Addition of Metastasis-Directed Therapy to Systemic Therapy for Oligometastatic Pancreatic Ductal Adenocarcinoma (EXTEND): A Multicenter, Randomized Phase II Trial

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ABSTRACT

PURPOSE The EXTEND trial tested the hypothesis that adding comprehensive metastasis-directed therapy (MDT) to chemotherapy would improve progression-free survival (PFS) over chemotherapy alone among patients with oligometastatic pancreatic ductal adenocarcinoma (PDAC).

METHODS EXTEND (ClinicalTrials.gov identifier: NCT03599765) is a multicenter, phase II basket trial randomly assigning patients with ≤five metastases 1:1 to MDT plus systemic therapy versus systemic therapy. Disease progression was defined by radiologic criteria (RECIST v1.1), clinical progression, or death. The primary end point was PFS in the per-protocol population, evaluated after all patients achieved at least 6 months of follow-up. Exploratory end points included systemic immune response measures.

RESULTS Between March 19, 2019, and February 13, 2023, 41 patients were randomly assigned and 40 were eligible for the primary analysis of PFS (19 patients in the MDT arm; 21 patients in the control arm). At a median follow-up time of 17 months, the median PFS time was 10.3 months (95% CI, 4.6 to 14.0) in the MDT arm versus 2.5 months (95% CI, 1.7 to 5.1) in the control arm. PFS was significantly improved by the addition of MDT to systemic therapy ($P = .030$ for stratified log-rank test) with a hazard ratio of 0.43 (95% CI, 0.20 to 0.94). No grade ≥3 or greater adverse events related to MDT were observed. Systemic immune activation events were associated with MDT and correlated with improved PFS.

CONCLUSION This study supports the addition of MDT to systemic therapy for patients with oligometastatic PDAC. Induction of systemic immunity is a possible mechanism of benefit. These results warrant confirmatory trials to refine treatment strategy and provide external validation.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

Long-term outcomes after frontline chemotherapy for metastatic pancreatic ductal adenocarcinoma (PDAC) are poor, with median progression-free survival (PFS) ranging from 5 to 7 months.[1-3] Patients with limited metastatic disease (oligometastatic) may have improved outcomes with strategies combining chemotherapy with comprehensive metastasis-directed therapy (MDT) to all sites of radiologically detectable disease.[4,5] Previous trials have demonstrated improved outcomes with MDT plus systemic therapy for several tumor types.[6,7] Retrospective evidence has suggested a potential benefit of MDT for patients with oligometastatic PDAC, including time off chemotherapy, although no randomized trials have been conducted to date.[8-11] The EXTEND trial tested the hypothesis that adding MDT to systemic therapy improves PFS for patients with oligometastatic PDAC.

CONTEXT

Key Objective

Among patients with oligometastatic pancreatic ductal adenocarcinoma (PDAC), does the combination of metastasis-directed therapy (MDT) and systemic therapy confer superior progression-free survival (PFS) compared with systemic therapy alone?

Knowledge Generated

The randomized phase II EXTEND trial demonstrates that adding MDT to standard-of-care systemic therapy improved PFS over systemic therapy alone for patients with oligometastatic pancreatic adenocarcinoma, with correlative analyses suggesting that enhanced systemic immunity is a possible mechanism of benefit. EXTEND provides the most robust evidence to date that an oligometastatic disease state exists in PDAC.

Relevance *(A.H. Ko)*

For carefully selected patients with limited sites of metastatic involvement of their pancreatic cancer, the addition of locoregional intervention to systemic treatment may provide therapeutic benefit.*

*Relevance section written by *JCO* Associate Editor Andrew H. Ko, MD, FASCO.

METHODS

Study Design

EXTEND is a phase II multicenter, randomized basket trial for patients with various solid tumors. Histology-specific baskets were prespecified and independently powered after a lead-in phase.[12] This trial was approved by the institutional review board at each participating institution. All patients provided consent.

Patients

Eligibility criteria included age ≥18 years, performance status 0-2, ≤four previous lines of systemic therapy for metastatic disease, and ≤five sites of metastatic disease amenable to MDT. Staging included computed tomography of the chest, abdomen, and pelvis with contrast and magnetic resonance imaging of the abdomen and/or liver as appropriate. Patients were enrolled at The University of Texas MD Anderson Cancer Center (TX), Community Health Network (IN), and Banner MD Anderson Cancer Center (AZ).

Random Assignment and Masking

Patients were randomly assigned 1:1 without masking to receive MDT for all active radiologic disease (metastasis plus primary tumor as applicable) with systemic therapy versus systemic therapy only. Stratification factors were number of metastatic lesions (1-2 *v* 3-5), number of previous lines of systemic therapy for metastatic disease (0-1 *v* >1), and cancer antigen 19-9 (CA19-9) level (<90 U/mL *v* ≥90 U/mL).

Procedures

MDT consisted of definitive local therapy; stereotactic ablative radiotherapy was recommended when feasible. Radiotherapy plans were reviewed in a quality assurance conference. Systemic therapy was chosen by the treating oncologist. For patients randomly assigned to the control arm, crossover to MDT was permitted at progression.

