotherapy will be administered at week 16 after the last dose of the combination, and the last infusion of monotherapy Durvalumab (MEDI4736) would occur at Week 48, unless withdrawal criteria are met.

Primary endpoints

To determine the safety in individual patients and Recommended Phase 2 Dose (RP2D) of immune checkpoint inhibition comprising either Durvalumab (MEDI4736) alone (Cohort A), Tremelimumab alone (Cohort B), or combined Durvalumab (MEDI4736) and Tremelimumab (Cohort C) along with SBRT in patients with unresectable locally advanced pancreatic cancer.

Additional studies

Changes in immune markers were also evaluated in tissues from all patients. Core biopsies were obtained at baseline (within 28 days prior to Day 1 Cycle 1) and a second time within 7 days of Day 1 Cycle 3. Peripheral blood samples for immune markers were collected at baseline and throughout the protocol at various time points. The final analysis of these data is not presented due to paucity of samples.

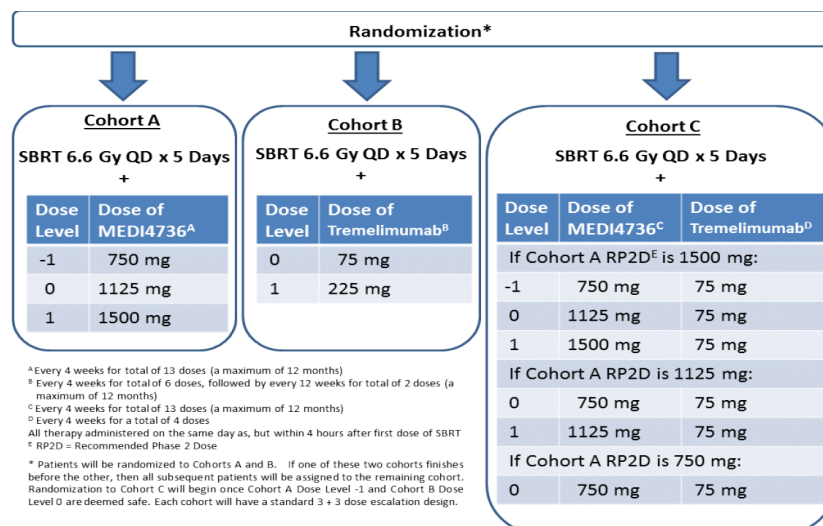


Figure 1. Dosing schema for trial, including Cohorts A, B, and C.

Results

Demographic information

Four patients were enrolled on trial prior to discontinuation of the study by the sponsor. 75% were male and 25% were female (Table 1). Only one of the four patients was over the age of 65, with a median age of 63.5 years. 50% of patients were black, 25% white, and 25% other. Patients were 50% Hispanic/Latino, and 50% non-Hispanic/Latino.

Cohort assignment

Two patients were assigned to Cohort A, which received Durvalumab (MEDI4736) alone with SBRT, and two patients were assigned to Cohort B, which received Tremelimumab alone with SBRT (Table 1). No patients were assigned to Cohort C, as the trial was terminated early due to slow accrual.

Adverse events

All patients reported at least one adverse event (AE), although all serious adverse events (SAEs; grade \geq 3) were experienced by only one patient (Table 2). See appendix for more detailed data regarding AEs and SAEs.

Treatment response

At the first assessment following cycle 2, one patient who was assigned

to cohort A demonstrated stable disease. Two patients, both of whom were assigned to cohort B, had disease progression (Table 1). The fourth enrollee was off-protocol prior to the end of cycle 2 due to noncompliance so efficacy data was not able to be obtained. This study therefore will not provide efficacy results.

Immune marker studies

Due to paucity of samples, no relevant conclusions could be drawn from analysis of immune markers.

