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Original Article – Editor's choice

Continuous Androgen Deprivation Therapy with or Without Metastasis-directed Therapy for Oligometastatic Prostate Cancer: The Multicenter Phase 2 Randomized EXTEND Trial

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Abstract

Background and objective: Oligometastatic prostate cancer (omPC) is characterized by limited metastases. We hypothesized that metastasis-directed therapy (MDT) to all sites of omPC combined with androgen deprivation therapy (ADT) would improve clinical outcomes.

Methods: In the multicenter phase 2 EXTEND trial, patients with omPC were randomized 1:1 to ADT versus MDT + ADT in two independently powered and randomized baskets, one using intermittent ADT and one using continuous ADT. The primary endpoint was progression-free survival (PFS). The secondary endpoints included radiologic PFS (rPFS) and castration resistance–free survival (CRFS). Here, the primary results of the continuous ADT basket, the combined analysis of both baskets, and translational immune correlatives are reported.

Key findings and limitations: From September 2018 through August 2022, 174 patients were randomized and were eligible for the primary analysis. In the continuous ADT basket ($N = 87$), the median PFS was 47 mo with MDT + ADT versus 22 mo with ADT (hazard ratio [HR], 0.50; one-sided $p = 0.036$). In the combined analysis, the median PFS was 36 mo with MDT + ADT versus 17 mo with ADT (HR, 0.45; $p < 0.001$). Radiologic PFS and CRFS were also superior with MDT + ADT. Durable clinical responses after MDT + ADT were associated with systemic Th1-polarizing cytokine upregulation and $CD8^+$ T-cell proliferation. Compared with ADT, MDT + ADT induced greater systemic immune activation, including T-cell receptor expansion/contraction, which we also observed in the independent ORIOLE trial of MDT. The greatest PFS benefit after MDT + ADT was observed in patients with systemic T-cell receptor expansion/contraction.

Conclusions and clinical implications: MDT + ADT improves PFS compared with ADT in omPC patients, meriting phase 3 confirmation. Hypothesis-generating immune responses warrant mechanistic validation and future trials with T-cell–targeted immunotherapies.

ADVANCING PRACTICE

What does this study add?
To the best of our knowledge, this is the first randomized trial to investigate the addition of metastasis-directed therapy to continuous androgen deprivation therapy for treating oligometastatic hormone-sensitive prostate cancer, and the second randomized trial to investigate this question for oligometastatic androgen deprivation-resistant prostate cancer. This study met its primary objective of improved progression-free survival (PFS) with the addition of metastasis-directed therapy. This study also revealed evidence of a longer-term benefit with metastasis-directed therapy in radiographic PFS and castration resistance–free survival, providing the first randomized evidence that metastasis-directed therapy meaningfully impacts the natural history of metastatic prostate cancer. A systemic benefit from local metastasis-directed therapy may arise from immunologic stimulation.

Clinical Relevance
Metastasis-directed therapy (MDT) has been shown to improve progression-free survival (PFS) for men with oligorecurrent prostate cancer when compared against observation alone or intermittent hormonal therapy (HT) alone. The EXTEND trial is the first randomized trial to evaluate the addition of MDT to continuous HT in hormone-sensitive disease, and included a subset of patients with castration-resistant disease. Overall, the addition of MDT significantly prolonged PFS (36 months vs. 17 months for the whole cohort); in patients with hormone-sensitive disease, castration-resistance-free survival was also prolonged – a novel discovery. Correlative analyses suggest that MDT induces T cell receptor repertoire modulation, and that induction portends a better prognosis. Overall, these results further strengthen the emerging role for MDT in metastatic prostate cancer. Associate Editor: L. Amar Kishan, MD.

Patient Summary
In this trial, we investigated whether the addition of radiation therapy to standard hormone therapy improved outcomes for patients with prostate cancer spread to a limited number of areas. We found that patients treated with radiation plus hormone therapy had better outcomes than patients treated with hormone therapy alone.

1. Introduction

Oligometastatic cancer is a distinct disease subset defined by a limited extent of metastases [1,2]. Comprehensive metastasis-directed therapy (MDT), which entails delivery of local therapy to all sites of radiologically detectable disease, has been shown to improve clinical outcomes in multiple tumor types [3–8]. EXTEND was therefore designed as an investigator-initiated, multicenter, open-label, phase 2 basket trial randomizing patients with one to five metastases to standard-of-care systemic therapy with or without MDT [9]. Six baskets (prostate continuous androgen deprivation therapy [ADT], prostate intermittent ADT, breast, kidney, pancreas, and other histologies) were independently powered toward the primary endpoint of progression-free survival (PFS) and randomized with distinct stratification factors and power calculations [10–12].

In advanced prostate cancer, ADT is the foundational systemic treatment and sensitizes prostate cancer to radiotherapy (RT)-induced cell death, partly due to inhibition of DNA repair machinery [13,14]. As ADT can induce cardiovascular, metabolic, and vasomotor adverse events, ADT is often utilized either intermittently (iADT) or continuously (cADT) [15]. The EXTEND trial enrolled two baskets of oligometastatic prostate cancer (omPC) patients: (1) iADT and (2) cADT. We previously reported the primary outcomes of the iADT basket, which demonstrated that MDT + iADT improved PFS compared with iADT alone [11]. The present study provides additional follow-up for patients in the iADT basket, primary clinical outcomes for the cADT basket, and a prespecified analysis pooling both the baskets. As RT has been proposed to induce systemic antitumor responses to cancer-associated antigens and neoantigens, systemic immune profiles were longitudinally evaluated [16–26].

2. Patients and methods

EXTEND (NCT03599765) is a phase 2, open-label, multicenter, randomized basket trial testing the hypothesis that MDT plus standard of care systemic therapy improves PFS compared with standard of care systemic therapy alone. Participants were enrolled at The University of Texas MD Anderson Cancer Center Texas Medical Center and Houston area locations (Texas, USA) and through the following hospitals in the integrated MD Anderson network: Banner MD Anderson Cancer Center (Arizona, USA), The University of Texas Health Science Center at San Antonio (Texas, USA), MD Anderson Cancer Center at Cooper (New Jersey, USA), and OhioHealth (Ohio, USA). Institutional review board approval was obtained at each participating institution. All participants signed written informed consent.

2.1. Inclusion and exclusion criteria

Men aged 18 yr or older with one to five omPC metastases amenable to MDT, with an Eastern Cooperative Group performance status score of 0–2, and with receipt of four or fewer lines of systemic therapy for metastatic disease were eligible (see the Supplementary material for the protocol). Prior definitive treatment of the primary prostate tumor was not required.

2.2. Randomization and masking

Patients were randomized 1:1 to receive MDT plus cADT or cADT alone without masking, using the dynamic randomization method by Pocock and Simon (Fig. 1) [65]. In the cADT randomization, stratification factors were as follows: one to two versus three to five metastatic lesions, zero to one versus two to four prior lines of systemic therapy for metastatic disease, and <5 versus ≥5 ng/ml prostate-specific antigen (PSA) level. Stratification factors for the iADT basket were reported previously and included number of metastases, number of prior systemic therapy lines, use of androgen receptor pathway inhibitors (ARPIs), and duration of ADT prior to enrollment [11].