Outcomes

The primary end point of PFS was measured from random assignment to radiologic progression, clinical progression, or death. Radiologic progression was defined by RECIST version 1.1 and assessed via central review (the Quantitative Imaging Analysis Core at MD Anderson) by an independent team of radiologists blinded to random assignment. Clinical progression was defined by the requirement to change therapeutic strategy to prevent undue suffering, death, or other harm related to clinical progression of disease as determined by the treating oncologist, such as progressive refractory tumor-related pain. Secondary end points included overall survival (OS), time to next-line systemic therapy, time to local failure, time to new lesion formation, toxicity, and quality of life. OS was evaluated in the intention-to-treat population; other end points were evaluated in the per-protocol population. Toxicity was graded per the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0. Events for cancer-specific survival were defined by deaths attributed to PDAC progression. Exploratory end points included measures of systemic immune response on the basis of previous data suggesting immunostimulatory effects of MDT (Data Supplement, Methods, online only).[13]

Statistical Analysis

With a one-sided type I error rate of 0.10, a sample size of 40 patients would have 80% power to detect an improvement in median PFS from 4 months to 8.5 months, corresponding to a hazard ratio (HR) of 0.471. PFS estimates were chosen by halving the observed magnitude of benefit seen in a randomized trial investigating MDT for oligometastatic non–small-cell lung cancer, which represented the only randomized data evaluating radiotherapy for oligometastasis at the time of trial design.[7]

Time-to-event outcomes were estimated by using the product limit estimator of Kaplan and Meier and compared with a stratified log-rank test, accounting for stratification factors at random assignment. Outcomes were also modeled using stratified Cox proportional hazards regression. Analyses were conducted with STAT/MP v17.0 (StataCorp, College Station, TX) and SAS v9.4 (SAS institute, Cary, NC). Significance was defined on the basis of two-sided testing as $P < .05$. The cutoff date for the primary analysis was September 1, 2023. This study is registered with ClinicalTrials.gov identifier: NCT03599765.

RESULTS

Between March 19, 2019, and February 13, 2023, we assessed 55 patients for eligibility and randomly assigned 41 patients (intention-to-treat population; n = 20 MDT, n = 21 control; Fig 1). A total of 40 patients received treatment (n = 19 MDT, n = 21 control) and formed the per-protocol population. Most patients had one to two metastases (n = 31, 78%), with primary-site disease not previously addressed by local therapy (n = 23, 58%). Of the 17 patients with previous primary-site local therapy, 13 were originally treated with primary-site surgery (MDT: n = 6; control: n = 7). All patients received chemotherapy after diagnosis of metastasis. Stratification factors were balanced (Table 1). Most patients had previous exposure to either folinic acid, 5-fluorouracil, irinotecan plus oxaliplatin or gemcitabine plus nab-paclitaxel (GA)-based chemotherapy (MDT: n = 18 [95%]; control: n = 19 [90%]; Data Supplement, Table S1). Before enrollment, 65% of patients (26 of 40) had received chemotherapy with stable disease from the most recent recurrence or progression; the median time on chemotherapy since the most recent progression was 2 months in each arm. Nine patients assigned to the MDT arm (47%) had previous disease progression on one or more lines of systemic therapy for metastatic disease, compared with six patients assigned to the control arm (29%). No patients had a history of polymetastatic disease (ie, induced oligometastasis), and there was a mixture of de novo oligometastasis and oligorecurrence (Table 1).

After random assignment to MDT, 31 metastases were treated with radiotherapy (94%). The two most common prescriptions were 50 Gy in four fractions and 70 Gy in 10 fractions (Data Supplement, Table S2). Two metastases were treated with radiofrequency ablation. All active primary tumors in the MDT arm (11 of 11) were treated with radiotherapy, most commonly 40 Gy in five fractions (Data Supplement, Table S3). Most patients (13 of 19, 68%)

