National Cancer Institute's Working Group on Biochemically Recurrent Prostate Cancer: Clinical Trial Design Considerations

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ABSTRACT

PURPOSE Biochemical recurrence (BCR) of prostate cancer (PCa) after definitive surgery and/or radiation (including salvage strategies) is a burgeoning area of clinical research inspired by ultrasensitive next-generation imaging. Most phase III trials in PCa have focused on metastatic disease, defined by conventional imaging. Despite the emergence of new imaging, clinical trial principles from metastatic studies will not optimize future BCR trials.

METHODS A Working Group convened at the National Cancer Institute on November 13, 2024 (NCI BCR WG). Key areas of discussion included nomenclature, baseline criteria for data capture, imaging considerations, delineation of high-risk populations to be targeted for trial development, requirements of metastasis-directed therapy (MDT) or hormonal therapy, quality-of-life considerations, and potential study end points.

RESULTS The NCI BCR WG defined the novel term "prostate-specific membrane antigen (PSMA)+BCR" to identify the emerging concept of recurrent PCa identifiable only on PSMA positron emission tomography (PET), overlapping with BCR and distinct from metastatic hormone-sensitive PCa as traditionally defined by conventional imaging. The WG suggested defining high-risk BCR with a prostate-specific antigen doubling time of ≤6 months, regardless of PET findings. The WG provided recommendations for baseline data capture and imaging requirements. Neither systemic therapy nor MDT were considered mandatory for control arms. The WG also discussed novel end points and quality-of-life metrics in this disease space.

CONCLUSION These discussions should inform future clinical BCR trials in this distinct disease space relative to metastatic disease defined by conventional imaging. The NCI BCR WG strongly advocates that future trials explore deintensification of treatment to minimize toxicity in this relatively indolent disease state.

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INTRODUCTION

Historically, rising serum prostate-specific antigen (PSA) after definitive surgery or radiation therapy for prostate cancer (PCa) indicated biochemical recurrence (BCR). It is a liquid biomarker–defined, minimal residual disease (MRD) state. While a subset of patients will have rapidly progressing disease, the majority of patients with BCR will have an indolent disease process with survival approaching a decade or more.[1] The fundamental characteristics of patients with BCR are different from those of patients with metastatic disease on conventional imaging, including computed tomography (CT) or technetium bone scan at initial diagnosis (metastatic castration-sensitive PCa [mCSPC]), or those diagnosed with metastatic findings on conventional imaging after androgen deprivation therapy (ADT)–based regimens (metastatic castration-resistant PCa; mCRPC).[2,3] Defining mCSPC/mCRPC based on conventional imaging versus positron emission tomography (PET) alone allows clear framing of this discussion. Unlike mCSPC, patients with BCR are

generally older (most ≥70 years), are asymptomatic, and have a longer expected survival (10+ years), and deferred or intermittent therapies have demonstrated noninferiority to early, continuous therapy.[2-4] Because of these key distinctions, patients with BCR require special consideration in clinical trial design relative to patients with mCSPC/mCRPC.

BCR may be initially treated with local salvage options, but unsuccessfully in up to 50% of patients, and PSA ultimately continues to rise, often signifying residual cancer.[5] Any detectable and confirmed PSA after radical prostatectomy (with or without salvage radiation) is considered BCR, whereas the Phoenix criteria have been conventionally used to define BCR after primary radiation.[6] Management for the postsalvage BCR population with no visible metastases on conventional imaging includes many options: intermittent or continuous systemic therapy or deferred therapy until metastasis on conventional imaging. If patients begin ADT and subsequently experience PSA rise with castrate-level testosterone, this is termed nonmetastatic CRPC. Molecular imaging, particularly prostate-specific membrane antigen (PSMA) PET/CT imaging, referred to as PSMA henceforth, now enables detection of subclinical disease in patients with BCR who have negative conventional imaging.[7-9] These new imaging technologies have blurred definitions of this disease space because (1) there are no precise, consensus definitions; (2) insufficient data exist to demonstrate that findings are actionable; and (3) the best data to improve survival are based on conventional imaging.[7] This has generated interest in radiation ablation (eg, stereotactic body radiation therapy) of molecular-imaging-identified metastatic sites, with small data sets suggesting clinical benefit, none of which have power to demonstrate the overall or radiographic progression-free survival (PFS) benefit.[10,11] Furthermore, the trials like the phase III EMBARK trial of enzalutamide with or without ADT in a select group of patients with BCR demonstrated a benefit for metastasis-free survival (MFS) by conventional imaging, but with associated toxicities.[4,7,12]

With increasing interest in clinical studies for BCR, it is important to consider unique aspects of BCR that differentiate it from mCSPC/mCRPC and how this should affect clinical trial design. Therefore, a committee of 30 PCa experts convened at the National Cancer Institute in Bethesda, MD, on November 13, 2024. The BCR Working Group (BCR-WG) participants have demonstrated a specific experience and/or nuanced understanding of clinical research in BCR populations. The meeting was not sponsored, and participants covered their own expenses to attend. The mission statement was to develop key strategic principles for clinical trial design for BCR in the postcurative-intent therapy setting. Key discussion areas included nomenclature, baseline criteria, imaging considerations, delineation of high-risk populations, therapeutic requirements, quality-of-life (QoL) considerations, and potential end points. The group used an approach based on the Nominal Group Technique for consensus-building: the cochairs provided a list of key discussion areas in advance, introduced each discussion area and key data for consideration, and then proposed questions for discussion.[13] Participants were invited to share opinions first, and then the group discussed and formulated summary statements. Finally, the manuscript draft was edited by all participants to ensure that it accurately reflected individual viewpoints.

These discussions should inform and encourage the development of future trials in this distinct clinical setting (Tables 1 and 2). Although this working group convened place before the recently reported overall survival (OS) benefit in the EMBARK trial, there remains a critical need to optimize future BCR studies, especially in the PSMA era.

PSMA-POSITIVE BCR: DISTINGUISHING A DISEASE STATE

In the pre-PSMA era, BCR was defined by a rising serum PSA in the absence of findings on conventional imaging,[1] whereas metastatic PCa has historically been defined as evaluable disease on conventional imaging per RECIST/PCWG3 criteria.[14] The incorporation of PSMA into clinical trial/practice requires additional levels of distinction, especially since PSMA alone has not been used to determine metastatic disease in any mature phase III trial.[15,16]

A recent analysis has demonstrated that the underlying genomics of patients with recurrent disease detected by conventional imaging is associated with more aggressive phenotypes than disease detected solely by molecular imaging.[17] This distinction that BCR and mCSPC are not equivalent is borne out in clinical trials as well. When mCSPC defined by conventional imaging is treated with enzalutamide and ADT, the OS rate at 5 years is 67% versus 87.3% PFS at 5 years in a BCR population.[4,18] With this understanding, there was unanimous agreement that mCSPC is not equivalent to BCR with PSMA+ findings and negative conventional imaging.