2.3. Procedures

Systemic therapy consisted of ADT with a luteinizing hormone-releasing hormone agonist or antagonist. At least 2 mo of ADT was required prior to enrollment. Following enrollment, in the iADT basket, ADT was given for 6 mo (±2 mo) and then held until progression; ADT was given continuously in the cADT basket. An ARPI was added at the discretion of the medical oncologist. MDT consisted of definitive-intent local therapy, which could be achieved with RT, surgery, or local ablation. In both arms, the primary tumor was treated with definitive RT, if not addressed previously by definitive local therapy, based on the STAMPEDE trial [27]. Baseline and follow-up imaging included computed tomography of the chest, abdomen, and pelvis with bone scan or positron emission tomography (PET) plus computed tomography with fluciclovine or prostate-specific membrane antigen (PSMA) tracers. Follow-up included PSA measurements every 12 wk after randomization for 2 yr and every 18 wk thereafter. As serial imaging is not typical or reimbursed for patients early in the natural history of metastatic prostate cancer, imaging was obtained when PSA increased by ≥1.0 ng/ml above the nadir or for clinical progression. Restaging imaging was based on the standard of care at the time of restaging and could include computed tomography or PET as discussed above.

2.4. Outcomes

The primary endpoint was PFS, defined by radiologic, biochemical, or clinical progression or death. Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) was assessed by a blinded central review (the Quantitative Imaging Analysis Core at MD Anderson). Biochemical progression was defined by the Prostate Cancer Working Group criteria as an increase in PSA level of ≥25% and PSA ≥2 ng/ml above the nadir [28]. Clinical progression was defined as the presentation of symptoms or, by the treating oncologists, as the need to change management strategy to prevent undue harm, morbidity, or mortality to the patient.

The secondary endpoints included castration resistance–free survival (CRFS), defined as the time from enrollment for patients with oligometastatic hormone-sensitive prostate cancer (omHSPC) to death or development of androgen

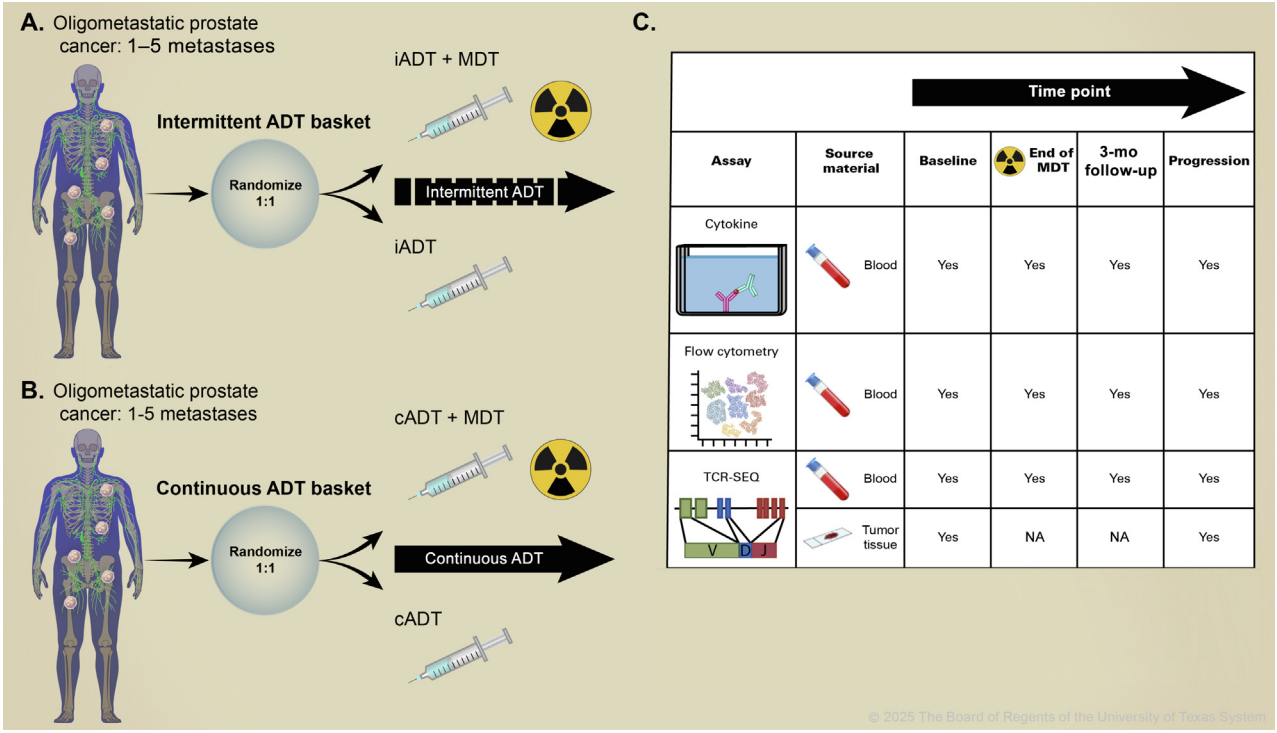

Fig. 1 – (A and B) Clinical and (C) translational study design of the phase 2 randomized EXTEND trial oligometastatic prostate cancer baskets. ADT = androgen deprivation therapy; cADT = continuous ADT; iADT = intermittent ADT; MDT = metastasis-directed therapy; NA = not applicable; TCR-SEQ = T-cell receptor sequencing.

deprivation-resistant prostate cancer (ARPC). ARPC (also referred to as castrate-resistant prostate cancer) was defined as PSA or radiologic progression with a castrate serum testosterone level of <50 ng/dl. Other secondary endpoints included radiologic PFS (rPFS), overall survival (OS), time to next-line systemic therapy, time to appearance of new lesions, local failure defined by RECIST in the MDT arm, safety assessed by the Common Terminology Criteria for Adverse Events version 4.0, and quality of life assessed by patient-reported outcome measures. Exploratory endpoints included translational immune profiling of peripheral blood and tumor tissue using flow cytometry, cytokine quantification, and T-cell receptor (TCR) sequencing (TCR-SEQ; Fig. 1). Assay details can be found in the Supplementary material.

2.5. Statistical analysis

A sample size of 87 patients was needed to have 80% power to detect an improvement in median PFS from 18 to 36 mo with MDT by using a one-sided log-rank test with a type 1 error of 0.10. This powering strategy using a type 1 error of 0.10 rather than 0.05 was chosen because of the trial's phase 2, basket design, enabling more efficient identification of superiority signals within each basket. Implicit in such a trial design is the understanding that the trial findings would require confirmation in large phase 3 trials powered to lower type 1 error risks. Accordingly, consistent with the power calculations, significance was set for the primary endpoint of PFS at $p < 0.10$ with one-sided testing, similar to other phase 2 randomized trials in oligometastatic cancers [4,29]. For all other analyses, significance was defined at $p < 0.05$ with two-sided testing. OS was analyzed in the intention-to-treat population; other efficacy endpoints were analyzed in the per-protocol population. Stratified log-rank tests and stratified Cox regressions compared the arms. For the cADT basket, stratification factors at randomization were used for the stratified Cox regressions. For the combined analyses, the Cox stratification factors were the basket identity (cADT vs iADT) and the two common randomization stratification factors (number of metastases and prior lines of systemic therapy). The analysis was triggered per protocol after the last patient enrolled had reached 18 mo of follow-up. Post hoc subgroup analyses were performed with unstratified univariable Cox regressions. Post hoc statistical analyses of the translational correlatives are described in the Supplementary material.