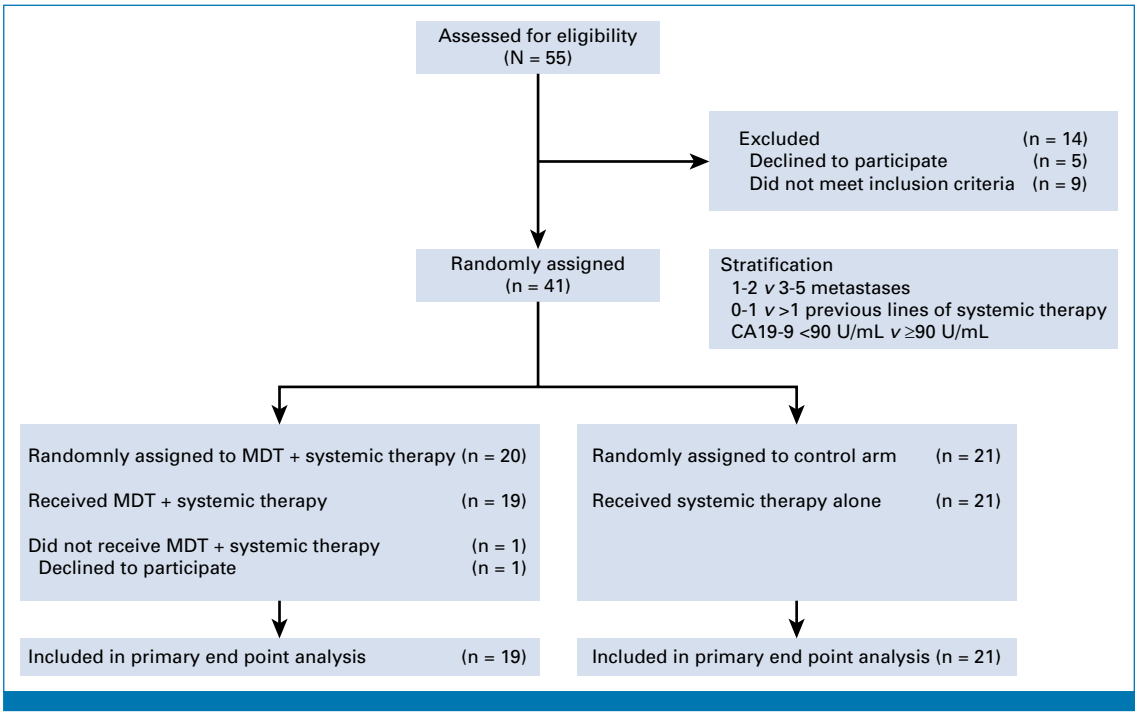

FIG 1. CONSORT diagram of trial screening, random assignment, and analysis. CA19-9, cancer antigen 19-9; MDT, metastasis-directed therapy.

TABLE 1. Demographic and Clinical Characteristics of the Per-Protocol Population by Treatment Allocation Group

Characteristic	MDT Arm	Control Arm
Age, years, median (min-max)	68 (31-84)	67 (45-75)
Gender, No. (%)		
Female	10 (53)	8 (38)
Male	9 (47)	13 (62)
Race, No. (%)		
Asian	1 (5)	1 (5)
Black or African American	1 (5)	6 (29)
White or Caucasian	17 (89)	14 (67)
Ethnicity, No. (%)		
Hispanic or Latino	2 (11)	1 (5)
Not Hispanic or Latino	17 (89)	19 (90)
Unknown	0	1 (5)
Number of metastatic lesions, No. (%)		
1-2	15 (79)	16 (76)
3-5	4 (21)	5 (24)
Sites of metastatic disease,[a] No. (%)		
Lung	6 (32)	4 (19)
Liver	11 (58)	15 (71)
Nonregional lymph node	2 (11)	1 (5)
Bone	2 (11)	0
Other[b]	0	2 (10)
Lung-limited disease, No. (%)	1 (5)	2 (10)
Previous lines of systemic therapy for metastasis with progression, No. (%)		
0	10 (53)	15 (71)
1	9 (47)	4 (19)
2	0	2 (10)
Cancer antigen 19-9, No. (%)		
<90 U/mL	10 (53)	11 (52)
≥90 U/mL	9 (47)	10 (48)
Oligometastasis state, No. (%)		
Synchronous	7 (37)	7 (33)
Metachronous	12 (63)	14 (67)
Induced oligometastasis from polymetastasis	0	0
Primary tumor not previously treated by local therapy,[c] No. (%)	11 (58)	12 (57)
Time from initial diagnosis to enrollment, months, median (min-max)	12 (5-29)	9 (4-88)
Time from metastatic diagnosis to enrollment, months, median (min-max)	4 (0.1-15)	5 (0.3-25)

Abbreviation: MDT, metastasis-directed therapy.

[a]Patients may have more than one site of disease. Thus, the number of patients per site does not sum to the total number of patients. The frequency shown reflects the percentage of patients in each arm with involvement of the listed disease site, which does not sum to 100% since patients may have more than one site of disease.

[b]Other sites: adrenal gland metastasis or soft tissue tumor deposit encasing the celiac artery after distal pancreatectomy.

[c]Local therapy including previous surgery, previous radiotherapy, or both. Two patients in each arm had primary site tumors treated by radiotherapy alone (without surgery) before trial enrollment.

allocated to MDT initiated MDT soon after random assignment; five patients received an additional cycle of chemotherapy, and one patient received two cycles before MDT (the median time of chemotherapy after random assignment before MDT was 0 months; IQR, 0-0.33). The most common systemic therapy after enrollment was GA-based chemotherapy (Data Supplement, Table S4). In the MDT arm, 10 patients underwent a chemotherapy break after MDT (before progression or censoring; median, 4 months; range, 1-12), and chemotherapy was de-escalated to single-agent maintenance in eight patients (median, 5 months; range, 4-10). In the control arm, two patients received a chemotherapy break (median, 4 months; range, 3-5), and five patients underwent de-escalation to single-agent

maintenance therapy (median, 2 months; range, 0.3-5). Altogether, 15 unique patients in the MDT arm and seven unique patients in the control arm had de-escalation to single-agent therapy and/or chemotherapy break. At the time of data cutoff, two patients in the MDT arm continued a chemotherapy break compared with zero in the control arm.

After a median follow-up of 17.3 months, the median PFS in the MDT arm was 10.3 months (95% CI, 4.6 to 14.0) compared with 2.5 months (95% CI, 1.7 to 5.1) in the control arm (Fig 2A). The difference in PFS was statistically significant (P = .030) in favor of the MDT arm with an HR of 0.43 (95% CI, 0.20 to 0.94). The probability of PFS at 1 year was 42% (95% CI, 19 to 64) in the MDT arm and 9% (95% CI, 1 to 29) in the control arm. A total of 13 events occurred in the MDT arm compared with 18 events in the control arm (Fig 3). Post hoc analysis identified baseline CA19-9 level as prognostic (≥90 U/mL *v* <90 U/mL; HR, 2.96 [95% CI, 1.40 to 6.24]; P = .004). Post hoc subgroup analysis suggested a similar benefit from MDT for patients with CA19-9 <90 U/mL (HR, 0.33 [95% CI, 0.11 to 1.05]; P = .06) and CA19-9 ≥90 U/mL (HR, 0.37 [95% CI, 0.14 to 0.99]; P = .048). CA19-9 trends after MDT were mixed, with decreases observed in four of nine patients (Data Supplement, Fig S1).