While oligometastatic disease may partially overlap with BCR, it is not synonymous (Fig 1). Oligometastatic disease has been defined by a limited number of findings (often 3 or 5), but this is independent of the imaging modality (overlapping use of conventional imaging and PSMA across studies).[19] Patients might have polymetastatic disease visible only on ultrasensitive imaging (eg, PSMA), but this does not meet either oligometastatic or mCSPC criteria. Furthermore, the term oligometastatic may include de novo/synchronous and recurrent/metachronous states. Even the term oligorecurrence does not allow for a patient who might have 5-10+ areas on PSMA. For these reasons, the BCR-WG agreed that a distinct term is required for BCR patients who have PSMA findings in the absence of conventional imaging findings.

The group unanimously agreed that PSMA+BCR is the most appropriate term for patients with BCR who have PSMA

TABLE 1. Summary of NCI BCR Working Group Discussion

Topic	NCI BCR Working Group Recommendations for Clinical Trial Design
Nomenclature: PSMA+BCR	PSMA+BCR defines a distinct disease state from mCSPC for patients with PSA recurrence after curative-intent therapy and PSMA evidence of disease but no findings on bone scan and a CT that is negative for disease per RECIST criteria, and noncastrate testosterone BCR remains appropriate for patients with detectable PSA and no findings on PSMA or conventional imaging although one should expect a prognosis shift towards better outcomes for patients in this disease state as they likely have lower overall tumor burden and potentially more indolent biology
Baseline imaging requirements: PSMA at minimum with bone findings requiring bone scan to define mCSPC *v* PSMA+BCR	Ideally, PSMA, CT/MRI, and bone scan could be done at baseline, but logistical complications are acknowledged PSMA scans at baseline at minimum Bone findings on PSMA should require confirmation with bone scan (CT bone windows not sufficient) Soft tissue findings >1.0 cm could require a CT based on resolution of CT accompanying PSMA
Defining high-risk BCR: PSADT less than 6 months	PSA doubling time <6 months is an appropriate threshold for high-risk BCR Remains unclear how PSMA total tumor volume (and number of lesions) factors into high-risk definition at this time
Role of MDT: Not a requirement	Trials need not require MDT but may be allowed on study Use as a stratification for randomization when possible, if prior MDT allowed or planned on study
Role of ADT or ARPI: Not a requirement	Enzalutamide ± ADT is not mandatory as a control arm or backbone for BCR trials Surveillance can be a reasonable arm for BCR trials
QoL/toxicity: Should be specific to the population	QoL metrics for BCR trials should primarily capture treatment-related toxicity Should be tailored to specific expected treatment toxicities Timing of QoL data is important in context of intermittent therapy/treatment suspensions Need to include all patients from point of randomization in analysis

Abbreviations: ADT, androgen deprivation therapy; ARPI, androgen pathway inhibitor; BCR, biochemical recurrence; CT, computed tomography; mCSPC, metastatic castration-sensitive prostate cancer; MDT, metastasis-directed therapy; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; PSADT, PSA doubling time: PSMA, prostate-specific membrane antigen; QoL, quality-of-life assessment.

findings that are below the level of detection on conventional imaging. The PSMA+BCR nomenclature should include patients with PSMA-avid findings beyond local regional disease (ie, metastatic) but would not use the term metastatic to avoid confusion for patients and providers with a metastatic literature study that conveys a more dire prognosis than PSMA+BCR where PSMA findings do not meet conventional imaging criteria. Furthermore, PSMA+BCR keeps the historical relevance of existing BCR literature/data and fits the existing definition of BCR, which already excludes findings on conventional imaging and requires a history of definitive therapy. This term may also be useful for clinical trial eligibility to decrease heterogeneity in study populations although traditional BCR prognostic factors

TABLE 2. Important Data to Capture in Future BCR Trials

Setting	Key Characteristics
Baseline	Definitive/curative-intent therapy Previous PSMA PET staging at initial diagnosis: Whether performed, and any findings Salvage/adjuvant therapy (including type) Original Gleason score, T/N stage, pretreatment PSA Time to PSA recurrence (end of curative-intent treatment to BCR1) Time to PSMA recurrence Previous ADT, ARPI, and in what disease setting Previous MDT and the number of lesions treated Response to previous MDT and duration Baseline PSMA findings (from typically within 2-3 months of enrollment) Pelvic only *v* beyond pelvis Defining nodes, visceral and bone findings on PSMA Baseline PSA and testosterone, confirming noncastrate status Baseline PSA doubling time Ideally calculated when PSA is over 0.5 ng/mL Should be calculated after testosterone recovery after ADT Should only use PSAs since most recent therapy
After treatment (for treatment-free survival analysis)	Time and type of next MDT, if performed Time and type of next systemic therapy, or therapy reinitiation QoL/toxicity (patient- and/or investigator-assessed) off treatment, with multiple time points if lingering toxicity is expected

Abbreviations: ADT, androgen deprivation therapy; ARPI, androgen receptor pathway inhibitor; BCR, biochemical recurrence; MDT, metastasis-directed therapy; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; QoL, quality-of-life.