3. Results

From September 2018 through August 2022, 265 patients were screened and 183 patients were randomized; 174 patients were eligible for the primary endpoint analysis in the per-protocol population (MDT + cADT, $n = 45$; cADT, $n = 42$; MDT + iADT, $n = 43$; and iADT, $n = 44$; Supplementary Fig. 1). ARPC was present in 41 (24%) of 174 patients, including 34 (39%) of 87 patients in the cADT basket (Supplementary Table 1). Staging imaging included conventional computed tomography plus bone scan for 102 patients (59%), fluciclovine PET for 50 patients (29%), and PSMA PET for 22 patients (13%). After enrollment, 95 (55%) of

174 patients were treated with ARPI combined with ADT, including 67 (50%) of 133 patients with omHSPC and 28 (68%) of 41 patients with oligometastatic ARPC (omARPC). Of the remaining 13 (32%) patients with omARPC without any ARPI, seven patients received ADT alone and six patients received MDT + ADT. In the MDT arm, 88 patients received definitive RT for 196 (100%) of 196 omPC metastases (Supplementary Table 2). Using an alpha/beta ratio of 3, the highest biologically effective dose of RT was similar between patients with omHSPC and omARPC (p = 0.99). An additional 28 (32%) of 88 patients in the MDT + ADT arm and 24 (28%) of 86 patients in the ADT arm with an untreated prostate received definitive prostate-directed RT per protocol (Supplementary Table 2).

3.1. Clinical outcomes

The cutoff date for the primary analysis was February 29, 2024. The median follow-up time of the cADT basket, estimated using the reverse Kaplan-Meier method, was 31 mo. The median PFS with MDT + cADT was 47 mo versus 22 mo with cADT only (hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.23–1.08; one-sided p = 0.036; Fig. 2A). Secondary endpoints for the cADT basket did not show significant differences (Table 1 and Supplementary Fig. 2).

The primary results of the iADT basket were reported previously [11]. With the cutoff date of February 29, 2024, for the updated outcomes, the median follow-up of the iADT basket was 47 mo. The median PFS with MDT + iADT was 28 mo versus 16 mo with iADT (HR, 0.44; 95% CI, 0.25–0.78, p = 0.005; Fig. 2B). The secondary endpoints rPFS, CRFS, time to new lesion, time to next-line systemic therapy, and OS are reported in the Supplementary material with updated follow-up; notably, rPFS was also significantly longer in the MDT + iADT arm (Supplementary Table 3 and Supplementary Fig. 3).

After a median follow-up of 42 mo for the combined analyses, PFS was significantly improved with MDT + ADT versus ADT (HR, 0.45; 95% CI, 0.30–0.69; p < 0.001; Fig. 2C). The median PFS after MDT + ADT was 36 mo versus 17 mo after ADT-only. Patient-level outcomes are presented in a swimmer's plot (Fig. 2D). Post hoc subgroup analysis revealed no evidence of heterogeneous treatment effects among multiple clinical subgroups of interest (all $p_{\text{interaction}}$ > 0.05; Supplementary Fig. 4). Post hoc multivariable analyses conditioning for known prognostic factors did not alter the significance of the MDT + ADT treatment effect (Supplementary Table 4).

MDT + ADT also improved the secondary endpoint of rPFS in the combined analysis (HR, 0.63; 95% CI, 0.40–0.97; p = 0.038; Supplementary Fig. 5A). Four (4.5%) patients in the MDT arm had RECIST-defined local failure. Among patients with omHSPC, MDT + ADT was associated with superior CRFS (HR, 0.40; 95% CI, 0.19–0.82; p = 0.01; Supplementary Fig. 5B). No significant differences were found