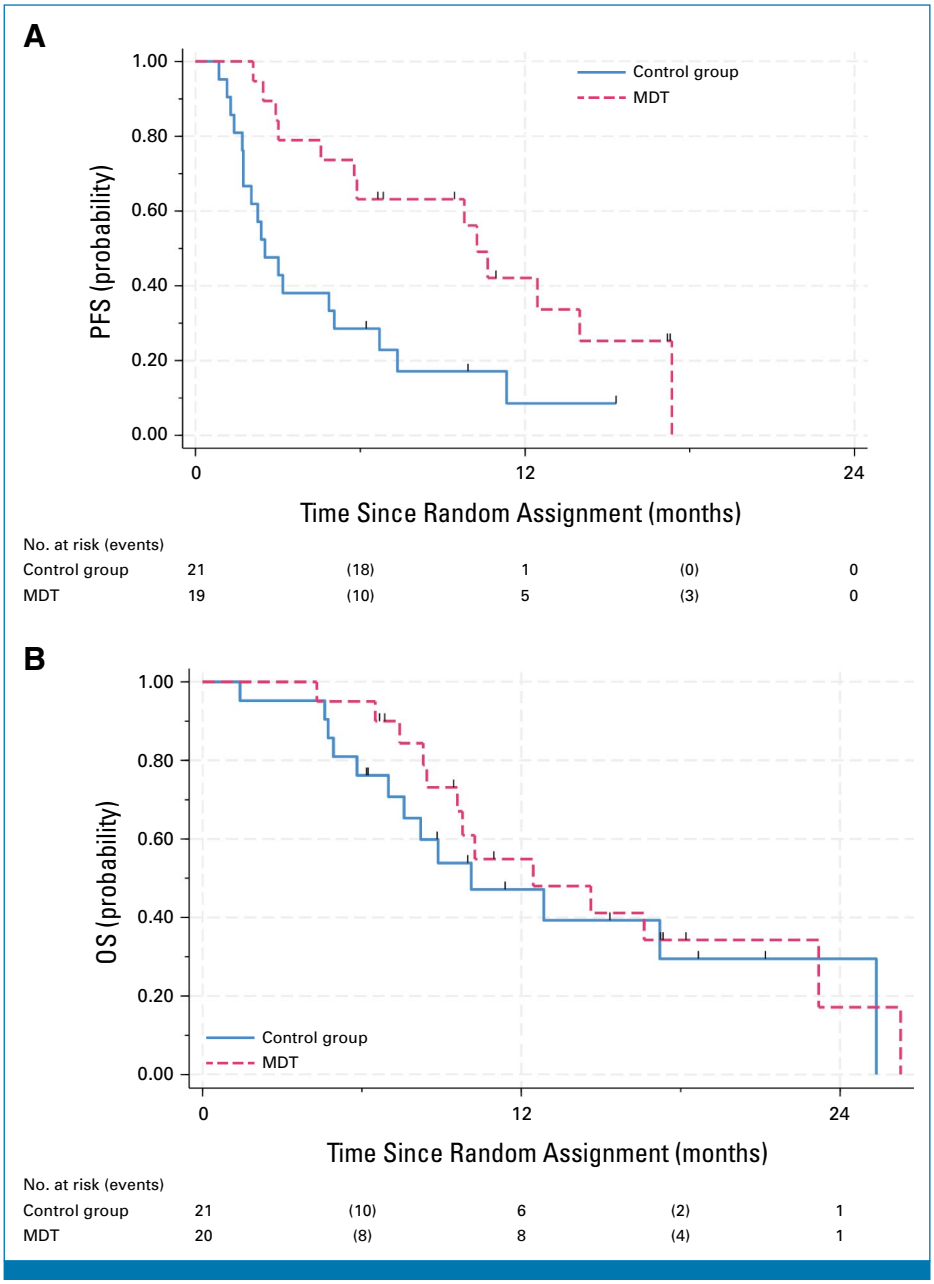

FIG 2. Kaplan-Meier curves comparing MDT plus systemic therapy versus systemic therapy alone for (A) PFS and (B) OS. MDT, metastasis-directed therapy; OS, overall survival; PFS, progression-free survival.