Discussion

In our study, we find the treatment combination of PD-L1 and CTLA-4 blockade with SBRT (6.6 Gy x 5) to be safe. Among the four patients, treatment was well-tolerated without discontinuation of treatment due to adverse events. Adverse events included those commonly seen with immunotherapy, such as LFT abnormalities, maculopapular rash, and diarrhea. Pulmonary embolism and duodenal ulcer leading to hemorrhage developed in two patients, neither of which was related to treatment. Pulmonary embolism is not a typical side effect of immunotherapy, but rather likely due to the hypercoagulable effect of malignancy, and the patient who developed a duodenal ulcer had known peptic ulcer disease. No dose-limiting toxicities were observed. Due to the small sample size of this study, complete safety data on the combination of SBRT and immunotherapy

Table 1. Demographic information, cohort assignment, and treatment response data for patients on trial. SD=stable disease; PD=progression of disease.

Participant	Sex	Ethnicity	Race	Age at enrollment	Stage at study entry	Cohort	Response (C3D1)
01-001	Male	Hispanic/Latino	White	70	T4,N0,M0	A	SD
01-002	Female	Not Hispanic/Latino	Black	54	T4,Nx,M0	B	PD
01-004	Male	Hispanic/Latino	Other-Spanish	63	T3,N1,M0	B	PD
01-005	Male	Not Hispanic/Latino	Black	64	T4,N1,M0	A	Not evaluable - did not remain on trial until C3

Table 2. List of all AEs seen in this study by maximum grade. Also indicated are the number of patients with AEs related to Durvalumab, SBRT, or not related to treatment, out of 4 patients evaluable for data, **=immune-related adverse events.

Adverse events	Maximum grade	Number of patients with Durvalumab-related AE	Number of patients with Tremelimumab- and/or SBRT- related AE	Number of patients with AE that was not treatment-related
LFT abnormalities**	4	1	0	0
Abdominal pain	3	0	0	1
Pulmonary embolism	3	0	0	1
Muscle weakness	3	1	0	0
Electrolyte abnormalities	3	0	0	1
Hematologic abnormalities	3	0	0	1
Duodenal hemorrhage	3	0	0	1
Autoimmune hepatitis**	3	1	0	0
Dehydration	2	0	0	1
Anorexia	1	0	0	1
Hypersomnia	1	0	0	1
Diarrhea**	1	0	1	0
Maculopapular rash**	1	1	0	0

Table 3. Serious Adverse Events (=Grade 3) seen with Durvalumab, Tremelimumab, and SBRT in this study, out of 4 patients evaluable for data. **=immune-related adverse events.

Serious adverse events	Durvalumab- related	Tremelimumab- and/or SBRT-related	Not treatment-related
LFT abnormalities**	1	0	0
Autoimmune hepatitis**	1	0	0
Muscle weakness	1	0	0
Lymphopenia	0	0	1
Pulmonary embolism	0	0	1
Duodenal hemorrhage	0	0	1
Abdominal pain	0	0	1
Hypophosphatemia	0	0	1

Table 4. Adverse Events (Grades 1 and 2) seen with Durvalumab, Tremelimumab, and SBRT in this study, out of 4 patients evaluable for data. **=immune-related adverse events.

Grade 1/2 adverse events	Durvalumab-related	Tremelimumab- and/or SBRT-related	Not treatment-related
LFT abnormalities*	1	0	0
Autoimmune hepatitis*	1	0	0
Muscle weakness	1	0	0
Maculopapular rash*	1	0	0
Diarrhea*	0	1	0
Hematologic abnormalities	0	0	1
Electrolyte abnormalities	0	0	1
Dehydration	0	0	1
Hypersomnia	0	0	1
Anorexia	0	0	1
Duodenal ulcer	0	0	1

could not be adequately assessed. Nevertheless, these preliminary results suggest feasibility of this treatment regimen. This is the first report using RT in combination with immunotherapy in LAPC.