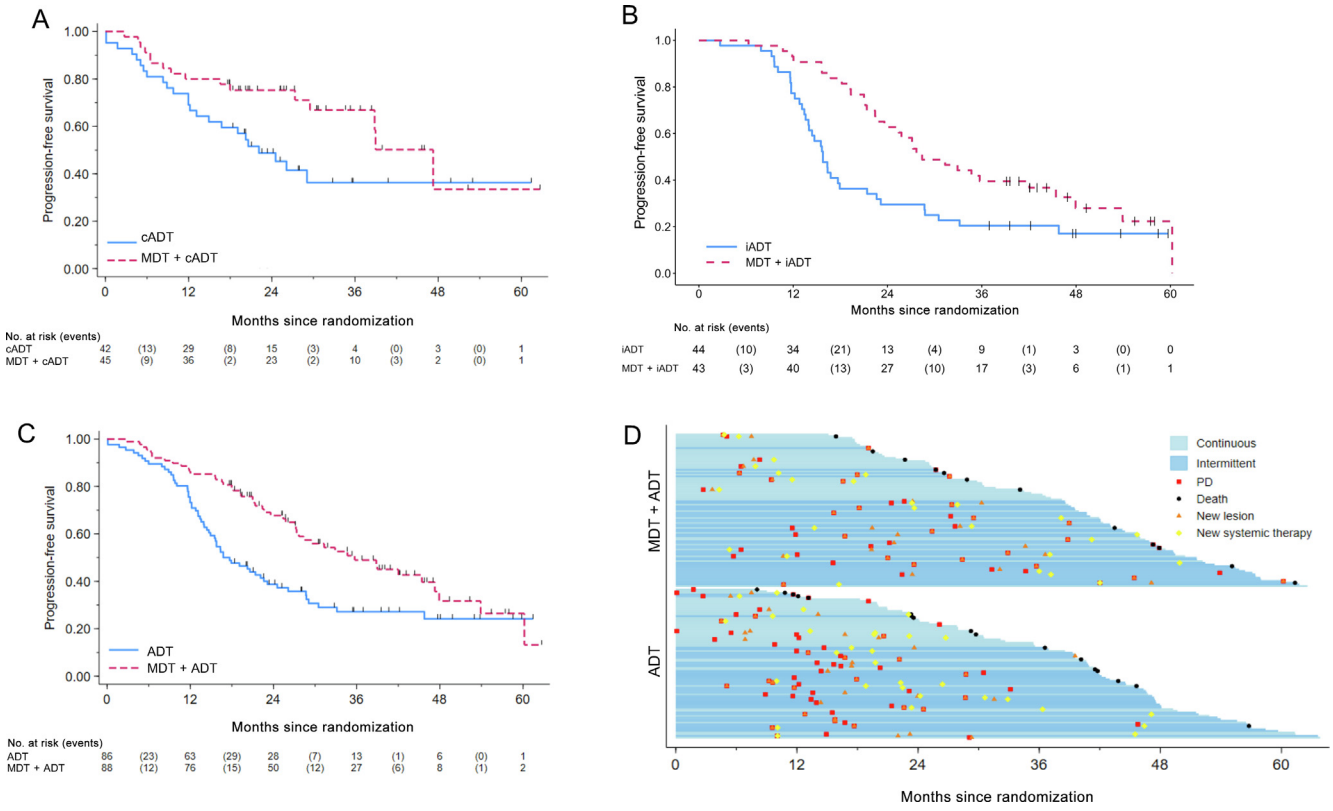

Fig. 2 – Kaplan-Meier curves of the primary endpoint of the continuous androgen deprivation therapy (cADT) basket, the updated intermittent androgen deprivation therapy (iADT) basket, and the primary endpoint of the combined analysis: (A) progression-free survival (PFS) in the cADT basket, (B) PFS in the iADT basket, (C) PFS in the combined analysis of the cADT and iADT baskets, and (D) swimmer's plot of patient-level outcomes. MDT = metastasis-directed therapy; PD = progressive disease.

Table 1 – Primary and secondary efficacy results of the continuous androgen deprivation therapy (ADT) basket and the combined analysis of both the cADT and the iADT basket

Endpoint	HR (95% CI)	*p* value	MDT + ADT, median (95% CI)	ADT, median (95% CI)
Combined analysis				
PFS	0.45 (0.30–0.69)	<0.001	36 (27–47)	17 (15–23)
rPFS	0.63 (0.40–0.97)	0.04	39 (30–48)	26 (22–46)
CRFS[a]	0.40 (0.19–0.82)	0.01	NE	NE
Time to new lesion	0.71 (0.45–1.12)	0.14	39 (30–NE)	29 (23–NE)
Time to next-line systemic therapy	0.82 (0.47–1.41)	0.47	NE	NE
OS	0.54 (0.24–1.21)	0.13	61	NE
cADT basket				
PFS	0.50 (0.23–1.08)	0.036[b]	47 (30–NE)	22 (13–NE)
rPFS	0.75 (0.33–1.67)	0.48	39 (30–NE)	NE
CRFS[a]	0.61 (0.19–1.93)	0.4	NE	NE
Time to new lesion	0.90 (0.39–2.06)	0.8	39 (30–NE)	NE
Time to next-line systemic therapy	1.35 (0.58–3.14)	0.48	NE	NE
OS	0.55 (0.18–1.68)	0.29	NE	NE

ADT = androgen deprivation therapy; cADT = continuous ADT; CI = confidence interval; CRFS = castration resistance–free survival; HR = hazard ratio; iADT = intermittent ADT; MDT = metastasis-directed therapy; NE = not estimable; OS = overall survival; PFS = progression-free survival; PSA = prostate-specific antigen; rPFS = radiologic PFS.

HRs with 95% CI values are from stratified Cox regression, and two-sided *p* values (except where noted) were from stratified log-rank. Stratification factors for the combined analysis included the stratification factors common to each basket at randomization (number of metastases and prior lines of systemic therapy) plus the basket identity. Stratification factors for the cADT analysis were the stratification factors at randomization including the number of metastases, prior lines of systemic therapy, and PSA.

[a] Evaluated only among patients with hormone-sensitive disease at enrollment.

[b] One-sided *p* value per protocol.

between arms in OS (HR, 0.54; 95% CI, 0.24–1.21; $p = 0.13$), time to next-line systemic therapy, or time to a new lesion (Supplementary Fig. 5C–E and Table 1).

No grade 4 or 5 toxicities were observed after MDT + ADT. Six grade 3 events were at least possibly attributable to MDT + ADT (spinal fracture, $n = 2$; hip fracture, $n = 1$; urinary tract pain, $n = 1$; prostate infection, $n = 1$; and lymphopenia, $n = 1$), as were two grade 3 events in the ADT arm (lymphopenia, $n = 1$, and noninfective cystitis, $n = 1$). Thirty-one grade 2 events were at least possibly attributable to MDT + ADT; the most common were noninfective cystitis ($n = 4$), diarrhea ($n = 4$), and urinary frequency ($n = 4$). The ADT-only arm experienced eight grade 2 events with at least possible attribution, most commonly fatigue ($n = 3$). Quality of life assessments, which were limited by response rates, did not show apparent differences between arms (Supplementary Table 5).

3.2. *Systemic immune responses induced after MDT + ADT*

To initially examine the hypothesis that durable clinical outcomes after MDT + ADT were partially attributable to the induction of systemic antitumor immune responses, patients in the MDT + ADT arm were first categorized as having either poor or durable responses, similar to other reports (Fig. 3A) [30,31]. This grouping was chosen to initially study the immune correlatives among a small patient subset on the rationale that a putative prognostic immune effect would be amplified in such a population. Poor responses were defined as PFS <1 yr, whereas durable response was defined as PFS ≥3 yr (which was the median PFS of the MDT + ADT arm).

Serum levels of IFN-γ and IL-12p70, which are critical for effective antitumor immune responses, were increased after MDT + ADT in patients with durable responses, but not in those with poor responses (Supplementary Fig. 6A) [20,32]. In line with these findings, patients with durable responses to MDT + ADT showed increased frequencies of markers of $CD8^+$ T-cell activation, with no changes seen in these markers within the poor response group (Supplementary Fig. 6A). These findings were also confirmed in all evaluable trial patients after MDT + ADT and were largely absent from the ADT arm (Supplementary Figs. 6B and 7).

Antigen-specific T-cell activation and proliferation lead to TCR clonal expansion. In parallel, T-cell clonotypes are also pruned selectively—termed TCR clonal contraction—which is often due to their ineffectiveness against specific antigens. TCR expansion and TCR contraction were both more common in the durable response group than in the poor response group (Fig. 3B) [33]. Furthermore, a random forest model identified TCR expansion as the most influential variable for predicting a clinical response (Fig. 3C). In all evaluable patients, TCR clonal expansion and contraction were significantly greater after MDT + ADT than after ADT (Fig. 3D). In a sensitivity analysis excluding patients who received prostate RT, TCR clonal expansion was persistently associated with MDT + ADT; moreover, TCR expansion was greater among patients in the MDT + ADT arm receiving prostate RT after enrollment than among patients in the MDT + ADT arm without prostate RT (Supplementary Fig. 8).