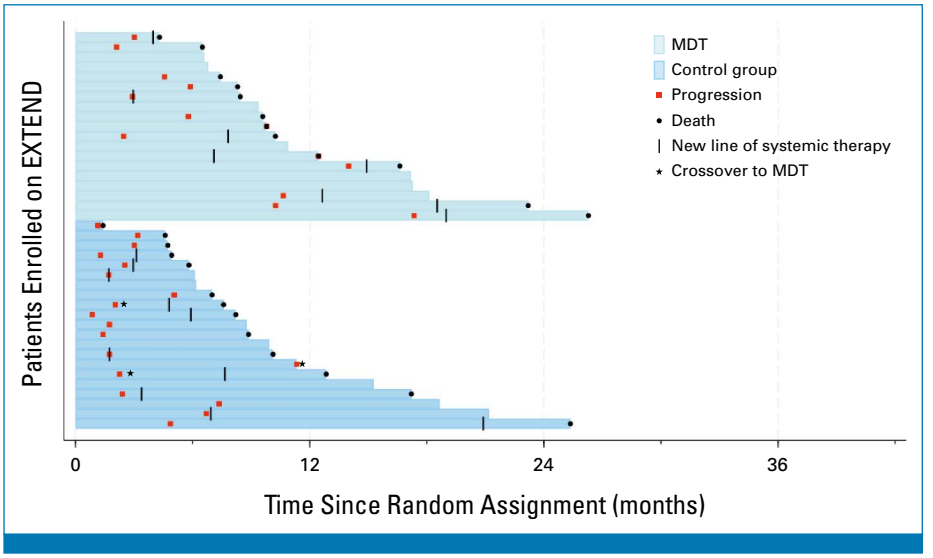

FIG 3. Swimmer plot showing patient-level outcomes after random assignment for each group. Red squares denote progression; black squares denote death; black lines denote a transition to next-line systemic therapy; stars denote crossover to MDT. MDT, metastasis-directed therapy.

New lesions developed in eight patients in the MDT arm and nine patients in the control arm at first progression (Data Supplement, Table S5). The median time to new lesion recurrence was 14 months in the MDT arm (95% CI, 6 to NA) versus 5 months in the control arm (95% CI, 3 to NA; HR, 0.51 [95% CI, 0.18 to 1.49]; $P = .22$; Data Supplement, Fig S2). The 12-month freedom from new lesion recurrence rate was 54% (95% CI, 25 to 76) in the MDT arm and 38% (95% CI, 11 to 63) in the control arm. RECIST-defined local failures occurred at first progression in four (21%) of 19 patients in the MDT arm and five (23%) of 21 patients in the control arm (Data Supplement, Table S5). Two RECIST-defined local failures in the MDT arm were interpreted by the unblinded clinical radiologist as postradiation edematous changes within 3 months of stereotactic ablative radiation. Subsequent off-protocol imaging for both of these patients showed no further increase in the size of these lesions according to the clinical radiologist.

The median time to next-line systemic therapy was 19 months in the MDT arm (95% CI, 8 to NA) versus 8 months in the control arm (95% CI, 3 to NA; HR, 0.53 [95% CI, 0.19 to 1.51]; $P = .24$; Data Supplement, Fig S3). The 12-month freedom from next-line systemic therapy rate was 76% (95% CI, 48 to 91) in the MDT arm and 50% (95% CI, 25 to 71) in the control arm. Of the 18 patients in the control arm alive at progression, three patients (17%) crossed over to MDT. Following crossover, the time to next-line systemic therapy for each patient was 2 months, 5 months, and not reached.

Twenty-six deaths occurred (13 in each group). The median OS for the MDT arm was 12 months (95% CI, 8 to 23) compared with 10 months (95% CI, 7 to NA) for the control arm (HR, 0.58 [95% CI, 0.25 to 1.34]; $P = .20$; Fig 2B). Deaths were attributed to PDAC in 23 cases and noncancer-related causes in three cases (specifically, dissection of thoracoabdominal aortic aneurysm, COVID-19 pneumonia, pulmonary embolism; MDT: n = 2 and control: n = 1). Post hoc median cancer-specific survival was 15 months in the MDT arm and 10 months in the control arm. Postprogression therapy was similar between arms (Data Supplement, Table S6).

No grade 4 or 5 treatment emergent adverse events (TEAEs) took place, regardless of attribution. Assessments of maximum grade across TEAEs per patient demonstrated three grade 3 TEAEs in the MDT group (attribution: not related to MDT; Data Supplement, Table S7). Quality-of-life comparisons were limited because of sample size and showed no apparent differences; baseline quality-of-life data are shown in the Data Supplement (Table S8).

Systemic $CD8^+$ T-cell activation was observed after MDT but not after systemic therapy alone (Fig 4). Proliferative $CD8^+$ T cells were greater at follow-up in the MDT arm compared with the control arm ($P = .02$; Data Supplement, Fig S4). Activated ($PD1^+$) or highly activated ($CD25^+$) $CD8^+$ T cells increased over time in the MDT arm, but not in the control arm (Fig 4A). High-dimensional clustering of $CD8^+$ T cells suggested coexpression of several activation markers and checkpoint receptors (Data Supplement, Figs S5 and S6). This activated population appeared to be preferentially induced after MDT (Data Supplement, Fig S7). Accompanying this induction was a rise in interleukin 15, a cytokine known to promote $CD8^+$ T-cell activation, in the MDT arm but not in the control arm (Fig 4B; Data Supplement, Fig S8). Monocyte chemoattractant protein-1 levels increased in the MDT arm; changes in monocyte populations were not observed (Data Supplement, Fig S9). T-cell receptor sequencing was completed for 674,343 T cells across 31 patients. T-cell receptor