Despite its novelty, the clinical and scientific rationale for this approach is supported by several studies assessing the combination of hypofractionated RT with immunotherapy. A phase I study evaluated a similar regimen to this study of Durvalumab/Tremelimumab and SBRT and reported both safety and tolerability in 59 patients, with significant treatment benefit [26]. However, this regimen was used in a patient population with metastatic pancreatic ductal carcinoma (mPDC), which is more advanced than the LAPC patients in this study. Additionally, the radiation dose and its relation to the first dose of immunotherapy were slightly different than in this study. Cohorts A1 and A2 in the study received Durvalumab every 2 weeks and either 8 Gy in one fraction of SBRT on day 1 or 25 Gy in five fractions on day -3 to +1. Cohorts B1 and B2 received Durvalumab/Tremelimumab every 4 weeks and either 8 Gy in one fraction of SBRT on day 1 or 25 Gy in five fractions on day -3 to +1. No dose-limiting toxicities were found. All patients experienced at least one treatment-related AE, but primarily Grade 1 or 2, with the most common AEs being lymphopenia, anemia, fatigue, thrombocytopenia, nausea, pruritus, elevated AST, diarrhea, hyponatremia, hypoalbuminemia, leukopenia, vomiting, skin rashes, and fever. The overall response rate was 5.1%.

Hypofractionated RT with 25Gy/5 (cohort 2) seemed to greatly improve outcomes, with an increased PFS and OS when compared to 8Gy x 1 (cohort 1) of each group. Median PFS increased from 1.7 months with Durvalumab with 8 Gy x 1 (cohort A1) and increased to 2.5 months with 25 Gy/5 fractions (cohort A2). Similarly, PFS increased from 0.9 months with combination.

Durvalumab/Tremelimumab (cohort B1) to 2.3 months in cohort B2 OS of 3.3 months in cohort A1 increased to 9.0 months in cohort A2, while OS of 2.1 months in cohort B1 increased to 4.2 months in cohort B2. This increase in PFS and OS suggests that hypofractionated RT may improve efficacy of immunotherapy, whereas one fraction of RT may yield less favorable efficacy outcomes. However, there may not be a benefit of Durvalumab and Tremelimumab over Durvalumab alone, as the A cohorts actually appeared to achieve numerically shorter PFS and OS than the B cohorts.

A phase II study reporting on 65 previously-treated mPDC patients who received both Durvalumab and Tremelimumab without SBRT also found that the treatment was well-tolerated, as only 4 of 64 patients (6%) discontinued treatment due to treatment-related adverse events. The objective response rate was 3.1% for patients receiving Durvalumab and Tremelimumab, and 0% for patients receiving Durvalumab alone [27]. In another phase Ib study of Durvalumab and Tremelimumab in advanced, metastatic, recurrent or unresectable cancer with multiple primaries in which no curative therapy exists, no infusion-related reactions were observed, although 2/14 patients discontinued treatment due to toxicity. Adverse events were manageable, primarily low-grade effects such as fatigue, rash, pruritus, and nausea [28]. Finally, a meta-analysis of 1,529 patients with various solid tumors

who received Durvalumab and/or Tremelimumab found them to be safe, with the most common adverse events being pruritus, fatigue, and LFT abnormalities [29].

The relevance of immunotherapy and RT as vital areas of investigation for patients with pancreatic cancer is illustrated by the ten trials that are currently using Durvalumab and/or Tremelimumab in this population, three of which also include RT. One study of unresectable pancreatic cancer is comparing the effects of one fraction of 8Gy versus five fractions of 5Gy with either Durvalumab alone or Durvalumab and Tremelimumab (NCT02311361). Another phase I/II study of patients with borderline resectable LAPC evaluates gemcitabine/nab-paclitaxel followed by Durvalumab with concurrent SBRT at 6.6 Gy x 5 fractions (NCT03245541). The final study includes patients with metastatic melanoma, metastatic non-small cell lung cancer, metastatic breast cancer, or metastatic pancreatic adenocarcinoma that has relapsed or been refractory to therapy (NCT02639026). These patients are treated with Durvalumab and Tremelimumab, along with RT given either as 17 Gy x 1 fraction, or 8 Gy x 3 fractions. In our study, efficacy could not be adequately assessed, as only four patients were enrolled, and only three patients completed two cycles of treatment. However, of these three patients, one patient had stable disease and two had disease progression. We eagerly await future data in both safety and efficacy, given the safety and tolerability we observed in our study and its strong preclinical potential for a synergistic immune response.