As TCR expansion and contraction represent distinct measures of an effective immune response, the composite term "TCR repertoire modulation" was defined as both TCR expansion and TCR contraction, and was found to be more common among the durable responders than among the poor responders and more common after MDT + ADT than after ADT in all evaluable patients (Fig. 3B and 3E). TCR repertoire modulation after MDT + ADT was also asso-

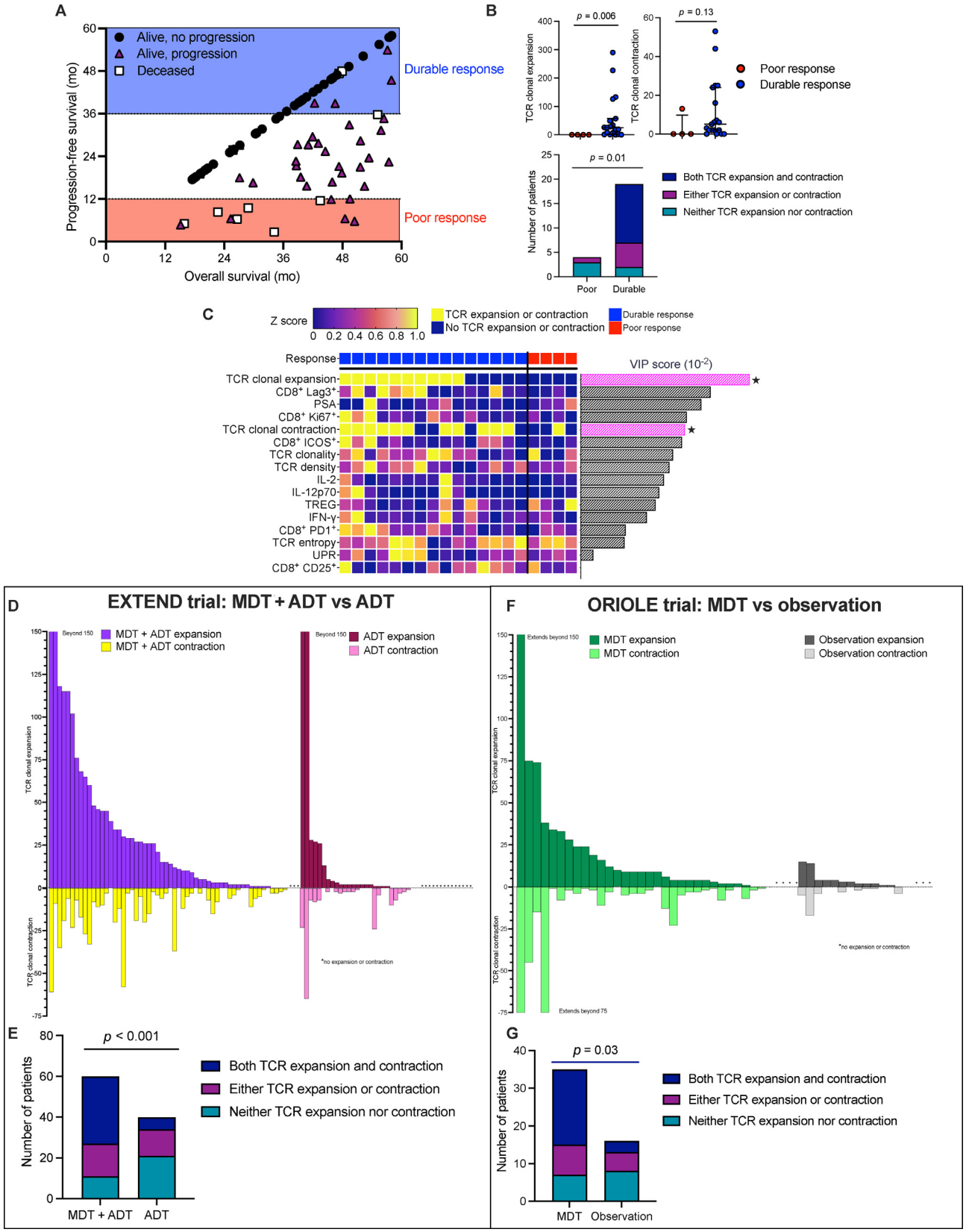

Fig. 3 – Metastasis-directed therapy (MDT) + androgen deprivation therapy (ADT) induces systemic immune responses associated with a durable response. (A) Plot of progression-free survival versus overall survival reveals extreme response groups. (B) T-cell receptor (TCR) expansion and contraction are associated with a durable versus poor response. The *p* values were determined by Mann-Whitney *U* test or chi-square test for continuous or categorical variables, respectively. (C) Identification of clinical and immunologic factors associated with extreme response groups, ordered by variable importance (VIP) scores estimated by a random forest model. In the heatmap, categories of TCR expansion and contraction are shown based on the definitions of the composite term TCR repertoire modulation (shown by asterisks), with VIP scores to denote these features that are also highlighted in pink. (D and E) TCR clonal expansion and contraction are greater after MDT + ADT than after ADT in all evaluable patients. The *p* values were determined by chi-square test. (F and G) TCR clonal expansion and contraction are greater after MDT than after observation in the independent ORIOLE trial. The *p* values were determined by chi-square test. PSA = prostate-specific antigen.

ciated with upregulation of Th1 polarizing cytokines, including IL-2, IFN-γ, and IL-12p70, and increased systemic frequencies of activated $CD8^+$ $Lag3^+$ and $CD8^+$ $Ki67^+$ T cells, highlighting its representativeness as a summary marker of the immune response (Supplementary Fig. 9). Lastly, using peripheral blood samples from the independent ORIOLE trial, which randomized men with omPC to either MDT or observation (without ADT), MDT remained associated with the induction of TCR expansion (p = 0.01), TCR contraction (p = 0.03), and TCR repertoire modulation (p = 0.03; Fig. 3F–G) [5].

A multivariable Cox model, stratified by the use of cADT versus iADT and adjusted for omHSPC versus omARPC status, revealed that patients with TCR repertoire modulation after MDT + ADT had better PFS than patients with neither TCR expansion nor TCR contraction (HR, 0.21; 95% CI, 0.06–0.76; p = 0.02; Fig. 4A). The adjusted median PFS of patients with TCR repertoire modulation was 60 mo versus 28 mo for patients with neither TCR expansion nor contraction, and the adjusted restricted mean PFS time gained was 11 mo (95% CI, 2–20 mo; p = 0.02; Fig. 4B). To reduce bias from overfitting, a sensitivity analysis penalizing the Cox estimates with Firth's correction was performed and still demonstrated a consistent association between immune response and outcome (HR, 0.23; 95% CI, 0.07–0.78; p = 0.02). Patient-level relationships between clinical and immune parameters and PFS for the full MDT + ADT cohort are shown in Fig. 4C.