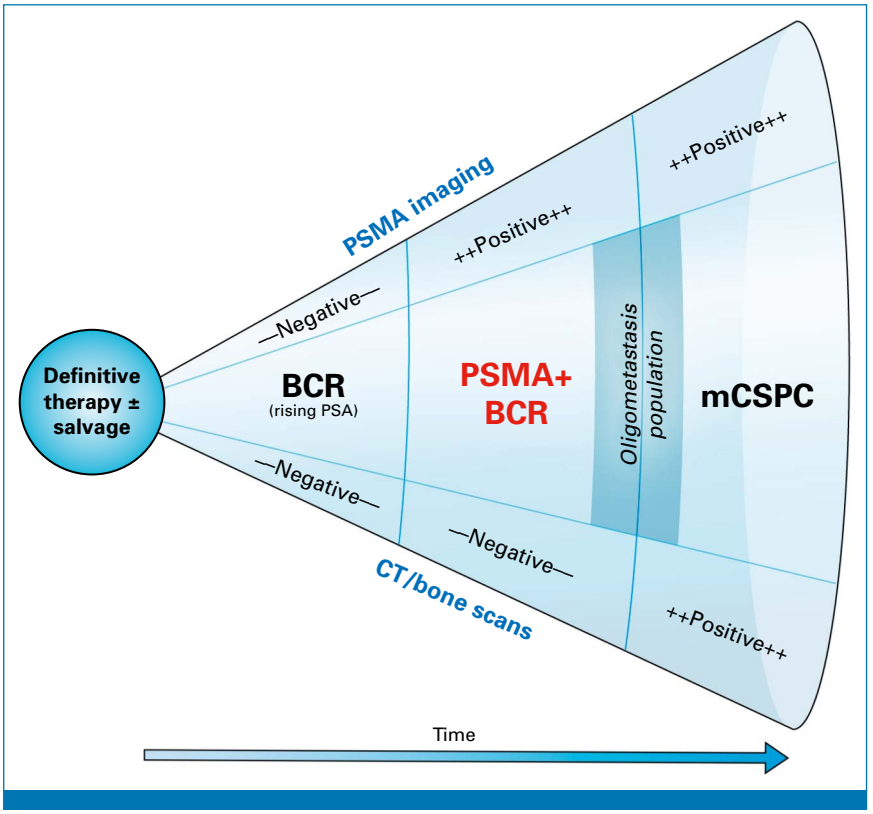

FIG 1. Distinguishing stages of recurrent prostate cancer. BCR is defined as a rising PSA after definitive therapy (possibly including salvage options). Initially, BCR is defined only by serum PSA levels when all imaging remains negative. Over time, likely as PSA rises, PSMA PET scans will identify sites of disease although CT (or MRI) and bone scan (conventional imaging) remain negative. This population defined most accurately as PSMA+BCR is distinct from mCSPC in that the conventional imaging remains negative and PSMA+BCR would not have been eligible for any of the mCSPC trials that have been completed to date. mCSPC includes only patients with disease detectable on CT (or MRI) or bone scan. It is worth noting that oligometastatic disease has been defined differently across numerous trials, but often has been more focused on a limited number of areas of disease rather than the imaging modality of detection. Thus, oligometastatic patients may have either mCSPC or PSMA+BCR as the imaging modality is not restricted in this definition. It is also worth noting that not all PSMA+BCR is oligometastatic as some patients with PSMA+BCR might have too many PSMA+ findings to meet the definition of oligometastatic across trials. BCR, biochemical recurrence; CT, computed tomography; mCSPC, metastatic castration-sensitive prostate cancer; MRI, magnetic resonance imaging; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

likely still matter and should still be captured (see below). Although the focus of this BCR-WG is on clinical trial development, the group proposed that the PSMA+BCR term be broadly adopted to better define this clinical disease state for patients and clinicians alike (Figs 2A-2C) in patients with BCR who get a PSMA. Distinguishing PSMA+BCR could limit unnecessary patient confusion/anxiety related to the classic definition of metastatic and associated OS, which is not representative of PSMA+BCR patients.

IMPORTANT DATA TO CAPTURE

The BCR-WG agreed that the characteristics listed in Table 2 should be captured for all patients on BCR clinical trials. Figure 3 illustrates collection of data from multiple rounds of previous therapy for BCR.

IMAGING: PSMA SCANS WITH CT/BONE SCANS PREFERRED, BONE SCANS SHOULD CONFIRM BONE FINDINGS

Although EMBARK was conducted before the era of widespread PSMA utilization, there is little doubt that most future BCR studies will use PSMA.[4] Some current phase III BCR studies require PSMA+ disease for eligibility. This is appropriate as it likely selects somewhat higher-risk patients (relative to PSMA PET-negative) and may also provide opportunities to evaluate therapeutic response, with the caveat