Pancreatic adenocarcinoma is a cancer with poor immunogenicity and low tumor mutational burden, which could explain the poor outcomes seen with immunotherapy in previous trials [30]. There are many methods being explored beyond RT that may improve the ability to utilize immunotherapy in this traditionally immunosuppressive cancer. First, optimization of drug delivery to the tumor, such as by conjugating immune check point inhibitors to a collagen-binding domain and IL-2, may increase response [31]. Nanoparticles that are MMP-2 sensitive and are conjugated to PD-L1 antibodies have also been shown to accumulate at the tumor site, leading to enhanced drug release where it is most needed [32]. Finding biomarkers that are able to predict individual response to immunotherapy would also be helpful in guiding patient selection for these drugs. A study that used clinical survival and RNA expression data from The Cancer Genome Atlas and performed Immunohistochemistry on 152 pancreatic adenocarcinoma patients found a PD-L1+/CD8^{high} patient population in whom PD-1 inhibitors may be especially efficacious in boosting CD8 response [33]. Specifically selecting for this PD-L1+/CD8^{high} subtype in future studies with Durvalumab may lead to improved outcomes. Finally, the use of imaging to more precisely monitor response to immunotherapy is on the horizon. Immuno-PET, a promising imaging modality which allows for visualization of immunotherapy targets using radiolabeled proteins, is being explored in several clinical trials [34]. In conjunction with RT and immunotherapy, as in this study, employing the above techniques may lead to further improved outcomes.

Conclusion

Of note, several ongoing trials are assessing the synergy of immune checkpoint inhibitors in other settings, such as with minimally invasive microwave ablation (NCT04156087). Other trials seek to treat pancreatic cancer using SBRT and novel immunotherapy such as M7824, an anti-PD-L1/TGF-beta2 receptor protein, and M9241, an immunocytokine composed of 2 IL-12 heterodimers (NCT04327986). By taking advantage of the wide variety of treatments becoming available, we look forward to discovering even more ways to combat this difficult-to-treat cancer.

Footnotes

CONSORT 2010 Statement: The authors have read the CONSORT 2010 Statement, and the manuscript was prepared and revised according to the CONSORT 2010 Statement.

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Appendix

Serious adverse events (grade ≥ 3 ; Table 3) seen in this study were: lymphopenia (1 patient, 25%), muscle weakness (1 patient, 25%), increased AST (1 patient, 25%), increased ALT (1 patient, 25%), increased bilirubin (1 patient, 25%), autoimmune hepatitis (1 patient, 25%), abdominal pain (1 patient, 25%), hypophosphatemia (1 patient, 25%), pulmonary embolism (1 patient, 25%), and duodenal hemorrhage (1 patient, 25%). The pulmonary embolism, duodenal hemorrhage, abdominal pain, hypophosphatemia, and lymphopenia were not due to treatment, whereas all others were possibly attributable to Durvalumab (MEDI4736). All of these serious adverse events were seen in only one patient. No grade 5 toxicities were observed.

Non-serious adverse events (grades 1 and 2; Table 4) included: muscle weakness (1 patient, 25%), increased AST (1 patient, 25%), increased ALT (1 patient, 25%), increased bilirubin (1 patient, 25%), thrombocytopenia (1 patient, 25%), maculopapular rash (1 patient, 25%), hyponatremia (1 patient, 25%), leukopenia (1 patient, 25%), lymphopenia (1 patient, 25%), anemia (1 patient, 25%), hypersomnia (1 patient, 25%), anorexia (1 patient, 25%), dehydration (1 patient, 25%), hypokalemia (1 patient, 25%), hypomagnesemia (1 patient, 25%), duodenal ulcer (1 patient, 25%), and diarrhea (1 patient, 25%). All patients demonstrated at least one adverse event. The adverse events possibly attributable to Durvalumab (MEDI4736) were: muscle weakness, increased AST, increased ALT, increased bilirubin, thrombocytopenia, maculopapular rash, and hyponatremia. Diarrhea was the only adverse event possibly attributable to either Tremelimumab or SBRT.

Immune-related side effects, all listed above, included: increased AST (1 patient, 25%), increased ALT (1 patient, 25%), increased bilirubin (1 patient, 25%), autoimmune hepatitis (1 patient, 25%), diarrhea (1 patient, 25%), and maculopapular rash (1 patient, 25%).