To ascertain whether MDT-induced expanded TCR clones are tumor specific, we analyzed available pre-MDT metastatic prostate cancer tissues, with paired serially collected blood samples, from two patients with TCR-SEQ. Patient "A" was an exceptional clinical responder, who lived for 4 yr after MDT and died without evidence of cancer recurrence (as serum PSA was undetectable prior to death). This patient had profound systemic expansion of prostate tumor-associated TCR clones after MDT to a pelvic soft tissue metastatic tumor deposit. By contrast, patient "B" was a poor responder and developed diffuse new metastases outside the RT field 3 mo after MDT while actively receiving ADT plus ARPI. This patient had no meaningful systemic expansion of prostate tumor-associated TCR clones after MDT + ADT (Supplementary Fig. 10). In a larger subset of patients, we then used pMTnet to assess the predicted *in silico* binding affinity of expanded and contracted TCR clones to the prostate cancer-associated antigens prostatic acid phosphatase (PAP) and PSMA. We chose PAP and PSMA based on previous work showing T-cell–specific responses toward these tumor-associated antigens [30]. TCR clones that systemically expanded after either MDT + ADT (in the EXTEND trial) or MDT (in the ORIOLE trial) had significantly greater numbers of strong binding interactions with PAP and PSMA than clones that were contracted (Fig. 5A). Strong binding interactions to PAP and PSMA were also greater among TCR clonotypes expanded after MDT + ADT or MDT only compared with patients undergoing observation (of note, human leukocyte antigen-typing needed for pMTnet-based prediction was unavailable for samples from the ADT arm; Fig. 5B). The TCR repertoire within unpaired pre-treatment primary or metastatic tumor tissues showed a similar number of binding interactions to PAP and PSMA as the systemic expanded clones (Fig. 5B). As a sensitivity analysis, we estimated shared antigen specificity between expanded T cells and viral clonotypes (taken from a public database) by using a different modeling strategy (GLIPH2). Overall, few TCR clones expanded by MDT + ADT or those residing within tumor tissue were predicted to bind viral epitopes, suggesting that these clones do not represent bystander T cells (Fig. 5C). Together, these findings further support the hypothesis that MDT + ADT induces effective antitumor systemic immune responses that translate to clinically meaningful improvements in systemic disease control (Fig. 5D).

4. Discussion

Oligometastatic cancer represents a distinct intermediate clinical and biological disease state between locoregional cancer and diffuse metastases [1]. Intervening in the progression of omPC to diffuse metastatic disease and inevitably lethal metastatic ARPC with definitive MDT may alter the natural history of this disease [34]. In the present study, the phase 2 EXTEND trial demonstrated that MDT + cADT compared with cADT improved PFS significantly, meeting the primary endpoint and providing the first randomized evidence supporting the addition of MDT to cADT in the omHSPC setting. In the combined analyses, longer-term endpoints of rPFS and CRFS were also superior in the MDT arm. Together, these findings support a paradigm of MDT + ADT providing a clinical benefit to omPC patients by delaying the inexorable progression of metastatic prostate cancer to the fatal disease state ARPC.

Other randomized trials have examined the role of MDT in omPC populations distinct from those in EXTEND. The STOMP and ORIOLE trials enrolled patients with one to three metachronous omHSPC metastases (mostly regional or nonregional lymph node metastases) and randomized them to MDT versus observation [35]. By contrast, the EXTEND trial: (1) enrolled patients with up to five synchronous or metachronous metastases, (2) allowed patients with either omHSPC or omARPC, and (3) evaluated MDT + ADT versus ADT. In ORIOLE, MDT improved PFS compared with observation; similarly, STOMP showed that MDT improved ADT-free survival [4,5]. In a combined update of both STOMP and ORIOLE, MDT was associated with improved PFS versus observation, although other secondary longer-term endpoints, such as rPFS or CRFS, were not demonstrated as superior, with the caveat that neither trial was powered for rPFS or CRFS [35]. Notably, although patients with synchronous metastases have historically been excluded from trials of MDT because of their poor overall prognosis, no treatment effect heterogeneity was observed among patients with synchronous or metachronous disease in the EXTEND study. Furthermore, post hoc subgroup analyses in EXTEND did not suggest evidence of treatment effect heterogeneity among omHSPC or omARPC groups. Taken together, these trials consistently showed a clinical benefit from MDT in omPC patients but indicated that MDT alone is likely insufficient to achieve long-term systemic disease control. To evaluate this question, the