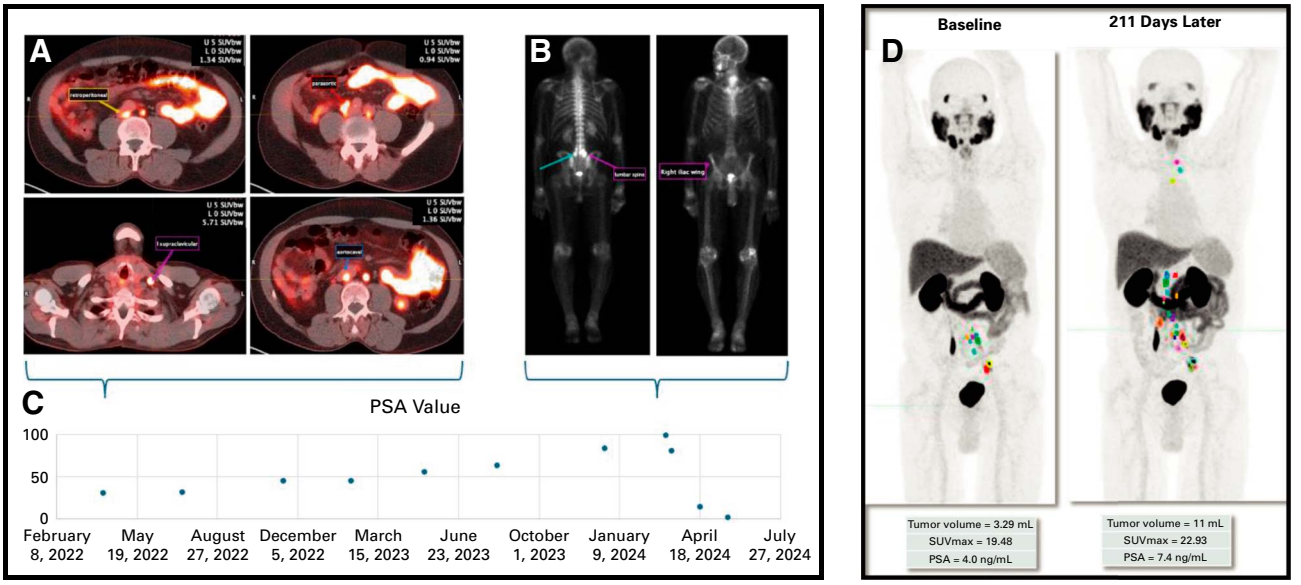

FIG 2. Definitions of progression on PSMA PET in BCR remain undefined. These cases highlight how little is known about the natural history of PSMA+BCR and PSMA PET progression in BCR. Case 1: (A) PSMA PET/CT demonstrating PSMA-avid subcentimeter LN at the time of BCR. Patient opted for surveillance. Serial CT torso and bone scans remained negative for 2 years, until (B) a bone scan showed new focal uptake along the right anterior iliac spine and lumbar spine. These findings led to the initiation of intensive ADT. Notably, PSMA-avid LN disease never progressed during that time. (C) PSA trend, with a PSADT of 12 months consistent with indolent behavior. Case 2: (D) RECIP 1.0 was primarily developed for more advanced disease but would define progression based on a 30% increase in PSMA tumor volume (PSMA-TV).[20] In this patient, PSMA-TV increased by >330% and includes new LN, but his PSA only increased from 4.0 to 7.44 ng/mL in the 211 days. This would be a PSADT of 7 months, which this committee would not define as high risk, and only has a metastatic risk of 27% at 5 years.[18] Nonetheless, this modest PSA increase is associated with more dramatic appearing changes on PSMA PET imaging quantitively in terms of PSMA-TV and distinct PSMA+ findings. Although only one case, this highlights that more prospective data are required to understand clinically meaningful thresholds of PSMA progression/changes in patients with PSMA+BCR. (This patient was enrolled on an immunotherapy trial but did not have a PSA response during this time period.) ADT, androgen deprivation therapy; BCR, biochemical recurrence; CT, computed tomography; LN, lymph node; PET, positron emission tomography; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time; PSMA, prostate-specific membrane antigen; TV, tumor volume.

that traditional BCR prognostic factors are not known to be trumped by PET findings (Fig 4).

Several suggested guidelines on PSMA interpretation have been published but are still evolving for the recurrent setting.[20] Qualitatively and quantitatively, PSMA PET parameters that can be studied include standardized uptake values (SUVmax and SUVmean) and tumor volumes (TVs) derived from PET pixel uptake and total lesional uptake. Analysis can occur on a lesional level or a patient level and could be compared with clinical variables and subsequent imaging to assess predictive capabilities. Because PET/CT scanners can have wide variability in SUV, especially with small lesions limiting interpatient comparisons, considering tumor-to-organ ratios may be useful.

An important pragmatic quandary is whether conventional imaging should be included in future studies. The BCR-WG was in general agreement that ideally baseline CT (or magnetic resonance imaging) and bone scan should also be obtained in parallel with PSMA to provide the cleanest definition of PSMA+BCR. Despite that understanding, there was also acknowledgment around the scheduling and potential reimbursement constraints of requiring multiple baseline imaging studies. Furthermore, if conventional imaging is performed after PSMA imaging, then readers ideally would be blinded to the PSMA PET imaging, so it does not influence the conventional imaging reading. One potential solution is to use diagnostic quality CT with intravenous contrast with the PET/CT. However, this might disrupt normal workflows, requiring special planning, and could entail a second billing event. This approach would not replace bone scintigraphy, but it may provide a compromise between accuracy and feasibility.

Despite acknowledged difficulties in getting bone scans in addition to PSMA, there was a strong consensus that PSMA-positive bone findings should be evaluated on technetium bone scan. The WG acknowledges that early metastatic bone disease may be positive only on PSMA and false positives with PSMA have been described in the ribs/pelvis. It is known that metastatic disease defined by bone scintigraphy (while potentially meeting criteria for separate specific studies in oligometastatic disease) may not be appropriate for studies in PSMA+BCR.[14,15] Such patients would generally receive ADT and likely an androgen receptor pathway inhibitor (ARPI)

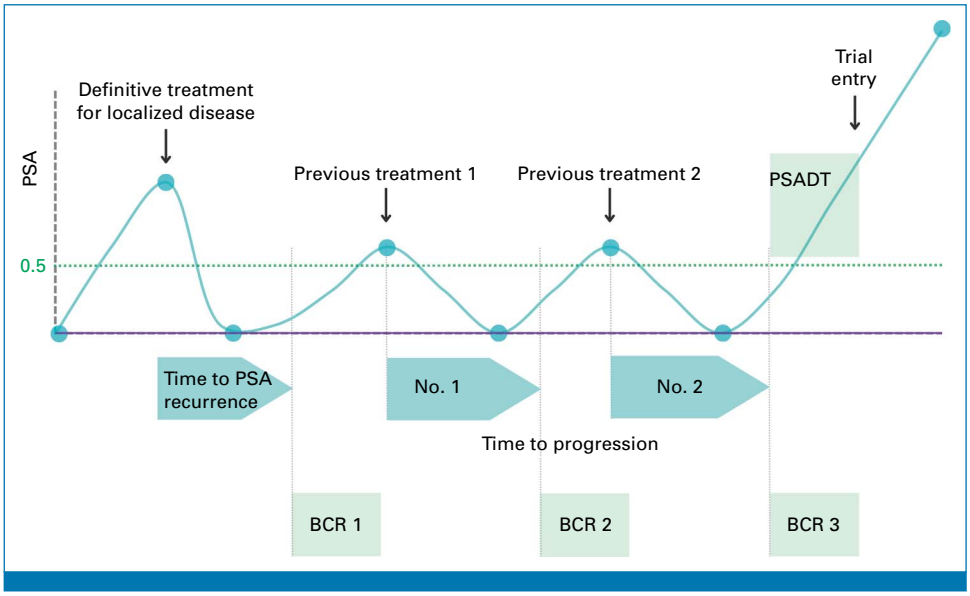

FIG 3. Recommended data capture at baseline for trials in BCR. This figure recognizes that patients in this space might have gone through multiple systemic and/or local therapies for BCR and/or oligometastatic recurrence and that response to previous therapies is important to capture as a prognostic factor (especially for MDTs) and potential modifiers of downstream therapies (if previous systemic therapies have durable effects beyond treatment). PSADT should be calculated only using values between most recent treatment and trial entry and only values ≥0.5 ng/mL. BCR, biochemical recurrence; MDTs, metastasis-directed therapies; PSA, prostate-specific antigen; PSADT, prostate-specific antigen doubling time.

based on the standard management of bone scan–defined mCSPC.[21] Furthermore, existing data highlight that disease seen on molecular imaging alone and not on conventional imaging is genomically disparate and likely has a more indolent natural history.[17] There should be caution about overinterpretation of PSMA-positive bone findings on CT bone windows not seen on bone scan. Historically, bone scans have been used to define metastatic disease in PCa, and thus, bone scans should be used to adjudicate PSMA bone findings.[14] Available data suggest that isolated PSMA-positive bone findings (negative conventional imaging) are found in a minority of patients (<10%), so special attention to this population should be feasible.[22] Importantly, false-positive findings are not uncommon with PSMA, especially isolated rib lesions without CT correlate and low SUVmax.[23] Biopsies of ambiguous PSMA findings should be performed as clinically indicated or unless otherwise defined in a specific protocol; however, given the overall indolent disease state, it is very reasonable instead to monitor lesions on subsequent imaging.