Author contributions

Wu J conceived and designed the study, developed methodology, interpreted the data, wrote and revised the manuscript; Atkinson EC acquired, analyzed and interpreted the data, wrote and revised the manuscript; Du K contributed to study design and methodology, gave administrative/technical/material support, revised and approved the study; Nguy S revised and approved the manuscript; Pavlick AC gave administrative/technical/material support, supervised the study, revised and approved the manuscript; Goldberg JD developed methodology, interpreted the data, revised and approved the manuscript; Becker D gave administrative/technical/material support, supervised the study, revised

and approved the manuscript; Shum E gave administrative/technical/material support, revised and approved the manuscript; Lee SY revised and approved the manuscript; Miller G gave administrative/technical/material support, revised and approved the manuscript; Chuy J gave administrative/technical/material support, revised and approved the manuscript; Leichman L contributed to study conception and methodology, gave administrative/technical/material support, supervised the study, and revised and gave final approval of the study.

Institutional review board statement

This study was reviewed and approved by the Institutional Review Board of New York University School of Medicine.

Clinical trial registration statement

This registration policy applies to prospective trials only.

Informed consent statement

All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement

The authors declare no potential conflicts of interest.

References

1. R, Siegel, Ma J and Zou Z. "Cancer Statistics." *CA Cancer J Clin* 64(2014): 9-29.
2. A, Nagrial, Chin VT and O'Connor C. "Role of chemoradiation in locally advanced pancreatic cancer: A systematic review and meta-analysis." *J Clin Oncol* 33(2015).
3. Sr, Loehrer PJ, Feng Y and Cardenes H. "Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial." *J Clin Oncol* 29(2011): 4105-4112.
4. MD, Chuong, Springett GM and Freilich JM. "Stereotactic body radiation therapy for locally advanced and borderline resectable pancreatic cancer is effective and well tolerated." *Int J Radiat Oncol Biol Phys* 86(2013): 516-522.
5. PA, Ott, Hodi FS and Robert C. "CTLA-4 and PD-1/PD-L1 blockade: new immunotherapeutic modalities with durable clinical benefit in melanoma patients." *Clin Cancer Res* 19(2013): 5300-5309.
6. L, Gelao, Criscitiello C and Esposito A. "Immune checkpoint blockade in cancer treatment: a double-edged sword cross-targeting the host as an innocent bystander." *Toxins* 6(2014): 914-933.
7. JD, Wolchok, Kluger H and Calahan MK. "Nivolumab and ipilimumab in advanced melanoma." *N Engl J Med* 369(2013): 122-133.
8. "U.S. Food and Drug Administration approves Opdivo (nivolumab) + Yervoy (ipilimumab) for patients with hepatocellular carcinoma (HCC) previously treated with sorafenib. Bristol Myers Squibb Press Release." (2020).
9. RJ, Motzer, Tannir NM and McDermott DF. "Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma." *N Engl J Med* 378(2018): 1277-1290.
10. J, Lutzky, Antonia SJ and Blake-Haskins A. "A phase I study of Durvalumab (MEDI4736), an anti-PDL1-antibody, in patients with advanced solid tumors." *J Clin Oncol* 32(2014): 5s, abstr 3001.
11. NH, Segal, Antonia SJ and Brahmer JR. "Preliminary data from a multi-arm expansion study of MEDI4736, an anti-PD-L1 antibody." *J Clin Oncol* 32(2014): 5s, abstr 3002.
12. M, Hilmi, Bartholin L and Neuzillet C. "Immune therapies in pancreatic