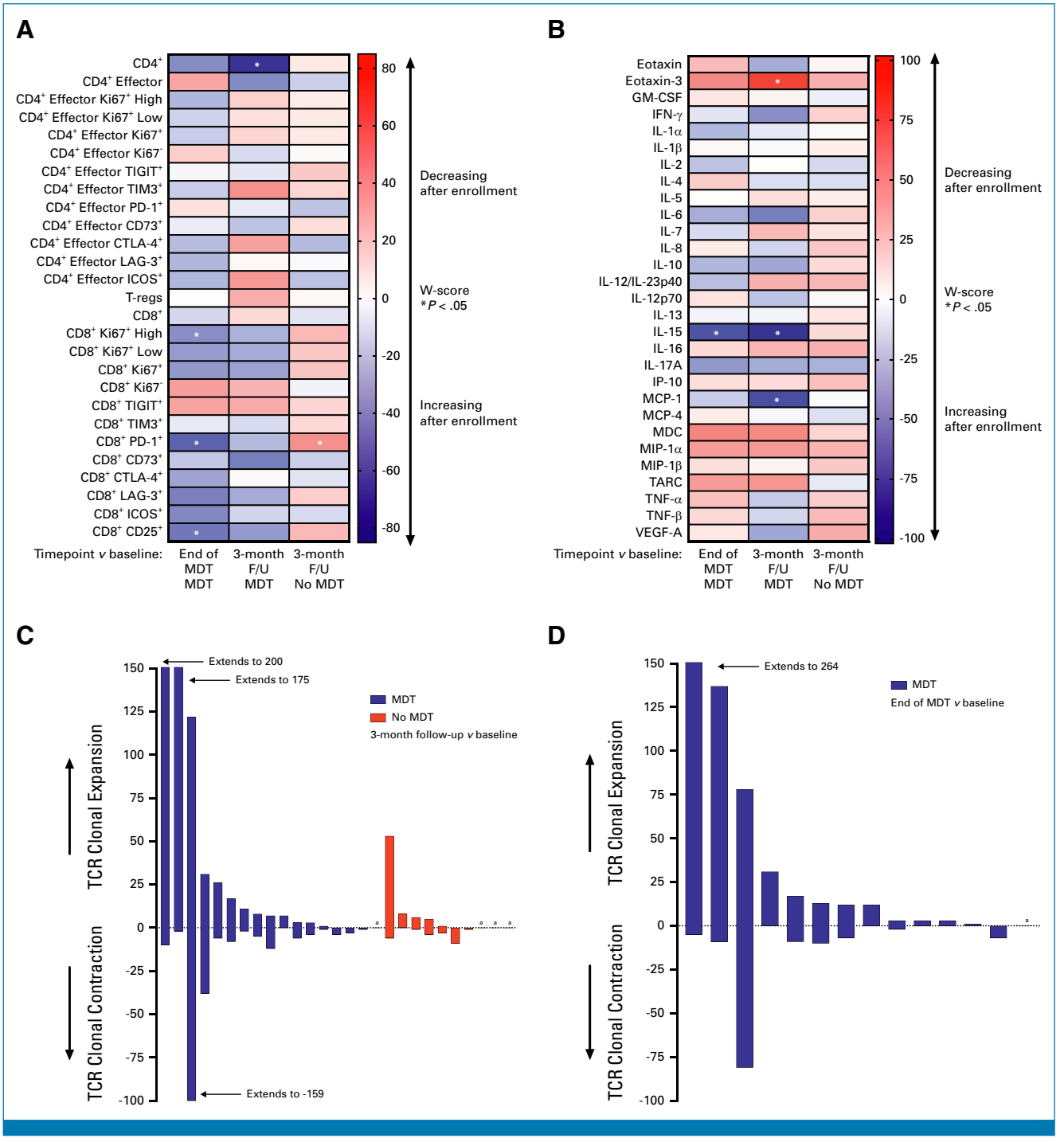

FIG 4. Changes over time in systemic immune features for the MDT plus systemic therapy group and the systemic therapy alone arm. (A) Changes in systemic T-cell populations from baseline in the MDT group (first column: end of radiotherapy *v* baseline; second column: 3-month follow-up *v* baseline) and the control group (third column: 3-month follow-up *v* baseline). *$P < .05$, Wilcoxon matched-pairs test. (B) Changes in systemic cytokine concentrations from baseline in the MDT group (first column: end of radiotherapy *v* baseline; second column: 3-month follow-up *v* baseline) and the control group (third column: 3-month follow-up *v* baseline). *$P < .05$, Wilcoxon matched-pairs test. (C) Number of T-cell receptor clones exhibiting expansion (positive *y*-axis) and contraction (negative *y*-axis) between 3-month follow-up versus baseline for the MDT group and control group, defined by a beta-binomial model with multiple comparisons adjustment. Each set of positive/negative bars represents an individual patient. (D) T-cell receptor clonal expansion and clonal contraction between end of radiotherapy versus baseline for the MDT group. F/U, follow-up; MDT, metastasis-directed therapy; TCR, T-cell receptor. [a]No expansion or contraction observed.