Another consideration was the size threshold requirements for lymph nodes (LNs), and this is potentially an area where PSMA+ BCR studies may use a variation on RECIST. Standard RECIST criteria define pathologic LN by CT short-axis dimensions of ≥1.5 cm.[14] There was discussion about these criteria being too stringent given the known indolent biology of LN-based disease in PCa.[24,25] The Working Group agreed that in PSMA+BCR, LNs ≤1.5-2.0 cm could be acceptable as in some studies (eg, ClinicalTrials.gov identifier: NCT06096870) and according to the PROMISE V2 criteria (>10 mm), and is consistent with previous nmCRPC trials.[26,27]

The consensus among the BCR-WG was that PSMA should be paired with conventional imaging when possible, but if not feasible, at the very least PSMA-positive bone findings should be evaluated with bone scan to differentiate mCSPC versus PSMA+BCR. Frequency of PSMA imaging will be dictated by individual protocols and could depend on the therapeutic interventions. For example, trials involving hormonal therapy may require less frequent imaging as PSA is a reliable biomarker and the therapeutics are known to be effective. By contrast, novel non–AR-targeting therapies may require more frequent imaging.

DEFINING HIGH-RISK BCR: PSA DOUBLING TIME LESS THAN SIX MONTHS

When developing trials in PSMA+BCR, defining risk is important for many reasons. Primary among them is that the need for intervention and tolerance for potential toxicity must be placed in the context of risk of clinical progression. Higher-risk populations will have higher event rates, making it easier to detect effects of study interventions.

PSA doubling time (PSADT) is among the best predictors of outcomes in BCR, much more so than absolute PSA value or Gleason score.[2,28,29] While it is unclear how PSMA findings

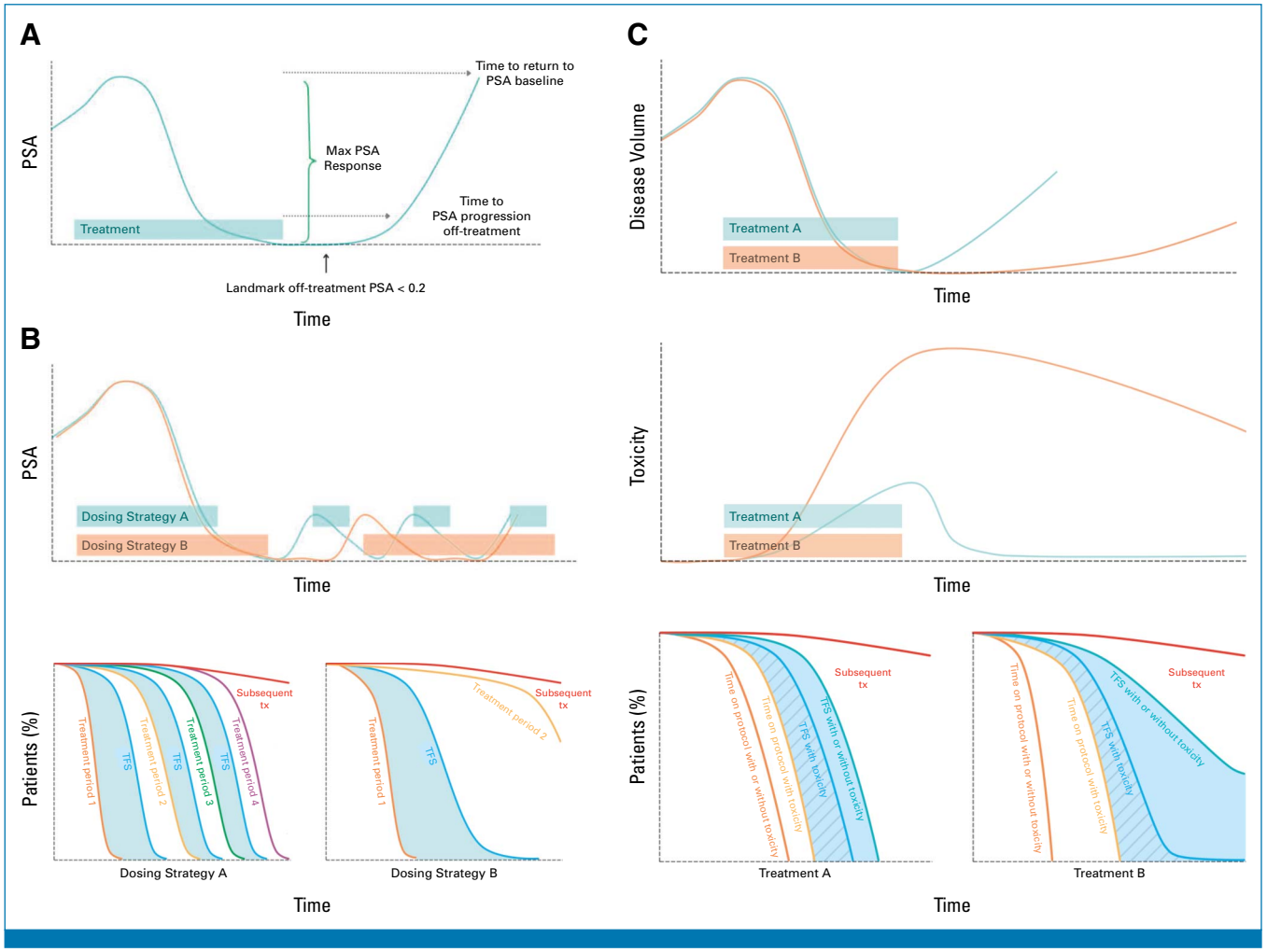

FIG 4. End points in BCR trials. (A) PSA kinetics can be captured in several ways. Importantly, the durability of the effect can be captured via landmark off-treatment undetectable PSA and time-to-event variables although PSA progression will precede return to previous PSA baseline. (B) Here, two dosing strategies are compared to maximize TFS. Dosing Strategy A is intermittent, whereas Dosing Strategy B is what was used in EMBARK (single discontinuation). TFS curves capture total time on/off treatment, and toxicity can be layered in (not shown). (C) Treatments A and B work equivalently well up-front, but Treatment B has more durability off treatment, at the cost of on- and off-treatment toxicity. TFS curves capture the trade-off of greater TFS versus greater time with toxicity on Treatment B. BCR, biochemical recurrence; PSA, prostate-specific antigen; TFS, treatment-free survival.