- ductal adenocarcinoma: Where are we now?." *World J Gastroenterol* 24(2018): 2137-2151.
13. JR, Brahmer, Tykodi SS and Chow LQ. "Safety and activity of anti-PD-L1 antibody in patients with advanced cancer." *N Engl J Med* 366(2012): 2455-2465.
 14. DT, Le, Wang-Gillam A and Picozzi Jr V. "A phase 2 randomized trial of GVAX pancreas and CRS-207 immunotherapy versus GVAX alone in patients with metastatic pancreatic adenocarcinoma." *J Clin Oncol* 32(2014): Suppl 3; abstract 177.
 15. Y, Lee, Auh SL and Wang Y. "Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment." *Blood* 114(2009): 589-595.
 16. C, Blanquicett, Saif MW and Buchsbaum DJ. "Antitumor efficacy of capecitabine and celecoxib in irradiated and lead-shielded, contralateral human BxPC-3 pancreatic cancer xenografts: clinical implications of abscopal effects." *Clin Cancer Res* 11(2005): 8773-8781.
 17. K, Camphausen, Moses MA and Menard C. "Radiation abscopal antitumor effect is mediated through p53." *Cancer Research* 63(2003):1990-1903.
 18. S, Demaria, Ng B and Devitt ML. "Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated." *Int J Radiat Oncol Biol Phys* 58(2004): 862-870.
 19. MZ, Dewan, Galloway AE and Kawashima N. "Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with antiCTLA-4 antibody." *Clin Cancer Res* 15: 5379-5388.
 20. S, Demaria, Kawashima N and Yang AM. "Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer." *Clin Cancer Res* 11(2005): 728-734.
 21. EB, Golden, Demaria S and Schiff PB. "An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer." *Cancer Immunol Res* 1(2013): 365-372.
 22. SC, Formenti, Demaria S. "Combining radiotherapy and cancer immunotherapy: A paradigm shift." *J Natl Cancer Inst* 105(2013): 256-265.
 23. J, Zeng, See AP and Phallen J. "Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas." *Int J Radiat Oncol Biol Phys* 86(2013): 343-349.
 24. VC, Twyman-Saint, Rech AJ and Maity A. "Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer." *Nature* 520(2015): 373-377.
 25. A, Azad, Yin Lim S and D'Costa Z. "PD-L1 blockade enhances response of pancreatic ductal adenocarcinoma to radiotherapy." *EMBO Mol Med* 9(2017): 167-180.
 26. C, Xie, Duffy AG, Gagandeep B. "Immune Checkpoint Blockade in Combination with Stereotactic Body Radiotherapy in Patients with Metastatic Pancreatic Ductal Adenocarcinoma." *Clin Cancer Res* 26(2020): 2318-2326
 27. EM, O'Reilly, Oh D and Dhani N. "Durvalumab With or Without Tremelimumab for Patients With Metastatic Pancreatic Ductal Adenocarcinoma: A Phase 2 Randomized Clinical Trial." *JAMA Oncol* 5(2019): 1431-1438.
 28. J, Nehra, Bradbury PA and Ellis PM. "A Canadian cancer trials group phase IB study of durvalumab (anti-PD-L1) plus tremelimumab (anti-CTLA-4) given concurrently or sequentially in patients with advanced, incurable solid malignancies." *Invest New Drugs* (2020).
 29. H, Yang, Shen K and Zhu C. "Safety and efficacy of durvalumab (MEDI4736) in various solid tumors." *Drug Des Devel Ther* 12(2018): 2085-2096.
 30. RE, Royal, Levy C and Turner K. "Phase 2 Trial of Single Agent Ipilimumab (Anti-CTLA-4) for Locally Advanced or Metastatic Pancreatic Adenocarcinoma." *J Immunother* 33(2010): 828-833.
 31. J, Ishihara, Ishihara A and Sasaki K. "Targeted antibody and cytokine cancer immunotherapies through collagen affinity." *Sci Transl Med* 11(2019): eaau3259.
 32. D, Wang, Wang T and Yu H. "Engineering nanoparticles to locally activate T cells in the tumor microenvironment." *Sci Immunol* 4(2019): eaau6584.
 33. L, Danilova, Ho WJ and Zhu Q. "Programmed cell death ligand-1 (PD-L1) and CD8 expression profiling identify an immunologic subtype of pancreatic ductal adenocarcinomas with favorable survival." *Cancer Immunol Res* 7(2019): 886-895.
 34. AE, Marciscano and Thorek DLJ. "Role of noninvasive molecular imaging in determining response." *Adv Radiat Oncol* 3(2018): 534-537.

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