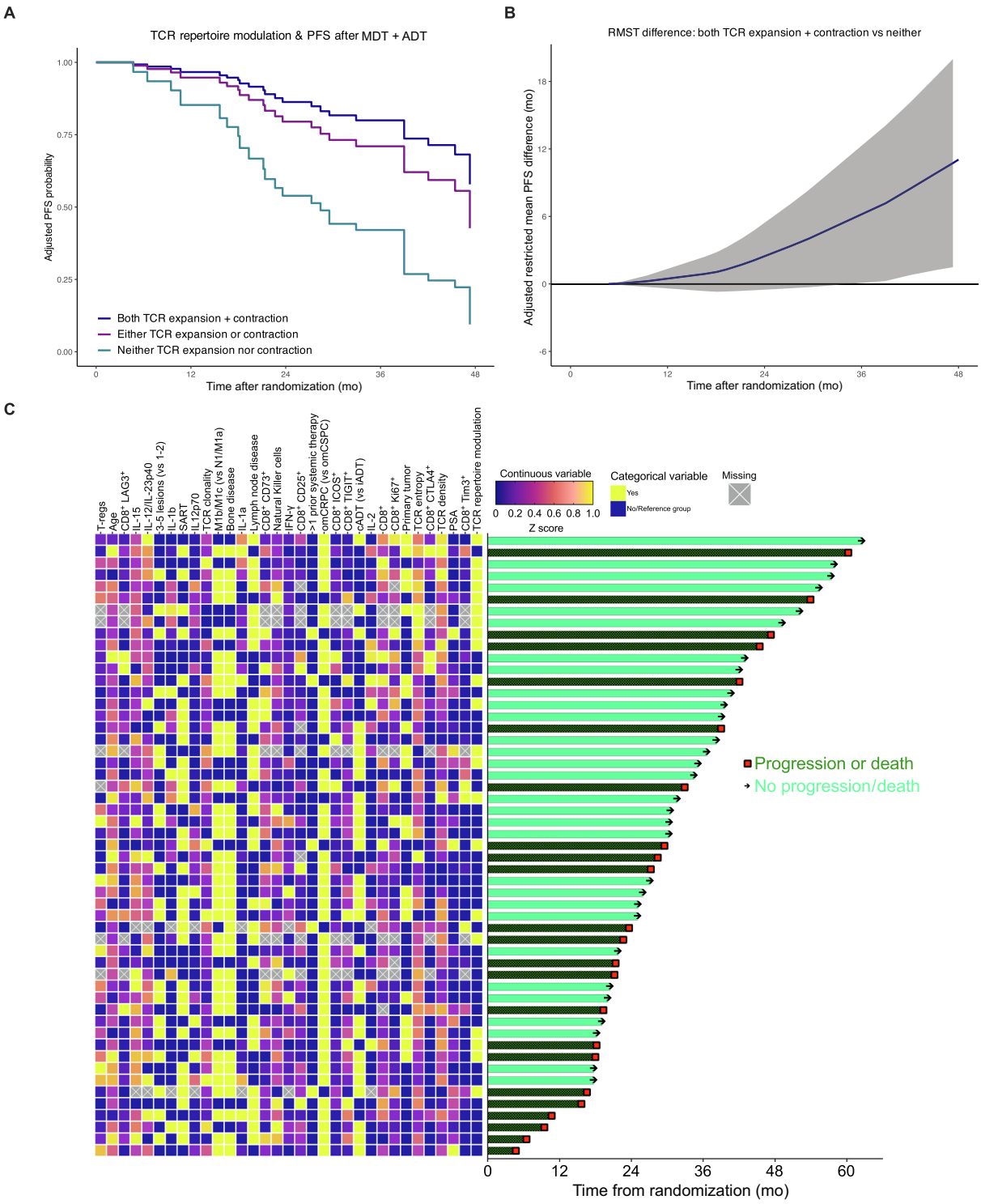

Fig. 4 – TCR expansion plus contraction is associated with improved PFS after MDT + ADT. (A) PFS probability after MDT + ADT for patients with TCR expansion/contraction (*n* = 21) versus no TCR expansion/contraction (*n* = 17), adjusted for cADT versus iADT and omARPC status. (B) Restricted mean PFS time difference between patients with TCR expansion/contraction after MDT + ADT and those with no TCR expansion/contraction. (C) Clinical and immunologic features associated with PFS after MDT + ADT. ADT = androgen deprivation therapy; cADT = continuous ADT; iADT = intermittent ADT; MDT = metastasis-directed therapy; omARPC = oligometastatic androgen deprivation-resistant prostate cancer; PFS = progression-free survival; RMST = restricted mean survival time; TCR = T-cell receptor.

RADIOSA trial compared MDT + ADT versus MDT alone for omHSPC, and found that multimodal treatment achieved superior PFS and rPFS [36]. However, combination treatment did not lengthen eugonadal PFS over MDT alone; because of this, for some patients, MDT alone may be reasonable especially with regards to quality of life considera-

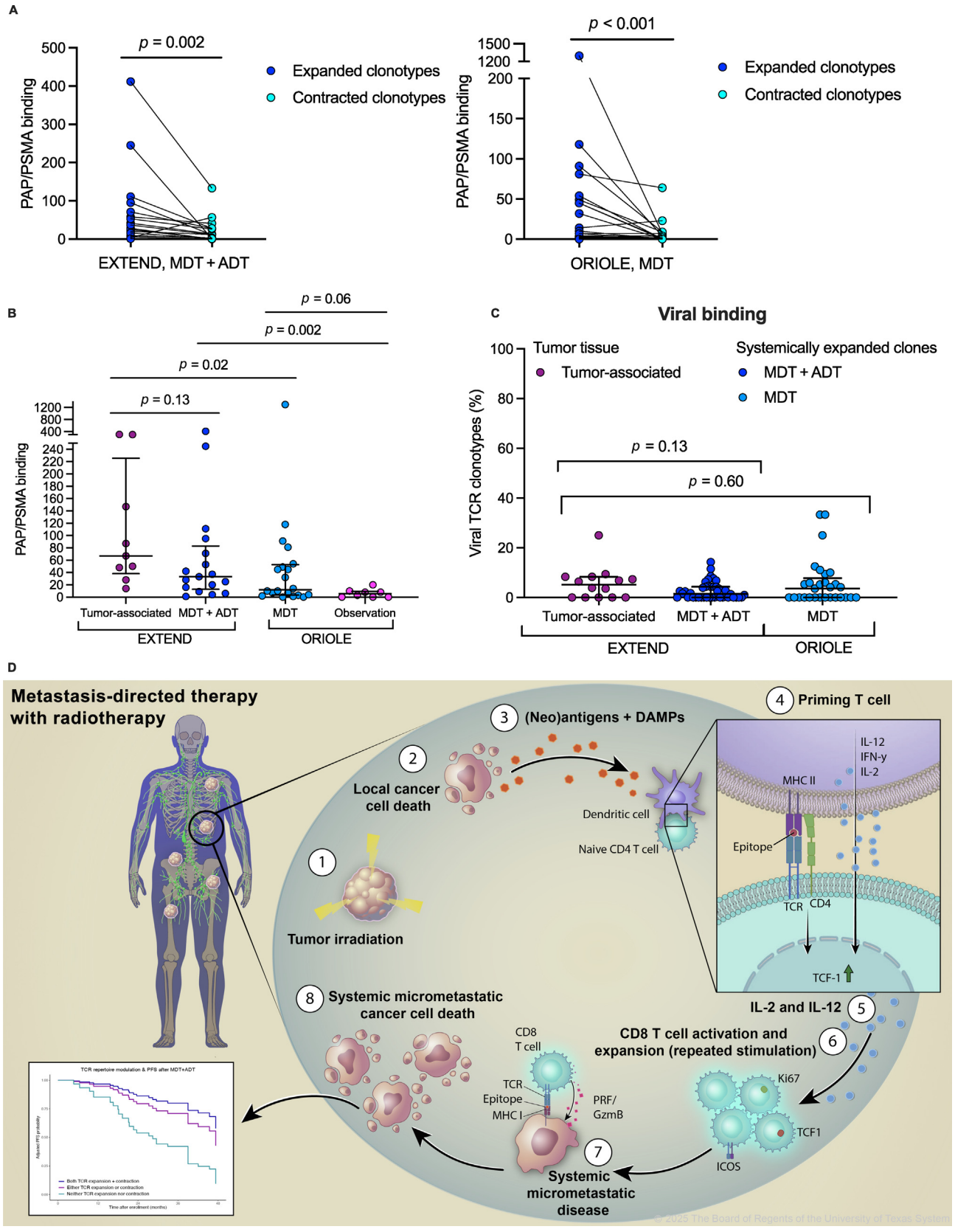

Fig. 5 – Expansion of tumor-specific T-cell receptor clonotypes after MDT. (A) Predicted binding interactions to prostatic acid phosphatase (PAP) or prostate-specific membrane antigen (PSMA) among expanded versus contracted clones after MDT + ADT in the EXTEND trial or after MDT only in the ORIOLE trial. The p values were determined by Mann-Whitney U test. (B) Comparison of predicted binding among expanded clones after MDT + ADT, MDT, and observation to the tumor-associated TCR repertoire. The p values were determined by Mann-Whitney U test. (C) Proportion of expanded clones after MDT + ADT or MDT with predicted affinity for viral epitopes compared with the tumor-associated TCR repertoire. The p values were determined by Mann-Whitney U test. (D) Illustration of the hypothesis that MDT + ADT induces effective antitumor systemic immune responses that promote systemic disease control. Neoantigens and DAMPs were not directly evaluated in this study but have been described previously [25,64]. ADT = androgen deprivation therapy; DAMP = damage-associated molecular pattern; MDT = metastasis-directed therapy; TCR = T-cell receptor.

tions. On the contrary, although ADT is the foundational systemic therapy for advanced prostate cancer, numerous clinical trials have demonstrated a clinical benefit from the addition of ARPI to ADT [37–49]. Along those lines, the ARTO trial randomized patients with omARPC to MDT + ADT + ARPI versus ADT + ARPI, finding that PFS was improved with the addition of MDT [8]. In EXTEND, the use of an ARPI was allowed, but not mandated. Although subgroup analyses did not show evidence of heterogeneous treatment effects in patients who were or were not treated with ARPIs, these were post hoc analyses that must be interpreted cautiously due to limited sample size. Future studies are needed to evaluate the value of adding ARPI to MDT + ADT, particularly in the omHSPC population.