can factor into the risk equation, it is likely that PSADT will remain important as pre-PSMA imaging-era data included primarily patients with PSAs above thresholds at which most patients will have PSMA findings (above 0.5-1.0 ng/mL). PSMA+BCR is a heterogeneous disease space, and traditional BCR prognostic factors should still be used for risk stratification.[2,8,28]

High risk is not an absolute concept. EMBARK enrolled patients with PSADT <9 months, but historical data indicate substantial heterogeneity within this category: the 5-year MFS rates defined by conventional imaging without treatment were 35%, 49%, and 73% with PSADT <3, 3-6, and 6-9 months, respectively.[29] Similarly, in EMBARK, the patients with a PSADT of 6-9 months had the smallest estimated treatment effect and greatest variability (hazard ratio [HR], 0.63 [95% CI, 0.32 to 1.22]).[4]

The BCR-WG agreed that the highest-risk BCR population had PSADT <3 months, but this was practically too restrictive for eligibility for a clinical trial. There was consensus among the BCR-WG that PSADT <6 months offered a reasonable balance of clinical risk and feasibility, especially for more toxic study treatments. The Working Group agreed that other populations with a slower (longer) PSADT beyond 6 months could be studied in trials, but such trials should involve treatments with lower toxicity and should acknowledge that surveillance is reasonable as standard-of-care. Furthermore, enrolling patients with lower risk (longer PSADT) may require larger sample size given their lower event

rates, competing causes of mortality, and potentially higher dropout rates.

METASTASIS-DIRECTED THERAPY IS NOT REQUIRED IN PSMA+BCR STUDIES

Ultrasensitive molecular imaging has increased the enthusiasm for metastasis-directed therapy (MDT), with some support from multiple phase II studies, albeit without clear and robust long-term survival data.[10,11,19,30,31] Prospective randomized data suggest that the median rPFS (or eugonadal PFS if concurrent ADT is used) is approximately 1-2 years.[10,19,32] Furthermore, studies have included variable imaging modalities (some with conventional imaging, some PET-only) to define oligometastases.

The BCR-WG considered potential definitions of oligometastatic disease, which have generally relied on arbitrary clinical thresholds of 3-5 lesions, with different imaging modalities.[10,11,19] In general, bone sites have been counted individually, whereas nodal chains are generally counted as one site and treated together given the high likelihood of involvement of adjacent PSMA-positive occult nodes. These are important baseline factors to consider in patients entering studies who have already received MDT cycles. This acknowledges that patients with previously treated oligometastases may still be included in the PSMA with or without BCR disease space, rather than being permanently labeled metastatic.

Furthermore, it is unclear how to incorporate MDT in PSMA+BCR studies. There are no phase III data or prospective OS benefit certifying MDT as the standard of care that should be mandated in PSMA+BCR; however, it is frequently used in both trials and clinical practice. The BCR-WG consensus was that if previous MDT is allowed or planned in a trial, it should be considered as a stratification factor in any random assignment.

While there are some ongoing postsalvage setting studies that could clarify the benefits of MDT in PSMA+BCR, most do not evaluate a control without MDT. Nonetheless, there is hope that future data will clarify benefits of MDT, but until then, current studies should not be constrained by the absence of these data.

ADT AND/OR ARPIs ARE NOT REQUIRED IN PSMA+BCR STUDIES

EMBARK, which evaluated enzalutamide with/without ADT in BCR, was an important step forward in defining BCR as a unique disease state worthy of further clinical investigation.[4] There was full agreement among the BCR-WG that EMBARK offers a therapeutic option, but not necessarily the single standard of care for all patients with BCR. As established above, the included high-risk population was likely overly broad.[2,29] Furthermore, even as we are now a decade past the seminal findings of CHAARTED in mCSPC, new phase III data are constantly emerging and treatment for mCSPC continues to evolve. This is likely the case with EMBARK as we await the publication of OS benefit data.

Toxicity is a paramount consideration when designing trials in BCR where patients often can live 5-10+ years without the development of symptomatic disease. Despite the benefits in EMBARK, there was a high discontinuation rate of >17% in both the enzalutamide-containing arms.[4] Patient compliance needs to be considered when designing BCR studies because lower-risk patients have greater latitude to discontinue therapy, which could lead to high levels of censored data, affecting statistical power and adding bias. Similarly, trials like EMBARK that blind a control arm to PSA rise pose problems for the field, given that previous trials in nmCRPC established the benefit of adding AR antagonists before radiographic progression, and may drive informative censoring, if patients get testing outside the study, prompting early withdrawal.[27,33-35]

Given this combined perspective, the BCR-WG was in full agreement that future BCR studies (with or without PSMA findings) should not require the use of ADT or ARPI. Again, for patients with a PSADT of <6 months, strong consideration should be given to treatments that will control disease in the short term, but investigators should not be constrained by designs that require enzalutamide with or without the ADT comparator arm or backbone. Indeed, this is already evident in the PSMA-DC trial (ClinicalTrials.gov identifier: NCT05939414) which is a phase III trial in PSMA+BCR not requiring ADT and/or ARPI.

BCR STUDIES REQUIRE APPROPRIATE QUALITY-OF-LIFE MEASURES

When EMBARK was launched in 2015, patient-reported outcomes (PROs) in PCa were focused on advanced disease. Thus, the PROs used were not the most appropriate for a BCR population in which cancer is rarely symptomatic, even with PSMA-positive findings.[36]

PROs in localized disease often focus on toxicity of treatment (eg, urinary, sexual health), whereas many PROs in advanced PCa focus on the evaluation of symptoms from disease with a goal of treating/preventing/delaying such symptoms, such as time to pain progression. PROs in BCR should be calibrated to better understand how a treatment is affecting the patient when there is no concern for near-term symptoms or death. Moreover, the choice of instrument will depend on the unique toxicities of the study treatment since the toxicity profiles of ADT, ARPIs, MDT, and other therapies are distinct. For example, PROs that include questions that elucidate symptoms of hot flushes, gynecomastia, and mastalgia would be important in this population.