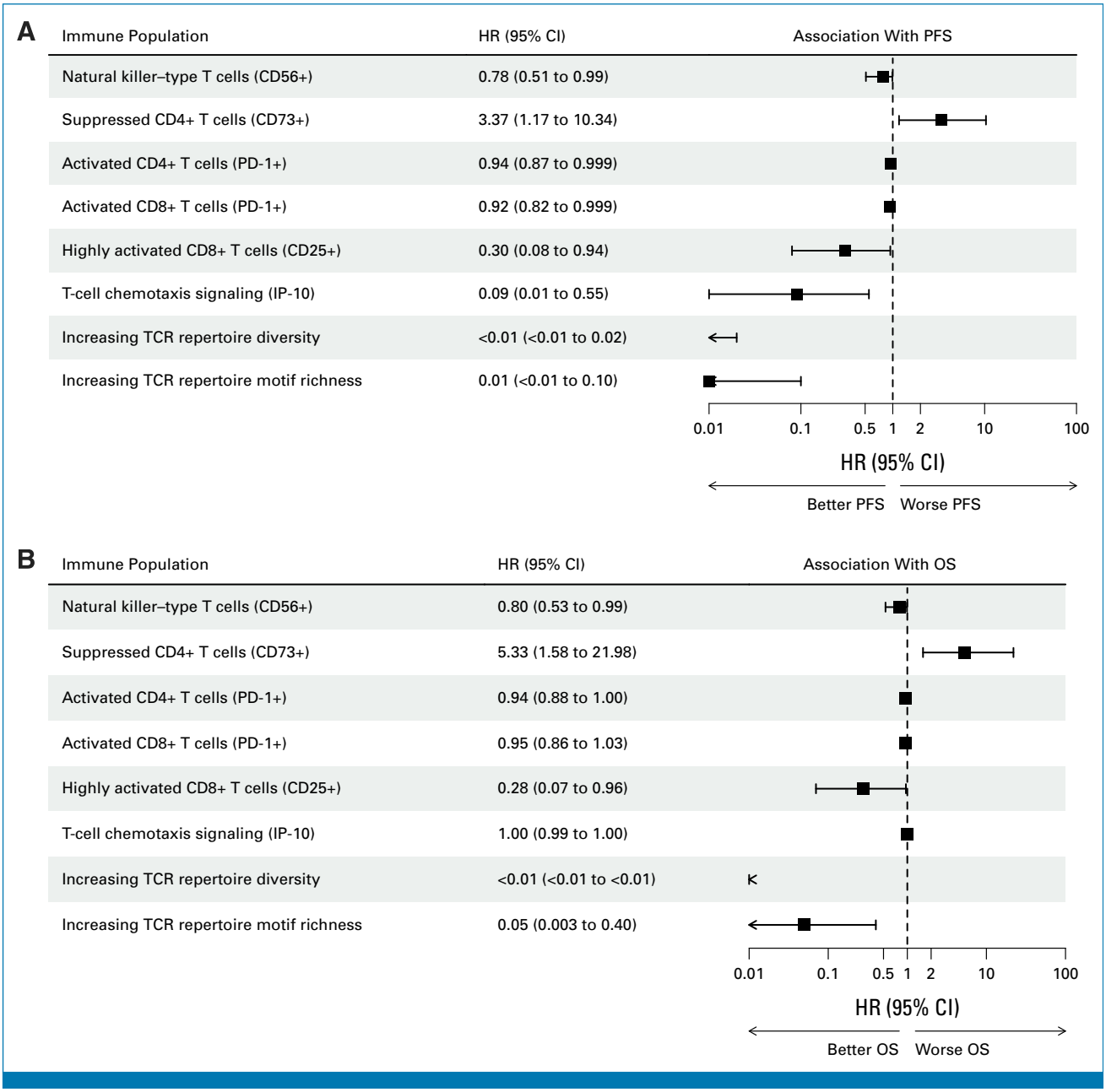

FIG 5. Associations of systemic immune features with (A) PFS and (B) OS by Cox proportional hazards regression. Factors obtained at the end of radiotherapy (collected only in the MDT arm) were assessed in the MDT arm only. Factors obtained at 3-month follow-up (collected in both arms) were adjusted by using randomization arm as a covariate. Each immune feature was evaluated in its own regression model. Natural killer–type T cells are $CD56^+$ $CD3^+$–expressing T cells at the end of radiotherapy. Suppressed $CD4^+$ T cells are $CD73^+$-expressing cells dichotomized at the median at 3-month follow-up. Activated $CD4^+$ T cells are $PD1^+$ at 3-month follow-up. Activated $CD8^+$ T cells are $PD1^+$ at 3-month follow-up. Highly activated $CD8^+$ T cells are $CD25^+$ dichotomized at the median at 3-month follow-up. T-cell chemotaxis signaling is the concentration of cytokine interferon-gamma-IP-10 at the end of radiotherapy. Increasing T-cell receptor repertoire diversity is the fold change between baseline and end of radiotherapy. Increasing T-cell receptor repertoire motif richness is the fold change between baseline and 3-month follow-up. HR, hazard ratio; IP-10, induced protein-10; MDT, metastasis-directed therapy; OS, overall survival; PFS, progression-free survival; TCR, T-cell receptor.

expansion, defined on the basis of a significant increase in the number of T-cell receptors with identical amino acid sequences, was observed prominently after MDT (Figs 4C and 4D). T-cell receptor expansion was associated with activated T cells ($PD1^+$ T cells; $\rho = 0.69$; $P = .01$) and highly activated $CD8^+$ T cells ($CD25^+$ T cells; $\rho = 0.69$; $P = .02$), suggesting that MDT-expanded T-cell receptor clones were also cytotoxic (Data Supplement, Fig S10).

Several markers of T-cell activation were associated with improved PFS and OS (Fig 5). Independent of random assignment, highly activated ($CD25^+$) T cells, natural killer–

type T cells ($CD56^+$), increasing T-cell receptor repertoire diversity, and increasing T-cell receptor–dominant motif richness were each associated with longer PFS and OS, whereas $CD73^+$ T cells (possibly immunosuppressed) were associated with shorter PFS and OS.