The results of EXTEND showed that, regardless of the ADT approach (iADT vs cADT), the addition of MDT to ADT improved measures of systemic disease control. MDT + ADT, but not ADT alone, was also associated with the induction of effective systemic antitumor immune responses. Accounting for other clinical factors, patients with significant immune responses immediately after MDT had better outcomes than patients without such responses. Previously, a phase 2 clinical trial of MDT in omARPC patients identified baseline and on-treatment changes in circulating effector T-cell populations associated with improved outcomes [17,18]. Similarly, the phase 2 RAVENS trial, which randomized patients to MDT with or without radium-223 dichloride, found that TCR unique productive rearrangements were associated with improved outcomes [50]. Patients with omPC, by virtue of being earlier in the natural history of disease, may uniquely benefit from MDT as they have not yet received multiple lines of systemic therapies that can promote an immunosuppressive tumor microenvironment (TME). Our exploratory findings suggest that comprehensive MDT yielded a clinically relevant antitumor immune response that may have contributed to the control of *micro*scopic disease, building on prior preclinical and clinical studies in prostate cancer as well as other histologies such as lung and pancreatic cancer [10,16–18,51]. Furthermore, these results linked TCR modulation as a candidate blood-based biomarker for clinical outcomes associated with MDT + ADT. This longitudinal, peripherally accessible blood biomarker is advantageous compared with tumor tissue-based biomarkers, which are often difficult to obtain, particularly at multiple time points.

The results of the EXTEND trial illuminate a path forward for future biomarker-informed trials of MDT + ADT combined with therapies that induce intratumor effector T-cell infiltration and activation (eg, anti–CTLA-4 antibodies, vaccines, or bispecific T-cell engagers) in patients with omPC [52–54]. These combinations are particularly important as previous evidence suggests that RT to primary prostate tumors may in fact decrease intratumoral $CD8^+$ T-cell populations, while increasing intratumoral myeloid cell density [55–58]. Immunosuppressive myeloid populations induced by RT could even be protumorigenic in certain contexts [59]. Interestingly, our data suggest that MDT-induced immune responses, at least systemically, may be stronger in the context of RT including the primary prostate tumor, which could be related to a greater (neo)antigen load or possibly immunobiological differences between metachronous and synchronous tumors. Other work has suggested that metastatic hormone-sensitive prostate cancer may be more immunoresponsive than localized prostate cancer or metastatic ARPC, which may add further clarity toward the findings we observed, since EXTEND largely enrolled patients with omHSPC [60]. Organ site niches, such as bone and lymph nodes, are also known to have distinct immune TMEs, which may further contribute to the differences observed in EXTEND compared with previous studies. Nonetheless, definitive conclusions from the current data are limited, as the primary prostate intratumoral TME was not evaluated directly, warranting preclinical mechanistic work to further study the hypothesis-generating findings of the present study.

Our study had several key limitations. There was heterogeneity in patient enrollment, with the inclusion of both omHSPC and omARPC, presence or absence of visceral disease, metachronous or synchronous presentations, and imaging modalities used for staging and restaging, and so the study's findings must be interpreted cautiously. The number of prior lines received in the metastatic setting (0–1 vs 2–4) was a stratification factor at randomization, consistent across all disease baskets of EXTEND. This stratification factor grouped some omARPC patients together with omHSPC patients, as there was no evidence at the trial design that MDT held differential treatment effects between these subgroups. While this may have theoretically reduced trial efficiency, the current evidence from the ARTO, GROUQ-PCS 9, and EXTEND trials does not suggest differential treatment effects of MDT in the omHSPC versus omARPC populations or in those treated with or without ARPIs [8,61,62]. In addition to a subgroup analysis, a multivariable analysis accounting for these factors in EXTEND did not alter the significance of the primary PFS endpoint, although such analyses warrant caution given their post hoc nature and merit further exploration in patient-level meta-analysis. As a phase 2 trial, EXTEND was neither powered nor designed to assess OS, and crossover to MDT at progression may confound estimation of treatment effects for this endpoint. In addition, median OS was not reached in either arm at the time of the primary analysis, and follow-up remains ongoing. Phase 3 studies will be needed to evaluate the effects of MDT on OS. Furthermore, whether systemic immune responses accurately reflect the local immune TME remains an ongoing question, as metastatic tissue specimens were limited in this study [63]. Although we leveraged computational modeling strategies based on the available samples for epitope prediction, a complete interpretation of these findings is limited due to a lack of assays identifying the specific mechanism of T-cell activation associated with MDT in omPC. Tumor-intrinsic factors, such as genomic instability, DNA damage, and cell cycle changes, may be evaluated for their influence on immune response in future mechanistic studies in immunocompetent model systems. Lastly, while immune responses were closely linked with outcomes in our study even with multivariable adjustment for clinical variables, the generalizability of this finding could be limited, as the burden of disease among the enrolled patients was generally low (eg, PSA

<5 ng/ml in 92% of patients). Validation of this finding in other patient cohorts is needed.

5. Conclusions

In summary, among patients with omPC, the addition of MDT to ADT improved PFS, rPFS, and CRFS, thus delaying the progression to lethal ARPC. This is the largest randomized study to date demonstrating improved clinical outcomes with MDT + ADT and is the first randomized trial to show that MDT improved CRFS, justifying confirmatory phase 3 clinical trials. The clinically meaningful improvements in measures of systemic disease control from MDT + ADT may be mediated in part by the induction of effective antitumor systemic immunity. These hypothesis-generating findings warrant mechanistic confirmation in preclinical models and may inform the development of blood-based immune biomarkers and future clinical trials combining MDT + ADT with T-cell–targeted immunotherapies.

***Author contributions*:** Alexander Sherry and Chad Tang had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Sherry, Siddiqui, Haymaker, Liu, Cohen, Reuben, Tran, Corn, Subudhi, Tang.
Acquisition of data: Sherry, Siddiqui, Haymaker, Medina-Rosales, Bathala, Seo, Hara, Lu, Troncoso, Chun, Ha, Mayo, Mok, Park, Phillips, Deek, Kovitz, Aparicio, Zurita, Pilie, Choi, Reuben, Tran, Corn, Subudhi, Tang.
Analysis and interpretation of data: All authors.
Drafting of the manuscript: Sherry, Siddiqui, Haymaker, Subudhi, Tang.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Sherry, Fellman, Liu, Tang.
Obtaining funding: Tran, Tang.
Administrative, technical, or material support: Haymaker, Tang.
Supervision: Tran, Corn, Subudhi, Tang.
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Data sharing statement: Deidentified patient-level data and all study-related documents can be made available with appropriate approval by the investigator team and research administrative offices. The study protocol is provided in the Supplementary material. Requests can be made to the corresponding author (Chad Tang) after full manuscript publication. Data sharing will be subject to appropriate data transfer agreements.

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Supplementary data

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