Defining appropriate PROs specific for BCR was beyond the scope of the BCR-WG, but there was uniform agreement that PROs developed for newly diagnosed metastatic or late-stage populations will not be best to inform studies completed in

TABLE 3. Considerations for End Points for Future BCR Studies

End Point	Consideration
Metastasis-free survival as defined by conventional imaging	Established end point and used in the EMBARK trial Unclear surrogacy for overall survival in BCR Unclear if future studies can maintain equipoise, deferring therapy given changes in serum PSA or PSMA perhaps observed outside of study
PSMA progression	PSMA is increasingly available and replacing conventional imaging Unclear what clinically relevant changes on PSMA equate to either treatment failure or clinically meaningful disease progression. Potential for discordance with conventional imaging
Treatment-free survival	Metric that measures cumulative time spent in different states: On/off treatment, with/without toxicity Captures the durability of treatment effects, positive (cancer control) and negative (off-treatment toxicity), and includes all studied patients rather than a subset contingent on a postrandomization event (eg, recovery of testosterone for eugonadal PFS) Requires data on time off therapy and time of treatment reinitiation and/or subsequent therapies. More easily interpretable if treatment reinitiation or subsequent therapy start is clearly defined (ie, by protocol)

Abbreviations: BCR, biochemical recurrence; PET, positron emission tomography; PFS, progression-free survival; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

BCR. The timing of PRO collection will also be critical in the context of intermittent therapies. Analyses should not be restricted to a subset of patients who achieve a treatment discontinuation trigger, and they should present both cumulative data and worst single time point as both cumulative and momentary toxicity may matter to patients.[36]

END POINTS OF FUTURE STUDIES

Metastasis-Free Survival

The BCR-WG agreed that designing trials in the PSMA+BCR space will be challenging regardless of the end point chosen (Table 3). It is important to note that previous efforts by the International Intermediate Clinical Endpoints in Cancer of the Prostate working group to establish MFS as a surrogate for OS are only applicable to the included curative-intent, localized-disease trials.[37,38] Thus, MFS is not a validated surrogate for OS in this setting. If the publication of pending EMBARK trial OS benefit yields robust findings, it may be difficult to justify end points that are not subsequently validated by OS, presuming that subsequent therapy is appropriately balanced and censoring is at a minimum. At the same time, EMBARK data alone will likely not validate MFS as a universal intermediate end point in the PSMA+BCR space.

EMBARK used MFS defined by conventional imaging, which is also used in the PSMA-DC study (ClinicalTrials.gov identifier: NCT05939414). Future studies using conventional imaging–based MFS will be challenging because of the ubiquitous availability of PSMA scans and a potential lack of equipoise by practitioners and patients alike. Will it be realistic to have PSMA+BCR patients (whose conventional imaging is likely to be negative for years) to forego PSMA outside of the trial? This issue will be especially pronounced in clinical settings where other therapies, including MDT, are available. PSA contamination has been a frequent problem in clinical trials involving blinding (including EMBARK). PSMA may present a similar obstacle in the future.[39] Thus, MFS based on conventional imaging may face pragmatic issues, limiting feasibility as a primary end point.

PFS2 is a concept used to assess the impact of systemic therapy on subsequent lines of therapy.[40] However, assuming that subsequent therapies are not protocol-defined, it faces a number of challenges, including difficulty in capturing data postprotocol and subsequent interpretation.

PSMA Progression

There is a natural desire to modify MFS or other imaging-based progression end points by incorporating PSMA imaging. Indeed, this is even the primary end point of an ongoing phase III trial.[41] While the BCR-WG expressed interest in this concept, there was a universal concern that we do not yet understand the significance of PSMA-detected progression. While criteria exist, its utility in patients with BCR is not fully defined.[20] Changes in PSMA TV that arbitrarily set thresholds (eg, 30%) might not have any clinical value in PSMA+BCR (Fig 2D).

More prospective data are required to understand what clinically meaningful PSMA imaging metrics in the BCR setting, such as PSMA-TV, are clinically useful (eg, ClinicalTrials.gov identifier: NCT05588128). Furthermore, it is not yet clear how to factor in treatment response, especially in therapies that may affect PSMA expression like ARPIs or Lu-PSMA-617.[42,43] In particular, PSMA flare may occur after AR-directed therapies, so increases in avidity or appearance of new lesions at early time points may not signify therapeutic resistance. More data are required to better understand this phenomenon in this setting. Efforts such as these will be critically important for defining the future roles and limitations of PSMA in guiding the treatment of patients with PSMA+BCR.

Treatment-Free Survival

Treatment-free survival (TFS) is a metric that offers a comprehensive, partitioned survival analysis approach to capture how patients spend cumulative survival time, on and off treatment, with and without side effects of treatment.[44-46] This is an approach borrowed from the Quality-adjusted Time Without Symptoms or Toxicity (Q-TWiST) metric developed in the context of adjuvant systemic therapy in early-stage breast cancer.[47,48] It defines a series of time-to-event end points and health states quantified by areas below and between Kaplan-Meier curves for the end points, using restricted mean survival times. Importantly, all patients are included from the point of random assignment, rather than selecting subsets based on a postrandomization event, like treatment discontinuation, recovery of testosterone, or response to treatment. TFS requires data capture of time off treatment, time of subsequent therapies, and serial toxicity/QoL data (Table 2).

While TFS has been primarily developed in the context of immunotherapy approaches for melanoma and kidney cancer, it is well suited for capturing the longitudinal experience of patients with BCR. First, it could help capture the trade-offs involved in starting versus deferring therapy.[45,46,49,50] Second, it could help compare different types of treatments with different latencies of effect or toxicity, which may be administered on different schedules. For example, ADT and ARPIs have very high initial response rates but generally have less durability after discontinuation and once testosterone recovers. (While eugonadal PFS can capture cancer-control durability after testosterone recovery, it captures only the subset of patients who have recovery, which happens variably and at variable times.[51] It also applies only to ADT-containing regimens.) By contrast, immunotherapies and radioligands might have lower initial response rates than hormonal therapy but might have more durability off treatment in regard to both efficacy and toxicity. In addition to accurately capturing cumulative patient experiences and trade-offs with these different strategies, the TFS end point could allow novel drug development to show unique advantages relative to traditional hormonal therapies, even if initial response rates and primary progression rates are inferior (Fig 3).