DISCUSSION

EXTEND is the first randomized trial evaluating MDT for patients with oligometastatic PDAC. This study demonstrates that MDT plus standard-of-care systemic therapy led to a substantial improvement in PFS compared with standard-of-care systemic therapy alone, without evidence of serious MDT-related adverse events. Secondary outcomes suggest that the mechanism of benefit from MDT may be attributable in part to systemic immune activation. Collectively, EXTEND represents the highest quality data on the management of oligometastatic PDAC to date. The combination of MDT plus systemic therapy is promising and should be tested in large-scale confirmatory trials to evaluate optimal timing and sequencing of MDT, refine selection criteria, and provide external validation.

In the context of three previous trials informing first-line therapy for metastatic PDAC, the median PFS time of 10 months observed in EXTEND after MDT and systemic therapy seems highly promising.[1-3] This PFS time is particularly striking as nearly half of the patients in the MDT arm had already progressed on one line of systemic therapy for metastatic disease before enrollment. The median PFS time of 2.5 months in the control arm mirrors other reports of efficacy of second-line systemic therapy.[14] Thus, as the PFS time of patients in the MDT arm is one of the longest reported in a clinical trial to date for metastatic PDAC, this study's findings have substantial clinical importance for patients with metastatic PDAC.

Given the increased risk of rapid distant disease spread in PDAC compared with other histologies, it was previously uncertain whether an oligometastatic disease state exists for PDAC.[10] Although multiple trials have shown that MDT is an effective strategy for oligometastatic tumors with indolent phenotypes, fewer trials have evaluated MDT for more aggressive disease biologies.[6,7,15-21] No other PDAC-specific trials have been reported, and tumor-agnostic studies, such as SABR-COMET or the National Health Service single-arm registry study, have not published PDAC-specific outcomes.[21,22] Thus, the EXTEND trial provides the strongest evidence to date in favor of the existence of an oligometastatic state in PDAC.

The mechanism(s) behind the benefit observed with MDT in EXTEND will require additional elucidation in translational designs. Cytoreduction by MDT may diminish tumor shedding and subsequent seeding.[23] MDT may also counter chemotherapy-resistant tumor clonogens. Some studies have also suggested that radiotherapy promotes activation and systemic trafficking of T cells targeted against tumor-specific neoantigens.[24] EXTEND supports this hypothesis, as systemic T-cell activation was preferentially observed after MDT, even with ongoing multiagent chemotherapy. This immune activation may be attributable, in part, to using comprehensive MDT to all radiologic disease rather than radiotherapy to a single metastasis, as comprehensive MDT may expose greater diversity of tumor neoantigens for immune presentation.[5,25] Following MDT, an activated systemic immune profile, supported by a diverse T-cell receptor repertoire, might promote immunosurveillance of distant microscopic disease, as suggested by our findings associating longer PFS and OS with activated systemic immunity after MDT.[26] MDT also eliminates macroscopic immunosuppressive stroma, leaving residual distant micrometastatic disease potentially more susceptible to immune inhibition. Although exploratory, these translational findings raise the hypothesis that comprehensive MDT exerts systemic benefits in patients with oligometastatic PDAC through induction of tumor-specific immunity and raises the possibility of synergistic benefit of MDT with immune checkpoint blockade. These exploratory concepts merit further study, particularly as differential clinical outcomes following MDT have now been observed between patients with diverse oligometastatic or oligoprogressive tumor histologies.[27,28]

There are several important limitations. First, enrollment criteria were intentionally broad to optimize accrual and reflect real-world conditions, although the study was not powered to evaluate the effect of heterogeneity on outcomes. The study was also not powered for OS; 13 deaths were observed in each arm at data cutoff. Crossover and noncancer-related deaths may have further influenced comparisons in a small trial. OS follow-up is ongoing. The current HR (0.58) suggests a potential OS signal in favor of MDT, despite more patients in the MDT arm having progressed on systemic therapy for metastatic disease before enrollment. Quality-of-life data were limited, in part because enrollment occurred predominantly during the COVID-19 pandemic. Finally, the definition of oligometastasis used in this trial (one to five metastases) may have simplified the complex multidimensional oligometastatic spectrum and does not account for molecular features.[29] International efforts are ongoing to refine the definition and characterization of oligometastasis.[30-33]

In the phase II EXTEND trial, PFS was improved from the combination of MDT plus systemic therapy compared with systemic therapy alone for patients with oligometastatic PDAC. This is the only randomized trial of patients with oligometastatic PDAC to date, and PDAC represents the most aggressive histology evaluated in an oligometastatic disease trial conducted. Our results support the efficacy and safety of adding MDT to standard-of-care chemotherapy for oligometastatic PDAC. Translational correlatives suggest a novel mechanism of action that may be exploited therapeutically. Additional studies are needed to validate these results and investigate potentially favorable immunostimulatory effects of MDT.

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A data sharing statement provided by the authors is available with this article at DOI https://doi.org/10.1200/JCO.24.00081. Deidentified patient-level data and all study-related documents can be made available with appropriate approval by the investigator team and research administrative offices. Study protocol is provided in the appendix. Requests can be made to C.T. after full manuscript publication. Data sharing will be subject to appropriate data transfer agreements.

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Addition of Metastasis-Directed Therapy to Systemic Therapy for Oligometastatic Pancreatic Ductal Adenocarcinoma (EXTEND): A Multicenter, Randomized Phase II Trial

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