FUTURE DIRECTIONS: FOCUS ON TREATMENT DE-ESCALATION IN BCR

In evaluating potential future studies, the BCR-WG calls for novel trial designs customized to the unique challenges of an asymptomatic, micrometastatic disease state with both variable but prolonged natural history and shifting definition based on evolving imaging modalities. Importantly, the quandaries faced in BCR will have growing relevance for other solid malignancies where tumor-informed ctDNA is increasingly used as an ultrasensitive MRD marker analogous to PSA.

The BCR-WG enthusiastically and unanimously endorsed de-escalation trials of two broad categories: (1) optimization of intermittent dosing strategies of hormonal agents to minimize cumulative treatment toxicity and (2) investigation of agents with durable activity beyond the treatment period to minimize the need for prolonged systemic therapy. This is the inevitable long-term evolution of BCR studies. We now see after the first decade of mCSPC treatment trials an initial attempt to de-escalate therapy in a subpopulation of that population.[52,53]

Patients with PSMA+BCR can have a very indolent disease state, and the BCR-WG agreed that there is no need to spend a period exclusively overtreating all patients with BCR before a need for de-escalation is acknowledged. Indeed, ongoing phase III studies in PSMA+BCR that have defined treatment periods may be considered de-escalation trials in that they require less continuous ADT than EMBARK, and even EMBARK investigators have signaled a desire for more intermittent use of ADT/ARPI based on their data.[41,44,54] The BCR-WG unanimously agrees that the next generation of BCR studies should not look solely to intensify therapies but also explore minimizing intervention and thus toxicity, while exploring biomarkers and traditional patient-level clinical data for this heterogenous population. It is through these more comprehensive approaches that we will maximize and expedite improved global clinical outcomes for patients with PSMA+BCR.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

National Cancer Institute's Working Group on Biochemically Recurrent Prostate Cancer: Clinical Trial Design Considerations

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Patents, Royalties, Other Intellectual Property: Combination PDL1 And TGF-beta Blockade in Patients With HPV+ Malignancies Publication number: 20200062849 Abstract: The invention provides a method of inhibiting a malignancy associated with human papilloma virus (HPV)

comprising administering to a subject an agent that blocks PD-L1 and TGF-beta pathways, thereby inhibiting a malignancy associated with HPV in the subject. No money is associated with this

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Research Funding: Bristol Myers Squibb (Inst), Amgen (Inst), Prometheus, Genentech (Inst), Seagen (Inst), Arcus Biosciences (Inst), Apollomics (Inst), Nektar (Inst), Revimmune (Inst), HUYA Bioscience International (Inst), AVEO (Inst), Xencor (Inst), Pfizer (Inst), Merck (Inst)
Travel, Accommodations, Expenses: Aveo, Seagen, Bayer, Genentech, Pfizer

Russell K. Pachynski
Stock and Other Ownership Interests: Pixie Biosciences, Inc
Consulting or Advisory Role: Bristol Myers Squibb, Pfizer/EMD Serono, Sanofi, Dendreon, Bayer, Blue Earth Diagnostics, Tolmar Therapeutics, Janssen Oncology, Eisai, Exelixis, MacroGenics
Speakers' Bureau: Merck, Bayer
Research Funding: Janssen Oncology, Pharmacyclics (Inst), Bristol Myers Squibb Foundation (Inst), Exelixis (Inst)
Patents, Royalties, Other Intellectual Property: Entitled: Method of Cell-Free DNA Analysis to Identify High-Risk Metastatic Prostate Cancer, Compositions comprising chemerin and methods of use thereof
Travel, Accommodations, Expenses: Genentech/Roche

Channing J. Paller
Consulting or Advisory Role: Dendreon, Omnitura, Exelixis, AstraZeneca, Janssen Oncology, Pfizer, Bayer
Research Funding: Lilly (Inst)
Travel, Accommodations, Expenses: Bayer

Edwin M. Posadas
Consulting or Advisory Role: Bayer
Speakers' Bureau: Bayer
Research Funding: Pfizer (Inst), EnviroTherapetuics, Inc (Inst)
Patents, Royalties, Other Intellectual Property: Patent on NanoVelcro Assay for CTCs in prostate cancer
Expert Testimony: Shook, Hardy & Bacon L.L.P

Kenneth J. Pienta
Stock and Other Ownership Interests: CUE Biopharma, PEEL Therapeutics, Kreftect, Inc
Consulting or Advisory Role: CUE Biopharma
Research Funding: Progenics
Travel, Accommodations, Expenses: CUE Biopharma

Meredith M. Regan
Honoraria: Bristol Myers Squibb, Merck
Consulting or Advisory Role: Tolmar, Bristol Myers Squibb, Tersera, AstraZeneca
Research Funding: Pfizer (Inst), Novartis (Inst), Bayer (Inst), Bristol Myers Squibb (Inst), Roche (Inst), bioTheranostics (Inst)

Laura A. Sena
Research Funding: Panbela Therapeutics (Inst)

Xiao X. Wei
Honoraria: OncLive
Consulting or Advisory Role: Novartis, Dendreon
Research Funding: Bristol Myers Squibb (Inst)
Travel, Accommodations, Expenses: Corvus Pharmaceuticals, Novartis

Evan Y. Yu
Consulting or Advisory Role: Bayer, Merck, Bristol Myers Squibb, Loxo/Lilly, Johnson and Johnson, AstraZeneca, Tolmar, Lantheus Medical Imaging
Research Funding: Dendreon (Inst), Merck (Inst), Seagen (Inst), Blue Earth Diagnostics (Inst), Bayer (Inst), Lantheus Medical Imaging (Inst), Tyra Biosciences (Inst)

Phuoc T. Tran
Honoraria: Reflexion Medical
Consulting or Advisory Role: Astellas Pharma, Regeneron, GenomeDx, Reflexion Medical, Dendreon, Reflexion Medical, Noxopharm, Janssen, Myovant Sciences, AstraZeneca, Bayer Health, Lantheus Medical Imaging, Novartis, Pfizer
Research Funding: Astellas Pharma (Inst), Reflexion Medical (Inst), Bayer Health (Inst)
Patents, Royalties, Other Intellectual Property: Compounds and Methods of Use in Ablative Radiotherapy. Patent filed 3/9/2012. PCT/US2012/028475. PCT/WO/2012/122471
Travel, Accommodations, Expenses: RefleXion Medical

Ravi A. Madan
Research Funding: Bayer

No other potential conflicts of interest were reported.